



# The Efficacy of Targeted Therapy in Veterinary Medicine

## Newsletter – September 2009

### Message to our readers

Welcome to the inaugural issue of the Masivet® Newsletter, a publication which is intended to share information and important clinical updates with the veterinary community. On November 17, 2008, the tyrosine kinase inhibitor, Masivet®, received European Medicines Agency approval for the treatment of canine mast cell tumors. This marked the first-ever approval of a drug for veterinary oncology. I hope that you will take the time to read and reflect on the contents of this monthly newsletter. We look forward to hearing back from you on your clinical experiences with Masivet®. Our commitment is to continuously innovate and build on the success of our first product. For those of you who are interested in participating in AB Science clinical trials, please be sure to read the section titled "Clinical Development Program with Masivet®".

In closing, I would like to thank you each and every one of you for your support. We look forward to being able to provide you and your patients with world-class medicines. It is an exciting time in veterinary oncology and we are proud to be able to help advance veterinary medicine through our commitment to innovation.

### How to order Masivet®

Masivet® can only be ordered by practitioners of veterinary medicine.

#### Online ordering and payment

If you are already registered with AB Science, you should have received a client ID number and password, which you may use to log in and order directly from our secured website [www.masivet.com](http://www.masivet.com). If not, please contact us at [masivet@ab-science.com](mailto:masivet@ab-science.com)

In the Masivet® website

- Click on "How to Order", and then on "Order". This will lead you to our Masivet® Ordering website
- Enter your client id number and password
- Select the quantities you wish to order
- Make online payment. You will immediately receive via email an acknowledgement confirming that your order is being processed.

If you are not yet registered with us, you need to open a client account. The process is very simple and only requires a few minutes of your time.

In the Masivet® website

- Click on "How to Order", and then on "Register". This will lead you to our Client Account Opening form
- Complete this form, and click on the Send button at the bottom of the page
- You will immediately receive via email an acknowledgement confirming that your account opening form has been received
- You will be contacted to confirm your professional eligibility to receive Masivet®
- Once your account is validated, you will receive via email your client id number and password, which you can use immediately to order Masivet®. The process usually takes less than few hours to complete.

#### Alternative

If online ordering and payment is not convenient, and you prefer to send us a purchase order first and make payment separately, please follow these instructions

In Masivet® website

- Click on "How to Order", and then on "Print Order Form"
- Complete the form and send it by fax at +33 1 4720 2411 or via email in pdf at [masivet@ab-science.com](mailto:masivet@ab-science.com)
- You will be contacted to confirm your order and any other information we may need to process your order
- Once your order is validated and processed, we will send you an invoice with details to make payment by check or wire transfer.

### Key Efficacy Information on Masivet® from the pivotal study follow-up

**Masivet® significantly increased long-term survival in grade 2/grade 3 non resectable MCT**

Time point	12 months		24 months	
	Masivet® N=95	Placebo N=25	Masivet® N=83	Placebo N=20
Number (%) of dogs alive	59 (62.1%)	9 (36.0%)	33 (39.8%)	3 (15.0%)
Fisher's p-value	0.024		0.040	

**Masivet® has demonstrated anti-metastatic potential:** In the pivotal study, the emergence of internal and lymph nodes metastases was much lower in the Masivet®-treated dogs (3.7% versus 17.1% for placebo,  $p=0.006$ ).



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## Optimising use of Tyrosine Kinase Inhibitors (TKIs) in Oncology

Unlike with chemotherapy, where the goal is to achieve a disappearance of the tumour (if not reached the survival time is worsened), the survival time with TKIs is improved as long as the tumour is not progressing. Therefore, **tumor control, and not tumor response, is the most important parameter with this class of drugs.**

**Tumour control at 6 months is predictive of long-term survival.** Response at 6 weeks is not predictive of long-term survival

Tumour Assessment at <b>6 weeks</b>	Alive at 12 months	Alive at 24 months
Responders (CR+PR)	60.8%	35.4%
Non-responders (SD+PD)	54.7%	28.2%
Tumour Assessment at <b>6 months</b>	Alive at 12 months	Alive at 24 months
Complete Response (CR)	93.3%	76.9%
Partial Response (PR)	100%	71.4%
Stabilisation (SD)	94.4%	80.0%
<b>Controlled Disease (CR+PR+SD)</b>	<b>95.1%</b>	<b>77.1%</b>
<b>Progressive Disease (PD)</b>	<b>41.4%</b>	<b>11.8%</b>

## Post Registration Case Reports

*These case reports should not be interpreted as an evidence of efficacy of Masivet® in the indications reported.*

We received numerous reports from the veterinary community on results with Masivet®. We would like to share these results with you. We encourage you to continue submitting cases of interest so that they can be shared to the broader community through this newsletter.

### In mast cell tumours

The first feedback from compassionate use confirmed a significant potential of Masivet® in chemo-multi-resistant and metastatic tumors. Dr Johan De Vos (Netherland) treated 15 cases of advanced MCTs with a response rate of 80%, including 66% of complete responses (CR). Control disease rate was 87% in this cohort.

Dog's name	Previous treatments	MCT grade	Metastases	Best response
Gizmo	chemo-resistant	grade 2		CR
Bo	chemo-resistant	grade 3	Yes	CR
Bongo	chemo-resistant	grade 3	Yes	CR
Tommie	Multiple chemo-resistant	grade 2		SD
Bunker	Multiple chemo-resistant	grade 2		PD
Doortje	Incomplete resection, multiple chemo-resistant	grade 3		CR
Porkie		NA	Yes	PD
Murphy	Prednisolone	grade 3	No	PR
Terra	Incomplete resection	grade 2	Yes	CR
Bowie	Too old for chemo !! (27 y.o.)	NA		PR
Lindy		grade 3		CR
Spikey	Incomplete resection	grade 3		CR
Lara	Recurrence post-surgery, chemo-intolerant	grade 2		CR
Moirra	Incomplete resection	grade 3		CR
Bailey	Recurrence post-radiation	grade 3		CR



Bongo (6y-old Shar Pei), presented with stage 3b, recurrent, metastatic, grade III MCT in the left tarsal region that was resistant to chemotherapy. A rapid improvement was observed within 7 days of treatment:

- Tumour volume decreased,
- Tumour ulceration progressively healed
- Lymph nodes were normal,
- Quality of life improved.

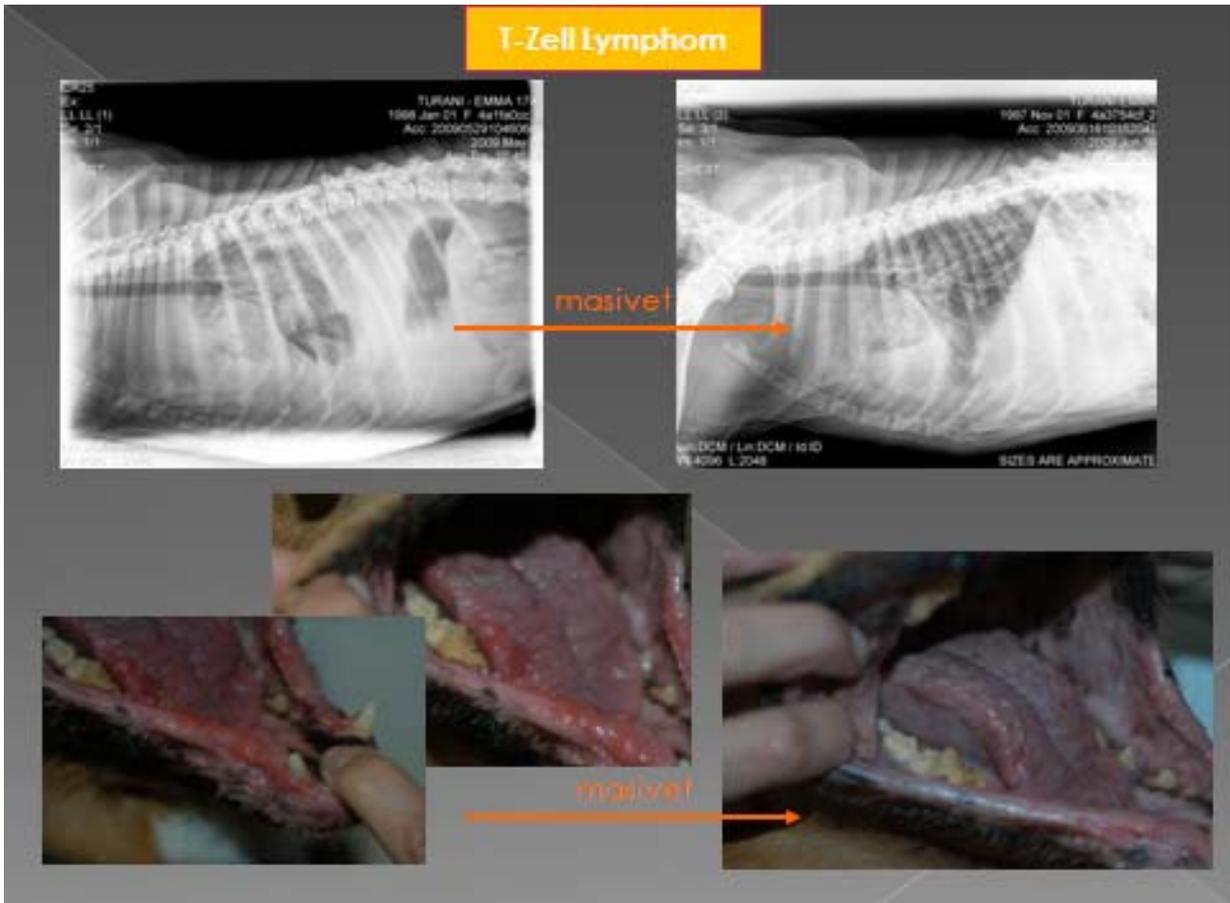
## T-cell lymphoma

In vitro, T-cell lymphoma cell lines have been shown to be particularly sensitive to the anti-proliferative action of Masivet® (*Masitinib is a chemosensitizer of canine tumor cell lines, DH Thamm et Al. 2008 VCS Annual Conference*).

Dr. L. Marconato (Italy) used Masivet® in two dogs with T-cell lymphoma with positive response, including one dog who is in complete remission.

- The first case is a T-cell mediastinal lymphoma. The dog was a labrador fs 12 years old. The dog was treated w CHOP-based protocol for 9 weeks, but disease progressed. She had massive pleural effusion. After 14 days the effusion decreased significantly. Subsequently, the disease progressed.
- The second case is a T-cell epitheliotropic lymphoma in the oral cavity (staging negative). The dog was a mixed-breed, fs, 11 years old. 14 days after having started Masivet®, she obtained complete remission. Then concurrent treatment with lomustine was initiated. The dog is still being treated w lomustine and Masivet®, and is in complete remission.





**Neurofibrosarcoma**

Dr. Arno Roos (Netherlands) used masitinib to treat a neurofibrosarcoma with a positive response.

Tara is an 11 year old mixed breed female dog, who was diagnosed in October 2007 with a neurofibrosarcoma. The tumour recurred despite treatment surgery and chemotherapy. Despite receiving metronomic therapy with endoxan and metacam since February 2009, the tumour grew rapidly. Treatment with Masivet® was initiated in April 2009. The tumor shrunk rapidly from over 5x4cm to 3x3cm. This efficacy may be explained by mast cells inhibition. This rationale was first hypothesised in by Badache A. et Al. in Oncogene. 1998 Aug 13;17(6):795-800. (Expression of Kit in neurofibromin-deficient human Schwann cells: role in Schwann cell hyperplasia associated with type 1 neurofibromatosis.)



## Clinical Development Program with Masivet®

Masivet® has an adequate profile for the control of mast cell dysfunction via inhibition of c-Kit and Lyn, and may also enhance the sensitivity of chemo-resistant tumours to cytotoxic chemotherapy, via inhibition of platelet-derived growth factor receptors (PDGFR  $\alpha$  and  $\beta$ ) and the Lyn/FAK pathway.

As a result, Masivet® is currently developed in the following oncology and inflammatory indications.

Species	Area	Indication	Treatment arms	Status
Dog	Oncology	Melanoma expressing mutated c-kit	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Merial vaccine</li> </ul>	Phase 2
		Melanoma expressing Non-mutated c-kit	<ul style="list-style-type: none"> <li>Doxorubicin + Masivet®</li> <li>Merial vaccine</li> </ul>	Phase 2
		T-cell lymphoma	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Doxorubicin + Masivet®</li> <li>Doxorubicin</li> </ul>	Phase 2
		Haemangiosarcoma	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Doxorubicin + Masivet®</li> <li>Doxorubicin</li> </ul>	Phase 2
		Histiocytic sarcoma	<ul style="list-style-type: none"> <li>Vinblastine + Masivet®</li> </ul>	Phase 2
		Osteosarcoma (post amputation)	<ul style="list-style-type: none"> <li>Carboplatin + Masivet®</li> <li>Gemcitabine + Masivet®</li> <li>Carboplatin</li> </ul>	Phase 2
		Bladder cancer	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Chemotherapy + Masivet®</li> </ul>	Phase 2
		Mammary tumours	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Chemotherapy + Masivet®</li> </ul>	Phase 2
	Inflammatory Disease	Atopic dermatitis	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Placebo</li> </ul>	Phase 3
		Arthritis	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Placebo</li> </ul>	Phase 2
Inflammatory Bowel Disease		<ul style="list-style-type: none"> <li>Masivet®</li> <li>Placebo</li> </ul>	Phase 2	
Cat	Inflammatory Disease	Asthma	<ul style="list-style-type: none"> <li>Masivet®</li> <li>Placebo</li> </ul>	Phase 2

*This list of indications reflects the development program of Masivet® in veterinary medicine and should not be interpreted as a list of indications in which Masivet® demonstrated efficacy.*

## Contact Us

For commercial inquiries: Please contact us at [masivet@ab-science.com](mailto:masivet@ab-science.com).  
 Detection of c-Kit mutation can be purchased from AB Science. For inquiries, please contact us at the above email address.

For clinical inquiries: To learn more about our on-going clinical development program with Masivet®, please contact us at [clinical@ab-science.com](mailto:clinical@ab-science.com)

