Masitinib is Safe and Effective in the Treatment of Dogs with Measurable Grade II and III Mast Cell Tumors

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Objective

- The purpose 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.
- 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.

Procedures

- Masitinib was administered per os at a dose of 12.5 mg/kg/day.
- No other treatment (chemotherapy, radiation therapy, or corticosteroids) was administered during the study period.
- Treatment effects were measured by time-to-tumor progression (TTP), progression-free-survival (PFS), response rate and toxicities.

Study Population included 202 dogs.

Parameter	Masitinib (n=161)	Placebo (n=41)	Total (n=202)
Age (years), mean ± SD	8.5 ± 3.0	8.7 ± 2.4	8.5 ± 2.8
Sex (Male), n (%)	68 (42.2%)	18 (43.9%)	86 (42.6%)
Time to treatment (months)	10.7 ± 19.3	12.0. ± 16.9	11.0 ± 18.8
Previous chemotherapy and/or radiotherapy			
Without, n (%)	122 (75.8%)	30 (73.2%)	152 (75.2%)
With, n (%)	39 (24.2%)	11 (26.8%)	50 (24.8%)
Surgical status			
Non-resectable	106 (65.8%)	26 (63.4%)	132 (65.3%)
Recurrent after surgery	55 (34.2%)	15 (36.6%)	70 (34.7%)
Line of treatment			
First-line	67 (41.6%)	18 (43.9%)	85 (42.1%)
Second-line or beyond	94 (58.4%)	23 (56.1%)	117 (57.9%)
KIT mutation status			
Mutated	40 (26.7%)	10 (25.6%)	50 (26.5%)
Wild type	110 (73.3%)	29 (74.4%)	139 (73.5%)
Tumor grade			
II	138 (85.7%)	35 (85.4%)	173 (85.6%)
III	23 (14.3%)	6 (14.6%)	29 (14.4%)

Safety

- 202 dogs were evaluated for safety (161 masitinib versus 41 placebo).
- 58 dogs entered the compassionate protocol, with up to 18 months of follow-up.
- 1199 adverse events occurred during the study. 88.8% of dogs in masitinib group had an adverse event in the course of treatment, versus 82.9% in the placebo group.
- The most frequently observed adverse events were diarrhea (36.6% versus 17.1%) and vomiting (46.0% versus 26.8%). These events were mild or moderate and short in duration.

	Diarrhea	Vomiting
Intensity Mild	86%	87%
Intensity Moderate	12%	10%
Duration		
Mean duration (days)	8	9
Occurence (% of treated dogs)		
After the first 90-days of treatment	21% (17% in placebo)	28% (27% in placebo)

- Other adverse events included fatigue, lethargy, and anorexia. The symptoms were reported equally in masitinib and placebo groups.
- Adverse events attributable to masitinib included neutropenia (6.2% versus 0% in placebo group), protein loss syndrome (6.8% versus 2.4% in placebo group), and hemolytic anemia (2.5% versus 0% in placebo group).
- Protein loss syndrome, characterized most consistently as proteinuria and hypoalbuminemia, resolved in 6/8 dogs. After experiencing severe proteinuria and hypoalbuminemia and developing subsequent decline in clinical condition, two dogs were euthanized. The protein loss syndrome was an unexpected event occurring in the masitinib and placebo-treated groups; though mild in the placebo group. The cause of this syndrome is unknown though Inhibition of PDFG-R is suspected.
- Hemolytic anemia was an unexpected event that occurred at a mean of 83 days of masitinib exposure.
- Decrease in neutrophil count was frequently observed with a 30% to 35% reduction when compared to baseline. Decreased neutrophil counts were associated with tumor response both in the placebo and masitinib groups.

Efficacy

Summary of masitinib Phase 3 Efficacy Results

		Median TTP (days)			Median OS (days)			OR at 6 months		
Category	N	Mb	Plc	*P*	Mb	Plc	*P*	Mb	Plc	*P*
All dogs	202	118	75	0.038	491	340	0.320	16.1	14.6	1.00
Non resectable	132	173	75	0.001	NR	340	0.149	22.6	7.7	0.10
Mutated KIT[a]	50	230	42	0.006	417	182	0.015	20.0	10.0	0.25
First-line										
All	85	253	75	0.001	NR	340	0.096	23.9	5.6	0.11
Mutated KIT[a]	25	NR	83	0.009	417	242	0.050	36.8	0.0	0.14
Wild-type KIT	53	253	66	0.008	NR	NR	0.722	20.9	0.0	0.18

Mb, masitinib; Plc, placebo; NR, not reached.

[a] Includes all mutations. Mutations were found in exons 8, 9, 11, 17, and all appear to cause constitutive activation of KIT (S. Letard et al., manuscript submitted).

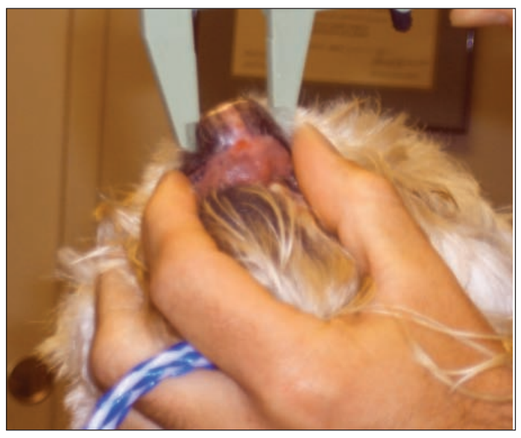
Objective Response Rate (ORR)

- There was no significant difference in ORR at day 112 and day168 for masitinib vs Placebo.

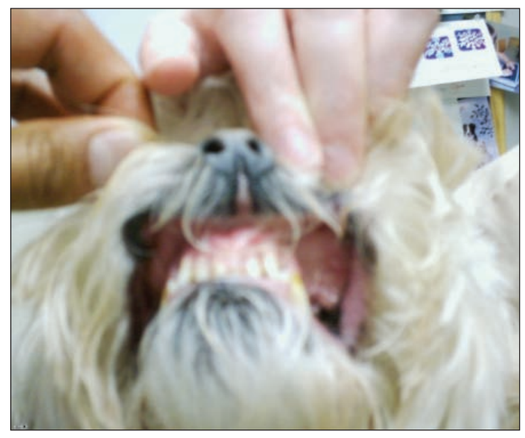
Masitinib Objective Responders

Einstein - 9 year old Shih Tzu Mix (Grade III MCT on Nostril and Upper Lip)

10/6/05
Day 0 - Pretreatment



12/29/05
Day 84 - Complete Response (CR)



CR-860+ Days (Continues to receive masitinib)

Time to Progression

- In the overall population, masitinib was significantly better than placebo on TTP (+43 days, P=0.038), with a trend of superiority on median OS (+151 days).
- In non-resectable tumors, masitinib was significantly better than placebo on TTP (+98 days, P=0.001), with a trend of superiority on median OS (Not reached versus 340 days) and on ORR at 6 months (22.6% versus 7.7%).
- In tumors expressing mutated c-Kit, masitinib was significantly better than placebo on TTP (+188 days, P=0.006), on median overall (+235 days, P=0.015).
- In first-line treatment, regardless of c-Kit status, masitinib was significantly better than placebo on TTP (+178 days, P=0.001).

Best Response Rate

Total population (n=202) Missing response data on 24 cases = response failure	
Placebo (n=41)	Masitinib (n=161)
12 (29%)	80 (50%)
p=0.02 (Chi square test)	

Conclusions

- Masitinib appears to be safe and effective at delaying tumor progression in dogs with recurrent or nonresectable grade II or grade III nonmetastatic MCT. This effect was more pronounced when masitinib was used as first-line therapy, regardless of whether the tumors expressed mutant or wild-type KIT.

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