Novel Treatment of Biologic and Molecular Targets for MDS-related Anemias and Higher Risk Disease

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Disclosure

I have the following financial relationships:

- Consultant: Amgen, Celgene, Janssen, Novartis
- Research support: Amgen, Celgene, Janssen, Novartis
MDS as a disease model of leukemogenesis

- Normal
- Low-risk MDS
- High-risk MDS
- AML

years
MDS as a disease model of leukemogenesis

Genetic "Hit"

Normal → Low-risk MDS → High-risk MDS → AML

years
Molecular Classification

Targets?

Normal  Low-risk MDS  High-risk MDS  AML

Papaemmanuil et al. Blood 2013
Therapeutic principles

Stimulation

Normal

Low-risk MDS

High-risk MDS

AML

Suppression

Normal

Low-risk MDS

High-risk MDS

AML
Therapy lower-risk MDS

Erythropoiesis-stimulating agents (ESA)

Normal → Low-risk MDS → High-risk MDS → AML
ESA Registration Trials in MDS

- IPSS low/int-1
- EPO<500
- <=4 RBCs/8 W.

Fenaux et al. EHA 2016, Platzbecker et al. EHA 2016
Darbepoetin-trial

Transfusions

% Transfused Weeks 5-24

59.2%
(29 / 49)

36.1%
(35 / 97)

p = 0.008

24-week Double-blind

Placebo

Darbepoetin alfa

Platzbecker et al. EHA 2016
Darbepoetin-trial
hematological response

24-week Double-blind

% Achieving IWG 2006 HI-E

Placebo: 0% (0 / 35)
Darbepoetin alfa: 14.7% (11 / 75)
p = 0.016

48-week Open-label

% Achieving IWG 2006 HI-E

Darbepoetin alfa: 34.7% (34 / 98)
EPO-alpha trial

Transfusions

Fenaux et al. EHA 2016
EPO-alpha trial
hematological response

<table>
<thead>
<tr>
<th>Subjects achieving erythroid response (primary endpoint)</th>
<th>Placebo n=45</th>
<th>Epoetin alfa n=85</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (4.4%)</td>
<td>27 (31.8%)</td>
<td>&lt;0.001</td>
<td></td>
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</tbody>
</table>

| Subjects with erythroid response at any time during the first 24 weeks* | 2 (4.4%) | 39 (45.9%) | <0.001 |

*Ad hoc analysis
Biomarkers of response to erythropoiesis-stimulating agents (ESA)

- EPO level <500 (100), <2 RBC units/month
Biomarkers of response to erythropoiesis-stimulating agents (ESA)

- EPO level <500 (100), <2 RBC units/month
- IPSS-R (low: 68% vs. high: 31%)
- Activated ERK pathway (p-ERK)
- Absence of aberrant flow markers (CD5/CD7)

Aberrant expression of CD5/CD7 defines a subset of MDS with high clonal burden.

**Clonality in red cell precursors**

Oelschlägel et al. Leukemia 2015
86% of the pts had at least one mutation (median number 2, range 0-6) >10 % of pts had 6 mutations.
Distribution of mutations according to response to ESA

<table>
<thead>
<tr>
<th>Number of mutations</th>
<th>HI-E (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>73</td>
</tr>
<tr>
<td>1</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>47</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
</tr>
</tbody>
</table>

Presence of $>2$ mutations predicted worse HI-E to ESA in lower risk MDS. 
$\leq 2$ mutations: 74%, vs $>2$ mutations: 46% (p=0.01)

Kosmider et al. Haematologica 2016
Anemia in del5q disease

- Lenalidomide

Oelschlägel et al. Haematologica 2015
List et al. Leukemia 2015
Beier et al. Leukemia Research 2015
Schuler et al. Leukemia 2016

Normal
Low-risk MDS
High-risk MDS
AML

Lenalidomide

TP53 mutation: 12%
Association with TI

Oelschlägel et al. Haematologica 2015
List et al. Leukemia 2015
Beier et al. Leukemia Research 2015
Schuler et al. Leukemia 2016

Mossner et al. Leukemia 2016
Transfusion independence LEN vs Placebo in non-del5q MDS

Median duration of response: 8 months

- LEN (n = 160)
- Placebo (n = 79)

Average baseline 28-day transfusion burden was associated with RBC-TI OR 2.985, p=0.035

Santini et al. JCO 2016
RBC-TI $\geq$ 8 Weeks Response by EPO level in LEN-treated Patients

Santini et al. JCO 2016
Response by Gene Mutation Status in LEN-treated non-del5q patients

Negoro et al. Leukemia 2016
Response by Gene Mutation Status in LEN-treated non-del5q patients

DNMT3Amut was associated with response
Chesnai et al. Blood 2016

Negoro et al. Leukemia 2016
LEN + EPO > LEN in non-del5q MDS?

Toma et al. Leukemia 2016

Duration 18.1 vs 14.6 m

LEN + EPO > LEN in non-del5q MDS?
Bone and hematopoiesis

*Osteohematology*

HSC → Osteoclast → Bone resorption → Osteocyte → Bone formation → Osteoblast → MSC

Scadden et al. Nature 2010
Bulycheva et al. Leukemia 2015
MDS is associated with loss of bone in mice and men

Weidner et al. EHA 2016
GDF-11 as a negative regulator of erythropoiesis

Suragani et al. Nature Medicine 2014
Luspatercept a TGF-beta ligand trap

Hemoglobin (g/dL)

Follow-up Period

Units Transfused

MDS-RS-MLD failure LEN, EPO

0.75 mg/kg (starting dose)

Weeks

Platzbecker et al. ASH 2014
## Erythroid Response

**Dose:** 0.75-1.75 mg/kg

![Image](image-url)

<table>
<thead>
<tr>
<th>Baseline EPO</th>
<th>RS Status</th>
<th>Base Study (3 mo. treatment) N=64</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>All</td>
<td>29/64 (45%)</td>
</tr>
<tr>
<td>EPO ≤ 500</td>
<td>All</td>
<td>25/48 (52%)</td>
</tr>
<tr>
<td></td>
<td>RS+</td>
<td>23/40 (58%)</td>
</tr>
<tr>
<td></td>
<td>RS-</td>
<td>2/8 (25%)</td>
</tr>
<tr>
<td>EPO &gt; 500</td>
<td>RS+</td>
<td>3/7 (43%)</td>
</tr>
<tr>
<td></td>
<td>RS-</td>
<td>1/7 (14%)</td>
</tr>
</tbody>
</table>

Platelet and neutrophil responses were observed as well.
Lower-risk LOW MDS

MDS <5% blasts, SF3B1 mutated

Malcovati et al. Blood 2015


**Lower-risk LOW MDS**

**Medalist trial:**

<5% blasts, RS+/SF3B1+, at least 2 RBC/8w, EPO>200 or ESA-failure

Malcovati et al. Blood 2015
Therapy of thrombocytopenia

Thrombopoiesis-stimulating agents (TSA)
Romiplostim/Eltrombopag

Normal Low-risk MDS High-risk MDS AML

Eltrombopag

Giagounidis et al. Cancer 2014
Platzbecker et al. Leukemia 2015
Oliva et. al. ASH 2015

Will et al. Blood 2012
Platzbecker et al. Haematologica 2014
Platzbecker et al. Lancet Haematology 2015
Mittelman et al. ASH 2016
Dickinson et al. ASH 2016
AZA-001 trial in high-risk disease

Log-Rank  \( p = 0.0001 \)

HR = 0.58 [95 % KI: 0.43–0.77]

CCR = Conventional Care Regime

Combination of Azacitidine and Lenalidomide in Myelodysplastic Syndromes or acute Myeloid Leukemia—a wise Liaison?

U. Platzbecker and U. Gerning

Treatment options for older patients with advanced myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML) are limited and the prognosis remains poor, thereby warranting development of novel therapies. Ablant epigenetic modifications, including altered DNA methylation, seem to contribute to the pathogenesis of these patients. In fact, hypomethylating agents (HMA) like azacitidine have been successfully used in clinical trials and achieved approval from health authorities. There is now growing evidence suggesting that the combination of drugs with different mechanisms of action might offer a potential benefit to these patients. This is especially done with the intention to synergize the positive effects of each drug on the defective hematopoiesis while sparing potential side effects and toxicities. Combination of HMA with histone deacetylase inhibitors, although mechanistically very tempting, have not yielded convincing improvement of the results in the majority of trials compared to single agent HMA treatment. Currently, combination therapies of azacitidine with lenalidomide appear to be promising thus making them an appealing option for treatment in these patients.

Leukemia (2013) 27, 1813–1819; doi:10.1038/leu.2013.140
### Rigosertib after HMA Failure

<table>
<thead>
<tr>
<th>Response</th>
<th>Rigosertib group (n=199)</th>
<th>Best supportive care group (n=100)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial response</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow complete response</td>
<td>39 (20%)</td>
<td>14 (14%)</td>
</tr>
<tr>
<td>Bone marrow partial response</td>
<td>14 (7%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>69 (35%)</td>
<td>15 (15%)</td>
</tr>
<tr>
<td>Failure</td>
<td>13 (7%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>48 (24%)</td>
<td>16 (16%)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>16 (8%)</td>
<td>47 (47%)</td>
</tr>
</tbody>
</table>

**Primary AZA Failure**

HR 0.72; p=0.06
Molecular Classification

Targets?

- Normal
- Low-risk MDS
- High-risk MDS
- AML

Papaemmanuil et al. Blood 2013
Mutation prevalence and susceptibility to immune therapy

Schumacher & Schreiber  Science 2015
Checkpoint modulation in MDS?
Novel targets

- Inflammasome (NLRP3, S100A9, TL-R2)
- CD33/CD123
- IDH Inhibitors
- Spliceosome modulators (H3B-8800)
- Gas6/Axl signaling (BGB324)
- Bcl-2 inhibition
We need broad clinical trial networks

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