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

With Expert Commentary by:

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Important Safety Information

Severe neutropenia (ANC <0.5 × 10⁹/L) was generally reversible by withholding Jakafi until recovery

Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi clinically indicated every 2 to 4 weeks until doses are stabilized, and then as neutropenia, which are each dose-related effects. Perform a withholding Jakafi until recovery

INTERVENE WITH JAKAFI 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 × 10⁹/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

Jakafi is a registered trademark of Incyte. © 2017, Incyte Corporation. All rights reserved. RUX-2216 12/17
Significantly more patients receiving Jakafi achieved the composite primary* and key secondary end points²,³

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

**Components of Primary End Point at Week 32²**

<table>
<thead>
<tr>
<th>Component</th>
<th>Jakafi (n=110)</th>
<th>BAT (n=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct Control</td>
<td>60%</td>
<td>19%</td>
</tr>
<tr>
<td>Spleen Volume Reduction</td>
<td>40%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

* Complete hematologic remission was defined as achieving hematocrit control (as specified in the primary end point), platelet count <400 x 10⁹/L, and white blood cell count <10 x 10⁹/L.²

**Durable response at week 80²**

- 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

**Durable count control**

- 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

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 V2.2018. © National Comprehensive Cancer Network® (NCCN®) 2018. All rights reserved. Accessed September 2017. To view the most recent and complete version of the guidelines, go online to NCCN.org. NCCN.org makes no warranties of any kind whatsoever regarding their contents, use or application and disclaims any liability for their application or use in any way.
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>Bruising&lt;sup&gt;a&lt;/sup&gt;</td>
<td>23</td>
<td>&lt;1</td>
<td>0</td>
<td>15</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness&lt;sup&gt;a&lt;/sup&gt;</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>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Urinary Tract Infections&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9</td>
<td>0</td>
<td>5</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Weight Gain&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7</td>
<td>&lt;1</td>
<td>1</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fluotulose</td>
<td>5</td>
<td>0</td>
<td>&lt;1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Herpes Zoster&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>0</td>
<td>&lt;1</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

<sup>a</sup> includes cutaneous, eczematous, hematomal, injection site hematomas, peripheral hematomas, vesicle puncture site hematomas, increased tendency to bruise, petechiae, purpura

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, 65% 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<sup>9</sup>/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<sup>9</sup>/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<sup>9</sup>/L (7% 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 hematological abnormalities reported for patients receiving treatment with jakafi or placebo in the placebo-controlled study.

**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.
in patients treated with Jakafi. Assess lipid parameters approximately 8-12 weeks following initiation of Jakafi. The effect of these lipid parameter elevations on cardiovascular morbidity and mortality has not been determined.

Jakafi, among the 155 patients treated with Jakafi, the most frequent adverse drug reactions were:

- Nausea (8%)
- Fatigue (15%)
- Headache (16%)
- Abdominal Pain (15%)
- Anemia (15%)
- Diarrhea (15%)
- Pruritus (14%)
- Dyspepsia (13%)
- Muscle Spasms (12%)
- Constipation (8%)

Other clinically important treatment-emergent adverse events observed in less than 6% of patients treated with Jakafi were:

- Weight gain
- Hypertension
- Urinary tract infections

Clinically relevant laboratory abnormalities are shown in Table 4.

**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 2-4% and miscarriage is 15-20% of clinically recognized pregnancies. Data: Animal Data

**Contraindications**

- Use in patients with active serious infections
- Use in patients with tuberculosis
- Use in patients with HIV infection
- Use in patients with severe neutropenia
- Use in patients with severe myelosuppression
- Use in patients with myelofibrosis

**Warnings and Precautions**

- Symptom Exacerbation Following Interruption or Discontinuation of Treatment with Jakafi
- Risk of Infection
- Non-Melanoma Skin Cancer

**Adverse Reactions**

- Anemia
- Arthralgia
- Asthenia
- Epistaxis
- Herpes Zoster
- Nausea
- Cough
- Edema
- Arthritis
- Increased ALT and AST
- Increased AST

**Description of Selected Adverse Drug Reactions:**

- **Anemia**: 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 ALT.

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

<table>
<thead>
<tr>
<th>Laboratory Parameter</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><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>72</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>58</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>27</td>
<td>5</td>
<td>&lt;1</td>
<td>24</td>
<td>3</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
<td>&lt;1</td>
<td>10</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>25</td>
<td>&lt;1</td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>23</td>
<td>0</td>
<td>0</td>
<td>23</td>
<td>&lt;1</td>
<td>0</td>
</tr>
<tr>
<td>Hypertriglycerolemia</td>
<td>16</td>
<td>0</td>
<td>0</td>
<td>13</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Notes:**

- National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0
- Includes abdominal pain, abdominal pain lower, and abdominal pain upper
- Includes dizziness and vertigo
- Includes dyspepsia and dyspepsia epigastric
- Includes edema and peripheral edema
- Includes herpes zoster and post-herpetic neuralgia
- Includes abnormal bleeding/hemorrhage

**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

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Jakafi (N=110)</th>
<th>Best Available Therapy (N=111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>16 (%)</td>
<td>19 (%)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>15 (%)</td>
<td>15 (%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (%)</td>
<td>7 (%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15 (%)</td>
<td>13 (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (%)</td>
<td>15 (%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>14 (%)</td>
<td>23 (%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>13 (%)</td>
<td>4 (%)</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>12 (%)</td>
<td>5 (%)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>9 (%)</td>
<td>8 (%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (%)</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Cough</td>
<td>8 (%)</td>
<td>5 (%)</td>
</tr>
<tr>
<td>Edema</td>
<td>8 (%)</td>
<td>7 (%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>7 (%)</td>
<td>6 (%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7 (%)</td>
<td>11 (%)</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>6 (%)</td>
<td>3 (%)</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>6 (%)</td>
<td>0 (%)</td>
</tr>
</tbody>
</table>

**Notes:**

- Presented are worst Grade values regardless of baseline
- 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].

**Nusinersen**

Nusinersen is not expected to increase the exposure of Jakafi.

**Gemtuzumab Ozogamicin**

Gemtuzumab ozogamicin is not expected to increase the exposure of Jakafi.

**Pharmacokinetics**

The elimination half-life of ruxolitinib is about 70 hours. The terminal half-life of unbound ruxolitinib in plasma is 2-3 times longer than the elimination half-life. The clearance of ruxolitinib is about 10-15% lower in patients with renal impairment than in patients with normal renal function.

**Pharmacodynamics**

Ruxolitinib is a potent and selective Janus kinase (JAK) inhibitor, which inhibits the JAK1 and JAK2 kinases. It binds with high affinity to the cytoplasmic domain of the JAK1 and JAK2 kinases, thereby inhibiting their catalytic activity.

**Metabolism**

Ruxolitinib is metabolized in the liver by CYP3A4 and CYP2C9. The major metabolite, GSK2508219, is about 60% of the parent drug in vivo. GSK2508219 is also a substrate for CYP3A4, CYP2C9, and CYP2C19.

**Biotransformation**

Ruxolitinib is extensively metabolized in the liver.

**Elimination**

Ruxolitinib is eliminated in the urine and feces, with about 20% of the dose excreted in the urine and about 60% of the dose excreted in the feces. The major metabolite, GSK2508219, is about 60% of the parent drug in vivo.

**Reversibility**

Ruxolitinib is reversibly cleared from plasma.

**Drug-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.
  - 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.
- Strong CYP3A4 inhibitors:
  - Concomitant administration of Jakafi with strong CYP3A4 inhibitors increases ruxolitinib exposure.
  - Increased exposure may increase the risk of exposure-related adverse reactions. Consider dose reduction when administering Jakafi with strong CYP3A4 inhibitors.
- Strong CYP3A4 inducers:
  - Concomitant administration of Jakafi with strong CYP3A4 inducers may decrease ruxolitinib exposure.
- Nusinersen:
  - Nusinersen is not expected to increase the exposure of Jakafi.
- Gemtuzumab ozogamicin:
  - Gemtuzumab ozogamicin is not expected to increase the exposure of Jakafi.

**Special Populations**

- Elderly:
  - The safety and effectiveness of Jakafi in patients aged 65 years and older, and 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 effect of renal impairment on the elimination of ruxolitinib is not known. Consider dose reduction when administering Jakafi to patients with renal impairment.
- Hepatic impairment:
  - The effect of hepatic impairment on the elimination of ruxolitinib is not known. Consider dose reduction when administering Jakafi to patients with hepatic impairment.

**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.

**Jakafi**

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U.S. Patent Nos. 7598257; 8413862; 8723693; 8822481; 8829013; 9079912

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RUX 3429
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. 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. 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 cm³ or more as assessed by magnetic resonance imaging or computed tomography, and no prior JAK inhibitor treatment. 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. 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.

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.

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.

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). 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. 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.
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...
SPECIAL MEETING REVIEW EDITION

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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.

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
2. Kiladjian JJ, Verstovsek S, Griesshammer M, et al. Results from the 208-week (4-year) follow-up of RESPONSE trial, a phase 3 study comparing ruxolitinib (rux) with best available therapy (BAT) for the treatment of polycythemia vera (PV) [ASH abstract 322]. Blood. 2017;130(suppl 1).

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.

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

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. 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).

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. The PROUD-PV/CONTINUATION-PV trial enrolled 254 patients with polycythemia vera in need of cytoreduction. Patients could be treatment-naïve 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.

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.

Outcomes at 24 months supported the efficacy of ropeginterferon alfa-2b in this population. The proportion of patients attaining a complete hematologic response—defined as a hematocrit less than 45% without phlebotomy, a platelet count less than 400 × 10⁹/L, and a white blood cell count less than 10 × 10⁹/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.
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

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 thrombocytemia 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...
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

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

**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

<table>
<thead>
<tr>
<th>Blast Count</th>
<th>n</th>
<th>Died</th>
<th>Median OS, months</th>
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<tbody>
<tr>
<td>MF-CP &lt;5%</td>
<td>1020</td>
<td>459</td>
<td>56 (95% CI, 49-60)</td>
</tr>
<tr>
<td>MF-CP 5-9%</td>
<td>123</td>
<td>81</td>
<td>36 (95% CI, 23-41)</td>
</tr>
<tr>
<td>MF-AP ≥10%</td>
<td>56</td>
<td>29</td>
<td>29 (95% CI, 11-31)</td>
</tr>
</tbody>
</table>

**Figure 5.** Survival (%)

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Died</th>
<th>Median OS, months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>33</td>
<td>17</td>
<td>54 (95% CI, 47-75)</td>
</tr>
<tr>
<td>No Ruxolitinib</td>
<td>90</td>
<td>64</td>
<td>27 (95% CI, 16-35)</td>
</tr>
</tbody>
</table>
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

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
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; \( P = 0.05 \)). Interferon dose and younger age did not predict responses to peginterferon. Factors associated with higher CR rates were the presence of \( \text{CALR} \) mutations, a lack of \( \text{TP53} \) mutations, and a lack of \( \text{ASXL1} \) 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.

References

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 × 10⁹/L, and 62.6% of patients had a platelet count of at least 200 × 10⁹/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.
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.

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.

Reference
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 type 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. A phase 2 study evaluated with lower-risk myelodysplastic syndrome. Dr Prithviraj Bose presented results at the 2017 ASH meeting.

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/polythemia 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 x 10^9/L vs 289 x 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.
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. 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), is fully enrolled. A multicenter, phase 2 trial of luspatercept in patients with myelofibrosis is currently enrolling.

**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).
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. In a historical cohort of 1832 patients with CMML, the median OS was 32 months. In contrast to myelodysplastic syndrome, in which azacitidine is associated with a significant improvement in OS, 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. 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. At the 2017 ASH meeting, Dr Eric Padron presented results of the phase 2 study, which enrolled 29 patients with CMML. 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, 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 24) had myeloproliferative neoplasm–CMML.

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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 ($P=0.03$). 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.

**References**


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.

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. A companion study, RESPONSE-2 \(\text{(Ruxolitinib Efficacy}\) and Safety in Patients With HU Resistant or Intolerant Polycythemia Vera vs Best Available Therapy), 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.

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 thrombocytopenia. 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. 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 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. 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. Ruxolitinib is a standard agent for myelofibrosis, and the first therapy approved for these patients. 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 Iannotti 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.13 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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