MYELODYSPLASTIC SYNDROME

- Hemant S. Murthy MD
- Division of Hematology/Oncology
- Associate Professor of Medicine
- Mayo Clinic Comprehensive Cancer Center- Florida
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MYELODYSPLASTIC SYNDROMES

• Heterogenous group of clonal malignant hematopoietic disorders sharing an ineffective production of one or more myeloid cell lines (accelerated apoptosis)
• Typically discrepancy between cellular marrow and peripheral cytopenias
• 10-30,000 cases per year in US
• Median age 76; M>F
• Ineffective hematopoiesis
  • Bleeding, anemia, infections
• Risk of transformation to AML
• Variable clinical course- need for prognostication

PATHOGENESIS OF MDS

• Arise from mutations in hematopoietic stem cells
• Genetic/hematologic conditions
• Extrinsic factors
  • T cell dysregulation, stromal cell abnormalities, inflammasome/inflammatory cytokines
• Familial MDS
  • Germline mutations
    • RUNX1, ANKRD26, CEBPA, DDX41, ETV6, TERC, TERT, SRP72, and GATA2
• Clonal hematopoiesis of indeterminate potential (CHIP)
  • mutations assc. with MDS present, but no dysplasia, cytopenias
<table>
<thead>
<tr>
<th>VAF</th>
<th>Dysplasia</th>
<th>Cytopenias</th>
<th>BM Blast %</th>
<th>Overall Risk</th>
<th>Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>-</td>
<td>-</td>
<td>&lt; 2%</td>
<td>N/A</td>
<td>Micro CHIP</td>
</tr>
<tr>
<td>~9%</td>
<td>-</td>
<td>-</td>
<td>&lt; 2%</td>
<td>Very Low</td>
<td>CHIP</td>
</tr>
<tr>
<td>~10-50%</td>
<td>-</td>
<td>-</td>
<td>&lt; 2%</td>
<td>Low</td>
<td>CCUS</td>
</tr>
<tr>
<td>~30-50%</td>
<td>+</td>
<td>+</td>
<td>&lt; 2%</td>
<td>Low</td>
<td>Lower Risk MDS</td>
</tr>
<tr>
<td>~40-50%</td>
<td>+</td>
<td>+</td>
<td>2-19%</td>
<td>High</td>
<td>Higher Risk MDS</td>
</tr>
<tr>
<td>~40-50%</td>
<td>+</td>
<td>+</td>
<td>20+%</td>
<td>Very High</td>
<td>sAML</td>
</tr>
</tbody>
</table>

Treatments:
- Micro CHIP: N/A
- CHIP: Observation
- CCUS: Obs/BSC/GF
- Lower Risk MDS: Obs/BSC/GF IMiD/IST
- Higher Risk MDS: HMA/HCST
- sAML: HMA/IC/HCST
PREDISPOSITIONS/ RISK FACTORS FOR MDS

- Age
  - Incidence increases with age
  - Uncommon Age <50
  - Most cases age 70’s, 80’s
- Sex (M>f)
- Prior chemotherapy/ radiotherapy
- Tobacco use
- Environmental
  - benzene
- Other heme disorders
  - Aplastic Anemia, PNH
- Genetic
  - Fanconi anemia
  - Shwachman-diamond syndrome
  - Diamond Blackfan anemia
  - Severe congenital neutropenia
  - Dyskeratosis congenita
- Familial MDS (rare)
MDS PRESENTATION

• Symptoms
  • Many present asymptomatic
  • Fatigue
  • Weakness
  • Frequent Infection
  • Bruising

• Physical signs
  • Eccymosis
  • Pallor

• CBC
  • Anemia
  • Macrocytic (MCV >100)
  • Neutropenia
    • Pelger-huet cells
  • Thrombocytopenia
MDS WHO 2022

• Genetically defined
  • MDS-5q
  • MDS-\textit{SF3B1}m
  • MDS-\textit{biTP53}

• Morphologically defined
  • MDS-LB low blasts
  • MDS-h \textit{hypocellular}
  • MDS-IB increased blasts
    • IB-1: 2-4\% PB blasts, 5-9\% BM blasts
    • IB-2: 5-19\% PB blasts, 10-19\% blasts or Auer rods
    • \textit{Fibrosis}: 2-19\% PB blasts, 5-19\% BM blasts

Khoury J et al. *Leukemia* 2022; 36:1703–1719
RISK STRATIFICATION

Factors
- CBC
- Blasts%
- Cytogenetics
- NGS
- models

Values
- Single lineage vs multiple
- <5% vs ≥ 5%
- Complex/-5/-7/-17
- TP53, MLL-PTD
- IPSS-molecular
# R-IPSS OUTCOMES

## IPSS-R Prognostic Score Values*

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast %</td>
<td>(\leq 2)</td>
<td>(&gt;2&lt;0%)</td>
<td>(5-10%)</td>
<td>(&gt;10%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>(\geq 10)</td>
<td>8-10</td>
<td>(&lt;8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>(\geq 100)</td>
<td>50-100</td>
<td>(&lt;50)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>(\geq 0.8)</td>
<td>0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## IPSS-R Cytogenetic Risk Groups*,,**

<table>
<thead>
<tr>
<th>Cytogenetic Prognostic Subgroups</th>
<th>Cytogenetic Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very good</td>
<td>-Y, del(11q)</td>
</tr>
<tr>
<td>Good</td>
<td>Normal, del(5q), del(12p), del(20q), double including del(5q)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>del(7q), +8, +19, i(17q), any other single or double independent clones</td>
</tr>
<tr>
<td>Poor</td>
<td>-7, inv(3)(13q)(d)el(3q), double including -7/del(7q), Complex: 3 abnormalities</td>
</tr>
<tr>
<td>Very Poor</td>
<td>Complex: &gt;3 abnormalities</td>
</tr>
</tbody>
</table>

## IPSS-R: Prognostic Risk Category Clinical Outcomes*

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>No. Pts</th>
<th>Very Low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk Score</td>
<td></td>
<td>(\leq 1.5)</td>
<td>(&gt;1.5-3)</td>
<td>(&gt;3-4.5)</td>
<td>(&gt;4.5-6)</td>
<td>(&gt;6)</td>
</tr>
<tr>
<td>Patients (%)</td>
<td>7012</td>
<td>19%</td>
<td>38%</td>
<td>20%</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td>Survival***</td>
<td>8.8</td>
<td>5.3</td>
<td>3.0</td>
<td>1.6</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>AML/25%***,^</td>
<td>NR</td>
<td>10.8</td>
<td>3.2</td>
<td>1.4</td>
<td>0.7</td>
<td></td>
</tr>
</tbody>
</table>

*Peter L. Greenberg et al. Blood 2012;120:2454-2465*
# MUTATIONS TIPS

<table>
<thead>
<tr>
<th>Gene</th>
<th>Correlation</th>
<th>Rx</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF3B1</td>
<td>Ring sideroblast</td>
<td>luspatercept</td>
</tr>
<tr>
<td>IDH1</td>
<td>Cbc ~</td>
<td>Ivosidenib HMA+VEN</td>
</tr>
<tr>
<td>IDH2</td>
<td>Cbc ~</td>
<td>Enasidenib HMA+VEN</td>
</tr>
<tr>
<td>FLT3</td>
<td>AML transformation</td>
<td>Gilteritinib</td>
</tr>
<tr>
<td>NPM1</td>
<td>AML-defining</td>
<td>CTX vs HMA+VEN</td>
</tr>
<tr>
<td>RUNX1</td>
<td>AML transformation</td>
<td>HMA+VEN</td>
</tr>
<tr>
<td>DDX41</td>
<td>Germline ?, cbc ~</td>
<td>HMA+VEN, LEN</td>
</tr>
<tr>
<td>STAT3</td>
<td>LGL</td>
<td>ISA</td>
</tr>
<tr>
<td>PIGA1</td>
<td>PNH</td>
<td>Complement inhibitor</td>
</tr>
<tr>
<td>UBA1</td>
<td>VEXAS</td>
<td>HMA, JAKi</td>
</tr>
<tr>
<td>TP53</td>
<td>T-MN</td>
<td>? PO DAC</td>
</tr>
</tbody>
</table>
MOL-IPSS

- Clinical-molecular prognostic model (IPSS-Molecular [IPSS-M]), pretreatment diagnostic or peridiagnostic samples from 2957 patients with MDS were profiled for mutations in 152 genes
- \( TP53^{\text{multihit}}, FLT3 \) mutations, and \( MLI^{\text{PTD}} \) top genetic predictors of adverse outcomes.
- \( SF3B1 \) mutations were associated with favorable outcome
- Compared with the IPSS-R, the IPSS-M improved prognostic discrimination across all clinical end points and restratified 46% of patients
Molecular International Prognostic Scoring System for Myelodysplastic Syndromes, Volume: 1, Issue: 7, DOI: (10.1056/EVIDoa2200008)

E Bernard et al. NEJM Evidence 2022;1:EVIDoa2200008.
Low-grade MDS

LUSPATERCEPT
- SF3B1m, MDS-RS, EPO >500

ESA
- EPO <500

TPO mimic
- Low PLT

LEN
- Del 5q

HMA
- 3-7 days
- Failure to prior lines, >1 cytopenia
LUSPATERCEPT

- TGFβ ligand and Smad Fusion protein inhibitor
- In lower-risk, Ring sideroblast-positive MDS:
  - Lupsatercept better in reducing rbc transfusion
    - More transfusion independence
    - Better Hb increase than placebo
  - Erythroid responses were durable, with approximately 40% of patients achieving RBC-TI sustained at 12 months of treatment
  - Well tolerated in this patient population
- FDA approved for thalassemia, MDS

Courtesy Alan List
MDS MEDALIST

- MDS-RS*
  - >18 years
  - IPSS-R:
    - VL, L, Int-1
  - TD (2/8wks)
  - ESA
    - Failure* or
    - not likely to respond

Luspatercept SC 1mg/Kg q 21 days
N=153

Placebo SC q 21 days
N= 76
MDS MEDALIST

The primary endpoint: RBC transfusion independence for at least 12 weeks with a concurrent mean Hg increase of at least 1.5 g/dL (weeks 1-24)
Primary endpoint: luspatercept superior to epoetin alfa

- Of 301 pts included in the efficacy analysis, 86 (58.5%) patients receiving luspatercept and 48 (31.2%) epoetin alfa achieved the primary endpoint
  - Achievement of the primary endpoint favored luspatercept or was similar to epoetin alfa for all subgroups analyzed

This prespecified interim analysis included 301 patients who had either completed 24 weeks of treatment or discontinued prior to completing 24 weeks of treatment.

Della Porta MG, et al. EHA 2023 [Abstract #S102]
Safety profile of luspatercept manageable and comparable to previous studies

- Exposure to luspatercept was ~2 times longer compared with epoetin alfa, providing a longer reporting period for AEs

<table>
<thead>
<tr>
<th></th>
<th>Luspatercept (N = 178)</th>
<th>Epoetin alfa (N = 176)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Heme-related TEAEs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>17 (9.6)</td>
<td>13 (7.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (6.2)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>9 (5.1)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>Leukocytopenia</td>
<td>2 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs of interest</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>26 (14.6)</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>26 (14.6)</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>23 (12.9)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>22 (12.4)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>21 (11.8)</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>21 (11.8)</td>
<td>7 (3.9)</td>
</tr>
<tr>
<td>TEE</td>
<td>8 (4.5)</td>
<td>5 (2.8)</td>
</tr>
</tbody>
</table>

Safety data are not exposure-adjusted.

111 deaths in each arm led to treatment discontinuation. One additional death occurred in the epoetin alfa arm after treatment discontinuation due to an AE; the death occurred during the 42-day safety follow up, which was considered a death during treatment but not counted as a death leading to treatment discontinuation. 2Deaths during treatment period and post-treatment period. TEE, thromboembolic event.

Della Porta MG, et al. EHA 2023 [Abstract #S102]
LUSPATERCEPT

- SC Q21 days
- Adjust dose based on response
- Hold if Hg >11.5
- FDA approved
- Works more if
  - Frontline
  - RS+
  - SF3B1+
  - Thrombocytosis+
  - LT
IMELSTAT

• First-in-class telomerase inhibitor
  • Targets cells with high telomerase activity and human telomerase reverse transcriptase expression, both of which have been reported in MDS

• IMERGE- global phase 2 clinical trial on LR-MDS resistant to ESA
  • Treatment with imetelstat achieved >1 year transfusion independence in 29% of RBC TD, ESA-R/R LR-MDS patients who were non-del(5q) and lenalidomide/HMA-naïve.
  • 24-week TI predicted a likelihood to achieve TI >1 year
IMERGE PHASE 3: STUDY DESIGN

- International, double-blind, randomized phase III trial

Patients with low-risk or intermediate 1–risk MDS (IPSS-R); R/R to ESA or EPO >500 mU/mL (ESA ineligible); RBC transfusion dependent (≥4 U/8 wk over 16 wk prestudy); non-del(5q); no prior lenalidomide or HMAs (N = 178)

- Primary endpoint: 8-wk RBC-TI
- Key secondary endpoints: 24-wk RBC-TI, TI duration, HI-E, safety
- Key exploratory endpoints: changes in VAF, PRO (FACIT-Fatigue)

No new safety signals were identified.

The most common Grade 3/4 AEs were thrombocytopenia and neutropenia, with similar rates of Grade ≥3 bleeding and infections on imetelstat and placebo.

In pts treated with imetelstat, cytopenias were manageable, of short duration, and >80% were reversible to Grade ≤2 within 4 wks.
IMPACT OF TREATMENT ON REDUCTION OF VAF

- Maximum Increase in Hb vs Maximum Reduction in SF3B1 VAF
  - Imetelstat (N = 67)
  - P-Value: < 0.001
  - Pearson Correlation Coefficient: -0.626

- Longest RBC-Ti Duration vs Maximum Reduction in SF3B1 VAF
  - Imetelstat (N = 78)
  - P-Value: < 0.001
  - Pearson Correlation Coefficient: -0.549

TET2, DNMT3A, or ASXL2 VAF reductions correlated with longer RBC-Ti duration

- Box plots showing the change in variant allele frequency in blood:
  - SF3B1: N = 78, P = 0.032
  - TET2: N = 38
  - DNMT3A: N = 12, P = 0.019
  - ASXL1: N = 6, P = 0.146

MDS-003: STUDY DESIGN

Eligibility
- Low-/Int-1-risk del(5q) MDS
- RBC transfusion ≥ 2 units/8 weeks
- ANC ≥ 500/mm³
- Platelets ≥ 50,000/mm³
- Leukocytes ≥ 12,000/mm³

Week: 0 6 12 18 24

Yes ➔ Continue
No ➔ Off study

Lenalidomide, p.o.
- 10 mg for 21 days of each 28-day cycle

Primary objective: erythroid response* (RBC-TI)
Secondary objectives: RBC-TI duration, cytogenetic response, tolerability

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 148 (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response, n (%)</td>
<td></td>
</tr>
<tr>
<td>RBC-TI (≥ 56 consecutive days without transfusion and Hb levels rose by 1 g/dL)</td>
<td>99 (67)</td>
</tr>
<tr>
<td>≥ 50% decrease in transfusions</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Total (RBC-TI + ≥ 50% decrease in transfusions)</td>
<td>112 (76)</td>
</tr>
<tr>
<td>Median Hb increase, g/dL (range)</td>
<td>5.4 (1.1–11.4)</td>
</tr>
<tr>
<td>Median time to response, weeks (range)</td>
<td>4.6 (1–49)</td>
</tr>
</tbody>
</table>

- RBC-TI achieved by 67% of lenalidomide-treated del(5q) patients
## LEN IN MDS 5Q TP53+

<table>
<thead>
<tr>
<th></th>
<th>TP53 wt</th>
<th>TP53 mu</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>59</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Median cycles</td>
<td>16</td>
<td>6</td>
<td>0.38</td>
</tr>
<tr>
<td>TI</td>
<td>75%</td>
<td>50%</td>
<td>0.2</td>
</tr>
<tr>
<td>TTR</td>
<td>4 months</td>
<td>4 months</td>
<td></td>
</tr>
<tr>
<td>event</td>
<td>25%</td>
<td>63%</td>
<td>0.045</td>
</tr>
<tr>
<td>progression</td>
<td>15%</td>
<td>25%</td>
<td>0.6</td>
</tr>
<tr>
<td>Median time to 25% AML</td>
<td>NR</td>
<td>18 m</td>
<td></td>
</tr>
<tr>
<td>OS, months</td>
<td>NR</td>
<td>43.2</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Table 1. Patient characteristics of all patients analyzed for TP53 mutations

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>TP53&lt;sup&gt;wt&lt;/sup&gt;</th>
<th>TP53&lt;sup&gt;mu&lt;/sup&gt;</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>59</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>54 (82)</td>
<td>11 (19)</td>
<td>2 (35)</td>
</tr>
<tr>
<td>Female</td>
<td>13 (18)</td>
<td>11 (19)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Median age range</td>
<td>70 (40-86)</td>
<td>70 (46-86)</td>
<td>74 (57-87)</td>
</tr>
<tr>
<td>MDS subtype, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDS U</td>
<td>2 (3)</td>
<td>2 (3)</td>
<td>0</td>
</tr>
<tr>
<td>RCMD (RA, RT)</td>
<td>13 (19)</td>
<td>12 (20)</td>
<td>1</td>
</tr>
<tr>
<td>RICMD</td>
<td>43 (64)</td>
<td>37 (63)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>RICMD-HS</td>
<td>9 (13)</td>
<td>8 (14)</td>
<td>1</td>
</tr>
<tr>
<td>Subtypes, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>55 (77)</td>
<td>47 (80)</td>
<td>7 (88)</td>
</tr>
<tr>
<td>RARS</td>
<td>9 (13)</td>
<td>8 (13)</td>
<td>1 (12)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (6)</td>
<td>4 (7)</td>
<td>0</td>
</tr>
<tr>
<td>FAS risk groups, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>42 (63)</td>
<td>35 (59)</td>
<td>7 (87)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>21 (31)</td>
<td>20 (34)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (6)</td>
<td>4 (7)</td>
<td>0</td>
</tr>
<tr>
<td>FAS-R risk groups, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>8 (13)</td>
<td>6 (10)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>Low</td>
<td>49 (73)</td>
<td>44 (75)</td>
<td>3 (62)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>6 (9)</td>
<td>5 (8)</td>
<td>1 (13)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (6)</td>
<td>4 (7)</td>
<td>0</td>
</tr>
<tr>
<td>Mean blood counts (bL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb (g/dL)</td>
<td>8.9 (1.3)</td>
<td>8.9 (1.3)</td>
<td>9.2 (1.5)</td>
</tr>
<tr>
<td>ANC (x 10&lt;sup&gt;9&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td>3.11 (1.3)</td>
</tr>
<tr>
<td>Platelets (x 10&lt;sup&gt;12&lt;/sup&gt;)</td>
<td></td>
<td></td>
<td>333 (265)</td>
</tr>
<tr>
<td>Ferritin (muG/L)</td>
<td>1301 (1306)</td>
<td>1405 (1399)</td>
<td>1277 (683)</td>
</tr>
<tr>
<td>Mean marrow blast count, % (SD)</td>
<td>2.0 (1.4)</td>
<td>2.3 (1.3)</td>
<td>1.6 (1.6)</td>
</tr>
<tr>
<td>Median number of PBPC transfusions 8 weeks before enrollment, n (range)</td>
<td>2 (0-10)</td>
<td>2 (0-8)</td>
<td>5 (0-10)</td>
</tr>
<tr>
<td>Median time from first diagnosis to treatment, months (range)</td>
<td>30 (2-183)</td>
<td>22 (1-181)</td>
<td>14 (2-99)</td>
</tr>
<tr>
<td>Median number of len cycles, n (range)</td>
<td>15 (1-49)</td>
<td>16 (1-49)</td>
<td>6 (1-28)</td>
</tr>
</tbody>
</table>

SINTRA-REV: STUDY DESIGN

- Multicenter, randomized, double-blind, placebo-controlled phase III trial

Patients with RBC-TI MDS; IPSS low or intermediate-1; Hb <12 g/dL; del(5q) ± other abnormality (N = 61)

Lenalidomide
5 mg/day on D1-28 of 28-day cycle (n = 40)

Placebo
5 mg/day on D1-28 of 28-day cycles (n = 21)

2:1

Primary endpoint: time to transfusion dependence

Secondary endpoints: erythroid response, cytogenetic response, duration of RBC-TI, change in Hb, bone marrow response, neutrophil/platelet changes, safety, OS, EFS, AML transformation, clonal evolution

Follow-up (108 Wk)

MDS assessment at 12 wk and every 6 mo thereafter

End of tx

Discontinue tx if no clinical benefit and/or PD and/or unacceptable toxicity; no crossover allowed
SINTRA-REV: TIME TO TRANSFUSION DEPENDENCY IN ITT POPULATION (PRIMARY ENDPOINT)

- **Time to Transfusion Dependency**

- **Cumulative Survival**

- **Median follow-up: 5.05 yr (range: 0.3-11)**

- **Table:***

<table>
<thead>
<tr>
<th></th>
<th>LEN (n = 40)</th>
<th>Placebo (n = 21)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events, n (%)</td>
<td>10 (25)</td>
<td>13 (65)</td>
<td>.005</td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.302 (0.132-0.692)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median time to TD, mo</td>
<td>NR</td>
<td>11.6</td>
<td>.003</td>
</tr>
</tbody>
</table>

Low grade MDS

MDS del 5q

MDS SF3B1/RS

MDS-LB

Failure

Trial

IDH1m

IDH2m

Ivosidenib

Enasidenib

Epo

ESA

HMA

Hg <10

Hg+ PLT/WBC

LUSP

ESA

MDS

LEN

Hg x3d

LUSP

@AlkaliDr

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Current Treatment Algorithm in HR-MDS

- **Transplant candidate?**
  - **YES**
    - Bridge to alloSCT
      - Single-agent HMA
      - HMA + novel combinations
      - AML-like chemotherapy
  
  - **NO**
    - Continuous HMA*
    - Clinical trial

*Maintain schedule with dosing interval and intensity for first 4-6 cycles for maximum benefit
AZA vs CCR in high risk MDS

**Graph:**
- **Proportion Surviving**
- **Time from Randomization (Months)**
- **Azacitidine**
- **CCR**
- **15 mos**
- **24.5 mos**

**Statistics:**
- **HR 0.58**
- **95% CO: 0.43 - 0.77**
- **P = 0.0001**

**Footnote:**
- **CCR: 7+3, LDAC, BSC**
- **Fenaux et al. Lancet Oncology 2009**
Azacitidine and Venetoclax in HR-MDS

Garcia J et al. ASH Annual Meeting 2021, Atlanta GA. Abstract 241

ORR Across Baseline Mutations

# Patients With Mutation

mORR 85%

CR
To transplant or not……

Biologic Assignment Trial of Reduced-Intensity Hematopoietic Cell Transplantation Based on Donor Availability in Patients 50-75 Years of Age With Advanced Myelodysplastic Syndrome

Ryotaro Nakamura, MD⁴; Wael Saber, MD, MS²; Michael J. Martens, PhD²; Alyssa Ramirez, BS⁴; Bart Scott, MD⁴; Betul Oran, MD⁵; Eric Leifer, PhD⁵; Roni Tamari, MD⁷; Asmita Mishra, MD⁶; Richard T. Maziarz, MD⁹; Joseph McGurk, DO¹⁰; Peter Westervelt, MD, PhD¹¹; Sumithira Vasu, MBBS¹²; Mrinal Patnaik, MBBS¹³; Rammurti Kamble, MD¹⁴; Stephen J. Forman, MD¹; Mikkael A. Sekeres, MD, MS¹⁵; Frederick Appelbaum, MD¹⁶; Adam Mendizabal, PhD¹⁷; Brent Logan, PhD²; Mary Horowitz, MD, MS²; and Corey Cutler, MD, MPH¹⁸; on behalf of the Blood and Marrow Transplant Clinical Trials Network

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Clinical outcomes
(Donor arm=260 and No donor arm=124 patients)
Quality of life similar in both groups
Comparison Between 5-Azacytidine Treatment and Allogeneic Stem-Cell Transplantation in Elderly Patients With Advanced MDS According to Donor Availability (VidazaAllo Study)

Nicolaus Kröger, MD; Katja Sackel, MD; Christine Weischenk, MD; Wolfgang Bethge, MD; Richard F. Schlenk, MD; Dominik Wolf, MD; Michael Stadler, MD; Guido Kobbe, MD; Gerald Wolf, MD; Gesine Bug, MD; Kerstin Schäfer-Eckart, MD; Christof Scheid, MD; Florian Nolte, MD; Jan Krönke, MD; Matthias Stelljes, MD; Dietrich Boelen, MD; Marion Heinzelmann, MD; Detlef Haase, MD; Hannes Buchner, PhD; Gabriele Bleckert, PhD; Aristoteles Giagounidis, MD; Uwe Platzbecker, MD; on behalf of the German MDS Study Group and the German Cooperative Transplant Study Group

J Clin Oncol 39:3318-3327. © 2021 by American Society of Clinical Oncology
Clinical outcomes
(HCT arm=81 and continuous 5-Aza arm=27)
Does transplant work even with high risk mutations such as TP53?

Versluis et al. JCO 2023
Eprenetapopt (APR-246) + HMA following Allo-hct

• 33 patients (14 AML, 19 MDS)
• Median age was 65 (range, 40-74) years.
• Median number of eprenetapopt cycles was 7 (range, 1-12).
• With a median follow-up of 14.5 months, the
  • median RFS was 12.5 months
  • 1-year RFS probability was 59.9% (95% CI, 41 to 74).
  • median follow-up of 17.0 months,
  • median overall survival (OS) was 20.6 months (95% CI, 14.2 to not estimable)
  • 1-year OS probability was 78.8% (95% CI, 60.6 to 89.3).
Conclusions

• Many recent advances in Prognostication and Treatment of MDS
  • M-IPSS
  • CHIP, CCUS

• New indications/ therapies for LR-MDS
  • Luspatercept, Imelstat

• Allo-hct with proven survival benefit in HR-MDS in older adults
  • Effective strategy even in TP53 myeloid neoplasm
Allo-HCT for high risk MDS (BMT CTN 1102)

• Allo-HCT with reduced intensity conditioning (RIC) in patients 50 to 75 years old with HR-MDS comparing patients with and without a (HLA)-matched donor.

• 384 total patients
  • 67.7% (260 patients) had a matched donor and
  • 32.3% (124 patients) did not have a matched donor and instead received HMA and/or supportive care

• HLA-matched donor experienced
  • increased OS (absolute improvement in 3-year OS was 21.3% [95% CI, 10.2-31.8; \( P = .0001 \)])
  • improved leukemia-free survival (absolute improvement in 3-year LFS was 15.2% [95% CI, 13.3-29.1; \( P = .003 \)])

• Interestingly, OS was significantly shorter in patients without response to HMA prior to alloSCT (HR, 1.64; \( P = .0097 \))
Assessing the Role of Venetoclax in Combination with Hypomethylating Agents in Higher Risk Myelodysplastic Syndromes

- Higher risk MDS at Moffitt Cancer Center (INT, H, VH)
- Compare: first line single agent HMA, first line HMA/Ven combination, HMA, but add Ven after HMA failure (R/R MDS HMA/Ven)

| Table 1: Baseline characteristics comparing HMA alone versus HMA/Ven first line therapy in higher risk MDS |
| --- | --- | --- | --- |
| | HMA IL | HMA/Ven IL | P value |
| n | 1127 | 35 | 2 |
| Age | mean 68.4 | 67.8 | .76 |
| Gender | Male | 66% | 71% | 5 |
| Race | White | 50% | 57% | .66 |
| Time | 24% | 23% | .86 |
| WHO 2016 | MDS-5q/5q- | 14% | 4% | .04 |
| | MDS-05 | 6% | 4% | 9% |
| | MDS-EB | 33% | 9% | 78% |
| | MDS-EB-2 | 26% | 9% | 89% |
| R-IPSS | Intermediate | 31% | 17% | .22 |
| | High | 31% | 27% | 95% |
| | Very high | 38% | 46% | .02 |
| Myeloblasts | NHL | M | 9 | 12 | < .005 |
| | WBC | Mean (g/dL) | 9 | 10.6 | < .005 |
| | ANC | Mean (g/dL) | 4 | 4.1 | < .005 |
| | Platelets | Median (g/dL) | 96 | 100 | 8 |
| Somatic Mutations (n: 546 sequenced) | TET2 | 16% | 0 | 3 |
| | IDH-2 | 5% | 5% | 9 |
| | IDH-1 | 5% | 5% | 7 |
| | ASAT-2 | 5% | 8% | .06 |
| | TP53 | 27% | 24% | 6 |
| | MLL | 4% | 11% | .07 |

HMA and add VEN later
**TP53 Mutations Predict Prognosis in MDS**

- p53 is a critical tumor suppressor protein that responds to cellular stress by inducing cell cycle arrest, senescence and/or apoptosis to eliminate precancerous and tumor cells.

- Mutations in the *TP53* gene (m*TP53*) are found in 5-10% of MDS and AML patients and predict for the most inferior OS (median OS 6-12 months).

- Confers poor prognosis in allo-SCT

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Thank you