

## STANDARD ARTICLE

# Recurrence-free interval 12 months after local treatment of mast cell tumors in dogs using intratumoral injection of tigilanol tiglate

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[Correction added on 27 January 2021, after first online publication: In the results section, “At 6 months, 66 patients were evaluable with 91% (60/66) remaining recurrence free. The evaluable patients decreased by 3% (2/66) from 6 to 12 months...” has been changed to, “At 6 months, 67 patients were evaluable with 90% (60/67) remaining recurrence free. The evaluable patients decreased by 4% (3/67) from 6 to 12 months...”]

**Abstract**

**Background:** Tigilanol tiglate (TT) is a novel small molecule approved by the European Medicines Agency for intratumoral treatment of mast cell tumors (MCTs) in dogs. In a randomized controlled clinical efficacy and safety study in the United States, 85 of 116 dogs that received a single TT injection achieved complete response (CR) of the treated MCT by day 28.

**Objective:** To evaluate the durability of the TT treatment response achieved at day 28 in the U.S. study by assessing MCT recurrence at the treatment site 6 and 12 months after TT administration.

**Animals:** Eighty-five dogs previously treated with TT.

**Methods:** Dogs that achieved CR at day 28 were assessed retrospectively for the presence or absence of MCT at the treatment site using records from clinical visits and telephone interviews with owners. Dogs unavailable at an assessment time were considered lost-to-follow-up and data for their last assessment used in the final analysis.

**Results:** By 12 months after TT treatment, 64 dogs remained evaluable, with 21 unavailable. Of evaluable patients, 57 (89%) remained tumor free at the treatment site and 7 (11%) had developed recurrence. All recurrences occurred within the first 6 months, predominantly (5/7, 71%) within the first 12 weeks.

**Conclusions and Clinical Importance:** Tigilanol tiglate provided a durable long-term local response for the treatment of MCT in dogs.

**KEYWORDS**

dog, EBC-46, intratumoral, MCT, surgical margins, tumor recurrence

**1 | INTRODUCTION**

Tigilanol tiglate (TT, also known as EBC-46) is a novel diterpene ester. The drug received registration approval from the European Medicines Agency in January 2020 for the treatment of nonresectable,

**Abbreviations:** CT, computed tomography; CR, complete response; HTFM, histologically tumor-free margins; MCT, mast cell tumor; TT, tigilanol tiglate (also known as EBC-46).

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	Time since TT treatment		
	Day 84	6 mo	12 mo
<i>Patient availability for evaluation at each assessment time</i>			
Number of dogs available for evaluation.	82	67	64
Cumulative number of dogs lost to follow-up comprising:			
(a) Loss of contact with owners.	1	15	16
(b) Died (unrelated to MCT disease).	2	3	5
<i>Assessment of MCT recurrence at the treatment site</i>			
Number of dogs with no recurrence at treatment site at each assessment time.	77	60	57
% of evaluable dogs with no recurrence at the treatment site at each assessment time.	94	90	89
Number of dogs where recurrence at treatment site is first recorded by each assessment time.	5	2	0
Cumulative incidence of recurrences at the treatment site by each assessment time.	5	7	7

Abbreviations: MCT, mast cell tumor; TT, tigilanol tiglate.

**TABLE 1** Summary, at each of three assessment times, of (a) the number of dogs available for evaluation of MCT recurrence at the treatment site, (b) sources of attrition of the dogs lost to follow-up, (c) number and % of evaluable dogs that had no MCT recurrence, and (d) number of MCT recurrences at the treatment site [Correction added on 27 January 2021, after first online publication: In Table 1, column “6 mo”: 66 has been changed to 67 and 91 has been changed to 90.]

**TABLE 2** Summary of age and tumor characteristics of the 5 dogs that died within 12 months of administration of single intratumoral injection of tigilanol tiglate

Time of recorded death	Patient age (years)	Tumor location	Tumor cytological grade	Target tumor	Cause of death, reason for euthanasia
Day 84	10	Thigh	Low suspected	CR	Primary OSA
Day 84	8	Hock	Low	CR	Pelvic mass/VC thrombosis
12 mo	8	Thorax	Low	CR	Unknown
12 mo	10	Axilla	Low	CR	Primary HGMCT, metastatic MCT
12 mo	12	Stifle	No grade available	CR	Syncope

Abbreviations: HGMCT, high-grade mast cell tumor; MCT, mast cell tumor; OSA, osteosarcoma; VC, vena cava.

nonmetastatic cutaneous mast cell tumor (MCT) and nonresectable, nonmetastatic SC MCT at or below the elbow or hock in dogs.<sup>1</sup> When administered intratumorally, TT elicits a rapid but localized inflammatory response with concurrent recruitment of immune cells, loss of tumor vasculature integrity, and induction of tumor cell death by oncosis.<sup>2-4</sup> The result is hemorrhagic necrosis and destruction of the tumor within 2 to 7 days, tumor slough by day 14, followed by resolution of the resulting wound.<sup>2,5</sup>

The efficacy and safety of TT for intratumoral treatment of MCT in dogs have been investigated in a randomized, sham-controlled, investigator- and owner-masked clinical study involving 123 dogs completed in the United States between 2016 and 2018.<sup>5</sup> In that study, dogs with eligible cutaneous or SC MCT (confirmed by fine-needle aspiration), were recruited at 11 participating veterinary clinics. The study had 2 phases. In the first phase, dogs were randomized in a 2 : 1 ratio to the TT treatment or control group. In the second phase, patients in both the TT-treated and control groups that did not achieve a complete response (CR) using Response Evaluation Criteria in Solid Tumors criteria<sup>6</sup> at day 28 were eligible to receive a treatment of TT at day 30. Patients in both phases were assessed at day 84 after

TT treatment.<sup>5</sup> In both phases of the study, 85 of the 116 dogs that had received a single TT treatment achieved CR at day 28, with no tumor recurrence in 94% of these dogs by day 84.<sup>5</sup> Here we evaluate the durability of this initial response to TT treatment by assessing the incidence of local MCT recurrence at the TT treatment site at 6 and 12 months after TT administration.

## 2 | METHODS

Medical records from eligible patients who participated in the U.S. efficacy study<sup>5</sup> were evaluated retrospectively. In that study, dogs with cutaneous MCTs located anywhere on the body and dogs with SC MCTs located at or distal to the elbow or hock were eligible for enrollment. Patients with documented metastatic disease were excluded because the aim of the study was evaluation of local tumor efficacy at day 28. Fine-needle aspirates of target MCTs were taken for subsequent cytological grading using the Scarpa method<sup>7</sup> by independent pathologists at the IDEXX Laboratory. Cytological grading was established as the grading method

**TABLE 3** Summary of age and tumor characteristics of the 7 dogs in which an mast cell tumor recurred at the treatment site during the 12 months after administration of single intratumoral injection of tilganol tiglalte

Time of recurrence	Patient age (years)	Tumor location	Tumor cytological grade	Tumor volume at treatment (cm <sup>3</sup> )
Day 84	11.2	Trunk	High	2.6
Day 84	11.6	Upper limb	Low	1
Day 84	7.0	Head	Low	1.8
Day 84	13.1	Lower limb	Low	9.1
Day 84	7.7	Head	Low	0.6
6 mo	7.9	Trunk	High suspected	0.3
6 mo	3.5	Upper limb	Low	1

instead of histological grading to minimize potential leakage of intratumoral TT through the biopsy procedure sampling site.<sup>5</sup> Eligible patients were randomized 2 : 1 to either the TT or untreated control group. Inclusion criteria for this follow-up cohort were patients who (a) achieved a CR at day 28 after a single intratumoral treatment in either the first or second phase of the clinical trial and (b) were available for follow-up over the first 12 months after TT treatment.

Data for the day 84 assessment of the tumor treatment site were collected under the original study protocol, whereas that for the subsequent 6 and 12 month assessment times were gathered (between June and August 2019) by staff at the participating clinics. These data were collated from medical records, including patient examinations, communication with owners, or both. If medical records indicated the patient was alive with no tumor recurrence at the last recorded visit, owners were contacted for further information where possible. Information confirming local tumor recurrence was recorded where applicable and the patient removed from further assessment. Deaths among the patients over the 12-month period were classified by the clinical investigators as either related or unrelated to MCT disease. Patients were deemed unavailable for assessment at a timepoint if the owner could not be contacted or in the event of death of the patient.

### 3 | RESULTS

Demographics and tumor characteristics for the 85 dogs that had achieved CR 28 days after a single TT treatment in the U.S. efficacy study are summarized in Table S1.

Over the period from day 84 to 12 months after TT treatment, the number of dogs available for evaluation decreased from 82 to 64 dogs (Table 1) with most of this attrition (76%; 16/21 dogs) caused by loss of contact with owners. No local recurrence of MCT was observed at the treatment site in most dogs available for evaluation at each assessment time (Table 1). At 6 months, 67 patients were evaluable with 90% (60/67) remaining recurrence free. The evaluable patients decreased by 4% (3/67) from 6 to 12 months with 89% (57/64) remaining recurrence free at 12 months after TT treatment. Local recurrence of MCTs at the treatment site only was recorded in 7 dogs (Table 1). All of these recurrences occurred within the first 6 months after treatment, with the majority (71%, 5/7) occurring before the end of the initial study at day 84 (Table 1). One dog with

recurrence of a high-grade MCT at the treatment site at 6 months concurrently developed additional MCTs elsewhere on the body and subsequently was euthanized. The remaining 5 dogs that died within 12 months of treatment were recurrence free at the target tumor treatment site (Table 2). One of these 5 dogs developed a high-grade MCT at a different anatomical site on the contralateral thorax with subsequent lymph node metastasis. This patient's target tumor was located in the axilla, low grade, and the dog remained recurrence free (Table 2) at the time of euthanasia.

Because of the small number of patients (n = 7) in which MCT recurred at the treatment site, statistical analysis was not performed to evaluate correlation between patient age, tumor location on the body, tumor cytological grade, or tumor volume and the potential for local recurrence at the TT treatment site (Table 3).

### 4 | DISCUSSION

Our results build on previously published findings from a U.S. clinical study that evaluated safety and efficacy of intratumorally administered TT for treating MCTs in dogs.<sup>5</sup> In that study, the primary efficacy result showed that 75% of dogs receiving a single injection of TT achieved CR in the treated tumor by day 28, with no recurrence in 94% of these dogs by day 84. Here we document longer term durability of that response and show that 12 months after administration of a single dose of TT, 89% of the 64 dogs available for evaluation were still tumor free at the original treatment site. We also found that when local recurrence did occur, it was most likely within the first 84 days with only 2 cases recorded after that time, both at the 6-month assessment. These results suggest that TT administered intratumorally results in durable local tumor control of the treated MCT in the majority of cases.

In veterinary oncology, complete surgical excision has been the primary treatment option for solitary masses, and cutaneous and SC MCTs are no exception. Although surgery is widely accepted as the standard of care for local tumor control, the extent of surgery to achieve histologically complete margins remains controversial. Debate is ongoing about the gross surgical margins necessary for histologically complete excision, with recommendations varying from a perimeter margin equidistant to tumor diameter to as wide as 3 cm and 1 fascial plane deep to the tumor.<sup>8-12</sup> Furthermore, classification of MCT surgical margins is complicated and challenging because of current

methodology. In dogs, MCTs commonly have peritumoral edema, reactive stromal cells and inflammatory cells, which include non-neoplastic mast cells. Currently, no method exists to distinguish neoplastic mast cells from normal mast cells, which requires pathologists to make the arbitrary decision that clusters of mast cells are neoplastic and individual mast cells are likely inflammatory.<sup>13</sup> In addition, the number of sections and measuring distance that determines completeness of excision are highly variable among pathologists. Nonetheless, the measurement of tissue margins as assessed by histopathological evaluation after surgery often is used to predict likelihood of recurrence, make clinical recommendations and monitor patients.

Tumor recurrence is more likely in cases where excision is considered incomplete, but recurrence still occurs in cases where the margins are considered histologically tumor-free margins (HTFM).<sup>14,15</sup> Investigators have reported recurrence rates of low-grade MCTs with complete excision as high as 28%,<sup>16-19</sup> and it is not surprising that incomplete excision has been associated with higher recurrence rates of up to 38%.<sup>14,17,20-22</sup> In 1 study, the recurrence rates of incompletely excised MCTs reported at 6, 12, and 24 months were 20%, 71%, and 86%, respectively, with a median time to relapse of 7.5 months. The frequency of relapse also increased albeit much less in the HTFM group with 6, 12, and 24 months relapse rates of 20%, 21%, and 28%, respectively.<sup>16</sup>

These studies suggest incomplete margins often are associated with risk of recurrence, but another important factor that has been associated with higher risk of recurrence is tumor grade. Several studies report the incidence of recurrence after incomplete surgical excision of low-to-intermediate-grade MCT as being low.<sup>9,18,23</sup> Therefore, the necessity for a wide surgical margin to achieve local tumor control may not be absolute for low-grade tumors.<sup>20</sup> Unfortunately, a meaningful comparison of any potential differences in local recurrence rates between high- and low-grade tumors in our study was not feasible because of the low incidence (4%) of high-grade tumors in the study compared to the general canine MCT patient population.<sup>24</sup>

Intratumoral TT results in tumor necrosis with subsequent slough of the necrotic tissue, thereby destroying viable tumor tissue and rendering evaluation for HTFM impossible. If HTFM is the standard of care for local control of MCTs, it is problematic to provide evidence for clean margins after intralesional TT treatment. Proposed methods of evaluating margins after TT treatment include thermographic assessment in combination with computed tomography (CT)<sup>25</sup> and biopsy for histological evaluation of the remaining wound edges after tumor slough. Although these approaches may provide valuable data, each has its challenges and drawbacks.

The use of time-assessed thermographic imaging is an attractive noninvasive method of visualizing TT's mode of action *in vivo*. A preliminary study using thermography and CT has shown the absence of residual disease in tissue margins of dogs that achieved a CR after TT treatment.<sup>25,26</sup> The *in vivo* gross evidence visible with thermographic imaging is helpful, but it does not provide histopathologic data to categorically validate tumor-free margins after TT-induced tumor slough.

Surgical biopsy assessment would provide more accurate assessment of microscopic margins, but this approach presents ethical and diagnostic dilemmas. First, patients enrolled in clinical studies are client-

owned pets with naturally occurring disease. The requirement for any invasive procedures in such patients must take into consideration the ethical boundaries of additional procedures and pain the patient must endure in such a study. Second, given the presence of mast cells in healing tissue,<sup>27</sup> the timing and evaluation of the biopsy tissue specimens from the healing tumor site required for maximal confidence in detecting residual disease and to determine HTFM would be complicated if not impossible. Finally, pathological preparation of tissue samples and methodology of evaluation also could affect the detection of residual MCT disease.

Treatment site surveillance and establishment of long-term recurrence-free interval often is the most practical method to evaluate patients in a clinical setting. In fact, despite confirmation of HTFM after surgery, often the primary recommendation from the veterinary practitioner is life-long monitoring of the surgical site for local recurrence.

Our study had some limitations. The study population consisted of patients from a controlled randomized study with the termination date defined as day 84, and no formal mechanism for longitudinal follow-up was provided. However, we believe the data gathered for patients beyond day 84 is robust and strongly indicative of the overall durability of efficacy. Several patients were lost to follow-up by the 12-month assessment point, a problem not unique to our study and an issue faced by many investigators performing longitudinal studies. Nonetheless, because the majority (5/7, 71%) of recurrences occurred within the first 12 weeks after TT administration, it appears that recurrences were effectively captured in the more robust design of the original protocol.

Our study provides supporting evidence that after administration of a single intratumoral dose of TT not only is good efficacy achieved at day 28, but the response has excellent durability 12 months later. Finally, we recognize the importance of establishing tumor-free recurrence beyond 1 year, and follow-up of these patients and others enrolled in MCT clinical trials in Australia is ongoing.

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## CONFLICT OF INTEREST DECLARATION

Drs Pamela Jones, Justine Campbell, Graham Brown, and Paul Reddell are employed by QBiotics Group Limited. QBiotics Group Limited owns the intellectual property and patents associated with tigilanol tiglate. Drs Chad Johannes receives payments as an independent consultant to QBiotics Group Limited.

## OFF-LABEL ANTIMICROBIAL DECLARATION

The authors declare no off-label use of antimicrobials.

**INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION**

Institutional animal ethics was not required for this study as it was under a U.S. Center for Veterinary Medicine—Food and Drug Administration Protocol—Investigational New Animal Drug (INAD) No. I-012436 (July 25, 2016).

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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