Nuclear Export Inhibitor KPT-8602 Is Highly Active Against Leukemic Blasts and Leukemia-Initiating Cells in Patient-Derived Xenograft Models of AML

Nuclear Exporter CRM1/XPO1

- major protein nuclear export receptor

- exports ~ 220 macromolecules that contain leucine-rich nuclear export signals (NES)

- mediates export of RNA substrates (e.g. rRNAs, viral mRNAs, cellular mRNAs)

- transports a variety of cancer proteins, including tumor suppressors, transcription factors, and cell cycle regulators
Overview of the XPO1-Mediated Pathway of Nuclear Export

XPO1

Targeted Inhibitor (KPT-SINE)

Monecke et al, FASEB J Review, 2014
Novel XPO1 inhibitors: KPT-SINE

• Developed based on the crystal structure of CRM1/XPO1 (target Cys\(^{528}\) in the cargo-binding groove)

• Orally bioavailable

• Selinexor (KPT-330) is in clinical phase I/II trials in adults and children with AML – Preliminary results show that selinexor alone or in combination is active at inducing remission in patients with relapsed or refractory AML

• Next generation SINE compound, KPT-8602, has over 30 times lower brain penetration than selinexor

• KPT-8602 is a more reversible inhibitor of XPO1 as compared to KPT-330
Experimental scheme to determine the activity of KPT-8602 against primary bulk cells

**Treatment Duration:**

4 weeks

**Treatment Response:**

Patient AML cells

Leukemia Progression

Vehicle Control

Selinexor (KPT-330)

M/Th or M/W/F

KPT-8602 (15 mg/kg)

Daily

NSG mice

hCD45+ in the BM

hCD45+ in the BM

hCD45+ in the BM

Patient AML cells

Leukemia Progression

Vehicle Control

Selinexor (KPT-330)

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KPT-8602 (15 mg/kg)

Daily

NSG mice

hCD45+ in the BM

hCD45+ in the BM

hCD45+ in the BM
KPT-8602 is Highly Active against Bulk AML Cells in PDX Models of Patient AML

KPT-8602 greatly reduces the number of bulk AML cells in PDX models of high-risk AML; 2 mice demonstrated no detectable AML cells in the bone marrow after 4 weeks of treatment.
Experimental scheme: Response of LICs to KPT-8602 treatment

After 4 weeks of Treatment

Vehicle
Selinexor
KPT-8602

Re-transplantation Assay

<table>
<thead>
<tr>
<th></th>
<th>10^5 hCD45+ cells</th>
<th>10^4 hCD45+ cells</th>
<th>10^3 hCD45+ cells</th>
<th>10^2 hCD45+ cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
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<td>Selinexor</td>
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<td>KPT-8602</td>
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</table>

Compare LIC frequencies between experimental groups
**KPT-8602 is Highly Active against AML LICs in PDX models**

<table>
<thead>
<tr>
<th>PDX model AML-CN</th>
<th>LIC freq.</th>
<th>Fold Reduction in LIC Frequency (compared to LIC frequency of Vehicle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1/1155</td>
<td>1</td>
</tr>
<tr>
<td>Selinexor</td>
<td>1/128923</td>
<td>111-fold</td>
</tr>
<tr>
<td>KPT-8602</td>
<td>1/504215</td>
<td>437-fold</td>
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</tbody>
</table>

KPT-8602 induced ~ **437 fold reduction in LIC frequency** in the surviving AML cell population

<table>
<thead>
<tr>
<th>PDX model MDS/AML</th>
<th>LIC freq.</th>
<th>Fold Reduction in LIC Frequency (compared to LIC frequency of Vehicle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1/4092</td>
<td>1</td>
</tr>
<tr>
<td>Selinexor</td>
<td>&lt;1/771218</td>
<td>&gt;150-fold</td>
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<tr>
<td>KPT-8602</td>
<td>&lt;1/681463</td>
<td>&gt;150-fold</td>
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</table>

KPT-8602 induced ~ **150 fold reduction in LIC frequency**

<table>
<thead>
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<th>PDX model AML-CK</th>
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<tbody>
<tr>
<td>Vehicle</td>
<td>1/311</td>
<td>1</td>
</tr>
<tr>
<td>Selinexor</td>
<td>1/280</td>
<td>0.9-fold</td>
</tr>
<tr>
<td>KPT-8602</td>
<td>1/157733</td>
<td>507-fold</td>
</tr>
</tbody>
</table>

KPT-8602 induced ~ **507 fold reduction in LIC frequency**
Cytotoxic chemotherapy targets AML bulk cells, but leaves LIC that cause relapse

Diagnosis

After Induction Chemotherapy

Relapse

LICs

Leukemic progenitor cells
KPT-8602 targets AML bulk and Leukemia Initiating Cells (LICs) with high efficiency.
The effects of KPT-8602 on normal human leukocytes and hematopoietic stem and progenitor cells

KPT-8602, like KPT-330, shows minimal toxicity against normal HSPCs
The effects of KPT-8602 on normal HSCs

<table>
<thead>
<tr>
<th>Normal human CD34+ Grafts</th>
<th>Secondary Transplant Normal HSC frequency</th>
<th>Fold Reduction in Normal HSC Frequency (compared to Frequency of Vehicle)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>1/7389</td>
<td>1</td>
</tr>
<tr>
<td>Selinexor</td>
<td>1/20496</td>
<td>↓ 2.77</td>
</tr>
<tr>
<td>KPT-8602</td>
<td>1/6264</td>
<td>↓ 0.85</td>
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KPT-8602, like KPT-330, shows minimal toxicity against normal HSCs
The effects of KPT-8602 on Survival of Complex Karyotype AML PDX Mice

<table>
<thead>
<tr>
<th>Months:</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</thead>
<tbody>
<tr>
<td>On Treatment</td>
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- Vehicle
- KPT-330
- KPT-8602

- Moribund
- AML cells detected
The effects of KPT-8602 on Survival of MDS/AML PDX Mice

Vehicle

KPT-330

KPT-8602

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<tr>
<th>Months:</th>
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- Red: Moribund
- Green: AML cells detected
- Purple: No AML cells detected
Conclusions

- KPT-8602 is highly active against bulk AML cells and LICs, but spares normal hematopoietic stem and progenitor cells.
- Both selinexor and KPT-8602 can completely eradicate leukemia cells in one of the two PDX models.
- KPT-8602 can be given daily to mice and has better tolerability compared to selinexor.
- Preliminary toxicology studies in rats and monkeys suggest that KPT-8602 has a substantially better tolerability profile, with reduced CNS-mediated side effects of anorexia and weight loss compared to selinexor.
- KPT-8602 will enter Phase I trials in early 2016 and based on our studies may prove useful to help eradicate LIC that may remain after induction chemotherapy.