5 Minute JournalClub

POST-ASH Issue 4, 2015

STOP 2G-TKI and EURO-SKI Trials of Discontinuation of Tyrosine Kinase Inhibitor Therapy for Patients with CML

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on up-front and salvage therapeutic options and modalities for the evaluation of treatment response in newly diagnosed and relapsed or refractory chronic myeloid leukemia (CML), myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Assess the recent results of the RESPONSE trial evaluating ruxolitinib for PV, and consider this information for the treatment of this disease in patients who are not responsive to or are intolerant of hydroxyurea.
- Appraise the effectiveness and tolerability of the investigational agents PRM-151 and imetelstat as single-agent therapy for patients with MF.
- Examine long-term efficacy and symptomatology results with ruxolitinib in patients with ET who are refractory to or intolerant of hydroxyurea.
- Compare and contrast the benefits and risks of discontinuing second-generation tyrosine kinase inhibitors for patients with CML in chronic phase.
- Analyze efficacy and safety results from Phase III trials evaluating dasatinib or ponatinib in comparison to imatinib for patients with CML in chronic phase.

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Consulting Agreements: Bristol-Myers Squibb Company, Genentech BioOncology, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi.

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Sigma-Tau Pharmaceuticals Inc, Sirtex Medical Ltd, Spectrum Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Teva Oncology, Tokai Pharmaceuticals Inc and VisionGate Inc.

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This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Onyx Pharmaceuticals, an Amgen subsidiary, Seattle Genetics and Takeda Oncology.

Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2015
Expiration date: May 2016

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POST-ASH Issue 4, 2015

To go directly to slides and commentary for this issue, **click here**.

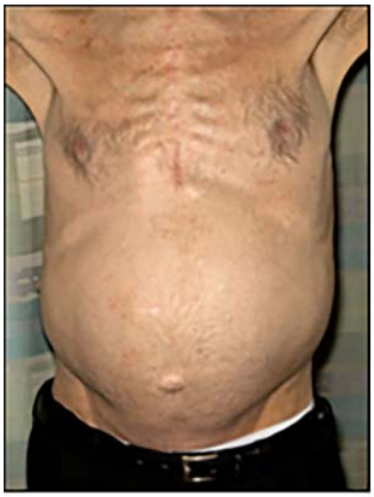
Many physicians (myself included) remember the day they first treated a patient with pulmonary edema from congestive heart failure and the exhilarating feeling of instantly relieving this profound symptomatology with the classic use of an intravenous diuretic and morphine. Medical oncology also provides many opportunities for these types of healing moments, and at the 2011 ASCO meeting the field was introduced to another powerful palliative tool for a disease desperately in need of one. Since the presentation of the aptly named COMFORT-I and II trials in Chicago, we have heard on many of our CME programs a myriad of moving patient case histories of individuals with myelofibrosis (MF) suffering from anorexia, weight loss, fatigue and massive uncomfortable spleens who experienced dramatic, life-altering changes within days or weeks of starting treatment with the JAK1/2 inhibitor ruxolitinib (rux).

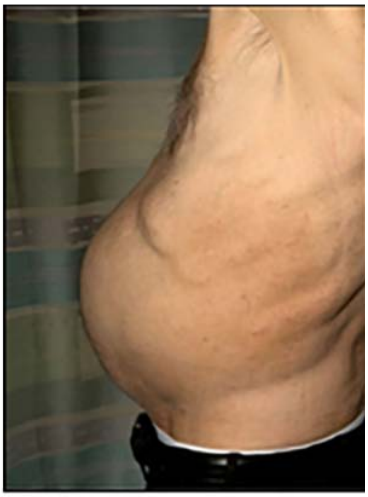
Perhaps not surprisingly, the myeloproliferative neoplasm (MPN) issue of our ASH highlight series focuses in large part on this fascinating therapy, which now is showing its colors in other diseases, including, interestingly enough, pancreatic cancer. We also provide an update on papers related to the other major part of MPNs, chronic myeloid leukemia (CML), and as such I met with one of the research giants in the field, Dr Jorge Cortes, who provides his take on the most important findings.

Jorge E Cortes, MD

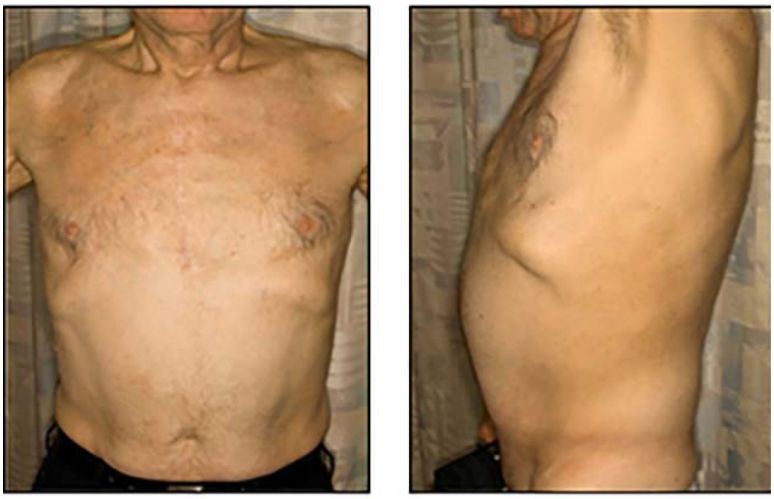
1. Rux in patients with lower-risk MF

The Phase III COMFORT trials focused on patients with intermediate-2 or high-risk MF, but there is no intuitive reason to believe that the palliative effects of this agent would not be similar in other symptomatic patients. At ASH we saw a **"real-world" retrospective analysis** evaluating 108 cases of patients with low- or intermediate-1-risk MF treated by 49 US-based hematologist-oncologists mainly due to symptomatology. Perhaps not surprisingly, marked improvement in spleen size and the severity of





fatigue and other related symptoms was observed with the use of rux. For example, moderate/severe splenomegaly decreased from 64% to 16% in low-risk MF and from 53% to 10% in intermediate-1-risk disease. These findings, along with his own clinical experience, have shaped Dr Cortes' belief that symptomatic patients can benefit from rux regardless of risk status.



Images courtesy of *OncoLog*, The University of Texas MD Anderson Cancer Center

ABOVE: Photos of a patient before therapy with an experimental JAK2 inhibitor show the distended abdomen caused by the enlarged spleen, a common symptom of myelofibrosis. **BELOW:** Photos taken after 2 months of therapy with a JAK2 inhibitor show a marked reduction in the patient's splenomegaly.

2. Rux in polycythemia vera (PV) and essential thrombocythemia (ET)

Perhaps the biggest MPN story at ASH was the presentation of more data from the landmark **Phase III RESPONSE trial** (originally presented last year at ASCO) demonstrating the clinical benefit of rux (10 mg BID) in patients with PV who were either intolerant of or experienced disease progression on hydroxyurea (HU). The initial data set was published in the *New England Journal* in January and revealed significant reductions in hematocrit, splenomegaly and severity of symptoms in patients randomly assigned to rux. Equally relevant, treatment was well tolerated — most patients had stable platelet counts, and secondary drops in hemoglobin were beneficial. Similar clinical improvements were observed in patients who crossed over to rux. Most importantly, as seen with the additional ASH data, patients who received rux experienced a dramatic positive impact on quality of life.

Based on the strength of these results, the FDA made rux the first drug ever approved for PV. In this regard, Dr Cortes has used the agent in patients who meet the criteria for the RESPONSE trial. However, he also believes that the definition of disease progression with PV should be expanded to include individuals with persistent symptomatology who, although not meeting the current criteria for disease progression, often experience dramatic improvements in symptoms with rux.

Several other data sets were unveiled in San Francisco that further support the concept of using rux in PV, including data from the **Phase III RELIEF trial** for patients with PV considered stable on HU but with some persistent symptoms, which demonstrated an improvement in symptoms by switching to rux rather than continuing on HU.

Finally, a Phase II study of rux in 39 patients with ET refractory to or intolerant of HU demonstrated rapid decreases in and normalization of platelet and white blood cell

counts. Hemoglobin levels initially decreased and then stabilized in most patients, and a marked improvement in symptomatology was also observed. As such, Dr Cortes and other investigators believe rux is rational to use in this patient population and are hopeful that this agent will also receive approval in ET for disease palliation.

3. New agents in MF: antifibrotics, telomerase inhibitors

Although much recent MF research has focused on JAK inhibitors, a number of other novel strategies are also being explored in this disease. In this regard, at ASH we saw an **early but encouraging report** of 27 patients receiving PRM-151, a recombinant form of an endogenous protein that is found at sites of inflammation and prevents fibrosis by inducing macrophage differentiation. What was most noteworthy from this study was that not only was the amount of fibrosis decreased in close to half of the patients, but hemoglobin and platelet counts also often improved along with signs and symptoms of the disease. Research on this and other similar agents is proceeding rapidly, and Dr Cortes is particularly interested in trials combining PRM-151 with rux.

Telomerase is known to become more active in MF as the disease progresses, and in a report of 33 patients receiving imetelstat — a novel agent that targets the RNA template of human telomerase reverse transcriptase — 7 patients (21%) experienced a complete or partial remission. Treatment was well tolerated, although myelosuppression was observed. Dr Cortes is intrigued by these data and also the early correlation of response with specific disease mutations.

4. Second-generation tyrosine kinase inhibitors (TKIs) in CML

With the likely availability of generic imatinib in the next year as a potentially less costly alternative, the value of nilotinib and dasatinib will be increasingly discussed and debated, and several new ASH data sets will likely be referred to as part of these conversations. Specifically, in San Francisco we saw the first presentation of data from the large **Phase III SPIRIT 2 trial**, which, like several other prior studies, compared dasatinib to imatinib in patients with newly diagnosed CML. Although the data are not yet fully mature, this study confirms what we have known from other trials, namely that treatment with second-generation TKIs results in improved rates of complete cytogenetic response, faster rates of molecular response and fewer transformations.

It wouldn’t be ASH if we weren’t treated to an update from the landmark DASISION trial, and in addition to continuing to show excellent long-term disease outcomes, this study yielded some interesting data on toxicity over time, specifically the most common complication of dasatinib, pleural effusions, which were observed in 20% of patients, causing discontinuation of treatment in 6%. In discussing this work, Dr Cortes pointed out that multiple studies have suggested that patients experiencing a pleural effusion on dasatinib might have better disease-related outcomes, although the biologic explanation remains to be defined.

None of the second-generation TKI CML papers presented in San Francisco was able to dispel the lack of progression-free or overall survival benefit to this point, and some

investigators prefer imatinib in lower-risk scenarios. Dr Cortes, however, believes that there is an important advantage for the newer agents but that salvage treatment for imatinib failure is delaying the detection of this benefit.

5. Current bottom line with ponatinib in CML

As you may remember, the **Phase III EPIC study** comparing ponatinib to imatinib was stopped in October 2013 because of the increased risk of cardiovascular events. As a result of this toxicity, access to ponatinib is currently restricted to patients with TKI-resistant disease or those with the T315I mutation. However, the updated data from this trial tell us that the agent is associated with faster, deeper and higher rates of response than imatinib and, by way of indirect comparison, perhaps also dasatinib and nilotinib.

In this regard, there is a strong belief among investigators that there is a direct relationship between dose and cardiovascular events, and for that reason ongoing studies are attempting to define a reduced dose that will produce equal efficacy with fewer complications.

6. In what situations, if any, is it safe to stop a TKI in CML?

A number of prospective trials (STIM, TWISTER and EURO SKI, which was presented at ASH) suggest that imatinib may be successfully discontinued for patients with deep and sustained molecular responses, and in San Francisco we saw evidence that the same may apply to second-generation TKIs. Specifically, the **STOP 2G-TKI study** evaluated treatment discontinuation in 52 patients in sustained complete molecular response receiving dasatinib or nilotinib for a median of 39 months, mostly after initial imatinib therapy.

At 24 months, the probability that patients remained in major molecular response off treatment was 57%. The relapses that did occur were mainly in the first 6 months after treatment discontinuation, but those patients responded to reinstitution of second-generation therapy. Importantly, patients receiving treatment because of prior resistance to imatinib were less likely to be able to stay off treatment. Despite this mounting body of data, like most CML investigators, Dr Cortes, although interested in seeing more research on this strategy, believes that for now TKI treatment should only be stopped as part of a clinical trial and with close monitoring.

Medical oncologists are hearing a lot nowadays about “value” in cancer care, which is roughly defined as the clinical benefits (and toxicities/complications) of a therapy relative to its financial cost, and there has been a lot of discussion about the importance of incorporating the perspectives of patients themselves in the value equation.

In this regard, it would be interesting to learn more from individuals who have actually experienced the clinical outcomes of therapy for MPNs about their perceptions of the value of treatment — particularly about what it means to face a disease that was

uniformly lethal in the past and to now live a normal lifespan (CML) or to experience progressive and devastating disease-related symptoms and suddenly feel well again (MF, PV, ET).

Next on this series we review ASH papers on acute leukemias and MDS and the surprising plenary presentation on the use of sorafenib in AML.

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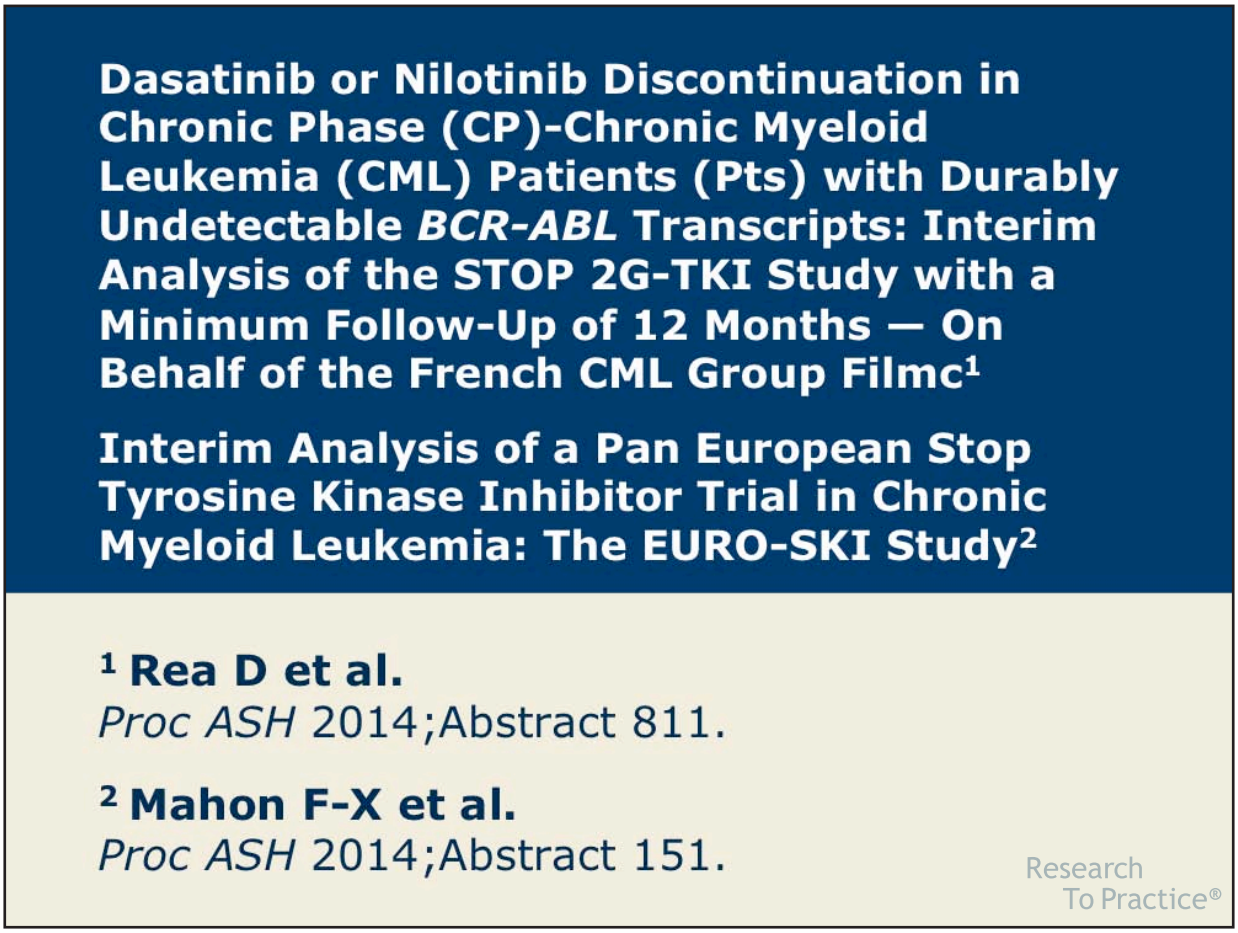
STOP 2G-TKI and EURO-SKI Trials of Discontinuation of Tyrosine Kinase Inhibitor Therapy for Patients with CML

Presentations discussed in this issue

Rea D et al. **Dasatinib or nilotinib discontinuation in chronic phase (CP)-chronic myeloid leukemia (CML) patients (pts) with durably undetectable BCR-ABL transcripts: Interim analysis of the STOP 2G-TKI study with a minimum follow-up of 12 months — On behalf of the French CML group Filmc.** *Proc ASH* 2014;**Abstract 811**.

Mahon FX et al. **Interim analysis of a pan European stop tyrosine kinase inhibitor trial in chronic myeloid leukemia: The EURO-SKI study.** *Proc ASH* 2014;**Abstract 151**.

Slides from presentations at ASH 2014 and transcribed comments from a recent interview with Jorge E Cortes, MD (1/14/15)



Dasatinib or Nilotinib Discontinuation in Chronic Phase (CP)-Chronic Myeloid Leukemia (CML) Patients (Pts) with Durably Undetectable *BCR-ABL* Transcripts: Interim Analysis of the STOP 2G-TKI Study with a Minimum Follow-Up of 12 Months — On Behalf of the French CML Group Filmc

Rea D et al.

Proc ASH 2014;Abstract 811.

Background

- Tyrosine kinase inhibitors (TKIs) targeting BCR-ABL have revolutionized the prognosis for patients with CML.
- However, these TKIs are considered to be nondefinitively curative and the current recommendation is to treat during the patient's entire lifespan.
- Results from prospective trials such as STIM, TWISTER and EURO-SKI suggest that imatinib may be successfully discontinued for patients with deep and sustained molecular responses (*Lancet Oncol* 2010;11:1029; *Blood* 2013;122:515; *Proc ASH* 2013;Abstract 379).
- **Study objective:** To report the feasibility of discontinuing second-generation (2G) TKIs in the French STOP 2G-TKI study.

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Study Methods

- **Eligibility:**
  - Adult patients with CP-CML
  - Receiving first-line dasatinib or nilotinib
  - Receiving dasatinib or nilotinib after receiving imatinib without prior allogeneic transplantation or progression to advanced-phase CML
- Patients were offered TKI discontinuation when presenting with:
  - B2A2 or B3A2 BCR-ABL transcript subtype
  - TKI treatment duration for at least 36 months
  - Complete molecular response ($CMR^{4.5}$) achieved and maintained for at least 24 months
- **Primary objective:** Treatment-free survival without loss of major molecular response (MMR).

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

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Study Methods (continued)

- After TKI discontinuation, *BCR-ABL* transcripts were monitored monthly during the first 12 months, every 3 months during the second year and every 3 to 6 months thereafter.
- Molecular relapse was defined by MMR loss on a single occasion and triggered TKI reintroduction.
- Data as of August 1, 2014 are reported for patients with at least 12 months of follow-up (n = 52):
  - Median follow-up was 32 months (range, 12-56).

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

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Patient Characteristics

Characteristic	n = 52
Median age (range)	60 years (34-81)
Female	61.5%
Sokal risk group: low/intermediate/high Unknown	58%/23%/13% 6%
Received 2G-TKI: After imatinib intolerance After suboptimal response or resistance to imatinib As up-front therapy	67% 23% 10%

- Median duration of CML: 83 months
- Median duration of TKI therapy: 78 months
- Median duration of 2G-TKI therapy: 39 months
- Median duration of $CMR^{4.5}$: 28 months

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

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Response

- Patients who lost major molecular response (MMR) after a median of 4 months: n = 24.
- No loss of complete hematologic response or progression to advanced-phase CML was observed.
- Treatment-free survival (TFS) without MMR loss:
  - 12-month probability, 61.4%
  - 24-month probability, 57%
- The majority of relapses occurred within 6 months.
- Landmark analysis of patients who were still in MMR without therapy at 6 months:
  - 12-month probability of TFS without MMR loss, 91.2%
  - 24-month probability of TFS without MMR loss, 84.7%

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

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Response (continued)

- All but 1 patient who lost MMR restarted 2G-TKI therapy and regained MMR after a median time of 3 months (1-8).
- Patients who achieved MMR without any therapy (n = 28):
  - These patients displayed varying patterns of spontaneous molecular response, including
    - Stable $CMR^{4.5}$ (n = 7)
    - Fluctuations between $CMR^{4.5}$ and molecular response ($MR^{4.5}$) (n = 9)
    - Fluctuations between $CMR^{4.5}$ and MR^{4} (n = 4)
    - Fluctuations between $CMR^{4.5}$ and MMR (n = 4)

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

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Impact of Clinicopathologic Factors on Clinical Outcome

- Factors without any impact on outcome:
  - Gender
  - Age
  - Prior interferon exposure
  - Type of 2G-TKI therapy
  - Treatment duration
  - Duration of $CMR^{4.5}$
- By contrast, a history of suboptimal response or resistance to imatinib was associated with:
  - A significantly lower chance of successful treatment discontinuation
  - A lower 12-month probability of TFS without MMR loss:
    - 41.7% versus 67.3% for other patients (p = 0.04)

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Author Conclusions

- 2G-TKI therapy can be safely and successfully discontinued in patients with CP-CML with long-lasting undetectable BCR-ABL transcript levels
  - Especially in those without a history of suboptimal response or imatinib resistance.
- Most molecular relapses observed had an early onset, and all were sensitive to the resumption of 2G-TKI therapy.
- The recurrence of low levels of detectable residual disease below MMR after 2G-TKI withdrawal did not automatically herald CML relapse and did not preclude the possibility of remaining treatment free.

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

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Investigator Commentary: Interim Analysis of the STOP 2G-TKI Trial After a Minimum of 12 Months of Follow-Up

This French group pioneered TKI discontinuation in CML and initially reported results from the STIM (Stop Imatinib) trial. In the STOP 2G-TKI study, the investigators assessed discontinuation after dasatinib or nilotinib administered first line or after failure of imatinib. In this study 61.4% of the patients remained relapse free in 12 months and 57% in 24 months. Consistent with the STIM results, this study demonstrated that some patients can maintain a good and durable remission — if not complete, at least a major molecular remission.

Investigators also evaluated factors that could predict the ability to maintain the remission. One identified factor is that a patient with CP-CML who has experienced true failure of or resistance to a prior drug is less likely to maintain a good response after treatment discontinuation. That's an important factor to keep in mind, that perhaps those patients are not the optimal candidates for treatment discontinuation, at least based on what we know today.

Interview with Jorge E Cortes, MD, January 14, 2015

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Interim Analysis of a Pan European Stop Tyrosine Kinase Inhibitor Trial in Chronic Myeloid Leukemia: The EURO-SKI Study

Mahon F-X et al.

Proc ASH 2014;Abstract 151.

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Background

- The tyrosine kinase inhibitors (TKIs) have dramatically changed the natural history of chronic myeloid leukemia (CML), leading to significant improvement in clinical outcome and survival rates.
- Results from prospective trials suggest that imatinib therapy may be safely and successfully discontinued in patients with CML with deep and sustained molecular responses (*Lancet Oncol* 2010;11:1029; *Blood* 2013;122:515).
- **Study objective:** To define prognostic markers to increase the rate of durable deep molecular response after stopping a TKI in the European Leukemia Net Stop TKI (EURO-SKI) study.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

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Study Methods

- **Eligibility (8 countries): n = 200**
  - Adult patients with CML in chronic phase (CP) on TKI treatment
  - Achievement of confirmed deep molecular response (MR^4, BCR-ABL <0.01%) for ≥1 y **and**
  - Undergoing TKI therapy for ≥3 y
  - No patient with CP-CML after progression on TKI therapy
- MR^4 confirmation was performed in 6 standardized laboratories.
- **Primary endpoint:** Duration of molecular response (defined by continuous major molecular response) after discontinuation of a TKI.
- A planned interim analysis was performed after 200 patients with eligible molecular results at month 6 were available to test the null hypothesis that relapse-free survival at 6 months is ≤40%.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

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Patient Characteristics

Characteristic	n = 200
Median age at diagnosis (range)	53.3 years (13.8-85.5)
Female	41.5%
Sokal risk group: High	18.2%
Patients with pretreated* CML	103 (51.5%)

* Mostly with hydroxyurea or interferon

- Patients who had received first-line imatinib: 97%
- Patients who had received first-line dasatinib: 1.5%
- Patients who had received first-line nilotinib: 1.5%
- Patients who switched to second-line TKI therapy due to intolerance (n = 24):
  - To dasatinib (n = 16); to imatinib (n = 2); to nilotinib (n = 6)
- The median time from diagnosis of CML to TKI cessation was 8 years.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Duration of Treatment and Molecular Response

Duration	n = 200
TKI treatment duration of <5 years	16%
5-8 years	36%
>8 years	48%
MR^4 duration of <2 years	8%
2-5 years	37%
5-8 years	39%
>8 years	16%

- Median duration of TKI treatment: 8 years (range, 3-12.6)
- Median duration of MR^4 before TKI discontinuation: 5.4 years (range, 1-11.7)
- For all eligible patients, a standardized European laboratory confirmed MR^4 assessment
- Because 123 out of 200 patients (61.5%) remained without relapse after the first 6 months, the null hypothesis was discarded ($p < 0.0001$)

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Disease Recurrence and Determination of Prognostic Significance of Molecular Response

Patients with disease recurrence (loss of MMR)	n/N (%)
With treatment for <8 years	43/92 (47%)
With treatment for >8 years	23/87 (26%)
p-value	0.005
Patients with MR^4*	**n/N (%)**
With MR^4 at <5 years but lost MMR at ≤6 months	33/71 (46%)
Patients with MR^4 >5 years	28/87 (32%)
p-value	0.07

MMR = major molecular response

* There was a trend for prognostic significance of MR^4 duration.

- No significant difference was observed for relapse within 6 months according to depth of molecular response at discontinuation (MR^4 vs $MR^{4.5}$ vs MR^5).

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Safety and Costs Associated with Discontinuation of TKI Therapy

- The discontinuation of TKI therapy was a safe procedure, but a substantial proportion of patients reported transitory musculoskeletal pain starting within weeks of imatinib discontinuation.
  - This phenomenon was described in 30% of Swedish patients as a "TKI withdrawal syndrome" (*J Clin Oncol* 2014;32(25):2821-3).
- Taking into account the cost of imatinib in Europe and time without treatment in the total study population at the most recent analysis, total savings for the community within the EURO-SKI trial were estimated at 7 million euros.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

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Author Conclusions

- With the employment of standardized molecular testing for patient selection within a TKI discontinuation trial in CML, the probability of staying in treatment-free remission could be higher than previously reported.
- As previously reported in the STIM (Stop Imatinib) trial, the preliminary results from this study confirm the prognostic impact of the duration of TKI therapy before stopping.
- The EURO-SKI trial will further elucidate the prognostic factors in order to increase the rate of durable deep molecular response after stopping TKI therapy.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

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Investigator Commentary: EURO-SKI — Interim Analysis of a Stop TKI Therapy Trial for Patients with CP-CML

This study focuses specifically on patients receiving a TKI as front-line therapy, whereas the STOP 2G-TKI study included patients who had received prior interferon or other drugs. A small cohort of patients switched TKIs because of intolerance but none because of resistance or disease progression on first-line TKI therapy. The patients were required to have a molecular response (MR^4). This allows even more disease detectable than $MR^{4.5}$, and MR^4 was only required to be sustained for at least 1 year. Relapse was defined as the loss of major molecular response.

The study demonstrated that 61.5% of the patients remained without relapse in the first 6 months. Six months is important because that is when the majority of relapses occur. In terms of the features predictive of a more durable response and the duration of treatment, patients who have received treatment for more than 8 years and those who have achieved deeper molecular responses for at least 5 years are less likely to experience relapse.

Interview with Jorge E Cortes, MD, January 14, 2015

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In summary, the STOP 2G-TKI and EURO-SKI trials show that some patients can stop TKI treatment and maintain some level of response. Before we can start applying this strategy to all our patients, we need to know the kind of response that the patients are achieving and understand that there has to be a strong commitment to monitoring the patients closely after they discontinue TKI therapy. This is because in this series the investigators have not reported any loss of hematologic responses or transformations. If care is not taken immediately and a patient experiences relapse without us recognizing what has occurred, it is likely that the disease will come back in a more aggressive form. This is an important factor to note, that TKI therapy discontinuation should be performed only on a clinical trial with careful and close monitoring.

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