A first-in-class Menin-MLL1 antagonist for the treatment of MLL-r and NPM1 mutant leukemias

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Syndax Pharmaceuticals
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I am an employee and shareholder of Syndax Pharmaceuticals, Inc.
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Overview of Mixed Lineage Leukemia-rearranged (MLL-r) and Nucleophosmin Mutant AML (NPM1c+ AML)

**MLL-r is caused by translocations at the MLL1 locus that create oncogenic MLL-fusion proteins**
- MLL-r is an acute leukemia that presents as ALL or AML, commonly diagnosed at presentation (FISH)
- *MLL*-rearrangements are found in ~5-10% of AML and ALL cases, for a combined incidence ~7000+/yr
- Targeting of MEN:MLL interaction in *MLL*-r cells blocks cell proliferation

**NPM1c+ AML is caused by mutations in NPM1 gene**
- NPM1c is one of the most common mutations found in AML, diagnosed with standard NGS panels
- NPM1c represents about 30% of all adult AML and an incidence of ~ 20,000/yr
- Targeting of MEN:MLL1 interaction in *NPM1c+ AML* inhibits cell proliferation
Menin-MLL binding inhibition leads to loss of the leukemic transcription program in MLLr/NPM1c, causing terminal differentiation of cells.

SNDX-5613 occupies the MLL1 binding pocket on Menin.

SNDX-5613 inhibits Menin-MLLr interaction.

Menin inhibitors cause significant changes in the transcription program by evicting Menin from chromatin.

<table>
<thead>
<tr>
<th>CELL LINE</th>
<th>LINEAGE</th>
<th>GENETIC LESION</th>
<th>IC50, nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL-60</td>
<td>AML</td>
<td>PML-RARα</td>
<td>&gt;2000</td>
</tr>
<tr>
<td>MOLM13</td>
<td>AML</td>
<td>MLL-AF9</td>
<td>13 +/- 9</td>
</tr>
<tr>
<td>THP1</td>
<td>AML</td>
<td>MLL-AF9</td>
<td>37 +/- 21</td>
</tr>
<tr>
<td>NOMO1</td>
<td>AML</td>
<td>MLL-AF9</td>
<td>30 +/- 12</td>
</tr>
<tr>
<td>ML2</td>
<td>AML</td>
<td>MLL-AF8</td>
<td>18 +/- 9</td>
</tr>
<tr>
<td>EOL1</td>
<td>AML</td>
<td>MLL-PTD</td>
<td>20 +/- 10</td>
</tr>
</tbody>
</table>

**MOLM13 (MLL-AF9)**

**Day 3**

**Free protein**

<table>
<thead>
<tr>
<th>Fraction#</th>
<th>~ 1 mDa</th>
<th>~ 2 mDa</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMSO</td>
<td>MEN</td>
<td>MEN</td>
</tr>
<tr>
<td>VTP 0.3uM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**MOLM13**

- **Day 2**
  - ZNF521
  - MRTNR1
  - PEX1
  - MED1
  - MEF2C
  - CASC10
  - MYO6
  - EFNA5
  - MNK1
  - NFR3
  - CNOT4
  - SOCS2
  - ADGPR2
  - ALDH1A1
  - RPE75
  - SGO1
  - SQRD1
  - SOBP
  - RHOBTB1
  - DYNC111
  - SKD1A1
  - APF71
  - CCDC144

- **Day 7**
  - ZNF521
  - MRTNR1
  - PEX1
  - MED1
  - MEF2C
  - CASC10
  - MYO6
  - EFNA5
  - MNK1
  - NFR3
  - CNOT4
  - SOCS2
  - ADGPR2
  - ALDH1A1
  - RPE75
  - SGO1
  - SQRD1
  - SOBP
  - RHOBTB1
  - DYNC111
  - SKD1A1
  - APF71
  - CCDC144

**SNDX-50469**

- Me
  - O=S=O
  - HNₙ
  - N
  - N
  - N
  - O
  - F

**K73me2 DOT1L**

- MLL1n retained
- MLL1n reduced

**HOXA cluster**

- MYB
- MEF2C
- MEIS1
- JMJ1D1C
Menin inhibitors have profound single-agent activity in MLL-r PDX models, producing deep and durable responses

- Significant survival benefit in 7/8 PDXs after single 28d treatment with SNDX-469
- Profound effects on PDX-MLL-1 and PDX-MLL-2 with event free survival >1 yr
- No treatment effect on control non-MLLr leukemia ALL-56 (Ph+)

Source: Krivtsov, A. Cancer Cell. 2019 Dec 9;36(6):660-673; Animals treated orally for 28 days with vehicle or VTP-50469 (MTD; 120 mg/kg bid)
Menin inhibitors also have profound single-agent activity in NPM1c PDX models, producing deep and durable responses.

- i.v. Engraft 5-75% PB Leukemia
- ~90 Day Treatment SNDX-50469 formulated in Chow

Uckelmann, HJ. Science. 2020 Jan 31;367(6477):586-590
SNDX-5613 pharmacologic profile shows high potency and specificity for Menin - MLL inhibition

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Summary of findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>in vitro / in vivo profile</strong></td>
<td></td>
</tr>
<tr>
<td>Binding $K_i$</td>
<td>0.149 nM</td>
</tr>
<tr>
<td>Cell based IC$_{50}$</td>
<td>10 – 20 nM</td>
</tr>
<tr>
<td><strong>in vivo (Plasma) IC$_{50}$ (nM)</strong></td>
<td></td>
</tr>
<tr>
<td>(Plasma) IC$_{50}$ (nM)</td>
<td>53 nM</td>
</tr>
<tr>
<td>Specificity (&gt;125 enzyme/receptor)</td>
<td>No off-target binding @10 µM</td>
</tr>
<tr>
<td><strong>ADME properties</strong></td>
<td></td>
</tr>
<tr>
<td>% F (r, d)</td>
<td>29, 65</td>
</tr>
<tr>
<td>i.v. $t_{1/2}$ (r, d)</td>
<td>2, 3.3</td>
</tr>
<tr>
<td>% unbound at 10 mM (PPB)</td>
<td>32%</td>
</tr>
<tr>
<td>CYP inhibition / induction</td>
<td>$&gt;$ 10 µM</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Primarily via CYP3A4</td>
</tr>
<tr>
<td><strong>Safety / toxicology</strong></td>
<td></td>
</tr>
<tr>
<td>Safety hERG IC$_{50}$</td>
<td>5 µM - 15 µM</td>
</tr>
<tr>
<td>GLP toxicity (r, d)</td>
<td>Consistent with primary MOA</td>
</tr>
<tr>
<td>Genotoxicity (Ames, MNT)</td>
<td>Negative</td>
</tr>
</tbody>
</table>
SNDX-5613 treatment provides significant survival benefit and leukemic control in aggressive MOLM-13 disseminated xenografts

**K-M Survival**

- **Day of Study**
  - Control Chow
  - 0.025% SNDX-5613
  - 0.05% SNDX-5613
  - 0.1% SNDX-5613
  - 0.2% SNDX-5613

- **Percent survival**

**MOLM-13 %hCD45+ PB**

- **SNDX-5613 Concentration in the Diets**
  - 0.025%
  - 0.05%
  - 0.1%
  - 0.2%
Steady-state plasma PK analysis clarifies the drug exposures required for leukemic control in MOLM-13 xenografts

**ss Plasma Levels**

<table>
<thead>
<tr>
<th>DOSE STRENGTH</th>
<th>AVE CONC</th>
<th>AUC&lt;sub&gt;0-24&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>ng/ml</td>
<td>ng*hr/ml</td>
</tr>
<tr>
<td>0.025</td>
<td>203</td>
<td>4900</td>
</tr>
<tr>
<td>0.05</td>
<td>573</td>
<td>13700</td>
</tr>
<tr>
<td>0.10</td>
<td>1425</td>
<td>34200</td>
</tr>
<tr>
<td>0.20</td>
<td>2713</td>
<td>65100</td>
</tr>
</tbody>
</table>

i.v. Engraft 5 days

28 Day Treatment

SNDX-5613 Formulated in Chow

MOLM-13 %hCD45⁺ PB
Maintain steady state levels above $IC_{95}$ (~600 ng/mL) for most of dosing interval

Maintain $C_{min}$ level above projected $IC_{90}$ (~300 ng/mL)

Minimum 24 h AUC of ~30,000 ng*h/mL
AUGMENT-101: Phase 1/2 trial of SNDX-5613, in patients with acute leukemia

**Phase 1:** Dose escalation

- Enrolling R/R acute leukemias*
- Accel. titration into 3+3 design
- 28-day cycle
- Starting dose = 113 mg PO BID

**Endpoints:** Safety, PK, RP2D

**Phase 2:** Expansion

- Adult MLL-r ALL
- Adult MLL-r AML
- Adult NPM1 mut AML

**Primary endpoint:** CR Rate (CR + CRh^)

* Unselected population; ^ CR = Complete response, CRh = Complete response with partial hematologic recovery; MLL-r = mixed lineage leukemia rearranged; NPM = nucleophosmin
Patient #1: 113 mg PO q12h

Patient Characteristics

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, Age</td>
<td>Male, 60 yr old</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Refractory AML</td>
</tr>
<tr>
<td>Mutational status</td>
<td>No MLLr or NPM1 mutation</td>
</tr>
<tr>
<td>Prior lines of therapy</td>
<td>3 (Aza, Dec/Ven, CLAG-M)</td>
</tr>
<tr>
<td>SNDX-5613 dose</td>
<td>113 mg PO q12 hr</td>
</tr>
<tr>
<td>DLT period</td>
<td>No DLTs</td>
</tr>
<tr>
<td>Day 28 response</td>
<td>Progressive disease</td>
</tr>
</tbody>
</table>

- Day 8 $C_{min} = 251$ ng/mL
- Day 8 est. $AUC_{0-24} = 12,200$ ng*h/ml

CR = Complete response, CRh = Complete response with partial hematologic recovery, CRi = complete remission with incomplete hematologic recovery
Patient #2: 226 mg PO q12h

Patient Characteristics

Gender, Age  Female, 69 yr old
Diagnosis  Refractory MPAL
Mutational status  MLL-TET1 fusion, FLT3 ITD
Prior lines of therapy  2 (chemo, gilteritinib)
SNDX-5613 dose  226 mg PO q12 h
DLT period  No DLTs; Grade 2 QTc resolved with dose reduced to 113 mg q12h
Day 28 response  CRi; beyond DLT period has improved to CR while on reduced dose

Patient #2: 226 mg BID Day 1 and Day 8

- Day 8 $C_{\text{min}} = 3030 \text{ ng/mL}$
- Day 8 est. $AUC_{0-24} = 93,900 \text{ ng*h/ml}$

CR = Complete response, CRh = Complete response with partial hematologic recovery, CRi = complete remission with incomplete hematologic recovery
## Response summary to date - Patients not on CYP3A4 Inhibitor

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age</th>
<th># Prior Tx</th>
<th>Mutational status</th>
<th>Dose</th>
<th>Meets target PK profile^</th>
<th>DLT period</th>
<th>Response Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>3</td>
<td>None*</td>
<td>113 q12</td>
<td>No</td>
<td>No DLTs</td>
<td>Progressive Disease/ off study</td>
</tr>
<tr>
<td>3</td>
<td>32</td>
<td>8</td>
<td>MLL-r t(5;11)</td>
<td>226 q12</td>
<td>No</td>
<td>No DLTs</td>
<td>No Response/ on study</td>
</tr>
</tbody>
</table>

5 pediatric patients (ages 1.5 – 10 years) all with MLL-rearrangements treated on single patient INDs:
- none were on CYP3A4 inhibitors
- none achieved the target PK profile
- and none had a response to date

PK exposures in pediatric patients generally consistent with adult exposures at equivalent dose

* Patient did not have either MLLr or NPM1 mutant AML; ^ Target PK profile defined as: (1) maintaining steady state levels above IC95 (~600 ng/mL) for most of dosing interval, (2) maintaining Cmin level above projected IC90 (~300 ng/mL) and (3) achieving a minimum 24 h AUC of ~30,000 ng*h/mL
## Response summary to date - Patients on Strong CYP3A4 Inhibitor

<table>
<thead>
<tr>
<th>Pt #</th>
<th>Age</th>
<th># Prior Tx</th>
<th>Mutational status</th>
<th>Dose</th>
<th>Meets target PK profile(^{\wedge})</th>
<th>DLT period</th>
<th>Response Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>69</td>
<td>2</td>
<td>MLL-r t(10;11) FLT3 ITD</td>
<td>226 q12 → 113 q12</td>
<td>Yes</td>
<td>No DLTs</td>
<td>Day 28 CRi - improved to CR FISH neg, Flow neg, on study</td>
</tr>
<tr>
<td>4</td>
<td>30</td>
<td>&gt;3</td>
<td>None*</td>
<td>226 q12</td>
<td>PK pending</td>
<td>Inevaluable</td>
<td>Progressive Disease off study</td>
</tr>
<tr>
<td>5</td>
<td>79</td>
<td>2</td>
<td>MLL PTD</td>
<td>226 q12</td>
<td>PK pending</td>
<td>No DLTs</td>
<td>Day 28: No Response on study</td>
</tr>
<tr>
<td>6</td>
<td>61</td>
<td>3</td>
<td>MLL-r t(9;11)</td>
<td>113 q12 → 113 QD</td>
<td>PK pending</td>
<td>No DLTs</td>
<td>Day 28 PRi blast count 40% → 20%; peripheral blood counts improving; FISH positive on study</td>
</tr>
</tbody>
</table>

*Patient did not have either MLLr or NPM1 mutant AML; \(^{\wedge}\)Target PK profile defined as: (1) maintaining steady state levels above IC\(_{95}\) (~600 ng/mL) for most of dosing interval, (2) maintaining Cmin level above projected IC\(_{90}\) (~300 ng/mL) and (3) achieving a minimum 24 h AUC of ~30,000 ng*h/mL.
Menin-MLL interaction inhibitors represent a novel, targeted therapy for Mixed Lineage Leukemia-rearranged (MLL-r) and NPM1 mutant AML.

SNDX-5613 is a potent, selective, orally available inhibitor of menin-MLL1:

- Attractive biopharmaceutical properties
- Monotherapy activity in multiple preclinical xenograft models
- Pharmacokinetics appear affected by concomitant CYP3A4 inhibition
- Clinical responses validate menin-MLL1 inhibition as a target for select patients with acute leukemia

Clinical investigation of SNDX-5613 is ongoing.
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