CML and Future Perspective

Hani Al-Hashmi, MD
Objectives

• Learning from CML history
• Outcome of interest to clinician
• Patient and community interest !!
Learning from CML history
Imatinib Changed the Therapeutic Landscape for Patients With Ph+ CML

<table>
<thead>
<tr>
<th>Best available therapy</th>
<th>5-Yr OS, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib*</td>
<td>93</td>
</tr>
<tr>
<td>IFN-α or SCT + second-line imatinib†</td>
<td>71</td>
</tr>
<tr>
<td>IFN-α or SCT‡</td>
<td>63</td>
</tr>
<tr>
<td>IFN-α</td>
<td>53</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>46</td>
</tr>
<tr>
<td>Busulfan</td>
<td>38</td>
</tr>
</tbody>
</table>

Diagnosis of CML

**Hematologic**
- Peripheral blood (with myeloid cells)
- Bone marrow (with myeloid hyperplasia)

**Cytogenetic**
- Chromosomal translocation \( t(9;22)(q34;q11) \)
- Karyotype (Ph chromosome)

**Molecular**
- Abnormal BCR-ABL
  - Lane 1: BCR-ABL+
  - Lane 2: BCR-ABL-
- FISH (BCR-ABL fusion)
  - Red: BCR
  - Green: ABL
  - Yellow: fusion

Sensitivity
Evolution of Treatment Goals


Best achievable response

Busulfan
Complete Hematologic Response (CHR)

IFN
Major Cytogenetic Response (CCyR)

Imatinib
Major Molecular Response (MMR)

2GTKI
Deeper Molecular Responses

Tumor Burden

Tumor Reduction

- \( \leq 10\% \approx 1\text{-log} \)
- \( \leq 1\% \approx 2\text{-log} \)
- \( \leq 0.1\%_{\text{IS}} \approx 3\text{-log} \)
- \( \leq 0.01\%_{\text{IS}} \approx 4\text{-log} \)
- \( \leq 0.0032\%_{\text{IS}} \approx 4.5\text{-log} \)
- \( \leq 0.0001\%_{\text{IS}} \approx 5\text{-log} \)

CMR\(^4\) and beyond

Discontinuation?

a Compared with baseline levels. CMR, complete molecular response; IFN, interferon; IS, international scale.
## European Leukemia Net Guidelines

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal Response</th>
<th>Suboptimal Response</th>
<th>Failure</th>
<th>Warnings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>High Risk CCA/Ph⁺³</td>
</tr>
<tr>
<td>3 mo</td>
<td>CHRM, at least minor CyR</td>
<td>No CyR</td>
<td>Less than CHRM</td>
<td>NA</td>
</tr>
<tr>
<td>6 mo</td>
<td>At least PCyR</td>
<td>Less than PCyR</td>
<td>No CgR</td>
<td>NA</td>
</tr>
<tr>
<td>12 mo</td>
<td>CCyR</td>
<td>PCyR</td>
<td>Less than PCyR</td>
<td>Less than MMR</td>
</tr>
<tr>
<td>18 mo</td>
<td>MMR</td>
<td>Less than MMR</td>
<td>Less than CCyR</td>
<td>NA</td>
</tr>
<tr>
<td>Anytime (during treatment)</td>
<td>Stable or improving MMR</td>
<td>Loss of MMR, Mutations¹</td>
<td>Loss of CHRM, Loss of CCyR, Mutations²</td>
<td>Increase in transcript levels CCA/Ph⁻⁻⁻</td>
</tr>
</tbody>
</table>

New recommendations marked in red

BCR-ABL1 kinase domain mutations (1) still sensitive to imatinib, (2) poorly sensitive to imatinib or other TKIs, (3) CCA/Ph⁺ -- "warning" factor at diagnosis, (i.e., clonal progression) is a marker of treatment failure. Two consecutive cytogenetic tests are required and must show the same CCA in at least 2 Ph⁺ cells.
**BCR-ABL/ABL Cutoff ~ 10% IS at 3 Mos Predicts Survival**

- **BCR-ABL/ABL ≤ 9.84%**
  - 8-yr OS: 93.3%

- **BCR-ABL/ABL > 9.84%**
  - 8-yr OS: 56.9%

*P < .001*

First-line Treatment Milestones Have Evolved

- The European LeukemiaNet (ELN) recommendations for optimal responses have shifted to deeper responses 3 to 6 months earlier in treatment\(^2\)
- Similarly, failure criteria occur 3 months earlier vs 2009 ELN recommendations

\[\begin{align*}
\text{CHR}^a, \geq \text{mCyR}^b \\
\text{PCy}^c \text{ and/or} \quad \text{BCR-ABL}^e \leq 10\% \\
\text{CCyR}^d \text{ and/or} \quad \text{BCR-ABL}^e < 1\% \\
\text{CCyR}^d \\
\text{MMR}^e \\
\text{Stable or improving MMR}^f
\end{align*}\]

\(a\) Platelet count < 450 \(\times\) 10^9/L, WBC < 10 \(\times\) 10^9/L, differential count without immature granulocytes, and < 5% basophils

\(b\) 36% to 65% Ph+ metaphases

\(c\) 1% to 35% Ph+ metaphases

\(d\) No Ph+ metaphases

\(e\) BCR-ABL \(\leq\) 0.1%

\(f\) BCR-ABL to ABL (or other housekeeping gene) ratio \(\leq\) 0.1%.

# The new CML milestones

<table>
<thead>
<tr>
<th>Time</th>
<th>Optimal response</th>
<th>Warning</th>
<th>Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td>High risk</td>
<td>Major route CCA/Ph+</td>
</tr>
<tr>
<td>3 mos.</td>
<td>BCR-ABL(^{IS}) ≤10%*&lt;br&gt;Ph+ ≤35% (PCyR)</td>
<td>BCR-ABL(^{IS}) &gt;10%*&lt;br&gt;Ph+ 36-95%</td>
<td>No CHR*&lt;br&gt;Ph+ &gt;95%</td>
</tr>
<tr>
<td>6 mos.</td>
<td>BCR-ABL(^{IS}) &lt;1%*&lt;br&gt;Ph+ 0% (CCyR)</td>
<td>BCR-ABL(^{IS}) 1-10%*&lt;br&gt;Ph+ 1-35%</td>
<td>BCR-ABL(^{IS}) &gt;10%*&lt;br&gt;Ph+ &gt;35%</td>
</tr>
<tr>
<td>12 mos.</td>
<td>BCR-ABL(^{IS}) ≤0.1%* (MMR)</td>
<td>BCR-ABL(^{IS}) 0.1-1%*</td>
<td>BCR-ABL(^{IS}) &gt;1%*&lt;br&gt;Ph+ &gt;0%</td>
</tr>
<tr>
<td>Then, and at any time</td>
<td>MMR or better</td>
<td>CCA/Ph- (-7, or 7q-)</td>
<td>Loss of CHR&lt;br&gt;Loss of CCyR&lt;br&gt;Loss of MMR, confirmed**&lt;br&gt;Mutations&lt;br&gt;CCA/Ph+</td>
</tr>
</tbody>
</table>

*and/or **in 2 consecutive tests, of which one ≥1%  IS: BCR-ABL on International Scale  

Baccarani et al, Blood 2013;122:872-884
Patients with EMR at 3 months had improved OS and PFS and a higher probability of subsequent deeper response vs patients without EMR.

5-Year OS

Patients with EMR had improved OS at 5 years

5-Year PFS

Patients with EMR had improved PFS at 5 years

MR4.5 by 5 Years

Patients with EMR had a higher probability of achieving MR4.5 by 5 years

Patients with EMR failure (BCR-ABL > 10% at 3 months) have significantly worse 5-year PFS.
Rates of EMR failure are lower on nilotinib 300 mg BID vs imatinib.

Cen, censored; EMR, early molecular response; Evt, events; Pts, patients.

* PFS rates reported consider each year to consist of twelve 28-day cycles.
OS by BCR-ABL Levels at 3 Months

Nilotinib 300 mg BID

- Patients with EMR failure (BCR-ABL > 10% at 3 months) have significantly worse 5-year OS
- Rates of EMR failure are lower on nilotinib 300 mg BID vs imatinib

Imatinib 400 mg QD

Cen, censored; EMR, early molecular response; Evt, events; Pts, patients.

*OS rates reported consider each year to consist of twelve 28-day cycles.

Data cutoff: May 22, 2013
PFS According to BCR-ABL Level at 3 Months

Dasatinib 100 mg QD
84% had ≤10% BCR-ABL

4-year PFS
≤10% = 91.8%
>10% = 67.1%
\[ P=0.0004 \]

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

4-year PFS
≤10% = 95.2%
>10% = 70.3%
\[ P<0.0001 \]

*Cortes et al., ESH, 2013.*

*Calculated from total number of evaluable patients with PCR assessments at 3 months.*
OS According to BCR-ABL Level at 3 Months

Dasatinib 100 mg QD
84% had ≤10% BCR-ABL

4-year OS
≤10% = 95.4% \( P=0.0092 \)
>10% = 82.9%

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

4-year OS
≤10% = 96.0% \( P=0.0021 \)
>10% = 84.0%

*Calculated from total number of evaluable patients with PCR assessments at 3 months.*
Fewer patients progressed with Nilotinib vs imatinib in ENESTnd

- Six times as many patients progressed to AP/BC on imatinib than on Nilotinib

**Progressions On Core Treatment**
(6-year follow-up)\(^a\)

\(^a\) Progression to AP/BC events included progressions to AP/BC (excluding clonal evolution) or CML-related deaths occurring on core treatment.

Fewer patients progressed with Dasatinib vs Imatinib in DASISION

- **No \( P \)-value** was provided for the difference in progression rates with dasatinib vs imatinib in DASISION

**Progressions During Treatment (5-year follow-up)**

\[ 8 \text{ (3\%)} \]
DASATINIB PATIENTS PROGRESSED (\( n = 259 \))

\[ 15 \text{ (5.8\%)} \]
IMATINIB PATIENTS PROGRESSED (\( n = 260 \))

\( a \) Progression events included increasing white blood cells despite appropriate therapeutic management, loss of CHR, partial CyR or CCyR, progression to AP/BC, or death.

Progressions on imatinib in ENESTnd and DASISION

- Approximately 7% of patients progressed to AP/BC with imatinib in both studies

**ENESTnd: On-Study Progressions With Imatinib**

<table>
<thead>
<tr>
<th>Years</th>
<th>Patients Progressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>21/283 (7%)</td>
</tr>
<tr>
<td>2 years</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td></td>
</tr>
<tr>
<td>6 years</td>
<td></td>
</tr>
</tbody>
</table>

**DASISION: On-Study Progressions With Imatinib**

<table>
<thead>
<tr>
<th>Years</th>
<th>Patients Progressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>19/260 (7%)</td>
</tr>
<tr>
<td>2 years</td>
<td></td>
</tr>
<tr>
<td>3 years</td>
<td></td>
</tr>
<tr>
<td>4 years</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td></td>
</tr>
</tbody>
</table>

Limitations: On-study Progressions with imatinib data come from different trials with different durations of follow-up. Progression was defined differently in each trial. No cross trial comparison can be made.

Goals of Therapy

- Prolong survival ✓
- Prevent progression ✓
  - Time at Risk ✓
- Quality of Life ✓
  - Reduce toxicities ✓
- Cost smart ✓
  - Treatment Free Remission

Outcome of interest to clinician
Evidence based medicine

• **More potent TKIs:**
  – Faster response
  – Deeper response

• **Lower risk for:**
  – Progression and transformation
  – Mutations

• **Signals toward better PFS and OS**
Making the decision

According to:

• Disease risk assessment
• Side Effect profile
• FDA and Saudi FDA approved.
The result is:

**Warning**

AS per ELN 2013 recommendations

Intermediate zone between optimal response and failure. Based on disease characteristics and patient's response to therapy, more frequent monitoring is required.
Patient and community interest !!
Life long TKIs Therapy !!!

• Occurrence of chronic low-grade adverse events
  – Impaired Quality of Life
  – Risk of inadequate drug compliance and poorer clinical outcome

• Eliasson L et al., Leuk Res, 2011;35(5):626-30
• Noens L et al., Blood, 2009;13:5401–5411
• Marin DJ et al., Clin Oncol, 2010;28:2381–2388
• Akker M van den et al., J Clin Epidemiol, 1998;51:367–375

• Akker M van den et al., EurJ GenPract, 1996;14:65–70
• Tasigna®Prescription information; September 2015.Novartis Pharma GmbH
• Glivec®Prescription information; May 2016.Novartis Pharma GmbH
• Bansal D et al., Pediatr Blood Cancer, 2012;59(3):481-4
Life long TKIs Therapy !!!

• Occurrence of chronic low-grade adverse events
  – Impaired Quality of Life
  – Risk of inadequate drug compliance and poorer clinical outcome

• Age-increasing incidence of multi-morbidity requires intake of several drugs, leading to a higher risk for medication interaction

- Marin DJ et al., Clin Oncol, 2010;28:2381–2388
- Akker M van den et al., J Clin Epidemiol, 1998;51:367–375
- Akker M van den et al., EurJ GenPract, 1996;14:65–70
- Tasigna®Prescription information; September 2015.Novartis Pharma GmbH
- Glivec®Prescription information; May 2016.Novartis Pharma GmbH
Life long TKIs Therapy !!!

- Occurrence of chronic low-grade adverse events
  - Impaired Quality of Life
  - Risk of inadequate drug compliance and poorer clinical outcome
- Age-increasing incidence of multi-morbidity requires intake of several drugs, leading to a higher risk for medication interaction
- No TKI during pregnancy and nursing

CAUSES BIRTH DEFECTS

DO NOT GET PREGNANT

- Marin DJ et al., Clin Oncol, 2010;28:2381–2388
- Akker M van den et al., J Clin Epidemiol, 1998;51:367–375
- Akker M van den et al., EurJ GenPract, 1996;14:65–70
- Tasigna® Prescription information; September 2015. Novartis Pharma GmbH
- Glivec® Prescription information; May 2016. Novartis Pharma GmbH
Life long TKIs Therapy !!!

- Occurrence of chronic low-grade adverse events
  - Impaired Quality of Life
  - Risk of inadequate drug compliance and poorer clinical outcome
- Age-increasing incidence of multimorbidity requires intake of several drugs, leading to a higher risk for medication interaction
- No TKI during pregnancy
- Negative impact on growth and development in children and adolescents

- Marin DJ et al., Clin Oncol, 2010;28:2381–2388
- Akker M van den et al., J Clin Epidemiol, 1998;51:367–375
- Akker M van den et al., EurJ GenPract, 1996;14:65–70
- Tasigna® Prescription information; September 2015. Novartis Pharma GmbH
- Glivec® Prescription information; May 2016. Novartis Pharma GmbH
Life long TKIs Therapy !!!

- Lifelong CML-therapy; Cost implications on the patient and the community

- Marin DJ et al., Clin Oncol, 2010;28:2381–2388
- Akker M van den et al., J Clin Epidemiol, 1998;51:367–375

- Akker M van den et al., EurJ GenPract, 1996;14:65–70
- Tasigna® Prescription information; September 2015.Novartis Pharma GmbH
- Glivec® Prescription information; May 2016.Novartis Pharma GmbH
TFR and QoL
Long-term Adherence to Imatinib Is Critical for Achieving Molecular Response

STIM study design

N=100

Start Imatinib

CMR

Sustained CMR for ≥ 2 years

STOP

Q-RT-PCR from peripheral blood every month in the first year and every 2 months thereafter

Molecular recurrence: positivity of BCR-ABL transcript in Q-RT-PCR confirmed by a second analysis point indicating the increase of one log in relation to the first analysis point, at two successive assessments, or loss of MMR at one point.

Five BCR-ABL analyses by Q-RT-PCR during these 2 years

Sixth datapoint checked in centralized laboratory

STIM1: Patients With Sustained Deep Molecular Responses on Imatinib Can Maintain TFR

Patients: n = 100
Events: n = 62 (61 molecular recurrence, 1 death)

Median follow-up: 65 months (range, 10–84)

- After 6 months: 10% risk of molecular relapse at 24 months

STIM: Low Sokal Score and Previous Imatinib ≥5y Are Prognostic For Reduced Relapse Risk

Survival without Molecular Relapse

At 24 Months:
- Sokal Low + IM > 5 y: 68% (95%CI: 45–83)
- Others: 33% (95%CI: 22–42)

P = .007

Survival Since Discontinuation of Imatinib

<table>
<thead>
<tr>
<th>Multivariate analysis (Cox model)</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sokal score</td>
<td>2.555 (1.278 -5.119)</td>
<td>0.008</td>
</tr>
<tr>
<td>IM duration (≥ 5 y vs &lt; 5 y)</td>
<td>0.582 (0.340 -0.995)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

Cost Saving

• Taking into account the cost of imatinib and the number of months without treatment.

The Saving in STIM (1 & 2) = 8.6 millions €
EURO-SKI Study Design

Patients included between May 2012 and December 2014

Inclusion criteria
TKI treatment at least 3 years
MR⁴ at least 1 year

Study start

Screening phase (Confirming MR⁴)

RQPCR q4w
RQPCR q6w
RQPCR Every 3rd month

Follow-up

≤ 6 weeks
Year 1
Year 2
Year 3

Informed consent
Stop TKI

Relapse defined as BCR-ABL > 0.1% (loss of MMR) on the IS at one time point

Courtesy of ELN
EURO-SKI: Molecular Relapse–Free Survival (n= 750)

- Longer duration of imatinib-therapy (optimal ≥ 5.8 years) correlates to higher probability of relapse-free survival at 6 months.

Events:
- Molecular relapse n = 348
- Death in remission n = 5

For patients who resumed treatment, median time to restart was 4.1 months.

EURO-SKI, European Stop TKI.
Richter et al, Haematologica 2016 [abstract S145]
Univariate analysis for relapse free survival at 6 months

Significant association
• Treatment duration with imatinib
• MR4 duration
• Duration of IFN pre-treatment

No significant association
• Age
• Gender
• Depth of molecular response (MR4.5 vs. not in MR4.5)
• any variable part of the Sokal, EURO, EUTOS or ELTS scores
ENEST freedom: Study Design

- Adult patients with ≥ 2 y frontline nilotinib
- Achieved MR4.5 on nilotinib
- Typical BCR-ABL transcripts

n = 215

Response required to attempt TFR:
- MR4.5 (assessed at central laboratory) prior to enrollment
- Sustained DMR\(^\text{a}\) during consolidation phase

DMR, deep molecular response; RQ-PCR, real-time quantitative polymerase chain reaction.
\(^\text{a}\) Sustained DMR is defined as the following results from the last 4 quarterly performed PCR assessments: MR4.5 at last assessment, no assessment worse than MR4, no more than 2 assessments between MR4 and MR4.5.
\(^\text{b}\) If no sustained DMR after this point, patients may continue to receive nilotinib in the prolonged continuation phase until the end of the study.

ENEST freedom: Kaplan-Meier Estimated Treatment-Free Survival

51.6% of patients (95% CI, 44.2%-58.9%) remained in TFR after 48 weeks (primary endpoint)

Nilotinib Results in Higher Rates of MR4.5 vs Imatinib

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

**ENEST1st**
- Nilotinib 300 mg BID (n = 1052)

---

BID, twice daily; MR4.5, BCR-ABL1 ≤ 0.0032%; ENESTnd, ENEST–Newly Diagnosed Patients; QD, once daily.

a Nominal P < 0.05 vs imatinib.

ENESTfreedom: Response to Nilotinib Re-initiation

- 50% of all retreated patients achieved MMR and MR4.5 by week 7.9 and week 15.0 of treatment reinitiation, respectively

### Table 1. Clinical studies of TKI discontinuation in patients with CML in chronic phase

<table>
<thead>
<tr>
<th>Study trials of imatinib discontinuation</th>
<th>N</th>
<th>Treatment before discontinuation</th>
<th>TFR</th>
<th>Median follow-up time, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>STIM\textsuperscript{1,2}</td>
<td>100</td>
<td>IFN then imatinib for $\geq 3$ y</td>
<td>43% at 6 mo, 38% at 60 mo</td>
<td>77</td>
</tr>
<tr>
<td>KIDS\textsuperscript{3}</td>
<td>156</td>
<td>Imatinib for $\geq 3$ y</td>
<td>59% at 24 mo</td>
<td>27</td>
</tr>
<tr>
<td>TWISTER\textsuperscript{2,7}</td>
<td>40</td>
<td>Imatinib for $\geq 3$ y</td>
<td>47% at 24 mo</td>
<td>42</td>
</tr>
<tr>
<td>ASTIM\textsuperscript{2,8}</td>
<td>80</td>
<td>Imatinib for $\geq 3$ y</td>
<td>64% at 24 mo</td>
<td>23</td>
</tr>
<tr>
<td>ISAV\textsuperscript{9}</td>
<td>112</td>
<td>IFN</td>
<td>48% at 36 mo</td>
<td>22</td>
</tr>
<tr>
<td>EURO-SKI\textsuperscript{2,10}</td>
<td>755</td>
<td>TKI $\geq 3$ y</td>
<td>Preliminary results</td>
<td>61% at 6 mo</td>
</tr>
<tr>
<td>STOP 2G-TKI pilot\textsuperscript{2,11}</td>
<td>60</td>
<td>Nilotinib or dasatinib</td>
<td>63% at 12 mo, 54% at 48 mo</td>
<td>47</td>
</tr>
<tr>
<td>ENESTFreedom\textsuperscript{2,12}</td>
<td>175</td>
<td>Nilotinib front line</td>
<td>52% at 11 mo</td>
<td>11</td>
</tr>
<tr>
<td>ENEStop\textsuperscript{2,13}</td>
<td>117</td>
<td>Second-line nilotinib</td>
<td>58% at 11 mo</td>
<td>11</td>
</tr>
<tr>
<td>($\geq 3$ y total; $\geq 2$ y nilotinib)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DADI\textsuperscript{2,14}</td>
<td>156</td>
<td>Dasatinib</td>
<td>49% at 6 mo, 48% at 12 mo</td>
<td>20</td>
</tr>
</tbody>
</table>
TKI Discontinuation/TFR
A Novel Treatment Milestone

• Multiple studies have consistently demonstrated the safety and feasibility of stopping treatment
• TKI discontinuation is an emerging goal of CML management and is happening right now
• Patient awareness of TFR has resulted in increasing need for who can appropriately discontinue TKI
• A sustained DMR and long-term TKI therapy seem to be necessary prior to attempting TFR
Are we ready for routine discontinuation?

• Treatment discontinuation may be considered in individual patients, if proper, high-quality, and certified monitoring can be ensured.

• Pre-requisites for safe stopping are:
  1. Institutional requirements for safe supervision
  2. Identification of typical BCR-ABL1 transcripts at diagnosis
  3. At least 5 years of TKI therapy
  4. Achievement of DMR (MR4 - MR4.5)
  5. Stability of DMR (at least MR4) for at least 2 years
HOPE