# 5 Minute JournalClub

POST-ASH Issue 4, 2015

# Results from the Phase III RESPONSE Trial of Ruxolitinib versus Best Available Therapy for Patients with Polycythemia Vera

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## CME INFORMATION

## OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on up-front and salvage therapeutic options and modalities for the evaluation of treatment response in newly diagnosed and relapsed or refractory chronic myeloid leukemia (CML), myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

## LEARNING OBJECTIVES

- Assess the recent results of the RESPONSE trial evaluating ruxolitinib for PV, and consider this information for the treatment of this disease in patients who are not responsive to or are intolerant of hydroxyurea.
- Appraise the effectiveness and tolerability of the investigational agents PRM-151 and imetelstat as single-agent therapy for patients with MF.
- Examine long-term efficacy and symptomatology results with ruxolitinib in patients with ET who are refractory to or intolerant of hydroxyurea.
- Compare and contrast the benefits and risks of discontinuing second-generation tyrosine kinase inhibitors for patients with CML in chronic phase.
- Analyze efficacy and safety results from Phase III trials evaluating dasatinib or ponatinib in comparison to imatinib for patients with CML in chronic phase.

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Consulting Agreements: Bristol-Myers Squibb Company, Genentech BioOncology, Lilly, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi; Contracted Research: Bristol-Myers Squibb Company, Celgene Corporation, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi.

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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: May 2015
Expiration date: May 2016

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POST-ASH Issue 4, 2015

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

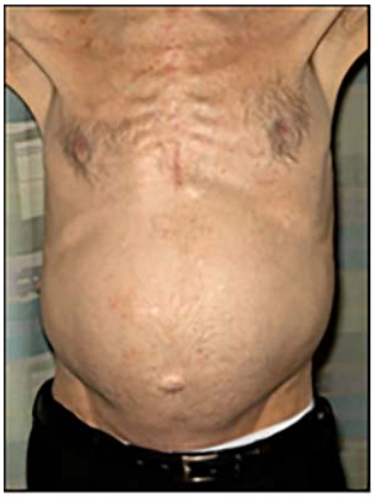
Many physicians (myself included) remember the day they first treated a patient with pulmonary edema from congestive heart failure and the exhilarating feeling of instantly relieving this profound symptomatology with the classic use of an intravenous diuretic and morphine. Medical oncology also provides many opportunities for these types of healing moments, and at the 2011 ASCO meeting the field was introduced to another powerful palliative tool for a disease desperately in need of one. Since the presentation of the aptly named COMFORT-I and II trials in Chicago, we have heard on many of our CME programs a myriad of moving patient case histories of individuals with myelofibrosis (MF) suffering from anorexia, weight loss, fatigue and massive uncomfortable spleens who experienced dramatic, life-altering changes within days or weeks of starting treatment with the JAK1/2 inhibitor ruxolitinib (rux).

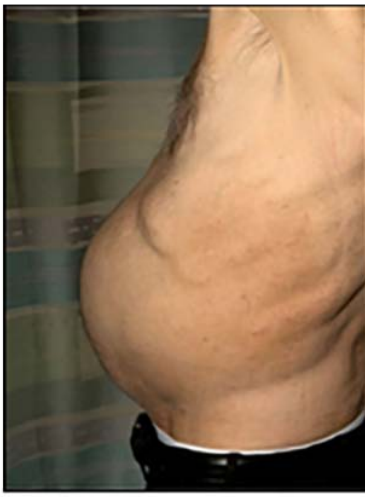
Perhaps not surprisingly, the myeloproliferative neoplasm (MPN) issue of our ASH highlight series focuses in large part on this fascinating therapy, which now is showing its colors in other diseases, including, interestingly enough, pancreatic cancer. We also provide an update on papers related to the other major part of MPNs, chronic myeloid leukemia (CML), and as such I met with one of the research giants in the field, Dr Jorge Cortes, who provides his take on the most important findings.

Jorge E Cortes, MD

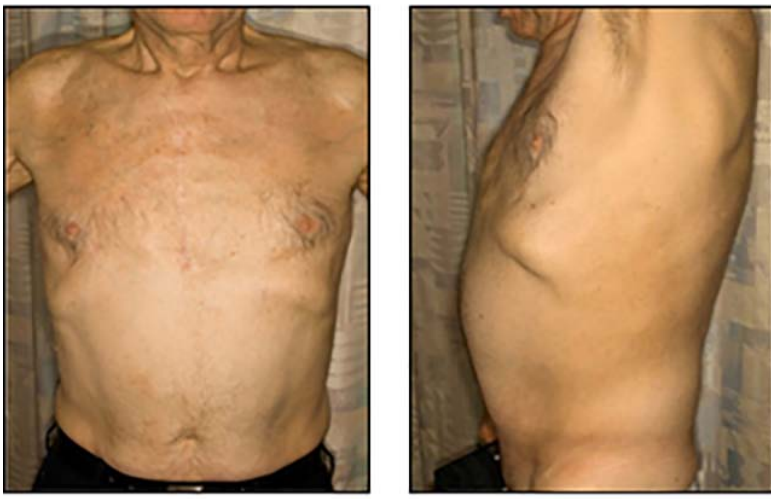
### 1. Rux in patients with lower-risk MF

The Phase III COMFORT trials focused on patients with intermediate-2 or high-risk MF, but there is no intuitive reason to believe that the palliative effects of this agent would not be similar in other symptomatic patients. At ASH we saw a **"real-world" retrospective analysis** evaluating 108 cases of patients with low- or intermediate-1-risk MF treated by 49 US-based hematologist-oncologists mainly due to symptomatology. Perhaps not surprisingly, marked improvement in spleen size and the severity of





fatigue and other related symptoms was observed with the use of rux. For example, moderate/severe splenomegaly decreased from 64% to 16% in low-risk MF and from 53% to 10% in intermediate-1-risk disease. These findings, along with his own clinical experience, have shaped Dr Cortes' belief that symptomatic patients can benefit from rux regardless of risk status.



Images courtesy of *OncoLog*, The University of Texas MD Anderson Cancer Center

**ABOVE:** Photos of a patient before therapy with an experimental JAK2 inhibitor show the distended abdomen caused by the enlarged spleen, a common symptom of myelofibrosis. **BELOW:** Photos taken after 2 months of therapy with a JAK2 inhibitor show a marked reduction in the patient's splenomegaly.

### 2. Rux in polycythemia vera (PV) and essential thrombocythemia (ET)

Perhaps the biggest MPN story at ASH was the presentation of more data from the landmark **Phase III RESPONSE trial** (originally presented last year at ASCO) demonstrating the clinical benefit of rux (10 mg BID) in patients with PV who were either intolerant of or experienced disease progression on hydroxyurea (HU). The initial data set was published in the *New England Journal* in January and revealed significant reductions in hematocrit, splenomegaly and severity of symptoms in patients randomly assigned to rux. Equally relevant, treatment was well tolerated — most patients had stable platelet counts, and secondary drops in hemoglobin were beneficial. Similar clinical improvements were observed in patients who crossed over to rux. Most importantly, as seen with the additional ASH data, patients who received rux experienced a dramatic positive impact on quality of life.

Based on the strength of these results, the FDA made rux the first drug ever approved for PV. In this regard, Dr Cortes has used the agent in patients who meet the criteria for the RESPONSE trial. However, he also believes that the definition of disease progression with PV should be expanded to include individuals with persistent symptomatology who, although not meeting the current criteria for disease progression, often experience dramatic improvements in symptoms with rux.

Several other data sets were unveiled in San Francisco that further support the concept of using rux in PV, including data from the **Phase III RELIEF trial** for patients with PV considered stable on HU but with some persistent symptoms, which demonstrated an improvement in symptoms by switching to rux rather than continuing on HU.

Finally, a Phase II study of rux in 39 patients with ET refractory to or intolerant of HU demonstrated rapid decreases in and normalization of platelet and white blood cell

counts. Hemoglobin levels initially decreased and then stabilized in most patients, and a marked improvement in symptomatology was also observed. As such, Dr Cortes and other investigators believe rux is rational to use in this patient population and are hopeful that this agent will also receive approval in ET for disease palliation.

### 3. New agents in MF: antifibrotics, telomerase inhibitors

Although much recent MF research has focused on JAK inhibitors, a number of other novel strategies are also being explored in this disease. In this regard, at ASH we saw an **early but encouraging report** of 27 patients receiving PRM-151, a recombinant form of an endogenous protein that is found at sites of inflammation and prevents fibrosis by inducing macrophage differentiation. What was most noteworthy from this study was that not only was the amount of fibrosis decreased in close to half of the patients, but hemoglobin and platelet counts also often improved along with signs and symptoms of the disease. Research on this and other similar agents is proceeding rapidly, and Dr Cortes is particularly interested in trials combining PRM-151 with rux.

Telomerase is known to become more active in MF as the disease progresses, and in a report of 33 patients receiving imetelstat — a novel agent that targets the RNA template of human telomerase reverse transcriptase — 7 patients (21%) experienced a complete or partial remission. Treatment was well tolerated, although myelosuppression was observed. Dr Cortes is intrigued by these data and also the early correlation of response with specific disease mutations.

### 4. Second-generation tyrosine kinase inhibitors (TKIs) in CML

With the likely availability of generic imatinib in the next year as a potentially less costly alternative, the value of nilotinib and dasatinib will be increasingly discussed and debated, and several new ASH data sets will likely be referred to as part of these conversations. Specifically, in San Francisco we saw the first presentation of data from the large **Phase III SPIRIT 2 trial**, which, like several other prior studies, compared dasatinib to imatinib in patients with newly diagnosed CML. Although the data are not yet fully mature, this study confirms what we have known from other trials, namely that treatment with second-generation TKIs results in improved rates of complete cytogenetic response, faster rates of molecular response and fewer transformations.

It wouldn’t be ASH if we weren’t treated to an update from the landmark DASISION trial, and in addition to continuing to show excellent long-term disease outcomes, this study yielded some interesting data on toxicity over time, specifically the most common complication of dasatinib, pleural effusions, which were observed in 20% of patients, causing discontinuation of treatment in 6%. In discussing this work, Dr Cortes pointed out that multiple studies have suggested that patients experiencing a pleural effusion on dasatinib might have better disease-related outcomes, although the biologic explanation remains to be defined.

None of the second-generation TKI CML papers presented in San Francisco was able to dispel the lack of progression-free or overall survival benefit to this point, and some

investigators prefer imatinib in lower-risk scenarios. Dr Cortes, however, believes that there is an important advantage for the newer agents but that salvage treatment for imatinib failure is delaying the detection of this benefit.

### 5. Current bottom line with ponatinib in CML

As you may remember, the **Phase III EPIC study** comparing ponatinib to imatinib was stopped in October 2013 because of the increased risk of cardiovascular events. As a result of this toxicity, access to ponatinib is currently restricted to patients with TKI-resistant disease or those with the T315I mutation. However, the updated data from this trial tell us that the agent is associated with faster, deeper and higher rates of response than imatinib and, by way of indirect comparison, perhaps also dasatinib and nilotinib.

In this regard, there is a strong belief among investigators that there is a direct relationship between dose and cardiovascular events, and for that reason ongoing studies are attempting to define a reduced dose that will produce equal efficacy with fewer complications.

### 6. In what situations, if any, is it safe to stop a TKI in CML?

A number of prospective trials (STIM, TWISTER and EURO SKI, which was presented at ASH) suggest that imatinib may be successfully discontinued for patients with deep and sustained molecular responses, and in San Francisco we saw evidence that the same may apply to second-generation TKIs. Specifically, the **STOP 2G-TKI study** evaluated treatment discontinuation in 52 patients in sustained complete molecular response receiving dasatinib or nilotinib for a median of 39 months, mostly after initial imatinib therapy.

At 24 months, the probability that patients remained in major molecular response off treatment was 57%. The relapses that did occur were mainly in the first 6 months after treatment discontinuation, but those patients responded to reinstitution of second-generation therapy. Importantly, patients receiving treatment because of prior resistance to imatinib were less likely to be able to stay off treatment. Despite this mounting body of data, like most CML investigators, Dr Cortes, although interested in seeing more research on this strategy, believes that for now TKI treatment should only be stopped as part of a clinical trial and with close monitoring.

Medical oncologists are hearing a lot nowadays about “value” in cancer care, which is roughly defined as the clinical benefits (and toxicities/complications) of a therapy relative to its financial cost, and there has been a lot of discussion about the importance of incorporating the perspectives of patients themselves in the value equation.

In this regard, it would be interesting to learn more from individuals who have actually experienced the clinical outcomes of therapy for MPNs about their perceptions of the value of treatment — particularly about what it means to face a disease that was

uniformly lethal in the past and to now live a normal lifespan (CML) or to experience progressive and devastating disease-related symptoms and suddenly feel well again (MF, PV, ET).

Next on this series we review ASH papers on acute leukemias and MDS and the surprising plenary presentation on the use of sorafenib in AML.

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# Results from the Phase III RESPONSE Trial of Ruxolitinib versus Best Available Therapy for Patients with Polycythemia Vera

## Presentations discussed in this issue

Mesa R et al. **The efficacy and safety of continued hydroxyurea therapy versus switching to ruxolitinib in patients with polycythemia vera: A randomized, double-blind, double-dummy, symptom study (RELIEF).** *Proc ASH* 2014;**Abstract 3168**.

Verstovsek S et al. **Long-term results from a phase II open-label study of ruxolitinib in patients with essential thrombocythemia refractory to or intolerant of hydroxyurea.** *Proc ASH* 2014;**Abstract 1847**.

## Slides from presentations at ASH 2014 and transcribed comments from a recent interview with Jorge E Cortes, MD (1/14/15)

**The Efficacy and Safety of Continued Hydroxyurea Therapy versus Switching to Ruxolitinib in Patients with Polycythemia Vera: A Randomized, Double-Blind, Double-Dummy, Symptom Study (RELIEF)[1]**

**Long-Term Results from a Phase II Open-Label Study of Ruxolitinib in Patients with Essential Thrombocythemia Refractory to or Intolerant of Hydroxyurea[2]**

[1] **Mesa R et al.**
*Proc ASH* 2014;Abstract 3168.

[2] **Verstovsek S et al.**
*Proc ASH* 2014;Abstract 1847.

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# The Efficacy and Safety of Continued Hydroxyurea Therapy versus Switching to Ruxolitinib in Patients with Polycythemia Vera: A Randomized, Double-Blind, Double-Dummy, Symptom Study (RELIEF)

**Mesa R et al.**

*Proc ASH* 2014;Abstract 3168.



## Background

- Polycythemia vera (PV) is characterized by erythrocytosis, thrombocytosis and/or leukocytosis and a broad range of disease-related symptoms such as thrombotic and cardiovascular events resulting in increased mortality rates.
- The most common first-line treatment for high-risk disease is hydroxyurea (HU).
- Previously, the Phase III RESPONSE trial demonstrated that ruxolitinib (RUX), a JAK1/JAK2 inhibitor, provided superior efficacy compared to best available therapy in patients with PV who were resistant to or intolerant of HU (*Proc ASCO* 2014;Abstract 7026).
- **Study objective:** To compare patient-reported symptoms in patients with PV continuing their HU therapy to those in patients switching to RUX treatment.

Mesa R et al. *Proc ASH* 2014;Abstract 3168.

# Phase III RELIEF Trial Design (NCT01632904)

**Eligibility (n = 110)**

Patients with PV
Patients receiving HU only for ≥12 weeks prior to study entry, stable dose for ≥4 weeks
No palpable splenomegaly **OR** no >2 phlebotomies within 6 months

R

**RUX (10 mg BID) + placebo (HU) (n = 54)**

**HU + placebo (RUX) (n = 56)**

- Dose adjustments were permitted for safety and efficacy.
- After week 16, patients could receive open-label RUX until week 48.
- All patients received low-dose aspirin unless contraindicated.
- **Primary endpoint:** Proportion of patients with a ≥50% reduction in Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) cytokine cluster score (TSS-C) at week 16.

Mesa R et al. *Proc ASH* 2014;Abstract 3168.

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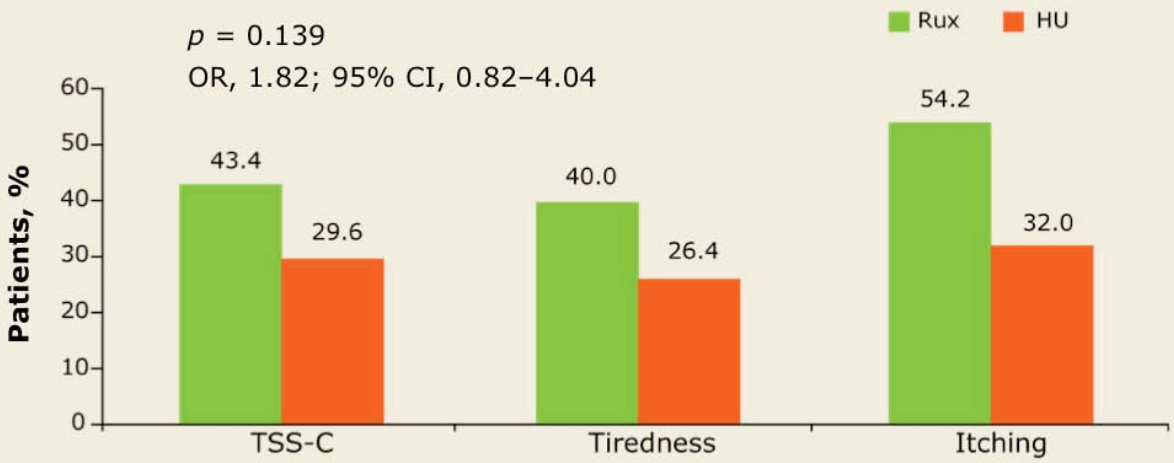
# Proportion of Patients with ≥50% Improvement in TSS-C and Individual Symptoms at Week 16




OR = odds ratio

- TSS-C comprises itching, tiredness, muscle ache, night sweats and sweats while awake

With permission from Mesa R et al. *Proc ASH* 2014;Abstract 3168.

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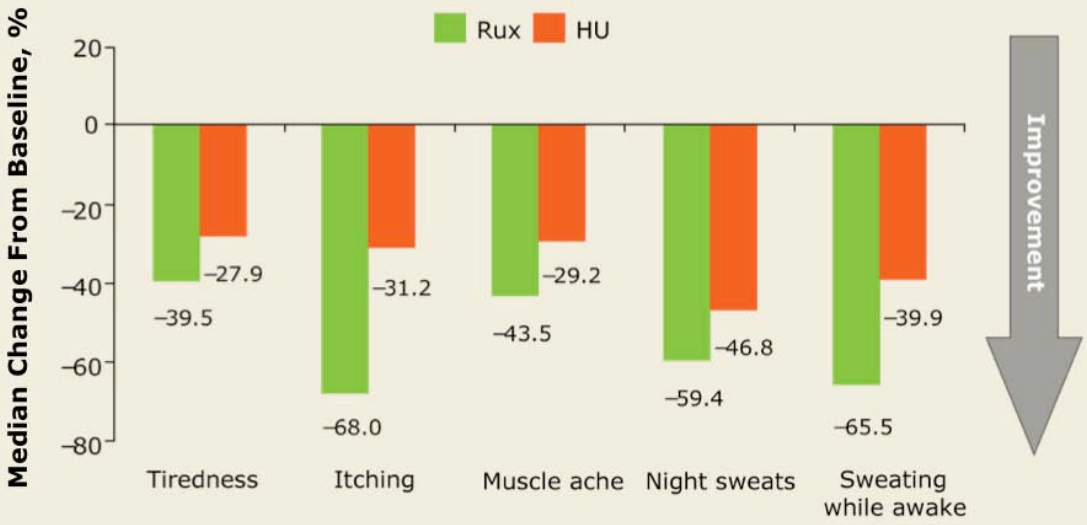
# Median Percentage Change from Baseline to Week 16 in Individual TSS-C Symptoms




- A greater proportion of patients who received RUX described their symptoms as "very much improved" or "much improved" at week 16 compared to those who received HU:
  - RUX (48.2%) versus HU (30.4%)

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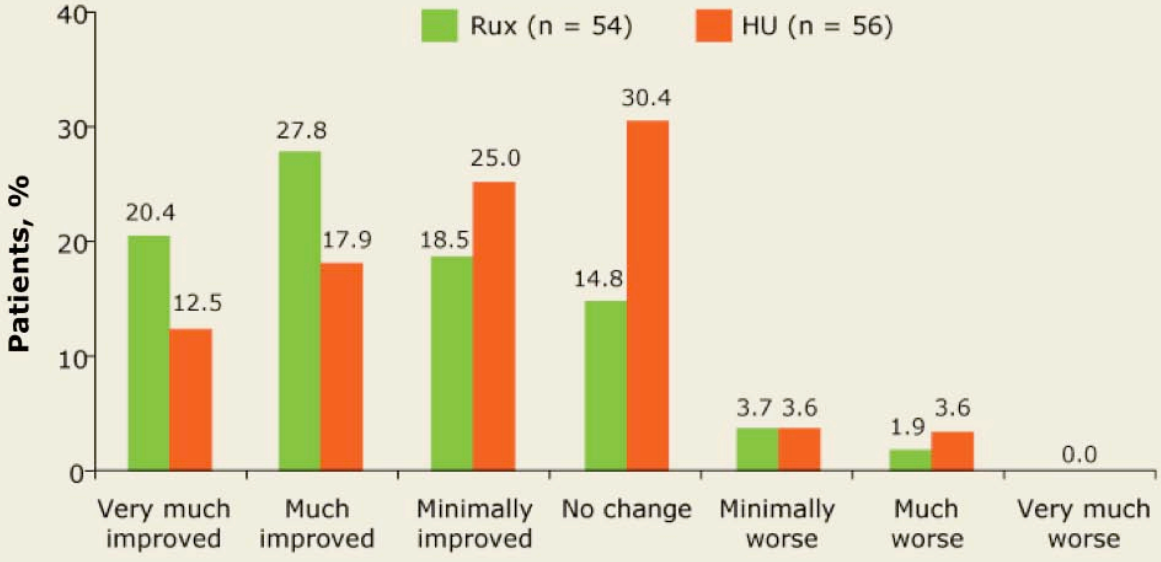
# Patient Global Impression of Change at Week 16*




* Patients missing: RUX (13.0%); HU (7.1%)

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# ≥50% Improvement in TSS-C According to Screening/Baseline Scores

| Patients with screening/baseline TSS-C ≤2 | RUX (n = 38) | HU (n = 44) | *p*-value |
|---|---|---|---|
| Response rate | 47.4% | 25.0% | 0.0346 |
| **Patients with screening/baseline TSS-C >2** | **RUX (n = 15)** | **HU (n = 10)** | ***p*-value** |
| Response rate | 33.3% | 50.0% | 0.4422 |

- Among patients reporting relatively stable TSS-C during the 3 weeks between screening and baseline (ratio ≤2), a significantly greater proportion receiving RUX vs HU achieved ≥50% improvement in TSS-C.
- Among patients with screening to baseline score ratios >2, the proportion of patients achieving this endpoint was not significantly different between RUX and HU.

Mesa R et al. *Proc ASH* 2014;Abstract 3168.

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# ≥50% Improvement in TSS-C According to Dose

| Patients | Dose change from baseline to weeks 13-16 | | |
|---|---|---|---|
| | Dose reduction | Consistent dose | Dose increase |
| RUX | 2/11 (18.2%) | 13/30 (43.3%) | 8/13 (61.5%) |
| HU | 0/9 (0%) | 12/35 (34.3%) | 4/12 (33.3%) |

- There was no correlation between individual changes in HU dose from baseline to weeks 13 through 16 and the percent change in TSS-C in the HU arm:
  - $r^2 = 0.030$
- Even patients maintaining the same HU dose from baseline to weeks 13 through 16 reported symptom improvement.

Mesa R et al. *Proc ASH* 2014;Abstract 3168.

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# Select Adverse Events (AEs)

| Event | RUX (n = 54) | | HU (n = 56) | |
|---|---|---|---|---|
| | All | Grade 3-4 | All | Grade 3-4 |
| Anemia | 37.0% | 0% | 23.2% | 0% |
| Fatigue | 20.4% | 1.9% | 10.7% | 1.8% |
| Headache | 16.7% | 0% | 5.4% | 0% |
| Dizziness | 13.0% | 0% | 8.9% | 0% |
| Nausea | 11.1% | 0% | 5.4% | 0% |
| Pruritus | 11.1% | 0% | 10.7% | 0% |
| Diarrhea | 9.3% | 0% | 19.6% | 0% |
| Thrombocytopenia | 9.3% | 0% | 26.8% | 1.8% |
| Constipation | 7.4% | 0% | 12.5% | 0% |
| Neutropenia | 3.7% | 3.7% | 12.5% | 1.8% |

Mesa R et al. *Proc ASH* 2014;Abstract 3168.

# Author Conclusions

- Among patients with generally well-controlled PV receiving a stable dose of HU, there was a positive trend in symptom improvement for those who switched to RUX versus those continuing on HU, although this trend was not statistically significant.
- The 34% response rate among patients who continued to receive a stable dose of HU was unexpected and led to an underpowered study. Explanations for this include:
  - Increased compliance with HU. However, current data suggest that HU treatment is not associated with a clinically relevant improvement in symptoms.
  - Closer medical follow-up and better availability of supportive measures.

Mesa R et al. *Proc ASH* 2014;Abstract 3168.

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# Author Conclusions (continued)

  - Reporting of higher symptom scores before treatment based on a mistaken belief that reporting lower scores might exclude the patient from the study.
  - Placebo effect. Patients knew that they had a 50% chance of receiving a novel agent with previously reported efficacy data in PV.
- Treatment was generally well tolerated.
  - Nonhematologic and hematologic adverse events were mainly Grade 1 or 2.

Mesa R et al. *Proc ASH* 2014;Abstract 3168.

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**Investigator Commentary: RELIEF — Efficacy and Safety of RUX versus Switching to HU in Patients with PV**

RELIEF is an interesting study because only patients who were receiving HU at a stable dose for the last 4 weeks before study entry were eligible. These patients cannot be considered to be refractory to HU. Although these patients were considered to be deriving some benefit from HU, they were still experiencing some PV-related symptoms. Patients were randomly assigned to either continue receiving that stable dose of HU or switch to RUX.

The study consistently demonstrated an improvement in symptoms by switching to RUX. For example, the proportion of patients with ≥50% reduction in TSS-C was 43.4% for RUX versus 29.6% for HU. In terms of tiredness, the proportion of patients with ≥50% reduction was 40% with RUX and 26.4% with HU. The proportion of patients with ≥50% reduction in itching was 54.2% with RUX and 32% with HU therapy. Overall, a trend for benefit with RUX was evident in all these aspects. Even though these patients were considered to be deriving some benefit with HU, switching to RUX added value. This study provides further evidence of the potential of RUX, an FDA-approved agent, in this patient population from the perspective of the symptoms that the patients experience.

***Interview with Jorge E Cortes, MD, January 14, 2015***

# Long-Term Results from a Phase II Open-Label Study of Ruxolitinib in Patients with Essential Thrombocythemia Refractory to or Intolerant of Hydroxyurea

**Verstovsek S et al.**

*Proc ASH* 2014;Abstract 1847.



## Background

- Essential thrombocythemia (ET) is a Philadelphia chromosome–negative myeloproliferative neoplasm (MPN) characterized by persistent thrombocytosis, excessive proliferation of megakaryocytes in the bone marrow and normal erythrocyte mass.
- As with the other Philadelphia chromosome–negative MPNs, ET is associated with dysregulated Janus kinase (JAK)-signal transduction and activation of transcription signaling.
- Ruxolitinib (RUX) is an oral JAK1/JAK2 inhibitor that has shown clinical benefit in patients with myelofibrosis and polycythemia vera (PV) (*NEJM* 2012;366:799; *Proc ASCO* 2014;Abstract 7026).
- **Study objective:** To determine the long-term efficacy and safety of RUX in patients with ET refractory to or intolerant of hydroxyurea (HU).

Verstovsek S et al. *Proc ASH* 2014;Abstract 1847.

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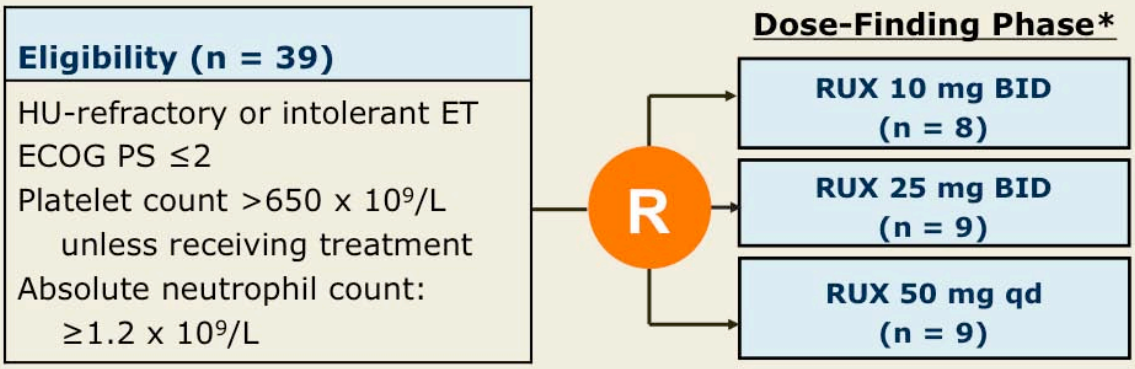
# Phase II Trial Design (NCT00726232)




* Patients were to remain on the initial treatment regimen for ≤8 weeks with dose adjustments allowed only for safety reasons during this time.

- Based on the dose-finding phase, the starting dose for the expansion phase was determined to be 25 mg BID; 13 additional patients enrolled at this dose.
- RUX therapy was administered in an outpatient setting in continuous 4-week cycles.
- **Primary endpoint:** Proportion of patients with a confirmed clinical partial (PR) or complete response (CR)

Verstovsek S et al. *Proc ASH* 2014;Abstract 1847.

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# Efficacy: Hemoglobin Levels, Platelet and White Blood Cell Counts and JAK2 Allele Burden

- At the time of data cutoff, the median exposure to RUX was 205.6 weeks (approximately 48 months).
- The median platelet count decreased rapidly after the initiation of therapy and remained relatively stable over time.
- The median white blood cell (WBC) count decreased rapidly during the first 4 weeks, followed by an increase and stabilization in the normal range.
- The median hemoglobin level decreased over the first 12 weeks of RUX administration, followed by stabilization throughout the follow-up period.
- The median percent change from baseline in JAK2V617F allele burden was:
  - Week 24 (n = 22): -2.8%
  - Week 48 (n = 20): +1.9%
  - Week 192 (n = 15): -33.3%

Verstovsek S et al. *Proc ASH* 2014;Abstract 1847.

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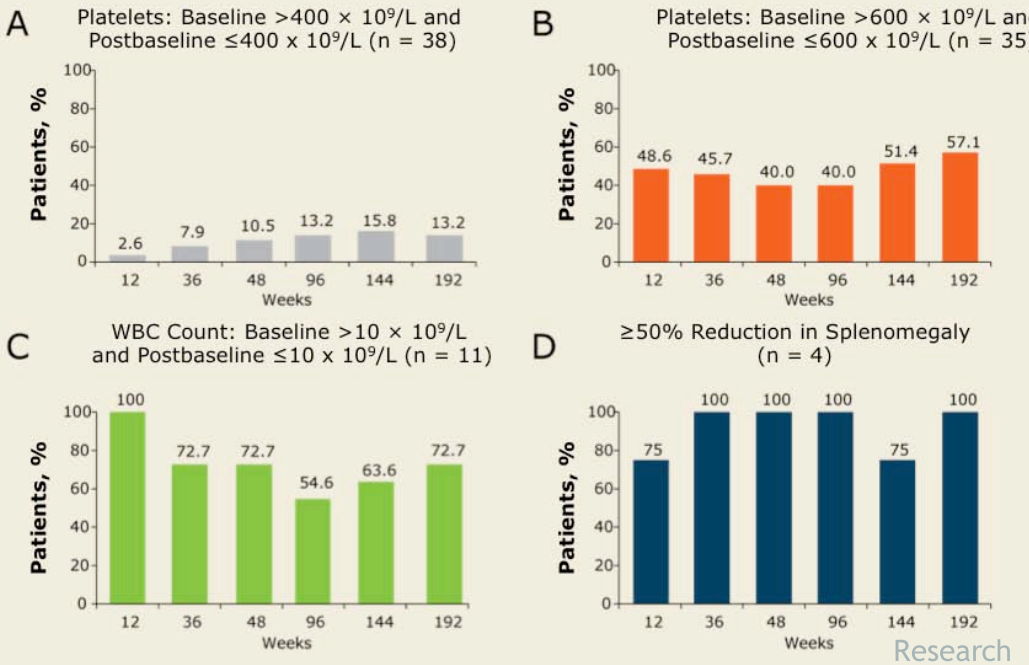
# Clinical Response to RUX Therapy

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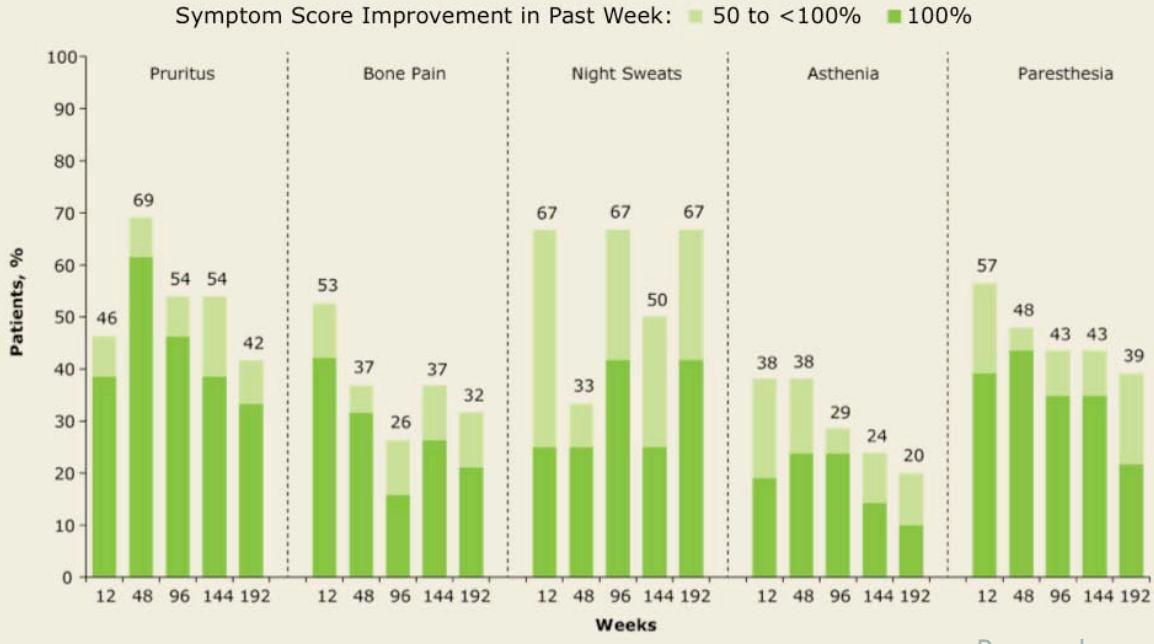
# Proportion of Patients with ≥50% or 100% Improvement in ET-Related Symptoms with RUX

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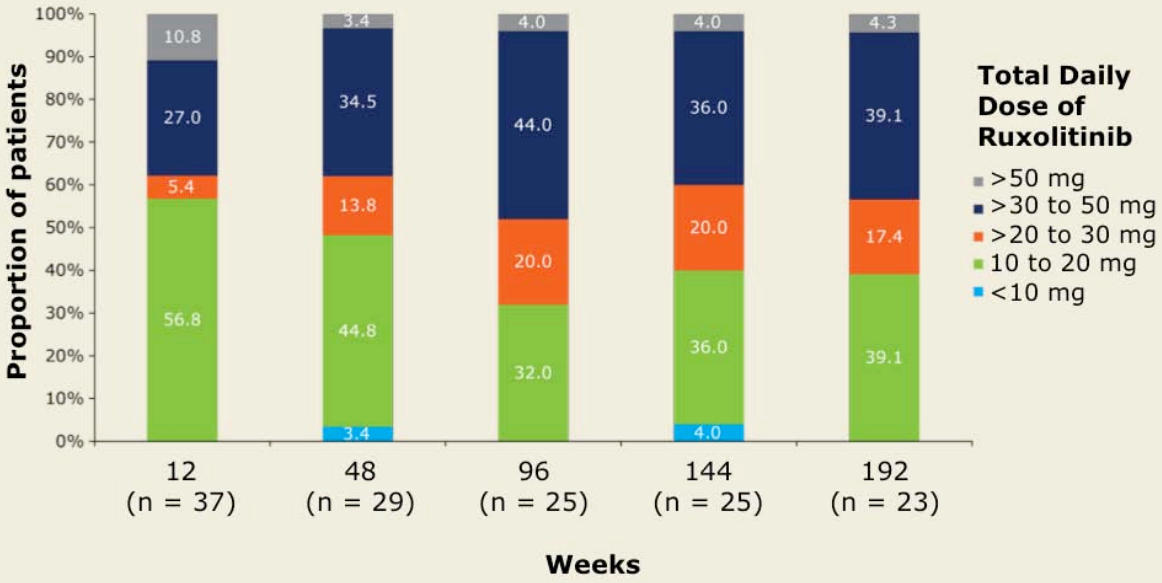
# RUX Dose Distribution Over Time

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# Select Adverse Events (AEs)

| Event (n = 39) | All grades | Grade 3-4 |
|---|---|---|
| Increased weight | 35.9% | 0% |
| Diarrhea | 28.2% | 0% |
| Cough | 25.6% | 0% |
| Headache | 25.6% | 5.1% |
| Hypercholesterolemia | 23.1% | 2.6% |
| Increased blood creatinine phosphokinase | 20.5% | 2.6% |
| Bronchitis | 20.5% | 2.6% |
| Hyperuricemia | 15.4% | 2.6% |

- New or worsening Grade 3-4 leukopenia, neutropenia and lymphopenia occurred in 3 patients each (7.7%).
- New or worsening Grade 3 anemia occurred in 1 patient (2.6%).
- No reports of acute myeloid leukemia or transformation to post-ET myelofibrosis.

Verstovsek S et al. *Proc ASH* 2014;Abstract 1847.

# Author Conclusions

- Treatment with RUX resulted in rapid and sustained improvements in platelet count, WBC count and splenomegaly in patients with ET who were refractory to or intolerant of HU.
- Rapid reductions in ET-related symptoms were noted during the study and were largely sustained through week 192.
- RUX was generally well tolerated:
  - Most adverse events observed were Grade 1 or 2.
- No new safety concerns were observed during long-term treatment with RUX in this cohort of patients with ET who were resistant to or intolerant of HU.

Verstovsek S et al. *Proc ASH* 2014;Abstract 1847.

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**Investigator Commentary: Long-Term Efficacy and Safety Results of a Phase II Trial of RUX in HU-Refractory or Intolerant ET**

The median exposure to RUX in this study was about 4 years. A significant improvement in platelet count was reported. With this long-term follow-up, one realizes that the response to RUX is valuable and durable. Elevated WBC counts were improved in some patients.

Splenomegaly is not uncommon in ET. However, for patients with splenomegaly, improvements in spleen size were observed. The assessment of ET-related symptoms also showed improvements. RUX was effective and well tolerated in this setting. Although RUX is not approved for this indication, this study demonstrated that patients with ET who are refractory to or intolerant of HU benefit from RUX therapy.

I believe that an attempt should be made to get RUX approved in this setting because the options are limited to drugs such as HU and anagrelide. Most of the patients had previously received HU, and 23.1% had received anagrelide. Part of the problem encountered is the definition of resistance to these agents. This problem will be solved as we learn more and become more comfortable with RUX. From the results of this study alone, I believe RUX is safe to use in this patient population.

***Interview with Jorge E Cortes, MD, January 14, 2015***

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