Anti-Tumor Activity of Selinexor (KPT-330), A First-In-Class Oral Selective Inhibitor of Nuclear Export (SINE) XPO1/CRM1 Antagonist in Patients (pts) with Relapsed / Refractory Multiple Myeloma (MM) or Waldenstrom's Macroglobulinemia (WM)

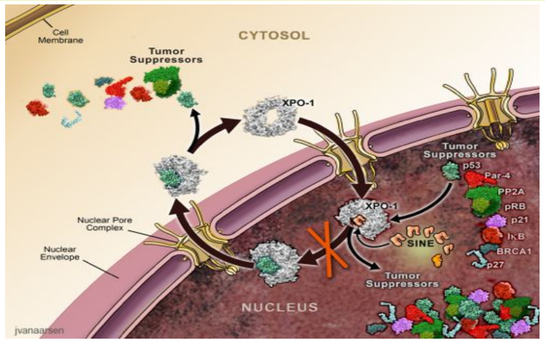
Christine Chen, MD[1], Martin Gutierrez, MD[2], Peter de Nully Brown[3], Nashat Gabrail, MD[4], Rachid Baz, MD[5], Donna E. Reece, MD[1], Michael Savona, MD[6], Suzanne Trudel, MD, MSC, FRCPC[1], David S. Siegel, MD, PhD[2], Morten Mau-Sorensen, MD[3], John Kuruvilla, MD, FRCPC[1], John C. Byrd, MD[7], Sharon Shacham, PhD, MBA[8], Tami Rashal, MD[8], Cindy YF Yau, MSc, CCRP[9], Dilara McCauley, PhD[8], Jean-Richard Saint-Martin[8], John McCartney, PhD[8], Yosef Landesman, PhD[8], Boris Klebanov[8], Greg Pond, PhD[9], Amit M. Oza, MBBS, MD[9], Michael Kauffman, MD, PhD[8], and Mansoor R Mirza, MD[3]

[1]Princess Margaret Cancer Centre, Toronto, Canada; [2]John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [3]Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark; [4]Gabrail Cancer Center, Canton, OH; [5]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [6]Sarah Cannon Research Institute, Nashville, TN; [7]The Ohio State University, Columbus, OH; [8]Karyopharm Therapeutics Inc., Natick, MA; [9]Ozmosis Research Inc, Toronto, ON, Canada;

ABSTRACT

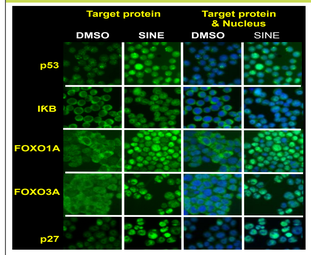
Background: Exportin 1 (XPO1/CRM1) is overexpressed in MM and was identified as an essential protein for MM cell growth. The majority of Tumor Suppressor Proteins (TSP) are transported out of the nucleus exclusively by XPO1, leading to their inactivation. Selinexor (KPT-330) is a potent, selective oral inhibitor of XPO1 and shows potent anti myeloma activity in preclinical models.
Methods: Patients (pts) with advanced, relapsed/refractory MM or WM were dosed with oral KPT-330 (8-10 doses / 4-week cycle) as part of a broad Phase 1 program (NCT 01607892) in advanced hematological malignancies. Standard dose limiting toxicity (DLT) definition was used. Detailed pharmacokinetic (PK) and pharmacodynamic (PDn) analyses and tumor biopsies on selected patients were performed. Response evaluation was performed every cycle. All pts in this study had documented progressive disease on study entry and were relapsed/refractory to at least one proteasome inhibitor and one immunomodulating agent.
Results: 26 MM and 3 WM pts were enrolled in 8 sites in the US, Canada, and Denmark. Median age 65 years (range 50-75); ECOG PS 0/1/2: 7/21/1; median number of prior regimens: 5.4 (range 1-13). Patients received KPT-330 across 7 dose levels (3 to 45 mg/m^2). Ten patients experienced drug-related grade 3/4 Adverse Events (AEs), including thrombocytopenia without bleeding (n=6), neutropenia (n=4), dehydration (n=1), hyponatremia (n=1). The most common grade 1/2 toxicities were gastrointestinal (GI) including nausea (22/29; 76%), anorexia (14/29; 48%), vomiting (9/29; 31%), diarrhea (7/29; 24%), weight loss (4/29; 14%), and dysgeusia (4/29; 14%). Grade 1/2 drug related fatigue was also observed in 16/29 or 55% of the patients. No grade ≥3 GI related AEs were observed. These side effects were well managed with supportive care. No clinically significant cumulative drug toxicities have been noted and patients have remained on therapy for > 8 months (median duration on therapy 89 days, range 8-393 days). Three pts died during the study, one due to *E.coli* sepsis, one due to renal dysfunction, and one to pneumonia, all events were deemed unrelated to study drug. PK analysis demonstrated total exposure increased with increasing dose, with no accumulation and without affecting half-life (5-7 hrs) or clearance of KPT-330. At 23 mg/m^2, exposure (C_{max} 289 ng/mL and $AUC_{0\text{-}inf}$ 2219 ng*h/mL) was comparable to anti tumor exposure observed in mice and dogs. Significant increases (2-5x) in leukocyte XPO1 mRNA levels (PDn marker) were observed at all doses, with higher doses demonstrating higher levels of XPO1 mRNA. Response was evaluable in 25 MM pts: Partial Response (PR) in 1 pt (4%), Minor Response (MR) in 4 pts (16%), Stable Disease (SD) in 15 pts (60%) and Progressive Disease (PD) in 4 pts (16%). Response was evaluable in 3 WM pts: all 3 pts (100%) achieved a Minor Response (MR). Evaluation of serial bone marrow samples from two patients confirms KPT-330-induced nuclear localization of multiple TSP as well as reduction in CD138+ MM cells. Dose escalation is ongoing at 45 mg/m^2 twice weekly.
Conclusions: Oral KPT-330 treatment is generally well tolerated, with favorable PK and PDn properties. Prolonged disease control and responses are observed in heavily pretreated patients with progressive MM whose disease is relapsed or refractory to available agents.

Mechanism of Action



- XPO1 (CRM1) is overexpressed in MM and is a vulnerable target in MM (Schmidt 2013, Tai 2013).
- XPO1 is the sole nuclear exporter of the majority of tumor suppressor proteins (TSP).
- XPO1 inhibition results in nuclear retention and reactivation of TSP leading to selective induction of apoptosis of MM cells while sparing normal B cells.
- KPT-330 is a novel, potent, oral Selective Inhibitor of Nuclear Export (SINE) currently being evaluated in Ph1 studies in relapsed/refractory solid and hematological malignancies.
- KPT-330 and other SINE compounds show potent anti-cancer activity in animal models of MM including reduced monoclonal spikes in the Vκ*MYC transgenic MM mouse, inhibited tumor growth in MM xenograft mice and increased survival of SCID mice with diffuse human MM bone lesions (Schmidt 2013, Tai 2013).
- SINE treatment also impaired osteoclastogenesis and bone resorption via blockade of RANKL-induced NFκB activation, without impacting osteoblasts and normal bone marrow stromal cells (Tai 2013).

SINE Induced Nuclear Localization in MM Cells *(In-Vitro)*



XPO1 inhibition with KPT-330 forces nuclear retention of its cargos, including the majority of Tumor Suppressor Proteins (TSP), Cell Cycle Regulators, and IκB (the inhibitor of NF-κB).

Nuclear retention leads to reactivation of these regulatory proteins leading to cell cycle arrest, NF-κB inhibition, and apoptosis induction in cells with damaged DNA (i.e., MM cells).

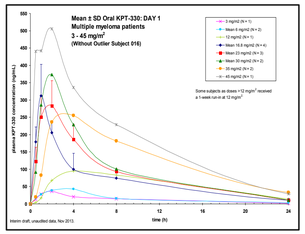
Ph1 Study of KPT-330 in Hematological Malignancies (NCT01607892)

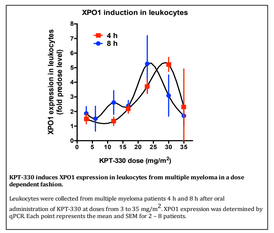
Patient Demographics

Characteristic N=29	
Median Age (Range)	65 (50 -75)
Male to Female	15 Males : 14 Females
Median Prior Treatment (Range)	5.4 (1-13)
Previously Treated with Carfilzomib or Pomalidomide	6 Patients : 11 Patients
ECOG PS 0:1:2	7 : 21 : 1
Free Light Chain Disease (Patients)	6

Dose	Number of MM/WM Subjects
3 mg/m^2	1
6 mg/m^2	2
12 mg/m^2	2
16.8 mg/m^2	5
23 mg/m^2	5
30 mg/m^2	2
35 mg/m^2	11
45 mg/m^2	1
Total	**29**

Pharmacokinetics and Pharmacodynamics





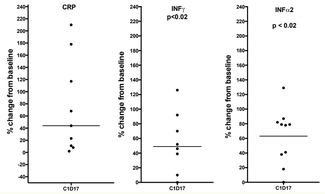
KPT-330 induces XPO1 expression in leukocytes from multiple myeloma in a dose dependent fashion.

Leukocytes were collected from multiple myeloma patients 4 h and 8 h after oral administration of KPT-330 at doses from 3 to 35 mg/m^2. XPO1 expression was determined by qPCR. Each point represents the mean and SEM for 2 – 8 patients.

KPT-330 Related Adverse Events Occurring in ≥ 2 Patients (N=29)

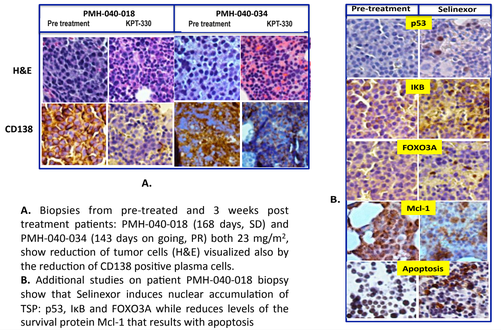
AE NAME	GRADE	KPT-330 Dose Levels (mg/m^2)								Total All N=29
		3	6	12	16.8	23	30	35	45	
Gastrointestinal, Constitutional, and Others		N=1	N=2	N=2	N=5	N=5	N=2	N=11	N=1	
Nausea	Grade 1	--	--	1 (50%)	2 (40%)	4 (80%)	--	1 (9%)	1 (100%)	31%
	Grade 2	1 (100%)	2 (100%)	1 (50%)	2 (40%)	--	1 (50%)	6 (54.5%)	--	45%
Anorexia	Grade 1	--	--	--	--	--	--	1 (9%)	--	3%
	Grade 2	--	2 (100%)	2 (100%)	2 (40%)	3 (60%)	1 (50%)	3 (27%)	--	45%
Fatigue	Grade 1	--	--	1 (50%)	1 (20%)	--	--	3 (27%)	--	17%
	Grade 2	--	2 (100%)	--	3 (60%)	1 (20%)	1 (50%)	3 (27%)	1 (100%)	38%
Vomiting	Grade 1	1 (100%)	1 (50%)	1 (50%)	1 (20%)	1 (20%)	1 (50%)	1 (9%)	--	24%
	Grade 2	--	--	--	1 (20%)	--	--	1 (9%)	--	7%
Diarrhea	Grade 1	1 (100%)	1 (50%)	--	2 (40%)	--	--	1 (9%)	--	17%
	Grade 2	--	--	--	1 (20%)	1 (20%)	--	--	--	7%
Weight Loss	Grade 1	1 (100%)	--	--	--	--	1 (50%)	1 (9%)	--	10%
	Grade 2	--	--	1 (50%)	--	--	--	--	--	3%
Taste Alteration	Grade 1	--	2 (100%)	--	1 (20%)	1 (20%)	--	--	--	14%
Dehydration	Grade 1	1 (100%)	--	1 (50%)	--	--	--	--	--	7%
	Grade 3	--	--	--	--	--	--	--	1 (100%)	3%
Dizziness	Grade 1	--	1 (50%)	--	1 (20%)	--	--	--	--	7%
Hyponatremia	Grade 2	--	--	--	--	1 (20%)	--	2 (18%)	--	10%
	Grade 3	--	--	--	--	--	1 (50%)	2 (18%)	--	10%
Blurred Vision	Grade 1	--	--	--	1 (20%)	--	--	--	--	3%
	Grade 2	--	--	--	--	1 (20%)	--	1 (9%)	--	7%
Hematological										
Thrombocytopenia	Grade 1	--	--	--	1 (20%)	--	--	--	--	3%
	Grade 3	--	--	--	1 (20%)	--	--	--	--	3%
	Grade 4	--	--	--	1 (20%)	1 (20%)	1 (50%)	2 (18%)	--	17%
Neutropenia	Grade 2	--	--	--	1 (20%)	1 (20%)	--	--	--	7%
	Grade 3	--	--	--	--	2 (40%)	--	--	--	7%
	Grade 4	--	--	--	1 (20%)	--	1 (50%)	--	--	7%
Anemia	Grade 1	--	--	--	1 (20%)	1 (20%)	--	--	--	7%
	Grade 2	--	--	--	1 (20%)	--	--	--	--	3%

KPT-330 Induced a Reduction In Circulating cytokine Levels (CRP, INFγ and INFα2)



Plasma samples from patients were analyzed by immunoassays to detect levels of C reactive Protein (CRP), Interferon γ (INFγ) and Interferon α2 (INFα2). Results indicate changes in cytokines levels of CRP, IFNγ and IFNα2 at Cycle 1 Day 17 versus plasma levels at baseline. Statistical analysis was performed using the Wilcoxon signed rank test

KPT-330 Reduction in CD138 Cells in BM Biopsy from MM Patients



A. Biopsies from pre-treated and 3 weeks post treatment patients: PMH-040-018 (168 days, SD) and PMH-040-034 (143 days on going, PR) both 23 mg/m^2, show reduction of tumor cells (H&E) visualized also by the reduction of CD138 positive plasma cells.
B. Additional studies on patient PMH-040-018 biopsy show that Selinexor induces nuclear accumulation of TSP: p53, IκB and FOXO3A while reduces levels of the survival protein Mcl-1 that results with apoptosis

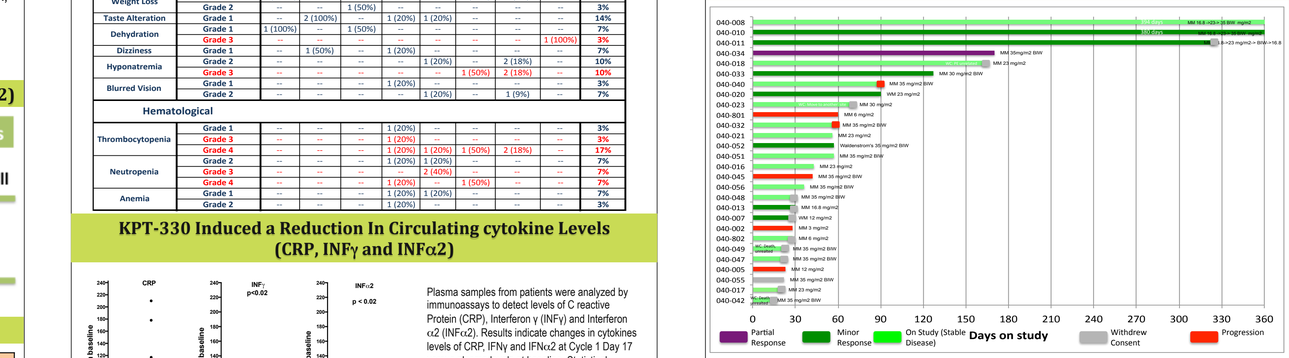
KPT-330 Activity in Rel/Ref MM/WM Patients

Responses in Arm 1 Multiple Myeloma and Waldenstrom's Macroglobulinemia Patients as of 4-Dec-2013

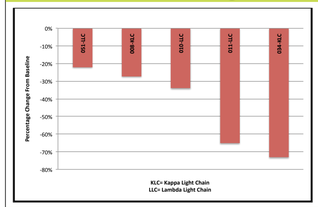
Cancer	Number of Pts Evaluated	Total PRs, MRs, and SD (%)	PR (%)	MR (%)	SD (%)	PD	WC
MM (All Doses)	25	20 (80%)	1 (4%)	4 (16%)	15 (60%)	4 (16%)	1 (4%)
MM (≥16.8mg/m^2)	21	19 (90%)	1 (5%)	4 (19%)	14 (66%)	1 (5%)	1 (5%)
WM	3	3 (100%)	--	3 (100%)	--	--	--

PR=Partial Response, MR=Minor Response, SD=Stable Disease, PD=Progressive Disease, WC=Withdrew Consent

Progression Free Survival of Rel/Ref MM/WM Patients on KPT-330



KPT-330 Appears to Show Potent Anti Myeloma Activity in Heavily Pretreated Light Chain Disease MM Patients



Patients (N=6, Evaluable N=5) with heavily pretreated, progressive Free Light Chain (FLC) MM disease were enrolled into the study as of November 1, 2013. FLC levels were reduced in all evaluable FLC patients enrolled to date. Patients -008 (Stable Disease) and -010 (Minor Response) with kappa and lambda FLC disease, respectively, have remained on study for >12 months with no significant cumulative toxicities. Patients -051 (Minor Response) and -034 (Partial Response) also remain on study as of December 4, 2013.

Conclusions

- XPO1 (CRM1) is overexpressed in MM and correlates with disease progression.
- XPO1 inhibition with KPT-330 results in nuclear retention and reactivation of TSP leading to selective induction of apoptosis of MM cells while sparing normal B cells.
- KPT-330 is given orally 2-3 times per week appears to be associated with low rates of Grade 3/4 events, along with significant but manageable Grade 1/2 gastrointestinal toxicities (anorexia, nausea).
- KPT-330 shows dose-dependent PK and PDn increases in relapsed/refractory myeloma.
- KPT-330 induces nuclear localization of TSP and reduction in Mcl-1 levels in MM patient biopsies.
- KPT-330 induces dose-dependent, durable disease stabilization and responses in MM patients whose disease has progressed on all other classes of anti-MM agents, including patients with FLC disease.
- These results show that single agent oral KPT-330 may have prolonged anti-MM activity in patients with heavily pretreated disease and rapid progression on study entry.

Contact Information: Dr. Christine I. Chen e-mail: Christine.Chen@uhn.ca