TREATING MYELOPROLIFERATIVE NEOPLASMS: SPOTLIGHT ON MYELOFIBROSIS

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Senior Director
Professional Education & Engagement
The Leukemia & Lymphoma Society
Rye Brook, NY
LEARNING OBJECTIVES

- Provide an overview of MPNs
- Apply diagnostic criteria for a correct diagnosis and grade
- Explain low-risk symptomatic myelofibrosis, intermediate, and high-risk primary or secondary, including genetic mutations, and risk stratification
- Apply data on approved treatments and clinical trials into clinical practice
- Implement strategies across the care team to educate and support patients

CE DESIGNATION

Physician Continuing Medical Education
In support of improving patient care, this activity has been planned and implemented by the Postgraduate Institute for Medicine and The Leukemia & Lymphoma Society. Postgraduate Institute for Medicine is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team. The Postgraduate Institute for Medicine designates this CME activity for a maximum of 1 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Registered Nursing Credit Designation
Approval for nurses has been obtained by the National Office of The Leukemia & Lymphoma Society under Provider Number CEP 5832 to award 1.0 continuing education contact hour through the California Board of Registered Nursing.

Interprofessional Continuing Education
This activity was planned by and for the healthcare team, and learners will receive 1 Interprofessional Continuing Education (IPCE) credit for learning and change.

Continuing Physician Assistant Education
Postgraduate Institute for Medicine has been authorized by the American Academy of PAs (AAPA) to award AAPA Category 1 CME credit for activities planned in accordance with AAPA CME Criteria. This activity is designated for 1 AAPA Category 1 CME credits. PAs should only claim credit commensurate with the extent of their participation.

Social Worker Continuing Education
The Leukemia & Lymphoma Society (LLS) Provider Number 1105, is approved as an ACE provider to offer social work continuing education by the Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) program. Regulatory boards are the final authority on courses accepted for continuing education credit. ACE provider approval period: 12/10/2023-12/10/2026. Social workers completing this course receive 1.0 clinical continuing education credit.

The Leukemia & Lymphoma Society (LLS) is recognized by the New York State Education Departments State Board for Social Work as an approved provider of continuing education for licensed social workers #SW-0117. LLS maintains responsibility for the program. Social workers will receive 1.0 clinical CE contact hour for this activity.
SPEAKERS

John Mascarenhas, MD
Director, Center of Excellence in Blood Cancers and Myeloid Disorders
Director, Adult Leukemia Program
Leader, Myeloproliferative Disorders Clinical Research Program
Tisch Cancer Institute, Division of Hematology/Oncology
Professor of Medicine
Icahn School of Medicine at Mount Sinai
New York, NY

Kathryn Johnson, DNP, MSc, FNP-BC
Clinical Program Manager
Tisch Cancer Institute
Icahn School of Medicine at Mount Sinai
New York, NY

DISCLOSURES

- **John Mascarenhas, MD**
  - **Research Funding:** Incyte, Novartis, BMS, CTI/SOBI, AbbVie, Geron, PharmaEssentia
  - **Consulting:** Incyte, Novartis, BMS, Geron, Kartos, Karyopharm, AbbVie, GSK, Galecto, PharmaEssentia, MorphoSys, Merck, Pfizer, and CTI/SOBI

- **Kathryn Johnson, DNP, MSc, FNP-BC**
  - **Speakers:** CTI Biopharma/SOBI

The PIM planners and others have nothing to disclose. The Leukemia & Lymphoma Society planners and others have nothing to disclose.
Case RH: Initial Presentation

RH is a 77-year-old woman who was referred to you by her primary care clinician for progressive fatigue and noted anemia.

- **Medical history**
  - Hypertension, well controlled on beta blocker
  - High cholesterol, on statin

- **Symptoms**
  - Mild fatigue, no systemic symptoms, and no spleen-related concerns

- **Physical exam findings**
  - Spleen 4 cm below LCM and nontender
  - No edema

- **Laboratory findings**
  - As shown on the right

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**Current labs:**
- Hgb = 9.2 g/dL
- PLT = 162 × 10^9/L
- Differential = 1% blasts

**BM biopsy:**
- Mutation = CALR
- Hypercellular with atypical MK in tight clusters
- Fibrosis = grade 2
- Karyotype = 46,XX

**NGS:**
Mutations = CALR, TET2

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Myelofibrosis Diagnosis and Risk Stratification
Myeloproliferative Neoplasms

- MF, PV, and ET are 3 Ph-negative MPNs characterized by increased myeloid/erythroid cell proliferation\(^1\)\(^-\)\(^4\)
- Chronic, unregulated proliferation may occur in ≥1 myeloid cell line, including erythrocytes, platelets, and sometimes granulocytes\(^5\)\(^-\)\(^7\)

CML, chronic myelogenous leukemia; ET, essential thrombocytopenia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera.


Incidence of MPNs

- PV: 0.84 per 100,000
- ET: 1.03 per 100,000
- PMF: 0.5–1 per 100,000
- AML + MPN: One-third of all heme malignancies

Which of the following constitutional symptoms is common in MF?

A. Fatigue
B. Weight loss
C. Night sweats
D. All of the above
MF Is a Progressive Disease

Time to progression is variable; most patients progress within first 10 years\(^1\)

- Pre-primary MF
- Overt primary MF
- Post-ET MF
- Post-PV MF

### Long-term complications\(^{1,2}\)
- Progressive cytopenias
- Progressive constitutional symptoms
- Progressive organomegaly/EMH

### Short-term complications\(^{1,2}\)
- Vascular events

### Leukemic transformation\(^{1,3,4}\)
Median time to transformation is 31 mo (range: 2 to 441 mo)\(^3\)

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DIPSS Plus Integrates Other Clinical and Cytogenetic Data

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIPSS int-1</td>
<td>1</td>
</tr>
<tr>
<td>DIPSS int-2</td>
<td>2</td>
</tr>
<tr>
<td>DIPSS HR</td>
<td>3</td>
</tr>
<tr>
<td>Unfav. cytogenetics</td>
<td>1</td>
</tr>
<tr>
<td>PLT &lt;100 x 10^9/L</td>
<td>1</td>
</tr>
<tr>
<td>Transfusion dep.</td>
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</table>

<table>
<thead>
<tr>
<th>Risk Categories/Score</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>LR</td>
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</tr>
<tr>
<td>Int-1</td>
<td>1</td>
</tr>
<tr>
<td>Int-2</td>
<td>2–3</td>
</tr>
<tr>
<td>HR</td>
<td>4–6</td>
</tr>
</tbody>
</table>

### Preferred Risk Stratification Tool for Primary MF Below Age 70

#### MIPSS-70

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hgb &lt; 10 g/dL</td>
<td>1</td>
</tr>
<tr>
<td>Leukocytes &gt; $25 \times 10^9$/L</td>
<td>2</td>
</tr>
<tr>
<td>PLT &lt; $100 \times 10^9$/L</td>
<td>2</td>
</tr>
<tr>
<td>Circulating blasts ≥ 2%</td>
<td>1</td>
</tr>
<tr>
<td>BM fibrosis grade ≥ 2</td>
<td>1</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>1</td>
</tr>
<tr>
<td><em>CALR</em> type 1 unmutated genotype</td>
<td>1</td>
</tr>
<tr>
<td>HMR mutations</td>
<td>1</td>
</tr>
<tr>
<td>≥ 2 HMR mutations</td>
<td>2</td>
</tr>
</tbody>
</table>

**Risk Group**

<table>
<thead>
<tr>
<th>Points</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 to 1</td>
<td>2 to 4</td>
<td>≥ 5</td>
</tr>
</tbody>
</table>

Online calculator for MIPSS-70 can be found at [http://www.mipss70score.it/](http://www.mipss70score.it/)

BM, bone marrow; PLT, platelets.


### Preferred Risk Stratification Tool for Primary MF in Ages 70+

#### MIPSS-70+ Version 2.0

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe anemia (Hgb &lt; 8 g/dL women, &lt; 9 g/dL men)</td>
<td>2</td>
</tr>
<tr>
<td>Moderate anemia (Hgb 8–9.9 g/dL women, 9–10.9 g/dL men)</td>
<td>1</td>
</tr>
<tr>
<td>Circulating blasts ≥ 2%</td>
<td>1</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>2</td>
</tr>
<tr>
<td>Absence of <em>CALR</em> type 1 mutation</td>
<td>2</td>
</tr>
<tr>
<td>High molecular risk (HMR) mutations</td>
<td>2</td>
</tr>
<tr>
<td>≥ 2 HMR mutations</td>
<td>3</td>
</tr>
<tr>
<td>Unfavorable karyotype</td>
<td>3</td>
</tr>
<tr>
<td>Very high-risk (VHR) karyotype</td>
<td>4</td>
</tr>
</tbody>
</table>

**Risk Group**

<table>
<thead>
<tr>
<th>Points</th>
<th>Very low</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1 to 2</td>
<td>3 to 4</td>
<td>5 to 8</td>
<td>9</td>
</tr>
</tbody>
</table>

Online calculator for MIPSS-70+ Version 2.0 can be found at [http://www.mipss70score.it/](http://www.mipss70score.it/)

Hgb, hemoglobin; IPSS, International Prognostic Scoring System.

Preferred Risk Stratification Tool for Secondary MF

**MYSEC-PM**

**MF Secondary to PV and ET Prognostic Model (MYSEC-PM)**

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>0.15 per patient year of age ((71 \times 0.15 = 10.65))</td>
</tr>
<tr>
<td>Hgb &lt; 11 g/dL</td>
<td>2</td>
</tr>
<tr>
<td>Circulating blasts ≥ 3%</td>
<td>2</td>
</tr>
<tr>
<td>Absence of (CALR) type 1 mutation</td>
<td>2</td>
</tr>
<tr>
<td>PLT &lt; 150 (\times 10^9)/L</td>
<td>1</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>1</td>
</tr>
</tbody>
</table>

**Risk Group**

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
</tr>
<tr>
<td>INT-1</td>
</tr>
<tr>
<td>INT-2</td>
</tr>
<tr>
<td>High</td>
</tr>
</tbody>
</table>

Online calculator for MYSEC can be found at [http://mysec-pm.eu](http://mysec-pm.eu)

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Prognostic Impact of Mutations in PMF

**JAK2 V617F vs CALR vs triple negative**

Symptom Burden in MF
**Wide Range of Constitutional Symptoms**

- Fever
- Fatigue
- Depression & anxiety
- Bone pain
- Night sweats
- Sexual dysfunction
- Pruritus
- Concentration issues
- Early satiety
- Weight loss

**Constellation of MF signs and symptoms**


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**Assessing Symptoms in MF**

**MPN-SAF TSS (MPN-10)**

- **Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)**
  - 10-symptom assessment scale for MPNs
  - Each symptom is rated on a 0 to 10 scale from absent (0) to worst imaginable (10)
  - Total possible score: 100

- **Symptom**
  - **1 to 10 (0 if absent) ranking**
  - 1 is most favorable and 10 least favorable

- **Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours**
  - (No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

- **Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1 to 10 (0 if absent) ranking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filling up quickly when you eat (early satiety)</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Inactivity</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Problems with concentration-compared to prior to my MPD</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Night sweats</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Itching (pruritus)</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Bone pain (diffuse not joint pain or arthritis)</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Fever (&gt;&gt;100 F)</td>
<td>[Table values]</td>
</tr>
<tr>
<td>Unintentional weight loss last 6 months</td>
<td>[Table values]</td>
</tr>
</tbody>
</table>

### Case RH: TSS and Risk Stratification

<table>
<thead>
<tr>
<th>MPN-SAF TSS and Clinical Parameters</th>
<th>Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (24 h)</td>
<td>4</td>
</tr>
<tr>
<td>Early satiety</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
</tr>
<tr>
<td>Inactivity</td>
<td>1</td>
</tr>
<tr>
<td>Concentration</td>
<td>0</td>
</tr>
<tr>
<td>Night sweats</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>0</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
<td>0</td>
</tr>
<tr>
<td><strong>TSS</strong></td>
<td><strong>5</strong></td>
</tr>
</tbody>
</table>

#### MIPSS-70+ V 2.0

<table>
<thead>
<tr>
<th>Prognostic Variable</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe anemia (Hgb &lt; 8 g/dL women, &lt; 9 g/dL men)</td>
<td>0</td>
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<tr>
<td><strong>Moderate anemia (Hgb 8–9.9 g/dL women, 9–10.9 g/dL men)</strong></td>
<td><strong>1</strong></td>
</tr>
<tr>
<td>Circulating blasts ≥ 2%</td>
<td>0</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>0</td>
</tr>
<tr>
<td>Absence of CALR type 1 mutation</td>
<td>0</td>
</tr>
<tr>
<td>High molecular risk (HMR) mutations</td>
<td>0</td>
</tr>
<tr>
<td>≥ 2 HMR mutations</td>
<td>0</td>
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<tr>
<td>Unfavorable karyotype</td>
<td>0</td>
</tr>
<tr>
<td>Very high-risk (VHR) karyotype</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td><strong>1</strong></td>
</tr>
</tbody>
</table>

**MIPSS70+ V 2.0 Risk Category**

- **Low (10-y OS = 56%)**

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### NCCN Guidelines

**Recommended Treatments for Lower Risk MF**

[www.NCCN.org](http://www.NCCN.org)
Case: RH

Initial Management and Follow-Up

- Diagnosis and baseline status
  - Primary MF with CALR mutation
  - Baseline TSS = 5
  - MIPSS-70+ risk category = Low

- Initial management
  - RH chooses watchful waiting with a follow-up visit in 6 months

- Changes at follow-up visit
  - Anemia has progressed
  - Now reporting some symptoms (mild night sweats and bone pain)

Current labs:
- Hgb = 7.9 g/dL
- PLT = 168 × 10⁹/L
- Differential = 1% blasts
- EPO = 550 mU/mL

BM biopsy:
- Mutation = CALR
- Hypercellular and atypical MK
- Blasts <5% by IHC
- Fibrosis = grade 2
- Karyotype = 46,XX

NGS:
Mutation = CALR, TET2

What would RH’s MIPSS-70+ risk group be now?

A. Low
B. Intermediate
C. High
D. Very high
What would RH’s MIPSS-70+ risk group be now?

A. Low
B. Intermediate
C. High
D. Very high

Case RH: **TSS and Risk Stratification**

<table>
<thead>
<tr>
<th>MPN-SAF TSS and Clinical Parameters</th>
<th>BL</th>
<th>6-Mo f/u</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue (24 h)</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Early satiety</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Inactivity</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Concentration</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Night sweats</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Unintentional weight loss</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>TSS</strong></td>
<td><strong>5</strong></td>
<td><strong>15</strong></td>
</tr>
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<td>0</td>
</tr>
<tr>
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<td>0</td>
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<tr>
<td><strong>Total Score</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

**MIPSS70+ V 2.0 Risk Category**

**INT (10-y OS = 37%)**
Impact and Management of Anemia in Myelofibrosis

Anemia in Myelofibrosis: Pathogenesis

Figure 1. The pathogenesis of anemia in myelofibrosis is the result of a multifactorial process, which is only partially understood. The relative contributions of each of the above etiologies vary from patient to patient, and this variability in pathogenesis may explain the variability in responses to different therapeutic modalities. RBC = red blood cell.

Anemia in MF

- Anemia presents in 35% to 54% of patients at diagnosis\(^1\)
- ~50% of patients with MF require ≥6 RBC transfusions/year
- Independent prognostic risk factor for leukemic transformation\(^2,3\)
- Up to 46% of patients become dependent on RBC transfusions within 1 year of diagnosis\(^4,5\)

**Proportion of patients with anemia**

<table>
<thead>
<tr>
<th>Percentage of patients</th>
<th>Diagnosis</th>
<th>≤1 year</th>
<th>&gt;1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>435</td>
<td>1,210</td>
<td>1,508</td>
</tr>
<tr>
<td>20</td>
<td>330</td>
<td>650</td>
<td>988</td>
</tr>
<tr>
<td>30</td>
<td>309</td>
<td>435</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>309</td>
<td>435</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>309</td>
<td>435</td>
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<td>60</td>
<td>309</td>
<td>435</td>
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</tr>
<tr>
<td>70</td>
<td>309</td>
<td>435</td>
<td></td>
</tr>
</tbody>
</table>

**RBC transfusions per patient/yr (2019)**

<table>
<thead>
<tr>
<th>No. of transfusions/yr</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,210</td>
</tr>
<tr>
<td>2</td>
<td>650</td>
</tr>
<tr>
<td>3</td>
<td>435</td>
</tr>
<tr>
<td>4</td>
<td>330</td>
</tr>
<tr>
<td>5</td>
<td>309</td>
</tr>
<tr>
<td>6</td>
<td>1,508</td>
</tr>
<tr>
<td>7</td>
<td>988</td>
</tr>
</tbody>
</table>

JAKi, JAK inhibitor; MF, myelofibrosis; RBC, red blood cell; yr, year.

Anemia Is Associated With Worsened Overall Survival in MF

**OS stratified by degree of anemia\(^1\)**

- No anemia - median survival 7.9 years
- Mild anemia - median survival 4.9 years
- Moderate anemia – median survival 3.4 years
- Severe anemia – median survival 2.1 years

**OS according to RBC transfusion dependency\(^2\)**

- Transfusion-independent
- Transfusion-dependent

NCCN Guidelines: Management of MF-Associated Anemia

www.NCCN.org

JAK Inhibitor Options Higher Risk MF
NCCN Guidelines: Treatment for Higher Risk MF

www.NCCN.org

JAK Inhibitors: Kinome Mapping

<table>
<thead>
<tr>
<th></th>
<th>IC$_{50}$ (nanomolar)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JAK1</td>
</tr>
<tr>
<td>Ruxolitinib$^{1,2}$</td>
<td>2.8</td>
</tr>
<tr>
<td>Fedratinib$^{1,3}$</td>
<td>105</td>
</tr>
<tr>
<td>Pacritinib$^{1,2,4}$</td>
<td>1280</td>
</tr>
<tr>
<td>Momelotinib$^{1,2,5}$</td>
<td>11</td>
</tr>
</tbody>
</table>

ACVR1, activin A receptor type 1; FLT3, FMS-like tyrosine kinase 3; IC$_{50}$, half-maximal inhibitory concentration; IRAK1, interleukin-1 receptor-associated kinase; TYK2, tyrosine kinase 2.

**Ruxolitinib**

<table>
<thead>
<tr>
<th>IC₅₀ (nanomolar)</th>
<th>JAK1</th>
<th>JAK2</th>
<th>JAK3</th>
<th>TYK2</th>
<th>ACVR1</th>
<th>IRAK1</th>
<th>FLT3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib¹-²</td>
<td>2.8</td>
<td>4.5</td>
<td>322</td>
<td>30</td>
<td>&gt;1000</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Fedratinib¹-³</td>
<td>105</td>
<td>3</td>
<td>&gt;1000</td>
<td>405</td>
<td>273</td>
<td>---</td>
<td>15</td>
</tr>
<tr>
<td>Pacritinib¹,²,⁴</td>
<td>1280</td>
<td>6.0</td>
<td>18.3</td>
<td>27</td>
<td>16.7</td>
<td>13.6</td>
<td>14.8</td>
</tr>
<tr>
<td>Momelotinib¹,²,⁵</td>
<td>11</td>
<td>18</td>
<td>155</td>
<td>17</td>
<td>52.5</td>
<td>---</td>
<td>401</td>
</tr>
</tbody>
</table>


**Ruxolitinib Phase III Trials: COMFORT-I and COMFORT-II**

**COMFORT-I: Randomized, double-blind, placebo-controlled, multicenter, phase III trial¹**

- Patients (≥18 yr) with int-2 or high-risk MF
- PMF, PPV-MF, or PET-MF
- PLT count ≥100,000
- Palpable spleen ≥5 cm
- PB <10%
- ECOG PS ≥3
- Refractory or intolerant to or not candidates for available therapy

N = 309

- **Primary endpoint:** Number of patients in whom ≥35% SVR was noted from baseline to week 24 as measured by MRI (or CT scan in applicable patients)
- **Secondary endpoints:** Proportion of patients with ≥50% reduction in TSS from baseline to week 24 as measured by the MFSAF 2.0, OS, duration of SVR

**COMFORT-II: Randomized, open-label, phase III trial²**

- PMF, PPV-MF, or PET-MF
- ≥18 yr
- Int-2 or high risk (IPSS)
- PLT count ≥100,000
- Palpable spleen ≥5 cm
- PB <10%
- ECOG PS ≥3

N = 219

- **Primary endpoint:** Number of patients with ≥35% SVR from baseline to week 48 as measured by MRI (or CT scan in applicable patients)
- **Key secondary endpoints:** ≥35% SVR from baseline to week 24, length of response, PFS, OS, and change in marrow morphology

**Ruxolitinib twice daily**

- 15 mg twice daily for PLT count 10⁰ to 200 × 10⁹/L
- 20 mg twice daily for PLT count >200 × 10⁹/L

n = 155

- Crossover for splenomegaly
  n = 30

**Placebo**

n = 154

**N = 1:1**

**Crossover for splenomegaly**

n = 18

**N = 2:1**

**Ruxolitinib twice daily**

- 15 mg twice daily for PLT count 10⁰ to 200 × 10⁹/L
- 20 mg twice daily for PLT count >200 × 10⁹/L

n = 146

**Crossover for splenomegaly**

n = 15

BAT, best available therapy; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group performance status; Int, intermediate; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PET-MF, postessential thrombocytopenia MF; PLT, platelet; PFS, progression-free survival; PMF, primary MF; PPV-MF, postpolycythemia vera MF; SVR, spleen volume reduction; TSS, Total Symptom Score.

COMFORT-I: Key Efficacy Endpoints

Primary endpoint: ≥35% SVR at 24 weeks

![Graph showing percent change from baseline for Ruxolitinib and Placebo groups.]

- 41.9% ruxolitinib vs 0.7% placebo had ≥35% SVR; P < .001

TSS at 24 weeks

![Graph showing percent change from baseline for Ruxolitinib and Placebo groups.]

- 50% Reduction

SVR responses were seen with ruxolitinib in JAK2 V617F-positive and JAK2 V617F-negative patients, relative to placebo.

OR, odds ratio.


COMFORT-I: Worst Hematologic Laboratory Test Abnormalities

<table>
<thead>
<tr>
<th>Hematologic Adverse Reactions</th>
<th>Ruxolitinib (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>Thrombocytopenia</td>
<td>69.7</td>
<td>12.9</td>
</tr>
<tr>
<td>Anemia</td>
<td>96.1</td>
<td>45.2</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.7</td>
<td>7.1</td>
</tr>
</tbody>
</table>

Hematologic adverse reactions rarely led to treatment discontinuation. The following percentages are from both phase III studies: anemia (0.3%), thrombocytopenia (0.7%), neutropenia (1.0%).

- Management of hematologic abnormalities:
  - **Thrombocytopenia**: Generally reversible; usually managed by reducing the dose or temporarily withholding ruxolitinib; if clinically indicated, platelet transfusions may be administered
  - **Anemia**: Some patients may require blood transfusions; dose modifications may also be considered
  - **Neutropenia (ANC <0.5 × 10^9/L)**: Generally reversible; managed by temporarily withholding ruxolitinib

ANC, absolute neutrophil count.

COMFORT-I: Mean Platelet Count and Hemoglobin Over Time


COMFORT-I: Spleen Volume and Symptom Scores

- Limited change from baseline in spleen volume and TSS with low-dose ruxolitinib\(^1,\text{a}\)
- Long-term maintenance with low-dose ruxolitinib has not shown responses in patients with myelofibrosis\(^2\)


---

**Spleen volume at week 24 by ruxolitinib dose\(^1\)**

<table>
<thead>
<tr>
<th>Ruxolitinib dose</th>
<th>Median change from baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-5.2</td>
</tr>
<tr>
<td>≤5 mg BID</td>
<td>-10.4</td>
</tr>
<tr>
<td>10 mg BID</td>
<td>-30.8</td>
</tr>
<tr>
<td>15 mg BID</td>
<td>-35.9</td>
</tr>
<tr>
<td>20 mg BID</td>
<td>-38.4</td>
</tr>
<tr>
<td>25 mg BID</td>
<td>-40.9</td>
</tr>
</tbody>
</table>

**TSS at week 24 by ruxolitinib dose\(^2\)**

<table>
<thead>
<tr>
<th>Ruxolitinib dose</th>
<th>Median change from baseline, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>-14.6</td>
</tr>
<tr>
<td>≤5 mg BID</td>
<td>-17.5</td>
</tr>
<tr>
<td>10 mg BID</td>
<td>-71.1</td>
</tr>
<tr>
<td>15 mg BID</td>
<td>-69.6</td>
</tr>
<tr>
<td>20 mg BID</td>
<td>-67.7</td>
</tr>
<tr>
<td>25 mg BID</td>
<td>-66.2</td>
</tr>
</tbody>
</table>
Case RH
New Management Approach

- Shared decision-making process
  - The options we discussed with RH were JAK inhibitors
  - First choice for her was ruxolitinib to address symptoms
  - RH’s treatment priority was improvement in symptoms and functionality
  - We chose ruxolitinib to balance symptom control and potential for worsening anemia

- Considerations in management approach
  - Starting dosage/ramp-up considerations: start low and titrate up to avoid significant anemia
  - Toxicity monitoring considerations: follow blood counts carefully, and transfuse RBC to support patient in first several months of treatment

Current labs:
- Hgb = 7.9 g/dL
- PLT = 168 x 10^9/L
- Differential = 1% blasts
- EPO = 550 mU/mL

BM biopsy:
- Mutation = CALR
- Fibrosis = grade 2
- Karyotype = 46,XX

NGS:
Mutation = CALR, TET2

Based on ruxolitinib labelling instructions, what would optimal/target dose of ruxolitinib be for RH with plt 168?

A. 5mg twice daily
B. 10mg twice daily
C. 15mg twice daily
D. 20mg twice daily
Based on ruxolitinib labelling instructions, what would optimal/target dose of ruxolitinib be for RH with plt 168?

A. 5mg twice daily
B. 10mg twice daily
C. 15mg twice daily
D. 20mg twice daily

Case RH
Response to Treatment

- Initial response at 3-month follow-up
  - RH is now feeling much better, with resolution of nights sweats and bone pain, and improvement in energy and activity level
  - Her Hgb has stabilized at 7.2 g/dL after initially requiring RBC transfusions
  - Her symptom burden is reduced (TSS = 2)
  - The plan is to continue ruxolitinib and follow up every 2 weeks

Current labs:
- Hgb = 7.9 g/dL
- PLT = 168 × 10⁹/L
- Differential = 1% blasts
- EPO = 550 mU/mL

BM biopsy:
- Mutation = CALR
- Fibrosis = grade 1
- Karyotype = 46,XX

NGS:
Mutation = CALR, TET2
**Ruxolitinib Discontinuation Over Time**

Approximately 50% of patients originally randomized to ruxolitinib remain on therapy at 3 years

COMFORT-I ruxolitinib discontinuation rates
- Year 1: 21%
- Year 2: 35%
- Year 3: 51%
- Year 5: 72%


**Outcomes After Ruxolitinib Discontinuation**

- Retrospective analysis of clonal evolution and outcomes after ruxolitinib discontinuation in an open-label phase I/II study (N = 56)

- Median OS = 14 mo
- Survival improved if baseline platelets ≥260 vs <260 × 10^9/L (HR = 2.7; P = .006)
- Survival improved if follow-up platelets ≥100 vs <100 × 10^9/L (HR = 4.1; P = .001)
- 35% of patients acquired a new mutation while on ruxolitinib, most commonly ASXL1

RUXOREL-MF (NCT03959371): An Ambispective Observational Study of Ruxolitinib-Treated Patients With MF

N = 209
Inclusion criteria
• ≥6 months of follow-up after RUX initiation
• Platelet count >50 × 10^9/L
• Spleen enlargement of at least 5 cm below the left costal margin
• IPSS intermediate-1 risk

RUX Dose at Treatment Initiation

<table>
<thead>
<tr>
<th>Dose</th>
<th>n</th>
<th>(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg BID</td>
<td>31</td>
<td>(14.8)</td>
</tr>
<tr>
<td>10 mg BID</td>
<td>45</td>
<td>(21.5)</td>
</tr>
<tr>
<td>15 mg BID</td>
<td>55</td>
<td>(26.3)</td>
</tr>
<tr>
<td>20 mg BID</td>
<td>78</td>
<td>(37.3)</td>
</tr>
</tbody>
</table>


3 Factors Predict Survival Benefit

RUX dose started
After 3 months
After 6 months
HR = 2.32
HR = 2.26
HR = 1.79

RBC transfusion needed
Spleen length reduction ≤30%
RUX dose <20 mg BID

Response to ruxolitinib after 6 months of treatment: RR6
Calculator at www.rr6.eu

Low risk Med. OS NR
Interm. risk Med. OS 61 mo.
High risk Med. OS 33 mo.

The RR6 model was validated in another cohort of patients (n = 40; P = .0276) treated with ruxolitinib at Moffitt Cancer Center.

COMFORT Studies: Ruxolitinib Overcomes Adverse Prognostic Effect of Anemia in MF

Anemia is not a contraindication for ruxolitinib use; Hgb changes on ruxolitinib treatment do not bear the same prognostic implications as Hgb changes that occur as a consequence of MF pathology.

Impact of Ruxolitinib on Survival in Real-Life Settings

OS in patients with newly diagnosed intermediate- to high-risk MF

10-year OS in PS-matched groups in the ERNEST study

Median OS with ruxolitinib vs HU: 6.7 vs 5.1 years; \( P = .001 \)
Case RH: no longer responding to ruxolitinib

RH had been taking ruxolitinib for 15 months with good response. She presents for a follow-up visit.

- Changes since previous visit
  - Previous spleen volume response is no longer being maintained; splenomegaly now at 9 below LCM
  - Anemia has worsened
  - PLT count has dropped below 100
  - Symptom burden has increased (night sweats, bone pains, spleen pressure)

Current labs:
- Hgb = 6.7 g/dL
- PLT = 40 × 10⁹/L
- Differential = 3% blasts

BM biopsy:
- Mutation = CALR
- Fibrosis = grade 2
- Karyotype = 46,XX

NGS:
Mutation = CALR, TET2

Based on NCCN guideline recommendations for patients with higher risk MF, which of the following could be considered for RH?

A. Fedratinib
B. Momelotinib
C. Pacritinib
D. Clinical trial
E. All of the above
Based on NCCN guideline recommendations for patients with higher risk MF, which of the following could be considered for RH?

A. Fedratinib
B. Momelotinib
C. Pacritinib
D. Clinical trial
E. All of the above

Fedratinib

<table>
<thead>
<tr>
<th></th>
<th>IC₅₀ (nanomolar)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>JAK1</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>2.8</td>
</tr>
<tr>
<td>Fedratinib</td>
<td>105</td>
</tr>
<tr>
<td>Pacritinib</td>
<td>1280</td>
</tr>
<tr>
<td>Momelotinib</td>
<td>11</td>
</tr>
</tbody>
</table>

**Fedratinib Clinical Trials: JAKARTA (phase III) and JAKARTA-2 (phase II)**

**JAKARTA: Phase III, randomized, double-blind, placebo-controlled trial**
- PMF, PPV-MF, or PET-MF
- Int-2 or high risk (IPSS)
- Palpable spleen ≥5 cm
- PLT count >50,000
- ECOG PS ≤2

N = 289

Fedratinib 500 mg daily
n = 97

Fedratinib 400 mg daily
n = 96

Placebo
n = 96

Crossover at 24 weeks**<sup>a</sup>
R 1:1

**JAKARTA-2: Phase II, single-arm, open-label, nonrandomized, multicenter study**
- PMF, PPV-MF, or PET-MF
- ≥18 yr
- Int-1, int-2, or high risk (IPSS)
- Palpable spleen ≥5 cm
- ECOG PS ≤2
- Resistant or intolerant to prior ruxolitinib
  - Ruxolitinib for ≥14 d
  - Resistant, 66%
  - Intolerant, 33%

N = 97

Fedratinib 400 mg daily

**Primary endpoint:** number of patients with ≥35% SVR from baseline to week 24 as measured by MRI (or CT scan in applicable patients)

**Key secondary endpoint:** proportion of patients with ≥50% reduction in TSS from baseline to week 24 as measured by the MFSAF 2.0

*Crossover prior to 24 weeks was permitted if patients experienced progressive disease as defined in the study protocol.


---

**Second-Line Fedratinib: Spleen Volume and Symptom Responses**

- Overall SVRR was 31% (95% CI: 22, 41) and symptom RR was 27% (95% CI: 18, 37)
- There was no statistically significant difference in SVRR or symptom RR between BL platelet count subgroups

**JAKARTA-2**

<table>
<thead>
<tr>
<th>BL platelet count</th>
<th>SVRR</th>
<th>Symptom RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 × 10⁹/L to &lt;100 × 10⁹/L</td>
<td>36.4% (95% CI: 20, 55)</td>
<td>38.7% (95% CI: 22, 58)</td>
</tr>
<tr>
<td>≥100 × 10⁹/L</td>
<td>28.1% (95% CI: 18, 41)</td>
<td>20.3% (95% CI: 11, 33)</td>
</tr>
</tbody>
</table>

Statistical comparisons between BL platelet count subgroups should be interpreted with caution due to small sample sizes.

RR, response rate; SVRR, spleen volume response rate.

## JAKARTA and JAKARTA-2: Safety

### Black Box Warning: Wernicke's Encephalopathy

### Adverse events occurring in JAKARTA\(^a\)

<table>
<thead>
<tr>
<th>Adverse Event, %(^a,1)</th>
<th>Fedratinib 400 mg (n = 96)</th>
<th>Placebo (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>66</td>
<td>16</td>
</tr>
<tr>
<td>Nausea</td>
<td>62</td>
<td>15</td>
</tr>
<tr>
<td>Anemia</td>
<td>40</td>
<td>14</td>
</tr>
<tr>
<td>Vomiting</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue or asthenia</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>10</td>
<td>4.2</td>
</tr>
</tbody>
</table>

### Adverse events occurring in JAKARTA-2

<table>
<thead>
<tr>
<th>TEAEs Reported in &gt;10% of Patients</th>
<th>ITT Population (N = 97)(^a)</th>
<th>Any Grade, n (%)</th>
<th>Grade 3–4, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>60 (62)</td>
<td>4 (4)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>54 (56)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>47 (49)</td>
<td>37 (38)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26 (27)</td>
<td>21 (22)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>40 (41)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>20 (21)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Pruritus</td>
<td>17 (18)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (16)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>13 (13)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>13 (13)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>12 (12)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>12 (12)</td>
<td>2 (2)</td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>12 (12)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>11 (11)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>11 (11)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>11 (11)</td>
<td>1 (1)</td>
<td></td>
</tr>
</tbody>
</table>

### Pacritinib

<table>
<thead>
<tr>
<th>IC(_{50}) (nanomolar)</th>
<th>JAK1</th>
<th>JAK2</th>
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<td>30</td>
<td>&gt;1000</td>
<td>---</td>
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<tr>
<td>Fedratinib(^1-3)</td>
<td>105</td>
<td>3</td>
<td>&gt;1000</td>
<td>405</td>
<td>273</td>
<td>---</td>
<td>15</td>
</tr>
<tr>
<td>Pacritinib(^1,2,4)</td>
<td>1280</td>
<td>6.0</td>
<td>18.3</td>
<td>27</td>
<td>16.7</td>
<td>13.6</td>
<td>14.8</td>
</tr>
<tr>
<td>Momelotinib(^1,2,5)</td>
<td>11</td>
<td>18</td>
<td>155</td>
<td>17</td>
<td>52.5</td>
<td>---</td>
<td>401</td>
</tr>
</tbody>
</table>

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Pacritinib: Selective JAK2, ACVR1, and IRAK1 Inhibitor

- Pacritinib is an oral JAK2, ACVR1, and IRAK1 inhibitor approved in 2022 for intermediate- or high-risk primary or secondary MF with platelet counts $<50 \times 10^9/L^1$
- Pacritinib has high selectivity for JAK2 over JAK3 and TYK2 and does not inhibit JAK1; this inhibitory profile results in minimal exacerbation of thrombocytopenias$^2$
- Pacritinib also strongly inhibits ACVR1, thus enhancing erythropoiesis and reducing transfusion dependence$^3$
- PERSIST-1 and PERSIST-2: phase III studies of pacritinib in 430 patients with MF$^1,4,5$
- Most frequent nonhematologic AEs: diarrhea, nausea, and peripheral edema$^1$

AE, adverse event.

Phase III Pacritinib Trials: PERSIST-1 and PERSIST-2

**PERSIST-1**$^1$

- **Key eligibility criteria**
  - Primary MF/secondary MF
  - No exclusion for baseline platelets
  - No prior JAK2 inhibitors allowed

- **Protocol**
  - 2:1 ratio ($n = 327$)

- **Study drugs**
  - Pacritinib 400 mg daily
  - BAT (excluding ruxolitinib)

**PERSIST-2**$^2$

- **Key eligibility criteria**
  - Primary MF/secondary MF
  - Platelets $\leq 100 \times 10^9/L$
  - Prior JAK2 inhibitors allowed

- **Protocol**
  - 1:1 ratio ($n = 311$)

- **Study drugs**
  - Pacritinib 200 mg twice daily
  - BAT (including ruxolitinib)

**Primary endpoint (week 24):**
- Percentage of patients with $\geq 35\%$ SVR

**Secondary endpoint:**
- Percentage of patients with $\geq 50\%$ reduction in TSS

**Co-primary endpoints (week 24):**
- Percentage of patients with $\geq 35\%$ SVR and
- Percentage of patients with $\geq 50\%$ reduction in TSS

PERSIST-2: Spleen Volume Responses ≥35% at Week 24

ITT population

![Graph showing ITT population with PAC 200 mg BID and BAT showing 22% vs 3% respectively with a p-value of .001.]

Patients with platelets <50 × 10⁹/L

![Graph showing patients with platelets <50 × 10⁹/L with PAC 200 mg BID and BAT showing 29% vs 3% respectively.]

Additional subgroup analyses demonstrated patients receiving pacritinib had SVR ≥35% regardless of subgroup (eg, sex, age, JAK2 V617F mutation status, prior treatment with JAK2 inhibitors, and baseline cytopenias)

ITT, intention-to-treat; PAC, pacritinib.

PERSIST-2: Hematologic Stability

Clinical improvement in hemoglobin levels in patients with baseline anemia

Baseline to week 24

![Graph showing clinical improvement in hemoglobin levels with PAC 200 mg BID and BAT showing 25% vs 12% respectively.]

Pacritinib reduced transfusion burden in patients not TI at baseline

Baseline to week 24

![Graph showing pacritinib reduced transfusion burden with PAC 200 mg BID and BAT showing 22% vs 9% respectively.]

Transfusion burden in patients who received ≥1 RBC transfusion on study

Units per month

Baseline to week 24

![Graph showing transfusion burden with PAC 200 mg BID and BAT showing 1.06 vs 0.67 respectively at week 24.]

TI defined according to Gale criteria (0 units over the course of 12 weeks).
*aInternational Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks prior; anemia defined as hemoglobin <10 g/dL.
T1 transfusion independent.
More Pacritinib Patients Had TI (Gale criteria)

**TI Conversion Rate**

<table>
<thead>
<tr>
<th></th>
<th>Pacritinib</th>
<th>BAT</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 41</td>
<td>37%</td>
<td>7%</td>
<td>.001</td>
</tr>
</tbody>
</table>

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
- Erythroid support agents were prohibited on the pacritinib arm

**Rate of TI (Gale criteria) through Week 24**

63

Improved Quality of Life Associated With 200 mg BID Pacritinib

64

- 56% reported “much improved” or “very much improved” in the 200-mg BID pacritinib arm
- 13% reported “much worse” in the BAT arm
PERSIST-2: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PAC 200 mg BID (n = 106)</th>
<th>BAT (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade AEs in &gt;15% of patients in either arm, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>48</td>
<td>15</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>34</td>
<td>24</td>
</tr>
<tr>
<td>Nausea</td>
<td>32</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>20</td>
<td>15</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>17</td>
<td>3</td>
</tr>
</tbody>
</table>

Grade ≥3 AEs in >5% of patients in either arm, %

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PAC 200 mg BID (n = 106)</th>
<th>BAT (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>32</td>
<td>18</td>
</tr>
<tr>
<td>Anemia</td>
<td>22</td>
<td>14</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>7</td>
<td>10</td>
</tr>
</tbody>
</table>

Serious AEs in >3% of patients in either arm, %

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PAC 200 mg BID (n = 106)</th>
<th>BAT (n = 86)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>

- Diarrhea with pacritinib most often occurred during weeks 1 through 8, was manageable, and resolved within 1 to 2 weeks
- Neurologic AEs and opportunistic infections rarely reported with pacritinib
- Safety outcomes with pacritinib were similar for those with <50 × 10⁹/L vs 50 to 100 × 10⁹/L platelets at baseline

Grade ≥3 events (pooled⁴)

- Bleeding
  - PAC 200 mg BID: 7%
  - BAT: 14%

- Cardiac
  - PAC 200 mg BID: 7%
  - BAT: 9%

Risk-Adjusted AEs of Interest

<table>
<thead>
<tr>
<th>Patients With Events per 100 Patient-Years at Risk</th>
<th>PAC203</th>
<th>PAC</th>
<th>BAT</th>
<th>BAT = RUX</th>
<th>Pooled PAC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cancers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy – excluding leukemic transformation⁴</td>
<td>0 (0/29.6)</td>
<td>8 (5/63.7)</td>
<td>7 (3/40.8)</td>
<td>11 (2/17.8)</td>
<td>5 (5/93.3)</td>
</tr>
<tr>
<td>Nonmelanoma skin cancer⁶</td>
<td>0 (0/29.6)</td>
<td>5 (3/64.2)</td>
<td>7 (3/40.8)</td>
<td>11 (2/17.8)</td>
<td>3 (3/93.8)</td>
</tr>
<tr>
<td><strong>Viral infections</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral infection⁵</td>
<td>7 (2/29.2)</td>
<td>5 (3/65.1)</td>
<td>12 (5/41.1)</td>
<td>11 (2/18.3)</td>
<td>5 (5/94.3)</td>
</tr>
<tr>
<td>Zoster⁶</td>
<td>0 (0/29.6)</td>
<td>0 (0/65.7)</td>
<td>2 (1/41.5)</td>
<td>6 (1/18.3)</td>
<td>0 (0/95.3)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>10 (3/29.1)</td>
<td>5 (3/64.1)</td>
<td>12 (5/40.8)</td>
<td>6 (1/18.3)</td>
<td>6 (6/93.1)</td>
</tr>
</tbody>
</table>

Risk-adjusted incidence rate calculated on the basis of exposure-adjusted incidence per 100 patient-years:

100 × (number of patients with an event/total patient-years at risk of the event)

- For patients with no event: (date last dose – date first dose) + 1/365.25
- For patients with an event: (date event – date first dose) + 1/365.25

*Includes all events within the Systems Order Class (SOC) "Neoplasms benign, malignant, and unspecified," excluding acute leukemia, myelofibrosis, and benign tumors; ⁴Includes basal cell and squamous cell carcinoma of the skin, as determined by medical review; ⁵Includes any infection event attributed to a specific virus (eg, cytomegalovirus reactivation, herpes keratitis), or described as being "viral" (eg, viral gastroenteritis, viral upper respiratory tract infection), as determined by medical review; ⁶Includes any infection event relating to "zoster" or "shingles," as determined by medical review.

PACIFICA: Phase III Pacritinib Trial – Enrollment Completed in United States (ongoing outside United States)

Key eligibility criteria
- Primary MF or secondary MF
- Platelet count <50 × 10^9/L
- DIPSS int-1, int-2, or high-risk disease
- Palpable splenomegaly ≥5 cm
- TSS ≥10 on MPN-SAF TSS 2.0
- ECOG PS 0–2
- Prior JAK inhibitor for ≤90 days allowed (or low-dose ruxolitinib for ≤180 days)

Primary endpoint:
SVR at 24 weeks

Secondary endpoints:
TSS at 24 weeks
OS
PGIC at 24 weeks

Physician’s choice includes any 1 of the following: low-dose ruxolitinib, corticosteroids, hydroxyurea, danazol. Investigators may select individual physician’s choice agents but cannot combine agents or give them sequentially; Crossover not permitted.

PGIC, Patient Global Impression of Change.

Momelotinib

<table>
<thead>
<tr>
<th></th>
<th>IC_{50} (nanomolar)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>JAK1</td>
</tr>
<tr>
<td>Ruxolitinib^{1,2}</td>
<td>2.8</td>
</tr>
<tr>
<td>Fedratinib^{1,3}</td>
<td>105</td>
</tr>
<tr>
<td>Pacritinib^{1,2,4}</td>
<td>1280</td>
</tr>
<tr>
<td>Momelotinib^{1,2,5}</td>
<td>11</td>
</tr>
</tbody>
</table>

Momelotinib: Emerging JAK1, JAK2, and ACVR1 Inhibitor

- Momelotinib is an inhibitor of JAK1, JAK2, and ACVR1 that recently received FDA approval\(^1,2\)
- SIMPLIFY-1 and SIMPLIFY-2: completed phase III trials of momelotinib in first-line and second-line settings\(^1,2\)
- MOMENTUM: ongoing phase III trial comparing momelotinib to danazol for MF with anemia\(^3\)
- Most frequent nonhematologic AEs: diarrhea, nausea, and asthenia/fatigue\(^3\)

---

Momelotinib Is a JAK1/JAK2 Inhibitor

**Momelotinib noninferior for spleen reduction but NOT noninferior for symptom improvement**

SRR, spleen response rate.

Momelotinib is a JAK1/JAK2 Inhibitor

Momelotinib was superior in terms of symptom response but not superior in terms of spleen response.


Momelotinib vs Danazol in Symptomatic, Anemic, JAKi-Experienced Patients: MOMENTUM Study

Previously treated with JAKi
Symptomatic (TSS ≥10)
Anemic (Hgb <10 g/dL)
Platelets ≥250 × 10⁹/L

Patients
N = 195

2:1 randomization
JAKi taper/washout ≥21 days

Double-blind treatment
Open-label crossover
Long-term follow-up

Day 1
MBB 200 mg daily + PBO
DAN 600 mg daily + PBO

Week 24

PBO, placebo.
**MOMENTUM: Transfusion Independence at Week 24**

*P = .0064 (noninferior)*

**Double-blind randomization period**

- **Momelotinib**
- **Danazol**

**Open-label period**

- **Momelotinib**
- **Danazol → Momelotinib**

**Transfusion independence rate, %**

<table>
<thead>
<tr>
<th>Transfusion independence rate, %</th>
<th>Baseline</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib (N = 130)</td>
<td>13%</td>
<td>20%</td>
</tr>
<tr>
<td>Danazol (N = 65)</td>
<td>15%</td>
<td>31%</td>
</tr>
</tbody>
</table>

**Mean hemoglobin levels (g/dL)**

<table>
<thead>
<tr>
<th>Weeks since randomization</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>0.00</td>
</tr>
<tr>
<td>8</td>
<td>0.00</td>
</tr>
<tr>
<td>12</td>
<td>0.00</td>
</tr>
<tr>
<td>16</td>
<td>0.00</td>
</tr>
<tr>
<td>20</td>
<td>0.00</td>
</tr>
<tr>
<td>24</td>
<td>0.00</td>
</tr>
<tr>
<td>28</td>
<td>0.00</td>
</tr>
<tr>
<td>32</td>
<td>0.00</td>
</tr>
<tr>
<td>36</td>
<td>0.00</td>
</tr>
<tr>
<td>40</td>
<td>0.00</td>
</tr>
<tr>
<td>44</td>
<td>0.00</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**No. of patients**

<table>
<thead>
<tr>
<th></th>
<th>Momelotinib</th>
<th>Danazol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>129</td>
<td>65</td>
</tr>
<tr>
<td>Week 24</td>
<td>105</td>
<td>54</td>
</tr>
</tbody>
</table>

**Mean hemoglobin levels (g/dL)**

<table>
<thead>
<tr>
<th>Weeks since randomization</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>4</td>
<td>0.00</td>
</tr>
<tr>
<td>8</td>
<td>0.00</td>
</tr>
<tr>
<td>12</td>
<td>0.00</td>
</tr>
<tr>
<td>16</td>
<td>0.00</td>
</tr>
<tr>
<td>20</td>
<td>0.00</td>
</tr>
<tr>
<td>24</td>
<td>0.00</td>
</tr>
<tr>
<td>28</td>
<td>0.00</td>
</tr>
<tr>
<td>32</td>
<td>0.00</td>
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<tr>
<td>36</td>
<td>0.00</td>
</tr>
<tr>
<td>40</td>
<td>0.00</td>
</tr>
<tr>
<td>44</td>
<td>0.00</td>
</tr>
<tr>
<td>48</td>
<td>0.00</td>
</tr>
</tbody>
</table>


---

**Momelotinib Survival and Safety**


---

**Table 3**

<table>
<thead>
<tr>
<th>Event</th>
<th>Group</th>
<th>Any grade</th>
<th>Grade ≥ 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-haematological abnormalities</td>
<td>Momelotinib-group (n=130)</td>
<td>71 (54%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>48 (37%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (8%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>8 (6%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>48 (37%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (28%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>31 (23%)</td>
<td>0 (0%)</td>
<td>1 (1%)</td>
</tr>
</tbody>
</table>

**Non-exhaustive list of haematological abnormalities**

- Anaemia
- Thrombocytopenia
- Neutropenia

**Data are n (%).** *Non-haematological abnormalities are based on laboratory values. The data shown are for events of the worst grade during the 24-week randomised treatment phase of the study regardless of whether this grade was a change from baseline.*

**Figure 3**

*Overall survival in the intention-to-treat population*

*Explanation: Mean estimates of overall survival in the intention-to-treat population from the time of randomisation to the data cutoff date (Dec. 3, 2023). The vertical line at week 24 indicates the transition between the double-blind randomization period and the open-label period when patients enrolling in the study started receiving open-label momelotinib treatment. P-value from a stratified rank test. HR (Momelotinib group vs Danazol group) from a stratified Cox proportional hazards model with a simple factor of treatment group and stratified by baseline covariates. N=not estimable.*

Case RH  
Change in Management

- New approach to management
  ▪ We chose to switch her to pacritinib 200 mg BID to address worsening anemia and thrombocytopenia, symptoms, and spleen volume

- Considerations in management approach
  ▪ **Approach to transition**: immediate switch; taper/ramp up is not needed due to poor disease control at current dosage
  ▪ **Dose modification considerations**: use full dose
  ▪ **Initial response at 3-month follow-up**
    ▪ RH’s symptoms have decreased significantly (TSS = 4)
    ▪ Her spleen volume has decreased by 40%; Hgb is 8.1 g/dL; PLT are 65K
    ▪ The plan is to continue pacritinib and follow up in 1 month

**Current labs:**
- Hgb = 8.1 g/dL
- PLT = 65 × 10⁹/L
- Differential = 3% blasts

**BM biopsy:**
- Mutation = JAK2V617F
- Hypercellular, atypical MK
- <5% blasts by IHC
- Fibrosis = grade 2
- Karyotype = 46,XX

**NGS:**
Mutation = CALR, TET2

Novel Agents in Development for MF
Preclinical Evidence Translates to the Clinic

- Aberrant trafficking of CD34+ MPN HSC
- Constitutive JAK-STAT signaling
- Epigenetic deregulation
- Elevated levels of IL-8
- Increased NFκB activity
- Increased BCL-2/XL expression
- Reduced TP53 activity (increased MDM2 expression)
- Constitutive telomerase expression in CD34+ MPN cells


Patient-centric Care Team

The Leukemia & Lymphoma Society

Navigator
Physician
Radiologist
Psychologist
Registered Dietitian
Pharmacist
Advanced Practice Provider
Information Specialist
Hematopathologist
Social Worker
Nurse
Integrative Therapist
Family
Patient-Centric Care Team

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- **Reach out** Monday–Friday, 9 am to 9 pm ET
  - Phone: 800.955.4572
  - Live chat: [www.LLS.org/IRC](http://www.LLS.org/IRC)
  - Email: LLS.org/ContactUs
  - HCP Patient Referral Form: [www.LLS.org/HCPreferral](http://www.LLS.org/HCPreferral)
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  - www.LLS.org/Podcast
  - www.LLS.org/Booklets

- www.LLS.org/MPN

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    - Urgent Need
    - Patient Aid
    - Travel Assistance
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    - LLS Community Social Media Platform
    - First Connection Peer to Peer Program

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