Abstract 35049

Long-term Survival in a Phase III Trial of Sunitinib in Imatinib-resistant/-intolerant Gastrointestinal Stromal Tumor with Novel Statistical Analysis to Account for Crossover

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Introduction

- Metastatic or unresectable gastrointestinal stromal tumor (GIST) is typically treated using imatinib mesylate, but approximately 12–14% of patients show primary resistance to imatinib,[1,2] more than 40% develop secondary imatinib resistance within approximately 2 years,[2,3] and a small percentage are intolerant of imatinib therapy.[4]
- Sunitinib malate (SUTENT®) is an oral multitargeted tyrosine kinase inhibitor of KIT, PDGFRs, VEGFRs, FLT3, CSF-1R, and RET with direct antitumor and antiangiogenic activities.[5–10]
- The objectives of this randomized, double-blind, placebo-controlled phase III trial were to assess the efficacy and safety of sunitinib in patients with advanced GIST following failure of imatinib therapy due to resistance or intolerance.
- Interim results from this trial demonstrated significant efficacy and acceptable tolerability in this patient population.[11] Based on these results:
  - subsequent treatment in the trial was unblinded
  - sunitinib received multinational approval for the treatment of advanced imatinib-resistant or -intolerant GIST.
- Per the design of the trial, patients randomized to receive placebo were given the opportunity to cross over to sunitinib treatment upon disease progression or study unblinding, potentially confounding the survival results obtained in this group.
- The trial continues to assess the efficacy, safety, and tolerability of sunitinib; however, as predicted, the crossover design results in conventional statistical methods giving rise to biased estimates of treatment effect for mature overall survival (OS) data.
- Here we report mature OS results from this study that were analyzed using a novel statistical method to estimate the difference in OS between the treatment groups as if the placebo patients had not crossed over to sunitinib treatment. In addition, we report other long-term efficacy, safety, and tolerability results from the study.

Methods

Study Population

- The study population comprises patients aged 18 years or older who met the following key inclusion criteria:
  - histologically proven malignant GIST, not amenable to surgery or other therapy with curative intent
  - failure of prior imatinib treatment due either to objective radiographic progression during imatinib treatment or to intolerance (grade 4 toxicity or unacceptable grade 2 or 3 toxicity persisting despite countermeasures)
  - evidence of unidimensionally measurable disease
  - Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1
  - adequate organ function.

Study Design and Dosing Regimen

- This was a randomized, double-blind, multicenter phase III trial of sunitinib vs. placebo conducted at 56 sites in Europe, USA, Australia, and Asia.
- Patients were randomized in a 2:1 ratio to receive treatment in repeated 6-week cycles consisting of 4 weeks of daily sunitinib (50 mg/day) or placebo followed by 2 weeks off treatment (Schedule 4/2).
- Patients on both treatment arms received best supportive care in addition to study treatment.
- At the time of documented disease progression, treatment assignments were unblinded and patients randomized to sunitinib were given the opportunity to continue treatment. Patients randomized to placebo were given the opportunity to cross over to sunitinib treatment, provided they met eligibility criteria (evidence of Response Evaluation Criteria in Solid Tumors [RECIST]-defined disease progression and ECOG PS 0–2).
- Figure 1 summarizes the overall design of this trial.

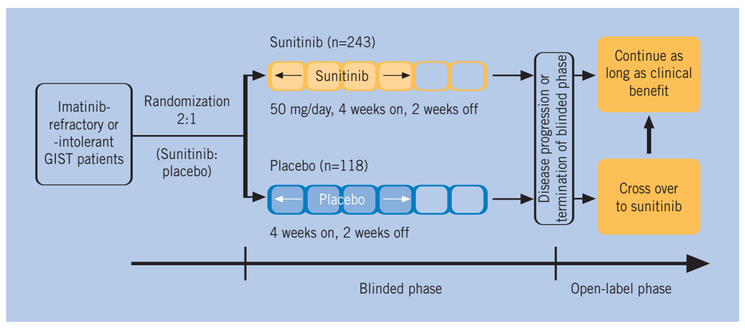

Figure 1. Trial design.

Study Endpoints and Assessments

- The primary efficacy endpoint was time to tumor progression (TTP), as defined using RECIST and evaluated by the investigators as well as an independent, third-party radiology laboratory.
- Secondary efficacy endpoints included OS, progression-free survival, and overall confirmed objective response rate (ORR).
- Safety and tolerability were assessed by monitoring adverse events (AEs) and clinical laboratory test results, and by physical examination.

Statistical Analysis

- Analyzed study populations included intention to treat (ITT; all patients randomized to treatment, for efficacy analyses) and per protocol (all patients who received at least one dose of assigned study treatment, for safety analyses).
- Time-to-event data were analyzed using the Kaplan–Meier method, log-rank test, and Cox model.
- In addition, OS was analyzed using the rank-preserving structural failure time (RPSFT) method to account for crossover.
  - This analysis was based on the ITT population, thus avoiding potential pitfalls and biases introduced with subgroup analyses.
  - This method, proposed by Robins and Tsiatis in 1991,[12] is a non-parametric model that produces a randomization-based effect estimator.

Results

Patient Characteristics and Disposition

- Beginning in December 2003, patients were randomized 2:1 to receive either sunitinib or placebo.
- The blinded phase of this trial was terminated early (January 2005) when a planned interim analysis revealed significantly longer TTP in patients treated with sunitinib vs. those treated with placebo.
- The interim analysis included 207 patients randomized to receive sunitinib and 105 patients randomized to receive placebo.[11]
- Enrollment continued until May 2005, by which time 361 patients had been randomized to receive either sunitinib (n=243) or placebo (n=118). The most recent analysis of data from these 361 patients (ITT population; March 2008) is presented here.
- Baseline patient characteristics and prior imatinib treatment history for all 361 patients are summarized in Table 1. Both treatment groups were well balanced for all characteristics.

Table 1. Baseline patient characteristics and prior treatment history.

Characteristic	Sunitinib (n=243)	Placebo (n=118)
Age, years: median (range)	57 (23–84)	55 (23–81)
ECOG PS 0/1/2 (%)	45/54/1	45/53/2
Male/female (%)	63/37	60/40
Tumor burden,* mm: median (range)	227 (18–722)	240 (29–749)
Most common metastatic sites (%)		
Liver mass/nodule	57	58
Peritoneal mass/nodule	41	38
Mesenteric adenopathy	11	13
Previous imatinib therapy: median (range)		
Daily dose, mg	502 (204–1,600)	483 (235–1,394)
Maximum dose, mg	800 (300–1,600)	800 (400–1,600)
Cumulative dose, g	372 (1–1,667)	377 (32–1,313)
Cumulative duration of treatment, weeks: median (range)	107 (0.3–206)	108 (11–231)
Imatinib treatment outcome (%)		
Progression ≤6/>6 months	17/77	17/80
Intolerance	5	3
Best response to imatinib (%)		
Complete response	4	1
Partial response	26	36
Stable disease	40	34
Progressive disease	28	27
Not applicable/missing	3	2

*Sum of longest diameters of target lesions.

- Of the 361 randomized patients, 235 and 115 comprised the sunitinib and placebo per-protocol populations, respectively, in the blinded phase of the study.
  - Ninety-four (39%) and 17 (14%) patients randomized to sunitinib or placebo, respectively, discontinued blinded treatment without crossing over to unblinded sunitinib treatment, with the primary reasons having been lack of efficacy (63 [26%] and eight [7%] patients, respectively) and AEs (23 [9%] and four [3%] patients, respectively).
- Of 247 patients who ultimately received open-label sunitinib treatment (due to disease progression or study unblinding), 148 and 99 had been randomized to the sunitinib or placebo groups, respectively. As of March 2008, 238 of these patients had discontinued treatment, with the primary reasons having been lack of efficacy (166 patients [67%]) and AEs (46 patients [19%]). Ten patients (4%) had completed treatment and nine patients (4%) were still on treatment.
- Ninety-nine of the 118 patients randomized to receive placebo (84%) crossed over to sunitinib treatment during the study (Figure 2). Although the crossover did not affect evaluation of the primary endpoint (TTP), it did make OS analyses more challenging because the placebo effect was no longer pure.
- Exposure to study drug across different phases of the trial is summarized in Table 2.

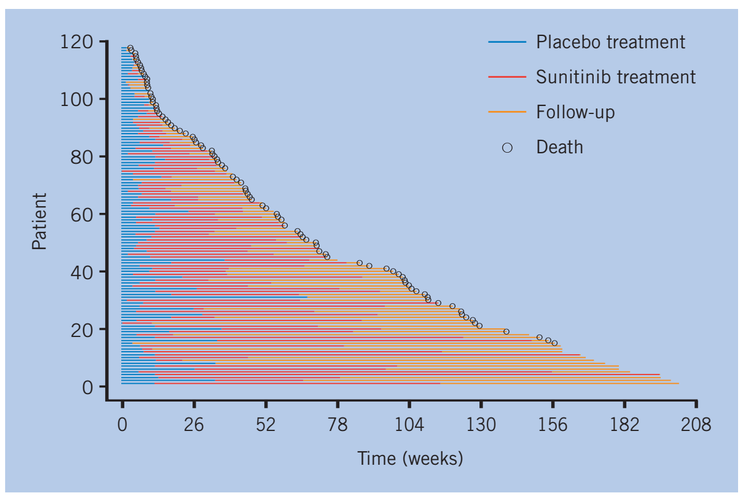

Figure 2. Treatment history of individual patients randomized to placebo.

Table 2. Exposure to study drug.*

	Blinded phase		Open-label phase	Blinded + open-label phases
	Sunitinib (n=235)	Placebo (n=115)	All patients† (n=247)	Sunitinib (n=241)
No. of cycles started: median (range)	2 (1–25)	1 (1–6)	5 (1–34)	6 (1–43)
Weeks on treatment:‡ median (range)	13 (2–153)	6 (2–36)	33 (1–185)	36 (2–214)§
Weeks on drug:¶ median (range)	8 (0.4–100)	4 (1–24)	21 (1–133)	22 (0.4–166)
Dose reductions: n (%)	27 (12)	0 (0)	72 (29)	67 (28)
Dose interruptions: n (%)	65 (28)	14 (12)	118 (48)	103 (43)
Reason for interruption: n (%)				
AE	54 (23)	10 (9)	97 (39)	86 (36)
Other	19 (8)	4 (4)	51 (21)	45 (19)
Missing	0 (0)	0 (0)	7 (3)	5 (2)

*Per-protocol population; †treatment = sunitinib, irrespective of randomization group; ‡from date of first dose to the earlier of termination date or 2 weeks after last dose; §n=234; ¶total number of days on which study drug was actually administered.

Efficacy

- The median TTP for the 99 patients randomized to receive placebo who crossed over to sunitinib treatment was 28.6 weeks (95% confidence interval [CI]: 22.0–41.0) and was similar to that observed during the blinded phase in the sunitinib group (28.9 weeks; 95% CI: 22.0–34.1). The median TTP for placebo-treated patients in the blinded phase was 6.4 weeks (95% CI: 4.4–10.1).
- Thirteen of these 99 patients achieved an objective partial response (for an ORR of 13%), compared with 19 patients (8%) on sunitinib in the blinded phase and none in the placebo group.
- The interim analysis of OS revealed that the relative risk of death was significantly reduced among patients randomized to sunitinib compared with those randomized to placebo, without the medians having been reached (hazard ratio [HR]: 0.49; 95% CI: 0.290–0.831; P=0.007; Figure 3A; Table 3).[11]
- With 84% of placebo-treated patients ultimately having crossed over to sunitinib (Figure 2), median OS estimated by the Kaplan–Meier method for the mature survival data was 73.9 weeks (95% CI: 61.3–85.7) vs. 64.9 weeks (95% CI: 45.7–96.0) for sunitinib and placebo, respectively. The OS results for the placebo group were confounded by the sunitinib treatment effect, and there was no statistically significant difference in OS between the groups (Figure 3B; Table 3).
- To address the bias created by the crossover of placebo patients to sunitinib treatment, OS analysis was performed using the RPSFT method, which yielded an estimated median OS for the placebo group of 35.7 weeks (95% CI: 25.7–49.8) based on the ITT population. This revealed a highly clinically significant sunitinib treatment effect (HR: 0.469; 95% CI: 0.277–0.873), comparable to that of the interim OS results (Figure 3C; Table 3).
- Superimposing the results obtained using RPSFT analysis of the mature OS data over those obtained in the interim analysis using the Kaplan–Meier method (Figure 3D) demonstrates the consistency between the two sets of results, further supporting the validity of the RPSFT method.

Safety and Tolerability

- Throughout the entire study, as in the blinded phase, the most common treatment-related AEs in the sunitinib arm were fatigue (47%), diarrhea (43%), nausea (36%), anorexia (28%), and dysgeusia (25%), which were mostly grade 1/2 (Table 4). The most common treatment-related grade 3/4 AEs were fatigue (10%), hypertension (7%), and hand–foot syndrome (6%).
- Incidences of non-hematologic AEs increased slightly with extended duration of sunitinib therapy.
- Over the entire study, in the group randomized to sunitinib, the incidence of treatment-related hypertension (all grades) was 19%. Treatment-related hypothyroidism (all grades) occurred in 13% of patients. The incidence of cardiac AEs of all grades was low (6%).
- For the patients randomized to sunitinib, across the entire study, hematologic laboratory abnormalities included reduced levels of hemoglobin (60%), neutrophils (59%), and platelets (41%), were mostly grade 1/2, and were similar in frequency to those of shorter-term sunitinib therapy (Table 5).

Table 3. OS estimated using different methods.

	Median (weeks; 95% CI)			
Phase of study	Sunitinib	Placebo	HR (95% CI)	P
Blinded phase, conventional methods*	Not reached	Not reached	0.491 (0.290–0.831)	0.007
Entire study, conventional methods	73.9 (61.3–85.7)	64.9 (45.7–96.0)	0.834 (0.647–1.076)	0.161
Entire study, RPSFT method	73.9 (61.3–85.7)	35.7 (25.7–49.8)	0.469 (0.277–0.873)†	0.161‡

*Interim analysis;[11] †empirical 95% CI was obtained using bootstrap samples; ‡a P value different than that derived by conventional methods cannot be assigned because OS derived using the RPSFT method is not based on observational data.

Table 4. Most common (>15%)* non-hematologic treatment-related AEs.†

	Blinded phase				Open-label phase		Blinded + open-label phases	
	Sunitinib (n=235)		Placebo (n=115)		All patients‡ (n=247)		Sunitinib§ (n=241)	
AE	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)
Fatigue	71 (30)	19 (8)	24 (21)	2 (2)	97 (39)	25 (10)	88 (37)	25 (10)
Diarrhea	73 (31)	8 (3)	9 (8)	0 (0)	77 (31)	11 (4)	92 (38)	12 (5)
Nausea	63 (27)	3 (1)	14 (12)	2 (2)	71 (29)	9 (4)	82 (34)	6 (2)
Anorexia	47 (20)	0 (0)	5 (4)	1 (1)	55 (22)	6 (2)	64 (27)	2 (1)
Dysgeusia	50 (21)	0 (0)	3 (3)	0 (0)	54 (22)	1 (0.4)	60 (25)	1 (0.4)
Vomiting	39 (17)	1 (0.4)	7 (6)	1 (1)	43 (17)	5 (2)	51 (21)	3 (1)
Yellow skin	42 (18)	0 (0)	5 (4)	0 (0)	51 (21)	0 (0)	49 (20)	0 (0)
Mucosal inflammation	34 (14)	2 (1)	0 (0)	0 (0)	40 (16)	5 (2)	44 (18)	4 (2)
Hypertension	21 (9)	11 (5)	5 (4)	1 (1)	36 (15)	19 (8)	29 (12)	18 (7)
Rash	35 (15)	2 (1)	6 (5)	0 (0)	36 (15)	1 (0.4)	43 (18)	3 (1)
Stomatitis	36 (15)	1 (0.4)	1 (1)	0 (0)	35 (14)	4 (2)	42 (17)	3 (1)
Dyspepsia	34 (14)	1 (0.4)	1 (1)	0 (0)	42 (17)	2 (1)	43 (18)	1 (0.4)
Headache	24 (10)	1 (0.4)	7 (6)	0 (0)	43 (17)	3 (1)	41 (17)	3 (1)
Hand–foot syndrome	19 (8)	9 (4)	1 (1)	0 (0)	44 (18)	13 (5)	30 (12)	14 (6)
Asthenia	28 (12)	6 (3)	2 (2)	2 (2)	28 (11)	12 (5)	30 (12)	13 (5)
Hair color changes	20 (9)	0 (0)	2 (2)	0 (0)	49 (20)	0 (0)	37 (15)	0 (0)

*Based on the sunitinib arm over the entire study; †per-protocol population; ‡treatment = sunitinib; §five grade 5 events deemed to be treatment-related occurred in this group (hepatic failure, left ventricular failure, cardiac arrest, cerebral ischemia, and multi-organ failure).

Table 5. Hematologic laboratory abnormalities.*

	Blinded phase				Open-label phase		Blinded + open-label phases	
	Sunitinib (n=235)		Placebo (n=115)		All patients† (n=247)		Sunitinib (n=241)	
Laboratory abnormality	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)	Grade 1/2 n (%)	Grade 3/4 n (%)
Hemoglobin	125 (53)	9 (4)	60 (52)	2 (2)	71 (29)	4 (2)	132 (55)	11 (5)
Neutrophils	106 (45)	24 (10)	4 (3)	0 (0)	58 (23)	16 (6)	113 (47)	28 (12)
Platelets	87 (37)	10 (4)	3 (3)	0 (0)	46 (19)	3 (1)	90 (37)	10 (4)

*Per-protocol population; †treatment = sunitinib.

Conclusions

- The long-term results from this phase III study reported here were consistent with the results obtained in the interim analysis,[11] demonstrating that sunitinib provides significant clinical benefit with acceptable tolerability to GIST patients resistant to or intolerant of imatinib.
- The long-term OS benefit of sunitinib relative to placebo was confirmed using RPSFT analysis.
  - With this method, the estimated median OS for patients on the sunitinib arm was twice that of patients on the placebo arm (73.9 weeks vs. 35.7 weeks; HR: 0.469).
  - This finding has implications for other crossover trials.
- Sunitinib demonstrated an acceptable and predictable safety profile with long-term treatment. AEs reported in sunitinib-treated patients were generally tolerable and manageable by dose reduction, dose interruption, or standard medical therapies.

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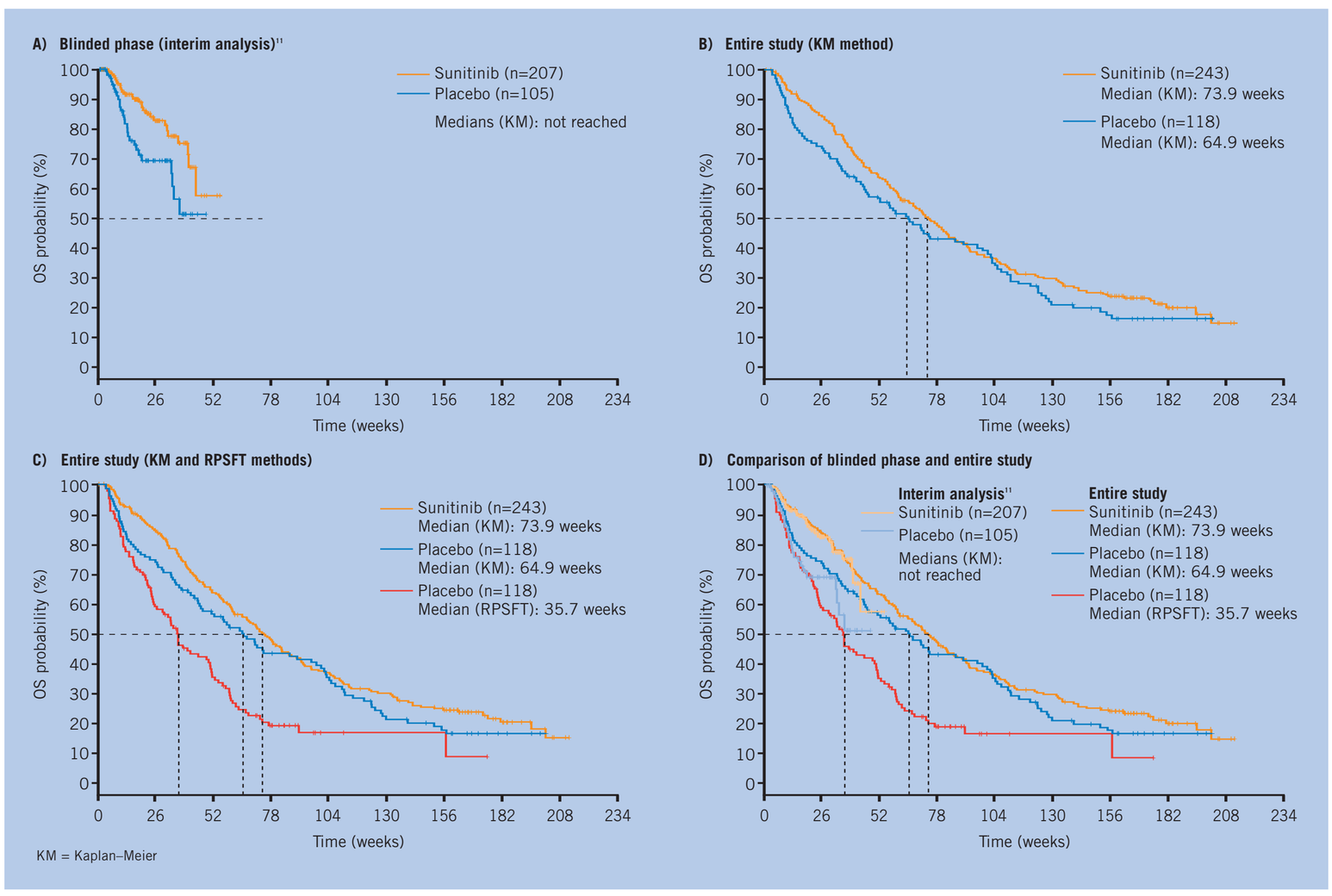

Figure 3. OS during different phases of the study.