Chronic Myeloid Leukemia
Treatment in Evolution

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Chronic Myeloid Leukemia: Treatment in Evolution

Palliative Treatments
- Arsenic
- Spleen irradiation

Curative Treatments
- Busulfan
- Hydroxyurea
- Combination chemotherapy
- Allogeneic Stem Cell Transplantation
- Interferon-α ± Cytarabine
- Auto-PBSCT
- Imatinib
- Dasatinib
- Nilotinib
- Ponatinib
- Bosutinib

Timeline:
- 1865
- 1903
- 1953
- 1964
- 1975
- 1983
- 2001
- 2016
Chronic Myeloid Leukemia: Treatment in Evolution

German CML Study Group, 2008

Years after diagnosis

Survival probability

N=2830

Primary imatinib, 2002-2008 (CML IV)
5-year survival, 93%

IFN or SCT + Second-line imatinib, 1997-2003
(CML IIIA) 5-year survival, 71%

IFN or SCT, 1995-2001 (CML III)
5-year survival, 63%

IFN, 1986-1994
5-year survival, 53%

Hydroxyurea, 1983-1994
Busulfan, 1983-1991

Years from diagnosis

Survival of 224 patients treated in 1st line by Imatinib (2000-2008)
Survival of 246 patients treated by IFNa (1986-1994)

Gambacorti – Passerini C et al.
Natl Cancer Inst. 2011
### Chronic Myeloid Leukemia: Treatment in Evolution

<table>
<thead>
<tr>
<th></th>
<th>2006</th>
<th>2009</th>
<th>2016</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1(^{st}) line</strong></td>
<td>Imatinib 400</td>
<td>Imatinib 400</td>
<td>Imatinib 400 Nilotinib (Dasatinib)</td>
</tr>
<tr>
<td><strong>2(^{nd}) line</strong></td>
<td>Allo-HSCT</td>
<td>Nilotinib</td>
<td>Nilotinib, Dasatinib, Allo-HSCT</td>
</tr>
<tr>
<td><strong>3(^{rd}) line</strong></td>
<td>Palliative TT</td>
<td>Palliative TT</td>
<td>Ponatinib, Bosutinib, Allo-HSCT</td>
</tr>
<tr>
<td><strong>Competitors</strong></td>
<td>Allo-HSCT, IFNa</td>
<td>none</td>
<td>TKI + IFNa</td>
</tr>
<tr>
<td><strong>Milestones</strong></td>
<td>CCyR, MMR</td>
<td>CCyR, MMR</td>
<td>Early MR, CMR</td>
</tr>
</tbody>
</table>
First Line of Treatment
- Age
- Co-Morbidities
- Scores: Sokal, Hasford, Eutos

Evaluation according to time
- Hematological Response
- Cytogenetic Response
- Molecular Response
The EUTOS Long-term Survival (ELTS) Score

- 2,205 adult patients with Ph+ and/or BCR-ABL1+ CML, imatinib-based treatment within six months from diagnosis.
- All patients had been enrolled in controlled clinical trials and became part of the in-study section of the EUTOS registry.

**ELTS Score**

\[
0.0025 \times \left( \frac{\text{age in completed years}}{10} \right)^3 + 0.0615 \times \text{spleen size below costal margin} + 0.1052 \times \text{blasts in peripheral blood} + 0.4104 \times \left( \frac{\text{platelet count}}{1000} \right)^{-0.5}
\]

*All variables should be evaluated at diagnosis of the patient.*

*Age should be given in completed years. The score was validated for patients above 18 years.*

*Spleen size should be inserted in cm below costal margin.*

*The percentage of blasts in peripheral blood should be rounded to an integer, e.g. 0, 2 or 7.*

*The platelet count should be given in \(10^9/L\).*

Pfirrmann et al. Leukemia 2016
The EUTOS Long-term survival (ELTS) Score

The ELTS score is rounded to four decimal places.

An ELTS score value \( \leq 1.5680 \) defines the low-risk group
An ELTS score value \( > 1.5680 \) but \( \leq 2.2185 \) defines the intermediate-risk group
An ELTS score value \( > 2.2185 \) defines the high-risk group

Cumulative incidence probability of dying because of CML
Update of newly-diagnosed Chronic Phase CML patients treated with 400 mg daily imatinib (IRIS trial)

CML patients have almost the survival of the normal population!

Estimated overall survival at 8 years is 85% (93% considering only CML-related deaths)

Expectations on Imatinib: IRIS 8-Yr Update Shows 37% Have Unacceptable Outcome

- Sustained CCyR on study: 53%
- No CCyR: 17%
- Lost CCyR: 15%
- Safety: 5%
- Lost → regained CCyR: 3%
- CCyR + other: 7%

*Unacceptable outcome.

ENESTnd: Comparison of Nilotinib and Imatinib in Newly Diagnosed CP CML

Stratified by Sokal risk

Patients diagnosed with Ph+ CP CML within 6 mos (N = 846)

- Nilotinib 300 mg BID (n = 282)
- Nilotinib 400 mg BID (n = 281)
- Imatinib 400 mg QD (n = 283)

Primary endpoint: MMR at 12 mos
Secondary endpoint: durable MMR at 24 mos
Other endpoints: time to MMR, CCyR by 12 mos, time to CCyR, EFS, PFS, OS, time to AP/BC

Chronic Myeloid Leukemia: Treatment in Evolution

**ENESTnd**: Comparison of Nilotinib and Imatinib in Newly Diagnosed CP CML

### MR^4^ and MR^4.5^

<table>
<thead>
<tr>
<th></th>
<th>Imatinib 400 mg QD n = 283</th>
<th>Nilotinib 300 mg BID n = 282</th>
<th>Nilotinib 400 mg BID n = 281</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of PFS events†</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated 5-year PFS, %</td>
<td>91.1</td>
<td>92.0</td>
<td>95.3</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>—</td>
<td>0.92 (0.51-1.65)</td>
<td>0.46 (0.23-0.95)</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>—</td>
<td>0.77</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Total deaths [deaths in patients with advanced CML†]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated 5-year OS, %</td>
<td>91.6</td>
<td>93.6</td>
<td>96.0</td>
</tr>
<tr>
<td>Hazard ratio (95% CI)</td>
<td>—</td>
<td>0.84 (0.45-1.58)</td>
<td>0.46 (0.22-0.98)</td>
</tr>
<tr>
<td><em>P</em> value</td>
<td>—</td>
<td>0.58</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*By 1 Year*, *By 4 Years*, *By 5 Years* indicate statistical significance.

Saglio et al. *Blood* 2013
DASISION: Comparison of Dasatinib and Imatinib in Newly Diagnosed CP CML

Stratified by Hasford risk score

Patients newly diagnosed with CP CML (N = 519)

Dasatinib 100 mg QD (n = 259)

Imatinib 400 mg QD (n = 260)

- Primary endpoint: confirmed CCyR at 12 mos
- Key secondary endpoints: MMR, time in confirmed CCyR, time to confirmed CCyR and MMR, PFS, OS

**DASISION: Comparison of Dasatinib and Imatinib in Newly Diagnosed CP CML**

**MR4**

<table>
<thead>
<tr>
<th>Months</th>
<th>Dasatinib 100 mg qd (n=259)</th>
<th>Imatinib 400 mg qd (n=260)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>12%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>17%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>22%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>35%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>42%</td>
<td>23%</td>
<td></td>
</tr>
</tbody>
</table>

\[ p = 0.0021 \]

**MR4.5**

<table>
<thead>
<tr>
<th>Months</th>
<th>Dasatinib 100 mg qd (n=259)</th>
<th>Imatinib 400 mg qd (n=260)</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>18%</td>
<td>12%</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>23%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>34%</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>37%</td>
<td>30%</td>
<td></td>
</tr>
</tbody>
</table>

\[ p = 0.030 \]

MR4 = BCR-ABL (IS) ≤ 0.01%;
MR4.5 = BCR-ABL (IS) ≤ 0.0032%;
IS = international Scale.

<table>
<thead>
<tr>
<th>Total number of deaths, n</th>
<th>19</th>
<th>21</th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated 4-year OS, %</td>
<td>92.9 (89.7-96.1)</td>
<td>92.1 (88.7-95.4)</td>
<td>HR=0.91 (0.49-1.69)</td>
</tr>
<tr>
<td>Estimated 4-year PFS, %</td>
<td>90.0 (86.0-93.9)</td>
<td>90.2 (86.3-94.1)</td>
<td>HR=1.04 (0.58-1.87)</td>
</tr>
</tbody>
</table>

Cortes JE et al. Blood 2013
Combination of TKI and IFN-α /

- **Stem Cells Ph1⁺ (Partially in G₀)**
- **Cells Ph1⁺ without auto renewal**

**Sensitive to TKI**

**Partially inhibited by TKI**

**Inhibition by TKI**
Peg-IFNa 2a + IM first line - SPIRIT study

Cumulative incidences

- MMR
- MR4
- >MR4.5

p<0.001

First Line of Treatment
- Age
- Co-Morbidities
- Scores: Sokal, Hasford, Eutos

Evaluation according to time
- Hematological Response
- Cytogenetic Response
- Molecular Response
- EMR
- Adverse Events / Mutationnal Status
Hammersmith, UK Retrospective Analysis
8 yr OS by 3 month BCR-ABL level

OS comparison \( P < 0.001 \)

<table>
<thead>
<tr>
<th>BCR-ABL ratio (IS) at 3 months</th>
<th>( n )</th>
<th>8-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \leq 9.84% ) (Low risk)</td>
<td>211</td>
<td>93.3%</td>
</tr>
<tr>
<td>( &gt; 9.84% ) (High risk)</td>
<td>68</td>
<td>56.9%</td>
</tr>
</tbody>
</table>

German CML IV Study: Long-term Outcomes According to BCR-ABL Levels at 3 Months

Randomized study of 1340 imatinib-treated patients (median follow-up 4.7 years)

Overall Survival

Progression Free Survival\(^a\)

\[
\text{OS at 5 yrs} \quad \begin{array}{lll}
<1\% & 233 & 97\% \\
1-10\% & 291 & 94\% \\
>10\% & 195 & 87\% \\
\end{array}
\]

\[
P=0.012
\]

\[
PFS^a \quad \begin{array}{lll}
<1\% & 233 & 96\% \\
1-10\% & 289 & 93\% \\
>10\% & 193 & 88\% \\
\end{array}
\]

\[
P=0.038
\]

\(\text{BCL-ABL (IS) at 3 mos} \quad n \quad \text{Years after diagnosis}
\]

\(\text{Years after diagnosis}
\]

\(\text{Survival probability}
\]

\(\text{Probability of PFS^a}
\]

\(\text{Hanfstein B et al.: ESH-iCML; 2011 (Estoril, Portugal)}\)
Dasatinib 100 mg QD
84% had ≤10% BCR-ABL

Imatinib 400 mg QD
64% had ≤10% BCR-ABL

3-Year PFS
≤10% = 93.1%
>10% = 68.2%  \[ P=0.0003 \]

3-Year PFS
≤10% = 95.9%
>10% = 75.3%  \[ P<0.0001 \]
Evènements Indésirables

Communs aux différents ITK
- Les troubles hématologiques:
  - Anémie (baisse de l’hémoglobine)
  - Neutropénie (baisse des neutrophiles)
  - Thrombopénie (baisse des plaquettes)
- L’asthénie
- Les céphalées
- L’hypophosphatémie

Nilotinib
- Non hématologiques
  - Hypokaliémie
  - Hypocalcémie
  - Hyperglycémie
  - Hypercholestérolémie
  - Hyperlipasémie
  - Perturbations du bilan hépatique
- Troubles cutanés
  - Eruption cutanée
  - Prurit
  - Sécheresse cutanée
- Risque d’accidents artériels

Imatinib
- Les troubles digestifs
  - Diarrhées
  - Nausées et vomissements
  - Douleurs abdominales
- Les hémorragies conjonctivales
- Les œdèmes
- Les troubles musculaires
  - crampes
  - myalgies
  - inflammations

Dasatinib
- Les épanchements de la plèvre
  (présence de liquide dans la Plèvre)
- L’hypertension artérielle pulmonaire
Impact of mutations on the chance of response to ITK2

Mutation analysis may guide the use of second generation inhibitors

>100 mutations

Y253H
E255K/V
F359V/C

T315A
V299L
F317L/I
- **First Line of Treatment**
  - Age
  - **Co-Morbidities**
  - **Scores**: Sokal, Hasford, Eutos
- **Evaluation according to time**
  - **Hematological Response**
  - **Cytogenetic Response**
  - **Molecular Response**
  - **EMR**
  - Adverse Events / Mutaionnal Status
- **Second Line of Treatment**
  - *Imatinib to Dasatinib or Nilotinib*
  - *Dasatinib to Nilotinib / Nilotinib to Dasatinib*
  - *Dasatinib or Nilotinib to Bosutinib or Ponatinib*
Bosutinib in TKI-Resistant Setting: Response Rate

<table>
<thead>
<tr>
<th>Response at Wk 24, n (%)</th>
<th>CP CML</th>
<th>Prior imatinib (n = 266)</th>
<th>Prior imatinib and dasatinib or nilotinib (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCyR</td>
<td>90 (33.8)</td>
<td>29 (26.9)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Response Rate by Wk 48, n (%)</th>
<th>AP CML (n = 69)</th>
<th>BP CML (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHR</td>
<td>21 (30.4)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>OHR</td>
<td>38 (55.1)</td>
<td>17 (28.3)</td>
</tr>
</tbody>
</table>

- ≥ 18 mos MCyR duration in 52.8% of patients with CP CML who received imatinib and achieved MCyR
- ≥ 9 mos MCyR duration in 51.4% of patients with CP CML who received imatinib and ≥ 1 additional TKI and achieved MCyR
### PACE Trial: Efficacy, Safety Outcomes (Median Follow-up: 10.1 Mos for CP CML)

Patients with CML or Ph-positive ALL resistant or intolerant to dasatinib or nilotinib or with emergent T315I mutation (≥ 2 TKIs: 93%, ≥ 3 TKIs: 58%)

<table>
<thead>
<tr>
<th>Response, %</th>
<th>CP CML (n = 271)</th>
<th>AP CML (n = 79)</th>
<th>BP CML/ALL (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R/I</td>
<td>T315I</td>
<td>R/I</td>
</tr>
<tr>
<td>CHR or MaHR*</td>
<td>94</td>
<td>91</td>
<td>60</td>
</tr>
<tr>
<td>MCyR</td>
<td>49</td>
<td>70</td>
<td>34</td>
</tr>
<tr>
<td>CCyR</td>
<td>37</td>
<td>66</td>
<td>20</td>
</tr>
<tr>
<td>MMR</td>
<td>23</td>
<td>50</td>
<td>9</td>
</tr>
</tbody>
</table>

Generally well tolerated: grade ≥ 3 AEs in ≥ 10% of patients: elevated lipase (10%), thrombocytopenia (28%), neutropenia (17%). But Problem of Cardiovascular Toxicity!

*Cortes JE, et al. ASCO 2012. Abstract 6503*
New highlights from ASH 2015
A 20 Gene Expression Signature That Predicts Early Molecular Response Failure in Chronic Phase CML Patients Treated with Frontline Imatinib

PBSC from 119 patients

Early molecular response (EMR) failure
BCR-ABL1 >10% @ 3 months

20 genes detected at diagnosis

IGFBP2, CD3E, RASGRP1, BNIP3L, ETS1, PDK1, METTL7A, HECA, COL8A2, PRSS57, TMEM167A, SPAST, FZD7, VPS41, CDKN1B, CPXM1, SEPT7, RPS28, SLX4IP, & SRSF11
CD93 is a Novel Biomarker of Leukemia Stem Cells in Chronic Myeloid Leukemia

- CD93 is a biomarker downregulated in myeloid malignancies (AML)
- It is a biomarker of Leukemic Stem Cells in CML which resists to TKI
- Could be a good biomarker of MRD (BCR-ABL+)
- Some studies are on going to inhibit Leukemic Stem Cells CD93+

*Kinstrie et al. Abstract 49*
OPTIM study

- Pharmacological Monitoring of Imatinib
- Dose adjustment of 2/3 of patients
- Ameliorate MMR rates at M12
- Important for new Imatinib generics

MMR by 12 months (post randomization)
Improved MMR in a magnitude similar to 2nd gen TKI

**Dasatinib+ IFN-α peg (Nordic group)**

**NordCML007 - Outline**

**CP-CML at debut**

- **Debulking phase**
  - Dasatinib 100mg OD
  - Pegltron 15ug/week

- **Combination phase**
  - Dasatinib 100mg OD
  - Pegltron 25ug/week

- **Observation phase**
  - Dasatinib 100 mg OD

- 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

Included from: Feb 2013 - May 2014

Historical reference population: DASISION

**MMR**

- M3: 0%
- M6: 20%
- M9: 40%
- M12: 60%
- M15: 80%
- M18: 100%

**MR4**

- M3: 0%
- M6: 10%
- M9: 30%
- M12: 50%
- M15: 70%
- M18: 90%

**MR4.5**

- M3: 0%
- M6: 5%
- M9: 15%
- M12: 30%
- M15: 45%
- M18: 60%

**No progressions**
- 5 pts failures (ELN): No mutations
- 3 patients switched to NIL
- 1 SCT

_Hjörth-Hansen H. et al. Abstract 477_
Dasatinib + IFN-α peg (French group)

Primary endpoint: Cumulative rate of MR4.5 by 12 months.
Secondary endpoints: Safety, doses, discontinuation, efficacy
Chronic Myeloid Leukemia: Treatment in Evolution

Nilotinib + IFN-α peg (French group)

Primary endpoint: Rate of confirmed molecular response 4.5 (MR4.5) at 12 months
Nilotinib + IFN-α peg (French group)

**Median FU : 48 months**

At last FU:

- 8 patients (19.5%) were in TFR for a median of 6.8 (0.5-9.5) months after 2-year consecutive MR4.5, and none lost MMR.

- One lymphoid blast crisis (died after allo-SCT).

- No additional grade 3-4 hematologic or biochemical toxicities occurring after 24 months.

- 10 patients (24%) switched for another TKI for insufficient cytogenetic or molecular response (2 patients) or for toxicity (8 patients).

- 5 patients presented cardio-vascular events (3 coronary stenosis, 1 brain stroke 1 PAOD)

*Nicolini FE et al. Abstract 1578*
T315I: Allo-HSCT or Ponatinib?

Matching patients T315I PACE versus EBMT Registry

Nicolini FE et al. Abstract 480
Chronic Myeloid Leukemia: Treatment in Evolution

**ABL001**
- Potent and selective allosteric inhibitor of BCR-ABL1 and ABL1/2
- Active against cell lines with ATP binding site BCR-ABL1 mutants and in murine BCR-ABL1+ tumor model
- Phase I trial ongoing
- Rapid absorption in humans
- Short half life: median 5-6h

**Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.**

**O’Hare T. et al. ASH Annual Meeting 2015. Abstract #1565.**

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**BCR-ABL1**
- **INACTIVE CONFORMATION**
- **ACTIVE CONFORMATION**

**ATP pocket**

**BCR-ABL1 kinase domain**

**SH2**

**SH3**

**O’Hare T. et al. ASH Annual Meeting 2015. Abstract #1565.**

**Ottmann O. et al. ASH Annual Meeting 2015. Abstract #138.**
Responses in patients with ≥ 3 months of follow-up on study (n = 29)

- No death on study
- Dose escalation is ongoing
- 5 dose-limiting toxicities:
  - Grade 3 lipase increase n=2 / Grade 2 myalgia/arthralgia n=1
  - Grade 3 acute coronary event n=1 / Grade 3 bronchospasm n=1

Molecular Recurrence-Free Survival (MRFS) after imatinib discontinuation – Median follow-up = 65 months.

(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

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

Molecular recurrence → Imatinib rechallenge

[Graph showing 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

Saving more than 10 Millions Euros !!!

### Annual price of TKI

<table>
<thead>
<tr>
<th>Country</th>
<th>Imatinib</th>
<th>Nilotinib</th>
<th>Dasatinib</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>92</td>
<td>115.5</td>
<td>123.5</td>
</tr>
<tr>
<td>Germany*</td>
<td>54</td>
<td>60</td>
<td>90</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>33.5</td>
<td>33.5</td>
<td>48.5</td>
</tr>
<tr>
<td>Canada</td>
<td>46.5</td>
<td>48</td>
<td>62.5</td>
</tr>
<tr>
<td>Norway</td>
<td>50.5</td>
<td>61</td>
<td>82.5</td>
</tr>
<tr>
<td>France</td>
<td>40</td>
<td>51.5</td>
<td>71</td>
</tr>
<tr>
<td>Italy</td>
<td>31</td>
<td>43</td>
<td>54</td>
</tr>
<tr>
<td>South Korea</td>
<td>28.5</td>
<td>26</td>
<td>22</td>
</tr>
<tr>
<td>Mexico</td>
<td>29</td>
<td>39</td>
<td>49.5</td>
</tr>
<tr>
<td>Argentina</td>
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<td>80</td>
</tr>
<tr>
<td>Australia</td>
<td>46.5</td>
<td>53.5</td>
<td>60</td>
</tr>
<tr>
<td>Japan</td>
<td>43</td>
<td>55</td>
<td>72</td>
</tr>
<tr>
<td>China</td>
<td>46.5</td>
<td>75</td>
<td>61.5</td>
</tr>
<tr>
<td>Russia</td>
<td>24</td>
<td>48.5</td>
<td>56.5</td>
</tr>
<tr>
<td>South Africa</td>
<td>43</td>
<td>28</td>
<td>54.5</td>
</tr>
</tbody>
</table>

Predicts 378 Billion USD saved by 2029

"...generic versions of the top 12 categories of biologic treatments with patent protections that have expired or that are due to expire in the near future could save Americans $67 billion to $108 billion over 10 years and $236 billion to $378 billion over 20 years."

Dr. Robert J. Shapiro, former Under Secretary of Commerce - report released February 11, 2008

http://www.youtube.com/watch?v=gAW85qRq535

Savings by year ($ in billions)

Experts in CML, Blood 2013
# Marketing opening for Imatinib generic

<table>
<thead>
<tr>
<th>PROTECTION EXPIRY YEAR</th>
<th>US</th>
<th>JAPAN</th>
<th>UK</th>
<th>FRANCE</th>
<th>GERMANY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diovan®, Diovan HCT®, Geodon®, Boniva®</td>
<td>Lipitor®, Amias, Seroquel®, Aricept®, Singulair®</td>
<td>Lipitor®, Amias, Seroquel®, Aricept®, Singulair®</td>
<td>Lipitor®, Amias, Seroquel®, Aricept®, Singulair®</td>
<td>Lipitor®, Amias, Seroquel®, Aricept®, Singulair®</td>
</tr>
<tr>
<td>2013</td>
<td>Oxycontin®, Aciphex®, Zometa®</td>
<td>Diovan®, Opana®ER, Asacol®</td>
<td>Viagra®, Xeloda®</td>
<td>Seretide®, Coaprovel, Xeloda®, Micardis®, Viagra®</td>
<td>Vani®, Zometa®, Atacand®, Coaprovel, Viagra®</td>
</tr>
<tr>
<td></td>
<td>Xeloda®, Celebrex®, Symbicort®</td>
<td>Xeloda®, Celebrex®, Symbicort®</td>
<td>Xeloda®, Celebrex®, Symbicort®</td>
<td>Xeloda®, Celebrex®, Symbicort®</td>
<td>Xeloda®, Celebrex®, Symbicort®</td>
</tr>
<tr>
<td></td>
<td>Prograf®, Glivec®, Abilify®</td>
<td>Prograf®, Glivec®, Abilify®</td>
<td>Prograf®, Glivec®, Abilify®</td>
<td>Seroplex®, Abilify®, Ebixa®, Risperdal®, Consta®</td>
<td>Seroplex®, Abilify®, Ebixa®, Risperdal®, Consta®</td>
</tr>
<tr>
<td>2014</td>
<td>Nexium®, Cymbalta®, Celebrex®, Symbicort®</td>
<td>Lunesta®, Restasis®, Evista®, Sandostatin® LAR, Actonel®</td>
<td>Abilify®, Cipralex®, Risperdal®, Consta®</td>
<td>Seroplex®, Abilify®, Ebixa®, Risperdal®, Consta®</td>
<td>Seroplex®, Abilify®, Ebixa®, Risperdal®, Consta®</td>
</tr>
<tr>
<td></td>
<td>Provigil®, Combivent®, Zyvox®, Prezista®, Avodart®</td>
<td>Lunesta®, Restasis®, Evista®, Sandostatin® LAR, Actonel®</td>
<td>Abilify®, Cipralex®, Risperdal®, Consta®</td>
<td>Seroplex®, Abilify®, Ebixa®, Risperdal®, Consta®</td>
<td>Seroplex®, Abilify®, Ebixa®, Risperdal®, Consta®</td>
</tr>
<tr>
<td>2015</td>
<td>Abilify®, Copaxone®, Gleevec®, Namenda®</td>
<td>Zyprexa®, Aducan®, Alimta®, Spiriva®, Symbicort®</td>
<td>Spriiva®, Cymbalta®, Alimta®</td>
<td>Spiriva®, Spiriva®, Copaxone®, Proteos®, Cymbalta®</td>
<td>Spiriva®, Spiriva®, Copaxone®, Alimta®, Cymbalta®</td>
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<tr>
<td></td>
<td>Gleevec®, Namenda®</td>
<td>Zyprexa®, Aducan®, Alimta®, Spiriva®, Symbicort®</td>
<td>Spriiva®, Cymbalta®, Alimta®</td>
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<td>Spiriva®, Spiriva®, Copaxone®, Alimta®, Cymbalta®</td>
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<tr>
<td>2016</td>
<td>Crestor®, Benicar®, Benicar HCT®, Cubicin®</td>
<td>Blopess, Baraclude®</td>
<td>Glivec®, Vfend®</td>
<td>Glivec®, Vfend®</td>
<td>Glivec®, Zyvoxid, Vfend®</td>
</tr>
</tbody>
</table>
Generic drugs market

Source: IMS Health, MIDAS, Market Segmentation, MAT Jun 2009, Rx only

- France
- UK
- Germany
- Spain
- Italy
- Turkey
In 2013, the estimated benefit from using generic drugs in France is more than 2.5 Billion Euros!
### Imatinib generics in Poland – economical considerations

*Regulation (Pharma Law): the price should be < 50% of original medicament*

12 generic preparations available

<table>
<thead>
<tr>
<th>No.</th>
<th>Generic’s Name</th>
<th>Pharma Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Imakrebin</td>
<td>Alvogen</td>
</tr>
<tr>
<td>2</td>
<td>Imatenil</td>
<td>Biofarm</td>
</tr>
<tr>
<td>3</td>
<td>Imatinib Accord</td>
<td>Accord Healthcare</td>
</tr>
<tr>
<td>4</td>
<td>Imatinib Actavis</td>
<td>Actavis Polska</td>
</tr>
<tr>
<td>5</td>
<td>Imatinib Apothex</td>
<td>Apothex</td>
</tr>
<tr>
<td>6</td>
<td>Imatinib medac</td>
<td>Medac</td>
</tr>
<tr>
<td>7</td>
<td>Imatinib Polfa</td>
<td>Polfa S.A.</td>
</tr>
<tr>
<td>8</td>
<td>Imatinib Teva</td>
<td>Teva Pharmaceuticals</td>
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<tr>
<td>9</td>
<td>Imatinib Zentiva</td>
<td>Zentiva</td>
</tr>
<tr>
<td>10</td>
<td>Meaxin</td>
<td>Krka</td>
</tr>
<tr>
<td>11</td>
<td>Nibix</td>
<td>Adamed</td>
</tr>
<tr>
<td>12</td>
<td>Telux</td>
<td>Nobilus Ent</td>
</tr>
</tbody>
</table>

*Initial price in many hospitals (result of a tender): app. 2%-5% of original imatinib*

*Current price in majority of hospitals (result of a tender): app. 5%-10% of original*
Polish Imatinib Generics Registry

1. The efficacy of imatinib generics at one-year
A. „de novo” patients; n = 40, (Nibix: 24, Meaxin:16)

Early molecular response RQ < 10% at 3 mo

Reduction of BCR/ABL to <1% at 6 mo
Polish Imatinib Generics Registry

1. The efficacy of imatinib generics at one-year

B. „switched” patients; n = 461, (Nibix: 343, Meaxin: 118)
Chronic Myeloid Leukemia: Treatment in Evolution

Polish Imatinib Generics Registry

1. The efficacy of imatinib generics at one-year

B. „switched” patients; n = 461, (Nibix: 343, Meaxin: 118)

Loss of responses under generics therapy

<table>
<thead>
<tr>
<th></th>
<th>MMR loss</th>
<th>CCyR loss</th>
<th>MR4,5 loss</th>
<th>MR fluctuations</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>2.4%</td>
<td>0.4%</td>
<td>4.5%</td>
<td>1.7%</td>
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</tbody>
</table>

Molecular response worsening under generics therapy

<table>
<thead>
<tr>
<th></th>
<th>0.5 log increase</th>
<th>1 log increase</th>
<th>2 log increase</th>
<th>3 log increase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.5%</td>
<td>5.1%</td>
<td>2.1%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>
Questions / difficultés soulevées avec les génériques

- Liberté de prescription du médecin
  Importance de la galénique
  Changement de produit fréquent par le pharmacien : patient perturbé

- Prix faible du produit : suspicion de moindre efficacité

- Dans de nombreux pays : base du remboursement est le prix du générique pas en France !

- Prix des génériques en France : 2 à 10 fois plus chers (GB et USA) car prix fixé par administration donc pas de concurrence
Générique de l’imatinib en France: dossier du groupe FI LMC

Importance du suivi moléculaire des patients Accompagner la prescription

Enjeu économique énorme : 10 milliard d’euros en 10 ans

L’arrivée du générique fait aussi baisser le prix du princeps
Chronic Myeloid Leukemia: Treatment in Evolution

Imatinib generic

Hematologic and Molecular Responses to Generic Imatinib in Patients With Chronic Myeloid Leukemia

Farnaz Razmkhah, MSc,1 Mohsen Razavi, MD,2 Farhad Zaker, PhD,1 Ahmad Kazemi, PhD,1 Shahin Negari, MSc,3 Parisa Rasighaemi, MSc,1 Mojdeh Kalantaromatamedi, MD,1 Mina Zarei, MD,2 Vahid Pazghakh, MSc1
(1Department of Hematology, Iran University of Medical Sciences, 2Department of Medicine, Iran University of Medical Sciences, 3Central Pathology Laboratory, Masih Daneshvari Hospital, Tehran, Islamic Republic of Iran)

DOI: 10.1371/journal.pmed.1000384

Abstract

Background: Imatinib mesylate is a drug used in treating chronic myeloid leukemia (CML). It induces apoptosis and inhibits cell proliferation. This study aimed to evaluate hematologic and molecular responses to Imatinib (Cipla Limited, Mumbai, India) in 30 chronic phase CML patients.

Methods: Physical examination, CBC test, and peripheral blood smear were performed in order to assess the hematologic response in patients. Molecular response was evaluated through quantitative assessment of BCR-ABL fusion gene expression by real-time reverse transcriptase polymerase chain reaction (RT-PCR). The correlation of molecular and hematologic responses with the patient’s age and sex and also with dosage and duration of Imatinib consumption was analyzed statistically.

Results: Ninety percent of the patients showed some sort of hematologic response that had no significant correlation with a patient’s age or sex, dosage, or duration of Imatinib consumption (P>0.05). Overall, 48.7% of patients showed complete molecular response (CMR), 43.3% showed partial molecular response, and 10% showed no molecular response (NMR) to Imatinib. A reverse significant correlation was noted between the type of molecular response and patient’s age (P<0.05). In contrast, no significant correlation was found between the type of molecular response and patient’s sex, dosage, or duration of Imatinib consumption (P>0.05).

Conclusion: Our study results indicate that molecular and hematologic responses to Imatinib were acceptably good and therefore its efficacy is comparable to that of more expensive brands like Gleevec.

Keywords: chronic myeloid leukemia, molecular response, hematologic response, Imatinib

Observational Study of Cemivil® (Imatinib) in Chronic Myeloid Leukaemia Patients in Jordan

PHASE IV OBSERVATIONAL CLINICAL STUDY

HIKMA QUALITY