One vs Three Years of Adjuvant Imatinib for Operable Gastrointestinal Stromal Tumor
A Randomized Trial

Heikki Joensuu, MD
Mikael Eriksson, MD
Kirsten Sundby Hall, MD
Jörg T. Hartmann, MD
Daniel Pink, MD
Jochen Schütte, MD
Giuliano Ramadori, MD
Peter Hohenberger, MD
Justus Duyster, MD
Salah-Eddin Al-Batran, MD
Marcus Schlemmer, MD
Sebastian Bauer, MD
Eva Wardelmann, MD
Maarit Sarlomo-Rikala, MD
Bengt Nilsson, MD
Harri Sihto, MSc
Odd R. Monge, MD
Petri Bono, MD
Raija Kallio, MD
Aki Vehtari, DSc
Mika Leinonen, MSc
Thor Alvegård, MD
Peter Reichardt, MD

Context Adjuvant imatinib administered for 12 months after surgery has improved recurrence-free survival (RFS) of patients with operable gastrointestinal stromal tumor (GIST) compared with placebo.

Objective To investigate the role of imatinib administration duration as adjuvant treatment of patients who have a high estimated risk for GIST recurrence after surgery.

Design, Setting, and Patients Patients with *KIT*-positive GIST removed at surgery were entered between February 2004 and September 2008 to this randomized, open-label phase 3 study conducted in 24 hospitals in Finland, Germany, Norway, and Sweden. The risk of GIST recurrence was estimated using the modified National Institutes of Health Consensus Criteria.

Intervention Imatinib, 400 mg per day, orally for either 12 months or 36 months, started within 12 weeks of surgery.

Main Outcome Measures The primary end point was RFS; the secondary end points included overall survival and treatment safety.

Results Two hundred patients were allocated to each group. The median follow-up time after randomization was 54 months in December 2010. Diagnosis of GIST was confirmed in 382 of 397 patients (96%) in the intention-to-treat population at a central pathology review. *KIT* or *PDGFRA* mutation was detected in 333 of 366 tumors (91%) available for testing. Patients assigned for 36 months of imatinib had longer RFS compared with those assigned for 12 months (hazard ratio [HR], 0.46; 95% CI, 0.32-0.65; $P<.001$; 5-year RFS, 65.6% vs 47.9%, respectively) and longer overall survival (HR, 0.45; 95% CI, 0.22-0.89; $P=.02$; 5-year survival, 92.0% vs 81.7%). Imatinib was generally well tolerated, but 12.6% and 25.8% of patients assigned to the 12- and 36-month groups, respectively, discontinued imatinib for a reason other than GIST recurrence.

Conclusion Compared with 12 months of adjuvant imatinib, 36 months of imatinib improved RFS and overall survival of GIST patients with a high risk of GIST recurrence.

Trial Registration clinicaltrials.gov Identifier: NCT00116935

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GASTROINTESTINAL STROMAL tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Gastrointestinal stromal tumors are usually found in the stomach or the small intestine but can occur at any site along the gastrointestinal tract and rarely elsewhere within the abdominal cavity.[1] The median age at presentation is 60 to 65 years, and the annual incidence approximately 10 cases per million.[2-4] Most GISTs (75% to 80%) harbor an activating mutation in the *KIT* oncogene and 5% to 10% in platelet-derived growth factor receptor-α (*PDGFRA*), which are important for tumor molecular pathogenesis.[5] The ma-

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Author Affiliations are listed at the end of this article.
Corresponding Author: Heikki Joensuu, MD, Department of Oncology, Helsinki University Central Hospital, Haartmaninkatu 4, PO Box 180, FIN-00029 Helsinki, Finland (heikki.joensuu@hus.fi).

lignancy potential of GIST varies from negligible in micro GIST to aggressive cancer.[6,7] Several stratification schemes are available for assessing the risk of recurrence when GIST has been resected with potential curative intent.[1,2,8-10]

Patients with advanced GIST usually respond to imatinib mesylate and other agents that inhibit *KIT* and *PDGFRA*, but eventually most patients have disease progression.[11,12] Adjuvant imatinib administered for 12 months after surgical removal of *KIT*-immunopositive GIST prolongs recurrence-free survival (RFS) compared with placebo, but its effect on survival is unknown. Recurrence of GIST is common during the first years following discontinuation of adjuvant imatinib, suggesting that 12 months of administration may be too short a time period.[13] We hypothesized that longer than 1 year of adjuvant imatinib treatment might be beneficial and compared 3 years of imatinib administration to 1 year of administration as adjuvant treatments for GIST patients who were considered to have a high risk of GIST recurrence following surgery.

METHODS

Patients were eligible when they were 18 years of age or older and had GIST removed at open surgery. A time interval of more than 1 week but less than 12 weeks was allowed between the date of surgery and the date of randomization. The GIST was required to be histologically diagnosed, to be *KIT* (CD117) positive in immunostaining, and to have a high estimated risk of recurrence according to the modified National Institutes of Health (NIH) Consensus Criteria with at least 1 of the following features: (1) the longest tumor diameter greater than 10.0 cm, (2) mitotic count greater than 10 mitoses per 50 high power fields of the microscope, (3) tumor diameter greater than 5.0 cm and mitotic count over 5, or (4) tumor rupture before surgery or at surgery.[8,9] The study participants were required to have Eastern Cooperative Oncology Group performance status 2 or less[14] and adequate renal, hepatic, and bone marrow function. We excluded patients who had inoperable, metastatic, or recurrent GIST; those who had congestive heart failure or myocardial infarction within 6 months of study entry or other severe or uncontrolled medical disease; patients with other invasive cancer diagnosed within 5 years prior to study entry; pregnant or breastfeeding patients; patients with human immunodeficiency virus infection; and patients who had received either chemotherapy or neoadjuvant imatinib for GIST prior to randomization. Patients who had operable intra-abdominal GIST metastases and could be rendered free from all macroscopic tumors at surgery were allowed to enter the study until October 2006, when the study protocol was amended and such patients were excluded.

Study Design and Treatment

In this prospective, open-label, multicenter, randomized, phase 3 study, the participants were assigned in a 1-to-1 ratio to treatment with oral imatinib, 400 mg once daily, either for 12 months or for 36 months as adjuvant treatments.

The primary objective was RFS, defined as the time period from the date of randomization to the date of first documentation of recurrence (with cytological or histological confirmation or with radiological evidence) or death, whichever occurred first; patients who were alive without recurrence were censored on the date of last follow-up. Second cancers were not considered events. The secondary objectives included treatment safety; overall survival, defined as the time period from the date of randomization to death censoring patients who were alive on the date of last follow-up; and GIST-specific survival, defined as the time period from the date of randomization to the date of death considered to be caused by GIST, censoring patients alive on the date of last follow-up and those who died from another cause on the date of death.

The study protocol was approved by the institutional review committees. The participants provided written informed consent prior to study entry. The study was conducted according to the Good Clinical Practice guidelines.

Randomization

Randomization was performed using computer-generated random numbers at the Scandinavian Sarcoma Group secretariat, Lund University, Sweden. Permutated blocks of 4 were used in random assignment of the patients into groups. At randomization, the patients were stratified into 2 strata: local disease (no tumor spillage and R0 resection [complete surgical removal of the tumor]) and intra-abdominal disease (tumor rupture or R1 resection [suspected microscopic residual tumor infiltration]). The result of randomization was communicated to the study centers by fax.

Procedures

Contrast enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis and CT of the chest or chest x-ray were mandatory staging examinations and were required within 28 days prior to the first dose of the study drug. Both groups had CT or MRI of the abdomen and pelvis at 6-month intervals during treatment and follow-up. Blood cell counts and chemistries were performed at 2- to 6-week intervals during the first year in the study, at 3-month intervals during the second and the third years in the study, and subsequently at 6-month intervals. Physical examination was done 4 weeks after study entry, subsequently at approximately 3-month intervals until 36 months in the study, and following this at 6-month intervals.

Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (http://ctep.cancer.gov). The dose of imatinib was modified when grade 3 or 4 hematological toxicity occurred or when grade 2 to 4 nonhematological toxicity was encountered. The dose was reduced to 300 mg once daily whenever grade 3 or 4 nonhematological tox-

icity occurred or when grade 2 nonhematological toxicity or grade 3 or 4 hematological toxicity recurred. No dose reductions were performed for grade 3 or 4 anemia.

Administration of other anticancer drugs, investigational drugs, radiation therapy, warfarin sodium, or granulocyte growth factors was not allowed. Loperamide was recommended for patients with grade 1 or 2 diarrhea to avoid interruption of imatinib dosing.

Tumor histological diagnosis and risk stratification were based on local pathology assessment. Mutation analysis of *KIT* and *PDGFRA* was not mandatory before study entry. After study entry, tumor histology was reviewed and mitosis counting was done centrally by 1 of 2 pathologists (E.W. or M.S.-R.). *KIT* (NCBI Entrez gene 3815) and *PDGFRA* (NCBI Entrez gene 5156) mutation analysis was carried out centrally at either the Department of Pathology, University of Bonn, or Biomedicum, University of Helsinki. *KIT* exons 9, 11, 13, and 17 and *PDGFRA* exons 12, 14, and 18 were screened for mutations.[15,16]

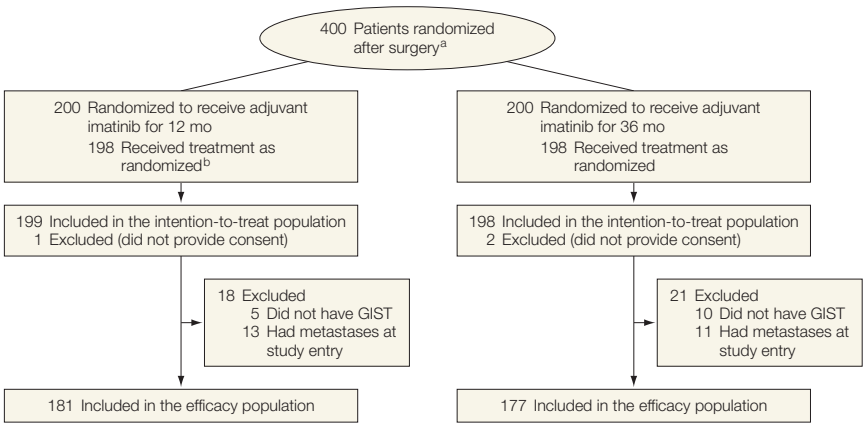
Statistical Analysis

The modified intention-to-treat population consisted of randomized patients who signed informed consent and the efficacy population of patients who signed informed consent, had centrally confirmed GIST, and did not have metastases resected prior to study entry. The safety population included patients who took at least 1 dose of the study medication.

The trial was initiated as a Scandinavian Sarcoma Group randomized phase 2 study with planned accrual of 80 patients. Once the Arbeitsgemeinschaft Internistische Onkologie joined the trial, the study power calculations were revised and the trial was expanded to a phase 3 trial in October 2004, when 46 patients had been entered. The final study sample size was estimated by simulating log-rank tests assuming a hazard ratio (HR) of 0.44 in favor of the 36-month group. At least 110 events were required in the efficacy population to achieve a power of 80% with 160 patients in each group using a 2-sided significance level of .05. Assuming a drop-out rate of 20%, we planned to randomize 200 patients to each group. Sample size calculation was performed with nQuery Advisor version 6.0 (Statistical Solutions).

Efficacy analyses are based on the efficacy population (the primary analysis population in the statistical analysis plan, approved on March 15, 2010) and the modified intention-to-treat population. 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. Frequency tables were analyzed using the χ^2 test or Fisher exact test. Survival between groups was compared using the Kaplan-Meier life-table method and unstratified log-rank test (*P* values) or an unstratified Cox proportional hazards model (HRs). The subgroup analyses were done similarly for each subgroup variable category at a time. Prognostic factors were analyzed using a Cox model with forward selection and backward elimination. All *P* values are 2-sided and not adjusted for multiple testing. Statistical analyses were performed with SAS version 9.2 for Windows (SAS Institute).

Figure 1. Flow of Patients in Study



ITT indicates intention-to-treat.
[a]The numbers of individuals screened for eligibility and the reasons for exclusion were not available.
[b]1 patient assigned to 12 months of imatinib was mistakenly treated with 36 months of imatinib.

RESULTS

Between February 4, 2004, and September 29, 2008, 200 patients were randomly assigned to the 12-month group and 200 to the 36-month group from 24 centers located in Finland, Germany, Norway, and Sweden. One patient assigned to the 12-month group and 2 assigned to the 36-month group were randomized without signing informed consent and were excluded from analysis. Fifteen patients (3.8%) treated with imatinib were diagnosed with tumors other than GIST at a central pathology review performed after study entry (another soft tissue sarcoma, 11; other lesion, 4) (FIGURE 1). Twenty-four patients (6.0%) who had undergone resection of intra-abdominal GIST metastases were entered, most before the protocol amendment in October 2006.

The characteristics of the patients and tumors were balanced between the groups (TABLE 1). Mutation analysis could be performed in 366 of 397 GISTs (92.2%). *KIT* or *PDGFRA* mutation was present in 333 of 366 tumors (91.0%), whereas 33 GISTS (9.0%) had wild type (no mutation detected). Seventeen patients (8.5%) assigned to the 12-month group and 11 (5.6%) assigned to the 36-month group had either intermediate-risk GIST (23 patients) or low-risk GIST (5 patients).

Efficacy

The median duration of follow-up, calculated from the date of randomization to the date of data collection closure (December 31, 2010), was 54 months (interquartile range [IQR], 41-66 months). Six patients (3.0%) in the 12-month group and 6 (3.0%) in the 36-month group were lost to follow-up. The date of data collection closure was triggered by 114 RFS events (GIST recurrence or death) in the efficacy population, at which time 134 events had accumulated in the modified intention-to-treat population. Of these, 84 occurred in the 12-month group and 50 in the 36-month group. Recurrence-free survival was longer in the 36-month group compared with the 12-month group (5-year RFS, 65.6% vs 47.9%, respectively; HR, 0.46; 95% CI; 0.32-0.65; $P < .001$) (FIGURE 2A). In an analysis stratified by the time in the study, there was no significant difference in the hazard of GIST recurrence or death between the 2 groups during the first 12 months after randomization (HR, 0.64; 95% CI, 0.26-1.57) or after 36 months of randomization (HR, 1.31; 95% CI, 0.65-2.62), but a substantial difference emerged during 12 to 24 months and 24 to 36 months after randomization (HR, 0.26; 95% CI, 0.13-0.53; and HR, 0.17; 95% CI, 0.07-0.39, respectively). The results on RFS remained similar when the analysis was carried out in the efficacy population (Figure 2B).

Fewer patients assigned to 36 months of imatinib administration died during the follow-up as compared with those assigned to the 12-month group (12 vs 25, respectively), and overall survival was longer in the 36-month group (5-year survival, 92.0% vs 81.7%, respectively; HR, 0.45; 95% CI, 0.22-0.89; $P = .02$) (Figure 2C). When overall survival analysis was restricted to the efficacy population, the result remained similar (5-year survival, 93.9% vs 81.7%, respectively; HR, 0.37; 95% CI, 0.16-0.85; $P = .02$) (Figure 2D). Survival specific to GIST tended to favor the 3-year group; 14 patients in the 12-month group and 7 in the 36-month group were considered to have died from GIST (5-year survival, 95.1% vs 88.5%, respectively; HR, 0.46; 95% CI, 0.19-1.14; $P = .09$).

Patients assigned to longer imatinib administration had more favorable RFS in the exploratory subgroup analyses predefined in the study statistical analysis plan (FIGURE 3). Patients with GIST with *KIT* exon 11 mutation benefited from the longer treatment, whereas no significant improvement over 12 months of imatinib was found in the subsets of patients whose GIST harbored *KIT* exon 9 mutation or *PDGFRA* mutation or patients who had no mutation in these genes, but the numbers of patients were small in these categories.

Table 1. Baseline Characteristics of Patients and Tumors[a]

Characteristics	No. (%)	
	12 mo of Imatinib (n = 199)	36 mo of Imatinib (n = 198)
Age, median (range), y	62 (23-84)	60 (22-81)
≤65	121 (61)	135 (68)
>65	78 (39)	63 (32)
Sex		
Women	95 (48)	101 (51)
Men	104 (52)	97 (49)
Eastern Cooperative Oncology Group performance status[b]		
0	169 (85)	170 (86)
1	26 (13)	27 (14)
2	2 (1)	0
Not available	2 (1)	1 (1)
Resected intra-abdominal metastases		
Yes	13 (7)	11 (6)
No	186 (93)	187 (94)
Completeness of surgery		
Complete resection (R0)	169 (85)	160 (81)
Microscopic residual tumor suspected (R1)	29 (15)	37 (19)
Not available	1 (1)	1 (1)
Primary tumor site		
Stomach	97 (49)	105 (53)
Small intestine	74 (37)	62 (31)
Colon or rectum	16 (8)	19 (10)
Other	11 (6)	11 (6)
Not available	1 (1)	1 (1)
Primary tumor diameter, median (range), cm	9 (2-35)	10 (2-40)
<5.1	29 (15)	18 (9)
5.1-10.0	91 (46)	81 (41)
>10.0	78 (39)	98 (50)
Not available	1 (1)	1 (1)

(continued)

Adverse Events

A larger proportion of patients discontinued imatinib in the 36-month group for reasons other than GIST recurrence compared with the 12-month group (51 [25.8%] vs 25 patients [12.6%], respectively; the reasons were adverse effect [27 vs 15], patient preference [11 vs 0], tumor histology not GIST [6 vs 6], and other or unspecified reason [7 vs 4]). Almost all study patients had at least 1 adverse event recorded; most events were graded mild in severity (TABLE 2). Grade-3 or -4 adverse events occurred in 65 (32.8%) and 39 (20.1%) patients assigned to the 36-month and 12-month groups, respectively, and adverse events leading to treatment discontinuation in 27 (13.6%) and 15 (7.5%) patients, respectively. The average daily imatinib dose was 393.1 mg and 394.3 mg in the 12-month and 36-month groups, respectively.

Eight (4.1%) and 4 (2.0%) patients in the 12-month and 36-month groups, respectively, had 1 or more adverse cardiac event. One patient was diagnosed with cardiac failure and 2 with myocardial infarction in the 12-month group; no one in the 36-month group had these diagnoses. Fourteen patients (7.2%) in the 12-month group and 13 (6.6%) in the 36-month groups, respectively, were diagnosed with a second cancer.

Table 1. Baseline Characteristics of Patients and Tumors[a] (continued)

Characteristics	No. (%) 12 mo of Imatinib (n = 199)	No. (%) 36 mo of Imatinib (n = 198)
Primary tumor mitotic count: local, median (range)[c]	10 (0-250)	8 (0-165)
<6/HPF	52 (26)	56 (28)
6-10/HPF	48 (24)	53 (27)
>10/HPF	85 (43)	69 (35)
Not available	14 (7)	20 (10)
Primary tumor mitotic count: central, median (range)[c]	6 (0-129)	4 (0-135)
<6/HPF	86 (43)	98 (49)
6-10/HPF	29 (15)	25 (13)
>10/HPF	74 (37)	59 (30)
Not available	10 (5)	16 (8)
Tumor rupture prior to or at surgery		
No	164 (82)	154 (78)
Yes	35 (18)	44 (22)
Tumor mutation type[d]		
KIT exon 9	12 (6)	14 (7)
KIT exon 11	129 (65)	127 (64)
PDGFRA exon 12	3 (2)	2 (1)
PDGFRA exon 18	22 (11)	19 (10)
PDGFRA exon 18 mutation D842V	18 (9)	14 (7)
Other mutation	3 (2)	2 (1)
Wild type for *KIT* and *PDGFRA*	19 (10)	14 (7)
Not available	11 (6)	20 (10)
Modified Consensus Classification Risk Group		
High risk	178 (89)	181 (91)
Intermediate risk	15 (8)	8 (4)
Low risk	2 (1)	3 (2)
Very low risk	0	0
Not available	4 (2)	6 (3)

Abbreviations: HPF, high power field of the microscope; *PDGFRA*, platelet-derived growth factor receptor-α gene.
[a] Data are median (range) or number (%). Percentages may not sum to 100 due to rounding.
[b] A value of 0 indicates that the patient is fully active; 1, the patient is symptomatic but completely ambulatory; and 2, the patient is symptomatic but spends less than 50% of time in bed during the day.
[c] Counts are per 50 high power fields of the microscope.
[d] Analyzed centrally after patient entry into the study.

COMMENT

Three years of adjuvant imatinib improved RFS of GIST patients with a high estimated risk for recurrence after surgery compared with 1 year of imatinib, with 65.6% and 47.9% of the patients, respectively, being alive without recurrence 5 years after study entry. This 5-year RFS achieved in the 3-year treatment group compares well with the expected 5-year RFS of approximately 45% reported from high-risk GIST patient populations treated with surgery alone.[17] The stratified survival analysis carried out suggests that the difference in favor of the 36-month group arose when the patients assigned to this group were receiving the drug while those assigned to the 12-month group were not taking the drug, whereas no significant difference in RFS was observed when both groups were either taking or not taking the drug.

The study was powered for RFS, but the difference in overall survival was also statistically significant. This likely resulted from efficacy of imatinib on GIST rather than from other, yet unidentified, beneficial effects of imatinib. The estimated 5-year survival in the 36-month group was 92.0% despite that the patients had high-risk GIST and 19.9% had tumor rupture, which is associated with high risk of recurrence.[18-20] Although treatments given for advanced GIST likely contribute substantially to survival, the 5-year survival achieved can be considered high. To our knowledge, the current randomized study is the first to report an overall survival benefit associated with an oral tyrosine kinase inhibitor administered as adjuvant treatment of human cancer.

Few patients had GIST recurrence while receiving imatinib (4 patients in the 12-month group and 12 in the 36-month group), suggesting that acquired resistance to adjuvant imatinib was infrequent. The first data from the current study participants whose GIST recurred after completion of adjuvant imatinib and who received imatinib as first-line treatment for advanced GIST suggest that most such patients respond to imatinib re-challenge and that the response rate may not differ markedly from that of imatinib-naive patients regardless of the duration of prior adjuvant imatinib treatment.[21]

We used the NIH Consensus Criteria for patient selection,[8] but also considered patients with ruptured GIST as high-risk patients.[18-20] Tumor mitotic count is a key factor in GIST risk stratification[17,22] but has limitations,[23] and making a distinction between the risk categories is associated with some uncertainty when the mitosis count is close to a cutoff that distinguishes the categories. Seventeen of 28 patients who entered the study despite not having high-risk GIST had tumor mitosis count or tumor size equal to the numerical cutoff value that differentiates the intermediate-risk group from the high-risk group. It is unknown how well the present findings on high-risk GIST can be applied to lower-risk GIST. Recurrence of GIST is relatively infrequent

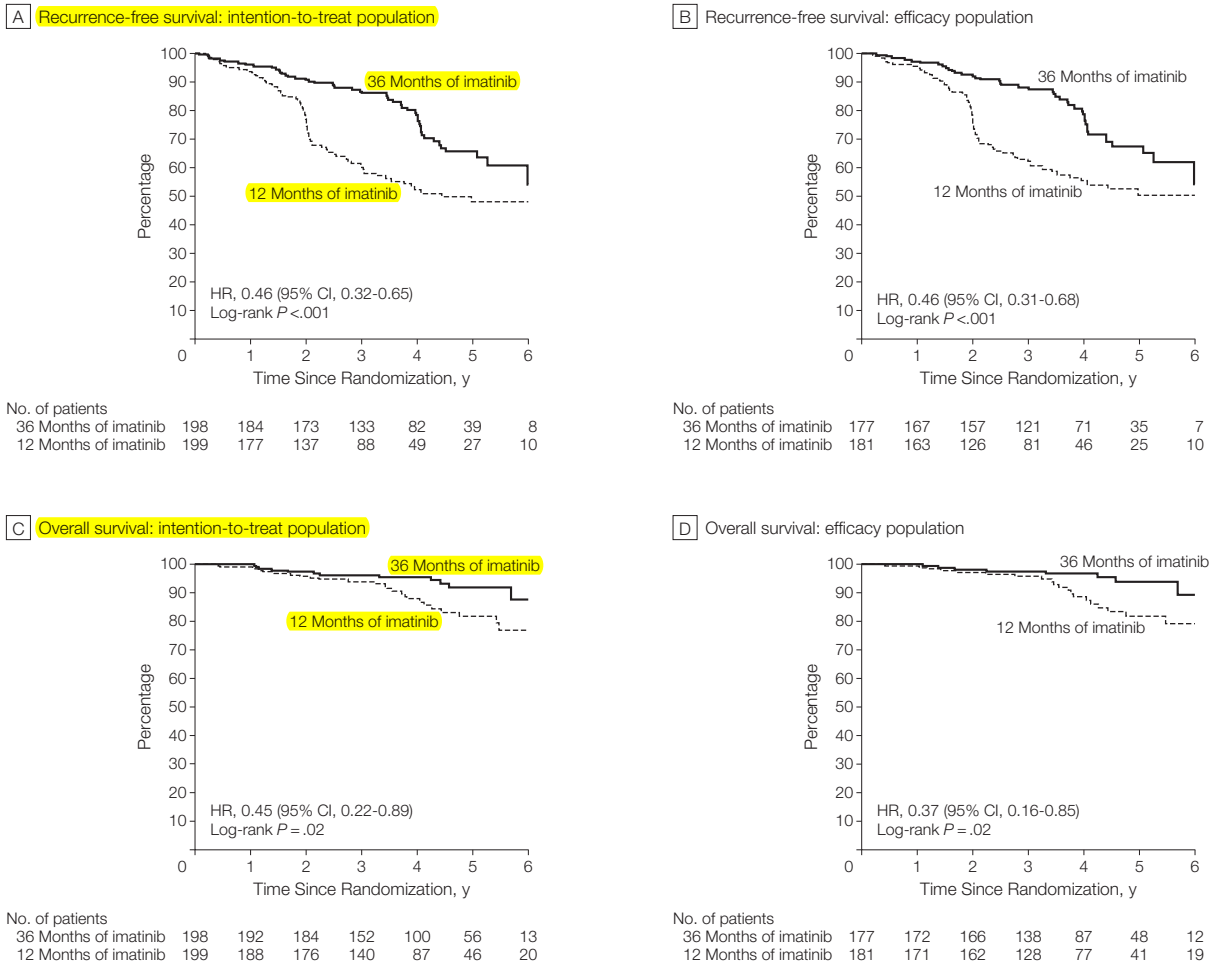
in the low- and intermediate-risk categories when the risk is stratified using the modified NIH Consensus Criteria, suggesting that the majority of such patients are cured by surgery.[17]

Imatinib was usually well tolerated, but almost all patients had mild adverse effects, and approximately a fourth of the patients assigned to the 36-month group and 13% of those assigned to the 12-month group discontinued imatinib early for a reason other than recurring GIST. Some patients might benefit from treatment durations longer than 3 years, but this hypothesis is best addressed within the context of a randomized trial, and the benefits, if any, need to be balanced with treatment-related toxicity. Imatinib has cardiac toxicity,[24] but we recorded few cardiac adverse events, suggesting that cardiac toxicity is relatively low.[25]

The study has some potential limitations. Although most high-risk GISTs recur early and imatinib is relatively well tolerated, longer follow-up may provide further information about safety and efficacy of adjuvant imatinib. Tumor mutation type likely influences sensitivity to imatinib,[26,27] and efficacy of imatinib in such subgroups warrants further research. Patients who had completely resectable intra-abdominal metastases were first allowed to enter the study, but discontinuation of imatinib administration in this subset of patients was no longer considered justified when the BRF-14 trial results became available.[28] Patient follow-up schedules during and after adjuvant imatinib treatment have not been evaluated, and the optimal schedules are unknown.

We conclude that 3 years of adjuvant imatinib administration improved recurrence-free and overall survival of GIST patients who are at a high risk of recurrence compared with 1 year of imatinib. The effect on overall survival was

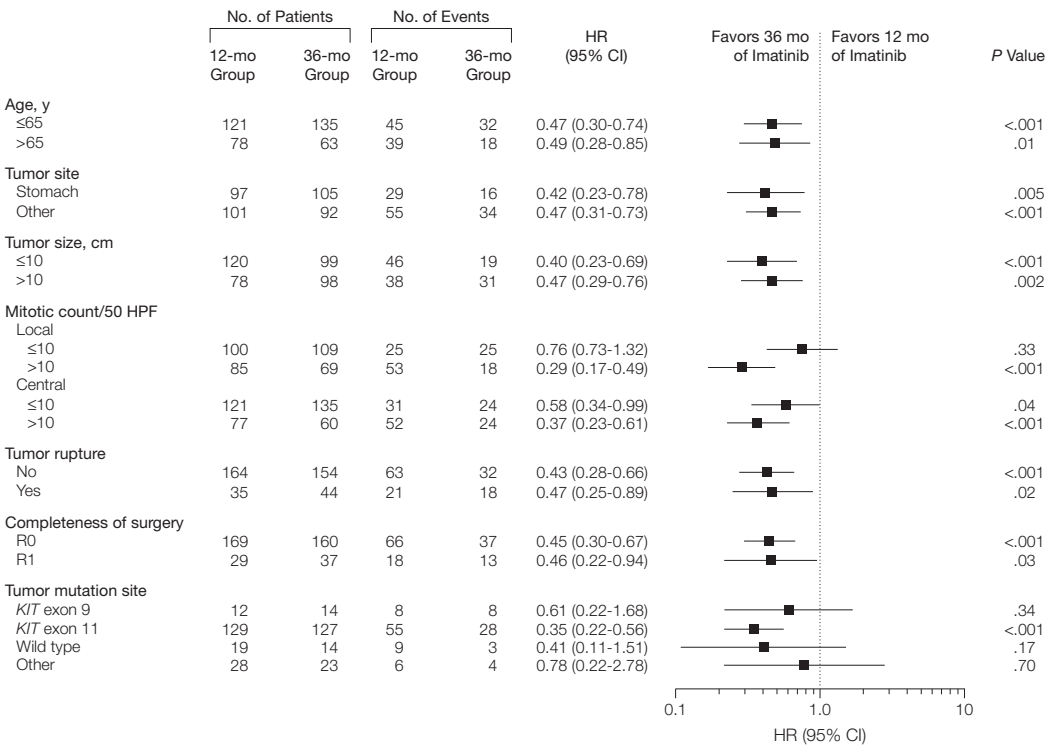
Figure 2. Comparison of Recurrence-Free Survival and Overall Survival Between Groups



Comparison of recurrence-free survival in the modified intention-to-treat population (A) and the efficacy population (B). Comparison of overall survival in the modified intention-to-treat population (C) and the efficacy population (D). The 3-year survival rates of patients assigned to 36 months of imatinib and those assigned to 12 months of imatinib are 86.6% vs 60.1% (A), 88.1% vs 62.1% (B), 96.3% vs 94.0% (C), and 97.6% vs 95.8% (D), respectively, and the 5-year survival rates, 65.6% vs 47.9% (A), 67.4% vs 50.3% (B), 92.0% vs 81.7% (C), and 93.9% vs 81.7% (D).

based on a relatively small number of deaths, and the study patients will continue to be followed up to confirm the overall survival benefit. Because GIST recurrence is frequent after discontinuation of adjuvant imatinib, studies that evaluate still longer treatments are warranted, as are studies that address novel agents and their combinations.

Figure 3. Treatment Effects on Recurrence-Free Survival in Subgroups



HPF indicates high power field of the microscope; HR, hazard ratio; R0, complete surgical removal of the tumor; and R1, surgery with suspected microscopic residual tumor infiltration or tumor rupture. Information about tumor site, tumor size, local mitosis count, central mitosis count, completeness of surgery, and tumor mutation site was missing in 2, 2, 34, 4, 2, and 31 cases, respectively (Table 1).

Table 2. Most Frequently Recorded Adverse Events

	No. (%)					
	All Grades			Grade 3 or 4		
Events	12-mo Group (n = 194)	36-mo Group (n = 198)	*P* Value[a]	12-mo Group (n = 194)	36-mo Group (n = 198)	*P* Value[a]
Any event	192 (99.0)	198 (100.0)	.24	39 (20.1)	65 (32.8)	.006
Hematological						
Anemia	140 (72.2)	159 (80.3)	.08	1 (0.5)	1 (0.5)	>.99
Leukopenia	67 (34.5)	93 (47.0)	.01	4 (2.1)	6 (3.0)	.75
Nonhematological						
Periorbital edema	115 (59.3)	147 (74.2)	.002	1 (0.5)	2 (1.0)	>.99
Fatigue	94 (48.5)	96 (48.5)	>.99	2 (1.0)	1 (0.5)	.62
Nausea	87 (44.8)	101 (51.0)	.23	3 (1.5)	1 (0.5)	.37
Diarrhea	85 (43.8)	107 (54.0)	.04	1 (0.5)	4 (2.0)	.37
Muscle cramps	60 (30.9)	97 (49.0)	<.001	1 (0.5)	2 (1.0)	>.99
Leg edema	64 (33.0)	81 (40.9)	.12	1 (0.5)	2 (1.0)	>.99
Biochemical						
Elevated blood lactate dehydrogenase	84 (43.3)	119 (60.1)	.001	0	0	
Elevated serum creatinine	59 (30.4)	88 (44.4)	.005	0	0	

[a] Fisher exact test.

Author Affiliations: Departments of Oncology (Drs Joensuu and Bono) and Pathology (Dr Sarlomo-Rikala), Helsinki University Central Hospital, Helsinki, Finland; Department of Oncology, Skåne University Hospital (Dr Eriksson) and Department of Cancer Epidemiology (Dr Alvegård), Lund University, Lund, Sweden; Department of Oncology, The Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway (Dr Sundby Hall); Department of Medical Oncology, Hematology, Immunology, Rheumatology, and Pulmonology, Medical Center, Eberhard-Karls-University, Tübingen, Germany (Dr Hartmann); Sarkomzentrum Berlin-Brandenburg, HELIOS Klinikum Berlin-Buch, Berlin, Germany (Drs Pink and Reichardt); Department of Oncology/Hematology, Marien Hospital, Düsseldorf, Germany (Dr Schütte); Department of Gastroenterology/Endocrinology, University of Göttingen, Göttingen, Germany (Dr Ramadori); Division of Surgical Oncology and Thoracic Surgery, Mannheim University Medical Center, Mannheim, Germany (Dr Hohenberger); III Medizinischen Klinik, Klinikum rechts der Isar, Munich, Germany (Dr Duyster); Klinik für Onkologie und Hämatologie am Krankenhaus Nordwest, Frankfurt, Germany (Dr Al-Batran); Department of Internal Medicine III, University Hospital-Großhadern, Ludwig Maximilians University, Munich (Dr Schlemmer); Sarcoma Center, West German Cancer Center, Essen, Germany (Dr Bauer); Department of Pathology, University of Cologne, Cologne, Germany (Dr Wardelmann); Department of Surgery, Sahlgrenska University Hospital, Gothenburg, Sweden (Dr Nilsson); Laboratory of Molecular Oncology, Biomedicum, University of Helsinki, Helsinki (Mr Sihto); Department of Oncology and Radiotherapy, Haukeland University Hospital, Bergen, Norway (Dr Monge); Department of Oncology and Radiotherapy, Oulu University Hospital, Oulu, Finland (Dr Kallio); Department of Biomedical Engineering and Computational Science, Aalto University, Espoo, Finland (Dr Vehtari); and 4Pharma, Turku, Finland (Mr Leinonen).

Author Contributions: Dr Joensuu had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Joensuu, Eriksson, Hall, Pink, Bono, Leinonen, Alvegård, Reichardt.
Acquisition of data: Joensuu, Eriksson, Hall, Hartmann, Pink, Schütte, Ramadori, Hohenberger, Duyster, Al-Batranm, Schlemmer, Bauer, Sarlomo-Rikala, Nilsson, Sihto, Monge, Bono, Kallio, Reichardt.
Analysis and interpretation of data: Joensuu, Eriksson, Hall, Schütte, Ramadori, Schlemmer, Wardelmann, Sihto, Monge, Bono, Leinonen, Reichardt.
Drafting of the manuscript: Joensuu, Eriksson, Hall, Sarlomo-Rikala, Vehtari, Reichardt.
Critical revision of the manuscript for important intellectual content: Joensuu, Eriksson, Hall, Hartmann, Pink, Schütte, Ramadori, Hohenberger, Duyster, Al-Batran, Schlemmer, Bauer, Wardelmann, Sarlomo-Rikala, Nilsson, Sihto, Monge, Bono, Kallio, Vehtari, Leinonen, Alvegård, Reichardt.
Statistical analysis: Joensuu, Vehtari, Leinonen.
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Study supervision: Joensuu, Eriksson, Schütte, Hohenberger, Schlemmer, Bauer, Nilsson, Reichardt.

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