5 Minute JournalClub

SPECIAL EDITION
Issue 2, 2011

A Report on the Results of the COMFORT-I and COMFORT-II Trials of the JAK1/JAK2 Inhibitor Ruxolitinib for Myelofibrosis

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting tens of thousands of attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for diverse forms of cancer.

LEARNING OBJECTIVE

- Evaluate emerging Phase III clinical data with the JAK1/2 inhibitor ruxolitinib, and consider this information for the clinical care of patients with myelofibrosis.

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This CME activity contains slides. To receive credit, the participant should review the slide presentations, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located on our website at ResearchToPractice.com/5MJCASCO2011/Myelofibrosis/CME.

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This activity is supported by educational grants from Bristol-Myers Squibb Company, Celgene Corporation and Genentech BioOncology.

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To go directly to the slides and investigator commentary for the featured abstracts, **click here**.

An oncology specialist would be hard pressed to find a better hour of television than the first half of the oral leukemia/myelodysplasia plenary session from ASCO 2011. This riveting segment of the conference, available for your viewing pleasure as part of the virtual meeting, began with 2 complementary presentations of Phase III trials evaluating the JAK1/2 inhibitor ruxolitinib **(ab 6500**, **ab LBA6501)** in patients with myelofibrosis. These were followed by a fascinating BCR-ABL mutation analysis from the ENESTnd CML study **(ab 6502)** comparing nilotinib to imatinib and then a brilliant follow-up discussion by Dr Ross Levine outlining a new paradigm in myeloproliferative disorders focused on the search for mutations and related novel blocking agents. These 3 presentations and 14 other compelling ASCO heme-onc data sets are detailed in our slide sets and profiled below in this, the second half of our super-succinct special edition *5-Minute Journal Club*.

1. Ruxolitinib in myelofibrosis

As mentioned above, this trial duet occupies a unique spot on the ASCO highlights reel, and while our understanding of the exact mechanism of action of this oral TKI may be somewhat hazy and may relate to reduction in elevated cytokine levels, what is crystal clear is that this uncommon but merciless disease has instantly entered a new era. The US-based COMFORT-I study evaluating ruxolitinib versus placebo had a number of interesting and innovative features, including the use of MRI to objectively evaluate spleen size and electronic daily diaries to record patient symptoms. The dramatic waterfall plots visibly illustrate how treatment at least temporarily reversed an otherwise downhill course in most patients.

2. CML

Dr Giuseppe Saglio presented the other previously discussed ASCO standout — the landmark substudy from the ENESTnd trial **(ab 6502)** demonstrating that prior to treatment patients had almost no BCR-ABL mutations but after therapy a fascinating panoply of alterations was observed in some individuals. Dr Levine predicted that in the near future, mutation assays will be regularly integrated into the treatment algorithm.

Additionally, 24-month follow-up from 2 key Phase III studies (ENESTnd **[ab 6511]** and DASISION **[ab 6510]**) was also unveiled in Chicago, suggesting greater efficacy and perhaps less toxicity with up-front treatment with the second-generation TKIs nilotinib and dasatinib when compared to imatinib.

3. Inotuzumab ozogamicin (our vote for name of the year)
This antibody-drug conjugate in the lineage of brentuximab vedotin in lymphoma and T-DM1 in HER2-positive breast cancer links an anti-CD22 antibody to a cytotoxic agent from the calicheamicins class (runner up). The ASCO findings **(ab 6507)** in relapsed/refractory ALL demonstrated some type of CR in 61% of patients.

4. Myeloma
For more than a year we have witnessed the evolution of data from 2 major trials (CALGB, French IFM group) demonstrating an impressive delay in disease progression but the suggestion of an increased risk of second primary cancers (SPC) with 2 years of lenalidomide maintenance following stem cell transplant (SCT). At ASCO, 3 additional reports **(ab 8007, ab 8008, ab 8009)** have for the moment reinforced the concept that if there is an SPC signal it is relatively modest in magnitude and far outweighed by the antimyeloma benefit of maintenance len.

The other much-discussed myeloma paper was a landmark Italian study **(ab 8020)** that for the first time evaluated the role of autologous SCT in the era of novel antimyeloma agents. A progression-free survival benefit was reported with SCT, but other maturing studies are evaluating this important question.

5. CLL
Maybe the most exciting development in B-cell neoplasm research is the rapid evolution of small molecules that block B-cell receptor signaling, and at ASCO we saw more to be optimistic about with a report on the Bruton's tyrosine kinase inhibitor PCI-32765 in CLL. In this Phase Ib/II single-agent study **(ab 6508)**, response rates in excess of 50% were observed with minimal toxicity.

6. Diffuse large B-cell lymphoma
The lack of progress in this common cancer since the introduction of rituximab was highlighted again this year with 1 trial failing to show an advantage with dose-dense R-CHOP **(ab 8000)** and another showing no important survival benefit to consolidation autotransplant after R-CHOP induction **(ab 8001)**.

7. AML
AML in the elderly — a true clinical conundrum — was the subject of 3 underwhelming ASCO reports. The first **(ab 6503)** showed a modest benefit that was counterbalanced by a relatively high early mortality rate when clofarabine was combined with Ara-C. The

second **(ab 6504)** demonstrated a modest benefit for decitabine, but discussant Dr Gail Roboz verbalized hope that better outcomes might be observed in her ongoing trial evaluating 10 days of decitabine combined with the proteasome inhibitor bortezomib. The third study **(ab 6505)** was a Phase I effort evaluating a sequential regimen of azacitidine and lenalidomide that resulted in CRs in 7 of 16 patients.

Finally, we saw another interesting AML study perhaps suggesting a new model for the real-time personalized treatment of the disease. In this Phase I/II trial **(ab 6506)**, the MEK1/2 inhibitor GSK1120212 was shown to have specific activity in patients with RAS mutations.

Coming soon, an online quintet of virtual presentations delving into new developments in non-small cell lung cancer.

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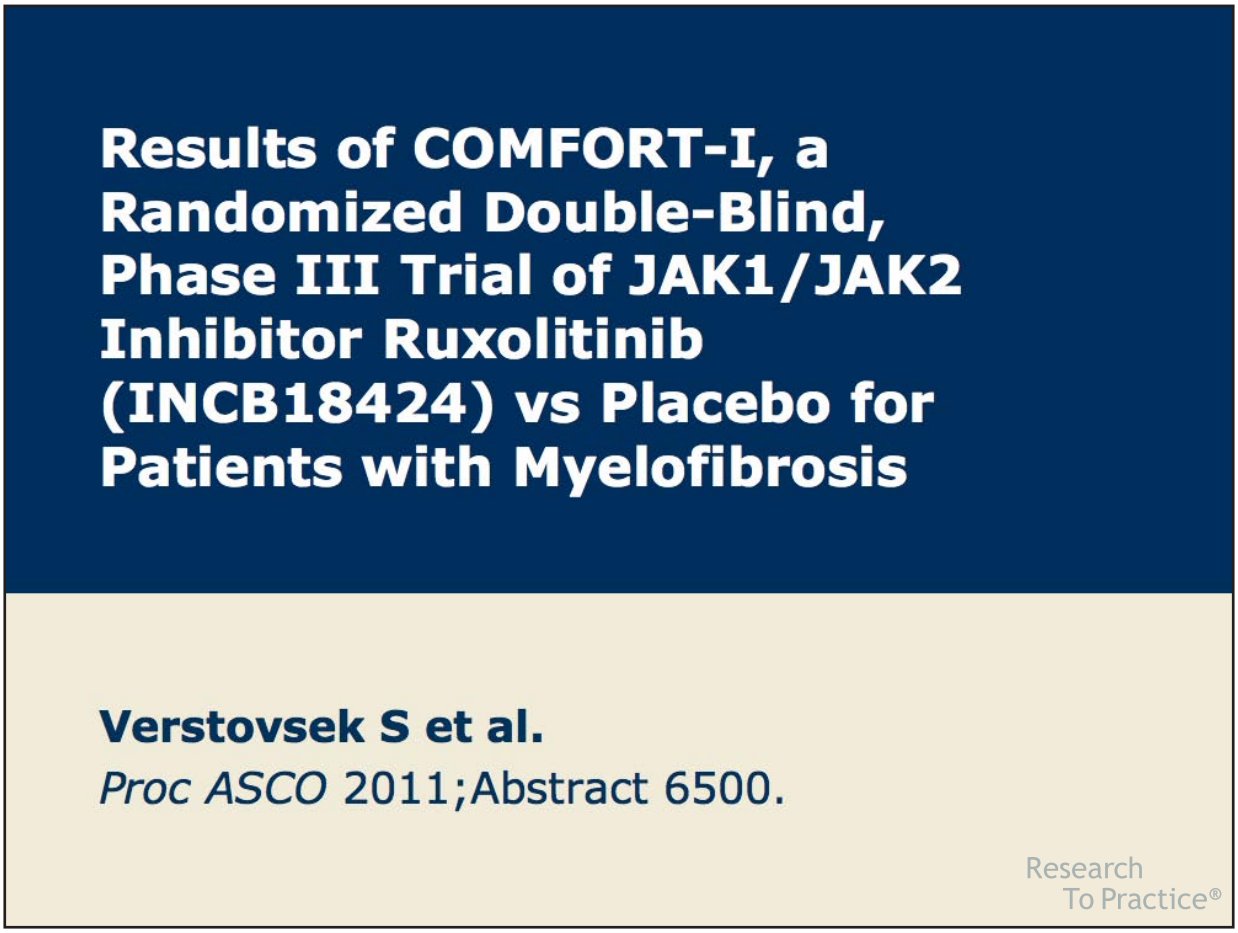
A Report on the Results of the COMFORT-I and COMFORT-II Trials of the JAK1/JAK2 Inhibitor Ruxolitinib for Myelofibrosis

Presentation discussed in this issue

Verstovsek S et al. **Results of COMFORT-I, a randomized double-blind phase III trial of JAK 1/2 inhibitor INCB18424 (424) versus placebo (PB) for patients with myelofibrosis (MF).** *Proc ASCO* 2011;**Abstract 6500**.

Slides from a presentation at ASCO 2011



Introduction

- Myelofibrosis (MF) is characterized by splenomegaly, debilatating symptoms, cytopenias and shortened survival.
- MF manifests as primary myelofibrosis (PMF), post-essential thrombocythemia MF (PET-MF) or post-polycythemia vera MF (PPV-MF).
- Treatment of MF with conventional drugs provides only palliative benefits (*Curr Opin Hematol* 2006;13:87).
- The JAK2 V617F mutation is found in about 50% of patients with MF and is associated with certain clinical signs such as splenomegaly (*Blood* 2007;110:4030).
- Selective JAK1/JAK2 inhibitor ruxolitinib (INCB018424) has been shown to be effective in preclinical models of myeloproliferative neoplasms (*Blood* 2010;115:3109).

Verstovsek S et al. *Proc ASCO* 2011;Abstract 6500.

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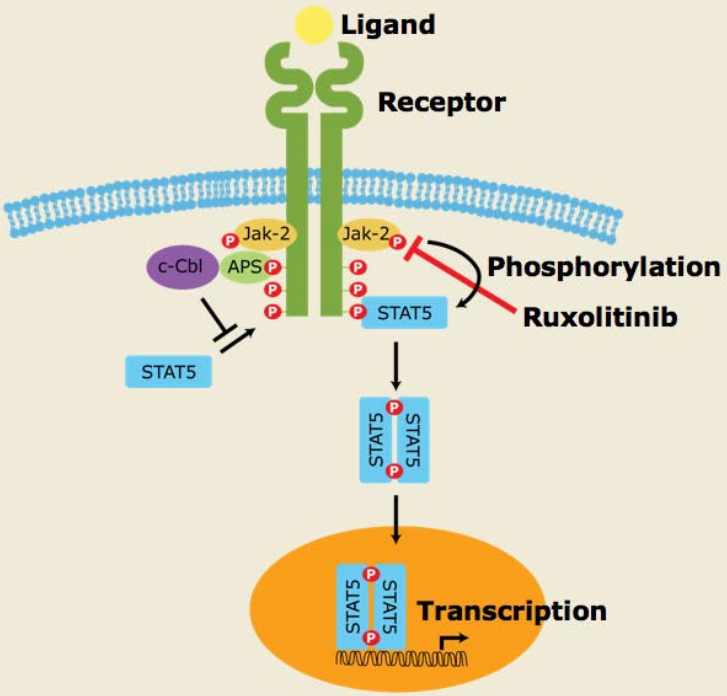
JAK2 Signaling Pathway



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COMFORT-I: A Phase III Trial of the JAK1/JAK2 Inhibitor Ruxolitinib

Eligibility

- PMF or PPV-MF or PET-MF
- Intermediate-2 or high risk by IWG-MRT criteria
- Palpable spleen ≥5 cm
- Platelet count ≥100 x 10^9/L
- JAK2 V617F positive or negative

R

- Ruxolitinib 15 or 20 mg BID
- Placebo*

* *Crossover to ruxolitinib arm allowed*

Ruxolitinib dose dependent upon starting platelet count:
15 mg BID if platelet count 100-200 x 10^9/L
20 mg BID if platelet count >200 x 10^9/L

Spleen volume measured by MRI every 12 weeks

Verstovsek S et al. *Proc ASCO* 2011;Abstract 6500.

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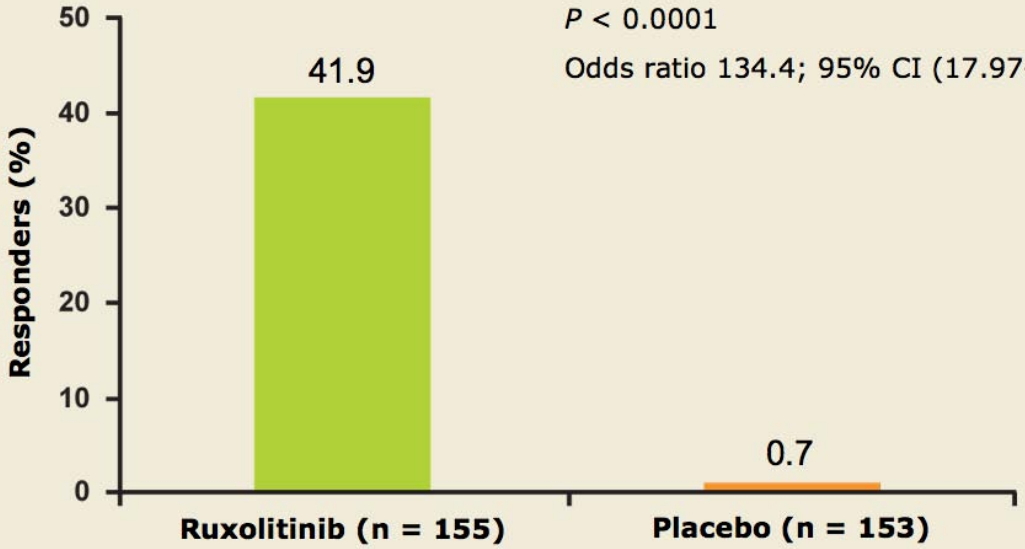
Primary Endpoint: Patients with ≥35% Decrease in Spleen Volume (Week 24)



P < 0.0001

Odds ratio 134.4; 95% CI (17.97-1,005)

Patients discontinuing prior to week 24 or who crossed over prior to week 24 were considered nonresponders.

With permission from Verstovsek S et al. *Proc ASCO* 2011;Abstract 6500.

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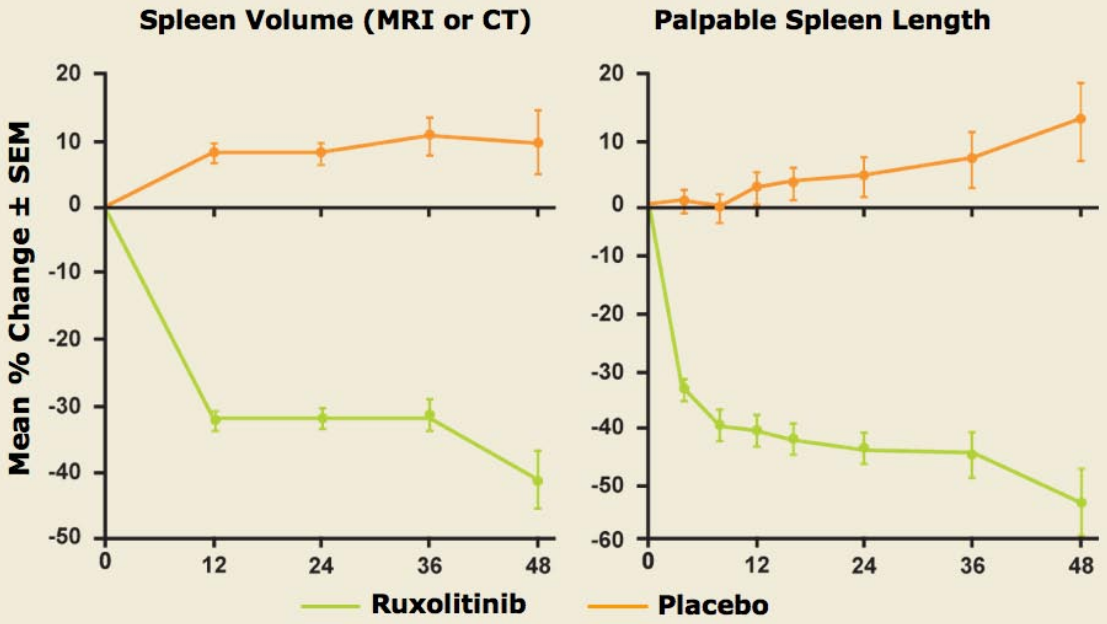
Mean Percent Change from Baseline in Spleen Size Over Time



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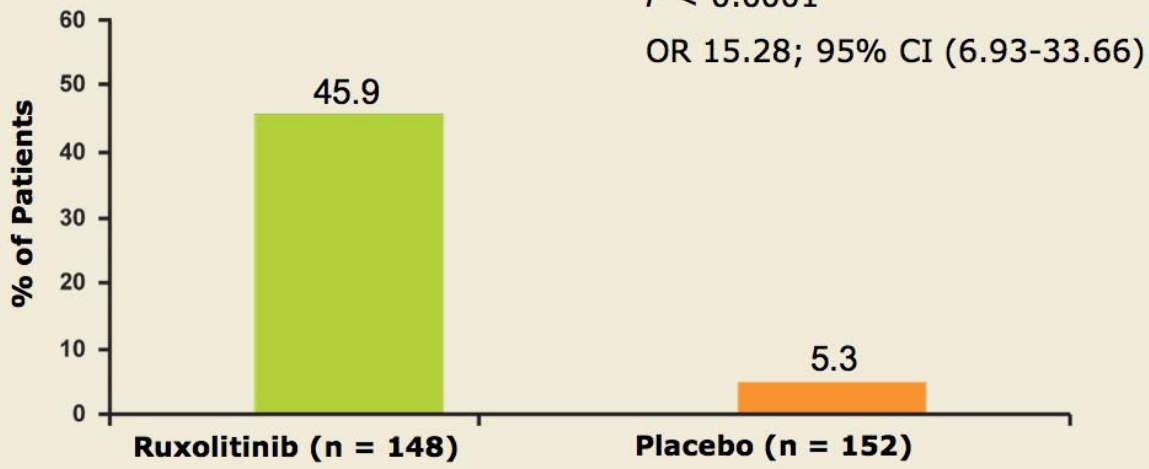
Percent of Patients with ≥50% Symptom Score Decrease (Week 24) — ITT



Symptom score = sum of scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the left ribs, and early satiety

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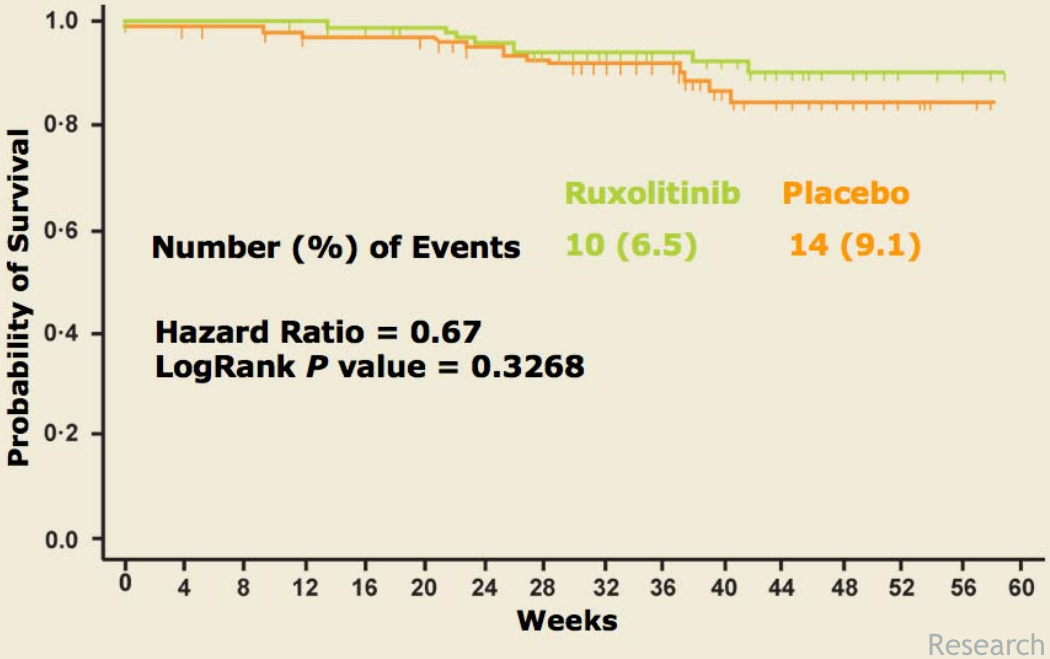
Overall Survival



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Hematology Laboratory Values (Worst Grade on Study*)

	Ruxolitinib, n = 155		Placebo, n = 151	
	Grade 3 %	Grade 4 %	Grade 3 %	Grade 4 %
Hemoglobin	34.2	11.0	15.9	3.3
Platelets	9.0	3.9	1.3	0
Neutrophils	5.2	1.9	0.7	1.3

* Patients are included at their worst on-study grade regardless of whether this represents a change from their baseline.

- Grade 3/4 anemia and thrombocytopenia were more common in those with higher baseline grade.
- Discontinuation of treatment because of anemia and thrombocytopenia was rare (1 patient in each treatment group for each event).

Verstovsek S et al. *Proc ASCO* 2011;Abstract 6500.

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Conclusions

- Ruxolitinib demonstrated marked and sustained clinical benefits in spleen size.
- Symptomatic burden was reduced in patients treated with ruxolitinib.
- Thrombocytopenia and anemia were among the most common adverse events associated with ruxolitinib, though they rarely led to treatment discontinuation.
- The results of this study, combined with those of the COMFORT-II trial (*Proc ASCO* 2011;Abstract LBA6501), demonstrate that ruxolitinib may become a treatment option for patients with MF.

Verstovsek S et al. *Proc ASCO* 2011;Abstract 6500.