

# Phase Ia/Ib Study of the Selective MET Inhibitor, Savolitinib, in Patients with Advanced Solid Tumors: Safety, Efficacy, and Biomarkers

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## Abstract

**Background:** Savolitinib has shown good tolerability and preliminary efficacy, but efficacy biomarkers require investigation. The main purpose of this study was to confirm in Chinese patients the recommended phase II dose (RP2D) of savolitinib and to explore overall benefit in tumors bearing c-Met aberration.

**Methods:** This was an open-label, multi-center, 2-part phase I study. A starting dose of 600 mg QD was initiated in the escalation phase, utilizing a 3+3 design with repeated QD and BID dosing. In the dose expansion phase, we enrolled patients with gastric cancer and non-small cell lung cancer (NSCLC) with documented c-met aberration into 5 cohorts to further explore biomarkers. c-Met overexpression and amplification were assessed by immunohistochemistry and FISH, respectively.

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**Results:** The safety analysis set included 85 patients. Only one dose-limiting toxicity (grade 3 fatigue) was reported in the 600 mg BID dosing group. The most frequent treatment-related adverse events were nausea (29.4%), vomiting (27.1%), and peripheral edema (21.2%). Notably, in gastric cancer, response was only observed in patients with MET amplification (copy number 9.7-18.4), with an objective response rate of 35.7% and a disease control rate of 64.3%. For patients with NSCLC bearing a MET exon 14 skipping mutation, obvious target lesion shrinkage was observed in 2 of 4 patients, although PR was not achieved.

**Conclusion:** The RP2D of savolitinib was established as 600 mg QD or 500 mg BID in Chinese patients. The promising response observed in patients with gastric cancer with c-met amplification and NSCLC with MET exon 14 skipping mutation warrants further investigation.

**ClinicalTrials.gov Identifier:** NCT0198555

**Key words:** savolitinib; C-met inhibitor; targeted therapy; biomarker.

### Lessons Learned

- The recommended dose for savolitinib monotherapy in Chinese patients was determined to be 500 mg BID or 600 mg QD.
- Responses were observed in gastric cancers with MET amplification with gene copy number of 9.7-18.4; signs of antitumor activity were observed in NSCLCs with exon 14 skipping mutation.
- Heterogeneity in response in target and non-target lesions was observed.

### Discussion

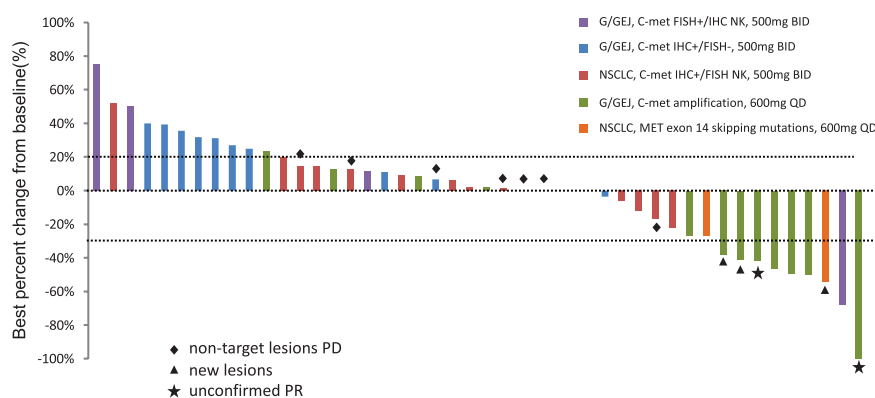
Savolitinib is a novel reversible and competitive c-Met kinase inhibitor that has shown antitumor activities that are highly related to c-Met in both in vitro and in vivo studies. Based on preliminary safety and pharmacokinetic (PK) data obtained from the phase I clinical trial in Australia, a starting dose of 600 mg QD was deemed to be reasonable. In phase Ib, we assessed the safety and efficacy of this drug in patients with advanced gastric cancers or NSCLCs harboring aberrant c-Met.

Similar PK characteristics were observed across comparable doses and regimens, with an approximate doubling of the AUC following BID dosing compared to QD dosing. Furthermore, no apparent differences were observed in the PK profiles of savolitinib throughout all dosing regimens between Chinese patients enrolled in this study and Caucasian patients enrolled in the Australian trial.

All patients received at least one dose of savolitinib and were included in the safety analyses ( $n = 85$ ). Treatment-related AEs (TRAEs) were predominantly grades 1-2, the most common grade  $\geq 3$  TRAEs were abnormal liver function ( $n = 7$ ), fatigue ( $n = 2$ ), diarrhea ( $n = 2$ ), and reduced appetite ( $n = 2$ ). We found that savolitinib was well tolerated up to 600 mg BID and no MTD was identified. The safety results were consistent with those of a previous first-in-human study conducted in Australia and those reported for other MET-specific inhibitors.

In the phase Ia study ( $n = 21$ ), in which c-Met gene or protein expression status was not tested, no patients experienced a partial or complete response (PR or CR). In the phase Ib dose expansion ( $n = 64$ ), we enrolled only patients with gastric cancer or non-small cell lung cancer (NSCLC) harboring MET aberration. The objective response rate (ORR) was 9.4% (6/64) in all patients, and the disease control rate was 39.1% (25/64). Notably, all PRs occurred in patients with gastric cancer with MET amplification rather than c-Met over-expression. In NSCLC bearing MET exon 14 skipping mutations, apparent tumor shrinkage (55% and 27%) in target lesions was observed in 2 of 4 patients, although no responses met PR criteria (Fig. 1). The efficacy observed in this cohort should be interpreted with caution because of the limited number of patients.

We further analyzed the relationship between efficacy and the c-Met gene copy number (GCN) in gastric cancer. Interestingly, all patients who achieved PR had a high MET GCN; the median (range) MET GCN was 13.2 (9.7-18.4) and 14.7 (4.1-26.7) among responders and non-responders, respectively. In addition, in the phase Ib trial, we found 2 patients with gastric cancer with high met GCNs achieved a PR in target lesions, but new lesions appeared simultaneously, indicating gastric cancer is quite heterogeneous and the MET status should be interpreted in the context of a tumor's genetic background to identify the true driver gene.



**Figure 1.** Waterfall plot of best tumor response and MET biomarker analysis; 46 patients shown in the figure were tumor-evaluable; the remaining 18 had either no baseline or no post-treatment tumor measurement data. Abbreviations: FISH, fluorescent in situ hybridization; IHC, immunohistochemistry; G/GEJ, gastric/gastroesophageal cancer; NSCLC, non-small cell lung cancer.

**TRIAL INFORMATION**

Disease	Advanced cancer/solid tumor only
Stage of disease/treatment	Metastatic/advanced
Prior therapy	More than 2 prior regimens
Type of study	Phase I, dose escalation + dose expansion
Primary endpoints	Safety, tolerability, maximum tolerated dose, recommended phase II dose
Secondary endpoint	Pharmacodynamics
Additional details of endpoints or study design	The study consisted of 2 parts: dose escalation (phase Ia) and dose expansion (phase Ib). The primary objectives were to evaluate the safety, tolerability, maximum tolerated dose (MTD), and RP2D of savolitinib. The secondary objective was to describe the PK and assess the clinical efficacy of savolitinib. Exploratory objectives included biomarker analysis. Safety and tolerability were evaluated through the incidence and nature of dose-limiting toxicities, adverse events (AEs), changes in vital signs, physical examination results, laboratory examination results, ECOG scores, and electroencephalography. TRAEs were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.3.1. Computed tomography was performed at baseline, on D1 of cycle 3 and D1 of every 2 subsequent cycles. The radiologic tumor response was assessed per RECIST version 1.1.
Investigator's analysis	Active and should be pursued further

**DRUG INFORMATION: DOSE ESCALATION**

Generic/working name	Savolitinib
Company name	Hutchison China MediTech Limited
Drug type	Small molecule
Drug class	MET—cMET
Dose	600 mg QD, 800 mg QD, 400 mg BID, 500 mg BID, 600 mg BID per
Route	oral (p.o.)
Schedule of administration	During the dose escalation phase, participants were sequentially enrolled in a classic “3+3” design to receive one of the 5 savolitinib regimens (600 mg QD, 800 mg QD, 400 mg BID, 500 mg BID, and 600 mg BID) on a 21-day cycle. Patients with QD administration received a single-dose of savolitinib, followed by a 7-day washout period, and then completed 21-day continuous savolitinib administration at the same dose level. Patients administered BID only received 21-day treatment cycles of savolitinib.

**DOSE ESCALATION TABLE**

Dose level	Dose of drug: savolitinib	Number enrolled	Number evaluable for toxicity
1	600 mg QD	4	4
2	800 mg QD	3	3
3	400 mg BID	4	4
4	500 mg BID	4	4
5	600 mg BID	6	6
Dose expansion			
	500 mg BID	46	46
	600 mg QD	18	18

**DRUG INFORMATION: DOSE EXPANSION**

Generic/working name	Savolitinib
Company name	Hutchison China MediTech Limited
Drug type	Small molecule
Drug class	MET—cMET
Dose	500mg BID, 600mg QD per
Route	Oral (p.o.)
Schedule of administration	Participants in cohorts A and B received the RP2D (500 mg BID) identified in the dose escalation phase. Based on previously reported data, a dose of 600 mg QD also inhibited the c-MET target and exhibited antitumor efficacy in early clinical trials. Therefore, participants in cohorts C and D received a dose of 600 mg QD (weight >50 kg) or 400 mg QD (weight ≤ 50 kg) to further evaluate the safety and efficacy of savolitinib. In the present study process, no patient received a dose of 400 mg QD.

**PATIENT CHARACTERISTICS: DOSE ESCALATION**

Number of patients, male	12
Number of patients, female	9
Stage	I: <i>n</i> = 1 III: <i>n</i> = 7 IV: <i>n</i> = 13
Age	Median (range): 57 (32-71) years
Number of prior systemic therapies	
Performance Status: ECOG	0—3 1—18 2—0 3—0 Unknown—0
Cancer types or histologic subtypes	Gastric/gastroesophageal junction cancer, 5 Colon cancer, 5 Rectum cancer, 4 Kidney cancer, 6 Others, 1

**PATIENT CHARACTERISTICS: DOSE EXPANSION**

Number of patients, male	43
Number of patients, female	21
Stage	I: <i>n</i> = 1 II: <i>n</i> = 1 III: <i>n</i> = 10 IV: <i>n</i> = 52
Age	Median (range): 59 (26-81) years
Number of prior systemic therapies	
Performance Status: ECOG	0—5 1—59 2—0 3—0 Unknown—0
Cancer types or histological subtypes	Lung cancer, 26 Gastric/gastrointestinal cancer, 38

**PRIMARY ASSESSMENT METHOD: DOSE ESCALATION**

Title	Toxicity
Number of patients screened	21
Number of patients enrolled	21
Number of patients evaluable for toxicity	21
Number of patients evaluated for efficacy	18
Evaluation method	National Cancer Institute's Common Terminology Criteria for Adverse Events v4.3.1

**PRIMARY ASSESSMENT METHOD: DOSE EXPANSION**

Title	Efficacy
Number of patients screened	855
Number of patients enrolled	64
Number of patients evaluable for toxicity	64
Number of patients evaluated for efficacy	45
Evaluation method	RECIST 1.1
Response assessment CR	<i>n</i> = 1 (1.6%)

Response assessment PR	<i>n</i> = 5 (7.6%)
Response assessment SD	<i>n</i> = 19 (29.7%)
Response assessment PD	<i>n</i> = 20 (31.3%)
Response assessment OTHER	<i>n</i> = 19 (29.7%)
(Median) duration assessments PFS	2.37 months, CI: 1.41-2.89

### ADVERSE EVENTS: DOSE ESCALATION, ALL DOSE LEVELS, ALL CYCLES

Name	*NC/NA	1	2	3	4	5	All grades
Nausea	71%	22%	6%	1%	0%	0%	29%
Vomiting	73%	18%	7%	2%	0%	0%	27%
Anorexia	81%	14%	2%	2%	0%	0%	19%
Edema limbs	84%	15%	1%	0%	0%	0%	16%
Fatigue	92%	5%	1%	2%	0%	0%	8%
Diarrhea	98%	0%	0%	2%	0%	0%	2%
Neutrophil count decreased	92%	5%	2%	1%	0%	0%	8%
Platelet count decreased	94%	4%	0%	2%	0%	0%	6%
Anemia	96%	2%	0%	1%	0%	0%	4%

Key treatment related adverse events, all cycles. See also [Table 1](#).

All patients received at least one dose of savolitinib and were included in the safety analyses (*n* = 85; [Table 2](#)). Treatment-related AEs occurred in 71 (83.5%) patients.

The most common TRAEs were nausea (29.4%), vomiting (27.1%), reduced appetite (18.8%), peripheral edema (16.5%), and abnormal liver function (16.5%). Treatment-related AEs were predominantly grades 1-2, the most common grade  $\geq 3$  TRAEs were abnormal liver function (*n* = 7), fatigue (*n* = 2), diarrhea (*n* = 2), and reduced appetite (*n* = 2). Overall, TRAE incidences were higher in the QD group than in the BID group (88% vs. 75%); however, patients in the BID group experienced more nausea and vomiting, and grade  $\geq 3$  TRAEs were more frequent in the BID group. Sixteen patients (18.8%) experienced serious TRAEs. Twenty patients (23.5%) discontinued treatment due to TRAEs, and dose adjustment or interruption due to TRAEs was reported in 15 patients (17.6%).

Five patients (5.9%) had fatal AEs; most (*n* = 4) were related to underlying disease. One patient from cohort A1 reported perforation and finally died 7 days after diagnosis. Only this death was deemed related to treatment by investigators.

\*NC/NA, no change from baseline/no adverse event.

### SERIOUS ADVERSE EVENTS

Name	Grade	Attribution
Inguinal hernia	3	Unrelated

One (1) serious adverse event (SAE), Grade 3 inguinal hernia, was reported in one patient treated with savolitinib 500 mg BID.

### ADVERSE EVENTS: DOSE EXPANSION, CYCLE 1

Name	*NC/NA	1	2	3	4	5	All grades
Nausea	0%	68%	26%	5%	0%	0%	100%
Vomiting	0%	53%	35%	12%	0%	0%	100%
Diarrhea	0%	75%	0%	25%	0%	0%	100%
Fatigue	0%	67%	17%	17%	0%	0%	100%
White blood cell decreased	0%	67%	33%	0%	0%	0%	100%
Anemia	0%	100%	0%	0%	0%	0%	100%
Platelet count decreased	0%	100%	0%	0%	0%	0%	100%
Edema limbs	0%	67%	33%	0%	0%	0%	100%
Alanine aminotransferase increased	0%	50%	25%	25%	0%	0%	100%

\*NC/NA, no change from baseline/no adverse event.

### SERIOUS ADVERSE EVENTS

Name	Grade	Attribution
Hepatic function abnormal	3	Probable
Interstitial lung disease	3	Probable
Diarrhea	3	Probable
Edema	3	Probable
Cardiotoxicity	3	Probable
Decreased appetite	3	Probable

Name	Grade	Attribution
Granulocytopenia	3	Probable
Thrombocytopenia	3	Probable

### DOSE-LIMITING TOXICITIES

Dose of drug: savolitinib	Dose of drug: savolitinib	Number enrolled	Number evaluable for toxicity	Number with a dose limiting toxicity	Dose limiting toxicity information
600 mg QD	600 mg QD	4	4	0	
800 mg QD	800 mg QD	3	3	0	
400 mg BID	400 mg BID	4	4	0	
500 mg BID	500 mg BID	4	4	0	
600 mg BID	600 mg BID	6	6	1	Grade 3 fatigue

### PHARMACOKINETICS/PHARMACODYNAMICS

Dose level (mg)	Dose of drug: savolitinib	Number enrolled	C <sub>max</sub> (ng/mL) mean ± SD	T <sub>max</sub> (hour) (min – max)	AUC 0-12 (hour × 12 ng/mL) mean ± SD	T <sub>1/2</sub> (hour) mean ± SD
600 mg QD		22	2432 ± 1093	2 (0.5-6)	17099 ± 7062	4.1 ± 0.8
800 mg QD		3	4133 ± 944	4 (2-4)	32167 ± 10966	3.6 ± 0.8
400 mg BID		4	2680 ± 982	2 (2-2)	13015 ± 4011	3.6 ± 1.1
500 mg BID		47	2830 ± 1218	4 (0.5-8)	15067 ± 6612	4.1 ± 2.6
600 mg BID		6	3113 ± 714	2 (2-6)	16490 ± 5917	3.0 ± 0.4

### ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion

Study completed

Investigator's Assessment

Active and should be pursued further

Dysregulation of the HGF/MET (c-Met, also called tyrosine protein kinase Met or hepatocyte growth factor receptor, is a protein that in humans is encoded by the MET gene. The protein possesses tyrosine kinase activity) signaling pathway has been implicated in the tumorigenesis of various human cancers.<sup>1-3</sup> Savolitinib is a novel reversible and competitive c-Met kinase inhibitor that has shown antitumor activities and is highly related to c-Met alterations in both in vitro and in vivo studies.<sup>4</sup> A first-in-human phase I clinical study of savolitinib was conducted in patients with advanced solid tumors in Australia using doses of 100-1000 mg QD and 300-500 mg BID showed preliminary efficacy in patients with papillary renal cell carcinoma with MET gene copy number (GCN) changes.<sup>5</sup> However, biomarkers of savolitinib need further investigation.

Thus, we conducted a phase Ia/Ib trial of savolitinib in Chinese patients with solid tumors. Savolitinib demonstrated a manageable safety profile and promising antitumor activity in gastric cancer with c-met amplification and NSCLC with MET exon 14 skipping mutation.

We found that savolitinib was well tolerated up to 600 mg BID and no MTD was identified. The safety results were consistent with those of a previous first-in-human study conducted in Australia and those reported by other MET-specific inhibitors.<sup>5-7</sup> Although the vast majority of patients (83.5%) reported TRAEs during treatment, most were grades 1-2 (Table 1). Notably, in the dose escalation phase, we found that patients in the BID cohorts experienced more nausea and vomiting than the QD cohorts. Fortunately, these AEs are easily manageable with the application of antiemetics in

clinical practice, and will not lead to more discontinuation or interruption events (Table 1).

The exposure to savolitinib reached steady state shortly after oral administration in the 500 mg BID group, and there was no significant drug accumulation. As the dose increased to 600 mg BID, the plasma exposure of savolitinib and its metabolite remained at the same level as that of 500 mg BID, indicating that the 600 mg BID dose may not enhance the inhibition of c-Met kinase phosphorylation relative to 500 mg BID (Table 3 and Fig. 3). Further, antitumor activity was observed at a dose of 600 mg QD in the phase I Australia study.<sup>5</sup> Therefore, based on the safety, tolerability, preliminary efficacy, and PK profile, 500 mg BID or 600 mg QD was determined as the recommended dose for savolitinib monotherapy in phase Ib/II studies.

Patients were not selected based on MET status in the phase Ia study (Fig. 2), and no objective response was observed in this part of the study, suggesting that savolitinib warrants further investigation in cancer patients with c-MET dysregulation. The most common mechanism of MET pathway abnormal activation in gastric cancer is via protein overexpression or MET gene amplification; therefore, we analyzed the relationship between efficacy and the 2 types of c-met aberrations in patients with gastric cancer in the phase Ib study. Notably, only patients with gastric cancer with C-MET amplification had a high response rate to savolitinib. We further analyzed the relationship between efficacy and the c-Met GCN in gastric cancer. Interestingly, all patients who experienced PR had tumors with a high MET GCN, with a median (range) MET GCN of 13.2 (9.7-18.4). The relationship between efficacy



and MET CNG is shown in Fig. 4. This is consistent with the findings of a previous study. In the reported VIKTORY umbrella trial, the ORR of savolitinib monotherapy in MET-amplified gastric cancer that had progressed on standard treatment reached 50% (10/20). Subsequent biomarker analysis revealed that among the 10 patients who achieved PR, 7 had a MET GCN >10 and 3 had a GCN of 5-10.<sup>8</sup> Therefore, when considering MET-targeted treatment options, MET amplification may be more predictive of response in gastric cancer than MET protein over-expression because the latter typically occurs in the background of other strong genetic events rather than as an isolated driver event.<sup>1,9,10</sup>

Aside from savolitinib, another highly selective small-molecule inhibitor of the MET receptor signaling pathway, AMG 337, has been investigated in gastric/GEJ adenocarcinoma.<sup>11</sup> Phase II results of AMG 337 showed antitumor activity in MET-amplified gastric/GEJ/esophageal adenocarcinoma with an ORR of 18%, and the median MET GCN of responders and non-responders was 7.7 (2.4-12) and 7.1 (2.0-20.4), respectively.<sup>12</sup> Subsequent biomarker analysis in both studies indicated that not all patients with high MET GCNs responded to MET inhibitors, while all patients with responding disease had a high GCN. This implies that the c-MET signaling pathway in gastric cancer is more complicated. It has been shown that the complexity of the MET signaling pathway, as well as the diverse resistance mechanisms (cross-talk, new mutations, upregulated gene amplification), all limited the clinical efficacy of MET inhibition.<sup>13</sup> However, gastric cancer is quite heterogeneous; in the phase Ib trial, 2 patients with gastric cancer with high MET GCNs achieved a PR in target lesions, but new lesions appeared simultaneously. Taken together, our findings indicate that the MET status should be interpreted in the context of a tumor's genetic background to identify the driver gene.

Several novel inhibitors have recently been approved in the treatment of NSCLC, including MET-specific inhibitors (capmatinib and tepotinib) and multiple-targeted inhibitors (crizotinib and cabozantinib).<sup>14,15</sup> The MET exon 14 skipping mutation has been validated as a biomarker in previous studies.<sup>16</sup> In the present study, while no PR was observed in cohort D, we observed apparent tumor shrinkage in 2 of 4 patients, supporting further investigation of savolitinib in NSCLC harboring MET exon 14 skipping mutation.

In summary, in this phase Ia/Ib clinical study, savolitinib demonstrated good tolerability and exhibited promising signs of antitumor activity in gastric cancers with MET amplification and NSCLC with exon 14 skipping mutation. Future studies are necessary to confirm the clinical efficacy and determine which signaling pathway contributes to resistance.

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## Conflict of Interest

The authors indicated no financial relationships.

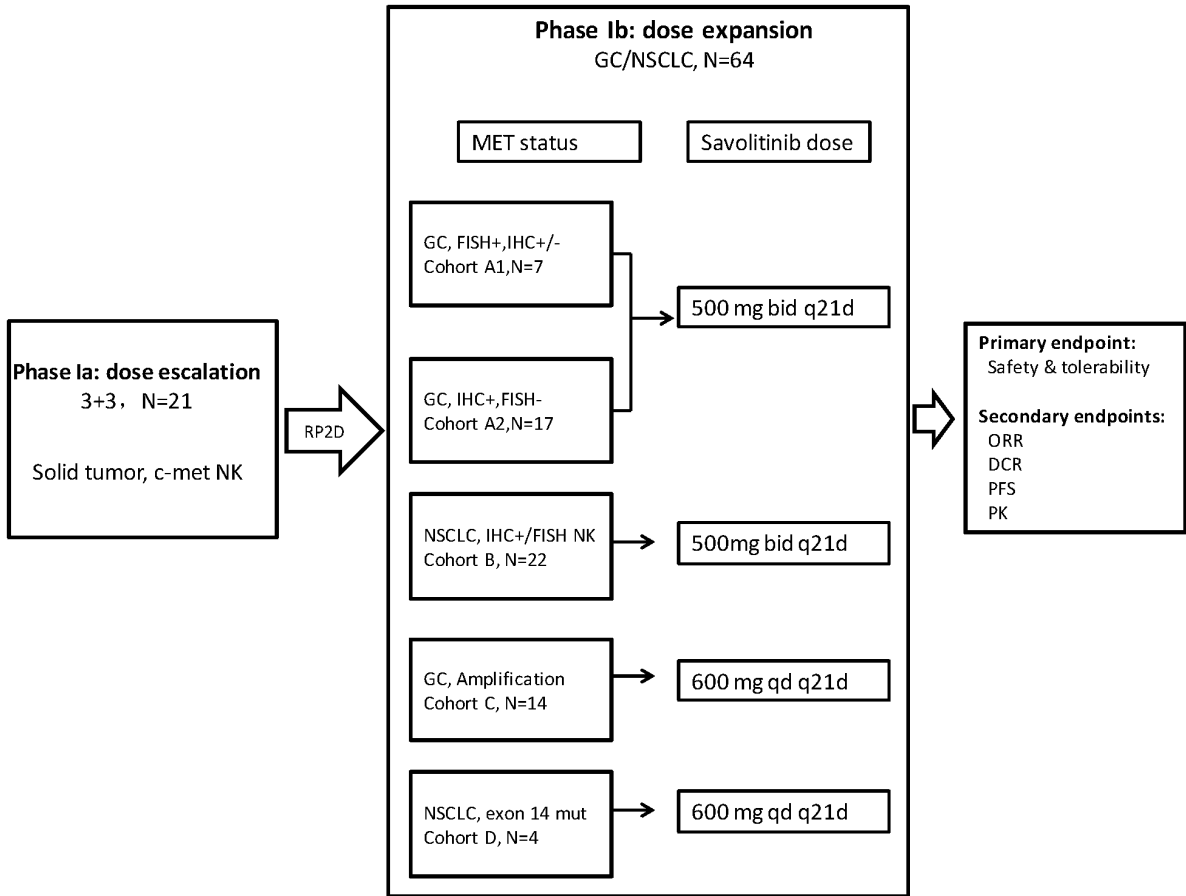
## Data Availability

The data underlying this article are available in the article and in its online supplementary material.

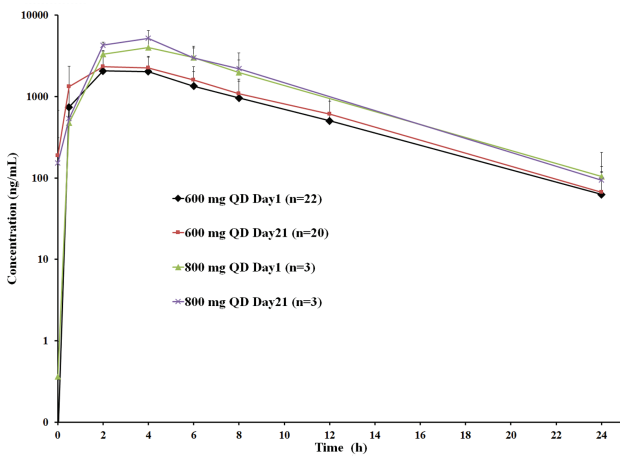
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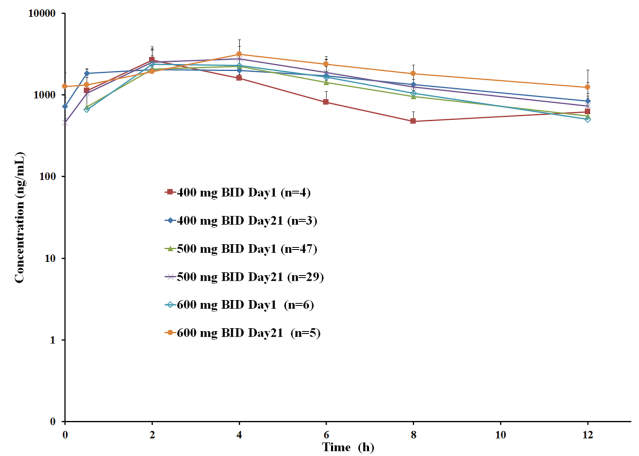
## FIGURES AND TABLES



**Figure 2.** Patient disposition (dose escalation and expansion). Phase Ia study followed a 3+3 design and a total of 21 patients being treated. A total of 64 patients were enrolled into 5 cohorts according to MET status in phase Ib study.



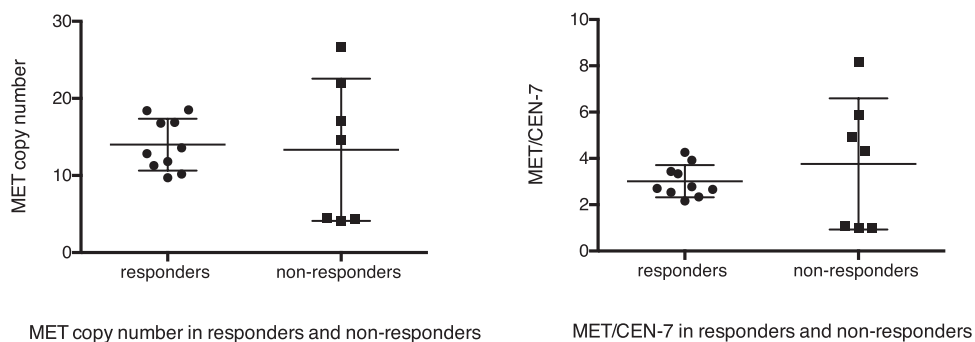
A



B

**Figure 3.** Plasma concentration-time of savolitinib after single and repeated dose of savolitinib at 600 mg QD, 800 mg QD (A) and 400 mg BID, 500 mg BID, and 600 mg BID (B).





**Figure 4.** The relationship between efficacy and MET CNG in gastric cancer patients. Responders: with tumor shrinkage in target lesions, *n* = 10; non-responders: without tumor shrinkage in target lesions, *n* = 7.

**Table 1.** Treatment-related safety summary.

Adverse events, <i>n</i> (%)	Dose escalation, mg					Dose expansion, mg		Overall <i>N</i> = 85
	600 QD ( <i>n</i> = 4)	800 QD ( <i>n</i> = 3)	400 bid ( <i>n</i> = 4)	500 bid ( <i>n</i> = 4)	600 bid ( <i>n</i> = 6)	500 bid ( <i>n</i> = 46) Cohort A+B	600 QD ( <i>n</i> = 18) Cohort C+D	
AE incidence	3 (75)	3 (100)	4 (100)	4 (100)	5 (83.3)	44 (95.7)	18 (100)	81 (95.3)
TRAE incidence	3 (75)	3 (100)	4 (100)	3 (75)	5 (83.3)	37 (80.4)	16 (88.9)	71 (83.5)
TRAE leading to treatment interruption	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	9 (19.6)	5 (27.8)	15 (17.6)
TRAE leading to treatment discontinuation	1 (25)	0 (0)	0 (0)	0 (0)	1 (16.7)	14 (30.4)	4 (22.2)	20 (23.5)
Treatment-related SAE	0 (0)	0 (0)	0 (0)	1 (25)	0 (0)	11 (23.9)	4 (22.2)	16 (18.8)
TRAE leading to death	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
DLT: Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	0 (0)	0 (0)	1 (1.2)
TRAE of any grade in ≥10% of patients								
Nausea	0 (0)	0 (0)	2 (50)	2 (50)	4 (66.7)	16 (34.8)	1 (5.6)	25 (29.4)
Vomiting	0 (0)	1 (33.3)	0 (0)	3 (75)	4 (66.7)	12 (26.1)	3 (16.7)	23 (27.1)
Decreased Appetite	0 (0)	1 (33.3)	1 (25)	2 (50)	2 (33.3)	9 (19.6)	1 (5.6)	16 (18.8)
Peripheral edema	1 (25)	1 (33.3)	2 (50)	0 (0)	0 (0)	5 (10.9)	5 (27.8)	18 (21.2)
Abnormal liver function	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	12 (26.1)	2 (11.1)	14 (16.5)
TRAEs grade 3 or higher								
Fatigue	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.7)	1 (2.2)	0 (0)	2 (2.4)
Hemoglobin decreased	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2.4)
Neutrophil count decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
Platelet count decreased	1 (25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)	2 (2.4)
Abnormal liver function	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	7 (15.2)	0 (0)	7 (8.2)
Diarrhea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.3)	0 (0)	2 (2.4)
Abdominal pain	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
Perforation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
Nausea	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
Vomiting	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
Decreased appetite	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (4.3)	0 (0)	2 (2.4)
Interstitial lung disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
ALB decreased	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.2)	0 (0)	1 (1.2)
Heart toxicity	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5.6)	1 (1.2)

Abbreviations: AE, adverse event; ALB, albumen; DLT, dose-limiting toxicity; SAE, serious adverse event; TRAE, treatment-related adverse events.

**Table 2.** Anti-tumor efficacy of savolitinib in dose-escalation and dose-expansion cohorts

Efficacy	Dose escalation (N = 21)	Dose expansion, mg					Total (N = 64)
		500 bid (n = 7) Cohort A1	500 bid (n = 17) Cohort A2	500 bid (n = 22) Cohort B	600 QD (n = 14) Cohort C	600 QD (n = 4) Cohort D	
CR, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (7.1)	0 (0)	1 (1.6)
PR, n (%)	0 (0)	1 (13.3)	0 (0)	0 (0)	4 (28.6)*	0 (0)	5 (7.8)
SD, n (%)	8 (38.1)	1 (13.3)	3 (17.6)	9 (40.9)	4 (28.6)	2 (50)	19 (29.7)
PD, n (%)	10 (47.6)	2 (28.6)	9 (53)	5 (22.7)	3 (21.4)	1 (25)	20 (31.3)
NE, n (%)	3 (14.3)	3 (42.9)	5 (29.4)	8 (36.4)	2 (14.3)	1 (25)	19 (29.7)
ORR, n (%)	0 (0)	1 (13.3)	0 (0)	0 (0)	5 (35.7)	0 (0)	6 (9.4)
DCR, n (%)	8 (38.1)	2 (28.6)	3 (17.6)	9 (40.9)	9 (64.3)	2 (50)	25 (39.1)
mPFS, 95% CI	NK	1.38 (0.33-46.95)	1.40 (0.95-1.45)	2.73 (1.41-4.07)	2.73 (1.41-4.07)	2.37 (1.84-6.90)	2.37 (1.41-2.89)

Abbreviations: CR, complete response; DCR, disease control rate; mPFS, median progression-free survival; NE, not evaluable; NK, not known; PD, progressive disease; PR, partial response; SD, stable disease.

**Table 3.** Pharmacokinetic parameters of savolitinib on circle 1 day 1 and circle 1 day 21 after repeated QD (600 mg, 800 mg) and bid (400 mg, 500 mg, 600 mg)

PK parameters	Day 1						Day 21					
	600 mg QD (n = 22)	800 mg QD (n = 3)	400 mg bid (n = 4)	500 mg bid (n = 47)	600 mg bid (n = 6)	600 mg QD (n = 20)	800 mg QD (n = 3)	400 mg bid (n = 3)	500 mg bid (n = 29)	600 mg bid (n = 4)		
<sup>a</sup> AUC <sub>0-4</sub> (ng·h mL <sup>-1</sup> )	17099 <sup>a,c</sup> (7062)	32167 <sup>a,c</sup> (10966)	13015 <sup>a,d</sup> (4011)	15067 <sup>a,d</sup> (6612)	16490 <sup>a,d</sup> (5917)	20005 <sup>a,c</sup> (6569)	37133 <sup>a,c</sup> (10923)	18467 <sup>a,d</sup> (4649)	21462 <sup>a,d</sup> (7531)	22260 <sup>a,d</sup> (9132)		
<sup>a</sup> AUC <sub>0-inf</sub> (ng·h mL <sup>-1</sup> )	17503 <sup>a</sup> (7282)	32733 <sup>a</sup> (11570)	13720 <sup>a</sup> (4652)	18864 <sup>a</sup> (9186)	17258 <sup>a</sup> (7198)	20415 <sup>a</sup> (6791)	37600 <sup>a</sup> (11130)	24300 <sup>a</sup> (3960)	28019 <sup>a</sup> (13911)	47950 <sup>a</sup> (44624)		
<sup>a</sup> C <sub>max</sub> (ng mL <sup>-1</sup> )	2432 <sup>a</sup> (1093)	4133 <sup>a</sup> (944)	2680 <sup>a</sup> (982)	2830 <sup>a</sup> (1218)	3113 <sup>a</sup> (714)	2962 <sup>a</sup> (1171)	5503 <sup>a</sup> (775)	2900 <sup>a</sup> (1317)	3429 <sup>a</sup> (1040)	3288 <sup>a</sup> (1398)		
<sup>b</sup> T <sub>max</sub> (h)	2 <sup>b</sup> (0.5-6)	4 <sup>b</sup> (2-4)	2 <sup>b</sup> (2-2)	4 <sup>b</sup> (0.5-8)	2 <sup>b</sup> (2-6)	2 <sup>b</sup> (0.5-6)	4 <sup>b</sup> (2-4)	4 <sup>b</sup> (1-6)	4 <sup>b</sup> (0.5-5.52)	4 <sup>b</sup> (4-8)		
<sup>a</sup> t <sub>1/2</sub> (h)	4.1 <sup>a</sup> (0.8)	3.6 <sup>a</sup> (0.8)	3.6 <sup>a</sup> (1.1)	4.1 <sup>a</sup> (2.6)	3.0 <sup>a</sup> (0.4)	3.88 <sup>a</sup> (0.7)	3.6 <sup>a</sup> (0.1)	3.5 <sup>a</sup> (0.9)	4.8 <sup>a</sup> (2.4)	8.6 <sup>a</sup> (10)		

Abbreviations: AUC, area under the curve; PK, pharmacokinetics.