Role of Second Generation Tyrosine Kinase Inhibitors in Newly Diagnosed CML

GIUSEPPE SAGLIO, MD
University of Torino, Italy
Outcome in 282 Patients Treated with Imatinib First Line in Hammersmith Hospital

In the natural history of the disease, progression would occur in almost 100% of the cases in rather short median time (3-4 years)
Survival of Patients after Progression Is Still Very Poor. Prevention of Progression Is the Goal of Therapy

% Alive

Median survival ~10.5 months

Imatinib

BCR-ABL TK inhibition

Number of Leukaemic cells & Propensity to progress

Risk of Progression
IRIS 8-Year Update: Majority of Events Occur Early

- Loss of CHR
- Loss of MCyR
- AP/BP
- Death during treatment

Registered TKIs in first-line CML treatment

- Imatinib 400 mg
- Nilotinib 300 mg BID
- Dasatinib 100 mg QD
ENESTnd: Study Design

**Randomized**

- N = 846
- 217 centers
- 35 countries

*Stratification by Sokal risk score*

Follow-up 5 years

3 years follow-up report at ASH 2011

ENESTnd: Cumulative Incidence of MMR

% With MMR

- Nilotinib 300 mg BID: 282
- Nilotinib 400 mg BID: 281
- Imatinib 400 mg QD: 283

By 1 Year:
- Nilotinib 300 mg BID: 55%, P < .0001
- Nilotinib 400 mg BID: 51%, P < .0001
- Imatinib 400 mg QD: 27%

Δ 24%-28%

By 2 Years:
- Nilotinib 300 mg BID: 71%, P < .0001
- Nilotinib 400 mg BID: 67%, P < .0001
- Imatinib 400 mg QD: 44%

Δ 17%-20%

By 3 Years:
- Nilotinib 300 mg BID: 73%, P < .0001
- Nilotinib 400 mg BID: 70%, P < .0001
- Imatinib 400 mg QD: 53%

Δ 17%-20%

3-5% of patients across treatment arms lost MMR
All nilotinib pts who remained on study after loss of MMR regained MMR


Rates of MMR were consistently higher in patients treated with nilotinib vs imatinib across Low, Intermediate, or High Sokal risk scores.


ENESTnd: Cumulative Incidence of MR4.5*

* Equivalent to BCR-ABl transcript levels of ≤ 0.0032% (IS).


ENESTnd 3 Year Update: Progression to AP/BC* on Core Treatment

- No new progressions occurred on core treatment since the 2-year analysis.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients, n</th>
<th>Proportion</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib 300 mg BID</td>
<td>2</td>
<td>0.7%</td>
<td>0.0059</td>
</tr>
<tr>
<td>Nilotinib 400 mg BID</td>
<td>3</td>
<td>1.1%</td>
<td>0.0185</td>
</tr>
<tr>
<td>Imatinib 400 mg QD</td>
<td>12</td>
<td>4.2%</td>
<td>P = .0003</td>
</tr>
<tr>
<td>Including Clonal Evolution</td>
<td>2</td>
<td>0.7%</td>
<td>P = .0085</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>1.8%</td>
<td>6.0%</td>
</tr>
</tbody>
</table>

*Progression to AP/BC or death following progression.


What Is the Nature of the Residual Population? Different with Different TKIs?
Progression to AP/BC According to Sokal Risk

<table>
<thead>
<tr>
<th>Progression to AP/BC, n</th>
<th>Total</th>
<th>Nilotinib 300 mg BID n = 282</th>
<th>Nilotinib 400 mg BID n = 281</th>
<th>Imatinib n = 283</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>17</td>
<td>2</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>By Sokal Risk, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Intermediate</td>
<td>10</td>
<td>1</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>High</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

Regardless of treatment, the majority of progressions occurred in patients with intermediate or high Sokal risk scores.

### Emergent Mutations According to Sokal Risk

<table>
<thead>
<tr>
<th>Patients with mutation(s), n</th>
<th>Total</th>
<th>Nilotinib 300 mg BID n = 282</th>
<th>Nilotinib 400 mg BID n = 281</th>
<th>Imatinib n = 283</th>
</tr>
</thead>
<tbody>
<tr>
<td>By Sokal Risk, n</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>4</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Intermediate</td>
<td>16</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>High</td>
<td>23</td>
<td>5</td>
<td>6</td>
<td>12</td>
</tr>
</tbody>
</table>

- Regardless of treatment, the majority of emergent mutations were identified in patients with intermediate or high Sokal risk scores.
**ENESTnd: BCR-ABL Mutations Identified on Treatment**

<table>
<thead>
<tr>
<th></th>
<th>Nilotinib 300 mg BID</th>
<th>Nilotinib 400 mg BID</th>
<th>Imatinib 400 mg QD</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>282</td>
<td>281</td>
<td>283</td>
</tr>
<tr>
<td>Patients with mutation(s), n</td>
<td>11</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Mutation category, n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T315I</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Less sensitive to nilotinib*</td>
<td>6</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>Other mutations†</td>
<td>2‡</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Multiple mutations§</td>
<td>3</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

* Mutations less sensitive to nilotinib: E255K/V, Y253H, and F359C/V.
† All mutations except E255K/V, Y253H, F359C/V and T315I.
‡ Of the 2 nilotinib-treated patients with other mutations, 1 had an E459K mutation and the other had a G250E mutation.
§ Multiple mutations were identified as follows for each arm. Nilotinib 300 mg BID: Y253H/F359V(1), E255K/T315I(1), T315I/F359V(1); Nilotinib 400 mg BID: Q252H/T315I(1), Y253H/T315I(1); Imatinib 400 mg QD: M244V/T315I(1), Y253H/F359I(1), H396R/M351T(1).
Individual mutation totals include patients > 1 mutation.

BID, twice daily; QD, once daily.


ENESTnd: Progression to AP/BC: Including Events After Discontinuation (ITT)*

- Off treatment progression information was prospectively collected for all patients every 3 months after discontinuation.

*Progression to AP/BC or CML-related death.

Survival After Progression to AP/BC (ENESTnd)

Median survival ~10.5 months

Progressed = 34
Died = 23
Alive = 11


Survival After Progression to AP/ BC (ENESTnd and IRIS)


Significantly fewer CML-related deaths on nilotinib than on imatinib, better overall survival
DASISION (CA180-056): Study Design

- Treatment-naïve CML-CP patients (N=519)
- 108 Centers
- 26 Countries

Randomized

- Dasatinib 100 mg QD (N=259)
- Imatinib 400 mg QD (N=260)

Primary endpoint: Confirmed CCyR (cCCyR) by 1 year

Long-term follow-up

Jabbour et al., EHA 2012

# DASISON: Patient Disposition and Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Dasatinib 100 mg QD N=258</th>
<th>Imatinib 400 mg QD N=258</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treated patients, n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still on treatment</td>
<td>183 (71)</td>
<td>179 (70)</td>
</tr>
<tr>
<td>Discontinued</td>
<td>75 (30)</td>
<td>79 (31)</td>
</tr>
<tr>
<td>Progression(^a)</td>
<td>17 (7)</td>
<td>18 (7)</td>
</tr>
<tr>
<td>Treatment failure</td>
<td>8 (3)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Adverse event (AE)</td>
<td>27 (11)</td>
<td>16 (6)</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td>20 (8)</td>
<td>12 (5)</td>
</tr>
<tr>
<td>Hematologic</td>
<td>7 (3)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Unrelated AE</td>
<td>6 (2)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Death(^b)</td>
<td>4 (2)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Poor/nonadherence</td>
<td>0 (0)</td>
<td>4 (2)</td>
</tr>
<tr>
<td>Other(^c)</td>
<td>13 (5)</td>
<td>26 (10)</td>
</tr>
</tbody>
</table>

\(^a\)Increasing WBC count; loss of CHR; loss of MCyR, including 30% rise in Ph+ metaphases and additional chromosomal abnormalities; or progression to AP/BP
\(^b\)Discontinuation due to death, which represents a subset of total deaths: 17 deaths overall in dasatinib arm, 20 deaths in imatinib arm
\(^c\)Includes consent withdrawal, loss to follow-up, pregnancy, patient request, and poor/nonadherence

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].
DASISION: Cumulative Incidence of MMR (BCR-ABL ≤0.1%)

Dasatinib 100 mg QD vs Imatinib 400 mg QD

By 1 year
- Dasatinib: 46%
- Imatinib: 23%

By 2 years
- Dasatinib: 64%
- Imatinib: 46%

By 3 years
- Dasatinib: 68%
- Imatinib: 55%

1.6-Fold higher likelihood of achieving MMR with dasatinib; HR=1.62 (1.30-2.02)

Hasford Risk Score
- Low: Dasatinib 83%, Imatinib 65%
- Intermediate: Dasatinib 65%, Imatinib 57%
- High: Dasatinib 61%, Imatinib 43%

## DASISION: Transformation To AP/BP CML by 3 Years

### Study Design

<table>
<thead>
<tr>
<th>Treatment</th>
<th>On study</th>
<th>Including follow-up beyond discontinuation (ITT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dasatinib 100 mg QD</td>
<td>8</td>
<td>11</td>
</tr>
<tr>
<td>Imatinib 400 mg QD</td>
<td>13</td>
<td>16</td>
</tr>
</tbody>
</table>

Number of Patients, n

<table>
<thead>
<tr>
<th>N</th>
<th>259</th>
<th>260</th>
</tr>
</thead>
</table>

*Yearly evaluations after discontinuation are currently stipulated per protocol; additional information on patient status may be provided by investigators at other times*

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].
## DASISION: Overall Survival (OS) and Progression Free Survival (PFS)

<table>
<thead>
<tr>
<th></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>Total number of deaths, a n</td>
<td>17</td>
<td>20</td>
<td>-</td>
</tr>
<tr>
<td>Estimated 3-year OS, %</td>
<td>93.7 (90.6-96.7)</td>
<td>93.2 (90.1-96.4)</td>
<td>HR=0.86 (0.45-1.65)</td>
</tr>
<tr>
<td>Estimated 3-year PFS, %</td>
<td>91.0 (87.4-94.7)</td>
<td>90.9 (87.1-94.6)</td>
<td>HR=1.00 (0.55-1.80)</td>
</tr>
</tbody>
</table>

aOn study treatment and in follow-up after discontinuation of randomized treatment

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].
No new on-treatment transformations to AP/BP CML have occurred on bosutinib since the 12-month primary analysis, compared with 3 new events on imatinib.

The majority of deaths (bosutinib, n = 5/7; imatinib, n = 9/13) occurred more than 28 days after treatment discontinuation.

- Deaths due to CML progression occurred in 6/7 patients receiving bosutinib and 10/13 patients receiving imatinib.

AP, accelerated phase; BP, blast phase.

Treatment failure/disease progression includes both on-treatment transformation to AP/BP and lack of efficacy. Patients were followed for up to 8 years from randomization (treatment plus long-term follow-up phases).

Degree of Molecular Response at Early Timepoints Predicts PFS and EFS

5-y PFS: 93% vs 72%; P = .0023

5-y EFS: 88% vs 77%; P = .012

Patients randomized to imatinib-based therapies in the German CML Study IV

BCR-ABL% (IS) at 3 months

< 10%

>10%
DASISION: Molecular and Cytogenetic Response at 3 Months

- **≤10% BCR-ABL at 3 Months**
  - BCR-ABL of <10% and ≤1% are not fully concordant with ≥PCyR and CCyR, respectively.
  - 96% and 83% of dasatinib and imatinib pts with ≥PCyR had <10% BCR-ABL, respectively.
  - 68% and 26% of dasatinib and imatinib pts with CCyR had ≤1% BCR-ABL, respectively.

- **PCyR/CCyR at 3 Months**
  - Calculated from total number of evaluable patients with PCR assessments at 3 months; restricted to subjects with B2A2 and B3A2 transcripts.

**Dasatinib 100 mg QD**

- 84% of patients had >1-10% BCR-ABL.
- 64% of patients had >1-10% BCR-ABL.

**Imatinib 400 mg QD**

- 81% of patients had CCyR.
- 67% of patients had CCyR.

*Jabbour J, et al. Haematologica. 2012;97(s1) [abstract 1106].*
ENESTnd: BCR-ABL Categories at 3 Months*

- **Nilotinib 300 mg BID (N = 258)**
  - ≤ 10%: 234 patients (91%)
  - > 1-10%: 176 patients (67%)
  - > 10%: 24 patients (9%)

- **Imatinib (N = 264)**
  - ≤ 10%: 24 patients (9%)
  - > 1-10%: 88 patients (33%)

**Reasons for unevaluable samples:**
- Atypical transcripts: 5 patients on nilotinib, 2 patients on imatinib
- Missing samples: 4 patients on nilotinib, 5 patients on imatinib
- Discontinued: 15 patients (incl. 1 progression) on nilotinib, 12 patients (incl. 1 progression) on imatinib

**PFS/OS events prior to 3 months:** 1 PFS event in each arm, no deaths

Advantages of Second Generation TKIs With Respect to Imatinib

✓ Faster and deeper responses
✓ Less progression events
✓ Earlier identification of patients with inferior outcome

– Higher and faster possibilities of treatment discontinuation?
Potential Options for CML First-line Therapy

– Imatinib or 2\textsuperscript{nd} generation TKIs as first-line therapy?

– 2\textsuperscript{nd} generation TKIs only for specific groups of patients like patients at a higher risk of progression, younger patients, etc……?  

– Still imatinib 400mg as initial therapy for most patients and than early switch to 2nd-gen TKIs in case of non-optimal response?
Non optimal response to Imatinib $\rightarrow$ 2\textsuperscript{nd} gen. TKIs

Clinical benefit?

Non optimal response to 2\textsuperscript{nd} gen. TKIs $\rightarrow$ ???

3\textsuperscript{rd} generation TKIs (like ponatinib)?
AlloSCT for specific patients?
Combination therapies?
Thank you!