New Oncology Therapeutics on the Horizon

"With nearly 20 FDA-approved monoclonal antibodies (MAbs) in the United States for treatment of various malignancies, passive immunotherapy is a key element in therapy guidelines in human oncology. Rituximab, a monoclonal antibody targeting the CD20 antigen on the surface of B-lymphocytes, was approved by the FDA in 1997 and has become a component of standard-of-care therapy for a number of human B-cell disorders. Expression of CD20 has been confirmed in canine B-cell lymphomas by immunohistochemistry using anti-human CD20 polyclonal antibodies that recognize the intracellular domains of CD20. Unfortunately, rituximab does not bind canine CD20 and thus cannot be utilized for passive immunotherapy in dogs. Development of monoclonal antibodies for treatment of B-Cell and T-cell lymphomas would represent a huge potential step forward in our ability to more effectively treat these aggressive cancers in dogs."

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Immuno-Oncology Developments for Canine Lymphoma

1. Anti-CD20 Monoclonal Antibody (MAb) for Aid in Treatment of Canine B-Cell (Aratana)
   Additional clinical studies are underway to further evaluate the best use and timing of this anti-CD20 monoclonal antibody in conjunction with cytotoxic chemotherapy.

2. Anti-DC52 Monoclonal Antibody for Aid in Treatment of Canine T-cell Lymphoma (Aratana)
   These studies, as well as further prospective clinical studies, will help define the best use of the anti-CD52 Mab along with cytotoxic chemotherapy in dogs with T-cell lymphoma.

3. Anti-CD20 Monoclonal Antibody (Elanco)
   From a panel of anti-canine CD20 monoclonal antibodies, generated by using a mouse hybridoma approach, the antibody 1E4-clgGB has been selected for further testing and development as an agent for the treatment of B-cell lymphoma.
4. Anti-DC20 Monoclonal Antibody (IDEXX)
A newly established anti-canine CD20 monoclonal antibody that can be used to identify B-cells by flow cytometry and that stably binds an epitope promoting macrophage-mediated phagocytosis of canine B-cell lymphoma cells in vitro has also recently been reported. This novel anti-canine CD20 mAb has been designated as 6C8. The 6C8 Mab may be useful as a diagnostic tool to phenotype B-cells, and could potentially be integrated as a tool for passive immunotherapy to treat dogs with B-cell disorders.

5. ImmunexFX™ Cancer Vaccine (Morphogenesis Inc)
A multi-indication cancer vaccine, ImmunexFX™ (in pre-clinical studies) have indicated that it acts by providing a priming action for the immune system. Pre-clinical studies studies have shown that the vaccine can be produced for and safely delivered to dogs with naturally occurring lymphoma and a study in dogs with B-cell lymphoma is reported to be underway.

6. Telemerase vaccine (Takia)
A DNA telomerase therapeutic vaccine is currently being studied in dogs with lymphoma. The survival time of vaccine/Chemo-treated dogs was significantly increased over historic controls of Chemo-treated animals (>97.8 versus 37 weeks, respectively, P = 0.001).

IMMUNO-ONCOLOGY DEVELOPMENTS FOR CANINE OSTEOSARCOMA

AT-014 (Aratana Therapeutics, Inc.)
In a study at the University of Pennsylvania, Dr. Nicola Mason administered AT-014 to 18 dogs with appendicular osteosarcoma following amputation and chemotherapy (4 doses of carboplatin). The median survival time of 11 historical control dogs was 316 days, the median survival time for the treated group has not yet been reached (p<0.0001). However, eleven of the 18 treated dogs have surpassed the MST of the control group and 8 were alive as of 3 December 2014. Adverse events were mild to moderate and primarily consisted of fever, lethargy, and nausea/vomiting.

SMALL MOLECULE INHIBITORS FOR CANINE LYMPHOMA

1. Verdinexor/KPT-335 is a novel orally bioavailable XPO1 inhibitor. A Phase I clinical trial of KPT-335 was performed in 17 dogs with non-Hodgkin lymphoma (NHL, naïve or relapsed), mast cell tumor or osteosarcoma. Clinical benefit (CB) including partial response to therapy (PR, n = 2) and stable disease (SD, n=7) was observed in 9/14 dogs with NHL with a median to progression (TTP0 for responders of 66 days (range 35-256 days). Toxicities were primarily gastrointestinal consisting of anorexia, weight loss, vomiting and diarrhea and were manageable with supportive care, dose modulation and administration of low dose prednisone; hepatotoxicity, anorexia and weight loss were the dose limiting toxicities. A phase 2b clinical trial of Verdinexor in dogs with newly-diagnosed or first time relapse lymphomas has been conducted. Verdinexor has received a Minor Use/Minor Species, or MUMS, designation from the Center for Veterinary Medicine (CVM) of the FDA for the treatment of lymphoma in dogs.
2. RV-1001 (Rhizen Pharmaceuticals)
P13 kinase (PI3K) is a protein involved in cell signaling. It has been shown that for lymphomas and leukemias, PI3K isoforms δ and γ are particularly important in maintaining tumor growth. RV-1001 is an orally bioavailable inhibitor of PI3K family members, having a strong binding affinity towards PI3Kδ. A phase I clinical trial performed in dogs with naïve or relapsed B or T-cell lymphoma was conducted. Nine dogs were entered into the clinical trial, (different dosages) One dog with T Cell has had a durable response to therapy and three additional dogs have had partial responses- objective response rate of 44%.

TOCENIB PHOSPHATE/PALLADIA (Zoetis)

First approved by the FDA in 2009, there are a number of recent publications to review that help to further define the best clinical use of this powerful therapeutic.

1. Pulse-dosed Palladia + lomustine for nonresectable canine mast cell tumor (MCT)
Forty-seven client owned dogs with measurable MCT were enrolled. Palladia was administered PO on days 1,3 of each cycle and 5 of a 21 day cycle at a target dosage of 2.75mg/kg. Lomustine was administered PO on day 3 of each cycle at a starting dosage of 50mg/m². All dogs were concurrently treated with diphenhydramine, omeprazole, and prednisone. Lomustine at a dosage of 50/mg/m² once every 3 weeks combined with pulse-dosed Palladia was well-tolerated. The objective response rate of 46% for this protocol is comparable to what previously has been reported for single-agent protocols, but considerably higher that that reported with single-agent lomustine. c-kit gene mutation status did not affect outcome. Pulse administration of Palladia was associated with a relatively low incidence of adverse gastrointestinal events, when compared with continuous exposure.

2. Maintenance Palladia following doxorubicin-based chemotherapy for canine splenic hemangiosarcoma (HSA)
This multicenter study evaluated the impact of treatment with Palladia on progression free survival in dogs with stage I or II HAS following splenectomy and single agent doxorubicin (DOX) chemotherapy. A total of 43 dogs (n=5 stage I; n=38 stage II) splenic HAS were enrolled. The median disease free interval (DFI) for all dogs enrolled in this study (n=43) was 138 days, and the median DFI for those dogs that went on to receive Palladia (n=31) was 161 days. The median survival time (ST) for all dogs enrolled in this study was 169 days, and the median ST for those dogs that went on to receive Palladia was 172 days.

3. Impact of Palladia/piroxicam/cyclophosphamide maintenance therapy on canine osteosarcoma (OSA)
In this randomized, prospective clinical trial, dogs with OSA free of gross metastatic disease (n=126) received carboplatin chemotherapy (4 doses) following amputation. On study entry, dogs were randomized to receive piroxicam/cyclophosphamide with or without Palladia (n=63 each) after completing carboplatin chemotherapy. The one-year survival rate for control dogs was 35% compared to 28% for dogs receiving Palladia. The addition of Palladia to metronomic piroxicam/cyclophosphamide therapy following amputation and carboplatin...
chemotherapy did not improve median DFI, OS or the 1-year survival range in dogs with OSA.

**CYTOTOXIC CHEMOTHERAPY DEVELOPMENTS FOR CANINE CANCER**

**1. PACCAL VET-CA1 (Oasmia Pharmaceutical)**
The active ingredient in PACCAL VET-CA1 is paclitaxel, an antimicrotubule agent that interferes with the dynamic instability of microtubules – the ability of microtubules to switch between phases of growth and shrink-age. PACCAL VET-CA1 works by stabilizing microtubules, so they can’t grow and shrink normally. Because microtubules play a central role in mitosis, this abnormal stabilization blocks cells (especially rapidly dividing ones) from completing mitosis, leading to cell death.

PACCAL VET-CA1 is labeled to treat:
Non resectable stage III, IV or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy; and
Resectable and non resectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy.

Federal law prohibits extra label (“off label) use of conditionally approved drugs. PACCAL VET-CA1 can only be utilized for the two labeled indications. This is different than fully approved drugs which, under certain conditions, can be legally prescribed for extra-label uses in animals. PACCAL VET-CA1 is now distributed in the US by Oasmia Pharmaceutical Inc.

**2. DOXOPHOS VET (Oasmia Pharmaceutical)**
DOXOPHOS VET is a patented formulation of doxorubicin which Oasmia is developing for the treatment of lymphoma. Oasmia is conducting a Phase I study of DOXOPHOS VET which will include approximately 15 dogs. The FDA has granted Oasmia MUMS Designation for DOXOPHOS VET for the indication of lymphoma. This product is now distributed in the US by Oasmia Pharmaceutical Inc.

**3. Rabacfosadine /VDC-1101 Tanovea ™ (VetDC)**
In June 2013, the FDA granted Tanovea a Minor Use/Minor Species (MUMS) designation for use in canine lymphoma, allowing VetDC to move forward toward filing for full regulatory approval. Tanovea is also currently being evaluated for use in cats with lymphoma.

VetDC is currently seeking veterinary hospitals who would be interested in participating in clinical trials with Tanovea.