Phase 1 Dose Escalation and Expansion Trial to Assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

David S. Hong,[1] Brian A. Van Tine,[2] Anthony J. Olszanski,[3] Melissa L. Johnson,[4] David Liebner,[5] Trupti Trivedi,[6] Quan Lin,[6] Erica Elefant,[6] Rebecca Dryer-Minnerly,[6] Jean-Marc Navenot,[6] Dennis Williams[6], Indu Ramachandran[6], Paula M. Fracasso,[6] Elliot Norry,[6] Marcus O. Butler[7]

[1]MD Anderson Cancer Center, Houston, TX, USA, [2] Washington University School of Medicine, St. Louis, MO, USA, [3]Fox Chase Cancer Center, Philadelphia, PA, USA, [4]Sarah Cannon Research Institute, Nashville, TN, USA, [5]Ohio State University Comprehensive Cancer Center, Columbus, OH, USA, [6]Adaptimmune, Philadelphia, PA, USA, [7]Princess Margaret Cancer Centre, Toronto, Ontario, Canada

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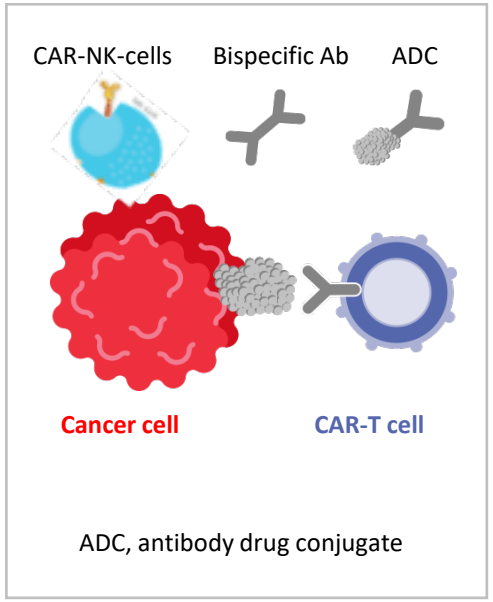
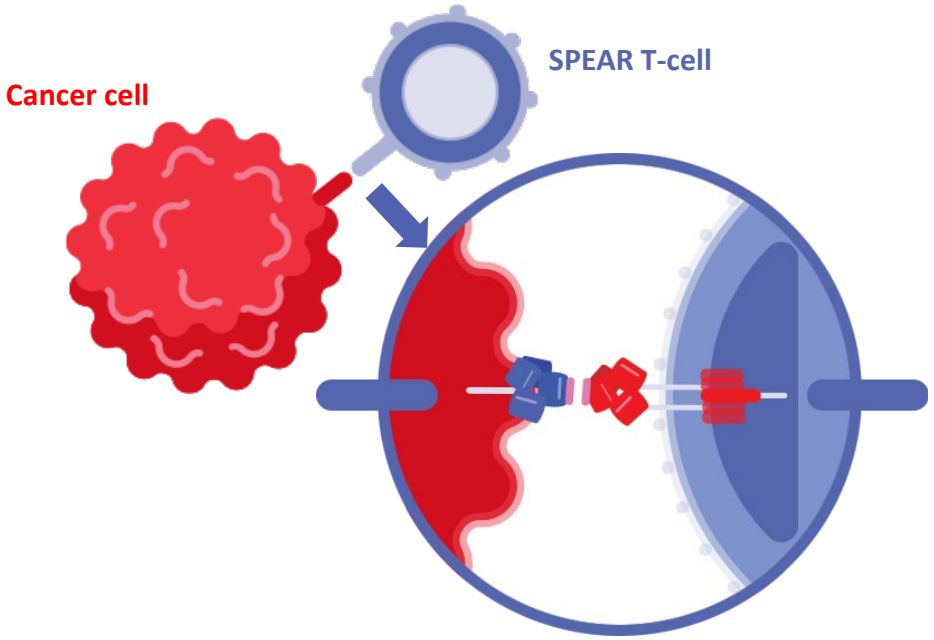
ADP-A2M4 SPEAR T-cells



ADC, antibody drug conjugate

TCR-based recognition
More options for targeting cancers
by enhancing the natural immune system



- T-cells scan HLA-peptides with TCRs
- Access to broader spectrum of intra- and extra-cellular proteins
- TCR is T-cell's natural receptor construct
- Ability to target solid tumors

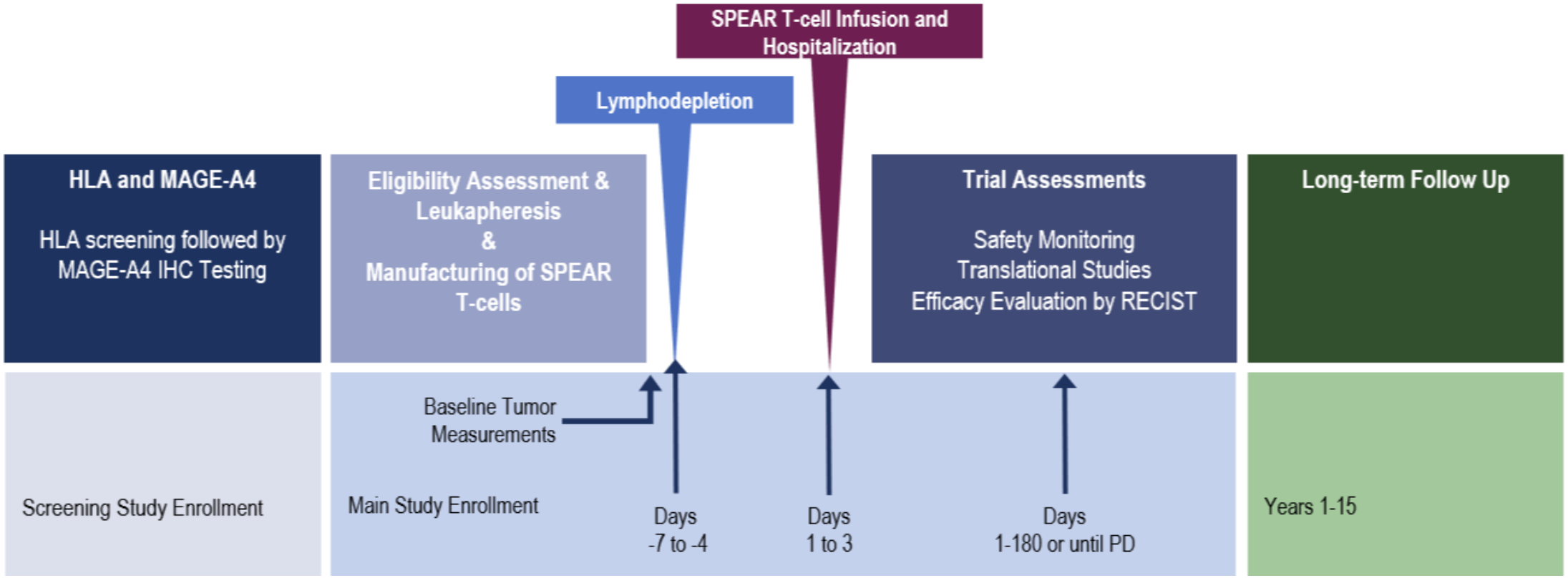
MoA Video:
https://youtu.be/zdI8IGXoQd0

Objectives

Phase 1 dose escalation, multi-tumor study to assess the safety, tolerability and antitumor activity of ADP-A2M4 in HLA-A2^{+} patients with MAGE-A4^{+} tumors (NCT03132922)

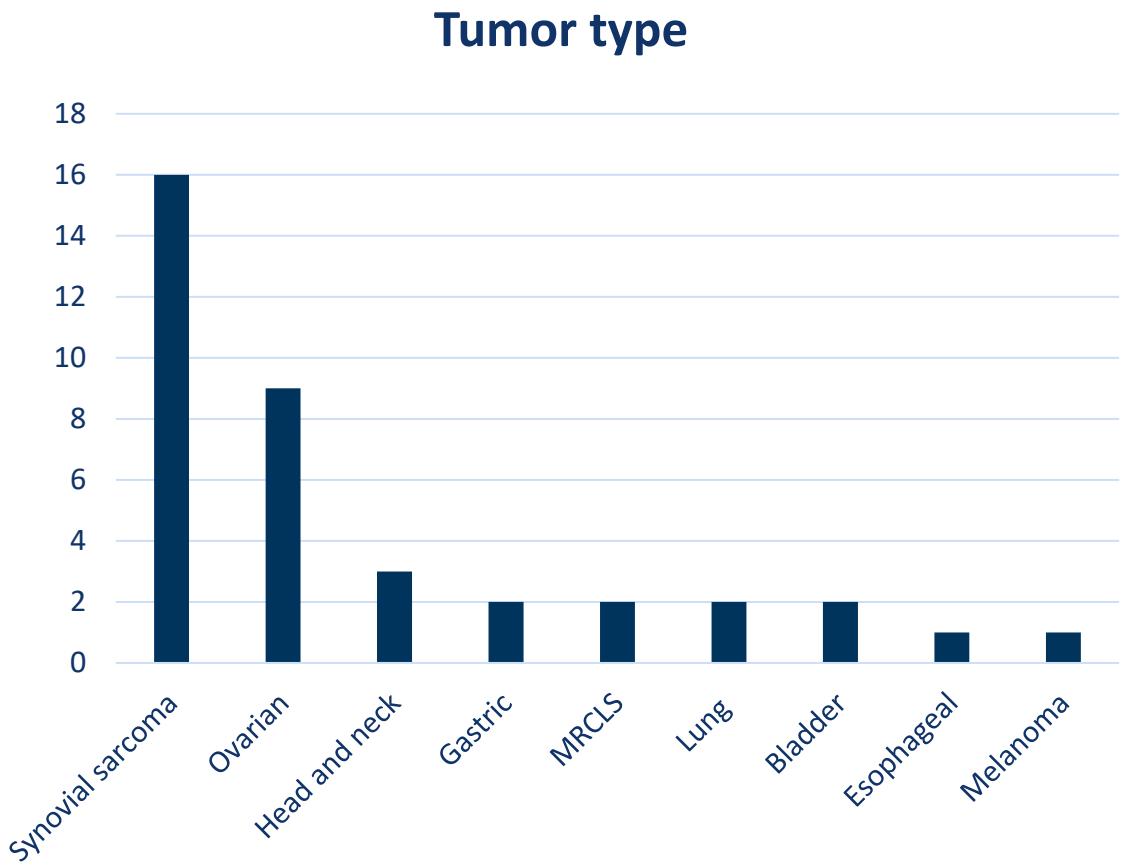
Primary	Safety and tolerability of ADP-A2M4 T-cell therapy
Secondary	Antitumor activity of ADP-A2M4 T-cells Potential therapy-related delayed adverse events for 15 years post-infusion
Exploratory	Persistence, phenotype, function of transduced and non-transduced T-cells Tumor and serum factors that may influence response or resistance

Methods: Study design



Patient characteristics

Characteristic	N=38
Sex, n (%)	
Male	22 (57.9)
Female	16 (42.1)
Median age, years (range)	58.0 (31-78)
Race, n (%)	
White	35 (92.1)
Asian	3 (7.9)
ECOG performance status, n (%)	
0	13 (34.2)
1	25 (65.8)
Prior lines systemic therapy, median (range)	3 (1, 8)
Cell dose x 10^9, median (range)	6.34 (0.1, 10)



ECOG, Eastern Cooperative Oncology Group; MRCLS, myxoid/round cell liposarcoma

Data cut-off April 6, 2020

Safety: Adverse events in ≥25% of patients

N=38; n (%)	Any grade	≥Grade 3
Patients with any AEs	37 (97.4)	37 (97.4)
Lymphopenia	37 (97.4)	37 (97.4)
Leukopenia	35 (92.1)	35 (92.1)
Neutropenia	35 (92.1)	34 (89.5)
Anemia	28 (73.7)	24 (63.2)
Fatigue	24 (63.2)	1 (2.6)
Nausea	23 (60.5)	0
Thrombocytopenia	23 (60.5)	18 (47.4%)
Pyrexia	22 (57.9)	0
CRS	19 (50.0)	2 (5.3)
Vomiting	19 (50.0)	1 (2.6)

N=38; n (%)	Any grade	≥Grade 3
Decreased appetite	16 (42.1)	2 (5.3)
Dyspnea	16 (42.1)	1 (2.6)
Diarrhea	14 (36.8)	0
Hypotension	14 (36.8)	4 (10.5)
Hypophosphatemia	13 (34.2)	11 (28.9)
Febrile neutropenia	12 (31.6)	12 (31.6)
Hyponatremia	12 (31.6)	8 (21.1)
Sinus tachycardia	12 (31.6)	0
Abdominal pain	10 (26.3)	1 (2.6)
Arthralgia	10 (26.3)	2 (5.3)
Rash	10 (26.3)	5 (13.2)

Most TEAEs were consistent with those typically experienced by cancer patients undergoing cytotoxic chemotherapy and/or cancer immunotherapy

AE, adverse event; TEAE, treatment-emergent AE; CRS, cytokine release syndrome

Data cut-off April 6, 2020

Safety: Related serious adverse events

N=38	Related SAE; n (%)
Patients with any related SAEs	13 (34.2)
CRS	9 (23.7)
Pyrexia	2 (5.3)
Aplastic anemia	1 (2.6)
Pancytopenia	1 (2.6)
Cerebrovascular accident	1 (2.6)
Neurotoxicity	1 (2.6)
Encephalopathy	1 (2.6)
Rash	1 (2.6)
Sepsis	1 (2.6)
ALT/AST/Alk Phos increased	1 (2.6)
Arrhythmia	1 (2.6)

- **There were 2 related Grade 5 (fatal) SAEs**
  - Aplastic anemia
    - 76-yr-old with synovial sarcoma
    - Associated with high-dose lymphodepletion*
    - AA has been seen with other T-cell therapies with high-dose lymphodepletion[1,2]
    - Protocol amended to a lower intensity lymphodepletion regimen and lower upper age limit
    - RT-PCR did not detect MAGE-A4 antigen in bone marrow
  - Cerebrovascular accident
    - 70-yr-old with ovarian cancer
    - High-dose lymphodepletion
    - G3 neurotoxicity – no brain edema
    - Concurrent atrial fibrillation and hypertension

*Flu 30 mg/m^2 x 4d, Cy 1800 mg/m^2 x 2d

[1]Mackall et al, J Clin Oncol 2016; [2]Van Tine et al, ESMO 2019 & CTOS 2019

CRS, cytokine release syndrome; SAE, serious adverse event

Data cut-off April 6, 2020

Best overall response: RECIST v1.1

	Overall	Synovial sarcoma	Non-sarcoma	Head & neck	Lung
n	38[1]	16	22	3	2
BOR partial response (%)	9 (23.7)	7 (43.8)	2 (9.1)	1 (33.3)	1 (50.0)
BOR stable disease (%)	18 (47.4)	7 (43.8)	11 (50.0)	1 (33.3)	0
BOR progressive disease (%)	7 (18.4)	1 (6.3)	6 (27.3)	1 (33.3)	1 (50.0)
Unknown or missing (%)	4 (10.5)	1 (6.3)	3 (13.6)	0	0
ORR (%)	23.7	43.8	9.1	33.3	50.0

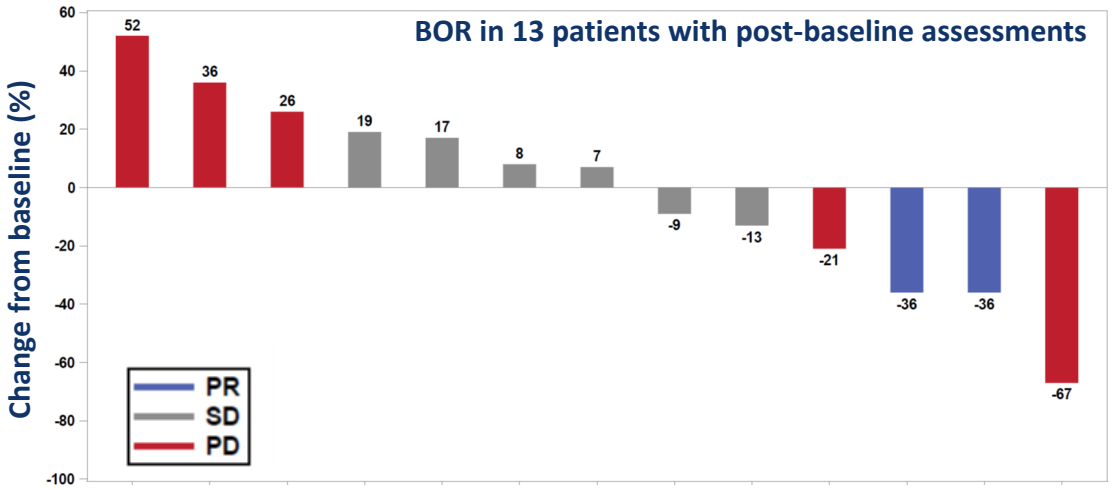
Responses in a broad range of cancers including:
synovial sarcoma, head & neck cancer, and lung cancer

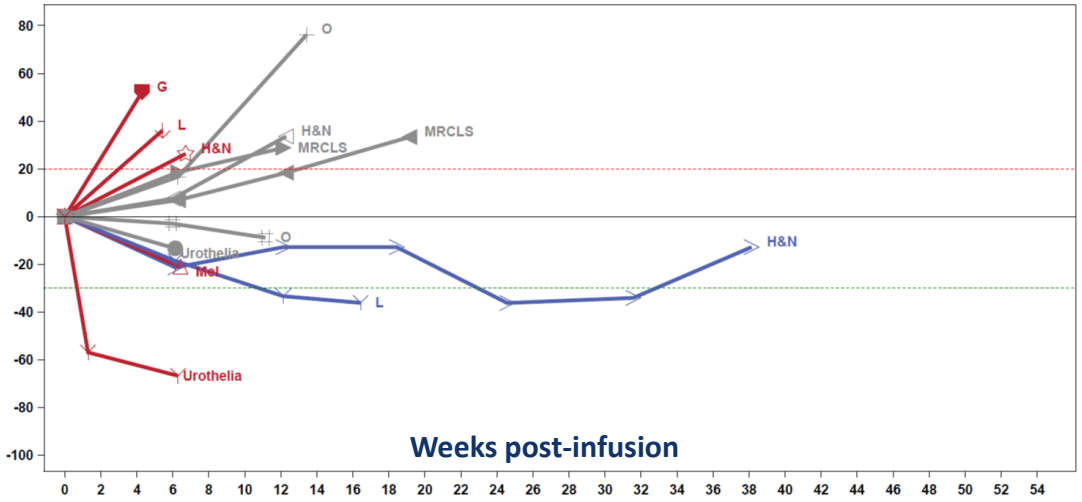
[1] N=38 pts, 16 synovial sarcoma, 22 non-sarcoma; For non-sarcoma, data presented for head & neck (3), lung cancer (2), not shown for 17 additional pts, detailed below:
Cohorts 1/2: 6 patients with ovarian cancer (5 SD, 1 PD) [ESMO 2018]
Cohort 3/Exp: 2 patients with bladder cancer (1 SD, 1 PD), 1 patient with esophageal cancer (missing), 2 patients with gastric cancer (1 PD, 1 missing), 1 patient with melanoma (PD), 2 patients with MRCLS (2 SD), 3 patients with ovarian (2 SD, 1 missing)

BOR, best overall response; SD, stable disease; PD, progressive disease

Data cut-off April 6, 2020

Anti-tumor activity in multiple cancers





Confirmed responses in lung cancer and head & neck cancer

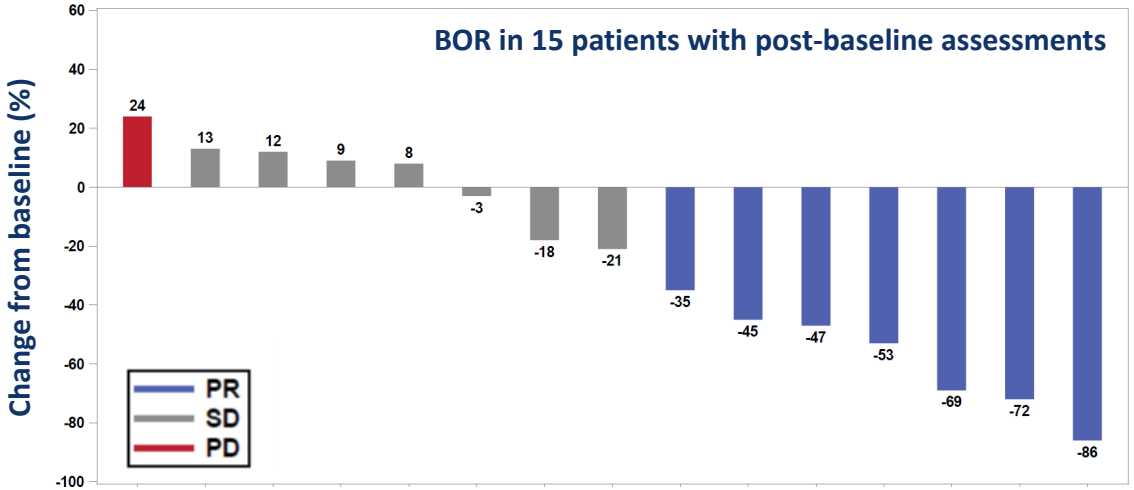
Tumor reductions in ovarian cancer, bladder cancer, and melanoma

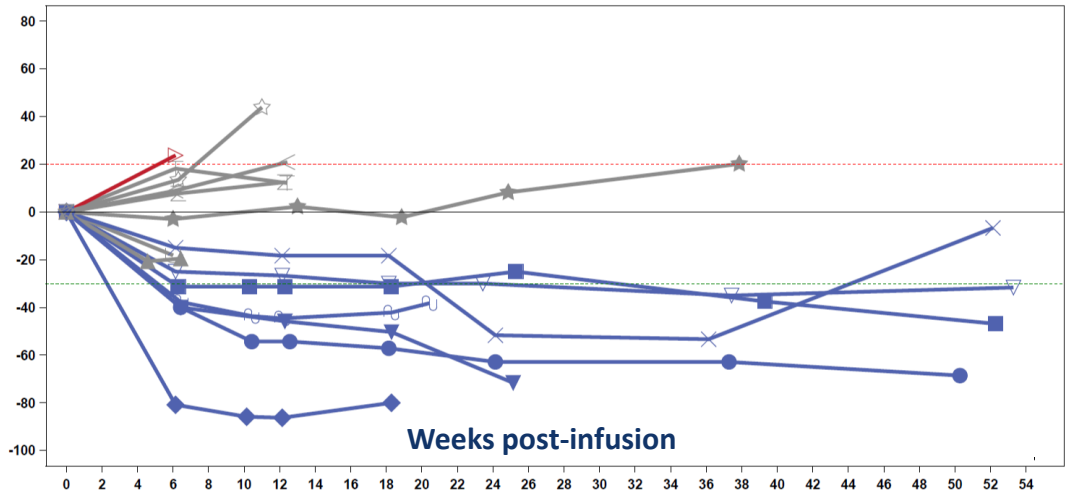
Data shown from patients in Cohort 3 and expansion phase; Data represent percent changes in sum of diameters in target lesions through progression or prior to surgical resection;
Sum of diameters = sum of the long diameters for non-nodal lesions and short axis for nodal lesions;
Reponses evaluated by RECIST v1.1

BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease

Data cut-off April 6, 2020

Durable responses in synovial sarcoma





Confirmed responses in 44% of patients

Disease control rate of ~90%

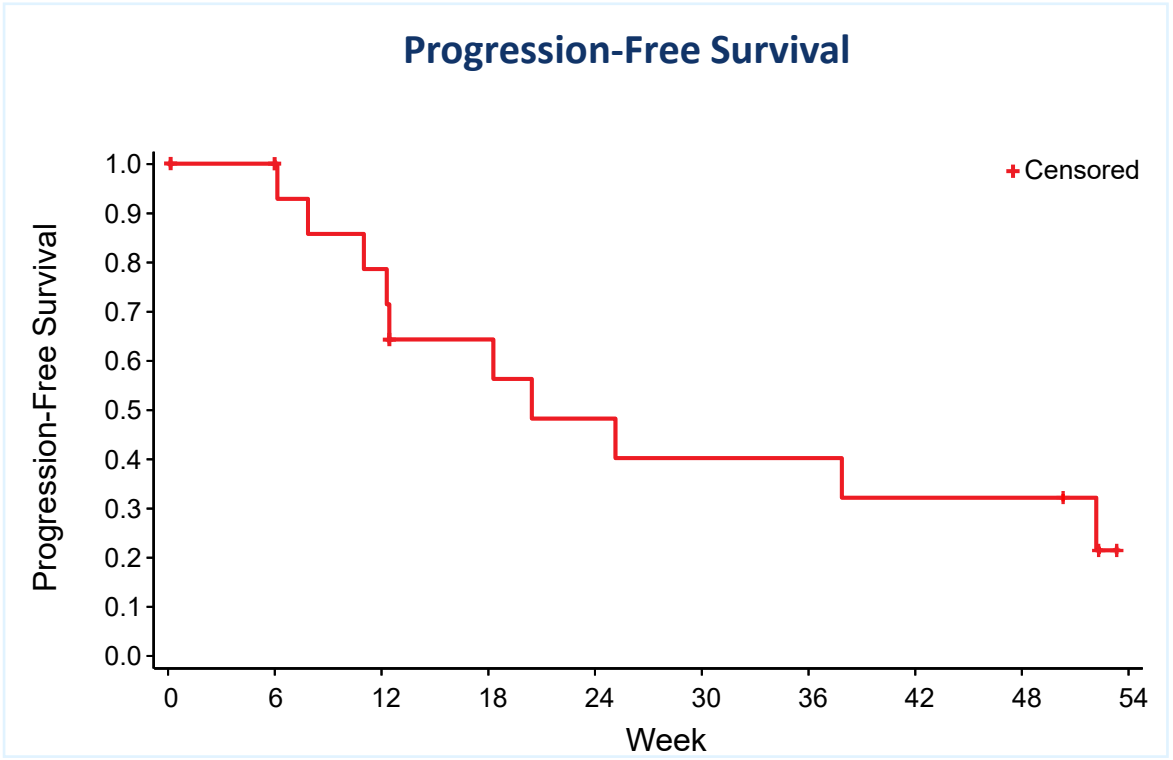
- ✓ **Responses were durable**: median duration of response was ~28 weeks (range: ~12 to 54 weeks)
- ✓ Additional patient with unconfirmed response after data cut-off

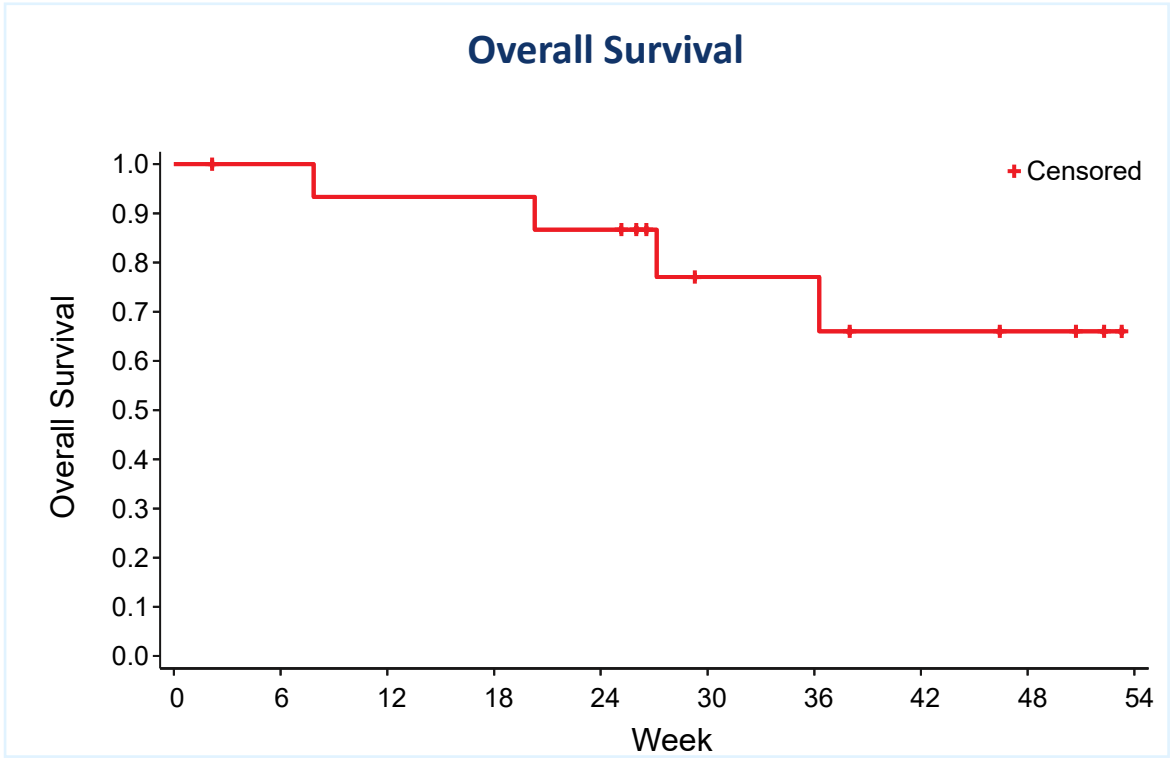
Data shown from patients in Cohort 3 and expansion phase; Data represent percent changes in sum of diameters in target lesions through progression or prior to surgical resection; Sum of diameters = sum of the long diameters for non-nodal lesions and short axis for nodal lesions; Reponses evaluated by RECIST v1.1

BOR, best overall response; PD, progressive disease; PR, partial response; SD, stable disease

Data cut-off April 6, 2020

PFS and OS in synovial sarcoma





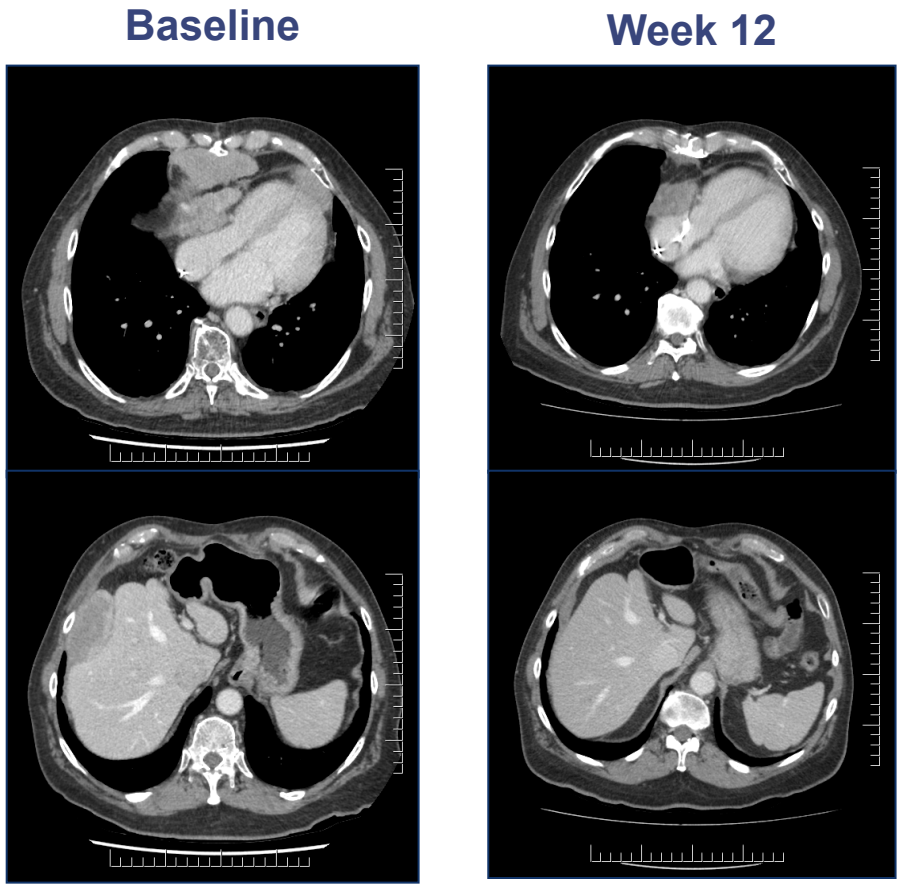
- Median PFS is ~20 weeks

- Median OS has not been reached

OS, overall survival; PFS, progression-free survival

Data cut-off April 6, 2020

Significant tumor reduction in synovial sarcoma



Large tumor reduction by RECIST v1.1

- 67-year-old male
  - 4-yr history of disease
  - Recurrence in the pericardium
  - Treated with debulking and ifosfamide
  - High MAGE-A4 expression (100% 3^{+})
- Infusion 9.95 x 10^{9} SPEAR T-cells
  - Grade 2 CRS and cytopenias post-infusion
- Baseline scans
  - High disease burden SLD 155 mm
  - Disease in the pericardium and liver
- Post-infusion scans
  - Large reduction (45%) in target tumor lesions at week 12
  - Continue reductions over time with 71% decrease in SLD
  - Disease progression at week 24 due to new non-target lesion

Conclusions

Phase 1 Dose Escalation and Expansion Trial to Assess Safety and Efficacy of ADP-A2M4 in Advanced Solid Tumors

Most adverse events were consistent with those typically experienced by cancer patients undergoing lymphodepletion cytotoxic chemotherapy, and cellular therapy

Promising efficacy

- Durable responses observed in subjects with synovial sarcoma
- Confirmed responses seen in subjects with other tumor types, i.e. head & neck cancer, and lung cancer

Exploratory biomarker analyses and other translational research is ongoing

Ongoing and planned trials with SPEAR T-cells targeting MAGE-A4

- ADP-A2M4 Phase 2 SPEARHEAD-1 Trial in synovial sarcoma & MRCLS (North America & Europe; NCT04044768)
- ADP-A2M4 combination with low dose radiation sub-study (North America; NCT03132922)
- Next-generation SURPASS trial with enhanced ADP-A2M4 SPEAR T-cells (North America & Europe; NCT04044859)
- Combination trial with ADP-A2M4 with a PD1 checkpoint inhibitor for patients with head & neck cancer will begin enrolling this year

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- For further questions please contact: dshong@mdanderson.org