



Key ASH Presentations
Issue 4, 2012

COMFORT-II Phase III Trial of Splenomegaly Reduction with Ruxolitinib in 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

- Counsel patients with JAK2 mutation-positive and mutation-negative myelofibrosis about the benefits and risks of ruxolitinib treatment.
- Recall ongoing clinical trials with new agents for the treatment of myeloproliferative neoplasms, and consent or refer appropriate patients for participation.

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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:

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No real or apparent conflicts of interest to disclose.

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

It's easy to criticize regulatory agencies, but it also seems that when stuff clearly works things can move along pretty quickly. This was the case following last June's spectacular ASCO presentations of 2 Phase III trials (COMFORT-I and II) demonstrating that the JAK1-2 inhibitor ruxolitinib had convincing and impressive activity in patients with myelofibrosis (MF). These landmark data led to FDA approval in November — immediately providing oncologists with both new hope and many additional questions about this unique disease.

I met with the principal investigator of the North American/Australian COMFORT-I trial, MD Anderson's Dr Srdan Verstovsek, to find out what happened at ASH to follow the ASCO explosion, but before diving into the data we talked about the human side of this profound saga. Dr Verstovsek recounted a number of very memorable real-life stories he has been part of in this new treatment era, including that of a 67-year-old Kansas man with JAK2 mutation-negative disease who had been down the "observation followed by hydroxyurea" route and then started to experience the misery this neoplasm can cause. In desperation 18 months ago he found his way to Houston, enrolled on a Phase I-II trial of ruxolitinib and almost immediately experienced shrinkage of his aching spleen (15 to 3 cm), increased mobility, weight gain and dramatic relief of constitutional symptoms. The patient recently sent Dr V a colorful postcard from a lifelong dream vacation with his wife in Costa Rica.

Dr Verstovsek reflected on what it's like to see people who thought they were doomed to indefinite misery feel good again, but he also cautioned that ruxolitinib "is a drug and not a magic pill." In that regard, it is clear that additional research is needed to bring about a profound sea change in this often relentless disease for which up until now we had no good answers. Below find Dr V's take on which MF happenings at ASH may help further shift the tide in coming years.

1. Ruxolitinib

Although only about half of patients with MF have JAK2V617F mutations, all have dysregulation of the JAK-STAT pathway and benefit from JAK inhibition. At ASH Dr Verstovsek presented an update of [COMFORT-I](#), including a survival benefit (HR = 0.50 with 13 versus 24 deaths), data showing that major symptom palliation was observed across all patient subsets (IPSS risk, age, V617F mutation, spleen size and Hb level) and that these effects were quickly lost when the drug was discontinued ([click here for a dramatic graphic](#)).

In addition, the tandem ASH presentation of the [COMFORT-II](#) European study follow-up demonstrated nearly identical spleen shrinkage across disease subtypes. [Another data set](#) presented by Dr Verstovsek suggested an important survival benefit for patients on MD Anderson Phase I-II trials of ruxolitinib compared to historical controls.

2. Pure JAK2 inhibitors

A number of other JAK inhibitors are currently being studied, and new data on several were reported at ASH. The first, pacritinib, is an oral JAK2 but not JAK1 inhibitor, but the waterfall plot for spleen size reduction from the Phase II study presented was similar to what was seen with ruxolitinib. The main downside of this agent was manageable GI toxicity, but of particular note, no myelosuppression was observed. Consequently this molecule and others like it may be particularly useful in patients with thrombocytopenia and anemia. The other JAK2 inhibitor that made an impression at ASH was SAR302503, which demonstrated not only efficacy and safety but also reduction in circulating JAK2V617F allele burden.

3. Pegylated interferon alpha-2a in polycythemia vera

Interferon has long been known to have significant activity in this disease, but the side effects have been prohibitive. Long-term follow-up (6.4 years) from this Phase II study of weekly administration of the more tolerable pegylated formulation of this therapy demonstrated that 94% of patients were still in hematologic response and 29% were able to stop treatment without further cytoreductive therapy. Dr Verstovsek notes that the elimination of clones with the JAK2 mutation as seen in this study does not occur with JAK inhibitors.

4. Panobinostat; pomalidomide

Dr V becomes visibly animated when he talks about future trials combining JAK inhibition with other novel strategies, and at ASH we saw more data on some potential partners, including the HDAC inhibitor panobinostat, which showed modest activity. However, what really tickles Dr V's fancy is the idea of combining JAK inhibitors with the IMiD pomalidomide, an agent that at ASH was again demonstrated to frequently alleviate anemia, a benefit usually not seen with JAK inhibitors.

Next we reconsider lung cancer and the most common patient subset in this ubiquitous disease: Patients with EGFR and ALK wild-type metastatic adenocarcinoma.

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COMFORT-II Phase III Trial of Splenomegaly Reduction with Ruxolitinib in Myelofibrosis

Presentation discussed in this issue

Harrison CN et al. **Ruxolitinib provides reductions in splenomegaly across subgroups: An analysis of spleen response in the COMFORT-II study.** *Proc ASH* 2011; **Abstract 279**.

Slides from a presentation at ASH 2011 and transcribed comments from recent interviews with Hagop M Kantarjian, MD (1/13/12) and Srdan Verstovsek, MD, PhD (1/25/12)

Ruxolitinib Provides Reductions in Splenomegaly Across Subgroups: An Analysis of Spleen Response in the COMFORT-II Study

Harrison CN et al.

Proc ASH 2011;Abstract 279.

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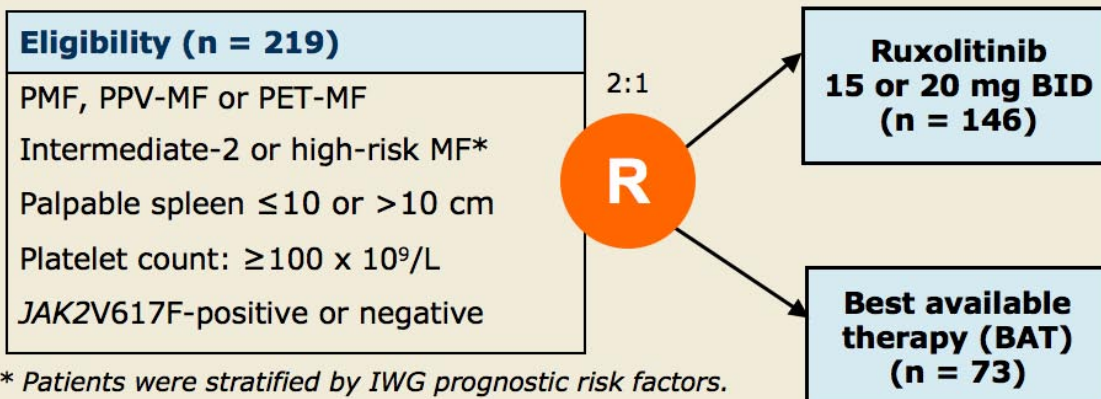
Background

- Ruxolitinib is a potent and selective inhibitor of JAK-STAT signaling that has demonstrated clinical benefits in patients with myelofibrosis (MF):
 - Reduction in splenomegaly, improved disease-related symptoms and quality of life (*Proc ASCO* 2011;Abstract 6500)
 - Prolonged overall survival (*Proc ASH* 2011;Abstract 278)
- MF manifests as primary MF (PMF), postpolycythemia vera MF (PPV-MF) or postessential thrombocythemia MF (PET-MF).
- **Current Study Objective:**
 - Perform subgroup analyses of ruxolitinib-treated patients achieving primary and key secondary endpoints on the COMFORT-II trial

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

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COMFORT-II Study Design

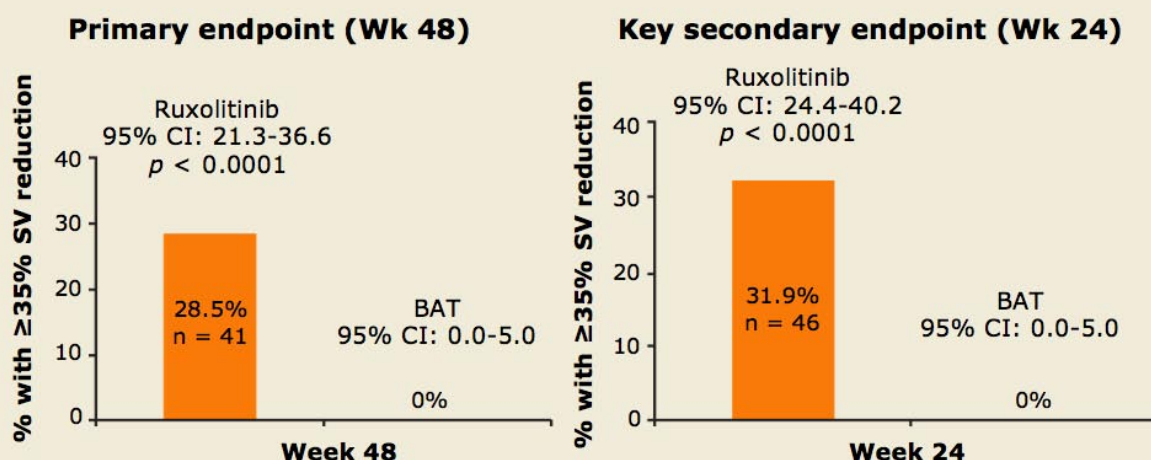


- Ruxolitinib dose dependent on starting platelet count:
 - 15 mg BID for platelet count 100-200 x 10⁹/L
 - 20 mg BID for platelet count >200 x 10⁹/L
- Patients on ruxolitinib with progressive disease were eligible for extension phase
- Crossover from BAT to ruxolitinib was allowed for patients with progressive disease

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

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Primary and Key Secondary Endpoints

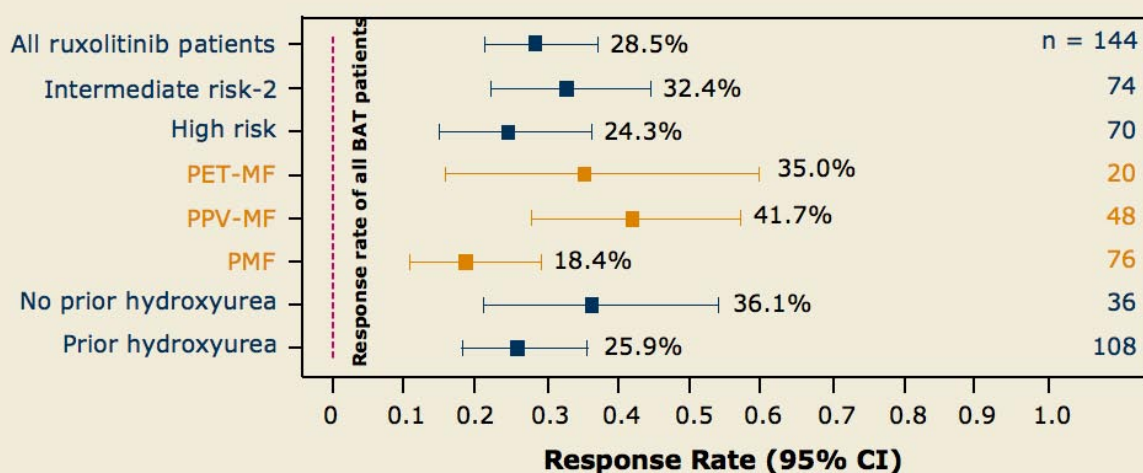


- Spleen volume (SV) was measured by MRI or CT for patients unable to undergo MRI.
- Median time to response was 12.3 weeks.
- Of 69 patients who achieved $\geq 35\%$ reduction in SV during the study, 64% did so at the first assessment.

Harrison CN et al. *Proc EHA* 2011;Abstract 1020.

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Proportion of Patients in Each Subgroup with $\geq 35\%$ Reduction in SV from Baseline at Week 48

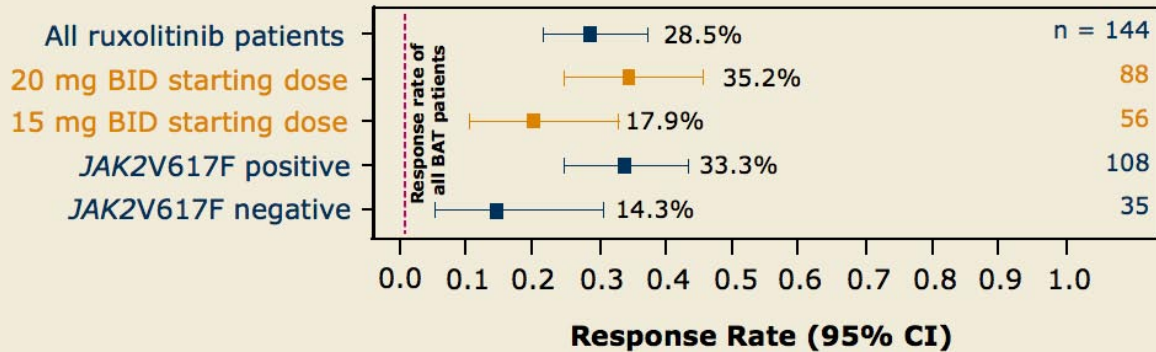


No significant differences in response rates among patients by MF risk category, MF subtype or prior exposure to hydroxyurea

With permission from Harrison CN et al. *Proc ASH* 2011;Abstract 279.

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Proportion of Patients in Each Subgroup with $\geq 35\%$ Reduction in SV from Baseline at Week 48

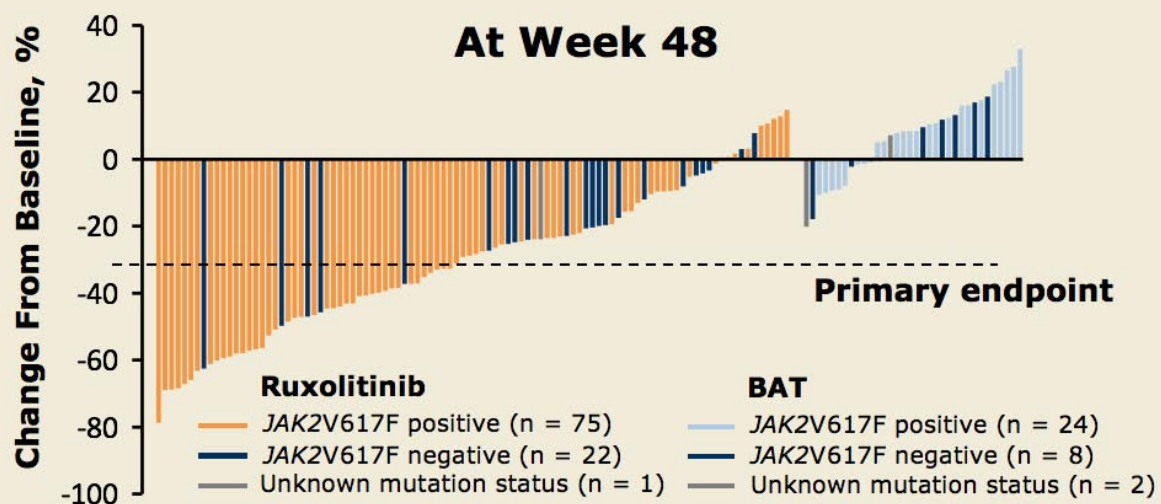


- Although statistically insignificant, there were some differences in response rates among patients based on starting ruxolitinib dose and JAK2V617F mutation status.

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Percent Change from Baseline in SV by JAK2V617F Mutation Status



At week 48, the majority of patients receiving ruxolitinib experienced reductions in SV, including those with JAK2V617F-positive (88%) and negative (91%) mutation status.

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Multivariate Analysis

Predictive factor for response at 48 weeks	Odds ratio	95% CI
Starting dose (15 vs 20 mg BID)	0.441	0.184-1.055
Gender (female vs male)	1.646	0.726-3.732
Age (≤ 65 vs > 65 years)	0.911	0.389-2.135
Baseline MF type: PMF vs PET-MF	0.237	0.063-0.891
With vs without prior hydroxyurea use	2.521	0.964-6.595
Baseline palpable spleen length (≤ 10 vs > 10 cm)	0.419	0.166-1.058
JAK2V617F mutation (negative vs positive)	0.383	0.112-1.310
High vs intermediate-2 risk	0.640	0.268-1.531

Odds ratio < 1 : Lower chance for response compared to reference
Odds ratio > 1 : Higher chance for response compared to reference

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

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Author Conclusions

- In this trial, 28.5% of patients who received ruxolitinib achieved $\geq 35\%$ reduction in SV from baseline compared to 0% of patients who received BAT ($p < 0.0001$).
- The results of a univariate subgroup analysis demonstrated that ruxolitinib was more effective than BAT at decreasing SV regardless of gender, age, mutation status, IWG risk category, baseline spleen size or ruxolitinib starting dose (data not shown).
- Multivariate analysis suggests an increase in response rate among patients with PET-MF in comparison to those with PMF.
 - Trends were noted for starting dose, palpable spleen length and JAK2V617F mutation status.

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

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Investigator Commentary: Ruxolitinib Provides Reduction in Splenomegaly Across Subgroups — COMFORT-II Study

Based on the results obtained from the COMFORT-I and COMFORT-II studies, I believe JAK2 inhibitors, including ruxolitinib, will become the established standard for the treatment of MF. The survival advantage reported in the COMFORT-I study added to the notion that ruxolitinib is an important treatment for MF.

Interview with Hagop M Kantarjian, MD, January 13, 2012

The results reported in this study are similar to what was seen in the COMFORT-I trial. Large improvements were observed in spleen size and symptoms for patients receiving ruxolitinib. Best available therapy did not provide any benefit. The spleen has a tendency to respond better to a higher dose. There is a dose response for spleen shrinkage but no dose response for symptom improvement. Patients can expect to feel better within 2 to 4 weeks after starting therapy, and the most benefit will be experienced within 2 to 3 months. Symptoms — weakness, fatigue, bone action pains, itching, sweating — are well controlled with ruxolitinib.

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