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Durable Responses in Patients with Synovial Sarcoma in the Phase 1 Trial of ADP-A2M4 (MAGE-A4)

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Disclosure Information: Brian A. Van Tine

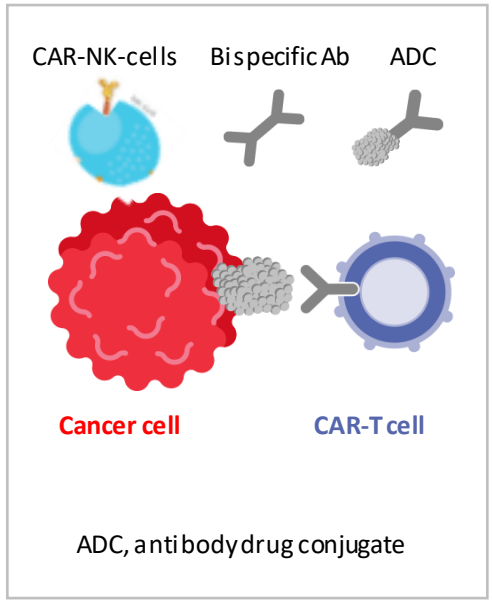
Personal financial interests

- Advisory Role/Consultant: Epizyme; CytRx; Janssen; Plexxicon
- Consultant, Advisory Role/Speaker, Research/Trial Support, Travel Support: Lilly
- Speaker Bureau: Caris
- Research Grant/Consulting/Ad Board: Pfizer
- Consultant: Bayer
- Research Grant: Merck; Tracon
- Advisory Board: Immune Design; Daiichi Sankyo
- Speaker: Adaptimmune

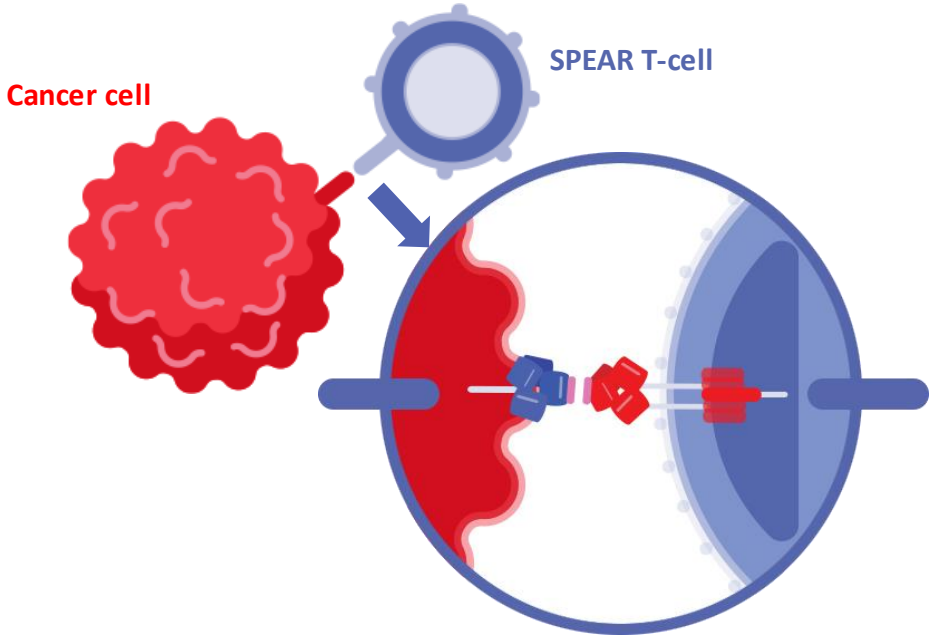
Institutional financial interests

- Research Grant: Lilly; Merck
- Trial Support: Oncothyreon; Gliknik; Celidex Therapeutics; ImClone Systems; Peregrine Pharmaceuticals; BIND Therapeutics; Regeneron Pharmaceuticals; MabVax Therapeutics; Millenium; AbbVie; Janssen Research Foundation; Jounce Therapeutics; EMD Serono; Puma Biotechnology; VentiRx Pharmaceuticals; Taiho Pharmaceuticals; Gilead Sciences; Incyte; Daiichi Pharmaceutical; Novartis; Pfizer; Acerta; Inventiv Health; Celgene; Sanofi; AstraZeneca; Merrimack Pharmaceuticals; Biothera Pharmaceuticals; Medimmune; Blueprint Medicines; Bristol-Myers Squibb; Enzychem Lifesciences Corporation; Eisai; Genentech; Corvus; Johnson & Johnson; Threshold Pharmaceuticals; Bayer; BeiGene; GlaxoSmithKline; Molecular Insight Pharmaceuticals; Gem Pharmaceuticals; Deciphera Pharmaceuticals; Forma Therapeutics, Bavarian Nordic; Hoffmann-LaRoche; Caris Life Sciences; Morphotek; Soligenix; Eleison Pharmaceuticals; AADi; Immune Design; TRACON Pharmaceuticals; NanoCarrier; Advenchen Laboratories; Karyopharm Therapeutics; Hutchison MediPharma

ADP-A2M4 SPEAR T-cells target MAGE-A4



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

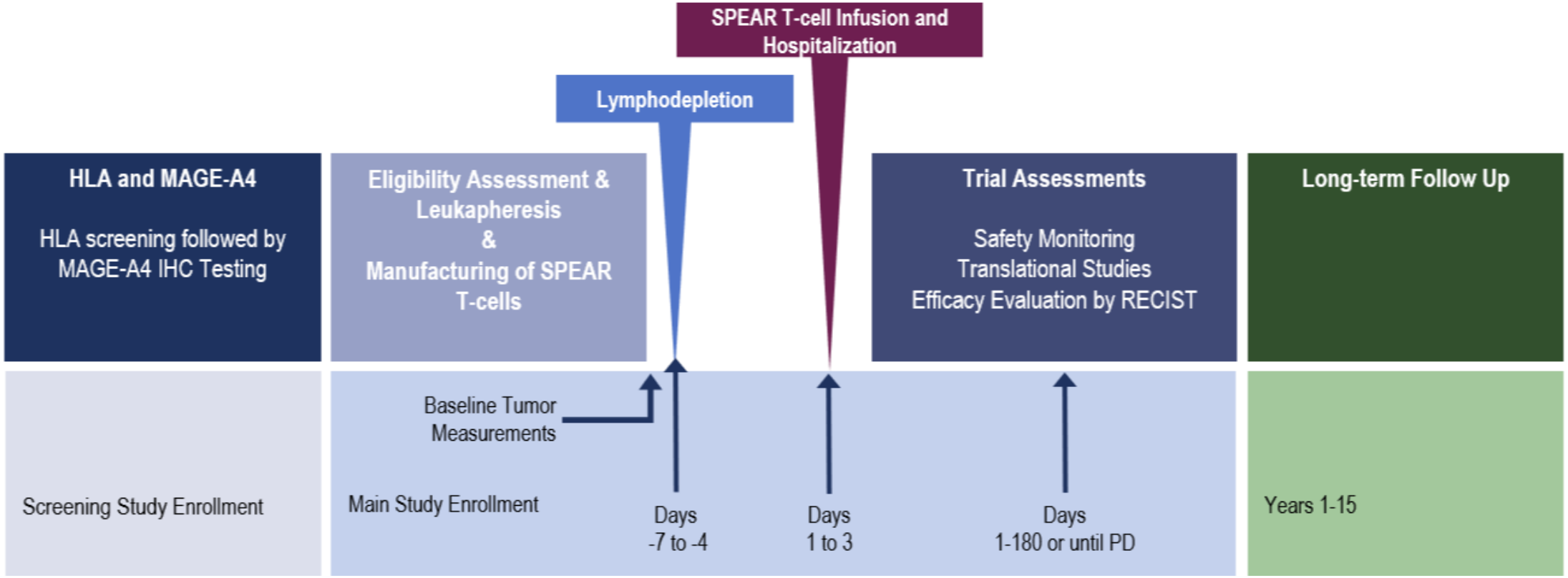
MoA Video:
https://youtu.be/zdI8IGXoQd0

Objectives

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

Primary	Safety and tolerability of ADP-A2M4 T-cell therapy
Secondary	Anti-tumor 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

Trial design



Patient characteristics

Characteristic	N=16
Sex, n (%)	
Male	10 (62.5)
Female	6 (37.5)
Median age, years (range)	49.0 (31–76)
Race, n (%)	
White	14 (87.5)
Asian	2 (12.5)
ECOG performance status, n (%)	
0	10 (62.5)
1	6 (37.5)

Characteristic	N=16
ECOG performance status, n (%)	
0	10 (62.5)
1	6 (37.5)
Median MAGE-A4 expression by H-score* (range)	249 (60 -300)
Prior lines systemic therapy, median (range)	2.5 (1, 6)
Most common systemic therapies	
Ifosfamide	16 (100.0)
Anthracycline (doxorubicin or epirubicin)	13 (81.2)
Pazopanib	7 (43.8)
Cell dose × 10^9, median (range)	9.28 (3.4, 10)

* H score is a method of assessing immunohistochemistry results. H-score is assigned using the following formula [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]. The final score ranges from 0 to 300

ECOG, Eastern Cooperative Oncology Group

Data cut-off September 1, 2020

Safety: Adverse events in ≥25% of patients

In general, patients have tolerated the treatment well with an acceptable safety profile
Most TEAEs consistent with those typically experienced by cancer patients undergoing cytotoxic chemotherapy or cancer immunotherapy

N=16; n (%)	Any grade	≥Grade 3
Patients with any AEs	16 (100)	16 (100)
Lymphopenia / lymphocyte count decreased	16 (100)	16 (100)
Cytokine release syndrome	14 (88)	2 (13)
Leukopenia / WBC decreased	14 (88)	14 (88)
Neutropenia / neutrophil count decreased	14 (88)	13 (81)
Fatigue	11 (69)	0
Nausea	10 (63)	0
Pyrexia	10 (63)	0
Thrombocytopenia / platelet count decreased	10 (63)	7 (44)
Anemia / RBC decreased	9 (56)	7 (44)
Diarrhea	8 (50)	0
Hypophosphatemia	8 (50)	7 (44)
Sinus tachycardia / tachycardia	7 (44)	0

N=16; n (%)	Any grade	≥Grade 3
Vomiting	7 (44)	0
Arthralgia	5 (31)	0
Decreased appetite	5 (31)	1 (6)
Dizziness	5 (31)	0
Dyspnea	5 (31)	0
Hypotension	5 (31)	1 (6)
Rash	5 (31)	3 (19)
Alanine aminotransferase increased	4 (25)	0
Cough	4 (25)	0
Headache	4 (25)	0
Musculoskeletal pain	4 (25)	0
Pruritus	4 (25)	0
Tumor pain	4 (25)	0

AE, adverse event; RBC, red blood cell count WBC, white blood cell count

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Safety: Related serious adverse events

N=16; n (%)	Related SAE
Patients with any related SAEs	9 (56)
Cytokine release syndrome	7 (44)
Pyrexia	1 (6)
Pancytopenia	1 (6)
Aplastic anemia	1 (6)
Arrythmia	1 (6)
Sepsis	1 (6)

SAE, serious adverse event

Data cut-off September 1, 2020

Safety: Prolonged Cytopenias

Patients with Grade 3 or 4 prolonged cytopenia at Week 4 post-infusion	N=16 n (%)
Patients with any cytopenia	9 (56)
Absolute neutrophil count (<1.0 x 10^9/L)	7 (44)
Platelets (<50 x 10^9/L)	6 (37)
Hemoglobin (<8 g/dL)	4 (25)

Patients may exhibit cytopenias for several weeks following lymphodepletion chemotherapy and ADP-A2M4 cell infusion

There was one related fatal SAE of aplastic anemia

- 76-yr-old with synovial sarcoma
- Received high-dose lymphodepletion (Flu 30 mg/m^2 x 4d, Cy 1800 mg/m^2 x 2d)
- Assessed as probably related to ADP-A2M4, fludarabine and cyclophosphamide
- Aplastic anemia 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

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

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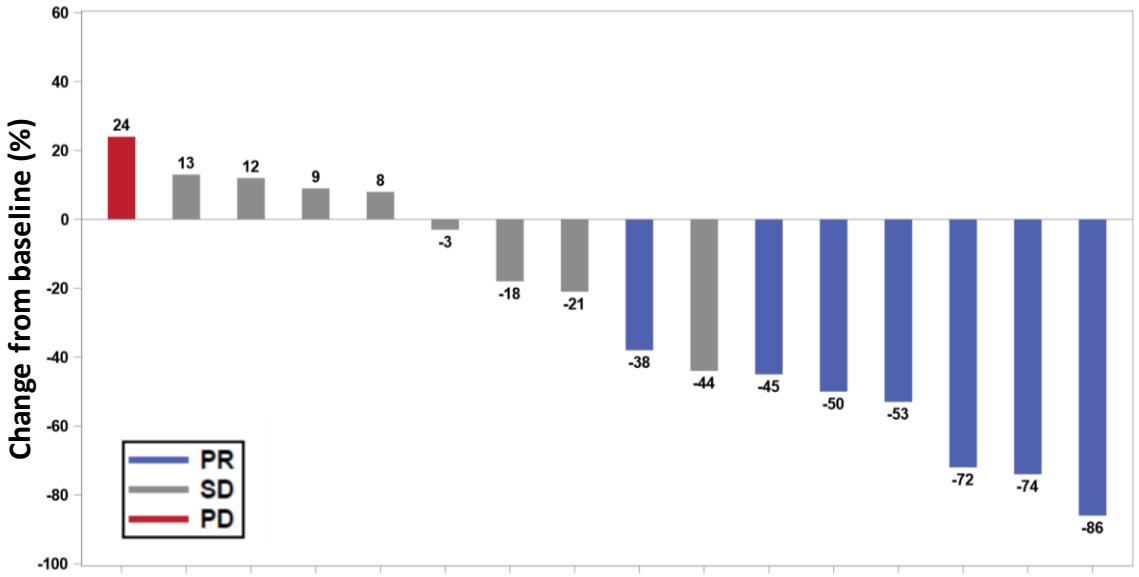
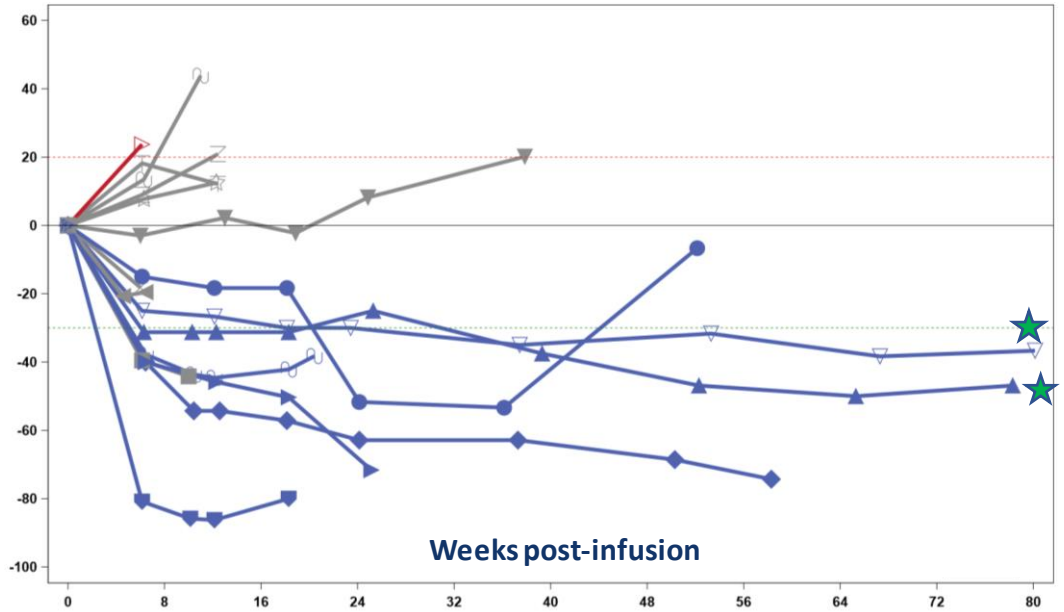
Durable responses in synovial sarcoma





Confirmed responses in 44% of patients

Disease control rate of 94% with 11 patients still alive at time of data cut-off

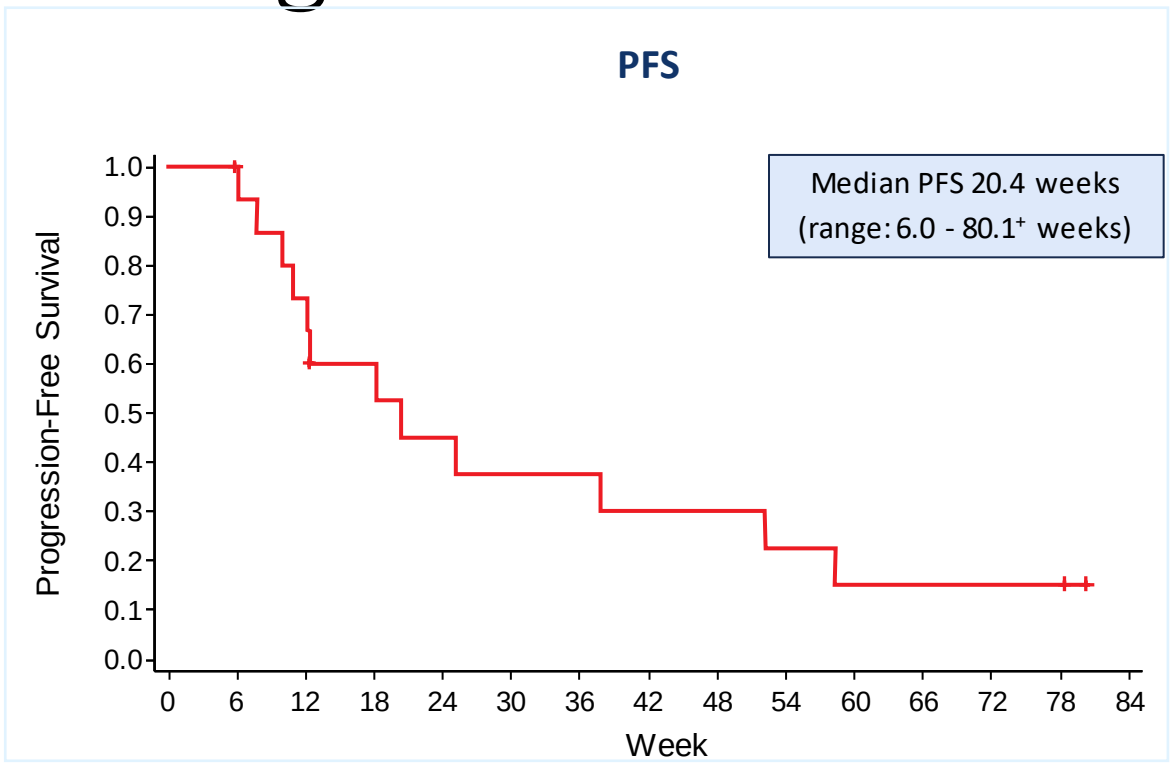
Responses were durable with a median duration of response of 28 weeks (range: 12-72+ weeks)

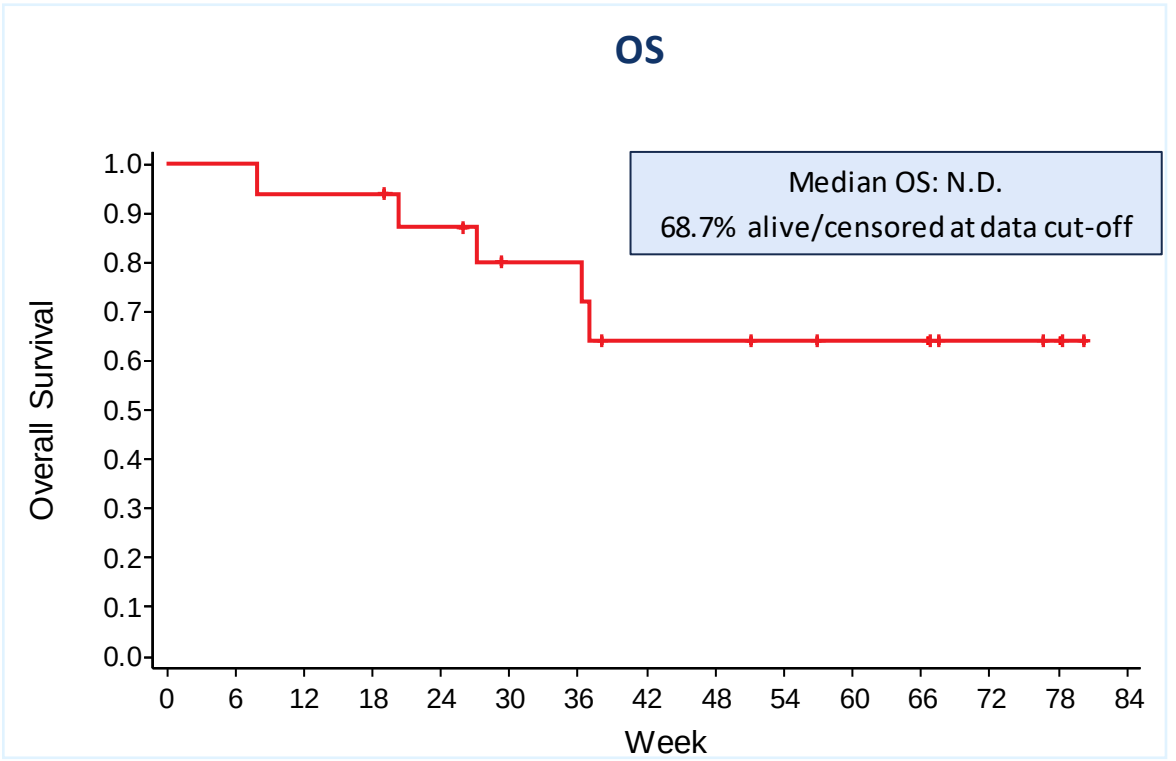
Data shown from patients in Cohort 3 and expansion phase; Data represent percent changes from Baseline in sum of diameters in target lesions through progression or prior to surgical resection;
Sum of diameters = sum of the long diameters for non-nodal lesions and short axis for nodal lesions;
Reponses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

PD, progressive disease; PR, partial response; SD, stable disease

Data cut-off September 1, 2020

Progression-free survival & Overall survival





+ Censored

OS, overall survival; PFS, progression-free survival; N.D., not determined

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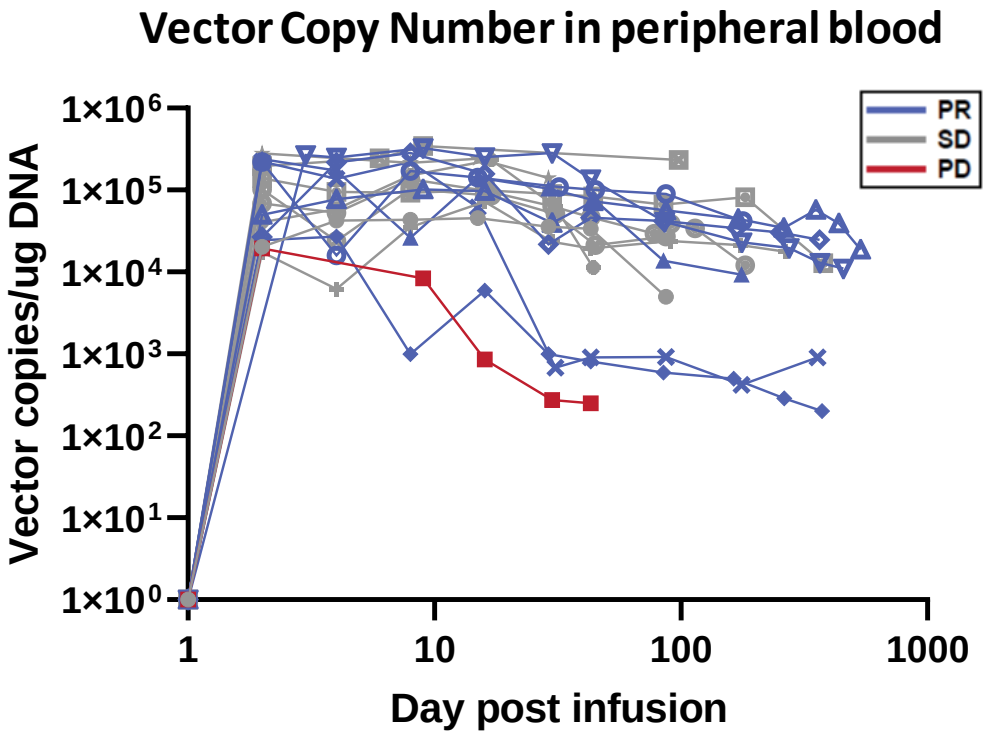
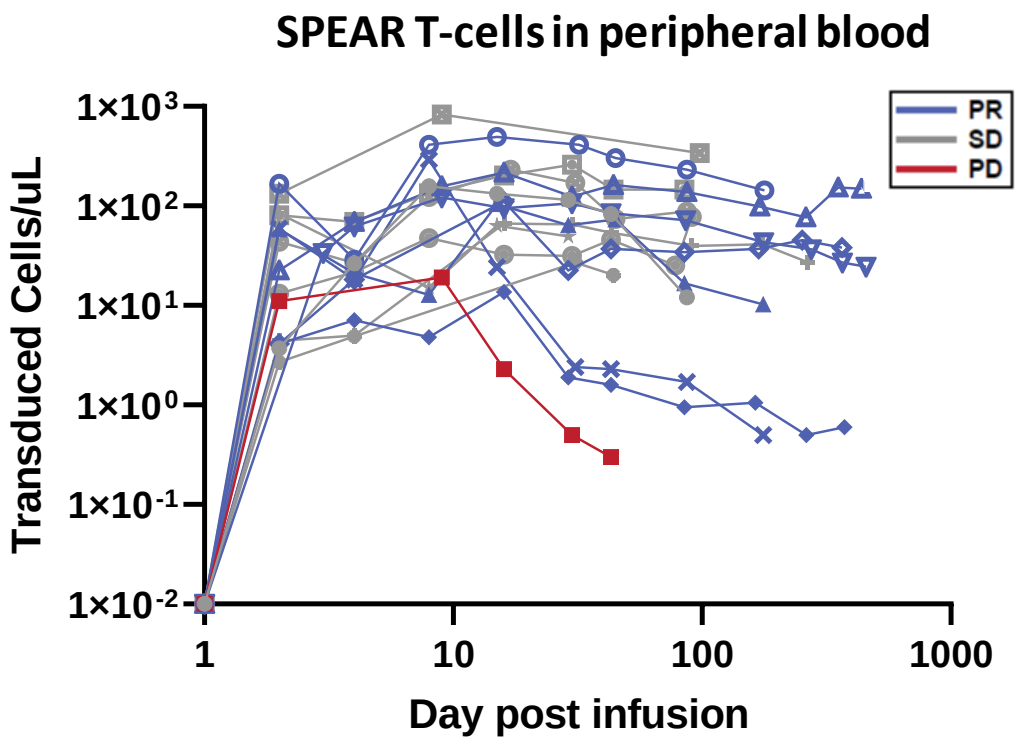
SPEAR T-cells detectable post-infusion





Vector copy number and SPEAR T-cells analyzed in peripheral blood post-infusion
Patient with progressive disease had fewer vector copy numbers (expansion) and fewer SPEAR T-cells detected

PD, progressive disease; PR, partial response; SD, stable disease

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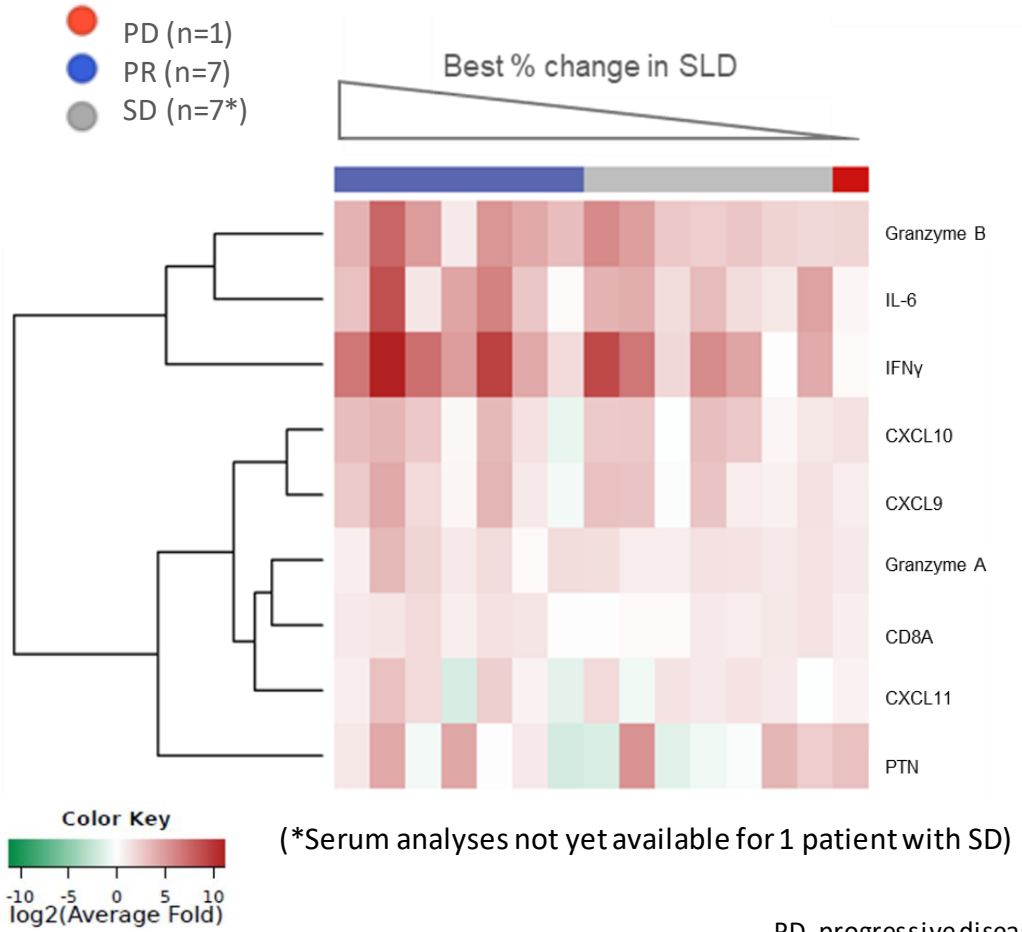
IFNγ-related pathway may be a biomarker of tumor response



(*Serum analyses not yet available for 1 patient with SD)

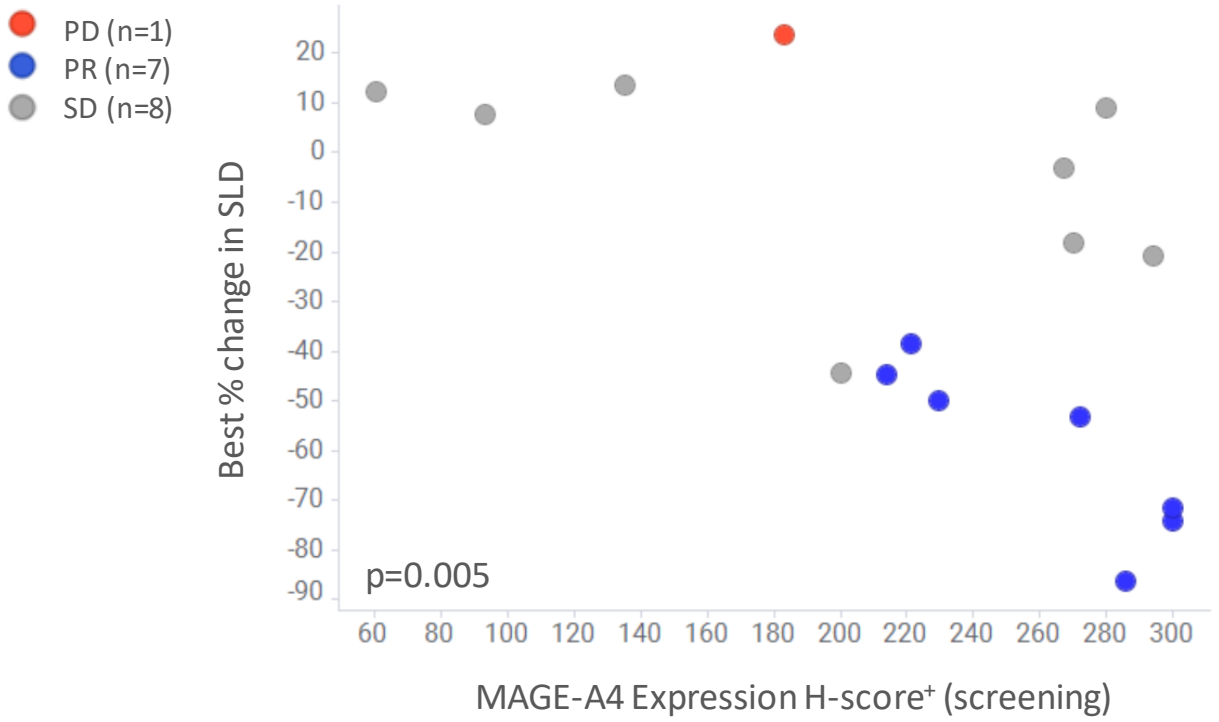
- Induction of IFNγ-related pathway is indicative of SPEAR T-cell functionality
- From analyses of 92 immuno-oncology related serum proteins, markers with greatest post-ADP-A2M4 related change included IFNγ and related markers

PD, progressive disease; PR, partial response; SD, stable disease

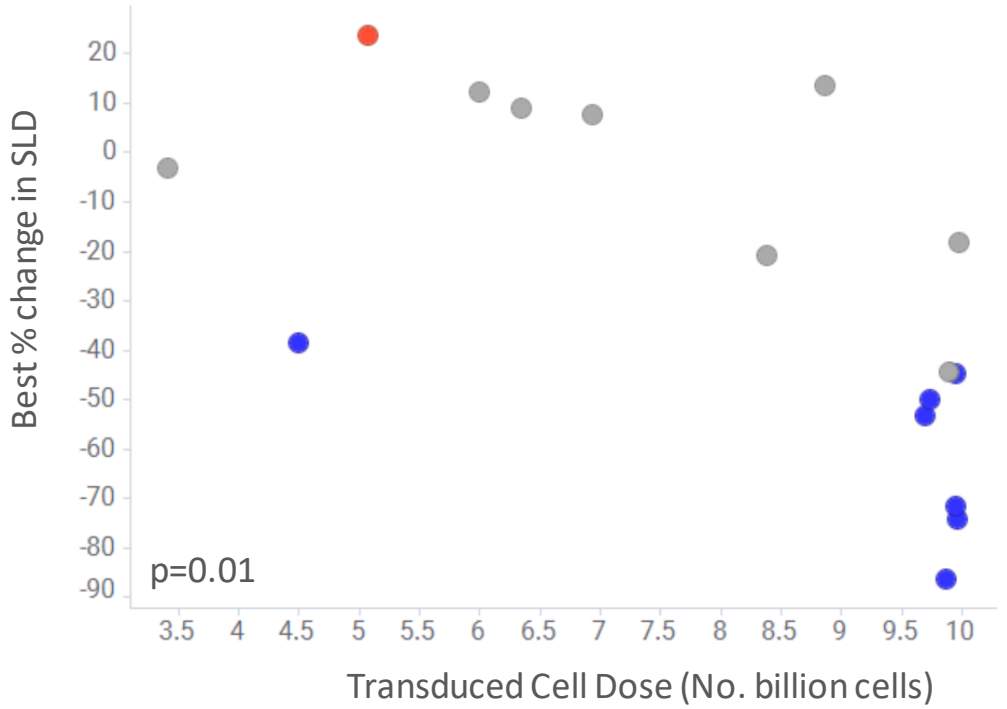
Data cut-off October 7, 2020

MAGE-A4 expression & transduced cell dose correlate with tumor reduction

Patients with relatively higher MAGE-A4 expression may have greater reduction in SLD



Patients with relatively greater transduced cell dose may have greater reduction in SLD



+ H score is a method of assessing immunohistochemistry results. H-score is assigned using the following formula [1 × (% cells 1+) + 2 × (% cells 2+) + 3 × (% cells 3+)]. The final score ranges from 0 to 300

PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameters (of target lesions)

Data cut-off September 1, 2020

Conclusions

- **Established safety profile**
  - Most adverse events were consistent with those typically experienced by cancer patients undergoing lymphodepletion cytotoxic chemotherapy, and cellular therapy
- **Efficacy**
  - High overall response rate with ongoing durable responses observed in an advanced synovial sarcoma population
- **Emerging translational profiles**
  - ADP-A2M4 SPEAR-T cells expand and persist after infusion
  - IFNγ pathway is an emerging biomarker of tumor response in synovial sarcoma
  - Greater reductions in SLD correlates with MAGE-A4 expression and transduced cell dose
- **ADP-A2M4 Phase 2 trial SPEARHEAD-1 (NCT04044768) in synovial sarcoma enrolling in North America and Europe**

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- For further questions please contact: bvantine@wustl.edu