Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

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Houston, Texas

Optimal Treatment of Myelofibrosis: Advances and Challenges

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MPN Disease Continuum: Shared Biology and Clinical Features

Polycythemia vera (PV)
Primary myelofibrosis (MF); Post-PV/ET MF
Essential thrombocythemia (ET)

MPN Subtype at Diagnosis | Estimated US prevalence per 100,000
--- | ---
ET | 44-57
PV | 10-57
Primary MF | 4-6

MPN Blast-phase; Acute myeloid leukemia

MPN Subtype at Diagnosis | 10-year Leukemic Transformation Rate
--- | ---
ET | 1%
PV | 0%
Primary MF | 25%
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Myelofibrosis: Disease Course and Complications

Early PMF
- Short term problem: vascular events
- Lead time: typically more than a decade

Overt PMF
- Post-ET/PV MF
- Progressive organomegaly
- Leukemic transformation
- MF related complications
- MF-related death

Post-ET/PV MF
- Progressive cytopenias
- Progressive organomegaly/EMH
- Progressive constitutional symptoms
- Leukemic transformation
- MF-related complications
- MF-related death

EMH=extramedullary hematopoiesis; ET=essential thrombocythemia; PMF=primary myelofibrosis; PV=polycythemia vera; PS=performance status; QOL=quality of life.

Assessment of Prognosis in MF

Prognostic Models of Myelofibrosis

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Distribution of Myelofibrosis Patients by the Different Prognostic Models

Prognosis: Impact of Driver and “High Molecular Risk” Non-Driver Mutations in PMF

MIPSS70 and MIPSS70-plus*
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Once We Are Done with Prognostication: “Clinical Needs” Oriented Current Therapy for MF

<table>
<thead>
<tr>
<th>Clinical need</th>
<th>Drugs/Intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>• Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>• Danazol</td>
</tr>
<tr>
<td></td>
<td>• Erythropoietin</td>
</tr>
<tr>
<td></td>
<td>• Thalidomide</td>
</tr>
<tr>
<td></td>
<td>• Lenalidomide</td>
</tr>
<tr>
<td>Symptomatic splenomegaly</td>
<td>• Ruxolitinib, fedratinib</td>
</tr>
<tr>
<td></td>
<td>• Hydroxyurea</td>
</tr>
<tr>
<td></td>
<td>• Cladribine, IMIDs</td>
</tr>
<tr>
<td></td>
<td>• Splenectomy</td>
</tr>
<tr>
<td>Extramedullary hematopoiesis</td>
<td>• Radiation therapy</td>
</tr>
<tr>
<td>Hyperproliferative (early) disease</td>
<td>• Interferon</td>
</tr>
<tr>
<td>Risk of thrombosis</td>
<td>• Low-dose ASA</td>
</tr>
<tr>
<td>Constitutional symptoms/QoL</td>
<td>• Ruxolitinib, fedratinib</td>
</tr>
<tr>
<td></td>
<td>• Corticosteroids</td>
</tr>
<tr>
<td>Accelerated/blastic Phase</td>
<td>• Hypomethylating agents</td>
</tr>
<tr>
<td>Improved survival</td>
<td>• allo SCT</td>
</tr>
<tr>
<td></td>
<td>• Ruxolitinb</td>
</tr>
</tbody>
</table>


MPN10 (Total Symptom Score)
An Easy Tool to Assess Symptoms in MPNs


What Does Ruxolitinib Do?

Patient Pre-Ruxolitinib Therapy
After 2 Months of Therapy

It is good for spleen and symptoms

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Ruxolitinib in IPSS-1 Patients
Higher Response Rate and Lower Toxicities

<table>
<thead>
<tr>
<th>Disease State</th>
<th>Spleen Response at Month 24</th>
<th>Incidence of Anemia</th>
<th>Incidence of Thrombocytopenia</th>
<th>Incidence of Infections</th>
<th>Incidence of Infections</th>
<th>Incidence of Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-2 and high-risk patients</td>
<td>55.9%</td>
<td>67%</td>
<td>13%</td>
<td>&gt;50%</td>
<td>30%</td>
<td></td>
</tr>
<tr>
<td>Intermediate-1-risk patients</td>
<td>36.9%</td>
<td>28.5%</td>
<td>11%</td>
<td>40%</td>
<td>19.9%</td>
<td></td>
</tr>
</tbody>
</table>

IPSS intermediate-1 patients may possibly achieve higher response rates and experience lower toxicities than patients with higher-risk disease.

Let’s Talk About Something Else…

Spleen Response Affects Outcomes of Ruxolitinib-Treated Patients With MF

Multicenter study (N = 234)²

Baseline factors associated with lower spleen response to RUX include High/Int-2 disease severity, spleen size >20 cm; high WBC; delay in RUX start after diagnosis, and titrated doses <10 mg BID.²,³
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Ruxolitinib Efficacy by Titrated Dose: COMFORT-I

- Avoid starting with low dose!
- If starting low, then ESCALATE quickly to maximum safe dose
- Doses less than 10 mg BID are not effective long term

Key Safety Issue: Myelosuppression of Ruxolitinib in COMFORT-I

Tips on Using Ruxolitinib

- Indicated for splenomegaly or MF-related symptoms (regardless of a risk of dying)
- Anemia is NOT contraindication
- Avoid ‘prophylactic underdosing’ - maintain maximum tolerated dose to achieve larger reductions in splenomegaly early during treatment
- Development of anemia DOES NOT affect benefits of JAK2 inhibitor
  - Manage anemia as alternative to early dose reductions
- Avoid abrupt interruption of ruxolitinib in patients responding well
- Be aware of rare possibility of opportunistic infections
- Monitor for skin cancer

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Type and Number of Mutations Predict Response to Ruxolitinib in MF

- ASXL1
- EZH2
- DNMT3

Bridging to Transplantation

ELN-EBMT Consensus

- Available evidence is not sufficient to recommend splenectomy as a standard pre-transplant procedure that should be decided on a case-by-case basis, preferably in controlled setting of registries or clinical trials.
- Pre-transplant JAK inhibitor therapy with ruxolitinib is indicated in patients with a symptomatic spleen and/or constitutional symptoms at least 2 months prior to allo-SCT; titrate to maximum tolerated dose then tapered in 5-7 days prior to and stopped day before conditioning.
- No recommendations on ruxolitinib post allo-SCT.

Outcomes in MF After Ruxolitinib Discontinuation

- Salvage therapy or re-challenge with ruxolitinib can provide responses after d/c.
- This continues to be an area of unmet clinical need in MF.
- Survival after ruxolitinib d/c poor, median 14 months.
- Shorter survival associated with low platelets at start (Plt <260 x 10^9/L; HR=2.7, P=0.006) and end of therapy (Plt <100 x 10^9/L; HR=4.1, P<0.001)
- 35% patients acquired a new mutation while receiving ruxolitinib; 61% ASXL1
- Patients showing clonal evolution had significantly shorter survival after d/c (6 vs 16 months, P=0.006)
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**JAKARTA: Phase 3 Study in the first line**

- Aged ≥18 years
- Diagnosis of
  - Primary MF
  - Post-PV MF
  - Post-ET MF
- Platelet count ≥50 x 10⁹/L
- High risk before randomization

**JAKARTA: Hematologic and Nonhematologic Events**

<table>
<thead>
<tr>
<th>Event</th>
<th>Fedratinib 400 mg (n = 96)</th>
<th>Grade 3 or 4</th>
<th>Fedratinib 500 mg (n = 97)</th>
<th>Grade 3 or 4</th>
<th>Placebo</th>
<th>Grade 3 or 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>63 (66)</td>
<td>5 (5)</td>
<td>54 (56)</td>
<td>5 (5)</td>
<td>15 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40 (42)</td>
<td>3 (3)</td>
<td>53 (55)</td>
<td>9 (9)</td>
<td>5 (5)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>61 (64)</td>
<td>0</td>
<td>49 (51)</td>
<td>6 (6)</td>
<td>14 (15)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>10 (10)</td>
<td>2 (2)</td>
<td>17 (18)</td>
<td>0</td>
<td>11 (12)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9 (9)</td>
<td>2 (2)</td>
<td>15 (16)</td>
<td>4 (4)</td>
<td>6 (6)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14 (15)</td>
<td>0</td>
<td>12 (13)</td>
<td>1 (1)</td>
<td>15 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15 (16)</td>
<td>6 (6)</td>
<td>10 (10)</td>
<td>5 (5)</td>
<td>9 (10)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Weight decrease</td>
<td>4 (4)</td>
<td>0</td>
<td>4 (4)</td>
<td>0</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>95 (99)</td>
<td>41 (43)</td>
<td>94 (98)</td>
<td>58 (60)</td>
<td>86 (91)</td>
<td>24 (25)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>60 (63)</td>
<td>16 (17)</td>
<td>55 (57)</td>
<td>26 (27)</td>
<td>48 (51)</td>
<td>9 (9)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>54 (57)</td>
<td>20 (21)</td>
<td>63 (66)</td>
<td>26 (27)</td>
<td>50 (52)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>45 (47)</td>
<td>6 (6)</td>
<td>51 (53)</td>
<td>15 (16)</td>
<td>18 (19)</td>
<td>3 (3)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>27 (28)</td>
<td>8 (8)</td>
<td>42 (43)</td>
<td>17 (18)</td>
<td>16 (17)</td>
<td>4 (4)</td>
</tr>
</tbody>
</table>

**JAKARTA-2: Open-Label Study in Patients with MF After Ruxolitinib Reanalysis at ASCO 2019**

- Aged ≥18 years
- Intermediate-2 or high-risk status
  - Primary MF
  - Post-PV MF
  - Post-ET MF
- Platelet count ≥50 x 10⁹/L
- Received RUX for ≥14 days prior to starting fedratinib
- Discontinued RUX for ≥14 days prior to starting fedratinib

**Fedratinib**
- Once daily, starting dose 400 mg
- Consecutive 4-week cycles

Reanalysis employed a more stringent definition of RUX failure:
- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n = 65, 82%) or intolerance (n = 14, 18%)

Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria:
- SVRR = 30%
- Symptoms RR = 27%
- Safety consistent with prior reports

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Thank You

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“Toward Improved Treatment Options”
JAK Therapy and Beyond in Clinical Trials

Rami S. Komrokji, MD
Professor of Medicine and Oncologic Sciences
University of South Florida College of Medicine
Vice, Chair, Malignant Hematology Department
Moffitt Cancer Center
Tampa, Florida

Optimizing Upfront Therapy

- Ruxolitinib is the standard of care for treatment of intermediate- and high-risk MF patients with splenomegaly and constitutional symptoms:
  - Where do other JAK inhibitors fit as first-line therapy and for who?
  - Can we make ruxolitinib better?
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JAK-2 Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Other Target</th>
<th>Phase</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>JAK-1</td>
<td>III</td>
<td>Approved</td>
</tr>
<tr>
<td>Fedratinib</td>
<td>FLT-3, RET</td>
<td>III</td>
<td>Approved</td>
</tr>
<tr>
<td>Pacritinib</td>
<td>FLT-3</td>
<td>III</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Momelotinib</td>
<td>JAK1, JNK1, TYK2, CDK2, RICJ2</td>
<td>III</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NS-018</td>
<td>SRC, FLT3, ABL</td>
<td>III</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>


Fedratinib in the Frontline

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Population</th>
<th>Response</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAKARTA-1</td>
<td>N = 289 Phase 3, randomized, placebo-controlled, 3-arm study (placebo, fedratinib 400 mg QD, fedratinib 500 mg QD)</td>
<td>Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥50×10^9/L, and splenomegaly</td>
<td>Spleen Fedratinib 400 mg: 36%</td>
<td>Gr 3/4 with placebo, fedratinib 400 mg, and fedratinib 500 mg: • Anemia 25%/43%/60% • Thrombocytopenia 9%/17%/27% • Diarrhea 0%/5%/5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TSS reduction &gt;50% Fedratinib 400 mg: 36%</td>
<td></td>
</tr>
<tr>
<td>JAKARTA-2</td>
<td>N = 309 Phase III, randomized, placebo-controlled</td>
<td>Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥100×10^9/L, and splenomegaly</td>
<td>Spleen 42%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TSS reduction &gt;50% 46%</td>
<td></td>
</tr>
<tr>
<td>JAKARTA-3</td>
<td>N = 219 Phase III, randomized, Ruxolitinib vs BAT</td>
<td>Patients ≥18 years with IPSS intermediate-2 or high-risk MF, platelet count ≥100×10^9/L, and splenomegaly</td>
<td>Spleen 32%</td>
<td>Gr 3/4 with ruxolitinib: • Anemia 42% • Thrombocytopenia 8%</td>
</tr>
</tbody>
</table>

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Pacritinib in the Frontline

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Population</th>
<th>Response</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>PERSIST-1</td>
<td>Phase 3 randomized, open-label</td>
<td>Eligible patients had intermediate- and high-risk MF, PPV-MF, or PET-MF, no platelets cutoff, and splenomegaly</td>
<td>Splenomegaly &gt;25%</td>
<td>Gr 3/4 with pacritinib: Anemia 17%, Thrombocytopenia 21%, Diarrhea 5%</td>
</tr>
<tr>
<td>PERSIST-2</td>
<td>Phase 3 randomized, open-label</td>
<td>Eligible patients had primary MF, PPV-MF, or PET-MF; ≤1 prior JAK2 inhibitors; and platelet counts ≤100K/µL</td>
<td>Splenomegaly and platelets</td>
<td>Gr 3/4 with pacritinib: Anemia 27%, Thrombocytopenia 31%, Diarrhea 5%</td>
</tr>
</tbody>
</table>

Momelotinib in the Frontline

Phase 3 trial in JAK inhibitor-naïve patients

<table>
<thead>
<tr>
<th>Efficacy Overview</th>
<th>Safety Overview</th>
</tr>
</thead>
<tbody>
<tr>
<td>Momelotinib (200 mg QD) 24 weeks</td>
<td>The most common grade ≥3 hematologic abnormalities in either group were thrombocytopenia and anemia</td>
</tr>
<tr>
<td>Ruxolitinib (20 mg Q2D) 24 weeks</td>
<td>Peripheral neuropathy 10%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Momelotinib</th>
<th>Ruxolitinib</th>
<th>Noninferior; (P = 0.011)</th>
<th>Noninferiority not met; (P = 0.98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35% reduction in spleen volume at week 24, %</td>
<td>26.5%</td>
<td>29%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% reduction in total symptom score, %</td>
<td>28.4%</td>
<td>42.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfusion rate, transfusion independence, and transfusion dependence were improved with momelotinib (all with nominal (P \leq 0.019))</td>
<td></td>
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</tr>
</tbody>
</table>

My Take on JAK Inhibitors in the Frontline

- Ruxolitinib remains the standard of care for intermediate and high-risk MF patients with platelets >100 x 10⁹/L
- Fedratinib has similar reported outcomes in terms of spleen response, less TSS score reduction, GI toxicity
- Pacritinib could become frontline choice for patients with thrombocytopenia
- Momelotinib could become a choice for patients with anemia
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Can We Make it Better: Ruxolitinib-based Therapy

<table>
<thead>
<tr>
<th>Partner</th>
<th>Mechanism of Action</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine</td>
<td>Histone deacetylase</td>
<td>II</td>
</tr>
<tr>
<td>Decitabine</td>
<td>Histone deacetylase</td>
<td>I</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>TGFRI inhibitor</td>
<td>II</td>
</tr>
<tr>
<td>Danazol</td>
<td>Androgen</td>
<td>II</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>IMD</td>
<td>II</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>IMD</td>
<td>II</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>IMD</td>
<td>II</td>
</tr>
<tr>
<td>PoloPa zta</td>
<td>IMD</td>
<td>II</td>
</tr>
<tr>
<td>HDAC inhibitors</td>
<td>HDAC</td>
<td>II</td>
</tr>
<tr>
<td>Zebularine</td>
<td>JAK</td>
<td>II</td>
</tr>
<tr>
<td>Bcl-2 inhibitors</td>
<td>Bcl-2</td>
<td>II</td>
</tr>
<tr>
<td>Parsaclisib</td>
<td>PI3Kδ</td>
<td>I</td>
</tr>
<tr>
<td>Lenvatinib</td>
<td>CDK4/6</td>
<td>II</td>
</tr>
<tr>
<td>CPI-0610</td>
<td>BET</td>
<td>I/II</td>
</tr>
</tbody>
</table>

Life Beyond Ruxolitinib

- Outcome after ruxolitinib failure is poor and MF treatment remains an unmet need:
  - What is ruxolitinib failure?
  - What is the role of other JAK inhibitors after ruxolitinib failure?
  - Are there any new drugs on the horizon?

Survival After Ruxolitinib Discontinuation Is Poor

Among 86 patients with MPN-MF who discontinued ruxolitinib in a phase 1/2 study:

- 35% died while taking ruxolitinib
- Median survival after discontinuation = 14 months
- Low platelet count* associated with shorter survival

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### Defining Ruxolitinib Failure: IWG

**Clinical Improvement (CI)**
The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia.

**Anemia Response**
- Transfusion-independent patients: a ≥ 20 g/L increase in hemoglobin level
- Transfusion-dependent patients: becoming transfusion-independent

**Spleen Response**
- A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable or
- A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥ 50%
- A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response
- A spleen response requires confirmation by MRI or computed tomography showing ≥ 35% spleen volume reduction.

**Symptoms Response**
A ≥ 50% reduction in the MPN-SAF TSS

**Progressive Disease**
- Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
- A ≥ 100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
- A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm
- Leukemic transformation confirmed by a bone marrow blast count of ≥ 20% or
- A peripheral blood blast content ≥ 20% associated with absolute blast count of ≥ 1 × 10^9/L that lasts at least 2 weeks

**Stable Disease**
Belonging to none of the above listed response categories

**Relapse**
No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
- Loss of anemia response persisting for at least 1 month or
- Loss of spleen response persisting for at least 1 month

---

### Defining Ruxolitinib Failure: Recent Clinical Trials

- **Refractory**: RUX Tx ≥ 3 mo with <10% SVR or <30% decrease in spleen size from BL
- **Relapsed**: RUX Tx ≥ 3 mo with regrowth, defined as <10% SVR or <30% decrease in spleen size from BL, following an initial response
- **Intolerant**: RUX Tx ≥ 28 d complicated by development of RBC transfusion requirement (≥2 units/mo for 2 mo); or grade ≥ 3 thrombocytopenia, anemia, hematoma/hemorrhage while on RUX
- **Suboptimal response**: ruxolitinib for ≥ 6 months with stable dose for ≥ 8 weeks. Palpable spleen >10 cm below left subcostal margin on physical examination or palpable spleen 5–10 cm below left subcostal margin on physical examination AND active symptoms of MF defined as 1 symptom score ≥ 5 or 2 symptom scores ≥ 3 each

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### Fedratinib as Second-line

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study Design</th>
<th>Population</th>
<th>Primary Outcome</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>JAKARTA-2</td>
<td>Single-arm, open-label, nonrandomized, phase 2, multicenter study</td>
<td>Ruxolitinib-resistant intermediate-risk intermediate, high-risk primary MF, post-ET/PV MF</td>
<td>Ruxolitinib-resistant</td>
<td>Discontinued due to AEs 19%</td>
</tr>
</tbody>
</table>

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JAKARTA-2 at ASCO 2019

- In the original JAKARTA-2 analysis, fedratinib demonstrated a 55% rate of ≥35% SVR in patients resistant or intolerant to RUX (≥14 days) per investigator assessment.
- Reanalysis employed a more stringent definition of RUX failure.

Main findings:
- 79/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (n = 65, 82%) or intolerance (n = 14, 18%).
- Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria:
  - SVRR = 30%
  - Symptoms RR = 27%

Pacritinib as Second-line

Momelotinib in Myelofibrosis: Simplify 2

Phase 3 trial in patients previously treated with ruxolitinib

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Momelotinib (n=104)</th>
<th>BAT (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥35% reduction in spleen volume at week 24 (n, %)</td>
<td>7 (7%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Proportion difference (95% confidence interval)</td>
<td>0.01 (0.09-0.10)</td>
<td>P = 0.90</td>
</tr>
</tbody>
</table>

Safety Overview:
- The most common grade ≥3 AEs were anemia (14% in the momelotinib group vs 14% in the BAT group), thrombocytopenia (7% vs 6%), and abdominal pain (1% vs 6%).
- Serious events were reported for 30% of patients in the momelotinib group and 23% of patients in the BAT group.
- Deaths due to AEs were reported for 6% of patients receiving momelotinib and 5% of patients receiving BAT.

Moving Beyond JAK Inhibitors

<table>
<thead>
<tr>
<th>Target</th>
<th>Agent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promotion of Apoptosis</td>
<td>SMAC-mimetics/AIP</td>
</tr>
<tr>
<td></td>
<td>BCL-2 inhibitors</td>
</tr>
<tr>
<td></td>
<td>LPSD1 inhibitors</td>
</tr>
<tr>
<td></td>
<td>XPO1 inhibitor</td>
</tr>
<tr>
<td></td>
<td>LCL-161</td>
</tr>
<tr>
<td></td>
<td>Navitoclax</td>
</tr>
<tr>
<td></td>
<td>MKT-768</td>
</tr>
<tr>
<td></td>
<td>Selinexor</td>
</tr>
<tr>
<td>Targeting Hematopoietic Stem Cell/Micro-environment</td>
<td>CD123</td>
</tr>
<tr>
<td></td>
<td>Tagraxofusp</td>
</tr>
<tr>
<td></td>
<td>PL-111</td>
</tr>
<tr>
<td>Modulation of TP53 Pathway</td>
<td>MDM2 antagonists</td>
</tr>
<tr>
<td></td>
<td>Ibasemutin</td>
</tr>
<tr>
<td></td>
<td>KRT-232</td>
</tr>
<tr>
<td>Targeting Fibrosis and Associated Cytokines</td>
<td>Pentaxin-2</td>
</tr>
<tr>
<td></td>
<td>PRM-151</td>
</tr>
<tr>
<td>Aurora Kinase Inhibition</td>
<td>LCL-161</td>
</tr>
<tr>
<td>Telomerase Inhibition</td>
<td>Navitoclax</td>
</tr>
<tr>
<td>Immunodomain and Extraterminal Protein Inhibition</td>
<td>BET -</td>
</tr>
<tr>
<td></td>
<td>CPI-0610</td>
</tr>
</tbody>
</table>


IMBARK Study: IMETELSTAT

- Study population
  - Int2/high-risk MF per DIPSS criteria
  - Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi
  - Subjects must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy and EITHER:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy
    - Worsening splenomegaly at any time after the start of JAKi therapy documented by:
      - Increase in spleen volume from nadir by 25% measured by MRI or CT
      - Increase in spleen size by palpation, CT, or ultrasound
  - Active symptoms of MF
  - Baseline measurable splenomegaly (palpable spleen 35 cm below LCM or ≥450 cm³ by MRI)
- Study design: phase II 2 doses 4.7 mg/kg q 3 weeks (n=48) and 9.4 mg/kg q 3 weeks (n=59)
  - 4.7 mg/kg arm closes and escalation allowed
  - Standard response criteria at week 24

*Adapted from IWG-MRT response criteria definition of progressive disease

SVR Per IRC at Week 24

- 6 (10.2%) subjects in the 9.4 mg/kg arm had ≥35% SVR at week 24
- 23 (37%) subjects in the 9.4 mg/kg arm had ≥10% SVR at week 24

At time of cut-off, 20 subjects in the 4.7 mg/kg and 44 subjects in the 9.4 mg/kg had week 24 MRI; however, ITT is used as denominator for percentages.
Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Symptom Response Based on TSS at Week 24

- 19 (32.2%) subjects in 9.4 mg/kg arm had ≥50% symptom response at week 24

Overall Survival (ITT) for Imetelstat at Different Dose Levels

- Median follow up: 27.4 months
- Median survival:
  - 19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg
  - 29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg

Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAK inhibitor or stem cell transplant and excluding subjects who were dose escalated or randomized after closure of the 4.7 arm), all generating similar results.

Median follow up: 27.4 months
Median survival:

- 19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg
- 29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg

Eligibility Criteria

IMbark Criteria

- Int-2/high-risk MF per DIPSS criteria
- Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
  - Subjects must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy and either of:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy or
    - Worsening splenomegaly at any time after the start of JAKi therapy documented by:
      - Increase in spleen volume from nadir by 25% measured by MRI or CT, or
      - Increase in spleen size by palpation, CT, or ultrasound
  - Active symptoms of MF
- Baseline measurable splenomegaly (palpable spleen ≥5 cm below LCM or ≥450 cm³ by MRI)

Real World Data (RWD) Criteria

- Collected from a single-center study at the Moffitt Cancer Center, patients who had discontinued ruxolitinib
- A closely matched cohort was identified using the guidelines for inclusion and exclusion criteria as defined in IMbark protocol
- Cohort consisted of patients with MF who had discontinued JAKi due to lack of time of response and were subsequently treated with BAT at the Moffitt Cancer Center from January 1998 to August 2018

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Statistically Significant Reductions in Risk of Death with Imetelstat Treatment Across Analyses

- Imetelstat conferred 65-67% lower risk of death compared to BAT in the unweighted analysis and per ATO and sIPTW weighting methods
- Results suggest favorable overall survival with imetelstat treatment when compared to closely matched RWD from patients treated with BAT


PRM-151 in MF: Study Design

- Open-label, randomized phase II trial
  - Primary endpoint: ORR by IWG consensus criteria for response to treatment in MF with myeloid metaplasia
  - Secondary endpoints: Safety, change in BM fibrosis, change in MPN-SAF score, PK

PRM-151 in MF

- Thirteen patients completed 72 weeks of treatment with PRM-151
  - PRM-151 well tolerated with few AEs (1 grade 3 and no grade 4 AEs)
  - Reductions in bone marrow fibrosis were observed at week 12 and sustained through week 72 (54%)
  - Median Hb level increased in pts with baseline Hb <10 g/L with decreased need for RBC transfusions; 5 patients had Hgb increase by 24% (3 out 5 became RBC TI)
  - Median platelet counts increased in patients with baseline plat <100 x 109/L with a decreased need for platelet transfusions. Among 9 patients with plat <100 x 109/L platelets increased by 37%
  - 62% experienced a symptom score reduction of >50% and 2 patients experienced >50% reduction in splenomegaly
- Stage 2 of study currently enrolling patients not eligible for ruxolitinib to receive single-agent PRM-151 4x week x 36 weeks with blind randomization to 3 different dosages with open-label extension option beyond 36 weeks

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My ASH 2019 Watch List

- Pacritinib
- BET inhibitors
- Navitoclax
- Luspatercept

Interactive Case Studies: Treatment Decisions After JAK Inhibitor “Failure”

Prithviraj Bose, MD
Associate Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

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Current Status: Ruxolitinib in MF

- A highly effective drug benefiting many patients
- Overall survival benefit with long-term follow up¹
- Anemia/thrombocytopenia may limit effective dosing; median duration of spleen response <3 years²,³
- Spleen response dose-dependent; correlates with survival⁴,⁵
- Resistance not due to mutations; ? due to “persistence”;⁶ re-challenge may help⁷
- Anemia due to rux not prognostically adverse;⁸ rux overcomes adverse prognosis of disease-related anemia⁹
- Prognosis after discontinuation is poor¹⁰,¹¹
- Definition of failure variable in clinical trials, unclear in clinical practice


Identification/Management of Progression/Resistance on Ruxolitinib

<table>
<thead>
<tr>
<th>Feature</th>
<th>Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spleen</td>
<td>Threshold: beyond baseline; ↑ by 5 cm, more symptomatic</td>
</tr>
<tr>
<td></td>
<td>Optimize dose of ruxolitinib</td>
</tr>
<tr>
<td></td>
<td>Switch to alternative JAK inhibitor (fedratinib now approved)</td>
</tr>
<tr>
<td></td>
<td>Consider splenectomy</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Review causes (eg, mood disturbance, other medications)</td>
</tr>
<tr>
<td></td>
<td>Optimize dose of ruxolitinib</td>
</tr>
<tr>
<td></td>
<td>Consider alternative treatments (eg, steroids, anthracyclines)</td>
</tr>
<tr>
<td></td>
<td>Switch to alternative JAK inhibitor (fedratinib now approved)</td>
</tr>
<tr>
<td>More anemia or thrombocytopenia</td>
<td>Exclude other causes (eg, drug-drug interaction)</td>
</tr>
<tr>
<td></td>
<td>Determine if it needs treating</td>
</tr>
<tr>
<td></td>
<td>Add EPO, danazol, low-dose thalidomide (50 mg/day)</td>
</tr>
<tr>
<td>Leukocytosis</td>
<td>Determine the threshold for treatment</td>
</tr>
<tr>
<td></td>
<td>Add hydroxyureaamide</td>
</tr>
<tr>
<td>Blasts</td>
<td>Threshold depends on rate of rise &lt;&lt; 10%/15%/20%</td>
</tr>
<tr>
<td></td>
<td>Expectant, consider adding HMA or newly JAK induction</td>
</tr>
</tbody>
</table>
**Ellen, an Older Patient Receiving Treatment for MF**

<table>
<thead>
<tr>
<th>Ellen is 75 years old, fit and active, with confirmed MF</th>
<th>She starts treatment with ruxolitinib</th>
<th>After at least 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>PS of 1</td>
<td>20 mg dose twice-daily</td>
<td>Rising splenomegaly</td>
</tr>
<tr>
<td>Constitutional symptoms, splenomegaly, normal platelets at baseline</td>
<td>She initially tolerates treatment well</td>
<td>Return of constitutional symptoms</td>
</tr>
</tbody>
</table>

**Case 1: Newer JAK Inhibitors an Option for Ellen**

- Ellen exhibits lack of response to ruxolitinib
- Use of fedratinib is an appropriate next step
- Emerging JAK inhibitors/clinical trials are likely treatment options in this setting
- Supported by JAKARTA-2 findings
- Other emerging JAK inhibitors with potential applications in this case include pacritinib (PERSIST-2) or momelotinib (SIMPPLY-2)
- Clinical trials (novel single agents or ruxolitinib-based combinations) also an option

**Towards a Consensus Definition of Ruxolitinib Failure: JAKARTA-2 Re-analysis at ASCO 2019**

- In the original JAKARTA-2 analysis, fedratinib demonstrated a 56% rate of ≥35% SVR in patients resistant or intolerant to RUX (≥14 days) per investigator assessment
- Reanalysis employed a more stringent definition of RUX failure
- Relapsed: Ruxolitinib treatment for ≥3 months with regrowth, defined as ≥10% SVR or ≥30% decrease in spleen size from baseline, following an initial response
- Refractory: Ruxolitinib treatment for ≥3 months with ≤10% SVR or ≥30% decrease in spleen size from baseline
- Intolerant: Ruxolitinib treatment for ≥28 days complicated by development of RBC transfusion requirement (≥2 units per month for ≥2 months), or grade 3 thrombocytopenia, anemia, hemorrhage and/or hemorrhage while receiving ruxolitinib

**Main Findings**

- SVR ≥35%: 78/97 enrolled patients (81%) met the more stringent criteria for RUX R/R (p = 66, 82%) or intolerance (p = 14, 18%)
- Clinically meaningful reductions in splenomegaly and symptom burden in patients with MF who met more stringent criteria
- DLIR = 50%
- Symptoms RR = 27%
- Safety consistent with prior reports

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Robert, a Patient on Long-Term Therapy With Ruxolitinib

Robert is a 70-year-old man diagnosed with MF 5 years earlier. Within the past 6 months, at the most recent clinic visit:

- 4.5-year treatment history of ruxolitinib
- Successful management of constitutional symptoms and splenomegaly
- Intermittent return of several constitutional symptoms (fatigue and joint/bone pain)
- Increasing spleen size (now 8 cm below costal margin)
- Falling counts (platelets now at 55 x 10⁹/L)

Case 2: Clinical Trial-Based Therapy

Robert is a candidate for second-line therapy, eager to pursue another option. Clinical trial-based therapy recommended:

- Many novel targeted strategies are being developed in clinical trials
- Options currently being assessed include bromodomain inhibitors (CPI-0610), MDM2 inhibitors (KRT-232), LSD1 inhibitors (IMG-7289), therapies targeting CD123 (tagraxofusp), etc.
- The telomerase inhibitor imetelstat, the anti-fibrotic agent PRM-1512 and the AURKA inhibitor alisertib have been studied in the post-ruxolitinib setting

IMBARK™ Trial: Major Inclusion Criteria

- Int-2/high-risk MF per DIPSS criteria
- Relapsed or refractory to JAKI defined as documented progressive disease during or after JAKI:
  - Patients must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKI therapy and EITHER:
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      - Increase in spleen size by palpation
- Active symptoms of MF
- Baseline measurable splenomegaly (palpable spleen ≥5 cm below LCM or ≥450 cm³ by MRI)

Improving Patient Outcomes in Myelofibrosis: Writing the Next Chapter in the JAK Inhibitor Story

Overall Survival (ITT) for Imetelstat at Different Dose Levels

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Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAKi or stem cell transplant and excluding patients who were dose escalated or randomized after closure of the 4.7 mg/kg arm), all generating similar results.


JAK2 Inhibitor “Persistence” and Ruxolitinib Re-challenge

- Unlike CML, mutations impairing TKI binding have not been described
- Type 1 JAK2 inhibitors are ATP-competitive and bind the kinase in its active conformation
- Signaling may continue unabated (i.e., “persist”) via heterodimerization of activated JAK2 with another member of the JAK family (JAK1 or TYK2) despite the presence of a type 1 JAK2 inhibitor
- May be reversed by temporary withdrawal of the drug and by type 2 JAK2 inhibitors, e.g., CHZ868
- Anecdotal reports of restoration of responsiveness to ruxolitinib by temporary withdrawal followed by re-challenge


Susan, a 55-year-old woman presents with

- Further Testing Shows
  - WBC: 32 x 10^9/L
  - Blasts: 1%
  - Hb: 14.5 g/dL
  - Platelets: 367 x 10^9/L
  - LDH: 675 units
- 20 mg dose twice-daily
- After 6 months, spleen has improved but remains 3 cm below costal margin
- Intermittent constitutional symptoms

Additionally, biopsy results and mutational analyses confirm a diagnosis of PMF.
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Case 3: Combination Therapy via a Clinical Trial

Susan is a classic case of “suboptimal response”

- Some benefit from JAK inhibitor therapy, but lack of complete success suggests a need for more potent therapy
- Many trials are testing JAK inhibitor-based combination in MF—Susan is likely a good candidate for such options: ruxolitinib + PI3Kδ (Parsaclisib, *umbrela*); ruxolitinib + BETi (CPI-0610); ruxolitinib + HSP90i (PLI-H71); ruxolitinib + Bcl-2/Bcl-xLi (navitoclax)

Definitions of sub-optimal response to ruxolitinib vary across trials


Suboptimal Response to Ruxolitinib (Parsaclisib Trial)

- Treated with ruxolitinib for ≥6 months with stable dose for ≥8 weeks immediately prior to enrollment
- Palpable spleen >10 cm below left subcostal margin on physical examination at screening
  OR
- Palpable spleen 5–10 cm below left subcostal margin on physical examination AND active symptoms of MF at the screening visit defined as one symptom score ≥5 or two symptom scores ≥3 each, using the Screening Symptom Form*

MF=myelofibrosis
Screening Symptom Form: 10-point scale for each of the 7 symptoms. Symptoms include: night sweats, pruritus, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain, and inactivity.

Challenging Scenarios: Evidence-based Solutions

Anemia

- Ruxolitinib + ESA ± danazol ± IMID
- Consider pacritinib* or momelotinib* or adding luspatercept* or setaxersen* or CPI-0610 to ruxolitinib

Thrombocytopenia

- <50 x10^9/L: Consider low dose ruxolitinib ± danazol ± IMID or pacritinib*
- <50 x10^9/L refractory to ruxolitinib: consider pacritinib*

*Investigational

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### Challenging Scenarios: Evidence-based Solutions (Cont'd)

**Progression of spleen and/or symptoms on ruxolitinib**
- Dose escalation or switch to alternative JAK inhibitor (e.g., fedratinib as per JAKARTA-2)
- Clinical trial of combination therapy
- Allo SCT if applicable (best before progression)

**Progression to accelerated or blast phase**
- Perhaps continue ruxolitinib; retrospective evidence of benefit (Masarova ASH 2017)
- Combination of ruxolitinib with an HMA
- Intensive chemo and allo SCT if appropriate

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Thank you
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