Myelodysplastic Syndromes
Patient and Care Giver Forum 2017

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Associate Professor of Medicine
The University of Chicago
Overview

• What is MDS?

• What are the Treatment Options?

• Clinical Trials for MDS
Myelodysplastic Syndromes

Cytopenias
- Low blood counts
- Infection, bleeding, fatigue

Morphologic dysplasia
- Evident on review of blood specimen and bone marrow biopsy
- Important in establishing subtype of MDS

Variable likelihood of AML evolution
- Propensity to transform into AML varies widely depending on MDS subtype and prognostic risk subset

Clonal hematopoietic stem cell diseases
- Inciting event is at the HSC level
Evolving Classification of MDS

FAB = French American British classification; WHO = World Health Organization classification
## Evolving Classification of MDS

<table>
<thead>
<tr>
<th>2016 Revision to the WHO Classification of MDS</th>
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<tr>
<td>MDS with single lineage dysplasia</td>
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<tr>
<td>MDS with ring sideroblasts (MDS-RS)</td>
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<tr>
<td>• MDS-RS and single lineage dysplasia</td>
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<td>• MDS-RS and multilineage dysplasia</td>
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<td>MDS with multilineage dysplasia</td>
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<td>MDS with excess blasts</td>
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<td>MDS with isolated del(5q)</td>
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<td>MDS, unclassifiable</td>
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<tr>
<td>Provisional entity: Refractory cytopenia of childhood</td>
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<td>Myeloid neoplasms with germ line predisposition</td>
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Arber DA et al, Blood 2016; 127: 2391-2405
Approach to the Individual Patient with MDS?
Step 1) Establish MDS Subtype

CLINICAL

MORPHOLOGIC

PHENOTYPIC
.cytochemical

Immunophenotypic
.(Cell surface protein expression)

CYTOGENETIC
.(chromosome analysis)

MOLECULAR GENETIC
.(analysis of gene mutations)
Step 2: Risk Stratify
Why Risk Stratify?

• Clinically and molecularly heterogeneous disease

• Outcomes varies substantially
  – Even within same morphologic subtypes

• Risk stratification facilitates tailoring of therapeutic interventions
Variables influencing Risk in MDS

- Cytogenetic risk group
- 5 major risk groups
- Mutational profiling
- Evolving field
- Depth of cytopenias
  - Hemoglobin
  - Neutrophil
  - Platelets
- Blast percent
  - Within normal limits
  - Increased
- Cytopenias
- Blast percent
- Gene mutations
- Cytogenetics
- Cytogenetic risk group
  - 5 major risk groups
## Prognostic systems for MDS

<table>
<thead>
<tr>
<th>Prognostic system</th>
<th>Age</th>
<th>PS</th>
<th>WBC or ANC</th>
<th>Plt</th>
<th>Hb</th>
<th>Transf</th>
<th>BM blast %</th>
<th>Cytogenetics</th>
<th>WHO class.</th>
<th>Ref</th>
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<tr>
<td>Bournemouth</td>
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<td>X</td>
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<td>Mufti, Br J Haem, 1985</td>
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<td>Spanish</td>
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<td>Sanz, Blood 1989</td>
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<td>Lille</td>
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<td>Morel, Leukemia 1996</td>
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<td>IPSS</td>
<td>X</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>Greenberg, Blood 1997</td>
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<td>WPSS</td>
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<td></td>
<td>Malcovati, JCO 2007</td>
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<tr>
<td>MDACC</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>Kantarjian, Cancer 2008</td>
</tr>
</tbody>
</table>
Revised International Prognostic Scoring System for MDS (IPSS-R)

- **Rationale:** To refine the IPSS, an important standard for assessing prognosis of primary untreated adult MDS patients (IPSS-R, N = 7,012).

- **IPSS Limitations:**
  - Validated in previously untreated patients with 1º MDS.
  - No. of cytopenias factored, but not severity, e.g., transfusion dep.
  - Limited number of cytogenetic abnormalities included, and high-risk abnormalities not accorded sufficient emphasis.

<table>
<thead>
<tr>
<th>Refinements of the IPSS-R beyond the IPSS</th>
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</thead>
<tbody>
<tr>
<td>New marrow blast categories</td>
</tr>
<tr>
<td>Refined cytogenetic abnormalities and risk groups</td>
</tr>
<tr>
<td>Evaluation of the depth of cytopenias</td>
</tr>
<tr>
<td>Inclusion of differentiating features</td>
</tr>
<tr>
<td>Prognostic model with 5 (vs. 4) risk Categories</td>
</tr>
</tbody>
</table>

Greenberg P et al, Blood 2012
# MDS Cytogenetic Scoring System (IPSS-R)

<table>
<thead>
<tr>
<th>Prognostic subgroups (% patients)</th>
<th>Cytogenetic abnormalities</th>
<th>Survival Years, median</th>
<th>AML evolution, 25% Years, median</th>
<th>Hazard ratios OS/AML</th>
<th>Hazard ratios OS/AML</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very good (4%)</strong></td>
<td>-Y, del(11q)</td>
<td>5.4</td>
<td>NR</td>
<td>0.7/0.4</td>
<td>0.5/0.5</td>
</tr>
<tr>
<td><strong>Good (72%)</strong></td>
<td>Normal, del(5q), del(12p), del(20q), double including del(5q)</td>
<td>4.8</td>
<td>9.5</td>
<td>1/1</td>
<td>1/1</td>
</tr>
<tr>
<td><strong>Intermediate (13%)</strong></td>
<td>del(7q), +8, +19, i(17q), any other single or double independent clones</td>
<td>2.7</td>
<td>2.6</td>
<td>1.5/1.8</td>
<td>1.6/2.2</td>
</tr>
<tr>
<td><strong>Poor (4%)</strong></td>
<td>-7, inv(3)/t(3q)/del(3q), double incl -7/del(7q), complex: 3 abn</td>
<td>1.5</td>
<td>1.7</td>
<td>2.3/2.3</td>
<td>2.6/3.4</td>
</tr>
<tr>
<td><strong>Very poor (7%)</strong></td>
<td>Complex: &gt;3 abnormalities</td>
<td>0.9</td>
<td>0.7</td>
<td>3.8/3.6</td>
<td>4.2/4.9</td>
</tr>
</tbody>
</table>

Greenberg et al., Blood, 2012
Cytogenetic Prognostic Subgroups

Overall Survival

- Very Good (N=81/34 events)
- Good (N=1809/890 events)
- Intermediate (N=529/312 events)
- Poor (N=148/109 events)
- Very Poor (N=187/158 events)

Risk of Progression to AML

- Very Good (N=81/34 events)
- Good (N=1809/890 events)
- Intermediate (N=529/312 events)
- Poor (N=148/109 events)
- Very Poor (N=187/158 events)

P (log-rank) <0.0001

Schanz et al., JCO 30:820, 2012
# IPSS-R: Prognostic Variables and Score Values

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetics</td>
<td>Very good</td>
<td>Good</td>
<td>Intermediate</td>
<td>Poor</td>
<td>Very Poor</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM blast %</td>
<td>≤2</td>
<td></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>50-100</td>
<td>&lt;50</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>ANC</td>
<td>≥0.8</td>
<td>&lt;0.8</td>
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</tr>
</tbody>
</table>

BM- bone marrow; ANC-absolute neutrophil count

Greenberg P et al, Blood 2012
**Stratification based on IPSS/IPSS-R**

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk Group</th>
<th>Median Survival in 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>≥ 2.5</td>
<td>High</td>
<td>0.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Points</th>
<th>Risk Score</th>
<th>Median survival in years</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1.5</td>
<td>Very Low</td>
<td>8.8</td>
</tr>
<tr>
<td>&gt; 1.5-3</td>
<td>Low</td>
<td>5.3</td>
</tr>
<tr>
<td>&gt;3-4.5</td>
<td>Intermediate</td>
<td>3.0</td>
</tr>
<tr>
<td>&gt;4.5-6</td>
<td>High</td>
<td>1.6</td>
</tr>
<tr>
<td>&gt;6</td>
<td>Very high</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Many patients with MDS have a cytogenetically normal subtype

Chart derived from data published by Greenberg et al, Blood, 1997
Recent cytogenetic data sets e.g. Schanz et al, JCO 2012 report similar percentages of patients with normal karyotype
Mutations Occur in the Majority > 90% of Patients with MDS

RNA splicing: SF3B1, SRSF2, U2AF1, U2AF2, ZRSR2
DNA methylation: TET2, DNMT3A, IDH1/2
Chromatin modification: ASXL1, EZH2
Transcription factor: TP53, EVI1, RUNX1, GATA2
RAS/receptor kinase pathways: NRAS, KRAS, CBL, JAK2

Chart is based on data from 944 MDS patients - Haferlach et al, Leukemia 2014

Odenike et al, ASCO Ed Book, 2015
The mutational status of five genes \textit{TP53}, \textit{EZH2}, \textit{ETV6}, \textit{RUNX1}, \textit{ASXL1} predicts poor prognosis in MDS

111 genes analyzed in 439 patients with MDS.

Within each IPSS subgroup, the presence of one or more of these mutations resulted in a decline in overall survival approximating that of next higher risk IPSS subtype.

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

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

Bejar R et al, NEJM 2011
SF3B1 mutations predict ring sideroblast morphology with isolated erythroid dysplasia and favorable prognosis.
Gene Mutations in MDS

• Frequent
  – Occurring in approximately 90% of patients
  – Median of 2-3 per patient (range 1-12)
  – More than 40 genes are recurrently mutated
  – Provided insights into pathogenesis of MDS

• Specific gene mutations also associated with prognosis and/or clinical phenotype
  – TP53, EZH2, ETV6, RUNX1, ASXL1- poor risk
  – SF3B1:ring sideroblasts- good risk
Can molecular and clinical risk factors be integrated?

Molecular variables only

Molecular+ Clinical variables

Haferlach et al, Leukemia 2014
STEP 3: Assess the need for therapy?
Indications for therapy

• Significant impairment in blood counts
  – predisposes to infections, bleeding, significant fatigue or other complications of the disease

• Higher risk disease
Treatment Options

Erythropoietin stimulating agent (ESA)
- Lower risk disease
- EPO sensitive disease
- Goal is to improve red cell count
- Includes erythropoietin (Procrit) and darbopoietin (Aranesp)

Hypomethylating agents
- Higher risk disease
- Goals are to improve blood counts, delay transformation to acute leukemia and improve survival
- Includes azacitidine (vidaza) and decitabine (dacogen)

Allogeneic stem cell transplantation
- Higher risk disease
- Goal is to improve survival and cure the disease
- Careful assessment of potential risks vs benefits is extraordinarily important

Treatment intensity
Hypomethylating agents

• Azacitidine and decitabine approved in the USA
• Improve bone marrow function and blood counts in 40 to 50% of patients
• Average time to onset of response is 2 to 4 months, but responses can take up to 6 months or longer to occur
• Risks include significant lowering of blood counts prior to onset of response
Azacitidine (AZA) versus Conventional Care Regimens (CCR) in Higher Risk MDS

Deletion 5 q MDS

- Deletion 5 q is the only cytogenetic abnormality
- Dysplasia in one or more lineages
- Blasts are generally not increased
- Excellent response to lenalidomide
Lenalidomide in lower risk MDS

• Immunomodulatory agent with pleitropic effects

• Significant activity in MDS with del 5q $^{1,2}$
  – Red cell transfusion independence rate of 67%
  – Sensitivity linked to haploinsufficiency of CSK1 in commonly deleted region of 5q$^3$

• Activity in non-del 5q is modest $^4$

• FDA approved for use in MDS associated with del 5q

1. List A et al, NEJM 2005
Risk Stratification by IPSS/R-IPSS

Lower risk + Need for therapy

- Non-Del 5q
  - ESAs if EPO <500 and anemic
  - Clinical trial or azanucleosides if pancytopenic and/or prior ESA exposure.
  - Consider IST

- Del 5q
  - Lenalidomide

Higher Risk

- Early referral for allogeneic SCT
- Hypomethylating agent based (HMA) therapy
- Clinical trial if prior HMA exposure

Odenike O, ASCO Education Session 2015
Clinical Trials in MDS
Anemia in non-del 5q MDS lower risk MDS unresponsive/refractory to ESAs

- Anemia remains a problematic issue in non-del 5qMDS
  - Combination of lenalidomide and EPO may also be beneficial

- Understanding the molecular pathways mediating anemia may lead to more effective targeted therapeutic approaches given the molecular heterogeneity of this disease

1. Toma A et al, Leukemia 30:897-905
Novel agents for the treatment of anemia in lower risk MDS
Luspatercept (ACE-536)

- Modified activin receptor type IIB (ActRIIB) fusion protein
  - Binds TGF beta ligands and modulates TGF beta signaling pathway
- Enhances erythropoiesis
- Early phase clinical trials demonstrate potential for anemia improvement in MDS
- Larger clinical trials in lower risk MDS would be worthwhile
A phase 3, randomized, double-blind study of luspatercept (ACE-536) in patients (pts) with Revised International Prognostic Scoring System (IPSS-R) very low- to intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts (RS) who require red blood cell (RBC) transfusions: The MEDALIST trial.

Uwe Platzbecker, Rami S. Komrokji, Pierre Fenaux, Guillermo Garcia-Manero, Ghulam J. Mufti, Mikkael A. Sekeres, Jennie Zhang, Aziz Benzohra, Abderrahmane Laadem, Bond Vo, Kenneth M. Attie, Alan F. List; Technical University Dresden, Dresden, Germany; Moffitt Cancer Center, Tampa, FL; Service d'Hématologie Séniors/Hôpital Saint-Louis, Université Paris 7, Paris, France; The University of Texas MD Anderson Cancer Center, Houston, TX; King's College Hospital, London, United Kingdom; Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; Celgene Corporation, Summit, NJ; Celgene Corporation, Boudry, Switzerland; Acceleron Pharma, Cambridge, MA

J Clin Oncol 34, 2016 (suppl; abstr TPS7076)
Luspatercept in lower risk MDS

- Double blind, placebo controlled 2:1 randomization in lower risk MDS unresponsive or refractory to ESAs (n=210)
- Primary endpoint is rate of RBC transfusion independence ≥ 8 weeks in first 24 weeks of treatment

- Lower risk MDS
- Red Blood Cell transfusion dependent
- Refractory or intolerant or low chance of response to erythropoiesis stimulating agents (ESAs)
Contemporary investigational approaches in MDS

• Novel formulations of azanucleosides
  – SGI-110
  – Oral decitabine+cytidine deaminase inhibitor
  – Oral azacitidine

• Immune checkpoint inhibitors
  – Pembrolizumab
  – Nivolumab
  – MEDI4736

• BCL2 Inhibitors

• Spliceosomal modulators

• Kinase inhibitors
  – MEK inhibitors
Successful Emulation of IV Decitabine Pharmacokinetics with an Oral Fixed-Dose Combination of the Oral Cytidine Deaminase Inhibitor (CDAi) E7727 with Oral Decitabine, in Subjects with Myelodysplastic Syndromes (MDS): Final Data of Phase 1 Study

Guillermo Garcia-Manero, MD, Olatoyosi Odenike, MD, Philip C. Amrein, MD, David P. Steensma, MD, Amy E. DeZern, MD, MHS, Laura C. Michaelis, MD, Stefan Faderl, MD, Hagop M. Kantarjian, MD, James N. Lowder, MD, Pietro Taverna, PhD, Aram Oganesian, PhD, Xiaoping Zhang, PhD, Mohammad Azab, MD and Michael R. Savona, MD
Oral formulations of hypomethylating agents?

- Hypomethylating agents bind to DNA methyltransferase resulting in progressive loss of DNMT activity and subsequent DNA hypomethylation.

- Orally available hypomethylating agents might permit extended administration schedules, prolonged hypomethylation, improved convenience.

- Hypomethylating agents are rapidly cleared in the gut and liver by cytidine deaminase (CDA) therefore not orally bioavailable.
ASTX727: Oral Decitabine plus oral cytidine deaminase inhibitor

Decitabine

E7727 CDA inhibitor

Inactive metabolite
ASTX727: Pharmacokinetics and Pharmacodynamics (n=43)

- Dose level of oral DAC 30mg plus 100mg E7727 achieves equivalent AUC as 20mg/m² IV DAC
- Similar toxicity profile
- Encouraging signs of clinical efficacy
Harnessing the Immune System in MDS
Hypomethylating agents (HMAs)

HMAs may act as immunosensitizer and facilitate immune recognition and cytotoxic T cell killing.

Goodyear O et al, Blood 2010;116:1908-18
Immune Check Point Inhibitors combined with Hypomethylating agents (HMAs)

• Anti PDL-1, anti-PD1, anti CTLa4
  – Block co-inhibitory molecules such as PD1/PDL1 or CTLa4, enhancing effector T cell response

• HMAs enhance expression of PD-1 and PDL-1 in MDS and may synergize with checkpoint inhibitors

## Immune checkpoint inhibition in MDS: Study Design

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Therapy</th>
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<tr>
<td>Cohort #1</td>
<td>Nivolumab 3 mg/kg IV q2 weeks</td>
</tr>
<tr>
<td>Cohort #2</td>
<td>Ipilimumab 3 mg/kg IV q3 weeks</td>
</tr>
<tr>
<td>Cohort #3</td>
<td>Nivolumab 3 mg/kg IV q2 weeks Ipilimumab 3 mg/kg IV q4 weeks</td>
</tr>
<tr>
<td>Cohort #4</td>
<td>Azacitidine 75 mg/m² IV x 5 days q28 Nivolumab 3 mg/kg IV on day 6 and 20</td>
</tr>
<tr>
<td>Cohort #5</td>
<td>Azacitidine 75 mg/m² IV x 5 days q28 Ipilimumab 3 mg/kg IV on day 6</td>
</tr>
<tr>
<td>Cohort #6</td>
<td>Azacitidine 75 mg/m² IV x 5 days q 28 Nivolumab 3 mg/kg IV on day 6 and 20</td>
</tr>
</tbody>
</table>
BCL2 inhibition in myeloid neoplasia

- BCL2 overexpression is associated with disease progression and drug resistance
- Venetoclax is a potent orally bioavailable inhibitor of BCL2
- Preclinical evidence of synergy with hypomethylating agents
- Ongoing clinical trials of venetoclax in combination with DEC or AZA
RNA splicing (spliceosomal mutations): **SF3B1, SRSF2, U2AF1, U2AF2, ZRSR2**; occur in >60% of patients with MDS

Chart is based on data from 944 MDS patients - **Haferlach et al, Leukemia 2014**
Odenike et al, ASCO Ed Book, 2015
H3B 8800, an orally bioavailable modulator of the SF3b Complex shows efficacy in Spliceosome – mutant myeloid malignancies

• Preferential inhibition of cell growth in spliceosome mutant cells compared to normal cells

• Activity in mouse models of spliceosome mutant myeloid malignancies

• Ongoing Phase I trial in relapsed refractory spliceosome mutant myeloid malignancies

Buonamici S, ASH 2016 abstract # 966
Ongoing trials in MDS at UCMC: Frontline trials (HMA naive)

IRB16-13: A randomized Phase II study evaluating the safety, pharmacokinetics and efficacy of venetoclax in combination with azacitidine compared with azacitidine alone in subjects with treatment naïve higher risk MDS*

IRB15-17: A Phase II, randomized, controlled, open-label, clinical study of the efficacy and safety of pevonedistat plus azacitidine versus single agent azacitidine in patients with higher risk MDS, CMML and low blast count AML

IRB16-0375: A randomized multicenter, open-label, phase II study evaluating the efficacy and safety of azacitidine subcut in combination with durvalumab in previously untreated subjects with higher risk MDS or in elderly AML subjects not eligible for hematopoietic stem cell transplantation

IRB14-0702: A Phase I/II Pharmacokinetic guided dose-escalation and dose confirmation study of ASTX727, a combination of the oral cytidine deaminase inhibitor (CDAi) E7727 with oral decitabine in subjects with MDS

Upcoming: Investigator initiated (IRB pending)- Phase I study of azacitidine plus the MEK inhibitor selumetinib*

*activation pending
Ongoing trials in MDS at UCMC (prior exposure to hypomethylating agents):

IRB 16-1519: A Phase 1b study evaluating the safety, pharmacokinetics and efficacy of venetoclax as a single agent and in combination with azacitididine in subjects with higher risk MDS after hypomethylating agent failure*

IRB16-0372: A Phase II, International, multicenter, randomized, open-label, parallel group study to evaluate the efficacy and safety of CC-486 (oral azacitididine) alone and in combination with durvalumab (MEDI4736) in subjects with myelodysplastic syndromes who fail to achieve an objective response to treatment with azacitididine for injection or decitabine

IRB14-0702: A Phase I/II Pharmacokinetic guided dose-escalation and dose confirmation study of ASTX727, a combination of oral cytidine deaminase inhibitor E7727 with oral decitabine in subjects with myelodysplastic syndromes

IRB16-1525 A Phase Ib dose escalation study to assess the safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of PLX51107 in subjects with advanced malignancies (this is a novel epigenetic modulator in the bromodomain inhibitor class)*

IRB15-1373 A Phase I/II and pharmacological study of OTS167 in patients with refractory or relapsed acute myeloid leukemia, acute lymphoblastic leukemia, advanced myelodysplastic syndromes, advanced myeloproliferative disorders or advanced CML

Upcoming: Investigator initiated (IRB pending)- Phase I study of azacitididine plus the MEK inhibitor selumetinib*

Upcoming: Phase I trial of the spliceosome inhibitor H3B 8800*

*activation pending
Summary

• MDS is a clinically and molecularly heterogeneous disease

• Individualized treatment approach is necessary

• There is a significant need for new therapies in MDS and several agents are under active clinical investigation
Our Patients and their Families.
Colleagues in the Leukemia/MDS, Transplant and Developmental Therapeutics Programs