Vebreltinib for Advanced Non−Small Cell Lung Cancer Harboring c-Met Exon 14 Skipping Mutation: A Multicenter, Single-Arm, Phase II KUNPENG Study

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ABSTRACT

PURPOSE The KUNPENG study aimed to evaluate the efficacy and safety of vebreltinib (also known as bozitinib, APL-101, PLB-1001, and CBT-101), a potent and highly selective inhibitor of c-mesenchymal-epithelial transition (*MET*), in patients with locally advanced or metastatic non−small cell lung cancer (NSCLC) harboring c-Met alterations.

METHODS This multicenter, multicohort, open-label, single-arm, phase II trial enrolled patients with c-Met dysregulated, locally advanced or metastatic NSCLC from January 2020 to August 2022 across 17 centers. Cohort 1 included patients with *MET* exon 14 skipping (*MET*ex14)−mutant NSCLC who had not previously received *MET* inhibitors. Participants were administered vebreltinib at a dosage of 200 mg twice a day in 28-day cycles. The primary end point was the objective response rate (ORR), and the key secondary end point was the duration of response (DoR), both evaluated by a blinded independent review committee according to the RECIST version 1.1.

RESULTS As of August 9, 2022, 52 patients had been enrolled in cohort 1, of whom 35 (67.3%) were treatment-naïve. The ORR reached 75% (95% CI, 61.1 to 86). Among treatment-naïve patients, the ORR was 77.1% (95% CI, 59.9 to 89.6), and in previously treated patients, it was 70.6% (95% CI, 44.0 to 89.7). The disease control rate was 96.2%, with a median DoR of 15.9 months, a median progression-free survival of 14.1 months, and a median overall survival of 20.7 months. The most common treatment-related adverse events were peripheral edema (82.7%), QT prolongation (30.8%), and elevated serum creatinine (28.8%).

CONCLUSION Vebreltinib has shown promising efficacy and a favorable safety profile in patients with *MET*ex14-mutant NSCLC.

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INTRODUCTION

The past decade has witnessed substantial progress in the development of targeted therapies for non−small cell lung cancer (NSCLC), specifically tailored to unique genetic aberrations.[1-3] Among these, alterations in the mesenchymal-epithelial transition (*MET*) gene are crucial for oncogenesis, encompassing *MET* exon 14 skipping (*MET*ex14) mutations, gene amplification, gene fusion, and protein overexpression.[4] Significantly, *MET*ex14 mutations are identified as an independent prognostic factor associated with diminished survival rates in patients with NSCLC.[5,6]

In pursuit of more effective treatments for patients with NSCLC harboring the *MET*ex14 alteration, spanning both previously treated and treatment-naïve cohorts, a range of tyrosine kinase inhibitors (TKIs) have yielded objective response rates (ORRs) between 49.2% and 68%.[7-10] However, these agents are linked with a notable frequency of treatment-related adverse events (TRAEs) of grade 3 or higher, recorded at 34.8% for tepotinib, 37.6% for capmatinib, 46% for savolitinib, and 54% for gumarontinib.[7,8,10,11] This underscores the imperative for treatment options that balance efficacy with a manageable safety profile.

Vebreltinib (also known as bozitinib, APL-101, PLB-1001, and CBT-101) stands out as a highly selective c-Met inhibitor. Its preclinical efficacy across various in vivo models heralds its potential as a potent antitumor agent.[12] Preliminary phase I study outcomes revealed an ORR of 66.7%

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CONTEXT

Key Objective
Can vebreltinib, a potent and highly selective inhibitor of c-mesenchymal-epithelial transition (*MET*), provide an effective and safe treatment option for patients with non–small cell lung cancer (NSCLC) with *MET* exon 14 skipping (*MET*ex14) mutations?

Knowledge Generated
Vebreltinib achieved notable objective response rates and a sustained duration of response in patients with *MET*ex14-positive NSCLC, regardless of previous treatment, baseline brain metastasis, mutation site, and alteration type. The safety of vebreltinib was acceptable and generally manageable.

Relevance *(T.E. Stinchcombe)*
Vebreltinib demonstrated activity and an acceptable rate of adverse events. These preliminary results justify additional studies.*

*Relevance section written by *JCO* Associate Editor Thomas E. Stinchcombe, MD.

alongside a tolerable safety profile in patients with advanced *MET*ex14-mutant NSCLC.[13] Leveraging these insights, the KUNPENG phase II study is designed to further investigate vebreltinib's therapeutic efficacy and safety in the treatment of patients with locally advanced or metastatic NSCLC harboring *MET*ex14 mutation.

METHODS

Study Design and Participants

This multicenter, multicohort, open-label, single-arm, phase II trial evaluated vebreltinib in patients with locally advanced or metastatic NSCLC characterized by c-Met dysregulation. Cohort 1 targeted patients with advanced NSCLC harboring *MET*ex14 mutations, naïve to c-Met inhibitor therapies. Cohorts 2 and 3 consisted of patients with c-Met amplification, who were either unsuitable for, had failed, or declined standard chemotherapy, without previous c-Met inhibitor therapy. Cohort 4 focused on patients with *MET*ex14 mutations who exhibited resistance after initial benefits from c-Met inhibitors. This manuscript details the results of vebreltinib in cohort 1.

Eligibility criteria included being 18 years or older, having stage IIIB-IV NSCLC confirmed histologically or cytologically, lacking epidermal growth factor receptor (*EGFR*) mutations, anaplastic lymphoma kinase (*ALK*) and *ROS1* rearrangements, and *KRAS* mutations; possessing *MET*ex14 mutations as verified by next-generation sequencing (NGS); maintaining an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; demonstrating adequate organ function; and no previous treatment with c-Met inhibitors. Key exclusion criteria were previous therapy targeting *MET* or hepatocyte growth factor and symptomatic

CNS metastases that were neurologically unstable or necessitated escalating steroid doses. The comprehensive inclusion and exclusion criteria are delineated in the Protocol (online only).

Ethical approval for the study was secured from the ethics committees of all participating centers. All participants provided written informed consent. The trial has been registered on ClinicalTrials.gov (identifier: NCT04258033).

Procedure

Participants were administered 200 mg of vebreltinib orally twice a day until disease progression or the emergence of intolerable toxicity. Dose modifications on the basis of adverse events (AEs) were permitted, encompassing reductions to 150 mg twice a day, and further to 100 mg twice a day. Treatment could be halted on the basis of the severity of AEs, with doses below 100 mg twice a day and any dose increases prohibited. Specific guidelines for dose modification are detailed in Appendix Figure A1 (online only). Participants who discontinued treatment for over 4 weeks were withdrawn from the study.

Efficacy assessments were carried out by both a blinded independent review committee (BIRC) and investigators in accordance with the RECIST version 1.1. These evaluations were conducted on the first day of the second cycle, then every two cycles up to cycle 12, and subsequently every three cycles after cycle 13, until disease progression, the commencement of another antitumor therapy, death, or withdrawal of consent. For those exiting the study, survival follow-up was conducted bimonthly via telephone for those not lost to follow-up or deceased. AEs were graded using the National Cancer Institute's Common Terminology

Criteria for Adverse Events (NCI CTCAE) version 5.0. Safety assessments encompassed AE monitoring, ECOG PS, laboratory tests, vital signs, and physical examinations.

A comprehensive NGS panel approach was used to precisely detect *MET*ex14 mutations among other genomic alterations. Results derived from tissue and blood samples were predominantly sourced from facilities certified by the Clinical Laboratory Improvement Amendments (CLIA) or the College of American Pathologists (CAP). Samples from non−CLIA- or CAP-certified facilities were subject to a rigorous validation process by a central laboratory. In cases where tissue samples were insufficient, blood samples were obtained for an exhaustive NGS analysis conducted by the central laboratory. Confirmation of *MET* gene amplification was also achieved through NGS reports from local laboratories.

End Points

The primary end point of the study was the ORR, as determined by the BIRC. The ORR is defined as the percentage of participants who achieved either a complete response (CR) or a confirmed partial response (PR). Secondary end points included the ORR as evaluated by investigators, disease control rate (DCR), duration of response (DoR), time to response (TTR), progression-free survival (PFS), and overall survival (OS).

Statistical Analysis

For cohort 1, the study required a sample size of 48 evaluable patients with *MET*ex14-positive NSCLC receiving vebreltinib at 200 mg twice a day to confidently reject the null hypothesis that the ORR was 40% or lower. This calculation was based on achieving an 80% power to detect an actual ORR of 60%, using a one-sided alpha of 2.5%. With an anticipated dropout rate of about 15%, the study aimed to enroll a minimum of 57 participants in this cohort.

The full analysis set (FAS) included all participants who had undergone baseline tumor assessment and received at least one dose (200 mg twice a day) of vebreltinib, with efficacy evaluations derived from this set. The safety set (SS) comprised all participants who were administered a minimum of one dose (200 mg twice a day) of the vebreltinib.

Statistical analyses were executed using SAS version 9.4 (SAS Institute, Cary, NC). The ORR, DCR, and their 95% CIs were determined using the Clopper-Pearson method. The chi-square test with continuity correction and Fisher's exact test were applied to assess differences in ORR among patients with various coexisting genetic alterations. TTR, DoR, PFS, and OS, along with their respective 95% CIs, were estimated using the Kaplan-Meier method. The log-rank test was used to compare PFS among patients with different coexisting genetic alterations.

RESULTS

Baseline Characteristics of Participants

Between January 17, 2020, and August 9, 2022, a total of 197 patients were screened across 17 sites in China. Of these, 16 individuals withdrew consent, and 68 were found ineligible because of not meeting inclusion criteria or meeting exclusion criteria, leading to 113 participants being enrolled in the study, including 52 in cohort 1. Up to the data cutoff date of August 9, 2022, data from these 52 patients were included in the FAS and the SS for analysis.

Within cohort 1, the median age was 71 years, with a range from 51 to 90 years. Males accounted for 55.8% (29 of 52) of the cohort, and the majority (90.4%, or 47 of 52) had an ECOG PS score of 1. A significant proportion (94.2%) identified as Han ethnicity. Among these patients, 35 were treatment-naïve, whereas 17 had received previous systemic antitumor therapy, excluding c-Met inhibitors (Table 1). In the subgroup analysis focusing on patients with brain metastases (n = 5), none underwent surgical intervention for their brain metastases before study entry, while two participants were administered radiation therapy targeting brain metastases (Fig 1).

Efficacy

Efficacy assessments conducted by the BIRC revealed that 39 of the 52 participants achieved either a CR or a PR, leading to a confirmed ORR of 75.0% (95% CI, 61.1 to 86.0) and a DCR of 96.2% (95% CI, 86.8 to 99.5) within the FAS. Graphical depictions of the maximum reduction in target lesion size from baseline alongside the duration of vebreltinib treatment for each patient are presented in Figure 2. With a median vebreltinib treatment span of 9.9 months, the median TTR was 1.0 month (95% CI, 1.0 to 2.8), the median DoR was 15.9 months (95% CI, 9.2 to 17.8), and the median PFS was 14.1 months (95% CI, 6.4 to 17.9; Fig 3A). The ORR, as determined by the investigators, was 69.2% (36 of 52 participants), with a median DoR of 15.7 months (Appendix Fig A2 and Table 2).

After a median follow-up period of 19.4 months, the median OS was 20.7 months (95% CI, 16.2 to not estimated [NE]). The survival rates at 6, 12, 18, and 24 months were 86.5%, 80.8%, 59.3%, and 44.5%, respectively (Fig 3B).

Efficacy by Baseline Characteristics

In the cohort of 35 treatment-naïve patients, the ORR confirmed by the BIRC was 77.1% (95% CI, 59.9 to 89.6; Fig 2C). The DCR for this subgroup reached 97.1% (95% CI, 85.1 to 99.9), with these patients achieving a median DoR of 16.5 months (95% CI, 9.2 to NE) and a median PFS of 14.5 months (95% CI, 6.3 to 20.3). For the 17 patients who had undergone previous treatments, the BIRC-confirmed ORR was

TABLE 1. Baseline Characteristics

Variable	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, No. (%)			
Male	29 (55.8)	18 (51.4)	11 (64.7)
Female	23 (44.2)	17 (48.6)	6 (35.3)
ECOG PS, No. (%)			
0	5 (9.6%)	5 (14.3)	0 (0.0)
1	47 (90.4%)	30 (85.7)	17 (100.0)
Smoking, No. (%)[a]			
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)
Histologic subtype, No. (%)			
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)
Disease stage, No. (%)			
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 antitumor treatment, No. (%)			
Chemotherapy		—	16 (94.1)
Target therapy		—	3 (17.6)
Immunotherapy		—	5 (29.4)

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; NSCLC, non–small cell lung cancer.
[a]S04001 missing smoking history information.

70.6% (95% CI, 44.0 to 89.7), with a DCR of 94.1% (95% CI, 71.3 to 99.9). This subgroup exhibited a median DoR of 15.3 months (95% CI, 3.7 to 17.8) and a median PFS of 7.7 months (95% CI, 3.7 to 20.2; Fig 3A and Table 2). The ORR assessed by investigators for the treatment-naïve and previously treated groups was 74.3% (95% CI, 56.7 to 87.5) and 58.8% (95% CI, 32.9 to 81.6), respectively (Fig 2C). The median OS was 20.3 months (95% CI, 16.2 to NE) for treatment-naïve patients and 20.7 months (95% CI, 13.7 to NE) for those previously treated.

In the specific subgroup of patients with brain metastases (n = 5), both the systemic ORR and DCR achieved a remarkable rate of 100.0% (95% CI, 47.8 to 100.0). These patients had a median DoR of 5.6 months (95% CI, 3.7 to NE) and a median PFS of 6.4 months (95% CI, 4.5 to NE; Appendix Fig A3). Detailed subgroup analyses are provided in Appendix Table A1.

Biomarker Analysis

In our cohort, 12 patients (23.1%) with co-occurring *MET* amplification showcased an ORR of 100.0% (95% CI, 73.5 to 100.0), a median DoR of 13.5 months (95% CI, 3.7 to NE), and a median PFS of 14.4 months (95% CI, 4.7 to NE; Appendix Table A1). Remarkably, the ORR in patients with concurrent *MET* amplification was significantly higher compared with those without (*P* = .024), although the PFS rates were similar (log-rank *P* = .518).

Among the 52 participants with advanced NSCLC harboring *MET*ex14 mutations, mutations at the splice donor site were identified in 33 patients (63.5%), whereas mutations at the splice acceptor site were present in 20 patients (38.5%). Two individuals had both mutation types simultaneously, and the mutation status of one patient remained unspecified. Patients with splice donor site mutations exhibited an ORR of 72.7% (95% CI, 54.5 to 86.7) and a median PFS of 17.5 months (95% CI, 6.3 to 20.3). For those with splice acceptor site mutations, the ORR was 80.0% (95% CI, 56.3 to 94.3), with a median PFS of 8.2 months (95% CI, 4.7 to 17.9). Patients carrying both mutation types demonstrated an ORR of 100.0% (95% CI, 15.8 to 100.0) and a median PFS of 15.1 months (95% CI, 10.0 to NE; Appendix Table A2 and Appendix Fig A3).
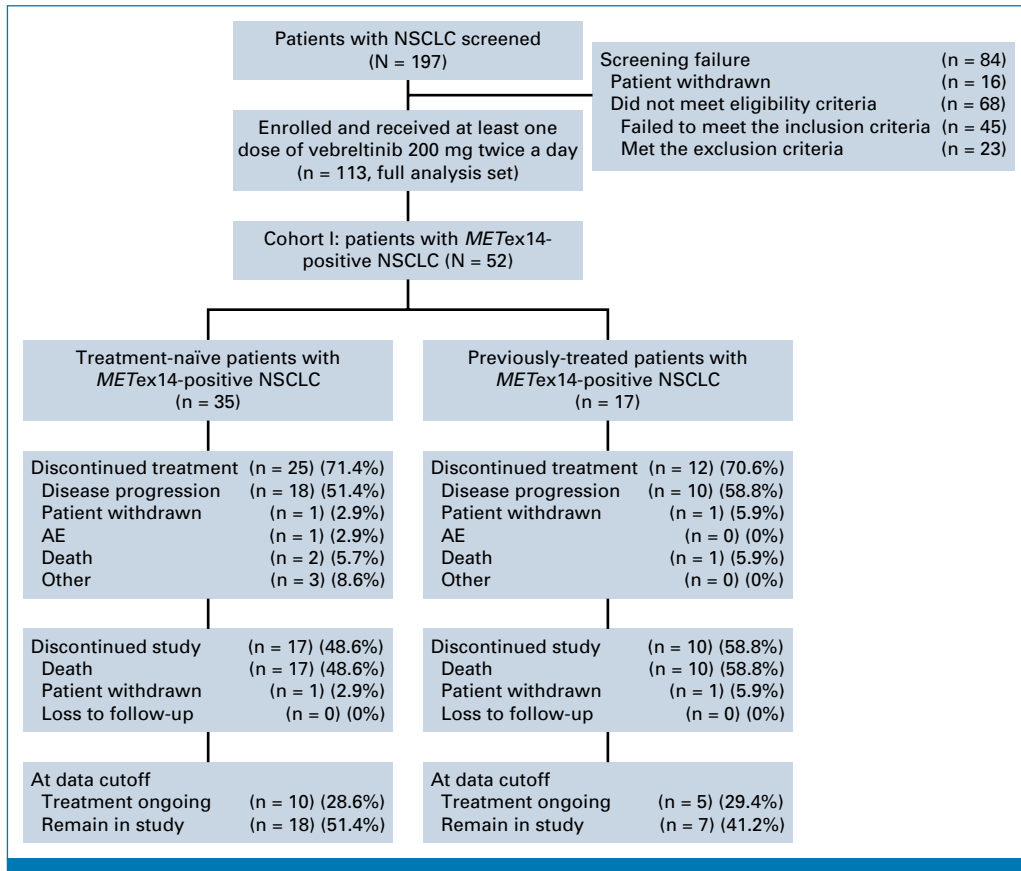
FIG 1. Flow diagram. In the treatment-naïve subgroup, discontinuations labeled as other included one patient who refused medication because of low back pain, one patient who had two medication interruptions in a relatively short interval (one because of severe acute coronary syndrome and one because of increased creatinine), and one patient who was assessed as unfit for further trial participation because of persistently reduced creatinine clearance. AE, adverse event; NSCLC, non−small cell lung cancer; *MET*ex14, *MET* exon 14 skipping.

Regarding alteration types, 29 patients (55.8%) presented solely with base substitutions, while 24 patients (46.2%) exhibited only base insertions or deletions (indels), and two individuals showed a combination of both base substitutions and indels. The specific genetic alteration of one patient remains undetermined. Among the patients with base substitutions, the ORR was 69.0% (95% CI, 49.2 to 84.7), with a median PFS of 17.5 months (95% CI, 6.3 to 20.3). For those harboring indels, the ORR reached 83.3% (95% CI, 62.6 to 95.3), with a median PFS of 8.2 months (95% CI, 4.7 to 14.5). Patients possessing both alteration types demonstrated outcomes consistent with those observed in the splice donor and splice acceptor site subgroups (Appendix Table A2 and Appendix Fig A3).

Vebreltinib showcased comparable efficacy in patients with *MET*ex14 mutations, irrespective of the mutation being at the splice donor or splice acceptor sites ($P = .853$ for ORR; log-rank $P = .100$ for PFS), as well as in those with either base substitutions or indels ($P = .253$ for ORR; log-rank $P = .062$ for PFS).

Safety

All (100.0%) participants reported at least one AE. A total of 32 individuals (61.5%) encountered AEs of grade 3 or higher severity. During the study, three participants (5.8%) died due to AEs: one due to acute pneumonia, another from pleural effusion, and a third patient deceased at home with causes remaining unspecified. These incidents were not considered related to vebreltinib treatment. Discontinuations of vebreltinib were noted in four patients (7.7%), with dosage reductions required for 11 participants (21.2%) and treatment suspensions in 26 individuals (50.0%). Serious adverse events were reported by 23 participants (44.2%), predominantly involving abnormal liver function and pleural effusion, each affecting four participants (7.7% of the cohort), followed by infectious pneumonia in two participants (3.8%). The rate of TRAEs was 98.1% (51 of 52 participants), with 48.1% (25 participants) experiencing TRAEs of grade 3 or higher. The most common TRAEs included peripheral edema (82.7%), QT prolongation (30.8%), and elevated serum creatinine (28.8%). Grade 3-4 TRAEs most frequently reported were peripheral edema (13.5%), abnormal liver
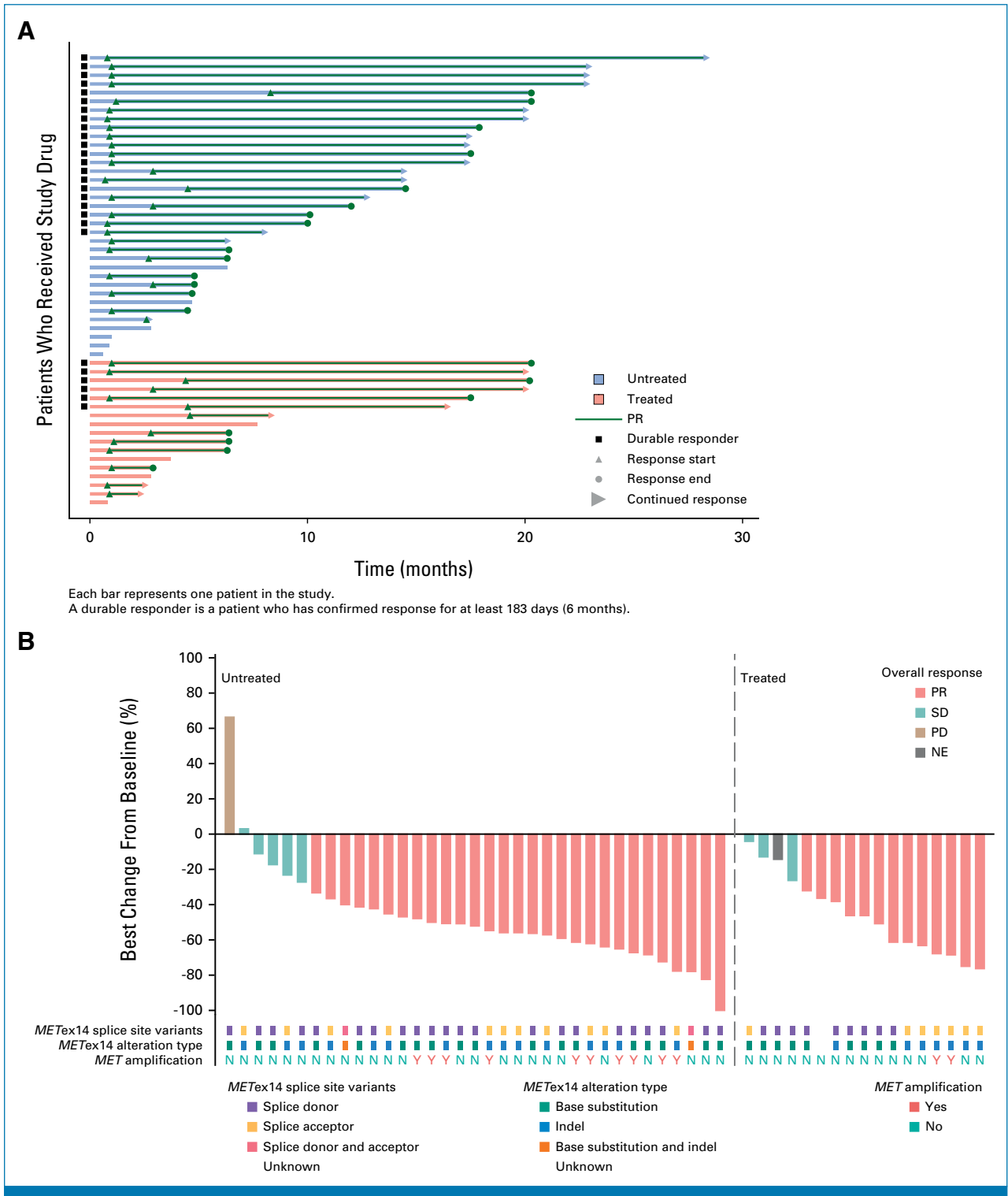
FIG 2. Antitumor activity of vebreltinib as assessed by blinded independent review committee. (A) Treatment exposure and response duration of patients. (B) The best percentage changes from baseline in target lesions of patients against *MET* exon 14 (*MET*ex14) splice site variants, alteration types, and *MET* amplification. Indels are insertion or deletion mutations. A durable responder is defined as a subject with a confirmed response lasting at least 183 days (6 months). (C) Subgroup analysis of ORR assessed by blinded independent review committee. ECOG PS, Eastern Cooperative Oncology Group performance status; *MET*ex14, *MET* exon 14; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease. (continued on following page)

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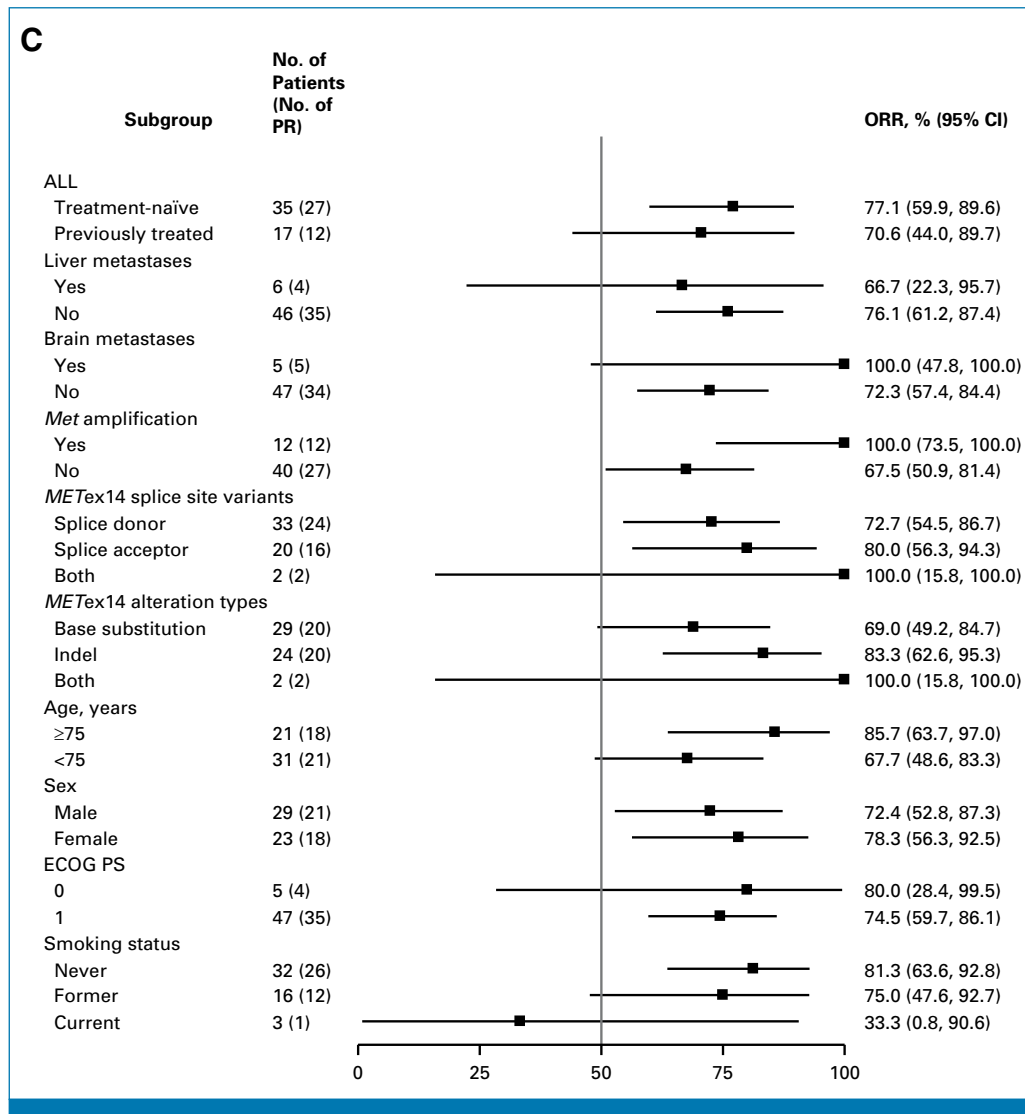| Subgroup	No. of Patients (No. of PR)	ORR, % (95% CI)
ALL		
Treatment-naïve	35 (27)	77.1 (59.9, 89.6)
Previously treated	17 (12)	70.6 (44.0, 89.7)
Liver metastases		
Yes	6 (4)	66.7 (22.3, 95.7)
No	46 (35)	76.1 (61.2, 87.4)
Brain metastases		
Yes	5 (5)	100.0 (47.8, 100.0)
No	47 (34)	72.3 (57.4, 84.4)
Met amplification		
Yes	12 (12)	100.0 (73.5, 100.0)
No	40 (27)	67.5 (50.9, 81.4)
*MET*ex14 splice site variants		
Splice donor	33 (24)	72.7 (54.5, 86.7)
Splice acceptor	20 (16)	80.0 (56.3, 94.3)
Both	2 (2)	100.0 (15.8, 100.0)
*MET*ex14 alteration types		
Base substitution	29 (20)	69.0 (49.2, 84.7)
Indel	24 (20)	83.3 (62.6, 95.3)
Both	2 (2)	100.0 (15.8, 100.0)
Age, years		
≥75	21 (18)	85.7 (63.7, 97.0)
<75	31 (21)	67.7 (48.6, 83.3)
Sex		
Male	29 (21)	72.4 (52.8, 87.3)
Female	23 (18)	78.3 (56.3, 92.5)
ECOG PS		
0	5 (4)	80.0 (28.4, 99.5)
1	47 (35)	74.5 (59.7, 86.1)
Smoking status		
Never	32 (26)	81.3 (63.6, 92.8)
Former	16 (12)	75.0 (47.6, 92.7)
Current	3 (1)	33.3 (0.8, 90.6)

FIG 2. (Continued).

function (9.6%), elevated alanine aminotransferase (7.7%), elevated aspartate aminotransferase (5.8%), anemia (5.8%), and infectious pneumonitis (5.8%; Table 3).

DISCUSSION

In this phase II clinical trial, vebreltinib showcased a remarkable ORR of 75.0% in the management of advanced NSCLC with *MET* exon 14 skipping mutations, alongside a sustained DoR (median, 15.9 months), regardless of previous treatment. This performance is consistent with other *MET* inhibitors, which have reported ORRs ranging from 42.9% to 68% and DoR spanning 8.3 to 18 months.[7,8,10,11] Furthermore, vebreltinib was characterized by a rapid onset of therapeutic action, evidenced by a median TTR of just 1 month. It is pertinent to acknowledge, however, that this rapidity could be partly attributed to the earlier restaging scans used in our study protocol (4 weeks) as opposed to the 6- to 8-week time frame commonly used in other studies.[7,9,10]

Vebreltinib's potent antitumor efficacy was observed across all patient subsets, including those without previous chemotherapy, underscoring its significant therapeutic promise. In treatment-naïve patients, vebreltinib achieved an ORR of 77.1%, a DCR of 97.2%, and a median DoR of 16.5 months. Remarkably, even in patients who had received previous systemic therapy, vebreltinib maintained robust efficacy, demonstrating an ORR of 70.6%, a DCR of 94.1%, and a median DoR of 15.3 months. These results, showcasing promising efficacy in both treatment-naïve and previously treated patient populations, position vebreltinib as a promising candidate in the therapeutic landscape of NSCLC.

The study revealed that vebreltinib treatment resulted in a median PFS of 14.1 months, outperforming the median PFS observed with gumarontinib (8.5 months),[7] tepotinib (11.2 months),[11] and savolitinib (6.8 months).[10] Additionally, the median OS after vebreltinib treatment was 20.7 months, surpassing the outcomes reported for
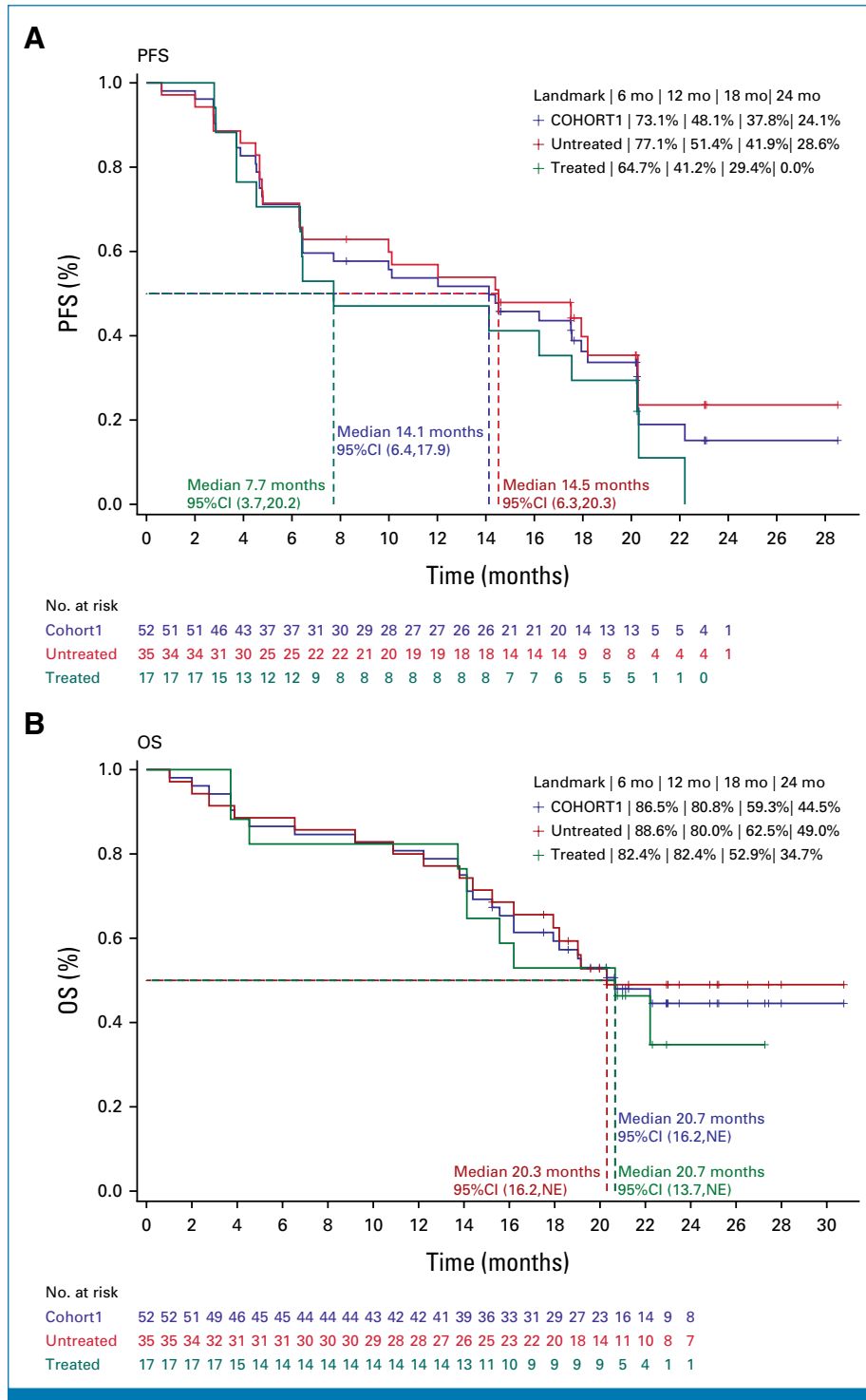
FIG 3. Kaplan-Meier estimate of (A) PFS assessed by blinded independent review committee and (B) OS. NE, not evaluable; OS, overall survival; PFS, progression-free survival.

tepotinib (17.1 months), gumarontinib (17.3 months), and savolitinib (12.5 months).[7,9,10] These results highlight vebreltinib's notable antitumor efficacy and its potential to improve survival, marking it as an important advancement in the treatment landscape for NSCLC, especially for those patients with *MET*ex14 mutations. Nonetheless, the

interpretation of these results necessitates a careful consideration of the variability in study designs and patient demographics across the studies.

In the cohort of patients with brain metastases (n = 5), vebreltinib was associated with a systemic ORR of 100%.

TABLE 2. Efficacy

Variable	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, No. (%)	27 (77.1)	12 (70.6)	39 (75.0)	26 (74.3)	10 (58.8)	36 (69.2)
95% CI	59.9 to 89.6	44.0 to 89.7	61.1 to 86.0	56.7 to 87.5	32.9 to 81.6	54.9 to 81.3
Best overall response, No. (%)						
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, No. (%)	34 (97.1)	16 (94.1)	50 (96.2)	34 (97.1)	14 (82.4)	48 (92.3)
95% CI	85.1 to 99.9	71.3 to 99.9	86.8 to 99.5	85.1 to 99.9	56.6 to 96.2	81.5 to 97.9
Duration of response, median, months (95% CI)	16.5 (9.2 to NE)	15.3 (3.7 to 17.8)	15.9 (9.2 to 17.8)	16.8 (5.6 to 19.4)	15.7 (3.7 to NE)	15.7 (7.4 to 19.4)
Time to response, median, months (95% CI)	1.0 (1.0 to 1.2)	1.9 (0.9 to 4.5)	1.0 (1.0 to 2.8)	1.0 (1.0 to 2.6)	2.7 (0.9 to 4.4)	1.0 (1.0 to 2.7)
PFS						
Median, months (95%CI)	14.5 (6.3 to 20.3)	7.7 (3.7 to 20.2)	14.1 (6.4 to 17.9)	12.0 (6.5 to 20.3)	8.2 (2.9 to NE)	10.5 (6.5 to 18.2)
6-month PFS (95% CI)	71.4 (53.4 to 83.5)	70.6 (43.1 to 86.6)	71.2 (56.8 to 81.5)	77.1 (59.5 to 87.9)	64.7 (37.7 to 82.3)	73.1 (58.8 to 83.1)
12-month PFS (95% CI)	56.9 (38.9 to 71.3)	47.1 (23.0 to 68.0)	53.7 (39.3 to 66.1)	51.4 (34.0 to 66.4)	41.2 (18.6 to 62.6)	48.1 (34.1 to 60.8)

Abbreviations: BIRC, blinded independent review committee; NE, not estimate; PFS, progression-free survival.

TABLE 3. TRAE

Event	Any Grade, No. (%)	Grade 3-4, No. (%)	Grade 3, No. (%)	Grade 4, No. (%)
At least one TRAE	51 (98.1)	25 (48.1)	25 (48.1)	3 (5.8)
Peripheral edema	43 (82.7)	7 (13.5)	7 (13.5)	0 (0.0)
QT prolongation	16 (30.8)	1 (1.9)	1 (1.9)	0 (0.0)
Elevated serum creatinine	15 (28.8)	1 (1.9)	1 (1.9)	0 (0.0)
Hypoalbuminemia	14 (26.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hypoproteinemia	13 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)
Anemia	13 (25.0)	2 (3.8)	2 (3.8)	0 (0.0)
Elevated aspartate ALT	12 (23.1)	4 (7.7)	4 (7.7)	0 (0.0)
Weight gain	12 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	12 (23.1)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated lipase	11 (21.2)	3 (5.8)	3 (5.8)	0 (0.0)
Hypocalcemia	9 (17.3)	0 (0.0)	0 (0.0)	0 (0.0)
Weakness	8 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Abnormal liver function	8 (15.4)	5 (9.6)	5 (9.6)	1 (1.9)
Ventricular premature contraction	8 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated AST	8 (15.4)	3 (5.8)	3 (5.8)	0 (0.0)
Elevated bilirubin	8 (15.4)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased platelet count	8 (15.4)	2 (3.8)	1 (1.9)	1 (1.9)
Hypokalemia	7 (13.5)	1 (1.9)	0 (0.0)	1 (1.9)
Nausea	7 (13.5)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated conjugated bilirubin	7 (13.5)	1 (1.9)	1 (1.9)	0 (0.0)
Sinus tachycardia	7 (13.5)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased white cell count	6 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Hyponatremia	6 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Elevated amylase	6 (11.5)	1 (1.9)	1 (1.9)	0 (0.0)
Hyperuricaemia	6 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	6 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased neutrophil count	4 (7.7)	1 (1.9)	1 (1.9)	0 (0.0)
Infectious pneumonia	2 (3.8)	1 (1.9)	1 (1.9)	0 (0.0)
Peripheral swelling	2 (3.8)	1 (1.9)	1 (1.9)	0 (0.0)
Decreased renal creatinine clearance rate	1 (1.9)	1 (1.9)	1 (1.9)	0 (0.0)
GI diseases	1 (1.9)	1 (1.9)	1 (1.9)	0 (0.0)

NOTE. TRAEs 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. No grade 5 TRAE occurred.
Abbreviation: TRAE, treatment-related adverse event.

Previous findings suggested vebreltinib's capability to cross the blood-brain barrier, as evidenced in phase I studies targeting patients with glioma harboring *MET* alterations.[14] Although this systemic ORR is promising and indirectly supports vebreltinib's potential therapeutic effect on CNS metastases, it is important to note that specific intracranial ORRs were not directly assessed in the current study. Previous research has underscored the prognostic significance of liver metastases in NSCLC, indicating poorer outcomes in patients treated with *EGFR* TKIs and immune checkpoint inhibitors.[15-17] Despite the small sample size, our findings suggest vebreltinib may offer benefits to patients with liver metastases and those age 75 years or older, warranting further investigation to validate these promising outcomes and explore personalized treatment strategies for NSCLC.

In our study, the indel subgroup showed a numerically higher ORR compared with the base substitution subgroup, nevertheless a numerically shorter DoR and PFS. This differs from the study of savolitinib, where despite similar ORRs, the indel subgroup showed a longer PFS.[10] Although no significant difference was observed in this study, these discrepancies highlight the complex interplay between genetic alterations and treatment efficacy. Given the small sample size and exploratory nature of our study, these preliminary findings emphasize the importance of additional research to elucidate the implications of different genetic alterations on treatment outcomes.

The occurrence of *MET*ex14 mutations alongside other driver mutations is uncommon, yet instances of *MET*ex14

mutations coexisting with *MET* amplification have been documented.[18] Savolitinib has demonstrated a numerically superior ORR and extended PFS in patients with concurrent *MET* amplification,[10] while capmatinib's effectiveness seemed unaffected by simultaneous *MET* amplification in patients with *MET*ex14-positive NSCLC.[8] In our study, an ORR of 100.0% was observed in 12 patients with coexisting *MET* amplification, a rate significantly higher than that in patients without, although PFS rates were similar. These results align with those from an initial phase I study of vebreltinib.[13] Besides, similar to findings with capmatinib,[8] responses to vebreltinib may differ among patients with various *MET*ex14 splice site variants and alteration types. Such findings emphasize the need for further studies to clarify the clinical implications of concurrent *MET* amplification in patients with *MET*ex14 mutation-positive NSCLC treated with *MET* inhibitors.

In this study, the most prevalent TRAEs were peripheral edema (82.7%), QT prolongation (30.8%), and elevated serum creatinine (28.8%). Notably, no grade 5 TRAEs were observed. The significant occurrence of peripheral edema, potentially linked to hypoalbuminemia and hypoproteinemia, warrants particular attention. Although the incidence of QT interval prolongation calls for careful monitoring of potential cardiac toxicity, it is important to highlight that most prolongations were of grade 1 and 2 severity, indicating generally mild effects. Moreover, instances of grade 3 QT prolongation were infrequent, with only one patient necessitating a brief pause in treatment. This individual was able to resume therapy at the initial dose after QT normalization, emphasizing the critical role of regular monitoring and educating patients on the safe use of vebreltinib, especially for those with existing cardiac conditions or taking other QT interval-affecting medications. However, given the study's limited sample size, vebreltinib's safety profile warrants further validation in larger-scale studies. Comparatively, the primary TRAEs associated with capmatinib were edema (51%) and nausea (45%).[8] Tepotinib was linked to a notable instance of a grade 5 TRAE.[9] The incidence of grade 3 or higher TRAEs for vebreltinib was

48.1%, a figure numerically in line with those reported for savolitinib and gumarontinib, at 46% and 54%, respectively.[10] Additionally, TRAEs related to gumarontinib led to permanent discontinuation in 8% of patients. These suggest that vebreltinib may offer a potentially more favorable safety profile for treating patients with *MET*ex14-positive NSCLC.

The enhanced ORR observed with vebreltinib is promising, likely because of its highly selective and specific inhibition of tumor cell proliferation and c-Met phosphorylation.[12] However, it is critical to acknowledge certain limitations. First, the study's patient population was exclusively from China, although the efficacy of *MET* inhibitor therapy in Asia may reflect that of the global population.[19] Additionally, the study did not collect post-treatment biopsy samples for drug resistance mechanism analysis. The small sample size further constrains the extrapolation of these findings to a broader, more heterogeneous patient population. In response, a global phase I/II study (ClinicalTrials.gov identifier: NCT03175224) is currently evaluating vebreltinib's efficacy in a wider population, aiming to deepen our understanding of its therapeutic value across diverse demographics. Moreover, an ongoing larger-scale phase IIIb study (ClinicalTrials.gov identifier: NCT05989542) is expected to provide additional clinical evidence, potentially overcoming drug resistance challenges and advancing the treatment of NSCLC with *MET*ex14 mutations. Fourth, the subgroup analyses were conducted on relatively small cohorts, which necessitates a cautious interpretation of the results. In particular, for the subgroup of patients with brain metastases, the small sample size precluded a specific assessment of intracranial response. This aspect will be addressed in future large-scale studies designed to provide more definitive insights into both systemic and intracranial efficacy.

The KUNPENG study offers evidence of vebreltinib's efficacy and safety for patients with locally advanced or metastatic *MET*ex14-positive NSCLC, highlighting its capacity to induce robust and durable responses alongside a favorable safety profile. Vebreltinib emerges as a viable therapeutic candidate for patients with *MET*ex14-positive NSCLC.

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DATA SHARING STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Other study data may be shared upon submission of a request to Beijing Pearl Biotechnology Co, Ltd. The data request will be reviewed, and if agreed, the requestors will need to sign a data sharing agreement.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Vebreltinib for Advanced Non–Small Cell Lung Cancer Harboring c-Met Exon 14 Skipping Mutation: A Multicenter, Single-Arm, Phase II KUNPENG Study

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APPENDIX

Flowchart of Dose Modification

Grade 3 or 4 AEs[a]

Recover from AEs to baseline or grade 1 after symptomatic treatment for ≤2 weeks

Discontinuation of vebreltinib

Not recover from AEs to baseline or grade 1 after >4 weeks of symptomatic treatment

Termination of vebreltinib

Resume vebreltinib 200 mg twice a day

2 weeks <symptomatic treatment ≤ 4 weeks, recover from AE to baseline or grade 1

Vebreltinib decreased to 150 mg twice a day

Recurrence of grade 3/4 AEs, which do not return to baseline or grade 1 after >4 weeks of symptomatic treatment

Termination of vebreltinib

Recurrence of grade 3/4 AEs, which return to baseline or grade 1 after ≤2 weeks of symptomatic treatment

Recurrence of grade 3/4 AEs, 2 weeks <symptomatic treatment ≤4 weeks, return to baseline or grade 1

Resume vebreltinib 150 mg twice a day

Vebreltinib decreased to 100 mg twice a day

Recurrence of grade 3/4 AEs, which do not return to baseline or grade 1 after >2 weeks of symptomatic treatment

Termination of vebreltinib

Recurrence of grade 3/4 AE, which return to baseline or grade 1 after ≤2 weeks of symptomatic treatment
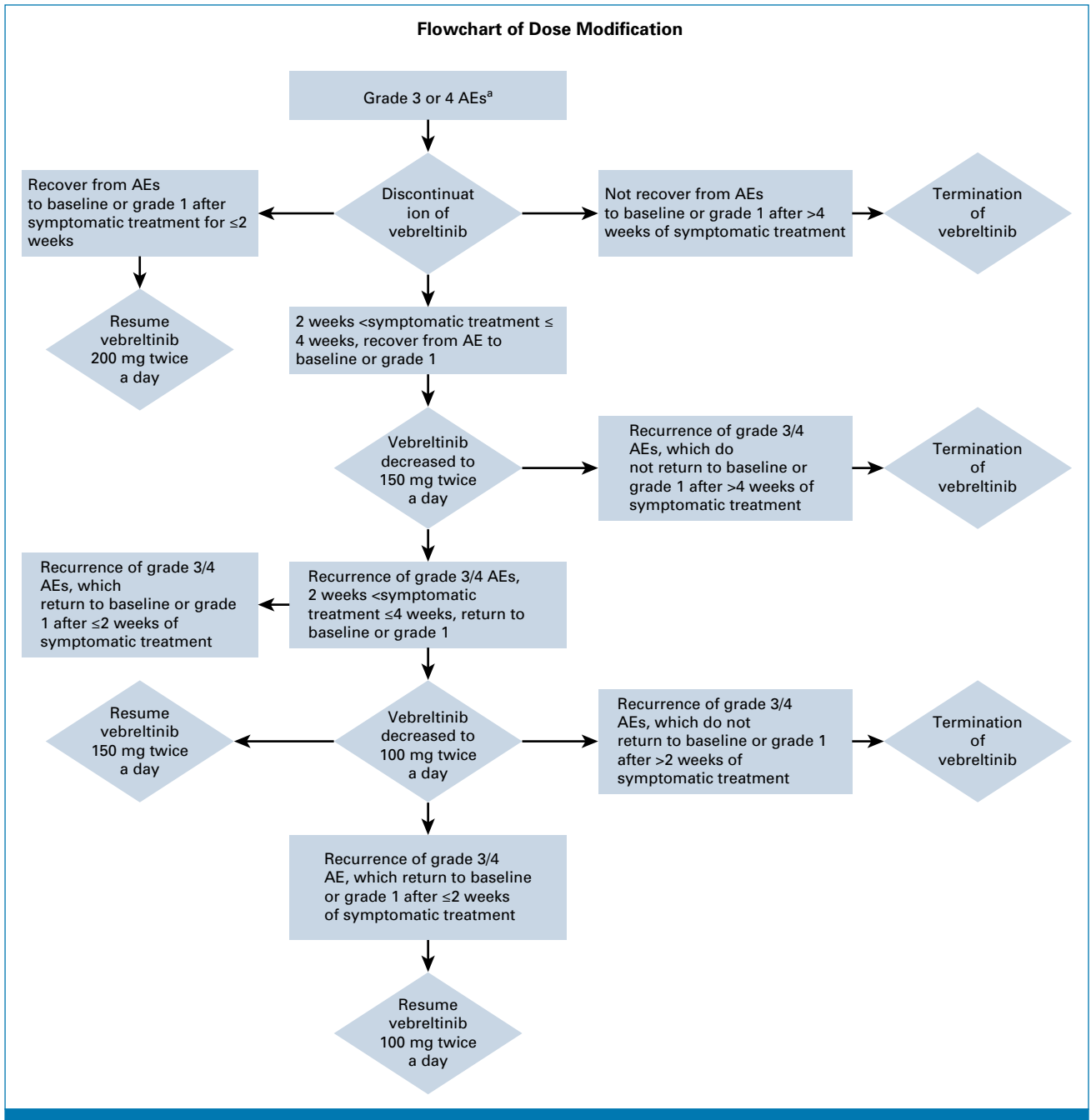
Resume vebreltinib 100 mg twice a day

FIG A1. Flowchart of dose modification. [a]Except for nausea, vomiting, diarrhea, constipation, or grade 3 and 4 nonhematologic toxicities that are considered manageable by the investigator. AE, adverse event.
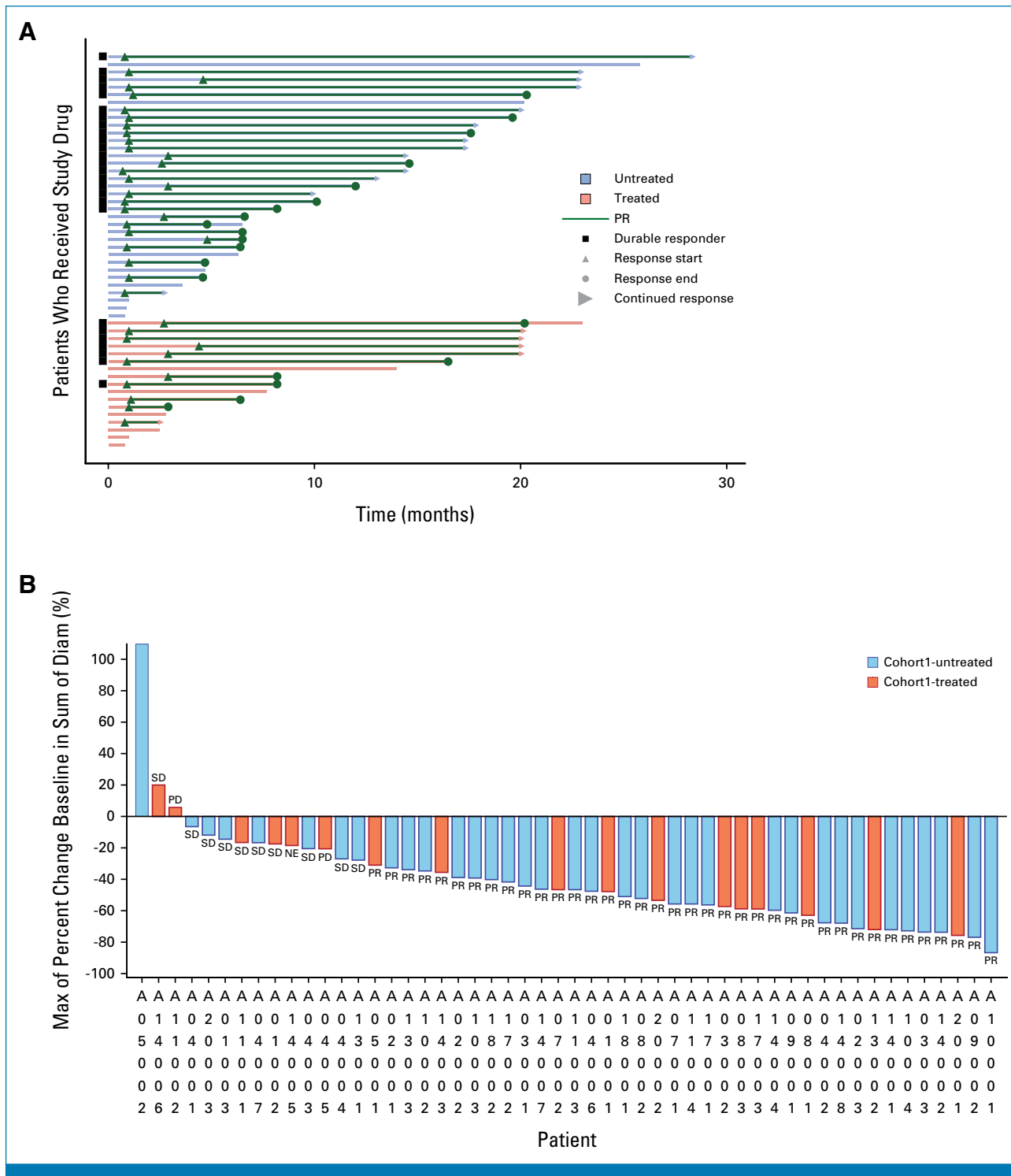
A

Patients Who Received Study Drug

Legend:
- Untreated
- Treated
- PR
- Durable responder
- Response start
- Response end
- Continued response

Time (months)

B

Max of Percent Change Baseline in Sum of Diam (%)

Legend:
- Cohort1-untreated
- Cohort1-treated

Patient

FIG A2. Antitumor activity of vebreltinib as assessed by investigator. (A) Treatment exposure and response duration of patients. (B) The best percentage changes from baseline in target lesions of patients. Each bar represents one subject in the study. A durable responder is a subject who has confirmed response for at least 183 days (6 months). NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.
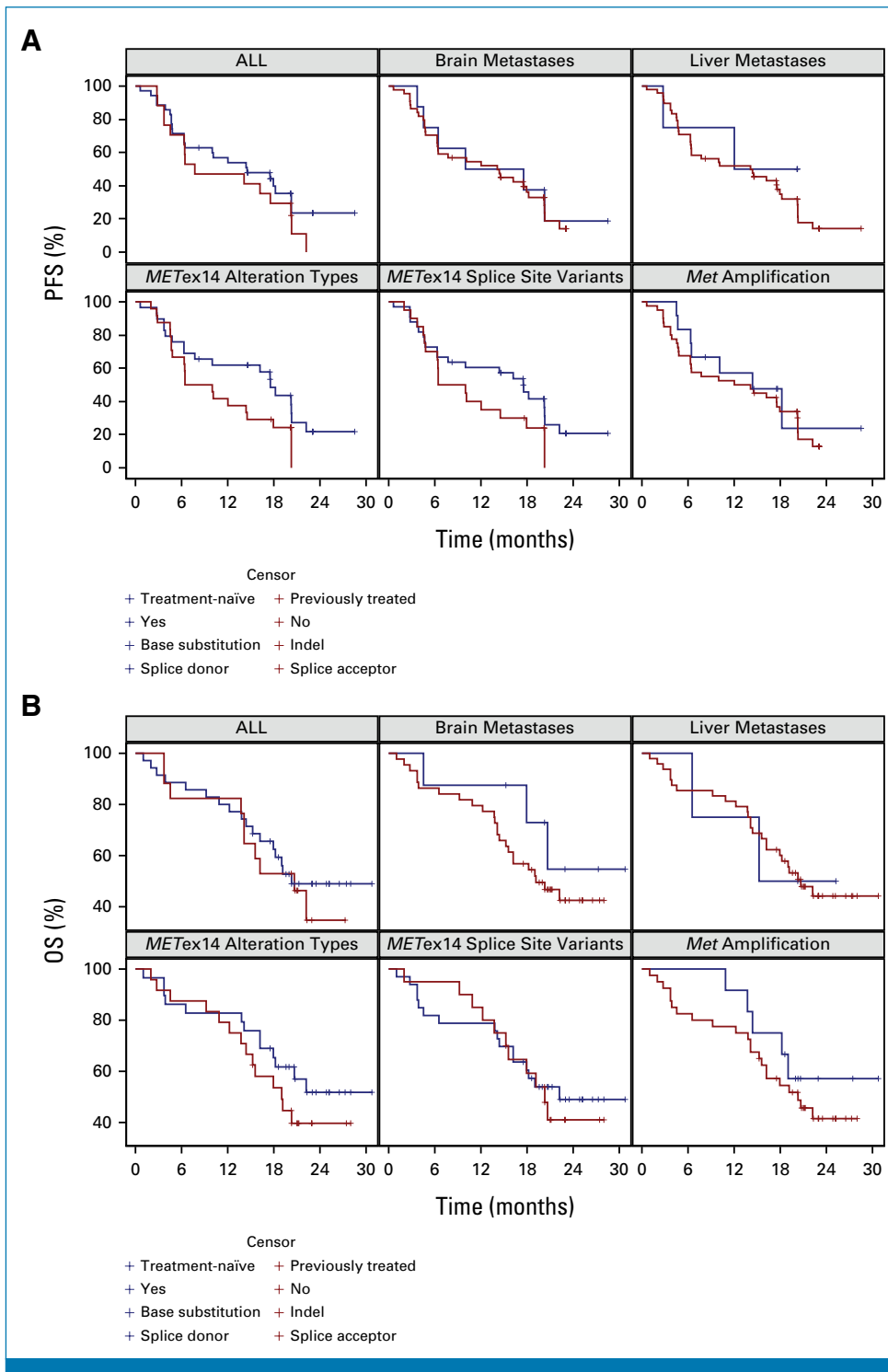
FIG A3. Subgroup analysis of (A) progression-free survival assessed by blinded independent review committee and (B) overall survival in patients with different metastases sites and different mutation sites. *MET*ex14, *MET* exon 14; OS, overall survival; PFS, progression-free survival.

TABLE A1. Subgroup Analysis on the Basis of *MET* Amplification, Liver Metastases, Brain Metastases, and Age

Variable	*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 to 100.0	50.9 to 81.4	22.3 to 95.7	47.8 to 100.0	63.7 to 97.0
Disease control rate, %	12 (100.0)	38 (95.0)	6 (100.0)	5 (100.0)	20 (95.2)
95% CI	73.5 to 100.0	83.1 to 99.4	54.1 to 100.0	47.8 to 100.0	76.2 to 99.9
Duration of response, median, months (95% CI)	13.5 (3.7 to NE)	15.9 (9.2 to 19.1)	9.2 (5.5 to NE)	5.6 (3.7 to NE)	19.1 (9.2 to NE)
6-month PFS rate (95% CI)	66.7 (33.7 to 86.0)	73.3 (53.7 to 85.7)	75.0 (12.8 to 96.1)	40.0 (5.2, 75.3)	78.9 (53.2 to 91.5)
12-month PFS rate (95% CI)	57.1 (25.4 to 79.6)	56.5 (37.1 to 72.0)	25.0 (0.9 to 66.5)	20.0 (0.8 to 58.2)	68.4 (42.8 to 84.4)
PFS, median, months (95% CI)	14.4 (4.7 to NE)	13.1 (6.3 to 17.9)	8.2 (2.8 to NE)	6.4 (4.5 to NE)	18.2 (6.3 to NE)
OS, months, median (95% CI)	NR (13.7 to NE)	20.3 (15.2 to NE)	14.5 (3.7 to NE)	17.9 (4.5 to NE)	NR (14.4 to NE)

Abbreviations: NE, not estimated; NR, not reached; OS, overall survival; PFS, progression-free survival.

TABLE A2. Subgroup Analysis of Subjects With *MET* Exon 14 Splice Site Variants and Alteration Types

Variable	Splice Donor (n = 33)	Splice Acceptor (n = 20)	SD and SA (BS and I, n = 2)	Base Substitution (n = 29)	Indel (n = 24)
Objective response rate, %	24 (72.7)	16 (80.0)	2 (100.0)	20 (69.0)	20 (83.3)
95% CI	54.5 to 86.7	56.3 to 94.3	15.8 to 100.0	49.2 to 84.7	62.6 to 95.3
Disease control rate, %	31 (93.9)	20 (100.0)	2 (100.0)	27 (93.1)	24 (100.0)
95% CI	79.8 to 99.3	83.2 to 100.0	15.8 to 100.0	77.2 to 99.2	85.8 to 100.0
Duration of response, months, median (95% CI)	16.7 (13.5 to NE)	9.2 (3.9 to 17.1)	10.6 (9.2 to NE)	17.3 (15.3 to NE)	9.2 (3.9 to 13.5)
6-month PFS rate (95% CI)	80.8 (59.8 to 91.5)	58.8 (32.5 to 77.8)	100.0 (100.0 to 100.0)	86.4 (63.4 to 95.4)	57.1 (33.8 to 74.9)
12-month PFS rate (95% CI)	72.5 (50.7 to 85.8)	29.4 (10.7 to 51.1)	0.0 (NE to NE)	76.5 (52.3 to 89.5)	33.3 (14.9 to 53.1)
PFS, months, median (95% CI)	17.5 (6.3 to 20.3)	8.2 (4.7 to 17.9)	15.1 (10.0 to NE)	17.5 (6.3 to 20.3)	8.2 (4.7 to 14.5)
OS, months, median (95% CI)	22.2 (16.2 to NE)	20.3 (13.7 to NE)	NR (17.9 to NE)	NR (16.2 to NE)	19.0 (13.7 to NE)

Abbreviations: BS, base substitution; I, indel; NE, not estimated; NR, not reached; OS, overall survival; PFS, progression-free survival; SA, splice acceptor; SD, splice donor.