Abstract #8557: **Efficacy and Safety of Vebreltinib in Patients with Advanced NSCLC Harboring MET Exon 14-Skipping: Results of 2.5-year follow-up in KUNPENG**

Jin-Ji Yang[1], Yan Zhang[2], Lin Wu[3], Jie Hu[4], Zhe-Hai Wang[5], Jing-Hua Chen[6], Yun Fan[7], Gen Lin[8], Qi-Ming Wang[9], Yu Yao[10], Jun Zhao[11], Yuan Chen[12], Jian Fang[13], Yong Song[14], Wei Zhang[15], Ying Cheng[16], Ren-Hua Guo[17], Xing-Ya Li[18], Yi-Long Wu[1]

[1]Guangdong Lung Cancer Institute, Guangdong Provincial People's Hospital and Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou, China; [2]A. Division of Thoracic Tumor Multimodality Treatment, Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China B. Lung Cancer Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China; [3]Thoracic Internal Medicine Oncology Department, Hunan Cancer Hospital, Changsha, China; [4]Pulmonary and critical care medicine, Zhongshan Hospital Affiliated to Fudan University, Shanghai, China; [5]Department of Medical Oncology, Shandong Cancer Hospital and Institute, Shandong First Medical University and Shandong Academy of Medical Sciences, Jinan, China; [6]Department of Medical Oncology, Shenzhen People's Hospital (The Second Clinical Medical College, Jinan University; The First Affifiliated Hospital, Southern University of Science and Technology), Shenzhen, China; [7]Department of Thoracic Medical Oncology, Zhejiang Cancer Hospital, Hangzhou, China; [8]Internal Medicine-Oncology Dept., Fujian Cancer Hospital and Fujian Medical University Cancer Hospital, Fuzhou, China; [9]Respiratory Department, The Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, China; [10]Oncology Department, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China; [11]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Thoracic Oncology, Peking University Cancer Hospital & Institute, Beijing, China; [12]Lung Cancer Department, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China; [13]Lung Cancer Department, Peking University Cancer Hospital & Institute, Beijing, China; [14]Department of Respiratory Medicine, Jinling Hospital, Nanjing University School of Medicine, Nanjing, China; [15]Lung Cancer Department, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; [16]Lung Cancer Department, Jilin Cancer Hospital, Changchun, China; [17]Lung Cancer Department, Jiangsu Provincial People's Hospital, Nanjing, China; [18]Oncology Department, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Background and objectives:

- MET exon 14 skipping mutation is present approximately 3% to 4% of non-small cell lung cancers (NSCLCs) and is associated with poorer survival rates.
- Vebreltinib (PLB1001), is a potent and highly selective c-MET inhibitor.
- Vebreltinib demonstrated superior objective response rate (ORR) benefits in locally advanced or metastatic non-small-cell lung cancer (NSCLC) patients with MET exon 14 (METex14) skipping mutations in the previous analysis of the phase II KUNPENG study .
- Here we present results from 2.5 years of follow-up of patients in cohort 1 in KUNPENG (NCT04258033).

Objectives:

- To investigate the efficacy and safety of vebreltinib in patients with advanced NSCLC harboring MET Exon 14-Skipping.

Methods:

- This is a multicenter, multi-cohort, open label phase II study.
- Tumor tissue was assessed for METex14 skipping mutation using next-generation sequencing (NGS) from CAP or CLIA certificated local or central laboratories.
- Patients in Cohort 1 received 200 mg of vebreltinib twice daily (28 days per cycle) until disease progression, death, AE leading to discontinuation or withdrawal of consent.
- The primary endpoint was ORR assessed by blinded independent review committee (BIRC).
- Secondary endpoints included investigator-assessed (INV) ORR, disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS) and overall survival (OS).

Patients:

- As of the data cutoff date (Aug 09, 2023), 52 patients were enrolled in Cohort 1. The median duration of follow-up was 19.1 months (range, 1.0-42.7) and the median duration of treatment was 9.9 months (range, 0.6-42.7).

Table1:Demographics and Baseline Disease Characteristics in Cohort 1 .

Variables	All (n=52)	Treatment-naive (n=35)	Previously-treated (n=17)
Age, years			
Mean (standard deviation)	71.3(8.3)	71.9(9.0)	70.0(6.5)
Median (min, max)	71.0(53.0,90.0)	71.0(53.0,90.0)	70.0(57.0,80.0)
Sex, n (%)			
Male	29(55.8)	18(51.4)	11(64.7)
Female	23(44.2)	17(48.6)	6(35.3)
Ethnicity, n (%)			
Han	49(94.2)	32(91.4)	17(100.0)
Others	3(5.8)	3(8.6)	0(0.0)
ECOG PS, n (%)			
0	5(9.6)	5(14.3)	0(0.0)
1	47(90.4)	30(85.7)	17(100.0)
Smoking, n (%)*			
Current	3(5.9)	2(5.9)	1(5.9)
Former	16(31.4)	10(29.4)	6(35.3)
Never	32(62.7)	22(64.7)	10(58.8)
Histological subtype, n (%)			
Adenocarcinoma	47(90.4)	31(88.6)	16(94.1)
Squamous carcinoma	1(1.9)	1(2.9)	0(0.0)
Large cell lung cancer	1(1.9)	0(0.0)	1(5.9)
NSCLC, not otherwise specified	3(5.8)	3(8.6)	0(0.0)
Staging, n (%)			
IIIB	5(9.6)	5(14.3)	0(0.0)
IIIC	4(7.7)	3(8.6)	1(5.9)
IV	43(82.7)	27(77.1)	16(94.1)
Previous systematic anti-tumor treatment, n (%)			
Chemotherapy	16(47.1)	0(0.0)	16(94.1)
Target therapy	3(8.8)	0(0.0)	3(17.6)
Immunotherapy	5(14.7)	0(0.0)	5(29.4)

*S04001 missing smoking history information.

Study design:

Cohort 1
advanced NSCLC with c-Met exon 14 mutation who have not received c-Met inhibitor therapy → Vebreltinib 200mg ,BID, 28 days/cycle

Endpoints

- Primary endpoint
  - ORR by blinded independent review committee (BIRC) per RECIST 1.1.
- Secondary endpoints
  - ORR by INV
  - disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS) and overall survival (OS).

Summary:

- Vebreltinib consistently showed promising efficacy and favorable safety in NSCLC patients with METex14 mutations.
- Phase IIIb study is currently ongoing and actively enrolling patients with the goal of accruing 131 patients.

Questions?

yangjinji@gdph.org.cn

Acknowledgments:

We thank the patients, their families and caregivers for their participation in the KUNPENG study. This study is sponsored by Beijing Pearl Biotechnology Co., Ltd. Avistone Biotechnology Limited.2

Efficacy:

- Per BIRC assessment, the ORR was 75% (95% CI: 61.1-86.0), the DCR was 96.2% (95% CI 86.8-99.5), the median duration of response (DoR) was 16.5 months (95% CI 9.2-19.4), the median time to response (TTR) was 1.0 month (95% CI 1.0-2.8) (Table 2).
- The median progression-free survival was 14.3 months (95% CI 6.4-18.2), and the median overall survival (OS) was 20.3 months (95% CI 16.2-29.7) (Figure 1-4). The 3-year OS rate was 35.1% (Table 2).

Table 2. Summary of Efficacy Assessed by BIRC and INV.

Variables	BIRC-assessed Treatment-naive (n=35)	BIRC-assessed Previously-treated (n=17)	BIRC-assessed All (n=52)	Investigator-assessed Treatment-naive (n=35)	Investigator-assessed Previously-treated (n=17)	Investigator-assessed All (n=52)
Objective response rate (%)	27(77.1)	12(70.6)	39(75.0)	26(74.3)	10(58.8)	36(69.2)
95% CI	59.9,89.6	44.0,89.7	61.1,86.0	56.7,87.5	32.9,81.6	54.9,81.3
Best overall response	0	0	0	0	0	0
Complete response (%)	0	0	0	0	0	0
Partial response (%)'	27 (77.1)	12 (70.6)	39 (75.0)	26 (74.3)	10 (58.8)	36 (69.2)
Stable disease (%)	7 (20.0)	4 (23.5)	11 (21.2)	8 (22.9)	4 (23.5)	12 (23.1)
Progressive disease (%)	1(2.9)	0	1(1.9)	1(2.9)	2(11.8)	3(5.8)
Not evaluable (%)	0	1(5.9)	1(1.9)	0	1(5.9)	1(1.9)
Disease control rate (%)	34(97.1)	16(94.1)	50(96.2)	34(97.1)	14(82.4)	48(92.3)
95% CI	85.1,99.9	71.3,99.9	86.8,99.5	85.1,99.9	56.6,96.2	81.5,97.9
Median duration of response, months (95% CI)	17.1(9.2,21.8)	15.3(3.7,19.4)	16.5(9.2,19.4)	16.8(5.6,19.4)	15.7(3.7,NE)	15.7(7.4,20.3)
Median time to response, months (95% CI)	1.0(1.0,1.2)	1.9(0.9,4.6)	1.0(1.0,2.8)	1.0(1.0,2.6)	2.7(0.9,4.4)	1.0(1.0,2.7)
Progression-free survival (95% CI)	14.5(6.3,20.3)	7.7(3.7,20.3)	14.3(6.4,18.2)	12.0(6.5,20.0)	8.2(2.9,22.1)	10.5(6.5,18.2)
Median OS, months (95% CI)	20.3(16.2,NE)	20.7(13.7,NE)	20.3(16.2,29.7)			
36-month OS (95% CI)	38.2(22.1,54.1)	29.4(10.7,51.1)	35.1(22.3,48.1)			

Figure 1. Swimmer Plot Base on Assessment from BIRC

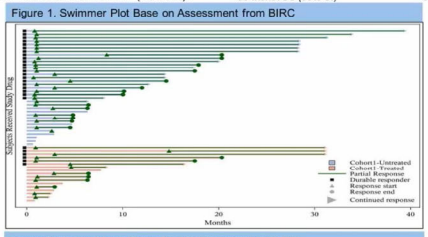


Figure 2. Change in Tumor Size Base on Assessment from BIRC

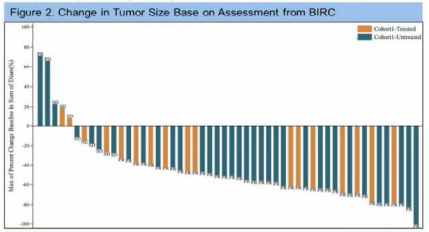


Figure 3. Kaplan-Meier Curve for PFS Assessed by BIRC

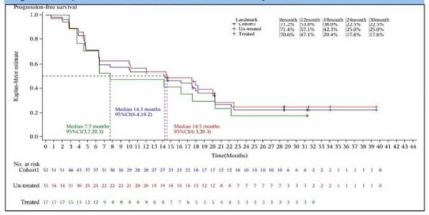


Figure 4. Kaplan-Meier Curve for OS

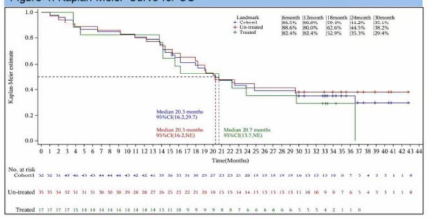
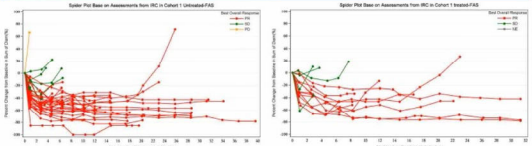


Figure 5. Spider Plot Base on Assessment from BIRC



Subgroup analysis :

- Patients with co-occurring of MET amplification (n=12) demonstrated an ORR and DCR were both 100.0% (95% CI, 73.5 to 100.0). The median DoR was 15.4 months (95% CI, 3.7 to 21.8), the median PFS was 16.3 months (95% CI, 4.7 to 22.5), and the median OS was 21.3 months (95% CI, 13.7 to NE).
- Among the six patients with liver metastases, the ORR was 66.7% (95% CI, 22.3 to 95.7), DCR was 100.0% (95% CI, 54.1 to 100.0), and the median DoR was 9.2 months (95% CI, 5.5 to NE). The median PFS was 8.2 months (95% CI, 2.8 to NE), and the median OS was 14.5 months (95% CI, 3.7 to NE).
- Among patients with baseline brain metastases (n=5), the ORR and DCR were both 100.0% (95% CI, 47.8 to 100.0). The median DoR was 5.6 months (95% CI, 3.7 to NE), the median PFS was 6.4 months (95% CI, 4.5 to NE), and the median OS was 17.9 months (95% CI, 4.5 to NE).
- Among patients aged 75 years or older (n=21), the ORR was 85.7% (95% CI, 63.7 to 97.0), DCR was 95.2% (95% CI, 76.2 to 99.9), and the median DoR was 19.1 months (95% CI, 9.2 to NE). The median PFS was also 18.2 months (95% CI, 6.3 to NE), and the median OS was 20.3 months (95% CI, 14.4 to NE)

Table 3 Subgroup Analysis Assessed by BIRC and INV

Variables	BIRC-assessed MET amp + (n=12)	BIRC-assessed MET amp - (n=40)	BIRC-assessed With liver metastases (n=6)	BIRC-assessed With brain metastases (n=5)	BIRC-assessed ≥75 years (n=21)	Investigator-assessed MET amp + (n=12)	Investigator-assessed MET amp - (n=40)	Investigator-assessed With liver metastases (n=5)	Investigator-assessed With brain metastases (n=8)	Investigator-assessed ≥75 years (n=21)
ORR (%)	12(100.0)	27(67.5)	4(66.7)	5(100.0)	18(85.7)	12(100.0)	24(60.0)	2(40.0)	6(75.0)	18(85.7)
DCR (%)	12(100.0)	38(95.0)	6(100.0)	5(100.0)	20(95.2)	12(100.0)	36(90.0)	4(80.0)	7(87.5)	20(95.2)
mDoR	15.4	16.5	9.2	5.6	19.1	8.7	18.6	NE	15.6	19.4
(95% CI)	(3.7,21.8)	(9.2,19.4)	(5.5,NE)	(3.7,NE)	(9.2,NE)	(3.7,19.4)	(5.6,28.1)	(9.2,NE)	(3.7,NE)	(5.6,28.9)
mPFS, mos	16.3	13.1	8.2	6.4	18.2	9.6	11.0	3.6	16.5	20.0
(95% CI)	(4.7,22.5)	(6.3,17.9)	(2.8,NE)	(4.5,NE)	(6.3,NE)	(4.7,20.0)	(6.4,20.3)	(0.8,NE)	(1.0,NE)	(6.5,29.9)
mOS, mos	21.3	20.3	14.5	17.9	20.3	21.3	20.3	6.5	NE	20.3
(95% CI)	(13.7,NE)	(15.2,36.5)	(3.7,NE)	(4.5,NE)	(14.4,NE)	(13.7,NE)	(15.2,36.5)	(1.0,NE)	(4.5,NE)	(14.4,NE)

Safety:

- The most common (≥20%) treatment-related adverse events (TRAEs) in all the 135 patients enrolled in this study were peripheral edema (56.3%), hypoalbuminemia (27.4%), hypoproteinemia (25.9%) and anemia (20.7%).
- TRAEs were mainly grade 1 or 2.
- No new safety signals were reported with long-term vebreltinib treatment.

Table 4 The Most Common (≥20%) Treatment-Related Adverse Events (TRAEs)

Event,n(%)	Any Grade	Grade 1	Grade 2	Grade≥3
Any TRAE	124(91.9)	120(88.9)	88(65.2)	51(37.8)
Peripheral edema	76(56.3)	56(41.5)	27(20.0)	10(7.4)
Hypoalbuminaemia	37(27.4)	18(13.3)	24(17.8)	0(0.0)
Hypoproteinemia	35(25.9)	20(14.8)	18(13.3)	0(0.0)
Anemia	28(20.7)	21(15.6)	7(5.2)	2(1.5)

Reference:

1. Frampton, Garrett M., et al. "Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors." *Cancer discovery* 5.8 (2015): 850-859.
2. Tong, Joanna H., et al. "MET amplification and exon 14 splice site mutation define unique molecular subgroups of non–small cell lung carcinoma with poor prognosis." *Clinical Cancer Research* 22.12 (2016): 3048-3056.
3. Fujino, Toshio, Kenichi Suda, and Tetsuya Mitsudomi. "Lung cancer with MET exon 14 skipping mutation: genetic feature, current treatments, and future challenges." Lung Cancer: Targets and Therapy (2021): 35-50.