PP01.104 - Vebreltinib Efficacy In *MET*ex14 Mutant NSCLC With or Without Concurrent *MET* Amplification, *MET* GCN Status Distributions Compared With Public Databases

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Introduction

- Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer, accounting for more than two-thirds of the cases, with a 5-year relative survival of only 21.7% in US. Approximately 3-4% of NSCLCs harbor *MET* exon 14 skipping mutations (*MET*ex14), and 1-6% NSCLCs contain *MET* amplification (*MET*amp).
- *MET*ex14 and *MET*amp are both independently targetable with MET tyrosine kinase inhibitors. Clinical trials with a number of MET inhibitors in NSCLC have selected patients with *MET*ex14, regardless of co-existence of *MET*amp status, measured by *MET* gene copy number (GCN). However, the distribution by *MET*amp status in *MET*ex14 NSCLC patients in those trials has yet been shown to reflect those of real-world patient population and the influence of these alterations on treatment sensitivity has not been widely published.
- Vebreltinib (APL-101, PLB1001, bozitinib) is an oral available small molecule, a tyrosine kinase inhibitor with high selectivity and potency for MET tyrosine kinase receptor. It is approved by the NMPA in China for the treatment of NSCLC with *MET*ex14. It is under-investigation for the treatment of a number of tumors with *MET* alterations worldwide.
- SPARTA-II and KUNPENG are both ongoing Phase 2, multi-cohort, open-label studies to evaluate efficacy and safety of vebreltinib in NSCLC patients with *MET* abnormalities.
- We describe the frequency of co-occurrence of *MET*ex14 and *MET*amp in NSCLC as well as the efficacy of the highly-selective MET inhibitor vebreltinib in *MET*ex14-mutant NSCLC with and without concurrent *MET*amp.

Methods

- Data from AACR Project GENIE and cBioPortal websites (queried May 8, 2023) were analyzed to determine the real-world distribution of *MET* GCN status in *MET*ex14 mutated NSCLCs
- NSCLC with *MET*ex14 patients with available GCN data from two ongoing open-label phase 2 studies, SPARTA-II (NCT03175224) and KUNPENG (NCT04258033), treated with vebreltinib, were analyzed for determining GCN distribution and to explore the efficacy of vebreltinib in *MET*ex14 NSCLC with or without *MET*amp.
- Eligible patients received vebreltinib 200 mg, twice a day orally as monotherapy for advanced NSCLC with *MET*ex14 abnormality with or without *MET*amp.
- Patients who had GCN assessment and first dosed prior to 2022-08-31 in SPARTA-II and who first dosed prior to 2021-12-31 in KUNPENG are included.
- Primary endpoint is overall response rate (ORR), supported by duration of treatment (DOR) and disease control rate (DCR). Safety assessment include treatment-emergent adverse events and clinical labs.
- Confirmed overall response is defined as complete response (CR) or partial response (PR) during the treatment period, confirmed by a subsequent evaluation no less than 4 weeks apart.
- Disease control rate (DCR) is defined as the rate of best overall response CR or PR or SD during the treatment period.

Demographics and Baseline Characteristics

- A total of 83 NSCLC patients with *MET*ex14 mutations and available GCN data were included in the analysis (50 patients from KUNPENG and 33 patients from SPARTA-II).
- Baseline characteristics were generally balanced in patients who received vebreltinib in these two ongoing phase 2 studies.
- The median treatment duration was 9.56 months, with SPARTA-II of 9.72 months and KUNPENG of 8.99 months.

		SPARTA-II (N=33)	KUNPENG (N=50)	Combined (N=83)
Age (years)	Mean (SD)	69.7 (9.2)	70.8 (8.1)	70.4 (8.5)
Gender, n (%)	Female	23 (69.7)	22 (44.0)	45 (54.2)
	Male	10 (30.3)	28 (56.0)	38 (45.8)
Race, n (%)	Asian	2 (6.1)	50 (100.0)	52 (62.7)
	White	29 (87.9)	0	29 (34.9)
	Other	2 (6.0)	0	2 (2.4)
Smoking History	Yes	16 (48.5)	18 (36.0)	34 (41.0)
	No	17 (51.5)	31 (62.0)	48 (57.8)
Baseline ECOG, n (%)	0	14 (42.4)	5 (10.0)	19 (22.9)
	1	19 (57.6)	45 (90.0)	64 (77.1)
Weight (kg)	Mean (SD)	66.4 (18.5)	59.9 (11.2)	62.5 (14.8)
Histology at diagnosis	Adenocarcinoma	27 (81.8)	43 (86.0)	70 (84.3)
	Large cell carcinoma	0	1 (2.0)	1 (1.2)
	Squamous cell carcinoma	4 (12.1)	1 (2.0)	5 (6.0)
	Other	2 (6.1)	4 (8.0)	6 (7.2)
Median Time from Diag. to First Dose (months)	All	6.5	1.3	2.0
	Naïve	2.2	0.9	1.4
	Previously treated	15.7	2.0	7.9
Staging at study entry	IIB	1 (3.0)	0	1 (1.2)
	IIIB/IIIC	1 (3.0)	8 (16.0)	9 (10.8)
	IV/IVA/IVB	31 (93.9)	42 (84.0)	73 (88.0)
Previously treated status, n (%)	Naïve	17 (51.5)	33 (66.0)	50 (60.2)
	Previously treated	16 (48.5)	17 (34.0)	33 (39.8)
Type of prior systemic cancer treatments, n (%)*	Chemotherapy only	2 (12.5)	12 (70.6)	14 (42.4)
	Immunotherapy(IO) only	2 (12.5)	1 (5.9)	3 (9.1)
	Chemotherapy + IO	12 (75.0)	4 (23.5)	16 (48.5)
Type of prior chemo-therapy, n (%)*	Platinum-containing agents	14 (87.5)	15 (88.2)	29 (87.9)
	Pemetrexed (anti-folate)	12 (75.0)	12 (70.6)	24 (72.7)
	Taxanes	6 (37.5)	2 (11.8)	8 (24.2)

Note: * Percentages are based on the number of previously treated patients who were pretreated refractory to or intolerant of standard therapies with no more than 3 lines of prior therapy excluding MET inhibitors. Two patients in SPARTA-II and three patients in KUNPENG used targeted therapy.

Results

Distribution by Gene Copy Number in Public Database and Vebreltinib Program

	# NSCLC	# NSCLC with *MET*ex14 & available GCN	Patient Distribution (%) GCN <4	GCN <6	GCN ≥6
AACR GENIE Patients (Public Database)	26141	428	83.6%	92.1%	7.9%
cBioPortal Patients (Public Database)	22018	210	91.9%	92.9%	7.1%
Vebreltinib Patients with GCN		83	91.6%	97.6%	2.4%

Distribution by Gene Copy Number in Vebreltinib Program

	SPARTA-II	KUNPENG	Combined
# *MET*ex14 NSCLC patients with GCN	33	50	83
GCN <4	31 (93.9%)	45 (90.0%)	76 (91.6%)
GCN 4 -<6	1 (3.0%)	4 (8.0%)	5 (6.0%)
GCN ≥6	1 (3.0%)	1 (2.0%)	2 (2.4%)

- Of *MET*ex14 NSCLC patients with available GCN data, 91.6% of the 83 NSCLC patients with GCN<4 (93.9% in SPARTA-II and 90% in KUNPENG, respectively) is quite close to 83.6% in AACR GENIE and 91.9% in cBioPortal public databases.

Response to Vebreltinib in NSCLC Patients with GCN <4 and ≥4 Assessed by IRC

	GCN < 4 SPARTA-II (N=31)	GCN < 4 KUNPENG (N=45)	GCN < 4 Combined (N=76)	GCN ≥ 4 SPARTA-II (N=2)	GCN ≥ 4 KUNPENG (N=5)	GCN ≥ 4 Combined (N=7)
Confirmed ORR, % (n)	54.8 (17)	71.1 (32)	64.5 (49)	50.0 (1)	100.0 (5)	85.7 (6)
95% CI*	[36.0, 72.7]	[55.7, 83.6]	[52.7, 75.1]	[1.3, 98.7]	[47.8, 100.0]	[42.1, 99.6]
Median DOR, Months	11.2	15.9	15.9	NR	NR	NR
95% CI	6.6, NE	5.6, 19.1	9.2, 17.9	NE, NE	3.7, NE	3.7, NE
Probability with DOR ≥ 12 Months	46.6%	51.2%	50.3%	100%	60.0%	66.7%
Disease Control Rate	77.4 (24)	95.6 (43)	88.2 (67)	100.0 (2)	100.0 (5)	100.0 (7)
95% CI*	[58.9, 90.4]	[84.9, 99.5]	[78.7, 94.4]	[15.8, 100.0]	[47.8, 100.0]	[59.0, 100.0]

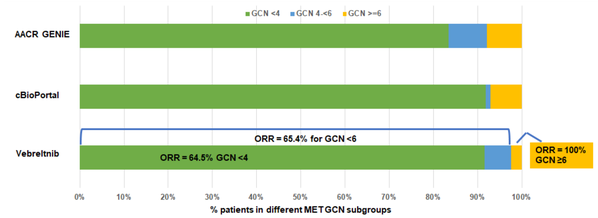
Note: CI = confidence interval; IRC: independent review committee; NE: not estimable; NR: not reached. *95% CI is estimated by using Clopper-Pearson method.

Response to Vebreltinib in NSCLC Patients with GCN <6 and ≥6 Assessed by IRC

	GCN < 6 SPARTA-II (N=32)	GCN < 6 KUNPENG (N=49)	GCN < 6 Combined (N=81)	GCN ≥ 6 SPARTA-II (N=1)	GCN ≥ 6 KUNPENG (N=1)	GCN ≥ 6 Combined (N=2)
Confirmed ORR, % (n)	53.1 (17)	73.5 (36)	65.4 (53)	100.0 (1)	100.0 (1)	100.0 (2)
95% CI*	[34.7, 70.9]	[58.9, 85.1]	[54.0, 75.7]	[2.5, 100.0]	[2.5, 100.0]	[15.8, 100.0]
Median DOR, Months	11.2	15.9	15.9			
95% CI	6.6, NE	9.2, 19.1	9.2, 17.9			
Probability with DOR ≥ 12 Months	46.6%	51.0%	50.3%			
Disease Control Rate	78.1 (25)	95.9 (47)	88.9 (72)			
95% CI*	[60.0, 90.7]	[86.0, 99.5]	[80.0, 94.8]			

Note: CI = confidence interval; IRC: independent review committee; NE: not estimable. *95% CI is estimated by using Clopper-Pearson method.

Overall Response Rate in *MET*ex14 NSCLC Patients with Different GCN



Treatment-Related Adverse Events Reported in >10% NSCLC with METex14

Preferred Term	SPARTA-II (N=33) All Grades n (%)	SPARTA-II (N=33) Grade ≥ 3 n (%)	KUNPENG (N=50) All Grades n (%)	KUNPENG (N=50) Grade ≥ 3 n (%)	Combined (N=83) All Grades n (%)	Combined (N=83) Grade ≥ 3 n (%)
Any Treatment-Related TEAEs	31 (93.9)	12 (36.4)	49 (98.0)	23 (46.0)	80 (96.4)	35 (42.2)
Edema	24 (72.7)	4 (12.1)	41 (82.0)	7 (14.0)	65 (78.3)	11 (13.3)
Hypoalbuminaemia	6 (18.2)	0	15 (30.0)	0	21 (25.3)	0
Alanine aminotransferase increased	8 (24.2)	2 (6.1)	12 (24.0)	4 (8.0)	20 (24.1)	6 (7.2)
Anaemia	3 (9.1)	0	13 (26.0)	1 (2.0)	16 (19.3)	1 (1.2)
Blood creatinine increased	2 (6.1)	0	14 (28.0)	0	16 (19.3)	0
Electrocardiogram QT prolonged	0	0	15 (30.0)	1 (2.0)	15 (18.1)	1 (1.2)
Nausea	8 (24.2)	0	7 (14.0)	0	15 (18.1)	0
Pruritus	3 (9.1)	0	11 (22.0)	0	14 (16.9)	0
Aspartate aminotransferase increased	6 (18.2)	2 (6.1)	7 (14.0)	3 (6.0)	13 (15.7)	5 (6.0)
Platelet count decreased	3 (9.1)	0	8 (16.0)	2 (4.0)	11 (13.3)	2 (2.4)
Weight increased	0	0	11 (22.0)	0	11 (13.3)	0
Hypocalcemia	1 (3.0)	0	9 (18.0)	0	10 (12.0)	0
Hypoproteinemia	0	0	10 (20.0)	0	10 (12.0)	0
Lipase increased	1 (3.0)	1 (3.0)	9 (18.0)	2 (4.0)	10 (12.0)	3 (3.6)
Amylase increased	4 (12.1)	0	5 (10.0)	0	9 (10.8)	0
Rash	4 (12.1)	0	5 (10.0)	0	9 (10.8)	0
Vomiting	3 (9.1)	0	6 (12.0)	0	9 (10.8)	0

Note: edema includes edema peripheral, generalized edema, face edema, edema, localized edema, edema genital, eyelid edema, peripheral swelling, scrotal edema, and penile edema.

- The incidence of treatment-related TEAEs was generally similar between two studies; treatment-related TEAEs of grade 3 or higher were reported in 42.2% of patients, with the most common being edema (13.3%) and ALT increase (7.2%).

Conclusions

- The majority of *MET*ex14 NSCLCs do not have co-occurring *MET*amp. The distribution of *MET* GCN status (whether with or without co-occuring *MET*amp) in *MET*ex14 NSCLC patients in vebreltinib phase 2 studies is similar to those in public databases.
- Vebreltinib appears efficacious in *MET*ex14 NSCLCs with or without co-occurring *MET*amp, particularly note-worthy in those with GCN<4. The safety profile is generally acceptable.

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We thank patients, their families and caregivers for participating in this clinical trial research staff / study teams at each participating site

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