The growing number of specialized oncology therapeutics available for dogs (TABLE 1) makes remaining current on the latest advances challenging, especially in general practice. Primary care veterinarians routinely diagnose cancer and often initiate client discussions regarding treatment options. Keeping up to date on current cancer treatments is important for presenting the latest in case management options to clients.

This article reviews the status, science, available key supporting data, and clinical use of several canine cancer therapeutics; however, no consensus guidelines on use of these agents currently exist. Do not hesitate to consult a board-certified veterinary oncologist regarding case selection advice when considering these treatment options for patients.

**LYMPHOMA**

Tanovea (rabacfosadine for injection)

**Approval status:** U.S. Food and Drug Administration (FDA) approved (2021)

**Manufacturer:** Elanco (Greenfield, Indiana)

**Mechanism of action:** Rabacfosadine is a prodrug of the nucleotide analogue 9-(2-phosphonylmethoxyethyl) guanine (PMEG), which interferes with DNA synthesis. It effectively loads lymphoid cells while reducing levels of PMEG in plasma and target organs of toxicity.1,2

**Indication:** Tanovea is labeled for the treatment of lymphoma in dogs.1 Off-label use in dogs with multiple myeloma has also been reported.

**Handling:** Chemotherapy-resistant gloves, goggles, and protective clothing should be worn when handling or administering Tanovea. Refer to the Occupational Safety and Health Administration (OSHA) for appropriate guidelines (osha.gov/hazardous-drugs/controlling-occx). See the package insert for the full list of warnings.1

**Administration:** Tanovea is administered at a dose of 1 mg/kg via 30-minute IV infusion once every 3 weeks for up to 5 treatments. Stepwise dose decreases (to 0.8 mg/kg, 0.66 mg/kg) or dose delays may be used to manage adverse events.1

**Key clinical data:** The pivotal clinical trial enrolled 158 dogs with naïve (untreated) or previously treated
(relapsed) lymphoma; 128 received Tanovea and 30 received placebo. The overall response rate (ORR) in all dogs was 73%; median progression-free survival was 82 days for all dogs and 151 days for dogs that responded. Dogs with B-cell lymphoma and those naïve to treatment responded better. One recent publication summarizing 3 separate studies in dogs with naïve lymphoma treated with Tanovea with or without prednisone showed an ORR of 87% and progression-free interval of 122 days. Additional studies have reported response in dogs with naïve lymphoma treated with an alternating Tanovea/doxorubicin protocol and dogs with previously treated lymphoma receiving Tanovea as a rescue therapy.

Most common side effects: Similar to other cytotoxic chemotherapeutics, the most commonly noted adverse effects include gastrointestinal signs (e.g., diarrhea, decreased appetite/anorexia, emesis, weight loss) and myelosuppression (neutropenia). One important potential toxicosis is the development of pulmonary fibrosis, which may be life-threatening, in approximately 5% of dogs. Based on the risk of this adverse event, Tanovea should not be used in West Highland White terriers and should be used with caution in other terrier breeds. Clients should be advised of this potentially fatal complication and monitoring (via serial thoracic radiographs) should be considered. Dermatopathies (e.g., otitis, alopecia, dermatitis, erythema, pruritis, hyperpigmentation, skin ulcerations, bacterial skin infections) are seen in 20% to more than 50% of dogs.

Clinical use: Current treatment considerations include use as single-agent therapy (with prednisone), in combination with multiagent chemotherapy protocols (potentially replacing doxorubicin in some versions of CHOP-based protocol [i.e., cyclophosphamide, doxorubicin, vincristine sulfate, prednisone]), or in an alternating Tanovea/doxorubicin protocol (1 drug given once every 3 weeks for a total of 3 treatments of each drug, 6 treatments total) in dogs with naïve or previously treated lymphoma.

**Laverdia-CA1 (verdinexor tablets)**  
**Approval status:** FDA conditional approval (2021)  
**Manufacturer:** Dechra Veterinary Products (Overland Park, Kansas)  
**Mechanism of action:** Laverdia-CA1 is a selective inhibitor of nuclear export that blocks exportin 1 (XPO1 or chromosome region maintenance protein 1), a regulatory protein responsible for exporting several tumor suppressor and growth regulatory proteins from the nucleus to the cytoplasm. By keeping these regulatory proteins within the nucleus, Laverdia-CA1 may help treat several types of cancer.

**Indication:** Laverdia-CA1 is labeled for the treatment of lymphoma in dogs.

**Handling:** Disposable chemotherapy-resistant gloves should be worn when handling tablets.

**Administration:** Initial starting dosage is 1.25 mg/kg PO twice per week (e.g., Monday and Thursday) with at least 72 hours between doses. Laverdia-CA1 should be administered with food. After 2 weeks, a dosage increase to 1.5 mg/kg twice per week can be considered, depending on how well the drug is tolerated and patient response to therapy.

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**TABLE 1 Currently Available Veterinary Oncology Therapeutics Approved or Licensed in the United States**

<table>
<thead>
<tr>
<th>TRADE NAME</th>
<th>COMPOUND NAME</th>
<th>MANUFACTURER</th>
<th>INDICATION</th>
<th>REGULATORY STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocidin*</td>
<td>Mycobacterium cell wall fraction</td>
<td>NovaVive</td>
<td>Mammary tumors</td>
<td>USDA licensed</td>
</tr>
<tr>
<td>Laverdia-CA1</td>
<td>Verdinexor</td>
<td>Anivive/Dechra</td>
<td>Lymphoma</td>
<td>FDA conditional approval (2021)</td>
</tr>
<tr>
<td>Onceptb</td>
<td>Canine melanoma vaccine, DNA</td>
<td>Merial/Boehringer Ingelheim</td>
<td>Melanoma</td>
<td>USDA licensed (2010)</td>
</tr>
<tr>
<td>Palladia</td>
<td>Toceranib phosphate</td>
<td>Zoetis</td>
<td>Mast cell tumor</td>
<td>FDA approved (2009)</td>
</tr>
<tr>
<td>Stelonta</td>
<td>Tigilanol tiglate</td>
<td>QBiotics/Virbac</td>
<td>Mast cell tumor</td>
<td>FDA approved (2020)</td>
</tr>
<tr>
<td>Tanovea</td>
<td>Rabacfosadine</td>
<td>VetDC/Elanco</td>
<td>Lymphoma</td>
<td>FDA approved (2021)</td>
</tr>
</tbody>
</table>

*a Published data on this therapeutic are limited at this time.  
b Currently only available to specialists.
Stelfonta is administered as an intratumoral injection via a 23-gauge needle and a single injection site, using a fanning motion to disperse drug throughout the tumor.

Key clinical data: In consideration for reasonable expectation of effectiveness, 58 dogs with lymphoma treated with Laverdia-CA1 (39 dogs also received prednisone) were evaluated. The ORR (those in complete or partial response) was 34.5%, with a median duration of response of 18 days (range, 7 to 187 days). The median time to tumor progression (TTP) in all dogs was 29.5 days (range, 7 to 244 days). A subset of dogs (n = 17; 29%) had TTP of at least 56 days.6,8

Most common side effects: Anorexia, vomiting, diarrhea, weight loss, and lethargy were the most common adverse events noted.7 Most were mild to moderate in nature and treated with supportive care as clinically indicated.6,8

Clinical use: Best clinical use will be more fully defined through additional prospective, randomized studies. Current treatment considerations include use as single-agent therapy (with prednisone), in combination with multiagent chemotherapy protocols, and/or as maintenance therapy after completion of multiagent chemotherapy protocols in dogs with naïve or previously treated lymphoma.

MAST CELL TUMORS

Stelfonta (tigilanol tiglate injection)

Approval status: FDA approved (2020)

Manufacturer: Virbac Animal Health, Inc. (Fort Worth, Texas)

Mechanism of action: Tigilanol tiglate is a novel diterpene ester that is a potent cellular signaling molecule. Anti-tumor effectiveness of tigilanol tiglate is believed to be due to 3 key mechanisms: direct oncolysis of tumor cells via disruption of mitochondrial function; protein kinase C activation resulting in an acute inflammatory response throughout the tumor that causes localized hypoxia and recruits innate immune cells; and destruction of tumor vasculature.9,10

Indication: Stelfonta is labeled for the treatment of nonmetastatic cutaneous (located anywhere on the body) or subcutaneous (located at or distal to the elbow or hock) mast cell tumors (MCTs) in dogs. Treated MCTs should be less than 10 cm³ in size (see label for calculation formula).9,10

Handling: Personal protective equipment (disposable gloves, protective eyewear, and a lab coat or gown) should be worn when handling Stelfonta. Caution is recommended during treatment to avoid accidental self-injection.9

Administration: Stelfonta is administered as an intratumoral injection via a 23-gauge needle and a single injection site, using a fanning motion to disperse the drug throughout the tumor. Tumor volume measurements and dosing calculations should be followed closely as outlined in the package insert. Consider sedating dogs for administration and post-treatment pain management medications as clinically indicated. Concomitant medications (prednisone/prednisolone, diphenhydramine, famotidine) must be administered as outlined due to potential for systemic effects of mast cell degranulation.9,10

Key clinical data: In the pivotal trial that enrolled 123 dogs with MCTs, 81 were treated with Stelfonta while 42 were in the untreated control group. Single treatment with Stelfonta resulted in 75% complete response by 28 days compared with 5.3% in the control group. No recurrence was noted in 93% of responding Stelfonta-treated dogs at 84 days post-treatment. Most wounds were healed by 28 to 42 days post-treatment. Wounds only rarely required bandaging or antibiotics.9,10 A separate publication that evaluated response at 12 months after Stelfonta treatment indicated that 89% remained tumor free at the treatment site; 11% had developed recurrence within the first 6 months after treatment.11

Most common side effects: The most commonly noted adverse effects (wound formation, injection site pain, lameness in treated limb, injection site bruising/erythema/edema) are directly related to the mechanism
of action of the drug. Other common side effects included vomiting, diarrhea, hypoalbuminemia, and anorexia. Most side effects were low grade and transient.9,10

Clinical use: Stelfonta should be considered as a local treatment option for nonmetastatic MCTs (<10 cm³) in dogs. This is especially appealing when surgery may not be a good option based on tumor location, patient status, or client considerations. Client education and setting appropriate expectations regarding wound formation and management are important for case management success. As histologic grade is not available for MCTs treated with Stelfonta (unless incisional biopsy is performed and the site allowed to heal for 14 days prior), utilizing other prognostic indicators is important. Obtaining a cytologic grade of the MCT and aspirating the regional lymph node (if possible) should be considered.

Palladia (toceranib phosphate tablets)

Approval status: FDA approved (2009)

Manufacturer: Zoetis Inc. (Kalamazoo, Michigan)

Mechanism of action: Receptor tyrosine kinases (RTKs) are a family of highly regulated cell signaling proteins that play a key role in normal cell growth and differentiation. Dysregulation of RTKs, resulting in continual signal activation, has been identified in several types of cancer in human and veterinary medicine. Members of the RTK family also play key roles in angiogenesis (new blood vessel development), an important process for tumor growth, survival, and metastasis. By inhibiting several members of the split-kinase family of RTKs, including vascular endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor-β (PDGFR-β), and Kit/stem cell factor receptor (SCFR), toceranib has an antiangiogenic as well as a direct antitumor role in treating canine MCTs12,13 and, potentially, other types of cancer.

Indication: Palladia is labeled for the treatment of dogs with recurrent cutaneous Patnaik grade II or III MCT.12 Evidence of biologic activity has been reported in several other types of cancer in dogs (BOX 1). Use of Palladia outside of the above indication is off-label use, and appropriate clarification and client education should be provided in these cases.

Handling: Palladia tablets have a protective film coating. They should not be split or broken apart. Gloves should be worn if handling broken or moistened tablets. Wash hands after handling tablets.12

Administration: The label dosage for Palladia is 3.25 mg/kg body weight PO q48h. Stepwise dose reductions to 2.25 mg/kg PO q48h or treatment delays may be used to manage adverse effects.12 The label dosage was defined as the maximum tolerated dose in early-phase clinical trials. A subsequent study demonstrated that a lower dosing range (2.4 to 2.9 mg/kg PO q48h) substantially reduces the associated adverse effect profile while maintaining therapeutic levels likely needed for biologic activity.27 This lower dosing range should be used as the starting dose. Based on ease of administration for clients, as well as protocols utilized in a number of published studies, less frequent administration (e.g., Monday, Wednesday, Friday of each week) is often elected rather than strictly every other day.

Key clinical data: Numerous publications in the veterinary literature show the therapeutic potential for Palladia against several types of cancer in dogs (BOX 1). Veterinarians should consult those specific references when discussing clinical expectations with clients.

Most common side effects: Gastrointestinal clinical signs (e.g., diarrhea, emesis, blood in stool, decreased

**BOX 1 Canine Cancers That May Benefit From Palladia Therapy**

- Apocrine gland anal sac adenocarcinoma (AGASACA)9,15
- Chemodectoma16,17
- Gastrointestinal stromal tumor (GIST)18
- Head and neck carcinoma14
- Inflammatory mammary carcinoma19
- Insulinoma20,21
- Mast cell tumor13,22
- Nasal carcinoma14,23
- Pheochromocytoma14
- Thyroid carcinoma14,25
- Transitional cell carcinoma26
appetite) were the most commonly reported adverse effects noted in dogs with MCTs treated at a dose range of 2.25 to 3.25 mg/kg PO q48h. Beyond gastrointestinal side effects and occasional myelosuppression (e.g., neutropenia, thrombocytopenia), important potential effects to note and monitor are hypertension, proteinuria, muscle pain (sometimes described as “cramping”) and hair coat/pigment changes.

Overall, Palladia is generally well tolerated and most adverse events are manageable with supportive therapy, dose modifications, or treatment delays. Client education and preparation are important so that potential adverse effects are recognized early. This allows for treatment discontinuation and/or supportive medications as appropriate before changes become severe or life threatening.

Clinical use: Palladia can be considered in a variety of different settings (treating bulky/gross tumor or postoperatively for microscopic disease) for many different tumors where potential biological activity has been documented (Box 1).

IMMUNOTHERAPIES
The immunotherapies discussed below are regulated by the U.S. Department of Agriculture (USDA) Center for Veterinary Biologics as autologous therapeutics but are not licensed. They are distributed as experimental products and are to be used under the supervision/prescription of a licensed veterinarian.

ELIAS Cancer Immunotherapy (ECI)
Manufacturer: ELIAS Animal Health (Olathe, Kansas)

Mechanism of action: Vaccine-enhanced adoptive T-cell treatment with cytokine (interleukin-2 [IL-2]) boost. The specific mechanism for this product is not well defined. The overall concept is that tumors contain multiple mutations, some of which can serve as neoantigens that may make the cancer cells more immunogenic. Combining the administration of autologous tumor cells with potent cytokine immune stimulation and cancer neoantigen-primed T cells is believed to increase the likelihood of success.

Indication: While this immunotherapy may have potential application to several different tumor types, the available published data are for osteosarcoma.

Handling: No chemotherapy-related handling needed.

Administration: Tumor tissue is removed (surgical excision or biopsy) and a personalized vaccine is produced. The vaccines are administered intradermally on a weekly to biweekly schedule. Two weeks later, T cells are collected by apheresis (specialized process/equipment required; typically performed by an oncologist). These cells are expanded and activated ex vivo and returned to the veterinarian for intravenous administration along with subcutaneous injections of IL-2. Overall, this is an approximate 6-week treatment timeline.

Key clinical data: One publication is available summarizing treatment of 14 dogs with osteosarcoma in a single-arm prospective study. Dogs were treated with amputation followed by ECI as outlined above; chemotherapy was not administered. Median survival time for all dogs was 415 days, with 5 dogs surviving >730 days. While these results are positive and encouraging, it is a small sample size. Additional studies with larger numbers of dogs are needed to further define the potential benefit of this therapeutic.

Most common side effects: Safety of this product has not been established. With premedication, most toxicoses were reported to be low grade and transient in nature. Gastrointestinal signs, lethargy, fever, and myelosuppression were among the most common side effects observed.

Clinical use: Based on the limited available data, this therapeutic is a reasonable consideration for dogs with osteosarcoma. Whether combination with chemotherapy in dogs with osteosarcoma could further enhance treatment outcomes is unknown. Therapeutic potential in dogs with other types of cancer remains to be defined.

Torigen Pharmaceuticals Autologous Prescription Product (tumor vaccine)
Manufacturer: Torigen Pharmaceuticals (Farmington, Connecticut)

Mechanism of action: This immunotherapy is produced using the patient’s tumor after surgical excision or biopsy. The concept is that specific therapeutic tumor antigens are often not well known or understood. By using a significant piece of the patient’s tumor, a larger variety of antigens are presented to the
immune system, which may increase the chances of a successful anticancer immune response. The product consists of deactivated patient tumor cells combined with adjuvant and particulate small intestinal submucosa. The exact mechanism of action is not well defined but may involve induction of Th1 immune response, which activates CD8+ cytotoxic T cells to act against deactivated tumor-associated antigens, allowing recognition of the tumor as foreign.30,31

Indication: Several different cancer types are listed in the company brochure, but the true indication is currently unknown.11

Handling: No chemotherapy-related handling needed.

Administration: Given by subcutaneous injection every 3 weeks for 3 treatments.31

Key clinical data: Efficacy in tumor-bearing dogs has not been established or published.

Most common side effects: Safety of this product has not been established. Reported side effects in dogs with a similar therapy included a low incidence of mild pyrexia, injection site swelling, and lethargy, which typically resolved without clinical intervention.32

Clinical use: The lack of published efficacy data makes it impossible to define best use of this therapy. The company brochure indicates that the product is for experimental use only.31

CONCLUSION

Many new cancer therapies for dogs can readily be incorporated into primary care practice. As with any new therapeutic, it is important for all members of the veterinary team (veterinarians, veterinary nurses, receptionists) to remain educated on the potential adverse effect profiles of these drugs to be able to answer client questions. Regional oncologists are excellent resources for professional questions regarding treatment options and best plans for coordination of treatment for cancer patients. TvP

References

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31. Torigen Pharmaceuticals. Personalized cancer treatment is now accessible [product brochure]. Accessed March 2, 2022. static1.squarespace.com/static/5a0e7fc69f8dceec6e149d29/1/5ec1e7beac3/35107c14ec87d/1589766093030/5531+Torigen+Brochure+V5+8JUL19.pdf


Disclosure

Dr. Johannes is a consultant, speaker, and advisory board member for Anivive, Elanco, and QBiotics, and receives honoraria for these activities. Dr. Johannes is a former employee of Pfizer Animal Health (now Zoetis, Inc.).

Chad M. Johannes

Dr. Johannes is an associate professor and director of the James L. Voss Veterinary Teaching Hospital at Colorado State University. His industry experience includes working as the former Medical Director at Aratana Therapeutics, Inc., and coordination of the launch of Palladia, the first FDA-approved veterinary cancer therapeutic, during his time with Pfizer Animal Health (now Zoetis, Inc.). Dr. Johannes’s practice experience includes primary care, specialty care, and academic settings. His areas of research interest include oncology therapeutic development, immunotherapeutics, and effective management of oncology treatment–related side effects.