



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

Last review date: September 2011

Expiration date: September 2012

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.

Neil Love, MD

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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

Presentations 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.**

Harrison CN et al. **Results of a randomized study of the JAK inhibitor ruxolitinib (INC424) versus best available therapy (BAT) in primary myelofibrosis (PMF), post-polycythemia vera-myelofibrosis (PPV-MF) or post-essential thrombocythemia-myelofibrosis (PET-MF).** *Proc ASCO 2011*; **Abstract LBA6501.**

Slides from a presentation at ASCO 2011

Results of a Randomized Study of the JAK Inhibitor Ruxolitinib (INC424) versus Best Available Therapy (BAT) in Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-MF)

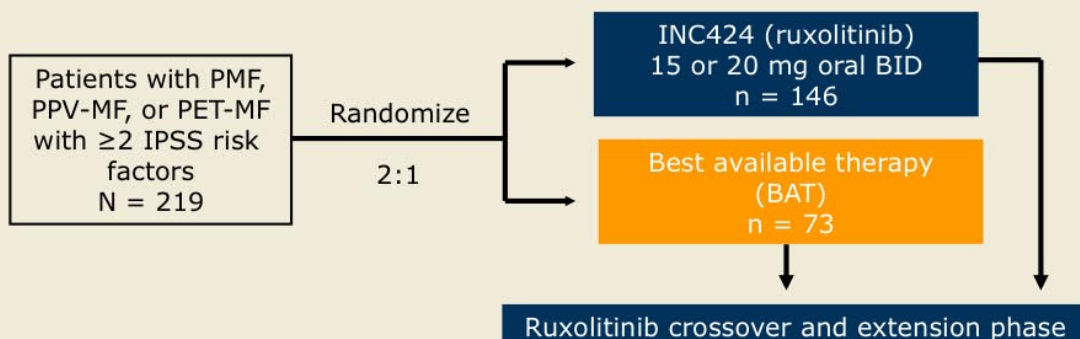
Harrison CN et al.

Proc ASCO 2011; Abstract LBA6501.

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COMFORT-II: Phase III Trial of JAK1/JAK2 Inhibitor Ruxolitinib versus BAT

- Randomized, open-label, multicenter Phase III trial
- Patients were stratified based on baseline IPSS risk category

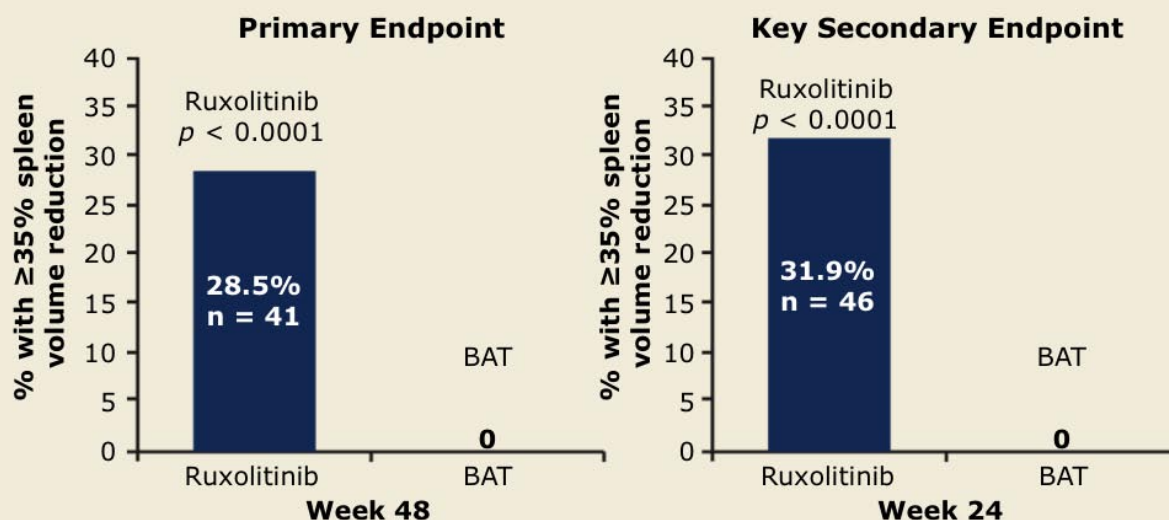


- Progression events that qualified for the crossover and extension phase:
 - Splenectomy
 - Progressive splenomegaly as defined by a 25% increase in spleen volume compared with the on-study nadir (including baseline)

Harrison CN et al. *Proc ASCO* 2011;Abstract LBA6501.

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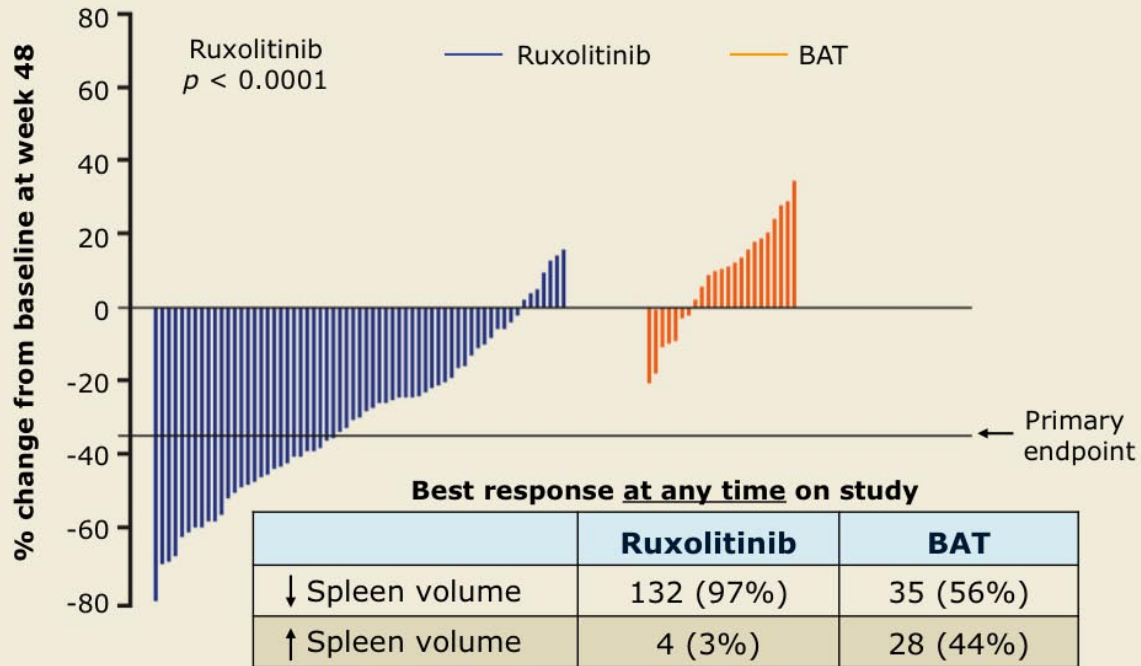
Patients with ≥35% Decrease in Spleen Volume at Weeks 24 and 48



- Median time to response = 12.29 weeks
- Of patients (n = 69) who achieved ≥35% reduction in spleen volume at any time during the study, 64% (n = 44) did so at the first assessment (at 12 weeks)

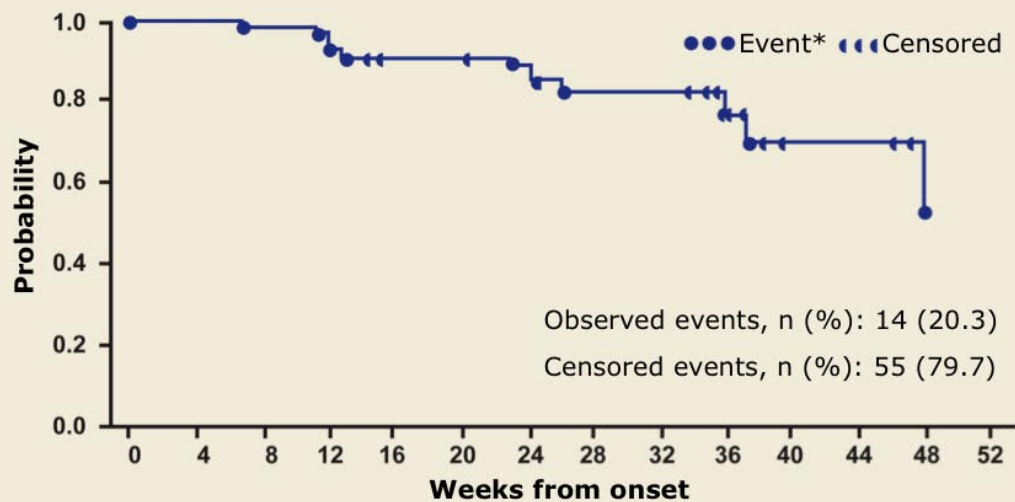
With permission from Harrison CN et al. *Proc ASCO* 2011;Abstract LBA6501.

Percent Change in Spleen Volume from Baseline



With permission from Harrison CN et al. *Proc ASCO 2011*;Abstract LBA6501.

Duration of Spleen Volume Reduction



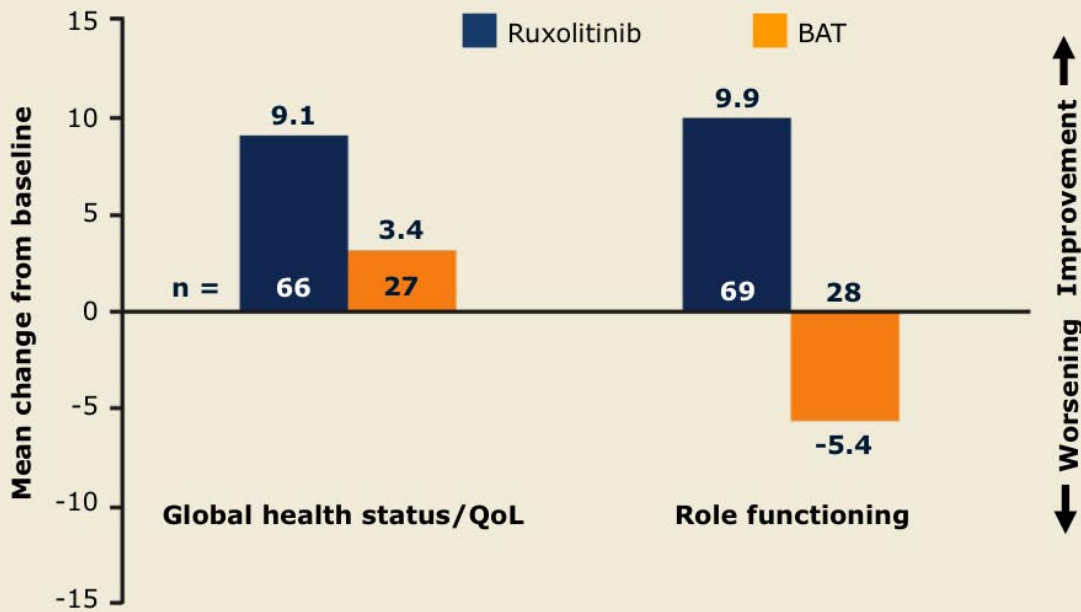
- Patients achieving $\geq 35\%$ spleen volume reduction at any time on study: 47.9%
- Median duration of reduction was not reached: 79.7% of patients still responding

* Event: $< 35\%$ reduction from baseline and $\geq 25\%$ increase from nadir

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With permission from Harrison CN et al. *Proc ASCO 2011*;Abstract LBA6501.

Change in EORTC QLQ-C30 Scores at Week 48 Compared to Baseline



• Improvements were seen by week eight and continued through week 48.

With permission from Harrison CN et al. *Proc ASCO* 2011;Abstract LBA6501.

Additional Secondary Endpoints

	Ruxolitinib (n = 146)	BAT (n = 73)	Hazard ratio	p-value
Progression-free survival	70%	74%	0.81	0.46
Leukemia-free survival	96%	95%	0.65	0.51
Overall survival	96%	95%	0.70	0.58

Harrison CN et al. *Proc ASCO* 2011;Abstract LBA6501.

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Hematology Laboratory Values (Worst Lab Grade on Study*†)

	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hemoglobin				
Ruxolitinib (n = 146)	16	38	34	8
BAT (n = 70)	23	40	21	10
Platelet count				
Ruxolitinib (n = 146)	32	28	6	2
BAT (n = 69)	16	6	4	3

* Occurring on the randomized treatment phase only

† Percentage is based on baseline total n

- The majority of patients (63% ruxolitinib, 67% BAT) had Grade 1 or 2 anemia at baseline.
- In both arms, all patients who entered the study had ≤Grade 1 thrombocytopenia at baseline.

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Harrison CN et al. *Proc ASCO* 2011;Abstract LBA6501.

Select Nonhematologic Adverse Events

	Ruxolitinib (n = 146)		BAT (n = 73)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Diarrhea	23%	1%	11%	0%
Peripheral edema	22%	0%	26%	0%
Asthenia	16%	1%	10%	1%
Dyspnea	16%	1%	18%	4%
Nasopharyngitis	15%	0%	14%	0%
Pyrexia	14%	2%	10%	0%
Nausea	13%	1%	7%	0%
Arthralgia	12%	1%	7%	0%
Cough	13%	0%	15%	1%
Fatigue	12%	1%	8%	0%

Harrison CN et al. *Proc ASCO* 2011;Abstract LBA6501.

Conclusions

- The study met its primary and key secondary endpoints with statistical significance.
- Ruxolitinib demonstrated significant and sustained improvement in splenomegaly, disease-related symptoms, functioning and quality of life.
- BAT-treated patients experienced progressive splenomegaly and either no change or worsening of symptoms.
- The safety profile of ruxolitinib was acceptable relative to the control.
- The data extend the positive results of the COMFORT-I trial, which compared ruxolitinib to placebo.
- Data from the COMFORT studies indicate that ruxolitinib has the potential to significantly improve the current treatment landscape for most patients with MF.

Harrison CN et al. *Proc ASCO* 2011;Abstract LBA6501.

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