Pre-Clinical and Early Clinical Activity of the Oral Selective Inhibitor of Nuclear Export (SINE) Exportin 1 (XPO1) Antagonist Selinexor (KPT-330) in Patients (pts) with Platinum Resistant/Refractory Ovarian Cancer (OvCa)

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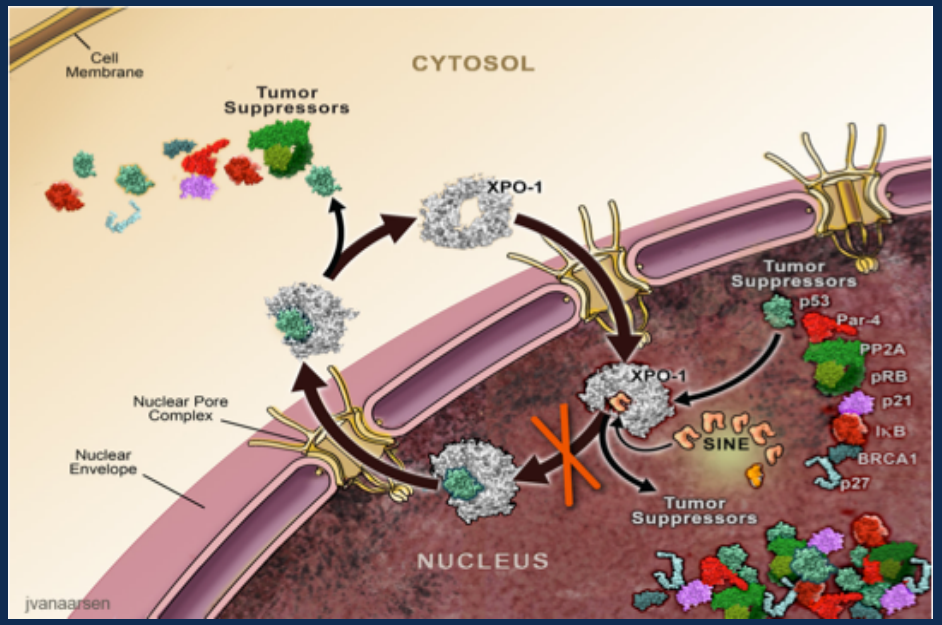

- XPO1 (CRM1) is overexpressed in solid tumors and hematological malignancies and its levels are often correlated with poor outcomes including in patients with ovarian carcinoma
- XPO1 is the sole nuclear exporter of most of the major tumor suppressor proteins (TSP)
- XPO1 inhibition by SINE results in nuclear restoration and reactivation of TSPs causing selective induction of apoptosis of malignant cells
- Selinexor is a novel, potent, oral SINE currently being evaluated in Ph1/2 studies in solid and hematological malignancies

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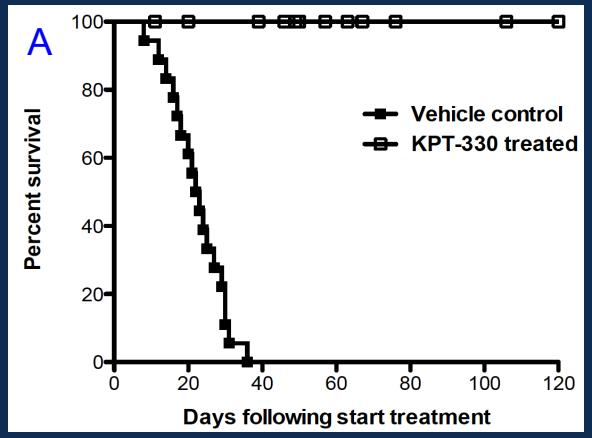
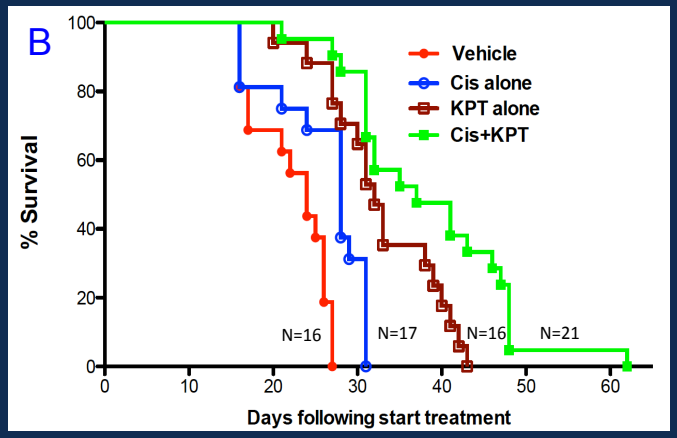
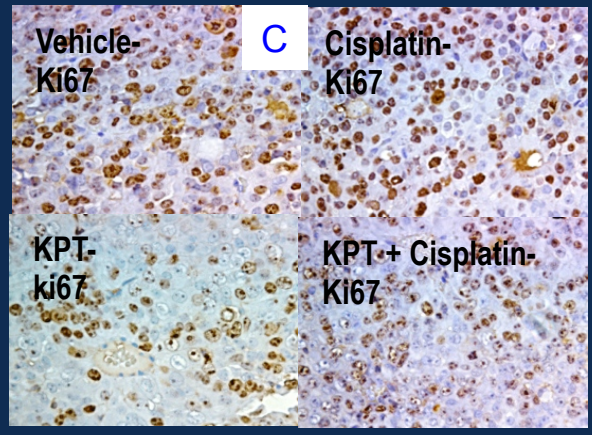
Selinexor Displays Potent Efficacy in Animal Models of Ovarian Cancer (OvCa)





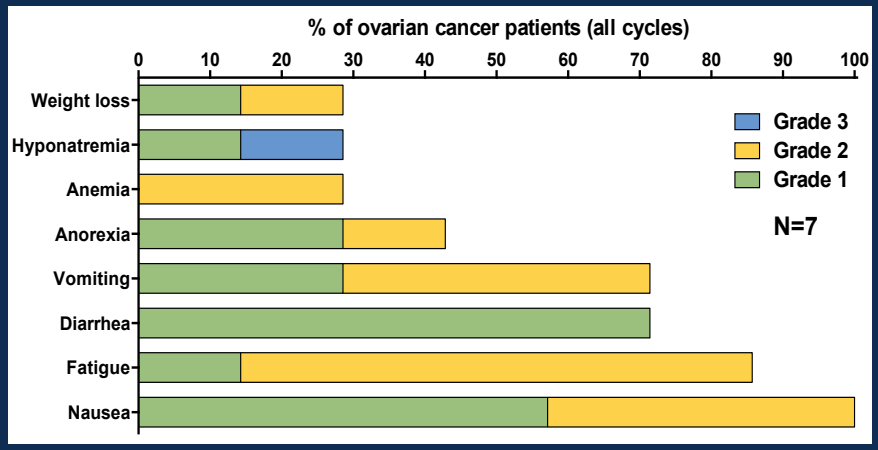


A. In a patient-derived OvCa mouse efficacy model, selinexor 10 mg/kg PO TIW improved survival when compared to controls (P<0.0001). No untreated mouse survived beyond 35 days while selinexor treated mice were all alive on Day 147.

B. In a Luciferase based mouse model of OvCa, single agent selinexor displayed better efficacy than cisplatin. In combination with cisplatin, selinexor nearly doubled OS when compared to cisplatin alone. (C) Histopathology on tumor samples indicated that treatment with selinexor and/or cisplatin reduced proliferation as indicated by lower Ki67. Selinexor also induced nuclear localization of TSPs and apoptosis (not shown).

Phase I Study of Selinexor in Solid Tumors and AEs in OvCa Patients

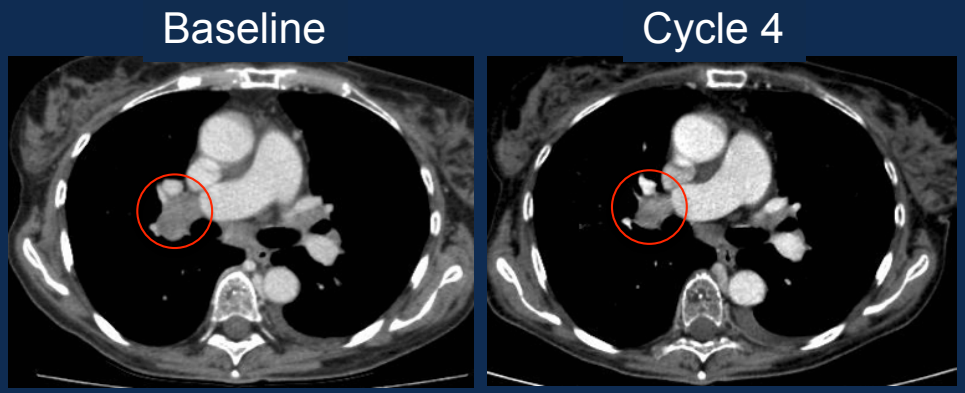
Characteristics of Patients with OvCa (N=7)	
Mean Age (Range)	55 (33-75)
Mean Prior Regimens (Range)	4.5 (2-9)
Previously Treated with Platinum	7/7
ECOG PS 0:1	3/4



- In a Phase I all-comers solid tumor trial (KCP-330-001, NCT01607905), Selinexor was administered to 2 OvCa patients at 30 mg/m^2 dose during dose escalation and to 5 additional patients at 35 mg/m^2 during dose expansion phases
- All OvCa patients had heavily pretreated platinum resistant/refractory disease
- Selinexor was associated primarily with Grade 1/2 toxicities, with most adverse events including nausea, vomiting, anorexia, fatigue and diarrhea
- Dose relationships were unclear, and supportive care generally diminished many of these toxicities allowing prolonged dosing
- Cumulative toxicities were rare, and no major organ dysfunction was noted

Clinical Activity and Patient 043-815 Case Report

Patient #	Prior Regimens	Best Response	Days on Study
043-815	Carbo/Taxol x2; IP Carbo x 2; Dox/Carbo; Veliparib; Paclitaxel	PR	156
043-046	Carbo/Taxotere; Doxil; Cis/Gemcitabine	SD	320+
043-047	Carbo/Taxol x3; Trebananib/Temsiro.;Ganitumab/MEK inh.	SD	115
043-024	Carbo/Taxol; Topotecan; Linsitinib/Taxol; Temsiro./Trebananib; PI3K inh./IGF mAb	PD	58
043-044	Carbo/Taxol; Carbo/Taxol/PI3K inh.	PD	23
043-031	Carbo/Taxotere/Cisplatin/Gemzar/N3699G; Carbo/Gem/Bevacizumab	NE/WC	9
043-023	Carbo/Taxol x2; Carbo/Gem/Bevaci.; Vintafolide/Dox; Paclitaxel/Cisplatin	NE/WC	22



Patient Profile: 60 year old female with OvCa diagnosed in February 2000. She was treated with **8** prior regimens including: **1)** Carbo/Taxol x 2; **2)** Intraperitoneal Carbo x2 with cyclophosphamide; **3)** Carbo/Docetaxel, Veliparib, Paclitaxel x2.
The patient remained on single agent oral selinexor for 156 days before developing probable clinical progression with small bowel obstruction. Her CA-125 decreased from 540 at baseline to 240 U/mL at Cycle 4

Conclusions on Selinexor in OvCa

- In two different mouse models of OvCa, selinexor displayed significant efficacy and prolonged survival, including additivity/synergy to cisplatin. Histopathological analyses on tumor samples indicated that selinexor treatment reduced proliferation, induced nuclear localization of TSPs, and increased apoptosis

- As part of an all-comers Phase I solid tumor study, patients with platinum resistant/refractory OvCa, selinexor given orally 2-3 times per week is associated with rare Grade 3 events, with manageable Grade 1/2 GI toxicities (anorexia, nausea, fatigue) reduced with supportive care

- In patients with platinum resistant/refractory OvCa, single agent oral selinexor induced durable disease stabilization and tumor size reduction at tolerable doses

- Further evaluation of selinexor for the treatment of ovarian cancer as a single agent (NCT02025985) is currently on-going and combination studies are planned