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ORIGINAL REPORT

# Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas

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## ABSTRACT

### Purpose
In 2004, we started an intergroup randomized trial of adjuvant imatinib versus no further therapy after R0-R1 surgery patients with localized, high- or intermediate-risk GI stromal tumor (GIST).

### Patients and Methods
Patients were randomly assigned to 2 years of imatinib 400 mg daily or no further therapy after surgery. The primary end point was overall survival; relapse-free survival (RFS), relapse-free interval, and toxicity were secondary end points. In 2009, given the concurrent improvement in prognosis of patients with advanced GIST, we changed the primary end point to imatinib failure–free survival (IFFS), with agreement of the independent data monitoring committee. We report on a planned interim analysis.

### Results
A total of 908 patients were randomly assigned between December 2004 and October 2008: 454 to imatinib and 454 to observation. Of these, 835 patients were eligible. With a median follow-up of 4.7 years, 5-year IFFS was 87% in the imatinib arm versus 84% in the control arm (hazard ratio, 0.79; 98.5% CI, 0.50 to 1.25; $P = .21$); RFS was 84% versus 66% at 3 years and 69% versus 63% at 5 years (log-rank $P < .001$); and 5-year overall survival was 100% versus 99%, respectively. Among 528 patients with high-risk GIST by local pathologist, 5-year IFFS was 79% versus 73%; among 336 centrally reviewed high-risk patients, it was 77% versus 73%, respectively.

### Conclusion
This study confirms that adjuvant imatinib has an overt impact on RFS. No significant difference in IFFS was observed, although in the high-risk subgroup there was a trend in favor of the adjuvant arm. IFFS was conceived as a potential end point in the adjuvant setting because it is sensitive to secondary resistance, which is the main adverse prognostic factor in patients with advanced GIST.

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## INTRODUCTION

GI stromal tumors (GISTs) are rare cancers, the treatment of which in the advanced stages of disease has been revolutionized by the introduction of tyrosine kinase inhibitors targeting KIT and/or platelet-derived growth factor receptor alpha.[1,2] From the earliest use of imatinib in advanced GIST, it was clear that the drug was highly effective, and this was confirmed with longer follow-up.[3-6] The

main limiting factor is secondary resistance, which is often determined by the occurrence in cellular subclones of secondary mutations in the same oncogene initially affected by the primary mutation. The median time to this secondary resistance is 1 to 3 years in the advanced setting.[5,6]

Thus, from the early years of imatinib use in advanced GIST, the sarcoma community conceived trials to test this therapy in the adjuvant setting.[7,8] In 2004, the European Organisation for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group launched a randomized clinical trial of adjuvant imatinib in collaboration with the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas. We aimed to select patients with GIST with an intermediate or high risk of relapse, following the consensus classification used at the time, aiming to exclude only patients with a low risk of relapse. We assumed that a benefit in relapse-free survival (RFS) could be expected, given the high effectiveness of imatinib in patients with advanced GIST. However, this expected benefit would be meaningful only if it resulted in an increase in the cure rate or a substantial delay in relapse without any decrease in the time to progression, when relapsing patients are rechallenged with imatinib. Therefore, we chose overall survival (OS) as the primary end point of our trial. However, at a planned interim analysis in March 2009, it became evident to the study independent data monitoring committee (IDMC) that the likely overall duration of the trial would make it prohibitive to keep OS as the primary end point, so there was a strong recommendation that the trial have an amended primary end point. Because RFS also may not have served as a satisfactory trial end point, we identified an alternative end point—imatinib monotherapy failure–free survival (IFFS; ie, time to resistance to imatinib)—determined by the date of switching to an alternate tyrosine kinase inhibitor. In agreement with the IDMC, we adopted IFFS as the new primary end point of the trial. In June 2012, the IDMC recommended the release of the interim analysis results with continuation of the study to the planned final analysis. This article reports the interim analysis, as per the amended study protocol, focusing on the new primary study end point.

## PATIENTS AND METHODS

### *Study Design and Participants*

This was a randomized, open-label, multicenter phase III trial performed at 112 hospitals in 12 countries (Australia, Belgium, Denmark, France, Germany, Italy, New Zealand, Poland, Singapore, Spain, the Netherlands, and United Kingdom). Patients could be randomly assigned if they had a histologically proven diagnosis of primary resected GIST, with positive immunostaining for KIT (CD117), with risk of relapse documented on the surgical specimen according to the 2002 National Institutes of Health (NIH) Consensus Diagnosis of GIST[9] as high risk (tumor size $>$ 10 cm, mitotic rate $>$ 10/50 HPF, or tumor size $>$ 5 cm and mitotic rate $>$ 5/50 HPF) or intermediate risk (tumor size $\leq$ 5 cm and mitotic rate 6/50 to 10/50 HPF or tumor size $>$ 5 to 10 cm and mitotic rate $\leq$ 5/50 HPF). Surgery had to be performed from 2 weeks to 3 months before random assignment, and surgical margins had to be either

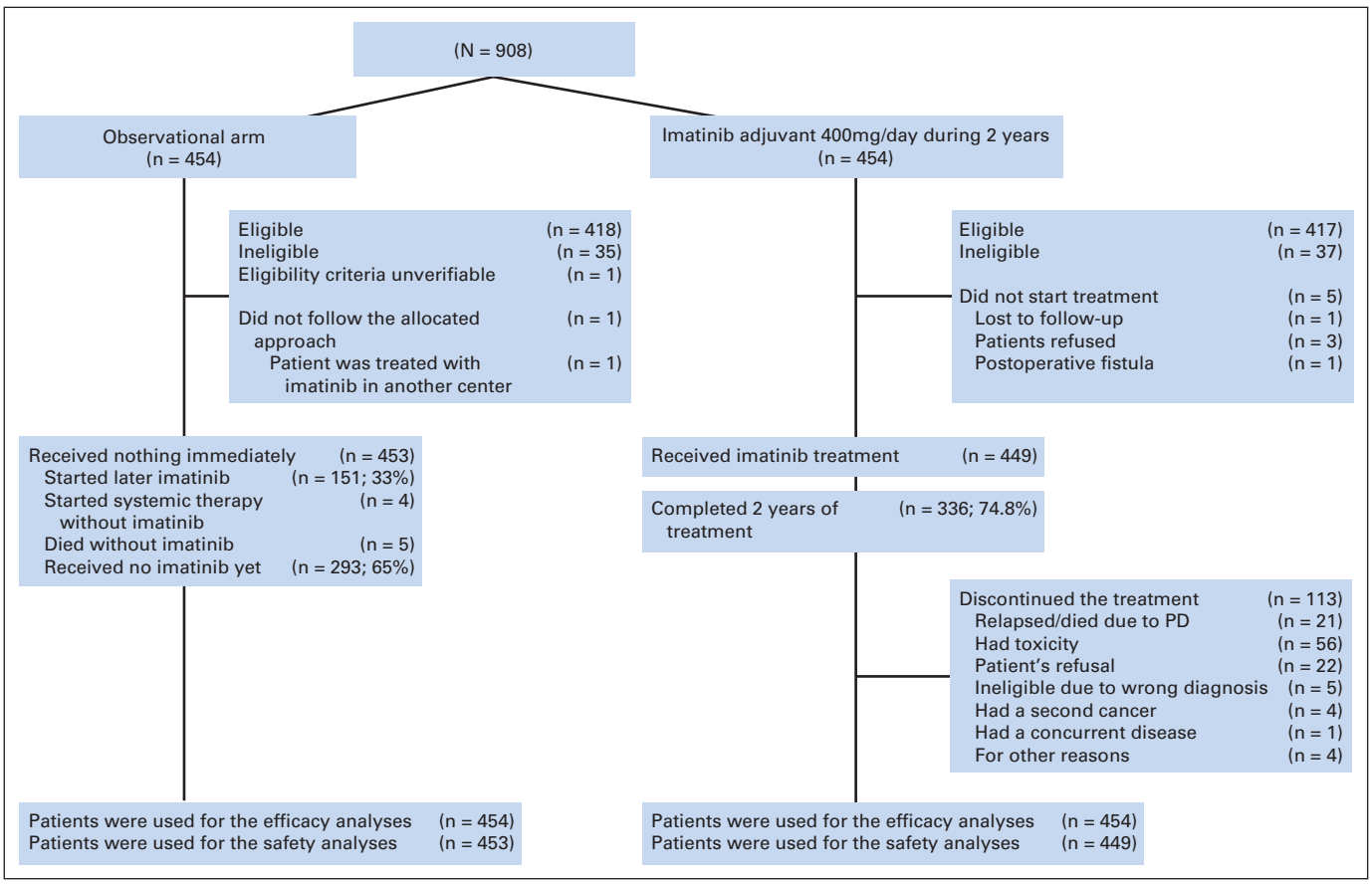


**Fig 1.** CONSORT diagram. PD, progressive disease.

R0 or R1. Intraoperative tumor rupture was coded as R1 and properly recorded by a panel of expert surgeons who had access to the original surgical reports. No prior radiation therapy or systemic treatment for GIST was allowed. Distant metastases were not permitted, including any peritoneal lesions not contiguous to the primary tumor; regional positive lymph nodes were permitted, if completely excised. Participants had to be age ≥ 18 years and have WHO performance status 0 to 2. Cardiac ejection function had to be assessed at baseline and during treatment. Severe and/or uncontrolled concurrent medical disease was not allowed, nor was any prior or ongoing other malignancy, except adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or cancer adequately treated with eradicative intent from which the patient had been continuously free for ≥ 5 years. Eligible patients were randomly assigned (using minimization) after surgery either to receive imatinib 400 mg per day for 2 years or to be observed without further antitumoral therapy. Randomization was stratified by center, risk category (high *v* intermediate), tumor site (gastric *v* other), and resection level (R0 *v* R1). Neither patients nor investigators were masked to treatment allocation. The study was approved by the institutional review board and/or ethics committee of each participating institution.

### Methods

In the adjuvant arm, imatinib was administered for 2 years, and treatment was discontinued in case of relapse of disease, unacceptable toxicity, or withdrawal from study. Dose modifications for hematologic and nonhematologic adverse events were foreseen in the protocol. The study protocol did not specify the treatment to be administered after relapse. However, guidelines were circulated after amending the protocol, recommending restarting imatinib at a dose of 400 mg daily or possibly 800 mg for patients with an exon 9 *KIT*-mutated GIST, with the only logical exception being those patients who experienced relapse during imatinib therapy.

While receiving treatment, patients underwent follow-up every week for the first month, then every 2 weeks for the second month, then monthly until the end of the sixth month of therapy, and subsequently every 3 months until treatment discontinuation. Chest x-ray and abdominal computed tomography scan or magnetic resonance imaging were required within 1 month before random assignment and every 3 months thereafter. After the end of treatment (treated arm) and after random assignment (control arm), follow-up was performed every 3 months until 2 years after random assignment, then every 4 months until 5 years had elapsed, and thereafter at least annually, at the discretion of the responsible physician.

### Outcomes

The study was originally designed with OS as the primary end point. Secondary end points were RFS, relapse-free interval, incidence of adverse events, and, as of December 2007, time to imatinib failure. The initial estimated sample size of 400 patients to be recruited over 5 years was increased to 900 patients in December 2007 to adjust for the larger-than-expected subgroup of patients recruited with low- and intermediate-risk tumors and the higher-than-expected survival rate in the control group. In March 2009, it became clear that the planned interim analysis of OS would not be feasible within a reasonable timeline; therefore, the IDMC recommended changing the primary end point. IFFS was chosen, and the study design was updated accordingly by an independent statistician. IFFS was determined from the date of random assignment to the date of the start of a new systemic treatment, the start of a combination of imatinib with a new systemic treatment, or death resulting from any cause, whichever occurred first. OS was measured from the date of random assignment to the date of death, whatever the cause. RFS was measured from the date of random assignment to the date of relapse (local and/or distant) or death, whichever occurred first. In the absence of such events, patients were censored at the date of last follow-up or the clinical cutoff date, whichever occurred first. Relapse-free interval was measured from the date of random assignment to the date of relapse. Death without relapse was considered a competing risk. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (version 3.0).

### Statistical Analysis

Improvement of IFFS was considered clinically significant if the risk of imatinib failure was decreased by 34.5% in the adjuvant treatment arm relative to the reference group, corresponding to a hazard ratio (HR) ≤ 0.655. To detect such a difference using a two-sided log-rank test and allowing for one interim analysis, a total of 196 events needed to be observed ($\beta = 0.2$). An interim analysis was planned and carried out after observation of 98 events, testing both for H0 and H1. A power family error spending function with a boundary parameter of 0.2 was used. An overall $\alpha$ level of 0.05 (two-sided test) was used, with a significance level of .015 dedicated to the interim analysis.

All efficacy analyses were carried out according to the intent-to-treat policy. These time-to-event end points were estimated using the Kaplan-Meier method and compared between treatment arms using two-sided log-rank tests. Safety analysis included patients who had started adjuvant therapy.

East software (version 5; Cytel, Cambridge, MA) was used to calculate sample size and stopping boundaries; we performed all other statistical analyses with SAS software (version 9.3; SAS Institute, Cary, NC). This report is based on all data available on January 1, 2012.

## RESULTS

In total, 908 patients were randomly assigned between December 8, 2004, and October 20, 2008: 454 to the adjuvant imatinib arm and 454 to the observation arm (Fig 1). All patient files were reviewed by the study coordinator and the clinical research physician at EORTC headquarters. Seventy-two patients (7.9%) did not meet the eligibility criteria: 67 had an inappropriate diagnosis, two were ineligible because of prior treatment, one had concurrent malignant disease, one had a prior cancer < 5 years ago, and one had a presentation highly suggestive of retroperitoneal sarcoma. Median age was 59 years (interquartile range [IQR], 49 to 68); 51% were men, 86% had performance status of 0, and 55% had a gastric GIST (Table 1). Table 2 summarizes the baseline risk level of enrolled patients: 380 patients (42%) were identified as low or intermediate risk and 528 (58%) as high risk. Central pathology review was available for 696 patients. Median time between

**Table 1.** Patient Demographic and Clinical Characteristics

| Characteristic | No. (%) | | |
|---|---|---|---|
| | Observation Arm (n = 454) | Imatinib Adjuvant Arm (n = 454) | Total (N = 908) |
| PS | | | |
| 0 | 380 (83.7) | 399 (87.9) | 779 (85.8) |
| 1 | 74 (16.3) | 54 (11.9) | 128 (14.1) |
| 2 | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| Sex | | | |
| Male | 234 (51.5) | 232 (51.1) | 466 (51.3) |
| Female | 220 (48.5) | 222 (48.9) | 442 (48.7) |
| Age, years | | | |
| ≤ 20 | 1 (0.2) | 3 (0.7) | 4 (0.4) |
| 20-40 | 29 (6.4) | 52 (11.5) | 81 (8.9) |
| 40-60 | 223 (49.1) | 189 (41.6) | 412 (45.4) |
| > 60 | 201 (44.3) | 210 (46.3) | 411 (45.3) |
| Median | 58 | 59 | 59 |
| Range | 20-89 | 18-86 | 18-89 |
| Q1-Q3 | 49-68 | 48-67 | 49-68 |
| Tumor site | | | |
| Gastric | 253 (55.7) | 250 (55.1) | 503 (55.4) |
| Other | 201 (44.3) | 204 (44.9) | 405 (44.6) |

Abbreviations: PS, performance status; Q, quartile.

  

**Table 2.** Baseline Risk

| Characteristic | No. (%) | | | | | |
|---|---|---|---|---|---|---|
| | Histopathology by Local Pathologist | | | Histopathology by Central Review | | |
| | Observation Arm (n = 454) | Imatinib Adjuvant Arm (n = 454) | Total (N = 908) | Observation Arm (n = 454) | Imatinib Adjuvant Arm (n = 454) | Total (N = 908) |
| Tumor | | | | | | |
| Non-GIST | | | | 5 (1.1) | 6 (1.3) | 11 (1.2) |
| GIST | 454 (100.0) | 454 (100.0) | 908 (100.0) | 333 (73.3) | 351 (77.3) | 684 (75.3) |
| Unknown | | | | 0 (0.0) | 1 (0.2) | 1 (0.1) |
| Not reviewed | | | | 116 (25.6) | 96 (21.1) | 212 (23.3) |
| Mitotic rate, HPF | | | | | | |
| ≤ 5/50 | 220 (48.5) | 201 (44.3) | 421 (46.4) | 172 (37.9) | 180 (39.6) | 352 (38.8) |
| 5-10/50 | 102 (22.5) | 110 (24.2) | 212 (23.3) | 61 (13.4) | 81 (17.8) | 142 (15.6) |
| > 10/50 | 132 (29.1) | 143 (31.5) | 275 (30.3) | 99 (21.8) | 92 (20.3) | 191 (21.0) |
| Not reviewed | | | | 122 (26.9) | 101 (22.2) | 223 (24.6) |
| Tumor size, cm | | | | | | |
| < 2 | 2 (0.4) | 1 (0.2) | 3 (0.3) | 5 (1.1) | 0 (0.0) | 5 (0.6) |
| 2-5 | 43 (9.5) | 53 (11.7) | 96 (10.6) | 23 (5.1) | 46 (10.1) | 69 (7.6) |
| 5-10 | 290 (63.9) | 283 (62.3) | 573 (63.1) | 222 (48.9) | 212 (46.7) | 434 (47.8) |
| ≥ 10 | 119 (26.2) | 117 (25.8) | 236 (26.0) | 83 (18.3) | 91 (20.0) | 174 (19.2) |
| Not reviewed | | | | 121 (26.7) | 105 (23.1) | 226 (24.9) |
| Risk category | | | | | | |
| Very low | | | | 2 (0.4) | 0 (0.0) | 2 (0.2) |
| Low | 7 (1.5) | 2 (0.4) | 9 (1.0) | 13 (2.9) | 19 (4.2) | 32 (3.5) |
| Intermediate | 185 (40.7) | 186 (41.0) | 371 (40.9) | 150 (33.0) | 162 (35.7) | 312 (34.4) |
| High | 262 (57.7) | 266 (58.6) | 528 (58.1) | 168 (37.0) | 168 (37.0) | 336 (37.0) |
| Not reviewed | | | | 121 (26.7) | 105 (23.1) | 226 (24.9) |

Abbreviation: GIST, GI stromal tumor.

last surgery and random assignment was 67 days (range, 13 to 112). Eighty-four percent of patients had an R0 resection.

Six patients did not start their allocated treatment: one patient in the observation arm received imatinib at another center, three patients refused adjuvant imatinib, one did not return to the clinic after being randomly assigned, and one had a postoperative fistula (Fig 1). Of the remaining 449 patients in the adjuvant imatinib arm, 336 (75%) completed 2 years of treatment (two patients continued with therapy for an extra half year); 22 (4.9%) stopped because of progression, 56 (12.5%) stopped because of toxicity (more information provided in Appendix Table A1, online only), 20 (4.5%) refused to follow the protocol, six discontinued because they were ineligible (five did not have GIST, and one had concurrent malignant disease), four developed a second cancer, and four stopped for other reasons. Among the 113 patients who discontinued treatment, 52 (46%) did so within 6 months. The most common grade 3 to 4 toxicities are summarized in Appendix Table A2 (online only).

Median follow-up was 4.7 years (IQR, 4.0 to 5.3) in the imatinib arm and 4.6 years (IQR, 3.8 to 5.2) in the observational arm. Figure 2A shows the IFFS curves by treatment arm; there was no significant difference (HR, 0.79; 98.5% CI, 0.50 to 1.25; $P = .21$). A total of 793 patients remained imatinib failure free (imatinib arm, n = 402 *v* observational arm, n = 391); 92 patients (n = 40 *v* 52) were switched to a systemic treatment other than imatinib (including 62 to sunitinib, 10 to nilotinib, and six to masitinib); 23 patients (n = 12 *v* 11) died without starting new systemic treatment.

Relapse occurred in 282 patients (imatinib arm, n = 121 *v* observational arm, n = 161), with RFS significantly better in the adjuvant imatinib arm (84% *v* 66% at 3 years; 69% *v* 63% at 5 years; log-rank $P < .001$; Fig 2B). OS is summarized in Figure 2C: 62 patients died (n = 33 *v* 29), mostly because of progressive disease (22 *v* 23), but survival did not differ between the two treatment arms (5-year survival rate: imatinib arm, 91.8% *v* observational arm, 92.7%). Sensitivity analyses with stratified Cox proportional hazards models showed similar results (data not shown).

On relapse, 105 patients received salvage imatinib. Figure 3 shows IFFS broken down between the intermediate- and the high-risk subgroups, as defined according to the NIH 2002 consensus classification. An additional nonpreplanned analysis was performed following the criteria of the more recent Armed Forces Institute of Pathology risk classification[8] of ruptured, high-risk (gastric: > 5 cm and > five mitoses; nongastric: > 10 cm or > five mitoses), and low- or intermediate-risk tumors (everything else). Figure 4 shows IFFS, RFS, and OS according to this classification, with a statistically significant difference in RFS, a nonstatistically significant trend in IFFS, and no difference in OS.

No significant differences in IFFS were found in the subgroup of patients with a tumor rupture. Figure 5 shows that their RFS continues to show differences according to baseline risk, despite the tumor rupture.

## DISCUSSION

This randomized trial of adjuvant imatinib for 2 years versus observation in patients with resected localized GIST showed no significant

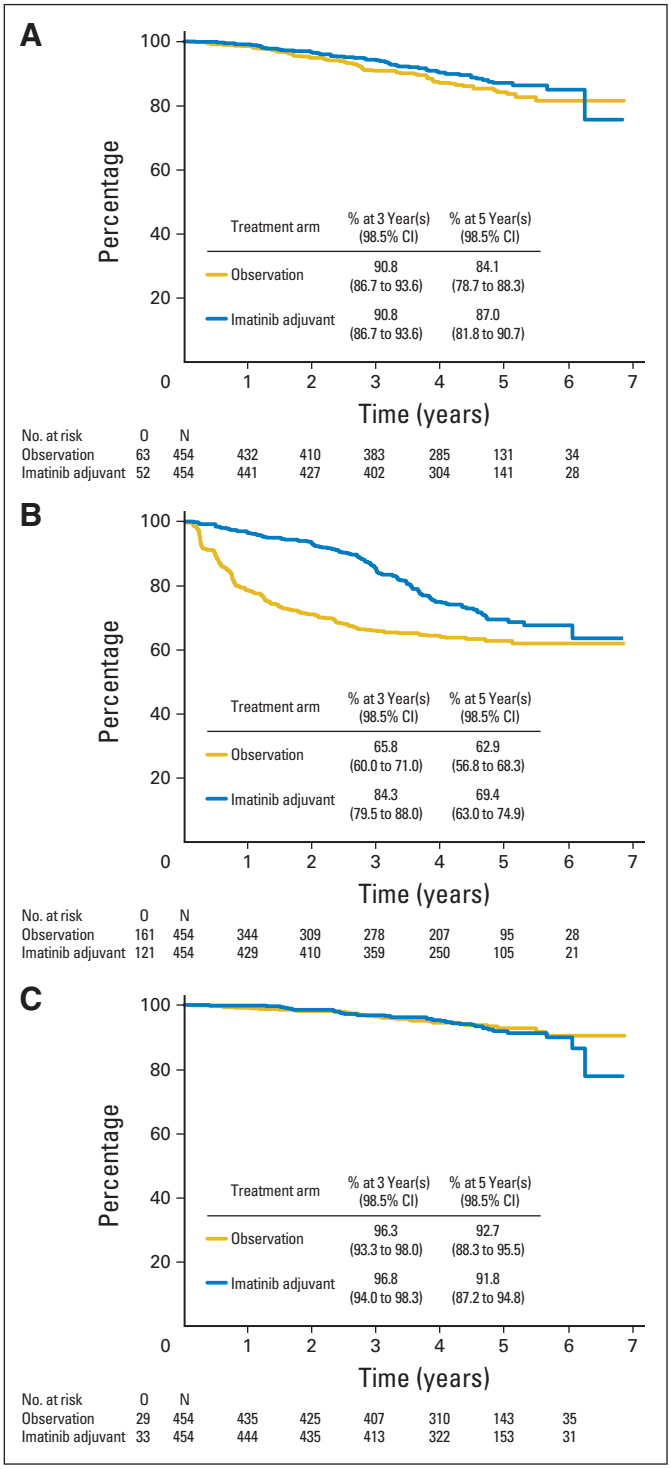


**Fig 2.** (A) Imatinib monotherapy failure–free, (B) relapse-free, and (C) overall survival by treatment arm. N, number of patients; O, number of observed events.

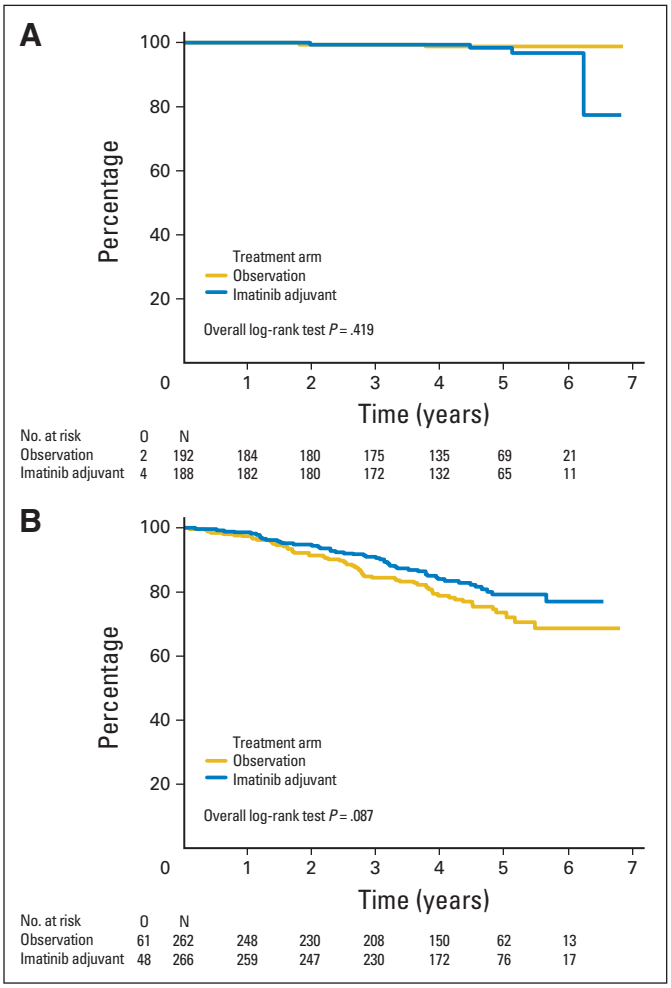


**Fig 3.** Imatinib monotherapy failure–free survival in (A) intermediate- and (B) high-risk patients, classified according to 2002 National Institutes of Health classification. N, number of patients; O, number of observed events.

difference in terms of IFFS, although in a nonpreplanned subgroup analysis a trend was observed in patients with high-risk tumors in favor of adjuvant therapy after complete surgery. This trial confirms the results of the two other published trials of adjuvant imatinib in patients with localized GIST (ie, RFS is substantially improved by adjuvant imatinib).[9,10] However, most of the benefit is lost after 1 to 3 years from the end of the adjuvant treatment period. Then, delaying relapse without a major decrease in the relapse rate may have a limited impact on OS of high-risk patients, as shown in another trial, although in our trial only a longer follow-up will allow us to fully explore OS and the surrogate meaning of IFFS. However, the trend of IFFS in the adjuvant arm at least suggests that exposure to imatinib in the adjuvant setting does not induce a selection pressure toward secondary resistance, at least within the time interval that adjuvant imatinib was administered in this study.

A weakness of this trial is that almost half of the enrolled patients had an intermediate risk of relapse according to current risk classifications. When conceiving the trial, we decided to include a range of risks to assess the extent of the benefit across the risk categories. Subsequently, the intermediate-risk category of the 2002 NIH consensus classification turned out to include a proportion of patients who had a low risk of relapse.[9,10,11] This is one of the main reasons why this trial was repeatedly amended to preserve its statistical power regarding substantial-risk patients. The analysis was therefore also broken down according to risk category as defined by the new Armed Forces Institute of Pathology classification, which more accurately reflects what is currently known about the risk of relapse across patients with localized GIST.[8]

  

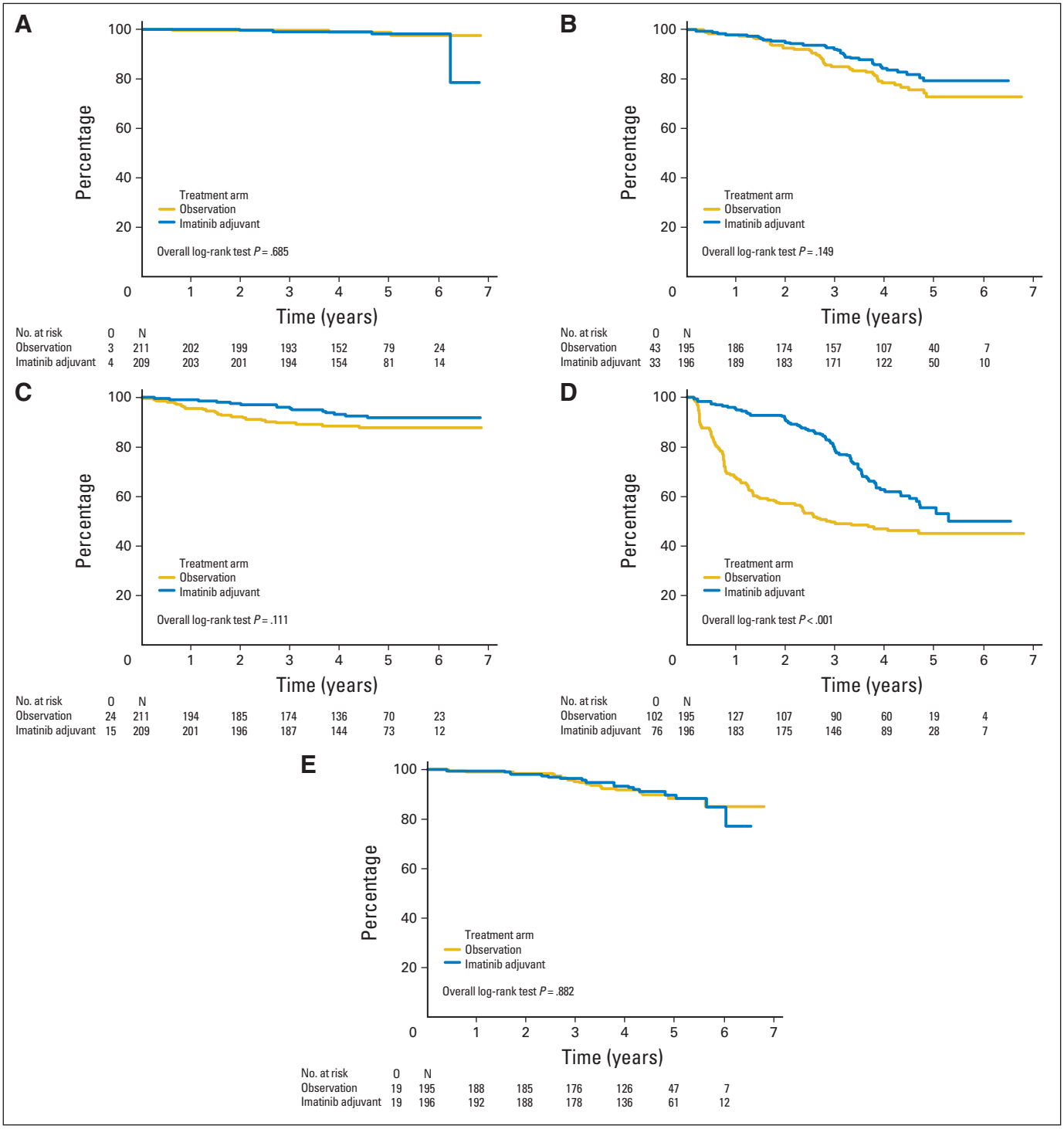


**Fig 4.** (A, B) Imatinib monotherapy failure–free, (C, D) relapse-free, and (E) overall survival by (A, C) intermediate and (B, D, E) high-risk classification according to Armed Forces Institute of Pathology. Only four events occurred in low- or intermediate-risk group, so curves not shown. N, number of patients; O, number of observed events.

We included patients with both R0 and R1 resections, given the lack of definitive proof that R1 patients have a worse prognosis, using marginal status as a stratification criterion.[12] We also included patients who had tumor rupture within the R1 stratum. Today, we know that tumor rupture substantially worsens prognosis of patients with GIST.[13] The proportion of these patients in this trial was 11%. Interestingly, we detected that the risk of relapse estimated with the three main prognostic factors may break down tumor rupture into different risk categories. Numbers are low, but it is possible that the inherent risk of relapse is not negligible in determining the final risk of patients with tumor rupture and also that different kinds of tumor rupture may actually exist. In this trial, a panel of surgeons reviewed surgical

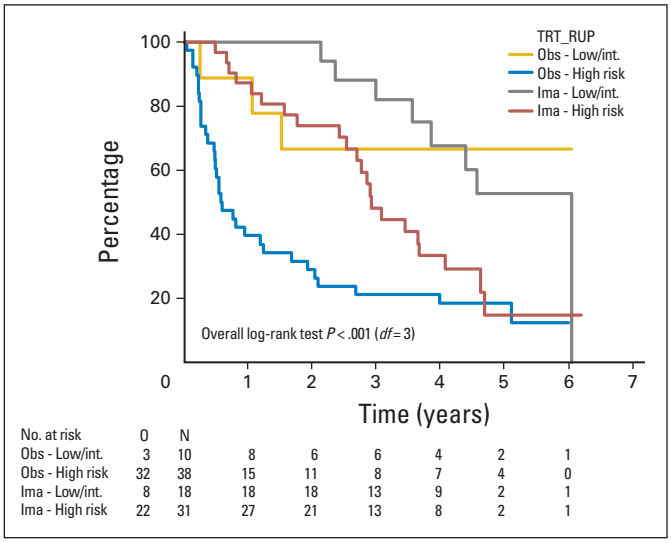


**Fig 5.** Relapse-free survival in patients with tumor rupture (TRT_RUP). Ima, imatinib; int, intermediate; Obs, observation.

reports in the original languages. Their findings will be the subject of a separate report.

In our trial, we centralized tumor samples to carry out mutational analysis. The final results of this analysis are still not available and will be the subject of a separate report. This will allow an assessment of the benefit of imatinib in non–exon 11 *KIT*-mutated GIST, as recently published with regard to the American College of Surgeons Oncology Group trial.[14] Thus, we will be able to estimate the effectiveness of adjuvant imatinib in imatinib-insensitive mutations and in wild-type GIST. Unfortunately, with the lack of any planned increase in dose for exon 9 *KIT*-mutated GIST, we will not be in a position to determine whether a lack of benefit, if any, in this category could be corrected by treating patients with 800 mg, as currently recommended by some institutions.[15]

Clearly, a crucial finding of adjuvant trials in GIST, including ours, has been that stopping adjuvant therapy is followed by relapse in at least most patients expected to experience relapse in the absence of any adjuvant therapy. It follows that adjuvant imatinib therapy does not seem to cure minimum residual disease in patients with resected GIST. Of course, the most logical consequence for clinical research is the attempt to prolong treatment duration, using the example of adjuvant hormonal therapies in hormone-sensitive cancers. We believe that this should be confined to the clinical research setting, not extended to clinical practice, for the same reasons why we originally chose to carry out a randomized clinical trial with a no-treatment arm having OS as its primary end point. In fact, trials should rule out a detrimental effect of prolonging the adjuvant treatment in terms of an earlier occurrence of secondary resistance. So far, using imatinib for 1, 2, or 3 years in the adjuvant setting has not resulted in any detrimental effect when the same therapy has been used on relapse.

In this sense, our primary end point (ie, survival interval to switching to alternate tyrosine kinase inhibitor from first used in the individual patient) will be validated—or not—by OS data on longer follow-up. If it is, it could be used as an intermediate end point to answer future questions on adjuvant molecularly targeted therapies in GIST and possibly other solid cancers. Of course, one should be aware of its inherent weaknesses. The main one is that it assumes that secondary resistance is an essentially irrecoverable outcome. So far, this is the case, by and large, in GIST, but clearly we all hope that additional-line agents, among those already available and those under intense research, will substantially alter the course of advanced disease after secondary resistance.[16,17] The second limitation is that protocols designed for the adjuvant use of a drug should also take into account treatment guidelines for relapse. In our trial, this was not done, although we later disseminated guidelines to all participating centers, thus limiting the proportion of patients who did not receive imatinib as their first treatment on relapse. However, we carried out sensitivity analyses and ruled out that the outcome of these patients under an intent-to-treat approach would have altered the general conclusions of this trial.

In the end, this trial adds to available evidence on the efficacy of adjuvant imatinib in GIST. We can confirm that RFS is significantly improved by adjuvant targeted therapy. It follows that a survival benefit would be consistent with the trend seen in our potential surrogate end point in the high-risk subgroup, although this will need to be assessed with longer follow-up. The issue of optimum adjuvant treatment duration remains a question for clinical research. Another question is whether new strategies of administering targeted therapies may be more effective (eg, by rotating regimens or combinations of more than one targeted agent), possibly guided by molecular biomarkers during treatment, such as liquid biopsy and others.[18]

## 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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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Time to Definitive Failure to the First Tyrosine Kinase Inhibitor in Localized GI Stromal Tumors Treated With Imatinib As an Adjuvant: A European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group Intergroup Randomized Trial in Collaboration With the Australasian Gastro-Intestinal Trials Group, UNICANCER, French Sarcoma Group, Italian Sarcoma Group, and Spanish Group for Research on Sarcomas**

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## Appendix

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**Table A1.** Toxicities Resulting in Early Stopping of Treatment Reported by Treating Physician for Each Patient

| Duration of Treatment (days) | Toxicity |
|---|---|
| 3 | Nausea and anorexia |
| 19 | Myocardial ischemia |
| 24 | Nausea and vomiting |
| 27 | Edema, hematomas, cramps |
| 32 | Rash, alopecia, neutropenia |
| 34 | Emesis |
| 39 | Diarrhea (treatment related) |
| 40 | Severe nausea and asthenia |
| 42 | Dyspnea, facial and periorbital edema |
| 43 | Dyspnea, fever, vomiting, diarrhea |
| 52 | Rash, edema, eosinophilia |
| 56 | Hepatic cytolysis |
| 59 | Hepatitis |
| 63 | Suspected pulmonary toxicity |
| 71 | Increase of transaminase |
| 75 | Cutaneous toxicity |
| 83 | Edema of superior and inferior limbs with cutaneous desquamation palpebral edema |
| 86 | Syncope, fatigue, anorexia |
| 88 | Grade 2 rash with pain, edema, ulceration |
| 97 | Diarrhea and limb edema |
| 98 | Diarrhea and dyspepsia |
| 101 | Emesis and nausea (grade 3) |
| 104 | Malnutrition, profuse diarrhea, limb edema |
| 105 | Rash and edema (grade 3) |
| 114 | ALT and AST increase |
| 115 | Rash/desquamation, edema, water retention |
| 121 | Mucositis (grade 3) |
| 127 | Cutaneous rash |
| 128 | Fatigue and erectile dysfunction |
| 139 | Diarrhea (grade 3) |
| 143 | Fatigue and nausea |
| 146 | Prolonged neutropenia |
| 189 | ALT and AST increase |
| 189 | Skin rash (grade 3) |
| 201 | Conjunctivitis (bleeding) |
| 228 | Myocardial infarction |
| 246 | Hepatotoxicity |
| 257 | Bilateral pulmonary infiltrates |
| 273 | Edema (head and neck), viral infection, cognitive disturbance, fatigue |
| 275 | Abdominal pain and total bilirubin increase |
| 305 | Asthenia (grade 2) |
| 310 | High transaminase level because of autoimmune hepatitis |
| 319 | High liver function tests |
| 431 | Depression (grade 3) |
| 441 | Vomiting and fatigue |
| 446 | Fatigue and edema (head and neck) |
| 466 | Pancreatitis |
| 474 | Pain in bones |
| 509 | Breathlessness and weight gain |
| 515 | Pneumonia, acute respiratory insufficiency, acute circulation insufficiency |
| 550 | Asthenia, mucositis, neutropenia, thrombocytopenia |
| 628 | Rash |
| 647 | Gastroenteritis and dehydration |
| 656 | Right arm pain (arthritis) |
| 685 | Thrombosis (grade 2) |
| 719 | Neutropenia |

**Table A2.** Main Toxicities (grade 3 and/or 4; reported in ≥ 2.5% of patients)

| Toxicity | Patients in Imatinib Arm (%) |
|---|---|
| Neutropenia | 6.2 |
| Weight loss or gain | 3.3 |
| Infections | 3.1 |
| ALT increase | 2.8 |