Welcome & Introductions

Dr. Sekeres’s slides are available for download at www.LLS.org/programs
Disclosures

Mikkael A. Sekeres, MD, MS, has affiliations with Celgene (Consultant).
• A heterogeneous clonal hematopoietic disorder derived from an abnormal multipotent progenitor cell
  – **Heterogeneous** = many different forms!
  – **Clonal** = genetic basis (genetics that you inherit)
  – **Hematopoietic** = starts in the bone marrow, affects blood cells
  – **Multipotent progenitor** = changes occur in one bone marrow cell and are passed along
• Characterized by a hyperproliferative bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis
Characterized by a hyperproliferative bone marrow, dysplasia of the cellular elements, and ineffective hematopoiesis

- **Hyperproliferative** = too many cells (for your age)
- **Dysplasia** = bad growing cells
- **Ineffective hematopoiesis** = can’t make normal red blood cells, platelets, and/or white blood cells

Incidence Rate = 4.9/100,000 per year

### MDS: Epidemiology

#### Men > Women


#### Whites > African-Americans

### MDS: Epidemiology

Cross-sectional analysis of 4514 MDS patients in the U.S. in 2005-7

<table>
<thead>
<tr>
<th>Age (Median)</th>
<th>Newly diagnosed</th>
<th>71 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Established</td>
<td>72-75 years</td>
</tr>
<tr>
<td>Sex (Mean)</td>
<td>Male (Newly diagnosed)</td>
<td>55%</td>
</tr>
<tr>
<td></td>
<td>(Established)</td>
<td>51-57%</td>
</tr>
<tr>
<td>Duration of MDS (Median)</td>
<td>13-16 months</td>
<td></td>
</tr>
<tr>
<td>MDS Status</td>
<td>Primary</td>
<td>88 – 93%</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>7 – 12%</td>
</tr>
<tr>
<td>Secondary</td>
<td>Chemotherapy</td>
<td>55 – 80%</td>
</tr>
<tr>
<td>Cause</td>
<td>Radiation</td>
<td>6 – 21%</td>
</tr>
<tr>
<td></td>
<td>Chemical exposure</td>
<td>2 – 9%</td>
</tr>
</tbody>
</table>

Sekeres et al. J National Cancer Inst 2008;100:1542

### MDS Basics: WHO Classification

<table>
<thead>
<tr>
<th>2008 Name</th>
<th>Abbrev.</th>
<th>2016 Name</th>
<th>Abbrev.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory cytopenia with unilineage dysplasia</td>
<td>RCU D (includes RA, RN and RT)</td>
<td>MDS with single lineage dysplasia</td>
<td>MDS-SLD</td>
</tr>
<tr>
<td>Refractory anemia with ring sideroblasts</td>
<td>RARS</td>
<td>MDS with ring sideroblasts</td>
<td>MDS-RS</td>
</tr>
<tr>
<td>MDS w/ isolated del(5q)</td>
<td>Del(5q)</td>
<td>unchanged</td>
<td>unchanged</td>
</tr>
<tr>
<td>Refractory cytopenia with multilineage dysplasia</td>
<td>RCMD</td>
<td>MDS with multilineage dysplasia (with ring sideroblasts)</td>
<td>MDS-MLD</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 1</td>
<td>RAEB-1</td>
<td>MDS with excess blasts, type 1</td>
<td>MDS-EB-1</td>
</tr>
<tr>
<td>Refractory anemia with excess blasts, type 2</td>
<td>RAEB-2</td>
<td>MDS with excess blasts, type 2</td>
<td>MDS-EB-2</td>
</tr>
<tr>
<td>MDS, Unclassifiable</td>
<td>MDS-U</td>
<td>unchanged</td>
<td>Unchanged</td>
</tr>
<tr>
<td>Refractory cytopenia(s) of childhood</td>
<td>RCC</td>
<td>unchanged</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>

Adapted from Arber et al. Blood 2016

Higher Risk
## Calculation of prognostic score

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>0.5</th>
<th>1.0</th>
<th>1.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>BM Blast %</td>
<td>&lt; 5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-29</td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Estimation of prognosis

<table>
<thead>
<tr>
<th>Overall Score</th>
<th>IPSS Subgroup</th>
<th>Median Survival (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>5.7</td>
</tr>
<tr>
<td>0.5-1.0</td>
<td>Intermediate-1</td>
<td>3.5</td>
</tr>
<tr>
<td>1.5-2.0</td>
<td>Intermediate-2</td>
<td>1.2</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Cytopenias: ANC < 1.5, HGB < 10.0, PLT < 100,000
Good Risk: [-Y,del(5q), del(20q),N1]; Intermediate Risk: [8+,other]; Poor Risk: [Chr. 7 abn, ≥3 abn]


## MDS Staging: IPSS-R Prognostic Score Variables

<table>
<thead>
<tr>
<th>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>V. Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>V. Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM Blast %</td>
<td>≤2</td>
<td>&gt;2-&lt;5%</td>
<td>5-10%</td>
<td>&gt;10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8-&lt;10</td>
<td>&lt;8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-&lt;100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### IPSS-R Prognostic Risk Categories/Scores

<table>
<thead>
<tr>
<th>RISK GROUP</th>
<th>Risk Score</th>
<th>Median Survival (Yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very Low</td>
<td>≤1.5</td>
<td>8.8</td>
</tr>
<tr>
<td>Low</td>
<td>&gt;1.5-3</td>
<td>5.3</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt;3-4.5</td>
<td>3.0</td>
</tr>
<tr>
<td>High</td>
<td>&gt;4.5-6</td>
<td>1.6</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt;6</td>
<td>0.8</td>
</tr>
</tbody>
</table>

MDS Prognosis Made Easy!!!

• **Lower Risk**
  – RA, RARS
  – RCMD, RCUD
  – MDS-U, MDS del (5q)
  – IPSS Low, Int-1 (0-1.0); **IPSS-R V. Low, Low, Int (<3.5)**

• **Higher Risk**
  – RAEB (-1, -2)
  – IPSS Int-2, High (≥ 1.5); **IPSS-R Int (>3.5), High, V. High**

---

**MDS mutation landscape 2017**

- **Proliferation**
  - BRAF (<1%)
  - GNAS (<1%)
  - JAK2 3%
  - CBL 2%
  - CDKN2A (<1%)
  - PTPN11 (<1%)

- **Impaired Differentiation**
  - RUNX1 9%
  - ETV6 3%
  - SETBP1 7%
  - TP53 8%

- **Epigenetic regulation**
  - EZH2 6%
  - DNMT3A (8%)
  - ASXL1 14%
  - TET2 21%
  - UTX 1%
  - IDH1/2 2%
  - ATRX 41%

- **Other**
  - SF3B1 22%
  - NPM1 (2%)
  - SF3A1 1%

- **Pre-mRNA splicing**
  - SF1 1%
  - PRPF40B 1%
  - U2AF1 8%
  - ZRSR2 5%
  - SRSF2 11%
  - ZNFA1 1%
  - U2AF65 (<1%)
  - SF1 1%

---

**IPSS independent good prognosis**

**IPSS independent poor prognosis**

**No clear independent effect**

MDS: Prognosis

---

4/7/2017
IPSS-R “molecular” (IPSS-Rm)

Training Cohort
C-Index = .74

Validation Cohort
C-Index = .65

Nazha et al. Leukemia 2016

MDS Overview
Treatment of Lower-risk Disease
Treatment of Higher-risk Disease
MDS: Lower-risk, Treatment Algorithm

Patient diagnosed with lower-risk MDS per IPSS (score ≤1.0) or IPSS-R (score ≤1.0). No transfusion needs, good quality of life. Isolated cytopenia. Multiple cytopenias.

- Anemia (Hgb <10 g/dl and/or transfusion-dependent, symptomatic)
- Thrombocytopenia (<20k/L or <50k/L with bleeding)
- Start anti-thymocyte globulin or hypomethylating agent or enroll into clinical trial

Start erythropoiesis stimulating agent or blood transfusions

No response or loss of response, or del(5q)
cytogenetic abnormality

- Start lenalidomide or enroll into clinical trial
- Start hypomethylating agent or enroll into clinical trial

MDS: Patient Selection for ESAs

RA, RARS, RAEB

- Score > +1: Good response (74%, n=34)
- Score –1 to +1: Intermediate response (23%, n=31)
- Score < –1: Poor response (7%, n=29)

Treatment response score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Score Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>s-epo U/L</td>
<td>&lt;100</td>
<td>+2</td>
</tr>
<tr>
<td>U/L</td>
<td>100–500</td>
<td>+1</td>
</tr>
<tr>
<td></td>
<td>&gt;500</td>
<td>–3</td>
</tr>
<tr>
<td>Transf</td>
<td>&lt;2 units/m</td>
<td>+2</td>
</tr>
<tr>
<td>U RBC/m</td>
<td>= or &gt;2 units/m</td>
<td>–2</td>
</tr>
</tbody>
</table>

MDS: Lower-risk, Treatment Algorithm

Patient diagnosed with lower-risk MDS per IPSS (score ≤1.0) or IPSS-R (score ≤4.0)

- No transfusion needs, good quality of life
- Isolated cytopenia
- Multiple cytopenias

1. Observe, follow blood counts every 1-6 months depending on stability
2. Anemia (Hgb <10 g/dl and/or transfusion - dependent), symptomatic
3. Thrombocytopenia (<20k/μL or <50k/μL with bleeding)
4. Start anti-thymocyte globulin or hypomethylating agent or enroll into clinical trial

Start erythropoiesis stimulating agent or blood transfusions

- No response, loss of response, or del(5q) cytogenetic abnormality
- Start lenalidomide or enroll into clinical trial

Start thrombopoietin agonists® or platelet transfusions or enroll into clinical trial

Sekeres and Gerds Hematology (ASH Educ Program) 2014.

MDS: TPO Agonists

26-Week Test Treatment Period

- Romiplostim 750 mcg weekly (N = 160)
- Placebo weekly (N = 80)

24-Week Extended Treatment Period

- Romiplostim 750 mcg weekly + standard of care (N = 160)
- Placebo weekly + standard of care (N = 80)

### MDS: TPO Agonists

#### Baseline platelets

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 43)</th>
<th>Romiplostim (N = 87)</th>
<th>Placebo (N = 40)</th>
<th>Romiplostim (N = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSBE (rate/100 pt-yr)</td>
<td>501.2</td>
<td>514.9</td>
<td>226.4</td>
<td>79.5</td>
</tr>
<tr>
<td></td>
<td>RR = 1.03, p = 0.827</td>
<td>RR = 0.35, p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTE (rate/100 pt-yr)</td>
<td>1778.6</td>
<td>1250.5</td>
<td>179.8</td>
<td>251.8</td>
</tr>
<tr>
<td></td>
<td>RR = 0.71, p&lt;0.0001</td>
<td>RR = 1.38, p = 0.1479</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


### Lower-risk MDS: TPO Agonists

#### 58 weeks of follow-up

<table>
<thead>
<tr>
<th></th>
<th>Romiplostim</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>17.9% (30)</td>
<td>20.7% (17)</td>
<td>0.86</td>
<td>0.47, 1.56</td>
</tr>
<tr>
<td>AML</td>
<td>6.0% (10)</td>
<td>4.9% (4)</td>
<td>1.20</td>
<td>0.38, 3.84</td>
</tr>
<tr>
<td>AML-free survival</td>
<td>19.6% (33)</td>
<td>23.2% (19)</td>
<td>0.85</td>
<td>0.48, 1.50</td>
</tr>
</tbody>
</table>

**Study design**

**Randomization**

2:1

Patients (N = 174)

- Eltrombopag + Standard care (n = 116)
- Placebo + Standard care (n = 58)

**Wk 24**

CR and R

- Eltrombopag + Standard care
- Standard Care

Dose start: 50 mg with increases every 2 weeks up to 300 mg daily.

**Platelet responses**

<table>
<thead>
<tr>
<th>Response</th>
<th>8 weeks Elt 41:placebo 17 Elt:Plac</th>
<th>24 weeks Elt 24:Placebo11 Elt:Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>R, n</td>
<td>12 : 0</td>
<td>5 : 3</td>
</tr>
<tr>
<td>CR, n</td>
<td>9 : 0</td>
<td>8 : 0</td>
</tr>
<tr>
<td>NR</td>
<td>20 : 17</td>
<td>11 : 8</td>
</tr>
<tr>
<td>Total responses, n</td>
<td>21 : 0</td>
<td>13 : 3</td>
</tr>
<tr>
<td>WHO bleeding grade ≥ 2, events</td>
<td>1 : 2</td>
<td>3 : 1</td>
</tr>
</tbody>
</table>

**Time to Response (TTR):**
- Eltrombopag: median 14 (IQR 8-39) days
- Placebo: median 85 (IQR 41-193) days (p =0.023) *

Median daily eltrombopag dose at response: 50 (IQR 50-150) mg.

Oliva Lancet Haematology 2017
Lower-risk MDS: Lenalidomide

MDS-001
N = 43
Phase I/II initiated 2002

Del 5q

MDS-003
N = 148
Phase II initiated 2003

Non del 5q

MDS-002
N = 214
Phase II initiated 2003

MDS-004
N = 205
Phase III initiated 2005

MDS-005
N = 205
Phase III initiated 2010
MDS: Phase 3 Lenalidomide in del(5q) Lower-risk

<table>
<thead>
<tr>
<th>RBC-TL, n (%) [95% CI]</th>
<th>Placebo</th>
<th>Lenalidomide 5 mg</th>
<th>Lenalidomide 10 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>mITT population</td>
<td>n = 51</td>
<td>n = 47</td>
<td>n = 41</td>
</tr>
<tr>
<td>Protocol defined (≥ 26 weeks)</td>
<td>3 (5.9) [1.2-16.2]</td>
<td>20 (42.6) [28.3-57.8]</td>
<td>23 (56.1) [39.7-71.5]</td>
</tr>
<tr>
<td>IWG 2000 (≥ 8 weeks)</td>
<td>4 (7.8) [2.2-18.9]</td>
<td>24 (51.1) [36.1-65.9]</td>
<td>25 (61.0) [44.5-75.8]</td>
</tr>
<tr>
<td>IWG 2006 (≥ 8 weeks)</td>
<td>3 (5.9) [1.2-16.2]</td>
<td>24 (51.1) [36.1-65.9]</td>
<td>25 (61.0) [44.5-75.8]</td>
</tr>
</tbody>
</table>


Lower-risk MDS: Lenalidomide in del(5q)

Median duration TI = 2.2 years

MDS-005: Study Design

**Pretreatment**
- LEN 10 mg, orally, QD

**Double-blind (DB) treatment**
- Matching placebo
- RBC-TI ≥ 8 weeks or erythroid response
- Discontinue DB phase

**Off-treatment**
- Continue DB phase until erythroid relapse or disease progression
- Long-term follow-up (≥ 5 years from randomization)
  - Overall survival
  - AML progression
  - Subsequent MDS treatments
  - SPMs

**Key inclusion criteria**
- Centrally reviewed IPSS Low or Int-1 risk MDS with karyotypes other than del(5q)
- RBC-TD
- Unresponsive or refractory to ESAs

**Key exclusion criteria**
- Not specified

Santini et al. JCO 2016;34:2988.

MDS-005: RBC-TI ≥ 8 Weeks

**Significantly more LEN patients achieved RBC-TI ≥ 8 weeks versus placebo (P < 0.001)**

![Graph showing RBC-TI ≥ 8 weeks](image)

Santini et al. JCO 2016;34:2988
MDS-005: Duration of RBC-TI ≥ 8 Weeks

The median duration of response was 32.9 weeks (95% CI 20.7–71.1) among RBC-TI ≥ 8 weeks responders with LEN.

Abstract # 92 Luspatercept Treatment Leads to Long Term Increases in Hemoglobin and Reductions in Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from the Phase 2 PACE-MDS Extension Study

Aristoteles Giagounidis, MD, PhD1, Uwe Platzbecker, MD2, Ulrich Germing, MD3, Katharina Götze, MD4, Philipp Kiewe, MD5, Karin Mayer, MD6, Oliver Ottmann, MD7, Markus Radsak, MD8, Thomas Wolff, MD9, Detlef Haase, MD10, Monty Hankin11, Dawn Wilson11, Xiaosha Zhang11, Adberrahmane Laadem, MD12, Matthew L. Sherman, MD11 and Kenneth M. Attie, MD11

1Marien Hospital Düsseldorf, 2Universitätsklinikum Carl Gustav Carus, Dresden, 3Universitätsklinikum Düsseldorf, 4Technical University of Munich, 5Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin, 6University Hospital Bonn, 7Universitätsklinikum Frankfurt, Goethe Universität, Frankfurt/Main, 8Johannes Gutenberg-Universität, Mainz, 9OncoResearch Lerchenfeld UG, Hamburg, 10Universitätsmedizin Göttingen, Germany; 11Acceleron Pharma, Cambridge, MA, 12Celgene Corporation, Summit, NJ, USA
Response Rates by Baseline Characteristics

- Majority of patients in extension study were RS+; ≥ 50% patients responded to luspatercept who had EPO up to 500 I/U or prior ESA treatment

<table>
<thead>
<tr>
<th></th>
<th>IWG HI-E N=32</th>
<th>RBC-TI* N=22</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>22/32 (69%)</td>
<td>11/22 (50%)</td>
</tr>
<tr>
<td>RS positive</td>
<td>21/29 (72%)</td>
<td>10/19 (53%)</td>
</tr>
<tr>
<td><strong>Baseline EPO</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200 U/L</td>
<td>16/20 (80%)</td>
<td>7/13 (54%)</td>
</tr>
<tr>
<td>200-500 U/L</td>
<td>5/7 (71%)</td>
<td>2/4 (50%)</td>
</tr>
<tr>
<td>&gt; 500 U/L</td>
<td>1/5 (20%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td><strong>Prior ESA Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12/19 (63%)</td>
<td>7/14 (50%)</td>
</tr>
<tr>
<td>No</td>
<td>10/13 (77%)</td>
<td>4/8 (50%)</td>
</tr>
</tbody>
</table>

* RBC-TI: RBC transfusion independent ≥ 8 weeks; includes 19 HTB patients and 3 LTB patients evaluable for transfusion independence (at least 2 Units over 8 weeks pre-treatment)

Data as of 31 Aug 2015
Low-dose HMAs in LR-MDS: Treatment

- Regimens:
  - DAC 20 mg/m² IV D1-3 every 4 weeks
  - AZA 75 mg/m² IV/SC D1-3 every 4 weeks

- Response assessment by modified IWG 2006

- Between 11/2012 and 10/2015, 91 pts with LR-MDS treated and evaluable for response

- Median duration of follow-up = 14 months (range: 2-30 months)

Low-dose HMAs in LR-MDS: Response

<table>
<thead>
<tr>
<th>Response</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>33 (36)</td>
</tr>
<tr>
<td>mCR</td>
<td>8 (9)</td>
</tr>
<tr>
<td>HI</td>
<td>13 (14)</td>
</tr>
<tr>
<td>ORR</td>
<td>54 (59)</td>
</tr>
<tr>
<td>SD</td>
<td>31 (34)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (7)</td>
</tr>
</tbody>
</table>

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)
• MDS Overview
• Treatment of Lower-risk Disease
• Treatment of Higher-risk Disease
MDS: Higher-risk, Treatment Algorithm

Patient diagnosed with higher-risk MDS per IPSS (score ≥ 2.5) or IPSS-R (score ≥ 4.5)

- Declines HCT and/or unsuitable donor, poor HCT CI score
- Immediate hypomethylating agent-based clinical trial or monotherapy x 24 cycles
- No response
- Hematologic improvement or better
- Continue hypomethylating therapy until loss of response/progression
- Clinical trial with novel agent(s) or consider cytotoxic therapy or best supportive care

Desires HCT, good HCT CI score

- Initiates search for MRD or 8/8 UMB
- Younger patient, higher blast percentage, good-risk cytogenetics
- Immediate hypomethylating agent-based therapy until time of HCT
- Intensive, AML-type induction chemotherapy
- Suitable donor identified
- HCT
- Monitor, consider post-remission therapy
- Suitable donor not identified
- Continue hypomethylating therapy until loss of response/progression

MDS: Higher-risk, Hypomethylating Therapy

Log-Rank p=0.0001

HR = 0.58 [95% CI: 0.43, 0.77]

ORR=35%


**MDS: Higher-risk, Hypomethylating Therapy**

**A**

- Median OS 10.1 vs. 8.5 months

---

**MDS: Higher-risk, Treatment Algorithm**

MDS: Higher-risk Therapy - HSCT

Test of Equality over Strata

<table>
<thead>
<tr>
<th>Test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-rank</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Low/Int-1 MDS

Koreth et al. JCO 2013;31:2662

MDS: Higher-risk Therapy - HSCT

Test of Equality over Strata

<table>
<thead>
<tr>
<th>Test</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log-rank</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Wilcoxon</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>-2Log(LR)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

Int-2/High MDS

Koreth et al. JCO 2013;31:2662
What happens when we add drugs together?

Higher-risk MDS

North American Intergroup Randomized Phase 2 MDS Study S1117: Study Design

Higher-risk MDS or CMML

(IPSS ≥1.5 and/or blasts ≥5%)

AZA (IV/SC) + LEN (PO)
75 mg/m²/d (d1-7) + 10mg/d x 21d
N=93

AZA (IV/SC) + Vorin (PO)
75 mg/m²/d (d1-7) + 300mg BID (d3-9)
N=92

Groups: SWOG, ECOG, Alliance, NCIC
Total Sample Size: 282/277
Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria
Secondary Objectives: OS, RFS, LFS
Power 81%, alpha 0.05 for each combo arm vs. AZA
06/2012 – 06/2014

Sekeres et al. JCO 2017
### North American Intergroup Randomized Phase 2 MDS Study S1117: Grade ≥3 Toxicities

<table>
<thead>
<tr>
<th>Toxicity Variable</th>
<th>AZA</th>
<th>AZA+LEN (P-value vs. AZA)</th>
<th>AZA+VOR (P-value vs. AZA)</th>
<th>Total n=271</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia (n)</td>
<td>10</td>
<td>13 (.66)</td>
<td>12 (.51)</td>
<td>36</td>
</tr>
<tr>
<td>GI (n)</td>
<td>4</td>
<td>12 (.10)</td>
<td>14 (.02)</td>
<td>28</td>
</tr>
<tr>
<td>Rash (n)</td>
<td>3</td>
<td>14 (&lt;.01)</td>
<td>1 (1)</td>
<td>17</td>
</tr>
<tr>
<td>Off Tx due to Toxicity/Side Effect/Complication</td>
<td>8%</td>
<td>20% (.05)</td>
<td>21% (.03)</td>
<td>18%</td>
</tr>
<tr>
<td>Non-protocol defined dose modifications</td>
<td>24%</td>
<td>43% (.002)</td>
<td>42% (.01)</td>
<td>33%</td>
</tr>
</tbody>
</table>

Sekeres et al. JCO 2017

### North American Intergroup Randomized Phase 2 MDS Study S1117: Response

<table>
<thead>
<tr>
<th>Response Variable</th>
<th>AZA</th>
<th>AZA+LEN (P-value vs. AZA)</th>
<th>AZA+VOR (P-value vs. AZA)</th>
<th>Total n=277</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Tx Duration (Wks)</td>
<td>25</td>
<td>24</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>Overall Response Rate (%)</td>
<td>38</td>
<td>49 (.16)</td>
<td>27 (.16)</td>
<td>38%</td>
</tr>
<tr>
<td>CR/PR/HI (%)</td>
<td>24/0/14</td>
<td>24/1/25</td>
<td>17/1/9</td>
<td>22/1/16%</td>
</tr>
<tr>
<td>CMML ORR (%)</td>
<td>5 (28)</td>
<td>13 (68) (.02)</td>
<td>2 (12) (.41)</td>
<td>37%</td>
</tr>
<tr>
<td>ORR Duration (median)</td>
<td>10 months</td>
<td>14 months (.41)</td>
<td>15 months (.31)</td>
<td>14 months</td>
</tr>
<tr>
<td>CMML ORR Duration (median)</td>
<td>15 months</td>
<td>14 months (.87)</td>
<td>24 months (.69)</td>
<td>15 months</td>
</tr>
</tbody>
</table>

Sekeres et al. JCO 2017
North American Intergroup Randomized Phase 2 MDS Study S1117: Response Duration By Number of Mutations

**Response duration**

- ORR was higher for **DNMT3A** (67% vs. 34%, \( p = .03 \)), lower for **SRSF2** (17% vs. 41%, \( p = .04 \)) and **ASXL1** (23% vs. 43%, \( P = .04 \)).
- Response duration was worse for **TET2** (\( p = .046 \)) and **TP53** (\( p = .003 \)).

**MDS Summary**

- In lower risk MDS promising results with
  - Lower dose HMA.
  - Eltrombopag for thrombocytopenia.
  - Luspatercept.

- Improving outcome in higher risk MDS remains an unmet need.
Thanks to You and LLS!

Cleveland Clinic Leukemia/MDS Program

Jaroslaw Maciejewski, MD, PhD
Sudipto Mukherjee, MD, PhD
Yogen Saunthararajah, MD
Hetty Carraway, MD, MBA
Anjali Advani, MD
Matt Kalaycio, MD
Ronald Sobecks, MD
Betty Hamilton, MD
Aaron Gerds, MD, MS
Aziz Nazha, MD
John Desamito, MD
Tracy Cinalli, RN
Jacqui Mau, RN
Christine Cooper, RN
Mary Lynn Rush, RN
Rachael Diligente, RN
Andrea Smith, RN
Eric Parsons, RN
Samjhana Bogati, RN
Barbara Pauic, RN, NP
Raychel Berardinelli, RN, NP
Camille Urban, RN, NP
Nina D'Ambrosio, RN, NP
Barb Tripp, RN, NP
Alicia Bitterice, RN, NP
Meghan Scully, RN, NP
Becky Habecker, BA
Chante Cavin, BA
Sarah Kaufman, BA
Dennis Kramarz, BA
Ben Pannell, BA
Allison Unger, BA
Jaime Fensterl, MS
Abby Statler, MPH
Donna Abounader, BA
Abigail Snow, BA
Justine DeAngelis, BA
Ziad Chartouni, BA
Brittani Demarest
Caitlin Swann, PharmD
Connie Cheng, PharmD

And Our Patients!!!

Q&A Session

Ask a question by phone:
• Press star (*) then the number 1 on your keypad

Ask a question by web:
• Click “Ask a question”
• Type your question
• Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.
Aplastic Anemia and MDS International Foundation

The world’s leading nonprofit health organization dedicated to patients and families living with aplastic anemia, MDS, PNH and related bone marrow failure diseases.

- **Free Educational Materials** in multiple languages: [www.aamds.org/materials](http://www.aamds.org/materials)
- **Online Academy** with over 100 classes and expert interviews: [www.aamds.org/learn](http://www.aamds.org/learn)
- **Free Patient and Family Conferences**: [www.aamds.org/conferences](http://www.aamds.org/conferences)
- **Personalized Support** through our Information Specialists: [help@aamds.org](mailto:help@aamds.org) or (800) 747-2820
- **Peer Support Network** with trained patient and caregiver volunteers: [www.aamds.org/psn](http://www.aamds.org/psn)
- **Community Connections** support groups led by local volunteers around the United States: [www.aamds.org/support/support-networks](http://www.aamds.org/support/support-networks)

**Learning is hope.**

(800) 747-2820 | help@aamds.org | www.aamds.org

---

Current and Emerging Therapies for Myelodysplastic Syndromes (MDS)

**SUPPORT RESOURCES**

- **Clinical Trials**: LLS provides personalized clinical trial navigation: [www.LLS.org/clinicaltrials](http://www.LLS.org/clinicaltrials)
- **What to ask**: Questions to ask your treatment team: [www.LLS.org/whattoask](http://www.LLS.org/whattoask)
- **Free education materials**: [www.LLS.org/booklets](http://www.LLS.org/booklets)
- **Additional information on MDS**: [www.LLS.org/mds](http://www.LLS.org/mds)
- **Join LLS Community**: Connect with others who share your diagnosis: [www.LLS.org/community](http://www.LLS.org/community)
- **Information Resource Center**: Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
  - **EMAIL**: infocenter@LLS.org
  - **TOLL-FREE PHONE**: (800) 955-4572