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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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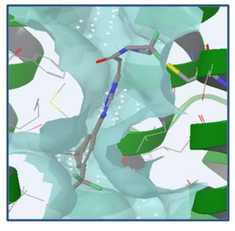
Abstract

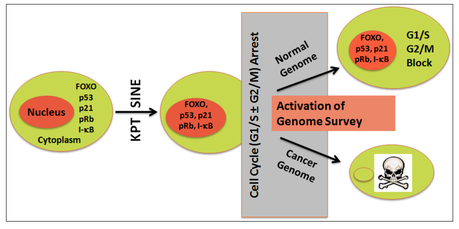
Introduction: SINE are Selective Inhibitors of Nuclear Export that block the activity of CRM1/XPO1, the major nuclear export protein in cells, forcing nuclear retention of key tumor suppressor and growth regulatory proteins ultimately resulting in tumor cell death. The purpose of these studies was to evaluate the *in vitro* activity of SINE against canine tumor cell lines and 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 IC_{50} concentrations ranging from 2-42 nM. A Phase 1 clinical trial of verdinexor was performed in 17 dogs with NHL (naive or relapsed), mast cell tumor or osteosarcoma. The maximum tolerated dose was 1.75 mg/kg given orally twice/week (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 9/14 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 tolerability 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 human 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.

Introduction





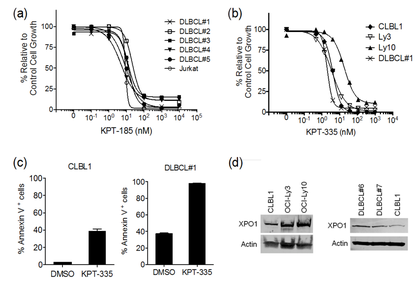
- Karyopharm has developed SINE compounds: orally bioavailable selective inhibitors of the nuclear export complex component CRM1.
- SINE force nuclear retention of key TSP/GRP resulting in death of tumor cells; most normal cells undergo cell cycle arrest and recovery following export block release.

Materials and Methods

- 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 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 starting at 1 mg/kg M/Th. An additional 6 dogs with NHL were entered into a dose expansion arm (1.5 mg/kg M/W/F) 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 M/Th or MWF. Evaluations were performed weekly for the first 4 weeks then every 2 weeks thereafter.

Results

Biologic Activity of SINE Compounds Against Canine Lymphoma Cells



IC_{50} (± S.D.) of SINE for human and canine lymphoma cells

	KPT-335	KPT-185	KPT-185 trans
Jurkat	0.3	8.7 ± 0.7	>1000
OCI-Ly3	2.1 ± 1.3	24.1	NP
OCI-Ly10	41.8 ± 21.0	246.2	NP
CLBL1	8.5 ± 4.1	NP	NP
Canine DLBCLs	-	13.3 ± 6.2	-
DLBCL#1	2.0	13.1	NP
DLBCL#2	NP	9.0	NP
DLBCL#3	NP	12.2	NP
DLBCL#4	NP	4.9	NP
DLBCL#5	NP	21.6	>1000

IC_{50}, 50% inhibitory concentration; DLBCL, diffuse large B-cell lymphoma; NP, not performed

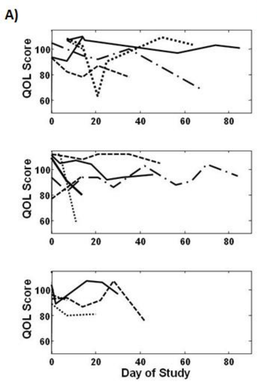
Figure 1. Response of canine tumor cell lines to SINE
(A) Jurkat cells and primary canine DLBCL cells (sample #1-5) were cultured 72 hours with log serial dilutions of KPT-185 and the cell viability was analyzed **(B)** Human and canine DLBCL cells were cultured for 72 hours with serial dilutions of KPT-335 and cell viability was assessed. **(C)** CLBL1 cells and primary canine DLBCL cells (sample #1) were treated with verdinexor (KPT-335) for 24 hours and analyzed for apoptosis by flow cytometry. **(D)** Expression of XPO1 in human and canine DLBCL cell lines was assessed by SDS-PAGE and immunoblotting; β-actin was the control.

Pharmacokinetics of Verdinexor in Healthy Dogs

Parameter	KPT-335 at1.5 mg/kg
Dose (mg/kg)	
Mean	1.46
SD	0.0542
SEM	0.0221
C_{max} (ng/mL)	
Mean	253
SD	88.3
SEM	36.1
T_{max} (hr)	
Mean	3.83
SD	2.71
SEM	1.11
$t_{1/2}$ (hr)	
Mean	3.88
SD	1.47
SEM	0.602
$AUC_{0-\infty}$ (h*ng/mL)	
Mean	1810
SD	216
SEM	88.2
$AUC_{0\text{-last}}$ (h*ng/mL)	
Mean	1760
SD	223
SEM	90.9

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.

Trends in Quality of Life in Dogs Treated with Verdinexor



	Average Change in QOL Score/Week	p-value
All Dogs	-0.55	0.13
On Study ≥28 d	-0.06	0.66
On Study ≥56 d	0.08	0.52

	One-Way ANOVA	Wilcoxin-Mann-Whitney
Group 1 vs. Group 2	0.79	0.66
Group 1 vs. Group 3	0.89	0.88
Group 2 vs. Group 3	0.67	0.55

Figure 2. Trends in quality of life (QOL)
An overall score was created based on answers to questions on the QOL questionnaire. These are represented graphically where each line represents a patient (**A** and **B**). Using linear mixed models, the overall QOL did not change significantly in dogs treated in either the **(A)** dose escalation portion (p=0.64) or **(B)** dose expansion portion(p=0.47) of the Phase 1 study. **(C)** In the Phase 2 study, the QOL did not change significantly in all dogs enrolled, dogs that remained on study for at least 28 days, or dogs that remained on study for at least 56 days. There was also no difference in QOL among dosing groups (Group 1: 1.5 mg/kg 3 times/week; Group 2: 1.25 m/kg 3 times/week; Group 3: 1.25 mg/kg 2 times/week).

Biologic Activity of Verdinexor in Canine NHL

Summary of Phase 1 and 2 trials

	N	SD >14 days	PR/CR	Clinical Benefit	Duration of Benefit
Phase 1					
Dose Escalation	14	7 (50%)	2 (14%)	9 (64%)	66 days (35-256)
Dose Expansion	6	2 (33%)	2 (33%)	4 (67%)	83 days (35-354)
Phase 2					
All	58	44 (76%)	20 (34%)	32 (55%)	71 days (21-273)
Naive B	28	25 (89%)	8 (29%)	16 (57%)	71 days (28-195)
Relapse B	14	8 (57%)	4 (29%)	6 (43%)	70 days (23-214)
Naive T	7	6 (86%)	4 (57%)	5 (71%)	42 days (21-273)
Relapse T	7	5 (71%)	4 (57%)	5 (71 %)	72 days (30-194)

SD > 14 days does not include dogs with SD at D14 if there was no evaluation time point after D14
Clinical benefit (CB) includes dogs with SD through D28 (with no PD events prior to D28) and PR/CR at any time during the study
Duration of benefit = time on study for all dogs with SD > 14 days or PR/CR

Summary of OR, DOR, TTP, and study duration for dogs on Phase 2 study for at least 8 weeks

Dog	Phenotype	Naive or Relapse	OR	Duration of CR/PR (days)	Time to Tumor Progression (days)	Study Duration (days)
01-01	B-cell	Naive	PR	14	70	126
01-03	B-cell	Naive			114	121
01-05	B-cell	Naive			73	80
01-06	B-cell	Naive	PR	14	70	195
01-07	T-cell	Relapse	PR	49	72	72
01-12	B-cell	Naive			71	85
01-13	B-cell	Relapse			112	112
01-14	T-cell	Relapse			56	56
02-01	B-cell	Naive	PR	21	105	105
02-05	T-cell	Relapse	CR	152	194	194
03-01	B-cell	Naive			21	67
03-04	B-cell	Naive	PR	36	71	71
04-01	B-cell	Relapse	PR	13	20	56
06-02	T-cell	Naïve	PR	36	62	119
06-03	T-cell	Naïve	PR	126	244	273
07-05	T-cell	Relapse	PR	21	42	103
08-01	B-cell	Naïve	PR	43	71	71
08-05	B-cell	Naïve	PR	98	182	182
08-06	B-cell	Relapse			84	84
08-07	B-cell	Relapse	PR	45	112	214

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 over long-term dosing with primarily grade 1 and 2 gastrointestinal toxicities that are readily managed 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.