Health-Related Quality of Life and Symptoms in Myelofibrosis Patients Treated With Ruxolitinib Versus Best Available Therapy


Symptoms in Myelofibrosis (MF)

- This complex of MF-associated symptoms can substantially compromise the quality of life (QoL) of patients with MF and can contribute to shortened survival

  - Anemia
  - Fatigue
  - Cachexia
  - Pruritus
  - Night sweats
  - Fever
  - Spleen-associated symptoms:
    - Early satiety
    - Pain
    - Limitations of movement
    - Dyspnea

Ruxolitinib is a potent and selective oral JAK1/2 inhibitor that has demonstrated rapid and durable reductions in splenomegaly, improved disease-related symptoms and QoL, and prolonged overall survival for patients with MF1-3.

COMFORT-II Study Design

- Patients were stratified by baseline IPSS risk category4

PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera-myalofibrosis; PET-MF, post-essential thrombocythemia-myelofibrosis; IPSS, International Prognostic Scoring System.


Primary and Key Secondary Endpoints

- Median time to response, 12.3 weeks
- Of the 69 patients who achieved ≥ 35% reduction in spleen volume at any time during the study, 44 (64%) did so at the first assessment

*CT for patients unable to undergo MRI.
MRI: magnetic resonance imaging; CT: computed tomography.
**Demographics and Baseline Patient Characteristics (ITT)**

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib (n = 146)</th>
<th>BAT (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, y ≤ 65 years, n (%)</td>
<td>67 (47)</td>
<td>66</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>83 (57)</td>
<td>42 (58)</td>
</tr>
<tr>
<td>Myelofibrosis type, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PMF</td>
<td>77 (53)</td>
<td>39 (53)</td>
</tr>
<tr>
<td>PPV-MF</td>
<td>48 (33)</td>
<td>20 (27)</td>
</tr>
<tr>
<td>PET-MF</td>
<td>21 (14)</td>
<td>14 (19)</td>
</tr>
<tr>
<td>Platelet count &gt; 200,000/µL, n (%)</td>
<td>88 (61)</td>
<td>47 (65)</td>
</tr>
<tr>
<td>High/intermediate-2 IPSS risk</td>
<td>49%/51%</td>
<td>49%/51%</td>
</tr>
<tr>
<td>JAK2 V617F positive, n (%)</td>
<td>110 (75)</td>
<td>49 (67)</td>
</tr>
<tr>
<td>Palpable spleen size below costal margin, median, cm</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Spleen volume, cm³, median</td>
<td>2408</td>
<td>2318</td>
</tr>
<tr>
<td>Prior hydroxyurea, n (%)</td>
<td>110 (75)</td>
<td>50 (68)</td>
</tr>
</tbody>
</table>

* Ruxolitinib, n = 144; BAT, n = 72.
* Normal spleen volume is 150 to 200 cm³.

**Patient Disposition**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Ruxolitinib (n = 146)</th>
<th>BAT (n = 73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still on randomized treatment by week 48</td>
<td>64% (94/146)</td>
<td>48% (35/73)</td>
</tr>
</tbody>
</table>

* An additional 29 patients (20%) continued ruxolitinib therapy in the extension phase of COMFORT-II.

**EORTC QLQ-C30 questionnaire**

| Patients with baseline and at least 1 postbaseline assessment (up to 48 weeks) | 89% (130/146) | 79% (58/73) |
| Completed week 48 assessment                                                        | 83% (78/94)   | 86% (30/35) |

**FACT-Lym questionnaire**

| Patients with baseline and at least 1 postbaseline assessment (up to 48 weeks) | 93% (135/146) | 82% (60/73) |
| Completed week 48 assessment                                                        | 82% (77/94)   | 86% (30/35) |

EORTC QLQ-C30, European Organisation For the Treatment of Cancer Quality of Life Questionnaire – Core 30; FACT-Lym, Functional Assessment of Cancer Treatment – Lymphoma.
Health-Related QoL Assessments

Validated instruments used at weeks 8, 16, 24, and 48, and not after disease progression or crossover

- **ECOG performance status**
- **EORTC QLQ-C30**
- **FACT-Lym**

Increasing disease specificity

EORTC QLQ-C30

- The EORTC QLQ-C30 consists of:
  - Global health status/QoL scale
  - 5 functional scales
    - Physical, role, emotional, cognitive, and social
  - 9 symptom scales
    - Fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact
**Health-Related QoL Assessments: FACT-Lym**

**Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)**

- FACT-Lym Total consists of:
  - FACT-G: a generic questionnaire of 27 items divided into 4 domains
    - Physical well-being
    - Social/family well-being
    - Emotional well-being
    - Functional well-being
  - Lymphoma subscale (LymS): a cancer-specific questionnaire of 15 items used to evaluate response to treatment
- FACT-Lym Trial Outcome Index (TOI)
  - TOI = physical + functional well-being + LymS

**Methods**

- Mixed-model analyses were used to evaluate treatment differences as a continuous variable
- Advantages of mixed-effect models include:
  - All data in one analysis
  - Use of all reported scores without loss of information
  - Allowance for treatment differences to vary by time
  - Adjusted for confounders including age, sex, baseline score, and prognostic risk category at randomization
- In the responder analysis, for each outcome score, responders were defined based on a minimally important difference (MID) defined as a change in score of at least the upper bound of previously published ranges
• Compared with the BAT arm, Global Health Status/QoL and the FACT-LymS were significantly improved in the ruxolitinib arm at weeks 8, 16, and 48

* Adjusted for age, sex, baseline score, and prognostic risk category.

* P < .05 for treatment difference (from the mixed model).

• The treatment effect between the high-risk and intermediate-risk-2 prognostic groups was not significantly different

* Adjusted for age, sex, baseline score, and prognostic risk category.

* P < .00 for treatment difference (from the mixed model).
EORTC QLQ-C30 QoL and Functional Scales
(Overall Across Time)

<table>
<thead>
<tr>
<th></th>
<th>Worsening</th>
<th>Improvement</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health status/QoL</td>
<td>-3.6</td>
<td>4.5</td>
<td>8.8 (3.9, 13.7)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>-6.6</td>
<td>6.0</td>
<td>8.0 (4.1, 12.0)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>-1.9</td>
<td>4.7</td>
<td>12.6 (6.2, 18.9)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>-0.3</td>
<td>4.1</td>
<td>6.6 (0.6, 12.5)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>-1.8</td>
<td>0.5</td>
<td>4.4 (-0.6, 9.5)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td></td>
<td></td>
<td>2.3 (-2.2, 6.9)</td>
</tr>
</tbody>
</table>

Overall Adjusted Mean Change From Baseline Score

*Adjusted for age, sex, baseline score, and prognostic risk category; † Ruxolitinib, n = 130, BAT, n = 58; ‡ Ruxolitinib, n = 125.
*P < .05 for treatment difference (from the mixed model); † Clinically significant difference.

EORTC QLQ-C30 Symptom Scales
(Overall Across Time)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Worsening</th>
<th>Improvement</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>-9.5</td>
<td>-10.5</td>
<td>-10.2 (-15.8, -4.5)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-10.8</td>
<td>-11.6</td>
<td>-11.6 (-17.6, -5.7)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>-10.7</td>
<td>-16.8</td>
<td>-16.3 (-21.5, -11.2)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>-6.1</td>
<td>-9.0</td>
<td>-9.5 (-16.4, -2.7)</td>
</tr>
<tr>
<td>Pain</td>
<td>-3.8</td>
<td>-4.6</td>
<td>-4.6 (-14.0, -2.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-1.8</td>
<td>-2.7</td>
<td>-2.7 (-5.6, 0.3)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>-0.8</td>
<td>1.2</td>
<td>1.2 (-4.1, 6.4)</td>
</tr>
<tr>
<td>Constipation</td>
<td>-0.3</td>
<td>-0.3</td>
<td>-0.3 (-5.0, 4.3)</td>
</tr>
</tbody>
</table>

Overall Adjusted Mean Change From Baseline Score

*Adjusted for age, sex, baseline score, and prognostic risk category; † Ruxolitinib, n = 125 to 130 patients; ‡ BAT, n = 56 to 58 patients.
*P < .01 for treatment difference (from the mixed model).
**FACT-Lymphoma Scores (Overall Across Time)**

- **Worsening**
- **Improvement**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ruxolitinib Mean Change</th>
<th>BAT Mean Change</th>
<th>Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FACT-Lym TOI</td>
<td>5.8 (3.9, 7.5)</td>
<td>6.4 (3.1, 9.8)</td>
<td>10.1 (6.7, 13.6)</td>
</tr>
<tr>
<td>FACT-Lym total</td>
<td>11.7 (7.2, 16.7)</td>
<td>12.0 (7.2, 16.7)</td>
<td>10.1 (6.7, 13.6)</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, baseline score, and prognostic risk category; b Ruxolitinib, n = 133.
* P < .001 for treatment difference (from the mixed model).

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**Responder Analysis**

- Clinically significant or minimally important difference (MID) is defined as a change in score of at least the upper bound of previously published ranges.

<table>
<thead>
<tr>
<th>QoL Outcome</th>
<th>Possible score</th>
<th>Analysis MID (published ranges)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC QLQ-C30 Global Health Status/QoL¹</td>
<td>0-100</td>
<td>10 (6-17)</td>
</tr>
<tr>
<td>FACT-G total²</td>
<td>0-108</td>
<td>7 (3-7)</td>
</tr>
<tr>
<td>FACT-Lym subscale³</td>
<td>0-60</td>
<td>5.4 (2.9-5.4)</td>
</tr>
<tr>
<td>FACT-Lym TOI³</td>
<td>0-116</td>
<td>11 (5.5-11)</td>
</tr>
<tr>
<td>FACT-Lym total³</td>
<td>0-168</td>
<td>11.2 (6.5-11.2)</td>
</tr>
</tbody>
</table>

Percentage of Responders

- Similar results were observed on the FACT-G total, FACT-Lym total, and FACT-Lym TOI subscales

* For patients with change from baseline scores at each visit. Patients with a best possible score at baseline were excluded from analysis. * P < .05 (Fisher exact test).

Conclusions

- This is a rigorous statistical analyses of QoL data from the COMFORT-II study across the 48 week duration of the study
- Both mixed-model and responder analyses show statistically significant benefit for ruxolitinib compared with conventional therapies (BAT) in both EORTC QLQ-C30 and FACT-Lym instruments
- QoL scores for BAT patients often worsened
- This demonstrates a clinically important, novel therapeutic benefit of ruxolitinib therapy
  - Ruxolitinib is approved in the United States by the Food and Drug Administration for the treatment of intermediate or high-risk MF
  - The Committee for Medicinal Products for Human Use of the European Medicines Agency has recently recommended the approval of ruxolitinib for the treatment of disease-related splenomegaly or symptoms
COMFORT-II
9 countries, 56 sites

Austria
Heinz Gisslinger, Vienna
Richard Greil, Salzburg
Holger Rumpold, Linz
Dominik Wolf, Innsbruck
Belgium
Laurent Knoops, Brussels
Andre Bosty, Yvoir
Robrecht De Bock, Antwerp
André Delannoy, La Louvière
Timothy Devos, Leuven
Jan Van Droogenbroeck, Brugge
Koen Van Eygen, Kontrijk
Pierre Zachée, Antwerpen
Hilde Demuyck, Roeselare
Koen Theunissen, Hasselt
The Netherlands
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Jo Kluiten-Nelmers, Groningen
Harry Schouten, Maastricht
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