Managing Chronic Myeloid Leukemia

R.A. Larson, M.W. Deininger
Treatments for chronic phase CML

- FDA approved for frontline and second-line indications:
  - Imatinib
  - Dasatinib
  - Nilotinib
  - Interferon
- FDA approved for second-line indications:
  - Bosutinib
  - Ponatinib
  - Omacetaxine mepesuccinate
- Allogeneic transplantation
### Front-line Randomized Trials in CML - CP

<table>
<thead>
<tr>
<th>Trial</th>
<th>Drugs</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IRIS</td>
<td>IM 400 vs IFN/AraC</td>
<td>Druker, NEJM 2006; Hughes, Blood 2010.</td>
</tr>
<tr>
<td>TOPS</td>
<td>IM 400 vs IM 800</td>
<td>Cortes, JCO 2010</td>
</tr>
<tr>
<td>GIMEMA</td>
<td>IM 400 vs IM 800</td>
<td>Baccarani, Blood 2009</td>
</tr>
<tr>
<td>SWOG 0325</td>
<td>IM 400 vs IM 800</td>
<td>Deininger, Br J Haem 2014</td>
</tr>
<tr>
<td>DASISION</td>
<td>IM 400 vs DAS 100</td>
<td>Kantarjian, NEJM 2010 and Blood 2012; Cortes, ASH 2014</td>
</tr>
<tr>
<td>SWOG 0325</td>
<td>IM 400 vs DAS 100</td>
<td>Radich, Blood 2012</td>
</tr>
<tr>
<td>SPIRIT</td>
<td>IM 400+/AraC or +/ PegIFN vs IM 600</td>
<td>Preudhomme, NEJM 2010.</td>
</tr>
<tr>
<td>CML IV</td>
<td>IM 400+/IFN vs IFN vs IM 800</td>
<td>Hehlmann, JCO 2014; Kalmanti, Leuk 2015</td>
</tr>
<tr>
<td>ENESTnd</td>
<td>IM 400 vs Nil 300 vs Nil 400</td>
<td>Saglio, NEJM 2010; Hughes, Blood 2014; Hochhaus, 2015</td>
</tr>
<tr>
<td>BELA</td>
<td>IM 400 vs BOS 500</td>
<td>Brummendorf, Br J Haem 2015</td>
</tr>
<tr>
<td>SPIRIT 2</td>
<td>IM 400 vs DAS 100</td>
<td>O’Brien, ASH 2014</td>
</tr>
<tr>
<td>EPIC</td>
<td>IM 400 vs Ponatinib 45</td>
<td>Lipton, ASH 2014</td>
</tr>
</tbody>
</table>
Levels of molecular response in CML:
MMR (major molecular response); MR⁴, MR⁴.⁵

<table>
<thead>
<tr>
<th>BCR-ABL (%)</th>
<th>Log reduction in BCR-ABL</th>
<th>Reduction in BCR-ABL</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td>1:10</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>1:100</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>1:1,000</td>
</tr>
<tr>
<td>0.1</td>
<td>3</td>
<td>1:10,000</td>
</tr>
<tr>
<td>0.01</td>
<td>4</td>
<td>1:100,000</td>
</tr>
<tr>
<td>0.0032</td>
<td>4.5</td>
<td>1:1,000,000</td>
</tr>
<tr>
<td>0.001</td>
<td>5</td>
<td>1:10,000,000</td>
</tr>
<tr>
<td>0.0001</td>
<td>6</td>
<td>1:100,000,000</td>
</tr>
</tbody>
</table>

MR⁰ (with currently available technology, this level of response cannot be assessed)

Level of response
Initial Testing

Minimal
- History and physical: record spleen size
- Complete blood count and basic metabolic profile
- Bone marrow aspirate
- Conventional cytogenetics

Optional
- Bone marrow trephine
- qPCR for BCR-ABL1

Situational
- FISH or qualitative for BCR-ABL1: Ph-negative karyotype
- Flow cytometry: Suspected progression to AP/BP
- HLA typing: Progression to AP/BP
## Recommended Monitoring

<table>
<thead>
<tr>
<th>Test</th>
<th>At diagnosis</th>
<th>On therapy</th>
<th>At failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Marrow karyotyping</td>
<td>yes</td>
<td>At 3, 6, 12 months or until CCyR, then annually</td>
<td>yes</td>
</tr>
<tr>
<td>qPCR (blood) for BCR-ABL1(IS)</td>
<td>(yes)</td>
<td>Every 3 months until MMR, then every 3-6 months</td>
<td>yes</td>
</tr>
<tr>
<td>FISH</td>
<td>no</td>
<td>If CCyR documented and qPCR IS unavailable</td>
<td>no</td>
</tr>
<tr>
<td>BCR-ABL1 mutation screen</td>
<td>no</td>
<td>no</td>
<td>yes</td>
</tr>
</tbody>
</table>

### Therapeutic Milestones NCCN vs. ELN

<table>
<thead>
<tr>
<th>Month</th>
<th>Optimal</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>ELN</td>
<td>Ph ≤35% or BCR-ABL1 &lt;10%</td>
<td>Ph &gt;65-95% or BCR-ABL1 &gt;10%</td>
</tr>
<tr>
<td></td>
<td>NCCN</td>
<td>Ph ≤35% or BCR-ABL1 ≤10%</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>ELN</td>
<td>Ph ≤0% and/or BCR-ABL1 &lt;1%</td>
<td>Ph &gt;1-35% and/or BCR-ABL1 1-10%</td>
</tr>
<tr>
<td></td>
<td>NCCN</td>
<td>Ph ≤35% or BCR-ABL1 ≤10%</td>
<td>NA</td>
</tr>
<tr>
<td>12</td>
<td>ELN</td>
<td>BCR-ABL1 &lt;0.1%</td>
<td>BCR-ABL1 0.1-1%</td>
</tr>
<tr>
<td></td>
<td>NCCN</td>
<td>Ph 0%</td>
<td>NA</td>
</tr>
</tbody>
</table>

References:

Cumulative incidence of MMR – ENESTnd after 5 years

- Nilotinib 300 mg twice daily
- Nilotinib 400 mg twice daily
- Imatinib 400 mg once daily

Patients With MMR, %

- By 1 Year: 55%, P < .0001
- By 2 Years: 71%, P < .0001
- By 3 Years: 73%, P < .0001
- By 4 Years: 76%, P < .0001
- By 5 Years: 77%, P < .0001

Months Since Randomization

MR^4.5 – on ENESTnd after 5 Years

Patients With MR^4.5, %

- Nilotinib 300 mg twice daily
- Nilotinib 400 mg twice daily
- Imatinib 400 mg once daily

By 1 Year: 11%, *P* < 0.0001
By 2 Years: 25%, *P* < 0.0001
By 3 Years: 32%, *P* < 0.0001
By 4 Years: 40%, *P* < 0.0001
By 5 Years: 54%, *P* < 0.0001

Hughes TP, et al. Blood 2014; 123(9); 1353-1360

CML, ASH 2015
DASISION: Cumulative MR Rates Over 5 Yrs

- Dasatinib 100 mg QD
- Imatinib 400 mg QD

% With MR

- By 1 year: 46% Dasatinib, 28% Imatinib
- By 2 years: 64% Dasatinib, 46% Imatinib
- By 3 years: 67% Dasatinib, 55% Imatinib
- By 4 years: 73% Dasatinib, 60% Imatinib
- By 5 years: 85% Dasatinib, 64% Imatinib

N
259
260

Cortes J et al, Blood 2014; 124; abstr 156
CML, ASH 2015: 12
### Systematic Review and Meta-Analysis of Randomized Trials Comparing Imatinib 400 mg/day vs Imatinib 800 mg/day

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Observed RR [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hehlmann 2011</td>
<td>663</td>
<td>1.78 [1.47, 2.15]</td>
</tr>
<tr>
<td>Baccarani 2014</td>
<td>476</td>
<td>1.15 [0.91, 1.45]</td>
</tr>
<tr>
<td>Deininger 2012</td>
<td>145</td>
<td>1.47 [1.01, 2.04]</td>
</tr>
</tbody>
</table>

Random Effects Model: 1.45 [1.10, 1.92]

- 45% higher probably of achieving MMR at 12 months with 800 mg (p=0.0088)

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Hoffmann, Hasford, & Hehlmann, ASH 2015, Abstr #2787
Systematic Review and Meta-Analysis of Randomized Trials Comparing Imatinib 400 mg/day vs Second Generation TKIs

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Observed RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saglio 2010</td>
<td>565</td>
<td>2.00 [1.55, 2.59]</td>
</tr>
<tr>
<td>Kantarjian 2010</td>
<td>418</td>
<td>1.54 [1.24, 2.17]</td>
</tr>
<tr>
<td>Cortes 2012</td>
<td>502</td>
<td>1.56 [1.22, 2.00]</td>
</tr>
<tr>
<td>Radich 2012</td>
<td>246</td>
<td>1.34 [1.05, 1.72]</td>
</tr>
</tbody>
</table>

Random Effects Model

- 61% higher probably of achieving MMR at 12 months with 2nd Gen TKI than with Imatinib 400 mg/day (95% CI, 1.37 – 1.91)

The University of Chicago Medicine & Biological Sciences

Hoffmann, Hasford, & Hehlmann.

ASH 2015, Abstr #2787
What is an Early Molecular Response?

- BCR/ABL1 transcript level ≤10%IS (International Scale)
  - At 3 months
  - At 6 months
- Importance: predicts for MMR and Survival
- Limitations: rate of decline may be more important than the absolute percentage (“halving time”).
- Not yet clear whether altering therapy for qRT-PCR level >10% leads to a better outcome.
- However, switching at 3 or 6 months if the BCR/ABL1 level were still >10% seems reasonable.
Outcomes (MMR) by EMR at 3 months (ENESTnd)

Nilotinib 300 mg BID

Imatinib 400 mg Daily

Hughes TP, et al. Blood 2014; 123(9); 1353-1360
ENESTnd: EMR ($\leq 10\%$ at 3 Months) by Sokal Risk Groups [age, spleen size, platelets, blast %]

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low (n = 97)</th>
<th>Intermediate (n = 91)</th>
<th>High (n = 70)</th>
<th>BCR-ABL level at 3 months:</th>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7 (7%)</td>
<td>7 (8%)</td>
<td>10 (14%)</td>
<td>$\leq 10%$</td>
<td>90 (93%)</td>
</tr>
<tr>
<td></td>
<td>34 (32%)</td>
<td>36 (39%)</td>
<td>60 (86%)</td>
<td>$&gt; 10%$</td>
<td>8 (8%)</td>
</tr>
</tbody>
</table>

Nilotinib 300 mg twice daily

Imatinib 400 mg once daily

Hughes TP, et al. Blood 2014; 123(9); 1353-1360
Rate of MR^{4.5} By 6 Years According to 3-Month BCR-ABL^{IS} Levels

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients With MR^{4.5} by 6 Years, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 144</td>
</tr>
<tr>
<td>Nilotinib 300 mg BID</td>
<td>73.6</td>
</tr>
<tr>
<td></td>
<td>P = .001</td>
</tr>
<tr>
<td></td>
<td>BC-ABL^{IS} ≤ 1%</td>
</tr>
<tr>
<td></td>
<td>n = 89</td>
</tr>
<tr>
<td></td>
<td>52.8</td>
</tr>
<tr>
<td></td>
<td>P &lt; .0001</td>
</tr>
<tr>
<td></td>
<td>BC-ABL^{IS} &gt; 1% - ≤ 10%</td>
</tr>
<tr>
<td></td>
<td>n = 24</td>
</tr>
<tr>
<td></td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>P = .02</td>
</tr>
<tr>
<td></td>
<td>BC-ABL^{IS} &gt; 10%</td>
</tr>
<tr>
<td></td>
<td>n = 136</td>
</tr>
<tr>
<td></td>
<td>75.0</td>
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<tr>
<td></td>
<td>P &lt; .0001</td>
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<tr>
<td></td>
<td>n = 95</td>
</tr>
<tr>
<td></td>
<td>45.3</td>
</tr>
<tr>
<td></td>
<td>P = .02</td>
</tr>
<tr>
<td></td>
<td>n = 28</td>
</tr>
<tr>
<td></td>
<td>21.4</td>
</tr>
<tr>
<td></td>
<td>P &lt; .0001</td>
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<tr>
<td></td>
<td>n = 43</td>
</tr>
<tr>
<td></td>
<td>72.1</td>
</tr>
<tr>
<td></td>
<td>P = .001</td>
</tr>
<tr>
<td></td>
<td>n = 133</td>
</tr>
<tr>
<td></td>
<td>36.3</td>
</tr>
<tr>
<td></td>
<td>BC-ABL^{IS} &gt; 10%</td>
</tr>
<tr>
<td></td>
<td>n = 68</td>
</tr>
<tr>
<td></td>
<td>15.9</td>
</tr>
</tbody>
</table>

ENESTnd trial, 2015

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

CML, ASH 2015
CML IV: BCR/ABL1 ≤1% and 0% Ph+ at 6 months both predict for 97% survival at 5 years.

63% of patients had BCR/ABL1 ≤1% at 6 months.

66% of patients had 0% Ph+ cells (CCyR) at 6 months.
ENESTnd: Overall Survival by BCR-ABL1 Levels at 3 Months (Nilotinib 300 mg BID)

OS rates at 4 years for ≤10% vs >10% BCR-ABL at 3 months: 97% vs 87%; P = .01

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Patients</th>
<th>Events</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1%</td>
<td>145</td>
<td>5</td>
<td>140</td>
</tr>
<tr>
<td>&gt;1–≤10%</td>
<td>89</td>
<td>2</td>
<td>87</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>24</td>
<td>3</td>
<td>21</td>
</tr>
</tbody>
</table>

Time Since Randomization (Months)

G Saglio et al. ASCO 2013
ENESTnd: Overall Survival by BCR-ABL1 Levels at 3 Months (Imatinib 400 mg daily)

OS rates at 4 years for ≤10% vs >10% BCR-ABL at 3 months: 99% vs 84%; \( P < .0001 \)

<table>
<thead>
<tr>
<th>Pat Evt Cen</th>
<th>≤1%</th>
<th>&gt;1–≤10%</th>
<th>&gt;10%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43</td>
<td>133</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>1</td>
<td>14</td>
</tr>
<tr>
<td></td>
<td>41</td>
<td>132</td>
<td>74</td>
</tr>
</tbody>
</table>

\( P = .10 \) for ≤10%, \( P < .0001 \) for >10%
TIDEL-II – a prospective trial of switching

- 210 new CML patients started Imatinib 600 mg/day
- Switched to Nilotinib 400 mg BID if:
  - BCR/ABL1 >10% at 3 months (n=25)
  - BCR/ABL1 >1% at 6 months (n=23)
  - BCR/ABL1 >0.1% at 12 months (n = 30)
- Outcomes:
  - At 2 years, 55% were still on imatinib; 30% were on nilotinib.
  - 73% had achieved MMR.
  - At 3 years, OS was 96%, & transformation-free survival was 95%.

### DASISION and ENESTnd, 5 Year Follow Up

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg qd, n = 259</th>
<th>Imatinib 400 mg qd, n = 260</th>
<th>Nilotinib 300 mg bid, n = 282</th>
<th>Imatinib 400 mg qd, n = 283</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cumulative MMR by 5 yr</strong></td>
<td>76% $^8$ vs imatinib, $P &lt; 0.002$</td>
<td>64% vs imatinib, $P &lt; 0.03$</td>
<td>77% $^*$ vs imatinib, $P &lt; 0.001$</td>
<td>60% $^*$</td>
</tr>
<tr>
<td><strong>MR$^{4,5}$ by 5 yr</strong></td>
<td>42% $^\dagger$ vs imatinib, $P = 0.04$</td>
<td>33% vs imatinib, $P &lt; 0.03$</td>
<td>54% $^*$ vs imatinib, $P &lt; 0.002$</td>
<td>31% $^*$</td>
</tr>
<tr>
<td><strong>Progression to AP/BC</strong></td>
<td>12 (4.6%)</td>
<td>19 (7.3%)</td>
<td>10 (3.5%) $^*_{\dagger}$</td>
<td>21 (7.4%)</td>
</tr>
<tr>
<td><strong>5-Year OS (ITT)</strong></td>
<td>91%</td>
<td>90%</td>
<td>94%</td>
<td>92%</td>
</tr>
<tr>
<td><strong>5-Year PFS</strong></td>
<td>85%</td>
<td>86%</td>
<td>92%</td>
<td>91%</td>
</tr>
</tbody>
</table>

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Larson et al. ASH 2014;
Hochhaus et al. ENESTnd, submitted 2015;
Corles et al. DASISION. Blood 2014; 124: abstr 158
Transformation to AP/BP CML by 5 Years -- DASISION

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg (n=259)</th>
<th>Imatinib 400 mg (n=260)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCR-ABL at 3 Months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>≤10% (n=198)</td>
<td>&gt;10% (n=37)</td>
</tr>
<tr>
<td>Transformation to AP/BP&lt;sup&gt;b&lt;/sup&gt;, n (%)</td>
<td>6 (3)</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

Cortes J et al, Blood 2014; 124: abstr 156
The importance of adherence for molecular response

Major molecular response

Complete molecular response

# Common side-effects from TKIs in CML

<table>
<thead>
<tr>
<th></th>
<th>Imatinib</th>
<th></th>
<th>Dasatinib</th>
<th></th>
<th>Nilotinib</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Gr 3&amp;4</td>
<td>All grades</td>
<td>Gr 3&amp;4</td>
<td>All grades</td>
<td>Gr 3&amp;4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4+</td>
<td>+</td>
<td>3+</td>
<td>+</td>
<td>4+</td>
<td>+</td>
</tr>
<tr>
<td>Skin rash</td>
<td>4+</td>
<td>2+</td>
<td>3+</td>
<td>+</td>
<td>4+</td>
<td>+</td>
</tr>
<tr>
<td>Nausea</td>
<td>4+</td>
<td></td>
<td>4+</td>
<td></td>
<td>3+</td>
<td>+</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4+</td>
<td>2+</td>
<td>4+</td>
<td>+</td>
<td>3+</td>
<td>+</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5+</td>
<td></td>
<td>4+</td>
<td></td>
<td>3+</td>
<td>+</td>
</tr>
<tr>
<td>Headache</td>
<td>3+</td>
<td></td>
<td>4+</td>
<td></td>
<td>4+</td>
<td></td>
</tr>
<tr>
<td>Edema</td>
<td>4+</td>
<td>2+</td>
<td>4+</td>
<td>2+</td>
<td>4+</td>
<td></td>
</tr>
<tr>
<td>Pl. Effusion</td>
<td>2+</td>
<td>+</td>
<td>2+</td>
<td>+</td>
<td>2+</td>
<td>+</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td></td>
<td></td>
<td></td>
<td>4+</td>
<td>3+</td>
<td></td>
</tr>
<tr>
<td>Elevated Lipase</td>
<td>4+</td>
<td>2+</td>
<td>4+</td>
<td>3+</td>
<td>4+</td>
<td>3+</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>4+</td>
<td>2+</td>
<td>4+</td>
<td>3+</td>
<td>5+</td>
<td>3+</td>
</tr>
</tbody>
</table>

2+, 1-5%; 3+, 5-10%; 4+, 10-50%; 5+, >50%

Apperley, Lancet Dec 5, 2014;
Incidence of Cardiovascular Events on ENESTnd

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Patients</th>
<th>Events</th>
<th>Censored</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib 300 twice daily</td>
<td>279</td>
<td>21</td>
<td>255</td>
</tr>
<tr>
<td>Nilotinib 400 twice daily</td>
<td>277</td>
<td>37</td>
<td>240</td>
</tr>
<tr>
<td>Imatinib 400 once daily</td>
<td>280</td>
<td>6</td>
<td>274</td>
</tr>
</tbody>
</table>

Hochhaus et al. ENESTnd. Submitted 2015
Adverse Events: Management Issues

**Imatinib**
- GI Toxicity
- Edema (pleural effusions rare)
- Rash
- Myalgia
- Diarrhea

**Nilotinib**
- Rash
- QTc prolongation
- Hepatotoxicity
- Lipase elevation
- Peripheral artery occlusion

**Dasatinib**
- Bleeding
- Pleural effusions
  (1%, grade 3 in DASISION)
- Pulmonary artery hypertension

---

**Initial Grade 3/4 Myelosuppression**

**Imatinib**
- Take on an empty stomach q 12 hrs.
- Avoid PPIs.
- Monitor ECG, glucose and lipase levels.

**Nilotinib**
- Once/day.
  Take with or without food.
  Avoid PPIs.

**Dasatinib**
- Once/day.
  Take with or without food.
  Avoid PPIs.

---

THE UNIVERSITY OF CHICAGO MEDICINE & BIOLOGICAL SCIENCES

CML, ASH 2015
Recognizing TKI Failure

- Failure to reach milestones
- Loss of CHR
- Loss of CyR
- Confirmed loss of MMR
- CCA/Ph+

Do not rush to conclusions

Non-compliance or drug interaction?

Laboratory error or imprecision?

No

Complete diagnostic workup
- Physical exam
- Bone marrow aspirate/biopsy
- Karyotyping
- BCR-ABL1 mutation screen
**Past Medical History**

<table>
<thead>
<tr>
<th>Condition</th>
<th>IM</th>
<th>NIL</th>
<th>DAS</th>
<th>BOS</th>
<th>PON</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POAD</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged QT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI Bleeding</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired LF</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombembolism</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Problems Potential:
- Green: Low
- Yellow: Somewhat elevated
- Orange: Elevated
- Red: Typically contraindicated

- Few absolute contraindications
- Many better or worse picks
- Clinical judgment crucial
Projected TKI prices when Imatinib becomes generic

Annual Cost in US Dollars

- Imatinib 400
- Generic Imatinib 400
- Generic Imatinib 800
- Dasatinib 100
- Nilotinib 300 BID
- Bosutinib 500
- Ponatinib 45
Is there a Best TKI for CML?

- Multiple treatment options
- Calculate the risk score; assess comorbidities and concomitant medications.
- Make the treatment fit the patient. Discuss benefits & risks & costs.
- Tolerability is important; nonadherence leads to poor outcomes. Minimize early side-effects.
- Achieving milestones is crucial; monitor on schedule and optimize therapy as needed.
- Manage comorbid conditions to reduce late toxicities.
Factors Influencing Selection of Salvage Therapy

- Disease phase
- BCR-ABL1 mutation analysis
- Previous treatment history
- Past medical history
Personalized Daily Doses of Imatinib By Therapeutic Drug Monitoring Increase the Rates of Molecular Responses in Patients with Chronic Myeloid Leukemia.

Final Results of the Randomized OPTIM Imatinib Study

Philippe Rousselot, MD, PhD
הקדמה

• רמות גבוהות של גלייבק בדם מביאות ל- MMRعمוק יוטר (Larson – IRIS).

• רמת התרופה שנמצאה עם תגובת טובה - נג/ml 

• רמת התורופה שנמצאה עם תגובת טובה - 1000 נג/ml
תדרים והשיטות

החולים:

• חולים עם CML חדשים עם גליבק לא עד 3 חמשים ימים מהתחלה 400 מ' ליום

• לכול מקום רמות גליבק בדםakhir שבועיים מהתחלה המתחבר

קבוצות טبول:

• החולים שהראו רמות גליבק 1000> חולקו ל- 2 קבוצות:

  קבוצת סטנדרטי:
  • החולים שלא הגיעו רמות גליבק 000> חולקו ל- 2 קבוצות:

    1. המשך טبول סטנדרטי
    2. העלה מנגנון גליבק כדי להגיעה ל-1000> קבוצה 3 - רמות גליבק 1000
特斯אות

נבדו 133 חולים.

- 47 (35%) – רמה גליבק 1000 <
- 86 (65%) – רמה גליבק 1000 >

חולים אלו חולקו ל-2 קבוצות: 1. המשיכו גליבק כרגיל
2. קבלו מינון גליבק בהתאם לרמה

בקבוצה שחיבלה גליבק בהתאם לרמה 1000 > פזור המינון היה:

- 500 מג' ליום - 13%
- 600 מג' ליום - 30%
- 800 מג' ליום - 34%
- 400 מג' ליום - 16%
- 300 מג' ליום - 7%
בדידותת לחתarus 12 חדשים:

视听节目 עם רמת גילברק 1000 ומעלה:
MMR 63% = 27/43

视听节目 עם רמת גילברק 1000 ומטה:
MMR 16% = 16/43

p = 0.031

הפסקת טפול דומה בכל הקבוצות – 18.8% אחרי 12 חדשים
34.1% אחרי 24 חדשים

תופעות לוואי דומות ב- 2 הקבוצות 58% ו- 51%.
מסקנות

• 1/3 מהחולים – מנון גליבק 400 מג' ליום התאים להם.
• 2/3 מהחולים – רמת התרופה לא היתה מספקת יולים להנות מטיפול מותאם אישית.

התוצאות תומכות במאמץ строки אינדייבידואלי של גליבק (כולל הגרעין הגנרייט CML של) כדי לחסוך תוצאות אופטיималь של טיפול ב-

הтомות תומכות במדף טיפול אינדיבידואלי של גליבק (כולל הגרעין הגנרייט CML של) כדי לחסום תוצאות אופטיималь של טיפול ב-

CML של}
STIM1 Study: Treatment Free Remission

Maintenance of Deep Molecular Response after TKI Discontinuation in ~ 40% of patients

Australian Study

Japanese Study


Withdrawal Syndrome Accompanies TKI Discontinuation in Some Patients

EuroSKI:
- 222 AEs in 98 patients reported
- 57 AEs in 31 patients were related to treatment stop, no grade 4

<table>
<thead>
<tr>
<th>Patients Grade 1-4 n</th>
<th>Patients Grade 3 n</th>
<th>AEs Grade 1-4 n</th>
<th>AEs Grade 3 n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Musculoskeletal pain, joint pain, arthralgia</td>
<td>13</td>
<td>3</td>
<td>10</td>
</tr>
<tr>
<td>Other (swelling, skin disorders, folliculitis, depressive episodes, fatigue, urticaria, weight loss)</td>
<td>8</td>
<td>0</td>
<td>16</td>
</tr>
</tbody>
</table>

- The Life After TKI Study (LAST; NCT02269267) will specifically look into this
- Patients with chronic myelogenous leukemia may not want to discontinue tyrosine kinase inhibitor therapy (#1584, poster, Saturday)
Discontinuation After 2G TKI

- Adult CP-CML patients
- TKI therapy for at least 3 years
- 2G-TKI frontline or after intolerance/resistance to imatinib
- Undetectable BCR-ABL* (CMR4.5) for at least 2 years

→ Primary objective: treatment-free survival in MMR

Rea et al. Blood (ASH) 2014; Abstract 811
Treatment-free Survival in MMR

- 24 patients lost MMR after a median time of 3.7 months (1.5-37.6).

At 12 months: 59.6% (95% CI: 46.2-72.9)
At 24 months: 57.4% (95% CI: 43.9-70.9)

KM analysis

Rae et al. Blood (ASH) 2014; Abstract 811
Long-term Follow-up of the French Stop Imatinib Study (STIM1) in Chronic Myeloid Leukemia Patients*

Gabriel Etienne, Delphine Réa, Joëlle Guilhot, François Guilhot, Françoise Huguet, Laurence Legros, Franck Nicolini Aude Charbonnier, Agnès Guerci, Bruno Varet, Philippe Rousselot, François-Xavier Mahon on behalf of the Intergroupe Français des Leucémies Myéloïdes Chroniques (FILMC) on behalf of the STIM Investigators

*This study is registered with ClinicalTrials.gov, number NCT00478985

Orlando, ASH 2015, abstract 85121
Introduction

- Imatinib can be safely discontinued if a sustained deep molecular response (DMR) have been achieved 1-9
  - No CML progression event was reported
  - A second DMR was achieved in most if not all patients after treatment resumption
- Rates of molecular recurrence (MR) ranged from 19 to 67% 1-9 depending on:
  - Definition of MR
  - Baseline characteristics of the study populations

(2) Mahon et al. Lancet Oncol 2010
(3) Takahashi et al. Haematologica 2012
(4) Yhim et al. Leuk Res 2012
(5) Ross et al. Blood 2013
(6) Thielen et al. Eur J Cancer 2013
(7) Rousselot et al. J Clin Oncol 2013
(8) Lee et al. Am J Hematology 2013
(9) Mori et al. Am J Hematology 2015
Introduction

→ In patients who have achieved a undetectable molecular residual disease* of at least 2 years on imatinib therapy, imatinib discontinuation was associated with:

TWISTER study ¹

- n=40; median follow-up of 43 months
- Probability of treatment-free remission at 2 years of 47%

STIM1 ²

- n=69; median follow-up of 24 months
- Molecular relapse-free survival of 41% at 1 year and 38% at 2 years

(1) Ross et al. Blood 2013
(2) Mahon et al. Lancet Oncol 2010
Introduction

- Several key issues remain to be determined:
  - Occurrence of late MR
  - Identification of predictive factors of MR

- We report the update of the STIM1 study based on the analysis of the all study population \((n=100)\) with a median follow-up of 65 months after imatinib discontinuation
STIM study design

N=100

Sustained CMR for ≥ 2 years on imatinib (5 assessments)

Q-RT-PCR every month in the first year and every 2 months in the second year and every 3-4 months thereafter

Year 1

Year 2

Year 3 and after

STOP

Molecular recurrence: positivity of BCR-ABL transcript confirmed by a second consecutive analysis point indicating an increase of one log or loss of MMR at one point.

Molecular recurrence \rightarrow Imatinib rechallenge

### Results: Baseline Characteristics of patients
(N=100, enrolled between July 2007 and Dec 2009)

<table>
<thead>
<tr>
<th></th>
<th>Imatinib de novo Patients (N=59)</th>
<th>Interferon Prior Imatinib patients (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex, (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>52</td>
<td>44</td>
</tr>
<tr>
<td>Female</td>
<td>48</td>
<td>56</td>
</tr>
<tr>
<td><strong>Age at Inclusion, years</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>58.1</td>
<td>60.7</td>
</tr>
<tr>
<td>Range</td>
<td>29-79</td>
<td>37-81</td>
</tr>
<tr>
<td><strong>Sokal Risk Score, (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>50</td>
<td>48</td>
</tr>
<tr>
<td>Intermediate</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>High</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Missing</td>
<td>0 / 0</td>
<td>2</td>
</tr>
<tr>
<td><strong>Time From Diagnosis to Imatinib Onset, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.1</td>
<td>27.2</td>
</tr>
<tr>
<td>Range</td>
<td>0-14</td>
<td>0.6-195</td>
</tr>
<tr>
<td><strong>Time From Diagnosis to Imatinib Discontinuation, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>57.3</td>
<td>94.8</td>
</tr>
<tr>
<td>Range</td>
<td>36-104</td>
<td>37-243</td>
</tr>
<tr>
<td><strong>Time Receiving Imatinib, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>55.7</td>
<td>64.3</td>
</tr>
<tr>
<td>Range</td>
<td>36-102</td>
<td>36-112</td>
</tr>
<tr>
<td><strong>Time From Imatinib Onset to Sustained CMR, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>18.5</td>
<td>15.5</td>
</tr>
<tr>
<td>Range</td>
<td>3-68</td>
<td>3-63</td>
</tr>
<tr>
<td><strong>CMR duration before Imatinib Discontinuation, months</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>34.9</td>
<td>37.9</td>
</tr>
<tr>
<td>Range</td>
<td>24-96</td>
<td>25-107</td>
</tr>
</tbody>
</table>
Molecular-recurrence (n=61 pts.)

- Median follow-up = 63 mo.
- 4 patients died after molecular recurrence (MR) of CML-unrelated causes
- MR: 80% within mo. 1-3, 15% within mo. 4-7 and 5% (n=3) within mo. 18 to 22

Cumulative incidence of MR

Number at risk 100 44 41 38 38 38 37 29 25 19 11 5 1 0
(Pleural mesothelioma, metastatic gastric adenocarcinoma, acute renal failure, cerebral hemorrhage, one case of each)
Molecular-recurrence (n=61 pts.)

- Median time to MR: 2.5 mo. (range, 0.8 to 22.2)
- 17 pts. have MMR loss at the date of confirmed MR
- 57 out of the 61 pts restarted TKI (imatinib, n=56; dasatinib, n=1)
- Median time from MR to treatment resumption was 2.1 mo. (0.7-15.6)
- 55 pts. achieved a second CMR with a median time of 4.2 mo. (1.5 to 15.8) after treatment resumption
- Median follow-up of 63 mo.:
  - None of the MR patients have CML event progression
  - Pts who achieved the first six months without recurrence, the probability of MR was 10% at 24 months.

* 4 pts. did not restarted treatment (patient convenience, n=3; chemotherapy for concomitant neoplasms, n=1)
Molecular recurrence-free patients (n=39 pts.)

- Median follow-up = 67 months

- One patient died of CML-unrelated cause (myocardial infarction) nine months after imatinib discontinuation.

- At the last available molecular evaluation, 37 out the 39 pts. were in CMR (MR^4 in the two others).

- 16 pts. (41%) maintained a stable CMR while the others (n=23, 59%) have intermittent positive BCR-ABL transcript detection without fullfilled the STIM1 definition of molecular recurrence.
Molecular Recurrence-free Survival (MRFS)

MRFS after imatinib discontinuation – Median Follow-up = 65 mo.
accounting for competing events (death in complete molecular remission without any relapse, n=1)

MRFS

43% (95% CI 33-52) at 6 months
38% (95% CI 32-51) at 24 months
38% (95% CI 28-47) at 84 months.

Number at risk 100 44 41 38 38 38 38 37 29 25 19 11 5 1 0

Months since Imatinib Discontinuation
Factors associated with molecular recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>No.</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis*</td>
<td>100</td>
<td>.04</td>
<td>.12</td>
</tr>
<tr>
<td>At imatinib discontinuation</td>
<td>100</td>
<td>.15</td>
<td></td>
</tr>
<tr>
<td>Gender (female vs male)*</td>
<td>100</td>
<td>.08</td>
<td>.05</td>
</tr>
<tr>
<td>Sokal risk score*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>99</td>
<td>.02</td>
<td>.01</td>
</tr>
<tr>
<td>Int. vs Low</td>
<td>99</td>
<td>.03</td>
<td>.02</td>
</tr>
<tr>
<td>High vs Low</td>
<td>99</td>
<td>.03</td>
<td>.03</td>
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<tr>
<td>Prior IFN treatment*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes vs No</td>
<td>100</td>
<td>.16</td>
<td>.14</td>
</tr>
<tr>
<td>Imatinib duration*</td>
<td>100</td>
<td>.14</td>
<td>.14</td>
</tr>
<tr>
<td>Time to CMR</td>
<td>100</td>
<td>.29</td>
<td>.50</td>
</tr>
<tr>
<td>CMR duration</td>
<td>100</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: Int., intermediate; IFN, interferon; CMR, complete molecular response

* Variable eligible for multivariable analysis.
Factors associated with molecular recurrence

Cumulative incidence of molecular relapse according to Sokal risk group

Sokal risk score
- Low
- Intermediate
- High

Number at risk
- High: 11 2 1 1 1 1 1 1 1 1 1 0
- Intermediate: 19 13 12 11 10 10 10 10 10 10 7 7 4 1 1 0
- Low: 49 29 27 26 26 26 26 26 25 21 17 15 10 4 1 0

Months since Imatinib Discontinuation

p = 0.02

p = 0.03
Conclusion

With a longer follow-up (65 mo.) after imatinib discontinuation

- No CML event progression have been reported
- Most if not all relapsing patients have achieved a second deep molecular response after TKI resumption
- Molecular recurrence was very rare after 6 months and no molecular recurrence was reported after 2 years

Imatinib discontinuation is safe provided that:

- A deep sustained molecular response have been achieved before discontinuation
- A close molecular monitoring is available after treatment cessation
Conclusion

- Sokal risk score continues to be a strong significant factor associated with MR suggesting that eradication of the leukemic clone may depend on intrinsic feature of the disease

- Half of the patients have been previously treated with IFN which limits the statistical analysis of predictive factors
Mature, adaptive-like CD56^{dim} NK cells in chronic myeloid leukemia patients in treatment free remission

6.12.2015 Mette Illander
Hematology Research Unit Helsinki,
University of Helsinki, Finland
**Imatinib discontinuation**

- Nearly half of patients who have achieved CMR are able to discontinue TKI therapy (Mahon et al. Lancet 2010)
- Patients without treatment still have residual disease left (Ross et. Al Blood 2013)
- *Does immune system play a role in disease control?*

![Graphs from Ross et. Al Blood 2013 and Mahon et al. Lancet 2010]

**Euro SKI Clinical study**

- Multicenter prospective trial estimating the molecular relapse-free survival after stopping TKI (survival without molecular relapse defined as BCR-ABL1 > 0.1% (MMR) on the IS)
- PIs: Susanne Saussele, FX Mahon
- Number of patients: 700
Study outline

EURO-SKI clinical trial (clinicaltrials.gov NCT01596114)

- Immuno-assay
  - 6 wk
  - Year 1: RG-PCR every month until 6 months, then every 3 months
  - Year 2: RG-PCR 2nd month
  - Year 3: RG-PCR every 2nd month

STOP TKI

EURO-SKI immunology substudy

- Imatinib treated CML patients (n=107)
- Dasatinib treated CML patients (n=15)
- Nilotinib treated CML patients (n=9)

Study start

- 1st year: Blood sampling time-points
  - 0, 1, 6, 12

- Lymphocyte subclasses analysed (n=101)
- Detailed immunophenotyping and functional analysis (n=40)
- Adaptive NK cells analysed at baseline (n=15) and 1 month (n=39) after discontinuation
NK cell proportion in successful discontinuation

Non-relapsing patients have more NK cells

- NK cell proportion: $p = 0.0003$
- NK cell count: $p = 0.0120$

Non-relapsing: patients without treatment for over 12 months
Early relapse: relapse before 6 months
Late relapse: relapse after 6 months

Study start: 1st year: 6 months: 12 months: 3rd year:

- Non-relapsing Early Relapse Late Relapse Healthy
Immunogenetics play a role

KIR2DL3+ and KIR2DL2+ genotypes are favorable to successful discontinuation

Relapsing
- KIR3DL2+KIR2DL2: 15.7%
- Absent 3DL2 or KIR2DL2: 84.3%
Total=19

Non-relapsing
- KIR3DL2+KIR2DL2: 36.8%
- Absent 3DL2 or KIR2DL2: 63.2%
Total=19
Cytokine secretion of NK cells correlates with relapse risk

High frequencies of CD16-NK cells secreting TNFα/IFNγ

NK cells from non-relapsing patients secrete more cytokines
Conclusions

- High amounts of adaptive-like NK cells in non-relapsing patients -> promoting T cells function: Shift from innate control to adaptive? -> long term control

- Low amounts of immature NK cells in early-relapsing patients -> no control at all -> early relapse

- High amounts of adaptive-like NK cells in late-relapsing patients -> Good innate control: Not capable of shifting from innate control to adaptive? -> short term innate control -> Late relapse
#477: Safety and Efficacy of Combination of Pegylated Interferon-α2b to Standard Dose Dasatinib in Newly Diagnosed CP-CML


for the Nordic CML Study Group (NCMLSG)
Rationale

Dasision, 4-year presentation

2 generation TKIs: Deeper responses than IM
Deep response a prerequisite for TFR

Chart details:
- MR^4 vs MR^4.5
- Graphs showing % with MR^4 and MR^4.5 over months
- Comparison of Dasatinib 100 mg QD vs Imatinib 400 mg QD
Lessons from IM +/- PegIFN studies

- Imatinib, 400 mg
- Imatinib, 600 mg
- Imatinib, 400 mg, and cytarabine
- Imatinib, 400 mg, and peginterferon alfa-2a

Cumulative Percentage

MMR %

Months since Randomization

Preudhomme
NEJM 363;26 2010
French SPIRIT

Simonsso
Blood 118;12 2011
NordCML002

PegIFN and DAS have different mechanisms of action.
Synergism in antitumoral immunity - autoimmunity??
Rationale for PegIFN dosing

Dose reductions and discontinuations in NordCML002 and French SPIRIT NordCML002 administered dose was 24µg/week
In spite of this: Effects!

TKI-treated CML patients have good QoL
For use of combinations in standard care tolerability is essential
Patient- and doctor-friendly strategy
NordCML007 - Outline CP-CML at debut

Debulking phase
- Dasatinib 100mg OD

Combination phase
- Dasatinib 100mg OD

Observation phase
- Dasatinib 100 mg OD

Rx
- PegIntron 15µg/week
- PegIntron 25µg/week

Month
0 3 6 12 15 18 24 END OF STUDY

Monitoring: PCR every 3 months + Karyotype: 3, 6, 12, 18 months (ELN standard)

Primary endpoint
- Rate of MMR at M12
- Study stops if excessive tox in run-in phase M6 (Phase IB)

Secondary endpoints:
- CCyR, MMR, MR4 MR4.5
  - at standard time points
  - Safety

ncml
STUDY GROUP
# Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Included patients (n)</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Male/female (n)</td>
<td>31/9</td>
<td></td>
</tr>
<tr>
<td>Mean and median age (range)</td>
<td>48 yrs (19-71)</td>
<td></td>
</tr>
<tr>
<td>Sokal score mean (range)</td>
<td>0.82 (0.52-2.78)</td>
<td>25%</td>
</tr>
<tr>
<td>Hasford score mean (range)</td>
<td>834 (0-2269)</td>
<td>15%</td>
</tr>
<tr>
<td>EUTOS score mean (range)</td>
<td>39.5 (0-134)</td>
<td>15%</td>
</tr>
</tbody>
</table>
## Adverse events within month 12

<table>
<thead>
<tr>
<th>Non-hematological AEs</th>
<th>Gr 2 (n)</th>
<th>Gr 3-4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Rash/dermatol</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Infections</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Depression/anxiety</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Flu-like symptoms</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Superficial edema</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pleural effusion +2</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hematological AEs</th>
<th>Gr 2 (n)</th>
<th>Gr 3-4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemical AEs</th>
<th>Gr 2 (n)</th>
<th>Gr 3-4 (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALAT</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Lipase</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>16</td>
<td>3</td>
</tr>
</tbody>
</table>

**Reversible, manageable and safe**
Discontinuations first year

DAS + Peg-IFN (n = 40)

Discontinued DAS

Discontinued Peg-IFN (continued on DAS)

Month

0

Grade 3 nonhem. AE (headache) n = 1
(never started Peg-IFN)

3

Hematological AE n = 2 (never started Peg-IFN)

Grade 4 hematological AE n = 1

Grade 2 nonhem. AE (arrhythmia) n = 1

Grade 2 nonhem. AE (fever/headache) n = 1

Grade 3 hematological AE n = 1

Grade 3 nonhem. AE (headache) n = 1

6

Moved away n = 1
(never started Peg-IFN)

9

Poor efficacy of DAS n = 1
(discontinued Peg-IFN at 4 mo.)

12

Grade 4 nonhem. AE (anaphylaxis) n = 1

Note: Two patients are included twice:
1: never started Peg-IFN (3 mo.), then moved away and discontinued DAS (6 mo.)
2: discontinued Peg-IFN due to grade 4 hematol. AE (4 mo.), then discontinued DAS due to poor efficacy (9 mo.)
## Dosing

<table>
<thead>
<tr>
<th>Dosing by M12</th>
<th>DAS</th>
<th>PegIFN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of assigned dose</td>
<td>91%</td>
<td>73%</td>
</tr>
<tr>
<td>Mean dose</td>
<td>91 mg/day</td>
<td>18 μg/week</td>
</tr>
<tr>
<td>Interruptions and dose reductions</td>
<td>47%</td>
<td>52%</td>
</tr>
<tr>
<td>Dose increase</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>
Are NordCML007 and Dasision cohorts really similar??

Same treatment for first 3 months

<table>
<thead>
<tr>
<th>Month 3</th>
<th>Dasision</th>
<th>NordCML007</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10%IS</td>
<td>16%</td>
<td>18%</td>
</tr>
<tr>
<td>MMR</td>
<td>8%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Intention-to-treat (ITT):
Data after discontinuations reported
(One pt moved M7 and we have no data thereafter)
Response was excellent – Major molecular response (MMR)

NordCML007

Dasision

NordCML007 = at time point vs. Dasision = cumulative response

NordCML007 = Near-complete data, singular missing data per time point
Response was excellent – MR4.5
Progressions and treatment switch

No progressions
5 pts failures (ELN): No mutations
3 patients switched to NIL
1 SCT
Impact of early molecular response (EMR) for MMR at M12

- MMR response rate (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;=10%</td>
<td>33</td>
</tr>
<tr>
<td>&gt;10%</td>
<td>6</td>
</tr>
</tbody>
</table>
Conclusions on safety

- Combination appears safe
- Toxicity is modest and manageable, but not negligible
- No new types of adverse events
- No apparent increase in autoimmunity
- Low rate of pleural effusions
- 80% of patients remain on PegIFN at M12!
Conclusions on efficacy

- Addition of PegIFN appears very promising
- Randomized DAS+/-PegIFN comparison warranted
- Analysis of biological substudies and QoL is ongoing
134 Combination of Dasatinib and Peg-Interferon Alpha 2b in Chronic Phase Chronic Myeloid Leukemia (CP-CML) First Line: Preliminary Results of a Phase II Trial, from the French Intergroup of CML (Fi-LMC)

Lydia ROY, MD
הקדמה

,nil 1 Shiite, Peg-IFNa 2a + imatinib (IM) נתגבה茂, CML.  

Second generation TKIs כימי ספיריסל ונוילוטיניב הראו תגובת דומה עד MR4.5.

המטרה

לבדק את התשובה של ספיריסל + Peg-IFNa2b + ספיריסל MR4.5 After 12 Weeks, המטרה היא*: 1. After 3,6,9 Weeks (3,6,9 Weeks)

בטיחות
שיטות והמורשים

• חולמים חדשים עם CML – CP

• 3 חולים ספיריסל – 100 เมג'.

• אחריו 3 חולים יקבלו במנון Peg-IFNa2b 30 מקג'/שבוע בתנאי:
  Lymph - >4000, ANC - >1500, PLAT - >100,000

• אם ספירת הדם לא מתאימה יקבלו יבלב ספיריסל בבלב 21 חודש

• סך התٶול המשולב – Peg-IFNa2b + ספיריסל – 21 חודש
הרצאות

• 79/81 황יל המוערכו
• 61 황יל (70%) – קבלו את התפולי המשולב בתום 3 חודשים.

תופעות לווי לאלור Peg-IFNa2b:

- ניטרופניה
- טירואידיטיס
- נשמת פלוירלי
- גדלת לymph Node
- טחורים
- פיסטולה רקטלית

תוחים ופיסטולה רקטילית.
rezultat - 2

יעילות טפול:
- בעבר 3 חשים טפול (ספריית בלבד) - PCR 10% < 85% מהחולים.
- MMR 16% - 3 חשים
  51% - 6 ח申し込み
  70% - 12 ח申し込み
- MR 4.5 10% - 3 ח申し込み
  20% - 6 ח申し込み
  30% - 9 ח申し込み
מסקנות

• הטפול המשולב Peg-IFNa2b + ספריייסל מביא לתגובת מודגולהיתعمוקה
cבר בשנה הראשה לטפול MR4.5

• עומק ומיחזור התגובה יוכלו לשנייה בשנית להכנית הפסקת הטפול לאחור

השגת התגובה הרצייה
Impact of Ponatinib versus allogeneic Stem Cell Transplant (SCT) on outcomes in patients with Chronic Myeloid Leukemia (CML) or Ph+ Acute Lymphoblastic Leukemia (Ph+ ALL) with the T315I mutation

Franck E. Nicolini, Grzegorz W. Basak, Dong-Wook Kim, Eduardo Olavarria, Javier Pinilla-Ibarz, Jane F. Apperley, Timothy P. Hughes, Dietger Niederwieser, Michael J. Mauro, Charles Chuah, Andreas Hochhaus, Giovanni Martinelli, Maral DerSarkissian, Andrew Kageleiry, Mo Yang, Hui Huang, Lisa J. McGarry, Hagop M. Kantarjian, Jorge E. Cortes
Background (1)

- In the pre-ponatinib era, the T315I mutation significantly shortens overall survival (OS) in imatinib-resistant patients with chronic phase (CP) CML\(^1,2\) (as shown in the figure below) and in other disease phases\(^2\).

- Allogeneic stem cell transplantation - in eligible patients - is able to rescue some patients\(^3\).

---

Background (2)

- Ponatinib has demonstrated significant efficacy in BCR-ABL T315I+ leukemias\(^1\) and is approved in the US and EU for adult patients with refractory CML or *de novo* Ph\(^+\) ALL and those with the T315I mutation\(^2,3\).

- Ponatinib represents an alternative treatment option to allogeneic SCT in eligible patients harboring the T315I mutation\(^4\), but differences in survival between such patients treated with ponatinib and allogeneic SCT have not been studied to date.

---

Study Overview

Study Objective: Comparison of overall survival (OS) among CML and de novo Ph* ALL patients with the BCR-ABL T315I* mutation treated with ponatinib versus allogeneic SCT.

Data sources pooled to conduct indirect comparison of ponatinib with allogeneic SCT:

- **PACE trial** – Single arm phase II clinical trial of ponatinib efficacy and safety.
  - Enrolled 449 patients from September 2010 to October 2011 who were resistant or intolerant to dasatinib or nilotinib or with the T315I mutation, in Ph* ALL and CML in all phases.

- **European Bone Marrow Transplant (EBMT) registry** (Myeloproliferative Neoplasias sub-committee of the Chronic Malignancies Working Party)
  - Included 222 CML and de novo Ph* ALL patients with the T315I mutation, resistant to TKI, from 1999 to 2010 (i.e., in the pre-ponatinib era).
Methods

Study Design
- Retrospective observational study
- Observation period spanned from the date of treatment intervention until the earliest of death or the end of data availability

Study Population
- Patients age 18 years or older with the T315I mutation detected by any mean, in any phase of CML or with de novo Ph+ ALL
- Allogeneic SCT patients in second chronic phase were excluded

Study Cohorts
- Two cohorts were evaluated:
  - Ponatinib (from PACE)
  - Allogeneic SCT (from EBMT Registry)
- Patients were also stratified by CML phase and Ph+ ALL
Methods

Study endpoint

- Overall survival (OS) was evaluated, with date of intervention as the index date
  - Median and interquartile range (IQR)
  - Hazard ratio (HR) and 95% confidence interval (CI)

Statistical analysis

- All analyses were stratified by CML phase and de novo Ph+ ALL
- Patient characteristics were assessed during the baseline period prior to intervention, summarized and compared between cohorts (p-values from Wilcoxon rank sum tests or chi-square tests as appropriate)
- Analyses were adjusted for age, gender, geographic region, and time from diagnosis to treatment initiation using inverse probability of treatment weights (IPTW) method
- Adjusted Kaplan-Meier survival curves were used to evaluate time to death (p-values from log-rank test)
- Adjusted Cox proportional hazards models were used to estimate HRs (p-values from Wald chi-square test)
CP-CML and AP-CML Patients’ Characteristics

<table>
<thead>
<tr>
<th></th>
<th>CP-CML</th>
<th></th>
<th>AP-CML</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ponatinib</td>
<td>SCT</td>
<td>p-value</td>
<td>Ponatinib</td>
</tr>
<tr>
<td>Age at index date (years), mean ± SD</td>
<td>53.2 ± 16.8</td>
<td>48.3 ± 12.7</td>
<td>0.202</td>
<td>54.6 ± 16.4</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td>38 (59.4%)</td>
<td>20 (76.9%)</td>
<td>0.115</td>
<td>12 (66.7%)</td>
</tr>
<tr>
<td></td>
<td>26 (40.6%)</td>
<td>6 (23.1%)</td>
<td>0.115</td>
<td>6 (33.3%)</td>
</tr>
<tr>
<td></td>
<td>48 (75.0%)</td>
<td>21 (80.8%)</td>
<td>0.558</td>
<td>11 (61.1%)</td>
</tr>
<tr>
<td>Duration of follow-up (months), mean ± SD</td>
<td>34.5 ± 14.8</td>
<td>32.3 ± 31.2</td>
<td>0.271</td>
<td>26.8 ± 17.2</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time from T315I detection to intervention (months), mean ± SD</td>
<td>0.4 ± 0.2</td>
<td>14.0 ± 14.6</td>
<td>&lt;0.001*</td>
<td>0.4 ± 0.2</td>
</tr>
<tr>
<td>Time from diagnosis to index date (months), mean ± SD</td>
<td>69.6 ± 50.4</td>
<td>47.3 ± 41.6</td>
<td>0.029*</td>
<td>91.7 ± 56.7</td>
</tr>
</tbody>
</table>

* p < 0.05
Adjusted OS of CP-CML Patients

**Survival (%)**

- **Ponatinib** (N = 64)
- **SCT** (N = 26)

**Months from treatment initiation**

<table>
<thead>
<tr>
<th></th>
<th>Ponatinib</th>
<th>SCT</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months), median (IQR)</td>
<td>NR (45.9 - NR)</td>
<td>103.3 (6.6 - 103.3)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.37 (0.16, 0.84)</td>
<td>Ref.</td>
<td>0.017*</td>
</tr>
</tbody>
</table>

* p-value < 0.05; Ref. = reference group; NR = not reached.
Adjusted OS of AP-CML Patients

![Survival curves for Ponatinib and SCT](image)

<table>
<thead>
<tr>
<th></th>
<th>Ponatinib (N = 18)</th>
<th>SCT (N = 8)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months), median (IQR)</td>
<td>NR (24.6 - NR)</td>
<td>55.6 (11.4 - NR)</td>
<td>0.889</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>0.90 (0.20, 4.10)</td>
<td>Ref.</td>
<td>0.889</td>
</tr>
</tbody>
</table>

* p-value. Ref. = reference group; NR = not reached.
Adjusted OS of BP-CML Patients

<table>
<thead>
<tr>
<th></th>
<th>Ponatinib (N = 24)</th>
<th>SCT (N = 17)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival (months), median (IQR)</td>
<td>7.0 (3.5 - 11.0)</td>
<td>10.5 (5.8 - 49.0)</td>
<td>0.026*</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>2.29 (1.08, 4.82)</td>
<td>Ref.</td>
<td>0.030*</td>
</tr>
</tbody>
</table>

* p-value < 0.05. Ref. = reference group, NR = not reached.
Conclusions

- First analysis to confirm that ponatinib was associated with significantly longer OS than allogeneic SCT in patients with CP-CML, and thus, may be a promising alternative for patients with CP-CML with the T315I mutation in this setting.

- OS was similar between intervention groups in AP-CML and longer for allogeneic SCT patients in BP-CML and de novo Ph+ ALL.
  - In patients with the T315I mutation with BP-CML, allogeneic SCT is a potentially curative therapeutic option in a fraction of patients.

- Further studies on this topic are warranted.

- Physicians should base decisions on the benefits and risks of each treatment option and availability of allogeneic donor.
תודה רבה

רק ברייאות

דר' ד. אטיאס
מנחת המרכז המטולוגי
 مركز רפואו בני ציון

מרכז רפואי בני ציון