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# Preliminary Results of Phase II KUNPENG Study of Vebreltinib in Patients (Pts) with Advanced NSCLC Harboring c-MET Alterations

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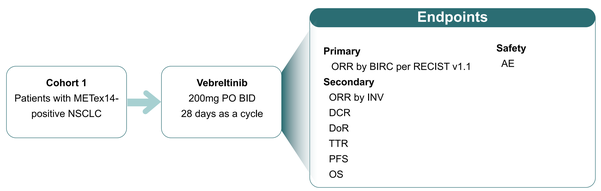
## Background

- MET signaling is implicated in cell proliferation, migration, invasion, and survival[1]. Genomic alterations in MET can manifest in driving oncogenesis in the form of MET exon 14 skipping mutations (METex14) or other activating mutations, MET gene amplification, gene fusion and MET protein overexpression[2]. METex14 is an independent prognostic factor associated with poorer survival rates in patients with NSCLC [3, 4].
- Patients with NSCLC harboring METex14, both previously treated and treatment-naïve, showed objective response rates (ORR) between 49.2% and 68% with existing therapies of MET inhibitors[5-8]. However, the incidence of treatment-related adverse events (TRAE) of grade 3 or higher was substantial[5, 6].
- ☒ Vebreltinib (bozitinib, APL-101, PLB-1001, CBT-101) is a potent highly selective c-MET inhibitor.
- In a phase I study, Vebreltinib has shown promising results in patients with NGS-identified advanced METex14 skipping NSCLC[9].
- This phase II study, open-label, multicenter and multi-cohort KUNPENG study evaluate the efficacy and safety of vebreltinib in locally advanced or metastatic NSCLC patients with c-MET alterations (NCT 04258033).

## Methods

- Eligible patients were ≥18 years of age, ECOG PS 0~1 with stage IIIB/IV NSCLC.
- Patients in Cohort 1 received 200 mg of Vebreltinib twice daily (28 days as a cycle) until disease progression, death, AE leading to discontinuation or withdrawal of consent.
- Primary endpoint was ORR assessed by blinded independent review committee (BIRC) per RECIST v1.1.
- 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).

**Figure 1.** Study Design




## Results

- **As of 09-Aug-2022, 113 patients were enrolled, among whom 52 patients had METex14 skipping mutations were in Cohort 1. (Table 1.)**

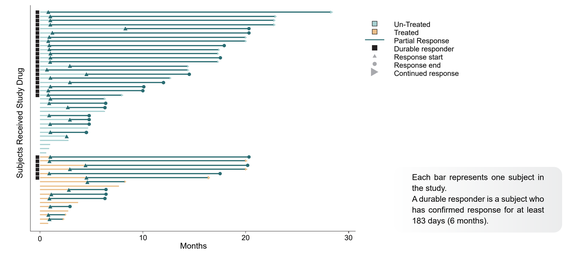
**Table 1**. Baseline characteristics

| Variables | Cohort 1 (N=52) | Treatment-naïve (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 (51.0, 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 (5.8) | 2 (5.9) | 1 (5.9) |
| Former | 16 (30.8) | 10 (29.4) | 6 (35.3) |
| Never | 32 (61.5) | 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 (94.1) |
| Target therapy | | | 3 (17.6) |
| Immunotherapy | | | 5 (29.4) |

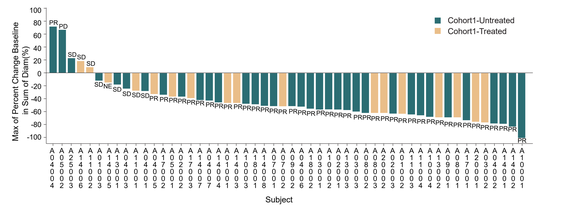
ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non-small-cell lung cancer.

- **Per BIRC, the primary endpoint ORR was 75% (95% CI: 61.1%~86.0%), with 39 participants achieved CR or PR. The treatment-naïve and previously treated patients displayed an ORR of 77.1% (95% CI, 59.9%~89.6%) and 70.6% (95% CI, 44.0%~89.7%), respectively. (Figure 2.)**

**Figure 2.** **A** Treatment exposure and response duration of patients

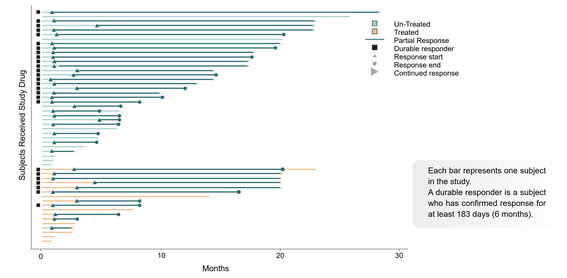



**B** The best percentage changes from baseline in target lesions of patients

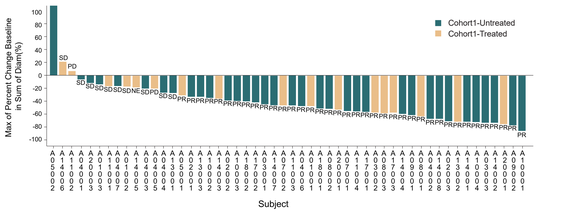



- **Per INV, ORR for the FAS population showed a confirmed CR or PR in 69.2% (36/52) of participants. The treatment-naïve and treated populations achieved an ORR of 74.3% (95% CI, 56.7%~87.5%) and 58.8% (95% CI, 32.9%~81.6%), respectively. (Figure 3.)**

**Figure 3.** **A** Treatment exposure and response duration of patients




**B** The best percentage changes from baseline in target lesions of patients



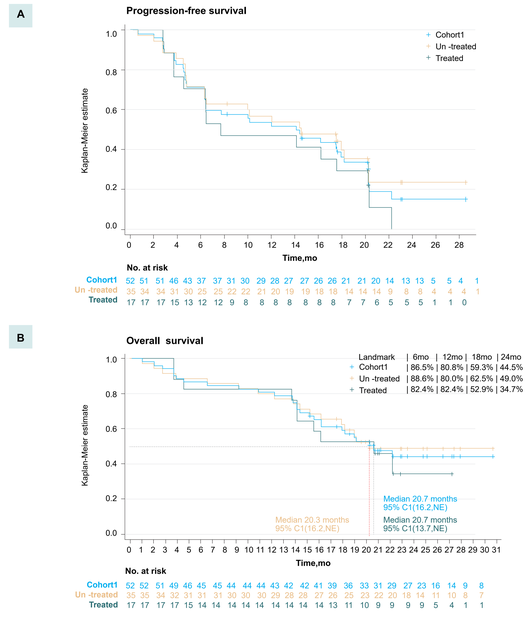

- **Per BIRC, DCR was 96.2% (95% CI, 86.8%~99.5%), median DoR was 15.9 months (95% CI, 9.2~17.8), and median TTR was 1.0 month (95% CI, 1.0~ 2.8). (Table 2.)**
- **The median PFS was 14.1 months (95% CI, 6.4~17.9) and the median OS was 20.7 months (95% CI, 16.2~NE). (Figure 4.)**

**Table 2**. Efficacy

| Variables | BIRC-assessed | | | Investigator-assessed | | |
|---|---|---|---|---|---|---|
| | Treatment-naïve (n=35) | Previously-treated (n=17) | All (n=52) | Treatment-naïve (n=35) | Previously-treated (n=17) | 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** | | | | | | |
| 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)** | 16.5 (9.2-NE) | 15.3 (3.7-17.8) | 15.9 (9.2-17.8) | 16.8 (5.6-19.4) | 15.7 (3.7-NE) | 15.7 (7.4-19.4) |
| **Median time to response, months (95% CI)** | 1.0 (1.0-1.2) | 1.9 (0.9-4.5) | 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** | | | | | | |
| Median, months (95% CI) | 14.5 (6.3-20.3) | 7.7 (3.7-20.2) | 14.1 (6.4-17.9) | 12.0 (6.5-20.3) | 8.2 (2.9-NE) | 10.5 (6.5-18.2) |
| **6-month progression-free survival (95% CI)** | 71.4 (53.4-83.5) | 70.6 (43.1-86.6) | 71.2 (56.8-81.5) | 77.1 (59.5-87.9) | 64.7 (37.7-82.3) | 73.1 (58.8-83.1) |
| **12-month progression-free survival (95% CI)** | 56.9 (38.9-71.3) | 47.1 (23.0-68.0) | 53.7 (39.3-66.1) | 51.4 (34.0-66.4) | 41.2 (18.6-62.6) | 48.1 (34.1-60.8) |

BIRC, blinded independent review committee; CI, confidence interval; NE, not estimate.

**Figure 4.** Kaplan-Meier estimate of (A) progression-free survival and (B) overall survival.




- **Subgroup analysis based on MET amplification, liver metastases, brain metastases and age (Table 3.)**
  - In patients with 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), and the median PFS was 6.4 months (95% CI, 4.5 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 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 not reached (95% CI, 14.4 to NE)
  - Patients with co-occurring of MET amplification (n=12, 23.1%) demonstrated an ORR of 100.0% (95% CI, 73.5 to 100.0), a median DoR that was 13.5 months (95% CI, 3.7 to NE), and a median PFS of 14.4 months (95% CI, 4.7 to NE). The ORR was significantly higher in patients with co-occurring of MET amplification than those without (P=0.024), while the PFS was comparable (log-rank P=0.518).

**Table 3**. Subgroup analysis based on MET amplification, liver metastases, brain metastases and age

| Variables | MET amplification + (n=12) | MET amplification - (n=40) | With liver metastases (n=6) | With brain metastases (n=5) | ≥75 years (n=21) |
|---|---|---|---|---|---|
| **Objective response rate (%)** | 12 (100.0) | 27 (67.5) | 4 (66.7) | 5 (100.0) | 18 (85.7) |
| 95% CI | 73.5, 100.0 | 50.9, 81.4 | 22.3, 95.7 | 47.8, 100.0 | 63.7, 97.0 |
| **Disease control rate (%)** | 12 (100.0) | 38 (95.0) | 6 (100.0) | 5 (100.0) | 20 (95.2) |
| 95% CI | 73.5, 100.0 | 83.1, 99.4 | 54.1, 100.0 | 47.8, 100.0 | 76.2, 99.9 |
| **Median duration of response, months (95% CI)** | 13.5 (3.7, NE) | 15.9 (9.2, 19.1) | 9.2 (5.5, NE) | 5.6 (3.7, NE) | 19.1 (9.2, NE) |
| **6-month progression-free survival rate (95% CI)** | 66.7 (33.7, 86.0) | 73.3 (53.7, 85.7) | 75.0 (12.8, 96.1) | 40.0 (5.2,75.3) | 78.9 (53.2, 91.5) |
| **12-month progression-free survival rate (95% CI)** | 57.1 (25.4, 79.6) | 56.5 (37.1, 72.0) | 25.0 (0.9, 66.5) | 20.0 (0.8, 58.2) | 68.4 (42.8, 84.4) |
| **Median progression-free survival, months (95% CI)** | 14.4 (4.7, NE) | 13.1 (6.3, 17.9) | 8.2 (2.8, NE) | 6.4 (4.5, NE) | 18.2 (6.3, NE) |
| | NR (13.7, NE) | 20.3 (15.2, NE) | 14.5 (3.7, NE) | 17.9 (4.5, NE) | NR (14.4, NR) |

CI, confidence interval, NE, not estimated; NR, not reached.

- **The incidence of TRAEs was 77.0% (87/113), with 31.0% (35/113) experiencing TRAEs of grade 3 or above. The most common TRAEs were peripheral edema (56.6%), hypoalbuminemia (22.1%) and hypoproteinemia (19.5%). (Table 4.)**

**Table 4**. Most common treatment-related adverse events (≥ 20% of patients)

| Event, n (%) | Any grade | Grade≥3 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| At least one TRAE | 87 (77.0) | 35 (31.0) | 32 (28.3) | 6 (5.3) |
| Peripheral edema | 64 (56.6) | 8 (7.1) | 8 (7.1) | 0 (0.0) |
| Hypoalbuminaemia | 25 (22.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Hypoproteinemia | 22 (19.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

TRAE of any grade considered to be related to study drug by the investigators in at least 10% of patients, or any grade 3 or 4 events reported in any patient are shown.
TRAE, treatment-related adverse event.
No grade 5 TRAE occurred.

## Conclusion

KUNPENG study offers promising evidence of the efficacy and safety of vebreltinib in patients with locally advanced or metastatic METex14-positive NSCLC. The results highlight capacity of vebreltinib to provide robust and durable responses with a favorable safety profile, signposting its potential as a therapeutic option for METex14-positive NSCLC.

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DOI# 00010454