From the Proceedings of the 2015 ACVIM Annual Forum (VC-003)

RABACFOSADINE AND PREDNISONE: EFFICACY OF A Q21 DAY ADMINISTRATION SCHEDULE IN CANINE LYMPHOMA

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Lymphoma is one of the most common canine cancers. While current therapies induce remission in most naïve dogs with lymphoma, drug-resistant relapse is common and there is a distinct need for novel agents. The acyclic nucleotide phosphonate 9-(2-phosphonylmethoxyethyl)-guanine (PMEG) forms an active phosphorylated metabolite, PMEGpp, in cells and causes cytotoxicity in dividing cells due to inhibition of DNA polymerases α, δ, and ε; however, PMEG's use as an anticancer agent is limited by poor cellular permeability and nonspecific toxicity. Rabacfosadine (VDC-1101/GS-9219/TANOVEATM), a novel double prodrug of PMEG, was designed to preferentially target lymphoid cells with significantly reduced systemic toxicity. Rabacfosadine has been administered on a variety of dosing schedules to dogs with lymphoma. Objective responses were noted in 100% of chemotherapy-naïve dogs and 60% of refractory dogs, with a median remission duration of 128 days. Given the ease of administration and equivalent activity with a q21-day administration schedule, we sought to generate additional data regarding efficacy of this regimen through completion of a prospective clinical trial. Additionally, we explored the potential of concomitant low-dose prednisone to mitigate previously observed cutaneous and pulmonary adverse effects.

Dogs with cytologically or histologically confirmed lymphoma were treated with rabacfosadine (0.82 mg/kg free base, as a 30-minute IV infusion once every 21 days). Dogs received concomitant prednisone (1 mg/kg PO QOD) throughout treatment. Dogs experiencing a complete response (CR) received 5 doses of rabacfosadine, followed by monthly rechecks. Complete clinicopathological assessment and clinical assessment of remission and adverse effects (AEs) were performed every 21 days. Response was assessed according to published VCOG criteria and AEs according to the VCOG-CTCAE v1.1.

74 dogs were prospectively enrolled. 63 were evaluable for response assessment and 73 were evaluable for progression free interval (PFI) assessment. While 13% of evaluable dogs were treatment-naïve and 29% had received a single line of previous treatment, the majority of dogs (59%) had received 2 or more lines of previous therapy. 50 evaluable dogs had B cell lymphoma and 13 had T cell lymphoma. The overall response rate (ORR) was 57% (25% CR, 32% PR). The ORR was 64% and 23% for B cell and T cell respectively. Degree of pre-treatment impacted response rate: the ORR was 88% in naïve dogs, 56% in dogs treated 2nd-line, and 51% in 3rd-line and beyond. The median PFI was 112 days for dogs experiencing a CR and 42 days for a PR (overall median PFI 41 days). Degree of pre-treatment significantly impacted PFI (164 d, 84 d and 32 d for naïve, 2nd-line and >2nd line respectively).

The majority of AEs were mild and self-limiting: gastrointestinal (GI) and hematologic AEs were most common. Grade 3 AEs included liver enzyme elevation (4), lethargy (4), GI (2) and urinary (1). 3 dogs experienced grade 4 hematologic toxicity, and 2 developed severe hemorrhagic gastroenteritis leading to euthanasia, several weeks after the first rabacfosadine treatment and therefore of uncertain attribution. 4 dogs experienced grade 1 dermatologic AEs, and 1 dog developed grade 1 pulmonary fibrosis.

In conclusion, rabacfosadine was generally well tolerated and had substantial antitumor activity in dogs with both treatment-naïve and refractory lymphoma when administered on a q21-day schedule. Response rates and PFI observed in this study are comparable to historical data with rabacfosadine when degree of pre-treatment is accounted for. There was a reduction in both the frequency and severity of AEs relative to historical data; however, it is not clear whether this is a result of less frequent dosing, concurrent prednisone, or lower cumulative rabacfosadine exposures in this heavily pre-treated population. Further studies are warranted to explore rabacfosadine at higher doses.