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Ten-Year Progression-Free and Overall Survival in Patients With Unresectable or Metastatic GI Stromal Tumors: Long-Term Analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group Intergroup Phase III Randomized Trial on Imatinib at Two Dose Levels

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ABSTRACT

Purpose
To report on the long-term results of a randomized trial comparing a standard dose (400 mg/d) versus a higher dose (800 mg/d) of imatinib in patients with metastatic or locally advanced GI stromal tumors (GISTs).

Patients and Methods
Eligible patients with advanced CD117-positive GIST from 56 institutions in 13 countries were randomly assigned to receive either imatinib 400 mg or 800 mg daily. Patients on the 400-mg arm were allowed to cross over to 800 mg upon progression.

Results
Between February 2001 and February 2002, 946 patients were accrued. Median age was 60 years (range, 18 to 91 years). Median follow-up time was 10.9 years. Median progression-free survival times were 1.7 and 2.0 years in the 400- and 800-mg arms, respectively (hazard ratio, 0.91; $P = .18$), and median overall survival time was 3.9 years in both treatment arms. The estimated 10-year progression-free survival rates were 9.5% and 9.2% for the 400- and 800-mg arms, respectively, and the estimated 10-year overall survival rates were 19.4% and 21.5%, respectively. At multivariable analysis, age (< 60 years), performance status ($0 \ v \geq 1$), size of the largest lesion (smaller), and *KIT* mutation (exon 11) were significant prognostic factors for the probability of surviving beyond 10 years.

Conclusion
This trial was carried out on a worldwide intergroup basis, at the beginning of the learning curve of the use of imatinib, in a large population of patients with advanced GIST. With a long follow-up, 6% of patients are long-term progression free and 13% are survivors. Among clinical prognostic factors, only performance status, *KIT* mutation, and size of largest lesion predicted long-term outcome, likely pointing to a lower burden of disease. Genomic and/or immune profiling could help understand long-term survivorship. Addressing secondary resistance remains a therapeutic challenge.

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INTRODUCTION

After the earliest informal reports of patients with advanced GI stromal tumors (GISTs) responding to the new agent imatinib, which was originally developed to target BCR-ABL in chronic myeloid leukemia, at the end of 2000, the decision was made to launch two twin clinical trials in North America and in Europe and Australia.[1-3] The trials were designed as randomized trials testing two different dose levels of imatinib, 400 and 800 mg daily.[4,5] The aim was to optimize the dosing of a drug that anecdotally was already known to be extraordinarily active and thus also to enable more patients with GIST to receive the drug

ASSOCIATED CONTENT

Appendix
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Data Supplement
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sooner in several countries. GIST had been defined as a separate entity just a few years earlier; these tumors were differentiated from mesenchymal neoplasms only during the 1990s and recognized as being marked by a characteristic driving oncogene mutation.[6,7] Imatinib was one of the first molecularly targeted drugs available in medical oncology.[8]

A total of 946 patients were entered onto this trial from 10 countries and two continents over approximately 1 year, whereas the US trial enrolled 746 patients over the same interval. Although it was already known that chemotherapy was largely inactive in GIST,[9] a significant added value of this trial was that clinicians worldwide had the formidable opportunity to learn new patterns of tumor response, the occurrence of secondary resistance, the potential of surgery for responding or progressing disease, and so forth. Hundreds of patients received imatinib before its approval by regulatory agencies, beginning in 2002.[10] With a long follow-up, it is logical to use these trials to look at the long-term impact of imatinib in advanced GIST. The first analyses of the two European-Australian and US trials were published in 2004 and 2008, respectively.[4,5] With a median follow-up in excess of 10 years, we report here on the updated analysis of our trial, coordinated by the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group and carried out on an intergroup basis with the Italian Sarcoma Group and the Australasian Gastrointestinal Trials Group.

PATIENTS AND METHODS

Study Design and Participants

This randomized, open-label, phase III study was open for accrual between February 2001 and February 2002 in 56 centers from 13 countries in Europe and Australia, New Zealand, and Singapore. Details on the study design have been published.[4] Main eligibility criteria included histologically proven advanced or metastatic GIST characterized by c-KIT expression. Patients were not required to have measurable disease. Previous chemotherapy was accepted but had to be discontinued for more than 4 weeks before study entry. Other criteria included age 18 years or older, WHO performance status less than 4, absolute neutrophil count greater than 1.5×10^9/L, platelet count greater than 100×10^9/L, serum creatinine up to 1.5× the upper limit of normal, and total bilirubin less than 1.5× the upper limit of normal. Genomic DNA was not foreseen as per protocol but was carried out on a subgroup of patients. Details have been published separately.[4] Institutional review boards approved the study protocol according to applicable laws in all participating countries. All patients gave written informed consent.

Eligible patients were randomly assigned centrally at the European Organisation for Research and Treatment of Cancer headquarters, via Internet or phone, to receive imatinib 400 mg either once a day or twice a day (800-mg daily dose). A minimization technique was used, stratified by hospital, measurability of disease (measurable *v* nonmeasurable), and performance status (0 to 2 *v* 3). Treatment allocation was not masked.

The study drug was taken orally once a day or twice a day (depending on the allocated treatment arm), directly after a meal. Dose modifications for adverse events were done according to the protocol. After dose reduction, re-escalation was not allowed. However, in case of disease progression in a patient allocated to 400 mg once daily, the patient was allowed to cross over to 400 mg twice daily, irrespective of the dose the patient was taking at the time of progression. Clinical assessments of safety, including medical history and physical examination, and laboratory assessments were done at baseline, every week during the first 2 months, every month between months 3 and 6, and every 3 months thereafter. Computed tomography scans were performed after 2, 4, and 6 months and every 3 months thereafter until disease progression. Treatment was continued until disease progression, unacceptable toxic effects (grade 3 or 4 adverse events that could not be resolved by comedication or dose reduction), or patient refusal. All patients were observed for survival (until death from any cause or withdrawal of consent).

In the subset of patients tested for mutations, *KIT* exons 9, 11, 13, and 17 were examined, and if any of these were detected, *PDGFRA* exons 12 and 18 were explored. If there were no mutations to these exons, patients were coded as wild type.[11]

Outcomes

The primary end point was progression-free survival (PFS), which was measured from the date of random assignment to the date of documented progression or death, whatever the cause. Patients who were alive and progression free at the last follow-up were censored. Secondary end points included overall survival (OS), response, safety, and quality of life. OS was measured from the date of random assignment to the date of death, whatever the cause. Patients alive at the time of the analysis were censored at the date of last follow-up. Response was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0.[12] Best response achieved from the entire period of protocol treatment (including after crossover from 400 mg once daily to twice daily) is reported. The response rate (RR) represents the proportion of patients achieving a complete and/or partial response.

For patients crossing over upon progression to 400 mg twice daily, PFS after crossover was determined from date of crossover to date of progression or death. In these patients, the growth modulation index (GMI) was estimated as the ratio of PFS after crossover to PFS before crossover (ie, PFS after crossover/PFS before crossover). A GMI greater than 1.33 has been proposed as an indication of an active next-line treatment.[13]

Statistical Analysis

The time-to-event end points of OS and PFS were estimated using the Kaplan-Meier method. The difference between the treatment arms is reported in terms of the estimated hazard ratio (HR) and corresponding CI and compared using a two-sided log-rank test. Comparison of RR between the treatment groups was done using a χ^2 test. Prognostic factors among baseline covariates were identified with univariable log-rank tests and multivariable Cox regression using backward selection for PFS and OS and with univariable χ^2 tests and multivariable logistic regression incorporating backward selection for RR.

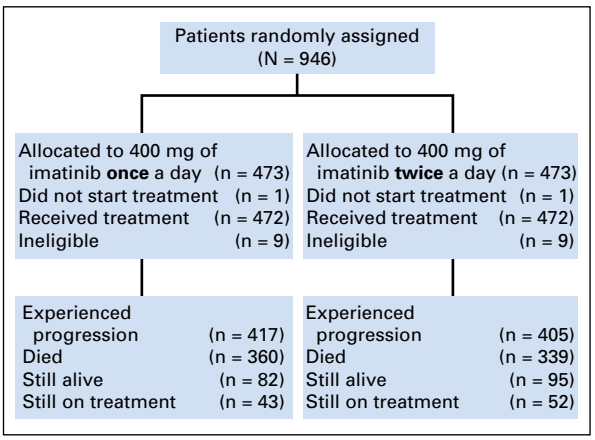

Fig 1. CONSORT diagram.

Table 1. Baseline Characteristics and Best Overall Response to Treatment

Characteristic and Response	No. of Patients (%)		
	Treatment		
	400 mg/d (n = 473)	800 mg/d (n = 473)	Total (N = 946)
Age, years			
< 40	38 (8.0)	34 (7.2)	72 (7.6)
40-50	87 (18.4)	89 (18.8)	176 (18.6)
50-60	122 (25.8)	106 (22.4)	228 (24.1)
60-70	138 (29.2)	144 (30.4)	282 (29.8)
> 70	88 (18.6)	100 (21.1)	188 (19.9)
Median	60	61	60
Interquartile range	49-67	50-69	49-68
WHO performance status			
0	217 (45.9)	219 (46.3)	436 (46.1)
1	191 (40.4)	192 (40.6)	383 (40.5)
2	48 (10.1)	44 (9.3)	92 (9.7)
3	17 (3.6)	18 (3.8)	35 (3.7)
Sex			
Male	283 (59.8)	290 (61.3)	573 (60.6)
Female	190 (40.2)	183 (38.7)	373 (39.4)
Time since primary diagnosis, months			
< 12	247 (52.2)	246 (52.0)	493 (52.1)
12-24	83 (17.5)	74 (15.6)	157 (16.6)
> 24	143 (30.2)	153 (32.3)	296 (31.3)
Prior treatment			
Surgery	410 (86.7)	392 (82.9)	802 (84.8)
Radiotherapy	26 (5.5)	37 (7.8)	63 (6.7)
Chemotherapy	156 (33.0)	155 (32.8)	311 (32.9)
Site of origin			
Abdominal	58 (12.3)	72 (15.2)	130 (13.7)
Gastric	161 (34.0)	158 (33.4)	319 (33.7)
Small bowel	124 (26.2)	114 (24.1)	238 (25.2)
Other GI	120 (25.4)	119 (25.2)	239 (25.3)
Other	10 (2.1)	10 (2.1)	20 (2.1)
Site of active disease			
Primary tumor	150 (31.7)	168 (35.5)	318 (33.6)
Liver	325 (68.7)	344 (72.7)	669 (70.7)
Lymph node	49 (10.4)	66 (14.0)	115 (12.2)
Lung	41 (8.7)	40 (8.5)	81 (8.6)
Bone	7 (1.5)	12 (2.5)	19 (2.0)
Skin	7 (1.5)	4 (0.8)	11 (1.2)
Brain	1 (0.2)	0 (0.0)	1 (0.1)
KIT mutation present			
Exon 11	118 (24.9)	130 (27.5)	248 (26.2)
Exon 9	28 (5.9)	34 (7.2)	62 (6.6)
Wild type	50 (10.6)	33 (7.0)	83 (8.8)
Other	10 (2.1)	13 (2.8)	23 (2.4)
Unknown	267 (56.4)	263 (55.6)	530 (56.0)
Baseline diameter largest lesion, mm			
Median	80.0	80.0	80.0
Range	10.0-800.0	10.0-370.0	10.0-800.0
Q1-Q3	50.0-120.0	49.0-120.0	50.0-120.0
Best overall response to treatment			
CR	33 (7.0)	32 (6.8)	65 (6.9)
PR	208 (44.0)	236 (49.9)	444 (46.9)
SD	160 (33.8)	141 (29.8)	301 (31.8)
PD	49 (10.4)	40 (8.5)	89 (9.4)
Early death	7 (1.4)	11 (2.3)	18 (1.9)
Unevaluable	16 (3.4)	13 (2.7)	29 (3.1)

Abbreviations: CR, complete response; PD, progressive disease; PR, partial response; Q, quartile; SD, stable disease.

Logistic regression analyses, adjusting for censoring before the considered cutoffs, were performed to investigate the association between baseline characteristics (including age, performance status, sex, prior surgery, prior radiotherapy, prior chemotherapy, site of metastases, and time between diagnosis and random assignment) and the probability of remaining progression free beyond 10 years and the probability of surviving beyond 10 years. This was done using the pseudo-value regression technique.[14,15]

All tests were performed with a significance level of $P = .05$ in the intent-to-treat population. This analysis is based on all clinical data received before the clinical cutoff date May 27, 2013.

RESULTS

In this study, 946 patients were randomly assigned to receive either imatinib 400 mg once daily (n = 473) or imatinib 400 mg twice daily (800 mg; n = 473). As summarized in Figure 1, 18 patients were ineligible for the study; six of these patients had another type of cancer, four had ineligible concomitant disease, and eight were ineligible for miscellaneous reasons. At the time of this analysis, the median follow-up time was 10.9 years (interquartile range, 8.1 to 11.3 years). Details of patient baseline characteristics have been reported previously.[4] Table 1 lists the most important clinical features by treatment arm. Thirty-three patients had nonmeasurable (but still visible) disease.

At the time of the analysis, 95 patients were still on protocol treatment. The major reason for protocol discontinuation was disease progression (67.6% of patients in both arms), followed by patient refusal (7.0% in 400-mg arm *v* 4.5% in 800-mg arm) and toxicity (5.3% in 400-mg arm *v* 5.9% in 800-mg arm). Among the 95 patients still on protocol treatment, median time on treatment was 9.6 years (interquartile range, 6.4 to 11.1 years). One hundred seventy-five patients underwent surgery while on study (35 and 96 patients underwent excision of residual responding disease and progressive disease, respectively).

No significant difference was observed between the two treatment arms in terms of PFS (HR for 400 mg *v* 800 mg, 0.91; 95% CI, 0.79 to 1.04; $P = .18$; Fig 2A) or OS (HR, 0.93; 95% CI, 0.80 to 1.07; $P = .31$; Fig 2B). Eight hundred twenty-two patients (417 and 405 patients in the 400- and 800-mg arms, respectively) were reported to have experienced progression on treatment. Six hundred ninety-nine patients (360 and 339 patients in the 400- and 800-mg arms, respectively) were reported to have died on study, including 596 patients (310 *v* 286 in 400- and 800-mg arm, respectively) as a result of progressive disease and/or toxicity, 14 as a result of cardiovascular disease, 13 as a result of infection unrelated to imatinib, 13 as a result of intercurrent death, two as a result of pulmonary complications, and 36 as a result of other reasons. For 25 patients, the cause of death is unknown. The estimated 10-year PFS rates were 9.5% and 9.2% for the 400- and 800-mg arms, respectively, and the estimated 10-year OS rates were 19.4% and 21.5%, respectively. Sixty-five patients (33 *v* 32 patients in the 400- and 800-mg arms, respectively) achieved a complete response, and 444 patients (208 *v* 236 patients, respectively) achieved a partial response (Table 1). There was no significant difference in RR between the two arms ($P = .08$).

Prognostic Factors

Appendix Table A1 (online only) reports on the univariable and multivariable prognostic factor analysis for PFS. Performance status, prior chemotherapy, diameter of longest lesion, and *KIT* mutation were found to be statistically significantly associated with PFS in univariable analyses as well as in a multivariable Cox regression model. Note that in the latter model, unknown *KIT* mutation status was taken into account as a separate category to reduce loss of patient information in the model estimation. In addition, *KIT* mutation status was confirmed to be predictive for PFS ($P = .01$; Fig 3A), whereby patients with a *KIT* exon 9 mutation significantly benefit from treatment with imatinib 800 mg daily (HR, 0.40; 95% CI, 0.22 to 0.72).

Appendix Table A2 (online only) summarizes the results of the prognostic factor analysis for OS. In the univariable analyses, age, performance status, prior surgery, prior radiotherapy, prior chemotherapy, diameter of longest lesion, and *KIT* mutation were found to be significantly associated with survival. Prior surgery and radiotherapy did not remain statistically significant prognostic factors in a multivariable model adjusting for the other baseline covariates, whereas sex became significant. *KIT* mutation status was not found to be prognostic for OS ($P = .23$; Fig 3B), but patients with a *KIT* exon 9 mutation had a significantly better survival with imatinib 800 mg daily (HR, 0.54; 95% CI, 0.31 to 0.96).

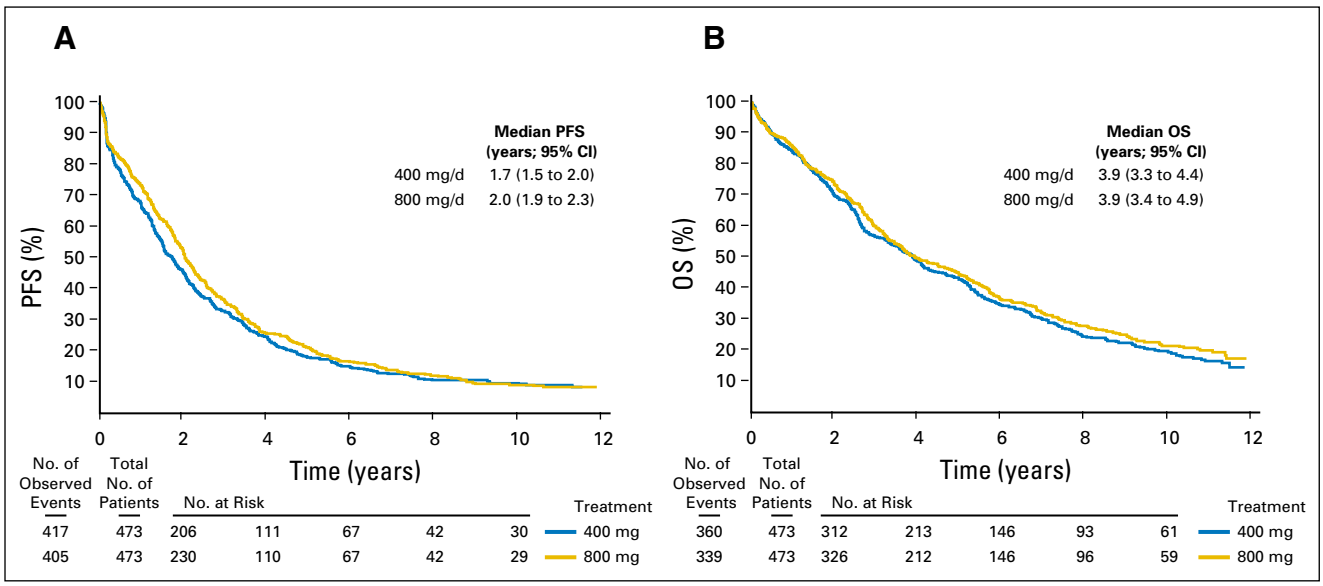

Fig 2. Kaplan-Meier plots of (A) progression-free survival (PFS) and (B) overall survival (OS).

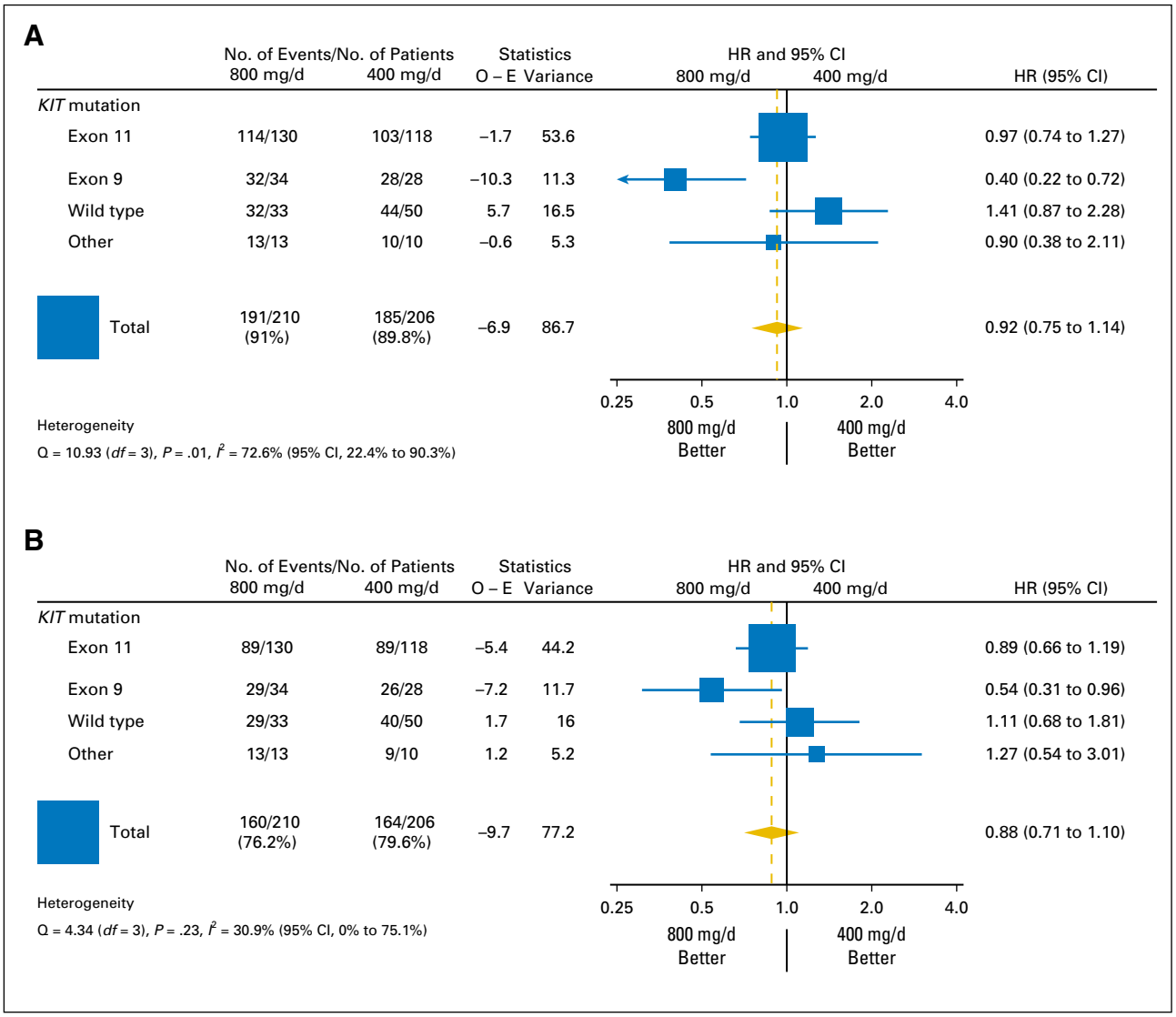

Fig 3. Forest plots for the interaction effect of *KIT* mutation status on treatment in predicting (A) progression-free survival and (B) overall survival. E, expected; HR, hazard ratio; O, observed.

Univariable prognostic factor analyses for RR only identified *KIT* mutation status as significant ($P < .01$), where patients with a *KIT* exon 11 mutation had a significantly higher odds of achieving a response compared with patients with *KIT* exon 9 mutations (odds ratio [OR], 4.35; 95% CI, 2.44 to 7.96), wild-type *KIT* (OR, 11.1; 95% CI, 5.88 to 20), or other mutation (OR, 3.13; 95% CI, 1.31 to 7.69).

Special Patient Subgroups

At the time of analysis, 59 patients (6.2%) had been alive and progression free for ≥ 10 years, whereas 69 patients (7.3%) were censored before 10 years. The baseline characteristics of these 59 patients are listed in Table 2. Table 2 also lists the results of the multivariable prognostic factor analysis, performed to assess the impact of the different baseline covariates on the probability of remaining progression free for at least 10 years, while adjusting for censoring before 10 years. Only the size of the largest lesion was identified as being significantly prognostic. In fact, the probability of remaining progression free for at least 10 years decreases as long as the lesion size increases.

Table 2 lists the baseline characteristics of the 120 patients (12.7%) who were still alive after 10 years of follow-up; 144 patients are considered censored before 10 years. The corresponding multivariable analysis, adjusting for censoring before 10 years, showed that age (< 60 years), performance status (0 *v* ≥ 1), size of the largest lesion (smaller), and *KIT* mutation (exon 11) were significant prognostic factors for the probability of surviving beyond 10 years.

Crossover

Of 417 patients in the 400-mg arm who experienced progression, 196 patients crossed over after progression according to protocol to the 800-mg arm, 103 continued imatinib off protocol, and 116 stopped imatinib entirely; for two patients, no follow-up data were available. Of the 196 patients who crossed

Table 2. Baseline Characteristics of Special Patient Subsets

Characteristic	Patients Progression Free at 10 Years (n = 59)			10-Year Survivors (n = 120)			Total Patients (N = 946), No. (%)
		Reduced Multivariable Model (backward selection)			Reduced Multivariable Model (backward selection)		
	No. of Patients (%)	Odds Ratio (95% CI)	*P*	No. of Patients (%)	Odds Ratio (95% CI)	*P*	
Treatment group, mg							
400	30 (50.8)			61 (50.8)			473 (50.0)
800	29 (49.2)			59 (49.2)			473 (50.0)
Age group, years						.03 (*df* = 3)	
< 40	4 (6.8)			13 (10.8)	1.00		72 (7.6)
40-50	11 (18.6)			23 (19.2)	0.57 (0.29 to 1.13)		176 (18.6)
50-60	19 (32.2)			40 (33.3)	0.82 (0.45 to 1.52)		228 (24.1)
≥ 60	25 (42.4)			44 (36.7)	0.48 (0.26 to 0.87)		470 (49.7)
Performance status						< .01 (*df* = 2)	
0	39 (66.1)			80 (66.7)	1.00		436 (46.1)
1	15 (25.4)			34 (28.3)	0.52 (0.35 to 0.79)		383 (40.5)
≥ 2	5 (8.5)			6 (5.0)	0.31 (0.10 to 0.95)		127 (13.4)
Sex							
Male	32 (54.2)			68 (56.7)			573 (60.6)
Female	27 (45.8)			52 (43.3)			373 (39.4)
Time since primary diagnosis, months							
< 12	30 (50.8)			59 (49.2)			493 (52.1)
12-24	11 (18.6)			21 (17.5)			157 (16.6)
> 24	18 (30.5)			40 (33.3)			296 (31.3)
KIT mutation						.01 (*df* = 2)	
Exon 11	17 (28.8)			38 (31.7)	1.00		248 (26.2)
Non–exon 11	5 (5.5)			10 (8.3)	0.24 (0.09 to 0.61)		168 (17.8)
Unknown	37 (62.7)			72 (60.0)	0.84 (0.56 to 1.25)		530 (56.0)
Prior treatment							
Surgery	52 (88.1)			104 (86.7)			802 (84.8)
Radiotherapy	3 (5.1)			4 (3.3)			63 (6.7)
Chemotherapy	15 (25.4)			35 (29.2)			311 (32.9)
Site of origin							
Abdominal	8 (13.6)			15 (12.5)			130 (13.7)
Gastric	21 (35.6)			40 (33.3)			319 (33.7)
Small bowel	15 (25.4)			30 (25.0)			238 (25.2)
Other GI	14 (23.7)			33 (27.5)			239 (25.3)
Other	1 (1.7)			2 (1.7)			20 (2.1)
Site of metastases (noncumulative overview)							
Primary tumor	21 (35.6)			39 (32.5)			318 (33.6)
Lymph node	4 (6.8)			11 (9.2)			115 (12.2)
Lung	3 (5.1)			4 (3.3)			81 (8.6)
Liver	44 (74.6)			83 (69.2)			669 (70.7)
Bone	0 (0.0)			0 (0.0)			19 (2.0)
Brain	0 (0.0)			0 (0.0)			1 (0.1)
Skin	0 (0.0)			0 (0.0)			11 (1.2)
Ascites	2 (3.4)			3 (2.5)			66 (7.0)
Pleural effusion	5 (8.5)			6 (5.0)			30 (3.2)
Baseline diameter of largest lesion, mm			.01 (*df* = 1)			< .01 (*df* = 1)	
Median	59.0	0.90* (0.83 to 0.97)		57.0	0.89* (0.83 to 0.95)		80.0
Range	15.0-240.0			10.0-260.0			10.0-800.0
Quartile 1-quartile 3	42.0-100.0			38.0-100.0			50.0-120.0
Unknown	4 (6.8)			6 (5.0)			30 (3.2)

*Per 10-mm increase.

over according to protocol, discontinuation has been documented for 194 patients, and median time on imatinib after crossover was estimated to be 3.6 months (95% CI, 2.6 to 4.7 months). One year after crossover, 17.4% of patients were estimated to still be on protocol treatment. PFS after crossover for these patients is compared with time to first progression in the same patient population in Figure 4. Thirty-four patients achieved a GMI greater than 1.33, whereas 145 patients had a GMI ≤ 1.

DISCUSSION

We report here a large, randomized, clinical trial performed in 946 patients with advanced GIST treated with imatinib by a community of researchers from 58 institutions on two continents at the beginning of their learning curve regarding this new molecularly targeted agent. With a median follow-up of more than 10 years, slightly less than 10% and 15% of patients became long-term

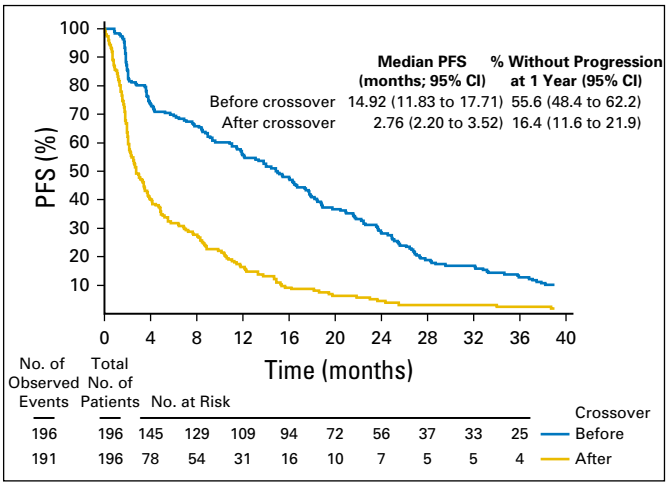

Fig 4. Progression-free survival before and after crossover of patients in the 400 mg/d arm to 800 mg/d arm (n = 196).

progression-free and long-term overall survivors, respectively. Median OS was 3.9 years, and median PFS was 1.9 years. An imatinib-sensitive mutational status and a low initial tumor burden were favorable prognostic factors, being related to a good tumor response and a good progression-free interval, respectively.[11,16]

With regard to the formal objective of this trial, which was comparing 400 *v* 800 mg of imatinib, data from the two twin trials point to a lack of any difference. Unfortunately, mutational analysis could not be foreseen by the protocol, given the time when the study was conceived. Thus, only a subset of patients were genotyped. The benefit in PFS for exon 9–mutated patients starting at 800 mg was already reported in a meta-analysis of the two twin trials.[17] Likewise, we had already reported the benefit of dose escalation to 800 mg at the time of progression.[18] In principle, open issues are which patient subgroups may benefit from dose escalation on progression and whether a policy of planned dose escalation on progression is actually inferior to starting at 800 mg for patients with exon 9 mutations. Starting at 800 mg in patients with exon 9–mutated GIST is recommended by some clinical practice guidelines, although there are regulatory barriers in some countries. Unfortunately, a formal comparison between starting at 400 mg, with subsequent escalation, and starting at 800 mg was unfeasible given the data available in this trial, because dose escalation was not carried out regularly and a selection bias would flaw any comparison.

The greater than 900 patients who were entered onto this trial may be viewed as having inherently unfavorable prognostic factors, because they were selected from patients waiting for any treatment at the time. Thus, their tumor burden was substantial, on average, and likely larger than that of average patients with advanced GIST who are starting imatinib today. Indeed, this study and others showed that tumor burden is a prognostic factor.[16] In addition, centers were at the beginning of their learning curve. Finally, GISTs are rare cancers that had been defined just a few years before this study.[6,19] All of these factors add to the value of these long-term results, which basically confirm the sharp improvement in PFS and OS that occurred in the past 15 years for patients with metastatic GIST. Indeed, the prognosis of patients with advanced GIST starting imatinib today might be better overall. However, secondary resistance has been proven to be a major limiting factor of molecularly targeted therapies in advanced solid cancers. In fact, in this trial, only 10% of patients were progression free at 10 years.

Indeed, the presence of a distinct, albeit limited, subset of long-term survivors, and even progression-free survivors, is of high interest clinically and biologically. It is still to be determined whether a subset of patients with metastatic GIST are liable to be cured by a highly active molecularly targeted agent such as imatinib. Many of these patients are continuing their treatment, because stopping therapy was demonstrated to result in tumor progression in most patients, although data are lacking in the subgroup of long-term survivors. A minority of patients in this study underwent surgery of residual disease, including responsive residual disease, but no conclusion can be drawn as a result of the small number of patients and the highly variable selection criteria for surgery, which was clearly unplanned as per protocol. The effect of surgery is the subject of a separate analysis.

Unfortunately, no major convincing clinical prognostic factors seem to predict for long-term survivorship, let alone progression-free survivorship. From this and other studies, we have learned that in advanced GIST the almost only predictive factor for response to imatinib is genotype. The main predictive factor for duration of response is tumor burden. No other relevant predictive or prognostic factors seem to exist, according to the best data available today, for long-term survivorship, assuming that good PS and the lack of previous chemotherapy are surrogates for disease burden. In other words, it is still to be determined whether the presence of a subgroup of long-term progression-free survivors is just the expression of the stochastic mechanisms of tumor resistance, being the tail of a random Gaussian distribution, or is the product of distinct features. Given the nature of this trial, we were unable to carry out any genomic profiling, immune characterization, and the like. Efforts to this end are ongoing in small series; however, the limited number of patients with GIST and their dispersion are obvious limiting factors. We hope that collaborative efforts on a global scale may be commenced. At this time, to improve GIST treatment, the priority is to try and prevent secondary resistance to tyrosine kinase inhibitors, either through other agents or by combinations or rotations of new or available agents, in the adjuvant and advanced settings.

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Disclosures provided by the authors are available with this article at jco.org.

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Appendix

Table A1. Univariable and Multivariable Analysis of Prognostic Factors for Progression-Free Survival

	Univariable Analysis		Multivariable Model After Backward Selection (N = 913)	
Covariate	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Treatment, mg		.18 (*df* = 1)		
400	1.00			
800	0.91 (0.79 to 1.04)			
Age, years		.17 (*df* = 4)		
< 40	1.00			
40-50	1.07 (0.79 to 1.44)			
50-60	1.08 (0.81 to 1.45)			
60-70	0.98 (0.74 to 1.30)			
> 70	1.26 (0.93 to 1.69)			
Performance status		< .01 (*df* = 3)		< .01 (*df* = 3)
0	1.00		1.00	
1	1.22 (1.05 to 1.41)		1.17 (1.00 to 1.36)	
2	1.74 (1.38 to 2.20)		1.52 (1.19 to 1.95)	
3	2.45 (1.73 to 3.47)		2.16 (1.51 to 3.10)	
Sex		.38 (*df* = 1)		
Male	1.00			
Female	0.94 (0.82 to 1.08)			
Time between diagnosis and registration, months		.69 (*df* = 2)		
< 12	1.00			
12-24	0.95 (0.79 to 1.16)			
> 24	0.94 (0.80 to 1.09)			
Prior surgery		.11 (*df* = 1)		
No	1.00			
Yes	0.86 (0.71 to 1.04)			
Prior radiotherapy		.10 (*df* = 1)		
No	1.00			
Yes	1.26 (0.96 to 1.66)			
Prior chemotherapy		.01 (*df* = 1)		.05 (*df* = 1)
No	1.00		1.00	
Yes	1.20 (1.04 to 1.38)		1.16 (1.00 to 1.35)	
Primary site		.52 (*df* = 4)		
Abdominal	1.00			
Small bowel	0.87 (0.69 to 1.08)			
Gastric	0.98 (0.78 to 1.23)			
Other GI	0.96 (0.76 to 1.21)			
Other	1.11 (0.68 to 1.83)			
Diameter of longest lesion		< .01 (*df* = 1)		< .01
Per 10-mm increase	1.03 (1.02 to 1.04)		1.02 (1.01 to 1.04)	
KIT mutation		< .01 (*df* = 3)		< .01 (*df* = 4)
Exon 11	1.00		1.00	
Exon 9	1.94 (1.45 to 2.58)		1.78 (1.32 to 2.40)	
Wild type	1.90 (1.46 to 2.47)		2.10 (1.60 to 2.76)	
Other	2.93 (1.89 to 4.54)		2.90 (1.84 to 4.57)	
Unknown			1.01 (0.86 to 1.19)	

Table A2. Univariable and Multivariable Analysis of Prognostic Factors for Overall Survival

Covariate	Univariable Analysis		Multivariable Model After Backward Selection (N = 913)	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Treatment, mg		.31 (*df* = 1)		
400	1.00			
800	0.93 (0.80 to 1.07)			
Age, years		< .01 (*df* = 4)		< .01 (*df* = 4)
< 40	1.00		1.00	
40-50	1.35 (0.95 to 1.91)		1.13 (0.79 to 1.61)	
50-60	1.50 (1.07 to 2.11)		1.45 (1.03 to 2.04)	
60-70	1.40 (1.00 to 1.95)		1.30 (0.93 to 1.81)	
> 70	2.19 (1.56 to 3.08)		2.02 (1.42 to 2.87)	
Performance status		< .01 (*df* = 3)		< .01 (*df* = 3)
0	1.00		1.00	
1	1.59 (1.35 to 1.87)		1.48 (1.25 to 1.75)	
2	2.38 (1.85 to 3.05)		1.84 (1.42 to 2.40)	
3	3.54 (2.46 to 5.09)		3.04 (2.09 to 4.42)	
Sex		.25 (*df* = 1)		.02 (*df* = 1)
Male	1.00		1.00	
Female	0.91 (0.79 to 1.06)		0.83 (0.70 to 0.97)	
Time between diagnosis and registration, months		.67 (*df* = 2)		
< 12	1.00			
12-24	0.95 (0.77 to 1.17)			
> 24	0.93 (0.79 to 1.10)			
Prior surgery		.03 (*df* = 1)		
No	1.00			
Yes	0.80 (0.65 to 0.98)			
Prior radiotherapy		.02 (*df* = 1)		
No	1.00			
Yes	1.41 (1.05 to 1.89)			
Prior chemotherapy		< .01 (*df* = 1)		< .01 (*df* = 1)
No	1.00		1.00	
Yes	1.29 (1.10 to 1.50)		1.31 (1.11 to 1.55)	
Primary site		.68 (*df* = 4)		
Abdominal	1			
Small bowel	0.99 (0.77 to 1.26)			
Gastric	0.89 (0.70 to 1.12)			
Other GI	0.89 (0.70 to 1.15)			
Other	1.09 (0.64 to 1.84)			
Diameter of longest lesion		< .01 (*df* = 1)		< .01 (*df* = 1)
Per 10-mm increase	1.04 (1.03 to 1.05)		1.03 (1.02 to 1.04)	
KIT mutation		< .01 (*df* = 3)		< .01 (*df* = 4)
Exon 11	1		1.00	
Exon 9	2.09 (1.54 to 2.83)		1.87 (1.36 to 2.57)	
Wild type	1.82 (1.37 to 2.40)		2.10 (1.57 to 2.81)	
Other	2.15 (1.38 to 3.36)		2.68 (1.68 to 4.28)	
Unknown			1.09 (0.90 to 1.31)	