Iron chelation and targeted therapy in MDS: Shifting the treatment paradigm

The 2nd Regional Symposium on Myelodysplastic Syndromes

Thursday 5 March
Tel Aviv, Israel
Please switch your mobile phones to silent

A microphone for the Q&A sessions will be available

Please complete evaluation form at the end of the symposium
# Iron chelation and targeted therapy in MDS: Shifting the treatment paradigm

This meeting is organized and sponsored by Novartis

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<tr>
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| 13:30–13:45 | Welcome and Introductions  
  *Faculty discussion:*  
  Are current therapies doing enough to meet the needs of patients with Myelodysplastic Syndromes? | Moshe Mittelman          |
| 13:45–14:00 | Rethinking treatment selection for patients with low-risk Myelodysplastic Syndromes | Emanuele Angelucci       |
| 14:00–14:15 | Moving towards a targeted approach for patients with Myelodysplastic Syndromes | Uwe Platzbecker          |
| 14:15–14:30 | Q&A  
  *Faculty discussion:*  
  Paving the way for novel therapeutic opportunities in Myelodysplastic Syndromes treatment  
  Meeting close | Moderator: Moshe Mittelman |

Meeting close
Welcome & introductions

Moshe Mittelman
Myelodysplastic Syndromes (MDS)

- A heterogeneous group of malignancies
- Bone marrow stem cell disease
- Peripheral blood cytopenias
  - Anemia
  - Neutropenia
  - Thrombocytopenia
- Risk of leukemic evolution

Emanuele Angelucci
Hematology and Hematopoietic Stem Cell Transplantation Center at the IRCCS San Martino University Hospital in Genoa, Italy

Uwe Platzbecker
Medical Clinic I, Hematology and Cellular Therapy at the University Hospital in Leipzig, Germany
Are current therapies doing enough to meet the needs of patients with MDS?

Panel discussion
What are the problems with current MDS treatments?
Are current therapies doing enough to meet the needs of patients with MDS? Questions (II)

Do complications occur more in transfusion-dependent MDS patients?

- Due to iron overload?
Are you satisfied with the current treatment landscape for patients with MDS?

Please raise your hand for YES
Rethinking treatment selection for patients with lower-risk Myelodysplastic Syndromes

Emanuele Angelucci
Disclosures

Honoraria from Novartis and Celgene, involvement in local advisory boards for Jazz Pharmaceuticals, Bluebird Bio, and Roche, and participation in DMC for Celgene and Vertex Pharmaceuticals Incorporated, and CRISPR Therapeutics.

DMC, data monitoring committee.
Correct diagnosis is **KEY** to the choice of treatment strategy

**Lower risk IPSS**
- Improve blood cytopenias
- Improve quality of life

**Higher risk IPSS**
- Delay disease progression
- Prolong survival

IPSS, International Prognostic Scoring System. Information provided by the speaker.
Correct diagnosis is **KEY** to the choice of treatment strategy

**Lower risk IPSS**
- Improve blood cytopenias
- Improve quality of life
- **Improve survival**

**Higher risk IPSS**
- Delay disease progression
- Prolong survival
Competitive risk of death in MDS subgroups

MDS, Myelodysplastic syndromes; RA, refractory anaemia; RAEB, RA with excess blasts; RARS, RA with ring sideroblasts; RCMD, refractory cytopenia with multi-lineage dysplasia.


Adapted from Giovanni Della Porta & Malcovati. 2009
Reduced survival is an inherent feature of MDS, even for low-risk subgroups

Life expectancy is shorter for US patients with MDS than for those with lung cancer\textsuperscript{a,b,1,2}

\begin{itemize}
  \item \textbf{Lung cancer:}
    \begin{itemize}
      \item Low risk: 8.0 years
      \item Int-I risk: 5.4 years
      \item Int-II risk: 2.4 years
      \item High risk: 1.2 years
    \end{itemize}

  \item \textbf{MDS:}
    \begin{itemize}
      \item Low risk: 5.7 years
      \item Int-I risk: 3.5 years
      \item Int-II risk: 1.1 years
      \item High risk: 0.4 years
    \end{itemize}
\end{itemize}

\textsuperscript{a} Adjusted for age (lung cancer, median 66 years of age; MDS, median 69 years of age) and risk/stage.\textsuperscript{1,2}
\textsuperscript{b} All histological subtypes.\textsuperscript{1,2}

AJJC-UICC, American Joint Committee on Cancer Union for International Cancer Control; IPSS, International Prognostic Scoring System; MDS, Myelodysplastic syndromes; US, United States.

Predictive factors of response and survival in MDS treated with erythropoietin and G-CSF: the GFM experience

Overall survival between IMRAW (untreated) and French-EPO (rEPO-treated) cohorts*

*P<0.001 between IMRAW and rEPO responders; P=0.17 between IMRAW and rEPO no-responders.
EPO, erythropoietin; rEPO, recombinant EPO; GFM, Groupe Francophone des Myélodysplasies; IMRAW, International MDS Risk Analysis Workshop; INT1, intermediate-1.
Figure and legend Copyright © 2020 American Society of Hematology.

Adapted from Park S, et al. 2008
Luspatercept in Patients with Lower-Risk MDS

Changes in mean hemoglobin levels over time

No. of Patients
Luspatercept 153 57 87 116 105 112 103 76 92 106 90
Placebo 76 32 36 41 47 44 52 29 44 47 44 32

Analysis Visit
Baseline C1 C2 C3 D1 D2 C1 D1 C2 D1 C3 D1 C4 D1 C5 D1

Mean Level (g/litre)

Changes in Mean Observed Hemoglobin Levels over time

Change from Baseline in Hemoglobin Level

No. of Patients
Luspatercept (with response) - 24 36 55 53 52 50 47 50 42 42
Luspatercept (without response) - 33 51 61 52 60 53 34 45 56 48
Placebo - 32 36 41 47 40 52 29 44 47 44

Analysis Visit
Baseline C1 C2 C3 D1 D2 C1 D1 C2 D1 C3 D1 C4 D1 C5 D1

Mean Change (g/dl)

Luspatercept* reduced the severity of anemia in patients with lower-risk myelodysplastic syndromes with ring sideroblasts....

*Luspatercept is not yet licensed for MDS indications in any country.
MDS, myelodysplastic syndromes.
Impact of increasing serum ferritin levels on overall survival of patients from the Leukemia Net Prospective Registry

OS of transfusion-dependent patients by baseline SF status (n=1000) (Kaplan-Meier survival estimates)

OS, overall survival; SF, serum ferritin.

Role of serum ferritin level on overall survival in patients with MDS: Results of a meta-analysis of observational studies

Forest plot of the subgroup analyses of the association of OS and SF according to SF≥1000 ng/mL and SF≥500 ng/mL cut-offs

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sample</th>
<th>Cut-off: &gt;1000 ng/mL RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chee</td>
<td>2008</td>
<td>77</td>
<td>1.21 (0.39, 3.75)</td>
<td>3.95</td>
</tr>
<tr>
<td>Park</td>
<td>2011</td>
<td>318</td>
<td>0.85 (0.40, 1.81)</td>
<td>8.92</td>
</tr>
<tr>
<td>Komrokji</td>
<td>2012</td>
<td>767</td>
<td>1.40 (1.78, 87.13)</td>
<td>8.92</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>1.33 (1.06, 1.67)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Sample</th>
<th>Cut-off: &gt;500 ng/mL RR (95% CI)</th>
<th>Weight %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kikuchi</td>
<td>2012</td>
<td>47</td>
<td>1.90 (1.03, 3.49)</td>
<td>50.42</td>
</tr>
<tr>
<td>Li</td>
<td>2013</td>
<td>191</td>
<td>3.53 (1.90, 6.56)</td>
<td>49.58</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td></td>
<td>2.58 (1.41, 4.74)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis.


Adapted from Pileggi C, et al. 2017
Development of tissue iron overload and tissue damage


Adapted from Angelucci E & Pilo F. 2016
Iron tissue toxicity

\[ \Sigma \text{Tissue Reactive Iron} \times \text{Genetics} \times \text{Environmental Factors} \times \text{Time} \]

"Iron toxicity depends on many factors in addition to the level of iron per se"

- There is a different relation (iron and damage) for different tissues
- Tissue toxicity sums (\(\Sigma\)) over time (\(\Delta\text{Time}\))
- It will likely never be possible to accurately predict toxicity from individual component factors

Not only the magnitude of iron overload is important, but the duration of exposure to toxic iron is important

GI, gastrointestinal; NTBI, non-transferrin-bound iron; LPI, labile plasma iron.
Studies demonstrating a survival benefit of chelation therapy presented limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Design</th>
<th>Survival</th>
<th>Non-chelated patients</th>
<th>Chelated patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leitch 2008</td>
<td>36</td>
<td>Retrospective</td>
<td>Median overall OS 40 months 4-year survival 43%</td>
<td>Not reached</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Rose 2010</td>
<td>97</td>
<td>Prospective follow-up</td>
<td>Median OS from diagnosis 53 months vs weak chelation NA</td>
<td>124 vs 85 months</td>
<td>124 months</td>
<td>&lt;0.0003</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neukirchen 2012</td>
<td>188</td>
<td>Matched pair analysis</td>
<td>Median OS 49 months</td>
<td>75 months</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td>Neukirchen 2012</td>
<td>417</td>
<td>Retrospective, registry</td>
<td>Median time to death in transfusion-dependent patients 30 months</td>
<td>67 months</td>
<td></td>
<td>NR</td>
</tr>
<tr>
<td>Komrokji 2011</td>
<td>97</td>
<td>Retrospective</td>
<td>Median OS 34 months</td>
<td>59 months</td>
<td></td>
<td>0.013</td>
</tr>
<tr>
<td>Delforge 2012</td>
<td>186</td>
<td>Retrospective</td>
<td>Median OS in Low/Int-1 37 months</td>
<td>126 months</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Zeidan 2012</td>
<td>4226</td>
<td>Retrospective, registry</td>
<td>Median survival 47 weeks HR for 27–52 weeks on DFX 1 HR for ≥53 weeks on DFX 1</td>
<td>110 weeks 0.77</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>de Witte 2012</td>
<td>1000</td>
<td>Prospective, registry</td>
<td>Adjusted HR 1</td>
<td>0.51 (0.19–1.32)</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Delforge 2014</td>
<td>127</td>
<td>Retrospective follow-up</td>
<td>Median OS 3.1 years</td>
<td>10.2 years</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Remacha 2015</td>
<td>263</td>
<td>Retrospective</td>
<td>Median OS 153 months</td>
<td>Not reached</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Langemeijer 2016</td>
<td>195/573</td>
<td>Registry</td>
<td>Adjusted HR 1.3 (0.95–1.7)</td>
<td>1</td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>Lyons 2017</td>
<td>599</td>
<td>Prospective, registry</td>
<td>Median OS from diagnosis 47.8 months</td>
<td>All 86.3 months ICT &gt;6 months: 98.7 months</td>
<td>5.2 years</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leitch 2018</td>
<td>239</td>
<td>Prospective, registry</td>
<td>Median OS from transfusion dependence 2.1 years</td>
<td>ICT &gt;6 months: 98.7 months</td>
<td>5.2 years</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

DFX, deferasirox; HR, hazard ratio; ICT, iron chelation therapy; Int-1, intermediate 1; OS, overall survival.

Data beyond 4 years are not shown, as few patients were followed at later timepoints. A stratified Cox regression model was used to provide estimates of the hazard ratio and associated Wald 95% confidence intervals.

Median EFS and survival probability estimates were obtained by Kaplan-Meier methodology. Number of patients censored refers to the previous time interval.

CI, confidence interval; EFS, event-free survival.

Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.

Adapted from Angelucci E, et al. 2020
The TELESTO prospective, randomized, placebo-controlled trial: Forest plot for EFS

<table>
<thead>
<tr>
<th>BM blasts</th>
<th>&lt;5% at baseline (N=193 – Ev: D=51, P=29)</th>
<th>≥5% at baseline (N=19 – Ev: D=8, P=6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Female (N=88 – Ev: D=19, P=12)</td>
<td>Male (N=137 – Ev: D=43, P=25)</td>
</tr>
<tr>
<td>Age group</td>
<td>&lt;65 years (N=108 – Ev: D=23, P=12)</td>
<td>≥65 years (N=117 – Ev: D=39, P=25)</td>
</tr>
<tr>
<td>Stratum</td>
<td>Low IPSS (N=75 – Ev: D=18, P=11)</td>
<td>Int-1 IPSS (N=150 – Ev: D=44, P=26)</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>0/1 (N=61 – Ev: D=14, P=14)</td>
<td>2/3 (N=118 – Ev: D=37, P=19)</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>1000 – &lt;2000 ng/mL (N=131 – Ev: D=37, P=22)</td>
<td>2000 – &lt;3000 ng/mL (N=59 – Ev: D=19, P=9)</td>
</tr>
<tr>
<td>Region</td>
<td>Asian (N=100 – Ev: D=21, P=15)</td>
<td>Non-Asian (N=125 – Ev: D=41, P=22)</td>
</tr>
<tr>
<td>All patients</td>
<td>(N=225 – Ev: D=62, P=37)</td>
<td></td>
</tr>
</tbody>
</table>

HR (D/P) and 95% CI

Adapted from Angelucci E, et al. 2020
The TELESTO prospective, randomized, placebo-controlled trial: EFS events

EFS events that occurred first as confirmed by the EAC (adjudication rate 44%)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Deferasirox (N=149) n (%)</th>
<th>Placebo (N=76) n (%)</th>
<th>All patients (N=225) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-fatal events confirmed by EAC*</td>
<td>14 (9.4)</td>
<td>12 (15.8)</td>
<td>26 (11.6)</td>
</tr>
<tr>
<td>Progression to AML</td>
<td>10 (6.7)</td>
<td>6 (7.9)</td>
<td>16 (7.1)</td>
</tr>
<tr>
<td>Hospitalization for CHF</td>
<td>1 (0.7)</td>
<td>3 (3.9)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Liver function impairment</td>
<td>1 (0.7)</td>
<td>1 (1.3)</td>
<td>2 (0.9)</td>
</tr>
<tr>
<td>Worsening of cardiac function</td>
<td>2 (1.3)</td>
<td>2 (2.6)</td>
<td>4 (1.8)</td>
</tr>
<tr>
<td>Deaths during treatment</td>
<td>48 (32.2)</td>
<td>25 (32.9)</td>
<td>73 (32.4)</td>
</tr>
</tbody>
</table>

*Investigators were asked to report any event that was even remotely possible to be an event to the EAC; only events confirmed by the EAC are included.

†A patient with multiple occurrences of the same event is counted only once in the component category.

Adapted from Angelucci E, et al. 2020

**TELESTO was not powered to detect differences between deferasirox and placebo for single-event categories of the composite primary endpoint for EFS**

AML, acute myeloid leukemia; CHF, congestive heart failure; EAC, endpoint adjudication committee; EFS, event-free survival. Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.
The TELESTO prospective, randomized, placebo-controlled trial: Exposure-adjusted AEs (>10% either arm)

All AEs, n
(Incidence rate per 100 subject treatment years)

IR = exposure-adjusted incidence rate: number of subjects with an event divided by the corresponding sum of the exposure duration for all subjects, where duration of exposure in subject treatment years (STY) is counted up to the first event (or EOT for subjects without an event)

Adapted from Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.
The TELESTO prospective, randomized, placebo-controlled trial: Exposure-adjusted AEs (>10% either arm)

**All AEs, n**
(Incidence rate per 100 subject treatment years)

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Adapted from Angelucci E, et al. 2020

AEs, adverse events; DFX, deferasirox; EOT, end of therapy.
Angelucci E, et al. Accepted for publication by Annals of Internal Medicine on Feb 7th 2020.
Several retrospective, registry and finally a prospective, randomized clinical trial (TELESTO) consistently demonstrated clinical benefit of iron chelation therapy in transfusion-dependent MDS.
Chelation indication and guidelines

On the assumptions that development of tissue damage requires:

- Iron burden accumulation and
- Long life expectancy

Usual indication to iron chelation required:

- Transfusion dependency
- Bulky iron accumulation (serum ferritin / number of transfusions / LIC)
- Lower IPSS risk category

IPSS, International Prognostic Scoring System; LIC, liver iron content.
Information provided by the speaker.
Iron toxicity depends on many factors in addition to the level of iron per se. Iron toxicity may not only depend on the degree of tissue iron accumulation but may also be related to chronic exposure to NTBI/LPI \( \rightarrow \) ROS. Not only the magnitude of iron overload is important, but also the duration of exposure to toxic iron. With modern disease-modifying treatment MDS patients’ survival is extended over the classical IPSS life expectancy. TELESTO trial demonstrated a clinical benefit after two years of chelation therapy.

IPSS, International Prognostic Scoring System; LPI, labile plasma iron; MDS, myelodysplastic syndromes; NTBI, non-transferrin bound iron; ROS, reactive oxygen species.

Information provided by the speaker.
Rethinking treatment selection for patients with lower-risk MDS

- Considering early chelation

- NTBI/LPI ideal chelation targets (not yet available) but transferrin saturation today reasonable surrogate

- Consider real life expectancy and additional risk in MDS patients

LPI, labile plasma iron; MDS, Myelodysplastic syndromes; NTBI, non-transferrin bound iron.

Opinions of the speaker.
A Multicenter, Italian Trial of Early Iron Chelation Therapy with Low Dose Deferasirox (Exjade®) in Patients with Low/Intermediate-1 Risk MDS at the Beginning of Transfusional Story

Emanuele Angelucci, MD, Mario Capasso, PhD, Matteo Giovanni Della Porta, MD Gian Luca Forni, Domenico Girelli, M.D., PhD, Esther Natalie Oliva, MD, Federica Pilo, MD, Marino Clavio, MD, Marta Riva, MD Annamaria Pelizzari, MD, Pasquale Nicola, MD, PhD, Daniela Cilloni, MD, PhD, Gianni Binotto, MD, Elena Crisà, MD and Valeria Santini

BACKGROUND

Most MDS patients require regular packed red blood cells (RBC) transfusions and finally most become transfusion dependent. One of the unavoidable consequences of transfusion therapy is iron overload which has been found to be deleterious for different categories of patients including MDS patients. So far tissue and organ damage have been directly and strictly connected to the amount of tissue iron deposition (i.e. a “bulky” disease). All the studies performed in the last years have linked survival to markers of iron accumulation (mainly indirect markers) such as serum ferritin.

Recent data support the notion that iron disease is not only a “bulky” disease exclusively secondary to iron accumulation but rather it is a toxic disease in which tissue damage is due to toxic iron forms (Non-Transferrin-Bound-Iron, NTBI, and Labile Plasma iron, LPI). These tissue reactive iron species are present in plasma since early phase of transfusion therapy or even before. NTBI and LPI emerge in the serum only once iron binding capacity is saturated in a rate over 60-70%. Notably these iron fractions are chelatable and can be removed from circulation by a chelator.

The scientific rationale for this study (ClinicalTrials.gov: NCT03920657; CICL670A117T) is the notion that iron-induced tissue damage is not only a process of progressive organs bulking through high-volumes iron deposition, but also a reactive iron species related “toxic” damage. Therefore, a timely early initiation of iron chelation may be of benefit before overt iron overload is seen.

Our hypothesis is that early and low dose Deferasirox film coated tablets (DFX-FCT) is well tolerated and is able to prevent iron accumulation, NTBI and LPI.

MDS and rIPSS diagnosis | Inclusion and exclusion criteria | 1 year DFX FCT 3.5 mg/kg/day monthly assessment | EoS
--- | --- | --- | ---
DFX, deferasirox; EOS, end of study; FCT, film coated tablets; MDS, myelodysplastic syndrome; rIPSS, Revised International Prognostic Scoring System

STUDY DESIGN AND METHODS

INCLUSION CRITERIA

- Patients must be affected by Myelodysplastic Syndrome (MDS)
- aged ≥ 18 years
- very low, low and intermediate revised IPSS stage
- limited history of transfusions (5-20 RBC units)
- chelation naïve
- Additional inclusion criteria are serum ferritin levels >350 ng/mL and transferrin saturation >60%.

In a recruitment period of 1 years, 60 patients from 10 Italian centers will be included in the study. DFX-FCT will be administered at the fixed dose of 3.5 mg/kg/day for the entire study year.

PRIMARY EFFICACY OBJECTIVE AND END POINT:
evaluate impact on of iron burden in one-year treatment in early phase of transfusion requirement by low dose DFX-FCT acting as prevention of iron accumulation as demonstrated by hepatic iron concentration determined by liver MRI (end of study versus baseline).

SECONDARY OBJECTIVES AND ENDPOINTS:
1. Definition of iron overload and oxidative stress in MDS at beginning of transfusion history
2. Demonstrating presence and quantitative changes of toxic serum iron forms and oxidative stress under low dose DFX-FCT therapy by regular NTBI, LPI and serum Malondialdehyde (MDA) monitoring.
3. Verify if regular suppression of the “free iron forms” prevent tissue iron accumulation by an absolute change in hepatic iron concentration end of study versus baseline
4. Evaluate the overall safety of low DFX-FCT dose in patients with lower risk MDS at the beginning of their transfusion history
5. Hemopoietic response

CONCLUSIONS

This prospective multicenter study has been designed to investigate the clinical benefit and safety of early chelation therapy with DFX-FCT in patients with MDS at the beginning of their transfusion history to verify the possibility to continually suppress tissue NTBI, LPI and Oxidative stress thus preventing iron accumulation and tissue damage.
Thank you for your very kind attention
Moving towards a targeted approach for patients with Myelodysplastic Syndromes

Uwe Platzbecker

This meeting is organized and sponsored by Novartis
Disclosures

Research support:

- Amgen
- Celgene Corporation
- Janssen Biotech
- Merck
- Novartis

Consultant

- Celgene
- Celgene Corporation
- Novartis
No drug will be useful for all types of MDS, but different pathways may be possible targets.


Adapted from Platzbecker U. 2019

Bcl-2, B-cell lymphoma 2; CAR, Chimeric antigen receptor; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DART, dual-affinity re-targeting antibody; DNMT, DNA methyltransferase; EPO, erythropoietin; FLT-3, FMS-like tyrosine kinase 3; HDAC, histone deacetylase; IDH1/2, isocitrate dehydrogenase; JAK, janus kinase; MDM2, murine double minute 2; NAE, NEDD8-activating enzyme; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; TGF-β-R, transforming growth factor beta receptor; TIM-3, T-cell immunoglobulin and mucin domain-3; TPO, thrombopoietin.
Classification MDS/AML: Quantitative

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.

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Classification MDS/AML: Quantitative

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

- Spliceosome
- Histone modification
- DNA methylation
- Transcription factors
- Signal transduction

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes.


This meeting is organized and sponsored by Novartis.
Classification MDS/AML: Quantitative

Implication of allelic states for treatment response

mTP53 ≠ mTP53

Hypomethylating agents

Lenalidomide

HSCT

Consideration of TP53 allelic state in correlative studies of treatment response

HMA, hypomethylating agent; HSCT, hematopoietic stem cell transplantation; TP53, tumor protein p53; WT, wild type.


Bernard E, et al. 2019

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Targeting TP53

- **Drugs having p53 independent activity:**
  - Anti-Bcl2 drug Venetoclax
  - Vosaroxin

- **Drugs competing for p53 binding to MDM2:**
  - Nutlin-3 (Roche)
  - HDM 201 (Novartis)
  - DS-3032 (Daiichi)

- 10-day regimen of Decitabine
- “Reconforming” mutated p53: APR 246

Venetoclax, vosaroxin, APR-346, nutlin-3, HDM 201 and DS-3032 are not yet licensed for MDS indications in Europe or Israel. Decitabine is not yet licensed for MDS indications in Europe. TP53, tumor protein p53; MDM2, murine double minute 2.

Information provided by the speaker.
Phase 2 study by the Groupe Francophone des Myélodysplasies (GFM)

Response in the 44 patients enrolled before June 2019

<table>
<thead>
<tr>
<th>Intention to treat</th>
<th>n=44</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of evaluation</td>
<td>Best response</td>
<td>After C3</td>
<td>After C6</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>55%</td>
<td>51%</td>
<td>51%</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>39%</td>
<td>25%</td>
<td>39%</td>
<td></td>
</tr>
<tr>
<td>mCR/MLFS</td>
<td>7%</td>
<td>12%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>0%</td>
<td>7%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>SD with HI</td>
<td>9%</td>
<td>7%</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Evaluable patients*</th>
<th>n=35</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of evaluation</td>
<td>Best response</td>
<td>After C3</td>
<td>After C6</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>66%</td>
<td>64%</td>
<td>64%</td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>49%</td>
<td>31%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>mCR/MLFS</td>
<td>9%</td>
<td>15%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>0%</td>
<td>9%</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>SD with HI</td>
<td>9%</td>
<td>9%</td>
<td>6%</td>
<td></td>
</tr>
</tbody>
</table>

3 patients underwent allogeneic SCT, one of them had started maintenance treatment post transplant

APR-346 is not yet licensed for MDS indications in Europe or Israel.
AML, acute myeloid lymphoma; AZA, azacitidine; CR, complete response; HI, hematologic improvement; mCR, marrow complete response; MDS, myelodysplastic syndrome; MLFS, morphologic leukemia-free state; ORR, overall response rate; PR, partial response; SCT, stem cell transplant; SD, stable disease; TP53, tumor protein p53.
IDH-Mutations

AML, acute myeloid leukemia; IDH, isocitrate dehydrogenase; MDS, myelodysplastic syndromes.
Enasidenib - IDH2 inhibitor

Evolution of response during Enasidenib treatment or responding
AML patients (n=71)

Enasidenib is not yet licensed for MDS indications in Europe or Israel.
AML, acute myeloid leukemia; CR, complete response; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; IDH, isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; PD, progressive disease; PR, partial response; SD, stable disease.

Adapted from Stein EM, et al. 2017
Screening

Cohort A
HR MDS relapsed / refractory after at least 6 cycles of AZA
n = 29

Cohort B
Untreated HR MDS without life threatening cytopenias
n = 29

Cohort C
LR MDS with anemia resistant to ESAs
n = 10

AZA, azacitidine; ESA, erythropoietin stimulating agent; HR, high risk; LR, low risk; MDS, myelodysplastic syndromes.

Information provided by the speaker.
Phase 2: Enasidenib + AZA in mIDH2-positive newly diagnosed AML

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>ENA + AZA (n=68)</th>
<th>AZA (n=33)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, n (%)</td>
<td>48 (71)</td>
<td>14 (42)</td>
<td>0.0064</td>
</tr>
<tr>
<td>CR</td>
<td>36 (53)</td>
<td>4 (12)</td>
<td>0.0001</td>
</tr>
<tr>
<td>CRi/CRp</td>
<td>7 (10)</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>PR</td>
<td>3 (4)</td>
<td>4 (12)</td>
<td></td>
</tr>
<tr>
<td>MLFS</td>
<td>2 (3)</td>
<td>2 (6)</td>
<td></td>
</tr>
<tr>
<td>Median time to first response, months (range)</td>
<td>1.9 (1–9)</td>
<td>2.0 (1–6)</td>
<td></td>
</tr>
<tr>
<td>Median DOR, months (95% CI)</td>
<td>24.1 (11–NR)</td>
<td>12.1 (3–15)</td>
<td></td>
</tr>
</tbody>
</table>

Median OS in the ENA + AZA group was 22.0 months, and in the AZA Only group was 22.3 months

- (HR 0.99 [95% CI: 0.52–1.87], P=0.9686)

Enasidenib is not yet licensed for MDS indications in Europe or Israel.

AML, acute myeloid leukemia; AZA, azacitidine; CI, confidence interval; CR, complete response; CRi, CR with incomplete hematologic recovery; CRp, CR with incomplete platelet recovery; DOR, duration of response; ENA, enasidenib; mIDH, mutant isocitrate dehydrogenase; MLFS, morphologic leukemia-free state; NR, not reached; ORR, overall response rate; OS, overall survival; PR, partial response.

Molecular targets

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

- **SF3B1**
- **SRSF2**

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2.

Information provided by the speaker.

This meeting is organized and sponsored by Novartis.
"Spliceosomal sickness"

**SF3B1-SRSF2-U2AF1**

- **WT/WT**  →  **Normal**
- **MUT/WT**  →  **Malignancies**
- **-/-**  →  **Hematopoietic Failure and Cell Death**
- **MUT/Inhibitor**  →  **Selective Cell Death**

MUT, mutant; WT, wild type; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2; U2AF1, U2 small nuclear RNA auxiliary factor 1. Seiler M, et al. *Nat Med.* 2018;24:497–504.
“Spliceosomal sickness”

SF3B1-SRSF2-U2AF1

<table>
<thead>
<tr>
<th>genotype</th>
<th>phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT/WT</td>
<td>Normal</td>
</tr>
<tr>
<td>MUT/WT</td>
<td>Malignancies</td>
</tr>
<tr>
<td>+/-</td>
<td>Hematopoietic Failure and Cell Death</td>
</tr>
<tr>
<td>MUT/Inhibitor</td>
<td>Selective Cell Death</td>
</tr>
</tbody>
</table>

H3B-8800 is not yet licensed for MDS indications in Europe or Israel.
MUT, mutant; WT, wild type; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2; U2AF1, U2 small nuclear RNA auxiliary factor 1. Seiler M, et al. Nat Med. 2018;24:497–504.

Based on Seiler M, et al. 2018

This meeting is organized and sponsored by Novartis.
Results of a clinical trial of H3B-8800, a splicing modulator, in patients with MDS, AML or CMML

Open-label, first-in-human, Phase I, dose escalation (3 + 3) study (NCT02841540)

<table>
<thead>
<tr>
<th>Outcome measure, n (%)</th>
<th>N=84</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response*</td>
<td>0</td>
</tr>
<tr>
<td>Partial response*</td>
<td>0</td>
</tr>
<tr>
<td>Bone marrow response</td>
<td>1(^\dagger) (1.2)</td>
</tr>
<tr>
<td>RBC transfusion dependence* at baseline</td>
<td>n=61</td>
</tr>
<tr>
<td>RBC transfusion independence ≥8 weeks</td>
<td>13(^\dagger) (21.3)</td>
</tr>
<tr>
<td>RBC transfusion independence ≥8 weeks</td>
<td>13(^\dagger) (21.3)</td>
</tr>
</tbody>
</table>

H3B-8800 is not yet licensed for MDS indications in Europe or Israel.

*International Working Group criteria; \(^\dagger\)One patient with CMML. Began in Cycle 1 and persisted through Cycle 13; \(^\dagger\)Ten patients with MDS/CMML and 3 patients with AML. Up to 28 weeks.

AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes.


This meeting is organized and sponsored by Novartis
Inhibition of Type 1 PRMTs and/or PRMT5

AML, acute myeloid leukemia; EXH2, enhancer of zeste homolog 2; PRMT, protein arginine N-methyltransferase; SF3B1, splicing factor 3b subunit 1; SRSF2, serine and arginine rich splicing factor 2 WT, wild type.


Synergistic and preferential killing of SF-mutant AML cells which depend on WT SF-activity and SF-driven aberrant splicing (e.g. EXH2 alternative splicing)

Adapted from Fong JY, et al. 2019

This meeting is organized and sponsored by Novartis
Spliceosome gene mutations found in MDS patients enhance inflammatory signalling in macrophages

IL-6-luc, interleukin-6 luciferase reporter construct; MDS, myelodysplastic syndrome; NFκb-luc, NFκB-dependent luciferase reporter construct; SF3B1, splicing factor 3b subunit 1; WT, wild type.


Adapted from Pollyea DA, et al. 2019
"Spliceosomal inflammation"


IRAK, interleukin-1 receptor-associated kinase 4; MAPK, mitogen-activated protein kinase; TLR/IL1R, toll-like receptor/interleukin-1 receptor; U2AF1, U2 small nuclear RNA auxiliary factor 1.

This meeting is organized and sponsored by Novartis.
Canakinumab, rilonacept and bortezomib are not yet licensed for MDS indications in Europe or Israel. Sallman DA, et al. Clin Lymphoma Myeloma Leuk. 2017;17:613–620. ASC, associated speck-like protein containing a caspase-recruitment domain; DAMPs, damage-associated molecular patterns; IL, interleukin; IRAKs, IL-1 receptor-associated kinases; Inh, inhibitor; neut., neutrophil; NOX, dihydrorhodamine-2-de-adenine dinucleotide phosphate oxidase; TGF-b, transforming growth factor-b; TLR, Toll-like receptor; TRAF6, tumor necrosis factor receptor-associated factor 6.
Inflammation driving ineffective hematopoiesis

Myeloid-derived suppressor cells

Images provided by speaker.
BFU-E, burst-forming unit-erythroid; CFU-GM, colony-forming unit–granulocyte-macrophage; HLA, human leukocyte antigen; MDS, myelodysplastic syndromes; MDSC, myeloid-derived suppressor cells.

Images from: Chen X, et al. 2013

This meeting is organized and sponsored by Novartis
Targeting the “Inflammasome”

The osteo-hematopoietic niche in MDS

HSPC, hematopoietic stem and progenitor cells; MDS, myelodysplastic syndrome; MSC, mesenchymal stem cell.


Adapted from Bulycheva E, et al. 2015
Transcriptional network analysis of mesenchymal elements in low-risk MDS

- Common, distinct molecular signature separating these cells molecularly from non-diseased stroma
- Activation of inflammatory programs
- Tissue-context dependent (lost in culture)

PCA on the transcriptomes of normal and LR-MDS mesenchymal cells

Example of GSEA plot revealing inflammatory response in the mesenchymal cells from LR-MDS


LR-MDS, low-risk myelodysplastic syndromes; FDR, false discovery rate; GSEA, gene set enrichment analysis; NES, normalized enrichment score; PCA, principal component analysis.

S100A8/S100A9 is induced during inflammatory processes including MDS

MDS, myelodysplastic syndromes.

Adapted from Schneider RK, et al. 2016

This meeting is organized and sponsored by Novartis
Targeting the “Inflammasome”

Immune checkpoint in MDS

Immunohistochemical analysis of PDL-1 and PD-1 membranous expression in CD34+ cell biopsy samples from MDS, CMML and AML patients

Bone marrow PD-L1
blast + blast -

Bone marrow PD-1
blast + blast -, stroma +

Cytospin PD-L1
blast + blast -

Cytospin PD-1
blast + partial blast -


AML, acute myeloid leukemia; CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; PD-1, programmed cell death protein 1; PDL, programmed cell death ligand.

Checkpoint modulation in HMA failure

Phase II trial of vorinostat + azacitidine

- A trend toward increased expression of PDL-1 and PD-1 in HMA resistant patients compared with HMA sensitive patients

**Induction of PD-L1 and PD-1 expression in patients treated with vorinostat + azacitidine (NCT00948064)**

Vorinostat is not yet licensed for MDS indications in Europe or Israel.

C, course; D, days on therapy; HMA, hypomethylating agent; PD-1, programmed cell death protein 1; PDL, programmed cell death ligand 1.


Adapted from Yang H, et al. 2014
Nivolumab or ipilimumab in combination with azacitidine

<table>
<thead>
<tr>
<th>Response</th>
<th>Frontline</th>
<th>HMA failure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nivo + AZA</td>
<td>Ipi + AZA</td>
</tr>
<tr>
<td></td>
<td>N=20</td>
<td>N=21</td>
</tr>
<tr>
<td>ORR</td>
<td>14 (70)</td>
<td>13 (62)</td>
</tr>
<tr>
<td>CR</td>
<td>8 (40)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>mCR + HI</td>
<td>2 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>mCR</td>
<td>3 (15)</td>
<td>7 (33)</td>
</tr>
<tr>
<td>HI</td>
<td>1 (5)</td>
<td>3 (14)</td>
</tr>
<tr>
<td>SD</td>
<td>0 (0)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>NR</td>
<td>5 (25)</td>
<td>5 (24)</td>
</tr>
</tbody>
</table>

Nivolumab and ipilimumab are not yet licensed for MDS indications in Europe or Israel.
AZA, azacitidine; CR, complete response; HI, hematologic improvement; HMA, hypomethylating agent; Ipi, ipilimumab; mCR, marrow complete response; Nivo, nivolumab; NR, no response; ORR, overall response rate; SD, stable disease.
Garcia-Manero et al. 2018
This meeting is organized and sponsored by Novartis.

Pembrolizumab in sAML molecular course

ASXL1, additional sex combs like 1; EB-1, excess blasts-1; IDH, isocitrate dehydrogenase; RUNX1, runt-related transcription factor 1; sAML, secondary acute myeloid leukemia; STAG2, stromal antigen 2.

TIM-3 role in immune response against cancer

Upon interaction with their ligands TIM-3 acts as a co-inhibitory receptor inhibiting the activity of different immune cell subtypes:¹,²

- Activated IFN-γ-producing T-cells
- FoxP3+ Treg cells
- Macrophages
- Dendritic cells

TIM-3 is expressed by leukemic stem cells²–⁴

- TIM-3 expression is seen to correlate with the severity of MDS and progression to AML
- TIM 3 activation is involved in LSC self renewal and activation, as well as immune escape in AML

AML, acute myeloid leukemia; IFN, interferon; LSC, leukemic stem cell; MDS, myelodysplastic syndromes; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3; Treg, regulatory T-cells.
MBG453 + decitabine in Phase Ib study for patients with HR-MDS and AML

MBG453 is not yet licensed for MDS indications in Europe or Israel. Decitabine is not yet licensed for MDS indications in Europe.

AML, acute myeloid leukemia; HR-MDS, high-risk myelodysplastic syndromes; TIM-3, T cell immunoglobulin and mucin domain-containing protein 3.

MBG453 + decitabine exhibits promising efficacy, with responses occurring at a median of 2.1 months

<table>
<thead>
<tr>
<th>Evaluative patients, n</th>
<th>HR-MDS (n=19)</th>
<th>Newly diagnosed unfit AML (n=22)</th>
<th>R/R AML (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>5 (26.3)</td>
<td>3 (17.6)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>mCR</td>
<td>4 (21.1)</td>
<td>2 (11.8)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>with HI</td>
<td>3 (15.8)</td>
<td>2 (11.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>SD</td>
<td>9 (47.4)</td>
<td>8 (47.1)</td>
<td>13 (52.0)</td>
</tr>
<tr>
<td>with HI</td>
<td>2 (10.5)</td>
<td>2 (11.8)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>PD</td>
<td>1 (5.3)</td>
<td>2 (11.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>0 (0.0)</td>
<td>3 (12.0)</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>ORR (CR, mCR, HI), n (%)</td>
<td>11 (57.9)</td>
<td>7 (41.2)</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[33.5–79.7]</td>
<td>[18.4–67.1]</td>
<td>[9.4–45.1]</td>
</tr>
</tbody>
</table>

*Patients who are ongoing with "No response" as best overall response as of data cut-off date.

MBG453 is not yet licensed for MDS indications in Europe or Israel. Decitabine is not yet licensed for MDS indications in Europe.

CR, complete response; CRi, AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRi, morphologic complete remission with incomplete blood count recovery; HI, hematologic improvement; HR-MDS, high-risk myelodysplastic syndromes; mCR, marrow complete response; ORR, overall response rate; PD, progressive disease; SD, stable disease; TF, treatment failure.

Thank you for your very kind attention
Paving the way for novel therapeutic opportunities in MDS treatment

Panel discussion
How do you see the future of MDS treatment?
Which emerging therapies could have the biggest impact?
How can mutation profiling benefit diagnosis and prognosis determination?
What is the role for combination strategies in MDS?
Are you optimistic that emerging treatments will provide a better future for patients with MDS?

Please raise your hand for YES
From The Tel Aviv Sourasky Medical Center

Images provided by the speaker.

This meeting is organized and sponsored by Novartis