Afami-cel TCR for Sarcoma

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DISCLOSURE INFORMATION

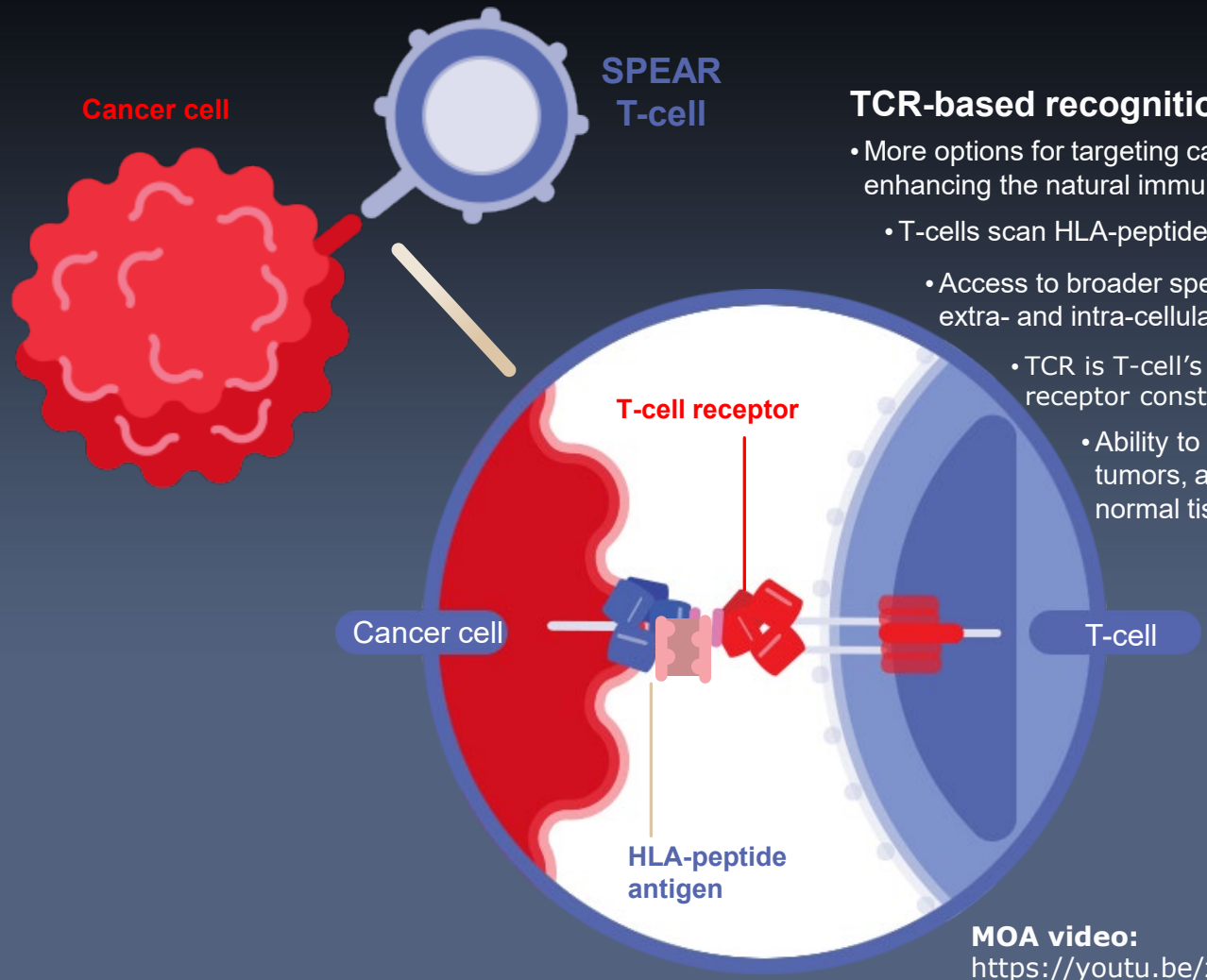
Personal financial interests

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

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; Hoffman-LaRoche; Caris Life Sciences; Morphotek; Soligenix; Eleison Pharmaceuticals; AADi; Immune Design; TRACON Pharmaceuticals; NanoCarrier; Advenchen Laboratories; Karyopharm Therapeutics; Hutchison MediPharma

Background



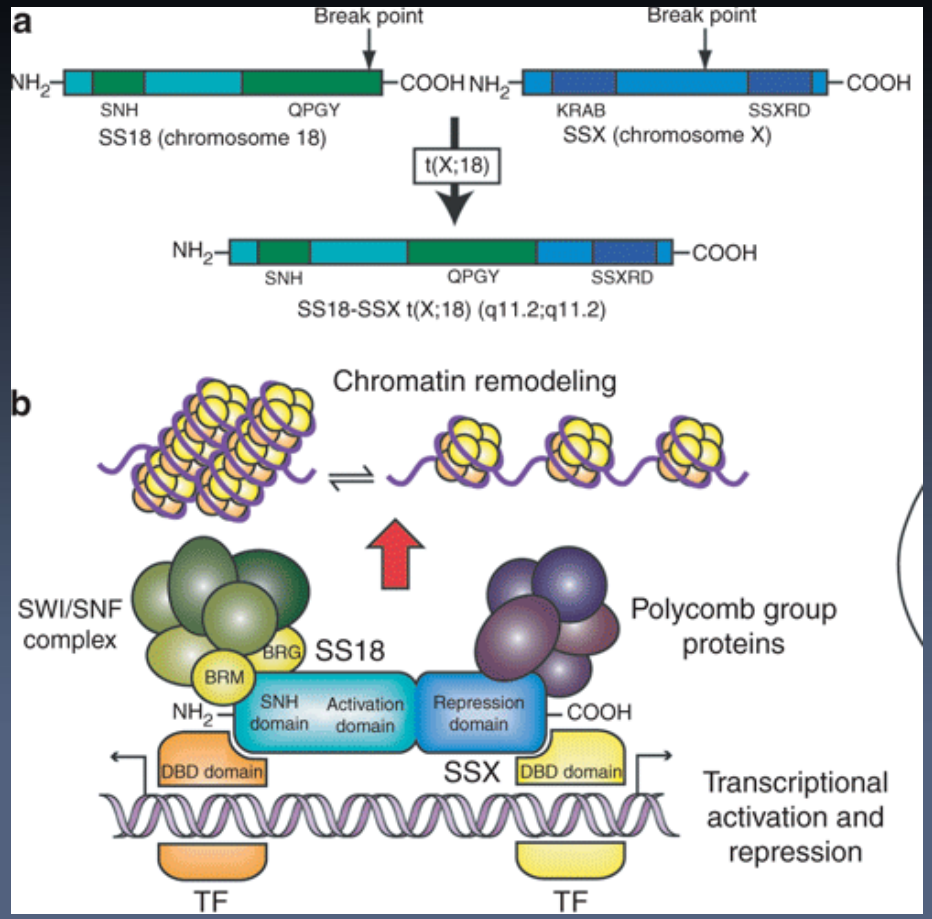
TCR-based recognition

- More options for targeting cancers by enhancing the natural immune system:
  - T-cells scan HLA-peptides with TCRs
    - Access to broader spectrum of extra- and intra-cellular proteins
      - TCR is T-cell's scan natural receptor construct
        - Ability to target solid tumors, as opposed to normal tissues

MOA video:
https://youtu.be/zdI8IGXoQd0

Synovial Sarcoma

- Synovial sarcoma (SS) is a lethal form of soft-tissue sarcoma with high metastatic potential
- Typically diagnosed in young adults between 15-40yo
- SS is associated with a gene fusion between transcription factors SYT and SSX, producing a hybrid transcription factor modulating SWI/SNF chromatin remodeling and gene expression
- No targeted chemotherapy has yet been developed for SS



Pediatric Research (2012) 72, 112–121

ADP-A2M4 (MAGE-A4) in patients with Synovial Sarcoma

- (NCT03132922)

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Background

- Synovial sarcoma represents ~10% of all soft tissue sarcomas
- Metastatic disease has poor prognosis
- MAGE-A4 is highly expressed in synovial sarcoma patients
    - A 2017 study[1] showed that 82% of synovial sarcoma tumor samples expressed MAGE-A4 by immunohistochemistry

[1]Iura et al, *Human Pathology* 2017

Objectives

- Phase 1 Dose Escalation, Multi-Tumor Study to Assess the Safety, Tolerability and Antitumor Activity of ADP-A2M4 in HLA-A2^{+} Subjects with MAGE-A4^{+} Tumors
- This presentation focuses on data from 12 patients with synovial sarcoma

Primary	• Evaluate safety and tolerability of ADP-A2M4 T-cell therapy
Secondary	• Evaluate the anti-tumor activity of ADP-A2M4 T-cells • Evaluate potential therapy-related delayed AEs for 15 years post-infusion
Exploratory	• Evaluate the persistence, phenotype and functionality of transduced and non-transduced T-cells • Characterize the tumor and serum factors that may influence response or resistance to ADP-A2M4 therapy

Safety: Adverse events ≥ Grade 3

Preferred Term	Grade ≥3 N (%)
Leukopenia	12 (100.0%)
Lymphopenia	12 (100.0%)
Neutropenia	10 (83.3%)
Anemia	5 (41.7%)
Hypophosphataemia	5 (41.7%)
Thrombocytopenia	4 (33.3%)
Rash	3 (25.0%)
Febrile neutropenia	3 (25.0%)
CRS	2 (16.7%)
Hyponatremia	2 (16.7%)
Acute kidney injury	1 (8.3%)
Acute left ventricular failure	1 (8.3%)

Preferred Term	Grade ≥3 N (%)
Aplastic anemia	1 (8.3%)
Arrhythmia	1 (8.3%)
Decreased appetite	1 (8.3%)
Endocarditis	1 (8.3%)
Endocarditis staphylococcal	1 (8.3%)
Hypermagnesemia	1 (8.3%)
Hypocalcemia	1 (8.3%)
Hypotension	1 (8.3%)
Influenza like illness	1 (8.3%)
Pancytopenia	1 (8.3%)
Pleural effusion	1 (8.3%)
Sciatica	1 (8.3%)
Sepsis	1 (8.3%)
Troponin increased	1 (8.3%)

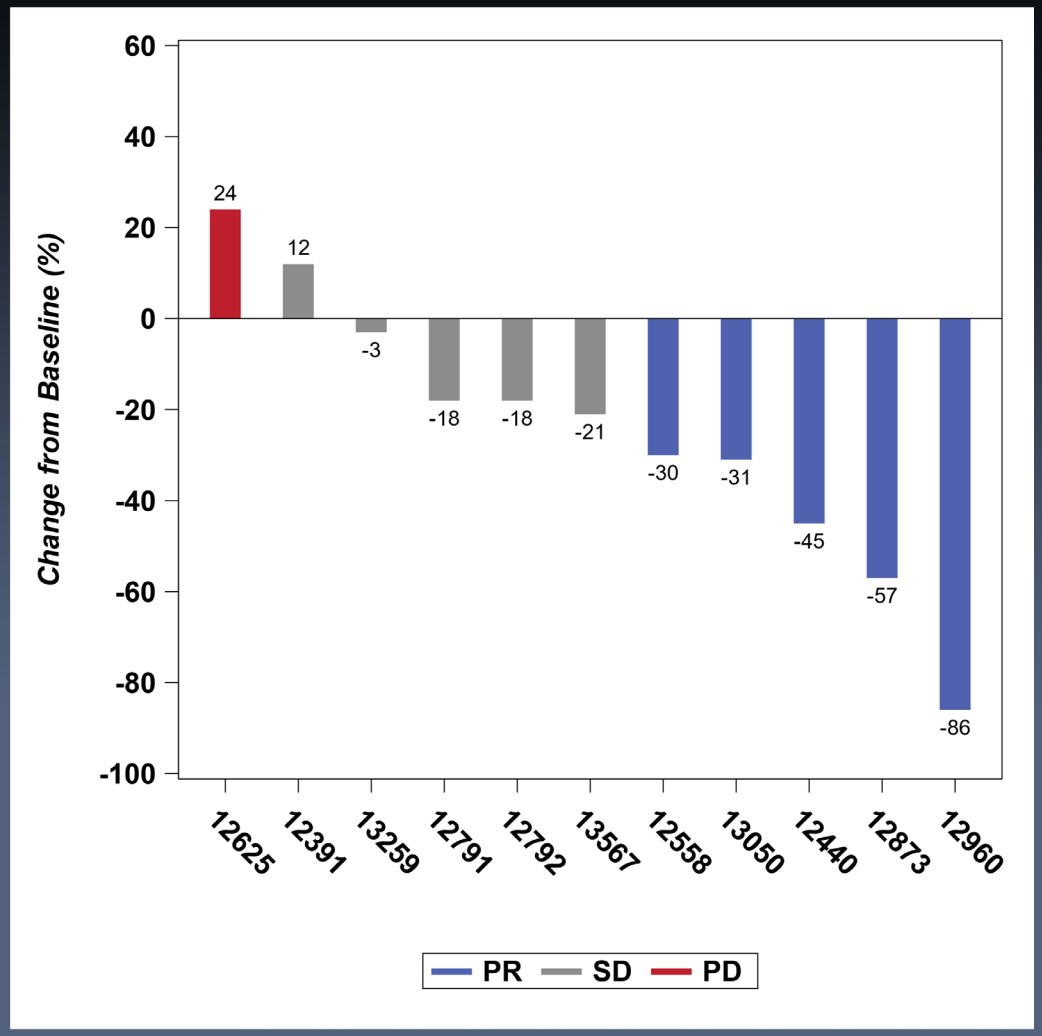
Adverse event of interest

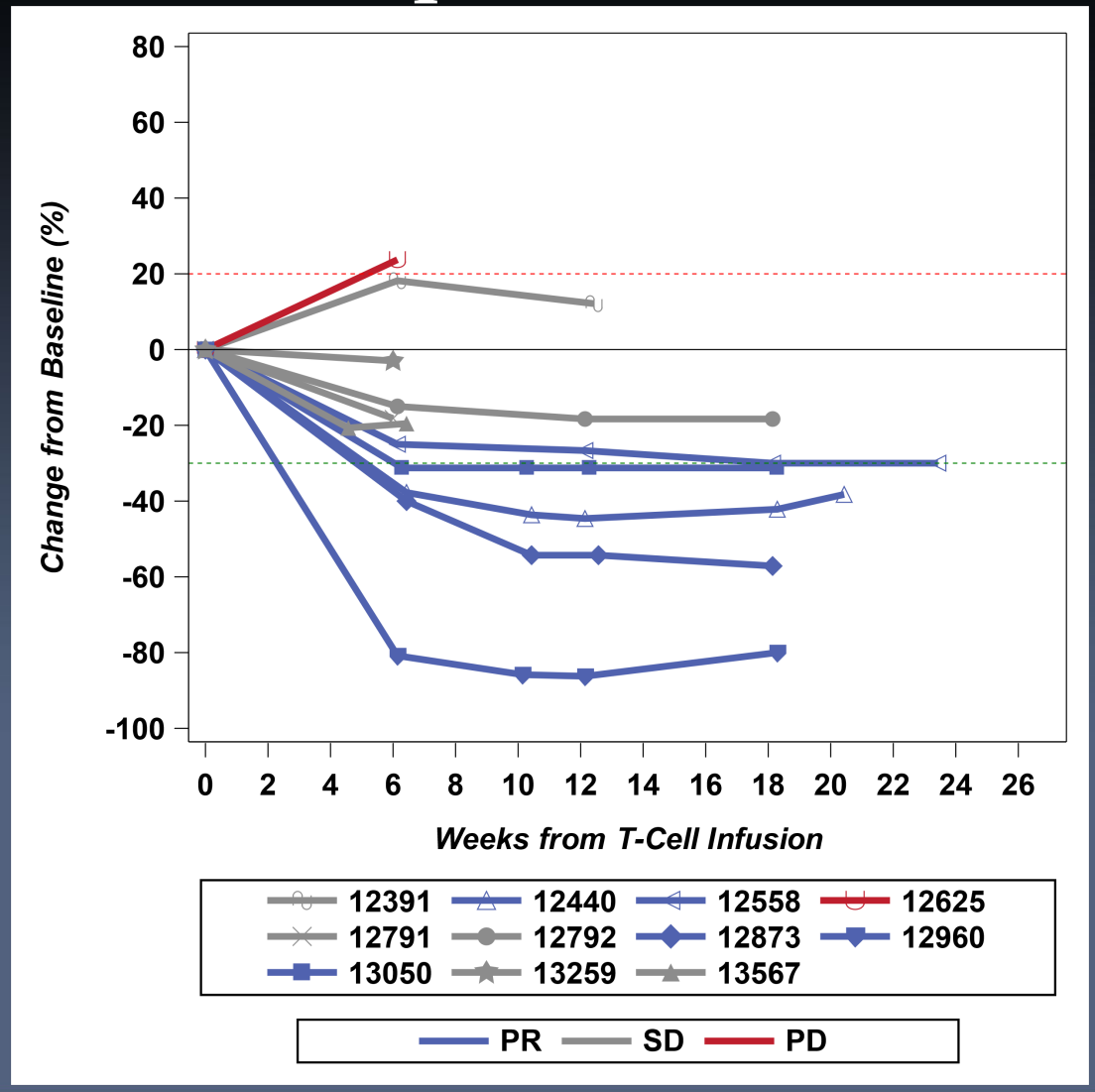
- Aplastic Anemia
- Three cases of fatal aplastic anemia in three different Phase 1 trials:
  - NY-ESO-1^{c259} : xx year-old patient with synovial sarcoma received a lymphodepletion regimen of X
  - ADP-A2M10 (MAGE-A10), a 66-year-old patient with NSCLC received a lymphodepletion regimen of of Flu 30 mg/m^2 x 4d, Cy 1800mg/m^2 x 2 days
  - ADP-A2M4 (MAGE-A4), a 76-year-old patient with synovial sarcoma received a lymphodepletion regimen of Flu 30 mg/m^2 x 4d, Cy 1800mg/m^2 x 2 days
- All cases were reported to the FDA
- RT-PCR and IHC did not detect the target antigens in the bone marrow

Caution should be used with heavily pretreated older patients; protocols have been amended

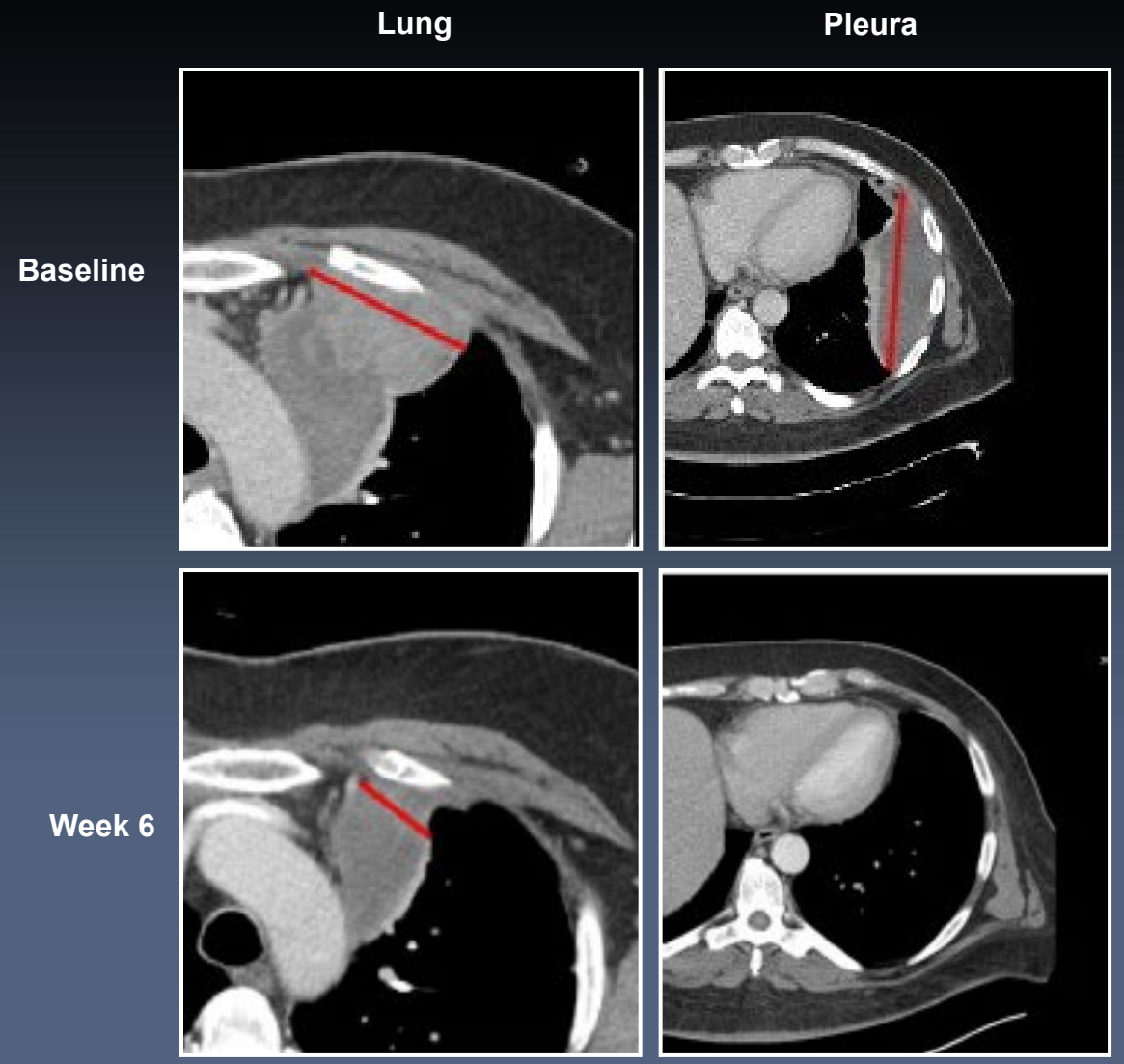
- Moderate lymphodepletion regimen: Flu 30 mg/m^2 x 4d, Cy 600 mg/m^2 x 3d
- Patients must be ≤75 years old

ADP-A2M4 Spear T-cells Induce clinical responses





Significant Tumor Reduction



86% decrease in RECIST 1.1 and significant symptom improvement

- 53-year-old male
- Longstanding history of synovial sarcoma
  - Treated with surgery, radiotherapy, and multiple chemotherapy regimens
- High MAGE-A4 expression in tumor
  - Baseline SLD* 24 cm
- 9.87 x 10^9 SPEAR T-cells
- Baseline scans
  - Extensive disease in the lung and pleura-based tumor masses
- Post-infusion
  - Grade 1 CRS and cytopenias
- Week 6 scans
  - One large pleura-based lesion disappeared and others reduced via RECIST 1.1 criteria

(*SLD = Sum of the Longest Diameter of the target lesions)

Final Analysis from SPEARHEAD-1 Cohort 1 of Afamitresgene Autoleucel ("Afami-cel" [Formerly ADP-A2M4]) in Advanced Synovial Sarcoma and Myxoid/Round Cell Liposarcoma

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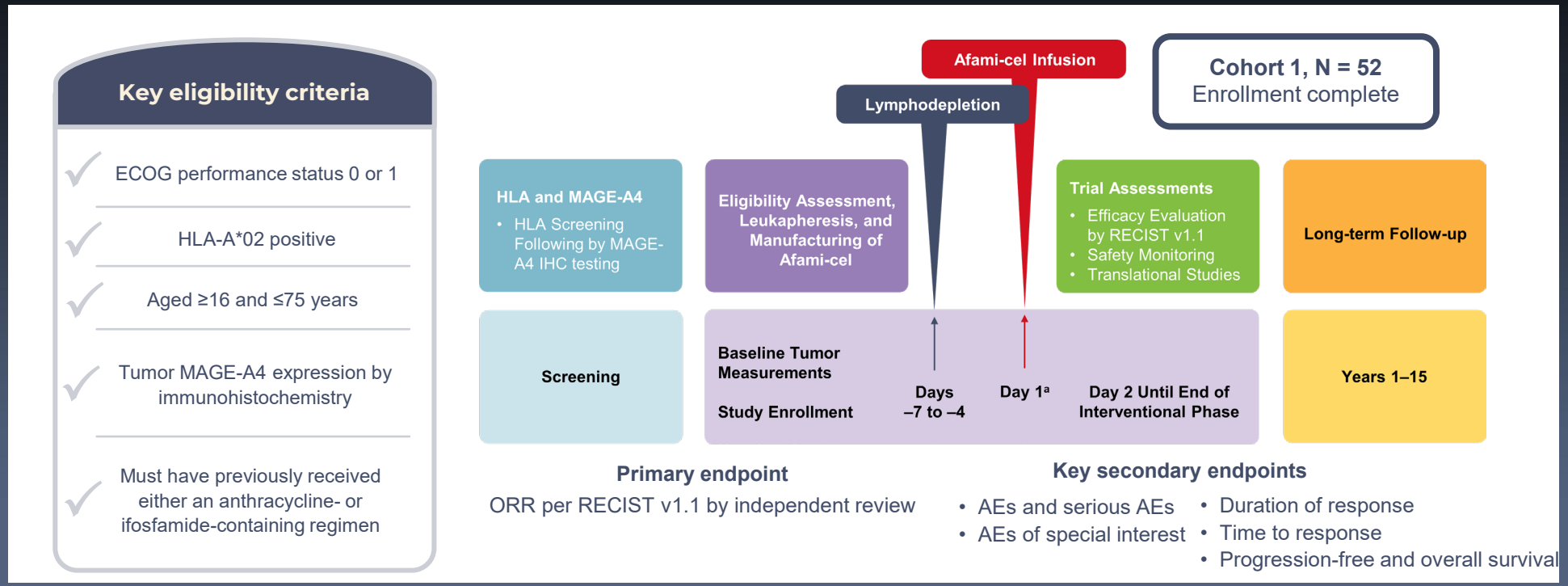
*At the time the study was conducted

SPEARHEAD-1 (NCT04044768) Trial Design

Phase 2 Trial of Afami-cel in Patients with Advanced Synovial Sarcoma or MRCLS



[a]Patient is hospitalized for T-cell infusion and discharged at the discretion of the investigator. AE, adverse event; ECOG, Eastern Cooperative Oncology Group; HLA, human leukocyte antigen; IHC, immunohistochemistry; MAGE-A4, melanoma-associated antigen A4; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Cohort 1: Baseline Patient and Disease Characteristics

Characteristic, mITT	N=52
Sex, n (%)	
Male	28 (53.8)
Female	24 (46.2)
Age, years, median (range)	41.0 (19, 73)
Race, n (%)	
White	45 (86.5)
Black or African American	2 (3.8)
Asian	3 (5.8)
Missing	2 (3.8)
Primary tumor type, n (%)	
Synovial sarcoma	44 (84.6)
MRCLS	8 (15.4)
Geographic region, n (%)	
North America	36 (69.2)
Europe/UK	15 (28.8)

Characteristic, mITT	N=52
MAGE-A4 expression, median H-score (range)	232.9 (112, 300)
Baseline target tumor lesion(s) ≥ 10 cm, n (%)	27 (51.9)
ECOG performance status, n (%)	
0	27 (51.9)
1	24 (46.2)
2	1 (1.9)
Prior lines of systemic therapy, median (range)	3 (1, 12)
Most common prior systemic therapy, n (%)	
Doxorubicin	49 (94.2)
Ifosfamide	48 (92.3)
Pazopanib	21 (40.4)
Received bridging therapy, n (%)	20 (38.5)
Pazopanib	11 (55)
Ifosfamide	3 (15)
Trabectedin	3 (15)
Other (doxorubicin, docetaxel, pegylated liposomal doxorubicin hydrochloride)	3 (15)

Data cut-off August 29, 2022. Cohort 1 data. H-score: 3 x percentage of strongly staining cells + 2 x percentage of moderately staining cells + percentage of weakly staining cells. ECOG, Eastern Cooperative Oncology Group; MAGE, melanoma-associated antigen A4; mITT, modified intent-to-treat population; MRCLS, myxoid/round cell liposarcoma.

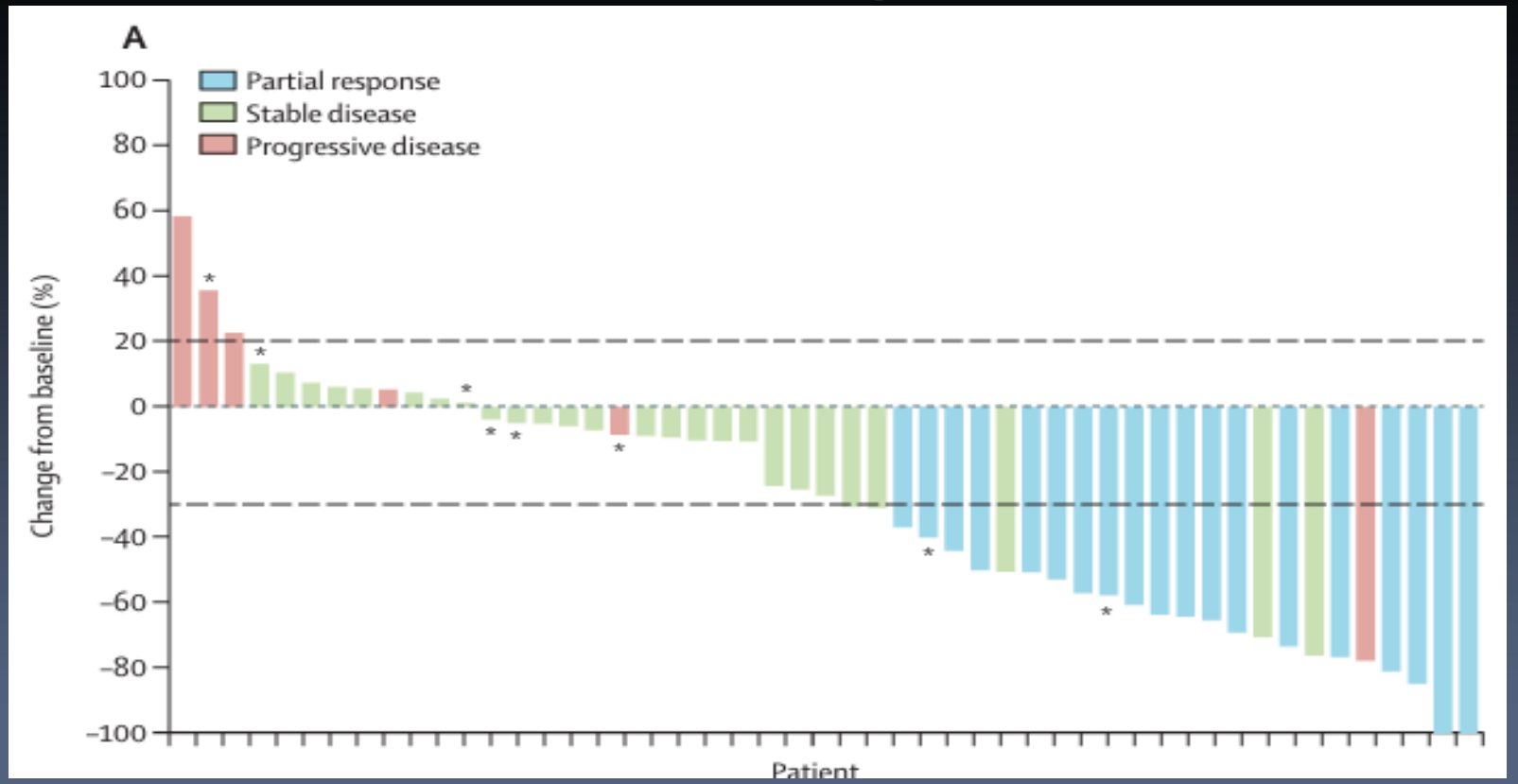
Responses per RECIST v1.1 by Independent and Investigator Reviews

	Independent review N=52	Investigator review N=52
Complete response, n (%)	0 (0)	2 (3.8)
Partial response, n (%)	19 (36.5)	17 (32.7)
Stable disease, n (%)	27 (51.9)	25 (48.1)
Progressive disease, n (%)	6 (11.5)	8 (15.4)
Overall response rate, % (95% CI)	**36.5 (23.62, 51.04)**	**36.5 (23.62, 51.04)**
Synovial sarcoma	38.6 (24.36, 54.50)	40.9 (26.34, 56.75)
MRCLS	25.0 (3.19, 65.09)	12.5 (0.32, 52.65)

- High level of concordance between independent and investigator reviews
- Primary endpoint uses independent review, which is shown going forward

Data cut-off August 29, 2022. Cohort 1 data. Overall response rate = complete responses + partial responses. RECIST, Response Evaluation Criteria in Solid Tumors.

Change From Baseline in Target Lesion SLD Colored by Best Overall Responses



Median time to response

- 4.9 weeks (range: 4.1, 12.1)

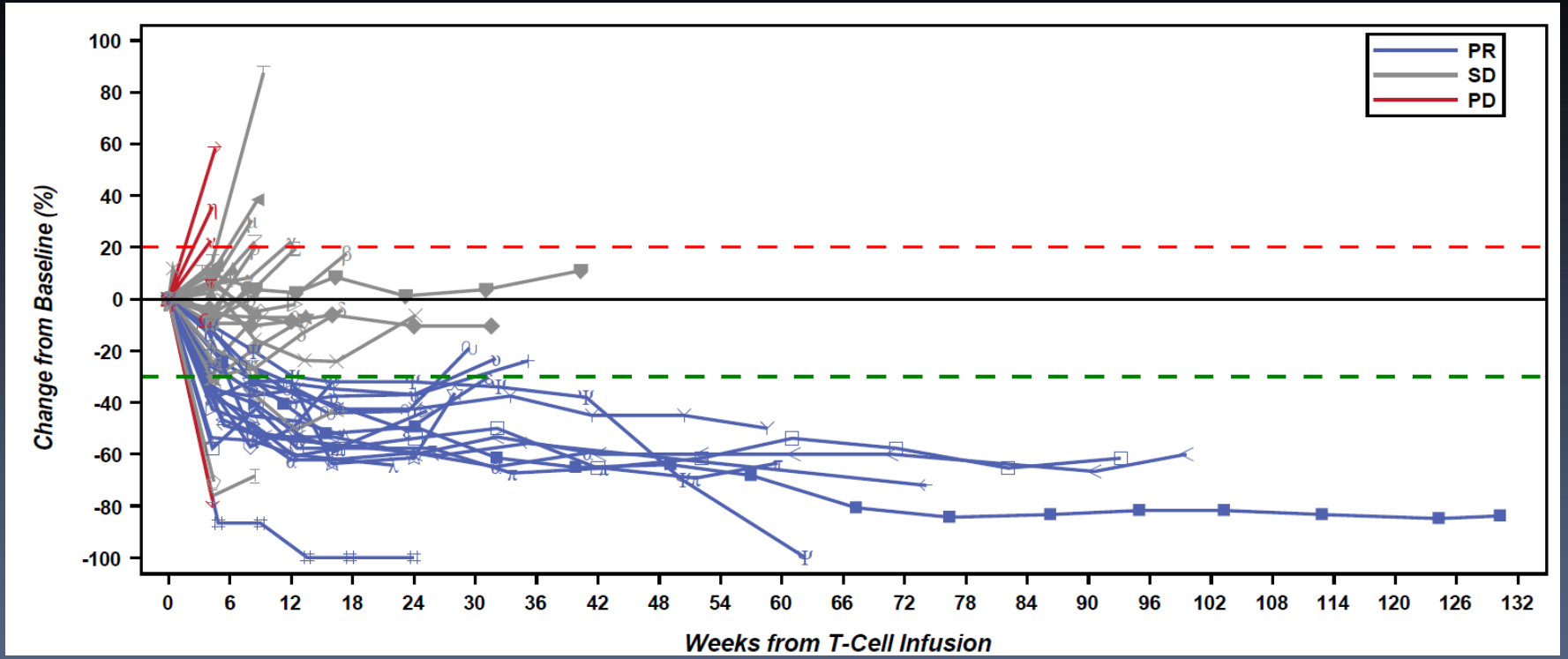
Median duration of response

- Synovial sarcoma: 50.3 weeks (range: 11.7, 122.0+)
- MRCLS: 18.2 weeks (range: 12.4, 24.0)

8 responses ongoing as of the data cut-off

Data cut-off August 29, 2022. Cohort 1 data. Data represent percent changes from baseline in sum of diameters (sum of the long diameters for non-nodal lesions and short axis for nodal lesions) in target lesions through progression or prior to surgical resection
MRCLS, myxoid/round cell liposarcoma; PD, progressive disease; PR, partial response; SLD, sum of longest diameters; SD, stable disease.

Change From Baseline in Target Lesion SLD Over Time Colored by Best Overall Responses



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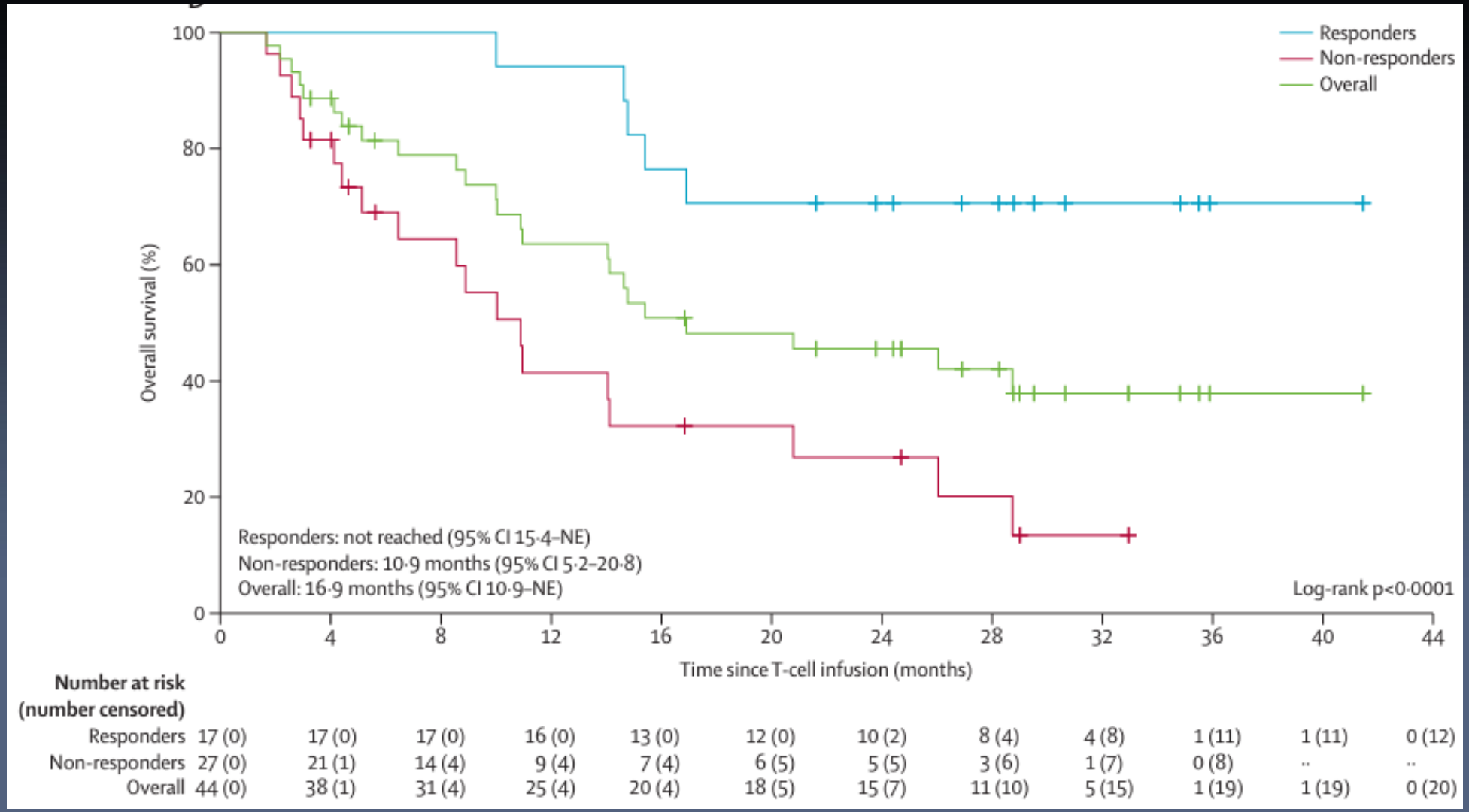
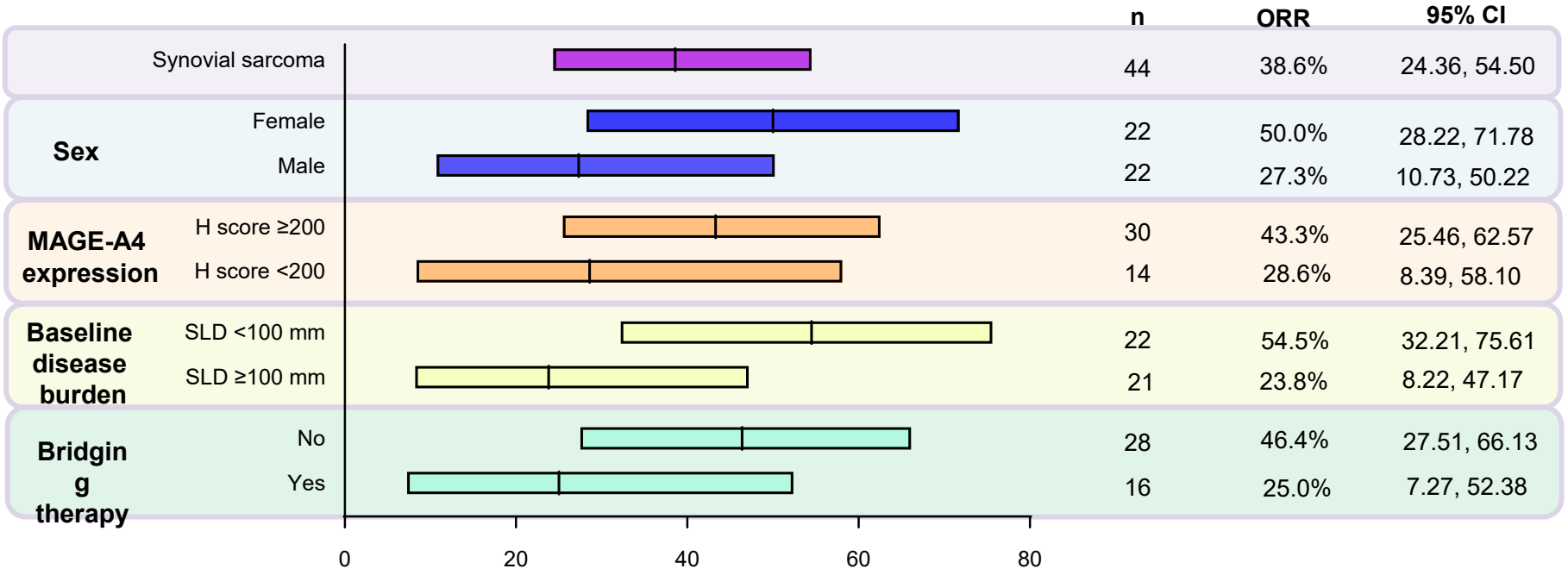
Stratified OS



Overall Response Rate in Subgroups of Patients with Synovial Sarcoma



Responses were similar among patients stratified by age, number of prior lines of systemic therapy, transduced cell dose, and cytokine release syndrome

Data cut-off August 29, 2022. Cohort 1 data. Overall response rate = complete responses + partial responses. Error bars show upper and lower 95% confidence intervals based on exact Clopper-Pearson (exact binomial) method. MAGE, melanoma-associated antigen A4; ORR, overall response rate; SLD, sum of longest diameters.

Conclusions

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)
- Next-generation SURPASS trial with enhanced ADP-A2M4 SPEAR T-cells (North America & Europe; NCT04044859)

Questions?