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Phase 1 dose-escalation study of oral tyrosine kinase inhibitor masitinib in advanced and/or metastatic solid cancers

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ABSTRACT

Background: Masitinib is a tyrosine kinase inhibitor with a pre-clinical profile suggesting greater affinity and selectivity *in vitro* for the wild-type c-Kit receptor and its juxtamembrane mutation than imatinib.

Methods: This dose-escalation study was conducted in patients with advanced and/or metastatic cancer to determine the maximum tolerated dose (MTD) for orally administered masitinib over a 12-week period. Secondary objectives were a clinical assessment of masitinib's activity in cancer patients and establishment of a pharmacokinetic profile.

Results: Forty patients with various solid tumours (predominantly GIST, 19 patients) were treated with masitinib at doses ranging between 0.7 and 17.2 mg/kg/day. Although the MTD was not formally reached, an acceptable dose for chronic use was identified at 12 mg/kg/day. Treatment-related AEs were frequent (38/40 patients), however, the majority were grade 1 or 2 and demonstrated dose dependency at higher concentrations. Pharmacokinetic results showed a linear, dose-dependent increase of C_{max} and AUC. One of two GIST patients with imatinib intolerance had a partial response at 11.1 mg/kg/day. About 29% of the imatinib-resistant GIST population and 38% of the overall population had stable disease.

Conclusions: The safety profile of masitinib at 12 mg/kg/day *b.i.d.* for the treatment of solid cancers appears favourable and compatible with a long-term regimen. Tumour control rate in imatinib-resistant patients was encouraging, hence, the activity of masitinib in c-Kit expressing tumours, such as GIST, warrants further exploration as first-line anticancer therapy as well as for imatinib-resistant patients.

1. Introduction

Tyrosine kinases (TKs) play a fundamental role in signal transduction, with the deregulated activity of these enzymes been involved in cancer and other proliferative disorders.[1] TKs may be cell surface receptors or cytoplasmic proteins.[2] Specific TK-inhibitors are of interest as potential therapies for solid tumours or as part of synergistic combination

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regimens. Molecular targeted therapies have been developed to limit tumour growth and metastatic diffusion in various ways and at different stages of cancer development.[3]

Deregulation of c-Kit, the stem cell factor receptor upon which some types of tumour cells depend for proliferation, has been implicated in a number of human cancers including gastro-intestinal stromal tumour (GIST), acute myelogenous leukaemia, small cell lung carcinomas, seminoma, ovarian cancer, breast carcinoma, colorectal carcinoma, neuroblastomas and mastocytosis.[3,4] Of these, GIST is exemplary of the strong relation between the SCF/c-Kit pathway and pathogenesis of cancer, with 90% of all GISTs showing overexpression of c-Kit, and 70–80% showing mutations, respectively.[5,6] The majority of these mutations are in-frame deletions and missense mutations clustered at the 5'-end of the juxtamembrane domain (exon 11). A rare mutation, an Ala502-Tyr503 duplication in exon 9, is specific for intestinal GISTs.[7,8]

Imatinib (Gleevec®, STI571; Novartis) is the forerunner of such therapeutic agents and an example of a TK inhibitor that not only competes with ATP and inhibits the activity of the Breakpoint Cluster Region-Abelson kinase (BCR-ABL), but also c-Kit or PDGF receptors (Table 1). Masitinib, the investigational drug of this study, is a novel TK inhibitor that potently inhibits wild-type (WT) c-Kit and its activated form, mutated in the juxtamembrane region (JM), PDGFRα, PDGFRβ, Lyn, and to a lesser extent FGFR3 and the FAK pathway. In cell proliferation assays, masitinib inhibits with an IC_{50} at 3 nM c-Kit JM, 150 nM c-Kit WT, 250 nM PDGFRα, PDGFRβ and 2.5 μMr FGFR3. In kinase assays, Lyn activity was inhibited with an IC_{50} of 400 nM and masitinib (1 μM) reduced FAK phosphorylation by 21% (Table 1). Due to its specificity masitinib may exhibit a better safety profile than other TK inhibitors and could therefore be effective in imatinib-intolerant patients. *In vivo* masitinib showed significant antitumour activity after intravenous (i.v.) or oral administration at well-tolerated doses in a BALB/c nude mouse model with a subcutaneous graft of a transgenic murine hematopoietic cell line, transfected with a gene encoding c-Kit JMΔ27. Masitinib given at either 100 or 200 mg/kg resulted in a complete dissolution of the tumour following a 10-day treatment (Dubreuil et al., submitted).

Table 1 – Inhibition of protein kinases: comparison of masitinib to imatinib.

Enzyme	IC_{50} (μM)	
	Masitinib	Imatinib[a]
c-Kit (exon 11 mutant)	0.003[b]	0.027[c]
c-Kit WT	0.15	0.41
PDGFRα, β	0.25, 0.02	0.4, 0,44
Lyn	0.4	2
FAK	5–10	n/a
ABL	1.5	0.2
FGFR3	2.5	5.7 (R1)
VEGFR1	>10	19.5
SRC	2	3

Concentrations causing a 50% reduction in kinase activity (IC_{50}) are given.
a From Deininger et al.[10]
b Determined in transfected cells.
c From Weisberg et al.[19]

In the present report we describe the results of a phase 1 study in patients with solid tumours. The primary objective was to identify the maximum tolerated dose (MTD) of orally administered masitinib as a single agent. Secondary objectives were to assess the safety, efficacy and the pharmacokinetic (PK) profile of masitinib in patients suffering from advanced cancer, as well as the antitumoural activity of masitinib to explore its potential in first-line or combination therapy in imatinib-resistant or -intolerant GIST patients, and in patients with c-Kit positive solid tumours naïve to imatinib.

2. Patients and methods

2.1. Study design

This was a multicentre, non-randomised, open-label, sequential cohort, dose-escalation phase1 study in adults with advanced and/or metastatic cancer (Fig. 1). Masitinib was administered *per os* for up to 12 weeks, or until unacceptable toxicity or documentation of disease progression (as defined in Response Evaluation Criteria in Solid Tumours [RECIST]).[9] Upon conclusion of the dose-escalation cohorts, GIST patients resistant or intolerant to imatinib and patients with c-Kit positive solid tumours, who received chemotherapy other than imatinib, were also evaluated for safety and antitumour activity of masitinib.

2.2. Patient selection

Patients with histologically proven advanced solid malignancies for which no standard alternative curative therapy could be proposed were eligible. All patients were required to have at least one measurable target site. Other eligibility criteria included the following: age $\geqslant$18 years, an Eastern Cooperative Oncology Group (ECOG) performance status between 0 and 2 and the absence of serious concomitant medical disorders. Additionally, patients had to exhibit adequate renal function (serum creatinine <1.5 times the upper limit of normal (ULN) or a calculated creatinine clearance >40 ml/min, adequate bone marrow function (WBC count >3500/mm,[3] absolute neutrophil count [ANC] >2000 mm^3, platelet count >$10^5/mm^3$ and haemoglobin >11 g/dl), and adequate liver function (total bilirubin value <1.5 times ULN, ALAT level <2.5 times ULN and ASAT <2.5 times ULN). An effective contraceptive method was requested for women of childbearing age and a negative pregnancy test was required prior to treatment administration. Patients were excluded if they were pregnant or nursing, had a known history of brain metastases, myocardial infarction or coronary disease, or had a history of gastro-intestinal (GI) disorder that could interfere with drug absorption. Patients with a history of any other malignancy, apart from *in situ* carcinoma of the cervix or basal cell carcinoma of the skin within five years prior to entry to the study, were also excluded. Patients could not have undergone surgery within the last six weeks and should not have been treated within the preceding four weeks to enrolment with any investigational drug, chemotherapy, radiotherapy, immunotherapy or hormonal therapy. The exclusion period was extended to six weeks for previous

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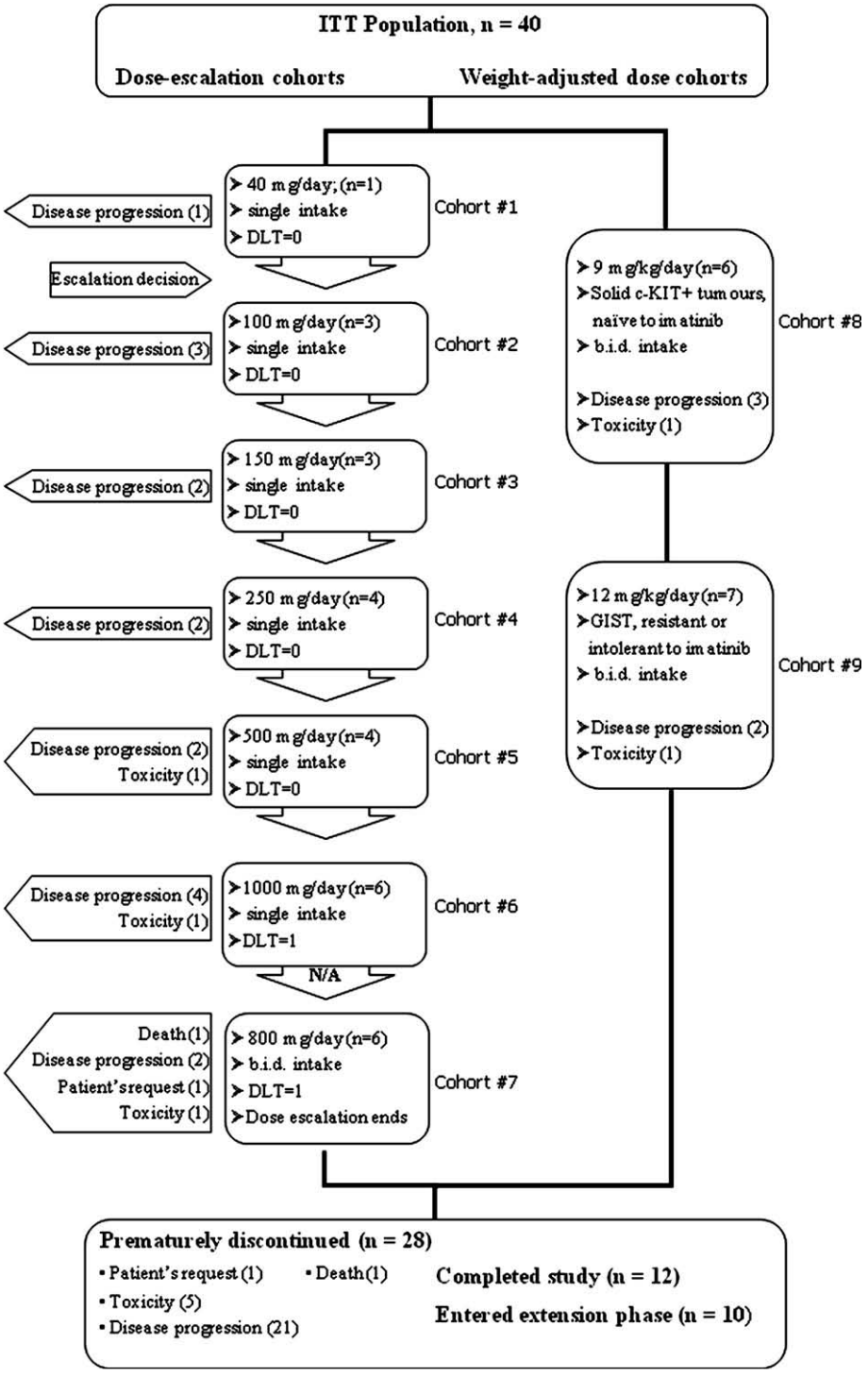

Fig. 1 – Participant flow, including summary of cohort safety profile, subsequent dose-escalation decision or study discontinuation.

treatments with nitrosureas or mitomycin C. Patients were informed about the experimental nature of this study, and signed an approved informed consent form before any investigational diagnostic or treatment was initiated. This study was conducted in accordance with the Declaration of Helsinki and each participating investigator followed guidelines established for Good Clinical Practice.

Concomitant treatments considered necessary for the patient's well-being were permitted, as well as radiotherapy to specific sites if considered mandatory by the treating physician. Drugs that interact with the same CYP450 isoenzymes (2C9, 2D6 and 3A4) as masitinib (e.g. acetaminophen) were avoided when possible due to the inherent risk of either reduced activity or enhanced toxicity of any concomitant med-

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ication. Other treatments interfering with GI absorption were avoided.

2.3. Study treatment and dosage

Masitinib was provided by AB Science (Paris, France) as capsule or coated tablet to be administered *per os*, approximately 1 h prior to meals. A safe starting dose was determined in accordance with FDA recommendations (Guidance for Industry, Dec 2002) following a previously established oral No Observed Adverse Effect Level (NOAEL) in dogs for masitinib of 15 mg/kg, equivalent to 8.1 mg/kg/day (Human Equivalence Dose of the NOAEL). Thus, in compliance with the FDA's recommended 10% safety margin, a patient weighing 60 kg would receive a starting dose of 40 mg masitinib (cohort #1). Dose escalation is summarised in Fig. 1. The schema was modified to switch from once daily from 40 to 1000 mg/day to bid at 800 mg as well as 9 mg/kg and 12 mg/kg.

Dose-limiting toxicity (DLT) was defined as grade 4 AE, or grade 3 non-haematological AE with emergent toxicity at least possibly related to the study treatment, in patients with normal values/status at baseline. The MTD was defined as the dose at which at least 3 of 6 patients experienced a dose-limiting toxicity (DLT).

2.4. Tumour assessment

Tumour measurements were performed at baseline and then at week 6, week 12 and 30 days after the last dose of masitinib by chest X-ray, computer tomography scan, or by magnetic resonance imaging. Assessment included clinical examination and imaging, with therapeutic response based upon RECIST guidelines.[9]. Patients showing stable disease (SD) after 12 weeks of treatment, i.e. control of the tumour, partial response (PR) or complete response (CR), were eligible to continue receiving masitinib after entering a compassionate programme.

2.5. Safety evaluation

Safety was evaluated weekly via monitoring of adverse events (AEs), vital signs and physical examination; and with bi-weekly ECG and clinical laboratory tests (biochemistry, haematology). Toxicity was graded according to the NCI-CTC v3.0 classification, with the treating physician assessing any possible relationship to the study drug.

2.6. Pharmacokinetics

Plasma and urinary PK analyses were performed for two metabolites of masitinib. Urinary samples were collected at pre-dose, then 0–12, 12–24 and 24–48 h after dosing. Venous blood samples were collected on days 1 and 14, before dosing and then repeatedly over a 12-hour post-treatment period. Plasma was analysed for masitinib using a validated analytical method. Model-independent, non-compartmental analysis (KINETICA Version 4.0, Innaphase, Champs-sur-Marne, France) was used to estimate PK parameters for masitinib including AUC and peak concentration (C_{max}).

2.7. Statistical analysis

Safety, PK and efficacy parameters are presented using descriptive statistics. The intent-to-treat population (ITT) was defined as those patients who had received at least one dose of masitinib and who had undergone at least one assessment of efficacy or safety.

3. Results

3.1. Patient characteristics

From January 2004 to March 2006, 40 patients were enrolled at three French centres. Patient characteristics are summarised in Table 2. The most frequent cancer was GIST in 19/40 patients (48%), and 39/40 patients (98%) had previously received at least one chemotherapy. About 18/40 patients had previously been treated with imatinib and one with gefitinib.

Seven sequential cohorts, composed of 27 patients with advanced solid tumours were generated, corresponding to masitinib doses of 0.4–17.5 mg/kg/day. Two additional groups were enrolled in order to better assess efficacy and toxicity in patients with imatinib-resistant GIST, and in patients with c-Kit$^+$ solid tumours (Fig. 1).

The subpopulation of 19 GIST patients, included 14 patients resistant to imatinib at 800 mg/day, two patients resistant to imatinib at 400 mg/day, one that received an unknown dose and two patients intolerant to imatinib at 300 mg/day.

3.2. Safety and DLTs

The safety population comprised all patients who had received at least one dose of masitinib ($N = 40$) with a reporting period spanning from the first dose of masitinib until 28 days after the last dose (7 days for the DLT). Patient exposure to masitinib was 101 ± 121 days (median 56 days). The criterion for MTD was not formally reached in the seven cohorts escalation (Table 3a). In total, 2/27 patients (7.4%) experienced at least one DLT during the study: one patient had elevated ALAT levels (cohort 6), and the second suffered from dehydration, hyperbilirubinaemia, renal insufficiency and died (cohort 7). Five other patients experienced DLTs in cohorts 8 and 9 (Table 3b and 3c).

The incidence of DTLs (7 patients) increased from 16.7% in the 6–12 mg/kg/day range to 36.4% in the highest range suggesting a threshold at 12 mg/kg/day.

A total of 38/40 patients (95%) experienced at least one treatment-related AE (Tables 3a and 3b). The most frequent drug-related AEs were GI disorders in 32/40 patients (80%), nausea in 22/40 patients (55%), diarrhoea in 21/40 patients (52.5%) and vomiting in 21/40 patients (52.5%), metabolic disorders in 28/40 patients (70%), blood and lymphatic system disorders in 27 patients (67.5%) and general disorders in 26 patients (65%) (Table 4).

The most frequent drug-related AE was GI toxicity in 32/40 patients (80%) including nausea in 22/40 patients (55%), diarrhoea in 21/40 patients (52.5%) and vomiting in 21/40 patients (52.5%). Nausea and vomiting were mostly of grades $\leqslant 2$ and occurred repeatedly throughout the study lasting for one or two days. Masitinib administration *b.i.d.* was better able to

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Table 2 – Baseline characteristics and dosing history, according to dose cohort.

Parameter	Total	40 mg/day	100 mg/day	150 mg/day	250 mg/day	500 mg/day	1000 mg/day	800 mg bid	9 kg/mg bid	12 kg/mg bid
Population; *n* (%)	**40 (100%)**	1/40 (2.5%)	3/40 (7.5%)	3/40 (7.5%)	4/40 (10%)	4/40 (10%)	6/40 (15%)	6/40 (15%)	6/40 (15%)	7/40 (17.5%)
Age (years)										
Mean (±SD)	**53 (11)**	63.0 (–)	50.0 (5.3)	42.7 (15.7)	48.0 (9.4)	50.8 (11.9)	52.2 (6.6)	61.7 (13.9)	47.7 (6.1)	59.7 (12.3)
Min–max	**25–79**	–	44–54	25–55	34–54	38–64	40–58	41–77	41–57	46–79
Sex										
Male *n* (%)	**22 (55)**	–	1/3 (33)	1/3 (33)	4/4 (100)	3/4 (75)	3/6 (50)	4/6 (67)	3/6 (50)	3/7 (43)
Female *n* (%)	**18 (45)**	1/1 (100)	2/3 (67)	2/3 (67)	–	1/4 (25)	3/6 (50)	2/6 (33)	3/6 (50)	4/7 (57)
Weight (kg)										
Mean (±SD)	**68 (16)**	59.0 (–)	62.8 (13.6)	68.7 (2.0)	68.9 (13.7)	60.0 (18.8)	83.0 (29.3)	62.5 (10.1)	70.1 (13.8)	63.9 (10.57)
Min–max	**38–121**	59–59	50–77	67.2–71	53–82	38–78	58–121	50–74	53.5–86.0	50.6–77.0
Treatment duration (days)										
Mean (±SD)	**93 (100)**	42 (–)	50 (12)	149 (161)	67 (47)	71 (37)	65 (73)	47 (28)	127 (169)	155 (115)
Median	**56**	–	56	58	71	58	40	44	39	147
Min–max	**6–440+**	–	36–57	54–335	9–118	42–126	15–211	6–80	10–440+	12–373+
Primary cancer; n (%)										
GIST	**19/40 (47.5)**	1/1 (100)	1/3 (33)	1/3 (33)	–	1/4 (25)	5/6 (83)	3/6 (50)	–	7/7 (100)
Cortico-suprarenal cancer	**2/40 (5)**	–	1/3 (33)	1/3 (33)	–	–	–	–	–	–
Mesothelioma	**5/40 (12.5)**	–	–	–	–	1/4 (25)	–	2/6 (33)	2/6 (33)	–
Thyroid cancer	**2/40 (5)**	–	–	–	1/4 (25)	–	1/6 (17)	–	–	–
Bladder cancer	**1/40 (2.5)**	–	–	–	–	–	–	1/6 (17)	–	–
Cancer not differentiated	**1/40 (2.5)**	–	–	–	–	1/4 (25)	–	–	–	–
Colorectal cancer	**2/40 (5)**	–	–	–	2/4 (50)	–	–	–	–	–
Prostatic adenocarcinoma	**1/40 (2.5)**	–	1/3 (33)	–	–	–	–	–	–	–
Thymoma	**3/40 (7.5)**	–	–	1/3 (33)	–	–	–	–	2/6 (33)	–
Non-small cell lung cancer	**1/40 (2.5)**	–	–	–	1/4 (25)	–	–	–	–	–
Neuroendocrine tumour	**1/40 (2.5)**	–	–	–	–	1/4 (25)	–	–	–	–
Cystic adenoid carcinoma	**1/40 (2.5)**	–	–	–	–	–	–	–	1/6 (17)	–
Duodenum adenocarcinoma	**1/40 (2.5)**	–	–	–	–	–	–	–	1/6 (17)	–

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Table 3a – Count of patients with adverse events within dose-escalation cohorts.

Number of patients with at least one AE[b]	All (N = 27)	#1 40 mg (N = 1)	#2 100 mg (N = 3)	#3 150 mg (N = 3)	#4 250 mg (N = 4)	#5 500 mg (N = 4)	#6 1000 mg (N = 6)	#7 800 mg[a] (N = 6)
AE grade > = 3	20 (74.1%)	1 (100%)	3 (100%)	2 (66.7%)	3 (75.0%)	3 (75.0%)	5 (83.3%)	3 (50.0%)
AE grade G4 or non-haematological G3	20 (74.1%)	1 (100%)	3 (100%)	2 (66.7%)	3 (75.0%)	3 (75.0%)	5 (83.3%)	3 (50.0%)
SAE	13 (48.1%)	0 (0.0%)	1 (33.3%)	3 (100%)	2 (50.0%)	0 (0.0%)	4 (66.7%)	3 (50.0%)
Suspected AE	26 (96.3%)	1 (100%)	3 (100%)	3 (100%)	3 (75.0%)	4 (100%)	6 (100%)	6 (100%)
Suspected AE grade > = 3	10 (37.0%)	1 (100%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	4 (66.7%)	3 (50.0%)
Suspected AE G4 or non-haematological G3 when normal or not at baseline	9 (33.3%)	1 (100%)	1 (33.3%)	1 (33.3%)	0 (0.0%)	0 (0.0%)	3 (50.0%)	3 (50.0%)
DLT (dose limiting toxicity)	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (16.7%)
Suspected SAE	5 (18.5%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (33.3%)	3 (50.0%)
Suspected AE leading to permanent discontinuation	6 (22.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (25.0%)	1 (25.0%)	1 (16.7%)	3 (50.0%)
Suspected AE leading to temporary interruption	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (16.7%)
Suspected AE leading to dose reduction	2 (7.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (16.7%)	1 (16.7%)

a Dose administered *bis in die*.

b Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC v3.0), which has a range of grades from 0 to 5 generally corresponding to: 0, no effect; 1, mild; 2, moderate; 3, severe; 4, life threatening; and 5, death.

manage nausea and vomiting. Diarrhoeas were relatively frequent at masitinib initiation and were generally well managed with symptomatic treatment.

Moreover, 3/40 patients (7.5%) experienced grade 3 toxicity: one patient for nausea, one patient for diarrhoea (>12 mg/kg/day) and one patient for vomiting (<3 mg/kg/day). Of 8/40 patients (20%) who permanently discontinued treatment, GI toxicity in 4/8 patients (50%) was the predominant reason.

Twenty-seven drug-related serious adverse events (SAEs) were experienced by 7/40 patients (17.5%). No SAE was observed below 6 mg/kg/day (N = 11), 3/18 patient (16.7%) at a dose level between 6 and 12 mg/kg/day; and in 4/11 patients (36.4%) above 12 mg/kg/day. Drug-related SAEs resolved during the study except for one fatal outcome. Four patients died during the study and one patient during the follow-up period. Death was attributed to disease progression in 4/5 patients (80%), with 1/5 patient (20%) having death attributed to drug toxicity by one of the recruiting centres (agreement between investigators in the centre). This patient was in the 800 mg/day *b.i.d.* group and died from renal insufficiency and dehydration on day eight (identified as DLT). However, upon review by an independent medical expert, death was attributed to acute renal failure and concomitant aggravating medication.

Eight permanent treatment interruptions were reported for the weight-adjusted groups: one patient at a dose level between 3 and 6 mg/kg/day (25%), two patients at a dose level between 6 and 12 mg/kg/day (11.1%) and five patients at a dose level >12 mg/kg/day (48.5%).

Two imatinib-intolerant patients (300 mg/day) received masitinib. One patient experienced only grade 1 AEs at 12.7 mg/kg/day during 199 days of treatment. The other patient presented grade 2 erythema and was treated at 5.3 mg/kg/day for 471 days following a 50% dose reduction.

3.3. *Pharmacokinetics*

Pharmacokinetic analysis was performed for the free base of masitinib, AB1003 and a metabolite, AB3280. Plasma samples collected on days 1 and 14 of treatment were analysed by dose cohort (in mg/day), and by weight-adjusted dose levels (in mg/kg/day). The PK analysis population, i.e. those patients for whom sufficient data were available, was $n = 28$ on day 14, with two patients excluded from analysis due to concomitant treatments. Following repeated administration of masitinib, i.e. PK data on day 14, comparison of C_{max} revealed a fourfold increase in the concentration of masitinib AB1003 versus that of masitinib's active metabolite AB3280. Absorption of masitinib had a mean T_{max} (AB1003) of between 1.7 and 4.7 h. Accordingly, the half-life averaged 24 h (range 18–36 h) without accumulation after 14 days of orally administered masitinib. Apparent clearance and volume of distribution of masitinib were high. Better correlations were observed with weight-adjusted doses, coefficients of correlation for AUC and C_{max} equalling 0.8 and 0.83, respectively. Analyses per sub-population showed a correlation of 0.83 and 0.91, respectively, between 3 and 6 mg/kg/day (N = 4), and 0.44 and 0.52 at the dose range 7–12 mg/kg/day (N = 10), respectively. This correlation is indicative of non-linearity in the oral bioavailability of masitinib and an increased systemic exposure if the drug is

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Table 3b – Count of patients with adverse events within weight-adjusted dose groups.

Number of patients with at least one AE[a]	All (N = 40)	<3 mg/kg/day (N = 7)	3–6 mg/kg/day (N = 4)	>6–12 mg/kg/day (N = 18)	>12 mg/kg/day (N = 11)
AE grade > = 3	29 (72.5%)	6 (85.7%)	3 (75.0%)	11 (61.1%)	9 (81.8%)
AE grade G4 or non-haematological G3	29 (72.5%)	6 (85.7%)	3 (75.0%)	11 (61.1%)	9 (81.8%)
SAE	17 (42.5%)	4 (57.1%)	2 (50.0%)	5 (27.8%)	6 (54.5%)
Suspected AE	38 (95%)	7 (100%)	3 (75.0%)	17 (94.4%)	11 (100%)
Suspected AE grade > = 3	17 (42.5%)	3 (42.9%)	0 (0.0%)	6 (33.3%)	8 (72.7%)
Suspected AE G4 or non-haematological G3 when normal or not at baseline	16 (40%)	3 (42.9%)	0 (0.0%)	6 (33.3%)	7 (63.6%)
DLT (dose limiting toxicity)	7 (17.5%)	0 (0.0%)	0 (0.0%)	3 (16.7%)	4 (36.4%)
Suspected SAE	7 (17.5%)	0 (0.0%)	0 (0.0%)	3 (16.7%)	4 (36.4%)
Suspected AE leading to permanent discontinuation	8 (20%)	0 (0.0%)	1 (25.0%)	2 (11.1%)	5 (45.5%)
Suspected AE leading to temporary interruption	4 (10%)	0 (0.0%)	0 (0.0%)	2 (11.1%)	2 (18.2%)
Suspected AE leading to dose reduction	4 (10%)	0 (0.0%)	0 (0.0%)	2 (11.1%)	2 (18.2%)

a Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC v3.0), which has a range of grades from 0 to 5 generally corresponding to: 0, no effect; 1, mild; 2, moderate; 3, severe; 4, life threatening; and 5, death.

Table 3c – DLTs after weight adjustment.

Patient's dose	Preferred term	Grade
8.2 mg/kg/day	Alanine aminotransferase increased	Grade 3
	Asthenia	Grade 3
	Asthenia	Grade 3
	Asthenia	Grade 3
	General physical health deterioration	Grade 3
9.3 mg/kg/day	Alanine aminotransferase increased	Grade 3
	Hypokalaemia	Grade 3
	Rash	Grade 3
9.4 mg/kg/day	Hyponatraemia	Grade 3
12.1 mg/kg/day	Erythema	Grade 3
	Pruritus	Grade 3
	Skin desquamation	Grade 3
12.7 mg/kg/day	Alanine aminotransferase increased	Grade 3
13 mg/kg/day	Nausea	Grade 3
16 mg/kg/day	Dehydration	Grade 4
	Hyperbilirubinaemia	Grade 3
	Renal insufficiency	Grade 4

given as a single administration, e.g. 800 mg/day, instead of 400 mg administered twice daily.

3.4. *Antitumour activity*

Tumour response was evaluated in the ITT population (N = 40) based upon RECIST, defined as the best confirmed response recorded from the start of treatment until disease progression. Assessment of the ITT population showed a clinical benefit in 16/40 patients (40%), with one patient in PR and 15 patients experienced SD (Table 5a).

In the imatinib-resistant group of 17/40 patients (43%), 5/17 patients (29.4%) had SD as best clinical response (Table 5b). In two GIST patients, intolerant to 300 mg/day imatinib, treatment with 12.7 mg/kg/day masitinib resulted in SD for one patient and PR in the other patient (even with a dose reduction to 5.3 mg/kg/day).

Twenty-one patients presented with tumours other than GIST and experienced a control disease rate of 42.9%. About 2/3 patients with mesothelioma were stable, and a third patient (mesothelioma with abdominal disease) had tumour reduction at 6 weeks (from 13 to 9 mm) but was withdrawn from the study by the investigator due to persisting paracentesis to treat ascites. About 2/3 patients with thymoma, and 2/2 patients with thyroid cancer had SD.

4. Discussion

This clinical study was the first administration of the TK inhibitor masitinib in patients with solid tumours targeting c-Kit, and has shown that this is a promising treatment option for patients having solid tumours, particularly GIST. Although the MTD was not reached in the dose-escalation cohorts, a dose of 12 mg/kg/day was considered as the maximal recommended dose in long-term treatment. Indeed, higher doses than 12 mg/kg/day increased the incidence of GI disorders that generally elicited poor patient compliance. Overall, 38 grade 3/4 drug-related adverse events occurred in 29 patients (72.5%) and only higher doses resulted in patient's exit from the study.

The observed antitumour activity of masitinib was encouraging in patients resistant to imatinib. Of 14 GIST patients, who were resistant to 800 mg/day imatinib, four had stable disease. One imatinib-intolerant patient (300 mg/day) had a PR at week 12 with a good safety profile. In the non-GIST population, 2/3 patients with thymoma and 2/2 with thyroid cancer had SD.

Masitinib is a highly selective TK inhibitor that *in vitro* has demonstrated a better pharmacological profile than imatinib for wild-type c-Kit receptor and its juxtamembrane mutation without additional toxicity (Dubreuil et al., submitted).[10] Moreover, *in vitro* data have shown that masitinib (1 μM) reduces focal adhesion kinase (FAK) activity by 21% and may de-

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Table 4 – Incidence of suspected adverse events per dose group, by System organ class.

System organ class/preferred term	All (N = 40)	<3 mg/kg/day (N = 7)	3–6 mg/kg/day (N = 4)	>6–12 mg/kg/day (N = 18)	>12 mg/kg/day (N = 11)
At least one AE	38 (95.0%)	7 (100%)	5 (83.3%)	15 (93.8%)	11 (100%)
Blood and lymphatic system disorders	27 (67.5%)	5 (71.4%)	5 (83.3%)	9 (56.3%)	8 (72.7%)
Cardiac disorders	3 (7.5%)	1 (14.3%)	1 (16.7%)	1 (6.3%)	
Eye disorders	9 (22.5%)	2 (28.6%)	1 (16.7%)	2 (12.5%)	4 (36.4%)
Gastro-intestinal disorders	32 (80.0%)	6 (85.7%)	3 (50.0%)	12 (75.0%)	11 (100%)
Nausea	22 (55.0%)	2 (28.6%)	2 (50.0%)	8 (44.4%)	10 (90.9%)
Diarrhoea	21 (52.5%)	5 (83.3%)	1 (33.3%)	8 (66.7%)	7 (63.6%)
Vomiting	21 (52.5%)	5 (83.3%)	3 (100%)	6 (50.0%)	7 (63.6%)
General disorders and administration site conditions	26 (65.0%)	4 (57.1%)	2 (50.0%)	12 (66.7%)	8 (72.7%)
Hepatobiliary disorders	11 (27.5%)	1 (14.3%)		4 (22.2%)	6 (54.5%)
Infections and infestations	1 (2.5%)				1 (9.1%)
Investigations	23 (57.5%)	3 (42.9%)	1 (25.0%)	12 (66.7%)	7 (63.6%)
Metabolism and nutrition disorders	28 (70.0%)	6 (85.7%)	1 (25.0%)	14 (77.8%)	7 (63.6%)
Musculoskeletal and connective tissue disorders	9 (22.5%)	1 (14.3%)	1 (25.0%)	2 (11.1%)	5 (45.5%)
Nervous system disorders	4 (10.0%)	1 (14.3%)		2 (11.1%)	1 (9.1%)
Psychiatric disorders	1 (2.5%)			1 (5.6%)	
Renal and urinary disorders	9 (22.5%)	2 (28.6%)	1 (25.0%)	3 (16.7%)	3 (27.3%)
Reproductive system and breast disorders	1 (2.5%)			1 (5.6%)	
Respiratory, thoracic and mediastinal disorders	1 (2.5%)			1 (5.6%)	
Skin and subcutaneous tissue disorders	14 (35.0%)	3 (42.9%)	1 (25.0%)	8 (44.4%)	2 (18.2%)
Vascular disorders	4 (10.0%)	1 (14.3%)		3 (16.7%)	

Table 5a – Best response in the ITT safety population.

	All patients (N = 40)	<3 mg/kg/day (N = 7)	3–6 mg/kg/day (N = 4)	>6–12 mg/kg/day (N = 18)	>12 mg/kg/day (N = 11)
CR	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
PR	1 (2.5%)	0 (0%)	0 (0%)	1 (5.6%)	0 (0%)
SD	15 (37.5%)	2 (28.6%)	2 (33.3%)	8 (44.4%)	3 (27.3%)
PD	19 (47.5%)	5 (71.4%)	2 (33.3%)	8 (44.4%)	4 (36.4%)
Missing or non evaluable	5 (12.5%)	0 (0%)	0 (0%)	1 (5.6%)	4 (36.4%)

Table 5b – Best response for the subpopulation of GIST patients and patients with other tumours.

	GIST (N = 19)	GIST imatinib intolerant (N = 2)	GIST imatinib resistant (N = 17)	GIST imatinib resistant (800 mg, N = 14)	Tumours other than GIST (N = 21)
PR	1 (5.3%)	1 (50.0%)			
SD	6 (31.6%)	1 (50.0%)	5 (29.4%)	4 (28.6%)	9 (42.9%)
PD	10 (52.6%)		10 (58.8%)	8 (57.1%)	9 (42.9%)
Missing or non-evaluable	2 (10.5%)		2 (11.8%)	2 (14.3%)	3 (14.2%)

lay metastasis due to the inhibition of the FAK pathway.[11] Masitinib has a high affinity for Lyn kinase (0.4 μM), a negative regulator of mast cell proliferation which associates with c-Kit.[12,13] Importantly, masitinib does not inhibit TKs associated with toxicity, e.g. src, VEGFR and Abl[14] (Table 1), and presents therefore a safety profile free from cardiotoxicity. In contrast, imatinib was designed as a selective inhibitor of the fusion tyrosine kinase BCR-ABL, primarily for chronic myeloid leukaemia, and was subsequently discovered to inhibit various other TKs, including c-Kit (Table 1).[10] This resulted in FDA approval for the treatment of patients with c-Kit positive, non-resectable and/or malignant GIST. However, no complete response was achieved with imatinib and primary, or secondary (acquired) resistance developed, a substantial problem in routine clinical practice.[15]. Moreover, imatinib has been associated with cardiotoxicity due to its inhibition

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of Abl.[14] Various attempts to improve further upon the efficacy of imatinib exist. Sunitinib (Sutent, Pfizer),[16] an inhibitor of multiple TKs including VEGFRs has shown efficacy not only in imatinib-resistant GIST but also has evidence of cardiotoxicity[17]; dasatinib (Sprycel, Bristol-Myers Squibb) was the first of second-line Abl inhibitors with FDA approval that targets src and other kinases besides BCR-ABL[15–19]; and nilotinib (Tasigna, Novartis) is a rational modification to the imatinib molecule for increased affinity and inhibition of Abl.[18]

Earlier trials have investigated c-Kit inhibitors in different tumour types (glioma, pancreas cancer and germ-cell tumour). The rationale of those therapies was based on the inhibition of a molecular target or the modulation of some chemotherapy resistance. Because of its higher specificity and safety, masitinib could be added to other therapies (chemotherapy, radiotherapy or targeted therapies) in such solid tumours.

5. Conclusion

In patients with various malignant solid tumours, the safety profile of masitinib appeared acceptable with mainly mild to moderate gastro-intestinal AEs. While the MTD was not formally reached in this study, doses higher than 12 mg/kg/day led to gastro-intestinal disorders and may be only compatible with short-term administration. Therefore, 12 mg/kg/day can be considered as the maximal recommended dose for long-term treatment with masitinib. The data from this phase 1 trial reinforce masitinib as a candidate for development in first-line treatment of GIST as well as other cancers eventually in combination with chemotherapy.

Conflict of interest

Authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence their work.

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