Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial

Ronald P DeMatteo, Karla V Ballman, Cristina R Antonescu, Robert G Maki, Peter W T Pisters, George D Demetri, Martin E Blackstein, Charles D Blanke, Margaret von Mehren, Murray F Brennan, Shreyaskumar Patel, Martin D McCarter, Jonathan A Polikoff, Benjamin R Tan, Kouros Owzar, on behalf of the American College of Surgeons Oncology Group (ACOSOG) Intergroup Adjuvant GIST Study Team

Summary

Background Gastrointestinal stromal tumour is the most common sarcoma of the intestinal tract. Imatinib mesylate is a small molecule that inhibits activation of the KIT and platelet-derived growth factor receptor α proteins, and is effective in first-line treatment of metastatic gastrointestinal stromal tumour. We postulated that adjuvant treatment with imatinib would improve recurrence-free survival compared with placebo after resection of localised, primary gastrointestinal stromal tumour.

Methods We undertook a randomised phase III, double-blind, placebo-controlled, multicentre trial. Eligible patients had complete gross resection of a primary gastrointestinal stromal tumour at least 3 cm in size and positive for the KIT protein by immunohistochemistry. Patients were randomly assigned, by a stratified biased coin design, to imatinib 400 mg (n=359) or to placebo (n=354) daily for 1 year after surgical resection. Patients and investigators were blinded to the treatment group. Patients assigned to placebo were eligible to crossover to imatinib treatment in the event of tumour recurrence. The primary endpoint was recurrence-free survival, and analysis was by intention to treat. Accrual was stopped early because the trial results crossed the interim analysis efficacy boundary for recurrence-free survival. This study is registered with ClinicalTrials.gov, number NCT00041197.

Findings All randomised patients were included in the analysis. At median follow-up of 19·7 months (minimum–maximum 0–56·4), 30 (8%) patients in the imatinib group and 70 (20%) in the placebo group had had tumour recurrence or had died. Imatinib significantly improved recurrence-free survival compared with placebo (98% [95% CI 96–100] *vs* 83% [78–88] at 1 year; hazard ratio [HR] 0·35 [0·22–0·53]; one-sided p<0·0001). Adjuvant imatinib was well tolerated, with the most common serious events being dermatitis (11 [3%] *vs* 0), abdominal pain (12 [3%] *vs* six [1%]), and diarrhoea (ten [2%] *vs* five [1%]) in the imatinib group and hyperglycaemia (two [<1%] *vs* seven [2%]) in the placebo group.

Interpretation Adjuvant imatinib therapy is safe and seems to improve recurrence-free survival compared with placebo after the resection of primary gastrointestinal stromal tumour.

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Introduction

Gastrointestinal stromal tumour has an estimated incidence in the USA of about 3000–4000 cases per year.[1,2] It typically arises in the stomach or small intestine, but can also occur occasionally in the rectum and rarely in the oesophagus or colon. About 85% of such tumours contain an activating mutation in the *KIT* proto-oncogene, whereas 3–5% can have a mutation in *PDGFRα*, the gene encoding platelet-derived growth factor receptor α (PDGFRα).[3–7] The mainstay of treatment for localised, primary gastrointestinal stromal tumour has been surgical resection. Postoperative adjuvant chemotherapy has not generally been recommended because conventional cytotoxic agents are ineffective against this tumour.[8] Unfortunately, the results of surgery alone have been inadequate, with up to 50% of patients developing tumour recurrence within 5 years and eventually dying from the disease.[9,10] The most frequent sites of initial tumour recurrence are the peritoneal surface and the liver.

Imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland) is an oral agent that is a selective molecular inhibitor of the KIT, PDGFRα, ABL, and BCR-ABL tyrosine kinases. Imatinib was first used for chronic myelogenous leukaemia, proving to be safe and achieving a complete haematological response in nearly all patients by inhibition of the BCR-ABL oncoprotein.[11] In 2000, imatinib was shown to be effective against metastatic gastrointestinal stromal tumour in the initial patient tested,[12] and efficacy was then confirmed in phase II[13,14] and phase III trials in metastatic disease.[15,16]

In view of the activity of imatinib, the proclivity for tumour recurrence after resection, and the scarcity of effective conventional chemotherapeutic agents, there was substantial rationale for testing the benefit of adjuvant imatinib in gastrointestinal stromal tumour.

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Memorial Sloan-Kettering Cancer Center, New York, NY, USA (Prof R P DeMatteo MD, C R Antonescu MD, R G Maki MD, Prof M F Brennan MD); **Mayo Clinic, Rochester, MN, USA** (K V Ballman PhD); **University of Texas MD Anderson Cancer Center, Houston, TX, USA** (Prof P W T Pisters MD, Prof S Patel MD); **Dana Farber Cancer Institute, Boston, MA, USA** (G D Demetri MD); **Mount Sinai Hospital, Toronto, ON, Canada** (M E Blackstein MD); **University of British Columbia and British Columbia Cancer Agency, Vancouver, BC, Canada** (Prof C D Blanke MD); **Fox Chase Cancer Institute, Philadelphia, PA, USA** (M von Mehren MD); **University of Colorado Denver School of Medicine, Aurora, CO, USA** (M D McCarter MD); **Kaiser Permanente Southern California, San Diego, CA, USA** (J A Polikoff MD); **Washington University School of Medicine in St Louis, St Louis, MO, USA** (B R Tan MD); **and Duke University, Durham, NC, USA** (K Owzar PhD)

Correspondence to: Ronald DeMatteo , Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA **dematter@mskcc.org**

We postulated that adjuvant treatment with imatinib would improve recurrence-free survival compared with placebo in patients who underwent resection of localised, primary gastrointestinal stromal tumour.

Methods

Patients

We undertook a randomised phase III, double-blind, placebo-controlled, multicentre trial between July 1, 2002, and April 18, 2007, in 230 institutions in USA and Canada. Patients were eligible for inclusion if they had a histological diagnosis of localised, primary gastrointestinal stromal tumour measuring at least 3 cm that expressed the KIT protein (CD117) by immunohistochemistry with the Dako antibody (DakoCytomation, Copenhagen, Denmark). The local institutional pathologist measured the size of the tumour, either before or after formalin fixation. Two pathologists undertook retrospective central pathological review to confirm the diagnosis. Patients were to be registered within 70 days after complete gross tumour resection (irrespective of microscopic margins) and start treatment by 84 days. The technique of resection was at the discretion of the individual surgeon.

Patients were at least 18 years of age with an Eastern Cooperative Oncology Group (ECOG)/Zubrod performance status of 2 or less. Within 28 days before trial registration, patients must have been deemed free of tumour by postoperative imaging that included a baseline chest radiograph (or chest CT) and a postoperative abdomen and pelvis CT scan with intravenous and oral contrast, or MRI with intravenous contrast. Additional inclusion criteria were adequate renal, haematological, and hepatic function, and a negative serum pregnancy test when applicable. Previous imatinib use or chemotherapy, radiation therapy, or investigational treatment after surgery was not allowed. Also excluded were patients with an active infection requiring antibiotics within 14 days before registration, women who were breastfeeding, patients with New York Heart Association class 3 or 4 cardiac disease, and patients taking full dose warfarin.

The study was approved by the institutional review board of each participating institution, and we obtained written informed consent from all patients.

Study design and procedures

Patients were randomly assigned, in a double-blind manner, to receive 1 year of adjuvant imatinib (Novartis Pharmaceuticals, Basel, Switzerland) at a dose of 400 mg per day or 1 year of placebo. Patients were assigned to take four capsules of 100 mg imatinib or placebo once a day with food. Imatinib and placebo capsules looked alike. We assessed patients at weeks 1, 2, 4, 6, 8, 12, 16, 20, and 24, then every 3 months until year 2, and then every 6 months until year 5 with physical examination; complete blood count with differential count, creatinine, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase; and assessment of adverse events. We graded toxic effects with the National Cancer Institute common terminology criteria for adverse events (version 3.0).[17] Attribution was recorded as definite, probable, possible, unlikely, or unrelated to therapy. Dose modifications were made for grade 3 and 4 events (excluding anaemias) that were thought to be at least possibly related to treatment. Patients kept a diary to record dose administration and adverse events. CT scans with intravenous and oral contrast (or MRI with intravenous contrast) of the abdomen and pelvis were done every 3 months for the first 2 years and then every 6 months for the next 3 years. At the time of reported tumour recurrence, the treatment group was unblinded after central review. A biopsy sample was mandatory and taken when medically feasible. Patients were not allowed to crossover before an observed recurrence. Patients who were unblinded for tumour recurrence were eligible for imatinib 400 mg per day if they had either been assigned to the imatinib group and already completed study therapy or assigned to the placebo group. Imatinib 800 mg per day could be prescribed if the patient was actively taking imatinib during recurrence.

Statistical analysis

The original primary endpoint was overall survival and we planned an accrual of 380 patients over 3·8 years with a minimum follow-up of 3 years. At a 0·05 one-sided level of significance, the log-rank test would have had 90% power to detect a minimum hazard ratio (HR) of 0·65, assuming exponential decay in both groups and uniform censoring. 6 months before the first planned efficacy interim analysis, the primary endpoint was changed to recurrence-free survival on the basis of discussions with Cancer Therapy Evaluation Program (CTEP) and the US Food and Drug Administration (FDA). The trial was designed at the end of 2000, when fewer than 150 patients with metastatic gastrointestinal stromal tumour had been treated worldwide. During the present trial, it became clear that the actual event (death) rate would be substantially lower than the putative event rate that was specified in the original statistical design because of the efficacy of imatinib in recurrent gastrointestinal stromal tumour and the crossover design that allowed patients who progressed on placebo to receive imatinib. Consequently, the study was vastly underpowered to show a difference in overall survival between taking imatinib immediately after surgery versus waiting until recurrence occurred.

In the revised statistical design, the putative median recurrence-free survival for the placebo group was assumed to be 3·5 years on the basis of historical data. From the time of the amendment, the intent was to accrue 600 more patients over 2·5 years (to reach a total of 803), with a minimum follow-up of 3 years. This

number would yield 90% power, at a 0·025 one-sided significance level, to detect a 40% improvement in recurrence-free survival in the imatinib group, corresponding to a median recurrence-free survival of 4·9 years for the imatinib group and an HR of 0·71.

Interim analyses for superiority and futility were scheduled every 6 months beginning in December, 2005. We used a truncated O'Brien-Fleming bound to monitor treatment efficacy.[18] Futility was monitored with a 0·0025 fixed level of significance at every interim analysis. This study was monitored by a data monitoring committee that was approved by CTEP and independent of the study sponsor (Novartis).

Patients were randomly assigned at the central office of the American College of Surgeons Oncology Group (ACOSOG) via a computer programme with a stratified biased coin design, with the objective of equal allocation to each group, and stratified by tumour size (≥3–<6 cm, ≥6–<10 cm, or ≥10 cm). Patients and investigators were blinded to the group that the patient was assigned.

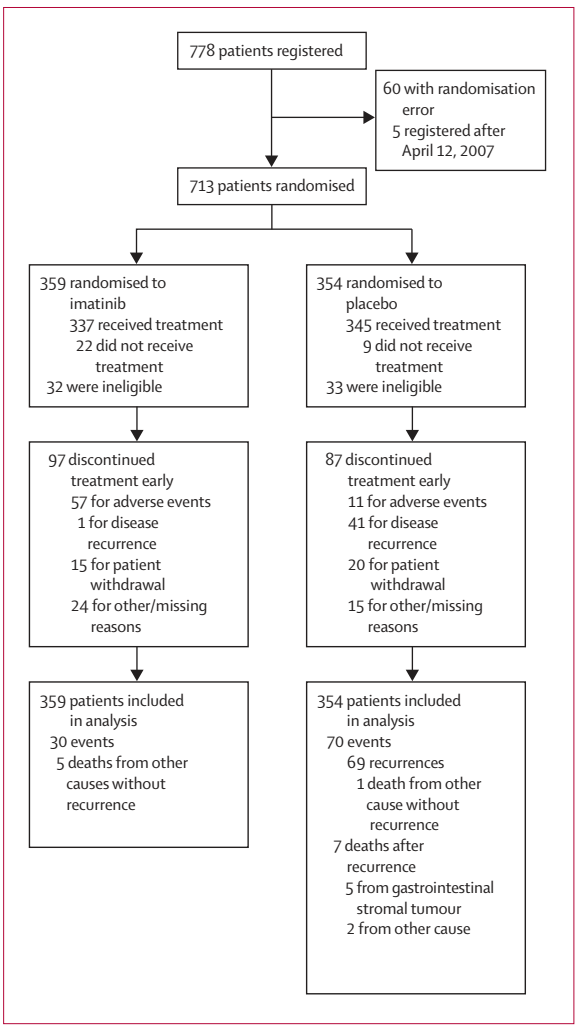

Figure 1: **Trial profile**

60 patients were misrandomised because of a programming error that assigned them to the placebo group. Patients, physicians, institutional review boards, and health authorities were notified of the error and the patients were removed from the study. No data were collected for these patients after their removal from the study, resulting in no follow-up information for these patients.

Recurrence-free survival was defined as the time from patient registration to the development of tumour recurrence or death from any cause. Overall survival was defined as the time from patient registration to death from any cause. Patients who were alive and free of recurrent disease on April 12, 2007, were censored for overall survival and recurrence-free survival. Intention-to-treat analyses were done for both recurrence-free and overall survival (ie, we analysed patients by randomised group). Both endpoints were estimated with the Kaplan-Meier method. We analysed differences in recurrence-free and overall survival between the groups with a one-sided log-rank test stratified by tumour size. HRs and 95% CIs were reported on the basis of a Cox proportion hazards regression model, which was also stratified by tumour size for recurrence-free survival. An unstratified Cox model was used for overall survival because of the few recorded

	Placebo (n=354)	Imatinib (n=359)
Age (years)	58 (18–91)	59 (18–88)
Sex		
Women	163 (46·0%)	189 (52·6%)
Men	191 (54·0%)	170 (47·4%)
Performance status		
0	265 (74·9%)	281 (78·3%)
1	81 (22·9%)	74 (20·6%)
2	8 (2·3%)	4 (1·1%)
Days between resection and randomisation	59 (15–96)	57 (20–74)
Tumour size		
≥3–<6 cm	149 (42·1%)	143 (39·8%)
≥6–<10 cm	119 (33·6%)	123 (34·3%)
≥10 cm	86 (24·3%)	93 (25·9%)
Margins		
R0	330 (93·2%)	325 (90·5%)
R1	23 (6·5%)	34 (9·5%)
Unknown	1 (0·3%)	0
Tumour origin		
Stomach	235 (66·4%)	209 (58·2%)
Small intestine	102 (28·8%)	125 (34·8%)
Rectum	5 (1·4%)	5 (1·4%)
Other	12 (3·4%)	18 (5·0%)
Unknown	0	2 (0·6%)

Data are median (minimum–maximum) or number (%). R0=negative microscopic margins. R1=positive microscopic margins.

Table 1: **Clinicopathological features**

	Placebo (n=345)				Imatinib (n=337)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Neutropenia	11 (3%)	8 (2%)	3 (<1%)	1 (<1%)	23 (6%)	26 (7%)	7 (2%)	5 (1%)
Fatigue	134 (39%)	51 (15%)	4 (1%)	0	117 (33%)	20 (5%)	5 (1%)	2 (<1%)
Dermatitis	75 (22%)	32 (9%)	0	0	54 (15%)	15 (4%)	11 (3%)	0
Abdominal pain	64 (18%)	10 (2%)	6 (1%)	0	61 (17%)	25 (7%)	12 (3%)	0
Nausea	144 (42%)	27 (8%)	4 (1%)	0	78 (22%)	14 (4%)	8 (2%)	0
Vomiting	60 (17%)	18 (5%)	2 (<1%)	0	37 (10%)	9 (2%)	8 (2%)	0
Diarrhoea	147 (43%)	42 (12%)	5 (1%)	0	79 (22%)	17 (4%)	10 (2%)	0
ALT	42 (12%)	6 (1%)	0	0	38 (11%)	9 (2%)	7 (2%)	2 (<1%)
AST	27 (7%)	3 (<1%)	0	0	31 (9%)	4 (1%)	4 (1%)	3 (<1%)
Oedema	96 (28%)	5 (1%)	1 (<1%)	0	220 (65%)	32 (9%)	7 (2%)	0
Hyperglycaemia	34 (9%)	6 (1%)	7 (2%)	0	27 (8%)	9 (2%)	2 (<1%)	0
Hypokaleamia	9 (2%)	1 (<1%)	3 (<1%)	0	28 (8%)	0	4 (1%)	0
Syncope	1 (<1%)	0	0	0	1 (<1%)	0	4 (1%)	0
Dyspnoea	16 (4%)	5 (1%)	2 (<1%)	0	13 (3%)	1 (1%)	4 (1%)	0

Data are number (%). ALT=alanine aminotransferase. AST=aspartate aminotransferase.

Table 2: **Common adverse events**

	Placebo (n=345)	Imatinib (n=337)
Grade 1	101 (29%)	81 (24%)
Grade 2	150 (43%)	148 (44%)
Grade 3	56 (16%)	86 (26%)
Grade 4	7 (2%)	15 (4%)
Grade 5	0 (0%)	3 (1%)

Data are number (%).

Table 3: **Maximum grade of adverse events per patient**

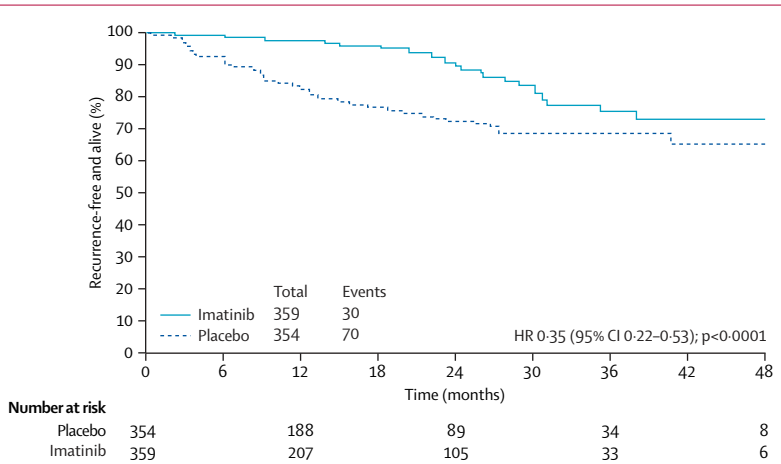

Figure 2: **Recurrence-free survival**

deaths. We used the placebo group as the HR denominator, so that HRs of less than one favour imatinib. The proportionality assumption of the Cox model was tested with Schoenfeld residuals, and was valid for all the analyses. For the safety analysis, we included all patients receiving one or more doses of their assigned treatment. We used χ^2 tests to compare categorical variables between the two groups. All analyses were done with SAS (version 8.2).

On the basis of the recommendation of the ACOSOG data and safety monitoring committee, accrual to the study was stopped on April 12, 2007, and the National Cancer Institute issued a press release of the preliminary findings that day because the trial results crossed the interim analysis efficacy boundary for recurrence-free survival. The final analysis includes all data collected through April 12, 2007.

This study is registered with ClinicalTrials.gov, number NCT00041197.

Role of the funding source

Employees of the study sponsor provided input regarding the study design, but did not participate in the collection, analysis, or interpretation of the data. Data were collected at the local institution and transferred electronically to the ACOSOG central database. The database was audited and updated by members of the Duke Clinical Research Institute, which received funding from the study sponsor. The results were analysed by the principal academic investigators. KVB and KO had full access to all the data in the study. This article was written by the lead author and reviewed by all authors, and was submitted to the sponsor for comments. RPD, KVB, and KO had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. The intention-to-treat analysis consisted of 713 patients. 60 of the 778 patients were excluded from the study because of a randomisation error and another five were excluded because they were registered after the study closure date. The intention-to-treat population included 65 (9%) patients who did not meet all eligibility requirements (figure 1). We undertook retrospective central pathology review in 631 (89%) patients, of whom 16 (3%) had another type of sarcoma (ten in imatinib group, six in placebo group). The other reasons for ineligibility were improper timing of baseline tests (laboratory or radiological) or surgery (eight in imatinib group, 18 in placebo group), incomplete baseline laboratory tests (five in imatinib group, one in placebo group), incomplete baseline radiological imaging (four in imatinib group, six in placebo group), no pathological review (one in each group), presence of metastatic disease (one in each group), additional primary cancer (one in imatinib group), inadequate margins (one in imatinib group), and one patient in the imatinib group withdrew consent before any treatement. Clinicopathological features were similar between the study groups (table 1).

Treatment was stopped prematurely in 184 (26%) patients (figure 1). Discontinuation was most likely due to adverse events in the imatinib group ($p<0·0001$) and to tumour recurrence in the placebo group ($p<0·0001$). A dose reduction or interruption, or both, occurred for

any reason in 59 (16%) patients in the imatinib group and 17 (5%) in the placebo group, and occurred because of adverse events in 52 (15%) and ten (3%) patients, respectively. When we analysed only the 682 patients who received at least one dose of either imatinib or placebo, 647 (95%) patients had at least one adverse event (333 in imatinib group, 314 in placebo group). Grade 1 and 2 events were common and mostly involved gastrointestinal effects (mild diarrhoea, nausea, and flatulence), headache, rash, periorbital or peripheral oedema, fatigue, or myalgias or arthralgias (table 2). 251 (73%) patients in the placebo group and 229 (68%) in the imatinib group had a grade 1 or 2 event (table 3). Grade 3 or 4 events occurred in 63 (18%) patients in the placebo group and 104 (31%) in the imatinib group.

By the final analysis of recurrence-free survival, 30 (8%) patients in the imatinib group and 70 (20%) in the placebo group had had events. With a median follow-up for surviving patients of 19·7 months (minimum–maximum 0–56·4), the estimated 1-year recurrence-free survival was 98% (95% CI 96–100) in the imatinib group versus 83% (78–88) in the placebo group (figure 2). The overall hazard ratio was 0·35 (0·22–0·53; p<0·0001). Although the trial was not designed to assess patient subsets, we analysed the effect of tumour size (the stratification factor) and noted that recurrence-free survival was longer in the imatinib group than in the placebo group in each size category (figure 3). Five (1%) patients died in the imatinib group, all from causes unrelated to gastrointestinal stromal tumour. Eight (2%) deaths arose in the placebo group, five of which were related to the tumour. At this time, there is no difference in overall survival (HR 0·66 [95% CI 0·22–2·03]; figure 4).

Discussion

Our results show that assignment to 1 year of adjuvant imatinib improved recurrence-free survival after the complete resection of primary gastrointestinal stromal tumour compared with placebo. Additionally, adjuvant imatinib was safe and well tolerated. The adverse event rate was low and consistent with imatinib use in chronic myelogenous leukaemia and metastatic gastrointestinal stromal tumour.[11,13] We did not record significant cardiac toxic effects that were noted by one group,[19] but refuted by others.[20]

We chose to stratify patients on the basis of tumour size only. Mitotic rate and tumour site have also been reported to have prognostic importance in retrospective studies of primary gastrointestinal stromal tumour. Notably, none of these tumour features has been validated prospectively. Furthermore, the method of determining mitotic rate has not been standardised, and the reproducibility of measurements by different pathologists (especially in a large, multicentre trial such as this study) has not been proven. Patients in the placebo group in this study provide a large prospective cohort of patients with primary gastrointestinal stromal tumour in which to identify risk factors for recurrence. This study also provides a large prospective assessment of recurrence with serial radiological imaging. Additional ad-hoc analyses related to risk factors for tumour recurrence will

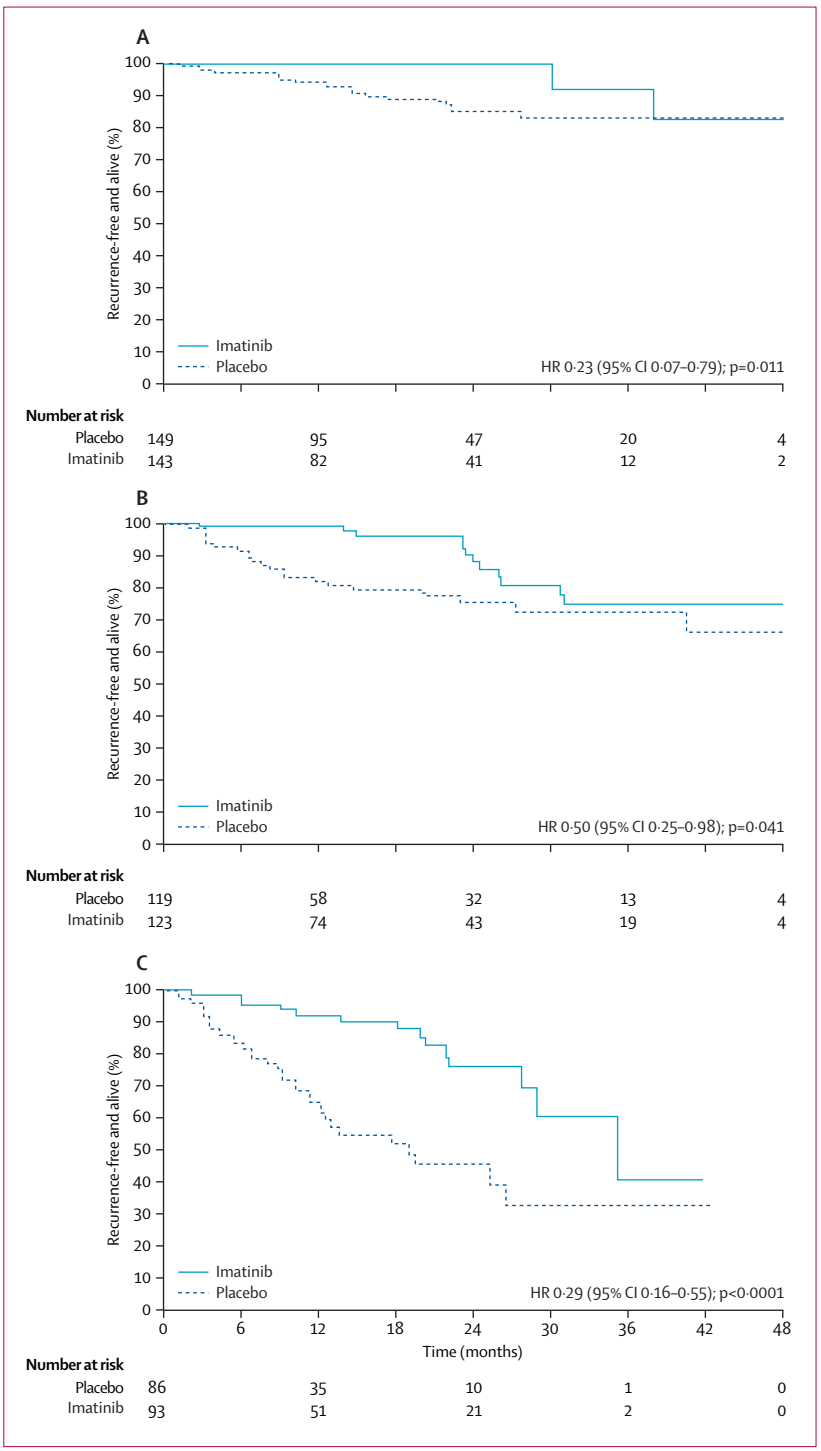

Figure 3: **Recurrence-free survival for tumour size 3 cm or greater and less than 6 cm (A), 6 cm or greater and less than 10 cm (B), and 10 cm or greater (C)**

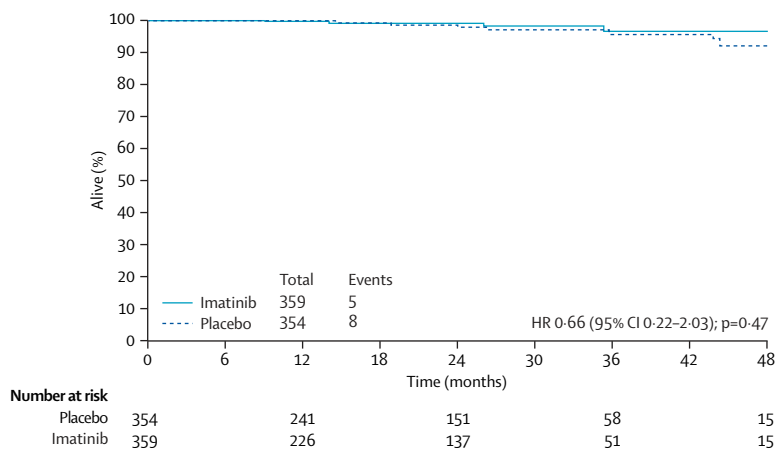

Figure 4: **Overall survival**

	N	Phase	Primary endpoint	Imatinib dose	PFS	OS
B2222	147	II	Response	400 mg per day; 600 mg per day	24 months median	57 months median
EORTC 62005	946	III	PFS	400 mg per day; 400 mg twice per day	22 months median*; 27 months median*†	69% at 2 years; 74% at 2 years
SWOG S0033	746	III	PFS/OS	400 mg per day; 400 mg twice per day	18 months median; 20 months median	55 months median; 51 months median

EORTC=European Organization for Research and Treatment of Cancer. SWOG=Southwest Oncology Group. PFS=progression-free survival. OS=overall survival. Based on references 13–16. *Estimate since actual number not stated in report. †p<0·05.

Table 4: **Summary of randomised controlled trials testing the benefit of imatinib in metastatic and unresectable gastrointestinal stromal tumour**

be forthcoming since central pathological and molecular analyses are underway.

During the year of assigned study therapy, there were 41 recurrences in the placebo group compared with only one in the imatinib group. Recurrence-free survival was increased in each of the three size categories on retrospective analysis. Adjuvant therapy is especially relevant for high-risk patients (eg, those with tumour size 10 cm or more, or high mitotic rate), who can have a greater than 50% chance of recurrence at 2 years in the absence of adjuvant therapy (figure 3C). Notably, the rate of recurrence in the imatinib group (figure 2) seems to increase after about 18 months from surgery (ie, 6 months after the completion of study therapy). This finding is consistent with a trial in metastatic gastrointestinal stromal tumour in which patients receiving imatinib with responding or stable disease developed tumour progression at a median of 6 months after randomisation to discontinue therapy.[21] Increased use of adjuvant imatinib could extend recurrence-free survival. Europe-based trials that are in progress are testing 0 versus 2 years (European Organization for Research and Treatment of Cancer [EORTC] trial 62024), and 1 versus 3 years of adjuvant imatinib therapy (Scandanavian Sarcoma Group [SSG] trial XVIII]), to assess overall and recurrence-free survival, respectively. The results are not expected for several years.

In metastatic gastrointestinal stromal tumour, imatinib achieves a partial response or stable disease in roughly 80% of patients, and a median survival of nearly 60 months (table 4).[13–16] Tumour mutation status predicts response to imatinib and survival. In a combined analysis of 1640 patients with metastatic gastrointestinal stromal tumour treated in two phase III trials, patients with *KIT* exon 11 mutations had the longest progression-free survival, those with a *KIT* exon 9 mutation had the worst outcome, and those without a *KIT* or *PDGFRα* mutation had an intermediate course.[22] Mutation studies are in progress in tumour specimens from this study.

Acquired resistance is a frequent event in patients with metastatic gastrointestinal stromal tumour who initially respond to imatinib. Tumour progression occurs at a median of 18–24 months,[15,16] commonly from the development of a secondary mutation in the *KIT* gene.[23–25] Once clinical progression develops, increased doses of imatinib or sunitinib—a multitarget tyrosine kinase inhibitor (Sutent, Pfizer, New York, NY, USA)—can restore tumour control in some patients, at least temporarily.[26,27] At present there are no other FDA approved agents for metastatic gastrointestinal stromal tumour. Thus, the possibility to delay or prevent recurrence with adjuvant treatment is crucial since acquired resistance to tyrosine kinase inhibitors eventually occurs in most patients with measurable metastatic tumour. How cumulative exposure to imatinib (ie, in the adjuvant and metastatic settings combined) affects the development of imatinib resistance is unknown.

That overall survival between the study groups is similar is not surprising in view of the fairly short follow-up time and the crossover design of the study, which allowed patients assigned to the placebo group to receive imatinib on tumour recurrence. Although imatinib is rarely curative in metastatic gastrointestinal stromal tumour,[15,16] it could eradicate residual microscopic disease in some patients after the removal of the primary tumour. Longer patient follow-up is necessary to establish whether adjuvant imatinib increases the cure rate of surgery alone for localised, primary gastrointestinal stromal tumour. Quality-of-life instruments were not used in this study. The advantage of improved recurrence-free survival by taking adjuvant imatinib has to be weighed against the potential toxic effects of the drug, even though it seems to be generally well tolerated.

In this study we excluded paediatric patients and those with gastrointestinal stromal tumours who did not have KIT staining by immunohistochemistry. Our findings are probably not applicable to paediatric patients with such tumours that typically lack *KIT* or *PDGFRα* mutations and seem to be more responsive to sunitinib

than to imatinib.[28,29] Our results might be relevant to the 4% of gastrointestinal stromal tumours that lack KIT expression, which often contain a *KIT* or *PDGFRα* mutation and can respond to imatinib.[30] Patients with specific mutations (ie, *PDGFRα* exon 18 D842V) that are known to be insensitive to imatinib in vitro and in metastatic gastrointestinal stromal tumour might not benefit from adjuvant imatinib.

We tested only the starting dose of 400 mg per day in this study. The recent meta-analysis of the two phase III studies in metastatic gastrointestinal stromal tumour showed that 800 mg compared with 400 mg per day did not change overall survival but slightly improved progression-free survival at 3 years (34% *vs* 30%).[22] In particular, patients with *KIT* exon 9 mutations who were given the 800 mg dose had greater progression-free survival than did those given the 400 mg dose. Further studies will be needed to establish whether doses greater than 400 mg per day should be used in the adjuvant setting.

With the advent of tyrosine kinase inhibitors, effective agents against gastrointestinal stromal tumour now exist. In this phase III adjuvant trial of targeted therapy after the resection of localised, primary gastrointestinal stromal tumour, our findings have shown that imatinib increases recurrence-free survival. Our findings will affect the management of patients with primary gastrointestinal stromal tumour and could have relevance to the adjuvant use of other molecular agents for cancer.

Contributors

RPD, CRA, RGM, PWTP, GDD, MEB, CDB, MvM, and MFB were responsible for the conception and design of the study. RPD, RGM, PWTP, GDD, MEB, CDB, MvM, MFB, SP, MDM, JAP, and BRT accrued the patients. RPD, KVB, RGM, PWTP, GDD, MEB, CDB, MvM, SP, MDM, JAP, BRT, and KO collected the data. RPD, KVB, CRA, RGM, PWTP, GDD, CDB, MvM, MFB, SP, and KO analysed the data. CRA did the pathological review. RPD, KVB, CRA, RGM, PWTP, MEB, CDB, MvM, MFB, SP, MDM, JAP, BRT, and KO wrote the report. The final manuscript was written by RPD with substantial input from the authors. All authors approved the final report.

Conflict of interest statement

RPD, RGM, PWTP, MEB, CDB, MvM, GDD, and SP report receiving honoraria from Novartis and have served on Novartis advisory boards. GDD has been a consultant for, received honaria and research support from, and served on the advisory board for several other companies that are not related to this study. All other authors declare that they have no conflict of interest.

Acknowledgments

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