Myelofibrosis: Disease Course and Complications

Early PMF

Short term: vascular events

Time: typically many years (~15y)

Overt PMF

Post-ET MF/post-PV MF

Progressive constitutional symptoms

Progressive organomegaly/EMH

Progressive cytopenias

MF-related complications*

Decreased QOL and PS
Progressive incapacitation
Immobility

Leukemic transformation (~25%)

Premature death

Time: variable (5-7 years common)

*Including cardiovascular events

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

Early/Prefibrotic Primary Myelofibrosis

- International, observational study in which patients with ET or rediagnosed prePMF were followed for disease progression (N = 1,104)

<table>
<thead>
<tr>
<th>Yrs Since Diagnosis</th>
<th>ET</th>
<th>Early/prefibrotic PMF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>5</td>
<td>0.75</td>
<td>0.75</td>
</tr>
<tr>
<td>10</td>
<td>0.50</td>
<td>0.50</td>
</tr>
<tr>
<td>15</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>20</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

**P < .001**

<table>
<thead>
<tr>
<th>Events</th>
<th>32</th>
<th>47</th>
<th>31</th>
<th>13</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>628</td>
<td>326</td>
<td>157</td>
<td>57</td>
</tr>
</tbody>
</table>

**Risk of Leukemic Transformation**

- Cumulative Incidence (%)
  - ET
  - prePMF

**Transformation to Overt MF**

- Cumulative Incidence (%)
  - ET
  - prePMF

**P = .04**

**P = .0012**
Simplified NCCN Guidelines for Treatment of MF: Based on Risk and Symptoms/Signs

Lower-risk

Asymptomatic ➔ observation or clinical trial

Symptomatic ➔ clinical trial or observation or ruxolitinib or peginterferon α-2a or Hydroxyurea

Transplant eligible ➔ allo-HSCT

or

Transplant ineligible ➔ ruxolitinib or fedratinib (either one for patients with platelets >50K)
or pacritinib (for patients with platelets <50K) or clinical trial

AND/OR

Transplant ineligible/anemia ➔ anemia therapy or clinical trial

Higher-risk

JAK inhibitors are not selective for mutated JAK2V617F protein

Lower-risk: MIPSS-70 ≤ 3; MIPPS-70+ ≤ 3; DIPSS-Plus ≤ 1; DIPSS ≤ 2; MYSEC-PM <14
Higher-risk: MIPSS-70 ≥ 4; MIPPS-70+ ≥ 4; DIPSS-Plus > 1; DIPSS > 2; MYSEC-PM ≥14

NCCN, National Comprehensive Cancer Network.
Prognostic factors

• Age > 65 years
• Constitutional symptoms
• Hb < 10 g/dL
• Leukocytes > 25 x 10⁹/L
• Blood blasts > 1%

Risk group #factors OS (y)

• Low 0 11
• Intermediate-1 1 8
• Intermediate-2 2 4
• High > 3 2

International Prognostic Scoring System (IPSS) in Primary Myelofibrosis
Impact of Driver and “High Molecular Risk” Mutations in Primary Myelofibrosis

CALR positive (22.7%) 17.7 yrs

JAK2 (65%) or MPL (4%) positive 9.2 and 9.1 yrs

Triple Negative (8.6%) 3.2 yrs

Many new prognostic scoring systems!

High molecular risk: IDH1/2, EZH2, ASXL1, SRSF2

• 2 or more HMR mutations also worsen survival

Distribution of Myelofibrosis Patients by Different Prognostic Models

MPN10
Total Symptom Score
[MPN-SAF]

An easy tool to assess symptoms in MPNs

- Inflammation
- Splenomegaly
- Anemia

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Value</th>
<th>Prognostic variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Early satiety</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Inactivity</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Problems with concentration</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Night sweats</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Itching</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Fever</td>
<td>0</td>
<td>(Absent) 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>0</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
</tbody>
</table>

MPN10 score: 0

• 23% of patients managed with watch and wait had high to moderate symptom burden
• Only 36% reported not currently experiencing symptoms

Despite a significant symptom burden in some untreated patients, around half of the physicians would still observe > 25% of patients at diagnosis

Myelofibrosis: What are JAK inhibitors for? Spleen and symptoms

- Dosed based on platelet number (not recommended for platelets <50K)
- It can cause anemia and thrombocytopenia
- Long-term ruxolitinib therapy prolongs survival (earlier intervention and better the spleen response, longer the survival)

COMFORT-II
Best spleen response at any time on study

- Median follow-up: 4.3 years

Ruxolitinib Efficacy by Titrated Dose: real-world evidence

- Phase 2 study and real-world data showed that doses less than 10mg BID are not effective long term
- If starting low, ESCALATE quickly to maximum safe dose

Overall Survival Improves with Spleen Length Reduction in Patients Receiving Ruxolitinib

Open-label, single-arm phase I/II study (N = 107)

- < 25% spleen length reduction (n = 23)
- ≥ 25% but < 50% spleen length reduction (n = 13)
- ≥ 50% spleen length reduction (n = 61)

For < 25% vs ≥ 50% spleen length reduction:
HR: 0.22 (95% CI: 0.10-0.51; P = .0001)

## Early intervention: Ruxolitinib in IPSS-1 Patients
### Higher Response Rate and Lower Toxicities

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Int-2 and high-risk patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMFORT-I (n = 155)⁴</td>
<td>41.9%</td>
<td>45%</td>
<td>13%</td>
<td>≈ 50%</td>
<td>21%⁵</td>
</tr>
<tr>
<td>COMFORT-II (n = 146)²</td>
<td>32%</td>
<td>42%</td>
<td>8%</td>
<td>≈ 50%</td>
<td>38%</td>
</tr>
<tr>
<td><strong>Int-1-risk patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JUMP INTM-1 (n = 163)³</td>
<td>56.9%</td>
<td>24.5%</td>
<td>11%</td>
<td>40%</td>
<td>19.6%</td>
</tr>
<tr>
<td>ROBUST trial (n = 14)⁴</td>
<td>50%</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Italian study (n = 70)⁵</td>
<td>54.7%</td>
<td>21.7%</td>
<td>2.9%</td>
<td>17.1%</td>
<td>17.1%</td>
</tr>
</tbody>
</table>

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

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Fedratinib in Myelofibrosis

Phase 3 JAKARTA Trial: Fedratinib vs. placebo in patients with Int-2/high-risk MF first line

<table>
<thead>
<tr>
<th>Fedratinib 400 mg</th>
<th>Fedratinib 500 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>37% Spleen volume reduction ≥ 35%</td>
<td>40% Spleen volume reduction ≥ 35%</td>
</tr>
<tr>
<td>40% Symptom burden reduction ≥ 50%</td>
<td>34% Symptom burden reduction ≥ 50%</td>
</tr>
<tr>
<td>14% Discontinuation due to AEs</td>
<td>25% Discontinuation due to AEs</td>
</tr>
</tbody>
</table>

N = 289

Phase 2 JAKARTA-2 Trial: Fedratinib in patients with Int-2/high-risk MF resistant or intolerant to ruxolitinib

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>Reanalysis (2019)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>55% Spleen volume reduction ≥ 35%</td>
<td>30% Spleen volume reduction ≥ 35%</td>
</tr>
<tr>
<td>11.0% Discontinuation due to AEs</td>
<td>27% Symptom burden reduction ≥ 50%</td>
</tr>
</tbody>
</table>

N = 97
*N = 79

## Fedratinib Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Fedratinib 400 mg (n = 96)</th>
<th>Fedratinib 500 mg (n = 97)</th>
<th>Placebo (n = 95)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
<td>All Grades</td>
</tr>
<tr>
<td><strong>Nonhematologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>66</td>
<td>5</td>
<td>56</td>
</tr>
<tr>
<td>Vomiting</td>
<td>42</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>Nausea</td>
<td>64</td>
<td>0</td>
<td>51</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Asthenia</td>
<td>9</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>15</td>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>99</td>
<td>43</td>
<td>98</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>63</td>
<td>17</td>
<td>57</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>57</td>
<td>21</td>
<td>66</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>47</td>
<td>6</td>
<td>53</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>28</td>
<td>8</td>
<td>44</td>
</tr>
</tbody>
</table>

### Black box warning
- Wernicke’s encephalopathy (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials.

### Considerations
- Measure and address thiamine levels prior to treatment initiation.
- Do not start fedratinib in patients with thiamine deficiency.

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Pacritinib vs. BAT in Thrombocytopenic Patients (PERSIST-2)

- PERSIST-2 study: prior JAK2 inhibitor allowed (48%), BAT included ruxolitinib (45%)
- Rarely myelosuppressive
- Causes GI side effects

- Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
- BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.

PERSIST-2: Hematologic Stability/Improvement

**Clinical Improvement in Hemoglobin Levels in Patients With Baseline Anemia, Baseline to Wk 24***

<table>
<thead>
<tr>
<th>Pacritinib (PAC 200 mg BID)</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>25%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Pacritinib Reduced Transfusion Burden in Patients Not TI at Baseline, Baseline to Wk 24**

<table>
<thead>
<tr>
<th>Pacritinib (PAC 200 mg BID)</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>22%</td>
<td>9%</td>
</tr>
</tbody>
</table>

**Transfusion Burden in Patients Who Received ≥1 RBC Transfusion on Study**

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Wk 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAC 200 mg BID</td>
<td>BAT</td>
</tr>
<tr>
<td>PAC 200 mg BID</td>
<td>BAT</td>
</tr>
</tbody>
</table>

TI defined according to Gale criteria (0 units over the course of 12 wk).

*International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 wk prior; anemia defined as hemoglobin <10 g/dL.

### PERSIST-2: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>PAC 200 mg BID (n = 106)</th>
<th>BAT (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any-grade AEs in ≥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>23</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>16</td>
</tr>
</tbody>
</table>

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

Transfusion dependence, high risk score and ASXL1/EZH2 mutations predict shorter time to failure in MF patients receiving JAK1/JAK2 inhibitor treatment.

Approach to the Treatment of Anemia in MF

erythropoietin (EPO) levels

- ADEQUATE ≥ 500 mIU/mL
  - Danazol, others
- INADEQUATE < 500 mIU/mL
  - ESA x 3 mos
    - No response
    - Response

NCCN guidelines
Momelotinib Inhibits JAK1, JAK2, and ACVR1 to Address MF Symptoms, Spleen, and Anemia

Dysregulated JAK-STAT signaling in MF drives overproduction of inflammatory cytokines, bone marrow fibrosis, systemic symptoms, and clonal proliferation resulting in extramedullary hematopoiesis and splenomegaly\(^1,2\)

Chronic inflammation also drives hyperactivation of ACVR1, elevated hepcidin, dysregulated iron metabolism, and anemia of MF\(^3,4\)

ACVR1, activin A receptor type 1; BMP, bone morphogenetic protein; EPOR, erythropoietin receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.

MOMENTUM Is an Ongoing Phase 3 Study of Momelotinib Versus DAN in Symptomatic, Anemic, JAKi-Experienced Patients

Previously treated with JAKi
Symptomatic (TSS ≥10)
Anemic (Hgb <10 g/dL)
Platelets ≥25×10⁹/L

Stratification:
▪ TSS
▪ Palpable spleen length
▪ Transfused units in prior 8 weeks
▪ Study site

Patients
N=195
2:1 randomization
JAKi taper/washout ≥21 days

Primary end point

Day 1

MMB 200 mg daily
+ PBO

Early crossover if confirmed progression

Week 24

MMB 200 mg daily

Place video here

ClinicalTrials.gov: NCT04173494.
a Danazol was selected as an appropriate comparator given its use to ameliorate anemia in patients with MF.3–5 b TSS response defined as achieving ≥50% reduction in TSS over the 28 days immediately before the end of week 24 compared with baseline. c TI response defined as not requiring red blood cell transfusion in the last 12 weeks of the 24-week randomized period, with all Hgb levels during the 12-week interval of ≥8 g/dL. d SRR defined as achieving a ≥25% or ≥35% reduction in spleen volume from baseline.

DAN, danazol; FPE, first patient enrolled; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; LPE, last patient enrolled; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; PBO, placebo; SRR, splenic response rate; TI, transfusion independence; TSS, total symptom score.

MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met1,2

<table>
<thead>
<tr>
<th></th>
<th>MFSAF TSS³ response rate (primary end point)</th>
<th>TI response² rate</th>
<th>SRR² (35% reduction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMB (N=130)</td>
<td>32 (24.6%)</td>
<td>40 (30.8%)</td>
<td>30 (23.1%)</td>
</tr>
<tr>
<td>DAN (N=65)</td>
<td>6 (9.2%)</td>
<td>13 (20.0%)</td>
<td>2 (3.1%)</td>
</tr>
<tr>
<td></td>
<td>P=.0095 (superior)</td>
<td>1-sided P=.0064 (noninferior)</td>
<td>P=.0006 (superior)</td>
</tr>
</tbody>
</table>

MOMENTUM Is an Ongoing Phase 3 Study of Momelotinib Versus DAN in Symptomatic, Anemic, JAKi-Experienced Patients

ClinicalTrials.gov: NCT04173494.

**MOMENTUM: Momelotinib vs Danazol**

*Transfusion Independence at Week 24, Mean Hemoglobin Over Time*

- **Transfusion Independence Rate (%):**
  - **Momelotinib (N=130):** 31% at Week 24, 20% at Baseline
  - **Danazol (N=65):** 15% at Week 24, 13% at Baseline
  - **P=0.0064 (Noninferior)**

- **Mean Hemoglobin Levels (g/dL):**
  - **Momelotinib** vs **Danazol** over **Weeks since Randomization**

*Defined as not requiring red blood cell transfusion in the terminal 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.

OS Was Improved in Patients Who Achieved Week 24 TI-R on Momelotinib, Including Those Randomized to DAN and Crossed Over to Momelotinib

For those patients randomized to momelotinib achieving week 24 TI-R, OS was significantly improved, consistent with observations in the SIMPLIFY studies.

Patients randomized to DAN achieving week 24 TI-R who then crossed over to momelotinib also trended toward longer OS.

DAN, danazol; HR, hazard ratio; NC, not calculable; OL, open-label; OS, overall survival; TI, transfusion independence; TI-R, transfusion independence response; TR, transfusion-requiring.
Novel Therapies for Myeloproliferative Diseases

Srdan Verstovsek, M.D., Ph.D.
Assistant Professor
Department of Leukemia
M. D. Anderson Cancer Center
Future Directions in MPDs

- Thalidomide + prednisone based combinations (with etanercept, or imatinib, or cytoxan)
- Thalidomide analogs (CC-5013) +/- prednisone
- Proteasome inhibitors (bortezomib)
- Hypomethylation agents (decitabine, azacitidine)
- Gleevec and PEG Intron
- Tyrosine kinase inhibitors of c-kit, PDGFR A and B
Thank You

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