Identification of Response Stratification Factors from Pooled Efficacy Analyses of Afamitresgene Autoleucel ("Afami-cel" [Formerly ADP-A2M4]) in Metastatic Synovial Sarcoma and Myxoid/Round Cell Liposarcoma Phase 1 and Phase 2 Trials

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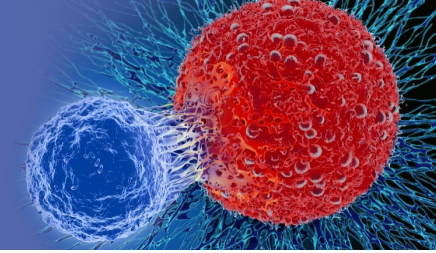


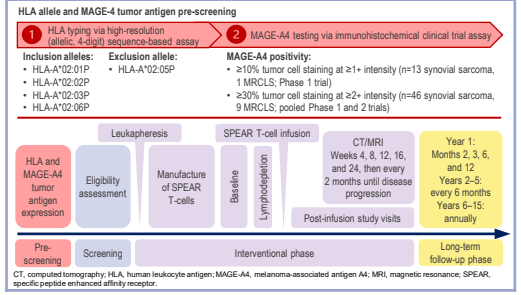
Introduction

- Afamitresgene autoleucel ("afami-cel" [formerly ADP-A2M4]) is an autologous, specific peptide enhanced affinity receptor T-cell therapy engineered to target melanoma-associated antigen A4 (MAGE-A4)-positive solid tumors in human leukocyte antigen (HLA)-A*02-eligible patients.
- There is a significant unmet need for treatment in patients with unresectable or metastatic synovial sarcoma after first-line systemic therapy.
- The pivotal, Phase 2 SPEARHEAD-1 trial (NCT04044768) is evaluating afami-cel in patients with synovial sarcoma or myxoid/round cell liposarcoma (MRCLS) in two cohorts.
  - The trial met its primary endpoint based on Cohort 1 data. As of September 1, 2021, the overall response rate (ORR) in 47 patients per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 by independent review was 34% with encouraging durability.[1]
- To identify potential stratification factors for response and assess whether response is a proxy for progression-free survival (PFS), we present pooled analyses using data from patients with synovial sarcoma or MRCLS in the prior Phase 1 trial (NCT03132922) of afami-cel and Cohort 1 of the Phase 2 SPEARHEAD-1 trial.

Methods

- The prior Phase 1 dose-escalation and expansion trial of afami-cel evaluated patients who were HLA-A*02 eligible with advanced cancers that expressed MAGE-A4 (NCT03132922):
  - Urinary bladder cancer, melanoma, head and neck cancer, ovarian cancer, non-small cell lung cancer, esophageal cancer, gastric cancer, synovial sarcoma, MRCLS, and esophagogastric junction cancer.
- SPEARHEAD-1 is a two-cohort, single-arm, Phase 2 trial in HLA-A*02-eligible patients with MAGE-A4-positive unresectable or metastatic synovial sarcoma or MRCLS (NCT04044768).
- In the pooled dataset from both trials, tumors were considered MAGE-A4 positive if ≥30% cancer cells had 2+ or 3+ staining intensity using an immunohistochemistry clinical trial assay (CTA), except for 13 patients with synovial sarcoma in the Phase 1 trial who were deemed MAGE-A4 positive with a CTA cut-off of 10%; MAGE-A4 tumor expression was evaluated as a histoscore (H-score[a] range: 0–300).
- Prior to afami-cel infusion (**Figure 1**), patients received a lymphodepletion (LD) chemotherapy regimen of fludarabine 30 mg/m^2 x4 days and cyclophosphamide 600 mg/m^2 x3 days, except for 4 patients with synovial sarcoma (Phase 1 trial) who received fludarabine 30 mg/m^2 x4 days and cyclophosphamide 1800 mg/m^2 x2 days.
- The pooled analyses reported here evaluated ORR per RECIST v1.1 by investigator review in patients with synovial sarcoma and MRCLS, stratified by 9 clinical subgroups. Safety was also investigated.
  - Data cut off was September 1, 2020 for Phase 1 trial and October 11, 2021 for SPEARHEAD-1
  - All analyses utilized the modified intention-to-treat (mITT) population, defined as all patients who received infusion of afami-cel.

Figure 1. Phase 1 and Phase 2 Trial Design



CT, computed tomography; HLA, human leukocyte antigen; MAGE-A4, melanoma-associated antigen A4; MRI, magnetic resonance; SPEAR, specific peptide enhanced affinity receptor.

Demographics and Baseline Characteristics

- In the pooled ITT population, 79 patients (synovial sarcoma, n=65; MRCLS, n=14) were enrolled and underwent leukapheresis; 70 patients (synovial sarcoma, n=60; MRCLS, n=10) received LD chemotherapy.
- In the pooled mITT population, 69 patients (synovial sarcoma, n=59; MRCLS, n=10) received afami-cel (Phase 1, n=18; Phase 2, n=51).
- All patients expressed at least one eligible HLA-A*02 allele.
- Median MAGE-A4 tumor H-score was higher in synovial sarcoma than in MRCLS (**Table 1**).
- Patients were heavily pretreated; median number of prior lines of therapy was 2, and most patients did not require bridging therapy.

Table 1. Pooled Baseline Characteristics of Patients who Received Afami-cel in the Prior Phase 1 Trial and Cohort 1 of the SPEARHEAD-1 Trial

Characteristic	Overall , N=69
Sex, n (%)	
Male	39 (56.5)
Female	30 (43.5)
Age, years, median (min, max)	42 (19, 76)
H-score, median (min, max)	229.67 (60.3, 300.0)
Synovial sarcoma (n=59)	256.5 (60.3, 300.0)
MRCLS (n=10)	179.5 (112.1, 229.7)
ECOG at baseline, n (%)	
0	38 (55.1)
1	30 (43.5)
2[a]	1 (1.4)
Bridging therapy, yes, n (%)	28 (40.6)
Transduced cells, min, max	2.12×10^9, 9.99×10^9
Prior lines of systemic therapy, median (min, max)	2 (1, 12)

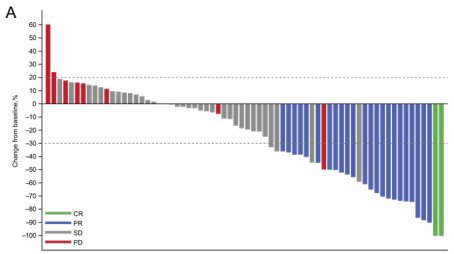
[a]After data cut-off (SPEARHEAD-1), patient was confirmed as ECOG 1. ECOG, Eastern Cooperative Oncology Group; MRCLS, myxoid/round cell liposarcoma.

Efficacy

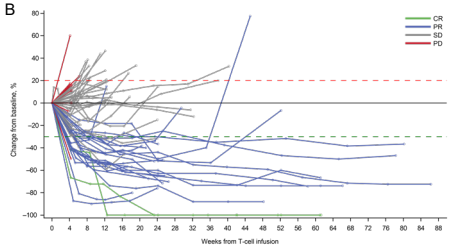
- Pooled investigator-assessed ORR was 36.2% overall (**Figure 2A**, **Table 2**).
  - In synovial sarcoma, ORR was 40.7% (2 complete responses and 22 partial responses including 2 patients who received the higher cyclophosphamide dose).
  - In MRCLS, ORR was 10.0% (1 partial response).
- Median duration of response was 52.0 weeks (**Figure 2B, Table 2**).
- Median PFS overall was 18.3 weeks (20.4 weeks in synovial sarcoma).
- In responders vs non-responders, median PFS was 58.3 vs 12.0 weeks (**Figure 3**; log-rank P<0.0001).
  - In synovial sarcoma, median PFS in responders was 58.3 vs 11.0 weeks in non-responders.
- Responses were observed across all 9 clinical subgroups (**Table 3**).
- Higher response rates were observed in patients with lower baseline tumor burden (sum of diameters <100 mm vs ≥100 mm), lower number of prior lines of systemic therapy (≤2 vs ≥3), and higher MAGE-A4 tumor H-score (≥200 vs <200; **Table 3**).
  - Similar results were observed among subgroups of patients with synovial sarcoma.

Figure 2. Investigator-Assessed Best Overall Response and Duration of Response per RECIST v1.1

- Pooled investigator-assessed ORR (n=69) was 36.2% (95% CI 24.99, 48.69).
  - Synovial sarcoma (n=59), 40.7% (95% CI 28.07, 54.25).



- Median duration of response was 52.0 weeks (95% CI 18.56, N/A).



CR, complete response; ORR, overall response rate; PD, progressive disease; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

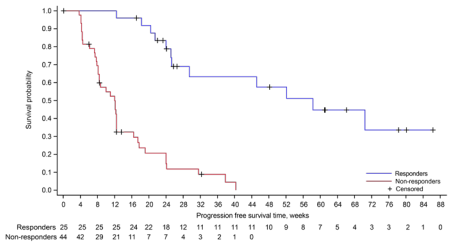
Table 2. Responses per RECIST v1.1 by Investigator Review

Response	Overall, N=69
ORR	
n (%) 95% CI[a]	25/69 (36.2) 24.99, 48.69
Complete response	
n (%)	2/69 (2.9)
Partial response	
n (%)	23/69 (33.3)
ORR, synovial sarcoma	
n (%) 95% CI[a]	24/59 (40.7) 28.07, 54.25
Disease control rate[b]	
n (%)	59/69 (85.5)

1 patient was not evaluable per RECIST v1.1. [a]Two-sided 95% CI based on exact Clopper-Pearson (exact Binomial) method. [b]Complete response + partial response + stable disease. CI, confidence interval; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors .

Figure 3. Kaplan-Meier Plot of Progression-Free Survival in Responders vs Non-Responders with Synovial Sarcoma or Myxoid/Round Cell Liposarcoma

- Responders (blue), median PFS 58.3 weeks.
- Non-responders (red), median PFS 12.0 weeks.
  - Log-rank test, P<0.0001.



PFS, progression-free survival.

Table 3. Overall Response Rate in Patients with Synovial Sarcoma and Myxoid/Round Cell Liposarcoma Stratified by 9 Clinical Subgroups

Subgroup	Overall response rate	
Baseline sum of diameters	<100 mm, n=34	≥100 mm, n=35
n (%) 95% CI	17/34 (50.0) 32.43, 67.57	8/35 (22.9) 10.42, 40.14
Prior lines of systemic therapy	≤2, n=35	≥3, n=34
n (%) 95% CI	17/35 (48.6) 31.38, 66.01	8/34 (23.5) 10.75, 41.17
H-score	<200, n=26	≥200, n=43
n (%) 95%CI	6/26 (23.1) 8.97, 43.65	19/43 (44.2) 29.08, 60.12
Bridging therapy	Yes, n=28	No, n=41
n (%) 95% CI	8/28 (28.6) 13.22, 48.67	17/41 (41.5) 26.32, 57.89
Transduced cell dose	$<7\times10^9$, n=28	$\geq 7\times10^9$, n=41
n (%) 95% CI	9/28 (32.1) 15.88, 52.35	16/41 (39.0) 24.20, 55.50
Any grade CRS	Yes, n=50	No, n=19
n (%) 95% CI	19/50 (38.0) 24.65, 52.83	6/19 (31.6) 12.58, 56.55
Age	<40 years, n=27	≥ 40 years, n=42
n (%) 95% CI	9/27 (33.3) 16.52, 53.96	16/42 (38.1) 23.57, 54.36
Sex	Male, n=39	Female, n=30
n (%) 95% CI	12/39 (30.8) 17.02, 47.57	13/30 (43.3) 25.46, 62.57
Geographical region	North America, n=55	Europe, n=14
n (%) 95% CI	21/55 (38.2) 25.41, 52.27	4/14 (28.6) 8.39, 58.10

CRS, cytokine release syndrome.

Safety

- Any grade and Grade ≥3 adverse events occurred in all patients.
- Scan QR code (bottom of poster) to view table of treatment-emergent adverse events occurring in ≥10% of patients.
- Treatment-emergent serious adverse events occurring in ≥5% of patients were cytokine release syndrome (CRS; 15.9%), pyrexia (7.2%), and pleural effusion (5.8%).
- Adverse events of special interest (**Table 4**) included CRS, prolonged cytopenia defined as any Grade ≥3 anemia, neutropenia, or thrombocytopenia at Week 4 post T-cell infusion, and immune effector cell-associated neurotoxicity syndrome (ICANS).
- One patient in the Phase 1 trial who received LD chemotherapy cyclophosphamide 1800 mg/m^2 x2 days had Grade 5 treatment-related pancytopenia on Day 55 caused by aplastic anemia, which led to reduction in cyclophosphamide to 600 mg/m^2 x3 days for the remainder of the Phase 1 trial and for SPEARHEAD-1.

Table 4. Summary of Adverse Events of Special Interest

Preferred term	Overall, N=69
Cytokine release syndrome	
Any grade, n (%)	50 (72.5)
Grade ≥3, n (%)	3 (4.3)
Time to onset, days, median (min, max)	2.0 (1, 23)
Time to resolution, days, median (min, max)	3.0 (1, 26)
Tocilizumab use, n (%)	27 (39.1)
Grade ≥3 cytopenia at Week 4 post infusion, n (%)	
Any	17 (24.6)
Anemia	7 (10.1)
Neutropenia	8 (11.6)
Thrombocytopenia	11 (15.9)
Immune effector cell-associated neurotoxicity syndrome, n (%)	
Any grade	1 (1.4)
Grade ≥3	0

Conclusions

- Pooled investigator-assessed ORR in heavily pretreated patients with synovial sarcoma or MRCLS was 36.2%, with a median duration of response of 52.0 weeks.
- Baseline tumor burden, prior systemic treatment history, and MAGE-A4 tumor expression levels are potentially important factors associated with response to afami-cel.
- A favorable benefit to risk profile was observed.
  - CRS was common but mostly low grade.
  - ICANS was uncommon.
  - Hematological toxicity was reversible with LD chemotherapy fludarabine 30 mg/m^2 x4 days and cyclophosphamide 600 mg/m^2 x3 days.
- Patients responding to afami-cel had a longer PFS than non-responders.
- These findings will inform future prognostic studies with afami-cel in soft-tissue sarcomas.

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References

1. Van Tine, et al. Paper 30: CTOS 2021; Virtual.

Footnotes and Abbreviations Used in Text

[a]H-score: 1 × (% of 1+ cells) + 2 × (% of 2+ cells) + 3 × (% of 3+ cells). CRS, cytokine release syndrome; HLA, human leukocyte antigen; ICANS, immune effector cell-associated neurotoxicity syndrome; LD, lymphodepletion; MAGE-A4, melanoma-associated antigen A4; mITT, modified intention-to-treat; MRCLS, myxoid/round cell liposarcoma; ORR, overall response rate; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

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