Discontinuation of Imatinib in Patients with Chronic Myeloid Leukemia Who Have Maintained Complete Molecular Response: Update Results of the STIM

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on behalf of the STIM Investigators
### Disclosures for François-Xavier Mahon, MD, PhD, Hematologist

In compliance with ACCME policy, ASH requires the following disclosures to the session audience:

<table>
<thead>
<tr>
<th>Category</th>
<th>Details</th>
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<tr>
<td>Research Support/P.I.</td>
<td>PHRC (french minister)</td>
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<td>No relevant conflicts of interest to declare</td>
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<td>No relevant conflicts of interest to declare</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: [N/A]
Background

- Imatinib treatment significantly improves survival in pts with CML.

- We previously demonstrated that Imatinib could be safely discontinued in pts with a sustained CMR, i.e., of at least 2 years duration.

- Little is known about whether treatment can safely be discontinued in the long term.

- We present the updated results from the first 100 pts included in the STIM study with a longer follow up.

STOP IMatinib TRIAL: Key Issues

- What is the risk of molecular recurrence after discontinuation with a longer follow up?
- Which category of patients may most benefit from treatment discontinuation?
- Is it safe to stop therapy?
STOP IMatinib TRIAL: Key Issues

- What is the risk of molecular recurrence after discontinuation with a longer follow up?
- Which category of patients may most benefit from treatment discontinuation?
- Is it safe to stop therapy?
Baseline characteristics of the 100 pts

- Number of patients included: 100
- Median age (range): 63 years (29–80)
- Gender distribution: 48 males, 52 females
- Patients with previous IFN treatment: 51
- De novo patients: 49
- Median Follow up: 34 months (range 9-50)
The overall probability of maintenance of CMR at 24 and 36 months was 39% (95% CI 29-48).

Molecular relapse occurred in 61 pts with 58 relapses occurring during the first 7 months 3 late relapses at month 19, 20 and 22, respectively.
STop IMatinib TRIAL: Key Issues

• What is the risk of molecular recurrence after discontinuation with a longer follow up?

• Which category of patients may most benefit from treatment discontinuation?

• Is it safe to stop therapy?
Kaplan-Meier estimates of CMR after discontinuation of imatinib in 100 patients with CML according to factor

By gender

At 24 Months:

- Male: 45% (95% CI: 31–59)
- Female: 33% (95% CI: 21–45)

p = 0.105
Kaplan-Meier estimates of CMR after discontinuation of imatinib in 100 patients with CML according to factor

By previous treatment

At 24 Months:
- IFN: 44% (95% CI: 30–58)
- No IFN: 33% (95% CI: 20–46)

p = 0.246
Kaplan-Meier estimates of CMR after discontinuation of imatinib in 100 patients with CML according to factor

By SOKAL score

At 24 Months:
- Low: 53% (95% CI: 38–66)
- Inter: 29% (95% CI: 16–44)
- High: 17% (95% CI: 03–41)
- Unk: 0%

Among the 11 patients with high Sokal risk score, 9 patients relapsed.
Freedom from Molecular Relapse by Median Duration of Imatinib Treatment

At 24 Months:

- $\geq 5$ years: 50% (95% CI: 35–63)
- $< 5$ years: 29% (95% CI: 17–41)

$p = 0.140$
## Logistic regression at 8 months: all early relapses included n = 58

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
<th># (final model)</th>
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<tbody>
<tr>
<td><strong>Age at Discontinuation</strong> §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No relapse</td>
<td>60</td>
<td>0.315</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>61</td>
<td></td>
<td></td>
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<tr>
<td><strong>Gender</strong> £</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48%</td>
<td>0.050</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>67%</td>
<td></td>
<td></td>
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<tr>
<td><strong>Sokal score</strong> £</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>45%</td>
<td>0.026</td>
<td>0.005</td>
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<tr>
<td>Intermediate</td>
<td>65%</td>
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<tr>
<td>High</td>
<td>83%</td>
<td></td>
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<tr>
<td><strong>Interferon</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>49%</td>
<td>0.060</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>67%</td>
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<tr>
<td><strong>Time to CMR</strong> §</td>
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<tr>
<td>No relapse</td>
<td>19</td>
<td>0.378</td>
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<tr>
<td>Relapse</td>
<td>17</td>
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<tr>
<td><strong>CMR duration</strong> §</td>
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<tr>
<td>No relapse</td>
<td>38</td>
<td>0.363</td>
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</tr>
<tr>
<td>Relapse</td>
<td>35</td>
<td></td>
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</tr>
<tr>
<td><strong>IM duration</strong> §</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No relapse</td>
<td>66</td>
<td>0.080</td>
<td>0.028</td>
</tr>
<tr>
<td>Relapse</td>
<td>55</td>
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§ Median (months)
£ Percentage relapsing

\# Logistic regression
Multivariate Analysis Cox model over all patients and all relapses

<table>
<thead>
<tr>
<th>Multivariate analysis Cox model</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
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<tr>
<td>Sokal score</td>
<td>2.555 (1.278 - 5.119)</td>
<td>0.008</td>
</tr>
<tr>
<td>IM duration &gt;60 months vs ≤60 months</td>
<td>0.582 (0.340 - 0.995)</td>
<td>0.047</td>
</tr>
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Final Model => 2 independent prognostic factors
Kaplan-Meier estimates of CMR after discontinuation of imatinib in 100 pts according to combined factors.

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

p = 0.007
What is the risk of molecular relapse after discontinuation with a longer follow up?

Which category of patients may most benefit from treatment discontinuation?

Is it safe to stop therapy?
All patients are sensitive after imatinib re-challenge

Among the 61 with molecular recurrence 10 are not in sustained CMR

Five return to CMR after imatinib rechallenge but exhibited a fluctuation in BCR-ABL transcripts.

Five pts did not return to CMR, with a median values of BCR-ABL level of 0.19% (0.005-0.8) because they did not want to take a treatment as soon as they relapsed.
Among the 39 pts without confirmed molecular relapse, 5 exhibited clearly a fluctuation in BCR-ABL transcript detection.
STOP IMatinib TRIAL: Key Issues

• What is the risk of molecular recurrence after discontinuation with a longer follow up?

• Which category of patients may most benefit from treatment discontinuation?

• Is it safe to stop therapy?

• Shall we speculate that we will increase the numbers of patients who stop treatment?
Discontinuation of Dasatinib or Nilotinib in Chronic Myeloid Leukemia (CML) Patients (pts) with Stable Undetectable Bcr-Abl Transcripts: Results From the French CML Group (FILMC)

Delphine Rea, MD¹*, Philippe Rousselot, MD, PhD²*, Franck E. Nicolini, MD, PhD³, Laurence Legros⁴*, Michel Tulliez⁵*, Stephane Giraudier, MD, PhD⁶*, Pascale Cony-Makhoul, MD⁷*, Francois Guilhot, MD, PhD⁸ and Francois-Xavier Mahon, MD, PhD⁹*
Conclusions

• I will recommend to propose discontinuation only in a clinical trial with close molecular monitoring.

• The most important factors to predict recurrence after discontinuation:
  i) the inherent nature of the disease (illustrate by the Sokal score).
  ii) the duration of therapy.

• Taking into account the number of months without treatment in the study at last analysis, the savings within the STIM trial were estimated at 4 millions Euros.