A Phase 1 Dose Escalation Study of the Oral Selective Inhibitor of Nuclear Export (SINE) KPT-330 (Selinexor) in Patients (pts) with Relapsed / Refractory Acute Myeloid Leukemia (AML)

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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 Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), NHL and other malignancies
- Exportin 1 (XPO1, CRM1) is the exclusive nuclear exporter of most TSPs
- Selinexor (KPT-330) is a covalent, oral Selective Inhibitor of Nuclear Export (SINE) that blocks XPO1
- Selinexor forces nuclear retention and activation of multiple TSPs
- Selinexor reduces proto-oncogene proteins including Flt3, c-Kit, 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 AML and other hematologic malignancies, largely independent of cytogenetics
- We present summary data from ongoing first-in-human Phase 1 study of oral selinexor in hematological malignancies (NCT01607892)
Phase 1, Open Label, Dose Escalation Study in Patients with Advanced, Hematological Malignancies

Study Design:
- Arm 2 included patients with AML.
- Doses 16, 23, 30, 40, 55 and 70 mg/m$^2$; 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:
- Patients with AML with no available standard treatments
- ECOG 0-1
- Documented progression at study entry

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

Non Hematologic:
- Grade $\geq 3$ excluding nausea/vomiting or electrolyte imbalances amenable to supportive care and AST/ALT lasting less than 7 days
- Grade $\geq 3$ fatigue lasting $\geq 5$ days while taking supportive care
Selinexor Phase 1 Study in AML: Patient Demographics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=65</th>
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<tbody>
<tr>
<td>Mean Age (range)</td>
<td>67 (24 – 89)</td>
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<tr>
<td>Male / Female</td>
<td>34 Males : 31 Females</td>
</tr>
<tr>
<td>Mean Prior Lines of Treatment (range)</td>
<td>3 (1 – 7)</td>
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<tr>
<td>ECOG performance status, 0/1</td>
<td>18 / 47</td>
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<table>
<thead>
<tr>
<th>Therapy Line for Disease</th>
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<tbody>
<tr>
<td>2nd Line AML</td>
<td>15 (23%)</td>
</tr>
<tr>
<td>3rd Line AML</td>
<td>13 (20%)</td>
</tr>
<tr>
<td>&gt; 3rd Line AML</td>
<td>28 (43%)</td>
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<tr>
<td>Unknown</td>
<td>9 (14%)</td>
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<table>
<thead>
<tr>
<th>AML Cytogenetic Risk</th>
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<tbody>
<tr>
<td>Favorable</td>
<td>10 (15%)</td>
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<tr>
<td>Intermediate</td>
<td>28 (43%)</td>
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<tr>
<td>Adverse</td>
<td>23 (35%)</td>
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<tr>
<td>Unknown</td>
<td>4 (6%)</td>
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Summary: Patients with AML enrolled in KCP-330-001 have heavily pretreated AML with disease that is progressing on study entry. The majority of patients have intermediate or poor cytogenetic risk. >50% are over 67 years old.
Selinexor Phase 1 Study: Safety

Selinexor Adverse Events (AEs, Overall)

- No DLTs were observed at any dose (16 – 70mg/m² administered 2-3 times weekly)
- The majority of adverse events are reversible Grade 1 and 2, primarily anorexia, nausea and fatigue.
- AEs are more common in Cycle 1, and decline in Cycles 2-3 with supportive care and some dose reductions.
- AEs did not show a clear dose response on incidence/severity, likely due to the implementation of required supportive care at higher doses, including appetite stimulants and anti-nausea agents.
- Cumulative toxicities are uncommon, and major organ dysfunction is rare.

Recommended Phase 2/3 Dose of Oral Selinexor for AML is 55 mg/m² twice weekly
Selinexor Phase 1 Study: Efficacy and Conclusions

• 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 AML cells.

• Common AEs are reversible nausea, anorexia and fatigue; extended dosing feasible with appetite stimulants and anti-nausea agents

• Objective Responses and reduction in BM blasts were observed in heavily pre-treated patients with AML

• Randomized Study of Selinexor 55mg/m² PO BIW vs. Physician’s Choice 2nd line elderly AML has begun

• Combination studies have begun or are planned.

<p>| Best Responses in Patients with AML as 13-May-2014 |
|-----------------|-------------|----------|--------|--------|--------|-----|-----|-----|</p>
<table>
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<tr>
<th>N</th>
<th>DCR</th>
<th>ORR</th>
<th>CR</th>
<th>CR(i)</th>
<th>PR</th>
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<td>63</td>
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<td>10</td>
<td>5</td>
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<tr>
<td>%</td>
<td>49%</td>
<td>16%</td>
<td>8%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
<td>33%</td>
<td>25%</td>
<td>25%</td>
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Selinexor Induces Blast Count Reductions

BM Blast cells were evaluated at screening and at the end of each cycle

* Excludes 14 patients who withdrew consent & 18 patients who clinically progressed before post treatment bone marrow biopsy

PRESENTED AT: ASCO 50th ANNIVERSARY MEETING