Non-transplant Therapy for MDS

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MDS Treatment Algorithm

Asymptomatic

Bone Marrow Function

Symptomatic

Observation

Epo/G-CSF

Lenalidomide
Azacitidine

Decitabine
Investigational

Azacitidine
Decitabine
Investigational

5q-
+8
5/7, 7q Complex

Intensive Chemotherapy
RIC SCT - Full Ablative

Low/Int-1

Survival

Blasts

Int-2/High

Survival

Blasts
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*

- Epoetin alfa (Procrit™)
- Darbepoetin alfa (Aranesp™)

**White cell growth factors**
*No survival benefit but may help decrease infx. Sometimes combined with red cell factors*

- Filgrastim, G-CSF (Neupogen™)
- Pegfilgrastim (Neulasta™)

**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*

- 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 and 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

ACTRII Ligand Traps

TGF-β superfamily

- GDF8: Myostatin
- Activin A
- GDF11: BMP11

- Extracellular space
- Cytoplasm
- Smad7
- Smad2,3
- Smad4
- Nucleus Transcription

- BMP: bone-morphogenetic proteins
- Heme Effects
- Bone Effects

Structure of Luspatercept and Sotatercept

(ACE-536)
Luspatercept
(ACE-011)
Sotatercept

- Modified Extracellular Domain of ActRIIB
- Fc Domain of human IgG, Antibody

Mechanism of action of Luspatercept

GDF-11 inhibits differentiation of erythropoiesis

- Hemoglobin
- BFU-E
- CFU-E
- ProE
- BasoE
- PolyE
- OrthoE
- Retic
- RBC

No
No
Yes
Yes
Yes
Yes

Phase 3 MEDALIST Study of Luspatercept* for Patients With Lower-Risk MDS-RS Requiring RBC Transfusions: Study Design and Patients

Key eligibility criteria
• Age ≥18 years
• IPSS-R very low-, low-, or intermediate-risk MDS with ringed sideroblasts (RS)
• Refractory, intolerant, or ineligible to receive ESAs
• Require RBC transfusions

Primary endpoint: RBC-TI for ≥8 weeks between week 1 and 24
Secondary endpoints: RBC-TI for ≥12 weeks between week 1 and 24, mHI-E (IWG 2006) for consecutive 56 days

Randomized 2:1

Luspatercept (n=153)
1.0 mg/kg titrated up to 1.75 mg/kg, if needed, SC q3w for ≥24 weeks

Placebo (n=76) q3w


<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Luspatercept (n=153)</th>
<th>Placebo (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>71 (40-95)</td>
<td>72 (26-91)</td>
</tr>
<tr>
<td>Median time from diagnosis, months (range)</td>
<td>44.0 (3-421)</td>
<td>36.1 (4-193)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>94 (61.4)</td>
<td>50 (65.8)</td>
</tr>
<tr>
<td>Median RBC units transfused over 8 weeks in the 16 weeks prior to treatment, n (range)</td>
<td>5 (1-15)</td>
<td>5 (2-20)</td>
</tr>
<tr>
<td>RBC units/8 weeks, % &lt;6</td>
<td>87 (56.9)</td>
<td>43 (56.6)</td>
</tr>
<tr>
<td>≥6</td>
<td>66 (43.1)</td>
<td>33 (43.4)</td>
</tr>
<tr>
<td>Baseline serum erythropoietin, n (%) &lt;200 IU/L</td>
<td>88 (57.5)</td>
<td>50 (65.8)</td>
</tr>
<tr>
<td>≥200 IU/L</td>
<td>64 (41.8)</td>
<td>26 (34.2)</td>
</tr>
<tr>
<td>Pre-transfusion Hb, median (range), g/dL</td>
<td>7.6 (6-10)</td>
<td>7.6 (5-9)</td>
</tr>
<tr>
<td>SF3B1 mutation, n (%)</td>
<td>141 (92.2)</td>
<td>65 (85.5)</td>
</tr>
</tbody>
</table>

*Luspatercept is investigational and not currently approved as part of any oncology regimen.
Phase 3 MEDALIST Study of Luspatercept for Patients With Lower-Risk MDS-RS Requiring RBC Transfusions: Results and Summary

- Compared with placebo, patients receiving luspatercept were more likely to achieve an mHI-E response (52.9% vs 11.8% during weeks 1–24; P<0.0001)

<table>
<thead>
<tr>
<th>Selected TRAEs, n (%)</th>
<th>Luspatercept (n=153)</th>
<th>Placebo (n=76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>41 (26.8)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>34 (22.2)</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>31 (20.3)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>31 (20.3)</td>
<td>6 (7.9)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>30 (19.6)</td>
<td>4 (5.3)</td>
</tr>
</tbody>
</table>

Summary
- Compared with placebo, luspatercept significantly reduced transfusion burden for patients with anemia and very low-, low-, and intermediate-risk MDS-RS requiring transfusions
- The safety profile for luspatercept was manageable in this patient population

*Defined as a reduction in transfusion of ≥4 RBC units/8 weeks or a mean Hb increase of ≥1.5 g/dL/8 weeks in the absence of transfusions.

Medalist Study

![Graph showing hemoglobin values over time for Luspatercept and Placebo groups.](image)

### Number of Patients

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>Luspatercept</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>153 57 87 116</td>
<td>76 32 36 41</td>
</tr>
<tr>
<td>1D 8</td>
<td>105 112</td>
<td>47 44</td>
</tr>
<tr>
<td>2D 15</td>
<td>103 76</td>
<td>52 29</td>
</tr>
<tr>
<td>3D 1</td>
<td>92</td>
<td>44</td>
</tr>
<tr>
<td>4D 1</td>
<td>¿</td>
<td>¿</td>
</tr>
<tr>
<td>5D 8</td>
<td>¿</td>
<td>¿</td>
</tr>
<tr>
<td>6D 1</td>
<td>¿</td>
<td>¿</td>
</tr>
<tr>
<td>7D 1</td>
<td>¿</td>
<td>¿</td>
</tr>
<tr>
<td>8D 1</td>
<td>¿</td>
<td>¿</td>
</tr>
<tr>
<td>Week 25</td>
<td>¿</td>
<td>¿</td>
</tr>
</tbody>
</table>
Key eligibility criteria
• Age ≥18 years
• MDS, with RCUD, RARS, RCMD-RS, or RCMD (by WHO)
• IPSS risk: low or intermediate-1/2
• Platelet count ≤30,000/uL or platelet-transfusion-dependence (requiring ≥4 platelet transfusions in 8 weeks prior to study), or Hb ≤9.0 g/dL or RBC transfusion-dependence (requiring ≥4 units of PRBCs in 8 weeks prior to study), or ANC ≤500

**Patient Characteristics**

<table>
<thead>
<tr>
<th>Median age, years (range)</th>
<th>65 (35-85)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis, %</td>
<td></td>
</tr>
<tr>
<td>AA</td>
<td>43</td>
</tr>
<tr>
<td>Hypoplastic MDS</td>
<td>17</td>
</tr>
<tr>
<td>Primary MDS</td>
<td>40</td>
</tr>
<tr>
<td>WHO Subtype, n (%)</td>
<td></td>
</tr>
<tr>
<td>RCUD</td>
<td>11 (37)</td>
</tr>
<tr>
<td>RCMD</td>
<td>11 (37)</td>
</tr>
<tr>
<td>MDS-U</td>
<td>6 (20)</td>
</tr>
<tr>
<td>RARS</td>
<td>2 (6)</td>
</tr>
<tr>
<td>IPSS, n (%)</td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>16 (53)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Poor</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Lines of treatment, n (%)</td>
<td></td>
</tr>
<tr>
<td>≥2</td>
<td>12 (40)</td>
</tr>
</tbody>
</table>

**Eltrombopag (n=30)**
50 mg/day, up to 150 mg/day, with dose increases of 25 mg q 2 weeks

**Primary endpoint:** Hematologic response at 16 or 20 weeks [Defined as either (1) an increase in platelet counts ≥20,000/uL or TI for ≥8 weeks, or (2) Hb increase of ≥1.5g/dL from baseline, or a reduction in RBC transfusions ≥50%, or (3) an increase in ANC ≥0.5x10^9/L or by ≥100% in patients with a baseline ANC <0.5x10^9/L]

*Eltrombopag is not currently approved for treatment of MDS/AML

Phase 2 Pilot Study of Eltrombopag for Patients With Low- to Intermediate-2-Risk MDS: Results and Summary

Efficacy
- 47% of patients (14/30) met the primary endpoint of hematological response; all responders continued eltrombopag on the extension arm
  - 10/14 responding patients achieved a robust response\(^a\) (RR) after a median treatment duration of 15 months (range 7-27 months)
  - PB cell counts significantly declined in 5/10 RR and eltrombopag was restarted per protocol
    - In 4 of these patients PB cell counts recovered
    - 1 patient did not achieve a second response
- Based on IPSS, 4/30 (13%) had PD, including 2 non-responders and 2 responders, at a median follow-up of 4 months (range, 3-35 months)
- NGS for somatic variants was performed in 29/30 patients
  - At baseline, 22/29 (76%) patients had ≥1 mutation: TET2 (14.5%), ASXL1 (12.5%), SF3B1 (8.3%), SETBP1 (8.3%), ATM (8.3%), and ZRSR2 (8.3%)
  - After eltrombopag, additional somatic variants in different genes were detected in 4/14 responders and 7/16 non-responders
    - The VAF of variants detected at both time points were similar
\(^a\)RR: stable hematopoiesis with Hb ≥10 g/dL, thrombocytes ≥50,000/L, and ANC ≥ 1000/L.

Summary
- Hematologic response with eltrombopag was achieved in 47% of patients
- Although there were no AML transformations observed on eltrombopag, 4 patients had progression of MDS
- 5/20 patients acquired new cytogenetic abnormalities with eltrombopag

<table>
<thead>
<tr>
<th>TRAEs (in &gt;5% of patients), n (%), Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased liver transaminases</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>5 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Jaundice</td>
<td>8 (27)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>3 (10)</td>
</tr>
<tr>
<td>Skin rash and pruritis</td>
<td>4 (13)</td>
</tr>
</tbody>
</table>

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

Survival and AML evolution after ATG

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\(^1,2\)
  - Pathogenetic difference in MDS of younger adults
- Responses are durable and may modify adverse effect of RBC-TI on OS\(^2\)
- Karyotype may influence IST response and disease biology
  - Low frequency of IST response in del(5q)\(^2\)
  - High response rate in trisomy 8\(^3\)
    - 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

**Response**
- Yes → Continue
- No → Off Study

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

**Week:**
- 0
- 6
- 12
- 18
- 24

**Multicenter Phase II Studies**

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

# 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

<table>
<thead>
<tr>
<th></th>
<th>Del(5q)</th>
<th>Non-del(5q)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion independence %</td>
<td>67</td>
<td>26</td>
</tr>
<tr>
<td>Total transfusion response %</td>
<td>76</td>
<td>43</td>
</tr>
<tr>
<td>Duration of independence</td>
<td>~2 years</td>
<td>41 weeks</td>
</tr>
</tbody>
</table>

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)\textsuperscript{b} and non-del (5q)\textsuperscript{a} MDS with RBC-TD

\begin{itemize}
  \item MDS-004 Multicenter, Randomized, Double-Blind Phase 3 Study\textsuperscript{2} (N = 139)\textsuperscript{b}
  \item MDS-005 Multicenter, Double Blind Phase 3 Study\textsuperscript{1} (N = 239)\textsuperscript{a}
\end{itemize}

\begin{itemize}
  \item Lenalidomide (n = 47) 5 mg on days 1 to 28 28-day cycles
  \item Lenalidomide (n = 41) 10 mg on days 1 to 21 28-day cycles
  \item Placebo (n = 51)
  \item Lenalidomide (n = 160) 10 mg on days 1 to 28 28-day cycles
  \item Placebo (n = 79)
\end{itemize}

Primary endpoint: RBC-TI (≥ 26 weeks)  
Primary endpoint: RBC-TI (≥ 8 weeks)

With or without additional chromosomal abnormalities. \textsuperscript{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.

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

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

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 a</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>

aResponding pts only.

*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)

12 Cycles
AZA x 5 days
q4-6 wks

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

# 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>Male</td>
<td>56</td>
<td>73</td>
</tr>
<tr>
<td>RBC transfusion dependent, %</td>
<td>44</td>
<td>39</td>
<td>48</td>
</tr>
<tr>
<td>FAB, %</td>
<td>RA</td>
<td>44</td>
<td>41</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

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

<table>
<thead>
<tr>
<th>del(5q), ≥ 2 U RBC/mo</th>
<th>EPO ≤ 500 mU/mL</th>
<th>ESA ± G-CSF</th>
<th>IST</th>
<th>IST</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt; 2 U RBC/mo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lenalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZA/DAC</td>
<td></td>
<td></td>
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<tr>
<td>Clinical Trial</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>EPO &gt; 500 mU/mL; ≥ 2 U RBC/mo</th>
<th>≤ 60 yrs old, Hypocellular marrow, HLA-DR15+, PNH+</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>IST → AZA/DAC Clinical Trial</td>
</tr>
<tr>
<td>no</td>
<td>IST → Lenalidomide Clinical Trial</td>
</tr>
</tbody>
</table>

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

Cumulative Proportion Surviving vs. Survival time (months)

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

$P < .0001$ for chelated vs nonchelated

EPIC Trial

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
TELESTO Phase 2 Study Design

**Age ≥ 18 years**
**Low or int-1 risk**
MDS Serum ferritin > 1000 µg/L and < 2500 µg/L

**Screening**
1 mo

<table>
<thead>
<tr>
<th>Deferasirox (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg/day (first 2 wks)</td>
</tr>
<tr>
<td>20 mg/kg/day (Wks 2-12)</td>
</tr>
<tr>
<td>Up to 40 mg/kg/day (after 12 wks)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg/kg/day (1st 2 weeks)</td>
</tr>
<tr>
<td>20 mg/kg/day (weeks 2-12)</td>
</tr>
<tr>
<td>Up to 40 mg/kg/day (after 12 weeks)</td>
</tr>
</tbody>
</table>

**Randomization**
(2:1 = Deferasirox/Placebo)

**EFS:** cardiac function, liver function, tAML and death

**Interim analysis:**
- at 50% of primary composite events (~ 3 yrs)
- at 75% of primary composite events (~ 4 yrs)

**IA**
54% chance to stop the trial depending on IA results

**Expected end of study**
TELESTO Results

Figure 1. Kaplan-Meier curve of event-free survival

Figure 2. Serum ferritin levels over time by treatment group

Angelucci et al. Blood 2018;132:234
# 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>
</table>
| 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  
                         ▪ A need to preserve organ function  
                         ▪ Candidates for allografts |

Treatment Options for Higher-risk MDS

• 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

AZA-001 Randomization Schema

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

VIDAZA® or BSC  
VIDAZA or LDAC  
VIDAZA or 7+3 Chemo

RANDOMIZE

VIDAZA (n=117)  
BSC (n=105)  
VIDAZA (n=45)  
LDAC (n=49)  
VIDAZA (n=17)  
7+3 Chemo (n=25)

## AZA-001 Trial: Baseline Clinical Characteristics*

<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></td>
<td></td>
<td></td>
<td>BSC, Only N=105</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (yrs)</td>
<td>69</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>≥65 (%)</td>
<td>68.1</td>
<td>76.0</td>
<td>77.1</td>
</tr>
<tr>
<td>FAB (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB</td>
<td>58.1</td>
<td>57.5</td>
<td>64.8</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>34.1</td>
<td>34.6</td>
<td>28.6</td>
</tr>
<tr>
<td>CMMoL</td>
<td>3.4</td>
<td>2.8</td>
<td>3.8</td>
</tr>
<tr>
<td>IPSS (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int-1</td>
<td>2.8</td>
<td>7.3</td>
<td>8.6</td>
</tr>
<tr>
<td>Int-2</td>
<td>42.5</td>
<td>39.1</td>
<td>43.8</td>
</tr>
<tr>
<td>High</td>
<td>45.8</td>
<td>47.5</td>
<td>43.8</td>
</tr>
<tr>
<td>WHO (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RAEB-1</td>
<td>7.8</td>
<td>9.5</td>
<td>12.4</td>
</tr>
<tr>
<td>RAEB-2</td>
<td>54.7</td>
<td>53.1</td>
<td>57.1</td>
</tr>
<tr>
<td>CMMoL-1</td>
<td>0.6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CMMoL-2</td>
<td>5.6</td>
<td>2.8</td>
<td>2.9</td>
</tr>
<tr>
<td>AML</td>
<td>30.7</td>
<td>32.4</td>
<td>25.7</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)


CI=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

Supportive Care n=114
Decitabine n=119
15 mg/m² IV 4h q8h, d 1-3 q6w ≤ 8 cycles

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

Response monitoring every 12 weeks
Response monitoring every 24 weeks
No PD
PD
Still CR
Stop RX
CR/PR/SD/HI

### 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
Venetoclax - a BCL2 specific inhibitor

A restoration of apoptosis through BCL2 inhibition

- BCL2: Pro-apoptotic protein
- Cancer cell survival
- Cancer cell death
- Activation of caspases
- Cytochrome c

Venetoclax inhibits BCL2, leading to the restoration of apoptosis.
Venetoclax + HMA

DiNardo et al. Blood 2019;133:7-17
Clinical Trials
Overall Survival After AZA Failure (HR-MDS)

Median OS is 5.6 months

AZA Failure = no response, lost response, progression, intolerance

Median follow-up: 15 months

Table 2. Distribution of Patients According to the Type of Failure

<table>
<thead>
<tr>
<th>Disease Status</th>
<th>No.</th>
<th>%</th>
</tr>
</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)

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

†P<0.001

ICPI

Nivolumab
Pembrolizumab
Ipilimumab
Atezolizumab
Increased PD-L1 Expression in HMA Failure

Aza + Vorinostat
Responders n=7
Resistance n=11

mRNA from PBMNC

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

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

LR MDS post HMA Failure. OS by Salvage Therapy

<table>
<thead>
<tr>
<th>n</th>
<th>Deaths</th>
<th>Med OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>88</td>
<td>65</td>
<td>10</td>
</tr>
<tr>
<td>83</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>26</td>
<td>15</td>
<td>39</td>
</tr>
<tr>
<td>91</td>
<td>67</td>
<td>17</td>
</tr>
</tbody>
</table>

\[ p=0.001 \]

S110: Guadecitabine

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

Inhibits cytidine deaminase
347:SG-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

Sebert et al. Blood 2016;128:347
**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%)

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

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

Continue treatment q4w until progression

Wk 16

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 $\leq 9$ months and/or total $\leq 9$ cycles in $\leq 12$ months
- $< 82$ years of age

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

2:1 Randomization

Rigosertib + best supportive care
$N = 150$

Primary Endpoint: Overall Survival

Physician’s Choice of Treatment + best supportive care
$N = 75$

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

**Thalidomide**
- Recently diagnosed patients (proportion): 1%
- Established patients (range across 6 surveys): 2-5%

**Decitabine (Dacogen)**
- Recently diagnosed patients (proportion): 2%
- Established patients (range across 6 surveys): 0-4%

**Lenalinomide (Revlimid)**
- Recently diagnosed patients (proportion): 8%
- Established patients (range across 6 surveys): 1-9%

**Azacitidine (Vidaza)**
- Recently diagnosed patients (proportion): 10%
- Established patients (range across 6 surveys): 8-11%

**G-CSF, GM-CSF or peg-filgrastim**
- Recently diagnosed patients (proportion): 16%
- Established patients (range across 6 surveys): 11-15%

**ESA (darbepoetin and/or erthropoietin)**
- Recently diagnosed patients (proportion): 58%
- Established patients (range across 6 surveys): 55-63%

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
- Transfusion therapy ± Iron chelation
- Epo < 500 → ESA ± GCSF
- Epo > 500 → ATG/CsA Lenalidomide Aza/Dec Clinical Trial
- del 5q → Lenalidomide

Intermediate-2 and High-risk

- HCT Candidate
  -IC, Aza / Dec??
  - Host and disease factors
  - Conventional RIC

- Not HCT Candidate
  -IC, Aza / Dec
  - Clinical Trial