ORIGINAL ARTICLE

Phase 1 Study of the Selective c-MET Inhibitor, HS-10241, in Patients With Advanced Solid Tumors

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ABSTRACT

Introduction: c-MET is an important therapeutic target for various cancers; however, the People's Republic of China currently retails only one specific c-MET inhibitor. Our preclinical study has revealed the high selectivity of HS-10241 to suppress c-MET. This phase 1 study aims to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of the selective c-MET inhibitor (HS-10241) in patients with advanced solid tumors.

Methods: Patients with locally advanced or metastatic solid tumors orally received a single or multiple dose of HS-10241 once daily or twice daily for 21 consecutive days, which included the following six regimens: 100 mg once daily, 200 mg once daily, 400 mg once daily, 600 mg once daily, 200 mg twice daily, and 300 mg twice daily. The treatment continued until disease progression, unacceptable toxicity, or treatment termination. The primary end point was the incidence of dose-limiting toxicity and maximal tolerated dose (MTD). Secondary end points included safety, tolerability, pharmacokinetics, and pharmacodynamics.

Results: A total of 27 patients with advanced NSCLC received HS-10241, and dose-limiting toxicity was observed in three patients after 600 mg once-daily HS-10241 treatment. For once-daily dosing, MTD was 400 mg, and for twice-daily dosing, the maximal safe escalated dose was 300 mg, and MTD was not reached. Nausea (48.1%, 13 of 27), fatigue (37.0%, 10 of 27), and anemia (33.3%, 9 of 27) are the three most frequent treatment-emergent adverse events. At 400 mg once daily, $C_{ss,max}$ was 5076 ng/mL and steady state area under the curve was 39,998 h × ng/mL. Patients (n = 5) with positive MET (*MET* exon 14-skipping, *MET* amplified, and MET immunohistochemistry 3+) had confirmed partial responses (n = 1) or stable disease (n = 3), with a disease control rate of 80.0%.

Conclusions: The selective c-MET inhibitor HS-10241 was well tolerated and had clinical activity in advanced NSCLC, especially in patients with positive MET. Furthermore, this study expounds on the therapeutic potential of HS-10241 in patients with cancer.

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Introduction

c-MET is a receptor tyrosine kinase encoded by the oncogene *MET* and functions in combination with HGF in normal cells. On specifically combining to HGF, c-MET changes its conformation and activates the protein tyrosine kinase in the intracellular domain. Subsequently, a series of tyrosine phosphorylation of certain proteins, such as PLCγ, PI3K, Ras, Src, Gab1, and Grb2, and their multiple substrates is induced. The cascade signals are amplified in the nucleus, causing various biological effects, such as regulating proliferation, differentiation, morphogenesis, and invasion.[1] HGF/c-MET signal has been reported to be abnormal in multiple cancer types, including hepatocellular carcinoma, NSCLC, gastric cancer, and colorectal cancer.[2]

Inhibiting c-MET signaling is an important strategy for cancer therapy. Currently, anticancer drugs under research and development are divided into the following four categories: c-MET selective drugs, nonselective drugs with multiple targets (such as crizotinib and capotinib), monoclonal antibodies, and bispecific antibodies.[3,4] Several c-MET highly selective drugs, such as capmatinib and tepotinib, have been approved by the Food and Drug Administration in 2020 to 2021 worldwide[5]; however, only one c-MET highly selective drug (savolitinib) is retailed in the People's Republic of China.[6,7] HS-10241, developed by Jiangsu Hansoh Pharmaceutical Co., Ltd., is also a highly specific tyrosine kinase inhibitor (TKI). The enzymatic activity determination of 60 protein kinases revealed that HS-10241 exerts a potent inhibitory effect on c-MET activity with an IC_{50} of 0.7 nM, which is less than those for of kinases that are all greater than 2800 nM. Therefore, HS-10241 has a very selective and specific inhibitory effect on c-MET enzymatic activity. According to our preclinical data (not published), HS-10241 specifically inhibits the growth of tumor cells with *c-MET* overexpression caused by gene copy number (GCN) expansion. It has strong activity against c-MET kinase both in vitro and in vivo and significantly inhibits the corresponding signals mediated by c-MET. It has stronger inhibiting effect on tumor cells in vitro than the control drugs SGX-523 and INJ-38877605 and has higher antitumor activity than SGX-523 in vivo. In addition, it is found safe at the indicated concentrations through a series of toxicologic experiments, including acute toxicity test, long-term toxicity test, and genotoxicity study. Furthermore, HS-10241 is mainly distributed in the lungs, stomach, skin, ovaries, uterus, and kidneys, but it is difficult for it to transpass the blood–brain barrier and enter into the brain tissue, where the HS-10241 content is far less than that in other organs.

Given the need for improved treatment options, this phase 1, first-in-human study was conducted in Chinese patients with advanced NSCLC to evaluate the safety, tolerability, pharmacokinetic (PK), and antitumor activity of HS-10241, with dose-limiting toxicity (DLT) and maximal tolerated dose (MTD) as primary end points.

Materials and Methods

Study Design and Treatment

This study is an open-label, multicenter, dose-escalation, phase 1 trial of HS-10241 in patients with advanced solid tumors (ClinicalTrials.gov identifier: NCT04477057). The participants orally received HS-10241 every day, subsequently evaluating the safety, tolerability, PK, MTD, and antitumor activity. The study was conducted in compliance with the Declaration of Helsinki, the Guideline for Good Clinical Practice of International Council for Harmonisation (E6), and all applicable laws and regulations.

Accelerated titration was applied to the initial dose group (100 mg quaque die or once daily), and the "Rolling Six" design was used for dose escalation in the higher dose groups. Therefore, one patient was enrolled in the 100 mg once-daily group and at least three and no more than six assessable patients in each of the other groups were guaranteed (Fig. 1). Dose escalation from 100 mg/d was based on the preclinical results, and subsequently, the escalation was guided by the occurrence of DLT and clinically relevant treatment-emergent adverse events (TEAEs). The initial cohorts received a single dose of HS-10241 (100 mg, 200 mg, 300 mg, 400 mg, or 600 mg) followed by a 7-day washout period before the start of repeated dosing. The once-daily (100 mg, 200 mg, 400 mg, and 600 mg) or twice-daily (twice daily: 200 and 300 mg) dosing of HS-10241 was assessed, exploring total daily doses between 100 and 600 mg. The duration of each continuous treatment cycle was 21 days (Fig. 1).

The primary objectives were to evaluate the safety and tolerability of HS-10241 for each regimen in patients with advanced solid tumors. The secondary objectives included PK characteristics and antitumor activity of HS-10241 in advanced solid tumors.

Patients

Patients with advanced solid tumors included in this study were those who had failed to respond to standard therapy or had no standard or effective existing therapy. The patients ($18 \leq$ age < 75) with solid tumors were histologically or cytologically confirmed, and written informed consent was obtained from all subjects. The patients' Eastern Cooperative Oncology Group

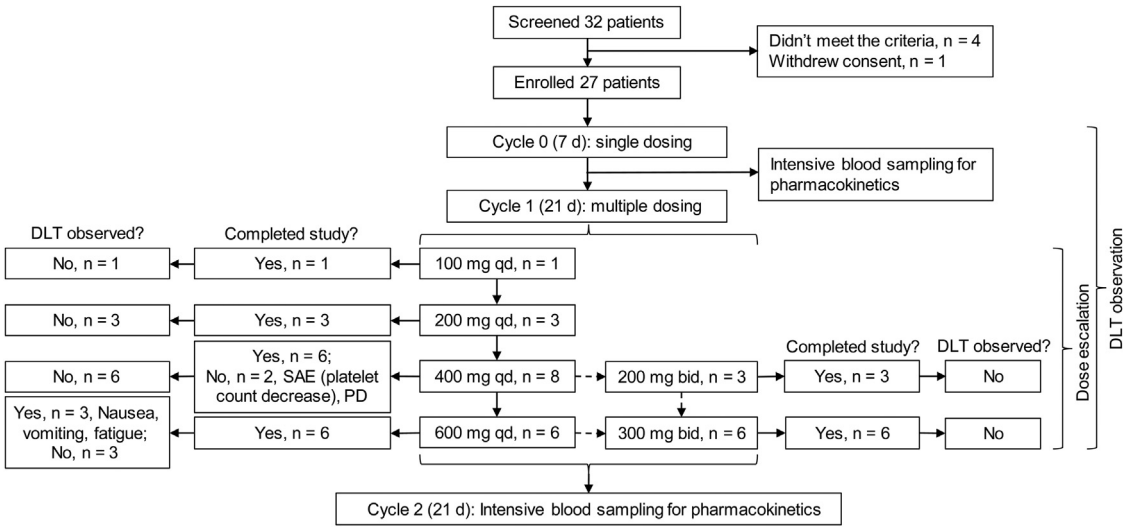

Figure 1. Procedure, patient allocation, and DLT observation in the trial. According to the results of DLT observation, the decision was made to change dosing or not. Completed the study: completed the first treatment cycle and DLT observation period, namely cycle 0 and cycle 1. bid, twice daily; DLT, dose-limiting toxicity; MTD, maximal tolerated dose; N, no; n, number; NA, not applicable; PD, progression of disease; qd, once daily; SAE, serious adverse event; Y, yes.

performance status scores were 0 to 1, and their life expectancy was at least 3 months. There was at least one measurable lesion that had not been locally treated or had progressed clearly after local treatment, with the longest diameter at a baseline greater than or equal to 10 mm (if it was a lymph node, the short axis was required to be $\geq$15 mm). Women of childbearing age required appropriate contraceptive measures during the research process. Breastfeeding during the screening or treatment phase, or within three months after treatment end, was not allowed. Moreover, male patients willing to use barrier contraception (namely condoms) were included. Patients who had received cytotoxic chemotherapeutics, experimental drugs, Chinese medicine treatment with antitumor indications, or other antitumor drugs within 2 weeks before the first administration, or greater than 30% bone marrow irradiation or extensive radiotherapy within 4 weeks before the first administration of HS-10241 were excluded. Detailed information on the inclusion and exclusion criteria is listed in the Supplementary Materials (Inclusion and exclusion criteria). *MET* status was not used as a criterion in initial recruitment, because the main purpose of phase 1 trials is usually to determine the drug's safety and tolerability.

The research protocol was reviewed and approved by the Human Research Ethics Committee at each institution.

Clinical Assessments

Patients were evaluated for toxicity throughout the trial, and all adverse events (AEs) were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events version 5.0. The DLT was defined as the toxicities related to the treatment between the first (cycle 0, day 1) and last HS-10241 dosing of the continuous 21-day treatment in the first cycle (cycle 1). The toxicities were not associated with the disease or its relevant treatments. Despite providing the best intervention treatment, the patients still had one or more of the following symptoms: (1) hematotoxicity: (a) grade 4 neutropenia lasting for more than 7 days; (b) neutropenia with fever (absolute neutrophil count $< 0.5 \times 10^9$/liter lasting for 24 h and body temperature $\geq 38.5^{\circ}$C); (c) grade 3 neutropenia with greater than or equal to grade 3 infection; (d) grade 4 thrombocytopenia lasting for more than 7 days and grade 3 thrombocytopenia with bleeding; and (e) grade 4 anemia, which cause could not be explained by the underlying disease; (2) nonhematological toxicity grade greater than or equal to 3 (Common Terminology Criteria for Adverse Events), including (a) persisting nausea, vomiting, diarrhea, and grade greater than or equal to 3 constipation, despite active supportive treatment; (b) prolonged corrected QT interval by Fredericia interval corrected using Fridericia's formula (absolute value >500 msec or >60 msec longer than baseline); (c) cardiotoxicity of grade greater than or equal to 3; (3) other toxicities: (a) exceeding the baseline, with clinical significance "and" or "or" unacceptable toxicity and judged as DLT by the Safety Review Committee; (b) leading to drug administration suspension for more than 21 days.

PK Analyses

Intensive blood sampling was performed after single dosing (cycle 0, day 1) and during cycle 2, day 1 (0, 0.5,

1, 1.5, 2, 4, 6, 8, 10, 12, and 24 h) after 21-day continuous dosing in cycle 1. Standard noncompartmental approach was used to generate PK parameters of HS-10241, including area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), accumulation ratio (R_{ac}, = $AUC_{multiple\ dose}/AUC_{single\ dose}$), and elimination half-life ($t_{1/2}$). The time dependence of PK on multiple doses was calculated using the ratio of AUC_{0}-t (area under the concentration-time curve from time 0 to the last measurable concentration using linear-log trapezoidal rule) at steady state to AUC at day 1.

Statistical Analysis

A statistical determination of the sample size was not required as the trial protocol followed a "Rolling Six" design, in which the total number of patients who participated depends on the required number of dose-escalation cohorts. The primary end point was the incidence of DLTs after the treatment or MTD. Summary statistics, such as mean, median, range, percentage, and appropriate variability measures, were calculated for each dose level. Secondary end points included safety, PKs after single or multiple dosing, and antitumor activity (indexes: overall response rate, disease control rate, duration of response, progression-free survival [PFS], and overall survival [OS]) of HS-10241, which were measured using descriptive statistics. Kaplan-Meier method was used to analyze OS and PFS.

Results

Patient Demographics, Baseline Characteristics, and Drug Exposure

A total of 32 patients with advanced solid tumors were selected from five different institutions in the People's Republic of China, and 27 patients (squamous carcinoma stage: IIIb, n = 1, IVa, n = 2; adenocarcinoma stage: IIIc, n = 1, IVa, n = 8, IVb, n = 14, IV, n = 1) were enrolled in the study between December 2019 (the first patient screened) and June 2021 (completed the study). The final analysis was performed for the data obtained on June 18, 2021.

The baseline characteristics of the patients and their tumors are found in Table 1. All patients enrolled in this study had NSCLC and were orally administrated with HS-10241 from a dose of 100 mg once daily, during which, accelerated titration was allowed as per the research protocol. A total of 27 patients received 100 mg once daily (n = 1), 200 mg once daily (n = 3), 400 mg once daily (n = 8), 600 mg once daily (n = 6), 200 mg twice daily (n = 3), and 300 mg twice daily (n = 6). Of the 27 patients, three (11.1%, one in 400 mg once daily and two in 600 mg once daily) had tumors with amplified *MET*, one (3.7%, the 400 mg once-daily group) had tumors harboring *MET* exon 14 skipping (*MET*Δex14) mutations and three (11.1%, all in 600 mg once-daily group) had MET-overexpressing tumors (overexpression 1+, n = 1; overexpression 3+, n = 2). Importantly, the patient with positive MET in the 400 mg once-daily group had amplification and *MET*Δex14.

Safety

Of all patients, only two (the 400 mg once-daily group) failed to finish the DLT observation period because of a serious AE (platelet count decreased, grade 3, C3D5) and progression of disease (Fig. 1). Three patients reported DLTs, all of whom were in the 600 mg once-daily treatment group. The DLTs included a case of grade 3 nausea with grade 3 vomiting, a case of grade 3 vomiting, and a case of grade 3 fatigue. Discontinuation of the trial in any part owing to death was absent. Nausea (48.1%, 13 of 27), fatigue (37.0%, 10 of 27), anemia (33.3%, 9 of 27), alanine transaminase (ALT) level increase (29.6%, eight of 27), aspartate transaminase (AST) level increase (29.6%, eight of 27), vomiting (29.6%, eight of 27), and hypoalbuminemia (29.6%, eight of 27) were the most frequently occurring TEAEs, with grades 1 to 2. As found in Table 2, 10 patients (37.0%) had TEAEs with grade greater than or equal to 3, with five of them present in the 600 mg once-daily group. Moreover, seven patients (25.9%) had treatment-related AEs with grade greater than or equal to 3, with four of them present in the 600 mg once-daily group; five patients (18.5%) had serious AEs (Supplementary Table 1), with three of them attributed to the treatment, including abnormal liver function (7.4%, two of 27) and platelet count decreased (3.7%, one of 27). Because of the TEAEs, dosing in five patients was suspended; however, no TEAE-related death was observed. AE (hepatitis E virus) led to permanent HS-10241 treatment discontinuation in one patient (3.7%) (600 mg once-daily treatment group), but it was considered certainly irrelevant to HS-10241 treatment. In addition, there were two cases of lower limb edema (7.4%, two of 27), whose subject identification is 10202 and 10301. The former was caused by hypoproteinemia and tumor progression, and the latter was mild (level I) and may be related with the treatment. The MTD of HS-10241 was determined to be 400 mg once daily. For twice-daily dosing, the maximal safe escalated dose was 300 mg, and MTD was not reached. On the basis of PKs, pharmacodynamics, and safety, further dose escalation was considered unnecessary.

Clinical Antitumor Efficacy of HS-10241

As of June 18, 2021, the median follow-up time (the duration of exposure) for 100 mg once daily, 200 mg

Table 1. Demographic and Baseline Data Characteristics of the Patients

Characteristics	100 mg qd (n = 1)	200 mg qd (n = 3)	400 mg qd (n = 8)	600 mg qd (n = 6)	200 mg bid (n = 3)	300 mg bid (n = 6)	Total (N = 27)
Age (y)							
Average (SD)	45 (NA)	61.7 (10.02)	58.8 (8.78)	58.3 (2.94)	53.3 (4.73)	57.5 (5.96)	57.6 (7.02)
Median (q1, q3)	45.0 (45.0, 45.0)	61.0 (52.0, 72.0)	58.0 (53.5, 66.0)	57.0 (56.0, 61.0)	55.0 (48.0, 57.0)	57.0 (56.0, 61.0)	57.0 (54.0, 61.0)
Sex, male, n (%)	0	2 (66.7)	4 (50.0)	3 (50.0)	1 (33.3)	2 (33.3)	12 (44.4)
ECOG PS, n (%)							
0	0	1 (33.3)	1 (12.5)	1 (16.7)	0	4 (66.7)	7 (25.9)
1	1 (100.0)	2 (66.7)	7 (87.5)	5 (83.3)	3 (100.0)	2 (33.3)	20 (74.1)
Pathologic type							
LUAD	1 (100.0)	3 (100.0)	8 (100.0)	4 (66.7)	3 (100.0)	5 (83.3)	24 (88.9)
LUSC	0	0	0	2 (33.3)	0	1 (16.7)	3 (11.1)
Prior anticancer treatment, n (%)							
Targeted therapy	1 (100.0)	3 (100.0)	5 (62.5)	4 (66.7)	3 (100.0)	3 (50.0)	19 (70.4)
Chemotherapy	1 (100.0)	3 (100.0)	6 (75.0)	5 (83.3)	2 (66.7)	6 (100.0)	23 (85.2)
Antiangiogenic therapy	0	0	2 (25.0)	2 (33.3)	0	4 (66.7)	8 (29.6)
Immunotherapy	0	2 (66.7)	2 (25.0)	3 (50.0)	0	4 (66.7)	11 (40.7)
Other	0	0	0	1 (16.7)	0	1 (16.7)	2 (7.4)
No. of prior lines of therapy, n (%)							
1	0	0	1 (12.5)	1 (16.7)	0	0	2 (7.4)
2	0	0	3 (37.5)	2 (33.3)	1 (33.3)	1 (16.7)	7 (25.9)
≥3	1 (100.0)	3 (100.0)	3 (37.5)	3 (50.0)	2 (66.7)	5 (83.3)	17 (63.0)
Brain metastases, n (%)							
Positive	0	1 (33.3)	5 (62.5)	0	3 (100.0)	1 (16.7)	10 (37.0)
Negative	1 (100.0)	2 (66.7)	3 (37.5)	6 (100.0)	0	5 (83.3)	17 (63.0)
MET overexpression, n (%)							
MET (+)	0	0	0	3 (50.0)	0	0	3 (11.1)
MET (−)	0	0	3 (37.5)	1 (16.7)	1 (33.3)	1 (16.7)	6 (22.2)
Not available	1 (100.0)	3 (100.0)	5 (62.5)	2 (33.3)	2 (66.7)	5 (83.3)	18 (66.7)
MET amplification, n (%)							
Amplified	0	0	1 (12.5)	2 (33.3)	0	0	3 (11.1)
Not amplified	0	0	2 (25.0)	0	1 (33.3)	2 (33.3)	5 (18.5)
Missing	1 (100.0)	3 (100.0)	5 (62.5)	3 (50.0)	2 (66.7)	4 (66.7)	18 (66.7)
MET exon 14 skipping, n (%)							
Positive	0	0	1 (12.5)	0	0	0	1 (3.7)
Negative	0	0	2 (25.0)	1 (16.7)	1 (33.3)	1 (16.7)	5 (18.5)
Missing	1 (100.0)	3 (100.0)	5 (62.5)	4 (66.7)	2 (66.7)	5 (83.3)	20 (74.1)

bid, twice daily; ECOG PS, Eastern Cooperative Oncology Group performance status; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NA, not applicable; q1, quartile 1; q3, quartile 3; qd, once daily.

Table 2. TEAEs and TRAEs

Adverse Events, n (%)	qd				bid		
	100 mg n = 1	200 mg n = 3	400 mg n = 8	600 mg n = 6	200 mg n = 3	300 mg n = 6	Total N = 27
TEAEs (grade ≥ 3)	0	0	3 (37.5)	5 (83.3)	1 (33.3)	1 (16.7)	10 (37.0)
TRAEs (grade ≥ 3)	0	0	2 (25.0)	4 (66.6)	0	1 (16.7)	7 (25.9)
Any SAE (including death)	0	0	2 (25.0)	1 (33.3)	1 (33.3)	1 (16.7)	5 (18.5)
SAEs considered related to treatment	0	0	2 (25.0)	0	0	1 (16.7)	3 (11.1)
Dose adjustment (reduction or suspension) owing to TEAEs	0	0	2 (25.0)	2 (33.3)	0	1 (16.7)	5 (18.5)
Abnormal liver function	0	0	1 (12.5)	0	0	1 (16.7)	2 (7.4)
AST increased	0	0	0	1 (16.7)	0	0	1 (3.7)
Platelet count decrease	0	0	1 (12.5)	0	0	0	1 (3.7)
Vomiting	0	0	0	2 (33.3)	0	0	2 (7.4)
Nausea	0	0	0	1 (16.7)	0	0	1 (3.7)
Hypoalbuminemia	0	0	0	1 (16.7)	0	0	1 (3.7)
Fatigue	0	0	0	1 (16.7)	0	0	1 (3.7)
Anemia	0	0	0	1 (16.7)	0	0	1 (3.7)

AE, adverse event; AST, aspartate transaminase; bid, twice daily; qd, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

once daily, 400 mg once daily, 600 mg once daily, 200 mg twice daily, and 300 mg twice daily was 336.0, 41.0, 42.0, 49.0, 43.0, and 73.5 days, respectively. Among the 27 subjects, two had partial remission (PR), of which one was finally confirmed PR (600 mg once-daily group) and the other stable disease (SD) (unconfirmed PR, 400 mg once daily group); eight had SD (including the unconfirmed PR), of which two were of the 600 mg once-daily group, three were of the 300 mg twice-daily group, and other three received 100 mg once daily, 200 mg once daily, and 400 mg once daily, respectively. As found in Table 3, all regimens, except 200 mg twice daily, had antitumor effects. Overall, nine patients (33.3%) achieved disease control, containing one (3.7%) PR and eight (29.6%) SD. Furthermore, the patients who received 600 mg once daily or 300 mg twice daily had better outcomes.

There were five MET positive cases (*MET* amplification, *MET* exon-14 skipping, or MET overexpression immunohistochemistry 3+) in this trial, with two of them revealing PR (600 mg once-daily group and 400 mg once-daily group, including the unconfirmed PR; Table 3), two having SD (600 mg once daily), and one revealing disease progression (600 mg once daily). Therefore, (Table 4), for patients with positive MET, the overall response rate (percentage of confirmed PR) was 20.0% (one of five), disease control rate (percentage of confirmed PR and SD lasting for 5 wk) was 80.0% (four of five), median PFS was 4.2 months (95% confidence interval: 1.1–not applicable), and OS time varied from

Table 3. BOR, ORR, DCR, OS Time, and PFS Time for Each Regimen

Adverse Events, n (%)	Qd				bid	
	100 mg (n = 1)	200 mg (n = 3)	400 mg (n = 8)	600 mg (n = 6)	200 mg (n = 3)	300 mg (n = 6)
BOR, n (%)						
PR	0	0	0	1 (16.7)	0	0
SD	1 (100.0)	1 (33.3)	1 (12.5)[a]	2 (33.3)	0	3 (50.0)
PD	0	2 (66.7)	5 (62.5)	2 (33.3)	3 (100.0)	2 (33.3)
Not assessable	0	0	2 (25.0)	1 (16.7)	0	1 (16.7)
ORR (%)	0	0	0	16.7	0	0
95% CI	NA-NA	NA-NA	NA-NA	0.4-64.1	NA-NA	NA-NA
DCR	100.0	33.3	12.5	50.0	0	50.0
95% CI	2.5-100.0	0.8-90.6	0.3-52.7	11.8-88.2	NA-NA	11.8-88.2
mOS (95% CI)	NA (NA-NA)	9.6 (2.8-NA)	7.7 (2.5-NA)	5.9 (1.0-NA)	NA (NA-NA)	NA (NA-NA)
mPFS (95% CI)	11.3 (NA-NA)	1.5 (1.5-NA)	1.5 (0.7-NA)	2.8 (1.0-NA)	1.6 (1.0-NA)	2.9 (1.4-NA)

[a]This case was first evaluated as SD, second PR, and third PD; therefore, the final BOR was SD.
bid, twice daily; BOR, best overall response; CI, confidence interval; DCR, disease control rate; mOS, median overall survival; mPFS, median progression-free survival; NA, not applicable; ORR, objective response rate; PD, progression of disease; PR, partial remission; qd, once daily; SD, stable disease.

Table 4. The Efficacy of HS-10241 in c-MET-Positive Cases

Subject ID	Regimen	c-MET Status	c-MET Detection Method(s)	EGFR Status	BOR	PFS (mo)	DoR (mo)	OS (mo)
10404	400 mg qd	Exon-14 skipping, amplified	NGS	None	SD[a]	4.2	NA	7.7
10403	600 mg qd	Amplified	NGS	L858R+, T790M+, EGFR amplified	PR	5.7	4.1	6.5
10502	600 mg qd	Overexpression 3+	NGS, IHC	Unknown	SD	3.0	NA	6.5
10505	600 mg qd	Overexpression 3+	NGS, IHC	Exon-19 mutation	PD	1.1	NA	5.2
10701	600 mg qd	Amplified	NGS	L858R+, G719X+	SD	2.8	NA	12.2[b]

[a]This case was first evaluated as SD, second PR, and third PD, and the final BOR was SD.
[b]The subject (ID: 10701) is still alive when data analysis was performed, and the OS was 12.2 months until then.
BOR, best overall response; DoR, duration of response; ID, identification; IHC, immunohistochemistry; NA, not applicable; NGS, next-generation sequencing; OS, overall survival; PD, progression of disease; PFS, progression-free survival; PR, partial remission; qd, once daily; SD, stable disease.

5.2 to 12.2 months. In addition, the duration of response of the only patient with confirmed PR was 4.1 months (Table 4).

In the finally confirmed PR patient, in the early stage (April 24, 2020–July 9, 2020; 1.6 mo) of HS-10241 treatment, the size of the metastatic tumor in organs such as the liver gradually decreased (Supplementary Fig. 1). Since September 29, 2020, computed tomography imaging results revealed that parts of the lung nodules and some of the multiple lymph nodes enlarged, and subsequently, nodules appeared on the left lower abdominal wall, though ascites around the liver continuously decreased for more than 4 months (Supplementary Fig. 1).

Pharmacokinetics

C_{max} and $AUC_{0-\infty}$ increased almost proportionally with increasing dose after single and multiple dosing for both once daily and twice daily HS-10241 administration (Supplementary Tables 2 and 3). Compared with the 400 mg once daily and 600 mg once daily, C_{max} and C_{min} (trough concentration) decreased and increased in the 200 and 300 mg twice daily groups (Fig. 2*A* and *B* and Supplementary Table 3), respectively, indicating a better safety for twice-daily dosing. After a single oral administration, HS-10241 was absorbed with a median t_{max} of 2.0 to 8.0 h, and $t_{1/2}$ of all 27 subjects varied from 10.80 to 16.72 h (Fig. 2*A* and Supplementary Table 2). Detailed information regarding geometric mean $t_{1/2}$, C_{max}, and AUC_{0-t} for single or multiple doses (including once daily and twice daily) is found in Supplementary Table 2.

Discussion

This phase 1 clinical trial reveals that the selective MET inhibitor, HS-10241, was well tolerated in patients with locally advanced or metastatic solid tumors. The MTD of HS-10241 was determined as 400 mg for once-daily dosing, and the MTD for twice-daily dosing was not reached (maximum dose investigated was 300 mg twice daily). In addition, the recommended phase 2 dose was recently established as 300 mg twice daily for combination therapy with almonertinib in the subsequent clinical trial (ClinicalTrials.gov identifier: NCT05430386). The two most frequent TEAEs in this study (nausea and fatigue) were the same as those of other reported selective MET inhibitors (savolitinib and tepotinib)[8–10]; however, other TEAEs, such as anemia, ALT level increased, AST level increased, and hypoalbuminemia, varied from one another but can be often seen in clinical trials of other type I MET inhibitors.[11–13] The increase in ALT and AST in some patients reflects certain hepatotoxicity; however, it is also observed in other trials of selective or nonselective MET inhibitors,

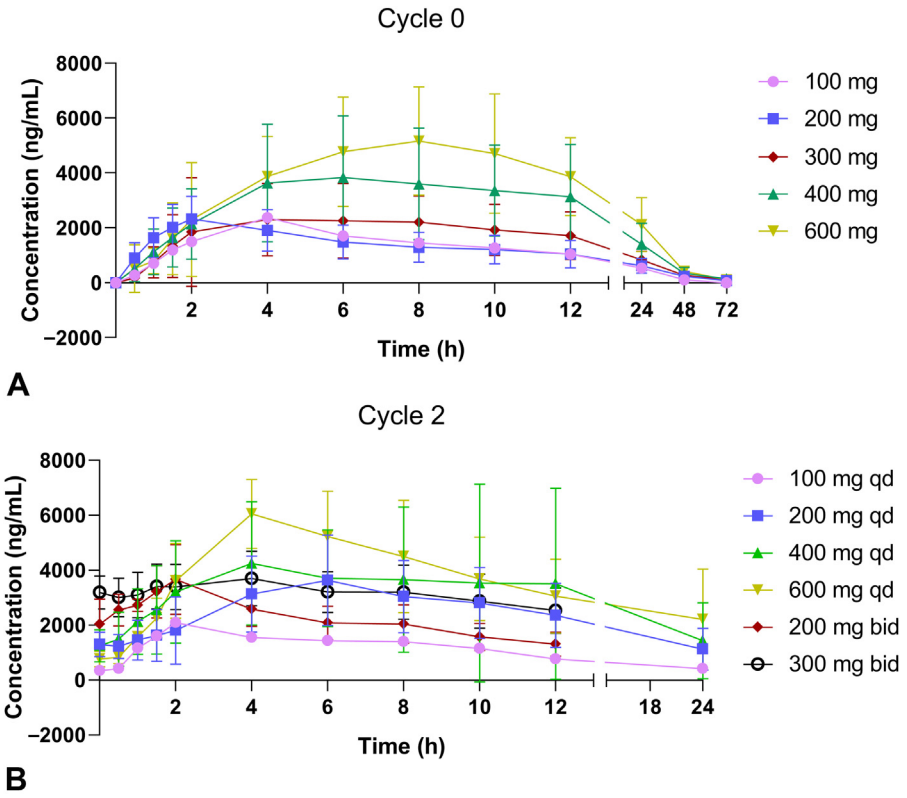

Figure 2. Plasma concentration-time profiles of HS-10241 after a single dose (in 7-d washout period, cycle 0) at 100, 200, 300, 400, and 600 mg (*A*) and after repeated dosing (*B*; in cycle 2). HS-10241 reached peak concentration levels by approximately 5 hours after administration. Concentration of HS-10241 is found on a log scale. cycle 0 (single dosing), cycle 2, where cycle was defined as a 21-day-continuous administration. bid, twice daily; qd, once daily.

such as the recently approved savolitinib in the People's Republic of China and a first-line drug crizotinib.[8,14,15] In addition, a case of tepotinib leading to intolerable peripheral edema in the patient was reported; however, MET inhibitor could be continued by switching to capmatinib.[16] In our study, the rate of peripheral edema is relatively low. Therefore, different MET inhibitors may lead to quite different AEs. In this situation, these c-MET inhibitors, including HS-10241, can be properly selected to avoid intolerable AEs.

Most trials failed to reveal efficacy owing to inappropriate patient selection criteria.[17] MET status was not a criterion in this trial because the main purpose was to investigate the drug's safety and dose tolerability. Nevertheless, using the limited five patients with positive MET (exon-14 skipping, amplified, or overexpression [3+]), we might be able to speculate that patients with cancer with positive c-MET may benefit more from HS-10241 targeting treatment. This was consistent to some extent with previous reports of selective MET inhibitors, wherein the antitumor activity of tepotinib seemed greatest in patients with MET immunohistochemistry 3+ (*MET* not amplified) tumors[9] and only those patients with papillary renal cell carcinoma with *MET* GCN changes (focal amplification or chromosome 7 gains) responded to savolitinib treatment. In addition, one patient with colorectal cancer and *MET* amplification reported the best response of SD with a 29.7% decrease in tumor size.[8] Notably, this speculation had its boundedness and needs further validation, because c-MET status in other patients was not available. In addition, one study indicated that the near-complete ($\geq$ 95%) inhibition of MET phosphorylation is necessary for tumor regression.[9] Therefore, this threshold, which may be a critical factor for the clinical application of c-EMT inhibitors, should also be considered in future.

*MET*Δex14 mutation causes the loss of juxtamembrane domain and forms a truncated receptor without Y1003 and c-Cbl binding sites, resulting in c-MET protein ubiquitination disorder and degradation rate reduction and the final activation of its downstream signals. *MET*Δex14 presents in only approximately 3% of patients with NSCLC,[18] and it can be found co-occurred with MET amplification in cancer (frequency 4%–40% in NSCLC),[18,19] which was also noticed in our present study (Table 4). It is believed that there are more co-occurring mutations in MET-amplified tumors compared with the *MET*Δex14-mutated tumors, and the co-mutation type depends on the degree of *MET*

amplification.[20] Therefore, maybe we should pay much more attention to *MET* amplification. *MET* amplification, caused by an increase in the GCN of the *MET* gene, is a common mechanism of resistance to treatment with EGFR TKIs in addition to the occurrence of T790 M mutation, with *MET* amplification or MET-based resistance occurring in up to 10% to 25% of patients with NSCLC who progress from first- to third-generation EGFR TKIs.[21] Patients with cancer who acquire *MET* amplification as a bypass to resist EGFR TKI therapy were found to have achieved symptomatic control or responsiveness to crizotinib treatment.[22] Clinical studies further confirm that a combinatorial regimen with either first- or third-generation EGFR TKI and c-MET inhibitors, such as savolitinib combined with crizotinib and gefitinib plus tepotinib or capmatinib, has encouraging antitumor activity in patients with NSCLC having EGFR mutation and *MET* amplification-mediated EGFR TKI resistance.[21–23] Mechanistically, amplified or exon 14 skipping-mutated c-MET crossreacts with EGFR proteins and possibly substitutes their activity, in which, a dominant player in resistance to EGFR-targeting agents ERBB3–PI3K–AKT signal axis is usually involved.[24–26] Therefore, the interaction between c-MET and EGFR could be decreased on c-MET reduction.[27] In EGFR TKI-resistant cancers, c-MET remains a rational target.[28,29] Therefore, HS-10241 in combination with EGFR inhibitor almonertinib will be used in the following phase 1b/2 trial for the treatment of patients with advanced NSCLC and positive EGFR mutation who have progressed after EGFR TKI treatment (ClinicalTrials.gov identifier: NCT05430386).

In summary, HS-10241 was well tolerated at a dose of 400 mg daily by patients with advanced solid tumors. Moreover, patients with MET-positive tumors seemingly benefited more from the treatment. The recommended phase 2 dose was 300 mg twice daily for HS-10241 in combination with almonertinib, and the phase 1b/2 trial evaluating the combination in Chinese patients with advanced NSCLC is now in the expansion stage (ClinicalTrials.gov identifier: NCT05430386).

CRediT Authorship Contribution Statement

Xiaorong Dong: Conception, Design, Administrative support, Technical support, Material support, Study supervision.

Xiaorong Dong, Xingya Li, Jianhua Chen: Development of methodology.

Xingya Li, Jianhua Chen, Shenglin Ma, Deguang Mu, Jie Hu, Shun Lu: Acquisition of data.

Xingya Li, Jianhua Chen, Shenglin Ma, Deguang Mu, Jie Hu, Shun Lu: Analysis and interpretation of data.

Xiaorong Dong, Xingya Li, Jianhua Chen: Writing, review or revision of the manuscript.

Xiaorong Dong, Xingya Li, Jianhua Chen, Shenglin Ma, Deguang Mu, Jie Hu, Shun Lu: Final approval of the version to be published and agree to be accountable for all aspects of the work.

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Data Availability Statement

The data generated in this study are available within the article and its supplementary data files.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100449.

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