A SPECIAL MEETING REVIEW EDITION

Highlights in Myeloproliferative Neoplasms
From the 2016 American Society of Hematology
Annual Meeting and Exposition

A Review of Selected Presentations From the 2016
American Society of Hematology Annual Meeting and Exposition
December 3-6, 2016 • San Diego, California

Special Reporting on:

• A Pooled Overall Survival (OS) Analysis of 5-Year Data From the COMFORT-I and COMFORT-II Trials of Ruxolitinib for the Treatment of Myelofibrosis (MF)

• Final Results From PROUD-PV, A Randomized Controlled Phase 3 Trial Comparing Ripeginterferon Alfa-2b to Hydroxyurea in Polycythemia Vera Patients

• Effects of Long-Term Ruxolitinib (RUX) on Bone Marrow (BM) Morphology in Patients With Myelofibrosis (MF) Enrolled in the COMFORT-I Study

• Examining the Clinical Features and Underlying Cardiovascular Risk Among Patients With Polycythemia Vera in the REVEAL Study

• Clinical Outcomes With Ruxolitinib (RUX) in Patients With Myelofibrosis (MF) Stratified By Transfusion Status: A Pooled Analysis of the COMFORT-I and -II Trials

• Interim Analysis of the Myeloproliferative Disorders Research Consortium (MPD-RC) 112 Global Phase III Trial of Front Line Pegylated Interferon Alpha-2a Vs. Hydroxyurea in High Risk Polycythemia Vera and Essential Thrombocythemia

• Current Mutational Landscape of Myeloproliferative Neoplasms

PLUS Meeting Abstract Summaries

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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 × 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 ruxolitinib treatment for myelofibrosis. 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.

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Significantly more patients receiving Jakafi achieved the composite primary\* and key secondary end points\*\*\*\*

Components of Primary End Point at Week 32\*

<table>
<thead>
<tr>
<th>Composite Primary End Point</th>
<th>Individual Components of Primary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct Control + Spleen Volume Reduction</td>
<td>Hct Control Without Phlebotomy</td>
</tr>
<tr>
<td>Jakafi (n = 110)</td>
<td>BAT (n = 112)</td>
</tr>
<tr>
<td>60%</td>
<td>19%</td>
</tr>
</tbody>
</table>

\* The composite primary end point was defined as hematocrit (Hct) control without phlebotomy 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 best available therapy in 222 patients with polycythemia vera. Patients enrolled in the study were resistant to or intolerant of hydroxyurea, required phlebotomy for Hct control, and had splenomegaly. All patients entered into a Hct control period, during which time Hct levels were maintained between 40% and 45% for 28 days before patients were randomized to Jakafi or best available therapy. Best available therapy included hydroxyurea (60%), interferon/pegylated interferon (12%), anagrelide (7%), pipobroman (2%), lenalidomide/thalidomide (5%), and observation (15%). Patients had been diagnosed with polycythemia vera for at least 24 weeks, had an inadequate response to or were intolerant of hydroxyurea, required phlebotomy, and exhibited splenomegaly. After week 32, patients were able to cross over to Jakafi treatment. An updated analysis was performed at week 80 only in patients originally randomized to Jakafi.

**Durable response at week 80\*

- 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.

\* 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.\*\*

**References:**

3. Jakafi.com/HCP

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 breast-feed.

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.
**WARNINGS AND PRECAUTIONS**

**Thrombocytopenia, Anemia and Neutropenia** Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia. [see Dosage and Administration (2.1) and Adverse Reactions (6.1) 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. 

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

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>All Grades* (%</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
<th>All Grades* (%)</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jakafi (N=155)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>23</td>
<td>&lt;1</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>18</td>
<td>&lt;1</td>
<td>0</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>9</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Weight Gain</td>
<td>7</td>
<td>&lt;1</td>
<td>0</td>
<td>1</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Flattulence</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

* National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), 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 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 polycythemia vera 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.
Headache 16 <1 19 <1
Abdominal Pain* 15 <1 15 <1
Diarrhea 15 0 7 <1
Dizziness* 15 0 13 0
Fatigue 15 0 15 3
Pruritus 14 <1 23 4
Dyspnea* 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* 8 0 7 0
Arthralgia 7 0 6 <1
Anemia 7 0 11 2
Epilepsy 6 0 3 0
Herpes Zoster¹ 6 <1 0 0
Nausea 6 0 4 0

¹ National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0
* Includes abdominal pain, abdominal pain lower, and abdominal pain upper
† Includes dyspnea and dyspnea exertional
‡ Includes peripheral edema

Table 4: Polycythemia Vera: Selected Laboratory Abnormalities in the Open-Label, Active-controlled Study up to Week 32 of Randomized Treatment²

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades¹</td>
<td>Grade 3</td>
</tr>
<tr>
<td>Hematology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemistry</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>15</td>
<td>0</td>
</tr>
</tbody>
</table>

DRUG INTERACTIONS: Drugs That Inhibit or Induce Cytochrome P450 Enzymes: Ruxolitinib is metabolized by CYP3A4 and to a lesser extent by CYP2C8. CYP3A4 inhibitors: The Cmax and AUC of ruxolitinib increased 33% and 91%, respectively following concomitant administration with the strong CYP3A4 inhibitor ketoconazole in healthy subjects. Concomitant administration with mild or moderate CYP3A4 inhibitors did not result in an exposure change requiring intervention [see Pharmacokinetics (12.3) in Full Prescribing Information]. When administering Jakafi with strong CYP3A4 inhibitors, consider dose reduction [see Dose and Administration (2.3) in Full Prescribing Information]. 

Ruxolitinib is a substrate for CYP3A4 and CYP2C9, and interacts with the CYP3A4 and CYP2C9 inhibitors at doses of 100 mg to 400 mg once daily, respectively [see Pharmacokinetics (12.3) in Full Prescribing Information]. Avoid the concomitant use of Jakafi with ruxolitinib doses of greater than 200 mg daily [see Dose and Administration (2.3) in Full Prescribing Information].

CYP3A4 inducers: The Cmax and AUC of ruxolitinib decreased 32% and 61%, respectively, following concomitant administration with the strong CYP3A4 inducer rifampin in healthy subjects. No dose adjustment is recommended; however, monitor patients frequently and adjust the Jakafi dose based on safety and efficacy [see Pharmacokinetics (12.3) in Full Prescribing Information].

USE IN SPECIFIC POPULATIONS: Pregnancy: Pregnancy Category C: Risk Summary: There are no adequate and well-controlled studies of Jakafi in pregnant women. In embryofetal toxicity studies, treatment with ruxolitinib resulted in an increase in late resorptions and reduced fetal weights at maternally toxic doses. Jakafi should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. 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 was no evidence of teratogenicity. However, 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 (54% the clinical exposure at the maximum recommended dose of 25 mg twice daily).

Nursing Mothers: It is not known whether ruxolitinib is excreted in human milk. Ruxolitinib and/or its metabolites were excreted in the milk of lactating rats with a concentration that was 13-fold the maternal plasma. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Jakafi, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Pediatric Use: The safety and effectiveness of Jakafi in pediatric patients have not been established.

Geriatric Use: Of the total number of patients with myelofibrosis 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: The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects [Ccr 72-164 mL/min (N=8)] and in subjects with mild [Ccr 33-79 mL/min (N=8)], moderate [Ccr 18-34 mL/min (N=8)], severe (Ccr 15-51 mL/min (N=8)]. Eight (8) additional patients with end stage renal disease requiring hemodialysis were also enrolled. The pharmacokinetics of ruxolitinib was similar in subjects with various degrees of renal impairment and in those with normal renal function. However, plasma AUC values of ruxolitinib metabolites increased with increasing severity of renal impairment. This was most marked in the subjects with end stage renal disease requiring hemodialysis. The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in metabolic exposure. Ruxolitinib is not removed by dialysis; however, the removal of some active metabolites by dialysis cannot be ruled out. When administering Jakafi to patients with myelofibrosis and moderate (Ccr 30-59 mL/min) or severe renal impairment (Ccr 15-25 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and moderate (Ccr 30-59 mL/min) or severe renal impairment (Ccr 15-25 mL/min). In all patients with end stage renal disease on dialysis, a dose reduction is recommended [see Dose and Administration (2.4) in Full Prescribing Information].

Hepatic Impairment: The safety and pharmacokinetics of single dose Jakafi (25 mg) were evaluated in a study in healthy subjects (N=8) and in subjects with mild (Child-Pugh A (N=8)), moderate (Child-Pugh B (N=8)), or severe hepatic impairment (Child-Pugh C (N=8)). The mean AUC for ruxolitinib was increased by 67%, 28% and 65%, respectively, in patients with mild, moderate and severe hepatic impairment compared to patients with normal hepatic function. The terminal elimination half-life was prolonged in patients with hepatic impairment compared to healthy controls (4.1-5.0 hours versus 2.8 hours). The change in the pharmacodynamic marker, pSTAT3 inhibition, was consistent with the corresponding increase in ruxolitinib exposure except in the severe (Child-Pugh C) hepatic impairment cohort where the pharmacodynamic activity was more prolonged in some subjects than expected based on plasma concentrations of ruxolitinib. When administering Jakafi to patients with myelofibrosis and any degree of hepatic impairment and with a platelet count between 50 X 10^9/L and 150 X 10^9/L, a dose reduction is recommended. A dose reduction is also recommended for patients with polycythemia vera and hepatic impairment [see Dose and Administration (2.4) 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 ruxolitinib.
A Pooled Overall Survival (OS) Analysis of 5-Year Data From the COMFORT-I and COMFORT-II Trials of Ruxolitinib for the Treatment of Myelofibrosis (MF)

Ruxolitinib is a selective Janus kinase (JAK) 1 and 2 inhibitor approved for the treatment of patients with intermediate-risk or high-risk myelofibrosis (MF). Ruxolitinib was approved based on results from the phase 3 COMFORT studies (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment), which enrolled patients with intermediate-2 or high-risk primary MF, post–polycythemia vera MF (PPV-MF), or post–essential thrombocythemia MF (PET-MF), with risk determined by the International Prognostic Scoring System (IPSS). The comparator arm was placebo in the double-blind COMFORT-I study and best available therapy in the COMFORT-II study. In both studies, the ruxolitinib starting dose was 15 mg twice daily for patients with platelet counts of 100 to 200 \times 10^9/L or 20 mg twice daily for patients with platelet counts greater than 200 \times 10^9/L. Dose modifications were permitted for safety and efficacy. Patients were allowed to cross over from the control arm to the ruxolitinib arm in the case of progressive splenomegaly (which was defined as a spleen volume increase of 25% or greater relative to baseline in COMFORT-I or relative to study nadir in COMFORT-II) or the occurrence of other protocol-defined progression events. In COMFORT-I, crossover was mandatory for patients receiving placebo following unblinding of treatment. In both studies, overall survival (OS) was a secondary endpoint and evaluated based on intent-to-treat analysis. The studies showed that ruxolitinib treatment reduced spleen size, improved disease-related symptoms and quality of life, and yielded a superior OS.

Five-year data from COMFORT-I and COMFORT-II were pooled for an exploratory evaluation of long-term OS in patients from the 2 studies. COMFORT-I randomly assigned 155 patients to ruxolitinib and 154 to placebo. COMFORT-II randomly assigned 146 patients to ruxolitinib and 73 to best available therapy. At 3 years’ follow-up, all remaining patients had crossed over from the control arm and were receiving treatment with ruxolitinib.

In the pooled ruxolitinib group, 162 patients (53.8%) had high-risk MF and 139 (46.2%) had intermediate-2 risk. After 5 years of follow-up, 128 patients (42.5%) had died in the ruxolitinib group compared with 117 (51.5%) in the control group. Median OS was 63.5 months with ruxolitinib vs 45.9 months in the control group, and ruxolitinib was associated with a 30% reduction in the risk of death (0.70; 95% CI, 0.54-0.91; \( P=0.0065 \)). After using rank-preserving structural failure time analysis to correct for the effect of crossover, median OS was 63.5 months with ruxolitinib vs 27.0 months in the control group, and ruxolitinib was associated with a 30% reduction in the risk of death (0.70; 95% CI, 0.54-0.91; \( P=0.0065 \)). An analysis that censored patients at the time of crossover also demonstrated a prolonged OS in patients treated with ruxolitinib (median OS, 63.5 months vs 28.3 months; HR, 0.53; 95% CI, 0.36-0.78; \( P=0.0013 \)). Among all patients treated with ruxolitinib, those with lower-risk disease demonstrated an OS that was not reached and was estimated at 102 months, whereas...
patients with high-risk disease demonstrated an OS of 50 months (HR, 2.86; 95% CI, 1.95-4.20; \(P < .0001\)). In the subgroup of patients with primary MF who were originally randomly assigned to ruxolitinib, median OS was significantly prolonged in patients with intermediate-2 risk vs those with high risk (HR, 2.55; 95% CI, 1.52-4.28; \(P = .0003\)).

After 5 years of follow-up, the analysis also demonstrated improved survival with ruxolitinib compared with historic controls. In patients with intermediate-2 primary MF, the estimated median OS was 5.8 years, with a lower 95% CI limit of 5.0 years compared with 4.0 years for historic controls. Among patients with high-risk primary MF, the median OS of historic controls was 2.3 years, and was estimated to be 2.8 years in ruxolitinib-treated patients, with a 95% CI lower limit of 2.5 years. Subgroup analyses exhibited a benefit with ruxolitinib regardless of the patients’ age, sex, disease type, risk status, \(JAK2\) \(V617F\) mutation status, baseline spleen volume, anemic status, white blood cell count, or platelet count.

**References**


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**Figure 1.** Ruxolitinib continued to show improvement in median overall survival in a pooled, 5-year analysis of data from the COMFORT-I and COMFORT-II trials. COMFORT, Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment. HR, hazard ratio; OS, overall survival; RPSFT, rank-preserving structural failure time model. Adapted from Verstovsek S et al. ASH abstract 3110. \(\text{Blood} \). 2016;128(suppl 22).
In a phase 2 trial of patients with polycythemia vera (PV) reported in 2008, pegylated interferon α-2a demonstrated normalization of myeloproliferation, reduction of vascular events, and a large decrease in cells harboring the JAK2 V617F mutation. However, interferon is associated with toxicities, including flu-like symptoms, depression, and autoimmune events, resulting in discontinuation rates of approximately 25%. Ropeginterferon α-2b is a novel isoform with a single polyethylene glycol moiety bound to a specific site on the interferon molecule. The monopegylated molecule has a longer half-life than unmodified interferon α and is administered once every 14 days, followed by once-per-month administration for maintenance. In a phase 2 study, ropeginterferon α-2b yielded an objective response rate (ORR) of 90%, including a complete response (CR) rate of 47% and a partial response (PR) rate of 43%. Most patients experienced a reduction in spleen size. Complete molecular remissions were observed in approximately 20% of patients, although they typically occurred after several months of treatment.

The multicenter parallel-group phase 3 PROUD-PV study (Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera) evaluated ropeginterferon α-2b vs hydroxyurea in patients with PV. The study's primary objective was demonstration of noninferiority of ropeginterferon α-2b compared with hydroxyurea based on the hematologic CR rate at 12 months of therapy. The noninferiority endpoint was chosen based on the relatively slow development of complete molecular remissions with ropeginterferon α-2b. Hematologic CR was defined as normal hematocrit, leukocyte and platelet counts, no need for phlebotomy in the preceding 3 months, and normal spleen size by central magnetic resonance imaging. Secondary objectives included response rates, individual response variables over time, rates of partial and complete molecular response, disease-related symptoms, quality of life, and adverse events (AEs). Enrolled patients had a diagnosis of PV based on World Health Organization 2008 criteria. Patients were treatment-naive and in need of cyto reduction, or they had received prior hydroxyurea and were not intolerant to treatment and did not achieve a CR. Patients with prior exposure to interferon-α were excluded, as were those with clinically relevant autoimmune disease or depression.

The 254 patients were randomly assigned to the 2 treatment arms. Baseline characteristics were well-balanced between the 2 arms. Patients had a median age of 60 years (range, 21-85 years), and 53% were female. Thirty-seven percent of patients had previously received hydroxyurea treatment. The median spleen length was 13.1 cm (range, 7.0-25.0 cm). Spleen size was normal or slightly enlarged in 90% of patients. In the ropeginterferon α-2b arm, the median plateau dose was 450 μg, which was reached from week 28. Dose reduction owing to an AE occurred in 25.2% of patients, and the 12-month discontinuation rate

**ABSTRACT SUMMARY** Final Results From the Phase 3 Trial ARETA Comparing a Novel, Extended-Release Anagrelide Formulation to Placebo in Essential Thrombocythaemia Patients With Defined Risk Status

An extended release formulation of anagrelide was evaluated in patients with ET in ARETA (Anagrelide Retard vs. Placebo: Efficacy and Safety in “At-Risk” Patients With Essential Thrombocythaemia), a parallel-group, patient- and sponsor-blinded, placebo-controlled, randomized phase 3 trial (Abstract 476). Eligible patients had a diagnosis of ET based on World Health Organization 2008 criteria, low platelet count, known JAK2 status, and at least 1 specified risk criterion. The study randomly assigned 146 patients to treatment, and 112 patients completed the first year of treatment. The trial met its primary endpoint, ET-related cardiovascular event–free survival (HR, 0.356; 95% CI, 0.16-0.79; P =.0008). In the extended-release anagrelide arm, 11.7% of patients progressed to high-risk status vs 26.1% in the placebo group (HR, 0.36; 95% CI, 0.16-0.81; P =.0048). Platelet counts normalized in the majority of patients treated with extended release anagrelide after 2 weeks of treatment. The safety profile was consistent with that observed with conventional anagrelide formulations, and included headache (41.6% with anagrelide vs 15.9% with placebo).
was 16.5%. In the hydroxyurea arm, the median plateau dose was 1250 mg, which was reached from week 8. Dose reduction owing to an AE occurred in 51.2% of patients, and the 12-month discontinuation rate was 12.6%.

Based on intent-to-treat analysis, the trial demonstrated noninferiority of ropeginterferon α-2b compared with hydroxyurea ($P=0.0028$). The hematologic CR rate after 12 months was 43.1% with ropeginterferon α-2b vs 45.6% with hydroxyurea (Figure 2). The per-protocol analysis yielded similar results, with 12-month hematologic CR rates of 44.3% for ropeginterferon α-2b vs 46.5% for hydroxyurea ($P=0.0036$). Spleen length was normal or close to normal in most patients at baseline, so the proportion of patients demonstrating normal spleen size after 12 months of treatment was not clinically relevant. Preliminary data in patients with 21 months of treatment demonstrated a higher rate of hematologic CRs with ropeginterferon α-2b vs hydroxyurea, underscoring the slow-acting nature of ropeginterferon α-2b treatment.

Ropeginterferon α-2b showed a superior safety profile vs hydroxyurea (Table 1). AEs of any grade were reported in 81.9% of the ropeginterferon α-2b group vs 87.4% of the hydroxyurea group. A treatment-related AE occurred in 59.6% vs 75.6%, respectively. A grade 3 AE occurred in 16.5% vs 20.5% of patients, respectively. No grade 3 AEs were observed in more than 10% of patients in either arm.

**References**


Effects of Long-Term Ruxolitinib (RUX) on Bone Marrow (BM) Morphology in Patients With Myelofibrosis (MF) Enrolled in the COMFORT-I Study

The phase 3 COMFORT-I and COMFORT-II studies showed that ruxolitinib improves splenomegaly, constitutional symptoms, and OS in patients with MF.\(^1,2\) Retrospective studies suggest that ruxolitinib may improve or stabilize bone marrow fibrosis by decreasing cellularity; reducing the population of plasma cells, macrophages, and megakaryocytes; and correcting megakaryocytic atypia.\(^3,4\)

A study of data from the COMFORT-I trial was conducted to assess changes in bone marrow fibrosis with long-term ruxolitinib use in patients with MF.\(^5\) COMFORT-I enrolled patients with intermediate-2 or high-risk primary MF, PPV-MF, or PET-MF. All patients had palpable splenomegaly. Crossover from the placebo arm to the ruxolitinib arm was permitted prior to study unblinding for patients with worsening of splenomegaly or splenic pain despite narcotic treatment. Bone marrow biopsies were obtained at baseline, at weeks 48 and 72, and approximately every 48 weeks thereafter for up to 5 years during treatment with ruxolitinib. Biopsies were reviewed independently in a blinded manner by 3 hematopathologists, with final grading based on consensus.

There were 3 patient subgroups: 36 patients randomly assigned to ruxolitinib; 15 patients randomly assigned to placebo, with bone marrow measurements available from baseline and week 48; and 21 patients who crossed over to ruxolitinib, with bone marrow measurements available at baseline plus at least 1 postbaseline measurement available after crossover. Change in bone marrow fibrosis grade from baseline was measured as improved (-3 to -1), stable (0), or worsened (1 to 3). Baseline characteristics were generally well-balanced among the 3 groups. Mean exposure to ruxolitinib was 136.0 ± 67.4 weeks in the ruxolitinib group and 129.1 ± 67.7 weeks in the crossover group.

All patients had baseline bone marrow biopsy data and corresponding sequential assessments. From baseline to week 48, bone marrow fibrosis grade improved for 7 of 30 patients randomly assigned to ruxolitinib (23%) and for 2 of 15 patients randomly assigned to placebo (13%; Figure 3). Among the 57 patients who received ruxolitinib, a significant shift toward improvement of bone marrow fibrosis grade was observed from baseline to the last evaluation of bone marrow fibrosis (\(P = .0119\)). Thirty-three percent of the patients with ruxolitinib exposure experienced an improvement in fibrosis, including 11 with improvement in -1 grade (19%), 7 with improvement in -2 grade (12%), and 1 with improvement in -3 grade (2%). Bone marrow fibrosis was stable in 28 patients (49%) and worsened (to grade 1) in 10 (18%). In the group of 57 patients who had received ruxolitinib treatment, the median time to a confirmed improvement in bone marrow fibrosis grade was 216 weeks, and the median duration of confirmed improvement was 192 weeks (Figure 4). In the same group, the median time to a confirmed stabilization of bone marrow fibrosis grade was 72 weeks, and the median duration of confirmed stabilization was not reached.

\[\text{Figure 3. In the COMFORT-I trial, improvement in bone marrow fibrosis grade from baseline to week 48 was reported for 23\% of patients treated with ruxolitinib (A) vs 13\% of patients treated with placebo (B). COMFORT, Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment. Adapted from Kvasnicka HM et al. ASH abstract 1949. Blood. 2016;128(suppl 22).}\]
ABSTRACT SUMMARY Phase-2 Study of Sotatercept (ACE-011) in Myeloproliferative Neoplasm-Associated Myelofibrosis and Anemia

An ongoing phase 2 study evaluated sotatercept in patients with primary MF, PPV-MF, or PET-MF (Abstract 478). The study evaluated dosages of 0.75 mg/kg and 1 mg/kg given every 3 weeks. The primary endpoint was the anemia response. Of 14 evaluable patients, 36% demonstrated a response. Responses were reported in 40% of 10 patients in the lower-dose cohort and in 25% of 4 patients in the higher-dose cohort. There were responses in 33% of 10 transfusion-dependent patients and 50% of 4 nontransfusion-dependent patients. Responses were seen in all of the 5 women enrolled, but in none of the 9 men. A total of 13 patients discontinued treatment, including 5 with no response, 2 who proceeded to stem cell transplant, 2 who experienced disease progression, 1 who transformed to acute myeloid leukemia, 1 who withdrew consent, 1 who developed unrelated medical problems, and 1 who had hypertension. Sotatercept demonstrated an excellent safety profile. All AEs were of grade 1 or 2, with the exception of 1 AE of grade 3 hypertension in 1 patient, which was considered possibly related to study treatment.

References

Examining the Clinical Features and Underlying Cardiovascular Risk Among Patients With Polycythemia Vera in the REVEAL Study

REVEAL (Prospective Observational Study of Patients With Polycythemia Vera in US Clinical Practices) is a multicenter, noninterventional, nonrandomized, prospective, observational, phase 4 study that is collecting data on PV patient demographics, disease burden, clinical management, patient-reported outcomes, and healthcare resource use in the United States. The study enrolled a total of 2544 adults with PV from 219 study sites, all of whom were under active management by a physician in a community or academic treatment center. Patient-reported outcomes and physician assessments are being collected for 36 months. Ten-year cardiovascular risk factors were adapted from the Framingham Heart Study for Cardiovascular Diseases.

A preliminary analysis of the REVEAL study included data from 2307 patients. At the time of enrollment, 77.3% of patients were classified as having high-risk PV, based on older age (≥60 years) and/or a history of thrombotic events. At enrollment, 91.5% of patients were under active management for their PV, with the most common treatments consisting of phlebotomy (34.0%), hydroxyurea (27.0%), and phlebotomy plus hydroxyurea (23.2%), all with or without concomitant aspirin. At least 1 underlying cardiovascular risk factor was observed in 86.0% of patients at enrollment, including hypertension (66.5%), history of smoking (46.2%), obesity (34.2%), hyperlipidemia (27.4%), diabetes (14.8%), and current smoking (10.9%).

Venous thrombotic events and arterial thrombotic events were recorded in 11.1% and 8.6% of patients, respectively. Among the 431 patients (18.7%) with a history of thrombotic events, 181 (42.0%) experienced a thrombotic event between the time of diagnosis and the time of enrollment. The events varied according to patients’ underlying cardiovascular risk factors (Figure 5). The most common venous thrombotic events were deep vein thrombosis (5.9%) and pulmonary embolism (2.5%), and the most common arterial thrombotic events were cerebrovascular arterial thrombosis, including transient ischemia (5.1%) and acute myocardial infarction (1.7%). The rate of thrombotic events was 10.5% among patients.
without any underlying cardiovascular risk factors, 23.6% in patients with hyperlipidemia, and 21.0% in patients with hypertension. Overall, rates of thrombotic events increased with the number of cardiovascular risk factors, from a low of 10.5% in patients with no risk factors to 23.7% in patients with 4 or more risk factors.

References


Clinical Outcomes With Ruxolitinib (RUX) in Patients With Myelofibrosis (MF) Stratified By Transfusion Status: A Pooled Analysis of the COMFORT-I and -II Trials

Pooled data from the COMFORT-I and COMFORT-II studies were evaluated to determine the relationship between transfusion requirements and clinical outcomes in MF patients treated with ruxolitinib. The analysis was based on data from 301 patients randomly assigned to receive ruxolitinib and 227 in the control group. Baseline anemia was reported in 45.8% of the ruxolitinib arm and 49.8% of the control arm. The need for transfusion was assessed at week 24 (Figure 6). Patients who did not require transfusion during weeks 13 to 24 were considered independent, and patients who required transfusion during weeks 17 to 24 were considered dependent. In the ruxolitinib group, a greater proportion of patients who were nonanemic at baseline (range, 73.4%-73.8%) achieved transfusion independence compared with those who had anemia at baseline (range, 15.5%-22.4%).

At week 24, transfusion independence vs nonindependence did not significantly impact OS among patients receiving treatment with ruxolitinib (P=0.1322). In contrast, transfusion status did significantly affect OS in the control group (P=0.0004). Similarly, transfusion dependence vs nondependence at week 24 did not significantly affect OS in the ruxolitinib group (P=0.4547; Figure 7). Median OS was significantly longer in the ruxolitinib arm vs the control arm among patients who were transfusion dependent (anemic at baseline, 200 vs 137 weeks; nonanemic, 271 vs 166 weeks; overall, P=0.002) or who became transfusion dependent (anemic at baseline, 210 vs 127 weeks; nonanemic, 292 vs 90 weeks; overall, P=0.0323).

Median OS was significantly improved with ruxolitinib overall, as
well as in the group of patients who were transfusion-dependent at week 24 ($P=0.0014$).

The median time to transfusion independence was 16.6 weeks in the ruxolitinib arm vs 12.0 weeks in the control arm. Among patients treated with ruxolitinib, the risk of transfusion dependence decreased after week 24 (from 0.51 at week 24 to 0.54 at week 36).

In patients treated with ruxolitinib, changes in spleen volume, body weight, and symptom scores from baseline were not affected by transfusion status. The probability that a patient would become transfusion-independent after 1 year of treatment was similar in both treatment groups. Among patients in the control arm, symptom scores were worse in patients who failed to achieve transfusion independence compared with those who did.

The authors concluded that transfusion requirements had little impact on clinical outcomes or treatment discontinuation within the ruxolitinib

**Figure 6.** Proportions of patients treated with ruxolitinib who were transfusion-independent at week 24 in the COMFORT trials. COMFORT, Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment; ITT, intent-to-treat. Adapted from Gupta V et al. ASH abstract 3118. Blood. 2016;128(suppl 2).3

**Figure 7.** Overall survival according to anemic status and need for transfusion among patients who received ruxolitinib in the COMFORT trials. COMFORT, Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment; OS, overall survival. Adapted from Gupta V et al. ASH abstract 3118. Blood. 2016;128(suppl 2).3
group. In contrast, among patients in the control arm, the need for transfusion was associated with reduced OS and worsened total symptom scores. After 24 weeks of treatment with ruxolitinib, rapid decreases were seen in the risk of becoming transfusion dependent, the number of units of red blood cells administered, and the monthly proportions of patients who required transfusions.

References

Interim Analysis of the Myeloproliferative Disorders Research Consortium (MPD-RC) 112 Global Phase III Trial of Front Line Pegylated Interferon Alpha-2a Vs. Hydroxyurea in High Risk Polycythemia Vera and Essential Thrombocytopenia

The optimal management of high-risk ET and PV remains unknown. Several studies have demonstrated a reduction of thrombotic risk with hydroxyurea therapy. Despite concerns regarding the leukemogenic potential of hydroxyurea, a clear correlation between hydroxyurea treatment and the development of acute leukemia has not been established. In phase 2 studies, interferon-α was associated with hematologic ORRs of greater than 75% and molecular CR rates of between 10% and 20%.

MPD-RC 112 (Myeloproliferative Disorders Research Consortium 112) is a global, randomized, phase 3 study conducted by the Myeloproliferative Disorders Research Consortium to compare first-line hydroxyurea vs pegylated interferon α-2a in patients with high-risk PV or ET. Patients were enrolled at 43 institutions in the United States, Canada, Europe, and Israel. The primary objective was to compare the hematologic CR rates (by European LeukemiaNet criteria) after 12 months of therapy based on blinded central review. Secondary objectives were to compare outcomes in the 2 treatment arms based on toxicity and tolerability; CR and PR rates; specific predefined toxicity and tolerance of therapy determined through the MPN Safety Assessment Form; survival and incidence of development of a myelodysplastic disorder, MF, or leukemic transformation; and impact of therapy on key disease biomarkers, including driver mutations. Key eligibility criteria included PV or ET by World Health Organization criteria, and high-risk disease, based on

ABSTRACT SUMMARY Preliminary Safety and Clinical Activity in a Phase 1 Study of BLU-285, a Potent, Highly-Selective Inhibitor of KIT D816V in Advanced Systemic Mastocytosis (SM)

Ninety-five percent of advanced aggressive systemic mastocytosis (SM) cases and related disorders are characterized by the oncogenic KIT D816V mutation. A phase 1 study was conducted to evaluate BLU-285, an oral inhibitor of KIT D816V, in patients with aggressive SM, SM with associated hematologic nonmast cell disorder, or mast cell leukemia (Abstract 477). Twelve patients received daily BLU-285 in 4-week cycles, with 3 + 3 escalation from 30 mg daily to 100 mg daily. Most AEs were of grade 1 or 2. Three patients experienced grade 3 alkaline phosphatase increase, and 1 patient experienced grade 3 thrombocytopenia. No grade 4 or 5 treatment-related events were reported. No dose reductions were required by toxicity. The 1 dose-limiting toxicity was grade 3 alkaline phosphatase elevation, and the maximum tolerated dose was not reached. A decrease from baseline in the proportion of mast cells in the bone marrow was observed in 6 of 8 patients, and tryptase decreased in 10 of 12 patients.
The 168 patients were randomly assigned to receive treatment with hydroxyurea or pegylated interferon α-2a. Data were available for 39 patients treated with hydroxyurea and 36 patients treated with pegylated interferon α-2a. Patient baseline characteristics were generally well-balanced between the 2 treatment arms. The 75 patients had a median age of 61 years (range, 20-85 years), and 47% were female.

Dose escalations were commonly used to achieve a hematologic response, resulting in a mean pegylated interferon α-2a dose of 90 μg weekly and a mean hydroxyurea dose of 6 g weekly. At the time of the interim analysis, 29 patients in the hydroxyurea arm and 33 patients in the pegylated interferon α-2a arm remained on therapy. ORR was 69% in the hydroxyurea arm vs 81% in the pegylated interferon α-2a arm; (P = .6). The primary endpoint of CR rate also did not differ significantly between the 2 arms (33% vs 28%, respectively; P = .6). Among the patients with PV, the proportion of those with hematocrit control at 12 months was 57% with hydroxyurea vs 76% with pegylated interferon α-2a (P = .19). Also among these patients, platelet control at 12 months was 73% in both treatment arms (P > .99).

Seven patients in each arm demonstrated a spleen response based on palpable splenomegaly, and 1 patient in the hydroxyurea arm experienced an increase in splenomegaly. Complete histopathologic bone marrow responses were observed in 36% of patients in the hydroxyurea arm vs 8% of patients in the pegylated interferon α-2a arm. These rates were 50% vs 20% in patients with ET, and 25% vs 0% in patients with PV. The JAK2 V617F burden decreased from 19.7% at baseline to 8.3% after 12 months of hydroxyurea treatment and decreased from 18.8% at baseline to 8.4% after 12 months of pegylated interferon α-2a treatment (Figure 8). Molecular responses among the 19 patients in the hydroxyurea arm included 22% CRs, 28% PRs, and 50% with no response. Similar outcomes were seen among the 22 patients receiving pegylated interferon α-2a (14%, 32%, and 54%, respectively).

Frequently reported AEs of any grade included depression (0% with...
hydroyxurea vs 28% with pegylated interferon α-2a; *P*<.001), dyspnea (3% vs 19%; *P*=.02), flu-like symptoms (3% vs 33%; *P*<.001), injection site reaction (0% vs 25%; *P*<.001), and pruritus (8% vs 28%; *P*=.03). The rate of grade 3 or higher AEs was 14% in the hydroxyurea arm vs 47% in the pegylated interferon α-2a arm (*P*=.002).

Comparative analyses of quality of life and symptom burden were presented separately by Dr Ruben Mesa.9 Within the first 6 months, the improvement in symptom burden was greater with pegylated interferon α-2a than hydroxyurea. However, the low-grade side effects of pegylated interferon α-2a, such as injection site reactions, flu-like symptoms, and myalgias, increased over time.

References

Myeloproliferative Neoplasms: Current Mutational Landscape of Myeloproliferative Neoplasms

At the 2016 ASH Education Program on MPNs, Dr Jamile Shammo reviewed the mutational landscape.10 Dr Shammo focused on the common genetic alterations in MPNs, including driver and nondriver mutations; their prognostic implications; and the potential impact of these mutations on selection of therapy and outcome. Hematopoiesis is dependent on numerous cytokine signaling pathways.2-4 In MPNs, the driver mutations are primarily found in JAK2, the myeloproliferative leukemia (MPL) gene, and calreticulin (CALR). A key signaling pathway involves cytokine or growth factor binding to MPL protein, activation of JAK1/2 and the signal transducers and activators of transcription (STAT) pathway, and nuclear transcription of genes involved in proliferation, survival, and differentiation. Mutations that induce constitutive activation of the signal transduction pathway controlled by *MPL* are key drivers of MPN pathogenesis.

Common Mutations in MPNs

The *JAK2* V617F mutation is present in greater than 90% of PV cases, and activating mutations in *JAK2* and *MPL* are the drivers in approximately 50% to 60% of patients with ET and MF.5,8 The importance of mutations in *CALR*, the gene that encodes calreticulin, was revealed in 2013 by whole-exome sequencing.9 *CALR* mutation was identified in the majority of ET and MF patients who lacked mutations in *JAK2* and *MPL*, and it is the key mutation in 30% to 40% of ET and MF patients. The mutations identified in *CALR* result in a frameshift such that the charge on the C-terminal peptide of calreticulin changes from negative to positive. The frameshift also causes loss of the C-terminal KDEL sequence that mediates retention in the endoplasmic reticulum. *CALR* mutation induces pathogenesis by allowing calreticulin to escape from the endoplasmic reticulum, after which it binds directly to *MPL*, activating the thrombopoietin receptor and the downstream JAK/STAT pathway.10-12 Genetic evaluation of *JAK2*, *MPL*, and *CALR* is not currently part of routine prognostic assessment in patients with primary MF. However, the prognostic impact of driver mutations in MF has been studied extensively. In a study of 617 patients with primary MF, 64.7% had a *JAK2* V617F mutation, 22.7% had a *CALR* exon 9 insertion or deletion, 4.0% carried a *MPL* mutation, and 8.6% had triple-negative disease, characterized by wild-type *JAK2*,...
CALR, and MPL. Median OS was highest in patients with a CALR mutation (17.7 years), followed by patients with a JAK2 mutation (9.2 years) and an MPL mutation (9.1 years). Median OS was lowest in patients with triple-negative disease, at 3.2 years. The group of patients with triple-negative disease also demonstrated the highest 10-year cumulative incidence of blast transformation, at 34.4%. In patients with JAK2, MPL, or CALR mutation, the 10-year cumulative incidences of blast transformation were 19.4%, 16.9%, and 9.4%, respectively. The patients with CALR mutation also exhibited reduced rates of anemia, thrombocytopenia, and leukocytosis compared with patients harboring the JAK2 V617F mutation. Dozens of CALR mutations have been identified, and the majority of mutations are either a type 1 deletion or type 2 fied, and the majority of mutations compared with patients harboring thrombocytopenia, and leukocytosis exhibited reduced rates of anemia, CALR patients with blast transformation were 19.4%, the 10-year cumulative incidences of blast transformation were 19.4%, 16.9%, and 9.4%, respectively. The patients with CALR mutation also exhibited reduced rates of anemia, thrombocytopenia, and leukocytosis compared with patients harboring the JAK2 V617F mutation. Dozens of CALR mutations have been identified, and the majority of mutations are either a type 1 deletion or type 2 insertion. CALR type 1 mutations are more commonly associated with MF. In patients who have ET and the CALR type 1 mutation, the risk of myelofibrotic transformation is higher. CALR type 2 mutations are more common in patients with ET, and these patients tend to have an indolent clinical course and a reduced risk of thrombosis.

In contrast to ET and MF, PV is associated with JAK2 driver mutations in greater than 90% of cases. In a study of 133 PV patients, the prevalence of nondriver mutations was evaluated by next-generation sequencing of a 27-gene panel. A driver mutation in JAK2 was found in 98% of patients. Mutations in genes other than JAK2, MPL, or CALR were observed in 44% of patients, with 1 mutation observed in 29% and 2 mutations observed in 14%. Of the 3 patients with wild-type JAK2, none expressed nondriver mutations. OS was negatively affected by the presence of mutations in SRSF2 (P=0.006) and RUNX1 (P=0.04), and by the presence of nondriver mutations. After a median follow-up of 9.8 years, median OS was 13 years in patients with no nondriver mutations, 11.5 years (HR, 1.7; 95% CI, 0.97-3.1) in those with 1 nondriver mutation, and 10 years (HR, 2.6; 95% CI, 1.3-5.2) in patients with 2 or more nondriver mutations (P=0.01). Similar findings have emerged in patients with ET, and therefore routine genetic profiling of patients with ET/PV is not currently recommended.

In patients with primary MF, mutations in ASXL1, EZH2, SRSF2, or IDH1/2 are associated with an increased risk of leukemic transformation. ASXL1 mutation was associated with reduced survival, independent of the Dynamic IPSS (DIPSS)-plus model, which includes clinical and cytogenetic variables. A molecular prognostic model incorporating CALR and ASXL1 mutations was investigated in 570 patients with primary MF. Initial derivation of the model was performed by stratification of 277 patients, with subsequent validation in 293 patients. Median OS was longest in patients with mutated CALR/wild-type ASXL1, at 10.4 years, and was shortest in patients with wild-type CALR/mutated ASXL1, at 2.3 years (HR, 5.9; 95% CI, 3.5-10.0 years). The prognostic significance of the CALR and ASXL1 mutations was maintained for patients within a single IPSS category.

Researchers have defined high–molecular risk patients as those having at least 1 mutation in ASXL1, EZH2, SRSF2, or IDH1/2. In a cohort of 537 European patients with primary MF, 31% were high–molecular risk, including 23.6% with 1 mutation and 7.4% with 2 or more mutated genes. Patients with no mutations in the 5 genes had a median OS of 12.3 years. Median OS was 7.0 years in patients with 1 mutation and 2.6 years in patients with 2 or more mutations (HR, 3.8; 95% CI, 2.6-5.7). The results were validated in a cohort of 260 patients at the Mayo Clinic, and the prognostic significance in both cohorts was independent of IPSS and DIPSS-plus. The presence of 2 or more detrimental mutations was also associated with reduced leukemia-free survival (HR, 6.2; 95% CI, 3.5-10.7).

**Therapy Choice and Outcome: Do Mutations Matter?**

Despite the advances in molecular analytical techniques, the major prognostic indicators in PV continue to be the patient’s age and history of thrombosis. Low-risk patients are those younger than 60 years with no history of thrombosis, and high-risk patients are ages 60 years or older and/or have a history of thrombosis. The CYTO-PV study (Cytoreductive Therapy in Polycythemia Vera) investigated the value of maintaining a hematocrit level of less than 45% in patients with PV and the JAK2 mutation. The study randomly assigned 365 patients to receive intensive treatment with phlebotomy, hydroxyurea, or both to achieve a hematocrit level of less than 45% or to receive less intensive treatment while maintaining a hematocrit level of 45% to 50%. The primary composite endpoint was time until death from cardiovascular or major thrombotic events. After a median follow-up of 31 months, primary endpoint events had occurred in 5 of 182 patients in the low-hematocrit group (2.7%) and 18 of 183 patients in the high-hematocrit group (9.8%; HR, 3.91; 95% CI, 1.45-10.53; P=0.007).

For patients with low-risk PV, phlebotomy is used to maintain a hematocrit level of less than 45%, and aspirin is recommended for primary antiplatelet prophylaxis in the absence of contraindications, along with aggressive control of cardiovascular risk factors, including obesity, smoking, hypertension, and diabetes. For patients with high-risk PV, phlebotomy is also used to maintain hematocrit levels below 45%. Additionally, hydroxyurea or interferon is used as first-line treatment for cytoreduction; busulfan is an option for older patients.
who may be unable to tolerate more aggressive treatment. Ruxolitinib is approved by the US Food and Drug Administration for the treatment of PV patients who are intolerant of hydroxyurea or have had an inadequate response.\textsuperscript{24}

Pegylated interferon α has been a mainstay of PV therapy for many years.\textsuperscript{25} In a phase 2 study of 40 patients with PV harboring JAK2 V617F, 37 patients experienced a hematologic response after 12 months of treatment with pegylated interferon α-2a, including 35 with hematologic CRs. Three patients were excluded from the analysis. The median proportion of granulocytes harboring the JAK2 V617F mutation decreased from 45% at baseline to 22% at 12 months, 5% at 24 months, and 3% at 36 months. At the time of the last analysis, molecular CRs were observed in 7 of 29 patients (24.1%). TET2 mutation has since emerged as a factor in PV and may influence the efficacy of treatment with interferon.\textsuperscript{26}

Risk factors in patients with ET include older age (>60 years), platelet level of greater than 1500 × 10\(^9\)/L, and a history of bleeding or thrombotic events. Cardiovascular risk factors should be managed in all patients. Aspirin is appropriate for patients with microvascular disturbance, cardiovascular risk, or JAK2 V617F mutation. However, aspirin is not appropriate for low-risk patients with a CALR mutation, owing to a lack of reduction in venous thrombotic events and increased bleeding events.\textsuperscript{27} In patients with high-risk disease, hydroxyurea or interferon-α is appropriate for first-line treatment. These 2 agents may also be considered for patients with extreme or symptomatic thrombocytosis. For second-line therapy, or in patients for whom hydroxyurea therapy is not an option, choices include interferon-α, anagrelide, and busulfan. Clinical trials may also be considered.

Identification of a transformed clone is essential to confirm a diagnosis of MF. Although numerous therapies are available for patients with MF, the only curative treatment is allogeneic stem cell transplant. Watchful waiting is appropriate for patients with early, low-risk MF as clinical trials have yet to establish the value of early treatment in this setting. Ruxolitinib is an option in patients who have high-risk disease, constitutional symptoms, and symptomatic splenomegaly. Clinical trials evaluating novel agents are another option. To manage anemia, appropriate therapies include erythropoiesis-stimulating agents, danazol, and prednisone. Ruxolitinib was approved for MF based on the phase 3 COMFORT trials.\textsuperscript{28,29} Both trials yielded a reduction in spleen size in patients with MF. In COMFORT-I, response to ruxolitinib was not associated with JAK2 mutation, age, type of MF, IPSS risk score, or baseline spleen length. Ruxolitinib was also shown to be effective in patients with high or low molecular risk.\textsuperscript{30} However, in a separate analysis of data from a phase 1/2 trial, ruxolitinib efficacy was reduced in patients with a larger number of mutations in a panel of genes recurrently mutated in hematologic malignancies (Figure 9).\textsuperscript{31} Patients with 2 mutations or fewer had 9-fold increased odds of a spleen response compared with patients harboring 3 or more mutations (OR, 9.37; 95% CI, 1.86-47.2), and patients with at least 3 mutations had a shorter time to treatment discontinuation and shorter OS.

Newer agents of interest include momelotinib, a JAK2 kinase inhibitor, and imetelstat, a telomerase inhibitor. In a phase 2 trial of patients with MF who were treated with momelotinib monotherapy, CALR and ASXL1 mutation status was associated with
SPECIAL MEETING REVIEW EDITION

Erasure inhibitor yielded a CR of 38%. Evaluation of imetelstat in refractory patients with wild-type CALR and ASXL1, and was 1.6 years in patients with wild-type CALR and mutated ASXL1. Imetelstat was evaluated in 33 patients with intermediate-2 or high-risk MF, yielding an ORR of 21% and a median duration of response of 18 months. The telomerase inhibitor yielded a CR of 38% in patients with a mutation in SF3B1 or U2AF1 vs 4% in patients without these mutations (P<.04), prompting evaluation of imetelstat in refractory anemia with ring sideroblasts.

Conclusion

Dr Shammo concluded that the identification of a driver mutation is now essential for the diagnosis of MPN. The driver mutation provides important prognostic information. More data are needed to understand the influence on treatment selection and outcome.

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Highlights in Myeloproliferative Neoplasms From the 2016 American Society of Hematology Meeting: Commentary

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The 2016 American Society of Hematology (ASH) meeting included many important abstracts in myeloproliferative neoplasms (MPNs). Analyses reinforced the long-term safety and benefits of ruxolitinib in myelofibrosis. Studies in polycythemia vera compared interferon with hydroxyurea to provide the first large-scale phase 3 data. Novel therapies, such as sotatercept and anagrelide, were also evaluated. Interesting data were provided for a less common MPN, systemic mastocytosis.

Ruxolitinib

In 2011, the US Food and Drug Administration approved ruxolitinib for the treatment of myelofibrosis. Several presentations at the ASH meeting provided long-term follow-up from studies of ruxolitinib, such as the COMFORT trials (Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment)1,2 and the compassionate use JUMP study (INC424 for Patients With Myelofibrosis, Post Polycythemia Vera Myelofibrosis or Post-Essential Thrombocythemia Myelofibrosis).3 Ruxolitinib remains the only approved therapy widely available throughout the world for myelofibrosis.

I was coauthor of a study presented by Dr Srdan Verstovsek, which analyzed combined survival data from COMFORT-I and COMFORT-II.4 Without question, ruxolitinib continues to be associated with a significant survival advantage compared with each of the control arms, whether placebo (in COMFORT-1) or best alternative therapy (in COMFORT-II). This advantage has been maintained despite the impact of crossover. In both COMFORT studies, most patients in the control arms transitioned to ruxolitinib, and the comparisons were made between patients who received ruxolitinib earlier vs later. These long-term data therefore suggest not only that ruxolitinib has a survival advantage, but that earlier treatment may be better than later treatment.

Other long-term analyses from the COMFORT studies also provided important data. Dr Vikas Gupta evaluated the impact of anemia.5 The analysis showed that the development of anemia, or any amount of anemia associated with the use of ruxolitinib, did not appear to have a negative impact on outcome or survival. The negative prognostic implications of disease-associated anemia may not occur with anemia induced by medication. There was always a question of whether the development of anemia was detrimental in these patients, and the results of this study provide assurance that it is not.

Dr Hans Michael Kvasnicka presented data from a long-term analysis of the COMFORT-1 trial to identify how ruxolitinib might affect bone marrow.6 The study identified a favorable impact, with improvement or stabilization in bone marrow fibrosis in many patients. This favorable impact took some time to recognize. Improvements were seen in patients treated for well over 48 weeks. It is not a surprise that the process is lengthy; stem cell transplant can take up to a year to resolve fibrosis.

Supporting these long-term analyses from the COMFORT trials are data from the single-arm JUMP study, which evaluated more than 2000 patients treated with ruxolitinib in an open-label, expanded-access protocol.7 Dr Lynda Foltz presented the results of the study.7 The key takeaways are that the safety and efficacy in this much broader population mirror the benefits seen in the COMFORT studies.1,2 Resolution of splenomegaly and other difficulties were very pronounced. The JUMP study included patients with intermediate-1 disease, and benefits were similar in these patients and in those with more advanced disease. These favorable observations further reinforce the safety and efficacy of ruxolitinib.
Interferon

Several studies at ASH evaluated long-acting interferon formulations. Dr Heinz Gisslinger presented results from the PROUD-PV trial (Pegylated Interferon Alpha-2b Versus Hydroxyurea in Polycythemia Vera), which compared pegylated interferon α-2b vs hydroxyurea in patients with polycythemia vera.8 Dr John Mascarenhas presented interim data from the MPD-RC 112 trial (Myeloproliferative Disorders Research Consortium 112), which compared pegylated interferon α-2a vs hydroxyurea in patients with high-risk polycythemia vera or essential thrombocytopenia.9

In both studies, within the first year of therapy, interferon was relatively equivalent to hydroxyurea in controlling blood counts and preventing vascular events. These studies are important because they provide the first randomized data that confirm the efficacy of interferon in this setting. There have been many single-arm institutional studies that have demonstrated the activity of interferon in these patients,10,11 but no randomized data showing equivalence.

I presented a parallel analysis of the MPD-RC study assessing quality of life and symptoms throughout the course of the therapy.12 It found that interferon may have a longer-term benefit in terms of better disease control at a molecular level among patients treated with extended therapy, but further analysis is needed. Currently, it is necessary to consider a patient’s individual factors, such as tolerability of a medication, age, and childbearing status, when deciding which therapy to use in the frontline setting.

Other Therapies

Anemia remains a significant unmet need in patients with myelofibrosis. Sotatercept is a novel therapy that has been active in other anemic disorders and aims to improve erythropoiesis in these patients.13 Dr Prithviraj Bose presented early results from an ongoing analysis of patients with primary myelofibrosis, post–polycythemia vera myelofibrosis, or post–essential thrombocytopenia myelofibrosis.14 Sotatercept was well-tolerated and improved anemia. The study authors are expanding their efforts to evaluate sotatercept in combination with ruxolitinib. If it is possible to preserve the benefits of Janus kinase (JAK) inhibition—in terms of splenomegaly symptoms and survival—while further improving anemia, then a combination regimen would be of interest. Other potential candidates for this approach might be patients who have anemia that overlaps with a phenotype resembling a myelodysplastic syndrome.

Dr Heinz Gisslinger presented results from a study comparing a long-acting anagrelide compound vs placebo in patients with intermediate-risk essential thrombocytopenia.15 This is an important study because there is no consensus on treatment in this setting. These patients are intermediate-risk, so they typically would not receive cytoreductive therapy. The study found that the long-acting anagrelide was safe and reasonably well-tolerated. Long-acting anagrelide was better than pure observation. A question raised at the ASH presentation concerned the lack of aspirin use in both arms. Some might argue that it would have been prudent to use aspirin in intermediate-risk patients. It is not clear whether the difference in event rates would have been erased by the use of aspirin. However, the study provides important information and suggests that intermediate-risk patients should receive treatment with something, whether it be cytoreduction, aspirin, or both.

Aspects of Disease Burden

Several abstracts focused on additional aspects of disease burden. To date, the observational REVEAL study (Prospective Observational Study of Patients With Polycythemia Vera in US Clinical Practices) is the largest study in polycythemia vera, with approximately 2300 patients.16,17 It is providing valuable information about these patients. At the ASH meeting, Dr Brady Stein presented an analysis of the underlying cardiovascular risk factors in these patients.17 The analysis showed that a high proportion of patients with polycythemia vera have cardiovascular risk factors. It is important to consider these risk factors when treating patients with a current or previous thromboembolic event. Other considerations include the patient’s smoking status, hypertension, obesity, hyperlipidemia, and diabetes.

The LANDMARK study was a survey of patients with MPNs. I helped lead the study in the United States, and data were published in 2016.18,19 At the ASH meeting, Dr Claire Harrison provided data for approximately 700 patients from Canada, Europe, Japan, and Australia.20 The results reinforced our understanding that these diseases are associated with significant symptom burden, and that they impact quality of life, as well as employment status.
and the ability to be fully employed. This analysis confirms that the burdens associated with MPNs in the United States occur worldwide. Another relevant finding is that patients with essential thrombocythemia or polycythemia vera can experience similar difficulties as patients with myelofibrosis.

**Uncommon MPNs**

Most studies in MPNs focus on essential thrombocythemia, polycythemia vera, and myelofibrosis, which are the most common of the BCR/ABL-negative MPNs. However, atypical MPNs can also cause significant difficulties. Patients with systemic mastocytosis can experience very severe disease burden. High amounts of mast cells can lead to increased rates of allergic reactions, organ damage, and other morbidities, as well as mortality. There are few treatment options.

These patients frequently have a genetic mutation in the kinase **KIT** D816V. BLU-285 is a highly targeted therapy designed to inhibit that mutation. Dr Mark Drummond presented results from a phase 1, dose-escalation study. The study showed that BLU-285 had significant disease activity and was safe and well-tolerated. BLU-285 decreased mast cell burden and improved the end organ effects of mastocytosis. This targeted therapy is now being evaluated in other diseases driven by KIT D816V, such as gastrointestinal stromal tumors.

**Conclusion**

Abstracts at the 2016 ASH meeting continue to highlight the number and sophistication of treatment options for patients with MPNs. There was further refinement of information regarding therapies in myelofibrosis. New data confirm the utility of ruxolitinib in this population. Interferon and long-acting anagrelide are new therapies that are relevant for polycythemia vera and essential thrombocythemia. Other analyses provided more information regarding the overall disease burden and the favorable impact of therapies. New targeted approaches, based on molecular mutations, have benefits in the less-common MPNs.

**Disclosure**

Dr. Mesa is a consultant for Novartis, AOP, Shire, Ariad, and Galene. He has performed research for Incyte, Gilead, CTI, Promedior, and Celgene.

**References**
