



Key ASH Presentations
Issue 8, 2012

Discontinuation of Imatinib, Dasatinib or Nilotinib in CML

CME INFORMATION

OVERVIEW OF ACTIVITY

The annual American Society of Hematology (ASH) meeting is unmatched in its importance with regard to advancements in hematologic cancer and related disorders. It is targeted by many members of the clinical research community as the optimal forum in which to unveil new clinical data. This creates an environment each year in which published results and new information lead to the emergence of many new therapeutic agents and changes in the indications for existing treatments across virtually all malignant and benign hematologic disorders. As online access to posters and plenary presentations is not currently available, a need exists for additional resources to distill the information presented at the ASH annual meeting for those clinicians unable to attend but desiring to remain up to date on the new data released there. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists, hematologists and hematology-oncology fellows in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Apply emerging clinical trial data to the rational selection of treatment with targeted tyrosine kinase inhibitors for patients with refractory or relapsed chronic myeloid leukemia.
- Assess the risks of molecular relapse after the discontinuation of treatment with targeted tyrosine kinase inhibitors in patients with chronic myeloid leukemia.
- Communicate the benefits and risks of therapy with multitargeted tyrosine kinase inhibitors for patients with newly diagnosed, relapsed or refractory chronic myeloid leukemia in chronic, accelerated or blast phase.
- Compare and contrast the benefits and adverse effects of continuous therapy with different targeted tyrosine kinase inhibitors in the treatment of chronic myeloid leukemia.

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To go directly to slides and commentary for this issue, [click here](#).

The 2009 ASH meeting marked a high point in the amazing and continuing evolution of the management of chronic phase chronic myelogenous leukemia (CML-CP) with the sudden appearance of several convincing Phase III data sets demonstrating that the second-generation BCR-ABL TKIs nilotinib and dasatinib resulted in improvements in a number of major short-term endpoints and were equally or better tolerated compared to imatinib. These and other recent findings also put into sharp focus the fact that despite the impressive steps forward during the last decade there is room for improvement in CML-related outcomes, including survival. For this issue of our series we briefly review 8 new ASH data sets addressing the following important CML questions:

1. [What is the role of second-generation TKIs?](#)

The weight of evidence for the newer agents continues to mount, and at ASH another round of related data sets was reported.

More follow-up on up-front nilotinib versus imatinib

The landmark IRIS trial that established the role of imatinib demonstrated that most disease progression events occurred within 3 years, and as such similar follow-up with the newer TKIs is critical. At ASH, 3-year data from the ENESTnd trial of nilotinib versus imatinib revealed continued separation of the curves for major and deeper molecular response. Importantly, in the imatinib arm a 6% rate of progression to accelerated phase and blast crisis (AP/BC) was observed compared to only 0.7% with 300 mg BID of nilotinib.

Switching TKIs at 1 year

Many/most investigators currently prefer nilotinib or dasatinib as first-line therapy, but any imatinib holdouts will be forced to strongly consider the compelling preliminary results from the ENESTcmr Phase III trial assessing the benefit of switching therapy for individuals who do not achieve complete molecular response (CMR) after treatment with imatinib. In the study, 207 patients in complete cytogenetic response (CCyR) but with detectable BCR-ABL less than 2 years after starting imatinib were randomly assigned

to either continue therapy or switch to nilotinib 400 mg BID. At 12 months of follow-up, the rate of confirmed CMR was 5.8% with imatinib compared to 12.5% for nilotinib.

Nilotinib 400 mg BID

The ENESTnd extension trial reported at ASH evaluated the higher 400-mg BID dose of nilotinib in patients with suboptimal response or treatment failure on imatinib or nilotinib at 300 mg BID. The findings illustrate clear-cut efficacy in patients treated with prior imatinib — even after dose escalation — and also point to a benefit in those escalated to the higher nilotinib dose. Currently, 300 mg BID is still the recommended starting dose up front.

2. Are there even newer TKIs with significant supportive trial data?

Ponatinib

Ponatinib has been previously shown to have notable activity in tumors with otherwise problematic T315I mutations, and the clinical impact of this agent in resistant or intolerant disease was once again displayed in an impressive Phase II trial of 403 patients reported at ASH.

Bosutinib

Another data set presented at ASH came from the Phase III BELA trial comparing bosutinib to imatinib in patients with newly diagnosed CML-CP. The study did not meet its primary endpoint of CCyR at 12 months partly due to early treatment discontinuation in about a quarter of the patients related to bosutinib-associated adverse effects, particularly GI toxicity (diarrhea). However, other endpoints favored the new TKI bosutinib — including a lower rate of progression to AP/BC — and the future role of the agent is still up for debate.

3. How early can suboptimal response be identified?

The answer just might be 3 months, based on findings from an ASH presentation showing that patients on imatinib with >10% BCR-ABL levels or >35% Ph+ cells at the 3-month time point had a 5-year survival rate of only 87%. Ongoing trials are evaluating an early switch to another TKI in these patients.

4. Can TKI treatment ever be stopped?

Although disease control is everyone's primary concern, lifelong TKI use introduces quality of life and financial constraints, and as such many have wondered if it is safe to stop therapy at some point. At ASH we saw results from the STIM study evaluating treatment discontinuation in 100 patients who received imatinib and experienced a CMR for at least 2 years. Interestingly, 61% of patients experienced molecular relapse upon

stopping therapy (almost all within 7 months). However, most went back into CMR with re-treatment. The ability to stay off the drug seemed to correlate with disease biology (Sokal score) and duration of therapy. Another ASH report of 25 patients who stopped either nilotinib or dasatinib seemed to reflect a similar conclusion, and indefinite treatment is still recommended outside a trial setting.

Next, our final ASH report: More data and perspectives on non-Hodgkin lymphoma and chronic lymphocytic leukemia.

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Discontinuation of Imatinib, Dasatinib or Nilotinib in CML

Presentations discussed in this issue

Mahon FX et al. **Discontinuation of imatinib in patients with chronic myeloid leukemia who have maintained complete molecular response: Update results of the STIM study.** *Proc ASH 2011*; [Abstract 603](#).

Rea D et al. **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).** *Proc ASH 2011*; [Abstract 604](#).

Slides from presentations at ASH 2011 and transcribed comments from a recent interview with Srdan Verstovsek, MD, PhD (1/25/12)

Discontinuation of Imatinib in Patients with Chronic Myeloid Leukemia Who Have Maintained Complete Molecular Response: Updated Results of the STIM¹

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)²

¹ **Mahon FX et al.**
Proc ASH 2011; Abstract 603.

² **Rea D et al.**
Proc ASH 2011; Abstract 604.

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

Mahon FX et al.

Proc ASH 2011;Abstract 603.

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Background

- Imatinib (IM) treatment significantly improves survival in patients with chronic myeloid leukemia (CML) (*J Clin Oncol* 2011;29:2514).
- A 12-month follow-up from the STIM study showed that IM can be safely discontinued in patients with a sustained complete molecular response (CMR) of ≥ 2 years duration (*Lancet Oncol* 2010;11:1029).
- Little is known about whether treatment can safely be discontinued in the long term.
- **Objective:** Assess the risk of molecular relapse after IM discontinuation after a median follow-up of 34 months.

Mahon FX et al. *Proc ASH 2011;Abstract 603.*

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STIM Study Methods

- Eligibility (N = 100):
 - Patients with CML who had discontinued IM (>2 years duration)
 - Sustained CMR for at least 2 years
 - Patients on prior immunomodulatory Rx (other than IFNa), treatment for other malignancies or allogeneic transplantation excluded
- Rate of relapse assessed by quantitative RT-PCR analysis (positive BCR-ABL transcripts, BCR-ABL/ABL ≥ 0.001).
- Analysis: Every month first year, every 2 months second year, every 3 months thereafter.

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

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Response Following IM Discontinuation and Rechallenge

- Molecular relapse: 61 patients
 - 58 relapses during first 7 months
 - 3 relapses at 19, 20 and 22 months
- Overall probability of maintenance of CMR at 24 and 36 months: 39%
- Patients in molecular relapse were sensitive to challenge with IM
 - 51 patients returned to CMR
 - 5 patients returned to CMR but with BCR-ABL transcript fluctuation
 - 5 patients did not return to CMR

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

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Multivariate Analysis of Relapse

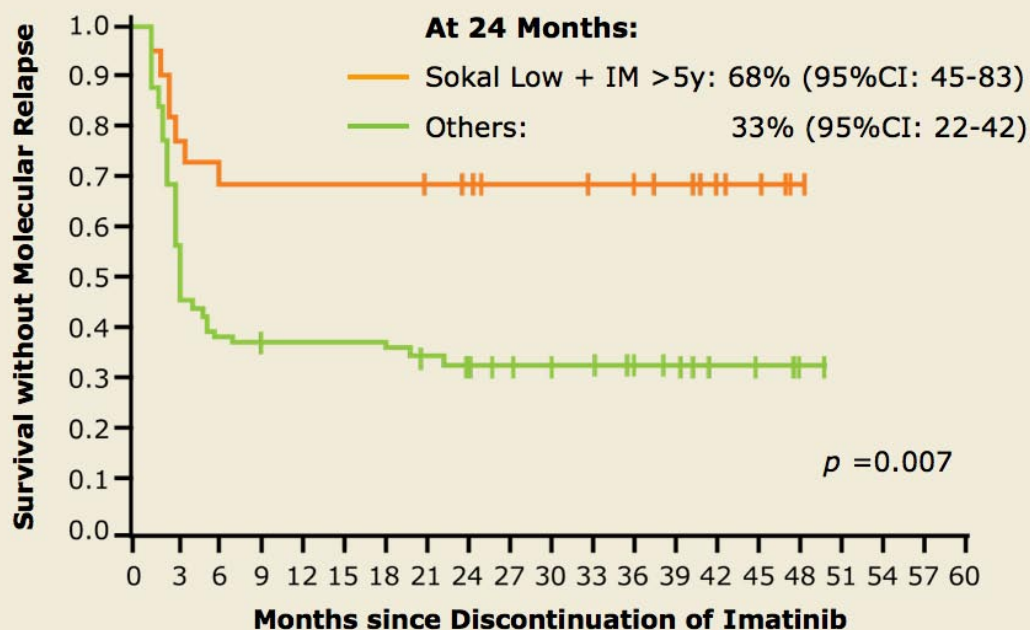
Multivariate analysis Cox model over all patients and all relapses		
Factor	Hazard ratio	p-value
Sokal score	2.555	0.008
Duration of IM therapy (>60 mo vs ≤60 mo)	0.582	0.047

In multivariate analysis of relapse at 8 months, using the Final model, a higher Sokal score ($p = 0.005$) and shorter IM duration ($p = 0.028$) were independent prognostic factors of relapse.

Mahon FX et al. *Proc ASH* 2011;Abstract 603.

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Kaplan-Meier Estimates of CMR After IM Discontinuation According to Combined Factors



With permission from Mahon FX et al. *Proc ASH* 2011;Abstract 603.

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Author Conclusions

- Discontinuation of IM is recommended only in a clinical trial with close molecular monitoring.
- The most important factors that can predict recurrence after discontinuation are:
 1. The inherent nature of the disease (illustrated by the Sokal score)
 2. The duration of therapy

Mahon FX et al. *Proc ASH 2011*;Abstract 603.

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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)

Rea D et al.

Proc ASH 2011;Abstract 604.

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Background

- Dasatinib and nilotinib, 2 highly potent second-generation TKIs (2G-TKI), have been approved in the front-line setting in chronic phase (CP)-CML. However, their curative potential remains uncertain.
- Most patients with CML relapse following treatment discontinuation and require lifelong TKI treatment.
- Results from the STIM trial suggest imatinib (IM) treatment may be discontinued in patients with stable undetectable molecular residual disease (UMRD) (*Lancet Oncol* 2010;11:1029).
- **Objective:** Evaluate the risk of losing major molecular responses (MMR) following discontinuation of 2G-TKI in patients with stable UMRD.

Rea D et al. *Proc ASH* 2011;Abstract 604.

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Study Design

- Eligibility (N = 25):
 - Patients with CP-CML and UMRD proposed discontinuation of 2G-TKI if:
 1. No prior progression to accelerated phase or blast crisis
 2. UMRD was sustained on therapy
- Sixteen patients evaluated with a median follow-up of 15 months.
- BCR-ABL transcripts measured by quantitative RT-PCR every month during first 6 months and every 2-3 months thereafter.
- Dasatinib or nilotinib reintroduced upon loss of MMR.

CP = chronic phase; UMRD was defined by undetectable BCR-ABL using quantitative RT-PCR; MMR = BCR-ABL/ABL internationally standardized (IS) ratio $\leq 0.1\%$ by 6 months

Rea D et al. *Proc ASH* 2011;Abstract 604.

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Response at the Start of 2G-TKI Therapy (Abstract Only)

Response (n = 16)	n
Chronic phase	1
Complete hematologic response	1
Partial cytogenetic response	2
Complete cytogenetic response, no MMR	3
MMR, detectable BCR-ABL transcripts	4
UMRD	5

- Dasatinib (n = 9) or nilotinib (n = 7) administered due to IM intolerance (n = 13) or resistance to IM (n = 1) or as a front-line drug (n = 1)
- Median time on 2G-TKI = 32 months
- Median duration of sustained UMRD = 27 months

Rea D et al. *Proc ASH* 2011;Abstract 604.

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Response Following Discontinuation (Abstract Only)

Response (n = 16)	n/mo
MMR lost (n)*	5
Median time off treatment (mo)	4
Stable UMRD or low levels of BCR-ABL (n)	11
Median time off treatment (mo)	13

* Treatment with 2G-TKI restarted in 4/5 and in another patient without MMR loss but with MRD. MMR and UMRD regained following reintroduction of treatment.

- Gender, age, Sokal risk group, type of 2G-TKI and duration of treatment and of UMRD prior to discontinuation did not differ markedly between patients who lost MMR and those with treatment-free persistent MMR.

Rea D et al. *Proc ASH* 2011;Abstract 604.

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Author Conclusions

- 2G-TKI may be safely discontinued in patients with CML and long-lasting UMRD under strict molecular monitoring conditions.
- The emergence of a low level of detectable residual disease below the MMR threshold after withdrawal of 2G-TKI may not automatically herald CML relapse and may not preclude the possibility to remain treatment-free.
- A longer follow-up is required to ascertain whether CML will recur. This study provides a basis for subsequent large-scale prospective trials.

Rea D et al. *Proc ASH* 2011;Abstract 604.

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Investigator Commentary: Discontinuation of TKI in Patients with CML

The 61 patients who experienced relapse in the STIM trial responded to rechallenge with IM. Of the patients, 39% maintained their CMR for several years, and this is rather impressive. Multivariate analysis showed that a high risk score and a short duration of IM therapy were 2 independent prognostic factors for prediction of molecular relapse after IM cessation. This suggests that these patients can potentially be taken off therapy and may not experience relapse. The disease may still be present at low levels that cannot be detected.

The patients in the Rea study received dasatinib or nilotinib before discontinuation and fared slightly worse than those on the STIM study. Following treatment discontinuation, some of these patients maintained CMR after a long follow-up. So in these patients you can achieve a functional cure. Whether we have the appropriate tools to assess who will or will not experience relapse after stopping therapy is the question. I don't believe that therapy should be routinely discontinued in practice, but this topic warrants further study.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012