5 Minute JournalClub

Key ASH Presentations

Issue 4, 2012

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CME Information

LEARNING OBJECTIVES

- Counsel patients with JAK2 mutation-positive and mutation-negative myelofibrosis about the benefits and risks of ruxolitinib treatment.
- Recall ongoing clinical trials with new agents for the treatment of myeloproliferative neoplasms, and consent or refer appropriate patients for participation.

CREDIT DESIGNATION STATEMENT

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CME Information (Continued)

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:

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No real or apparent conflicts of interest to disclose.

Consistent Benefit of Ruxolitinib Over Placebo in Spleen Volume Reduction and Symptom Improvement Across Subgroups and Overall Survival Advantage: Results from COMFORT-I

Verstovsek S et al.

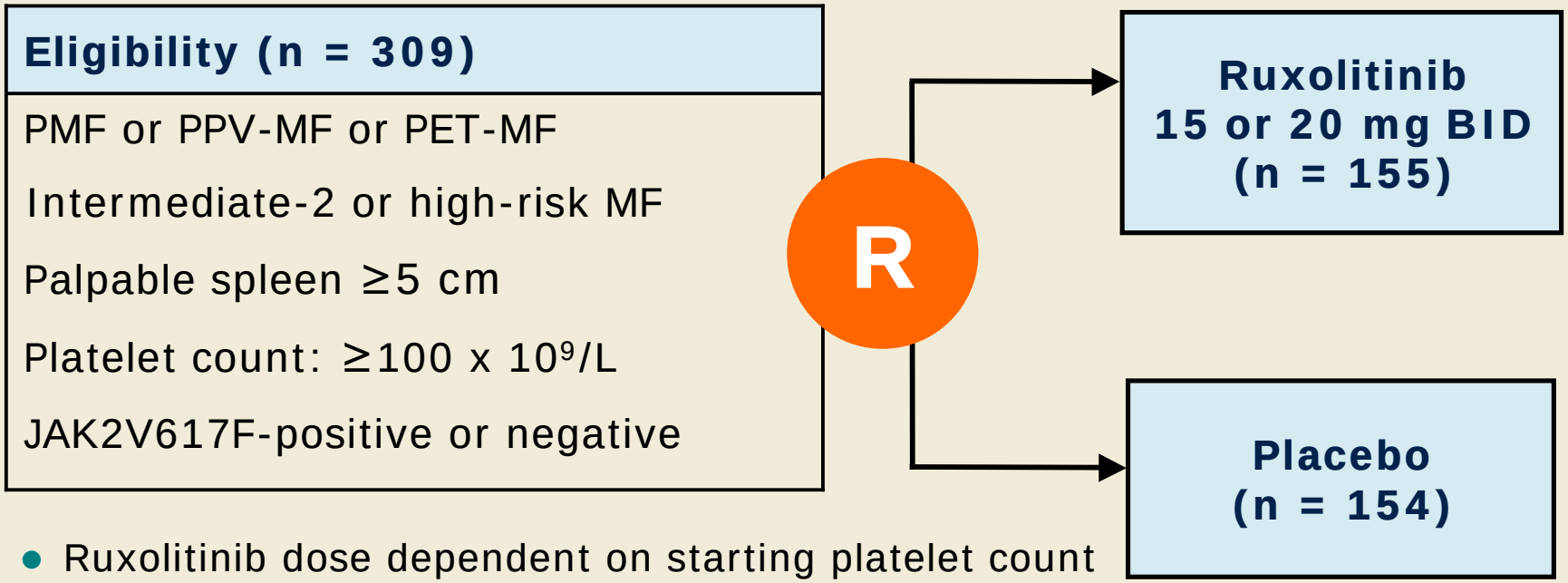
Proc ASH 2011;Abstract 278.

Background

- Dysregulated JAK-STAT signaling resulting from gain-of-function mutations such as JAK2V617F and/or increased levels of circulating inflammatory cytokines plays a key role in the pathogenesis of myelofibrosis (MF).
- MF manifests as primary MF (PMF), postpolycythemia vera MF (PPV-MF) or postessential thrombocythemia MF (PET-MF).
- Ruxolitinib, a selective inhibitor of JAK1 and 2, has demonstrated clinical activity in MF including the reduction in spleen volume and improvements in MF-related symptoms in the COMFORT-I double-blind placebo-controlled trial (*Proc ASCO* 2011;Abstract 6500).
- **Objective:**
  - Assess the efficacy of ruxolitinib across patient subgroups and update overall survival (OS) in the COMFORT-I trial.

Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

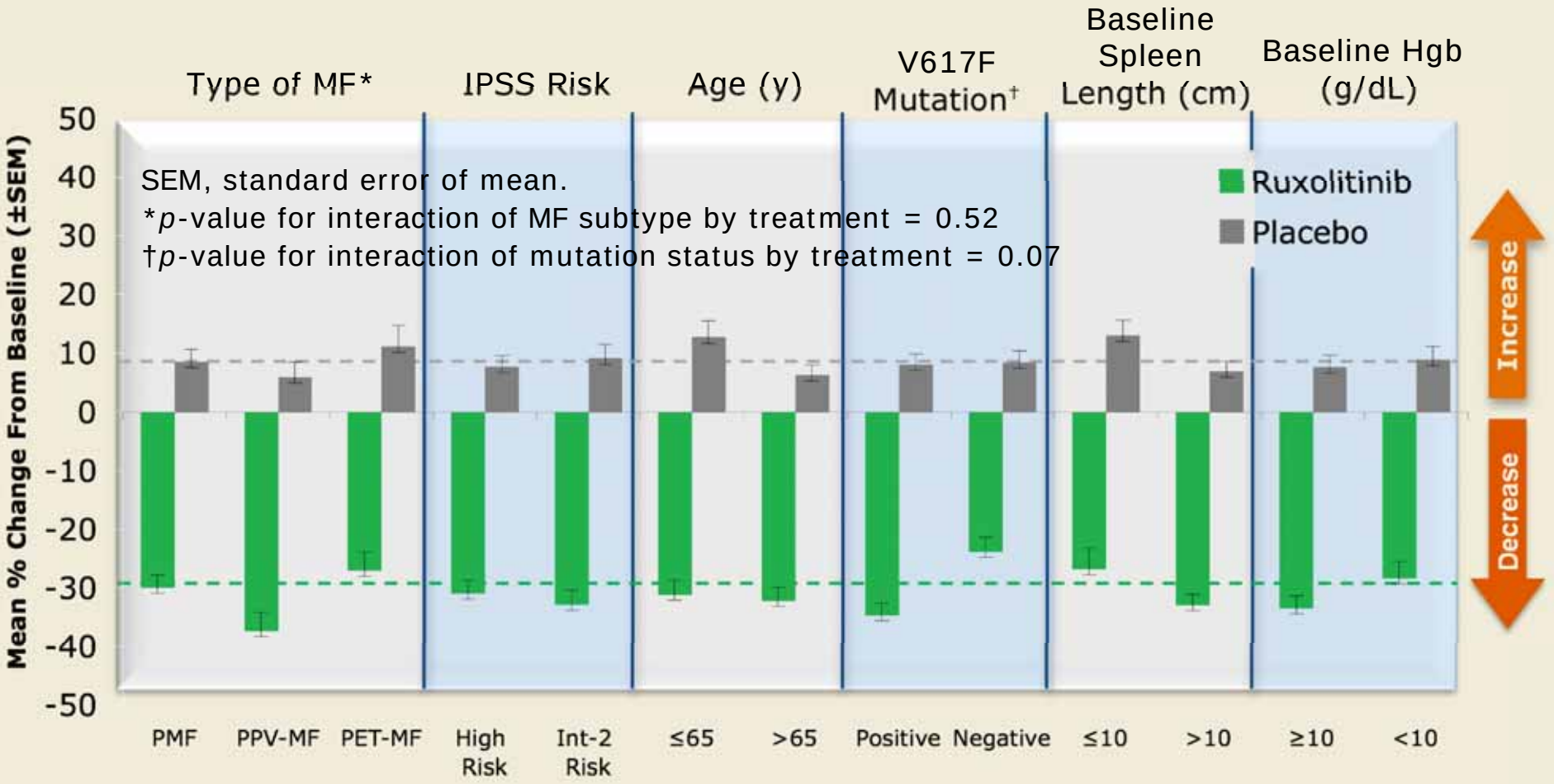
COMFORT-I Study Design



- Ruxolitinib dose dependent on starting platelet count
  - 15 mg BID for platelet count: 100-200 x 10^9/L
  - 20 mg BID for platelet count: >200 x 10^9/L
- Spleen volume (SV) was measured by MRI every 12 weeks
- Crossover from placebo to ruxolitinib was allowed prior to week 24
- Daily assessment of symptoms from day -7 through week 24
- Total symptom score (TSS): sum of all symptom scores except inactivity

Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

SV: Percent Change from Baseline to Week 24



Dashed lines represent the mean percent change from baseline for overall treatment group

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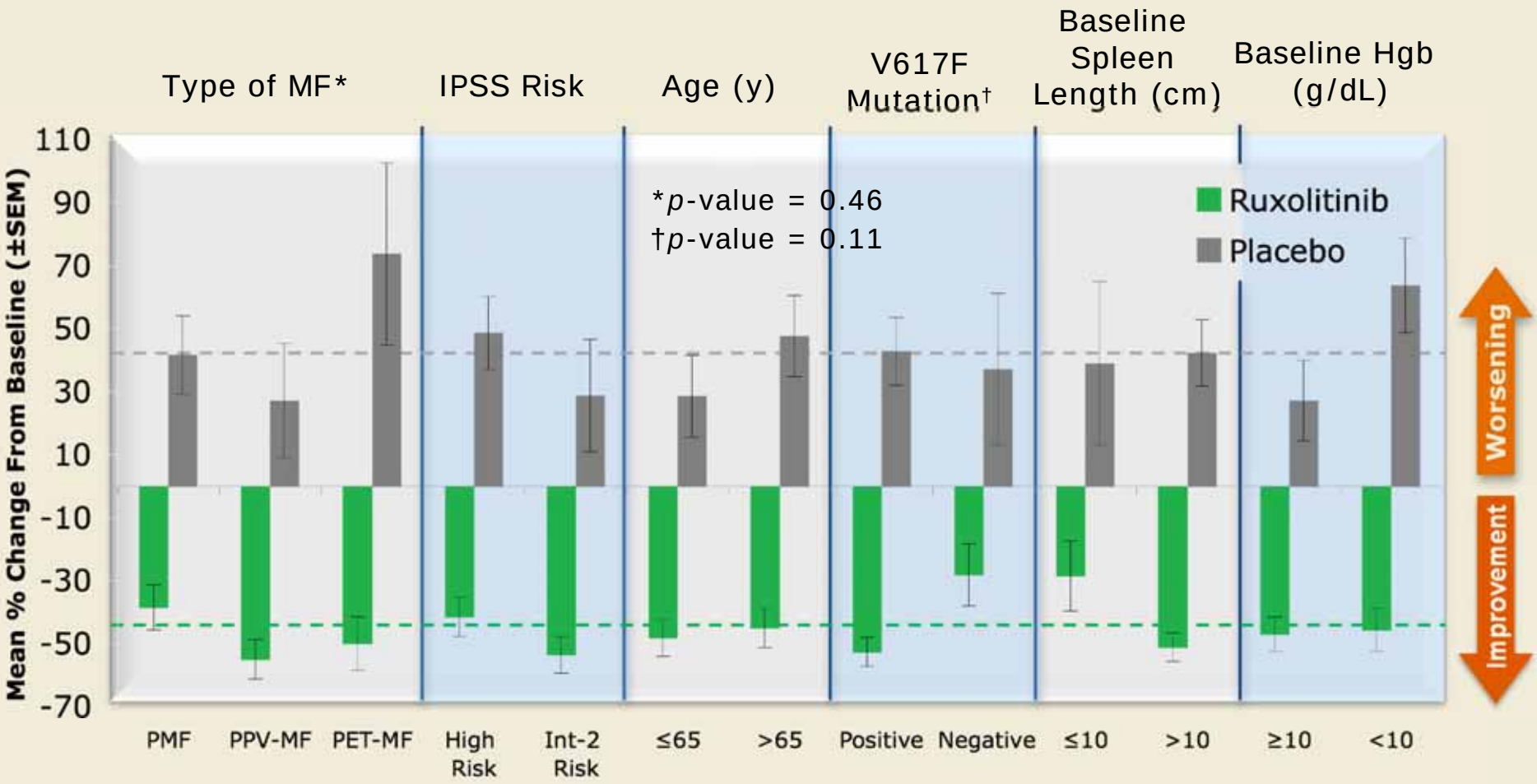
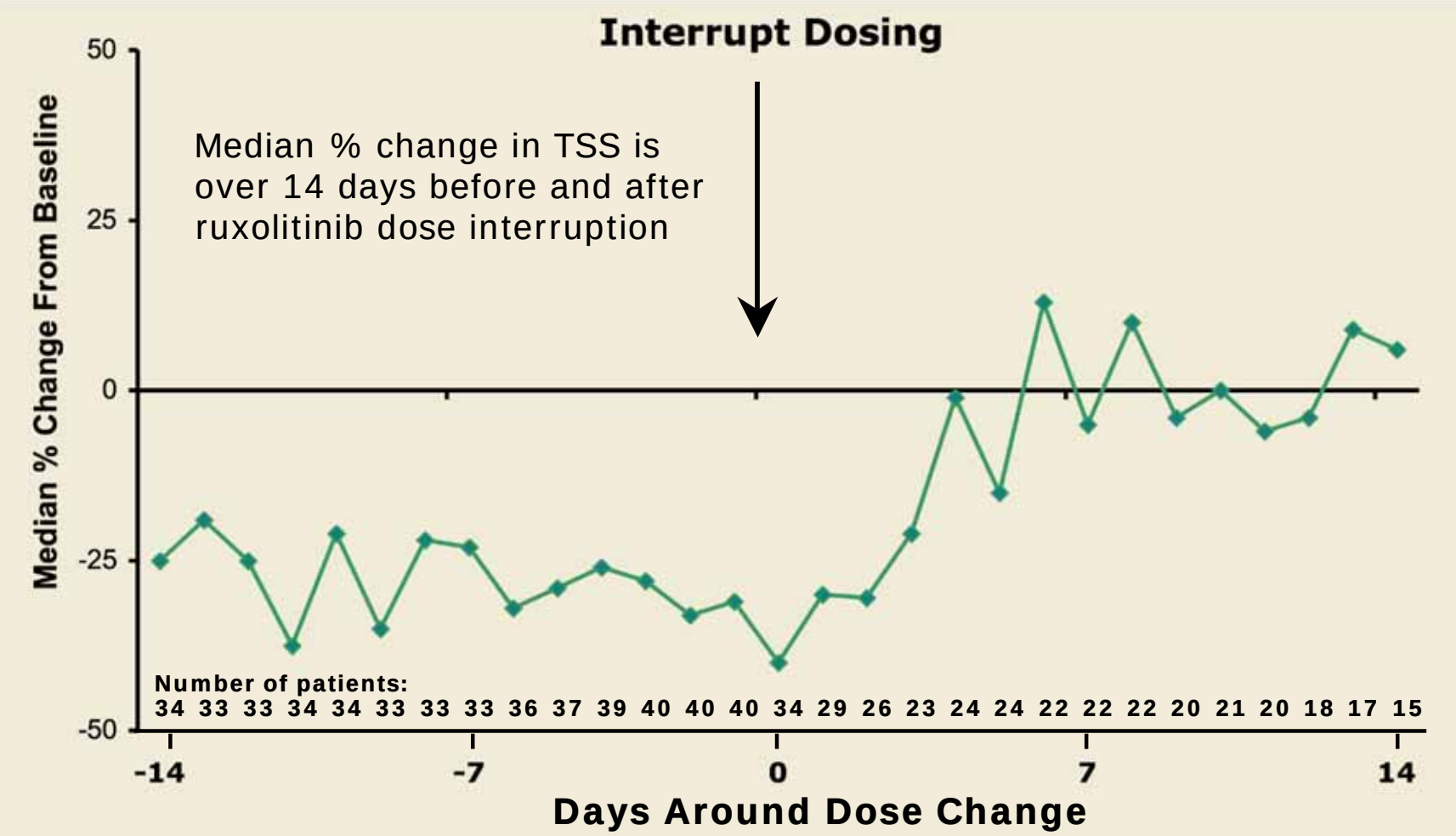
TSS: Percent Change from Baseline to Week 24



Dashed lines represent the mean percent change from baseline for overall treatment group

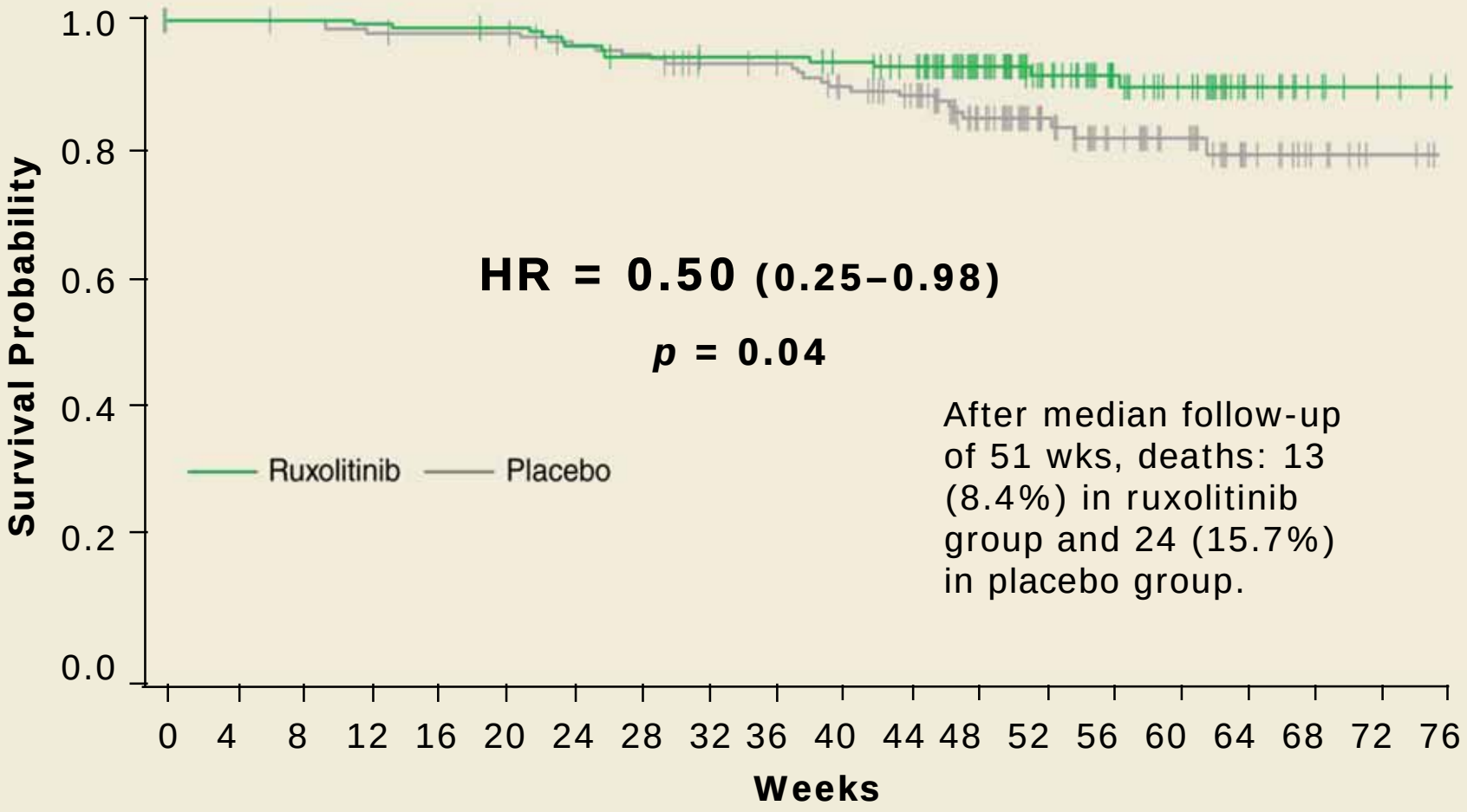
With permission from Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

TSS After Therapy Interruption: Symptoms Return to Baseline in ≤7 d



With permission from Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

OS Update: Intention-to-Treat Population



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Conclusions

- Ruxolitinib treatment yielded benefits across all subgroups.
- After dose interruption, MF-related symptoms gradually returned to baseline levels.
- This updated analysis of the COMFORT-I trial shows a significant overall survival benefit with ruxolitinib treatment.

Verstovsek S et al. *Proc ASH* 2011;Abstract 278.

Investigator Commentary: Benefit of Ruxolitinib over Placebo: Results from COMFORT-I

COMFORT I was the first study in the development of ruxolitinib and one of the studies that led to its FDA approval. The majority of patients exposed to ruxolitinib showed a significant decrease in SV and TSS improvements. The benefits are durable because this JAK1/2 inhibitor controls the underlying abnormality. Every patient with MF has dysregulation in the JAK/STAT pathway. The disease has 16 or more different mutations, and half of the patients have the JAK2V617F mutation. Ruxolitinib is active in patients with or without the JAK2 mutation. The most common side effects of ruxolitinib are treatment-emergent thrombocytopenia and anemia and require dose modification. When therapy is stopped the symptoms return to baseline. Hence we suggest therapy be tapered off.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

This study showed that ruxolitinib provided a significant advantage in terms of enhancing the quality of life by reducing symptoms and improving survival. The survival advantage was a positive finding and suggests ruxolitinib is an important breakthrough for MF. The improvement in quality of life suggests that this drug will be the standard of care for patients with MF.

Interview with Hagop M Kantarjian, MD, January 13, 2012

Ruxolitinib Provides Reductions in Splenomegaly Across Subgroups: An Analysis of Spleen Response in the COMFORT-II Study

Harrison CN et al.

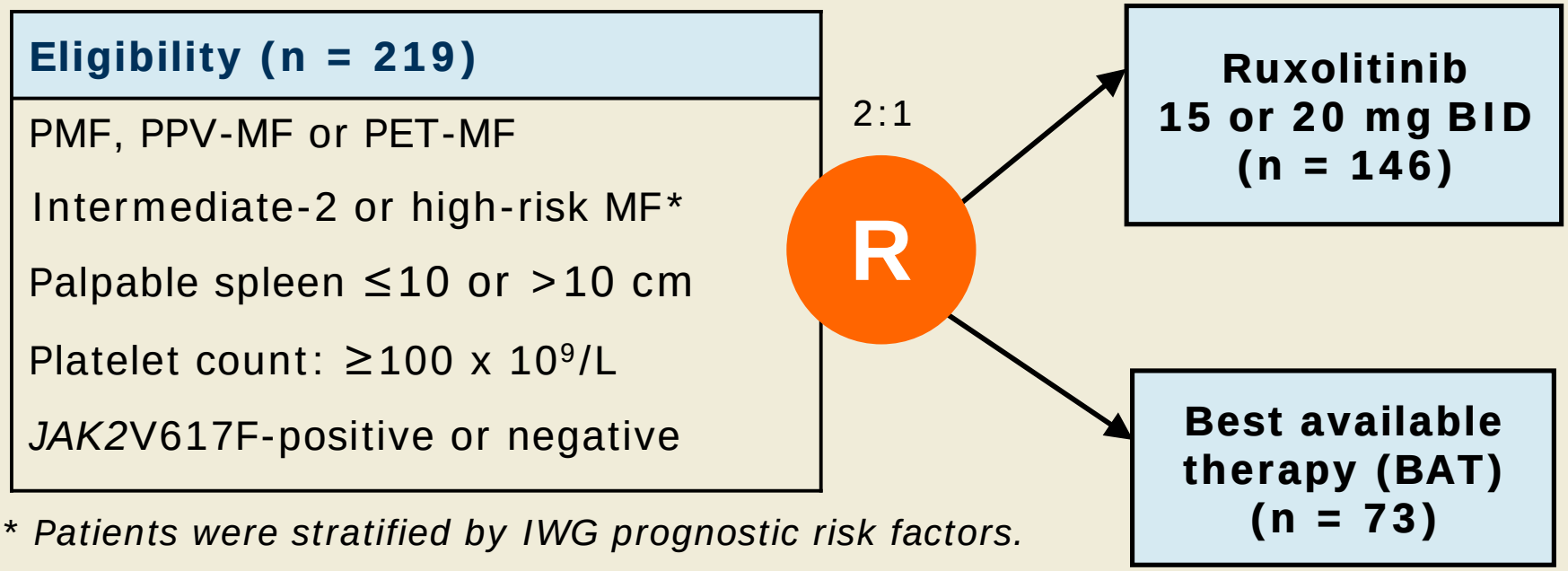
Proc ASH 2011;Abstract 279.

Background

- Ruxolitinib is a potent and selective inhibitor of JAK-STAT signaling that has demonstrated clinical benefits in patients with myelofibrosis (MF):
  - Reduction in splenomegaly, improved disease-related symptoms and quality of life (*Proc ASCO* 2011;Abstract 6500)
  - Prolonged overall survival (*Proc ASH* 2011;Abstract 278)
- MF manifests as primary MF (PMF), postpolycythemia vera MF (PPV-MF) or postessential thrombocythemia MF (PET-MF).
- **Current Study Objective:**
  - Perform subgroup analyses of ruxolitinib-treated patients achieving primary and key secondary endpoints on the COMFORT-II trial

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

COMFORT-II Study Design

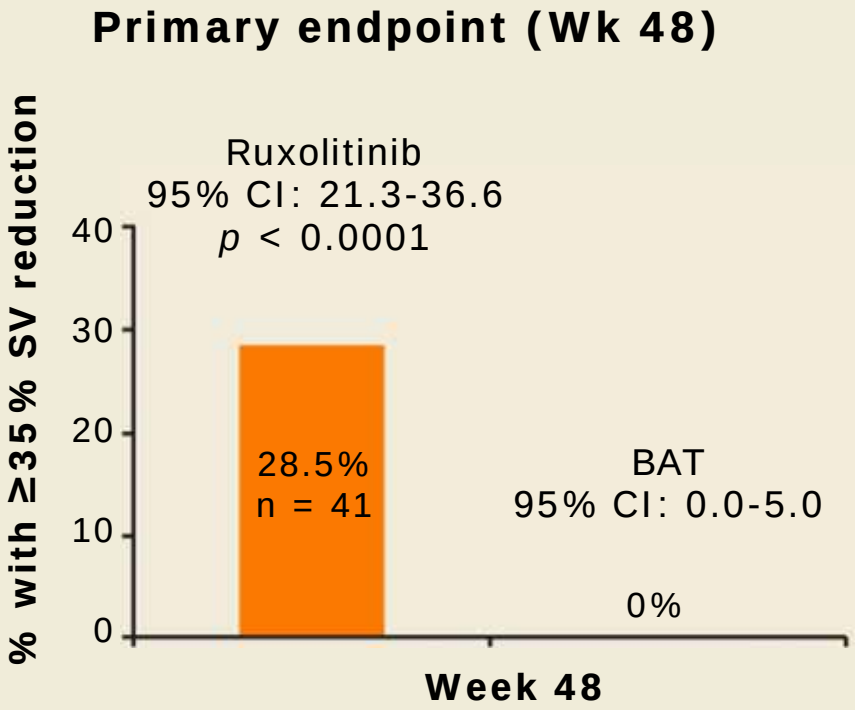


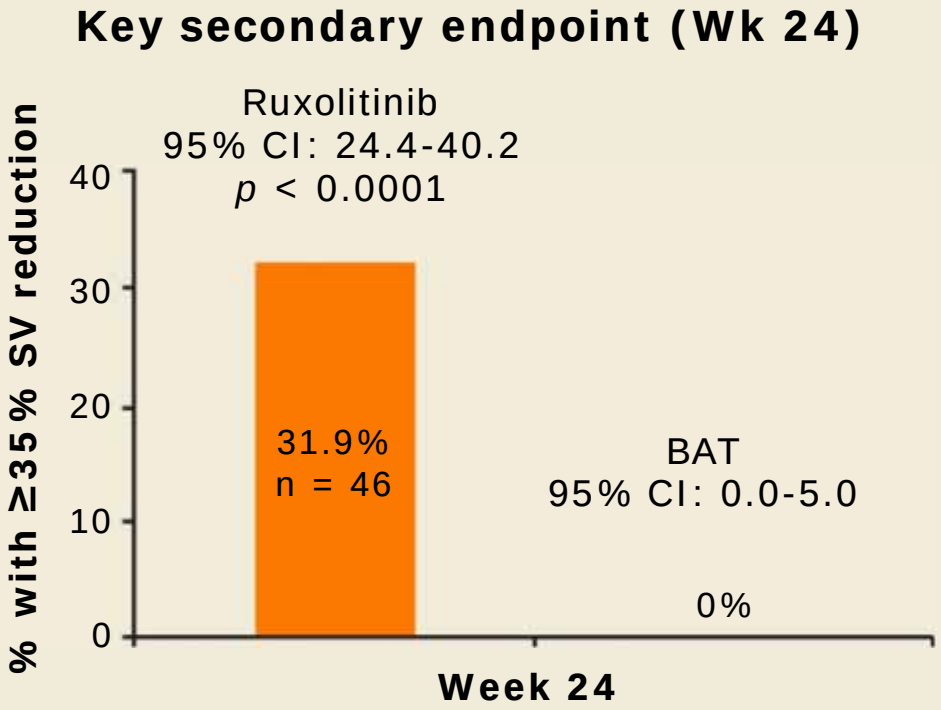
* *Patients were stratified by IWG prognostic risk factors.*

- Ruxolitinib dose dependent on starting platelet count:
  - 15 mg BID for platelet count 100-200 x 10^9/L
  - 20 mg BID for platelet count >200 x 10^9/L
- Patients on ruxolitinib with progressive disease were eligible for extension phase
- Crossover from BAT to ruxolitinib was allowed for patients with progressive disease

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

Primary and Key Secondary Endpoints

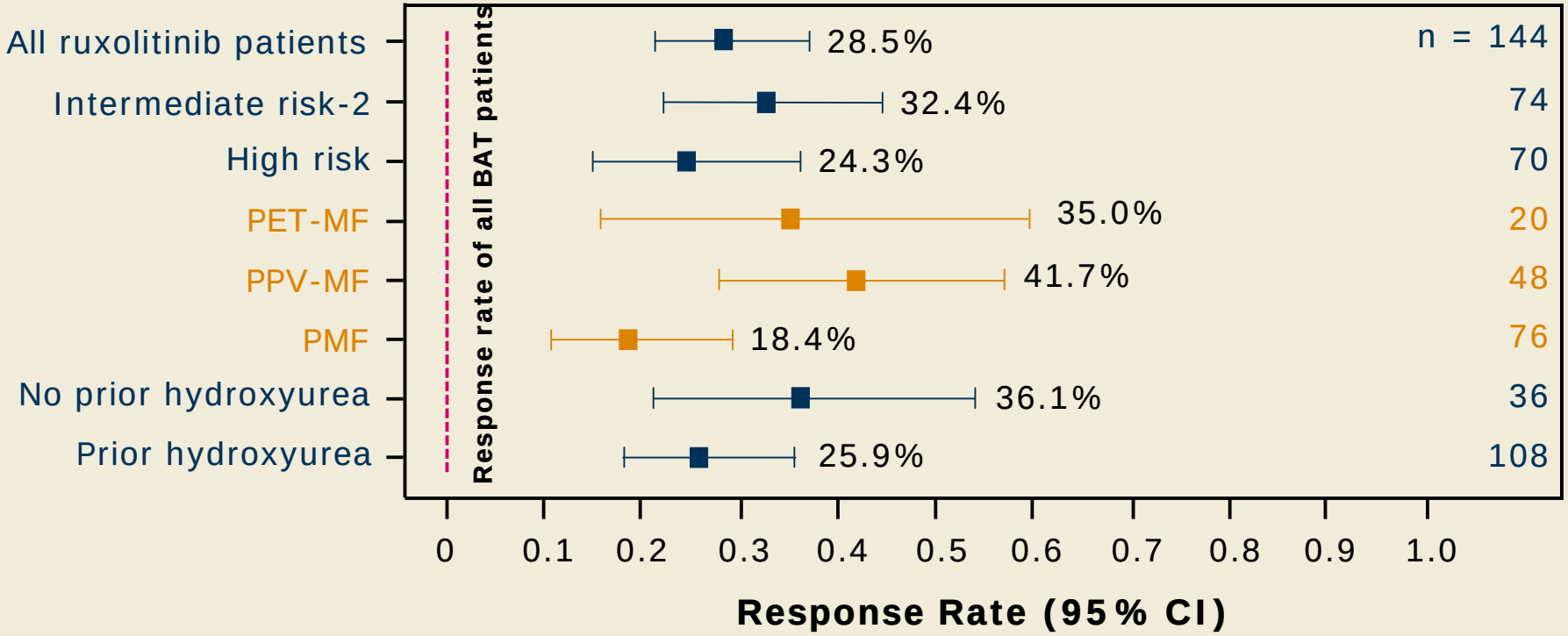




- Spleen volume (SV) was measured by MRI or CT for patients unable to undergo MRI.
- Median time to response was 12.3 weeks.
- Of 69 patients who achieved ≥35% reduction in SV during the study, 64% did so at the first assessment.

Harrison CN et al. *Proc EHA* 2011;Abstract 1020.

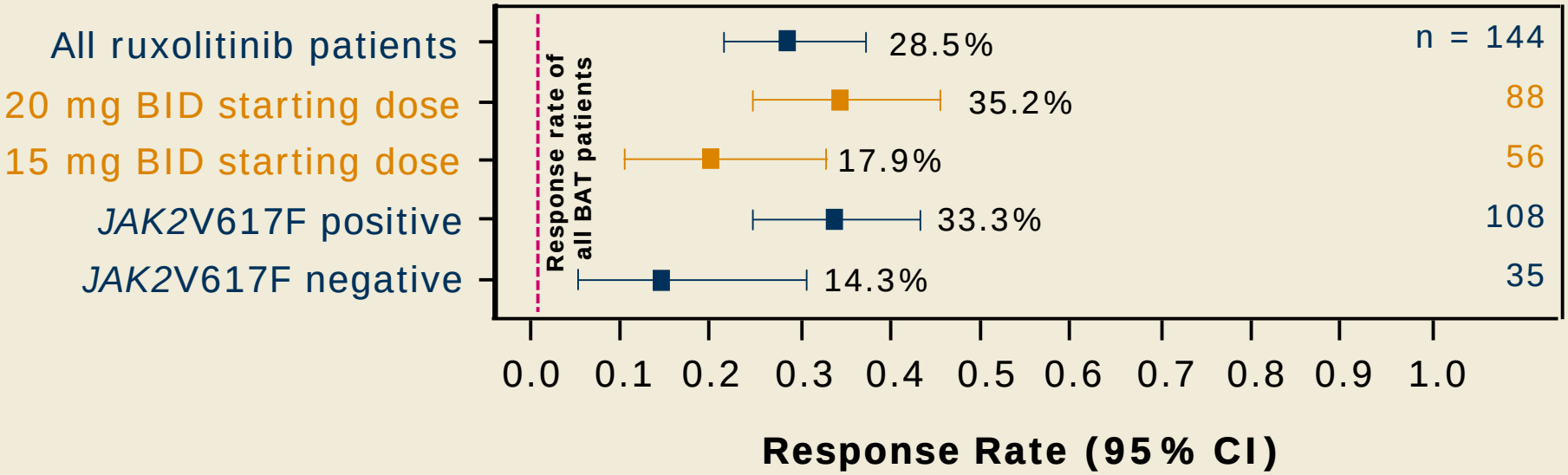
Proportion of Patients in Each Subgroup with ≥35% Reduction in SV from Baseline at Week 48



No significant differences in response rates among patients by MF risk category, MF subtype or prior exposure to hydroxyurea

With permission from Harrison CN et al. *Proc ASH* 2011;Abstract 279.

Proportion of Patients in Each Subgroup with ≥35% Reduction in SV from Baseline at Week 48



- Although statistically insignificant, there were some differences in response rates among patients based on starting ruxolitinib dose and *JAK2*V617F mutation status.

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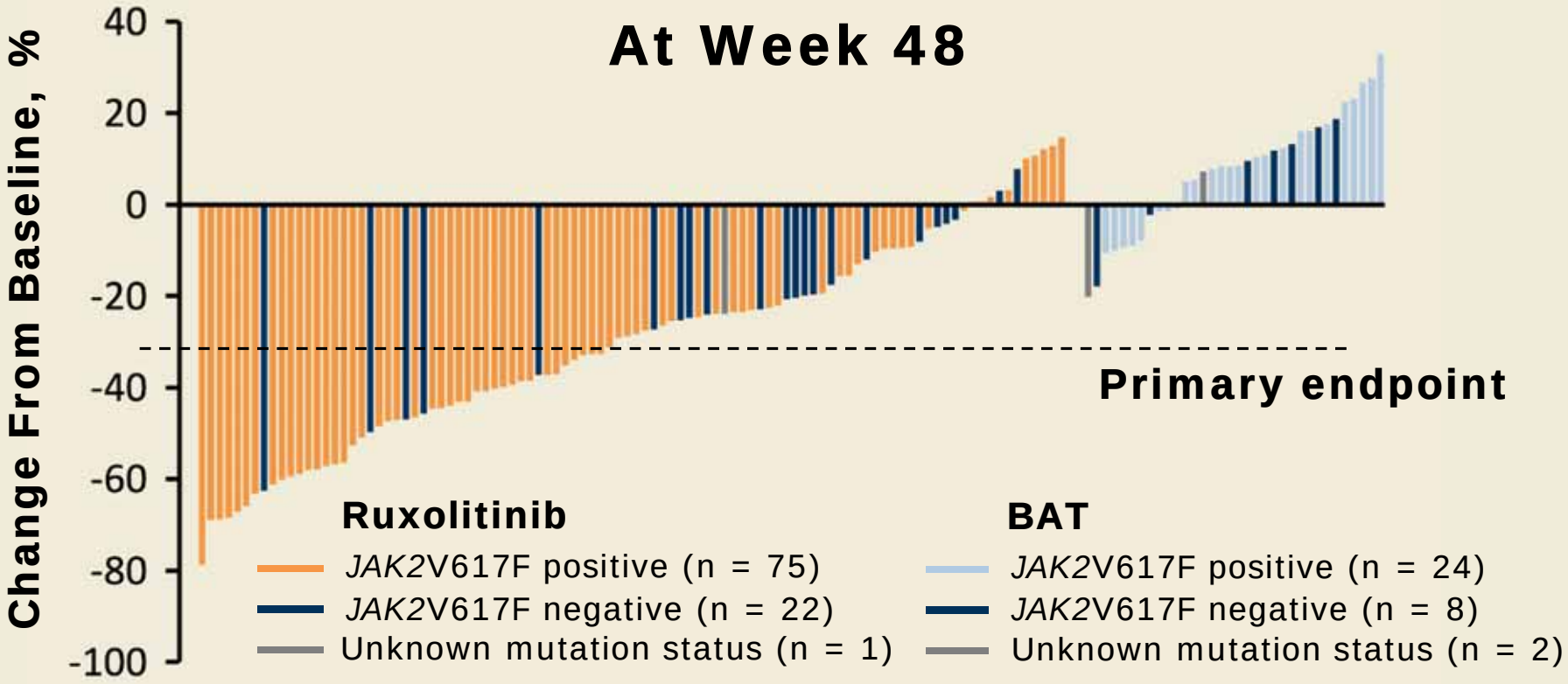
Percent Change from Baseline in SV by *JAK2*V617F Mutation Status



At week 48, the majority of patients receiving ruxolitinib experienced reductions in SV, including those with *JAK2*V617F-positive (88%) and negative (91%) mutation status.

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Multivariate Analysis

Predictive factor for response at 48 weeks	Odds ratio	95% CI
Starting dose (15 vs 20 mg BID)	0.441	0.184-1.055
Gender (female vs male)	1.646	0.726-3.732
Age (≤65 vs >65 years)	0.911	0.389-2.135
Baseline MF type: PMF vs PET-MF	**0.237**	**0.063-0.891**
With vs without prior hydroxyurea use	2.521	0.964-6.595
Baseline palpable spleen length (≤10 vs >10 cm)	0.419	0.166-1.058
*JAK2*V617F mutation (negative vs positive)	0.383	0.112-1.310
High vs intermediate-2 risk	0.640	0.268-1.531

Odds ratio <1: Lower chance for response compared to reference
Odds ratio >1: Higher chance for response compared to reference

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

Author Conclusions

- In this trial, 28.5% of patients who received ruxolitinib achieved ≥35% reduction in SV from baseline compared to 0% of patients who received BAT ($p < 0.0001$).
- The results of a univariate subgroup analysis demonstrated that ruxolitinib was more effective than BAT at decreasing SV regardless of gender, age, mutation status, IWG risk category, baseline spleen size or ruxolitinib starting dose (data not shown).
- Multivariate analysis suggests an increase in response rate among patients with PET-MF in comparison to those with PMF.
  - Trends were noted for starting dose, palpable spleen length and *JAK2*V617F mutation status.

Harrison CN et al. *Proc ASH* 2011;Abstract 279.

Investigator Commentary: Ruxolitinib Provides Reduction in Splenomegaly Across Subgroups — COMFORT-II Study

Based on the results obtained from the COMFORT-I and COMFORT-II studies, I believe JAK2 inhibitors, including ruxolitinib, will become the established standard for the treatment of MF. The survival advantage reported in the COMFORT-I study added to the notion that ruxolitinib is an important treatment for MF.

Interview with Hagop M Kantarjian, MD, January 13, 2012

The results reported in this study are similar to what was seen in the COMFORT-I trial. Large improvements were observed in spleen size and symptoms for patients receiving ruxolitinib. Best available therapy did not provide any benefit. The spleen has a tendency to respond better to a higher dose. There is a dose response for spleen shrinkage but no dose response for symptom improvement. Patients can expect to feel better within 2 to 4 weeks after starting therapy, and the most benefit will be experienced within 2 to 3 months. Symptoms — weakness, fatigue, bone action pains, itching, sweating — are well controlled with ruxolitinib.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

Comparison of Outcomes of Advanced Myelofibrosis Patients Treated with Ruxolitinib (INCB018424) to Those of a Historical Control Group: Survival Advantage of Ruxolitinib Therapy

Verstovsek S et al.

Proc ASH 2011;Abstract 793.

Background

- Myelofibrosis (MF) is a myeloproliferative neoplasm associated with splenomegaly, cytopenias and fibrosis of the bone marrow.
- Ruxolitinib is a JAK1/2 inhibitor with established clinical benefit in the treatment of MF by improving spleen size and quality of life (*NEJM* 2010;363(12):1117).
- Patients with high-risk MF, in particular, demonstrate poor outcomes with a median survival of 2 years (*Am J Hematol* 2011;86(12):1017).
- **Objectives:**
  - Compare survival outcomes of patients with MF receiving ruxolitinib to those of a matched historical control group.
  - Determine the long-term durability of reductions in spleen size and improvements in symptoms with ruxolitinib.

Verstovsek S et al. *Proc ASH* 2011;Abstract 793.

Patient Characteristics

MDACC Phase I/II study cohort (n = 107)	Historical control cohort (n = 310)
PMF or PPV-MF or PET-MF Newly diagnosed with intermediate- to high-risk MF Required therapy including those refractory or intolerant to prior therapy ECOG PS ≤2	Identified from 3 large databases of patients with MF – MD Anderson Cancer Center (MDACC) – University of Pavia, Italy – Hospital Niguarda ca' Granda, Milan, Italy Matched to MDACC cohort based on eligibility criteria of the Phase I/II trial that evaluated the efficacy and safety of ruxolitinib (*NEJM* 2010;363(12):1117).

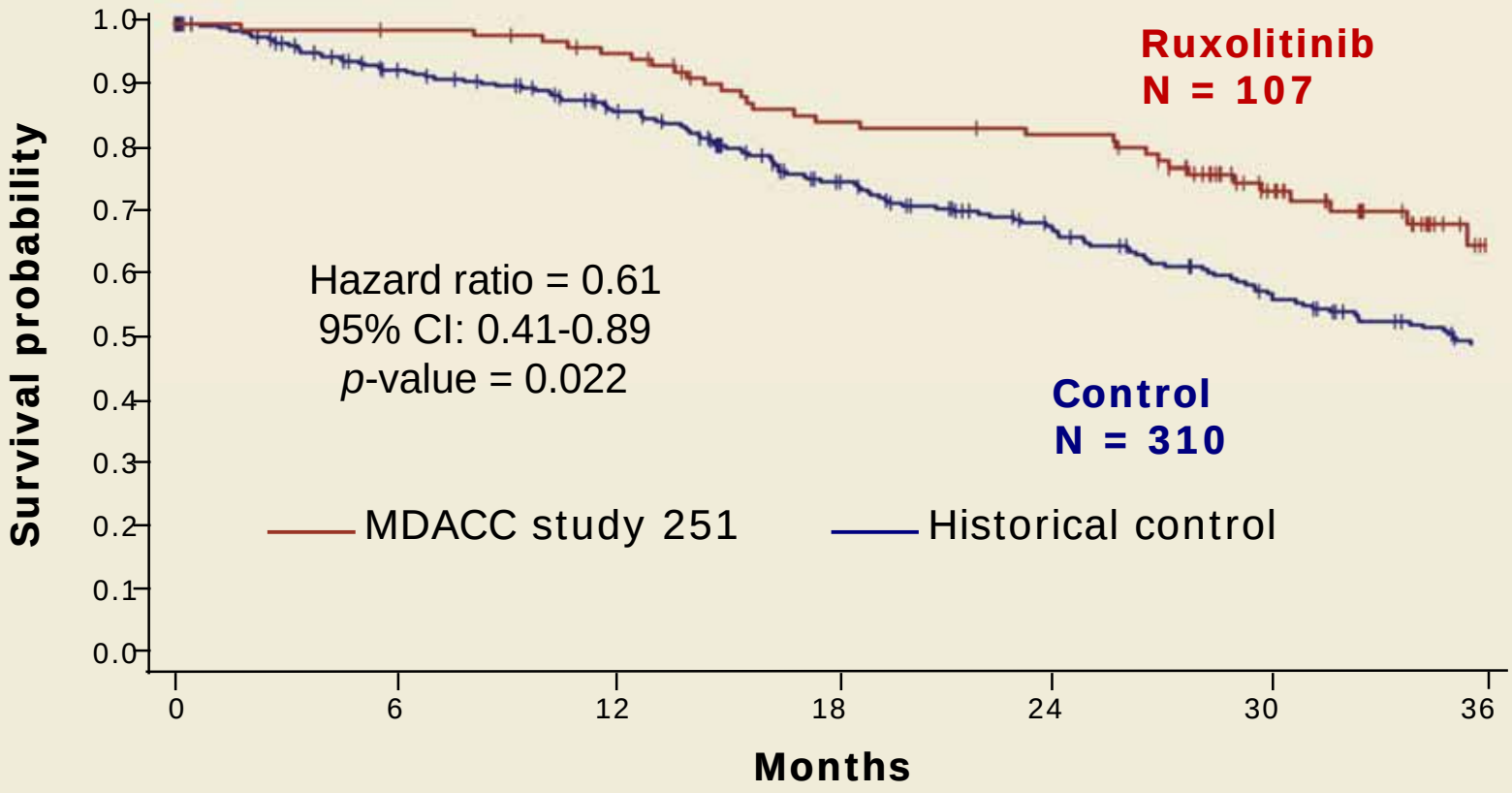
Verstovsek S et al. *Proc ASH* 2011;Abstract 793.

Baseline Demographics

	MDACC cohort (n = 107)	Historical cohort (n = 310)
Treatment	**Ruxolitinib**	**Conventional or investigational therapies**
IPSS risk category High Intermediate-2 Intermediate-1	 59% 32% 9%	 53% 47% 0%
Median palpable spleen length	19 cm	6 cm
Median platelet count	277 x 10^9/L	265 x 10^9/L

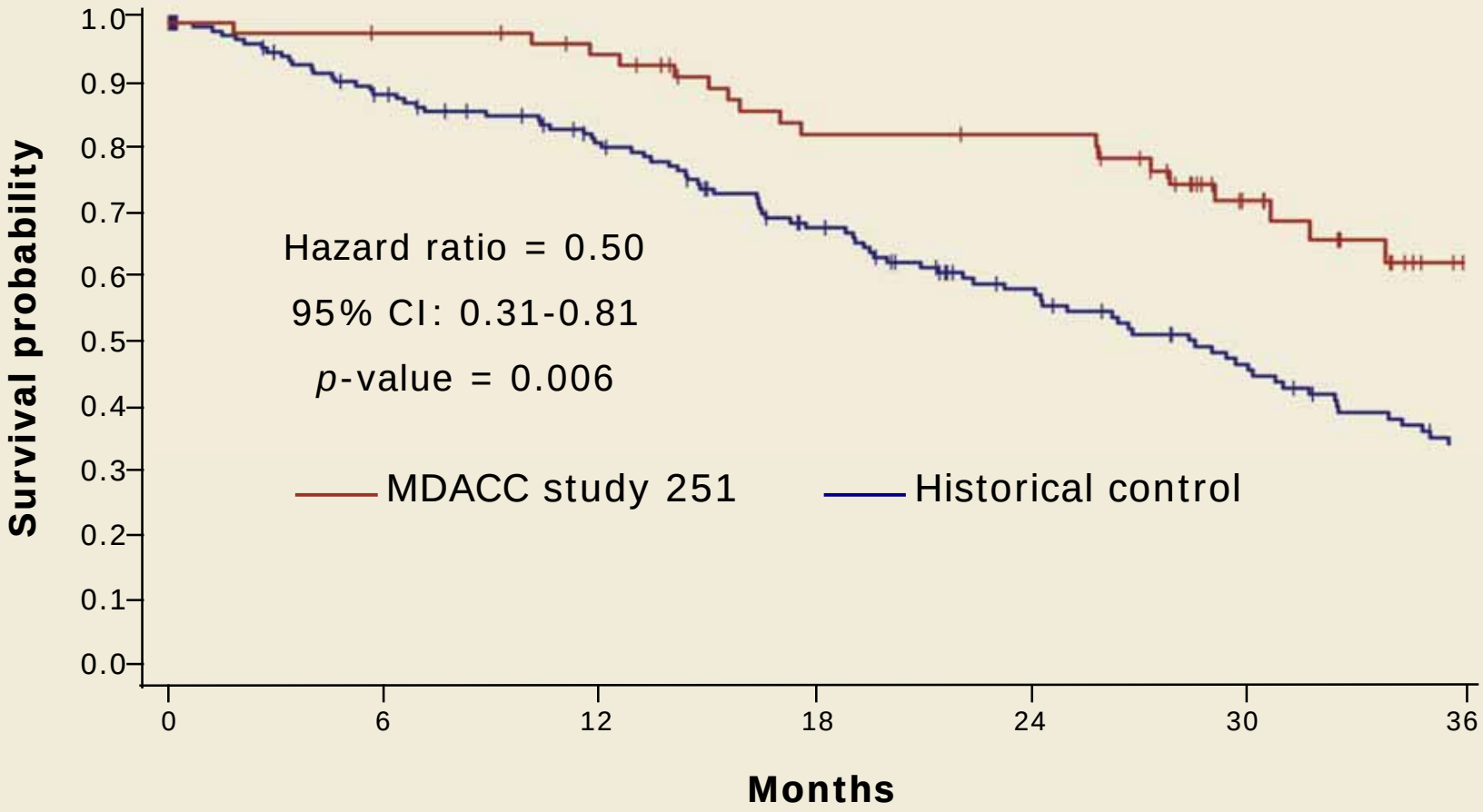
Verstovsek S et al. *Proc ASH* 2011;Abstract 793.

Overall Survival (OS): MDACC Study Cohort vs Historical Cohort



With permission from Verstovsek S et al. *Proc ASH* 2011;Abstract 793.

OS: MDACC vs Historical Category (High-Risk Category)



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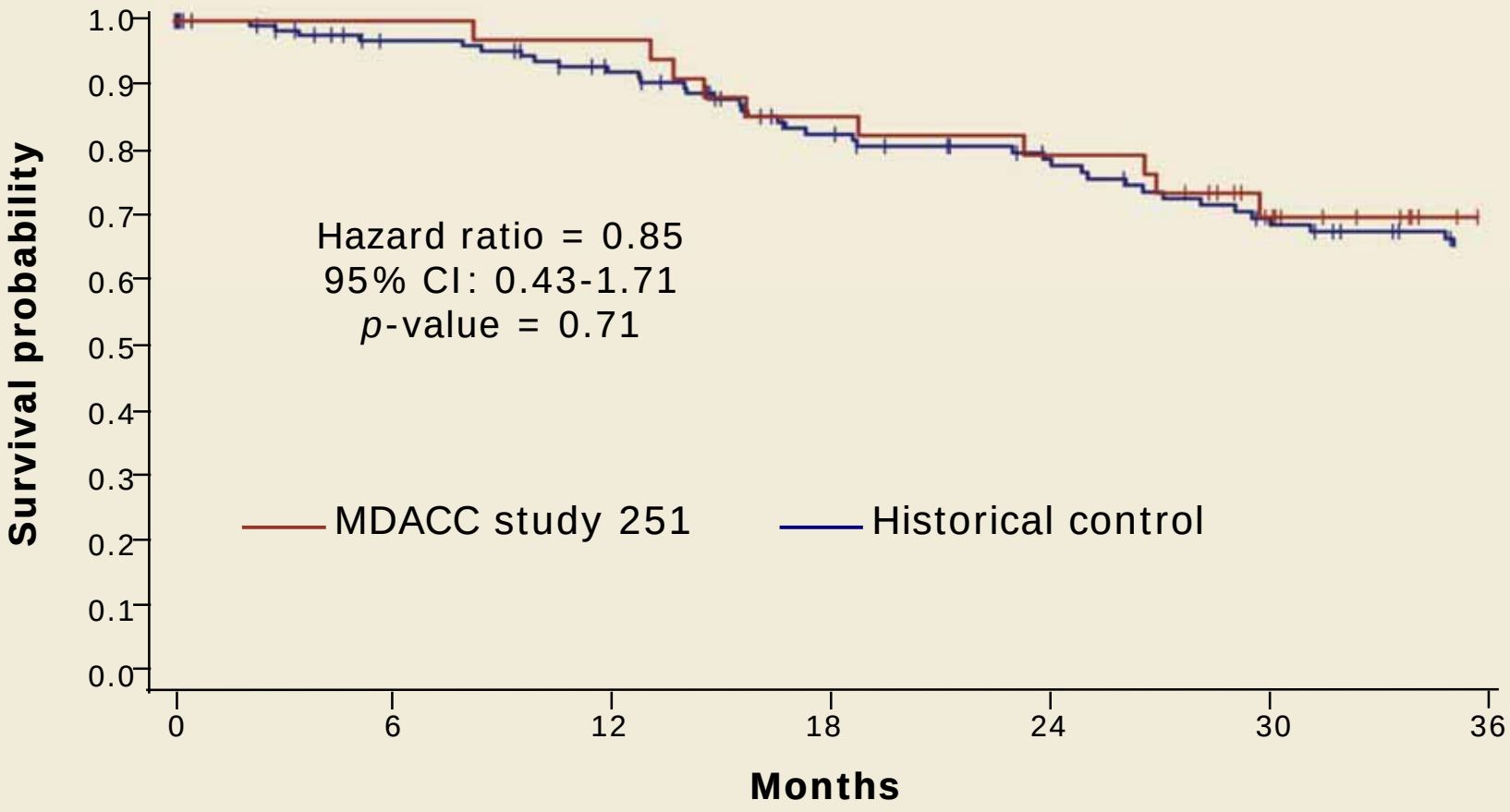
OS: MDACC vs Historical (Intermediate-2 Risk Category)



With permission from Verstovsek S et al. *Proc ASH* 2011;Abstract 793.

Author Conclusions

- Ruxolitinib demonstrated durable reductions in spleen size and myelofibrosis symptoms in the MDACC cohort.
- Fewer deaths in the MDACC ruxolitinib-treated patient cohort were observed than in the historical group of patients.
- After a median follow-up period of 32 months, ruxolitinib was well tolerated in the MDACC cohort.
- The overall survival analysis demonstrated clinical benefits with ruxolitinib treatment over the matched historical control cohort ($p = 0.022$).

Verstovsek S et al. *Proc ASH* 2011;Abstract 793.

Investigator Commentary: Outcomes among Patients with Advanced Myelofibrosis Treated with Ruxolitinib versus Historical Control

The clinical benefits of ruxolitinib in MF are durable because it inhibits JAK1/JAK2, the underlying abnormality of the disease. All patients with MF have dysregulated JAK-STAT pathways for one reason or another, whereas half of the patients exhibit a mutation in the JAK2 tyrosine kinase enzyme. Many of these patients with genetic mutations/abnormalities in the JAK-STAT pathway have multiple mutations, which led to an underlying dysfunction in signaling. Therefore, ruxolitinib is beneficial in controlling the signs and symptoms of MF in patients with or without JAK2 mutations and regardless of the characteristics of the patient subgroup.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

Results of a Phase II Study of Pacritinib (SB1518), a Novel Oral JAK2 Inhibitor, in Patients with Primary, Post-Polycythemia Vera, and Post-Essential Thrombocythemia Myelofibrosis[1]

SAR302503: Interim Safety, Efficacy and Long-Term Impact on JAK2 V617F Allele Burden in a Phase I/II Study in Patients with Myelofibrosis[2]

[1]Komrokji RS et al.
Proc ASH 2011;Abstract 282.

[2]Pardanani A et al.
Proc ASH 2011;Abstract 3838.

Results of a Phase II Study of Pacritinib (SB1518), a Novel Oral JAK2 Inhibitor, in Patients with Primary, Post-Polycythemia Vera, and Post-Essential Thrombocythemia Myelofibrosis

Komrokji RS et al.

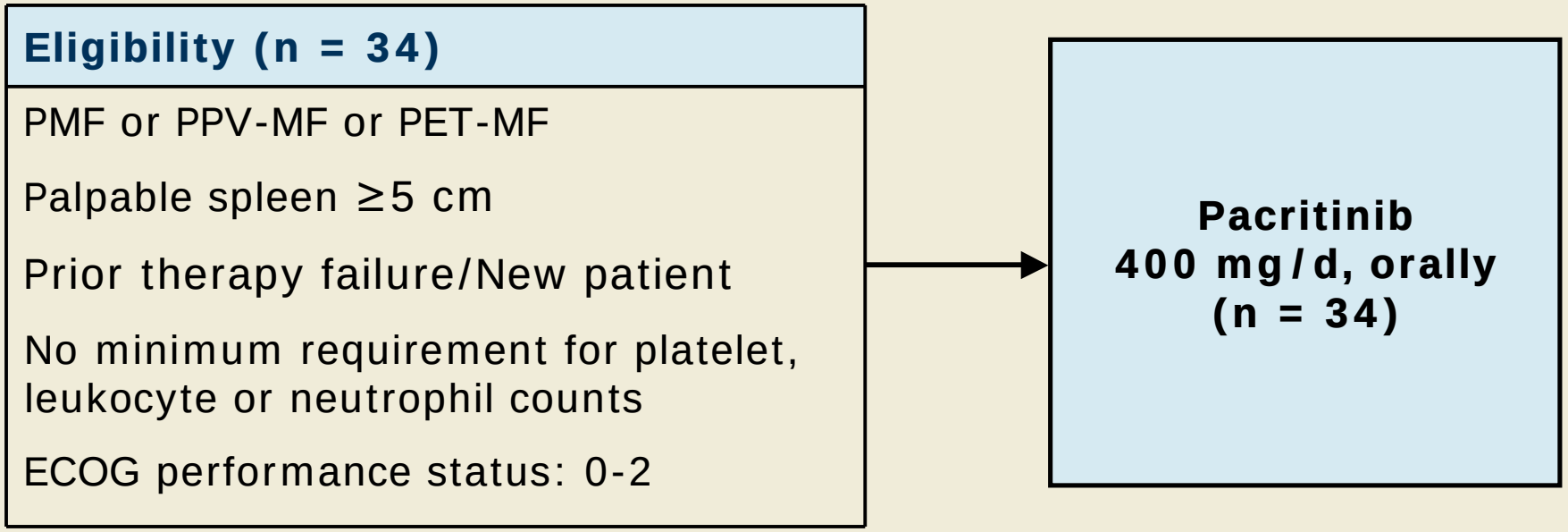
Proc ASH 2011;Abstract 282.

Background

- The JAK2V617F mutation is associated with myelofibrosis (MF).
- Pacritinib is a potent inhibitor of both wild-type JAK2 and the JAK2V617F mutant form.
- Previous Phase I studies showed that pacritinib was well tolerated with meaningful clinical benefit and an acceptable safety profile in patients with MF (ASH 2009;Abstract 3905; ASH 2010;Abstract 3082).
- **Objective:**
  - Assess the spleen response rate (SRR), duration of spleen response, safety, tolerability and effect on MF-related symptoms of pacritinib in patients with MF.

Komrokji RS et al. *Proc ASH* 2011;Abstract 282.

Trial Design



- > Primary MF (PMF); postpolycythemia vera MF (PPV-MF); postessential thrombocythemia MF (PET-MF)
- > Spleen volume (SV) was measured by MRI every 12 wks (volume targets 25%/35% reduction)
- > Physical examination (PE) of SV was assessed every 4 wks
- > SRR defined as ≥35% reduction in MRI-measured SV between baseline and week 24

Komrokji RS et al. *Proc ASH* 2011;Abstract 282.

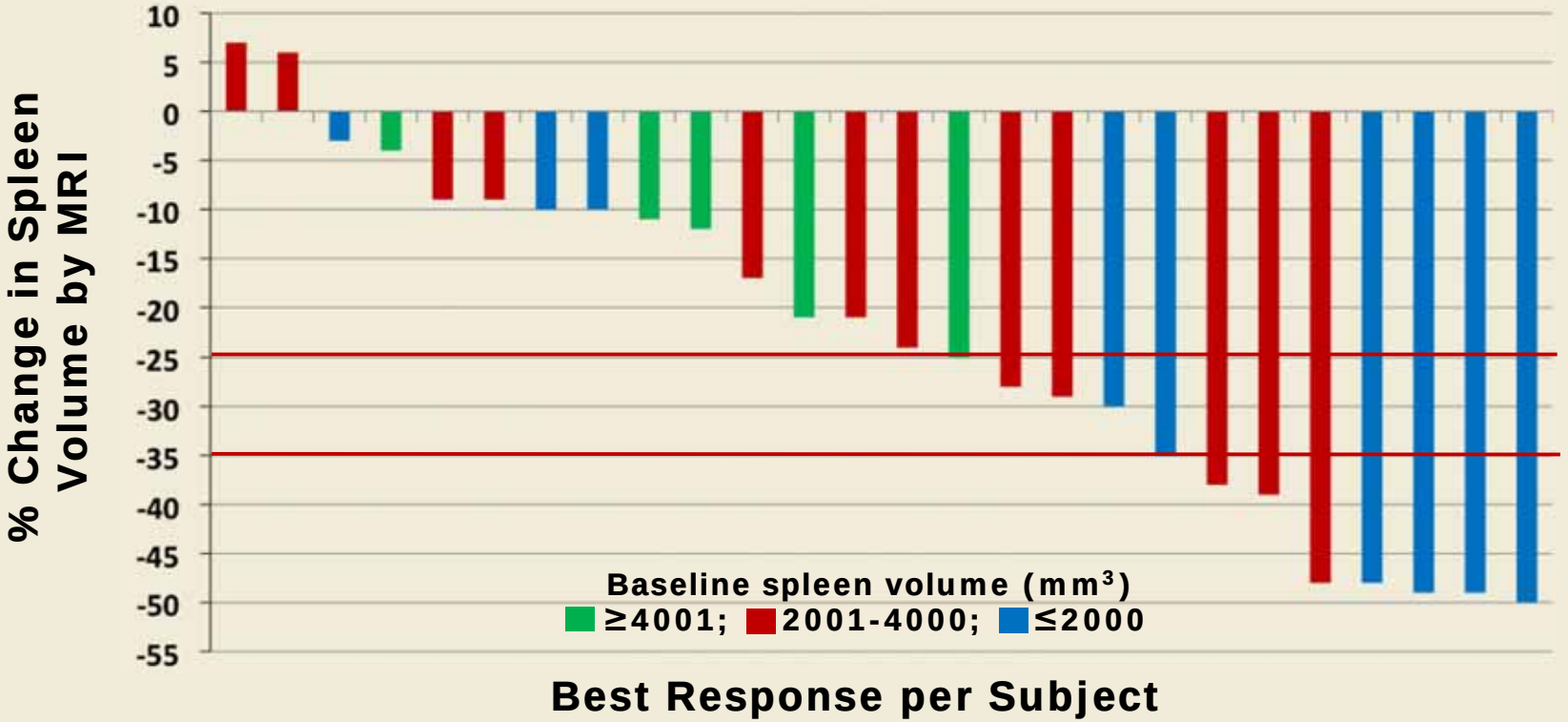
Efficacy of Pacritinib in Reduction of Splenomegaly as a Function of Baseline Platelet Count

Spleen response	Patients with baseline platelet count ≤150,000 (n = 19)	All patients (n = 34)
Patients with at least 50% reduction in SV by PE	42%	41%
Patients with at least 35% reduction in SV by MRI	26%	24%
Patients with at least 25% reduction in SV by MRI	37%	35%

Reduction of splenomegaly was observed with similar frequency in patients with normal or low platelet counts.

Komrokji RS et al. *Proc ASH* 2011;Abstract 282.

Effect of Pacritinib on Reduction of Splenomegaly by MRI Analysis



> Thirty-five percent of patients had ≥25% reduction, 24% had ≥35% reduction of splenomegaly.
> Eight patients did not have postbaseline response by MRI (hence, not included).
> Median response duration is ongoing and has not been reached; median ≥257 days.
> Median time to response was 84.5 days.

With permission from Komrokji RS et al. *Proc ASH* 2011;Abstract 282.

Adverse Events

Adverse event (n = 34)	Grade 1/2	Grade 3/4
Diarrhea	64%	9%
Nausea	41%	0%
Vomiting	24%	0%
Fatigue	15%	6%
Increased ALT/AST	12%	9%
Abdominal pain	12%	0%
Anorexia	12%	0%
Flatulence	18%	0%
Ageusia/dysgeusia	12%	0%
Alopecia	12%	0%

Possible drug-related events leading to discontinuation (n): Increased bilirubin (1), thrombocytopenia (1), allergic reaction (1), nausea (1), pruritus (1).

Komrokji RS et al. *Proc ASH* 2011;Abstract 282.

Safety Summary

- Pacritinib was generally well tolerated, and toxicities were readily manageable:
  - The majority of AEs were Grade 1 or 2.
  - Gastrointestinal toxicities (diarrhea, nausea, vomiting) were the most prominent but were easily managed.
- No problematic myelosuppression was observed.
- Pacritinib was equally tolerated by patients with normal platelet counts and those with thrombocytopenia and anemia.

Komrokji RS et al. *Proc ASH* 2011;Abstract 282.

Author Conclusions

- Pacritinib is an active drug for the treatment of PMF, PPV-MF and PET-MF splenomegaly and MF-related symptoms regardless of baseline thrombocytopenia.
- Once-daily dosing is well tolerated, with manageable gastrointestinal toxicity as the main side effect.
- Minimal effect of pacritinib on existing cytopenias in patients with MF provides an important therapeutic niche.

Komrokji RS et al. *Proc ASH* 2011;Abstract 282.

Investigator Commentary: Results of a Phase II Study of Pacritinib in Patients with Myelofibrosis

Pacritinib inhibits JAK2 but not JAK1. Although it has no anti-inflammatory effect, it decreases spleen size and improves quality of life in a good number of patients. It may not be as effective as JAK1 and 2 inhibitors such as ruxolitinib, but its effect is seen primarily in patients with low blood cell counts. Because ruxolitinib potentially decreases platelets and red blood cell counts, the effect of pacritinib in these patients was fostered.

Pacritinib does not induce myelosuppression and as such was equally effective in patients with low platelet counts and in those with normal counts. Although it causes adverse events including nausea, vomiting and diarrhea, pacritinib may offer a solution in the treatment of MF in patients with low platelet counts.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

SAR302503: Interim Safety, Efficacy and Long-Term Impact on JAK2 V617F Allele Burden in a Phase I/II Study in Patients with Myelofibrosis

Pardanani A et al.

Proc ASH 2011;Abstract 3838.

Background

- Dysregulation of the JAK-STAT pathway is associated with myelofibrosis (MF).
- SAR302503 is an oral selective small-molecule inhibitor of JAK2 kinase.
- A previous Phase I trial showed that SAR302503 was well tolerated and produced significant reductions in JAK2V617F allele burden and durable clinical benefits in patients with MF (*JCO* 2011;29:789).
- **Objective:**
  - Report updated safety and efficacy results of SAR302503 in patients with MF with long-term follow-up.
  - Analyze JAK2V617F allele burden (JAB) in this patient cohort

Pardanani A et al. *Proc ASH* 2011;Abstract 3838.

Trial Design

SAR302503

Eligibility (n = 59)

PMF or PPV-MF or PET-MF

Intermediate- to high-risk MF

Platelet count ≥50 x 10^9/L

Dose-escalation cohort
(n = 28)
30-800 mg/d, orally
q4wks x 6 cycles

Dose-confirmation cohort
(n = 31)
680 mg/d, orally
q4wks x 6 cycles

→ Extension study*
(n = 43)

* After 24 weeks, patients could enter extension study if treatment was beneficial and well tolerated. Dosage used was the same as that which the patient last received.

Pardanani A et al. *Proc ASH* 2011;Abstract 3838.

Spleen Volume (SV) Reduction (Abstract Only)

Treatment time (n)	Median (cm)	Range (cm)	Patients with ≥50% SV reduction
Baseline (n = 58)	18.0	4-38	Not applicable
6 months (n = 57)	9.0	0-30	54.4%
12 months (n = 42)	9.0	0-28	66.7%
18 months (n = 36)	8.5	0-33	52.8%
24 months (n = 31)	8.0	0-30	54.8%
30 months (n = 18)	7.5	0-16	61.1%
36 months (n = 9)	3.0	0-16	66.7%

Pardanani A et al. *Proc ASH* 2011;Abstract 3838.

JAK2V617F Allele Burden (JAB) (Abstract Only)

Treatment cycle	JAB	Range	*p*-value
Baseline (n = 51)	20%	3-100%	0.03
versus			
24 cycles (n = 21)	9%	0-100%	
Treatment cycle	**JAB >20% at baseline**	**Range**	***p*-value**
Baseline (n = 23)	60%	23-100%	0.03
versus			
24 cycles (n = 12)	21%	6-100%	

Pardanani A et al. *Proc ASH* 2011;Abstract 3838.

Author Conclusions

- With SAR302503 treatment, a clinically significant and durable decrease in spleen size was observed in patients with MF.
- The reduction in circulating JAK2V617F allele burden was durable.
- No unique safety issues have been identified with continued dosing of SAR302503 (data not shown).
- A SAR302503 dose of 400 to 500 mg/day represents the optimal balance between safety and efficacy in patients with MF. These 2 doses constitute the experimental arms of an upcoming Phase III study (NCT01437787).

Pardanani A et al. *Proc ASH* 2011;Abstract 3838.

Investigator Commentary: SAR302503 — Efficacy and Long-Term Effects in Patients with Myelofibrosis

Currently, about 10 different JAK2 tyrosine kinase inhibitors are being evaluated in clinical studies. They all act by preventing ATP from binding to the JAK2 enzyme and so are not specific for the JAK2 mutation. Because all patients with MF have overactive JAK2, these agents are effective in any patient with MF. The difference among these inhibitors is the ability to affect other members of the JAK family. For instance, ruxolitinib and the CYT-387 compound inhibit both JAK1 and 2. This capability may be particularly advantageous over others because inflammatory cytokines, which play important roles in the pathophysiology of MF, are inhibited by the dual targeting of JAK1 and JAK2.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

Complete Hematological Molecular and Histological Remissions without Cytoreductive Treatment Lasting After Pegylated-Interferon α-2a (peg-IFNα-2a) Therapy in Polycythemia Vera (PV): Long Term Results of a Phase 2 Trial

Turlure P et al.

Proc ASH 2011;Abstract 280.

Background

- Recently, 2 Phase II studies showed promising results of efficacy, tolerance and molecular responses of peg-IFNα-2a therapy in polycythemia vera (PV) and essential thrombocythemia (ET) (*Blood* 2008;112:3065; *Cancer* 2007;110:2012).
- As a result, there is renewed interest in peg-IFNα-2a therapy in patients with myeloproliferative neoplasms (MPN).
- **Objective:**
  - Analyze the long-term efficacy and safety of peg-IFNα-2a treatment in the PVN1 trial, a Phase II study of peg-IFNα -2a in PV, after a median follow-up of 6.4 years.

Turlure P et al. *Proc ASH* 2011;Abstract 280.

Study Methods

- The PVN1 trial (NCT00241241) is a Phase II open-label study of efficacy and safety of peg-IFNα-2a in 40 patients with PV, enrolled from 09/2004 to 09/2005.
- The long-term effects of peg-IFNα-2a were evaluated after a median follow-up time of 6.4 years according to the European LeukemiaNet (ELN) criteria by the analysis of:
  - Hematological response
  - Molecular response
  - Histological response
- Molecular response was assessed by measuring JAK2V617F allele burden in granulocytes of patients with serial samples.
- The median time since diagnosis was 6 months.

Turlure P et al. *Proc ASH* 2011;Abstract 280.

Hematological Responses at Last Evaluation (Abstract Only)

Hematological response (HR)	Responding patients (n = 34)*
Overall HR	94%
Complete response (HCR)	82%
Partial response (HPR)	12%
Disease relapse	6%

* Median follow-up time: 77.4 mo; median duration of peg-IFNα-2a therapy: 47.4 mo
* Patients not analyzed: 4 pts were not evaluable and 2 pts were lost to follow-up (FU)

> During FU, 20 patients (59%) stopped treatment after a median time of 42 mo.
> Out of those who stopped, 13 patients (38%) received no other cytoreductive therapy.
  – 10/13 were still in HCR off therapy after mean observation of 28+ mo.

Turlure P et al. *Proc ASH* 2011;Abstract 280.

Molecular and Histological Responses (Abstract Only)

Molecular response (%V617F)	Patients (n = 29)
Overall molecular response	83%
Complete response (CR)	28%
Patients with TET2 mutation	14%
Patients with TET2 mutant allele burden decrease with treatment	0

Mean %V617F: 47% at baseline, 10% at 72 mo

Histological responses:

- Analysis of bone marrow (BM) biopsies in some patients in HCR after discontinuation of peg-IFNα-2a revealed normalized BM morphology fulfilling the ELN criteria.
- BM biopsies from these patients excluded myelofibrosis evolution as a cause for "apparent" remission.

Turlure P et al. *Proc ASH* 2011;Abstract 280.

Adverse Events (AEs) (Abstract Only)

AEs leading to discontinuation	Number of patients
Fatigue	2
Depression	1
Grade 2 neuropathy	1
Arthralgia	1
Thyroiditis	1
Auto-antibodies	1
Liver enzyme elevation	1

- No unexpected AEs in spite of long-term use of peg-IFNα-2a: Median of 45.5 mo
- No patient experienced any vascular event during follow-up

Turlure P et al. *Proc ASH* 2011;Abstract 280.

Author Conclusions

- Ninety-four percent of patients with PV treated with peg-IFNα-2a were still in HR (median follow-up 6.4 years).
- Out of the patients still in HR, 82% had CR.
- Patients (29%) who could stop peg-IFNα-2a treatment remained in HR without further cytoreductive therapy after a median observation time of 28+ months to 64+ months.
- Histological CR was also achieved in selected patients.
- A major and sustained molecular response in %V617F was confirmed in 83% of patients.
  - Out of these patients, 28% achieved complete molecular response.
  - Patients with TET2 mutated clones appeared resistant to peg-IFNα-2a
- No vascular events were observed and no new safety concerns arose with prolonged use of peg-IFNα-2a.

Turlure P et al. *Proc ASH* 2011;Abstract 280.

Investigator Commentary: Complete Hematological, Molecular and Histological Remissions After peg-IFNα-2a Therapy in Polycythemia Vera (PV): Long-Term Results

Traditionally, interferon is occasionally used in early-stage MPN, ET and PV as an agent useful in patients not responding well to front-line therapies such as hydroxyurea. However, interferon has been associated with low-grade chronic toxicities related to myelosuppression, loss of hair, thyroid problems, depression and more. Few patients can tolerate the therapy. Now this study shows that administration of pegylated IFN, a new preparation of IFN, at a dose of 45 to 90 mg/wk is highly effective in normalizing counts in about 80% to 90% of patients with ET and PV. The results obtained in this study in terms of eliminating clones with JAK2 mutation are not attainable with JAK2 inhibitors because they are not specific for the mutation but only control disease signs and symptoms. Therefore, these data show that peg-IFNα-2a can lead to long-term molecular and histological remission.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

Prolonged Low Dose Therapy with a Pan-Deacetylase Inhibitor, Panobinostat (LBH589), in Patients with Myelofibrosis[1]

Phase II Study of Low-Dose Pomalidomide in Patients with Myelofibrosis and Significant Anemia (Hemoglobin <10g/dL)[2]

Pomalidomide Therapy for Myelofibrosis: Analysis of Results from Three Consecutive Clinical Trials[3]

[1] **Mascarenhas J et al.** *Proc ASH* 2011;Abstract 794.

[2] **Shastri A et al.** *Proc ASH* 2011;Abstract 1757.

[3] **Begna K et al.** *Proc ASH* 2011;Abstract 1759.

Prolonged Low Dose Therapy with a Pan-Deacetylase Inhibitor, Panobinostat (LBH589), in Patients with Myelofibrosis

Mascarenhas J et al.

Proc ASH 2011;Abstract 794.

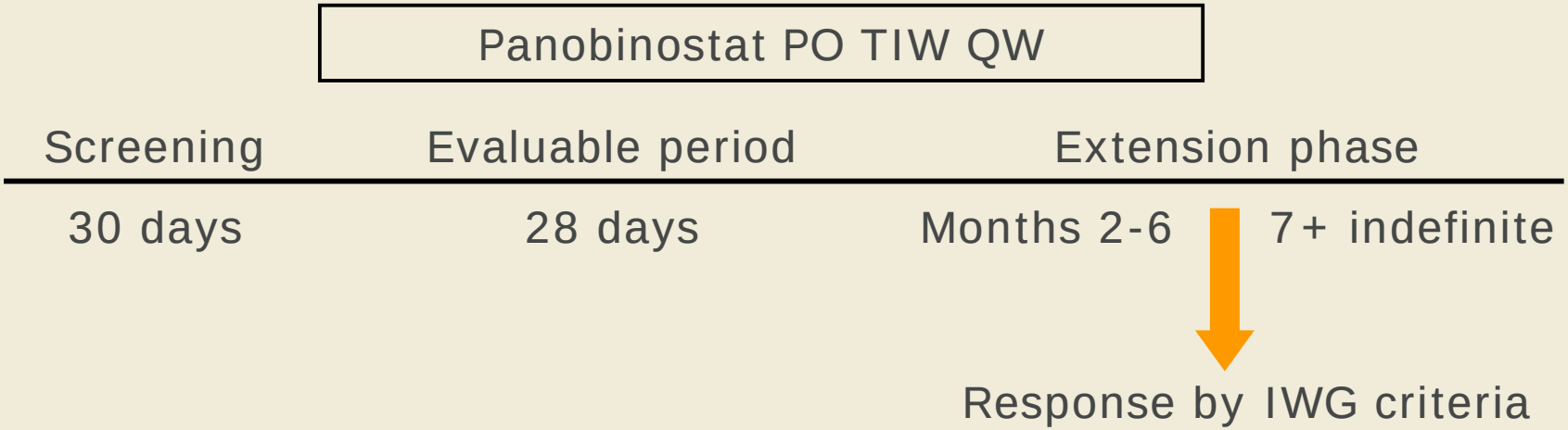
Background

- Panobinostat (LBH589) is a novel pan-HDAC (histone deacetylase) inhibitor that specifically enhances the deacetylation of histone and nonhistone cellular proteins.
- Panobinostat has potent antiproliferative activity against a broad range of tumor cell lines, and this activity is associated with increased histone acetylation.
- A preliminary Phase I study in patients with myelofibrosis showed evidence of clinical responses and identified reversible thrombocytopenia as the dose-limiting toxicity (*Proc ASH* 2009;Abstract 308).
- **Current study objective**: Evaluate the effects of long-term administration of panobinostat in patients enrolled in the extension phase of the Phase I trial.

Mascarenhas J et al. *Proc ASH* 2011;Abstract 794.

Phase I Study Design

- Phase I, open-label, single-center, standard cohort, dose-escalation study
- Eighteen patients with MF (Lille classification: Intermediate to high risk) enrolled
- Three doses of panobinostat: 20 mg, 25 mg or 30 mg PO TIW QW
- Cycle = 28 days



Mascarenhas J et al. *Proc ASH* 2011;Abstract 794.

Reduction in Splenomegaly from Baseline

% reduction from baseline in palpable splenomegaly by cycles						
Cycle	**1**	**2**	**3**	**4**	**5**	**6**
Mean	25%	26%	30%	52%	77%	58%
Median	23%	28%	22%	38%	93%	65%
Range	-6 to 100%	0-100%	0-100%	0-100%	23-100%	31-100%

Mascarenhas J et al. *Proc ASH* 2011;Abstract 794.

Characteristics of Patients Evaluable for Response at 6 Months (n = 5)

Patient no.	4	7	11	15	18
MF subtype	PMF	PMF	PMF	Post-ET MF	Post-PV MF
LBH589 dose	20 mg	20 mg	30 mg	25 mg	20 mg
Cycles on study	23	33	6	24	16
JAK2 status	*JAK2*V16F	WT	*JAK2*V16F	WT	*JAK2*V16F
Best response by IWG-MRT	CI-anemia CI-spleen	CI-spleen	SD	**Near CR**	SD

CI = clinical improvement; SD = stable disease; CR = complete response

Mascarenhas J et al. *Proc ASH* 2011;Abstract 794.

Select Adverse Events (30 Months Follow-Up)

Event (N = 18)	Any grade	Grade 3/4
Diarrhea	94%	0
Anemia	56%	39%
Thrombocytopenia	39%	28%
Musculoskeletal pain	39%	0
Nausea	39%	0
Neutropenia	17%	17%

Other adverse events of any grade: Fatigue (33%), emesis (11%), anorexia (11%), constipation (11%), paresthesias (11%)
Patients (n) who discontinued treatment due to a related adverse event: Anemia (4), thrombocytopenia (3), prolonged QTc (1)

Mascarenhas J et al. *Proc ASH* 2011;Abstract 794.

Author Conclusions

- In patients with MF, low doses of panobinostat can reduce splenomegaly and are tolerable.
- Prolonged treatment with panobinostat alleviates symptoms, improves anemia and reverses pathologic bone marrow changes (data not shown).
- Signal for activity of panobinostat has led to the initiation of a Phase II study for patients with MF (#NCT01298934).
- The successful use of panobinostat may require prolonged administration and transfusional support as determined by MF severity.

Mascarenhas J et al. *Proc ASH* 2011;Abstract 794.

Investigator Commentary: Prolonged Low-Dose Therapy with Panobinostat for Patients with Myelofibrosis

In this study panobinostat was tested as a single agent in patients with myelofibrosis. Benefits in terms of improvement in blood count, reduction in spleen size and amelioration of symptoms were observed in some patients.

Myelofibrosis is a disease that can shorten life expectancy. Average life expectancy is 5 to 7 years and patients usually die from progression of the disease rather than transformation to acute leukemia. The causes of death are related to progression of the enlarged spleen and liver, ultimately resulting in cardiac failure and lung failure.

One way of improving the efficacy of JAK2 inhibitors like ruxolitinib for the treatment of myelofibrosis is to combine them with other drugs like panobinostat. Perhaps because of their synergistic activity, we could expect that when used together the efficacy would be better than with each of them separately. I believe that the next wave of clinical studies for myelofibrosis will look at combination treatment strategies.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012

Phase II Study of Low-Dose Pomalidomide in Patients with Myelofibrosis and Significant Anemia (Hemoglobin <10g/dL)

Shastri A et al.

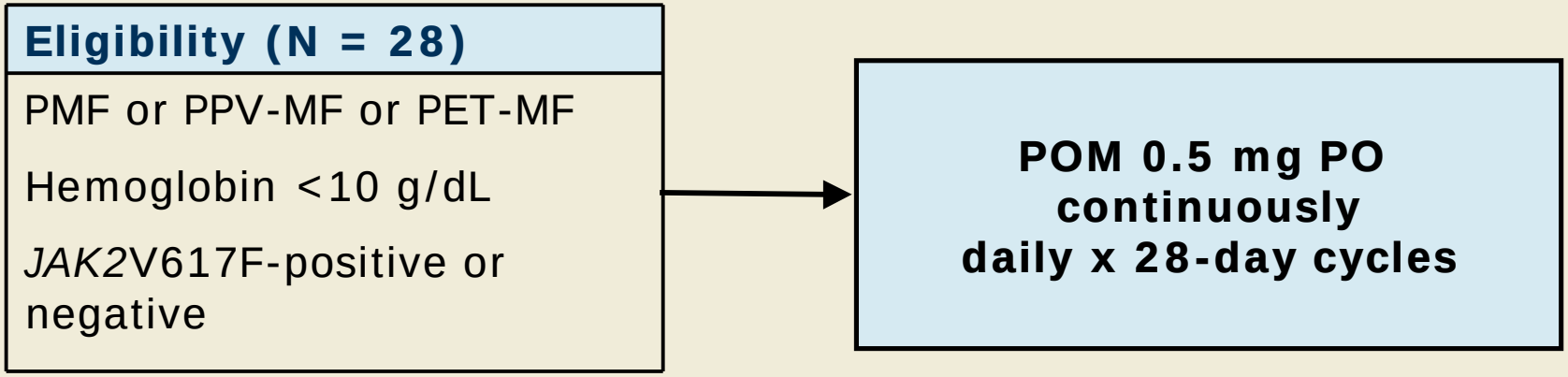
Proc ASH 2011;Abstract 1757.

Background

- A Phase II trial demonstrated that low-dose pomalidomide (POM) is effective at increasing hemoglobin levels and eliminating the need for transfusions as measured by IWG-MRT criteria in patients with *JAK2*V16F mutation-positive myelofibrosis (MF) (*Leukemia* 2011;25:301).
- The ongoing Phase III trial of single-agent POM in MF is currently utilizing a more robust and clinically meaningful set of transfusion dependency criteria known as the "Gale criteria" (*Leuk Res* 2011;35:8).
- **Objective:**
  - Assess the efficacy of single-agent, low-dose POM in improving hemoglobin levels and reducing transfusion dependency based on the Gale criteria in patients with MF and significant anemia.

Shastri A et al. *Proc ASH* 2011;Abstract 1757.

Phase II Study Design



PMF = primary MF; PPV-MF = postpolycythemia vera MF; PET-MF = postessential thrombocythemia MF

Use of anagrelide on study was allowed to control high platelet counts, if indicated. Other concomitant therapies, such as growth factors, were not allowed.

Shastri A et al. *Proc ASH* 2011;Abstract 1757.

Results Summary (Abstract Only)

- After median follow-up of more than 1 year, 11 (40%) patients remain on study:
  - Twelve patients were taken off study due to lack of response.
  - Two patients had disease that transformed to acute leukemia.
  - Three patients died from unrelated causes.
- By the Gale criteria, 2 of 8 transfusion-dependent patients achieved transfusion independence:
  - Both patients had JAK2 mutation-negative disease and did not have splenomegaly.
- No patients experienced sustained increase in hemoglobin of 2 g/dL from baseline.
- There were no instances of Grade 3/4 neutropenia, thrombocytopenia or nonhematologic toxicity.

Shastri A et al. *Proc ASH* 2011;Abstract 1757.

Author Conclusions

- Low-dose, oral POM administered to patients with MF and significant anemia had modest clinical activity as measured by the Gale criteria:
  - Two of 8 transfusion-dependent patients achieved transfusion independence on study.
- Low-dose POM was well tolerated and had a good safety profile in this patient group.

Shastri A et al. *Proc ASH* 2011;Abstract 1757.

Pomalidomide Therapy for Myelofibrosis: Analysis of Results from Three Consecutive Clinical Trials

Begna K et al.

Proc ASH 2011;Abstract 1759.

Background

- Pomalidomide is a second-generation IMiD that is active in the treatment of myelofibrosis (MF)-associated anemia.
- An analysis was conducted on long-term follow-up data for 82 patients with MF who received single-agent pomalidomide during 3 consecutive Phase I and II clinical trials at the Mayo Clinic (5/2007 to 1/2010).
- **Current study objective:** Evaluate the anemia response rate obtained with single-agent pomalidomide.

Begna K et al. *Proc ASH* 2011;Abstract 1759.

Study Designs and Select Patient Characteristics (n = 82)

Designs of studies included in analysis

- Phase I dose-escalation study (2.5-3.5 mg/day), n = 19
- Phase II low-dose pomalidomide (0.5 mg/day), n = 58
- Phase II randomized study (2 mg/day), n = 5

Select patient characteristics

- Median age: 67 years
- RBC transfusion dependence at study entry, n = 63 (77%)

Begna K et al. *Proc ASH* 2011;Abstract 1759.

Treatment Retention and Response* Over Time (Abstract Only)

	Treatment retention (%)	Anemia response (%)
Start of treatment (n = 82)	100%	27%
6 months FU	55%	26%
12 months FU	29%	23%
24 months FU	9%	9%
36 months FU	2%	2%

* IWG-MRT criteria

Anemia response occurred in the first 6 months in 21 of 22 responders (96%).
Median time for response = 2.3 months; median response duration = 16.5 months.

Begna K et al. *Proc ASH* 2011;Abstract 1759.

Anemia Response Rates among Patient Subgroups* (Abstract Only)

	Anemia response (%)	*p*-value
Palpable spleen size		
<10 cm below costal margin	44%	0.002
≥10 cm above costal margin	10%	
JAK2 mutated	30%	0.2
JAK2 nonmutated	15%	
Increase in basophil count, 1st month		
≥50% increase	39%	0.001
<50% increase	6%	

* Anemia response rate was not significantly affected by karyotype, transfusion need or leukocyte count.

Begna K et al. *Proc ASH* 2011;Abstract 1759.

Author Conclusions

- Anemia response to pomalidomide therapy in MF
  - Often occurs in the first 6 months of treatment.
  - Is more likely to occur in the presence of *JAK2*V617F.
  - Is more likely to occur in the absence of marked splenomegaly.
- Long-term treatment with pomalidomide may be associated with sensory peripheral neuropathy in a subset of patients:
  - Among 24 patients who received pomalidomide for at least 12 months, Grade 1 sensory neuropathy was observed in 4 (16%) patients.

Begna K et al. *Proc ASH* 2011;Abstract 1759.

Investigator Commentary: Pomalidomide Therapy for Myelofibrosis

Three studies of pomalidomide in MF have been published, and it was noted that when administered at a low dose pomalidomide had the potential to improve red blood cell counts by a mechanism that is currently not understood. Pomalidomide has not had an effect on other aspects of the disease, such as spleen size. Its evaluation in ongoing Phase III studies is focused on improvement of red blood cell counts in patients with MF who are anemic.

If pomalidomide is demonstrated to have true value in the current Phase III, placebo-controlled randomized study, then in the future it would be worthwhile to evaluate combining it with the JAK2 inhibitors. This would allow for a 2-pronged approach, with the JAK2 inhibitors affecting spleen size and symptom control and pomalidomide affecting red blood cell counts and anemia.

Interview with Srdan Verstovsek, MD, PhD, January 25, 2012