Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

January 2019 Volume 17, Issue 1, Supplement 2

A SPECIAL MEETING REVIEW EDITION

Highlights in Myeloproliferative Neoplasms From the 60th American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 60th American Society of Hematology Annual Meeting • December 1-4, 2018 • San Diego, California

Special Reporting on:

- Long-Term Efficacy and Safety (5 Years) in RESPONSE, a Phase 3 Study Comparing Ruxolitinib With Best Available Therapy in Hydroxyurea-Resistant/Intolerant Patients With Polycythemia Vera
- Results of the Myeloproliferative Neoplasms—Research Consortium (MPN-RC) 112 Randomized Trial of Pegylated Interferon Alfa-2a (PEG) Versus Hydroxyurea Therapy for the Treatment of High-Risk Polycythemia Vera and High-Risk Essential Thrombocythemia
- Safety and Efficacy of Combined Ruxolitinib and Thalidomide in Patients With Myelofibrosis: Initial Results of a Phase II Study
- Evidence for Superior Efficacy and Disease Modification After Three Years of Prospective Randomized Controlled Treatment of Polycythemia Vera Patients With Ropeginterferon Alfa-2b Vs HU/BAT
- Updated Results of a Phase 2 Study of Ruxolitinib in Combination With 5-Azacitidine in Patients With Myelofibrosis
- Imetelstat Is Effective Treatment for Patients With Intermediate-2 or High-Risk Myelofibrosis Who Have Relapsed on or Are Refractory to Janus Kinase Inhibitor Therapy: Results of a Phase 2 Randomized Study of Two Dose Levels
- Ruxolitinib for the Treatment of Inadequately Controlled Polycythemia Vera Without Splenomegaly: 156-Week Follow-Up From the Phase 3 RESPONSE-2 Study
- Addressing the Adequacy of Current MPN Pain Management Strategies: An International Survey of 502 Patients By the MPN Quality-of-Life Study Group

PLUS Meeting Abstract Summaries

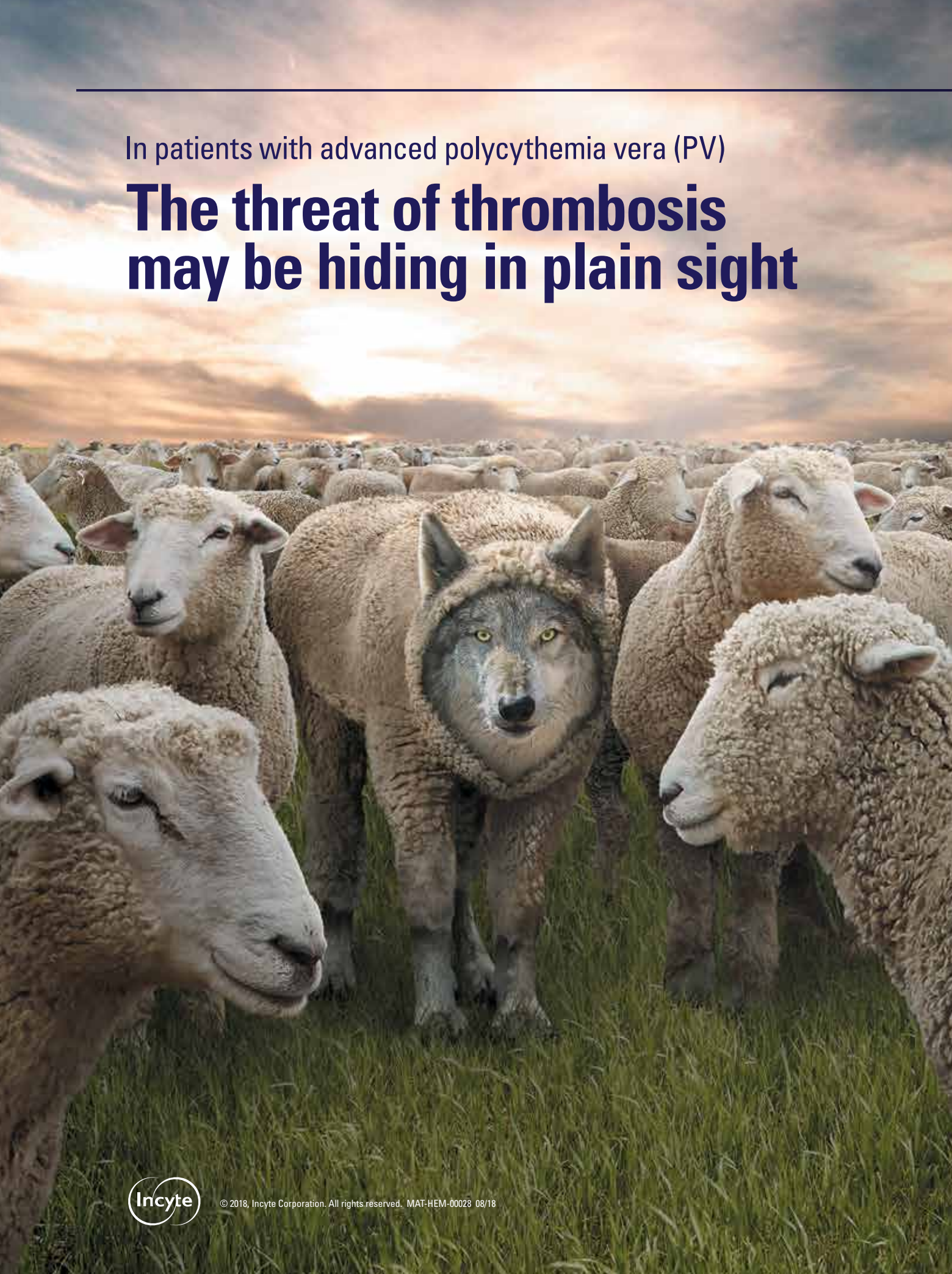
With Expert Commentary by:
Ruben A. Mesa, MD
Director, UT Health San Antonio Cancer Center
Mays Family Foundation Distinguished University Chair
Tenured Professor of Medicine
University of Texas Health Science Center
San Antonio, Texas

ON THE WEB:
hematologyandoncology.net

Indexed through the National Library of Medicine
(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

In patients with advanced polycythemia vera (PV)

The threat of thrombosis may be hiding in plain sight



Incyte

© 2018, Incyte Corporation. All rights reserved. MAT-HEM-00028 08/18

Look beyond Hct for factors that increase your patients' risk

PV may become advanced in a subset of patients despite treatment with hydroxyurea* and phlebotomy, resulting in ineffective disease control.[1-4]

*After maximum tolerated dose of hydroxyurea.

Actively monitor for these clinical characteristics of advanced PV

Elevated Hct ≥45% led to serious consequences

Evidence from the CYTO-PV study:
Elevated Hct ≥45% was associated with a 4-fold higher rate of cardiovascular death and major thrombosis when Hct levels were managed between 45% and 50% compared with an Hct level managed to <45% (HR, 3.91; 95% CI, 1.45 to 10.53; *P* = 0.007).[5†]

Elevated WBC counts >11 × 10^9/L increased the risk of thrombosis[‡]

Additional analysis from the CYTO-PV study:
In a multivariable time-dependent analysis, **the risk of thrombosis was statistically significant in patients with WBC counts >11 × 10^9/L** (HR, 3.9; 95% CI, 1.24-12.3; *P* = 0.02).[6]

CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera; Hct, hematocrit; HR, hazard ratio; WBC, white blood cell.

† In the CYTO-PV study of 365 adult patients with PV treated with phlebotomy, hydroxyurea, or both, patients were randomized to 1 of 2 groups—either the low-Hct group (n = 182; with more intensive therapy to maintain a target Hct level <45%) or the high-Hct group (n = 183; with less intensive therapy to maintain a target Hct level of 45% to 50%). Baseline characteristics were balanced between the groups. Approximately 50% of patients had received an initial diagnosis of PV within 2 years prior to randomization. 67.1% of patients (n = 245) were at high risk because of age ≥65 years or previous thrombosis. The composite primary end point was the time until cardiovascular death or major thrombosis.[5]

‡ In an analysis from the CYTO-PV study, there was a trend for increased risk of thrombosis with WBC count >7 × 10^9/L (ie, hazard ratio >1) that became statistically significant in patients with WBC counts >11× 10^9/L. Results were adjusted for age, gender, cardiovascular risk factors, previous thrombosis, and Hct levels.[6]

References: 1. Parasuraman S et al. *Exp Hematol Oncol.* 2016;5:3. **2.** Mascarenhas J. *Clin Lymphoma Myeloma Leuk.* 2016;16suppl:S124-S129. **3.** Rumi E, Cazzola M. *Blood.* 2017;129(6):680-692. **4.** Spivak JL et al. *N Engl J Med.* 2014;371(9):808-817. **5.** Marchioli R et al. *N Engl J Med.* 2013:368(1):22-33. **6.** Barbui T et al. *Blood.* 2015;126(4):560-561.

Learn more at
ThreatofThrombosis.com

Long-Term Efficacy and Safety (5 Years) in RESPONSE, a Phase 3 Study Comparing Ruxolitinib With Best Available Therapy in Hydroxyurea-Resistant/Intolerant Patients With Polycythemia Vera

The most common myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia, and primary myelofibrosis.[1] Patients with MPN are prone to thromboembolic and hemorrhagic events, and are at risk for progression to myelofibrosis or acute myeloid leukemia. Common treatments, such as hydroxyurea, can reduce symptoms and help control the disease. However, approximately one-fourth of patients are resistant to treatment or cannot tolerate it. PV is characterized by mutations in Janus kinase (*JAK*) 2 that result in constitutive activation of the JAK/signal transducers and activators of transcription (STAT) pathway. Ruxolitinib is a JAK1/2 inhibitor that was evaluated in the international, open-label phase 3 RESPONSE trial (Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 [INCB018424] Tablets Versus Best Available Care) of patients with PV who were resistant or intolerant to hydroxyurea.[2-5] Enrolled patients were phlebotomy-dependent and had splenomegaly.

The study randomly assigned 122 patients to receive the best available treatment (BAT) or ruxolitinib (10 mg twice daily). The BAT was selected by the treating physician, and patients in this arm could cross over into the ruxolitinib arm. The primary treatment phase was for 80 weeks, followed by extended treatment through week 256. The primary endpoint was conducted at week 32 and included hematocrit control and a reduction in spleen volume of at least 35%. In the initial analysis, the primary endpoint was achieved in 21% of patients in the ruxolitinib arm vs 1% in the standard therapy arm ($P<.001$).[3] Complete hematologic control was superior with ruxolitinib (24% vs 9%; $P=.003$).

A final analysis of efficacy and safety in the RESPONSE trial was conducted after 256 weeks of treatment (ie, 224 weeks after the initial analysis).[6] After the primary analysis at week 32, 98 patients in the ruxolitinib arm crossed over to the BAT arm. Treatment was completed by 65.5% in the ruxolitinib arm, 1% in the BAT arm, and 65.3% among those who crossed over to the ruxolitinib arm. At the time of the final analysis, 6 of 25 primary responders in the ruxolitinib arm had disease progression. Based on Kaplan-Meier analysis, the estimated probability of maintaining a primary response at week 256 was 0.74 (95% CI, 0.51-0.88). The estimated probability of maintaining hematocrit control at week 256 was 0.73 (95% CI, 0.60-0.83), and the estimated probability of maintaining a reduction of at least 35% in spleen volume at week 256 was 0.72 (95% CI, 0.34-0.91). The median duration of primary response was not reached (Figure 1). Seventy patients (63.6%) achieved an overall clinicohematologic response by week 32. Among these patients, 21 (30%) had progressed by week 256. The estimated probability of maintaining a clinicohematologic response at week 256 was 0.67 (95% CI, 0.54-0.77), and the median duration of clinicohematologic response was not reached (Figure 2). The median overall survival (OS) by intention-to-treat analysis was similar for both arms (hazard ratio [HR], 0.95; 95% CI, 0.38-2.41).

Rates of grade 3/4 adverse events (AEs) were low in both arms. In the ruxolitinib arm, the reported grade 3/4 hematologic AEs included anemia (0.9%) and thrombocytopenia (1.2%). The most common grade 3/4 nonhematologic AEs were infection (3.5%), followed by increased weight (0.7%)

ABSTRACT SUMMARY Long-Term Efficacy and Safety of Recombinant Interferon Alpha-2 Vs. Hydroxyurea in Polycythemia Vera: Preliminary Results From the Three-Year Analysis of the Daliah Trial—A Randomized Controlled Phase III Clinical Trial

The Daliah trial (A Study of Low Dose Interferon Alpha Versus Hydroxyurea in Treatment of Chronic Myeloid Neoplasms) compared interferon alfa-2a or -2b vs hydroxyurea in patients with MPN (Abstract 580). Patients ages 60 years or younger were randomly assigned to treatment with interferon alfa-2a or -2b, whereas older patients were randomly assigned to receive interferon alfa-2a, interferon alfa-2b, or hydroxyurea. After 36 months of therapy, younger and older patients treated with interferon alfa-2a or -2b showed similar rates of discontinuation, AEs, and serious AEs. Older patients treated with interferon alfa-2a or -2b or hydroxyurea had similar rates of overall response ($P=.17$) and hematologic CR ($P=.23$). However, analysis with the last observation carried forward showed a significant improvement in hematologic CR in older patients treated with interferon vs hydroxyurea (49% vs 19%; $P=.045$). Among older patients, interferon treatment was associated with a greater likelihood of maintaining a hematologic CR ($P=.048$) or molecular partial response ($P=.01$)

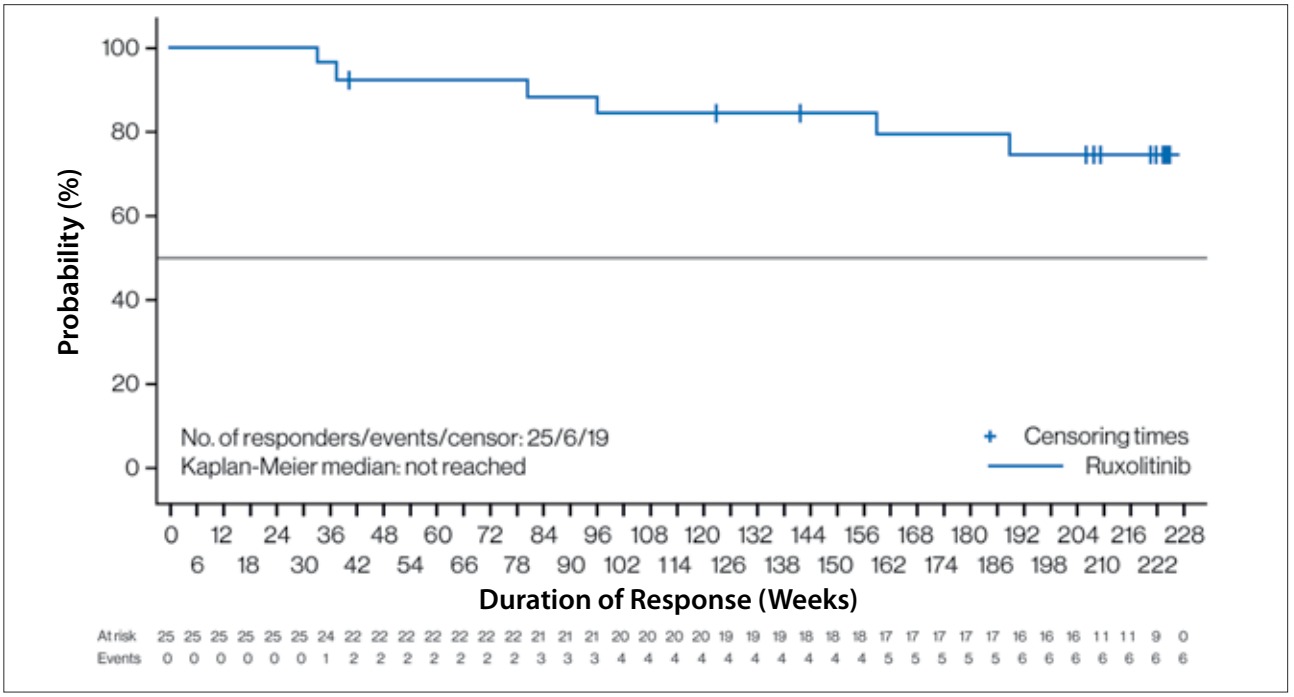


Figure 1. Durability of the primary response among patients with polycythemia vera who received ruxolitinib in the phase 3 RESPONSE trial. RESPONSE, Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 [INCB018424] Tablets Versus Best Available Care. Adapted from Kiladjian JJ et al. ASH abstract 322. *Blood*. 2017;130(suppl 1).[4]

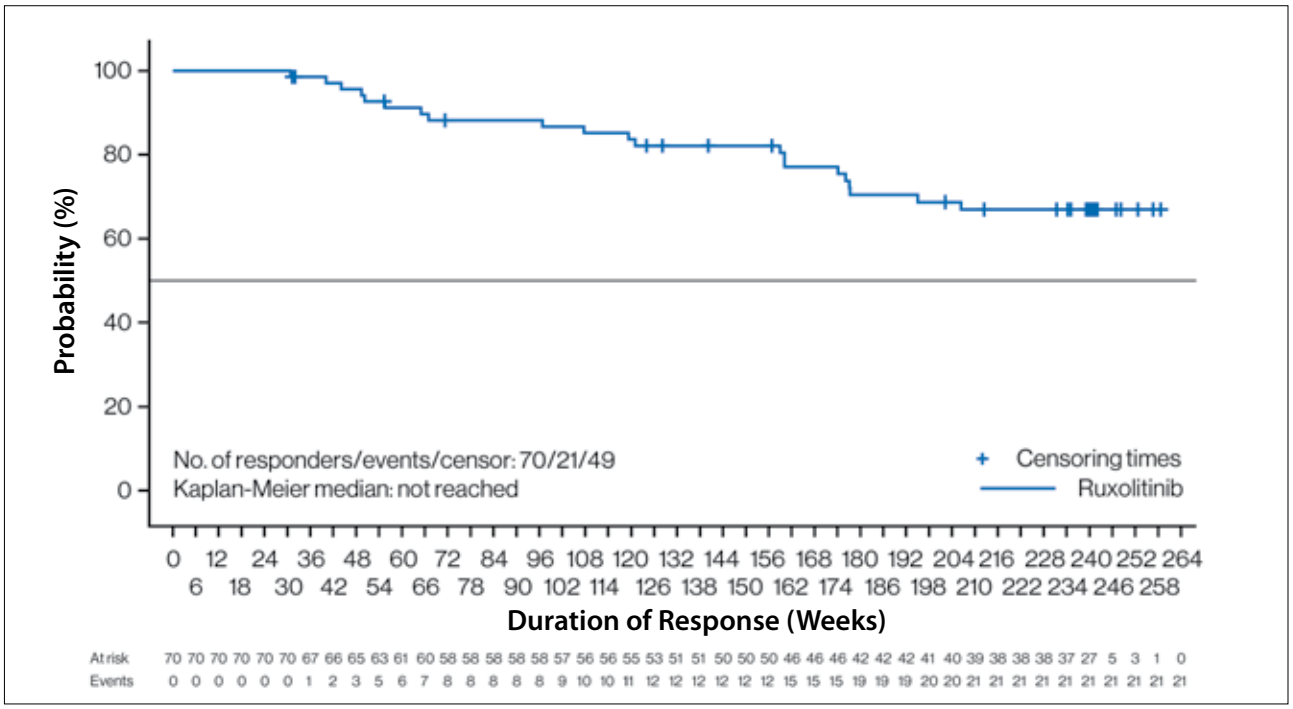


Figure 2. Durability of the overall clinicohematologic response among patients with polycythemia vera who received ruxolitinib in the phase 3 RESPONSE trial. RESPONSE, Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 [INCB018424] Tablets Versus Best Available Care. Adapted from Kiladjian JJ et al. ASH abstract 322. *Blood*. 2017;130(suppl 1).[4]

and thromboembolic events (0.7%). Rates of secondary malignancies per hundred patient-years of exposure were 7.0% in the ruxolitinib arm, 4.1% in the BAT arm, and 4.5% in the crossover population. Two deaths occurred in the ruxolitinib arm during study treatment. One patient died of malignant neoplasm, which was considered unrelated to ruxolitinib. The other patient died of gastric adenocarcinoma, which was considered related to treatment with ruxolitinib. Four patients in the crossover population died, and all of the associated AEs were considered unrelated to ruxolitinib treatment.

References

1. Greenfield G, McPherson S, Mills K, McMullin MF. The ruxolitinib effect: understanding how molecular pathogenesis and epigenetic dysregulation impact therapeutic efficacy in myeloproliferative neoplasms. *J Transl Med*. 2018;16(1):360.
2. Vannucchi AM. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(17):1670-1671.
3. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.
4. Kiladjian JJ, Verstovsek S, Griesshammer M, et al. Results from the 208-week (4-year) follow-up of RESPONSE trial, a phase 3 study comparing ruxolitinib (RUX) with best available therapy (BAT) for the treatment of polycythemia vera (PV) [ASH abstract 322]. *Blood*. 2017;130(suppl 1).
5. Verstovsek S, Vannucchi AM, Griesshammer M, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial. *Haematologica*. 2016;101(7):821-829.
6. Kiladjian JJ, Zachee P, Hino M, et al. Long-term efficacy and safety (5 years) in RESPONSE, a phase 3 study comparing ruxolitinib (RUX) with best available therapy (BAT) in hydroxyurea (HU)-resistant/intolerant patients (pts) with polycythemia vera (PV) [ASH abstract 1753]. *Blood*. 2018;132(suppl 1).

Results of the Myeloproliferative Neoplasms—Research Consortium (MPN-RC) 112 Randomized Trial of Pegylated Interferon Alfa-2a (PEG) Versus Hydroxyurea Therapy for the Treatment of High-Risk Polycythemia Vera and High-Risk Essential Thrombocythemia

In patients with MPNs, activities of interferon alfa include antiproliferative, immunomodulating, and anticlonal effects. Associated toxicities, however, limit the use of this treatment. Pegylated interferon alfa has an improved pharmacologic profile and is less immunogenic and toxic than the nonpegylated molecule. The Myeloproliferative Disorders Research Consortium conducted an international phase 3 study to compare first-line pegylated interferon alfa-2a vs hydroxyurea in patients with high-risk PV or essential thrombocythemia.[1] Eligible patients had essential thrombocythemia or PV based on World Health Organization revised diagnostic criteria.[2] High risk features included older age (≥60 years); previously documented thrombosis, erythromelalgia, or migraine (or hemorrhage for patients with essential thrombocythemia); splenomegaly that was significant (>5 cm) or symptomatic; high platelet counts; and diabetes and/or hypertension requiring pharmacologic therapy. Study participants had been diagnosed with PV or essential thrombocythemia within the previous 5 years and were treatment-naive (defined as <3 months of treatment with hydroxyurea). Essential thrombocythemia response criteria were modified from the European LeukemiaNet criteria. A complete response (CR) was defined by a hematocrit of 45% or less without phlebotomy, a platelet count of 400 × 10^9/L or less, a white blood count below 10 × 10^9/L, normal spleen size on imaging, and no disease-related symptoms. A partial response was defined as a hematocrit of 45% or less without phlebotomy or a response in any 3 of the other 4 criteria for a CR. Bone marrow response evaluation criteria were adapted from the European LeukemiaNet recommendations.[3] The trial's primary endpoint was the rate of complete hematologic response after 12 months of therapy.[4] Secondary endpoints included toxicity, survival, cardiovascular events, and biomarker analysis, as well as the incidences of myelodysplastic disorder, myelofibrosis, and leukemic transformation.

The study randomly assigned 39 patients to the hydroxyurea arm and 36 to the pegylated interferon alfa-2a arm. After 12 months of treatment, the CR rate was 33% with hydroxyurea and 28% with pegylated interferon alfa-2a (P=.6).[5] The objective response rate (ORR) was 69% with hydroxyurea vs 81% with pegylated interferon alfa-2a. The results did not cross the boundary for halting the trial, so additional patients were enrolled into each arm. The final analysis included 168 patients.[1]

The baseline patient characteristics were generally well-balanced between the 2 arms. Patients in the hydroxyurea arm were slightly older (63 vs 60 years; P=.02). In the entire study population, 42% were female, 58% were older than 60 years, 48% had essential thrombocythemia, and 82% had an Eastern Cooperative Oncology Group performance status of 0. The median disease duration was 2.8 months (range, 0.4-84.2 months), and 27% of patients had a history of thrombosis. The median spleen length as measured by ultrasound was 12.4 cm (range, 0-22 cm), and the median hematocrit level was 43.5% (range, 40%-70.2%). The median follow-up was 89.9 weeks (range, 0-292.3 weeks), and the median treatment duration was 86.0 weeks (range, 0-287.3 weeks). Six

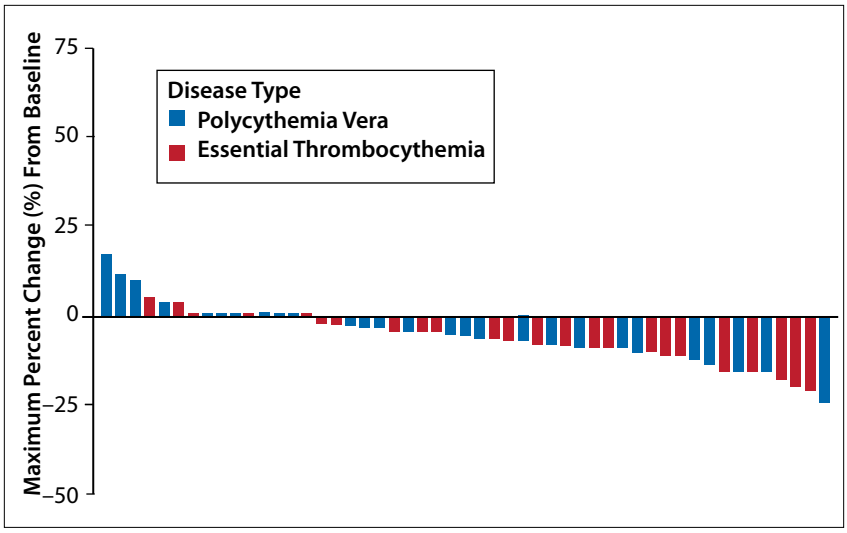


Figure 3. Spleen reduction as measured by ultrasound among patients treated with hydroxyurea in the MPN-RC 112 trial of pegylated interferon alfa-2a vs hydroxyurea therapy in high-risk polycythemia vera and essential thrombocythemia. MPN-RC, Myeloproliferative Neoplasms—Research Consortium. Adapted from Mascarenhas JO et al. ASH abstract 577. *Blood*. 2018;132(suppl 1).[1]

ABSTRACT SUMMARY A Phase 2 Study of the Safety and Efficacy of INCB050465, a Selective PI3Kδ Inhibitor, in Combination With Ruxolitinib in Patients With Myelofibrosis

A phase 2 study evaluated parsaclisib (INCB050465), a phosphoinositide 3-kinase (PI3K) δ inhibitor, plus ruxolitinib in patients with myelofibrosis who experienced a suboptimal response with ruxolitinib monotherapy (Abstract 353). The study enrolled 10 patients into the safety run-in portion of the trial, and an additional 21 patients into the randomized phase. The regimen consisted of ruxolitinib plus parsaclisib at 10 mg or 20 mg, administered daily for 8 weeks, then every week. Spleen volume was reduced in 56% of patients (15/27) at week 12 and in 63% of patients (12/19) at week 24. The combination treatment was generally well-tolerated, with no dose-limiting toxicities during the safety run-in portion. AEs frequently observed with PI3K-δ inhibitors were uncommon, and 17 patients remained on therapy for longer than 6 months.

patients (3.6%) in the hydroxyurea arm never started treatment. Forty-one patients (48%) in the hydroxyurea arm and 40 in the pegylated interferon alfa-2a arm (49%) discontinued treatment owing to study closure by the sponsor. Treatment discontinuation owing to an AE occurred in 9 patients (10%) in the hydroxyurea arm and 12 (15%) in the pegylated interferon alfa-2a arm.

After 12 months of treatment, the CR rate was 37.2% in the hydroxyurea arm, with CRs reported in 45.2% of patients with essential thrombocythemia and 29.5% of those with PV. In the pegylated interferon alfa-2a arm, the CR rate was 35.4%, with CRs in 43.6% of the essential thrombocythemia patients and 27.9% of the PV patients. The ORR was 69.8% in the hydroxyurea arm vs 78.0% in the pegylated interferon alfa-2a arm. After 24 months of treatment, data were evaluable for 54 patients in the hydroxyurea arm and 52 in the pegylated interferon alfa-2a arm. With hydroxyurea, the CR rate was 20.4%, with CRs in 25% of patients with essential thrombocythemia and 16.7% of those with PV. In the pegylated interferon alfa-2a arm, the overall CR rate was 28.8%, with CRs in 37.5% of those with essential thrombocythemia and 25% of those with PV (*P*=.22). The partial response rate was 20.4% with hydroxyurea vs 30.8% with pegylated interferon alfa-2a (*P*=.04). The ORR was 40.7% vs 59.6%, respectively (*P*=.22).

Spleen size by ultrasound changed by a median of –5.2% (range, –24.1% to 16.9%) with hydroxyurea (Figure 3) vs a median of –5.7% (range, –36.7% to 53.8%) with pegylated interferon alfa-2a. Among 109 patients treated for 12 months, the bone marrow CR rate was 23.1% (12/52) with hydroxyurea vs 5.3% (3/57) with pegylated interferon alfa-2a (*P*=.01). Among 113 patients with 24-month data, the best bone marrow responses included 18 CRs with hydroxyurea (33.3%) vs 10 CRs with pegylated interferon alfa-2a (16.9%; *P*=.052).

Patient baseline mutational status was evaluated for *JAK2* and 9 other genes with the goal of establishing a genetic signature that predicted response to treatment. However, no clear relationship emerged. Among the patients with the *JAK2* mutation, the CR rate was 28.3% (15/53) with hydroxyurea and 36.2% (17/47) with pegylated interferon alfa-2a. A small number of patients had a mutated calreticulin (*CALR*) gene; the CR rates in these patients were 100% (3/3) with hydroxyurea vs 33.3% (2/6) with pegylated interferon alfa-2a. Baseline karyotypic abnormalities were observed in 20% of the hydroxyurea arm and 11% of the pegylated interferon alfa-2a arm. Three patients in each arm lost the karyotypic abnormality after 24 months of treatment. This abnormality emerged in 3 patients in the hydroxyurea arm and 1 in the pegylated interferon alfa-2a arm. No

clear association was detected between cytogenetic status and clinical response or bone marrow response.

Grade 3/4 mucositis was more common in the hydroxyurea arm (1.3% vs 0%). Grade 3/4 AEs that were more common with pegylated interferon alfa-2a included hypertension (7.3% vs 2.6%), fatigue (6.1% vs 2.6%), headache (3.7% vs 0%), and flu-like symptoms (2.4% vs 0%). AEs of grade 3 or higher were observed in 27.5% of patients in the hydroxyurea arm vs 46.3% in the pegylated interferon alfa-2a arm. AEs of grade 4 or higher were observed in 6 patients (3.7%) in the overall study population, including 4 patients in the hydroxyurea arm and 2 in the pegylated interferon alfa-2a arm. In the hydroxyurea arm, notable events included 1 death from lung cancer, 1 major cardiovascular event, 1 case of myelofibrosis, and 1 case of myelodysplastic syndrome. In the pegylated interferon alfa-2a arm, 1 patient experienced a cerebral vascular accident.

References

1. Mascarenhas JO, Kosiorek HE, Prchal JT, et al. Results of the Myeloproliferative Neoplasms—Research Consortium (MPN-RC) 112 randomized trial of pegylated interferon alfa-2a (PEG) versus hydroxyurea (HU) therapy for the treatment of high risk polycythemia vera (PV) and high risk essential thrombocythemia (ET) [ASH abstract 577]. *Blood*. 2018;132(suppl 1).
2. Spivak JL, Silver RT. The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal. *Blood*. 2008;112(2):231-239.
3. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. *Blood*. 2013;121(23):4778-4781.
4. Barosi G, Birgegard G, Finazzi G, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. *Blood*. 2009;113(20):4829-4833.
5. Mascarenhas JO, Prchal JT, Rambaldi A, et al. Interim analysis of the Myeloproliferative Disorders Research Consortium (MDP-RC) 112 global phase III trial of front line pegylated interferon alpha-2a vs. hydroxyurea in high risk polycythemia vera and essential thrombocythemia [ASH abstract 479]. *Blood*. 2016;128(suppl 22).

Safety and Efficacy of Combined Ruxolitinib and Thalidomide in Patients With Myelofibrosis: Initial Results of a Phase II Study

Myelofibrosis is often accompanied by anemia and thrombocytopenia.[1] In a double-blind trial of 309 patients with intermediate-2 or high-risk myelofibrosis, ruxolitinib demonstrated a significant reduction in spleen volume at 24 weeks vs placebo (41.9% vs 0.7%; $P<.001$).[2] Spleen response was maintained during treatment. Total symptom scores improved by at least 50% after 24 weeks of treatment in 45.9% of patients treated with ruxolitinib vs 5.3% of those treated with placebo ($P<.001$). Ruxolitinib, however, was associated with higher rates of grade 3/4 anemia (45.2% vs 19.2%) and thrombocytopenia (12.9% vs 1.3%). Thalidomide is an immune-modulator that, alone or in combination with prednisolone, has improved anemia and thrombocytopenia in patients with myelofibrosis.[1] Although thalidomide is associated with significant toxicities, low-dose treatment may achieve a desirable balance between efficacy and toxicity.

A multicenter, 2-stage, phase 2 study (A Clinical Study to Test the Effects of Ruxolitinib and Thalidomide Combination for Patients With Myelofibrosis) investigated ruxolitinib plus thalidomide in patients with myelofibrosis.[3] The study included a treatment-naive cohort, as well as patients receiving treatment with ruxolitinib. Patients taking ruxolitinib at the time of enrollment must have been on therapy for at least 3 months, achieved a stable dose for a minimum of 4 weeks immediately before enrollment, and had a suboptimal response (less than a partial response or disease progression). The enrollment criteria included an absolute neutrophil count of at least 1000 and a platelet count of at least 50,000. The trial excluded patients who had thromboembolic disease within the prior 6 months and those with known hypercoagulability.

ABSTRACT SUMMARY PRM-151 in Myelofibrosis: Efficacy and Safety in an Open-Label Extension Study

An open-label extension study evaluated PRM-151, a recombinant human pentraxin-2 molecule, in patients with myelofibrosis (Abstract 686). Patients in the main part of the study received PRM-151 (10 mg/kg, weekly or monthly) alone or in combination with ruxolitinib for 6 cycles. Eighteen patients in the extension study continued with PRM-151 at 10 mg/kg monthly, with or without ruxolitinib, up to cycle 48. The median time on study was 30.9 months. The median best change in spleen size was –26%, and the median best change in total symptom score was –64%. By cycle 48, the mean hemoglobin level had increased and the number of patients requiring transfusions had decreased. In half of patients (9/18), reticulin grade improved. Collagen grade improved in 44% of patients (8/18). Among AEs that were possibly related to study treatment, there were 2 reports of grade 3 AE anemia. No grade 4/5 events were reported, and no serious AE was considered related to study treatment.

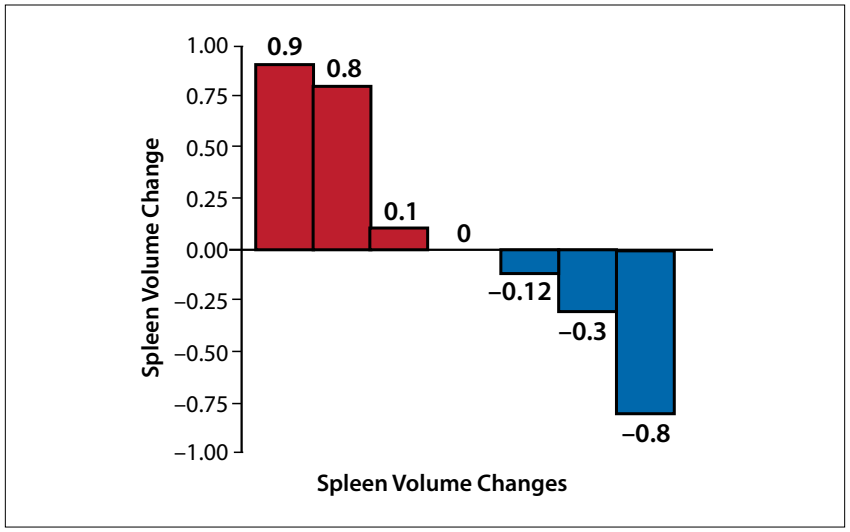


Figure 4. Changes in spleen volume among patients with myelofibrosis treated with ruxolitinib plus thalidomide in a phase 2 trial. Adapted from Rampal RK et al. ASH abstract 354. *Blood*. 2018;132(suppl 1).[3]

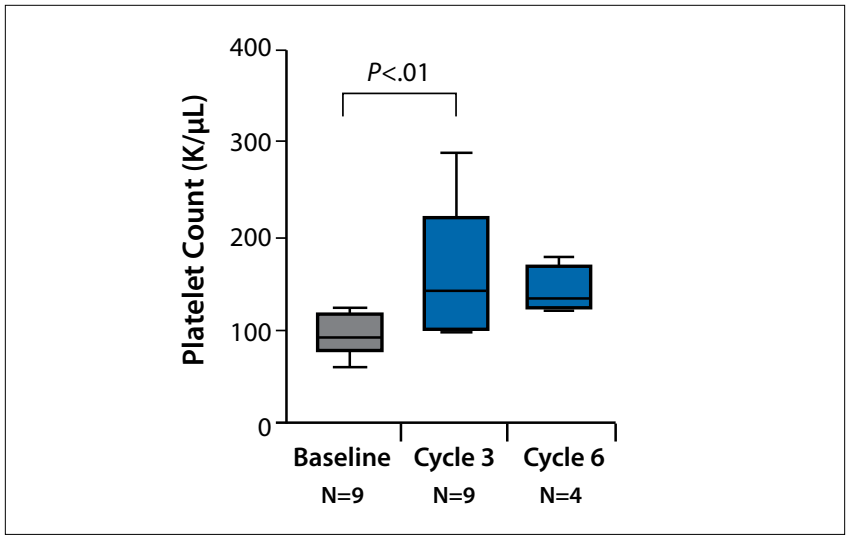


Figure 5. Changes in platelet count among myelofibrosis patients with thrombocytopenia at baseline who were treated with ruxolitinib plus thalidomide in a phase 2 trial. Patients were enrolled in the combination phase, and had received at least 3 months of treatment. Adapted from Rampal RK et al. ASH abstract 354. *Blood*. 2018;132(suppl 1).[3]

Treatment-naive patients received ruxolitinib monotherapy for 12 weeks during the run-in phase. Those with less than a partial response continued with combination study treatment. Combination therapy consisted of ruxolitinib plus thalidomide (50 mg daily). Disease response was assessed after six 28-day cycles of treatment and was based on 2013 response criteria.[4] Platelet responses were defined as major (≥75% increase), intermediate (50% to 74% increase), or minor (25% to 49% increase). The primary objective was to determine the efficacy of ruxolitinib plus thalidomide in patients with myelofibrosis.

Among the 21 study participants, the median age was 70 years (range, 43-85 years), 28.5% were female, and the median disease duration was 28 months (range, 0-178). Nine patients (42.8%) had received prior therapies. The median baseline spleen volume was 1.4 L (range, 0.3-3.1 L). The median baseline hemoglobin level was 8.9 g/dL (range, 6.5-15 g/dL), and the median baseline platelet level was 118 × 10^9/L (range, 49-791/dL). Two-thirds of patients were dependent on red blood cell transfusions. More than 80% of patients had a *JAK2* mutation.

Among 10 evaluable patients, 4 demonstrated clinical improvement based on symptom responses and anemia responses. One patient exhibited a spleen response. Major platelet responses occurred in 6 patients, and 4 patients developed stable disease. Spleen volume decreased in 3 patients (by –.12, –.30, and –.80; Figure 4), and the total symptom score improved in 4 patients (by –1, –5, –14, and –26). Twelve patients had a baseline hemoglobin level of less than 10 g/dL, and this level tended to increase in these patients after 6 cycles of combination treatment. Among 4 evaluable patients who were not transfusion-dependent at baseline, the mean hemoglobin level also increased after 6 cycles of ruxolitinib plus thalidomide. Platelet counts improved with combination treatment, with a significant increase observed after 3 treatment cycles in 9 patients with baseline thrombocytopenia (P<.01; Figure 5). The improvement was maintained after 6 cycles of treatment. Among 4 patients who completed at least 12 cycles of combination therapy, all had an initial platelet increase, and the increase persisted in 3 patients. Hemoglobin levels increased in 3 of the 4 patients and were maintained in 2 patients.

The most common grade 1/2 nonhematologic AEs were dizziness (33.3%), pain (33.3%), fevers (26.6%), and dyspnea (26.6%). Grade 3/4 nonhematologic AEs included limb edema and diarrhea in 1 patient each (6.7%). Treatment-emergent grade 3/4 neutropenia and deep vein thrombosis each occurred in

1 patient (6.7%). Twelve patients (57%) withdrew from the study, most commonly owing to investigator decision (33.3%), AEs (16.6%), and progression to accelerated-phase disease (16.6%). One patient each (8.3%) discontinued treatment owing to allogeneic stem cell transplant, thrombocytosis requiring hydroxyurea, patient decision, and noncompliance.

References

1. Bose P, Verstovsek S. Management of myelofibrosis-related cytopenias. *Curr Hematol Malig Rep*. 2018;13(3):164-172.
2. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366(9):799-807.
3. Rampal RK, Verstovsek S, Devlin SM, et al. Safety and efficacy of combined ruxolitinib and thalidomide in patients with myelofibrosis: initial results of a phase II study [ASH abstract 354]. *Blood*. 2018;132(suppl 1).
4. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. *Blood*. 2013;122(8):1395-1398.

Evidence for Superior Efficacy and Disease Modification After Three Years of Prospective Randomized Controlled Treatment of Polycythemia Vera Patients With Ropeginterferon Alfa-2b Vs HU/BAT

Interferons have been successfully used to treat PV for 3 decades, demonstrating high rates of hematologic response, independence from phlebotomy, and improvement of pruritus.[1] Sustained reductions in *JAK2* V617F allele burden have been observed, consistent with direct targeting of the PV cells. However, one-fourth of patients discontinue treatment based on associated toxicities, such as flu-like symptoms, mood disorders, and autoimmunity. Ropeginterferon is a pegylated form of interferon alfa-2b with an extended half-life that is compatible with administration every 2 weeks.[2,3] In vitro studies have shown that ropeginterferon can inhibit the proliferation of cell lines with *JAK2* mutations while sparing cells with wild-type *JAK2* and normal CD34-positive cells.[3] This modified interferon formulation also inhibited the in vitro growth of erythroid colonies in progenitors derived from PV patients. An open-label phase 1/2 study of PV patients showed an ORR of 90% with low toxicity.[2]

A randomized phase 3 trial compared ropeginterferon alfa-2b vs standard therapy in patients with PV.[4] The study enrolled treatment-naive patients who required cytoreduction and patients who had previously received hydroxyurea for less than 3 years without a CR. Prior to randomization, patients were stratified based on age, prior hydroxyurea exposure, and prior treatment. After randomization, patients initially received 12 months of treatment with ropeginterferon alfa-2b or hydroxyurea. After 12 months of treatment, patients in the ropeginterferon alfa-2b arm continued to receive the same treatment, whereas patients in the control arm received BAT. Treatment during the second phase of the study continued for up to 5 years. The primary objectives of this analysis were to assess the long-term efficacy of ropeginterferon alfa-2b vs BAT in patients who completed the first 12 months of study treatment. Outcomes included the investigator-assessed hematologic response rate and changes in disease burden.

Among the 171 patients enrolled into the second phase of the study, 95 were randomly assigned to ropeginterferon alfa-2b and 76 to the control treatment. At study entry, these patients had a median age of 58 to 59 years (range, 30-85 years), and half were female. The median disease duration was 1.8 months (range, 0-146 months) in the ropeginterferon alfa-2b arm vs 1.6 months (range, 0-92 months) in the control arm. In the ropeginterferon alfa-2b arm, 31.6% of patients had received prior treatment with hydroxyurea, and the median spleen length was 13.5 cm (range, 8.5-25.0 cm). Disease-related symptoms at baseline were noted in 15.8% of patients, and the mean *JAK2* V617F allele burden was 42.8%±23.0%. In the control arm, 26.3% of patients had received prior hydroxyurea treatment, and the median spleen length was 12.8 cm (range, 7.5-22.0 cm). Symptoms related to disease were observed in 22.4% of patients, and the mean *JAK2* V617F allele burden was 42.9%±23.0%. The mean hematocrit was 48.3%±5.3% in the ropeginterferon arm and 49.9%±5.5% in the control arm. During year 3, the median doses were 425 µg every 2 weeks for ropeginterferon alfa-2b and 1000 mg daily for hydroxyurea.

The rate of hematologic CR was superior with ropeginterferon alfa-2b treatment after approximately 2 years, and the difference was maintained at month 36 (HR, 1.38; 95% CI, 1.07-1.79; Figure 6). The rates of complete hematologic response after 36 months of treatment were 71% with ropeginterferon alfa-2b vs 51% with the control therapy. The rate of hematologic CR plus improvement in disease burden was significantly improved with ropeginterferon alfa-2b after 36 months of treatment (52.6% vs 37.8%; HR, 1.42; 95% CI, 1.01-2.00; *P*=.0437).

Hydroxyurea yielded an initial molecular response, based on reduction of *JAK2* V617F clones, but this response was not maintained over time. In contrast, after 36 months of

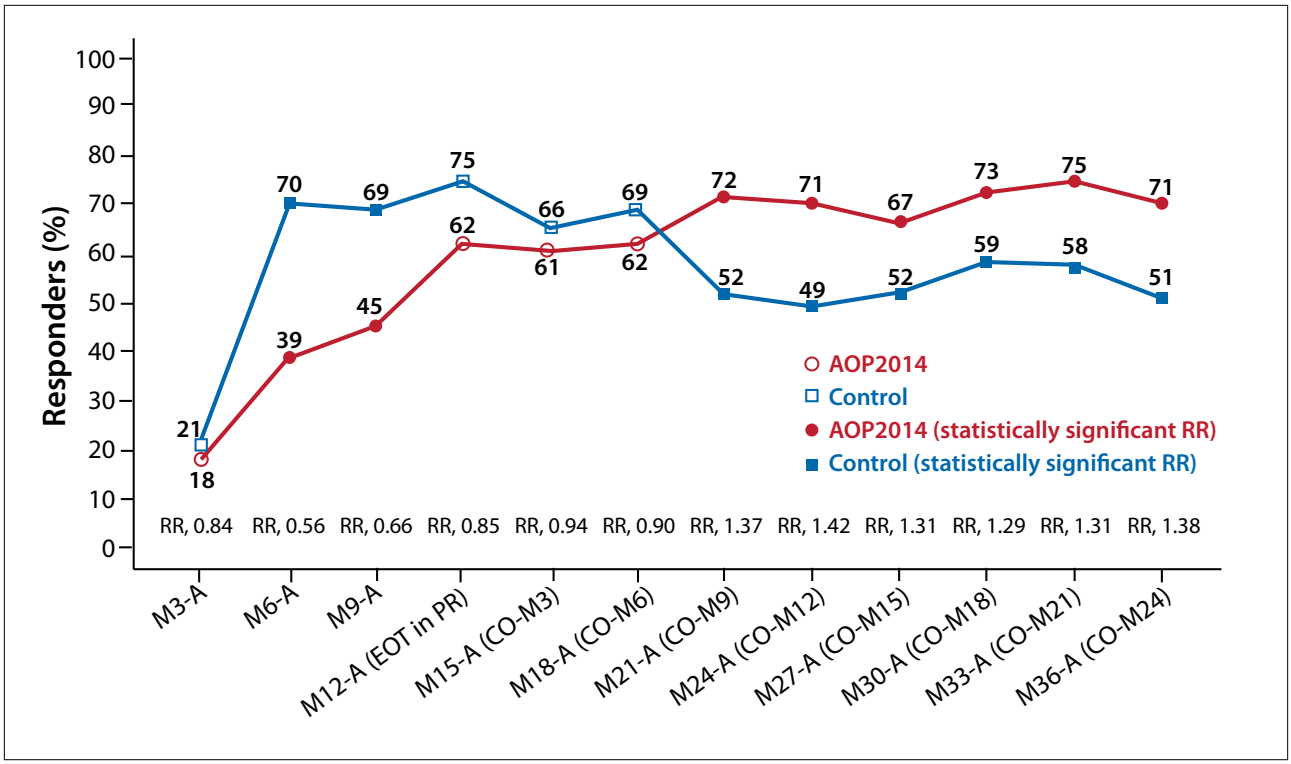


Figure 6. Complete hematologic response in a phase 3 trial comparing ropeginterferon alfa-2b vs standard therapy in patients with polycythemia vera. Data for the full analysis set are shown. A, AOP2014; AOP2014, ropeginterferon alfa-2b; CO, control; EOT, end of treatment; M, month; PR, partial response; RR, relative risk. Adapted from Gisslinger H et al. ASH abstract 579. *Blood*. 2018;132(suppl 1).[4]

ABSTRACT SUMMARY Ruxolitinib Therapy Improves Renal Function in Patients With Primary Myelofibrosis

A retrospective analysis evaluated the effect of first-line ruxolitinib therapy on renal function in 100 patients with primary myelofibrosis (Abstract 4296). The control arm included 105 patients with primary myelofibrosis who received first-line therapy with an agent other than ruxolitinib, matched by age, sex, and estimated glomerular filtration rate. Compared with the control group, patients treated with first-line ruxolitinib were more likely to experience renal improvement (81% vs 58%; *P*<.001). A renal improvement of greater than 10% was achieved in 73% of the ruxolitinib arm vs 50% of the control arm (*P*=.01), after a median treatment duration of 11 or 7 months, respectively. Multivariate analysis showed an independent association between renal improvement of at least 10% and treatment with ruxolitinib (odds ratio [OR], 3; 95% CI, 1.6-5.5; *P*<.001) and nonwhite race (OR, 15.8; 95% CI, 2-127; *P*=.01). Prolonged failure-free survival was associated with renal improvement of greater than 10% (HR, 1.4; 95% CI, 1.1-2; *P*=.02) and ruxolitinib treatment (*P*=.01).

treatment, ropeginterferon alfa-2b was associated with a higher rate of molecular responses (66% vs 27%; HR, 2.31; 95% CI, 1.56-3.42), as well as a higher relative change from baseline (*P*<.0001). A significant correlation was observed between hematologic CR and *JAK2* V617F allele burden at 12, 24, and 36 months, with a Pearson correlation of –.31 (*P*=.0092) at 36 months. In an exploratory analysis, most patients had stable cytogenetics, with aberrations present both at baseline and at 12 months. Deleterious cytogenetic lesions emerged in 3 patients in the hydroxyurea arm during the first 12 months of treatment. In another exploratory analysis, targeted next-generation sequencing was used to evaluate non-*JAK2* genes that are associated with myeloid disorders. This analysis revealed that, after 24 months of treatment, ropeginterferon alfa-2b yielded a reduction in non-*JAK2* disease alleles that was significantly greater than that obtained with the control treatment (*P*=.036).

The most common treatment-related AEs in the control arm were thrombocytopenia (32.9% vs 25.2%), leukopenia (30.3% vs 22.1%), anemia (28.9% vs 10.5%), and decreased platelet count (10.5% vs 0%). Treatment-related AEs that were more common in the ropeginter-

feron alfa-2b arm included increased gamma-glutamyl transferase (11.6% vs 2.6%), increased alanine aminotransferase (10.5% vs 0%), and myalgia (10.5% vs 3.9%). Long-term safety data showed 3 malignancies in the ropeginterferon alfa-2b arm vs 4 malignancies in the control arm. Two patients in the control arm developed acute myeloid leukemia vs none in the ropeginterferon alfa-2b arm.

References

1. Kiladjian JJ, Mesa RA, Hoffman R. The renaissance of interferon therapy for the treatment of myeloid malignancies. *Blood*. 2011;117(18):4706-4715.
2. Gisslinger H, Zagrijtschuk O, Buxhofer-Ausch V, et al. Ropeginterferon alfa-2b, a novel IFNα-2b, induces high response rates with low toxicity in patients with polycythemia vera. *Blood*. 2015;126(15):1762-1769.
3. Verger E, Soret-Dulphy J, Maslah N, et al. Ropeginterferon alpha-2b targets JAK2V617F-positive polycythemia vera cells in vitro and in vivo. *Blood Cancer J*. 2018;8(10):94.
4. Gisslinger H, Klade C, Georgiev P, et al. Evidence for superior efficacy and disease modification after three years of prospective randomized controlled treatment of polycythemia vera patients with ropeginterferon alfa-2b vs. HU/BAT [ASH abstract 579]. *Blood*. 2018;132(suppl 1).

Updated Results of a Phase 2 Study of Ruxolitinib in Combination With 5-Azacitidine in Patients With Myelofibrosis

In a phase 2 trial of patients with myelofibrosis, single-agent treatment with 5-azacitidine, an inhibitor of DNA methyltransferase, yielded responses in 24% after a median 5 months of treatment.[1] The median response duration was 4 months. The combination of ruxolitinib plus 5-azacitidine has shown promise in patients with myelofibrosis, reducing splenomegaly with acceptable toxicity.[2]

Ruxolitinib plus 5-azacitidine was evaluated in a prospective, single-arm phase 2 study of patients with myelofibrosis.[3,4] Eligible patients had less than 20% blasts. Key exclusion criteria included prior treatment with 5-azacitidine or ruxolitinib, a platelet level of less than 50 × 10^9/L, and/or an absolute neutrophil count of less than 1.0 × 10^9/L. Treatment included a 3-month run-in phase with ruxolitinib, which was administered at 10 mg to 25 mg twice daily. The dose of 5-azacitidine was 25 mg/m^2 for 5 days starting with cycle 4, but was initiated earlier in patients with increased proliferation or blasts. The dose could be increased by up to 75 mg/m^2. The primary endpoint was the overall response according to criteria from the International Working Group–Myeloproliferative Neoplasms Research and Treatment.[5]

The 54 enrolled patients had a median age of 66 years (range, 48-87 years), 63% were male, and 52% had received prior treatment. Myelofibrosis subcategories included post–essential thrombocythemia myelofibrosis (n=11), post-PV myelofibrosis (n=12), and primary myelofibrosis (n=31). Twenty percent of patients had high-risk disease, and splenomegaly of 5 cm or more was observed in 78% of patients. The median hemoglobin level was 10.6 g/dL (range, 6.8-16.2 g/dL), and the median platelet level was 272 × 10^9/L (range, 68-1070 × 10^9/L). At least 10% blasts in the peripheral blood was noted in 13% of patients, and 93% had a European Myelofibrosis Network fibrosis score of MF-2 or MF-3. Abnormal cytogenetics were reported in 44% of patients, and 59% had a mutation in the *JAK2* gene. Additional nondriver mutations were detected in half of the tested patients (19/38).

After a median follow-up of 34 months (range, 1-64+ months), the ORR was 72% and included 2 partial responses (4%). Measures of clinical improvement included a better total symptom score in 28%, decreased spleen length plus an improved total symptom score in 19%, decreased spleen length only in 13%, an improved total symptom score plus hemoglobin level in 4%, decreased spleen length plus a cytogenetic CR in 4%, and an improved total symptom score plus a cytogenetic CR in 2%. Among patients with a palpable spleen length of at least 5 cm at baseline,

ABSTRACT SUMMARY Updated Results From an Open-Label, Multicenter, Expanded Treatment Protocol Phase 3b Study of Ruxolitinib in Patients With Polycythemia Vera Who Were Hydroxyurea Resistant or Intolerant and for Whom No Alternative Treatment Was Available

An open-label, single-arm, expanded-access, phase 3b trial evaluated the safety and efficacy of ruxolitinib in 161 PV patients with resistance or intolerance to hydroxyurea who had no other standard treatment options (Abstract 1774). At week 24, 45.3% of patients had achieved hematocrit control and 18.0% achieved hematologic remission. A spleen response was observed in 86.7% of patients at any point during the study, and the response was maintained at the end of treatment. A reduction of at least 50% in total symptom score from baseline was achieved in 33.8% of patients by the end of treatment. No new safety signals were raised. The most common AEs of any grade were anemia (31.8/110.2 person-years) and headache (24.5/110.2 person-years).

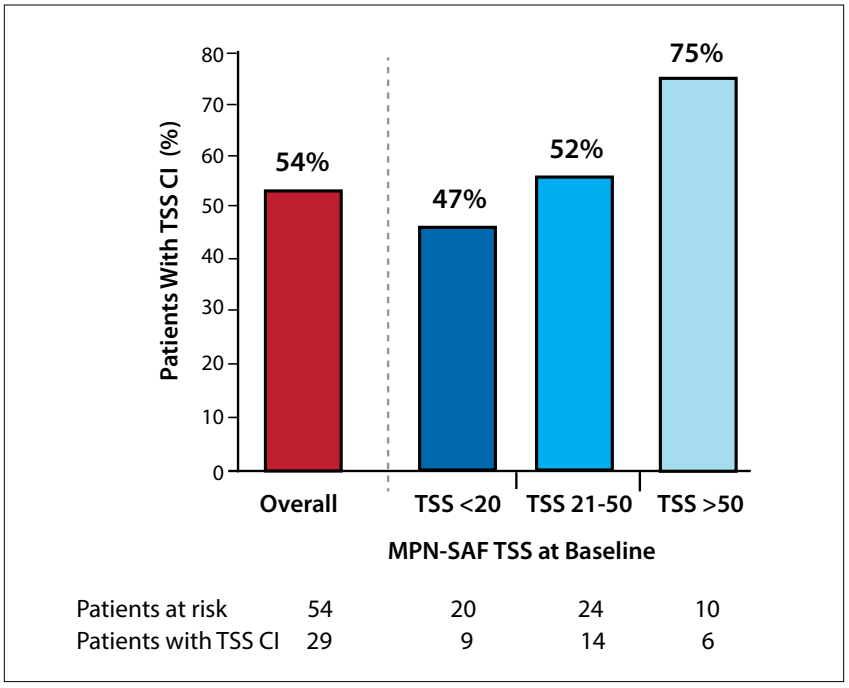


Figure 7. Clinical improvement as measured by the total symptom score among patients with myelofibrosis treated with ruxolitinib plus 5-azacitidine. CI, clinical improvement; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, total symptom score. Adapted from Masarova L et al. ASH abstract 352. *Blood*. 2018;132(suppl 1).[3]

ABSTRACT SUMMARY Alisertib (MLN8237), an Oral Selective Inhibitor of Aurora Kinase A, Has Clinical Activity and Restores GATA1 Expression in Patients With Myelofibrosis

Alisertib, an oral inhibitor of aurora kinase A, was evaluated in 24 patients with myelofibrosis in an investigator-sponsored, multicenter pilot study (Abstract 688). Patients received alisertib (50 mg, twice daily) for 7 days during each 21-day cycle. The median number of treatment cycles was 7.5 (range, 1-29). Among evaluable patients, 32% (7/22) had a symptom response, 29% (4/14) had a spleen response, and 11% (1/19) had an anemia response. Reasons for study discontinuation included disease progression or no response (46%), toxicity (17%), and withdrawal (8%). Improvements were observed in megakaryocyte morphology, GATA1 staining, and bone marrow fibrosis. Among 7 patients who were treated for a median of 23 cycles (range, 8-23 cycles), 4 had a symptom response only, 2 had spleen and symptom responses, and 1 had an anemia response. Grade 4 AEs included neutropenia (21%) and thrombocytopenia (8%). Four serious AEs were reported.

78% demonstrated a response. Clinical improvement in spleen length was observed in 48% of patients at 24 weeks and in 55% at any time during the study. A decrease in palpable spleen length of more than 50% was observed in 57% of patients at 24 weeks and in 64% of patients at any time during the study. The median time until clinical improvement in spleen length was 1.8 months (range, 0.5-18 months), and the median duration of improvement was not reached. The clinical improvement in spleen length was maintained in nearly all patients evaluated at 6 or 12 months.

After the addition of 5-azacitidine, the ORR was 23%, and a decrease of at least 50% in palpable spleen length was observed in 37% of patients (10/37). The median time until response after the addition of 5-azacitidine was 4.4 months (range, 0.2-16.5 months), and the 5-azacitidine dose was increased in 31% of patients during the study. Bone marrow responses, based on levels of reticulin, collagen, and osteosclerosis, were observed in 60% of patients (21/35). The median time until bone marrow response was 12 months (range, 6-18 months). Clinical improvement, as measured by the total symptom score, was reported in 54% of patients overall (Figure 7). The median OS was not reached.

The most common AEs of any grade included infection (31%), constipation (18%), nausea (13%), and fever (13%). The most common grade 3/4 AEs included infection (13%) and fever (7%). Grade 3/4 nausea was observed in 2% of patients. No patients discontinued treatment based on nonhematologic toxicities. Newly onset grade 3/4 hematologic toxicities included anemia (35%), thrombocytopenia (26%), and neutropenia (20%).

References

1. Quintás-Cardama A, Tong W, Kantarjian H, et al. A phase II study of 5-azacitidine for patients with primary and post-essential thrombocythemia/polycythemia vera myelofibrosis. *Leukemia*. 2008;22(5):965-970.
2. Assi R, Kantarjian HM, Garcia-Manero G, et al. A phase II trial of ruxolitinib in combination with azacytidine in myelodysplastic syndrome/myeloproliferative neoplasms. *Am J Hematol*. 2018;93(2):277-285.
3. Masarova L, Verstovsek S, Cortes JE, et al. Updated results of phase 2 study of ruxolitinib in combination with 5-azacitidine in patients with myelofibrosis [ASH abstract 352]. *Blood*. 2018;132(suppl 1).
4. Masarova L, Verstovsek S, Hidalgo-Lopez JE, et al. A phase 2 study of ruxolitinib in combination with azacitidine in patients with myelofibrosis. *Blood*. 2018;132(16):1664-1674.
5. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. *Blood*. 2013;122(8):1395-1398.

Imetelstat Is Effective Treatment for Patients With Intermediate-2 or High-Risk Myelofibrosis Who Have Relapsed on or Are Refractory to Janus Kinase Inhibitor Therapy: Results of a Phase 2 Randomized Study of Two Dose Levels

Imetelstat is a 13-nucleotide oligomer that targets the RNA template of human telomerase.[1,2] In 33 patients with intermediate- or high-risk myelofibrosis, imetelstat led to a CR or partial response in 21%. Bone marrow fibrosis was reversed in all 4 patients with a CR.[3] Treatment-related grade 3/4 AEs included thrombocytopenia, neutropenia, and anemia. Imetelstat was further evaluated in a phase 2 trial at 2 dose levels in patients with myelofibrosis who had relapsed after JAK inhibitor therapy or were refractory to treatment.[4] Enrolled patients had intermediate- or high-risk myelofibrosis with documented progressive disease either during or after JAK inhibitor treatment. Patients had active symptoms of myelofibrosis and measurable splenomegaly at baseline. The primary endpoints were spleen response rate and symptom response rate, both measured at week 24. Patients were stratified by spleen size and platelet levels and then randomly assigned to treatment with imetelstat at 4.7 mg/kg (n=48) or 9.4 mg/kg (n=59). After an interim analysis at 12 weeks, the lower-dose arm was closed and patients could cross over into the higher dose arm.

The trial enrolled 107 patients at 55 institutions. The median treatment duration was 26.9 weeks (range, 0.1-118.1 weeks). The patients' median age was 68.0 years (range, 31-86 years), and 63% were male. Myelofibrosis subtypes included primary disease (59%), post–essential thrombocythemia (18%), and post-PV (23%). High-risk disease was reported in 41%. The median spleen length by palpation was 18 cm (range, 3-35 cm), and 62% of patients had a spleen length of at least 15 cm. The median total symptom score was 23 (range, 3-58). Twenty-four percent of patients were dependent on red blood cell transfusions, and the median platelet count was 147 × 10^9/L (range, 65-1097 × 10^9/L).

The median follow-up was 22.6 months (range, 0.2-27.4 months) for the primary analysis of efficacy and safety. Among the 107 patients, 93% discontinued study treatment, including 25% who did so owing to AEs. The other most common reasons for discontinuation included withdrawal by patient or refusal of treatment (21%), progressive disease (16%), and lack of efficacy (16%). Among the 57 patients (53%) who terminated study participation, 45 (42%) had died, 11 (10%) withdrew, and 1 (1%) was lost to follow-up. Among 105 patients with available biomarker data, 98% had at least 1 mutation and 74% had 3 or more. Twenty-five percent of patients were negative for mutations in *MPL* and *CALR*, and also lacked the *JAK2* V617F mutation. A high-risk molecular profile was reported in 68% of patients.

At week 24, based on intention-to-treat analysis of patients treated with 9.4 mg/kg of imetelstat, spleen volume was reduced by at least 35% in 6 patients (10%) and by at least 10% in 23 patients (37%). Among patients treated with the lower dose, none experienced a spleen volume reduction of 35% or higher; spleen volume was reduced by a lower amount in some patients. Based on total symptom score, 19 patients (32%) in the higher-dose imetelstat arm had a symptom response of at least 50% at week 24 vs 3 (6%) in the lower-dose arm. Bone marrow fibrosis assessments were available for 20 patients in the lower-dose arm and 37 patients in the higher-dose arm. In the lower-dose arm, 8% of patients had an improvement in bone marrow fibrosis, 31% were stable, and 2% worsened. In the higher-dose arm, 25% showed improvement, 25% were stable, and 12% worsened. After a median follow-up of 27.4 months, the median OS was 19.9 months (95% CI, 17.1 to not evaluable) in

ABSTRACT SUMMARY The PIM Kinase Inhibitor TP-3654 in Combination With Ruxolitinib Exhibits Marked Improvement of Myelofibrosis in Murine Models

Preclinical studies were conducted to characterize TP-3654, an inhibitor of PIM1, alone and in combination with ruxolitinib (Abstract 54). In vitro, TP-3654 reduced the proliferation of human hematopoietic cells expressing *JAK2* V617F, synergistically increased apoptosis of *JAK2* V617F mutated cell lines when combined with ruxolitinib, and inhibited proliferation of ruxolitinib-resistant cells. Treatment of ruxolitinib-resistant cells with TP-3654 inhibited cell proliferation in a dose-dependent manner. In homozygous *JAK2* V617F knock-in mice, combined treatment with TP-3654 and ruxolitinib significantly improved splenomegaly, reduced counts of peripheral white blood cells and neutrophils, and lowered levels of $Lin^-Sca\text{-}1^+c\text{-}kit^+$ cells and granulocytes in the bone marrow and spleen. The combination also dramatically reduced levels of fibrosis in the bone marrow and spleen. Similar results were observed in MPL-W515L knock-in mice.

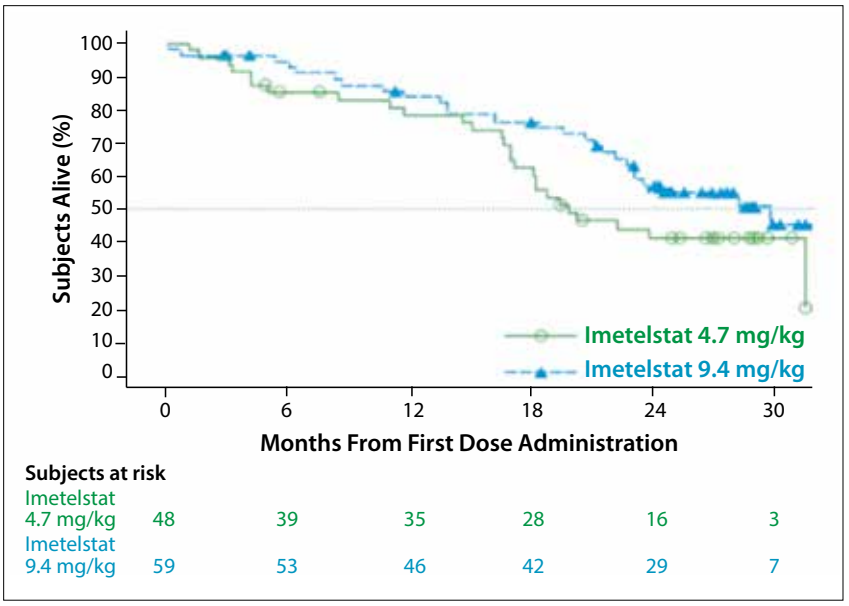


Figure 8. Overall survival in a study of imetelstat given at doses of 4.7 mg/kg and 9.4 mg/kg. Adapted from Mascarenhas JO et al. ASH abstract 685. *Blood*. 2018;132(suppl 1).[4]

the lower-dose arm vs 29.9 months (95% CI, 22.8 to not evaluable) in the higher-dose arm (Figure 8). In the higher-dose arm, patients without mutations in *JAK2*, *CALR*, or *MPL* had a superior survival compared with those who had mutations in all 3 genes (not evaluable vs 24.6 months).

In the higher-dose arm, the most common treatment-emergent hematologic AEs of grade 3 or higher included thrombocytopenia (41%), anemia (39%), neutropenia (32%), and leukopenia (14%). The most common treatment-emergent grade 3/4 nonhematologic AEs included asthenia (10%) and fatigue (7%). Most grade 3/4 cytopenias were reversible within 4 weeks. No hepatic toxicities related to imetelstat occurred.

References

1. Asai A, Oshima Y, Yamamoto Y, et al. A novel telomerase template antagonist (GRN163) as a potential anticancer agent. *Cancer Res*. 2003;63(14):3931-3939.
2. Herbert BS, Gellert GC, Hochreiter A, et al. Lipid modification of GRN163, an N3′—>P5′ thio-phosphoramidate oligonucleotide, enhances the potency of telomerase inhibition. *Oncogene*. 2005;24(33):5262-5268.
3. Tefferi A, Lasho TL, Begna KH, et al. A pilot study of the telomerase inhibitor imetelstat for myelofibrosis. *N Engl J Med*. 2015;373(10):908-919.
4. Mascarenhas JO, Komrokji RS, Cavo M, et al. Imetelstat is effective treatment for patients with intermediate-2 or high-risk myelofibrosis who have relapsed on or are refractory to Janus kinase inhibitor therapy: results of a phase 2 randomized study of two dose levels [ASH abstract 685]. *Blood*. 2018;132(suppl 1).

Ruxolitinib for the Treatment of Inadequately Controlled Polycythemia Vera Without Splenomegaly: 156-Week Follow-Up From the Phase 3 RESPONSE-2 Study

The phase 3 RESPONSE-2 trial evaluated ruxolitinib vs BAT in patients with PV who were resistant to or intolerant of hydroxyurea and had no palpable splenomegaly.[1,2] Eligible patients were phlebotomy-dependent. The study randomly assigned 149 patients to ruxolitinib (10 mg, twice daily) or BAT. Patients in the BAT arm were allowed to cross over to ruxolitinib starting at week 28. The study's primary objective was the proportion of patients achieving hematocrit control at week 28. The key secondary endpoint was the proportion of patients achieving a hematologic CR at week 28, defined as the presence of hematocrit control, a white blood cell count below 10×10^9/L, and a platelet count below 400×10^9/L.

Long-term safety and efficacy data were available after a median follow-up of 156 weeks.[3] At the time of data cutoff, 87.8% of patients in the ruxolitinib arm were still on treatment while all of the patients randomly assigned to BAT had discontinued, and 79.3% of patients in the BAT arm had crossed over to ruxolitinib. In the ruxolitinib arm, the most common reasons for treatment discontinuation included AEs (5.4%) and withdrawal of consent (2.7%). In the BAT arm, the most common reasons were AEs (13.8%), withdrawal of consent (3.4%), death (1.7%), and disease progression (1.7%). The median duration of exposure to treatment was 168.5 weeks (range, 0.1-208.4 weeks) in the ruxolitinib arm, 28.4 weeks (range, 6.7-83.0 weeks) in the BAT arm, and 137.0 weeks (range, 2.7-176.1 weeks) with ruxolitinib in the patients who crossed over. Overall, among patients treated with ruxolitinib, the dose was reduced in 58.1% and interrupted in 18.9%.

Among the 47 patients with hematocrit control at week 28, 29 (61.7%) had durable hematocrit control at week 156, and the estimated median duration of hematocrit control had not been reached (Figure 9). Among

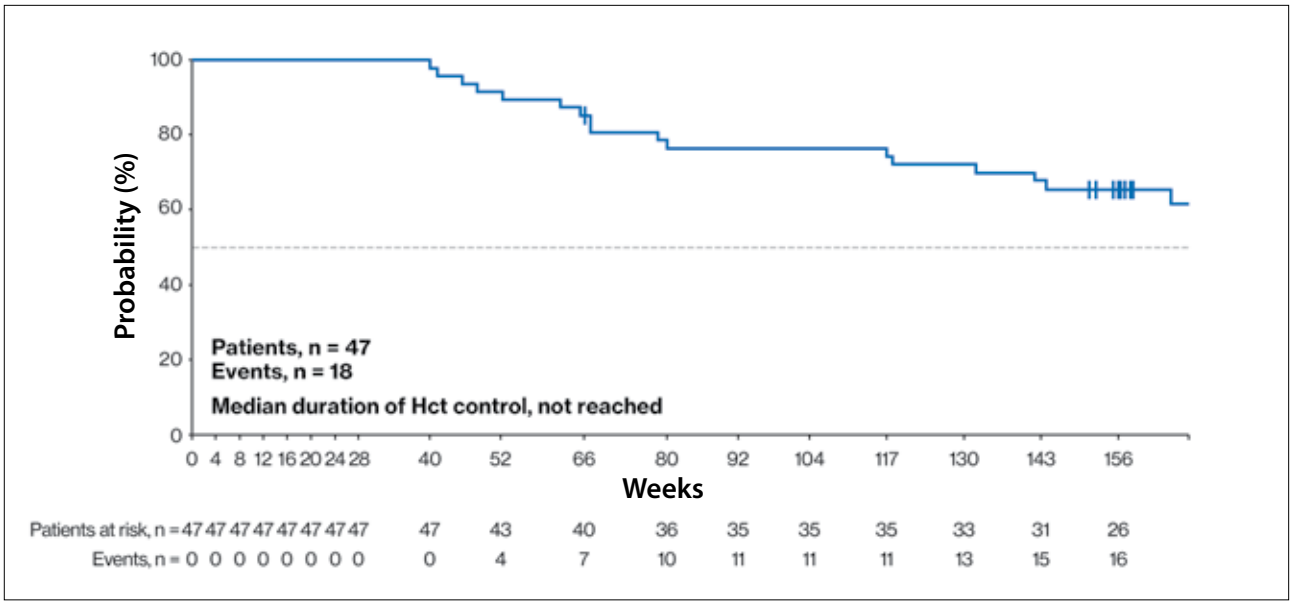


Figure 9. Durability of hematocrit control among patients treated with ruxolitinib in the RESPONSE-2 trial. RESPONSE-2, Ruxolitinib for the Treatment of Inadequately Controlled Polycythaemia Vera Without Splenomegaly. Adapted from Passamonti F et al. ASH abstract 1754. *Blood*. 2018;132(suppl 1).[3]

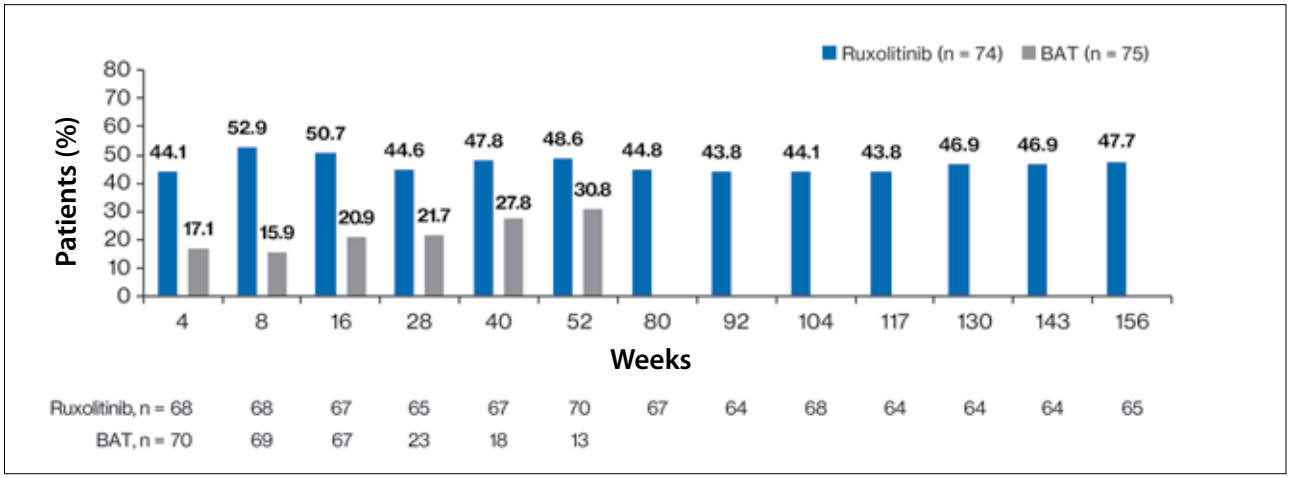


Figure 10. Patients with a 50% or greater reduction from baseline in MPN-SAF TSS in the RESPONSE-2 trial. BAT, best available therapy; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; RESPONSE-2, Ruxolitinib for the Treatment of Inadequately Controlled Polycythaemia Vera Without Splenomegaly; TSS, total symptom score. Adapted from Passamonti F et al. ASH abstract 1754. *Blood*. 2018;132(suppl 1).[3]

the 17 patients who achieved a hematologic CR at week 28, 4 (23.5%) maintained the response at week 156, and the estimated median duration of hematologic CR was 35.9 weeks (95% CI, 13.7-110.3 weeks). In the ruxolitinib arm, 48% of patients had a reduction of at least 50% in the total symptom score at week 156, reflecting durable improvement in symptoms of PV (Figure 10). Patients treated with ruxolitinib also experienced improvement in all 5 categories of the EuroQol EQ-5D-5L assessment. Among patients who crossed over to ruxolitinib treatment, the mean hematocrit level decreased to 45% or less by week 16 and remained low through week 112. The *JAK2* V617F allele burden decreased in patients who crossed over to ruxolitinib, with a mean allele burden of 65.1% at baseline vs 43.9% at week 156. Eight patients randomly assigned to ruxolitinib had a reduction in allele burden of more than 50%.

No new safety signals were raised. In the ruxolitinib arm, the only grade 3/4 hematologic AE was leukocytosis (0.9 per 100 person-years). The most

common nonhematologic grade 3/4 AEs were hypertension (3.4 per 100 person-years) and increased weight (1.3 per 100 person-years). Serious AEs were observed in 24 patients (32.4%) randomly assigned to ruxolitinib and in 15 patients (25.9%) who crossed over to ruxolitinib from the BAT arm. Nonmelanoma skin cancer was the most common secondary malignancy and was present at rates of 3.4/100 person-years in the ruxolitinib arm, 2.8/100 person-years in the crossover patients, and 1.9/100 person-years in the BAT arm.

References

1. Griesshammer M, Saydam G, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly: 80-week follow-up from the RESPONSE-2 trial. *Ann Hematol*. 2018;97(9):1591-1600.
2. Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. *Lancet Oncol*. 2017;18(1):88-99.
3. Passamonti F, Palandri F, Saydam G, et al. Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly: 156-week follow-up from the phase 3 RESPONSE-2 study [ASH abstract 1754]. *Blood*. 2018;132(suppl 1).

Addressing the Adequacy of Current MPN Pain Management Strategies: An International Survey of 502 Patients By the MPN Quality-of-Life Study Group

For patients with MPN, quality of life is significantly impacted by debilitating pain syndromes, commonly including bone and abdominal pain. The MPN Quality of Life Study Group investigated the prevalence and management of MPN pain using surveys posted on websites covering MPN education and advocacy.[1,2] Dr Holly Geyer presented the results of 2 studies: one on pain management strategies and the other on opioid-related complications. Survey questions in the first study explored patient viewpoints on pain, the relationship between MPN-related pain and other chronic pain syndromes, and the impact of pain therapies. Patients completed the Barriers Questionnaire II, which assesses patient barriers to pain management, and the MPN-10 instrument, which assesses MPN patient symptoms.[3,4] Survey questions covered patient demographics, pain history, treatments, barriers to available therapies, and satisfaction with treatment. Among 502 patients who completed the survey, the overall symptom burden was moderate, and 42.3% were dissatisfied with their current pain management. Abdominal pain was reported by 65.6% of patients and bone pain by 60.4%. The mean symptom scores for both abdominal and bone pain were 3.1 and 3.0, respectively, indicating a low to moderate symptom burden. In the survey, 47.1% of patients had a history of chronic pain before the onset of MPN. Among these patients, the pain level stayed the same in 26.2%, worsened in 28.3%, and significantly worsened in 14.5% after the diagnosis of MPN. Opioid use was reported by 31.7% of patients with myelofibrosis, 12.5% of those with PV, and 7.1% of those with essential thrombocythemia. Medication, including acetaminophen, anti-inflammatory agents, and short-acting opioids, was taken regularly by 42.1% of patients to control abdominal pain, bone pain, and/or headaches. Patients were less likely to report a therapeutic benefit from treatments for headache compared with abdominal or bone pain. Prayer/meditation and daily exercise were also used to manage pain.

The second study evaluated opioid use and risk factors for negative outcomes using the MPN-10 and opioid-specific surveys. Among 502 patients, 43.5% discussed pain during doctor visits. Among the 69 patients on active opioid therapy, high-risk features for adverse outcomes included a history of mental health disorders in 60.9%, of substance abuse in 20.3%, and of respiratory disease in 33.3%. Based on criteria from the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, 5.9% of these patients scored "mild" and 2.9% scored "moderate" for opioid use disorder. Nearly one-fourth of patients taking opioids scored at moderate to high risk for opioid use disorder according to the modified Opioid Risk Tool. Compared with patients not receiving opioids, patients on opioid therapy had more frequent and severe symptoms, such as abdominal pain (88.4% vs 61.0%; $P<.001$), unintentional weight loss (41.2% vs 21.4%; $P=.001$), and bone pain (87.0% vs 53.9%; $P<.001$). These patients were also more likely to report regularly taking pain medications (85.5% vs 34.5%; $P<.0001$) and exploring nonpharmacologic treatments to manage symptoms. Satisfaction with their current pain plan was reported by 42.0% of patients receiving opioid therapy vs 62.2% of patients who were not.

References

1. Geyer HL, Scherber RM, Mazza G, et al. Addressing the adequacy of current MPN pain management strategies: an international survey of 502 patients by the MPN Quality of Life Study Group [ASH abstract 4298]. *Blood*. 2018;132(suppl 1).
2. Geyer HL, Scherber RM, Mazza G, et al. Prevalence and risk factors for opioid-related complications in patients with myeloproliferative neoplasms: an international survey of 502 patients by the MPN Quality of Life Study Group [ASH abstract 4297]. *Blood*. 2018;132(suppl 1).
3. Gunnarsdottir S, Donovan HS, Serlin RC, Voge C, Ward S. Patient-related barriers to pain management: the Barriers Questionnaire II (BQ-II). *Pain*. 2002;99(3):385-396.
4. Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. *Blood*. 2011;118(2):401-408.

Highlights in Myeloproliferative Neoplasms From the 60th American Society of Hematology Annual Meeting: Commentary

Ruben A. Mesa, MD
Director, UT Health San Antonio Cancer Center
Mays Family Foundation Distinguished University Chair
Tenured Professor of Medicine
University of Texas Health Science Center
San Antonio, Texas

Presentations at the 60th American Society of Hematology (ASH) annual meeting provided insights into new approaches to the management of myeloproliferative neoplasms. There were combination studies with ruxolitinib and pegylated interferon alfa-2a, as well as trials evaluating novel targets such as the telomerase (with imetelstat) and fibrosis (with PRM-151). Additionally, there were patient-centered scientific discussions on current limitations in the care of patients with myeloproliferative neoplasms, with a focus on opportunities in pain management and opioid use.

Pegylated Interferon Alfa-2a

The randomized phase 3 MPD-RC 112 study, from the Myeloproliferative Disorders Research Consortium, compared pegylated interferon alfa-2a vs hydroxyurea as frontline therapy among patients with high-risk polycythemia vera or essential thrombocytopenia.[1] It was the first such study in these patients. The data showed that both agents had a significant impact in helping to control blood counts and achieve an appropriate clinical response. Through a year of follow-up, the treatments were noninferior to each another. The overall response rate was 78.0% with pegylated interferon alfa-2a and 69.8% with hydroxyurea. This beneficial finding is the first demonstration that the efficacy of pegylated interferon alfa-2a is at least equivalent to that of hydroxyurea. There were slightly different toxicity profiles. Grade 1/2 adverse events that were more common with hydroxyurea included fatigue (seen in 53.0% vs 23.2%) and mucositis (10.0% vs 1.2%). In the pegylated interferon alfa-2a arm, the more common grade 1/2 adverse events included headache (21.9% vs 12.5%) and flu-like symptoms (21.9% vs 2.5%). These events did not impact rates of discontinuation, but they are a factor to be considered. In a separate quality-of-life analysis, also presented at the 60th ASH meeting, both agents showed efficacy and improved symptoms related to myeloproliferative neoplasms.[2]

Dr Heinz Gisslinger provided a long-term follow-up analysis of a phase 3 randomized study, conducted in Europe, that compared ropeginterferon interferon alfa-2b vs hydroxyurea as upfront therapy in patients with polycythemia vera.[3,4] Among patients treated with ropeginterferon interferon alfa-2b, the response rate was 70.5% at months 24 and 36. In the control arm, response rates were 49.3% at 24 months and 51.4% at 36 months. This long-term analysis confirmed earlier reports demonstrating favorable responses and tolerable toxicity in the pegylated interferon arm.[4] There was also a suggestion of a greater degree of molecular control with pegylated interferon.

Ruxolitinib

Dr Jean-Jacques Kiladjian presented 5-year follow-up data from the RESPONSE trial (Study of Efficacy and Safety in Polycythemia Vera Subjects Who Are Resistant to or Intolerant of Hydroxyurea: JAK Inhibitor INC424 [INCB018424] Tablets Versus Best Available Care).[5] In the initial report from the RESPONSE trial, ruxolitinib significantly improved the primary endpoint—a composite of hematocrit control through week 32 and at least a 35% reduction in spleen volume at week 32—vs best available therapy. This endpoint was demonstrated by 21% vs 1% of patients, respectively (P<.001).[6] Subsequent analyses confirmed that responses were durable.[7,8]

The 5-year report demonstrated continued efficacy and durable responses in patients treated with ruxolitinib who had completed the study through 5 years. Ruxolitinib showed continued improvements in the endpoints of hematocrit control, phlebotomy independence, improvement in symptoms, and achievement of a hematologic response. According to Kaplan-Meier analysis, the estimated duration of maintaining primary response at 224 weeks (starting from week 32) was 0.74. The duration of hematocrit control at 224 weeks (starting from week 32) was 0.73.

Long-term, there did not appear to be an imbalance in the rate of toxicities with ruxolitinib compared with the best available therapy. Ruxolitinib was associated with slightly more cases of herpes zoster infections, although rates were less than 5%, and a slightly higher risk of nonmelanoma skin cancers. Overall, this follow-up analysis continues to support the long-term benefits of treatment with ruxolitinib for polycythemia vera.

Dr Raajit Rampal presented results from a combination study of ruxolitinib and thalidomide.[9] Thalidomide was added to ruxolitinib after 3 months in patients who had been treated with a stable dose of ruxolitinib but still had residual cytopenias or less than a partial response. The analysis provided data for 10 evaluable patients from MD Anderson Cancer Center and Memorial Sloan Kettering Cancer Center. Clinical improvement was seen in 40% of patients. Among patients with baseline thrombocytopenia, 60% had an increase in platelets sufficient to consider them responders. Three patients had an anemia response. In addition, some patients had improvements in transfusion dependence or anemia. In a small number of patients, symptomatic difficulties improved. The main toxicities were those previously seen with thalidomide; there was some dizziness and low-grade neuropathy that was not overly problematic.

A study from MD Anderson Cancer Center evaluated ruxolitinib plus azacitidine in treatment-naive patients with myelofibrosis.[10] Azacitidine was added to treatment after patients had received ruxolitinib for 4 cycles. Azacitidine is utilized in patients who have advanced disease with increases in blasts. The researchers believed that the addition of azacitidine seemed to augment preexisting responses in splenomegaly in some patients with symptoms and in some patients with cytopenias. The objective response rate was 72%. The combination of ruxolitinib plus azacitidine led to no significant unexpected toxicities in the trial. The adverse events included the expected cytopenias and low-grade gastrointestinal toxicities that can develop in these patients

Novel Agents

Studies on novel agents provided some promising data. Dr John Mascarenhas presented long-term follow-up of a phase 2 study of imetelstat.[11] The analysis showed safety and efficacy in patients with problematic myelofibrosis. The novel mechanism of action of this drug is telomerase inhibition. Toxicities included cytopenias and elevated liver function levels. Imetelstat is clearly an active drug, and future studies of this agent, either alone or in combination, are warranted.

PRM-151 is an antifibrosing agent. A study by Dr Serge Verstovsek and colleagues provided long-term follow-up for a study of PRM-151 either alone or in combination with ruxolitinib.[12] The study showed safety and efficacy, and some ability to improve fibrosis. A randomized study of single-agent PRM-151 has completed accrual.[13]

Pain in Myeloproliferative Neoplasms

My colleague Dr Holly Geyer presented 2 studies examining pain in patients with myeloproliferative neoplasms.[14,15] These survey research studies were conducted at the University of Texas Health Science Center. Up to 40% of patients with myeloproliferative neoplasms had unmet needs for pain control. Less than half of patients (41%) reported that their doctor discussed pain during visits, indicating an unmet gap for the discussion of adequate pain control. These studies suggest that there are opportunities to more closely examine better ways to control pain among patients with myeloproliferative neoplasms.

Disclosure

Dr Mesa is a consultant for Novartis, Sierra Oncology, and La Jolla Pharmaceutical Company. He has received research funding from Incyte, Celgene, CTI BioPharma, and AbbVie.

References

1. Mascarenhas JO, Kosiorek HE, Prchal JT, et al. Results of the Myeloproliferative Neoplasms - Research Consortium (MPN-RC) 112 randomized trial of pegylated interferon alfa-2a (PEG) versus hydroxyurea (HU) therapy for the treatment of high risk polycythemia vera (PV) and high risk essential thrombocythemia (ET) [ASH abstract 577]. *Blood*. 2018;132(suppl 1).
2. Mesa RA, Kosiorek HE, Mascarenhas J, et al. Impact on MPN symptoms and quality of life of front line pegylated interferon alpha-2a vs. hydroxyurea in high risk polycythemia vera and essential thrombocythemia: results of Myeloproliferative Disorders Research Consortium (MPD-RC) 112 global phase III trial [ASH abstract 3032]. *Blood*. 2018;132(suppl 1).
3. Gisslinger H, Klade C, Georgiev P, et al. Evidence for superior efficacy and disease modification after three years of prospective randomized controlled treatment of polycythemia vera patients with ropeginterferon alfa-2b vs. HU/BAT [ASH abstract 579]. *Blood*. 2018;132(suppl 1).
4. Gisslinger H, Klade C, Georgiev P, et al. Final results from PROUD-PV a randomized controlled phase 3 trial comparing ropeginterferon alfa-2b to hydroxyurea in polycythemia vera patients [ASH abstract 475]. *Blood*. 2016;128(suppl 22).
5. Kiladjian JJ, Zachee P, Hino M, et al. Long-term efficacy and safety (5 years) in RESPONSE, a phase 3 study comparing ruxolitinib (RUX) with best available therapy (BAT) in hydroxyurea (HU)-resistant/intolerant patients (pts) with polycythemia vera (PV) [ASH abstract 1753]. *Blood*. 2018;132(suppl 1).
6. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. *N Engl J Med*. 2015;372(5):426-435.
7. Verstovsek S, Vannucchi AM, Griesshammer M, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial. *Haematologica*. 2016;101(7):821-829.
8. Kiladjian JJ, Verstovsek S, Griesshammer M, et al. Results from the 208-week (4-year) follow-up of RESPONSE trial, a phase 3 study comparing ruxolitinib (rux) with best available therapy (BAT) for the treatment of polycythemia vera (PV) [ASH abstract 322]. *Blood*. 2017;130(suppl 1).
9. Rampal RK, Verstovsek S, Devlin SM, et al. Safety and efficacy of combined ruxolitinib and thalidomide in patients with myelofibrosis: initial results of a phase II study [ASH abstract 354]. *Blood*. 2018;132(suppl 1).
10. Masarova L, Verstovsek S, Cortes JE, et al. Updated results of phase 2 study of ruxolitinib in combination with 5-azacitidine in patients with myelofibrosis [ASH abstract 352]. *Blood*. 2018;132(suppl 1).
11. Mascarenhas JO, Komrokji RS, Cavo M, et al. Imetelstat is effective treatment for patients with intermediate-2 or high-risk myelofibrosis who have relapsed on or are refractory to Janus kinase inhibitor therapy: results of a phase 2 randomized study of two dose levels [ASH abstract 685]. *Blood*. 2018;132(suppl 1).
12. Verstovsek S, Hasserjian RP, Pozdnyakova O, et al. PRM-151 in myelofibrosis: efficacy and safety in an open label extension study [ASH abstract 686]. *Blood*. 2018;132(suppl 1).
13. ClinicalTrials.gov. A phase 2 study of PRM-151 in subjects with myelofibrosis. https://clinicaltrials.gov/ct2/show/NCT01981850. Identifier: NCT01981850. Accessed January 3, 2019.
14. Geyer HL, Scherber RM, Mazza G, et al. Addressing the adequacy of current MPN pain management strategies: an international survey of 502 patients by the MPN Quality of Life Study Group [ASH abstract 4298]. *Blood*. 2018;132(suppl 1).
15. Geyer HL, Scherber RM, Mazza G, et al. Prevalence and risk factors for opioid-related complications in patients with myeloproliferative neoplasms: an international survey of 502 patients by the MPN Quality of Life Study Group [ASH abstract 4297]. *Blood*. 2018;132(suppl 1).


H&O