CO124

Comparative Effectiveness of Afami-cel in Synovial Sarcoma Using Unanchored Matching-Adjusted Indirect Comparisons

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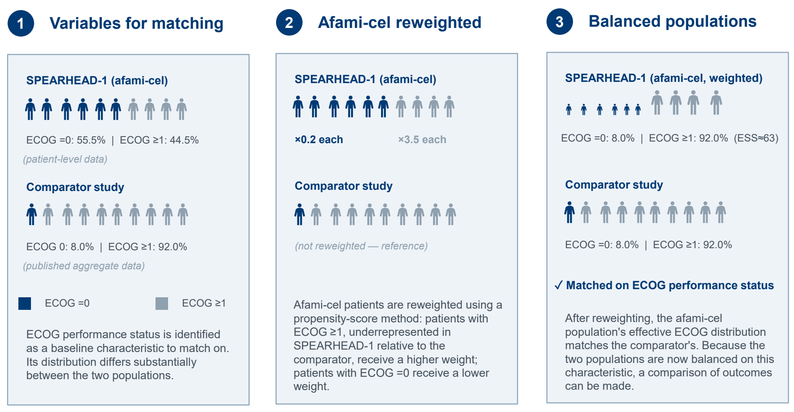
INTRODUCTION

- Synovial sarcoma (SyS) is a rare, aggressive mesenchymal malignancy that accounts for approximately 5%–10% of all soft tissue sarcomas (STS);[1,2] metastatic spread is observed in 50–70 % of patients[1,3] and prognosis is poor (median overall survival [OS] <2 years).[4]
- In the second-line and later-line setting (≥2L), SyS responds poorly to standard targeted or chemotherapy, with objective response rates (ORRs) of 4.5–13.5% in prospective clinical trials.[5–7]
- Melanoma-associated antigen A4 (MAGE-A4) is a cancer-testis antigen expressed in ~70% of human leukocyte antigen (HLA)-A*02-eligible SyS tumors[8] with restricted normal-tissue expression, making it a promising T-cell receptor (TCR) target.[9]
- Afamitresgene autoleucel (afami-cel) is an autologous TCR-T cell therapy targeting MAGE-A4 presented by HLA-A*02;[10] Food and Drug Administration (FDA)-approved (accelerated 2024; full approval June 2026[11]) based on SPEARHEAD-1[2,12] for adult or pediatric patients 12 years of age and older with advanced (unresectable or metastatic) SyS who have received prior chemotherapy.
- No randomized trials directly compare afami-cel with standard ≥2L therapies in SyS; indirect comparisons can address this evidence gap.

METHODS

- A targeted literature review (TLR) was conducted in PubMed, complemented by an online search, to identify studies reporting ORR, OS, or progression-free survival (PFS) for SyS patients in the 2L setting; N>10 per SyS arm were required.
- Study design, baseline characteristics and ORR were extracted from the comparator studies; Kaplan-Meier curves for OS and PFS were digitized and reconstructed.
  - Baseline characteristics of the overall STS population were extracted if not reported separately for SyS patients.
- Unanchored matching-adjusted indirect comparisons (MAIC)[13] using patient-level data from SPEARHEAD-1 (as of 27 Dec 2025) were conducted, reweighing (propensity-score method) afami-cel patients to match baseline characteristics (age, sex, race, Eastern Cooperative Oncology Group [ECOG] performance status, prior lines of therapy) of the comparator studies, see **Figure 1** for an illustration of the methodology.
  - To assess the matching performance, the effective sample size (ESS) was calculated.
- Weighted odds ratios (OR) for ORR and hazard ratios (HR) for OS/PFS with 95% confidence intervals (CIs) were estimated using conventional estimators, with weights rescaled to the ESS.[14]

Figure 1. Illustration of the MAIC methodology

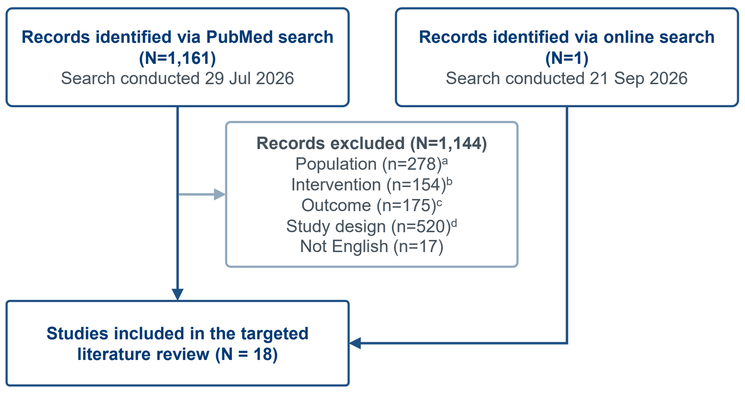


ECOG: Eastern Cooperative Oncology Group performance status, MAIC: matching-adjusted indirect comparison.

RESULTS: TLR and comparator studies

- The TLR (date of the updated PubMed search: 29 Jul 2026, date of the online search: 21 Sep 2026) identified 18 studies reporting outcomes for SyS patients across seven drugs; pazopanib (4 studies), trabectedin (5), gemcitabine/docetaxel (3), regorafenib (2), catequentinib (2), eribulin (1), afami-cel (1) (Figure 2, Table 1).
- Eleven publications reported results from prospective studies (Phase 2–3 randomized or non-randomized trials or pooled Phase 2 trials) and 7 from retrospective analyses (Table 1).
- SPEARHEAD-1 patient-level data included N=137 evaluable patients.
- Comparator populations were generally older (mean age 41–55 years) with fewer patients receiving ≥2 prior lines of therapy than in SPEARHEAD-1 (Table 1).

Figure 2. PRISMA flow diagram



Record excluded due to [a] population studied not of interest (e.g., not on synovial sarcoma, in the first-line setting); [b] intervention studied (e.g., surgical study, radiation therapy, not approved in the United States) not of interest; [c] outcomes of interest (i.e., objective response rate, overall survival, progression-free survival) not reported; [d] study design not of interest (e.g., review, protocol, preclinical study, ≤10 synovial sarcoma patients included).

Table 1. Overview of included studies

Study	Drug	N	Age, years	Male, %	White, %	ECOG =0, %	≥2L, %	ORR, %	OS	PFS
Prospective studies										
SPEARHEAD-1, Final Study Data	AFA	137	40.0	53.3	86.1	55.5 (99.3[b])	72.3 (2.6[c])	43.8	✓	✓
van der Graaf 2012 (PALETTE)[a,15]	PAZ	25	53.2	41.0	72.0	48.0	54.0	NR	✓	✓
Sleijfer 2009 (EORTC 62043)[5]	PAZ	38	39.7	60.5	NR	55.3	31.6	13.5	✓	✓
Le Cesne 2012[a,6]	TRA	45	44.8	52.0	NR	60.0	2.0[c]	7.0	✓	✓
Takahashi 2017[a,16]	TRA	17	43.5	58.0	NR	58.0	1.5[c]	6.0	NR	✓
Tansir 2023[7]	G/D	22	34.8	59.0	NR	59.0[b]	50.0	5.0	✓	✓
Mir 2016 (REGOSARC)[17]	REG	13	46.5	62.0	NR	54.0	84.0	8.0	✓	✓
Fernandes 2025[18]	REG	25	39.5	56.0	NR	8.0	2.5[c]	12.0	✓[d]	✓
Van Tine 2021 (APROMISS)[19]	CAT	52	43.5	38.5	NR	NR	NR	5.8	NR	✓
Chi 2018[a,20]	CAT	47	44.8	60.0	NR	30.0	NR	17.0	NR[e]	NR[e]
Schöffski 2011[21]	ERI	19	44.8	74.0	NR	74.0	NR	5.0	✓	✓
Retrospective analyses										
Bilici 2023[a,22]	PAZ	62	52.0	42.2	NR	85.5[b]	29.2	48.4	✓	✓
Nakamura 2016[a,23]	PAZ	18	53.8	62.2	NR	26.9	80.8	11.1	NR[e]	NR[e]
Kobayashi 2020[a,24]	TRA	18	48.5	56.4	NR	47.9	87.9	16.7	NR[e]	NR[e]
Sanfilippo 2015[25]	TRA	61	40.0	42.6	NR	NR	2.8[c]	15.0	NR	✓
Palmerini 2021[a,26]	TRA	40	55.3	42.6	NR	62.7	2.0[c]	15.4	✓	✓
Pender 2018[27]	G/D	21	41.3	71.0	NR	NR	95.2	4.8	✓	✓
Pollack 2020[d,28]	G/D	249	46.3	58.2	NR	NR	74.7	NR	✓	✓

[a] Baseline characteristics for overall STS population, as not available for SyS subgroup. [b] ECOG≤1. [c] Mean number of prior lines of therapy. [d] Median survival and number of events reported. [e] Median survival without confidence interval or number of events reported. [f] Overall SyS subgroup treated with 1L systemic anti-cancer therapy, but results are reported for 2L treatment.
2L, second line; AFA, afami-cel; CAT, catequentinib; ECOG, Eastern Cooperative Oncology Group; ERI, eribulin; G/D, gemcitabine/docetaxel; NR, not reported; ORR, objective response rate; OS, overall survival; PAZ, pazopanib; PFS, progression-free survival; REG, regorafenib; STS, soft tissue sarcoma; SyS, synovial sarcoma; TRA, trabectedin.

RESULTS: Matching and effective sample size

- ESS ranged from 5.4 to 130.96 across the 17 comparator studies, reflecting a 96.0 to 4.4% reduction in the original sample size of N=137 of SPEARHEAD-1, respectively (**Table 2**).
- Studies with a reduction of >80% (Tansir 2023[7], Bilici 2023[22]) reflect large baseline differences.

Table 2. Effective sample size and % reduction after matching to comparator studies

Comparator study	Drug	Study N	ESS (from N=137)	% reduction
Prospective studies				
APROMISS[19]	CAT	52	118.3	13.7%
REGOSARC[17]	REG	13	103.8	24.3%
Chi 2018[20]	CAT	47	98.9	27.8%
Schöffski 2011[21]	ERI	19	91.3	33.3%
Takahashi 2017[16]	TRA	17	75.4	44.9%
Fernandes 2025[18]	REG	25	63.0	54.0%
Le Cesne 2012[6]	TRA	45	49.0	64.2%
PALETTE[15]	PAZ	25	48.2	64.8%
EORTC 62043[5]	PAZ	37	40.8	70.2%
Tansir 2023[7]	G/D	22	5.4	96.0%
Retrospective analyses				
Sanfilippo 2015[25]	TRA	61	131.0	4.4%
Pollack 2020[28]	G/D	249	113.6	17.1%
Pender 2018[27]	G/D	21	98.1	28.4%
Kobayashi 2020[24]	TRA	18	88.6	35.3%
Nakamura 2016[23]	PAZ	18	51.0	62.8%
Palmerini 2021[26]	TRA	40	38.1	72.2%
Bilici 2023[22]	PAZ	62	20.7	84.9%

ESS: effective sample size. ESS is the number of SPEARHEAD-1 patients (N=137) effectively retained after reweighting; % reduction is relative to N=137. Rows are ordered by descending ESS. Shading indicates matching reliability: green = ESS ≥50 (good overlap); amber = ESS 25–49 (moderate, interpret with caution); red = ESS <25 (poor overlap, results less reliable). Study N is the synovial sarcoma population reported by the comparator study; drug abbreviations as defined in Table 1.

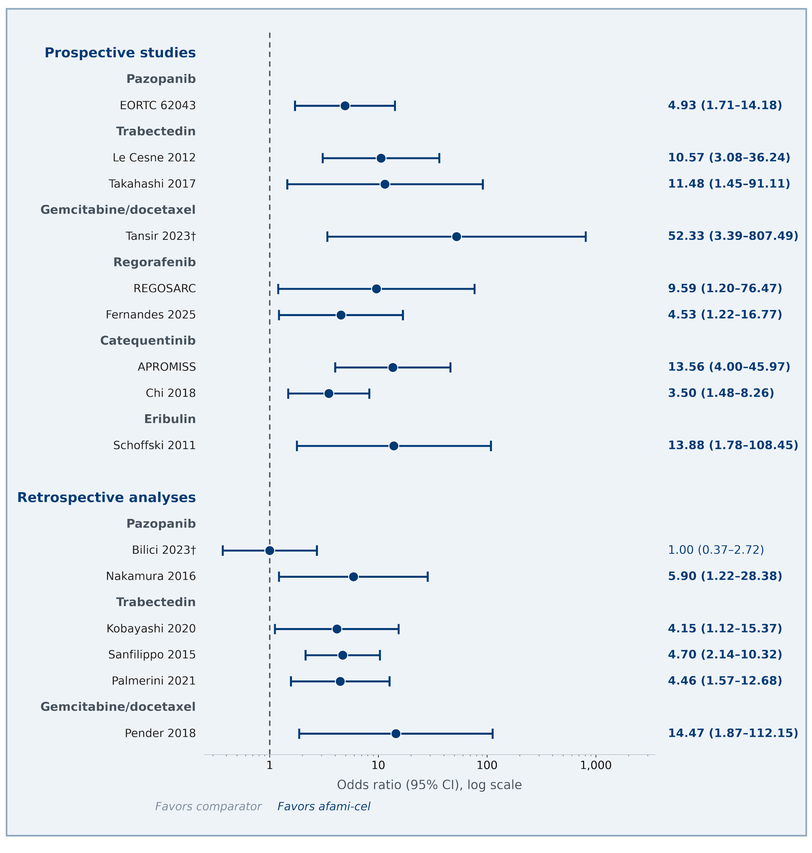
CONCLUSIONS

- **Unanchored MAICs support favorable comparative effectiveness of afami-cel versus standard ≥2L systemic therapies for SyS.**
- **ORR was significantly higher with afami-cel versus 14 comparator studies with reported ORR across pazopanib, trabectedin, gemcitabine/docetaxel, regorafenib, catequentinib and eribulin, and equivalent for one retrospective single-institution comparator study (pazopanib).**
- **OS was significantly improved with afami-cel versus five out of 11 comparator studies with reported OS; results were directionally favorable, but not statistically significant in the remainder.**
- **PFS findings were more heterogeneous, with a statistically significant benefit with afami-cel in four out of 14 comparator studies with reported PFS, and results favoring the comparator were not statistically significant.**
- **Since afami-cel requires confirmed HLA-A*02/MAGE-A4 eligibility and has a lead time for manufacturing, these results support testing patients early after diagnosis rather than waiting until second- or third-line therapy is needed to ensure that afami-cel can be considered without delay should SyS progress or metastasize.**

RESULTS: Objective response rate

- Across 9 prospective comparator studies with ORR reported, afami-cel had statistically higher odds of response; across 5 retrospective studies, afami-cel had statistically higher odds of response; for 1 retrospective study, Bilici 2023,[22] responses were equivocal (**Figure 3**)

Figure 3. Forest plot of ORR odds ratios

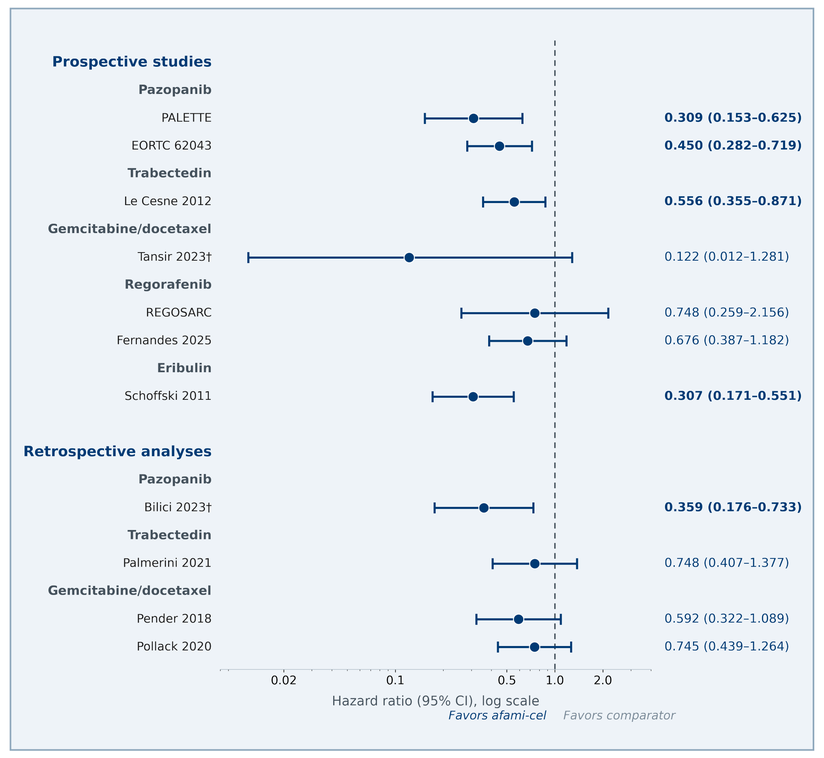


CI, confidence interval; ORR, objective response rate. **Bold** means statistically significant (95% CI excludes 1).
†Very low ESS (Table 2).

RESULTS: Overall survival and progression-free survival

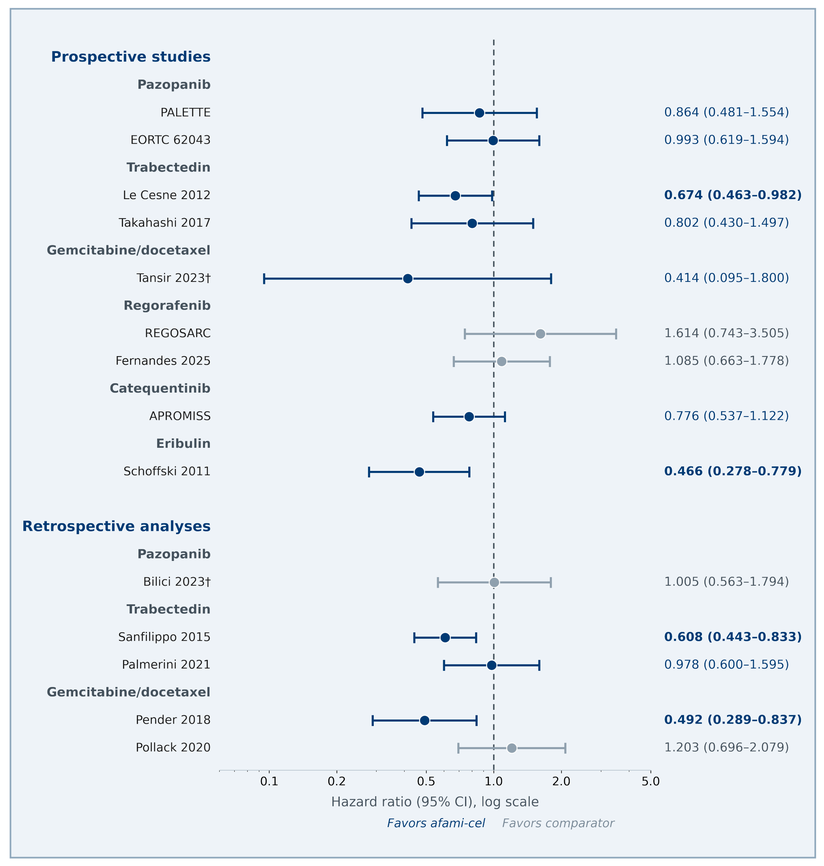
- Across all 11 studies with reported OS, afami-cel had a lower hazard of death, significant for 4 out of 7 prospective studies (pazopanib, trabectedin, and eribulin) and for 1 out of 4 retrospective analyses (pazopanib) (Figure 4).
- PFS favored afami-cel in 7 out of 9 prospective studies (significant for trabectedin and eribulin) and in 3 out of 5 retrospective analyses (significant for trabectedin and gemcitabine/docetaxel), with none of the results favoring the comparator being statistically significant (Figure 5).

Figure 4. Forest plot of OS hazard ratios



CI, confidence interval; OS, overall survival. **Bold** means statistically significant (95% CI excludes 1).
†Very low ESS (Table 2).

Figure 5. Forest plot of PFS hazard ratios



CI, confidence interval; HR, hazard ratio; PFS, progression-free survival. HR<1 favors afami-cel. **Bold** means statistically significant (95% CI excludes 1).
†Very low ESS (Table 2).

LIMITATIONS

- These indirect comparisons may be limited by residual confounding from unmeasured prognostic factors, small sample sizes and underlying study methodology of the comparator studies and matching to the overall STS population when baseline characteristics were not available for the SyS group.

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Abbreviations: 2L, second line; AFA, afami-cel; CAT, catequentinib; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; ERI, eribulin; ESS, effective sample size; G/D, gemcitabine/docetaxel; HLA, human leukocyte antigen; HR, hazard ratio; MAGE-A4, melanoma-associated antigen A4; MAIC, matching-adjusted indirect comparison; NR, not reported; OR, odds ratio; ORR, objective response rate; OS, overall survival; PAZ, pazopanib; PFS, progression-free survival; REG, regorafenib; STS, soft tissue sarcoma; SyS, synovial sarcoma; TCR, T-cell receptor; TLR, targeted literature review; TRA, trabectedin.

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