Discontinuation versus continuation of imatinib in patients with advanced gastrointestinal stromal tumours (BFR14): exploratory long-term follow-up of an open-label, multicentre, randomised, phase 3 trial

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Summary

Background The long-term impact of tyrosine kinase inhibitor (TKI) discontinuation on resistance and survival in patients with advanced gastrointestinal stromal tumours (GIST) is unclear. We report the exploratory long-term outcomes of patients with advanced GIST stopping imatinib in the BFR14 trial.

Methods BFR14, an open-label, randomised, phase 3 trial, was done in 17 comprehensive cancer centres or hospitals across France. Patients with advanced GIST aged 18 years or older with an Eastern Cooperative Oncology Group performance status of 0–3, no previous treatment with imatinib, and no previous malignancy were eligible. Patients were treated with oral imatinib 400 mg daily. Patients with a complete or partial response, or stable disease, according to Response Evaluation Criteria in Solid Tumours (1.0) at 1 year, 3 years, and 5 years from the start of treatment were randomly assigned (1:1) to treatment discontinuation until progression (interruption group) or treatment continuation until progression (continuation group). Randomisation was done centrally with computer-generated permuted blocks of two and six patients stratified by participating centre and presence or absence of residual disease on CT scan. The primary endpoint was progression-free survival. Secondary endpoints included time to imatinib resistance and overall survival. Analyses were conducted on an intention-to-treat basis in all randomly assigned patients who were not lost to follow-up. This trial is registered with ClinicalTrial.gov, NCT00367861.

Findings Between May 12, 2003, and March 16, 2004, after 1 year of imatinib, 32 patients were randomly assigned to the interruption group and 26 to the continuation group. Between June 13, 2005, and May 30, 2007, after 3 years of imatinib, 25 patients were randomly assigned to the interruption group and 25 to the continuation group. Between Nov 9, 2007, and July 12, 2010, after 5 years of imatinib, 14 patients were randomly assigned to the interruption group and 13 to the continuation group. Median follow-up was 235·2 months (IQR 128·8–236·6) after the 1-year randomisation, 200·9 months (190·2–208·4) after the 3-year randomisation, and 164·5 months (134·4–176·4) after the 5-year randomisation. Median progression-free survival in the interruption group versus the continuation group after 1 year of imatinib was 6·1 months (95% CI 2·5–10·1) versus 27·8 months (19·5–37·9; hazard ratio [HR] 0·36 [95% CI 0·20–0·64], log-rank p=0·0003), after 3 years of imatinib was 7·0 months (3·5–11·7) versus 67·0 months (48·8–85·6; 0·15 [0·07–0·32], log-rank p<0·0001), and after 5 years of imatinib was 12·0 months (9·0–16·6) versus not reached (NR; NR–NR; 0·13 [0·03–0·58], log-rank p=0·0016). The median time to imatinib resistance after 1 year of imatinib was 28·7 months (95% CI 18·1–39·1) versus 90·6 months (25·3–156·1; HR 0·93 [95% CI 0·51–1·71], log-rank p=0·82), after 3 years was 66·2 months (43·0–89·6) versus 127·3 months (15·0–239·7; 0·35 [0·17–0·72, log-rank p=0·0028), and after 5 years was 58·6 months (0·0–167·4) versus NR (NR–NR; 0·24 [0·05–1·12], log-rank p=0·049). Median overall survival after 1 year of imatinib was 56·0 months (95% CI 30·3–82·9) versus 105·0 months (20·6–189·6; HR 0·84 [95% CI 0·46–1·54], log-rank p=0·57), after 3 years was 104·0 months (90·7–118·7) versus 134·0 months (89·7–178·3; 0·40 [0·20–0·82], log-rank p=0·0096), and after 5 years was NR (NR–NR) versus 110·4 months (82·7–154·1; 1·28 [0·41–3·99]; log-rank p=0·67).

Interpretation Imatinib interruption in patients with GIST without progressive disease is not recommended. Imatinib interruption in non-progressing patients with GIST was associated with rapid progression, faster resistance to imatinib, and shorter overall survival in the long-term follow-up when compared with imatinib continuation in patients after 3 years and 5 years of imatinib.

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Research in context

Evidence before this study

We searched PubMed for research articles published in any language from database inception to March 31, 2024, using the terms "GIST", "advanced", "imatinib", "interruption", and "drug holidays". The search retrieved less than 40 publications related to this topic. In patients with metastatic gastrointestinal stromal tumours (GIST), imatinib treatment is generally administered until progression or intolerance. The randomised BFR14 study showed that imatinib interruption in patients with advanced GIST with stable or responding tumours after 1, 3, or 5 years, was associated with a higher risk of progression than was no interruption. Subsequent tumour control was obtained upon imatinib reintroduction without an effect on resistance to imatinib or overall survival in the initial report of BFR14 after 1 year and 3 years of follow-up. Treatment holiday is therefore occasionally proposed to patients based on these observations. An analysis of the long-term impact of imatinib interruption in these three randomised cohorts is presented here.

Added value of this study

After long-term follow-up, patients with advanced GIST randomly assigned to the interruption groups after 3 and 5 years had a significantly shorter time to imatinib resistance, with a significantly shorter overall survival for those randomly assigned at 3 years. Imatinib treatment interruption should be discouraged in these patients.

Implications of all the available evidence

In patients with advanced GIST, imatinib treatment should be continued without interruption until progression or intolerance. Because faster resistance to this tyrosine kinase inhibitor (TKI) emerged in the long term for patients with GIST in whom treatment was interrupted, similar studies should be conducted in patients with other cancers with activated mutated kinases treated with TKIs and treatment interruption in such patients should be proposed with caution and evaluated prospectively. Long-term analysis of randomised trials testing TKI in patients with advanced cancer are encouraged.

Introduction

Imatinib is the standard first-line treatment for advanced gastrointestinal stromal tumours (GIST) in patients with imatinib-sensitive mutations.[1–5] Whether treatment interruption affects the emergence of resistance to imatinib or patient survival is unclear.

BFR14 was a randomised trial that explored the effect of imatinib interruption versus imatinib continuation after 1 year, 3 years, and 5 years of treatment in patients with at least stable disease at the time of randomisation.[6–8] At each time period, two groups were compared: treatment discontinuation and restart at progression (interruption group) or continuation of the treatment until progression (continuation group). Treatment interruption was associated with rapid progression of the disease in patients randomly assigned to the interruption groups after 1 year, 3 years, and 5 years.[6–8] However, all patients responded again (according to Response Evaluation Criteria in Solid Tumours [RECIST]) when imatinib was reinstated, and no detectable effect of treatment interruption on imatinib resistance or overall survival was observed at the time of initial publications, which were reported with a median follow-up ranging from 27 months (IQR 23–31) to 35 months (31–38) from randomisation.[6–12] Nonetheless, in 44% of patients who responded again, the quality of response was reduced (eg, partial response instead of complete response).[9–12]

Currently, continuous imatinib treatment is recommended to be given until progression or intolerance in patients with advanced GIST, but the evidence suggesting an absence of an effect on survival from the BFR14 study and others supported possible treatment holidays when needed or requested by patients. Similar conclusions were obtained in other malignancies that are sensitive to imatinib, such as chronic myeloid leukaemia: randomised trials have shown that treatment interruption is safe, without treatment recurrence in about 50% of patients.[13–16]

In this follow-up analysis, we explored the long-term impact of treatment interruption on progression-free survival, time to imatinib resistance, and overall survival in patients with GIST.

Methods

Study design and participants

BFR14 (NCT00367861) was an open-label, randomised, phase 3 trial done across 17 comprehensive cancer centres or hospitals in France. The protocol and amendments are available in the appendix. Inclusion criteria were age 18 years or older; a histologically proven, locally advanced unresectable or metastatic GIST with immunohistochemical documentation of KIT (also known as CD117) expression; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–3; no previous treatment with imatinib; no previous malignancy; and normal renal, cardiac, and hepatic function. Patients previously treated with chemotherapy were eligible, but no other kinase inhibitor treatments were allowed. Information on sex was collected from patients' medical records. No information on ethnicity can be collected according to the law in France. No concurrent therapy was allowed.

After 1 year, 3 years, or 5 years of imatinib treatment, patients with controlled disease (ie, complete response, partial response, or stable disease at the time of randomisation) were eligible for random assignment to

See Online for appendix

interruption of imatinib until progression according to RECIST and then reintroduction of imatinib (interruption group) or continuation of imatinib until progression or intolerance (continuation group). Imatinib was therefore given until progression, intolerance, or randomisation to the interruption group. The random assignment at 3 years or 5 years of a patient previously randomly assigned to the continuation group at 1 year or 3 years was allowed to enable faster accrual and also occasionally at the request of the patient. Patients in the interruption group at year 1 or 3 could not be randomly assigned at a subsequent timepoint (3 years or 5 years). Patients gave written informed consent explaining the randomisation procedure at study inclusion. At the time of each randomisation, consent was requested again. The protocol was reviewed and validated by a French Ethics Committee (CCPPRB, Lyon C) as prescribed according to the national legislation on clinical trials and the European directives.

Randomisation and masking

Registration and randomisation were centrally performed by a coordination research assistant located at the coordination centre using a dedicated application. A statistician generated the randomisation list using SAS software (version 9.4). Patients were randomly assigned (1:1) to the interruption group or the continuation group. Randomisation was stratified by participating centre and presence or absence of residual disease on CT scan, with a permuted block design (blocks of two [first block] and then six patients [ten blocks] were used). Allocation of the treatment was performed in the Bureau d'Etude Clinique Thérapeutique of the Centre Léon Bérard (Lyon, France). The treatment allocation was unmasked for both the physician and the patient. The statistician had no access to the randomisation module during the study. For any randomisation, the investigator had to fill in and send by fax the randomisation file with specified inclusion criteria and stratification variables to the coordination centre. The coordination research assistant proceeded to randomisation, completed the form with attributed group, and faxed it again to the investigator.

Procedures

Imatinib was given orally at 400 mg per day, with an increase up to 600 mg per day upon tumour progression. CT or MRI was used for response evaluation. Assessments were conducted per investigator choice, with the majority of CT scans done every month initially for 3 months, then every 3 months. Response was established by the clinical site and not centrally reviewed. Patients who refused randomisation once they reached the randomisation period were offered the option of continuing or stopping imatinib and followed up according to the same schedule. Mutations in *KIT* or *PDGFRA* were assessed on the initial tumour tissues using the Sanger sequencing technique or next-generation sequencing.

Outcomes

The primary endpoint was progression-free survival after 1 year, 3 years, and 5 years of imatinib treatment calculated from the date of randomisation to the date of progressive disease or death from any cause, or to last follow-up for living patients (censored observation).[6–8] The main secondary endpoints were overall survival, response rate (complete or partial responses according to RECIST [1.0]) after reinitiation of imatinib in the interruption group,[8–12] time to imatinib resistance, defined as the time between randomisation to the date of progressive disease or last follow-up,[16] and prognostic impact of known driver molecular alterations. Time to imatinib resistance has been previously used as the primary endpoint for the EORTC 62024 study comparing 2 years of adjuvant imatinib versus no treatment in patients with localised GIST at risk of relapse.[17,18]

The other secondary endpoints of quality of life of patients before and during treatment and feasibility of curative surgery of metastases during imatinib treatment have been previously reported[6–8] and are not updated in this study.

Statistical analysis

When the study was designed in 2002, the following hypotheses were used for calculation of the sample size. Assuming that the 1-year progression-free survival in the continuation group (after reaching a complete response, partial response, or stable disease at 1 year) is 90%, the objectives were to show that, at worst, the 1-year progression-free survival in the interruption group was not less than 75%. With a two-sided test significance level of 10% (α=0·10), and a power (1–β) of 0·90, the required number of patients was 76 in each group, and the total sample size for this study was 152 randomly assigned patients. Considering both 70% progression-free survival after a 1-year period of treatment and a 20% rate of refusal of randomisation, the number of patients to be included was 284.

During the study, an interim monitoring stopping scheme using Lee-type boundaries was used. Accordingly, it was possible to stop the trial if the progression rate exceeded 20% in the interruption group: the first analysis was scheduled when the first 14 patients would be evaluable for response in the interruption group. First, if more than five progressions were observed, a data monitoring committee was scheduled to assess the results, and if the progression rate in the interruption group was confirmed, the trial would be stopped with the conclusion that the interruption of imatinib until further progression should not be further investigated. Second, if five or fewer progressions were observed, the randomisation process would continue until 29 patients were evaluable for response in the interruption group. At this date, a second

analysis would be performed: if ten or more progressions were observed, the data monitoring committee would again assess the results of each group of the study and decide whether to continue accrual. If nine or fewer progressions were observed among the first 29 patients, accrual would continue until its planned end. The randomisation continued until the number of events were reached in the interruption groups and was stopped when the sponsor was informed of all progressions. Because of the delay of transmission of the information of progression, more patients than planned might have been included. Ten progressions were documented in the first 29 patients of the interruption group after the first randomisation at 1 year, while 32 patients had been randomly assigned. Similarly, ten progressions were reported in the first 25 patients randomly assigned to the interruption group after the randomisation at 3 years. Six progressions were reported in the first 14 patients randomly assigned to the interruption group at 5 years. It is important to note that only randomisation was stopped when the number of events were reached in the interruption group. Accrual in the overall BFR14 cohort continued.

Because the number of events crossed these boundaries at each randomisation, randomisation was stopped before 29 patients were included in the interruption group in the first randomisation periods (1 year and 3 years), and before 15 patients in the interruption group were randomly assigned at 5 years.

In 2023, all centres that had randomly assigned at least one patient in one of the three periods were recontacted to provide an update of the primary and secondary endpoints (response, overall survival, and progression-free survival) and subsequent treatments of the randomly assigned patients. Subsequent lines of treatment were collected as well as duration of these treatments.[1,19–24] All randomly assigned patients were included in current analyses on an intention-to-treat basis, except those lost to follow-up.

Survival curves (progression-free survival, time to imatinib resistance, and overall survival) were plotted according to the Kaplan–Meier method and compared using the log-rank test. Median progression-free survival, time to imatinib resistance, and overall survival were assessed after each randomisation. Time to imatinib resistance after the 12-year follow-up and 15-year overall survival were assessed as exploratory analyses. Differences were considered to be significant if the p value was 0·05 or less. For progression-free survival, patients were censored at the time of their last follow-up without an event (progression or death). No informative censoring was done. For time to imatinib resistance, patients were censored at the time of their last follow-up without an event (progression while taking imatinib at a 400 mg daily dose or lower). For overall survival, patients were censored if they were alive at the time of the update. A prespecified exploratory analysis of GIST-specific survival was also conducted: GIST-specific survival was calculated from the date of randomisation to the date of death from GIST, or last follow-up. Patients who died of an unrelated cause were censored at the date of death. The χ^2 or Fisher exact tests were used to compare categorical variables, including the analysis investigating the correlation between *KIT* mutations (eg, codon 557 and 558 deletions, exon 11 mutations, any other *KIT* mutations, and patients without documented mutations) and overall survival.

We also did a post-hoc analysis of time to imatinib resistance censoring patients who were assigned to the continuation group at the 1 year or 3 year randomisation but subsequently randomly assigned to the interruption group at 3 years or 5 years. Specifically, patients who were first randomly assigned to the continuation group at 1 year and then to the interruption group at year 3 and patients who were first randomly assigned to the continuation group at 3 years and then to the interruption group at year 5 were censored at the date of the randomisation to the interruption group.

Other post-hoc analyses were conducted. We analysed the population of patients assigned to the interruption groups who had not relapsed in the 5 years after randomisation and compared their characteristics (age, sex, mutation, and complete response) at randomisation versus those of patients assigned to the interruption groups who progressed within 5 years after randomisation. Progression-free survival with subsequent lines of treatment were also calculated: progression-free survival for the second-line, third-line, and fourth-line treatment was calculated from the first day of this line of treatment (in second, third, or fourth line) to the date of progression or death or last follow-up.

Statistical analyses were performed using SPSS (version 23).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 1, 2002, and May 31, 2009, 432 patients enrolled in the study, of whom 102 were randomly assigned to treatment and included in the intention-to-treat analyses presented here. Between May 12, 2003, and March 16, 2004, after 1 year of imatinib, 58 patients with a complete response, a partial response, or stable disease were randomly assigned: 32 to the interruption group and 26 to the continuation group. Between June 13, 2005, and May 30, 2007, after 3 years of imatinib, 50 patients with complete response, partial response, or stable disease were randomly assigned: 25 to the interruption group and 25 to the continuation group. Between Nov 9, 2007, and July 12, 2010, after 5 years of imatinib, 27 patients with complete response, partial response, or stable disease were randomly assigned: 14 to the interruption group and

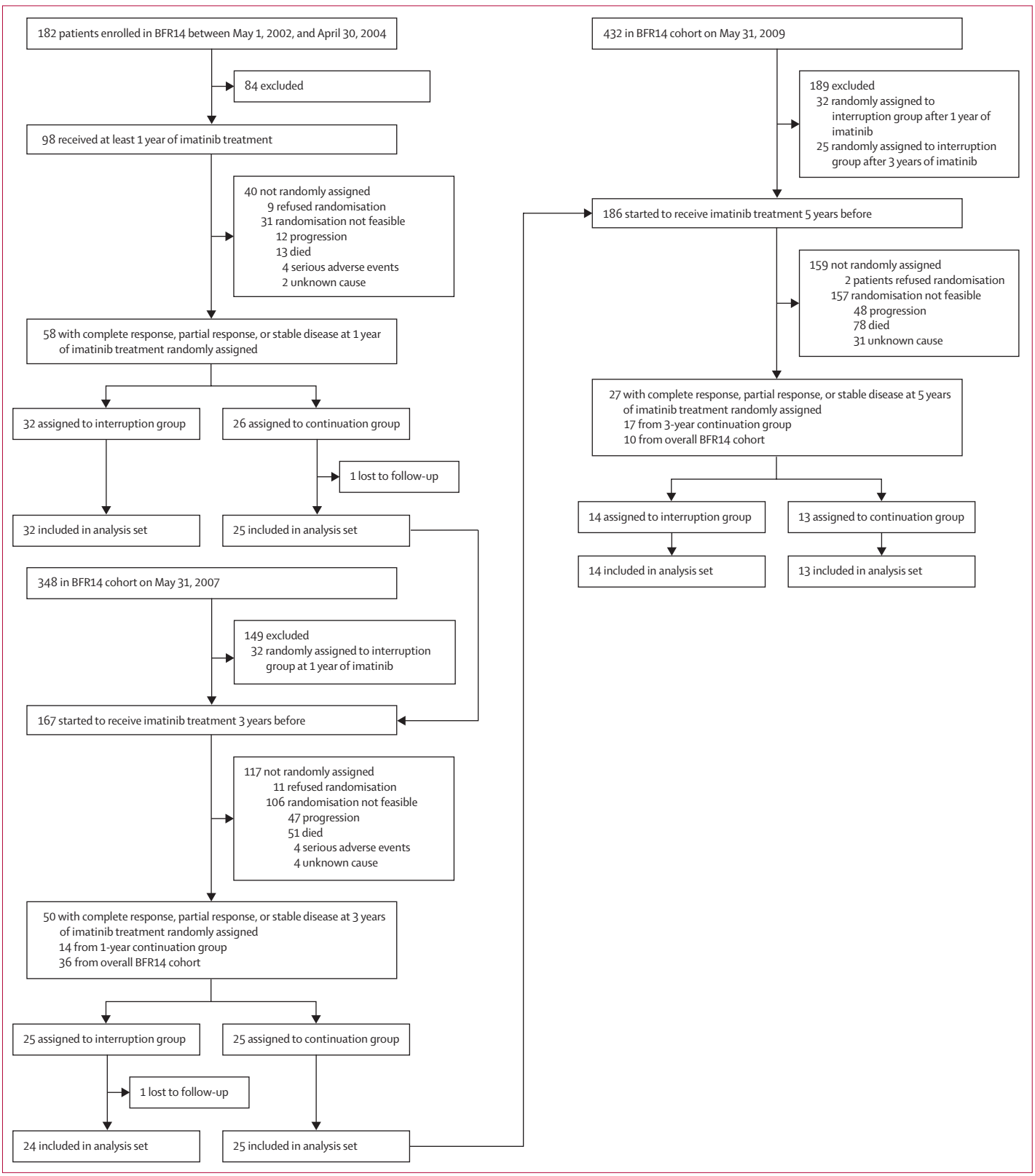

Figure 1: **Trial profile**

13 to the continuation group (figure 1). All but three patients were receiving 400 mg per day at the time of randomisation. Three patients were receiving a dose of 300 mg per day at the time of randomisation (one at the 1-year randomisation and two at the 3-year randomisation). One patient in the continuation group was lost to follow-up at the 1-year randomisation, and one patient in the interruption group was lost to follow-up at the 3-year randomisation; these patients were excluded from analyses. Tables 1–3 present the clinical, biological, and treatment characteristics of patients included in analyses, with further details in the appendix (p 2). No patient in the continuation group stopped treatment. However, three patients in the interruption group (two at 1 year and one at 3 years) continued the treatment. Median follow-up was 235·2 months (IQR 128·8–236·6) after the 1-year randomisation, 200·9 months (190·2–208·4) after the 3-year randomisation, and 164·5 months (134·4–176·4) after the 5-year randomisation.

Median progression-free survival in the interruption group was significantly shorter than that in the continuation group after 1 year of imatinib (6·1 months [95% CI 2·5–10·1; 30 events] *vs* 27·8 months [19·5–37·9; 21 events]; HR 0·36 [95% CI 0·20–0·64], log-rank p=0·0003; figure 2A), after 3 years of imatinib (7·0 months [3·5–11·7] *vs* 67·0 months [48·8–85·6]; 0·15 [0·07–0·32], log-rank p<0·0001; figure 2B), and after 5 years of imatinib (12·0 months [9·0–16·6] *vs* not reached [NR; NR–NR]; 0·13 [0·03–0·58], log-rank p=0·0016; figure 2C).

The median time to imatinib resistance in the interruption group was not significantly different to that in the continuation group after 1 year of imatinib (28·7 months [95% CI 18·1–39·1; 24 events] *vs* 90·6 months [25·3–156·1; 19 events]; HR 0·93 [95% CI 0·51–1·71], log-rank p=0·82; figure 3A). The median time to imatinib resistance in the interruption group was significantly shorter than that in the continuation group at both 3 years (66·2 months [95% CI 43·0–89·6; 21 events] *vs* 127·3 months [15·0–239·7; 12 events]; HR 0·35 [95% CI 0·17–0·72], log-rank p=0·0028; figure 2B) and 5 years (58·6 months [0·0–167·4; nine events] *vs* NR [NR–NR; two events]; 0·24 [0·05–1·12], log-rank p=0·049; figure 2C). In a post-hoc analysis, at 12 years, the proportion of patients alive in the interruption group versus the continuation group after the 3-year randomisation was 9% (95% CI 3–14) versus 50% (39–61) and after the 5-year randomisation was 33% (20–46) versus 83% (72–94). 14 (56%) of 25 patients in the continuation group after 1 year of imatinib and 17 (68%) of 25 patients in the continuation group after 3 years of imatinib were randomly assigned to the interruption group of the subsequent randomisation dates (figure 1). The appendix (p 3) shows the time to imatinib resistance of patients randomly assigned at 1 year and 3 years censored at the date of subsequent randomisation. Eight patients

	Interruption group (n=32)	Continuation group (n=25)
Age, years	60·2 (11·8)	55·5 (14·9)
Sex		
Female	10 (31%)	12 (48%)
Male	22 (69%)	13 (52%)
Site of GIST		
Stomach	10 (31%)	8 (32%)
Small bowel not otherwise specified	15 (47%)	9 (36%)
Colon or rectum	2 (6%)	3 (12%)
Other	5 (16%)	5 (20%)
Metastatic sites		
Peritoneum	11 (34%)	9 (36%)
Liver	15 (47%)	16 (64%)
Largest lesion, mm	64·6 (61·8)	71·8 (56·5)
KIT mutations		
Exon 11	15 (47%)	16 (64%)
Unknown	16 (50%)	7 (28%)
RECIST-based response at randomisation		
Complete	11 (34%)	11 (44%)
Partial	19 (59%)	12 (48%)
Stable disease	2 (6%)	2 (8%)

Data are mean (SD) or n (%). GIST=gastrointestinal stromal tumours. RECIST=Response Evaluation Criteria in Solid Tumours.

Table 1: **Characteristics of patients randomly assigned after 1 year of imatinib treatment**

	Interruption group (n=24)	Continuation group (n=25)
Age, years	60·6 (11·9)	61·2 (16·9)
Sex		
Female	17 (71%)	12 (48%)
Male	7 (29%)	13 (52%)
Site of GIST		
Stomach	5 (28%)	13 (52%)
Small bowel not otherwise specified	14 (58%)	8 (32%)
Colon or rectum	2 (8%)	1 (4%)
Other	3 (12%)	3 (12%)
Metastatic sites		
Peritoneum	9 (36%)	7 (29%)
Liver	17 (68%)	15 (63%)
Largest lesion, mm	56·5 (49·5)	63·4 (44·8)
KIT mutations		
Exon 11	13 (54%)	18 (72%)
Unknown	9 (37%)	6 (25%)
RECIST-based response at randomisation		
Complete	9 (37%)	10 (40%)
Partial	13 (54%)	13 (52%)
Stable disease	2 (8%)	2 (8%)

Data are mean (SD) or n (%). GIST=gastrointestinal stromal tumours. RECIST=Response Evaluation Criteria in Solid Tumours.

Table 2: **Characteristics of patients randomly assigned after 3 years of imatinib treatment**

were censored at the time of the 3-year randomisation and eight other patients were censored at the time of the 5-year randomisation.

Median overall survival in the interruption group was not significantly different to that in the continuation group at 1 year of imatinib (56·0 months [95% CI 30·3–82·9; 24 deaths] *vs* 105·0 months [20·6–189·6; 19 deaths]; HR 0·84 [95% CI 0·46–1·54], log-rank p=0·57; figure 4A). Median overall survival in the interruption group was significantly shorter than that in the continuation group after 3 years of imatinib (104·0 months [95% CI 90·7–118·7; 20 deaths] *vs* 134·0 months [89·7–178·3; 14 deaths]; HR 0·40 [95% CI 0·20–0·82], log-rank p=0·0096). 15-year overall survival was 5% (95% CI 0·1–10) versus 40% (29–50), respectively, in a post-hoc analysis (figure 4B). Median overall survival after 5 years of imatinib was not significantly different between the interruption group and the continuation group (NR [95% CI NR–NR; six events] *vs* 110·4 months [82·7–154·1; six events]; HR 1·28 [95% CI 0·41–3·99]; log-rank p=0·67; figure 4C).

71 patients had died at the time of the updated analysis, including 11 (15%) from unrelated causes (two from stroke, one from myocardial infarction, one from depression, one from chronic renal failure, one from accident, and five from an unknown event unrelated to GIST) and four (6%) from second cancers (one from prostate cancer, one from oesophagus cancer, one from myelodysplasia, and one from lung cancer). The GIST-specific overall survival in the continuation and interruption groups at 1 year, 3 years, and 5 years is presented in the appendix (pp 4–5).

56 (90%) of 62 patients in whom mutations were analysed had mutations in *KIT* exon 11 (tables 1–3); no correlation was observed between mutations in *KIT* exon 11 versus other mutations and overall survival (16 [29%] of 56 patients died *vs* two [33%] of six; p=0·81). A marginally higher proportion of patients with genetic deletions involving codons 557 and 558, versus patients with other documented mutations, were reported to have died of a GIST during the observation period (12 of 15 *vs* 22 of 45, p=0·049). No differences were observed in the other groups tested (*KIT* exon 9 [p=0·93], point mutations [p=0·90], deletions and insertions [p=0·85] *vs* others with documented molecular analysis).

We then compared progression-free survival in second, third, and fourth lines of treatment in the continuation and interruption groups of the three different years of randomisation (table 4). Sunitinib treatment is presented specifically in the second line because it became the standard second-line treatment during the trial. Progression-free survival in second and third line was not different between the continuation and interruption groups. Progression-free survival in the fourth line was longer in patients previously randomly assigned to the continuation groups; however, patient numbers are very small (table 4).

	Interruption group (n=14)	Continuation group (n=13)
Age, years	58·4 (11·8)	62·3 (15·4)
Sex		
Female	7 (50%)	5 (38%)
Male	7 (50%)	8 (62%)
Site of GIST		
Stomach	8 (57%)	7 (54%)
Small bowel not otherwise specified	5 (36%)	3 (23%)
Colon or rectum	1 (7%)	1 (8%)
Other	0	2 (15%)
Metastatic sites		
Peritoneum	5 (36%)	50 (38%)
Liver	11 (79%)	10 (77%)
Largest lesion, mm	56·3 (57·1)	55·2 (47·5)
KIT mutations		
Exon 11	10 (71%)	8 (62%)
Unknown	4 (29%)	5 (38%)
RECIST-based response at randomisation		
Complete	8 (57·1%)	7 (54%)
Partial	5 (35·7%)	4 (31%)
Stable disease	1 (7%)	2 (15%)

Data are mean (SD) or n (%). GIST=gastrointestinal stromal tumours. RECIST=Response Evaluation Criteria in Solid Tumours.

Table 3: **Characteristics of patients randomly assigned after 5 years of imatinib treatment**

Five patients (three women and two men) had no progression 5 years after random assignment to one of the interruption groups. Two of these patients were assigned after 1 year and three after 5 years. These patients were still alive and progression free at the last follow-up of 86 months, 236 months after year 1 randomisation and 92, 139, 178 months after year 5 randomisation, and have not restarted imatinib treatment. The median age of these five patients was 67 years (IQR 63–68) versus 62 years (51–71) of other patients. All had an ECOG performance status of 0 at the start of treatment and two had documented somatic *KIT* alterations: one point mutation Val599Gly and one deletion of codons 551–557. Four had a complete response as the best response before randomisation and none was re-operated on in the advanced phase of cancer: all four had a complete response obtained with imatinib only. Overall, four (17%) of 24 patients in the interruption groups while in complete response at randomisation versus one (2%) of 41 patients in the interruption groups while not in complete response are alive and progression free in the long term after stopping imatinib (p=0·038).

Discussion

These updated results of the randomised BFR14 trial show that the interruption of imatinib after 3 years and 5 years of administration in patients with advanced GIST results not only in rapid re-progression of the disease, as

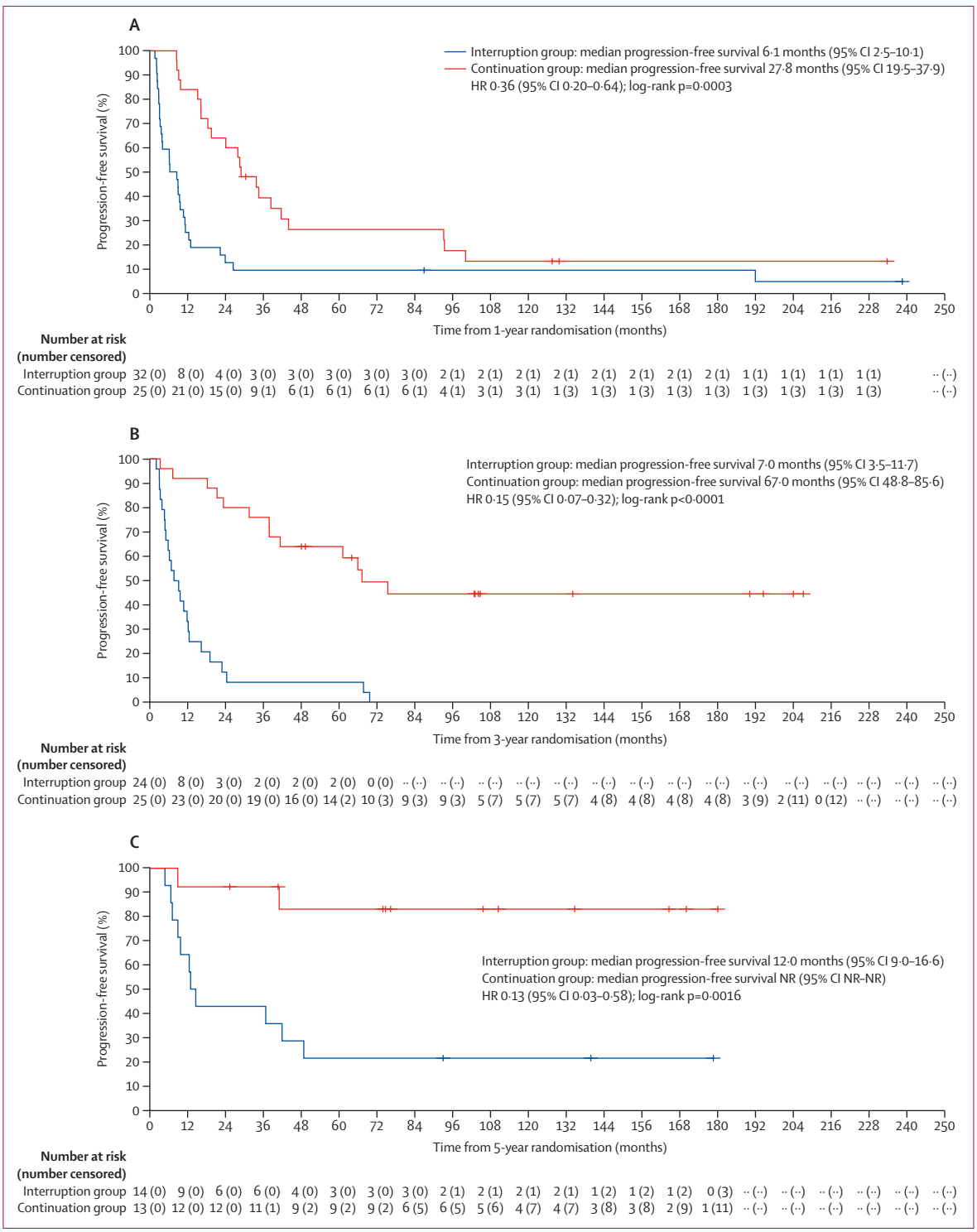

Figure 2: **Progression-free survival after randomisation at 1 year (A), 3 years (B), and 5 years (C) from start of imatinib**
Vertical lines denote censored patients. HR=hazard ratio. NR=not reached.

previously reported, but also in faster development of resistance to imatinib in the long term. A shorter overall survival was also observed in patients in the interruption group versus the continuation group at 3 years. These survival differences, increasing beyond 10 years, could be observed only with the very long follow-up reported in

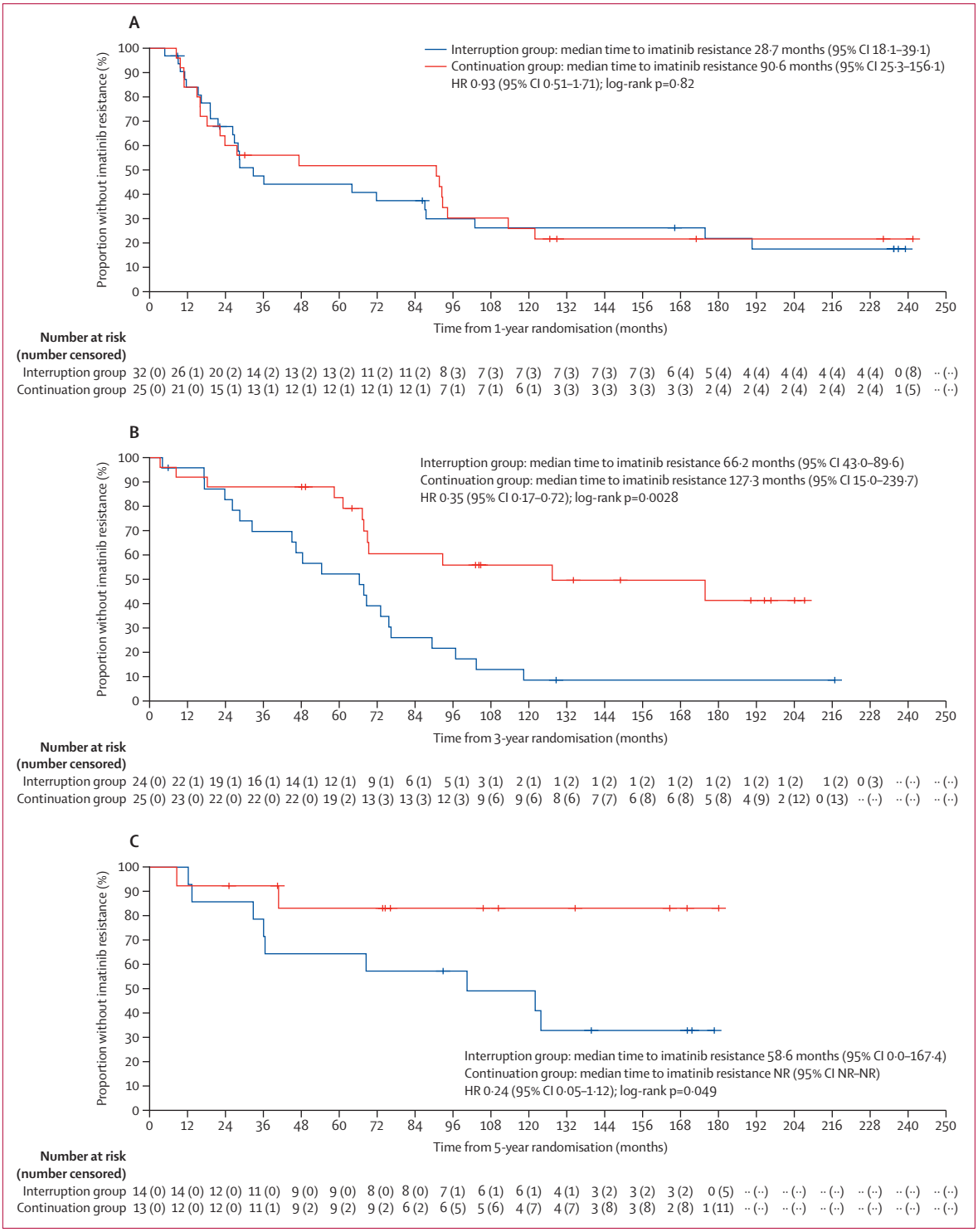

Figure 3: **Time to imatinib resistance after randomisation at 1 year (A), 3 years (B), and 5 years (C) from start of imatinib**
Vertical lines denote censored patients. HR=hazard ratio. NR=not reached.

the present study. To our knowledge, this randomised study has the longest follow-up (13–20 years) of any study assessing the impact of the discontinuation of a TKI in patients with advanced cancer.

The faster development of resistance with TKI treatment interruption versus continuation has not been previously reported. In all treatment guidelines for GIST, it is recommended that imatinib treatment be

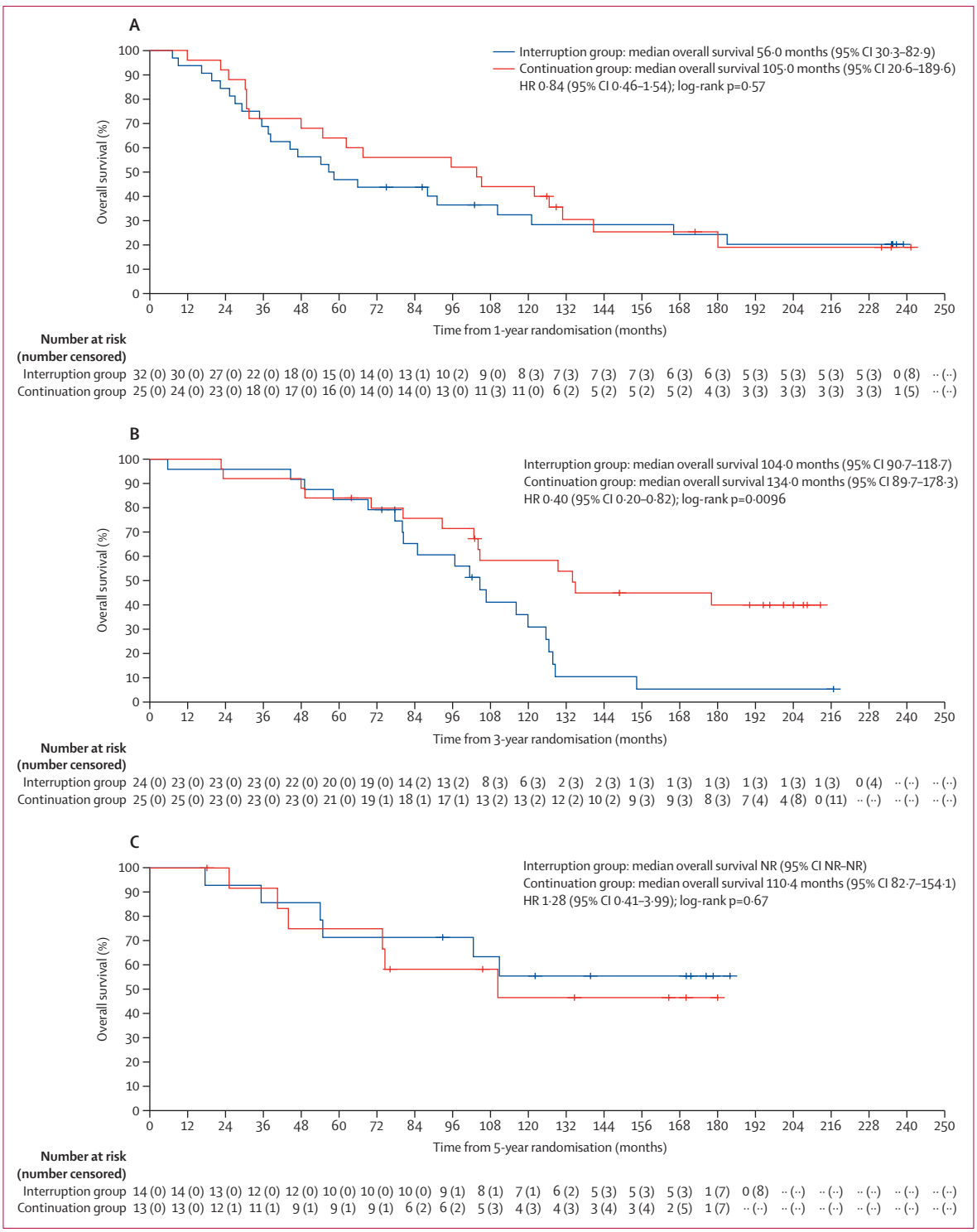

Figure 4: **Overall survival after randomisation at 1 year (A), 3 years (B), and 5 years (C) from start of imatinib**
Vertical lines denote censored patients. HR=hazard ratio. NR=not reached.

maintained until progression or intolerance in patients with advanced GIST, but, in routine practice, treatment interruption is often requested by patients. Given the absence of an effect of treatment interruption on overall survival and resistance to imatinib observed in the first reports of the BFR14 study,[6–8] flexibility for

interruption is occasionally proposed. But the results shown here indicate that imatinib interruption should be considered with caution.

The deleterious impact of treatment interruption was not detected in the group of patients randomly assigned at 1 year. The median time to imatinib resistance was longer in the continuation group than in the interruption group, but survival curves superimposed in the longer term. The lack of difference in the 1-year randomisation groups might have been related to the fact that some patients in the continuation group at 1 year were subsequently randomly assigned to the interruption group at 3 years or 5 years. However, in a sensitivity analysis that censored patients in the continuation group at 1 year who were subsequently randomly assigned to the interruption group at 3 years or 5 years, no significant difference was observed in favour of the continuation group. Patients randomly assigned at 1 year have not shown as long a duration of imatinib sensitivity as those without progression after 3 years and 5 years, and many will progress between year 1 and 3 years or 5 years. The progression-free survival curves show that at 10 years of follow-up, most patients in both groups randomly assigned at 1 year had a progression event, whereas this is not the case in patients in the continuation groups after 3 years and 5 years. The continuation of imatinib by patients in the interruption groups—ie, treatment protocol violation—could have accounted for this result (two of the patients in the interruption group at 1 year and one at 3 years continued the treatment). The impact of treatment interruption on the risk of developing imatinib resistance is therefore more important in patients with long-term imatinib-sensitive GIST.

Importantly, overall survival was significantly shorter in the interruption group at 3 years. Because the progression-free survival and overall survival of patients after the first line of treatment were similar in the continuation and interruption groups, we interpret this overall survival difference as being a direct consequence of the more rapid emergence of resistance in the interruption group.

Overall survival was not significantly different in the continuation and interruption groups randomly assigned after 5 years of treatment. In the 3-year randomisation group, the survival difference favouring the continuation group was observed at 15 years of follow-up and beyond, but not before. One can speculate that the absence of difference between the interruption and continuation groups at 5 years might be due to a shorter follow-up, the small size of the cohort, or both. The trial was stopped for accrual because of the higher number of events in the interruption group, with fewer than 15 patients randomly assigned per group at year 5. In patients randomly assigned after 5 years, an even longer follow-up, of more than 13 years, might be needed. Of note, the GIST-specific survival showed a greater magnitude of difference between the two groups after the 5-year randomisation. We interpret the absence of an overall survival difference in the 1-year cohort as a consequence of the absence of difference in time to imatinib resistance, given the observed similar efficacy of subsequent lines of treatment. Again, the duration of tumour control with subsequent lines of treatment was not found to be different in the continuation group versus the interruption group, suggesting that imatinib interruption specifically affects the time to imatinib resistance and not the efficacy of TKI given in subsequent lines.[19–24]

These observations contrast with those previously reported with adjuvant imatinib in patients with GIST. Treatment interruption after 3 years of adjuvant treatment, which is the standard treatment duration for high-risk tumours,[1–5] has not been reported to be associated with a shorter time to imatinib resistance.[18] In the randomised 62024 trial of 2 years of adjuvant imatinib versus no treatment in patients with high-risk and intermediate-risk GIST, no significant difference was observed for time to imatinib resistance, which was the primary endpoint.[17] The faster development of imatinib resistance after treatment interruption might be observed only in patients in whom macroscopic metastatic disease has been observed.

Although no biological material remains in BFR14 to test this hypothesis, an interpretation of our results could be that the interruption of imatinib allows the expansion of resistant subclones, harbouring secondary resistant mutations,[25–30] which would lead to

	Patients/events	Median progression-free survival (SE)	p value
Second-line treatments*			
All	..	..	0·33
Interruption group	31/31	11·6 (11·7)	..
Continuation group	11/11	10·4 (9·0)	..
Sunitinib	..	..	0·093
Interruption group	26/26	13·0 (12·2)	..
Continuation group	6/6	9·8 (5·3)	..
Third-line treatments†	..	..	0·19
Interruption group	20/20	9·26 (10·7)	..
Continuation group	4/4	3·7 (2·4)	..
Fourth-line treatments‡	..	..	0·0019
Interruption group	12/12	6·5 (8·2)	..
Continuation group	4/4	20·5 (20·7)	..

*Included sunitinib (n=32), AMG706 (n=3), masitinib (n=2), imatinib (n=2), imatinib plus cyclophosphamide (n=2), and imatinib plus RAD001 (n=1); sunitinib is specifically presented because it became the standard second-line treatment during the time of the trial. †Included sorafenib (n=7), sunitinib (n=4), nilotinib (n=3), regorafenib (n=3), imatinib (n=2), imatinib plus RAD001 (n=2), pazopanib (n=2), and imatinib plus cyclophosphamide (n=1). ‡Included imatinib (n=4), sorafenib (n=3), pazopanib (n=2), regorafenib (n=2), lenvatinib (n=1), sunitinib (n=1), nilotinib (n=1), imatinib plus sunitinib (n=1), and imatinib plus RAD001 (n=1).

Table 4: **Progression-free survival with subsequent lines of treatment**

faster clinical resistance. However, subclones presenting secondary mutations were shown to proliferate more slowly than those without secondary mutations in previous reports.[1] Alternatively, a higher tumour volume would lead to a higher probability of secondary mutations after restarting imatinib. The rate of secondary mutations is likely to be dependent on the number of dividing tumour cells and the mutation rate per cell division. We reported that the best response after imatinib reintroduction was often not as good as the response before the interruption. Because the response to imatinib reintroduction is not consistently available for all patients, we could not correlate best response to reintroduction and the subsequent risk of progression in this study. With current circulating tumour DNA technologies, it could be feasible to explore the emergence of molecular resistance more accurately, but this technology was not available at the time our study began. This is an important topic to explore in future clinical studies. In the 2000s, the molecular analysis of GIST was less consistently available, explaining the large proportion of patients without available molecular information.

This study has several limitations. First, although long-term follow-up (>5 years) was one of the objectives of BFR14, a specific date was not defined for last follow-up in the protocol. The small number of patients in both the continuation and interruption groups, which was prespecified to limit the risk to the patients, also limits statistical power. The successive randomisation at subsequent timepoints, although only in patients previously randomly assigned to the continuation groups at year 1 and year 3, also limits the power of the analysis of subsequent randomisations. The post-hoc analysis censoring patients at the time of subsequent randomisation supports the finding favouring the continuation groups for time to imatinib resistance but also has insufficient power. The small proportion of patients with available molecular characterisation at randomisation and at progression is also a limitation. Further studies including technologies such as circulating tumour DNA might inform the biological mechanisms accounting for the faster emergence of resistance in the interruption groups. Quality of life and adverse events were previously reported in the initial phase of the study,[6–8] at the time of randomisation and 1 month and 6 months after randomisation, but less than 50% of patients completed the quality-of-life questionnaires administered at that time. No systematic update for adverse events was done in this long-term follow-up.

Despite our results, is there a group of patients for whom imatinib interruption could be safe and useful? Five patients from the interruption group who did not reinstate imatinib are alive and progression free. Four of the five patients had a complete response after imatinib, but they represent less than 20% of the patients in the interruption group. Therefore, this interruption strategy cannot be recommended as routine for any patients. Interruption of imatinib in patients with a complete absence of circulating tumour DNA warrants further study.

If a TKI must be received without discontinuation for patients with advanced, oncogene-addicted cancer, this has important practical and economic consequences. Reporting the long-term follow-up of adjuvant studies testing these agents would be informative. Our observations therefore have implications for other diseases treated with imatinib and other TKIs. In chronic myeloid leukaemia, imatinib interruption in patients in molecular complete remission has been reported to result in molecular relapse mostly in the first 6 months.[12–16] Although these two cancers are different, they share imatinib as a therapeutic standard. The differences in the two disease settings point to the fact that each cancer model should be assessed specifically for the question of the duration or interruption of the treatment.

It will thus be interesting to explore whether faster resistance to imatinib can also be detected in the long term in cancers with a strong driver mutation in a tyrosine kinase.[31,32] To our knowledge, no randomised trial has been done to test TKI treatment discontinuation in patients with solid tumours that have mutations in, for example, *EGFR*, *ALK*, *ROS1*, *RET*, or *NTRK*. The present results could encourage exploration of whether faster resistance is also observed in other cancer types.

In conclusion, this study shows that imatinib interruption after 3 years of treatment in patients with advanced GIST is associated with faster emergence of resistance to imatinib and an increased risk of death. These observations have possible relevance for chronic myeloid leukaemia and other cancers treated with TKIs. These findings also show the value of long-term updates of randomised studies to identify optimal therapeutic strategies for patients with advanced cancer.

Contributors

J-YB and ALC: conceptualisation, funding acquisition, and supervision. J-YB, QD, and SC: data curation. J-YB and QD: formal analysis. J-YB and ALC: funding acquisition. All authors: investigation; procurement of resources to conduct clinical trial at their site; validation of the final version of the Article; and review, editing and final approval of the report. DP, SC, JYB, and ALC: methodology and project administration. J-YB, QD, ALC, SC, and DP: full access to and verification of the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

J-YB reports grants from NETSARC+, INTERSARC+, and LYRICAN+ from INCA (to the institution), DEpGyn RHU and LYRICAN+ from the Agence Nationale de la Recherche (to the institution), and ERN EURACAN from the EU commission (to the institution); research support from Novartis, Deciphera, and Bayer (to the institution); membership of steering committees for the Intrigue and Motion studies for Deciphera; and membership of the supervisory boards of Transgène and Innate Pharma. IR-C reports research grants from Bristol Myers Squibb (BMS); consulting fees from and participation on data safety boards of Adaptimmune, Agenus, Amgen, AstraZeneca, BMS, Clovis, Daiichi Sankyo, Deciphera, Eisai, EQRX, GSK, MacroGenics, Merck Serono, Mersana, MSD, Novartis, Onxeo, Roche, and Sutro Biopharma. NP reports research grants from Bayer. DP reports travel grants from

Roche and Novartis. ALC reports honoraria from Deciphera and Pharmamar. All other authors declare no competing interests.

Data sharing

Completely de-identified participant data can be made available upon reasonable request to the corresponding author after approval of a proposal by the sponsor and the investigators, with a signed data access agreement.

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References

1 Blay JY, Kang YK, Nishida T, von Mehren M. Gastrointestinal stromal tumours. *Nat Rev Dis Primers* 2021; **7:** 22.

2 de Pinieux G, Karanian-Philippe M, Le Loarer F, et al. Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. *PLoS One* 2021; **16:** e0246958.

3 Casali PG, Blay JY, Abecassis N, et al. Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2022; **33:** 20–33.

4 Blay JY, Hindi N, Bollard J, et al. SELNET clinical practice guidelines for soft tissue sarcoma and GIST. *Cancer Treat Rev* 2022; **102:** 102312.

5 von Mehren M, Kane JM, Riedel RF, et al. NCCN Guidelines® Insights: Gastrointestinal Stromal Tumors, Version 2.2022. *J Natl Compr Canc Netw* 2022; **20:** 1204–14.

6 Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. *J Clin Oncol* 2007; **25:** 1107–13.

7 Le Cesne A, Ray-Coquard I, Bui BN, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. *Lancet Oncol* 2010; **11:** 942–49.

8 Ray-Coquard I, Bui BN, Adenis A, et al. Risk of relapse with imatinib (IM) discontinuation at 5 years in advanced GIST patients: Results of theBFR14 randomized phase III study comparing interruption versus continuation of IM at 5 years of treatment: a French Sarcoma Group Study. *Proc Am Clin Oncol* 2010; **28:** (suppl 15): 10032–1003 (abstr).

9 Patrikidou A, Chabaud S, Ray-Coquard I, et al. Influence of imatinib interruption and rechallenge on the residual disease in patients with advanced GIST: results of the BFR14 prospective French Sarcoma Group randomised, phase III trial. *Ann Oncol* 2013; **24:** 1087–93.

10 Blay JY, Pérol D, Le Cesne A. Imatinib rechallenge in patients with advanced gastrointestinal stromal tumors. *Ann Oncol* 2012; **23:** 1659–65.

11 Blay JY, Adenis A, Ray-Coquard I, Cassier PA, Le Cesne A. Is there a role for discontinuing imatinib in patients with advanced gastrointestinal stromal tumour? *Curr Opin Oncol* 2009; **21:** 360–66.

12 Patrikidou A, Domont J, Chabaud S, et al. Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group. *Eur J Cancer* 2016; **52:** 173–80.

13 Dulucq S, Astrugue C, Etienne G, Mahon FX, Benard A. Risk of molecular recurrence after tyrosine kinase inhibitor discontinuation in chronic myeloid leukaemia patients: a systematic review of literature with a meta-analysis of studies over the last ten years. *Br J Haematol* 2020; **189:** 452–68.

14 Campiotti L, Suter MB, Guasti L, et al. Imatinib discontinuation in chronic myeloid leukaemia patients with undetectable BCR-ABL transcript level: a systematic review and a meta-analysis. *Eur J Cancer* 2017; **77:** 48–56.

15 Thielen N, van der Holt B, Cornelissen JJ, et al. Imatinib discontinuation in chronic phase myeloid leukaemia patients in sustained complete molecular response: a randomised trial of the Dutch-Belgian Cooperative Trial for Haemato-Oncology (HOVON). *Eur J Cancer* 2013; **49:** 3242–46.

16 Mahon FX, Réa D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol* 2010; **11:** 1029–35.

17 Casali PG, Le Cesne A, Velasco AP, et al. 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), and Spanish Group for Research on Sarcomas (GEIS). *Ann Oncol* 2021; **32:** 533–41.

18 Joensuu H, Eriksson M, Sundby Hall K, et al. Survival outcomes associated with 3 years vs 1 year of adjuvant imatinib for patients with high-risk gastrointestinal stromal tumors: an analysis of a randomized clinical trial after 10-year follow-up. *JAMA Oncol* 2020; **6:** 1241–46.

19 Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet* 2006; **368:** 1329–38.

20 Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381:** 295–302.

21 Mir O, Cropet C, Toulmonde M, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. *Lancet Oncol* 2016; **17:** 632–41.

22 Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020; **21:** 923–34.

23 Bauer S, Jones RL, Blay JY, et al. Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE): a randomized, open-label, phase III trial. *J Clin Oncol* 2022; **40:** 3918–28.

24 Kang YK, George S, Jones RL, et al. Avapritinib versus regorafenib in locally advanced unresectable or metastatic GI stromal tumor: a randomized, open-label Phase III study. *J Clin Oncol* 2021; **39:** 3128–39.

25 Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. *J Clin Oncol* 2006; **24:** 4764–74.

26 Wardelmann E, Merkelbach-Bruse S, Pauls K, et al. Polyclonal evolution of multiple secondary *KIT* mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. *Clin Cancer Res* 2006; **12:** 1743–49.

27 Desai J, Shankar S, Heinrich MC, et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. *Clin Cancer Res* 2007; **13:** 5398–405.

28 Serrano C, Mariño-Enríquez A, Tao DL, et al. Complementary activity of tyrosine kinase inhibitors against secondary kit mutations in imatinib-resistant gastrointestinal stromal tumours. *Br J Cancer* 2019; **120:** 612–20.

29 Serrano C, Vivancos A, López-Pousa A, et al. Clinical value of next generation sequencing of plasma cell-free DNA in gastrointestinal stromal tumors. *BMC Cancer* 2020; **20:** 99.

30 Arshad J, Roberts A, Ahmed J, et al. Utility of circulating tumor DNA in the management of patients with GI stromal tumor: analysis of 243 patients. *JCO Precis Oncol* 2020; **4:** 66–73.

31 Tsuboi M, Herbst RS, John T, et al. Overall survival with osimertinib in resected EGFR-mutated NSCLC. *N Engl J Med* 2023; **389:** 137–47.

32 Solomon BJ, Ahn JS, Dziadziuszko R, et al. Het al. Efficacy and safety of adjuvant alectinib versus chemotherapy in patients with early-stage ALK+ non-small cell lung cancer (NSCLC). *Ann Oncol* 2023; **34** (suppl 2)**:** S1295–96.