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A SPECIAL MEETING REVIEW EDITION

Highlights in Myeloproliferative Neoplasms From the 2017 American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the 2017 American Society of Hematology Annual Meeting and Exposition • December 9-12, 2017 • Atlanta, Georgia

Special Reporting on:

- Results From the 208-Week (4-Year) Follow-Up of the RESPONSE Trial, a Phase 3 Study Comparing Ruxolitinib With Best Available Therapy for the Treatment of Polycythemia Vera
- Ropeginterferon Alfa-2b Induces High Rates of Clinical, Hematological and Molecular Responses in Polycythemia Vera: Two-Year Results From the First Prospective Randomized Controlled Trial
- Characteristics and Survival of Patients With Chronic Phase Myelofibrosis and Elevated Blasts (5-9%), and the Effect of Therapy With the JAK2 Inhibitor Ruxolitinib
- Single-Arm Salvage Therapy With Pegylated Interferon Alfa-2a for Patients With High-Risk Polycythemia Vera or High-Risk Essential Thrombocythemia Who Are Either Hydroxyurea-Resistant or Intolerant: Final Results of the Myeloproliferative Disorders–Research Consortium Protocol 111 Global Phase II Trial
- Primary Analysis of JUMP, a Phase 3b, Expanded-Access Study Evaluating the Safety and Efficacy of Ruxolitinib in Patients With Myelofibrosis (N=2233)
- Sotatercept (ACE-011) Alone and in Combination With Ruxolitinib in Patients With Myeloproliferative Neoplasm–Associated Myelofibrosis and Anemia
- Promising Results of a Phase 1/2 Clinical Trial of Ruxolitinib in Patients With Chronic Myelomonocytic Leukemia

PLUS Meeting Abstract Summaries

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Jakafi®
ruxolitinib (tablets)

In patients with polycythemia vera uncontrolled with hydroxyurea

PROVIDE THE PATH THAT MAY LEAD TO MORE CONTROL

INTERVENE WITH JAKAFI

Indications and Usage

Jakafi is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

Important Safety Information

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated
- Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi
- Severe neutropenia (ANC $<0.5 \times 10^9$/L) was generally reversible by withholding Jakafi until recovery
- Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly
- Tuberculosis (TB) infection has been reported. Observe patients taking Jakafi for signs and symptoms of active TB and manage promptly. Prior to initiating Jakafi, evaluate patients for TB risk factors and test those at higher risk for latent infection. Consult a physician with expertise in the treatment of TB before starting Jakafi in patients with evidence of active or latent TB. Continuation of Jakafi during treatment of active TB should be based on the overall risk-benefit determination
- Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate
- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus (HBV) infections. Monitor and treat patients with chronic HBV infection according to clinical guidelines

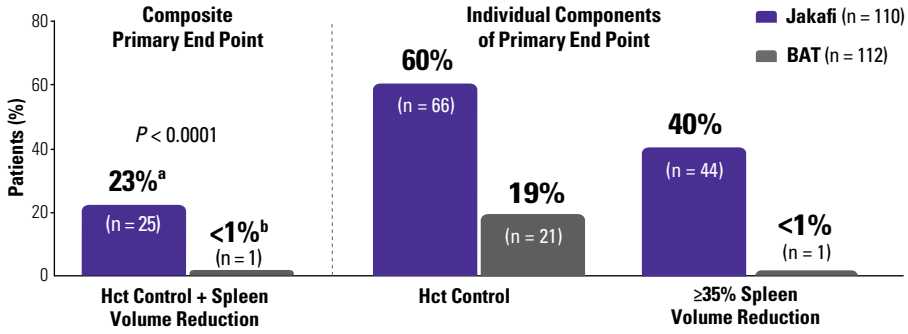
Incyte

Significantly more patients receiving Jakafi achieved the composite primary* and key secondary end points[2,3†]

Jakafi is indicated for treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

National Comprehensive Cancer Network® (NCCN®) recommends ruxolitinib as a treatment option for patients with polycythemia vera who have had an inadequate response to or are intolerant of cytoreductive therapy[1]

Components of Primary End Point at Week 32[2]



BAT, best available therapy; CI, confidence interval; Hct, hematocrit.

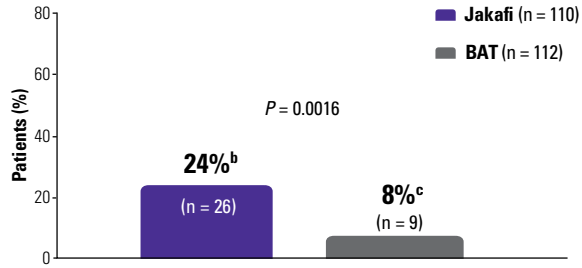
[a] 95% CI, 15%-32%

[b] 95% CI, 0%-5%

* The composite primary end point was defined as Hct control without phlebotomy eligibility and a ≥35% spleen volume reduction as measured by CT or MRI. To achieve the Hct control end point, patients could not become eligible for phlebotomy between weeks 8 and 32. Phlebotomy eligibility was defined as Hct >45% that is ≥3 percentage points higher than baseline or Hct >48% (lower value).

† The RESPONSE (Randomized study of Efficacy and Safety in POlycythemia vera with JAK iNhibitor ruxolitinib verSus bEst available care) trial was a randomized, open-label, active-controlled phase 3 trial comparing Jakafi with BAT in 222 patients with polycythemia vera. All patients were required to demonstrate Hct control between 40% and 45% prior to randomization. BAT included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). Patients enrolled in the study had been diagnosed with polycythemia vera for at least 24 weeks, had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy for Hct control, and exhibited splenomegaly. After week 32, patients were able to cross over to Jakafi treatment. A durability analysis was performed at week 80 in the original Jakafi arm.

Patients Achieving Complete Hematologic Remission[2a]



Durable response at week 80[2]

- 19 of 25 patients (76%) who achieved a primary response at week 32 in the Jakafi arm maintained their response
- 51 of 66 patients (77%) who achieved Hct control at week 32 in the Jakafi arm maintained their response
- 43 of 44 patients (98%) who achieved a ≥35% spleen volume reduction at week 32 in the Jakafi arm maintained their response
- 15 of 26 patients (58%) who achieved complete hematologic remission at week 32 in the Jakafi arm maintained their response

BAT, best available therapy; CI, confidence interval.

[a] Complete hematologic remission was defined as achieving hematocrit control (as specified in the primary end point), platelet count ≤400 × 10^9/L, and white blood cell count ≤10 × 10^9/L.[2,3]

[b] 95% CI, 16%-33% [c] 95% CI, 4%-15%

Durable count control

- When discontinuing Jakafi, myeloproliferative neoplasm-related symptoms may return within one week. After discontinuation, some patients with myelofibrosis have experienced fever, respiratory distress, hypotension, DIC, or multi-organ failure. If any of these occur after discontinuation or while tapering Jakafi, evaluate and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi without consulting their physician. When discontinuing or interrupting Jakafi for reasons other than thrombocytopenia or neutropenia, consider gradual tapering rather than abrupt discontinuation
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred. Perform periodic skin examinations
- Treatment with Jakafi has been associated with increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides. Assess lipid parameters 8-12 weeks after initiating Jakafi. Monitor and treat according to clinical guidelines for the management of hyperlipidemia
- The three most frequent non-hematologic adverse reactions (incidence >10%) were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or fluconazole or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breastfeed during treatment and for two weeks after the final dose

Please see Brief Summary of Full Prescribing Information for Jakafi on the following pages.

To learn more about intervening with Jakafi, visit **Jakafi.com/HCP**.

References: 1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.2.2018. © National Comprehensive Cancer Network, Inc. 2017. All rights reserved. Accessed September 7, 2017. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. **2.** Jakafi Prescribing Information. Wilmington, DE: Incyte Corporation. **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.

Jakafi®
ruxolitinib (tablets)

BRIEF SUMMARY: For Full Prescribing Information, see package insert.

CONTRAINDICATIONS None.

WARNINGS AND PRECAUTIONS Thrombocytopenia, Anemia and Neutropenia Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [*see Dosage and Administration (2.1) in Full Prescribing Information*]. Manage thrombocytopenia by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding Jakafi until recovery [*see Adverse Reactions (6.1) in Full Prescribing Information*]. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated [*see Dosage and Administration (2.1.1) and Adverse Reactions (6.1) in Full Prescribing Information*]. **Risk of Infection** Serious bacterial, mycobacterial, fungal and viral infections have occurred. Delay starting therapy with Jakafi until active serious infections have resolved. Observe patients receiving Jakafi for signs and symptoms of infection and manage promptly. *Tuberculosis* Tuberculosis infection has been reported in patients receiving Jakafi. Observe patients receiving Jakafi for signs and symptoms of active tuberculosis and manage promptly. Prior to initiating Jakafi, patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Risk factors include, but are not limited to, prior residence in or travel to countries with a high prevalence of tuberculosis, close contact with a person with active tuberculosis, and a history of active or latent tuberculosis where an adequate course of treatment cannot be confirmed. For patients with evidence of active or latent tuberculosis, consult a physician with expertise in the treatment of tuberculosis before starting Jakafi. The decision to continue Jakafi during treatment of active tuberculosis should be based on the overall risk-benefit determination. *Progressive Multifocal Leukoencephalopathy* Progressive multifocal leukoencephalopathy (PML) has occurred with Jakafi treatment. If PML is suspected, stop Jakafi and evaluate. *Herpes Zoster* Advise patients about early signs and symptoms of herpes zoster and to seek treatment as early as possible if suspected [*see Adverse Reactions (6.1) in Full Prescribing Information*]. *Hepatitis B* Hepatitis B viral load (HBV-DNA titer) increases, with or without associated elevations in alanine aminotransferase and aspartate aminotransferase, have been reported in patients with chronic HBV infections taking Jakafi. The effect of Jakafi on viral replication in patients with chronic HBV infection is unknown. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines. **Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi** Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi: fever, respiratory distress, hypotension, DIC, or multi-organ failure. If one or more of these occur after discontinuation of, or while tapering the dose of Jakafi, evaluate for and treat any intercurrent illness and consider restarting or increasing the dose of Jakafi. Instruct patients not to interrupt or discontinue Jakafi therapy without consulting their physician. When discontinuing or interrupting therapy with Jakafi for reasons other than thrombocytopenia or neutropenia [*see Dosage and Administration (2.5) in Full Prescribing Information*], consider tapering the dose of Jakafi gradually rather than discontinuing abruptly. **Non-Melanoma Skin Cancer** Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with Jakafi. Perform periodic skin examinations. **Lipid Elevations** Treatment with Jakafi has been associated with increases in lipid parameters including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi therapy. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

ADVERSE REACTIONS The following serious adverse reactions are discussed in greater detail in other sections of the labeling: • Thrombocytopenia, Anemia and Neutropenia [*see Warnings and Precautions (5.1) in Full Prescribing Information*] • Risk of Infection [*see Warnings and Precautions (5.2) in Full Prescribing Information*] • Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi [*see Warnings and Precautions (5.3) in Full Prescribing Information*] • Non-Melanoma Skin Cancer [*see Warnings and Precautions (5.4) in Full Prescribing Information*]. **Clinical Trials Experience in Myelofibrosis** Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of Jakafi was assessed in 617 patients in six clinical studies with a median duration of follow-up of 10.9 months, including 301 patients with MF in two Phase 3 studies. In these two Phase 3 studies, patients had a median duration of exposure to Jakafi of 9.5 months (range 0.5 to 17 months), with 89% of patients treated for more than 6 months and 25% treated for more than 12 months. One hundred and eleven (111) patients started treatment at 15 mg twice daily and 190 patients started at 20 mg twice daily. In patients starting treatment with 15 mg twice daily (pretreatment platelet counts of 100 to 200 X 10^9/L) and 20 mg twice daily (pretreatment platelet counts greater than 200 X 10^9/L), 65% and 25% of patients, respectively, required a dose reduction below the starting dose within the first 8 weeks of therapy. In a double-blind, randomized, placebo-controlled study of Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were thrombocytopenia and anemia [*see Table 2*]. Thrombocytopenia, anemia and neutropenia are dose related effects. The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache [*see Table 1*]. Discontinuation for adverse events, regardless of causality, was observed in 11% of patients treated with Jakafi and 11% of patients treated with placebo. Table 1 presents the most common adverse reactions occurring in patients who received Jakafi in the double-blind, placebo-controlled study during randomized treatment.

Table 1: Myelofibrosis: Adverse Reactions Occurring in Patients on Jakafi in the Double-blind, Placebo-controlled Study During Randomized Treatment

	Jakafi (N=155)			Placebo (N=151)		
Adverse Reactions	**All Grades[a] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Bruising[b]	23	<1	0	15	0	0
Dizziness[c]	18	<1	0	7	0	0
Headache	15	0	0	5	0	0
Urinary Tract Infections[d]	9	0	0	5	<1	<1
Weight Gain[e]	7	<1	0	1	<1	0
Flatulence	5	0	0	<1	0	0
Herpes Zoster[f]	2	0	0	<1	0	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes contusion, ecchymosis, hematoma, injection site hematoma, periorbital hematoma, vessel puncture site hematoma, increased tendency to bruise, petechiae, purpura
[c] includes dizziness, postural dizziness, vertigo, balance disorder, Meniere's Disease, labyrinthitis
[d] includes urinary tract infection, cystitis, urosepsis, urinary tract infection bacterial, kidney infection, pyuria, bacteria urine, bacteria urine identified, nitrite urine present
[e] includes weight increased, abnormal weight gain
[f] includes herpes zoster and post-herpetic neuralgia

Description of Selected Adverse Drug Reactions: Anemia In the two Phase 3 clinical studies, median time to onset of first CTCAE Grade 2 or higher anemia was approximately 6 weeks. One patient (<1%) discontinued treatment because of anemia. In patients receiving Jakafi, mean decreases in hemoglobin reached a nadir of approximately 1.5 to 2.0 g/dL below baseline after 8 to 12 weeks of therapy and then gradually recovered to reach a new steady state that was approximately 1.0 g/dL below baseline. This pattern was observed in patients regardless of whether they had received transfusions during therapy. In the randomized, placebo-controlled study, 60% of patients treated with Jakafi and 38% of patients receiving placebo received red blood cell transfusions during randomized treatment. Among transfused patients, the median number of units transfused per month was 1.2 in patients treated with Jakafi and 1.7 in placebo treated patients. **Thrombocytopenia** In the two Phase 3 clinical studies, in patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was approximately 8 weeks. Thrombocytopenia was generally reversible with dose reduction or dose interruption. The median time to recovery of platelet counts above 50 X 10^9/L was 14 days. Platelet transfusions were administered to 5% of patients receiving Jakafi and to 4% of patients receiving control regimens. Discontinuation of treatment because of thrombocytopenia occurred in <1% of patients receiving Jakafi and <1% of patients receiving control regimens. Patients with a platelet count of 100 X 10^9/L to 200 X 10^9/L before starting Jakafi had a higher frequency of Grade 3 or 4 thrombocytopenia compared to patients with a platelet count greater than 200 X 10^9/L (17% versus 7%). **Neutropenia** In the two Phase 3 clinical studies, 1% of patients reduced or stopped Jakafi because of neutropenia. Table 2 provides the frequency and severity of clinical hematology abnormalities reported for patients receiving treatment with Jakafi or placebo in the placebo-controlled study.

Table 2: Myelofibrosis: Worst Hematology Laboratory Abnormalities in the Placebo-Controlled Study[a]

	Jakafi (N=155)			Placebo (N=151)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Thrombocytopenia	70	9	4	31	1	0
Anemia	96	34	11	87	16	3
Neutropenia	19	5	2	4	<1	1

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

Additional Data from the Placebo-controlled Study 25% of patients treated with Jakafi and 7% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in alanine transaminase (ALT). The incidence of greater than or equal to Grade 2 elevations was 2% for Jakafi with 1% Grade 3 and no Grade 4 ALT elevations. 17% of patients treated with Jakafi and 6% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in aspartate transaminase (AST). The incidence of Grade 2 AST elevations was <1% for Jakafi with no Grade 3 or 4 AST elevations. 17% of patients treated with Jakafi and <1% of patients treated with placebo developed newly occurring or worsening Grade 1 elevations in cholesterol. The incidence of Grade 2 cholesterol elevations was <1% for Jakafi with no Grade 3 or 4 cholesterol elevations. **Clinical Trial Experience in Polycythemia Vera** In a randomized, open-label, active-controlled study, 110 patients with PV resistant to or intolerant of hydroxyurea received Jakafi and 111 patients received best available therapy [*see Clinical Studies (14.2) in Full Prescribing Information*]. The most frequent adverse drug reaction was anemia. Table 3 presents the most frequent non-hematologic treatment emergent adverse events occurring up to Week 32. Discontinuation for adverse events, regardless of causality, was observed in 4% of patients treated with Jakafi.

Table 3: Polycythemia Vera: Treatment Emergent Adverse Events Occurring in ≥ 6% of Patients on Jakafi in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment

	Jakafi (N=110)		Best Available Therapy (N=111)	
Adverse Events	**All Grades[a] (%)**	**Grade 3-4 (%)**	**All Grades (%)**	**Grade 3-4 (%)**
Headache	16	<1	19	<1
Abdominal Pain[b]	15	<1	15	<1
Diarrhea	15	0	7	<1
Dizziness[c]	15	0	13	0
Fatigue	15	0	15	3
Pruritus	14	<1	23	4
Dyspnea[d]	13	3	4	0
Muscle Spasms	12	<1	5	0
Nasopharyngitis	9	0	8	0
Constipation	8	0	3	0
Cough	8	0	5	0
Edema[e]	8	0	7	0
Arthralgia	7	0	6	<1
Asthenia	7	0	11	2
Epistaxis	6	0	3	0
Herpes Zoster[f]	6	<1	0	0
Nausea	6	0	4	0

[a] National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
[b] includes abdominal pain, abdominal pain lower, and abdominal pain upper
[c] includes dizziness and vertigo
[d] includes dyspnea and dyspnea exertional
[e] includes edema and peripheral edema
[f] includes herpes zoster and post-herpetic neuralgia

Other clinically important treatment emergent adverse events observed in less than 6% of patients treated with Jakafi were: Weight gain, hypertension, and urinary tract infections. Clinically relevant laboratory abnormalities are shown in Table 4.

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment[a]

	Jakafi (N=110)			Best Available Therapy (N=111)		
Laboratory Parameter	**All Grades[b] (%)**	**Grade 3 (%)**	**Grade 4 (%)**	**All Grades (%)**	**Grade 3 (%)**	**Grade 4 (%)**
Hematology						
Anemia	72	<1	<1	58	0	0
Thrombocytopenia	27	5	<1	24	3	<1
Neutropenia	3	0	<1	10	<1	0
Chemistry						
Hypercholesterolemia	35	0	0	8	0	0
Elevated ALT	25	<1	0	16	0	0
Elevated AST	23	0	0	23	<1	0
Hypertriglyceridemia	15	0	0	13	0	0

[a] Presented values are worst Grade values regardless of baseline
[b] National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0

DRUG INTERACTIONS **Fluconazole** Concomitant administration of Jakafi with fluconazole doses greater than 200 mg daily may increase ruxolitinib exposure due to inhibition of both the CYP3A4 and CYP2C9 metabolic pathways [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Avoid the concomitant use of Jakafi with fluconazole doses of greater than 200 mg daily [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Strong CYP3A4 inhibitors** Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors [*see Dosage and Administration (2.3) in Full Prescribing Information*]. **Strong CYP3A4 inducers** Concomitant administration of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure [*see Clinical Pharmacology (12.3) in Full Prescribing Information*]. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [*see Clinical Pharmacology (12.3) in Full Prescribing Information*].

USE IN SPECIFIC POPULATIONS **Pregnancy: Risk Summary** When pregnant rats and rabbits were administered ruxolitinib during the period of organogenesis adverse developmental outcomes occurred at doses associated with maternal toxicity (*see Data*). There are no studies with the use of Jakafi in pregnant women to inform drug-associated risks. The background risk of major birth defects and miscarriage for the indicated populations is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. The background risk in the U.S. general population of major birth defects is 2% to 4% and miscarriage is 15% to 20% of clinically recognized pregnancies. **Data:** *Animal Data* Ruxolitinib was administered orally to pregnant rats or rabbits during the period of organogenesis, at doses of 15, 30 or 60 mg/kg/day in rats and 10, 30 or 60 mg/kg/day in rabbits. There were no treatment-related malformations. Adverse developmental outcomes, such as decreases of approximately 9% in fetal weights were noted in rats at the highest and maternally toxic dose of 60 mg/kg/day. This dose results in an exposure (AUC) that is approximately 2 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In rabbits, lower fetal weights of approximately 8% and increased late resorptions were noted at the highest and maternally toxic dose of 60 mg/kg/day. This dose is approximately 7% the clinical exposure at the maximum recommended dose. In a pre- and post-natal development study in rats, pregnant animals were dosed with ruxolitinib from implantation through lactation at doses up to 30 mg/kg/day. There were no drug-related adverse findings in pups for fertility indices or for maternal or embryofetal survival, growth and development parameters at the highest dose evaluated (34% the clinical exposure at the maximum recommended dose of 25 mg twice daily). **Lactation: Risk Summary** No data are available regarding the presence of ruxolitinib in human milk, the effects on the breast fed infant, or the effects on milk production. Ruxolitinib and/or its metabolites were present in the milk of lactating rats (*see Data*). Because many drugs are present in human milk and because of the potential for thrombocytopenia and anemia shown for Jakafi in human studies, discontinue breastfeeding during treatment with Jakafi and for two weeks after the final dose. **Data:** *Animal Data* Lactating rats were administered a single dose of [^{14}C]-labeled ruxolitinib (30 mg/kg) on postnatal Day 10, after which plasma and milk samples were collected for up to 24 hours. The AUC for total radioactivity in milk was approximately 13-fold the maternal plasma AUC. Additional analysis showed the presence of ruxolitinib and several of its metabolites in milk, all at levels higher than those in maternal plasma. **Pediatric Use** The safety and effectiveness of Jakafi in pediatric patients have not been established. Jakafi was evaluated in a single-arm, dose-escalation study (NCT01164163) in 27 pediatric patients with relapsed or refractory solid tumors (Cohort A) and 20 with leukemias or myeloproliferative neoplasms (Cohort B). The patients had a median age of 14 years (range, 2 to 21 years) and included 18 children (age 2 to < 12 years), and 14 adolescents (age 12 to <17 years). The dose levels tested were 15, 21, 29, 39, or 50 mg/m^2 twice daily in 28-day cycles with up to 6 patients per dose group. Overall, 38 (81%) patients were treated with no more than a single cycle of Jakafi, while 3, 1, 2, and 3 patients received 2, 3, 4, and 5 or more cycles, respectively. A protocol-defined maximal tolerated dose was not observed, but since few patients were treated for multiple cycles, tolerability with continued use was not assessed adequately to establish a recommended Phase 2 dose. The safety profile in children was similar to that seen in adults. **Geriatric Use** Of the total number of patients with MF in clinical studies with Jakafi, 52% were 65 years and older, while 15% were 75 years and older. No overall differences in safety or effectiveness of Jakafi were observed between these patients and younger patients. **Renal Impairment** Reduce the Jakafi dosage when administering Jakafi to patients with MF and moderate (CLcr 30 mL/min to 59 mL/min as estimated using Cockcroft-Gault) or severe renal impairment (CLcr 15mL/min to 29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for patients with PV and moderate (CLcr 30 to 59 mL/min) or severe renal impairment (CLcr 15 to 29 mL/min) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for all patients with ESRD on dialysis [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. **Hepatic Impairment** Reduce the Jakafi dosage when administering Jakafi to patients with MF and any degree of hepatic impairment (Child-Pugh Class A, B and C) and with a platelet count between 50 X 10^9/L and 150 X 10^9/L [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*]. Reduce the Jakafi dosage for patients with PV and hepatic impairment (Child-Pugh Class A, B and C) [*see Dosage and Administration (2.4) and Clinical Pharmacology (12.3) in Full Prescribing Information*].

OVERDOSAGE There is no known antidote for overdoses with Jakafi. Single doses up to 200 mg have been given with acceptable acute tolerability. Higher than recommended repeat doses are associated with increased myelosuppression including leukopenia, anemia and thrombocytopenia. Appropriate supportive treatment should be given. Hemodialysis is not expected to enhance the elimination of Jakafi.

Revised: December 2017 RUX-2429

Results From the 208-Week (4-Year) Follow-Up of the RESPONSE Trial, a Phase 3 Study Comparing Ruxolitinib With Best Available Therapy for the Treatment of Polycythemia Vera

The global, multicenter, open-label, phase 3 RESPONSE trial (Randomized Study of Efficacy and Safety in Polycythemia Vera With JAK Inhibitor INCB018424 Versus Best Supportive Care) established the efficacy and safety of the Janus kinase (JAK) 1/2 inhibitor ruxolitinib in patients with polycythemia vera who are resistant or intolerant to hydroxyurea.[1] At the 2017 American Society of Hematology (ASH) meeting, investigators presented updated findings that confirmed the long-term safety and efficacy of ruxolitinib in this population.[2] The definition of resistance or intolerance to hydroxyurea was based on the European LeukemiaNet criteria. Other enrollment requirements included a need for phlebotomy for hematocrit control, a spleen volume of 450 cm^3 or more as assessed by magnetic resonance imaging or computed tomography, and no prior JAK inhibitor treatment.[1] Patients who had a hematocrit below 40% or above 45% underwent a 28-day prerandomization hematocrit control period.

A total of 222 patients were randomly assigned 1:1 to ruxolitinib starting at 10 mg twice daily (n=110) or to a standard therapy (n=112), which consisted of any single agent considered by the treating physician to be the best available therapy. In the ruxolitinib arm, patients could receive dose increases in order to achieve and maintain a hematocrit above 45% without phlebotomy, to reduce spleen size, and to normalize counts of white blood cells and platelets.[1] Patients in the standard-therapy arm could cross over to the ruxolitinib arm at week 32 if they had not met the primary endpoint, or at a later time if they became eligible for phlebotomy and/or developed splenomegaly progression.[1,2] By week 80 (1.5 years), no patients remained in the control arm. Patients receiving ruxolitinib continued in an extended treatment phase. At the time of the analysis, all patients had at least 4 years of follow-up. The study is ongoing, with 37% of patients in the ruxolitinib arm and 38% of crossover patients receiving ruxolitinib at the time of the analysis. The treatment was completed as per protocol in approximately 30% of patients.[2]

The most common reasons for treatment discontinuation in the ruxolitinib arm were adverse events (AEs; 14%) and disease progression (11%). In the standard-therapy arm, 89% of discontinuations were attributed to lack of efficacy. The median treatment exposure was 225 weeks in the ruxolitinib arm, 189 weeks in the ruxolitinib crossover group, and 34 weeks in the standard-therapy arm.[1]

In the initial report from the RESPONSE trial, ruxolitinib demonstrated a significant improvement in the primary endpoint—a composite of hematocrit control through week 32 and at least a 35% reduction in spleen volume at week 32—over best available therapy. This endpoint was attained by 21% vs 1% of patients, respectively (P<.001).[1] At the 2017 ASH meeting, Dr Jean Jacques Kiladjian presented results of a preplanned analysis from the RESPONSE trial assessing the long-term safety and efficacy of ruxolitinib after a follow-up period of 4 years.[2] Among the 25 patients in the ruxolitinib arm with a primary response to treatment, 6 had developed disease progression. A Kaplan-Meier analysis showed a 73% probability that patients would maintain their primary response for 4 years (Figure 1), including a 73% probability of maintaining hematocrit control and an 86% probability of maintaining spleen response. The median duration of the primary response was not reached.

ABSTRACT SUMMARY Hydroxycarbamide Plus Aspirin Vs Aspirin Alone in Intermediate Risk Essential Thrombocythemia: Results of the PT-1 International, Prospective, Randomized Clinical Trial

The open-label, randomized PT-1 trial (Primary Thrombocythaemia 1) compared the efficacy and safety of hydroxyurea plus aspirin vs aspirin alone in patients with intermediate-risk essential thrombocythemia (Abstract 319). The study randomly assigned patients to hydroxyurea plus aspirin (n=182), with a target platelet count of 200 × 10^9/L to 400 × 10^9/L, or to aspirin alone (n=176). The primary composite endpoint was the proportion of patients with arterial or venous thrombosis, serious hemorrhage, or death from vascular causes. In each arm, 11 events occurred, for an incidence of 0.9 vascular events per 100 patient-years. Platelet counts, hemoglobin levels, and white blood cell counts were significantly higher in the control arm than the hydroxyurea arm for the first 5 to 6 years of the study, after which the confidence intervals began to overlap in line with treatment changes. There were no significant differences in any AEs between study arms or any differences in patient-reported quality-of-life. The investigators concluded that aspirin alone is appropriate for these patients, until they develop another indication that requires cytoreduction.

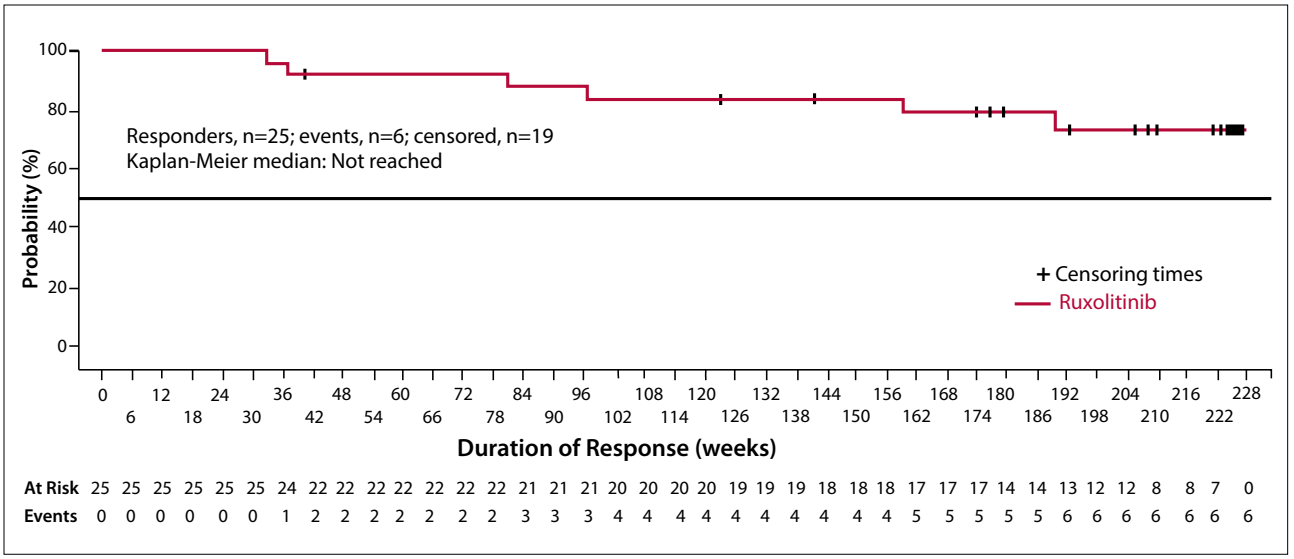


Figure 1. The durability of primary response among patients treated with ruxolitinib in the RESPONSE trial. Adapted from Kiladjian JJ et al. ASH abstract 322. *Blood*. 2017;130(suppl 1).[2]

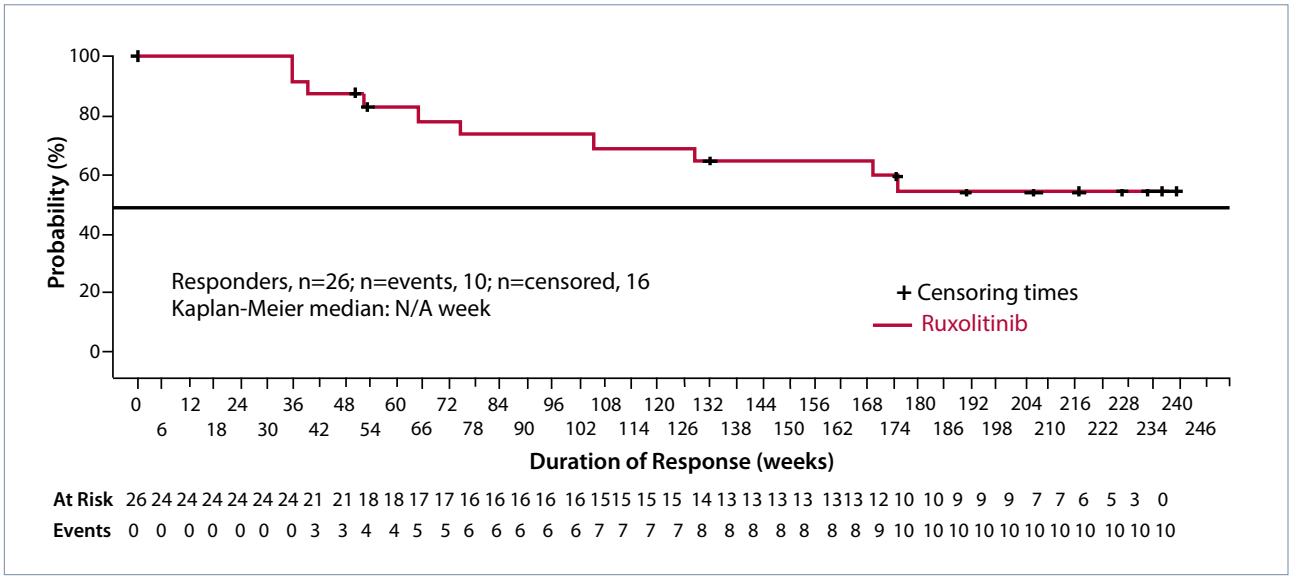


Figure 2. The durability of complete hematologic remission among patients treated with ruxolitinib in the RESPONSE trial. Adapted from Kiladjian JJ et al. ASH abstract 322. *Blood*. 2017;130(suppl 1).[2]

The median duration of complete hematologic remission (defined as hematocrit control, platelet count ≤400 × 10^9/L, and white blood cell count ≤10 × 10^9/L) also was not reached after 4 years, with 54% of patients remaining in a complete hematologic response (Figure 2). Among these patients, 48% had a leukocyte response and 48% maintained their platelet count. Responses were also durable when assessed by clinicohematologic parameters. Among the 70 patients (63.6%) with an overall clinicohematologic response at week 32, 49 remained without progression after 4 years. An estimated 67% of patients maintained a clinicohematologic response at 4 years. The median response duration was not reached.

In an intent-to-treat analysis of overall survival (OS) not accounting for crossover, the estimated 5-year OS rate was 90.6% with ruxolitinib vs 87.7% with standard therapy. Dr Kiladjian noted that these outcomes were more favorable than would be expected based on prior data for patients with resistance or intolerance to hydroxyurea.

A safety analysis showed similar toxicity rates in the ruxolitinib arm vs the crossover population. Hematologic

AEs did not appear to worsen with continued ruxolitinib, and there was a suggestion of some improvement in hematologic parameters with extended ruxolitinib exposure. Anemia of any grade was reported in 9% per 100 patient-years in each group at 4 years, with a reduction from 13% per 100 patient-years in the ruxolitinib arm and 14.9% per 100 patient-years in the crossover group at 1.5 years. At 4 years, thrombocytopenia was reported at a rate of 4.6% per 100 patient-years in the ruxolitinib arm and 1.3% per 100 patient-years in the crossover arm, down from 6.1% and 2.7% per 100 patient-years, respectively, at 1.5 years.

Rates of nonhematologic AEs also appeared to decline somewhat during the study. The most common nonhematologic AE was infection, reported in approximately 20% per 100 patient-years among the ruxolitinib cohort at 4 years. At 1.5 years, this rate was 28% to 29% per 100 patient-years. Rates of herpes zoster infection were approximately 5% per 100 patient-years at 4 years. Rates of thromboembolic AEs were low in both arms at 4 years, at 1.2% per 100 patient-years in the ruxolitinib arm and 2.9% per 100 patient-years in the crossover arm, compared with 1.8% and 4.1% per 100 patient-years, respectively, at 1.5 years. Dr Kiladjian noted that few thromboembolic events occurred between 1.5 years and 4 years.

ABSTRACT SUMMARY A Two-Part Study of Givinostat in Patients With Polycythemia Vera: The Maximum Tolerated Dose Selection and the Proof of Concept Final Results

A phase 1b/2 study evaluated givinostat, an investigational oral histone deacetylase inhibitor, in patients with uncontrolled polycythemia vera (Abstract 253). The phase 1 portion of the study, conducted in 12 patients with *JAK2* V617F–positive polycythemia vera, established 100 mg twice daily as the maximum tolerated dose. The phase 2 study enrolled 35 patients (mean age, 58 years; range, 39-80 years). Previous treatments included aspirin in 74% and hydroxyurea in 46%. Nearly half of patients (45%) had high-risk polycythemia vera (meaning they were ≥60 years and/or had previous thrombosis). Hypertension (controlled by treatment) was reported in 40%. Among 31 evaluable patients, givinostat was associated with an ORR of 81% after 3 months and 83% at 6 months (as assessed by European LeukemiaNet response criteria). Grade 3 diarrhea occurred in 11% of patients, and 9% developed grade 3 hematologic AEs. No grade 4 or 5 AEs occurred. A pivotal trial is planned to further evaluate the efficacy and safety of givinostat for this indication.

Rates of progression were low among ruxolitinib-treated patients, with less than 1% of patients diagnosed with acute myeloid leukemia (AML) and 2% diagnosed with myelofibrosis by 4 years. Rates of other secondary malignancies were less than 1%, with the exception of nonmelanoma skin cancer, which occurred at a rate of 3.6% per 100 patient-years among patients in the ruxolitinib arm without a history of nonmelanoma skin cancer and a rate of 18.6% per 100 patient-years among those with a history of this disease. Since the analysis performed at week 80, an additional death occurred that was considered to be treatment-related: a patient in the ruxolitinib arm died from adenocarcinoma.

References

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Ropeginterferon Alfa-2b Induces High Rates of Clinical, Hematological and Molecular Responses in Polycythemia Vera: Two-Year Results From the First Prospective Randomized Controlled Trial

Interferon is known to consistently induce high rates of hematologic response, phlebotomy independence, and improvement of symptoms in patients with polycythemia vera.[1] Moreover, interferons appear to induce sustained reduction of mutant *JAK2* alleles, suggesting the possibility that the disease can be modified by targeting specific malignant clones.[2]

Newer formulations of interferon have improved the convenience of administration. Ropeginterferon alfa-2b is a novel mono-PEGylated interferon that is administered once every 2 weeks (once monthly in the long-term maintenance setting) using a prefilled, dose-adjustable pen that allows for self-administration. Several clinical trials have recently been conducted evaluating the efficacy and safety of

ropeginterferon in patients with polycythemia vera. The open-label, multicenter, phase 2 PEGINVERA study (Safety Study of Pegylated Interferon Alpha 2b to Treat Polycythemia Vera) demonstrated the long-term efficacy and safety of ropeginterferon alfa-2b administered once monthly as maintenance treatment in patients with polycythemia vera.[3] The randomized, phase 3 PROUD-PV study (Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera) was the first to compare interferon against hydroxyurea and demonstrated the noninferiority of ropeginterferon alfa-2b vs hydroxyurea at 12 months (as assessed by the complete hematologic response rate).[4]

At the 2017 ASH meeting, Dr Heinz Gisslinger presented results from a continuation of the PROUD-PV trial, called CONTINUATION-PV, which evaluated the efficacy and safety of ropeginterferon after a median treatment duration of 2.7 years, allowing for 2-year efficacy analyses and safety data for up to 3.6 years of treatment.[5] The PROUD-PV/CONTINUATION-PV trial enrolled 254 patients with polycythemia vera in need of cytoreduction. Patients could be treatment-naive or pretreated with hydroxyurea. (Those who had received hydroxyurea were not resistant to it.) Patients were stratified based on age, use of previous hydroxyurea, and prior thrombotic events. They were randomly assigned to 12 months of ropeginterferon or hydroxyurea. After 12 months, patients could roll over to the CONTINUATION-PV study. Patients in the control arm could switch to their physician's choice of best available therapy, but crossover to ropeginterferon was not allowed. The CONTINUATION-PV study enrolled 171 patients, with 95 in the ropeginterferon arm and 76 in the control arm.[5]

In both arms, the median duration of disease was 1.2 months. Splenomegaly was reported in 7.4% of patients in the ropeginterferon arm and 10.5% of patients in the control arm. Disease-related symptoms were present in 15.8% vs 22.4%, respectively. Investigators reported no selection bias based on baseline parameters between the PROUD-PV cohort and the subset of patients enrolled in CONTINUATION-PV.

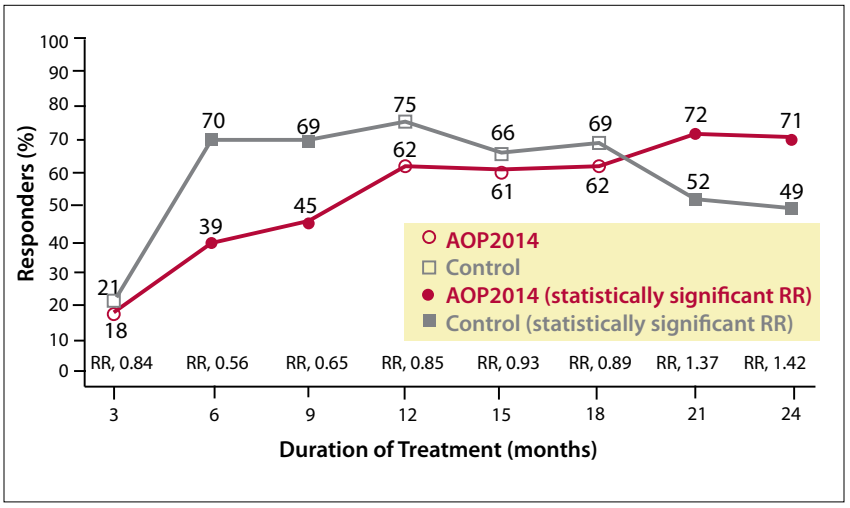

Figure 3. Complete hematologic response at 24 months among patients treated with ropeginterferon alfa-2b (AOP2014) or hydroxyurea (control) in the CONTINUATION-PV trial. RR, relative risk. Adapted from Gisslinger H et al. ASH abstract 320. *Blood.* 2017;130(suppl 1).[5]

Outcomes at 24 months supported the efficacy of ropeginterferon alfa-2b in this population.[5] The proportion of patients attaining a complete hematologic response—defined as a hematocrit less than 45% without phlebotomy, a platelet count less than 400 × 10^9/L, and a white blood cell count less than 10 × 10^9/L—was significantly higher in the ropeginterferon arm vs the control arm (70.5% vs 49.3%; *P*=.0101; Figure 3). There was no significant difference between ropeginterferon and the control treatment in the proportion of patients attaining a complete hematologic response and improvement in disease burden at 24 months (49.5% vs 36.6%; *P*=.1183). Among patients treated with ropeginterferon, the partial molecular response rate at 24 months was significantly higher, at 68.1% vs 34.7% (*P*=.0002). Hematologic, clinical, and molecular response rates increased between months 12 and 24 in the ropeginterferon arm, but decreased over the same period in the control arm.

After a median treatment duration of 2.7 years, the safety analysis showed similar outcomes to those previously reported. Approximately 90% of patients in each arm developed an AE. The rate of treatment-related AEs was 70.1% in the ropeginterferon arm and 77.2% in the control arm. Grade 3 or higher AEs occurred in 27.6% vs 26.0%. The most common treatment-related AEs were thrombocytopenia, reported in 19.7% of patients in the ropeginterferon arm vs 26.8% of patients in the control arm, leukopenia (18.9% vs 22.0%), anemia (9.4% vs 22.0%; *P*=.0091), and increased gamma-glutamyltransferase (11.0% vs 0%; *P*<.0001).

Endocrine disorders occurred in 3.9% of patients in the ropeginterferon arm and 0.8% of those in the control arm. Psychiatric disorders occurred in 2.4% and 0.8% of patients, respectively. Cardiac/vascular disorders developed in 10.2% vs 5.5% of patients. Tissue disorders (rheumatoid arthritis, Sjogren's syndrome) occurred

ABSTRACT SUMMARY Open Label, Phase I Study of Single Agent Oral RG7388 (Idasanutlin) in Patients With Polycythemia Vera and Essential Thrombocythemia

Idasanutlin is a novel antagonist of MDM2, a negative regulator of p53. At the 2017 ASH meeting, Dr John Mascarenhas presented results of a phase 1 study evaluating idasanutlin in patients with *JAK2* V617F–positive polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea and/or interferon (Abstract 254). Patients without a partial response or better after cycle 6 were eligible to receive peginterferon in addition to idasanutlin. Among the 12 patients enrolled, 11 had polycythemia vera and 1 had essential thrombocythemia. The median age was 63.5 years (range, 32-83 years), the median duration of disease was 43.9 months, and 10 patients had received prior hydroxyurea. Idasanutlin was well-tolerated, with no dose-limiting toxicities. No hematologic AEs were reported. Three patients developed grade 3 nonhematologic AEs. Gastrointestinal toxicity occurred and was generally manageable. Idasanutlin was associated with an ORR of 58% (7 of 12) as monotherapy and 50% (2 of 4) in combination with peginterferon. Improvements in symptoms and bone marrow responses were also noted. Idasanutlin is being evaluated in a global, single-arm, phase 2 trial in patients with polycythemia vera with hydroxyurea resistance or intolerance.

in 1.6% of patients in the ropeginterferon arm and no patients in the control arm. Secondary malignancies in the ropeginterferon arm included 1 case each of spermatocytic seminoma, adrenal neoplasm, and glioblastoma, which were not considered related to treatment. Secondary malignancies in the control arm included 2 cases of acute leukemia, 2 cases of basal cell carcinoma, and 1 case of malignant melanoma.

In vitro analyses of the *JAK2* allelic burden over time suggested that interferon provided a sustained targeting of *JAK2* that was observable 2 years of treatment. Non-*JAK2* mutations also appeared to be affected by interferon, with the allelic burden decreasing substantially throughout 24 months in the ropeginterferon arm, but increasing over time in the control arm.

References

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Characteristics and Survival of Patients With Chronic Phase Myelofibrosis and Elevated Blasts (5-9%), and the Effect of Therapy With the JAK2 Inhibitor Ruxolitinib

The JAK2 inhibitor ruxolitinib has improved survival in patients with chronic-phase myelofibrosis who have less than 10% blasts in the bone marrow. Characteristics and outcomes for chronic-phase patients with a blast count from 5% to 9% have not been defined. To assess disease characteristics, survival, and the efficacy of ruxolitinib in this subgroup, Dr Lucia Masarova and colleagues conducted a retrospective review of patients treated for myelofibrosis at the MD Anderson Cancer Center between 1984 and 2015.[1] The cohort included 832 patients with primary myelofibrosis (69%), 169 patients with post–essential thrombocythemia myelofibrosis (14%), and 198 patients with post–polycythemia vera myelofibrosis (17%). Sixty-three percent of patients were newly diagnosed.

Most patients (85%) had less than 5% blasts in the peripheral blood or bone marrow. A range of 5% to 9% blasts was reported in 10% of patients, and 5% of patients had a range of 10% to 19% (indicating accelerated-phase myelofibrosis). Patients with chronic-phase myelofibrosis and 5% to 9% blasts shared more clinical characteristics with patients who had accelerated-phase myelofibrosis than with those who had chronic-phase myelofibrosis and less than 5% blasts. For example, median hemoglobin levels were 11.5 g/dL in patients with chronic-phase myelofibrosis with less than 5% blasts, 10 g/dL in patients

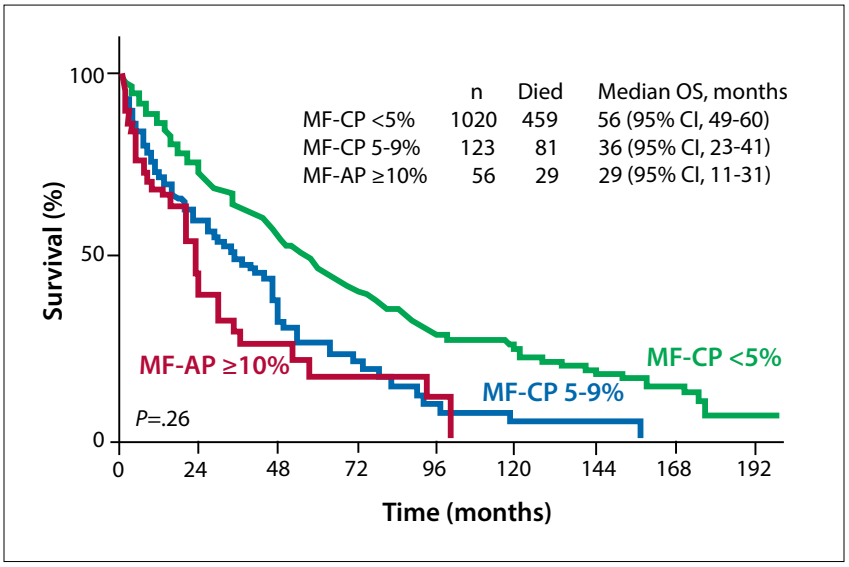

Figure 4. Survival according to blast count among patients with chronic phase or accelerated-phase myelofibrosis. AP, accelerated phase; CP, chronic phase, MF, myelofibrosis. Adapted from Masarova L et al. ASH abstract 201. *Blood.* 2017;130(suppl 1).[1]

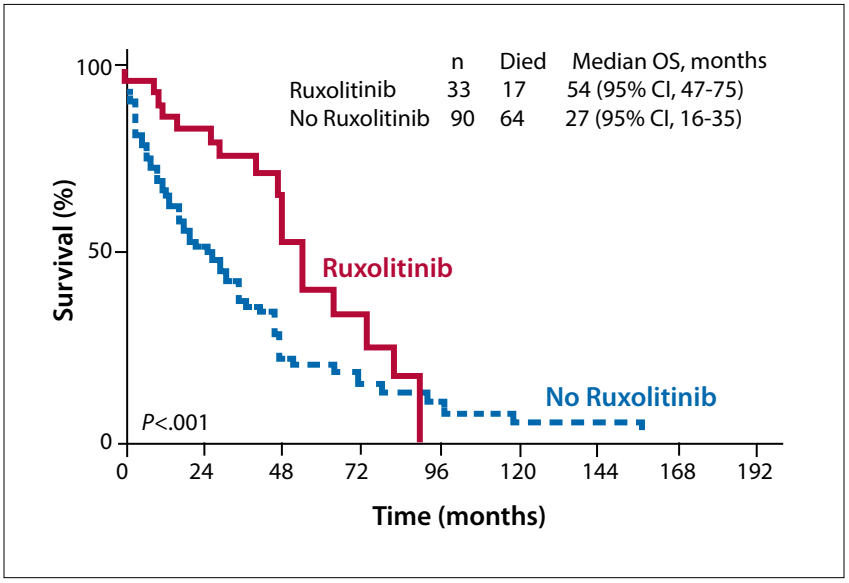

Figure 5. Treatment with ruxolitinib was associated with a survival benefit among patients with chronic-phase myelofibrosis with a high blast count of 5% to 9%. Adapted from Masarova L et al. ASH abstract 201. *Blood.* 2017;130(suppl 1).[1]

with 5% to 9% blasts, and 9 g/dL in patients with accelerated-phase myelofibrosis. Median platelet levels were 217 × 10^9/L, 187 × 10^9/L, and 167 × 10^9/L, respectively. White blood cell levels were 9.5 × 10^9/L, 14 × 10^9/L, and 13 × 10^9/L.

In patients with chronic-phase myelofibrosis, those with elevated blasts were also more likely than patients with lower blast levels to be symptomatic (85% vs 71%), to have an unfavorable karyotype (20% vs 10%), to have splenomegaly (60% vs 48%), to be at intermediate-2 or high risk according to the Dynamic International Prognostic Scoring System (DIPSS; 55% vs 38%), and to have additional molecular mutations beyond *JAK2* (27% vs 15%). For all of these parameters, characteristics in patients with 5% to 9% blasts were more similar to those seen in patients with accelerated-phase myelofibrosis than in patients with chronic-phase myelofibrosis with less than 5% blasts.

Approximately 70% of patients received at least 1 line of treatment during the follow-up period. Patients with higher blast counts tended to receive more therapies. At least 3 therapies were administered to 8% of patients with less than 5% blasts, 36% of patients with 5% to 9% blasts, and 54% of patients with accelerated-phase myelofibrosis. Stem cell transplant was undertaken in 15%, 13%, and 11% of patients, respectively. Ruxolitinib was administered to 32% of patients with less than 5% blasts, for a median treatment duration of 20 months; 27% of patients with 5% to 9% blasts, for a median treatment duration of 26 months; and 11% of patients with accelerated-phase myelofibrosis, for a median treatment duration of 6 months. Spleen response rates were 65%, 48%, and 60%, respectively. Ruxolitinib was most often used as monotherapy. When used in combination, the most common therapies included azacitidine and immunomodulatory agents.

Regardless of the treatment, survival outcomes declined with increasing blast count. The median OS was 56 months in patients with less than 5% blasts, 36 months in patients with 5% to 9% blasts, and 29 months in patients with accelerated-phase myelofibrosis (Figure 4). There was no significant difference in survival between patients with accelerated-phase myelofibrosis and those with 5% to 9% blasts. In contrast, the hazard ratio for survival among patients with less than 5% blasts vs those with 5% to 9% blasts was 0.58 (95% CI, 0.37-0.66).

Ruxolitinib was associated with a survival benefit among patients with chronic-phase myelofibrosis with low

or high blast counts. Among patients with less than 5% blasts, median OS was 61 months with ruxolitinib and 52 months without ruxolitinib (*P*<.02). Among patients with 5% to 9% blasts, the median OS was 54 months with ruxolitinib and 27 months without ruxolitinib (*P*<.001), representing a doubling of survival among ruxolitinib-treated patients (Figure 5). Outcomes among patients with accelerated-phase myelofibrosis were similar to those in patients with 5% to 9% blasts who did not receive ruxolitinib. In the patients with accelerated-phase myelofibrosis, the median OS was 23 months with ruxolitinib and 26 months without ruxolitinib. However, only 6 patients in this group received ruxolitinib, and therefore the patient numbers were insufficient to determine the effects on survival.

There did not appear to be a benefit with the use of combination approaches compared with ruxolitinib monotherapy. However, investigators cautioned against overinterpreting these findings, given the small number of patients who received combination approaches.

Rates of progression to AML increased with the blast count. Among the patients who received ruxolitinib, AML developed in 9% of patients with less than 5% blasts, 21% of patients with 5% to 9% blasts, and 17% of patients with accelerated-phase myelofibrosis. Among patients not treated with ruxolitinib, AML rates were 11%, 33%, and 52%, respectively. Dr Masarova noted that the patient numbers were too low to draw firm conclusions about the effect of ruxolitinib on progression to AML. She concluded that patients with chronic-phase myelofibrosis and 5% to 9% blasts represent a previously undefined high-risk patient population with adverse characteristics and survival outcomes similar to those seen in patients with accelerated-phase myelofibrosis.

Reference

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Single-Arm Salvage Therapy With Pegylated Interferon Alfa-2a for Patients With High-Risk Polycythemia Vera or High-Risk Essential Thrombocythemia Who Are Either Hydroxyurea-Resistant or Intolerant: Final Results of the Myeloproliferative Disorders–Research Consortium Protocol 111 Global Phase II Trial

Hydroxyurea resistance and intolerance in patients with essential thrombocythemia and polycythemia vera is an infrequent but challenging scenario, as it is independently associated with shorter survival and increased risk of transformation to acute leukemia.[1] Interferon therapy has been shown to induce clinical and molecular responses in essential thrombocythemia and polycythemia vera, providing a rationale for prospectively evaluating peginterferon alfa-2a in the treatment of patients with essential thrombocythemia or polycythemia vera who are resistant or intolerant to hydroxyurea.

At the 2017 ASH meeting, Dr Abdulraheem Yacoub presented results from the final analysis of the MPD-RC 111 (Myeloproliferative Disorders Research Consortium 111) trial, an investigator-initiated, international, single-arm phase 2 study that evaluated peginterferon alfa-2a in patients with high-risk essential thrombocythemia (n=65) or polycythemia vera (n=50) with hydroxyurea resistance or intolerance.[2] The primary endpoint was the proportion of patients with an overall response. Complete response (CR) was defined as complete resolution of disease symptoms, normalization of spleen on imaging, and—in patients with polycythemia vera—correction of hematocrit to less than 45% without phlebotomy.

The median age of the enrolled patients was 64 years (range, 20-85 years). Splenomegaly was present in 18.5% of patients with essential thrombocythemia and 56.0% of those with polycythemia vera. The median duration of disease was 37.3 months for essential thrombocythemia (range, 0.4-291 months) and 54.8 months for polycythemia vera (range, 0.5-394 months). Hydroxyurea therapy was administered to 63.5% of patients, for a median duration of 22.5 months (range, 1.0-153 months). A baseline mutational analysis revealed driver mutations and nondriver mutations at rates that would be expected for patients who have high-risk myeloproliferative neoplasms. The median duration of therapy with peginterferon

ABSTRACT SUMMARY Phase 2 Trial of Single-Agent Cobimetinib for Adults With *BRAF* V600-Mutant and Wild-Type Histiocytic Disorders

The MEK inhibitor cobimetinib was evaluated in a phase 2 trial in 16 adults with histiocytosis (Abstract 257). Patients could be refractory to treatment or newly diagnosed. Patients with newly diagnosed disorders had multisystem disease or single-system disease that was associated with end-organ dysfunction or that was unlikely to benefit from available treatment. Patients were required to have *BRAF* V600–wild type disease or *BRAF* V600E–positive disease. All patients had been intolerant to a *BRAF* inhibitor, or they lacked access to one. The study excluded patients with an active infection requiring intravenous antibiotics, with renal pathology or risk factors for retinal vein occlusion, or with clinically significant cardiac function. The metabolic response rate was 87.5% (14 of 16), including 9 CRs. There were no reports of progressive disease. The median time to best response was 2.6 months (range, 1.8-10.8 months), and the median duration of response was 6.6 months (range, 1.0-20.8 months). Responses were observed regardless of *BRAF* status. The safety and tolerability of cobimetinib were similar to those reported in other studies. Symptom scores, anxiety, and depression improved significantly over the course of the study. At the time of the analysis, 12 patients were continuing on treatment, 2 patients had withdrawn consent, 1 patient had died from unrelated pneumonia, and 1 patient had developed treatment-related retinal vein occlusion.

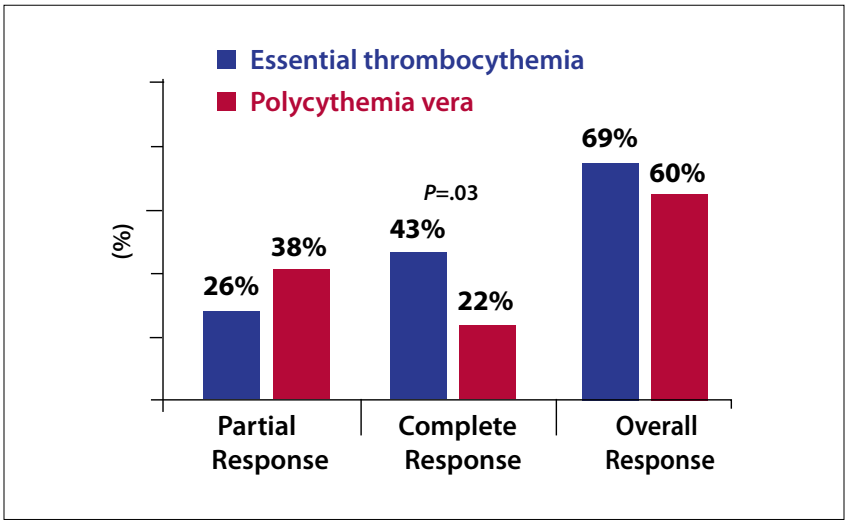

Figure 6. Response at 12 months in a study of peginterferon alfa-2a in patients with high-risk essential thrombocythemia or polycythemia vera with hydroxyurea resistance or intolerance. Adapted from Yacoub A et al. ASH abstract 321. *Blood.* 2017;130(suppl 1).[2]

was 78.5 weeks for patients with essential thrombocythemia (range, 1-245 weeks) and 82 weeks for those with polycythemia vera (range, 4-209 weeks); 72% of patients received more than 12 months of peginterferon. The median administered doses of peginterferon were 102.7 µg in the essential thrombocythemia cohort and 128.7 µg in the polycythemia vera cohort.

In an intent-to-treat analysis, the overall response rate (ORR) was 69% in the essential thrombocythemia cohort and 60% in the polycythemia vera cohort (Figure 6). CR rates were 43% and 22%, respectively. Dr Yacoub noted that 96% of responses were observed in the first 12 months. The median duration of disease was significantly shorter in patients with responses to interferon vs those without responses (33.8 vs 68.1 months; *P*=.05). Interferon dose and younger age did not predict responses to peginterferon. Factors associated with higher CR rates were the presence of *CALR* mutations, a lack of *TP53* mutations, and a lack of *ASXL1* mutations.

The safety profile was as expected for peginterferon, with the most common grade 3/4 toxicities including hematologic AEs (n=9), gastrointestinal and alanine aminotransferase/aspartate aminotransferase abnormalities (n=9), cutaneous manifestations (n=6), and skin cancers (n=6). AEs led to discontinuation in 13.9% of patients. No treatment-related deaths or major bleeding events were reported. Three major cardiovascular events were reported. Two transformations occurred during the follow-up period, including 1 case of essential thrombocythemia that transformed to AML and 1 case of polycythemia vera that transformed to myelofibrosis.

An analysis of variant allele frequency of driver gene mutations by next-generation sequencing showed heterogeneous responses. In 41.3% of patients, the reduction of variant allele frequency exceeded 20%. In 20.6% of patients, the reduction in variant allele frequency was more than 50%. Bone marrow responses were observed in 8 of 68 evaluable patients (11.1%), and 7 of these patients also attained a clinical response. Progression to grade 2+ (0-3) reticulin fibrosis was observed in 7 patients. Cytogenetic assessments revealed acquisition of a simultaneous trisomy of 8 and 9 in 1 patient with a normal baseline karyotype. Clearing

of baseline molecular and cytogenetic abnormalities occurred in 3 patients with polycythemia vera, who also attained a complete clinical response at 12 months.

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Primary Analysis of JUMP, a Phase 3b, Expanded-Access Study Evaluating the Safety and Efficacy of Ruxolitinib in Patients With Myelofibrosis (N=2233)

The phase 3b JUMP expanded access trial (JAK Inhibitor Ruxolitinib in Myelofibrosis Patients) is evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis in countries without access to ruxolitinib outside of a clinical trial setting.[1] Patients were also ineligible for another ruxolitinib trial. The study is the largest to evaluate ruxolitinib in myelofibrosis, and it includes 2233 patients who received treatment at 279 sites across 26 countries in North America, South America, Europe, Asia, and Africa. Enrolled patients had intermediate-2–risk or high-risk myelofibrosis according to the International Prognostic Scoring System (IPSS) criteria, with or without splenomegaly, or intermediate-2–risk myelofibrosis with a palpable spleen. Ruxolitinib was dosed based on the platelet count, with doses ranging from 5 mg to 20 mg twice daily. Treatment was continued for up to 24 months.

The median age of enrolled patients was 67.0 years (range, 18-89 years). The mean time since the initial diagnosis was 51.7 months. The myelofibrosis subtypes included primary myelofibrosis (in 59.4%), post–polycythemia vera myelofibrosis (in 23.8%), and post–essential thrombocythemia myelofibrosis (in 16.7%). The patients' mean hemoglobin level was 109.3 g/dL, and 38.3% of patients had a hemoglobin level of less than 100 g/L. The mean platelet count was 238.6 × 10^9/L, and 62.6% of patients had a platelet count of at least 200 × 10^9/L. Prior treatments included hydroxyurea in 59.3% of patients and transfusions in 25.9%. Nearly a third of patients (31.9%) had at least 1% peripheral blasts. The median palpable spleen length was 12.0 cm (range, 0.5-45.0 cm).

Treatment was completed per protocol in 57.5% of patients. Among the patients who discontinued treatment early, the most common reasons were AEs (18.1%) and disease progression (9.1%). The most common AEs leading to discontinuation were thrombocytopenia (3.5%), infections (2.6%), and anemia (2.0%). Dose modifications and interruptions were required in 67.4% and 27.2% of patients, respectively. The most common grade 3/4 hematologic AEs were anemia (34.8%), thrombocytopenia (16.5%), and neutropenia (4.6%). Median hemoglobin levels declined during the first 8 to 12 weeks of treatment, and then increased to near-baseline levels after week 12. Median platelet levels declined during the first 4 weeks, and then remained stable. The most

ABSTRACT SUMMARY Long-Term Outcome of Patients With MPN-Associated Myelofibrosis Treated With Peg-Interferon-α2a, a French Intergroup of Myeloproliferative Neoplasms Study

Investigators from the French Intergroup of Myeloproliferative Neoplasms presented updated results from an observational study evaluating the efficacy and safety of peginterferon alfa-2a in 62 patients with myelofibrosis (Abstract 323). After a median follow-up of 58 months, 48% of patients were alive and 26% were still receiving peginterferon, for a 5-year actuarial OS of 55%. Progression to AML occurred in 8 patients (13%), with 3 events occurring during the first year of treatment. The median OS was 7.4 years overall, ranging from 4.6 years in DIPSS high-risk patients to 6.9 years in patients with intermediate-2 risk. Median OS was not reached in patients with low-risk myelofibrosis. Median OS was 13.5 years in patients with *CALR* mutations and 7 years in patients with *JAK2* mutations ($P<.0001$). The most common reasons for stopping interferon were resistance (40%) and intolerance (32%). Among the patients who required treatment modifications, 33% switched to ruxolitinib. After these patients stopped interferon, their median OS was 22 months. Investigators noted that the presence of additional mutations beyond *JAK2* was associated with a worse prognosis.

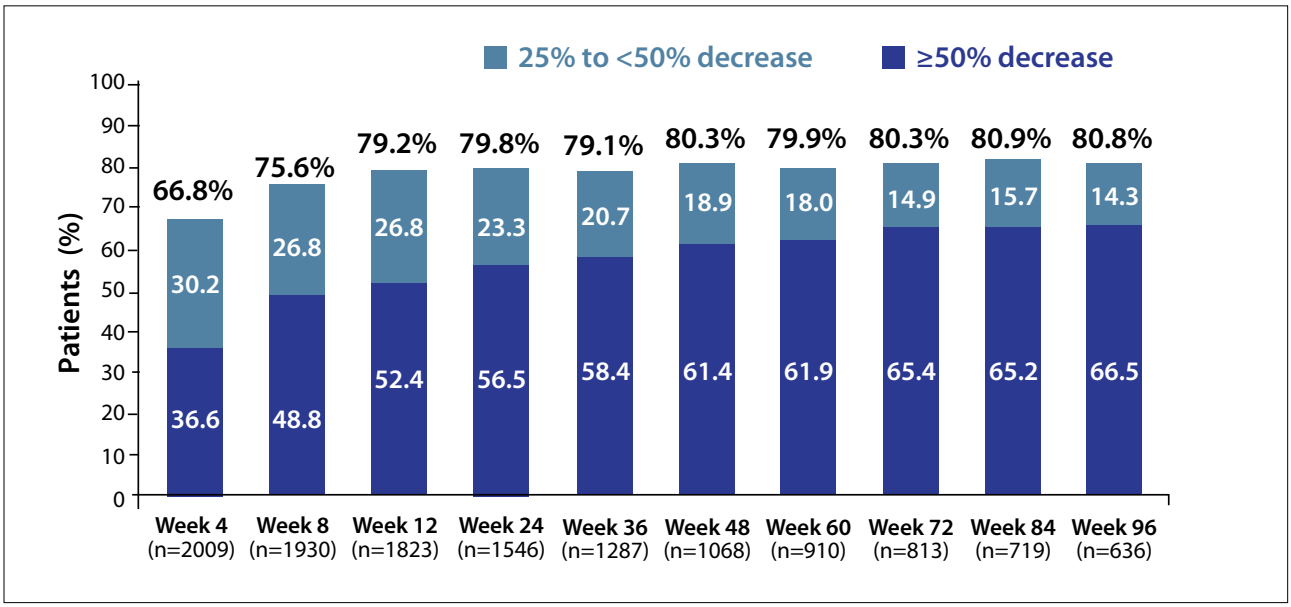

Figure 7. Reduction in spleen length from baseline among patients with myelofibrosis treated with ruxolitinib, as reported in the phase 3b JUMP expanded access trial. Adapted from Al-Ali HK et al. ASH abstract 4204. *Blood.* 2017;130(suppl 1).[1]

common grade 3/4 nonhematologic AEs were pneumonia (4.7%), pyrexia (2.4%), asthenia (2.1%), and dyspnea (2.0%). The secondary malignancies included acute leukemia (2.0%), basal cell carcinoma (1.4%), and squamous cell carcinoma (1.2%).

A reduction of 50% or more from baseline in palpable spleen length was seen in 56.5% of patients at week 24 and in 61.4% of patients at week 48 (Figure 7). Reductions of 25% to 50% were observed in 23.3% at week 24 and 18.9% at week 48. The median time to first documentation of a reduction in spleen length of at least 50% was 5.8 weeks (range, 2.6-236.1 weeks), and the estimated probability of maintaining a spleen response was 87% at 48 weeks and 80% at 96 weeks. The best overall response based on criteria from the International Working Group for Myelofibrosis Research and Treatment was 58% among patients with a baseline spleen length of 5 cm to 10 cm and 61% among patients with a baseline spleen length of more than 10 cm. Stable disease was reported in 40% and 38% of these patients, respectively.

ABSTRACT SUMMARY Phase I/II Trial of Glasdegib in Heavily Pre-Treated Patients With Primary or Secondary Myelofibrosis

Glasdegib is an oral inhibitor of the Hedgehog pathway, which may contribute to myeloid lineage differentiation and splenic fibrosis in myelofibrosis. A phase 1b/2 trial is evaluating glasdegib in patients with myelofibrosis who had previously received at least 1 JAK inhibitor. Results from the lead-in cohort were presented (Abstract 258). The study enrolled 21 patients, of whom 11 (52%) were refractory to JAK inhibition. The mean age of patients was 69.3 years (range, 58-83 years). Glasdegib reduced spleen volume in 5 of 21 patients. One patient had a positive anemia response, and another had an improvement in absolute neutrophil count. The most common treatment-emergent AEs were dysgeusia (62%), muscle spasms (57%), alopecia (38%), decreased appetite (33%), and fatigue (33%).

Clinically meaningful improvements in symptoms were reported as early as 4 weeks after treatment began. These improvements were maintained over time. At each time point, approximately 55% of patients had a response based on the Functional Assessment of Cancer Therapy–Lymphoma Total Score, and 45% to 53% of patients had a response based on the Functional Assessment of Chronic Illness Therapy–Fatigue scale.

After a median follow-up of 60 weeks, the estimated OS rate was 93% at week 48 and 87% at week 96. Estimated leukemia-free survival rates were 92% and 85%, respectively. After a median follow-up of 55 weeks, estimated PFS rates were 89% at week 48 and 80% at week 96.

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Sotatercept (ACE-011) Alone and in Combination With Ruxolitinib in Patients With Myeloproliferative Neoplasm–Associated Myelofibrosis and Anemia

Sotatercept (also known as ACE-011) is a first-in-class activin receptor IIA ligand trap that contains the extracellular domain of activin receptor type IIA linked to the fragment crystallizable domain of human immunoglobulin G1. By sequestering ligands of transforming growth factor beta, sotatercept prevents the blockade of terminal erythroid differentiation. Sotatercept promotes erythropoiesis in preclinical models and has demonstrated efficacy in preventing anemia in patients with lower-risk myelodysplastic syndrome.[1] A phase 2 study evaluated the efficacy and safety of sotatercept administered as monotherapy or with ruxolitinib in patients with myelofibrosis. Dr Prithviraj Bose presented results at the 2017 ASH meeting.[2]

The study enrolled patients with primary myelofibrosis or post–polycythemia vera/essential thrombocythemia myelofibrosis with a hemoglobin level below 10 g/dL for at least 84 days. Patients received sotatercept monotherapy (0.75 mg/kg or 1 mg/kg subcutaneously every 2 weeks) or sotatercept (0.75 mg/kg subcutaneously every 3 weeks) plus a stable dose of ruxolitinib. Responses were assessed after at least 84 days of treatment. In patients with anemia, a response was defined as an improvement in hemoglobin of at least 1.5 g/dL from baseline that lasted 84 days or longer. In patients dependent on transfusion, response was defined as achievement of transfusion independence per criteria from the International Working Group–Myeloproliferative Neoplasms Research and Treatment.

In the sotatercept monotherapy cohort (n=24), the median age was 66.5 years (range, 47-84 years). Diagnoses included primary myelofibrosis (n=20) and post–essential thrombocythemia/polycythemia vera myelofibrosis (n=4). The median hemoglobin level was 7.5 g/dL (range, 4.7-8.7 g/dL; Figure 8). Driver mutations included *JAK2* (n=16), *CALR* (n=3), and *MPL* (n=3). Eight patients had an abnormal karyotype. DIPSS categories included intermediate-2 risk (n=19) and high risk (n=5). Most patients (16 of 24) had grade 3 bone marrow fibrosis. Splenomegaly was present in 13 patients (54%), and 19 patients (79%) had received previous treatment for it.

Sotatercept monotherapy was associated with a response rate of 38.9%, with 7 of 18 evaluable patients attaining responses, including 4 of 7 patients with anemia (57%) and 3 of 11 patients with transfusion independence (27%). Responses occurred at dose levels of 0.75 mg/kg (n=4) and 1 mg/kg (n=3). Patients received a median of 5 cycles of therapy (range, 1-35+ cycles), with a median time on study of 3.6 months (range, 1-25+ months). The median time to the start of the response was 7 days (range, 1-22 days), and the median duration of response was 12 months (range, 5-24+ months). Treatment was ongoing at the time of analysis in 2 of 18 patients, and each of these patients had received 35 cycles of therapy. Three patients required multiple treatment interruptions owing to a hemoglobin

ABSTRACT SUMMARY Age Is Not a Predictive Marker in Molecularly Annotated Elderly Patients With Myelofibrosis Treated With Ruxolitinib: A Multicenter Study on 277 Patients

Dr Francesca Palandri and colleagues retrospectively assessed outcomes and molecular features among 277 patients with myelofibrosis who were ages 64 years or older when starting ruxolitinib (Abstract 1642). Nearly 40% of patients were ages 75 years or older. Risk was assessed with the IPSS criteria. Patients ages 75 years or older were more likely than those younger than 75 years to be intermediate-2 risk or high risk (96% vs 89%; *P*=.024). Older patients had a lower median platelet count (211 × 10^9/L vs 289 × 10^9/L; *P*=.003) and more comorbidities. As a result, older patients had a lower starting dose of ruxolitinib. At 6 months, 35.9% of 209 evaluable patients had a spleen response, and 83.7% of 221 evaluable patients had a symptom response. In the first 6 months, rates of grade 2 or higher anemia, thrombocytopenia, and infections were 33.6%, 21.7%, and 29.2%, respectively. Age did not appear to affect rates of toxicities, responses, or disease courses. Overall, 39% of patients discontinued ruxolitinib after a median of 12.5 months. Acute leukemia developed in 22 patients (8%). After a median follow-up of 19.5 months, 65 patients (23%) died, most commonly from myelofibrosis (40%), acute leukemia (15%), infection (14%), and heart disease (11%). Older age and lower body mass index were significantly associated with shorter survival. Molecular analyses, performed in 48 patients (median age, 72.5 years), revealed high–molecular risk mutations in 61%. The most frequent mutations were *ASXL1* and *EZH2*. A trend was identified between high molecular risk (as indicated by ≥3 variants) and shorter event-free survival and leukemia-free survival.

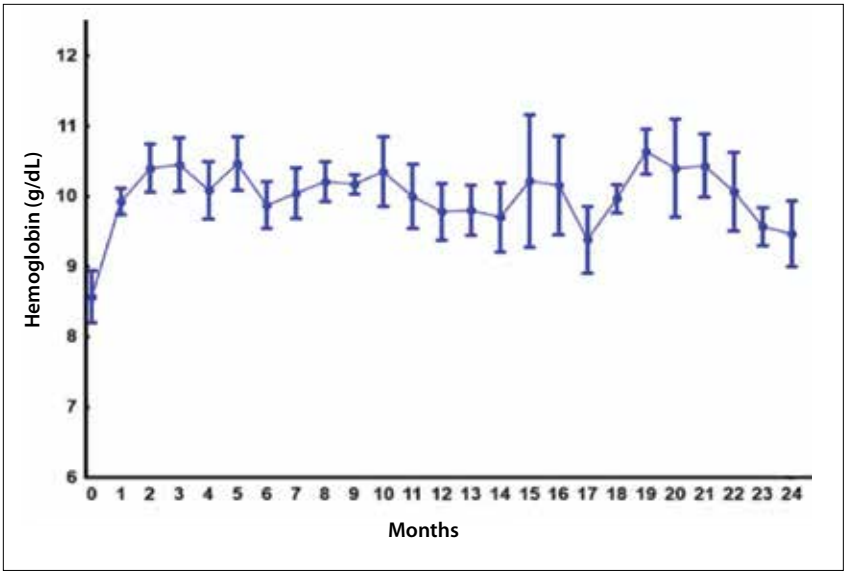

Figure 8. Mean levels of hemoglobin over time in patients who responded to treatment with sotatercept alone or in combination with ruxolitinib. Adapted from Bose P et al. ASH abstract 255. *Blood.* 2017;130(suppl 1).[2]

ABSTRACT SUMMARY Safety and Efficacy of Ruxolitinib in an Open-Label, Multicenter, Expanded Treatment Protocol in Patients With Polycythemia Vera Who Are Hydroxyurea Resistant or Intolerant and for Whom No Alternative Treatments Are Available

A global, single-arm, open-label, multicenter, expanded-access phase 3b trial evaluated ruxolitinib in 75 patients with polycythemia vera who were resistant or intolerant to hydroxyurea (Abstract 2918). All enrolled patients lacked alternative treatments and were ineligible for another polycythemia vera trial. The patients' median age was 68 years, and the median time since diagnosis was 65.3 months (range, 5.4-396.8 months). Prior thromboembolic events were reported in 28% of patients. After a median of 43 weeks of ruxolitinib, the most common AEs were anemia (21%), pruritus (13%), headache (13%), and asthenia (13%). No grade 3/4 AEs were reported. Hematocrit was controlled in 69.3% of patients, and peripheral blood count remissions were seen in 22.7% of patients. Most patients (94.6%) achieved a reduction in spleen length from baseline of at least 50%. Ruxolitinib was also associated with improvements in symptom scores in 35.6% of evaluable patients at week 24.

level of 11.5 g/dL or higher. The most frequent reasons for discontinuation of sotatercept monotherapy were lack of response (n=7), myelofibrosis progression (n=5), allotransplant (n=3), and patient decision (n=3). Among the 7 patients with responses, 5 patients discontinued therapy. The reasons were myelofibrosis progression in 3, allogeneic transplant in 1, and inability to comply with study visits in 1.

Among the patients treated with sotatercept and ruxolitinib (n=11), the median age was 68 years (range, 57-84 years). Diagnoses included primary myelofibrosis (n=9) and post–polycythemia vera/myelofibrosis (n=2). The median hemoglobin level was 7.2 g/dL (range, 4.6-9.1 g/dL). Driver mutations included *JAK2* (n=8), *CALR* (n=2), and *MPL* (n=1). Six patients had an abnormal karyotype. The most common DIPSS category was intermediate-2 risk (n=7), followed by high risk (n=4). Five patients had grade 2 bone marrow fibrosis, and 5 patients had grade 3. No patients had splenomegaly. The median ruxolitinib dose was 10 mg twice daily (range, 5-20 mg twice daily).

The sotatercept/ruxolitinib regimen was associated with a response rate of 30% (3 of 10 evaluable patients). All responses occurred among the 6 patients with anemia. Patients received a median of 7 cycles of therapy (range, 3-13 cycles), with a median time on study of 5 months (range, 1-16+ months). Responses were observed beginning at 7 days, 14 days, and 140 days. The responses lasted for at least 3 months, 4 months, and 15 months. Treatment was ongoing at the time of analysis in 5 patients. Six patients discontinued treatment, 3 based on lack of response and 3 owing to allotransplant. AEs potentially related to sotatercept included grade 3 hypertension in 3 patients, grade 2 hypertension in 2 patients, and an elevated urine microalbumin creatinine ratio in 2 patients.

The trial continues to accrue patients, with a planned enrollment of 60. Other studies are evaluating the novel agent luspatercept (ACE-536), which has demonstrated promising activity in patients with anemia associated with low-risk myelodysplastic syndromes.[3] The pivotal trial of luspatercept, MEDALIST (A Study of Luspatercept [ACE-536] to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes),[4] is fully enrolled. A multicenter, phase 2 trial of luspatercept in patients with myelofibrosis is currently enrolling.[5]

ABSTRACT SUMMARY Interim Phase 2 Clinical Trial Results for LCL161, an Oral Smac Mimetic, in Patients With Intermediate- or High-Risk Myelofibrosis

Interim results were presented from a phase 2 trial evaluating the oral SMAC mimetic LCL161 in patients with intermediate-risk or high-risk myelofibrosis (Abstract 256). Among the 38 enrolled patients, the median age was 72 years, and the median platelet count was 47 × 10^9/μL. Nearly 25% of patients had the *ASXL1* mutation. The ORR was 26%, and the median response duration was 9.2 months. Responses included symptom improvement in 7 patients (18%), anemia response in 5 (13.2%), spleen response in 1 (3%), and cytogenetic remission in 1 (3%). The most common toxicities of any grade were fatigue (55%), nausea/vomiting (50%), pain (34%), and dizziness/vertigo (32%). Grade 3/4 AEs included thrombocytopenia (8%), anemia (5%), syncope (5%), and nausea/vomiting (3%). Dose reductions were required in 29% of patients, most commonly because of grade 2 fatigue (n=8). At the time of the analysis, 58% of patients were off-study, for reasons including lack of response (n=12) and progressive disease (n=5).

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Promising Results of a Phase 1/2 Clinical Trial of Ruxolitinib in Patients With Chronic Myelomonocytic Leukemia

Outcomes tend to be poor among patients with chronic myelomonocytic leukemia (CMML). This heterogeneous myeloid neoplasm is characterized by peripheral monocytosis and risk of progression to AML.[1] In a historical cohort of 1832 patients with CMML, the median OS was 32 months.[1] In contrast to myelodysplastic syndrome, in which azacitidine is associated with a significant improvement in OS,[2] no disease-modifying therapy has been developed for CMML that can alter the natural history.

Preclinical data demonstrating the sensitivity of CMML cells to granulocyte-macrophage colony-stimulating factor (GM-CSF) and a link between the GM-CSF pathway and JAK2 inhibition suggest that the JAK2 inhibitor ruxolitinib could have potential activity against CMML.[3] Based on the preclinical rationale, a phase 1/2 trial was undertaken to evaluate the safety and activity of ruxolitinib in patients with CMML. Results from a multicenter, phase 1 trial conducted in 20 patients established 20 mg twice daily as the recommended dose for phase 2 testing.[4] At the 2017 ASH meeting, Dr Eric Padron presented results of the phase 2 study, which enrolled 29 patients with CMML.[5] The phase 2 study used a Simon's 2-stage design, with 10 patients treated in the first stage, and the second stage undertaken if 1 of 10 patients responded in the first stage. Eligibility requirements included CMML as defined by criteria from the World Health Organization (WHO), age older than 18 years, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2, and life expectancy exceeding 3 months. Among the exclusion criteria were a platelet count below 35 × 10^9/L, an absolute neutrophil count below 250/mm^3, a serum creatinine level of 2.0 mg/dL or higher, and serum total bilirubin exceeding 1.5 × the upper limit of normal. A 28-day washout period was required after use of any cytotoxic chemotherapeutic agents or experimental agents.

The median age of the enrolled patients was 69 years (range, 44-87 years), and most patients were male (55%). The study used 3 different classification systems to assess risk. With the World Health Organization classification, CMML-1 was identified in 85% of evaluable patients (22 of 26) and CMML-2 in 15% (4 of 26). With the French-American-British scoring system, 42% of patients (11 of 25) had myelodysplastic syndrome CMML and 58% (14 of 25) had myeloproliferative neoplasm–CMML. With the

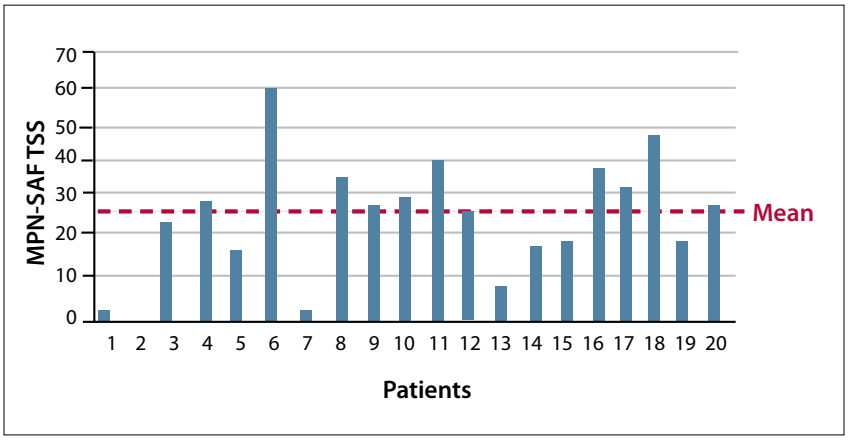

Figure 9. The total symptom score as measured by the MPN-SAF among patients with chronic myelomonocytic leukemia treated with ruxolitinib. MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, total symptom score. Adapted from Padron E et al. ASH abstract 320. *Blood.* 2017;130(suppl 1).[5]

MD Anderson Scoring System, 72% (18 of 25) were lower risk and 28% (7 of 25) were higher risk. Approximately 19% of evaluable patients (6 of 26) had received prior hypomethylating agents, and 81% had not. Splenomegaly was present in 57% of evaluable patients (13 of 23). The median white blood cell count was 20.8 × 10^3/dL (range, 2.1-142.6 × 10^3/dL), and the median absolute monocyte count was 8.05 × 10^3/dL (range, 1.1-58 × 10^3/dL).

Three patients developed grade 3 or higher treatment-emergent toxicities, which included anemia and thrombocytopenia. One case of anemia required transfusion support. The most common reason for treatment discontinuation was disease progression, reported in 10 patients. Responses included 3 bi-lineage and tri-lineage hematologic responses as assessed by the criteria for myelodysplastic syndrome from the 2006 International Working Group. One patient had a CR in the bone marrow. Among the 13 patients with splenomegaly at baseline, 6 experienced a reduction in spleen size of 50% or more (according to physical examination). The clinical benefit rate accounting for cytopenia and splenomegaly was 46% among evaluable patients (11 of 24). The median duration of response was 219 days, and several patients remained on treatment for longer than a year. After a median follow-up of 11.5 months, the median OS was 19.7 months.

After adjusting for age, global MD Anderson Score, WHO subtype, and the mean interval from diagnosis to treatment, the median OS was 59.2 months in ruxolitinib-treated patients vs 30.9 months in historical controls (P=.03).[1] Ruxolitinib was also associated with a significant improvement in symptoms, based on changes in the Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (Figure 9). A particular benefit was observed in patients with a total symptom score at baseline of 25 or higher. Investigations into biomarkers suggested that levels of RANTES/chemokine (C-C motif) ligand 5 (CCL5), receptor for advanced glycation end products (RAGE), chemokine (C-X-C motif) ligand 9 (CXCL9), and interleukin 10 may predict responses to ruxolitinib. No gene or pathway was significantly associated with response.

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Highlights in Myeloproliferative Neoplasms From the 2017 American Society of Hematology Annual Meeting: Commentary

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New management strategies for polycythemia vera and myelofibrosis were presented at the 2017 American Society of Hematology (ASH) meeting. Several trials focused on ruxolitinib, a Janus kinase (JAK) inhibitor that was approved by the US Food and Drug Administration (FDA) for myelofibrosis in 2011 and for polycythemia vera in 2014. Data were also presented for the biologic agent pegylated interferon alfa-2a and for a new anemia treatment, sotatercept.

Polycythemia Vera

Hydroxyurea is the standard therapy for patients with polycythemia vera. It is highly effective in controlling the blood cell count, decreasing hematocrit levels to below 45%, eliminating the need for phlebotomy, and normalizing white cells and platelets. It can decrease splenomegaly and improve quality of life. Attempts are being made to challenge the role of hydroxyurea in the first-line setting with new iterations of long-acting interferons, which might be able to achieve the same goals while exerting biological activity on the disease itself. Dr Heinz Gisslinger presented the 2-year results for the first prospective, randomized controlled trial comparing ropeginterferon with hydroxyurea.[1] Ropeginterferon is being tested in Europe. It is not approved by the FDA. This study compared 2 active agents as first-line therapy in patients with polycythemia vera. The goal is to control the red blood cell count by decreasing hematocrit to below 45%, normalize the white cells and platelets, eliminate any symptomatic splenomegaly, and control systemic symptoms related to the disease. The 2-year update showed a high degree of efficacy for ropeginterferon, which is a biologic agent injected under the skin every 2 weeks (and sometimes even once a month). In comparison, the standard therapy, hydroxyurea, is a chemotherapy pill that is taken daily.

In this updated analysis, after a prolonged period of 2 years, ropeginterferon appeared to be more effective than hydroxyurea in achieving clinically relevant goals. In addition, ropeginterferon significantly decreased the number of cells in the patient samples with a *JAK2* mutation. The so-called *JAK2* allele burden is a biological parameter that possibly indicates a direct biological effect on the disease itself, which is not usually seen with a chemotherapy agent. In 2018, we are looking forward to studies in the United States of ropeginterferon in polycythemia vera and possibly in essential thrombocytopenia, which will hopefully lead to approval of this valuable medication in this country.

At the 2017 ASH meeting, Dr Abdulraheem Yacoub presented a summary of data for single-arm salvage therapy with long-acting pegylated interferon alfa-2a in patients with high-risk polycythemia vera or high-risk essential thrombocytopenia previously treated with hydroxyurea.[2] Final results of this single-arm, open-label study showed that pegylated interferon alfa-2a was highly active in controlling red and white blood cells and platelets, and in eliminating the need for phlebotomy among this population of patients in need of new therapy. These data substantiate our understanding of the benefits of interferons in diseases that manifest primarily with an elevation of the blood cell count—particularly polycythemia vera, but also essential thrombocythemia. None of the interferon agents have been approved so far in the United States, but biologic agents such as the pegylated interferons are highly valuable, certainly in younger patients or women who plan to become pregnant.

Dr Jean-Jacques Kiladjian presented a 4-year follow-up analysis 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).[3] This trial tested ruxolitinib in patients with polycythemia vera previously treated with hydroxyurea. Ruxolitinib was compared with the best available therapy—basically, whatever treatment the doctor selected. In polycythemia vera, the immediate goal of therapy is to decrease the blood cell count to normal levels, eliminate painful splenomegaly if present, and improve quality of life. In the RESPONSE trial, ruxolitinib was better than the best available

therapy, and it was approved based on this study.[4] A companion study, RESPONSE-2 (Ruxolitinib Efficacy and Safety in Patients With HU Resistant or Intolerant Polycythemia Vera vs Best Available Therapy),[5] was similar in design and confirmed the results from the initial RESPONSE trial. Two phase 3 studies therefore substantiate the benefit of ruxolitinib in the second-line setting for polycythemia vera, particularly in controlling the red blood cell count (meaning a decrease of hematocrit to <45%), normalizing white cells, normalizing platelets, eliminating polycythemia vera–related systemic symptoms, and eliminating symptomatic splenomegaly.

The 4-year follow-up analysis showed a continuous high rate of response, meaning that when patients responded, the response persisted for a long period—years. In addition, there were no new toxicities. Based on the initial data, the toxicities associated with ruxolitinib in patients with polycythemia vera included occasional myelosuppression, occasional shortness of breath, and low-grade diarrhea. In general, the occurrence of these events remained consistently very low throughout the 4 years of follow-up. It is necessary, however, to be aware that occasional atypical infections can occur in patients treated with ruxolitinib across all indications, not just polycythemia vera. Herpes zoster is an example.[6]

In conclusion, ruxolitinib is a highly valuable therapy. It is effective for a long period of time, and it is not toxic. Ruxolitinib is a welcome addition to the armamentarium for polycythemia vera in the second-line setting after hydroxyurea.

Myelofibrosis

Myelofibrosis is the most aggressive of the myeloproliferative neoplasms, and the goal of therapy is different than for the earlier-stage diseases, polycythemia vera and essential thrombocythemia. In more benign conditions, the goal of therapy is to control the blood cell count and improve quality of life, and, with that, decrease the thromboembolic risk that corresponds with a high blood cell count. In myelofibrosis, there are 3 main clinical problems. The first relates to poor quality of life owing to body wasting, the inability to walk, weight loss, night sweats, low-grade fevers, itching, and bone aches and pains. The second set of clinical problems are progressive symptomatic splenomegaly and enlargement of the liver. The third is continuous failure in the bone marrow production of the blood cells, which leads to the eventual development of anemia, thrombocytopenia, and neutropenia. Ruxolitinib can counteract splenomegaly and disease symptoms. Ruxolitinib can even improve survival in patients with chronic-phase disease.[7] Standard prognostication of myelofibrosis depends on multiple biological parameters and clinical findings. The central prognostic feature is the percent of blasts, or leukemic cells, in the blood or bone marrow. Accelerated-phase myelofibrosis refers to patients with 10% to 20% blasts. These patients have a poor outcome, which ruxolitinib does not usually improve. They are usually referred to bone marrow transplant as soon as possible. When the percentage of blasts in the blood and marrow is more than 20%, the outcome is very poor. This diagnosis is referred to as acute myeloid leukemia secondary to chronic myeloproliferative neoplasm. Successful treatment of these patients that allows them to undergo transplant is rare.

Dr Lucia Masarova reported results from a study that analyzed characteristics of patients with myelofibrosis and elevated blasts and evaluated the impact of ruxolitinib.[8] Among these patients, there is a previously unrecognized group with 5% to 9% of blasts in the blood or bone marrow. It is therefore possible to divide patients with myelofibrosis into 4 subgroups: those with chronic phase with a low percentage of blasts, 0% to 4%; those with chronic phase with an elevated percentage of blasts, 5% to 9%; those with accelerated phase, with the percentage of blasts ranging from 10% to 20%; and those with a percentage of blasts exceeding 20%, who have acute myeloid leukemia. The significance of this study is that patients with 5% to 9% of blasts have an intermediate prognosis. They have aggressive clinical characteristics with a poor quality of life and a poor bone marrow reserve, and they require multiple therapies. Their clinical characteristics, risk of progression, and outcome are similar to those seen in patients with accelerated-phase disease. These findings suggest that it might be possible to identify—based solely on the given percent of blasts in blood or bone marrow—a group of patients who may require a different therapeutic approach than those with a lower percent of blasts. Ruxolitinib appears to prolong life in patients with chronic-phase disease and either low (0%-4%) or elevated (5%-9%) blasts. To summarize, this study identified a group of chronic-phase patients with a higher blast percentage, who might require different therapeutic approaches from other chronic-phase patients.

Dr Haifa Kathrin Al-Ali presented a primary analysis of the large, expanded-access, phase 3b JUMP study (JAK Inhibitor Ruxolitinib in Myelofibrosis Patients), which evaluated the safety and efficacy of ruxolitinib in patients with myelofibrosis throughout the world.[9] Ruxolitinib is a standard agent for myelofibrosis, and the first therapy approved for these patients.[10] Ruxolitinib is typically prescribed for patients with symptomatic splenomegaly or general myelofibrosis-related systemic symptoms. In many countries, however, the ruxolitinib label calls for it to be prescribed based on the risk of dying, as assessed by a prognostic scoring system with 4 risk categories: low, intermediate-1, intermediate-2, and high. In these

countries, ruxolitinib is used only in patients with intermediate-2 or high-risk disease.

The JUMP study enrolled more than 2000 patients worldwide. The most significant finding from the study is confirmation that ruxolitinib improves symptomatic splenomegaly and myelofibrosis-related symptoms to the same extent as initially reported in phase 3 clinical studies that led to its approval. Unlike phase 3 studies that enrolled only intermediate-2 and high-risk patients, the JUMP study enrolled patients from 3 risk categories: the earlier-stage intermediate-1 risk (with a palpable spleen), intermediate-2 risk, and high risk. Not surprisingly, improvement in splenomegaly symptoms was seen among patients in all of the risk categories. Therefore, the utility of ruxolitinib as a therapy for myelofibrosis does not depend on the patient's risk of dying. It is valuable to use ruxolitinib to treat a patient with symptomatic splenomegaly or myelofibrosis-related systemic symptoms, regardless of his or her risk of dying.

Earlier stages of myelofibrosis are categorized by proliferative markers such as a high white cell count and high platelets, but also by limited splenomegaly and minimal disease symptoms. A long-standing treatment approach for these patients has been the biologic agent interferon, which improves systemic symptoms; controls high red blood cells, white cells, and platelets; and, possibly, delays disease progression. However, no study has been able to confirm that interferon exerts a biological benefit or improves progression-free survival in patients with myelofibrosis. Dr Jean-Christophe Ianotto presented intriguing findings of a study evaluating the long-term use of pegylated interferon alfa-2a in French patients with myelofibrosis.[11] The study documented desirable clinical benefits in controlling the blood cell count and disease-related symptoms. Pegylated interferon alfa-2a also decreased the number of cells with the active mutation found in patients' bone marrow or blood, and possibly prolonged the time to disease progression. Like previous studies in this setting, this study did not have a control arm to provide confirmation that interferon therapy can prolong survival, extend the time to next therapy, or prevent progression of the disease. However, these results may lead in the near future to prospective, randomized studies comparing interferon with other therapy, or observation, to prevent progression in early-stage myelofibrosis.

The standard therapy for patients with myelofibrosis who have symptomatic splenomegaly or systemic symptoms is ruxolitinib. Ruxolitinib can help many patients for a prolonged period. It does not, however, eliminate the disease or prevent progression. Much work is needed to optimize the use of ruxolitinib, perhaps by combining it with other agents to maintain benefit for a longer period. Ruxolitinib does not improve anemia, which is a key clinical feature of myelofibrosis. In some patients, single-agent ruxolitinib might even worsen anemia. There are no effective therapies for anemia. Therefore, a presentation by Dr Prithviraj Bose on the investigative anti-anemia agent sotatercept was valuable.[12] Sotatercept is injected under the skin every 3 weeks. The study had 2 arms. In one arm, single-agent sotatercept was administered to patients with myelofibrosis whose major clinical manifestation was anemia. In the other arm, sotatercept was administered to treat anemia in patients with myelofibrosis who were already receiving a stable dose of ruxolitinib to counteract splenomegaly symptoms. In this preliminary analysis, anemia was improved by approximately 40% in both arms, which is a good sign for the future development of sotatercept. This trial was conducted in a single center, and plans are in place for new studies with this class of agents (eg, luspatercept). Global randomized studies of luspatercept will determine the optimal dose and schedule for this agent, and whether it can be combined with ruxolitinib in patients with myelofibrosis who have anemia.[13,14] Treatment of anemia in patients with myelofibrosis is an area of unmet need. The results for sotatercept are promising and may lead to a new approved agent for these patients.

Disclosure

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