5 Minute JournalClub

POST-ASH Issue 3, 2013

EXPAND: A Phase Ib Dose-Finding Study of Ruxolitinib in Patients with Myelofibrosis and Low Platelet Counts

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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

- 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.

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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

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POST-ASH Issue 3, 2013

Does the JAK1/2 inhibitor ruxolitinib benefit patients with myelofibrosis without JAK2 mutations?...and more

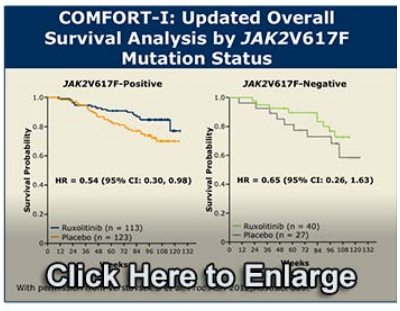
To go directly to slides and commentary for this issue, **click here**.

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.

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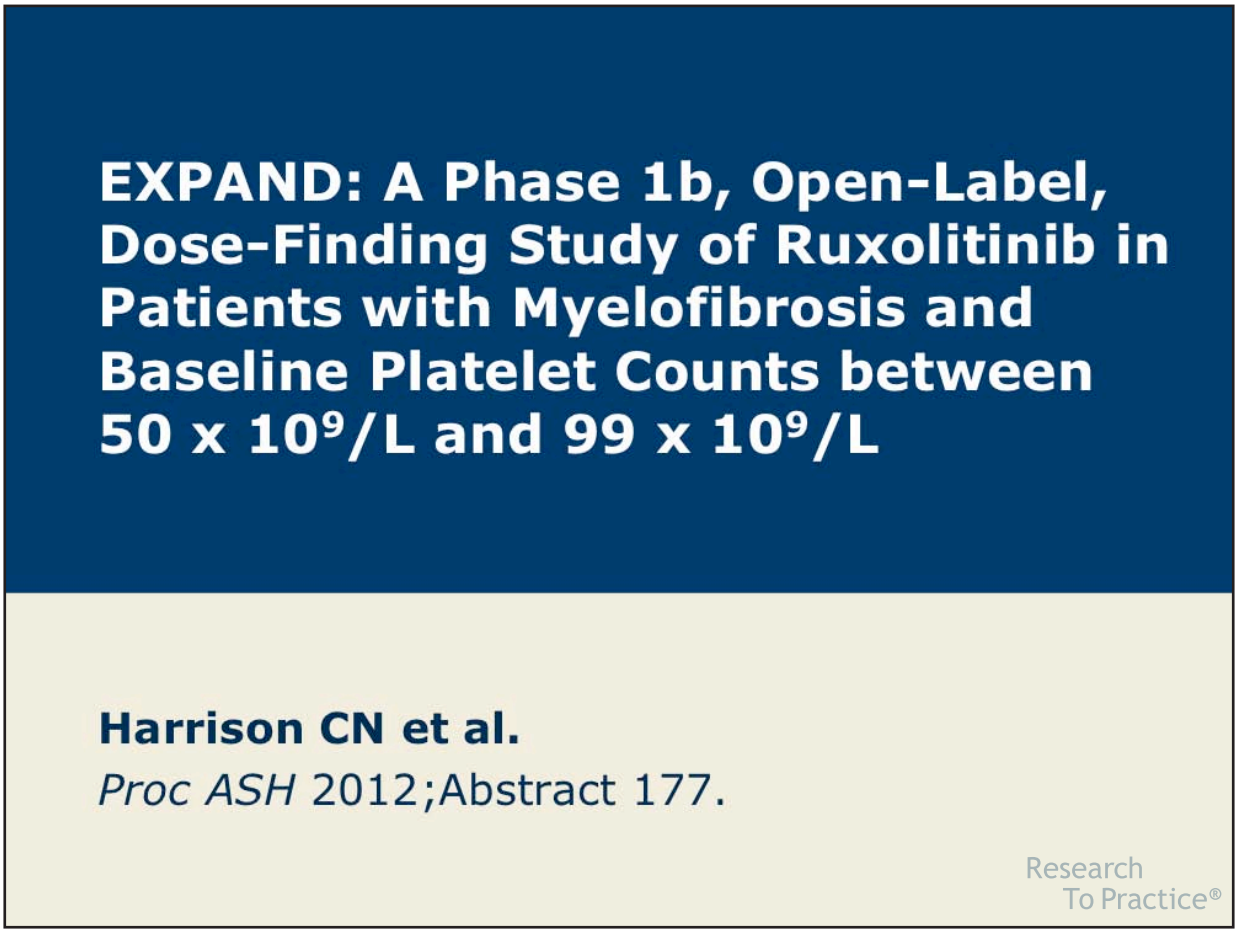
EXPAND: A Phase Ib Dose-Finding Study of Ruxolitinib in Patients with Myelofibrosis and Low Platelet Counts

Presentation discussed in this issue

Harrison CN et al. **Expand: A Phase 1b, open-label, dose-finding study of ruxolitinib in patients with myelofibrosis and baseline platelet counts between 50 x 10^9/L and 99 x 10^9/L.** *Proc ASH* 2012;**Abstract 177**.

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



Background

- Ruxolitinib, a JAK1/JAK2 inhibitor, has demonstrated rapid, durable reductions in splenomegaly and improved myelofibrosis (MF)-associated symptoms and quality of life in the Phase III COMFORT-I and -II studies (*N Engl J Med* 2012;366(9):799; *N Engl J Med* 2012;366(9):787).
- To date, there has been limited experience with patients who have baseline thrombocytopenia with platelet (PLT) counts <100 × 10^9/L as this patient population was excluded from the COMFORT studies.
- **Study objective:** To evaluate the safety of ruxolitinib and to establish the maximum safe starting dose (MSSD) in patients with MF who have baseline platelet counts 50 × 10^9/L to 99 × 10^9/L.

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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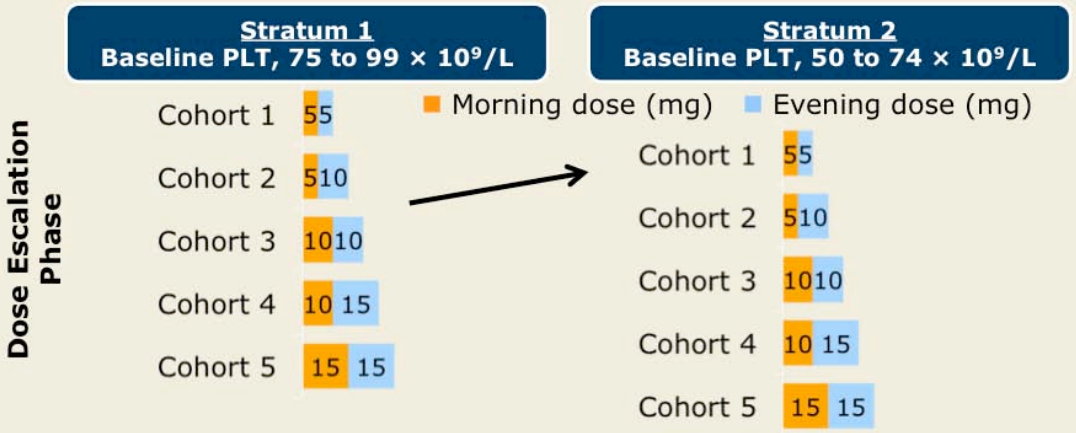
EXPAND: Dose-Escalation Phase Schema



- Patients will receive increasing doses until the MSSD is determined.
  - Escalation from a given dose level to the following one will occur only if both that dose level and the previous one are deemed safe.
  - Each dose level in stratum 2 will be open to patients only if both that dose level and the following one have been deemed safe in stratum 1.
  - A minimum of 9 patients from each stratum must be treated at the dose declared to be the MSSD.

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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EXPAND: Safety Expansion Phase Schema

Stratum 1
Baseline PLT, 75 to 99 × 10^9/L

Stratum 2
Baseline PLT, 50 to 74 × 10^9/L

- In the safety expansion phase, the safety and tolerability of the MSSD will be further evaluated to establish that it is suitable for use in the low-platelet population.
- 20 patients (10 from each stratum) additional to those treated at the MSSD during dose escalation will be treated at the respective MSSD for their stratum.

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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Patient Disposition

Stratum 1 (PLT, 75 to 99 × 10^9/L)					
n	**Cohort 1** 5 mg/5 mg	**Cohort 2** 5 mg/10 mg	**Cohort 3** 10 mg/10 mg	**Cohort 4** 10 mg/15 mg	**Cohort 5** 15 mg/15 mg
Enrolled	4	3	4	3	Enrolling
Evaluable	3	3	3	2	
Ongoing	2	2	3	3	
Stratum 2 (PLT, 50 to 74 × 10^9/L)					
n	**Cohort 1** 5 mg/5 mg	**Cohort 2** 5 mg/10 mg	**Cohort 3** 10 mg/10 mg	**Cohort 4** 10 mg/15 mg	**Cohort 5** 15 mg/15 mg
Enrolled	3	3	Ongoing	Not open	
Evaluable	3	3			
Ongoing	3	3			

- The median duration of exposure to ruxolitinib was 65.5 days (range, 1-256 days)

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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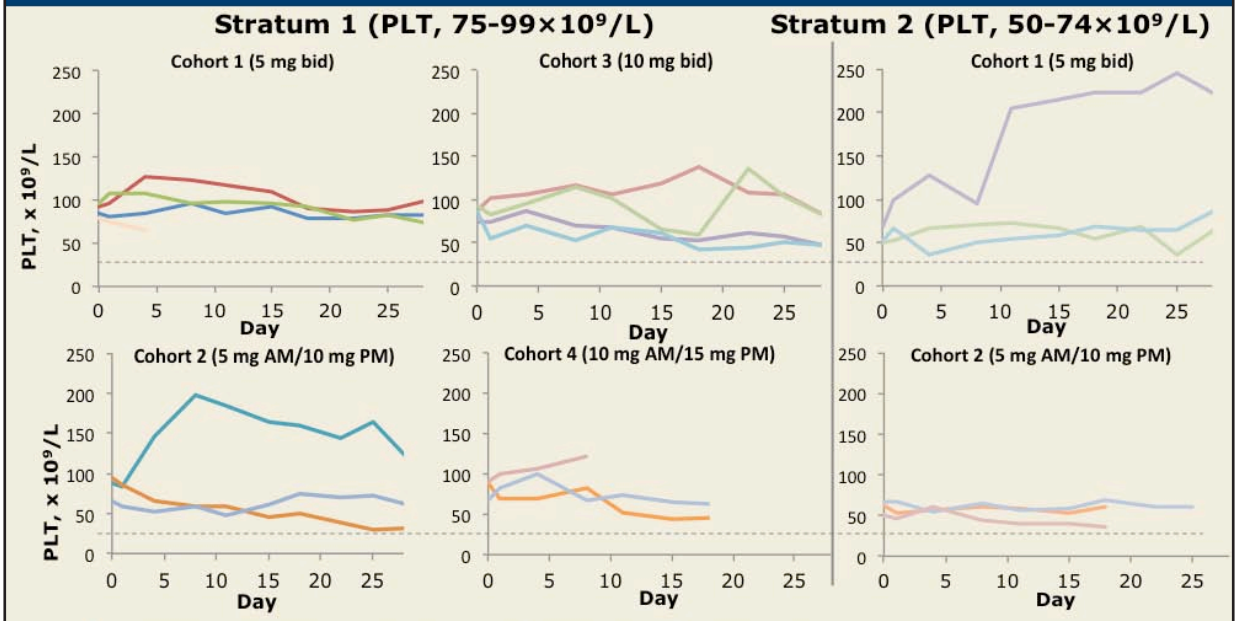
Platelet Counts During the First 28 Days (DLT Period)



- Dose changes within the first 28 days were not allowed
- PLT counts of <25 × 10^9/L constitute a DLT

With permission from Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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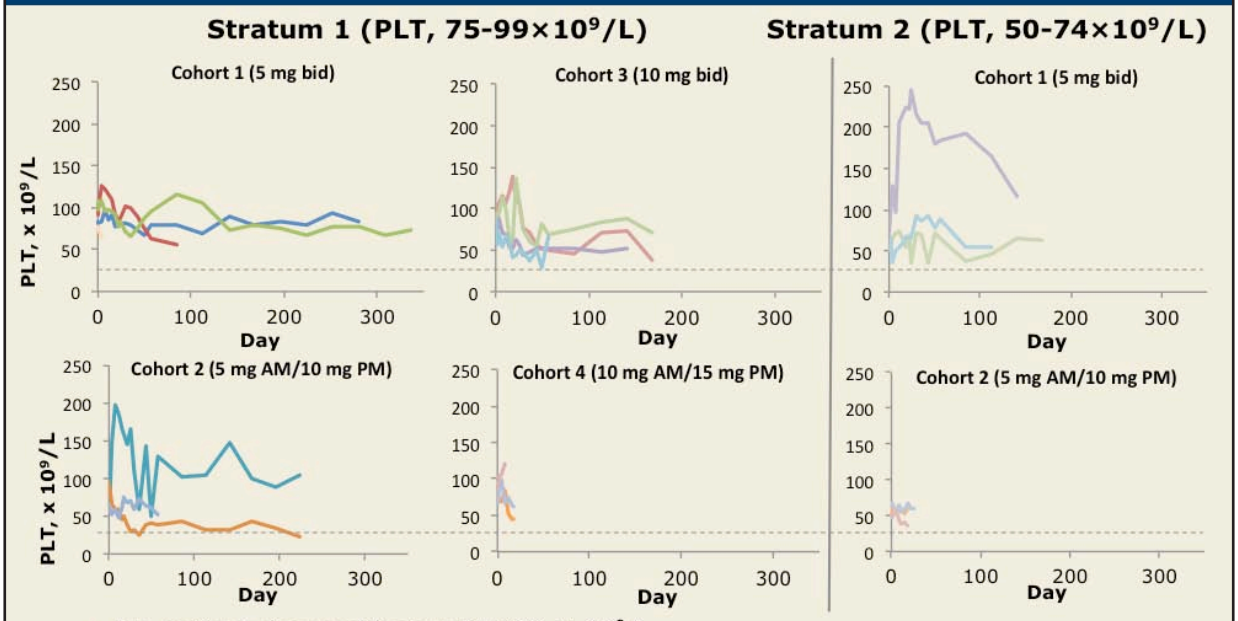
Platelet Counts up to Data Cutoff



- No patient dropped below PLT 20 × 10^9/L
- The lowest PLT count on study was 22 × 10^9/L

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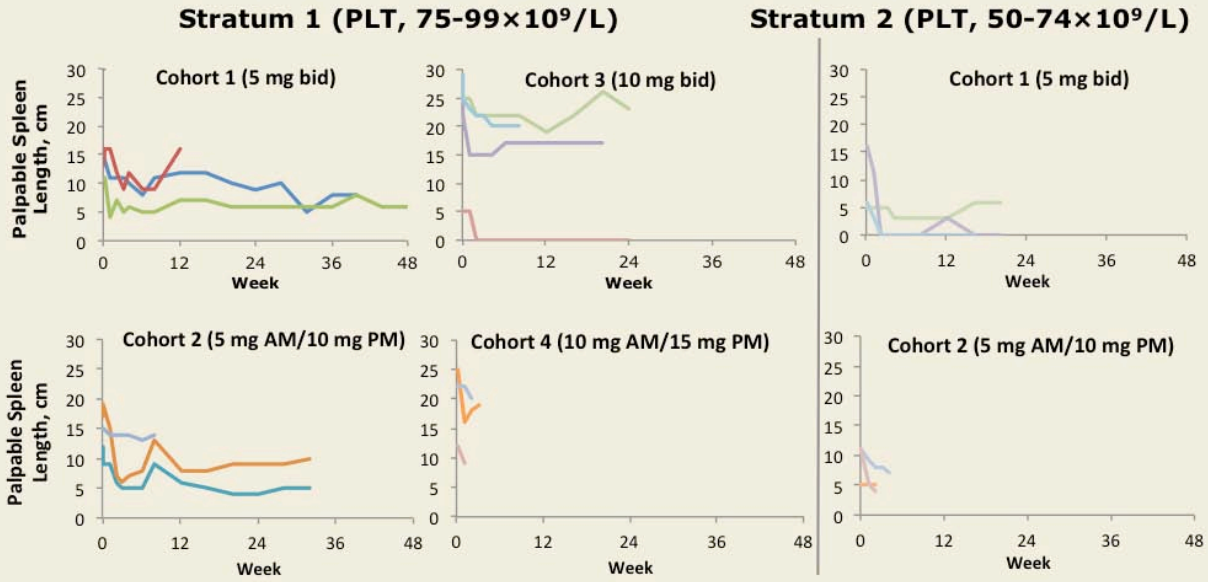
Efficacy: Spleen Length Over Time



- 3 of 18 evaluable patients (17%) achieved a 100% reduction in palpable spleen length in at least 1 postbaseline assessment

With permission from Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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DLTs and Serious Adverse Events (SAEs)

Dose-limiting toxicity

- No DLTs were reported for 17 evaluable patients during the first 28 days of treatment

Serious adverse events

- 7 patients experienced SAEs
  - 2 related to study drug (anemia, gastrointestinal hemorrhage)

Discontinuations due to adverse events

- 3 patients discontinued because of AEs; none related to study drug
  - 1 patient had general health deterioration
  - 1 patient had blood bilirubin increased (secondary to gallstones)
  - 1 patient had third-nerve paralysis and granulocytic sarcoma

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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Author Conclusions

- No DLTs have occurred to date, and this study is ongoing.
  - Stratum 1 (PLTs 75-99 × 10^9/L) is ongoing at 15 mg bid
  - Stratum 2 (PLTs 50-74 × 10^9/L) is ongoing at 10 mg bid
- Toxicities were similar to those reported in previous studies of ruxolitinib, and no patient has discontinued due to thrombocytopenia.
  - No patient dropped below PLT 20 × 10^9/L
  - No Grade 3-4 hemorrhagic events were reported (data not shown)
- Treatment with ruxolitinib led to spleen length reductions from baseline in 17 of 20 patients.
  - 3 patients experienced complete resolution of palpable splenomegaly as best response on study
  - Spleen length reductions were similar to those observed in the COMFORT studies

Harrison CN et al. *Proc ASH* 2012;Abstract 177.

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Investigator Commentary: Phase Ib EXPAND Trial of Ruxolitinib for Patients with MF and Low Baseline Platelet Counts

The COMFORT-I and COMFORT-II studies, which evaluated the efficacy and safety of ruxolitinib for patients with MF, only enrolled patients who had platelet counts of 100 x 10^9/L or more. This study investigated whether ruxolitinib could be administered to patients with mild to moderate thrombocytopenia.

This is a classical Phase I study including small cohorts of patients for whom the ruxolitinib dose was gradually escalated. Patients with platelet counts between 50 and 99 x 10^9/L were included in the study. A small number of patients experienced an increase in platelets counts as a consequence of therapy. This is probably because thrombocytopenia was secondary to platelet sequestration by the spleen rather than poor production in the bone marrow.

This study is still ongoing and without definitive data.

Interview with Moshe Talpaz, MD, February 19, 2013

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