Targeted Treatment in MDS

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No relevant financial relationships to disclose.
Which of the following statements relevant to targeted treatment in MDS is correct?

a) Degradation of a kinase encoded by a gene within the common deleted region provides the therapeutic window for targeting the del(5q) clone.

b) Haploinsufficiency may offer a prefential vulnerability for therapeutic targeting of MDS clones.

c) Mis-splicing by mutated splicing factors results in a non-classical path to haploinsufficiency of target genes in spliceosome-mutant MDS.

d) Inhibition of wild-type spliceosome may provide a way to preferentially target MDS with splicing factor mutations.

e) All the above.
Outline

• Critical issues for targeted therapy in MDS

• Targeting MDS-defining genetic lesions

• Targeting pan-myeloid drivers in MDS

• Targeting functional consequences of MDS driver genetic lesions
Critical issues for targeted treatment in MDS

- Genetic heterogeneity
- Genetic complexity
- Extra clonal and context-dependent variables
- Patient-related variables (age, extra-hematologic comorbidities)
Landscape of somatic mutations in MDS

Genetic heterogeneity of MDS

UniPv Registry
N=442 pts

205 Genetic Profiles

232 Genotypes
Genetic complexity of MDS

Del(5q) SF3B1 mutation

University of Pavia - Registry

Blood. 2013;122:3616-27
Targeting MDS-specific genetic lesions
the paradigm of del(5q)

Presumptive evidence of primary MDS

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>−5 or del(5q)</td>
<td>10-15</td>
</tr>
<tr>
<td>−7 or del(7q)</td>
<td>10</td>
</tr>
<tr>
<td>i(17q) or t(17p)</td>
<td>2-3</td>
</tr>
<tr>
<td>del(12p) or t(12p)</td>
<td>1-2</td>
</tr>
<tr>
<td>del(11q)</td>
<td>1-2</td>
</tr>
<tr>
<td>−13 or del(13q)</td>
<td>1-2</td>
</tr>
<tr>
<td>del(9q)</td>
<td>1</td>
</tr>
<tr>
<td>idic(X)(q13)</td>
<td>1</td>
</tr>
<tr>
<td>inv(3)(q21q26.2)</td>
<td>1</td>
</tr>
<tr>
<td>t(6;9)(p23;q34)</td>
<td>1</td>
</tr>
<tr>
<td>t(3;21)(p26.2;q22.1)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>t(1;3)(p36.3;q21.2)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>t(11;15)(q23;p13.3)</td>
<td>&lt;1</td>
</tr>
<tr>
<td>t(2;11)(p21;q23)</td>
<td>&lt;1</td>
</tr>
</tbody>
</table>

# Lenalidomide in the Myelodysplastic Syndrome with Chromosome 5q Deletion

Alan List, M.D., Gordon Dewald, Ph.D., John Bennett, M.D., Aristotle Giagounidis, M.D., Azra Raza, M.D., Eric Feldman, M.D., Bayard Powell, M.D., Peter Greenberg, M.D., Deborah Thomas, M.D., Richard Stone, M.D., Craig Reeder, M.D., Kenton Wride, M.S., John Patin, M.S., Michele Schmidt, R.N., Jerome Zeldis, M.D., Robert Knight, M.D., for the Myelodysplastic Syndrome-003 Study Investigators

<table>
<thead>
<tr>
<th>Eligibility: IPSS Low/Int-1 del(5)(q31), Transfusion dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response</td>
</tr>
<tr>
<td>Median baseline Hb</td>
</tr>
<tr>
<td>Median Hb at response</td>
</tr>
<tr>
<td>Complete cytogenetic remission</td>
</tr>
</tbody>
</table>
Vulnerability of 5q- clone to lenalidomide consequent to gene haploinsufficiency

Persistent malignant stem cells in MDS del(5q) in remission

Predictive value for disease progression during lenalidomide of mutations in *TP53* in MDS del(5q)

Diagnosis and treatment of primary MDS in adults: *Recommendations from the European LeukemiaNet*

Patients with 5q deletion, a low or intermediate-1 IPSS score, and evidence of TP53 mutation have a significantly higher risk of transformation to AML, which should be considered in the choice between lenalidomide and alternative therapeutic options (recommendation level D).

Summary

- Targeting of MDS founding lesions is effective and may result in (cyto)genetic remission
- Haploinsufficiency represents a targetable vulnerability of MDS clones
Mis-splicing patterns associated with spliceosome mutations contribute to MDS through a non-classical path to haploinsufficiency

SF3B1 mutation is a founding driver mutation in MDS and identifies a distinct subset of MDS with ring sideroblasts.

Genetic determinants of clinical phenotype and disease outcome in \textit{SRSF2}^{P95}-mutated myeloid neoplasms

\begin{itemize}
  \item Mutant \textit{SRSF2}^{P95}
  \begin{itemize}
    \item + \textit{JAK2}
    \item or \textit{MPL}
    \item $\rightarrow$ MPN
    \item (PMF)
    \item + \textit{TET2}
    \item or \textit{SETBP1}
    \item $\rightarrow$ MDS/MPN
    \item (CMML)
    \item + \textit{STAG2}
    \item or \textit{RUNX1}
    \item or \textit{IDH1/2}
    \item $\rightarrow$ MN with EB or AML
    \item + other mutant genes
    \item $\rightarrow$ MDS without EB
  \end{itemize}
\end{itemize}

\[\text{Overall Survival}\]

\[\text{Months}\]

Todisco et al. Manuscript submitted
Therapeutic targeting of RNA splicing in MDS

Pladienolides

H3B-8800

Session: 637. Myelodysplastic Syndromes—Clinical Studies: Targeting Gene Mutations in MDS
Monday, December 9, 2019: 10:30 AM
W311ABCD, Level 3 (Orange County Convention Center)

673 - Steensma et al. Results of a Clinical Trial of H3B-8800, a Splicing Modulator, in Patients with Myelodysplastic Syndromes (MDS), Acute Myeloid Leukemia (AML) or Chronic Myelomonocytic Leukemia (CMML)

Therapeutic targeting of RNA splicing in MDS

Sulfonamides

- indisulam
- CQS
- tasisulam

PRMTs inhibitors

Han et al. Science 2017;356:eaal3755

Summary

- Targeting of MDS founding lesions is effective and may result in (cyto)genetic remission.
- Haploinsufficiency represents a targetable vulnerability of MDS clones.
- Hematopoietic cells with spliceosomal gene mutations are preferentially susceptible to additional splicing perturbations as compared to cells without such mutations.
- Modulation of spliceosome function may provide a new therapeutic avenue in genetically defined subsets of individuals with MDS or AML.
Outline

• Critical issues for targeted therapy in MDS

• Targeting MDS-defining genetic lesions

• Targeting pan-myeloid drivers in MDS

• Targeting functional consequences of MDS driver genetic lesions
Landscape of somatic mutations in MDS

Prognostic and predictive value of TP53 mutations in MDS

Pharmacological reactivation of p53 as a strategy to treat cancer

Synergistic effects of PRIMA-1\textsuperscript{Met} (APR-246) and Azacitidine in TP53-mutated MDS and AML

Session: 637. Myelodysplastic Syndromes—Clinical Studies: Targeting Gene Mutations in MDS
Monday, December 9, 2019: 10:30 AM
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676 - \textit{Sallman et al.} Phase 2 Results of APR-246 and Azacitidine (AZA) in Patients with TP53 mutant Myelodysplastic Syndromes (MDS) and Oligoblastic Acute Myeloid Leukemia (AML)

677 – \textit{Cluzeau et al.} APR-246 Combined with Azacitidine (AZA) in TP53 Mutated Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML). a Phase 2 Study By the Groupe Francophone Des Myélodysplasies (GFM)

<table>
<thead>
<tr>
<th>NCT Number</th>
<th>Title</th>
<th>Status</th>
<th>Study Results</th>
<th>Conditions</th>
<th>Interventions</th>
<th>Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT03931291</td>
<td>APR-246 in Combination With Azacitidine for TP53 Mutated AML or MDS Following Allogeneic SCT</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>AML, MDS</td>
<td>Drug: APR-246</td>
<td>Phase 2</td>
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<tr>
<td>NCT03745716</td>
<td>APR-246 &amp; Azacitidine for the Treatment of TP53 Mutant MDS</td>
<td>Recruiting</td>
<td>No Results Available</td>
<td>MDS</td>
<td>Drug: APR-246 + azacitidine Drug: Azacitidine</td>
<td>Phase 3</td>
</tr>
<tr>
<td>NCT03072043</td>
<td>Phase 1b/2 Safety and Efficacy of APR-246 w/Azacitidine for tx of TP53 Mutant Myeloid Neoplasms</td>
<td>Active, not recruiting</td>
<td>No Results Available</td>
<td>MDS, AML, MPN, CMML</td>
<td>Drug: APR-246 Drug: Azacitidine</td>
<td>Phase 1</td>
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<tr>
<td>NCT03588078</td>
<td>Study of the Safety and Efficacy of APR-246 in Combination With Azacitidine</td>
<td>Active, not recruiting</td>
<td>No Results Available</td>
<td>MDS, AML, MPN, CMML</td>
<td>Drug: APR-246 Drug: Azacitidine</td>
<td>Phase 1</td>
</tr>
</tbody>
</table>

\textit{J Intern Med. 2015;277:248-259}
**Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML**

**Official Title (NCT02074839):**
A Phase I, Multicenter, Open-Label, Dose-Escalation and Expansion, Safety, Pharmacokinetic, Pharmacodynamic, and Clinical Activity Study of Orally Administered AG-120 in Subjects With Advanced Hematologic Malignancies With an IDH1 Mutation

**Key Inclusion Criteria:**
- ≥18 years of age.
- IDH1 R132 gene-mutated advanced hematologic malignancy.
- ECOG PS of 0 to 2.

**Patients**
- 268 patients enrolled
- 258 received study medication
- 179 patients with relapsed or refractory AML

**Enasidenib in mutant IDH2 relapsed or refractory AML**

**Official Title (NCT01915498):**
Phase 1/2 Study of AG-221 in Subjects With Advanced Hematologic Malignancies With an IDH2 Mutation

**Inclusion Criteria:**
- Phase 1:
  - Refractory or relapsed AML or untreated AML (≥60 yrs not candidates for standard therapy);
  - Diagnosis of MDS-EB-1 or -EB-2, or high-risk IPSS-R, recurrent or refractory, or intolerant to established therapy.
- Phase 2: IDH2 gene-mutated relapsed or refractory AML

**Patients**
- 239 patients enrolled
- 176 patients relapsed/refractory AML

*N Engl J Med 2018;378:2386-2398*

*Blood 2017;130:722-731*
Session: 637. Myelodysplastic Syndromes—Clinical Studies: Targeting Gene Mutations in MDS
Monday, December 9, 2019: 10:30 AM
W311ABCD, Level 3 (Orange County Convention Center)

674 – Cortes et al. Olutasidenib (FT-2102) Induces Rapid Remissions in Patients with IDH1-Mutant Myelodysplastic Syndrome: Results of Phase 1/2 Single Agent Treatment and Combination with Azacitidine

678 - Richard-Carpentier et al. Preliminary Results from the Phase II Study of the IDH2-Inhibitor Enasidenib in Patients with High-Risk IDH2-Mutated Myelodysplastic Syndromes (MDS)
SRSF2-IDH1/2 mutant represent a biological continuum spanning from MDS to AML

Outline

• Critical issues for targeted therapy in MDS

• Targeting MDS-defining genetic lesions

• Targeting pan-myeloid drivers in MDS

• Targeting functional consequences of MDS driver genetic lesions
Targeting ineffective erythropoiesis

Luspatercept Response in Patients with Low-Intermediate Risk MDS

- Phase 2, multicenter, open-label study
- Endpoints: IWG HI-E, RBC-TI (≥ 8 weeks)
- High proportion of responses in patients with ring sideroblasts (69% vs 43%), and SF3B1 mutation (77% vs 40%)

Relationship between SF3B1 mutation, erythroid marrow activity and hepcidin to ferritin ratio in MDS

A Phase 3, Double-blind, Randomized Study to Compare the Efficacy and Safety of Luspatercept (ACE-536) Versus Placebo for the Treatment of Anemia Due to the IPSS-R Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes in Subjects With Ring Sideroblasts Who Require Red Blood Cell Transfusions (NCT02631070)

Methods:
IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS-RS according to the WHO 2016 criteria; refractory, intolerant, or ineligible to receive erythropoiesis-stimulating agents (ESAs); required RBC transfusions. Patients were randomized 2:1 to receive either luspatercept, at a starting dose level of 1.0 mg/kg with titration up to 1.75 mg/kg, if needed, or placebo, subcutaneously every 3 weeks for ≥ 24 weeks. The primary endpoint was RBC transfusion independence (RBC-TI) for ≥ 8 weeks between week 1 and week 24.

Results:
Patients received a median of 5 RBC units (range 1-20) transfused over 8 weeks during the 16 weeks prior to treatment. At baseline, 138 (60.3%), 58 (25.3%), and 32 (14.0%) patients had serum erythropoietin levels < 200 IU/L, 200-500 IU/L, and > 500 IU/L, respectively. A total of 218 (95.2%) patients had previously received ESAs. Overall, 206 (90.0%) patients had an SF3B1 mutation. Of 153 patients receiving luspatercept, 58 (37.9%) achieved the primary endpoint of RBC-TI for ≥ 8 weeks compared with 10 of 76 patients (13.2%) receiving placebo (odds ratio [OR] 5.1, \( P < 0.0001 \)). Of those receiving luspatercept, 43 of 153 (28.1%) achieved the key secondary endpoint of RBC-TI for ≥ 12 weeks (weeks 1-24) compared with 6 of 76 (7.9%) receiving placebo (OR 5.1, \( P = 0.0002 \)).

Conclusions:
Treatment with luspatercept resulted in a significantly reduced transfusion burden compared with placebo in patients with anemia due to IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS with RS, who require RBC transfusions.

The role of Bcl-2-related proteins in MDS and AML secondary to MDS

Blockade of BCL-2 proteins efficiently induces apoptosis in high-risk MDS

Blood. 2000;96:3932-8

Leukemia 2016;112–123
Session: 637. Myelodysplastic Syndromes—Clinical Studies

4241 - Brian et al., Combined Venetoclax and Hypomethylating Agent (HMA) Therapy Induces High Response Rates in Patients with Myelodysplastic Syndrome Including Patients Previously Failing HMA.

568 – Wei et al. A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax in Combination with Azacitidine in Treatment-Naïve Patients with Higher-Risk Myelodysplastic Syndrome.

565 – Zeidan et al. A Phase 1b Study Evaluating the Safety and Efficacy of Venetoclax As Monotherapy or in Combination with Azacitidine for the Treatment of Relapsed/Refractory Myelodysplastic Syndrome.
Which of the following statements relevant to targeted treatment in MDS is correct?

a) Degradation of a kinase encoded by a gene within the common deleted region provides the therapeutic window for targeting the del(5q) clone.

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