**PRECLINICAL 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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**Aim:** Increased XPO1 expression has been linked to progression of OvCa. Nearly all tumor suppressor proteins (TSPs) are transported out of the nucleus exclusively by XPO1 and thereby inactivated. The XPO1 inhibitor, Selinexor, forces the nuclear retention and activation of >10 TSPs resulting in OvCa cell death.

**Methods:** SINE induced TSP nuclear localization and induction of apoptosis were tested in OvCa cell lines and patient-derived cells. Combination with cisplatin was assessed in vitro & patient-derived xenograft models (30 mg/m\(^2\) po, 3 times/week). An on-going Phase 1 (KCP-330-002, NCT01607905) in pts with solid tumors, oral selinexor (8-10 doses/4-week cycle) was administered to pts with heavily pretreated OvCa that were progressing on study entry. Response was evaluated every 2 cycles (RECIST 1.1).

**Results:** SINE potently induced cell death in platinum-sensitive and -resistant OvCa cell lines (IC50s < 0.12 µM). Nuclear accumulation and activation of p53 & other TSP was shown. In all 25 patient-derived cell lines tested, SINE induced potent cytotoxicity and showed marked synergy with cisplatin. Synergy was also observed in an in vivo murine model, resulting in increased overall survival. Seven pts with OvCa resistant/refractory to platinum and other agents (median age 55 yrs; ECOG PS 0/1: 3/4; median prior therapies: 5) were treated with 30-35 mg/m\(^2\) oral selinexor. No grade 4 AEs were reported. The most common AEs (Grade 1/2/3) were fatigue (14%/71%/0%), nausea (57%/43%/0%), diarrhea (71%/0%/0%), & vomiting (29%/43%/0%); manageable with supportive care. PK analysis showed Cmax of 0.5-1 µM & AUC0-inf 2800-4000 ng*h/mL, which exceed levels in vitro and in animal models. RECIST response was evaluable in 5 pts: 1 PR (5 months), 2 SD (4 & 10+ months) and 2 PD.

**Conclusions:** Selinexor treatment provides synergistic activity with cisplatin in preclinical models. In pts, selinexor shows preliminary single agent antitumor activity against heavily pretreated platinum resistant/refractory OvCa. A single agent phase 2 study is ongoing (NCT02025985) & combination studies are planned.

**Disclosure:** All authors have declared no conflicts of interest.