Abstract 34980

Detailed Analysis of Survival and Safety with Sunitinib in a Worldwide Treatment-use Trial of Patients with Advanced Imatinib-resistant/intolerant GIST

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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-R1, and RET with direct antitumor and antiangiogenic activities.[5–10]
- Sunitinib has received multinational approval for the treatment of imatinib-resistant or -intolerant GIST and advanced renal cell carcinoma.

Objectives and Study Endpoints

- The main objective of this ongoing study is to provide access to sunitinib to GIST patients who might benefit from this therapy, but who are ineligible for sunitinib clinical trials because of pre-specified entry criteria, or for whom there are no GIST trials available in a particular country in which regulatory approval has not yet been granted.
- No formal hypothesis testing was planned, but the following clinical endpoints are evaluated:
  - safety and tolerability
  - objective response rate in patients with measurable disease
  - time to tumor progression (TTP)
  - overall survival (OS).

Methods

Study Population

- The study population comprises patients aged 18 years or older (country-specific protocol amendments allow patients as young as 12 years to enroll), meeting the following key patient inclusion criteria:
  - histologically confirmed malignant GIST that is not amenable to standard therapy with curative intent
  - undergone screening and found to be ineligible for participation in ongoing sunitinib clinical studies
  - the potential to derive clinical benefit from treatment with sunitinib, as judged by the investigator
  - failed prior treatment with imatinib mesylate, defined either as progression of disease or as significant toxicity that precluded further treatment with imatinib
  - resolution of all acute toxic effects of prior therapy or surgical procedure to grade ≤1
  - adequate organ function.
- Patients meeting any of the following criteria are excluded:
  - current treatment in another clinical trial
  - symptomatic central nervous system metastases
  - symptomatic congestive heart failure, myocardial infarction, or coronary artery bypass graft in the previous 6 months
  - ongoing severe or unstable angina or unstable arrhythmia requiring medication
  - pregnancy or breastfeeding
  - any severe acute or chronic medical or psychiatric condition or laboratory abnormality making the patient inappropriate for entry into the study.

Study Design and Dosing Regimen

- This is an ongoing, multicenter, open-label treatment-use trial.
- Sunitinib is administered to patients in repeated 6-week cycles at a starting dose of 50 mg once daily on a 4/2 schedule (4 weeks on treatment, followed by 2 weeks off treatment). Provision is made for dose reduction in the event of toxicity.
- Treatment is continued for as long as there is evidence of disease control in the judgment of the investigator. Survival is monitored for up to 2 years after the last dose of sunitinib.

Assessment

- Tumor measurements/assessments are performed as per local standard of care.
- Safety and tolerability are assessed by monitoring adverse events (AEs) and laboratory abnormalities, and by physical examination.
- Toxicities are graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 3.0.

Statistical Analysis

- The number of patients to be enrolled was not predetermined and no inferential analyses were planned due to the nature of this study.
- Descriptive statistics (mean, standard deviation, median, minimum and maximum values) are utilized to summarize all continuous data. All categorical data are summarized using frequencies and percentages.
- The study population for updated efficacy and safety analyses includes all patients enrolled in the study receiving at least one dose of sunitinib (intent-to-treat [ITT] population).
- TTP and OS are estimated using the product-limit method of Kaplan and Meier.

Results

Patient Characteristics

- As of December 2007, 1,126 patients were enrolled in the study and 1,117 patients comprised the ITT population.
- Patient baseline characteristics and prior treatment history are summarized in Table 1.

Table 1. Baseline patient characteristics and prior treatment history.

	Sunitinib (N=1,117)
Age in years, median (range)	59 (10–92)*
Male/female, n (%)	665 (60)/451 (40)*
ECOG PS, n (%)	
0	420 (38)
1	515 (46)
2	134 (12)
>2	38 (3)
Missing	10 (1)
GIST histology, n (%)	
Epithelioid	120 (11)
Spindle cell	589 (53)
Epithelioid and spindle cell	148 (13)
Other	252 (23)
Missing	8 (1)
Previous systemic chemotherapy, n (%)	
Yes	225 (20)
No	839 (75)
Missing	53 (5)
Previous radiotherapy, n (%)	
Yes	78 (7)
No	983 (88)
Missing	56 (5)
Reason for stopping imatinib, n (%)	
PD within 6 months of start	150 (13)
PD beyond 6 months of start	862 (77)
Intolerance	104 (9)
Missing	1 (0.1)
Time between last imatinib dose and first sunitinib dose in days, median (range)	15 (1–1,423)†

ECOG PS = Eastern Cooperative Oncology Group performance status;
PD = progressive disease.
*One patient missing; †25 patients missing.

Treatment

- Patients had started a median of five cycles of sunitinib treatment (range, 1–33) and were treated (period from first dose to termination or 2 weeks after last dose) for a median of 30 weeks (range, 0.1–152).
- Overall, 661 patients (59%) had dose interruptions, of which 79% were due to an AE. Four hundred and sixty-five patients (42%) had dose reductions, of which 70% were to 37.5 mg, 29% were to 25 mg, and 1% was to 12.5 mg (these patients had their daily dose prescribed below 50 mg for any reason at any time during the study).
- Nine hundred and six patients (81%) discontinued treatment for any reason (Table 2).

Table 2. Patient disposition.

	Sunitinib (N=1,117), n (%)
Missing/ongoing	199 (18)
Completed treatment	12 (1)
Discontinuations	906 (81)
Reason for discontinuation	
AE	214 (19)
Consent withdrawn	166 (15)
Lack of efficacy	510 (46)
Other	16 (1)

Efficacy

- The ITT population was followed up for a median of 51 weeks (range, 0.1–159).
- The median estimated TTP was 41 weeks (95% CI: 36–47; Figure 1A).
- Five hundred and sixty-four patients (50%) in the ITT population were alive at time of data cut-off. The median estimated OS was 75 weeks (95% CI: 68–84; Figure 1B).

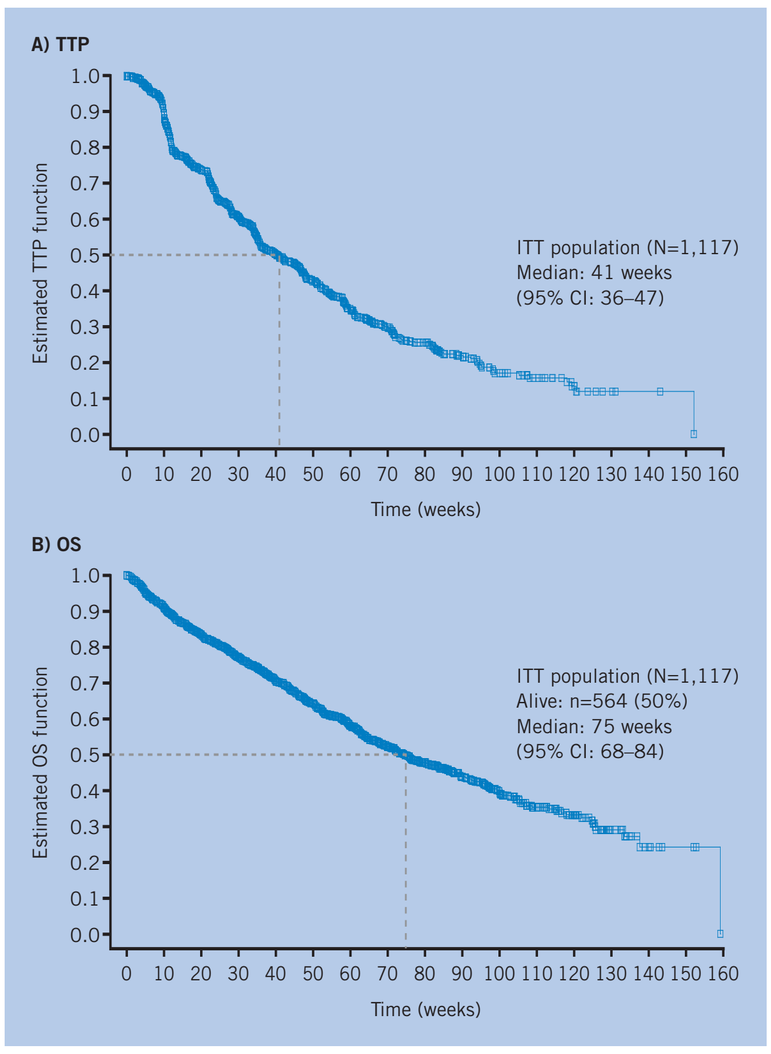

Figure 1. Overall TTP and OS with sunitinib.

- Figure 2 compares survival data for subgroups based on individual baseline factors and prior imatinib treatment history.

Safety

- Fatigue (42%), diarrhea (39%), and nausea (28%) were the most commonly reported treatment-related non-hematologic AEs (Table 3). These were mainly grade 1 or 2 in severity.
- Fatigue (8%), hand–foot syndrome (8%), hypertension (5%), and diarrhea (5%) were the most commonly reported treatment-related non-hematologic grade 3/4 AEs.
- Treatment-related hypothyroidism (all grades) was reported in 10% of patients.
- Treatment-related hematologic AEs included thrombocytopenia (19%), neutropenia (18%), and anemia (14%; Table 4). Most events were grade 1 or 2. Febrile neutropenia was reported in only three patients.

Table 3. Most common (≥20%) treatment-related non-hematologic AEs.

	Sunitinib (N=1,117)			
AE	Grades 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total* n (%)
Fatigue	374 (33)	88 (8)	3 (0.3)	465 (42)
Diarrhea	383 (34)	55 (5)	0 (0)	439 (39)
Nausea	291 (26)	23 (2)	0 (0)	315 (28)
Hand–foot syndrome	210 (19)	86 (8)	2 (0.2)	298 (27)
Anorexia	230 (21)	22 (2)	1 (0.1)	253 (23)
Mucosal inflammation	229 (21)	20 (2)	1 (0.1)	250 (22)
Stomatitis	228 (20)	20 (2)	1 (0.1)	249 (22)
Hypertension	188 (17)	58 (5)	2 (0.2)	248 (22)
Vomiting	210 (19)	25 (2)	2 (0.2)	237 (21)

*Twenty-three grade 5 events deemed to be treatment-related have occurred in the study, including one case of diarrhea and one of nausea.

Table 4. Treatment-related hematologic AEs.

	Sunitinib (N=1,117)			
AE	Grades 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Thrombocytopenia	156 (14)	44 (4)	13 (1)	213 (19)
Neutropenia	119 (11)	76 (7)	6 (1)	201 (18)
Anemia	108 (10)	37 (3)	14 (1)	159 (14)

- Treatment-related AEs related to cardiac function included heart failure, congestive heart failure, myocardial infarction, reduced ejection fraction, and pulmonary edema (all ≤0.6%; Table 5).
- Incidences of grade 3/4 laboratory abnormalities associated with renal function included hyponatremia (5%), hypocalcemia (4%), and elevated creatinine levels (3%).
- Incidences of grade 3/4 laboratory abnormalities associated with liver function included elevated lipase (8%), alkaline phosphatase (5%), total bilirubin (4%), aspartate aminotransferase (3%), alanine aminotransferase (3%), and amylase (1%).

Table 5. Treatment-related AEs related to cardiac function.

	Sunitinib (N=1,117)				
AE	Grades 1–2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Heart failure*	1 (0.1)	4 (0.4)	0 (0)	2 (0.2)	7 (0.6)
Congestive heart failure	2 (0.2)	2 (0.2)	2 (0.2)	0 (0)	6 (0.5)
Myocardial infarction	0 (0)	0 (0)	1 (0.1)	1 (0.1)	2 (0.2)
Ejection fraction†	2 (0.2)	1 (0.1)	0 (0)	0 (0)	3 (0.3)
Pulmonary edema	0 (0)	1 (0.1)	0 (0)	0 (0)	1 (0.1)

*Includes acute heart failure.
†Includes reduced ejection fraction.

Conclusions

- Based on results from this treatment-use trial, sunitinib appears to be generally well tolerated in patients with imatinib-resistant or -intolerant advanced GIST who were ineligible for other sunitinib clinical trials.
- The safety profile observed in this study was similar to that seen with sunitinib in a prior phase III GIST study,[11] with most AEs mild to moderate in severity.
- Sunitinib was effective in the treatment of patients with advanced GIST after imatinib failure, corroborating previous studies. The median estimated TTP and OS from this ongoing study are 41 and 75 weeks, respectively.
- Subgroup analysis suggested that age, ECOG PS, and prior imatinib dosage may be important prognostic factors affecting the clinical outcome in this patient population, but further studies are required to confirm this.

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Acknowledgements

This study was supported by funding from Pfizer Inc.
Editorial assistance was provided by ACUMED® (Tytherington, UK) with funding from Pfizer Inc.
Presented at the Connective Tissue Oncology Society 14th Annual Meeting, London, UK, November 13–15, 2008.

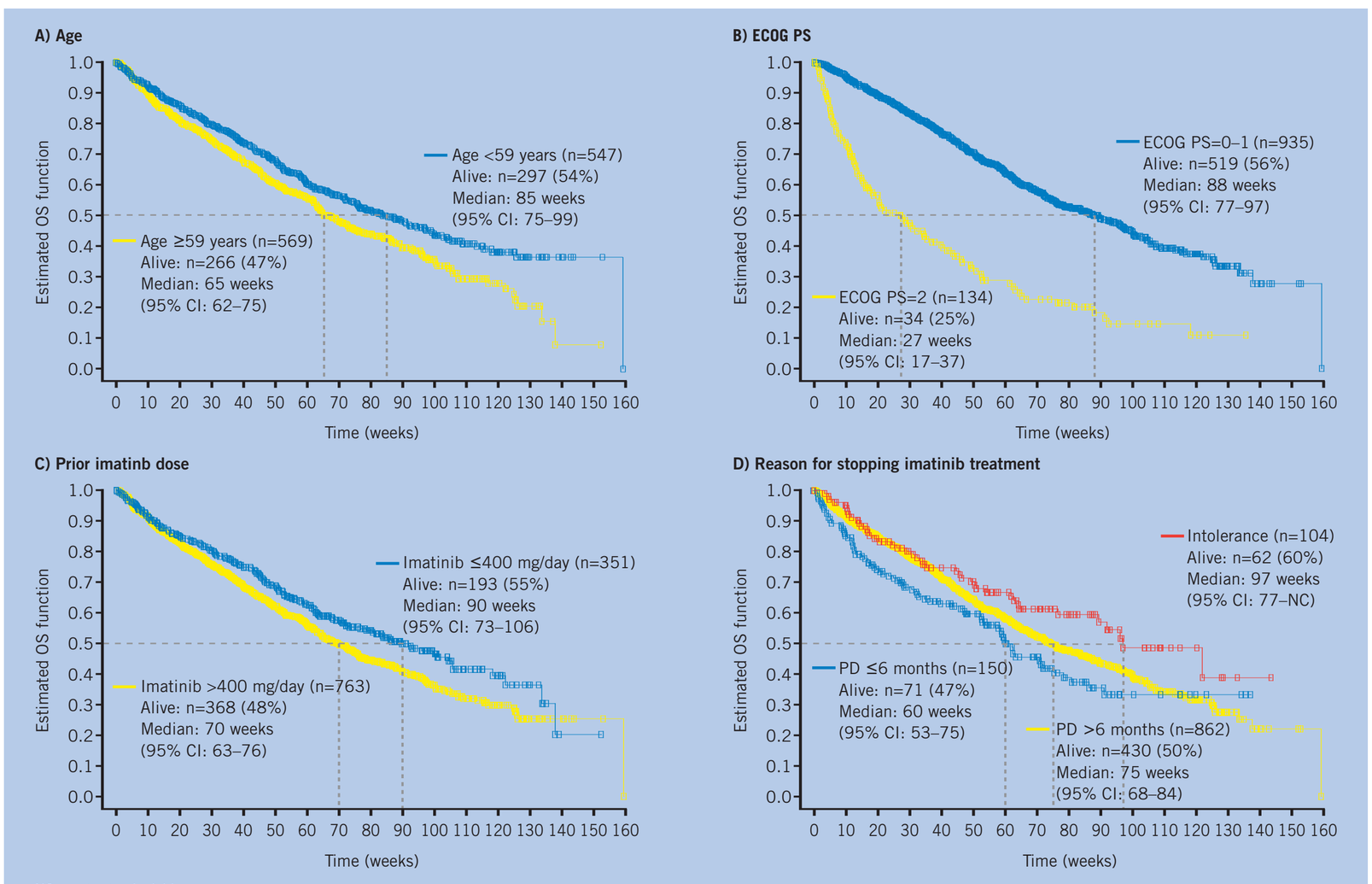

Figure 2. OS for subgroups based on individual baseline factors and prior imatinib treatment history.