Evaluation of the Novel, Orally Bioavailable Selective Inhibitor of Nuclear Export (SINE) KPT-335 (Verdinexor) in Spontaneous Canine Cancer: Results of Phase I and Phase II Clinical Trials

Abstract P1090
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Abstract
Selective Inhibitors of Nuclear Export (SINE) transiently block CRM1/XPO1, the major nuclear export protein in cells, forcing nuclear retention of key tumor suppressor and growth regulatory proteins ultimately resulting in tumor cell death. Aims: Here we evaluated the in vitro activity of SINE against canine tumor cell lines and investigated the biologic activity of verdinexor (KPT-335) in companion dogs with spontaneous cancers as proof of principle for human clinical studies.

Methods: Cytotoxicity assays were performed in several canine cancer cell lines including those derived from non-Hodgkin lymphomas (NHL). SINE compounds induced growth inhibition and apoptosis. NHL cell lines were particularly sensitive with IC50s of 2 - 42 nM. Phase 1 and Phase 2 clinical trials of oral verdinexor were given to companion dogs with mast cell tumors, osteosarcomas, or NHL at doses of 1 - 7 mg/kg.

Results: Seventeen dogs with NHL (naive or relapsed) were enrolled in a Phase 1 clinical trial. The maximum tolerated dose was 1.75 mg/kg, given orally twice weekly (Monday/Thursday). Objective responses included Partial Responses (PR) in 2 - 42 nM. In Phase 1 and Phase 2 clinical trials of oral verdinexor were given to companion dogs with mast cell tumors, osteosarcomas, or NHL at doses of 1 - 7 mg/kg.

Results

In vitro assays: NHL cell lines, canine diffuse large B cell lymphoma cells, melanoma cell lines and osteosarcoma cell lines were treated with verdinexor (KPT-335) and assessed for effects on proliferation, cell survival, and XPO1 expression.

Pharmacokinetics: Full PK was performed in healthy dogs to assess verdinexor oral bioavailability and determine the effects of feeding on drug absorption.

Phase 1 study: Dogs (n=17) with NHL, MCT, and metastatic OSA were treated with verdinexor in a planned 3 x 3 dose escalation starting at 1 mg/kg M/Th. An additional 6 dogs with NHL were entered into a dose expansion arm (1.5 mg/kg MWF). Dogs were evaluated weekly with physical exam, bloodwork (CBC, chemistry panel, coagulation panel) and response/toxicity assessment.

Phase 2 study: Dogs with naive or relapsed B or T NHL received verdinexor at 1.5 mg/kg or 1.25 mg/kg given M/Th or MWF. Evaluations were performed weekly for the first 4 weeks then every 2 weeks thereafter.

Conclusions
KPT-335 is a novel, orally bioavailable SINE compound which exhibits a unique mechanism of action and demonstrates significant preclinical and phase I/II clinical activity in NHL and other canine cancers. Further clinical trials and studies are ongoing to determine the role of KPT-335 in improving outcomes for dogs with NHL and other cancers.