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Outcomes of patients with metastatic gastrointestinal stromal tumors (GIST) treated with multi-kinase inhibitors other than imatinib as first-line treatment

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ABSTRACT

Background Imatinib is the standard first-line therapy in metastatic gastrointestinal stromal tumours (GIST). Investigational multi-kinase inhibitors (MKIs) such as nilotinib, dasatinib or masitinib have been tested as first-line therapies in phase II/III studies. This might theoretically result either in increased survival or in early emergence of resistance to approved MKIs.

Methods To assess whether using MKIs other than imatinib in first line decreases imatinib efficacy in second line for patients with GIST, a retrospective chart review was performed from 2005 to 2011 in two French tertiary centres of patients with GIST who received investigational MKIs (in phase II/III trials) as first-line treatment, followed by imatinib as second line.

Results Of 46 patients, (55% women, median age 55 years (range 24–81)), 22 (47%) had a *KIT* exon 11 mutation, 1 a *KIT* exon 9 mutation (2%), 1 a *PDGFRA D842V* mutation (2%). Out of 46 patients, 21 (46%) received masitinib, 17 (37%) received dasatinib and 8 (17%) received nilotinib as first-line treatment with a median progression-free survival of 18.0 months (95% CI: 8.5 to 25.5). Median time to imatinib failure was 19.7 months (95% CI: 13.5 to 29.0). Median time to second relapse was 48.7 months (95% CI: 31.2 to 72.0). Median overall survival from time of initial metastasis diagnosis was 5.7 years (95% CI: 4.5 to 7.4).

Conclusions Patients with GIST who received investigational MKIs as first-line treatment and imatinib as second line had a time to second relapse longer than that observed historically with imatinib in first line, suggesting that using MKIs other than imatinib in first line does not decrease the efficacy of subsequent treatment lines.

Key questions

What is already known about this subject?

- Imatinib is the standard first-line therapy in metastatic gastrointestinal stromal tumours (GIST). Using an investigational multi-kinase inhibitor (MKI) as first-line treatment before imatinib in metastatic GIST might theoretically result either in increased progression-free survival (PFS) (by the addition of a new line of treatment), or in early emergence of resistance to approved MKIs.

What does this study add?

- A retrospective chart review was performed in patients with GIST who received investigational MKIs (in phase II/III trials) as first-line treatment, followed by imatinib as second line in two tertiary cancer centres in France. Median PFS on first-line treatment was 18.0 months (95% CI: 8.5 to 25.5), median time to failure with imatinib was 19.7 months (95% CI: 13.5 to 29.0), median time to second relapse was 48.7 months (95% CI: 31.2 to 72.0) and median overall survival from time of initial diagnosis was 5.7 years (95% CI: 4.5 to 7.4).

How might this impact on clinical practice?

- Patients with GIST who received investigational MKIs as first-line treatment followed by imatinib had a time to second relapse longer than that observed historically with imatinib in first line, suggesting that using MKIs other than imatinib in first line does not decrease the efficacy of subsequent treatment lines.

INTRODUCTION

Gastrointestinal stromal tumour (GIST) is the most common mesenchymal tumour of the digestive tract, representing around 1% of all intestinal neoplasms.[1] Around 75%–80% of GISTs exhibit oncogenic *KIT* mutations,[2] and another 8%–10% exhibit platelet-derived growth factor receptor alpha (*PDGFRA*) mutations.[3] Currently, imatinib is the standard first-line therapy for patients with advanced/metastatic GIST[4] (other than those with *PDGFRA D842V* mutations[5]), since it improves the overall survival (OS)[6] and yields objective response rates close to 60%. Nevertheless,

secondary imatinib failure occurs due to the emergence of resistance mutations in *KIT*, resulting in a median progression-free survival (PFS) of 37.5–44.8 months.[7–9] Three multi-kinase inhibitors (MKIs) are approved by the US Food and Drugs Administration in patients with imatinib-resistant GIST: sunitinib (after progression on and/or intolerance to imatinib[10]), regorafenib (approved for patients previously treated with imatinib and sunitinib[11]) and most recently ripretinib.[12] Despite the development of these active salvage-targeted therapies, the median OS averages 5 years (55–76 months).[13–15]

During the past decade, investigational MKIs potentially active against *KIT*-resistance mutations and other protein kinases have been developed, including nilotinib, dasatinib and masitinib. These drugs have been evaluated as first-line treatment for advanced GIST. Indeed, the ENESTg1 phase III study showed a better efficacy of imatinib versus nilotinib as first-line treatment of advanced GIST.[16] In a phase II non-comparative study, masitinib appeared to be effective as a first-line treatment, with outcomes comparable with historical data on imatinib in terms of safety and response.[17] Lastly, an open-label phase II study of dasatinib showed a median PFS of 13.6 months.[18]

The use of these MKIs in the first-line setting might theoretically result either in increased survival (by the addition of a new line of active treatment), or in the early emergence of resistance to approved MKIs (and especially imatinib). The present study aimed to assess whether using investigational MKIs in first line could impact the efficacy of imatinib in second line, and subsequent lines of treatment.

Table 1 Patients characteristics

Patients characteristics	n	%
Gender		
Female	26	57%
Male	20	43%
Age (years): median (range)	55	(24-81)
Metastatic sites at diagnosis		
Liver	26	57%
Peritoneum	23	50%
Lung	2	4%
Adrenal gland	1	2%
Locally advanced	1	2%
Mutational status		
KIT exon 11 mutation	22	48%
KIT exon 9 mutation	1	2%
PDGFRA D842V mutation	1	2%
KIT exon 13 mutation	1	2%
Wild-type for *KIT* and *PDGFRA*	7	15%
Unknown	15	33%
Imatinib in the adjuvant setting	0	0%
First-line multi-kinase inhibitors		
Masitinib	21	46%
Dasatinib	17	37%
Nilotinib	8	17%

PATIENTS AND METHODS

Adult patients with metastatic GIST were identified through patient databases of two referral centres in France from 2005 to 2020. This retrospective study was approved by the Institutional Review Board (IRB) of both institutions. Inclusion criteria were as follows: GIST diagnosis confirmed by expert pathological review within the French Pathology network for mesenchymal tumours (RRePS), and first-line treatment with an investigational MKI (in the context of phase II/III clinical trials, followed by imatinib as second-line treatment). Clinical characteristics and treatment-related outcomes were retrospectively collected by hospital chart review. Data were collected in compliance with the IRB guidelines of each institution. Median PFS for the first-line setting was defined as the time between treatment initiation and disease progression or death, or the date of last follow-up in patients alive without progression. Median time to imatinib failure (TIF) was defined as the time between imatinib initiation and disease progression (despite dose adjustments) or death, or the date of last follow-up in patients alive without progression. Median time to second relapse (TT2R) was defined as the time between initiation of first-line treatment and progression under imatinib or death, or the date of last follow-up in patients alive without progression.

Study endpoints were PFS, TIF, TT2R and OS. Descriptive statistics were used to describe the study population. Kaplan-Meier method was used for survival analyses. A Cox model was used for analyses of potential prognostic factors. All statistical analyses were performed using the NCSS2020 software.

RESULTS

Of 46 identified patients, 26 (57%) were women and the median age was 55 years (range 24–81). The most common metastatic sites were liver (57%) and peritoneum (50%). Regarding mutational status, 22 patients (48%) had a *KIT* exon 11 mutation, 1 a *KIT* exon 9 mutation (2%), 1 a *PDGFRA D842V* mutation (2%). Of the 22 patients with a *KIT* exon 11 mutation, 1 patient had an additional *KIT* exon 13 mutation. Seven patients were wild type for *KIT* and *PDGFRA*. The mutational status was unknown in 15 pts (33%) (due to lack of material). No patient had received imatinib in adjuvant setting. All patients' characteristics are summarised in table 1.

Overall, 21 patients (46%) received masitinib, 17 (37%) received dasatinib and 8 patients (17%) received nilotinib. Reasons for stopping first-line MKI were: progressive

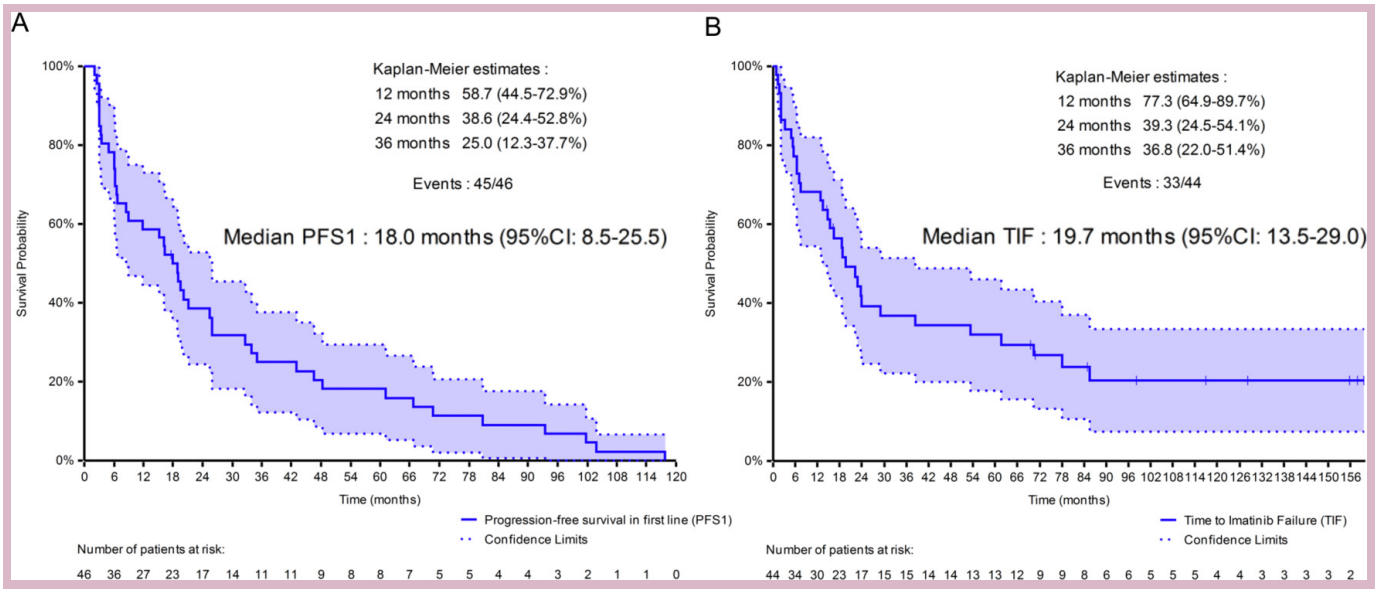

Figure 1 (A) Kaplan-Meier estimate of progression-free survival for the first-line setting (PFS1; that is, for nilotinib, dasatinib or masitinib). (B) Kaplan-Meier estimate of median time to imatinib failure (TIF) as a second-line setting.

disease (32 patients, 70%), toxicity (6 patients, 13%), complete response (3 patients, 7%), planned end of study (2 patients, 4%) or local treatments with curative intent (surgery or radiofrequency ablation, 3 patients, 7%). The toxicity of imatinib in second-line therapy was similar to that observed with imatinib as first-line therapy.

Median PFS on first-line treatment was 18.0 months (95% CI: 8.5 to 25.5) (figure 1A). Median TIF in second line was 19.7 months (95% CI: 13.5 to 29.0) (figure 1B). Median TT2R was 48.7 months (95% CI: 31.2 to 72.0) (figure 2).

Beyond first-line MKI and second-line imatinib, 29 patients received subsequent treatments, with a median number of 2 (range 0–7). Twenty-seven (59%) received sunitinib, 15 (33%) sorafenib, 8 (17%) nilotinib, 7 (15%) regorafenib, 6 (13%) pazopanib, 5 (11%) imatinib+cyclophosphamide, 3 (7%) a rechallenge with imatinib and 3 (7%) dasatinib. Nine patients also received other investigational drugs.

After a median follow-up of 68.3 months (95% CI: 53.7 to 96.6), 34 patients (73.9%) had died. The median OS was 5.7 years (95% CI: 4.5 to 7.4) (figure 3). Using a Cox model, survival did not differ by gender or genotype (*KIT* exon 11 mutations vs others).

DISCUSSION

Imatinib has deeply improved the outcomes of patients with advanced/metastatic GIST.[6] First-line PFS depends on molecular subtypes, ranging from 12.3 to 39.4 months in the BFR14 trial.[8] Most recently, avapritinib was approved for the treatment of *PDGFRA*-mutated GIST,[5] which should from now on be analysed separately. However, despite optimisation of imatinib

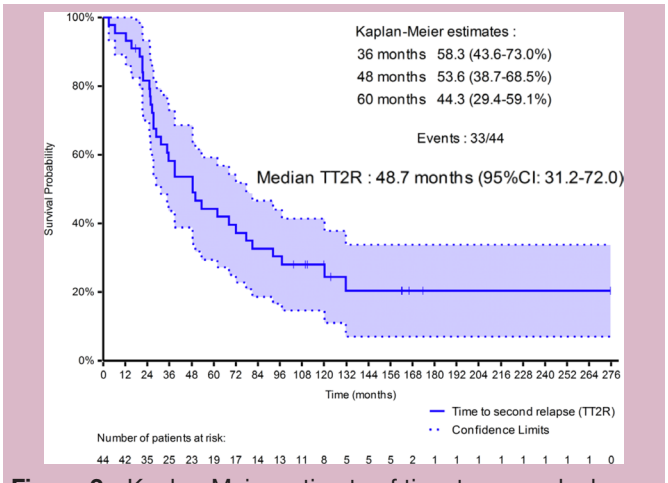

Figure 2 Kaplan-Meier estimate of time to second relapse (TT2R).

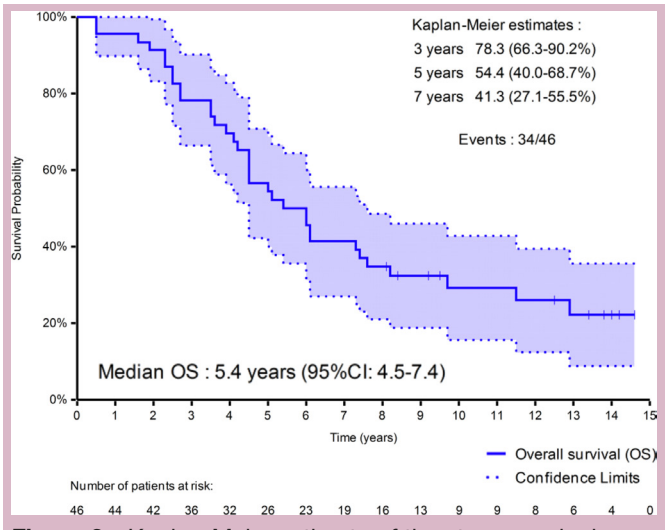

Figure 3 Kaplan-Meier estimate of time to second relapse.

administration, secondary progression due to acquired resistance to imatinib is a real challenge, and new strategies are needed in treatment-naïve advanced GIST. Due to the molecular heterogeneity of GIST wild type for *KIT* and *PDGFRA*, future trials will probably have to take into account this feature.[19]

Studies have been designed to explore the efficacy of investigational MKIs as first-line treatment before imatinib.[16–18] Of note, the toxicity profile of such investigational MKIs appeared less favourable than that of imatinib.[16–18] Nevertheless, these might either add an additional line of treatment, shifting the moment of secondary progression, or in the contrary induce a decreased efficacy of imatinib when used in second line due to cross-resistance or early emergence of imatinib-resistance mutations.

In the present analysis, patients with GIST who had received investigational MKIs as first-line treatment followed by imatinib had a median TT2R of 48.7 months, longer than the PFS observed historically with first-line imatinib (around 30 months).[15] This suggests that using MKIs other than imatinib as first-line treatment does not decrease the efficacy of imatinib in second line.

Importantly, improved molecular diagnostics might allow the selection of MKI according to a patient's individual primary and secondary mutations. As an illustration, data from the ENESTg1 phase III study showed that nilotinib was inactive in patients with *KIT* exon 9 mutations.[16] Therefore, further studies are needed to identify patients with GIST who would benefit from MKIs other than imatinib in the first-line setting.

Most patients in this cohort received a median number of two systemic treatment lines after first-line MKI and imatinib, meaning a total median number of four lines of MKI, but few of them were rechallenged with imatinib.[20] Of note, only seven patients received regorafenib (that was not approved at the time of progression beyond sunitinib for other patients). Whether the present findings could be similar in patients treated with recent drugs active in advanced GIST beyond the second line (pazopanib, ripretinib and cabozantinib[12 21 22]) will have to be explored. In particular, future studies will have to explore the impact of early use of investigational MKIs on OS, which will probably significantly differ from that observed in the present study due to the approval of new treatment lines in advanced, imatinib-resistant GIST.

In conclusion, patients with GIST who received MKIs other than imatinib as first-line treatment followed by imatinib had a TT2R longer than the PFS observed historically with first-line imatinib, suggesting that using MKIs other than imatinib in first line does not decrease the efficacy of imatinib in second line. Further comparative studies are needed to confirm these findings.

Contributors AB collected and analysed data, contributed to interpretation of data and drafted the manuscript, figures and tables. AD collected data and reviewed the final manuscript. AC contributed to data analysis. EN contributed to data collection. JA, ER, MK and VH contributed to data collection and interpretation of data. SD, MB, MF, CH, PM and ALC reviewed the manuscript. J-YB contributed to interpretation of data and reviewed the manuscript. OM designed the study, collected data, analysed data and reviewed the manuscript. All authors approved the final version of the manuscript.

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Ethics approval Study was approved by Gustave Rousy IRB (Registration Number: 2020-45).

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