Therapies for Higher Risk MDS Patients: Optimizing HMA Approaches and Use of Novel Agents

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Defining Higher risk MDS

• Higher risk MDS = higher chance of AML transformation and worse overall survival.
• Historically IPSS is the most common tool used to define higher risk MDS.
• 1/3 of MDS patients are classified as int-2 or high risk by IPSS with expected overall survival < 1.5 years
My MDS Risk Stratification

- very low risk R-IPSS +/- 1 HR somatic mutation (SM).
- Low risk R-IPSS no HR SM
- Very low/low/intermediate R-IPSS with SF3B1 SM.

- Low risk R-IPSS + 1 HR SM.
- Intermediate risk R-IPSS no HR SM.

- Intermediate risk R-IPSS + HR SM
- Very high and high risk R-IPSS.
- Complex monosomy karyotype.
- > 3 HR SM.
- P53 mutation.
Treatment Algorithm 2017: Higher-Risk MDS

- start HMA
  - AHSCT candidate
    - Donor
      - Favorable (Co-morbidities functional status) → AHSCT
      - Unfavorable
        - continue HMA
          - 1ry or 2ndry failure
            - Investigational

modified from NCCN. Clinical practice guidelines in oncology. MDS. 2016.
Allogeneic Hematopoietic Stem Cell Transplantation remains the only curative option for MDS patients.

Impact of *TP53* Mutation & Age on AlloHCT

**OS by TP53 Mutation Status**

- 100% survival at 0 years post-transplantation.
- TP53 mutation (red line) shows a significantly lower survival rate compared to No TP53 mutation (black line) with a p-value of <0.001.

**No. at Risk**

<table>
<thead>
<tr>
<th>TP53 Status</th>
<th>&lt;40 yr of age</th>
<th>40 yr of age</th>
<th>≥40 yr of age</th>
</tr>
</thead>
<tbody>
<tr>
<td>No TP53 mutation</td>
<td>214</td>
<td>159</td>
<td>133</td>
</tr>
<tr>
<td>TP53 mutation</td>
<td>1010</td>
<td>598</td>
<td>396</td>
</tr>
</tbody>
</table>

**OS by TP53 Mutation & Age**

- Graph showing survival rates with TP53 mutation status and age groups.
- Graph highlights different survival rates with TP53 mutation and age categories.

Lindsley RC, et. al. NEJM 2017; 376: 536.
AZA-001 Trial: Azacitidine Significantly Improves Overall Survival

HR: 0.58 (95% CI: 0.43-0.77; log-rank $P = .0001$)

Change in response with continued treatment in patients with stable disease as best response.

Outcomes of Patients with MDS Who Achieve Stable Disease after Treatment with HMA: MDSCC Experience n=846

- Patients who achieved a BR of SD had a longer OS compared to patients with PD.
- Of patients with SD at 4-6 months, 20% achieved a better response at a later time point.
- Patients with SD who subsequently achieved CR had superior OS compared to patients who remained with SD (28.1 vs. 14.4 months, respectively, $p=.04$). Nazha et al, Leuk Res. 2016 Feb;41:43-7.
HMA Outcomes MDSCRC

- Among 459 patients treated with HMA as first line for higher risk disease, response was evaluable in 432 pts.

- Overall Response Rate (ORR) defined as HI or better was 43% which is very similar to ORR reported in AZA-001 and S117 studies.

- The median survival time from diagnosis was 19.6 mo (95% CI: (18.3, 22.0))

<table>
<thead>
<tr>
<th>IWG 2006 Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>69 (16)</td>
</tr>
<tr>
<td>mCR</td>
<td>8 (2)</td>
</tr>
<tr>
<td>PR</td>
<td>47 (11)</td>
</tr>
<tr>
<td>HI</td>
<td>59 (14)</td>
</tr>
<tr>
<td>SD</td>
<td>174 (40)</td>
</tr>
<tr>
<td>PD</td>
<td>75 (17)</td>
</tr>
</tbody>
</table>

Komrokji et al, Blood 2015 126:909
### HMA Outcomes MDSCRC

Overall Survival from start for HMA as first line therapy

<table>
<thead>
<tr>
<th>IWG 2006 Response</th>
<th>Median OS (months)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>28.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>mCR</td>
<td>13.6</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>20.2</td>
<td></td>
</tr>
<tr>
<td>HI</td>
<td>18.0</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>12.5</td>
<td></td>
</tr>
</tbody>
</table>

CR was associated with better outcome compared to HI, SD and PD response groups and mCR/PR/HI combined group. Pts with mCR/PR/HI combined group had better outcome compared to PD (p=0.06). 

Komrokji et al, Blood 2015 126:909
EORTC-06011: Overall Survival with Decitabine Treatment

Treatment With AZA OR ICT Prior AHSCT

AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.41
(95% CI: 0.83-2.42; P = NS)
ICT-AZA v AZA alone: HR = 3.08
(95% CI: 1.38-6.85; P = .006)

AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.48
(95% CI: 0.90-2.44; P = NS)
ICT-AZA v AZA alone: HR = 2.72
(95% CI: 1.38-5.34; P = .01)

AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.35
(95% CI: 0.73-2.46; P = NS)
ICT-AZA v AZA alone: HR = 1.87
(95% CI: 0.69-5.06; P = NS)

AZA alone: HR = 1
ICT alone v AZA alone: HR = 1.23
(95% CI: 0.55-2.76; P = NS)
ICT-AZA v AZA alone: HR = 2.50
(95% CI: 0.89-7.05; P = .08)

Azacitidine Maintenance after AHSCT

  - N= 45, majority AML patients (n=37).
  - Excluded active disease, active GVHD, active infections.
  - MTD AZA 32mg/m² SQ for 5 days SQ X 4 cycles.
  - Median EFS 18.2 mo (95% CI: 11.9-NR), One year EFS and OS 58% and 77%
- Mishra et al. Leukemia Research, vol 55, S1, April 2017, Page S48
MDS with Founder TP53 Mutations are Highly Responsive to Decitabine

  - 116 MDS/AML treated with decitabine 20 mg/m²/d x 10d q 28d
  - exome sequencing pretreatment & serially
  - ORR higher in fav/int cytogenetic risk vs. unfavorable (29/43 [67%] vs. 24/71 [34%], \( P < 0.001 \))
  - Higher ORR in *TP53* mutant vs. Wt (21/21 [100%] vs. 32/78 [41%], \( P < 0.001 \))
  - CR/Cri higher in *TP53* mutant vs. Wt (13/21 [62%] vs. 26/78 [33%], \( P = 0.04 \))

  - 109 MDS treated with decitabine 20 mg/m²/d x 5d q 28d
  - CR rate higher in *TP53* mutant vs. Wt (10/15 [66.7%] vs. 20/94 [21%], \( P = 0.001 \))
  - No difference in ORR (*TP53* mutant, 11/15 [73%] vs. 63/94 [67%] Wt)
  - Poor OS in *TP53* \( _{mu} \) MDS (median, 14 vs. 39 mos; \( P = 0.012 \))
Rate of Clearance of Somatic Gene Mutations in Decitabine Treated Patients

Clearance of $TP53_{mu}$ Clones

Change in VAF by Somatic Mutation

Overall Survival by TP53 Mutation Status

**OS in $TP53_{mu}$ vs. Wt**

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>80</td>
<td>200</td>
</tr>
<tr>
<td>60</td>
<td>400</td>
</tr>
<tr>
<td>40</td>
<td>600</td>
</tr>
<tr>
<td>20</td>
<td>800</td>
</tr>
<tr>
<td>0</td>
<td>1000</td>
</tr>
</tbody>
</table>

Median OS
- $TP53_{Mu}$: 12.7 mos
- $TP53_{Wt}$: 15.4 mos

**OS with HSCT by TP53 Mutation**

<table>
<thead>
<tr>
<th>Survival (%)</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>80</td>
<td>200</td>
</tr>
<tr>
<td>60</td>
<td>400</td>
</tr>
<tr>
<td>40</td>
<td>600</td>
</tr>
<tr>
<td>20</td>
<td>800</td>
</tr>
<tr>
<td>0</td>
<td>1000</td>
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</table>

P = 0.99

**No. at Risk**

<table>
<thead>
<tr>
<th></th>
<th>TP53 mutation</th>
<th>Wild-type TP53</th>
</tr>
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<tbody>
<tr>
<td>12/10</td>
<td>21</td>
<td>78</td>
</tr>
<tr>
<td>11/9</td>
<td>20</td>
<td>51</td>
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<td>10/8</td>
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<td>31</td>
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<td>9/7</td>
<td>4</td>
<td>16</td>
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<tr>
<td>8/6</td>
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<td>7</td>
</tr>
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<td>24</td>
</tr>
<tr>
<td></td>
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<td>24</td>
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<tr>
<td></td>
<td></td>
<td>16</td>
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<td></td>
<td></td>
<td>10</td>
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<td></td>
<td></td>
<td>5</td>
</tr>
</tbody>
</table>

Response to Azacitidine in $TP53_{mu}$ MDS

- Retrospective analysis of 54 MDS patients with treated with azacitidine 75 mg/m$^2$/d x 7d q 4 wks
- $TP53$ mutation assessed by BM IHC and validated by NGS
- ORR (CR, PR, HI) higher in $TP53_{mu}$ vs Wt (11/24 [46%] vs. 4/29 [14%], $P=0.008$)
- Median OS 8.2 mos in $TP53_{mu}$ vs. 13.7 mos Wt ($P=NS$) excluding pts receiving HSCT

Miller-Thomas C, et. al. Haematologica 2014; Epub.
Improving outcome: HMA and beyond

• Better identification of patients who benefit from therapy:
  “clinical or biomarker predictors of response”

• Improve rate or duration of response
  “Combination strategies”

• Novel agents
Comparison of Risk Stratification Tools in Predicting Outcomes of Patients with Higher-Risk MDS Treated with Azanucleosides

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>N (%)</th>
<th>Median OS in months (95%CI)</th>
<th>Risk Group</th>
<th>N (%)</th>
<th>Median OS in months (95%CI)</th>
<th>Risk Group</th>
<th>N (%)</th>
<th>Median OS in months (95%CI)</th>
<th>Risk Group</th>
<th>N (%)</th>
<th>Median OS in months (95%CI)</th>
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<tr>
<td><strong>IPSS</strong></td>
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<td></td>
<td><strong>IPSS-R</strong></td>
<td></td>
<td></td>
<td><strong>FPSS</strong></td>
<td></td>
<td></td>
<td><strong>MDAPSS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>0 (0)</td>
<td>--</td>
<td>Very low*</td>
<td>0 (0)</td>
<td>--</td>
<td>Low</td>
<td>40 (6.3)</td>
<td>36.89 (23.50, 57.92); fmi = 0.179</td>
<td>Low*</td>
<td>10 (1.6)</td>
<td>--</td>
</tr>
<tr>
<td>INT-1</td>
<td>0 (0)</td>
<td>--</td>
<td>Low</td>
<td>6 (0.9)</td>
<td>56.71 (25.80, 124.67); fmi = 0.152</td>
<td>INT</td>
<td>490 (77.6)</td>
<td>17.90 (16.48, 19.44); fmi = 0.115</td>
<td>INT-1</td>
<td>54 (8.5)</td>
<td>31.95 (19.26, 53.00); fmi = 0.161</td>
</tr>
<tr>
<td>INT-2</td>
<td>192 (30.4)</td>
<td>17.95 (16.30, 19.76); fmi = 0.0687</td>
<td>INT</td>
<td>68 (10.8)</td>
<td>35.04 (23.66, 51.88); fmi = 0.175</td>
<td>High</td>
<td>102 (16.1)</td>
<td>10.91 (9.40, 12.66); fmi = 0.142</td>
<td>INT-2</td>
<td>184 (29.1)</td>
<td>20.91 (17.84, 24.50); fmi = 0.039</td>
</tr>
<tr>
<td>High</td>
<td>440 (69.6)</td>
<td>16.13 (13.92, 18.70); fmi = 0.0273</td>
<td>High</td>
<td>213 (33.7)</td>
<td>20.76 (18.21, 23.66); fmi = 0.080</td>
<td>High</td>
<td>384 (60.8)</td>
<td>14.29 (12.98, 15.73); fmi = 0.026</td>
<td>High</td>
<td>323 (51.1)</td>
<td>19.42 (17.33, 21.77); fmi = 0.235</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Very High</td>
<td>345 (54.6)</td>
<td>13.77 (12.30, 15.41); fmi = 0.060</td>
<td></td>
<td></td>
<td></td>
<td>Very High</td>
<td>273 (43.2)</td>
<td>14.85 (13.37, 16.50); fmi = 0.156</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>N/A**</td>
<td>10 (1.6)</td>
<td>13.96 (7.69, 25.34); fmi = 0.627</td>
</tr>
</tbody>
</table>

Somatic Mutations & Response to Azanucleosides

- 213 pts receiving azanucleosides (100 LR-MDS)
- NGS analysis of 40 myeloid genes to assess relation to response & OS
- Clonal TET2 mutations predicted response (OR 1.99, \(P = .036\)) when subclones unlikely to be detected by Sanger sequencing (VAF<10%) were treated as wild-type (WT).
- Response rate highest in TET2 mutant patients without ASXL1 mutations (OR 3.65, \(P = .009\)).
- Mutant TP53 (HR 2.01, \(P = .002\)) associated with shorter OS

Can we tailor therapy accordingly?

A. HMA Overall Response Rate

B. Duration of HMA Treatment

C. DNA Methylation Mutations and HMA

Sallman, et. al. ASH 2016
### Randomized HMA combination Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Combination</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>SWOG</td>
<td>Aza vs Aza/len vs Aza/Vorinostat</td>
<td>x</td>
</tr>
<tr>
<td>ECOG</td>
<td>Aza vs Aza/entinostat</td>
<td>x</td>
</tr>
<tr>
<td>MEI</td>
<td>Aza vs Aza/pracinostat</td>
<td>x</td>
</tr>
<tr>
<td>Tetralogic</td>
<td>Aza vs Aza/Birinapant</td>
<td>x</td>
</tr>
</tbody>
</table>

Sekeres, et. al. BLOOD 2014; 124, LBA-5.
Donnellan et al, ASCO 2016. Abstract # 7060
# Ongoing HMA combination Studies

<table>
<thead>
<tr>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZA + Venetoclax</td>
</tr>
<tr>
<td>AZA + Pevonedistat</td>
</tr>
<tr>
<td>AZA + PDL-1/CTLA-4 inhibitors</td>
</tr>
<tr>
<td>AZA + APR-246</td>
</tr>
</tbody>
</table>
Phase Ib Study: Frontline Venetoclax + HMAs in Elderly AML Pts

- Open-label, nonrandomized, 2-arm, 2-stage study

Endpoints

- Safety: MTD, DLTs, RP2D, AEs, early deaths, PK
- Efficacy: ORR per IWG AML criteria, response duration, TTP, PFS, OS, MRD (assessed after cycles 1 and 4, then every 12 weeks)
- Exploratory: mutational profiling and BCL-2 characterization, molecular markers, ex vivo testing of pt samples

Pats with untreated AML, 65 yrs of age or older, adverse or intermediate-risk cytogenetics, ineligible for standard induction therapy (N = 34)

Safety, PK, dose finding

Venetoclax* + Decitabine
20 mg/m² Days 1-5, IV 28-day cycles
(n = 18)

Venetoclax* + Azacitidine
75 mg/m² Days 1-7, IV/SC 28-day cycles
(n = 16)

*In each arm, 1 cohort received venetoclax 400 mg and 2 cohorts received 800 mg.

Expansion stage: safety and efficacy confirmation

1 HMA combo (RP2D)

Venetoclax + HMA (n = 40)

Frontline Venetoclax + HMAs in Elderly AML

Pts: Best Response

- 30/34 pts had bone marrow assessment at end of cycle 1
  - > 50% reduction in bone marrow blasts: 28 (93%)
  - CR/CRi: 24 pts; median time to CR/CRi: 29.5 days (range: 24-112)

- Median days on study: 106.5 (range: 6-305)

<table>
<thead>
<tr>
<th>Best Response, %</th>
<th>Venetoclax/Decitabine</th>
<th>Venetoclax/Azacitidine</th>
<th>ITT Response (N = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>400 mg (n = 6)</td>
<td>800 mg (n = 12)</td>
<td>400 mg (n = 4)</td>
</tr>
<tr>
<td>ORR (CR/CRi/PR)</td>
<td>50</td>
<td>83</td>
<td>100</td>
</tr>
<tr>
<td>CR</td>
<td>33</td>
<td>17</td>
<td>75</td>
</tr>
<tr>
<td>CRi</td>
<td>17</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>MLFS</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>RD</td>
<td>17</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>33</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

NIVO or IPI ± AZA in MDS: Study Design

- Open-label, nonrandomized phase II study with 6 treatment cohorts

Pts aged 18 yrs or older with WHO MDS; ECOG PS ≤ 2; adequate organ function; no prior tx, or HMA failure*; no history of inflammatory or autoimmune disease or HIV; no active HCV infection (N = 54)

HMA Failure Cohorts†

<table>
<thead>
<tr>
<th>Cohort #1</th>
<th>Nivolumab 3 mg/kg IV Q2W (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort #2</td>
<td>Ipilimumab 3 mg/kg IV Q3W (n = 18)</td>
</tr>
<tr>
<td>Cohort #3</td>
<td>Nivolumab 3 mg/kg IV Q2W + Ipilimumab 3 mg/kg IV Q4W</td>
</tr>
<tr>
<td>Cohort #4</td>
<td>Azacitidine 75 mg/m² IV x 5d Q4W + Nivolumab 3 mg/kg IV D6, D20 (n = 21)</td>
</tr>
<tr>
<td>Cohort #5</td>
<td>Azacitidine 75 mg/m² IV x 5d Q4W + Ipilimumab 3 mg/kg IV D6</td>
</tr>
<tr>
<td>Cohort #6</td>
<td>Azacitidine 75 mg/m² IV x 5d Q4W + Nivolumab 3 mg/kg IV D6</td>
</tr>
</tbody>
</table>

Tx-Naive Cohorts

- Available for current analysis
- Not included in current analysis

*Last HMA cycle within 4 mos no other tx after HMA.
†AZA added if no response or progression after 6 cycles.

### NIVO or IPI ± AZA in MDS: Response

- **Median number of treatment cycles:** 3 (range: 1-11)

<table>
<thead>
<tr>
<th>Outcome, n (%)</th>
<th>HMA Failure</th>
<th>Treatment-Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivolumab (n = 15)</td>
<td>Ipilimumab (n = 18)</td>
</tr>
<tr>
<td>ORR</td>
<td>0</td>
<td>5 (28)</td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>1 (6)</td>
</tr>
<tr>
<td>mCR</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>No response</td>
<td>8 (53)</td>
<td>9 (50)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (40)</td>
<td>2 (11)</td>
</tr>
<tr>
<td>SD</td>
<td>1 (7)</td>
<td>NR</td>
</tr>
<tr>
<td>HI-N</td>
<td>NR</td>
<td>2 (11)</td>
</tr>
<tr>
<td>HI-P</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>TE</td>
<td>NR</td>
<td>2 (11)</td>
</tr>
</tbody>
</table>

APR-246 (PRIMA\textsuperscript{MET}) Restores Wild-type p53 Function

- Most \textit{TP53} gene mutations are single AA missense mutations in the DNA-binding domain
- APR-246 covalently binds to cysteines in mutant p53 or p63
- Reconstitutes WT conformation & function in mutant proteins by stabilizing protein folding
- Intrinsic & additive \textit{in vitro} schedule-dependent cytotoxicity with azacitidine

Phase Ib/II Study of APR-246 Combined with Azacitidine in *TP53* mutant MDS or AML

**TP53 mutant MDS/AML**

**APR d1-4 iv AZA d4-10**

**Response**
Continue APR + AZA

**Week:** 0

**Cycle q 28d x 6**

**Eligibility:** MDS, MDS/MPN or AML with mu-*TP53* & no prior azanucleoside therapy

**Dose reductions:** 67.5 mg/kg, level -1, 50.6 mg/kg, level -2, 33.8 mg/kg. If no DLT in 6 patients treated at dose level 1, proceed to Phase 2

**Primary endpoint:** proportion of patients alive at 6 months.

**Secondary endpoints:** safety & tolerance, IWG 2006 response rate

PI: Sallman D. Evan’s MDS Consortium.
Outcome After HMA Failure in Higher-Risk MDS is poor

<table>
<thead>
<tr>
<th>Institution</th>
<th>N</th>
<th>AZA Failures, n</th>
<th>AML Progression, n (%)</th>
<th>Median OS, Mos</th>
<th>OS at 12 Mos, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moffitt[^1]</td>
<td>151</td>
<td>59</td>
<td>12 (20.3)</td>
<td>5.8</td>
<td>30</td>
</tr>
<tr>
<td>GFM[^2]</td>
<td>435</td>
<td>NR</td>
<td>NR</td>
<td>5.6</td>
<td>29</td>
</tr>
<tr>
<td>MDACC[^3]</td>
<td>NR</td>
<td>87</td>
<td>25 (29)</td>
<td>4.3</td>
<td>28</td>
</tr>
</tbody>
</table>

*Includes AZA001, J9950, J0443 studies.
†Decitabine only.

Defining HMA failure

**Primary failure (lack of primary response) 25%**

- Clear evidence of disease progression on therapy or death on treatment
- Median OS 4.7 mo (Rigosertib study), 5.5 mo (MCC database)

**Secondary failure ≈ 75%**

- Loss of initial response or probably only stable disease after 9 cycles.
- Median OS 6.9 mo (MCC database)
- 25% AML progression at time of failure
Salvage Therapy After Azacitididine Failure: GFM and AZA001 Studies

*Log-rank comparison of BSC vs intensive CT ($P = .04$), investigational therapy ($P < .001$), or alloSCT ($P < .001$).
†Comparison of intensive CT vs investigational therapy ($P = .05$), intensive CT vs ASCT ($P = .008$), or IT vs ASCT ($P = .09$).

Prognostic models after HMA failure

<table>
<thead>
<tr>
<th>Parameter at HMA failure</th>
<th>Score</th>
<th>Beta</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECOG Performance status &gt; 1</td>
<td>1.0</td>
<td>0.56</td>
<td>0.01</td>
</tr>
<tr>
<td>Very poor Cytogenetic (complex karyotype &gt; 3 abnormalities)</td>
<td>1.0</td>
<td>0.57</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age at diagnosis, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 75 - ≤ 84</td>
<td>1.0</td>
<td>0.52</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>&gt; 84</td>
<td>2.0</td>
<td>0.90</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Bone Marrow Blast &gt; 20 %</td>
<td>0.75</td>
<td>0.36</td>
<td>0.01</td>
</tr>
<tr>
<td>Transfusion dependent (yes vs no)</td>
<td>0.75</td>
<td>0.39</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Platelets</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 30</td>
<td>1.0</td>
<td>0.54</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Nazha et al, Hematologica 2016
# New HMA

<table>
<thead>
<tr>
<th>Agent</th>
<th>mechanism</th>
<th>Preliminary results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CC-486</td>
<td>Oral azacitidine</td>
<td>• In phase I study, 41 patients received SC and oral azacitidine. Dose-limiting toxicity (grade 3/4 diarrhea) occurred at the 600-mg dose and MTD was 480 mg. <strong>Overall response rate was 35% in previously treated patients and 73% in previously untreated patients.</strong>&lt;br&gt;• In Phase 2, Patients with LR-MDS received 300 mg CC-486 once daily for 14 days (n=28) or 21 days (n=27) of repeated 28-day cycles. <strong>Overall response was attained by 36% of patients receiving 14-day dosing and 41% receiving 21-day dosing. RBC TI rates were similar with both dosing schedules (31% and 38%, respectively).</strong></td>
</tr>
<tr>
<td>SGI-110</td>
<td>dinucleotide of decitabine and deoxyguanosine that protects it from deamination</td>
<td>• In a phase I study that included 14 patients with MDSs after HMA failure, SGI-110 had a 4.5-fold longer half-life than decitabine. An equivalent or higher area under the curve was reached with lower Cmax compared with reference levels from intravenous decitabine.&lt;br&gt;• A dose-dependent increase in demethylation was observed up to 60 mg/m2 daily for 5 days.&lt;br&gt;• In the phase II part of the study for treatment-naive elderly patients with AML or refractory/relapsed AML, 43% and 16% remission rates were reported.</td>
</tr>
<tr>
<td>ASTX727</td>
<td>Fixed dose oral cytidine deaminase inhibitor E7727 with oral decitabine</td>
<td>• AEs are consistent with IV decitabine with no GI toxicity.&lt;br&gt;• <strong>ASTX727 is clinically active 33% response rate in phase I, 50% had prior HMA.</strong>&lt;br&gt;• The fixed oral dose of 30 mg decitabine and 100 mg E7727 results in decitabine AUC equivalent to 20 mg/m2 IV and will be further studied in a Phase 2 trial in HMA naive MDS.</td>
</tr>
</tbody>
</table>

---

**References:**

Garcia Manero et al, Leukemia 2016 Apr;30(4):889-96
Savona et al, ASH 2015, abstract # 1683
ONTIME Trial: Primary Efficacy Results – ITT

Medians:
- RIG: 8.2 mo
- BSC: 5.9 mo

Stratified log-rank P = 0.33
HR = 0.87 (95% CI: 0.67-1.14)

Median Overall Survival for Pts with Primary HMA Failure


Medians:
- RIG 8.6 mo
- BSC 5.3 mo

Stratified log-rank P = 0.040
HR = 0.69 (95% CI: 0.49-0.98)
ONTIME Trial: Conclusions

• Primary endpoint of OS did not reach statistical significance in the ITT population
  – 2.3-month improvement in median OS in the ITT population

• Rigosertib treatment-related improvement in OS was noted in the following well-balanced subgroups:
  – Primary HMA failure (64% of pts: HR = 0.69; p = 0.04)
  – IPSS-R Very High Risk (45% of pts: HR = 0.56; p = 0.005)
  – Cytogenetic criteria also important prognostic factors
    • Monosomy 7 (HR = 0.24; p = 0.003)
    • Trisomy 8 (HR = 0.34; p = 0.035)

• Continuous IV infusion with rigosertib had a favorable safety profile in this population of elderly pts with HR MDS

Therapeutic Targeting of Myeloid Malignancies with Spliceosome Gene Mutations by Synthetic Lethality

• splicing gene mutations are always heterozygous point mutations at specific residues
• This single amino acid change results in wide-spread aberrant mRNA splicing & non-sense decay
• Splicing gene mutations are mutually exclusive suggesting intolerance of further RNA splicing perturbations .

Lee SC, et. al. ASH 2015; 4a.
Therapeutic Targeting of Spliceosome Mutant Myeloid Malignancy by Synthetic Lethality

Lee S, et al., ASH 2015, Abstract # 4
E7107 Treatment Prolongs Survival of Srsf2-mutant AML

Established MLL-AF9 AML

Srsf2^{+/+}\hspace{5pt}

Srsf2^{P95H/+}

250,000 Cells/mouse

1x 450 Rad

C57BL/6 recipients

Day 8 Check Blood GFP (pre-Tx)

Treatment (10x doses)

Vehicle

E7107 (1mg/kg)

E7107 (4mg/kg)

Lee S, et al., ASH 2015, Abstract # 4
Phase I/II Study of H3B-8800 in Patients with Splicing Gene (SG) Mutant MDS & AML

Eligibility: LR-MDS (Low/Int1, RBC or platelet TD), HR-MDS (Int-2/High risk, HMA failure), CMML (1 prior thx), AML (R/R or not induction candidate) + SG mutation

Dose escalations: 0.5 mg, 1.0 mg, 2.0 mg, 3.5 mg, 5.0 mg, 7 mg daily

Primary endpoint: safety & tolerance; Expansion: response rate.
Enasidenib in m/DH2 MDS: Response

- 7 of 13 pts (54%) with prior HMA responded to enasidenib
- Median time to response: 21 days (range: 10-87)

<table>
<thead>
<tr>
<th>Response, n/N (%)</th>
<th>MDS Pts (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR*</td>
<td>10/17 (59)</td>
</tr>
<tr>
<td>CR†</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>PR†</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>mCR†</td>
<td>3/11 (27)</td>
</tr>
<tr>
<td>Any HI</td>
<td></td>
</tr>
<tr>
<td>▪ Erythrocytes</td>
<td>5/17 (29)</td>
</tr>
<tr>
<td>▪ Platelets</td>
<td>3/15 (20)</td>
</tr>
<tr>
<td>▪ Neutrophils</td>
<td>4/12 (33)</td>
</tr>
<tr>
<td>▪ Trilineage improvement</td>
<td>4/10 (40)</td>
</tr>
<tr>
<td>▪ Bilineage improvement</td>
<td>2/5 (40)</td>
</tr>
</tbody>
</table>

*CR + PR + mCR + HI.
†Investigator-assessed; pts had ≥ 5% BM blasts at BL.

Response to standard 3+7 Induction chemotherapy

<table>
<thead>
<tr>
<th>Institution</th>
<th>Response</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moffitt</td>
<td>9/24 (29%)</td>
<td>3</td>
</tr>
<tr>
<td>GFM</td>
<td>3/22 (14%)</td>
<td>8.9</td>
</tr>
<tr>
<td>MDACC</td>
<td>3/10 (30%)</td>
<td>?</td>
</tr>
</tbody>
</table>

CPX-351 Uses a Nano-Scale Delivery Complex

- 100 nm bilamellar liposomes
- 5:1 molar ratio of cytarabine to daunorubicin
- 1 unit = 1.0 mg cytarabine plus 0.44 mg daunorubicin

Phase 1 Data
- Fixed molar ratio maintained for 24 hours after final dose
- Drug exposure was maintained for 7 days
- CPX-351 had potent anti-leukemic efficacy
- CPX-351 was well-tolerated

Phase 3 Study of CPX-351 vs Standard Induction in Older Patients with Newly Diagnosed High-Risk (Secondary) AML

**Primary Endpoint:** Overall survival

- **Key Eligibility**
  - Previously untreated
  - Ages 60-75 years
  - Able to tolerate intensive therapy
  - PS 0-2

- **Stratifications:**
  - 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
  - 60-69 years
  - 70-75 years

- **Induction (1-2 cycles)**
  - Patients in CR or CRi:
    - CPX-351 n=153
    - First Induction
      - 100 units/m²
      - Days 1, 3 and 5
      - Cytarabine 100mg/m² x 7 d
      - Daunorubicin 60mg/m² x 3 d
    - Re-induction
      - 100 units/m²
      - Days 1 and 3
      - Cytarabine 100mg/m² x 5 d
      - Daunorubicin 60mg/m² x 2 d
    - Consolidation
      - 65 units/m²
      - Days 1 and 3
      - Cytarabine 100mg/m² x 5 d
      - Daunorubicin 60mg/m² x 2 d

- **Follow-up:**
  - Death OR
  - 5 years

---

*Lancet J. ASCO Annual Meeting. 2016 Abstract #7000*
Response Rates

Note: Percentages reflect number with endpoint out of column total. Odds ratios are calculated with the 7+3 arm as the reference group.

P-value is from a comparison of rates between treatment arms and is based on the Mantel-Haenszel test stratifying by age and AML type.

<table>
<thead>
<tr>
<th></th>
<th>CPX-351 (n=153)</th>
<th>7+3 (n=156)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR</strong> Patients (%)</td>
<td>37.3</td>
<td>25.6</td>
</tr>
<tr>
<td><strong>CR + CRi</strong> Patients (%)</td>
<td>47.7</td>
<td>33.3</td>
</tr>
</tbody>
</table>

Odds Ratio (95% Conf. Int.)

- CR: 1.69 (1.03, 2.78)
- CR + CRi: 1.77 (1.11, 2.81)

Lancet J. ASCO Annual Meeting. 2016 Abstract #7000
CPX-351 Improves Overall Survival

Kaplan-Meier Curve for Overall Survival

ITT Analysis Population

<table>
<thead>
<tr>
<th></th>
<th>Events/N</th>
<th>Median Surv. (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPX-351 7+3</td>
<td>104/153</td>
<td>9.56 (6.60, 11.86)</td>
</tr>
<tr>
<td></td>
<td>132/156</td>
<td>5.95 (4.99, 7.75)</td>
</tr>
</tbody>
</table>

Hazard Ratio = 0.69
p-value = 0.005
Proposal for HR-MDS Treatment Algorithm

P53 VAF > 40%
- Clinical trial
  - Decitabine
    - P53 clearance
      - AHSCT

P53 VAF < 20%
- TET-2 MT VAF > 10%/ASXL-1 WT
  - YES
    - AHSCT candidate
  - NO
    - HMA
      - Cytopenia/Myeloblasts > 10%
        - YES
          - HMA prior to AHSCT
        - NO
          - Observe prior to AHSCT

- Prior response or no prior HMA
- Loss of CD33 donor chimerism

? AHSCT at time of HMA failure
Acknowledgement

Patients and caregivers

Moffitt MDS Program
Alan List
Eric Padron
Jeffrey Lancet
David Sallman
PK Burnette
Sheng Wei
Dana Rollison
Najla Al Ali
Lisa Nardelli

MDS Clinical Consortium
Edward P Evans Foundation
Aplastic Anemia and MDS Foundation

Rami.komrokji@moffitt.org