Safety and Anti-tumor Activity of Selinexor (KPT-330), a First-in-Class, Oral XPO1 Selective Inhibitor of Nuclear Export (SINE) - A Phase I Study Expanded with Colon Cancer Cohort

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ABSTRACT

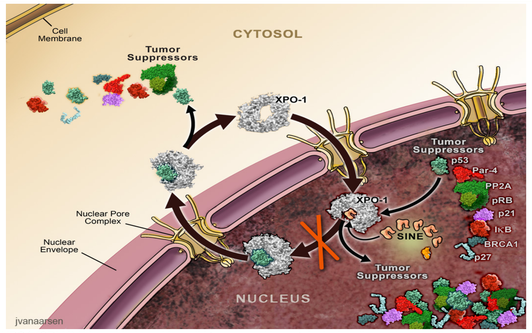
Background: Tumor suppressor proteins (TSP) are inactivated by their export from the nucleus by Exportin 1 (XPO1/CRM1). The oral selective inhibitor of nuclear export Selinexor (KPT-330) restores the nuclear localization and function of TSP and shows a broad anti-tumor activity in animal models. Here we report on the treatment of a subset of patients (pts) with metastatic colorectal cancer (CRC) in a phase I trial of KPT-330

Methods: Objectives were to determine the recommended phase 2 dose, evaluate safety, pharmacokinetics (PK), pharmacodynamics (PDn), and tumor response (RECIST 1.1) of KPT-330 administered in two different schedules with 8 or 10 doses in a 28-day cycle. An expansion cohort of 15 pts with CRC was planned.

Results: Thirty-five pts with CRC were treated with KPT-330 across nine doses (3-40 mg/m^2) including 15 pts in the expansion cohort (30-35 mg/m^2). Median age was 59 yrs and median number of prior regimens was 3. The maximum tolerated dose (MTD) of the 10-dose per cycle schedule was 30 mg/m^2. MTD for the 8-dose per cycle schedule has not been reached. Nineteen pts experienced drug related grade 3-4 adverse events (AEs) including hyponatremia (n=9), fatigue (n=8), thrombocytopenia (n=4), anemia (n=4) anorexia (n=3), dehydration (n=2), hyperglycemia (n=1), nausea (n=1), and cataract (n=1). The most common grade 1-2 drug related AEs were nausea (71%), anorexia (51%), fatigue (49%), vomiting (57%), taste alteration (49%), weight loss (46%) and blurred vision (20%) with no objective findings except for worsening of pre-existing cataracts in 1 patient. KPT-330 plasma concentrations C_{max} was dose proportional and half life was between 4.0 – 7.2 hrs. Significant increases (2-20x) in PDn marker XPO1 mRNA in circulating leukocytes were observed at all doses. Analysis of tumor biopsies confirmed nuclear localization of TSP and induction of apoptosis following KPT-330. Carcinoembryonic Antigen (CEA) levels decreased in 5 of 17 tested pts. One pt had a partial response (PR) at 23 mg/m^2, 10 patients had stable disease (SD) ≥8 weeks including 4 patients with stable disease ≥25 weeks in 35 evaluable pts.

Conclusions: Preliminary signals of antitumor activity in CRC pts were observed. KPT-330 is generally well tolerated and prolonged drug exposure is feasible. KPT-330 induces Exportin in leucocytes and apoptosis in tumor biopsies with restoration of the nuclear location of TSP.

Mechanism of Action



- XPO1 (CRM1) is overexpressed in solid tumors and hematological malignancies and its levels are often correlate with poor outcomes.
- XPO1 is the sole nuclear exporter of major tumor suppressor proteins (TSP). XPO1 inhibition results in nuclear restoration and reactivation of TSP leading to selective induction of apoptosis of colon cancer cells.
- KPT-330 is a novel, potent, oral Selective Inhibitor of Nuclear Export (SINE) currently being evaluated in Ph1 studies in solid and hematological malignancies.
- SINE showed potent anti cancer activity in animal models of colon cancer.
- SINE treatment blocks Topoisomerase I (TOPO1) nuclear export and sensitizes colon cancer to TOPO1 inhibitors.

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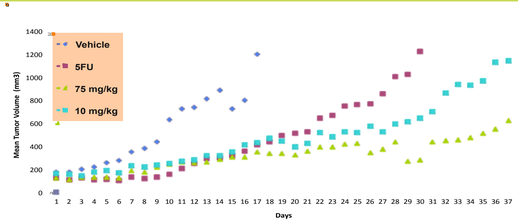
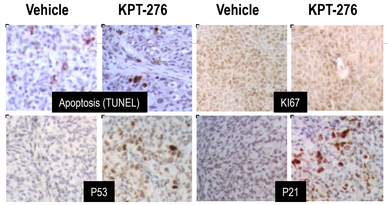
SINE Induced Nuclear Localization in CRC Cells



KPT-276, a SINE with moderate oral bioavailability, inhibits growth of HCT-116 colon cancer (p53^{wt}, K-ras G13D) xenograft with marked (>2X) survival advantage. HCT-116 cells were injected on both flanks of mice. When tumor reached ~175mm^3, KPT-276 was given by either subcutaneously (SC) 10mg/kg or 75mg/kg QDx5 each week (Day 1 in the above graph). 5-FU was used a control.



KPT-276 treated HCT-116 xenografts show increased TUNEL$^+$ cells indicative of DNA breakage seen in apoptotic cells, low levels of Ki67 and marked upregulation of p53 and p21 *in situ* indicating that KPT-276 induces nuclear localization and elevates levels of these proteins.

Phase 1 Study of KPT-330 in Solid Tumors

Dose Escalation: Relapsed Solid Tumors

All Comers (including 22 with CRC) CRC Dose Expansion Patients (N=15)

Dose Escalation: Colorectal Cancer (N=13)

Other: Sq H&N,Cervical, NSCLC (N=12), Prostate (N=6), Ovarian (N=7), GBM (N=6)

Clinicaltrials.gov: NCT01607905

KPT-330 Patient Demographics

Characteristic N=35	
Median Age (Range)	59 (40 -77)
Male to Female	20 Males : 15 Females
Median Prior Regimens* (Range)	3 (2-8)
Previously Treated with Regorafenib	10 Patients
ECOG PS 0:1	8 : 27

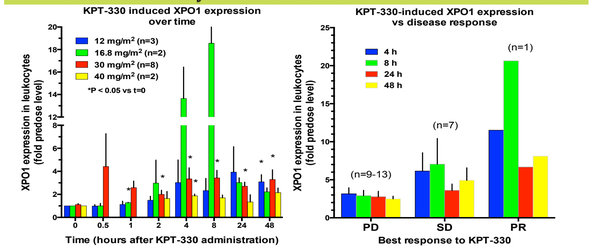
KPT-330 Pharmacokinetics

Dose (mg/m^2)	N	C_{max} (ng/mL)	T_{max} (h)	AUC_{t-t} (ng*h/mL)	AUC_{inf} (ng*h/mL)	$t_{½}$ (h)
3	1	29.5	1.0	325	346	6.0
12	5	168	2.0	1,649	1,709	5.7
20	3	289	2.0	2,392	2,423	6.0
23	1	345	2.0	2,876	2,885	5.7
28	1	503	1.0	3,854	3,865	5.7
30	11	410	2.0	4,158	4,191	7.2
35	1	481	4.0	4,237	4,315	4.0
40	3	633	4.0	6,775	6,803	6.2

KPT-330 Pharmacokinetics Profile:

- Oral absorption was rapid, with median T_{max} ranging from 1.0 - 4.0 h and independent of dose.
- Plasma KPT-330 exposure was dose-proportional with consistent dose proportionality in C_{max} and AUC observed between doses of 12 – 40 mg/m^2.
- The half life was short, with mean $T_{½}$ values ranging from 4.0 – 7.2 h, independent of dose.

KPT-330 Pharmacodynamics & Pharmacokinetics in CRC Patients



KPT-330 induced XPO1 mRNA expression in leukocytes is sustained over 48 hours after a single dose and the magnitude of XPO1 induction trends higher in responsive patients.

Quantitative PCR was used to measure XPO1 mRNA expression in leukocytes from CRC patients collected over a 48 h time course following administration of KPT-330.

A) XPO1 mRNA expression in leukocytes as a function of dose and time. Bars represent mean and std error.

B) XPO1 mRNA expression in leukocytes as a function of time after the first dose of 3 – 40 mg/m^2 KPT-330 vs tumor response. Bars represent mean and std error.

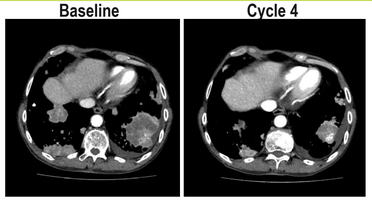
KPT-330 Related Adverse Events Occurring at least Once in ≥2 Patients (N=35)

KPT-330 Activity in CRC Patients

Responses in Colorectal Patients as of 15-Jan-2014

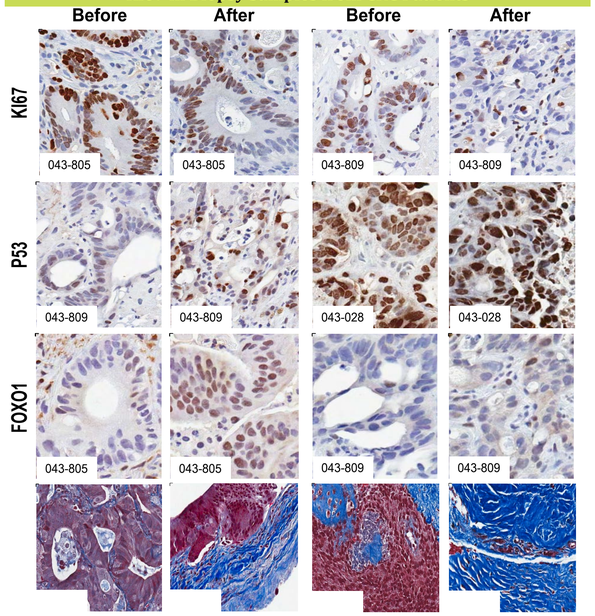
Number of Pts Evaluated	Total PRs & SD (%)	PR (%)	SD (%)	PD	WC
35	12 (34%)	1 (3%)	11* (31%)	21 (60%)	2 (6%)

Patient 043-805 Case Report



Patient Profile: 70 year old male with Kras mutant CRC with lung metastases. Prior therapies include:
1) Bevacizumab + Xeloda + Oxaliplatin (2008).
2) Avastin + 5-FU + Leukovorin + Irinotecan (2009).
3) Everolimus, Erbitux and irinotecan (2011).
4) Gemcitabine and Xeloda (2012).
5) KPT-330 dosing at 23 mg/m^2. PR in Cycle 4 and stayed on study for 227 days.

KPT-330 Induces Nuclear Localization, Apoptosis and Reduction in Ki67 in Biopsy Samples from CRC Patients



-Immunohistochemical staining for the proliferation marker Ki67 and the apoptosis marker P53 on patient biopsies before and after KPT-330 treatment (3-4 weeks). Entire sections were imaged using Aperio ScanScope AT Turbo at 20x magnification. Nuclear staining was quantified using Definiens™ software. Masson's trichrome immunohistochemical staining of patients core needle biopsies demonstrate a dose dependent increase is tumor surrounding stroma (blue staining) post KPT-330 treatment.

-Reduction in Ki67 were observed in patient's biopsies (043-805 PR 227 days on treatment and 043-809 SD 63 days on treatment), post treatment with KPT-330. Increased nuclear localization of p53 (043-809 and 043-028 SD 63 days on treatment) and FOXO1 (043-805 and 043-809) were observed. Interestingly, an increase in stoma levels were observed in the biopsies of patients 043-805 and 043-014 SD 183 days on treatment.

Conclusions

- KPT-330 (Selinexor) is a novel, potent, oral Selective Inhibitor of Nuclear Export (SINE) that blocks XPO1, and is currently being evaluated in Phase 1 studies in advanced malignancies.
- XPO1 is the sole nuclear exporter of major tumor suppressor proteins (TSP). XPO1 inhibition with KPT-330 results in nuclear restoration and reactivation of TSP leading to selective induction of apoptosis of cancer cells, while sparing normal cells.
- In patients with heavily pretreated colon cancer, who received all approved drug classes and have progressive disease on study entry, single agent KPT-330 can induce durable disease stabilization and tumor size reduction at tolerable doses.
- 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, fatigue)
- KPT-330 induces reduction in proliferation markers, nuclear localization of p53 and death of colon cancer cells in some patients on this phase 1 study.
- Further evaluation of KPT-330 for the treatment of colorectal cancer as a single agent and in combination is planned.