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ORIGINAL REPORT

Adjuvant Imatinib for High-Risk GI Stromal Tumor: Analysis of a Randomized Trial

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A B S T R A C T

Purpose

Three years of adjuvant imatinib therapy are recommended for patients with GI stromal tumor (GIST) with high-risk features, according to survival findings in the Scandinavian Sarcoma Group XVIII/AIO (Arbeitsgemeinschaft Internistische Onkologie) trial. To investigate whether the survival benefits have persisted, we performed the second planned analysis of the trial.

Patients and Methods

Eligible patients had macroscopically completely excised, *KIT*-positive GIST with a high risk of recurrence, as determined by using the modified National Institutes of Health criteria. After surgery, the patients were randomly assigned to receive imatinib for either 1 or 3 years. The primary objective was recurrence-free survival (RFS), and the secondary objectives included survival.

Results

A total of 400 patients were entered onto this open-label study between February 4, 2004, and September 29, 2008. During a median follow-up of 90 months, 171 recurrences and 69 deaths were detected. Patients assigned to the 3-year group had longer RFS than those assigned to the 1- year group; 5-year RFS was 71.1% versus 52.3%, respectively (hazard ratio [HR], 0.60; 95% CI 0.44 to 0.81; $P < .001$), and survival was 91.9% versus 85.3% (HR, 0.60; 95% CI, 0.37 to 0.97; $P = .036$). Patients in the 3-year group survived longer in the subset with centrally confirmed GIST and without macroscopic metastases at study entry (93.4% *v* 86.8%; HR, 0.53; 95% CI, 0.30 to 0.93; $P = .024$). Similar numbers of cardiac events and second cancers were recorded in the groups.

Conclusion

Three years of adjuvant imatinib therapy results in longer survival than 1 year of imatinib. High 5-year survival rates are achievable in patient populations with high-risk GIST.

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INTRODUCTION

GI stromal tumor (GIST) is one of the most common single types of soft tissue sarcoma.[1] GIST usually arises from the GI tract and rarely, at other intra-abdominal sites. Approximately 60% of GISTs are cured with surgery, but metastases are frequent.[2] The malignancy potential of GIST varies greatly.[3,4] Several risk-stratification tools are available for assessment of the risk of recurrence after macroscopically complete surgery.[5-9] Most GISTs with high-risk features recur within 5 years after surgery,[9] which leads to substantial mortality. Activating mutations in *KIT*, which encodes the KIT receptor tyrosine kinase, or *PDGFRA*, which encodes the platelet-derived growth factor receptor-α receptor tyrosine kinase, are considered critically important in the molecular pathogenesis of most GISTs.[10] Patients with advanced GIST frequently achieve durable responses when treated with tyrosine kinase inhibitors, such as imatinib or sunitinib.[11,12]

Adjuvant imatinib treatment improves recurrence-free survival (RFS) of patients who have undergone surgery for GIST,[13-15] but whether adjuvant imatinib also improves overall survival is uncertain. In the Scandinavian Sarcoma Group (SSG) XVIII/Arbeitsgemeinschaft Internistische Onkologie (AIO) trial, investigators compared 3- versus 1-year administration of adjuvant imatinib in the treatment of patients with GIST and a high

estimated risk of recurrence after surgery. Patients treated with imatinib for 3 years had statistically significantly longer overall survival, but this observation was based only on 37 deaths and a relatively short median follow-up of 4.5 years.[15] Frequently cited treatment guidelines recommend that 3-year adjuvant imatinib therapy should be considered in patients with GIST and a high estimated risk of recurrence, given the findings from the SSGXVIII/AIO trial.[16,17] However, two other large, randomized trials did not demonstrate that adjuvant imatinib improved overall survival compared with either placebo[18] or observation.[14]

To investigate the influence of adjuvant imatinib on survival in the treatment of GIST, we carried out the second planned analysis of the SSGXVIII/AIO trial after longer follow-up in the patients.

PATIENTS AND METHODS

Patients

Patients age 18 years or older with histologically verified *KIT*-positive GIST removed with open surgery were eligible. The GIST had to have a high estimated risk of recurrence defined according to the modified National Institutes of Health Consensus Criteria: diameter greater than 10.0 cm, greater than 10 mitoses per 50 high-power microscopic field, tumor diameter greater than 5.0 cm and mitotic count greater 5, or tumor rupture.[9] The study participants had to have an Eastern Cooperative Oncology Group performance status of 2 or lower and adequate hepatic, renal, and bone marrow functions. Excluded patients had inoperable, metastatic, or recurrent GIST; an interval of greater than 12 weeks between the date of surgery and the date of random assignment; congestive heart failure or myocardial infarction within 6 months of the study entry; other severe or uncontrolled medical disease, HIV infection, or other invasive cancer diagnosed within 5 years of study entry; breast-feeding or pregnant status, and either neoadjuvant imatinib therapy or chemotherapy for GIST before random assignment. Surgery was either R0 resection, which was complete surgical removal of the tumor, or R1 resection, which was suspected microscopic residual tumor infiltration, or tumor rupture. Patients who had macroscopic GIST metastases resected at the time of surgery were allowed to enter the study until the study protocol was amended in October 2006. Thereafter, such patients were excluded.

The study was registered (identifier NCT00116935), approved by the institutional review committees, and conducted according to the Good Clinical Practice guidelines. The participants provided written informed consent before random assignment.

Design and Treatment

This was an open-label, randomized, multicenter, phase III study. The participants were assigned in a 1:1 ratio to imatinib 400 mg once daily given orally for either 12 or 36 months as adjuvant treatment for GIST after surgery. Imatinib was taken with food.

Random Assignment

Random assignment was performed at the SSG secretariat, Lund University, Sweden. Random numbers were generated with a computer, and permutated blocks with a size of four were used to assign patients into the groups. The patients were stratified into two strata that consisted of local disease, defined as no tumor spillage and R0 resection, and intra-abdominal disease, defined as spillage or R1 resection, at the time of random assignment. The study group assignment was communicated to the study sites by fax.

Procedures

Staging was performed with contrast-enhanced computed tomography (CT) or magnetic resonance imaging of the abdomen and the pelvis, and with CT or radiography of the chest within 28 days before the initiation of adjuvant imatinib. CT or magnetic resonance imaging of the abdomen and the pelvis was performed at 6-month intervals in each group during treatment and follow-up until month 84 of the study and then annually. Blood cell counts and chemical tests were performed at 2- to 6-week intervals during the first year of the study, at 3-month intervals during the second and the third years, at 6-month intervals until study month 84, and then annually. Physical examination was performed 4 weeks after study entry, at intervals of approximately 3 months until 36 months into the study, then at 6-month intervals until 84 months of the study, and then annually.

Adverse events were reported on structured forms during adjuvant treatment, whereas cardiac events and second cancers were captured throughout the follow-up. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0. The dosage of imatinib was reduced to 300 mg once daily whenever grade 3 or 4 nonhematologic toxicity occurred or when grade 2 nonhematologic toxicity or grade 3 or 4 hematologic toxicity recurred.[15] Dosage reductions were not performed for anemia. Administration of granulocyte growth factors, other anticancer or investigational drugs, or radiotherapy was not allowed.

Local pathologists made the histologic diagnosis of GIST and performed risk stratification. Tumor histology and risk stratification were reviewed centrally. Mutation analysis of *KIT* (Ensembl accession number ENSG00000157404) and *PDGFRA* (Ensembl accession number ENSG00000134853) was not mandated at study entry, but *KIT* exons 9,

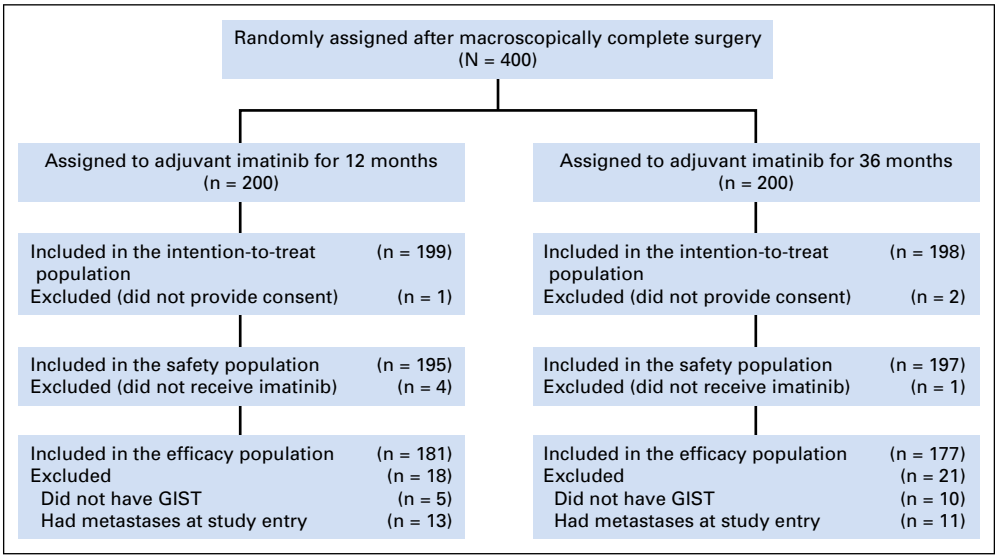

Fig 1. CONSORT diagram. GIST, GI stromal tumor.

11, 13, and 17, and *PDGFRA* exons 12 and 18 were sequenced centrally during the study.[15]

Statistical Analysis

The primary objective was RFS. RFS was defined as the interval between the date of random assignment and the date of first documentation of GIST recurrence, which was confirmed with either cytologic or histologic tissue biopsy or with radiologic evidence, or death, whichever occurred first. Patients who were alive without evidence for recurrence on the date of last follow-up were censored. Secondary objectives included overall survival and treatment safety. Overall survival was defined as the period from the date of random assignment to death as a result of any cause, and patients who were alive on the date of last follow-up were censored.

The current analysis was scheduled to be done 3 years after the first analysis of the trial. The data collection cutoff dates for the first analysis[15] and the current analysis were December 31, 2010, and December 31, 2013, respectively. The main purpose of the current, second, planned analysis of the trial was to compare overall survival between the groups after additional follow-up of the patients.

The randomly assigned patients who signed informed consent formed the intention-to-treat (ITT) population. Patients who signed informed consent, in whom GIST was confirmed at the central pathology assessment, and who did not have overt metastases before study entry formed the efficacy population, or the proper adjuvant population. Patients who received one or more doses of adjuvant imatinib were included in the safety population. Efficacy analyses were based on both the ITT population and the efficacy

Table 1. Demographic and Clinical Characteristics in the Intention-To-Treat Population

Characteristic	Adjuvant Imatinib Therapy			
	12 Months (n = 199)		36 Months (n = 198)	
	No.	%	No.	%
Median (range) age, years	62 (23-84)		60 (22-81)	
Sex				
Male	104	52	97	49
Female	95	48	101	51
Median (range) body mass index, kg/m^2	24.5 (16.6-42.1)		24.9 (15.2-42.8)	
ECOG performance status				
0	169	85	170	86
1	26	13	27	14
2	2	1	0	0
Not available	2	1	1	1
GIST confirmed at central pathology review				
Yes	189	95	182	92
No	5	3	10	5
Not available	5	3	6	3
Resected intra-abdominal metastases				
Yes	13	7	11	6
No	186	93	187	94
Tumor location				
Stomach	97	49	105	53
Small intestine	74	37	62	31
Colon or rectum	16	8	19	10
Esophagus	1	1	1	1
Retroperitoneal space	3	2	5	3
Other	7	4	5	3
Not available	1	1	1	1
Median (range) tumor diameter, cm	9 (2-35)		10 (2-40)	
Tumor mitotic count (per 50 microscope high-power fields, by central assessment)				
< 6	86	43	98	49
6-10	29	15	25	13
> 10	74	37	59	30
Not available	10	5	16	8
Tumor rupture before or at surgery				
No	164	82	154	78
Yes	35	18	44	22
Mutation location				
KIT exon 9	12	6	14	7
KIT exon 11	130	65	129	65
KIT exon 13	3	2	2	1
PDGFRA exon 12 or 18	25	13	21	11
PDGFRA exon 18 at codon D842	18	9	15	8
None, wild-type *KIT* and *PDGFRA*	18	9	14	7
Not available	11	6	18	9

NOTE. Percentages may not equal 100% because of rounding.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; GIST, GI stromal tumor.

population, which is the primary analysis population defined in the statistical analysis plan for the study written in March 2010. The subgroup analyses were predefined in the statistical analysis plan. Patients lost to follow-up were censored on the date of the last follow-up visit.

Sample size was estimated after RFS simulations with a log-rank test and the assumption of an overall hazard ratio (HR) of 0.44 between the groups, by allowing the relative HR to change over time and between the on-treatment and off-treatment phases.[15] A minimum of 110 events were required in the efficacy population to have a power of 80% with 160 patients in each group on the basis of a two-sided significance level of .05. A drop-out rate of 20% was assumed, and 200 patients were entered per group.

Statistical analyses were carried out with SAS for Windows (version 9.3; SAS Institute, Cary, NC). Survival between groups was compared by using the Kaplan-Meier life-table method and an unstratified log-rank test (*P* values) and unstratified Cox proportional hazards model. The subgroup analyses were performed similarly, and each subgroup variable category was entered at a time. A piecewise Cox regression model was used to estimate the hazard for recurrence within specific time periods. The χ^2 test or Fisher's exact test was used to analyze frequency tables. The *P* values were two tailed and were not adjusted for multiple testing.

RESULTS

Patients

A total of 400 patients were entered onto the study from 24 hospitals in Finland, Germany, Norway, and Sweden between February 4, 2004, and September 29, 2008. Of the 200 patients randomly assigned to each group, three patients had been randomly assigned without signing informed consent and were excluded from the analysis. Therefore, the ITT cohort consisted of 397 patients: 199 patients in the 12-month group and 198 in the 36-month group. Fifteen (3.8%) patients did not have GIST, as determined at the central pathology review carried out after patient entry onto the study, and 24 other patients (6.0%) had undergone resection of intra-abdominal GIST metastases before study entry. These patients also were excluded from the efficacy population, which, therefore, consisted of 358 patients: 181 patients in the 12-month group and 177 in the 36-month group (Fig 1). Characteristics of the patients and tumors in the ITT population are provided in Table 1, and those of the efficacy population are given in Appendix Table A1 (online only).

Survival

When data capture ended, the median duration of follow-up was 90 months: 89 months in the 12-month group and 90 months in the 36-month group. Five (2.5%) and seven (3.5%) patients in the 12- and 36-month groups, respectively, were lost to follow-up. None of the patients crossed over between the groups.

Ninety-seven of 171 detected recurrences occurred in the 12-month group, and 74, in the 36-month group. Patients assigned to 36 months of imatinib therapy had RFS longer than that of patients

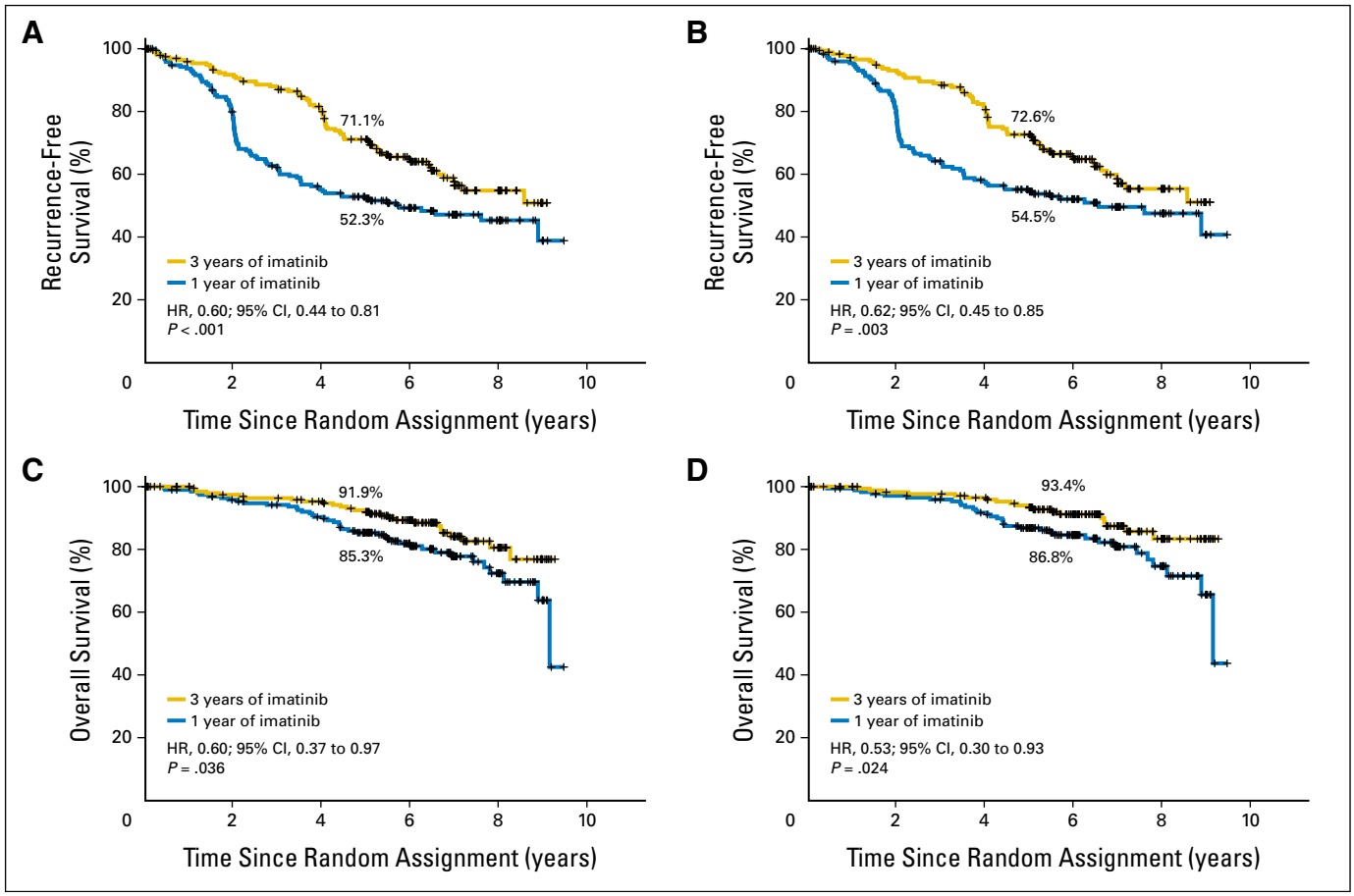

Fig 2. Recurrence-free survival in the (A) intention-to-treat population and the (B) efficacy population. Overall survival in the (C) intention-to-treat population and the (D) efficacy population. Five-year survival rates are provided. HR, hazard ratio.

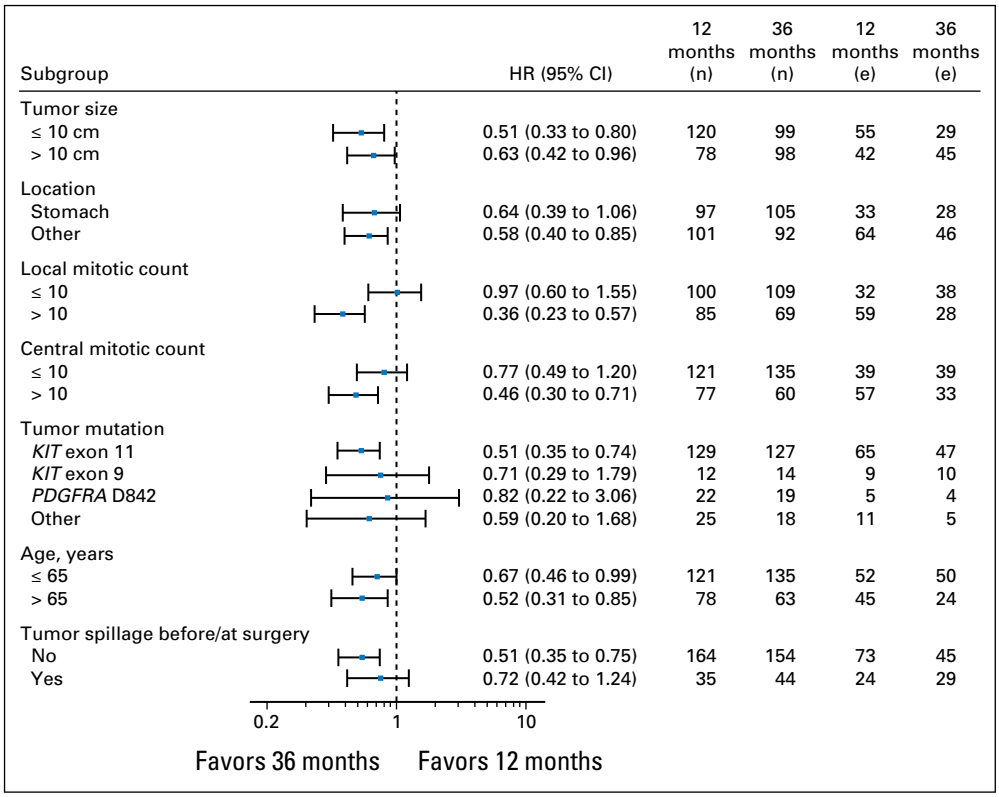

Fig 3. Forest plot shows recurrence-free survival in selected subgroups. (e), number of events observed in each subgroup; HR, hazard ratio; (n), number of patients in each subgroup.

assigned to 12 months of imatinib; the 5-year RFS rates were 71.1% and 52.3%, respectively (HR, 0.60; 95% CI 0.44 to 0.81; $P < .001$; Fig 2). In the subset of patients with centrally confirmed GIST and without macroscopic metastases at study entry (ie, the efficacy population), 5-year RFS was 72.6% in the 36-month group and 54.5% in the 12-month group (HR, 0.62; 95% CI, 0.45 to 0.85; $P = .003$). In a Cox model stratified by the time on study, the hazard of tumor recurrence was smaller in the 3-year group between study months 12 and 36 than the 1-year group (HR, 0.22; 95% CI, 0.13 to 0.38; $P < .001$). In contrast, no significant difference was observed between the groups during the first year after random assignment (HR, 0.65; 95% CI, 0.27 to 1.59) or after study month 36 (HR, 1.40; 95% CI, 0.87 to 2.26).

Sixty-nine patients died during follow-up: 42 in the 12-month group and 27 in the 36-month group. Overall survival favored the 3-year group compared with the 1-year group in the ITT population, in which 5-year survival was 91.9% versus 85.3% (HR, 0.60; 95% CI, 0.37 to 0.97; $P = .036$), and in the efficacy population, in which 5-year overall survival was 93.4% versus 86.8% (HR, 0.53; 95% CI, 0.30 to 0.93; $P = .024$).

When RFS analyses were carried out in the ITT population in the subgroups predefined in the statistical analysis plan, patients treated with imatinib for 3 years tended to have a decreased risk of having an RFS event (Fig 3). In these exploratory analyses with limited statistical power, patients with GIST with greater than 10 mitotic counts per 50 high-power microscopic field, those without GIST rupture, and those with a mutation in *KIT* exon 11 appeared to obtain the greatest benefit from the prolonged treatment.

Adverse Events

The safety population consisted of 392 patients: 194 patients in the 12-month group, and 198 patients in the 36-month group. The rates of adverse events recorded during adjuvant treatment have been previously reported.[15] At least one adverse event was recorded in all patients but two, but most of the events were mild. The most frequent adverse events were anemia, periorbital edema, and fatigue. Fifty-three (26.8%) of 198 patients in the 36-month group and 25 (12.6%) of 199 patients in the 12-month group discontinued imatinib early for reasons other than GIST recurrence. Adverse events that led to imatinib discontinuation occurred in 27 (13.6%) and 15 (7.7%) patients in the 36- and 12-month groups, respectively.

Sixteen (4.1%) patients had a cardiac event during the follow-up: 10 (5.2%) in the 12-month group and six (3.0%) in the 36-month group. One patient from the 12-month group had cardiac failure, and myocardial infarction was diagnosed in two patients in each group (Appendix Table A2, online only). In 41 (10.5%) of 392 patients, a second cancer was detected after random assignment: 19 (9.8%) in the 12-month group and 22 (11.1%) in the 36-month group. Prostate cancer was the most frequently diagnosed second cancer, which occurred in seven patients in the12-month group and five in the 36-month group (Appendix Table A3, online only). The median age when prostate cancer was detected was 67 years (range, 61 to 80 years).The median time from the date of random assignment to the date of prostate cancer diagnosis was 15 months (range, 1 to 64 months).The median Gleason score was 7 (range, 5 to 9; Appendix Table A4, online only).

DISCUSSION

Patients who underwent surgery for high-risk GIST achieved longer RFS and survival when treated with adjuvant imatinib for 3 years compared with those who received imatinib for 1 year after a median

follow-up of 7.5 years. This finding confirmed the early survival results of the trial.[15] Imatinib was moderately well tolerated, although approximately 25% the patients treated with adjuvant imatinib for 3 years discontinued the treatment early for reasons other than GIST progression. The low HR for overall survival suggest a relatively large proportional reduction in the numbers of deaths with the longer treatment, but the CIs were wide because of the relatively small numbers of deaths observed, despite the relatively long follow-up time.

Two other randomized trials have been conducted to evaluate adjuvant imatinib in the treatment of GIST. Both of these trials also enrolled lower-risk patients with GIST and investigated durations of adjuvant imatinib that were fewer than 3 years. In the American College of Surgeons Oncology Group (ACOSOG) Z9001 trial (NCT00041197),[13] patients who had undergone surgery for GIST $\geq$ 3 cm in diameter were assigned to receive either imatinib or placebo for 12 months. In this study, patients treated with imatinib had longer RFS, but no significant difference in overall survival was found between the groups during a median observation time of 6.2 years.[18] Similarly, in a trial sponsored by the European Organization for Research and Treatment of Cancer (EORTC 62024; NCT00103168), investigators compared 2 years of adjuvant imatinib with observation in a patient population with high- or intermediate-risk GIST. Patients treated with adjuvant imatinib had longer RFS, but no significant survival benefit emerged during a median follow-up of 4.7 years.[14] Because low- or intermediate-risk GIST is cured with surgery alone in the great majority of patients,[9] most such patients do not benefit from adjuvant imatinib treatment. Hypothetically, these results suggest that obtaining overall survival benefit may require durable administration of imatinib and that the patients at high risk for recurrence are the optimal target population.

To our knowledge, the survival rates observed are the highest reported in high-risk GIST; greater than 90% of the patients in the 3-year group survived for 5 years or longer after study entry. We speculate that, other than adjuvant imatinib, two procedures were crucially important for achieving the high overall survival rates: longitudinal monitoring of the abdomen with CT to detect GIST recurrence early when the tumor bulk was still small and restarting of imatinib after recurrence was detected. Patients with metastatic GIST who have small tumor bulk at the time of imatinib initiation survive longer than those with large tumor bulk,[19] and the risk for drug resistance–conferring mutations to emerge may be higher when the tumor bulk at the time imatinib is started is larger. Most GISTs that recur after adjuvant imatinib therapy respond to imatinib reinstitution.[20]

Imatinib has been reported to have cardiac toxicity,[21] but only one patient had cardiac failure. This observation suggested that cardiac toxicity of adjuvant imatinib at the 400 mg daily dosage is low. The numbers of second cancers detected after study entry were similar in the two groups. In 12 patients, prostate cancer was diagnosed. Prostate cancer is frequent in the elderly male populations, and a large study based on the US SEER database did not reveal an excess of prostate cancers among adults with chronic myeloid leukemia who were treated with imatinib.[22] Conversely, a few patients had increases in serum prostate-specific antigen concentrations without changes in the serum testosterone level in a phase II trial in which imatinib was administered after local therapy for prostate cancer.[23] Mast cells express *KIT* strongly,[24]can be inhibited by imatinib, and might influence the behavior of prostate cancer.[25,26] More data about the long-term safety of adjuvant imatinib therapy are needed.

The study had a few limitations. We treated all patients with the standard 400-mg dose of imatinib, but evidence from patients with advanced GIST suggested that the 800-mg daily dosage of imatinib is more effective than the 400-mg dose when GIST harbors a mutation in *KIT* exon 9.[27] We allowed patients with the *PDGFRA* D842V mutation to enter the study, but it has now become evident that GISTs with this mutation are imatinib resistant; therefore, such patients likely do not benefit from adjuvant imatinib.[28] Similarly, many patients who have neither *KIT* nor *PDGFR* mutations are unlikely to benefit from adjuvant imatinib,[18] and they might benefit more from agents that target the vascular endothelial growth factor receptors.[29]

In conclusion, patients with high-risk GIST treated with adjuvant imatinib for 3 years had longer RFS and survival than patients treated for 1 year, and they achieved high 5-year survival rates. Almost all patients had adverse effects, but most tolerated imatinib relatively well. Trials to evaluate adjuvant imatinib therapy for greater than 3 years have now been initiated.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Final approval of manuscript: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Demographic and Clinical Characteristics in the Efficacy Population

Characteristic	Adjuvant Imatinib Therapy			
	12 Months (n = 181)		36 Months (n = 177)	
	No.	%	No.	%
Median (range) age, years	62	(23-84)	60	(22-81)
Sex				
Male	96	53	88	50
Female	85	47	89	50
Median (range) body mass index, kg/m^2	24.5 (16.8-42.1)		24.8 (15.2-42.8)	
ECOG performance status				
0	155	86	151	85
1	22	12	25	14
2	2	1	0	0
Not available	2	1	1	1
GIST confirmed at central pathology review				
Yes	181	100	177	100
No	0	0	0	0
Resected intra-abdominal metastases				
Yes	0	0	0	0
No	181	100	177	100
Tumor location				
Stomach	91	50	100	56
Small intestine	68	38	55	31
Colon or rectum	11	6	15	8
Esophagus	1	1	0	0
Retroperitoneal space	3	2	3	2
Other	6	3	3	2
Not available	1	1	1	1
Median (range) tumor diameter, cm	9 (2-35)		10 (2-40)	
Tumor mitotic count (per 50 microscope high-power fields, by central assessment)				
< 6	80	44	85	48
6-10	27	15	25	14
> 10	68	38	56	32
Not available	6	3	11	6
Tumor rupture before or at surgery				
No	149	82	136	77
Yes	32	18	41	23
Mutation location				
KIT exon 9	12	7	14	8
KIT exon 11	123	68	121	68
KIT exon 13	2	1	2	1
PDGFRA exon 12 or 18	23	13	20	11
PDGFRA exon 18 at codon D842	16	9	14	8
None, wild-type *KIT* and *PDGFRA*	14	8	10	6
Not available	7	4	10	6

NOTE. Percentages may not add up to 100 because of rounding.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; GIST, GI stromal tumor.

Table A2. Cardiac Adverse Events Registered in the Safety Population

	Imatinib Therapy					
	Arm A: 12 Month (n = 194)		Arm B: 36 Months (n = 198)		Total (N = 392)	
Adverse Event	No.	%	No.	%	No.	%
Any cardiac event	10	5.2	6	3.0	16	4.1
Myocardial infarction	2	1.0	2	1.0	4	1.0
Cardiac failure	1	0.5	0	0	1	0.3
Coronary artery disease	2	1.0	2	1.0	4	1.0
Other cardiac disease	6	3.1	3	1.5	9	2.3

Table A3. Number of Second Cancers Detected in the Safety Population

	No. of Second Cancers		
	Imatinib Therapy		
Cancer	12 Months (n = 194)	36 Months (n = 198)	Total (N = 392)
Any	19	22	41
Prostate	7	5	12
Melanoma	3*	1	4
Basal cell carcinoma	3*	1	4
Neuroendocrine carcinoma	1	2	3
Renal	1	2	3
Lymphoma	0	3	3
Thyroid	1	1	2
Colorectal	1	1	2
Lung	1	1	2
Bladder	0	1	1
Brain neoplasm	0	1	1
Breast	0	1	1
Chronic lymphocytic leukemia	0	1	1
Peritoneal	1	0	1
Uterine	0	1	1

*One patient in the 12-month group had a diagnosis of both melanoma and basal cell carcinoma of the skin. One other patient in the 12-month group had renal oncocytoma, and one patient in the 36-month group had melanoma in situ. The malignancy grade of the brain neoplasm was not available.

Table A4. Patients in Whom Prostate Cancer Was Diagnosed After Study Entry

Patient No.	Age at Random Assignment (years)	Time From Random Assignment to Detection of Prostate Cancer (months)	Prostate Cancer Confirmed Histologically	TNM Classification	Gleason Score
1	68	12	Yes	NA	NA
2	67	9	Yes	NA	5
3	69	1	Yes	NA	8
4	67	7	Yes	T1cN0M0	7
5	66	64	Yes	T3aN1MO	7
6	67	4	Yes	T2cN0M0	8
7	61	17	Yes	T2aN0M0	7
8	65	25	Yes	T1N0M1	8
9	66	23	Yes	T3N0M0	6
10	61	56	Yes	T3NxM0	9
11	68	48	Yes	NA	6
12	80	13	Yes	T2N0M0	6

Abbreviation: NA, not available.