

A pooled analysis of clinical outcome in driver-gene negative non-small cell lung cancer patients with MET overexpression treated with gumarontinib

Yongfeng Yu, Wen Dong, Yanxia Shi, Rong Wu, Qitao Yu, Feng Ye, Chengzhi Zhou , Xiaorong Dong, Xingya Li, Yongsheng Li, Zhen Li, Lin Wu, Yueyin Pan, Hong Shen, Dehua Wu, Zhongyuan Xu, Jinsheng Wu, Nong Xu, Yanru Qin, Aimin Zang, Jingdong Zhang, Jianya Zhou, Xiaotao Zhang , Yanqiu Zhao, Fugen Li, Huizhen Wang, Qi Liu, Zhenyong Han, Jin Li and Shun Lu 

Abstract

Background: MET overexpression represents the most *MET* aberration in advanced non-small-cell lung cancer (NSCLC). However, except *MET* exon 14 (*MET*ex14) skipping mutation was recognized as a clinical biomarker, the role of MET overexpression as a predictive factor to MET inhibitor is not clear.

Objectives: The purpose of the pooled analysis is to explore the safety and efficiency of gumarontinib, a highly selective oral MET inhibitor, in drive-gene negative NSCLC patients with MET overexpression.

Design and methods: NSCLC patients with MET overexpression [immunohistochemistry (IHC) $\geq 3+$ as determined by central laboratory] not carrying epidermal growth factor receptor mutation, *MET*ex14 skipping mutation or other known drive gene alternations who received Gumarontinib 300 mg QD from two single arm studies were selected and pooled for the analysis. The efficacy [objective response rate (ORR), disease control rate (DCR), duration of response, progression-free survival (PFS) and overall survival (OS)] and safety [treatment emergent adverse event (TEAE), treatment related AE (TRAЕ) and serious AE (SAE) were assessed.

Results: A total of 32 patients with MET overexpression were included in the analysis, including 12 treatment naïve patients who refused or were unsuitable for chemotherapy, and 20 pre-treated patients who received ≥ 1 lines of prior systemic anti-tumour therapies. Overall, the ORR was 37.5% [95% confidence interval (CI): 21.1–56.3%], the DCR was 81.3% (95% CI: 63.6–92.8%), median PFS (mPFS) and median OS (mOS) were 6.9 month (95% CI: 3.6–9.7) and 17.0 month (95% CI: 10.3–not evaluable), respectively. The most common AEs were oedema (59.4%), hypoalbuminaemia (40.6%), alanine aminotransferase increased (31.3%).

Conclusion: Gumarontinib showed promising antitumour activity in driver-gene negative locally advanced or metastatic NSCLC patients with MET overexpression, which warranted a further clinical trial.

Trial registration: ClinicalTrials.gov identifier: NCT03457532; NCT04270591.

Keywords: gumarontinib, MET overexpression, NSCLC, pooled analysis

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Correspondence to:

Jin Li
Department of Medical
Oncology, Shanghai East
Hospital, Tongji University,
150 Jimo Road, Pudong
New Area, Shanghai
200123, China
lijin@csco.org.cn

Shun Lu
Department of Medical
Oncology, Shanghai Chest
Hospital, Shanghai Jiao
Tong University School of
Medicine, No. 241 Huaihai
West Road, Shanghai
200030, China
shunlu@sjtu.edu.cn

Yongfeng Yu
Department of Medical
Oncology, Shanghai Chest
Hospital, Shanghai Jiao
Tong University School of
Medicine, Shanghai, China

Wen Dong
Department of Respiratory
Medicine, Hainan Cancer
Hospital, Haikou, China

Yanxia Shi
Internal Medicine
Department, Sun Yat-Sen
University Cancer Center,
Guangzhou, China

Rong Wu
Second Medical Oncology
Breast Tumors, Shengjing
Hospital of China Medical
University, Shenyang,
China

Qitao Yu
Department of Respiratory
Oncology, Guangxi Medical
University Cancer Hospital,
Nanning, China

Feng Ye
Department of Medical
Oncology, The First
Affiliated Hospital of
Xiamen University, Fujian,
China

Chengzhi Zhou
Department of Oncology,
The First Affiliated
Hospital of Guangzhou
Medical University,
Guangzhou, China

Xiaorong Dong

Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

Xingya Li

Oncology Department, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China

Yongsheng Li

Internal Medicine-Oncology and Phase I Clinical Trial Center, Chongqing University Cancer Hospital, Chongqing, China

Zhen Li

Internal Medicine 5, Linyi Cancer Hospital, Linyi, China

Lin Wu

Second Department of Thoracic Medicine, Hunan Cancer Hospital, Changsha, China

Yueyin Pan

Department of Oncology and Chemotherapy, Anhui Provincial Hospital, Hefei, China

Hong Shen

Department of Medical Oncology, The Second Affiliated Hospital of Zhejiang University School of Medicine, Hangzhou, China

Dehua Wu

Radiotherapy Department, Nanfang Hospital, Southern Medical University, Guangzhou, China

Zhongyuan Xu

Nanfang Hospital National Drug Clinical Trial Institution, Nanfang Hospital, Southern Medical University, Guangzhou, China

Jinsheng Wu

Department of Radiotherapy, The First Affiliated Hospital of Hainan Medical University, Haikou, China

Nong Xu

Internal Medicine-Oncology, The First Affiliated Hospital, Zhejiang University, Hangzhou, China

Yanru Qin

Department of Medical Oncology, The First Affiliated Hospital of Zhengzhou University of Medicine, Zhengzhou, China

Aimin Zhang

Department of Medical Oncology, Affiliated Hospital of Hebei University, Baoding, China

Introduction

Lung cancer remains a leading cause of cancer-related mortality worldwide.¹ About 85% of lung cancer is non-small cell lung cancer (NSCLC), and about 70% lung cancer patients are stage IIIB or IV at first diagnosis and have lost the opportunity for radical surgery or radical radiation therapy,² palliative radiotherapy and/or chemotherapy are the main treatments for these patients, but the prognosis is poor, with a 5-year survival rate of only about 15%.³ Currently, the choice of second-line or subsequent treatment for driver-gene negative advanced NSCLC is almost similar in National Comprehensive Cancer Network, American Society of Clinical Oncology, European Society for Medical Oncology, Chinese Society of Clinical Oncology and Japanese Lung Cancer Society guidelines, mainly include docetaxel, pemetrexed, albumin-paclitaxel or immune checkpoint inhibitors (if not used in front-line therapy).⁴⁻⁶ The overall objective response rate (ORR) is less than 10%, and the median progression-free survival (PFS) and median overall survival (OS) are no more than 4 and 7–9 months, respectively.^{5,7} So, there is still an unmet clinical need for the subsequent treatment of driver-gene negative advanced NSCLC patients.

Cellular-mesenchymal to epithelial transition factor (c-Met), an important member of a subfamily of receptor tyrosine kinases, also known by the alias hepatocyte growth factor (HGF) receptor, plays a critical role in tumour proliferation, invasive growth and angiogenesis.⁸ *MET* aberration mainly include three types: *MET* exon 14 (*MET*ex14) skipping mutation, *MET* amplification (*MET*amp) and *MET* overexpression.^{9,10} Among these, *MET*ex14 skipping mutations occur in approximately 3% of NSCLC cases,¹¹ *MET*amp occurs at a rate of 1–5% in treatment-naïve NSCLC patients,¹² but 18% after osimertinib treatment of epidermal growth factor receptor (*EGFR*) mutated patients.¹³ *MET* overexpression ranges from 15% to 70%, which depends on the antibody assay and positive threshold.¹⁴ *MET*ex14 skipping mutation is believed to be an independent driver mutation in NSCLC and is usually mutually exclusive from other drivers.¹⁵ Currently, *MET*ex14 skipping mutation was recognized as a clinical biomarker for stratifying NSCLC patients based on their predicted response to *MET* inhibitors. Four selective type Ib small molecule *MET* inhibitors targeting *MET*ex14 skipping mutations, including Tepotinib,¹⁶ Capmatinib,¹⁷

Savolitinib¹⁸ and Gumarontinib,¹⁹ were approved or conditionally approved and have become a new standard of care in NSCLC. The combination of *MET* inhibitor with *EGFR* inhibitor targeting *MET*amp also showed promising efficacy for those *MET*amp-driven *EGFR* inhibitor resistant NSCLC patients.^{20,21} However, *MET* overexpression, its role as a predictive factor was not clear although high *MET* expression rather than *MET*amp may be associated with a poor prognosis.^{22,23}

Gumarontinib (company code SCC244) is a highly selective, oral *MET* inhibitor. Gumarontinib demonstrated a favourable safety profile in preclinical study²⁴ and in preliminary clinical research.²⁵ Gumarontinib has been conditionally approved by National Medical Products Administration for *MET*ex14 skipping mutation positive, locally advanced or metastatic NSCLC.¹⁹ Given the crucial significance of *MET* overexpression in NSCLC population, we pooled data of driver-gene negative NSCLC patients with *MET* overexpression and with or without *MET*amp from two single arm studies to (1) explore the efficacy and safety of Gumarontinib; (2) evaluate whether *MET* overexpression [immunohistochemistry (IHC)3+] could serve as a useful predictor for identifying patients who are likely to benefit from anti-*MET* therapy.

Materials and methods

Patient eligibility

The analysis is performed based on the pooled data from the phase Ib of two single-arm studies, SCC244-104 study (NCT03457532) and SCC244-108 study (NCT04270591). The SCC244-104 study evaluates the safety, tolerability, pharmacokinetics characters and preliminary efficacy of gumarontinib in patients with *MET* alterations in histologically or cytologically confirmed locally advanced or metastatic solid tumours. The SCC244-108 study evaluates the efficacy and safety of gumarontinib in patients with locally advanced or metastatic NSCLC including pulmonary sarcomatoid carcinoma (stage IIIB, IIIC or IV) harbouring *MET* alterations. Both studies included the patients were adult ≥ 18 years old at the time of informed consent; ECOG performance status: 0–1 and adequate bone marrow reserve, renal and liver function; at least one measurable lesion according to RECIST 1.1. All the patients were administered gumarontinib 300 mg orally

continuous once daily in 21-day treatment cycles until disease progression, unacceptable adverse events (AEs), withdrawal of consent or other criteria for termination of study treatment, whichever is earlier. There are no breaks in dosing between cycles.

In this pooled analysis, only advanced NSCLC patients who failed the standard treatment or no standard treatment (including patients who were intolerant to chemotherapy, who were unsuitable for chemotherapy as judged by the investigator or who refused chemotherapy) with MET overexpression (IHC $\geq 3+$ as determined in central laboratory) not carrying *EGFR* mutation, *MET*ex14 skipping mutation or other known drive gene mutation, and without previous EGFR-tyrosine kinase inhibitor (TKI) treatment were included.

The studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The protocol and all its amendments were approved by the ethics committees from each participating centre. All participants provided written informed consent before enrolment.

Assessments

Safety. The severity of AEs was judged in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (SCC244-104 study) and 5.0 (SCC244-108 study). Patients were monitored by physical examination, vital signs (blood pressure and heart rate), Electrocardiogram (ECG) and laboratory test (haematology, coagulation function, biochemistry and urinalysis), and results worsened compared with baseline was reported during the study. And AEs were monitored continuously during the study from the time when the informed consent was signed to 28 days after the last dose of gumarontinib.

Efficacy. Radiographic tumour size assessment was evaluated by investigators were performed at baseline and every 6–8 weeks using computed tomography and magnetic resonance imaging scans, and evaluation method, instrument and technical parameters were consistent throughout the study. Tumour responses were assessed according to the tumour response criteria in the RECIST version 1.1.

The primary end point was to assess the preliminary efficacy and safety of gumarontinib in patients with *MET* alternation. ORR was defined as the proportion of patients with a best overall response of complete response (CR) or partial response (PR) from the first dose to the first disease progression (as per RECIST 1.1). CR/PR may be confirmed by another tumour assessment with at least 4 weeks apart. PFS was defined as the time from start treatment to disease progression or death for any cause (whichever is earlier).

Biomarker analysis. Archived tumour tissue was analysed for MET protein expression level by IHC. Membrane MET expression level was determined centrally *via* IHC using CONFIRM anti-Total MET SP44 rabbit monoclonal primary antibody (Clinical Trial Assays, CTA1) on Ventana Benchmark Ultra Platform in CAP controlled area within the Oncology and Immunology Unit of WuXi AppTec (China, Wuxi) for the patients from SCC244-104 study, whereas Abcam rabbit monoclonal (EP1454Y) to MET-N-terminal (CTA2) was used to detect MET protein expression level within the AmoyDx BioTec for those patients from SCC244-108 study. The CTA1 demonstrated 90.9% sensitivity, 91.3% specificity and 91.1% accuracy in the methodology validation report; and the CTA2 exhibited 100% sensitivity, specificity and accuracy in the methodology validation report. MET overexpression was defined as positive if tumours with a score of 3+ ($\geq 50\%$ of all tumour cells staining with strong intensity) in this pooled study.

*MET*amp was detected by fluorescence *in situ* hybridization (FISH). FISH assays were performed using *MET* SpectrumRed and *CEP7* SpectrumGreen DNA probes (Vysis; Abbott Laboratories) (China, Shanghai) in central lab of WuXi AppTec (SCC244-104 study) and AmoyDx (SCC244-108 study). *MET*amp was defined either as the threshold of *MET* gene copy number (GCN) per nucleus greater than or equal to 4.0 signals (GCN ≥ 4) or as the ratio of *MET* to *CEP7* greater than or equal to 2.0 ($MET/CEP7 \geq 2$).

Statistical analysis. No formal statistical hypothesis testing was conducted. ORR and disease control rate (DCR) results were summarized by treatment naïve or pre-treated group. ORR was also summarized by patients with

Jingdong Zhang
Gastroenterology
Department, Liaoning
Cancer Hospital and
Institute, Shenyang, China

Jianya Zhou
Department of Respiratory
Medicine, The First
Affiliated Hospital of
Zhejiang University School
of Medicine, Hangzhou,
China

Xiaotao Zhang
Radiotherapy Department,
The Affiliated Qingdao
Central Hospital of
Qingdao University,
Qingdao, China

Yanqiu Zhao
Department of Medical
Oncology, Affiliated Cancer
Hospital of Zhengzhou
University, Zhengzhou,
China

Fugen Li
Huizhen Wang
Qi Liu
Zhenyong Han
Haihe Biopharma Co., Ltd,
Shanghai, China

METamp and without *METamp*. Ninety-five percent confidence intervals (CIs) were calculated using the Clopper–Pearson method based on the exact binomial distribution based on investigator assessment. For time-to-event endpoints [duration of response (DoR), PFS and OS], the median DoR, median PFS, median OS and their survival curves were estimated by Kaplan–Meier method by patients previously treated or not.

The reporting of this study conforms to the STROBE statement²⁶ (Supplemental File named ‘STROBE-cohort_checklist’).

Results

Patients’ demographics and baseline characteristics

At the data cutoff date of 11 July 2023, a total of 32 NSCLC patients from 22 centres in China were filtered and pooled in the analysis, and each study included 16 patients (Supplemental Figure 1). The ORR was 43.8% (95% CI: 19.8–70.2%) for the 16 patients from SCC244-104 study, and 31.3% (95% CI: 11.7–58.7%) for the 16 patients from SCC244-108 study. The SCC244-104 study and SCC244-108 study did not show substantial differences in ORR due to different antibodies used in CTAs. Furthermore, considering the similar performance of the two CTAs in their respective methodology validation reports, we indirectly infer that the two assays are equivalent in methodology. Ultimately, the pooled dataset included 12 treatment naïve patients who refused or unsuitable for chemotherapy, and 20 pre-treated patients who received ≥ 1 lines of prior systemic anti-tumour therapies (Table 1). These patients were all with MET overexpression (IHC $\geq 3+$ as determined by central laboratory) not carrying *METex14* skipping or *EGFR* mutation and no previous EGFR-TKI treatment. When *MET* GCN ≥ 4 , 10 of the 32 patients had only MET overexpression without *METamp*, and the remaining 22 patients were with *METamp* in addition to MET overexpression (Table 1). These 32 patients were also used for the safety and efficacy analysis. Overall, most patients were male (26/32), the median age was 61 years (range: 44–83) and more patients had smoking history (20/32). Patient demographic and baseline characteristics were summarized in Table 1.

Safety

Among the 32 patients, all had at least one AE that emerged or worsened after initiation of a trial drug until 28 days after the last dose of the trial drug, the most common treatment emergent adverse events (TEAEs) occurred in at least 30% of patients included oedema (62.5%), hypoalbuminaemia (53.1%), alanine aminotransferase increased (37.5%), anaemia (34.4%), aspartate aminotransferase increased (34.4%) and decreased appetite (31.3%). At least one treatment-related TEAEs were reported in all patients who received gumarontinib. The most frequent treatment-related AEs (occurring in $\geq 20\%$ of patients) were oedema (59.4%), hypoalbuminaemia (40.6%), alanine aminotransferase increased (31.3%), aspartate aminotransferase increased (25.0%), nausea (25.0%) and vomiting (25.0%). Grade ≥ 3 treatment-related AEs occurred in 11 patients (34.4%), with oedema (6.3%) being the most common (Table 2), others are only happened in one patient. Among the 32 patients, 11 (34.4%) patients reported serious TEAEs with 7 (21.9%) patients judged to be related to the treatment. Except for decreased appetite, which was reported in 2 (6.3%) patients, all other SAEs were reported in 1 patient each. The common treatment-related AEs that occurred were similar to those observed in other gumarontinib studies,¹⁹ most are grade 1 or 2, and most are manageable and controllable.

Efficacy

The efficacy results were summarized in Table 3. Among the 32 patients, none achieved a CR, while 12 patients had a PR, 7 in the pre-treated group, 5 in the treatment naïve group; and 14 patients exhibited stable disease. The confirmed ORR was 37.5% (95% CI: 21.1–56.3%) in all patients, 41.7% (95% CI: 15.2–72.3%) in treatment-naïve patients and 35.0% (95% CI: 15.4–59.2%) in pre-treated patients (Table 3). The DCR was 81.3% (95% CI: 63.6–92.8%) in all patients, 91.7% (95% CI: 61.5–99.8%) in treatment naïve and 75.0% (95% CI: 50.9–91.3%) in pre-treated patients (Table 3). Figure 1(a) displayed the maximum percentage change from baseline in target lesions for each patient. Fifteen (53.6%) patients showed target lesions shrank by more than 30% from baseline. Tumour response was still maintained ongoing in 4 of 12 responders by the data cutoff date [Figure 1(b)]. The median follow-up time was

Table 1. Demographics and baseline characteristics.

Characteristic	SCC244 300 mg QD (N=32)		
	Treatment naïve (N=12)	Pre-treated (N=20)	Total (N=32)
Gender, <i>n</i> (%)			
Male	10 (83.33)	16 (80.00)	26 (81.25)
Female	2 (16.67)	4 (20.00)	6 (18.75)
Age (years)			
<i>n</i>	12	20	32
Mean (SD)	63.9 (11.02)	59.9 (9.21)	61.4 (9.95)
Median	66.0	60.5	61.0
Q1, Q3	56.9, 70.9	55.5, 64.2	57.8, 65.0
Min, Max	45, 77	44, 83	44, 83
Smoking status, <i>n</i> (%)			
Never	4 (33.33)	8 (40.00)	12 (37.50)
Current	1 (8.33)	0	1 (3.13)
Former	7 (58.33)	12 (60.00)	19 (59.38)
Screening ECOG performance status, <i>n</i> (%)			
0	2 (16.67)	5 (25.00)	7 (21.88)
1	10 (83.33)	15 (75.00)	25 (78.13)
Number of prior lines of therapy, <i>n</i> (%)			
1	0	16 (80.00)	16 (50.00)
2	0	3 (15.00)	3 (9.38)
3	0	0	0
>3	0	1 (5.00)	1 (3.13)
Brain metastasis at baseline, <i>n</i> (%)			
Yes	4 (33.33)	6 (30.00)	10 (31.25)
No	8 (66.67)	14 (70.00)	22 (68.75)
MET amplification			
Yes	9 (75.00)	13 (65.00)	22 (68.75)
No	3 (25.00)	7 (35.00)	10 (31.25)

ECOG, Eastern Cooperative Oncology Group; SD, standard deviation.

14.7 months. Among the total 12 PR patients, median DoR was 10.3 months [95% CI: 2.8–not evaluable (NE)] (Supplemental Figure 2 and Table 3).

Median PFS was 6.9 months (95% CI: 3.6–9.7) in all patients, 7.4 months (95% CI: 5.5–14.5) in treatment naïve and 4.0 months (95% CI: 2.8–9.7) in pre-treated patients [Figure 2(a) and

Table 2. Summary of treatment-related TEAEs $\geq 10\%$ by grouped PT and maximum CTCAE grade.

Characteristic	SCC244 total (N=32)		
	All grades, n (%)	Grade ≥ 3 , n (%)	SAE, n (%)
Subjects with any treatment-related TEAEs	32 (100)	11 (34.4)	
Oedema	19 (59.4)	2 (6.3)	1 (3.1)
Hypoalbuminaemia	13 (40.6)	0	1 (3.1)
Alanine aminotransferase increased	10 (31.3)	0	
Aspartate aminotransferase increased	8 (25.0)	0	
Nausea	8 (25.0)	1 (3.1)	1 (3.1)
Vomiting	8 (25.0)	0	
Decreased appetite	7 (21.9)	1 (3.1)	2 (6.3)
Headache	7 (21.9)	1 (3.1)	1 (3.1)
Blood bilirubin increased	6 (18.8)	0	
Anaemia	5 (15.6)	1 (3.1)	
Neutropenia	5 (15.6)	1 (3.1)	
Blood creatine phosphokinase increased	4 (12.5)	1 (3.1)	
Electrocardiogram QT prolonged	4 (12.5)	1 (3.1)	
Fatigue	4 (12.5)	0	1 (3.1)
Gamma-glutamyltransferase increased	4 (12.5)	0	
Hyponatraemia	4 (12.5)	0	
Leukopenia	4 (12.5)	0	
Thrombocytopenia	4 (12.5)	0	

TEAE defined as AEs that were reported or worsened on or after the start of study drug dosing up to 28 days after the last dose of study drug, or up to end of the study for treatment-related SAEs. Preferred terms are sorted in descending frequency. An AE with relationship missing (unknown) is counted as related. A subject with multiple occurrences of an AE is counted only once in the AE category. A subject with multiple grades for an AE is only counted under the maximum grade.

AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; PT, Preferred Term; TEAE, treatment-emergent adverse event.

Table 3]. Median OS was 17.0 months (95% CI: 10.3–NE) in all patients, 23.5 months (95% CI: 6.3–NE) in treatment naïve and 13.9 months (95% CI: 3.3–NE) in pre-treated patients [Figure 2(b) and Table 3].

Biomarker analysis

At a cutoff of *MET* GCN ≥ 4 , the ORR was 30% (95% CI: 6.7–65.2%) (3 responders in 10 patients) for the patients with *MET* overexpression only (*MET*amp-negative group, hereafter negative group) and 40.9% (95% CI:

20.7–63.6%) (9 responders in 22 patients) for patients with concurrent *MET* overexpression and *MET*amp (*MET*amp-positive group, hereafter positive group).

To evaluate whether *MET* IHC3+ can serve as a potential independent representative of *MET* overexpression as a clinical biomarker, we conducted a more in-depth analysis. Figure 3(a) and (b) utilized two different *MET*amp measurements, *MET* GCN and *MET*/*CEP7* ratio, respectively, to observe the distribution of patients in negative and positive groups at various integer

Table 3. Efficacy summary in MET overexpression NSCLC patients treated with gumarontinib.

Characteristic	Treatment naïve	Pre-treated	Total
<i>N</i>	12	20	32
ORR	5 (41.7%)	7 (35.0%)	12 (37.5%)
ORR 95% CI	[15.2–72.3]	[15.4–59.2]	[21.1–56.3]
Best overall response, <i>n</i> (%)			
CR	0	0	0
PR	5	7	12
SD	6	8	14
PD	1	2	3
NA	0	3	3
DCR	11 (91.7%)	15 (75.0%)	26 (81.3%)
DCR 95% CI	[61.5–99.8]	[50.9–91.3]	[63.6–92.8]
Median DoR (month)	10.3	13.2	10.3
DoR 95% CI	[3.6–NE]	[2.7–NE]	[2.8–NE]
Median PFS (month)	7.4	4.0	6.9
PFS 95% CI	[5.5–14.5]	[2.8–9.7]	[3.6–9.7]
Median OS (month)	23.5	13.9	17.0
OS 95% CI	[6.3–NE]	[3.3–NE]	[10.3–NE]
CI, confidence interval; CR, complete response; DCR, disease control rate; DoR, duration of response; NA, not available; NE, not evaluable; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.			

cutoff values. For instance, in Figure 3(b), at a *MET/CEP7* ratio cutoff of 2, there were 17 patients in the positive group, with 9 showing CR or PR, whereas 15 patients were in the negative group, with 3 showing CR or PR. At a *MET/CEP7* ratio cutoff of 4, only 4 patients were in the positive group, with 3 showing CR or PR, whereas 28 patients were in the negative group, with 9 showing CR or PR. Overall, with increasing cutoff values, the number of patients in the positive group decreased, whereas the number in the negative group increased. Additionally, an analysis of the relationship between patients' frontline treatment and efficacy was added. In Figure 3(c), for the pre-treated subgroup, when the *MET/CEP7* ratio cutoff was ≥ 2 and < 4 , the curves for *MET*-negative and *MET*-positive intersected, but they no longer intersected after a cutoff of 4. In Figure 3(d), for the treatment-naïve subgroup,

there was no observed intersection of curves when the *MET/CEP7* ratio cutoff was ≥ 2 . Furthermore, in Figure 3(c) and (d), similarly, with increasing cutoff values, the number of patients in the positive group decreased, whereas the number in the negative group increased.

Discussion

Currently, the second-line or subsequent treatment for driver-gene negative advanced NSCLC is mainly chemotherapy or immune checkpoint inhibitors (if not used in front-line therapy).^{4–6} However, the overall ORR is less than 10%, and the median PFS and median OS are no more than 4 and 7–9 months, respectively.^{4,5} There are still greatly clinical unmet needs for these NSCLC patients. Currently, *MET*ex14 skipping mutation is recognized as an independent driver mutation in NSCLC and is usually mutually exclusive from

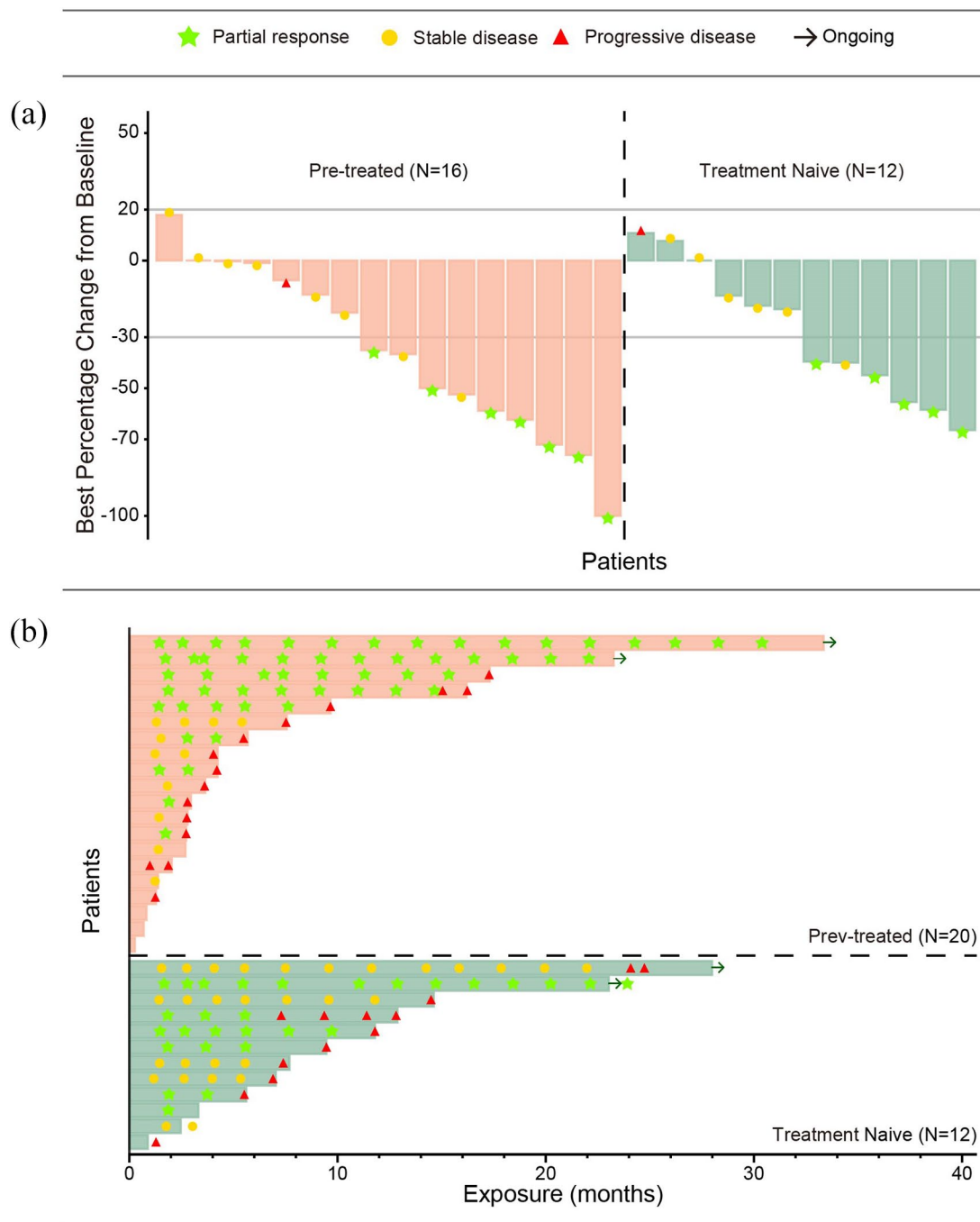


Figure 1. (a) Waterfall plot displaying the maximum percentage change from baseline in target lesions for each NSCLC patient with MET overexpression (IHC3+). (b) Swimmer plot illustrating the duration of response for each NSCLC patient with MET overexpression (IHC3+). IHC, immunohistochemistry; NSCLC, non-small-cell lung cancer.

other drivers.¹⁵ It is used as a clinical biomarker for stratifying NSCLC patients based on their predicted response to MET inhibitors. However, MET overexpression, the most occurred among the *MET* alterations, its role as oncogenic driver events remains under debate.

Very little clinical trials were conducted based on MET inhibitor monotherapy in driver-gene negative NSCLC population with MET overexpression, BPI-9016M, a novel TKI targeting c-Met. A clinical trial performed in locally advanced or metastatic NSCLC showed BPI-9016M

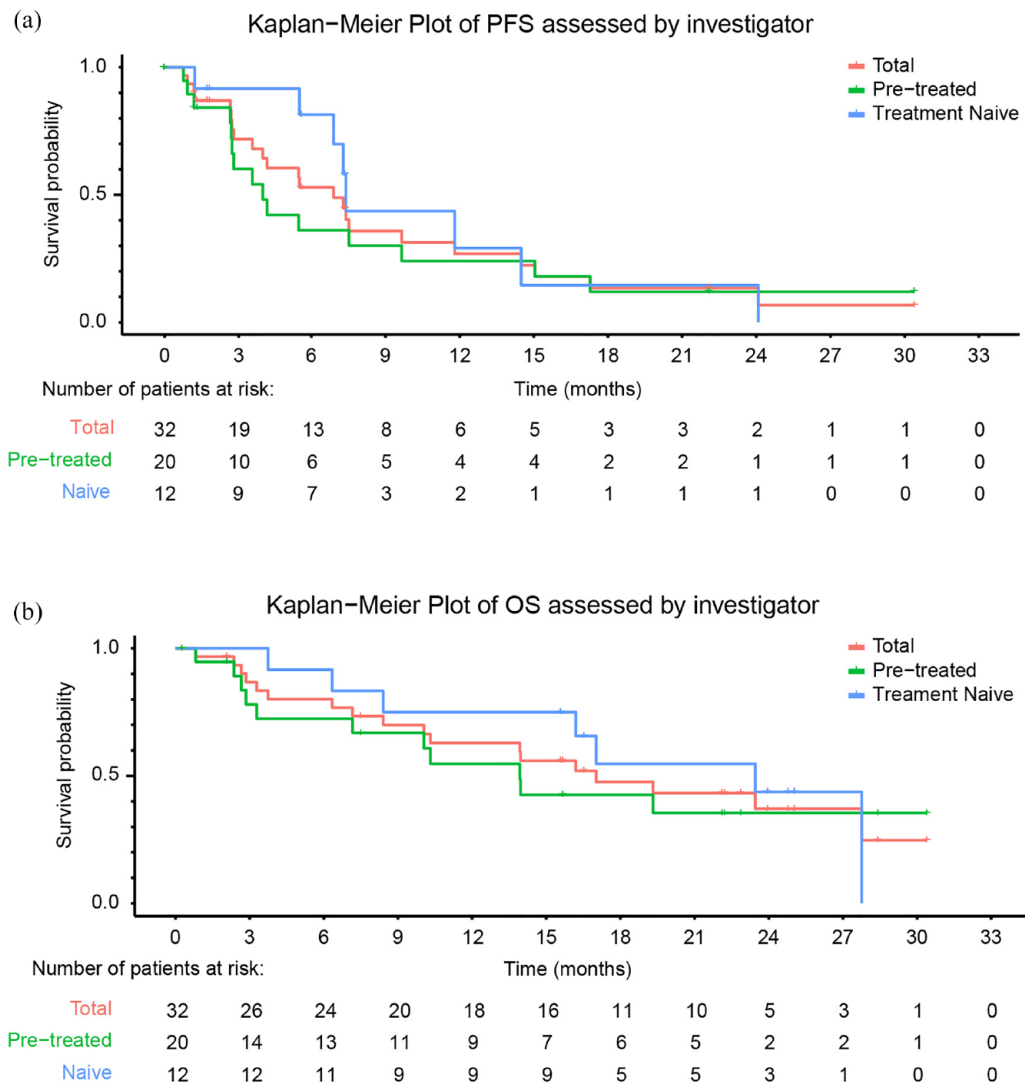


Figure 2. Kaplan–Meier plot of (a) PFS assessed by investigator and (b) OS assessed by investigator. OS, overall survival; PFS, progression-free survival.

monotherapy exhibited limited efficacy in MET overexpression or *MET*ex14 skipping mutation patients. Only one PR patient was observed. ORR was 2.6% (1/38, 95% CI: 0.1–13.8%) in all 38 patients. The median PFS and OS were 1.9 months (95% CI: 1.9–3.7) and 10.3 months (95% CI: 7.3–NE) in all 38 patients, respectively.²⁷ Two previous phase III trials assessed the efficacy of the combination of MET inhibitor/antibody plus Erlotinib in previously treated NSCLC patients with chemotherapy regimens.^{28,29} Tivantinib is a potent non-ATP competitive-selective MET-TKI. The MARQUEE phase III study (NCT01244191), the exploratory subgroup analysis showed OS was prolonged [median OS: 8.8 months (Erlotinib + tivantinib)

versus 5.0 months (Erlotinib + placebo); Hazard ratio (HR), 0.56; 95% CI, 0.35–0.89 for Erlotinib plus Tivantinib in the *EGFR* wild-type, *KRAS* wild-type and MET high (defined as high if membranous staining intensity was ≥ 2 in $\geq 50\%$ of tumour cells) subgroup.²⁸ Onartuzumab is a monoclonal antibody targeting c-Met. The phase III METLung trial (NCT01456325) examined the efficacy and safety of Onartuzumab plus Erlotinib in patients with locally advanced or metastatic NSCLC. Erlotinib with or without Onartuzumab in previously treated advanced NSCLC patients with MET overexpression (defined as $\geq 50\%$ of tumour cells with MET IHC scores of 2+ or 3+) showed worse survival rate.²⁹

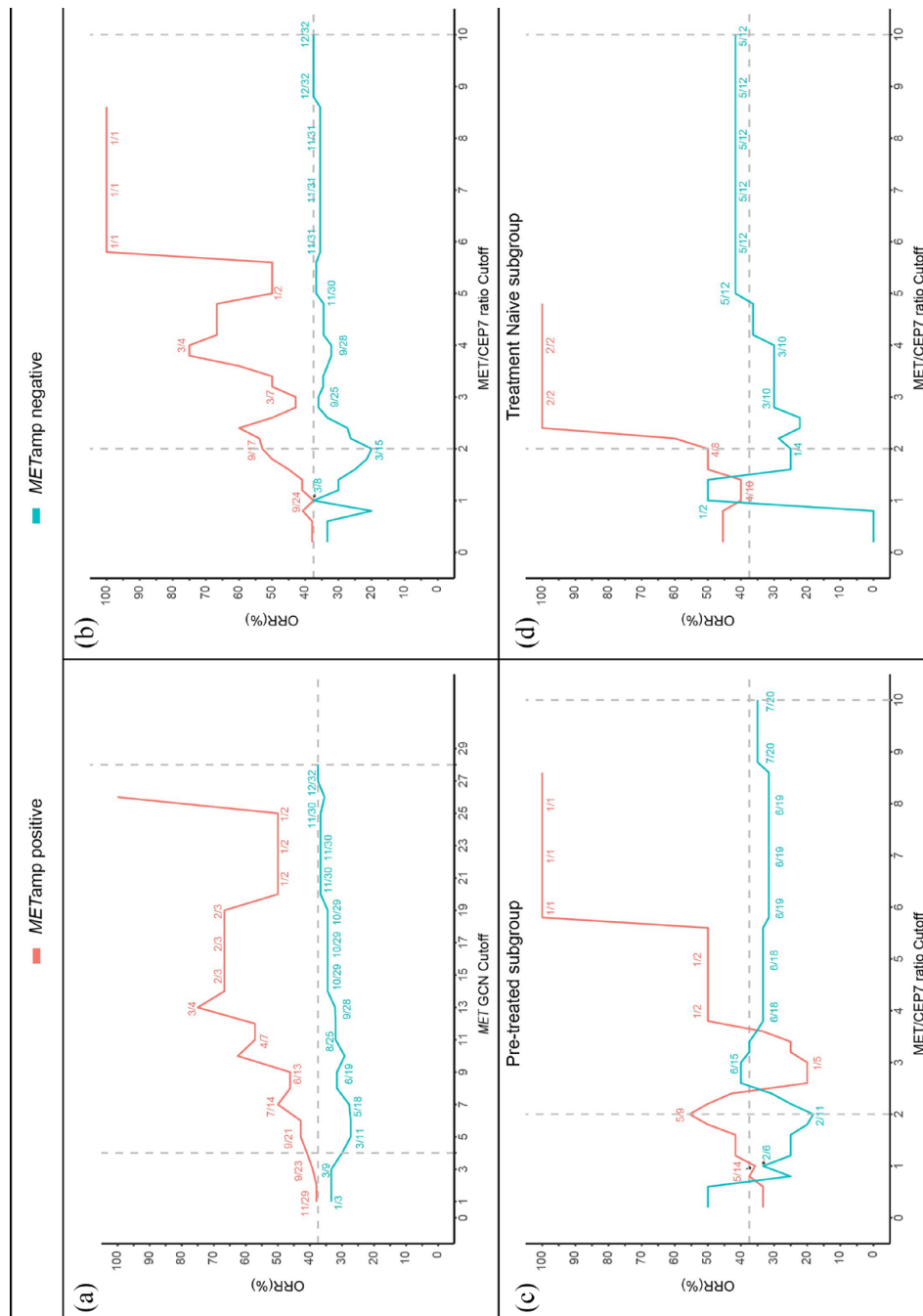


Figure 3. Biomarker analysis. (a, b) The distribution of NSCLC patients with MET IHC3+ in MET amplification negative and MET amplification positive groups at various integer cutoff values based on MET GCN and MET/CEP7 ratio measurement, respectively, and the ORR at different cutoff values. (c, d) Analysis of the relationship between patients' frontline treatment and efficacy based on MET/CEP7 (Chromosome Enumeration Probe 7) ratio measurement in the pre-treated subgroup (c) and in the treatment-naïve subgroup (d).

GCN, gene copy number; IHC, immunohistochemistry; NSCLC, non-small cell lung cancer.

In our pooled analysis, gumarontinib 300mg showed promising antitumour activity in the 32 patients. The overall ORR was 37.5% (95% CI: 21.1–56.3%), 41.7% (95% CI: 15.2–72.3%) in treatment naïve and 35.0% (95% CI: 15.4–59.2%) in pre-treated patients. Median PFS was 6.9 months (95% CI: 3.6–9.7) overall, 7.4 months (95% CI: 5.5–14.5) in treatment naïve and 4.0 months (95% CI: 2.8–9.7) in pre-treated patients. Median OS was 17.0 months (95% CI: 10.3–NE) overall. Compared with the efficacy of standard chemotherapy, the other MET inhibitors, like BPI-9016M and Tivantinib, and the antibody Onartuzumab above, the preliminary results of gumarontinib 300 in NSCLC patients with MET overexpression were favourable both in pre-treated and treatment naïve patients, suggesting MET overexpression may be a potential molecular predictive biomarker for the driver-gene negative NSCLC patients, might help precisely expand the NSCLC population that would benefit from the clinical use of gumarontinib. Thus, an open-label, multicentre, randomized, phase III study (CTR20230451; <http://www.chinadrugtrials.org.cn/>) of gumarontinib *versus* docetaxel in driver-gene negative locally advanced or metastatic NSCLC patients with MET overexpression who have progressed after immunotherapy and platinum-based chemotherapy is ongoing to confirm this finding.

So far, MET overexpression is not sufficient as an independent predictive biomarker to guide clinical practice, meaning even if MET overexpression is detected, an assessment of *METamp* status is still necessary. If *METamp* is confirmed, consideration may be given to the use of MET-TKI. This is because not all MET overexpression is caused by *METamp*, and *METamp* indeed serves as a specific predictive biomarker to guide the application of MET-TKI.³⁰ However, what is the probability of *METamp* in the case of MET overexpression? The correlation between MET overexpression and *de novo METamp* is relatively low.³¹ A study involving 181 cases of non-targeted therapy-treated lung adenocarcinoma patients showed that among MET overexpression positive patients (*H* score ≥ 200), only 1% had *METamp* (detected by FISH, $MET/CEP7 \geq 2.2$), *METamp* could still be detected in samples that were negative for MET overexpression.³¹ Nevertheless, in the TATTON study, among *EGFR*-mutated NSCLC patients with MET overexpression ($\geq 50\%$ tumour cells with MET IHC scores 3+) who developed acquired resistance after a prior

EGFR-TKI treatment, 80% (16/20) of them were concurrently found to have *METamp* ($MET\ GCN \geq 5$ or $MET/CEP7 \geq 2$).³² In advanced NSCLC patients lacking driver-gene mutations and exhibiting MET overexpression (IHC3+), the correlation between *METamp* fold and efficacy remains unknown. Therefore, this study also deeply investigated this question. Figure 3 illustrates that, whether based on the *MET* GCN [Figure 3(a)] or *MET/CEP7* ratio [Figure 3(b)], across different cutoff values, the longitudinal distribution of patients treated with gumarontinib within the MET IHC3+ population changed between *METamp*-negative and *METamp*-positive subgroups, with increasing cutoff values, the number of patients in the *METamp*-positive group decreased, whereas the number in the *METamp*-negative group increased. Overall, the ORR in the *METamp*-positive subgroup is higher than that in the *METamp*-negative subgroup. Specifically, within the *METamp*-positive subgroup, the trend of ORR increases with the amplification fold. In the *METamp*-negative subgroup, the ORR to gumarontinib remains relatively stable, ranging from 30% to 37.5%. Taken together, it can be inferred that the efficacy data are predominantly influenced by MET overexpression. This inference is supported by the increasing number of patients included in the *METamp*-negative subgroup as the cutoff values increase, indicating that the patients with only MET overexpression, no amplification demonstrates the promising efficacy, and MET IHC3+ could potentially serve as an independent representative of MET overexpression as a clinical biomarker.

However, we must acknowledge the limitations of this study. Firstly, this study based on two single arm studies, the retrospective design was therefore prone to selection bias. Secondly, the patient number was limited ($n = 32$) in our study.

Conclusion

In summary, in this pooled study, gumarontinib showed promising clinical efficacy in driver-gene negative locally advanced or metastatic NSCLC patients with *MET* overexpression and warranted a phase III study to further evaluated.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical

Practice Guideline. The SCC244-104 study (NCT03457532) and SCC244-108 study (NCT04270591) were approved by the ethics committees from each participating centre. The patients in this pooled study were from 22 centres, the names of the ethics committees from the 22-participating centres, as well as the approval numbers or IDs, were listed in the Supplemental File named 'Ethics committee list'.

Consent for publication

Not applicable.

Author contributions

Yongfeng Yu: Investigation; Supervision.

Wen Dong: Investigation; Supervision.

Yanxia Shi: Investigation; Supervision.

Rong Wu: Investigation; Supervision.

Qitao Yu: Investigation; Supervision.

Feng Ye: Investigation; Supervision.

Chengzhi Zhou: Investigation; Supervision.

Xiaorong Dong: Investigation; Supervision.

Xingya Li: Investigation; Supervision.

Yongsheng Li: Investigation; Supervision.

Zhen Li: Investigation; Supervision.

Lin Wu: Investigation; Supervision.

Yueyin Pan: Investigation; Supervision.

Hong Shen: Investigation; Supervision.

Dehua Wu: Investigation; Supervision.

Zhongyuan Xu: Investigation; Supervision.

Jinsheng Wu: Investigation; Supervision.

Nong Xu: Investigation; Supervision.

Yanru Qin: Investigation; Supervision.

Aimin Zang: Investigation; Supervision.

Jingdong Zhang: Investigation; Supervision.

Jianya Zhou: Investigation; Supervision.

Xiaotao Zhang: Investigation; Supervision.

Yanqiu Zhao: Investigation; Supervision.

Fugen Li: Investigation; Writing – review & editing.

Huizhen Wang: Formal analysis; Writing – original draft.

Qi Liu: Formal analysis; Writing – original draft.

Zhenyong Han: Formal analysis; Software.

Jin Li: Investigation; Supervision.

Shun Lu: Investigation; Supervision.

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Competing interests

The authors declare that there is no conflict of interest.


Availability of data and materials

Supplemental data and materials for this article are available online.

ORCID iDs

Chengzhi Zhou  <https://orcid.org/0000-0002-1758-0035>

Xiaotao Zhang  <https://orcid.org/0000-0001-7213-4970>

Shun Lu  <https://orcid.org/0000-0001-8833-7262>

Supplemental material

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