MPN UPDATE 2017

DAVID S. SNYDER, M.D.

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DISCLOSURES

I am a consultant for Ariad, BMS, Gilead, Incyte and Novartis.
The Classic MPN Subtypes: An Overview

- **Polycythemia vera (PV)**
  - Overproduction of red blood cells (RBCs), often with increased white blood cells (WBCs) and platelets
  - Variable risk of vascular events and MPN-related symptoms (e.g., enlarged spleen, constitutional symptoms)

- **Essential thrombocythemia (ET)**
  - Overproduction of platelets
  - Variable risk of vascular events and MPN-related symptoms

- **Myelofibrosis (MF)**
  - May arise de novo (primary MF [PMF]) or following PV or ET (post-PV MF or post-ET MF)
  - Variable clinical features (i.e., splenomegaly, cytopenias, constitutional symptoms)
  - Significantly reduces life expectancy
Driver Mutations in MPNs: Activating the JAK-STAT Signaling Pathway

- In 2005, JAK2 gene mutation (JAK2V617F) was found in a high percentage of patients with MPNs.
- A variety of other gene mutations (e.g., MPL, CALR) are present in ET and PMF patients with non-mutated JAK2.

Role of cytokine receptors in the oncogenic properties of JAK2V617F and CALR mutants.

Frequency and distribution of mutations.

Keyur P. Patel et al. Blood 2015;126:790-797
**MPN Disease Continuum: Shared Biology and Clinical Features**

- Polycythemia vera
- Essential thrombocythemia
- Primary myelofibrosis; Post PV/ET myelofibrosis
- MPN Blast-phase; Acute myeloid leukemia

<table>
<thead>
<tr>
<th>MPN Subtype at Diagnosis</th>
<th>10-year Leukemic Transformation Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential thrombocythemia</td>
<td>1%</td>
</tr>
<tr>
<td>Polycythemia vera</td>
<td>4%</td>
</tr>
<tr>
<td>Primary myelofibrosis</td>
<td>20%</td>
</tr>
</tbody>
</table>

Myeloproliferative Neoplasms

**WORKUP**
- H&P, including spleen size by palpation, evaluation of thrombotic/hemorrhagic events and cardiovascular risk factors
- CBC with differential
- Comprehensive metabolic panel with uric acid, lactate dehydrogenase (LDH), and liver function tests (LFTs)
- FISH or RT-PCR for BCR-ABL1 to exclude the diagnosis of CML; if BCR-ABL1-positive, See NCCN Guidelines for Chronic Myelogenous Leukemia
- Examination of blood smear
- Bone marrow aspirate and biopsy with trichrome and reticulin stain
- Bone marrow cytogenetics (karyotype ± FISH)
- Molecular testing for JAK2 V617F mutations; if negative, test for CALR and MPL mutations (for patients with ET and MF) and JAK2 Exon 12 mutations (for patients with PV)
- Assessment of symptom burden using MPN Symptom Assessment form (MPN-SAF)
- Documentation of transfusion/medication history
- Human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplant (HCT)
- Serum erythropoietin (EPO) level
- Serum iron studies
- Coagulation tests to evaluate for acquired von Willebrand disease (VWD) and/or other coagulopathies in selected patients
- Prothrombin time (PT), partial thromboplastin time (PTT), Fibrinogen
- Von Willebrand Factor Antigen (VWF) measurement
- Von Willebrand Ristocetin Cofactor (VWF:RCO) activity

**DIAGNOSIS**
- Primary myelofibrosis (PMF)
- Post-PV or Post-ET MF
- Polycythemia vera (PV)
- Essential thrombocytemia (ET)

**Note:** All recommendations are category 2A unless otherwise indicated.

Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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POLYCYTHEMIA VERA
### WHO PV criteria

#### Major criteria

1. Hemoglobin >16.5 g/dL in men
   - Hemoglobin >16.0 g/dL in women
   - or
   - Hematocrit >49% in men
   - Hematocrit >48% in women
   - or
   - increased red cell mass (RCM)

2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)

3. Presence of $JAK2V617F$ or $JAK2$ exon 12 mutation

#### Minor criterion

- Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion.
Clinical Features of Polycythemia Vera (PV)

- **Overproduction of red blood cells (erythrocytosis)**
  - Often with increased white blood cells and platelets
  - Patients may have splenomegaly

- **Cardiovascular complications due to thrombosis or hemorrhage**
  - Thrombotic events can be arterial (CVA, ACS), venous (DVT, PE, as well as affecting unusual locations such as splanchnic circulation), and microcirculatory

- **Symptoms**
  - May include pruritus, fatigue, shortness of breath, dizziness, and symptoms due to splenomegaly

- **Potential to progress to post-PV MF or AML**

Risk Classification for Patients with PV

- Historically, cardiovascular complications are the most common cause of mortality in patients with PV\(^1\)
- Conventional PV risk factors are prognostic for thrombosis, and not based on survival\(^2\)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Conventional Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• Age &lt; 60 years&lt;br&gt;• No thrombosis history</td>
</tr>
<tr>
<td>High</td>
<td>• Age ≥ 60 years&lt;br&gt;and/or&lt;br&gt;• Thrombosis history</td>
</tr>
</tbody>
</table>

Risk-Adapted Management of Patients with PV¹

- Hematocrit (HCT) control is a key therapeutic goal
  - Maintaining HCT < 45% significantly decreases the risk of cardiovascular death and major thrombotic events²

<table>
<thead>
<tr>
<th>Conventional Risk Category</th>
<th>Risk Variables</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>• Age &lt; 60 years</td>
<td>• Phlebotomy, and</td>
</tr>
<tr>
<td></td>
<td>• No thrombosis history</td>
<td>• Correction of CV risk factors, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aspirin</td>
</tr>
<tr>
<td>High</td>
<td>• Age ≥ 60 years and/or</td>
<td>• Cytoreduction*, and</td>
</tr>
<tr>
<td></td>
<td>• Thrombosis history</td>
<td>• Correction of CV risk factors, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Aspirin, and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Phlebotomy</td>
</tr>
</tbody>
</table>

*First-line cytoreductive therapy is hydroxyurea or interferon alfa; busulfan reserved for age >75 years.

Phlebotomy and Aspirin in PV Management

**Phlebotomy**
- Reduces hematocrit (HCT) (hyperviscosity); goal is HCT <45%\(^1\)
- Does not control systemic symptoms or progressive symptomatic splenomegaly well \(^2\)
- Iron deficiency is common with repeated phlebotomies\(^2\)
  - Associated with fatigue, cognitive impairment, increased pulmonary artery pressure

**Low-dose aspirin**
- Persistently enhanced platelet activation contributes to the higher risk of thrombosis in patients with PV\(^3,4\)
- Placebo-controlled ECLAP trial (N= 518): low-dose aspirin can safely prevent thrombotic complications in patients with PV who have no contraindications to aspirin\(^4\)
- Screening for acquired von Willebrand syndrome is recommended before administrating aspirin in the presence of extreme thrombocytosis\(^5\)

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Hydroxyurea (HU) in PV Management

- HU is often used as a first-line cytoreductive treatment for patients with PV who are at high-risk for vascular complications\(^1,2\)
- Clinical activities\(^2\)
  - Controls myeloproliferation
  - Reduces splenomegaly
  - May reduce risk of major thrombosis (limited evidence in PV)\(^3\)
- Side effects\(^2\)
  - Myelosuppression, leg ulcers, hyperpigmentation, fever, alopecia, increased risk of squamous cell carcinoma

**Pegylated Interferon-α2a is an Acceptable Alternative to HU in PV**

Phase II studies: Treatment with PEG-IFN-α2a or α2b resulted in high rates of complete hematologic and molecular response, and low rates of thrombosis.1-3

*IFN α2a (n=40)*

<table>
<thead>
<tr>
<th>Proportion of Responders (%)</th>
<th>Complete</th>
<th>Partial</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>70</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

*Complete response included absence of thrombosis*

**Ongoing global randomized phase III studies:**
- PEG-IFN-α2a vs HU in high-risk PV and ET (NCT01259856)
- Novel monopegylated IFN-α2b in high-risk PV and ET (NCT01949805)

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 Thrombocytocemia (NCT01258856)

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Conclusions

• No difference in hematologic CR between the two arms at 12 months
• BM pathologic responses are more frequent in HU arm at 12 months
• No difference in molecular response rates between the arms at 12 months
• Toxicity is not a major reason for discontinuation in either arm at 12 months
• Comparative analysis of QOL and symptom burden also presented at this meeting Mesa et al ASH 2016
• Longer term follow up of the entire study population may show meaningful differences in response and toxicity between these two agents over time
• Final analysis of MPD-RC 112 will establish optimal first line therapy for high risk ET/PV
Criteria

- **HU Resistance** - After 12 weeks of HU, at a total dose $\geq 2$ g/day:
  - Need for phlebotomy to maintain HCT at $<45\%$
  - Elevated platelet and WBC counts or
  - $<50\%$ reduction in splenomegaly or failure to completely relieve splenomegaly symptoms

- **HU Intolerance**
  - Leg ulcers or other unacceptable HU-related toxicity
  - ANC $<1 \times 10^9$/L or Hgb $<10$ g/dL

Karen A.

### Ruxolitinib (JAK1/JAK2 Inhibitor) for Patients with HU-Refractory or Intolerant PV

<table>
<thead>
<tr>
<th>Approved Indication</th>
<th>US Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with intermediate or high-risk MF, including primary MF, post-PV MF, and post-ET MF</td>
<td>2011</td>
</tr>
<tr>
<td>Patients with PV who have had an inadequate response to or are intolerant of hydroxyurea *</td>
<td>Dec 2014</td>
</tr>
</tbody>
</table>

* For PV, the approved starting dose is 10 mg orally twice daily.

Jakafi (ruxolitinib) prescribing information, 2014.
Treatment Summary

• Contemporary treatment for patients with PV combines:
  – Modification of CV risk factors
  – Phlebotomy (HCT target <45%)
  – Antiplatelet/anticoagulation therapy
  – First-line cytoreductive therapy: HU or IFN-alfa
  – Second-line: Ruxolitinib for patients resistant to or intolerant of HU
    • Other options may include PEG-IFN or busulfan
ESSENTIAL THROMBOCYTHEMIA
Clinical Features of Essential Thrombocythemia (ET)

- **Overproduction of platelets (thrombocythemia)**\(^1,^2\)
  - Elevation in platelet count ≥450 x 10⁹/L
- **Cardiovascular complications due to bleeding and thrombosis**
- **Symptoms are variable and may be due to:**\(^3\)
  - Microvascular complications (e.g., headache, dizziness, paresthesia, erythromelalgia, blurred vision)
  - Macrovascular complications (e.g., myocardial infarction, stroke, pulmonary embolus)
  - Constitutional symptoms (e.g., fatigue, night sweats, itching [pruritus], weight loss)
  - Splenomegaly and associated symptoms
- **Potential for progression to post-ET MF or AML**
  - May also evolve to PV

### WHO criteria for ET

<table>
<thead>
<tr>
<th>WHO ET criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major criteria</strong></td>
<td></td>
</tr>
<tr>
<td>1. Platelet count $\geq 450 \times 10^9/L$</td>
<td></td>
</tr>
<tr>
<td>2. BM biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers</td>
<td></td>
</tr>
<tr>
<td>3. Not meeting WHO criteria for $BCR-ABL1^+$ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms</td>
<td></td>
</tr>
<tr>
<td>4. Presence of $JAK2$, $CALR$, or $MPL$ mutation</td>
<td></td>
</tr>
<tr>
<td><strong>Minor criterion</strong></td>
<td></td>
</tr>
<tr>
<td>Presence of a clonal marker or absence of evidence for reactive thrombocytosis</td>
<td></td>
</tr>
</tbody>
</table>

Diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion.
Key Issues in ET Management

• Normalization of platelet count (cytoreduction) to decrease thrombotic risk potential
  – Stroke and heart attack are the main concerns
• Correction of other CV risk factors
  – Weight reduction, blood pressure control, glucose control in diabetic patients, smoking cessation
• Improvement in disease-related symptoms
Thrombotic Risk Assessment

- High-risk features predictive of future thrombotic complications
  - Age > 60 years
  - Prior history of thrombosis
- IPSET Prognostic Features (2012)
  - Age > 60 years (2 points)
  - Prior history of thrombosis (1 point)
  - Leukocytes >11 x 10⁹/L (1 point)

IPSET Risk Group:
0 points: Low
1-2 points: Intermediate
3-4 points: High

CALR and JAK2 mutations represent 2 disease spectrums in essential thrombocythemia whereby cases with mutated CALR are characterized by higher platelet levels, lower hemoglobin and leukocyte counts, and lower thrombosis risk compared with JAK2-mutated patients.

Chao M P, and Gotlib J. Blood 2014;123:1438-1440
Systemic Therapy for ET

- In low-risk asymptomatic ET, observation is appropriate
- High-risk ET:
  - Daily low-dose aspirin is standard practice for most patients, if not contraindicated*
    - Due to high risk of bleeding in patients with platelet counts >1500 x 109/L, cytoreduction may be considered prior to aspirin initiation
  - **Cytoreductive therapy:**
    - Hydroxyurea (HU) is the first-line treatment of choice
    - Anagrelide is generally considered 2nd-line therapy if resistant or intolerant to HU
    - IFN-alfa is used for young patients, pregnant women, or patients who are refractory/intolerant to HU
    - Consider clinical trials for patients who are intolerant to or have progressed on all 3 approved agents

*Aspirin is not universally recommended - typically for those with JAK2 positive ET, CV risk factors, or microvascular symptoms.

MYELOFIBROSIS

May arise de novo (primary MF) or following PV or ET (post-PV MF or post-ET MF)
### WHO criteria for overt PMF

#### WHO overt PMF criteria

<table>
<thead>
<tr>
<th>Major criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3*</td>
</tr>
<tr>
<td>2. Not meeting WHO criteria for ET, PV, <em>BCR-ABL1</em> CML, myelodysplastic syndromes, or other myeloid neoplasms</td>
</tr>
<tr>
<td>3. Presence of <em>JAK2</em>, <em>CALR</em>, or <em>MPL</em> mutation or in the absence of these mutations, presence of another clonal marker, † or absence of reactive myelofibrosis ‡</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of at least 1 of the following, confirmed in 2 consecutive determinations:</td>
</tr>
<tr>
<td>a. Anemia not attributed to a comorbid condition</td>
</tr>
<tr>
<td>b. Leukocytosis ≥11 × 10⁹/L</td>
</tr>
<tr>
<td>c. Palpable splenomegaly</td>
</tr>
<tr>
<td>d. LDH increased to above upper normal limit of institutional reference range</td>
</tr>
<tr>
<td>e. Leukoerythroblastosis</td>
</tr>
</tbody>
</table>

**Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion**
Clinical Features of Myelofibrosis (MF)

- **Bone marrow fibrosis**
- **Splenomegaly**
  - Splenomegaly-associated symptoms include abdominal pain/discomfort, early satiety
- **Cytopenias**
  - Anemia, thrombocytopenia
- **Constitutional symptoms**
  - Include fatigue, night sweats, pruritus (itching), bone aches, weight loss
MKs play a central role in MPN pathogenesis.
Prognostic Models for Myelofibrosis

At diagnosis of primary MF:
• International Prognostic Scoring System (IPSS)\(^1\)
  – Factors associated with a worse prognosis: Age >65 yrs, constitutional symptoms, Hgb <10 g/dL, WBC count > 25 x 10^9/L, blood blasts ≥1%

Valid at diagnosis and at any point in the course of disease:
• Dynamic International Prognostic Scoring System (DIPSS)\(^2\)
  – Gives more prognostic weight to the presence of disease-related anemia
• DIPSS-plus\(^3\)
  – Incorporates abnormal karyotype as an independent negative prognostic factor for overall and leukemia-free survival

### Myeloproliferative Neoplasm Symptom Assessment Form

**Total Symptom Score (MPN-SAF TSS-10 Items)**

(Recommended for monitoring symptoms during the course of treatment)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1 to 10 (0 if absent) ranking</th>
<th>1 is most favorable and 10 least favorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours*</td>
<td><em>(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Filling up quickly when you eat (early satiety)</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Inactivity</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Problems with concentration- compared to prior to my MPD</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Numbness/Tingling (in my hands and feet)</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Night sweats</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Itching (pruritus)</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Bone pain (diffuse not joint pain or arthritis)</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
<tr>
<td>Fever (&gt;100 F)</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)</em></td>
<td></td>
</tr>
<tr>
<td>Unintentional weight loss last 6 months</td>
<td><em>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</em></td>
<td></td>
</tr>
</tbody>
</table>

*Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.*

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Kaplan-Meier analysis of survival of PMF patients stratified according to the risk categories defined by a clinical-molecular prognostic model.

Kaplan-Meier analysis of survival of PMF patients stratified according to their driver mutation.

No. of patients at risk:

<table>
<thead>
<tr>
<th>Driver Mutation</th>
<th>Total</th>
<th>72</th>
<th>37</th>
<th>19</th>
<th>9</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALR mutant</td>
<td>140</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JAK2 mutant</td>
<td>396</td>
<td>135</td>
<td>39</td>
<td>13</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>MPL mutant</td>
<td>25</td>
<td>10</td>
<td>5</td>
<td>3</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Triple negative</td>
<td>53</td>
<td>11</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Risk-Adapted Treatment of Myelofibrosis

Low Risk
Minimally symptomatic → Observation or Interferon
Many symptoms → JAK2 inhibitor

Intermediate-1
JAK2 inhibitor or allogeneic HSCT or anemia treatment

Intermediate-2
JAK2 inhibitor or allogeneic HSCT or anemia treatment

High Risk
Allogeneic HSCT or JAK2 inhibitor or anemia treatment

Anemia treatment may include: IMID, androgens, erythropoietin; clinical trial, splenectomy

HSCT, hematopoietic stem cell transplantation.

# Ruxolitinib is the Only JAK Inhibitor Approved for Treatment of Myelofibrosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>**COMFORT-I (N = 309)**¹</td>
<td>Ruxolitinib vs. placebo in pts with intermediate- or high-risk MF</td>
<td>• 41.9% (ruxolitinib) vs 0.7% (placebo) had ≥35% reduction in spleen volume² at week 24 (P &lt; 0.001)</td>
</tr>
<tr>
<td>**COMFORT-II (N = 219)**²</td>
<td>Ruxolitinib vs. best available therapy (BAT) in pts with intermediate- or high-risk MF</td>
<td>• 32% (ruxolitinib) vs 0% (BAT) had ≥ 35% reduction in spleen volume² at week 24 (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

¹ As assessed by MRI

---

Summary: Ruxolitinib in Patients with MF (including PMF, post-PV MF, and post-ET MF)

- **COMFORT-I and COMFORT-II phase III trials:**
  - **Efficacy**
    - Spleen size reduction, significant improvement in symptoms, quality of life, performance status
    - Not selective for JAK2V617F (i.e., benefits patients with and without JAK2 mutation)
    - Possible prolongation of life in patients with advanced disease
  - **Safety**
    - Myelosuppression (not a cause for stopping therapy)
Kaplan-Meier analysis of time to event outcomes.

Keyur P. Patel et al. Blood 2015;126:790-797
HSCT is a reasonable option for otherwise healthy patients with intermediate -2 or high-risk PMF

- HSCT is the only potentially curative treatment approach
- Young, otherwise fit patients may be candidates

- Therapeutic efficacy is mediated via:
  - Antineoplastic effect of pre-transplant conditioning regimen
  - Alloimmune graft versus leukemia effect

- Reduced intensity conditioning may be considered for:
  - Older patients
  - Patients with comorbidities that preclude them from myeloablative conditioning regimens

Allogeneic Hematopoietic Stem Cell Transplantation for MF

- **Challenges**
  - Significant risk of treatment-related morbidity and mortality
  - Optimal timing of transplant
  - Patient selection (DIPSS Int-2 and High-risk)
  - Choice of conditioning regimen

- **Barriers to HCT success**
  - Regimen related-toxicities (hepatotoxicity)
  - Graft failure (poorly understood)
  - Acute and chronic graft versus host disease (GVHD)
  - Poor performance status (symptomatic splenomegaly, debilitating constitutional symptoms, anemia)

MPN Conclusions

- The MPNs (PV, ET, MF) are progressive hematopoietic diseases with shared biology and clinical features
  - JAK-STAT pathway activation is hallmark of these diseases
  - MPNs are associated with significant complications, including thrombosis, splenomegaly, cytopenias, constitutional symptoms
  - Patients can have high symptom burden regardless of the subtype
  - Risk of leukemic transformation, especially for MF
- Treatment strategies can vary depending on the individual’s risk status and management needs
- JAK2 inhibitor therapy (ruxolitinib) is improving the outlook for many patients with MF or HU-resistant/intolerant PV, but it does not cure these diseases
What Next?

- To increase benefits seen with JAK inhibitors (splenomegaly, symptoms) as well as to bring additional benefits (e.g., control anemia, BM fibrosis; clone elimination; reduce risk of transformation)
- To reduce unwanted side effects (anemia, thrombocytopenia) but maintain clinical benefits
- To improve stem cell transplant results
- To improve outcomes in patients in blast-phase (BP-MPN)
Post-MPN AML demonstrates limited response to conventional AML therapy

Safety and efficacy of combined Ruxolitinib and Decitabine in patients with blast-phase MPN and post-MPN AML: Results of a Phase I study (Myeloproliferative Diseases Research Consortium 109 trial)

Raajit K. Rampal, MD, PhD, John O. Mascarenhas, MD, MS, Heidi E. Kosiorek, MS, Dmitriy Berenzon, MD, Elizabeth Hexner, MD, Camille N. Abboud, MD, Marina Kremyanskaya, MD PhD, Rona Singer Weinberg, PhD, Mohamed E Salama, M.D., Gianni Tognoni, Giuseppe Prosperini, Alessandra Di Lelio, Eliseo Serone, Lorenzo Marfisi, Lonette Sandy, Mark Lawrence Heaney, MD, PhD, Ross L. Levine, MD, Ruben A. Mesa, MD, Amylou C. Dueck, PhD and Ronald Hoffman
Conclusions

• The combination of Ruxolitinib (up to a dose of 50mg BID) and Decitabine was safely administered to patients with no MTD established.

• Patients in the 10mg BID cohort had the longest duration of therapy.

• The highest CR/CRi rate was observed in the 50mg BID cohort; however, the largest proportion of adverse events was observed in this cohort.
Conclusions

• The RP2D is 25mg BID for one cycle followed by 10mg BID for all subsequent cycles.

• Molecular response data and evaluation of response by the proposed MPN-BP criteria are underway.
### Ongoing Ruxolitinib Combination Trials in Myelofibrosis

<table>
<thead>
<tr>
<th>Ruxolitinib + Second Agent (class)</th>
<th>Development Stage</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine (Hypomethylation)</td>
<td>Phase III</td>
<td>NCT01787487</td>
</tr>
<tr>
<td>Lenalidomide (IMID)</td>
<td>Phase II</td>
<td>NCT01375140</td>
</tr>
<tr>
<td>Pomalidomide (IMID)</td>
<td>Phase I/II</td>
<td>NCT01644110</td>
</tr>
<tr>
<td>PRM-151 (Antifibrosing)</td>
<td>Phase II</td>
<td>NCT01981850</td>
</tr>
<tr>
<td>Panobinostat (HDAC inhibitor)</td>
<td>Phase I/II</td>
<td>NCT01693601</td>
</tr>
<tr>
<td>LDE-225 (Hedgehog inhibitor)</td>
<td>Phase I/II</td>
<td>NCT01787552</td>
</tr>
<tr>
<td>BKM-120 (PI3-kinase inhibitor)</td>
<td>Phase I</td>
<td>NCT01730248</td>
</tr>
</tbody>
</table>

### What Next?

**Novel JAK2 Inhibitors**

<table>
<thead>
<tr>
<th>Agent - Targets</th>
<th>Phase I/II Results</th>
<th>Status – Disease and/or Design</th>
<th>ClinicalTrials.gov Identifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib (CYT387) – JAK1, JAK2</td>
<td>• Reduced splenomegaly, improved symptoms, and reduced anemia/ RBC transfusion-dependence&lt;br&gt;• Grade 3-4 thrombocytopenia in 32%</td>
<td>Phase III - Versus ruxolitinib in Int- and high-risk MF (ruxolitinib naïve)&lt;br&gt;Phase III –Versus Best Available Therapy (BAT) in Anemic or Thrombocytopenic MF patients treated with ruxolitinib</td>
<td>NCT01969838&lt;br&gt;NCT02101268</td>
</tr>
<tr>
<td>Pacritinib (SB1518) – JAK2, FLT3</td>
<td>• Reduced splenomegaly, improved symptoms&lt;br&gt;• Limited provocation of cytopenias, particularly in patients with baseline thrombocytopenia&lt;br&gt;• Most adverse events gastrointestinal</td>
<td>Phase III- 2 trials (PERSIST-I and PERSIST-II) - Versus best available therapy (BAT) in MF patients without and with baseline thrombocytopenia, respectively.</td>
<td>NCT01773187&lt;br&gt;NCT02055781</td>
</tr>
<tr>
<td>INCB-039110 JAK1</td>
<td></td>
<td>Phase II - MF</td>
<td>NCT01633372</td>
</tr>
<tr>
<td>NS-018 - JAK2</td>
<td></td>
<td>Phase I/II - MF</td>
<td>NCT01423851</td>
</tr>
</tbody>
</table>

- Several JAK2 inhibitors have been removed from clinical trials due to toxicity and/or insufficient activity (fedratinib, CEP-701, XL019, LY278544, BMS-911543, AZD 1480)

Imetelstat: First-in-class Telomerase Inhibitor

Imetelstat

- First telomerase inhibitor in clinical development

- 13-mer modified oligonucleotide with palmitoyl lipid tail

- Competitively binds to RNA template of telomerase

- Potent inhibitor of telomerase enzyme activity
  - $IC_{50} = 0.5-10$ nM (cell-free)
  - $IC_{50} = 0.15-1.77$ µM (cell-based)

- Long half-life in bone marrow, spleen and liver
  - Tissue $t_{1/2} = 50-90$ hr in rodents
  - Predicted human $t_{1/2} = 41$ hr with doses 7.5-11.7 mg/kg
Baseline Clinical and Laboratory Characteristics, including Mutational Status, of the Seven Patients Who Had a Complete or Partial Remission after Treatment with Imetelstat.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Dosing Group</th>
<th>Best Response</th>
<th>Age and Sex</th>
<th>Type of MF</th>
<th>Risk Status</th>
<th>Palpable Spleen Size</th>
<th>Hemoglobin g/dl</th>
<th>White-Cell Count ×10^9/liter</th>
<th>Platelet Count</th>
<th>Karyotype</th>
<th>JAK2, CALR, or MPL</th>
<th>ASXL1</th>
<th>IDH1 or IDH2</th>
<th>U2AF1, SF3B1, or SRSF2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>CR</td>
<td>73-yr-old man</td>
<td>Primary</td>
<td>Intermediate-2</td>
<td>Spleen edge palpable</td>
<td>Transfusion-dependent</td>
<td>5.5</td>
<td>153</td>
<td>Normal</td>
<td>JAK2</td>
<td>WT</td>
<td>WT</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>CR</td>
<td>53-yr-old woman</td>
<td>Post-PV</td>
<td>Intermediate-2</td>
<td>7 cm</td>
<td>12.5</td>
<td>12.1</td>
<td>848</td>
<td>Normal</td>
<td>JAK2</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>CR</td>
<td>73-yr-old man</td>
<td>Primary</td>
<td>Intermediate-2</td>
<td>Spleen edge palpable</td>
<td>Transfusion-dependent</td>
<td>9.6</td>
<td>286</td>
<td>Normal</td>
<td>JAK2</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
</tr>
<tr>
<td>4</td>
<td>B</td>
<td>CR</td>
<td>79-yr-old man</td>
<td>Post-ET</td>
<td>High</td>
<td>10 cm</td>
<td>10.2</td>
<td>26.3</td>
<td>585</td>
<td>Loss of Y chromosome</td>
<td>JAK2</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
</tr>
<tr>
<td>5</td>
<td>A</td>
<td>PR</td>
<td>76-yr-old man</td>
<td>Primary</td>
<td>High</td>
<td>5 cm</td>
<td>Transfusion-dependent</td>
<td>15.1</td>
<td>337</td>
<td>Normal</td>
<td>JAK2</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>PR</td>
<td>67-yr-old man</td>
<td>Primary</td>
<td>Intermediate-2</td>
<td>Not palpable</td>
<td>9.0</td>
<td>12.8</td>
<td>2525</td>
<td>Del(9)(q13q22) +9</td>
<td>JAK2</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>PR</td>
<td>69-yr-old man</td>
<td>Primary</td>
<td>High</td>
<td>8 cm</td>
<td>11.3</td>
<td>32.9</td>
<td>766</td>
<td>Normal</td>
<td>JAK2</td>
<td>WT</td>
<td>WT</td>
<td>WT</td>
</tr>
</tbody>
</table>

* The median time to the onset of response in these seven patients was 3.5 months (range, 1.4 to 7.2), and the median duration of response was 18 months (range, 13 to 20+) for complete responses (CR) and 10 months (range, 7 to 10+) for partial responses (PR). Details on treatment response in individual patients as of the data-cutoff date of December 5, 2014, are provided in the Supplementary Appendix. ET denotes essential thrombocythemia, MF myelofibrosis, Mut mutation, PV polycythemia vera, and WT wild-type.

† Patients in group A received imetelstat every 3 weeks, and patients in group B received imetelstat weekly for 4 weeks, followed by once every 3 weeks.

‡ Risk was classified according to the Dynamic International Prognostic Scoring System Plus, which categorizes patients in one of four risk groups (low, intermediate-1, intermediate-2, and high risk) on the basis of a number of risk factors.25

Conclusions

• Imetelstat was found to be active in patients with myelofibrosis but also had the potential to cause clinically significant myelosuppression.
Conventional and molecular risk factors for patients with MPNs. Information is from studies discussed in the “Risk stratification” section.

<table>
<thead>
<tr>
<th>Essential thrombocyttemia</th>
<th>Polycythemia vera</th>
<th>Primary myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Thrombosis:</strong></td>
<td><strong>Thrombosis:</strong></td>
<td><strong>Survival &amp; leukemic transformation:</strong></td>
</tr>
<tr>
<td>• previous thrombosis</td>
<td>• previous thrombosis</td>
<td>• age &gt;65 years</td>
</tr>
<tr>
<td>• age ≥ 60 years</td>
<td>• age ≥ 60 years</td>
<td>• presence of constitutional symptoms</td>
</tr>
<tr>
<td>• JAK2 (V617F)</td>
<td>• JAK2 (V617F)-mutant allele burden&gt;50%</td>
<td>• anemia (Hb &lt;10 g/dL)</td>
</tr>
<tr>
<td><strong>Bleeding:</strong></td>
<td><strong>Myelofibrotic transformation:</strong></td>
<td>• leukocytosis (WBC count &gt;25 x 10^9/L)</td>
</tr>
<tr>
<td>• previous major bleeding</td>
<td>• JAK2 (V617F)</td>
<td>• thrombocytopenia (&lt;100 x 10^9/L)</td>
</tr>
<tr>
<td>• high PLT count (≥1500 x 10^9/L)</td>
<td><strong>Leukemic transformation:</strong></td>
<td>• circulating blasts (≥1%)</td>
</tr>
<tr>
<td><strong>Polycythemic transformation:</strong></td>
<td>• co-operating mutations in myeloid genes</td>
<td>• degree of bone marrow fibrosis</td>
</tr>
<tr>
<td>• JAK2 (V617F)</td>
<td><strong>Survival:</strong></td>
<td>• unfavorable karyotype</td>
</tr>
<tr>
<td><strong>Myelofibrotic transformation:</strong></td>
<td>• co-operating mutations in myeloid genes</td>
<td>• driver mutation (triple negative vs JAK2/MPL vs CALR mutation)</td>
</tr>
<tr>
<td>• CALR mutation</td>
<td><strong>Leukemic transformation:</strong></td>
<td>• co-operating mutations in myeloid genes</td>
</tr>
<tr>
<td>• co-operating mutations in myeloid genes</td>
<td>• previous thrombosis</td>
<td>• co-operating mutations in myeloid genes</td>
</tr>
<tr>
<td><strong>Leukemic transformation:</strong></td>
<td>• leukocytosis</td>
<td><strong>Primary myelofibrosis</strong></td>
</tr>
<tr>
<td>• co-operating mutations in myeloid genes</td>
<td>• co-operating mutations in myeloid genes</td>
<td><strong>Survival &amp; leukemic transformation:</strong></td>
</tr>
<tr>
<td><strong>Survival:</strong></td>
<td><strong>Survival:</strong></td>
<td>• age &gt;65 years</td>
</tr>
<tr>
<td>• previous thrombosis</td>
<td>• previous thrombosis</td>
<td>• presence of constitutional symptoms</td>
</tr>
<tr>
<td>• leukocytosis</td>
<td>• leukocytosis</td>
<td>• anemia (Hb &lt;10 g/dL)</td>
</tr>
<tr>
<td>• co-operating mutations in myeloid genes</td>
<td>• co-operating mutations in myeloid genes</td>
<td>• leukocytosis (WBC count &gt;25 x 10^9/L)</td>
</tr>
</tbody>
</table>

Elisa Rumi, and Mario Cazzola Blood 2017;129:680-692