Exploratory Analysis of Overall Survival among Non-Small Cell Lung Cancer (NSCLC) Patients with Mutated KRAS in a Phase 2 Trial of Mecbotamab Vedotin (CAB-AXL-ADC)

Poster #98P

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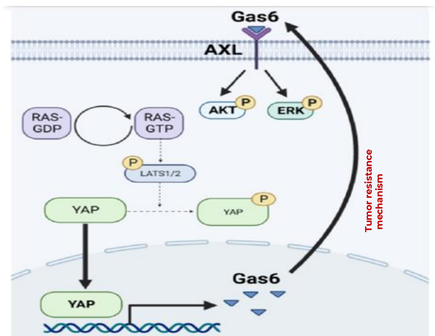
Background

- Activating mutations in KRAS are associated with a more aggressive clinical phenotype and is a poor prognostic factor for DFS and OS in NSCLC.[1-4]
- High unmet need remains for pts with treatment-refractory KRAS-mutated NSCLC; ORR and mOS previously reported as 9.2%-13.2% and 11.3 months, respectively, when treated with docetaxel.[5,6]
- 30% of pts NSCLC tumors harbor activating gene mutations of KRAS.
- No agents have received full marketing authorization for mKRAS NSCLC.

AXL overexpression drives adaptive resistance to KRAS inhibitors and immune checkpoint inhibitors.[7,8]

- AXL, a cell-surface transmembrane RTK signaling mediates adaptive resistance to mKRAS tumors due to upregulation of the AXL ligand GAS6 **(Figure 1).**[7]
- Part of the TAM receptor tyrosine kinase family (including TYRO3 and MER RTK), AXL has been associated with poor prognosis in cancer patients.[8]
- AXL expression is common in treatment-resistant tumors.[9,10]
  - Drives cell growth, stemness, survival, migration and EMT transition. Its presence on cancer cells is a poor prognostic indicator.
  - AXL overexpression enables adaptive resistance to KRAS inhibitors and immune checkpoint inhibitors (ICI).[7,8]
  - KRAS activation leads to changes in gene expression, including induction of AXL expression.[11]
- **mKRAS and AXL co-expression is functionally linked, driving treatment resistance.**
  - 70-85% of mKRAS NSCLC expresses AXL by IHC, greater based on mRNA expression.
  - AXL expression is frequently observed in treatment resistant tumors[4-8] and mKRAS is an oncogenic driver stimulating AXL signaling and control of EMT.[7,9,10,12,13]

Figure 1. Mutated KRAS leads to upregulation and activation of AXL expression.



Adapted from Morimoto et al. Cancer Letters 587 (April 2024)

The AXL targeted ADC, mecbotamab vedotin (Mec-V) drives immunogenic cell death via its auristatin payload (MMAE).

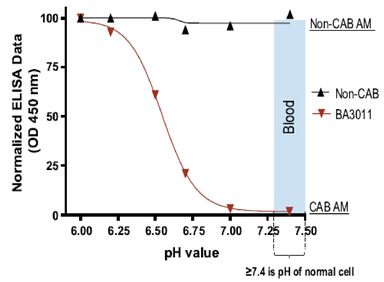
Mecbotamab vedotin (Mec-V; BA3011) is a Conditionally Active Biologic (CAB) anti-AXL ADC (CAB-AXL-ADC)

CABs are:

- Engineered to conditionally and reversibly bind to AXL under the low-pH conditions (pH 5.3–6.7) on the surface of cancer cells, thus sparing normal tissues. **(Figure 2)**
- Not masked or caged like prodrugs and therefore does not require enzymatic cleavage for activation.
- Designed to reduce off-tumor AEs without increasing immunogenicity, avoid tissue-mediated drug disposition, and improve PK.

- Mec-V:
  - Has a drug-to-antibody ratio (DAR) of 4 with a protease cleavable linker-payload (vcMMAE) for release in the cytoplasm of the cancer cell.
  - CAB selectively enables targeting of AXL-expressing tumor cells to induce ICD.[16]
  - The MMAE payload used by Mec-V contributes to immune control, thereby combining direct cytotoxicity with immune modulation, which likely converts NSCLC to a more indolent disease, supporting the observed improved OS.[8,17]
- Mec-V can eliminate AXL expressing cancer initiating cells that drive treatment resistance and subsequent treatment failure.[14]
- Resulting cell death drives immunologic response that may further contributes to improved OS.[15]

Figure 2. Mec-V binds to target antigen under TME conditions.



Binding of Mec-V to human AXL at different pH conditions was determined by ELISA. CABs preferentially bind at tumor pHs (5.3-6.7) and do not bind at the alkaline pH of healthy cells (≥7.4).

Methods

Study Design

- This multicenter, Phase 2, open-label trial evaluated the efficacy and safety of BA3011 in advanced, treatment-refractory NSCLC.
- Eligible patients included confirmed locally advanced or metastatic NSCLC, age ≥18 years, ECOG performance status of 0 or 1, treatment failure of a PD-1/L1 inhibitor or approved therapy for EGFR or ALK genomic tumor aberrations, AXL+ tumor staining (TmPS ≥1%).
- Pts received either Mec-V 1.8 mg/kg monotherapy Q2W or Q2W +/- nivolumab.

Results

All results are from a data cut of January 18, 2025, unless otherwise specified.

Screened population

- 113 screening samples were evaluated for KRAS mutation status and AXL expression by IHC assay.
- Multiple variants of the KRAS mutation were detected in 27 screening samples.
- AXL was expressed by NSCLC tumors among 19 of 27 pts with mKRAS NSCLC (70% AXL-positive, TMPS ≥ 1%).
- 9 of 11 (82%) samples with the G12C KRAS mutation were AXL-positive (TMPS ≥ 1%).

Patient disposition

78 pts with refractory stage IV NSCLC were enrolled and received either Mec-V monotherapy or Mec-V + nivolumab.

- 45 of 78 pts (58%) received Mec-V Q2W. **(Table 1)**
- 17 of 45 pts (31%) had KRAS-mutated tumors.
- Most pts (60%) had PD-L(1) positive tumor expression.
- Median of 19.3 months follow-up.

Prior therapies among mKRAS NSCLC pts receiving Mec-V Q2W (n=17)

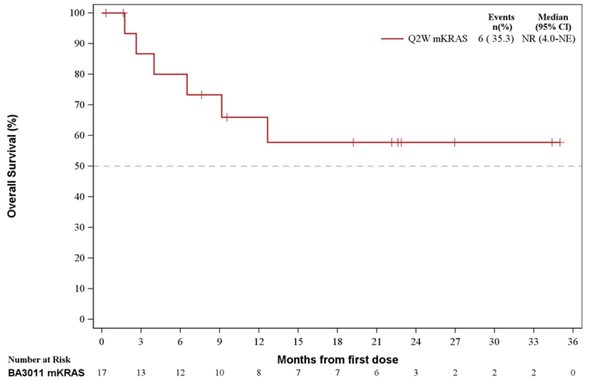
- Heavily pre-treated population – pts received a median of 3 prior lines of therapy.
- All pts received prior anti-PD-1; 15 pts received prior platinum therapy.

Results continued

Table 1. Clinical characteristics of 45 pts who received Mec-V Q2W.

	Q2W (n=26)	Q2W + nivo (n=19)	Total (N=45)
Age, mean (range), y	67 (53–80)	68 (50–81)	67 (46–82)
Sex, n (%)			
Male	13 (50)	8 (42)	21 (47)
Female	13 (50)	11 (58)	24 (53)
ECOG performance, n (%)			
0	8 (31)	3 (16)	11 (24)
1	18 (69)	16 (84)	34 (75)
KRAS mutation status, n (%)			
wtKRAS	15 (58)	12 (63)	27 (60)
mKRAS	10 (38)	7 (37)	17 (38)
Unknown	1 (4)	0	1 (2)
# of Prior Systemic Therapy (%)			
1	4 (15)	2 (11)	6 (13)
2	7 (27)	5 (26)	12 (27)
3+	15 (58)	12 (12)	27 (60)
Prior Anti-PD-(L)1 Therapy	23 (89)	18 (95)	41 (91)

Figure 3. Overall survival of 17 pts with mKRAS NSCLC who received Mec-V Q2W.



Efficacy among 16 pts with mKRAS NSCLC who received Mec-V Q2W*

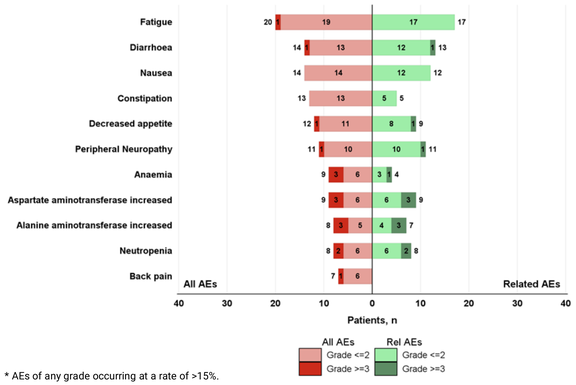
- Disease control rate = 81% (13/16)
- Objective response rate = 25% (4/16)
- Overall survival (Figure 3):
  - 1-year: 66% (95% CI: 37-84)
  - 2-year: 58% (95% CI: 29-79)
- Median OS not reached (95% CI: 4.0-not estimable [NE])

* One treated pt withdrew consent for follow-up evaluation.

Safety among 45 treated pts who received Mec-V Q2W (Figure 5)

- All grade: fatigue (44%), diarrhea (31%), nausea (31%), constipation (29%), decreased appetite (27%), peripheral neuropathy (24%).
- G3/4: AST elevation (7%), ALT elevation (7%), anemia (7%).
- Most related AEs were low grade.
- Related G3/4 AEs occurred in 12 of 45 pts (27%).
- No related G5 AEs were observed.
- Four (9%) pts discontinued treatment due to related AEs.

Figure 5. Most frequent* AEs among 45 pts who received Mec-V Q2W.



* AEs of any grade occurring at a rate of >15%.

Conclusions

- **Mec-V, an CAB-AXL-targeting ADC, achieved landmark overall survival of 66% and 58%, at one- and two-years, respectively, among patients with treatment-refractory mKRAS NSCLC.**
- **Mec-V provided pan-mKRAS antitumor activity with a manageable safety profile.**
- **Prolonged patient survival was observed after Mec-V treatment, regardless of the heterogeneous subsequent therapies that patients received, potentially differentiating Mec-V from other mKRAS NSCLC therapies.**

Abbreviations

2Q3W, twice every 3 weeks; ADC, antibody-drug conjugate; AE, adverse event; ALK, anaplastic lymphoma kinase; BA3011, mecbotamab vedotin; BTD, Breakthrough Therapy designation; CI, confidence interval; DFS, disease-free survival; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; EMT, epithelial-to-mesenchymal transition; KRAS, Kirsten rat sarcoma oncogene homologue; mKRAS, mutated Kirsten rat sarcoma oncogene homologue; MMAE, monomethyl auristatin E; NE, not estimable; NSCLC, non-small cell lung cancer; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1/L1, programmed cell death protein 1/ligand 1; Q2W, once every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; RTK, receptor tyrosine kinase; SD, standard deviation; TMPS, tumor membrane percent score.

Acknowledgements and Funding

This study was funded by BioAtla, Inc.

Clinical Trial Identifier

A Phase 2 Multi-center, Open-label Study Of BA3011 As Monotherapy And In Combination With PD-1 Inhibitor in Patients With NSCLC Who Had Prior Disease Progression On PD-1.
Clinical Trial Registry Number: NCT0468131.

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Disclosures

KLR: Consulting or advisory role with: AstraZeneca, Genentech, Daiichi Sankyo/Lilly, Janssen Oncology, GlaxoSmithKline, Novocare, Merus, Pfizer, and Novartis; Research funding from: Genentech/Roche, Janssen Oncology, Elevation Oncology, Daiichi Sankyo/Astra Zeneca, and Blueprint Medicines.

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