PHASE I STUDY OF SELINEXOR, A SELECTIVE INHIBITOR OF NUCLEAR EXPORT, IN COMBINATION WITH FLUDARABINE AND CYTARABINE IN CHILDREN WITH RELAPSED OR REFRACTORY LEUKEMIA

Thomas B Alexander¹, Norman J Lacayo², John Choi³, Raul C. Ribeiro¹, ⁴, Ching-Hon Pui¹, ⁴, and Jeffrey E Rubnitz¹, ⁴

Departments of Oncology¹ and Pathology³, St. Jude Children’s Research Hospital; Lucile Packard Children’s Hospital Stanford and Stanford Cancer Institute², Stanford University; and the Department of Pediatrics⁴, University of Tennessee Health Science Center, College of Medicine, Memphis, Tennessee
Selinexor: Novel Anti-Cancer Agent: Restores Tumor Suppressors & Reduces Oncoproteins

Tumor Suppressors

Cell Membrane

Nuclear Membrane

Nuclear Envelope

XPO-1

CYTOPLASM

SINE

p53
Par-4
PP2A
pRB
p21
IkB
BRCA1
p27
eIF4E
(myc,bcl2)
XPO1 expression is prognostic and selinexor is active in leukemia models

Objectives

Primary:
• Determine the safety profile and maximal tolerated dose of selinexor when given in combination with fludarabine and cytarabine

Secondary:
• Characterize the pharmacokinetics of oral selinexor after the first dose and at steady-state, as well as in combination with fludarabine and cytarabine
• Estimate the overall response rate of selinexor given with fludarabine and cytarabine in patients with relapsed or refractory hematologic malignancies
Inclusion Criteria

- Any relapse of AML, MPAL
- 2nd or greater relapse ALL

Phase 1 with expansion planned at MTD

- Combination therapy
- Rolling 6 design
- Four dose levels of selinexor (30mg/m², 40mg/m², 55mg/m², 70mg/m²)
## Patient characteristics

### 18 patients enrolled

<table>
<thead>
<tr>
<th>Disease</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>15</td>
</tr>
<tr>
<td>MPAL</td>
<td>2</td>
</tr>
<tr>
<td>ETP-ALL</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory</td>
<td>4</td>
</tr>
<tr>
<td>1st Relapse (all early)</td>
<td>7</td>
</tr>
<tr>
<td>2nd Relapse</td>
<td>7</td>
</tr>
<tr>
<td>Previous Transplant</td>
<td>10</td>
</tr>
</tbody>
</table>

### Selinexor dose

<table>
<thead>
<tr>
<th>Disease type</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>30 mg/m²</td>
</tr>
<tr>
<td>AML t(6;12)</td>
<td>30 mg/m²</td>
</tr>
<tr>
<td>Secondary AML -7</td>
<td>30 mg/m²</td>
</tr>
<tr>
<td>MPAL</td>
<td>40 mg/m²</td>
</tr>
<tr>
<td>AML t(6;9)</td>
<td>40 mg/m²</td>
</tr>
<tr>
<td>AML</td>
<td>40 mg/m²</td>
</tr>
<tr>
<td>AML -7</td>
<td>55 mg/m²</td>
</tr>
<tr>
<td>ALL -&gt; MPAL t(4;11)</td>
<td>55 mg/m²</td>
</tr>
<tr>
<td>AML, M7</td>
<td>55 mg/m²</td>
</tr>
<tr>
<td>AML, M0</td>
<td>55 mg/m²</td>
</tr>
<tr>
<td>AML, t(3;5)</td>
<td>55 mg/m²</td>
</tr>
<tr>
<td>AML</td>
<td>70 mg/m²</td>
</tr>
<tr>
<td>AML, t(8;21)</td>
<td>70 mg/m²</td>
</tr>
<tr>
<td>AML -&gt; ETP-ALL</td>
<td>70 mg/m²*</td>
</tr>
<tr>
<td>AML</td>
<td>70 mg/m²*</td>
</tr>
</tbody>
</table>

### 17 eligible for toxicity evaluation

### 15 eligible for response evaluation
PK testing shows dose proportional levels

Day 1 Mean ± SD Plasma Selinexor Concentration

Day 22 Mean ± SD Plasma Selinexor Concentration

PK testing shows dose proportional levels

<table>
<thead>
<tr>
<th>Selinexor Dose (mg/m²)</th>
<th>No. of patients</th>
<th>C_max (ng/mL)</th>
<th>T_max (hours)</th>
<th>AUC₀⁻₈h (ng*h/mL)</th>
<th>AUC₀⁻₄₈ (ng*h/mL)</th>
<th>t½ (hours)</th>
<th>No. of patients</th>
<th>C_max (ng/mL)</th>
<th>T_max (hours)</th>
<th>AUC₀⁻₈h (ng*h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>4</td>
<td>537 ± 281</td>
<td>3 ± 1.5</td>
<td>2171 ± 618</td>
<td>4351 ± 513</td>
<td>6 ± 1</td>
<td>3</td>
<td>414 ± 124</td>
<td>4 ± 1</td>
<td>2239 ± 494</td>
</tr>
<tr>
<td>40</td>
<td>3</td>
<td>475 ± 157</td>
<td>2 ± 3.5</td>
<td>2311 ± 934</td>
<td>5440 ± 940</td>
<td>7 ± 2</td>
<td>3</td>
<td>420 ± 87</td>
<td>4 ± 2</td>
<td>1785 ± 376</td>
</tr>
<tr>
<td>55</td>
<td>4</td>
<td>776 ± 200</td>
<td>4 ± 0</td>
<td>5663 ± 3438</td>
<td>9838 ± 2413</td>
<td>8 ± 2.5</td>
<td>6</td>
<td>976 ± 665</td>
<td>3 ± 1</td>
<td>4627 ± 2484</td>
</tr>
<tr>
<td>70</td>
<td>5</td>
<td>996 ± 224</td>
<td>4 ± 1</td>
<td>4986 ± 979</td>
<td>10564 ± 1638</td>
<td>7 ± 1</td>
<td>3</td>
<td>1188 ± 474</td>
<td>2 ± 1</td>
<td>7035 ± NA</td>
</tr>
</tbody>
</table>
Change in levels of *XPO1* mRNA by dose and duration of selinexor exposure
Cerebellar toxicity is a reversible dose limiting toxicity in pediatrics

Maximal Tolerated Dose is 55 mg/m²

Cerebellar Toxicity – Occurred at 70 mg/m² of selinexor
  • First Case – pain, aphasia, weakness, ataxia
    • MRI – restricted diffusion in cerebellum
  • Second Case – significant ataxia, truncal instability
    • MRI – restricted diffusion in cerebellum

Hyponatremia
  • Grade 3 hyponatremia in 12 of 17 evaluable cases
  • Nadir: range 123-132 mEq/L, median 128.5 mEq/L
  • Asymptomatic and easily correctable in all cases
Selinexor can induce differentiation

Day 0

Day 15

t(6;9)
2nd relapse

t(8;21)
1st relapse
MRD negative complete responses observed at day 15 and end of course 1

Single Agent Response (Day 15)

- 2 patients with CR, both MRD negative
  - 1 was in second relapse, 1 had refractory disease
MRD negative complete responses observed at day 15 and end of course 1

Single Agent Response (Day 15)
- 2 patients with CR, both MRD negative
  - 1 was in second relapse, 1 had refractory disease

Combination Response (End of course 1)
- 7/15 with CR or CRi
- 5 of responses were MRD negative

Can we predict responses?
Summary

Selinexor in combination with fludarabine cytarabine:

1. Cerebellar toxicity is the dose limiting toxicity
2. PK / PD results show expected concentration, half life and on target effects
3. MRD negative complete responses were observed and response rate will be further explored in a Phase II study
4. The search for predictive markers continues...
Acknowledgements

Jeffrey Rubnitz, MD
Karyopharm Therapeutics Inc., Newton, MA
Stanley Pounds, PhD
Support Staff – Jeana Cromer, Kathy Jackson, Tad McKeon, Linda Holloway, Heidi Clough

Funding
• Cancer Center Support (CORE) grant P30 CA021765-30 from the National Institutes of Health
• Center of Excellence Grant from the State of Tennessee
• American Lebanese Syrian Associated Charities (ALSAC)

References

