



POST-ASH Issue 3, 2013

**Efficacy, Hematologic Effects
and Dose of Ruxolitinib in Patients
with Myelofibrosis and Low
Platelet Counts**

For more visit ResearchToPractice.com/5MJCASH2013

Research
To Practice®

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.

ACCREDITATION STATEMENT

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2013/3/CME.

CONTENT VALIDATION AND DISCLOSURES

Research To Practice (RTP) is committed to providing its participants with high-quality, unbiased and state-of-the-art education. We assess potential conflicts of interest with faculty, planners and managers of CME activities. Real or apparent conflicts of interest are identified and resolved through a conflict of interest resolution process. In addition, all activity content is reviewed by both a member of the RTP scientific staff and an external, independent physician reviewer for fair balance, scientific objectivity of studies referenced and patient care recommendations.

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
Associate Chief, Division of Hematology/Oncology
Director, Hematologic Malignancies
University of Michigan Medical Center
Ann Arbor, Michigan

Advisory Committee: Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; **Contracted Research:** Abbott Laboratories, Bristol-Myers Squibb Company, Celgene Corporation, Incyte Corporation, Millennium: The Takeda Oncology Company, Novartis Pharmaceuticals Corporation, Sanofi; **Speakers Bureau:** Novartis Pharmaceuticals Corporation.

EDITOR — Dr Love is president and CEO of Research To Practice, which receives funds in the form of educational grants to develop CME activities from the following commercial interests: AbbVie Inc, Algeta US, Allos Therapeutics, Amgen Inc, ArQule Inc, Astellas, Aveo Pharmaceuticals, Bayer HealthCare Pharmaceuticals, Biodesix Inc, Biogen Idec, Boehringer Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb Company, Celgene Corporation, Daiichi Sankyo Inc, Dendreon Corporation, Eisai Inc, EMD Serono Inc, Foundation Medicine Inc, Genentech BioOncology, Genomic Health Inc, Gilead Sciences Inc, Incyte Corporation, Lilly USA LLC, Medivation Inc, Merck, Millennium: The Takeda Oncology Company, Mundipharma International Limited, Novartis Pharmaceuticals Corporation,

Onyx Pharmaceuticals Inc, Prometheus Laboratories Inc, Regeneron Pharmaceuticals, Sanofi, Seattle Genetics, Spectrum Pharmaceuticals Inc and Teva Oncology.

RESEARCH TO PRACTICE STAFF AND EXTERNAL REVIEWERS — The scientific staff and reviewers for Research To Practice have no real or apparent conflicts of interest to disclose.

This educational activity contains discussion of published and/or investigational uses of agents that are not indicated by the Food and Drug Administration. Research To Practice does not recommend the use of any agent outside of the labeled indications. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications and warnings. The opinions expressed are those of the presenters and are not to be construed as those of the publisher or grantors.

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

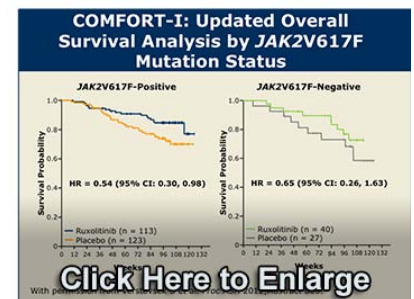
To go directly to slides and commentary for this issue, [click here](#).

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

Research To Practice

Miami, Florida

Research To Practice is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

Research To Practice designates this enduring material for a maximum of 1.25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This activity is supported by educational grants from Celgene Corporation, Genentech BioOncology/ Biogen Idec, Millennium: The Takeda Oncology Company, Seattle Genetics and Teva Oncology.

Efficacy, Hematologic Effects and Dose of Ruxolitinib in Patients with Myelofibrosis and Low Platelet Counts

Presentation discussed in this issue

Talpaz M et al. **Efficacy, hematologic effects, and dose of ruxolitinib in myelofibrosis patients with low starting platelet counts (50-100 x 10⁹/L): A comparison to patients with normal or high starting platelet counts.** *Proc ASH 2012;Abstract 176.*

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

Efficacy, Hematologic Effects and Dose of Ruxolitinib in Myelofibrosis Patients with Low Platelet Starting Counts (50-100 x 10⁹/L): A Comparison to Patients with Normal or High Starting Platelet Counts

Talpaz M et al.

Proc ASH 2012;Abstract 176.

Research
To Practice®

Background

- The Phase III COMFORT-I trial demonstrated clinical benefit with ruxolitinib (RUX) for patients with myelofibrosis (MF) with or without the JAK2V617F mutation at starting doses of 15 or 20 mg PO BID (*NEJM* 2012;366(9):799-807).
- Reversible declines in platelet counts and hemoglobin (Hgb) can occur with RUX but are rarely treatment-limiting factors.
- Given the potential risk of bleeding complications, patients with MF with low platelet counts represent an important subset.
- **Study objective:** To assess an alternative strategy starting with a lower RUX dose with subsequent dose escalations in the treatment of MF in patients with low platelet counts.

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Research
To Practice®

Phase II INCB018424-258 Study Design

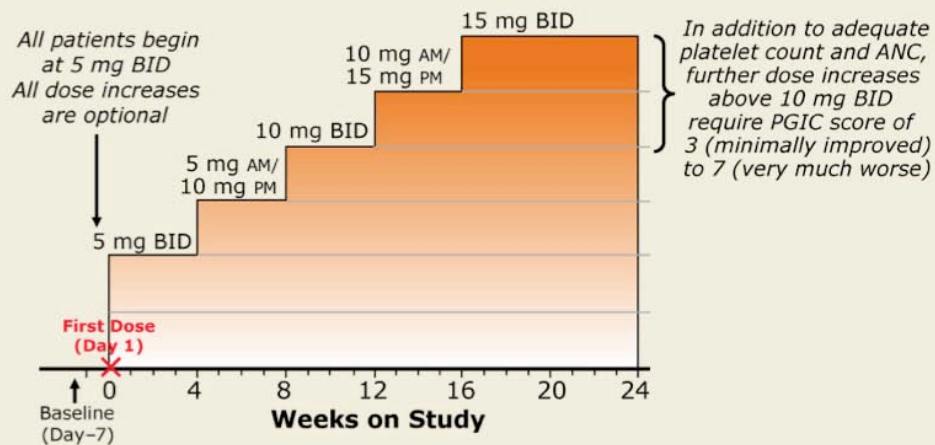
- Eligibility:
 - Primary, postpolycythemia vera or postessential thrombocytopenia MF with symptoms
 - Platelet counts of 50-100 x 10⁹/L
 - Intermediate-1, intermediate-2 or high-risk MF
- Assessments:
 - Spleen volume by MRI or CT: Baseline, week 24
 - Spleen palpation: Each study visit
 - Modified MF symptom assessment form v2.0*: Daily
 - Patient Global Impression of Change (PGIC): Every study visit starting at week 4
 - EORTC QLQ-C30: Baseline, weeks 4, 12, 24

* Total Symptom Score: Average of the daily sum of individual symptom scores over time (baseline: 7 d; week 24: 28 d) except inactivity

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Research
To Practice®

Dosing Schedule



- Dose reductions required for platelet count $\geq 25 \times 10^9/L$ to $35 \times 10^9/L$
- Dose interruptions required for platelet count $< 25 \times 10^9/L$, absolute neutrophil count $< 0.5 \times 10^9/L$ or Grade ≥ 2 active hemorrhage
- Dosing could be restarted or re-escalated when platelet count was $\geq 35 \times 10^9/L$

Talpaz M et al. *Proc ASH 2012*;Abstract 176.

Research
To Practice®

Efficacy at Week 24: Study 258 versus COMFORT-I

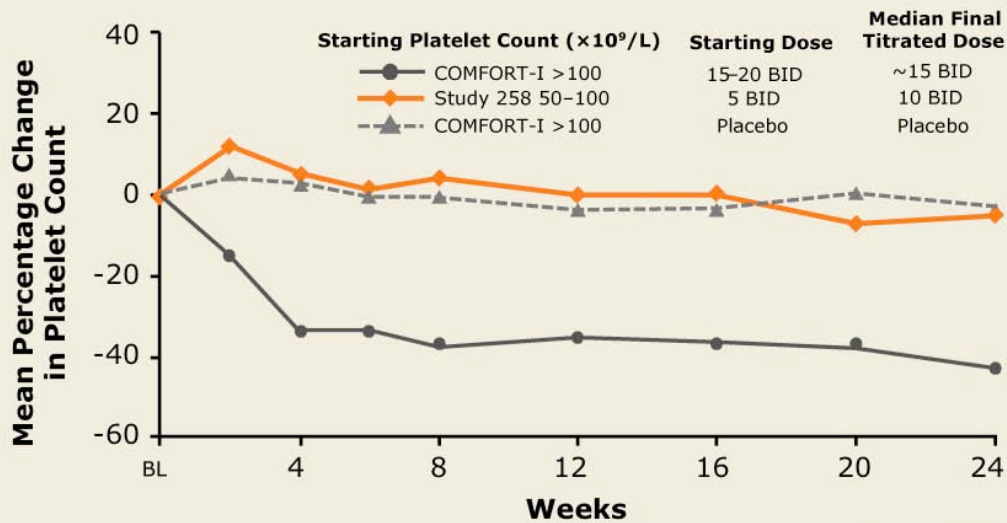
Efficacy parameter	Study 258 (n = 22*)	COMFORT-I	
		RUX (n = 155)	Placebo (n = 154)
$\geq 50\%$ reduction in TSS	36.4%	45.9%	5.3%
$\geq 35\%$ reduction in spleen volume	33.3%	41.9%	0.7%
Much/very much improvement on PGIC	59.1%	60.0%	7.8%
Mean change from baseline			
QLQ-C30 fatigue subscale [†]	-23.4	-14.8	1.8
QLQ-C30 global health/QoL [‡]	16.2	12.3	-3.4

* Maximum number of evaluable patients; [†] Negative changes indicate improvement; [‡] Positive changes indicate improvement

Talpaz M et al. *Proc ASH 2012*;Abstract 176.

Research
To Practice®

Changes in Platelet Counts During Study 258 and COMFORT-I

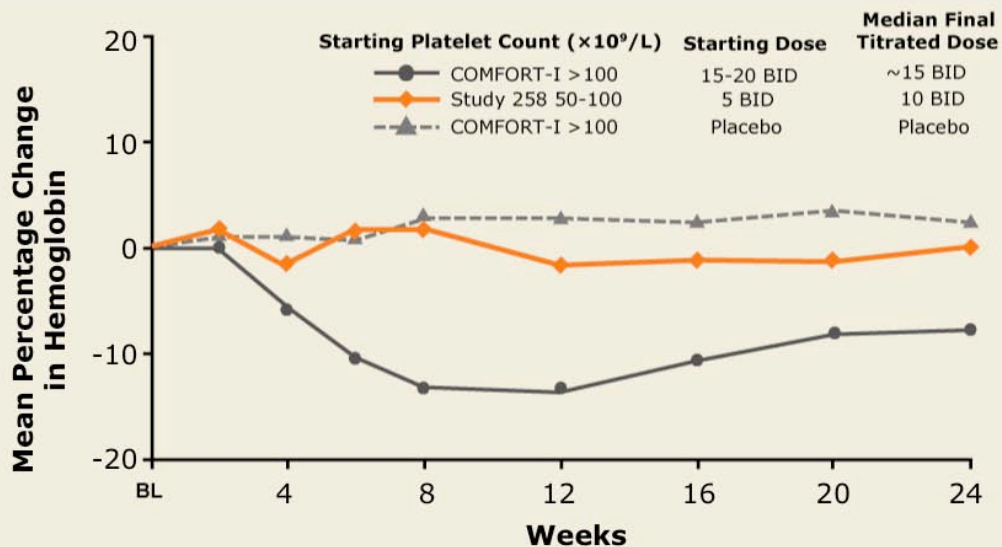


Mean percentage change in platelet counts were comparable in RUX-treated patients in Study 258 and placebo-treated patients in COMFORT-I.

With permission from Talpaz M et al. *Proc ASH 2012*;Abstract 176.

Research
To Practice®

Changes in Hgb in Patients without Transfusions During Study 258 and COMFORT-I



Decreases in Hgb levels in Study 258 were of lesser magnitude compared to patients receiving RUX and similar to patients receiving placebo in COMFORT-I.

With permission from Talpaz M et al. *Proc ASH 2012*;Abstract 176.

Research
To Practice®

Study 258 Select Adverse Events (Regardless of Causality)

Adverse event (n = 41)	Overall	Grade 3/4
Nonhematologic adverse events		
- Diarrhea	13 (31.7%)	2 (4.9%)
- Fatigue	9 (22.0%)	2 (4.9%)
- Nausea	9 (22.0%)	2 (4.9%)
Bleeding events		
- Subdural hematoma (secondary to fall)	1 (2.4 %)	0
- Hematochezia	1 (2.4 %)	0
- Hemorrhoidal hemorrhage	1 (2.4 %)	0
- Epistaxis	1 (2.4 %)	0

Dose reduction for adverse event: 6 (14.6%) patients

Adverse event leading to death: 2 (4.9%) patients, COPD (n = 1), unknown (n = 1)

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Research
To Practice®

Author Conclusions

- For patients with baseline platelet counts of $50\text{--}100 \times 10^9/\text{L}$, starting at a RUX dose of 5 mg BID and titrating to 10 mg BID or greater resulted in spleen volume reductions and improvements in symptoms and QoL that were consistent with COMFORT-I.
- Decreases in mean Hgb were of lesser magnitude compared to RUX-treated patients in COMFORT-I.
- Changes in mean platelet count were similar to patients receiving placebo in COMFORT-I.
- These findings suggest that titration to 10 mg BID may be an effective and well-tolerated approach for patients with MF starting with or developing low Hgb or platelet count, while higher doses are beneficial for patients with higher Hgb and platelet count and those with inadequate response to 10 mg BID.

Talpaz M et al. *Proc ASH* 2012;Abstract 176.

Research
To Practice®

Investigator Commentary: Efficacy, Safety and Dose of Ruxolitinib for Patients with MF with Low Starting Platelet Counts

This study determined whether ruxolitinib should be administered to patients with mild to moderate thrombocytopenia. The take-home message was that the vast majority of patients can be treated if they have a platelet count from 50 to 100 x 10⁹/L. Most of these patients will end up receiving ruxolitinib therapy at 15 to 20 mg/d. In addition, the responses observed were slightly lower than was observed in the COMFORT-I and II trials, with about 35% of patients experiencing a reduction in spleen volume to a level of partial response. About 40% of the patients experienced ≥50% reduction in symptoms. Anemia was much less pronounced, probably due to the gradual dose escalation. This strategy is likely to be adopted by physicians. An interesting finding was the identification of a small group of 5 patients, or about 11% of the total study population, who experienced an increase in platelet counts after therapy as opposed to a decrease. This was most likely because thrombocytopenia was secondary to platelet sequestration by the spleen rather than poor bone marrow production. These patients were diagnosed early and had a better prognosis. The other patients had a predictable drop in platelets.

Interview with Moshe Talpaz, MD, February 19, 2013

Research
To Practice®