5 Minute JournalClub

Key ASH Presentations
Issue 4, 2012

COMFORT-I Phase III Trial of the Benefit of Ruxolitinib versus Placebo on Spleen Volume Reduction and Symptom Improvement

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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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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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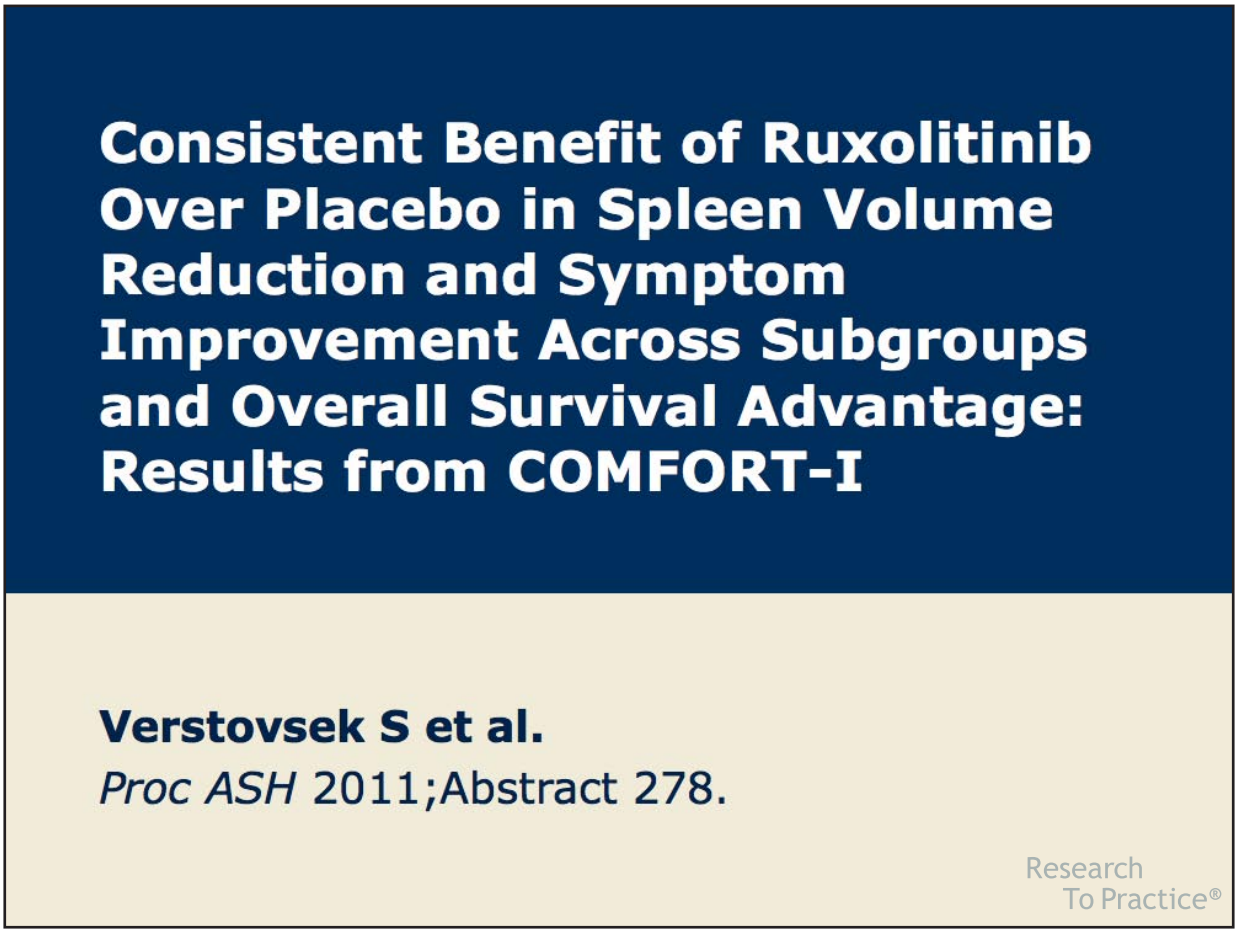
COMFORT-I Phase III Trial of the Benefit of Ruxolitinib versus Placebo on Spleen Volume Reduction and Symptom Improvement

Presentation discussed in this issue

Verstovsek S et al. **Consistent benefit of ruxolitinib over placebo in spleen volume reduction and symptom improvement across subgroups and overall survival advantage: Results from COMFORT-I.** *Proc ASH* 2011;**Abstract 278**.

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)



Background

- Dysregulated JAK-STAT signaling resulting from gain-of-function mutations such as JAK2V617F and/or increased levels of circulating inflammatory cytokines plays a key role in the pathogenesis of myelofibrosis (MF).
- MF manifests as primary MF (PMF), postpolycythemia vera MF (PPV-MF) or postessential thrombocythemia MF (PET-MF).
- Ruxolitinib, a selective inhibitor of JAK1 and 2, has demonstrated clinical activity in MF including the reduction in spleen volume and improvements in MF-related symptoms in the COMFORT-I double-blind placebo-controlled trial (*Proc ASCO* 2011;Abstract 6500).
- **Objective:**
  - Assess the efficacy of ruxolitinib across patient subgroups and update overall survival (OS) in the COMFORT-I trial.

Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

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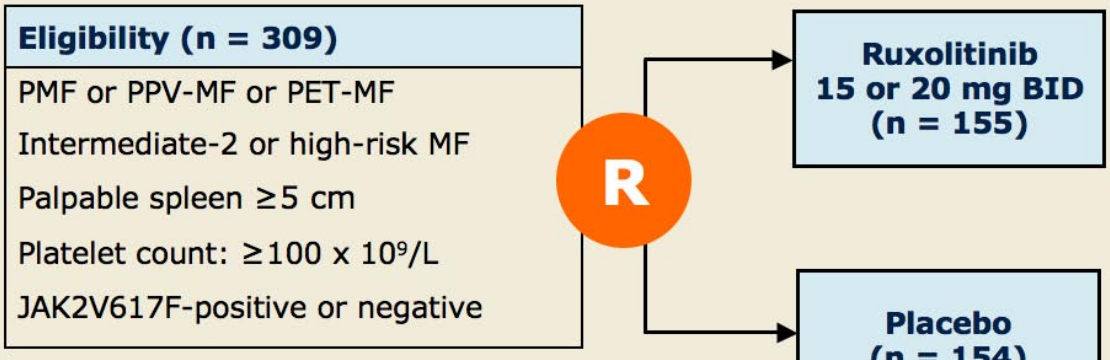
COMFORT-I Study Design



- Ruxolitinib dose dependent on starting platelet count
  - 15 mg BID for platelet count: 100-200 x 10^9/L
  - 20 mg BID for platelet count: >200 x 10^9/L
- Spleen volume (SV) was measured by MRI every 12 weeks
- Crossover from placebo to ruxolitinib was allowed prior to week 24
- Daily assessment of symptoms from day -7 through week 24
- Total symptom score (TSS): sum of all symptom scores except inactivity

Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

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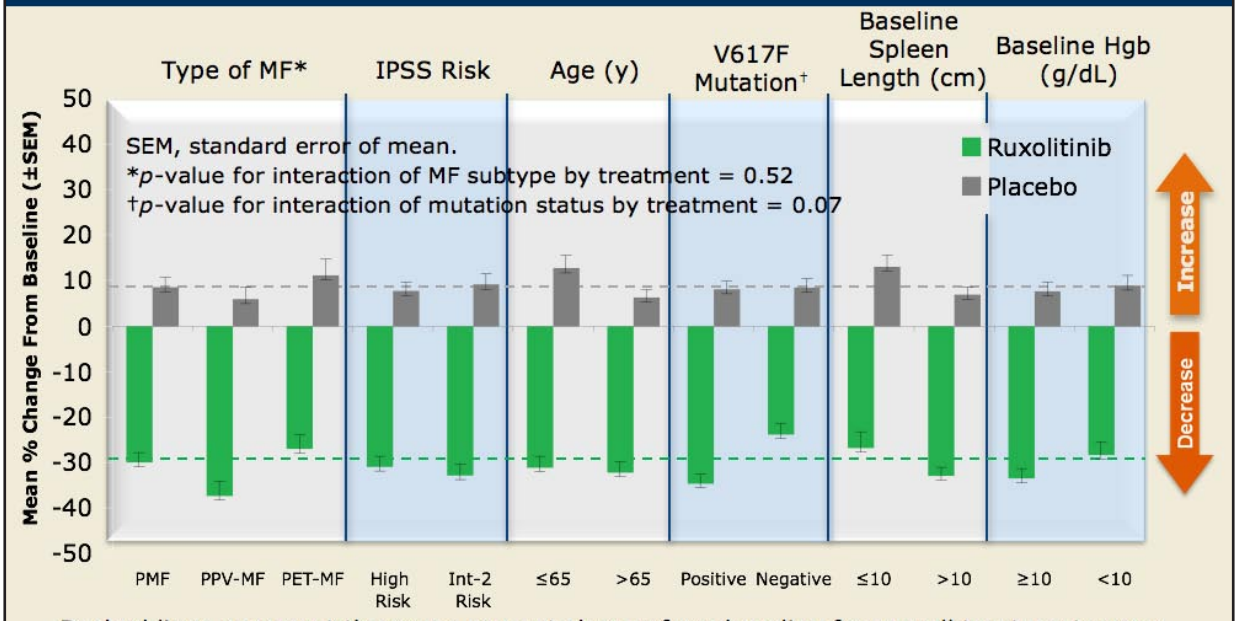
SV: Percent Change from Baseline to Week 24



Dashed lines represent the mean percent change from baseline for overall treatment group

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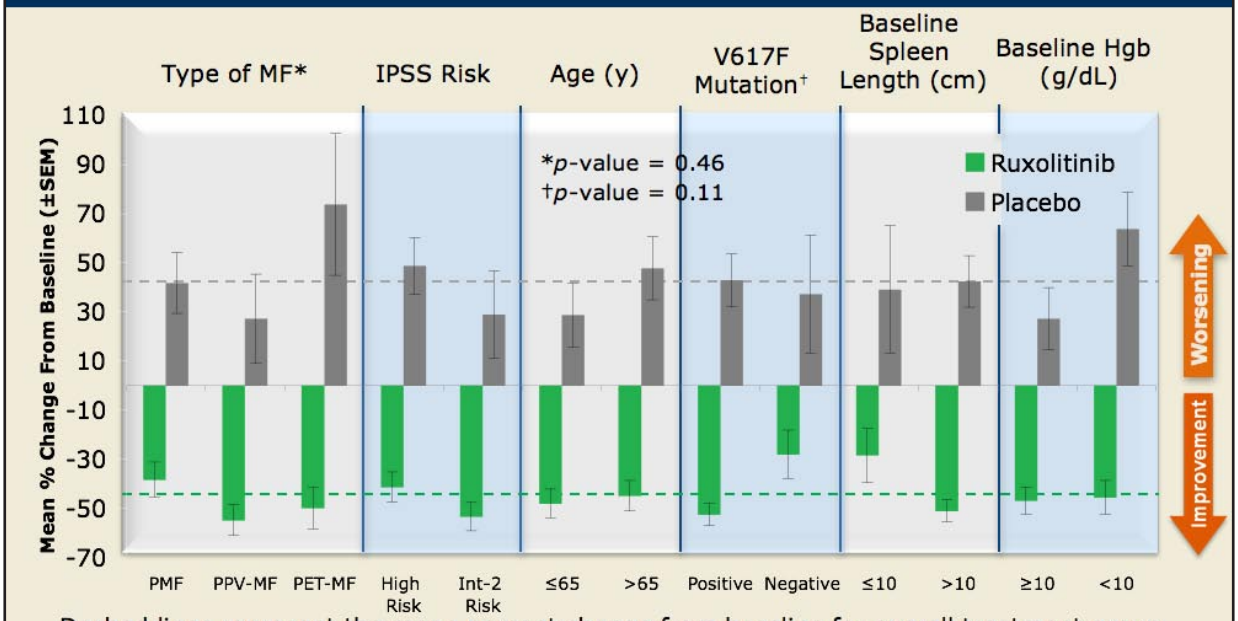
TSS: Percent Change from Baseline to Week 24



Dashed lines represent the mean percent change from baseline for overall treatment group

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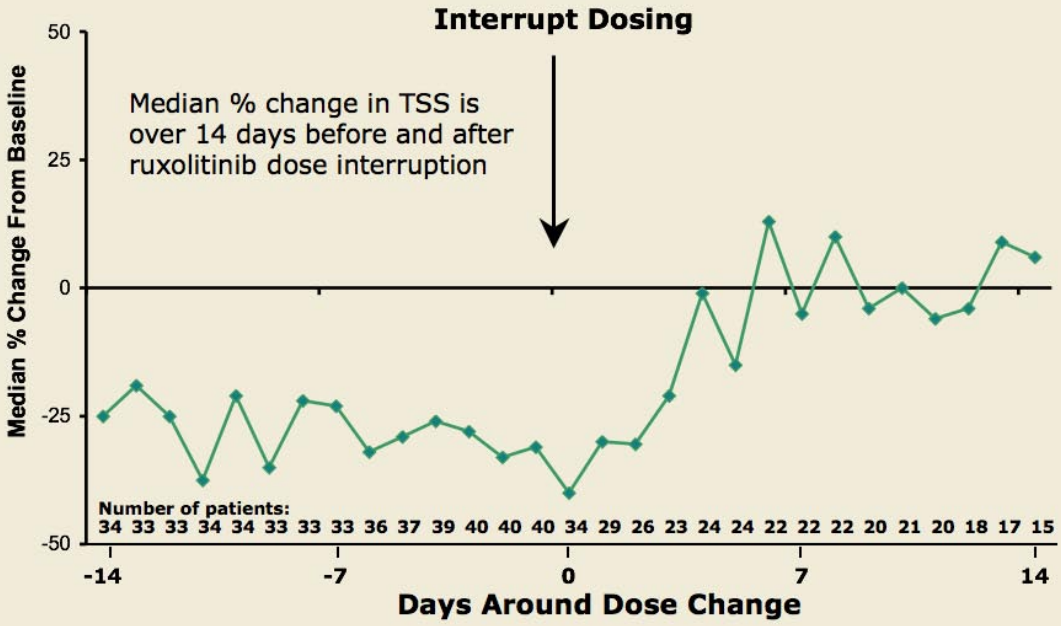
TSS After Therapy Interruption: Symptoms Return to Baseline in ≤7 d



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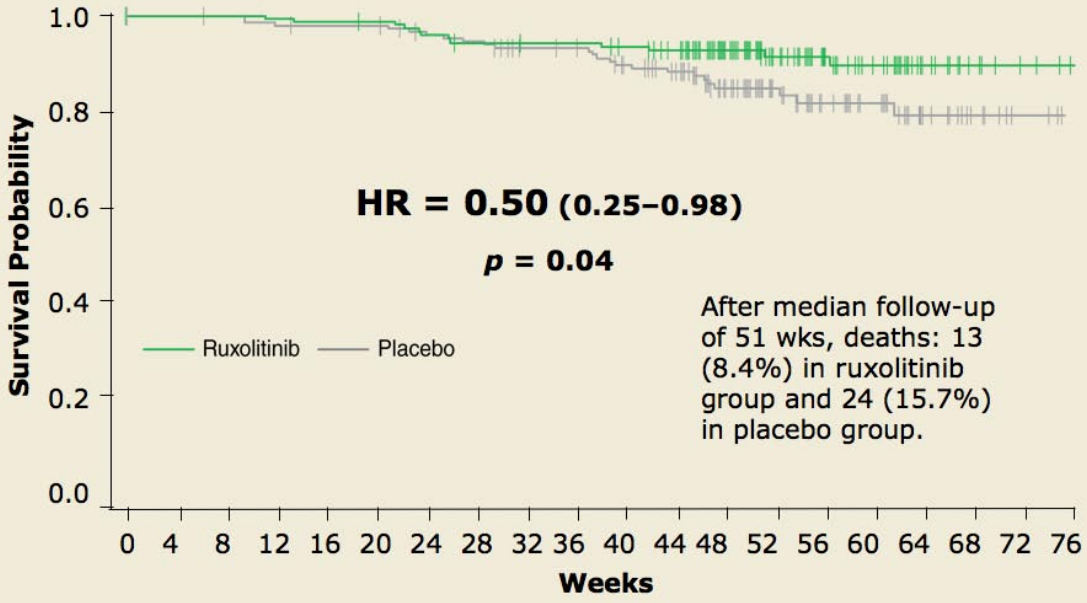
OS Update: Intention-to-Treat Population



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Conclusions

- Ruxolitinib treatment yielded benefits across all subgroups.
- After dose interruption, MF-related symptoms gradually returned to baseline levels.
- This updated analysis of the COMFORT-I trial shows a significant overall survival benefit with ruxolitinib treatment.

Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

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Investigator Commentary: Benefit of Ruxolitinib over Placebo: Results from COMFORT-I

COMFORT I was the first study in the development of ruxolitinib and one of the studies that led to its FDA approval. The majority of patients exposed to ruxolitinib showed a significant decrease in SV and TSS improvements. The benefits are durable because this JAK1/2 inhibitor controls the underlying abnormality. Every patient with MF has dysregulation in the JAK/STAT pathway. The disease has 16 or more different mutations, and half of the patients have the JAK2V617F mutation. Ruxolitinib is active in patients with or without the JAK2 mutation. The most common side effects of ruxolitinib are treatment-emergent thrombocytopenia and anemia and require dose modification. When therapy is stopped the symptoms return to baseline. Hence we suggest therapy be tapered off.

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

This study showed that ruxolitinib provided a significant advantage in terms of enhancing the quality of life by reducing symptoms and improving survival. The survival advantage was a positive finding and suggests ruxolitinib is an important breakthrough for MF. The improvement in quality of life suggests that this drug will be the standard of care for patients with MF.

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