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## 1 BACKGROUND

Imatinib mesylate (also known as Glivec®) was designed as a specific inhibitor of the BCR-ABL tyrosine kinase and developed primarily for chronic myeloid leukaemia (CML). In fact it does inhibit too c-KIT and PDGFR, thus allowing treatment of GIST patients and occurrence of various secondary toxic effects due to its incomplete selectivity. Development of secondary resistances to imatinib is of importance in GIST patients

Masitinib Mesylate (MM; AB1010) selectively inhibits wild-type and juxtamembranous mutated (JM) c-KIT, PDGFR and FGFR3.

When tested in vitro, AB1010 appeared to be an inhibitor of CYP2C9, CYP2D6 and CYP3A4/5 in human liver microsomes

	Masitinib IC <sub>50</sub>
c-kit	0.1 to 0.3 µM
JM c-kit	5 nM
PDGFR	0.25 to 10 nM
FGFR3	1 to 2 µM

## 2 OBJECTIVES & STUDY DESIGN

This phase I clinical trial was the first administration of AB1010 in patients with advanced solid malignancies. This is a Phase I, open label, sequential-cohort, dose-escalation study. The first part of the study was done in a monocentric setting (Institut Gustave Roussy) and encompassed patients with various histological solid malignancies. The second part of the study was open to two additional centers (Centre Léon Berard and Institut Bergonié) to allow for extra-recruitment of GIST patients.

### Primary Objective

To assess the safety and tolerability of oral AB1010 administered orally as a single agent in patients with solid tumors, i.e. to define the MTD of the drug.

### Secondary Objectives

- To assess the pharmacokinetic profile of AB1010 in human subjects with cancer
- To assess the clinical activity of AB1010.

### Additional Objectives

- To determine the MTD of AB1010 in patients with GIST resistant to imatinib mesylate.
- To determine the MTD of AB1010, in patient with solid tumors, naive to imatinib mesylate, with c-kit positive tumors.

## 3 STUDY DOSING & STUDY POPULATION

### DOSING REGIMENS:

- Once daily for a continuous period of 2 weeks (14 days)
- AB1010 was to be taken 1 hour prior to food intake.
- During the study, several changes in treatment administration were decided
  - Due to gastrointestinal toxicity, the daily treatment dose was divided in two doses
  - The interruption of 3 days between Week 2 and Week 3 was cancelled
- AB1010 being mainly metabolized by liver enzymes (in particular CYP2C9, CYP2D6 and CYP3A4), co-administration of agents known as liver enzymes inhibitors were to be avoided unless there was overriding clinical need. Also, concomitant treatments with drugs interfering with gastro-intestinal absorption were to be avoided

### INCLUSION CRITERIA

- Histologically proven advanced solid malignancy for which no recognized therapy was available or for which standard therapy had failed.
- Age ≥ 18 years.
- Women using effective contraception, post-menopausal or surgically sterile
- Adequate bone marrow function defined as absolute neutrophil count (ANC) > 1.5 x 10<sup>9</sup>/L, and platelets (PTL) > 75 x 10<sup>9</sup>/L. This inclusion criterion was changed by Amendment No. 1 as: ANC > 2.0 x 10<sup>9</sup>/L, PTL > 100 x 10<sup>9</sup>/L, leukocytes (total WBC) e 3.5 x 10<sup>9</sup>/L, lymphocytes e 10<sup>9</sup>/L, and hemoglobin e 11 g/dL in women and e 12 g/dL in men.
- Adequate liver function, defined as serum transaminases <2.5x ULN, or bilirubin <1.5x ULN.
- Adequate renal function defined as serum creatinine <1.5x ULN or creatinine clearance > 40mL/min
- ECOG Performance Status ≤ 2
- Signed informed consent

### EXCLUSION CRITERIA

- Failure to recover from the effects of previous chemotherapy, radiotherapy or immunotherapy prior to enrollment.
- Had received any of the following within the specified time frame prior to study drug administration:
  - An investigational agent within 4 weeks
  - Previous therapy for malignancy within 4 weeks, including any chemotherapy, immunotherapy, biologic or hormonal therapy (6 weeks for nitrosoureas or mitomycin C)
  - Surgery within 6 weeks
- Patients with a history of any other malignancy, other than in situ carcinoma of the cervix or basal cell carcinoma of the skin, within the 5 years prior to study drug treatment.
- Known central nervous system metastases clinically expressed.
- Myocardial infection, severe/unstable angina.
- Digestive disorders involving absorption or leading to major modifications of bioavailability.

## 4 RESULTS

### PATIENTS CHARACTERISTICS

- 40 patients were enrolled from January 2004 to March 2006. 38 patients have been analyzed in this progress report.
- 27 patients received masitinib at 7 escalating daily dose levels: 40 mg (1 patient), 100 mg (3 patients), 150 mg (3 patients), 250 mg (4 patients), 500 mg (4 patients), 1000 mg (6 patients) and 800 mg (6 patients). Two additional cohorts were subsequently added: 6 patients with solid c-kit+ tumors naive to Imatinib Mesylate (IM) received MM at a dose of 9 mg/kg/day and 7 patients with gastrointestinal stromal tumors (GIST) resistant to IM received MM at a dose of 12 mg/kg/day.

Table 1: Patients Characteristics

No of Subjects		38
Median Age (Range)		54 (25-77)
Gender	Male	21 (55)
	Female	17 (45)
ECOG (PS)	0	15 (39)
	1	20 (53)
	2	3 (8)
Prior imatinib		14
Tumor Types	GIST	15
	Corticoadrenal	2
	Mesothelioma	5
	Thyroid cancer	2
	Bladder cancer	1
	ACUP	1
	Colorectal cancer	2
	Prostate	1
	Thymoma	3
	NSCLC	1
	Neuroendocrine	1
Cystic adenoid cancer	1	
Duodenum cancer	1	
Cardia adenocarcinoma	1	
Stomach cancer	1	

### SAFETY

- Frequent drug-related adverse events (97% of patients), but generally mild to moderate intensity (34% patients with grade 3-4 drug-related adverse events).
- Overall, 10/38 patients (26%) experienced at least one DLT during the study. The most frequent DLTs were: nausea and vomiting in 2 patients, hepatic disorders in 2 patients, asthenia in 2 patients.
- Four patients died during this study, 2 due to disease progression, one for massive necrosis of a large GIST tumor and one for renal failure considered by the investigator as related to the study drug.
- The MTD was not formally achieved in this trial, but doses of 13.5 and 15 mg/kg (dose level of 1000 mg) lead to limiting toxicities when taking into account grade 2 drug-related gastro-intestinal disorders. The dose of 12 mg/kg is thus considered as the recommended dose for long term treatment

Table 2: Reasons for premature withdrawal

	40 mg/day	100 mg/day	150 mg/day	250 mg/day	500 mg/day	1000 mg/day	800 mg/day	9 mg/kg	12 mg/kg	All
	N=1	N=3	N=3	N=4	N=4	N=6	N=6	N=6	N=5	N=38
Disease progression	1	2	2	2	1	4	2	3	1	18
Patient's request	-	-	-	-	-	-	1	-	-	1
Death	-	-	-	-	-	1	-	-	-	1
Toxicity	-	-	-	1	1	1	1	1	1	5
Other	-	1	-	-	1	-	-	-	-	2
All	1	3	2	2	3	5	5	4	2	27

### PHARMACOKINETICS

- Pharmacokinetic analysis showed a proportional and linear increase of C<sub>max</sub> and AUC according to the dose or dose/kg.
- The non-linearity seen in the oral bioavailability of AB1010 considerably increases its systemic exposure if the drug is given as a single administration of 800 mg in place of two daily administrations of 400 mg.

Table 3: Most frequently reported adverse events related to the study drug by worst NCI-

SOC Preferred term	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
<b>Gastro-intestinal disorders</b>					
Diarrhoea	n (%) 19 (100)	12 (63)	6 (32)	1 (5)	-
Vomiting	n (%) 21 (100)	14 (67)	6 (29)	1 (5)	-
Nausea	n (%) 21 (100)	9 (43)	11 (52)	1 (5)	-
<b>Blood disorders</b>					
Anemia	n (%) 19 (100)	11 (58)	6 (32)	2 (11)	-
Lymphopenia	n (%) 15 (100)	5 (30)	9 (60)	1 (7)	-
Leukopenia	n (%) 7 (100)	2 (29)	5 (71)	-	-
<b>Investigations</b>					
ASAT increased	n (%) 17 (100)	12 (71)	5 (29)	-	-
ALAT increased	n (%) 12 (100)	6 (50)	3 (25)	3 (25)	-
GGT increased	n (%) 11 (100)	4 (36)	5 (45)	1 (9)	1 (9)
ALP increased	n (%) 10 (100)	7 (70)	1 (10)	2 (20)	-
Blood creatinine increased	n (%) 7 (100)	6 (86)	1 (14)	-	-
Weight decreased	n (%) 6 (100)	5 (83)	-	1 (17)	-
<b>Hepatobiliary disorders</b>					
Hyperbilirubinemia	n (%) 10 (100)	6 (60)	3 (30)	1 (10)	-
<b>Metabolism and nutrition disorders</b>					
Anorexia	n (%) 19 (100)	11 (58)	8 (42)	-	-
Hypoalbuminemia	n (%) 12 (100)	5 (42)	3 (25)	4 (33)	-
Hypocalcemia	n (%) 15 (100)	12 (80)	3 (20)	-	-
Hypokalaemia	n (%) 6 (100)	5 (83)	-	1 (17)	-
Hyponatremia	n (%) 10 (100)	7 (70)	-	2 (20)	1 (10)
Hypophosphataemia	n (%) 12 (100)	4 (33)	6 (50)	2 (17)	-
<b>General disorders</b>					
Asthenia	n (%) 21 (100)	8 (38)	10 (48)	3 (14)	-
Edema peripheral	n (%) 8 (100)	6 (75)	2 (25)	-	-
<b>Eye disorders</b>					
Eye lid edema	n (%) 7 (100)	7 (100)	-	-	-
<b>Skin disorders</b>					
Face edema	n (%) 5 (100)	4 (80)	1 (20)	-	-
Periorbital edema	n (%) 4 (100)	4 (100)	-	-	-
Rash	n (%) 2 (100)	1 (50)	-	1 (50)	-
<b>Renal disorders</b>					
Proteinuria	n (%) 6 (100)	2 (33)	4 (67)	-	-
All edema	n (%) 19 (100)	16 (84)	3 (16)	-	-

### PRELIMINARY EFFICACY

- 1 patient had partial response. Patient 9-03, a 53-year old woman, was included with an adenocarcinoma of the cardia diagnosed on Day -253 (8.4 months before inclusion). She was treated with AB1010 for 12 weeks at the dose of 11.11 mg/kg. Partial response was noticed at Week 12. This patient is still under treatment.
- 14 (34%) patients had stable disease. Among those 14 patients, only 6 patients (16% of the overall population) continued AB1010 administration after Week 12. The long-lasting SD included GIST, and cystic-adenoid carcinoma patients
- 15 patients enrolled in the study were resistant to Imatinib. No complete response or partial response occurred in such patients.
- 16 (47%) had disease progression.
- The median time to progression was 7.7 weeks
- No complete response occurred

Table 5: Best clinical response

	40 mg/day	100 mg/day	150 mg/day	250 mg/day	500 mg/day	1000 mg/day	800 mg/day	9.0 mg/kg	12.0 mg/kg	All
	N=1	N=3	N=3	N=4	N=4	N=6	N=6	N=6	N=5	N=38
Complete response	-	-	-	-	-	-	-	-	-	-
Partial response	-	-	-	-	-	-	-	-	1	1
Stable disease	1	1	2	2	1	2	3	2	2	14
Progressive disease	1	2	2	1	2	3	2	2	1	16
Not evaluable	-	-	-	-	-	2	3	1	1	7

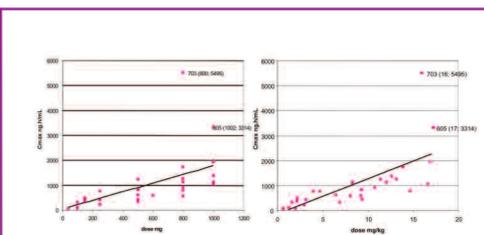
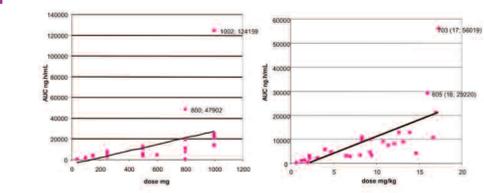


Figure 2 : AUC as a function of dose



## 5 - CONCLUSIONS

This study was the first administration of AB1010 in patients with solid tumors. In these patients with various oncological pathologies, the safety profile of AB1010 appeared acceptable; with mainly mild to moderate gastro-intestinal adverse events. The intensity of side-effects clearly relates to the dose.

Even if the MTD was not formally achieved in this trial, doses higher than 15 mg/kg/day lead to gastrointestinal disorders which are probably not compatible with a long term administration of this drug. The dose of 12 mg/kg is thus considered as the recommended dose for long term treatment

The Pharmacokinetic results showed a proportional and linear increase of C<sub>max</sub> and AUC according to the dose.

In this study, one patient had a partial response at Week 12 and 6 (16%) a stable disease for over 12 weeks. The median time to progression was 7.7 weeks.

This drug is currently being investigated in several phase II trials among a wide range of tumor types including pancreatic cancer, GIST and dermato-fibro-sarcomas

