5 Minute JournalClub

POST-ASH Issue 4, 2015

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CME Information

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.

CME Information (Continued)

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FACULTY DISCLOSURES

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:

CME Information (Continued)

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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.

5 MinuteJournalClub

POST-ASH Issue 4, 2015

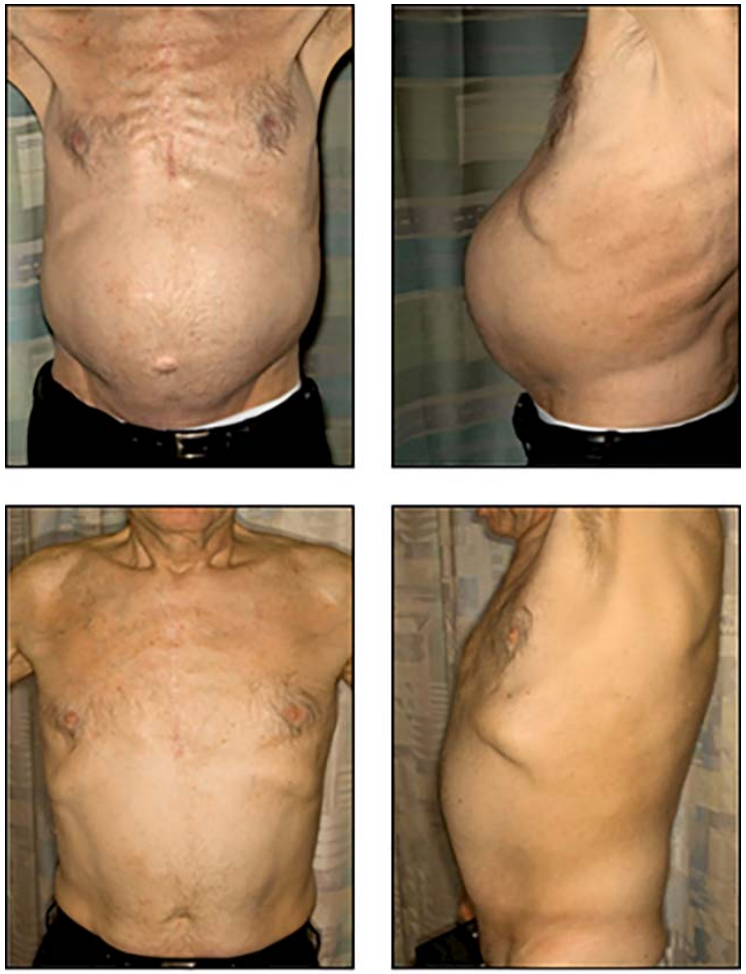
Many physicians (myself included) remember the day they first treated a patient with pulmonary edema from congestive heart failure and the exhilarating feeling of instantly relieving this profound symptomatology with the classic use of an intravenous diuretic and morphine. Medical oncology also provides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

Neil Love, MD
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Real-World Assessment of Clinical Outcomes in Lower-Risk Myelofibrosis Patients Receiving Treatment with Ruxolitinib

Davis KL et al.

Proc ASH 2014;Abstract 1857.

Background

- The Phase III COMFORT-I trial demonstrated that ruxolitinib (RUX) improves both splenomegaly- and nonsplenomegaly-related constitutional symptoms in patients with intermediate-2 and high-risk myelofibrosis (MF) (*NEJM* 2012;366:799).
- However, few trial-based assessments of RUX for patients with lower-risk MF have been conducted, and no studies to date have made such assessments in real-world populations.
- **Study objective:** To assess changes in spleen size and constitutional symptoms during RUX treatment among patients with lower-risk MF in real-world clinical settings.

Davis KL et al. *Proc ASH* 2014;Abstract 1857.

Study Methods

- A retrospective, observational review of anonymized medical record data collected in January 2014 by 49 hematologists and oncologists in the United States.
- The study was exploratory, with the use of descriptive analyses only.
- Minimum target accrual:
  - Patients with intermediate-1-risk MF (n = 50)
  - Patients with low-risk MF (n = 25)
- Predetermined maximum number of patients on study (n = 110).
- Spleen size and constitutional symptoms were retrospectively observed at MF diagnosis, at RUX initiation and at best response while on RUX.

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).

Study Methods (continued)

- Spleen size was captured via predefined categories:
  - No splenomegaly (spleen not palpable)
  - Very mild or mild splenomegaly (<10 cm palpated)
  - Moderate splenomegaly (10-20 cm palpated)
  - Severe splenomegaly (>20 cm palpated)
- Symptoms of interest included those captured in the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), based on medical notes recorded at each time point and categorized as:
  - Mild,
  - Moderate, or
  - Severe
- Findings on the 7 most commonly observed MPN-SAF symptoms are presented in this study.

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).

Eligibility Criteria

- Patients diagnosed with lower-risk MF
- International Prognostic Scoring System score of 0-1
- First treatment with RUX ≥3 months before the medical record abstraction date
- Age ≥18 years at RUX initiation
- Patients with a complete medical history from MF diagnosis until the medical record abstraction date
- Patients who never enrolled in an MF-related interventional trial

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).

Patient Characteristics

Characteristic	Low risk (n = 25)	Intermediate-1 risk (n = 83)
≤65 years of age	100%	~80%
Male	60%	69%
JAK2 V617F-mutant MF	56%	72%
Patients still receiving RUX at MRAD	92%	77%

MRAD = medical record abstraction date

- RUX start dates spanned from January 2012 to November 2013.
- The median observed RUX exposure time was approximately 8 months in both risk groups.

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).

Spleen Size Measurements

- Patients with low-risk MF
  - The combined proportion of patients with moderate or severe splenomegaly (≥10-cm palpated spleen) decreased from 64% at MF diagnosis to 16% at best response during RUX treatment.
- Patients with intermediate-1-risk MF
  - Similar findings were observed: The proportion of patients with moderate or severe splenomegaly decreased from 53% at MF diagnosis to 10% at best response.

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).

Constitutional Symptoms of Interest During RUX Treatment

- General fatigue was the most commonly observed constitutional symptom in both groups of patients (low-risk and intermediate-1-risk MF).
- Shifts in symptom severity from more severe to less severe were observed in both groups of patients.
- Among patients with low-risk MF, the proportion with moderate or severe fatigue decreased from 90% at MF diagnosis to 37% at best RUX response.
- Among patients with intermediate-1-risk MF, the decrease was from 76% at MF diagnosis to 42% at best response.
- For most other symptoms, similar improvements in severity distribution were observed.

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).

Author Conclusions

- Patients with low-risk and those with intermediate-1-risk MF experienced a substantial decrease in spleen size from MF diagnosis through RUX treatment in real-world clinical settings.
- Furthermore, for most symptoms examined, there was a distinct improvement in the distribution of symptom severity at the time of best response during RUX treatment.
- These findings suggest that patients with lower-risk MF may benefit clinically from RUX treatment.
- Further studies are needed to assess adverse effects and evaluate the benefit-risk tradeoff of RUX therapy.

Davis KL et al. *Proc ASH* 2014;Abstract 1857 (Abstract only).

Investigator Commentary: Evaluation of Clinical Outcomes in Low-Risk and Intermediate-1-Risk MF Treated with RUX

This is an interesting study because it addresses 2 important questions. First, whether a clinical trial really reflects what you would expect in general practice because many features change when you take them to a broader audience, such as the selection of patients and expertise in managing the therapeutic agent. Second, it focuses on patients with low-risk and intermediate-1-risk MF, whereas much experience has been generated in the higher-risk patient population. All patients had received RUX because they had symptoms of MF such as splenomegaly. The study essentially demonstrated that RUX can produce a significant reduction in spleen size.

The percentage of patients in the moderate to severe splenomegaly category was reduced significantly from 64% at diagnosis to 16% with RUX. Similar findings were observed in the low-risk and intermediate-1-risk groups. Evaluation showed benefit with RUX for many general symptoms. Fatigue decreased from 90% to 37% of patients with low-risk MF. Clearly patients with indications for treatment benefit from RUX in general and community practice, even those with low-risk MF. My clinical experience aligns with the benefits shown in this study, even though RUX is indicated only for patients with intermediate- and high-risk disease.

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

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]

Clinical Benefit of Ruxolitinib Treatment After Crossover from Best Available Therapy in Patients with Polycythemia Vera: Analysis of the RESPONSE Trial[3]

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

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

[3] **Kiladjian J-J et al.**
Proc ASH 2014;Abstract 3181.

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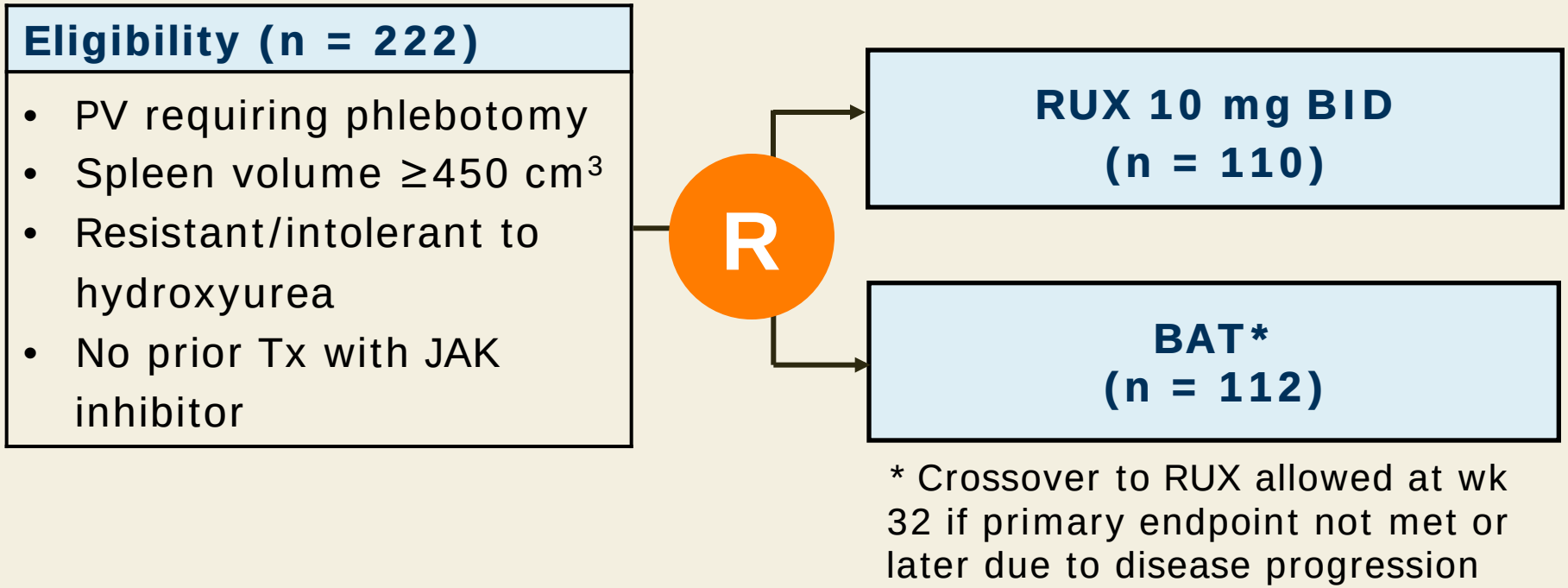
N Engl J Med 2015;372(5):426-35.

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



* 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.

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

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.

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).

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).

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).

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).

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

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.

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.

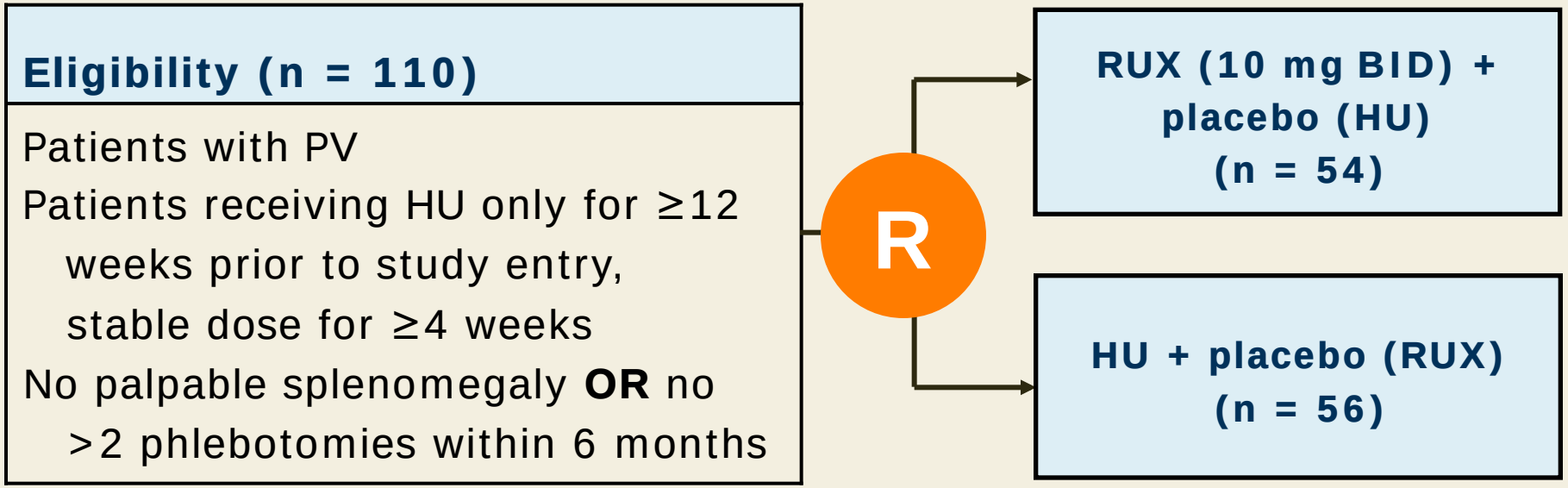
Proc ASH 2014;Abstract 3168.

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.

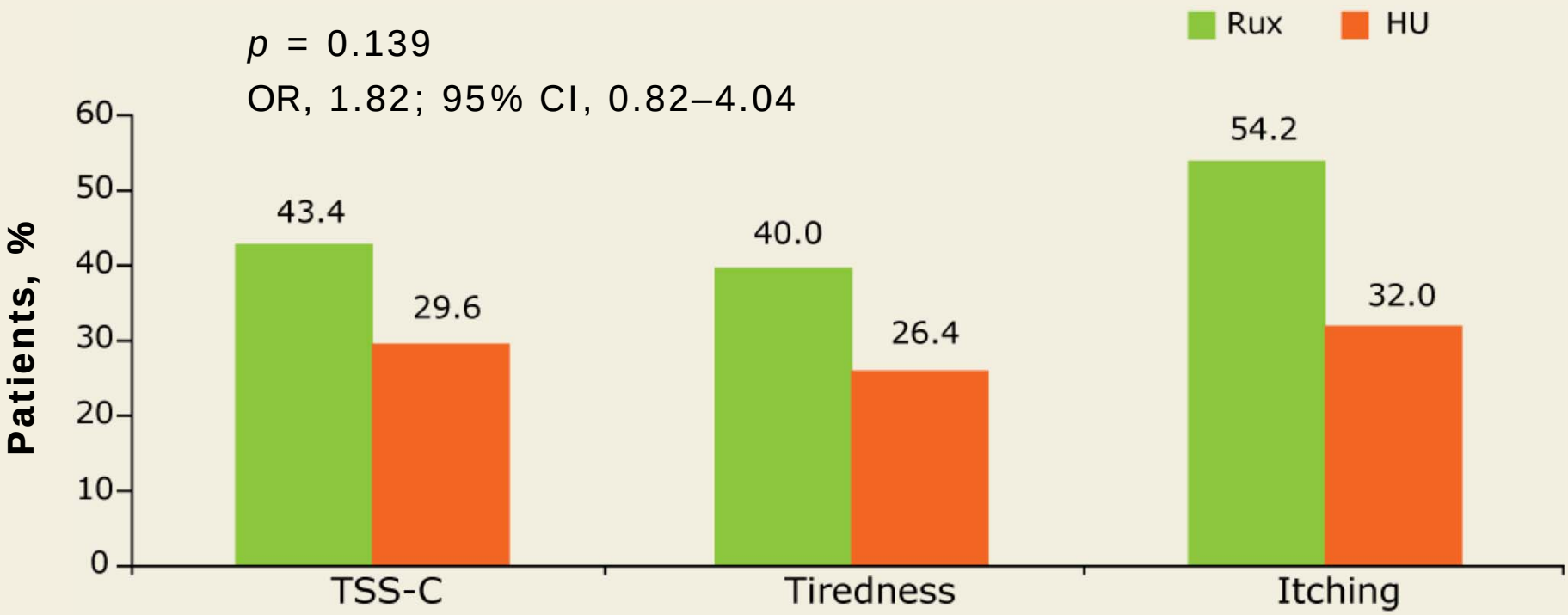
Phase III RELIEF Trial Design (NCT01632904)



- 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.

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

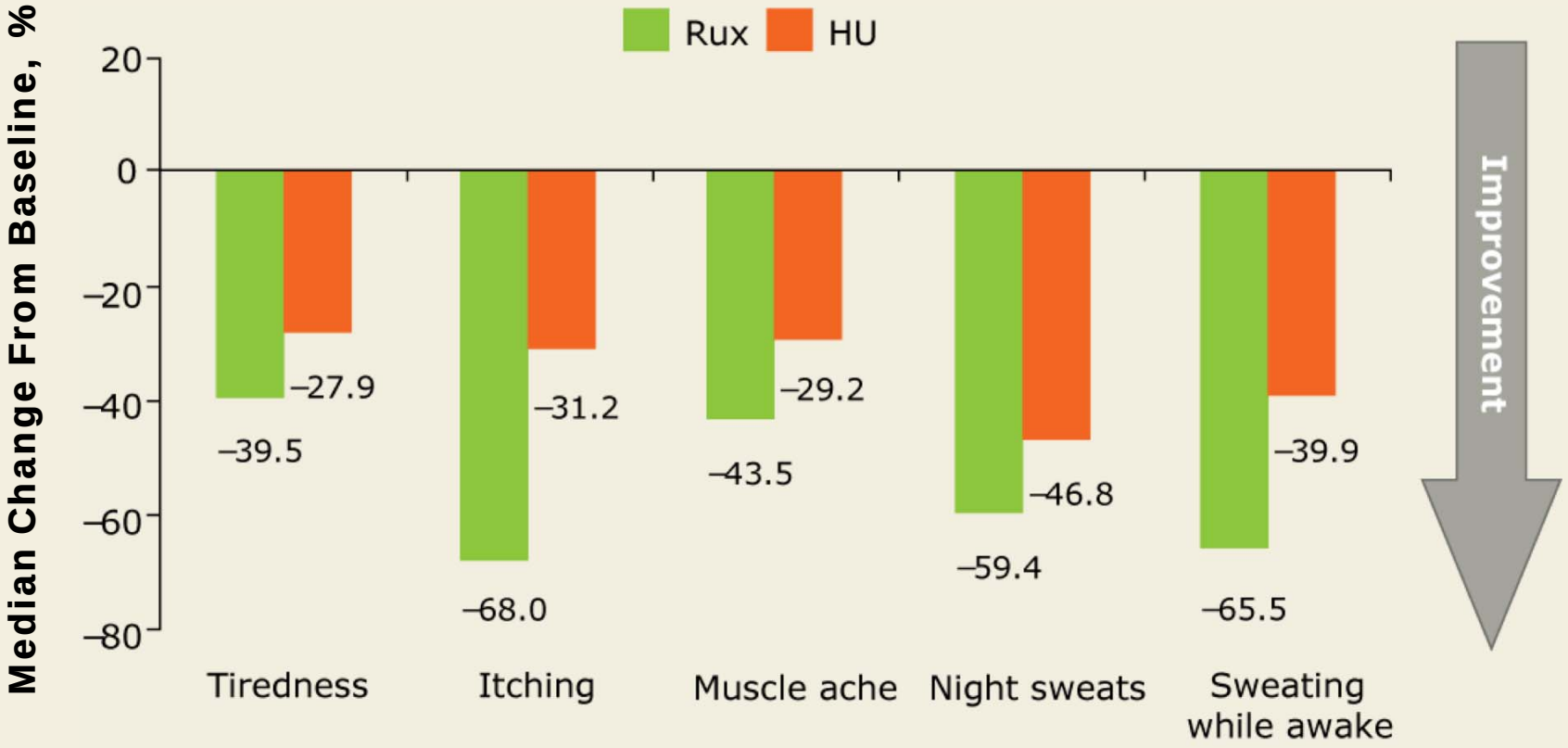


OR = odds ratio

- 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.

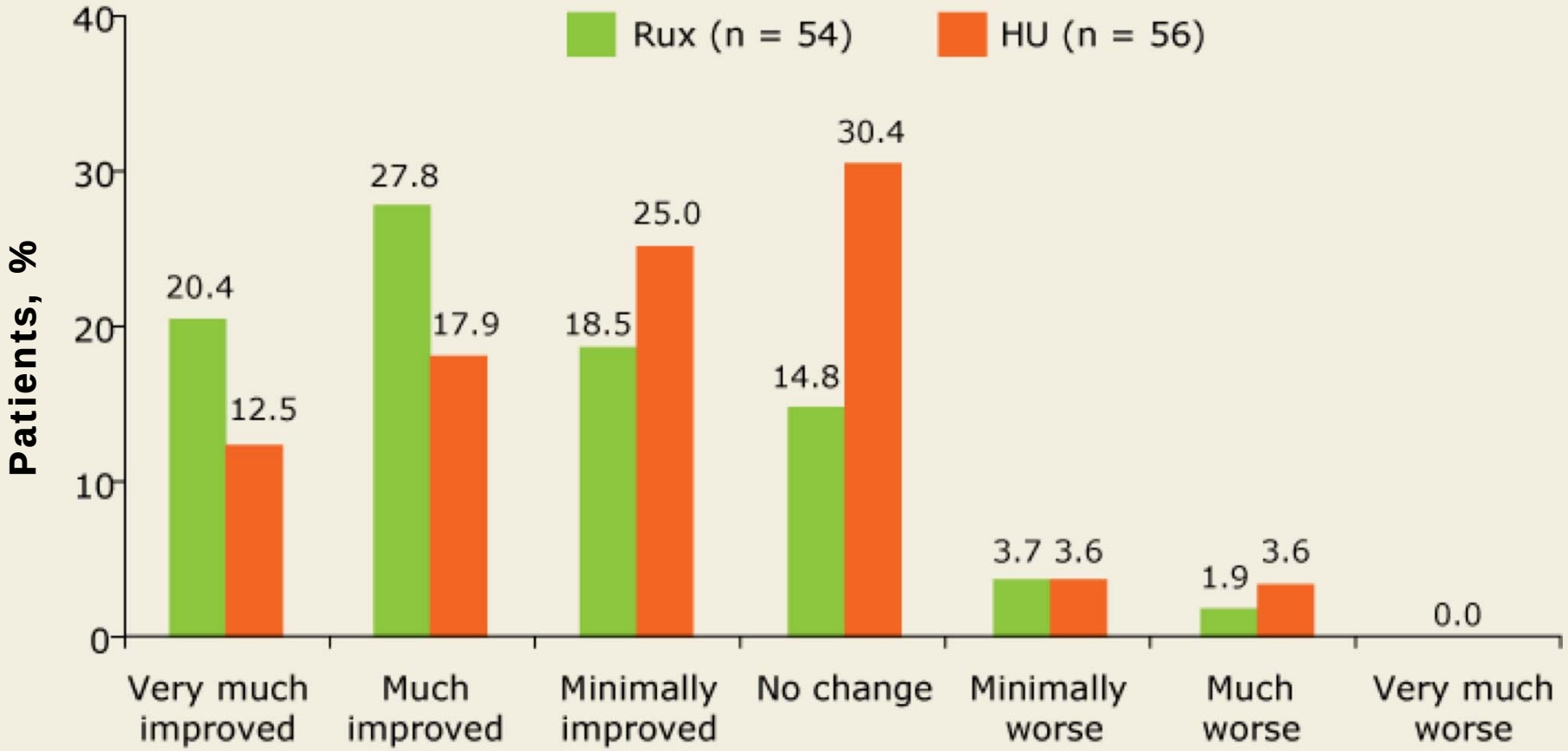
Median Percentage Change from Baseline to Week 16 in Individual TSS-C Symptoms



- 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%)

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

Patient Global Impression of Change at Week 16*



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

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

≥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.

≥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.

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.

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.

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.

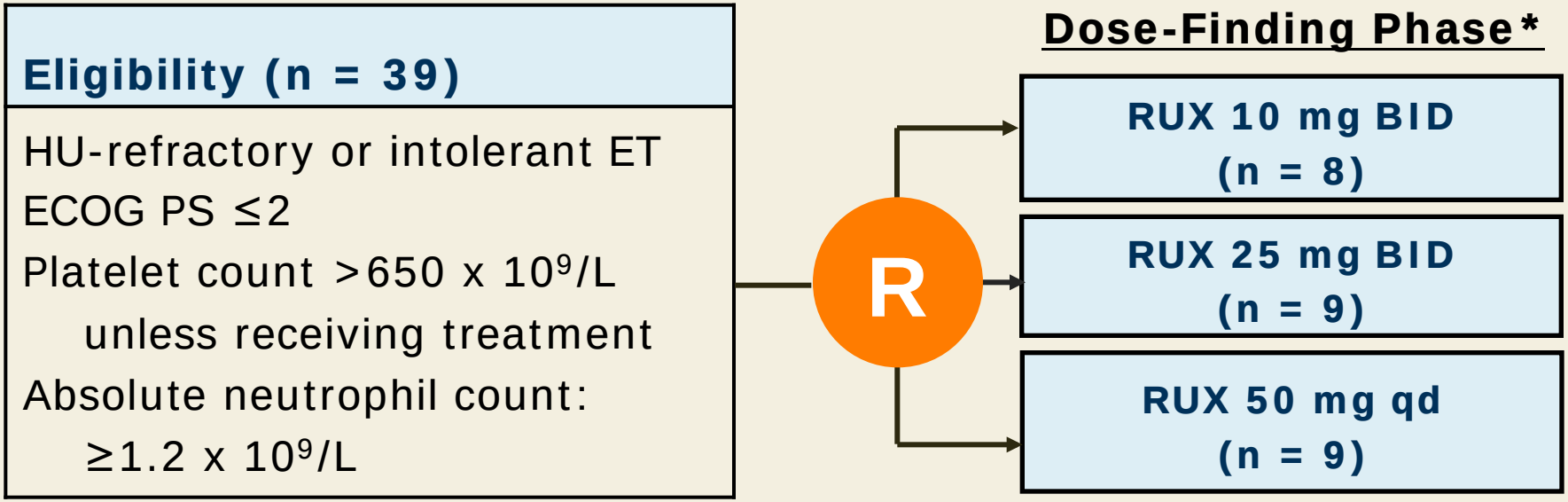
Proc ASH 2014;Abstract 1847.

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.

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)

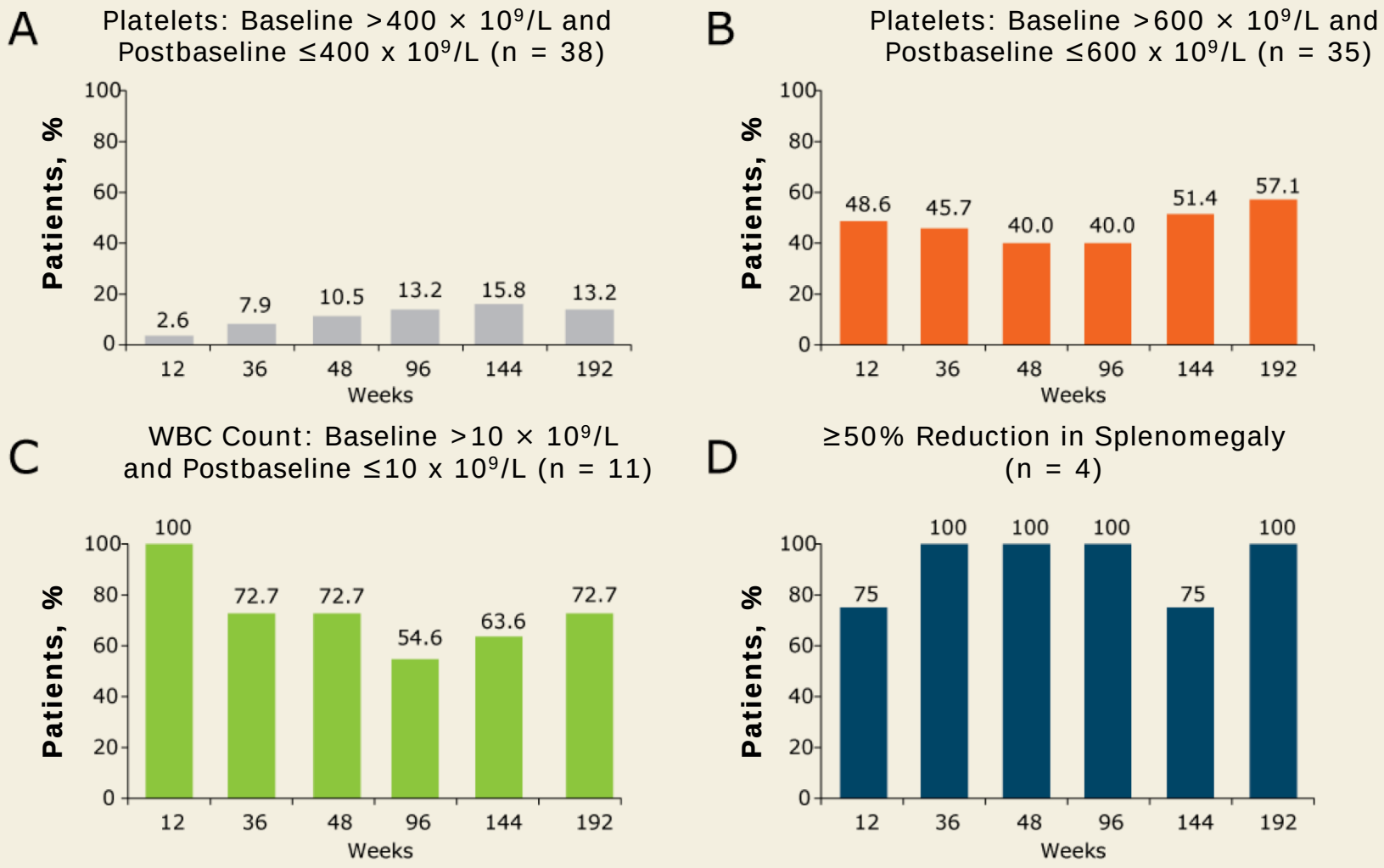
Verstovsek S et al. *Proc ASH* 2014;Abstract 1847.

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.

Clinical Response to RUX Therapy



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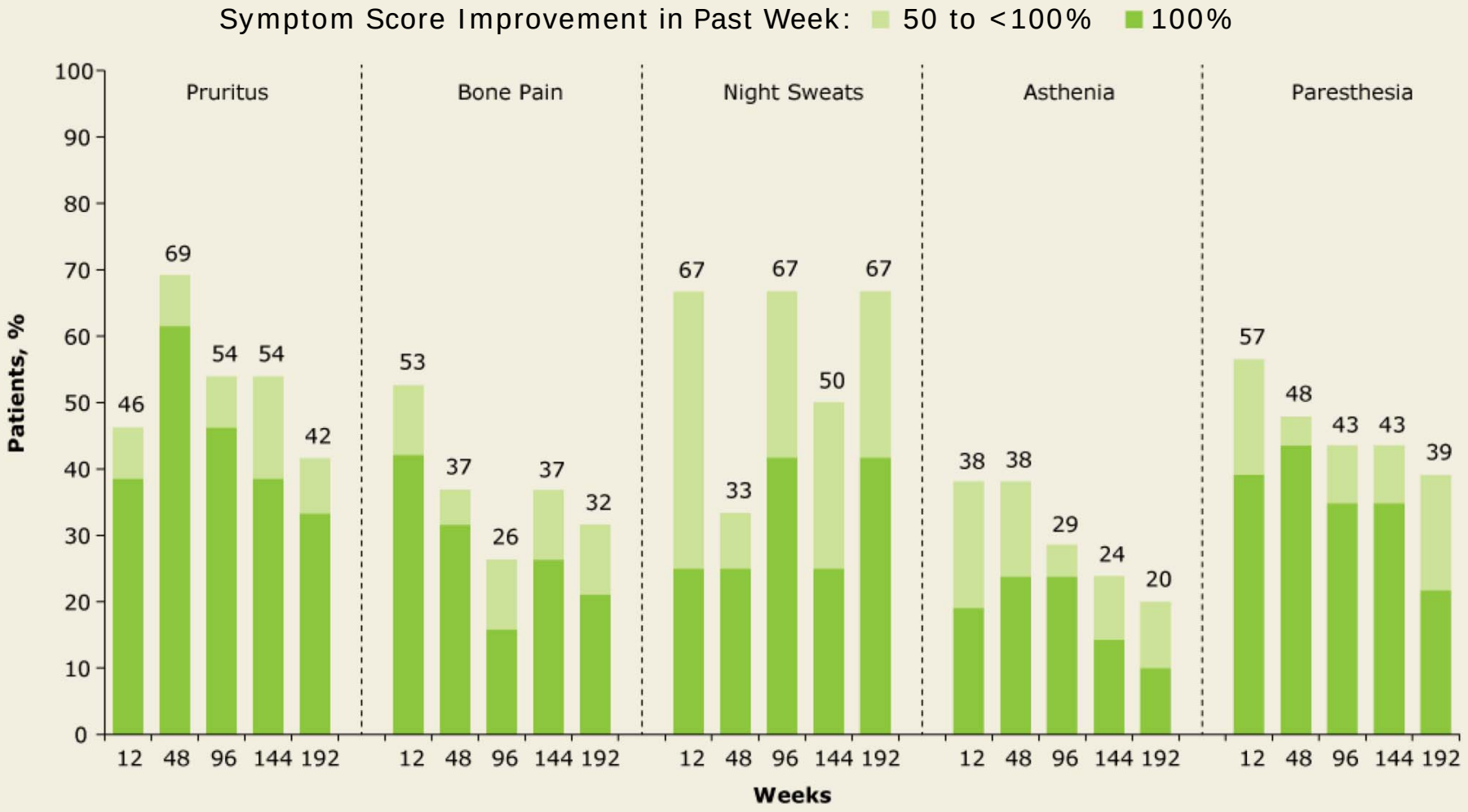
Proportion of Patients with ≥50% or 100% Improvement in ET-Related Symptoms with RUX



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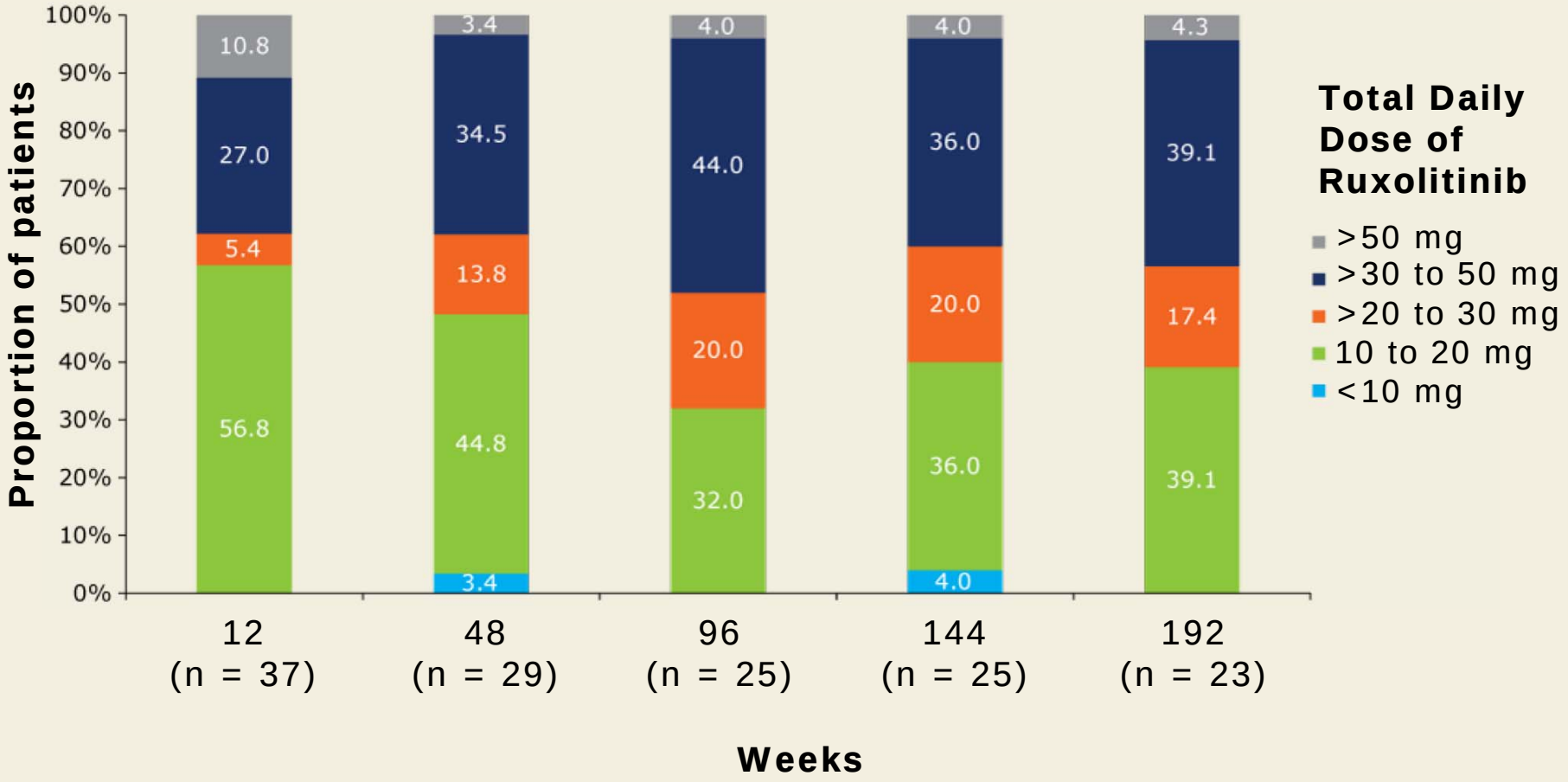
RUX Dose Distribution Over Time



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

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.

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

Phase 2 Trial of PRM-151, an Anti-Fibrotic Agent, in Patients with Myelofibrosis: Stage 1 Results[1]

Imetelstat, a Telomerase Inhibitor, Therapy for Myelofibrosis: A Pilot Study[2]

[1] **Verstovsek S et al.**
Proc ASH 2014;Abstract 713.

[2] **Tefferi A et al.**
Proc ASH 2014;Abstract 634.

Phase 2 Trial of PRM-151, an Anti-Fibrotic Agent, in Patients with Myelofibrosis: Stage 1 Results

Verstovsek S et al.

Proc ASH 2014;Abstract 713.

Background

- PRM-151 (PRM) is a recombinant form of pentraxin-2, an endogenous human protein that acts at sites of tissue damage, inducing macrophage differentiation to prevent and reverse fibrosis.
- PRM has broad antifibrotic activity in multiple preclinical models of established fibrotic diseases and no dose-limiting toxicities in Phase I trials (*Proc ATS* 2013;Abstract D94).
- Myelofibrosis (MF) is a myeloid cancer characterized by progressive bone marrow (BM) fibrosis with resultant anemia, abnormal platelet/leukocyte counts, extramedullary hematopoiesis and a well-defined symptom complex.
- **Study objective:** To investigate the potential of PRM to reduce BM fibrosis and to improve key disease features, including abnormal blood counts, symptoms and splenomegaly in patients with MF.

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Ongoing Simon-2-Stage Phase II Trial Design (NCT01981850)

Eligibility

PMF, post-PV MF, post-ET MF

DIPSS

- Intermediate-1 or -2 risk
- High risk

Grade ≥2 BM fibrosis

For cohorts treated with RUX:

- No current therapy/on a stable dose of RUX for ≥12 weeks and no spleen improvement for ≥4 weeks

Stage 1 (n = 27)

PRM (IV) 10 mg/kg q1wk

PRM (IV) 10 mg/kg q4wk

PRM (IV) 10 mg/kg q1wk + RUX

PRM (IV) 10 mg/kg q4wk + RUX

Stage 2 (n = 120)

Any treatment from Stage 1 with ≥1 response

PMF = primary MF; post-PV MF = postpolycythemia vera MF; post-ET MF = postessential thrombocythemia MF; RUX = ruxolitinib

- Schedule: PRM loading on days 1, 3, 5, then weekly or every 4 weeks, with or without RUX, for 24 weeks
- **Primary endpoint:** Overall response rate (ORR)

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

BM Fibrosis Reduction in 11 Out of 25* Patients

BM fibrosis grade at BL	Best BM fibrosis grade after baseline (BL)			
	Grade 3 (n)	Grade 2 (n)	Grade 1 (n)	Grade 0 (n)
Grade 3 (n = 15)	7	4	3	1
Grade 2 (n = 8)	0	5	3	0
Grade 1 (n = 2)	0	1	1	0

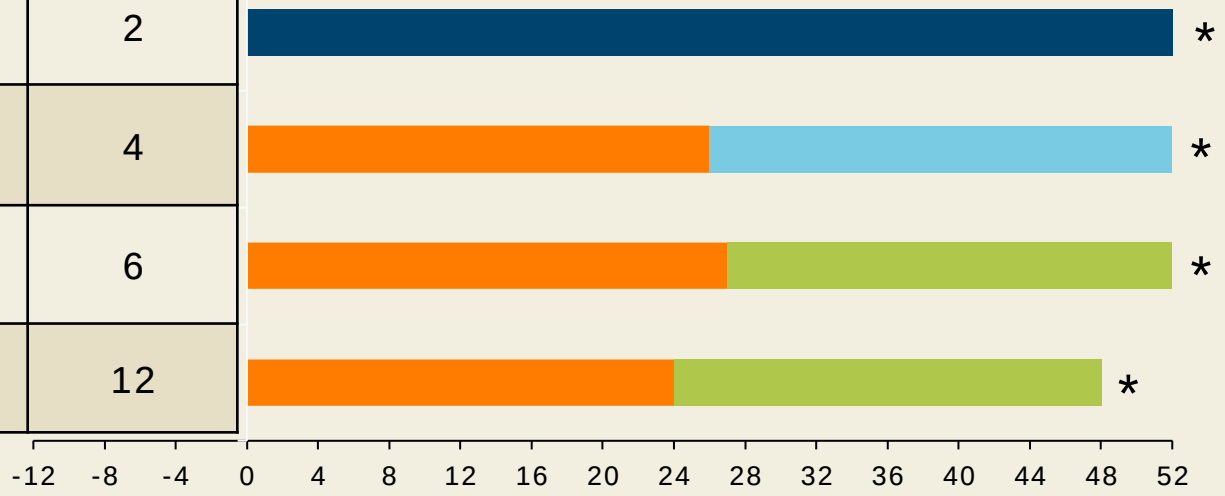
* Two patients had only BL BM. One patient with reduction in BM fibrosis grade had progressive disease (increased splenomegaly) and was not counted as a BM response.

- Reduction in BM fibrosis was associated with normalization of BM architecture:
  - Normal erythroid clustering (p = 0.07)
  - Normal or decreased myeloid-to-erythroid ratio (p = 0.02)
  - Fewer paratrabecular megakaryocytes (p = 0.07)

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Improvements in Hemoglobin (Hgb) Levels

Patient #	Baseline Hgb (g/L)	Baseline Transfusions in 12 weeks pre-C1D1	Best Hgb (g/L) without transfusion
101-004	81	2	103
101-002	97	4	122
101-005	86	6	98
101-006	77	12	105



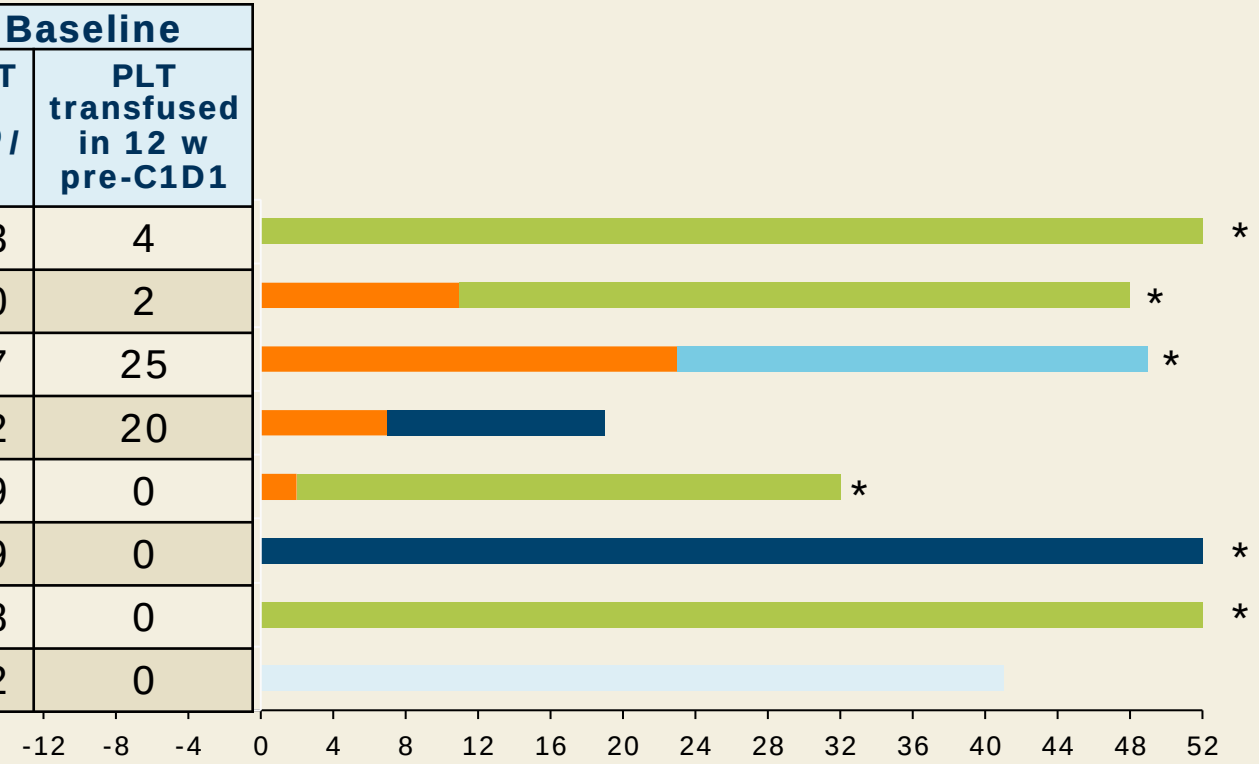
* Patients still on treatment and being followed

- 4 out of 15 patients with baseline Hgb <100 g/L showed improvements

With permission from Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Improvements in Platelet Counts

Patient #	Baseline PLT x 10^9/L	Baseline PLT transfused in 12 w pre-C1D1	Best PLT ($x10^9$/L) without transfusions
101-003	23	4	43
101-006	10	2	31
101-011	17	25	29
101-001	22	20	28
101-008	19	0	56
101-004	89	0	163
101-005	18	0	64
103-001	32	0	78



* Patients still on treatment and being followed

- 8 out of 14 patients with baseline platelets <100 x 10^9/L showed improvements

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Association between BM Fibrosis Reduction and Hematologic Improvements

Patients with improvements in BM fibrosis, hemoglobin level or platelet counts

Group	Weeks since last prior MF therapy	Bone marrow fibrosis	Hemoglobin	Platelets
PRM-151 QW	57	Stable	Stable	Improved
	3	Improved	Improved	Improved
	No prior therapy	Improved	Stable	Stable
	No prior therapy	Improved	Stable	Stable
PRM-151 Q4W	41	Stable	Stable	Improved
	60	Stable	Improved	Improved
	8	Improved	Improved	Improved
	8	Improved	Stable	Improved
	70	Improved	Stable	Stable
PRM-151 QW + RUX	52	Improved	Stable	Improved
	96	Improved	Stable	Stable
PRM-151 Q4W + RUX	156	Improved	Improved	Stable
	96	Stable	Stable	Improved
	83	Improved	Stable	Stable
	77	Improved	Stable	Stable

With permission from Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Summary of the Efficacy of PRM in MF

- ORR at 24 weeks of treatment: 11/26 (43%)
  - 1 patient with BM and symptom response was not included
  - ≥2 responses per treatment arm surpassed criteria to advance to Stage 2 of study
- Patients still on study at >24 weeks in extension (n = 14)
- ORR at 36 weeks of treatment: 13/26 (50%)
  - BM responses (n = 10)
  - International Working Group symptom responses (n = 4)
  - Patients with baseline Hgb <10 g/L and/or platelet count <100 x 10^9/L with improvements in Hgb and/or platelet counts: 10/21 (47.6%)
- Most patients had reductions in symptom scores
- Patients had modest reductions in spleen size by palpation
- Monthly dosing improvements were equivalent to that observed with weekly dosing schedules.

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Adverse Events (AEs)*

Grade 1–2	PRM q1wk (n = 8)	PRM q4wk (n = 7)	PRM q1wk + RUX (n = 6)	PRM q4wk + RUX (n = 6)
Diarrhea	25%	0%	0%	17%
Fatigue	13%	0%	17%	0%
Infusion site bruising	0%	0%	33%	0%
Oral herpes	0%	0%	17%	17%
Joint swelling	13%	0%	17%	0%
Headache	0%	0%	33%	0%

* Possibly or probably related to PRM and occurring in >1 patient; no related Grade 3-4 AEs in >1 patient

- 5 possibly related serious AEs: abdominal pain, sialadenitis, pneumonia (all recovered), gastroenteritis/pneumonia (resulting in death in an 85-year-old patient)
- 2 unrelated deaths due to pneumonia, multiorgan failure and cardiac arrest

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Author Conclusions

- Benefits of treatment with PRM:
  - Decreases in BM fibrosis
  - Improvements in hemoglobin levels and platelet counts, including transfusion independence
  - Reduction in symptoms
  - Modest reductions in splenomegaly
- Benefits of PRM increase with longer treatment duration:
  - Increase in the number of patients who benefited from therapy
  - Increase in the magnitude and duration of benefit
- PRM was safe and well tolerated when used alone and in combination with a stable dose of ruxolitinib.
- The Stage 2 portion of the study will be opening soon.

Verstovsek S et al. *Proc ASH* 2014;Abstract 713.

Investigator Commentary: Efficacy and Safety of PRM in MF

Interestingly, PRM is a recombinant form of pentraxin-2, a protein that acts in areas of inflammation. It induces macrophage differentiation and prevents or reverses fibrosis where there's injury. The primary idea for this study was that with the use of this agent in patients with MF, fibrosis could be reversed. An important question was also to determine whether that reversal resulted in benefits such as improved hematopoiesis. Patients received PRM at 2 different dosing schedules with or without ruxolitinib. About a third of the patients had a significant reduction in BM fibrosis, impressive because such responses are uncommon.

It appears that by improving BM fibrosis it is possible to improve hematopoiesis, with 47.6% of patients showing improvement in their hemoglobin level and/or platelet counts at 36 weeks of treatment. About 60% of patients with baseline platelet counts $<100 \times 10^9$/L had improvement. These are still early results from only 27 patients enrolled on Stage I of the study. However, PRM is an agent that we need to keep our eyes on because it may have a role in the treatment of MF. It will be interesting to know what happens when it is used in combination with ruxolitinib. This may open up lots of possibilities if PRM maintains this level of activity.

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

Imetelstat, a Telomerase Inhibitor, Therapy for Myelofibrosis: A Pilot Study

Tefferi A et al.

Proc ASH 2014;Abstract 634.

Background

- Current drugs for myelofibrosis (MF), including JAK inhibitors, do not induce complete or partial remissions.
- Imetelstat is a 13-mer lipid-conjugated oligonucleotide that targets the RNA template of human telomerase reverse transcriptase.
- Previously, a Phase II study of imetelstat for patients with essential thrombocythemia demonstrated platelet-lowering activity accompanied by reduction in *JAK2*V617F allele burden (*Proc ASH* 2012;Abstract 179).
- **Study objective:** To determine the efficacy and safety of imetelstat in patients with high-risk or intermediate-2-risk MF using the refined Dynamic International Prognostic Scoring System (DIPSS plus).

Tefferi A et al. *Proc ASH* 2014;Abstract 634.

Open-Label Pilot Trial Design (NCT01731951)

Eligibility (n = 33)

PMF, post-PV MF, post-ET MF

DIPSS plus

- Intermediate-2 risk
- High risk

No chemotherapy, immuno-modulatory or suppressive agent, corticosteroid, JAK inhibitor or growth factor therapy ≤14 days before entry

Imetelstat
9.4 mg/kg (IV)
Every 3 weeks
(Cohort A)

Imetelstat
9.4 mg/kg (IV)
Every week x 3 → every 3 weeks
(Cohort B)

PMF = primary MF; post-PV MF = postpolycythemia vera MF; post-ET MF = postessential thrombocythemia MF

- **Primary endpoint:** Overall response rate (ORR)

Tefferi A et al. *Proc ASH* 2014;Abstract 634.

Responses

Response rate	n = 33
ORR*	7 (21.2%)
Complete response (CR)	4 (12.1%)
Partial response (PR)	3 (9.1%)

* Occurring at a median of 5 cycles (range 1-9)

- All 4 patients who achieved CR experienced a reversal of bone marrow fibrosis.
- 6 out of 7 patients remain in remission after a median follow-up of 9.9 months.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

Other Responses

- Patients who are transfusion dependent (n = 13)
  - Improvement in anemia: 4 (31%)
- Patients who experienced >50% reduction in palpable spleen size out of 23 evaluable patients: 9 (39%)
- Patients with marked leukocytosis (white blood cell count >25 x 10^9/L) (n = 10)
  - ≥50% reduction in leukocyte count: 8 (80%)
- A majority of patients experienced a resolution of leukoerythroblastosis
- Patients with thrombocytosis (n = 12)
  - Normalization of platelet count with treatment: 9 (75%)

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

Laboratory Correlative Studies

Gene	CR/PR rates		
	Mutated	Unmutated	*p*-value
JAK2	27%	0%	0.3
ASXL1	0%	32%	0.07
SF3B1/U2AF1	38%	4%	0.036

- Grade ≥3 neutropenia or thrombocytopenia was more likely to occur in *JAK2*-unmutated ($p = 0.02$) and *ASXL1*-mutated cases ($p = 0.049$).
- Multicytokine panel screening showed significant differences between baseline and post-treatment samples involving several cytokines, including IL-1b, IL-5, IL-7, IL-17, VEGF, IL-8 and TNF-α ($p < 0.001$ for all).
- CR/PR rate did not correlate with baseline cytokine levels.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

Treatment-Related Adverse Events (AEs)

Event	n = 33
Intracranial hemorrhage (Grade 5)	3%
Upper gastrointestinal hemorrhage (Grade 5)*	3%
Neutropenia (Grade 4)	18%
Thrombocytopenia (Grade 4)	21%
Anemia (Grade 3)	27%

* Not related to treatment

- Grade ≥3 nonhematologic AEs were seen in only 1 patient.
- Regardless of attribution, treatment-emergent Grade 1 or 2 liver function test abnormalities affected bilirubin (46%), ALP (52%), AST (55%) and ALT (24%).
- There were 3 instances of Grade 3 ALP elevation and 1 of Grade 3 bilirubin elevation.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

Author Conclusions

- This study identifies imetelstat as an active drug in patients with MF.
  - However, it also reveals its potential to cause significant myelosuppression.
- The association between CR/PR rates and specific mutations suggests potential targeted activity that might be exploited for patient and disease selection.

Tefferi A et al. *Proc ASH* 2014;Abstract 634 (Abstract only).

Investigator Commentary: Results from a Pilot Study of Imetelstat for Patients with MF

In many cancer types, targeting telomerases is an interesting approach. Telomerases are known to become more active in MF as the disease progresses. Imetelstat specifically inhibits human telomerase reverse transcriptase. This is a small pilot study of imetelstat in 33 patients with primary or secondary MF. Impressively, 7 patients (21%) achieved complete remissions. The main toxicity associated with imetelstat is myelosuppression. Neutropenia and thrombocytopenia were each observed in about 20% of patients, and 27% of the patients experienced Grade 3 anemia.

Some correlation was apparent between response and mutational status. Patients harboring JAK2 mutations responded better than those without. The reverse is true for the ASXL1 mutation: Patients with unmutated disease responded better than those harboring the mutant form. A subset of patients may exist who are particularly prone to respond to this agent. This is another study requiring us to keep our eyes open to see what happens with the drug. So far, the data presented are attractive.

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

Final Study Results of the Phase III Dasatinib versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056)[1]

SPIRIT 2: An NCRI Randomised Study Comparing Dasatinib with Imatinib in Patients with Newly Diagnosed CML[2]

[1] **Cortes J et al.**
Proc ASH 2014;Abstract 152.

[2] **O'Brien S et al.**
Proc ASH 2014;Abstract 517.

Final Study Results of the Phase III Dasatinib versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056)

Cortes J et al.

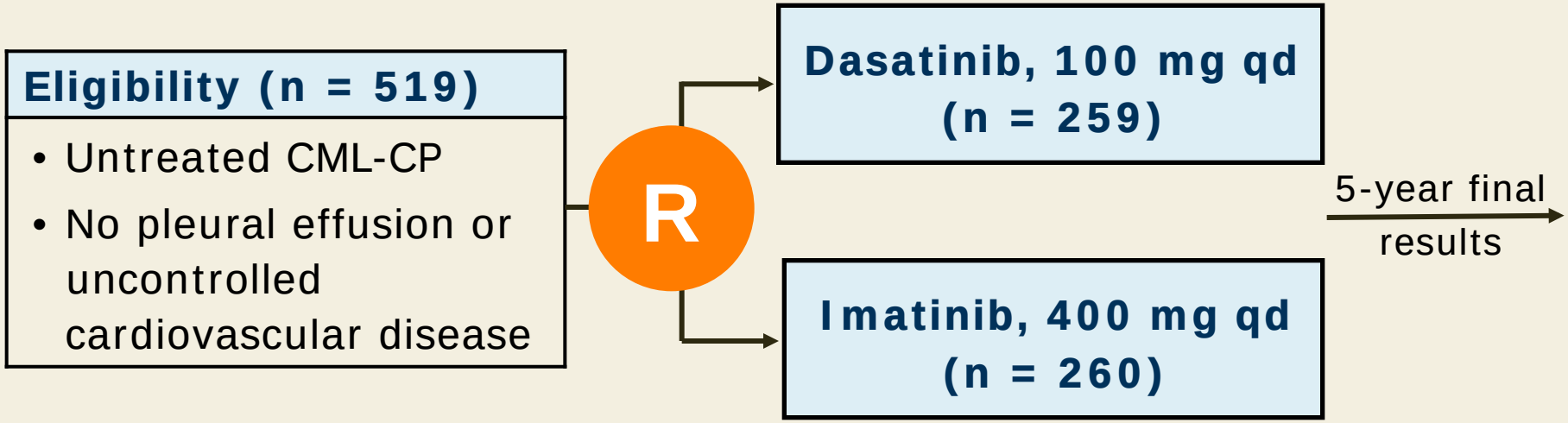
Proc ASH 2014;Abstract 152.

Background

- The second-generation tyrosine kinase inhibitor dasatinib is standard first-line therapy for patients with CML-CP
- Patients with newly diagnosed CML-CP treated with dasatinib (compared to imatinib) in the DASISION trial demonstrated
  - Improved rates of confirmed complete cytogenetic response
  - Faster rates of molecular response
  - An acceptable safety profile (*Blood* 2012;119(5):1123; *Blood* 2014;123(4):494-500)
- **Study objective:** To report final, 5-year analysis from DASISION comparing the efficacy and safety of dasatinib to that of imatinib for patients with newly diagnosed CML-CP

Cortes J et al. *Proc ASH* 2014;Abstract 152.

Phase III DASISION Trial Design



- **Primary endpoint:** Confirmed complete cytogenetic response (cCCyR) at 12 months

Cortes J et al. *Proc ASH* 2014;Abstract 152; www.clinicaltrials.gov.

Efficacy: Response and Survival at 5 Years

	Dasatinib (n = 259)	Imatinib (n = 260)	Hazard ratio	*p*-value
Cumulative 5-y MMR	76%	64%	NR	0.0022
Cumulative 5-y $MR^{4.5}$	42%	33%	NR	0.0251
Estimated 5-y PFS	85%	86%	1.06	NR
Estimated 5-y OS	91%	90%	1.01	NR

MMR = major molecular response; NR = not reported; MR = molecular response; PFS = progression-free survival; OS = overall survival

- cCCyR for dasatinib vs imatinib: 77% vs 66%, *p* = 0.007 at 1 year; 83% vs 78%, *p* = 0.187 at 5 years
- Number of deaths: n = 26 on each arm
- Transformations to both accelerated and blast phase CML on study or after discontinuation: dasatinib, 4.6%; imatinib, 7.3%

Cortes J et al. *Proc ASH* 2014;Abstract 152.

Five-Year Responses and Outcomes by BCR-ABL (≤10% or >10%) at 3 Months

Outcome	Dasatinib (n = 259)			Imatinib (n = 260)		
	≤10%	>10%	*p*-value	≤10%	>10%	*p*-value
BCR-ABL at 3 months (%)	84	16	—	64	36	—
CCyR/MMR/ $MR^{4.5}$ (%)	94/87/54	41/38/5	—	92/81/48	59/41/12	—
5-y OS (%)	94	81	0.0028	95	81	0.0003
5-y PFS (%)	89	72	0.0014	93	72	<0.0001
5-y TFS (%)	97	83	0.0004	97	80	<0.0001

TFS = transformation-free survival

Cortes J et al. *Proc ASH* 2014;Abstract 152.

Author Conclusions

- Final 5-year analysis confirms that compared to imatinib, patients who received dasatinib had
  - Faster times to response
  - Higher cumulative rates of molecular responses
  - Fewer transformations to accelerated or blast phase
- Progression-free and overall survival rates were similar between treatment arms
- Achievement of BCR-ABL ≤10% at 3 months is associated with significantly higher progression-free and overall survival by 5 years
- Safety profile remains consistent, with no new safety signals identified
  - Pleural effusion occurred throughout 5 years (20%) but did not impair the ability of patients to obtain a response. Six percent of patients with pleural effusion discontinued treatment
  - Arterial ischemic events were uncommon (dasatinib 5%, imatinib 2%)

Cortes J et al. *Proc ASH* 2014;Abstract 152.

Investigator Commentary: Final Results of the Phase III DASISION Trial of Dasatinib versus Imatinib in Newly Diagnosed CML-CP

DASISION established dasatinib as one of the standard treatments for CML. The rate of cCCyR at 12 months, which was the primary endpoint, was shown in a previous publication to be significantly better for patients who received dasatinib, and this led to approval of the drug.

The current study reports on the final, 5-year data. It continues to show the superiority of dasatinib over imatinib with most of the endpoints assessed. The rate of cCCyR at 5 years was 83% versus 78% in favor of dasatinib. Importantly, the differences in MMR rates are maintained at 5 years in favor of dasatinib. Also, the rate of transformation to accelerated and blast phase is lower with dasatinib compared to imatinib. This is important because disease that transforms is difficult to treat, and, unfortunately, many of these patients do not survive. BCR-ABL transcripts ≤10% at 3 months correlate with long-term outcome and occurred more frequently on the dasatinib arm.

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

continued

Investigator Commentary: Final Results of the Phase III DASISION Trial of Dasatinib versus Imatinib in Newly Diagnosed CML-CP (continued)

We are not yet seeing a difference in overall progression-free survival or overall survival. The question that arises is why no difference is evident in survival outcomes when responses are superior with dasatinib. I believe the reason is that patients who receive imatinib can be salvaged. I think that with longer follow-up we will start to observe a separation of the curves in favor of dasatinib.

In terms of toxicity, there were no unexpected adverse events. The major side effect with dasatinib is pleural effusions, and they can occur late in the treatment phase. Most pleural effusions are Grade 1 or 2 and are manageable. Only 6% of the patients had to discontinue dasatinib because of pleural effusions. There is a trend toward better responses with the development of pleural effusions. My approach is usually not to immediately switch therapy for patients with pleural effusions. Most of these patients can be cared for with treatment interruptions, dose adjustments, corticosteroids and diuretics.

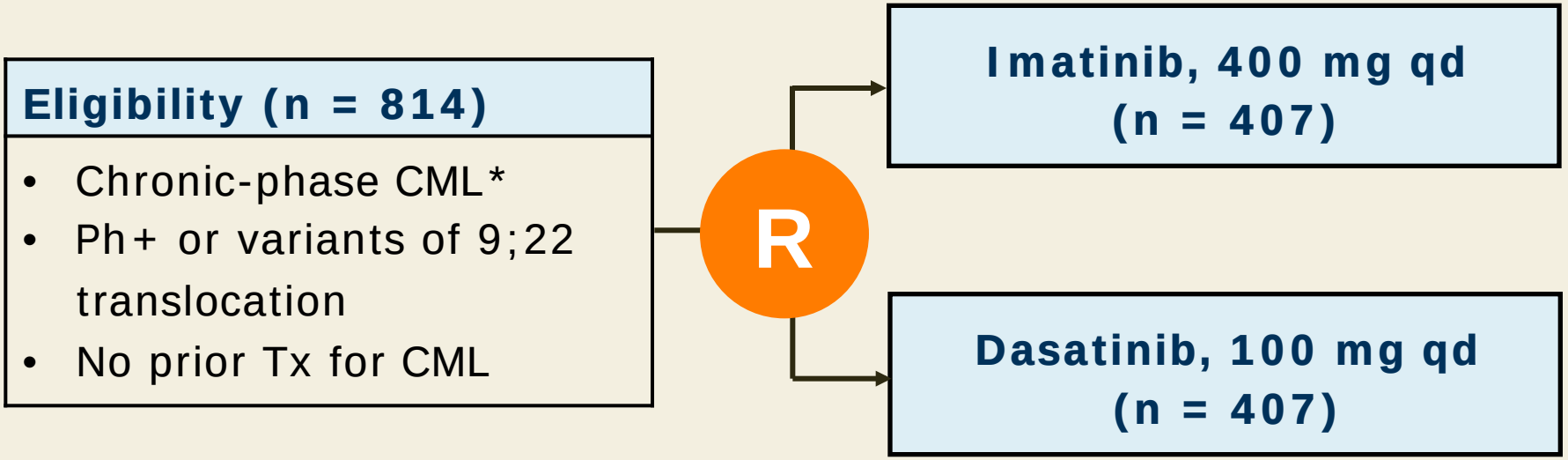
Interview with Jorge E Cortes, MD, January 14, 2015

SPIRIT 2: An NCRI Randomised Study Comparing Dasatinib with Imatinib in Patients with Newly Diagnosed CML

O'Brien S et al.

Proc ASH 2014;Abstract 517.

Phase III SPIRIT 2 Trial Design



* Within 3 months of diagnosis

CML = chronic myeloid leukemia

- **Primary endpoint:** Event-free survival (5 y)
- **Secondary endpoints** include rates of complete cytogenetic response (CCR), major molecular response (MMR), MR^3, BCR-ABL1/ABL1 ratio <0.1%, overall survival and toxicity

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

Cytogenetics at 12 Months

Best response	Imatinib (n = 406)	Dasatinib (n = 406)	*p*-value
Major cytogenetic response	209 (51.5%)	228 (56.2%)	0.181*
CCR	169 (41.6%)	217 (53.4%)	<0.001*

* Analyses missing for 181 of 406 patients on the imatinib arm and 166 of 406 patients on the dasatinib arm

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

PCR Response

PCR at 12 months	Imatinib (n = 406)	Dasatinib (n = 406)	*p*-value
Achieved MR^3	43.1%	58.4%	<0.001
Achieved $MR^{4.5}$	5.9%	13.3%	0.001

Association of PCR Response with Pleural Effusion

PCR <0.1% (MR^3)	Imatinib (n = 406)	Dasatinib (n = 406)
No pleural effusion	43.2%	56.3%*
With pleural effusion	33.3%	65.6%*

* Difference between arms not significant

PCR = polymerase chain reaction analysis of the BCR-ABL transcript levels

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

Select Adverse Events (AEs)

All grade AEs	Imatinib (n = 406)	Dasatinib (n = 406)
Pleural effusion	0.7%	22.2%
Vomiting	13.1%	12.1%
Diarrhea	32.0%	25.4%
Headache	13.5%	25.4%
Thrombocytopenia	48.5%	69.2%

- Grade 3 or 4 thrombocytopenia: imatinib, 4.7%; dasatinib, 13.5%
- No significant differences in the rate of cardiovascular AEs
- Total deaths: imatinib, 2.2%; dasatinib, 2.5%

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

Author Conclusions

- This is the largest investigator-conducted randomized trial of dasatinib versus imatinib, with a median follow-up of 3 years
- Both drugs were generally well tolerated:
  - 512 of 812 patients (62.9%) continue on study medication
  - Imatinib is associated with GI toxicity; dasatinib with pleural effusions, headaches
  - No difference in cardiovascular events
- MR^3 rate at 1 year: imatinib, 43%; dasatinib, 58%
- 774 of 812 patients (95.3%) remain alive:
  - Imatinib, 95.5%; dasatinib, 95.0%
- No difference in progression-free or overall survival

O'Brien S et al. *Proc ASH* 2014;Abstract 517.

Investigator Commentary: SPIRIT 2 Study Comparing Dasatinib to Imatinib for Newly Diagnosed CML

This study, like the DASISION trial, compared dasatinib to imatinib for patients with newly diagnosed CML. The primary endpoint was event-free survival at 5 years. The median follow-up for this interim analysis was 3 years, so the analysis does not address the primary endpoint.

A significant difference was evident in the rate of MMR (MR^3) in favor of dasatinib. An interesting correlation between MR^3 and pleural effusion was observed. Patients who had a pleural effusion had an MR^3 rate of 65%, whereas for those with no pleural effusion it was 56%. The difference was not statistically significant, but a trend is apparent for better responses in patients who have pleural effusions. That observation has also been made in other studies. The rate of CCR also trended in favor of dasatinib, but many data are missing, so it is difficult to draw a conclusion.

The toxicity profile was similar to what we observed in the DASISION study. The rates of thrombocytopenia and pleural effusions were higher with dasatinib, whereas with imatinib more gastrointestinal toxicities were noted. The rates of arterial cardiovascular events and hypertension were higher in the dasatinib arm, although the difference was not significant. All patients receiving tyrosine kinase inhibitors (TKIs) should be monitored for cardiovascular events.

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

continued

Investigator Commentary: SPIRIT 2 Study Comparing Dasatinib to Imatinib for Newly Diagnosed CML (continued)

This is the third randomized study that demonstrates the superiority of dasatinib versus imatinib, the other studies being the DASISION and the SWOG-S0325 trials. It is reassuring that higher rates of response, earlier and deeper responses and a favorable toxicity profile with dasatinib can be confirmed in independent studies.

We also know that although the benefit with second-generation TKIs is greater for patients who are at high risk, those who are at low risk also benefit. A higher rate of MMR and deeper responses are observed with newer TKIs. However, that does not translate into a survival benefit. Future studies will have to address the role of imatinib in the treatment of CML given the cost issues and the fact that a generic version of imatinib should be available soon.

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

Epic: A Phase 3 Trial of Ponatinib Compared with Imatinib in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CP-CML)

Lipton JH et al.

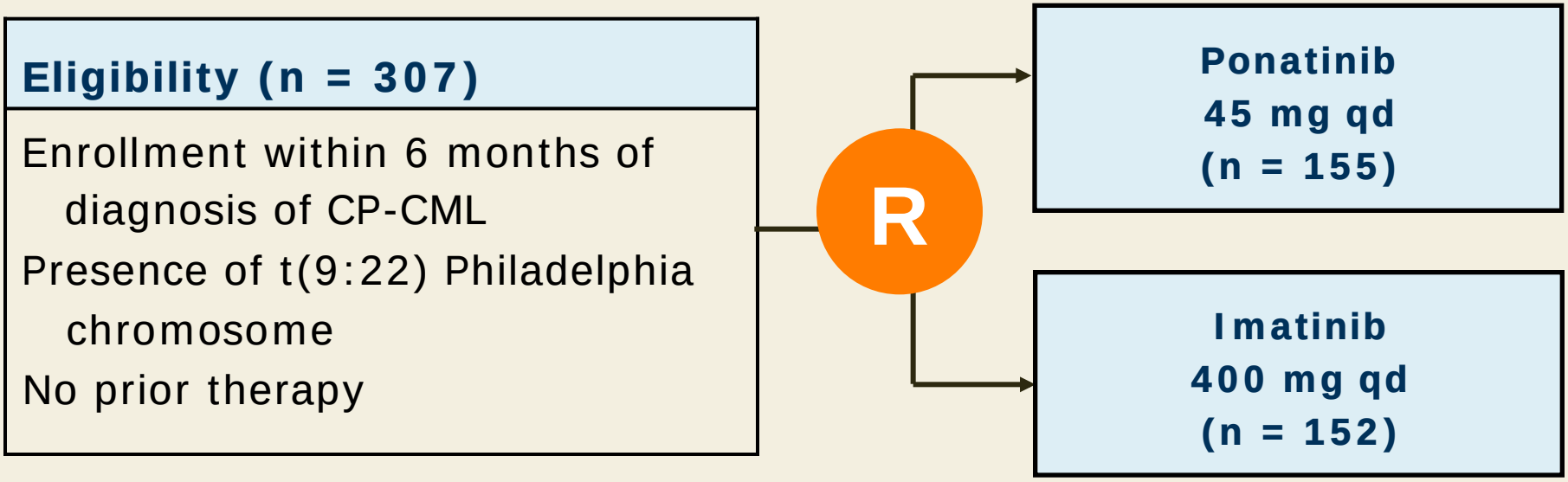
Proc ASH 2014;Abstract 519.

Background

- Ponatinib is an approved potent oral tyrosine kinase inhibitor (TKI) active against native and mutated forms of BCR-ABL, including T315I.
- The Phase II PACE study demonstrated that ponatinib is highly active in patients with heavily pretreated Philadelphia chromosome–positive leukemia (*NEJM* 2013;369:1783).
- The Phase III EPIC trial was established to assess the activity and tolerability of ponatinib versus imatinib in patients with newly diagnosed CP-CML.
  - However, on October 18, 2013, the trial was terminated due to arterial thrombotic events in the ponatinib clinical program and due to patient safety considerations.
- **Study objective:** To report the efficacy and safety of ponatinib in the EPIC trial up to the point of termination.

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Phase III EPIC Trial Design



- Patients were stratified by Sokal risk score: low (<0.8) vs intermediate (0.8 to 1.2) vs high (>1.2) before randomization.
- Dose modification was allowed on both arms to manage toxicity. The maximum dose allowed was 45 mg daily (ponatinib) or 800 mg daily (imatinib).
- In the imatinib arm, dose escalation was allowed in case of suboptimal response.
- **Primary endpoint:** Rate of major molecular response (MMR) at 12 months.

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

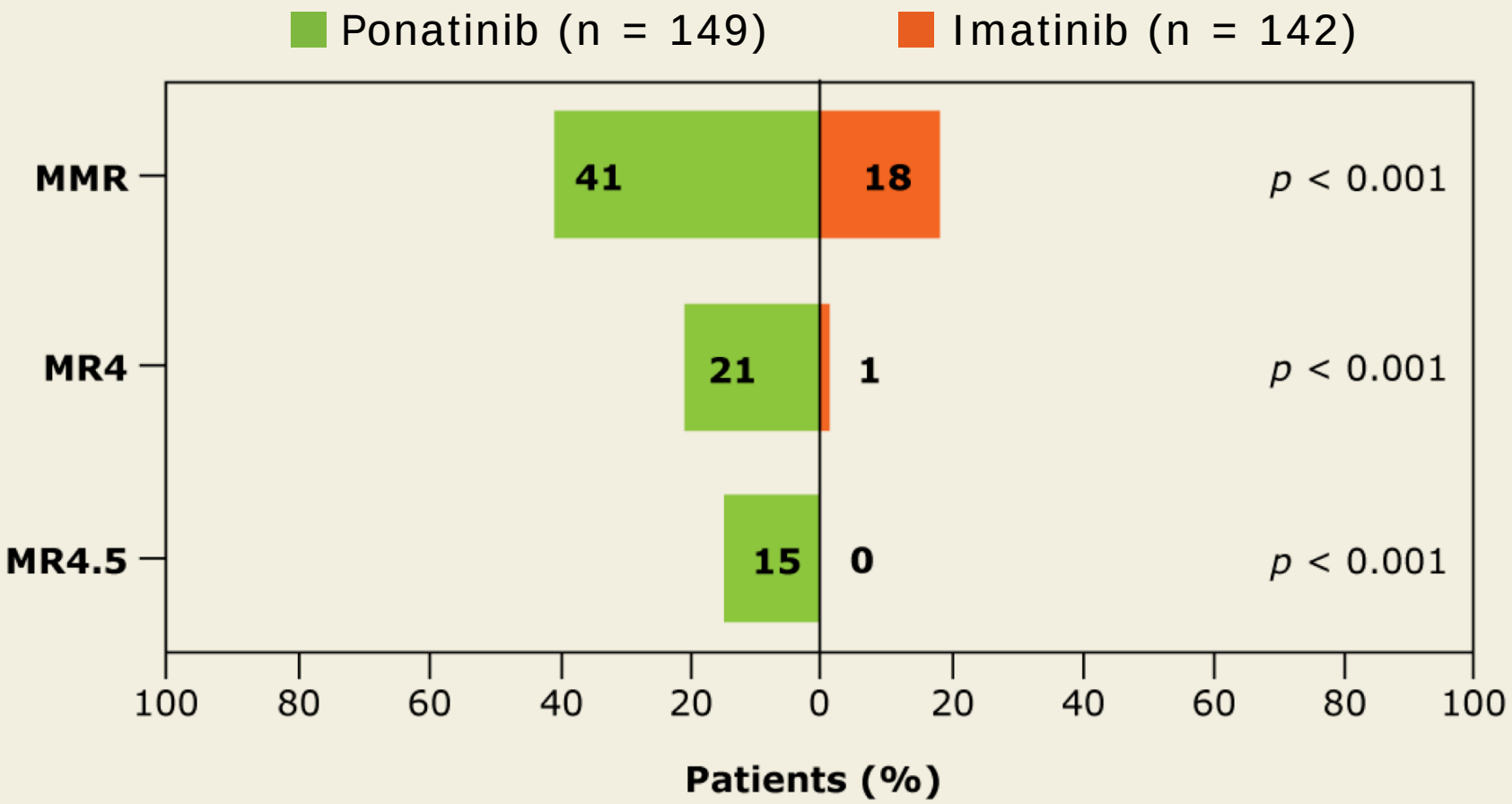
Achievement of <10% BCR-ABL Transcript at 3 Months

Evaluable patients	Ponatinib (n = 109)	Imatinib (n = 114)	*p*-value
All patients	94%	68%	<0.001
By Sokal risk score	**Ponatinib**	**Imatinib**	***p*-value**
Low risk (n = 45, 50)	98%	76%	0.002
Intermediate risk (n = 44, 45)	96%	69%	0.002
High risk (n = 20, 19)	85%	42%	0.008

- Median follow-up time: 5.1 months

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

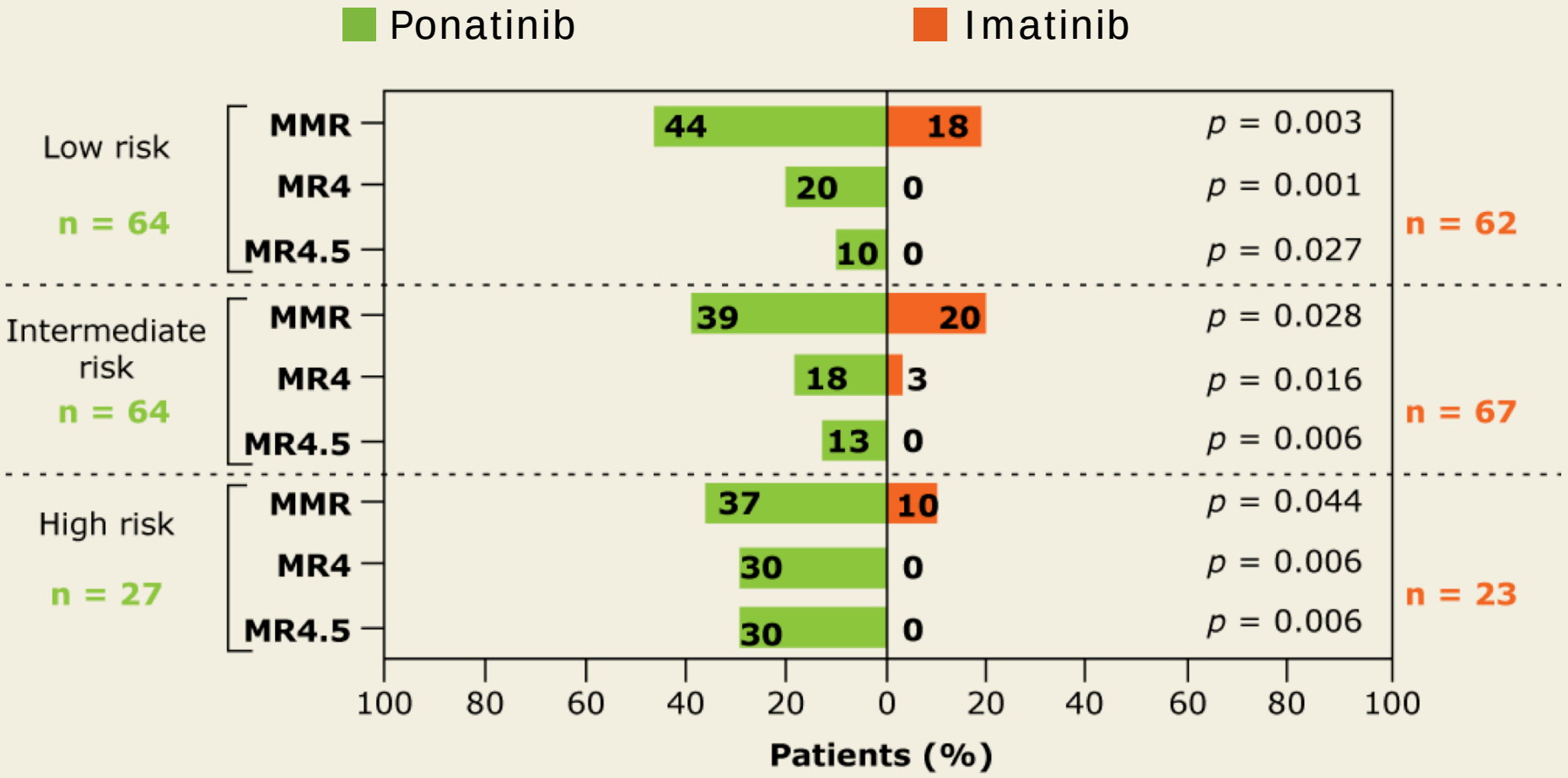
Best Overall Molecular Response at Any Time: Evaluable Patients



- Median time to MMR: 100 days (ponatinib) versus 169 days (imatinib)

With permission from Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Best Molecular Response at Any Time by Sokal Risk Score: Evaluable Patients



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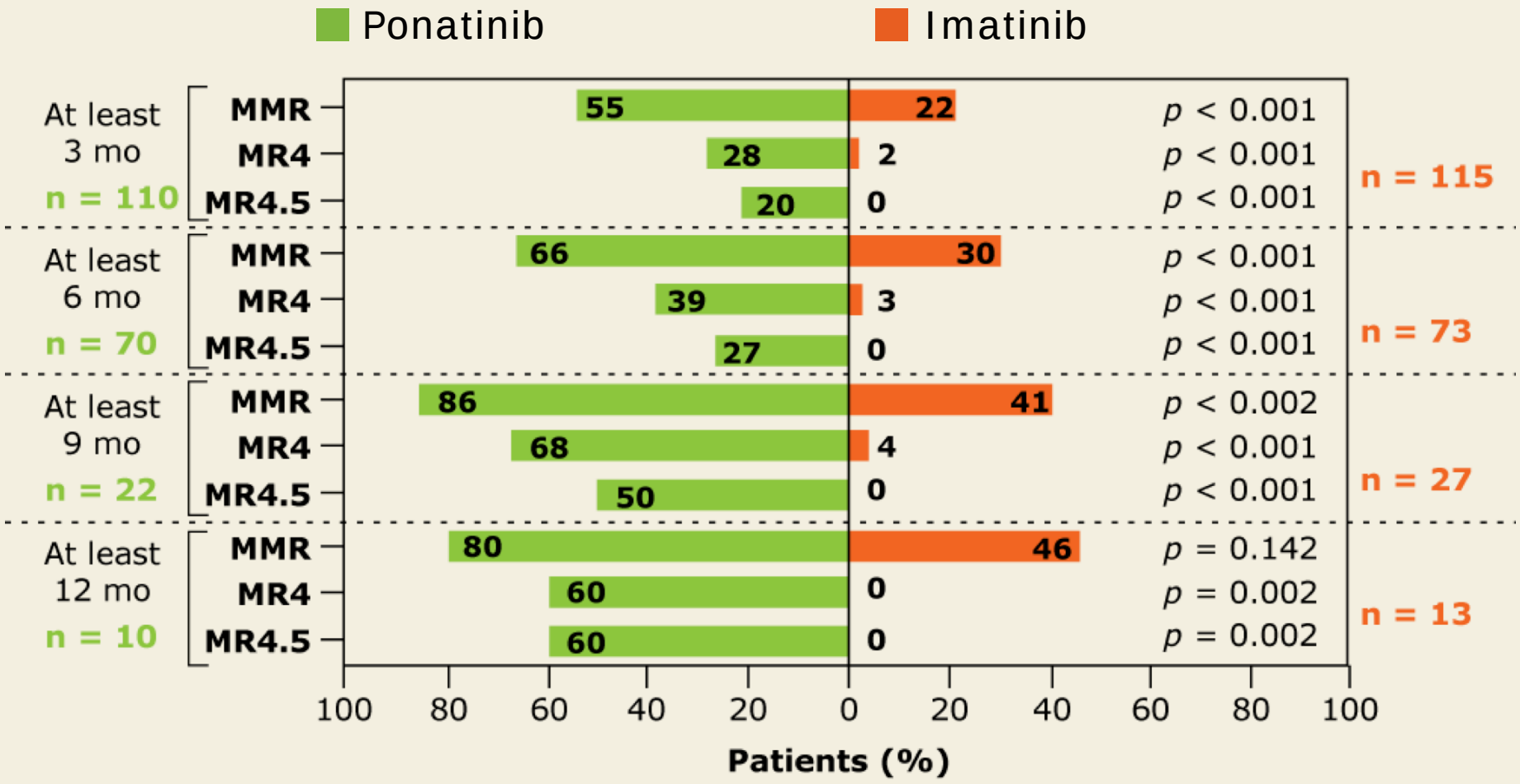
Molecular Response After 3, 6, 9 or 12 Months: Evaluable Patients



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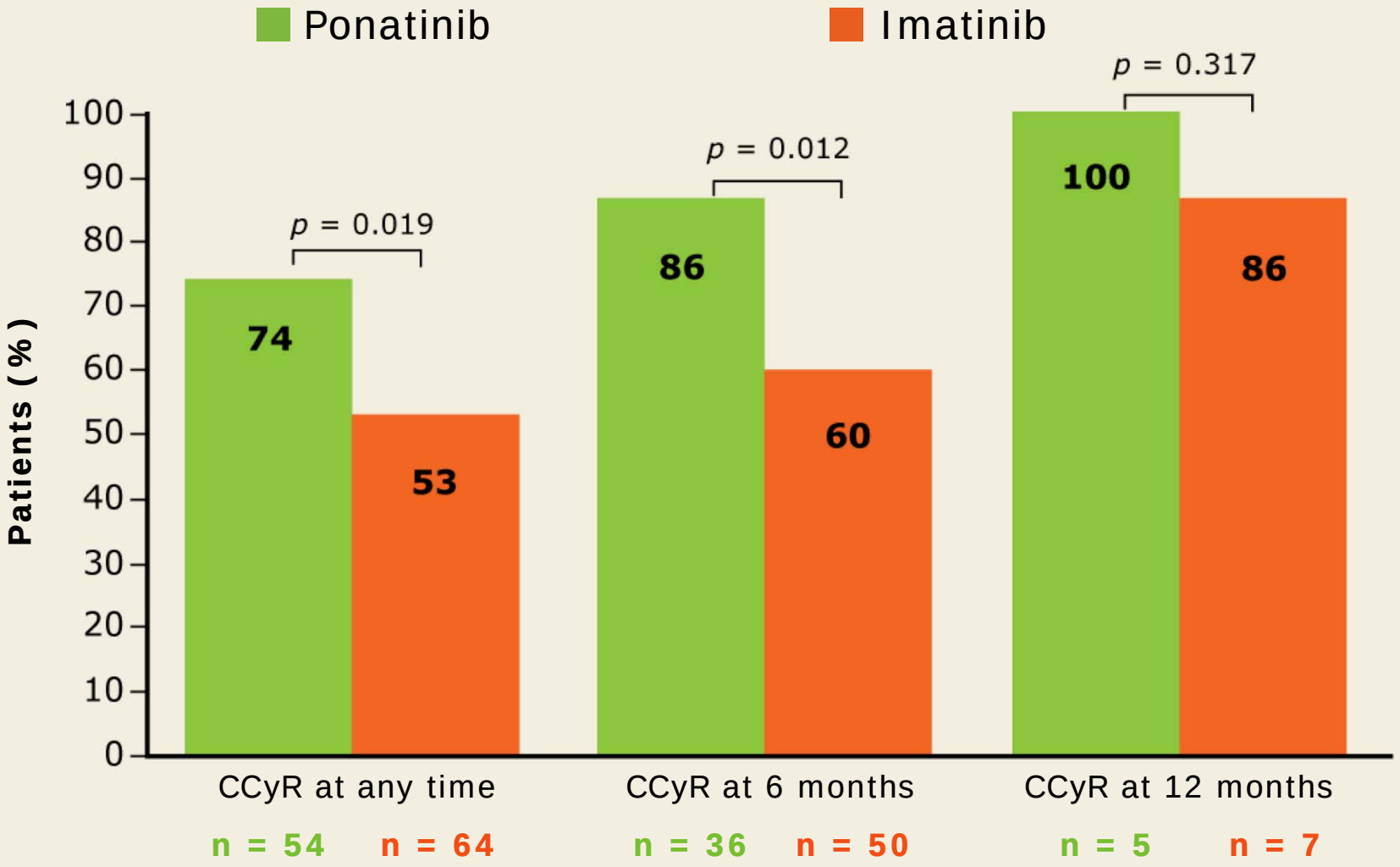
Complete Cytogenetic Response: Evaluable Patients



With permission from Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Select Adverse Events (AEs) Occurring in >15% of Patients

Event	Ponatinib (n = 154)		Imatinib (n = 152)	
	All	Grade 3-4	All	Grade 3-4
Rash	38%	7%	16%	1%
Abdominal pain	36%	3%	10%	0%
Headache	33%	1%	13%	0%
Increased lipase	27%	14%	7%	2%
Myalgia	26%	1%	18%	0%
Thrombocytopenia	25%	12%	14%	7%
Nausea	22%	1%	34%	0%
Arthralgia	19%	1%	15%	1%
Hypertension	18%	5%	2%	0%

- 1 patient on each arm had Grade 5 pneumonia

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Patients with Treatment-Emergent Vascular Occlusive Events

Events	Ponatinib (n = 154)		Imatinib (n = 152)	
	All	Grade 3-4	All	Grade 3-4
Arterial thrombotic AEs	7%	7%	2%	0.7%
Cardiovascular AEs	3%	3%	0.7%	0%
Cerebrovascular AEs	2%	2%	0.7%	0.7%
Peripheral vascular AEs	2%	2%	0.7%	0%
Venous thromboembolic AEs	0.6%	0.6%	0%	0%

- Time to onset of vascular occlusive events:
  - 10 to 233 days (ponatinib) versus 2 to 156 days (imatinib)
- Of the 12 patients who received ponatinib and experienced vascular occlusive AEs, 11 had ≥1 risk factor or relevant medical history.

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Author Conclusions

- Despite early termination of the EPIC trial, preliminary analyses of data suggest improved efficacy with ponatinib compared to imatinib:
  - <10% BCR-ABL at 3 months: 94% (ponatinib) vs 68% (imatinib). This endpoint correlates with overall survival
  - With ponatinib response rates were higher and responses were deeper and more rapid than with imatinib
- More adverse events were reported in the ponatinib arm:
  - Higher incidence of Grade 3 or 4 and serious adverse events
  - More patients experienced vascular occlusive events
- A dose-ranging trial of ponatinib in refractory CML is planned to evaluate benefit and risk of alternate dosing regimens (NCT02398825).

Lipton JH et al. *Proc ASH* 2014;Abstract 519.

Investigator Commentary: EPIC — A Phase III Trial of Ponatinib versus Imatinib in Newly Diagnosed CP-CML

The EPIC trial design was based on the principle that ponatinib would be active because it is a potent drug that targets all mutations in CML. Because it can prevent the emergence of resistant clones, it was thought that ponatinib could result in better outcomes and prevent the emergence of mutations. Unfortunately, as the data started to emerge from this study, ponatinib was associated with the risk of arteriothrombotic events. As a result, the study was terminated with only 307 patients.

Very few patients were on the trial for 12 months, which was the primary endpoint. However, at 3 months, 94% of patients had <10% BCR-ABL transcript level with ponatinib, whereas only 68% achieved this with imatinib. This response rate is higher than what is observed with dasatinib or nilotinib. Clearly ponatinib is effective at producing deep responses. The major problem with ponatinib is arteriothrombotic events, with a significant proportion of patients (7%) experiencing this side effect with ponatinib versus 2% on the imatinib arm. Notably, this is after a short exposure, with a median follow-up of 5.1 months. Although ponatinib is a useful drug, we need to be mindful of the cardiovascular arteriothrombotic events.

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

continued

Investigator Commentary: EPIC — A Phase III Trial of Ponatinib versus Imatinib in Newly Diagnosed CP-CML (continued)

The cardiovascular adverse events with ponatinib seem to be similar to those observed with other TKIs but more frequent. In my practice, I involve a cardiologist from the beginning of any TKI therapy to help me address all these issues and minimize the risk for the patient. In the case of ponatinib, I start every patient on aspirin to decrease the risk of heart attack in individuals who are older. I am hoping that this approach will improve the safety in patients who need ponatinib.

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

Dasatinib or Nilotinib Discontinuation in Chronic Phase (CP)-Chronic Myeloid Leukemia (CML) Patients (Pts) with Durably Undetectable *BCR-ABL* Transcripts: Interim Analysis of the STOP 2G-TKI Study with a Minimum Follow-Up of 12 Months — On Behalf of the French CML Group Filmc[1]

Interim Analysis of a Pan European Stop Tyrosine Kinase Inhibitor Trial in Chronic Myeloid Leukemia: The EURO-SKI Study[2]

[1] **Rea D et al.**
Proc ASH 2014;Abstract 811.

[2] **Mahon F-X et al.**
Proc ASH 2014;Abstract 151.

Dasatinib or Nilotinib Discontinuation in Chronic Phase (CP)-Chronic Myeloid Leukemia (CML) Patients (Pts) with Durably Undetectable *BCR-ABL* Transcripts: Interim Analysis of the STOP 2G-TKI Study with a Minimum Follow-Up of 12 Months — On Behalf of the French CML Group Filmc

Rea D et al.

Proc ASH 2014;Abstract 811.

Background

- Tyrosine kinase inhibitors (TKIs) targeting BCR-ABL have revolutionized the prognosis for patients with CML.
- However, these TKIs are considered to be nondefinitively curative and the current recommendation is to treat during the patient's entire lifespan.
- Results from prospective trials such as STIM, TWISTER and EURO-SKI suggest that imatinib may be successfully discontinued for patients with deep and sustained molecular responses (*Lancet Oncol* 2010;11:1029; *Blood* 2013;122:515; *Proc ASH* 2013;Abstract 379).
- **Study objective:** To report the feasibility of discontinuing second-generation (2G) TKIs in the French STOP 2G-TKI study.

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Study Methods

- **Eligibility:**
  - Adult patients with CP-CML
  - Receiving first-line dasatinib or nilotinib
  - Receiving dasatinib or nilotinib after receiving imatinib without prior allogeneic transplantation or progression to advanced-phase CML
- Patients were offered TKI discontinuation when presenting with:
  - B2A2 or B3A2 BCR-ABL transcript subtype
  - TKI treatment duration for at least 36 months
  - Complete molecular response ($CMR^{4.5}$) achieved and maintained for at least 24 months
- **Primary objective:** Treatment-free survival without loss of major molecular response (MMR).

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Study Methods (continued)

- After TKI discontinuation, *BCR-ABL* transcripts were monitored monthly during the first 12 months, every 3 months during the second year and every 3 to 6 months thereafter.
- Molecular relapse was defined by MMR loss on a single occasion and triggered TKI reintroduction.
- Data as of August 1, 2014 are reported for patients with at least 12 months of follow-up (n = 52):
  - Median follow-up was 32 months (range, 12-56).

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Patient Characteristics

Characteristic	n = 52
Median age (range)	60 years (34-81)
Female	61.5%
Sokal risk group: low/intermediate/high Unknown	58%/23%/13% 6%
Received 2G-TKI: After imatinib intolerance After suboptimal response or resistance to imatinib As up-front therapy	67% 23% 10%

- Median duration of CML: 83 months
- Median duration of TKI therapy: 78 months
- Median duration of 2G-TKI therapy: 39 months
- Median duration of CMR$^{4.5}$: 28 months

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Response

- Patients who lost major molecular response (MMR) after a median of 4 months: n = 24.
- No loss of complete hematologic response or progression to advanced-phase CML was observed.
- Treatment-free survival (TFS) without MMR loss:
  - 12-month probability, 61.4%
  - 24-month probability, 57%
- The majority of relapses occurred within 6 months.
- Landmark analysis of patients who were still in MMR without therapy at 6 months:
  - 12-month probability of TFS without MMR loss, 91.2%
  - 24-month probability of TFS without MMR loss, 84.7%

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Response (continued)

- All but 1 patient who lost MMR restarted 2G-TKI therapy and regained MMR after a median time of 3 months (1-8).
- Patients who achieved MMR without any therapy (n = 28):
  - These patients displayed varying patterns of spontaneous molecular response, including
    - Stable $CMR^{4.5}$ (n = 7)
    - Fluctuations between $CMR^{4.5}$ and molecular response ($MR^{4.5}$) (n = 9)
    - Fluctuations between $CMR^{4.5}$ and MR^{4} (n = 4)
    - Fluctuations between $CMR^{4.5}$ and MMR (n = 4)

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Impact of Clinicopathologic Factors on Clinical Outcome

- Factors without any impact on outcome:
  - Gender
  - Age
  - Prior interferon exposure
  - Type of 2G-TKI therapy
  - Treatment duration
  - Duration of $CMR^{4.5}$
- By contrast, a history of suboptimal response or resistance to imatinib was associated with:
  - A significantly lower chance of successful treatment discontinuation
  - A lower 12-month probability of TFS without MMR loss:
    - 41.7% versus 67.3% for other patients ($p = 0.04$)

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Author Conclusions

- 2G-TKI therapy can be safely and successfully discontinued in patients with CP-CML with long-lasting undetectable BCR-ABL transcript levels
  - Especially in those without a history of suboptimal response or imatinib resistance.
- Most molecular relapses observed had an early onset, and all were sensitive to the resumption of 2G-TKI therapy.
- The recurrence of low levels of detectable residual disease below MMR after 2G-TKI withdrawal did not automatically herald CML relapse and did not preclude the possibility of remaining treatment free.

Rea D et al. *Proc ASH* 2014;Abstract 811 (Abstract only).

Investigator Commentary: Interim Analysis of the STOP 2G-TKI Trial After a Minimum of 12 Months of Follow-Up

This French group pioneered TKI discontinuation in CML and initially reported results from the STIM (Stop Imatinib) trial. In the STOP 2G-TKI study, the investigators assessed discontinuation after dasatinib or nilotinib administered first line or after failure of imatinib. In this study 61.4% of the patients remained relapse free in 12 months and 57% in 24 months. Consistent with the STIM results, this study demonstrated that some patients can maintain a good and durable remission — if not complete, at least a major molecular remission.

Investigators also evaluated factors that could predict the ability to maintain the remission. One identified factor is that a patient with CP-CML who has experienced true failure of or resistance to a prior drug is less likely to maintain a good response after treatment discontinuation. That's an important factor to keep in mind, that perhaps those patients are not the optimal candidates for treatment discontinuation, at least based on what we know today.

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

Interim Analysis of a Pan European Stop Tyrosine Kinase Inhibitor Trial in Chronic Myeloid Leukemia: The EURO-SKI Study

Mahon F-X et al.

Proc ASH 2014;Abstract 151.

Background

- The tyrosine kinase inhibitors (TKIs) have dramatically changed the natural history of chronic myeloid leukemia (CML), leading to significant improvement in clinical outcome and survival rates.
- Results from prospective trials suggest that imatinib therapy may be safely and successfully discontinued in patients with CML with deep and sustained molecular responses (*Lancet Oncol* 2010;11:1029; *Blood* 2013;122:515).
- **Study objective:** To define prognostic markers to increase the rate of durable deep molecular response after stopping a TKI in the European Leukemia Net Stop TKI (EURO-SKI) study.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Study Methods

- **Eligibility (8 countries): n = 200**
  - Adult patients with CML in chronic phase (CP) on TKI treatment
  - Achievement of confirmed deep molecular response (MR^4, BCR-ABL <0.01%) for ≥1 y **and**
  - Undergoing TKI therapy for ≥3 y
  - No patient with CP-CML after progression on TKI therapy
- MR^4 confirmation was performed in 6 standardized laboratories.
- **Primary endpoint:** Duration of molecular response (defined by continuous major molecular response) after discontinuation of a TKI.
- A planned interim analysis was performed after 200 patients with eligible molecular results at month 6 were available to test the null hypothesis that relapse-free survival at 6 months is ≤40%.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Patient Characteristics

Characteristic	n = 200
Median age at diagnosis (range)	53.3 years (13.8-85.5)
Female	41.5%
Sokal risk group: High	18.2%
Patients with pretreated* CML	103 (51.5%)

* Mostly with hydroxyurea or interferon

- Patients who had received first-line imatinib: 97%
- Patients who had received first-line dasatinib: 1.5%
- Patients who had received first-line nilotinib: 1.5%
- Patients who switched to second-line TKI therapy due to intolerance (n = 24):
  - To dasatinib (n = 16); to imatinib (n = 2); to nilotinib (n = 6)
- The median time from diagnosis of CML to TKI cessation was 8 years.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Duration of Treatment and Molecular Response

Duration	n = 200
TKI treatment duration of <5 years	16%
5-8 years	36%
>8 years	48%
MR^4 duration of <2 years	8%
2-5 years	37%
5-8 years	39%
>8 years	16%

- Median duration of TKI treatment: 8 years (range, 3-12.6)
- Median duration of MR^4 before TKI discontinuation: 5.4 years (range, 1-11.7)
- For all eligible patients, a standardized European laboratory confirmed MR^4 assessment
- Because 123 out of 200 patients (61.5%) remained without relapse after the first 6 months, the null hypothesis was discarded ($p < 0.0001$)

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Disease Recurrence and Determination of Prognostic Significance of Molecular Response

Patients with disease recurrence (loss of MMR)	**n/N (%)**
With treatment for <8 years	43/92 (47%)
With treatment for >8 years	23/87 (26%)
p-value	0.005
Patients with MR^4*	**n/N (%)**
With MR^4 at <5 years but lost MMR at ≤6 months	33/71 (46%)
Patients with MR^4 >5 years	28/87 (32%)
p-value	0.07

MMR = major molecular response

* There was a trend for prognostic significance of MR^4 duration.

- No significant difference was observed for relapse within 6 months according to depth of molecular response at discontinuation (MR^4 vs $MR^{4.5}$ vs MR^5).

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Safety and Costs Associated with Discontinuation of TKI Therapy

- The discontinuation of TKI therapy was a safe procedure, but a substantial proportion of patients reported transitory musculoskeletal pain starting within weeks of imatinib discontinuation.
  - This phenomenon was described in 30% of Swedish patients as a “TKI withdrawal syndrome” (*J Clin Oncol* 2014;32(25):2821-3).
- Taking into account the cost of imatinib in Europe and time without treatment in the total study population at the most recent analysis, total savings for the community within the EURO-SKI trial were estimated at 7 million euros.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Author Conclusions

- With the employment of standardized molecular testing for patient selection within a TKI discontinuation trial in CML, the probability of staying in treatment-free remission could be higher than previously reported.
- As previously reported in the STIM (Stop Imatinib) trial, the preliminary results from this study confirm the prognostic impact of the duration of TKI therapy before stopping.
- The EURO-SKI trial will further elucidate the prognostic factors in order to increase the rate of durable deep molecular response after stopping TKI therapy.

Mahon F-X et al. *Proc ASH* 2014;Abstract 151 (Abstract only).

Investigator Commentary: EURO-SKI — Interim Analysis of a Stop TKI Therapy Trial for Patients with CP-CML

This study focuses specifically on patients receiving a TKI as front-line therapy, whereas the STOP 2G-TKI study included patients who had received prior interferon or other drugs. A small cohort of patients switched TKIs because of intolerance but none because of resistance or disease progression on first-line TKI therapy. The patients were required to have a molecular response (MR^4). This allows even more disease detectable than $MR^{4.5}$, and MR^4 was only required to be sustained for at least 1 year. Relapse was defined as the loss of major molecular response.

The study demonstrated that 61.5% of the patients remained without relapse in the first 6 months. Six months is important because that is when the majority of relapses occur. In terms of the features predictive of a more durable response and the duration of treatment, patients who have received treatment for more than 8 years and those who have achieved deeper molecular responses for at least 5 years are less likely to experience relapse.

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

continued

Investigator Commentary: EURO-SKI — Interim Analysis of a Stop TKI Therapy Trial for Patients with CP-CML

In summary, the STOP 2G-TKI and EURO-SKI trials show that some patients can stop TKI treatment and maintain some level of response. Before we can start applying this strategy to all our patients, we need to know the kind of response that the patients are achieving and understand that there has to be a strong commitment to monitoring the patients closely after they discontinue TKI therapy. This is because in this series the investigators have not reported any loss of hematologic responses or transformations. If care is not taken immediately and a patient experiences relapse without us recognizing what has occurred, it is likely that the disease will come back in a more aggressive form. This is an important factor to note, that TKI therapy discontinuation should be performed only on a clinical trial with careful and close monitoring.

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