Frontline Selinexor and Chemotherapy Is Highly Active in Older Adults with Acute Myeloid Leukemia (AML)

Timothy S. Pardee, MD, PhD¹, Kristin M. Pladna, M.S.²*, Susan Lyerly, P.A.-C.²*, Sarah Dralle²*, Megan Manuel, NP²*, Leslie Renee Ellis, MD, MSHPEd², Dianna S. Howard, MD², Rupali Bhave, M.D.²* and Bayard L. Powell, MD²
Conflicts of Interest

- Co-Chief Medical Officer of Rafael Pharmaceuticals
- Speaker/Consultant for (in the last 2 years):
  - Celgene/BMS
  - Amgen
  - Pharmacypclics/Janssen
  - AbbVie
- Advisory Board Member for:
  - CBM Biopharma
- Research Support From
  - Karyopharm
  - Rafael Pharmaceuticals
  - Spherix Intellectual Property
Acute Myeloid Leukemia (AML) Background

- An aggressive, abnormal proliferation of immature myeloid cells (myeloblasts) that fail to differentiate
- Leads to progressive marrow failure and death
- Median age at diagnosis is 68 (disease of older patients)
- An estimated 21,450 new cases in 2019 in the US
- Associated mortality is high with an estimated 10,920 deaths in 2019 in the US
- 28.3% of patients surviving at 5 years (2009-2015)
AML Prognosis, Age

- Median Age at Diagnosis is 68
- 70% of all AML patients are >60
- Outcomes are dismal
- Resistance to standard therapy is common

Selinexor: Novel, First-in-Class, Small Molecule, Selective Inhibitor of Nuclear Export (SINE) XPO1

- Oral drug given 1-2 times per week (PDn t$_{1/2}$ ~48 hrs)
- No known drug-drug interactions
  - None through CYP450s or other enzymes
  - No effect on QTc intervals
- Forms a covalent adduct at cysteine 528 (C528) in the XPO1 cargo binding pocket
- Inhibits XPO1-mediated nuclear export of TSPs and oncogenic mRNAs resulting in G1/G2 arrest and apoptosis
- Potent anti-myeloma, lymphoma and leukemia effects in preclinical models
- Preclinical evidence of therapeutic window between cancer cells and normal cells
- Has been shown to sensitize AML cells to anthracyclines
- Phase I/II studies have been done in Frontline and RR AML
Inclusion Criteria

• Key Inclusion Criteria
  • Patients must have histologically or cytologically documented newly diagnosed de novo Acute Myeloid Leukemia (non-APL) that has not yet been treated. Hydrea is acceptable.
  • Patients must not have a secondary AML (defined as a history of prior radiation therapy or systemic chemotherapy, antecedent MDS, MPN or CMML)
  • Hydroxyurea may be used to control leukocytosis, provided that it is without Grade >2 toxicity, and can be taken until start of therapy.
  • Age >60 years.
Study Design

1:3 Randomization

Cycle 1

Arm 1: S.O.C.

Day 1-7: Cytarabine 100 mg/m²/day
Day 1-3: Daunorubicin 60 mg/m²/day

Arm 2: Selinexor

Day 1-7: Cytarabine 100 mg/m²/day
Day 1-3: Daunorubicin 60 mg/m²/day

Days 1 and 3: Twice weekly selinexor 60 mg (flat dose) for 3 weeks

Day 14: Bone marrow biopsy

Cycle 2 if needed (for persistent leukemia)

Day 1-2: Daunorubicin 60 mg/m²/day
Day 1-5: Cytarabine 100 mg/m²/day

Day 1-2: Daunorubicin 60 mg/m²/day
Day 1-5: Cytarabine 100 mg/m²/day

Days 1 and 3: Twice weekly selinexor 60 mg (flat dose) for 3 weeks
Study Design

Consolidation therapy (up to 4 cycles)

Arm 1: S.O.C.

Arm 2: Selinexor

Remission bone marrow biopsy
Day 28-42

Day 1-3: High dose Cytarabine
≤ 70 years: 1.5 g/m²/day
> 70 years: 1 g/m²/day

Day 1-6: High dose Cytarabine
≤ 70 years: 1.5 g/m²/day
> 70 years: 1 g/m²/day

Days 1 and 3: Twice weekly selinexor 60 mg for weeks 1-3

Maintenance therapy

Continues until unacceptable toxicity or recurrence

Once weekly (Days 1 and 8) selinexor 60 mg or highest tolerated dose every 3 weeks until relapse or unacceptable toxicity
Demographics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>All (n=28)</th>
<th>Standard Arm (n=7)</th>
<th>Selinexor Arm (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median Age (range)</strong></td>
<td>69 (60-75)</td>
<td>74 (60-75)</td>
<td>67 (61-73)</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>12/28</td>
<td>0/7</td>
<td>12/21</td>
</tr>
<tr>
<td><strong>ELN 2017 Cytogenetic Risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Poor</strong></td>
<td>32% (9/28)</td>
<td>43% (3/7)</td>
<td>29% (6/21)</td>
</tr>
<tr>
<td><strong>Intermediate</strong></td>
<td>39% (11/28)</td>
<td>14% (1/7)</td>
<td>48% (10/21)</td>
</tr>
<tr>
<td><strong>Good</strong></td>
<td>24% (7/28)</td>
<td>43% (3/7)</td>
<td>19% (4/21)</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>4% (1/28)</td>
<td>0% (0/7)</td>
<td>5% (1/21)</td>
</tr>
</tbody>
</table>
### Mutational Data

<table>
<thead>
<tr>
<th>Cohort</th>
<th>All (n=28)</th>
<th>Standard Arm (n=7)</th>
<th>Selinexor Arm (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DNMT3A</td>
<td>25% (7/28)</td>
<td>43% (3/7)</td>
<td>19% (4/21)</td>
</tr>
<tr>
<td>NPM1</td>
<td>25% (7/28)</td>
<td>43% (3/7)</td>
<td>19% (4/21)</td>
</tr>
<tr>
<td>SRSF2</td>
<td>21% (6/28)</td>
<td>14% (1/7)</td>
<td>24% (5/21)</td>
</tr>
<tr>
<td>TET2</td>
<td>21% (6/28)</td>
<td>43% (3/7)</td>
<td>14% (3/21)</td>
</tr>
<tr>
<td>ASXL1</td>
<td>18% (5/28)</td>
<td>0% (0/7)</td>
<td>24% (5/21)</td>
</tr>
<tr>
<td>IDH1</td>
<td>14% (4/28)</td>
<td>14% (1/7)</td>
<td>14% (3/21)</td>
</tr>
<tr>
<td>RUNX1</td>
<td>14% (4/28)</td>
<td>14% (1/7)</td>
<td>14% (3/21)</td>
</tr>
<tr>
<td>NRAS</td>
<td>11% (3/28)</td>
<td>14% (1/7)</td>
<td>10% (2/21)</td>
</tr>
<tr>
<td>WT1</td>
<td>11% (3/28)</td>
<td>43% (3/7)</td>
<td>0% (0/21)</td>
</tr>
<tr>
<td>TP53</td>
<td>4% (1/28)</td>
<td>0% (0/7)</td>
<td>5% (1/21)</td>
</tr>
</tbody>
</table>
Toxicity

- 60 day mortality 10% (2/21) selinexor arm, 14% (1/7) in SOC arm
- 33% (7/21) patients in selinexor arm with prolonged thrombocytopenia (>4 weeks following neutrophil recovery, transfusion dependent in 1)
- Diarrhea most common AE resulting in dose holding, dose modifications
# Efficacy

<table>
<thead>
<tr>
<th>Cohort</th>
<th>All (n=28)</th>
<th>Standard Arm (n=7)</th>
<th>Selinexor Arm (n=21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Residual Disease on Nadir Marrow</td>
<td>19% (5/27)</td>
<td>50% (3/6)</td>
<td>10% (2/21)</td>
</tr>
<tr>
<td>Complete Remission (CR)</td>
<td>68% (19/28)</td>
<td>43% (3/7)</td>
<td>76% (16/21)</td>
</tr>
<tr>
<td>MRD Negative CR</td>
<td>81% (13/16)</td>
<td>NA</td>
<td>81% (13/16)</td>
</tr>
<tr>
<td>Overall Response (CR+CRi)</td>
<td>75% (21/28)</td>
<td>43% (3/7)</td>
<td>86% (18/21)</td>
</tr>
<tr>
<td>No CR/CRi</td>
<td>26% (7/28)</td>
<td>57% (4/7)</td>
<td>14% (3/21)</td>
</tr>
<tr>
<td>Went on to Transplant</td>
<td>29% (8/28)</td>
<td>14% (1/7)</td>
<td>33% (7/21)</td>
</tr>
<tr>
<td>Relapsed After CR</td>
<td>24% (5/21)</td>
<td>33% (1/3)</td>
<td>22% (4/18)</td>
</tr>
</tbody>
</table>
Survival

Overall Survival

Control Median OS = 265 Days
Selinexor Median OS = 839 Days

p = 0.0472
Progression Free Survival

Control (n=7) Median PFS = 108 Days
Selinexor (n=21) Median PFS = 558 Days

p = 0.1319
Cytarabine ExposureInduces Oxygen Consumption in AML

Pardee et. al. Clin Ca Res. 2018 May 1;24(9):2060-2073

OCR=Oxygen Consumption Rate
OCR is a Source of Resistance to Cytarabine *In Vitro*

Pardee et al. *Clin Ca Res.* 2018 May 1;24(9):2060-2073

OCR=Oxygen Consumption Rate
Selinexor Blocks Increased OCR

**Basal OCR**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>OCR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>100</td>
</tr>
<tr>
<td>Ara-C 50nM</td>
<td>150</td>
</tr>
<tr>
<td>Sel 25nM</td>
<td>200</td>
</tr>
<tr>
<td>Ara-Sel</td>
<td>100</td>
</tr>
</tbody>
</table>

OCR=Oxygen Consumption Rate
Selinexor Sensitizes AML to Ara-C

**M F L 2**

- Vehicle
- Sel 25nM
- Ara 50nM
- 25/50

**O C I - A M L 3**

- Vehicle
- Sel 25nM
- Ara 125nM
- 25/125

**R N 2**

- Vehicle
- Sel 10nM
- Ara 75nM
- 10/75

% Viable
Summary

• Selinexor in combination with 7+3 appears highly active in fit elderly patients
• Selinexor provided a significant survival benefit in this small randomized trial
• Toxicities appeared manageable with similar 60 day mortality
• Fixed 60 mg dose is deserving of additional study in a larger randomized trial
• Selinexor may impair nuclear/mitochondrial communication needed for resistance to cytarabine
Acknowledgements

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• Enzo Palma
• Natty Schramm

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• Karyopharm

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