Established and Novel Agents for Myelodysplastic Syndromes

Mikkael A. Sekeres, MD, MS
Professor of Medicine
Director, Leukemia Program
• MDS Overview
• Disease Mechanisms
• Treatment of Lower-risk Disease
• Treatment of Higher-risk Disease
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• Disease Mechanisms
• Treatment of Lower-risk Disease
• Treatment of Higher-risk Disease
2008 World Health Organization (WHO) Classification of Chronic Myeloid Neoplasms

Requirements: <20% bone marrow blasts
No AML-defining chromosomal abnormality

Myeloproliferative neoplasms (MPN)
- Chronic myelogenous leukemia (CML)
- Polycythemia vera (PV)
- Essential thrombocytopenia (ET)
- Primary myelofibrosis
- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia, not otherwise categorized (CEL-NOC)
- Hypereosinophilic syndrome (HES)
- Mast cell disease (MCD)
- MPN, unclassifiable

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN)
- Chronic myelomonocytic leukemia (CMML)
- Juvenile myelomonocytic leukemia (JMML)
- Atypical chronic myeloid leukemia (aCML)
- MDS/MPN, unclassifiable

Myelodysplastic syndromes (MDS)
- Refractory cytopenia with multilineage dysplasia
- 3 categories:
  - Refractory anemia (RA)
  - Refractory anemia with ring sideroblasts (RARS)
  - Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with excess blasts - 1 (RAEB-1)
- Refractory anemia with excess blasts - 2 (RAEB-2)
- MDS with isolated del(5q)
- MDS, unclassifiable

Neoplasms with eosinophilia and abnormalities of PDGFRA, PDGFRB, or FGFR1
- Neoplasms with PDGFRA rearrangement
- Neoplasms with PDGFRB rearrangement
- Neoplasms with FGFR1 rearrangement (refractory anemia with ring sideroblasts syndrome)

Lower Risk
- 5-9% Blasts

10-19% Blasts

≥ 20% Blasts = AML!
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>
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<tbody>
<tr>
<td>BM Blast %</td>
<td>&lt; 5</td>
<td>5-10</td>
<td>11-20</td>
<td>21-29</td>
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<tr>
<td>Cytogenetics</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td></td>
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<tr>
<td>Cytopenias</td>
<td>0/1</td>
<td>2/3</td>
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Estimation of prognosis

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

### MDS Overview: IPSS-R

#### IPSS-R Prognostic Risk Categories/Scores

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

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<th>3</th>
<th>4</th>
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</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>V. Good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>V. Poor</td>
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<tr>
<td>BM Blast %</td>
<td>≤2</td>
<td>&gt;2-&lt;5%</td>
<td>5-10%</td>
<td>&gt;10%</td>
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<tr>
<td>Hemoglobin</td>
<td>≥10</td>
<td>8-&lt;10</td>
<td>&lt;8</td>
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<td></td>
<td></td>
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<tr>
<td>Platelets</td>
<td>≥100</td>
<td>50-&lt;100</td>
<td>&lt;50</td>
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<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
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</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**

• **Higher Risk**
  - RAEB (-1, -2)
  - IPSS Int-2, High (≥ 1.5); **IPSS-R High, V. High**
• MDS Overview
• **Disease Mechanisms**
• Treatment of Lower-risk Disease
• Treatment of Higher-risk Disease
Clonal Hematopoiesis with Somatic Mutations Is a Common, Age-Related Condition Associated with Adverse Outcomes

Siddhartha Jaiswal, MD, PhD, Pierre Fontanillas, Jason Flannick, Alisa Manning, Peter Grauman, Brenton G. Mar, MD, PhD, R. Coleman Lindsley, MD, PhD, Craig Mermel, Noel Burtt, Alejandro Chavez, John M. Higgins, MD, Vladislav Moltchanov, Leena Kinnunen, Heikki Koistinen, Claes Ladenvall, Gad Getz, Ph.D., Adolfo Correa, Stacey Gabriel, PhD, Sekar Kathiresan, Heather Stringham, Michael Boehnke on behalf of GoT2D, Brian Henderson on behalf of SIGMA T2D, Mark McCarthy on behalf of T2D-GENES, Jaako Tuomilehto, Christopher A. Haiman, Sc.D., Leif Groop, Gil Atzmon, James Wilson, Donna S. Neuberg, ScD, David Altshuler and Benjamin L Ebert, MD, PhD
Age-related mutations associated with clonal hematopoietic expansion and malignancies

Mingchao Xie1,2,7, Charles Lu1,2, Jiayin Wang1,2, Michael D McLellan1, Kimberly J Johnson1, Michael C Wendt1,6, Joshua F McMichael1, Heather K Schmidt1, Venkata Yellapantula1,2, Christopher A Miller1, Bradley A Ozenberger1,2, John S Welch1,6, Daniel C Link1,6, Matthew J Walter1,6, Elaine R Mardis1,2,4,6, John F Dispersio1,6, Feng Chen1,6, Richard K Wilson1,2,4,6, Timothy J Ley1,2,4,6 & Li Ding1,2,4,6

Clonal Hematopoiesis and Blood-Cancer Risk Inferred from Blood DNA Sequence

Giulio Genovese, Ph.D., Anna K. Kähler, Ph.D., Robert E. Handsaker, B.S., Johan Lindberg, Ph.D., Samuel A. Rose, B.S., Samuel F. Bakhour, M.D., Ph.D., Kimberly Chambert, M.S., Eran Mick, B.S., Benjamin M. Neale, Ph.D., Menachem Fromer, Ph.D., Shaun M. Purcell, Ph.D., Oscar Svantesson, M.S., Mikael Landén, Ph.D., Martin Höglund, M.D., Ph.D., Sören Lehmann, M.D., Ph.D., Stacey B. Gabriel, Ph.D., Jennifer L. Moran, Ph.D., Eric S. Lander, Ph.D., Patrick F. Sullivan, M.D., Pamela Sklar, M.D., Ph.D., Henrik Grönbäck, M.D., Ph.D., Christina M. Hultman, Ph.D., and Steven A. McCarroll, Ph.D.

Age-Related Clonal Hematopoiesis Associated with Adverse Outcomes

Siddhartha Jaiswal, M.D., Ph.D., Pierre Fontanillas, Ph.D., Jason Flannick, Ph.D., Alisa Manning, Ph.D., Peter V. Grauman, B.A., Brenton G. Mar, M.D., Ph.D., R. Coleman Lindsley, M.D., Ph.D., Craig H. Mermel, M.D., Ph.D., Noel Burtt, B.S., Alejandro Chavez, M.D., Ph.D., John M. Higgins, M.D., Vladislav Moltchanov, Ph.D., Frank C. Kuo, M.D., Ph.D., Michael J. Kluk, M.D., Ph.D., Brian Henderson, M.D., Leena Kinnunen M.Sc., Heikki A. Koistinen, M.D., Ph.D., Claes Ladenvall, Ph.D., Gad Getz, Ph.D., Adolfo Correa, M.D., Ph.D., Benjamin F. Banahan, Ph.D., Stacey Gabriel, Ph.D., Sekar Kathiresan, M.D., Heather M. Stringham, Ph.D., and Mark I. McCarthy, M.D., for T2D-GENES; Michael Boehnke, Ph.D., for GoT2D; David Altshuler, M.D., Ph.D., for SIGMA T2D; and Jaakko Tuomilehto, M.D., Ph.D., Christopher Haiman, Sc.D., Leif Groop, M.D., Ph.D., Gil Atzmon, Ph.D., James G. Wilson, M.D., Donna Neuberg, Sc.D., David Altshuler, M.D., Ph.D., and Benjamin L. Ebert, M.D., Ph.D.
Clonal evolution

Embryogenesis  Premalignant lesion  Cancer

Age
Clonal hematopoiesis of indeterminate potential (CHIP)

Exome sequencing of peripheral blood from >17,000 individuals

Jaiswal et al., *NEJM* 2014
DNMT3A is frequently mutated
Most subjects had only one mutation
CHIP increases the risk of hematologic malignancy
Clonal hematopoiesis is associated with reduced overall survival

<table>
<thead>
<tr>
<th>All-cause mortality</th>
<th>HR(CI 95%)</th>
<th>Events/No. at risk</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>No mutation (referent)</td>
<td></td>
<td>698/4886</td>
<td></td>
</tr>
<tr>
<td>Mutation present</td>
<td>1.4 (1.1-1.8)</td>
<td>69/246</td>
<td>0.018</td>
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</table>

Cox proportional hazards models which included age, gender, and diabetes status as covariates, with results for cohorts analyzed as a fixed-effects meta-analysis
Clonal hematopoiesis is associated with higher risk of heart attack and stroke

Regression models were adjusted for age, sex, BMI, lipids, blood pressure, and smoking.
• MDS Overview
• Disease Mechanisms
• **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 ≤4.0)

No transfusion needs, good quality of life

Isolated cytopenia

- Observe, follow blood counts every 1-6 months depending on stability
- Anemia (Hgb <10 g/dl and/or transfusion dependent), symptomatic

- Start erythropoiesis stimulating agent or blood transfusions

Multiple cytopenias

- Start anti-thymocyte globulin or hypomethylating agent or enroll into clinical trial
- Thrombocytopenia (<20k/L or <50k/L with bleeding)

- Start thrombopoietin agonists* or platelet transfusions or enroll into clinical trial

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

- Start lenalidomide or enroll into clinical trial

No response or loss of response

- Start hypomethylating agent or enroll into clinical trial

Sekeres and Gerds Hematology 2014.
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

- Observe, follow blood counts every 1-6 months depending on stability
- Anemia (Hgb <10 g/dl and/or transfusion - dependent), symptomatic
  - Start erythropoiesis stimulating agent or blood transfusions
  - No response, loss of response, or del(5q) cytogenetic abnormality
    - Start lenalidomide or enroll into clinical trial
- Thrombocytopenia (<20k/L or <50k/L with bleeding)
  - Start thrombopoietin agonists* or platelet transfusions or enroll into clinical trial
  - No response or loss of response

Start anti-thymocyte globulin or hypomethylating agent or enroll into clinical trial

Sekeres and Gerds Hematology 2014.
Efficacy and Safety of Lenalidomide Versus Placebo in RBC Transfusion-Dependent Patients With IPSS Low or Intermediate-1-Risk Myelodysplastic Syndromes Without del(5q) and Unresponsive or Refractory to Erythropoiesis-Stimulating Agents: Results From a Randomized Phase 3 Study (CC-5013-MDS-005)

Valeria Santini¹, Antonio Almeida², Aristoteles Giagounidis³, Stefanie Gröpper³, Anna Jonasova⁴, Norbert Vey⁵, Ghulam J. Mufti⁶, Rena Buckstein⁷, Moshe Mittelman⁸, Uwe Platzbecker⁹, Ofer Shpilberg¹⁰, Ron Ram⁸, Consuelo del Canizo¹¹, Norbert Gattermann¹², Keiya Ozawa¹³, Alberto Risueno¹⁴, Kyle J. MacBeth¹⁵, Jim Zhong¹⁶, Francis Séguy¹⁷, Albert Hoenekopp¹⁷, C.L. Beach¹⁶, Pierre Fenaux¹⁸

¹AOU Careggi, University of Florence, Firenze, Italy; ²Instituto Português de Oncologia de Lisboa Francisco Gentil, Lisboa, Portugal; ³Marien Hospital Düsseldorf, Düsseldorf, Germany; ⁴Charles University General Hospital 1st Department of Medicine, Prague, Czech Republic; ⁵Institut Paoli-Calmettes Centre Régional de Lutte Contre le Cancer, Marseille, France; ⁶King’s College Hospital, London, UK; ⁷Sunnybrook Health Sciences Centre, Toronto, ON, Canada; ⁸Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; ⁹Medical Clinic and Polyclinic I, University Hospital, Technical University Dresden, Dresden, Germany; ¹⁰Assuta Medical Center, Tel Aviv, Israel; ¹¹Hospital Universitario de Salamanca, Salamanca, Spain; ¹²Heinrich-Heine-Universität, Düsseldorf, Germany; ¹³The Institute of Medical Science, The University of Tokyo, Tokyo, Japan; ¹⁴Celgene Institute for Translational Research Europe (CITRE), Seville, Spain; ¹⁵Celgene Corporation, San Francisco, CA, USA; ¹⁶Celgene Corporation, Summit, NJ, USA; ¹⁷Celgene International, Boudry, Switzerland; ¹⁸Service d’Hématologie Séniors, Hôpital Saint-Louis, Université Paris 7, Paris, France
MDS-005: Study Design

**Pretreatment**

- Matching placebo

**Double-blind (DB) treatment**

- LEN 10 mg, orally, QD<sup>a</sup>

- RBC-TI ≥ 8 weeks or erythroid response

**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

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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

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<sup>a</sup>LEN 5 mg for patients with creatinine clearance 40–60 mL/min.
Significantly more LEN patients achieved RBC-TI ≥ 8 weeks versus placebo ($P < 0.001$)

MDS-005: RBC-TI ≥ 8 Weeks

- LEN (n = 160):
  - 26.9% of patients achieved RBC-TI ≥ 8 weeks

- Placebo (n = 79):
  - 2.5% of patients achieved RBC-TI ≥ 8 weeks
MDS-005: Time to RBC-TI ≥ 8 Weeks

90% of the patients with RBC-TI ≥ 8 weeks responded within 4 cycles of treatment.

Proportion of patients with RBC-TI ≥ 8 weeks

Time to onset of response (weeks)

- LEN (n = 41)
- Placebo (n = 1)

37%, 1 cycle
44%, 2 cycles
66%, 3 cycles
90%, 4 cycles
The median duration of response was 32.9 weeks (95% CI 20.7–71.1) among RBC-TI ≥ 8 weeks responders with LEN.

Log-rank $P = 0.6389$ + Censored

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<thead>
<tr>
<th>Duration of response (weeks)</th>
<th>LEN</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>0</td>
<td>41</td>
<td>1</td>
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<tr>
<td>12</td>
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<td>48</td>
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<td>60</td>
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<td>72</td>
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<td>84</td>
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<tr>
<td>120</td>
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CI, confidence interval.
Luspatercept (ACE-536) Increases Hemoglobin and Reduces Transfusion Burden in Patients with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS): Preliminary Results from a Phase 2 Study

Uwe Platzbecker, MD

U Platzbecker¹, U Germing², A Giagounidis³, K Goetze⁴, P Kiewe⁵, K Mayer⁶, O Ottman⁷, M Radsak⁸, T Wolff⁹, D Haase¹⁰, M Hankin¹¹, D Wilson¹¹, A Laadem¹², M Sherman¹¹ and K Attie¹¹

¹Universitätsklinikum Carl Gustav Carus, Dresden; ²Universitätsklinikum Düsseldorf; ³Marien Hospital Düsseldorf; ⁴Technical University of Munich; ⁵Onkologischer Schwerpunkt am Oskar-Helene-Heim, Berlin; ⁶Universitätsklinikum Bonn; ⁷Klinikum der J.W. Goethe-Universität Frankfurt; ⁸University Medical Center - Johannes Gutenberg-Universität, Mainz; ⁹OncoResearch Lerchenfeld UG, Hamburg; ¹⁰Department of Hematology and Medical Oncology, University Medicine of Göttingen, Germany; ¹¹Acceleron Pharma, Cambridge, MA; ¹²Celgene Corporation, Summit, NJ, USA

Study supported by Acceleron and Celgene
Luspatercept PACE-MDS Study Overview

- Phase 2, multicenter, open-label, dose-finding study in IPSS low/int-1 MDS
- **Eligibility criteria:** EPO >500 U/L or nonresponsive/refractory to ESA; no prior azacitidine or decitabine; no current lenalidomide, ESA, G-CSF

- **Primary efficacy endpoints**
  - Low Transfusion Burden (LTB, <4U RBC/8 weeks, Hgb <10 g/dL):
    Hemoglobin increase of ≥ 1.5 g/dL for ≥ 2 weeks
  - High Transfusion Burden (HTB, ≥4U RBC/8 weeks):
    Reduction of ≥4U or ≥50% units transfused over 8 weeks

- Luspatercept administered SC every 3 weeks for 3 months
## Baseline Characteristics

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<th>All Patients</th>
<th>N = 26</th>
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<tr>
<td>Age, yr, median (range)</td>
<td>71 (27-88)</td>
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<tr>
<td>Sex, males (%)</td>
<td>13 (50%)</td>
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<tr>
<td>Prior ESA treatment, n (%)</td>
<td>14 (54%)</td>
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<tr>
<td>Prior lenalidomide treatment, n (%)</td>
<td>5 (19%)</td>
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<tr>
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<th>Low Transfusion Burden (LTB)</th>
<th>N = 7 (27%)</th>
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<tr>
<td>Hemoglobin, g/dL, median (range)</td>
<td>9.1 (8.3-9.7)</td>
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<tr>
<td>Units RBC/8 weeks, median (range)</td>
<td>0 (0-2)</td>
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<table>
<thead>
<tr>
<th></th>
<th>High Transfusion Burden (HTB)</th>
<th>N = 19 (73%)</th>
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<tbody>
<tr>
<td>Units RBC/8 weeks, median (range)</td>
<td>6 (4-13)</td>
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</table>

Data as of 03 Oct 2014
# Efficacy Summary: HI-E Response Rate

<table>
<thead>
<tr>
<th>Patient Subgroup</th>
<th>0.125-0.5 mg/kg (N=9) n (%)</th>
<th>0.75-1.75 mg/kg (N=17) n (%)</th>
</tr>
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<tbody>
<tr>
<td>LTB patients (N=7)</td>
<td>0/2 (0%)</td>
<td>2/5 (40%)</td>
</tr>
<tr>
<td>HTB patients (N=19)</td>
<td>2/7 (29%)</td>
<td>5/12 (42%)</td>
</tr>
<tr>
<td>All patients (N=26)</td>
<td>2/9 (22%)</td>
<td>7/17 (41%)</td>
</tr>
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</table>

**HI-E (IWG):**
- **LTB:** Hemoglobin increase ≥1.5 g/dL for ≥8 weeks
- **HTB:** Reduction of ≥4 units RBCs transfused over 8 weeks

HI-E, hematologic improvement-erythroid

IWG, International Working Group

LTB, low transfusion burden; HTB, high transfusion burden

Data as of 03 Oct 2014
An Open-Label, Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Low- or Intermediate (Int)-1-Risk Myelodysplastic Syndromes (MDS) or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML) and Anemia Requiring Transfusion

Rami Komrokji\textsuperscript{1}, Guillermo Garcia-Manero\textsuperscript{2}, Lionel Ades\textsuperscript{3}, Abderrahmane Laadem\textsuperscript{4}, Bond Vo\textsuperscript{4}, Thomas Prebet\textsuperscript{5}, Aspasia Stamatoulas\textsuperscript{6}, Thomas Boyd\textsuperscript{7}, Jacques Delaunay\textsuperscript{8}, David P. Steensma\textsuperscript{9}, Mikkael A. Sekeres\textsuperscript{10}, Odile Beyne-Rauzy\textsuperscript{11}, Jun Zou\textsuperscript{4}, Kenneth M. Attie\textsuperscript{12}, Matthew L. Sherman\textsuperscript{12}, Pierre Fenaux\textsuperscript{13}, Alan F. List\textsuperscript{14}

Part 1: Dose finding

- Enroll \leq 20 evaluable patients per dose level
- Sotatercept 0.1 mg/kg SC q3w
- Sotatercept 0.3 mg/kg SC q3w
- Sotatercept 0.5 mg/kg SC q3w
- Sotatercept 1.0 mg/kg SC q3w
- Sotatercept 2.0 mg/kg SC q3w

Assess erythroid hematologic response after 5–8 cycles of treatment

- Response
  - Continue treatment q3w
  - Progression or therapeutic failure
    - Discontinue treatment
- No response
  - Discontinue treatment

Assess MDS and OS every 6 months, up to 24 months following first treatment

Part 2: Recommended dose (as determined by steering committee) in Part 1 carried over into Part 2 with enrollment of 15 additional patients

Komrokji et al. 3251a
An Open-Label, Phase 2, Dose-Finding Study of Sotatercept (ACE-011) in Patients With Low- or Intermediate (Int)-1 Risk Myelodysplastic Syndromes (MDS) or Non-Proliferative Chronic Myelomonocytic Leukemia (CMML) and Anemia Requiring Transfusion

Rami Komrokji¹, Guillermo Garcia-Manero², Lionel Ades³, Abderrahmane Laadem⁴, Bond Vo⁴, Thomas Prebet⁵, Aspasia Stamatoullas⁶, Thomas Boyd⁷, Jacques Delaunay⁸, David P. Steensma⁹, Mikkael A. Sekeres¹⁰, Odile Beyne-Rauzy¹¹, Jun Zou⁴, Kenneth M. Attie¹², Matthew L. Sherman¹², Pierre Fenaux¹³, Alan F. List¹⁴

<table>
<thead>
<tr>
<th>Table 2. Transfusion Response Among HTB Patients</th>
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<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Sotatercept dose group</strong></td>
</tr>
<tr>
<td>0.1 mg/kg (n = 7)</td>
</tr>
<tr>
<td>0.3 mg/kg (n = 6)</td>
</tr>
<tr>
<td>0.5 mg/kg (n = 17)</td>
</tr>
<tr>
<td>1.0 mg/kg (n = 15)</td>
</tr>
<tr>
<td><strong>Overall (N = 45)</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Transfusion burden reduction</td>
</tr>
<tr>
<td>≥ 4 RBC units/56 days, n (%)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>4 (67)</td>
</tr>
<tr>
<td>7 (41)</td>
</tr>
<tr>
<td>8 (53)</td>
</tr>
<tr>
<td>19 (42)</td>
</tr>
<tr>
<td>Duration of longest response, median (range), days</td>
</tr>
<tr>
<td>NA (62–144)</td>
</tr>
<tr>
<td>68</td>
</tr>
<tr>
<td>150</td>
</tr>
<tr>
<td>88</td>
</tr>
<tr>
<td>106</td>
</tr>
<tr>
<td>RBC-TI ≥ 56 days, n (%)</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1 (17)</td>
</tr>
<tr>
<td>2 (12)</td>
</tr>
<tr>
<td>2 (13)</td>
</tr>
<tr>
<td>5 (11)</td>
</tr>
</tbody>
</table>

HTB, high transfusion burden; NA, not applicable; RBC, red blood cell; RBC-TI, RBC transfusion independence.
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

- Observe, follow blood counts every 1-6 months depending on stability
- Anemia (Hgb < 10 g/dl and/or transfusion-dependent), symptomatic
- Thrombocytopenia (<20k/L or <50k/L with bleeding)

Multiple cytopenias

- 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

- No response, loss of response
  - Start hypomethylating agent or enroll into clinical trial

*Suggested for symptomatic anemia only.
Lower-risk MDS: TPO Agonists

### Lower-risk MDS: TPO Agonists

<table>
<thead>
<tr>
<th></th>
<th>Baseline platelets &lt; 20x10⁹/L</th>
<th>Baseline platelets ≥ 20x10⁹/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N = 43)</td>
<td>Romiplostim (N = 87)</td>
</tr>
<tr>
<td>CSBE (rate/100 pt-yr)</td>
<td>501.2</td>
<td>514.9</td>
</tr>
<tr>
<td>RR = 1.03, p = 0.827</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTE (rate/100 pt-yr)</td>
<td>1778.6</td>
<td>1250.5</td>
</tr>
<tr>
<td>RR = 0.71, p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### 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>

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

Patient diagnosed with higher-risk MDS per IPSS (score \( \geq 1.5 \)) 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 \( \geq 6 \) cycles
    - Hematologic improvement or better: Continue hypomethylating therapy until loss of response/progression
    - No response: Clinical trial with novel agent(s) or consider cytotoxic therapy or best supportive care

- Desires HCT, good HCT CI score
  - Initiate search for MRD or 8/8 URD
    - Older patient, lower blast percentage, intermediate/poor-risk cytogenetics: Immediate hypomethylating agent-based therapy until time of HCT
    - Younger patient, higher blast percentage, good-risk cytogenetics: Intensive, AML-type induction chemotherapy
      - Suitable donor not identified: Continue hypomethylating therapy until loss of response/progression
      - Suitable donor identified: HCT
      - Suitable donor not identified: Monitor, consider post-remission therapy

MDS: Higher-risk, Treatment Algorithm

Patient diagnosed with higher-risk MDS per IPSS (score ≥1.5) or IPSS-R (score >4.5)

- Declines HCT and/or unsuitable donor, poor HCT CI score
- Desires HCT, good HCT CI score

Immediate
hypomethylating agent-based clinical trial or monotherapy x ≥6 cycles

Hematologic improvement or better
Continue
hypomethylating therapy until loss of response/progression

No response
Clinical trial with novel agent(s) or consider cytotoxic therapy or best supportive care

Higher-risk MDS

Investigator CCR
Tx Selection

Randomization

Conventional care regimens

- Best Supportive Care [n=105]
- Low Dose Ara-C [n=49]
- Std Chemo (7 + 3) [n=25]

AZA 75 mg/m²/d x 7 d q28 d [n=179]

Higher-risk MDS: AZA

Log-Rank \( p = 0.0001 \)

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

Difference: 9.4 months

Higher-risk MDS: DAC

DAC 15 mg/m² q8⁰ x 3 d q6w [n=119]

Higher-risk MDS

Randomization

Best Supportive Care [n=114]

Higher-risk MDS: DAC

Median OS 10.1 vs. 8.5 months

First clinical results of a randomized phase 2 study of SGI-110, a novel subcutaneous hypomethylating agent, in 102 patients with Intermediate or High Risk MDS or CMML

On Behalf of the SGI-110 Investigative Team

Guillermo Garcia Manero¹, Ellen Ritchie², Katherine Walsh³, Michael Savona⁴, Patricia Kropf⁵, Casey O’Connell⁶, Raoul Tibes⁷, Naval Daver¹, Elias Jabbour¹, Scott Lunin⁸, Todd Rosenblat⁹, Karen Yee¹⁰, Wendy Stock¹¹, Elizabeth Griffiths¹², Joseph Mace¹³, Nikola Podoltsev¹⁴, Jesus Berdeja⁴, Jean-Pierre Issa¹⁵, Woonbok Chung¹⁵, Sue Naim¹⁶, Pietro Taverna¹⁶, Yong Hao¹⁶, Mohammad Azab¹⁶, Hagop Kantarjian¹, Gail Roboz²

¹ MD Anderson Cancer Center, Houston, TX, ² Weill Cornell Medical College, New York, NY, ³ The Ohio State University, Columbus, OH, ⁴ Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN, ⁵ Fox Chase Cancer Center, Philadelphia, PA, ⁶ USC Keck School of Medicine, University of Southern California, Los Angeles, CA, ⁷ Mayo Clinic Arizona, Scottsdale, AZ, ⁸ Florida Cancer Specialist, Englewood, FL, ⁹ New York Presbyterian/Columbia University Medical Center, New York, NY, ¹⁰ Princess Margaret Cancer Center, Toronto, Canada, ¹¹ University of Chicago Medical Center, Chicago, IL, ¹² Roswell Park Cancer Institute, Buffalo, NY, ¹³ Florida Cancer Specialists, St Petersburg, FL, ¹⁴ Yale University School of Medicine, New Haven, CT, ¹⁵ Fels Institute, Temple University, Philadelphia, PA, ¹⁶ Astex Pharmaceuticals Inc., Dublin, CA.
Randomized Phase 2 Study of SGI-110 in MDS/CMML

Major Eligibility

Previously Treated MDS/CMML
or
Treatment Naïve MDS/CMML

• IPSS Int-1,2 and HR
• ECOG PS 0-2
• Adequate hepato-renal function

Biologically Effective Dose
60 mg/m² daily x 5

Highest Well Tolerated Dose
90 mg/m² daily x 5

Treatment continued until unacceptable toxicity, disease progression

Primary Endpoint: Overall Response Rate (CR, PR, mCR, HI)
Secondary Endpoints: Transfusion independence, LINE-1 demethylation, time to AML, overall survival

IWG 2006 MDS Response Criteria

Data presented with data cutoff end of July 2014

1
## SGI-110: Patients Characteristics By MDS Status

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Prev. Treated (n=53)</th>
<th>Tx Naïve (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age, (range)</td>
<td>72.5 (52-89)</td>
<td>71.7 (18-85)</td>
</tr>
<tr>
<td>Gender, M n (%)</td>
<td>32 (60)</td>
<td>35 (71)</td>
</tr>
<tr>
<td>ECOG PS %: 0/1/2</td>
<td>21/58/21</td>
<td>27/67/6</td>
</tr>
<tr>
<td>Disease Category (IPSS) n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Int-1</td>
<td>4 (8)</td>
<td>23 (47)</td>
</tr>
<tr>
<td>Int-2</td>
<td>13 (25)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>High Risk</td>
<td>24 (45)</td>
<td>9 (18)</td>
</tr>
<tr>
<td>CMML</td>
<td>10 (19)</td>
<td>12 (24)</td>
</tr>
<tr>
<td>Median BM Blast % (range)</td>
<td>8 (0-19)</td>
<td>3 (0-14)</td>
</tr>
<tr>
<td>Median Neutrophils (10⁹/L)</td>
<td>0.81</td>
<td>1.64</td>
</tr>
<tr>
<td>Median Platelets (10⁹/L)</td>
<td>37</td>
<td>62.5</td>
</tr>
<tr>
<td>Median Hb (g/dL)</td>
<td>9.30</td>
<td>9.10</td>
</tr>
<tr>
<td>Prior decitabine or azacitidine n(%)</td>
<td>51 (96)</td>
<td>1 (2)¹</td>
</tr>
<tr>
<td>Randomized Dose (n)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg/m²</td>
<td>26</td>
<td>27</td>
</tr>
<tr>
<td>90 mg/m²</td>
<td>27</td>
<td>22</td>
</tr>
</tbody>
</table>

¹Patient received only 1 prior cycle of HMA
# SGI-110: Best Response by MDS Status

<table>
<thead>
<tr>
<th>Response Category(^1)</th>
<th>Prev Treated (n=53)</th>
<th>Tx Naïve (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Response rate n (%)</td>
<td>Response rate n (%)</td>
</tr>
<tr>
<td>CR</td>
<td>2 (3.8)</td>
<td>7 (14.3)</td>
</tr>
<tr>
<td>mCR</td>
<td>9 (17.0)</td>
<td>3 (6.1)</td>
</tr>
<tr>
<td>HI</td>
<td>1 (1.9)</td>
<td>9 (18.4)</td>
</tr>
<tr>
<td>CR+mCR</td>
<td>11 (20.8)</td>
<td>10 (20.4)</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>12 (22.7)</td>
<td>19 (38.8)</td>
</tr>
</tbody>
</table>

\(^1\)International Working Group 2006 MDS Response Criteria
What happens when we add drugs together?
A 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 [LBA – 5]

Mikkael A. Sekeres, MD, MS, Megan Othus, PhD, Alan F. List, MD, Olatoyosi Odenike, MD, Richard M. Stone, MD., Steven D. Gore, MD, Mark R. Litzow, MD, Rena Buckstein, MD, Mario R. Velasco, MD, Rakesh Gaur, MD, MPH, Ehab Atallah, MD, Eyal C. Attar, MD, Frederick R. Appelbaum, MD, Harry P. Erba, MD, PhD
North American Intergroup Randomized Phase 2 MDS Study S1117: **Study Design**

**Higher-risk MDS or CMML**

- **AZA (IV/SC)**
  - 75 mg/m²/d (d1-7)
  - N=92

- **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=91

**Groups:** SWOG, ECOG, Alliance, NCIC

**Total Sample Size:** 276

**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**

03/2012 – 06/2014

Sekeres et al. ASH 2014: LBA - 5
### 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=260</th>
</tr>
</thead>
<tbody>
<tr>
<td>Febrile neutropenia (n)</td>
<td>10</td>
<td>13 (0.66)</td>
<td>13 (0.51)</td>
<td>36</td>
</tr>
<tr>
<td>Gl (n)</td>
<td>4</td>
<td>11 (0.10)</td>
<td>23 (&lt;0.001)</td>
<td>38</td>
</tr>
<tr>
<td>Rash (n)</td>
<td>2</td>
<td>12 (0.01)</td>
<td>1 (1)</td>
<td>15</td>
</tr>
<tr>
<td>Off Tx due to Toxicity/Side Effect/Complication</td>
<td>9%</td>
<td>23% (.04)</td>
<td>24% (.03)</td>
<td>19%</td>
</tr>
<tr>
<td>Non-protocol defined dose modifications</td>
<td>23%</td>
<td>41% (.01)</td>
<td>36% (.05)</td>
<td>33%</td>
</tr>
</tbody>
</table>
## 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=260</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Tx Duration (Wks)</td>
<td>25</td>
<td>24</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Overall Response Rate (%)</td>
<td>37</td>
<td>39 (.1)</td>
<td>24 (.07)</td>
<td>33</td>
</tr>
<tr>
<td>CR/PR/HI (%)</td>
<td>24/0/13</td>
<td>18/1/19 (.66)</td>
<td>15/1/7 (.12)</td>
<td>19/1/13</td>
</tr>
<tr>
<td>CMML ORR (%)</td>
<td>33 (n=15)</td>
<td>59 (.15) (n=19)</td>
<td>13 (.41) (n=16)</td>
<td>34</td>
</tr>
<tr>
<td>Relapse-free Survival (median)</td>
<td>7 months</td>
<td>8 months (.45)</td>
<td>11 months (.29)</td>
<td>7 months</td>
</tr>
<tr>
<td>Relapse-free survival, on Tx &gt;6 months (median)</td>
<td>7 months</td>
<td>7.5 months (.74)</td>
<td>13 months (.11)</td>
<td>8.5 months</td>
</tr>
</tbody>
</table>
North American Intergroup Randomized Phase 2 MDS Study S1117: Relapse-free Survival (II) All Responders on Tx >6 Months

Relapse–free survival for patients on therapy > 6 months

<table>
<thead>
<tr>
<th></th>
<th>Months since response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>30</td>
<td>1</td>
</tr>
</tbody>
</table>

N at risk

<table>
<thead>
<tr>
<th></th>
<th>Aza</th>
<th>Aza+Len</th>
<th>Aza+Vor</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>21</td>
<td>28</td>
<td>15</td>
</tr>
</tbody>
</table>

Aza vs Aza+Len log–rank p = 0.74
Aza vs Aza+Vor log–rank p = 0.11
Aza vs Combo arms log–rank p = 0.6

Sekeres et al. ASH 2014: LBA - 5
No differences in ORR comparing AZA + LEN or AZA + VOR to AZA monotherapy.

Some subgroups may have benefitted from AZA-based combinations.

Signal of RFS improvement with AZA + VOR; EFS/OS data maturing and analyses by cytogenetic subgroups pending.
Overall Survival and Subgroup Analysis from a Randomized Phase III Study of Intravenous Rigosertib vs Best Supportive Care in Patients with Higher-risk Myelodysplastic Syndrome After Failure of Hypomethylating Agents (ONTIME Trial of ON 01910)

ONTIME Trial: Study Design

- Phase III, randomized, controlled, safety & efficacy study comparing rigosertib + BSC* vs BSC* alone (2:1)
  - Adult pts who had relapsed after, failed to respond to, or progressed during HMA therapy
  - 299 pts enrolled at 87 sites in US and Europe
  - Rigosertib administered as 1800 mg/24 hr for 72 hrs as a continuous IV ambulatory infusion

- Pts stratified by bone marrow blast count (5-19% vs 20-30%)
  - Additional information on the relationship between OS and BMBL is available in Poster #3259

- Primary endpoint = overall survival

- Analysis based on 242 events (deaths; ≥ 80% maturity)

- Median follow-up of >18 months

*BSC=Best supportive care: RBC & platelets; growth factors; hydroxyurea to manage blastic crises when pts transition to leukemia; pts on the BSC arm also allowed low-dose cytarabine, as medically justified.
# ONTIME Trial: Primary Efficacy Results - ITT

<table>
<thead>
<tr>
<th></th>
<th>Rigosertib N = 199</th>
<th>BSC N = 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (%) of deaths</td>
<td>161 (81%)</td>
<td>81 (81%)</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>17.6</td>
<td>19.5</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>8.2</td>
<td>5.9</td>
</tr>
<tr>
<td>95% CI</td>
<td>6.0 - 10.1</td>
<td>4.1 - 9.3</td>
</tr>
<tr>
<td>Stratified HR (rigosertib/BSC)</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.67 - 1.14</td>
<td></td>
</tr>
<tr>
<td>Stratified log-rank p-value*</td>
<td>0.33</td>
<td></td>
</tr>
</tbody>
</table>

* Stratification factor: bone marrow blast at randomization (5-19% versus 20-30%)
Per Prebet 2011, “Primary HMA Failure” was defined as either no response to or progression during HMA therapy.
ONTIME Trial: Conclusions

• Primary endpoint of OS did not reach statistical significance in the ITT population
  – 2.3-month improvement in median OS in the ITT population

• Rigosertib treatment-related improvement in OS was noted in the following well-balanced subgroups:
  – Primary HMA failure (64% of pts: HR = 0.69; p = 0.04)
  – IPSS-R Very High Risk (45% of pts: HR = 0.56; p = 0.005)
  – Cytogenetic criteria also important prognostic factors
    • Monosomy 7 (HR = 0.24; p = 0.003)
    • Trisomy 8 (HR = 0.34; p = 0.035)

• Continuous IV infusion with rigosertib had a favorable safety profile in this population of elderly pts with HR MDS
• The molecular landscape of MDS is becoming much more complex, and is being folded into clinical prognostic schemes.

• Therapy for lower-risk disease addresses specific cytopenias, particularly anemia.

• Standard therapy for higher-risk disease is HMA monotherapy; more data coming with combos.

• The next regulatory frontier is in the relapsed/refractory setting for lower- and higher-risk disease.
Thanks!

Cleveland Clinic Leukemia/MDS Program

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Cassandra Zimmerman, BA
Connie Cheng, PharmD

And Our Patients!!!