Novel agents and combinations for the treatment of MDS

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Université Paris 7
GFM

MDS Foundation ASH 2013 symposium
DISCLOSURES

• I have the following financial relationships:
  Contracted Research for: Celgene, Janssen, Novartis, Roche
Novel agents and combinations for the treatment of MDS

- current issues in the treatment of MDS
- Maximizing the use of available drugs in MDS
- New drugs in MDS
Novel agents and combinations for the treatment of MDS

• current issues in the treatment of MDS

• Optimizing the use of available drugs in MDS

• New drugs in MDS
Current issues in the treatment of MDS

• Higher risk MDS (IPSS high and int 2)
  – Hypomethylating agents (HMA) only moderately improve survival
  – Prognosis after HMA failure is very poor
  – Patients with complex karyotype have a very poor outcome irrespective of treatment (including allogeneic stem cell transplantation)
AZA 001 trial: Overall Survival:
Azacitidine vs CCR  (Lancet Oncol, 2009)

Log-Rank  \( p=0.0001 \)
HR = 0.58 [95% CI: 0.43, 0.77]

Proportion Surviving

Time (months) from Randomization
Outcome of High-Risk Myelodysplastic Syndrome After Azacitidine Treatment Failure

Thomas Prébet, Steven D. Gore, Benjamin Esterni, Claude Gardin, Raphael Itzykson, Sylvain Thepot,

Prébet et al

<table>
<thead>
<tr>
<th>Type of salvage</th>
<th>N</th>
<th>ORR</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unknown</td>
<td>165</td>
<td>NA</td>
<td>3.6</td>
</tr>
<tr>
<td>Best supportive care</td>
<td>122</td>
<td>NA</td>
<td>4.1</td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
<td>32</td>
<td>0/18</td>
<td>7.3</td>
</tr>
<tr>
<td>Intensive chemotherapy</td>
<td>35</td>
<td>3/22</td>
<td>8.9*</td>
</tr>
<tr>
<td>Investigational therapy</td>
<td>44</td>
<td>4/36</td>
<td>13.2*†</td>
</tr>
<tr>
<td>Allogeneic transplantation</td>
<td>37</td>
<td>13/19</td>
<td>19.5**</td>
</tr>
</tbody>
</table>

Overall Survival (%) vs Time Since AZA Failure (days)
Survival by 5-group cytogenetic classification.

Impact of Cytogenetics on Outcome in MDS treated With Azacitidine. A Collaborative Study in 878 Patients
M Sébert, ASH 2013, abst n° 389


Patients with complex karyotype respond poorly to HMA and allo SCT
Main issues in the treatment of MDS

- **Lower risk MDS (IPSS low and int 1)**
  - Some lower risk MDS have in fact relatively poor prognosis (especially with IPSS-R and/or presence of genes mutations)

- **Anemia**
  - *non del 5 patients*:
    - respond to erythropoietic stimulating agents (ESA) in only 50% of the cases
    - for a median of 2 years
  - *Del 5q patients*:
    - 65% responses to Lenalidomide (LEN)
    - median response duration to LEN 2.2 years

- **Thrombocytopenia**
  - TPO receptor agonists in clinical trials
Mutation frequency : 10/55 pts
(18%)
Novel agents and combinations for the treatment of MDS

• current issues in the treatment of MDS

• Optimizing the use of available drugs in MDS

• New drugs in MDS
Optimizing the use of available treatments in MDS

• Hypomethylating agents

• Lenalidomide

• *Combined to other available drugs*:
  
  – *ESA*
  
  – *Chemotherapy (anthracyclines, AraC)*

  – *Iron chelating drugs (deferasirox)*
Optimizing the use of available treatments in MDS

- Hypomethylating agents
- Lenalidomide
- Combined to other available drugs:
  - *ESA*
  - *Chemotherapy* (*anthracyclines, AraC*)
  - *Iron chelating drugs* (*deferasirox*)
36 patients (18 phase 1, 18 phase 2)

**ORR 72%: 16 (44%) CR, and 10 (28%) HI**.

- Median CR duration 17+ months
- median OS 37+ months in CR patients, and 13.6 months for the entire cohort.
Combinations of hypomethylating agents and other drugs

- **AZA+ Idarubicin** (L Adès, ASH 2012)
  35% CR+PR

- **Intensive AZA (5 d/2 w)** (L Adès, ASH 2013 n° 1513)
  70% responses

- **AZA+ deferasirox** (O Hermine, ongoing)
« Pick a winner approach » with AZA: randomized phase II trial

- 5 AZACYTIDINE 75 mg/m² x 7 jours
- VALPROIC ACID
- 5 AZACYTIDINE 75 mg/m² x 7 jours
- IDARUBICIN
- 5 AZACYTIDINE 75 mg/m² x 7 jours
- LENALIDOMIDE
- 5 AZACYTIDINE 75 mg/m² x 7 jours

Raffoux et al. '08
Sekeres et al. '07
Optimizing the use of available treatments in MDS

- Hypomethylating agents

- **Lenalidomide**

- Combined to other available drugs:
  - ESA
  - Chemotherapy (anthracyclines, AraC)
  - Iron chelating drugs (desferroxamine, deferasirox)
Optimizing LEN use in lower risk MDS with del 5q?

Joint analysis MDS 003 and MDS 004 trials
Sekeres, ASH 2013, abstract n° 390

Figure 2: Red Blood Cell Transfusion Independence Response for Subjects in MDS-003 and the Double-blind Phase of MDS-004 (ITT Populations)
## MDS-004: cytogenetic response

(Blood, 2011)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 51)</th>
<th>LEN 5 mg (n = 46)</th>
<th>LEN 10 mg (n = 41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytogenetic response, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>0</td>
<td>10.9*</td>
<td>24.4**</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>0</td>
<td>6.5</td>
<td>17.1</td>
</tr>
<tr>
<td>CR + PR</td>
<td>0</td>
<td>17.4</td>
<td>41.5</td>
</tr>
</tbody>
</table>

## MDS 003: Cytogenetic response

(List, NEJM 2006)

<table>
<thead>
<tr>
<th>Response</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>45%</td>
</tr>
<tr>
<td>PR</td>
<td>28%</td>
</tr>
<tr>
<td>CR+PR</td>
<td>73%</td>
</tr>
</tbody>
</table>
Figure 5. Duration of RBC-TI (≥ 26 weeks) by CyR (MDS-003 and MDS-004)
MDS-003/004: progression to AML and CyR

- Achievement of CyR associated with significantly reduced risk of AML
MDS-003/004: Overall survival and CyR

- Achievement of CyR associated with significantly increased OS
Avoid decreasing too much the dose of LEN in lower risk MDS with del 5q?

- Neutropenia and thrombocytopenia are the dose limiting factors, especially during first 8-12 weeks
  - During first 8-12 weeks, if profound cytopenias, use:
    - G-CSF for ANC
    - TPO receptor agonists for platelets
- Later on, try to reincrease the dose...
Treatment of lower risk MDS with del 5q failing LEN?

Azacitidine Treatment for LEN-Resistant MDS with Del 5q
R Komrokji, C Bally, ASH 2012

- 36 del(5q) MDS patients treated with AZA after LEN failure
- 50% response
- Median duration of response 12 months
- Median OS was 22 months
Molecular risk-guided treatment comparing LEN versus LEN+ AZA in LEN-naive del(5q) MDS with TP53 mutation

**AVATAR – STUDY**

By GFM and GMDS-SG

L. Adès and U. Platzbecker
Using LEN in Higher risk MDS with del 5q?

- Higher risk MDS with del 5q
  - Karyotype generally very complex
  - Very poor response to intensive chemotherapy and HMA alone
Lenalidomide in higher risk MDS and AML with del 5q : phase I-II trial (Adès, Blood, 2009)

- LEN 10mg/d 21 days/ month
- 43 patients evaluable after at least one cycle

<table>
<thead>
<tr>
<th>Cytogenetics</th>
<th>n</th>
<th>CR</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>isolated del 5q</td>
<td>9</td>
<td>6</td>
<td>67%</td>
</tr>
<tr>
<td>Single additional abn</td>
<td>11</td>
<td>1</td>
<td>9%</td>
</tr>
<tr>
<td>&gt;1</td>
<td>27</td>
<td>0</td>
<td>0%</td>
</tr>
</tbody>
</table>
Treatment of higher risk MDS with complex karyotypes including del 5q (L Adès)

- Patients « fit » for intensive chemotherapy: DNR+ AraC+ LEN (ASH 2013, abst n° 620)

- Patients « unfit » for intensive chemotherapy: AZA+ LEN (ASH 2013, abst n° 2750)
Phase II chemotherapy + LEN in higher risk MDS and AML with del 5q  L. Ades et al., ASH 2011, # 508

- n=63, median age 67
  - RAEB 2 (n=15), AML (n=48)
  - del 5q31 (complex in 81%)

- Treatment

<table>
<thead>
<tr>
<th>Induction</th>
<th>Consolidations (x6)</th>
<th>Maintenace</th>
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</thead>
<tbody>
<tr>
<td>1ère cohort</td>
<td>- DNR 45 mg/m² x3</td>
<td>- DNR 45 mg/m² x1</td>
</tr>
<tr>
<td></td>
<td>- ARAC 200 mg/m²x7</td>
<td>- ARAC 60 mg/m²x 10</td>
</tr>
<tr>
<td></td>
<td>- Lénalidomide 10 mg x 21</td>
<td>- Lénalidomide 10 mg x 14</td>
</tr>
<tr>
<td>2ème cohort</td>
<td>- DNR 60 mg/m² x3</td>
<td>- DNR 60 mg/m² x1</td>
</tr>
<tr>
<td></td>
<td>- ARAC 200 mg/m²x7</td>
<td>- ARAC 60 mg/m²x 10</td>
</tr>
<tr>
<td></td>
<td>- Lénalidomide 10 mg x 21</td>
<td>- Lénalidomide 10 mg x 14</td>
</tr>
</tbody>
</table>
Phase II chemotherapy + LEN in higher risk MDS and AML with del 5q L. Ades et al., ASH 2011, # 508

- **Toxicity**
  - Median duration of cytopenias: 23d

- **Overall response:** 63%
  - CR: 49%  PR: 10%  marrow CR: 5%

- **DFS:** median 9 months

- **OS:** median 8 months (13 months in responder)
Can LEN be used in anemia of lower risk MDS without del 5q?

<table>
<thead>
<tr>
<th>Feature</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response, n (%)</td>
<td>Total</td>
</tr>
<tr>
<td>major</td>
<td>58 (27%)</td>
</tr>
<tr>
<td>Minor (&gt; 50% ↓)</td>
<td>36 (17%)</td>
</tr>
<tr>
<td>major + minor</td>
<td>94 (44%)</td>
</tr>
</tbody>
</table>

Raza (Blood, 2008)
Duration of transfusion independence

Proportion transfusion free

Del 5q

Non del 5q

Time (weeks)

Ongoing

Discontinued
**INCLUSION CRITERIA**

- Lower risk MDS
  Low and Int-1 IPSS
- Without del 5q
- Transfusion dependency
  \( \geq 4 \text{ RBC units during 8 wks before randomization} \)
- ESA failure
  \( \geq 12 \text{ consecutive wks} \)
  \( \geq 60,000 \text{ UI or 250µg /w} \)
  or relapse after response

**RANDOMIZATION**

- Arm LEN
  LEN 10 mg/d x 21d every 28 days
  x 4 cycles of 28 days

- Arm LEN + EPO
  LEN 10 mg/d x 21days every 28 days
  + EPO beta 60,000 U/Week

**RESPONDERS (IWG 2006)**

- LEN 10 mg/day x 21days every 28 days
  Until relapse

- LEN 10 mg/day x 21days every 28 days
  + EPO beta 60,000 U/Week

**Evaluation after the 4th cycle**

A Toma et al, ASCO 2013
IWG 2006 Erythroid response (primary endpoint)
(ITT population, n=129)

<table>
<thead>
<tr>
<th>Erythroid response (IWG 2006)</th>
<th>LEN + EPO N = 65</th>
<th>LEN N = 64</th>
<th>RR1.7 p= 0.043</th>
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<tbody>
<tr>
<td></td>
<td>40 %</td>
<td>23.4 %</td>
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</table>
# Erythroid response

(patients who received >= 4 cycles n= 99)

<table>
<thead>
<tr>
<th></th>
<th>LEN + EPO N = 50</th>
<th>LEN N = 49</th>
<th>RR = 1.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythroid response (IWG 2006)</td>
<td>52%</td>
<td>30.6%</td>
<td>p= 0.03</td>
</tr>
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</table>

Presented by: Andréa Toma, MD PhD - APHP - France
Novel agents and combinations for the treatment of MDS

- current issues in the treatment of MDS
- Optimizing the use of available drugs in MDS
- New drugs in MDS
New drugs in MDS

• HDAC inhibitors

• Chemotherapy
  – Clofarabine
  – Sapacitabine

• Immunotherapy

• Signal transduction inhibitors

• TPO agonist receptors
  – Romiplostin
  – Eltrombopag
New drugs in MDS

• HDAC inhibitors

• Chemotherapy
  – Clofarabine
  – Sapacitabine

• Immunotherapy

• Signal transduction inhibitors

• TPO agonist receptors
  – Romiplostin
  – Eltrombopag
Decitabine With or Without Valproic Acid in Patients With MDS and AML

Eligibility criteria:
- MDS by FAB of any age
- AML age > 60
- No good-risk AML
- No prior high-dose chemotherapy
- No prior decitabine > 1 cycle or azacitidine > 2 cycles

Decitabine 20 mg/m² IV/1 h daily days 1-5 q 4 weeks

Valproic acid 50 mg/kg/day p.o. days 1-7 q 4 weeks
Phase II randomized trial AZA ± Entinostat

Response (IWG 2000)

<table>
<thead>
<tr>
<th></th>
<th>AZA alone</th>
<th>AZA + Entinostat</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>RP</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>HI (3 lines)</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>HI (1 o 2 lines)</td>
<td>12%</td>
<td>19%</td>
</tr>
<tr>
<td>No Response</td>
<td>57%</td>
<td>56%</td>
</tr>
</tbody>
</table>

Overall survival

- **p=0.15**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total</th>
<th>Died</th>
<th>Censored</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine</td>
<td>68</td>
<td>40</td>
<td>28</td>
<td>17.7</td>
</tr>
<tr>
<td>Azacitidine+Entinostat</td>
<td>68</td>
<td>47</td>
<td>21</td>
<td>12.8</td>
</tr>
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</table>
A Phase I/II study of vorinostat in combination with 5-azacitidine in patients with MDS

(Silverman L, updated in ASH 2013 abst n° 386)

5-azacitidine

Vorinostat – cohorts 1-4

Vorinostat – cohorts 5-7

Vorinostat – cohort 8

0  7  14  21  28
Day

### Azacitidine and Vorinostat in MDS / AML – NYCC 6898
( updated in ASH 2013 abst n° 386)

#### Response

<table>
<thead>
<tr>
<th>Description</th>
<th>Count</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>Enrolled</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Evaluable for response</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Overall Response*</td>
<td>18</td>
<td>(82%)†</td>
</tr>
<tr>
<td>CR</td>
<td>9</td>
<td>(41%)</td>
</tr>
<tr>
<td>CRI</td>
<td>3</td>
<td>(14%)</td>
</tr>
<tr>
<td>CR+CRi</td>
<td>12</td>
<td>(55%)</td>
</tr>
<tr>
<td>PR</td>
<td>5</td>
<td>(05%)</td>
</tr>
<tr>
<td>HI</td>
<td>5</td>
<td>(23%)</td>
</tr>
<tr>
<td>Stable</td>
<td>2</td>
<td>(09%)</td>
</tr>
<tr>
<td>NR</td>
<td>2</td>
<td>(09%)</td>
</tr>
<tr>
<td>Transfusion Independence (n = 13)</td>
<td>11</td>
<td>(84%)</td>
</tr>
</tbody>
</table>
New drugs in MDS

• HDAC inhibitors

• Chemotherapy
  – Clofarabine
  – Sapacitabine

• Immunotherapy

• Signal transduction inhibitors

• TPO agonist receptors
  – Romiplostin
  – Eltrombopag
A Randomized Study of 2 Dose Levels of Intravenous Clofarabine in the Treatment of Patients With Higher-Risk Myelodysplastic Syndrome

Stefan Faderl, MD¹; Guillermo Garcia-Manero, MD¹; Elias Jabbour, MD¹; Farhad Ravandi, MD¹; Gautam Borthakur, MD¹; Zeev Estrov, MD¹; Varsha Gandhi, PhD²; Anna L. Byrd, RN¹; Monica Kwari, RN¹; Jorge Cortes, MD¹; and Hagop M. Kantarjian, MD¹

- 15 mg/m2 vs 30 mg/m2 x 5 days of IV clofarabine
- 58 patients including (60%) who received prior DNMT inhibitors
- **ORR 36% (41% at 15 mg/m2 and 29% at 30 mg/m2) including 26% CR**
- Median survival 7.4 months for all patients, 13.4 months for responders, and 21.7 months for CR.

Cancer, 2012
Phase I study of very low dose clofarabine in MDS resistant to AZA (T Braun, ASCO 2102)

- Three escalating dosing levels
  - 5, 7.5, 10 mg/m² daily X 5

- Two parallel cohorts
  - standard D1 to 5 (cohort A)
  - alternate D1, 3, 5, 8 and 10 (cohort B)

- 26% ORR rate
Oral sapacitabine for the treatment of acute myeloid leukaemia in elderly patients: a randomised phase 2 study

Hagop Kantarjian, Stefan Faderl, Guillermo Garcia-Manero, Selina Luger, Parameswaran Venugopal, Lori Maness, Meir Wetzler, Steven Coutre, Wendy Stock, David Claxton, Stuart L Goldberg, Martha Arellano, Stephen A Strickland, Karen Seiter, Gary Schiller, Elias Jabbour, Judy Chiao, William Plunkett


- 200 mg /12h for 7 days (group A); 300 mg /12h for 7 days (group B); and 400 mg /12h for 3 days each week for 2 weeks (group C)
- 105 AML patients aged >70 years: 86 patients previously untreated and 19 at first relapse
- Myelosuppression important
- 1-year OS 35% in group A, 10% in group B, and 30% in group C
- The 400 mg dose schedule had the best efficacy profile
New drugs in MDS

• HDAC inhibitors

• Chemotherapy
  – Clofarabine
  – Sapacitabine

• Immunotherapy

• Signal transduction inhibitors

• TPO agonist receptors
  – Romiplostin
  – Eltrombopag
Alemtuzumab in lower risk MDS (Sloand, JCO, 2010)

- IPSS int-1 et int-2 and predictive factors of response to immunosuppression
- Alemtuzumab: 1mg IV test, then 10 mg IV/d x 10 d
- 24 patients evaluable; 20 (83%) responses,
- Cytogenetic response in 5 of 7 patients with anomalies, including monosomy 7

ASH 2013: Abstract n° 593 Alemtuzumab Is Safe and Associated With High Response Rates In Selected Patients With MDS

Vishal N. Ranpura, MD

- N=40
- ORR was 64% with 21% CR
Hydroxyurea, azacitidine and gemtuzumab ozogamicin therapy in patients with previously untreated non-M3 acute myeloid leukemia and high-risk myelodysplastic syndromes in the elderly: results from a pilot trial

SUCHA NAND¹, JOHN GODWIN¹, SCOTT SMITH¹, KEVIN BARTON¹, LAURA MICHAELIS¹, SERHAN ALKAN², RANJITHA VEERAPPAN², KAREN RYCHLIK³, ELIZA GERMANO⁴, & PATRICK STIFF¹

- N= 20 received HU followed by AZA 75 mg/m2 for 7 days and Gentuzumab ozogamycin (GO) 3 mg/m2 on day 8
- 14(70%) achieved CR
- median duration of remission 8 months, median survival 10 months

Decitabine combined with fractionated gemtuzumab ozogamicin therapy in patients with relapsed or refractory acute myeloid leukemia

Saeeda Chowdhury, Stuart Seropian and Peter W. Marks*

- 12 AML, median of three prior regimens
- Decitabine 20 mg/m2x5
- GO 5mg/m2 on days 6, 9, and 12

5 patients achieved a complete response (42%)

Am J Hemat, 2009
A phase II trial of azacitidine and gemtuzumab ozogamicin therapy in older patients with acute myeloid leukemia

Sucha Nand, Megan Othus, John E. Godwin, Cheryl L. Willman, Thomas H. Norwood, Dianna S. Howard, Steven E. Coutre, Harry P. Erba and Frederick R. Appelbaum

- azacitidine, 75 mg/m² x 7 and GO 3 mg/m² on day 8
- 88 Good Risk: 44% CR.
- 59 Poor Risk: 35% CR.

Gemtuzumab ozogamicin in combination with vorinostat and azacitidine in older patients with relapsed or refractory acute myeloid leukemia: a phase 1/2 study

by Roland B. Walter, Bruno C. Medeiros, Kelda M. Gardner, Kaysey F. Orłowski, Leonel Gallegos, Bart L. Scott, Paul C. Hendrie, and Elihu H. Estey

Haematologica 2013 [Epub ahead of print]

Vorinostat (400 mg/ days 1-9), AZA (75 mg/m²/d x7), GO (3 mg/m² on days 4 and 8)

43 patients, 10 achieved CR and 8 CRi (overall response rate of 41.9%)
A Novel CD16xCD33 Bispecific Killer Cell Engager (BiKE) Mediates a Double Hit For NK Cells To Target CD33+ MDS Cells and Myeloid Derived Suppressor Cells (MDSCs) At All Disease Stages

Michelle K. Gleason, PhD
New drugs in MDS

• HDAC inhibitors

• Chemotherapy
  – Clofarabine
  – Sapacitabine

• Immunotherapy

• Signal transduction inhibitors

• TPO agonist receptors
  – Romiplostin
  – Eltrombopag
<table>
<thead>
<tr>
<th>Family</th>
<th>Molecule</th>
<th>Trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>P38 MAP kinase inhibitors</td>
<td>SCIO-469, ARRY- 614</td>
<td>NCT00113893</td>
</tr>
<tr>
<td>Activin and TGF-β receptor ligand trap</td>
<td>ACE- 011 &amp; ACE 536</td>
<td>NCT 01736683</td>
</tr>
<tr>
<td>Multikinase Inhibitor (Plk/Akt/PI3)</td>
<td>Onconova-01910</td>
<td>NCT00906334</td>
</tr>
<tr>
<td>P13K/mTOR inhibitors</td>
<td>Deferolimus, Temsirolimus, Everolimus,</td>
<td>NCT00819546 NCT00086125</td>
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<tr>
<td>P13K/AKT Inhibitors</td>
<td>Perifosine</td>
<td>NCT00301938</td>
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<tr>
<td>EGF Receptor Inhibitor</td>
<td>Erlotinib</td>
<td>NCT01085838 NCT00977548</td>
</tr>
<tr>
<td>GSTPI-1 inhibitor</td>
<td>Ezatiostat</td>
<td>NCT00700206 NCT01422486 NCT01459159</td>
</tr>
<tr>
<td>Farnesyl Transferase Inhibitors</td>
<td>Tipifarnib, Lonafarnib</td>
<td>NCT00005845 NCT00045396 NCT00050154 NCT00034684 NCT00005967</td>
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<tr>
<td>Mek Inhibitor</td>
<td>GSK1120212</td>
<td>NCT00920140</td>
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</tbody>
</table>
Treatment of higher risk myelodysplastic syndrome patients unresponsive to hypomethylating agents with ON 01910.Na

Mahesh Seetharam¹, Alice C. Fan², Mai Tran², Liwen Xu³, John P. Renschler³, Dean W. Felsher³, Kunju Sridhar⁴, Francois Wilhelm⁵, Peter L. Greenberg⁶
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² Department of Medicine (Oncology), Stanford University Cancer Center, Stanford, CA, USA
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Phase I clinical trial of oral rigosertib in patients with myelodysplastic syndromes

Summary

The multi-kinase inhibitor rigosertib (ON 01910.Na) induces mitotic arrest and apoptosis in myeloblasts, while sparing normal cells. The purpose of this study was to determine the pharmacokinetic profile, maximum tolerated dose, and clinical activity of rigosertib in patients with myelodysplastic syndromes.

- Ongoing phase III trial vs BSC or LD araC in higher risk MDS having failed HMA
- Preliminary results in lower risk MDS (Raza, ASH 2013, abstract 2745)
Randomized phase II Study of Volasertib, a *Polo-Like Kinase Inhibitor* + LDAC Versus LDAC alone in Previously Untreated AML Ineligible for Intensive Treatment

*J Maertens et al, ASH 2012*

**Volasertib + LDAC:** 31% CR or CRi

**LDAC alone** 11%  

*(P = 0.0277)*

Remissions with V + LDAC observed across genetic groups, including pts with adverse cytogenetics.
• 11 of 38 (29%) RBC transfusion-dependent patients had Erythroid (HI-E) response

• median duration of HI-E was 34 weeks.
Randomized, dose-escalation study of the p38α MAPK inhibitor SCIO-469 in patients with myelodysplastic syndrome

Leukemia (2013) 27, 977–980; doi:10.1038/leu.2012.264

- 18/ 62 (29%) HI in each hematopoietic lineage
- 11 (18%) major (10%) or minor (8%) erythroid response
- duration of response 63 days to 4.2 years.

Phase 1 Dose-Escalation/Expansion Study Of ARRY-614 In Patients With IPSS Low/Int-1 Risk Myelodysplastic Syndromes  G Garcia Manero

ASH 2013, abstract n°387
A multicenter phase 2 study of the farnesyltransferase inhibitor tipifarnib in intermediate- to high-risk myelodysplastic syndrome

- **26 (32%) responses:** 12 (15%) CRs and 14 (17%) HI; 37 (45%) stable disease
- **CR median response duration** 11.5 months (2.0-22),
- **Median OS** 11.7 months
A Phase I/II trial of Erlotinib (ERLO) in higher risk MDS after AZA failure

S Thépot, Int MDS meeting, Berlin, 2013

<table>
<thead>
<tr>
<th>Diagnostic (WHO)</th>
<th>N = 30</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAEB-2 AML</td>
<td>18</td>
<td>60%</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IPSS</th>
<th>N = 30</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Int-2</td>
<td>10</td>
<td>33%</td>
</tr>
<tr>
<td>High failure</td>
<td>13</td>
<td>43%</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>23%</td>
</tr>
</tbody>
</table>

- 20% responses
  - 1CR
  - 1 marrow CR
  - 4 HI (2 HI E and 2 HI P)
- 7 stable disease without HI
How to use new drugs in MDS?

• Higher risk MDS
  – After HMA failure
    • Alone
    • As « add on » therapy
  – For first line in combination with HMA

• Lower risk MDS (mainly anemic patients)
  – After ESA failure (non del 5q) or LEN failure (del 5q)
  – Alone or combined to ESA or LEN respectively
Demonstration of additional benefit in adding LEN to AZA in patients with higher-risk MDS


- 18 higher-risk MDS patients were treated with AZA+ LEN for 7 cycles, after which LEN was discontinued in 8 patients who achieved CR

- 3 patients relapsed on monotherapy at 12, 19, and 24 months,

- LEN then resumed in combination with AZA. Each patient recaptured CR, sustained for 5, 7, and 7+ months.
« Add on » approach

- AZA+ Vorinostat in patients having failed AZA alone (T Prébet, N Vey)

- AZA+ LDE 225 (Anti SMO) in patients having failed AZA alone (T Prébet, N Vey)
New drugs in MDS

• HDAC inhibitors

• Chemotherapy
  – Clofarabine
  – Sapacitabine

• Immunotherapy

• Signal transduction inhibitors

• TPO agonist receptors
  – Romiplostin
  – Eltrombopag
Romiplostim in MDS: Structure

• Fc-peptide fusion protein (peptibody)

  - Fc Domain
  - TPO-R Binding Domain (including spacer regions)

• No sequence homology with eTPO
• Stimulates platelet production via the same mechanism as eTPO
• Approved for the treatment of chronic ITP
Safety and Efficacy of Romiplostim in Patients With Lower-Risk Myelodysplastic Syndrome and Thrombocytopenia

- lower-risk MDS, platelet count < 50 x109/L
- 3 injections of 300, 700, 1,000, or 1,500 ug romiplostim at weekly intervals
- durable platelet response for 8 consecutive weeks in 19 patients (46%).
- 15% transient increases in marrow blasts
Results of a Randomized, Double-Blind Study of Romiplostim Versus Placebo in Patients with Low or Int-1 Risk MDS and Thrombocytopenia

A Giagounidis et al (submitted)

N = number of patients randomized. BM, bone marrow; EOS, end of study; IP, investigational product (romiplostim or placebo); LTFU, long-term follow-up
**TABLE 2.** Bleeding events and platelet transfusions in 26-week test treatment period

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Romiplostim</th>
<th>Treatment Difference (95% CI), P-value(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients(^b)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSBE, mean no. per patient at Week 26</td>
<td>1.94</td>
<td>1.47</td>
<td>HR = .83 (.66, 1.05), P = .13</td>
</tr>
<tr>
<td>All bleeding events / 100 pt-ys</td>
<td>3786.4</td>
<td>3459.9</td>
<td>RR = .922 (.86, .99), P = .026</td>
</tr>
<tr>
<td>No. bleeding events CTCAE grade 3 or above / 100 pt-ys</td>
<td>133.9</td>
<td>101.5</td>
<td>RR = .780 (.53, 1.16)</td>
</tr>
<tr>
<td>No. bleeding events CTCAE grade 4 (life-threatening)</td>
<td>1 / 83</td>
<td>2 / 167</td>
<td></td>
</tr>
<tr>
<td>No. bleeding events CTCAE grade 5 (fatal)</td>
<td>3 / 83</td>
<td>0 / 167</td>
<td></td>
</tr>
<tr>
<td>Protocol-defined platelet transfusions rate / 100 pt-ys</td>
<td>1013.5</td>
<td>748.9</td>
<td>RR = .766 (.66, .88), P &lt; .001</td>
</tr>
<tr>
<td>Total platelet transfusions / 100 pt-ys</td>
<td>1195.2</td>
<td>983.6</td>
<td>RR = 0.849 (.75, .97), P = .013</td>
</tr>
<tr>
<td>Total platelet transfusion units / 100 pt-ys</td>
<td>3120.2</td>
<td>2221.8</td>
<td>RR = .739 (.68, .80), P &lt; .001</td>
</tr>
<tr>
<td><strong>Baseline platelets &lt; 20 x 10^9/L(^c)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSBE rate / 100 pt-ys</td>
<td>501.2</td>
<td>514.9</td>
<td>RR = 1.03 (.79, 1.35)</td>
</tr>
<tr>
<td>Platelet transfusion / 100 pt-ys</td>
<td>1778.6</td>
<td>1250.5</td>
<td>RR = .71 (.61, .82), P &lt; .0001</td>
</tr>
<tr>
<td><strong>Baseline platelets ≥ 20 x 10^9/L(^d)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSBE rate / 100 pt-ys</td>
<td>226.4</td>
<td>79.5</td>
<td>RR = .35 (.21, .59), P &lt; .0001</td>
</tr>
<tr>
<td>Platelet transfusion rate / 100 pt-ys</td>
<td>179.8</td>
<td>251.8</td>
<td>RR = 1.38 (.89, 2.15)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CSBE, clinically significant bleeding events; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; pt-yr, patient-year; RR, relative risk (used as the Poisson regression model was applied because of the low event incidence).

\(^a\)Romiplostim vs. placebo.

\(^b\)Placebo, n = 83; romiplostim, n = 167.

\(^c\)Placebo, n = 43; romiplostim, n = 87.

\(^d\)Placebo, n = 40; romiplostim, n = 80.
Figure 2. Incidence of AML, on Treatment and During Long-term Follow-up to March 2013

Incidence Rate (%)

Number of Patients at Risk:

Placebo: 82 70 55 49 46 29 16 8 1
Romiplostim: 168 141 119 102 88 46 19 9 1

Time (Months)

HR = 1.14 (95% CI: 0.48, 2.62)

Includes all randomized patients who received at least 1 dose of the investigational product. Cumulative incidence rates are estimated using the Kaplan-Meier methods.
Total observational time is the time from randomization to the last available long-term contact or end-of-study for patients who did not enter long-term follow-up.
HR, hazard ratio; CI, confidence interval.

Figure 4. AML-Free Survival, on Treatment and During Long-term Follow-up to March 2013

AML-Free Survival Probability

Number of Patients at Risk:

Placebo: 83 71 56 50 47 30 17 8 1
Romiplostim: 167 140 118 101 87 45 18 9 1

Time (Months)

HR 1.07 (0.72, 1.58)

Includes all randomized patients who received at least 1 dose of the investigational product.
Total observational time is the time from randomization to the last available long-term contact or end-of-study for patients who did not enter long-term follow-up.
HR, hazard ratio; CI, confidence interval.
Phase 2 study of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving azacitidine therapy

Hagop M. Kantarjian, Francis J. Giles, Peter L. Greenberg, Ron L. Paquette, Eunice S. Wang, Janice L. Gabrilove, Guillermo Garcia-Manero, Kuolung Hu, Janet L. Franklin and Dietmar P. Berger

Randomized*
\[ n = 40 \]

Placebo
\[ n = 13 \]
Completed
\[ n = 10 (77\%) \]
Discontinued
\[ n = 3 (23\%) \]
Reasons for discontinuation:
- Adverse event = 3 (23\%)
- Febrile neutropenia, bacteremia and endocarditis, fungal pneumonia

Romiplostim 500 µg
\[ n = 13 \]
Completed
\[ n = 8 (62\%) \]
Discontinued
\[ n = 5 (38\%) \]
Reasons for discontinuation:
- Adverse event = 2 (15\%)
- Staphylococcal sepsis, pancytopenia
- Consent withdrawn = 1 (8\%)
- AML progression = 1 (8\%)
- Alternative therapy = 1 (8\%)

Romiplostim 750 µg
\[ n = 14 \]
Completed
\[ n = 9 (64\%) \]
Discontinued
\[ n = 5 (36\%) \]
Reasons for discontinuation:
- Adverse event = 1 (7\%)
- Hypotension
- Consent withdrawn = 2 (14\%)
- Administrative decision = 1 (7\%)
- Other = 1 (7\%)


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Effect of romiplostim on median platelet counts on day 1 of each treatment cycle (left panel) and on median platelet counts at nadir during each treatment cycle (right panel).

Effect of romiplostim on the incidence of clinically significant thrombocytopenic events (left panel) and platelet transfusions (right panel).

**ORIGINAL ARTICLE: CLINICAL**

A randomized controlled trial of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving decitabine

Peter L. Greenberg¹, Guillermo Garcia-Manero², Michael Moore³, Lloyd Damon⁴, Gail Roboz⁵, Kuolung Hu⁶, Allen S. Yang⁶ & Janet Franklin⁶

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**Figure 1. Disposition of patients during the study.**
A randomized, double-blind, placebo-controlled phase 2 study evaluating the efficacy and safety of romiplostim treatment of patients with low or intermediate-1 risk myelodysplastic syndrome receiving lenalidomide

Eunice S Wang1*, Roger M Lyons3, Richard A Larson3, Sunil Gandhi4, Delong Liu5, Carmen Matei6, Bart Scott7, Kuolung Hu8 and Allen S Yang8

Methods: Patients were assigned to weekly placebo (n = 12) or romiplostim 500 μg (n = 14) or 750 μg (n = 13) for four 28-day lenalidomide cycles.

Figure 3 Median platelet counts during the treatment period. Bars of line graph represent standard deviations. Broken horizontal line is at 50 x 10^9/L.
Effect of the nonpeptide thrombopoietin receptor agonist Eltrombopag on bone marrow cells from patients with acute myeloid leukemia and myelodysplastic syndrome

Britta Will, Masahiro Kawahara, Julia P. Luciano, Ingmar Bruns, Samir Parekh, Connie L. Erickson-Miller, Manuel A. Aivado, Amit Verma and Ulrich Steidl

- Eltrombopag increased megakaryocytic differentiation and formation of normal megakaryocytic colonies in patients with AML and MDS.
- Marrow mononuclear cells did not show increased proliferation, or increased clonogenic capacity with Eltrombopag (0.1 to 30 mg/mL).

At 0.1 mg/mL, eltrombopag significant increased in the number of megakaryocytic colonies in MDS patients and healthy controls.

Eltrombopag did not change in the proliferation rate or the survival characteristics of patient CD34+ cells.
Efficacy and Safety of Eltrombopag for the Treatment of Thrombocytopenia of Low and Int 1 MDS: Prospective, Randomized, Single-Blind, Placebo-Controlled Trial (EQoL-MDS)

E Oliva, ASH 2012

- 69 patients
- Eltrombopag or placebo (2:1 ratio)
- 50 mg /d initial dose with 50 mg increases every 2 weeks
- 17 patients (10 on active drug – Arm A)
- 5/10 cases on the eltrombopag arm obtained a CR (4 with 50 mg, and 1 with 100 mg)
Groupe Francophone des Myélodysplasies

- Activates clinical trials in MDS (35 centers in France and Belgium + Switzerland, Tunisia)

- Website: www.gfmgroup.org

- Online registry of French MDS cases

- Close cooperation with:
  - a patient support group
  - the International MDS Foundation
  - the European Leukemia Net