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Phase II study of oral masitinib mesilate in imatinib-naïve patients with locally advanced or metastatic gastro-intestinal stromal tumour (GIST) ☆

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ABSTRACT

Background: Masitinib is a tyrosine kinase inhibitor with greater *in vitro* activity and selectivity for the wild-type c-Kit receptor and its juxtamembrane mutation than imatinib, without inhibiting kinases of known toxicities. This phase II study evaluated masitinib as a first-line treatment of advanced GIST.

Patients and methods: Imatinib-naïve patients with advanced GIST received oral masitinib at 7.5 mg/kg/d. Efficacy end-points included response rate (RR) at 2 months, best response according to RECIST, metabolic response rate, disease control rate (DCR), progression-free survival (PFS) and overall survival rate (OS).

Results: Thirty patients were enrolled with a median follow-up of 34 months. The most frequent grade 3–4 toxicities were rash (10%) and neutropaenia (7%). Two patients withdrew due to treatment-related adverse events. At 2 months, RR was 20% according to response evaluation criteria in solid tumours (RECIST) and 86% according to FDG-PET response criteria. Best responses were a complete response in 1/30 patient (3.3%), partial response in 15/30 patients (50%), stable disease in 13/30 patients (43.3%) and progressive disease in 1/30 patient (3.3%); (DCR: 96.7%). Median time-to-response was 5.6 months (0.8–23.8 months). Estimated median PFS was 41.3 months with PFS rate of 59.7% [37.9; 76.0] and 55.4 [33.9; 72.5] at 2 and 3 years, respectively. The OS at 2 and 3 years was stable at 89.9% [71.8; 96.6].

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Conclusions: Masitinib appears to be effective as a first-line treatment of advanced GIST with comparable results to imatinib in terms of safety and response. PFS and in particular OS data show promise that masitinib may provide sustainable benefits. There is sufficient compelling evidence to warrant a phase III clinical trial.

1. Introduction

Gastro-intestinal stromal tumours (GISTs) are malignant tumours that arise from precursors of interstitial cells of Cajal in the gastrointestinal tract.[1] About 95% of GIST tumours are positive for c-Kit expression, and 85–90% of GISTs have a gain-of-function mutation of either c-Kit (75–80% of tumours) or platelet-derived growth factor receptor α (PDGFRα, 8–10% of tumours).[2–5] Imatinib, an inhibitor targeting these two tyrosine kinase receptors, improved the outcome of patients with advanced GIST from a pre-imatinib 2-year overall survival rate (OS) of 25%, to approximately 70–80% after its introduction.[6–8] Unfortunately, resistance to imatinib occurs at a median time of 20–24 months, mostly due to the acquisition of additional mutations in the KIT gene, yielding imatinib-resistant c-Kit proteins.[9,10] Despite an increase of imatinib daily dose[8,11] and the emergence of active salvage-targeted therapies in imatinib-resistant GIST patients,[12] the majority of patients eventually die from their disease, with a median OS of approximately 60 months.[13]

Masitinib mesilate (AB1010) is a novel tyrosine kinase inhibitor (TKI) that potently inhibits wild-type (WT) c-Kit, its constitutively activated mutated form in the juxtamembrane (JM) region, PDGFRα, and PDGFRβ (IC_{50} of 150, 3, 250 and 20 nM, respectively), as well as Lyn and to a lesser extent the focal adhesion kinase (FAK) pathway.[14] Masitinib also showed anti-tumour activity in an *in vivo* model of tumour growth, with complete resorption of the tumour at doses of 30 and 45 mg/kg.[14] In a phase I study on solid tumours, including 19 patients with GIST (17 imatinib-resistant and 2 imatinib-intolerant patients), one imatinib-intolerant patient had a partial response (PR) with masitinib followed by tumour exeresis and six other patients (32%), one intolerant and five resistant to imatinib, had stable disease (SD) as their best response.[15] Doses of 7.5 mg/kg/d administered in two intakes were well tolerated. Pharmacokinetic analysis from this phase 1 study was shown to correlate better with weight-adjusted dose levels (mg/kg/d) rather than fixed dose levels (mg/d), prompting masitinib to be developed with a weight-adjusted dosing strategy. This is analogous to the dosing of cytotoxic drugs in oncology, and offers the opportunity to more accurately optimise dosing than is possible for drugs developed (and regulated) under fixed dose regimens.

Considering masitinib's superior affinity for c-Kit; a selectivity profile that suggests it may exhibit better safety than other tyrosine inhibitors[14]; and the possibility to individualise treatment by merit of weight-adjusted dosing, thus overcoming the potential initial imatinib dose-effect on progression-free survival (PFS) in GIST patients[7,11,16]; it is predicted that masitinib could potentially be efficient as a first-line treatment. This study was performed to evaluate the efficacy and safety of masitinib in patients with inoperable, non-pretreated advanced GIST.

2. Patients and methods

2.1. Patient selection and treatment

Patients aged over 18 years with inoperable, non-pretreated, histologically proven locally advanced or metastatic, c-Kit positive GIST, were eligible to participate. Each patient had measurable tumour lesions according to response evaluation criteria in solid tumours (RECIST)[17] and an Eastern Cooperative Oncology Group (ECOG) performance status of $\leqslant 2$. Exclusion criteria included: inadequate organ function defined via blood tests, severe liver or cardiac failure, and severe neurological or psychiatric disorders. Patients receiving a concomitant treatment within 4 weeks before inclusion, and pregnant or lactating women were also excluded. This study was approved by the Institutional Review Board (CCPPRB) of Hôpital Necker, Paris, France and carried out in compliance with the Declaration of Helsinki and good clinical practices guideline. Written informed consent was obtained from all patients.

Masitinib was supplied as 100 and 200 mg tablets, administered orally at 7.5 mg/kg/d, in two intakes. If grade 3 (non haematology) or grade 4 (all) toxicity occurred, treatment was interrupted until toxicity returned to baseline value, then resumed without modification. If grade 3 (non haematology) or grade 4 (all) toxicity reoccurred, treatment was interrupted until toxicity returned to baseline value, then the dose was reduced by 100 mg/d. If grade 3 (non haematology) or grade 4 (all) toxicity still persisted after dose reduction, masitinib was definitively discontinued. A switch to imatinib mesilate (400 mg/d) was proposed in case of disease progression or patient withdrawal.

2.2. Safety and efficacy evaluation

Safety was assessed for all patients receiving at least one dose of masitinib with toxicity graded according to the Common Toxicity Criteria Version 3.0. All adverse events (AEs), including abnormal serology or haematology, were recorded regardless of causality.

The primary efficacy end-point was response rate (RR) after 2 months of masitinib treatment according to RECIST, using computed tomography (CT). Secondary efficacy end-points were the evaluation of metabolic response[18] using [18F]fluorodeoxyglucose-positron emission tomography

(FDG-PET) and assessment of disease control rate, PFS and OS. For each patient, all efficacy parameters were recorded on the first day of treatment (baseline) prior to administration of masitinib, then on weeks 2, 4, 8, and 16, and every 12 weeks thereafter (extension phase).

Time-to-event analyses were calculated from the date of first masitinib intake to the date of event (documented progression or death). Patients who had not progressed at the date of last tumour assessment were censored at that date for PFS. Patients alive at the time of the analysis were censored at the date of last contact for OS.

2.3. Statistical analysis

Simon minimax two-stage design was used for this prospective, multicenter, single-group, phase II trial. Fourteen patients were initially enrolled, with recruitment of an additional ten patients being dependent on the occurrence of at least one objective RECIST response. This population was further extended to a total of 30 patients to ensure a sufficient evaluable population for all end-points; the type I(α) error was 5% (two-sided) for all analyses. Quantitative variables were described by the number of filled and missing data, mean, standard deviation, median, minimum and maximum. Qualitative variables were described by the number of missing data and, for each modality, frequency and percentage (referring to filled data). Time-to-event data were described using Kaplan–Meier (KM) estimates. The median was provided with its 95% confidence interval (95% CI). PFS rates were given every 6 months with KM estimates. All data analyses and reporting procedures used SAS v9.1 in a Windows XP operating system environment.

Table 1 – Demographics and clinical characteristics of patients.

Parameter	ITT population (N = 30)	
Age (years)	Mean ± SD	57 ± 14
	Median	58
	Range	34–82
Sex, N (%)	Female	12 (40%)
	Male	18 (60%)
Weight (kg)	Mean ± SD	75 ± 15
	Median	75
	Range	51–115
ECOG performance status, N (%)	0	23 (77%)
	1	7 (23%)
Previous treatments/ medication for GIST	Surgery	21 (70%)
	Biopsy	4 (13%)
	Other	2 (7%)
c-Kit status	Positive	29 (96.7%)
	Negative	1 (3.3%)
Time since diagnosis (months)	Mean ± SD	22 ± 28
	Median	13
	Range	0–131

ECOG: Eastern Cooperative Oncology Group and SD: standard deviation.

3. Results

3.1. Patient characteristics

Between June 2005 and April 2007, 30 patients were enrolled from five centres across France. Patient characteristics at inclusion are summarised in Table 1. At the cut-off date of April 2009, the median follow-up duration was 33.7 months (range 7.7–45.4 months). All analyses are reported for the intent-to-treat population (ITT), defined as all enrolled patients (N = 30). Two protocol deviations were revealed following pathology review, with two patients having been misdiagnosed as having GIST; one had a low grade endometrial stromal tumour and the other had an aggressive fibromatosis.

Four patients terminated prematurely before the fourth month: one patient for progressive disease (PD), one on the investigator's decision and two patients for AEs (non treatment-related, grade 3 paresis and treatment-related, grade 3 cheilitis and skin toxicity). During the extension period, 13 patients terminated the study: one patient for protocol violation (endometrial stromal tumour), eight patients for disease progression, two patients for AEs (one died from non treatment-related post-surgical complication and the other had treatment-related, grade 3 psoriasis), and two patients for other reasons (one patient developed a metastatic prostate cancer necessitating systemic chemotherapy and one discontinued therapy after radiofrequency ablation of liver metastasis).

3.2. Safety assessment

Safety analyses were performed on the ITT population (Table 2). All patients reported at least one treatment-related AE; 14/30 patients (47%) experienced at least one grade 3 treatment-related AE, of which rash was the most frequent at 3/30 patients (10%); and 1/30 patient (3.3%) reported one grade 4 AE (skin exfoliation). A total of 14 serious adverse events (SAE) were experienced by 8/30 patients (27%), three of which were treatment-related (worsening of a concomitant psoriasis and anaemia). The most frequent treatment-related toxicities per patient were: asthenia (83%), diarrhoea (57%), eye oedema (47%), nausea (47%), muscle spasms (40%), cutaneous rash (40%), abdominal pain (33%), pruritus (33%), vomiting (23%), upper abdominal pain (23%) and peripheral oedema (20%). Treatment-related oedemas (all types) were experienced by 21/30 patients (70%).

Six patients (20%) had their dose reduced by 100 or 200 mg/d (three patients each), following grade 3–4 AEs, and 16/30 patients (53.3%) had treatment interruption for more than 8 d. Reasons for treatment interruptions were non-haematological AEs for 13/30 patients (43%) (treatment-related for 12 of them), treatment-related haematological toxicity for 1/30 patient (3%) and surgery for 2/30 patients (6.7%). The most frequent treatment-related, non-haematological AEs leading to interruptions were skin toxicity, oedema and asthenia. Thirteen out of 30 patients (43%) were still undergoing treatment with masitinib at the cut-off date (12 at the same initial dose), with treatment duration from 26.5 to 45.4 months.

Table 2 – Frequent adverse events (>10%) in patients receiving masitinib, and their suspected relationship to masitinib.

Number (%) of patients (N = 30)	Suspected[a]		All causalities	
	All grades	G3 + G4	All grades	G3 + G4
Haematological events				
Anaemia	4 (13.3%)	1 (3.3%)	6 (20.0%)	1 (3.3%)
Neutropaenia	5 (16.7%)	2 (6.7%)	5 (16.7%)	2 (6.7%)
Non-haematological events				
Asthenia	25 (83.3%)	1 (3.3%)	27 (90.0%)	1 (3.3%)
Diarrhoea	17 (56.7%)	1 (3.3%)	18 (60.0%)	1 (3.3%)
Abdominal pain	10 (33.3%)	1 (3.3%)	16 (53.3%)	2 (6.7%)
Nausea	14 (46.7%)		15 (50.0%)	
Eye oedema	14 (46.7%)	1 (3.3%)	14 (46.7%)	1 (3.3%)
Muscle spasms	12 (40.0%)		12 (40.0%)	
Rash	12 (40.0%)	3 (10.0%)	12 (40.0%)	3 (10.0%)
Pruritus	10 (33.3%)	1 (3.3%)	11 (36.7%)	1 (3.3%)
Vomiting	7 (23.3%)		10 (33.3%)	
Abdominal pain upper	7 (23.3%)		9 (30.0%)	
Oedema peripheral	6 (20.0%)		8 (26.7%)	
Eyelid oedema	7 (23.3%)		7 (23.3%)	
Erythema	5 (16.7%)		6 (20.0%)	
Mucosal inflammation	5 (16.7%)	1 (3.3%)	5 (16.7%)	1 (3.3%)
Dry skin	4 (13.3%)		4 (13.3%)	
Lacrimation increased	4 (13.3%)		4 (13.3%)	
Myalgia	4 (13.3%)		4 (13.3%)	

[a] *Suspected*: treatment-related or not assessable; G3: grade 3 AE; and G4: grade 4 AE.

3.3. *Efficacy assessment*

During the Simon first stage, 4/14 patients had a confirmed PR after 2 months of treatment, instigating the study's Simon second stage. Efficacy results are presented in Table 3. Among the ITT population there were: 6/30 PR (20%), 23/30 SD (76.7%) and 1/30 PD (3.3%) after 2 months of masitinib treatment. Best response (RECIST) was analysed until the cut-off date: complete response (CR), PR, SD and PD were recorded for 1/30 (3.3%), 15/30 (50%), 13/30 (43.3%), and 1/30 (3.3%) patients, respectively. The overall response rate (CR + PR) was 16/30 (53.3%) patients (95% CI [34.3; 71.7]) with a disease control rate (CR + PR + SD) of 29/30 (96.7%) patients (95% CI [82.8; 99.9]). Median time to first objective response was 5.6 months (range: 0.8–23.8 months).

Metabolic response was assessed for 17/30 patients (56.7%), of which 3/30 patients (10%) had a negative FDG-PET at baseline. Of the 13/30 (43.3%) and 14/30 patients (47.7%) who were evaluable after 1 and 2 months of treatment, respectively: 9/13 (69.2%) had a partial metabolic response (PMR) and 4/13 (30.8%) had a stable metabolic disease (SMD) after 1 month; whilst 3/14 (21.4%) had a complete metabolic response (CMR), 9/14 (64.3%) had a PMR, and 2/14 (14.3%) had a SMD, after 2 months. The metabolic re-

Table 3 – Response rates.

Response (RECIST); N (%)	2 months (N = 30)	Best response (N = 30)
CR	0 (0.0%)	1 (3.3%)
PR	6 (20.0%)	15 (50.0%)
CR + PR [95% CI]	6 (20.0%) [7.7; 38.6]	16 (53.3%) [34.3; 71.7]
SD	23 (76.7%)	13 (43.3%)
CR + PR + SD [95% CI]	29 (96.7%) [82.8; 99.9]	29 (96.7%) [82.8; 99.9]
PD	1 (3.3%)	1 (3.3%)
Metabolic response	At 1 month (N = 13)	At 2 months (N = 14)
CMR	0 (0.0%)	3 (21.4%)
PMR	9 (69.2%)	9 (64.2%)
CMR + PMR [95% CI]	9 (69.2%) [38.6–90.9]	12 (85.7%) [57.2–98.2]
SMD	4 (30.8%)	2 (14.3%)

CR: complete response, PR: partial response; CR + PR: overall response rate; SD: stable disease; CR + PR + SD: disease control rate; PD: progressive disease; CMR: complete metabolic response, PMR: partial metabolic response; CMR + PMR: metabolic response rate; and SMD: stable metabolic disease.

Table 4 – PFS, PFS rates, OS and OS rates.

PFS	
Median	41.3 months
[95% CI]	[17.4–NR]
PFS rate (%) [95% CI]	
6 months	88.9 [69.4; 96.3]
12 months	76.8 [55.3; 88.9]
18 months	64.0 [42.0; 79.5]
24 months	59.7 [37.9; 76.0]
30 months	55.4 [33.9; 72.5]
36 months	55.4 [33.9; 72.5]
42 months	27.7 [2.0; 65.7]
OS	
Median	NR
[95% CI]	[NR; NR]
OS rates (%) [95% CI]	
12 months	96.7 [78.6; 99.5]
24 months	89.9 [71.8; 96.6]
36 months	89.9 [71.8; 96.6]

PFS: progression-free survival; OS: overall survival; and NR: not reached.

sponse rate (CMR + PMR) after 2 months of treatment was 12/14 (85.7%) patients (95% CI [57.2; 98.2]).

Time-to-event analysis revealed 12 events (11 progressions and one death) with 18/30 patients (60%) censored for PFS: six patients withdrew from the study without progression and 12 progression-free patients were still receiving masitinib at the cut-off date. The estimated 6-month, 1-year, 2-year and 3-year PFS rates were 88.9% (95% CI [69.4; 96.3]), 76.8% [55.3; 88.9], 59.7% [37.9; 76.0] and 55.4% [33.9; 72.5], respectively (Table 4). Median PFS was 41.3 months [17.4 months; not reached] according to KM analysis (Fig. 1A). Median OS was not reached (Fig. 1B and Table 4), with 1 year survival rate of 96.7% [78.6; 99.5], and 2- and 3-year survival rates each at 89.9% [71.8; 96.6].

3.4. *Mutational analysis*

Biopsy material was collected from 29/30 patients (96.7%) to assess their c-Kit status. Sufficient biopsy material was available to perform mutational analysis for 15/30 patients (50%): 10/30 patients (33.3%) had a GIST harbouring a *c-kit* exon 11 mutation, 1/30 patient (3.3%) had double *c-kit* exon 11 and 13 mutations, 3/30 patients (10%) had a WT c-Kit, and 1/30 patient (3.3%) had a GIST harbouring the *PDGFRα* mutation (D842V).

4. Discussion

Imatinib has dramatically improved the outcome of patients with advanced GIST, becoming the model for targeted therapy in solid tumours.[6–8] However, despite near optimal compliance in the majority of patients and extended administration of imatinib,[19] the risk of secondary progression due to acquired resistance to imatinib persists over time.[9,10] This highlights the need for new strategies in non-pretreated advanced GIST to increase the rate of complete remission and the duration of progression arrest rate.

It has been shown that some patients benefit from a higher than the standard imatinib dose, suggesting that individualised treatment could be a critical option in the initial management of advanced GIST patients. This is evidenced by imatinib at 800 mg/d producing improved PFS, as compared to the standard dose of 400 mg/d,[20] in patients whose GIST harbours an exon 9 mutation[16,21]; the relationship between imatinib plasma levels and progression[22]; and the fact that one third of patients progressing under imatinib at 400 mg/d clearly benefited from the higher dose regimen.[8,11] In contrast to imatinib's fixed dosing strategy, masitinib has been developed with patient weight-adjusted dosing in mind.[15] Given its higher selectivity for c-Kit,[14] a patient-optimised dose of masitinib could possibly provide a significant therapeutic benefit; although dose increments smaller than the 100 mg used in this study are likely to be required to achieve such optimisation.

As expected with the selectivity profile of masitinib,[14] no cardiac side-effects have been observed to date. Occurrences of the most common masitinib-related haematological AEs (neutropaenia and anaemia) were substantially lower compared to imatinib at standard dose.[7] The most frequently reported masitinib-related, non-haematological AEs were similar to those reported with imatinib in front-line treatment,[7] with the exception of rash and abdominal pain that occurred at a higher frequency for masitinib. In general, AEs occurred early during the course of treatment, which is consistent with the known safety profile of tyrosine kinase inhibitors[23,24]; the majority of AEs showing a clear decrease in frequency for the 24/30 patients (80%) treated beyond 6 months (data not shown). The implication here is that treatment tolerance is likely to improve after the initial 6 months, thereby, making masitinib more appropriate for any long-term treatment regimen. At the cut-off date, 12/30 patients (40%) were still receiving masitinib at the same initial daily dose.

Early resistance to imatinib has been defined as progression occurring within the first 6 months of treatment in patients who showed no response. It is observed in 10–15% of patients and appears to result from intrinsic factors present before treatment start.[10] In this study only 1/30 patient (3.3%) never benefited from masitinib, suggesting that masitinib may be less susceptible to early resistance; although further investigation is required to confirm this hypothesis.

The objective response (RECIST) and metabolic response rate at 2 months are in the range of those observed with imatinib.[7,25] Combinations of morphologic (computed tomography) and functional imaging techniques such as FDG-PET or dynamic contrast enhanced-ultrasonography (DCE-US)[26] highlight again the discrepancy between the biological (cellular level) and clinical (radiological level) activities of TKIs in GIST.[6,27,28] As observed with imatinib, masitinib induces changes in the tumour structure, such as decreased tumour vascularity, haemorrhage or necrosis, cystic or myxoid degeneration, that are consistent with a therapeutic activity with or without a change in tumour volume. When these three different radiological tumour assessments were applied to the same patients, masitinib was found to induce tumour response in only 20% of evaluable patients according to changes in tumour size (RECIST) but in 86% of patients according to

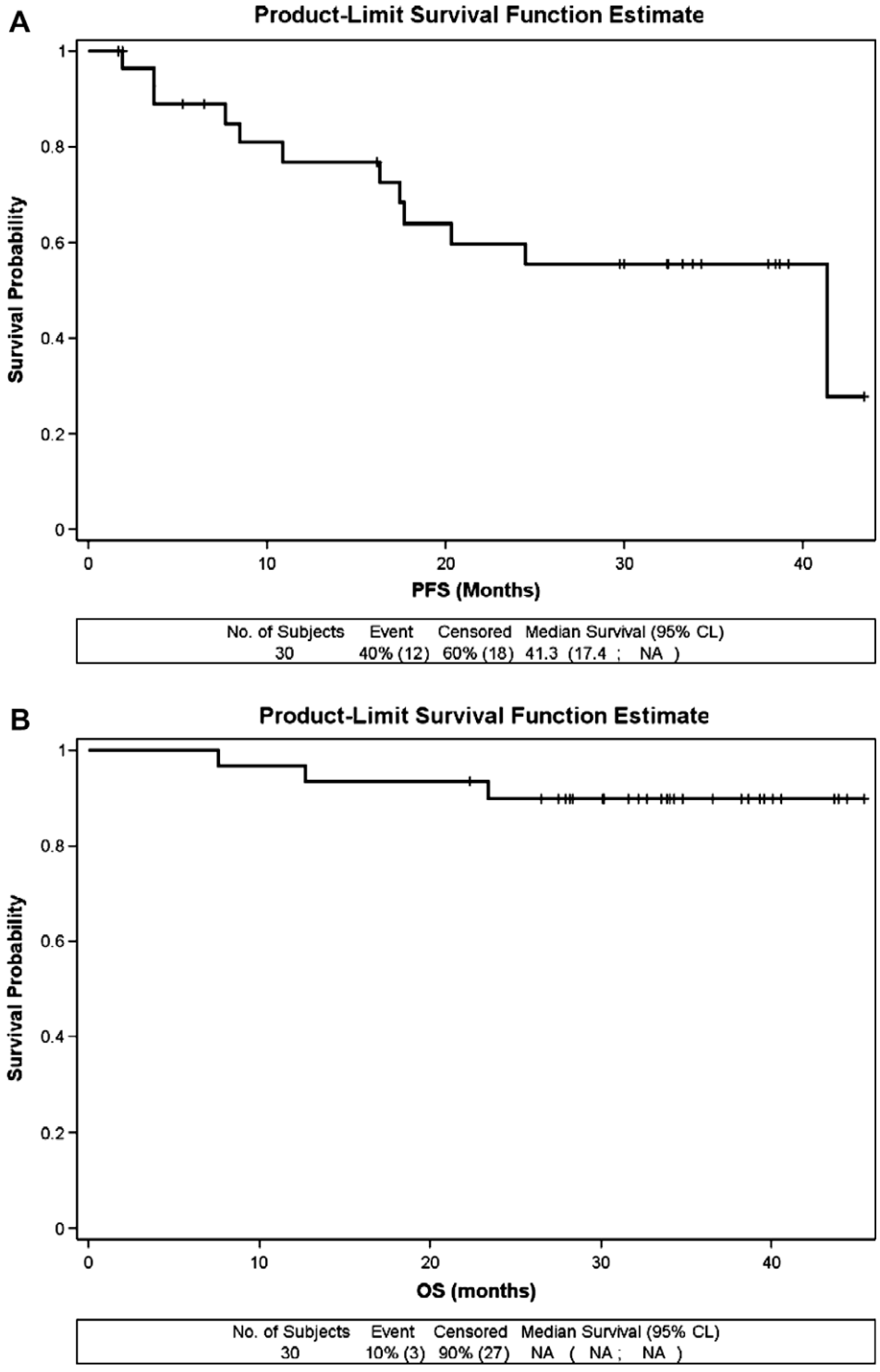

Fig. 1 – Kaplan–Meier analyses of progression-free survival (A) and overall survival (B).

metabolic response using FDG-PET and in 75% of patients assessed with DCE-US,[29] after 2 months of masitinib. Interestingly, one patient with an FDG-PET CMR observed after 2 months of masitinib had a decrease but not a disappearance of contrast uptake with DCE-US performed concomitantly, suggesting that this less expensive tool assessing both tumour size and structure may be a more reliable measure of the residual activity of GIST tumour cells than FDG-PET. As for imatinib[26] and other TKIs,[29] a decrease of contrast uptake assessed with DCE-US, 7 and 14 d after the beginning of masitinib, correlates with a good response on CT scan at 2 months.[29]

As already reported, RECIST is not optimal for an early response assessment of c-Kit inhibitors in GIST patients[30] since

the pattern of radiological response has no prognostic value for further outcome, except for PD.[31] However, RECIST assessment can be used for practical decision making since absence of progression according to RECIST turned out to be an excellent predictive marker of benefit with masitinib in terms of PFS. Consequently, masitinib needs to be continued as long as there is no progression according to RECIST; an absence of tumour progression under masitinib being equivalent to tumour response.

Twelve of the 16 patients who withdrew from the study (eight for PD, three for AEs, and one on the investigator's decision) were switched to imatinib-treatment. Of the eight patients progressing under masitinib, six received imatinib at 800 mg/d and two received imatinib at 400 mg/d, with a median exposure of 5.4 months. Six of these patients discontinued imatinib for AEs or progression, the remainder (one at each dose level) showed some relevant disease stabilisation. This suggests that the use of a less selective c-Kit inhibitor (i.e. imatinib) in second-line therapy precludes any relevant activity in terms of tumour volume reduction and that therefore, patients progressing under masitinib are candidates for alternative second-line targeted therapies.[12] Of those patients intolerant to masitinib; one died, one had PD and switched to an alternative second-line therapy, and the other showed a PR.

This study was designed to assess the objective response rate according to RECIST at 2 months under masitinib, although the time to secondary resistance to masitinib (i.e. PFS) would have been a more relevant activity screening end-point (as with imatinib or sunitinib). Despite this study's small number of patients (with a majority of GIST harbouring a *c-kit* exon 11 mutation), a median follow-up of 33.7 months and the limited validity of comparison with phase III trials; the median PFS (41.3 months), as well as the 2- and 3-year PFS rates (60% and 55%, respectively) observed with masitinib, compare favourably with those of imatinib at 400 mg/d.[7,13]

In summary, the activity of masitinib in GIST could in part be due to: (1) its potent inhibition of WT and JM c-Kit that limits tumour proliferation and emergence of resistant cell clones; (2) its partial inhibition of the FAK pathway that may limit the development of metastases, thus, slowing down progression[32]; and (3) individual adaptation of the daily dose that may offer an optimal dose over time. Indications that masitinib provides sustainable benefits, as evidenced by the 2 and 3 year OS data, are promising, but its impact on OS has to be further determined with a follow-up of those responding patients (43%) still receiving treatment, as well as progressing patients who went on to receive alternative treatments.[13]

Results from this study help to further establish the therapeutic role of TKIs that selectively inhibit c-Kit.[6,7,8,13] Moreover, within the limitations of an uncontrolled phase 2 trial, this study shows that masitinib may offer an effective and relatively well-tolerated treatment for non-pretreated, inoperable, locally advanced or metastatic GIST patients. Confirmatory phase III trials comparing masitinib to imatinib in first-line treatment are warranted to validate these findings and to further investigate the long-term efficacy and safety of masitinib.

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Conflict of interest statement

Dr. Le Cesne receives honoraria from Novartis, Pfizer and Pharmamar. Dr. Blay receives honoraria from Novartis, Pfizer, Pharmamar and GSK. Dr. Olivier Hermine is a shareholder and scientific advisor to the study sponsor, AB Science. Alain Moussy is a shareholder and employee of the study sponsor, AB Science. No other conflicts of interest have been declared.

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