Management of Secondary AML (sAML); New Directions in AML Care

Geoffrey L Uy, MD
Secondary AML

- AML which occurs after antecedent MDS or MPN (sAML): 25-35%
- Complication of cytotoxic chemotherapy and/or radiation administered for unrelated disease (tAML): 10-20% of AML
  - Alkylator/ionizing radiation: 5-10 yr latency, loss of chromosome 5/7, TP53
  - DNA topoisomerase inhibitor related: 1-5 yr latency, rearrangements of 11q23/KMT2A
- Compared to *de novo* AML
  - Higher frequency of adverse-risk karyotype
  - More likely to be older, have poor PS and comorbidity

Granfeldt Østgård et al. JCO 2015; 33:3641-3649.
Patterns of clonal evolution during the progression of MDS to secondary AML

Clonal evolution during progression from MDS to secondary AML

Outcome of AML receiving intensive therapy

Granfeldt Østgård et al. JCO 2015; 33:3641-3649.
CPX-351 (Cytarabine:Daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary Acute Myeloid Leukemia

**Key Eligibility**
- Ages 60-75 years
- Untreated AML
- High-risk AML
  - Therapy-related AML
  - AML with history of MDS w/ and w/out prior HMA therapy
  - AML with history of CMML
  - *de novo* AML with MDS karyotype

**CPX-351**
- Liposomal formulation of Daunorubicin:cytarabine 1:5 molar ratio
- Maintains drug exposure for 7 days
- Selective uptake by leukemic vs normal cells in bone marrow of leukemia-bearing mice

**Primary Endpoint:** Overall survival

CPX-351-301 Study

**Median overall survival (95% CI)**
- 7+3 group: 5.95 (4.99-7.75)

**Hazard ratio (95% CI)**
- CPX-351 (n=153): 0.70 (0.55-0.91)
- 7+3 (n=156): 0.70 (0.55-0.91)

**Patients (%)**
- CPX-351 (n=153): 37.3
- 7+3 (n=156): 47.7

Transplant Outcomes in CPX-351-301

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CPX-351 (n=53)</th>
<th>7+3 (n=39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-69 yrs</td>
<td>37 (70)</td>
<td>33 (85%)</td>
</tr>
<tr>
<td>70-75 yrs</td>
<td>16 (30)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>HCT in CR/CRI</td>
<td>39 (75)</td>
<td>24 (62)</td>
</tr>
</tbody>
</table>

Adverse Events in CPX-351-301

Hematologic Recovery

<table>
<thead>
<tr>
<th></th>
<th>CPX-351 (n=58)</th>
<th>7 + 3 (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC ≥ 500/uL, median</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>Platelets ≥ 50,000/uL, median</td>
<td>36.5</td>
<td>29</td>
</tr>
</tbody>
</table>

Early Mortality

<table>
<thead>
<tr>
<th></th>
<th>CPX-351</th>
<th>7 + 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality at 30 days</td>
<td>5.9%</td>
<td>10.6%</td>
</tr>
<tr>
<td>Mortality at 60 days</td>
<td>13.7%</td>
<td>21.2%</td>
</tr>
</tbody>
</table>

Outcomes in CPX-351-301 by TP53 status

<table>
<thead>
<tr>
<th>Status</th>
<th>Median Survival (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mutated</td>
<td>5.7 (3.0-7.6)</td>
</tr>
<tr>
<td>unmutated</td>
<td>10.9 (7.0-26.3)</td>
</tr>
</tbody>
</table>

Median Survival (95% CI)
Decitabine + Venetoclax in TP53 AML

Azacitidine / Venetoclax in VIALE-A

Magrolimab: Macrophage Immune Checkpoint Inhibitor Targeting CD47

- CD47 is a “do not eat me” signal that is overexpressed in multiple cancers, including acute myeloid leukemia, leading to macrophage immune evasion
- Magrolimab, an IgG4 anti-CD47 monoclonal antibody (mAb), eliminates tumor cells through macrophage phagocytosis
- Magrolimab is being investigated in multiple cancers with >500 patients dose

Sallman et al., ASH 2020
5F9005 Study: Magrolimab in Combination With AZA in AML and MDS

- A magrolimab priming dose (1 mg/kg) and dose ramp-up were utilized to mitigate on-target anemia
- Data from the AML expansion cohort are presented

**Primary Objectives**
1. Safety of magrolimab alone or with AZA
2. Efficacy of magrolimab + AZA in untreated AML/MDS

**Secondary Objectives**
1. Pharmacokinetics, pharmacodynamics, and immunogenicity of 5F9
2. Additional measures of efficacy (DOR, PFS, OS)

**Exploratory Objective**
To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

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- Dose ramp-up from 1 mg/kg to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing.
- IPSS-R: Revised International Prognostic Scoring System.
Magrolimab + AZA Induces High Response Rates in AML

- Magrolimab + AZA induces a 63% ORR and 42% CR rate in AML, including similar responses in TP53-mutant patients
- Median time to response is 1.95 months (range 0.95 to 5.6 mo), more rapid than AZA monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + AZA efficacy compares favorably to AZA monotherapy (CR rate 18%–20%)\(^1,2\)

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**Best Overall Response**

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>All AML (N=43)</th>
<th>TP53-mutant AML (29)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>27 (63%)</td>
<td>20 (69%)</td>
</tr>
<tr>
<td>CR</td>
<td>18 (42%)</td>
<td>13 (45%)</td>
</tr>
<tr>
<td>CRi</td>
<td>5 (12%)</td>
<td>4 (14%)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (2%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>MLFS</td>
<td>3 (7%)</td>
<td>2 (7%)</td>
</tr>
<tr>
<td>SD</td>
<td>14 (33%)</td>
<td>8 (28%)</td>
</tr>
<tr>
<td>PD</td>
<td>2 (5%)</td>
<td>1 (3%)</td>
</tr>
</tbody>
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Preliminary Median Overall Survival Is Encouraging in Both TP53 Wild-Type and Mutant Patients

- The median OS is 18.9 months in TP53 wild-type patients and 12.9 months in TP53-mutant patients
- This initial median OS data may compare favorably to venetoclax + hypomethylating agent combinations (14.7-17.5 mo in all-comers,1,3 5.2–7.2 mo in patients who are TP53 mutant2,3)
- Additional patients and longer follow-up are needed to further characterize the survival benefit

* NE, not evaluable.

Menin Inhibitors for KMT2A (MLL) rearranged and NPM1\textsuperscript{mut} AML

- **KMT2A (MLL)**
  - histone methyltransferase that regulates gene expression via chromatin remodeling
  - >120 fusion partners have been described in acute leukemia
  - Associated with infantile leukemia, topoisomerase II inhibitors t-AML

- **Menin**: scaffold protein that interacts with cell signaling and gene regulators

- Orally available menin inhibitors currently in P1/2 studies
  - KO-539
  - SNDX-5613

KO-539 Shows Encouraging Early Clinical Activity

Clinical activities observed in 6 patients (efficacy evaluable = 8)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Mutational Profile</th>
<th>CYP3A4 inhibitor</th>
<th># of prior regimens</th>
<th>Clinical Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>400 mg</td>
<td>RUNX1, SRSF2, ASXL1, TET2, STAG2, BCOR, PTPN11</td>
<td>Yes</td>
<td>3</td>
<td>Decreased peripheral blasts</td>
</tr>
<tr>
<td>200 mg</td>
<td>U2AF1, TET2, p53, DNMT3A, PTPN11</td>
<td>No</td>
<td>4</td>
<td>Stable disease</td>
</tr>
<tr>
<td></td>
<td>NPM1, FLT3-ITD, TET2, CUX1</td>
<td>Yes</td>
<td>4</td>
<td>Morphological leukemia-free state</td>
</tr>
<tr>
<td>100 mg</td>
<td>NPM1, DNMT3A, KMT2D</td>
<td>Yes</td>
<td>7</td>
<td>CR, MRD-</td>
</tr>
<tr>
<td>50 mg</td>
<td>SETD2, RUNX1</td>
<td>Yes</td>
<td>2</td>
<td>CR, MRD+</td>
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</table>

*Expanded to characterize PK

Data as of 02 November 2020

Wang et al., ASH 2021
# ASH Abstracts in AML

<table>
<thead>
<tr>
<th>Title</th>
<th>Presenter</th>
<th>Time</th>
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<tbody>
<tr>
<td><strong>Abstract 2316.</strong> Phase 1b Study of Lower-Dose CPX-351 Plus Venetoclax As First-Line Treatment for Patients with AML Who Are Unfit for Intensive Chemotherapy: Preliminary Safety and Efficacy Result</td>
<td>Geoffrey L. Uy</td>
<td>Sunday, December 12, 2021, 6:00 PM-8:00 PM</td>
</tr>
<tr>
<td><strong>Abstract 1268.</strong> Preliminary Results By Age Group of Treatment with CPX-351 Plus Venetoclax in Adults with Newly Diagnosed AML: Subgroup Analysis of the V-FAST Phase 1b Master Trial</td>
<td>Vinod A. Pullarkat</td>
<td>Saturday, December 11, 2021, 5:30 PM-7:30 PM</td>
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<tr>
<td><strong>Abstract 3426</strong> A Phase 3, Randomized, Open-Label Study Evaluating the Safety and Efficacy of Magrolimab in Combination with Azacitidine in Previously Untreated Patients with TP53-Mutant Acute Myeloid Leukemia</td>
<td>Naval Daver</td>
<td>Monday, December 13, 2021, 6:00 PM-8:00 PM</td>
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<tr>
<td><strong>Abstract 699.</strong> Safety and Efficacy of Menin Inhibition in Patients (Pts) with MLL-Rearranged and NPM1 Mutant Acute Leukemia: A Phase (Ph) 1, First-in-Human Study of SNDX-5613 (AUGMENT 101)</td>
<td>Eytan M. Stein</td>
<td>Monday, December 13, 2021, 3:15 PM</td>
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<tr>
<td><strong>Abstract 540</strong> A Pilot Study of CPX-351 for Transplant Eligible, Higher Risk Patients with Myelodysplastic Syndrome</td>
<td>Megan A. Jacoby</td>
<td>Sunday, December 12, 2021, 4:30 PM-6:00 PM</td>
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