Median OS of 21.5 months among 44 patients with treatment-refractory leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma treated with mecbotamab vedotin, an AXL-targeting ADC

Abstract #523

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Background

AXL, a cell-surface receptor tyrosine kinase, is highly expressed in a wide variety of solid tumors including several STS subtypes

- Despite advances in therapy, sarcomas remain a significant unmet need with median OS among patients with treatment-refractory soft tissue sarcomas (STS) treated with either trabectedin, pazopanib, dacarbazine or eribulin previously reported to range from 11.5 to 13.6 months **(Figure 4)**[1-4]
- AXL expression has been shown to drive increased metastasis, resistance to chemotherapy, and poor outcomes[5]
- Previous clinical experience with Mec-V demonstrated antitumor activity regardless of AXL expression by tumor as assessed by immunohistochemistry

Mecbotamab Vedotin (Mec-V) is conditionally active biologic (CAB) anti-AXL ADC

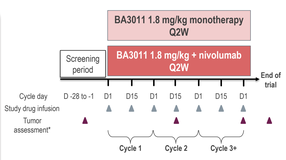
- CABs:
  - Are not masked or caged prodrugs and do not require enzymatic cleavage for activation
  - Conditionally and reversibly bind to AXL under the low-pH conditions (pH 5.3–6.7) of the TME, sparing normal tissues
  - Reduce off-tumor AEs without increasing immunogenicity, avoid tissue-mediated drug disposition, and improve PK[4]
- Mec-V (Conditionally Active Biologic (CAB)-AXL-ADC) is designed to reduce off-tumor toxicity and improve pharmacokinetics by conditionally binding to AXL under low-pH conditions (pH 5.3-6.7) of the tumor microenvironment[6,7]
- As previously reported, every-other-week delivery of Mec-V attained disease control in 43% of patients with treatment-refractory sarcomas
- Partial responses were observed among patients with osteosarcoma and undifferentiated pleomorphic sarcoma (UPS; reported previously)

Trial Design

Figure 1. Phase 2, Part 1 open-label study design

Key Eligibility Criteria

- ≥12 years of age
- AXL-expressing† locally advanced, unresectable, or metastatic sarcoma
- Measurable disease by RECIST v1.1
- Received ≥1 regimen containing anthracycline and ≤3 prior lines of approved systemic therapy for histologic subtypes that typically receive chemotherapy‡



Endpoints

- DCR (objective response or stable disease for ≥12 weeks)
- Number of responders (complete or partial)
- PFS rate at week 12
- OS
- TEAEs

†Tumor membrane percent score ≥50%.
‡Prior chemotherapy was not required for histologic subtypes that do not typically receive chemotherapy.
*Tumor assessment by CT or MRI every 6 weeks from C1D1 until 12 weeks, then every 8 weeks up to 1 year, then every 12 weeks thereafter.

Results

Patient characteristics and disposition

- As of March 25, 2025 data cut, 79 pts with soft tissue sarcoma received Mec-V 1.8mg/kg Q2W (monotherapy) (n=54) or 1.8 mg/kg Q2W + nivolumab (combination) (n=25); **(Table 1)**
- Pts had previously received a median of 2 prior lines of therapy (range 0-10)
- Pts received a mean of 15 weeks of Mec-V (range 2-63 weeks)
- Current efficacy analysis characterizes overall survival among subset of pts with leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcomas (N=44)

Table 1. Patient demographics

Patient Characteristic	Monotherapy (N=54)	Combination (N=25)	Total (N=79)
Age, y, mean (range)	57 (23-78)	55 (25-80)	56 (23-80)
ECOG Status, n (%)			
0	23 (43)	12 (48)	35 (44)
1	31 (57)	13 (52)	44 (56)
# of prior systemic therapies, n (%)			
1	12 (22)	4 (16)	16 (20)
2	17 (32)	12 (48)	29 (37)
3+	24 (44)	9 (36)	33 (42)
Not entered	1 (2)	0	1 (1)
Sarcoma Subtype, (n, %)			
Leiomyosarcoma	19 (35)	8 (32)	27 (34)
Undifferentiated pleomorphic sarcoma	6 (11)	2 (8)	8 (10)
Liposarcoma	8 (15)	1 (4)	9 (11)
Other soft tissue sarcoma	21 (39)	14 (56)	35 (44)

Safety

- Mec-V was generally well-tolerated with a manageable safety profile
- Most TEAEs were low grade and reversible; related G3 or G4 TEAE of special interest were neutropenia (21%), hepatic transaminase elevations (16%), and hyperglycemia (3%)
- No ocular AE or interstitial lung disease was observed; no treatment-related death was observed
- Treatment-related discontinuations (n=8): [G2 peripheral neuropathy (n=5), G2 ileus (n=1), G1 fatigue, G3 pancreatitis (n=1)]

Table 2. Summary of AEs

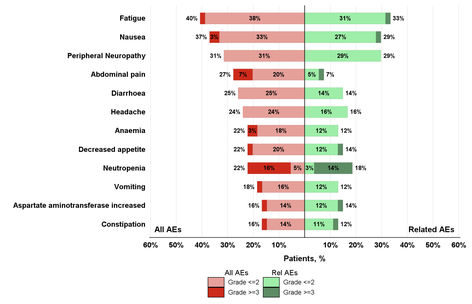
	Monotherapy (N=54)	Combination (N=25)	Total (N=79)
Any Adverse Events, (n, %)	52 (96)	23 (92)	75 (95)
Related Adverse Events, (n, %)	44 (82)	20 (80)	64 (81)
G3 AE	15 (28)	8 (32)	23 (29)
G4 AE	2 (4)	2 (8)	4 (5)
Any related serious AE, (n, %)	4 (7)	5 (20)	9 (11)
Related AEs leading to death, (n, %)	0	0	0
Related AEs leading to treatment discontinuation, (n, %)	7 (13)	1 (4)	8 (10)

Relatedness was assessed by the investigator. Missing responses were counted as related.

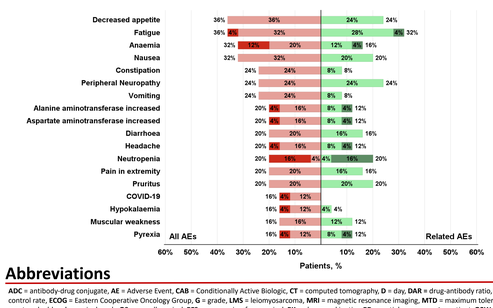
Mec-V Q2W monotherapy and combination regimens were both reasonably well-tolerated

Figure 2. Most frequent TEAE >15%

A. Mec-V Q2W monotherapy (n=54)



B. Mec-V Q2W in combination with anti-PD-1 (n=25)



Efficacy

LMS, Liposarcoma, and UPS pts treated with Mec-V experienced meaningfully longer median OS when compared to approved agents

- Two pts achieved partial response: **(Table 3)**
  - 1 pt with LMS who received Mec-V combination
  - 1 pt with UPS who received Mec-V monotherapy
- Median PFS for Mec-V monotherapy and combination was 2.5 and 2.7 months, respectively compared with 1.5-4.6 months for approved agents **(Figure 3)**[6-8]
- 12-month OS was 73% compared with ~50% historic 12-month OS for approved agents in patients with recurrent STS **(Figure 4)**[6,9,10]
- Median OS in Mec-V monotherapy vs. Mec-V + nivo combination therapy was 18.4 vs 22.9 months, respectively, across STS subtypes with 45% of events recorded **(Table 3, Figure 5)**
- Median OS (95% CI):
  - LMS: 19.0 (7.9, 29.9)
  - Liposarcoma: 21.7 (3.7, NE)
  - UPS: 21.5 (5.0, NE)

Table 3: Summary of antitumor activity amongst patients treated with Mec-V 1.8 mg/kg Q2W monotherapy and in combination with anti-PD-1 antibody

	Mec-V Q2W (n=33)*	Mec-V + nivo Q2W (n=11)	Total (N=44)
DCR (n, %)	17 (52)	6 (55)	23 (52)
PR (n, %)	1 (3)	1 (9)^	2 (5)
SD (n, %)	16 (49)	5 (46)	21 (48)
PD (n, %)	15 (46)	5 (46)	20 (46)
ORR (n, %)	1 (3)	1 (9)	2 (5)
Median PFS (months, 95% CI)	2.5 (1.4, 5.8)	2.7 (1.3, 8.8)	2.5 (1.4, 4.6)
Median OS (months, 95% CI)	18.4 (7.2, NE)	22.9 (14.2, NE)	21.5 (14.2, 29.9)

*one patient was not evaluable
^confirmed

Figure 3: PFS of Mec-V was generally consistent with current approved agents[6-8]

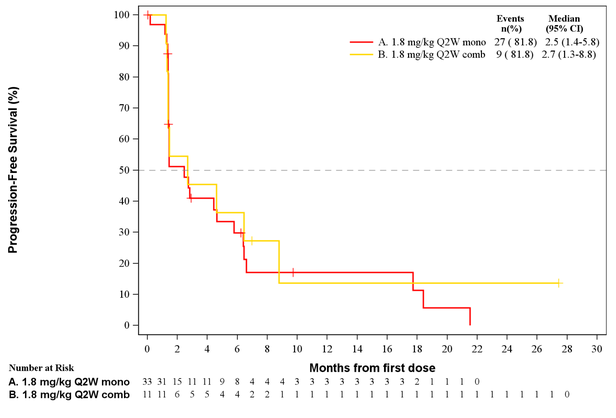


Figure 4. Overall Survival analysis of Mec-V Q2W monotherapy versus Mec-V Q2W in combination with anti-PD-1 antibody (N=44)

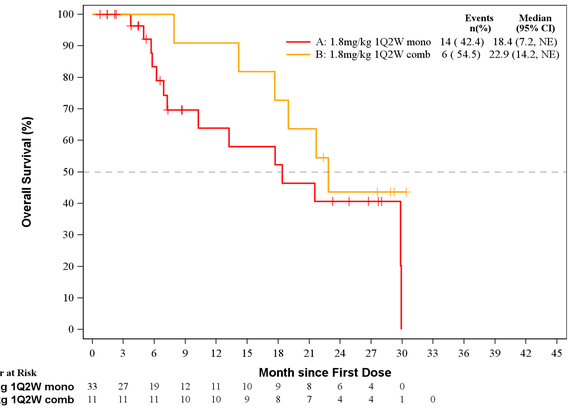
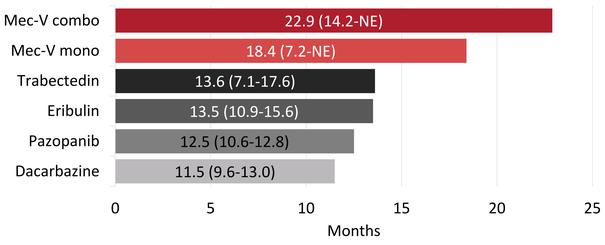


Figure 5. Mec-V mono and combo associated with longer median OS compared to approved agents (11.5-13.6 months)[6,9,10]



Conclusions

- **Among pts with treatment-refractory leiomyosarcoma, liposarcoma, and undifferentiated pleomorphic sarcoma, treatment with Mec-V, a conditionally binding, AXL-targeting ADC achieved a median overall survival of 21.5 months compared with ~12 months with approved agents**
- **The observed safety profile of Mec-V as monotherapy, and in combination with anti-PD-1 antibody, was manageable and consistent with conditional binding of the AXL target restricted to the tumor microenvironment**
- **In the context of reported historical OS data from approved treatments, overall survival findings with Mec-V are provocative**

Abbreviations

ADC = antibody-drug conjugate, **AE** = Adverse Event, **CAB** = Conditionally Active Biologic, **CT** = computed tomography, **D** = day, **DAR** = drug-antibody ratio, **DCR** = disease control rate, **ECOG** = Eastern Cooperative Oncology Group, **G** = grade, **LMS** = leiomyosarcoma, **MRI** = magnetic resonance imaging, **MTD** = maximum tolerated dose, **NE** = not evaluable, **nivo** = nivolumab, **OS** = overall survival, **PFS** = progression-free survival, **PK** = pharmacokinetics, **PR** = partial response, **pt** = patient, **Q2W** = every 2 weeks, **RECIST** = Response Evaluation Criteria in Solid Tumors, **STS** = soft tissue sarcoma, **TEAE** = treatment-emergent adverse event; **TME** = tumor microenvironment, **UPS** = undifferentiated pleomorphic sarcoma, **v** = version.

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Disclosures

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Clinical Trial Identifier

CAB-AXL-ADC Safety and Efficacy Study in Adult and Adolescent Patients With Sarcoma.
Clinical Trial Registry Number: NCT03425279

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