Agonistes du récepteur de la thrombopoïétine dans les SMD et AA

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Romiplostim – un peptidomimétique

- Nplate® est un peptibody protéine qui comprend deux sous-unités de chaîne simple, chacune ayant deux domaines
  - Un domain Fc qui augmente la demi-vie dans le sang circulant1
  - Un domaine TPO-R d'adhésion qui confère l'activité biologique1,2
  - Pas de homologie de séquence avec l'eTPO2
  - Chaque sous-unité a deux domaines d’adhésion TPO-R

TPO-R = thrombopoeitin receptor; eTPO = estimated TPO.
Eltrombopag: Non-peptide, Oral Platelet Growth Factor

- Small molecule TPO-R agonist (mw = 442)
- Interacts with TPO-R differently than endogenous TPO
- Does not prime platelets for activation
- Stimulates megakaryocyte proliferation and differentiation
- Increases platelet counts in thrombocytopenic patients

Thrombopoietin: Mechanism of Action

signal transduction:

thrombopoietin

inactive receptor

active receptor

Cell membrane

Cytoplasm

Increased platelet production

NEJM. 2006;354:2034-45.
Eltrombopag: Mechanism of Action

Signal Transduction

Increased platelet production

<table>
<thead>
<tr>
<th>Information</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients entered</td>
<td>3,259</td>
</tr>
<tr>
<td>Platelet counts at diagnosis</td>
<td>2,900</td>
</tr>
<tr>
<td>Information on bleeding at diagnosis</td>
<td>1,347</td>
</tr>
<tr>
<td>Information on platelet transfusion during course of disease</td>
<td>1,250</td>
</tr>
<tr>
<td>Morphology of platelets and megakaryocytes</td>
<td>2,475</td>
</tr>
<tr>
<td>IPSS score</td>
<td>1,064</td>
</tr>
</tbody>
</table>
Thrombocytopenie dans les SMD

<table>
<thead>
<tr>
<th>IPSS</th>
<th>%</th>
<th>Platelets median × 10^9/L (range)</th>
<th>&lt;20 000/μL (%)</th>
<th>&lt;50 000/μL (%)</th>
<th>Bleeding at diagnosis (%)</th>
<th>Platelet transfusion in course of disease (%)</th>
<th>Bleeding as cause of death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>20</td>
<td>240 (10–1500)</td>
<td>2</td>
<td>7</td>
<td>5</td>
<td>12</td>
<td>14</td>
</tr>
<tr>
<td>Int 1</td>
<td>31</td>
<td>100 (2–999)</td>
<td>8</td>
<td>21</td>
<td>26</td>
<td>29</td>
<td>14</td>
</tr>
<tr>
<td>Int 2</td>
<td>21</td>
<td>77 (2–701)</td>
<td>8</td>
<td>28</td>
<td>27</td>
<td>35</td>
<td>12</td>
</tr>
<tr>
<td>High</td>
<td>28</td>
<td>60 (3–809)</td>
<td>17</td>
<td>40</td>
<td>43</td>
<td>32</td>
<td>13</td>
</tr>
</tbody>
</table>

Taux plaquettaires et hémorragie (grades 1-4) au moment du diagnostic et relation avec le temps de survie

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Platelet counts x 10^3</th>
<th>Bleeding, %</th>
<th>Median survival from diagnosis, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>150</td>
<td>&lt;20</td>
<td>20</td>
<td>7</td>
</tr>
<tr>
<td>250</td>
<td>20-50</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td>490</td>
<td>50-100</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>366</td>
<td>100-150</td>
<td>5</td>
<td>22</td>
</tr>
<tr>
<td>941</td>
<td>Normal</td>
<td>2</td>
<td>41</td>
</tr>
</tbody>
</table>

U. Germing, Düsseldorf MDS registry, Data on file
Nombre de décès attribués à une hémorragie

<table>
<thead>
<tr>
<th>Known cause of death</th>
<th>n</th>
<th>1,082</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease related, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td>32</td>
</tr>
<tr>
<td>Bleeding</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td><strong>Not disease related, %</strong></td>
<td></td>
<td>11</td>
</tr>
</tbody>
</table>

U. Germing, Düsseldorf MDS registry, Data on file
Transfusion plaquettaires régulières dans les SMD

Thrombocytopénie <20–30/nl dans les SMD en relation avec classification OMS/FAB

Thrombocytopenie <20–30 dans les SMD en relation avec l’IPSS

Hémorragie fatale

Survie et développement de LAM

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Coefficient</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPSS poor-risk karyotype</td>
<td>2.14 (1.63-2.80)</td>
<td>&lt;.0001</td>
<td>0.137</td>
<td>1</td>
</tr>
<tr>
<td>Blasts in BM &gt;5%</td>
<td>2.30 (1.77-2.98)</td>
<td>&lt;.0001</td>
<td>0.133</td>
<td>1</td>
</tr>
<tr>
<td>Platelet count &lt;30 x 10^9/L</td>
<td>2.27 (1.50-3.44)</td>
<td>&lt;.0001</td>
<td>0.212</td>
<td>1.5</td>
</tr>
<tr>
<td>Age &gt;70 years</td>
<td>1.56 (1.19-2.03)</td>
<td>.004</td>
<td>0.135</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin level &lt;8 g/dL</td>
<td>1.56 (1.15-2.10)</td>
<td>.004</td>
<td>0.153</td>
<td>1</td>
</tr>
<tr>
<td>Neutrophils &lt;0.5 x 10^9/L</td>
<td>1.58 (1.15-2.17)</td>
<td>.004</td>
<td>0.161</td>
<td>1</td>
</tr>
</tbody>
</table>

Survie et développement de LAM

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Coefficient</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status ≥ 2</td>
<td>0.267</td>
<td>2</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-64</td>
<td>0.179</td>
<td>1</td>
</tr>
<tr>
<td>&gt;65</td>
<td>0.368</td>
<td>2</td>
</tr>
<tr>
<td>Platelets, × 10^9/L &lt;30</td>
<td>0.418</td>
<td>3</td>
</tr>
<tr>
<td>30-49</td>
<td>0.270</td>
<td>2</td>
</tr>
<tr>
<td>50-199</td>
<td>0.184</td>
<td>1</td>
</tr>
<tr>
<td>Hemoglobin &lt;12 g/dL</td>
<td>0.274</td>
<td>2</td>
</tr>
<tr>
<td>Bone marrow blasts, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-10</td>
<td>0.222</td>
<td>1</td>
</tr>
<tr>
<td>11-29</td>
<td>0.260</td>
<td>2</td>
</tr>
<tr>
<td>WBC &gt;20 × 10^9/L</td>
<td>0.258</td>
<td>2</td>
</tr>
<tr>
<td>Karyotype: Chromosome 7 abnormality or complex ≥3 abnormalities</td>
<td>0.479</td>
<td>3</td>
</tr>
<tr>
<td>Prior transfusion, yes</td>
<td>0.107</td>
<td>1</td>
</tr>
</tbody>
</table>

Survie et développement de LAM

Survie et développement de LAM

Thrombocytopénie et association avec anomalies moléculaires
Summary

- PLT <100 in app. 50% of MDS pts. at diagnosis
- Correlation with disease risk
- PLT <30 rather infrequent in LR-MDS
- Fatal bleeding seems equally distributed in MDS
- Number of PLT is predictive of outcome within different scoring systems
- Bleeding, infection, AML evolution
- Correlation with survival and AML risk
Romiplostim in MDS. Study Design

- **IPSS low/int-1 MDS on supportive care only, with PLTs 1) ≤20×10^9/L or 2) ≤50×10^9/L with a history of bleeding. Stratified by baseline IPSS (low, int-1) and PLT count (<20, 20-50×10^9/L).**
- **Enrollment:** July 2008 to March 2011; 250 pts. IP dose adjusted by PLT count.
- **After completing Rx, pts moved to long-term follow-up (LTFU) for 5 years.**

**Study Design:**

- **Screening**
- **Randomization**
- **26-Week Treatment Period**
  - **Romiplostim** 750 mcg weekly (N = 160)
  - **Placebo weekly (N = 80)**
- **24-Week Treatment Continuation**
  - **Romiplostim** 750 mcg weekly + standard of care (N = 160)
  - **Placebo weekly + standard of care (N = 80)**

**Weeks:**

- Week 1
- Week 26
- Week 30
- Week 54
- Week 58

**BM Biopsy**

Giagounidis et al., Cancer 2014
Clinical Benefits Based on Baseline Platelet Count at Study Entry (Platelet <20 or 20-50x10^9/L)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N = 43)</th>
<th>Romiplostim (N = 87)</th>
<th>Placebo (N = 40)</th>
<th>Romiplostim (N = 80)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSBE (rate/100 pt-yr)</td>
<td>501.2</td>
<td>514.9</td>
<td>226.4</td>
<td>79.5</td>
</tr>
<tr>
<td>RR</td>
<td>1.03, p = 0.83</td>
<td>RR = 0.35, p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTE (rate/100 pt-yr)</td>
<td>1778.6</td>
<td>1250.5</td>
<td>179.8</td>
<td>251.8</td>
</tr>
<tr>
<td>RR</td>
<td>0.71, p&lt;0.0001</td>
<td>RR = 1.38, p = 0.15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- For patients with a baseline platelet count <20K there was a significant decrease in platelet transfusion events.
- For patients with a baseline platelet count 20-50K there was a significant decrease in clinically significant bleeding events.

Giagounidis et al., Cancer 2014
# Romiplostim in MDS. AML: Updated Data (Jan 2015)

<table>
<thead>
<tr>
<th>Event</th>
<th>%, (n)</th>
<th>Romiplostim</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AML to week 58</td>
<td>17.9% (30)</td>
<td>20.7% (17)</td>
<td>0.86</td>
<td>0.47, 1.56</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6.0% (10)</td>
<td>4.9% (4)</td>
<td>1.20</td>
<td>0.38, 3.84</td>
<td></td>
</tr>
<tr>
<td>AML to Jan 2015</td>
<td>11.3% (19)</td>
<td>11% (9)</td>
<td>1.02</td>
<td>0.46, 2.27</td>
<td></td>
</tr>
<tr>
<td>Death to week 58</td>
<td>16.8% (28)</td>
<td>16.9% (14)</td>
<td>1.03</td>
<td>0.54, 1.95</td>
<td></td>
</tr>
<tr>
<td>Death to Jan 2015</td>
<td>53.3% (89)</td>
<td>53% (44)</td>
<td>1.01</td>
<td>0.7, 1.45</td>
<td></td>
</tr>
<tr>
<td>AML-free survival to 58</td>
<td>80.2%</td>
<td>76.8%</td>
<td>0.86</td>
<td>0.49, 1.51</td>
<td></td>
</tr>
<tr>
<td>AML-free survival to Jan 2015</td>
<td>45.5%</td>
<td>54.2%</td>
<td>1.03</td>
<td>0.72, 1.47</td>
<td></td>
</tr>
</tbody>
</table>

While RAEB-1 patients were 14% of the study population, they made up 69% of AML cases.

Kantarjian, H et al. Abstract at ASH annual meeting, 2015
Romiplostim in MDS. Survival (through July 2012)
LTFU data out to 3 years

<table>
<thead>
<tr>
<th></th>
<th>Romiplostim</th>
<th>Placebo</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>38.1% (64)</td>
<td>37.8% (31)</td>
<td>1.08</td>
<td>0.70, 1.67</td>
</tr>
<tr>
<td>AML</td>
<td>8.9% (15)</td>
<td>8.5% (7)</td>
<td>1.15</td>
<td>0.47, 2.85</td>
</tr>
<tr>
<td>AML-free survival</td>
<td>60.7% (66)</td>
<td>61% (32)</td>
<td>1.09</td>
<td>0.71, 1.68</td>
</tr>
</tbody>
</table>

(x) = x patients

Giagounidis et al., Cancer 2014
### Romiplostim Clinical Efficacy in Selected Groups

<table>
<thead>
<tr>
<th>Platelet Count (x10^9/L)</th>
<th>Clinically Relevant Endpoints in Practice</th>
<th>Results in this study</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-50</td>
<td><em>Platelet Transfusions not routine:</em> Bleeding Reduction</td>
<td>CSBE reduced RR = 0.35 (95% CI: 0.21, 0.59) p&lt;0.0001, n = 120, 48%</td>
</tr>
<tr>
<td>&lt;20</td>
<td><em>Patients Transfused Routinely:</em> Platelet Transfusion Reduction</td>
<td>PTE reduced RR = 0.71 (95% CI: 0.61, 0.82) p&lt;0.0001, n = 130, 52%</td>
</tr>
<tr>
<td>&lt;10</td>
<td><em>Worst group refractory to platelet transfusions:</em> Platelet Count Improvement</td>
<td>HI-P improved responses 7% vs. 30% Diff = 23% (95% CI: -6%, 46%) p = 0.23, n = 34, 14%</td>
</tr>
</tbody>
</table>

CSBE = clinically significant bleeding events, PTE = protocol-defined PLT Tx events

Giagounidis et al., Cancer 2014
Platelet (HI-P), Erythroid (HI-E), and Neutrophil (HI-N) Responses

Romiplostim treatment was associated with erythroid and neutrophil responses in addition to platelet responses.  

Romiplostim treatment was associated with erythroid and neutrophil responses in addition to platelet responses.

Giagounidis et al., Cancer 2014
EUROPE

Prospective validation of a predictive model of response to romiplostim in patients with IPSS low or intermediate-1 risk myelodysplastic syndrome (MDS) and thrombocytopenia - the EUROPE-trial by the GFM and GMDSSG

**Sponsor:** EMSCO (GMIHO)

**PI:** Prof. Platzbecker, Univ. Dresden; Prof. Adès, Paris

**CRO u. Monitoring:** GWT Dresden
Eltrombopag has antiproliferative effects on leukemic cells

- Antiproliferative effects and significant cell death in AML cells exposed to eltrombopag in liquid suspension culture.  
  - eltrombopag alone inhibited proliferation of many AML cell lines and primary AML cell cultures, but not normal cells
  - the addition of other cytokines (G-CSF, Epo or TPO) did not affect the decrease in proliferation and cell death.
- Eltrombopag inhibits the proliferation of leukemia cells via reduction of intracellular iron and induction of differentiation.
- Eltrombopag inhibits other cancer cell lines in culture

1Kalota, Blood 2010; 2Sugita, Leukemia 2012; 3Erickson-Miller, Leuk Res 2010; 4Roth, Blood 2012
In Vitro Response of K562 Cells Treated With Eltrombopag in the Absence or Presence of rhTPO, rhEPO, or rhG-CSF
Randomized, double-blind, placebo-controlled, phase I/II study of eltrombopag in high risk MDS and AML

**Study Design**

**Eligibility criteria**
- Advanced MDS/AML (10-50% blasts)
- Relapsed/refractory or ineligible to standard Tx
- Platelet transfusions or PLT <30,000/µL

**Randomization**
Stratified by karyotype and baseline BM blasts

**Placebo**
6 months

**Eltrombopag**
6 months

**Extension**

Bone marrow examinations every 3 months on treatment
Median Platelet Counts and 56-Day Transfusion Independence

Placebo      Eltrombopag

Transfusion Independence (%)

Placebo: 21%  Eltrombopag: 38%

P = 0.098
Bone marrow and peripheral blasts

Platzbecker et al. Lancet Haematology 2015, 2:, e417–e426
Overall Survival

Estimated Survival Function

Time Since Randomization (Weeks)

Placebo: 15.7 weeks
Eltrombopag: 27.0 weeks

Median Overall Survival

HR=0.71; \( P=0.19 \); 95% CI, 0.40–1.27

Platzbecker et al. Lancet Haematology 2015, 2:, e417–e426
Study design of Eltrombopag Study in low-risk MDS

Patients (N = 174)

Randomization

2:1

Eltrombopag + Standard care (n = 116)

Placebo + Standard care (n = 58)

Wk 24

CR and R

Eltrombopag + Standard care

Standard Care

Dose start: 50 mg with increases every 2 weeks up to 300 mg daily.
## Characteristics of patients

<table>
<thead>
<tr>
<th></th>
<th>Whole group N=70</th>
<th>Eltrombopag N=46</th>
<th>Placebo N=24</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age, yrs (SD)</strong></td>
<td>68 (13)</td>
<td>69 (11)</td>
<td>66 (16)</td>
<td>0.594</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>32 (46)</td>
<td>19 (41)</td>
<td>13 (54)</td>
<td>0.305</td>
</tr>
<tr>
<td><strong>Median MDS duration, months (IQR)</strong></td>
<td>9 (2-38)</td>
<td>9 (2-39)</td>
<td>9 (2-18)</td>
<td>0.504</td>
</tr>
<tr>
<td><strong>IPSS risk, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>22 (31)</td>
<td>12 (26)</td>
<td>10 (42)</td>
<td>0.183</td>
</tr>
<tr>
<td>Int-1</td>
<td>48 (69)</td>
<td>34 (74)</td>
<td>14 (58)</td>
<td></td>
</tr>
<tr>
<td><strong>Cytogenetics, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>52</td>
<td>36</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>-Y</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Del20q</td>
<td>9</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Del5q</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>+8</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>+15</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Del11q</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>
Mean changes in PLT counts at 8 and 24 weeks

At 8 weeks median PLT counts increased from 18 (IQR 10-25) Gi/L to 44 (IQR 18-70) Gi/L in the eltrombopag arm vs no significant change in the placebo arm.
## Other hematological responses

<table>
<thead>
<tr>
<th>Response</th>
<th>8 weeks, (Elt N=41, Plac=17)</th>
<th>24 weeks, (Elt N=24, Plac=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Elt:Plac</td>
<td>Elt:Plac</td>
</tr>
<tr>
<td>Erythroid response</td>
<td>4 : 0</td>
<td>4 : 0</td>
</tr>
<tr>
<td>Neutrophil response</td>
<td>4 : 1</td>
<td>1 : 1</td>
</tr>
</tbody>
</table>

At 8 weeks, 4 cases experienced erythroid responses:
- 2 stable, 1 MDS progression, 1 liver toxicity.
- 2 additional cases at 24 weeks

At 8 weeks, 4 cases experienced neutrophil responses:
- 1 was stable, 1 experienced MDS progression, 1 retrieved consent, 1 had AML evolution.

**Complete remissions** (normalization of bone marrow morphology):
- At 3 months in 2 patients on eltrombopag
- At 6 months in 4 additional patients on eltrombopag

Elt = eltrombopag; Plac = placebo
# Grade 3-4 Non Hematological Adverse Events

**Eltrombopag arm - Related grade III-IV AE in 9 patients (19%):**
- Nausea and/or vomit (6)
- Hyperbilirubinemia (1)
- Asthenia (1)
- Hypertransaminasemia (3)
- Pruritus (1)

**Eltrombopag arm - Unrelated grade III-IV AE in 13 patients (28%):**
- Pneumonia (5)
- Ascites (2)
- Heart failure (2)
- Arrhythmia (1)
- Bronchitis (1)
- Sepsis (2)
- Death for sepsis (1)
- Renal failure (1)
- Microembolism (1)
- Pain (1)
- Pancreatitis (1)
- Syncope (1)
- Dysuria (1)

**Placebo arm - 4 patients (17%) experienced grade III-IV AE**
- Pneumonia (2)
- Perianal abscess (1)
- Gastric pain (1)
- Fever of unknown origin (1)

AE = adverse events
Coombination trials of TPO-analogs in MDS

• Several exploratory phase II trials completed
• Patient numbers inadequate to provide definite benefit in reduction of clinically significant thrombocytopenic events
• Variable degrees of thrombocytopenia allowed
• Imbalanced MDS disease characteristics
• Assumption of very high primary response rates (50% differences in bleeding)

Brierley & Steensma, Br J Haematol, 2015
Phase 2 study of romiplostim in patients with low- or intermediate-risk myelodysplastic syndrome receiving azacitidine therapy

Randomized
n = 40

Placebo
n = 13
Completed
n = 10 (77%)
Discontinued
n = 3 (23%)
Reasons for discontinuation:
Adverse event = 3 (23%)
(febrele 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%)

Hagop M. Kantarjian et al. Blood 2010;116:3163-3170
Effect of romiplostim on the incidence of clinically significant thrombocytopenic events (left panel) and platelet transfusions (right panel).

Clinically Significant Thrombocytopenic Events

<table>
<thead>
<tr>
<th>Incidence (%, 95% CI)</th>
<th>Placebo</th>
<th>500 µg</th>
<th>750 µg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 13</td>
<td>n = 13</td>
<td>n = 14</td>
</tr>
</tbody>
</table>

Platelet Transfusions

<table>
<thead>
<tr>
<th>Incidence (%, 95% CI)</th>
<th>Placebo</th>
<th>500 µg</th>
<th>750 µg</th>
</tr>
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</tbody>
</table>

Hagop M. Kantarjian et al. Blood 2010;116:3163-3170
Effect of romiplostim on the median platelet counts over time.

Hagop M. Kantarjian et al. Blood 2010;116:3163-3170
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).

Hagop M. Kantarjian et al. Blood 2010;116:3163-3170
SAA Eltrombopag Study im Rezidiv

N=25, Start 50mg/d up to 150mg/d

ORR 44%
- 9 PLT
- 6 Hb
- 9 ANC

before

after
Effets long-terme de L`eltrombopag dans l`AA

• 40 % réponse à long terme
• 12% ont arrêté l`eltrombopag, temps median sans traitement ultérieur >13 mois
• 19% développement d`anomalies chromosomiques
• Aucun cas de transformation en LAM
ATG (cheval) plus ciclosporine plus eltrombopag

- 88 patients
- ATG et Cyclosporine A; EPAG ajoutée 150 mg
- Age median 32 ans
- 26% vSAA, 34% clones HPN
- Overall response: 92%, CR: 54% pour cohorte d1-180

Townsley D; ASH abstracts 2015
Summary

• TPO-receptor agonists do show HI-P in a relevant proportion of patients in MDS and AA.
• Patients ≥5% BM blasts should not be treated with romiplostim, data on eltrombog awaited
• MDS: In some cases: trilineage responses of long duration
• Long-term data lacking
• Combination with antileukemic drugs possible, ongoing study