

Safety, tolerability, and pharmacokinetics of simotinib, a novel specific EGFR tyrosine kinase inhibitor, in patients with advanced non-small cell lung cancer: results of a phase Ib trial

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Purpose: The aim of this phase Ib study (clinicaltrials.gov: NCT01772732) was to assess safety, tolerability, and pharmacokinetics (PKs) of simotinib (a novel EGFR tyrosine kinase inhibitor) in patients with advanced non-small cell lung cancer (NSCLC) and *EGFR* gene mutation.

Patients and methods: 41 patients with *EGFR* gene mutations were enrolled and received simotinib orally administered twice daily with dose escalating from 100 to 650 mg in 28 days cycle. Safety and tolerability were assessed through the study. Blood samples were collected for PK analysis on Days 1, 8, 9, 10, 15, 22 and 29. Tumor response was assessed at baseline, on Day 29 and every 8 weeks thereafter.

Results: Simotinib was well tolerated, with no dose-limiting toxicities. Maximum tolerated dose (MTD) was not found. 95.1% of patients experienced at least one adverse event (AE), and most of them were mild or moderate. Rash (41.5%) and diarrhea (56.1%) were the most frequently reported AEs. Simotinib was rapidly absorbed and eliminated with average T_{max} ranging from 1 to 4 hrs and $T_{1/2}$ ranging between 6.2 and 13.0 hrs after multiple-dose administration. No dose–response relationship between dose and exposure was observed after multiple-dose administration. 39.3% of the enrolled patients achieved a partial response and 46.3% had stable disease. Median progression-free survival and overall survival were 9.9 (CI% 4.7; 12.1) months and 14.6 (95%CI 12.3; 22.5) months, respectively.

Conclusion: Simotinib was well tolerated, with manageable AEs at doses of up to 650 mg and MTD was not reached. Further studies to explore higher doses are ongoing.

Keywords: simotinib, EGFR, non-small cell lung cancer, toxicity, pharmacokinetics

Introduction

Worldwide lung cancer remains one of the leading causes of cancer-related deaths. In 2012, it was responsible for 19.4% (1.6 million) of all deaths due to cancer.¹ Non-small cell lung cancer (NSCLC) represents up to 87.0% of the total lung cancer cases, is associated with 30–40% 1-year net survival rate, and many patients are diagnosed with advanced disease due to its insidious onset.^{2,3} Despite introduction of molecular-targeted therapies and histology-based cytotoxic chemotherapy, the survival of these patients is limited.⁴

EGFRs are highly expressed in a number of human tumors and are associated with poor prognosis.⁵ In patients with NSCLC, the overall reported prevalence of *EGFR*-gene mutations is 33.1%, with higher prevalence in women, Asian populations (India, China,

Japan and Taiwan), non-smokers and in those with adenocarcinoma.⁶ Also, their presence is associated with significantly longer survival of these patients as compared to *EGFR* wild type (13.3 vs 30.9 months, $P < 0.001$).⁴ The introduction of *EGFR* tyrosine kinase inhibitors (*EGFR*-TKIs) in the therapy of NSCLC has been an important step-forward with significant clinical benefit especially in those harboring *EGFR* mutations.^{7–11}

Simotinib (Simcere Pharmaceutical Group, Nanjing, China) is a novel selective and specific TKI acting through inhibition of *EGFR* tyrosine kinase activity which showed favorable tolerability profile in preclinical studies.^{12,13} *In vitro* studies showed that simotinib inhibits in a dose-dependent manner *EGFR* and the growth of human A431 tumor cells with high expression of *EGFR*, with no significant activity on other investigated kinases.¹² It has a half maximal inhibitory concentration of 19.9 nM on *EGFR*. *In vivo*, simotinib has been shown to exert its antitumor activity by inhibiting *EGFR* phosphorylation in nude xenograft model. Preclinical toxicology studies demonstrated that simotinib has a favorable tolerability. The common toxicities include weight loss, diarrhea, salivation, and alopecia. Our previous phase Ia study in 12 healthy volunteers showed that simotinib was well tolerated and had an average clearance (CL) $T_{1/2}$ of 8–12 hrs in the dose range of 25–500 mg, suggesting that twice-daily administration is recommended.¹²

Here, we report the results of a phase Ib study with the primary objective to investigate the safety and tolerability of multiple ascending doses of simotinib in patients with advanced NSCLC and *EGFR* gene mutations. Secondary objectives were to evaluate the pharmacokinetic (PK) profile and to explore the preliminary anti-tumor activity of simotinib in these patients.

Material and methods

Study design and treatment

This was a single center, non-randomized, dose escalation phase Ib study performed between April 2013 and July 2015 in National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Beijing, China (clinicaltrials.gov: NCT01772732). Eligible patients were sequentially assigned to receive a cycle of simotinib (flat doses of 100, 200, 300, 400, 500, and 650 mg, respectively) following a 3+3 dose escalation design according to a modified Fibonacci scheme. Simotinib was orally

administered twice per day for 28 days (treatment phase); no other chemotherapy regimens were allowed during the study. After the completion of the enrollment procedure, patients were assigned to receive one of the studied doses and continued with the assigned dose during the treatment period. Enrollment of patients in subsequently higher dose level group, and thus dose escalation, begun only if no dose-limiting toxicity (DLT) was observed in any of the treated patients in the lower dose level group during the 28-day treatment period. The maximum tolerated dose (MTD) was considered as reached, and thus defined, if >1 patient developed DLT at any dose level.

Simotinib was manufactured by Simcere Pharmaceutical Group and was packed and labeled by the manufacturer which was also the study sponsor.

Following the screening/enrollment visit, during the treatment phase, each patient underwent 7 study evaluations on Days 1 (first study drug administration), 8, 9, 10, 15, 22, and 29. During these visits, samples were collected for PK analysis. After the treatment phase, patients were followed, every 8 weeks until disease progression, death, or study termination. Safety and toxicity were collected through the study. Tumor evaluation was performed by imaging techniques (computed tomography [CT] or magnetic resonance imaging) at study enrollment (Baseline), on Day 29 and every 8 weeks thereafter.

Study population

Adult patients at 18–65 years of age, with histologically confirmed advanced NSCLC with *EGFR* gene mutations (*E19del*, *L858R*, *L861Q*, *G719X*, etc.) and relapsed following therapy with at least one platinum-based regimens were enrolled. Additionally, to be eligible patients had to have an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2, an estimated life expectancy ≥ 12 weeks, adequate bone marrow, liver and renal functions (absolute neutrophil count $\geq 1.5 \times 10^9/L$, platelet count $\geq 80 \times 10^9/L$, hemoglobin value ≥ 90 g/L, serum bilirubin $< 2 \times UNL$, liver transaminase levels $\leq 2 \times UNL$ or $\leq 5 \times UNL$ if liver metastasis, estimated creatinine CL ≥ 60 mL/min or serum creatinine levels $\leq 1.5 \times UNL$). Women of childbearing potential had to have a negative pregnancy test within 7 days prior to treatment start and had to use an approved contraceptive method during the study; men were enrolled if they were surgically sterile or agreed to use an approved contraceptive method during the study.

Exclusion criteria included evidence of interstitial lung disease, idiopathic pulmonary fibrosis identified by CT examination performed at baseline; left ventricular ejection fraction (LVEF) <50%; central nervous system metastasis recently diagnosed which had not been treated by surgery or radiotherapy; previous therapy with EGFR-TKIs or other relevant molecular targeted drugs; treatment with rifampin, rifabutin, rifapentine, dexamethasone, phenytoin sodium, carbamazepine, phenobarbital, *Hypericum perforatum*, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, or telithromycin at study enrollment; any unstable systemic disorders (including active infection, uncontrollable hypertension, unstable angina pectoris, congestive heart failure, liver and kidney disorders or metabolism disease); other malignancies diagnosed within the last 5 years with the exception of completely cured cervical cancer in situ, or basal and squamous cell skin cancer; history of neurologic or psychiatric disorders, including epilepsy or dementia.

Assessment of safety and toxicity

Safety analyses, the primary outcome of this study, were performed in the safety population, which included all patients who received at least one dose of simotininib.

During the study, adverse events (AEs), serious adverse events (SAEs), and hematological toxicity by general physical examination, special examinations (chest X-ray, electrocardiogram, echocardiography) and laboratory investigations were collected. Blood samples for safety laboratory investigations were collected on Days 1, 8, 15, 22 and 29, before study drug administration and included hematological assessment, and assessment of liver and renal functions. Toxicities were described and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTC AE) version 4.0.

DLT was defined as any of the following drug-related AEs: blood pressure >150/100 mmHg that could not be controlled with medication; a decrease of the LVEF >10% or symptoms suggestive for cardiac dysfunction; grade 4 diarrhea or grade 3 diarrhea twice a day or with a duration longer than 24 hrs, or diarrhea treated with active medication (loperamide and intravenous fluid replacement were permitted); vomiting \geq grade 3 which could not be controlled by active treatment; renal toxicity \geq grade 2; liver toxicity \geq grade 3; rate-corrected QT interval (QTc) \geq 500 ms; severe rash or other skin disorders which could not be controlled by

therapy, or with a duration over 2 week or re-occurring pruritus; grade 4 neutropenia (absolute neutropenia count $<0.5 \times 10^9/L$) with a duration \geq 5 days, or grade 3 or 4 febrile neutropenia (temperature $\geq 38.5^\circ C$); thrombocytopenia ($\leq 25 \times 10^9/L$), or use of blood or its component for the therapy of thrombocytopenic hemorrhage; other grade 4 hematologic toxicities or grade 3 non-hematologic toxicities.

Assessment of pharmacokinetics

Blood samples (2 mL) for simotininib PK analysis were collected on Day 1 (0.05 hrs before the first dose and 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12, 24 hrs after dosing); Days 8, 9 and 10 (0.05 hrs before the administration of the first dose of simotininib/day); Day 15 (0.05 hr before the administration of the first dose/day, 0.5, 1, 1.5, 2, 4, 6, 8, 10, 12 hrs after dosing) and Days 22 and 29 (0.05 hr before the administration of the first dose/day). Samples were analyzed by liquid chromatography with mass spectrometry detection using multiple reaction monitoring and following a procedure previously described.¹⁴ The lower limit of quantification for simotininib was 1 ng/mL. PK parameters (area under the plasma concentration-time curve from time 0 to infinity; area under the plasma concentration-time curve from time 0 to the last measured concentration [AUC_{0-last}]; clearance [CL]; maximum drug concentration [C_{max}]; minimum drug concentration [C_{min}]; terminal half-life [$t_{1/2}$]; time to reach the maximum concentration [T_{max}]; apparent volume of distribution) were calculated from individual serum concentration-time profile of simotininib using Phoenix WinNonlin 6.0 software.

Assessment of clinical antitumor activity

Clinical antitumor activity analysis was performed in the full analysis population (which included all enrolled patients who received at least one dose of simotininib) and per-protocol population. Antitumor responses (complete and partial responses) were assessed by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) using imaging techniques at Baseline, on Day 29 following the first study drug administration and every 8 weeks thereafter until disease progression, death, or study termination. Objective response rate (ORR) was calculated as the number of patients with complete or partial response denominated by the total number of patients dosed. The assessed efficacy outcomes also included progression-free survival (PFS) and overall survival (OS). PFS was measured from the date of the first drug administration until the date of documentation of disease progression or

death from any cause. OS was measured from the date of the first drug administration until the date of death from any cause.

Statistical analysis

Based on 3+3 study design and dose escalation, the estimated sample size was 24–30 patients fulfilling the inclusion criteria and without any exclusion criteria. No primary statistical endpoint was used to justify this planned sample.

Statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). Safety, toxicity, PK and antitumor activity were assessed using descriptive statistics, and PFS and OS were analyzed using the Kaplan–Meier method.

Ethics approval and informed consent

Study protocol and all study related materials were approved by the review board of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College Beijing, China. The study was conducted according to Good Clinical Practice Guidelines, Declaration of Helsinki, local laws and regulations. All patients provided written informed consent prior to study participation.

Results

Patient characteristics

Between April 2013 to July 2015, 41 patients fulfilling the inclusion criteria and without any exclusion criteria were enrolled and received at least one dose of simotininib. Full analysis population and safety population comprised all these 41 patients. We enrolled 28 men and 13 women with age ranging between 37 and 65 years. ECOG performance was 0–1 in 39 patients, and 2 in 2 patients. All patients had adenocarcinoma and the majority had a TNM staging of IV. Baseline characteristics, including *EGFR* mutation type, are shown in Table 1. All patients harbored mutations of exons 18, 19 or 21 of *EGFR*. Specifically, of the 41 patients enrolled, 27 had a single 19 exon deletion, 13 had L858R point mutation in exon 21 and 1 had an exon 18 deletion. None presented mutations in exon 20 of *EGFR*.

Toxicity and DLT

At least one AE was reported in 39 of the 41 enrolled patients (95.1%) and at least one study drug-related AE was reported in 38 of the 41 enrolled patients (92.7%). The most frequently

Table 1 Baseline patient characteristics

Characteristics	Number of patients
Enrolled	41
Gender (male/female)	28/13
Median age (range), years	57 (37–65)
ECOG PS	
0–1	39
2	2
TNM staging	
IIIA	1
IIIB	3
IV	37
Pathology	
Adenocarcinoma	41
<i>EGFR</i> gene-mutation type	
Exon 18	1
Exon 19	27
Exon 20	0
Exon 21	13
Subgroup of <i>EGFR</i> mutation	
19–1 loss	27
21–1 L858R	13
18 loss	1

Abbreviations: ECOG PS, Eastern Cooperative Group performance status; TNM, TNM staging system.

reported AEs were diarrhea and rash, reported in 56.1% and 41.5% of the participants, respectively. Other reported AEs were pruritus (reported for 24.4% of patients), neutropenia (26.8%), anemia (22.0%), increased level of aminotransferase (19.5%) and bilirubin (17.1%), and fatigue (24.4%). AEs of grade ≥ 3 were reported in 7 patients (17.1%; 3 patients in the 500 mg group and 4 patients in the dose groups below 500 mg [1 per each dose group]). SAEs were reported in 2 patients (4.8%; in 400 mg and 500 mg dose group, respectively); death occurred during the treatment phase in 1 patient who received 400 mg dose. One patient (2.4%) who received 500 mg discontinued the study. No trend of increasing overall frequency of AEs with increasing dose of simotininib was observed (Table 2). At least 1 study drug-related AE was reported in all patients in the 100, 200, 300, and 650 mg dose groups, and in 86.7% and 91.7% of patients in the 400 and 500 mg dose groups, respectively. With regard to specific AEs, frequencies of rash, aminotransferase elevation and fatigue were higher in patients who received 500 and 650 mg of simotininib as compared to those who received 400 mg simotininib. Cardiovascular toxicities were rare and reported in patients who received ≥ 400 mg simotininib.

Table 2 Overview of adverse events in safety population

	100 mg N=2	200 mg N=3	300 mg N=3	400 mg N=15	500 mg N=12	650 mg N=6	Total N=41
Skin and subcutaneous tissue disorders							
Rash, n (%)	1 (50.0)	2 (66.7)	0	2 (13.3)	9 (75.0)	3 (50)	17 (41.5)
Pruritus, n (%)	2 (100)	2 (66.7)	1 (33.3)	4 (26.7)	1 (8.3)	0	10 (24.4)
Blood and lymphatic systems disorders							
Neutropenia, n (%)	0	3 (100)	1 (33.3)	3 (20.0)	2 (16.7)	2 (33.3)	11 (26.8)
Erythrocyte reduction, n (%)	0	1 (33.3)	0	4 (26.7)	2 (16.7)	2 (33.3)	9 (22.0)
Hepatobiliary disorder							
Aminotransferase elevation, n (%)	0	0	1 (33.3)	2 (13.3)	2 (16.7)	3 (50.0)	8 (19.5)
Bilirubin elevation, n (%)	0	2 (66.7)	2 (66.7)	1 (6.7)	2 (16.7)	0	7 (17.1)
Gastrointestinal disorder							
Diarrhea, n (%)	0	3 (100)	3 (100)	7 (46.7)	7 (58.3)	3 (50.0)	23 (56.1)
General disorders							
Fatigue, n (%)	2 (100)	1 (33.3)	2 (66.7)	2 (13.3)	3 (25.0)	0	10 (24.4)

Abbreviations: n/N, number of patients; %, percentage of patients.

None of the reported AEs fulfilled pre-set criteria for DLT for any of the doses used during dose escalation and an MTD was not reached.

Pharmacokinetics

PK parameters were calculated for all patients enrolled and are summarized in Tables 3 and 4. Single-dose PK results for the first dosing interval showed that exposure increased with dose escalation and roughly showed a linear dynamic increasing from the 100 mg dose to the 650 mg dose. Mean C_{max} increased from 56.5 ng/mL in the 100 mg dose to 828.5 ng/mL in the 650 mg dose. Mean AUC_{0-last} ranged between 405.6 ng·hr/mL in the 100 mg dose and 4,652.1 ng·hr/mL in the

650 mg dose. For multi-dosing, no significant differences were found for $T_{1/2}$ and T_{max} in sequential cohorts from 200 to 650 mg. Significant differences between doses were reported in C_{max} , AUC_{0-last} and CL but with no consistent dose-proportional increase in exposure with increasing dose ($P < 0.05$ for all). The highest C_{max} and AUC_{0-last} were observed in the 300 mg and 500 mg cohorts, followed by the 400 and 650 mg cohorts. For CL, the highest value was observed in the 650 mg cohort, followed by the 400, 500 and 200 mg doses.

Clinical antitumor activity

By the database lock date, 40 of the 41 patients enrolled received efficacy assessment according to RECIST criteria.

Table 3 Pharmacokinetic results for single dose of simoninib

Parameters (mean ± SD)	100 mg N=2	200 mg N=3	300 mg N=3	400 mg N=15	500 mg N=12	650 mg N=6
$T_{1/2}$, h	5.3±0.3	12.2±3.5	9.2±1.0	13.3±6.3	28.0±33.8	29.7±32.2
T_{max} , h	1.8 (1.5–2.0)	2.0 (2.0–2.0)	1.5 (1.5–2.0)	2.0 (1.0–8.0)	1.8 (0.5–4.0)	2.0 (1.0–6.0)
C_{max} , ng/mL	56.5±18.2	333.0±35.4	552.5±388.2	566.4±372.0	514.5±316.4	828.5±849.0
AUC_{0-last} , ng·hr/mL	405.6±94.8	2,339.6±479.9	2,814.0±764.5	3,581.9±1,868.5	3,791.0±2,741.1	4,652.1±3,442.1
$AUC_{0-∞}$, ng·hr/mL	466.2±129.9	2,955.0±564.0	3,243.8±776.1	4,962.1±3,141.7	6,483.8±5,008.4	7,648.4±3,028.7
CL, L/h	223.1±62.2	68.9±13.2	95.2±22.8	127.4±117.6	200.5±300.1	97.7±39.2
V_d , L	1,704.0±385.8	1,250.1±579.7	1,286.1±438.6	2,097.2±1,506.8	7,166.6±12,246.1	3,873.8±3,378.1

Abbreviations: AUC_{0-t} , area under the curve from time 0 to the last measurable plasma concentration; $AUC_{0-∞}$, area under the curve from time 0 to infinity; CL, total body clearance; C_{max} , maximum plasma concentration; T_{max} , time to maximum concentration; $T_{1/2}$, half-life; V_d , volume distribution.

Table 4 Pharmacokinetic results for multi-dosing of simotininib

Parameters (mean±SD)	100 mg N=2	200 mg N=3	300 mg N=3	400 mg N=15	500 mg N=12	650 mg N=6
$T_{1/2}$, h	6.2	9.6±4.2	10.4±7.8	13.0±11.8	8.4±2.8	9.2±1.9
T_{max} , h	1.0(0–2.0)	4.0 (2.0–4.0)	1.5 (1.0–2.0)	2.0 (0–8.0)	1.8 (1.0–6.0)	2.0 (1.5–8)
C_{max} , ng/mL	130.3±70.3	447.0±258.8	1,519.0±1,132.8	767.9±338.1	1,396.0±534.8	650.8±234.7
C_{min} , ng/mL	54.5±32.1	207.0±152.7	288.0±117.4	251.6±127.0	378.3±132.0	214.3±84.8
C_{avg} , ng/mL	76.7±29.1	328.4±224.1	501.2±254.8	437.1±182.9	651.6±161.9	384.6±133.3
$AUC_{0-∞}$, ng·hr/mL	920.4±349.2	3,940.9±2,689.0	6,013.9±3,058.1	5,245.7±2,194.4	7,819.8±1,942.3	4,615.7±1,599.7
$AUC_{0-∞}$, ng·hr/mL	956.9	6,571.6±3,241.2	9,728.6±1,648.2	10,577.7±5,867.6	12,780.6±3,894.7	8,193.3±3,211.2
CL, L/h	148.5	66.1±45.1	57.3±29.1	99.5±70.4	67.7±17.2	156.3±55.6
V_d , L	1323.3	1,050.0±1,020.6	1,019.6±1,077.5	2,000.6±3,169.6	811.3±326.9	2,021.8±635.7

Abbreviations: $AUC_{0-∞}$, area under the curve from time 0 to the last measurable plasma concentration; $AUC_{0-∞}$, area under the curve from time 0 to infinity; CL, total body clearance; C_{max} , maximum plasma concentration; C_{avg} , average plasma concentration; T_{max} , time to maximum concentration; $T_{1/2}$, half-life; V_d , volume distribution.

Full analysis population comprised 41 patients and per-protocol population 40 patients. Of the 41 patients enrolled, 16 (39.0%) achieved a partial response and 19 (46.3%) had stable disease as best response after the treatment period. Progressive disease was reported as best response for 5 patients (12.0%). All patients with partial response or stable disease received simotininib at doses of ≥ 200 mg. In addition, 5 of the 18 patients with brain metastases achieved partial response on these metastases. Twelve patients with brain metastases received simotininib 500 mg and partial response was achieved in 2 (16.7%) of them; 6 patients with brain metastases received simotininib 650 mg and partial response was achieved in 3 (50%) of them. During the whole study (treatment phase and follow-up period), 7 deaths were reported: 2 in the 100 mg group, 3 in the 200 mg group, 1 in the 300 mg group and 1 in the 400 mg group. The survival rate at 1-year was 88.2%. Median PFS was 9.9 months (95%CI: 4.7; 12.1) and median OS was 14.6 months (95%CI: 12.3; 22.5).

Tumor lesion measurements are depicted in Figure 1. Tumor shrinkage or growth are given as percentage change from baseline tumor measurement. Tumor decrease from baseline was reported in 36 patients (87.8% of the patients enrolled).

Discussion

This phase Ib study showed that simotininib was well tolerated and had a favorable safety profile in patients with advanced NSCLC and *EGFR* mutations. No DLT was observed, and MTD was not reached at doses up to 650 mg. Skin and gastro-intestinal toxicities were the most frequently reported AEs. Most AEs were at grades ≤ 3 , and no increase in the overall frequency of AEs with increasing doses of simotininib was observed.

The reported AEs are consistent with the known toxicity profile of other *EGFR*-TKIs, such as erlotinib, gefitinib, afatinib, icotinib, and cetuximab, in which rash and gastro-intestinal side-effects are the most frequently reported drug-related AEs.^{15–18} For example, results of clinical trials showed frequencies of diarrhea at 40.0–67.9% for erlotinib,^{19,20} 27.0–58.2% for gefitinib^{21–24} and 87.0% for afatinib,²⁵ similar to that observed in this phase I study (56.1%). Mechanisms involved in skin and gastro-intestinal toxicities of *EGFR*-TKIs are either a reversible or an irreversible tyrosine kinase blockade. *EGFR* is highly expressed at epithelial level and is involved in the maintenance of mucosal and skin integrity.²⁶ Preclinical research showed that simotininib reduces the expression of cell junction gene *afadin-6*, a target of *EGFR*/Ras/MAPK signaling

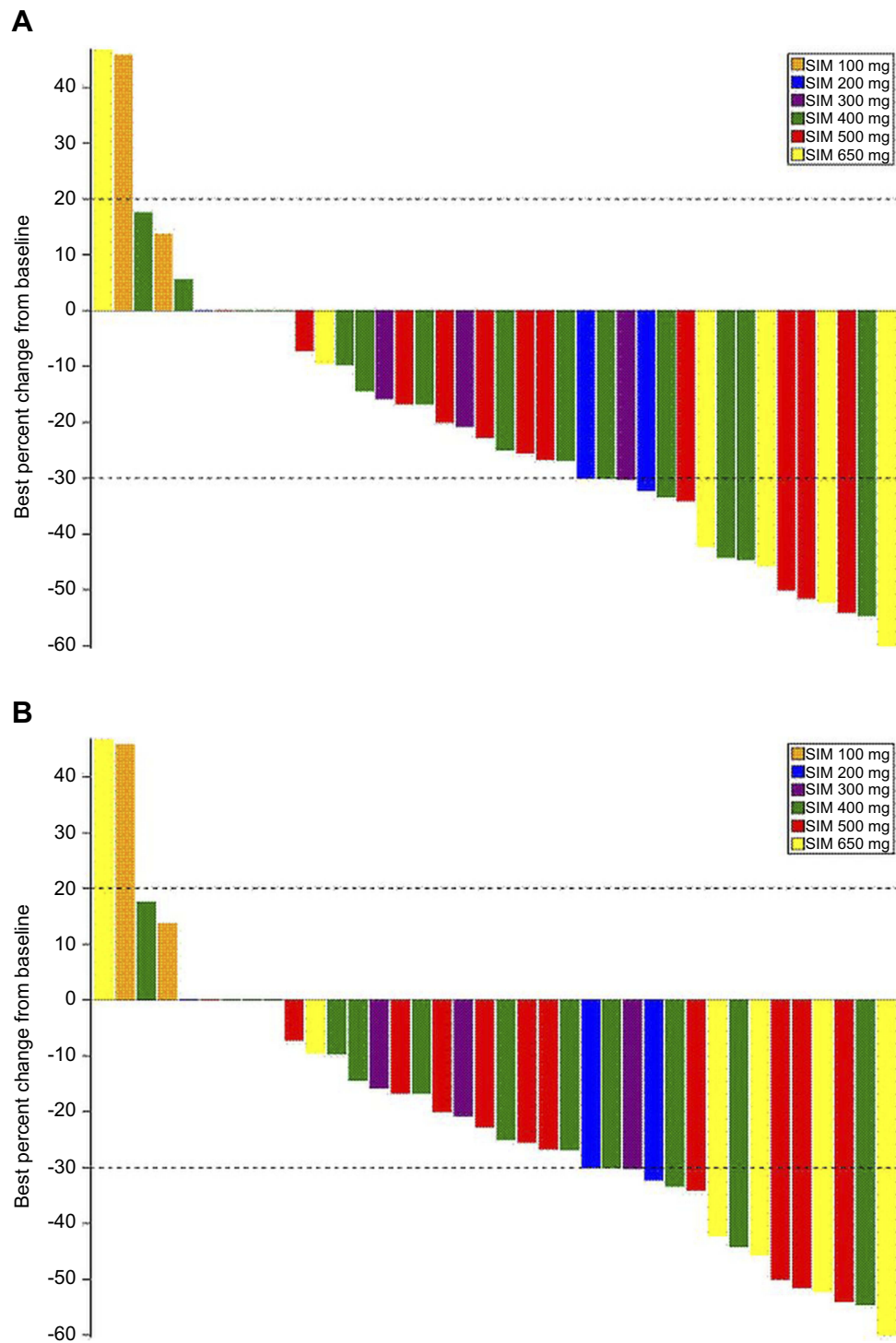


Figure 1 Waterfall plot of best percent change from baseline in sum of target lesion dimensions from baseline. **(A)** Full analysis population and **(B)** per protocol population ($n=40$).

pathway, resulting in higher paracellular permeability at the level of intestinal epithelium.²⁷

Another frequently reported toxicity of EGFR-TKIs is hepatotoxicity. In this NLSC study, aminotransferase elevations were reported in 19.5% of all patients enrolled. It was

reported only in dose cohorts of 300–650 mg, with the highest frequency in the 650 mg cohort. Although the sample size is limited to draw a definitive conclusion, these results suggest that hepatic toxicity of simotinib is mild but may increase with increasing dose. Our results for

simotinib are in line with previous reports on hepatotoxicity for other EGFR-TKIs in the treatment of NLSC patients. The majority of studied drugs in this class are reported to induce hepato-toxicity,²⁸ with the all-grade hepatotoxicity frequency ranging from <10% for gefitinib²⁴ and erlotinib²⁹ to 48% for gefitinib.³⁰ Among potential causes associated with this wide range of incidences of hepatotoxicity were the differences in duration of treatment (frequency increased with exposure duration), race and potential exacerbation of preexisting liver disease.³⁰

No cardiovascular events meeting the DLT criteria were reported in this study. Given the encouraging results, a new study exploring higher simotinib doses is ongoing and to date 3 patients have received 800 mg simotinib and 1 received 1,000 mg simotinib. In patients who received 800 mg simotinib, decreased blood pressure of <90/60 mmHg occurred in all patients, bradycardia in 1 patient and dose reduction due to cardiovascular events in 1 patient.

The PK results showed a good bioavailability of orally administered simotinib. C_{\max} following single dose PK assessment was achieved in 1.5–2.0 hrs for all doses, faster than that reported for gefitinib in cancer patients (3 hrs post-dose).³¹ Although single-dose PK analysis showed increasing exposure with dose escalation, multiple-dose PK results showed no consistent dose-proportional increase in exposure with doses over 300 mg. C_{\max} , $AUC_{0-\text{last}}$ and CL increased proportionally with dose up to 300 mg. From 300 mg these parameters were significantly different among doses used but with no trend of increase with increasing dose used. T_{\max} appeared to be independent of doses used. Maximum concentration was observed at 1.5 hrs after 300 mg and at 2.0 hrs after 200, 400, and 650 mg in PK results for a single dose. For PK analysis after multiple dosing, maximum concentration was reached at 1.5–2.0 hrs after 300, 400, 500, and 650 mg doses, while the lowest and the highest T_{\max} were observed for the 100 and 200 mg doses, respectively. These observations suggest considerable inter-patient variation of exposure after administration of multiple doses. This inter-patient variability was also reported for gefitinib, with a reported variability of 1.5-fold post single-dose exposure.³¹ The $T_{1/2}$ of 8–13 hrs for 200–650 mg doses is consistent with our previous studies in healthy volunteers,¹² suggesting that twice daily administration is appropriate.

Encouraging evidence of antitumor activity of simotinib was observed in this study. 39.3% of the patients enrolled achieved a partial response and 46.3% of the patients had stable disease with doses ranging from 200 to 650 mg.

Median PFS after a single cycle of simotinib was 9.9 months. These results are similar to those reported for gefitinib and erlotinib which ranged from 9.2 to 10.8 months in NSCLC patients with *EGFR* mutations.^{7,32,33} Additionally, we observed an objective response in the treatment of brain metastases with doses between 200 and 650 mg. There have been increased interest in exploring the potential role of EGFR-TKI agents in the treatment of NSCLC patients with brain metastases.³⁴ It has been shown that the frequency of brain metastases is higher in NSCLC patients with *EGFR* mutations as compared to wild type *EGFR*.³⁵ Due to blood–brain barrier, only low concentrations of cytotoxic agents can be delivered into the central nervous system. The concentration has been shown to be higher for EGFR-TKI agents, which are small molecules, and thus may cross blood–brain barrier easier and may be more effective than standard chemotherapy.^{36,37} It has been shown that the concentration of EGFR-TKI agents in cerebrospinal fluid increases with higher doses and increasing doses in those patients with brain metastases who did not respond to lower doses may result in disease control.^{38–40} Gefitinib, erlotinib and afatinib have been shown to have impressive effect on brain metastases with 60–80% response rates.^{41,42} In our patients we observed a similar effect – the percentage of patients with brain metastases who achieved a partial response increased with higher simotinib doses (16% with 500 mg simotinib and 50% with 650 mg). These results are encouraging and indicate an antitumor activity of simotinib at investigated doses comparable to that reported for other EGFR-TKIs already approved.⁴³ Given that DLT has not been observed in this study and that there was a trend in increased ORR and partial response of brain metastases with increased simotinib doses, we hypothesize that the antitumor activity of simotinib may be further improved at higher doses. Future head-to-head comparison clinical trials may be warranted to investigate whether higher simotinib doses may improve the response rate and survival of NSCLC patients with mutated *EGFR* as compared to existing EGFR-TKIs.

The small numbers of patients enrolled in the 100, 200 and 300 mg cohorts is a limitation of this study that we must acknowledge. This limitation was due to that nature of this early phase trial and the design chosen for this study (3+3 dose escalation design according to a modified Fibonacci scheme). The small numbers of patients in these groups may have influenced the frequencies of AEs reported in the 100–300 mg groups. Future trials enrolling a larger number of patients will allow

a better characterization of the safety profile of simotinib. Also, in our study we noticed partial response or stable disease only in patients who received a simotinib dose ≥ 200 mg and that the majority of deaths due to disease progressions occurred in the 100, 200 and 300 mg dose groups. All these support our observations that higher simotinib doses may be associated with higher chances of achieving a stable disease or a partial response.

Conclusion

This study showed that twice-daily simotinib, a novel EGFR-TKI, has a favorable safety profile, is orally bioavailable and has good antitumor activity in advanced NSCLC patients with *EGFR* mutations. The safety profile and PK results were similar to those reported in healthy volunteers and in studies with other EGFR-TKIs. Studies exploring higher doses of simotinib (800 and 1,000 mg) and its use in the treatment of NSCLC patients with brain metastases are ongoing. These studies will allow a better characterization of the simotinib efficacy and safety profile and the selection of a simotinib dose with optimal benefit/risk ratio for these patients.

Abbreviation list

AE, adverse event; AUC_{0-last} , area under the plasma concentration-time curve from time 0 to the last measured concentration; CL, clearance; C_{max} , maximum drug concentration; C_{min} , minimum drug concentration; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; LVEF, left ventricular ejection fraction; MTD, maximum tolerated dose; NCI CTC AE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetic; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious adverse event; $T_{1/2}$, terminal half-life; TKI, tyrosine kinase inhibitors; T_{max} , time to reach the maximum concentration.

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The sponsor participated in the trial design and facilitated the overall operational process, including data collection and statistical analyses, documentation of trial reports. The sponsor was also involved in the decision to publish this manuscript.

Author contributions

All authors had a significant contribution to the conception and design of the study, data acquisition, or analysis and interpretation of data, drafted the article or revised it critically for important intellectual content, approved the final version to be published and accept to be accountable for all aspects of the work.

Disclosure

Dr Xing-Sheng Hu, Dr Sheng Yang, Dr Ning Li, Dr Lin Wang, Dr Yuan-Yuan Song and Dr Yuan-Kai Shi report non-financial support from Jiangsu Sincere Pharmaceutical Co. Ltd and grants from the Chinese National Major Project for New Drug Innovation during the conduct of the study. Hua Mu is employee of Jiangsu Sincere Pharmaceutical Co. Ltd. Dr Xiao-Hong Han reports grants from Chinese National Major Project for New Drug Innovation, during the conduct of the study; Dr Hua Mu reports nothing from Sincere Pharmaceutical Group, outside the submitted work. The authors report no other conflicts of interest in this work.

Data availability

Individual patient data are confidential and thus they cannot be made publicly available.

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