10089 **General Poster Session (Board #53B), Sun, 8:00 AM-12:00 PM**

Masitinib in imatinib-naive advanced gastrointestinal stromal tumor (GIST): Five-year follow-up of the French Sarcoma Group phase II trial.

Axel Le Cesne, Jean-Yves Blay, Binh Bui Nguyen, Olivier Bouche, Julien Domont, Angela Cioffi, Julie Le Boulicaut, Alain Moussy, Olivier Hermine, Antoine Adenis; Institut Gustave Roussy, Villejuif, France; University Claude Bernard Lyon I, Centre Léon Bérard, Lyon, France; Institut Bergonie, Bordeaux, France; University Hospital Robert Debre, Reims, France; AB Science, Paris, France; Necker Hospital, Paris, France; Centre Oscar Lambret, Lille, France

Background: Masitinib is a tyrosine kinase inhibitor that in vitro has greater activity and selectivity than imatinib against KIT. This multicenter, open label, phase 2 study evaluated efficacy and safety of masitinib as a first-line treatment of advanced GIST. Initial results with a median follow-up of 34 months, were previously reported in EJC 2010. We present here 5-year follow-up data from the same series with updated safety and survival data. **Methods:** Imatinib-naïve patients (pts) with inoperable, advanced GIST received oral masitinib (7.5 mg/kg/day) until progression, refusal or toxicity. **Results:** Thirty pts with a median age of 58 years (60% of males) were included from 06/2005 to 04/2007 in 5 institutions. At the cut-off date of 13/09/2011, 7/30 pts (23%) were still under treatment with median follow-up of 65 months and the median overall survival (OS) had not yet been reached (NR). The 5-year OS rate was 61.5% (95% CI [41.1;76.6]) (see Table). Among patients with confirmed KIT exon 11 mutation, 8/9 pts (89%) were still alive with one pt having died from non-treatment related causes (surgical complication) following a complete response while receiving masitinib. No additional progressions have been reported giving a total of 14 events (13 progressions and 1 death). Updated median PFS was 41.3 months (95% CI [17.5;53.8]).No additional grade 3/4 adverse events have been reported. **Conclusions:** Long term results of masitinib confirm an interesting activity with prolonged PFS and OS. The median PFS rate in masitinib compares very favorably to that of imatinib, which is reported as 18 months (JCO 26:626, 2008). The 5-year OS rates for masitinib in the overall and exon 11 populations also compare favorably to imatinib, both of which are reported at ≤50% for imatinib (JCO 26:626, 2008; JCO 28:1247, 2010). These results support the head to head comparison with imatinib in the currently ongoing phase 3 randomized clinical trial in first line advanced GIST pts.

	All (N=30)	Exon 11 (n=9)
Median OS (months) [95%CI]	NR [53;NR]	NR [65;NR]
Month-36	86.5% [68.0;94.7]	88.9% [43.3;98.4]
48	76.2% [56.4;87.9]	88.9%
60	61.5% [41.1;76.6]	88.9%
72	55.9% [34.7;72.6]	71.1% [23.3;92.3]

2012 ASCO Annual Meeting – June 01-05, Chicago

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[1]Institut Gustave Roussy (Villejuif) ; [2]Centre Léon Bérard (Lyon); [3]Institut Bergonié (Bordeaux); [4]Hôpital Robert Debré (Reims); [5]AB Science (Paris); [6]Hôpital Necker (Paris); [7]Centre Oscar Lambret (Lille), France

Full poster
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Background

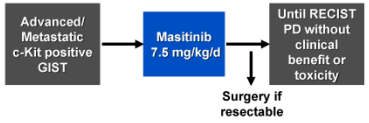
- Masitinib (AB Science, Paris, France) is a tyrosine kinase inhibitor (TKI) that, *in vitro*, has greater activity and selectivity than imatinib (IM) against wild-type c-Kit receptor (150 nM vs. 250 nM, respectively), against activated mutant c-Kit found in GIST such as exon 11 (0.5 nM vs. 2 nM) and exon 9 (40 nM vs. 100 nM), and against resistant mutants (secondary resistance) such as exon 14 (2 µM vs. 3.5 µM).
- Masitinib does not inhibit kinases that are linked to toxic events such as Abl and Src. [1]

Objectives

- IM-naïve patients with inoperable, advanced GIST received oral masitinib (7.5 mg/kg/day) until progression without clinical benefit, refusal or toxicity.
- Efficacy variables included response rate, best response (RECIST), progression free survival (PFS) and overall survival (OS).
- Initial results with a median follow-up of 34 months, were previously reported [2]. Presented here are 5-year follow-up safety and survival data from the same series (all patients had a follow-up of at least 60 months).

Study design

- Inclusion criteria:
  - No prior TKI, including as adjuvant therapy
  - ECOG Performance Status 0-1
- Patients with study treatment withdrawal were treated according to standard practice (mainly with another TKI).



Patient characteristics

Number of patients		30
Male		18 (60%)
Age (years) Mean ± SD [Min ; Max]		57 ± 14 [34 ; 82]
ECOG status	0	23 (77%)
	1	7 (23%)
GIST localization	Stomach	14 (47%)
	Small intestine	10 (33%)
	Large intestine	1 (3%)
	Other	5 (17%)
Presence of metastases		27 (90%)
Sum of target lesions dia. (mm) Mean ± SD [Min ; Max]		107 ± 77 [19 ; 333]
Positive c-Kit status		29 (97%)
Genomic analysis (n = 16)		
	Wild-type	3 (19%)
	Exon 11	9 (56%)
	Exon 11 + Exon 13	2 (13%)
	PDGFRα / Other	1 (6%) / 1 (6%)

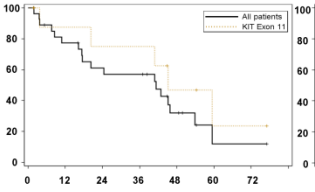
Treatment exposure

- Median treatment exposure: 33.5 months (range: 1.3; 77.8).
- Cut-off date: May 2nd, 2012.

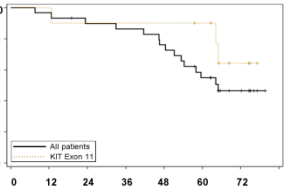
5 pts under study treatment (20%)	✓ 4 pts ongoing without progression or tumor resection ✓ 1 pt ongoing with tumor resection
25 pts withdrawn from study (80%)	✓ 15 pts with progression (RECIST) ✓ 5 pts with adverse event: 2 cutaneous toxicity; 1 CNS ischemia; 1 death post surgery; 1 CPK increase. ✓ 2 pts wrongly included (uterine stromal sarcoma and fibromatosis) ✓ 1 pt with appearance of prostatic cancer ✓ 1 pt with liver metas. became resectable ✓ 1 pt investigator decision

5-year updated PFS and OS

Progression-free Survival
Median follow-up of 72 months



Overall Survival
Median follow-up of 72 months



PFS	All	Exon 11
N	30	10
Events	19 (63%)	5 (50%)
Censored	11 (37%)	5 (50%)
Median PFS	41 months	45 months
[95%CI]	[18; 54]	[20; NA]

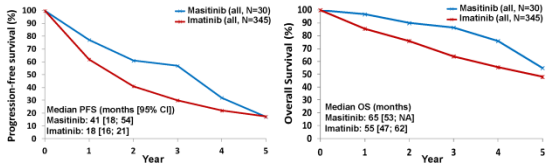
OS	All	Exon 11
N	30	10
Events	15 (50%)	3 (30%)
Censored	15 (50%)	7 (70%)
Median OS	65 months	Not Reached
[95%CI]	[53; NA]	[64; NA]

- Five patients showed prolonged response: 4/5 had *KIT* exon 11 mutation (1 missing data), 3/5 experienced complete response and 2/5 partial response.

Historical comparison with imatinib

- Despite the limited validity of comparison with phase III trials, OS and PFS with masitinib appear to compare favorably to those of imatinib at 400 mg [3, 4, 5].

Historical comparison of OS and PFS (overall population) from the masitinib phase 2 study with the imatinib phase III study



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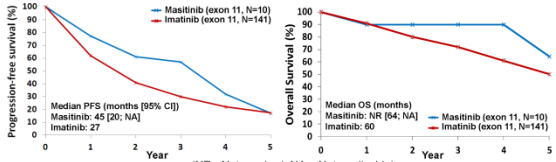

(NR= Not reached; NA = Not applicable)

Long term safety

- Single agent masitinib at 7.5 mg/kg/day was well tolerated:
  - AEs were frequent (30/30 pts), albeit mild.
  - Most common AEs were: asthenia (87%), diarrhea (57%), eyelid edema (57%), nausea (47%), muscle spasms (43%), and rash (37%).
- 14 pts (47%) reported at least one grade 3 or 4 related AE.
  - The most common treatment related grade 3 toxicities were: rash (10%) and neutropenia (7%), with one patient presenting a grade 4 skin exfoliation (3%).
  - No related death. No related life-threatening event.
- No relevant long-term toxicities have been reported. Only two grade 3/4 related AEs after 24 months of treatment: grade 3 anemia (M24), and grade 3 CPK increase (M29). No grade 3/4 related AE after 3 years of treatment.

Conclusion

- This 5-year follow-up data substantiates that masitinib has an effective and sustainable activity in IM-naïve GIST patients.
- Despite the limited validity of comparison with phase III trials, the median PFS and OS in masitinib compare favorably to those of imatinib.
- Adverse events occurred mainly during the first year, particularly over the initial 3 months, with good long term tolerance experienced thereafter.
- **These results support the head to head comparison with imatinib in the ongoing phase III randomized clinical trial in first line advanced GIST patients.**

Related presentation: Poster Board #: 54G General Poster Session: Sarcoma.
Masitinib in comparison to imatinib as first line therapy of patients with advanced GIST: A randomized phase 3 trial.

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References: [1] Dubreuil, PLoSONE 2009. [2] Le Cesne, EJC 2010. [3] Blanke, JCO 26:626, 2008. [4] Heinrich, JCO 26;5360, 2008. [5] Gastrointestinal Stromal Tumor Meta-Analysis Group, JCO 28:1247, 2010.

Background

- Masitinib (AB Science, Paris, France) is a tyrosine kinase inhibitor (TKI) that, *in vitro*, has greater activity and selectivity than imatinib (IM) against wild-type c-Kit receptor and activated mutant (exon 9 or 11) or secondary resistant (exon 14) c-Kit found in GIST.

IC_{50} (nM)	Masitinib	Imatinib
KIT wild-type	150	250
KIT exon 9	40	100
KIT exon 11	0.5	2.0
KIT exon 14	2.0	3.5

- Masitinib does not inhibit kinases that are linked to toxic events such as Abl and Src [Dubreuil, PLoSONE 2009].

Objectives

- IM-naïve patients with inoperable, advanced GIST received oral masitinib (7.5 mg/kg/day) until progression without clinical benefit, refusal or toxicity.
- Efficacy variables included response rate, best response (RECIST), progression free survival (PFS) and overall survival (OS).
- Initial results with a median follow-up of 34 months, were previously reported [Le Cesne, EJC 2010]. Presented here are 5-year follow-up safety and survival data from the same series (all patients had a follow-up of at least 60 months).

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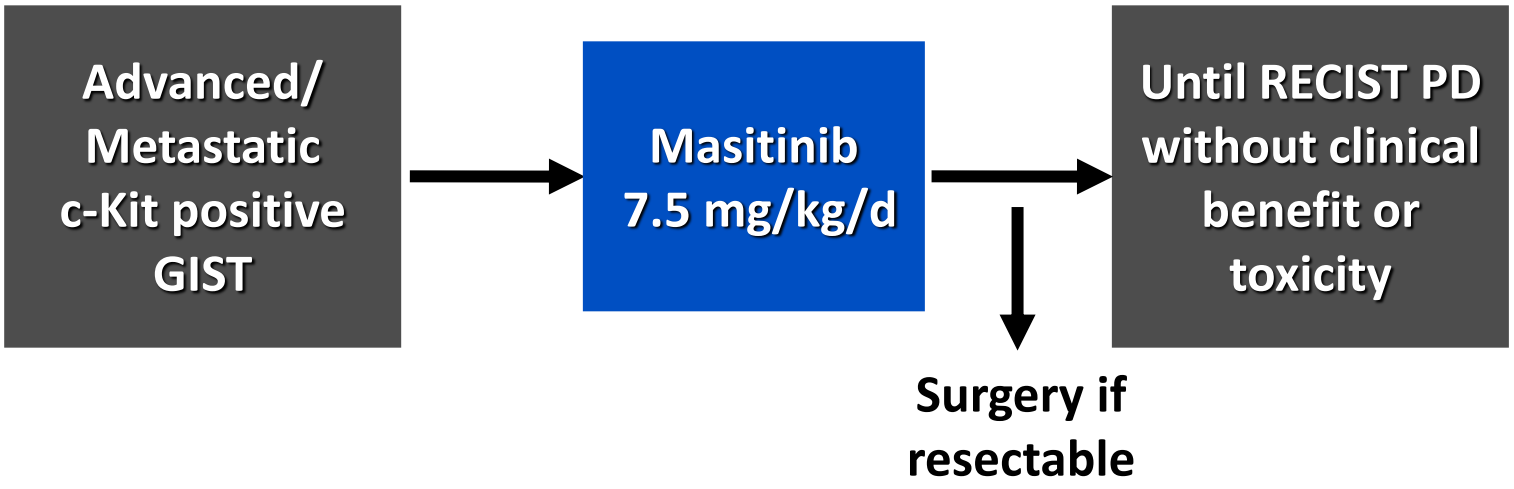

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Patient characteristics (2)

Number of patients	30
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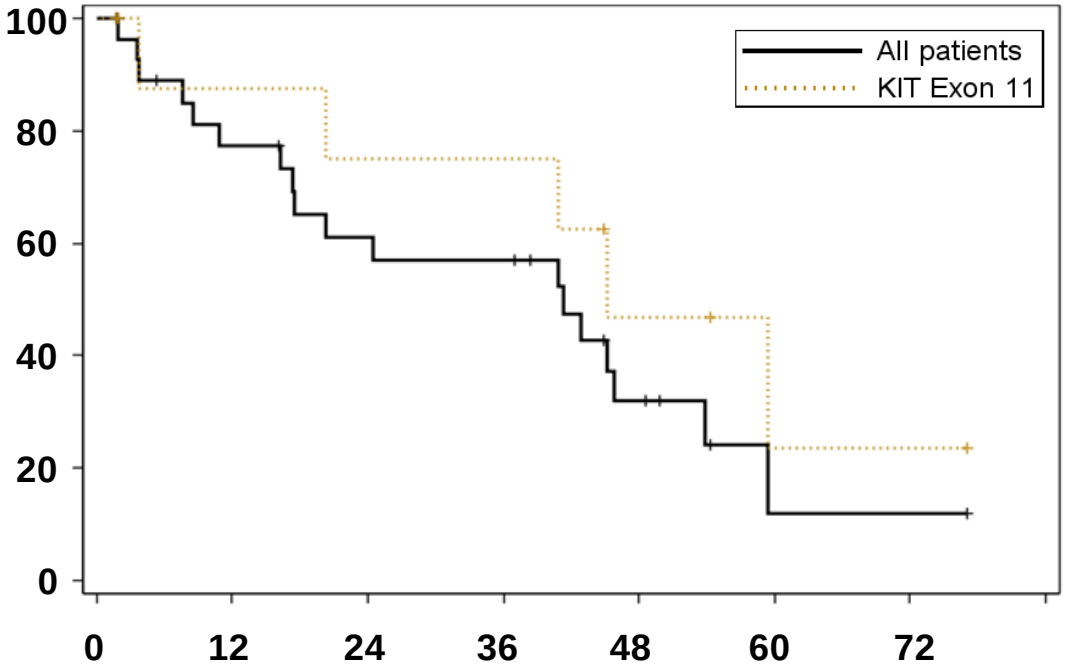
5-year updated PFS and OS (1)

Progression-free Survival

Median follow-up of 72 months



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5-year updated PFS and OS (2)

Overall Survival

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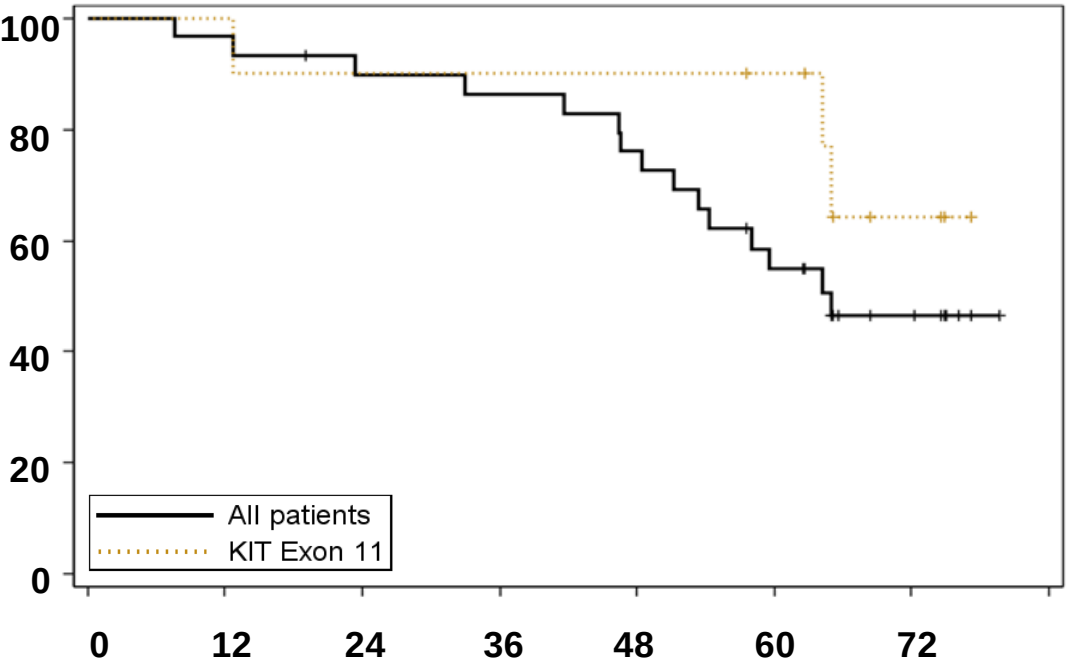

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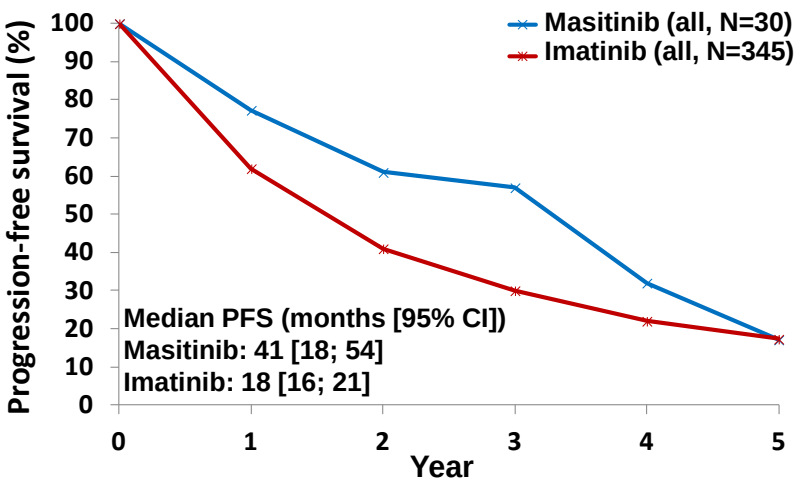

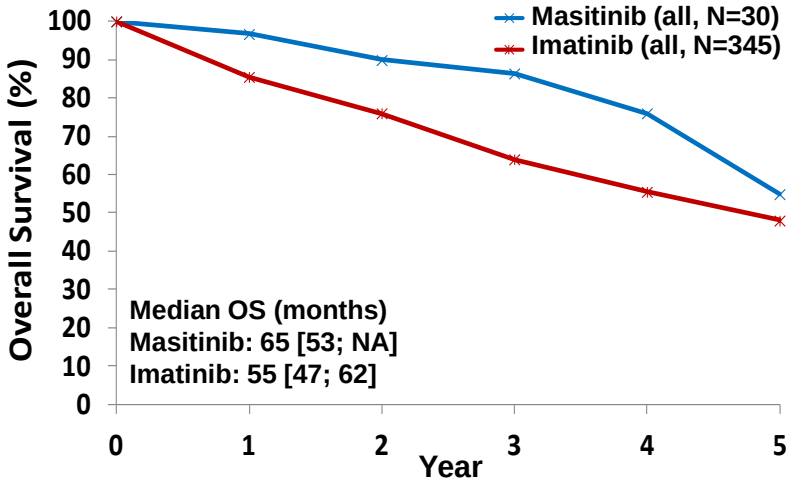

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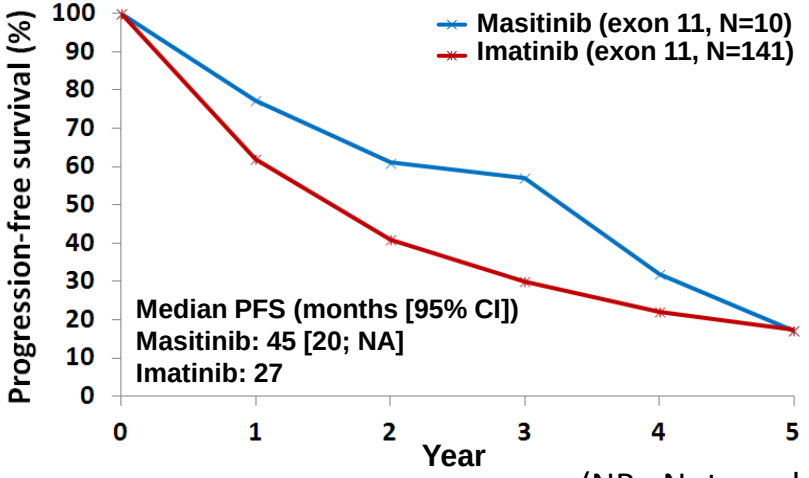

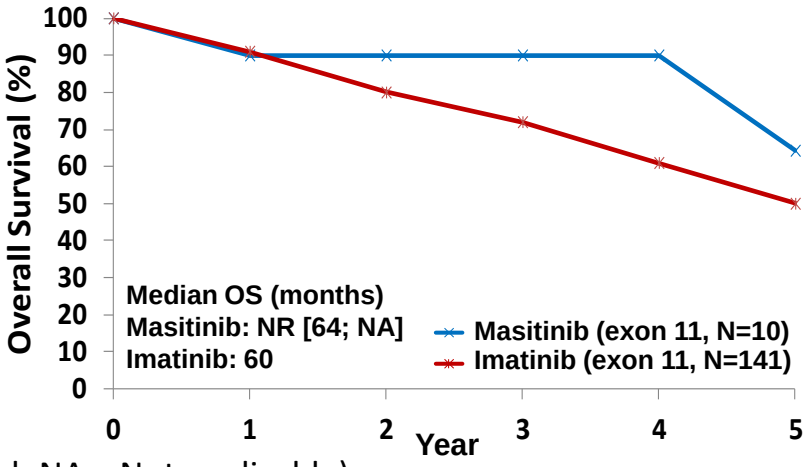

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