Efficacy and Safety of Ripretinib in Chinese Patients with Advanced Gastrointestinal Stromal Tumors as a Fourth- or Later-Line Therapy: A Multicenter, Single-Arm, Open-Label Phase II Study

Jian Li[1], Shirong Cai[2], Yongjian Zhou[3], Jun Zhang[4], Ye Zhou[5], Hui Cao[6], Xin Wu[7], Yanhong Deng[8], Zhao Huang[9], Juan Dong[9], and Lin Shen[1]

ABSTRACT

Purpose: This is a phase II multicenter, single-arm, open-label study assessing the efficacy, safety, and pharmacokinetics (PK) of ripretinib in Chinese patients with advanced gastrointestinal stromal tumor (GIST) as a fourth- or later-line therapy. It was designed to show consistency with the phase III INVICTUS study.

Patients and Methods: Patients with disease progression on (or intolerance to) prior imatinib, sunitinib, and at least one other drug were recruited to receive ripretinib 150 mg once daily continuously in 28-day cycles. The primary endpoint was progression-free survival (PFS) based on independent radiologic review (IRR). Secondary efficacy endpoints included objective response rate (ORR) based on IRR and overall survival. Safety endpoints included the incidence and severity of adverse events (AE).

Results: Between April 2020 and August 2020, 39 patients were enrolled. All were included in the safety analysis while 38 were included in the efficacy analysis. By primary data cut-off (February 26, 2021), the median PFS [90% confidence interval (CI)] was 7.2 (2.9–7.3) months; the lower bound of the 90% CI exceeded 1 month, fulfilling the standard of bridging success. The ORR (95% CI) based on IRR was 18.4% (7.7%–34.3%). Treatment-related treatment-emergent AEs (TRAE) were reported in 37 (94.9%) patients. The majority of TRAEs were of grade 1/2. A total of 6 patients (15.4%) experienced grade 3/4 TRAEs.

Conclusions: The results demonstrated that ripretinib can clinically improve the outcomes of Chinese patients with advanced GIST as a fourth- or later-line therapy. The efficacy, safety, and PK profiles of ripretinib are consistent with those in the global patient population.

Introduction

Gastrointestinal stromal tumor (GIST) is the most common mesenchymal cell tumor of the gastrointestinal tract, accounting for 1% to 3% of malignant gastrointestinal tumors (1). The cellular growth in most GISTs is driven by activating mutations in receptor tyrosine kinase proto-oncogene, receptor tyrosine kinase (*KIT*), or platelet-derived growth factor receptor α (*PDGFRA*; ref. 2). As such, targeting *KIT* and *PDGFRA* using tyrosine kinase inhibitors (TKI) has become the standard treatment for patients with advanced or metastatic GIST (3). TKIs such as imatinib (first-line treatment), sunitinib (second-line treatment), regorafenib (third-line treatment), and avapritinib (for the treatment of GIST with *PDGFRA* exon 18 mutations) have improved the outcomes of patients (4, 5), but progressive disease (PD) can still occur, largely driven by secondary mutations in *KIT* or *PDGFRA* (3). Secondary mutations can hinder the binding of TKIs sterically and could result in incomplete inhibition (2). Moreover, several types of secondary mutations can happen concurrently (6). Therefore, there exists an unmet need for therapies that are able to tackle a broad spectrum of *KIT* or *PDGFRA* mutations.

Ripretinib is a novel switch-control TKI designed to inhibit both *KIT* and *PDGFRA* kinase signaling via a dual mechanism of action (6). Enzymatic and GIST cell line studies have shown that ripretinib can inhibit a wide range of primary and secondary drug-resistant mutants of *KIT* and *PDGFRA* (6, 7). To evaluate the efficacy and safety of ripretinib as a fourth- or later-line therapy in patients with advanced GIST, the international, pivotal phase III INVICTUS study was conducted (8). The primary analysis of INVICTUS showed that ripretinib achieved a significantly longer progression-free survival (PFS) than placebo [HR: 0.15; 95% confidence interval (CI), 0.09–0.25; $P < 0.0001$; median PFS: ripretinib 6.3 months vs. placebo 1.0 month; ref. 8]. Moreover, the long-term mature data of INVICTUS demonstrated that ripretinib provided clinically meaningful improvements in overall survival (OS; HR: 0.41; 95% CI, 0.26–0.65; median OS: ripretinib 18.2 months vs. placebo 6.3 months) and objective response rate (ORR; ripretinib 11.8% vs. placebo 0%; ref. 9). In May 2020, the FDA approved ripretinib for the treatment of adult patients with advanced GIST who have received prior treatment with three or more kinase inhibitors, including imatinib (6).

The current study aimed to assess the efficacy, safety, and pharmacokinetics (PK) profile of ripretinib in Chinese patients with advanced GIST who have received previous treatment

[1]Peking University Cancer Hospital & Institute, Beijing, China. [2]The First Affiliated Hospital, Sun Yat-sen University, Guangzhou, China. [3]Fujian Medical University Union Hospital, Fuzhou, China. [4]The First Affiliated Hospital of Chongqing Medical University, Chongqing, China. [5]Fudan University Shanghai Cancer Center, Shanghai, China. [6]Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China. [7]Chinese PLA General Hospital, Beijing, China. [8]The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China. [9]R&D Department, Zai Lab (Shanghai) Co., Ltd, Shanghai, China.

Corresponding Author: Lin Shen, Peking University Cancer Hospital & Institute, 52 Fucheng Road, Beijing, China. Phone: 139-1121-9511; E-mail: linshenpku@163.com

Clin Cancer Res 2022;28:3425–32

doi: 10.1158/1078-0432.CCR-22-0196

Translational Relevance

Despite treatments with tyrosine kinase inhibitors (TKI), secondary mutations can still drive disease progression in advanced or metastatic gastrointestinal stromal tumor (GIST). Previously, no effective standard therapy was available after third-line therapy. The situation has improved with ripretinib, a novel switch-control TKI inhibiting various primary and secondary drug-resistant mutants of *KIT* and *PDGFRA*. This trial is the first phase II study to report the efficacy, safety, and pharmacokinetics (PK) profiles of ripretinib in Chinese patients with advanced GIST who have received previous treatment with three or more kinase inhibitors. The study demonstrated that ripretinib can clinically improve patients' outcomes. The efficacy and safety profiles were consistent with those in the pivotal, global phase III INVICTUS study, and the PK profile mirrored that of the global patients. This study met the preset standard of bridging success and supported the use of ripretinib as fourth- or later-line treatment in Chinese patients with advanced GIST.

with three or more kinase inhibitors. This study was designed to show consistency with the INVICTUS study. As such, if the efficacy and safety results from this study mirror those from the INVICTUS study, it would lend support to the use of ripretinib in China as a fourth- or later-line treatment option for patients with GIST.

Patients and Methods

This study (ClinicalTrials.gov, NCT04282980) was a phase II, single-arm, open-label study conducted across nine centers in China, which assessed the efficacy and safety of ripretinib in Chinese patients with advanced GIST who had progressed on prior three or more kinase inhibitors. It was a bridging study of the phase 3 INVICTUS study. The bridging study was designed to assess the consistency with the global phase III study, and therefore allowed extrapolation of the global patients' data to the Chinese patients if the efficacy, safety, and PK profiles of the Chinese patients echo those of the global population.

The work was conducted in accordance with the International Conference on Harmonization guidelines on Good Clinical Practice (ICH E6), the regulatory requirements in China, and the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all patients prior to study entry. Study protocol, informed consent form (ICF), and information provided to the patients were reviewed and approved by the Independent Ethics Committee (IEC) of Peking University Cancer Hospital and Institute (Beijing, China).

Study population

This study targeted patients with advanced GIST who had received three or more prior lines of kinase inhibitors. The proportion of patients with four or more prior lines of treatment was restricted to ≤40% of the enrollment. Eligible patients were ≥18 years old, with histologically confirmed advanced GIST, and must have progressed on imatinib, sunitinib, and at least one other drug, or have documented intolerance to any of these treatments. The patients should have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 with adequate organ function and bone marrow reserve. Patients were excluded if they (i) had anticancer therapies, including investigational therapies or procedures, within 14 days or five times the half-life of the anticancer therapies (whichever was longer) prior to the first dose of study drug, (ii) had used ripretinib before, (iii) had another malignancy previously or currently, the natural history or treatment of which could interfere with the safety or efficacy evaluation of ripretinib, or (iv) had known active central nervous system metastases. For the full inclusion and exclusion criteria, please see the Supplementary Data.

Study procedures

Patients received ripretinib 150 mg once daily continuously in 28-day cycles until the occurrence of a protocol-specified event for treatment discontinuation such as PD, intolerable toxicity, or patient request for withdrawal. Upon disease progression based on independent radiologic review (IRR) assessment, patients were given the option to continue ripretinib at an increased dose of 150 mg twice daily, or continue treatment with the same dose, or discontinue ripretinib. Efficacy and safety results reported in this manuscript do not include data collected during ripretinib treatment after disease progression. The full list of protocol-specified events for treatment discontinuation is provided in the Supplementary Data.

The first 15 patients received intensive PK blood sampling after a single dose of ripretinib 150 mg during days −7 to −1 (the intensive blood sampling period) before starting to receive continuous ripretinib treatment (the treatment period), and again on day 15 of continuous ripretinib treatment.

Tumor assessments by enhanced CT were conducted at screening, then once in each of the first four cycles (inclusive), and subsequently, once every two cycles. In cases of allergy to CT contrast enhancement agents, MRI could be performed for abdominal and pelvic examinations with plain CT scanning for the chest, as long as the examination methods were consistent during the study. For treatment discontinuation for reasons other than PD, death, withdrawal of ICF or loss to follow-up, radiographic tumor assessments were continued at the same frequency as during treatment until PD or the start of new anticancer therapy, whichever occurred first.

An initial indication of a partial response (PR) or complete response (CR) based on IRR must be confirmed ≥4 weeks later.

Treatment interruption or dosage reduction was allowed at any time during the study for patients experiencing intolerable toxicity. Dose reduction modifications were: (i) from 150 mg once daily to 100 mg once daily, and further to 50 mg once daily for patients receiving the original dose, and (ii) from 150 mg twice daily to 100 mg twice daily, and further to 150 mg once daily for patients receiving the increased dose after disease progression. If patients could not tolerate 50 mg once daily or experienced PD after dose reduction, the study treatment was to be discontinued.

Safety assessments included adverse events (AE), laboratory parameters, vital signs, physical examinations, electrocardiograms (ECG), left ventricular ejection fraction (LVEF), dermatologic and ophthalmologic examinations, and ECOG performance status.

All patients were followed up for AEs and procedures until 30 days (±5 days) following the last dose of study drug. After that, all patients were contacted every 1 month (±5 days) to collect long-term survival data and follow up on subsequent antitumor treatment status, until withdrawal of consent, loss to follow-up, or death from any cause.

Outcomes

The primary endpoint was PFS based on IRR, defined as the interval between the date of the first dose of study drug during the treatment period [cycle 1 day 1 (C1D1)] and the date of the first PD as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 GIST-Specific Standard (10) or the date of death due to any cause, whichever occurred earlier.

The key secondary efficacy endpoint was ORR based on IRR, which was defined as the proportion of patients with confirmed CR or PR based on IRR.

The other secondary efficacy endpoints included: (i) OS, defined as the interval between C1D1 and death due to any cause, (ii) time to best response (TBR) based on IRR, defined as the interval between C1D1 and the date of the first confirmed CR or PR, (iii) PFS based on investigator assessment, and (iv) disease control rate (DCR) based on IRR, defined as the proportion of patients with a confirmed response (CR or PR) or a stable disease (SD) lasting for at least 12 weeks from C1D1.

Safety endpoints included: (i) the incidence and severity of AEs, AEs of special interest (AESI), and serious AEs (SAE) during the study (including the intensive blood sampling period) and (ii) the incidence of AEs resulting in dose reduction, interruption, and discontinuation of the study drug.

PK parameters assessed included time to maximum plasma concentration (T_{max}), maximum plasma concentration (C_{max}), and area under the concentration-time curve (AUC), all calculated based on the plasma concentrations of ripretinib and its active metabolite DP-5439.

Statistical analysis

Assuming an enrollment duration of 6 months, a follow-up duration of 2 months, and a drop-out rate of 15%, approximately 35 patients were to be enrolled to have at least 90% probability of observing the lower limit of a two-sided 90% CI of the median PFS (mPFS) being greater than 1 month (i.e., bridging success). The null hypothesis was in accordance with the assumption made in the sample size determination of the INVICTUS trial, which assumed an mPFS of 4.5 months for ripretinib and 1.0 month for placebo (8).

Efficacy analyses were performed using the efficacy analysis set (EAS), consisting of all patients who had started to receive continuous ripretinib treatment since C1D1. PFS time and OS time were summarized using the Kaplan–Meier method with CIs for the medians estimated using Brookmeyer and Crowley method. Duration of response was analyzed using the same method among patients with confirmed responses. TBR was analyzed among patients with confirmed responses using descriptive statistical methods. ORR and DCR were summarized using numbers and percentages, and the 95% CI calculated using an exact probability method based on binomial distribution.

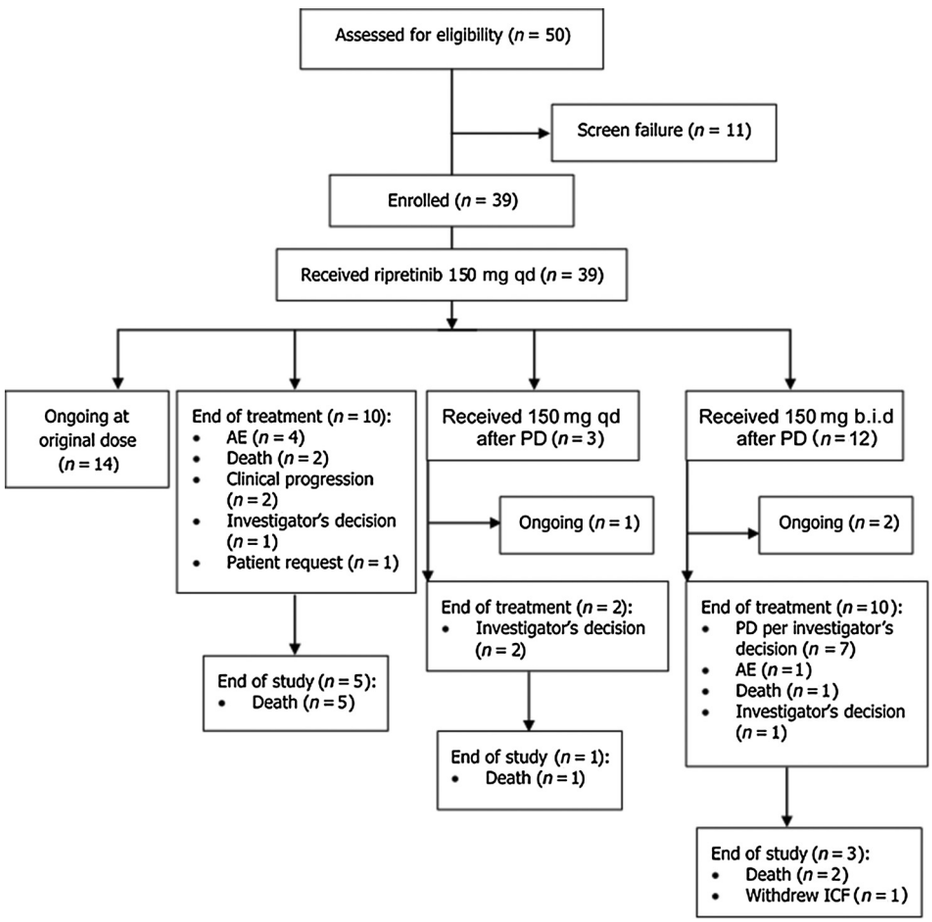

Figure 1.
Patient disposition. qd, once daily; b.i.d, twice a day.

Safety analysis was based on the safety set (SS), defined as all patients who received at least one dose of study drug. Safety results were descriptively summarized.

PK results were based on the PK set, defined as all patients who received at least one dose of the study drug and had at least one plasma concentration data point of ripretinib or DP-5439. PK results were descriptively summarized.

Data availability

The data generated in this study are available upon request from the corresponding author.

Results

Patient disposition and baseline characteristics

Between April 2020 and August 2020, 39 patients were enrolled, and all received at least one dose of study drug (**Fig. 1**). The primary data cut-off date was 26 February 2021.

Of the 39 patients, 1 patient discontinued treatment due to PD during the intensive PK blood sampling period and a total of 38 patients who entered the continuous treatment period were included in the EAS.

Baseline characteristics are described in **Table 1**. Most of the patients received three prior lines of treatment. The site of primary tumor was predominantly the small intestine. The majority of patients had documented primary tumor mutations in *KIT* exon 11 ($n = 30$, 76.9%) or *KIT* exon 9 ($n = 7$, 17.9%).

Table 1. Baseline patient characteristics.

Patient characteristics	Ripretinib ($n = 39$)
Age, median (range), years	55.1 (36.8–73.6)
18–64, *n* (%)	32 (82.1)
≥65, *n* (%)	7 (17.9)
Gender, *n* (%)	
Male	27 (69.2)
Female	12 (30.8)
ECOG performance status, *n* (%)	
0	7 (17.9)
1	28 (71.8)
2	4 (10.3)
Number of prior treatment, *n* (%)	
3	33 (84.6)
≥4	6 (15.4)
Site of primary tumor, *n* (%)[a]	
Gastric	9 (23.1)
Small intestine (including duodenum, jejunum, and ileum)	28 (71.8)
Colon/rectum/appendix	1 (2.6)
Posterior peritoneum/omentum/mesentery	0
Abdominal cavity/pelvic cavity/liver	0
Other	1 (2.6)
Available tumor mutation gene, *n* (%)[a]	
KIT exon 9	7 (17.9)
KIT exon 11	30 (76.9)
KIT exon 13/14/17/18	15 (38.5)
PDGFRA exon 12/14/18	0
KIT and *PDGFRA* wild-type	2 (5.1)

[a]Entry categories are not mutually exclusive; any patient fulfilling the description of a specific category was counted under that category, and the patient may be simultaneously counted in >1 category, such that the sum of percentages may exceed 1.

Efficacy

In the EAS, by the primary data cut-off, 50.0% (19/38) of the patients experienced PD based on IRR or death (**Fig. 2**). The mPFS (90% CI) was 7.2 (2.9–7.3) months; the lower bound of the 90% CI exceeded 1 month, fulfilling the standard of bridging success. The mPFS (90% CI) based on investigator assessment was 7.20 (4.50–not estimable) months. The concordance between IRR and investigator in PD/non-PD assessment, defined as the percentage of patients with the same assessment outcomes from IRR and investigator, was 84.2%.

In the EAS, by the primary data cut-off, 18.4% (7/38) of the patients had confirmed PR based on IRR, 34.2% (13/38) had SD lasting for ≥12 weeks from C1D1, and no patient had confirmed CR. The ORR (95% CI) based on IRR was 18.4% (7.7%–34.3%). The DCR (95% CI) based on IRR was 52.6% (35.8%–69.0%). In total, 71.1% (27/38) of the patients achieved a confirmed objective response or an SD lasting for ≥6 weeks from C1D1 based on IRR. Among patients with confirmed response, the median TBR (range) was 1.9 (1.0–3.8) months, while the median duration of response (90% CI) was 5.88 (5.68–not estimable) months (**Fig. 3**). Based on IRR, 24 (63.2%) patients had target lesions shrinkage from baseline. The best percent change from baseline in sum of diameters of target lesions was shown in **Fig. 4A**, while the percent change from baseline in sum of diameters of target lesions was shown in **Fig. 4B**.

By the primary data cut-off, 7 of the 38 patients in the EAS had died, and the mOS was not reached. By the latest data cut-off (September 27, 2021), the median OS (mOS) was not reached and the 1-year OS rate (95% CI) was 65.0% (47.38%–77.97%).

Safety

By primary data cut-off, the median (range) relative dose intensity of ripretinib was 100% (91.2%–102.4%). The incidence of treatment-related treatment-emergent adverse events (TRAE) is summarized in **Table 2**. TRAEs were reported in 37 (94.9%) patients. TRAEs reported in ≥20% of patients were alopecia, bilirubin conjugated increased, anemia, blood bilirubin increased, asthenia, palmar-plantar erythrodysaesthesia syndrome, and myalgia. The majority of TRAEs were of grade 1/2. A total of 6 patients (15.4%) experienced grade 3/4 TRAEs, including anemia in 2 (5.1%) patients and the following AEs that occurred in 1 (2.6%) patient each: blood bilirubin increased, diarrhea, blood bilirubin unconjugated increased, aspartate aminotransferase increased, blood creatinine increased, hyperuricemia, hypertriglyceridemia, hypokalemia, cardiac dysfunction, acute

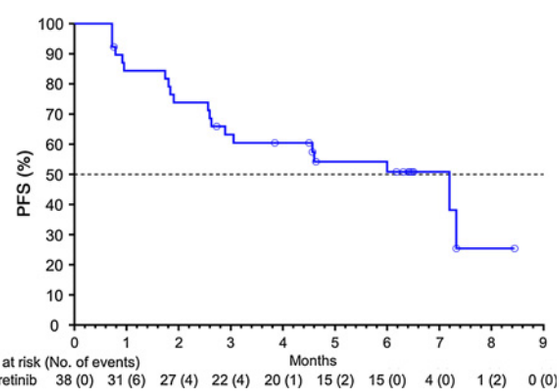

Figure 2.
Kaplan–Meier curve of PFS based on IRR (EAS).

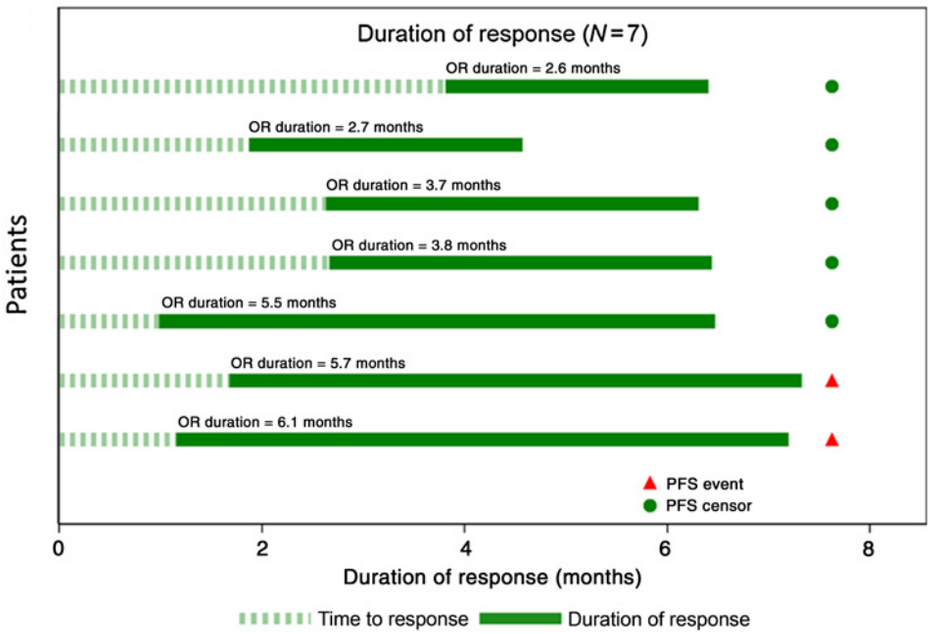

Figure 3.
Duration of response in 7 patients who achieved confirmed PR based on IRR (EAS). The placement of the red triangles and green circles is irrespective of the horizontal axis and conveys no temporal information. OR, overall response.

kidney injury, intra-abdominal fluid collection, and hyperamylasemia. Treatment-related SAEs were reported in 2 patients (5.1%), with cardiac dysfunction, acute kidney injury, intra-abdominal fluid collection, and anemia occurring in one of these patients and interstitial lung disease in the other patient. TRAEs leading to dose reduction, dose interruption, and treatment discontinuation occurred in 1 (2.6%), 7 (17.9%), and 1 (2.6%) patients respectively, while there was no TRAE leading to death. There was 1 case of hypertension reported as TRAE and it was of grade 1. No grade 3/4 hypertension occurred in this study.

PK profile

After a single dose of ripretinib 150 mg once daily ($n = 15$) in Chinese patients, the median T_{max} was 4.00 hours and 23.4 hours for ripretinib and DP-5439, respectively. The median C_{max} (range) for ripretinib and DP-5439 were 691 (266–1120) ng/mL and 375 (70–1,020) ng/mL, respectively. The median AUC from time 0 to 24 hours postdose [$AUC_{0-24hours}$ (range)] for ripretinib and DP-5439 were 5,930 (3,340–14,200) hours × ng/mL and 5,890 (1,280–19,800) hours × ng/mL, respectively. After 15 days of continuous dosing ($n = 13$; continuous dosing data unavailable for 2 patients from the PK set due to deaths), the median T_{max} were 6.00 hours for both ripretinib and DP-5439. The median C_{max} (range) for ripretinib and DP-5439 were 833 (308–1,700) ng/mL and 1,250 (276–1,930) ng/mL, respectively. The median AUC from time 0 to 12 hours postdose [$AUC_{0-12hours}$ (range)] for ripretinib and DP-5439 were 6610 (2,760–15,900) hours × ng/mL and 11,400 (2,450–18,600) hours × ng/mL, respectively. The mean change in plasma concentration of ripretinib and DP-5439 over time after a single dose of ripretinib was presented in Supplementary Fig. S1A, while that after continuous doses of ripretinib were presented in Supplementary Fig. S1B of the Supplementary data. The change in plasma concentration of ripretinib and DP-5439 over time in individual patients after a single dose of ripretinib was presented in Supplementary Fig. S2A, while that after continuous doses of ripretinib were presented in Supplementary Fig. S2B of the Supplementary data.

Discussion

This phase II study evaluated ripretinib in Chinese patients with advanced GIST as a fourth- or later-line therapy, with the aim of bridging the results from the international INVICTUS study to the Chinese population to show consistency with global data. The efficacy and safety of ripretinib observed in this study were consistent with those demonstrated in the patient population in INVICTUS.

This study met its primary endpoint. The mPFS (90% CI) based on IRR was 7.2 (2.9–7.3) months, statistically greater than the prespecified threshold of 1 month and indicative of successful bridging. These mPFS results were in line with those from the INVICTUS study [6.3 months (95% CI, 4.6–6.9) for ripretinib, versus 1.0 month (95% CI, 0.9–1.7) for placebo], patients in the ripretinib arm had an 85% reduced risk of disease progression or death which was statistically significant (HR: 0.15; stratified log-rank test $P < 0.0001$) compared with placebo (8). Historical data showed that the mPFS of patients with GIST became progressively shorter with each further line of therapy: 5.6 months for second-line sunitinib, 4.8 months for third-line regorafenib, and a mere 1.8 months for third- or later-line imatinib (rechallenge after failure of imatinib; refs. 2, 11). As such, the improvements in mPFS achieved by ripretinib in this study and the INVICTUS study represent valuable clinical benefit for patients with advanced GIST, who currently have no effective standard therapy available after third-line therapy.

The ORR (95% CI) in this study was 18.4% (7.7%–34.3%), while that in the INVICTUS study was 11.8% (95% CI, 5.8%–20.6%; ref. 9). In previous studies, ORR were 6.8% for second-line sunitinib, 4.5% for third-line regorafenib and 0% for third- or later-line imatinib (rechallenge after failure of imatinib), respectively (2, 11). In addition, in this study, 20 patients receiving ripretinib had SD lasting for at least 6 weeks, 13 patients had SD lasting for at least 12 weeks, and the DCR based on IRR was 52.6%. Previous studies have demonstrated that the absence of tumor progression is an important marker of therapeutic benefit in patients with GIST (12, 13). As such, the

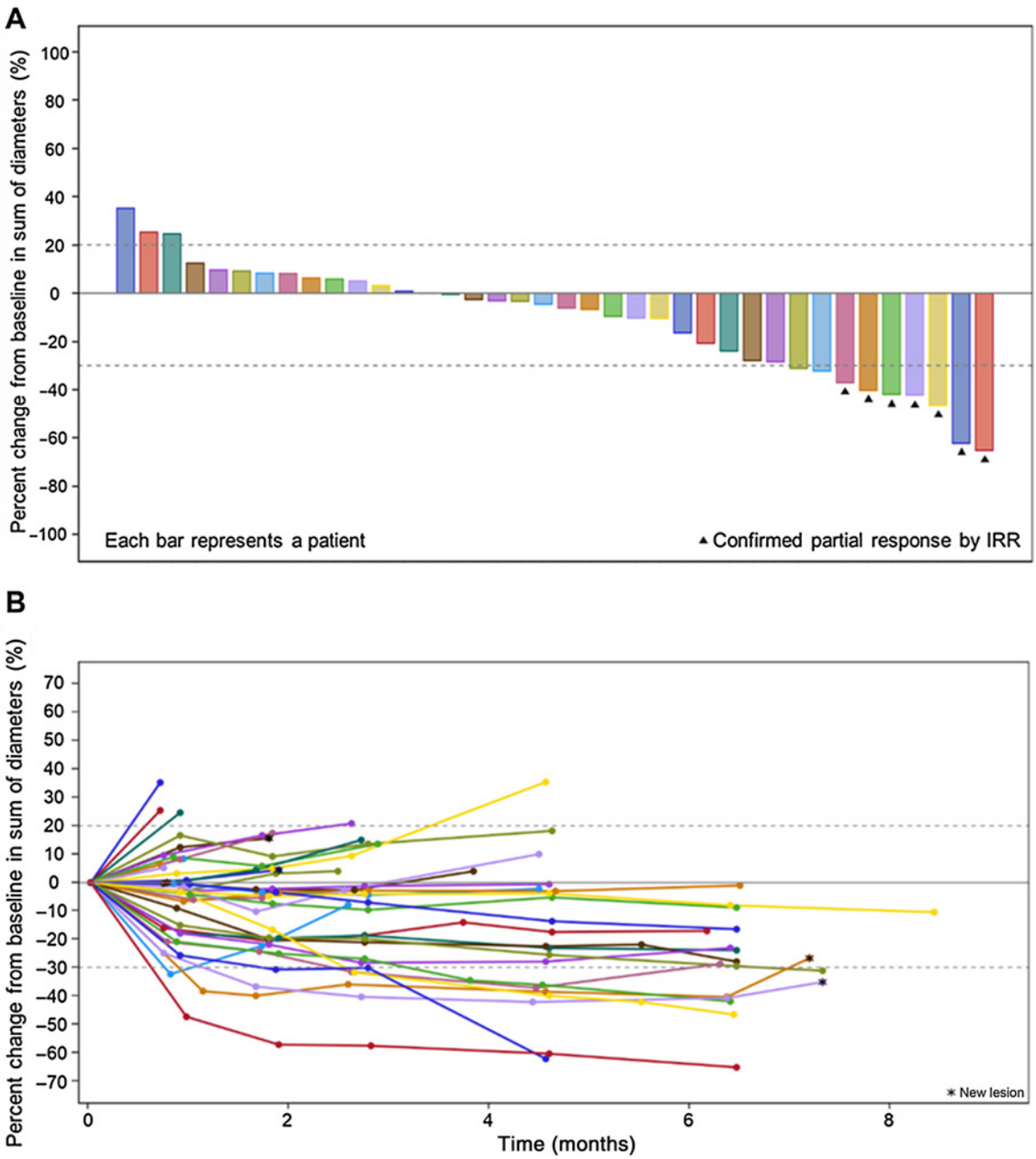

Figure 4.

A, Best percent change from baseline in sum of diameters of target lesions by IRR (EAS). Dashed lines at 20% and −30% represent threshold values for PD and PR respectively, subject to protocol-specified confirmation test. **B,** Percent change from baseline in sum of diameters of target lesions by IRR (EAS). Each line represents a patient. Dashed lines at 20% and −30% represent threshold values for PD and PR respectively, subject to protocol-specified confirmation test.

prolonged stable disease observed among patients in this study also represents clinically relevant benefit of ripretinib.

By both the primary and the latest data cut-off, the OS data in this study were immature since mOS was not reached, and the OS follow-up is ongoing. In the INVICTUS study, a clinically meaningful improvement in overall survival was demonstrated in its long-term mature data, which revealed an mOS of 18.2 months with ripretinib versus 6.3 months with placebo (HR: 0.41; 95% CI, 0.26–0.65; ref. 9). Based on currently available data, the 1-year OS rate (95% CI) in this study was 65.0% (47.38%–77.97%; ref. 14), in line with that from the long-term mature data of INVICTUS [65.1% (53.6%–74.5%); ref. 9]; a similarly promising result for mOS might be expected from this study when more OS data become available.

In this study, a specific *KIT* or *PDGFRA* mutational status was not required for patient enrollment. The frequencies of primary mutations and *KIT/PDGFRA* wild-type in this study were consistent with those reported in the literature (15–17). Secondary resistance mutations in GIST patients usually occur in the kinase switch pocket (*KIT* exon 13/

Table 2. Summary of TRAEs (SS).

TRAEs, *n* (%)	Ripretinib (*n* = 39)
Overall population	
TRAEs	
Any	37 (94.9)
Grade 3/4	6 (15.4)
Treatment-related SAE	2 (5.1)
TRAEs leading to dose interruption	7 (17.9)
TRAEs leading to dose reduction	1 (2.6)
TRAEs leading to treatment discontinuation	1 (2.6)
TRAEs leading to death	0
Treatment-related AESI	0
Most common TRAEs[a]	
Alopecia	17 (43.6)
Bilirubin conjugated increased	10 (25.6)
Anemia	9 (23.1)
Blood bilirubin increased	9 (23.1)
Asthenia	9 (23.1)
Palmar-plantar erythrodysaesthesia syndrome	8 (20.5)
Myalgia	8 (20.5)

[a]The most common TRAEs were reported in at least 20% of the patients.

14 or *PDGFRA* exon 14/15) or in the activation loop (*KIT* exon 17/18 or *PDGFRA* exon 18; ref. 7, 18). In this study, a total of 15 (38.5%) patients had *KIT* exon 13/14/17/18 mutations at baseline according to prior detection. As such, ripretinib in this study significantly improved the mPFS and demonstrated antitumor activity as fourth- or later-line treatment for GIST in a patient population with unselected tumor mutation status. These results were consistent with those from the INVICTUS study.

In this study, ripretinib demonstrated a tolerable safety profile, with no TRAE leading to death and no new safety signal was identified. The safety profile was consistent with that in the INVICTUS study. TRAEs were well managed by symptomatic treatment and dose modifications (interruptions or reductions) and rarely led to discontinuation of study treatment. The incidence of grade 3/4 TRAEs was low, with anemia being the only grade 3/4 TRAE occurring in ≥5% of patients.

In this study, the PK parameters of ripretinib after the single-dose administration in 15 Chinese patients exhibited high variability, a phenomenon also observed with 24 global patients in DCC-2618–01–001, the international phase I study of ripretinib. After the continuous administration, the PK parameters of ripretinib based on Chinese patients ($N = 13$) from this study were similar, the median values of PK parameters (C_{max} and AUC) in Chinese patients were slightly higher than that in global patients ($N = 11$) from DCC-2618–01–001 (2) while the ranges (minimum–maximum) were mostly overlapped. In this study, after the continuous administration, the median C_{max} (range) for ripretinib and DP-5439 were 833 (308–1,700) ng/mL and 1,250 (276–1,930) ng/mL respectively, while these were 707 (476–1,360) ng/mL and 848 (285–1,470) ng/mL, respectively, in DCC-2618–01–001. The median $AUC_{0-12hours}$ (geometric coefficient of variation, %) for ripretinib and DP-5439 were 6,610 (2,760–15,900) hours × ng/mL and 11,400 (2,450–18,600) hours × ng/mL, respectively, in the current study, while those in DCC-2618–01–001 were 5,244 (3,922–10,154) hours × ng/mL and 7,234 (2,523–11,731) hours × ng/mL, respectively.

Limitations of this study included the small sample size, which made it difficult to stratify patients by more baseline variables and perform subgroup analyses. In addition, this study lacked a placebo group for efficacy and safety comparison.

In conclusion, the results of this study demonstrated that ripretinib can clinically improve the outcomes of Chinese patients with advanced GIST as a fourth- or later-line therapy. The efficacy and safety profiles of ripretinib are consistent with those in the global phase III INVICTUS study. The median values of PK parameters (C_{max} and AUC) in Chinese patients were slightly higher than that in global patients from DCC-2618–01–001 while the ranges (minimum–maximum) were mostly overlapped. This study met the preset standard of bridging success and provides evidence for the use of ripretinib as fourth- or later-line treatment in Chinese patients with advanced GIST.

Authors' Disclosures

J. Dong and Z. Huang are employees of Zai Lab, and have stock options. No disclosures were reported by the other authors.

Authors' Contributions

J. Li: Conceptualization, data curation, formal analysis, writing–review and editing. **S. Cai:** Data curation, formal analysis, writing–review and editing. **Y. Zhou:** Data curation, formal analysis, writing–review and editing. **J. Zhang:** Data curation, formal analysis, writing–review and editing. **Y. Zhou:** Data curation, formal analysis, writing–review and editing. **H. Cao:** Data curation, formal analysis, writing–review and editing. **X. Wu:** Data curation, formal analysis, writing–review and editing. **Y. Deng:** Data curation, formal analysis, writing–review and editing. **Z. Huang:** Data curation, formal analysis, writing–review and editing. **J. Dong:** Data curation, formal analysis, writing–review and editing. **L. Shen:** Conceptualization, supervision, funding acquisition, writing–review and editing.

Acknowledgments

This study was sponsored by Zai Lab, Shanghai. The authors thank the patients and their families, the investigators, and site study staff who took part in this study. Ning Li, BSc (Costello Medical, Singapore), provided medical writing and editorial assistance on the basis of the authors' input and direction which was funded by Zai Lab, in accordance with Good Publication Practice guidelines (http://www.ismpp.org/gpp3). The manuscript was developed in collaboration with Deciphera, which provided valuable input.

The publication costs of this article were defrayed in part by the payment of publication fees. Therefore, and solely to indicate this fact, this article is hereby marked "advertisement" in accordance with 18 USC section 1734.

Note

Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

Received January 20, 2022; revised May 19, 2022; accepted June 8, 2022; published first June 10, 2022.

References

1. Sorour MA, Kassem MI, Ghazal AE-HA, El-Riwini MT, Nasr AA. Gastrointestinal stromal tumors (GIST) related emergencies. Int J Surg 2014;12:269–80.
2. Janku F, Abdul Razak AR, Chi P, Heinrich MC, Von Mehren M, Jones RL, et al. Switch control inhibition of KIT and PDGFRA in patients with advanced gastrointestinal stromal tumor: a phase I study of ripretinib. J Clin Oncol 2020;38:3294–303.
3. Zalcberg JR, Heinrich MC, George S, Bauer S, Schöffski P, Serrano C, et al. Clinical benefit of ripretinib dose ecalation after disease progression in advanced gastrointestinal stromal tumor: an analysis of the INVICTUS study. Oncologist 2021;26:e2053–60.
4. Patel SR, Reichardt P. An updated review of the treatment landscape for advanced gastrointestinal stromal tumors. Cancer 2021;127:2187–95.

5. George S, Chi P, Heinrich MC, von Mehren M, Jones RL, Ganjoo K, et al. Ripretinib intrapatient dose escalation after disease progression provides clinically meaningful outcomes in advanced gastrointestinal stromal tumour. Eur J Cancer 2021;155:236–44.
6. Zalcberg JR. Ripretinib for the treatment of advanced gastrointestinal stromal tumor. Therapeutic Advances in Gastroenterology 2021;14:17562848211008177.
7. Smith BD, Kaufman MD, Lu W-P, Gupta A, Leary CB, Wise SC, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. Cancer Cell 2019; 35:738–51. e9.
8. Blay J-Y, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923–34.
9. von Mehren M, Heinrich M, George S, Zalcberg J, Bauer S, Gelderblom H, et al. 1540P Ripretinib as ≥ 4th-line treatment in patients with advanced gastrointestinal stromal tumor: Long-term update from the phase III INVICTUS study. Ann Oncol 2021;32:S1120–1.
10. Demetri GD, Reichardt P, Kang Y-K, Blay J-Y, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet North Am Ed 2013;381: 295–302.
11. Kang Y-K, Ryu M-H, Yoo C, Ryoo B-Y, Kim HJ, Lee JJ, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175–82.
12. Le Cesne A, Van Glabbeke M, Verweij J, Casali PG, Findlay M, Reichardt P, et al. Absence of progression as assessed by response evaluation criteria in solid tumors predicts survival in advanced GI stromal tumors treated with imatinib mesylate: the intergroup EORTC-ISG-AGITG phase III trial. J Clin Oncol 2009; 27:3969.
13. Dudeck O, Zeile M, Reichardt P, Pink D. Comparison of RECIST and Choi criteria for computed tomographic response evaluation in patients with advanced gastrointestinal stromal tumor treated with sunitinib. Ann Oncol 2011;22:1828–33.
14. Li J. Efficacy and safety of ripretinib in patients with advanced gastrointestinal stromal tumors: Analysis of a single-arm, phase 2 trial. In: Proceedings of the 2021 CTOS Virtual Annual Meeting; 2021 Nov 10–13.
15. Oppelt PJ, Hirbe AC, Van Tine BA. Gastrointestinal stromal tumors (GISTs): point mutations matter in management, a review. J Gastrointest Oncol 2017;8: 466.
16. Mavroeidis L, Metaxa-Mariatou V, Papoudou-Bai A, Lampraki AM, Kostadima L, Tsinokou I, et al. Comprehensive molecular screening by next generation sequencing reveals a distinctive mutational profile of KIT/PDGFRA genes and novel genomic alterations: results from a 20-year cohort of patients with GIST from north-western Greece. ESMO Open 2018;3:e000335.
17. Indio V, Ravegnini G, Astolfi A, Urbini M, Saponara M, De Leo A, et al. Gene expression profiling of PDGFRA mutant GIST reveals immune signatures as a specific fingerprint of D842V exon 18 mutation. Front Immunol 2020;11: 851.
18. Nemunaitis J, Bauer S, Blay J-Y, Choucair K, Gelderblom H, George S, et al. Intrigue: phase III study of ripretinib versus sunitinib in advanced gastrointestinal stromal tumor after imatinib. Future Oncol 2020;16:4251–64.