



POST-ASH Issue 3, 2013

**COMFORT-I and COMFORT-II:
Long-Term Results with Ruxolitinib
for Myelofibrosis**

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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

- Appraise recent clinical research findings on the long-term efficacy and safety of ruxolitinib for patients with myelofibrosis, and apply this information to clinical practice.
- Evaluate the efficacy and dose-finding studies of ruxolitinib in patients with myelofibrosis who have low platelet counts.
- Compare and contrast the benefits and risks of homoharringtonine-based induction regimens for patients with de novo acute myeloid leukemia.
- Evaluate the efficacy and safety of quizartinib for patients with FLT3-ITD-positive or negative acute myeloid leukemia.

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

Moshe Talpaz, MD
Alexander J Trotman Professor of Leukemia Research
Associate Director of Translational Research, UM Comprehensive Cancer Center
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This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva 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: March 2013

Expiration date: March 2014

Does the JAK1/2 inhibitor ruxolitinib benefit patients with myelofibrosis without JAK2 mutations?...and more

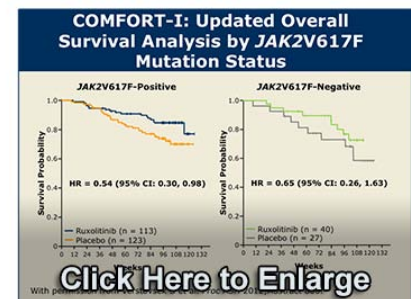
To go directly to slides and commentary for this issue, [click here](#).

Medical oncologists love to see clinical trial results that are so impressive that the effectiveness of a therapy can be immediately understood simply by viewing a single graphic. Because of this, the relatively recent innovation of waterfall plots — especially those in which the majority of the bars point down — has increasingly been used to provide poignant and memorable snapshots of antitumor efficacy.

In this regard, a unique series of waterfall plots presented at the June 2011 ASCO meeting caused an immediate stir and are still being talked about today. These startling graphics did not plot tumor size but disease-related symptoms and spleen size in the seminal Phase III COMFORT-I and II trials evaluating the JAK1/2 small molecule inhibitor ruxolitinib (Rux) in patients with myelofibrosis (MF). In addition to the rapid and profound impact in the treated group, another fascinating aspect of the waterfall plots was what was going on in the control patients, and there the bars were moving north fast, suggesting that these trials were intervening in patients who were very ill and getting worse quickly. These data paved the way for the almost immediate FDA approval of this agent for patients with intermediate-2 and high-risk MF.

In Atlanta we saw an additional year of follow-up from these studies, including my favorite graphic from the entire ASH meeting (see below), showing side by side the survival benefit seen in COMFORT-I for patients with and without JAK2 mutations.

There is considerable debate about the mechanisms that produce the often-profound symptomatic benefit with Rux, and some have postulated it's related to the suppression of release of cytokines implicated in the pathogenesis of MF clinical progression. Regardless, the clear practical message is that this is not BRAF-positive melanoma or EML4-ALK-positive non-small cell lung cancer and symptomatic patients with MF should be considered for therapy with Rux regardless of JAK2 mutation status.



In this issue of our post-ASH series we review the COMFORT updates and two related MF papers along with data sets in acute myelogenous leukemia (AML), where several intriguing agents are showing promising results.

1. COMFORT trial updates

Perhaps the MF investigators chose the COMFORT trial acronym to symbolize the profound palliative effect of Rux that had been observed even in early Phase I-II studies. **The initial published** Phase III data were derived with a median of about a year of follow-up, and now that another year has passed the results keep getting better. Perhaps the most important and “comforting” message is that most patients have maintained responses and are continuing to enjoy significant symptom palliation. In addition, an important effect on overall survival has been demonstrated in both trials in spite of the fact that crossover after progression on the control arm was allowed and occurred in more than two thirds of patients. The two ASH COMFORT updates are loaded with practical clinical information, which is summarized in the attached slide set, and it’s clear that this disease has entered a new era.

2. Use of Rux in patients with platelet counts (PC) of 50,000-100,000

MF can be associated with decreased PC through a variety of mechanisms, and Rux itself causes reversible declines in PC and hemoglobin levels, although these are rarely treatment limiting. The COMFORT trials required a minimum PC of 100,000, but the lack of an effective palliative alternative pushed investigators to determine if this agent could be safely and beneficially used in patients falling below this threshold. Two separate ASH papers evaluated a cautious stepwise approach in patients with PC between 50,000 and 100,000. In **the North American trial** led by Dr Moshe Talpaz patients started at 5 mg BID and escalated up, usually targeting a 10-mg BID dose. Interestingly, although patients in the COMFORT trials received 15 or 20 mg BID, those treated in these two new studies at reduced doses seemed to experience similar treatment benefit.

Unfortunately, there are currently no data to guide management of patients with PC under 50,000, and as such this situation probably warrants consideration of referral to a tertiary center, where many studies are being conducted with a plethora of promising agents in MF.

3. AML update: Homoharringtonine (HHT, otherwise known as omacetaxine)

On one of our upcoming audio programs Dr Hagop Kantarjian spins a fascinating tale of herbal drug development in China under Mao Zedong, and one of the positive outcomes (in addition to ATRA and arsenic) was this plant alkaloid that has significant activity in AML (and was recently approved in CML). In a prominent ASH report of a Phase III AML trial done in China, cytarabine (C) and an anthracycline (A) combined with HHT

resulted in more CRs and better survival but also more deaths during induction than CA alone. These findings have led to both optimism and caution as this fascinating agent is further developed.

4. More on AML: Quizartinib, a potent FLT3 receptor inhibitor

FMS-like tyrosine kinase 3 (FLT3) internal tandem duplications can be found in up to a third of patients with AML and are associated with high blast counts, increased rates of relapse and reduced survival. In an effort to potentially exploit this target, quizartinib was evaluated in a Phase II trial with 2 cohorts reported separately at ASH and revealed impressive responses in patients both without and, more commonly, with FLT3 mutations, and the drug, which was well tolerated other than prolonged QT intervals, stabilized a number of patients, enabling transplant. Enthusiasm from these findings has led to Phase III trials in FLT3-mutant AML, including efforts to combine quizartinib with the classic 3 + 7 regimen up front.

Next on this ASH highlights series we consider Hodgkin and T-cell lymphoma, where more good news on the CD30 antibody-drug conjugate brentuximab vedotin was unveiled in Atlanta.

Neil Love, MD

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COMFORT-I and COMFORT-II: Long-Term Results with Ruxolitinib for Myelofibrosis

Presentations discussed in this issue

Verstovsek S et al. **Long-term outcome of ruxolitinib treatment in patients with myelofibrosis: Durable reductions in spleen volume, improvements in quality of life, and overall survival advantage in COMFORT-I.** *Proc ASH 2012*; **Abstract 800**.

Cervantes F et al. **Long-term safety, efficacy, and survival findings from Comfort-II, a Phase 3 study comparing ruxolitinib with best available therapy (BAT) for the treatment of myelofibrosis (MF).** *Proc ASH 2012*; **Abstract 801**.

Slides from presentations at ASH 2012 and transcribed comments from a recent interview with Moshe Talpaz, MD (2/19/13)

Long-Term Outcome of Ruxolitinib Treatment in Patients with Myelofibrosis: Durable Reductions in Spleen Volume, Improvements in Quality of Life, and Overall Survival Advantage in COMFORT-I¹

Long-Term Safety, Efficacy, and Survival Findings from COMFORT-II, a Phase 3 Study Comparing Ruxolitinib with Best Available Therapy (BAT) for the Treatment of Myelofibrosis (MF)²

¹ Verstovsek S et al.

Proc ASH 2012; Abstract 800.

² Cervantes F et al.

Proc ASH 2012; Abstract 801.

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Long-Term Outcome of Ruxolitinib Treatment in Patients with Myelofibrosis: Durable Reductions in Spleen Volume, Improvements in Quality of Life, and Overall Survival Advantage in COMFORT-I

Verstovsek S et al.

Proc ASH 2012;Abstract 800.

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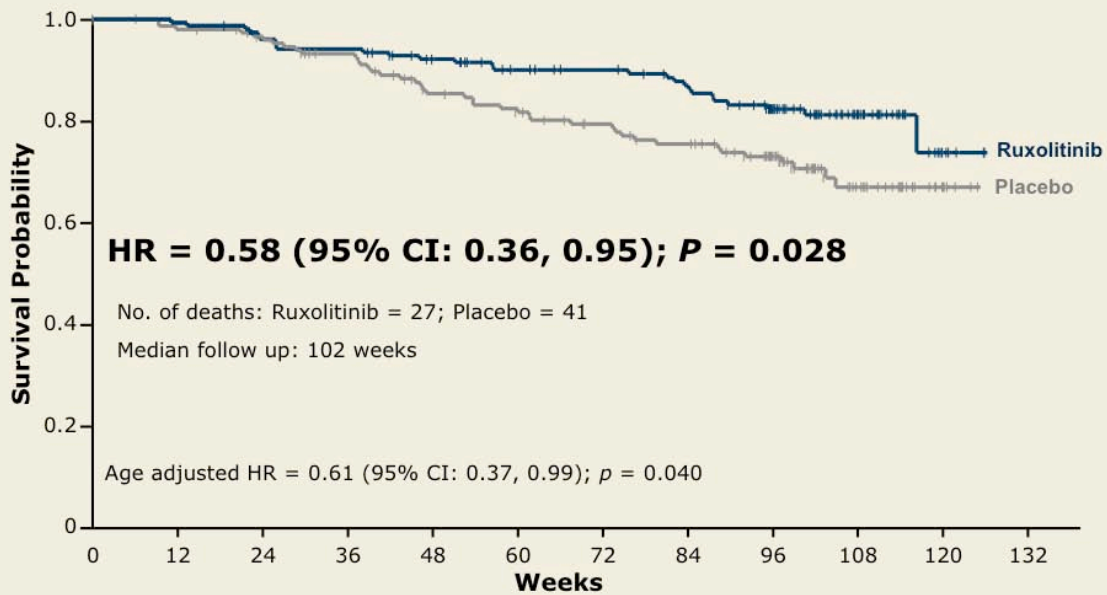
Background

- Ruxolitinib is a potent JAK1/JAK2 inhibitor that has shown superiority over placebo or conventional therapies for the treatment of myelofibrosis (MF).
- In the Phase III COMFORT-I and COMFORT-II studies, ruxolitinib demonstrated reductions in splenomegaly and an improvement in MF-related symptoms, quality of life (QoL) and overall survival (*N Engl J Med* 2012;366(9):799; *N Engl J Med* 2012;366(9):787).
- **Study objective:** To describe the long-term efficacy and safety of ruxolitinib on the COMFORT-I study with 1 year of additional follow-up beyond previously published data (median follow-up ~24 months).

Verstovsek S et al. *Proc ASH 2012;Abstract 800.*

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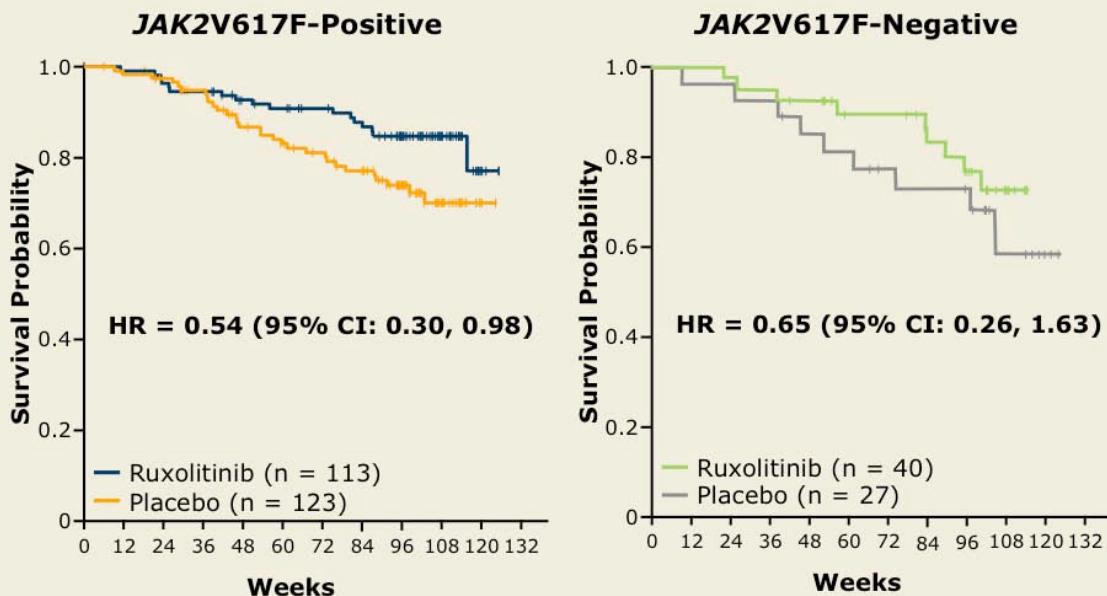
COMFORT-I: Updated Overall Survival Analysis – ITT Population



With permission from Verstovsek S et al. *Proc ASH 2012*;Abstract 800.

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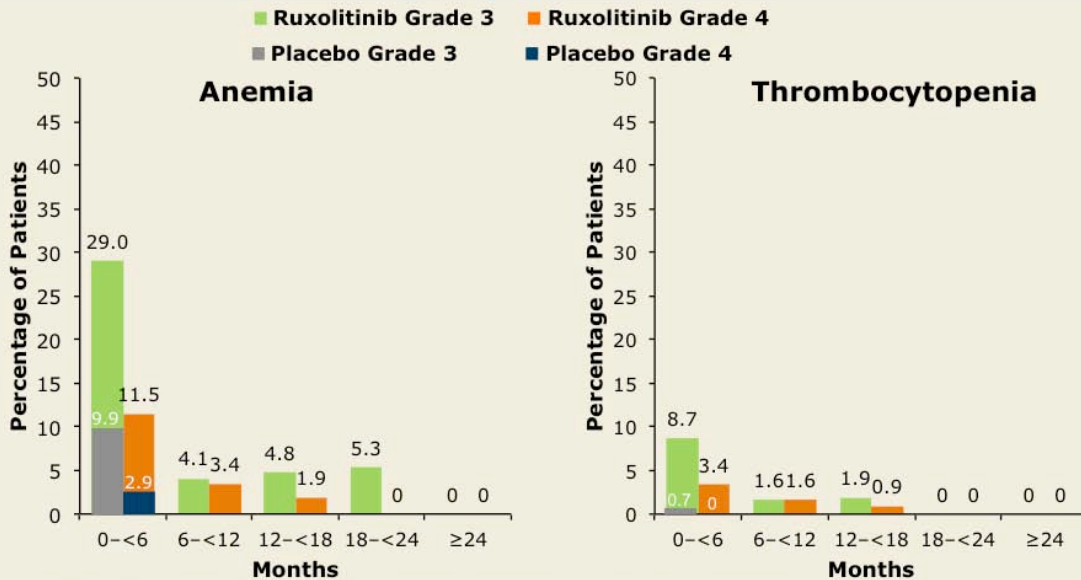
COMFORT-I: Updated Overall Survival Analysis by *JAK2V617F* Mutation Status



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COMFORT-I: Incidence of New-Onset Grade 3 or 4 Anemia and Thrombocytopenia Over Time

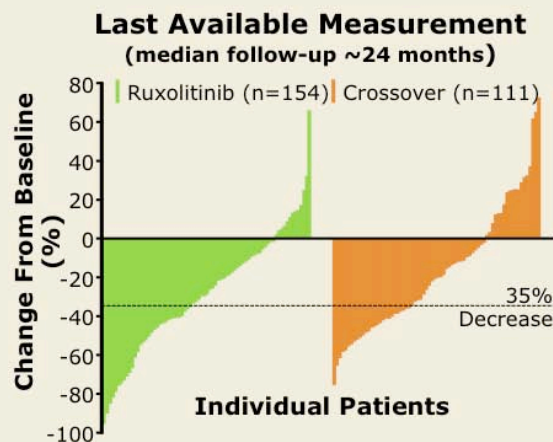


- All patients receiving placebo at the primary analysis crossed over or discontinued within 3 months of the primary analysis; therefore, data for patients receiving placebo is shown for 0-<6 months only

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COMFORT-I: Spleen Volume Reduction

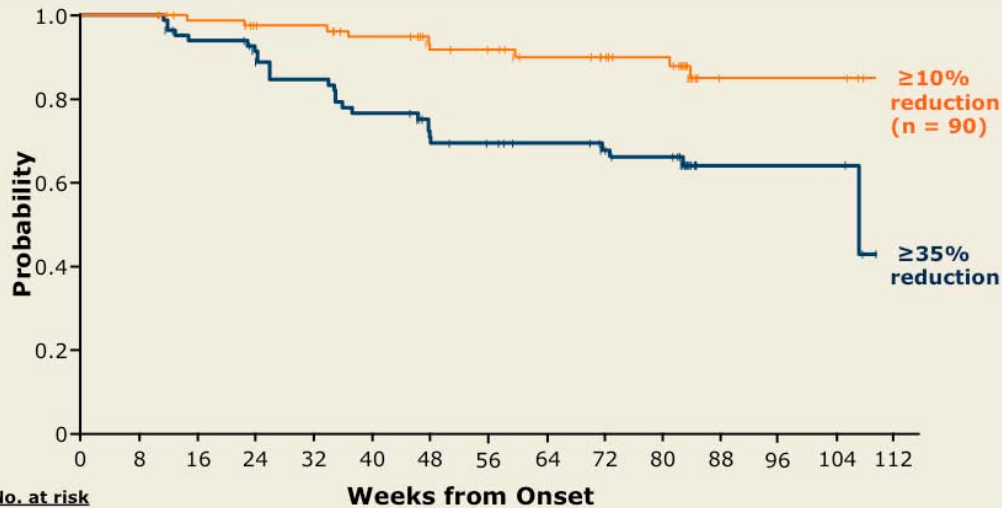


- The majority of ruxolitinib-treated patients maintained a spleen volume reduction.
- The majority of crossover patients experienced spleen volume reduction relative to baseline.

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COMFORT-I: Durability of Spleen Volume Reduction



No. at risk

90 84 75 72 63 57 52 47 43 41 35 4 4 4

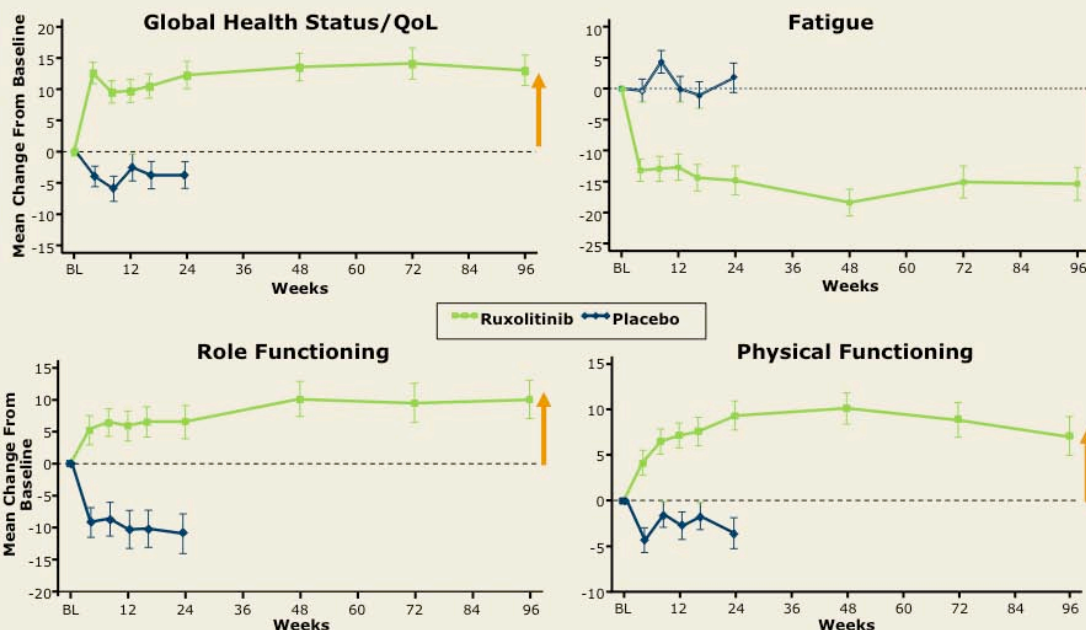
- 90/155 (58%) had a 35% reduction at any time point during the study
- 64% maintained a ≥35% reduction for at least 2 years

≥35% reduction: Time from first 35% reduction to <35% reduction and 25% increase from nadir.
 ≥10% reduction: Time from first 35% reduction to <10% reduction from baseline.

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COMFORT-I: Updated QoL Over Time (Assessed by EORTC QLQ-C30)



Arrows indicate improvement.

With permission from Verstovsek S et al. *Proc ASH 2012*;Abstract 800.

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Author Conclusions

- Ruxolitinib continues to be associated with a survival advantage relative to placebo in the COMFORT-I study.
- Reductions in spleen volume and improvements in symptoms and QoL were sustained.
- Incidence of new-onset Grade 3 or 4 anemia and thrombocytopenia decreased with longer-term therapy:
 - Proportion of patients receiving RBC transfusions decreased over time to rates similar to placebo (data not shown).
- After initiating ruxolitinib at 15 or 20 mg BID, patients titrated to a mean dose of ~10 to 15 mg BID with longer-term treatment (data not shown).
- These data reinforce the durable efficacy and longer-term safety of ruxolitinib in patients with myelofibrosis regardless of *JAK2V617F* mutation status.

Verstovsek S et al. *Proc ASH 2012*;Abstract 800.

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Long-Term Safety, Efficacy, and Survival Findings from COMFORT-II, a Phase 3 Study Comparing Ruxolitinib with Best Available Therapy (BAT) for the Treatment of Myelofibrosis (MF)

Cervantes F et al.

Proc ASH 2012;Abstract 801.

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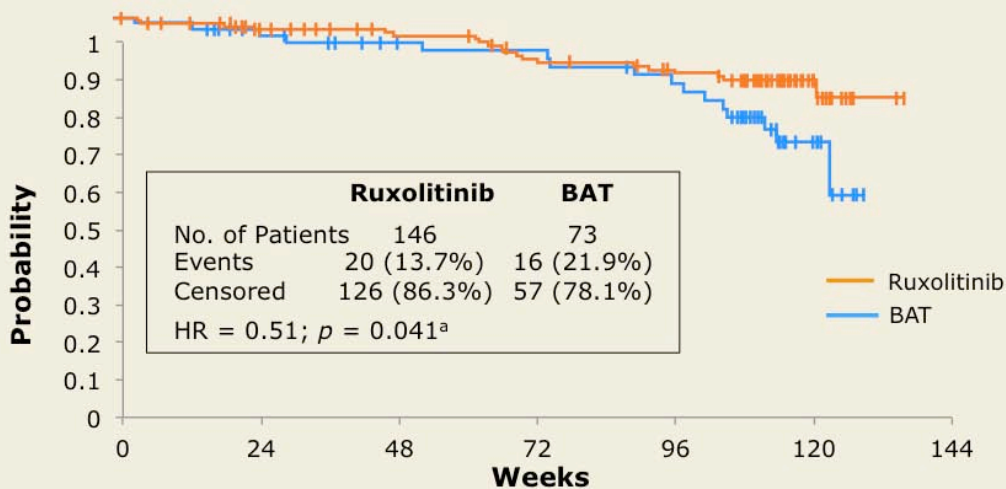
Background

- The primary and key secondary endpoints of the COMFORT-II trial were both met (*N Engl J Med* 2012;366:787).
 - The proportion of patients achieving a response (defined as a $\geq 35\%$ reduction in spleen volume) at week 24 was 32% and 0% ($p < 0.001$) with ruxolitinib and best available therapy (BAT), respectively.
 - The proportion of patients achieving a response at 48 weeks was 28% and 0% ($p < 0.001$), respectively.
- **Study objective:** To update the efficacy and safety findings of COMFORT-II with longer follow-up (median 28 months; cutoff March 1, 2012)

Cervantes F et al. *Proc ASH* 2012;Abstract 801.

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COMFORT-II: Updated Overall Survival Analysis



^a P value for log-rank test is provided for descriptive purposes and was not adjusted for multiple comparisons.

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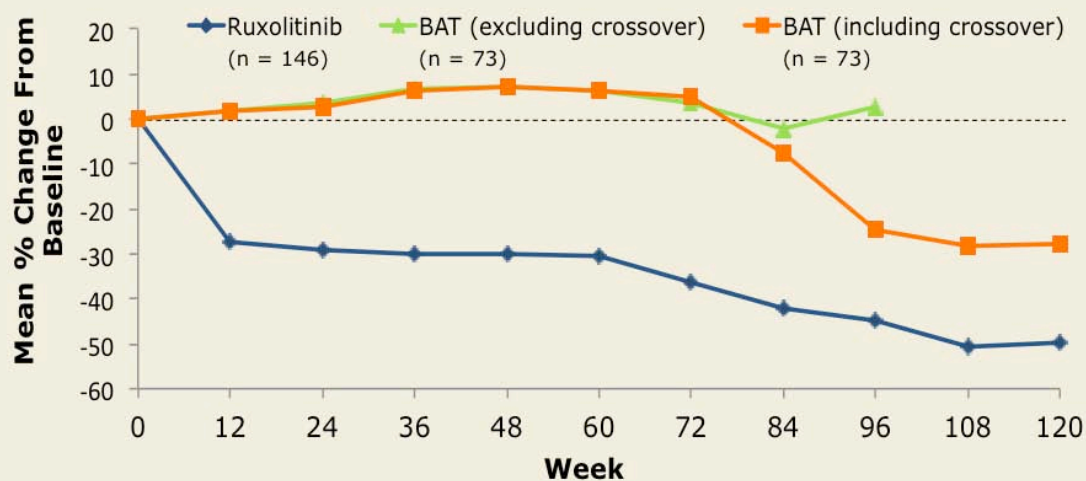
COMFORT-II: Summary of Overall Survival Analysis

- Median survival time not yet reached for both arms:
 - OS is an exploratory endpoint in this trial. At this cutoff, there are <30% events in both arms
- Many early censored observations:
 - Lost to follow-up: BAT, 27% vs ruxolitinib, 14%
 - Survival follow-up was initially not collected (addressed later by an amendment)
 - Efforts to collect survival information ongoing
- Despite the above limitations and the switch of a majority of BAT patients to ruxolitinib, there is an apparent survival benefit favoring ruxolitinib in an ITT analysis:
 - HR = 0.51 (95% CI, 0.26-0.99), $p = 0.041$

Cervantes F et al. *Proc ASH 2012*;Abstract 801.

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COMFORT-II: Updated Percent Change in Spleen Volume

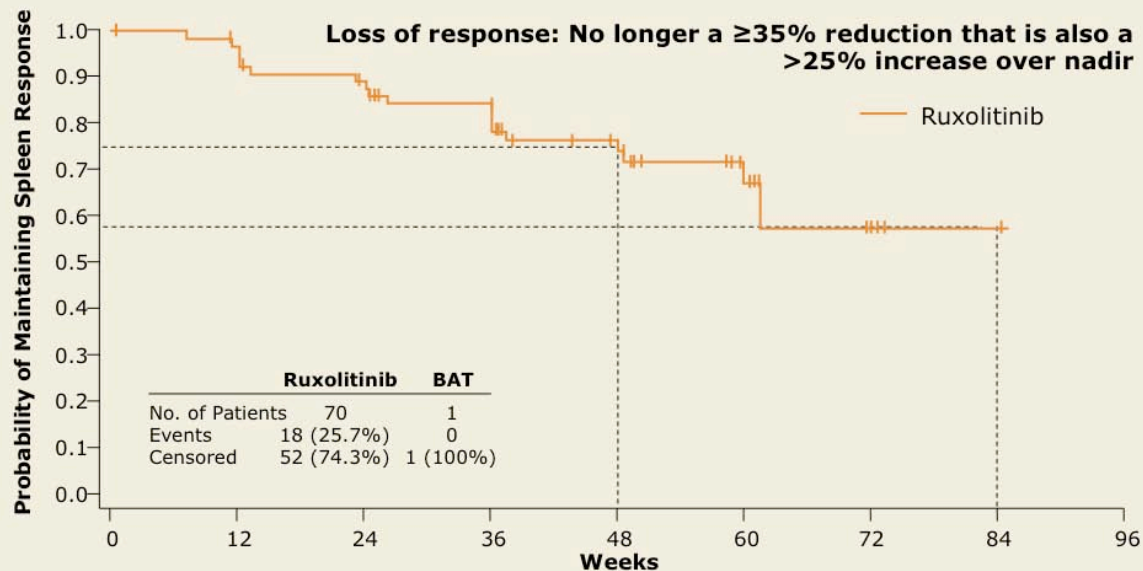


- BAT patients who crossed over to ruxolitinib had reductions in spleen volume after crossover.

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COMFORT-II: Duration of Spleen Response



- Patients have a 58% probability of maintaining their response for 84 weeks.
- The median duration of spleen response has not yet been reached.

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Author Conclusions

- Ruxolitinib provided rapid and durable reductions in splenomegaly that were sustained over 2 years of treatment in the majority of patients on the COMFORT-II trial.
- Ruxolitinib was well tolerated, with the majority of patients remaining on study after more than 2 years of therapy (data not shown):
 - No adverse events after ruxolitinib discontinuation were observed with longer follow-up.
- Longer follow-up suggests a relative reduction in the risk of death with ruxolitinib compared to BAT:
 - This finding is consistent with the survival advantage observed in COMFORT-I (*Proc ASH 2012*;Abstract 800) and with the comparison of patients in a Phase I/II study with matched historical controls (*Blood 2012*;120(6):1202).

Cervantes F et al. *Proc ASH 2012*;Abstract 801.

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Investigator Commentary: COMFORT-I and II — Updated Phase III Trial Results with the JAK1/JAK2 Inhibitor Ruxolitinib for MF

One of the most important findings of the updated results of the COMFORT-I study is the sustained splenic response, especially among patients who experienced $\geq 35\%$ reduction in spleen volume. Even though some regression of response was observed, the durability of spleen volume reduction of $\geq 10\%$ was maintained and ongoing beyond 2 years in the majority of the patients. Stable and ongoing improvements in symptoms are also impressive, and the modest survival advantage is confirmed in patients who received ruxolitinib compared to placebo.

The updated results of the COMFORT-II study of ruxolitinib versus best available therapy demonstrated survival benefits that should also be interpreted with caution. Spleen volume reductions were sustained, particularly in the group of patients with the deepest response. The development of anemia remains an issue with JAK2 inhibitors. However, at a ruxolitinib dose of 10 mg BID, it was limited to a few months and then tended to return to baseline levels. It is important to emphasize the lack of impact of JAK2 mutations. Responses and survival benefits were seen equally among patients with or without JAK2 mutations.

Interview with Moshe Talpaz, MD, February 19, 2013