Myelodysplastic Syndromes:
Patient Forum

Michael Keng, MD
December 15, 2018

MDS: Overview

- Epidemiology and “Staging”
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease
- Clinical Trials and Future Directions
- Conclusions

MDS: Epidemiology and Staging

- A heterogeneous clonal hematopoietic
disorder derived from an abnormal
multipotent progenitor cell

- Characterized by a hyperproliferative
bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis

**MDS is a Cancer!!!**

Disclosures

- Agios – Advisory Board

MDS: Epidemiology and Staging

- Shared features:
  - Ineffective differentiation and low blood counts
  - Clonal expansion of abnormal cells
  - Risk of transformation to acute leukemia

- Afflicts 15,000 – 45,000 people annually

- Incidence rises with age (mean age 71)
**MDS Staging: Epidemiology**

Cross-sectional analysis of 4514 MDS patients in the U.S. in 2005-7

<table>
<thead>
<tr>
<th>Age (Median)</th>
<th>Newly diagnosed</th>
<th>71 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Established</td>
<td>72-73 years</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sex (Mean)</th>
<th>Male (Newly diagnosed)</th>
<th>55%</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Established)</td>
<td>51-57%</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Duration of MDS (Median)</th>
<th>13-16 months</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>MDS Status</th>
<th>Primary</th>
<th>88 - 93%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Secondary</td>
<td>7 - 12%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Cause</th>
<th>Chemotherapy</th>
<th>55 - 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>6 - 21%</td>
<td></td>
</tr>
<tr>
<td>Chemical exposure</td>
<td>2 - 9%</td>
<td></td>
</tr>
</tbody>
</table>

Sekeres et al. J National Cancer Inst 2008;100:1542

**MDS Staging: Epidemiology**

Median age ~71 years; increased risk with aging

Peaks 5-7 years following exposure

Peaks 1-3 years following exposure

*Sekeres et al. J National Cancer Inst 2008;100:1542*

**MDS Staging: Epidemiology**

**MDS Staging: Epidemiology**

**Environmental**

**Inborn**

AGING

- Exposure to DNA alkylating agents (chlorambucil, melphalan, cyclophosphamide)
- Exposure to topoisomerase II inhibitors (etoposide, anthracyclines)
- Exposure to ionizing radiation
- Environmental / occupational exposures (hydrocarbons etc.)

Antecedent acquired hematological disorders

- Aplastic anemia (15-20%)
- PNH (5-25%)

Fanconi anemia

Familial Platelet Disorder with AML (Fanconi-Anemia, "FPD-AML") (RUNX1, CEBA)

Topoisomerase II inhibitors

Medullary carcinoma

Myelodysplastic Syndromes (MDS)

Myeloproliferative Neoplasms

T-GL

For MDS diagnosis, you will need:

- Bone Marrow Aspirate/Biopsy
- Complete Blood Count with white cell differential
- Karyotype (chromosome analysis)

Additionally:

- MDS FISH panel and Flow cytometry
- Genetic Testing

*Slide by Dr. David Steensma*
Cytopenia(s):

- Hb < 11 g/dL, or
- ANC < 1.5 X 10^9/L, or
- Platelets < 100 X 10^9/L

MDS “Decisive” criteria:

- > 10% dysplastic cells in 1 or more lineages, or
- 5-19% blasts, or
- Abnormal karyotype typical for MDS, or
- Evidence of clonality (by FISH or another test)

Other causes of cytopenia and morphological changes EXCLUDED:

- Vitamin B12/folate deficiency
- HIV or other viral infection
- Copper deficiency
- Alcohol abuse
- Medications (esp. methotrexate, azathioprine, recent chemotherapy)
- Autoimmune conditions (ITP, Felty syndrome, SLE etc.)
- Congenital syndromes (Fanconi anemia etc.)
- Other hematological disorders (aplastic anemia, LGL disorders, MPN etc.)

MDS Staging:

**Diagnosis**

- **Milestone Characteristics & Treatment**


**MDS Staging: IPSS**

**Calculation of Prognostic Score**

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM Blast %</td>
<td>&lt; 5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-29</td>
<td></td>
</tr>
<tr>
<td>Cyto genetics</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Estimation of Prognosis**

<table>
<thead>
<tr>
<th>Overall Score</th>
<th>IPSS Subgroup</th>
<th>Median Survival (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Intermediate-1</td>
<td>3.3</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>&gt; 2.5</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Cytopenias:

- ANC < 1.5 X 10^9/L
- HGB < 10.0
- PLT < 100,000

Good Risk:

- [Ydel/iso, del(20q), Nl];

Intermediate Risk:

- [8+, other];

Poor Risk:

- [Chr. 7 abn, > 3 abn]


MDS: Epidemiology and Staging

- IPSS Refinement - IPSS-R

- Gene mutations

- WHO Revision

- WHO FDA Approval

- FAB

- IWG Criteria

- Prognostic Score

- Reclassification - Gene mutations

- 2016 - Revised (FAB)

MDS: Epidemiology and Staging

- NCCN Guidelines Version 2.2019
- Myelodysplastic Syndromes

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- ANC < 1.5 X 10^9/L
- HGB < 10.0
- PLT < 100,000

Good Risk:

- [Ydel/iso, del(20q), Nl];

Intermediate Risk:

- [8+, other];

Poor Risk:

- [Chr. 7 abn, > 3 abn]

### MDS Staging: IPSS-R Prognostic Score

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>V. Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>V. Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast %</td>
<td>≤2</td>
<td>&gt;2-5%</td>
<td>5-10%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8-10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-100</td>
<td>50</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>≤0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**IPSS-R Prognostic Risk Categories/Scores**

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>Risk Score</th>
<th>Median Survival (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>≤1.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3.0</td>
<td>5.3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3.0-4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5-6.0</td>
<td>1.6</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;6.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>


### MDS Prognosis Made Easy!!!

- **Lower Risk**
  - RA, RARS
  - RCMD, RCUD
  - MDS-U, MDS del (5q)
  - IPSS Low, Int-1 (0-1.0); IPSS-R V. Low, Low

- **Higher Risk**
  - RAEB (-1, -2)
  - IPSS Int-2, High (≥ 1.5); IPSS-R High, V. High

### MDS Staging: Prognosis

#### Asymptomatic

- Bone Marrow Function
- Observation
- Epo/G-CSF
- Lenalidomide
- Azacitidine
- Decitabine
- Investigational
- 5q-
- Azacitidine
- Decitabine
- Investigational

- Intensive Chemotherapy
- RIC SCT - Full Ablative

#### Symptomatic

- Transfusion
- Symptomatic

### MDS: Overview

- Epidemiology and “Staging”
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease
- Clinical Trials and Future Directions
- Conclusions

### MDS: Lower-Risk Treatment Algorithm

Sekeres and Gerds Hematology 2014.

### MDS: Lower-Risk Treatment Algorithm

Sekeres and Gerds Hematology 2014.
### MDS: Lower-Risk Treatment Algorithm

**Anemia**
- Packed red blood cells
  - Adverse effects due to immune mechanisms
  - Iron overload
  - Volume overload

**Neutropenia**
- Granulocyte transfusion
  - Laborious, short-lived effect
  - Not widely available
  - Clinical utility unproven

**Thrombocytopenia**
- Platelet transfusion
  - Transfusion reactions, HLA sensitization

### MDS: Lower-Risk ESA Response Rate

**Patient diagnosed with lower-risk MDS per IPSS (FAB, 1985-2005)**

- **Good response (74%, n=34)**
  - s-epo $<100$
  - U/L $100-500$
  - $>500$
  - Transf $<3$ units/m
  - U RBC/m $= or >2$ units/m

- **Intermediate response (23%, n=31)**

- **Poor response (7%, n=29)**

**RA, RARS, RAEB**

**Score > +1**
- **Score -1 to +1**
- **Score < -1**

### MDS: Lower-Risk ESA Patient Selection

**Blood Transfusion Reactions, HLA Sensitization**

**Iron Overload**

**Volume Overload**

**Transfusion Therapy**

**Platelet Transfusion**

**Red Cell Growth Factors**

**ESAs**

**Epoetin alfa (Procrit™)**

**Darbepoetin alfa (Aranesp™)**

**Filgrastim, G-CSF (Neupogen™)**

**Pegfilgrastim (Neulasta™)**

**Romiplostim (NPLate™)**

**Eltrombopag (Promacta™)**

**Transfusion Reactions**

**Laborious, short-lived effect**

**Not widely available**

**Clinical utility unproven**

**Adverse effects due to immune mechanisms**

**Medicare only pays for these if Hb <10 g/dL**

**Safety concerns in solid tumors**, not yet in MDS

**White cell growth factors**

**No survival benefit but may help decrease infx.**

**Sometimes combined with red cell factors**

**Platelet growth factors**

**New; risks still being defined in MDS. Reports of increased blasts in a few patients**

**Only FDA-approved for immune thrombocytopenia and AA**

**ESAs RR ~40%**

**Golshayan et al. Br J Haem 2007;137:125.**

**MDS: Lower-Risk ESA Response Rate**

**N = 1587 (1985-2005)**

**Growth factors**

**EPO**

**EPO + G-CSF**

**GM-CSF**

**G-CSF**

**ESAs Response Rate**

**Duration of response (median months, range)**

**Response rate CR/PR HL-E HI/SF**

**RA, RARS, RAEB**

**Score > +1**
- **Score -1 to +1**
- **Score < -1**

**Overall Survival by Treatment**

**MDS ≤ RAEB-1, Hgb < 9.5, plt >30,000. Fe RR 34% for ESA vs. 8.8% SC p=0.001**

**Crossover allowed after 4 months**

**No difference in Leukemic transformation**

**Responders lived longer than non-responders**

MDS: Lower-Risk Treatment Algorithm

Sekeres and Gerds Hematology 2014

MDS: Lower-Risk Lenalidomide


MDS: Lower-Risk Lenalidomide in del(5q)


MDS: Lower-Risk Lenalidomide in Non-del(5q)


MDS: Lower-Risk Lenalidomide in Non-del(5q)

MDS: Lower-Risk
Lenalidomide in Non-del(5q)

MDS-002/003: Treatment-Related Adverse Events

<table>
<thead>
<tr>
<th>Grade ≥ 3 Adverse Events, %</th>
<th>Non-del(5q)</th>
<th>del(5q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>20</td>
<td>44</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Rash</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>


Grade ≥ 3 Adverse Events, %

- Thrombocytopenia
- Neutropenia
- Rash
- Diarrhea
- Fatigue

MDS: Lower-Risk
Lenalidomide Summary

- MDS-004/005 confirmed results of MDS-003/002
  - Efficacy of 10 mg comparable between studies
    - Transfusion independence by IWG (61% vs 67%)
  - MDS-004 supports 10 mg as appropriate starting dose
    - Higher TI for 10 mg
    - Mean duration of TI: 106 wks
    - Greater proportion of cytogenetic responses vs 5 mg (42% vs 17%)
- No significant differences in hematological toxicity
- The rate of transformation to AML is comparable to the literature
- MDS-002/005 provided evidence that lenalidomide could be a choice for anemia treatment in lower-risk non-del(5q) pts with adequate platelets and neutrophil count
- Lenalidomide mechanism of action is karyotype dependent, suppressing the clone in del(5q) and promoting erythropoiesis in non-del(5q)


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**MDS: Lower-Risk**

**TPO Agonists**

**Hi-P: Development Cohort**

<table>
<thead>
<tr>
<th>Baseline TPO:</th>
<th>Score +3 (N = 69)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 pg/ml</td>
<td>30.7%</td>
</tr>
<tr>
<td>500-2000 pg/ml</td>
<td>29.6%</td>
</tr>
<tr>
<td>&gt;2000 pg/ml</td>
<td>17.4%</td>
</tr>
</tbody>
</table>

Prior platelet transfusion:
- <6 units: 17.4%
- 6-10 units: 44.9%
- >10 units: 17.4%


**MDS: Lower-Risk**

**Treatment Algorithm**

Patient diagnosed with lower-risk MDS per IWG criteria (median age >60 years or lower)

- No significant need for transfusion of ESA/RBC
- No infections requiring hospitalization

Start with TPO agonists

- Start therapy at baseline
- No response or low response

Start with hydroxyurea

- Start in patients with lower-risk MDS
- No response, poor response, or adverse effect

Start with lenalidomide

- Start in patients with lower-risk MDS
- No response, poor response, or adverse effect

Sekeres and Gerds Hematology 2014.

**MDS: Lower-Risk**

**ATG**

** IWG RR = 31%**

**Median Duration = 16.4 Months**

Passweg et al. JCO 2011;29:303.


**MDS: Lower-Risk**

**DAC**

**Randomized Phase 2 Study in Low/Int-risk MDS (n=65)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schedule A (n=43)</th>
<th>Schedule B (n=22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response</td>
<td>Overall improvement rate</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Complete response</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>MAR response</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Partial response</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hematologic improvement</td>
<td>3</td>
</tr>
</tbody>
</table>

Garcia-Manero et al. JCO 2013;31:2548

**MDS: Lower-Risk**

**HMA**

**Lower-risk MDS Patients Treated with HMA (N=290/438)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Median TFS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15 months</td>
<td>17 months</td>
</tr>
</tbody>
</table>

Jabbour et al. for MDS CRC Cancer 2014.


- Age is the strongest variable for IST response
- Pathogenetic difference in MDS of younger adults
- Responses are durable and may modify adverse effect of RBC-TI on OS
- Karyotype may influence IST response and disease biology
  - Low frequency of IST response in del(5q)
  - High response rate in trisomy 8
- NIH 8/17 (47%)
- WT1 amplification with specific cellular response
- Autoimmune hematopoietic suppression may select for +8 expansion
**MDS: Lower Risk**

**HMA**

**Study Design**

- Open-label phase II study
- Randomized by Simon's adaptive design; patients more likely to be assigned to treatment arm
- Median follow-up: 20 mos
- Primary endpoints: ORR defined as CR, PR, marrow CR, or hematologic improvement
- Response assessed by modified IWG 2006 criteria
- Secondary endpoints: safety, cytogenetic response, transfusion independence, EFS, OS

**Safety**

<table>
<thead>
<tr>
<th>Nonhematologic AEs, <em>n (%)</em></th>
<th>Decitabine (n = 73)</th>
<th>Azacitidine (n = 40)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>11 (15)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (8)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (4)</td>
<td>6 (15)</td>
</tr>
<tr>
<td>Infections/Infectious fevers</td>
<td>5 (7)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (3)</td>
<td>2 (5)</td>
</tr>
</tbody>
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*All grade 1/2 except where indicated. Grade 3 or 4 if G1.*

- Both HMAs well tolerated; no grade 4 AEs
- Cycle delays: 38% in decitabine arm, 20% in azacitidine arm
- Dose reductions: 12% in decitabine arm, 5% in azacitidine arm

**Conclusions**

- Both low-dose HMAs showed activity, were well tolerated in adult pts with LR MDS and no prior HMA use
  - ORR: 60%
  - 1-yr EFS: 65%
  - 1-yr OS: 85%
- Significantly higher ORR (70% vs 49%; *P = .03*) reported with decitabine vs azacitidine; particularly among pts with ≥ 5% blasts (100% vs 36%; *P < .001*)
- Open-label, randomized phase II trial now ongoing to compare low-dose decitabine, low-dose azacitidine, azacitidine x 5 days, and best supportive care in a LR MDS pt population

**Other - Transfusions**

- Transfusion-dependent patients had a significantly shorter OS than transfusion-independent patients (HR: 2.16; *P < .001* overall)

Development of transfusional iron overload is a significant independent prognostic factor for overall survival and evolution to AML.


MDS: Lower-Risk
Other – Ferritin

OS
Probablility

Time Without AML
Probablility

0.2
0.4
0.6
0.8
1.0

0.2
0.4
0.6
0.8
1.0

Ferritin < 1000 µg/L
Ferritin ≥ 1000 µg/L

P < .0001

P < .0001


MDS: Lower-Risk
Other – Chelation

Characteristic
NCCN
MDS Foundation

Transfusion status
• Received > 20 RBC transfusions
• Continuing transfusions
• Transfusion dependent, requiring 2 units/mo for > 1 yr

Serum ferritin level
• > 2500 µg/L
• 1000 µg/L

MDS risk
• IPSS: Low or intermediate-1 risk
• IPSS: Low or Int-1 WHO: RA, RARS and 5q-

Patient profile
• Candidates for allografts
• Life expectancy > 1 yr and no comorbidities that limit progress
• Need to preserve organ function
• Candidates for allografts

Median OS From Diagnosis, Mos
Nonchelated: 48.7
Chelated (n = 263): 96.8
Chelated ≥ 6 mos (n = 191): 102.5

Proportion Surviving

MDS: Lower-Risk
Other – Ferritin

Pr<.0001 for chelated vs nonchelated


MDS: Lower-Risk
Summary Anemia

• Assess potential causes of anemia
• Supplement with iron, folate, vitamin B as needed
• RBC transfusion support for symptomatic patients

EPO ≤ 500 mU/mL
≥ 2 U RBC/mo

EPO > 500 mU/mL;
≥ 2 U RBC/mo

< 2 U RBC/mo

≤ 60 yrs old, lymphocytic, RA, RAEB, RARS

Leukemia

ESA ± G-CSF

Lenalidomide

AZA/DAC

Clinical Trial

AZA/DAC

Clinical Trial

IST

Clinical Trial

Adapted from NCCN. Clinical practice guidelines in oncology. MDS. v2.2017.

MDS: Overview

• Epidemiology and “Staging”
• Treatment of Lower-risk Disease
• Treatment of Higher-risk Disease
• Clinical Trials and Future Directions
• Conclusions

MDS: Higher-Risk Treatment Algorithm


MDS: Higher-Risk AZA


MDS: Higher-Risk AZA


Drug Combinations?
MDS: Overview

- Epidemiology and “Staging”
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease
- Clinical Trials and Future Directions
- Conclusions

MDS: Clinical Trials and Future Direction

We have to do BETTER.

MDS: Clinical Trials and Future Direction HRMDS

Median OS 5.6 months at HMA failure for HR MDS

<table>
<thead>
<tr>
<th>Time Since Azacitidine Failure (days)</th>
<th>Median follow-up: 15 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>300</td>
<td>50</td>
</tr>
<tr>
<td>720</td>
<td>75</td>
</tr>
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<td>1,080</td>
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<table>
<thead>
<tr>
<th>Disease Status</th>
<th>N=455</th>
<th>No.</th>
<th>%</th>
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<tbody>
<tr>
<td>Relapsed refr.</td>
<td>239</td>
<td>52</td>
<td>11</td>
</tr>
<tr>
<td>Stable disease</td>
<td>91</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>136</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>Secondary failure</td>
<td>104</td>
<td>23</td>
<td>5</td>
</tr>
<tr>
<td>Failure after DH</td>
<td>32</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Failure after RH</td>
<td>12</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Failure after AHD</td>
<td>128</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td>CRD intolerance</td>
<td>42</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Without ongoing response</td>
<td>29</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Durin response to AZA</td>
<td>13</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

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</tbody>
</table>

MDS: Clinical Trials and Future Direction HRMDS

<table>
<thead>
<tr>
<th>Type of salvage</th>
<th>N</th>
<th>ORR</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated</td>
<td>32</td>
<td>16A</td>
<td>4.1</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>32</td>
<td>16A</td>
<td>7.3</td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>36</td>
<td>322</td>
<td>8.9</td>
</tr>
<tr>
<td>Intensive therapy</td>
<td>34</td>
<td>406</td>
<td>13.2*</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>37</td>
<td>1319</td>
<td>19.5*</td>
</tr>
</tbody>
</table>

P<0.001

MDS: Clinical Trials and Future Direction

Immunotherapy

- Early results with short follow-up (median 3 cycles) suggest nivolumab and ipilimumab well tolerated as single agent or with azacitidine
- Nearly 30% ORR with ipilimumab in pts who failed HMA therapy shows promising single-agent activity as salvage therapy
- Nivolumab did not show single-agent activity as salvage therapy
- Encouraging early 65% ORR when combined with azacitidine in previously untreated pts
- Additional treatment cohorts ongoing
- Investigators suggest that future randomized trials are warranted

ETCTN Trial 10026 - Ipilimumab and Decitabine
- Relapsed MDS patients with 5% blasts or greater
  After allogeneic stem cell transplant
  OR
  After 4 cycles of hypomethylating agent

MDS: Clinical Trials and Future Direction

SGI-110
Second-generation hypomethylating agent
- SC dinucleotide of decitabine and deoxyguanosine
- longer half-life; more extended decitabine exposure

15 pts with higher-risk MDS
- Median age 74; all had previous aza/decitabine
- 5 responders (33%), duration 28-224 days

O’Connell C et al, EHA 2013, abstract P189

SGI-110 in MDS/CMML/AML after AZA failure
- GDAC 60 mg/m²/day Day 1-5 q 28 days
  - Median 3 cycles
- N=56; 15 refractory and 41 relapsed
- 9 responded (16%)
  - 1 CR, 2CRp, 5 marrow CR, 1 HI
- Median duration of response 9 months
- Median OS 6.7 mos
  - 33 died: 14 progression, 13 infection, 1 bleeding, 5 other


Phase III ONTIME: Rigosertib: PLK and PI3K inhibitor; a novel synthetic benzyl styryl sulfone that is cytotoxic against a variety of human tumor cell lines
- Patients with higher-risk MDS (RAEB/RAEB1, CMML, relapsed/refractory after aspirin/azacytidine) (planned N = 270)
- Continue treatment q4w until progression

Rigosertib (ON 01910.Na) + BSC
1800 mg/d x 3 days q2w (n = 180)
Best Supportive Care
LoDAC, hydroa, GFs (n = 90)

Stratified by blast % (5% to 19% vs 20% to 30%)

• Primary endpoint: OS (HR: 0.62)
• Secondary endpoints: IWG response, transformation to AML, infection, bleeding, QoL

Garcia-Manero et al. Lancet Oncology 2016;17:496-508

Garcia-Manero et al Lancet Oncology 2016;17:496-508
INSPIRE - Rigosertib

**MDS: Clinical Trials and Future Direction**

**INSPIRE - Rigosertib**

A Phase III, International, Randomized, Controlled Study of Rigosertib versus Physician’s Choice of Treatment in Patients with Myelodysplastic Syndrome after Failure of a Hypomethylating Agent

- Eligibility:
  - MDS subtypes RAEB-1, RAEB-2, or RAEB-t
  - Progression or failure to respond to HMA
  - HMA treatment duration, ≥5 months
  - < 82 years of age

- **Randomization**
  - Rigosertib + best supportive care
  - Physician’s Choice of Treatment + best supportive care
  - N = 350

- **Primary Endpoints:**
  - Overall Survival

New Hypomethylating Agents

- guadecitabine (SGI-110, oral)
- CC486 (oral form of azacitidine)
- cedazuridine (ASTX727, orally fixed-dose combination of decitabine and a cytidine deaminase inhibitor)

Imetelstat (telomerase inhibitor)

- studied in myeloproliferative neoplasms and transfusion independence rates were ~30%

Other Targets

- IDH 1 and 2 – Ivosidenib and Enasidenib
- HIF – Roxadustat
- Need targets for TP53
  - Decitabine – 10 day regimen
  - APR-246, a TP53 modulator

**MEDALIST Trial**

Background and Rationale

- Patients with lower-risk (LR) transfusion-dependent MDS have a poorer prognosis, with greater risk of progression to AML and inferior overall survival compared with patients with transfusion-independent MDS
- RBC transfusion-dependent LR, non-del(5q) MDS patients have a transient response to ESA's, with an attendant risk of iron overload and secondary organ complications
- Few treatment options exist for the large number of patients with LR MDS who are either refractory to or become unresponsive to ESA's

**MEDALIST Trial**

Luspatercept

- Luspatercept is a first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythroprogenitor in MDS models
- In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC transfusion independence in patients with MDS-RS vs other subtypes
MEDALIST Trial Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

**Patient Population**
- MDS 6 (2016): ≥ 15% to ≤ 30% or ≥ 30% to ≤ 35% blasts
- NHL: ≤ 35% blasts
- Previous MDS therapy
- Prior SCT response: no response or partial response

**Randomise 2:1**

**Inclusion Criteria**
- Age ≥ 18 years
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2
- Karnofsky performance status ≥ 60
- Platelet count ≥ 20 x 10^9/L
- Absolute neutrophil count ≥ 1.5 x 10^9/L

**Exclusion Criteria**
- Symptomatic hepatic or splenic vein thrombosis
- Active infection
- Active inflammatory disease
- History of CNS disease

**Lupiflucopert 1.8 mg/kg (I.v.) every 21 days**
- Placebo (0.2 ml) every 21 days

**Gloves & Gowns Assessment (week 26 & every 6 months)**
- Treatment discontinued if lack of clinical benefit or drug progression per RECIST criteria

**Secondary Endpoints**
- Response rate
- Duration of response
- Hb response
- Hb change from baseline

**Additional secondary endpoints:**
- Hb-E (HBC 2006 criteria) for any consecutive 56-day period
- Reduction in red blood cell transfusion burden ≥ 50% in 36 weeks or
- Mean Hb increase of ≥ 1.5 g/dL in 36 weeks

**List A, et al. ASH 2018. Abstract 001.**

### MEDALIST Trial Demographics and Baseline Disease Characteristics

**Table:**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Lupiflucopert</th>
<th>Placebo</th>
</tr>
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<tbody>
<tr>
<td>Age, median (range), years</td>
<td>66 (21-81)</td>
<td>68 (25-78)</td>
</tr>
<tr>
<td>MDS, at diagnosis</td>
<td>66 (21-81)</td>
<td>68 (25-78)</td>
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<tr>
<td>Time since diagnosis, median (range), months</td>
<td>13 (1-52)</td>
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</tr>
<tr>
<td>Females, n (%)</td>
<td>20 (38)</td>
<td>22 (38)</td>
</tr>
<tr>
<td>Prior SCT response, n (%)</td>
<td>15 (28)</td>
<td>15 (28)</td>
</tr>
<tr>
<td>Prior SCT response, median (range), weeks</td>
<td>2 (0-104)</td>
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**List A, et al. ASH 2018. Abstract 001.**

### MEDALIST Trial Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks

**Table:**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Lupiflucopert (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC-TI ≥ 8 weeks</td>
<td>58 (37.9)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>30.2–46.1</td>
<td>6.5–22.9</td>
</tr>
</tbody>
</table>

**List A, et al. ASH 2018. Abstract 001.**

### MEDALIST Trial Duration of RBC-TI Response in Primary Endpoint Responders

**Graph:**

**MDS: Clinical Trials and Future Direction**

**MEDALIST Trial**
Secondary Endpoint: Erythroid Response (Hb-E)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Luspatercept</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved ≥ 2 g/dL (n = 130)</td>
<td>57 (44.3)</td>
<td>36 (28.2)</td>
</tr>
<tr>
<td>Reduction of ≥ 1 g/dL (wks)</td>
<td>37 (28.2)</td>
<td>17 (13.1)</td>
</tr>
<tr>
<td>Hb increase of ≥ 1 g/dL (wks)</td>
<td>5 (3.8)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>MDS (C)</td>
<td>4.12 (2.05)</td>
<td>5.56 (3.29)</td>
</tr>
<tr>
<td>ΔHb (g/dL)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
</tbody>
</table>

**MEDALIST Trial**
Change in Hemoglobin Concentration

- Median peak hemoglobin increase in luspatercept responders: 2.95 g/dL (1.4-5.4 g/dL)


**MDS: Clinical Trials and Future Direction**

**MEDALIST Trial**
Safety Summary

<table>
<thead>
<tr>
<th>Drug</th>
<th>Luspatercept (n = 130)</th>
<th>Placebo (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with ≥ 1 TEAEs, n(%)</td>
<td>130 (98.5)</td>
<td>78 (59.2)</td>
</tr>
<tr>
<td>Patients with ≥ 2 serious TEAEs</td>
<td>130 (100.0)</td>
<td>35 (26.9)</td>
</tr>
<tr>
<td>Patients with Grade 3 or 4 TEAEs</td>
<td>5 (4.7)</td>
<td>5 (3.8)</td>
</tr>
<tr>
<td>Patients with TEAEs leading to death</td>
<td>5 (3.8)</td>
<td>4 (3.1)</td>
</tr>
<tr>
<td>Patients with a ≥ 7% change in Hb, n (%)</td>
<td>130 (100.0)</td>
<td>78 (59.2)</td>
</tr>
</tbody>
</table>

* Progression to ANLL occurred in 4 patients (3.1%) in the luspatercept arm and 2 patients (1.5%) in the placebo arm.


**MDS: Clinical Trials and Future Direction**

Overall proportion of recently diagnosed patients (n = 670) and range of established patients across six surveys (n = 3844) taking specific types of therapeutics at the time of the survey

| ESA (darbepoeitin and/or arthropoeitin) | 58% | 55-61% |
| Azacitidine (Vidaza)                   | 16% | 12-13% |
| G-CSF, GM-CSF or pegfilgrastim          | 8%  | 6-13%  |
| Lenalidomide (Revlimid)                 | 8%  | 6-13%  |
| Decitabine (Decadron)                   | 2%  | 0-4%   |
| Thalidomide                              | 1%  | 0.5-2% |

Only 4% of recently dx or established patients were considered for transplant
Only 1% of recently dx or established patients were enrolled into clinical trials
Established patients (range across 6 surveys)


**MDS: Clinical Trials and Future Direction**

**MEDALIST Trial**
Changes in the IPSS-R

- Increasing IPSS score (A)
- Low IPSS-R risk patients (B)
- Intermediate IPSS-R risk patients (C)

Gene Mutations with Prognostic Relevance
Favorable: SF3B1
Unfavorable: RUNX1, ASXL1, EZH2, TET2, TET6, DNMT3A, U2AF1, NRAS

Reja P. Haematologica 2014; 99: 956.
MDS: Clinical Trials and Future Direction

- Epidemiology and “Staging”
- Treatment of Lower-risk Disease
- Treatment of Higher-risk Disease
- Clinical Trials and Future Directions
- Conclusions

MDS: Overview

- MDS is the most common myeloid malignancy, with survival curves that rival those of lung cancer.
- Therapy for lower-risk disease addresses specific cytopenias, and in some cases karyotypic abnormalities.
- Therapy for higher-risk disease should be started immediately, and can prolong survival.
- The next regulatory frontier is in the relapsed/refractory setting for lower- and higher-risk disease

MDS: Conclusions

- Thanks!
- University of Virginia Leukemia/MDS Program
- And Our Patients & Families!!!