State of the art testing in high-resource countries

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Current recommendations for molecular monitoring in CML

**European LeukemiaNet recommendations**¹:

- Molecular monitoring every 3 months
- Once MMR achieved, RQ-PCR every 3 to 6 months
  - Mutational testing:
    - Treatment failure
    - Before switching TKIs

**National Comprehensive Cancer Network guidelines**²:

- Molecular monitoring every 3 months
- Once CCyR achieved, RQ-PCR every 3 months
  - After 3 years: RQ-PCR every 3-6 months
  - MMR with ≥1-log ↑ BCR-ABL: RQ-PCR in 1 to 3 months
  - Mutational testing:
    - Suboptimal response
    - Loss of response
    - Progression to AP/BC

¹ Baccarani et al., Blood. 2013;122(6):872-84;
Predictors of performing response monitoring in patients with chronic-phase chronic myeloid leukemia (CP-CML) in a prospective observational study (SIMPLICITY)

Stuart L. Goldberg¹, Jorge Cortes², Carlo Gambacorti-Passerini³, H. Jean Khoury⁴, Michael Mauro⁵, Mauricette Michallet⁶, Ron Paquette⁷, Bengt Simonsson⁸, Aimee Foreman⁹, Lawrence Rasouliyan¹⁰, Hesham Mohamed¹¹, Milayna Subar¹¹, Teresa Zyczynski¹¹
Simplicity Study
US/EU Distribution

- 34% US
- 66% EU
Table 1: Patient Demographics at Initiation of First-Line TKI

<table>
<thead>
<tr>
<th>CHARACTERISTIC</th>
<th>IMATINIB</th>
<th>DASATINIB</th>
<th>NILOTINIB</th>
<th>ALL PATIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort, N</td>
<td>415</td>
<td>383</td>
<td>325</td>
<td>1083</td>
</tr>
<tr>
<td>Male</td>
<td>235 (56.9%)</td>
<td>181 (52.8%)</td>
<td>180 (55.4%)</td>
<td>566 (55.0%)</td>
</tr>
<tr>
<td>Female</td>
<td>180 (43.4%)</td>
<td>162 (47.2%)</td>
<td>145 (44.6%)</td>
<td>467 (45.0%)</td>
</tr>
<tr>
<td>Median age at initiation of first-line TKI (IQR)</td>
<td>50.7 (47.3–70.3)</td>
<td>51.1 (45.9–66.0)</td>
<td>53.0 (44.0–64.0)</td>
<td>56.5 (45.0–67.2)</td>
</tr>
<tr>
<td>Median age at diagnosis, years (IQR)</td>
<td>59.0 (47.0–70.0)</td>
<td>55.0 (45.0–65.0)</td>
<td>53.0 (43.0–64.0)</td>
<td>56.0 (45.0–67.0)</td>
</tr>
<tr>
<td>Patients &lt;65 years of age at diagnosis, n (%)</td>
<td>265 (33.9%)</td>
<td>254 (74.1%)</td>
<td>245 (75.4%)</td>
<td>764 (70.5%)</td>
</tr>
<tr>
<td>Patients ≥65 years of age at diagnosis, n (%)</td>
<td>150 (36.1%)</td>
<td>89 (25.9%)</td>
<td>80 (24.9%)</td>
<td>319 (29.5%)</td>
</tr>
<tr>
<td>Median time from first-line TKI to end of follow-up, months (range)</td>
<td>20.6 (21.2–33.0)</td>
<td>18.4 (9.5–25.5)</td>
<td>20.0 (11.1–30.3)</td>
<td>23.0 (14.2–30.4)</td>
</tr>
<tr>
<td>Region, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EU</td>
<td>172 (41.4%)</td>
<td>95 (27.7%)</td>
<td>103 (31.7%)</td>
<td>370 (34.2%)</td>
</tr>
<tr>
<td>US</td>
<td>243 (58.6%)</td>
<td>248 (72.3%)</td>
<td>222 (68.3%)</td>
<td>713 (65.8%)</td>
</tr>
<tr>
<td>Still on first-line TKI at the end of 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>40 (11.1%)</td>
<td>26 (26%)</td>
<td>35 (10.8%)</td>
<td>107 (9.5%)</td>
</tr>
<tr>
<td>Yes</td>
<td>366 (98.2%)</td>
<td>266 (74.9%)</td>
<td>280 (89.2%)</td>
<td>942 (90.5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>3 (0.7%)</td>
<td>21 (6.1%)</td>
<td>10 (3.1%)</td>
<td>34 (3.1%)</td>
</tr>
<tr>
<td>ECOG performance status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 – Fully active</td>
<td>121 (57.6%)</td>
<td>117 (56.1%)</td>
<td>120 (54.5%)</td>
<td>358 (52.5%)</td>
</tr>
<tr>
<td>1 – Restricted strenuous activity</td>
<td>75 (35.7%)</td>
<td>53 (28.9%)</td>
<td>59 (31.7%)</td>
<td>185 (30.6%)</td>
</tr>
<tr>
<td>2 – Ambulatory and capable of all self-care, no work</td>
<td>12 (5.7%)</td>
<td>4 (2.3%)</td>
<td>8 (3.2%)</td>
<td>22 (3.8%)</td>
</tr>
<tr>
<td>3 – Capable of only limited self-care</td>
<td>1 (0.5%)</td>
<td>3 (1.7%)</td>
<td>0 (0.0%)</td>
<td>4 (0.7%)</td>
</tr>
<tr>
<td>4 – Completely disabled</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
<td>1 (0.5%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Practice type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academic</td>
<td>210 (50.8%)</td>
<td>163 (47.9%)</td>
<td>164 (50.5%)</td>
<td>537 (50.6%)</td>
</tr>
<tr>
<td>Community center</td>
<td>205 (49.4%)</td>
<td>180 (52.1%)</td>
<td>161 (49.5%)</td>
<td>548 (49.4%)</td>
</tr>
</tbody>
</table>
SIMPLICITY: Real-World Monitoring Rates Are Low, Particularly At 3 Months


CyR, cytogenetic response; ELN, European LeukemiaNet; MR, molecular response; NCCN, National Comprehensive Cancer Network.
CML Treatment Goals Have Become More Ambitious Over Time

CHR, complete hematologic response;
CCyR, complete cytogenetic response;
MMR, major molecular response, 3-log reduction from IRIS baseline (IS);
MR^4, MR^4.5, 4-log / 4.5 log reduction from IRIS baseline (IS);
TFR, treatment free remission, maintenance of MMR without therapy.

Applying an International Scale Conversion Factor Can Significantly Alter Patient Results and Clinical Decisions

Without a CF, a laboratory cannot report if the patient achieved MMR or not.
Laboratory-specific CFs can be determined by comparing BCR-ABL values obtained with RQ-PCR in individual laboratories to a set of verified samples of known value from a central reference laboratory.

BCR-ABL values determined in each laboratory are then multiplied by the appropriate, unique CF to convert to the IS.

These CFs allow laboratories to compare a patient’s results over time (serial monitoring) and permit comparisons between other laboratories with validated CFs.

L’evoluzione del Labnet: diffusione dei lab sul territorio

- **2007**: 14 labs
- **2008**: 32 labs
- **2009-2010**: 37 labs
- **2012**: 47 labs

*Up to 15th Nov 2013*
L'evoluzione del Labnet: diffusione dei centri sul territorio

- 2007: 0 centri
- 2008: 6 centri
- 2009-2010: 92 centri
- 2012: 149 centri
- 2013: 164 centri
LA LEUCEMIA MIELOIDE CRONICA: ALLEANZA OLTRE LA TERAPIA

# di lab EUTOS: 5
# di centri Labnet: 164
# di lab standardizzati: 56

Leukemic cells

Full Blood Count (CHR)
Cytogenetic (CCR)
PCR
“Undetectable”

MR:
- 96% >10-4
- 97% >10-4.5

Graph:
- 47% 2014
- 60% 2015*

*Dato aggiornato a Febbraio 2015
CML Treatment Goals Have Become More Ambitious Over Time

**Goals of Treatment**

- **Ph+ CML Diagnosis**
- **CHR**
- **CCyR**
- **MMR / MR³**
- **MR⁴ / MR⁴.⁵**
- **TFR**

**Time on Treatment**

CHR, complete hematologic response;
CCyR, complete cytogenetic response;
MMR, major molecular response, 3-log reduction from IRIS baseline (IS);
MR⁴, MR⁴.⁵, 4-log / 4.5 log reduction from IRIS baseline (IS);
TFR, treatment free remission, maintenance of MMR without therapy.

Next generation BCR-ABL testing:

Cepheid GeneXpert instrument

- Cartridge based platform using 200ul blood for p210 BCR-ABL1
  - RNA extraction
  - Reverse-transcription
  - nested RQ-PCR
  - Result determination and conversion to IS

Sensitivity comparable to standard RQ-PCR until MMR.............
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