

Phase III Randomized, Intergroup Trial Assessing Imatinib Mesylate At Two Dose Levels in Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing the Kit Receptor Tyrosine Kinase: S0033

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A B S T R A C T

Purpose

To assess potential differences in progression-free or overall survival when imatinib mesylate is administered to patients with incurable gastrointestinal stromal tumors (GIST) at a standard dose (400 mg daily) versus a high dose (400 mg twice daily).

Patients and Methods

Patients with metastatic or surgically unresectable GIST were eligible for this phase III open-label clinical trial. At registration, patients were randomly assigned to either standard or high-dose imatinib, with close interval follow-up. If objective progression occurred by Response Evaluation Criteria in Solid Tumors, patients on the standard-dose arm could reregister to the trial and receive the high-dose imatinib regimen.

Results

Seven hundred forty-six patients with advanced GIST from 148 centers across the United States and Canada were enrolled onto this trial in 9 months. With a median follow-up of 4.5 years, median progression-free survival was 18 months for patients on the standard-dose arm, and 20 months for those receiving high-dose imatinib. Median overall survival was 55 and 51 months, respectively. There were no statistically significant differences in objective response rates, progression-free survival, or overall survival. After progression on standard-dose imatinib, 33% of patients who crossed over to the high-dose imatinib regimen achieved either an objective response or stable disease. There were more grade 3, 4, and 5 toxicities noted on the high-dose imatinib arm.

Conclusion

This trial confirms the effectiveness of imatinib as primary systemic therapy for patients with incurable GIST but did not show any advantage to higher dose treatment. It appears reasonable to initiate therapy with 400 mg daily and to consider dose escalation on progression of disease.

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors affecting the gastrointestinal tract. Previously, no systemic treatment had shown meaningful clinical activity against GISTs, and patients who could not be cured surgically had a grim prognosis.¹⁻³ The potential effectiveness of tyrosine kinase inhibitors, however, was well supported. Many untreated GISTs express a single mutated oncogenic kinase, usually KIT (85% to 88% of cases), while a smaller percentage of patients possess oncogenic mutations in the platelet-derived growth factor receptor α

gene (PDGFR α ; 5% to 7%) or have no detectable kinase mutations (10%).^{4,5}

Imatinib mesylate is an oral small-molecule competitive inhibitor of multiple tyrosine kinases, including KIT and PDGFR α .⁶⁻⁸ Preclinical studies on GIST cell lines confirmed antineoplastic activity, as did early clinical trials.⁹⁻¹³ On these trials, patients were assigned to imatinib at doses ranging from 400 to 800 mg daily, with no dose clearly showing superiority. A randomized phase II study of 400 versus 600 mg of daily imatinib showed no significant differences in any efficacy end points.^{12,13} This trial, S0033, was designed to compare the progression-free and overall survival

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rates for conventional dose imatinib versus higher doses, in patients with advanced GISTs.

PATIENTS AND METHODS

Patients were required to have measurable or nonmeasurable, visceral or intra-abdominal biopsy-proven GISTs, which were not surgically curable. Tumors had to express CD117 by immunohistochemical staining with the DAKO (Carpenteria, CA) antibody. Patients had to be ≥ 15 years old, possess a Zubrod performance status 0 to 3, and they could not have any known brain metastases. Although any number of prior chemotherapy regimens were allowed, no prior drugs (including biologic therapy) were allowed within 28 days of registration, nor was surgery permissible within 14 days. Toxicities from prior therapy must have resolved to \leq grade 1. Adequate renal, hepatic, and hematopoietic function were required. Patients were excluded if they exhibited class 3 or 4 cardiac problems or any severe medical conditions. Patients could not be pregnant or nursing. Computed tomography/magnetic resonance imaging or pertinent physical examination was required within 28 days before registration. Therapeutic coumadin was not allowed, but low-molecular weight heparin and prophylactic mini-dose coumadin were acceptable. Institutional review board approval at each participating center and written informed consent from each subject were obtained (Fig 1).

Dosage and Administration

On registration, patients were randomly assigned by the Southwest Oncology Group (SWOG) Statistical Center to one of two dose levels of imatinib, using a dynamic balancing algorithm program stratified by Zubrod performance status (0 to 2 v 3) and disease status (measurable v nonmeasurable). Patients on arm A received 400 mg of imatinib orally once daily, and patients assigned to arm B received 400 mg of imatinib twice daily. There was no blinding of drug administration. Patients were treated until disease progression or unacceptable toxicity. Toxicities were assessed using the National Cancer Institute Common Toxicity Criteria, version 2.0.¹⁴

Imatinib was withheld in the event of any clinically significant \geq grade 2 toxicity, until resolution to \leq grade 1, except as noted in "Hematologic Toxicity." If event was grade 2, imatinib could be reintroduced at the same dose, whereas any grade 3 or 4 toxicities required in mandatory dose reduction on restarting imatinib (400 mg reduced to 300 mg daily on arm A; 800 mg reduced to 400 mg on arm B). A second dose reduction following similar rules was allowed (to 200 or 300 mg daily, respectively). No dose delays or modifications were required for hematologic grade 2 toxicities. The use of growth factors was permitted but not recommended.

Required assessments included history and physical examinations at day 7 and at least monthly for 6 months, then every 3 months. Complete blood counts were performed weekly, and liver function testing twice monthly for the first 2 months, then monthly times 6, then every 3 months. Radiographic

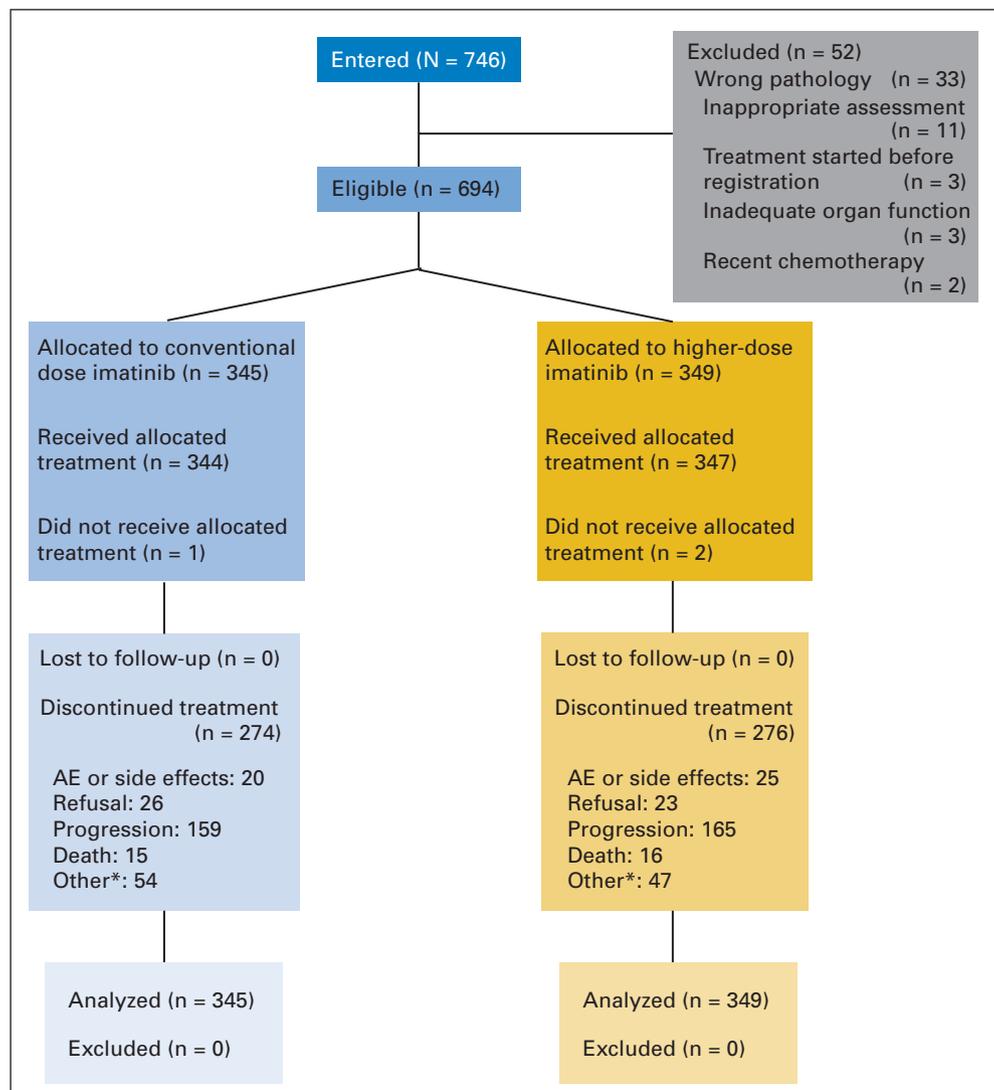


Fig 1. CONSORT diagram. AE, adverse event.

assessments were performed at the end of month 2 and then every 3 months thereafter. Radiographic assessments were performed using the same modality as had been performed at baseline. Responses were assessed by Response Evaluation Criteria in Solid Tumors (RECIST), and confirmation of any response was required after 4 weeks.

If progression was documented, patients initially randomly assigned to high-dose imatinib were removed from study protocol and offered continued care per local standard. Patients whose GISTs progressed objectively on conventional-dose imatinib could crossover to high-dose imatinib, as long as they continued to meet the eligibility criteria specified for initial trial entry.

Statistical Considerations

The primary end points for this study were progression-free and overall survival. Assuming an 18-month median progression-free survival on the conventional-dose imatinib regimen, the a priori hypothesis was that high-dose drug would be judged superior if there were a true relative increase in survival of 40%. The study had a goal of enrolling 600 eligible patients, with accrual estimated to take 2 years, plus an additional year of follow-up. This sample size was sufficient to detect a hazard ratio for survival of 1.4 with 85% power, using a two-sided test, with a .05 significance level. This sample size would allow the detection of a hazard ratio of 1.4 for progression-free survival with 92% power.

All eligible patients were included in the survival analysis, by assigned treatment and according to the intent-to-treat principle. Patients who were never treated were not included in the toxicity analyses. All survival curves were calculated using the Kaplan-Meier product limit method.¹⁵

The following potential prognostic factors were investigated for impact on survival using Cox regression models: age, sex, race (white *v* nonwhite), performance status (0 to 1 *v* 2 to 3), lung involvement (yes or no), time since initial diagnosis, primary disease site (small bowel *v* other), baseline WBC count, hemoglobin level, absolute neutrophil and platelet counts, and baseline albumin (≤ 3.5 *v* > 3.5 g/dL). Initially each factor was assessed in univariate fashion. Factors found to be significant ($P = .05$) were included in multivariate models. The multivariate analyses of progression-free and overall survival models were assessed using backward selection.

RESULTS

Seven hundred forty-six patients were entered between December 15, 2000, and September 1, 2001, from SWOG, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, M.D. Anderson Cancer Center (Houston, TX), and the National Cancer Institute of Canada. Fifty-two (6.9%) were ineligible for the following reasons: central pathology review (31 patients; 14 were KIT- and 17 diagnosed with other histologies), disease not appropriately assessed before registration ($n = 10$), initiation of treatment before registration ($n = 3$), inadequate organ function ($n = 3$), revised institutional pathology review ($n = 2$), prior chemotherapy within 28 days ($n = 2$), and prestudy labs not completed within 14 days ($n = 1$). Thus, this analysis was based on 694 patients. Median follow-up for active patients was 4.5 years.

Patient characteristics were well-balanced between arms (Table 1). Median age was 61.9 and 61.5 years on arms A and B, respectively. Fifty-four percent in each arm were male, and 96% each had a performance status of 0 to 2. The overwhelming majority (94% and 95%) had measurable disease.

Antitumor Response

The overall benefits of imatinib were consistent with previous reports (Table 2). There were no significant differences in response rates between arms. For patients on arm A, complete responses were seen in 5% and confirmed partial responses in 40%, for an overall

Table 1. Patient Characteristics at Study Entry

Characteristic	STI-571			
	400 mg/day (n = 345)		800 mg/day (n = 349)	
	No.	%	No.	%
Age, years				
Median		61.9		61.5
Range		18-87		18-94
Sex				
Male	187	54	189	54
Female	158	46	160	46
Race/ethnicity				
White	273	79	289	83
Black	37	11	37	11
Asian	25	7	20	6
Pacific Islander	2	1	0	0
Native American	2	1	1	0
Unknown	6	2	2	1
Performance status				
0-2	332	96	336	96
3	13	4	13	4
Type of disease				
Measurable	323	94	333	95
Nonmeasurable	22	6	16	5

response rate of 45%. An additional 9% of patients had unconfirmed responses. On arm B, complete responses were seen in 3% and confirmed partial responses in 42%, for an overall objective response rate of 45%. In addition, 7% of patients on arm B had unconfirmed responses. Stable disease was seen in 25% of patients on arm A and 22% on arm B. Progressive disease was equivalent across both arms, occurring in 12% and 10%, respectively.

Of the 345 eligible patients randomly assigned to conventional-dose imatinib, 278 have progressed or died, with a median progression-free survival of 18 months (95% CI, 16 to 21 months) and a 2-year progression-free survival rate of 41% (95% CI, 36% to 47%; Fig 2). Two hundred sixty-seven of 349 eligible patients randomly assigned to high-dose imatinib progressed or died with a median progression-free survival of 20 months (95% CI, 17 to 25 months) and a 2-year progression-free survival of 46% (95% CI, 41% to 51%). Progression-free survival did not differ significantly between arms (two-sided $P = .13$ adjusted for stratification).

Overall survival was clearly not superior with administration of high-dose imatinib. Of the 345 eligible patients on arm A, 168 died,

Table 2. Best Response to Imatinib

Response	STI-571			
	400 mg/day		800 mg/day	
	No.	%	No.	%
Complete response	17	5	12	3
Partial response	137	40	148	42
Stable/no response	85	25	76	22
Progressive disease/early death	42	12	37	10
Assessment inadequate	34	10	52	15
Total	345	100	349	100

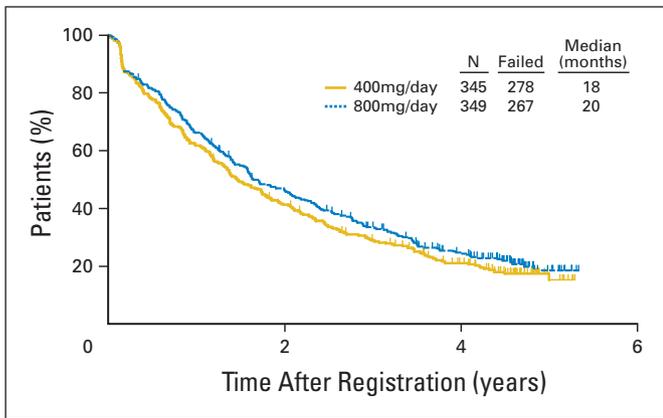


Fig 2. Progression-free survival.

with a median overall survival of 55 months (95% CI, 47 to 62 months) and a 2-year overall survival estimate of 76% (95% CI, 72% to 81%; Fig 3). On the high-dose imatinib arm, 174 of 349 eligible patients died, with a median overall survival of 51 months (95% CI, 46 to 60 months) and a 2-year survival estimate of 72% (95% CI, 67% to 77%); two-sided of $P = .83$, adjusted for stratification. The estimated hazard ratio of conventional-dose to high-dose imatinib is 0.98 (95% CI, 0.79 to 1.21).

Central pathology review was performed retrospectively on 432 patients. Three hundred ninety-five (91%) were judged to be KIT-positive GISTs. Thirteen (3%) were KIT-negative GISTs. The response rates and progression-free survival did not differ by KIT expression status (negative, median progression-free survival of 16 months; 95% CI, 2 to 25 months; and positive, median progression-free survival of 21 months; 95% CI, 18 to 25 months; Appendix Fig A1, online only). Although arising from an unplanned subset analysis, a significant difference in overall survival was noted in favor of the KIT-positive GISTs compared with KIT-negative GISTs (median overall survival 53 v 31 months, $P = .02$; Appendix Fig A2, online only).

Safety and Tolerability

Imatinib was reasonably well tolerated overall, although mild to moderate toxicities were common. Sixty-eight of patients (20%) on arm A, and ninety-two on arm B (27%) experienced \geq grade 3

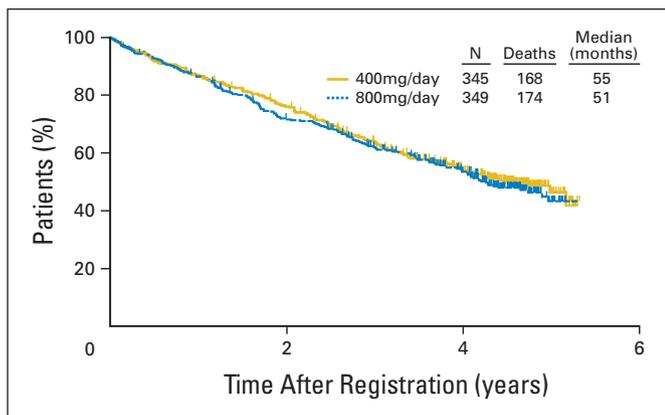


Fig 3. Overall survival.

hematologic toxicity (Table 3). Specifically, 32 on arm A (9%) and 47 on arm B (14%) experienced \geq grade 3 anemia, with 24 (7%) and 34 (10%), respectively, demonstrating severe or greater neutropenia. Twenty-one patients (6%) and forty-eight patients (14%), respectively, had grade 3 to 5 cardiac toxicity. Thirty-one patients (9%) and fifty-four patients (16%) had grade 3 or 4 gastrointestinal toxicity, manifested as nausea or diarrhea. Eighteen patients (5%) and thirty-eight patients (11%) had grade 3 to 5 hemorrhage. Overall, serious adverse events and deaths were more common in the high-dose imatinib arm, as were dose delays and reductions. Overall, 149 patients (43%) on arm A experienced grade 3 to 5 toxicities. Two-hundred nineteen (63%) on high-dose imatinib had grade 3 to 5 toxicities. Two low-dose patients (1%) and nine high-dose patients (3%) experienced possible treatment-related deaths: four high-dose patients died from gastrointestinal bleeding. One high-dose patient died from cerebrovascular ischemia, one from shortness of breath and bronchitis, and another from infection combined with arrhythmia, liver failure, and confusion. Two other unspecified deaths cannot be ruled out as treatment-related.

Dose Modifications/Delivered Dose Intensity

Information on dose modifications was available on 330 patients for those enrolled on the conventional-dose arm, and for 333 on the high-dose arm (Appendix Table A1, online only). For patients on arm A, at least one dose delay was recorded in 124 patients (38%), and 52 (16%) had at least one dose reduction, most commonly from rash, edema, or gastrointestinal bleeding. For patients initially randomly assigned to arm B, 198 patients (59%) had at least one dose delay and 192 (58%) had at least one dose reduction due primarily to edema, nausea, or fatigue. Seventy-seven patients crossing over to high-dose imatinib had complete dosing information. In this subset, 18 patients (23%) had at least one dose delay and 14 (18%) had at least one dose reduction, due to edema or rash. Thus, reductions in ideally planned dose intensity occurred in approximately 40% of patients on the trial, with dose reductions being significantly more common ($P < .0001$) in patients treated initially with high-dose imatinib. Clinical outcomes were compared for patients who received full-dose therapy versus patients who required at least one dose delay or reduction. There were no differences noted in estimated progression-free or overall survival.

Additional Results After Crossover

After progression of disease, 133 patients randomly assigned to conventional-dose imatinib were subsequently registered to the high-dose crossover arm. One patient subsequently died from cardiac ischemia and another from gastrointestinal bleeding, while nine others (7%) reported grade 4 toxicities. Of the 117 patients assessable for response following crossover, three had confirmed partial responses, for a response rate of 3% (95% CI, 1% to 7%). Thirty-three patients (28%; 95% CI, 20% to 37%) experienced stable disease. Of the 118 eligible patients with follow-up, 99 died or progressed with a median progression-free survival of 5 months (95% CI, 2 to 10 months; Fig 4, online only). In the crossover cohort, 76 have died with a median overall survival of 19 months (95% CI, 13 to 23 months) starting from the date of registration to crossover (Appendix Fig A3, online only).

Prognostic Factors

The following cofactors were identified in univariate analysis as statistically significant with respect to progression-free survival: sex, performance status, baseline WBC count, absolute neutrophil count,

Table 3. Grade 3-5 Adverse Events Related to Treatment

Adverse Event	STI-571												
	400 mg/day (n = 344)						STI-571 800 mg/day (n = 347)						
	Grade						Grade						
	3		4		5		3		4		5		
No.	%	No.	%	No.	%	No.	%	No.	%	No.	%		
Death, cause undetermined	0	0	0	0	0	0	0	0	0	0	0	2	1
Allergy/immunology	0	0	0	0	0	0	1	< 0.5	0	0	0	0	0
Auditory/hearing	0	0	0	0	0	0	1	< 0.5	0	0	0	0	0
Blood/bone marrow	52	15	15	4	1	< 0.5	65	19	27	8	0	0	0
Cardiovascular													
Arrhythmia	5	2	0	0	0	0	3	1	0	0	1	< 0.5	
General	15	4	3	1	0	0	36	10	8	2	0	0	
Constitutional symptoms	12	4	2	1	0	0	27	8	2	1	1	< 0.5	
Dermatology/skin	13	4	1	< 0.5	0	0	25	7	1	< 0.5	0	0	
Gastrointestinal	28	8	3	1	0	0	51	15	3	1	0	0	
Hemorrhage	14	4	2	1	2	1	27	8	7	2	4	1	
Hepatic	12	4	0	0	0	0	7	2	5	1	1	< 0.5	
Infection/febrile	13	4	2	1	0	0	18	5	3	1	2	1	
Neutropenia													
Metabolic/laboratory	7	2	0	0	0	0	7	2	3	1	0	0	
Musculoskeletal	2	1	0	0	0	0	2	1	0	0	0	0	
Neurology	9	3	3	1	0	0	8	2	0	0	2	1	
Ocular/visual	0	0	0	0	0	0	2	1	0	0	0	0	
Pain	35	10	2	1	0	0	38	11	4	1	0	0	
Pulmonary	5	2	2	1	0	0	13	4	0	0	0	0	
Renal/genitourinary	3	1	0	0	0	0	5	1	2	1	0	0	
Syndrome	0	0	0	0	0	0	1	< 0.5	0	0	0	0	
Maximum grade for any adverse event	120		27		2		162		48		9		

platelets, hemoglobin, and albumin (Appendix Table A2, online only). Multivariate analyses showed that patients with performance status of 2 to 3 ($P < .0001$) and patients with high baseline absolute neutrophil counts ($P = .0008$) had worse progression-free survival. In addition, the following prognostic factors were identified as statistically significant for overall survival in univariate analysis: age, sex, performance status, prior chemotherapy, maximum tumor diameter, baseline WBC count, platelets, hemoglobin, absolute neutrophil count, bilirubin, and baseline albumin (Appendix Table A3, online only). Multivariate analyses showed that older age ($P = .0017$), poorer

performance status ($P < .0001$), male sex ($P = .0279$), high absolute neutrophil counts ($P = .0009$), and low albumin ($P = .0030$) were significantly associated with worse overall survival.

DISCUSSION

Molecularly targeted therapy with imatinib mesylate can inhibit the etiologic aberrant cell signaling mechanisms in GISTs, leading to major objective responses and prolonged disease control. Prior studies have noted that imatinib can be effectively and safely administered across a broad dose range.¹¹⁻¹³ Specifically, the US-Finland phase II randomized trial in GISTs identified both 400 and 600 mg daily as safe and effective doses,¹³ and the US Food and Drug Administration approved both doses for patients with advanced GISTs in 2002. An European Organisation for Research and Treatment of Cancer (EORTC) trial in GISTs identified the maximum tolerated dose of imatinib for treatment of GIST as 800 mg daily; however, higher dose levels were associated with unacceptably severe gastrointestinal irritation and edema.^{11,16} As early phase studies did not clearly identify an optimal imatinib dose, this large-scale phase III randomized clinical trial was designed to test whether high-dose imatinib (800 mg daily) might enhance clinical benefits compared with conventional dose (400 mg daily). This study is now reported with median follow-up time of 4.5 years, enhancing the robustness of the overall survival analysis.

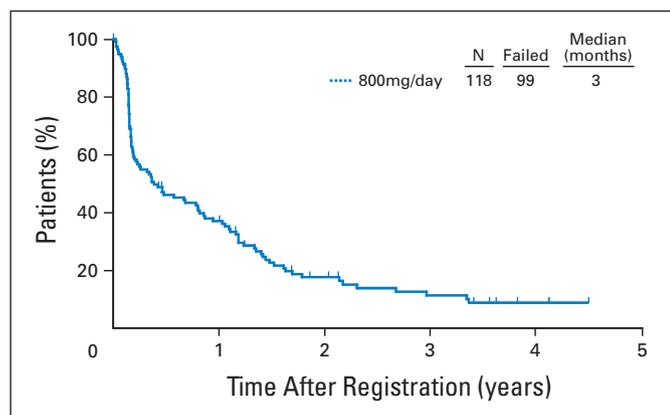


Fig 4. Progression-free survival cross over.

This randomized trial confirmed substantial clinical activity for imatinib, at either dose. Median 2-year survival of patients with presumed GISTs on prior SWOG chemotherapy trials (S8616 and S9627) was 26%. This can be contrasted with the higher than 70% 2-year survival for patients treated on S0033. No significant clinical or statistical superiority was noted for high-dose imatinib as initial therapy for patients with advanced GISTs, compared with conventional-dose imatinib. In addition, tolerability of high-dose imatinib as initial therapy was significantly less favorable than conventional-dose imatinib with a greater incidence of severe (including fatal) adverse events.

A somewhat larger EORTC phase III trial, utilizing identical treatment arms, initially reported a statistically significant improvement in progression-free survival for patients with GISTs who received 800 mg of daily imatinib.¹⁷ With further follow-up, the difference in progression-free survival became statistically insignificant.¹⁸ Neither the current trial nor the EORTC-led trial found higher-dose imatinib led to any other major clinical benefits such as improved response rates or higher stable disease rates. Importantly, neither trial indicates any suggestion of an overall survival benefit from the high-dose imatinib. The design of both trials was intentionally made similar, and results will be combined in a preplanned meta-analysis.

Objective response rates on S0033 may be artifactually low as a result of the use of RECIST. These criteria have recently been reported to be less than ideal, because responding GISTs which become cystic can actually enlarge, a change coded as progressive disease under RECIST. Indeed, a recent study found responses using RECIST did not correlate with time to progression, though changes in tumor density were linked to ultimate outcome.¹⁹ In addition, S0033 may have shown lower than expected response rates because of the requirement of confirmation of response. Unconfirmed responses occurred in 9% and 7% of patients on arms A and B, respectively.

There were substantial differences between median progression-free and median overall survival for both treatment groups. Several possible explanations exist. As stated earlier, RECIST may erroneously declare patients to have progressive disease, when they truly are responding or at least stable. Second, many trial participants stayed on imatinib even after being found to have progressed. Resistance to imatinib and perhaps other tyrosine kinase inhibitors is not all or nothing. Some clones in the progressing patient may retain imatinib sensitivity, as suggested by the strong anecdotal data patients with slowly progressive disease taken off imatinib may become ill from cancer and die very quickly. Finally, imatinib was the only active agent known for GISTs when this trial was started. Sunitinib was subsequently US Food and Drug Administration–approved for use in advanced GISTs, and multiple other drugs entered clinical testing. It is possible patients taken off study were given effective salvage agents.

This trial found that patients with GISTs that progressed on conventional-dose imatinib still have a reasonable chance of achieving disease control by escalating dose. This phenomenon was also noted in previous phase II and III trials of imatinib.^{12,14,20} Approximately 25% to 33% of patients who dose escalate stop progressing and do not need other salvage therapies for variable periods. Patients who dose escalate after taking 400 mg daily also appear to tolerate higher doses better. The benefit from dose escalation makes it even more reasonable for patients with advanced GISTs to start treatment with 400 mg per day and to escalate to 800 mg if progression occurs.

This trial showed several factors were associated with better progression free (good performance status, low baseline absolute neutrophil counts) or overall (young age, good performance status, female sex, low absolute neutrophil counts, and high albumin) survival. The EORTC phase III trial reported low baseline hemoglobin and high baseline granulocyte levels predicted for early resistance to imatinib, while large tumor size, high granulocyte count, nongastric primary tumor, and treatment with 400 mg daily were independently associated with late resistance.²¹ None of these factors on S0033 showed an interaction with treatment dose, however, and they are not suitable for use in selecting whether to offer patients 400 or 800 mg of imatinib. It is possible that mutational analysis may help in dose selection. The EORTC phase III trial showed patients with exon 9 mutations had superior progression-free survival when initially treated with a higher dose of imatinib (800 v 400 mg daily).²² These data, as well as a combined mutational meta-analysis of S0033 and EORTC information, were strong enough for the National Comprehensive Cancer Network to recommend, in a nonuniform consensus statement, the use of higher-dose drug for patients with known exon 9 mutations.²³ Final analyses from S0033, as well as the combined mutational meta-analysis of S0033 and EORTC data, are pending.

In summary, this trial confirmed the safety and efficacy of imatinib mesylate when used to treat patients with incurable GISTs. It showed 800 mg daily, versus 400 mg daily, is a more toxic but not more effective dose. Four hundred mg daily remains the standard of care when imatinib is used to treat incurable GISTs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).