A precision medicine approach to MDS?

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March 6, 2020
I have no relevant financial relationships to disclose.
Myelodysplastic syndromes: what does precision medicine look like?

- Assess diagnosis
  - (Define pathogenesis of the disease)
- Define the natural history of disease
- Define response to therapy (and mechanism of response for specific therapies?)
- Determine duration or intensity of therapy
- Determine choice of therapy
- Be a target for therapy
Diagnosis of MDS: morphology + cytogenetic abnormalities

- Numerical chromosomal losses or gains
- Large interstitial deletions (5q-, 7q-, 20q-, 17p)
- Translocations \([t(5;12), t(5;11), t(3;21)]\)
- Unbalanced translocations
- Flow cytometry
- Molecular studies (gene expression, genetics, epigenetics)
Somatic gene mutations in patients with MDS

Haferlach et al. Leukemia. 2014 28(2):241-7
What is my diagnosis?

Peripheral cytopenias
Bone marrow morphology incl. percent blasts
Cytogenetics
VAF

T Moyo & M Savona; Cur Hem Malign Rep 2016
Clinical Effect of Point Mutations in Myelodysplastic Syndromes

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

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

* The model was generated from a stepwise Cox regression model that included the International Prognostic Scoring System (IPSS) risk category (based on the percentage of blasts in bone marrow, the karyotype, and the number of cytopenias [see Table 2 in the Supplementary Appendix]), age, sex, and mutation status for genes that were mutated in 1% or more of the 428 samples for which the IPSS classification was recalculated. Age was included in the analysis as a categorical variable on the basis of a best-split algorithm showing a significant difference in overall survival between patients less than 55 years of age and those 55 years of age or older (see Table 8 in the Supplementary Appendix).
O.S. based on IPSS Risk Category & Mutation Status

Inactivating mutations of the histone methyltransferase gene \emph{EZH2} in myeloid disorders

Thomas Ernst\textsuperscript{1,3,11}, Andrew J Chase\textsuperscript{1,2,11}, Joannah Score\textsuperscript{1,2}, Claire E Hidalgo-Curtis\textsuperscript{1,2}, Catherine Bryant\textsuperscript{1,2}, Amy V Jones\textsuperscript{1,2}, Katherine Waghorn\textsuperscript{1,2}, Katerina Zoi\textsuperscript{4}, Fiona M Ross\textsuperscript{1,2}, Andreas Reiter\textsuperscript{5}, Andreas Hochhaus\textsuperscript{3}, Hans G Drexler\textsuperscript{6}, Andrew Duncombe\textsuperscript{7}, Francisco Cervantes\textsuperscript{8}, David Oscier\textsuperscript{9}, Jacqueline Boulwood\textsuperscript{10}, Francis H Grand\textsuperscript{1,2} & Nicholas C P Cross\textsuperscript{1,2}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure2.pdf}
\caption{Survival and expression analysis. (a,b) Kaplan-Meier analysis showing overall survival (a) and progression-free survival (b) of the 134 individuals with MDS/MPN for whom follow-up data was available (CMML, \textit{n} = 77; aCML, \textit{n} = 44; MDS/MPN-U, \textit{n} = 13). None of the individuals with \emph{EZH2} mutations in this analysis had cytogenetically visible abnormalities of chromosome 7. (c) The survival of individuals with homozygous mutations was shorter than those with heterozygous \emph{EZH2} mutations, although the difference was not significant (\textit{P} = 0.089).}
\end{figure}
Prognostic Significance of ASXL1 Mutations in Patients With Myelodysplastic Syndromes


ABSTRACT

Purpose
To study the incidence and prognostic impact of mutations in Additional sex comb-like 1 (ASXL1) in a large cohort of patients with myelodysplastic syndrome (MDS).

Patients, Materials, and Methods
Overall, 193 patients with MDS and 65 healthy volunteers were examined for ASXL1 mutations by direct sequencing and for expression levels of ASXL1. The prognostic impact of ASXL1 mutation and expression levels was evaluated in the context of other clinical and molecular prognostic markers.

Results
Mutations in ASXL1 occurred with a frequency of 20.7% in MDS (n = 40 of 193) with 70% (n = 28) of mutations being frameshift mutations and 30% (n = 12) being heterogeneous point mutations leading to translational changes. ASXL1 mutations were correlated with an intermediate-risk karyotype (P = .002) but not with other clinical parameters. The presence of ASXL1 mutations was associated with a shorter overall survival for frameshift and point mutations combined (hazard ratio [HR], 1.744; 95% CI, 1.08 to 2.82; P = .024) and for frameshift mutations only (HR, 2.06; 95% CI, 1.21 to 3.50; P = .008). ASXL1 frameshift mutations were associated with a reduced time to progression of acute myeloid leukemia (AML; HR 2.35; 95% CI, 1.17 to 4.74; P = .017). In multivariate analysis, when considering karyotype, transfusion dependence, and IDH1 mutation status, ASXL1 frameshift mutations remained an independent prognostic marker in MDS (overall survival: HR, 1.85; 95% CI, 1.03 to 3.34; P = .040; time to AML progression: HR, 2.39; 95% CI, 1.12 to 5.03; P = .024).

Conclusion
These results suggest that ASXL1 mutations are frequent molecular aberrations in MDS that predict an adverse prognostic outcome. Screening of patients for ASXL1 mutations might be useful for clinical risk stratification and treatment decisions in the future.

J Clin Oncol 29:2499-2506. © 2011 by American Society of Clinical Oncology
Effect of DNMT3A mutations on MDS outcome

M. Walter et al Leukemia 25: 1153; 2011
Clinical Significance of SF3B1 Mutations

*Prolonged EFS independent of age, gender and karyotype.

Papaemmanuil E, et al. NEJM 2011; 365: 1384
Two hypomethylating agents FDA-approved for MDS pts

Can we enrich for responding patients?

L. Silverman et al Cancer 2002

H. Kantarjian et al Cancer 2006

Decitabine (n=61)
Supportive Care (n=57)

Azacitidine
Supportive Care

p=.007
MYELOID NEOPLASIA

*TET2* mutations predict response to hypomethylating agents in myelodysplastic syndrome patients

Rafael Bejar,1 Allegra Lord,2 Kristen Stevenson,3 Michal Bar-Natan,4 Albert Pérez-Ladaga,1 Jacques Zaneveld,5 Hui Wang,5 Bennett Caughey,1 Petar Stojanov,6 Gad Getz,6 Guillermo Garcia-Manero,7 Hagop Kantarjian,7 Rui Chen,5 Richard M. Stone,4 Donna Neuberg,3 David P. Steensma,4 and Benjamin L. Ebert2,6

1Division of Hematology and Oncology, University of California San Diego Moores Cancer Center, La Jolla, CA; 2Division of Hematology, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA; 3Department of Biostatistics and Computational Biology and 4Department of Medical Oncology, Division of Hematological Malignancies, Dana-Farber Cancer Institute, Boston, MA; 5Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX; 6Broad Institute of Harvard and Massachusetts Institute of Technology, Cambridge, MA; and 7Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX

**Key Points**

- Higher abundance *TET2* mutations are associated with increased response to hypomethylating agents, particularly when *ASXL1* is not mutated.
- *TP53* and *PTPN11* mutations are associated with shorter overall survival after hypomethylating agent treatment, but do not predict response.
**TET2 Mutations Sensitize MDS Clones to Azanucleosides**

- 213 pts rcving azanucleosides (100 LR-MDS)
- NGS analysis of 40 myeloid genes to assess relation to response & OS
- Clonal *TET2* mutations predicted response (OR 1.99, \( P = .036 \)) when subclones unlikely to be detected by Sanger sequencing (VAF<10%) were treated as wild-type (WT).
- Response rate highest in *TET2* mutant patients without *ASXL1* mutations (OR 3.65, \( P = .009 \)).
- Mutant *TP53* (HR 2.01, \( P = .002 \)) associated with shorter OS but not drug response

**OS by TP53 Mutation Status**

## Response to HMA Treatment by Mutational Status

<table>
<thead>
<tr>
<th>Institution</th>
<th># Pts.</th>
<th>Gene(s)</th>
<th>Overall Mutant</th>
<th>Response WT (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFM</td>
<td>86</td>
<td>TET2</td>
<td>11/13 (85)*</td>
<td>34/73 (47)</td>
<td>0.01</td>
</tr>
<tr>
<td>Taussig (#3461a)</td>
<td>88</td>
<td>DNMT3A,TET2,IDH1/2</td>
<td>12/28 (64)</td>
<td>21/60 (35)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DNMT3A</td>
<td>6/7 (86)</td>
<td>33/81 (41)</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TET2</td>
<td>12/18 (67)</td>
<td>27/70 (39)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASXL1</td>
<td>11/13 (85)</td>
<td>14/37 (38)</td>
<td>0.003</td>
</tr>
<tr>
<td>OSU^ (#944a)</td>
<td>46</td>
<td>DNMT3A</td>
<td>6/8 (75)</td>
<td>13/38 (34)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*includes mCR in ORR.

^AML pts treated with decitabine.

Mutation allele burden remains unchanged in chronic myelomonocytic leukaemia responding to hypomethylating agents

Jane Merlevede¹,²,*; Nathalie Dron¹,²,³,*; Tingting Qin⁴; Kristen Meldi⁴; Kenichi Yoshida⁵; Margot Morabito¹,²; Emilie Chautard⁶; Didier Auboeuf⁷; Pierre Fenaux⁸; Thorsten Braun⁹; Raphael Itzykson⁸; Stéphane de Botton¹,²; Bruno Quesnel¹⁰; Thérèse Commes¹¹; Eric Jourdan¹²; William Vainchenker¹,²; Olivier Bernard¹,²; Noemie Pata-Merci³; Stéphanie Solier¹,²; Velimir Gayevskiy¹³; Marcel E. Dinger¹³; Mark J. Cowley¹³; Dorothée Selimoglu-Buet¹,²; Vincent Meyer¹⁴; François Artiguenave¹⁴; Jean-François Deleuze¹⁴; Claude Preudhomme¹⁰; Michael R. Stratton¹⁵; Ludmil B. Alexandrov¹⁵,¹⁶,¹⁷; Eric Padron¹⁸; Seishi Ogawa⁵; Serge Koscielny¹⁹; Maria Figueroa⁴ & Eric Solary¹,²,²⁰
Myelodysplastic syndromes: what does precision medicine look like?

• Assess diagnosis
• (Define pathogenesis of the disease)
• Define the natural history of disease

Define response to therapy
• Determine duration or intensity of therapy
• Determine choice of therapy
• Be a target for therapy
Integrative Genomics Identifies the Molecular Basis of Resistance to Azacitidine Therapy in Myelodysplastic Syndromes

Ashwin Unnikrishnan,1,2,26,* Elii Papaemmanuli,3,4,28 Dominik Beck,1,2,5,28 Nandan P. Deshpande,6,7 Arjun Verma,1,2,3 Ashu Kumar,9 Petter S. Woll,10,11 Laura A. Richards,9 Kathy Knezevic,1,2 Vashe Chandrakanthan,1,2 Julie A.I. Thoms,1,2 Melinda L. Tursky,1,2,9,12 Yizhou Huang,1,2,5 Zara Ali,9 Jake Olivier,13 Sally Galbraith,13 Austin G. Kulasekaranaraj,14 Magnus Tobiasson,10 Mohsen Karimi,10 Andrea Pellagatti,15 Susan R. Wilson,13,16 Robert Lindeman,17 Boris Young,17 Raj Ramakrishna,18 Christopher Arthur,19 Richard Stark,20 Philip Crispin,21 Jennifer Curnow,22,27 Pauline Warburton,23 Fernando Roncolato,24 Jacqueline Boullwood,15 Kevin Lynch,25 Sten Einrik W. Jacobsen,10,11 Ghulam J. Mufti,14 Eva Hellstrom-Lindberg,16 Marc R. Wilkins,6,7,26 Karen L. MacKenzie,9 Jason W.H. Wong,1,2 Peter J. Campbell,3,29,* and John E. Pimanda1,2,17,29,36,*

1Adult Cancer Program, Lowy Cancer Research Centre, UNSW, Sydney, NSW 2052, Australia
2Prince of Wales Clinical School, UNSW, Sydney, NSW 2052, Australia
B. Responders vs. Non-responders

C. AZA untreated patients

D. Upregulated in Responders

<table>
<thead>
<tr>
<th>Pathways</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitotic Roles of Polo-Like Kinase</td>
<td>5.01E-15</td>
</tr>
<tr>
<td>Cell Cycle Control of Chromosomal</td>
<td>6.31E-12</td>
</tr>
<tr>
<td>Replication</td>
<td></td>
</tr>
<tr>
<td>Cell Cycle: G2/M DNA Damage</td>
<td>1.26E-11</td>
</tr>
<tr>
<td>Checkpoint Regulation</td>
<td></td>
</tr>
<tr>
<td>Estrogen-mediated S-phase Entry</td>
<td>6.31E-11</td>
</tr>
<tr>
<td>Cyclins and Cell Cycle Regulation</td>
<td>4.37E-08</td>
</tr>
<tr>
<td>Pyrimidine Dihydropyrimidines De</td>
<td>7.08E-07</td>
</tr>
<tr>
<td>Novel Biosynthesis I</td>
<td></td>
</tr>
<tr>
<td>Cell Cycle: G1/S Checkpoint Regulation</td>
<td>7.76E-07</td>
</tr>
</tbody>
</table>

D. Upregulated in Non-Responders

<table>
<thead>
<tr>
<th>Pathways</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Integrin Signaling</td>
<td>1.00E-06</td>
</tr>
<tr>
<td>Phospholipase C Signaling</td>
<td>5.37E-06</td>
</tr>
<tr>
<td>Signaling by Rho Family GTPases</td>
<td>2.04E-05</td>
</tr>
<tr>
<td>ERK/ERK Signaling</td>
<td>4.07E-05</td>
</tr>
<tr>
<td>p70S6K Signaling</td>
<td>1.07E-04</td>
</tr>
<tr>
<td>Tsc Kinase Signaling</td>
<td>1.86E-04</td>
</tr>
<tr>
<td>FAK Signaling</td>
<td>4.27E-04</td>
</tr>
<tr>
<td>Paxillin Signaling</td>
<td>1.05E-03</td>
</tr>
<tr>
<td>PI3K/AKT Signaling</td>
<td>3.24E-03</td>
</tr>
<tr>
<td>GoI Signaling</td>
<td>2.95E-06</td>
</tr>
<tr>
<td>G Beta Gamma Signaling</td>
<td>9.77E-06</td>
</tr>
<tr>
<td>cAMP-mediated signaling</td>
<td>2.45E-03</td>
</tr>
</tbody>
</table>
Primary BM CD34+ cells are cultured in methylcellulose. After 2 weeks, DNA from individual colonies is extracted and each colony is genotyped for somatic mutations.

- **PD 7153 (Responder)**:
  - All CFU colonies:
    - Pre-treatment (n=90)
    - C6d28 (n=93)

- **PD 7166 (Non-responder)**:
  - All CFU colonies:
    - Pre-treatment (n=91)
    - C6d28 (n=89)

The graphs show the distribution of wild type/wild type (w.t./w.t.), wild type/mutant (w.t./mut.), and mutant/mutant (mut./mut.) colonies for each condition.
Figure 4. AZA Therapy Induces Pro-inflammatory Pathways In Vivo in Responders

(A) GSEA plots illustrating strong enrichment for inflammatory and immune response pathways in vivo at C6d28 compared with pre-treatment in AZA responders. NES and FDR for the gene sets are indicated.

(B) GSEA plot showing enrichment for a previously identified set of immune genes whose expression is induced by AZA treatment (Li et al., 2014).

(C) Significant enrichment for a number of immune- and inflammation-related pathways upregulated in vivo at C6d28 in AZA responders, as identified by IPA.
Clinical Evolution and Bone Marrow Failure in Lower Risk MDS

Lower Risk MDS

AML

Stable Cytopenias

Progressive BM Failure

Cytopenias
Targeted resequencing analysis of 31 genes commonly mutated in myeloid disorders in serial samples from myelodysplastic syndrome patients showing disease progression

Leukemia (2016) 30, 247–250; doi:10.1038/leu.2015.129

The myelodysplastic syndromes (MDS) are clonal disorders of the...
Can epigenetic profiles help explain biology and predict clinical outcome in low-risk MDS?

**Diagnosis**
- **Low-risk MDS**
  - Baseline Sample
  - Follow-up Sample
  - Diagnosis Low-risk MDS

**Stable MDS**
- No changes in CBC/Transfusion requirement for 18 m.
  - Within 18 m.
  - Progressive cytopenias
  - Spike in BM blasts <20%
  - Increased Transfusion requirement

**Progressive MDS**
- Follow-up Sample
Progressive MDS presents with a higher mutational burden at diagnosis

(A) Stable MDS at baseline
(B) Progressive MDS at baseline

TET2  RUNX1  ASXL1  CBL  ETV6  EZH2  FLT3  PHF6  SF3B1  TP53  TYK2  CEBPA  IDH2  JAK1  KRAS  NRAS  TET1  WT1

p-value: NS for all mutations

p-value: 0.007

T. Qin et al. Leukemia 2019
Epigenetic differences at diagnosis correlate with disease progression in low risk MDS

Unsupervised analysis

Supervised analysis

T. Qin et al. Leukemia 2019
Epigenetic distances increase with disease progression

Unsupervised analysis

Supervised analysis

T. Qin et al. Leukemia 2019
Progressive MDS shows greater epigenetic variability

T. Qin et al. Leukemia 2019
SUMMARY I

- Low-risk MDS is epigenetically heterogeneous
- DNA methylation profiles and mutational burden at diagnosis correlate with clinical evolution
- These differences have the potential to be harnessed as clinical biomarkers predictive of outcome
- Progression of low-risk MDS to greater marrow failure correlates with increased epigenetic variability; this may reflect the appearance of competing clones rather than the emergence of a single dominant clone
Myelodysplastic syndromes: what does precision medicine look like?

- Assess diagnosis
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del(5q) MDS: caused by gene haploinsufficiency

Loss of a micro RNA and thrombocytosis  

Coordinate loss of a microRNA and protein-coding gene cooperate in the pathogenesis of 5q- syndrome  

Activation of p53 and apoptosis of immature red cells  
Pellagatti et al. Blood. 2010 Apr 1;115(13):2721-3  
Dutt et al. Blood. 2011 Mar 3;117(9):2567-76

Haploinsufficiency of RPS14 phenocopies the disease in normal hematopoietic progenitor cells  

Lenalidomide triggers ubiquitination and degradation of CSNK1A1; del(5q) cells have one copy of CSNK1A1; they are selectively depleted
Spliceosome gene mutations in myeloid neoplasms

**Dose Finding Phase**  
[n=58]

- 0.125 mg/kg SC q21d
- 0.25 mg/kg SC q21d
- 0.5 mg/kg SC q21d
- 0.75 mg/kg SC q21d
- 1.0 mg/kg SC q21d
- 1.75 mg/kg SC q21d

**Extension Phase**  
[PACE n=32]

**Eligibility**

- Low/Int-1 IPSS
- Hgb < 9 g/dl
- ESA failure or 
- Epo >500 mU/ml

**Principal Objective:**

LTB: Low transfusion burden (<4U/8wk, Hb<10): Hb increase ≥ 1.5 g/dL; HTB: High transfusion burden (≥4U/8wk): 4U or 50% decrease U/8wk
MEDALIST: Phase 3 Randomized Double-blind Study of Luspatercept vs Placebo in Transfusion-Dependent LR-MDS With Ring Sideroblasts [ACE-536-MDS-001]

Eligibility: Non-del(5q) MDS with \( \geq 15\% \) RS, VL-Int. IPSS-R, \( \geq 2 \) U PRBC/8 wks, prior ESA

Key Exclusions: Prior treatment with IMiDs, azanucleosides or IST; ANC < 500, plat<50K

Stratification: RBC transfusion burden (< 6 vs \( \geq 6 \) U/8wk), IPSS-R VL/Low vs. Int.

Primary end-point: Transfusion Independence x \( \geq 8 \) weeks
Myelodysplastic syndromes: what does precision medicine look like? How has it evolved?

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Leukemic IDH1 and IDH2 Mutations Result in a Hypermethylation Phenotype, Disrupt TET2 Function, and Impair Hematopoietic Differentiation

Maria E. Figueroa,1,12 Omar Abdel-Wahab,2,3,12 Chao Lu,4,12 Patrick S. Ward,4 Jay Patel,2 Alan Shih,2,3 Yushan Li,1 Neha Bhagwat,2 Aparna Vasanthakumar,5 Hugo F. Fernandez,6 Martin S. Tallman,3 Zhuoxin Sun,7 Kristy Wolniak,8 Justine K. Peeters,9 Wei Liu,10 Sung E. Choe,10 Valeria R. Fantin,10 Elisabeth Paitta,11 Bob Löwenberg,9 Jonathan D. Licht,8 Lucy A. Godley,5 Ruud Delwel,9 Peter J.M. Valk,9 Craig B. Thompson,4* Ross L. Levine,2,3,* and Ari Melnick1,*

1Division of Hematology/Oncology, Weill Cornell Medical College, New York, NY 10065, USA
2Human Oncology and Pathogenesis Program

Significance

Aberrant epigenetic programming is a hallmark of cancer and yet very little is known concerning the mechanisms through which this occurs. Here we demonstrate that leukemic neomorphic mutations of the α-ketoglutarate metabolism genes IDH1 and IDH2 that generate the aberrant metabolite 2HG induce DNA hypermethylation and impair differentiation in hematopoietic cells. These effects are caused in part through inhibition of TET2, a DNA demethylase enzyme also mutated in leukemia. IDH1/2- and TET2-mutant primary AML cells displayed a similar defect in epigenetic programming consisting of global hypermethylation and a gene-specific methylation signature. This work identifies IDH1/2- and TET2-mutant leukemias as a biologically distinct disease subtype, and links cancer metabolism with epigenetic control of gene expression.
Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia

Eytan M. Stein,1,2,‡ Courtney D. Dinardo,3,† Daniel A. Pollyea,4 Amir T. Fathi,5,6 Gail J. Roboz,2,7 Jessica K. Altman,8
Richard M. Stone,9 Daniel J. DeAngelo,9 Ross L. Levine,1 Ian W. Flinn,10 Hagop M. Kantarjian,3 Robert Collins,11
Manish R. Patel,12 Arthur E. Frankel,11 Anthony Stein,13 Mikkael A. Sekeres,14 Ronan T. Swords,15 Bruno C. Medeiros,16
Christophe Willekens,17,18 Paresh Vyas,19,20 Alessandra Tosolini,21 Qiang Xu,21 Robert D. Knight,21 Katharine E. Yen,22
Sam Agresta,22 Stephane de Botton,17,18,† and Martin S. Tallman1,2,‡

A

Screening
37% BM blasts

Cycle 1 Day 15
Evidence of cellular differentiation

Cycle 3 Day 1
4% BM blasts

B

Blasts
Promyelocytes
Mature Granulocytes
Lymphocytes

Courtesy of Misha Roshal, MD, PhD
SRSF2 Mutations Contribute to Myelodysplasia by Mutant-Specific Effects on Exon Recognition
E7107 splicing inhibitor
Interfering with RNA splicing
Myelodysplastic syndromes: what does precision medicine look like? How has it evolved?

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Allotransplantation outcomes based on mutational status

**RUNX1**
- Not mutated: Blue line
- Mutated: Yellow line
- $P = .008$

**ASXL1**
- Not mutated: Blue line
- Mutated: Yellow line
- $P = .003$

**TP53**
- Not mutated: Blue line
- Mutated: Yellow line
- $P = .001$

MG Della Porta et al JCO 2016
Allotransplant outcomes based on mutational status

MG Della Porta et al JCO 2016
APR-246 (PRIMA\textsuperscript{MET}) Restores WTP53 Function

Khoo et al., Nature Reviews Drug Discovery; 2014

Phase I/II study of APR-246 with Aza in \textit{TP53} mutant MDS or AML

\begin{itemize}
  \item \textit{TP53} mutant MDS/AML
  \item APR d1-4 iv
  \item AZA d4-10
  \item Response: Continue APR + Aza
\end{itemize}

Week: 0  Cycle q 28d x 6  24
TP53 mutations assoc. w CTLA4 & PDL1 expression

The Cancer Genome Atlas (TCGA) data set for AML.
C Response

- Patients with a response
- Patients without a response

Proportion of Patients

- TP53
- SRSF2
- RUNX1
- TET2
- IDH2
- NPM1
- DNMT3A
- NRAS
- ASXL1
- SF3B1
- IDH1
- U2AF1

P < 0.001
P = 0.04
P = 0.05
Mutation Clearance after Transplantation for Myelodysplastic Syndrome


ABSTRACT

BACKGROUND
Allogeneic hematopoietic stem-cell transplantation is the only curative treatment for patients with myelodysplastic syndrome (MDS). The molecular predictors of disease progression after transplantation are unclear.

METHODS
We sequenced bone marrow and skin samples from 90 adults with MDS who underwent allogeneic hematopoietic stem-cell transplantation after a myeloablative or reduced-intensity conditioning regimen. We detected mutations before transplantation using enhanced exome sequencing, and we evaluated mutation clearance by using error-corrected sequencing to genotype mutations in bone marrow samples obtained 30 days after transplantation. In this exploratory study, we evaluated the association of a mutation detected after transplantation with disease progression and survival.
A Disease Progression

![Cumulative Incidence (%) for Disease Progression](image)

- Day 30 (+), RIC
- Day 30 (+), MAC
- Day 30 (-), RIC
- Day 30 (-), MAC

P < 0.001 by Gray's test

B Disease Progression or Death

![Patients Who Survived without Progression (%) for Disease Progression or Death](image)

P = 0.02 by proportional-hazards chi-square test

**No. at Risk**

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<th>No. at Risk</th>
<th>Maximum VAF &lt;0.5%, RIC</th>
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Post-transplant HMA therapy?
Myelodysplastic syndromes
-key questions to address-

• What is the basis for the impaired differentiation seen in MDS patients?
• What accounts for the increased cell death in MDS bone marrow?
• What is the basis for the clonal dominance of MDS stem cells over the normal HSCs?
• What accounts for the progressive cytopenias in MDS?
• Why is lenalidomide so effective in RBC transfusion dependent 5q- MDS?
• How do 5-azacytidine and decitabine work in MDS?
• How much of the disease relates to aberrant immunity and an abnormal microenvironment?

Are there good targets for alloreactive immune cells?
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