The Efficacy of Targeted Therapy in Veterinary Medicine

Kinavet CA1® tablets are indicated for the treatment of recurrent (post surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

Mast Cell Tumor

Description and epidemiology

Mast cell tumor (MCT), also known as a mastocytoma, is the most common cutaneous malignant neoplasm in dogs, accounting for 16 to 21% of all skin tumors. The behavior and progression of MCTs are highly heterogeneous. They range from well differentiated, slow-growing tumors with a low potential for metastasis; to undifferentiated, aggressive tumors with a high potential for metastasising to local lymph nodes, the liver, spleen and bone marrow.

Signs

The appearance of MCTs can be varied, from a wart-like nodule or a soft subcutaneous lump (similar on palpation to a benign lipoma) to an ulcerated skin mass. All lumps should be checked by fine needle aspiration. They are usually solitary, but in many cases there are multiple MCTs.

Manipulation of the tumor may result in redness and swelling from release of mast cell granules, also known as Darier’s sign, and prolonged local hemorrhage. In cases of highly malignant tumors, signs may also include loss of appetite, vomiting, diarrhea and anemia. The presence of these signs usually indicates the spread of mast cells throughout the body. If a large amount of histamine is released at one time, it can result in ulceration of the stomach and duodenum (present in up to 25% of cases), or disseminated intravascular coagulation. When metastasis does occur, it is usually to the liver, spleen, lymph nodes and bone marrow.

Mast cell tumor grading

A surgical biopsy is required to determine the grade of the tumor (from Grade I: low potential for metastasis, to Grade III: highly aggressive metastasis). The grade depends on how well the mast cells are differentiated, mitotic activity, location within the skin, invasiveness and the presence of inflammation or necrosis. To better assess the proliferative activity in the tumor biopsy and the prognostic, it is useful to stage the tumor using Ki-67, especially for Grade II MCTs.

Mast cells and c-Kit

Mast cell tumors are formed by the uncontrolled proliferation of neoplastic mast cells. Normal mast cells are also involved in this over proliferation, first being attracted by mediators released from mast cells at the tumor site, then participating through release of their own mediators. The proliferation and survival of mast cells are controlled by c-Kit, the receptor of the stem cell factor (SCF). C-Kit is a receptor tyrosine kinase regulating mast cell growth, differentiation, degranulation and survival, via multiple kinase pathways. Because of this mechanism, Kinavet CA1® inhibits c-Kit dependent mast cell proliferation and induces apoptosis.

Kinavet CA1® is a tyrosine kinase inhibitor

Masitinib, the active ingredient of Kinavet CA1®, specifically and selectively targets various isoforms of c-Kit, including wild-type c-Kit and constitutively active c-Kit mutations in the extracellular domain (exons 8 and 9) or the juxtamembrane domain (exon 11), which are found in 30% of MCTs. Because of this mechanism, Kinavet CA1® inhibits c-Kit dependent mast cell proliferation and induces apoptosis.

Kinavet CA1® also inhibits PDGFR, FGFR3, Lyn and FAK, presenting interesting perspectives for treatment of other cancers and for preventing metastasis proliferation as a single or combined anticanter agent. Moreover, Kinavet CA1’s mechanism of action in controlling the proliferation, differentiation and degranulation of mast cells suggests potential benefits for other mast cell dysfunctions and related complications.

Kinavet CA1® is Efficient in Grade II/III MCTs

Study design of the Kinavet CA1® registration clinical trial

The clinical trial conducted by AB Science to demonstrate the efficacy of masitinib in the treatment of MCT was a multicenter, multinational, randomized, double-blind, placebo-controlled (4:1), 2 year follow-up study.

The population studied was formed by 202 client-owned dogs with either Grade II or Grade III cutaneous MCTs, non resectable or in recurrence after surgery without nodal or visceral metastases. Three criteria have been evaluated: MCT response, time-to-progression (TTP) and survival.

Kinavet CA1® significantly delays TTP

Surgery remains the option of choice whenever possible, however, when the tumor is not resectable, Kinavet CA1® proved to be significantly effective in delaying tumor progression (173 versus 75 days; p=0.001) regardless of the presence or absence of the mutation on c-Kit. TTP was improved in the Placebo mutant form (241 versus 83 days; p=0.002) or wild-type form of c-Kit (140 versus 75 days; p=0.027).

Kinavet CA1® improves 12 and 24 month survival rates

Survival rates at 12 and 24 months in dogs in nonresectable tumors

<table>
<thead>
<tr>
<th>Survival rates</th>
<th>12-months</th>
<th>24-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinavet CA1® (n=95)</td>
<td>Placebo N=25</td>
<td>Kinavet CA1® (n=83)</td>
</tr>
<tr>
<td>Alive</td>
<td>59 (62.1%)</td>
<td>9 (36.0%)</td>
</tr>
<tr>
<td>Fisher’s p-value</td>
<td>0.024</td>
<td>0.030</td>
</tr>
</tbody>
</table>

It is important to note that complete response rate at 24 months was observed regardless of the presence of c-Kit mutations:

• 15.8% of dogs with mutated c-Kit tumors
• 5.2% of dogs with wild-type c-Kit tumors

Kinavet CA1® has an anti-metastatic potential

Kinavet CA1® affects other tumoral processes such as metastasis. As demonstrated in this clinical study, the instance of internal and lymph node metastases was much lower in the Kinavet CA1® treated dogs (p=0.006). This effect is possibly explained by the combined inhibition of Lyn, FAK, PDGFR and mast cell activation. This leads to lower angiogenesis, lower adhesion, lower invasion, and therefore, lower metastasis.
A New Paradigm in Veterinary Oncology Therapy

It is the control of the tumor that is correlated to survival

With the introduction of tyrosine kinase inhibitors (TKI) in the treatment of human cancer, came also a change in the treatment objectives. Unlike in chemotherapy, where the goal is to achieve a disappearance of the tumor, the survival with TKIs in veterinary medicine is improved as long as the tumor is not progressing. TKIs have the ability to stop progression of the tumor, thereby, resulting in a longer survival time even when a tumor is still present but controlled.

Assessment of response and progression at 6 months is more appropriate than 6 weeks

Due to a wide variation in the size and morphology of MCTs, a 6 week short-term response (response rate according to the WHO size-based definition) appears to be an erroneous assessment of a TKI’s effectiveness and not predictive of survival.

Long-term survival versus tumor assessment at 6 weeks and 6 months

<table>
<thead>
<tr>
<th>Tumor assessment at 6 weeks</th>
<th>Alive at 12 months</th>
<th>Alive at 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (CR+PR)</td>
<td>60.8%</td>
<td>35.9%</td>
</tr>
<tr>
<td>Non-responders (SD+PD)</td>
<td>54.7%</td>
<td>28.2%</td>
</tr>
<tr>
<td>Tumor assessment at 6 months</td>
<td>Alive at 12 months</td>
<td>Alive at 24 months</td>
</tr>
<tr>
<td>Complete Response (CR)</td>
<td>93.3%</td>
<td>76.9%</td>
</tr>
<tr>
<td>Partial Response (PR)</td>
<td>100%</td>
<td>71.4%</td>
</tr>
<tr>
<td>Stabilisation (SD)</td>
<td>94.4%</td>
<td>80.0%</td>
</tr>
<tr>
<td>Controlled Disease (CR+PR+SD)</td>
<td>95.1%</td>
<td>77.1%</td>
</tr>
<tr>
<td>Progressive Disease (PD)</td>
<td>41.4%</td>
<td>11.8%</td>
</tr>
</tbody>
</table>

Study results show that survival probabilities are similar between responders and stabilized patients. Tumor response was evaluated at 6, 12 and 24 months. After 2 years of treatment, the median survival was not reached for dogs with controlled disease at 6 months. Indeed, 77% of dogs with controlled disease at 6 months are still alive after more than 2 years of follow up. In conclusion, tumor response to TKI treatment at 6 months is predictive of long-term survival.

Masitinib Clinical Development Program

Although Kinavet CA1® is a highly selective kinase inhibitor, its target profile leads to numerous therapeutic possibilities.

Several other canine cancer indications are being investigated for masitinib, including lung, pancreas, colon and multiple myeloma. The beneficial action of Kinavet CA1® in oncology results from the ability of Kinavet CA1® to: (1) block the proliferation of tumoral cell lines; (2) slow down tumor progression and reduce the emergence of metastases; and (3) potentiate the effect of cytotoxic chemotherapies in various cancer cell lines, including melanoma, osteosarcoma, hemangiosarcoma, histosarcoma, for combination therapies.

Mast cells are involved in normal immune reactions, as well as pathological reactions observed in chronic inflammatory diseases, such as atopic dermatitis, asthma, irritable bowel syndrome and rheumatoid arthritis. By merit of a combined inhibition on c-Kit and Lyn, Kinavet CA1® is particularly efficient in controlling the proliferation, differentiation and degranulation of mast cells. Thus, Kinavet CA1® has further potential in the treatment of mast cell dysfunctions and related complications.

The following clinical development program for Kinavet CA1® has been implemented.

**Oncology:**
- Phase 3 pivotal study in the treatment of canine mast cell tumor (Japan)
- Phase 2 study in canine melanoma (single agent and in combination with doxorubicin)
- Phase 2 study in canine T cell lymphoma (single agent / doxorubicin combination)
- Phase 2 study in canine haemangiosarcoma (single agent / doxorubicin combination)
- Phase 2 study in canine histiocytoma (vinblastin combination)
- Phase 2 study in canine osteosarcoma (carboplatin and gemcitabin combinations)

**Inflammatory diseases:** Kinavet CA1® as a single agent
- Phase 3 pivotal study in canine atopic dermatitis
- Phase 2 in canine arthritis
- Phase 2 in canine inflammatory bowel disease
- Phase 2 in feline asthma

How to Use Kinavet CA1®

Kinavet CA1® is an easy-to-use oral therapy

Indication: The treatment of recurrent (post surgery) or nonresectable Grade II or III cutaneous mast cell tumors in dogs that have not previously received radiotherapy and/or chemotherapy except corticosteroids.

Contraindications: Do not use Kinavet CA1® in dogs suffering from liver or renal function impairment and in dogs with anemia or with neutropenia.

Dosage: 12.5 mg/kg once daily.

Administration: Oral route. Gloves do not need to be worn to safely handle Kinavet CA1®. To avoid exposure to drug, wash hands with soap and water after administering. Not for use in humans. Keep this and all medications out of the reach of children. Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to the handling precautions on the label. Kinavet CA1® may harm an unborn baby (cause birth defects).

Kinavet CA1® is well tolerated

The most frequent adverse reactions were:
- Mild to moderate diarrhea and vomiting are commonly reported. These symptoms are partially linked to the tumor itself, and manageable with a symptomatic treatment (anti-H2).
- Decreased appetite, asthenia, peripheral edema and alopecia were observed in 3 to 10% of dogs.
- Generally moderate anemia, hemolysis anemia and ALT increase were described in 2 to 3% of dogs.
- Mild to moderate diarrhea and vomiting are commonly reported. These symptoms are partially linked to the tumor itself, and manageable with a symptomatic treatment (anti-H2).
- Decreased appetite, asthenia, peripheral edema and alopecia were observed in 3 to 10% of dogs.
- Generally moderate anemia, hemolysis anemia and ALT increase were described in 2 to 3% of dogs.

Dogs must be monitored carefully and professional judgment should be used to determine the need for dose reduction in the event of possible significant adverse reaction.

Please refer to the package insert for dose adjustment rules.

Effective use has not been demonstrated for Kinavet CA1®. A reasonable expectation of effectiveness for conditional approval was based on TTP in a subpopulation of dogs.

It is a violation of federal law to use this product other than as directed in the labeling.

For more information or to order Kinavet CA1®, please call 973-218-2436.

---