

Complete Longitudinal Analyses of the Randomized, Placebo-Controlled, Phase III Trial of Sunitinib in Patients with Gastrointestinal Stromal Tumor following Imatinib Failure

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Abstract

Purpose: To analyze final long-term survival and clinical outcomes from the randomized phase III study of sunitinib in gastrointestinal stromal tumor patients after imatinib failure; to assess correlative angiogenesis biomarkers with patient outcomes.

Experimental Design: Blinded sunitinib or placebo was given daily on a 4-week-on/2-week-off treatment schedule. Placebo-assigned patients could cross over to sunitinib at disease progression/study unblinding. Overall survival (OS) was analyzed using conventional statistical methods and the rank-preserving structural failure time (RPSFT) method to explore cross-over impact. Circulating levels of angiogenesis biomarkers were analyzed.

Results: In total, 243 patients were randomized to receive sunitinib and 118 to placebo, 103 of whom crossed over to open-label sunitinib. Conventional statistical analysis showed that OS converged in the sunitinib and placebo arms (median 72.7 vs. 64.9 weeks; HR, 0.876; $P = 0.306$) as expected, given the cross-over design. RPSFT analysis estimated median OS for placebo of 39.0 weeks (HR, 0.505, 95% CI, 0.262–1.134; $P = 0.306$). No new safety concerns emerged with extended sunitinib treatment. No consistent associations were found between the pharmacodynamics of angiogenesis-related plasma proteins during sunitinib treatment and clinical outcome.

Conclusions: The cross-over design provided evidence of sunitinib clinical benefit based on prolonged time to tumor progression during the double-blind phase of this trial. As expected, following cross-over, there was no statistical difference in OS. RPSFT analysis modeled the absence of cross-over, estimating a substantial sunitinib OS benefit relative to placebo. Long-term sunitinib treatment was tolerated without new adverse events. *Clin Cancer Res*; 18(11); 3170–9. ©2012 AACR.

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Translational Relevance

We present complete longitudinal analyses, including final overall survival (OS), from the pivotal phase III study that led to regulatory approval of sunitinib in patients with advanced imatinib-resistant/intolerant gastrointestinal stromal tumor. We show the confounding effect of the cross-over design of the study (patients could switch from placebo to sunitinib) on OS: conventional intent-to-treat analysis showed that OS converged in the treatment arms, showing no statistical difference, despite statistically significant differences in tumor control rates. However, using the exploratory rank-preserving structural failure time method to model the absence of cross-over, we estimated that sunitinib conferred a long-term OS benefit relative to placebo (73 vs. 39 weeks). We also analyzed circulating biomarkers of angiogenesis during sunitinib treatment and found no consistent associations with clinical outcome. Finally, these long-term exposure data showed that no new safety concerns emerged with extended sunitinib treatment.

Introduction

The key pathogenic event causing the neoplastic phenotype for the majority of gastrointestinal stromal tumors (GIST) has been shown to be mutation of the genes encoding KIT (stem cell factor receptor) or platelet-derived growth factor receptor α (PDGFR- α), resulting in constitutively activated signaling through these receptor tyrosine kinases (RTK; refs. 1–3). The oral multitargeted RTK inhibitor sunitinib malate targets a number of RTKs, including KIT, PDGFRs- α and - β , and VEGF receptors (VEGFR)-1, -2, and -3 (4–9), thereby blocking key kinases involved in maintaining the survival and proliferation of GIST cells and signals of tumor-related angiogenesis.

Previously reported results of the planned interim analysis of a double-blind, placebo-controlled, randomized phase III study of sunitinib in patients with GIST following imatinib failure showed significant clinical benefit from sunitinib treatment with acceptable safety (10). On the basis of these results, sunitinib received multinational regulatory approval for the treatment of advanced imatinib-resistant or imatinib-intolerant GIST (9, 10).

Following unblinding due to the positive impact of sunitinib on time to tumor progression (TTP), all patients randomized to receive placebo were offered the opportunity to cross over to open-label sunitinib treatment (10). This trial was designed knowing that cross-over to an active agent would necessarily confound any estimate of treatment effect on overall survival (OS) using conventional statistical methods. We now report final results from this study, including OS and toxicities observed with long-term sunitinib administration; OS was analyzed using both conventional statistical techniques and an exploratory method to estimate this effect of cross-over on survival. To expand on the previously

reported finding that the extent of reduction in plasma soluble (s)KIT during sunitinib treatment correlated strongly with improved clinical outcome in this study (11), we examined possible associations between plasma levels of the angiogenesis-related proteins VEGF-A, sVEGFR-2, and sVEGFR-3 and sunitinib efficacy in a subset of patients.

Materials and Methods

Study population

The study population comprised adults with histologically proven GIST for whom prior imatinib treatment had failed due to resistance or intolerance, an Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1 , and adequate hepatic, renal, and cardiac function as described previously (10).

Study design and treatment

Patients were randomized 2:1 to receive double-blind treatment in repeated 6-week cycles of 4 weeks of daily sunitinib (50 mg) or placebo followed by 2 weeks off treatment (Supplementary Fig. S1). At the time of disease progression or termination of the double-blind phase of the study (whichever occurred first), treatment assignments were unblinded, and patients randomized to sunitinib were permitted to continue treatment. Eligible patients randomized to placebo were allowed to cross over to open-label sunitinib treatment. The study conformed to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The institutional review boards of participating study centers approved the protocol. All participants provided written informed consent.

Clinical assessments

The primary efficacy endpoint of this study was TTP. Secondary efficacy endpoints included OS, progression-free survival (PFS), and overall confirmed objective response rate (ORR). Tumor imaging studies, which have been described previously (10), were carried out at baseline, on day 28 of each treatment cycle, and at the end of treatment, or more frequently as required; disease assessments were made using Response Evaluation Criteria in Solid Tumors (12). Primary analysis of response-based efficacy endpoints used assessments from an independent, third-party, core imaging laboratory.

Safety was evaluated by analysis of adverse events (AE), physical examinations, vital signs, ECOG PS, laboratory tests, and cardiac function assessments as previously described (10). AEs were graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Assessment of plasma protein biomarkers

VEGF-A, sVEGFR-2, and sVEGFR-3 were chosen for evaluation on the basis of their relationship to known sunitinib molecular targets, their established roles in VEGF-related signaling and angiogenesis, and on reproducible plasma

pharmacodynamics obtained in sunitinib trials in a number of tumor types (13–15). Blood was collected in heparinized tubes predose at baseline, on days 14 and 28 of cycle 1, and on days 1 and 28 of subsequent cycles. Plasma samples were stored at -70°C ; storage duration was within the period covered by stability assessment for each protein analyzed. Plasma concentrations of VEGF-A, sVEGFR-2, and sVEGFR-3 were determined using ELISA kits from R&D Systems. The VEGF-A assay measured the VEGF-A165 and VEGF-A121 isoforms. Plasma sVEGFR-2 and sVEGFR-3 were measured using assays that detect the extracellular domains of the respective full-length receptors without cross-reactivity. The sVEGFR-2 and sVEGFR-3 assays were calibrated against recombinant proteins consisting of extracellular receptor domains. All assays were run under Good Laboratory Practice conditions, and performance specifications of each ELISA were validated for their intended purpose according to established guidelines (16).

In the placebo arm, plasma protein values obtained after cross-over to sunitinib treatment were excluded from analysis, and TTP values from these patients were censored at cross-over. The correlative analyses reported here represent evaluations of specific individual biomarker hypotheses as described above, and corrections for multiple comparisons were not applied. The numbers of samples analyzed (at baseline: sunitinib arm, $n = 68$ – 88 ; placebo arm, $n = 33$ – 60) were comparable with those analyzed in earlier sunitinib trials in several tumor types (13–15).

Statistical analyses

Efficacy analyses were based on the intent-to-treat (ITT) population (all patients randomized), comparing the treatment arms as randomized. Safety analyses were conducted on the per-protocol patient population (who received 1 dose or more of assigned blinded study treatment) and the population that received 1 or more dose of open-label sunitinib treatment (Supplementary Fig. S2). Time-to-event data (including those stratified by exploratory biomarkers) were analyzed using the Kaplan–Meier method, log-rank test, and Cox proportional hazards model.

In addition, OS was analyzed using the rank-preserving structural failure time (RPSFT) method (17). This method assumes that treatment does not change the order of events (i.e., it preserves rank), but alters the time at which events occur, with treatment prolonging survival by a multiplicative factor [$\exp(\psi)$ in the model]. Thus, the structural or causal assumption of this failure time (i.e., survival time) model is that time is proportional for an individual patient (in contrast to the assumption underlying the Cox proportional hazards model, in which there is a multiplicative relationship between the hazard rates of any 2 patients, which is constant over time). This analysis (done on the ITT population) accounts for cross-over by estimating the treatment effect in the placebo arm (as randomized) by relating a patient's observed event time to the treatment effect parameter ψ and the event time that would reasonably be estimated to occur in the absence of cross-over. If T is the

observed event time for a patient who crossed over from placebo to open-label sunitinib treatment and T_p is the time on placebo, then $U = T_p + \exp(\psi)(T - T_p)$, in which U is the event time that would have been observed if no treatment had been given and $\exp(\psi)$ is the multiplicative effect of having started treatment. The patients' times on treatment after cross-over ($T - T_p$) are adjusted to reflect what would have happened if they had stayed on placebo. ψ is estimated by computing U for a range of possible values of ψ and finding the value that yields a zero in the log-rank test statistic when the 2 treatment arms are compared using time U (as one would expect no difference between the 2 arms before treatment due to randomization).

The RPSFT method does not require that cross-over and prognosis are independent, and estimation of U would have incurred this type of bias without proper handling (18, 19). The recensoring procedure described by Robins and Tsiatis (14) was therefore employed to overcome this potential bias. The HR comparing treatment with sunitinib and placebo following RPSFT analysis was estimated by carrying out a Cox regression analysis on the observed event times in the sunitinib arm and the estimated U values for cross-over patients or the observed event times for other patients in the placebo arm. Because the P value obtained in this Cox model does not reflect the uncertainty inherent in the treatment effect parameter ψ , the P value obtained in the conventional ITT analysis was used with the HR obtained following RPSFT analysis (18, 19).

Results

From December 2003 through January 2005, 312 patients from Europe, the USA, Australia, and Asia were enrolled and randomized (2:1; sunitinib, $n = 207$; placebo, $n = 105$) in double-blind fashion. The double-blind phase was terminated in January 2005 when a planned interim analysis revealed significantly longer TTP for those randomized to sunitinib versus placebo (10). Following the interim analysis, enrollment continued through May 2005, ultimately with 361 patients from 56 sites randomized to either sunitinib ($n = 243$) or placebo ($n = 118$); both arms were well balanced for demographic and prior imatinib treatment characteristics (Table 1). Patient disposition and flow throughout of the study are shown in Supplementary Fig. S2. This report presents data analysis from the full ITT population of 361 patients.

Randomized patients who received drug per protocol before unblinding of study medication included 228 in the sunitinib and 114 in the placebo arms, respectively (Supplementary Fig. S2). Sixty-three percent of placebo patients received open-label sunitinib following disease progression. All patients ultimately discontinued blinded treatment (reasons shown in Supplementary Fig. S2); 63% and 87% of sunitinib and placebo patients, respectively, received open-label sunitinib. By study end, among the 255 patients who received open-label sunitinib, 246 had discontinued treatment, primarily due to disease progression (68%) or AEs (20%; Supplementary Fig. S2), the most common of which

Table 1. Baseline patient characteristics and prior imatinib treatment history

	ITT population		Biomarker subset	
	Sunitinib (n = 243)	Placebo (n = 118)	Sunitinib (n = 88)	Placebo (n = 60)
Median age, y (range)	57 (23–84)	55 (23–81)	57 (28–81)	55 (26–81)
Sex, n (%)				
Male	152 (63)	71 (60)	52 (59)	41 (68)
Female	91 (37)	47 (40)	36 (41)	19 (32)
ECOG performance status, n (%)				
0	109 (45)	53 (45)	42 (48)	30 (50)
1	131 (54)	63 (53)	45 (51)	30 (50)
2	3 (1)	2 (2)	1 (1)	0 (0)
Median tumor burden ^a , mm (range)	227 (18–722)	240 (29–749)	218 (45–707)	243 (29–749)
Most common metastatic sites, n (%)				
Liver mass/nodule	138 (57)	68 (58)	67 (76)	44 (73)
Peritoneal mass/nodule	100 (41)	45 (38)	44 (50)	29 (48)
Mesenteric adenopathy	26 (11)	15 (13)	11 (13)	11 (18)
Previous imatinib therapy				
Median maximum daily dose, mg (range)	800 (300–1,600)	800 (400–1,600)	800 (300–1,600)	800 (400–1,600)
Median cumulative treatment duration, wk (range)	107 (0.3–206)	108 (11–231)	104 (7–195)	105 (12–174)
Treatment outcome, n (%)				
Progression ≤6 mo	42 (17)	20 (17)	16 (18)	10 (17)
Progression >6 mo	188 (77)	94 (80)	68 (77)	47 (78)
Intolerance	13 (5)	4 (3)	4 (5)	3 (5)
Best response, n (%)				
Complete response	9 (4)	1 (1)	3 (3)	0 (0)
Partial response	62 (26)	43 (36)	20 (23)	22 (37)
Stable disease	97 (40)	40 (34)	44 (51)	20 (33)
Progressive disease	68 (28)	32 (27)	18 (21)	17 (28)
Not applicable/missing	7 (3)	2 (2)	2 (2)	1 (2)
Time since diagnosis				
Median, y (range)	3.2 (0.2–26.8)	3.3 (0.2–16.4)	3.2 (0.2–15.7)	3.2 (0.5–9.5)

^aSum of longest diameters of target lesions.

were abdominal pain, fatigue, and thrombocytopenia (each $n = 4$). Nine patients (4%) completed study treatment and enrolled in a continuation protocol.

Treatment was administered across the double-blind and open-label phases of the trial for a median of 22 weeks (range, 0.4–170) among the 241 patients who were randomized to the sunitinib arm and received blinded and/or open-label sunitinib (Table 2). Dosing interruptions and/or dose reductions in this group were required in 42% and 28% of patients, respectively.

Efficacy

Over the entire trial including open-label treatment, with median follow-up of 41.7 months [95% confidence interval (CI), 40.3–43.8], median OS for the sunitinib versus placebo arms was 72.7 weeks (95% CI, 61.3–83.0) versus 64.9 weeks (95% CI, 45.7–96.0), respectively (Fig. 1A, Table 3) as estimated using the Kaplan–Meier method (with 28% and 24% of patients alive, respectively). It is important to

note that the "placebo arm" results in this analysis included survival data for patients who received open-label sunitinib [i.e., 103 of 118 patients randomized (87%); Supplementary Figs. S2 and S3], and this difference was not statistically significant ($P = 0.306$; HR, 0.876; 95% CI, 0.679–1.129; Table 3). To correct for the expected confounding impact on survival of cross-over of placebo-treated patients to open-label sunitinib, an exploratory analysis of OS was carried out using the RPSFT method, which calculated a median OS for the placebo arm of 39.0 weeks (95% CI, 28.0–54.1; Fig. 1A, Table 3). In this exploratory analysis, sunitinib nearly (1) doubled median OS and (2) halved the hazard of death versus placebo (HR, 0.505; 95% CI, 0.262–1.134; $P = 0.306$; Table 3).

The median TTP among all patients in the final ITT population was 26.6 weeks (95% CI, 16.0–32.1) versus 6.4 weeks (95% CI: 4.4–10.0) in the sunitinib versus placebo arms, respectively (Table 3). Patients in the placebo arm exhibited an almost 3-fold greater risk of disease

Table 2. Exposure to study drug

	Double-blind phase		Open-label phase	Double-blind + open-label phases
	Sunitinib ^a (n = 228)	Placebo ^a (n = 114)	All patients ^b (n = 255)	Sunitinib (n = 241)
Median no. of cycles started (range)	2 (1–15)	1 (1–6)	6 (1–37)	6 (1–44)
Median weeks on treatment ^c (range)	12 (1–88)	6 (1–36)	34 (1–197)	34 (1–216)
Median weeks on drug ^d (range)	8 (0.4–57)	4 (1–24)	20 (1–140)	22 (0.4–170)
Dosing interruptions, n (%)	62 (27)	14 (12)	118 (46)	102 (42)
Reason for interruption, n (%)				
AE	51 (82 ^e)	10 (71 ^e)	98 (83 ^e)	86 (84 ^e)
Other	19 (31 ^e)	4 (29 ^e)	54 (46 ^e)	47 (46 ^e)
Dose reductions, n (%)	26 (11)	0 (0)	72 (28)	67 (28)

^aPer-protocol population.

^bTreatment = sunitinib, irrespective of randomization arm.

^cFrom date of first dose to the earlier of either the termination date or 2 weeks after the last dose.

^dTotal number of weeks on which study drug was actually administered.

^ePercentage based on all patients who had dosing interruptions.

progression compared with those randomized to sunitinib treatment (HR, 0.339; 95% CI, 0.244–0.472; $P \leq 0.001$). Similar results were obtained for PFS (Table 3). At final analysis, among the 99 placebo-treated patients who subsequently received open-label sunitinib treatment (Supplementary Fig. S2), median TTP was 10.4 weeks (95% CI, 4.3–22.0) on open-label sunitinib treatment.

Partial responses (PR) were observed in 16 sunitinib-treated patients (ORR, 7%) versus none in placebo-treated patients (Table 3). The ORR among placebo-treated patients who subsequently received open-label sunitinib treatment was 10%, comprising 9 PRs and 1 complete response.

Safety

Safety results across the entire study are presented in Table 4. Results shown for the double-blind phase differ from the previously reported interim analysis (10) only by the inclusion of results for patients randomized subsequent to the interim analysis. Sunitinib-treated patients during the double-blind phase had relatively short-term exposure to the drug (median 8 weeks of drug; Table 2). In contrast, the 241 patients who were randomized to and received blinded and/or open-label sunitinib treatment represent the group with the greatest longitudinal exposure to sunitinib (median 22 weeks on drug). In this group, the most common treatment-related nonhematologic AEs were fatigue (47%), diarrhea (43%), and nausea (37%; Table 4). The most frequent treatment-related nonhematologic grade 3/4 AEs among these patients were fatigue (10%), hypertension (8%), and hand-foot syndrome, asthenia, and diarrhea (5% each). The frequencies of non-hematologic AEs in these patients who received extended sunitinib therapy were slightly higher than those reported in the sunitinib arm during the double-blind phase.

The frequency of treatment-related hypertension (any grade) on sunitinib increased from 12% during blinded

treatment to 20% across the entire study. In contrast, the frequency of treatment-related cardiac AEs overall was 11% during the double-blind phase and 12% over the entire study [comprising decreased ejection fraction (8%) and left ventricular dysfunction (2%) as the most frequent events]. Over the course of the study, one patient experienced congestive heart failure (grade 2) that was considered related to sunitinib treatment; this event resolved during a dosing delay with appropriate supportive therapy. The rate of treatment-related hypothyroidism (all grades) increased with extended sunitinib treatment from 3% during the double-blind phase to 13% for the entire trial. Hypothyroidism did not result in any treatment discontinuations.

Hematologic laboratory abnormalities among patients who received sunitinib across the entire study included reduced levels of hemoglobin (60%), neutrophils (59%), and platelets (41%). Most of these abnormalities were grade 1/2 and were similar in frequency to those seen during blinded sunitinib treatment.

During blinded treatment, 4 treatment-related deaths were reported in the sunitinib arm (2%; cardiac arrest, cerebral ischemia, left ventricular failure, and multiorgan failure) and 2 (2%; cardiac arrest, gastrointestinal hemorrhage) in the placebo arm. In addition, 4 treatment-related deaths were reported during open-label sunitinib treatment or follow-up [hepatic encephalopathy, hepatic failure, melena, and pneumonia (as coded from the Medical Dictionary for Regulatory Activities)].

Circulating biomarkers of angiogenesis

Levels of plasma VEGF-A, sVEGFR-2, and sVEGFR-3 were measured on days 1 and 28 of cycles 1 to 3 (i.e., after 2 weeks off-treatment and after 4 weeks on-treatment, respectively) and on cycle 1 day 14 (C1;D14) in a subset of patients in both study arms. Overall, this patient subset was similar to the ITT population with regard to baseline demographic

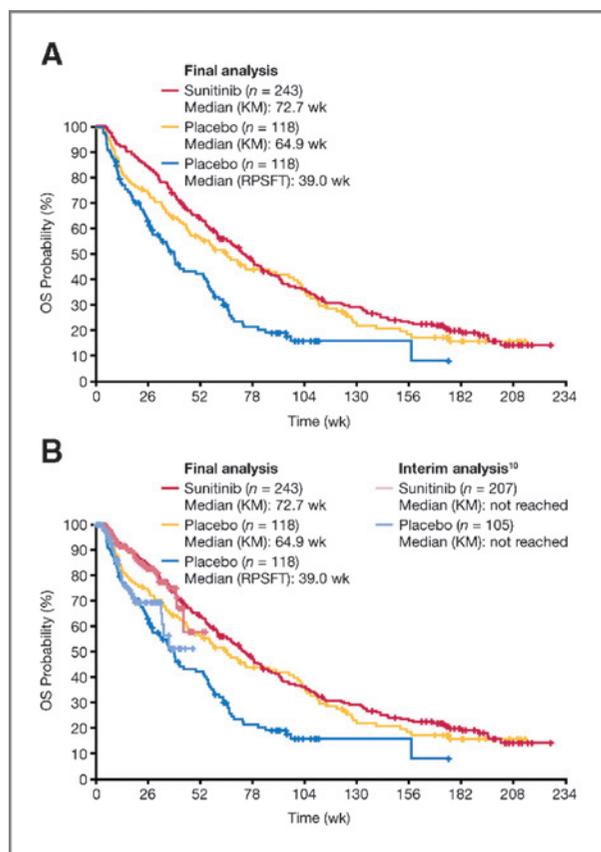


Figure 1. OS across the entire study: A, final analysis; B, final and interim analyses. KM, Kaplan–Meier method; RPSFT, rank-preserving structural failure time method.

and prior imatinib treatment characteristics, with the 2 treatment arms generally well balanced for these parameters (Table 1). Exceptions were higher percentages of patients

with metastases in the liver or peritoneum in both treatment arms and a higher proportion of men in the placebo arm of the biomarker subset compared with the ITT population.

Changes from baseline in plasma levels of VEGF-A, sVEGFR-2, and sVEGFR-3 correlated with sunitinib treatment on this intermittent dosing schedule (Supplementary Fig. S4), as has been reported in other sunitinib studies (13–15). In the placebo arm, there were no significant changes in the levels of these proteins at any time point. Between-treatment differences were significant ($P < 0.001$) at all time points tested after treatment initiation (except for VEGF-A on C2;D1 and C3;D1).

Possible associations between levels of VEGF-A, sVEGFR-2, or sVEGFR-3 and clinical outcomes (TTP or OS) were also evaluated at these time points (Supplementary Tables S1 and S2). Significant associations are shown in Fig. 2. In the sunitinib arm, low baseline levels (below median) of sVEGFR-2 and reduced levels on C1;D14 relative to baseline were associated with significantly prolonged TTP and OS (Fig. 2A–D). Reductions in sVEGFR-3 on C1;D14 compared with baseline were also associated with longer TTP (Fig. 2E). In the placebo arm, reductions in VEGF-A relative to baseline were significantly associated with longer TTP for both C1;D28 (Fig. 2F) and C2;D1 (Supplementary Table S1). No other significant associations between plasma VEGF-A, sVEGFR-2, or sVEGFR-3 levels and TTP or OS through C3;D28 were found.

The predictive value of the ratio of each plasma protein biomarker to baseline at each time point analyzed and other baseline patient characteristics (age, sex, ECOG PS, time since diagnosis, maximum daily dose of prior imatinib treatment, and baseline tumor size) was assessed in uni- and multivariate analyses of the 2 treatment arms separately as well as in the entire population. Several parameters were found to have significant associations with TTP or OS in univariate analyses in one arm or the other. However, in

Table 3. Efficacy results

Endpoint	Median (95% CI)		HR (95% CI)	P
	Sunitinib (n = 243)	Placebo (n = 118)		
TTP, wk	26.6 (16.0–32.1)	6.4 (4.4–10.0)	0.339 (0.244–0.472)	<0.001
PFS, wk	22.9 (10.9–28.0)	6.0 (4.4–9.7)	0.347 (0.253–0.475)	<0.001
Best overall response, n (%)				
Partial response	16 (7)	0		
Stable disease	128 (53)	50 (42)		
Progressive disease	45 (19)	44 (37)		
Missing/unevaluable	54 (22)	24 (20)		
Overall ORR, % (range)	7 (4–11)	0	7 (3–10) ^a	0.004
OS, wk				
Conventional methods	72.7 (61.3–83.0)	64.9 (45.7–96.0)	0.876 (0.679–1.129)	0.306
RPSFT method	72.7 (61.3–83.0)	39.0 (28.0–54.1)	0.505 (0.262–1.134) ^b	0.306 ^c

^aDifference between overall ORRs in sunitinib and placebo arms, % (95% CI of difference).

^bEmpirical 95% CI was obtained using 100,000 bootstrap samples.

^cThe RPSFT method does not alter the P value obtained using the conventional ITT method.

Table 4. Nonhematologic AEs and hematologic laboratory abnormalities

AE or laboratory abnormality	<i>n</i> (%)							
	Double-blind phase				Open-label phase		Double-blind and open-label phases	
	Sunitinib ^a (<i>n</i> = 228)		Placebo ^a (<i>n</i> = 114)		All patients ^b (<i>n</i> = 255)		Sunitinib (<i>n</i> = 241)	
	Grades ^c		Grades ^c		Grades ^c		Grades ^c	
	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4
Treatment-related nonhematologic AEs ^d								
Fatigue	67 (29)	18 (8)	23 (20)	2 (2)	102 (40)	26 (10)	88 (37)	25 (10)
Diarrhea	69 (30)	8 (4)	8 (7)	0 (0)	81 (32)	12 (5)	91 (38)	13 (5)
Nausea	60 (26)	3 (1)	14 (12)	2 (2)	74 (29)	9 (4)	82 (34)	6 (3)
Skin discoloration	62 (27)	0 (0)	5 (4)	0 (0)	77 (30)	0 (0)	72 (30)	0 (0)
Anorexia	46 (20)	0 (0)	5 (4)	1 (1)	58 (23)	6 (2)	66 (27)	2 (1)
Dysgeusia	50 (22)	0 (0)	3 (3)	0 (0)	54 (21)	1 (0.4)	60 (25)	1 (0.4)
Vomiting	38 (17)	1 (0.4)	7 (6)	1 (1)	44 (17)	5 (2)	51 (21)	3 (1)
Mucosal inflammation	32 (14)	1 (0.4)	0 (0)	0 (0)	42 (17)	6 (2)	44 (18)	4 (2)
Hypertension	18 (8)	9 (4)	4 (4)	1 (1)	39 (15)	21 (8)	29 (12)	18 (8)
Rash	34 (15)	2 (1)	6 (5)	0 (0)	37 (15)	1 (0.4)	43 (18)	3 (1)
Stomatitis	35 (15)	1 (0.4)	1 (1)	0 (0)	36 (14)	4 (2)	42 (17)	3 (1)
Dyspepsia	33 (14)	1 (0.4)	1 (1)	0 (0)	45 (18)	2 (1)	44 (18)	1 (0.4)
Headache	24 (11)	1 (0.4)	7 (6)	0 (0)	43 (17)	3 (1)	41 (17)	3 (1)
Asthenia	25 (11)	6 (3)	2 (2)	2 (2)	31 (12)	12 (5)	30 (13)	13 (5)
Hand-foot syndrome	16 (7)	8 (4)	1 (1)	0 (0)	44 (17)	12 (5)	29 (12)	13 (5)
Hair color changes	19 (8)	0 (0)	2 (2)	0 (0)	50 (20)	0 (0)	37 (15)	0 (0)
Hypothyroidism	6 (3)	1 (0.4)	1 (1)	0 (0)	35 (14)	5 (2)	26 (11)	6 (2)
Cardiac disorders	22 (10)	2 (1)	2 (2)	0 (0)	14 (5)	3 (1)	25 (10)	3 (1)
Decreased EF	15 (7)	2 (1)	2 (2)	0 (0)	3 (1)	0 (0)	16 (7)	2 (1)
LV dysfunction	3 (1)	0 (0)	0 (0)	0 (0)	4 (2)	1 (0.4)	5 (2)	0 (0)
Hematologic laboratory abnormalities								
Hemoglobin	124 (54)	9 (4)	60 (53)	2 (2)	ND	ND	132 (55)	11 (5)
Leukocytes	126 (55)	8 (4)	7 (6)	0 (0)	ND	ND	136 (56)	8 (3)
Neutrophils	105 (46)	23 (10)	4 (4)	0 (0)	ND	ND	113 (47)	28 (12)
Lymphocytes	85 (37)	26 (11)	34 (30)	2 (2)	ND	ND	58 (38)	28 (12)
Platelets	87 (38)	10 (4)	3 (3)	0 (0)	ND	ND	90 (37)	10 (4)

Abbreviations: EF, ejection fraction; LV, left ventricular; ND, not determined.

^aPer-protocol population.

^bTreatment = sunitinib.

^cGrade 5 events are described in the text.

^dReported in 15% or more of patients based on the sunitinib arm over the entire study or of particular clinical interest.

multivariate analysis, significant associations were only found between OS in the sunitinib arm and baseline tumor size, baseline sVEGFR-2, and sVEGFR-2 C1;D14 ratio to baseline (Supplementary Table S3).

Discussion

These longer term analyses from this large randomized, placebo-controlled, multicenter study provide new insights into the significant clinical activity of sunitinib in imatinib-

resistant/intolerant GIST patients. The trial was designed with TTP as the primary endpoint, with the expectation that the majority of patients assigned to placebo would subsequently cross over to open-label sunitinib. In an earlier analysis that reflected the double-blind phase of the trial, sunitinib resulted in significantly longer OS versus placebo (HR, 0.49; 95% CI, 0.29–0.83; *P* = 0.007; ref. 10). In the final analysis following all cross-overs, Kaplan–Meier estimates of OS for the 2 treatment arms converged, with 87%

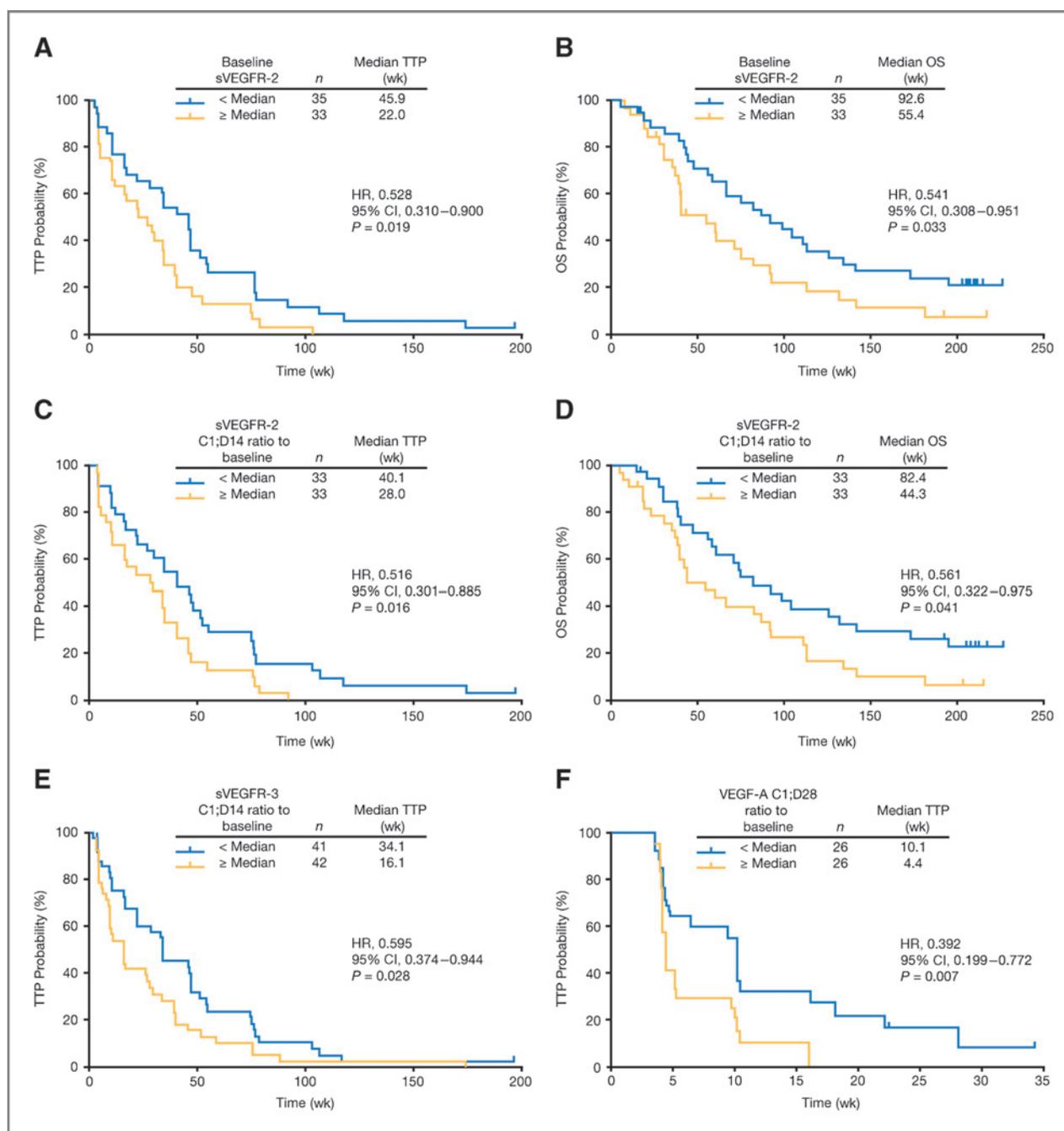


Figure 2. Significant associations found between levels of circulating biomarkers of angiogenesis and TTP or OS. A–E, sunitinib arm. F, placebo arm. Median values used for stratification: A and B (baseline sVEGFR-2), 9,159 pg/mL; C and D (sVEGFR-2 ratio to baseline, C1;D14), 0.727; E (sVEGFR-3 ratio to baseline, C1;D14), 0.694; F (VEGF-A ratio to baseline, C1;D28), 0.957.

of patients randomized to placebo successfully able to receive sunitinib following progressive disease or unblinding. This cross-over study was not powered to show an OS difference, as cross-over patients were still regarded as part of the ITT placebo arm for the purpose of survival analysis, as the comparison was based on the randomization. Exploratory analysis using the RPSFT method suggested that sunitinib confers a long-term OS benefit relative to placebo.

With this method, the estimated median OS for patients in the sunitinib arm was almost twice that of patients in the placebo arm (72.7 vs. 39.0 weeks). Using RPSFT analysis to "correct for cross-over," this analysis estimated an HR (0.505; 95% CI, 0.262–1.134) that was further from the null than that obtained using conventional statistical methods (0.876; 95% CI, 0.679–1.129), as expected given that cross-over would reduce the treatment effect size between

the 2 arms. The data obtained by this method were highly consistent with those obtained for blinded placebo treatment in the interim analysis using conventional methods (Fig. 1B), supporting the validity of this method. RPSFT analysis also avoids potential biases introduced through subgroup analyses, as it is based on the ITT population.

Overall, the patients who crossed over from placebo to open-label sunitinib showed benefits that were only somewhat more limited than those of patients initially randomized to blinded sunitinib treatment, validating the placebo-controlled cross-over design of the study. However, there was some indication that delaying initiation of sunitinib treatment compared unfavorably to earlier dosing with sunitinib, as median TTP after cross-over in the placebo arm was 10.4 weeks.

Sunitinib exhibited a safety profile consistent with prior reports over the extended course of this study, and AEs were generally manageable and reversible using standard medical therapy with or without dosing interruption and/or dose reduction. Without having specifically analyzed the timing or duration of AEs, the results showed that although the frequency of nonhematologic AEs increased slightly with long-term sunitinib treatment, there were no major changes in the overall safety profile. Fatigue remained the most commonly reported AE (Table 4), although a large proportion of fatigue in this population may be attributable to the burden of advanced GIST given the frequency of this AE reported in the placebo arm during the double-blind phase. As with other angiogenesis inhibitors (20), the frequency of hypertension increased with extended sunitinib treatment, whereas the incidence of other cardiac AEs did not increase. Indeed, the most frequent of these ("decreased ejection fraction") seemed to occur primarily during the double-blind phase of the trial (8% vs. 1% during open-label treatment, with the caveat that although regularly scheduled periodic assessments of cardiac function were only mandated during the double-blind phase of the study, such assessments were conducted if clinically indicated to monitor patients on this trial at all times). As expected with sunitinib (9, 21), the incidence of hypothyroidism increased with time on treatment from 3% during the double-blind phase to 13% for the entire trial (and thyroid dysfunction may have been underreported because thyroid stimulating hormone levels were not required to be monitored prospectively). However, most cases were mild to moderate in severity (11%) and easily managed using thyroid hormone replacement therapy.

A secondary objective of this trial was to examine potential correlations between clinical outcomes and plasma biomarkers of angiogenesis that are related to known molecular targets of sunitinib. The plasma pharmacodynamics of VEGF-A, sVEGFR-2, and sVEGFR-3 during 4-week-on/2-week-off sunitinib dosing were similar to those previously reported for these proteins in renal cell carcinoma, hepatocellular carcinoma, and breast cancer (13–15). In the present study, no consistent associations were observed between changes in plasma levels of these angiogenesis-related proteins and either TTP or OS. These

findings contrast markedly with the strong associations obtained at several time points between reductions in plasma levels of sKIT and improved clinical outcome that have been reported previously in this study (11) and in a phase II GIST study in which sunitinib was administered on a continuous daily dosing schedule (22). Taken together, these findings for circulating proteins related to molecular targets of sunitinib support the view that inhibition of activated KIT represents the primary mechanism for the clinical activity of this multitargeted tyrosine kinase inhibitor in GIST (23).

In conclusion, these efficacy and safety results from the complete longitudinal data of this worldwide phase III study further support prior reports that sunitinib provides significant clinical benefit to GIST patients whose disease is resistant to, or who are intolerant of, imatinib therapy.

Disclosure of Potential Conflicts of Interest

G.D. Demetri has received commercial research support from Pfizer, Novartis, Ariad, Johnson & Johnson, Bristol-Myers Squibb, Infinity, and Daiichi-Sankyo, and has served as a consultant for Pfizer, Novartis, Ariad, Johnson & Johnson, Genentech, Infinity, Bayer, EMD-Serono, GlaxoSmithKline, Amgen, Daiichi-Sankyo, ArQule, Enzon, and Millenium/Takeda. He has also served as a member of an advisory board for ZioPharm. C.R. Garrett, L. Paz-Ares, and J. Verweij have served as consultants or members of advisory boards for Pfizer. P. Schöffski has received a commercial research grant, other commercial research support, and honoraria from speakers bureau from and has served as a consultant or member of an advisory board for Pfizer. M.H. Shah has received a commercial research grant from Pfizer. H.I. Hurwitz has received a commercial research grant and has served as a consultant or member of an advisory board for Pfizer. A. Le Cesne has received honoraria from speakers bureau from Pfizer, Novartis, and Pharmamar. D. Goldstein has received commercial research grants from Pfizer, Cellgene, and Amgen, and has received honoraria from and served as a member of advisory boards for Pfizer, Novartis, Bayer, GlaxoSmithKline, and Roche. J.-Y. Blay has received honoraria from speakers bureau from and has served as a consultant or member of advisory boards for Pfizer and Novartis. G.A. McArthur has received commercial research grants from Pfizer and Novartis. Q. Xu has served as a consultant for Pfizer. C.S. Harmon is a previous employee of and has had an ownership interest in Pfizer. X. Huang, V. Tassell, and D.P. Cohen are employees of and have ownership interests in Pfizer. P.G. Casali has received honoraria for lectures and/or for serving in an advisory role for Pfizer, Novartis, and Bayer.

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