Veterinary Oncology

REVIEW Open Access

Tyrosine kinase inhibitors in canine solid tumours: a systematic review of indications, response and safety

Fernanda Barthelson Carvalho de Moura[1], Renee Laufer Amorim[1] and Carlos Eduardo Fonseca-Alves[1*]

Abstract

Tyrosine kinase inhibitors (TKI) are targeted therapeutic agents offering precise cancer treatment by disrupting pathways critical for abnormal cell proliferation and survival. In veterinary oncology, TKI initially emerged as a targeted therapeutic approach for managing mast cell tumors, and have been applied to treat other solid tumors in dogs. However, the use of TKI for solid tumors remains challenging. Therefore, this study aimed to perform a systematic review of the use of TKI in canine solid tumors. A comprehensive literature search was conducted across PubMed for studies published from 1986 to July 2025 according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses' guidelines. The terms used were "Tyrosine kinase inhibitors" and "dogs" for the systematic review. Studies were selected based on tyrosine kinase expression in neoplastic processes and the use of TKIs in both in vitro and in vivo settings in dogs. A thorough investigation of PubMed and relevant reference lists revealed 200 studies that met this review's inclusion criteria. The studies were further categorized into therapeutic targeting of canine malignancies and the clinical applicability of commonly used TKIs in dogs. The search yielded 36 publications investigating the direct clinical applications of TKIs in solid tumors. Mast cell tumors (MCTs), osteosarcomas, hepatocellular carcinomas, and transitional cell carcinomas were the most frequently reported types of tumors treated with TKIs. The current literature indicates that toceranib, masitinib, imatinib, lapatinib, sorafenib, vemurafenib, trametinib, dasatinib, and sunitinib are tyrosine kinase inhibitors (TKIs) that have been previously investigated. It is evident from this review that more research is needed to uncover new indications in canine oncology and bridge the knowledge gaps between common human and canine cancers, such as melanomas, carcinomas, and hemangiosarcomas, in the scenario of TKIs.

Keywords Targeted therapeutic agents, Canine solid tumors, Canine

*Correspondence:
Carlos Eduardo Fonseca-Alves
carlos.e.alves@unesp.br
[1]School of Veterinary Medicine and Animal Science, São Paulo State University – UNESP, Botucatu 18618-681, SP, Brazil

© The Author(s) 2025. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc-nd/4.0/.

Introduction

Tyrosine kinase inhibitors (TKIs) are targeted therapeutic agents that block specific enzymes involved in cell signaling [1, 2]. Some TKIs have been tested for toxicity in dogs and offer precise treatment for cancers by disrupting the pathways that are critical for abnormal cell proliferation and survival [3–6].

In veterinary oncology, TKIs initially emerged as a targeted therapeutic approach for managing mast cell tumors and were subsequently applied to treat other solid tumors in dogs [7, 8]. Studies are being conducted on other solid tumors in dogs to increase the understanding of TKIs. For example, one study evaluated the in vitro activity of masitinib mesylate in canine splenic hemangiosarcoma cell lines exposed to increasing concentrations of the drug. This treatment reduced proliferation and induced apoptosis in all cell lines, an effect that was mediated by caspase-3/7 activation [9].

Vemurafenib, a drug that has been tested in dogs with BRAF-mutated urothelial carcinoma, blocks the expression of this protein [10] and has a significant antitumor effect. Trametinib is a tyrosine kinase inhibitor that acts on the MAP kinase (MAPK) pathway [11], which is the signaling pathway that is commonly deregulated in human cancer patients and is similarly activated in several malignancies in dogs [12]. Sunitinib and dasatinib are drugs that are increasingly used in experimental studies, especially for angiogenic tumors and sarcomas [13, 14].

Despite this research, the use of TKIs in solid tumors remains challenging. It is important to organize previous research findings to identify gaps in an attempt to help encourage and promote future research aimed at understanding the utility of TKIs in canine solid tumors. In addition to better understanding the efficacy of TKIs based on the tumor-specific composition and response, studies that associate TKI use with tumor gene expression, which are rare in veterinary medicine, are essential. To identify knowledge gaps and support veterinary oncologists in providing more individualized treatment for their patients, it is crucial to organize and synthesize previous research. Therefore, the purpose of this study was to conduct a systematic review of TKI use in canine solid tumors.

Materials and methods

Review topics

Therapeutic options in veterinary oncology for treating solid tumors in dogs involve a targeted approach with TKI use. In veterinary oncology, therapeutic options for treating solid tumors in dogs include targeted approaches such as the use of TKIs.

Study design

This systematic review and the individual participant data (IPD) meta-analysis protocol were based on published PRISMA-IPD guidelines adapted to the topic of interest in the veterinary field [15]. The MEDLINE/PubMed databases were searched on July 03, 2025, for eligible studies published in English for all indexed years (i.e., from 1986 to July 2025) using the search strategy shown in Fig. 1. The terms used for the systematic review were "tyrosine kinase inhibitors" and "dogs". We selected previous studies that evaluated tyrosine kinase expression in neoplastic processes and the use of TKIs in both in vitro and in vivo settings in dogs.

Inclusion and exclusion criteria

This review included studies evaluating TKIs for which dosage protocols had been previously defined for use in canine clinical practice. Studies were included only if they reported clinical response data, such as objective response, complete response, partial response, stable disease, and/or progressive disease, following TKI therapy. Studies written in English were included without restrictions on country of origin.

The exclusion criteria were nonoriginal studies, such as book chapters, congresses, abstracts, dissertations, theses, narrative reviews, integrative reviews, other systematic reviews, and articles that lacked clear ethical approval. Studies that were not open access, were published in languages other than English, involved TKIs used in species other than dogs, focused on other kinases with limited research in canine oncology, or presented single case reports were also excluded from this review.

Statistical analysis and data synthesis

All extracted data were reported in a standardized data extraction table with information such as authors/year, study type, and outcomes assessed. A descriptive analysis of the included studies on solid tumor types and treatments was performed, and frequencies and percentages were reported. The data were analyzed using Microsoft Excel (version 365). The data are presented as pie charts for the relative frequencies of the main tumors and therapeutic findings.

To support data synthesis and streamline the manuscript preparation, the authors used ChatGPT (OpenAI, GPT-4) to assist in summarizing the literature and organizing structured content (e.g., tabular overviews of TKIs). All AI-assisted output was critically reviewed, edited, and verified by the authors to ensure accuracy, originality, and alignment with the scientific context. This usage complies with Springer Nature's authorship and ethical guidelines. No AI tool was used for final data interpretation or authorial decision-making.

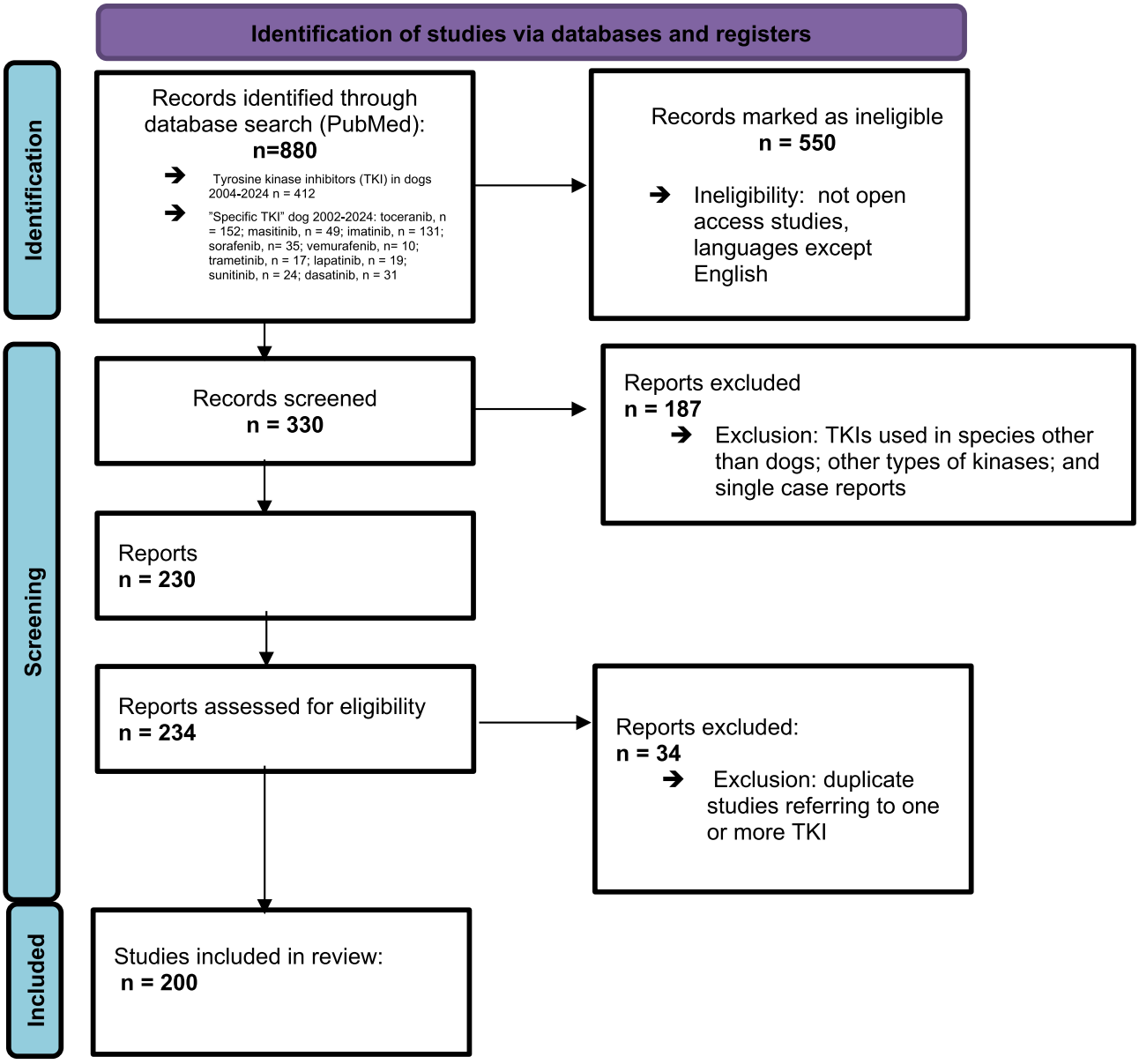


Fig. 1 PRISMA flowchart representing the [15] search strategy ('tyrosine kinase' dog OR canine) AND ('toceranib' dog OR canine) AND ('masitinib' dog OR canine) AND ('imatinib' dog OR canine) AND ('sorafenib' dog OR canine) AND ('vemurafenib' dog OR canine) AND ('trametinib' dog OR canine) AND ('lapatinib' dog OR canine) AND ('sunitinib' dog OR canine) AND ('dasatinib' dog OR canine)

To assess the antitumor response with each TKI, the data were collected from each article, and the articles were assessed according to the Veterinary Cooperative Oncology Group (VCOG) recommendations [16]. The antitumor response was classified as a complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD) [16]. For data visualization and table construction, each tumor subtype and its respective antitumoral response were extracted and separated. If the information could not be retrieved, we used "not evaluated" (NE). When the antitumor response was available for the same histological subtype in more than one study, a mean response was provided.

To summarize the data and to obtain better visualization of data related to efficacy and antitumor response, we extracted data from each selected paper with available data (CR, PR, SD and PD) and the percentage of response (CR, PR and SD for at least 4 weeks), created a heatmap (Fig. 3) and included the final antitumor rate in a table (Table 1). All extracted data were reported in a standardized data extraction table with information such as author/year, study type, and outcomes assessed, as shown in the Supplementary Material Table.

Table 1 Table with response rates (%), overall survival (days) and PFS (days) by tumor type

Tumor	CR	PR	SD	PD
MCT[a]	22.0	45	20.0	13.0
OSA[b]	10.0	30	35.0	25.0
HSA[c]	5.0	25	40.0	30.0
AGASACA[d]	12.0	35	30.0	23.0
Melanoma	3.0	25	20.0	52.0
TCC[b]	8.0	30	30.0	32.0
Lymphom[a]	15.0	20	40.0	25.0
GIST[e]	100.0	0	0.0	0.0
InvUC[f]	2.3	25	20.5	52.2
Others	32.0	35	25.0	29.5

Tumor	Overall Survival (days)	PFS (days)
MCT[a]	491	118.0
OSA[b]	242	149.0
HSA[c]	215	105.0
AGASACAd	509	134.0
Melanoma	119	66.0
TCCb	210	210.0
Lymphoma	85	60.5
GIST[e]	360	360.0
InvUC[f]	448	140.0
Others	219	146.0

[a]*MCT* Mast cell tumors

[b]*OSA* osteosarcoma

[c]*HSA* hemangiosarcoma

[d]*AGASACA* Apocrine gland anal sac adenocarcinoma

[e]*GIST* Gastrointestinal stromal tumors

[f]*InvUC* Invasive urothelial carcinoma

Results

A total of 412 studies involving TKIs in dogs were identified in PubMed from 1986 to July 2025. Separate studies were conducted for each TKI (toceranib, masitinib, imatinib, sorafenib, vemurafenib, trametinib, lapatinib, sunitinib, and dasatinib), totaling 880 studies on TKIs in dogs. A total of 550 records were marked as ineligible for the review because they were not open-access studies or were in languages other than English.

From the 880 studies, 330 were selected for this review on the basis of their application in routine canine clinics. Tyrosine kinases used in other noncanine species, other kinases with few studies in canine oncology patients, and single case reports were excluded ($n = 187$). The studies were further categorized into therapeutic targeting in canine malignancies and the clinical applicability of commonly used TKIs in dogs. Duplicate studies that referred to one or more TKIs were excluded and considered only once ($n = 234$). The search revealed 200 publications on the expression of TKIs in solid tumors (PRISMA Flowchart, Fig. 1) [15].

Mast cell tumors (MCTs), carcinomas, sarcomas, insulinomas, chemodectomas, lymphomas, melanoma, pheochromocytoma, and GIST were the most common tumors treated with TKI therapy. Toceranib was the most common TKI used to treat tumors in the clinic, followed by masitinib, imatinib, sorafenib, trametinib, vemurafenib, lapatinib and dasatinib (Table 1). No studies directly investigated the use of sunitinib in treating canine tumors (Fig. 2). However, studies were found that explored its indirect use, such as testing the translational efficacy of toceranib and sunitinib in both humans and canines. Thus, information regarding the dose and activity of sunitinib for the clinical treatment of canine tumors is available, which is why this TKI was included in the present review [2].

The studies reported variable response rates (%), which were mostly related to the different tumor subtypes assessed and the TKIs used. A high antitumor response of canine MCTs was observed with toceranib and masitinib. Furthermore, toceranib demonstrated good performance in terms of PR and SD in both mono- and combined-therapy settings, with high survival rates in patients with nasal carcinoma. Additionally, toceranib monotherapy showed a good partial response for AGASACA. Conversely, the antitumor response was considered mild to low for the different subtypes of carcinomas and sarcomas. Imatinib was considered to provide high antitumor response rates in gastrointestinal stromal tumors (GISTs). Some combinations lacked data (blank cells), suggesting gaps in the literature. Notably, these were descriptive analyses and conclusions derived from the studies. However, importantly, the number of studies comparing TKIs with clinical explorations was highly variable (i.e., other TKIs had scarce or incomplete data), making consistent comparisons difficult.

Toceranib and masitinib showed a predominance of partial response (PR) with modest rates of CR and SD in the studies. An improvement in PR and complete response (CR) rates was observed with combination therapies, especially with toceranib. Other TKIs had scarce or incomplete data, suggesting that the evidence base remained limited for full comparisons (Fig. 3). The associations of TKIs with chemotherapy and other antineoplastic drugs were also assessed, as shown in the Supplementary Table. The TKIs toceranib, masitinib and imatinib had a large number of studies in association with other antineoplastic drugs. Conversely, vemurafenib, lapatinib, sorafenib and trametinib are emerging drugs with few pharmacokinetic studies, and no studies presenting antitumor responses were identified (Fig. 4). The final antitumor response to the use of TKIs with antineoplastic drugs seemed to be similar. However, the response duration varied among the studies, highlighting the need for prospective studies to draw conclusions.

In general, PFS appeared to be longer with combined therapy versus monotherapy, indicating the potential benefit of combined therapies in preventing tumor

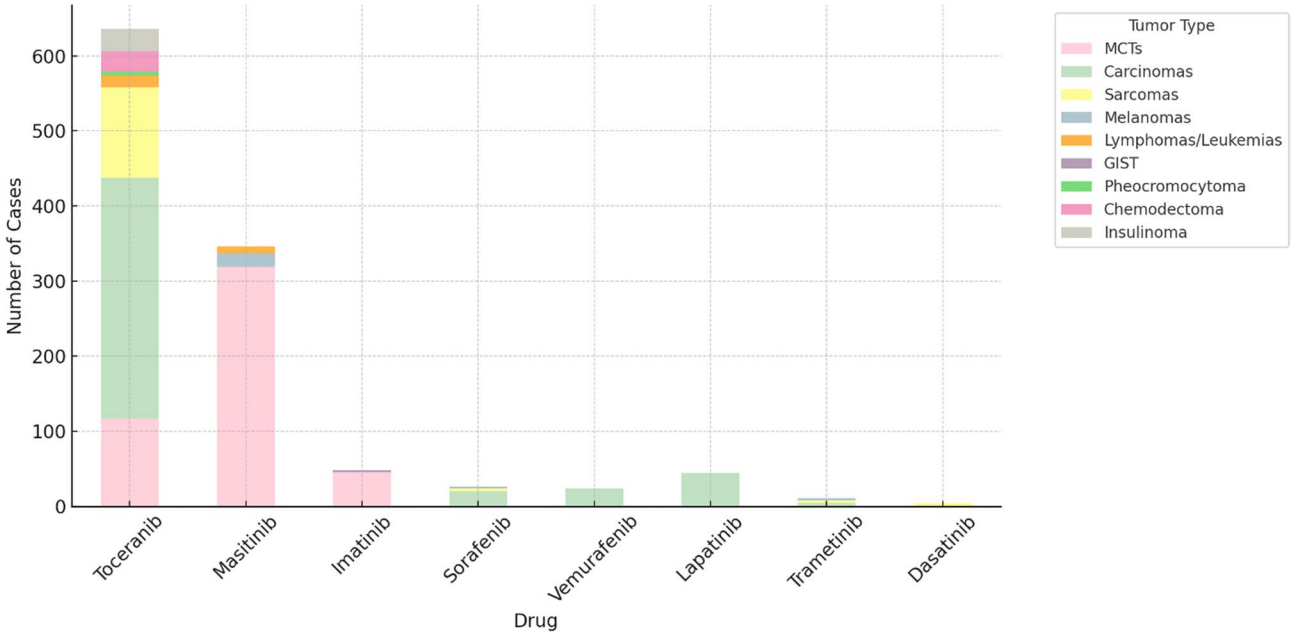


Fig. 2 Distribution of TKI-treated cases per tumor type. Mast cell tumors (MCTs) ($n=481/1139$), carcinomas ($n=428/1139$), sarcomas ($n=135/1139$), insulinomas ($n=30/1139$), chemodectomas ($n=27/1139$), lymphomas ($n=26/1139$), melanoma ($n=23/1139$), pheochromocytomas ($n=5/1139$) and GIST ($n=3/1139$) were the most common tumors treated with TKI therapy. Toceranib was the most common TKI used for the clinical treatment of tumors ($n=41/200$), followed by masitinib ($n=5/200$), imatinib ($n=4/200$), sorafenib ($n=3/200$), trametinib ($n=2/200$), vemurafenib, lapatinib and dasatinib ($n=1/200$)

progression. Toceranib and masitinib had the highest averages for both monotherapy and combination therapy, especially for OS. Some TKIs did not have complete OS/PFS data, suggesting that the evidence base is still limited for full comparisons (Fig. 3).

Toceranib

Toceranib is a TKI that acts on many targets, including c-kit, VEGFR and PDGFR [17–24]. Toceranib gained approval for treating canine mast cell tumors in 2009 [25–35] but has since shown efficacy in treating other neoplasms ($n=39$), including carcinomas (nasal, mammary, adeno-, urothelial, hepatocellular, pancreatic, thyroid, and pituitary), sarcomas (osteosarcoma and hemangiosarcoma), gastrointestinal stromal tumors (GISTs), adrenal tumors (i.e., pheochromocytoma), heart-based tumors, aortic chemodectoma, mesothelioma, insulinoma, leukemia and lymphomas (Fig. 2) [36–80]. The adverse effects of toceranib administration include proteinuria, thyroid dysfunction, gastrointestinal toxicity, and tumor resistance [69–74]. Studies involving monotherapy, multimodal therapeutic approaches, and toceranib have been reported in the literature. For example, chemotherapeutic drugs (vinblastine, doxorubicin, carboplatin, and cyclophosphamide), immunomodulatory drugs (nonsteroidal anti-inflammatory agents, i.e., piroxicam and prednisolone), and repurposing drugs (thalidomide and losartan) have previously been tested with toceranib, and other TKI combinations (imatinib and sorafenib) have been studied in combination or in comparison with toceranib. Its safety for use alone or in combination with other drugs, surgery, or radiotherapy is well known and characterized as long-term or palliative support for solid tumors in dogs [36, 38, 39, 48–52, 58, 61, 75–87]. Different doses of toceranib have been established as therapies for solid canine tumors (Fig. 5).

Masitinib

Studies have shown that masitinib is a tyrosine kinase inhibitor that acts on c-KIT and PDGFR (α and β) targets [88, 89] and is used for the treatment of canine mastocytomas expressing c-KIT gene mutations [7, 20, 25, 89–99]. Studies have investigated its ability to inhibit the JAK2/STAT5 signaling pathway, which is also known to be involved in mastocytoma progression [37, 100–110]. Some studies have been conducted to investigate other solid tumors and masitinib ($n=5$), such as MCTs, melanoma and lymphoma (Fig. 2) [93, 94, 97, 101] and [103]. Fewer studies have examined monotherapy and multimodal therapeutic approaches with masitinib compared with those involving toceranib. However, its association with doxorubicin in comparison to imatinib has been reported [110]. One study reported the use of masitinib for the treatment of atopic dermatitis and showed its ability to decrease and modulate the inflammatory processes involved in the disease [111]. Doses of masitinib have

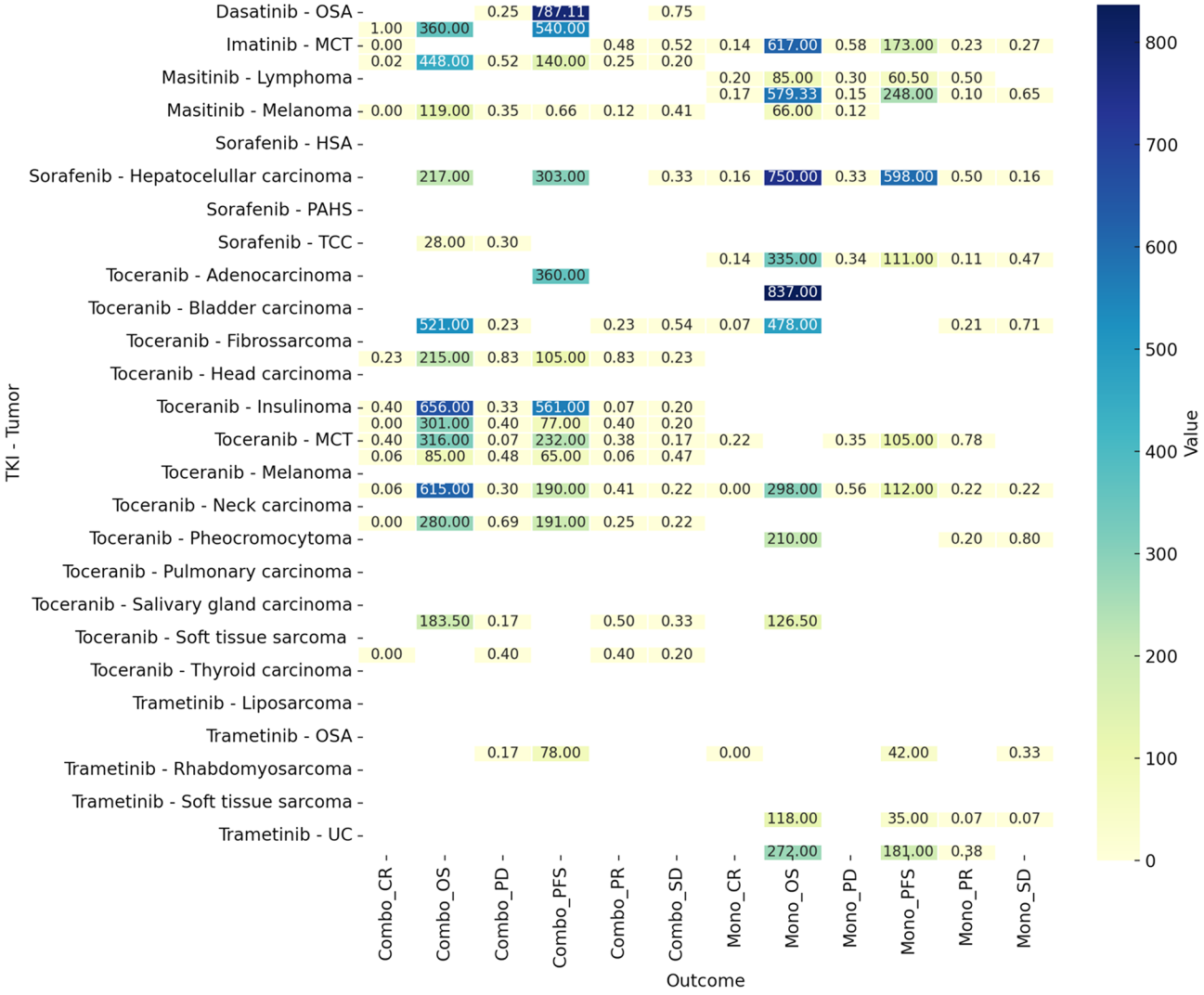


Fig. 3 Heatmap showing a graphical condensed and comparative view of the main therapeutic outcomes by TKI and tumor type. **Rows** represent combinations of TKIs and tumors. **Columns** show the main outcomes of monotherapy and combination therapy. **Darker cells** indicate higher values, such as a higher response rate or longer survival. **Lighter cells** indicate lower values, such as a lower response rate or lower survival. **Blank cells** represent the information that could not be retrieved (NE)

been established as therapies for solid canine tumors, using a dose of 12.5 mg/kg. The most common adverse events reported in studies with masitinib included vomiting, diarrhea, decreased appetite, lethargy, and mild neutropenia [93, 94, 97, 101] and [103].

Imatinib

Studies have shown that imatinib is a tyrosine kinase inhibitor that acts on c-KIT, BCR-ABL, and PDGFR [2, 99, 112–122]. Imatinib is usually used in solid tumor cases presenting resistance or intolerance to toceranib or masitinib [123–137]. Some studies have investigated the use of imatinib for the treatment of various tumors ($n = 4$), including mastocytomas and GISTs (Fig. 2) [46, 96, 131, 136]. There are fewer studies involving monotherapy and multimodal therapeutic approaches with imatinib compared with those involving toceranib and masitinib. However, some studies have reported its association with chemotherapy drugs (doxorubicin and vinblastine) and immunomodulatory drugs (prednisone) and compared its target effects with those of masitinib and dasatinib [109]. One preclinical study investigated the use of imatinib, a repurposing drug, as an antiviral agent [138]. The adverse effects of imatinib administration that were previously explored are diastolic dysfunction and ventricular early repolarization in anesthetized dogs, and imatinib inevitably induces tumor resistance [139, 140]. Its safety for use alone or in combination with other drugs and in surgery is well established in the literature [141, 142]. Imatinib 10 mg/kg has been established as a therapeutic option for solid canine tumors [46, 96, 131, 136].

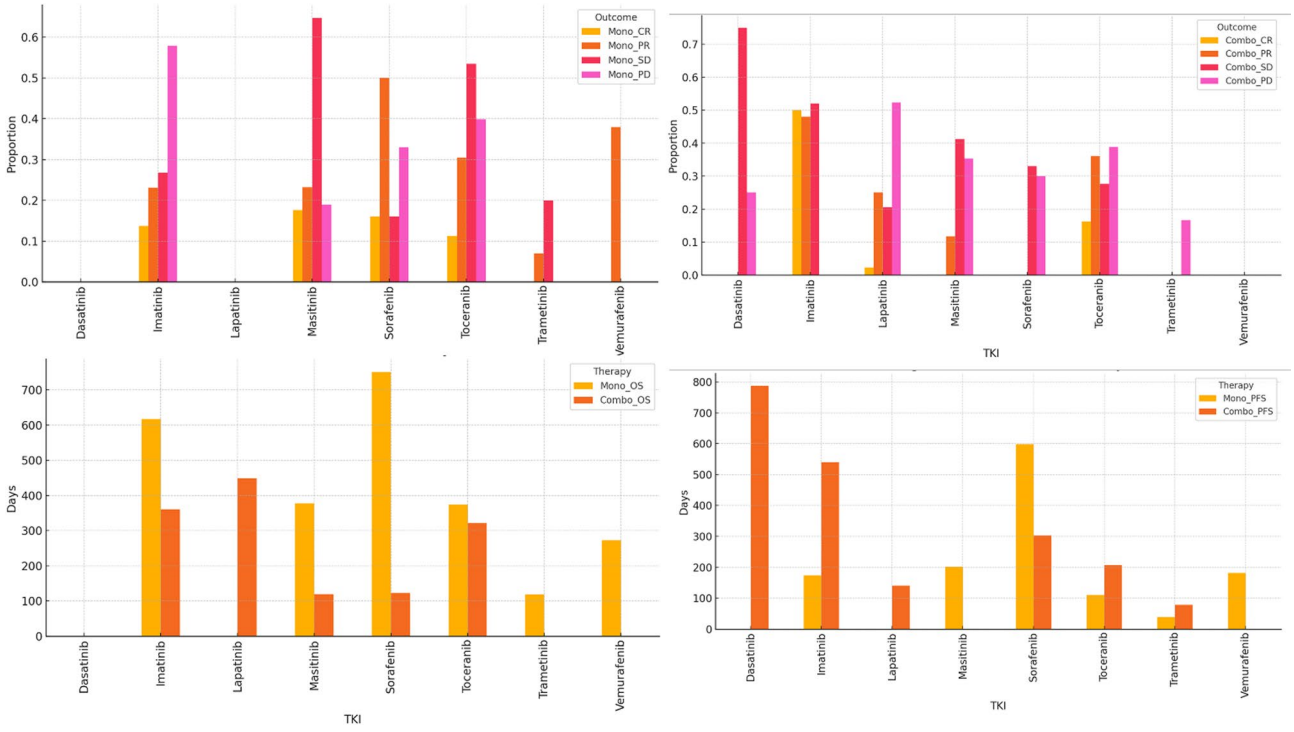


Fig. 4 Bar graphs showing the proportion of response rates (CR, PR, SD, PD) between TKI monotherapy (mono) and combination therapy (combo) and the mean overall survival (OS) and progression-free survival (PFS) per TKI and therapeutic modality

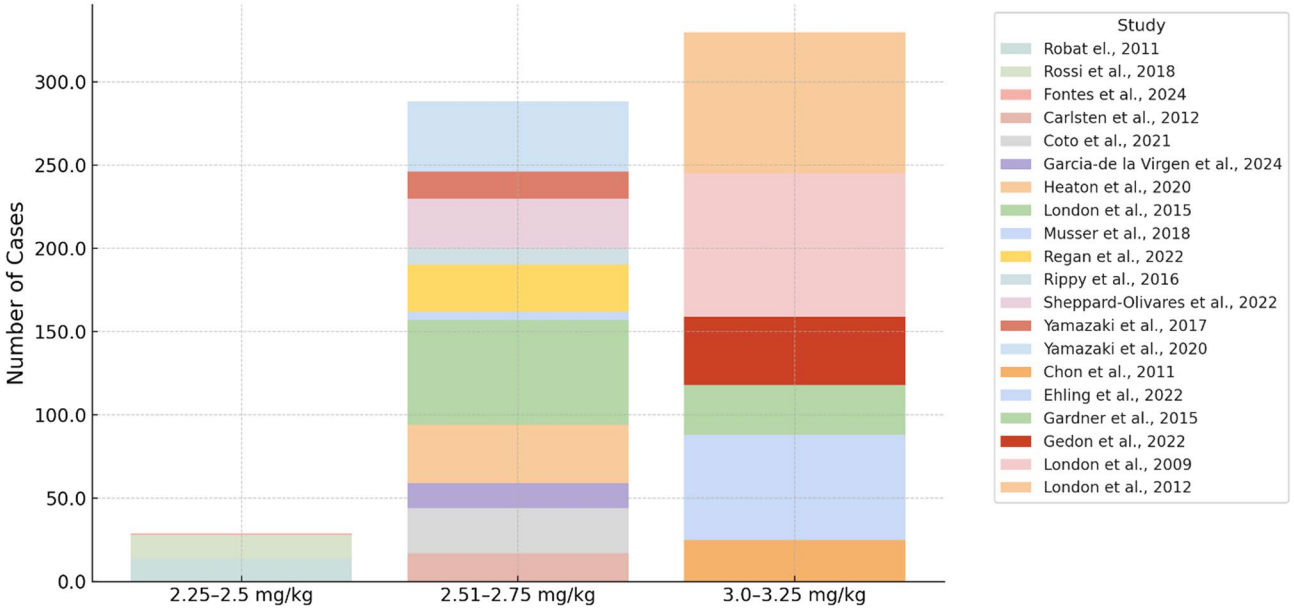


Fig. 5 Number of patients treated with toceranib in different studies on the basis of dosage and number of cases

Sorafenib

Sorafenib is a multitarget tyrosine kinase inhibitor that acts on multiple targets, including VEGFR, PDGFR, RAF, KIT, and FLT-3 [143–157]. Its use in dogs has not been approved for specific veterinary indications. However, sorafenib has been explored in preclinical studies and off-label cases ($n = 3$) to treat neoplasms that share similar molecular mechanisms with those targeted in humans, such as carcinomas (hepatocellular, mammary, gastric, and transitional cells), sarcomas (osteosarcoma and hemangiosarcoma), or BRAF-resistant tumors (Fig. 2) [136, 152, 157]. One study compared sorafenib and toceranib for hepatocellular carcinoma in vitro [156]. Another study evaluated and noted the synergistic effects of

doxorubicin and sorafenib in canine osteosarcoma cells [153]. Sorafenib was considered well tolerated in one study involving oral administration in oncological canine patients [157]. Sorafenib 3 mg/kg has been established as a therapy for solid canine tumors [132, 148, 153].

Vemurafenib

Studies have shown that vemurafenib is a tyrosine kinase inhibitor that acts on BRAF [148]. Only a few studies ($n = 2$) have examined vemurafenib in vivo to treat dogs with BRAF-mutated urothelial carcinoma (Fig. 2) [149]. In dogs with BRAF-mutated invasive urothelial carcinoma, vemurafenib treatment leads to immune-related transcriptomic changes similar to those observed in humans, specifically, early T-cell infiltration followed by immune failure as the cancer progresses [10]. Two studies compared the effects of vemurafenib with those of trametinib and sorafenib in vitro [10, 158, 159]. These findings, along with the drug's safety profile, antitumor effects, and resistance patterns in dogs, strongly support the use of canine InvUC as a valuable model for advancing BRAF-targeted therapies in human medicine. A vemurafenib dose of 37.50 mg/kg has been established as a therapy for solid canine tumors [10].

Trametinib

Studies have shown that trametinib is a tyrosine kinase inhibitor that acts on the ERK, AKT, and MAP kinase (MAPK) pathways [11, 12, 158–161]. In veterinary medicine, use of trametinib is still in the experimental phase and has been explored mainly in preclinical studies for canine neoplasms ($n = 1$), such as carcinomas (urothelial and squamous cells), sarcomas (osteosarcoma, rhabdomyosarcoma, soft tissue sarcoma and liposarcoma) and melanomas, which share molecular characteristics with human tumors (Fig. 2) [12]. One study compared trametinib and imatinib in vitro [162]. Another study evaluated the effects of trametinib against oral squamous cell carcinoma; the drug produced ~ 40% and ~ 80% tumor regression in tumor cells in vitro, and a partial response was observed in one patient (PR 16,6%) [158]. A 0.025 mg/kg dose of trametinib has been established as a therapeutic option for solid canine tumors [12]. Trametinib toxicity has been described, and dose limiting is fundamental considering G3 toxicity, such as hypertension, proteinuria, ALKP elevation, and lethargy [12].

Lapatinib

Studies have shown that lapatinib is a tyrosine kinase inhibitor that blocks EGFR1 and HER-2 and modulates MAP kinase (MAPK) pathways [163–166]. Lapatinib has the potential to be used in veterinary practice to treat dogs with pulmonary, invasive urothelial, and mammary carcinomas and gliomas [164–167]. Among the studies of lapatinib as a treatment option for tumors ($n = 1$), one used lapatinib to treat patients with invasive urothelial carcinoma (Fig. 2) [168]. Two studies have evaluated lapatinib safety in canines [169, 170]. It was considered well tolerated in studies in which it was orally administered to dogs. A study in which lapatinib was used to treat invasive urothelial carcinoma reported possible side effects of diarrhea, rash, fatigue, nausea, and vomiting [169–171]. Lapatinib 25,00 mg/kg has been established as a therapy for solid canine tumors [169, 170].

Sunitinib

Studies have shown that sunitinib is a tyrosine kinase inhibitor that inhibits multiple tyrosine kinases, including c-KIT, VEGFR, and PDGFR, similar to toceranib and imatinib [172]. Studies are being conducted to evaluate the efficacy of these agents in inhibiting tumor angiogenesis and blocking stromal and tumor proliferation [147]. In veterinary medicine, sunitinib has been investigated mainly for canine neoplasms and has been applied in experimental studies and off-label cases. Studies have been conducted on leukemia and insulinoma [13, 173]. Toxicity studies have been conducted in dogs, and sunitinib is considered to be well tolerated in canine species [174]. One side effect that was previously explored with TKIs and also observed with sunitinib is diastolic dysfunction and ventricular early repolarization; however, these side effects are less significant than those of imatinib, so it may be an interesting drug to explore for cardiopathy patients [175, 176]. One study reported a synergistic effect when combined with cisplatin, which reduced its nephrotoxicity [177]. Two other studies explored and compared sunitinib and toceranib for non-mast cell neoplasia, which showed promise for clinical use in canine patients with cancer [178]. However, no studies have established dose escalation for sunitinib for canine solid tumors; it is mentioned only as a second-line treatment for tumors resistant to toceranib and imatinib. In the studies where it was mentioned, the dose used was not mentioned [179].

Dasatinib

Dasatinib is a tyrosine kinase inhibitor that inhibits multiple tyrosine kinases, including the c-KIT, PDGFR, BCR-ABL and EPHA2, ERK and AKT pathways [142, 178–180]. Dasatinib has been investigated for canine neoplasms because it acts on receptors related to tumor growth [114, 143]. Studies have been previously conducted on mastocytoma, carcinoma (mammary), and sarcoma (histiocytic sarcoma, osteosarcoma, and hemangiosarcoma) in vitro [14]. One study explored the use of dasatinib for the clinical treatment of dogs with osteosarcoma ($n = 1$) (Fig. 2) [181]. Another study investigated the effects of the combination of dasatinib and loratadine

on tumor growth [182]. Additionally, a study compared dasatinib with imatinib in relation to a report on tumor resistance and showed that it was a possible therapeutic target [91, 134, 140]. One side effect that was previously explored with TKIs such as toceranib and with dasatinib is gastrotoxicity [183]. Dasatinib 0.75 mg/kg has been established as a therapy for solid canine tumors [181].

Discussion

This systematic review highlights the growing relevance of TKIs in veterinary oncology, particularly in dogs, where these agents have been progressively integrated for the treatment of different tumors. The clinical use of TKIs for solid tumors in dogs is promising, and toceranib, imatinib, and masitinib have been studied extensively. Unlike in human oncology, the use of TKIs is not guided by predictive markers [184, 185]. Human patients are usually screened for specific markers according to each tumor subtype, and a precision medicine approach is applied to redirect therapy. In dogs, little is known about the association of predictive markers with the application of precision medicine [169]. Maeda et al. [169] evaluated the antitumor response to lapatinib on the basis of the HER-2 immunoscore (0, 1+, 2+ or 3+) using immunocytochemistry and identified a strong association between the lapatinib antitumor response and the HER-2 2+ and 3+ scores. Moreover, HER-2 activation seems to be important in canine lung adenocarcinoma [169, 186], and HER-2^{V659E} mutations have been identified in blood samples from dogs affected by this tumor subtype. Therefore, the HER-2^{V659E} mutation may represent an interesting predictive marker.

Interestingly, Yamazaki et al. [39] evaluated the adjuvant effect of toceranib in dogs with different carcinomas and compared VEGFR-2 expression in the first tumor biopsy with the same tumor after relapse. Two groups were assessed (carcinoma treated with only surgery versus surgery with adjuvant toceranib), and dogs that received toceranib experienced a longer survival time and decreased VEGFR-2 expression when the tumor relapsed. These findings indicated that toceranib was effective for blocking VEGFR-2 expression and that tumor relapse may be associated with the activation of a different pathway. In this context, VEGFR-2 may represent an interesting predictive marker for the antitumor response to toceranib. Additionally, immunohistochemistry screening of VEGFR-2, EGFR-1, PDGFR-beta, ERK1/ERK2 (MAPK), KIT and HER-2 has been proposed as a possible predictive panel for TKI selection [187]. However, additional studies are needed to validate the use of predictive markers for the selection of different TKIs for canine cancer treatment.

Among the TKIs analyzed, toceranib (TOC) has emerged as the most widely studied and clinically applied drug, especially in canine MCTs [1, 29, 30, 83]. Initially, TOC was approved for the management of canine MCTs because of its ability to inhibit mutated KIT, and subsequent studies have demonstrated broader efficacy across a variety of non-MCT solid tumors, including carcinomas (mammary, nasal, hepatocellular, thyroid, and urothelial), sarcomas (osteosarcoma and hemangiosarcoma), gastrointestinal stromal tumors (GISTs), and even neuroendocrine neoplasms, such as insulinomas and pheochromocytomas [39, 68, 76, 77]. The mechanism of action of toceranib involves the inhibition of multiple targets, including VEGFR, PDGFR, and c-KIT, which are commonly expressed in the tumor vasculature and stromal compartments of solid neoplasms. This multitarget activity may be attributed to its antiangiogenic and antiproliferative effects across tumor types. However, clinical response rates vary considerably among different tumor types, with MCTs showing the highest objective response rates (up to 75%), whereas carcinomas and sarcomas typically exhibit lower or more variable responses (20–45%) [39]. Therefore, TOC has also been widely used for different solid tumors with no specific criteria [36–79]. Overall, the use of TOC in solid tumors has provided controversial results, which we believe could be related to the lack of predictive markers to select tumors capable of activating TOC targets.

Despite the controversial response rates in non-MCT tumors, TOC is frequently used in palliative settings or as an adjuvant therapy, particularly for inoperable, recurrent, or metastatic solid tumors [36, 38, 39, 48–52, 58, 61, 79–87]. Its oral administration, relative safety profile, and possibility for long-term use make it a valuable option in veterinary oncology, especially when combined with surgery, chemotherapy, or immunomodulatory agents [36, 39, 49, 188]. Notably, studies suggest that the benefits of toceranib may extend beyond tumor shrinkage; in some cases, it may contribute to disease stabilization, improved quality of life, and prolonged progression-free survival [48–52].

Nevertheless, resistance mechanisms and treatment-limiting adverse effects (such as gastrointestinal toxicity, proteinuria, and thyroid dysfunction) remain important considerations for its long-term administration [73–78]. Further studies of biomarker identification, optimal dosing strategies, and patient stratification are essential to increase the efficacy of toceranib in a broader range of canine solid tumors.

Masitinib and imatinib represent two of the most frequently studied TKIs in veterinary medicine after TOC, and both show clinical relevance, primarily in tumors expressing mutated or overexpressed c-KIT [7, 8, 20, 25, 72–99]. In this review, masitinib demonstrated a high response rate in canine MCTs, with objective response rates reaching 70%; these rates are highly comparable

to those observed with toceranib [92, 93, 97, 101] and [103]. Most studies of masitinib have focused on MCTs, particularly in dogs that harbor activating c-KIT mutations, reinforcing its targeted mechanism of action via c-KIT and PDGFR inhibition. However, imatinib is less studied in canine MCTs since masitinib blocks the same receptors and there is a commercial product available for dogs (in contrast to imatinib). Nevertheless, the use of masitinib beyond MCTs remains limited, with only isolated reports for melanomas, sarcomas, and carcinomas and no robust efficacy data across tumor types [92, 93, 97, 101] and [103]. Additionally, few studies have investigated masitinib in multimodal therapy protocols, although some have reported combinations with doxorubicin or comparative analyses with imatinib, highlighting the need for broader clinical trials to assess its role beyond c-KIT–driven neoplasms [96]. Interestingly, the potential anti-inflammatory and immunomodulatory properties of masitinib (demonstrated in studies on atopic dermatitis) raise the question of whether adjunct immunologic effects may contribute to tumor control in select cases, but this remains speculative in oncology [111].

Imatinib, conversely, has demonstrated a broader spectrum of applications, showing efficacy not only in MCTs (60%) but also in leukemias (65%) and gastrointestinal stromal tumors (75%). Its action on BCR-ABL, c-KIT, and PDGFR makes it particularly relevant in tumors with mutational activation of these pathways [46, 96, 131] and [136]. Moreover, imatinib has been evaluated as an alternative for patients who are resistant or intolerant to toceranib or masitinib, and several studies have explored its combined use with chemotherapy or corticosteroids. In those settings, response rates improved (e.g., from 55% in monotherapy to 70% in combination therapy), although the studies varied in design and treatment duration [46, 96, 131] and [136].

However, the use of imatinib has been associated with cardiotoxicity, including diastolic dysfunction and early ventricular repolarization, which may restrict its use in patients with preexisting cardiac conditions [139, 140]. Furthermore, the development of resistance to imatinib, as described in both human and veterinary oncology, underscores the importance of molecular monitoring and potential sequencing with other TKIs, such as dasatinib and sunitinib [178, 181].

Taken together, both masitinib and imatinib have demonstrated clinical utility in MCTs, especially when c-KIT mutations are present, but their broader use in canine oncology requires more robust, prospective, and controlled studies. Future studies that incorporate molecular profiling, pharmacogenomics, and combination protocols could help to expand their indications and optimize patient selection, particularly in less responsive tumor types such as sarcomas and carcinomas [143].

Sorafenib has demonstrated moderate efficacy in aggressive tumors, particularly carcinomas and sarcomas. While it is not as widely used as toceranib or imatinib, its experimental application in refractory tumors shows potential, especially in combination regimens. In one study of canine hepatocellular carcinoma cell lines, the efficacy of toceranib and sorafenib was tested [42]. Another study designed to evaluate the efficacy of first-line sorafenib in the treatment of 13 canine patients with hepatocellular carcinoma reported a 56% objective response (CR + PR), with overall survival and PFS rates of 750 and 598 days, respectively, using a monotherapy treatment regimen [157]. Sorafenib was well tolerated when administered orally in canine cancer patients [136, 152, 157].

Vemurafenib has shown promising results in BRAF-mutated tumors, especially in certain melanomas and carcinomas. Its targeted use makes it particularly effective when molecular profiling guides treatment, although its clinical use remains limited [10]. In that study, 24 patients received vemurafenib, with 38% achieving a PR, 272 OS and 181 PFS [10]. In 18% of the dogs, dermatological lesions were observed, a known pharmacodynamic effect of vemurafenib that has also been reported in humans [10].

Lapatinib has been used in studies targeting HER2-positive carcinomas and gliomas, with variable results. It remains largely experimental, and its use in combination with other drugs has not been widely evaluated [164, 166–169, 189]. One study used piroxicam in combination with combined therapy to treat patients with invasive urothelial carcinoma and achieved a 27.3% objective response with OS and PFS rates of 448 and 140 days, respectively [169]. Two studies have evaluated lapatinib safety in canines [171, 172] and found it to be well tolerated with oral administration in dogs. The study in which lapatinib was used to treat invasive urothelial carcinoma reported possible side effects of diarrhea, rash, fatigue, nausea, and vomiting. These side effects are associated with piroxicam or PD, but further studies are needed to evaluate the clinical response and eventual consequences associated with this TKI [169–171].

Trametinib has been evaluated in melanomas and carcinomas, which are often selected for MAPK pathway-driven tumors. While data are limited, its targeted mechanism suggests a role in personalized veterinary oncology approaches [162]. One trial of histiocytic sarcoma in dogs has been reported [190], which provides potential information on the pharmacokinetics and applicability of this drug in veterinary oncology [190]. In one study, the use of trametinib demonstrated a 49.9 objective response with a PFS of 78 days [12]. Studies of

vemurafenib, lapatinib and trametinib were mostly conducted as monotherapies. However, this observation reveals a key limitation given the low number of clinical studies conducted with this TKI.

Sunitinib has been evaluated in a limited number of studies. It has been primarily examined in sarcomas and highly vascular tumors owing to its antiangiogenic and multikinase inhibitory properties. While clinical response rates were modest, the drug showed potential in patients who were refractory to first-line treatments. Combination therapy was explored in isolated studies and suggested a slight improvement in disease stabilization, although adverse effects such as myelosuppression and gastrointestinal toxicity were also noted. Overall, sunitinib remains a promising but underexplored option in veterinary oncology that warrants further investigation in controlled trials [13, 172]. Dasatinib has been primarily used in sarcomas with mild to moderate efficacy. Combination therapy appeared to modestly improve outcomes, although its use is still considered exploratory in veterinary medicine [174, 175]. These two TKIs are promising for the treatment of veterinary oncological patients, but further studies of their applicability in clinical contexts are needed.

The current literature suggests that MCTs [7, 19, 22, 24, 25, 27–32, 81, 83, 91–93, 96, 98, 111, 116, 122–124, 127, 128, 131, 135, 139, 169, 178, 180–193], osteosarcomas [37, 48, 51, 52, 63, 88, 107, 154, 193–195], hepatocellular carcinoma [146, 152, 155, 184–186], and transitional cell carcinoma [6, 21, 148, 153, 169] are the most common neoplasms associated with TKIs. Canine cancers, such as melanomas, lymphomas, and hemangiosarcomas, have not been studied for therapeutic targeting or clinical applications. Studies of these tumors are still needed since research previously conducted in other neoplasm types has demonstrated different response rates by tumor type and TKI. Studies that associate TKI use with tumor gene expression are fundamental to better understand TKI efficacy [142]. In addition to efficacy, the clinical utility of TKIs in veterinary oncology is influenced by several factors. Resistance mechanisms, such as secondary c-KIT mutations or activation of bypass signaling pathways (e.g., PI3K/AKT or MAPK), have been reported in both canine MCTs and human oncology, which potentially limits long-term TKI responsiveness [8].

No predictive marker is usually used in veterinary medicine, so most patients are treated randomly. However, there is a need for molecular profiling and monitoring during treatment to guide therapeutic adjustments or combination regimens [142]. Furthermore, cost and accessibility remain critical challenges in real-world settings. While some TKIs, such as toceranib phosphate, are approved for veterinary use (e.g., by the FDA in the United States), others are off-label or require compounding, which can increase costs and limit availability depending on regional regulatory frameworks (i.e., the EMA in Europe) [19, 24]. Incorporating these considerations into treatment planning in addition to efficacy and safety may promote more sustainable, individualized, and accessible oncology care for companion animals across different healthcare contexts [142].

Combination therapies are well established in human oncology, but they remain underexplored in veterinary medicine. This gap may be partly due to the predominant use of TKIs as monotherapy, which is often introduced after conventional first-line treatments have failed. As a result, these agents are frequently administered to patients with more aggressive or advanced-stage tumors [1]. Among the TKIs, toceranib, masitinib, and imatinib are the most extensively studied in combination with other antineoplastic agents. Toceranib is commonly utilized both as a single drug and in combination with chemotherapy; it enhances progression-free survival, particularly when combined with agents such as vinblastine or cyclophosphamide [35, 37, 38, 47–51, 57, 60, 74–86]. For example, another study reported an odds ratio of 1.74 when comparing outcomes between dogs treated with toceranib alone and those that received a combination of toceranib and radiotherapy [36]. Two studies explored the effects of masitinib and imatinib [104, 108] and showed that toceranib, masitinib and imatinib significantly improved the efficacy of combined therapies. In contrast, agents such as vemurafenib, lapatinib, sorafenib, and trametinib are considered emerging drugs, and limited data are available on their pharmacokinetics and antitumor efficacy in veterinary patients [12, 48–52, 58, 87, 109, 110, 169].

The most frequently reported side effect of the use of TKIs in dogs is gastrointestinal toxicity. There are reports that toceranib causes a lower frequency of proteinuria and thyroid dysfunction as well as induction of acquired tumor resistance [69–74]. Masitinib has een associated with atopic dermatitis, although this has been less detailed in the literature [111]. Imatinib has been associated with diastolic dysfunction and early ventricular repolarization and with tumor resistance [139, 140]. Sorafenib is well tolerated in dogs, with few adverse effects reported in a limited number of studies. Vemurafenib, trametinib and dasatinib have reported grade 3 toxicities similar to those of TOC [10, 12]. Lapatinib is well tolerated but can cause diarrhea, rash, fatigue, nausea and vomiting [169, 170]. Sunitinib, although rarely studied in dogs, has a favorable safety profile and a lower incidence of cardiovascular effects compared with imatinib; it is being explored for patients with heart disease [175].

One limitation of this review is the potential publication bias inherent in the inclusion criteria because only peer-reviewed and published studies were considered. This approach potentially excluded unpublished data or negative results that might influence the overall conclusions. Additionally, heterogeneity in study designs,

Table 2 Review key takeaways

TKI	Best Responding Tumors	Comparative Outcome	Use with Chemo
Toceranib	MCTs, Carcinomas, Sarcomas	High efficacy in MCTs; mixed elsewhere	Frequent; enhanced PFS
Masitinib	MCTs	Similar to toceranib	Sometimes
Imatinib	GIST, MCTs	Good in KIT mutations	In leukemias
Sorafenib	Carcinomas, Sarcomas	Moderate in aggressive tumors	Experimental
Vemurafenib	Carcinomas	Promising in BRAF-mutated tumors	Limited
Lapatinib	Carcinomas (HER2+)	Variable, mostly experimental	Rare
Trametinib	Carcinomas, Melanomas	Limited studies, promising in MAPK+	Experimental
Sunitinib	Sarcomas, Vascular Tumors	Modest response; underexplored	Occasional; slight benefit
Dasatinib	Sarcomas	Mild to moderate	Sometimes

dosages, tumor types, and outcome measures across the included studies limits direct comparisons and pooled interpretations. For example, the diversity of studies introduces different toceranib doses. The lack of standardized response criteria in veterinary oncology also poses a challenge for the consistent evaluation of efficacy.

Conclusion

This review highlights the diversity in the efficacy, tumor specificity, and application strategies of tyrosine kinase inhibitors (TKIs) in veterinary oncology. Among the agents evaluated, toceranib remains the most extensively studied, particularly for mast cell tumors (MCTs), where it demonstrates consistent and high clinical efficacy, especially when used in combination with chemotherapeutic agents. Masitinib, although used more narrowly, shows comparable results in MCTs. Imatinib stands out for its role in tumors with KIT mutations, such as GISTs and hematopoietic malignancies, where combination therapy improves outcomes. Other TKIs, such as sorafenib, vemurafenib, and trametinib, are promising in selected molecular contexts (e.g., BRAF or MAPK pathway alterations) but remain under clinical validation. Lapatinib and dasatinib exhibit limited but emerging utility, often in experimental contexts, whereas sunitinib, although less frequently studied, has potential in vascularized or resistant sarcomas, especially when combined with other agents. Overall, TKI-based therapy offers a targeted, increasingly personalized approach to managing neoplasms in companion animals. Future efforts should focus on prospective controlled studies, molecular profiling, and standardized response metrics to better define the clinical roles and optimal combinations of TKIs in veterinary oncology (Table 2).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s44356-025-00036-1.

Supplementary Material 1

Acknowledgements
We thank the School of Veterinary Medicine and Animal Science of São Paulo State University for their support and encouragement during this study.

Authors' contributions
FBCM and CEFA performed data curation and formal analysis; FBCM and CEFA investigation and methodology; FBCM and CEFA writing original draft; RLA writing review and editing the manuscript. CEFA supervised, validated and visualized the entire study. All the authors have read and approved the final version of the manuscript.

Funding
This research was funded by the São Paulo Research Foundation (FAPESP) [grant number 2024/06823-3] and the National Council for Scientific and Technological Development (CNPq) [grant number 302977/2021-0].

Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 31 May 2025 / Accepted: 1 August 2025
Published online: 24 September 2025

References

1. London CA. Small molecule inhibitors in veterinary oncology practice. Veterinary Clin North America: Small Anim Pract. 2014;44:893–908.
2. Londhe P, Gutwillig M, London C. Targeted therapies in veterinary oncology. Veterinary Clin North America: Small Anim Pract. 2019;49:917–31.
3. Fonseca-Alves CE, Palmieri C, Dagli MLZ, Laufer-Amorim R. Editorial: Precision Medicine in Veterinary Oncology. Front Vet Sci. 2021; 14;8:718891.
4. Mason NJ, Gnanandarajah JS, Engiles JB, Gray F, Laughlin D, Gaurnier-Hausser A, et al. Immunotherapy with a HER2-Targeting *Listeria* induces HER2-Specific immunity and demonstrates potential therapeutic effects in a phase I trial in canine osteosarcoma. Clin Cancer Res. 2016;22:4380–90.
5. Sakai O, Ogino S, Tsukui T, Igase M, Mizuno T. Development of a monoclonal antibody for the detection of anti-canine CD20 chimeric antigen receptor expression on canine CD20 chimeric antigen receptor-transduced T cells. J Vet Med Sci. 2021;83:21–0326.
6. Marconato L, Sabattini S, Marisi G, Rossi F, Leone VF, Casadei-Gardini A. Sorafenib for the treatment of unresectable hepatocellular carcinoma: preliminary toxicity and activity data in dogs. Cancers (Basel). 2020;12:1272.
7. Miller RL, Van Lelyveld S, Warland J, Dobson JM, Foale RD. A retrospective review of treatment and response of high-risk mast cell tumours in dogs. Vet Comp Oncol. 2016;14:361–70.
8. London CA. Kinase dysfunction and kinase inhibitors. Vet Dermatol. 2013;24:181.
9. Lyles SE, Milner RJ, Kow K, Salute ME. *In vitro* effects of the tyrosine kinase inhibitor, masitinib mesylate, on canine hemangiosarcoma cell lines. Vet Comp Oncol. 2012;10:223–35.

10. Rossman P, Zabka TS, Ruple A, Tuerck D, Ramos-Vara JA, Liu L, et al. Phase I/II trial of Vemurafenib in dogs with naturally occurring, *BRAF* -mutated urothelial carcinoma. Mol Cancer Ther. 2021;20:2177–88.
11. Peralta S, Katt W, Balkman C, Butler S, Carney P, Todd-Donato A, Drozd M, Duhamel G, Fiani N, Ford J, Grenier J, Hayward J, Heikinheimo K, Hume K, Moore E, Puri R, Sylvester S, Warshaw S, Webb S, White A, Wright A, Cerione R. Opportunities for targeted therapies: trametinib as a therapeutic approach to canine oral squamous cell carcinomas. Res Sq [Preprint]. 2024 May 2:rs.3.rs-4289451. doi: https://doi.org/10.21203/rs.3.rs-4289451/v1
12. Takada M, Kitagawa K, Zhang Y, Bulitta JB, Moirano S, Jones A, et al. Population pharmacokinetics, pharmacodynamics and safety properties of Trametinib in dogs with cancer: A phase I dose escalating clinical trial. Vet Comp Oncol. 2024;22:410–21.
13. Burkholder TP, Clayton JR, Rempala ME, Henry JR, Knobeloch JM, Mendel D, et al. Discovery of LY2457546: a multi-targeted anti-angiogenic kinase inhibitor with a novel spectrum of activity and exquisite potency in the acute myelogenous leukemia-Flt-3-internal tandem duplication mutant human tumor xenograft model. Invest New Drugs. 2012;30:936–49.
14. Takada M, Parys M, Gregory-Bryson E, Vilar Saavedra P, Kiupel M, Yuzbasiyan-Gurkan V. A novel canine Histiocytic sarcoma cell line: initial characterization and utilization for drug screening studies. BMC Cancer. 2018;18:237.
15. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. J Clin Epidemiol. 2021;134:178–89.
16. Nguyen SM, Thamm DH, Vail DM, London CA. Response evaluation criteria for solid tumours in dogs (v1.0): a veterinary cooperative oncology group (VCOG) consensus document. Vet Comp Oncol. 2015;13(3):176–83. https://doi.org/10.1111/vco.12032. Epub 2013 Mar 28. PMID: 23534501.
17. Aluai-Cunha C, Matos A, Amorim I, Carvalho F, Rêma A, Santos A. Immunohistochemical expression of Platelet-Derived growth factor receptor β (PDGFR-β) in canine cutaneous peripheral nerve sheath tumors: A preliminary study. Vet Sci. 2022;9:345.
18. Setyo LC, Donahoe SL, Shearer PL, Wang P, Krockenberger MB. Immunohistochemical analysis of expression of VEGFR2, KIT, PDGFR-β, and CDK4 in canine urothelial carcinoma. J Vet Diagn Invest. 2023;35:109–15.
19. Weishaar KM, Ehrhart EJ, Avery AC, Charles JB, Elmslie RE, Vail DM, et al. c-Kit mutation and localization status as response predictors in mast cell tumors in dogs treated with prednisone and Toceranib or vinblastine. J Vet Intern Med. 2018;32:394–405.
20. Gil da Costa RM. C-kit as a prognostic and therapeutic marker in canine cutaneous mast cell tumours: from laboratory to clinic. Vet J. 2015;205:5–10.
21. Urie BK, Russell DS, Kisseberth WC, London CA. Evaluation of expression and function of vascular endothelial growth factor receptor 2, platelet derived growth factor receptors-alpha and -beta, KIT, and RET in canine apocrine gland anal sac adenocarcinoma and thyroid carcinoma. BMC Vet Res. 2012;8:67.
22. Walters L, Martin O, Price J, Sula MM. Expression of receptor tyrosine kinase targets < scp > pdgfr -β, <scp > VEGFR2 and < scp > kit in canine transitional cell carcinoma</scp >. Vet Comp Oncol 2018;16.(1): E117-E122.
23. Kurita S, Miyamoto R, Tani H, Kobayashi M, Sasaki T, Tamura K, et al. Genetic alterations of *KIT* during clonal expansion and subsequent acquisition of resistance to Toceranib in a canine mast cell tumor cell line. J Vet Pharmacol Ther. 2019;42:673–81.
24. Gattino F, Maniscalco L, Iussich S, Biasato I, Martano M, Morello E, et al. PDGFR-α, PDGFR-β, VEGFR-2 and CD117 expression in canine mammary tumours and evaluation of the in vitro effects of Toceranib phosphate in neoplastic mammary cell lines. Vet Rec. 2018;183:221–221.
25. Horta RDS, Giuliano A, Lavalle GE, Costa MP, de Araújo RB, Constantino-Casas F, Dobson JM. Clinical, histological, immunohistochemical and genetic factors associated with measurable response of high-risk canine mast cell tumours to tyrosine kinase inhibitors. Oncol Lett. 2018 Jan;15(1):129-136.
26. Knight BJ, Wood GA, Foster RA, Coomber BL. Beclin-1 is a novel predictive biomarker for canine cutaneous and subcutaneous mast cell tumors. Vet Pathol. 2022;59:46–56.
27. Alonso-Miguel D, Valdivia G, García-San José P, Alonso-Diez Á, Clares I, Portero M, et al. Clinical outcome of dogs diagnosed with canine inflammatory mammary cancer treated with metronomic cyclophosphamide, a cyclooxygenase-2 inhibitor and Toceranib phosphate. Vet Comp Oncol. 2022;20:179–88.
28. Bavcar S, de Vos J, Kessler M, de Fornel P, Buracco P, Murphy S, et al. Combination Toceranib and lomustine shows frequent high grade toxicities when used for treatment of non-resectable or recurrent mast cell tumours in dogs: A European multicentre study. Vet J. 2017;224:1–6.
29. London CA, Malpas PB, Wood-Follis SL, Boucher JF, Rusk AW, Rosenberg MP, et al. Multi-center, Placebo-controlled, Double-blind, randomized study of oral Toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (Either local or Distant) mast cell tumor following surgical excision. Clin Cancer Res. 2009;15:3856–65.
30. Carlsten KS, London CA, Haney S, Burnett R, Avery AC, Thamm DH. Multicenter prospective trial of hypofractionated radiation treatment, toceranib, and prednisone for measurable canine mast cell tumors. J Vet Intern Med. 2012;26:135–41.
31. YANCEY MF, MERRITT DA, LESMAN SP, BOUCHER JF, MICHELS GM. Pharmacokinetic properties of Toceranib phosphate (PalladiaTM, SU11654), a novel tyrosine kinase inhibitor, in laboratory dogs and dogs with mast cell tumors. J Vet Pharmacol Ther. 2010;33:162–71.
32. Thamm DH, Weishaar KM, Charles JB, Ehrhart EJ. Phosphorylated KIT as a predictor of outcome in canine mast cell tumours treated with Toceranib phosphate or vinblastine. Vet Comp Oncol. 2020;18:169–75.
33. Akiyoshi M, Hisasue M, Neo S, Akiyoshi M. Precursor-targeted immune-mediated anemia in a dog with a stage IV mast cell tumor and bone marrow infiltration. Vet Clin Pathol. 2021;50:151–7.
34. Burton JH, Venable RO, Vail DM, Williams LE, Clifford CA, Axiak-Bechtel SM, et al. Pulse-Administered Toceranib phosphate plus lomustine for treatment of unresectable mast cell tumors in dogs. J Vet Intern Med. 2015;29:1098–104.
35. Sobierajska P, Serwotka-Suszczak A, Targonska S, Szymanski D, Marycz K, Wiglusz RJ. Synergistic effect of Toceranib and nanohydroxyapatite as a drug delivery Platform—Physicochemical properties and in vitro studies on mastocytoma cells. Int J Mol Sci. 2022;23:1944.
36. Ehling TJ, Klein MK, Smith L, Prescott D, Haney S, Looper J, et al. A prospective, multi-centre, veterinary radiation therapy oncology group study reveals potential efficacy of Toceranib phosphate (Palladia) as a primary or adjuvant agent in the treatment of canine nasal carcinoma. Vet Comp Oncol. 2022;20:293–303.
37. Ranieri G, Gadaleta CD, Patruno R, Zizzo N, Daidone MG, Hansson MG, et al. A model of study for human cancer: spontaneous occurring tumors in dogs. Biological features and translation for new anticancer therapies. Crit Rev Oncol Hematol. 2013;88:187–97.
38. Iwaki Y, Lindley SES, Bergman N, Smith BF, Pondugula SR. An evaluation of the combination effect of zoledronate and chemotherapeutic agents in canine osteosarcoma cells. Front Vet Sci 2024;11:1327377.
39. Yamazaki H, Tanaka T, Mie K, Nishida H, Miura N, Akiyoshi H. Assessment of postoperative adjuvant treatment using Toceranib phosphate against adenocarcinoma in dogs. J Vet Intern Med. 2020;34:1272–81.
40. Korec DI, Louke DS, Breitbach JT, Geisler JA, Husbands BD, Fenger JM. Characterization of receptor tyrosine kinase activation and biological activity of Toceranib phosphate in canine urothelial carcinoma cell lines. BMC Vet Res. 2021;17:320.
41. Hume KR, Rizzo VL, Cawley JR, Balkman CE. Effects of Toceranib phosphate on the Hypothalamic-Pituitary-Thyroid axis in Tumor-Bearing dogs. J Vet Intern Med. 2018;32:377–83.
42. YAMAZAKI H, MIURA N, LAI YC, TAKAHASHI M, GOTO-KOSHINO Y, YASUYUKI M, et al. Effects of Toceranib phosphate (Palladia) monotherapy on multidrug resistant lymphoma in dogs. J Vet Med Sci. 2017;79:1225–9.
43. Lee JY, Bae K, Kim JH, Han HJ, Yoon HY, Yoon KA. Establishment and characterization of six canine hepatocellular carcinoma cell lines. Front Vet Sci 2024;11.
44. Heaton CM, Fernandes AFA, Jark PC, Pan X. Evaluation of Toceranib for treatment of apocrine gland anal sac adenocarcinoma in dogs. J Vet Intern Med. 2020;34:873–81.
45. Gedon J, Kessler M, Schmidt JM. Frontal sinus carcinoma in forty-one dogs (2001–2022). Vet Comp Oncol. 2023;21:231–9.
46. Treggiari E, Giantin M, Ferro S, Romanelli G. Canine Gastrointestinal stromal tumours treated with surgery and Imatinib mesylate: three cases (2018-2020). J Small Anim Pract. 2023;64:161–7.
47. Blaxill JE, Bender H, Hoon QJ, Sow JW, Cheng KY, Bennett PF. Gastrointestinal stromal tumor (GIST) presenting as a multilocular cystic intra-abdominal mass in a dog. BMC Vet Res. 2022;18:415.
48. Garcia-de la Virgen M, Del Portillo Miguel I, Maiques E, Pérez Roger I, Poch E, Borrego J. Impact of Toceranib phosphate and carprofen on survival and quality of life in dogs with inflammatory mammary carcinomas. Vet Sci. 2024;11:430.
49. London CA, Gardner HL, Mathie T, Stingle N, Portela R, Pennell ML, et al. Impact of toceranib/piroxicam/cyclophosphamide maintenance therapy on outcome of dogs with appendicular osteosarcoma following amputation

and carboplatin chemotherapy: A Multi-Institutional study. PLoS ONE. 2015;10:e0124889.
50. Rossi F, Sabattini S, Vascellari M, Marconato L. The impact of toceranib, piroxicam and thalidomide with or without hypofractionated radiation therapy on clinical outcome in dogs with inflammatory mammary carcinoma. Vet Comp Oncol. 2018;16:497–504.
51. Gardner HL, London CA, Portela RA, Nguyen S, Rosenberg MP, Klein MK, et al. Maintenance therapy with Toceranib following doxorubicin-based chemotherapy for canine Splenic hemangiosarcoma. BMC Vet Res. 2015;11:131.
52. Regan DP, Chow L, Das S, Haines L, Palmer E, Kurihara JN, et al. Losartan blocks osteosarcoma-Elicited monocyte recruitment, and combined with the kinase inhibitor toceranib, exerts significant clinical benefit in canine metastatic osteosarcoma. Clin Cancer Res. 2022;28:662–76.
53. Sánchez-Céspedes R, Accornero P, Miretti S, Martignani E, Gattino F, Maniscalco L, et al. In vitro and in vivo effects of Toceranib phosphate on canine osteosarcoma cell lines and xenograft orthotopic models. Vet Comp Oncol. 2020;18:117–27.
54. Fontes GS, Piegols HJ, Lapsley JM, Bracha S, Selmic LE. Outcome in dogs with invasive adrenal gland tumors that did not pursue adrenalectomy. J Am Vet Med Assoc. 2024;262:1–5.
55. Pérez ML, Culver S, Owen JL, Dunbar M, Kow K, Breen M, et al. Partial cytogenetic response with Toceranib and prednisone treatment in a young dog with chronic monocytic leukemia. Anticancer Drugs. 2013;24:1098–103.
56. Jang JK. Phase 1 Dose-Escalation study with LEC/Chtnt-3 and Toceranib phosphate (Palladia) in dogs with spontaneous malignancies. J Cancer Sci Ther 2015;07(6):167-174.
57. Rippy SB, Gardner HL, Nguyen SM, Warry EE, Portela RF, Drost WT, et al. Erratum to: A pilot study of toceranib/vinblastine therapy for canine transitional cell carcinoma. BMC Vet Res. 2016;12:291.
58. Keyerleber MA, Barber LG. Pilot study evaluating the tolerability of a 3 Gy × 10 daily fraction 3D-conformal palliative radiation therapy protocol plus Toceranib for the treatment of measurable carcinomas in the dog. Vet Radiol Ultrasound. 2022;63:798–806.
59. NISHIYAMA Y, MARUO T, FUKUYAMA Y, ODAKA Y, KAWATA E, UENO H, et al. Pre-clinical/clinical trials of thrice-weekly administration of a combination of tegafur/gimeracil/oteracil (TS-1) and Toceranib phosphate in dogs with intranasal tumors. J Vet Med Sci. 2024;86:23–0455.
60. London C, Mathie T, Stingle N, Clifford C, Haney S, Klein MK, et al. Preliminary evidence for biologic activity of Toceranib phosphate (Palladia ®) in solid tumours. Vet Comp Oncol. 2012;10:194–205.
61. Mendez Valenzuela CR, Shin K, Weng HY, Plantenga JM, Vanhaezebrouck IF. Radiotherapy for canine apocrine gland anal sac adenocarcinoma: survival outcomes and side effects of a palliative treatment protocol of 20 Gy in five consecutive fractions. Vet Sci. 2024;11:219.
62. Hocker SE, Higginbotham ML, Schermerhorn T, Henningson J. Receptor tyrosine kinase expression and phosphorylation in canine nasal carcinoma. Res Vet Sci. 2017;115:484–9.
63. Elliott JW. Response and outcome following Toceranib phosphate treatment for stage four anal sac apocrine gland adenocarcinoma in dogs: 15 cases (2013–2017). J Am Vet Med Assoc. 2019;254:960–6.
64. Kim C, Matsuyama A, Mutsaers AJ, Woods JP. Retrospective evaluation of Toceranib (Palladia) treatment for canine metastatic appendicular osteosarcoma. Can Vet J. 2017;58:1059–64.
65. Lew FH, McQuown B, Borrego J, Cunningham S, Burgess KE. Retrospective evaluation of canine heart base tumours treated with Toceranib phosphate (Palladia): 2011-2018. Vet Comp Oncol. 2019;17:465–71.
66. Hicks KA, Leeper HJ, Curran KM. Retrospective evaluation of Toceranib phosphate (Palladia) in the treatment of canine carcinomatosis and mesothelioma. Vet Comp Oncol. 2024;22:245–54.
67. Berger EP, Johannes CM, Jergens AE, Allenspach K, Powers BE, Du Y, et al. Retrospective evaluation of Toceranib phosphate (Palladia®) use in the treatment of Gastrointestinal stromal tumors of dogs. J Vet Intern Med. 2018;32:2045–53.
68. Musser ML, Taikowski KL, Johannes CM, Bergman PJ. Retrospective evaluation of Toceranib phosphate (Palladia®) use in the treatment of inoperable, metastatic, or recurrent canine pheochromocytomas: 5 dogs (2014–2017). BMC Vet Res. 2018;14:272.
69. Bernabe LF, Portela R, Nguyen S, Kisseberth WC, Pennell M, Yancey MF, et al. Evaluation of the adverse event profile and pharmacodynamics of Toceranib phosphate administered to dogs with solid tumors at doses below the maximum tolerated dose. BMC Vet Res. 2013;9:190.
70. Piscoya SL, Hume KR, Balkman CE. A retrospective study of proteinuria in dogs receiving Toceranib phosphate. Can Vet J. 2018;59:611–6.
71. YANCEY MF, MERRITT DA, WHITE JA, MARSH SA. Distribution, metabolism, and excretion of Toceranib phosphate (PalladiaTM, SU11654), a novel tyrosine kinase inhibitor, in dogs. J Vet Pharmacol Ther. 2010;33:154–61.
72. Tjostheim SS, Stepien RL, Markovic LE, Stein TJ. Effects of Toceranib phosphate on systolic blood pressure and proteinuria in dogs. J Vet Intern Med. 2016;30:951–7.
73. Prebble AR, Weishaar KM, Thamm DH, Leary D, LaRue SM, Martin T, et al. Increased incidence of Gastrointestinal toxicity in canine cancer patients treated with concurrent abdominal radiation therapy and Toceranib phosphate. Vet Comp Oncol. 2022;20:142–53.
74. Harper A, Blackwood L, Mason S. Investigation of thyroid function in dogs treated with the tyrosine kinase inhibitor Toceranib. Vet Comp Oncol. 2020;18:433–7.
75. Woo IS, Kim YR, Kim SW, Choi JY, Yoon HY, Bae K, et al. Successful post-incomplete resection management of Gastrointestinal stromal tumor using Imatinib based on adenosine triphosphate-based tumor sensitivity assay in a dog. Can Vet J. 2024;65:553–8.
76. de Vos J, Ramos Vega S, Noorman E, de Vos P. Primary frontal sinus squamous cell carcinoma in three dogs treated with piroxicam combined with carboplatin or Toceranib. Vet Comp Oncol. 2012;10:206–13.
77. Mitchell L, Thamm DH, Biller BJ. Clinical and Immunomodulatory effects of Toceranib combined with Low-Dose cyclophosphamide in dogs with cancer. J Vet Intern Med. 2012;26:355–62.
78. Kim YR, Park JH, Bae K, Yoon KA, Kim JH. Exposure-Response relationships for Toceranib in dogs with solid tumors: A pilot study. Anim (Basel). 2025;15(7):1025.
79. Chalfon C, Marconato L, Galac S, Tardo AM, Zandvliet M, Fracassi F, Del Baldo F, Ghisoni G, Pisoni L, Finotello R. Toceranib phosphate for the treatment of dogs with high-risk adrenal gland tumours: 16 cases (2019–2023). J Small Anim Pract. 2025;66(6):412–9.
80. Coto GM, Musser ML, Tropf MA, Ward JL, Seo YJ, Mochel JP, Johannes CM. A Multi-Institutional retrospective analysis of Toceranib phosphate for presumed or confirmed canine aortic body chemodectomas. Front Vet Sci. 2021;8:635057.
81. Sheppard-Olivares S, Bello NM, Johannes CM, Hocker SE, Biller B, Husbands B, Snyder E, McMillan M, McKee T, Wouda RM. Toceranib phosphate in the management of canine insulinoma: A retrospective multicentre study of 30 cases (2009–2019). Vet Rec Open. 2022;9(1):e27.
82. Todd JE, Nguyen SM, White J, Langova V, Thomas PM, Tzannes S. Combination vinblastine and palladia for high-grade and metastatic mast cell tumors in dogs. Can Vet J. 2021;62:1335–40.
83. Halsey CH, Gustafson DL, Rose BJ, Wolf-Ringwall A, Burnett RC, Duval DL, et al. Development of an in vitro model of acquired resistance to Toceranib phosphate (Palladia®) in canine mast cell tumor. BMC Vet Res. 2014;10:105.
84. Alonso-Miguel D, García-San José P, González Sanz S, Clarés Moral I, Pérez-Alenza M. Evaluation of palliative therapy, alone or in combination with Toceranib phosphate, in dogs diagnosed with metastatic or recurrent beta-cell neoplasia. N Z Vet J. 2021;69:234–9.
85. LeBlanc AK, Miller AN, Galyon GD, Moyers TD, Long MJ, Stuckey AC, PRELIMINARY EVALUATION OF SERIAL 18 FDG-PET/CT TO ASSESS RESPONSE TO TOCERANIB PHOSPHATE THERAPY IN CANINE CANCER, et al. Vet Radiol Ultrasound. 2012;53:348–57.
86. Pan X, Tsimbas K, Kurzman ID, Vail DM. Safety evaluation of combination < scp > ccnu and continuous Toceranib phosphate (Palladia ®) in tumour-bearing dogs: a phase I dose-finding study. Vet Comp Oncol. 2016;14:202–9.
87. Robat C, London C, Bunting L, McCartan L, Stingle N, Selting K, et al. Safety evaluation of combination vinblastine and Toceranib phosphate (Palladia®) in dogs: a phase I dose-finding study. Vet Comp Oncol. 2012;10:174–83.
88. Gentilini F, Turba ME, Dally C, Takanosu M, Kurita S, Bonkobara M. The secondary KIT mutation p.Ala510Val in a cutaneous mast cell tumour carrying the activating mutation p.Asn508Ile confers resistance to masitinib in dogs. BMC Vet Res. 2020;16:64.
89. Dolgin E. Therapies: progressive steps. Nature. 2016;540:S7–9.
90. MAEDA S. Second era of molecular-targeted cancer therapies in dogs. J Vet Med Sci. 2023;85:23–0204.
91. Hadzijusufovic E, Peter B, Herrmann H, Rülicke T, Cerny-Reiterer S, Schuch K, et al. NI-1: a novel canine mastocytoma model for studying drug resistance and IgER-dependent mast cell activation. 2012;67:858–68.

92. Smrkovski OA, Essick L, Rohrbach BW, Legendre AM. Masitinib mesylate for metastatic and non-resectable canine cutaneous mast cell tumours. Vet Comp Oncol. 2015;13:314–21.
93. Hahn KA, Oglivie G, Rusk T, Devauchelle P, Leblanc A, Legendre A, et al. Masitinib is safe and effective for the treatment of canine mast cell tumors. J Vet Intern Med. 2008;22:1301–9.
94. Bauer K, Hadzijusufovic E, Cerny-Reiterer S, Hoermann G, Reifinger M, Pirker A, et al. IL-4 downregulates expression of the target receptor CD30 in neoplastic canine mast cells. Vet Comp Oncol. 2017;15:1240–56.
95. Klose K, Packeiser E, Granados-Soler J, Hewicker-Trautwein M, Murua Escobar H, Nolte I. Evaluation of the therapeutic potential of masitinib and expression of its specific targets < scp > c-Kit, PDGFR -α, PDGFR -β, and Lyn in canine prostate cancer cell lines. Vet Comp Oncol. 2022;20:641–52.
96. Hahn KA, Legendre AM, Shaw NG, Phillips B, Ogilvie GK, Prescott DM, et al. Evaluation of 12- and 24-month survival rates after treatment with masitinib in dogs with non-resectable mast cell tumors. Am J Vet Res. 2010;71:1354–61.
97. Grant J, North S, Lanore D. Clinical response of masitinib mesylate in the treatment of canine macroscopic mast cell tumours. J Small Anim Pract. 2016;57:283–90.
98. Semba Y, Yamamoto S, Takahashi S, Shinomiya T, Nagahara Y. c-kit inhibitor masitinib induces reactive oxygen species-dependent apoptosis in c-kit-negative HepG2 cells. Eur J Pharmacol. 2022;931:175183.
99. TAKEUCHI Y, FUJINO Y, FUKUSHIMA K, WATANABE M, NAKAGAWA T, OHNO K, et al. Biological effect of tyrosine kinase inhibitors on three canine mast cell tumor cell lines with various *KIT* statuses. J Vet Pharmacol Ther. 2012;35:97–104.
100. Keller A, Wingelhofer B, Peter B, Bauer K, Berger D, Gamperl S, et al. The < scp > JAK2 / <scp > STAT5 signaling pathway as a potential therapeutic target in canine mastocytoma</scp >. Vet Comp Oncol. 2018;16:55–68.
101. Giuliano A, Dobson J. Prospective clinical trial of masitinib mesylate treatment for advanced stage III and IV canine malignant melanoma. J Small Anim Pract. 2020;61:190–4.
102. Rathore K, Alexander M, Cekanova M. Piroxicam inhibits Masitinib-induced cyclooxygenase 2 expression in oral squamous cell carcinoma cells in vitro. Translational Res. 2014;164:158–68.
103. Holtermann N, Kiupel M, Kessler M, Teske E, Betz D, Hirschberger J. Masitinib monotherapy in canine epitheliotropic lymphoma. Vet Comp Oncol. 2016;14:127–35.
104. Thamm DH, Rose B, Kow K, Humbert M, Mansfield CD, Moussy A, et al. Masitinib as a chemosensitizer of canine tumor cell lines: A proof of concept study. Vet J. 2012;191:131–4.
105. Marech I, Patruno R, Zizzo N, Gadaleta C, Introna M, Zito AF, et al. Masitinib (AB1010), from canine tumor model to human clinical development: where we are? Crit Rev Oncol Hematol. 2014;91:98–111.
106. Ustun-Alkan F, Bakırel T, Üstüner O, Anlas C, Cinar S, Yıldırım F, et al. Effects of tyrosine kinase inhibitor-masitinib mesylate on canine mammary tumour cell lines. J Vet Res. 2021;65:351–9.
107. Bourn J, Cekanova M. Cyclooxygenase inhibitors potentiate receptor tyrosine kinase therapies in bladder cancer cells in vitro. Drug Des Devel Ther. 2018;12:1727–42.
108. Fahey CE, Milner RJ, Kow K, Bacon NJ, Salute ME. Apoptotic effects of the tyrosine kinase inhibitor, masitinib mesylate, on canine osteosarcoma cells. Anticancer Drugs. 2013;24:519–26.
109. Milovancev M, Helfand SC, Marley K, Goodall CP, Löhr CV, Bracha S. Antiproliferative effects of masitinib and Imatinib against canine oral fibrosarcoma in vitro. BMC Vet Res. 2016;12:85.
110. Zandvliet M, Teske E, Chapuis T, Fink-Gremmels J, Schrickx JA. Masitinib reverses doxorubicin resistance in canine lymphoid cells by inhibiting the function of < scp > p -glycoprotein. J Vet Pharmacol Ther. 2013;36:583–7.
111. Cadot P, Hensel P, Bensignor E, Hadjaje C, Marignac G, Beco L, et al. Masitinib decreases signs of canine atopic dermatitis: a multicentre, randomized, double-blind, placebo-controlled phase 3 trial. Vet Dermatol. 2011;22:554–64.
112. Kobayashi M, Kuroki S, Kurita S, Miyamoto R, Tani H, Tamura K, et al. A decrease in ubiquitination and resulting prolonged life-span of KIT underlies the KIT overexpression-mediated Imatinib resistance of KIT mutation-driven canine mast cell tumor cells. Oncol Rep. 2017;38:2543–50.
113. Hoshino-Yoshino A, Kato M, Nakano K, Ishigai M, Kudo T, Ito K. Bridging from Pre-clinical to clinical studies for tyrosine kinase inhibitors based on pharmacokinetics/pharmacodynamics and toxicokinetics/toxicodynamics. Drug Metab Pharmacokinet. 2011;26:612–20.
114. Bonkobara M. Dysregulation of tyrosine kinases and use of Imatinib in small animal practice. Vet J. 2015;205:180–8.
115. Taouji S, Higa A, Delom F, Palcy S, Mahon FX, Pasquet JM, et al. Phosphorylation of Serine palmitoyltransferase long Chain-1 (SPTLC1) on tyrosine 164 inhibits its activity and promotes cell survival. J Biol Chem. 2013;288:17190–201.
116. Ishizuka M, Nagai S, Sakamoto KQ, Fujita S. Plasma pharmacokinetics and CYP3A12-dependent metabolism of c-kit inhibitor Imatinib in dogs. Xenobiotica. 2007;37:503–13.
117. Downing S, Chien MB, Kass PH, Moore PF, London CA. Prevalence and importance of internal tandem duplications in exons 11 and 12 of c- kit in mast cell tumors of dogs. Am J Vet Res. 2002;63:1718–23.
118. Gleixner KV, Rebuzzi L, Mayerhofer M, Gruze A, Hadzijusufovic E, Sonneck K, et al. Synergistic antiproliferative effects of KIT tyrosine kinase inhibitors on neoplastic canine mast cells. Exp Hematol. 2007;35:1510–21.
119. Breedveld P, Pluim D, Cipriani G, Wielinga P, van Tellingen O, Schinkel AH, et al. The effect of Bcrp1 (Abcg2) on the *In vivo* pharmacokinetics and brain penetration of Imatinib mesylate (Gleevec): implications for the use of breast cancer resistance protein and P-Glycoprotein inhibitors to enable the brain penetration of Imatinib in patients. Cancer Res. 2005;65:2577–82.
120. Lin TY, Bear M, Du Z, Foley KP, Ying W, Barsoum J, et al. The novel HSP90 inhibitor STA-9090 exhibits activity against Kit-dependent and -independent malignant mast cell tumors. Exp Hematol. 2008;36:1266–77.
121. Amagai Y, Tanaka A, Matsuda A, Oida K, Jung K. The phosphoinositide 3-Kinase pathway is crucial for the growth of canine mast cell tumors. J Vet Med Sci. 2013;75:791–4.
122. London CA. Tyrosine kinase inhibitors in veterinary medicine. Top Companion Anim Med. 2009;24:106–12.
123. Nakano Y, Kobayashi M, Bonkobara M, Takanosu M. Identification of a secondary mutation in the KIT kinase domain correlated with imatinib-resistance in a canine mast cell tumor. Vet Immunol Immunopathol. 2017;188:84–8.
124. Ohmori K, Kawarai S, Yasuda N, Tanaka A, Matsuda H, Nishimura R, et al. Identification of c-kit mutations-independent neoplastic cell proliferation of canine mast cells. Vet Immunol Immunopathol. 2008;126:43–53.
125. Nakano Y, Kobayashi T, Oshima F, Fukazawa E, Yamagami T, Shiraishi Y, et al. Imatinib Responsiveness in Canine Mast Cell Tumors Carrying Novel Mutations of *c-KIT*Exon 11. Journal of Veterinary Medical Science 2014;76:545–8.
126. Pawlak A, Ziolo E, Kutkowska J, Blazejczyk A, Wietrzyk J, Krupa A, et al. A novel canine B-cell leukaemia cell line. Establishment, characterisation and sensitivity to chemotherapeutics. Vet Comp Oncol. 2017;15:1218–31.
127. Li R, Wu H, Sun Y, Zhu J, Tang J, Kuang Y et al. A novel canine mammary cancer cell line: preliminary identification and utilization for drug screening studies. Front Vet Sci 2021;8:665906.
128. Malone EK, Rassnick KM, Wakshlag JJ, Russell DS, Al-Sarraf R, Ruslander DM, Johnson CS, Trump DL. Calcitriol (1,25-dihydroxycholecalciferol) enhances mast cell tumour chemotherapy and receptor tyrosine kinase inhibitor activity in vitro and has single-agent activity against spontaneously occurring canine mast cell tumours. Vet Comp Oncol. 2010 Sep;8(3):209-20.
129. Marconato L, Bettini G, Giacoboni C, Romanelli G, Cesari A, Zatelli A, et al. Clinicopathological features and outcome for dogs with mast cell tumors and bone marrow involvement. J Vet Intern Med. 2008;22:1001–7.
130. Kim JH, Song M, Kang GH, Lee ER, Choi HY, Lee C, et al. Combined treatment of 3-hydroxyflavone and Imatinib mesylate increases apoptotic cell death of Imatinib mesylate-resistant leukemia cells. Leuk Res. 2012;36:1157–64.
131. Isotani M, Ishida N, Tominaga M, Tamura K, Yagihara H, Ochi S, et al. Effect of tyrosine kinase Inhibition by Imatinib mesylate on mast cell tumors in dogs. J Vet Intern Med. 2008;22:985–8.
132. Rossi G, Bertani C, Mari S, Marini C, Renzoni G, Ogilvie G, et al. Ex vivo evaluation of Imatinib mesylate for induction of cell death on canine neoplastic mast cells with mutations in c-Kit exon 11 via apoptosis. Vet Res Commun. 2013;37:101–8.
133. Deininger MWN, Holyoake TL. Can we afford to let sleeping dogs. lie? Blood. 2005;105:1840–1.
134. Dickerson EB, Marley K, Edris W, Tyner JW, Schalk V, MacDonald V, et al. Imatinib and dasatinib inhibit hemangiosarcoma and implicate PDGFR-β and Src in tumor growth. Transl Oncol. 2013;6:158–IN7.
135. Chen W, Liu I, Tomiyasu H, Lee J, Cheng C, Liao AT, et al. Imatinib enhances the anti-tumour effect of doxorubicin in canine B-cell lymphoma cell line. Vet J. 2019;254:105398.
136. Macedo TR, de Queiroz GF, Casagrande TAC, Alexandre PA, Brandão PE, Fukumasu H, et al. Imatinib mesylate for the treatment of canine mast cell tumors: assessment of the response and adverse events in comparison with the conventional therapy with vinblastine and prednisone. Cells. 2022;11:571.

137. Kretz O, Weiss HM, Schumacher MM, Gross G. *In vitro* blood distribution and plasma protein binding of the tyrosine kinase inhibitor Imatinib and its active metabolite, CGP74588, in rat, mouse, dog, monkey, healthy humans and patients with acute lymphatic leukaemia. Br J Clin Pharmacol. 2004;58:212–6.
138. Ananthula HK, Parker S, Touchette E, Buller RM, Patel G, Kalman D, et al. Pre-clinical Pharmacokinetic evaluation to facilitate repurposing of tyrosine kinase inhibitors nilotinib and Imatinib as antiviral agents. BMC Pharmacol Toxicol. 2018;19:80.
139. Chiba K, Kambayashi R, Onozato M, Goto A, Izumi-Nakaseko H, Takei Y, et al. Imatinib induces diastolic dysfunction and ventricular early-repolarization delay in the halothane-anesthetized dogs: class effects of tyrosine kinase inhibitors. J Pharmacol Sci. 2022;150:154–62.
140. Kobayashi M, Kuroki S, Tanaka Y, Moriya Y, Kozutumi Y, Uehara Y, et al. Molecular changes associated with the development of resistance to imatinib in an imatinib-sensitive canine neoplastic mast cell line carrying a < scp > KIT c.1523A>T mutation. Eur J Haematol 2015;95:524–31.
141. Kamath AV, Wang J, Lee FY, Marathe PH. Pre-clinical pharmacokinetics and in vitro metabolism of dasatinib (BMS-354825): a potent oral multi-targeted kinase inhibitor against SRC and BCR-ABL. Cancer Chemother Pharmacol. 2008;61:365–76.
142. Arita S, Arita N, Hikasa Y. Therapeutic effect of low-dose Imatinib on pulmonary arterial hypertension in dogs. Can Vet J. 2013;54:255–61.
143. Vicente IST, de Moura FBC, Rozolen JM, Anjos DS dos, Sobral RA, Alves CEF. Analysis of VEGFR-2 and PDGFR-2 expression in canine splenic hemangiosarcoma to identify drug repositioning candidates. Brazilian Journal of Veterinary Medicine. 2024;46:e001524.
144. Wilhelm SM, Adnane L, Newell P, Villanueva A, Llovet JM, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther. 2008;7:3129–40.
145. Wu JD, Cui YJ, Zhou YG, Tang LQ, Zhang CM, Liu ZP. Tubulin Colchicine site binding agent LL01 displays potent antitumor efficiency both in vitro and in vivo with suitable drug-like properties. Invest New Drugs. 2020;38:29–38.
146. Braun D, Kim TD, le Coutre P, Köhrle J, Hershman JM, Schweizer U. Tyrosine kinase inhibitors noncompetitively inhibit MCT8-Mediated Iodothyronine transport. J Clin Endocrinol Metab. 2012;97:E100–5.
147. Tanaka T, Motegi T, Mori M, Sumikawa N, Maeda K, Iimori Y, et al. Candidate genes in canine hepatocellular carcinoma for molecular targeted therapy. BMC Res Notes. 2024;17:357.
148. James J, Ruggeri B, Armstrong RC, Rowbottom MW, Jones-Bolin S, Gunawardane RN, et al. CEP-32496: A novel orally active BRAFV600E inhibitor with selective cellular and *In vivo* antitumor activity. Mol Cancer Ther. 2012;11:930–41.
149. Jung H, Bae K, Lee JY, Kim JH, Han HJ, Yoon HY, et al. Establishment of canine transitional cell carcinoma cell lines harboring BRAF V595E mutation as a therapeutic target. Int J Mol Sci. 2021;22:9151.
150. Prado MCM, Macedo S, de AL, Guiraldelli GG, de Faria Lainetti P, Leis-Filho AF, Kobayashi PE et al. Investigation of the prognostic significance of vasculogenic mimicry and its Inhibition by Sorafenib in canine mammary gland tumors. Front Oncol 2019;9:1445.
151. Mali KK, Gavhane YN, Chakole RD. Natural Polymer-Based nanogel for pH-Responsive delivery of Sorafenib Tosylate in hemangiosarcoma. AAPS PharmSciTech. 2024;25:83.
152. Cawley JR, Stewart SD, Mochel JP, Veluvolu S, Khanna C, Fenger JM. Pharmacokinetic exposures associated with oral administration of Sorafenib in dogs with spontaneous tumors. Front Vet Sci 2022;9:888483.
153. Yang YT, Yuzbasiyan-Gurkan V. Sorafenib and doxorubicin show synergistic effects in human and canine osteosarcoma cell lines. Int J Mol Sci. 2022;23:9345.
154. Yokota S, Yonezawa T, Momoi Y, Maeda S. Sorafenib inhibits tumor cell growth and angiogenesis in canine transitional cell carcinoma. J Vet Med Sci. 2022;84:21–0478.
155. Wolfesberger B, Tonar Z, Gerner W, Skalicky M, Heiduschka G, Egerbacher M, et al. The tyrosine kinase inhibitor Sorafenib decreases cell number and induces apoptosis in a canine osteosarcoma cell line. Res Vet Sci. 2010;88:94–100.
156. Qiao L, Qin S, Weng N, Li B, Luo M, Zhang Z, et al. Discovery of canine drug Toceranib phosphate as a repurposed agent against human hepatocellular carcinoma. Liver Int. 2023;43:928–44.
157. Foskett A, Manley C, Naramore R, Gordon I, Stewart B, Khanna C. Tolerability of oral Sorafenib in pet dogs with a diagnosis of cancer. Veterinary Medicine: Res Rep. 2017;8:97–102.
158. Katt WP, Balkman CE, Butler SD, Byron M, Carney PC, Todd-Donato AB, Drozd ME, Duhamel GE, Evans JM, Fiani N, Ford JC, Grenier JK, Hayward JJ, Heikinheimo K, Hume KR, Moore ES, Puri R, Sylvester SR, Warshaw SL, Webb SM, White AC, Wright AL, Cerione RA, Peralta S. The MEK inhibitor Trametinib is effective in inhibiting the growth of canine oral squamous cell carcinoma. Sci Rep. 2025;15(1):7069.
159. Elbadawy M, Sato Y, Mori T, Goto Y, Hayashi K, Yamanaka M, et al. Antitumor effect of Trametinib in bladder cancer organoid and the underlying mechanism. Cancer Biol Ther. 2021;22:357–71.
160. Wei BR, Peer CJ, Richardson WJ, Hewitt SM, Figg WD, Simpson RM. Pharmacokinetics and tolerability of the dual TORC1/2 inhibitor sapanisertib in combination with the MEK inhibitor Trametinib in dogs. Front Vet Sci 2022;9:1056408.
161. YAMAMOTO M. Protein phosphatase 6 regulates Trametinib sensitivity, a mitogen-activated protein kinase kinase (MEK) inhibitor, by regulating MEK1/2-ERK1/2 signaling in canine melanoma cells. J Vet Med Sci. 2023;85:23–0274.
162. Mittapalli RK, Vaidhyanathan S, Sane R, Elmquist WF. Impact of P-Glycoprotein (ABCB1) and breast cancer resistance protein (ABCG2) on the brain distribution of a novel BRAF inhibitor: Vemurafenib (PLX4032). J Pharmacol Exp Ther. 2012;342:33–40.
163. Maeng H, Kim E, Chough C, Joung M, Lim JW, Shim C, et al. Addition of amino acid moieties to lapatinib increases the anti-cancer effect via amino acid transporters. Biopharm Drug Dispos. 2014;35:60–9.
164. Kaji K, Yonezawa T, Yonezawa T, Momoi Y, Maeda S. Antitumor effects of lapatinib on HER2-positive canine prostatic carcinoma cell lines. Open Vet J. 2024;14:1259.
165. YOSHIMOTO S, KATO D, KAMOTO S, YAMAMOTO K, TSUBOI M, SHINADA M, et al. Detection of human epidermal growth factor receptor 2 overexpression in canine anal sac gland carcinoma. J Vet Med Sci. 2019;81:1034–9.
166. Fonseca-Alves CE, Leis-Filho AF, Lacerda ZA, de Faria Lainetti P, Amorim RL, Rogatto SR. Lapatinib antitumor effect is associated with PI3K and MAPK pathway: an analysis in human and canine prostate cancer cells. PLoS ONE. 2024;19:e0297043.
167. Sakai K, Maeda S, Saeki K, Nakagawa T, Murakami M, Endo Y, et al. Antitumour effect of lapatinib in canine transitional cell carcinoma cell lines. Vet Comp Oncol. 2018;16:642–9.
168. Leis-Filho AF, de Faria Lainetti P, Emiko Kobayashi P, Fonseca-Alves CE, Laufer-Amorim R. Effects of lapatinib on HER2-Positive and HER2-Negative canine mammary carcinoma cells cultured in vitro. Pharmaceutics. 2021;13:897.
169. Lorch G, Sivaprakasam K, Zismann V, Perdigones N, Contente-Cuomo T, Nazareno A, et al. Identification of recurrent activating *HER2* mutations in primary canine pulmonary adenocarcinoma. Clin Cancer Res. 2019;25:5866–77.
170. Maeda S, Sakai K, Kaji K, Iio A, Nakazawa M, Motegi T, et al. Lapatinib as first-line treatment for muscle-invasive urothelial carcinoma in dogs. Sci Rep. 2022;12:4.
171. Noguchi S, Inoue M, Ichikawa T, Kurozumi K, Matsumoto Y, Nakamoto Y, et al. The NRG3/ERBB4 signaling cascade as a novel therapeutic target for canine glioma. Exp Cell Res. 2021;400:112504.
172. YU TW, YAMAMOTO H, MORITA S, FUKUSHIMA R, ELBADAWY M, USUI T, et al. Comparative pharmacokinetics of tyrosine kinase inhibitor, lapatinib, in dogs and cats following single oral administration. J Vet Med Sci. 2024;86:23–0448.
173. Wu K, Rodrigues L, Post G, Harvey G, White M, Miller A, et al. Analyses of canine cancer mutations and treatment outcomes using real-world clinicogenomics data of 2119 dogs. NPJ Precis Oncol. 2023;7:8.
174. Sheppard-Olivares S, Bello NM, Johannes CM, Hocker SE, Biller B, Husbands B et al. Toceranib phosphate in the management of canine insulinoma: A retrospective multicentre study of 30 cases (2009–2019). Vet Rec Open 2022;9:e27.
175. Mao Y, Xia Z, Zhang X, Zong Y, Zhu L, Yuan B, et al. Evaluation of subchronic toxicity of SIM010603, a potent inhibitor of receptor tyrosine kinase, after 28-day repeated oral administration in SD rats and beagle dogs. Food Chem Toxicol. 2012;50:1256–70.
176. Wada T, Ando K, Naito AT, Nakamura Y, Goto A, Chiba K, et al. Sunitinib does not acutely alter left ventricular systolic function, but induces diastolic dysfunction. Cancer Chemother Pharmacol. 2018;82:65–75.
177. Suddek GM. Sunitinib improves chemotherapeutic efficacy and ameliorates cisplatin-induced nephrotoxicity in experimental animals. Cancer Chemother Pharmacol. 2011;67:1035–44.
178. Frezoulis P, Harper A. The role of Toceranib phosphate in dogs with non-mast cell neoplasia: A systematic review. Vet Comp Oncol. 2022;20:362–71.

179. Sakuma H, Tomiyasu H, Tani A, Goto-Koshino Y, Tani H, Ohno K, et al. Anti-tumor effects of inhibitors of ERK and Akt pathways in canine Histiocytic sarcoma cell lines. Vet J. 2024;308:106264.
180. Takeuchi Y, Fujino Y, Watanabe M, Nakagawa T, Ohno K, Sasaki N, et al. Aberrant autophosphorylation of c-Kit receptor in canine mast cell tumor cell lines. Vet Immunol Immunopathol. 2010;137:208–16.
181. Ito K, Miyamoto R, Tani H, Kurita S, Kobayashi M, Tamura K et al. Effect of dasatinib in a xenograft mouse model of canine Histiocytic sarcoma and in vitro expression status of its potential target < scp > epha 2. J Vet Pharmacol Ther 2018;41:e45-e48.
182. Marley K, Gullaba J, Seguin B, Gelberg HB, Helfand SC. Dasatinib modulates invasive and migratory properties of canine osteosarcoma and has therapeutic potential in affected dogs. Transl Oncol. 2015;8:231–8.
183. Hadzijusufovic E, Peter B, Gleixner KV, Schuch K, Pickl WF, Thaiwong T, et al. H1-receptor antagonists terfenadine and Loratadine inhibit spontaneous growth of neoplastic mast cells. Exp Hematol. 2010;38:896–907.
184. Pang J, Dalziel G, Dean B, Ware JA, Salphati L. Pharmacokinetics and absorption of the anticancer agents dasatinib and GDC-0941 under various gastric conditions in Dogs – Reversing the effect of elevated gastric pH with betaine HCl. Mol Pharm. 2013;10:4024–31.
185. De Luca A, Normanno N. Predictive biomarkers to tyrosine kinase inhibitors for the epidermal growth factor receptor in non-small-cell lung cancer. Curr Drug Targets. 2010;11(7):851–64.
186. Coupe N, Harrison M, Chua W, de Souza P. Biomarkers for tyrosine kinase inhibitors in renal cell cancer. Transl Androl Urol. 2012;1(4):216–22.
187. Brunetti B, de Biase D, Millanta F, Muscatello LV, Di Oto E, Marchetti R, Laddaga EL, De Leo A, Tallini G, Bacci B. Protein expression, amplification, and mutation of HER2 gene in canine primary pulmonary adenocarcinomas: preliminary results. Anim (Basel). 2024;14(18):2625.
188. Dos Anjos DS, Civa PAS, Werner J, Vicente IST, Fonseca-Alves CE. Immunohistochemistry screening of different tyrosine kinase receptors in canine solid Tumors-Part I: proposal of a receptor panel to predict therapies. Int J Mol Sci. 2024;25(15):8438.
189. Klopfleisch R, Meyer A, Schlieben P, Bondzio A, Weise C, Lenze D, et al. Transcriptome and proteome analysis of tyrosine kinase inhibitor treated canine mast cell tumour cells identifies potentially kit signaling-dependent genes. BMC Vet Res. 2012;8:96.
190. Tufts Cummings Veterinary Medical Center. Pilot study of a MEK inhibitor in dogs with histiocytic sarcoma, <https://trials.vet.tufts.edu/clinical_trials/pilot-study-of-a-mek-inhibitor-in-dogs-with-histiocytic-sarcoma/# (2022). [Google Scholar]).
191. Gardner HL, London CA, Portela RA, Nguyen S, Rosenberg MP, Klein MK, Clifford C, Thamm DH, Vail DM, Bergman P, Crawford-Jakubiak M, Henry C, Locke J, Garrett LD. Maintenance therapy with toceranib following doxorubicin-based chemotherapy for canine splenic hemangiosarcoma. BMC Vet Res. 2015 Jun 11;11:131.
192. Olsen JA, Thomson M, O'Connell K, Wyatt K, Isotani M, Ishida N, Tominaga M, Tamura K, Yagihara H, Ochi S et al. Combination vinblastine, prednisolone and toceranib phosphate for treatment of grade II and III mast cell tumours in dogs. Vet Med Sci. Effect of Tyrosine Kinase Inhibition by Imatinib Mesylate on Mast Cell Tumors in Dogs. J Vet Intern Med 2008;22:985–8.
193. Halsey CHC, Thamm DH, Weishaar KM, Burton JH, Charles JB, Gustafson DL, et al. Expression of phosphorylated KIT in canine mast cell tumor. Vet Pathol. 2017;54:387–94.
194. Kobie K, Kawabata M, Hioki K, Tanaka A, Matsuda H, Mori T, et al. The tyrosine kinase inhibitor Imatinib [STI571] induces regression of xenografted canine mast cell tumors in SCID mice. Res Vet Sci. 2007;82:239–41.
195. Laver T, London CA, Vail DM, Biller BJ, Coy J, Thamm DH. Prospective evaluation of Toceranib phosphate in metastatic canine osteosarcoma. Vet Comp Oncol 2018;16:E23-E29.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.