Characterization of Mutated KRAS Genotype and Clinical Outcomes in Patients With Advanced NSCLC Treated With Mecbotamab Vedotin, a CAB-AXL-ADC

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Background

- 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 mo, respectively, when treated with docetaxel.[1,2]
- KRAS mutations:
  - Occur in ≈30% of pts with NSCLC, with KRAS G12C (40%) being the most prevalent alteration.[3]
  - Associated with increased AXL expression, with 85% of pts with KRAS G12C-mutated NSCLC overexpressing AXL.[4]
- Mutant KRAS (mKRAS) and AXL co-expression is linked, driving treatment resistance **(Figure 1)**.
- AXL is a cell-surface, transmembrane receptor protein tyrosine kinase highly expressed in several solid tumor types.[5-7]
- AXL overexpression enables adaptive resistance to KRAS inhibitors and immune checkpoint inhibitors.[4,8]
- In lung cancers, upregulation of AXL is associated with poorer clinical outcomes.[5-7]
- Mecbotamab vedotin (Mec-V; BA3011) is a Conditionally Active Biologic anti-AXL ADC (CAB-AXL-ADC).
- CABs:
  - Conditionally and reversibly bind to AXL under the low-pH conditions (pH 5.3–6.7) of the TME, sparing normal tissues **(Figures 2 and 3)**.
  - Not masked or caged and do not require enzymatic cleavage for activation.
  - Reduce off-tumor AEs without increasing immunogenicity, avoid tissue-mediated drug disposition, and improve PK.[9]
- As reported at the IASLC North America 2023 meeting, Mec-V Q2W monotherapy showed promising antitumor activity in pts with extensively pretreated, post–anti-PD-(L)1 therapy, non-squamous NSCLC with AXL expression (RR, 27.8%).
- This exploratory analysis characterized the antitumor activity of Mec-V in pts with mKRAS NSCLC.

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

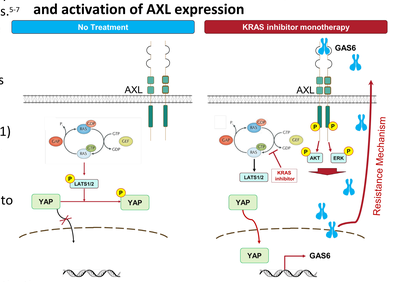
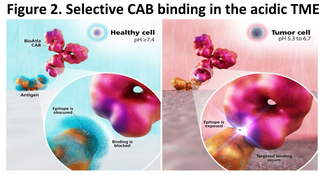
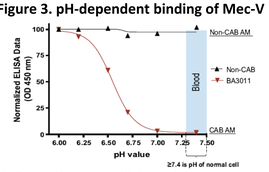


Figure 2. Selective CAB binding in the acidic TME



Note: The acidity of the tumor cell surface unveils binding sites on targets that are normally shielded in a physiologic pH environment ≥7.4. CABs bind to these unveiled sites on cancer cells that are otherwise shielded on healthy cells.

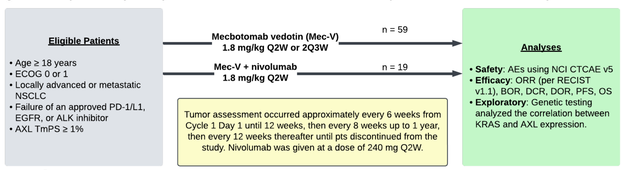
Figure 3. pH-dependent binding of Mec-V



Note: 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

Figure 4. Exploratory analysis of KRAS variants and AXL co-expression in Phase 2 study



Results

Screened Population

- 113 screening samples were evaluated for KRAS mutation status and AXL expression by IHC assay.
- KRAS mutation was detected in 27 screening samples.
  - 19 of 27 (70.3%) AXL-positive (TmPS ≥ 1%).
  - 9 of 11 (82%) samples with the G12C KRAS mutation were AXL-positive (TmPS ≥ 1%).

Disposition

- All results are from a live database of October 24, 2024, unless otherwise specified.
- 78 pts with AXL-positive stage IV NSCLC were enrolled and received either Mec-V monotherapy (n=59) or Mec-V + nivolumab (n=19); 24 pts (31%) had KRAS-mutated tumors **(Table 1)**.
- Heavily pretreated population: pts received a median of 3 prior lines of therapy.
- Most pts (60.3%) had PD-L(1) positive tumor expression.
- All pts with mKRAS NSCLC (n=24) and 86% of pts with wtKRAS NSCLC (n=50) received prior anti-PD-(L)1.

Results (continued)

Table 1. Patient clinical characteristics

	Q2W (n=26)	2Q3W (n=33)	Q2W + nivo (n=19)	Total (N=78)
Age, mean (range), y	67 (53–80)	67 (46–82)	68 (50–81)	67 (46–82)
Sex, n (%)				
Male	13 (50)	16 (49)	8 (42)	37 (47)
Female	13 (50)	17 (52)	11 (58)	41 (53)
ECOG performance, n (%)				
0	8 (31)	7 (21)	3 (16)	18 (23)
1	18 (69)	26 (79)	16 (84)	60 (77)
KRAS mutation status, n (%)				
wtKRAS	15 (58)	23 (70)	12 (63)	50 (64)
mKRAS	10 (38)	7 (21)	7 (37)	24 (31)
Unknown	1 (4)	3 (9)	0	4 (5)[a]
# of Prior Systemic Therapy (%)				
1	4 (15)	3 (9)	2 (11)	9 (12)
2	7 (27)	8 (24)	5 (26)	20 (26)
3+	15 (58)	22 (67)	12 (12)	49 (63)
Prior Therapies				
Anti-PD-(L)1	23 (89)	30 (91)	18 (95)	71 (91)

[a]Two responders did not have an additional biopsy sample for KRAS mutation assessment.

Safety (as of July 10, 2024)

- Among all pts (N=78), most related AEs were low grade; no grade 5 related AEs were observed **(Table 2)**; 6 (7%) pts discontinued treatment owing to related AEs.
- Most frequent AEs (all grades): fatigue (36%), diarrhea (33%), decreased appetite (32%), neuropathy (31%) **(Table 3)**. Most frequent grade 3-4 AEs: neutropenia (13%), anemia (5%).

Table 2. Summary of AEs

Number of pts with any, n (%)	Q2W (n=26)	2Q3W (n=33)	Q2W + nivolumab (n=19)	Total (N=78)
AE	26 (100)	33 (100)	19 (100)	78 (100)
Related grade 3 or 4 AE[a]	10 (39)	12 (36)	4 (21)	28 (33)
Related serious AE	4 (15)	3 (9)	1 (5)	8 (9)
Related AE leading to treatment discontinuation	1 (4)	4 (12)	1 (5)	6 (7)
Related AE leading to death	0	0	0	0

Note: Relatedness was assessed by the investigator. Missing responses were counted as related.
[a]No grade 5 related AEs were observed.

Table 3. Most frequent AEs of any grade (>15% of patients)

	Q2W (n=26)		2Q3W (n=33)		Q2W + nivolumab (n=19)		Total (N=78)	
	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4	All grades	Grade 3–4
Number of pts with any AE, n (%)	26 (100)	17 (65)	33 (100)	18 (55)	19 (100)	9 (47)	78 (100)	44 (56)
Fatigue	12 (46)	1 (4)	8 (24)	2 (6)	8 (42)	0	28 (36)	3 (4)
Diarrhea	8 (31)	1 (4)	12 (36)	2 (6)	6 (32)	0	26 (33)	3 (4)
Decreased appetite	6 (23)	1 (4)	13 (39)	0	6 (32)	0	25 (32)	1 (1)
Neuropathy[a]	8 (31)	1 (4)	12 (36)	0	4 (21)	0	24 (31)	1 (1)
Nausea	6 (23)	0	9 (27)	0	8 (42)	0	23 (29)	0
Neutropenia[b]	9 (35)	3 (12)	8 (24)	7 (21)	1 (5)	0	18 (23)	10 (13)
Constipation	8 (31)	0	9 (27)	1 (3)	5 (26)	0	22 (28)	1 (1)
Anemia	3 (12)	1 (4)	5 (15)	1 (3)	6 (32)	2 (11)	14 (18)	4 (5)
AST increased	5 (19)	2 (8)	5 (15)	0	4 (21)	1 (5)	14 (18)	3 (4)
ALT increased	5 (19)	2 (8)	5 (15)	0	3 (16)	1 (5)	13 (17)	3 (4)
Arthralgia	3 (12)	0	7 (21)	0	3 (16)	0	13 (17)	0
Back pain	4 (15)	0	7 (21)	0	3 (16)	1 (5)	14 (18)	1 (1)

[a]Derived from neuropathy peripheral, peripheral motor neuropathy, and peripheral sensory neuropathy.
[b]Derived from neutropenia and neutrophil count decreased.

Efficacy

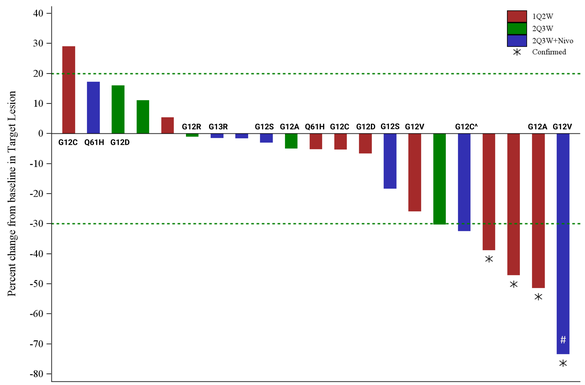
- Among 21 evaluable pts with mKRAS NSCLC (3 with G12C mutations):
  - 6 responses (ORR, 28.6%; including 1 pt previously treated with sotorasib) **(Table 4, Figure 5)**.
  - 1 pt treated with Mec-V + nivolumab Q2W continues in CR after >2 years of follow-up.
- Median overall survival with mKRAS tumor genotype was not reached (6.5-NE; 1 year OS >50%) vs 8.7 (5.8-10.2) mo for pts with wtKRAS **(Figure 7)**.

Table 4. Efficacy of Mec-V among evaluable[a] patients with mKRAS NSCLC

Efficacy analyses	mKRAS NSCLC (N=21)
Responses, confirmed + unconfirmed[b]	6 (29%)
Responses, confirmed[b]	4 (19%)
Disease control rate[c]	15 (71%)
Duration of confirmed response, median (95% CI)	4.8 mo (2.3-NE)
Progression-free survival, median (95% CI)	4.6 mo (1.7-5.3)
Overall survival, median (95% CI)	Not reached (6.5-NE)

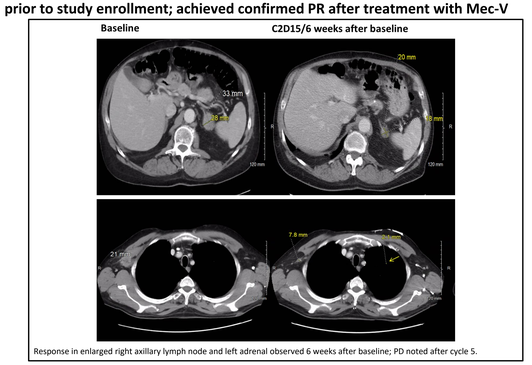
[a]Evaluable pts had at least 1 scan after treatment with study drug. Prior to the first scan, 2 pts withdrew consent, and 1 pt discontinued owing to AE.
[b]Expressed as n (%).
[c]Disease control was defined as any CR, PR, or SD.

Figure 5. Best percentage change from baseline in target lesion (n=21 evaluable patients)



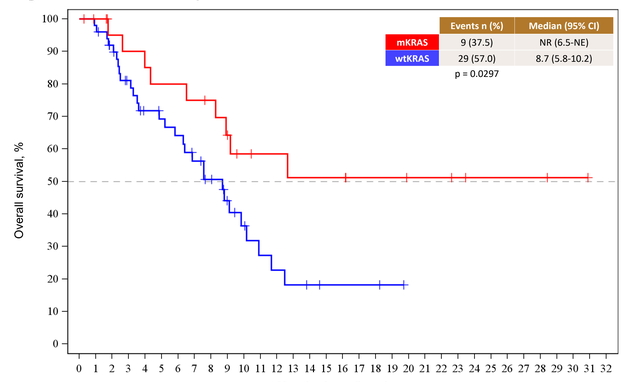
^Pt previously treated with sotorasib.
#Complete response, as defined by the disappearance of all pathologic lymph nodes.

Figure 6. Radiological scans of a 60-year-old man with KRAS G12C–mutated lung adenocarcinoma who experienced progression after docetaxel and sotorasib therapy prior to study enrollment; achieved confirmed PR after treatment with Mec-V



Response in enlarged right axillary lymph node and left adrenal observed 6 weeks after baseline; PD noted after cycle 5.

Figure 7. Overall survival in patients with mKRAS vs wtKRAS NSCLC treated with Mec-V



Note: Analysis is ongoing with several patients in long-term survival follow-up.

Conclusions

- **Among all Mec-V-treated pts with NSCLC, mOS was meaningfully longer among pts with tumors expressing mKRAS (not reached: 1 year OS >50%) vs wtKRAS (8.7 mo).**
- **Pan-mKRAS activity evidenced by multiple antitumor responses observed across 9 different mKRAS variants.**
- **AXL was highly expressed by mKRAS NSCLC.**
- **Treatment with Mec-V was well tolerated with a manageable safety profile.**
- **A randomized trial of Mec-V vs standard of care is planned for pts with treatment-refractory mKRAS NSCLC.**

References

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Abbreviations

2Q3W, days 1 and 8 every 21 days; ADC, antibody–drug conjugate; AE, adverse event; ALK, anaplastic lymphoma kinase; BOR, best overall response; CAB, conditionally active biologic; CI, confidence interval; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ELISA, enzyme-linked immunosorbent assay; IHC, immunohistochemistry; KRAS, kirsten rat sarcoma virus; Mec-V, mecbotamab vedotin; mKRAS, mutant KRAS; mOS, median overall survival; NCI, National Cancer Institute; NE, not estimable; NSCLC, non–small cell lung cancer; NR, not reached; ORR, objective response rate; OS, overall survival; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PFS, progression free survival; PK, pharmacokinetics; pt, patient; Q2W, once every 2 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; TME, tumor microenvironment; TmPS, tumor membrane percent score; v, version; wtKRAS, wild-type KRAS.

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