Myelodysplastic Syndrome

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CONFLICTS OF INTEREST

Advisory Board meetings: Merck, Molmed, Jazz Pharmaceuticals
Translation for lay people

- Myelo (=bone marrow)
- Dysplastic (=looks funny)
- Syndrome (=we don’t really know what it is)
Patients: limited understanding, lack of insight

- An Internet-based survey of 348 MDS patients
  - 80% reported that their MDS was first described as a “bone marrow disorder,”
  - 6% to 7% indicated their MDS was first described as either “cancer” or “leukemia.”
  - 42% did not know their blast percentage.

- A separate Internet-based survey of 349 MDS patients
  - 33% did not know their MDS subtype.

Oncologist 2011;16(6):904-911
Characteristics of this “syndrome”

- Ineffective hematopoiesis with **cytopenia**
- **Dysplastic** morphology
- **Clonal disorder** of hematopoietic stem cells
- Tendency to evolve to **acute leukemia**

Mortality: cytopenia and AML transformation
Components of MDS Diagnosis

- Clonal hematopoiesis
- Cytopenia
- Dysplastic morphology
Diagnostic Challenges

- Overlap “bone marrow failure” syndrome
  - Aplastic anemia
    - red cell aplasia
    - amegakaryocytic thrombocytopenia
    - agranulocytosis
  - “Hypoplastic MDS”
  - Large granular lymphocyte disease (CD3/CD8/CD57, TCR gene rearrangement)
  - Co-existing PNH clone
- Idiopathic thrombocytopenic purpura
- Metabolic (B12, copper deficiency)
- Other systemic medical illnesses associated with cytopenia (infectious disease, autoimmune disease, liver disease etc.)
MDS as a spectrum of hematologic condition

Young NS. Ann Int Med 2002
Somatic mutations and clonal hematopoiesis in aplastic anemia

NEJM 2015; 373: 35-47
Somatic mutations and clonal hematopoiesis in aplastic anemia
### Indolent Myeloid Hematopoietic Disorders

- Idiopathic Cytopenias of Unknown Significance (ICUS)
- Idiopathic Dysplasia of Unknown Significance (IDUS)
- Clonal Hematopoiesis of Indeterminate Potential (CHIP)
- Clonal Cytopenias of Unknown Significance (CCUS)

<table>
<thead>
<tr>
<th>Feature</th>
<th>ICUS</th>
<th>IDUS</th>
<th>CHIP</th>
<th>CCUS</th>
<th>MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic mutation</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Clonal karyotypic abnormality</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>Marrow dysplasia</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Aplastic anemia with clonal hematopoiesis?
Components of MDS diagnosis and spectrum

- Clonal hematopoiesis
- Cytopenia
- Dysplastic morphology
- CHIP
- ICUS
- IDUS
- CCUS
# Definition of Cytopenia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC (x10⁹/L)</td>
<td>&lt;1.8 (WHO/IPSS)  &lt;1.5 (2007 MDS Consensus)</td>
</tr>
<tr>
<td>HGB (g/dL)</td>
<td>&lt;10 (WHO/IPSS)  &lt;11 (2007 MDS Consensus)  &lt;12/13 (WHO anemia definition)</td>
</tr>
<tr>
<td>Platelets (x10⁹/L)</td>
<td>&lt;100 (WHO/IPSS)  &lt;150 (normal reference)</td>
</tr>
</tbody>
</table>

### WHO 2016 - MDS

#### WHO 2016
- MDS with single lineage dysplasia
- MDS with ring sideroblasts (MDS-RS)
  - MDS-RS and single lineage dysplasia
  - MDS-RS and multilineage dysplasia
- MDS with multilineage dysplasia
- MDS with excess blasts
- MDS with isolated del(5q)
- MDS, unclassifiable

#### WHO 2008
- Refractory cytopenia with unilineage dysplasia (RCUD)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with ring sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia and ring sideroblasts (RCMD-RS)
- MDS with isolated del(5q)
- MDS, unclassifiable (MDS,U)
- Refractory anemia excess blasts (RAEB)

*Provisional entity: refractory cytopenia of childhood myeloid neoplasms with germ line predisposition*

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML), BCR-ABL1−
- Juvenile myelomonocytic leukemia (JMML)
- MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T)
- MDS/MPN, unclassifiable

MDS/MPN diagnostic criteria
- Anemia associated with erythroid lineage dysplasia with or without multilineage dysplasia, $15\%$ ring sideroblasts, $1\%$ blasts in PB and $5\%$ blasts in the BM
- Persistent thrombocytosis with platelet count $\geq 450 \times 10^{9}/L$
- Presence of a SF3B1 mutation or, in the absence of SF3B1 mutation, no history of recent cytotoxic or growth factor therapy that could explain the myelodysplastic/myeloproliferative features†
- No BCR-ABL1 fusion gene, no rearrangement of PDGFRA, PDGFRB, or FGFR1; or PCM1-JAK2; no (3;3)(q21;q26), inv(3)(q21q26) or del(5q)‡
- No preceding history of MPN, MDS (except MDS-RS), or other type of MDS/MPN
# MDS-defining cytogenetic abnormalities (WHO 2016)

<table>
<thead>
<tr>
<th>Unbalanced</th>
<th>Primary MDS</th>
<th>Therapy-related MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>-7 or del(7q)</td>
<td>10%</td>
<td>50%</td>
</tr>
<tr>
<td>-5 or del(5q)</td>
<td>10%</td>
<td>40%</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>3-5%</td>
<td></td>
</tr>
<tr>
<td>-13 or del(13q)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(11q)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>del(9q)</td>
<td>1-2%</td>
<td></td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td>1-2%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Balanced</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;16)(q23;p13.3)</td>
<td>3%</td>
</tr>
<tr>
<td>t(3;21)(q26.2;q22.1)</td>
<td>2%</td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
<td>1%</td>
</tr>
<tr>
<td>t(2;11)(p21;q23)</td>
<td>1%</td>
</tr>
<tr>
<td>inv(3)(q21q26.2)</td>
<td>1%</td>
</tr>
<tr>
<td>t(6;9)(p23;q34)</td>
<td>1%</td>
</tr>
</tbody>
</table>

+8, -Y, and del(20q) are common in MDS, but can occur in non-neoplastic conditions and are not MDS-defining.
Prognosis

IPSS
cytopenia, cytogenetics, %blasts

International Prognostic Scoring System (IPSS)\textsuperscript{s,t}

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>Marrow blasts (%)\textsuperscript{u}</td>
<td>&lt;5 5-10 11-20 21-30</td>
</tr>
<tr>
<td>Karyotype\textsuperscript{v}</td>
<td>Good Intermediate Poor</td>
</tr>
<tr>
<td>Cytopenia\textsuperscript{w}</td>
<td>0/1 2/3</td>
</tr>
</tbody>
</table>

A

International MDS Risk Classification

Survival

- Low: 267 pts
- Int-1: 314 pts
- Int-2: 179 pts
- High: 56 pts

B

AML Evolution

- Low: 235 pts
- Int-1: 295 pts
- Int-2: 171 pts
- High: 58 pts

Blood 1997; 89(6): 2079-2088
# Revised International Prognostic Scoring System (IPSS-R)

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Score value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
</tr>
<tr>
<td>Marrow blasts (%)</td>
<td>≤2</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
</tr>
</tbody>
</table>

**IPSS-R Risk category (%) IPSS-R pop.**

- **VERY LOW (19)**: Overall score ≥1.5, Median survival (y) in the absence of therapy 8.8, 25% AML progression (y) in the absence of therapy Not reached
- **LOW (38)**: >1.5-3, 5.3, 10.8
- **INT (20)**: >3-4.5, 3, 3.2
- **HIGH (13)**: >4.5-6, 1.6, 1.4
- **VERY HIGH (10)**: >6, 0.8, 0.7


y Cytogenetic risks: Very good = -Y, del(11q); Good = Normal, del(5q), del(12p), del(20q), double including del(5q); Intermediate = del(7q), +8, +19, i(17q), any other single or double independent clones; Poor = -7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities; Very poor = Complex: >3 abnormalities.

![Graph showing survival based on IPSS-R prognostic risk-based categories](image)

**Figure 3.** Survival based on IPSS-R prognostic risk-based categories. Survival related to MDS patients’ prognostic risk categories (Kaplan-Meier curves, n = 7012; Dxy 0.43, P < .001). The number of patients in each category and their proportional representation are shown in Table 1.
Somatic Mutations

Splicing Factors (~50%)
- SF3B1 (18%)
- U2AF1 (12%)
- SRSF2 (12%)
- ZRSR2 (5%)
- Others (5%)
Rarely co-occur with each other

Both Splicing Factors (SF) & Epigenetic Regulators (ER) Overlap (25%)

Epigenetic Regulators (~45%)
- TET2 (20%)
- ASXL1 (15%)
- DNMT3A (12%)
- EZH2 (5%)
- IDH1/2 (5%)
- Others (5%)
Often co-occur except for TET2 and IDH

TP53 and no SF or ER (~5%)
Often complex karyotypes with frequent del(5q), abnormal chromosome 7, and monosomies
Other mutations less frequent

No Common Abnormality (~5%)
Karyotype Abnormality Only (~5%)

Mutations in Other Genes Only (~15%)
- Transcription Factors
  RUNX1, ETV6, PHF6, GATA2, ...
- Kinase Signalling
  NRAS, KRAS, JAK2, CBL, ...
- Cohesins
  STAG2, SMC3, RAD21, ...
- DNA Repair
Clinical Effect of Point Mutations in Myelodysplastic Syndromes

Rafael Bejar, M.D., Ph.D., Kristen Stevenson, M.S., Omar Abdel-Wahab, M.D., Naomi Galili, Ph.D., Björn Nilsson, M.D., Ph.D., Guillermo Garcia-Manero, M.D., Hagop Kantarjian, M.D., Azra Raza, M.D., Ross L. Levine, M.D., Donna Neuberg, Sc.D., and Benjamin L. Ebert, M.D., Ph.D.

- Genomic approaches: next-generation sequencing and mass spectrometry–based genotyping,

- Bone marrow aspirate from 439 patients wit MDS.

- Association with clinical variables
Mutations of genes in tyrosine-signaling pathways (JAK2, CBL, and NRAS–KRAS–BRAF) were largely mutually exclusive (Fig. 1).

TET2 mutations, in contrast, overlapped with lesions in nearly every other mutated gene, suggesting that TET2 mutations have a pathogenic role that is at least partially independent of other abnormalities.

## Risk factors for OS

### Table 2. Hazard Ratios for Death in a Multivariable Model.*

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥55 yr vs. &lt;55 yr</td>
<td>1.81 (1.20–2.73)</td>
<td>0.004</td>
</tr>
<tr>
<td>IPSS risk group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-1 vs. low</td>
<td>2.29 (1.69–3.11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate-2 vs. low</td>
<td>3.45 (2.42–4.91)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High vs. low</td>
<td>5.85 (3.63–9.40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mutational status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TP53 mutation present vs. absent</td>
<td>2.48 (1.60–3.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>EZH2 mutation present vs. absent</td>
<td>2.13 (1.36–3.33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ETV6 mutation present vs. absent</td>
<td>2.04 (1.08–3.86)</td>
<td>0.03</td>
</tr>
<tr>
<td>RUNX1 mutation present vs. absent</td>
<td>1.47 (1.01–2.15)</td>
<td>0.047</td>
</tr>
<tr>
<td>ASXL1 mutation present vs. absent</td>
<td>1.38 (1.00–1.89)</td>
<td>0.049</td>
</tr>
</tbody>
</table>
OS according to IPSS and mutation status
(TP53, EZH2, ETV6, RUNX1, or ASXL1)

Landscape of genetic lesions in MDS
Landscape of genetic lesions in MDS

N=944
Diagnostic Challenges - Examples

45yo F with hypocellular BM, 45,X in 15/20 metaphases
  -> slowly responded to ATG/CSA (turned to be mosaic Turner)

80yo F with severe pancytopenia and hypocellular BM, 13q- in cytogenetics
  -> responded to ATG/CSA/promacta

50yo F, thrombicytopenia, trisomy 8, morphologic dysplasia in BM, Plt-assoc Ab positive
  -> responded to prednisone/eltrombopag

60 yo F with a h/o aplastic anemia with a response to ATG/CSA, who developed recurrent cytopenia with trisomy 8 and PNH clone
  -> eventually evolved into hemolytic PNH currently on eculizumab (trisomy 8 undetectable)
Diagnostic Challenges - Examples

51yo male: thrombocytopenia (~50k/ul), mild anemia, no PNH, hypocellular marrow, no clear dysplasia

Cytogenetics:  
- Clone 1: 46,XY,+1,der(1;7)(q10;p10)[4]
- Clone 2: 46,XY,+1,der(1;12)(q10;q10)[5]
### Germline mutations with predisposition for MDS/AML/MPN

<table>
<thead>
<tr>
<th>Familial MDS/AML</th>
<th>Classical Inherited BMF Syndrome</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>RUNX1</td>
<td>• TERT/TERC</td>
<td>• TP53 (Li-Fraumeni)</td>
</tr>
<tr>
<td>GATA1</td>
<td>• FANC genes</td>
<td>• PTPN11, CBL,</td>
</tr>
<tr>
<td>ETV6</td>
<td>• Fanconi anemia</td>
<td>• KRAS</td>
</tr>
<tr>
<td>CEBPA</td>
<td>• DKC</td>
<td>• NF1</td>
</tr>
<tr>
<td>DDX41</td>
<td>• ELA2, HAX1, GFI1</td>
<td>• BLM</td>
</tr>
<tr>
<td>ANKRD26</td>
<td>• Congenital neutropenia</td>
<td>• ATG2B/GSKIP</td>
</tr>
<tr>
<td>SRP72</td>
<td></td>
<td>• BRACA1/2</td>
</tr>
</tbody>
</table>
Management Approaches

- **Supportive care**
  - Transfusions
  - Growth factors (EPO if EPO level <500μg/ml, G+Epo for MDS-RS)
  - IV access, iron chelation

- **MDS-directed therapy**
  - Hypomethylating agents: 5-azacitidine, decitabine
  - Lenalidomide
  - Immunosuppressive therapy (overlap BM failure)

- **Conventional chemotherapy:** cyto-reductive
  - 7+3, FLAG, MEC, clofarabine, low-dose cytarabine, etc.

- **Potentially curative therapy**
  - Allogeneic HCT
Goals of Therapy

- Cure
- Improve the natural history
  - prolong life
  - delay transformation
- Symptomatic support

Weigh against side effects/risks
Can’t get wrong by referring to clinical trials.
RBC transfusions, EPO

- RBC transfusion parameter: to be individualized (7-9 g/dl)
- Lower parameters may not always reduce transfusions...
- EPO: if <500 iu/l
- EPO plus GCSF: to be considered for MDS-RS
Iron Chelation Therapy

- Survival benefit? Benefit in hematopoiesis by reducing free radicals? in retrospective studies (no prospective randomized trial data)
- Currently approved agents are inconvenient (deferroxamine) or costly and not well-tolerated by many patients (deferasirox).
- TELESTO trial: multicenter, randomized, double-blind, placebo-controlled trial of deferasirox on low-risk MDS patients with iron overload (NCT00940602)
- New formulation of deferasirox: Jadenu

NCCN guideline: IPSS low, int-1, Target ferritin: 1000 ng/ml
- >20 transfusions, or
- Anticipated ongoing RBC transfusions, or
- Serum ferritin >2500 ng/ml
Potential risk to augment myeloblast proliferation

The rate of progression to AML was not increased with romiplostim therapy in lower-risk MDS,

Platelet transfusion needs and clinically significant bleeding events were reduced with active therapy.

Decreased frequency of dose reductions or delays in patients receiving lenalidomide therapy.
TPO Receptor Agonists

Median platelet counts over time.

Kantarjian et al. JCO 2010;28:437-444
Lenalidomide

Forty-three patients with transfusion-dependent or symptomatic anemia received lenalidomide at doses of 25 or 10 mg per day or of 10 mg per day for 21 days of every 28-day cycle.

Erythroid Response rate:
5q31.1: 83%
normal karyotype: 57%
other karyotypic abnormalities: 12%

Phase II, N=148, 10mg/d continuous or 21d

- 112 had a reduced (>50%) need for transfusions (76%)
- 99 patients (67%): TI regardless of the karyotype complexity.
- Median time to response, 4.6 weeks; range, 1 to 49
- Sustained response: the median duration of TI had not been reached after a median of 104 weeks of follow-up.
- Cytogenetic response:
  - 62 of 85 had cytogenetic improvement (38: complete cytogenetic remission).

Ph-2 study of lenalidomide in transfusion-dependent, low/int1–risk MDS with karyotypes other than -5q

Table 4. Modified IWG 2000 erythroid response to lenalidomide

<table>
<thead>
<tr>
<th>Variable</th>
<th>Continuous daily dosing, n = 100*</th>
<th>21-day dosing, n = 114*</th>
<th>All patients, n = 214</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response, no (%) [95% CI]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion independence and 10 g/L Hb or more increase</td>
<td>27 (27)</td>
<td>29 (25)</td>
<td>56 (26) [20-33]</td>
</tr>
<tr>
<td>50% or greater decrease in no. of transfusions</td>
<td>15 (15)</td>
<td>22 (19)</td>
<td>37 (17) [12-23]</td>
</tr>
<tr>
<td>Total transfusion response</td>
<td>42 (42)</td>
<td>51 (45)</td>
<td>93 (43) [37-50]</td>
</tr>
<tr>
<td>Median time to transfusion independence, wk (range)</td>
<td>7.4 (1-24)</td>
<td>4.1 (1-39)</td>
<td>4.8 (1-39)</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, median (range)†</td>
<td>79 (62-97)</td>
<td>81 (61-106)</td>
<td>80 (61-106)</td>
</tr>
<tr>
<td>Response, median (range):‡</td>
<td>116 (91-168)</td>
<td>110 (73-180)</td>
<td>116 (73-180)</td>
</tr>
<tr>
<td>Increase, median (range)</td>
<td>33 (15-92)</td>
<td>31 (10-98)</td>
<td>32 (10-98)</td>
</tr>
</tbody>
</table>

Table 5. TI response by baseline FAB type, IPSS risk category, cytogenetic findings, and transfusion burden

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
<th>Patients with TI response, no. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAB type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>47</td>
<td>16 (34)</td>
</tr>
<tr>
<td>RARS</td>
<td>86</td>
<td>30 (35)</td>
</tr>
<tr>
<td>RAEB</td>
<td>24</td>
<td>6 (25)</td>
</tr>
<tr>
<td>CMML</td>
<td>20</td>
<td>3 (15)</td>
</tr>
<tr>
<td>RAEB-t</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>AML</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Missing</td>
<td>31</td>
<td>1 (3)</td>
</tr>
<tr>
<td>IPSS risk category</td>
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</tr>
<tr>
<td>Low</td>
<td>92</td>
<td>31 (34)</td>
</tr>
<tr>
<td>Intermediate-1</td>
<td>76</td>
<td>23 (30)</td>
</tr>
<tr>
<td>Intermediate-2/high</td>
<td>8</td>
<td>0</td>
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<tr>
<td>Missing</td>
<td>38</td>
<td>2 (5)</td>
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<tr>
<td>Cytogenetic findings</td>
<td></td>
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</tr>
<tr>
<td>Normal karyotype</td>
<td>160</td>
<td>42 (28)</td>
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<tr>
<td>Abnormal karyotype</td>
<td>47</td>
<td>13 (28)</td>
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<tr>
<td>Missing</td>
<td>7</td>
<td>1 (14)</td>
</tr>
</tbody>
</table>

Blood. 2008;111:86-93
Hypomethylating Agents

Randomized Controlled Trial of Azacitidine in Patients With the Myelodysplastic Syndrome: A Study of the Cancer and Leukemia Group B


J Clin Oncol 20:2429-2440
Table 4. Demographic and Clinical Characteristics at Study Entry

<table>
<thead>
<tr>
<th></th>
<th>Aza C</th>
<th>Supportive Care</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Randomized</td>
<td>99</td>
<td>52</td>
<td>92</td>
</tr>
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<td>CMMoL</td>
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<td>Other*</td>
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<td>IPSS risk group†</td>
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<td>Range</td>
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<td>Patients requiring RBC transfusions‡</td>
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<td>Time from diagnosis to study entry</td>
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<td>Range</td>
<td>1 day-6.4 years</td>
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<td>2 days-6 years</td>
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Abbreviation: IPSS, International Prognostic Scoring System.
*Includes 19 AML, one unclassifiable acute leukemia, and one undefined MDS.
†Complete cytogenetic data to determine the IPSS score were only available for 81 patients.
‡During the 3 months preceding study entry.
Table 6. Analysis of Response

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<tr>
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<th>Aza C</th>
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<td></td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
<td>%</td>
<td>No. of Patients</td>
<td>%</td>
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<td>No. evaluated</td>
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<td></td>
<td>92</td>
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<td>CR</td>
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<td>7*</td>
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<td>0</td>
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<td>10</td>
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<td>PR</td>
<td>16</td>
<td>16*</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>4</td>
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<td>Improved</td>
<td>37</td>
<td>37*</td>
<td>5</td>
<td>5</td>
<td>16</td>
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<tr>
<td>Total</td>
<td>60</td>
<td>60*</td>
<td>5</td>
<td>5</td>
<td>23</td>
<td>47</td>
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</table>

*Significant differences between the arms in CR rate (P = .01), CR + PR rate (P < .0001), and CR + PR + improvement rate (P < .0001) were observed.

Fig 2. Duration of response. Measured from time of initial response to relapse in patients with CR, PR, or improvement and estimated according to the method of Kaplan-Meier.
Fig 3. Time to AML transformation or death. Measured from entry on study to the time of first event, either transformation to AML or death, and estimated according to the Kaplan-Meier method.

Fig 5. Overall survival by randomized arm and estimated according to the Kaplan-Meier method. Patients who were initially in the supportive care group and crossed over to treatment with azacitidine are included in the supportive care group in this plot.
Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study

<table>
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<th>Total ITT (n=179)</th>
<th>BSC only (n=222)</th>
<th>Low-dose cytarabine (n=94)</th>
<th>Intensive chemotherapy (n=42)</th>
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<td></td>
<td>Azacitidine</td>
<td>CCR (n=179)</td>
<td>Azacitidine (n=117)</td>
<td>Azacitidine (n=45)</td>
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<td>69 (42-83)</td>
<td>70 (38-88)</td>
<td>69 (52-83)</td>
<td>69 (42-82)</td>
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<td></td>
<td>57 (32%)</td>
<td>43 (24%)</td>
<td>33 (28%)</td>
<td>14 (31%)</td>
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<td></td>
<td>122 (68%)</td>
<td>136 (76%)</td>
<td>84 (72%)</td>
<td>31 (69%)</td>
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<td>Age (years)</td>
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<td>≤64</td>
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<td>132 (74%)</td>
<td>119 (67%)</td>
<td>81 (69%)</td>
<td>39 (87%)</td>
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<tr>
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<td>47 (26%)</td>
<td>60 (34%)</td>
<td>36 (31%)</td>
<td>6 (13%)</td>
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<tr>
<td>≥65</td>
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<td></td>
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</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>104 (58%)</td>
<td>103 (58%)</td>
<td>69 (59%)</td>
<td>27 (60%)</td>
</tr>
<tr>
<td>Women</td>
<td>61 (34%)</td>
<td>62 (35%)</td>
<td>38 (33%)</td>
<td>15 (33%)</td>
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<td>FAB classification</td>
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<td>RAEB</td>
<td>6 (3%)</td>
<td>5 (3%)</td>
<td>5 (4%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>76 (43%)</td>
<td>70 (39%)</td>
<td>48 (41%)</td>
<td>22 (49%)</td>
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<tr>
<td>CMMol.</td>
<td>82 (46%)</td>
<td>85 (48%)</td>
<td>57 (49%)</td>
<td>19 (42%)</td>
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<td>IPSS classification</td>
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<tr>
<td>Intermediate-1</td>
<td>5 (3%)</td>
<td>13 (7%)</td>
<td>4 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Intermediate-2</td>
<td>76 (43%)</td>
<td>70 (39%)</td>
<td>48 (41%)</td>
<td>22 (49%)</td>
</tr>
<tr>
<td>High</td>
<td>82 (46%)</td>
<td>85 (48%)</td>
<td>57 (49%)</td>
<td>19 (42%)</td>
</tr>
<tr>
<td></td>
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</table>
Figure 3: Overall survival

Proportion surviving

Number at risk
- Azacitidine 179
- Conventional care 179

Time from randomisation (months)

Azacitidine

Conventional care

P = 0.0001
• 233 patients (median age: 70 years, range: 60-90)
• 53% had poor-risk cytogenetics,
• The median MDS duration at random assignment: 3 months.
• Primary end point: overall survival (OS).
• Decitabine (15 mg/m2) iv over 4 hours 3x/day for 3 days in 6-week cycles
• No cross over
Long-term outcome of higher-risk MDS patients treated with azacitidine: an update of the GFM compassionate program cohort

Figure 1. Updated Kaplan-Meier estimates of overall survival (OS) of our previously reported cohort of 282 higher-risk myelodysplastic syndromes (MDS) patients treated with azacitidine, with a median follow-up of 41.3 months. (A) Global cohort (n = 282). (B) Cohort according to our risk stratification: low (n = 30, median OS: 32.1 month); intermediate (int; n = 191, median OS: 15.0 months); high (n = 48; median OS: 6.1 month; log-rank test: $P < 10^{-4}$).
## Survival Outcomes from HMA trials

<table>
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<tr>
<th>Design/Therapy</th>
<th>Total</th>
<th>Overall Survival</th>
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<tr>
<td>Cohort: Outcome after AZA-failure</td>
<td>435</td>
<td>15% (2 year)</td>
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<tr>
<td>Cohort: Prognostic Factors in Compassionate Use AZA</td>
<td>282</td>
<td>~20% (3 year by survival curve)</td>
</tr>
<tr>
<td>Ph III: Low-Dose Decitabine vs. BSC</td>
<td>233</td>
<td>19% (2 year)</td>
</tr>
<tr>
<td>Ph III: European AZA-001: AZA vs. BSC</td>
<td>358</td>
<td>50.8% (2 year), ~30% (3 year by survival curve)</td>
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<tr>
<td>Ph III: Decitabine vs. BSC</td>
<td>170</td>
<td>Not available</td>
</tr>
<tr>
<td>Ph III: CALGB AZA vs. BSC</td>
<td>191</td>
<td>~45% (2 year), ~25% at (3 year by survival curves)</td>
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<tr>
<td>Retrospective: HCT in 60-70 yo vs. No Donor + AZA</td>
<td>178</td>
<td>23% (2 year)</td>
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<tr>
<td>Decision Analysis (&lt;60yo)</td>
<td>184</td>
<td>&lt;5% for high, ~20% for Int 2 (3 year by survival curve)</td>
</tr>
</tbody>
</table>
Poor outcome after azacitidine treatment failure

A

Overall Survival (%)

Time Since AZA Failure (days)

B

Overall Survival (%)

Time Since AZA Failure (days)

Prebet et al. J Clin Oncol 29:3322
Poor outcome after azacitidine treatment failure

Prebet et al. J Clin Oncol 29:3322
A phase II trial of **azacitidine** (75 mg/m$^2$/d x 5 days) in combination with **lenalidomide** (10 mg/d x 21 days (28-day cycle) for higher-risk MDS.
- overall response rate of 72% (CR: 44%)
- median CR duration of 17+ months (range, 3-39+)
- median overall survival of 37+ months (range, 7-55+) for CR patients, 13.6 months for the entire cohort (range, 3-55).

Phase I study evaluated the combination of **azacitidine and vorinostat** in MDS and AML patients. There were no serious non-hematologic toxicities, and responses were seen in up to 86% of patients.
Combination Therapy

Randomized Phase II Study of Azacitidine Combined with Lenalidomide or with Vorinostat Vs. Azacitidine Monotherapy in Higher-Risk Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML): North American Intergroup Study SWOG S1117 (Sekeres at al. ASH 2014 Late Breaking Abstract 5)

Higher-risk MDS (IPSS Int-2 or High and/or bone marrow blasts ≥5%) and CMML patients (pts) with <20% blasts

- AZA (75 mg/m2/d on d1-7 of a 28d cycle)
- AZA + LEN (10 mg/d on d1-21), or
- AZA + VOR (300 mg BID on d3-9).
<table>
<thead>
<tr>
<th>Variable</th>
<th>AZA n=92 (33%)</th>
<th>AZA+LEN n=93 (34%)</th>
<th>AZA+VOR n=91 (33%)</th>
<th>Total n=276 (100%)</th>
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<tbody>
<tr>
<td>Median Age (yrs)</td>
<td>70 (43, 89)</td>
<td>71 (51, 87)</td>
<td>71 (28, 93)</td>
<td>70 (28, 93)</td>
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<tr>
<td>Female</td>
<td>31 (34)</td>
<td>32 (34)</td>
<td>22 (24)</td>
<td>81 (31)</td>
</tr>
<tr>
<td>MDS/CMML</td>
<td>77 (84)/15 (16)</td>
<td>74 (80)/19 (20)</td>
<td>75 (82)/16 (18)</td>
<td>226 (82)/50 (18)</td>
</tr>
<tr>
<td>tMDS</td>
<td>7 (8)</td>
<td>6 (6)</td>
<td>5 (5)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Baseline WBC (x10³)</td>
<td>3 (1, 205)</td>
<td>3 (0, 533)</td>
<td>3 (0, 65)</td>
<td>3 (0, 533)</td>
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<tr>
<td>Baseline Platelet count (x10³)</td>
<td>68 (8, 4000)</td>
<td>75, (3, 452)</td>
<td>62 (3, 1462)</td>
<td>68 (3, 4000)</td>
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<td>Baseline Median Blast %</td>
<td>8 (0, 22)</td>
<td>10 (0, 20)</td>
<td>10 (1, 18)</td>
<td>9 (0, 22)</td>
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<td>IPSS Low</td>
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<td>6 (2)</td>
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<td>IPSS Int-1</td>
<td>22 (27)</td>
<td>21 (23)</td>
<td>29 (34)</td>
<td>72 (28)</td>
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<tr>
<td>IPSS Int-2</td>
<td>39 (47)</td>
<td>46 (50)</td>
<td>41 (48)</td>
<td>126 (48)</td>
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<tr>
<td>IPSS High</td>
<td>20 (24)</td>
<td>23 (25)</td>
<td>14 (16)</td>
<td>57 (22)</td>
</tr>
<tr>
<td>Baseline RBC Transfusion Dependence</td>
<td>50 (57)</td>
<td>48 (53)</td>
<td>54 (61)</td>
<td>152 (57)</td>
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</tbody>
</table>
≥Grade 3 AE (AZA:AZA+LEN:AZA+VOR)
- febrile neutropenia (10:13:13)
- gastrointestinal disorders (4:11:23)
- infections (2:3:3)
- rash (2:12:1).

**ORR (N=290): 33%**
CR: 19%, PR: 1%, HI: 13%
RFS (median): 7 months.

**ORR in study arms:**
AZA: 36%
AZA+LEN: 37% (p=1.0),
AZA+VOR: 22% (p=.07)

**CR/PR/HI rates:**
AZA: 23%/0%/13%
AZA+LEN: 18%/1%/17% (CR p=.47)
AZA+VOR 14%/1%/7% (CR p=.18)
Newer Therapy?

Phase 2, randomized, double-blind study of pracinostat in combination with azacitidine in patients with untreated, higher-risk myelodysplastic syndromes

Cancer. 2017 May 15;123(6):994-1002

The combination of azacitidine with pracinostat did not improve outcomes in patients with higher-risk MDS.

Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial.

Rigosertib is a small molecule inhibitor, which simultaneously inhibits PI3K and PLK signaling pathways. No improvement over BSC


344 A Phase II Study Evaluating the Combination of Nivolumab (Nivo) or Ipilimumab (Ipi) with Azacitidine in Pts with Previously Treated or Untreated Myelodysplastic Syndromes (MDS)

No single agent activities. ASH 2016 abstract#344
Allogeneic HCT

- The only potentially curative treatment
- Eliminates malignant hematopoietic clones through conditioning chemo-radiotherapy and graft-versus-leukemia (GVL) effects
- Restores hematopoiesis with donor-derived progenitor cells
- Associated with significant risks of transplant-related mortality/morbidity (GVHD, infection, organ toxicity, graft failure)
HCT outcomes for patients with MDS – impact of donor source (CIBMTR data)

Table 1
Multivariate Analysis of a Cohort of Adult MDS Patients Who Underwent HLA-Identical Sibling HCT or 8/8 or 7/8 Matched Unrelated Donor (MUD) HCT From 2002 to 2006

<table>
<thead>
<tr>
<th></th>
<th>Transplant-Related Mortality</th>
<th>Relapse</th>
<th>Treatment Failure (Death or Relapse)</th>
<th>Mortality</th>
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<tr>
<td></td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
<td>RR (95% CI)</td>
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<tr>
<td></td>
<td>P</td>
<td>P</td>
<td>P</td>
<td>P</td>
</tr>
<tr>
<td>8/8 MUD vs. MRD</td>
<td>1.43 (1.06-1.95)</td>
<td>.85 (.60-1.18)</td>
<td>1.13 (.91-1.42)</td>
<td>1.24 (.98-1.56)</td>
</tr>
<tr>
<td>7/8 MUD vs. MRD</td>
<td>1.80 (1.23-2.63)</td>
<td>1.02 (.66-1.60)</td>
<td>1.47 (1.10-1.96)</td>
<td>1.62 (1.21-2.17)</td>
</tr>
<tr>
<td>7/8 MUD vs. 8/8 MUD</td>
<td>1.25 (.91-1.72)</td>
<td>1.21 (.81-1.81)</td>
<td>1.29 (1.00-1.66)</td>
<td>1.30 (1.01-1.68)</td>
</tr>
</tbody>
</table>

Challenges in HCT for MDS

• Who and when?
  ➢ Age, co-morbidities?
  ➢ Subtypes/IPSS risk categories?

• How?
  ➢ Conditioning
  ➢ Donor source (MRD, MUD, Cord, Haplo)
  ➢ GVHD prophylaxis
  ➢ Pre- and post-HCT therapy to reduce relapse
    ▪ pre-HCT cytoreduction (HM agents, high-intensity induction)
    ▪ post-HCT HM agents/ MRD monitoring
Transplant is not a gamble....
# Dealer’s Up Card

<table>
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<tr>
<th>Your Hand</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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If doubling down after splitting is not allowed, then just hit the following:

- 2, 2 and 3, 3 vs. 2 and 3
- 4, 4 vs. 5 and 6
- 6, 6 vs. 2

- HIT
- STAND
- DOUBLE DOWN
- SPLIT
A decision analysis of allogeneic BMT for MDS: delayed transplantation for low-risk MDS is associated with improved outcome

BMT cohort: BM graft ablative conditioning, sibling donor, tacrolimus-MTX

Markov decision model

Coverage with Evidence Development

- CMS issued a decision memo in Aug 2010 allowing “coverage with evidence development (CED)”
  - Suggests insufficient evidence
    - “..evidence does not demonstrate that the use of HCT improves health outcomes in Medicare beneficiaries with MDS.”
    - “paucity of evidence regarding the use of HCT in patients with MDS who are 65 years or older”
  - Will cover costs of HCT if patients enrolled in a study that will provide CMS with data (“evidence”) to determine the value of the procedure in the Medicare population
Role of RIC-HCT in Older Patients

Figure 2. US alloHCTs for MDS patients older than 65 years from 2005 to 2013. BMT indicates bone marrow transplant.

Role of RIC-HCT in Older Patients With De Novo MDS: An International Collaborative Decision Analysis

RIC, 60-70yo, MUD/MRD

IPSS Low/Int-1

IPSS Int-2/High

Blue area: superior QALE

Koreth et al J Clin Oncol 2013; 31:2662-2670
HLA-matched allogeneic HCT improves outcome of higher risk MDS: SFGM-TC and GFM

162 patients with MDS (50: no donor, 112: donor)
Median age: 60 years (range: 50–70).

<table>
<thead>
<tr>
<th>IPSS</th>
<th>no donor</th>
<th>donor</th>
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<tbody>
<tr>
<td>Int-1</td>
<td>5 (10%)</td>
<td>8 (7%)</td>
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<tr>
<td>Int-2</td>
<td>28 (56%)</td>
<td>75 (67%)</td>
</tr>
<tr>
<td>High</td>
<td>12 (24%)</td>
<td>22 (20%)</td>
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Figure 1. Overall survival according to donor availability: no donor group and donor group. Donor group include all patients with either an HLA matched sibling or an unrelated donor.
BMT CTN 1102: A Multi-Center Biologic Assignment Trial Comparing Reduced Intensity Allogeneic Hematopoietic Cell Transplant to Hypomethylating Therapy or Best Supportive Care in Patients Aged 50-75 with Intermediate-2 and High Risk Myelodysplastic Syndrome

Corey Cutler, MD MPH, Ryotaro Nakamura, MD

3-yr overall survival
3-yr LFS
QOL benefit
Cost Effectiveness
HCT is effective in patients >70yo.

**Outcomes and Survival Rates**

- **OS** (Overall Survival): 24 Months KM Est = 0.658 (95% CI: 0.499-0.777)
- **PFS** (Progression-Free Survival): 24 Months KM Est = 0.607 (95% CI: 0.452-0.730)
- **mGRFS** (Modified Graft Versus Host Disease-Free Survival): 24 Months KM Est = 0.329 (95% CI: 0.194-0.470)

**Patients-at-Risk**:

- OS: 53, 33, 20, 14, 10, 4
- PFS: 53, 28, 18, 12, 9, 3
- mGRFS: 53, 16, 10, 5, 4

**Graph Details**:

- X-axis: Months from Transplant
- Y-axis: Probability
- Censor: 0.329 (0.194-0.470) at 24 Months

Manuscript in review
FluMel conditioning and Tacrolimus+Sirolimus as GVHD prophylaxis for MDS (n=59)

Grade II-IV aGVHD: 35.4% (III-IV:18.6%)
Allogeneic HCT for therapy-related MDS

K–M curves for overall survival

Cumulative Incidence Curves
NRM and relapse are treated as competing risks

Aldoss et al. Haematologica 2017
Somatic mutations in t-MDS

TP53
RUNX1
SETBP1
U2AF1
TET2
ASXL1
DNMT3A
PTPN11
ZRSR2
STAG2
SRSF2
EZH2

ETV6
CBL
SF3B1
PHF6
NRAS
KMT2D
KMT2A
JAK2
GATA2
CDKN2A
ATM

Genetic Alteration
Truncating Mutation
Inframe Mutation
Missense Mutation

TP53

# Mutations

p.Arg273Cys/His/Ser

0 100 200 300 393 aa

Aldoss et al. Haematologica 2017
Impact of somatic mutations in HCT for t-MDS

**K-M surves for overall survival by TP53 status**

- No TP53 mutation
- with TP53 mutation

HR = 1.12 95% CI (0.49, 2.57)  
P-value = 0.79

**K-M surves for overall survival by high risk mutation**

- No high risk mutation
- with high risk mutations

HR = 1.29 95% CI (0.60, 2.74)  
P-value = 0.52

TP53

TP53, EZH2, ETV6, RUNX1, or ASXL1

Aldoss et al. Haematologica 2017
MDS initial diagnosis (using WHO 2008 diagnostic criteria, supplemented by novel genomics approaches)

Is there a need for treatment now?

- No: Clinical monitoring
- Yes (Lower-risk): Development of a need for therapy

Individualized risk assessment, using IPSS-R or other tools

Is anemia isolated, or the major problem?

- No, other important cytopenias are also present
  - No (Higher-risk): Is the patient a transplant candidate?
    - No:Azacitidine or decitabine (i.e., HMA) until disease progression, relapse, or drug intolerance
    - Yes: AlloSCT, perhaps with HMA or chemotherapy as bridging therapy
  - Yes (Lower-risk): Serum EPO <500 U/L?
    - No: Optimal approach is unclear; consider G-CSF or TPO agonist, HMA, IST, clinical trial
    - Yes: Optimal approach is unclear consider HMA, IST, androgens, lenalidomide (if not already used), or clinical trial

Is del5q present?

- No: Lenalidomide; if sEPO <500 U/L, ESA trial before or after
- Yes: ESA ± G-CSF

Failure

Optimal therapy unclear consider HMA, IST, or clinical trial

Enrollment in a clinical trial, or palliative/supportive care
Summary

Diagnosis and Evaluation
- View the condition as a spectrum, from aplastic anemia, CHIP, overlap BMF/CHIP to “RAEB-T”/AML
- Consider underlying pathogenesis (immune-mediated cytopenia vs. clonal expansion/hematopoietic failure)

Management
- “Best” supportive care
- Disease-specific therapies: clinical trial opportunities
- Individualized goal of treatment
- Early referral to HCT discussions