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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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:

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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**.

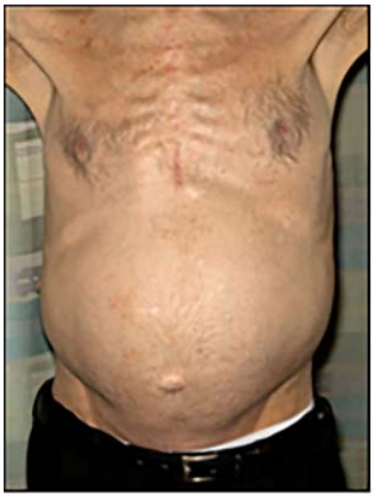
Many physicians (myself included) remember the day they first treated a patient with pulmonary edema from congestive heart failure and the exhilarating feeling of instantly relieving this profound symptomatology with the classic use of an intravenous diuretic and morphine. Medical oncology also provides 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).

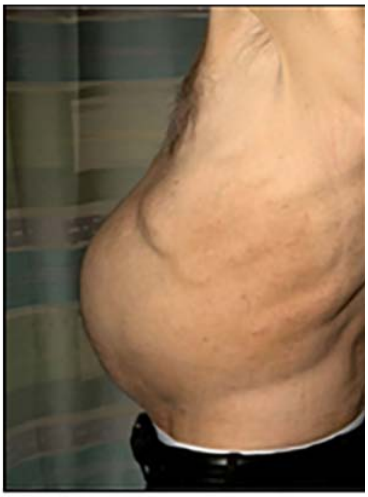
Perhaps not surprisingly, the myeloproliferative neoplasm (MPN) issue of our ASH highlight series focuses in large part on this fascinating therapy, which now is showing its colors in other diseases, including, interestingly enough, pancreatic cancer. We also provide an update on papers related to the 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

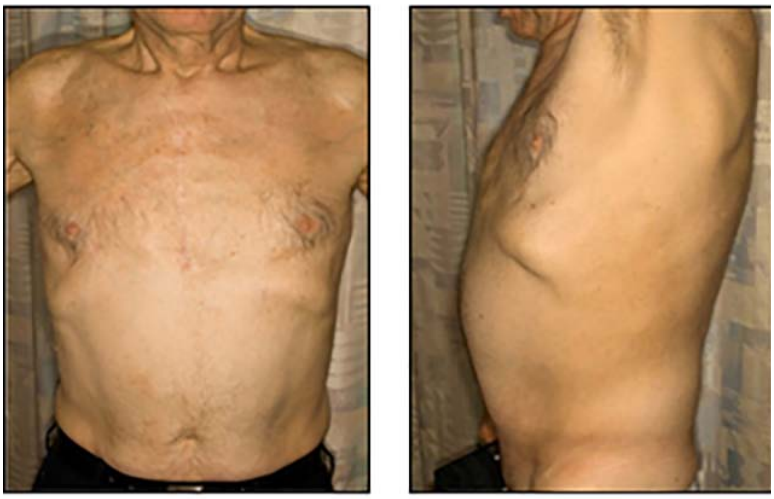
1. Rux in patients with lower-risk MF

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

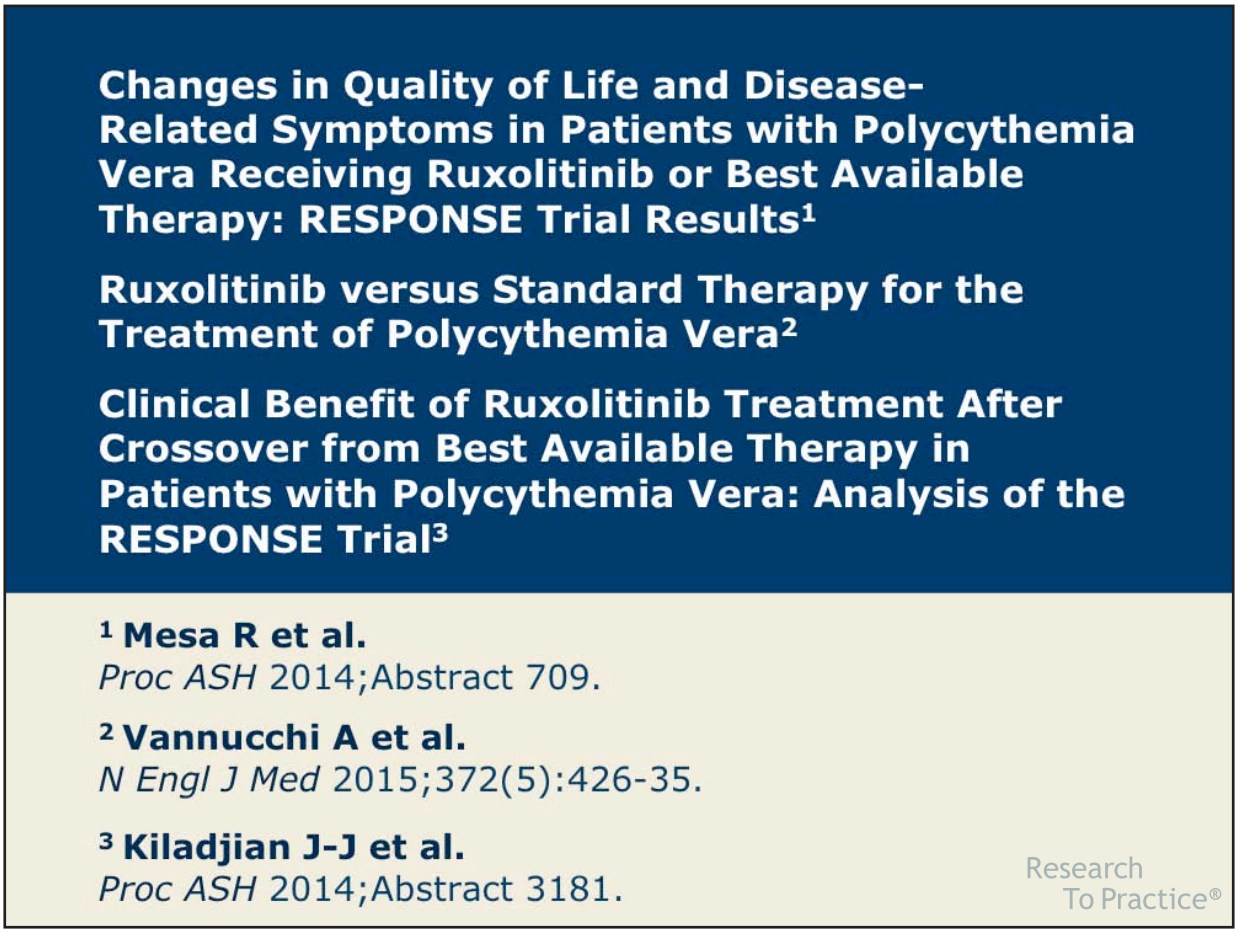
Presentations discussed in this issue

Mesa R et al. **Changes in quality of life and disease-related symptoms in patients with polycythemia vera receiving ruxolitinib or best available therapy: RESPONSE trial results.** *Proc ASH* 2014;**Abstract 709**.

Vannucchi AM et al. **Ruxolitinib versus standard therapy for the treatment of polycythemia vera.** *N Engl J Med* 2015;372(5):426-35. **Abstract**

Kiladjian J-J et al. **Clinical benefit of ruxolitinib treatment after crossover from best available therapy in patients with polycythemia vera: Analysis of the RESPONSE trial.** *Proc ASH* 2014;**Abstract 3181**.

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



Changes in Quality of Life and Disease-Related Symptoms in Patients with Polycythemia Vera Receiving Ruxolitinib or Best Available Therapy: RESPONSE Trial Results[1]

Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera[2]

[1] **Mesa R et al.**
Proc ASH 2014;Abstract 709.

[2] **Vannucchi A et al.**
N Engl J Med 2015;372(5):426-35.

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Background

- Primary results from the Phase III RESPONSE study indicated that ruxolitinib (RUX) was effective at achieving hematocrit (Hct) control, reducing spleen volume and improving symptoms compared to best available therapy (BAT) for patients with polycythemia vera (PV)(*Proc ASCO* 2014;Abstract 7026).
- RUX was recently approved by the FDA for patients with PV who have had an inadequate response to or are intolerant of hydroxyurea.
- **Current study objective:** To evaluate the effect of RUX on PV-related symptoms and quality-of-life measures in the RESPONSE trial.

Mesa R et al. *Proc ASH* 2014;Abstract 709; Vannucchi A et al. *N Engl J Med* 2015; 372(5):426-35.

Phase III RESPONSE Trial Design

Eligibility (n = 222)

- PV requiring phlebotomy
- Spleen volume ≥450 cm^3
- Resistant/intolerant to hydroxyurea
- No prior Tx with JAK inhibitor

R

RUX 10 mg BID (n = 110)

BAT* (n = 112)

* Crossover to RUX allowed at wk 32 if primary endpoint not met or later due to disease progression

Composite Primary Endpoint: Hct control and ≥35% reduction in spleen volume at week 32

- Patients with a Hct <40% or >45% entered a Hct control period before randomization; those having an Hct of 40% to 45% within 14 d before d 1 proceeded to randomization.

Mesa R et al. *Proc ASH* 2014;Abstract 709; Vannucchi A et al. *N Engl J Med* 2015; 372(5):426-35.

Primary Response at Week 32

Response	RUX (n = 110)	BAT (n = 112)	*p*-value
Composite primary endpoint	20.9%	0.9%	<0.001
≥35% reduction in spleen volume	38.2%	0.9%	—
Hct control	60.0%	19.6%	—

- Significantly more patients in the RUX group than in the BAT group had a complete hematologic response:
  - 23.6% vs 8.9%, $p = 0.003$

Mesa R et al. *Proc ASH* 2014;Abstract 709; Vannucchi A et al. *N Engl J Med* 2015; 372(5):426-35.

Reduction of ≥50% in MPN-SAF and Symptom Clusters at Week 32

Score/symptom cluster	RUX	BAT
MPN-SAF all 14 symptoms (n = 74; 81)	49%	5%
Cytokine symptom cluster (n = 74; 80)	64%	11%
Hyperviscosity symptom cluster (n = 71; 80)	37%	13%
Splenomegaly symptom cluster (n = 63; 71)	62%	17%

MPN-SAF = Myeloproliferative Neoplasm Symptom Assessment Form

Mesa R et al. *Proc ASH* 2014;Abstract 709; Vannucchi A et al. *N Engl J Med* 2015; 372(5):426-35.

Median Percentage Change in Scores for Select Symptoms Included in MPN-SAF

MPN-SAF symptom	Median change in score*	
	RUX	BAT
Sweating while awake	-100	-4.4
Night sweats	-99.5	3.9
Itching	-94.9	-2.1
Early satiety	-93.9	0
Dizziness	-80.2	7.9
Abdominal discomfort	-65.9	1.4

* Change from baseline to week 32 in the score for each symptom. Negative values indicate a reduction in severity of symptoms.

Mesa R et al. *Proc ASH* 2014;Abstract 709; Vannucchi A et al. *N Engl J Med* 2015; 372(5):426-35.

Select Adverse Events (AEs)

AEs to week 32	RUX (n = 110)		BAT (n = 111*)	
	All grades	Grade ≥3	All grades	Grade ≥3
Anemia	43.6%	1.8%	30.6%	0%
Thrombocytopenia	24.5%	5.4%	18.9%	3.6%
Lymphopenia	43.6%	16.4%	50.5%	18%
Neutropenia	1.8%	0.9%	8.1%	0.9%
Fatigue	14.5%	0%	15.3%	2.7%
Pruritus	13.6%	0.9%	22.5%	3.6%

* One patient withdrew consent and did not receive the study treatment.

Through week 32, thromboembolic events occurred in 1 patient in the RUX group versus 6 patients in the BAT arm.

Vannucchi A et al. *N Engl J Med* 2015;372(5):426-35.

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Author Conclusions

- For patients who had an inadequate response to or unacceptable side effects from hydroxyurea, RUX was superior to standard therapy in controlling the Hct and reducing spleen volume.
- Treatment with RUX was associated with greater and clinically meaningful improvements in PV-related symptom burden and quality-of-life measures compared to standard therapy.

Mesa R et al. *Proc ASH* 2014;Abstract 709; Vannucchi A et al. *N Engl J Med* 2015; 372(5):426-35.

Investigator Commentary: Ruxolitinib versus Standard Therapy for the Treatment of PV

RUX was recently approved for PV. This study demonstrated that treatment with RUX results in an improvement in both objective measures, such as the number of phlebotomies, and symptoms. A number of tools were used to assess quality of life and symptoms. Most of the symptoms got worse with the BAT, whereas they improved in the majority of patients receiving RUX. This is another reason why this drug was approved and should be considered for patients who have PV.

With RUX, responses occur early and symptoms improve quickly. Over time, benefit can be noted in other measures such as reduction in phlebotomies. RUX is well tolerated. The dose of RUX used is slightly lower (ie, 10 mg) than for other indications. We know that the drop in hemoglobin is beneficial in PV. The drop in platelets is not as significant. Patients should be monitored, but low platelet count hasn't been a big problem for these patients. This study provides further evidence of the potential benefit of this new drug now available for PV.

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

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Clinical Benefit of Ruxolitinib Treatment After Crossover from Best Available Therapy in Patients with Polycythemia Vera: Analysis of the RESPONSE Trial

Kiladjian J-J et al.

Proc ASH 2014;Abstract 3181.

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Background

- Patients with high-risk polycythemia vera (PV) commonly receive hydroxyurea (HU). However, a subgroup of patients become intolerant of or resistant to HU.
- Ruxolitinib (RUX) was recently approved by the FDA for patients with PV who have had an inadequate response to or are intolerant of HU and was shown to be superior to best available therapy (BAT) in these patients in the RESPONSE trial (*Proc ASCO* 2014;Abstract 7026).
- **Current study objective:** To evaluate the efficacy of RUX treatment in patients on the RESPONSE trial who crossed over from BAT, relative to their original BAT treatment and relative to RUX in patients originally randomly assigned to RUX.

Kiladjian J-J et al. *Proc ASH* 2014;Abstract 3181 (Abstract only).

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Effect of RUX on Phlebotomy Requirement

	BAT	Switch to RUX	RUX
Patients not requiring phlebotomy*	25%	79%	74%
Phlebotomy procedures adjusted for 100 patient-years	196.8	38.5	34.1

* Up to 32 weeks of therapy

Kiladjian J-J et al. *Proc ASH* 2014;Abstract 3181 (Abstract only).

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Effect of RUX on Spleen Volume

Spleen volume	BAT	Switch to RUX	RUX
Reduction from baseline at any visit	49%	73%	88%
Patients with ≥35% reduction	1.8%	38.5%	60%

Kiladjian J-J et al. *Proc ASH* 2014;Abstract 3181 (Abstract only).

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Author Conclusions

- Treatment with RUX after crossover from BAT resulted in improved clinical outcomes compared to original BAT treatment.
- These findings support the primary RESPONSE trial results and further validate the efficacy of RUX in this patient population.

Kiladjian J-J et al. *Proc ASH* 2014;Abstract 3181 (Abstract only).

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Investigator Commentary: Clinical Benefit of RUX After Crossover from BAT in PV — Analysis of the RESPONSE Trial

This study demonstrated a dramatic improvement in outcomes after patients switched to RUX. For example, during the first 32 weeks, 25% of patients did not require a phlebotomy. After they switched to RUX, 79% of patients did not require a phlebotomy. Many outcomes were almost as good as those for patients who started on RUX. The proportion of patients who had a 35% reduction in spleen volume, which has become the standard for evaluating the spleen, was only 1.8% with BAT. It improved to 38.5% after the crossover but was 60% for patients who were initially randomly assigned to RUX. So starting early is ideal once you've identified that a patient's disease is refractory to HU, which is the indication for RUX in PV.

The drug should also be considered for patients who are deriving some benefit from HU but still have symptoms. I believe we need to reassess our definition of what being refractory to HU means. Given that we now have an alternate treatment option, perhaps our definition is a little too strict. The persistence of symptoms should be considered as indicating refractoriness, and we should start to consider switching therapy in that setting.

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