Masitinib: Long-term Efficacy Follow-up Data on Pivotal Phase 3 Study in the Treatment of Dogs with Measurable Grade II and III Mast Cell Tumors

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Objectives

- We conducted a multicenter, randomized, double-blind, placebo-controlled (4:1) clinical field study of 202 client-owned dogs, with or without prior treatment, having measurable cutaneous grade II or III mast cell tumors without nodal or visceral metastasis.
- The initial 6-month treatment period of this phase III clinical trial was to determine the safety and therapeutic potential of masitinib in dogs with cutaneous, non-metastatic, grade II or III mast cell tumors.
- Dogs with controlled disease (either complete response, partial response, or stable disease) upon completion of the initial protocol period could enter into a compassionate program and were monitored quarterly for survival status to dermine the long term efficacy potential of masitinib.

Procedures

- Masitinib was administered per os at a dose of 12.5 mg/kg/day
- We measured tumor response (complete, partial, stable) at 12 months and 24 months to evaluate Response rate, Time to Tumor Progression, and Progression Free Survival
- We recorded survival status at 12 months and 24 months to evaluate Progression Free Survival, Overall Survival, and Survival Rate

Follow-up study population

The follow-up data were analyzed in the overall study population and across 3 main clinically relevant subgroups (dogs with non resectable tumors, dogs in first line of treatment, and dogs with tumors expressing mutated c-kit).

Number of observed cases	Baseline		Month 12		Month 24	
	Masitinib	Placebo	Masitinib	Placebo	Masitinib	Placebo
All						
for tumor response	161	41	117	34	108	34
for survival status	161	41	145	38	120	31
Non resectable tumor						
for tumor response	106	26	76	23	68	23
for survival status	106	26	93	24	77	20
First line treatment						
for tumor response	67	18	48	16	42	16
for survival status	67	18	56	16	47	14
Mutated c-kit						
for tumor response	40	10	22	8	21	8
for survival status	40	10	35	9	31	8

Tumor Response Rate

Masitinib induced significant controlled disease rate at 12 months.

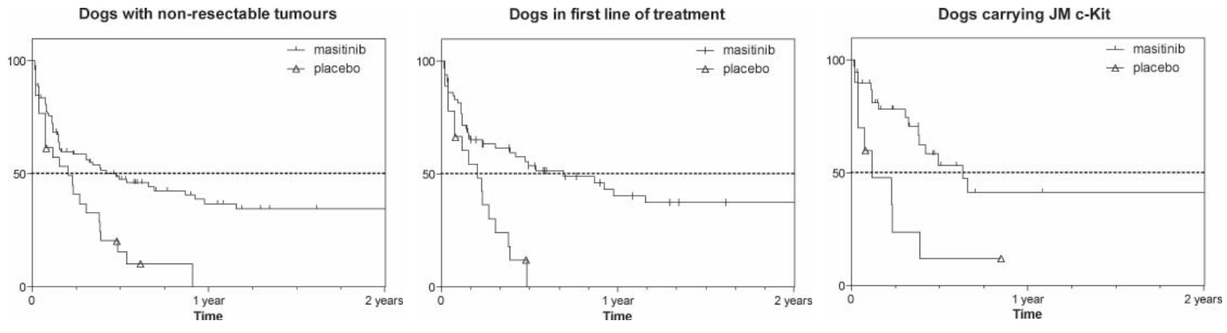
Masitinib was able to achieve complete responses at 12 months, sustainable at 24 months (14% in first line treatment, around 25% in dogs with mutated c-kit, around 13% in non resectable tumors, as opposed to 0% in placebo).

Time-point	12-month			24-month		
Groups	Masitinib	Placebo	Fisher's p-value	Masitinib	Placebo	Fisher's p-value
All						
Complete response	13 (11.1%)	1 (2.9%)	0.193	9 (8.3%)	1 (2.9%)	0.452
Controlled disease	27 (23.1%)	2 (5.9%)	0.026	14 (13%)	1 (2.9%)	0.119
Non resectable tumor						
Complete response	12 (15.8%)	0 (0%)	0.063	8 (11.8%)	0 (0%)	0.195
Controlled disease	24 (31.6%)	0 (0%)	<0.001	13 (19.1%)	0 (0%)	0.033
First line treatment						
Complete response	7 (14.6%)	0 (0%)	0.178	6 (14.3%)	0 (0%)	0.173
Controlled disease	19 (39.6%)	0 (0%)	0.002	9 (21.4%)	0 (0%)	0.052
Mutated c-kit						
Complete response	6 (27.3%)	0 (0%)	0.155	5 (23.8%)	0 (0%)	0.283
Controlled disease	7 (31.8%)	0 (0%)	0.143	6 (28.6%)	0 (0%)	0.148

Time to tumor progression

Masitinib significantly delayed time to tumor progression, in the overall population and in all subgroups of population.

Kaplan Meier estimate	Median [95%CI] (days)		Hazard ratio [95%CI]	Log-Rank
	Masitinib	Placebo		p-value
All	118 [83; 173]	75 [30; 140]	1.53 [1.03; 2.27]	0.033
Non resectable tumor	173 [84; 336]	75 [28; 138]	2.19 [1.34; 3.59]	0.001
First line treatment	253 [112 ;730]	75 [28 ;112]	2.86 [1.52 ;5.36]	<0.001
Mutated c-kit	230 [139; .]	42 [14; 141]	3.12 [1.32; 7.40]	0.006



Progression free survival

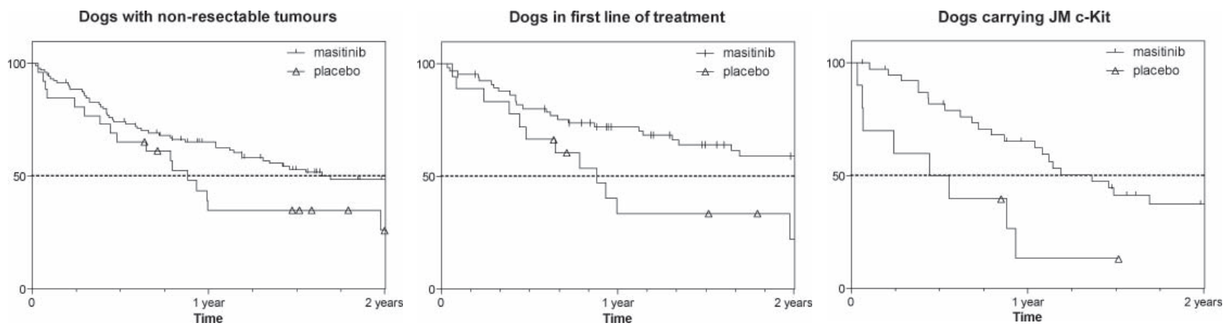
Masitinib significantly extended progression free survival in all subgroups of population

Kaplan-Meier estimate	Median [95%CI] (days)		Hazard ratio [95%CI]	Log-Rank
	Masitinib	Placebo		p-value
All	107 [77; 140]	75 [28; 140]	1.37 [0.94; 2.00]	0.099
Non resectable tumor	142 [60; 240]	79 [28; 138]	1.94 [1.21; 3.11]	0.005
First line treatment	181 [84 ;408]	76 [28 ;112]	2.47 [1.37 ;4.45]	0.002
Mutated c-kit	160 [138; 289]	62.5 [14; 141]	2.35 [1.08; 5.11]	0.025

Overall Survival

Masitinib significantly extended overall survival in first line of treatment and in dogs with mutated c-kit tumors

Kaplan-Meier estimate	Median [95%CI] (days)		Hazard ratio [95%CI]	Log-Rank
	Masitinib	Placebo		p-value
All	517 [396; 779]	340 [176; .]	1.15 [0.73; 1.80]	0.549
Non resectable tumor	617 [433; 938]	322 [176; 721]	1.63 [0.94; 2.83]	0.078
First line treatment	823 [600 ;.]	322 [176 ;721]	2.20 [1.11 ;4.38]	0.021
Mutated c-kit	498 [380; 792]	182 [24; 340]	2.91 [1.27; 6.70]	0.009



Survival Rate

Masitinib significantly increased survival rate at 24 months in first line of treatment and at 12 months in all subgroups of population

Time-point	12-month			24-month		
Groups	Masitinib	Placebo	Fisher's p-value	Masitinib	Placebo	Fisher's p-value
All	82 (56.6%)	16 (42.1%)	0.144	37 (30.8%)	7 (22.6%)	0.506
Non resectable tumor	57 (61.3%)	9 (37.5%)	0.041	28 (36.4%)	3 (15.0%)	0.105
First line treatment	38 (67.9%)	6 (37.5%)	0.042	23 (48.9%)	2 (14.3%)	0.030
Mutated c-kit	22 (62.9%)	1 (11.1%)	0.008	9 (29.3%)	0 (0.0%)	0.160

Prevention of metastasis

Masitinib significantly prevented the emergence of metastasis

Number (%) of dogs	All (N=202)	Treatment		
		Masitinib (N=161)	Placebo (N=41)	Fisher p-value
New cutaneous lesions	52 (25.7%)	41 (25.5%)	11 (26.8%)	0.844
Metastases to	13 (6.4%)	6 (3.7%)	7 (17.1%)	0.006
Lymph nodes	10 (5%)	5 (3.1%)	5 (12.2%)	0.031
Internal organs	5 (2.5%)	2 (1.2%)	3 (7.3%)	0.058

Conclusion

- In the overall study population of dogs with grade 2/3 mast cell tumors, non-resectable or recurrent post-surgery, masitinib significantly improved time to progression and significantly reduced the frequency of metastases to lymph nodes or internal organs. At 24 months, 8.3% of observed cases were still in complete response suggesting that masitinib was curative in this subset of patients. Finally, masitinib increased survival rate by 34.4% at 12 months (56.6% versus 42.1% under masitinib and placebo respectively) and by 36.3% at 24 months (30.8% versus 22.6% under masitinib and placebo respectively). Overall, median survival time was 517 days under masitinib versus 340 days under placebo (+177 days).
- In dogs with non-resectable tumors, masitinib significantly improved time to progression. At 12 months, tumor response (+21.5%, p=0.020) and controlled disease (+31.6%, p<0.001) rates were significantly higher under masitinib than under placebo. At 24 months, 11.8% of observed cases were still in complete response suggesting that masitinib was curative in this subset of patients and controlled disease rate remained significantly higher under masitinib than under placebo (+19.1%, p=0.033). Masitinib significantly increased survival rate by 63.5% at 12 months (61.3% versus 37.5% under masitinib and placebo respectively, p=0.041). Overall, median survival time was 617 days under masitinib versus 322 days under placebo (+295 days).
- In dogs in first line of treatment, masitinib significantly improved time to progression. At 12 months, controlled disease rate was significantly higher under masitinib than under placebo (+39.6%, p=0.002). At 24 months, 14.3% of observed cases were still in complete response suggesting that masitinib was curative in this subset of patients. Finally, masitinib increased survival rate by 81.1% at 12 months (67.9 versus 37.5% under masitinib and placebo respectively, p=0.042) and by 242% at 24 months (48.9% versus 14.3% under masitinib and placebo respectively, p=0.030). Overall, median survival time was 823 days under masitinib versus 322 days under placebo (+501 days, p=0.021).
- In dogs with tumors expressing mutated c-kit, masitinib significantly improved time to progression. At 24 months, 23.8% of observed cases were still in complete response suggesting that masitinib was curative in this subset of patients. Masitinib significantly increased survival rate by 467% at 12 months (62.9% versus 11.1% under masitinib and placebo respectively, p=0.008). At 24 months, all dogs under placebo had died while 29.3% of dogs under masitinib were still alive. Overall, median survival time was 498 days under masitinib versus 182 days under placebo (+316 days, p=0.009).

The study was supported by funding from AB Science

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