THE FUTURE IS NOW – NEW ONCOLOGY THERAPEUTICS

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IMMUNO-ONCOLOGY DEVELOPMENTS

The area of immuno-oncology is rapidly expanding in human medicine and these advances are having significant impact on treatment options for many types of cancer. The most active areas of development within this realm include monoclonal antibodies (MAb) and therapeutic anti-cancer vaccines. In recent years, immuno-oncology therapeutics tailored for canine and feline oncology patients have gained attention. Although many of these therapeutics are in the earlier stages of development, they hold strong potential and are beginning to become clinically available for patient care.

Anti-Cancer Monoclonal Antibodies

1. **Monoclonal Antibody for Aid in Treatment of Canine B-cell Lymphoma (Aratana)**
   This caninized MAb (Blontress®, AT-004) was fully licensed by the USDA in January 2015 as an aid in the treatment of canine B-cell lymphoma. Initial clinical data presented in abstract form showed signs of biologic activity[1-3] however no peer-reviewed data is available to date. Additional clinical studies are reportedly underway to further evaluate the best use and timing of this MAb in conjunction with cytotoxic chemotherapy, however it is not widely commercially available at this time. Aratana has stated that scientific studies suggest that Blontress is not as specific to the CD20 target as expected.[4]

2. **Monoclonal Antibody for Aid in Treatment of Canine T-cell Lymphoma (Aratana)**
   This caninized MAb (Tactress®, AT-005) received conditional licensure by the USDA in January 2014 as an aid in the treatment of canine T-cell lymphoma. The stated target of this MAb, CD52, has not yet been described in canine lymphoma cells. Aratana has conducted two prospective studies to further evaluate AT-005 in conjunction with cytotoxic chemotherapy (CHOP-based protocol and lomustine) for treatment of canine T-cell lymphoma. Unfortunately, the MAb does not seem to be adding significant progression free survival in these two studies. Aratana has also stated that scientific studies suggest that AT-005 is not as specific to the CD52 target as expected.[4] Tactress remains available to many veterinary oncologists however no peer-reviewed clinical evidence of efficacy has been published at this time.

3. **Anti-CD20 Monoclonal Antibody for Canine Lymphoma (Elanco)**
   The generation and characterization of a rituximab-like anti-CD20 antibody intended as a candidate treatment for canine B-cell lymphoma has been described.[5] Monoclonal antibody 1E4 binds to approximately the same location in the extracellular domain of CD20 as rituximab, and 1E4-based chimeric antibodies co-stain canine B cells in flow cytometric analysis of canine leukocytes using an anti-canine CD21 antibody. Chimeric monoclonal antibodies were assembled. Both 1E4-cIgGB and 1E4-cIgGC were observed to significantly deplete B-cell levels in healthy beagle dogs. The *in vivo* half-life of 1E4-cIgGB in a healthy dog was ~14 days. The antibody 1E4-cIgGB has been selected for further development as an agent for the treatment of canine B-cell lymphoma.[5]

Therapeutic Anti-Cancer Vaccines

1. **Canine Lymphoma Vaccine, DNA (Merial)**
   This xenogeneic murine CD20 DNA therapeutic vaccine for use in dogs with B-cell lymphoma was conditionally licensed by the USDA in September 2015. Utilizing a similar technology platform as Oncept® for canine melanoma, the anti-CD20 vaccine is administered using a needle-free transdermal device. A prospective, multi-center clinical trial in dogs with B-cell lymphoma receiving CHOP-based chemotherapy followed by 4 doses of anti-CD20 vaccine has been described but results have not yet been published.[6]

2. **Canine Osteosarcoma Vaccine (Aratana Therapeutics, Inc.)**
   A recombinant HER2/neu expressing Listeria therapeutic vaccine (AT-014) is being studied as an aid in the treatment of canine osteosarcoma. In a study conducted 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 (MST) of historical control dogs was 423 days; the MST for the treated group was 956 days (p=0.014). Adverse events were mild to moderate and primarily consisted of fever, lethargy, and nausea/vomiting.[7] Additional safety studies are currently being enrolled and AT-014 is under review by the USDA.

3. **Feline IL-2 Immunomodulator (Merial)**
   Feline IL-2 Immunomodulator is a recombinant canarypox virus (ALVAC) expressing feline interleukin-2 (IL-2). This therapeutic was approved by EMA in 2013 (Oncept IL-2). Conditional license was granted by USDA in March 2015 (indicated to delay postsurgical recurrence of feline fibrosarcoma in adult cats with stage 1 disease).[8] A recent report outlines adjuvant treatment of feline injection-site sarcomas with this immunotherapy in complement to surgery and brachytherapy.[9]

SMALL MOLECULE INHIBITOR DEVELOPMENTS

1. **Verdinexor/KPT-335 for Canine Lymphoma (Karyopharm Therapeutics)**
   KPT-335 is a novel orally bioavailable XPO1 inhibitor. Exportin 1 (XPO1) is the sole nuclear exporter of several major tumor suppressor and growth regulatory proteins. Expression of XPO1 is known to be upregulated in a variety of both hematologic malignancies and solid tumors and this correlates with a poor prognosis.[10] A Phase I clinical trial of KPT-335 was performed in 17 dogs with non-Hodgkin lymphoma (NHL, naive or relapsed), mast cell tumor or osteosarcoma. The maximum tolerated dose was 1.75 mg/kg given orally twice/week. Clinical benefit including partial response (PR, n = 2) and stable disease (SD, n = 7) was observed in 9/14 dogs with NHL with a median time to progression (TTP) for responders of 66 days (range 35–256 days). Toxicities were primarily gastrointestinal and were manageable; hepatotoxicity, anorexia and weight loss were the dose limiting toxicities.[14] A Phase 2b clinical trial of Verdinexor in dogs with lymphoma 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 lymphomas in dogs.[11]

2. **RV-1001 for Canine Lymphoma (Rhizen Pharmaceuticals)**
   PI3 kinase (PI3K) is a protein involved in cell signaling. It has been shown that for lymphomas and leukemias, PI3K isoforms γ and δ 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 with oral dosing beginning at 10mg/kg PO q24h and escalating to 25mg/kg PO q24h.[12] Nine dogs have been entered into the Phase I clinical trial beginning at a dose of 10 mg/kg q24h using a standard 3x3 design. One dog with T cell NHL has had a durable complete response to therapy (10 mg/kg), and 3 additional dogs have had partial responses (15 mg/kg [n=2] and 25 mg/kg [n=1]) for an objective response rate of 44%.[13]

CYTOTOXIC CHEMOTHERAPEUTIC DEVELOPMENTS

1. **Paccal Vet®-CA1 (Oasmia Pharmaceutical)**
   The active ingredient in Paccal Vet-CA1 is paclitaxel, an antimicrotubule agent that works by stabilizing microtubules. Paccal Vet-CA1 has conditional approval and is labeled to treat: 1) Nonresectable stage III, IV, or V mammary carcinoma in dogs that have not received previous chemotherapy or radiotherapy; and 2) Resectable and nonresectable squamous cell carcinoma in dogs that have not received previous chemotherapy or radiotherapy. Federal law prohibits extra-label use of conditionally approved drugs meaning that Paccal Vet-CA1 can only be utilized for the two labeled indiations.[14]

2. **Doxophos® Vet (Oasmia Pharmaceutical)**
   Doxophos Vet is a patented formulation of doxorubicin which is being developed for treatment of canine lymphoma. Oasmia is reportedly conducting a Phase I study of Doxophos Vet which will include approximately 15 dogs. The FDA has granted MUMS Designation for Doxophos Vet for the indication of canine lymphoma.[15]

3. **Rabacfosadine/VDC-1101/Tanovea™ (VetDC)**
   Tanovea is a prodrug of the nucleotide analogue 9-(2-phosphonylmethoxyethyl) guanine (PMEG). A phase I/II trial was conducted in 38 dogs with non-Hodgkin lymphoma (NHL) using different dose schedules. Thirty (79%) dogs receiving Tanovea monotherapy achieved clinical remission [23 (61%) CR and 7 (18%) PR] and responses were noted in all eight treatment cohorts. Dose-limiting toxicities were generally manageable and reversible and included dermatopathy, neutropenia, and gastrointestinal signs. Two dogs developed signs of pulmonary dysfunction after they had been withdrawn from study after completing all Tanovea treatments.[16] In June 2013, the FDA granted Tanovea MUMS designation for use in canine lymphoma, allowing VetDC to move toward filing for full regulatory approval. Tanovea is also currently being evaluated for use in cats with lymphoma.[17]

ONCOLOGY SUPPORTIVE THERAPEUTIC DEVELOPMENTS

1. **Canalevia™ (Jaguar Animal Health)**
   Canalevia is a canine-specific formulation of crofelemer, isolated and purified from the *Croton lechleri* tree and having anti-secretory properties. As an oral, enteric-coated, twice daily formulation of crofelemer, Canalevia is being developed for the treatment of chemotherapy-induced diarrhea, or CID, in dogs. The product is not absorbed systemically at the therapeutic dose, but acts locally in the gastrointestinal tract. Jaguar is pursuing a Minor Use/Minor Species (MUMS) approval from the CVM for Canalevia for CID in dogs. If conditional approval is received, Jaguar expects to launch Canalevia for CID in dogs in 2016.[18,19]

2. **Entyce®/Capromorelin/AT-002 (Aratana Therapeutics, Inc.)**
   Capromorelin is an orally active small molecule that mimics the action of ghrelin which causes growth hormone secretion and appetite stimulation. Capromorelin has been shown to cause increased food intake and weight gain in both laboratory and client-owned dogs.[20,21] Additionally, capromorelin has been demonstrated to cause increases in IGF-1 and increased food intake and body weight in cats.[22] Capromorelin received FDA approval in May 2016. Based on current timelines, Aratana anticipates commercialization of capromorelin for treatment of inappetence in dogs in February 2017.[23] This therapeutic has significant potential to positively impact the treatment of inappetence related to chemotherapy and/or underlying cancer in our canine and feline patients.

3. **Galliprant®/Grapiprant/AT-001 (Aratana Therapeutics, Inc.)**
   Grapiprant is a selective antagonist of the EP4 receptor, one of four receptors that mediates the action of prostaglandin E_2 (PGE_2). This receptor is believed to play a key role in mediating pain associated with osteoarthritis. Long-term safety in laboratory dogs has been demonstrated.[24] FDA approval was granted in March 2016 and commencement of commercialization (with Elanco) is anticipated in late 2016.[25] This may provide an alternate pain management therapeutic for cancer patients experiencing chronic pain.

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