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

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Abstract

Introduction: SINEs are Selective Inhibitors of Nuclear Export that block the activity of CRM1/XPO1, the major nuclear export protein in cells, and thereby retention of key tumor suppressor and growth regulatory proteins ultimately resulting in tumor cell death. The purpose of these studies was to evaluate the in vitro activity of SINE against canine tumor cell lines and to investigate the biologic activity of the SINE compound verdinexor (KPT-335) in dogs with spontaneous cancer as proof of principle for human clinical studies.

Results: Several different canine tumor cell lines including those derived from non-Hodgkin lymphoma (NHL) exhibited growth inhibition and apoptosis in response to SINE treatment; NHL cells were particularly sensitive with IC50 concentrations ranging from 2-42 nM. A Phase 1 clinical trial of verdinexor was performed in 17 dogs with NHL (naïve or relapsed), mast cell tumor or osteosarcoma. The maximum tolerated dose was 1.75 mg/kg given orally twice weekly (Monday/Thursday) although biologic activity was observed at 1 mg/kg. Clinical benefit including partial response to therapy (PR, n=2) and stable disease (SD, n=7) was observed in 8/14 dogs with NHL with a median time to progression (TTP) for responders of 66 days (range 35-256). A dose expansion study was performed in 6 dogs with NHL given 1.5 mg/kg verdinexor Monday/Wednesday/Friday; CB was observed in 4/6 dogs with a median TTP for responders of 83 days (range 35-354). Toxicities were primarily gastrointestinal and were manageable with supportive care, dose modulation and administration of low dose prednisone. A validated health related Quality of Life (QOL) form used to assess dogs during treatment demonstrated that the overall QOL did not decrease in dogs during treatment supporting the notion that clinical toxicities associated with verdinexor are generally well tolerated. A subsequent Phase 2 study was performed in 58 dogs with either newly diagnosed or relapsed NHL. Verdinexor was administered initially at 1.5 mg/kg MWF, but this was changed to 1.25 mg/kg M-Th secondary to anorexia and weight loss; dose escalation was permitted to 1.5 mg/kg on the M-Th regimen. The objective response rate was 34% (1 CR, 19 PR) and 20 dogs (34%) stayed on study drug for 8 weeks or longer with PR or SD. Dogs with T cell lymphoma, a form of disease considered to be biologically aggressive and challenging to treat with cytotoxic chemotherapy had particularly good objective responses to therapy (71% in naïve disease, 57% in relapsed disease). As with the Phase 1 study, the QOL did not change significantly over the study duration in all dogs enrolled indicating good quality of life across both short term and long term use.

Conclusions: These data demonstrate that the novel orally bioavailable XPO1 inhibitor verdinexor exhibits single agent biologic activity in a relevant spontaneous large animal model of NHL. The clinical trials in dogs with verdinexor supported subsequent evaluation of the closely related selinexor (KPT-330) in people yielding similar findings with respect to biologic activity and adverse events.

Materials and Methods

In vitro assays: NHL cell lines, canine diffuse large B cell lymphoma cell lines and osteosarcoma cell lines were treated with verdinexor (KPT-335) and assessed for effects on proliferation, cell survival, and CRM1 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 study to 1 mg/kg MWF. 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 naïve or relapsed B or T NHL received verdinexor at 1.5 mg/kg or 1.25 mg/kg given MTh or MWF. Evaluations were performed weekly for the first 4 weeks then every 2 weeks thereafter.

A single dose of 1.5 mg/kg verdinexor was administered to healthy beagle dogs 30 minutes after a meal. Plasma samples were taken over 24 hrs to assess drug levels.

Materials and Methods

Biologic Activity of SINE Compounds Against Canine Lymphoma Cells

Figure 1. Response of canine tumor cell lines to SINE

(A) Jural cells and primary canine DLBCL cells (sample #1-5) were cultured 72 hours with log serial dilutions of KPT-185 and the cell viability was analyzed (B) Human and canine DLBCL cells were cultured for 72 hours with serial dilutions of KPT-335 and cell viability was assessed by (CD) BCL cells and primary canine DLBCL cells (sample #1) were treated with verdinexor (KPT-335) for 24 hours and analyzed by flow cytometry for cell cycle and cell proliferation (F) Expression of XPO1 in human and canine DLBCL cell lines was assessed by SDS-PAGE and immunoblotting. (G) rbXPO1 was the control.

Conclusions

These data indicate that a proportion of dogs with both B and T NHL, either naïve or relapsed, benefit from verdinexor treatment as evidenced by both objective response to therapy and prolonged disease stabilization; dogs with T cell disease, typically refractory to therapy, seem to experience significant benefit.

Verdinexor exhibits an excellent safety profile on long-term dosing with primarily grade 1 and 2 gastrointestinal toxicities that are readily manageable with concomitant medications and no negative impact on quality of life during therapy.

Selinexor (KPT-330 – a structurally analogous compound to verdinexor, KPT-335) is currently in human clinical trials and has demonstrated similar activity and tolerability in hematopoietic neoplasia further validating XPO1 as a relevant target for therapeutic intervention across multiple species.