Phase IV Study of Sunitinib in Chinese Patients with Imatinib-Resistant or Imatinib-Intolerant Gastrointestinal Stromal Tumors

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Received: April 25, 2017 / Published online: September 25, 2017
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ABSTRACT

Introduction: Sunitinib is approved in China for treatment of gastrointestinal stromal tumors (GIST), after disease progression on, or intolerance to, imatinib. However, available data from prospective clinical trials on its efficacy and

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safety in Chinese patients is limited. Our objective is to determine the efficacy and safety of sunitinib in Chinese patients with imatinib-resistant/intolerant GIST.

Methods: An open-label, single-arm, multicenter, phase IV study was performed in Chinese patients with imatinib-resistant/intolerant GIST. Sunitinib was administered orally in 6-week cycles of 4 weeks on-treatment (50 mg once daily) and 2 weeks off-treatment. The primary endpoint was progression-free survival (PFS). Tumors were assessed every 6 weeks for the first 24 weeks and every 12 weeks thereafter. Responses were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.

Results: A total of 60 patients were enrolled, of whom 59 were treated with sunitinib. All patients were Asian, and mean age was 55.1 years. Median PFS was 46.4 weeks (95% CI 33.6–53.1). An objective response (complete or partial) was observed in 11/58 (19%) patients. Median overall survival was 111.3 weeks (95% CI 75.4–167.1), median time to tumor progression was 47.3 weeks (95% CI 34.1–59.3), and median time to tumor response was 22.6 weeks (95% CI 10.4–57.3). The most common adverse events included leukopenia, fatigue, hand-foot syndrome, and neutropenia. No new safety concerns were identified.

Conclusions: This study confirms that sunitinib is active and well tolerated in Chinese

patients with imatinib-resistant/intolerant GIST.

ClinicalTrials.gov identifier: NCT00793871.

Funding: Pfizer Inc, USA.

Keywords: Chinese; Efficacy; Gastrointestinal stromal tumors; Imatinib-resistant/intolerant; Safety; Sunitinib

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract [1, 2]. The majority originate in the stomach or small intestine and are characterized by overexpression of the KIT receptor tyrosine kinase (RTK) and by *KIT* gene mutations that trigger constitutive receptor activation [1, 3, 4]. Less common GIST subsets are associated with gain-of-function mutations in platelet-derived growth factor receptor (PDGFR)- α , or express no known RTK mutation [2, 5].

Standard treatment for localized GISTs is complete surgical excision; however, recurrence is common, as are liver and peritoneal metastases [6, 7]. For advanced GIST, conventional chemotherapy and radiation therapy are largely ineffective [8]. Imatinib mesylate, an RTK inhibitor targeting KIT, PDGFR- α , PDGFR- β , and BCR-ABL, is considered standard first-line treatment [7] and has markedly improved outcomes in advanced GIST since its introduction over a decade ago. However, ~10% do not respond to first-line imatinib therapy (primary resistance), and the great majority who do respond eventually develop disease progression, usually due to secondary resistance mutations in KIT or PDGFR- α [2, 9]. Although imatinib dose escalation from the standard 400 to 800 mg/day can temporarily overcome resistance in some cases [10, 11], this approach is not suitable for all patients.

Sunitinib malate is an oral multitargeted RTK inhibitor with activity against KIT, PDGFR- α , PDGFR- β , vascular endothelial growth factor receptors-1–3, fms-like tyrosine kinase-3 receptor, colony-stimulating factor receptor type 1R, and glial cell line-derived neurotrophic factor

receptor (rearranged during transfection) [12–16]. Sunitinib has become standard treatment for imatinib-resistant/intolerant GIST after its approval based on the interim analysis of a randomized phase III study, which showed that time to progression (TTP)—the primary endpoint—was significantly longer with sunitinib ($n = 207$) than with placebo ($n = 105$; 27.3 vs. 6.4 weeks; hazard ratio 0.33, $p < 0.0001$) [17]. Approved for imatinib-resistant/intolerant GIST in the USA and Europe in January and July 2006, respectively, sunitinib (50 mg/day in the 4-weeks-on/2-weeks-off schedule) was licensed for this indication by the China Food and Drug Administration (CFDA) in October 2007. However, only 17 of the 361 patients who ultimately participated in the phase III study were Asian [18] [data on file, Pfizer]. Limited data are available, other than a study in Chinese patients with imatinib-resistant/intolerant GIST that compared the label-approved schedule with the 37.5 mg/day continuous dosing schedule [19]. Hence, additional efficacy and safety data were needed in Chinese patients, to fulfil CFDA requirements for license renewal of sunitinib for this indication. Here, we report results of a phase IV post-approval commitment study designed for this purpose. Its primary objective was to assess progression-free survival (PFS) in Chinese GIST patients after disease progression on, or intolerance to, imatinib. Secondary objectives included evaluation of additional efficacy endpoints and safety and tolerability.

METHODS

Patients

The study recruited patients ≥ 18 years with diagnosis of GIST confirmed by histopathology and not treatable by surgery, radiation, or combined modality therapy with curative intent. Patients had to have unidimensionally measurable disease (one or more malignant tumor masses, measurable by computed tomography [CT] or magnetic resonance imaging [MRI]) and prior imatinib treatment failed (defined by disease progression according to Response Evaluation Criteria in Solid

Tumors [RECIST] version 1.0 or World Health Organization criteria or by occurrence of significant toxicity that precluded further treatment). Radiographic evidence of progression on imatinib was confirmed by the principal investigator before enrollment. Imatinib intolerance was defined by life-threatening adverse events (AEs; i.e. grade 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events [NCI CTCAE], version 3.0), or by grade 2/3 AEs that occurred at a moderate dose (e.g. 400 mg/day) and persisted despite standard precautionary measures. Other inclusion criteria included: Eastern Cooperative Oncology Group performance status (ECOG PS) 0/1; adequate organ function; last imatinib dose administered ≥ 1 week before enrollment; and resolution of all acute toxic effects of imatinib, surgery, radiotherapy, or cryotherapy to NCI CTCAE grade ≤ 1 . Signed informed consent was obtained for all patients.

Exclusion criteria included: prior chemotherapy, chemoembolization therapy, immunotherapy, or any other investigational cancer agent after the last imatinib dose; surgery, radiotherapy, and/or cryotherapy of imatinib-resistant disease (except palliative radiotherapy if ≥ 1 measurable non-irradiated lesion remained); major surgery within 4 weeks or radiation therapy within 2 weeks of study entry; grade 3 hemorrhage within 4 weeks; diagnosis of secondary malignancy within 5 years (except for treated basal cell carcinoma, squamous cell skin cancer or cervical cancer); history of brain metastasis, spinal cord compression, carcinomatous meningitis, or CT/MRI evidence of brain/leptomeningeal disease; cardiovascular disease within 12 months or ongoing cardiac dysrhythmias, atrial fibrillation, or prolonged QT interval; uncontrolled thyroid abnormality or hypertension; ongoing anticoagulant treatment (except low-dose warfarin for deep vein thrombosis prophylaxis); treatment with cytochrome P450 (CYP) 3A4 inhibitors or inducers within 7 or 12 days, respectively; HIV-positive status; and pregnancy/breastfeeding.

Study Design

This was an open-label, single-arm, phase IV study performed at four centers in China between November 2008 and June 2014 (ClinicalTrials.gov identifier: NCT00793871). Patients received sunitinib in repeated 6-week cycles comprising 4 weeks of sunitinib 50 mg once daily followed by 2 weeks off-treatment (schedule 4/2). The same schedule was used in the phase III trial of sunitinib in imatinib-resistant/intolerant GIST [17]. Sunitinib was supplied in bottles of 28 hard gelatin capsules, each containing 12.5 mg of drug. Patients were required to return all bottles at the end of each cycle so compliance could be assessed by counting remaining capsules. Dose interruptions and reductions to 37.5 or 25 mg once daily were permitted for dose-limiting toxicity. Patients who required > 6 weeks interruption (including the 2-week off-treatment period) or doses < 25 mg were discontinued from the study. Other discontinuation criteria included disease progression, requirement for different anticancer treatment, and consent withdrawal. After discontinuation and a 28-day follow-up period, patients were followed up to collect information on further antitumor therapy and survival.

Tumor assessments were performed by CT or MRI at screening (≤ 21 days before treatment start), every 6 weeks for the first 24 weeks of the study and thereafter every 12 weeks, whenever disease progression was suspected, and at discontinuation (if not done within the past 6 weeks [first 24 weeks of the study] or 12 weeks [after week 24]). In the event of partial or complete response, confirmatory imaging was performed ≥ 4 weeks later. If a patient discontinued without evidence of tumor progression, tumor assessments continued until progression or initiation of another anticancer treatment. The study was conducted in accordance with the principles of the Declaration of Helsinki and in compliance with International Conference on Harmonization Good Clinical Practice guidelines. The protocol was approved by the relevant independent ethics committees.

Study Outcomes

Determination of anti-tumor efficacy was based on objective tumor assessments classified per RECIST version 1.0. The primary endpoint was PFS, defined as time from first study treatment to documentation of objective tumor progression or death from any cause, whichever occurred first. Objective response rate (ORR) was calculated as the proportion of patients who had a best response of complete or partial response. Other efficacy outcomes were defined as the time from first treatment to the date of: (1) death due to any cause (overall survival [OS]); (2) first documentation of objective tumor progression or death due to tumor progression (TTP); or (3) first documentation of objective tumor response that was subsequently confirmed (time to tumor response [TTR]). Response duration was defined as the time from first documentation of objective tumor response that was subsequently confirmed to first documentation of objective tumor progression or death due to any cause. Safety outcomes included AEs, clinical laboratory tests, physical examination, ECOG PS, vital signs, and electrocardiograms (ECGs). AE severity was graded according to NCI CTCAE version 3.0.

Statistical Methods

The planned sample size ($n = 60$) was selected according to CFDA requirements. PFS, OS, TTP, TTR, and response duration were analyzed in the safety population (which included all enrolled patients who started treatment) using the Kaplan–Meier method. Median values for these parameters are presented along with the two-sided 95% CIs calculated using the Brookmeyer and Crowley method. ORR analysis used the per-protocol population, which included all treated patients with an adequate baseline assessment. The Clopper–Pearson method was used to calculate 95% CI for ORR.

RESULTS

Patient Characteristics and Treatment

Sixty patients were enrolled, 59 of whom were treated with sunitinib and included in the safety population. The per-protocol population excluded the untreated patient plus an additional patient with no reported lesion at baseline. All patients were Asian and approximately two-thirds were male (Table 1). Mean age was 55.1 years (range 29–82). The most common locations of primary GIST diagnosis were the stomach and small intestine. Spindle cell histology was the most common histopathology classification. All patients were imatinib-resistant, with the exception of two patients who were imatinib-intolerant.

Median treatment duration was 223 days (range 28–1288), and the median number of treatment cycles commenced and completed were both 8 (range 1–46). Treatment compliance was ~ 99%. Most patients (49/59 [83.1%]) received concomitant medications; the most common was granulocyte-colony stimulating factor ($n = 28$).

Efficacy

Primary Endpoint

Overall, 47/59 (79.7%) patients had objective disease progression ($n = 41$ [69.5%]) or died without objective progression ($n = 6$ [10.2%]). Estimated median PFS was 46.4 weeks (95% CI 33.6–53.1 weeks). Twelve patients were censored for PFS; main reasons were a gap > 24 weeks between progressive disease or death and the most recent adequate assessment ($n = 5$), receipt of a new anticancer treatment prior to tumor progression ($n = 3$), and entry into follow-up for progression ($n = 2$).

Secondary Endpoints

The ORR was 11/58 (19.0% [95% CI 9.9–31.4]). All 11 patients had a partial response; no complete responses were reported. Thirty-eight

Table 1 Patient demographics and other baseline characteristics (safety population)

	<i>N</i> = 59
Age, years	
Mean (SD)	55.1 (12.2)
Range	29–82
Male, <i>n</i> (%)	39 (66.1)
Asian, <i>n</i> (%)	59 (100)
BMI, ^a kg/m ²	
Mean (SD)	22.7 (3.0)
Range	16.6–28.4
Weight, kg	
Mean (SD)	62.6 (11.5)
Range	44.0–84.0
Height, cm	
Mean (SD)	165.7 (8.2)
Range	148–184
Location of primary diagnosis, <i>n</i> (%)	
Stomach	24 (40.7)
Small intestine/bowel	18 (30.5)
Colon	2 (3.4)
Rectum	2 (3.4)
Other	13 (22.0)
Histopathological classification, <i>n</i> (%)	
Spindle cell	33 (55.9)
Epithelioid	2 (3.4)
Mixed spindle cell and epithelioid	2 (3.4)
Other	22 (37.3)
Involved disease sites, ^b <i>n</i> (%)	
Liver	38 (64.4)
Lung	5 (8.5)
Lymph node: mediastinum	1 (1.7)
Lymph node distant	5 (8.5)
Lymph node regional	1 (1.7)
Pelvis	26 (44.1)

Table 1 continued

	<i>N</i> = 59
Peritoneum	12 (20.3)
Other	24 (40.7)
Involved disease sites, ^b <i>n</i> (%)	
1	15 (25.4)
2	23 (39.0)
3	15 (25.4)
4	3 (5.1)
> 4	2 (3.4)
Not reported	1 (1.7)

BMI body mass index, *SD* standard deviation

^a Calculated as weight/(height × 0.01)²

^b Involved sites included both target and non-target sites; sites with multiple lesions were counted once

(65.5%) patients had stable disease and six (10.3%) patients had objective progression. No early deaths were reported. By the data cut-off, 50/59 (84.7%) patients had died: 48 due to GIST, one due to lung infection, and one due to gastrointestinal hemorrhage. Median OS was 111.3 weeks (95% CI 75.4–167.1 weeks). In total, 9/59 patients (15.3%) were censored. Of these, seven (11.9%) patients were alive at the end of study period and two (3.4%) patients were lost to follow-up. Tumor progression events were seen in 40 (67.8%) patients; median TTP was 47.3 weeks (95% CI 34.1–59.3 weeks). A total of 19 (32.2%) patients were censored, with the main reason being off treatment prior to progression (*n* = 13) and death on treatment without progression (*n* = 3). Eleven (18.6%) patients showed a confirmed objective tumor response; median TTR was 22.6 weeks (95% CI 10.4–57.3 weeks). The median response duration was 48.1 weeks (95% CI 35.0–92.1 weeks).

Safety

Overall, 58/59 (98.3%) patients experienced at least one AE; the majority were considered treatment-related. The most common AEs of any grade and causality were leukopenia,

fatigue, hand-foot syndrome, neutropenia, decreased platelet count, decreased hemoglobin, decreased neutrophil count, increased aspartate aminotransferase, and skin discoloration (Table 2). Grade 4 AEs were reported in eight (13.6%) patients (neutropenia [$n = 3$] and decreased hemoglobin, anemia, thrombocytopenia, bile duct stenosis, and peripheral motor neuropathy [all $n = 1$]). Grade 5 AEs were reported in five (8.5%) patients (disease progression [$n = 3$] and lung infection and gastrointestinal hemorrhage [both $n = 1$]). Eleven (18.6%) patients discontinued due to AEs. Nine (15.3%) patients had dose reductions due to AEs and 28 (47.5%) temporarily discontinued due to

AEs. Twelve patients experienced serious AEs, seven of which were nonfatal. No deaths and three nonfatal serious AEs (cardiac failure, rectal hemorrhage, and neutropenia) were considered due to study treatment. Clinical laboratory tests, physical examination, ECOG PS, vital signs, and ECGs did not reveal any remarkable findings.

DISCUSSION

This phase IV post-approval commitment study investigated the efficacy and safety of sunitinib in 59 patients with imatinib-resistant/intolerant

Table 2 Most common adverse events (any causality and any grade; safety population)

	All grade	Grade 3	Grade 4	Grade 5
<i>n</i> (%)				
Any adverse event	58 (98.3)	27 (45.8)	8 (13.6)	5 (8.5) ^a
Leukopenia	38 (64.4)	8 (13.6)	0	0
Fatigue	31 (52.5)	3 (5.1)	0	0
Hand-foot syndrome	30 (50.8)	6 (10.2)	0	0
Neutropenia	29 (49.2)	8 (13.6)	3 (5.1)	0
Platelet count decreased	26 (44.1)	10 (16.9)	0	0
Hemoglobin decreased	23 (39.0)	4 (6.8)	1 (1.7)	0
Neutrophil count decreased	22 (37.3)	9 (15.3)	0	0
Aspartate aminotransferase increased	21 (35.6)	2 (3.4)	0	0
Skin discoloration	20 (33.9)	0	0	0
White blood cell count decreased	19 (32.2)	3 (5.1)	0	0
Diarrhea	18 (30.5)	1 (1.7)	0	0
Hypertension	17 (28.8)	2 (3.4)	0	0
Proteinuria	16 (27.1)	2 (3.4)	0	0
Anemia	15 (25.4)	1 (1.7)	1 (1.7)	0
Thrombocytopenia	15 (25.4)	4 (6.8)	1 (1.7)	0
Alanine aminotransferase increased	14 (23.7)	2 (3.4)	0	0
Blood bilirubin increased	13 (22.0)	2 (3.4)	0	0
Blood urea increased	13 (22.0)	0	0	0

Data are shown for adverse events that occurred in $\geq 20\%$ of patients

^a Lung infection ($n = 1$; 1.7%), disease progression ($n = 3$; 5.1%), and gastrointestinal hemorrhage ($n = 1$; 1.7%)

GIST at four centers in China. Median PFS was 46.4 weeks (95% CI 33.6–53.1). In the placebo-controlled phase III GIST study that provided the basis for approval of sunitinib in China and elsewhere, median PFS at the main interim analysis was 24.1 weeks (95% CI 11.1–28.3 weeks) [17]. The ORR in this phase IV study was 19% and median TTP was 47.3 weeks. In the phase III study, ORR was 7% and median TTP was 27.3 weeks [17]. Median TTR was 22.6 weeks in this phase IV study and 10.4 weeks in the phase III study [17]. Median OS was 111.3 weeks (95% CI 75.4–167.1 weeks) in this study and 72.7 weeks [95% CI 61.3–83.0 weeks] in the phase III trial [18]. Median OS in this trial (111.3 weeks; i.e. 25.6 months) was similar to that in GIST patients who received sunitinib on an alternate dosing schedule (23.5 months [95% CI 21.8–27.0 months]) after imatinib failure [20].

As the current study employed a single-arm, nonrandomized controlled design, the patient population enrolled was selective (e.g. patients were relatively young and 64.4% had only 1–2 disease sites); hence, comparisons between the phase III study and the current study are limited [17, 18]. In addition, without imatinib reimbursement in China, imatinib-refractory/intolerant patients in the current study may have switched to sunitinib earlier as part of a clinical trial rather than undergo imatinib dose escalation/salvage. It is possible that the early switching to sunitinib may have contributed to the improved PFS seen in the current study. Furthermore, it is important to note that five patients were censored from the PFS analysis due to a gap > 24 weeks. This means that five patients in the PFS analysis setting missed at least two tumor assessment time points (> 24 weeks), which impacted and limited the interpretation due to censoring of the time point and a much shorter interval being recorded. Finally, favorable results in the current study may have also been due to increased experience with sunitinib (e.g. improved awareness of AE management). However, the fact that observed efficacy data with sunitinib were at least as favorable as those reported in the phase III study provides reassurance regarding the activity of this multi-targeted RTK

inhibitor in Chinese GIST patients for whom imatinib failed or who cannot tolerate imatinib.

As expected, most patients experienced AEs during the study. However, only 19% discontinued sunitinib due to AEs, and most AEs could be adequately managed by dose reductions and/or interruptions. In general, the safety profile of sunitinib in Chinese patients in this study was similar to that of the phase III study, in which the most common AEs were hematologic disorders and the most common treatment-related AEs were fatigue, diarrhea, skin discoloration, and nausea [17, 18]. Some differences were noted, such as a higher incidence of hand-foot syndrome in the current study compared with the phase III study (51% and 13%, respectively), which are similar to findings from a phase IV study of sunitinib in Chinese patients with metastatic renal cell carcinoma [21]. However, overall, no new safety concerns were identified. These findings are consistent with a population pharmacokinetic analysis performed across 14 studies, which suggested no clinically significant differences in sunitinib pharmacokinetics between Asian and non-Asian patients [22].

Aside from these studies, relatively little is known about the efficacy and safety of sunitinib in Asian GIST patients. However, the available data suggest that sunitinib is active and well tolerated. In a single-arm retrospective study, 55 Chinese patients with recurrent/metastatic GIST, resistant or intolerant to imatinib, received sunitinib for at least one cycle [19]. Median PFS with schedule 4/2 was 30 weeks (95% CI 12.8–47.2), whereas median PFS with a continuous daily dose of 37.5 mg was 35 weeks (95% CI 24.6–45.4). Median OS was 86 weeks and most AEs were grade 1/2 [19]. In a single-center retrospective analysis of 88 Korean GIST patients wherein initial imatinib therapy failed, median TTP and OS with sunitinib were 7.1 and 17.6 months, respectively. The most common grade 3/4 AEs included neutropenia, thrombocytopenia, and hand-foot syndrome [23]. A phase I/II study in Japanese patients with imatinib-resistant/intolerant GIST showed that sunitinib pharmacokinetics and clinical outcomes in this population were similar to those in studies of predominantly Western patients [24].

Contemporarily, in the personalized medicine era, sunitinib has shown clinical benefit in all major GIST mutational subtypes, particularly in patients with wild-type or *KIT* exon 9 genotype and against GISTs with secondary *KIT* exon 13 or 14 mutations. Patients with exon 9 mutations require an escalated dose of imatinib [25], whereas certain patients, especially those with exon 11 mutations, show no benefit from imatinib dose escalation [26]. More recent studies [27, 28] showed improved efficacy in sunitinib-treated patients with primary mutations in *KIT* exon 9 compared with exon 11. A limitation of the current study is that correlation between mutational status and sunitinib efficacy and safety were not examined. The selection of imatinib-refractory GIST patients based on biomarkers should be explored in Chinese practice.

CONCLUSION

In conclusion, this study provides confirmation that sunitinib is active and well tolerated in Chinese patients with imatinib-resistant/intolerant GIST. The safety profile of sunitinib was as expected. These data confirm the place of sunitinib in the routine treatment of this patient population.

ACKNOWLEDGEMENTS

This study was sponsored, funded and conducted by Pfizer Inc. (New York, NY, USA). Employees of Pfizer were involved in the study design and collection, analysis, and interpretation of data. Medical writing support and article publication costs were funded by Pfizer. Medical writing support was provided by Andy Gannon and Fiona Chaplin at ACUMED® (New York, NY, USA), an Ashfield Company, part of UDG Healthcare plc, with funding from Pfizer Inc. Editorial support was provided by Jaya Vas, PhD, of Engage Scientific Solutions, and funded by Pfizer Inc. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity

of the work as a whole, and have given final approval for the version to be published. All authors had full access to all of the data in this study and take complete responsibility for the integrity of the data and accuracy of the data analysis.

Disclosures. Carlos Linn is a full-time employee of Pfizer, and declares stocks from Pfizer. Qiao Wang is a former Pfizer employee and declares no conflict of interest. Li-Qiang Yang is a former Pfizer employee and declares stocks from Pfizer. Lin Shenn, Yan Sun, Jian-Ming Xu and Shu-Kui Qin have nothing to disclose.

Compliance with Ethics Guidelines. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients included in the study. The protocol was approved by the relevant independent ethics committees.

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