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REVIEW

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Comparative aspects of mast cell neoplasia in animals and the role of *KIT* in prognosis and treatment

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Abstract

Mast cell neoplasia clinical presentation and biological behaviour vary considerably across mammalian species, ranging from a solitary benign mass to an aggressive systemic malignancy. Mutations in the *KIT Proto-Oncogene Receptor Tyrosine Kinase (KIT)* gene are common molecular abnormalities involved in mast cell tumorigenesis. *KIT* mutations often occur in dog, cat and human neoplastic mast cells and result in altered Kit protein structure and function. In dogs, certain *KIT* mutations are associated with more malignant and lethal disease. In contrast, *KIT* mutations in feline and human mast cell neoplasms are not correlated with prognosis, but are of value in diagnosis and treatment planning in humans. *KIT* genetic abnormalities have not been well investigated in other species, although aberrant cytoplasmic Kit protein staining detected in neoplasms of the ferret, horse and cow resembles aberrant Kit staining patterns detected in neoplastic mast cells of dogs, cats and humans. Mutations within *KIT* are classified as either regulatory-type or enzymatic pocket-type mutations according to their location within the *KIT Proto-Oncogene*. Mutations within the enzymatic pocket domain confer tumour resistance to tyrosine kinase inhibitors (TKIs). Hence, knowledge of tumour *KIT* mutation status adds valuable information for optimizing patient treatment strategies. The use of TKIs in combination with conventional chemotherapeutics has opened a new treatment avenue for patients unresponsive to existing drugs. This review highlights the similarities and differences of mast cell neoplasia in mammals with a special focus on the involvement of *KIT* in the canine and feline forms in comparison to human mast cell neoplasia.

KEYWORDS
animals, humans, mast cells, mastocytosis, mutation, proto-oncogene

1 | MAST CELL FUNCTION AND MALIGNANCY

Mast cells are derived from pluripotent CD34+ haematopoietic progenitor cells and are normally found throughout the body in bone marrow, connective tissue, the skin, the gastrointestinal tract and the respiratory tract (Siebenhaar, Redegeld, Bischoff, Gibbs, & Maurer, 2018). Mast cells are normal components in both innate and adaptive immune responses to bacterial and parasitic infections and they are notorious for the role they play in allergic reactions (Siebenhaar et al., 2018). Mast cell activation in response to antigens causes mast cell degranulation and release of various cytokines and chemokines into the blood, thereby facilitating host immune responses (Siebenhaar et al., 2018).

Mast cell neoplasia is characterized by abnormal mast cell proliferation and accumulation (Bodemer et al., 2010; Siebenhaar et al.,

2018). Neoplastic mast cell masses can spontaneously degranulate, releasing bioactive molecules which can exert serious and potentially fatal effects, such as anaphylaxis, gastric and duodenal ulceration or perforation, glomerular disease and haemorrhage.

In dogs, mast cell tumours (MCTs) are a common skin cancer and have extremely varied clinical appearance and biological behaviour. In other species, such as cats, MCTs are less common and have less variable biological behaviour. In humans, mast cell neoplasia, termed mastocytosis, often presents as a systemic disease rather than a defined mass and varies from benign disease in infants to aggressive malignancies in adults (Kiszewski, Duran-Mckinster, Orozco-Covarrubias, Gutierrez-Castrellon, & Ruiz-Maldonado, 2004). Despite these distinct differences in behaviour and clinical manifestation, an underlying molecular abnormality shared by neoplastic mast cells in different species is mutation of the *KIT Proto-Oncogene Receptor Tyrosine Kinase* gene.

2 | ROLE OF *KIT* IN MAST CELL TUMOURIGENESIS

The *KIT* gene was first discovered in the Hardy-Zuckerman 4 feline sarcoma virus (HZ4-FeSV) (London et al., 1999). This acute transforming retrovirus causes fibrosarcomas in cats. The transforming activity of HZ4-FeSV is carried by the oncogene *V-KIT* which is thought to have arisen through truncation and transduction of feline *KIT* sequences in the feline leukaemia virus (Yarden et al., 1987).

The *KIT* gene encodes Kit, a transmembrane tyrosine kinase receptor (TKR) protein that is involved in the development, proliferation and function of mast cells, melanocytes, interstitial cells of Cajal and haematopoietic stem cells (Lennartsson, Jelacic, Linnekin, & Shivakrupa, 2005). Kit protein structure comprises an extracellular region including five immunoglobulin-like domains, a transmembrane domain and an intracellular region. The intracellular region includes the juxtamembrane domain and two tyrosine kinase domains separated by a kinase insert (Lennartsson et al., 2005; Ma et al., 1999). Kit protein activation by haematopoietic stem cell factor triggers distinct downstream signalling cascades within the cell inducing mast cell development, survival, proliferation, secretory function and chemotaxis (Lennartsson et al., 2005; Letard et al., 2008).

Mutations within *KIT* are common in several human cancers including mastocytoma, gastrointestinal stromal tumours, melanoma and acute myeloid leukaemia (Longley, Reguera, & Ma, 2001). Point mutations, initially discovered in HMC-1 cells derived from a human patient with mast cell leukaemia and then later in mouse and rat mastocytomas, suggested that mutations in *KIT* play a role in mast cell oncogenesis (Furitsu et al., 1993; Tsujimura et al., 1994, 1995). Comparison of the whole canine Kit protein sequence with the sequence from mice and humans shows 82% and 88% homology, respectively (London et al., 1999; Ma et al., 1999). High protein sequence conservation across species raised speculation about whether *KIT* mutations could be found also in MCTs of other species. Indeed, at least 51 unique gain-of-function mutations in the *KIT* gene have been identified in mast cell neoplasms of humans, cats and dogs (Downing, Chien, Kass, Moore, & London, 2002; Giantin et al., 2012; Haenisch, Nothen, & Molderings, 2012; Hahn et al., 2008; Isotani et al., 2010; Letard et al., 2008; London et al., 1999; Ma et al., 1999; Marconato et al., 2014; Nakano et al., 2014; Riva, Brizzola, Stefanello, Crema, & Turin, 2005; Takeuchi et al., 2013; Webster et al., 2006; Zemke, Yamini, & Yuzbasiyan-Gurkan, 2002). Studies also document over 80 other nucleotide substitutions and frameshift mutations in neoplastic mast cells from these species, although these have not been confirmed to be Kit activating. While some identified nucleotide substitutions are silent or species-specific, many result in non-conservative amino acid changes and hence, may contribute to mast cell malignancy (Giantin et al., 2012; Haenisch et al., 2012; Hahn et al., 2008; Isotani et al., 2006; Letard et al., 2008; Marconato et al., 2014; Nakano, Kobayashi, Bonkobara, & Takanosu, 2017; Sabattini et al., 2017; Takeuchi et al., 2013; Zemke et al., 2002).

Gain-of-function mutations within the *KIT* gene disrupt normal Kit protein function, leading to constitutive Kit activation in the absence of ligand binding (Furitsu et al., 1993; Letard et al., 2008; Nakano et al., 2017). These mutations can be classified into two groups according to their location within the gene: regulatory-type mutations or enzymatic pocket-type mutations (Longley et al., 2001).

In humans, cats and dogs, Kit protein regulatory regions commonly affected by mutations include the extracellular ligand-binding fifth immunoglobulin-like domain, encoded by exons 8 and 9, and the juxtamembrane domain, encoded by exon 11, that regulates inhibition of Kit activation (Lennartsson et al., 2005; Longley et al., 2001). *KIT* mutations occurring in exons 13–21, encoding the intracellular kinase domains of the Kit protein, are termed enzymatic pocket-type mutations.

2.1 | Tyrosine kinase inhibitors

Receptor tyrosine kinases, such as Kit, are candidates for molecular targeted therapy. Tyrosine kinase inhibitors (TKIs) are used in human and veterinary medicine to treat mast cell neoplasms harbouring *KIT* mutations. TKIs bind directly to the ATP-binding site in tyrosine kinase proteins, including Kit, blocking TKR autophosphorylation, preventing activation caused by regulatory-type mutations and thereby preventing initiation of downstream signalling cascades (London, 2009). Consequently, neoplastic mast cell proliferation and tumour growth are inhibited.

The change in Kit protein structure resulting from mutations in the enzymatic pocket domain leads to decreased affinity of TKIs for the binding site. Neoplastic mast cells harbouring this mutation type are resistant to most TKI therapeutics (Nakano et al., 2017; Verstovsek et al., 2006). Hence, the location of *KIT* mutations within the gene influences whether the tumour will be responsive or resistant to treatment with TKIs, and therefore, the mutation location is of prognostic importance.

3 | CANINE MCTS

In dogs (*Canis lupus familiaris*), cutaneous MCTs have been reported to occur in 335 per 100,000 animals and account for 10%–21% of all skin neoplasms (Leidinger, Freeman, Kirtz, Hooijberg, & Sick, 2014; Withrow, MacEwen, Vail, & Page, 2013). Canine prognosis and treatment options are affected by patient signalment, clinical signs, and tumour anatomical location, growth rate, size, gross appearance (e.g. ulceration), metastasis, post-surgical recurrence, clinical stage and tumour histological grade (Blackwood et al., 2012; Mullins et al., 2006). The presence of multiple lesions should be considered in prognosis but does not necessarily indicate more aggressive disease (Kiupel, Webster, Miller, & Kaneene, 2005; Murphy, Sparkes, Blunden, Brearley, & Smith, 2006). Unlike human patients, there is no unequivocal evidence of familial MCT inheritance in dogs, although boxers and other breeds of bulldog descent appear to be more predisposed to MCT development (Leidinger et al., 2014; Mochizuki, Motsinger-Reif, Bettini, Moroff, & Breen, 2017).

3.1 | Canine MCT prognosis

Histological grade is currently the single most powerful prognostic factor for dogs with cutaneous MCTs and has been described in depth (Table 1) (Blackwood et al., 2012; Kiupel & Camus, 2019; Kiupel et al., 2011; Patnaik, Ehler, & MacEwen, 1984). The two established grading schemes, Patnaik and Kiupel, are not applicable to subcutaneous, visceral or mucosal MCTs or MCTs of other species due to differences in tumour biology and histological features. Clinical staging according to the World Health Organisation (WHO) Clinical Staging System for canine MCTs is regarded by some as an important prognostic indicator, with non-metastatic lower clinical stages (stages 0 and I) having a better prognosis than higher stages, with an exception outlined below. Clinical stage II is defined as a single tumour with regional lymph node metastasis. Assessment of regional nodes is most accurately accomplished by node excision and histopathology (Ferrari et al., 2018; Weishaar, Thamm, Worley, & Kamstock, 2014). A worse outcome for dogs with clinical stage II than with clinical stage 0/I MCT has been documented (Krick, Billings, Shofer, Watanabe, & Sorenmo, 2009; Murphy et al., 2006; Weishaar et al., 2014). Furthermore, dogs with clinical stage II tumours derive a survival benefit from excision of the metastatic nodes (Marconato et al., 2018). Clinical stage III includes multiple dermal tumours or one large infiltrating tumour with or without regional lymph node involvement. In a retrospective study, the median survival time of eight dogs with stage II disease was 431 days, whereas the median survival time for 50 dogs with stage III or stage I disease was not reached (Murphy et al., 2006). In this study, most dogs included in stage III had multiple tumours without lymph node metastasis. Evidence that dogs with multiple tumours either synchronously or in series do not have a worse prognosis than dogs with single tumours indicates that the WHO staging system needs revision to improve prognostic acumen (Horta et al., 2018; Mullins et al., 2006; Murphy et al., 2006). Amendments to the current WHO clinical staging criterion have been proposed (Horta et al., 2018).

3.2 | Canine *KIT* mutations

Between 8% and 29% of canine MCTs carry a regulatory-type mutation in exon 8, 9 or 11 (Giantin et al., 2012; Hahn et al., 2008; Horta et al., 2018; Letard et al., 2008; Marconato et al., 2014; Mochizuki, Thomas, Moroff, & Breen, 2017). Exon 11 internal tandem duplications (ITDs) comprise 60%–74% of these mutations and are prevalent in 18% of tumours (Giantin et al., 2012; Hahn et al., 2008; Letard et al., 2008; Marconato et al., 2014; Mochizuki, Thomas, et al., 2017; Webster et al., 2006). *KIT* mutation frequency increases with increasing tumour histological grade and exon 11 ITDs are associated with decreased survival times and the increased chance of tumour recurrence and metastasis (Table 1) (Downing et al., 2002; Horta et al., 2018; Letard et al., 2008; Tamlin et al., 2017). Although less frequent, ITDs in exon 8 as well as insertions, deletions and nucleotide substitutions in exons 8, 9, 11, 14 and 17 are of functional significance (Giantin et al., 2012; Hahn et al., 2008; Letard et al., 2008; Mochizuki, Thomas, et al., 2017; Nakano et al., 2017; Zemke et al., 2002).

In one study, the homozygous deletion of the entire intron 11 of canine *KIT* was detected in 49% of MCT samples compared to 13% in control, non-cancerous tissue (Reguera, Ferrer, & Rabanal, 2002). The intron 11 deletion was correlated with higher grade, more aggressive MCTs. However, this large deletion has not been reported in any other molecular studies evaluating genomic DNA. The presence of a *KIT*-derived pseudogene was suspected because of the apparent intron 11 deletion. However, we aligned the canine *KIT* gene coding sequence (GenBank accession number AF044249, nucleotide bases 1737-1899) to the canine reference genome (CanFam3.1; GCF_000002285.3) using National Center for Biotechnology Information Basic Local Alignment Search Tool and found no alignments outside the annotated *KIT* gene, indicating that a *KIT* pseudogene is unlikely to exist (data not shown). Sample contamination with RNA may explain homozygous intron 11 deletion. The described primers produce a wild-type, genomic DNA amplicon of 448 base pairs and an RNA amplicon of 165 base pairs (Reguera et al., 2002). Differing concentrations of contaminating RNA between MCT samples could lead to favourable PCR amplification of the smaller PCR product, resulting in apparent homozygous intron 11 deletion in some samples. This is speculative and further research is necessary for clarification.

3.3 | Other genetic mechanisms implicated in canine mast cell malignancy

Cellular proliferative markers AgNOR, Ki-67, PCNA and Kit protein have been investigated by immunohistochemical evalutation for their use as independent or supplementary prognostic markers to histological grade. The extent of their use in prognosis has been well summarized previously (Blackwood et al., 2012; Kiupel & Camus, 2019).

TABLE 1 Canine mast cell tumour prognosis, incidence and *KIT* mutation prevalence according to the Patnaik and Kiupel histological grading schemes

Histological grade	Histological grade frequency[a]	*KIT* mutation prevalence[a,b]	Prognosis
Patnaik grade I	8%–53%	0%–6%	• Generally benign with low chance of recurrence. • Surgery alone is often curative. • Predictably good long-term prognosis. • 12-month survival probability up to 100%.
Patnaik grade II	59%–76%	6%–35%	• Unpredictable biological behaviour. • Unclear treatment recommendations. • Discordance among pathologist when grading. • 12-month survival probability 87%–92%.
Patnaik grade III	5%–26%	33%–71%	• Biologically aggressive with high probability of local recurrence and metastasis. • Requires aggressive therapeutic management. • Poor long-term prognosis. • 12-month survival probability 16%–46%.
Kiupel low-grade	59%–89%	4%–13%	• Good long-term prognosis. • Median survival times of more than 2 years. • 12-month survival probability 95%.
Kiupel high-grade	11%–41%	14%–52%	• Increased chance of metastasis or recurrence. • Poor long-term prognosis. • Median survival times of less than 4 months. • 12-month survival probability 24%.
References	Giantin et al. (2012), Leidinger et al. (2014), Mochizuki, Motsinger-Reif, et al. (2017), Patnaik et al. (1984), Kiupel et al. (2011), Mochizuki, Thomas, et al. (2017), Tamlin et al. (2017), Sabattini, Scarpa, Berlato, and Bettini (2015), Murphy, Sparkes, Smith, Blunden, and Brearley (2004)	Downing et al. (2002), Giantin et al. (2012), Webster et al. (2006), Zemke et al. (2002), Mochizuki, Thomas, et al. (2017), Tamlin et al. (2017)	Kiupel et al. (2011), Sabattini et al. (2015), Murphy et al. (2004)

[a]Studies with less than 49 tumour samples were omitted from this Table as deemed too small to be an accurate representation of true grade incidence/mutation prevalence according to the sample size calculation equation described by Naing, Winn, and Rusli (2006). A 95% level of confidence and precision of 10% was used in the calculations based on the prevalence determined by Webster et al. (2006).
[b]Prevalence includes mutations in *KIT* exons 8, 9 and 11.

Some genes known to be mutated in human mast cell diseases have been evaluated in MCTs from dogs (Zorzan, Hanssens, Giantin, Dacasto, & Dubreuil, 2015). Mutations in the *TET2* gene are present in up to 27% of all human systemic mastocytosis (SM) patients but only 2.7% of canine MCTs harbour *TET2* genetic aberrations (Damaj et al., 2014; Zorzan et al., 2015). No other genes known to be frequently mutated in human SM cases have been shown to be mutated in canine MCT samples (Zorzan et al., 2015).

However, single-nucleotide substitutions in the *GNAI2* gene and in various hyaluronidase genes on CFA14 and CFA20 are significantly associated with increased risk of MCT development in golden retriever dogs (Arendt et al., 2015). The *GNAI2* and hyaluronidase genes are involved in cellular signalling and cancer metastasis, respectively, and are associated with various types of human cancers. The exact involvement of these genes in canine cancers, and more specifically in canine MCT pathogenesis, has not been investigated.

Transcriptomic and proteomic analyses comparing low-grade MCTs with good patient prognosis and high-grade tumours with poor patient prognosis have identified a variety of differentially expressed genes and proteins potentially involved in mast cell aetiology and pathogenesis in dogs (Giantin et al., 2016; Schlieben et al., 2012). The roles of these various genes and proteins have not been further evaluated.

Global DNA methylation is a known heritable epigenetic modulator of gene expression. Hypomethylation of proto-oncogenes up-regulates gene expression, potentially favouring carcinogenesis and a more aggressive tumour type. DNA hypomethylation predominates in poorly differentiated, high-grade canine MCTs and may represent a novel target for epigenetic therapy (Morimoto et al., 2017).

3.4 | Treatment of canine MCTs

Clinical treatment of MCTs is based on tumour size, location, histological grade and evidence of metastasis (Blackwood et al., 2012).

Common MCT treatment recommendations and conventional therapies have been outlined elsewhere (Blackwood et al., 2012). The use of TKIs is the subject of ongoing research.

Toceranib, the most commonly used TKI in veterinary medicine, is licensed to treat non-resectable or recurrent grade II and III canine cutaneous MCTs in the USA (Anon, 2009), EU (Anon, 2019) and Australia (Agricultural & Veterinary Chemicals, 2011). Toceranib was originally developed as an antiangiogenic agent but was later found to possess potent anti-tumour characteristics by inhibiting Kit autophosphorylation and mast cell proliferation (Halsey et al., 2014). Early studies reported successful use of toceranib in treatment of recurrent MCTs which failed standard therapies, with tumours more likely to respond if harbouring a *KIT* exon 11 ITD (London et al., 2003, 2009). Canine overall survival time, time to tumour progression and the duration of tumour response to toceranib were not influenced by tumour ITD mutation status (London et al., 2003, 2009). Furthermore, in these studies not all animals possessing an ITD responded to treatment. It is possible that unresponsive animals had MCTs which harboured a secondary mutation in the enzymatic domain of *KIT*, inducing tumour TKI resistance (Halsey et al., 2014; Nakano et al., 2017). In a more recent study, an objective response rate (ORR: complete response or partial response) of 46% to toceranib therapy was observed (Weishaar et al., 2018), mimicking earlier observations (ORR = 37%–50%) (London et al., 2003, 2009). The difference in ORR between dogs with ITD-mutant and non-ITD mutant MCTs was not statistically analysed in this study, although, overall canine survival was not influenced by tumour ITD status (Weishaar et al., 2018). In the studies by London and colleagues, progression free survival times were significantly increased in dogs with non-mutant MCTs compared to dogs with ITD-mutant MCTs, however, this did not retain significance in a multivariable model (London et al., 2003, 2009). In the study by Weishaar and colleagues, a higher proportion of dogs with MCTs responded to treatment with toceranib than to treatment with vinblastine (46% vs. 30%, respectively), but this difference was not statistically significant (Weishaar et al., 2018). Given the greater expense and potentially more frequent and severe adverse events accompanying toceranib therapy, vinblastine is likely to remain a primary therapeutic option, regardless of tumour mutation status, with toceranib as a rescue therapy.

The TKI masitinib mesylate is not currently licensed for use in the USA (Anon, 2018) but is used in the EU (Anon, 2013) to treat non-resectable grade II and III cutaneous canine MCTs with confirmed mutated *KIT*. It is not licensed for use in Australia. Masitinib significantly improves overall survival of dogs with recurrent or non-resectable grade II or III MCTs harbouring a regulatory-type *KIT* mutation compared with results for placebo-treated dogs (Hahn et al., 2010, 2008). Time to tumour progression is also increased in masitinib-treated dogs compared to placebo-treated animals, regardless of tumour mutation status (Hahn et al., 2010, 2008). Tumour response to masitinib treatment was more pronounced in dogs with no prior chemotherapeutic treatment, suggesting that chemotherapy may select for growth of TKI-resistant neoplastic cells, limiting the effectiveness of masitinib treatment (Hahn et al., 2008). Complete tumour response, partial tumour response or stable disease at 6 months after masitinib treatment initiation has a high predictive value for 12- and 24-month survival, whereas tumour response at 6 weeks does not provide predictive value (Hahn et al., 2010). As the majority of studies evaluated patient response to TKIs for less than 6 months, the results must be interpreted carefully when estimating long-term health benefits for dogs receiving TKI therapeutics.

Tyrosine kinase inhibitor-resistant tumours harbouring enzymatic pocket-type mutations may still be susceptible to combination therapy involving the use of TKIs with conventional chemotherapeutic agents. A phase I/II study evaluating combination therapy of toceranib with lomustine in 41 dogs determined the maximally tolerated dose of the drugs in a pulse delivery setting, and concluded that the combined therapy was well tolerated and had value in the treatment of some dogs with high-grade unresectable or metastatic MCTs (Burton et al., 2015). Tumour *KIT* mutation status did not influence response to the treatment (Burton et al., 2015). Complete response for more than 1 year was observed in 2 of 10 dogs in a study using the same drug combination with a different administration schedule that was, however, not well tolerated by the dogs (Bavcar et al., 2017).

In a retrospective study of 40 dogs with grade II or III MCTs, toceranib in combination with vinblastine was used as adjuvant or neoadjuvant therapy with surgery or as medical palliative therapy alone. Overall, the treatment was reasonably well tolerated, and in 29 patients with measureable disease, initial response rates (complete response and partial response) of 90% were observed (Olsen, Thomson, O'Connell, & Wyatt, 2018).

Tyrosine kinase inhibitor-independent means of canine MCT therapy are currently under investigation for use against MCTs resistant to TKIs and conventional chemotherapeutic agents.

4 | FELINE MCTS

The clinical manifestations of mast cell neoplasia in domestic cats (*Felis catus*) include visceral (splenic, intestinal) disease as well as cutaneous MCT. Cutaneous MCTs are the second most common type of skin cancer in the cat, representing up to 21% of all cutaneous feline neoplasms in the USA (Withrow et al., 2013). Clinical understanding of feline MCT biological behaviour is relatively poor and most prognostic markers have a relatively weak correlation with survival. Mitotic index is probably the strongest prognostic indicator for cats with cutaneous MCT, with high index associated with worse clinical outcome although there is considerable variability (Blackwood, 2015; Sabattini et al., 2013). Ki-67 score and staining of aberrant cytoplasmic Kit protein localization are correlated with mitotic index but add no supplementary prognostic value to that achieved by mitotic index evaluation alone (Blackwood, 2015). The Patnaik and Kiupel histological grading systems provide no

prognostically useful information for feline cutaneous MCTs. Instead, tumours have been histologically classified based on cellular and nuclear morphology as either atypical or mastocytic type tumours (Blackwood, 2015). Mastocytic tumours can be further divided into well-differentiated or poorly differentiated tumours, both sub-types of which can present with pleomorphic cells (Blackwood, 2015). However, there are no official guidelines for feline cutaneous MCT histological classification and, hence, there are inconsistencies in the definitions of histological sub-types between published reports. These discrepancies in histological classifications and correlations with prognosis have been described previously (Blackwood, 2015). To overcome this, a recent study of 25 cats suggests a two-tier histological classification of feline cutaneous MCTs (Sabattini & Bettini, 2019). High-grade tumours are categorized by the presence of >5 mitotic figures per 10 high-power fields and at least two of the following three criteria: tumour diameter >1.5 cm, irregular nuclear shape and nucleolar prominence/chromatin clusters. According to this grading scheme, cats with high-grade tumours had a significantly shorter median overall survival (349 days) compared to cats with low-grade tumours (not reached, $p < .001$).

MCTs are the most common cause of splenic disease in cats. Affected cats are usually older than 10 or 11 years and there is no sex predilection (Evans, O'Brien, Allstadt, Gregor, & Sorenmo, 2018; Sabattini et al., 2017). The disease frequently involves multiple other viscera and bone marrow. There is no consensus on which factors significantly influence prognosis (Evans et al., 2018).

MCTs of the gastrointestinal tract are rare, but rank as the third most common intestinal tumour in cats, following lymphoma and adenocarcinoma, and have been previously viewed as an aggressive form of feline MCT disease (Barrett et al., 2018). Cats with poorly differentiated intestinal MCTs, fitting a description of feline intestinal sclerosing MCT, survive 2–30 days compared with 28–538 days for cats with well- or moderately differentiated tumours (Sabattini et al., 2016). Feline intestinal sclerosing MCT is seldom reported, but the short survival for cats with this variant is agreed, although there is disagreement as to whether the tumours are characterized by a low or high mitotic index (Halsey, Powers, & Kamstock, 2010; Sabattini et al., 2016). Intestinal sclerosing MCTs reportedly exhibit different histological appearance to gastrointestinal MCTs, and histological guidelines for diagnosis are yet to be developed (Halsey et al., 2010; Sabattini et al., 2016).

4.1 | Feline *KIT* mutations

In cats, 56%–68% of cutaneous and splenic MCTs harbour *KIT* mutations primarily in exons 8 and 9, but mutations in exons 6 and 11 also exist (Isotani et al., 2006, 2010; Sabattini et al., 2017, 2013). ITDs in exon 8 are the most prevalent and are Kit protein activating (Hadzijusufovic et al., 2009). Cases of tumours with two simultaneous *KIT* mutations have been recorded but significant correlations between mutation status and prognosis have not been documented (Isotani et al., 2010; Sabattini et al., 2017, 2013). Gain-of-function mutations in feline intestinal MCTs have not been documented (Sabattini et al., 2016).

4.2 | Treatment of feline MCT

Treatment of feline MCTs has been reviewed recently.(Blackwood, 2015; Blackwood et al., 2012) Surgical excision is standard of care for cutaneous atypical MCTs, which are generally thought to be benign (Blackwood, 2015). Spontaneous tumour regression has been reported in younger cats, reminiscent of paediatric mastocytosis in humans (Chastain, Turk, & O'Brien, 1988; Wilcock, Yager, & Zink, 1986). However, over the last three decades there have been no additional published cases and, hence, the existence of the spontaneously regressing variant in cats is uncertain. Cats with pleomorphic poorly differentiated mastocytic MCTs are at risk of unfavourable outcome, hence, post-operative adjuvant radiation therapy and/or chemotherapy has been recommended for these cats (Blackwood, 2015).

Data using TKIs for treatment of MCTs in cats are scant, and prospective studies are lacking. An objective response was recorded in a cat with systemic and cutaneous MCT after treatment with imatinib (Isotani et al., 2006). A follow-up investigation demonstrated an objective response in five of eight cats with *KIT*-mutated MCTs and in one of two cats without *KIT* mutations (Isotani et al., 2010). Low animal numbers, previous therapeutic drug administration and short follow-up times limit the interpretation of this study. Retrospectively, toceranib phosphate was assessed as well tolerated by cats. Complete or partial responses were documented in 35 of 50 cats treated for cutaneous, visceral and gastrointestinal MCTs with toceranib alone or in combination with corticosteroids (Berger et al., 2017). Other TKIs, including midostaurin, nilotinib and dasatinib, show dose-dependent growth-inhibitory effects on exon 8 ITD *KIT* mutant neoplastic feline mast cells in vitro (Hadzijusufovic et al., 2009). Mutations in the enzymatic pocket domain of *KIT* have not been documented in feline MCTs, making TKIs an attractive therapeutic option.

Splenectomy is the standard therapy for cats with splenic mastocytosis and provides longer disease-free survival than chemotherapy alone (856 days vs. 342 days, respectively) (Evans et al., 2018). Cats with intestinal MCT historically carry a guarded prognosis and metastasis to mesenteric lymph nodes is common (Barrett et al., 2018; Morrice, Polton, & Beck, 2019; Sabattini et al., 2016). However, recent literature describes variable biologic behaviour of feline gastrointestinal MCT with the overall median survival time of 31 cats to be 531 days in one study (Barrett et al., 2018) and 35% of cats surviving more than 1-year post-diagnosis in a different study which included a case where no treatment or surgery was received (Sabattini et al., 2016).

5 | MAST CELL NEOPLASIA IN OTHER ANIMALS

Mast cell cancer is well documented in humans, cats and dogs but is also a frequent skin cancer in the ferret and has been documented in various other species including domesticated ungulates, non-human

primates, birds and reptiles (Table 2). As with cats, the histological grading schemes that are useful for canine cutaneous MCTs cannot be applied to MCTs of other animals due to interspecies differences in clinical and histological disease manifestation.

5.1 | Ferret (Mustela putorius furo)

Mast cell tumours represent up to 44% of all cutaneous and subcutaneous neoplasms in ferrets (Avallone et al., 2016). The tumours are typically benign and neither local recurrence after surgical excision nor metastatic disease has been reported (Vilalta et al., 2016). Histologically, most ferret MCTs consist of well-differentiated mast cells where mitotic figures are rare and, similar to cats, few eosinophils are present (Vilalta et al., 2016). In one study of 15 tumours from 10 ferrets, neither haematoxylin and eosin nor Toluidine blue staining detected mast cell granules in histologic sections (Vilalta et al., 2016). However, in cytologic preparations of 12 tumours stained with Toluidine blue or Wright's–Giemsa stains, metachromatic granules were visualized in all cases, but not in any case stained with Modified Wright's stain (Vilalta et al., 2016). The discrepancy in Toluidine blue staining between cytology and histology in ferret MCTs is confusing and could lead to misdiagnosis. In the same study, all tumours had either cytoplasmic or membrane immunostaining with Kit (Vilalta et al., 2016). As would be expected from the lack of reported tumour recurrence or metastasis, there was no relationship between Kit immunostaining and prognosis (Vilalta et al., 2016).

5.2 | Horse (Equus ferus caballus)

Mast cell tumours comprise 3.4% of all cutaneous equine tumours, at least in the Pacific Northwest of the USA (Valentine, 2006). Equine MCTs appear most frequently on the head as a single nodule; multiple lesions are not indicative of malignant disease and may occur in any anatomical area of the skin (Ressel, Ward, & Kipar, 2015). Arabian horses appear to be more at risk compared to other breeds but no sex predilection has been described (Mair & Krudewig, 2008; Ressel et al., 2015). Similar to MCTs in ferrets, equine MCTs follow a benign disease course and appear histologically well differentiated with a low mitotic rate. Aberrant cytoplasmic Kit staining is detected by immunohistochemistry in 15% of cases but is not correlated to malignant disease or a worse prognosis, albeit numbers were low (n = 9) (Ressel et al., 2015). Metastatic MCT behaviour and MCT-related death in horses are seldom documented and the necessity for treatment is questionable, although some owners opt for therapy for the cosmetic appearance of the horse. Surgery alone is curative in the majority of cases and other therapies including surgical laser ablation and intralesional injection with methylprednisone acetate appear to be effective, non-invasive treatment options (Mair & Krudewig, 2008).

5.3 | Cow (Bos taurus)

In cattle, MCTs comprise less than 1% of all bovine neoplasms (Hill, Langheinrich, & Kelley, 1991). Reports range from multiple MCTs randomly distributed over the entire body with or without organ involvement to single visceral lesions (Hill et al., 1991; Khodakaram-Tafti, Eshraghi, Geramizadeh, Shaterzadeh-Yazdi, & Taghipur-Bazargani, 2015; Perez et al., 1999). Published data predominantly describe MCTs affecting Holstein cattle, however, statistical evidence of breed predisposition does not exist (Hill et al., 1991; Khodakaram-Tafti et al., 2015; Perez et al., 1999). Curiously, neoplastic mast cells appear well differentiated in cattle, even in cases with metastasis (Hill et al., 1991). Whether the tumours progress to lethal disease is unknown because individuals are often euthanized due to poor carcass quality. The most recent record of a bovine MCT was of a 4-year-old female Holstein with multiple cutaneous lesions (Khodakaram-Tafti et al., 2015). The authors were able to demonstrate Kit protein immunohistochemistry in a cow for the first time (Khodakaram-Tafti et al., 2015).

5.4 | Pig (Sus scrofa domesticus)

Mast cell neoplasia in pigs is rarely reported and can range from well differentiated, benign lesions to malignant and metastatic cancer (Bundza & Dukes, 1982; Newman & Rohrbach, 2012). In one study, multiple cutaneous and visceral MCTs were reported in three pigs, two of which were simultaneously diagnosed with eperythrozoonosis (Bundza & Dukes, 1982). In a recent case report, staining with Toluidine Blue or Giemsa was inconclusive and the diagnosis of MCT was based on positive Kit and tryptase immunohistochemistry (Williams, Annetti, & Nagy, 2018). Rare cases of mast cell leukaemia in miniature pigs have been reported with a poor outcome (Sipos, Hirschberger, Breuer, Zenker, & Elicker, 2010).

5.5 | Other species

Mast cell neoplasia is reported in a variety of species and ranges from solitary, benign tumours to malignant, systemic disease. Case reports of visceral MCT have been documented in a number of the big cat species, perhaps resembling the disease in the domestic cat and reflecting the close genetic relation between these species (Table 2).

Mast cell tumour is occasionally reported in non-human primates (Table 2). Three macaques and a baboon were observed with benign MCT with similar histological appearance to that of indolent SM in humans (Colgin & Moeller, 1996; Jones, MacKenzie, & Robinson, 1974; Seibold & Wolf, 1973; Zoller & Kaspareit, 2010). A fourth macaque harboured subcutaneous MCT metastatic to the local lymph nodes and internal organs (Tsugo et al., 2017). Immunohistochemical staining of membranous Kit protein was comparable between humans and this macaque case (Tsugo et al., 2017).

6 | MASTOCYTOSIS IN HUMANS

Similar to the disease in dogs and cats, mastocytosis in humans can range from a spontaneously regressing skin lesion to a highly

TABLE 2 Documented cases of vertebrates infrequently diagnosed with mast cell neoplasia

Species	Age (years)	Sex	MCT Type	Affected organs	Outcome
Big cats					
Cheetah (*Acinonyx jubatus*)	13	F	Visceral (spleen)	Metastatic (larynx)	Non-MCT-related death (Owston, Ramsay, & Rotstein, 2008)
Cougar (*Puma concolor*)	9 months	M	Visceral	Stomach	Alive at end of study (Martin, Lewis, Lin, & Jacobson, 1985)
Indian lion (*Panthera leo*)	16	F	Cutaneous	Multiple skin tumours (>20)	Euthanized (Stolte & Welle, 1995)
Jaguar (*Panthera onca*)	26	F	Visceral (jejunum)	Metastatic (liver, kidneys)	Died during anaesthesia (Castro, Werther, Godoy, Borges, & Alessi, 2003)
Tiger (*Panthera tigris*)	6	M	Visceral (spleen)	Metastatic (liver, lymphoid, kidney, pulmonary organs)	Died during anaesthesia (Graille, Huyghe, & Nicolier, 2013)
	14	M	Visceral	Metastatic (LN, lung, liver)	Euthanized due to other causes (Owston et al., 2008)
Miscellaneous mammals					
African hedgehog (*Atelerix albiventris*)	~1	F	Subcutaneous	Metastatic (lymph node)	Euthanized (Raymond, White, & Janovitz, 1997)
	>1	F	Cutaneous	Confined to skin	U (Raymond & Garner, 2001)
	>1	U	Cutaneous	Confined to skin	U (Raymond & Garner, 2001)
	3	U	Cutaneous	Metastatic (lymph)	U (Raymond & Garner, 2001)
Llama (*Lama glama*)	9	F	Cutaneous	Multiple cutaneous tumours	Alive at end of study (Lin, Hamberg, Pentecost, Wellman, & Stromberg, 2010)
Nubian goat (*Capra aegagrus hircus*)	4	F	Systemic mastocytosis	Heart, lung, liver, spleen, lymph, bone marrow	MCT-related death (Khan, Sagartz, Koenig, & Tanaka, 1995)
	6 weeks	F	Cutaneous (ear)	Confined to skin	Alive at end of study (Allison & Fritz, 2001)
Pacific Walrus (*Odobenus rosmarus divergens*)	>15	F	Visceral (lung)	Non-metastatic	Discovered at slaughter (Seguel, Stimmelmayr, Howerth, & Gottdenker, 2016)
Richardson's ground squirrel (*Spermophilus richardsonii*)	4	F	Cutaneous	Metastatic (lymph)	U (He et al., 2009)
Sheep (*Ovis aries*)	U	U	Visceral (liver)	Metastasis (lymph)	Discovered at slaughter (Johnstone, 1972)
	U	U	Visceral (liver)	Metastasis (hepatic)	Discovered at slaughter (Johnstone, 1972)
Non-human primates					
Baboon (*Papio sp.*)	Young	U	Cutaneous (neck)	Confined to skin	Discovered at necropsy (Jones et al., 1974)
Cynomolgus macaque (*Macaca fascicularis*)	3	M	Systemic mastocytosis	Liver, caecum	Non-MCT-related euthanasia (Zoller & Kaspareit, 2010)
Japanese macaque (*Macaca fuscata*)	19	F	Subcutaneous	Metastatic (lymph, kidney, peritoneum, mammary lobule)	MCT-related death (Tsugo et al., 2017)

(Continues)

TABLE 2 (Continued)

Species	Age (years)	Sex	MCT Type	Affected organs	Outcome
Rhesus macaque (*Macaca mulatta*)	7	M	Cutaneous (thorax)	Confined to skin	Alive at end of study (Colgin & Moeller, 1996)
	Adult	F	Subcutaneous (thigh)	-	U (Seibold & Wolf, 1973)
Birds					
Burrowing owl (*Speotyto cunicularia*)	U	U	Cutaneous (oral)	Confined to skin	Released, lost to follow-up (Schmidt & Okimoto, 1992)
Chicken (*Gallus gallus domesticus*)	5	F	Cutaneous (multiple)	Metastasis (lung)	Discovered at slaughter (Hafner & Latimer, 1997)
	1.5	M	Cutaneous (eyelid)	Confined to skin	Alive at end of study (Patnaik & Mohanty, 1970)
	Adult	F	Multiple, cutaneous	Confined to skin	Discovered at slaughter (Hall, Mosier, & Degraw, 1994)
Great horned owl (*Bubo virginianus*)	Adult	M	Cutaneous	Multiple (eye, ear)	Dead (Swayne & Weisbrode, 1990)
Lovebird (*Agapornis personata*)	12	F	Cutaneous	Metastatic (kidney, liver, spleen, periovarian, bone marrow)	MCT-related death (Dallwig, Whittington, Terio, & Barger, 2012)
Pueo (*Asio flammeus sandwichensis*)	U	U	Cutaneous (upper eyelid)	Confined to skin	MCT-related euthanasia (Schmidt & Okimoto, 1992)
Reptiles					
African fat-tailed gecko (*Hemitheconyx caudicinctus*)	3	F	Systemic	Liver, kidneys, skeletal muscle, bones, spleen, uterus, ovaries and lungs	MCT-related death (Rovira, Holzer, & Credille, 2014)
Boa constrictor (*Boa constrictor constrictor*)	U	U	Malignant	Cutaneous	U (Frye, 1994)
Desert tortoise (Xerobates agassizii)	U	U	Cutaneous	Cutaneous	U (Frye, 1994)
Eastern kingsnake (*Lampropeltis getulus getulus*)	16	M	Cutaneous	Metastatic (liver, heart, lung, kidney, spleen)	MCT-related death (Schumacher et al., 1998)
Giant Galapagos tortoise (*Geochelone nigra vicina*)	Subadult	F	Cutaneous	Confined to skin	Healthy 11 months post-surgery (Santoro et al., 2008)
Green iguana (*Iguana iguana*)	Adult	F	Cutaneous	Mastocytosis of periphery	Euthanized (Reavill et al.,)
Amphibians					
Axolotl (*Ambystoma mexicanum*)	11–17 (18 animals)	U	Cutaneous	Single or multiple lesions, some metastatic (skeletal muscle)	Dead (Harshbarger, Chang, DeLanney, Rose, & Green, 1999)
Tiger salamander (*Ambystoma tigrinum*)	Neotenic (6 animals)	U	Cutaneous	Single or multiple lesions, some metastatic (skeletal muscle)	Dead (Harshbarger et al., 1999)

Note: male (M), female (F), unknown (U).
Abbreviation: MCT, mast cell tumour.

aggressive, multisystem malignancy. Mastocytosis is divided into two main groups based on the presence or absence of extracutaneous organ involvement: cutaneous mastocytosis (CM) and SM. While CM and SM present differently, the disorders exhibit common genetic abnormalities in the *KIT* gene (Bodemer et al., 2010; Valent, Akin, & Metcalfe, 2017).

6.1 | Human CM

Cutaneous mastocytosis, also referred to as urticaria pigmentosa, is isolated to the skin, with no other organ involvement and represents 80% of all mastocytosis cases in humans (Siebenhaar et al., 2018). CM is more common in infants but can occur at any age and is more frequent in males than in females with a ratio of up to 1.8:1 (Bodemer et al., 2010; Kiszewski et al., 2004). Paediatric CM describes the disease in infants and has a favourable prognosis, often spontaneously regressing once the individual reaches adolescence (Kiszewski et al., 2004). In a minority of cases, paediatric CM progresses into mast cell activation syndrome, a multisystem inflammatory disorder of chronic mast cell hyper-reactivity, or SM, a proliferative and accumulative neoplastic mast cell disease of one or multiple organs (Valent et al., 2017). Both are malignant forms of the disease.

6.2 | Human SM

Classification of SM is based on mast cell morphology and immunohistochemistry and includes five sub-variants according to the WHO classification system (Valent et al., 2017). With increasing severity, these sub-classifications are: indolent SM, smouldering SM, SM with associated haematologic non-mast cell lineage disease neoplasm, aggressive SM and mast cell leukaemia. All sub-variants are characterized by extracutaneous organ involvement and gain-of-function mutations in the *KIT* gene.

6.3 | Familial mastocytosis

Familial predisposition to mastocytosis is evident in up to 13% of human cases but the exact mode of inheritance is unclear (Bodemer et al., 2010). Mastocytosis can occur in the presence or absence of *KIT* mutations and there is no apparent relationship between a patient's genotype and familial or spontaneous disease development (Bodemer et al., 2010). Familial mastocytosis is known to pass through generations from parent to offspring, although it appears that *KIT* mutations are not inherited (Wohrl et al., 2013). Instead the mutations arise somatically, potentially as a secondary event resulting from a common germline abnormality predisposing individuals to familial disease (Bodemer et al., 2010; Jawhar et al., 2015).

6.4 | *KIT* mutations in human patients

In contrast to dogs and cats, mutations are more frequent in the enzymatic domain of *KIT* in human SM patients. Approximately 44% of paediatric mastocytosis patients and less than 5% of adult SM patients harbour a regulatory-type *KIT* mutation, in either exon 8, 9 or 11 (Bodemer et al., 2010; Haenisch et al., 2012). Comparatively, enzymatic-type *KIT* mutations are detected in mastocytoma or bone marrow biopsies in over 80% of adult and paediatric human patients with mastocytosis (Bodemer et al., 2010; DeAngelo et al., 2017). The commonest *KIT* mutation is a nucleotide substitution occurring in exon 17 at codon 816 where aspartic acid is replaced with valine (D816V). Unlike in dogs, tumour *KIT* mutation status in humans is not correlated with survival or disease progression (Bodemer et al., 2010). However, mutation status is a minor criterion for mastocytosis diagnosis and is clinically relevant when deciding optimal treatment regimens for mastocytosis patients.

6.5 | Other genetic mutations involved in human mastocytosis

Mutations in various genes encoding splicing factors *SRSF2*, *SF3B1* and *U2AF1*, epigenetic regulators *ASXL1*, *DNMT3A* and *TET2*, the transcription factor *RUNX1* and signalling molecules *JAK2*, *CBL*, *KRAS* and *NRAS* are frequently identified and co-exist with *KIT* mutations in SM patients (Damaj et al., 2014; DeAngelo et al., 2017; Jawhar et al., 2015; Jawhar, Schwaab, et al., 2016; Traina et al., 2012). Mutations in *ASXL1*, *DNMT3A*, *RUNX1* and *SRSF2* are predictive of overall patient survival and aberrations in other genes predict response to particular treatment types (Jawhar, Schwaab, et al., 2016; Traina et al., 2012). Mutations in these genes have not been investigated in other species in relation to MCTs.

6.6 | Treatment of mastocytosis

Therapy is seldom sought for human patients with CM due to its benign clinical course, however, some CM cases may require antihistamines and corticosteroids to stabilize symptoms (Kiszewski et al., 2004). Conversely, patients with mast cell leukaemia experience average survival times of less than 12 months even with the best treatment available (Valent et al., 2017).

Various TKIs have been investigated for therapeutic use against mastocytosis. Imatinib and masitinib mesylate show efficacy for patients with wild-type *KIT* mast cell neoplasia (Lortholary et al., 2017). However, they are not a suitable treatment option for many patients due to the high prevalence of the D816V mutation which confers drug resistance (Siebenhaar et al., 2018; Valent et al., 2017).

The TKI nilotinib exhibits potent growth-inhibitory and pro-apoptotic activity against mast cells harbouring the regulatory-type *KIT* mutation D560G (Verstovsek et al., 2006) There is conflicting evidence regarding the activity of nilotinib against wild-type and D816V mutant mast cells (Hochhaus et al., 2015; Verstovsek et al., 2006).

Tyrosine kinase inhibitors that demonstrate growth-inhibitory activity against both wild-type and *KIT* D816V mutant neoplastic mast cells include dasatinib, midostaurin and ponatinib (Gleixner et al., 2007, 2013). Combination therapies evaluating in vitro cooperative antineoplastic effects of dasatinib with cladribine, midostaurin and ponatinib show synergistic, anti-proliferative and apoptotic

effects against D816V neoplastic mast cells (Gleixner et al., 2007, 2013). Ponatinib also down-regulates phosphorylation of the tyrosine kinase protein LYN and the transcription factor STAT5, suggesting that ponatinib may contribute to neoplastic mast cell growth inhibition in a Kit-independent manner (Gleixner et al., 2013).

A compelling new therapy for SM patients with D816V mutation is the use of BLU-285, a potent and selective inhibitor of the Kit activation loop. In vitro, BLU-285 blocks autophosphorylation of D816V mutant Kit as well as phosphorylation of downstream Kit signalling proteins (AKT and STAT3), thereby inducing cellular apoptosis (DeAngelo et al., 2017; Drummond et al., 2016; Jawhar, Naumann, et al., 2016). In phase I human clinical trials, BLU-285 was well tolerated by patients and mast cell burden in peripheral blood, bone marrow and organs decreased (DeAngelo et al., 2017; Drummond et al., 2016). Moreover, BLU-285 shows efficacy in D816V SM patients resistant to the TKI midostaurin (Drummond et al., 2016; Jawhar, Naumann, et al., 2016). Such therapies may be of value in the veterinary setting as well.

7 | CONCLUSIONS AND PROSPECTS

Mast cell neoplasia is most often described in dogs but has been observed in numerous other mammals, birds and reptiles. Despite differences in the clinical presentation and biological behaviour documented across species, a common genetic anomaly exists within the *KIT Proto-Oncogene* of neoplastic mast cells. Mutations in *KIT* are regularly identified in neoplastic mast cells of dogs, cats and humans and contribute to mast cell carcinogenesis. The *KIT* gene is also likely to be implicated in the disease within other species as determined by aberrant cytoplasmic Kit protein staining in ferrets, horses and cattle.

The dog is particularly susceptible to MCT disease, but *KIT* is not the sole genetic contributor to tumour development. Genetic alterations frequently detected in human mastocytosis patients are not common in the dog and few other genes have been explored as potential causative factors in dogs. Thus, the exact molecular events and genetic predispositions contributing to the establishment and growth of canine MCTs remain unknown.

Mast cell neoplasia is generally well managed in most feline and human cases, however, presents a therapeutic problem in the dog due to its varied biological nature. TKIs are approved for use in veterinary medicine for the treatment of unresponsive or recurrent high-grade canine MCTs harbouring a regulatory-type *KIT* mutation. The place of TKIs in canine MCT treatment is not entirely clear but they appear to provide a useful addition to standard therapies. Combination therapies supplementing the use of conventional chemotherapeutic agents with TKIs are being explored and hold promise as new treatment opportunities for canine MCT patients.

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