**SINE treatment blocks Topoisomerase I (TOPO1) nuclear export and sensitizes colon cancer to TOPO1**

**Objectives**

- Determine the recommended phase 2 dose, evaluate safety, pharmacokinetics (PK), pharmacodynamics (PD), and tumor response (RECIST 1.1) of KPT-330
- Evaluate the safety, PK, PD, and antitumor activity of KPT-330 in patients with colorectal cancer

**Methods**

- A phase 1 study was conducted
- Patients included in the colorectal cancer cohort were previously treated with at least 2 regimens from the following: bevacizumab, cetuximab, irinotecan, fluoropyrimidines, oxaliplatin, and targeted agents
- Dose escalation was conducted with 7 patients per dose level
- The dosing of KPT-330 was 2-3 times per week

**KPT-330 Pharmacokinetics Profile**

- The plasma KPT-330 exposure was dose-proportional and half life was between 4.0 – 7.2 h, independent of dose
- Significant increases (2-20x) in PDn were observed, especially in patients with colorectal cancer

**KPT-330 Pharmacodynamics & Pharmacokinetics in CRC Patients**

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Plasma KPT-330 AUC 0/t (ng*h/mL)</th>
<th>Plasma KPT-330 Cmax (ng/mL)</th>
<th>Plasma KPT-330 t1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.0</td>
<td>3.1</td>
<td>18</td>
<td>6.0</td>
</tr>
<tr>
<td>3.0</td>
<td>2.1</td>
<td>12</td>
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</tr>
<tr>
<td>2.0</td>
<td>1.1</td>
<td>10</td>
<td>5.7</td>
</tr>
</tbody>
</table>

**Phase 1 Study of KPT-330 in Solid Tumors**

**SINE Induced Nuclear Localization in CRC Cells**

- A monoclonal antibody to CBP (SINE 600) was detected in colorectal cancer biopsies
- KPT-330 induced XPO1 mRNA expression in leukocytes is sustained over 48 hours after a single dose and the magnitude of the effect increases from 4.0 to 7.2 h

**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-induced Exportin 1 (XPO1) inhibition sensitizes CRC to TOPO1

**KPT-330**

- A SINE compound that binds and blocks TOPO1 nuclear export
- modulates TOPO1 nuclear export and sensitizes colon cancer to TOPO1

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**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 Expanding with Colorectal Cancer Cohort**

**Abstract**

Background: Tumor suppressor proteins (TSPs) are targeted by the nuclear localization and function of TSP and shows a broad tumor-limited activity in animal models. Here we report on the treatment of a subset of patients with metastatic colorectal cancer (CRC) in a Phase I trial of KPT-330.

Methods: Dose expansions were determined by the recommendation of the phase 2 dose evaluation, safety analysis, pharmacokinetics (PK), pharmacodynamics (PD), and tumor response (RECIST 1.1). KPT-330 administration was in two different schedules with 8 or 10 doses in 28 or 22 days. An escalation cohort of 15 pts with CRC was planned.

Results: Thirty-five pts with CRC were treated with KPT-330. A total of 31 pts were treated in the dose escalation cohort (4.0 ± 3.0 mg/m2, including 10 pts in the expansion cohort (20 ± 3.0 mg/m2). Median age was 59 yrs and median number of prior regimens was 3. The maximum tolerated dose (MTD) of the 3 dose per cycle schedules was 30 mg/m2, MTD for the 8-dose per cycle schedule has not been reached. Nephrotoxicity experienced drug-related renal events (grade = 4 events) in 3 pts on the 30 mg/m2 group. A total of 2 pts had grade 1 anemia, 1 pt had grade 4 anemia, 1 pt had grade 2 nystagmus, 1 pt had grade 3 hyperbilirubinemia, 1 pt had grade 3 anemia, 1 pt had grade 1 nystagmus.

The most common grade 3-4 adverse events (AEs) were lymphopenia (27%), thrombocytopenia (20%) and neutropenia (17%). Other grade 3 AEs were weight loss (46%) and blurred vision (20%) with no objective

MTD for the 8-dose per cycle schedule has not been reached. Nineteen pts experienced drug related AEs of grade 3 or 4: nausea (57%), vomiting (57%), taste alteration (49%), weight loss (46%) and blurred vision (20%) with no objective

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-induced Exportin 1 (XPO1) inhibition sensitizes CRC to TOPO1.