Original Article

Clinical Outcomes of Patients With Advanced Gastrointestinal Stromal Tumors: Safety and Efficacy in a Worldwide Treatment-Use Trial of Sunitinib

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BACKGROUND: The objectives of this study were to provide sunitinib to patients with gastrointestinal stromal tumor (GIST) who were otherwise unable to obtain it and to collect broad safety and efficacy data from a large population of patients with advanced GIST after imatinib failure. (ClinicalTrials.gov identifier NCT00094029). **METHODS:** Imatinibresistant/ intolerant patients with advanced GIST received sunitinib on an initial dosing schedule of 50 mg daily in 6-week cycles (4 weeks on treatment, 2 weeks off treatment). Tumor assessment frequency was according to local practice, and response was assessed by investigators according to Response Evaluation Criteria in Solid Tumors version 1.0. Overall survival (OS) and safety were assessed regularly. Post hoc analyses evaluated different patterns of treatment management. **RESULTS:** At final data cutoff, 1124 patients comprised the intent-to-treat population, and 15% of these patients had a baseline Eastern Cooperative Oncology Group performance status ≥2. The median treatment duration was 7.0 months. The median time to tumor progression was 8.3 months (95% confidence interval [CI], 8.0-9.4 months), the median OS was 16.6 months (95% CI, 14.9-18.0 months), and 36% of patients were alive at the time of analysis. Patients for whom the initial dosing schedule was modified exhibited longer median OS (23.5 months) than those who were treated strictly according to the initial dosing schedule (11.1 months). The most common treatment-related grade 3 and 4 adverse events were hand-foot syndrome (11%), fatigue (9%), neutropenia (8%), hypertension (7%), and thrombocytopenia (6%). Treatment-related adverse events associated with cardiac function (eg, congestive heart failure and myocardial infarction) were reported at frequencies of ≤1% each. **CONCLUSIONS:** This treatment-use study confirms the long-term safety and efficacy of sunitinib in a large international population of patients with advanced GIST after imatinib failure.***Cancer*** **2015;121:1405-13**. *© 2015 American Cancer Society.*

KEYWORDS: sunitinib, gastrointestinal stromal tumor, treatment-use trial, long-term safety, efficacy, worldwide.

INTRODUCTION

Sunitinib malate (SUTENT; Pfizer Inc., New York, NY) is an oral, multitargeted tyrosine kinase inhibitor (TKI) approved for the treatment of patients with advanced gastrointestinal stromal tumor (GIST) after disease progression on or intolerance to the moderately selective TKI imatinib mesylate. Sunitinib inhibits several oncogenically relevant receptor tyrosine kinases, including KIT and platelet-derived growth factor receptor-α,[1,2] both of which have been implicated in the pathogenesis of GIST.[3-5] The efficacy and safety of sunitinib in imatinib-resistant/imatinib-intolerant patients were established in a pivotal phase 3, randomized, placebo-controlled study, which demonstrated a 4-fold increase in the time to progression (TTP) for sunitinib versus placebo.[6,7]

We report the final results from a worldwide treatment-use study, the main objective of which was to provide access to sunitinib to patients with GIST who might benefit from this therapy but who had no other means of obtaining the drug (eg, they were ineligible for other sunitinib clinical trials, no GIST trials were available in a particular country, or

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Correction added after first online publication: On 26 December 2018 ClinicalTrials.gov identifier NCT00094029 was added to abstract.

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regulatory approval had not yet been granted). This study, the largest trial conducted in any single type of sarcoma to date, provided an opportunity to evaluate the long-term safety and efficacy of sunitinib in an inclusive, international patient population. It also allowed us to perform exploratory analyses evaluating treatment scenarios that emerged during the study and differed from the initial dosing schedule (IDS) (sunitinib 50 mg daily on a 4-week-on/2-week-off treatment schedule [schedule 4/2]), and it provided an opportunity to evaluate continuing versus discontinuing TKI therapy after disease progression.

MATERIALS AND METHODS

Patients and Study Design

Patient eligibility criteria included age $\geq$18 years for all centers (certain centers enrolled patients aged $<$18 years when allowed by the institutional review board/independent ethics committee); histologically confirmed, malignant GIST not amenable to standard therapy with curative intent after failure of prior imatinib therapy (because of either disease progression or intolerance); ineligibility for participation in ongoing sunitinib clinical studies; potential to derive clinical benefit from sunitinib treatment; resolution of all acute toxic effects from any prior therapy or surgical procedure to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade $\leq$1[8]; and adequate organ function. Exclusion criteria included current treatment in another therapeutic clinical trial, central nervous system metastases, and cardiovascular disease. The study conformed to the principles of the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. The institutional review boards/independent ethics committees of participating study centers approved the protocol. All participants provided written, informed consent.

Sunitinib Dosage and Administration

The IDS for sunitinib was 50 mg daily on schedule 4/2. A protocol amendment implemented in May 2006 allowed patients to switch to 37.5 mg on a continuous daily dosing (CDD) schedule as an alternative. Dose reductions were permitted in the event of toxicity. Because of the flexibility allowed investigators in the study, treatment scenarios other than the IDS were used by physicians to optimize patient tolerability; these are termed alternative dosing schedules (ADSs) in this report, noting that the phrase "flexible dosing" was used previously in a preliminary presentation of these results.[9] Sunitinib dosing was continued as long as there was evidence of disease control/clinical benefit in the investigator's judgment; and survival was monitored for $\leq$2 years from the date of the final sunitinib dose or until July 2008, whichever came first.

Study Assessments

The frequency of tumor assessments/measurements was not specified in the protocol but was determined according to the local standard of care for GIST. Objective responses and TTP were assessed by investigators using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.[10] Overall survival (OS) was monitored. Safety and tolerability were assessed by monitoring adverse events (AEs) and laboratory abnormalities and by history and physical examination of patients. Toxicities were evaluated every 14 days during cycle 1, on days 1 and 28 of cycle 2, on day 1 of all subsequent cycles, at the end of treatment/withdrawal, and approximately 28 days after the final sunitinib dose and were graded using CTCAE version 3.0.

Statistical Analysis

Because of the nature of this trial, the number of patients enrolled was not predetermined, and no inferential analyses or hypothesis testing were planned. The study population (intention-to treat [ITT] population) for efficacy and safety analyses comprised all patients who received at least 1 dose of sunitinib. TTP and OS were estimated using the Kaplan-Meier method.

Post Hoc Analyses

Post hoc analyses were performed to evaluate patients' clinical outcomes after stratification based on patterns of sunitinib dosing that emerged during the study. In 1 analysis, patients were dichotomized based on whether they were treated by strict adherence to the IDS throughout the study (ie, without any changes in dose level or schedule) or whether the dose and/or schedule they received was modified at any time during the study (ie, to dose levels other than 50 mg daily and/or schedules other than schedule 4/2, including the CDD schedule, noting that these changes were not defined prospectively but were derived post hoc from data review). In the other analysis, patients were dichotomized based on whether sunitinib therapy was continued or stopped after objective investigator-assessed progressive disease (PD). Hazard ratios were not calculated for these post hoc analyses.

RESULTS

Between September 2004 and December 2007, 1131 patients were enrolled in the study at 108 sites in 34 countries. At final data cutoff (November 2011), 1124 patients (99%) had received at least 1 dose of sunitinib (ITT

TABLE 1. Baseline Patient Characteristics and Prior Imatinib Treatment History in Patients Who Received Sunitinib, N = 1124

Characteristic	No. of Patients (%)
Age: Median [range], y	59 [10-92]
Sex	
Male	672 (60)
Female	452 (40)
Race/ethnicity	
White	858 (76)
Black	38 (3)
Asian	201 (18)
Unknown	27 (2)
ECOG PS	
0	420 (37)
1	521 (46)
2	135 (12)
3	33 (3)
4	5 (<1)
Unknown	10 (1)
Time since original diagnosis: Median [range], mo	39.4 [0.7-364.7]
Reasons for stopping prior imatinib therapy	
Progression ≤6 mo	153 (14)
Progression >6 mo	871 (77)
Intolerance	99 (9)
Unknown	1 (<1)
Maximum prior imatinib dose: Median [range], mg	600 [200-2400]
Time between last imatinib dose and first sunitinib dose: Median [range], d	14 [1-1423]

Abbreviation: ECOG PS, Eastern Cooperative Oncology Group performance status.

population) (Table 1). The percentage of patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2 was 15%. Baseline characteristics of the patient subgroups evaluated in the post hoc analyses are listed in Table 2.

The median number of sunitinib cycles started was 5 (range, 1-62 cycles started) (Table 3). The median treatment duration was 7.0 months (range, <0.1 to 75.4 months), and 363 patients (32%) remained on treatment for >1 year. Overall, 592 patients (53%) had dosing interruptions; in 470 patients (42%), these interruptions were related to AEs. Four hundred eighty-four patients (43%) had dose reductions. Patients in the ADS group remained on treatment longer than those in the IDS group (median, 9 vs 3 cycles started) (Table 4). They also had a longer median time on drug, a higher median total dose administered, and more dosing interruptions. Patients who continued on treatment after PD remained on treatment longer (median, 9 vs 4 cycles started from treatment initiation) and had a longer median time on drug and a higher median total dose administered than those who did not continue treatment.

Efficacy

The ITT population was followed for a median of 34.6 months (95% confidence interval [CI], 33.0-37.3 months). The median estimated TTP was 8.3 months (95% CI, 8.0-9.4 months) (Fig. 1A). Four hundred eight patients (36%) in the ITT population were alive at the time of analysis, and the median estimated OS was 16.6 months (95% CI, 14.9-18.0 months) (Fig. 1B). The overall confirmed objective response rate (ORR) was 8% (95% exact CI, 6%-10%). Sixty percent of patients had stable disease as their best response, and 45% were progression free for >6 months.

The median TTP was 12.7 months (95% CI, 11.1-14.1 months) in the ADS group compared with 5.2 months (95% CI, 4.4-5.5 months) in the IDS group (Fig. 2A). At the time of analysis, 218 patients in the ADS group (42%) and 186 patients in the IDS group (31%) were alive. The median OS was 23.5 months (95% CI, 21.8-27.0 months) and 11.1 months (95% CI, 9.9-12.5 months) in the ADS and IDS groups, respectively (Fig. 2B). Patients who continued on sunitinib after PD did so for a median of 4.7 months after PD. The median OS from the start of treatment among patients who remained on treatment after PD was 22.8 months (95% CI, 20.4-24.7 months) and 13.2 months (95% CI, 11.7-14.5 months) among those who did not remain on treatment (Fig. 3).

Safety and Tolerability

Fatigue (42%), diarrhea (40%), hand-foot syndrome (32%), and nausea (29%) were the most commonly reported, treatment-related, nonhematologic AEs (Table 5). These were mainly grade 1 or 2 in severity. Hand-foot syndrome (11%), fatigue (9%), hypertension (7%), and diarrhea (5%) were the most commonly reported, treatment-related, nonhematologic grade 3 or 4 AEs. Treatment-related hypothyroidism (any grade), which was defined based on elevated thyroid-stimulating hormone level and symptomatology according to CTCAE, was reported in 13% of patients. The frequencies of treatment-related grade 3 or 4 neutropenia, thrombocytopenia, and anemia were 8%, 6%, and 5%, respectively (Table 5). Febrile neutropenia was reported in only 3 patients (all in the ADS group). Treatment-related AEs associated with cardiac function included heart failure, congestive heart failure, myocardial infarction, reduced ejection fraction, and pulmonary edema (as reported by investigators; ≤1% each) (Table 6). Seventeen grade 5 AEs (2%) considered to be related to treatment were reported in the study (Table 5). Fifty-three percent of patients had a dosing interruption or a dose reduction

TABLE 2. Baseline Patient Characteristics of Patients Stratified in Post Hoc Analyses

Characteristic	No. of Patients (%)			
	IDS, n = 599	ADSs, n = 525	Sunitinib Continued After PD, n = 380	Sunitinib Stopped After PD, n = 324
Age: Median [range], y	59 [16-92]	59 [10-89]	58 [10-84]	59 [11-89]
Sex				
Male	390 (65)	282 (54)	253 (67)	192 (59)
Female	209 (35)	243 (46)	127 (33)	132 (41)
Race/ethnicity				
White	486 (81)	372 (71)	292 (77)	239 (74)
Black	19 (3)	19 (4)	15 (4)	8 (2)
Asian	79 (13)	122 (23)	63 (17)	69 (21)
Unknown	15 (3)	12 (2)	10 (3)	8 (2)
ECOG PS				
0	217 (36)	203 (39)	166 (44)	115 (35)
1	265 (44)	256 (49)	165 (43)	164 (51)
2	86 (14)	49 (9)	38 (10)	40 (12)
3	20 (3)	13 (2)	10 (3)	2 (1)
4	4 (1)	1 (<1)	0 (0)	0 (0)
Unknown	7 (1)	3 (1)	1 (<1)	3 (1)

Abbreviations: ADSs, alternative dosing schedules; ECOG PS, Eastern Cooperative Oncology Group performance status; IDS, initial dosing schedule; PD, progressive disease.

TABLE 3. Discontinuations and Treatment in Patients Who Received Sunitinib, N = 1124

Variable	No. of Patients (%)
Discontinuations from study	1112 (99)
Lack of efficacy	719 (64)
Consent withdrawn	186 (17)
Adverse event	169 (15)
Decision of sponsor	23 (2)
Protocol violation	8 (1)
Lost to follow-up	7 (1)
No. of treatment cycles started: Median [range]	5 [1-62]
Time drug was administered: Median [range], mo	4.6 [<0.1-56.9]
Time on treatment: Median [range], mo[a]	7.0 [<0.1-75.4]
Patients with dosing interruptions	592 (53)
Adverse event-related[b]	470 (42)
Other[b]	248 (22)
Days with interruptions: Median [range], %	5 [0-96]
Patients with dose reductions[c]	484 (43)
Total dose: Median [range], mg	6075 [38-69,950]
Average daily dose: Median [range], mg	50 [15-53]

[a] For schedule 4/2 (sunitinib 50 mg daily on a 4-week-on/2-week-off treatment schedule), time on treatment was the period starting from the date of first dose and ending at the earlier of the termination date or the last dose date plus the planned off-treatment period (2 weeks) for a cycle. For the continuous daily dosing schedule, time on treatment was the period starting from the date of first dose and ending at the last dose date.
[b] Dosing could be interrupted for more than 1 reason.
[c] These comprised patients who had their daily dose prescribed below the assigned dose for any reason at any time during the study.

because of an AE, and the most common were hand-foot syndrome (10%); fatigue (8%); and diarrhea, vomiting, and abdominal pain (6% each).

Incidences of grade 3 or 4 laboratory abnormalities associated with renal function included hyponatremia (6%), hypocalcemia (4%), and elevated creatinine levels (2%). Incidences of grade 3 or 4 laboratory abnormalities associated with liver function included elevated levels of lipase (19%), alkaline phosphatase (6%), total bilirubin (5%), aspartate aminotransferase (4%), alanine aminotransferase (2%), and amylase (1%).

The overall rate of treatment-related AEs was higher among patients in the ADS group (98%) compared with those in the IDS group (86%) (Table 7). However, the proportion of patients who permanently discontinued sunitinib because of AEs was higher in the IDS group than in the ADS group (34% vs 26%, respectively). The most common treatment-related AEs in both groups were fatigue, diarrhea, and hand-foot syndrome, which were mainly grade 1 or 2. When adjusted for duration of treatment, the overall incidences of AEs as well as incidences of the most common AEs (with the exception of hypothyroidism) were lower in the ADS group than in the IDS group (Table 7). In addition, when adjusted for duration of treatment, incidences of the most common grade 3 or 4 events were similar or slightly higher in the ADS group versus the IDS group, with the exception of anemia, which was higher in the IDS group.

The overall rate of treatment-related AEs was somewhat higher among patients who continued sunitinib treatment after PD (96%) compared with those who did not continue sunitinib (93%) (Table 8). The most common treatment-related AEs in both groups were diarrhea, fatigue, and hand-foot syndrome, which were mainly grade 1 or 2 and occurred at a higher rate among patients

TABLE 4. Treatment of Patients Stratified in Post Hoc Analysis

Variable	Median [Range] or No. of Patients (%)			
	IDS, n = 599	ADSs, n = 525	Sunitinib Continued After PD, n = 380	Sunitinib Stopped After PD, n = 324
No. of treatment cycles started	3 [1-50]	9 [1-62]	9 [1-62]	4 [1-35]
Time drug was administered, mo	2.4 [<0.1-46.0]	8.1 [<0.1-56.9]	8.1 [0.4-56.9]	3.7 [<0.1-31.9]
Time on treatment, mo[a]	3.6 [<0.1-69.3]	12.7 [0.3-75.4]	12.5 [0.7-74.2]	5.5 [<0.1-52.0]
Patients with dosing interruptions	216 (36)	376 (72)	231 (61)	141 (44)
Adverse event-related[b]	153 (26)	317 (60)	179 (47)	113 (35)
Other[b]	84 (14)	164 (31)	115 (30)	52 (16)
Days with interruptions, %	6 [0-96]	5 [0-60]	3 [0-49]	6 [0-96]
Patients with dose reductions[c]	0 (0)	484 (92)	213 (56)	122 (38)
Total dose, mg	3600 [50-69,950]	9838 [38-65,962]	10,112 [450-65,962]	5238 [50-42,000]
Average daily dose, mg	50 [50-50]	41 [15-53]	46 [15-53]	50 [27-50]

Abbreviations: ADSs, alternative dosing schedules; IDS, initial dosing schedule; PD, progressive disease.
[a] For schedule 4/2 (sunitinib 50 mg daily on a 4-week-on/2-week-off treatment schedule), time on treatment was the period starting from the date of first dose and ending at the earlier of the termination date or the last dose date plus the planned off-treatment period (2 weeks) for a cycle. For the continuous daily dosing schedule, time on treatment was the period starting from the date of first dose and ending at the last dose date.
[b] Dosing could be interrupted for more than 1 reason.
[c] These were patients who had their daily dose prescribed below the assigned dose for any reason at any time during the study.

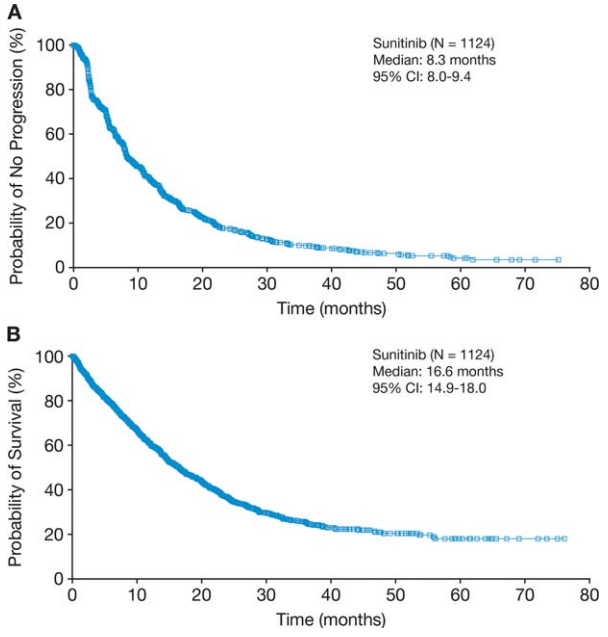

Figure 1. (A) The time to progression and (B) overall survival are illustrated in the intent-to-treat population. CI indicates confidence interval.

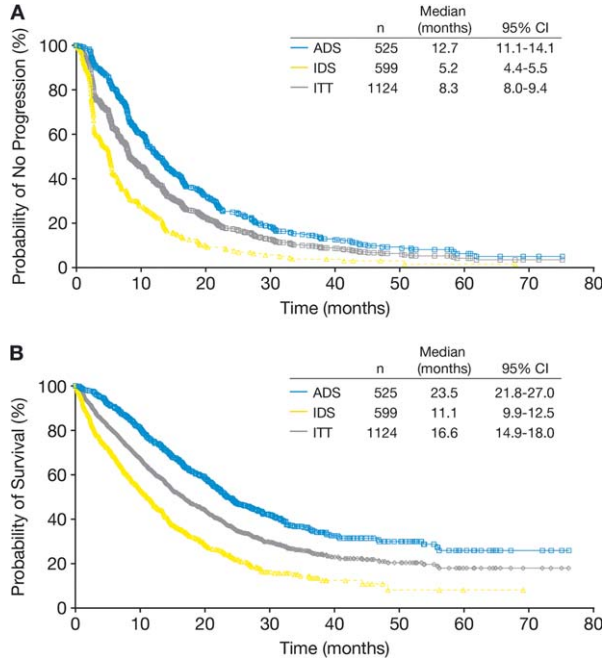

Figure 2. (A) The time to progression and (B) overall survival are illustrated in patients who received sunitinib only on the initial dosing schedule (IDS) or who ultimately received alternative dosing schedules (ADSs). Results for the intent-to-treat (ITT) population are shown for comparison.

who continued treatment after PD than in those who did not continue treatment.

DISCUSSION

The results of this treatment-use study demonstrate the efficacy and long-term safety of sunitinib in an international population of patients with advanced GIST after failure of imatinib. With >1100 patients enrolled, this is the largest trial conducted in any type of sarcoma to date. The trial, as a treatment-use study, involved a broader and more inclusive patient population than previous sunitinib studies in GIST (eg, 15% of patients had a baseline

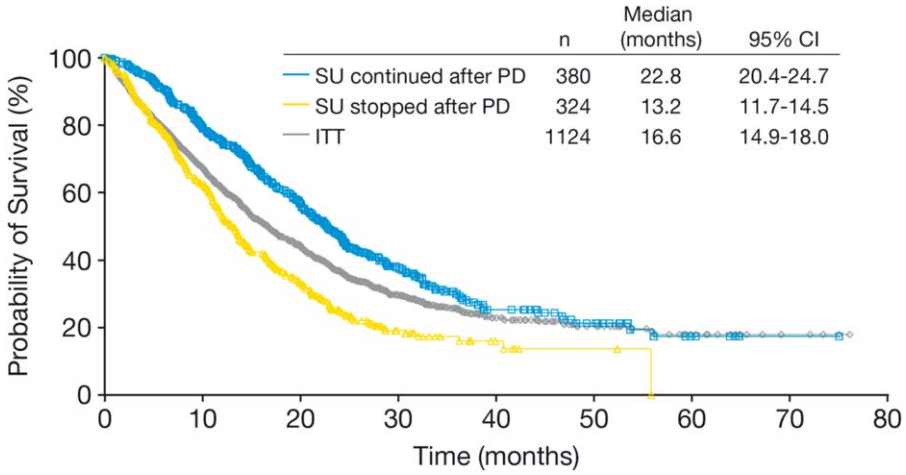

Figure 3. Overall survival is illustrated from the start of treatment in patients who continued or discontinued sunitinib (SU) treatment after progressive disease (PD). Results for the intent-to-treat (ITT) population are shown for comparison. CI indicates confidence interval.

ECOG PS ≥2), and the safety and efficacy results reflect experience with sunitinib in a population that more robustly represents routine clinical practice.

Although the presence of measurable disease was not an eligibility criterion in this study and tumor response was monitored according to the local standard of care with no mandatory frequency of radiologic assessment specified in the protocol, data on the best response were collected based on RECIST. The observed ORR (8%) was consistent with that reported in the phase 1/2 and pivotal phase 3 trials of sunitinib in GIST (7%)[7,11] but was lower than that in the phase 2 trial with sunitinib given by CDD (13%).[12] However, tumor response data were missing for 158 patients (14%). The median TTP in the current study (8.3 months or 36.0 weeks) was higher than that reported in the phase 3 study (26.6 weeks)[7] and was similar to the median progression-free survival reported in the phase 2 CDD study (34 weeks).[12] These differences may have been caused by the lower frequency of tumor assessments in the current study or by differences in the patient populations in the 2 studies. The median OS in the current study was 16.6 months (or 72.1 weeks) and represents an important addition to our understanding of the survival benefit that long-term treatment with sunitinib can provide to such a large international patient population. Although the median OS in the current study was lower than that reported in the phase 2 CDD study (107 weeks),[12] it was very similar to that reported in the phase 3 study (72.7 weeks).[7] Overall, these current data are comparable to those previously reported, despite the relatively high proportion of patients (15%) with baseline ECOG PS ≥2 (compared with 1%-2% of patients with an ECOG PS of 2 in the phase 3 and CDD studies[7,12]).

In post hoc analysis stratifying patients according to whether they continued or discontinued sunitinib treatment after PD, those who continued treatment had improved outcomes (prolonged OS). Although these results must be interpreted with caution and require validation in prospective clinical trials for confirmation, they do suggest the benefits of continuing treatment despite PD, depending on alternatives available for an individual patient. The difference observed between the 2 groups, in part, may reflect different tumor biologies (ie, patients whose disease progressed more slowly may have continued treatment more frequently than patients whose disease progressed more rapidly). Tumor mutational differences, as well as differences in interlesional and/or intralesional genetic heterogeneity, also may have been underlying factors; unfortunately, tumor mutational analysis was not conducted across this study. The results may also have been affected by selection bias: frequencies of prognostic factors (known or unknown) may have differed between the 2 subgroups. In addition, the groups may have differed in the treatments that patients received after discontinuing sunitinib, but this information is not available. Nonetheless, these results agree with recent findings obtained with imatinib, suggesting that continued TKI treatment or TKI rechallenge in patients with GIST is beneficial.[13,14]

In the current study, dosing interruptions and/or reductions were implemented in a relatively high proportion of patients (53% and 43%, respectively). This active management of sunitinib dosing allowed prolonged

treatment in many patients (median treatment duration, 7.0 months, with >30% of patients treated for >1 year) and resulted in a relatively low proportion of patients discontinuing treatment because of an AE (15%) compared with those who stopped treatment because of lack of efficacy (64%). Results from post hoc analysis comparing clinical outcomes in patients who ultimately received sunitinib on ADSs versus those who received only the IDS suggest that this prolonged treatment may have led to improved outcomes, including prolonged TTP and OS. Although several factors may have contributed to these improvements, it is likely that close follow-up and prompt dose modification allowed patients to avoid certain toxicities and to receive therapy for a longer period. Although these results suggest a possible benefit in individualization of treatment, prospective data comparing the approved dosing schedule (50 mg daily on schedule 4/2) for sunitinib with other dosing schedules in GIST are currently lacking. Although the current treatment-use protocol was not designed to address the question of whether dosing schedules other than that approved might provide advantages for some patients, and although the post hoc analyses were conducted solely for the purpose of hypothesis generation, 1 important lesson that can be taken from these results is that the management of AEs early and often is an important key to optimizing treatment.

TABLE 5. The Most Common Treatment-Related Adverse Events in Patients Who Received Sunitinib, N = 1124[a]

	No. of Patients (%)			
Adverse Event	Grade 1&2	Grade 3	Grade 4	Any Grade[b]
Any adverse event	433 (39)	480 (43)	100 (9)	1030 (92)
Nonhematologic				
Fatigue	380 (34)	94 (8)	3 (<1)	477 (42)
Diarrhea	394 (35)	59 (5)	1 (<1)	454 (40)
Hand-foot syndrome	240 (21)	121 (11)	2 (<1)	363 (32)
Nausea	304 (27)	23 (2)	0 (0)	327 (29)
Decreased appetite	277 (25)	24 (2)	1 (<1)	302 (27)
Hypertension	214 (19)	72 (6)	2 (<1)	288 (26)
Stomatitis	236 (21)	21 (2)	1 (<1)	258 (23)
Mucosal inflammation[c]	234 (21)	22 (2)	1 (<1)	258 (23)
Vomiting	219 (19)	25 (2)	3 (<1)	247 (22)
Dysgeusia	180 (16)	0 (0)	0 (0)	180 (16)
Rash	164 (15)	11 (1)	0 (0)	175 (16)
Skin discoloration	172 (15)	1 (<1)	0 (0)	173 (15)
Dyspepsia	145 (13)	0 (0)	0 (0)	145 (13)
Hypothyroidism	131 (12)	10 (1)	2 (<1)	143 (13)
Peripheral edema	130 (12)	5 (<1)	0 (0)	135 (12)
Asthenia	97 (9)	33 (3)	1 (<1)	131 (12)
Yellow skin	123 (11)	2 (<1)	0 (0)	125 (11)
Pain in extremity	114 (10)	7 (1)	0 (0)	121 (11)
Headache	116 (10)	6 (1)	1 (<1)	123 (11)
Hair color changes	109 (10)	0 (0)	0 (0)	109 (10)
Abdominal pain	93 (8)	12 (1)	2 (<1)	107 (10)
Hematologic				
Thrombocytopenia	160 (14)	48 (4)	15 (1)	223 (20)
Neutropenia	122 (11)	83 (7)	7 (1)	212 (19)
Anemia	120 (11)	42 (4)	19 (2)	181 (16)
Leukopenia	123 (11)	15 (1)	0 (0)	138 (12)

[a] These were events that occurred in ≥10% of patients in the intent-to-treat population.
[b] Seventeen grade 5 events that were considered to be treatment-related occurred in the study (cardiac failure, n = 2; and death, disease progression, embolism, gastrointestinal hemorrhage, hemolysis, hepatic failure, hepatotoxicity, multiorgan failure, myocardial infarction, performance status decrease, peritoneal hemorrhage, pulmonary embolism, rectal hemorrhage, sepsis, and tumor hemorrhage occurred in 1 patient each).
[c] One patient was missing data on mucosal inflammation.

The safety profile of sunitinib in the current treatment-use study, with its relatively long duration of treatment, was very similar to that observed in the sunitinib phase 1, 2, and 3 GIST studies. Individual AEs were mostly mild to moderate in severity, and the rates of grade 3 or 4 AEs were similar to those reported in previous studies,[7,11,12] although the total frequency of grade 3 or 4 AEs (52%) was higher than that of grade 1 or 2 AEs (39%). No new or unexpected toxicities were observed with long-term exposure to sunitinib.

The frequencies of AEs that are known as part of the sunitinib safety profile and require monitoring, such as hypothyroidism and hypertension, also were consistent with those in previous reports.[7,11,12] Treatment-related cardiovascular AEs of any grade were reported at low

TABLE 6. Clinically Relevant Treatment-Related Adverse Events Related to Cardiac Function in Patients Who Received Sunitinib, N = 1124

	No. of Patients (%)				
Adverse Event	Grade 1&2	Grade 3	Grade 4	Grade 5	Any Grade
Heart failure[a]	1 (<1)	5 (<1)	1 (<1)	2 (<1)	9 (1)
Congestive heart failure	2 (<1)	2 (<1)	2 (<1)	0 (0)	6 (1)
Myocardial infarction	0 (0)	0 (0)	3 (<1)	1 (<1)	4 (<1)
Ejection fraction[b]	2 (<1)	1 (<1)	0 (0)	0 (0)	3 (<1)
Pulmonary edema	0 (0)	1 (<1)	0 (0)	0 (0)	1 (<1)

[a] These events included acute heart failure.
[b] These events included reduced ejection fraction.

TABLE 7. The Most Common Treatment-Related Adverse Events in the Initial Dosing Schedule and Alternative Dosing Schedules Patient Groups: Overall Incidence and Incidence Adjusted for Duration of Treatment[a]

	IDS, n = 599 [319 Total Patient-Years]				ADSs, n = 525 [734 Total Patient-Years]			
	Any Grade[b]		Grade 3&4		Any Grade[c]		Grade 3&4	
Adverse Event	No. (%)	PPY	No. (%)	PPY	No. (%)	PPY	No. (%)	PPY
Any adverse event	516 (86)	162	197 (33)	62	514 (98)	70	383 (73)	52
Fatigue	175 (29)	55	19 (3)	6	302 (58)	41	78 (15)	11
Diarrhea	161 (27)	50	10 (2)	3	293 (56)	40	50 (10)	7
Hand-foot syndrome	124 (21)	39	17 (3)	5	239 (46)	33	106 (20)	14
Nausea	117 (20)	37	3 (1)	1	210 (40)	29	20 (4)	3
Decreased appetite	112 (19)	35	7 (1)	2	190 (36)	26	18 (3)	2
Mucosal inflammation	99 (17)	31	6 (1)	2	159 (30)	22	17 (3)	2
Stomatitis	94 (16)	29	2 (<1)	1	164 (31)	22	20 (4)	3
Hypertension	91 (15)	29	17 (3)	5	197 (38)	27	57 (11)	8
Vomiting	90 (15)	28	7 (1)	2	157 (30)	21	21 (4)	3
Thrombocytopenia	80 (13)	25	21 (4)	7	143 (27)	19	42 (8)	6
Dysgeusia	76 (13)	24	0 (0)	0	104 (20)	14	0 (0)	0
Neutropenia	73 (12)	23	24 (4)	8	139 (26)	19	66 (13)	9
Anemia	66 (11)	21	29 (5)	9	115 (22)	16	32 (6)	4
Skin discoloration	65 (11)	20	0 (0)	0	108 (21)	15	1 (<1)	<1
Rash	56 (9)	18	2 (<1)	1	119 (23)	16	9 (2)	1
Hypothyroidism	28 (5)	9	4 (1)	1	115 (22)	16	8 (2)	1

Abbreviations: ADSs, alternative dosing schedules; IDS, initial dosing schedule; PPY, patients per patient-year.
[a] These were events that occurred in ≥20% of patients in either group.
[b] Eleven grade 5 adverse events that were deemed treatment-related occurred in the IDS group.
[c] Six grade 5 adverse events that were deemed treatment-related occurred in the ADS group.

TABLE 8. The Most Common Treatment-Related Adverse Events Among Patients Who Continued Sunitinib and Those Who Discontinued Sunitinib After Disease Progression[a]

	No. of Patients (%)			
	Sunitinib Continued After PD, n = 380		Sunitinib Stopped After PD, n = 324	
Adverse Event	Any Grade[b]	Grade 3&4	Any Grade[c]	Grade 3&4
Any adverse event	363 (96)	214 (56)	300 (93)	152 (47)
Diarrhea	186 (49)	25 (7)	114 (35)	11 (3)
Fatigue	182 (48)	38 (10)	132 (41)	18 (6)
Hand-foot syndrome	150 (39)	54 (14)	102 (31)	37 (11)
Hypertension	140 (37)	34 (9)	77 (24)	25 (8)
Nausea	138 (36)	6 (2)	76 (23)	6 (2)
Decreased appetite	114 (30)	5 (1)	83 (26)	7 (2)
Stomatitis	101 (27)	11 (3)	83 (26)	9 (3)
Neutropenia	99 (26)	46 (12)	54 (17)	17 (5)
Vomiting	89 (23)	6 (2)	76 (23)	11 (3)
Thrombocytopenia	87 (23)	24 (6)	57 (18)	17 (5)
Dysgeusia	84 (22)	0 (0)	43 (13)	0 (0)
Mucosal inflammation	77 (20)	5 (1)	63 (19)	6 (2)
Anemia	75 (20)	23 (6)	47 (15)	13 (4)
Skin discoloration	74 (19)	0 (0)	46 (14)	1 (<1)

Abbreviation: PD, progressive disease.
[a] These were events that occurred in ≥20% of patients in either group.
[b] One grade 5 event that was deemed treatment-related occurred in this group.
[c] Two grade 5 events that were deemed treatment-related occurred in this group.

frequencies (all ≤1%), consistent with long-term results from the phase 3 study, in which the total incidence of cardiac AEs of all grades was 12%.[7] A higher frequency of congestive heart failure (8%) was reported in a retrospective, adjudicated analysis of 75 patients at a single center in a noncomparative, open-label, phase 1/2 study of sunitinib in GIST.[15] The differences in frequencies of cardiovascular events reported in those studies may reflect the different methodologies used. Although routine monitoring of patients with cardiac risk factors is now recommended,[16] this approach was not standard practice when the current trial was initiated in 2004; consequently, neither baseline assessment of left ventricular function nor prospective monitoring of specific cardiovascular AEs were mandated in this study. Nevertheless, the majority of cardiac AEs were managed by cardiologists in this study according to standard practice. A retrospective, adjudicated analysis of cardiovascular AEs based on data from sunitinib phase 3 studies that included comparator arms (the phase 3 GIST study and a phase 3 study in renal cell carcinoma) indicated that, although hypertension, hypertensive crises, and left ventricular ejection fraction decreases occurred significantly more frequently with sunitinib treatment, congestive heart failure (and several other cardiovascular AEs) did not.[17]

This treatment-use study adds to the existing body of evidence supporting the safety and efficacy of sunitinib

in an international population of patients with advanced GIST after imatinib failure who were ineligible for other sunitinib clinical trials. The results observed here confirm those reported in the more restricted and selected population of patients accrued to the pivotal phase 3 study. With appropriate dose adjustment, many patients tolerate prolonged dosing with sunitinib and benefit from a median delay in progression of their disease of approximately 8 months.

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CONFLICT OF INTEREST DISCLOSURES

Dr. Reichardt has served in a consultancy/advisory role for and received honoraria from Pfizer, Novartis, and Bayer. Dr. Kang has served in a consultancy/advisory role for and received honoraria from Pfizer. Dr. Rutkowski has served in a consultancy/advisory role for Novartis, Bayer, and Bristol-Myers Squibb and has received honoraria from Pfizer, Novartis, Roche, MSD Pharmaceuticals, and Bristol-Myers Squibb. Dr. Rosen, Dr. Gelderblom, and Dr. Biasco have received research funding from Pfizer. Beatrice Seddon has received honoraria from Pfizer. Dr. Yalcin has served in a consultancy/advisory role for Pfizer, Novartis, Roche, Sanofi, Bayer, and Amgen. Dr. Fumagalli has received other remuneration from Pfizer and Novartis. Dr. Hurwitz has served in a consultancy/advisory role for Genentech, Roche, Sanofi, Amgen, and Regeneron; has received honoraria from Roche; and has received research funding from Genentech, Roche, Sanofi, Bristol-Myers Squibb, and Novartis. Dr. Demetri has served in a consultancy/advisory role for Pfizer, Bayer, Novartis, Sanofi-Aventis, GlaxoSmithKline, Foundation Medicine, Ariad, Kolltan Pharmaceuticals, and Blueprint Medicines; has received research funding from Pfizer, Bayer, Novartis, Sanofi-Aventis, and GlaxoSmithKline; has provided expert testimony for Bayer and GlaxoSmithKline; and owns stock in Kolltan Pharmaceuticals and Blueprint Medicines. Dr. Matczak, Dr. Chen, and Dr. Lechuga are Pfizer employees and own stock in the company. Dr. Fly and an immediate family member are Pfizer employees and own stock in the company.

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