# Final analysis of the randomized trial on imatinib as an adjuvant in localized gastrointestinal stromal tumors (GIST) from the EORTC Soft Tissue and Bone Sarcoma Group (STBSG), the Australasian Gastro-Intestinal Trials Group (AGITG), UNICANCER, French Sarcoma Group (FSG), Italian Sarcoma Group (ISG), Spanish Group for Research on Sarcomas (GEIS)

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Running head: adjuvant imatinib in localized GIST
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## Highlights

- In this randomized trial, adjuvant imatinib for 2 years in localized GIST significantly prolonged relapse-free survival (RFS)
- In the high-risk subgroup, there was a trend toward a better long-term imatinib-failure-free survival
- This is consistent with the German/Scandinavian trial results, supporting current therapy with adjuvant imatinib for 3 years

**Abstract (from ESMO abstract)**

**Background** In 2004, we started an intergroup randomized trial of adjuvant imatinib versus no further therapy after R0-R1 surgery in localized, high/intermediate-risk GIST patients. Interim analysis results were published in 2015 upon recommendation from an independent data review committee. We report the final outcome of the study.

**Methods** This was a randomized, open label, multicenter phase III trial performed at 112 hospitals in 12 countries. Patients were randomized to 2 years (yrs) of imatinib, 400 mg daily, or no further therapy after surgery. The primary end-point was imatinib failure-free survival (IFFS), while relapse-free survival (RFS), relapse-free interval (RFI), overall survival (OS) and toxicity were secondary end-points. Adjusting for the interim analyses, results on IFFS were assessed on a 4.3% significance levels; for the other endpoints, 5% was used.

**Results** 908 patients were randomized between January 2005 and October 2008, 454 to imatinib and 454 to observation. 835 patients were eligible. With a median follow-up of 9.1 years, 5 (10)-year IFFS was 87% (75%) in the imatinib arm versus 83% (74%) in the control arm (HR=0.87, 95.7% CI [0.65; 1.15], p=0.31); RFS was 70% versus 63% at 5 years and 63% vs 61% at 10 years, (HR=0.71, 95% CI [0.57; 0.89], p=0.002); OS was 93% versus 92% at 5 years and 80% versus 78% at 10 years (HR=0.88, 95% CI [0.65; 1.21], p=0.43). Among 526 patients with high-risk GIST by local pathology, 10-year IFFS and RFS were 69% versus 61%, and 48% versus 43%, respectively.

**Conclusions** With 9.1 years of follow-up, a trend toward better long-term IFFS in imatinib-treated patients was observed in the high-risk subgroup. Although the difference was not statistically significant and the surrogacy value of such an end-point is not validated, this may be seen as supporting the results reported by the Scandinavian/German trial, showing a sustained small but significant long-term OS benefit in high risk GIST patients treated with 3 years of adjuvant imatinib.

Key words: gastrointestinal stromal tumours (GIST), imatinib, adjuvant

**Introduction – from previous manuscript still**

GISTs are rare cancers, whose treatment in the advanced phase of disease has been a model of the way targeted therapies may impact the prognosis of sensitive advanced solid cancers (1, 2). Imatinib is able to provide a median survival in excess of 5 years in the advanced setting, with a proportion of patients becoming long-term progression-free survivors in the range of 10% (3-5). The main limiting factor is secondary resistance, with a median time to its occurrence in the range of 2 years. Thus, it was logical to conceive imatinib as an adjuvant to surgery, looking at its prognostic impact on minimal residual disease.

In 2004, the EORTC STBSG launched a randomized clinical trial of adjuvant imatinib in collaboration with AGITG, UNICANCER, ISG and GEIS. We decided to include all GIST patients with an "intermediate" or "high" risk of relapse, following the consensus classification used at the time, thus only excluding patients with low risk disease. In subsequent years, a proportion of those eligible patients would have been considered to have a low risk as well. When designing the trial, we believed that a benefit in relapse-free survival (RFS) was more than likely, and decided that a meaningful benefit would have been in place only if it resulted in an increase in the cure rate, or, at least, in a substantial delay of relapses, provided no decrease in the time to progression was to occur when re-challenging relapsing patients with imatinib. Therefore, we chose overall survival (OS) as the primary end point of the trial. At a planned interim analysis in March 2009, it was clear to the study Independent Data Monitoring Committee (IDMC) that keeping OS as the primary end-point would have been incompatible with a reasonable duration of the trial. We then conceived another primary end-point, imatinib failure-free survival (IFFS), as an estimate of the time to resistance to imatinib, pragmatically defined as a survival interval to the date of switching to an alternate tyrosine kinase inhibitor at any time during or following the adjuvant period. As per recommendations of the

IDMC, the interim analysis was published in 2015, while continuing the study follow-up to the planned final analysis; this is reported in this paper (6).

## 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, UK). Patients could be randomized 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 NIH Consensus Diagnosis of GIST (9), as "high-risk" (tumor size >10 cm; or mitotic rate >10/50HPF; or tumor size >5 cm and mitotic rate >5/50HPF), or "intermediate-risk" (tumor size ≤5 cm and mitotic rate 6-10/50HPF; or tumor size > 5-10 cm and mitotic rate ≤5/50HPF). Surgery had to be performed from 2 weeks to 3 months before randomization and surgical margins had to be either R0 or R1. Eligible patients were randomized (using minimization) after surgery either to receive imatinib (400 mg/day) for 2 years, or to be followed without further antitumoral therapy. Randomization was stratified by center, risk category (high vs intermediate), tumor site (gastric vs other) and resection level (R0 vs R1). Neither patients nor investigators were masked to treatment allocation.

The study was approved by the institutional review boards and/or ethics committees 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 hematological and non-hematological adverse events were foreseen in the protocol. The study protocol did not specify the treatment to be administered following relapse. However, guidelines were circulated after amending the protocol, recommending re-starting imatinib at the dose of 400 mg daily, and possibly 800 mg for patients with an exon 9 *KIT*-mutated GIST, with the only logical exception of those patients who relapsed during imatinib therapy.

While on treatment, patients were followed every week for the first month, then every 2 weeks for the second month, then monthly until the end of the 6th month of therapy, and subsequently every 3 months until treatment discontinuation. Chest X-ray and abdominal CT scan or MRI were required within one month prior to randomization, and every 3 months thereafter. After the end of treatment (treated arm) and after randomization (control arm) follow-up was performed every 3 months until 2 years after randomization, then every 4 months until 5 years had elapsed, and thereafter at least annually, at the discretion of the responsible physician.

*Outcomes*

Details of the historical amendments to this study have been previously provided (REF JCO 2015). After study amendment, the primary endpoint of this study was "Imatinib monotherapy failure-free survival" (IFFS), determined from the date of randomization to the date of start of a new systemic treatment, a combination of imatinib with any new systemic treatment or death from any cause, whichever occurred first. Secondary end-points were relapse-free survival (RFS), overall survival (OS) and incidence of adverse events. RFS was measured from the date of randomization 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 cut-off date, whichever occurred first. Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE), 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) of 0.655 or less. 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. After careful review, the Independent Data Monitoring Committee recommended release of the interim results (REF JCO 2015). A Power Family error spending function with a boundary parameter equal to 0.2 was used. An overall alpha level of 0.05 (two-sided test) was used, with a significance level of 0.015 dedicated to the interim analysis and 0.043 remaining available for the final analysis.

All efficacy analyses were carried out according to the intent to treat (ITT) policy. These time-to-event endpoints were estimated using Kaplan-Meier method and compared between the treatment arms using Cox models adjusted for the stratification factors. Safety analysis included patients who had started adjuvant therapy.

East (version 6.4) was used to calculate sample size and stopping boundaries; we did all other statistical analyses with SAS (version 9.4). This trial was registered with ClinicalTrials.gov, number NCT00103168. This report is based on all data available on July 12, 2017.

**Results**

In total, 908 patients were randomized between December 08, 2004 and October 20, 2008; 454 were in the adjuvant imatinib arm and 454 in the observation arm (see Figure 1). All patient files were reviewed by the study coordinator and the clinical research physician at the EORTC Headquarter. Seventy two (7.9%) patients did not meet the eligibility criteria: 67 had an inappropriate diagnosis, 2 were ineligible due to prior treatment, 1 had concurrent malignant disease, 1 had a prior cancer less than 5 years ago and 1 had a presentation highly suggestive of retroperitoneal sarcoma. Median age was 59 years (IQR 49-68), 51% were male, 86% had performance status (PS) 0, 55% of patients had a gastric GIST (Table 1).

Median follow-up for the final analysis was 9 years (IQR: 8-10). Figure 2A shows the IFFS curves by treatment arm. There was no significant difference between the arms (adjusted HR = 0.87, 95.7% CI 0.65–1.15, p = 0.307). 706 patients remained imatinib-failure free (358 vs 348), 142 patients (66 vs 76) were switched to a systemic treatment other than imatinib (including 99 patients

to sunitinib, 12 to masitinib and 9 to nilotinib), and 60 patients (30 vs 30) died without starting new systemic treatment.

Relapse or death occurred in 326 patients (155 vs 171), with RFS significantly better in the adjuvant imatinib arm than in the observation arm (adjusted HR = 0.71, 95% CI 0.57-0.89, p = 0.002; Figure 2B). RFS rates were 70% versus 63% at 5 years and 62.5% versus 61% at 10 years. For OS, 158 patients died (75 vs 83), mostly due to progressive disease (49 vs 56). There was no OS significance difference between the treatment arms (adjusted HR = 0.88, 95% CI 0.65-1.21, p = 0.429; Figure 2C). In addition, survival did not differ between the two treatment arms in terms of point estimate rates (10-year survival rates 80% vs 78% in the imatinib arm vs. observational arm, respectively). Sensitivity analyses with log-rank tests showed similar results (not presented here).

Two hundred ninety-nine patients received salvage imatinib on relapse (138 in the imatinib arm and 161 in the observation arm).

Figure 3 shows IFFS, RFS and OS broken down between the intermediate- and the high-risk subgroups following the criteria of the more recent AFIP risk classification (10) into ruptured tumors, high-risk tumors (Gastric: >5 cm AND >5 mitoses; non-gastric: >10 cm OR >5 mitoses) and low/intermediate risk tumors (everything else).

No significant differences in IFFS or OS were found in the subgroup of patients with a tumor rupture (Figure 4).

**Discussion**

This is the final analysis of a randomized trial of adjuvant imatinib for two years versus observation in patients with resected localized GIST. It showed no significant difference in terms of its primary end-point, i.e., IFFS, though a marked difference in RFS was observed, confirming available evidence that adjuvant therapy with imatinib in GIST substantially delays relapse, with a limited impact on more definitive end-points. In fact, at a non pre-planned subgroup analysis, a trend of IFFS in favor of adjuvant therapy was observed in patients with high-risk tumors. If one assumed

IFFS to be a surrogate end-point for OS, this would be consistent with the possibility that adjuvant therapy may give some OS benefit in the long run, as observed in one of the other published trials, but the benefit would be limited.

Indeed, OS was the original primary end-point of this trial. Given what was already known at the time the study protocol was drafted, we wrote in its rationale that "one may expect a striking benefit on the short-medium term in terms of relapse-free survival, but it is left to demonstrate whether this benefit may translate into a survival benefit". Given the formidable impact of imatinib on prognosis of GIST, we had then to give up OS as the primary end-point of this study, but we consistently decided not to replace it with RFS. In agreement with the IDMC, we worked out IFFS as a new primary end-point, assuming it could be the best conceivable surrogate for OS. In principle, IFFS corresponds to a survival interval to switching to an alternate tyrosine kinase inhibitor from the first used in the patient. The rationale why it could be a surrogate for OS is that the molecular landscape of GIST is so profoundly altered after secondary resistance to imatinib, with substantial molecular heterogeneity, that a limited benefit is foreseeable, at the moment, with any salvage therapy. Thus, it is logical that OS will be severely affected when secondary resistance arises. In practice, IFFS is marked by secondary resistance as its failure time, even if this occurs after imatinib has been re-established following relapse. On the contrary, the drawback of relapse as the failure time is that, after it occurs, imatinib can still be exploited, possibly for long periods of time. Then the patient could respond, and survival will be prolonged by the delay in relapse. The patient may respond less, and survival will be the same or even shorter than in patients not receiving imatinib as an adjuvant. Thus, under the only assumption that in most cases secondary resistance can be impacted to a limited extent by therapies, a first targeted therapy failure-free survival end-point like IFFS may be a potential surrogate for OS in adjuvant trials on targeted therapies in solid cancers. However, although there is a clinical rationale supporting IFFS as a potential surrogate endpoint for OS, in the absence of data from other trials, no formal analysis of surrogacy could be performed at the time

being. We believe that, if validated, such an end-point could be of great interest for trials on the adjuvant use of molecularly-targeted therapies in solid cancers. A practical limitation is that the protocol should at least foresee recommendations on how to treat patients at relapse. Of course, this was not done in our study protocol and is thus a limitation of this trial. However, we later provided guidelines to participating institutions about selecting imatinib as treatment on relapse, and we carried out sensitivity analyses on the final results, which do not seem to alter conclusions.

Therapeutically, what this and the other published trials clearly show is that up to 3 years of adjuvant imatinib do not lead to harm (7, 8). On the contrary, a statistically significant survival benefit was shown in the German-Scandinavian trial on 3 years versus 1, and the IFFS non-statistically significant trend in this trial may be regarded as being consistent with, and complementing, it, also considering that treatment duration was 2 years. Thus, an adjuvant therapy interval of 3 years is the standard today, while ongoing randomized trials are looking at the efficacy of longer intervals, i.e., 5 and 6 years, following an uncontrolled study exploring 5 years (9). Interestingly, in the face of the well-known good safety profile of imatinib, excluding relapsing patients, 21% of patients randomized to imatinib did not complete their 2-year adjuvant treatment period. This parallels what was observed in the other adjuvant trials: in the German/Scandinavian trial, 27% in the 3-year group and 13% in the 1-year group stopped their therapy earlier due to reasons other than recurrence. This should be factored in when planning trials on adjuvant therapy with oral therapies administered continuously. Clearly, even low-grade toxicities from continuous therapies may impact patient's quality of life substantially. Unfortunately, this trial did not foresee any formal quality of life assessment. Of course, another reason for early treatment interruptions within trials may well be the experimental intent perceived by patients.

This was a large trial that was repeatedly amended in order to preserve its statistical power on patients having a significant risk of relapse. In fact, when the study was conceived, we decided to enroll patients with an intermediate and high risk of relapse according to the 2002 NIH Consensus classification (10). Actually, some of these patients then turned out to carry a low risk of relapse (11, 12). This is the reason why we broke down the analysis according to widely accepted current risk criteria, namely according to the AFIP classification. In practice, we singled out patients with a risk of relapse >50%, and this is the patient population in which a trend of IFFS in favour of adjuvant imatinib was seen. In fact, it is currently common practice to treat those patients with such a risk, while sharing the decision with patients with a risk in the 30-50% (13).

In this trial, we included patients with both R0 and R1 resections, as well as patients who had tumor rupture (within the R1 stratum). The proportion of the latter was 11%. A panel of surgeons reviewed original surgical reports and their findings are the subject of a separate paper now published (14). This showed that presence of R1 margins was not associated with worse OS when patients with rupture were excluded. Likewise, the prognostic correlations of mutational analysis will be the subject of a distinct analysis. Indeed, at the time when this trial was conceived we could not exclude imatinib-insensitive mutations or modulate drug dosages depending on the kind of KIT mutation.

The final analysis of this trial confirms the efficacy of adjuvant therapy with imatinib in localized GIST in terms of RFS. For both OS and its potential surrogate we defined in this trial, i.e., IFFS, the study data did not show an effect in favor of adjuvant therapy overall, but a trend was observed in the high-risk group. This is consistent with the OS benefit recently reiterated in the German/Scandinavian trial and may attenuate a mismatch between RFS and OS that undoubtedly marks the efficacy of adjuvant targeted therapy in GIST (8). At the moment, adjuvant therapy with imatinib for 3 years is standard treatment in GISTs with a significant risk of relapse (13).

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**Figure 1: Consort diagram.**

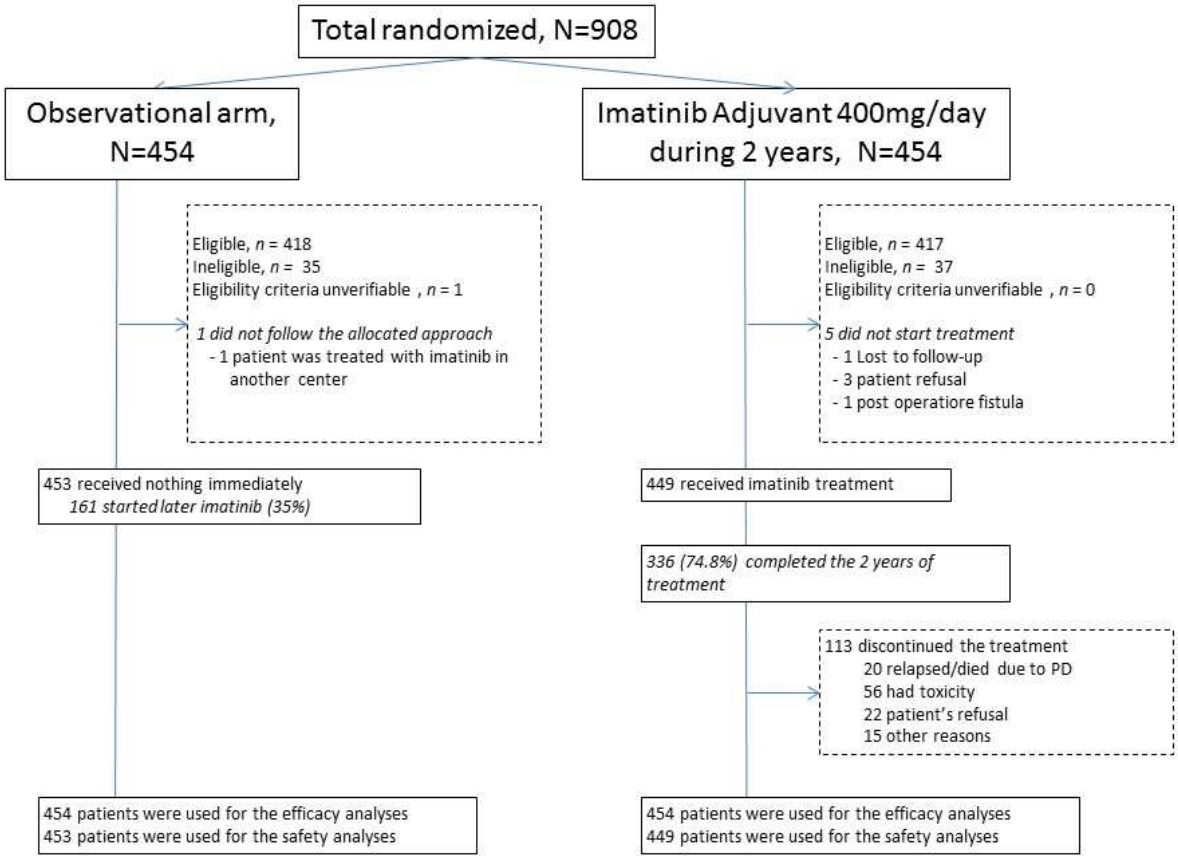
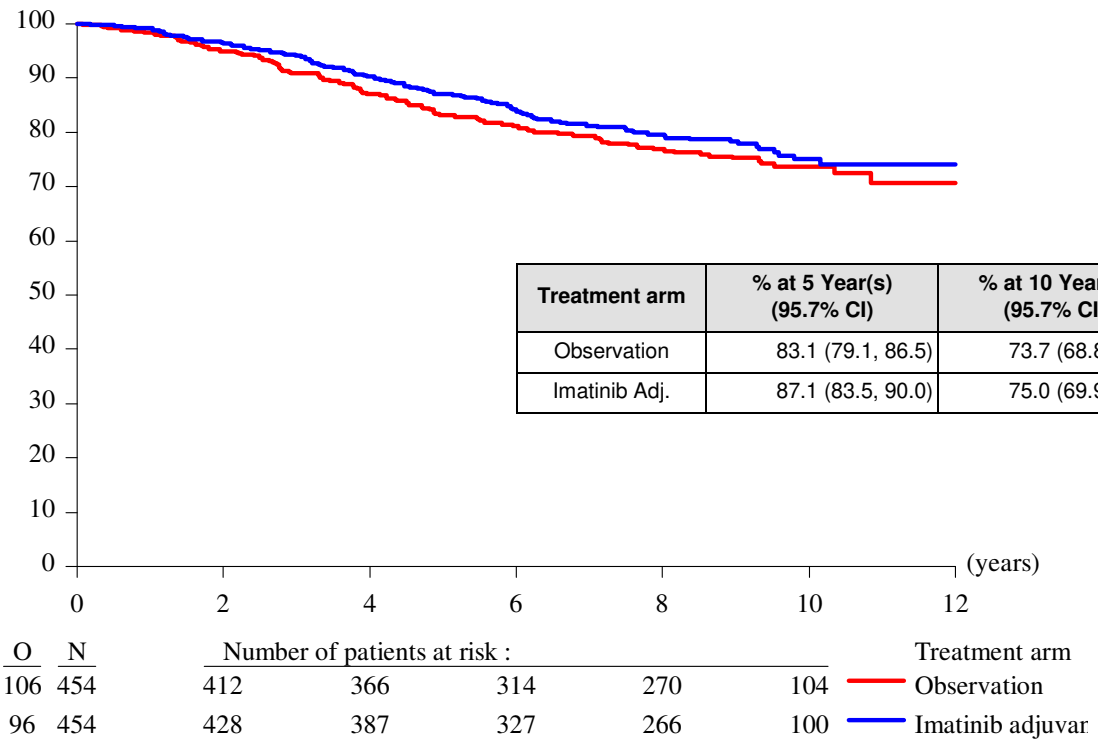


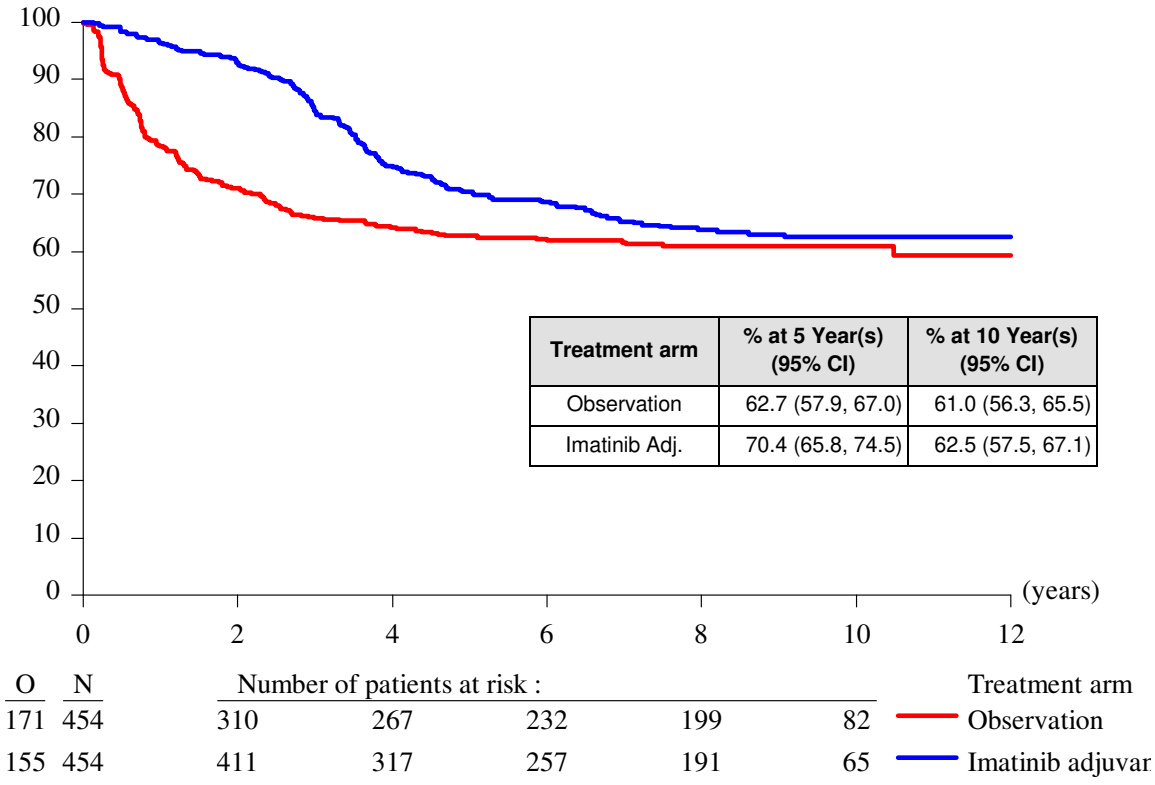
**Figure 2: Imatinib Monotherapy Failure-Free Survival (A), Relapse-Free Survival (B) and Overall Survival (C) by treatment arm.**

**A**



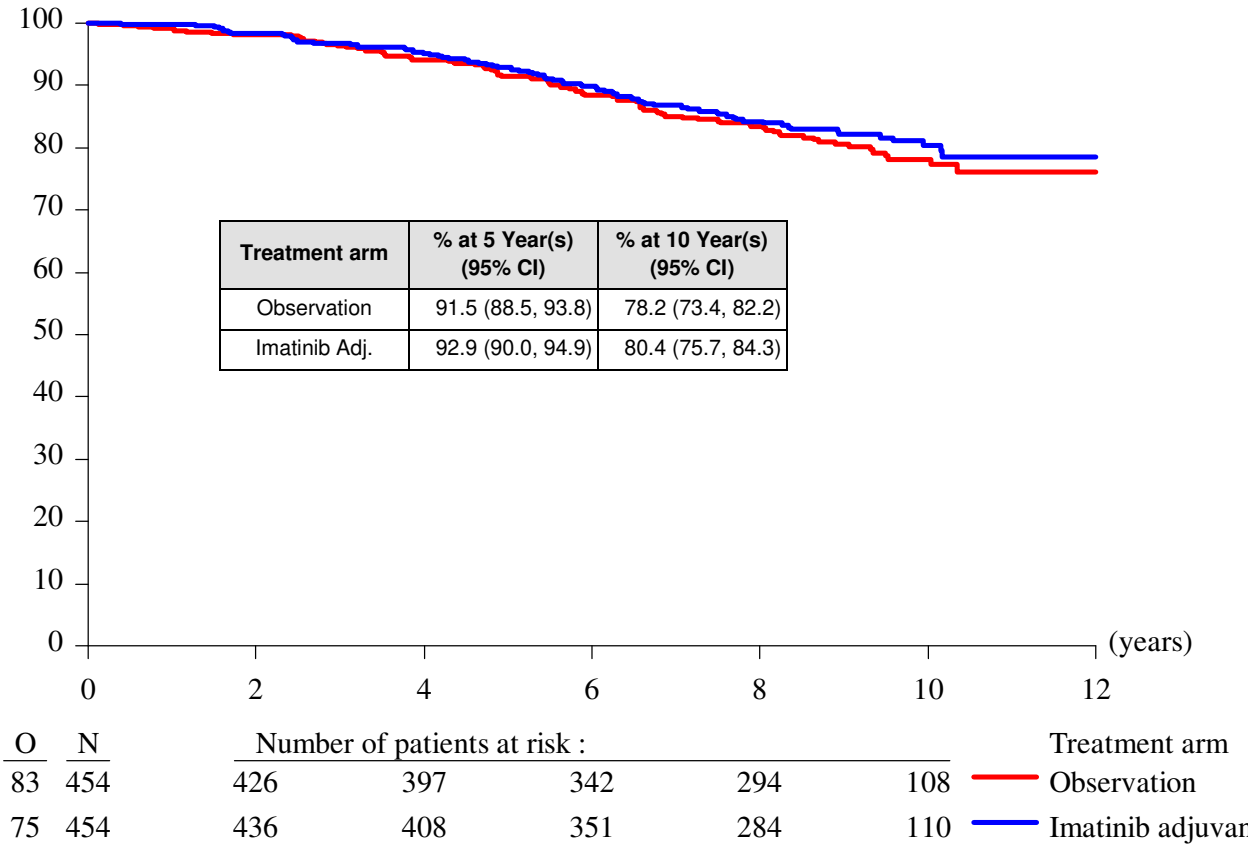

| Treatment arm | % at 5 Year(s) (95.7% CI) | % at 10 Year(s) (95.7% CI) |
|---|---|---|
| Observation | 83.1 (79.1, 86.5) | 73.7 (68.8, 78.0) |
| Imatinib Adj. | 87.1 (83.5, 90.0) | 75.0 (69.9, 79.5) |

**B**




| Treatment arm | % at 5 Year(s) (95% CI) | % at 10 Year(s) (95% CI) |
|---|---|---|
| Observation | 62.7 (57.9, 67.0) | 61.0 (56.3, 65.5) |
| Imatinib Adj. | 70.4 (65.8, 74.5) | 62.5 (57.5, 67.1) |

**C**

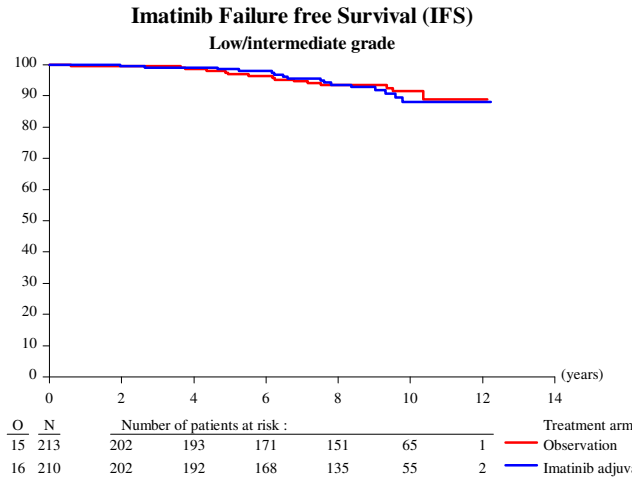



| Treatment arm | % at 5 Year(s) (95% CI) | % at 10 Year(s) (95% CI) |
|---|---|---|
| Observation | 91.5 (88.5, 93.8) | 78.2 (73.4, 82.2) |
| Imatinib Adj. | 92.9 (90.0, 94.9) | 80.4 (75.7, 84.3) |

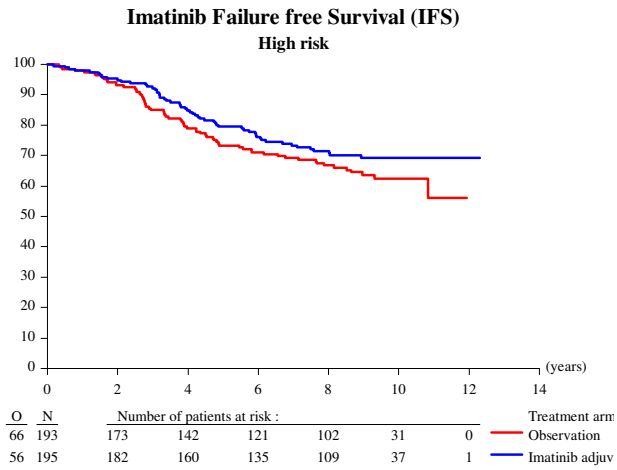
| O | N | Number of patients at risk : | | | | | Treatment arm |
|---|---|---|---|---|---|---|---|
| 83 | 454 | 426 | 397 | 342 | 294 | 108 | Observation |
| 75 | 454 | 436 | 408 | 351 | 284 | 110 | Imatinib adjuvar |

**Figure 3: Imatinib Monotherapy Failure-Free Survival (A-B), and Overall Survival (C-D) by intermediate (A,C) or high risk (B,D) classification according to AFIP.**

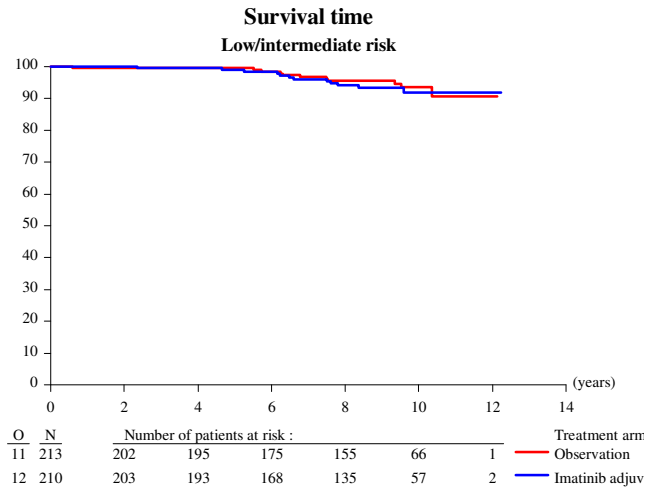
**A**




**B**




**C**




**D**

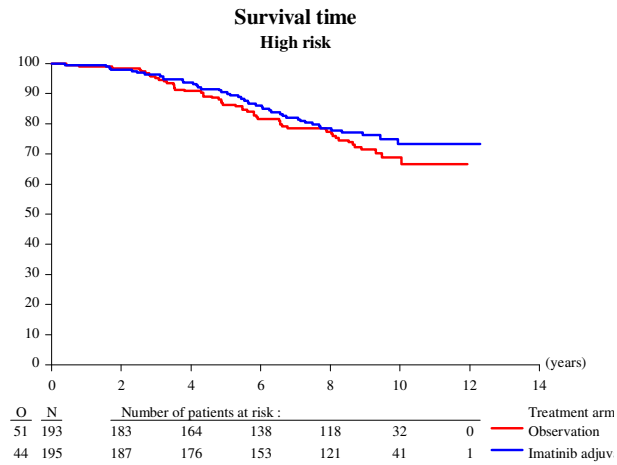
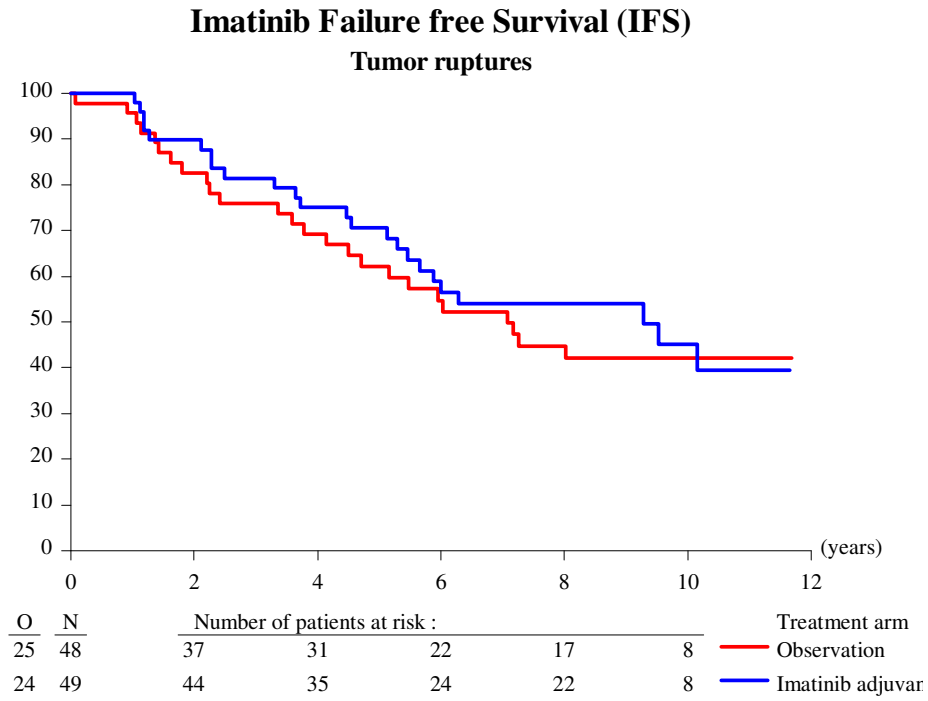


**Figure 4: Imatinib Failure free survival (A) and overall survival (B) for patients with tumor rupture.**

**A**




**B**

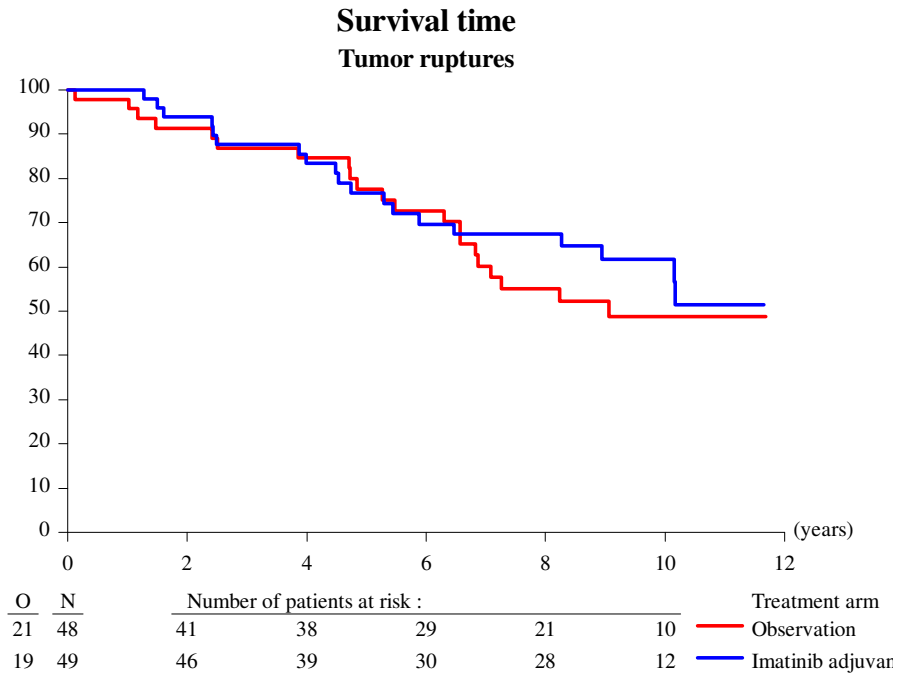


**Table 1: Main patient characteristics.**

| | Treatment arm | | |
|---|---|---|---|
| | Observation (N=454) | Imatinib adjuvant (N=454) | Total (N=908) |
| | N (%) | N (%) | N (%) |
| **Performance Status** | | | |
| **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) |
| **Gender** | | | |
| **Male** | 234 (51.5) | 232 (51.1) | 466 (51.3) |
| **Female** | 220 (48.5) | 222 (48.9) | 442 (48.7) |
| **Age (years)** | | | |
| **<=20 years** | 1 (0.2) | 3 (0.7) | 4 (0.4) |
| **20-40 years** | 29 (6.4) | 52 (11.5) | 81 (8.9) |
| **40-60 years** | 223 (49.1) | 189 (41.6) | 412 (45.4) |
| **>60 years** | 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** | 254 (55.9) | 250 (55.1) | 504 (55.5) |
| **Other** | 200 (44.1) | 204 (44.9) | 404 (44.5) |