Poster #: P154

Interim Safety and Efficacy Results from Phase 1/2 Study of Mecbotamab Vedotin (BA3011), a CAB-AXL-ADC, in Patients with Advanced Sarcoma

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INTRODUCTION

- Mecbotamab vedotin (BA3011) is a conditionally active biologic anti-AXL antibody-drug conjugate (CAB-AXL-ADC) being developed as an anticancer therapy for patients with advanced solid tumors.
- Conditional and reversible binding by CABs is designed to reduce off-tumor toxicity and immunogenicity, avoid tissue-mediated drug deposition, and improve pharmacokinetics (PK).
- AXL is a cell-surface transmembrane receptor protein tyrosine kinase highly expressed in several tumor types including sarcoma. Increased AXL expression has been associated with tumor resistance to chemotherapy, programmed death-1 (PD-1) inhibitors, molecular targeted therapy, and radiation therapy.

OBJECTIVE

- In the current study, we sought to identify the safety profile, recommended Phase 2 dose (RP2D), and preliminary evidence of antitumor activity of BA3011 in patients with advanced sarcoma or other solid tumors.

METHODS

- Study BA3011-001 is an ongoing, multi-center, open-label, Phase 1/2 first-in-human trial of BA3011.
- In Phase 1 (NCT03425279), BA3011 is administered once (Q3W) or twice (2Q3W) every 3 weeks via intravenous (IV) infusion.
- Phase 2 (NCT03425279), is an open label assessment of the efficacy and safety of BA3011 alone and in combination with a PD-1 inhibitor in patients 12 years of age or more with AXL-expressing tumor membrane percent score (TmPS) ≥ 50 with advanced refractory sarcoma who have measurable disease and documented progression.
- Interim Phase 1 data from this study are described here, with results from 4 additional sarcoma patients included that were not available at the time of abstract submission.

RESULTS

Patient Disposition and Baseline Demographics

- Median (range) age of patients was 58.0 (24–80) years, 57.7% were female, 84.6% were White, with 69.2% having an ECOG score of 0 and 30.8% have a score of 1.
- Phase 1 sarcoma patients had on average received 4 or more prior lines of therapy.
- In Phase 1, a total of 60 patients have received BA3011 at dose levels from 0.3 to 3.0 mg/kg Q3W, and 1.2 to 1.8 mg/kg 2Q3W, including 26 patients with sarcoma.
- 227 sarcoma patients have been tested so far for AXL tumor membrane expression as part of the IHC assay validation work and in phase 1 & 2 studies with approximately 50% having a TmPS ≥ 70. AXL appears to be expressed at a consistent rate across all sarcoma subtypes tested.

Safety

- No clinically meaningful on-target toxicity to normal AXL-expressing tissue was observed, with a low rate of constipation. Dose-limiting toxicities were limited to monomethyl auristatin E (MMAE) conjugate-associated toxicity at the highest dose tested, including reversible neutropenia.
- In Phase 1 sarcoma patients, there were no treatment-emergent adverse events (TEAEs) leading to death, and treatment-related TEAEs in 2 (7.7%) patients led to treatment discontinuation (**Table 1**).
- Eleven patients had grade 3 related TEAEs and 1 patient had grade 4 neutropenia, which generally were MMAE related, including reversible myelosuppression, transient liver enzyme elevations and metabolic disturbances (**Table 2**).
- Transient grade 1-2 liver enzyme elevations seen during cycle 1 treatment generally did not re-occur upon re-treatment. Creatinine levels were generally unchanged throughout treatment.
- In Phase 1 sarcoma patients, an SAE related to treatment (grade 2 hepatic encephalopathy) occurred in 1 patient (**Table 1**).

Recommended Phase 2 Dose / Pharmacokinetics

- The RP2D was determined to be 1.8 mg/kg Q2W based on an integrated evaluation of Phase 1 data, including PK modeling.
- The PK profile of BA3011 was approximately dose proportional; in Phase 1 the half-life was determined to be approximately 4 days.

Efficacy

- BA3011 antitumor activity correlated with higher levels of AXL tumor membrane expression in sarcoma patients.
- Of 7 treatment refractory sarcoma patients with baseline TmPS ≥ 70 and dosed at 1.8mg/kg (Q3w or 2Q3w), 4 had confirmed partial responses (**Figures 1 & 2**).
- Prolonged response to therapy in sarcoma patients in this ongoing study is demonstrated in **Figure 3**.

Table 1. Overview of Adverse Events – Sarcoma Patients in Phase 1

Characteristic	BA3011 0.3 mg/kg (Q3W) (N=1)	BA3011 1.8 mg/kg (Q3W) (N=2)	BA3011 2.4 mg/kg (Q3W) (N=2)	BA3011A 1.2 mg/kg (2Q3W) (N=2)	BA3011A 1.8 mg/kg (2Q3W) (N=19)	Total (N=26)
Any TEAE	1 (100.0)	2 (100.0)	2 (100.0)	2 (100.0)	19 (100.0)	26 (100.0)
TEAE with CTCAE grade 3 or 4	0	1 (50.0)	1 (50.0)	2 (100.0)	13 (68.4)	17 (65.4)
Related TEAEs with CTCAE grade 3 or 4	0	0	1 (50.0)	0	11 (57.9)	12 (46.2)
Any serious TEAE	0	1 (50.0)	1 (50.0)	0	7 (36.8)	9 (34.6)
Any related serious TEAE [a]	0	0	0	0	1 (5.3)	1 (3.8)
TEAE leading to treatment discontinuation	0	0	0	0	2 (10.5)	2 (7.7)
Related TEAE leading to treatment discontinuation [b]	0	0	0	0	2 (10.5)	2 (7.7)
TEAEs leading to death	0	0	0	0	0	0

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; Q3W = every 3 weeks; TEAE = treatment-emergent adverse event
[a] Related serious TEAE: Hepatic encephalopathy, CTCAE Grade 2
[b] Neuropathy peripheral, CTCAE grade 2; fatigue, CTCAE grade 2

Table 2. Most Frequent Treatment-Emergent Adverse Events (≥ 20%, All TEAEs All Grades) and Any Related Grade 3/4 TEAEs – Sarcoma Patients in Phase 1

	All TEAEs			Related TEAEs		
Total (N=26)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)	All Grades n (%)	Grade 3 n (%)	Grade 4 n (%)
Patients with at least one TEAE	26 (100.0)	15 (57.7)	2 (7.7)	22 (84.6)	11 (42.3)	1 (3.8)
Fatigue	16 (61.5)	0	0	11 (42.3)	0	0
Nausea	14 (53.8)	1 (3.8)	0	10 (38.5)	1 (3.8)	0
Alanine aminotransferase increased	12 (46.2)	0	0	10 (38.5)	0	0
Aspartate aminotransferase increased	11 (42.3)	1 (3.8)	0	11 (42.3)	1 (3.8)	0
Bone pain	7 (26.9)	0	0	1 (3.8)	0	0
Constipation	7 (26.9)	1 (3.8)	0	4 (15.4)	0	0
Diarrhea	7 (26.9)	0	0	5 (19.2)	0	0
Neutrophil count decreased	7 (26.9)	4 (15.4)	1 (3.8)	7 (26.9)	4 (15.4)	1 (3.8)
Alopecia	6 (23.1)	0	0	6 (23.1)	0	0
Arthralgia	6 (23.1)	0	0	1 (3.8)	0	0
Blood alkaline phosphatase increased	6 (23.1)	0	0	5 (19.2)	0	0
Decreased appetite	6 (23.1)	0	0	4 (15.4)	0	0
Vomiting	6 (23.1)	1 (3.8)	0	5 (19.2)	1 (3.8)	0
Anemia	4 (15.4)	2 (7.7)	0	1 (3.8)	1 (3.8)	0
Hypokalemia	4 (15.4)	3 (11.5)	0	4 (15.4)	3 (11.5)	0
Peripheral neuropathy	4 (15.4)	1 (3.8)	0	4 (15.4)	1 (3.8)	0
Hyponatremia	3 (11.5)	2 (7.7)	0	1 (3.8)	1 (3.8)	0
Lymphocyte count decreased	2 (7.7)	1 (3.8)	0	2 (7.7)	1 (3.8)	0
Blood bilirubin increased	1 (3.8)	1 (3.8)	0	1 (3.8)	1 (3.8)	0
Stomatitis	1 (3.8)	1 (3.8)	0	1 (3.8)	1 (3.8)	0

Abbreviations: TEAE = treatment-emergent adverse event

Figure 1. Percent Change in Sum of Target Lesions (Best Response) – Sarcoma Patients in Phase 1 with AXL TmPS ≥ 70 at a Dose of 1.8 mg/kg Q3W (d1) or 2Q3W (d1,8)

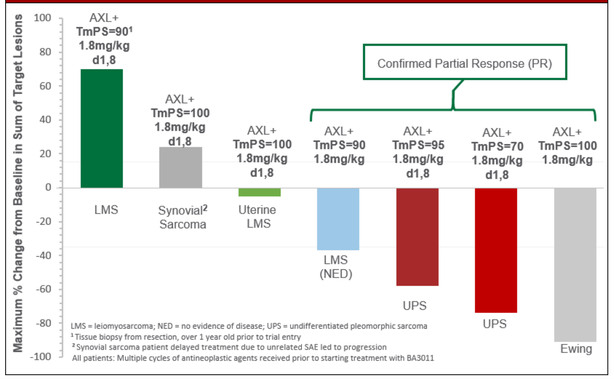


Figure 2. Percent Change in Sum of Target Lesions (Best Response) by AXL TmPS Category – Evaluable Sarcoma Patients in Phase 1 at All Doses Tested

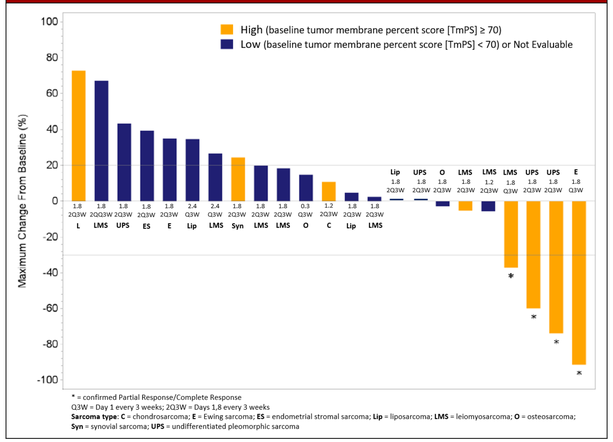
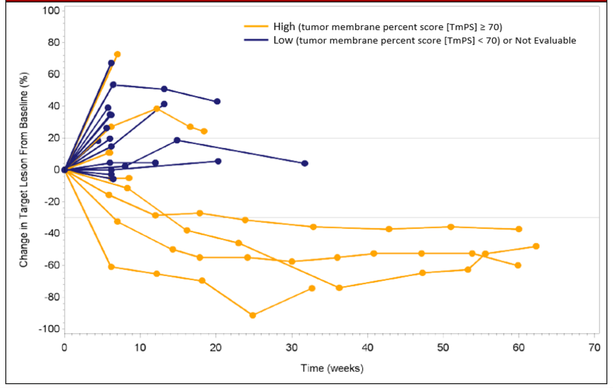


Figure 3. Percent Change in Sum of Target Lesions by Visit and AXL TmPS Category – Evaluable Sarcoma Patients in Phase 1 at All Doses Tested



CONCLUSIONS

- Based on preliminary efficacy and safety results from this study, the benefit-risk profile of BA3011 monotherapy appears to be favorable in patients with sarcoma.
- No clinically meaningful on-target toxicity was observed.
- In Phase 1 sarcoma patients, evidence of antitumor activity was observed, with higher AXL tumor membrane expression correlating with response.
- These results suggest focused enrollment of patients with high levels of AXL tumor membrane expression may result in increased clinical benefit.
- AXL appears to be expressed at a consistent rate throughout all sarcoma subtypes tested; a larger sample size for some subtypes is required to confirm these findings. Phase 2 is ongoing in patients with AXL-expressing advanced treatment refractory sarcoma.

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