Non-transplant Therapy for MDS

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MDS Treatment Algorithm

Asymptomatic

Observation

Epo/G-CSF

Lenalidomide
Azacitidine

Decitabine
Investigational

Symptomatic

Bone Marrow Function

Transfusion

Low/Int-1

Survival

Blasts

Azacitidine
Decitabine
Investigational

Int-2/High

Intensive Chemotherapy
RIC SCT - Full Ablative

5q-

+8

5/7, 7q
Complex
Treatment Options for Lower-risk MDS

- Transfusion Support
- Growth Factors
- Lenalidomide/Revlimid
- Azacitidine
- Clinical Trial
**MDS: Transfusion Therapy**

- **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
Growth Factors

**Red cell growth factors**
*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*

- Epoetin alfa (Procrit™)
- Darbepoetin alfa (Aranesp™)
- Filgrastim, G-CSF (Neupogen™)
- Pegfilgrastim (Neulasta™)
- Romiplostim (NPLate™)
- Eltrombopag (Promacta™)
# Growth Factors in MDS

<table>
<thead>
<tr>
<th>Patient Criteria</th>
<th>Probability of Response¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion need &lt; 2 units per mo <strong>and</strong> serum EPO &lt; 500 units/L</td>
<td>74%</td>
</tr>
<tr>
<td>Only one of the above criteria</td>
<td>23%</td>
</tr>
<tr>
<td>Neither criteria</td>
<td>7%</td>
</tr>
</tbody>
</table>

- Epo 10,000 u/day x 5 days + GCSF 75-300 mcg/day 3 x week¹
- Other studies suggest no benefit with adding GCSF²
- 10% marrow myeloblasts no benefit²
- GSCF not recommended for neutropenic prophylaxis³
  - Intermittent use in patients with severe infection and neutropenia
- Tepo-mimetics under investigation⁴
  - 46% platelet response, 2 patients progressed to AML

Epo-G vs. S.C.

Overall Survival by Treatment

MDS ≤ RAEB-1, hgb < 9.5, plt > 30,000, Fe RR 34% for ESA vs. 5.8% SC p=0.001
Crossover allowed after 4 months
No difference in Leukemic transformation
Responders lived longer than non-responders

Log Rank Test p = 0.28

Erythropoietin (EPO) + Granulocyte-Colony Stimulating Factor (G-CSF) Treatment Associated with Better Overall Survival: Comparison of Nordic Countries (3 Phase II trials 1990-1999) vs Untreated Italian Cohort

Survival*

AML evolution*

Nordic group: n=129
Italian group n=272

All patients Hgb <10g/dL or transfusion dependent

*WHO-group, karyotype, ANC, Plt, RBC U/month, age, gender
ATG Therapy in MDS

- Phase II study of ATG
  - 61 RA, RARS, RAEB (FAB)
  - Transfusion dependent
  - 40 mg/kg/day x 4 days

- 21/61 (34%) patients with major HI-E
  - Younger age <58
  - HLA - DR 15
  - Shorter duration of RBC tfn

Does ATG Prolong Survival?

Int-1 MDS ≤60 years

IST=ATG 40 mg/kg/day x 4 days + CSA 5-12 mg/kg/day

5.2 vs. >8.1 yrs
P=0.001

6.9 vs. >8.2 yrs
P=0.002

Immunosuppressive Therapy (IST): Summary

- Age is the strongest variable for IST response\textsuperscript{[1,2]}
  - Pathogenetic difference in MDS of younger adults
- Responses are durable and may modify adverse effect of RBC-TI on OS\textsuperscript{[2]}
- Karyotype may influence IST response and disease biology
  - Low frequency of IST response in del(5q)\textsuperscript{[2]}
  - High response rate in trisomy 8\textsuperscript{[3]}
    - NIH 8/17 (47%)
    - WT1 amplification with specific cellular response
    - Autoimmune hematopoietic suppression may select for +8 expansion

Lenalidomide (REVLIMID®, Celgene)

- No significant neurotoxicity, somnolence, or constipation
- Potent modulator of myelosuppressive properties

Lenalidomide in Transfusion-Dependent Patients With Low/Int-1 MDS (MDS-002/003)

Eligibility
RBC transfusion ≥ 2 U/8 wk
16 wk transfusion Hx
ANC > 500/μL
Platelets > 50,000/μL
de novo MDS
Low/Int-1 MDS

Lenalidomide
Dosing
10 mg po × 21/28 d
10 mg po qd

Week: 0 6 12 18 24

Primary endpoint: transfusion independence
Secondary endpoints: cytogenetic response, pathologic response, safety

MDS-003: del 5q31.1 (n=148)
MDS-002: other (n=214)

RESPONSE
Yes → Continue
No → Off Study

Raza et al. Blood 2008;111:86-93

MDS-003: 80%
MDS-002: 55%
Dose Reduction
5 mg qd
5 mg qod
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>Pruritus</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>

Lenalidomide: Duration of Transfusion Independence

- **Transfusion independence %**
  - Del(5q): 67
  - Non-del(5q): 26
- **Total transfusion response %**
  - Del(5q): 76
  - Non-del(5q): 43
- **Duration of independence**
  - Del(5q): ~2 years
  - Non-del(5q): 41 weeks

**Key**
- Green circles: Ongoing
- Red squares: Discontinued

Raza et al. *Blood* 2008;111:86-93
Lenalidomide in Transfusion-Dependent Patients With Low/Int-1 MDS MDS-004/005

Double-Blind Randomized Placebo Control Trial

- 2 randomized trials using lenalidomide for the treatment of patients with primary, lower-risk (IPSS low/Int-1–risk), del(5q)\(^b\) and non-del (5q)\(^a\) MDS with RBC-TD

**MDS-005 Multicenter, Double Blind Phase 3 Study\(^1\)**
(N = 239)\(^a\)

- **Lenalidomide**
  - 10 mg on days 1 to 28 (n = 160) 28-day cycles

- **Placebo**
  - (n = 79)

Primary endpoint: RBC-TI (≥ 8 weeks)

**MDS-004 Multicenter, Randomized, Double-Blind Phase 3 Study\(^2\)**
(N = 139)\(^b\)

- **Lenalidomide**
  - (n = 47)
  - 5 mg on days 1 to 28 28-day cycles

- **Lenalidomide**
  - (n = 41)
  - 10 mg on days 1 to 21 28-day cycles

- **Placebo**
  - (n = 51)

Primary endpoint: RBC-TI (≥ 26 weeks)

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\(^a\) With or without additional chromosomal abnormalities.  
\(^b\) Modified intent-to-treat population.

del, deletion; Int, intermediate; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; TD, transfusion dependence; TI, transfusion independence.

**MDS-004 Study Design**

**Double-blind phase**<sup>b</sup>: Len 5 mg or 10mg vs PBO

- **LEN**, orally
  - **5 mg/day** for 28 days of each 28-day cycle
- **LEN**, orally
  - **10 mg/day** for 21 days of each 28-day cycle
- Placebo

**Responders (at least minor erythroid response at week 16):**
- Continued double-blind treatment for up to 52 weeks, relapse or progression

**Non responders:**
- Discontinued double-blind treatment and entered open-label treatment or withdrew from study

- **Key inclusion criteria:** centrally-confirmed IPSS-defined Low- or Int-1-risk MDS with del(5q) +/- additional cytogenetic abnormalities, and RBC-transfusion dependency (no consecutive 56 days without transfusion within last 112 days)
  - Patients with ANC < 500 cells/mcL or platelet count < 25,000/mcL were excluded
- **Primary endpoint:** RBC-TI for ≥ 26 weeks (absence of transfusions during consecutive 26 weeks on treatment and increase hemoglobin > 1 g/dL from baseline
- **Secondary endpoints:** erythroid response, duration of RBC-TI, cytogenetic response, time to AML progression from randomization, and adverse events

<sup>a</sup> Patients stratified by IPSS score and cytogenetic complexity prior to randomization.

<sup>b</sup> Bone marrow assessments were performed at baseline, 12 weeks, and every 24 weeks thereafter. ANC, absolute neutrophil count; IPSS, International Prognostic Scoring System; LEN, lenalidomide; MDS, myelodysplastic syndromes; PBO, placebo; RBC-TI, red blood cell transfusion independence.

Consistent results were observed in the ITT population (N = 205).

Achievement of RBC-TI for ≥ 26 weeks was not affected by age, gender, FAB classification, IPSS risk, time from diagnosis, cytogenetic complexity, baseline platelet counts, or number of cytopenias at baseline.

Hemoglobin increased over time with a maximum median Hgb change in responders of LEN 5 mg of 5.1 g/dL and LEN 10 mg of 6.3 g/dL.

*P < 0.001 vs placebo. Bars represent 95% CI.

* mITT population defined as patients with centrally-confirmed MDS who received ≥ 1 dose (N = 138). CI, confidence interval; FAB, French-American-British; IPSS, International Prognostic Scoring System; Hgb, hemoglobin; IWG, International Working Group; LEN, lenalidomide; mITT, modified intent-to-treat; RBC-TI, red blood cell transfusion independence.

MDS-005 Lenalidomide in non-del 5q MDS

Table. Key efficacy data.

<table>
<thead>
<tr>
<th>Response</th>
<th>LEN (n = 160)</th>
<th>PBO (n = 79)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC-TI ≥ 56 days, n (%)</td>
<td>43 (26.9)*</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>Duration of RBC-TI ≥ 56 days, median (95% CI), weeks&lt;sup&gt;a&lt;/sup&gt;</td>
<td>32.9 (20.7–71.1)</td>
<td>NE (NE–NE)</td>
</tr>
<tr>
<td>RBC-TI ≥ 168 days, n (%)</td>
<td>28 (17.5)</td>
<td>0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Responding pts only.

<sup>*</sup>P < 0.001.

NE, not estimable.

Summary: Lenalidomide Treatment in Low-/ Intermediate-1–Risk MDS

- MDS-004/005 confirmed results of MDS-003/002\(^{[1,2]}\)
  - 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 (41% 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\(^{[3,4]}\)
- Lenalidomide mechanism of action is karyotype dependent, suppressing the clone in del(5q) and promoting erythropoiesis in non-del(5q)\(^{[5]}\)

Randomized Phase II Study of Alternative Azacitidine Dose Schedules

Study Design (N = 151)

- 5-2-2: 75 mg/m² (n = 50)
- 5-2-5: 50 mg/m² (n = 51)
- 5: 75 mg/m² (n = 50)

Eligibility
- All FAB
- Cytopenia
- ECOG PS: 0-3

12 Cycles
- AZA x 5 days q4-6 wks

IWG 2000 HI

## Baseline Demographics/Disease Characteristics for All Randomized Patient (N = 151)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AZA 5-2-2 (N = 50)</th>
<th>AZA 5-2-5 (N = 51)</th>
<th>AZA 5 (N = 50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (range)</td>
<td>73 (37-88)</td>
<td>76 (54-91)</td>
<td>76 (47-93)</td>
</tr>
<tr>
<td>Gender, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>56</td>
<td>73</td>
<td>66</td>
</tr>
<tr>
<td>RBC transfusion dependent, %</td>
<td>44</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>FAB, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>44</td>
<td>41</td>
<td>44</td>
</tr>
<tr>
<td>RARS</td>
<td>14</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>RAEB</td>
<td>28</td>
<td>33</td>
<td>28</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>CMMoL</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

Hematologic Improvement

Patients counted only once for best response in an improvement category.

Minor improvement at top of HI columns.

Anemia Management Algorithm 2015:
Low- or Intermediate-1 Risk MDS

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

Adapted from NCCN. Clinical practice guidelines in oncology. MDS. v.2.2015.
Is Transfusion Dependency an Issue in MDS?

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

*Excludes isolated 5q-

Survival by Transfusion Burden

Serum Ferritin Is Predictive of Survival and Risk of AML in MDS

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

Prospective Chelation Study in Lower-Risk MDS: 48-Mo Update—OS

- 5-yr noninterventional registry study of 600 patients with lower-risk MDS and transfusional iron overload treated with or without chelation
- At 48 mos, chelated patients had significantly longer OS vs nonchelated

Median OS From Diagnosis, Mos
- Nonchelated (n = 337): 48.7
- Chelated (n = 263): 96.8
- Chelated ≥ 6 mos (n = 191): 102.5

Prospective 1-year phase 2 trial with deferasirox
Primary endpoint reduction in serum ferritin

Gatterman et al. Leuk Res. 2010;34(9):1143-1150
Gatterman et al. Haematologica 2012;97(9):1364-1371
## MDS Patients Who Are Likely to Benefit Most From Management Iron Overload

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>NCCN(^1)</th>
<th>MDS Foundation(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion status</td>
<td>▪ Received &gt; 20 RBC transfusions</td>
<td>▪ Transfusion dependent, requiring 2 units/mo for &gt; 1 yr</td>
</tr>
<tr>
<td></td>
<td>▪ Continuing transfusions</td>
<td></td>
</tr>
<tr>
<td>Serum ferritin level</td>
<td>▪ &gt; 2500 μg/L</td>
<td>▪ 1000 μg/L</td>
</tr>
<tr>
<td>MDS risk</td>
<td>▪ IPSS: low or intermediate-1 risk</td>
<td>▪ IPSS: Low- or Int-1</td>
</tr>
<tr>
<td></td>
<td>▪ WHO: RA, RARS and 5q-</td>
<td>▪ WHO: RA, RARS and 5q-</td>
</tr>
<tr>
<td>Patient profile</td>
<td>▪ Candidates for allografts</td>
<td>▪ Life expectancy &gt; 1 yr and no comorbidities that limit progress</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ A need to preserve organ function</td>
</tr>
<tr>
<td></td>
<td></td>
<td>▪ Candidates for allografts</td>
</tr>
</tbody>
</table>

Treatment Options for Higher-risk MDS

• HCT
• Azacitidine/Vidaza
• Decitabine/Dacogen
• Clinical Trial
Methyltransferase Inhibitor (MTI) Induces DNA Hypomethylation and Gene Activation

- Azacitidine (AZA) is incorporated into DNA in lieu of cytosine residue
- Inactivates DMT
- Leads to formation of newly synthesized DNA with unmethylated cytosine residues
- Results in hypomethylation and transcription of previously quiescent genes

(N=358)
Physician Choice of 1 of 3 Conventional Care Regimens
(Best Supportive Care (BSC) or LDAC or 7+3 Chemo)

VIDAZA® or BSC
n=222

VIDAZA or LDAC
n=94

VIDAZA or 7+3 Chemo
n=42

VIDAZA (n=117)

BSC (n=105)

VIDAZA (n=45)

LDAC (n=49)

VIDAZA (n=17)

7+3 Chemo (n=25)
<table>
<thead>
<tr>
<th></th>
<th>VIDAZA® N=179</th>
<th>CCR N=179</th>
<th>CCR Regimens N=179</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (yrs)</td>
<td>69</td>
<td>70</td>
<td>BSC, Only N=105</td>
</tr>
<tr>
<td>≥65 (%)</td>
<td>68.1</td>
<td>76.0</td>
<td>LDAC N=49</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7+3 Chemo N=25</td>
</tr>
<tr>
<td><strong>FAB (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB</td>
<td>58.1</td>
<td>57.5</td>
<td></td>
</tr>
<tr>
<td>RAEB-T</td>
<td>34.1</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>CMMoL</td>
<td>3.4</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td><strong>IPSS (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int-1</td>
<td>2.8</td>
<td>7.3</td>
<td></td>
</tr>
<tr>
<td>Int-2</td>
<td>42.5</td>
<td>39.1</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>45.8</td>
<td>47.5</td>
<td></td>
</tr>
<tr>
<td><strong>WHO (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB-1</td>
<td>7.8</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>RAEB-2</td>
<td>54.7</td>
<td>53.1</td>
<td></td>
</tr>
<tr>
<td>CMMoL-1</td>
<td>0.6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>CMMoL-2</td>
<td>5.6</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td>30.7</td>
<td>32.4</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers may not add up to 100%, some patient information unknown*
AZA-001 Trial: VIDAZA® Significantly Improves Overall Survival (OS)

Log-rank \( P=0.0001 \)

\( HR=0.58 \) (95% CI: 0.43-0.77)


Cl=confidence interval; HR=hazard ratio; ITT=intent-to-treat.
AZA-001: Hematologic Improvement (2000 IWG)

### AZA-001: Grade 3/4 Adverse Events

(≥ 2% of Patients)*

<table>
<thead>
<tr>
<th>Adverse Events, n (%)</th>
<th>Azacitidine (n = 175)</th>
<th>BSC Only (n = 102)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>159 (91)</td>
<td>70 (69)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>149 (85)</td>
<td>72 (71)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>26 (15)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Anemia</td>
<td>100 (57)</td>
<td>67 (66)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>22 (13)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>8 (5)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>7 (4)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6 (3)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>4 (2)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (1)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

*When any grade of the reactions occurs in ≥ 5% of azacitidine-treated patients.

Randomized Phase III Study of Low-Dose Decitabine for Patients With Higher-Risk MDS

EORTC-06011

Eligibility criteria n=223:
• Intermediate- or high-risk MDS or CMML
• Age ≥ 60 years
• Blast cell count 11%-30% or ≤ 10% with poor cytogenetics

Stratification
- Cytogenetics risk group
- IPSS
- Primary vs secondary
- Study center

Decitabine n=119
15 mg/m² IV 4h q8h, d 1-3 q6w ≤ 8 cycles

Decitabine n=114
15 mg/m² IV 4h q8h, d 1-3 q6w ≤ 8 cycles

Supportive Care n=114

Response monitoring every 12 weeks
CR/PR/SD/HI

CR/PR/SD/HI

Response monitoring every 24 weeks
No PD

PD

Stop RX

Still CR

# Reason for going off-protocol

<table>
<thead>
<tr>
<th>Reason</th>
<th>Supportive care N=114 (100%)</th>
<th>Decitabine N=119 (100%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal completion</td>
<td>19 (16.7%)</td>
<td>31 (26.1%)</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>55 (48.2%)</td>
<td>40 (33.6%)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>NA</td>
<td>19 (16.0%)</td>
</tr>
<tr>
<td>Prolonged cytopenia</td>
<td>NA</td>
<td>5 (4.2%)</td>
</tr>
<tr>
<td>Death</td>
<td>17 (14.9%)</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>Refusal</td>
<td>14 (12.3%)</td>
<td>6 (5.0%)</td>
</tr>
<tr>
<td>Protocol violations</td>
<td>5 (4.4%)</td>
<td>3 (2.5%)</td>
</tr>
<tr>
<td>Ineligible</td>
<td>1 (0.9%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (2.6%)</td>
<td>3 (2.5%)</td>
</tr>
</tbody>
</table>

**Median time to off-study:** 112 days vs 180 days

EORTC-06011: Overall Survival with Decitabine Treatment

Median (months): 10.1 vs 8.5
HR = 0.88, 95% CI (0.66, 1.17)
Logrank test: p=0.38

No survival advantage for DAC?

- Number of treatments courses given
- Different populations and comparator groups
  - MDS duration
  - Cytogenetic risk groups
  - Performance status
- How the drug was given
- There is a true difference between aza and dac
Clinical Trials
Increased PD-L1 Expression in HMA Failure

Aza + Vorinostat
Responders n=7
Resistance n=11

PD-L1
p=0.08

PD-L2
p=0.23

Group 0: no PDL-2 expression induction
Group 1: PDL-2 expression induction

mRNA from PBMNC

Yang et al. Leukemia 2014;28:1280-88
Atezolizumab

Safety Evaluation

Cohort A
HMA R/R-MDS
Atezolizumab
1200 mg IV q3w (12 mo)
n = 10

Cohort B
HMA R/R-MDS
Induction (six cycles)
Atezolizumab: 840 mg IV q2w
Azacitidine: 75 mg/m² SC Days 1-7 q28d
Maintenance (6 mo)
Atezolizumab: 1200 mg IV q3w
n = 10

Cohort C1
1L MDS
Atezolizumab: 840 mg IV q2w
Azacitidine: 75 mg/m² SC Days 1-7 q28d
(treat until loss of clinical benefit)
n = 6

Expansion

Cohort C2
1L MDS
Atezolizumab: 840 mg IV q2w
Azacitidine: 75 mg/m² SC Days 1-7 q28d
(treat until loss of clinical benefit)
n = 14

Primary endpoint: ORR by IWG criteria
Overall Survival After AZA Failure (HR-MDS)

Median follow-up: 15 months

Median OS is 5.6 months
AZA Failure= no response, lost response, progression, intolerance

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>No.</th>
<th>%</th>
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</thead>
<tbody>
<tr>
<td>Primary failure*</td>
<td>229</td>
<td>55</td>
</tr>
<tr>
<td>Stable disease</td>
<td>91</td>
<td>24</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>138</td>
<td>31</td>
</tr>
<tr>
<td>Secondary failure†</td>
<td>164</td>
<td>36</td>
</tr>
<tr>
<td>Failure after CR</td>
<td>32</td>
<td>7</td>
</tr>
<tr>
<td>Failure after PR</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Failure after HI</td>
<td>120</td>
<td>27</td>
</tr>
<tr>
<td>AZA intolerance</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td>Without ongoing response</td>
<td>29</td>
<td>6</td>
</tr>
<tr>
<td>During response to AZA</td>
<td>13</td>
<td>3</td>
</tr>
</tbody>
</table>

N=435

HR MDS post AZA failure OS by Salvage Therapy

Overall Survival (%)

Time Since AZA Failure (days)

Type of salvage | N | ORR | Median OS (months)
--- | --- | --- | ---
Unknown | 165 | NA | 3.6
Best supportive care | 122 | NA | 4.1
Low-dose chemotherapy | 32 | 0/18 | 7.3
Intensive chemotherapy | 35 | 3/22 | 8.9*†
Investigational therapy | 44 | 4/36 | 13.2*†
Allogeneic transplantation | 37 | 13/19 | 19.5*†

†P<0.001

OS and TFS After HMA Failure (LR-MDS)

HMA Failure= no response (6 cycles), lost response, progression to AML, intolerance

Median OS is 17 months

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Events</th>
<th>Months</th>
</tr>
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<tbody>
<tr>
<td>OS*</td>
<td>290</td>
<td>204</td>
<td>17</td>
</tr>
<tr>
<td>TFS*</td>
<td>290</td>
<td>201</td>
<td>15</td>
</tr>
<tr>
<td>OS</td>
<td>438</td>
<td>315</td>
<td>15</td>
</tr>
<tr>
<td>TFS</td>
<td>438</td>
<td>318</td>
<td>12</td>
</tr>
</tbody>
</table>

*Karyotype data available at time of failure

LR MDS post HMA Failure. OS by Salvage Therapy

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Deaths</th>
<th>Med OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>88</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>conventional</td>
<td>83</td>
<td>52</td>
<td>28</td>
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<tr>
<td>SCT</td>
<td>26</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>investigational</td>
<td>91</td>
<td>67</td>
<td>17</td>
</tr>
</tbody>
</table>

$p=0.001$

S110: Guadecitabine

- Cytidine
- 5-aza-2'-deoxycytidine (decitabine)
- 5-azacytidine
- Guanosine

Inhibits cytidine deaminase
347:SG-110 in MDS/CMML/AML after AZA failure

- GDAC 60 mg/m$^2$/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

ASTRAL-2 Design

**MDS or CMML** Patients who failed or progressed on full course of prior **HMA** and any other prior active anticancer therapy

408 patients

Study treatment randomization 2:1

**Guadecitabine**
(n=272)
60 mg/m2/d x5 Q28d
+ Best Supportive Care

***Requires 6 cycles of treatment

**Treatment Choice (TC)**
(n=136)

Low dose Cytarabine (LDAC) **or**
20 mg/m2 SC or IV once daily for 14 days in 28 day cycles (other schedules are allowed per institutional and standard practices)

Intensive Chemotherapy (IC) 7+3 **or**
Cytarabine 100-200 mg/m2/day (7 days) and an anthracycline per institutional standard practice (3 days)

Best Supportive Care (BSC) only
Per institution standard/practice

Primary Analyses (OS) after at least 316 death events have occurred

**Note:** All treatment options (guadecitabine and TC) may include BSC options
Phase III ONTIME: Rigosertib in Higher-Risk MDS After HMA Failure

- Rigosertib: PLK and PI3K inhibitor; a novel synthetic benzyl styryl sulfone that is cytotoxic against a variety of human tumor cell lines

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

Patients with higher-risk MDS (FAB, RAEB/t, CMML), relapsed/refractory after azacitidine or decitabine (planned N = 270)

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

Wk 16

Continue treatment q4w until progression

Rigosertib (ON 01910.Na) + BSC
1800 mg/d x 3 days q2w
(n = 180)

Best Supportive Care
LoDAC, hydrea, GFs
(n = 90)

Garcia-Manero et al. Lancet Oncology; 2016;17:496-508
Subset analysis indicated improved responses with primary failure

ONTIME 2

**Eligibility:**
- MDS subtypes RAEB-1, RAEB-2, or RAEB-t
- Progression or failure to respond to HMA
- Total HMA treatment duration of ≤ 9 months and/or total ≤ 9 cycles in ≤ 12 months
- < 82 years of age

**Stratification:**
- VHR vs non-VHR per IPSS-R
- North America vs Europe vs Asia

**Randomization:**
- 2:1
- Rigosertib + best supportive care $N = 150$
- Physician’s Choice of Treatment + best supportive care $N = 75$

**Primary Endpoint:**
Overall Survival

---

Best supportive care = red blood cell and platelet transfusions, and growth factors (growth factors, granulocyte colony-stimulating factor (G-CSF), erythropoietin, and thrombopoietin)
U.S. treatment approaches to MDS

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

- ESA (darbepoetin and/or erthropoietin): 58% (55-63%)
- Azacitidine (Vidaza): 16% (11-15%)
- G-CSF, GM-CSF or peg-filgrastim: 10% (8-11%)
- Lenalinomide (Revlimid): 8% (1-9%)
- Decitabine (Dacogen): 2% (0-4%)
- Thalidomide: 1% (2-5%)

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.

Conclusions: Non-Transplant Therapy for MDS

- Transfusion support plus SC is an appropriate choice for some patients with MDS
- Growth factors remain the most common treatment choice for MDS
- IST is an appropriate choice for some patients with low/int-1 risk MDS
- Lenalidomide indicated for rec cell TD low/int-1 risk del (5q) MDS
- Aza has been shown to improve OS in patients with int-2/high risk MDS
- The role of iron-chelation remains controversial pending results of a RCT TELESTO
MDS Treatment Algorithm

Low-risk and Intermediate-1

Anemia / Neutropenia / Thrombocytopenia

Intermediate-2 and High-risk

HCT Candidate

Not HCT Candidate

Allo HCT

IC, Aza / Dec??

Host and disease factors

Conventional

RIC

Clinical Trial

Transfusion therapy ± Iron chelation

del 5q → Lenalidomide

Epo < 500 → ESA ± GCSF

Epo > 500 → ATG/CsA Lenalidomide Aza/Dec Clinical Trial

HCT Candidate

Clinical Trial

Intermediate-1

Clinical Trial