

Long-Term Efficacy, Safety, and Subgroup Analysis of Savolitinib in Chinese Patients With NSCLCs Harboring *MET* Exon 14 Skipping Alterations



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ABSTRACT

Introduction: Savolitinib has been found to have encouraging antitumor activity and a favorable safety profile in Chinese patients with pulmonary sarcomatoid carcinoma and other NSCLCs with *MET* exon 14 skipping alterations (*MET* ex14 positive) at the primary analysis of a phase 2 study. Here, we present the long-term efficacy and safety data of savolitinib, including subgroup analyses.

Methods: This multicenter, single-arm, open-label, phase 2 study in the People's Republic of China enrolled *MET* inhibitor-naive adults with locally advanced or metastatic *MET*ex14-positive NSCLC (NCT02897479). Oral savolitinib at a dose of 400 or 600 mg was administered once daily (body weight dependent). The primary objectives of the final analysis were long-term overall survival (OS) and subgroup analyses by previous systemic treatment, NSCLC subtypes, and brain metastases.

Results: At the final analysis cutoff date (June 28, 2021), a total of 70 patients were enrolled and receiving savolitinib, and median follow-up was 28.4 (interquartile range: 26.2–36.3) months. The median OS was 12.5 months (95% confidence interval [CI]: 10.5–21.4 [18- and 24-mo OS rates, 42.1% and 31.5%, respectively]). Median OS in pretreated or treatment-naive patients was 19.4 (95% CI: 10.5–31.3) and 10.9 (95% CI: 7.5–14.0) months, respectively; it was 10.6 months (95% CI: 4.6–14.0) in patients with pulmonary sarcomatoid carcinoma, 17.3 months (95% CI: 10.6–23.6) in other NSCLC subtypes, and 17.7 months (95% CI: 10.5–not evaluable) in patients with brain metastases. No new safety signals emerged with prolonged follow-up and exposure.

Conclusions: The updated results further confirm the favorable benefit and acceptable safety of savolitinib in Chinese patients with *MET*ex14-positive NSCLC.

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Keywords: Savolitinib; Non-small cell lung cancer; *MET*ex14 skipping mutations; Pulmonary sarcomatoid carcinoma; *MET* tyrosine kinase inhibitors

Introduction

Lung cancer is one of the most common cancers and is the leading cause of cancer-related mortality in the world.¹ NSCLC accounts for approximately 85% of all lung cancers in the People's Republic of China.² Pulmonary sarcomatoid carcinoma (PSC), a highly invasive subtype of pulmonary cancer that accounts for

approximately 0.3% to 3.0% of all pulmonary malignancies,^{3–6} constitutes a heterogeneous group of NSCLC.⁷ Patients with PSC have a poorer prognosis with limited treatment options compared with those with other NSCLC subtypes.^{8–10} In previous studies, the overall 5-year survival rate in patients with PSC who were operated at an early stage was approximately 20% to 30%, lower than that in patients with other NSCLCs at early stage at 55% to 80%.⁹ Median time to recurrence was 11.3 months in patients with PSC, compared with 61.4 months in patients with NSCLC.⁷

Approximately 0.1% to 3% of patients with NSCLC have *MET* exon 14 (*MET*ex14) skipping,^{11,12} which rises to up to 22% in patients with PSC.¹³ The mutation occurs more frequently in elderly patients, females, and nonsmokers and is associated with a worse prognosis.^{12,13} The contribution of *MET*ex14 mutations to adverse outcomes in NSCLC may be related to its wide-ranging role in the human body. The *MET* proto-oncogene encodes a receptor tyrosine kinase activated by HGF¹⁴ that is involved in cellular proliferation, motility, migration, and invasion in multiple organ systems embryonically and through adulthood.^{15–17} Oncogenic activation of *MET* can be caused by point mutations in the tyrosine kinase domain, increases in the number of gene copies, and protein overexpression.^{18,19} The most often acquired activating mutations of *MET* lead to *MET*ex14 skipping alterations, in which exon 14 is skipped during *MET* mRNA splicing.²⁰ *MET*ex14 skipping results in the formation of a shortened receptor that preserves affinity for HGF but lacks the juxta membrane domain, resulting in a loss of negative regulatory function. This leads to receptor accumulation and prolonged activation by HGF.²¹

Current first-line treatment options for the treatment of advanced PSC have limited efficacy. For platinum-based chemotherapy, median progression-free survival (PFS) and overall survival (OS) in patients with PSC are estimated at approximately 2 and 6 months, respectively.^{3,22} Several studies have revealed the beneficial effects of *MET* inhibitors in patients with *MET*-driven NSCLC.^{23–26} Nevertheless, the efficacy of *MET* tyrosine kinase inhibitors (TKIs) in patients with PSC remains poorly described with limited clinical literature available.

Brain metastases often develop in lung cancers with disease progression, which are associated with a high morbidity and poor prognosis.²⁷ The reported incidence of patients with brain metastases in NSCLC was approximately 20% at diagnosis.²⁸ Despite the available treatments for brain metastases of targetable molecular drivers such as *EGFR*, *ALK*, and *ROS1*,²⁸ there are limited

options for other patients who are negative for the above-mentioned targets. For the patients with lung adenocarcinoma lacking driver genes (*EGFR*, *KRAS*, *ALK*, *ROS1*, and *RET* negative) in an East Asian population, 37.8% of them were found with *MET*ex14 skipping alterations,²⁹ suggesting an unmet clinical need for them if they will develop a brain metastasis.

Savolitinib is a potent and highly selective oral MET TKI that has been investigated in NSCLC^{30–33} and other solid tumors.^{31,34–37} We have previously reported the promising efficacy and tolerability of savolitinib in patients with NSCLC harboring *MET*ex14 skipping mutations.³⁸ In the phase 2 study, we investigated the efficacy and safety profile of savolitinib in MET inhibitor-naïve Chinese patients with locally advanced or metastatic *MET*ex14-positive NSCLCs, including PSC, the first time that this subgroup was adequately represented in a trial evaluating MET TKIs. In the previously published data, at a median follow-up of 17.6 months, savolitinib was found to have an independent review committee-assessed objective response rate (ORR) of 49.2% in the tumor-response-evaluable set (TRES) and median PFS and OS of 6.8 and 12.5 months, respectively.³⁸ In the subgroup analysis, promising results were observed with savolitinib among 25 patients with PSC; 10 patients had a partial response (ORR 40.0%, 95% confidence interval [CI]: 21.1–61.3), with a median duration of response (DOR) of 17.9 months (95% CI: 4.1–not evaluable) and a median PFS of 5.5 months (95% CI: 2.8–6.9), as assessed by the independent review committee.³⁸

Here, we report the updated results of the same trial, with an additional 10 months of data spanning August 2020 to June 2021, including subgroup analyses by previous systemic treatment (yes versus no), NSCLC subtypes (PSC versus other NSCLCs), and brain metastases.³⁸

Materials and Methods

Study Design and Participants

The methods of this study have been previously described in detail.³⁸ Briefly, this was a phase 2, multicenter, single-arm, open-label study conducted in 32 hospitals in the People's Republic of China ([ClinicalTrials.gov](https://clinicaltrials.gov) identifier: NCT02897479). Eligible patients (≥ 18 y of age) had histologically diagnosed, locally advanced or metastatic PSC or other NSCLC subtypes with *MET*ex14 skipping alterations that did not have *EGFR*, *ALK*, or *ROS1* alterations (determined at screening) and had not previously received MET-targeted treatment. Patients had progressed on or were found to have intolerance toward one or more

standard treatments or were deemed clinically unsuitable for standard treatment by investigators. Detailed inclusion and exclusion criteria are listed in the Supplementary Data (page numbers 1–2).

This study was conducted in accordance with the Declaration of Helsinki and Guidelines for Good Clinical Practice. The protocol and its amendments were approved by the ethics committees from each participating center. All patients provided written informed consent before enrollment. The full study protocol and a summary of protocol amendments are provided in the Supplementary Data (page numbers 15–127).

Procedures

Oral savolitinib was taken once daily, with patients weighing greater than or equal to 50 kg receiving 600 mg and patients weighing less than 50 kg receiving 400 mg. Treatment was continued until disease progression, death, intolerable toxicity, initiation of another anti-tumor therapy, noncompliance, patient withdrawal, or patient discontinuation. Radiographic tumor evaluation was done at baseline, every 6 weeks within the first year after the first dose of savolitinib, and every 12 weeks thereafter until treatment discontinuation. Tumor response was measured according to Response Evaluation Criteria in Solid Tumors version 1.1.³⁹

Outcomes

The primary objective of this final analysis was to evaluate OS, 18- and 24-month OS rates. The secondary objectives were to evaluate other tumor responses, which are as follows: PFS, including 12- and 15-month PFS rates, ORR, disease control rate (DCR), DOR, and time to response (TTR). Long-term exposure to savolitinib and safety are also reported. All adverse events (AEs) were recorded from the point of signing of informed consent to 30 days after the last dose, and they were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03. Treatment-related AEs were adjudicated by the investigators.

Statistical Analysis

The statistical analysis plan was as described for the previous analysis of this study.³⁸ The full analysis set (FAS) included all patients who received at least one dose of savolitinib. The TRES (per protocol) comprised all treated patients with a measurable lesion at baseline and at least one adequate scheduled postbaseline tumor assessment or the presence of disease progression, confirmed by radiology assessment. DCR, DOR, and TTR were assessed in both the

TRES and the FAS. PFS, OS, and safety were assessed in the FAS. Investigator-assessed responses were summarized in both FAS and TRES, and only investigator assessment, PFS, DOR, DCR, and ORR are reported in this report. In the prespecified subgroup analysis, activity according to pathologic tumor subtype (PSC versus other NSCLC subtypes) and previous systemic treatment (treatment-naïve versus previously treated patients) in the FAS have been evaluated. In a post hoc analysis, activity in patients with brain metastases from the FAS has been evaluated.

All statistical analyses were performed using SAS version 9.4. PFS, TTR, DOR, and OS were estimated by the Kaplan-Meier method. Censored rules for these time-to-event efficacy indicators were the same as previously described.³⁸ The statistical analysis plan is provided in the Supplementary Data (page numbers 128–172).

Results

Patient Characteristics

Of the 592 patients who were prescreened, 70 were enrolled and received at least one dose of savolitinib; these patients comprised the FAS (Fig. 1). The investigator-assessed TRES comprised 62 patients. In patients included in the final analysis, as of June 28, 2021, the median follow-up among the 70 enrolled patients was 28.4 (interquartile range: 26.2–36.3) months. The median age of patients in the FAS was 68.7 years (Table 1). Of patients in the prespecified subgroups, 25 patients (36%) had PSC (versus 64% with other NSCLC subtypes, $n = 45$) and 42 patients (60%) had received antitumor systemic treatment previously for advanced disease (versus 40% in treatment-naïve patients, $n = 28$). In addition, 15 patients (21%) had brain metastases at baseline. The proportion of the patients aged 75 years or above was 23% ($n = 16$) in the FAS and 24% ($n = 6$) and 27% ($n = 4$) in the PSC and brain metastases subgroups, respectively. Patient characteristics were similar in the subgroups and the FAS (Table 1). Adenocarcinoma was the most common pathologic subtype ($n = 40$, 89%) among patients with other subtypes of NSCLC ($n = 45$). Patient demographics in the other NSCLC subtype group and in patients in the PSC group were similar, although more patients with PSC were nonsmokers ($n = 29$, 64% versus $n = 13$, 52%). Patients who had not received systemic antitumor treatment previously were older (with a median age of 74.5 y) than those who had received treatment (median age of 67.7 y), and 50% were nonsmokers. In addition, more patients with PSC ($n = 13$, 46%) were treatment naïve, and only 29% ($n = 12$) of the pretreated patients had PSC. A higher proportion of patients with brain metastases were nonsmokers ($n = 11$, 73%) compared with all other

subgroups; 13% of the patients ($n = 2$) in this subgroup had PSC.

Eight patients received 400 mg of savolitinib, and 62 patients received 600 mg of savolitinib, with a median number of treatment cycles of 9.5 (range: 0.7–32.6) and 10.0 (range: 0.2–76.2), respectively (Supplementary Table 1). More than 25% of the enrolled patients (either dose) continued treatment for more than or equal to 12 months. The median duration of exposure to the study medication was 6.9 months, and the median relative dose intensity was 89.7% (Supplementary Table 1).

Efficacy

In the FAS, median OS was 12.5 months (95% CI: 10.5–21.4) (Fig. 2A). The 18- and 24-month OS rates in the FAS were 42.1% (95% CI: 30.2–53.5) and 31.5% (95% CI: 20.8–42.7), respectively. The median OS was 19.4 months (95% CI: 10.5–31.3) in pretreated patients and 10.9 months (95% CI: 7.5–14.0) in treatment-naïve patients. The 18- and 24-month OS rates for the pretreated patients were 50% (95% CI: 34.2–64.6) and 38% (95% CI: 22.8–52.2), respectively; in treatment-naïve patients, the 18- and 24-month OS rates were 30% (95% CI: 14.1–47.1) and 22% (95% CI: 9.1–39.1), respectively. In patients with PSC and other NSCLC subtypes, median OS was 10.6 months (95% CI 4.6–14.0) and 17.3 months (95% CI: 10.6–23.6), respectively. In patients with PSC, 18- and 24-month OS rates were 30% (95% CI: 13.4–48.4) and 26% (95% CI: 10.5–43.9), respectively. The 18- and 24-month OS rates were 49% (95% CI: 33.5–62.8) and 35% (95% CI: 21.0–48.9) in patients with other NSCLC subtypes. Median OS in patients with brain metastases was 17.7 months (95% CI: 10.5–not evaluable); 18- and 24-month OS rates in these patients were 50% (95% CI: 22.9–72.2) and 36% (95% CI: 13.0–59.4), respectively.

In the FAS, the median investigator-assessed PFS was 6.9 months (95% CI: 4.6–8.3); 12- and 15-month PFS rates were 31% (95% CI: 19.6–42.6) and 25% (95% CI: 15.0–36.9), respectively (Fig. 2B). Among patients with PSC, 12- and 15-month PFS rates were 22% (95% CI: 8.0–40.1) and 22% (95% CI: 8.0–40.1), compared with 36% (95% CI: 20.9–51.0) and 27% (95% CI: 13.7–41.9) in patients with other NSCLC subtypes, respectively. In patients with previous treatment, 12- and 15-month PFS rates were 37% (95% CI: 21.6–52.3) and 28% (95% CI: 14.9–43.5) versus 21% (95% CI: 7.8–39.3) and 21% (95% CI: 7.8–39.3) in treatment-naïve patients, respectively. In patients with brain metastases, 12- and 15-month PFS rates were 31% (95% CI: 9.5–55.4) and 31% (95% CI: 9.5–55.4), respectively.

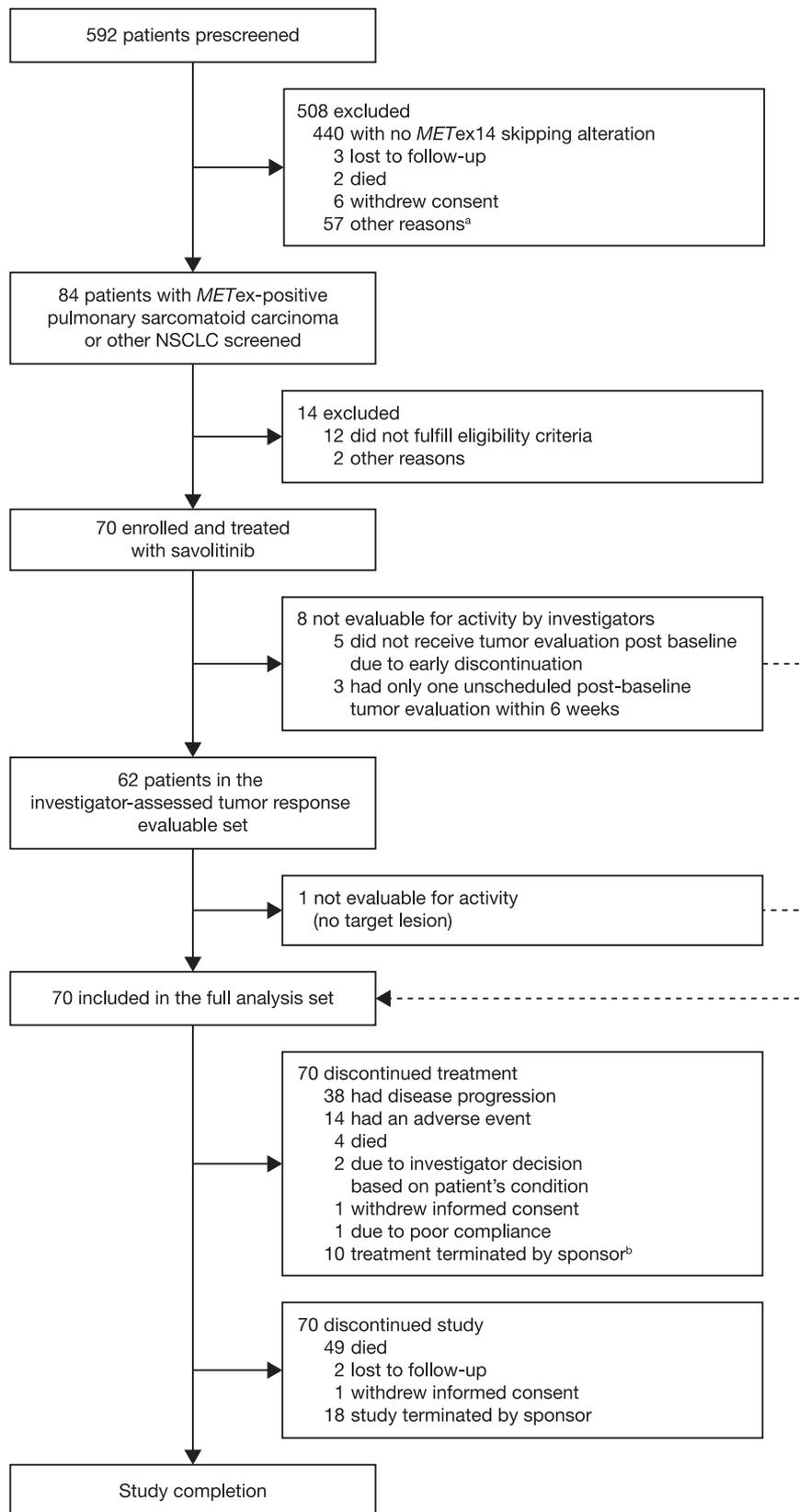


Figure 1. CONSORT diagram of the trial flow. ^aOthers mainly included insufficient samples or lack of qualified samples for gene testing. ^bThere were 10 patients who did not meet the end-of-treatment criteria at the end of the study but continued to receive the medication as a sponsor’s gift after the study ended. METex14, MET exon 14.

Table 1. Baseline Demographics and Disease Characteristics by Subgroups in the Full Analysis Set (N = 70)

Characteristics	Full Analysis Set (N = 70)	Type of Primary Tumor		Previous Antitumor Systemic Treatment Status		Brain Metastases Status	
		Pulmonary Sarcomatoid Carcinoma (n = 25)	Other NSCLC Subtypes (n = 45)	Pretreated (n = 42)	Treatment Naive (n = 28)	Brain Metastases (n = 15)	Nonbrain Metastases (n = 55)
Demographics, n (%)							
Age							
Median (range) ^a	68.7 (51.7-85.0)	69.3 (54.1-84.8)	68.1 (51.7-85.0)	67.7 (51.7-84.8)	74.5 (56.0-85.0)	68.6 (51.7-84.8)	68.7 (51.9-85.0)
<75 y	54 (77)	19 (76)	35 (78)	38 (90)	16 (57)	11 (73)	43 (78)
≥75 y	16 (23)	6 (24)	10 (22)	4 (10)	12 (43)	4 (27)	12 (22)
Sex							
Female	29 (41)	8 (32)	21 (47)	17 (40)	12 (43)	7 (47)	22 (40)
Male	41 (59)	17 (68)	24 (53)	25 (60)	16 (57)	8 (53)	33 (60)
Smoking history							
Nonsmokers	42 (60)	13 (52)	29 (64)	28 (67)	14 (50)	11 (73)	31 (56)
Smokers	28 (40)	2 (48)	16 (46)	14 (33)	14 (50)	4 (27)	24 (44)
Disease characteristics, n (%)							
ECOG performance status^b							
0	12 (17)	3 (12)	9 (20)	8 (19)	4 (14)	3 (20)	9 (16)
1	57 (81)	22 (88)	35 (78)	34 (81)	23 (82)	12 (80)	45 (82)
3	1 (1)	0	1 (2)	0	1 (4)	0	1 (2)
Disease stage at primary diagnosis							
III	10 (14)	3 (12)	7 (16)	7 (17)	3 (11)	2 (13)	8 (15)
IV	50 (71)	15 (60)	35 (78)	30 (71)	20 (71)	13 (87)	37 (67)
Histology, n (%)							
Pulmonary sarcomatoid carcinoma	25 (36)	25 (100)	0	12 (29)	13 (46)	2 (13)	23 (42)
Other NSCLC subtypes	45 (64)	0	45 (100)	30 (71)	15 (54)	13 (87)	32 (58)
Adenocarcinoma	40 (57)		40 (89)	27 (64)	13 (46)	13 (87)	27 (49)
Squamous cell carcinoma	3 (4)		3 (7)	2 (5)	1 (4)	0	3 (5)
Adenosquamous carcinoma	1 (1)		1 (2)	1 (2)	0	0	1 (2)
Other	1 (1)		1 (2)	0	1 (4)	0	1 (2)
Brain involvement at baseline	15 (21)	2 (8)	13 (29)	11 (26)	4 (14)	N/A	N/A
Previous treatments							
Previous antitumor systemic treatment							
Yes	42 (60)	12 (48)				11 (73)	31 (56)
No	28 (40)	13 (52)	15 (33)	N/A	N/A	4 (27)	24 (44)

^aData are median (%), min-max for age.^bNo patients were in other categories for these characteristics.

ECOG, Eastern Cooperative Oncology Group; max, maximum; min, minimum; N/A, not applicable.

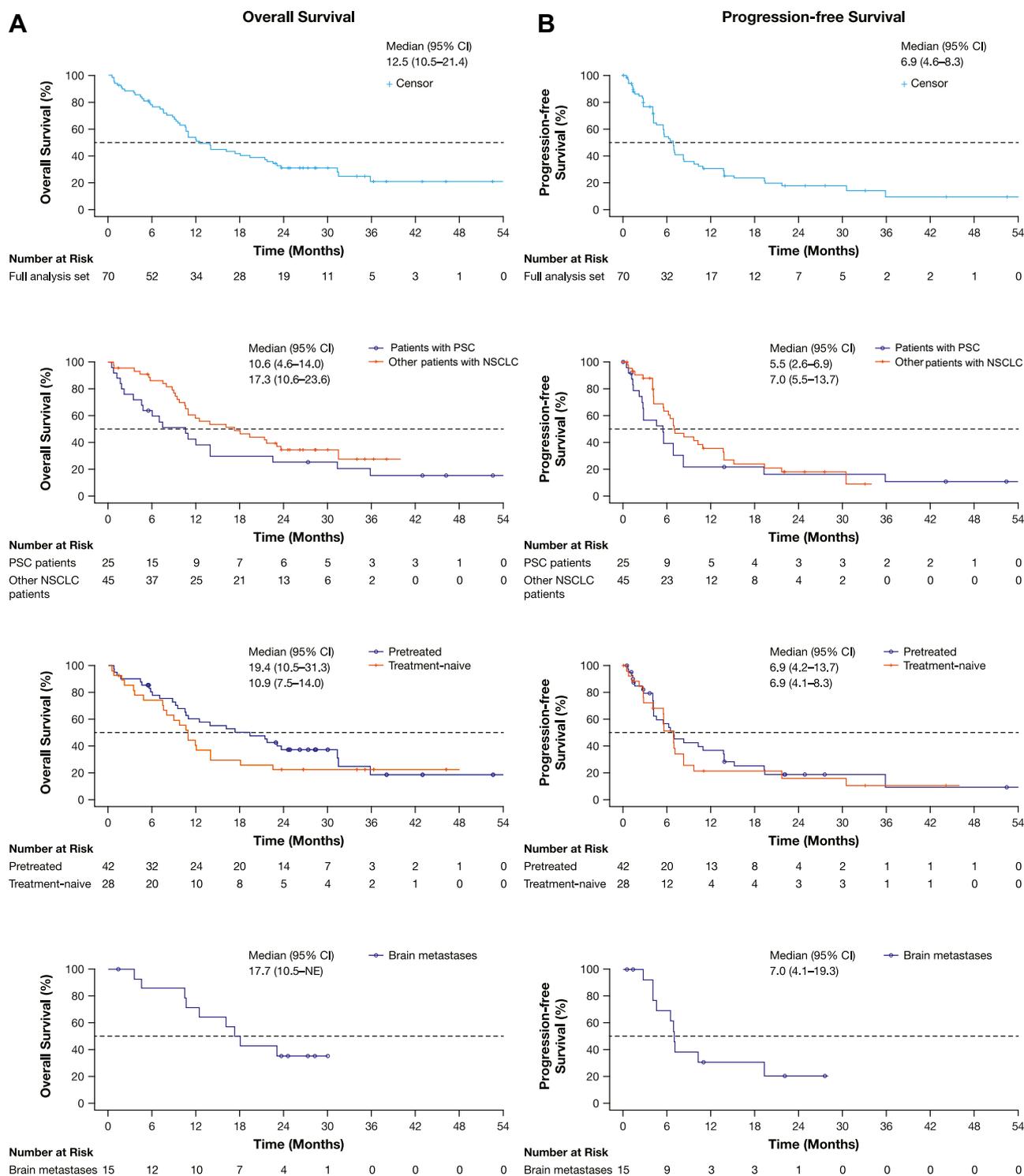


Figure 2. (A) Overall survival and (B) progression-free survival in patients who received savolitinib in the full analysis set and by subgroups. CI, confidence interval; NE, not evaluable; PSC, pulmonary sarcomatoid carcinoma.

The tumor response outcomes in each prespecified subgroup are summarized in Table 2. In the 62 patients included in the TRES, investigator-assessed ORR was 53% (95% CI: 40.1–66.0). In patients with PSC and patients with other NSCLC subtypes, ORR was 50% (95% CI: 27.2–72.8) and 55% (95% CI: 38.7–

70.2), respectively. Patients who received previous treatment for advanced disease had an ORR of 53% (95% CI: 35.8–69.0), whereas ORR was 54% (95% CI: 32.8–74.5) in treatment-naive patients. The DCR reached 92% (95% CI: 82.2–97.3) in the TRES. Median DOR and TTR in the TRES were 6.9 months (95% CI:

Table 2. Investigator-Assessed Responses in the Tumor-Response-Evaluable Set and the Full Analysis Set

Investigator-Assessed Responses	Tumor-Response-Evaluable Set (n = 62)		Full Analysis Set (N = 70)	
ORR, n (% , 95% CI)	33 (53.2%, 40.1-66.0)		33 (47.1%, 35.1-59.5)	
DCR, n (% , 95% CI)	57 (91.9%, 82.2-97.3)		57 (81.4%, 70.3-89.7)	
Median DOR, ^a mo (95% CI)	6.9 (4.9-12.5)		N/A	
Median TTR, ^a mo (95% CI)	1.4 (1.4-1.5)		N/A	
	Type of Primary Tumor		Type of Primary Tumor	
	PSC (n = 20)	Other NSCLC Subtypes (n = 42)	PSC (n = 25)	Other NSCLC Subtypes (n = 45)
ORR, n (% , 95% CI)	10 (50.0%, 27.2-72.8)	23 (54.8%, 38.7-70.2)	10 (40.0%, 21.1-61.3)	23 (51.1%, 35.8-66.3)
DCR, n (% , 95% CI)	18 (90.0%, 68.3-98.8)	39 (92.9%, 80.5-98.5)	18 (72.0%, 50.6-87.9)	39 (86.7%, 73.2-95.0)
Median DOR, ^a mo (95% CI)	12.4 (3.2-NE)	5.6 (3.8-12.3)	N/A	N/A
Median TTR, ^a mo (95% CI)	1.4 (1.3-1.4)	1.4 (1.4-1.5)	N/A	N/A
	Previous Antitumor Systemic Treatment Status		Previous Antitumor Systemic Treatment Status	
	Pretreated (n = 38)	Treatment Naive (n = 24)	Pretreated (n = 42)	Treatment Naive (n = 28)
ORR, n (% , 95% CI)	20 (52.6%, 35.8-69.0)	13 (54.2%, 32.8-74.5)	20 (47.6%, 32.0-63.6)	13 (46.4%, 27.5-66.1)
DCR, n (% , 95% CI)	34 (89.5%, 75.2-97.1)	23 (95.8%, 78.9-99.9)	34 (81.0%, 65.9-91.4)	23 (82.1%, 63.1-93.9)
Median DOR, ^a mo (95% CI)	10.9 (3.2-17.7)	5.6 (3.8-7.0)	N/A	N/A
Median TTR, mo (95% CI)	1.4 (1.4-1.5)	1.4 (1.4-1.8)	N/A	N/A
	Brain Metastases Status		Brain Metastases Status	
	Brain Metastases (n = 14)	Nonbrain Metastases (n = 48)	Brain Metastases (n = 15)	Nonbrain Metastases (n = 55)
ORR, n (% , 95% CI)	9 (64.3%, 35.1-87.2)	24 (50.0%, 35.2-64.8)	9 (60.0%, 32.3-83.7)	24 (43.6%, 30.3-57.7)
DCR, n (% , 95% CI)	14 (100.0%, 76.8-100.0)	43 (89.6%, 77.3-96.5)	14 (93.3%, 68.1-99.8)	43 (78.2%, 65.0-88.2)
Median DOR, ^a mo (95% CI)	4.9 (2.7-17.7)	7.0 (5.5-13.9)	N/A	N/A
Median TTR, ^a mo (95% CI)	1.5 (1.4-5.5)	1.4 (1.4-1.5)	N/A	N/A

^aDOR and TTR were analyzed in the tumor-response-evaluable set.

CI, confidence interval; DCR, disease control rate; DOR, duration of response; N/A, not applicable; NE, not evaluable; ORR, objective response rate; PSC, pulmonary sarcomatoid carcinoma; TTR, time to response.

4.9–12.5) and 1.4 months (95% CI: 1.4–1.5), respectively.

Safety

All 70 treated patients reported at least one treatment-emergent AEs (TEAEs) (Table 3). The most common study drug-related TEAEs of any grade were peripheral edema (56%, n = 39), nausea (46%, n = 32), increased alanine aminotransferase (39%, n = 27), and increased aspartate aminotransferase (37%, n = 26). Among the 32 patients (46%) who experienced a study drug-related grade greater than or equal to 3 TEAE, the most frequent was increased aspartate aminotransferase in nine patients (13%). Serious TEAEs occurred in 35 patients (50%). There were 16 patients (22.9%) who experienced at least one TEAE leading to discontinuation of study medication. Furthermore, 22 patients (31.4%) had an AE that led to dose interruption and 31 patients (44.3%) had an AE that led to dose reduction; among

these events, pyrexia (15.7%), increased aspartate aminotransferase (12.9%), increased alanine aminotransferase (11.4%), and peripheral edema (11.4%) were the most common. Nine on-study deaths owing to AEs occurred; the death of one patient with PSC owing to tumor lysis syndrome was considered to be probably related to savolitinib by the investigator. Further details regarding this grade 5 AE have been previously reported.³⁸

Discussion

The updated efficacy results for savolitinib remain consistent with the interim data³⁸; the OS and PFS benefits of savolitinib (12.5 and 6.9 mo, respectively) reported in the final analysis also compared favorably with historical data in Korean patients with advanced METexon14-positive NSCLC treated with first-line chemotherapy (OS = 9.5 mo, PFS = 4.0 mo,

Table 3. Treatment-Related Adverse Events in the Full Analysis Set (N = 70)

Adverse Events, n (%)	All-Cause Adverse Events		Treatment-Related Adverse Events	
	Any Grade	Grade \geq 3	Any Grade	Grade \geq 3
Any event	70 (100)	46 (66)	70 (100)	32 (46)
Event occurring in \geq 20%* of patients:				
Edema peripheral	40 (57)	6 (9)	39 (56)	6 (9)
Nausea	37 (53)	0	32 (46)	0
Hypoalbuminemia	29 (41)	1 (1)	16 (23)	0
Alanine aminotransferase increased	27 (39)	7 (10)	27 (39)	7 (10)
Aspartate aminotransferase increased	27 (39)	9 (13)	26 (37)	9 (13)
Decreased appetite	24 (34)	0	14 (20)	0
Vomiting	23 (33)	0	18 (26)	0
Pyrexia	21 (30)	1 (1)	11 (16)	1 (1)
Anemia	19 (27)	1 (1)	12 (17)	1 (1)
Hypokalemia	18 (26)	5 (7)	7 (10)	2 (3)
Cough	18 (26)	0	0	0
Blood creatinine increased	15 (21)	1 (1)	14 (20)	1 (1)
Asthenia	14 (20)	0	12 (17)	0
Blood bilirubin increased	14 (20)	0	13 (19)	0
Hypoproteinemia	14 (20)	0	12 (17)	0
Upper respiratory tract infection	14 (20)	2 (3)	0	0

*Ranked by all-cause adverse events at any grade.

respectively)⁴⁰ and data in East Asian patients who received treatment other than specific MET inhibitors (OS = 6.7 mo).⁴¹ Clinically meaningful antitumor activity was observed with savolitinib, regardless of histologic type, previous antitumor treatment, and the presence of brain metastases.

Two phase 2 studies have been conducted to investigate the efficacy and safety of the other class Ib MET TKIs in patients with METex14-positive NSCLC. In the VISION study, ORR was 46% and median DOR was 11.1 months in a phase 2 study of 99 patients with NSCLC with METex14 skipping mutations who were receiving tepotinib.⁴² The median OS was 17.1 months in the primary analysis set; only one patient (1%) in this group had tumors with sarcomatoid features, but the data were not mature. In the phase 2 GEOMETRY mono-1 trial of patients with NSCLC with a METex14 skipping mutation, ORR was 41% (n = 69) in previously treated patients who received capmatinib and ORR was 68% (n = 28) in treatment-naive patients who received capmatinib.⁴³ The median DOR was 5.4 months in pretreated patients and 9.7 months in those who were treatment naive,⁴³ and median OS was 13.6 months and 20.8 months,⁴⁴ respectively. The markedly higher ORR observed with capmatinib in treatment-naive patients remains unexplained, though it may be owing to the limited number of patients included in the study. The authors further highlight an overall decline in health in patients with longer disease duration and the evolution of resistant clones during first-line therapy as other

possible causes for the high ORR observed in treatment-naive patients receiving capmatinib.⁴³ The results from the GEOMETRY mono-1 and VISION trials led to accelerated approval of capmatinib and tepotinib by the U.S. Food and Drug Administration for the treatment of patients with metastatic NSCLC harboring METex14 skipping alterations.^{45,46} In contrast to the GEOMETRY mono-1 trial, the present study consisted of older patients (the median age of enrolled patients was 74.5 and 71 years,⁴³ respectively) who were treatment naive at baseline and a specific subpopulation of patients with PSC (46% and none,⁴³ respectively). Similarly, a substantially higher proportion of patients with PSC were enrolled in the present study in the FAS (36%) compared with the VISION study of tepotinib (1%).⁴² Nevertheless, the observed antitumor activity of savolitinib was similar to tepotinib and capmatinib, despite the inclusion of patient subgroups which may be associated with poorer outcomes. ORRs of the treatment-naive and pretreated patients were 54% and 53% in the present study, respectively. Importantly, on the basis of our previous results of this phase 2 study, savolitinib has been conditionally approved by National Medical Products Administration in the People's Republic of China for the treatment of adult patients with locally advanced or metastatic NSCLC harboring METex14 skipping alterations who have progressed or are intolerant to standard platinum-based chemotherapy.

All three approved class Ib MET TKIs have been observed to be efficacious in patients with brain

metastases, which warrants further investigation. The ORR and median DOR of tepotinib in patients with brain metastases were 55% and 9.5 months, respectively.⁴² The ORR in patients with measurable CNS metastasis receiving capmatinib was similar, at 54%.⁴⁷ In the present study, the ORR in patients with brain metastases (n = 15) was 64%, although the sample size of this subgroup was small.

The generally acceptable safety profiles of class Ib MET TKIs in patients with NSCLC have been found. Peripheral edema (63%), nausea (26%), increased blood creatinine (18%), and hypoalbuminemia (16%) were the common AEs for tepotinib.⁴² Similarly, peripheral edema (42%), nausea (33%), increased blood creatinine (20%), and vomiting (19%) were observed with capmatinib.⁴³ Treatment-related AEs that occurred in patients receiving savolitinib were as expected, and no new safety signals were identified in the final analysis. TEAE leading to discontinuation and dose interruption or dose reduction is similar with previous report, revealing long-term treatment can be tolerated. Notably, interstitial pneumonia is still not observed in this long-term follow-up study.

Of particular interest are the efficacy outcomes in patients with PSC in our trial. To our knowledge, this is the first study evaluating MET TKIs in which a pre-defined subgroup analysis and adequate representation of this population were included. PSC was a histologic subtype of particular interest in this study because of the high frequency of *MET*14 skipping alterations and the poor prognosis in patients with this subtype. In the VISION study, only one patient had tumors with sarcomatoid features on histologic analysis⁴²; in GEOMETRY mono-1, no patient had tumors with sarcomatoid features on histologic analysis,⁴³ a characteristic that has been associated with the presence of *MET*14 skipping mutations. Even in the early stages, PSC is associated with poor outcomes, and patients undergoing any currently known treatment options (such as platinum-based chemotherapy and radiotherapy) have a poor prognosis.⁴⁸ It is therefore crucial that further therapeutic options with acceptable efficacy be made available for this difficult-to-treat population. Our data suggest that savolitinib may be such an option. Patients with PSC had a shorter median OS compared with those with other NSCLC subtypes (10.6 versus 17.3 mo), likely owing to the poorer prognosis of patients with PSC.⁸⁻¹⁰ The longer median OS in the pretreated subgroup in comparison with the treatment-naïve subgroup (19.4 versus 10.9 mo) should be interpreted with caution; the treatment-naïve subgroup comprised a greater fraction of patients with PSC (46% versus 29% in the pretreated patients) and median age was higher (74.5 y versus 67.7 y in the pretreated patients), which may have confounded the efficacy results. Median OS was 17.7

months in the patients with brain metastases in *MET*14-positive NSCLC. Nevertheless, we should note the small sample size (n = 15) and the sample proportion of patients with PSC (n = 2, 13%) in this subgroup. Thus, data interpretation of savolitinib in the brain metastases subgroup should be cautious. In summary, currently available data for MET TKIs validate *MET*14 skipping mutations as important oncogenic targets and underscore the need for upfront and routine testing for the identification of this oncogenic driver among patients with metastatic and advanced NSCLC.

This study has several limitations. First, it has a single-arm design, although options for controlled trials are limited. Second, the cohorts were comprised solely of Chinese patients, meaning studies are needed to evaluate the efficacy and safety of savolitinib in patients of other ethnicities. Third, though our study included the first pre-defined PSC subgroup analyzed, the overall sample size was still small. The ongoing phase 3 study (NCT 04923945) will further evaluate the efficacy, safety, and tolerability of savolitinib in previously treated or treatment-naïve patients with locally advanced or metastatic NSCLC with *MET*14 skipping mutations.

Clinically meaningful efficacy and outcomes have been observed with savolitinib in patients with advanced NSCLC harboring *MET*14 skipping alterations, in addition to an acceptable safety profile. Results were consistent across subgroup analyses. Patients with PSC in our trial responded favorably to savolitinib. Therefore, savolitinib could prove to be a valuable asset in the management of this rare and difficult-to-manage pulmonary malignancy.

CRediT Authorship Contribution Statement

Shun Lu: Conceptualization, Review and editing, Investigation, Resources, Project administration, Supervision, Funding acquisition.

Jian Fang, Xingya Li, Lejie Cao, Jianying Zhou, Qisen Guo, Zongan Liang, Ying Cheng, Liyan Jiang, Nong Yang, Zhigang Han, Jianhua Shi, Yuan Chen, Hua Xu, Helong Zhang, Gongyan Chen, Rui Ma, Sanyuan Sun, Yun Fan: Investigation, Resources, Review, and Project administration.

Songhua Fan, Jie Yu, Puhua Lu: Conceptualization, Visualization, Review and editing, Supervision.

Xian Luo: Methodology, Software, Validation, Formal analysis, Data curation, Review and editing.

Weiguo Su: Conceptualization, Review.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO*

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