Advancements and Novel Options in MDS: What Does the Future Hold for Us?
Advancements in MDS:

What does the Future Hold For us

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Conflict of interest disclosure

- Consulting/honoraria: BluePrint Medicines, GERON, OncLive
- Advisory board member/honoraria: Sierra Oncology, Stemline Therapeutics, Morphosys, Taiho, and Novartis
- I WILL include discussion of investigational or off-label use of a product in my presentation
Outline

• Definition and Epidemiology of MDS
• Pathogenesis and making a diagnosis of MDS

• 2022 Updates in:
  o MDS subtype / classification
  o Prognostic risk score of MDS

• Approved treatments and Advancements for lower-risk MDS
• Approved treatments and Advancements for higher-risk MDS
How would you define MDS?

- Myelodysplastic syndromes (MDS) comprise a heterogeneous group of malignant clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis, dysplastic changes and risk of transformation to acute myeloid leukemia.

- MDS IS A BONE MARROW CANCER

**MYELODYSPLASTIC NEOPLASMS**

*New terminology and grouping framework*

The classification introduces the term *myelodysplastic neoplasms* (abbreviated MDS) to replace myelodysplastic syndromes, under-scoring their neoplastic nature and harmonizing terminology with MPN. These clonal haematopoietic neoplasms are defined by
Epidemiology of MDS – SEER DATA

- Captured as “cancer” – 2001
- 13,400 new cases per year
- Incidence Rate 4.7/100,000
- Male preponderance (M:F 1.5-2.0)

Zeidan AM et al. Blood Rev. 2018 (SEER data, based on the November 2017 submission)
Incidence Rates Based on a claims-based Algorithm

- Patients ≥65 years
- Incidence of 75/100,000 vs. 20/100,000 reported by SEER

Cogle CR et al. Blood 2011
Age at diagnosis and Overall Survival

Median age at diagnosis 77 years

5 year overall survival rate in MDS ~ 31%

Zeidan AM et al. Blood Rev. 2018 (SEER data, based on the November 2017 submission)
Hematopoiesis

- Myeloid Family

- Lymphoid Family
Diagnosis and Marrow Dysplasia

- Dysplastic changes in > 10% of cells
  - Peripheral cytopenias
  - Increased blasts
  - Increased ring sideroblasts

- Defining karyotype/genomic abnormality

- 2022: Defining genetic abnormality (Gene mutation)

What are Chromosomes (DNA/Genetic Material)

Chromosome

- **p arm** (short arm structure)
- **Centromere** (constricted point where the two chromatids are held together)
- **q arm** (long arm structure)
- **DNA molecule** (strands of DNA are formed into compact structures inside of the chromosome by proteins called histones)
# MDS Defining Cytogenetic Abnormalities

## Table 18. Cytogenetic abnormalities sufficient to diagnose AML with myelodysplasia-related changes when ≥20% PB or BM blasts are present and prior therapy has been excluded

<table>
<thead>
<tr>
<th>Cytogenetic abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complex karyotype (3 or more abnormalities)</strong></td>
</tr>
<tr>
<td>del(17q)/t(17p)</td>
</tr>
<tr>
<td>del(13q)</td>
</tr>
<tr>
<td>del(11q)</td>
</tr>
<tr>
<td>del(12p)/t(12p)</td>
</tr>
<tr>
<td>idic(X)(q13)</td>
</tr>
<tr>
<td><strong>Unbalanced abnormalities</strong></td>
</tr>
<tr>
<td>−7/del(7q)</td>
</tr>
<tr>
<td>del(5q)/t(5q)</td>
</tr>
<tr>
<td><strong>Balanced abnormalities</strong></td>
</tr>
<tr>
<td>t(11;16)(q23.3;p13.3)</td>
</tr>
<tr>
<td>t(3;21)(q26.2;q22.1)</td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
</tr>
<tr>
<td>t(2;11)(p21;q23.3)</td>
</tr>
<tr>
<td>t(5;12)(q32;p13.2)</td>
</tr>
<tr>
<td>t(5;7)(q32;q11.2)</td>
</tr>
<tr>
<td>t(5;17)(q32;p13.2)</td>
</tr>
<tr>
<td>t(5;10)(q32;q21.2)</td>
</tr>
<tr>
<td>t(3;5)(q25.3;q35.1)</td>
</tr>
</tbody>
</table>

Genomic Landscape of MDS: 944 patients

- 90% had 1 or more driver mutations (median: 3/pt, [0-12])
## I. MDS Subtypes: 2016 WHO Classification of MDS

<table>
<thead>
<tr>
<th>Category</th>
<th>Abbreviation</th>
<th>Bone Marrow Blast %</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with Single-lineage dysplasia</td>
<td>MDS-SLD</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MDS with multi-lineage dysplasia</td>
<td>MDS-MLD</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MDS with ring sideroblasts &amp; Single lineage dysplasia</td>
<td>MDS-RS-SLD</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MDS with ring sideroblasts and multi-lineage dysplasia</td>
<td>MDS-RS-MLD</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>MDS with isolated del(5q)</td>
<td>Del(5q) MDS</td>
<td>&lt;5%</td>
</tr>
<tr>
<td><strong>MDS with excess blasts -1</strong></td>
<td>MDS-EB1</td>
<td>5-9%</td>
</tr>
<tr>
<td><strong>MDS with excess blasts -2</strong></td>
<td>MDS-EB2</td>
<td>10-19%</td>
</tr>
<tr>
<td>MDS unclassifiable with 1% PB blasts, SLD with pancytopenia or based on cytogenetic abnormalities</td>
<td>MDS-U</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Refractory cytopenia of childhood</td>
<td>RCC</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

*Allow for treatment options:*
- Presence of SF3B1 mutation – MDS-Ring Sideroblasts – Luspatercept
- Presence of del(5q) – Lenalidomide

MDS Subtypes: 2022 WHO and International Consensus Classification of MDS

• What I need to know:

1. Number of dysplastic cell lines (1 or more)
2. Presence of del(5q) as the sole abnormality ± 1 additional abnormality
3. Percentage of blasts
4. Presence of SF3B1 mutation
5. Presence of TP53 mutation/multiple TP53 mutations
<table>
<thead>
<tr>
<th></th>
<th>Dysplastic lineages</th>
<th>Cytopenias</th>
<th>Cytoses*</th>
<th>BM and PB Blasts</th>
<th>Cytogenetics†</th>
<th>Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with mutated SF3B1 (MDS-SF3B1)</td>
<td>Typically ≥1‡</td>
<td>≥1</td>
<td>0</td>
<td>&lt;5% BM</td>
<td>Any, except isolated del(5q), −7/del(7q), abn3q26.2, or complex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;2% PB</td>
<td>SF3B1 (≥ 10% VAF), without multi-hit TP53, or RUNX1</td>
<td></td>
</tr>
<tr>
<td>MDS with del(5q) [MDS-del(5q)]</td>
<td>Typically ≥1‡</td>
<td>≥1</td>
<td>Thrombocytosis allowed</td>
<td>&lt;5% BM</td>
<td>del(5q), with up to 1 additional, except −7/del(7q)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;2% PB§</td>
<td>Any, except multi-hit TP53</td>
<td></td>
</tr>
<tr>
<td>MDS, NOS without dysplasia</td>
<td>0</td>
<td>≥1</td>
<td>0</td>
<td>&lt;5% BM</td>
<td>−7/del(7q) or complex</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;2% PB§</td>
<td>Any, except multi-hit TP53 or SF3B1 (≥ 10% VAF)</td>
<td></td>
</tr>
<tr>
<td>MDS, NOS with single lineage dysplasia</td>
<td>1</td>
<td>≥1</td>
<td>0</td>
<td>&lt;5% BM</td>
<td>Any, except not meeting criteria for MDS-del(5q)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;2% PB§</td>
<td>Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1</td>
<td></td>
</tr>
<tr>
<td>MDS, NOS with multilineage dysplasia</td>
<td>≥2</td>
<td>≥1</td>
<td>0</td>
<td>&lt;5% BM</td>
<td>Any, except not meeting criteria for MDS-del(5q)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;2% PB§</td>
<td>Any, except multi-hit TP53; not meeting criteria for MDS-SF3B1</td>
<td></td>
</tr>
<tr>
<td>MDS with excess blasts (MDS-EB)</td>
<td>Typically ≥1‡</td>
<td>≥1</td>
<td>0</td>
<td>5-9% BM, 2-9% PB§</td>
<td>Any</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any, except multi-hit TP53</td>
<td></td>
</tr>
<tr>
<td>MDS/AML</td>
<td>Typically ≥1‡</td>
<td>≥1</td>
<td>0</td>
<td>10-19% BM or PB</td>
<td></td>
<td>Any, except AML-defining¶</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Any, except NPM1, bZIP CEBPA or TP53</td>
<td></td>
</tr>
</tbody>
</table>
Myeloid neoplasms with mutated TP53 (Table 21)

This disease category encompasses separate diagnoses of MDS, MDS/AML, and AML with mutated TP53 (including pure erythroid leukemia), according to the blast percentage. These diseases are grouped together because of their overall similar aggressive behavior irrespective of the blast percentage, warranting a more unified treatment strategy across the blast spectrum.\textsuperscript{120,127} The presence of multihit TP53 mutations in

<table>
<thead>
<tr>
<th>Type</th>
<th>Cytopenia</th>
<th>Blasts</th>
<th>Genetics</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS with mutated TP53</td>
<td>Any</td>
<td>0-9% bone marrow and blood blasts</td>
<td>Multi-hit TP53 mutation* or TP53 mutation (VAF &gt; 10%) and complex karyotype often with loss of 17p\textsuperscript{†}</td>
</tr>
<tr>
<td>MDS/AML with mutated TP53</td>
<td>Any</td>
<td>10-19% bone marrow or blood blasts</td>
<td>Any somatic TP53 mutation (VAF &gt; 10%)</td>
</tr>
<tr>
<td>AML with mutated TP53</td>
<td>Not required</td>
<td>$\geq$20% bone marrow or blood blasts or meets criteria for pure erythroid leukemia</td>
<td>Any somatic TP53 mutation (VAF &gt; 10%)</td>
</tr>
</tbody>
</table>

Table 21. Myeloid neoplasms with mutated TP53

Arber et al. Blood. 2022
Prognostic risk score of MDS – Lower-risk vs Higher-risk

• International Prognostic Scoring System (IPSS, 1997)

• Revised IPSS (2012)

• IPSS-Molecular (IPSS-M) (2022)

• 4 major elements to calculate risk score:
  1. Counts (Absolute neutrophil count/ANC, hemoglobin level, platelet count)
  2. Bone marrow blast %
  3. Cytogenetics/chromosomal study
  4. Genomic abnormalities/Mutations
# International Prognostic Scoring System (IPSS)

<table>
<thead>
<tr>
<th>Cytogenetic risk group</th>
<th>Categories and Associated Scores</th>
<th>Points</th>
<th>Median survival (years)</th>
<th>Time to 25% of patients progressing to AML (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Good</td>
<td>0</td>
<td>5.7</td>
<td>9.4</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td>0.5</td>
<td>3.5</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>1</td>
<td>1.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Marrow blast proportion</td>
<td>&lt;5%</td>
<td>1.5</td>
<td>0.4</td>
<td>0.2</td>
</tr>
<tr>
<td></td>
<td>5%-10%</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>11%-20%</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>21%-30%</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of cytopenias</td>
<td>0/1</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2/3</td>
<td>0.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Karyotype definitions:**
- **Good:** Normal; -Y; del (5q); del (20q)
- **Poor:** Complex (≥3 abnormalities); abnormal chromosome 7.
- **Intermediate:** All others.

# Revised International Prognostic Scoring System (IPSS-R)

## Categories and Associated Scores

<table>
<thead>
<tr>
<th>Category</th>
<th>Scores</th>
<th>Points</th>
<th>% Patients</th>
<th>Median Survival (years)</th>
<th>Median Survival for pts &lt;60 years (years)</th>
<th>Time to 25% of patients progressing to AML (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cytogenetic risk group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>0</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>Good</td>
<td>1</td>
<td>2-3</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>2</td>
<td>4-5</td>
<td>20%</td>
<td>3.0</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
<td>5-6</td>
<td>13%</td>
<td>1.5</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td>Very Poor</td>
<td>4</td>
<td>&gt;6.0</td>
<td>10%</td>
<td>0.8</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td><strong>Marrow blast proportion</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤2%</td>
<td>0</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>&gt;2 - &lt;5%</td>
<td>1</td>
<td>2</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>5 - 10%</td>
<td>2</td>
<td>3-4</td>
<td>20%</td>
<td>3.0</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>3</td>
<td>&gt;4</td>
<td>13%</td>
<td>1.5</td>
<td>2.1</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥10 g/dL</td>
<td>0</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>8 - &lt;10 g/dL</td>
<td>1</td>
<td>2</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>&lt;8 g/dL</td>
<td>1.5</td>
<td>&gt;2</td>
<td>20%</td>
<td>3.0</td>
<td>5.2</td>
<td>3.2</td>
</tr>
<tr>
<td><strong>Absolute neutrophil count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥0.8 x 10^9/L</td>
<td>0</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>&lt;0.8 x 10^9/L</td>
<td>0.5</td>
<td>&gt;2</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥100 x 10^9/L</td>
<td>0</td>
<td>0-1.5</td>
<td>19%</td>
<td>8.8</td>
<td>Not reached</td>
<td>Not reached</td>
</tr>
<tr>
<td>50 - 100 x 10^9/L</td>
<td>0.5</td>
<td>2</td>
<td>38%</td>
<td>5.3</td>
<td>8.8</td>
<td>10.8</td>
</tr>
<tr>
<td>&lt;50 x 10^9/L</td>
<td>1</td>
<td>&gt;2</td>
<td>20%</td>
<td>3.0</td>
<td>5.2</td>
<td>3.2</td>
</tr>
</tbody>
</table>

Molecular International Prognostic Scoring System

- [https://mds-risk-model.com/](https://mds-risk-model.com/)

### IPSS-M Risk Calculator for Myelodysplastic Syndromes (MDS)

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>Cytogenetics</th>
<th>Molecular Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLL PTD</td>
<td>Yes</td>
<td>Not Assessed</td>
</tr>
<tr>
<td>FLT3 ITD or TKD</td>
<td>Yes</td>
<td>Not Assessed</td>
</tr>
</tbody>
</table>

*Genes (individual weights):

- **ASXL1**
  - Non-mutated
  - Mutated
  - Not Assessed

- **CB1**
  - Non-mutated
  - Mutated
  - Not Assessed

- **DNMT3A**
  - Non-mutated
  - Mutated
  - Not Assessed

- **ETV6**
  - Non-mutated
  - Mutated
  - Not Assessed

- **EZH2**
  - Non-mutated
  - Mutated
  - Not Assessed

- **IDH2**
  - Non-mutated
  - Mutated
  - Not Assessed

- **KRAS**
  - Non-mutated
  - Mutated
  - Not Assessed

- **NPM1**
  - Non-mutated
  - Mutated
  - Not Assessed

- **NRAS**
  - Non-mutated
  - Mutated
  - Not Assessed

- **RUNX1**
  - Non-mutated
  - Mutated
  - Not Assessed

- **SRSF1**
  - Non-mutated
  - Mutated
  - Not Assessed

- **U2AF1**
  - Non-mutated
  - Mutated
  - Not Assessed

*Genes (number of residual mutations):

- **BCOR**
  - Non-mutated
  - Mutated
  - Not Assessed

- **BCORL1**
  - Non-mutated
  - Mutated
  - Not Assessed

- **CEBPA**
  - Non-mutated
  - Mutated
  - Not Assessed
2022 IPSS-M Classification

A. Hazard ratio (from average patient)

B. Leukemia-free survival

C. Probability of LFS

D. IPSS-R vs IPSS-M

Bernard et al. NEJM Evidence 2022
Prognostic risk score of MDS: Lower vs. Higher-risk MDS

• **Lower Risk MDS**
  - International prognostic scoring system (IPSS) **Low-risk, Intermediate-1 risk (0-1.0)**
  - Revised-IPSS: **Very low risk, low-risk and intermediate risk (<3.5)**
  - Molecular-IPSS: **Very low, low and Moderate-Low Scores**
  - Morphology: **MDS without excess blasts**

• **Higher Risk MDS**
  - International prognostic scoring system (IPSS) **Int-II, high risk**
  - Revised-IPSS: **Intermediate, High and Very high risk**
  - Molecular IPSS: **Moderately High, High and Very High**
  - Morphology: **MDS-Excess Blasts 1/2**
Treatment Goals and Advancements in Lower-risk MDS

- Improve blood counts and decrease transfusion requirements
- Improve quality of life and symptom burden
- Only curative option is allogeneic hematopoietic cell transplant
- Timing to initiate treatment is key ---- always consider the following 2 factors:
  1. Blood Counts
  2. Patient’s Symptom Burden
Treatment Goals in Higher-risk MDS

• Prevent disease progression to acute leukemia

• Prolong survival

• Only curative option is allogeneic hematopoietic cell transplant
Figure 1: U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) drug approvals for Myelodysplastic syndromes

MDS Diagnosed per WHO 2016 Criteria

Calculate International prognostic scoring system (IPSS) and Revised IPSS (IPSS-R) Scores

IPSS <1.5
IPSS-R ≤3.5

Lower-Risk MDS

Is Anemia the main or only cytopenia?

Yes

Is Del(5q) present?

No

Yes

Best Approach is not clear; options include Hypomethylating agent (HMA), clinical trial, best supportive care or HSCT

Is Erythropoietin (EPO) level <500?

No

Yes

Erythropoietin Stimulating Agent (ESA) ≥12 weeks until treatment failure

Treatment Failure

Consider antithymocyte globulin ± cyclosporine; hypomethylating agent; Clinical trial; Best supportive care or Hematopoietic stem cell transplant (HSCT)

Treatment Failure

Lenalidomide or ESA (if EPO <500)

No

Yes

Figure 2: Novel and Approved therapies for Lower-risk Myelodysplastic Syndromes.

Low risk MDS

- Approved
- Commonly used
- Clinical evaluation

Established therapies
- ESA: e.g. Epoetin-α
- TPO-RA: e.g. Eltrombopag, Hetcrombopag
- Telomerase inhibitor: e.g. Imetelstat (Imerge)
- HIF-PH inhibitor: e.g. Roxadustat
- IRAK4 inhibition: e.g. emavusentib
- NRLP3 inhibitor: e.g. DFV910
- IL-1β antibody: e.g. canakimumab
- TLR2 monomeric antibody: e.g. Tomaralimab
- SYK inhibitor: e.g. Fostamatinib

Investigational therapies
- TG-β superfamily ligand trap in MDS-RS: e.g. Jaspacetrap

Both decitabine-cedazuridine and oral azacitidine are currently evaluated in LR-MDS

Lenalidomide

Hypomethylating agents e.g. azacitidine & decitabine

Being evaluated in LR-MDS as both front line (COMMANDS) and second line (LUSPLUS); and non-TD w/o RS (LENNON)
The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia With Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

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

<table>
<thead>
<tr>
<th>RBC-TI ≥ 8 weeks</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1–24, n (%)</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>
<tr>
<td>P value(^a)</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate). CI, confidence interval.
MEDALIST Trial
Duration of RBC-TI Response in Primary Endpoint Responders

Probability of Maintaining RBC-TI

Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)

- Median DOR luspatercept 30.6 weeks
- Median DOR PL arm was 13.6 weeks

<table>
<thead>
<tr>
<th>Duration of RBC-TIa (week)</th>
<th>Luspatercept</th>
<th>Placebo</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>18</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>29</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>37</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>49</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>80</td>
<td>58</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>90</td>
<td>10</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>100</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>110</td>
<td>3</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

- Median DOR luspatercept 30.6 weeks
- Median DOR PL arm was 13.6 weeks

Number of patients
- Luspatercept: 58 49 37 29 22 18 10 6 3 2 1 1 0
- Placebo: 10 9 3 2 2 2 0

During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.
Treatment With Imetelstat Provides Durable Transfusion Independence (TI) in Heavily Transfused Non-Del(5q) Lower Risk MDS (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis Stimulating Agents (ESAs)

**Uwe Platzbecker¹, Pierre Fenaux², David P. Steensma³, Koen Van Eygen⁴, Azra Raza⁵, Ulrich Germing⁶, Patricia Font⁷, Maria Diez-Campelo⁸, Sylvain Thepot⁹, Edo Vellenga¹⁰, Mrinal M. Patnaik¹¹, Jun Ho Jang¹², Helen Varsos¹³, Esther Rose¹³, Jacqueline Bussolari¹³, Fei Huang¹⁴, Laurie Sherman¹⁴, Faye Feller¹⁴, Souria Dougherty¹⁴, Libo Sun¹⁴, Ying Wan¹⁴, Aleksandra Rizo¹⁴, Valeria Santini¹⁵**

¹University Clinic Leipzig (DE), ²Hospital Saint-Louis, University Paris Diderot (FR), ³Dana-Farber Cancer Institute (US), ⁴Algemeen Ziekenhuis Groeninge (BE), ⁵Columbia University Medical Center (US), ⁶Universitätsklinik Düsseldorf, Heinrich-Heine-Universität (DE), ⁷Hospital General Universitario Gregorio Marañon (SP), ⁸The University Hospital of Salamanca (SP), ⁹CHU Angers (FR), ¹⁰University Medical Center Groningen (NE), ¹¹Mayo Clinic, Rochester (US), ¹²Samsung Medical Center, Sungkyunkwan University School of Medicine (KO), ¹³Janssen Research & Development, LLC (US), ¹⁴Geron Corporation (US), ¹⁵MOS Unit, AOU Careggi-University of Florence (IT)
Phase 2/3 Study Design

Enrollment Complete

Phase 2
single arm, open label
LR MDS R/R to ESA

Imetelstat (n=38)
7.5 mg/kg IV q4w

Currently Enrolling

Phase 3
double-blind, placebo-controlled
N~170

Imetelstat (n~115)
7.5 mg/kg IV q4w

Stratification:
- Transfusion burden (≤6 vs. >6 units)
- IPSS risk category (low vs intermediate-1)

Placebo (n~55)

Results from Phase 2 recently published online ahead of print: 2020 Oct 27;JCO2001895

- LR MDS patients:
  - Non-del(5q), IPSS Low or Int-1
  - Relapsed/Refractory to ESA or EPO >500 mU/ml; HMA/Len naïve
  - Transfusion dependent: ≥ 4 units RBC/8 weeks over 16 week pre-study period

- Primary Endpoint: 8-week RBC Transfusion Independence (TI)

- Key Secondary Endpoints: 24-week RBC TI/Duration of TI/HI-E

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; Len, lenalidomide; LR, low risk; RBC, red blood cell; R/R, relapsed/refractory

UT Southwestern
Simmons Cancer Center
Meaningful and Durable Transfusion Independence (TI) with Imetelstat Treatment

<table>
<thead>
<tr>
<th>Parameters</th>
<th>N = 38</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-week TI, n (%)</td>
<td>16 (42)</td>
</tr>
<tr>
<td>Time to onset of 8-week TI, weeks, median (range)</td>
<td>8.3 (0.1-40.7)</td>
</tr>
<tr>
<td>Duration of TI, weeks, median (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>**88.0 (23.1 – 140.9)*&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cumulative duration of TI ≥ 8 weeks&lt;sup&gt;b&lt;/sup&gt;, median (95% CI)&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Hb rise ≥ 3.0 g/dL during TI&lt;sup&gt;c&lt;/sup&gt;, n (%)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>24-week TI, n (%)</td>
<td>12 (32)</td>
</tr>
<tr>
<td>Hb rise ≥ 3.0 g/dL during TI&lt;sup&gt;c&lt;/sup&gt;, n (%)</td>
<td>11 (29)</td>
</tr>
<tr>
<td>1-year TI, n (%)</td>
<td>11 (29)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Kaplan Meier method; <sup>b</sup>Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment; <sup>c</sup>Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks).

CI, confidence interval; Hb, hemoglobin

*Longest TI > 2.7 years
Calculate International prognostic scoring system (IPSS) and Revised IPSS (IPSS-R) Scores

IPSS >1.5
IPSS-R ≥3.5

Higher-Risk MDS

Patient desires and suitable for bone marrow transplant, younger patient with good performance status & available stem cell donor

Yes

Initiate bone marrow transplant work up. In the meantime treat with HMA or intensive chemotherapy depending on patient age, bone marrow blast percentage and cytogenetic risk group

No

Hypomethylating agent (HMA) for ≥6 cycles OR clinical trial option

Clinical Trial option or best supportive care

Outcomes of Hypomethylating Therapy in Higher-risk MDS
Azacitidine and Decitabine

Lubbert et al. JCO. 2011
Figure 3: Novel and Approved Therapies for Higher-Risk Myelodysplastic Syndromes

High risk MDS

- Approved
- Commonly used
- Clinical evaluation

HMA based therapies

- Hypomethylating agents: e.g. azacitidine, decitabine, or C-DEC
- *also being evaluated as monotherapy

Other investigational therapies

- IDH inhibitors: e.g. Ivosidenib/Enasidenib
- *also being evaluated as monotherapy

- FLT3 inhibitors: e.g. gilteritinib

- RAS inhibitor: e.g. regorafenib

- Splicing modulator: e.g. HS-88800

- MDM2 inhibitor: e.g. Siremadlin

- Exporin 1 inhibitor: e.g. Etanercept

- CPX-351

Immunotherapies: e.g. PD-L1, PD-1, anti-CTLA4 monoclonal antibody
- *also being evaluated as monotherapy

Selective NEDD8 inhibitor: e.g. Pevonedistat

Targeting TP53: e.g. APR-246
- *also being evaluated as monotherapy

Selective RARA agonist: e.g. Tamibistroten

HMA inhibition: e.g. Emsansertib

Promising Clinical Trial >> Options – Higher-Risk MDS

- Combination of Magrolimab with azacitidine vs azacitidine alone (completed enrollment, awaiting results)

- Combination of Venetoclax with azacitidine vs azacitidine alone (enrolling)
Magrolimab + Aza in Patients With MDS and AML: Study Design

- Multicenter, single-arm phase Ib study
  - Current analysis reports data from expansion phase

Patients with untreated AML ineligible for induction CT or untreated MDS classed intermediate to very high risk by IPSS-R (N = 68)

Safety Evaluation

| Magrolimab 1, 30 mg/kg QW* + Aza 75 mg/m² Days 1-7 (n = 6) |

Expansion

| Magrolimab 1, 30 mg/kg QW or Q2W* + Aza 75 mg/m² Days 1-7 (n = 68) |

*Patients received magrolimab 1 mg/kg priming dose, followed by dose ramp-up to 30 mg/kg by Wk 2, continued thereafter.

- Primary endpoints: safety, efficacy
- Secondary endpoints: magrolimab PK, PD, immunogenicity
- Exploratory endpoints: CD47 receptor occupancy, immune activity markers, molecular profiling


Slide credit: clinicaloptions.com
### Magrolimab + Aza in Patients With MDS and AML: Response

<table>
<thead>
<tr>
<th>Best Overall Response, n (%)</th>
<th>MDS (n = 33)</th>
<th>AML (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>30 (91)</td>
<td>16 (64)</td>
</tr>
<tr>
<td>CR</td>
<td>14 (42)</td>
<td>10 (40)</td>
</tr>
<tr>
<td>CRi</td>
<td>NA</td>
<td>4 (16)</td>
</tr>
<tr>
<td>PR</td>
<td>1 (3)</td>
<td>1 (4)</td>
</tr>
<tr>
<td>MLFS/marrow CR</td>
<td>8 (24)*</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Hematologic improvement</td>
<td>7 (21)</td>
<td>NA</td>
</tr>
<tr>
<td>SD</td>
<td>3 (9)</td>
<td>8 (32)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

- Median TTR: 1.9 mos; median OS: NR (either arm)
- 6-mo CR rate, MDS patients: 56%
- 9 of 58 (16%) patients received alloSCT

<table>
<thead>
<tr>
<th>Outcome, n (%)</th>
<th>MDS (n = 33)</th>
<th>AML (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC transfusion independence</td>
<td>11/19 (58)</td>
<td>9/14 (64)</td>
</tr>
<tr>
<td>Complete cytogenetic response</td>
<td>9/26 (35)</td>
<td>6/12 (50)</td>
</tr>
<tr>
<td>MRD negativity in responders</td>
<td>6/30 (20)</td>
<td>8/16 (50)</td>
</tr>
<tr>
<td>Median DoR, mos (range)</td>
<td>NR (0.03+ to 10.4+)</td>
<td>NR (0.03+ to 15.1+)</td>
</tr>
<tr>
<td>Median follow-up, mos (range)</td>
<td>5.8 (2.0 to 15.0)</td>
<td>9.4 (1.9 to 16.9)</td>
</tr>
</tbody>
</table>

*4 patients had marrow CR and hematologic improvement.
Magrolimab + Aza in Patients With MDS and AML: Response in Patients With TP53 Mutation

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MDS TP53 Mutant (n = 12)</th>
<th>AML TP53 Mutant (n = 4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>9 (75)</td>
<td>3 (75)</td>
</tr>
<tr>
<td>CR, n (%)</td>
<td>5 (42)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>CRi/marrow CR, n (%)</td>
<td>4 (33)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Complete cytogenetic response, n/N (%)*</td>
<td>4/8 (50)</td>
<td>3/3 (100)</td>
</tr>
<tr>
<td>MRD negativity in responders, n/N (%)</td>
<td>4/9 (44)</td>
<td>0</td>
</tr>
<tr>
<td>Median DoR, mos</td>
<td>NR (0.03+ to 15.1)</td>
<td>NR (0.03+ to 5.2+)</td>
</tr>
<tr>
<td>6-mo survival probability, %</td>
<td>91</td>
<td>100</td>
</tr>
<tr>
<td>Median follow-up, mos (range)</td>
<td>8.8 (1.9 to 16.9)</td>
<td>7 (4.2 to 12.2)</td>
</tr>
</tbody>
</table>

*Responders with cytogenetic abnormalities at baseline.
Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination With Azacitidine for the Treatment of Patients With Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study

Jacqueline S. Garcia,¹ Andrew H. Wei,² Uma Borate,³ Chun Yew Fong,⁴ Maria R. Baer,⁵ Florian Nolte,⁶ Joseph Jurcic,⁷ Meagan A. Jacoby,⁸ Wan-Jen Hong,⁹ Uwe Platzbecker,¹⁰ Olatoyosi Odenike,¹¹ Ilona Cunningham,¹² Ying Zhou,¹³ Bo Tong,¹³ Leah Hogdal,¹³ Rajesh Kamalakar,¹³ Jessica E. Hutti,¹³ Steve Kye,¹³ Guillermo Garcia-Manero¹⁴
Response Rates and Transfusion Independence

- ORR: 79%
- Median DoR: 12.9 months (min–max, 12.1–16.8)
- Median DoR after CR: 13.8 months (min–max, 6.5–20.9)
- Median time to CR: 2.6 months (min–max, 1.2–19.6)
- For patients receiving Ven 400 mg (RP2D; n=51)
  - 84% of patients achieved ORR
  - 47% achieved ORR by Cycle 2
  - 78% achieved ORR by Cycle 3
  - 35% of patients achieved CR

Transfusion independence rate

<table>
<thead>
<tr>
<th>Transfusion Independence</th>
<th>n (% of N=78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC and platelet</td>
<td>51 (65)</td>
</tr>
<tr>
<td>RBC</td>
<td>52 (67)</td>
</tr>
<tr>
<td>Platelet</td>
<td>60 (77)</td>
</tr>
</tbody>
</table>

A total of 16 patients (21%) went on to receive poststudy transplants; 7 received bone marrow transplant; and 9 received stem cell transplant.

- Aza, azacitidine; CR, complete remission; DoR, duration of response; IWG 2006, International Working Group 2006; mCR, marrow CR; NE, not evaluable; NR, not reported; ORR, objective response rate; PD, disease progression; PR, partial response; RBC, red blood cell; RP2D, recommended phase 2 dose; SD, stable disease; Ven, venetoclax

Data cutoff: June 30, 2020

Slide Courtesy: Dr. Garcia
Allogeneic Transplant – Lower-Risk MDS Decision Model

Allogeneic Transplant – Higher-Risk MDS Decision Model

Summary FDA Approved treatments in MDS

- Lenalidomide for deletion 5q MDS
- Luspatercept for MDS-RS or MDS/MPN-RS-T
- Hypomethylating agents (Azacitidine, Decitabine, Decitabine-cedazuridine)

- Commonly used off-label:
  - Erythropoietin stimulating agents (erythropoietin and darbepoetin)
  - Lenalidomide for non-del(5q) MDS
  - Immunosuppressive therapy (Antithymocyte globulin (ATG) and cyclosporine)
Putting it all together!

1. Observation
2. Transfusion support (best supportive care)
3. Erythropoietin Stimulating Agents
4. Lenalidomide
5. Luspatercept
6. Hypomethylating agents (HMAs): Azacitidine or decitabine
7. Allogeneic Stem Cell Transplant
8. Clinical Trial Options

1. For all lower-risk MDS without transfusion needs
2. ALL patients needing it
3. Lower-risk MDS, with low EPO level (<500) and anemia
4. Lower-risk MDS, deletion 5q and anemia
5. Lower-risk MDS with ring sideroblasts (SF3B1) and anemia
6. ALL Higher-risk MDS (eligible or ineligible for transplant)
7. High-risk MDS and patient eligible/wanting transplant
8. Always encouraged when available
Our patients, caregivers and patient advocates

Bone marrow transplant team

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Yazan Madanat, M.D.
Stephen Chung, M.D.
Madhuri Vusirikala, M.D.
Farrukh Awan, M.D.
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Oluwatomiade Fatunde
Joyce Wang
Yiqing Zhang

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