Background: We previously demonstrated that interruption of imatinib mesylate (IM) in responding patients (pts) with advanced gastrointestinal stromal tumours (GISTs) results in rapid reprogression. The impact of interruption on residual disease in patients with advanced GIST: results of the BFR14 prospective French Sarcoma Group randomised, phase III trial

A. Patrikidou1, S. Chabaud2, I. Ray-Coquard2, B. N. Bui3, A. Adenis4, M. Rios5, F. Bertucci6, F. Duffaud7, C. Chevreau8, D. Cupissol9, J. Domont1, D. Pérol2, J. Y. Blay10 & A. Le Cesne1,∗, for the French Sarcoma Group

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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

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tumour, quality of response and secondary resistance has not been fully investigated.

**Patients and methods:** Within the BRF14 study, 71 non-progressing patients were randomly assigned in the interruption arms after 1, 3 or 5 years. IM was resumed in the case of progressive disease (PD). Tumour status at randomisation, relapse and after IM rechallenge, progression-free survival (PFS) and time to secondary resistance were analysed.

**Results:** At data cut-off, 51 of 71 patients had restarted IM following documented PD. Eighteen patients (35%) progressed on known lesions only, while 33 patients (65%) had new lesions, with concomitant progression of known lesions in 17 patients. Only 8 (42%) of complete remission (CR) patients and 12 (52%) of partial response (PR) patients at randomisation achieved a new CR and PR. Patients progressing rapidly after interruption had a poorer prognosis.

Tumour status at randomisation influenced time to progression after rechallenge.

**Conclusion:** In advanced GIST patients interrupting IM, quality of response upon reintroduction did not reach the tumour status observed at randomisation. Rapid progression after imatinib interruption is associated with poor PFS after reintroduction.

**Key words:** GIST, imatinib mesylate, rechallenge

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**introduction**

Gastrointestinal stromal tumours (GISTs) are malignant tumours that arise from the precursor cells of the interstitial cells of Cajal in the gastrointestinal tract [1–3]. Imatinib mesylate (IM), a small-molecule inhibitor that targets the two frequently mutated tyrosine kinase receptors, has dramatically improved the outcome of patients with advanced GISTs, from a 5-year overall survival (OS) rate of 10% before the imatinib era to around 50% since its introduction [4–6]. Imatinib treatment induces tumour control in 90% of all patients. The evaluation of treatment efficacy is complex, but it is considered that patients in complete remission (CR), partial response (PR) and patients in stable disease (SD) at 6 months according to RECIST have a similar OS [5–7].

Unfortunately, despite its continuous administration, secondary resistance to imatinib occurs at a median time of 20–24 months [4–6, 8], mostly due to the acquisition of additional mutations in the KIT gene, yielding imatinib-resistant KIT proteins [9–11]. Whether treatment continuation or interruption may limit or favour this resistance selection process and thus impact on the clinical outcome is not known.

The BFR14 trial of the French Sarcoma Group addressed this question by randomising patients after 1, 3 and 5 years of treatment with imatinib. We previously reported that imatinib interruption in patients in whom disease control has been achieved is associated with a major risk of rapid progression in the vast majority of patients. Following interruption after 1 year of treatment, the median time to progression was 6.1 months, 81% of patients relapsing within the first year after treatment interruption [12]. Similarly, the median PFS following imatinib interruption in responders after 3 years of treatment was 9 months, 68% of patients relapsing within 1 year following interruption, even in patients considered in CR before randomisation [13].

Finally, interruption of imatinib after 5 years of treatment also results in a rapid progression, since 45% of the patients assigned to the interruption group had relapsed during the first year of follow-up, whereas no further progression was noted in any patient randomly assigned to continue treatment at the time of analysis ($P = 0.032$) [14]. Overall, it seems that imatinib treatment, even if prolonged up to 3 or 5 consecutive years, is not sufficient to eradicate the remaining persistent GIST cells and to cure patients with advanced GISTs [13].

Whether imatinib interruption influences the duration of imatinib activity following rechallenge and secondary resistance is unclear. Tumour control is obtained in the majority of patients when imatinib is resumed upon progression. Time to secondary resistance to imatinib was similar in the two therapeutic arms for the two treatment length randomisation cohorts [12, 13], suggesting that imatinib interruption does not prevent nor promote the emergence of imatinib resistance in GIST cells. However, this study was not powered to demonstrate any difference in OS.

The aim of this exploratory analysis was to assess the quality of response upon imatinib reintroduction at progression in patients randomly assigned in the interruption arms of the BFR14 trial. Furthermore, we assessed the effect of duration of imatinib interruption on the time to secondary resistance when imatinib was rechallenged.

**patients and methods**

**BFR14 population**

The BFR14 trial is an open-label multicentre randomised, phase III trial allocating treatment interruption versus maintenance in non-progressing patients with advanced GIST who received oral imatinib 400 mg/day. The protocol was reviewed and validated by a national ethics committee according to the national and European directives. The original design of the trial aimed to assess the effect of imatinib interruption in patients with non-progressive disease (PD) after 1 year of treatment [12]. Two subsequent amendments were implemented to allow randomisation after 3 years of treatment [13] and more recently after 5 years [14]. The inclusion criteria were age of at least 18 years, histological confirmation of locally advanced and/or metastatic GIST, immunohistochemical documentation of c-KIT (CD117) expression and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were imatinib-naive, with no history of previous malignancy and were required to have normal renal, cardiac and hepatic functions. No concurrent anticancer therapy was allowed. All patients gave written informed consent before inclusion.
study procedures

All study procedures were as previously published [12–14]. Imatinib was given orally at 400 mg per day, as a single daily dosing. Clinical and biological tolerance was assessed weekly during the first month of treatment, every 2 weeks for the following month, then monthly for 3 months and every 3 months thereafter. Tumour assessments were carried out every 2 months for the first 6 months and every 3 months thereafter. The response was graded according to the RECIST criteria version 1.0 [15].

Patients with controlled disease i.e. CR, PR or SD were eligible for random assignment between discontinuation of imatinib (interruption group) and maintenance of imatinib until PD or intolerance (continuation group). Patients who refused random assignment continued to receive imatinib and were followed-up in a similar manner. According to the protocol, imatinib was resumed at the dose used before assignment in the case of PD in the interruption group until further progression, intolerance or patient refusal. In the case of progression under imatinib 400 mg/day, patients received a high-dose imatinib regimen (600–800 mg daily).

The primary objective was to compare progression-free survival (PFS) between the two groups. The secondary objectives included OS, response rate according to RECIST after imatinib reintroduction in the interruption group and time to secondary resistance in both the groups, which represented time to progression while receiving imatinib 400 mg/day—i.e. first progression in the continuation group and progression after reintroduction of imatinib in the interruption group. The results have been reported elsewhere [12–14].

imatinib rechallenge substudy

The current exploratory analysis aimed to evaluate the effect of imatinib rechallenge in the progressing GIST patients who had previously been randomly assigned in the discontinuation therapeutic arm at the three different time points as mentioned above. The tumour response status (according to RECIST) and tumour size at the time of randomisation, at relapse and after imatinib rechallenge (best response) were analysed and compared. Since the impact of the imatinib-free interval on the subsequent outcome of patients remains unknown, the median PFS after imatinib rechallenge was analysed in regard with the duration of treatment interruption (within 6 months, 6–12 months and >12 months). The time to secondary resistance to imatinib was calculated from the date of randomisation to the date of first progression under imatinib 400 mg/day corresponding to the second progression for those patients randomly assigned in the interruption arm.

statistics

The survival curves were plotted according to the Kaplan–Meier method and compared using a log-rank test. PFS was calculated from the date of randomisation to the date of progression or last follow-up. PFS after rechallenge and time to secondary resistance were calculated from the date of IM reintroduction to the date of new progression under treatment or last follow-up. Statistical analysis was carried out using the SAS version 9.3 software (SAS Institute, Cary, NC).

results

population data

The BRF14 study was initiated in June 2002 and closed in July 2009. The consort diagram for this subgroup analysis is presented in Figure 1. Seventy-one non-progressing patients were randomly assigned in the interruption arms after 1 year (32 patients), 3 years (25 patients) and 5 years (14 patients) of imatinib treatment. Outcome results of the BRF14 trial for the 1-year randomisation phase were made available to all patients, and imatinib rechallenge was proposed to all patients without PD in the interruption arm. Three patients restarted imatinib without documented PD and they are not included in the present analysis. Following imatinib interruption, 54 of 71 patients progressed. Two of them refused to restart imatinib at progression and one had no follow-up after imatinib reintroduction. The present analysis is carried out on the 51 patients with documented PD for whom imatinib was

Figure 1. Consort diagram.
reintroduced and all evaluation data were available (Figure 1). Data cut-off was in January 2012.

The mean age of the 51 patient cohort was 60 years (SD, 11.7 years), with a median age of 62.4 years (range 30–79 years). There were 27 male (53%) and 24 female patients (47%). The ECOG performance status was 0 in ~60% of patients, 1 in 40% of the cohort and unknown in three patients. In terms of metastatic status, 49% of patients had liver metastases, 21% had peritoneal metastases, 12% of patients had combined liver and peritoneal metastases and 18% had other metastatic sites. The median tumour size at inclusion was 8.9 cm (0 to 38.4 cm), with a mean size (SD) of 11.5 cm (8.7). At the time of randomisation, this median tumour size had decreased by 69% (27 mm; 0–33.8 cm). At randomisation, the categories of response according to RECIST were as follows: CR, 35% (18/51 patients); PR, 47% (24/51 patients) and SD, 18% (9/51 patients). Table 1 shows tumour response status at randomisation and median tumour size of cohorts at the three randomisation time points.

**IM interruption**

The median PFS observed on these 51 progressive patients was 6.0, 7.1 and 10.8 months after random assignment to the interruption group at 1, 3 and 5 years, respectively (Figure 2). Twenty patients relapsed within the first 6 months after imatinib interruption, 20 between 6–12 months and eleven progressions occurred ≥12 months after IM interruption (Figure 3). The quality of tumour status at randomisation influenced the time to progression after imatinib interruption (Figure 4); the median PFS were 3.2, 6.1 and 10.5 months, respectively, for patients exhibiting a SD, PR and CR at randomisation (log-rank test, \( P = 0.0375 \)). Among the 51 patients, 18 patients (35%) exhibited a progression of the previous known target lesions, while 33 patients (65%) had new lesions (with concomitant progression of known lesions in 17 patients). Of the randomisation CR patients, 11.1% progressed on old lesions, 61.1% on new lesions and 27.8% on both. The respective figures for the randomisation PR patients were 45.8%, 16.6% and 37.5%, while for the randomisation SD patients were 55.5%, 11.1% and 33.4%.

**IM rechallenge: tumour response**

Following rechallenge with imatinib, all but two patients responded again, with a tumour control rate (CR + PR + SD) after rechallenge of 96% (Table 2). Both the patients experiencing PD after rechallenge were in partial response before randomisation and were randomly assigned to IM interruption after 1 year. Rechallenge of imatinib conferred clinical benefit rates of 92%, 100% and 100% for the 1-, 3- and 5-year cohorts, respectively.

The best response following imatinib rechallenge according to RECIST in regard with response status at randomisation is summarised in Table 2. The rate of objective response (CR and PR) was significantly higher in the patients who had also shown objective response at randomisation, but clinical benefit (CR, PR, SD), separately assessed or overall, did not reach the initial response percentages. Indicatively, only 42% (8/19

Table 1. Tumour response at randomisation

<table>
<thead>
<tr>
<th>Randomisation time point</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 year</td>
</tr>
<tr>
<td>Number of patients</td>
<td>25 (49.0%)</td>
</tr>
<tr>
<td>Response at randomization</td>
<td></td>
</tr>
<tr>
<td>Complete remission (CR)</td>
<td>8 (32%)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>12 (48%)</td>
</tr>
<tr>
<td>Stable disease (SD)</td>
<td>5 (20%)</td>
</tr>
<tr>
<td>Median tumour size</td>
<td>Median (min,max)</td>
</tr>
</tbody>
</table>
patients) of the initial CR achieved a new CR, and 52% (12/23 patients) of the initial PR achieved a new PR.

**IM rechallenge: PFS and time to secondary resistance**

PFS after imatinib rechallenge did not significantly differ between progression of pre-existing residual masses and appearance of new lesions. Time to secondary resistance (second progression) did, however, seem to differ according to the prior imatinib-free interval, with patients who had a shorter previous imatinib-free interval progressing quicker after imatinib rechallenge (Figure 3). A second PD was observed in 70% (14/20) of patients who relapsed in the first 6 months after imatinib interruption, in 45% (9/20) of patients who relapse between 6 and 12 months and 18% (2/11) of those who relapse after 12 months (P = 0.019, chi-square test).

The corresponding 2-year PFS was significantly different: 30% (95% CI 12–50), 62% (95% CI 37–80) and 75% (95% CI 31–93), respectively (Figure 3).

**discussion**

The objective of the present analysis was to evaluate the effect of imatinib rechallenge in progressing GIST patients who had previously been treated with imatinib but interrupted in a context of prolonged tumour control at three different time points according to the BFR14 trial. This randomised trial has clearly demonstrated that imatinib interruption results in rapid progression in most GIST patients with advanced disease, whatever the pattern of response achieved under imatinib treatment. A more prolonged follow-up is needed to carefully analyse the behaviour of patients not yet progressing in the interruption arms. The results also strongly suggest that patients in CR under imatinib still have residual disseminated, persistent active tumour cells, and show that it is not safe to interrupt imatinib on the basis of a complete response, as defined with the standard morphological criteria, even after long-lasting treatment [13].

Prolonged administration of an active drug in advanced malignant diseases obviously selects for patients with favourable prognostic factors regarding the outcome and predictive factors for drug sensitivity. Despite this selection process and favourable patient characteristics at the time of randomisation (35% of CR, median tumour size 27 mm), these patients have progressed rapidly after imatinib interruption, 40 of 51 patients within the first year after imatinib interruption, including 2 of 4 (50%) patients considered in CR and randomly assigned in the interruption arm after 5 years of imatinib treatment. Imatinib alone does not seem sufficient to eliminate the remaining dormant GIST cells and to cure patients with metastatic GIST.

The kinetics of progression after imatinib interruption appears to be more influenced by the size of the residual mass (CR > PR > SD) at interruption than by the duration of imatinib treatment before interruption (Figures 2 and 4). This observation is in line with previously reported results on the correlation of tumour bulk and PFS [6]. Since the rate of CR increases from 32% (patients randomly assigned at 1 year) to 67% (patients randomly assigned at 5 years), the above-mentioned influence could explain in part the increase of the median time to progression from 6 to 12 months in the two patient cohorts, respectively [12, 14]. Moreover, the median tumour size at randomisation in the interruptions arm decreases from 35 mm to 0 between the 1-year and 5-year time points of randomisation, respectively (Table 1). Interestingly, the great majority (13/19 patients, 68%) of patients in CR at randomisation developed new lesions rather that recurrence on known sites, while patients exhibiting a PR or a DS eventually progressed on both old and new lesions (Table 2).

Two of the secondary objectives of the BFR14 trial included the response rate according to RECIST after imatinib reintroduction in the interruption group, and time to secondary resistance, i.e. the time from the date of randomisation until the date where patients developed a progression.

### Table 2. Best response at imatinib mesylate (IM) rechallenge

<table>
<thead>
<tr>
<th>Response at randomization</th>
<th>Complete remission (CR)</th>
<th>Partial response (PR)</th>
<th>Stable disease (SD)</th>
<th>Progressive disease (PD)</th>
<th>All</th>
<th>Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 8</td>
<td>8 (100.0%)</td>
<td>7 (30.4%)</td>
<td>4 (22.2%)</td>
<td>0 (0.0%)</td>
<td>19 (37.3%)</td>
<td>Fisher Exact P = 0.004</td>
</tr>
<tr>
<td>N = 23</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N = 18</td>
<td></td>
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<tr>
<td>N = 2</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>N = 51</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

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[Figure 4. Progression-free survival (PFS) according to the response at the time of randomisation.](#)

**Table 2.** Best response at imatinib mesylate (IM) rechallenge
progression while receiving imatinib 400 mg/day (second progression in the interruption arm). A new tumour control after imatinib rechallenge was obtained in 96% of cases and in all patients randomly assigned in the interruption arm after 3 and 5 years of treatment. It can be argued that the two patients who did not benefit from imatinib reintroduction had already developed a biological secondary resistance to imatinib at the time of the randomisation at 1 year, not yet documented by a RECIST progression before randomisation. Despite this high rate of tumour control, this exploratory analysis demonstrates that the quality of response achieved when imatinib was resumed at progression did not reach the tumour status observed at the time point when patients had initially stopped the treatment. Only 42% (8/19 patients) of CR and 52% (12/23 patients) of PR observed at the time of randomisation achieved a new CR and PR, respectively, as best response when imatinib was restarted.

Although the number of patients is small for significance, time to secondary resistance and OS do not differ between the continuation and interruption arms and in the two consecutive randomisations (1 and 3 years) [12, 13], suggesting the lack of effect of treatment continuation or interruption on the imatinib-resistance selection. This study was not powered to demonstrate any difference on OS; however, the high rate of tumour control achieved with re-initiation of treatment could allow physicians to deliver periods of imatinib-free interval in cases of prolonged and uncomfortable side-effects or prolonged periods of ‘drug holidays’ in the case of reimbursement problems in some countries. According to our present results, these free intervals have to be considered with caution, since a rapid progression, a poorer quality of volumetric response at imatinib rechallenge and the growth of remaining persistent/resistant cells could impact the prolonged outcome of patients. For all these reasons, treatment interruption should not be recommended outside clinical trials unless patients experience substantial toxic effects.

Although imatinib interruption may not affect the emergence of therapeutic resistance, the duration of response after imatinib rechallenge seems to be also influenced by the prior imatinib-free interval, since patients progressing rapidly after interruption had a dismal prognosis compared with those exhibiting a progression after ≥6 months. These results could be interpreted by the biological characteristics of GIST but also by the mutational status [16].

These data observed in advanced GISTs need to be considered and explored in the adjuvant setting [17, 18], where the optimal duration of imatinib remains unknown and where reintroduction of imatinib is the standard of care in case of disease recurrence [18–22].

funding

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disclosure

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Phase II prospective study with sorafenib in advanced soft tissue sarcomas after anthracycline-based therapy

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Introduction: We investigated the activity and safety of sorafenib, a multitargeted tyrosine-kinase inhibitor, in patients with advanced soft tissue sarcomas (STS).

Patients and methods: An open-label nonrandomised multicentre phase II study was conducted in advanced STS patients pre-treated with anthracycline-based chemotherapy. Patients received sorafenib 400 mg twice daily for 28 days. The primary end point was the progression-free survival (PFS) rate at 6 months. Toxicity was assessed. Clinical outcomes were evaluated in all histologies and in leiomyosarcoma (L) and angiovascular sarcomas (A).

Results: Between November 2006 and January 2010, 101 patients (36 L, 19 A, and 46 others) were enrolled; 76 patients per-protocol (PP) and 100 per intention-to-treat (ITT) were assessable for the primary end point. In the PP analysis, 11 (14.5%) achieved partial response and 25 (32.9%) stable disease; 6-month PFS rates were all histologies, 34.5%; L, 38.4%; and A, 56.3%. In the ITT analysis, 11 (14.5%) achieved partial response and 25 (32.9%) stable disease; 6-month PFS rates were all histologies, 34.5%; L, 38.4%; and A, 56.3%. In the ITT analysis, 11 (14.5%) achieved partial response and 25 (32.9%) stable disease; 6-month PFS rates were all histologies, 34.5%; L, 38.4%; and A, 56.3%. In the ITT analysis, 11 (14.5%) achieved partial response and 25 (32.9%) stable disease; 6-month PFS rates were all histologies, 34.5%; L, 38.4%; and A, 56.3%

Conclusions: Sorafenib appears to be a promising option in leiomyosarcoma patients. This finding warrants further evaluation in histology-driven trials.

Key words: angiosarcoma, leiomyosarcoma, soft tissue sarcoma, sorafenib, vascular sarcoma

Introduction

Soft tissue sarcomas (STS) are rare heterogeneous mesenchymal neoplasms, accounting for <1% of adult malignancies, with a median survival of ~1 year. Several studies have been conducted to find an effective systemic therapy, but currently the number of active drugs is very limited. Results of phase II trials with single or combined regimens, including second- and third-generation agents, showed objective response rates of ~16%–36% [1–3].

Recent advances in the knowledge of molecular characteristics and the prognosis of STS [4, 5] and the