Beyond Hypomethylating Agents:

Combination Therapies in MDS

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Director, Leukemia Program

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Beyond HMAs | Agenda

- Predicting Responders to HMAs
- Combinations – Lower-risk
- Combinations – Higher-risk
- Conclusions
Beyond HMAs | Agenda

- Predicting Responders to HMAs
- Combinations – Lower-risk
- Combinations – Higher-risk
- Conclusions
Beyond HMAs  |  Mutation Risk

Driver genes can be classified into molecular subtypes differentially associated with disease severity

Somatic mutations may predict response or resistance to HMA:

- \textit{TET2} mutations may predict response
- \textit{ASXL1} may predict resistance
- \textit{TP53} mutations may predict response

Challenges with these data:

- Response might be higher but the mutation is not a biomarker
- Genomic data are complex

Nazha A, et al. JCO Prec Oncol 2019;3
Beyond HMAs | Mutations/Response
Beyond HMAs | Mutations/Response

Patient 1
- ASXL1
- TET2
- RUNX1

Patient 2
- TP53
- RCOR
- SRSF2

HMA Response

HMA Resistance

Nazha A, et al. JCO Prec Oncol 2019;3
Beyond HMAs | Mutations/Response

Responders

Non-Responders

N = 433 Patients treated with HMAs  Validated in 113 Patients enrolled in S1117

Nazha A, et al. JCO Prec Oncol 2019;3
Beyond HMAs | Mutations/Response

Results: Association Rules

**Training**

<table>
<thead>
<tr>
<th>Association Rules (Resistance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1, NF1</td>
</tr>
<tr>
<td>ASXL1, EZH2, TET2</td>
</tr>
<tr>
<td>ASXL1, EZH2, RUNX1</td>
</tr>
<tr>
<td>EZH2, SRSF2, TET2</td>
</tr>
<tr>
<td>ASXL1, EZH2, SRSF2</td>
</tr>
<tr>
<td>ASXL1, RUNX1, SRSF2</td>
</tr>
<tr>
<td>ASXL1, TET2, SRSF2</td>
</tr>
<tr>
<td>ASXL1, BCOR, RUNX1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Association Rules (Response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2, RUNX1, SRSF2</td>
</tr>
</tbody>
</table>

- 31% pts
  - ≥ 3 mutations/sample
- 29% pts
  - Very Low/Low risk by IPSS-R
- ORR to HMAs = 43%
- Median # mutations per patient = 3 (range, 0-9)

Accuracy: 87%

Nazha A, et al. JCO Prec Oncol 2019;3
### Group Median OS (m)

<table>
<thead>
<tr>
<th>Group</th>
<th>Median OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 3 mut/sample</td>
<td>28.2</td>
</tr>
<tr>
<td>( \geq 3 ) mut/sample w/o rules (69%)</td>
<td>22.8</td>
</tr>
<tr>
<td>( \geq 3 ) mut/sample w rules (31%)</td>
<td>14.6</td>
</tr>
</tbody>
</table>

**Beyond HMAAs | Mutations/Response**

Nazha A, et al. JCO Prec Oncol 2019;3
Beyond HMAs | Agenda

- Predicting Responders to HMAs
- **Combinations – Lower-risk**
- Combinations – Higher-risk
- Conclusions
Lower-risk MDS | Ameliorating Anemia: LEN

Key inclusion criteria
- Centrally reviewed IPSS Low or Int-1-risk MDS with karyotypes other than del(5q)
- RBC-TD
- Unresponsive or refractory to ESAs

Pretreatment

Double-blind (DB) treatment

Off-treatment

Matching placebo

LEN 10 mg, orally, QD

RBC-TI ≥ 8 weeks or erythroid response

Long-term follow-up (≥ 5 years from randomization)
- Overall survival
- AML progression
- Subsequent MDS treatments
- SPMs

Discontinue DB phase

W 24

Santini et al. JCO 2016;34:2988
Significantly more LEN patients achieved RBC-TI ≥ 8 weeks versus placebo ($P < 0.001$)

Santini et al. JCO 2016;34:2988
List et al, Abstract 824: Combined Treatment with Lenalidomide and Epoetin Alfa in Epo refractory Non-Deletion 5q [Del(5q)] MDS: E2905 Phase III Study

- Randomized Phase III low risk non-del(5q) ESA resistant or high endogenous EPO level (>500).
- Len 10 mg/day * 21 versus Len plus EPO 60K/week
- 205 patients randomized - 14 not treated due to EPO shortage
- Median transfusion burden 4 U/8 weeks
- 93% prior ESA; 18% prior DNMTi

AF List et al. ASH 2019; Abstract 824
**LEN +/- EPO**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Lenalidomide plus EPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>96</td>
<td>99</td>
</tr>
<tr>
<td>Major Erythroid Response</td>
<td>11 (11.5%)</td>
<td>28 (28.3%)</td>
</tr>
</tbody>
</table>

**After 16 weeks of therapy**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide</th>
<th>Lenalidomide plus EPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>64</td>
<td>73</td>
</tr>
<tr>
<td>Major Erythroid Response</td>
<td>10 (16%)</td>
<td>28 (39%)</td>
</tr>
</tbody>
</table>

**CROSSOVER To COMBO**

| Major Erythroid Response | 11/44              |

**Duration of MER**

<table>
<thead>
<tr>
<th>Median (months)</th>
<th>Lenalidomide</th>
<th>Lenalidomide plus EPO</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

AF List et al. ASH 2019; Abstract 824
Fenaux et al, Luspatercept: RBC-TI ≥ 8 weeks Achieved any time during treatment period

Patients Achieving RBC-TI ≥ 8 Weeks Any Time During the Treatment Period (%)

- Luspatercept (n = 153): 47.7%
- Placebo (n = 76): 15.8%

\[ P < 0.0001^a \]
\[ \text{OR (95\% CI)}^a: 5.978 \ (2.840–12.581) \]

Fenaux et al. ASH 2019, Abstract 841
## The L2 Regimen

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Lenalidomide Schedule</th>
<th>Luspatercept Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5 mg PO days 1-21</td>
<td>1.0 mg/kg day 1</td>
</tr>
<tr>
<td>2</td>
<td>5 mg PO days 1-21</td>
<td>1.33 mg/kg SC day 1</td>
</tr>
<tr>
<td>3</td>
<td>5 mg PO days 1-21</td>
<td>1.75 mg/kg SC day 1</td>
</tr>
</tbody>
</table>

**Phase IB/II**
Lower-risk, Non-Del(5q)
N = 40
Beyond HMAs | Agenda

- Predicting Responders to HMAs
- Combinations – Lower-risk
- **Combinations – Higher-risk**
- Conclusions
Log-Rank  $p=0.0001$

$HR = 0.58 \ [95\% \ CI: 0.43, 0.77]$

$\text{ORR}=35\%$

50.8%

24.4 months

15 months

26.2%

AZA

CCR

Median OS 10.1 vs. 8.5 months

ECOG E1905

Eligible patients (no prior azacitidine):

• **MDS** (higher risk; if IPSS low/INT-1 risk, then platelets <50 x 10^9/L or ANC<500)
• **CMML** with WBC <12 x 10^9/L
• **AML** with multilineage dysplasia and WBC ≤30 x 10^9/L for ≥4 weeks

**Primary Endpoint:**

IWG 2000 responses with hematological normalization (CR+PR+trilineage HI)

Azacitidine SC 50 mg/m² x 10 days every 28 days, plus Entinostat (MS-275) 4 mg/m² PO days 3 and 10 each cycle

Prebet et al. JCO 2014;32:1242
# E1905 study results

<table>
<thead>
<tr>
<th>Response / AE</th>
<th>Arm A (n=68) (azacitidine monotherapy)</th>
<th>Arm B (n=68) (combination therapy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response (CR)</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Trilineage hematological improvement (tHI)</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Qualifying Response (CR+PR+tHI)</td>
<td>31%</td>
<td>24% (p=NS)</td>
</tr>
<tr>
<td>Other hematological improvement</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>Any response</td>
<td>43%</td>
<td>44%</td>
</tr>
<tr>
<td>Grade IV thrombocytopenia</td>
<td>44%</td>
<td>63% (p=0.07)</td>
</tr>
<tr>
<td>Grade III/IV fatigue</td>
<td>13%</td>
<td>23% (p=0.13)</td>
</tr>
</tbody>
</table>
Aza + Pracinostat in MDS: Study Design

- Intermediate Risk-2 or High Risk MDS Patients Previously Untreated w/ HMA

  - Pracinostat + Azacitidine
  - Placebo + Azacitidine

- 102 evaluable patients: one-to-one randomization
- Azacitidine: 75 mg/m² 7 days I.V./sq every 28 days
- Pracinostat or placebo P.O. 60 mg 3 days/week for 3 weeks
- Cycles repeated every 28 days until disease progression, lack of benefit, or intolerance

## Aza + Pracinostat in MDS: Summary of Response

<table>
<thead>
<tr>
<th>Best Response</th>
<th>Pracinostat</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Remission</td>
<td>20%</td>
<td>33%</td>
</tr>
<tr>
<td>Partial Remission</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Marrow CR</td>
<td>28%</td>
<td>22%</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>26%</td>
<td>29%</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>22%</td>
<td>10%</td>
</tr>
<tr>
<td>CR, within 180 days</td>
<td>18%</td>
<td>33%</td>
</tr>
</tbody>
</table>
## Aza + Pracinostat in MDS: Summary of Response

<table>
<thead>
<tr>
<th>RESPONSE</th>
<th>Pracinostat</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological improvement</td>
<td>35%</td>
<td>55%</td>
</tr>
<tr>
<td>Erythroid response (HI – E)</td>
<td>28%</td>
<td>45%</td>
</tr>
<tr>
<td>Platelet response (HI – P)</td>
<td>31%</td>
<td>53%</td>
</tr>
<tr>
<td>Neutrophil response (HI – N)</td>
<td>26%</td>
<td>39%</td>
</tr>
<tr>
<td>Clinical benefit rate (CR + PR + HI + mCR)</td>
<td>53%</td>
<td>63%</td>
</tr>
<tr>
<td>Cytogenetic response</td>
<td>42%</td>
<td>55%</td>
</tr>
<tr>
<td>Cytogenetic CR</td>
<td>24%</td>
<td>29%</td>
</tr>
<tr>
<td>Cytogenetic PR</td>
<td>18%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Higher-risk MDS or CMML

(IPSS ≥1.5 and/or blasts ≥5%)

- **AZA (IV/SC)**
  - 75 mg/m²/d (d1-7)
  - N=92

- **AZA (IV/SC) + LEN (PO)**
  - 75 mg/m²/d (d1-7) + 10mg/d x 21d
  - N=93

- **AZA (IV/SC) + Vorin (PO)**
  - 75 mg/m²/d (d1-7) + 300mg BID (d3-9)
  - N=92

Groups: SWOG, ECOG, Alliance, NCIC

Total Sample Size: 282/277

Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria

Secondary Objectives: OS, RFS, LFS

Power 81%, alpha 0.05 for each combo arm vs. AZA

06/2012 – 06/2014

## Higher-risk MDS | Combinations

<table>
<thead>
<tr>
<th>Variable</th>
<th>AZA</th>
<th>AZA+LEN</th>
<th>AZA+VOR</th>
<th>Total n=277</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs, range)</td>
<td>69 (42, 88)</td>
<td>70 (51, 86)</td>
<td>70 (28, 93)</td>
<td>70 (28, 93)</td>
</tr>
<tr>
<td>Female</td>
<td>31 (34)</td>
<td>32 (34)</td>
<td>22 (24)</td>
<td>81 (31)</td>
</tr>
<tr>
<td>CMML</td>
<td>18 (20)</td>
<td>19 (20)</td>
<td>16 (18)</td>
<td>53 (19)</td>
</tr>
<tr>
<td>tMDS</td>
<td>7 (8)</td>
<td>6 (6)</td>
<td>5 (5)</td>
<td>19 (7)</td>
</tr>
<tr>
<td>Baseline ANC (x10^3)</td>
<td>2 (0, 110)</td>
<td>1 (0, 336)</td>
<td>2 (0, 36)</td>
<td>2 (0, 336)</td>
</tr>
<tr>
<td>Baseline Platelet count (x10^3)</td>
<td>70 (8, 4000)</td>
<td>75 (3, 452)</td>
<td>62 (3, 1462)</td>
<td>68 (3, 4000)</td>
</tr>
<tr>
<td>Baseline Median Blast %</td>
<td>8 (0, 22)</td>
<td>10 (0, 20)</td>
<td>10 (1, 18)</td>
<td>9 (0, 22)</td>
</tr>
</tbody>
</table>

### Higher-risk MDS | Combinations

<table>
<thead>
<tr>
<th>Toxicity Variable</th>
<th>AZA</th>
<th>AZA+LEN (P-value vs. AZA)</th>
<th>AZA+VOR (P-value vs. AZA)</th>
<th>Total n=271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia (n)</td>
<td>10</td>
<td>13 (.66)</td>
<td>12 (.51)</td>
<td>36</td>
</tr>
<tr>
<td>GI (n)</td>
<td>4</td>
<td>12 (.10)</td>
<td><strong>14 (.02)</strong></td>
<td>28</td>
</tr>
<tr>
<td>Rash (n)</td>
<td>3</td>
<td><strong>14 (&lt;.01)</strong></td>
<td>1 (1)</td>
<td>17</td>
</tr>
<tr>
<td>Off Tx due to Toxicity/Side Effect/Complication</td>
<td>8%</td>
<td><strong>20% (.05)</strong></td>
<td><strong>21% (.03)</strong></td>
<td>18%</td>
</tr>
<tr>
<td>Non-protocol defined dose modifications</td>
<td>24%</td>
<td><strong>43% (.002)</strong></td>
<td><strong>42% (.01)</strong></td>
<td>33%</td>
</tr>
</tbody>
</table>

## Higher-risk MDS | Combinations

<table>
<thead>
<tr>
<th>Response Variable</th>
<th>AZA</th>
<th>AZA+LEN (P-value vs. AZA)</th>
<th>AZA+VOR (P-value vs. AZA)</th>
<th>Total n=277</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Tx Duration (Wks)</td>
<td>25</td>
<td>24</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Overall Response Rate (%)</td>
<td>38</td>
<td>49 (.16)</td>
<td>27 (.16)</td>
<td>38%</td>
</tr>
<tr>
<td>CR/PR/HI (%)</td>
<td>24/0/14</td>
<td>24/1/25</td>
<td>17/1/9</td>
<td>22/1/16%</td>
</tr>
<tr>
<td>CMML ORR (%)</td>
<td>5 (28)</td>
<td>13 (68) (.02)</td>
<td>2 (12) (.41)</td>
<td>37%</td>
</tr>
<tr>
<td>ORR Duration (median)</td>
<td>10 months</td>
<td>14 months (.41)</td>
<td>15 months (.31)</td>
<td>14 months</td>
</tr>
<tr>
<td>CMML ORR Duration (median)</td>
<td>15 months</td>
<td>14 months (.87)</td>
<td>24 months (.69)</td>
<td>15 months</td>
</tr>
</tbody>
</table>

Higher-risk MDS | Combinations

Overall Survival

Aza vs Aza+Len log-rank p = 0.55
Aza vs Aza+Vor log-rank p = 0.1
Aza vs Combo arms log-rank p = 0.2

Comparisons are between combination arms and AZA monotherapy

Higher-risk MDS | Combinations

Overall Survival After Failure

- Aza
- Aza+Len
- Aza+Vor

Aza vs Aza+Len log-rank p = 0.72
Aza vs Aza+Vor log-rank p = 0.031
Aza vs Combo arms log-rank p = 0.14

Survival probability vs Weeks since failure

N at risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>83</th>
<th>44</th>
<th>29</th>
<th>17</th>
<th>7</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aza</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aza+Len</td>
<td>84</td>
<td>46</td>
<td>31</td>
<td>20</td>
<td>8</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Aza+Vor</td>
<td>86</td>
<td>58</td>
<td>36</td>
<td>20</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

Higher-risk MDS | Targeting TP53

APR-246 binds covalently to p53...

...restores wt p53 conformation & activity...

...and triggers cell cycle arrest and apoptosis


Median duration of follow-up = 10.8 months

Wei et al, Abstract 568 – AZA plus Venetoclax for HR-MDS

- Phase 1b study
- Untreated *de novo* MDS, IPSS Int-2 or high risk, not planning intensive chemo or transplant
- Ven days 1-14 (400 mg/day, no ramp up)
  - Prophylactic antimicrobials required
- 57 patients
  - Med Age 71 (26-85);
  - IPSS-R very high risk: 60%
Wei et al, Abstract 568 – AZA plus Venetoclax for HR-MDS: Response Rates

Excludes patients of arm C (Aza only); Objective response rate (ORR) includes [complete remission (CR) + marrow complete remission (mCR) + partial remission (PR)]; # of patients with PR=0; per IWG (Cheson et al., Blood/2006;108:419-425)

DoR: Duration of response; HI: hematological improvement; HI-E: hematologic improvement in erythroids; HI-N: hematologic improvement in neutrophils; HI-P: hematologic improvement in platelet count; n: patients with favorable outcomes; N: patients eligible for evaluating outcomes

Median time to CR, months (range) 2.2 (1.2-11.1)

12-mo estimate of DoR after CR, % (95% CI) 83.3 (2.3, 97.5)

mCR with HI (HI-E, HI-P or HI-N), n/N (%) 10/22 (45.5)
Abstract 569 – AZA plus Magrolimab for HR-MDS

• CD47 is a macrophage immune checkpoint and "Do Not Eat Me" signal in MDS
• Magrolimab targets CD47 and synergizes with AZA in preclinical models
• Phase 1b study
• Untreated MDS, IPSS-R intermediate or higher risk disease
  – Magro dose ramp up to 30mg/kg weekly in C1 to mitigate on-target anemia
  – AZA given at standard 75mg/m2 D1-7 doses
• 35 patients
  – Med Age 70 (47-80);
  – IPSS-R high or very high risk disease: 65%
• Safety profile consistent with AZA monotherapy; on-target anemia seen but mitigated with ramp up (median Hgb drop 0.4 g/dL with first dose)

Sallman et al. ASH 2019 Abstract #569.
### AZA plus Magrolimab for HR-MDS – Preliminary Efficacy

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1L MDS N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>12 (50%)</td>
</tr>
<tr>
<td>CRI</td>
<td>-</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
</tr>
<tr>
<td>MLFS/marrow CR</td>
<td>8 (33%)</td>
</tr>
<tr>
<td></td>
<td>4 with marrow CR + HI</td>
</tr>
<tr>
<td>Hematologic improvement (HI)</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>SD</td>
<td>2 (8%)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
</tr>
<tr>
<td>RBC transfusion independence¹</td>
<td>4/9 (44%)</td>
</tr>
<tr>
<td>Complete cytogenetic response in responders²</td>
<td>5/19 (26%)</td>
</tr>
<tr>
<td>MRD negativity in responders</td>
<td>5/22 (23%)</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>Not reached (0.03+ – 9.76+)</td>
</tr>
<tr>
<td>Median follow-up [range] (months)</td>
<td>6.4 [2.0 – 14.4]</td>
</tr>
</tbody>
</table>

Med OS not reached
5 patients received allogeneic HSCT

Sallman et al. ASH 2019 Abstract #569.
BRIGHT MDS & AML 1012 Study Design

- BRIGHT MDS & AML 1012 (NCT02367456) is an ongoing open-label, multicenter, phase 1b trial
- Key eligibility criteria:
  - Patients were aged ≥18 years
  - Newly diagnosed AML, higher-risk MDS, and CMML
  - Clinical indication for treatment with AZA for AML or MDS
  - No prior treatment with a Smoothened inhibitor and/or a hypomethylating agent

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML cohort (n=30) • De novo or secondary AML</td>
<td>Glasdegib + AZA • Glasdegib 100 mg once daily • AZA (75 mg/m²/day) on Days 1–7 of a 28-day cycle</td>
<td>Primary • Rate of CR</td>
</tr>
<tr>
<td>MDS cohort (n=30) • MDS (intermediate, high, or very high risk by IPSS-R) or CMML</td>
<td></td>
<td>Secondary • Overall survival • Disease-specific efficacy measures • Time to and duration of CR • Safety • Pharmacokinetic analysis</td>
</tr>
</tbody>
</table>


AML=acute myeloid leukemia; AZA=azacitidine; CMML=chronic myelomonocytic leukemia; CR=complete remission; IPSS-R=Revised International Prognostic Scoring System; MDS=myelodysplastic syndrome
MDS Cohort: Overall Survival With Best Overall Response

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>4 (13.3)</td>
</tr>
<tr>
<td>PR</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>HI without CR or PR</td>
<td>3 (10.0)</td>
</tr>
<tr>
<td>CR + PR + HI without CR or PR</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>mCR</td>
<td>5 (16.7)</td>
</tr>
<tr>
<td>SD</td>
<td>8 (26.7)</td>
</tr>
</tbody>
</table>

**AZA=azacitidine; BOR=best overall response; CMML=chronic myelomonocytic leukemia; CR=complete remission; EOT=end of treatment; HI=hematologic improvement; mCR=marrow complete remission; MDS=myelodysplastic syndrome; PD=progressive disease; PR=partial remission; SD=stable disease**
MDS Cohort: Preliminary Overall Survival

**All Patients**

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>30</th>
<th>29</th>
<th>28</th>
<th>27</th>
<th>26</th>
<th>23</th>
<th>22</th>
<th>19</th>
<th>18</th>
<th>9</th>
<th>8</th>
<th>8</th>
<th>7</th>
<th>7</th>
<th>4</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Events (%)</td>
<td>Glas + AZA</td>
<td>10/30 (33.3)</td>
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<tr>
<td>mOS (95% CI), mo</td>
<td>15.8 (9.3–NE)</td>
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</tbody>
</table>

**IPSS-R Genetic Risk Category**

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<th>No. at risk</th>
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<th>4</th>
<th>3</th>
<th>3</th>
<th>3</th>
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<th>3</th>
<th>2</th>
<th>2</th>
<th>2</th>
<th>2</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Events (%)</td>
<td>Intermediate</td>
<td>0/4 (0)</td>
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<td>mOS (95% CI), mo</td>
<td>NE (NE–NE)</td>
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<tr>
<td></td>
<td>High</td>
<td>4/14 (28.6)</td>
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<tr>
<td>mOS (95% CI), mo</td>
<td>NE (4.7–NE)</td>
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<tr>
<td></td>
<td>Very high</td>
<td>5/9 (55.6)</td>
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<tr>
<td>mOS (95% CI), mo</td>
<td>15.8 (0.5–NE)</td>
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</tbody>
</table>

*Risk category based on 27 MDS patients alone.*

AZA = azacitidine; CI = confidence interval; Glas = glasdegib; IPSS-R = Revised International Prognostic Scoring System; MDS = myelodysplastic syndrome; mo = months; mOS = median overall survival; NE = not evaluable
Beyond HMAs | **Other Combos**

- AZA + Checkpoint inhibitors
- AZA + Other HDAC-I
- AZA + Pevonedistat
- AZA + IDHi (or IDHi alone)
- AZA + mAb (or mAb alone)
- AZA + Rigosertib

(or DAC + any of the above)
Beyond HMAs | Agenda

- Predicting Responders to HMAs
- Combinations – Lower-risk
- Combinations – Higher-risk
- Conclusions
Beyond HMAs | Conclusions

- Predicting response to HMAs coming of age
- Combos in lower-risk MDS focused on anemia
- Combos in higher-risk take different mechanism of action approaches or on genetics

Our drugs fail our patients! Our patients don’t fail our drugs.
Thanks!!!

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And Our Patients!!!

April 2020!