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CLINICAL TRIAL REPORT

Safety and activity of masitinib in combination with gemcitabine in patients with advanced pancreatic cancer

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Abstract
Purpose To evaluate the efficacy and safety of masitinib combined with gemcitabine in patients with advanced pancreatic cancer.
Patients and methods Twenty-two non-randomised patients with unresectable, locally advanced ($n = 9$) or metastatic pancreatic cancer ($n = 13$) received oral masitinib (9 mg/kg/day) combined with standard gemcitabine. All patients were naıve to systemic chemotherapy or radiotherapy. The primary endpoint was time-to-progression (TTP) with efficacy and safety analyses performed on the intent-to-treat population. Secondary endpoints included overall survival (OS), as well as, subgroup analyses according to baseline disease, and performance status.
Results Overall median TTP was 6.4 months (95% CI [2.7–11.7]); 8.3 and 2.7 months, respectively, for locally advanced and metastatic patients; 6.4 and 0.8 months, respectively, for patients with KPS [80–100] or KPS [70]. Median OS was 7.1 months (95% CI [4.8–17.0]); 8.4 and 6.8 months for locally advanced or metastatic patients, respectively; 8.0 and 4.4 months in patients with KPS [80–100] or KPS [70], respectively. The 18-month observed survival rate was similar for locally advanced (22%) and metastatic patients (23%) and reached 28% for KPS [80–100] patients. The most common suspected adverse events were nausea, vomiting, rash, diarrhoea, peripheral oedema, anaemia, lymphopenia, thrombocytopenia, pyrexia, neutropenia, asthenia, leucopoenia, and abdominal pain, and most were of grades 1–2 severity.
Conclusions The efficacy and safety of masitinib combined with gemcitabine are encouraging, with extended survival and median TTP that support initiation of a phase 3 trial.

Keywords Advanced pancreatic cancer · Masitinib · Gemcitabine · c-kit · FGFR · PDGFR

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Introduction

Although the incidence rates of pancreatic cancer have been stable over the past few decades, the mortality rate remains obstinately high [1]. The median survival after diagnosis is 3–6 months and 9–12 months for patients with metastatic and locally advanced disease, respectively; and an overall 5-year survival rate below 5% [2]. Metastases, high levels of carbohydrate antigen 19–9 (CA 19–9), and an Eastern Cooperative Oncology Group (ECOG) status ≥2 are all associated with a poor prognosis [3].

Gemcitabine is accepted as the standard therapy for patients with locally advanced, unresectable, or metastatic pancreatic adenocarcinoma, with a median overall survival (OS) of 6 months and 1-year survival rate of 21% [4–7]. Its combination with erlotinib, a tyrosine kinase inhibitor targeting epidermal growth factor receptors (EGFRs), was recently approved as first-line treatment for patients with unresectable pancreatic cancer. This combination was found to modestly extend survival in a clinical trial, with a median OS (6.24 months) 2 weeks longer than that for gemcitabine monotherapy (5.91 months), a hazard ratio of 0.82 ($P = 0.038$) and 1-year survival rate of 23% (c.f. 17% for gemcitabine monotherapy treatment arm $P = 0.023$) [8]. However, the continuing poor prognosis and lack of effective treatments for pancreatic cancer highlights the need for new and more effective therapies.

The expression of platelet-derived growth factor (PDGF), PDGF receptors (PDGFRs), and c-kit has been observed in pancreatic cancer cells [9–11]. It is thought that these growth factors act in an autocrine and/or paracrine manner to stimulate pancreatic cancer growth. The focal adhesion kinase (FAK), a non-receptor tyrosine kinase, is also detected in pancreatic cancer cells [12]. FAK plays an important role in the regulation of cell signalling, adhesion, migration, apoptosis, cell cycle progression and resistance to conventional therapies [13–17]. Therefore, small molecule drugs that can selectively inhibit these particular tyrosine kinases or their signalling pathways are likely to be of benefit in a number of neoplastic diseases [18, 19].

Masitinib is a selective kinase inhibitor that blocks c-kit, PDGFR, Lyn, and to a lesser extent the fibroblast growth factor receptor 3 (FGFR3) tyrosine kinase activities, without inhibiting kinases of known toxicities. It is also able to block the FAK pathway in cells through the inhibition of FAK phosphorylation activity, without blocking its enzymatic activity. In vitro tests have shown that gemcitabine-resistant pancreatic tumour cell lines were resensitised to gemcitabine when used in combination with masitinib, possibly in part through inhibition of the FAK pathway. Preliminary in vitro data show that masitinib (1 μM) reduces FAK activity by 21% and that masitinib partially inhibits FAK auto-activation. Also, a mouse model of pancreatic cancer has demonstrated that tumour cells produce chemokines that recruit mast cells, which in turn may provide metalloproteases and growth factors, for tumour growth, angiogenesis, and tumour invasion [20]. Because of its inhibitory activity on c-kit, masitinib is able to block mast cell survival, both in vitro and in vivo in mice and in mast cell tumours in dogs [21]. Altogether, this could provide a mechanism of action for masitinib on pancreatic cancer through the reduction of tumour progression or the inhibition of mast cell migration and activation, or both. Moreover, phase 1 and 2 studies in patients with cancer [22, 23] have proven masitinib to be safe and relatively well tolerated.

Hence, the pharmacological and safety profiles of masitinib provided a compelling rationale to investigate its activity in combination with gemcitabine in patients with pancreatic cancer.

Patients and methods

This study was an open-label, multicentre, non-randomised, phase 2 clinical trial. Patients were recruited from nine centres in France from June to November 2006.

Patients

Based upon an 80% power to detect a median time-to-progression (TTP) of at least 2.8 months, rejecting the hypothesis of a median TTP of 1.4 month (α-level is set at 5% one-sided), a sample population of 22 patients was required. Patients enrolled in this study had a histologically or cytologically confirmed non-resectable, locally advanced or metastatic pancreas adenocarcinoma with measurable tumour lesions of longest diameter ≥20 mm using conventional techniques (or ≥10 mm using spiral CT scan). Patients also had to be ≥18 years old, with life expectancy ≥3 months and had a Karnofsky performance status (KPS) ≥70%. Exclusion criteria included inadequate organ function defined via blood test levels, history of other malignancies (except in situ carcinoma of the cervix or basal cell carcinoma of the skin) within the 5 years prior to treatment, myocardial infarction in the previous 6 months, severe/unstable angina, severe neurological or psychiatric disorders, or pregnancy. No prior or concomitant chemotherapy, radiotherapy, immunotherapy, biological or hormonal therapy were allowed. This study was approved by an ethical committee (6 February 2006; CPP Necker, Paris, France) and carried out in accordance with the Declaration of Helsinki and Good Clinical Practices Guidelines. All patients signed an informed consent form.

Treatment

Oral masitinib, supplied as 100- and 200-mg tablets, was administered daily at 9 mg/kg/day (corresponding to approximately 600 mg/day) divided in two intakes, during meals. The safety of this dose was supported by a dose-escalation phase 1 study in patients with solid tumours, who were orally administered up to 1,000 mg/day (corresponding to a weight-adjusted dose of $\leq$20 mg/kg/day for patients weighing $\geq$50 kg) [23]. Although the maximum-tolerated dose (MTD) was not formally reached, the dose of 12 mg/kg/day was established as the effective MTD for long-term administration.

Gemcitabine was administered weekly at 1,000 mg/m^2 body surface area via a 30-min IV infusion, for up to seven consecutive weeks, followed by a week off-treatment. Subsequent gemcitabine cycles consisted of weekly infusions for three consecutive weeks per 4-week period.

Systemic corticosteroids and/or therapeutic anticoagulation with low molecular weight heparin or a mini-dose of warfarin (e.g. 1 mg/day) were permitted. Other investigational therapies or anticancer drugs (other than gemcitabine) and certain other agents (e.g. phenytoin or high-dose warfarin) were prohibited to avoid cytochrome P450 competition. Haematopoietic growth factors were prohibited during the first 4 weeks of treatment but allowed thereafter for patients with documented cytopenia. Patients on bisphosphonate therapy for at least 2 months prior to entry could continue this therapy.

Dose reduction or removal from therapy

If grade 3 toxicity occurred (National Cancer Institute Common Terminology Criteria for Adverse Events, NCI CTCAE v3.0 classification), treatment was suspended until resolution and then resumed at the same dosage. If grade 3 toxicity reoccurred, treatment was interrupted until toxicity resolved and then resumed with a dose reduction of 1.5 mg/kg/day for masitinib. Grade 4 toxicity required a similar interruption in treatment but was accompanied by an immediate reduction in masitinib dosage upon resumption of therapy. Patients were withdrawn from the trial if grade 3–4 toxicities reoccurred despite dose reduction. Dose reduction and interruption of gemcitabine were also permissible at the treating physician's discretion and following the standard practice for that drug. Treatment with the other drug continued if either masitinib or gemcitabine was temporarily interrupted. Treatment was discontinued for adverse events (AE), progression, or withdrawal of consent. Complete end of study data were collected within 2 weeks after the final treatment.

Pharmacokinetics

Blood samples were collected at Day 1 and Day 14 (predose, 1, 2, 4, 6, 8 h, and if possible 12 h after intake). Analyses were performed by ADME BIOANALYSES (Vergeze, France). Plasma levels for masitinib and its major metabolite were assayed using an analytical method (PKK/MOA/059 version 4) previously validated by ADME BIOANALYSES.

Efficacy and safety assessment

All patients who received at least one dose of masitinib were included in the intent-to-treat analysis (ITT population). A Data Review Committee defined the per protocol (PP) population of 19 patients, with three patients disqualified due to absence of any post-baseline tumour assessment. All analyses were, however, performed using the ITT population unless otherwise stated. Tumour assessments were scheduled at baseline, week 4, 8, 12, and every 8 weeks thereafter. The primary efficacy endpoint was TTP according to the response evaluation criteria in solid tumours (RECIST) [24]. Secondary objectives were overall survival (OS), observed survival rate, best overall response (RECIST), and clinical benefit; the latter being analysed according to methodology used in the study of gemcitabine treatment and defined as the improvement of pain intensity, analgesic consumption, PS (performance status), and weight of patients [7].

Time-to-progression was defined as the delay between the first administration of treatment and disease progression. Patients who were progression-free or lost to follow-up at the time of analysis were censored at the time of their last tumour assessment for TTP. Best overall response and clinical benefit response have been previously defined [7, 24] and were assessed every 4 weeks over the study duration with a response classified as being a confirmed response at the next measurement. OS was measured from the initiation of treatment until patient death with assessment every 4 weeks.

Subgroup analyses were performed according to disease status at baseline (metastatic cancer versus locally advanced tumour) or KPS status at baseline (KPS [80–100] vs. KPS [70]). This exploratory analysis was conducted in part to reveal possible bias arising from inclusion of a heterogeneous patient population with differing prognoses and to test whether any response to masitinib follow predicted prognostic trends.

Safety was monitored until 17 October 2008 according to the NCI CTCAE v3.0 in all patients receiving at least one dose of masitinib. All AEs, including abnormal serology or haematology, were recorded regardless of causality,

with the treating physician assessing any possible relationship to the study drug.

Statistical analyses

The type I (α) error was 5% (two-sided) for all analyses. For each modality, qualitative variables were described by their frequencies and percentage referring to filled data. The number of missing data was also specified. For comparison of qualitative variables (tumour response, clinical benefit response), Fisher exact test was used. For the TTP, Kaplan–Meier estimates were plotted, and the median with its 95% confidence interval was calculated. Kaplan–Meier estimate of the TTP rates was provided at 6 and 12 months. For OS, Kaplan–Meier estimates were plotted, and the median with its 95% confidence interval was calculated. As no censoring occurred until month 20, observed OS is equal to estimated OS. Survival rates were provided at 6, 12, and 18 months. The log rank test was used for comparison of survival data (OS, TTP) between subgroups according to baseline disease and performance status. An a priori threshold of TTP >2.1 months was defined as being a positive response for the masitinib plus gemcitabine combination and hence the minimum acceptable TTP to justify further clinical trials. This threshold was based on the study's power calculation; if the lower bound for median TTP is higher than 2.12 months, the null hypothesis is rejected. Furthermore, this limit of efficacy approximates the medium TTP of 2.33 months reported from the benchmark study for gemcitabine treatment by Burris et al. [7]. All data analyses and reporting procedures used SAS v9.1 in a Windows XP operating system environment.

Results

A total of 22 patients with unresectable, locally advanced or metastatic pancreatic cancer were enrolled from nine centres in France. Patient baseline characteristics are described in Table 1. The average dose of masitinib received was 8.8 ± 0.8 mg/kg/day. The median duration of masitinib was 56 days (range 6–490) and 145 days for patients with locally advanced tumour. The median number of gemcitabine injections in the total population was eight (range 1–42), and median cumulative dose was 14,413 mg (range 1,520–47,904). One patient reported AEs suspected to be related to the study drug (nausea, vomiting, and general physical health deterioration) that led to dose reduction. During the study, 4/22 patients (18%) also had their gemcitabine dose reduced. The main reasons for treatment termination were progression for nine patients (41%); AEs for seven patients (32%); withdrawn consent for three patients (14%); and one patient (5%) each for death; alteration of general status; and investigator's decision.

Table 1 Demographics and clinical characteristics of patients

Parameter	ITT population ($N = 22$)	
Age (years)	Median	64
	Range	45–78
Gender; *N* (%)	Female	12 (55%)
	Male	10 (45%)
Time since diagnosis (months)	Median	0.6
	Range	0–6.6
Median CA 19-9 (kU/mL)	Median	0.6
	Range	0–98.8
Previous surgery for pancreatic cancer	*N*	2/22 (9%)
Disease status; *N*	KPS [80–100]	18/22 (82%)
	KPS [70]	4/22 (18%)
	Locally advanced	9/22 (41%)
	Metastatic	13/22 (59%)

Time to progression

Efficacy results are presented in Table 2. The primary endpoint of median TTP was 6.4 months (95% CI [2.7–11.7]). As expected, patients with locally advanced tumours had a longer median TTP than did patients with metastatic cancer (8.3 months, 95% CI [4.6–11.7] and 2.7 months, 95% CI [1.0-NR], respectively, $P = 0.058$). Similarly, patients with a better performance status (KPS 80–100) had a longer median TTP (6.4 months, 95% CI [2.7–11.7]) than did patients with KPS [70] (0.8 month, 95% CI [0.6–1.0], $P < 0.0001$). The estimated rates of patients without progression at 6 and 12 months were 50.8% (95% CI [NR-NR]) and 12.7% (95% CI [0.7–41.9]), respectively. All patients with KPS [70] had progressed by 6 months. For patients with locally advanced tumour, the estimated progression-free rates at 6 and 12 months were 68.6% (95% CI [21.3–91.2]) and 17.1% (95% CI [0.8–52.6]), respectively, and 57.0% (95% CI [NR-NR]) and 14.3% (95% CI [0.8–45.7]), respectively, for patients with KPS [80–100].

Overall survival

Median OS was 7.1 months (95% CI [4.8–17.0]) (Table 2; Fig. 1a). In the metastatic subgroup, median OS was 6.8 months (95% CI [4.8–9.2]) compared to 8.4 months for locally advanced patients (95% CI [4.4–17.2], $P = 0.59$, Fig. 1b). Patients with KPS [80–100] had a median OS of 8.0 months (95% CI [4.9–17.2]), whereas it was 4.4 months for patients with KPS [70] (95% CI [1.3–7.4], $P = 0.06$, Fig. 1c).

The survival rate of patients (ITT population) was 63.6% at 6 months (95% CI [40.3–79.9]), 31.8% at 12 months

Table 2 Summary of efficacy outcomes with subgroup analysis according to baseline status

	ITT population ($N = 22$)	Sub analysis (disease status)			Sub analysis (KPS status)		
		Locally advanced ($N = 9$)	Metastatic ($N = 13$)	P value	KPS [80–100] ($N = 18$)	KPS [70] ($N = 4$)	P value
Median TTP (months) (95% CI)	6.4 [2.7; 11.7]	8.2 [4.6; 11.7]	2.7 [1.0; NR]	0.058	6.4 [2.7; 11.7]	0.8 [0.6; 1.0]	<0.0001
Patient without progression (%)[a]							
6 months	51	69	NC		57	0	
12 months	13	17	NC		14	0	
Median OS (month) [95% CI]	7.1 [4.8; 17.0]	8.4 [4.4; 17.2]	6.8 [4.8; 9.2]	0.59	8.0 [4.9; 17.2]	4.4 [1.3; 7.4]	0.06
Observed survival rate (%)							
6 months [95% CI]	63.6 [40.3; 79.9]	55.6 [20.4; 80.5]	69.2 [37.3; 87.2]		66.7 [40.4; 83.4]	50.0 [5.8; 84.5]	
12 months [95% CI]	31.8 [14.2; 51.1]	44.4 [13.6; 71.9]	23.1 [5.6; 47.5]		38.9 [17.5; 60.0]	0	
18 months [95% CI]	22.7 [8.3; 41.4]	22.2 [3.4; 51.3]	23.1 [5.6; 47.5]		27.8 [10.1; 48.9]	0	
Disease control rate (%) [95% CI]	72.7 [49.8; 89.3]	88.9 [51.8; 99.7]	61.5 [31.6; 86.1]		88.9 [65.3; 98.6]	0.0 [0; 60.2]	

	$N = 18$	$N = 8$	$N = 10$	$N = 16$	$N = 2$
Clinical benefit response (%) [95% CI]	22.2 [6.4; 47.6]	37.5 [8.5; 75.5]	10.0 [0.3; 44.5]	25.0 [7.3; 52.4]	0 [0.0; 84.2]

[a] Estimated rate based upon assessable patients at relevant time points (not the ITT population). *NC* not calculable, *NR* not reached

(95% CI [14.2–51.1]), and 22.7% at 18 months (95% CI [8.3–41.4]) (Table 2). For patients with KPS [80–100], survival rates were 66.7% at 6 months (95% CI [40.4–83.4]), 38.9% at 12 months (95% CI [17.5–60.0]), and 27.8% at 18 months (95% CI [10.1–48.9]); whereas patients with KPS [70] had a survival rate of 50.0% at 6 months (95% CI [5.8–84.5]) and 0.0% at 12 months. Patients with metastatic cancer had a survival rate of 69.2% at 6 months (95% CI [37.3–87.2]) and 23.1% at 12 and 18 months (95% CI [5.6–47.5]). Patients with locally advanced disease had a survival rate of 55.6% at 6 months (95% CI [20.4–80.5]), 44.4% at 12 months (95% CI [13.6–71.9]), and 22.2% at 18 months (95% CI [3.4–51.3]).

Best response

One confirmed partial response (PR) was recorded in a patient with locally advanced cancer with a KPS [80–100]. In addition, four unconfirmed PR were reported. The overall disease control rate (partial response plus stable disease) was 72.7% (16/22, Table 2). For locally advanced patients, the disease control rate was 88.9% (8/9) and 61.5% for metastatic patients (8/13). Patients with KPS [80–100] had a disease control rate of 88.9% (16/18), whereas all patients with KPS [70] progressed immediately.

Clinical benefit

Four patients had an evaluation time of less than 4 weeks and were excluded from clinical benefit analysis. Of the 18 patients evaluated, three patients with locally advanced cancer (38%) and one patient with metastatic cancer (10%), all with KPS [80–100], had a clinical benefit as defined previously (Table 2).

Safety

The most frequent (>10% of patients) AEs with their causalities are listed in Table 3. At the cut-off date for safety (17 October 2008), all 22 patients enrolled had experienced at least one dose of masitinib. All 22 patients (100%) experienced at least one AE (regardless of causalities), of which 21 patients (95.5%) reported at least one AE suspected to be related to the study drug or not assessable (suspected AE). One patient reported a suspected grade 4 neutropenia. The most common haematological grade 3 suspected AEs were anaemia (22.7%), lymphopenia (22.7%), neutropenia (18.2%), and leucopenia (18.2%). The most common non-haematological grade 3 suspected AE was asthenia (13.6% of patients). A total of 506 AEs were reported, of which 261 (52%) were suspected to be related to the study drug, the majority of which were of grade 1–2 severity.

One patient's death was reported to be due to several AEs (two syncopes, severe abdominal pain, hypotension, grade 2 anaemia, acute renal failure, and respiratory distress syndrome) and was suspected to be related to the study drug at the time of occurrence. However, masitinib had been interrupted for 6 days before these fatal AEs occurred. Since masitinib's clearance half-life is 17 h, the complete wash-out of masitinib was probably reached. Thus, the death of this patient is most unlikely related to masitinib. Four other deaths occurred during this study but none were suspected to be treatment related.

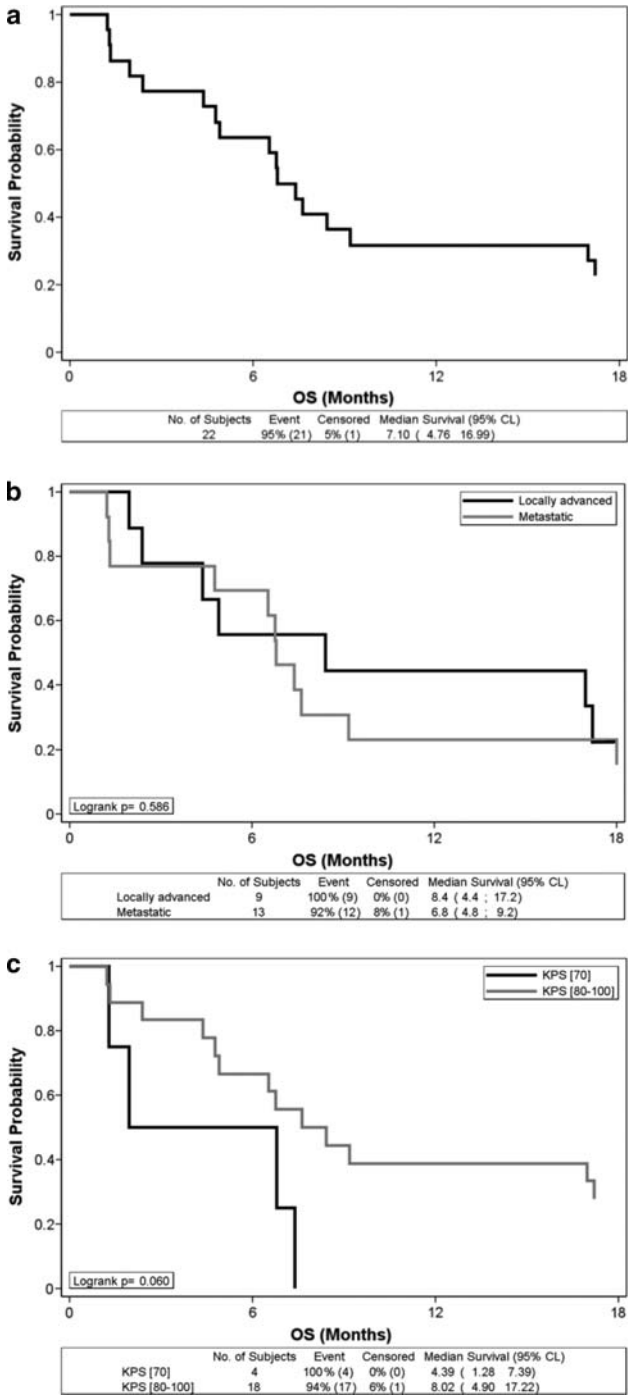

Fig. 1 Kaplan–Meier estimates of overall survival in: **a** the ITT population; **b** according to the disease status at baseline, locally advanced versus metastatic; and **c** performance status at baseline, KPS [70] versus KPS [80–100]

Pharmacokinetics

Mean Day 1 C_{max} values for AB1003 (freebase of masitinib) and its major metabolite were 464 and 110 ng/mL, respectively. At Day 14, these were 857 and 271 ng/mL, respectively. Mean extrapolated 24-h area under the curve ($AUC_{0–24}$) values for the first day of treatment were 4,035 and 1,536 ng/mL/h for AB1003 and its major metabolite, respectively. At Day 14, these were 12,369.8 and 4,976.5 ng/mL/h, respectively. These pharmacokinetic values were similar to values from an earlier trial in patients with solid tumours treated with masitinib monotherapy [23] and provided a plasma concentration of masitinib over 1.7 μM.

Discussion

This open, multicentre, non-randomised, phase 2 study evaluated the efficacy and safety of masitinib combined with gemcitabine in patients with locally advanced or metastatic pancreatic cancer. The combination of masitinib with gemcitabine resulted in a median TTP of 6.4 months, which is above our defined limit for efficacy of 2.1 months. Considering that the baseline health status of this study's population was superior to some other studies, then taking a more conservative threshold of 4.1 months, derived from a population consisting solely of locally advanced patients receiving gemcitabine treatment [25], shows an improved efficacy with masitinib is still evident. Despite the small number of patients in this study, results are promising in regard to those published for gemcitabine monotherapy or gemcitabine plus erlotinib [5, 7, 8], for which the median TTP values ranged from 2.3 to 3.8 months. Similarly, this study's median OS of 7.1 months and survival rates of 64 and 32% at 6 and 12 months, respectively, compared favourably to those of gemcitabine and gemcitabine plus erlotinib (median OS of 6 and 6.2 months, respectively and 12-month survival rates of 21 and 23%, respectively).

Although the occurrence of AEs in the ITT population was high, with 95% of patients experiencing at least one AE suspected to be related to the study drug, the majority of these were of grade 1–2 severity. The total incidence of suspected grade 3/4 AEs (82%) was comparable to those published for cetuximab plus gemcitabine and cisplatin (82%) [26], gemcitabine plus cisplatin (78%) [26], and gemcitabine plus erlotinib at 150 mg/d (78%) [8]. As would be expected, the combination of gemcitabine plus masitinib produced greater toxicity than observed with masitinib monotherapy in patients with cancer; total incidence of grade 3/4 suspected AEs being 33 and 78% at masitinib doses of 6–12 and >12 mg/kg/day, respectively [23]. Overall, the masitinib plus gemcitabine combination was reasonably tolerated.

In general, AEs associated with tyrosine kinase inhibitors occur early during the course of treatment [27, 28], with the majority of AEs showing a clear decrease in frequency after the first few months of treatment. For masitinib, this trend has been observed in non-oncologic patients

Table 3 Adverse events reported in patients undergoing combination therapy with gemcitabine and masitinib (>10% of patients)

Preferred term	All causalities			Suspected relationship to study drug (or not assessable)		
	All Grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
At least one toxicity	22 (100)	22 (100)	4 (18.2)	21 (95.5)	18 (81.8)	1 (4.5)
Haematological events						
Anaemia	15 (68.2)	7 (31.8)		8 (36.4)	5 (22.7)	
Neutropenia	10 (45.5)	6 (27.3)	2 (9.1)	6 (27.3)	4 (18.2)	1 (4.5)
Thrombocytopenia	9 (40.9)	1 (4.5)		6 (27.3)	1 (4.5)	
Lymphopenia	8 (36.4)	6 (27.3)		7 (31.8)	5 (22.7)	
Leucopoenia	6 (27.3)	4 (18.2)		5 (22.7)	4 (18.2)	
Haemoglobin	3 (13.6)	1 (4.5)				
Non-haematological events						
Nausea	16 (72.7)	1 (4.5)		14 (63.6)	1 (4.5)	
Diarrhoea	15 (68.2)	2 (9.1)		11 (50.0)	2 (9.1)	
Pyrexia	13 (59.1)	1 (4.5)		6 (27.3)		
Vomiting	12 (54.5)			11 (50.0)		
Asthenia	11 (50.0)	5 (22.7)	1 (4.5)	6 (27.3)	3 (13.6)	
Rash	11 (50.0)	2 (9.1)		11 (50.0)	2 (9.1)	
Oedema peripheral	9 (40.9)			8 (36.4)		
Abdominal pain	7 (31.8)	1 (4.5)		4 (18.2)		
Constipation	7 (31.8)			2 (9.1)		
Hypoalbuminemia	7 (31.8)	1 (4.5)				
Pleural effusion	7 (31.8)					
Ascites	5 (22.7)					
Dyspnoea	5 (22.7)	2 (9.1)		1 (4.5)	1 (4.5)	
Cough	4 (18.2)					
Mucosal inflammation	4 (18.2)			1 (4.5)		
Abdominal pain upper	3 (13.6)					
Anorexia	3 (13.6)	1 (4.5)		2 (9.1)	1 (4.5)	
Aspartate aminotransferase	3 (13.6)	2 (9.1)		1 (4.5)	1 (4.5)	
Back pain	3 (13.6)					
Blood alkaline phosphatase increased	3 (13.6)	1 (4.5)		1 (4.5)		
Blood bilirubin increased	3 (13.6)	1 (4.5)	1 (4.5)	1 (4.5)		
Flatulence	3 (13.6)			1 (4.5)		
General physical health deterioration	3 (13.6)	1 (4.5)		1 (4.5)		

(rheumatoid arthritis, mastocytosis) receiving approximately 6 mg/kg/day for >3 months and in patients with cancer (GIST) receiving approximately 7.5 mg/kg/day for >6 months. Such time analysis was not feasible for this study, because only 8/22 patients (36%) received treatment for over 90 days. However, based upon related knowledge of the safety profile of tyrosine kinase inhibitors, it is not unreasonable to expect some reduction in the frequency and severity of AEs for those patients receiving treatment beyond 6 months.

Because of the increased survival, other treatments received by the 17 patients who exited the study (five patients died while in the study) were assessed. Information was available from 14 of these patients. Most frequent post-study treatments were the combination FOLFOX 4 or gemcitabine (six patients), capecitabine or 5-fluorouracil (five patients) or oxaliplatin (four patients). Most of these post-study treatments were administered for a short period of time, ranging from 1 to 2.6 months. Treatments given for more than 5 months were the combination FOLFOX 4 (two patients, 7.3 and 9.5 months, respectively), taxol (one patient, 5.9 months), and gemcitabine (one patient, over 21 months). None of these post-study treatments are novel treatments; therefore, they should not have impacted survival more than what is known from published survival data after treatment with gemcitabine, suggesting that the

improved overall survival of these patients can be attributed to the addition of masitinib.

More recently, phase 2 trials evaluating the addition of a monoclonal antibody (either anti-EGFR cetuximab or anti-VEGF bevacizumab) to gemcitabine combined with a platinum derivative in pancreatic cancer showed no improvement in terms of survival over the combination of gemcitabine and the platinum derivative alone [26, 29, 30]. Our data presented here appear to be similar to those of the combinations of gemcitabine with either cisplatin (median OS: 9.0 months [31]) or oxaliplatin (median OS: 7.5 months [32]), but the addition of a platinum derivative to gemcitabine resulted in a high incidence of grade 3 peripheral sensory neuropathy [31] or of grade 3 or 4 myelosuppression [32], suggesting that masitinib might have a lower incidence of severe AEs.

Previous studies have shown that the cancer's stage and the patient's performance status at enrolment are prognosis factors for survival [5, 8, 31, 33]. Indeed, patients with a poor health status at enrolment (KPS [70], 4/22 patients, 18%) survived less than a year. When these patients were excluded from the analysis, the overall survival rate at 18 months for KPS [80–100] patients was 28%. The healthiest patients, with locally advanced tumour, had very similar median OS and median TTP, which is counter-intuitive. This might be explained by the fact that four out of nine of these patients were censored for TTP because of death without progression. The delay between progression and death for the five other patients were 2.2, 8.0, 8.7, 10.8, and 11.5 months. Although the stage of cancer is usually a prognosis factor for survival, patients with metastatic cancer or locally advanced tumours had equivalent survival rates at 18 months (23 and 22%, respectively). Their median OS was not statistically different, whereas their median TTP was 2.7 and 8.3 months, respectively. This suggests that the addition of masitinib to gemcitabine acts on the general survival of patients with metastases with a higher efficacy than on tumour progression. One hypothesis is that the partial inhibition of FAK pathway by masitinib would eliminate the most aggressive clones without inhibiting general cell proliferation, and/or prevent engraftment of new metastases. Similarly, the important overall disease control rate (72.7%) could also be explained by a possible mechanism of resensitisation of gemcitabine-resistant pancreatic tumour cells through the inhibition of FAK pathway by masitinib, as observed in our pre-clinical studies, thereby impeding adherence properties, cell migration, and metastasis. It is also possible that masitinib inhibition of PDGFR could reduce the interstitial pressure within the tumour, thus increasing chemotherapy uptake [34, 35]. Furthermore, masitinib may decrease tumour cells' invasiveness and tumour progression through its inhibition of c-kit by blocking mast cell migration, activation, and production of angiogenic factors including VEGF and metalloproteases [20]. Finally, the improvement of general status and pain observed in some patients could also be related to such mast cell inhibition.

Conclusion

Results from this study should be interpreted within the restrictions of an uncontrolled phase 2 trial; that is, a relatively small population with a lower proportion of metastatic patients and higher proportion of KPS $\geq$80 than comparative phase 3 trials. These limitations notwithstanding, this study does provide promising proof-of-concept results regarding disease-related symptom improvement and survival in advanced pancreatic cancer following gemcitabine and masitinib combination treatment. These data support the initiation of a confirmatory phase 3 clinical trial to compare the combination of gemcitabine with masitinib to gemcitabine alone.

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