Myelodysplastic Syndromes
“What is on the horizon?”

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Myelodysplastic Syndromes (MDS)

• A group of malignant hematopoietic neoplasms characterized by:
  – Bone marrow failure with resultant cytopenia and related complications
  – Evidence of clonality by cytogenetic abnormalities or somatic gene mutations.
  – Dysplastic cytologic morphology is the hallmark of the disease
  – Tendency to progress to AML

• Overall incidence 3.7-4.8/100,000
  – In US (true estimates ≈37,000-48,000)

• Median age: 70 yrs; incidence: 34-47/100,000 >75 yrs

AML = acute myeloid leukemia.
MDS the spectrum?

<table>
<thead>
<tr>
<th></th>
<th>Traditional ICUS</th>
<th>MDS by WHO 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHIP</td>
<td>Non-clonal ICUS</td>
</tr>
<tr>
<td>Clonality</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>–/+</td>
<td>–</td>
</tr>
<tr>
<td>Cytopenias</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>BM Blast %</td>
<td>&lt; 5%</td>
<td>&lt; 5%</td>
</tr>
<tr>
<td>Overall Risk</td>
<td>Very Low</td>
<td>Very Low</td>
</tr>
</tbody>
</table>

Are these two the same? Does morphologic dysplasia matter?

CCUS = clonal cytopenias of undetermined significance; ICUS = idiopathic cytopenias of undetermined significance; CHIP = clonal hematopoiesis of indeterminate potential; LR = lower risk, HR = higher risk
### Risk Groups for the IPSS-R

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Points</th>
<th>% of Patients</th>
<th>Median survival, years</th>
<th>Time until 25% of patients develop AML, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very low</td>
<td>≤ 1.5</td>
<td>19 %</td>
<td>8.8</td>
<td>Not reached</td>
</tr>
<tr>
<td>Low</td>
<td>&gt; 1.5 – 3</td>
<td>38 %</td>
<td>5.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Intermediate</td>
<td>&gt; 3 – 4.5</td>
<td>20 %</td>
<td>3.0</td>
<td>3.2</td>
</tr>
<tr>
<td>High</td>
<td>&gt; 4.5 – 6</td>
<td>13 %</td>
<td>1.6</td>
<td>1.4</td>
</tr>
<tr>
<td>Very High</td>
<td>&gt; 6</td>
<td>10 %</td>
<td>0.8</td>
<td>0.73</td>
</tr>
</tbody>
</table>

Somatic Gene Mutations Improve Precision of the IPSS-R

Summary of Risk Stratification

- very low risk R-IPSS +/- 1 HR somatic mutation (SM).
- Low risk R-IPSS no HR SM
- Very low/low/intermediate R-IPSS with SF3B1 SM.

- Low risk R-IPSS + 1 HR SM.
- Intermediate risk R-IPSS no HR SM.

- Intermediate risk R-IPSS + HR SM
- Very high and high risk R-IPSS.
- Complex monosomy karyotype.
- > 3 HR SM.
- P53 mutation.
Anemia Management Algorithm in LR-MDS 2019

- **Epo<200mU/mL <2U RBC/mo**
  - **ESA**
  - **Non-del5q**
    - LEN+/- Epo
    - AZA 5 day

- **Del (5q) Iso- or +1**
  - **Lenalidomide**
  - **Del5q**

- **Epo>200mU/mL >2U RBC/mo**
  - **Age**
    - >60
      - **SF3B1 Mu+**
      - MDS > 24 mos
    - <60
      - No SGM or **SF3B1 Mu-**
      - HLA-DR15+,+8
  - **Non-del5q pathway**
  - **IST**

*SGM, somatic gene mutation.
Excess Smad2/3 Signaling Suppresses Late-Stage RBC Maturation in MDS

Bone marrow microenvironment

TGF-β ligands (e.g. GDF15, GDF11, BMP6, activin A) negatively regulate late erythropoiesis

Luspatercept releases maturation block

SCF, IL-3, EPO

EPO-responsive, EPO-dependent

500 cells, 8–64 cells

Sustained Hb increase

Rapid Hb increase

• Mobilizes cells from precursor pools into blood
• Effect relies on continuous formation of late-stage precursors from earlier progenitors

The MEDALIST Trial: Results of a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) Associated Anemia With Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

Luspatercept is an investigational first-in-class erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit aberrant Smad2/3 signaling and enhance late-stage erythropoiesis in MDS models\(^1\)

In a phase 2 study in LR, non-del(5q) MDS, luspatercept yielded a high frequency of transfusion reduction or RBC-TI in patients with MDS-RS vs other subtypes\(^2\)

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**Luspatercept**

ActRIIB / IgG1 Fc recombinant fusion protein

- Modified extracellular domain of ActRIIB
- Human IgG1 Fc domain

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ActRIIB, human activin receptor type IIB; IgG1 Fc, immunoglobulin G1 fragment crystallizable; RBC-TI, red blood cell transfusion independence; RS, ring sideroblasts; TGF-β, transforming growth factor beta.
MEDALIST Trial
Study Design – A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study

**Patient Population**
- MDS-RS (WHO): ≥ 15% RS or ≥ 5% with SF3B1 mutation
- < 5% blasts in bone marrow
- No del(5q) MDS
- IPSS-R Very Low-, Low-, or Intermediate-risk
- Prior ESA response
  - Refractory, intolerant
  - ESA naive: EPO > 200 U/L
- Average RBC transfusion burden ≥ 2 units/8 weeks
- No prior treatment with disease-modifying agents (e.g. iMIDs, HMAs)

**Randomize 2:1**

**Luspatercept 1.0 mg/kg (s.c.) every 21 days**
- n = 153
  - Dose titrated up to a maximum of 1.75 mg/kg

**Placebo (s.c.) every 21 days**
- n = 76
  - Disease & Response Assessment week 24 & every 6 months
    - Treatment discontinued for lack of clinical benefit or disease progression per IWG criteria; no crossover allowed

Subjects followed ≥ 3 years post final dose for AML progression, subsequent MDS treatment and overall survival

Data cutoff: May 8, 2018 includes last subject randomized + 48 weeks.
EPO, erythropoietin; HMA, hypomethylating agent; iMID, immunomodulatory drug; IWG, International Working Group; s.c., subcutaneously; SF3B1, splicing factor 3b subunit 1; WHO, World Health Organization.
## MEDALIST Trial
Primary Endpoint: Red Blood Cell Transfusion Independence ≥ 8 Weeks

<table>
<thead>
<tr>
<th>RBC-TI ≥ 8 weeks</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1–24, n (%)</td>
<td>58 (37.9)</td>
<td>10 (13.2)</td>
</tr>
<tr>
<td>95% CI</td>
<td>30.2–46.1</td>
<td>6.5–22.9</td>
</tr>
<tr>
<td><em>P value</em>[^a]</td>
<td><em>&lt; 0.0001</em></td>
<td></td>
</tr>
</tbody>
</table>

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

**Number of patients**

<table>
<thead>
<tr>
<th>Luspatercept</th>
<th>58</th>
<th>49</th>
<th>37</th>
<th>29</th>
<th>22</th>
<th>18</th>
<th>10</th>
<th>6</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>10</td>
<td>9</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a* During indicated treatment period. Patients who maintained RBC-TI at the time of analysis are censored.

Median duration (weeks) (95% CI): 30.6 (20.6–40.6) vs 13.6 (9.1–54.9)
MEDALIST Trial
Secondary Endpoint: Erythroid Response (HI-E)

<table>
<thead>
<tr>
<th>Achieved HI-E&lt;sup&gt;a&lt;/sup&gt; (weeks 1–24), n (%)</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved HI-E&lt;sup&gt;a&lt;/sup&gt;</td>
<td>81 (52.9)</td>
<td>9 (11.8)</td>
</tr>
<tr>
<td>Reduction of ≥ 4 RBC units/8 weeks</td>
<td>52/107 (48.6)</td>
<td>8/56 (14.3)</td>
</tr>
<tr>
<td>(baseline transfusion burden ≥ 4 units/8 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb increase of ≥ 1.5 g/dL</td>
<td>29/46 (63.0)</td>
<td>1/20 (5.0)</td>
</tr>
<tr>
<td>(baseline transfusion burden &lt; 4 units/8 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>44.72–61.05</td>
<td>5.56–21.29</td>
</tr>
<tr>
<td>P value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Achieved HI-E&lt;sup&gt;a&lt;/sup&gt; (weeks 1–48), n (%)</th>
<th>Luspatercept (n = 153)</th>
<th>Placebo (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved HI-E&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90 (58.8)</td>
<td>13 (17.1)</td>
</tr>
<tr>
<td>Reduction of ≥ 4 RBC units/8 weeks</td>
<td>58/107 (54.2)</td>
<td>12/56 (21.4)</td>
</tr>
<tr>
<td>(baseline RBC transfusion burden ≥ 4 units/8 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb increase of ≥ 1.5 g/dL</td>
<td>32/46 (69.6)</td>
<td>1/20 (5.0)</td>
</tr>
<tr>
<td>(baseline RBC transfusion burden &lt; 4 units/8 weeks)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>50.59–66.71</td>
<td>9.43–27.47</td>
</tr>
<tr>
<td>P value&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt; 0.0001</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Defined as the proportion of patients meeting the HI-E criteria per IWG 2006 criteria (Cheson et al. 2006) sustained over a consecutive 56-day period during the indicated treatment period.

<sup>b</sup> Luspatercept compared with placebo, Cochran–Mantel–Haenszel test.
Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agent Who Are Lenalidomide and HMA Naive

David P. Steensma, MD, Uwe Platzbecker, MD, Koen Van Eygen, MD, Azra Raza, MD, Valeria Santini, MD, Ulrich Gerning, MD, PhD, Patricia Font, MD, Irina Samarina, MD, Maria Díez-Campelo, MD, PhD, Sylvain Thepot, MD, Edo Vellenga, MD, Mrinal M. Patnaik, MD, MBBS, Jun Ho Jang, MD, PhD, Jacqueline Bussolari, PhD, Laurie Sherman, BSN, Libo Sun, PhD, Helen Varsos, MS, RPh, Esther Rose, MD and Pierre Fenaux, MD, PhD

1Dana-Farber Cancer Institute (US), 2University Hospital Carl Gustav Carus, Dresden (DE), 3Algemeen Ziekenhuis Groeninge, Kortrijk (BE), 4Columbia University Medical Center (US), 5MDS Unit, AOU Careggi-University of Florence (IT), 6Heinrich-Heine-Universität, Düsseldorf (DE), 7Hospital General Universitario Gregorio Marañon, Madrid (ES), 8Emergency Hospital of Dzerzhinsk, Nizhny Novgorod (RU), 9The University Hospital of Salamanca (ES), 10CHU Angers (FR), 11University Medical Center Groningen (NE), 12Mayo Clinic, Rochester (US), 13Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul (KO), 14Janssen Research & Development, LLC (US), 15Hôpital Saint-Louis, Université Paris (FR)

ASH 2018 Abstract #463
Background: IMerge/NCT02598661 (Part 1) Study Design

Patients with MDS

- IPSS Low or Int-1
- Relapsed / refractory to ESA or ineligible for ESA
- Transfusion dependent (≥4u RBC/8 weeks)
- ANC ≥ 1.5 x 10^9/L
- Platelets ≥ 75 x 10^9/L

1° Endpoint: 8-Week RBC TI
2° Endpoints: 24-Week RBC TI / Time to TI / TI duration / TR (HI-E: Transfusion Reduction by ≥ 4 RBC units over 8 weeks) / MDS response per IWG / Overall survival / Incidence of AML / Safety

Exploratory: telomerase activity / hTERT / telomere length / genetic mutations

Pre-medication: diphenhydramine, hydrocortisone 100-200 mg (or equivalent)

Supportive care: RBC transfusions, myeloid growth factors per local guidelines

Imetelstat Treatment

7.5 mg/kg IV q4w (2-hr infusion)

AML, acute myeloid leukemia; ANC, absolute neutrophil count; HI-E, hematologic improvement-erythroid; IWG, International Working Group; TI, transfusion independence; TR, transfusion reduction.

Among the patients achieving durable TI, all showed a Hb rise of ≥ 3.0 g/dL compared to baseline during the transfusion-free interval.
Proposal for HR-MDS Treatment Algorithm

**P53 VAF > 40%**
- Clinical trial
- Decitabine
- HMA
- ? AHSCT at time of HMA failure
- AHSCT

**P53 VAF < 20%**
- TET-2 MT VAF > 10%/ASXL-1 WT
  - NO
  - AHSCT candidate

  **YES**
  - Decitabine
  - HMA
  - AHSCT

  **Cytopenia/ Myeloblasts > 10%**
  - NO
  - HMA
  - Observe prior to AHSCT

  **YES**
  - HMA
  - HMA prior to AHSCT
Phase 1b/2 Combination Study of APR-246 and Azacitidine (AZA) in Patients with TP53 Mutant Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML)

David A Sallman¹, Amy DeZern², David P Steensma³, Kendra Sweet¹, Thomas Cluzeau⁴, Mikkael Sekkeres⁵, Guillermo Garcia-Manero⁶, Gail Roboz⁷, Amy McLemore¹, Kathy McGraw¹, John Puskas¹, Ling Zhang¹, Chirag Bhagat⁸, Jiqiang Yao⁹, Najla H Al Ali¹, Eric Padron¹, Roger Tell¹⁰, Jeffrey E. Lancet¹, Pierre Fenaux¹¹, Alan F List¹ and Rami S Komrokji¹

¹Malignant Hematology Department, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA.; ²Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA; ³Department of Medical Oncology, Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; ⁴Cote D’azur University, Nice Sophia Antipolis University, Hematology Department, CHU Nice, Nice, France; ⁵Department of Hematology and Medical Oncology, Cleveland Clinic, Cleveland, OH, USA; ⁶Department of Leukemia, MD Anderson Cancer Center, Houston, TX, USA; ⁷Weill Cornell Medical College, New York, NY, USA; ⁹Cancer Informatics Core, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL, USA; ¹⁰Aprea Therapeutics, Stockholm, Sweden; ¹¹Hospital St Louis, Paris 7 University, Paris, France.

2018 ASH Abstract # 3091
APR-246 (PRIMA\textsuperscript{MET}) Restores Wild-type p53 Function

- Most \textit{TP53} gene mutations are single AA missense mutations in the DNA-binding domain
- APR-246 covalently binds to cysteines in mutant p53 or p63
- Reconstitutes WT conformation \& function in mutant proteins by stabilizing protein folding
- Intrinsic \& additive \textit{in vitro} schedule-dependent cytotoxicity with azacitidine

\textit{Khoo et al., Nature Reviews Drug Discovery; 2014, 13, 217-36}
Study Design

- **TP53** mutant (mTP53) HMA naïve MDS and AML (≤ 30% blasts)

### Dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Admin.</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>APR-246</td>
<td>Ph1b: 50 / 75 / 100 mg/kg LBM&lt;br&gt;Ph2: 4500 mg fixed dose</td>
<td>i.v.</td>
<td>6 hr</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>75 mg/m²</td>
<td>s.c. (or i.v.)</td>
<td>-</td>
</tr>
</tbody>
</table>

### Assessment Schedule

- **ENROLL**
- **APR-246** Lead-in
- **APR-246 + AZA** 3 cycles
- **APR-246 + AZA** 3 cycles

### Endpoints

- **Phase 1b**
  - Primary: Safety
  - Secondary: ORR, PFS, OS, TP53 VAF

- **Phase 2**
  - Primary: CR rate
  - Secondary: ORR, PFS, OS, TP53 VAF
Treatment Duration and Response

**Best Response at Cutoff**

<table>
<thead>
<tr>
<th></th>
<th>Ph1b</th>
<th>Ph2</th>
<th>MDS</th>
<th>AML</th>
<th>All</th>
<th>AZA Historical</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Evaluable Patients</strong></td>
<td>11</td>
<td>9</td>
<td>15</td>
<td>5</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Response Rate</strong></td>
<td>100%</td>
<td>89%</td>
<td>93%</td>
<td>100%</td>
<td>95%</td>
<td>30-50%</td>
</tr>
<tr>
<td><strong>CR Rate</strong></td>
<td>82%</td>
<td>56%</td>
<td>67%</td>
<td>80%</td>
<td>70%</td>
<td>20-30%</td>
</tr>
</tbody>
</table>
The First-in-Class Anti-CD47 Antibody Hu5F9-G4 is Well Tolerated and Active Alone or with Azacitidine in AML and MDS Patients: Initial Phase 1b Results

David A Sallman¹, William Donnellan², Adam Asch³, Daniel Lee⁴, Monzr Al Malki⁵, Guido Marcucci⁵, Daniel Pollyea⁶, Suman Kambhampati⁷, Rami Komrokji¹, Joanna Van Elk⁸, Ming Lin⁸, James Y Chen⁸, Jens-Peter Volkmer⁸, Chris Takimoto⁸, Mark Chao⁸, Paresh Vyas⁹

¹Moffitt Cancer Center, Tampa, FL; ²Sarah Cannon Research Institute, Nashville, TN; ³University of Oklahoma, Oklahoma City, OK, City of Hope, Duarte, CA; ⁴Columbia University, New York, NY; ⁵City of Hope, Duarte, CA; ⁶University of Colorado, Denver, CO; ⁷Healthcare Midwest, Kansas City, MO; ⁸Forty Seven, Inc., Menlo Park, CA; ⁹University of Oxford, Oxford, UK
Targeting Macrophages Leverages the Innate Immune System in the Fight Against Cancer

Macrophages are a key part of the innate immune system serving as first responder cells:
- Phagocytose cells displaying abnormal “eat me” signals, including cancer cells
- Recruit, activate, and present cancer cell antigens to T cells

- CD47 is a “do not eat me” signal on cancers that enables macrophage immune evasion
- CD47 is the dominant macrophage checkpoint overexpressed on most cancers
- Increased CD47 expression predicts worse prognosis in AML patients
- 5F9 is a First-in-class Macrophage Immune Checkpoint Inhibitor Targeting CD47
- 5F9 Synergizes with Azacitidine to Induce Remissions in AML Xenograft Models

AML Patients

Majeti, Chao et al., Cell 2009
5F9005 Study Design: 5F9 Alone or in Combination with Azacitidine in AML and MDS

5F9 Monotherapy Safety Run-in Cohort (N=10)

Relapsed/refractory (r/r) AML or MDS

5F9: 1, 30 mg/kg* twice weekly

↓

5F9 + AZA Combo Safety Evaluation (N=6)

untreated AML ineligible for induction chemotherapy or untreated MDS intermediate to very high risk by IPSS-R

5F9: 1, 30 mg/kg* weekly AZA: 75 mg/m² D1-7

Expansion (N=30)

5F9: 1, 30 mg/kg* weekly AZA: 75 mg/m² D1-7

*Dose ramp up from 1 to 30 mg/kg by week 2, then 30 mg/kg maintenance dosing

Primary objectives

1) Safety of 5F9 alone or with AZA
2) Efficacy of 5F9 in r/r AML/MDS and 5F9+AZA in untreated AML/MDS

Secondary objectives

1) PK, PD and immunogenicity of 5F9
2) Additional measures of efficacy (DOR, PFS, OS)

Exploratory objectives

1) To assess CD47 receptor occupancy, markers of immune cell activity, and molecular profiling in AML/MDS

o A 5F9 priming dose (1 mg/kg) and dose ramp up was utilized to mitigate on target anemia
o 5F9 monotherapy safety was confirmed in r/r AML/MDS patients prior to 5F9+AZA combination
Anti-Leukemic Activity is Observed with 5F9 Monotherapy and in Combination with AZA in AML and MDS

<table>
<thead>
<tr>
<th>Best Overall Response</th>
<th>R/R AML/MD</th>
<th>1L AML</th>
<th>1L MDS</th>
<th>5F9 mono N=10</th>
<th>5F9+AZA N=14</th>
<th>5F9+AZA N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>1 (10%)</td>
<td>9 (64%)</td>
<td>11 (100%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>5 (36%)</td>
<td>6 (55%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRi</td>
<td>0</td>
<td>2 (14%)</td>
<td>-</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MLFS/ marrow CR</td>
<td>1 (10%)</td>
<td>2 (14%)</td>
<td>4 (36%)</td>
<td>2 with marrow CR+HI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic improvement (HI)</td>
<td>-</td>
<td>-</td>
<td>1 (9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>7 (70%)</td>
<td>5 (36%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>2 (20%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Response assessments per 2017 AML ELN criteria and 2006 IWG MDS criteria; Patients with at least one post-treatment response assessment are shown "-" not applicable

- 5F9 monotherapy has an ORR of 10% in r/r AML/MDS
- 5F9+AZA has an ORR of 100% in MDS, 64% in AML which compares favorably to AZA monotherapy
- ORR Median time to response is more rapid (1.9 months) than AZA alone
Deep and Potential Durable Responses Seen in 5F9 + AZA Treated Patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1L AML N=14</th>
<th>1L MDS N=11</th>
</tr>
</thead>
<tbody>
<tr>
<td>RBC transfusion independence</td>
<td>9/14 (64%)</td>
<td>-</td>
</tr>
<tr>
<td>Complete cytogenetic response in responders*</td>
<td>2/7 (29%)</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td>MRD negativity in responders</td>
<td>3/9 (33%)</td>
<td>2/10 (20%)</td>
</tr>
<tr>
<td>Median duration of response (months)</td>
<td>NR (0.03+ - 8.3+)</td>
<td>NR (0.5+ - 4.3+)</td>
</tr>
<tr>
<td>Median follow-up [range] (months)</td>
<td>3.8 (1.9 - 10.3)</td>
<td>3.7 (2.5 - 6.8)</td>
</tr>
</tbody>
</table>

Minimal residual disease (MRD) was evaluated by multiparameter flow cytometry. Hematologic improvement (HI-E, HI-P, HI-N) defined per 2006 IWG MDS criteria. Cytogenetic response defined per 2003 and 2006 IWG criteria; NE: not reached. *Cytogenetic responses shown for all responding patients with abnormal cytogenetics at baseline. “-” not applicable.

- No responding patient has relapsed or progressed on 5F9 + AZA
- Multiple patients have improved responses over time
- MRD negativity has been observed (time to MRD negativity ranged from 1.7 to 6.1 months)
- 5/20 (25%) of responding patients have successfully received an allogeneic stem cell transplant
- The longest patient in response is in CR 9+ months on therapy and ongoing
On Target Anemia is a Pharmacodynamic Effect and is Mitigated with a 5F9 Priming and Maintenance Dosing Regimen

Hemoglobin changes on 5F9+AZA therapy in AML/MDS

- Aging RBCs can be cleared by CD47 blockade leading to an on target anemia
- A priming dose mitigates on target anemia through a temporary/mild decline in hemoglobin by clearing aged RBCs with reticulocytosis
- Anemia returns to baseline with treatment with 5F9 even at higher maintenance doses (30mg/kg)
- A mild hemoglobin drop (mean of 0.5 g/dL) with the priming dose was observed with 5F9+AZA
- Many patients have had hemoglobin improvement and decrease in transfusion frequency while on 5F9+AZA therapy
## Defining HMA failure

### Primary failure (lack of primary response) 25%

- Clear evidence of disease progression on therapy or death on treatment
- Median OS 4.7 mo (Rigosertib study), 5.5 mo (MCC database)

### Secondary failure ≈ 75%

- Loss of initial response or probably only stable disease after 9 cycles.
- Median OS 6.9 mo (MCC database)
- 25% AML progression at time of failure
Prognostic models after HMA failure

Parameter at HMA failure | Score | Beta | P
--- | --- | --- | ---
ECOG Performance status > 1 | 1.0 | 0.56 | 0.01
Very poor Cytogenetic (complex karyotype > 3 abnormalities) | 1.0 | 0.57 | < 0.001
Age at diagnosis, years
> 75 - ≤ 84 | 1.0 | 0.52 | < 0.001
> 84 | 2.0 | 0.90 | < 0.001
Bone Marrow Blast > 20% | 0.75 | 0.36 | 0.01
Transfusion dependent (yes vs no) | 0.75 | 0.39 | < 0.001
Platelets
< 80 | 1.0 | 0.54 | < 0.001

Nazha et al., Hematologica 2016
<table>
<thead>
<tr>
<th>Agent</th>
<th>mechanism</th>
<th>Preliminary results</th>
</tr>
</thead>
</table>
| **CC-486** | Oral azacitidine | • In phase I study, 41 patients received SC and oral azacitidine. Dose-limiting toxicity (grade 3/4 diarrhea) occurred at the 600-mg dose and MTD was 480 mg. Overall response rate was 35% in previously treated patients and 73% in previously untreated patients.  
• In Phase 2, Patients with LR-MDS received 300 mg CC-486 once daily for 14 days \( (n=28) \) or 21 days \( (n=27) \) of repeated 28-day cycles. Overall response was attained by 36% of patients receiving 14-day dosing and 41% receiving 21-day dosing. RBC TI rates were similar with both dosing schedules (31% and 38%, respectively). |
| **SGI-110** | dinucleotide of decitabine and deoxyguanosine that protects it from deamination | • In a phase I study that included 14 patients with MDSs after HMA failure, SGI-110 had a 4.5-fold longer half-life than decitabine. An equivalent or higher area under the curve was reached with lower Cmax compared with reference levels from intravenous decitabine.  
• A dose-dependent increase in demethylation was observed up to 60 mg/m\(^2\) daily for 5 days.  
• In the phase II part of the study for treatment-naïve elderly patients with AML or refractory/relapsed AML, 43% and 16% remission rates were reported. |
| **ASTX727** | Fixed dose oral cytidine deaminase inhibitor E7727 with oral decitabine | • AEs are consistent with IV decitabine with no GI toxicity.  
• ASTX727 is clinically active 33% response rate in phase I, 50% had prior HMA.  
• The fixed oral dose of 30 mg decitabine and 100 mg E7727 results in decitabine AUC equivalent to 20 mg/m\(^2\) IV and will be further studied in a Phase 2 trial in HMA naïve MDS |

**Garcia Manero et al, Leukemia 2016 Apr;30(4):889-96**  
**Garcia Manero et al, J Clin Oncol. 2011 Jun 20; 29(18): 2521–2527**  
**Kantarjian HM, et al. ASH 2013. Abstract 497.**  
**Savona et al, ASH 2015, abstract # 1683**
Enasidenib in m/IDH2 MDS: Response

<table>
<thead>
<tr>
<th>Response, n/N (%)</th>
<th>MDS Pts (N = 17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR*</td>
<td>10/17 (59)</td>
</tr>
<tr>
<td>CR†</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>PR†</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>mCR†</td>
<td>3/11 (27)</td>
</tr>
</tbody>
</table>

Any HI
- Erythrocytes: 5/17 (29)
- Platelets: 3/15 (20)
- Neutrophils: 4/12 (33)
- Trilineage improvement: 4/10 (40)
- Bilineage improvement: 2/5 (40)

- 7 of 13 pts (54%) with prior HMA responded to enasidenib
- Median time to response: 21 days (range: 10-87)

*CR + PR + mCR + HI.
†Investigator-assessed; pts had ≥ 5% BM blasts at BL.

Ivosidenib for mIDH-MDS

- 12 MDS patients demonstrated a 91.7% ORR and a CR rate of 41.7%.
- Among 13 patients progressed to AML after HMA failure CR/CRh (4/13) 33%
Out of the box

• Shifting HMA+Venetoclax or add on Venetoclax (n=19, ORR 47%, 56% proceeded to Allo-SCT) (unpublished data)

• RAS mutations- Trametinib?

• CBL mutations- Dasatinib?
Induction after HMA failure


Table 1A: Baseline characteristics of the entire cohort.

<table>
<thead>
<tr>
<th>Clinical Parameter</th>
<th>CLA/GM</th>
<th>7+3</th>
<th>CPX-351</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>65 (33-82)</td>
<td>66 (26-81)</td>
<td>69 (36-82)</td>
<td>ns</td>
</tr>
<tr>
<td>Female</td>
<td>78 (68.4%)</td>
<td>59 (63.4%)</td>
<td>18 (52.9%)</td>
<td>0.4937</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Favorable Karyotype</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.1944</td>
</tr>
<tr>
<td>Intermediate Karyotype</td>
<td>62/107 (57.9%)</td>
<td>51/78 (65.4%)</td>
<td>22/31 (71.0%)</td>
<td>0.1944</td>
</tr>
<tr>
<td>Poor</td>
<td>45/107 (42.1%)</td>
<td>27/78 (34.6%)</td>
<td>9/31 (29.0%)</td>
<td>0.1944</td>
</tr>
<tr>
<td><strong>WBC (mean)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4.401 (0.47-34.50)</td>
<td>4.16 (0.88-18.0)</td>
<td>8.52 (0.40-50.35)</td>
<td>0.0013</td>
</tr>
<tr>
<td>Female</td>
<td>9.36 (2.30-14.30)</td>
<td>9.66 (4.0-14.17)</td>
<td>8.9 (6.0-13.0)</td>
<td>0.3869</td>
</tr>
<tr>
<td><strong>Hb</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2.04 (0.00-28.8)</td>
<td>1.75 (0.07-6.5)</td>
<td>3.3 (0.25-2.2)</td>
<td>0.0902</td>
</tr>
<tr>
<td>Female</td>
<td>126 (8-1233)</td>
<td>102 (2-834)</td>
<td>78 (2-350)</td>
<td>0.0497</td>
</tr>
<tr>
<td><strong>BM Blasts (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>33.3% (20-96%)</td>
<td>36.9% (20-93%)</td>
<td>34.7% (9-76)</td>
<td>0.1797</td>
</tr>
<tr>
<td>Female</td>
<td>141 (88.7%)</td>
<td>79 (84.9%)</td>
<td>28 (82.4%)</td>
<td>0.5991</td>
</tr>
<tr>
<td>HMA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azacitidine</td>
<td>110 (88.7%)</td>
<td>79 (84.9%)</td>
<td>28 (82.4%)</td>
<td>0.5991</td>
</tr>
<tr>
<td>Decitabine</td>
<td>14 (11.3%)</td>
<td>14 (15.1%)</td>
<td>6 (17.6%)</td>
<td>0.5991</td>
</tr>
<tr>
<td><strong>Median number of HMA cycles</strong></td>
<td>6 (1-47)</td>
<td>4 (1-72)</td>
<td>5 (1-36)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Table 1B: Responses to the three induction chemotherapy regimens.

<table>
<thead>
<tr>
<th>Responses to treatment (CLA/GM)</th>
<th>CLA/GM n=114</th>
<th>7+3 n=93</th>
<th>CPX-351 n=34</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRI</td>
<td>60 (53%)</td>
<td>56 (60%)</td>
<td>19 (55.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>No response</td>
<td>40 (35%)</td>
<td>56 (60%)</td>
<td>19 (55.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death</td>
<td>14 (12%)</td>
<td>7 (8%)</td>
<td>1 (2.9%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Reinduction</td>
<td>5 (13%)</td>
<td>35 (63%)</td>
<td>7 (36.8%)</td>
<td>0.0013</td>
</tr>
<tr>
<td>CR/CRI after reinduction</td>
<td>3 (6%)</td>
<td>11 (31%)</td>
<td>2 (28.6%)</td>
<td>0.276</td>
</tr>
<tr>
<td>Allogeneic stem cell transplant (alloSCT)</td>
<td>42 (70.0%)</td>
<td>19 (63.3%)</td>
<td>7 (50.0%)</td>
<td>0.154</td>
</tr>
<tr>
<td>Median OS</td>
<td>7.27 months</td>
<td>7.63 months</td>
<td>7.07 months</td>
<td>0.888</td>
</tr>
</tbody>
</table>

Table 1C: Responses to induction regimens for patients with > 4 cycles of hypomethylating agent.

<table>
<thead>
<tr>
<th>Responses to treatment (HMA &gt;4 cycles)</th>
<th>CLA/GM n=68</th>
<th>7+3 n=47</th>
<th>CPX-351 n=20</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/CRI</td>
<td>34 (50.0%)</td>
<td>12 (25.5%)</td>
<td>5 (25%)</td>
<td>0.0068</td>
</tr>
<tr>
<td>No response</td>
<td>25 (36.8%)</td>
<td>31 (66.0%)</td>
<td>14 (70.0%)</td>
<td>0.0068</td>
</tr>
<tr>
<td>Death</td>
<td>9 (13.2%)</td>
<td>4 (8.5%)</td>
<td>1 (5.0%)</td>
<td>0.0068</td>
</tr>
<tr>
<td>Reinduction</td>
<td>3</td>
<td>20</td>
<td>5 (25%)</td>
<td>0.0068</td>
</tr>
<tr>
<td>CR/CRI after reinduction</td>
<td>1</td>
<td>7</td>
<td>1 (20.0%)</td>
<td>0.0068</td>
</tr>
<tr>
<td>Allogeneic stem cell transplant (alloSCT)</td>
<td>24</td>
<td>4</td>
<td>2 (10.0%)</td>
<td>0.0068</td>
</tr>
<tr>
<td>Median OS</td>
<td>5.7 months</td>
<td>8.67 months</td>
<td>5.47 months</td>
<td>ns</td>
</tr>
</tbody>
</table>

Figure 1: Overall survival of CPX-351 treated patients with prior HMA treatment.
### MDS: Lower risk

#### Upfront: first line

**ESA Naive**

- **MCC 19872**
  
  "Commands Study"
  
  Luspatercept (ACE-536) vs. ESA for low risk MDS.
  
  CRC: William Prada
  
  PI: Komrokji

#### 2nd line after ESA failure

**ESA failure**

- **MCC 19430**
  
  Sponsor: TEW
  
  Phase I/II TEW TGFB inhibitor for lower risk MDS
  
  CRC: Lisa Nardelli
  
  PI: Dr. Komrokji

**HMA candidate**

- **MCC 19939**
  
  Oral Decitabine
  
  CRC: William Prada
  
  PI: Sallman

**HMA failure**

- **MCC XXXX**
  
  Canakinumab/darbepoetin
  
  CRC: TBD
  
  PI: Sallman

- **MCC XXXX**
  
  Luspatercept
  
  CRC: TBD
  
  PI: komrokji

**MCC 19658**

SX682 for HMA failure MDS

CRC: William Prada

PI: Sallman

**Legend:**

- Light Blue: Actively Accruing
- Gray: Closed to Accrual
- Yellow: Long-Term Follow-Up
- Purple: Pending
- Green: Final Closed
- Future considered
A Phase 1b/2 Study Evaluating the Safety and Efficacy of Canakinumab with Darbepoetin alpha in Patients with Lower-Risk MDS who have Failed ESA

**Study population**
- Very low/low/intermediate R-IPSS risk MDS.
- Transfusion dependent anemia.
- ESA failure or low chance of response in non-del5q.
- ESA and lenalidomide failure in del5q.

<table>
<thead>
<tr>
<th>Phase 1b (n=9-18)</th>
<th>Dose Level</th>
<th>Canakinumab (mg)</th>
<th>Darbepoetin alpha (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>S.C q 4 weeks</td>
<td>S.C q 2 weeks</td>
<td></td>
</tr>
<tr>
<td>-1</td>
<td>75</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>1 (Starting dose)</td>
<td>150</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>300</td>
<td>300</td>
<td></td>
</tr>
</tbody>
</table>

**Primary end point**
- MTD & RP2D

**Phase II (n=29)**
- RP2D
- Stage 1: 10 patients & Stage2: 19 patients

**Primary end point**
- HI-IWG 2016 criteria
- safety

**Correlative studies:**
- Determine recurrent gene mutations utilizing a targeted next generation sequencing (NGS) myeloid panel at study entry and serially throughout treatment to assess changes in somatic mutation landscape. Comparison between responding and non-responding patients will be performed using qualitative analyses.

- To characterize *in vivo* IL-1β inhibition, as determined by inflammatory pathway analysis via serial high sensitivity CRP, un-neutralized IL-1β, peripheral blood ASC specks, circulating oxidized mitochondrial DNA, S100A9 and comprehensive cytokine profiling.

- Evaluation of innate immune and pyroptosis biomarker indices including ASC specks by flow cytometry and IL-1β, S100A9 and oxidized mitochondrial DNA by ELISA in PB plasma; ASC speck immunofluorescence on mononuclear cells by flow cytometry. In BM will evaluate changes in MDSC number by flow cytometry, colony forming capacity (CFC) and pyroptosis biomarkers.

**PI:** David Sallman
LB100: PP2A inhibitor

<table>
<thead>
<tr>
<th>Phase 1 Dose Escalation</th>
<th>LB-100 starting dose 1.75 mg/m²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose Escalation Scheme:</td>
<td></td>
</tr>
<tr>
<td>• If no DLT in first 3 pts, escalate to next dose level.</td>
<td></td>
</tr>
<tr>
<td>• If DLT in 1 or 3 pts in cohort, enroll 3 more pts to same dose level; if DLT in 1 of 6 pts, escalate to next dose level.</td>
<td></td>
</tr>
<tr>
<td>• If 2 of 6 pts in cohort have DLT, dose escalation ceases and MTD is previous dose level.</td>
<td></td>
</tr>
<tr>
<td>• If no DLT by dose level 2, dose level 2 is MTD</td>
<td></td>
</tr>
<tr>
<td>MTD of LB-100 Single Agent</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Phase 2 Simon two-stage</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Enroll total of 21 patients at MTD (including Phase 1b patients treated at MTD)</td>
<td></td>
</tr>
<tr>
<td>Simon two-stage, Stage 1:</td>
<td></td>
</tr>
<tr>
<td>• ≤ 2 responders, study end</td>
<td></td>
</tr>
<tr>
<td>• &gt; 2 responders, proceed to Stage 2</td>
<td></td>
</tr>
<tr>
<td>Simon two-stage, Stage 2:</td>
<td></td>
</tr>
<tr>
<td>• Enroll additional 20 patients at MTD (n=41)</td>
<td></td>
</tr>
<tr>
<td>• If ≤ 6 responders, insufficient evidence for further study of LB-100.</td>
<td></td>
</tr>
<tr>
<td>• If &gt; 6 responders, sufficient evidence to support Phase 3 trial</td>
<td></td>
</tr>
</tbody>
</table>

Change in PP2Acα Relative Expression by Lenalidomide Response

- **Baseline**
- **Response**
- **Failure**

*Graphs showing changes in PP2Acα relative expression with IHC and Q-PCR measurements.*
MDS: Higher risk

Upfront: first line

**MCC 19322**
Ph. II Azacitidine and anti-CD47 monoclonal antibody
CRC: Yainet Sanchez
PI: Sallman

**MCC 19825**
IIT: MDS consortium
Phase III: Azacitidine +/- APR 246 for p53 mutated MDS/AML
CRC: Lisa Nardelli
PI: Sallman

**MCC 20061**
Phase II: CPX-351 for HR-MDS
CRC: William Prada
PI: Sallman

2nd line after standard therapy

**MCC xxxx**
Phase III Azacitidine/Tim-

**MCC 19658**
SX682 for HMA failure MDS
CRC: William Prada
PI: Sallman

**Immune Therapy**

**MCC 19862**
PRGN-3006 CD33 CART
CRC: ICE
PI: Sallman

**MCC 20039**
NKG2D CAR-T
CRC: ICE
PI: Sallman