A First-in-Class, First-in-Human Phase I Trial of KPT-330 (Selinexor), a Selective Inhibitor of Nuclear Export (SINE) in Patients (pts) with Advanced Solid Tumors


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Selective Inhibitors of Nuclear Export (SINE)

- Cancer cells can inactivate their Tumor Suppressor Proteins (TSPs) via nuclear export
- XPO1 is elevated in solid tumors (e.g., melanoma, ovarian, cervical, pancreas, prostate cancers) and hematological malignancies
- Exportin 1 (XPO1, CRM1) is the only nuclear exporter of most TSPs
- Selinexor (KPT-330) is a covalent, oral selective inhibitor of nuclear export (SINE) XPO1
- Selinexor forces nuclear retention and activation of multiple TSPs
- Selinexor treatment reduces proto-oncogene proteins including MYC, BCL2/BCL6, MDM2, Cyclin D and elevates IκB, leading to inhibition of NF-κB
- Selinexor shows robust anti-cancer activity in multiple preclinical models of solid tumors including melanoma, GBM, prostate, ovarian, lung, colon and pancreatic cancers
- Summary data from ongoing first in human phase 1 study of oral Selinexor in solid tumors malignancies (NCT01607905)
Phase 1, Open Label, Dose Escalation Study at 6 Sites in US, Canada and Denmark in Patients with Advanced, Metastatic Solid Tumors

**Study Design:**
- Doses 3,6,12,17,23,30,35,40,50,65 and 85mg/m²; 10 doses/cycle (2-3 doses/week) or 8 doses/cycle (twice weekly) or 4 doses/cycle (once weekly)
- Modified “3+3” design

**Major Eligibility Criteria:**
- Solid tumor patients with no available standard treatments
- ECOG 0-1
- Documented progression at study entry

**DLT Definition**
- ≥ 3 missed doses in 28 days at target dose
- Discontinuation of a patient due to a toxicity in Cycle 1

**Non Hematologic:**
- Grade ≥3 (nausea/vomiting, electrolyte imbalances must be supported first and AST/ALT lasting more than 7 days)
- Grade ≥3 fatigue lasting ≥5 days while taking supportive care

**Hematologic:**
- Grade 4 neutropenia ≥7 days
- Febrile neutropenia
- Grade 4 thrombocytopenia that persists for ≥5 days, or Grade ≥3 with bleeding
Selinexor Phase 1 Study: Patient Demographics and Dose Limiting Toxicities

<table>
<thead>
<tr>
<th>Dose</th>
<th>Doses/Cycle</th>
<th>DLT</th>
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</thead>
<tbody>
<tr>
<td>40 mg/m²</td>
<td>10</td>
<td>Grade 3 dehydration</td>
</tr>
<tr>
<td>40 mg/m²</td>
<td>10</td>
<td>Missed 3 doses in cycle 1 due to drug AE (Grade ≤2)</td>
</tr>
<tr>
<td>35 mg/m²</td>
<td>8</td>
<td>Grade 3 Nausea, Vomiting, Fatigue</td>
</tr>
<tr>
<td>85 mg/m²</td>
<td>8</td>
<td>Grade 3 Hyponatremia</td>
</tr>
<tr>
<td>85 mg/m²</td>
<td>8</td>
<td>Acute cerebellar syndrome with markedly improving ataxia and dysarthria. No other CNS toxicities were observed in the other &gt;300 patients treated with selinexor</td>
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The MTD / RP2D of Oral Selinexor is 65 mg/m² twice weekly
The majority of adverse events are reversible Grade 1 and 2, primarily nausea, anorexia and fatigue. Thrombocytopenia is the most common hematologic adverse event, rarely with bleeding. AEs are more common in Cycle 1, and decline in Cycles 2-3 due to supportive care and dose reductions. The lack of dose-response with many adverse events is likely due to the implementation of required supportive care: appetite stimulants and anti-nausea agents. Cumulative toxicities are uncommon, and major organ dysfunction is rare.
Selinexor (KPT-330) is a covalent, oral SINE XPO1 antagonist that forces nuclear restoration and reactivation of TSP and reduces proto-oncogenes leading to the selective apoptosis of cancer cells.

- Common AEs are reversible nausea, anorexia, fatigue and thrombocytopenia.
- Extended dosing feasible with appetite stimulants and anti-nausea agents.
- Selinexor can arrest disease progression and induce responses across a variety of heavily pretreated, progressing solid tumors.
- Phase 2 single agent (RP2D: 65mg/m² PO BIW) and combination studies have begun or are planned.