Myeloproliferative Neoplasms (MPNs): Diagnosis, Treatment, and Side Effects Management

LEARNING OBJECTIVES

- Describe the types of myeloproliferative neoplasms, including myelofibrosis, polycythemia vera, and essential thrombocythemia
- Identify tests used to diagnose disease and monitor treatment
- Explain the overarching goals of treatment for the various types of myeloproliferative neoplasms
- Explain approved and emerging treatment options for all myeloproliferative neoplasms, including stem cell transplantation, and the role of clinical trials
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments
- Identify resources for patients, caregivers and healthcare providers
Myeloproliferative Neoplasms:
Diagnosis, Treatment, and Side Effects Management

Michael Mauro, MD
Leader, Myeloproliferative Neoplasms Program
Leukemia Service
Memorial Sloan Kettering Cancer Center

Charlene Kabel, PharmD, BCOP
Clinical Pharmacy Specialist
Leukemia Service, Department of Pharmacy
Memorial Sloan Kettering Cancer Center

Carolanne Carini, BSN, RN, BMTCN
Office Practice Nurse, Medical Oncology
Memorial Sloan Kettering Cancer Center

New York, NY
MPN Overview: Timeframes

**Premature death**
- PV
- ET
- Early PMF

**Overt PMF**
- Post ET/PV MF

**Progressive constitutional symptoms**
- Leukemic transformation
- Progressive organomegaly/EMH
- Progressive cytopenias
- Premature death

**Short term: Vascular events**
- Lead time: Typically years (>10)
- Time: Variable; 3-5 years common

**EMH**, extramedullary hematopoiesis; **ET**, essential thrombocythemia; **MF**, myelofibrosis; **PMF**, primary myelofibrosis; **PV**, polycythemia vera

---

**JAK2 V617F Mutation Discovery in MPNs: “The Other BCR-ABL”**

**March 18, 2005**

Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders

**March 24, 2005**

Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis

**April 28, 2005**

Letters to nature
JAK2 Signaling in MPNs: Finding the “Driver”

Wild-type JAK2: Normal signaling

JAK2 V617F: Enthusiastic signaling

<table>
<thead>
<tr>
<th>Disease</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>PV</td>
<td>~95%</td>
</tr>
<tr>
<td>ET</td>
<td>~50-60%</td>
</tr>
<tr>
<td>PMF</td>
<td>~50-60%</td>
</tr>
</tbody>
</table>

Frequency and Distribution of “Driver” and Other Mutations in Patients With MPNs

### Multivariate Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR (95% CI)</th>
<th>P</th>
<th>Weighted value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;60 yrs</td>
<td>3.8 (2.60-5.51)</td>
<td>&lt;.0001</td>
<td>1.5</td>
</tr>
<tr>
<td>Hgb &lt;100 g/L</td>
<td>1.4 (1.01-1.99)</td>
<td>.04</td>
<td>.5</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>1.5 (1.27-2.76)</td>
<td>.002</td>
<td>.5</td>
</tr>
<tr>
<td>PLT &lt;200x10^9/L</td>
<td>0.5 (0.37-0.44)</td>
<td>&lt;.0001</td>
<td>1.0</td>
</tr>
<tr>
<td>Triple Negativity</td>
<td>3.5 (2.20-6.94)</td>
<td>&lt;.0001</td>
<td>1.5</td>
</tr>
<tr>
<td>JAK2/MPL mutation</td>
<td>1.8 (1.12-3.00)</td>
<td>.025</td>
<td>.5</td>
</tr>
<tr>
<td>ASXL1 mutation</td>
<td>1.4 (1.06-1.99)</td>
<td>.02</td>
<td>.5</td>
</tr>
<tr>
<td>SRSF2 mutation</td>
<td>2.7 (2.08-3.50)</td>
<td>.02</td>
<td>.5</td>
</tr>
</tbody>
</table>

Molecular International Prognostic Scoring System\(^1\) in Myelofibrosis

Refines prognostic stratification within the IPSS categories

\(^1\) Mutation-Enhanced International Prognostic Scoring System

---

### Molecular Prognosis in Myelofibrosis

**NCCN Guidelines Version 3.2019: Myeloproliferative Neoplasms**

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Primary Myelofibrosis (PMF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAK2</td>
<td>Intermediate prognosis and higher risk of thrombosis compared to patients with CALR mutation(^1)</td>
</tr>
<tr>
<td>MPL W515LK</td>
<td>Intermediate prognosis and higher risk of thrombosis compared to patients with CALR mutation(^1)</td>
</tr>
<tr>
<td>CALR</td>
<td>Improved survival compared to JAK2 mutation and &quot;triple-negative&quot; PMF(^1)</td>
</tr>
<tr>
<td>CALR Type 1/Type 1-like</td>
<td>Improved overall survival compared to CALR type 2/type 2-like and JAK2 V617F mutation(^1)</td>
</tr>
<tr>
<td>&quot;Triple Negative&quot; (non-mutated JAK2, MPL, and CALR)</td>
<td>Inferior leukemia-free survival compared to patients with JAK2- and/or CALR-mutated PMF(^1)</td>
</tr>
<tr>
<td>ASXL1</td>
<td>Independently associated with inferior overall survival(^1) and leukemia-free survival(^1)</td>
</tr>
<tr>
<td>EZH2</td>
<td>Independently associated with inferior overall survival(^1)</td>
</tr>
<tr>
<td>IDH1/2</td>
<td>Independently associated with inferior leukemia-free survival(^1)</td>
</tr>
<tr>
<td>SRSF2</td>
<td>Independently associated with inferior overall survival and leukemia-free survival(^1)</td>
</tr>
<tr>
<td>Combined CALR and ASXL1 status</td>
<td>Survival longest for CALR+ASXL1(+) patients (median 19.4 years) and shortest in CALR+JAK2(+) patients (median 2.3 years)(^1)</td>
</tr>
<tr>
<td>TP53</td>
<td>Associated with leukemic transformation(^1)</td>
</tr>
</tbody>
</table>

## Molecular Prognosis in Polycythemia Vera

### NCCN Guidelines Version 3.2019
**Myeloproliferative Neoplasms**

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Polycythemia Vera (PV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASXL1/ SRSF2/ IDH1/21</td>
<td>The presence of at least 1 of these &quot;adverse variants/mutations&quot; is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age, IPG prognostic model for PV, and karyotype. Adverse variants/mutations also affected myelofibrosis-free survival.</td>
</tr>
<tr>
<td>JAK2 exon 12 mutation</td>
<td>Patients with JAK2 exon 12-mutated PV exhibit younger age, increased mean hemoglobin/ hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared to those with JAK2 V617F-mutated PV. However, both JAK2 mutations are associated with similar rates of thrombosis, evolution to myelofibrosis or leukemia, and death.</td>
</tr>
</tbody>
</table>

## Molecular Prognosis in Essential Thrombocythemia

### NCCN Guidelines Version 3.2019
**Myeloproliferative Neoplasms**

<table>
<thead>
<tr>
<th>Mutated Gene</th>
<th>Essential Thrombocythemia (ET)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALR</td>
<td>Lower-risk of thrombosis compared to JAK2-mutated ET&lt;sup&gt;1,3&lt;/sup&gt; No difference in overall survival or myelofibrotic or leukemic transformation compared to JAK2-mutated ET&lt;sup&gt;1,3&lt;/sup&gt; CALR mutation does not modify the IPSET score for predicting thrombosis in patients with ET&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>TPS3</td>
<td>Associated with inferior leukemia-free survival in multivariate analysis&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
<tr>
<td>SH2B3/IDH1/2AF1/ SF3B1/EZH2/TP53&lt;sup&gt;5&lt;/sup&gt;</td>
<td>The presence of at least 1 of these “adverse variants/mutations” is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age and karyotype&lt;sup&gt;5&lt;/sup&gt; Adverse variants/mutations also affect myelofibrosis-free survival&lt;sup&gt;7&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
## Assessing MPN Patient Risk: Prognostic Models

<table>
<thead>
<tr>
<th>IPSET (ET—3 groups) Survival thrombosis risk</th>
<th>PV Risk (4 groups) Survival leukemia rates</th>
<th>DIPSS (PMF—4 groups) Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>≥ 60 (2 points) vs &lt; 60</td>
<td>≥ 67 (2 points), &lt; 60 (0)</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>≥ 11 (1 point) vs &lt; 11 x 10^9/L</td>
<td>≥ 15 (1 point) vs &lt; 15 x 10^9/L</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt; 10 (2 points) vs ≥ 10 g/dL</td>
<td>Constitutional symptoms</td>
</tr>
<tr>
<td>Blast</td>
<td>≥ 1% (1 point) vs &lt; 1%</td>
<td>Prior thrombosis</td>
</tr>
<tr>
<td>Risk group point cutoffs</td>
<td></td>
<td>Yes (1 point) vs No</td>
</tr>
</tbody>
</table>

IPSET, International Prognostic Score of Thrombosis for Essential Thrombocythemia; DIPSS, Dynamic International Prognostic Scoring System

### Symptom Burden in MPNs

- **Abdominal Pain**
- **Nausea**
- **Early Satiety**
- **Weight Loss**

- **Pruritus**
- **Bone Pain**
- **Fever**

- **Fatigue**
- **Night sweats**
- **Inactivity**

- **Concentration**
- **Vertigo**
- **Headaches**
- **Lightheadedness**
- **Dizziness**
- **Numbness/tingling**
- **Insomnia**

![Symptom Burden in MPNs](image)

*Courtesy of E. Mesa, MD*
Formally Assessing MPN Symptom Burden: Symptom Assessment Form

- MF–SAF 2009 (19 items)
- MF–SAF 2.0 (7 items 2011) JCO 2012
- Vascular and Ψ Sx 9 items
- Constitutional Sx 5 items
- Spleen Sx 4 items
- Brief Fatigue Inventory (BFI) – 9 items
- QOL 1 Item
- MPN–SAF 2011 (27 items) Blood 2011
- MPN–SAFTSS MPN10 (10 items 2012) JCO 2013
- MPN–SAF Languages
  - English
  - French
  - German
  - Spanish
  - Dutch
  - Swedish
  - Italian
  - Portuguese
  - Mandarin
  - Japanese
  - Hebrew
  - Czech

Signs and Symptoms of MPNs: Often Under-Queried...

MPN Symptom Assessment

NCCN Guidelines Version 3.2019
Myeloproliferative Neoplasms

MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS; MPN-18)†
(Recommended for monitoring symptoms during the course of treatment)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1 to 10 (0 if absent) ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>(No Fatigue)</td>
<td>1 is most favorable and 10 best favorable</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>(Absence) 0 1 2 3 4 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>(Absence) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Bone pain (Diffuse not joint pain or arthritis)</td>
<td>(Absence) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Unintentional weight loss last 6 months</td>
<td>(Absence) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
</tbody>
</table>


Myelofibrosis
Clinical Features of Myelofibrosis

- **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

WHO Criteria for Diagnosis of Overt Primary Myelofibrosis

- **ALL 3 major criteria plus at least 1 minor criteria**

### Major Criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
2. Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, MDS, or other myeloid neoplasms
3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis

### Minor Criteria
At least 1 of the following, confirmed in 2 consecutive determinations:
1. Anemia not attributed to a comorbid condition
2. Leukocytosis ≥ 11 × 10^9/L
3. Palpable splenomegaly
4. LDH increased to above upper normal limit of institutional reference range
5. Leukoerythroblastosis
The “Driver” Mutation and Other Alterations Affect Outcome in MF

The mutational status of JAK2, MPL and CALR and the presence and number of other relevant mutations (ASXL1, SRSF2, EZH2, IDH1/2) provide IPSS/DIPSS-plus independent prognostic information.

- CALR mutant
- JAK2 mutant
- MPL mutant
- Triple negative

Hazard Ratio:
- 2.3 for JAK2 V617F (P<.001)
- 2.6 for MPL (P=.009)
- 6.2 for Triple Negative (P<.001)

Memorial Sloan Kettering Cancer Center

Risk Stratification in Myelofibrosis

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WBC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin &lt;10 g/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral blood blasts &gt;1%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC Transfusion support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karyotype (±8, -7, -5, i17q, 12p-, inv3, 11q23 or complex)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutation status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2008 IWG-MRT Diagnostic Criteria for Post-PV MF and Post-ET MF

<table>
<thead>
<tr>
<th>Diagnostic criteria for post-PV MF</th>
<th>Diagnostic criteria for post-ET MF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REQUIRED CRITERIA</strong> (2 are required)</td>
<td><strong>REQUIRED CRITERIA</strong> (2 are required)</td>
</tr>
<tr>
<td>1. Documentation of a previous diagnosis of ET or PV as defined by the WHO criteria</td>
<td>1. Anemia and a ≥ 2 mg/dL decrease from baseline hemoglobin level</td>
</tr>
<tr>
<td>2. Bone marrow fibrosis grade 2/3 (on a 0-3 scale) or grade 3/4 (on a 0-4 scale)</td>
<td>2. A leukoerythroblastic peripheral blood picture</td>
</tr>
<tr>
<td><strong>ADDITIONAL CRITERIA (2 are required)</strong></td>
<td><strong>ADDITIONAL CRITERIA (2 are required)</strong></td>
</tr>
<tr>
<td>1. Anemia or sustained loss of requirement for either phlebotomy (in the absence of cytoreductive therapy) or for cytoreductive treatment for erythrocytosis</td>
<td>3. Increasing splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly</td>
</tr>
<tr>
<td>2. A leukoerythroblastic peripheral blood picture</td>
<td>4. Increased lactate dehydrogenase (above reference level)</td>
</tr>
<tr>
<td>3. Increasing splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly</td>
<td>5. Development of ≥ 1 of 3 constitutional symptoms: &gt; 10% weight loss in 6 months, night sweats, unexplained fever (&gt; 37.5°C)</td>
</tr>
</tbody>
</table>

Risk-Adapted Treatment of Myelofibrosis

**Low Risk**
- Asymptomatic: Observation or clinical trial
- Symptomatic: JAK2 inhibitor, interferon, or clinical trial

**INT-1**
- Observation, JAK2 inhibitor, AlloSCT, anemia treatment, or clinical trial

**INT-2 & High Risk**
- Transplant candidates: AlloSCT
- Non-transplant candidate: Clinical trial or JAK2 inhibitor +/- anemia treatment

Anemia treatment may include: Immunosomodulatory Imide drugs (IMID), androgens, erythropoiesis stimulating agents; clinical trial, splenectomy

---

**Interferon for the Treatment of Myelofibrosis**

<table>
<thead>
<tr>
<th>Author, Year, study design</th>
<th>N</th>
<th>Intervention</th>
<th>CR/PR/ORR</th>
<th>Grade 3 - 4 ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jabbour E et al. 2007, Prospective</td>
<td>11</td>
<td>PEG-INF-a-2b (Peg-Introl®) 2.3 mcg/kg SC weekly (median dose: 1.5 mcg/kg weekly)</td>
<td>9%/0%/NR</td>
<td>Fatigue, myalgias, weakness, thrombocytopenia</td>
</tr>
<tr>
<td>Silver RT et al. 2013, Prospective single-arm trial</td>
<td>32</td>
<td>rIFN-a-2b (Intron A®) 500,000–1 million units SC thrice weekly PEG-INF-a-2a (Pegasys®) 45 mcg SC weekly</td>
<td>9.4%/3%/5%/8%</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Ianotto JC et al. 2013, Retrospective</td>
<td>62</td>
<td>PEG-INF-a-2a (Pegasys®) 45 mcg SC weekly</td>
<td>ORR: 69 – 83% Spleen reduction: 46.5%</td>
<td>Anemia, thrombocytopenia, leukopenia</td>
</tr>
</tbody>
</table>

PEG-INF-a-2b (Peg-Introl®): Pegylated interferon-alpha-2b (Peg-Introl®)
rIFN-a-2b (Intron A®): Interferon-alpha-2b
PEG-INF-a-2a (Pegasys®): Pegylated interferon-alpha-2b (Peg-Introl®)
Interferon From a Pharmacist’s Perspective

- Data supporting the use of 3 different formulations
  - PEG-INF-α-2b (Peg-Intron®), rIFN-α-2b (Intron A®), PEG-INF-α-2a (Pegasys®)
- Initial dosing
  - Dependent on formulation
- Dose adjustments
  - Renal impairment
  - Hematologic toxicity
- Drug interactions
  - No major interactions
- Warnings and precautions
  - Cytopenias, cognitive impairment, cutaneous reactions, GI hemorrhage, hepatotoxicity, hypersensitivity reactions, new or worsening depression, ophthalmic effects, pancreatitis, and pulmonary effects
- Administration
  - SC injection
- Dosage forms
  - Pre-filled syringes and solution for injection
- Storage
  - Store in the refrigerator
- Cost
  - $3,600 – $4,500/month
- Drug acquisition
  - Not FDA approved for any MPN
  - Will likely require prior authorization
- Disposal
  - Sharps container
  - Adhere to state laws

Ruxolitinib (Jakafi®) in Myelofibrosis

<table>
<thead>
<tr>
<th>COMFORT-I (N = 309)</th>
<th>Ruxolitinib (Jakafi®) vs. placebo in pts with intermediate- or high-risk MF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 41.9% (ruxolitinib [Jakafi®]) vs 0.7% (placebo) had ≥35% reduction in spleen volume at week 24 (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>COMFORT-II (N = 219)</th>
<th>Ruxolitinib (Jakafi®) vs. best available therapy (BAT) in pts with intermediate- or high-risk MF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• 32% (ruxolitinib [Jakafi®]) vs 0% (BAT) had ≥35% reduction in spleen volume at week 24 (P &lt; 0.001)</td>
</tr>
</tbody>
</table>

Effect of Spleen Volume Reduction on MF-Related Symptoms, QoL

Total Symptom Score

<table>
<thead>
<tr>
<th>Spleen Volume Reduction</th>
<th>Mean % Change From Baseline ± SEM</th>
<th>Improvement/Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Placebo</td>
<td>-60.0 ± 12.0 (n=99)</td>
<td></td>
</tr>
<tr>
<td>&lt;10% Ruxolitinib (Jakafi®)</td>
<td>-50.0 ± 11.0 (n=20)</td>
<td>P &lt;.001</td>
</tr>
<tr>
<td>10% - &lt;35% Ruxolitinib (Jakafi®)</td>
<td>-40.0 ± 10.0 (n=46)</td>
<td>P &lt;.001</td>
</tr>
<tr>
<td>≥35% Ruxolitinib (Jakafi®)</td>
<td>-30.0 ± 9.0 (n=60)</td>
<td>P &lt;.001</td>
</tr>
</tbody>
</table>

Global Health Status/ QoL Score

<table>
<thead>
<tr>
<th>Spleen Volume Reduction</th>
<th>Mean % Change From Baseline ± SEM</th>
<th>Improvement/Worsening</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Placebo</td>
<td>-30.0 ± 10.0 (n=98)</td>
<td></td>
</tr>
<tr>
<td>&lt;10% Ruxolitinib (Jakafi®)</td>
<td>-20.0 ± 9.0 (n=22)</td>
<td>P =.4176</td>
</tr>
<tr>
<td>10% - &lt;35% Ruxolitinib (Jakafi®)</td>
<td>-10.0 ± 8.0 (n=46)</td>
<td>P &lt;.001</td>
</tr>
<tr>
<td>≥35% Ruxolitinib (Jakafi®)</td>
<td>0.0 ± 7.0 (n=64)</td>
<td>P &lt;.001</td>
</tr>
</tbody>
</table>

COMFORT-II: Mean Percentage Change in Spleen Volume Over Time

<table>
<thead>
<tr>
<th>Time (Week)</th>
<th>Mean % Change From Baseline ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>29.0 ± 5.0 (Ruxolitinib)</td>
</tr>
<tr>
<td>0</td>
<td>28.0 ± 5.0 (BAT excluding crossover)</td>
</tr>
<tr>
<td>0</td>
<td>27.0 ± 5.0 (BAT including crossover)</td>
</tr>
</tbody>
</table>

COMFORT-I: Non-Hematologic Adverse Events in ≥10%

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ruxolitinib (Jakafi®), n = 155</th>
<th>Placebo, n = 151</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>23</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Ecchymosis</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Dizziness</td>
<td>15</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>10</td>
<td>3</td>
</tr>
</tbody>
</table>

Ruxolitinib (Jakafi®): Survival Data

<table>
<thead>
<tr>
<th>Survival Endpoint</th>
<th>COMFORT-I</th>
<th>COMFORT-II</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RUX (n=155) vs Placebo (n=154)</td>
<td>RUX (n=146) vs Best available therapy (n=73)</td>
</tr>
<tr>
<td></td>
<td>Median follow-up</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>OS at 1 year</td>
<td>0.50 (0.25–0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td>OS at 2 years</td>
<td>0.58 (0.36–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>OS at 3 years</td>
<td>0.69 (0.46–1.03)</td>
<td>0.067</td>
</tr>
</tbody>
</table>

Combined Survival Data for COMFORT-I and COMFORT-II

<table>
<thead>
<tr>
<th>Survival Endpoint</th>
<th>Median follow-up</th>
<th>HR (95% CI)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS at 5 years</td>
<td>0.70 (0.54–0.92)</td>
<td>0.0065</td>
<td></td>
</tr>
</tbody>
</table>
Summary: Ruxolitinib (Jakafi®) in Patients With Myelofibrosis

- 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
    - Infection risk

Ruxolitinib (Jakafi®) From a Pharmacist’s Perspective

- Initial dosing
  - Dependent on platelet count and renal/hepatic function
- Dose adjustments
  - Renal impairment
  - Hepatic impairment
  - Hematologic toxicity
- Drug interactions
  - CYP3A4 and CYP2C9
- Warnings and precautions
  - Cytopenias, infection, discontinuation syndrome, non-melanoma skin cancers, & lipid elevations; Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi:
    - fever
    - respiratory distress
    - hypotension
    - DIC
    - multi-organ failure
- Administration
  - Regardless of food
  - Via nasogastric tube
- Dosage forms
  - 5, 10, 15, 20, and 25 mg tablets
- Cost
  - $12,703.20/month
- Drug acquisition
  - Specialty pharmacies only
Fedratinib (Inrebic®): The Second Approved JAK Inhibitor for MF

- Phase II study of primary and secondary MF previously exposed to ruxolitinib (Jakafi®; n=97)
  - DIPSS INT-1 with constitutional symptoms
  - INT/High Risk
  - Splenomegaly ≥5cm below left CM
  - Platelets >50,000
- 1st endpoint: ≥35% reduction in spleen volume at 24 weeks
- 2nd endpoint: ≥50% reduction in total symptom score at 24 weeks
- Fedratinib (Inrebic®) 400 mg QD

Prior RUX (Jakafi®) Response:

Fedratinib (Inrebic®) Response:

Toxicity raised distinct novel AEs
- 39% ≥ 1 dose reduction; most common for GI
- 19% discontinuation for AEs
- Most common AEs anemia, thrombocytopenia

During study concern over risk of Wernicke encephalopathy (WE): acute neurological condition characterized by a clinical triad of ophthalmoparesis with nystagmus, ataxia, and confusion, generally caused by thiamine deficiency
- Grade 3 encephalopathy in one patient, adjudicated to be hepatic not Wernicke

FDA Label:
Fedratinib (Inrebic®) From a Pharmacist’s Perspective

- Initial dosing
  - 400 mg PO daily
  - Baseline PLT >50
- Dose adjustments
  - Renal impairment
  - Hematologic toxicity
  - Non-hematologic toxicity
- Drug interactions
  - CYP3A4 and CYP2C19
- Warnings and precautions
  - Encephalopathy (Wernicke’s), GI toxicity (N/V/D), cytopenias, hepatotoxicity

Check thiamine level prior to initiating treatment. Replete thiamine BEFORE starting fedratinib (Inrebic®)

Patient Case: BP

- 60-year-old male with no major past medical history
- Presentation: Fatigue, pruritus, abdominal discomfort, 15-lb weight loss
- Physical exam: Splenomegaly by palpation (extends 8 cm below the left costal margin)

<table>
<thead>
<tr>
<th>Diagnostics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>55x10^9/L (reference range: 4.3-10.5x10^9/L)</td>
</tr>
<tr>
<td>Peripheral blasts</td>
<td>3%</td>
</tr>
<tr>
<td>Hgb</td>
<td>8.1 g/dL (reference range: Male, 13.8 to 17.2 g/dL)</td>
</tr>
<tr>
<td>Platelets</td>
<td>130x10^9/L (reference range: 150-400x10^9/L)</td>
</tr>
<tr>
<td>LDH</td>
<td>1000 IU/L (reference range: 105 - 333 IU/L)</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Atypical megakaryocytes and proliferation; grade 3 reticulin fibrosis</td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Normal karyotype</td>
</tr>
<tr>
<td>Diagnostic molecular pathology</td>
<td>BCR-ABL negative, JAK2V617F mutation</td>
</tr>
</tbody>
</table>
Patient Case: BP

- Based on the patient’s presentation, laboratory, and bone marrow biopsy findings, does the patient meet the criteria for PMF?
  - Yes
  - No

- **ALL 3 major criteria plus at least 1 minor criteria**

**Major Criteria**

1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
2. Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, MDS, or other myeloid neoplasms
3. Presence of JAK2, CALR, or MPL mutation or in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis

**Minor Criteria**

- At least 1 of the following, confirmed in 2 consecutive determinations:
  1. Anemia not attributed to a comorbid condition
  2. Leukocytosis ≥ 11 x 10⁹/L
  3. Palpable splenomegaly
  4. LDH increased to above upper normal limit of institutional reference range
  5. Leukoerythroblastosis

BP’s Risk Status

**Patient Review:** This 60-year-old man presented with constitutional symptoms and splenomegaly, WBC 55 x 10⁹/L, peripheral blasts 3%, Hgb 8.1 g/dL, platelets 130 x 10⁹/L, megakaryocyte atypia and grade 3 reticulin fibrosis, and JAK2V617F mutation.

What is the IPSS risk status of this newly-diagnosed PMF patient?

A. Low
B. Intermediate-1
C. Intermediate-2
D. High

**IPSS Risk Assessment for PMF**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>No. of Risk Factors</th>
<th>Risk Level</th>
<th>Median OS, mo.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 yrs</td>
<td>0</td>
<td>Low</td>
<td>135</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>1</td>
<td>Intermediate-1</td>
<td>95</td>
</tr>
<tr>
<td>Hgb &lt; 10 g/dL</td>
<td>2</td>
<td>Intermediate-2</td>
<td>4.8</td>
</tr>
<tr>
<td>WBC count &gt; 25 x 10⁹/L</td>
<td>2</td>
<td>Intermediate-2</td>
<td>4.8</td>
</tr>
<tr>
<td>Blood blasts ≥ 3%</td>
<td>3</td>
<td>High</td>
<td>27</td>
</tr>
</tbody>
</table>
Treatment Options for BP

• **Patient Review:** 60-year-old man presented with constitutional symptoms and splenomegaly, WBC 55 x 10^9/L, peripheral blasts 3%, Hgb 8.1 g/dL, platelets 150 x 10^9/L, megakaryocyte atypia and grade 3 reticulin fibrosis, a JAK2 V617F mutation, and an IPSS score of 4.

What is/are the best treatment options for BP?
- A. Rituximab (Rituxan®)
- B. Allogeneic stem cell transplant
- C. Ruxolitinib (Jakafi®)
- D. Interferon
- E. Both B and C
- F. None of the above

Treatment for BP

• While allogeneic SCT would be a potentially curative option, BP opted against proceeding with transplant. As such, his hematologist would like to prescribe ruxolitinib (Jakafi®) and comes to you as the pharmacist to assist with dosing and acquisition of the drug.

**Dosing Considerations**
- PLT count: 150 x 10^9/L
- CrCl = 120 mL/hr
- Hepatic function: Normal
- Based on FDA labeling, the patient's dose would be 15 mg PO BID

**Drug Acquisition**
- Insurance information
- Specialty pharmacy
- Consider starting with 5-mg tablets
- Follow-up with specialty pharmacy
- Assess financial feasibility
  - Identify co-pay assistance programs
  - Follow-up with patient
Polycythemia Vera

WHO Criteria for Diagnosis of PV

- **Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion**

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hgb &gt; 16.5 g/dL or HCT &gt; 49% in men or Hgb &gt; 16.0 or HCT &gt; 48% in women or increased red cell mass</td>
<td></td>
</tr>
<tr>
<td>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)</td>
<td></td>
</tr>
<tr>
<td>3. Presence of JAK2V617F or JAK2 exon 12 mutation</td>
<td></td>
</tr>
<tr>
<td>1. Subnormal serum erythropoietin level</td>
<td></td>
</tr>
</tbody>
</table>

Risk-Adapted Management of Patients With PV

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

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

*Cytoreductive therapy includes hydroxyurea, interferon alfa, or busulfan for patients age >75 years

Cyto-PV Study: The Benefit of “Tight” HCT Control and WBC Reduction

Cyto-PV Study: Events

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Aspirin</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI</td>
<td>1.0%</td>
<td>1.0%</td>
<td>0.98</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.0%</td>
<td>1.0%</td>
<td>0.98</td>
</tr>
<tr>
<td>Death</td>
<td>1.0%</td>
<td>1.0%</td>
<td>0.98</td>
</tr>
</tbody>
</table>

ECLAP Trial – Study Design

**Inclusion Criteria**
- Diagnosis of PV
- No contraindications of aspirin

**Primary Endpoint:**
- Cumulative rate of nonfatal MI, stroke, or death CV causes
- Cumulative rate of nonfatal MI, stroke, PE, major VTE, or death from CV causes

**Secondary Endpoints:**
- Fatal or nonfatal cerebrovascular events, fatal or nonfatal cardiac events, and major and minor thrombotic complications
ECLAP Trial – Results

<table>
<thead>
<tr>
<th>End Point</th>
<th>Aspirin (N=253)</th>
<th>Placebo (N=265)</th>
<th>Relative Risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal MI, nonfatal stroke, PE, major VTE, or death from CV causes</td>
<td>8 (3.2)</td>
<td>21 (7.9)</td>
<td>0.4 (0.18–0.91)</td>
<td>0.03</td>
</tr>
<tr>
<td>Nonfatal MI, nonfatal stroke, PE, DVT, or death from any cause</td>
<td>13 (5.1)</td>
<td>29 (10.9)</td>
<td>0.47 (0.25–0.91)</td>
<td>0.02</td>
</tr>
<tr>
<td>Major or minor thrombosis</td>
<td>17 (6.7)</td>
<td>41 (15.5)</td>
<td>0.42 (0.24–0.74)</td>
<td>0.003</td>
</tr>
<tr>
<td>Any Bleeding</td>
<td>23 (9.1)</td>
<td>14 (5.3)</td>
<td>1.82 (0.94–3.53)</td>
<td>0.08</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>3 (1.2)</td>
<td>2 (0.8)</td>
<td>1.62 (0.27–9.71)</td>
<td>0.60</td>
</tr>
<tr>
<td>Minor Bleeding</td>
<td>20 (7.9)</td>
<td>12 (4.5)</td>
<td>1.81 (0.90–3.70)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

Summary

- Low-dose aspirin can safely prevent thrombotic complications in patients with PV who have no contraindications to aspirin therapy
- If patients encounter gastrointestinal discomfort with aspirin consider adding H₂-antagonist
- Patients with extreme thrombocytosis (i.e. platelets > 1,000 x10⁹/L) should be screened for acquired Von Willebrand syndrome
Hydroxyurea (Hydrea®, Droxia™, Mylocel™) in PV Management

- Usually used as a first-line cytoreductive treatment
  - Controls myeloproliferation
  - Reduces splenomegaly
  - May reduce risk of major thrombosis
- Side effects
  - Myelosuppression
  - Leg ulcers
  - Hyperpigmentation
  - Fever
  - Alopecia
  - Increased risk of squamous cell carcinoma
  - Longstanding controversy re: leukemogenic risk

Definition of HU Resistance/Intolerance

1. Need for phlebotomy to keep HCT < 45% after 3 months of at least 2 g/day of HU
2. Uncontrolled myeloproliferation:
   - Platelet count > 400 x 10^9/L AND WBC > 10 x 10^9/L after 3 months of at least 2 g/day HU
3. Failure to reduce massive splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of HU
4. ANC < 1.0 x 10^9/L OR platelet count < 100 x 10^9/L or Hgb <10.0 g/dL at the lowest dose of HU required to achieve a CR or PR
5. Presence unacceptable HU non-hematological toxicities:
   - Leg ulcers
   - Mucocutaneous manifestations
   - Gastrointestinal symptoms
   - Pneumonitis
   - Fever at any dose of HU
Interferon in the Treatment of PV

**Phase II studies**: Treatment with PEG-IFN-α2a (Pegasys®) or α2b (Peg-Intron®) resulted in high rates of complete hematologic and molecular response, and low rates of thrombosis.

**IFN α2a (Pegasys®) (n=40)**

<table>
<thead>
<tr>
<th>PV</th>
<th>Complete</th>
<th>Partial</th>
<th>No response</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>70</td>
<td>10</td>
<td>20</td>
</tr>
</tbody>
</table>

**JAK2V617F Mutant Allele (%)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>64</td>
<td>52.8</td>
<td>37.16</td>
<td>15.8</td>
<td>12.2</td>
</tr>
</tbody>
</table>

Interferon Tolerability in PV

**All patients**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Flu</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Mucositis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Anaemia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Patients treated at 90 mcg/week**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Reproduction</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Memorial Sloan Kettering Cancer Center

### Ropeginterferon in the Treatment of PV

<table>
<thead>
<tr>
<th>Author, Year, study design</th>
<th>N</th>
<th>Intervention</th>
<th>Response</th>
<th>ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gisslinger H et al. Blood. 2015 PEGINVERA Phase III</td>
<td>Phase I = 25 Phase II = 26</td>
<td>Phase I = rIFN-α-2b (Intron A®) 50-540 µg SC every 2 weeks (no MTD) Phase II = Response driven dosing up to 540 µg SC every 2 weeks (median dose: 250 µg SC every 2 weeks)</td>
<td>Dose &lt;300 µg (n=37): 43% (CR)/43% (PR) Dose ≥300 µg (n=14): 57% (CR)/43% (PR)</td>
<td>Common: Pruritus, arthralgia, fatigue, headache, diarrhea, influenza-like illness, vertigo Serious: Psychiatric ADR (31%), autoimmune thyroiditis (2 pts)</td>
</tr>
<tr>
<td>Gisslinger H et al. Blood. 2016 ASH Abstract PROUD-PV Phase III</td>
<td>254</td>
<td>rIFN-α-2b (Intron A®) with response driven dosing up to 540 µg SC every 2 weeks (median dose: 450 µg SC every 2 weeks) HU with CBC driven dosing (median dose: 1250 mg) *Treatment for 12 months</td>
<td></td>
<td>No difference in endocrine disorders, psychiatric disorders, cardiac/vascular disorders, and tissue disorders. 5 secondary malignancies in HU group vs. 0 in rIFN-α-2b (Intron A®) group</td>
</tr>
<tr>
<td>Gisslinger H et al. Blood. 2017 Mature results from PROUD-PV called CONTINUATION-PV</td>
<td>371</td>
<td>rIFN-α-2b (Intron A®) with response driven dosing up to 540 µg SC every 2 weeks (median dose: 450 µg SC every 2 weeks) BAT</td>
<td>CHR: 70.5% vs. 49.3%, p = 0.0101 Partial molecular response: 49.5% vs. 36.6%, p = 0.1183</td>
<td>Thrombocytopenia (19.7% vs. 26.8%), leukopenia (38.5% vs. 23%), anemia (9.4% vs. 23%), increased GGT (11% vs. 0%), endocrine (3.9% vs. 0.8%), and psychiatric (2.4% vs. 0.8%)</td>
</tr>
</tbody>
</table>

### Ruxolitinib (Jakafi®) in PV – RESPONSE Trial

**Primary Endpoint:**
- Proportion of patients who had both HCT control and a reduction ≥ 35% in spleen volume from baseline at week 32

**Secondary Endpoints:**
- Response rates
- Symptom reduction
- Safety

**Inclusion Criteria**
- Adult patients with PV who were resistant to HU

**Investigator’s choice of best available therapy (BAT)**

**Week 32: Crossover**

**BAT:** interferon or pegylated interferon, pipobroman, anagrelide, lenalidomide, thalidomide, or no medication
Ruxolitinib (Jakafi®)
Jakafi® is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea


Jakafi® (Ruxolitinib) [package insert]. Wilmington, DE. 2016.

### RESPONSE Trial – Safety Results

**Patients, %** | **Ruxolitinib (Jakafi®)** (n = 110) | **BAT** (n = 111) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Anemia</td>
<td>43.6</td>
<td>1.8</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>24.5</td>
<td>5.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1.8</td>
<td>0.9</td>
</tr>
</tbody>
</table>

- Most common grade 3/4 non-hematologic adverse events in the ruxolitinib (Jakafi®) arm: dyspnea (2.7%) and asthenia (1.8%)  
- Rate of herpes zoster infection was higher in the ruxolitinib (Jakafi®) group (6.4% vs 0; all grade 1-2)  
- Thromboembolic events occurred in 1 patient receiving ruxolitinib (Jakafi®) and in 6 patients receiving standard therapy
### Treatment Summary

- Treatment for patients with PV combines:
  - Modification of CV risk factors
  - Phlebotomy (HCT target <45%)
  - Antiplatelet therapy
  - First-line cytoreductive therapy: HU or IFN-alfa
  - Second-line: Ruxolitinib (Jakafi®) for patients resistant to or intolerant of HU
  - Other options may include PEG-IFN or busulfan

### PV-Associated Pruritus

<table>
<thead>
<tr>
<th>Feature</th>
<th>PV-associated pruritus</th>
<th>Idiopathic AP</th>
<th>AP of the elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yrs)</td>
<td>59 (range 21–89)</td>
<td>29.4 (females), 34.5 (males)</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Gender distribution (F:M)</td>
<td>1:1</td>
<td>1:1</td>
<td>3:1</td>
</tr>
<tr>
<td>Family history</td>
<td>None</td>
<td>33%</td>
<td>None</td>
</tr>
<tr>
<td>Relationship of pruritus to water</td>
<td>Usually follows contact with water at any temperature, but less frequently after contact with cold water</td>
<td>Hot water causes symptoms in 50% and cold water in 35% of patients</td>
<td>Itching is invariably absent during bathing, but starts soon after (during drying)</td>
</tr>
<tr>
<td>Clinical features</td>
<td>Distributed over torso and extensor surface of limbs, lower rate of arterial thrombosis, negative impact on QoL</td>
<td>Onset of itching is upon contact with water, duration averages 40 min, condition is usually unremitting, psychiatric symptoms may be present</td>
<td>Fair color, dry scaly skin, females have more severe symptoms, itching begins in lower extremities and spreads upwards, but spares head, symptoms are worse in winter, and are progressive</td>
</tr>
<tr>
<td>Histopathological features</td>
<td>Increased skin mast cells, mononuclear cells and eosinophils, itching correlates with homozygosity for the JAK2V617F mutation</td>
<td>Normal number of skin mast cells, acetylcholine mediated, increased cutaneous fibrinolytic activity</td>
<td>Non-specific lymphocytic perivenular infiltrate</td>
</tr>
</tbody>
</table>

Management of PV-Associated Pruritus

Typically Effective
- Interferon-α
- Ruxolitinib (Jakafi®)
- SSRIs
- Phototherapy

Mixed Results
- Anti-histamines

Typically Ineffective
- Cytoreductive therapy
- Phlebotomy

SSRIs, Selective Serotonin Reuptake Inhibitors

Patient Case: SO
- 66 yo M with a history of a right lower extremity DVT
- Presentation: fatigue, persistent pruritus, and headaches
- Physical exam: No evidence of splenomegaly by palpation

Diagnostics 4/15/2008

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6.7 x 10^9/L</td>
<td>4.3-10.5 x 10^9/L</td>
</tr>
<tr>
<td>Peripheral blasts</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>Hgb</td>
<td>18.1 g/dL</td>
<td>Male, 13.8 to 17.2 g/dL</td>
</tr>
<tr>
<td>HCT</td>
<td>54% (reference range: Male, 38.8 to 52%)</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>223 x 10^9/L</td>
<td>reference range: 150-400 x 10^9/L</td>
</tr>
<tr>
<td>Bone Marrow Biopsy</td>
<td>Hypercellular, trilineage hematopoiesis with pleomorphic, mature megakaryocytes</td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Normal karyotype</td>
<td></td>
</tr>
<tr>
<td>Diagnostic molecular pathology</td>
<td>BCR-ABL negative, JAK2V617F mutation</td>
<td></td>
</tr>
<tr>
<td>Erythropoietin level</td>
<td>&lt;1.0 mIU/mL (reference range: 2.6 – 18.5 mIU/mL)</td>
<td></td>
</tr>
</tbody>
</table>
**Patient Case: BP**

- Based on the patient's presentation, laboratory, and molecular findings does the patient meet the criteria for PV?
  - Yes
  - No

- All 3 major criteria, or the first 2 major criteria and the minor criterion

**Major Criteria**
- Hgb > 16.5 g/dL or HCT > 49% in men or Hgb > 16.0 or HCT > 48% in women or increased red cell mass
- BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
- Presence of JAK2V617F or JAK2 exon 12 mutation

**Minor Criteria**
- Subnormal serum erythropoietin level

---

**BP’s Risk Status**

**Patient Review:** This 66-year-old man presented with fatigue, persistent pruritus, and headaches, WBC 6.7 x 10^9/L, Hgb 18.1 g/dL, HCT 54%, platelets 223 x 10^9/L, a JAK2V617F mutation, and a previous history of a DVT.

What is the risk status of this patient with newly-diagnosed PV?
- A. Low
- **B. High**
Patient Case: BP

- **Patient Review:** This 66-year-old man presented with fatigue, persistent pruritus, and headaches, WBC 6.7 x 10^9/L, Hgb 18.1 g/dL, HCT 54%, platelets 223 x 10^9/L, a JAK2 V617F mutation, and a previous history of a DVT.

What is/are the best treatment options for BP?
A. Hydroxyurea
B. Aspirin
C. Ruxolitinib (Jakafi®)
D. Interferon
E. Both A and B
F. None of the above

---

Patient Case: BP

- **Patient Review:** This 66-year-old man presented with fatigue, persistent pruritus, and headaches, WBC 6.7 x 10^9/L, Hgb 18.1 g/dL, HCT 54%, platelets 223 x 10^9/L, a JAK2 V617F mutation, and a previous history of a DVT. He was placed on hydroxyurea (Hydrea®, Droxia™, Mylocel™) and tolerated it well until today when he presented to clinic with leg ulcers, increasing Hgb and HCT, and a return of his constitutional symptoms.

What should we do now?

a. Continue hydroxyurea, but increase the dose
b. **Consider starting ruxolitinib (Jakafi®)**
c. Admit the patient to start 7+3 chemotherapy
Essential Thrombocythemia

Diagnosis of Essential Thrombocythemia

- WHO Diagnosis of ET requires ALL 4 major criteria or the first 3 major criteria and the minor criterion

Major Criteria
1. Platelet count ≥ 450 x 10^9/L
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
3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, MDS, or other MPNs
4. Presence of JAK2, CALR, or MPL mutation

Minor Criteria
1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis

ET Risk Assessment

- **IPSET Prognostic Features**
  - Age > 60 years (2 points)
  - Prior history of thrombosis (1 point)
  - Leukocytes >11 x 10^9/L (1 point)

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

<table>
<thead>
<tr>
<th>Conventional Risk Category</th>
<th>Risk Variables</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>None</td>
<td>Observation, Correction of CV risk factors</td>
</tr>
<tr>
<td>High</td>
<td>Age ≥ 60 years OR Thrombosis history OR Platelet count ≥1500 x 10^9/L</td>
<td>Cytoreduction*, and Correction of CV risk factors, and Aspirin**</td>
</tr>
</tbody>
</table>

*Hydroxyurea (Hydrea®, Droxia™, Mylocel™) is the first-line treatment of choice. Anagrelide (Agylin®) is generally 2nd-line therapy if resistant or intolerant to HU. IFN-a is used for young patients, pregnant women, or patients who are refractory/intolerant to HU.

**Acquired Von Willebrand syndrome should be assessed if platelet count is ≥ 1000 x 10^9/L.
**Interferon in the Treatment of ET**

Treatment with PEG-IFN-α2a (Pegasys®) resulted in high rates of complete hematologic and molecular response, and low rates of thrombosis.

![Graph showing response rates](image)

**Interferon Tolerability in ET**

### All patients

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Depression</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mucositis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

### Patients treated at 90 mcg/week

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Elevated LFTs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Anagrelide (Agrylin®) for Treatment of ET: ANAHYDRET Study

Prospective, randomized, noninferiority phase III study

Inclusion Criteria
- High-risk patients with ET
- Treatment naive

N = 122
Anagrelide (Agrylin®) 0.5 mg PO BID

N = 137
Hydroxyurea (Hydrea®, Droxia™, Mylocel™) 1500 mg/day


Figure 3. Event-free survival for ET-related events for patients who were reclassified as having WHO-ET (“true-ET”). The HR (95% CI) is presented after an observation time of 6 years.
Safety of Anagrelide (Agrylin®) in ANAHYRDET Study

Table 5. Safety profile according to organ classes

<table>
<thead>
<tr>
<th>Organ manifestations</th>
<th>Symptoms</th>
<th>No. of patients</th>
<th>Agrylin group</th>
<th>Hydroxyurea group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections and infestations</td>
<td>Herpes (mucous, labial, rectal)</td>
<td>1</td>
<td>4</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infections (viral, influenza-like)</td>
<td>12</td>
<td>28</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>Anemia</td>
<td>11</td>
<td>24</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Epistaxis</td>
<td>6</td>
<td>15</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Leukopenia</td>
<td>1</td>
<td>27</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>29</td>
<td>22</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vertigo</td>
<td>5</td>
<td>14</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Dizziness</td>
<td>7</td>
<td>2</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Hypertension</td>
<td>14</td>
<td>4</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Palpitations</td>
<td>30</td>
<td>3</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>13</td>
<td>3</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
<td>Bronchitis</td>
<td>3</td>
<td>8</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Abdominal pain</td>
<td>11</td>
<td>11</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diarrhea</td>
<td>17</td>
<td>10</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other gastrointestinal events</td>
<td>11</td>
<td>14</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Alopecia</td>
<td>0</td>
<td>5</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin disorders</td>
<td>7</td>
<td>16</td>
<td>&lt;.01</td>
<td></td>
</tr>
</tbody>
</table>

Anagrelide (Agrylin®) From a Pharmacist’s Perspective

- **Initial dosing**
  - 0.5 mg PO BID
  - Dose adjust to platelet count to <600, ideally between 150-400
- **Dose adjustments**
  - Hepatic impairment
  - Hematologic toxicity
- **Drug interactions**
  - Antiplatelet and anticoagulation
- **Warnings and precautions**
  - Bleeding risk, cardiovascular, pulmonary hypertension, pulmonary toxicity, renal abnormalities
- **Administration**
  - Regardless of food
- **Dosage forms**
  - 0.5 and 1 mg capsules
- **Cost**
  - $669.60/month
- **Drug acquisition**
  - Retail pharmacy
Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial

**Prospective, parallel, phase II, randomized, open-label trial**

**Inclusion Criteria**
- Adult patients with ET who were resistant or intolerant to HU

**Primary Endpoint:**
- Achievement of CR within 1 year of treatment

**Secondary Endpoints:**
- Partial response
- Duration of response
- Overall response
- Safety
- Symptom reduction
- Survival

**Ruxolitinib (Jakafi®) 25 mg PO BID**

**PLT 100-300; 20 mg PO BID**

**Investigator's choice of best available therapy (BAT)**

**N = 58**

**BAT:** Assigned according to physician's choice but had to be an active agent; change of and combination of BAT therapies were permitted with the aim of achieving a CR

**Inclusion Criteria**
- Adult patients with ET who were resistant or intolerant to HU

**Prospective, parallel, phase II, randomized, open-label trial**

**Harrison CN et al. Blood. 2017;130(17):1889-1897.**

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib (Jakafi®)</th>
<th>BAT</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>46.5%</td>
<td>44.2%</td>
<td>0.40</td>
</tr>
<tr>
<td>PR</td>
<td>46.5%</td>
<td>51.9%</td>
<td>*Not reported</td>
</tr>
<tr>
<td>OS</td>
<td>0.98</td>
<td>0.98</td>
<td>0.99</td>
</tr>
<tr>
<td>PFS</td>
<td>0.93</td>
<td>0.96</td>
<td>0.97</td>
</tr>
<tr>
<td>Thrombotic event</td>
<td>17.2%</td>
<td>5.8%</td>
<td>0.09</td>
</tr>
<tr>
<td>Hemorrhagic event</td>
<td>1.7%</td>
<td>8.9%</td>
<td>0.14</td>
</tr>
<tr>
<td>Maximum % TSS reduction at any point during first 12 months</td>
<td>32%</td>
<td>0%</td>
<td>0.03</td>
</tr>
<tr>
<td>Symptom response at 2 months</td>
<td>19%</td>
<td>3%</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Harrison CN et al. Blood. 2017;130(17):1889-1897.**
Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial

Overview of assigned therapy switches and discontinuations per treatment arm

<table>
<thead>
<tr>
<th>Grade 3/4</th>
<th>Ruxolitinib (Jakafi®)</th>
<th>BAT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>21%</td>
<td>0%</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>3.4%</td>
<td>0%</td>
<td>0.32</td>
</tr>
<tr>
<td>Infection</td>
<td>15.5%</td>
<td>3.5%</td>
<td>0.03</td>
</tr>
</tbody>
</table>


Patient Case: MT

- 62-year-old man had elevated platelet count (780 x 10^9/L) was recently admitted for a DVT
- History, examination, and laboratory tests (iron status, inflammatory markers, rheumatoid disease and malignancy screening) did not reveal underlying cause

Diagnostics

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>9.6 x 10^9/L</td>
<td>4.3-10.5 x 10^9/L</td>
</tr>
<tr>
<td>Hgb</td>
<td>14.3 g/dL</td>
<td>Male, 13.8 to 17.2 g/dL</td>
</tr>
<tr>
<td>Platelets</td>
<td>775 x 10^9/L</td>
<td>150-400 x 10^9/L</td>
</tr>
<tr>
<td>Bone Marrow Biopsy</td>
<td>Increased megakaryocytes with prominent large hyperlobulated forms; reticulin is not increased</td>
<td></td>
</tr>
<tr>
<td>Cytogenetics</td>
<td>Normal karyotype</td>
<td></td>
</tr>
<tr>
<td>Diagnostic molecular pathologic</td>
<td>BCR-ABL negative, JAK2V617F mutation present</td>
<td></td>
</tr>
</tbody>
</table>

DVT, Deep vein thrombosis
Patient Case: MT

- Does MT meet the diagnostic criteria for ET?
  A. Yes
  B. No

Major Criteria
1. Platelet count ≥ 450 × 10^9/L
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
3. Not meeting WHO criteria for BCR-ABL1+ CML, PV, PMF, MDS, or other MPNs
4. Presence of JAK2, CALR, or MPL mutation

Minor Criteria
1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Patient Case: MT

- Patient Review: 62-year-old man had elevated platelet count (780 × 10^9/L), was found to have a DVT and subsequently diagnosed with ET.

What initial treatment should MT start to reduce the risk of thrombosis?
A. Rituximab (Rituxan®)
B. Hydroxyurea (Hydrea®, Droxia™, Mylocel™).
C. Aspirin
D. Busulfan (Busulfex® and Myleran®)
E. Both B and C
Stem Cell Transplant Use in MPNs

- SCT *almost* exclusively for MF/MPN-BP
- In MF evolving risk/benefit analysis for use

"Problematic" MF & SCT Eligible

**Question 1**
Timing?
- Urgent
- Delayed
- Never

**Allo SCT**

**Question 2**
Pre-Transplant Therapy?
- JAK Inhibition?
- Cytoreduction?
- Iron chelation?

**Question 3**
Posttransplant Therapy?
- JAK Inhibition?
- Interferon?
- other?

MPN-BP, myeloproliferative neoplasms in blast phase

MPN Conclusions

- MPNs are chronic and variably progressive, hematopoietic diseases with shared biology, clinical features, and molecular basis
- Proper diagnosis is essential given overlaps
- Patient-reported symptom burden is crucial and quantifiable through treatment
- Treatment strategies can vary depending on the individual’s risk status and management needs
- Thrombosis is a shared risk and antiplatelet therapy a mainstay for a majority of patients

- Ruxolitinib (Jakafi®) represented a major paradigm shift and can significantly improve the outlook for many patients with MF or HU-resistant/intolerant PV, but it does not cure these diseases
- Interferon may offer significant benefit, but toxicity warrants careful patient selection and monitoring
- Novel therapies for MPNs are needed, and a number of strategies are in development
  - Novel JAK pathway inhibitors
  - Antifibrotics
  - Telomerase inhibitors
  - Combination approaches (hypomethylating agents + JAK inhibitors in BP, numerous in early disease)
Resources

- The Leukemia & Lymphoma Society
- MPN Advocacy Network
- NCCN
- Patient Access Network
- Needymeds.org

Nursing Care in the Treatment and Side Effect Management of Myeloproliferative Neoplasms

Carolanne Carini, BSN, RN, BMTCN
Office Practice Nurse, Medical Oncology
Memorial Sloan Kettering Cancer Center
Treatment Goals

- Reduction in life-threatening disease sequelae
- Slow/reduce disease progression
- Improve quality of life

Common Symptoms

- Vascular
  - Micro- and microvascular
    - Neurologic, Cognitive, Cardiac, Pulmonary
- Inflammation
- Proliferation
- Gastrointestinal
Splenomegaly

- Prevalent in MF, also common in PV and ET
- Symptoms:
  - Early satiety
  - Abdominal fullness
  - Nausea
  - Increased abdominal girth
- Nursing interventions
Pruritus

- Most common in PV
- Related to increased number of mast cells
- Worse after showering
- Treatment

Constitutional Symptoms

- Associated with inflammation in bone marrow and throughout the body
- Common symptoms:
  - Fatigue
  - Night sweats
  - Bone pain
  - Low-grade fevers
  - Weight loss
Treatment: Therapeutic Phlebotomy

- Used in PV patients
- Remove approximately 450 cc of blood
- Target HCT<45%
- Nursing implications:
  - Monitor patient labs
  - Hydration
  - What to avoid
  - What to expect

Treatment: ASA

- Low-dose aspirin to prevent thrombotic complications

- Nursing implications:
  - Review patient history
  - Monitor for sign of bleeding
  - Very high platelets and Von Willebrand disease
Treatment: Hydroxyurea

- Cytoreductive agent, reduce risk of thrombotic events by managing blood levels

- Nursing Implications:
  - Monitor blood counts
  - Immune suppression
  - Dermatologic changes

Treatment: Interferon

- Used to control erythrocytosis and thrombocytosis

- Nursing Implications:
  - Monitor labs
  - Administered subcutaneously
  - Local reactions
  - Side effects
Conclusions

• Focus on symptom recognition and assessment
• Educate on lifestyle changes and strategies for cardiovascular risk reduction
• Collaborate with interdisciplinary team

RESOURCES FOR YOU & YOUR PATIENTS
FROM THE LEUKEMIA & LYMPHOMA SOCIETY (LLS)
WWW.LLS.ORG
**LLS RESOURCES FOR HEALTHCARE PROFESSIONALS**

Online and in-person CE/CME webinars, symposia & rounds
Free CME & CE  [www.LLS.org/CE](http://www.LLS.org/CE)

Podcast series for healthcare professionals
*Conversations with experts about diagnosing & treating blood cancers*  [www.LLS.org/HCPpodcast](http://www.LLS.org/HCPpodcast)

HCP palm card – User friendly links to resources for you & your patients
[www.LLS.org/CE](http://www.LLS.org/CE)

**LLS RESOURCES FOR PATIENTS AND CAREGIVERS**

- **Information Specialists** – disease information, emotional support, financial, travel & co-pay assistance, local support through LLS patient access field team. Also send free materials to patients & HCPs.

- **Nutrition Consultations** – One-on-one consultations from certified dietitian Specialists can serve as a resource for your HCP team
  M - F, 9 am to 9 pm ET:
  - Phone: (800) 955-4572
  - Live chat:  [www.LLS.org/InformationSpecialists](http://www.LLS.org/InformationSpecialists)
  - Email: infocenter@LLS.org

- **Additional support for patients & caregivers** –  [www.LLS.org/Support](http://www.LLS.org/Support)

- **Booklets on disease, treatment, & support** -  [www.LLS.org/Booklets](http://www.LLS.org/Booklets)

- **Webinars, videos, in-person programs** -  [www.LLS.org/Programs](http://www.LLS.org/Programs) & [www.LLS.org/Educationvideos](http://www.LLS.org/Educationvideos)
CLINICAL TRIAL NURSE NAVIGATORS

Help patients find and enroll in clinical trials based on highly detailed individualized assessments

www.LLS.org/Navigation

602 patients provided with in-depth clinical trial navigation and support in past year

THANK YOU

We have one goal: A world without blood cancers