JAK2 Inhibitors: where do we stand?

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# Main Clinical Problems in MF

<table>
<thead>
<tr>
<th>Clinical need</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia (Hb &lt;10 g/dL)</td>
<td>36%</td>
</tr>
<tr>
<td>Leukocytosis (&gt;25x10⁹/L)</td>
<td>10%</td>
</tr>
<tr>
<td>Thrombocytopenia (&lt;100x10⁹/L)</td>
<td>16%</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>83%</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>65%</td>
</tr>
<tr>
<td>Extramedullary hematopoiesis</td>
<td>1-3%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>7.2%</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>27%</td>
</tr>
<tr>
<td>Leukemia transformation</td>
<td>13%</td>
</tr>
</tbody>
</table>
Traditional Therapeutic Options for MF

Medicines for Anemia
• Prednisone
• Androgens
• EPO
• Thalidomide +/- prednisone

Medicines for Anemia & Spleen
• Lenalidomide +/- prednisone

Medicines for Spleen
• Hydroxyurea
• Busulfan
• 2-CDA
• Splenectomy
• Splenic Radiation

Medicines for Symptoms
• Prednisone

“BAT”
JAK-STAT Signaling

- A well characterized signaling pathway involved in normal hematopoiesis (blood making), inflammation, and immune function

- Four members of JAK family
  - JAK1, JAK2, JAK3 and Tyk2
  - Promiscuous signaling (!)

- JAK2 specifically mediates cytokine signaling for red blood cells and platelets (its inhibition causes anemia and low platelets)
JAK2V617F in MPN: 2005

- Acquired mutation in a gene
- Results in constitutively active JAK2 tyrosine kinase (always active enzyme)
- Causes disease in mice (PV → MF)
- Present in ~50% of ET and MF patients, ~97% PV
JAK2V617F in MPN: 2013

- Other mutations identified (about 20 so far); clonal hyperharchy → “multiclonal” state
- JAK2 mutation is not a cause for the disease presence in humans; just contributor to the disease existence
- JAK-STAT pathway dysregulation, regardless of JAK2 mutational status, is a key pathologic feature of MPNs
JAK2 Inhibitors

- Not selective for mutated JAK2V617F enzyme
- Lowering of platelets and red blood cells is expected side effect due to inhibition of normal JAK2
- Elimination of the disease unlikely
- However: may benefit patient with and without JAK2V617F mutation
<table>
<thead>
<tr>
<th>JAK inhibitor (Company)</th>
<th>Diseases and studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>CEP701 (Cephalon)</td>
<td>MF: phase II finished and I/II (new formulation) ongoing</td>
</tr>
<tr>
<td>AZD1480 (AstraZeneca)</td>
<td>MF: phase I finished, development stopped</td>
</tr>
<tr>
<td>XL019 (Exelixis)</td>
<td>MF: phase I finished, development stopped</td>
</tr>
<tr>
<td>NS-018 (NS Pharma)</td>
<td>MF: phase I ongoing</td>
</tr>
<tr>
<td>BMS-911543 (BMS)</td>
<td>MF: phase I ongoing</td>
</tr>
<tr>
<td>LY2784544 (Lilly)</td>
<td>ET/PV/MF: phase I finished, phase II ongoing</td>
</tr>
<tr>
<td>SB1518 (CTI/S*Bio)</td>
<td>MF: phase I/IIx2 completed, phase III ongoing</td>
</tr>
<tr>
<td>CYT387 (YM/Cytopia)</td>
<td>MF: phase I/II QD completed; phase I/II BID completed</td>
</tr>
<tr>
<td>SAR302503/TG101348 (Sanofi/Targegen)</td>
<td>MF: phase I/II completed; phase II completed, phase III completed</td>
</tr>
<tr>
<td>INCB018424/Ruxolitinib (Incyte/Novartis)</td>
<td>MF: phase I/II and III completed and approved; phase II (for pts with low platelets) ongoing</td>
</tr>
</tbody>
</table>
Evaluation of JAK2 Inhibitors in MF

Efficacy:
- Splenomegaly
- Quality of life/Performance status
- Anemia

Toxicity:
- Blood cell suppression, other?
Benefits of JAK Inhibitor Therapy in MF

Splenomegaly
Splenomegaly in MF Patient Pre-Therapy
Splenomegaly after 2 Months of Therapy
Rapid and Durable Impact on Spleen Size in Patients With and Without JAK2V617F Mutation

- JAK mutation POSITIVE; N = 33
- JAK mutation NEGATIVE; N = 6

Spleen length, cm

Time on Therapy (days)
Spleen Volume Decrease by MRI

BEFORE THERAPY

AFTER 6 MONTHS

53% decrease in spleen volume, 32% decrease in liver volume
## Spleen Volume Response: Ruxolitinib vs. BAT

### Table: Spleen Volume Response

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Spleen volume</td>
<td>132 (97%)</td>
<td>35  (56%)</td>
</tr>
<tr>
<td>↑ Spleen volume</td>
<td>4  (3%)</td>
<td>28  (44%)</td>
</tr>
</tbody>
</table>

**Graph: COMFORT-II**

Best spleen response at any time on study

- **Ruxolitinib (n = 136)**
- **BAT (n = 63)**

- **35% Decrease**
Reduction in MF-Related Symptoms by Spleen Volume Reduction at Week 24

Total Symptom Score

Mean % Change From Baseline ± SEM

All Placebo  
- <10%  
- 10 to <35%  
- ≥35%

Ruxolitinib  
Spleen Volume Reduction

n = 99  
- n = 20  
P = .0004

- n = 46  
P < .0001

- n = 60  
P < .0001

P value vs all placebo.
• 90/155 (58%) had a 35% reduction at any time point during the study
• 64% maintained a ≥35% reduction for at least 2 years
Benefits of JAK Inhibitor Therapy in MF

Quality of life/Performance status
## Improvement in Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Ruxolitinib</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>-9.5</td>
<td>-7.0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>-10.8</td>
<td>-10.7</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>-10.7</td>
<td>-10.8</td>
</tr>
<tr>
<td>Insomnia</td>
<td>-10.7</td>
<td>-10.8</td>
</tr>
<tr>
<td>Pain</td>
<td>-6.1</td>
<td>-3.8</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>-3.8</td>
<td>-1.7</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>-1.7</td>
<td>-0.9</td>
</tr>
<tr>
<td>Constipation</td>
<td>-0.9</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

*Overall Adjusted Mean Change From Baseline Score*
Duration of Symptom Improvement

**Global Health Status/QoL**

- **Ruxolitinib**
- **Placebo**

**Fatigue**

- **Ruxolitinib**
- **Placebo**

**Role Functioning**

- **Ruxolitinib**
- **Placebo**

**Physical Functioning**

- **Ruxolitinib**
- **Placebo**

Arrows indicate improvement.
Evaluation of JAK2 Inhibitors in MF

Anemia
Hemoglobin levels on JAK inhibitor therapy

- In general no significant improvement
Impact on Blood and Bone Marrow

In general:

• High white blood cells and high platelets decrease to normal levels

• Red blood cell count does not significantly improve

• Bone marrow fibrosis does not change, stays stable
# JAK2 Inhibitor Side Effects from Phase II Studies

<table>
<thead>
<tr>
<th></th>
<th>GI</th>
<th>Anemia</th>
<th>Platelets</th>
<th>Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SAR302503</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SB1518</td>
<td>X</td>
<td></td>
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<td>CYT387</td>
<td></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
What happens if the therapy with JAK2 inhibitor is interrupted?

- Return of the symptoms within 7 days
### Serious Adverse Events After Therapy Interruption

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Ruxolitinib (n = 155)</th>
<th>Placebo (n = 151)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total with interruption, n</td>
<td>49</td>
<td>54</td>
</tr>
<tr>
<td>Total SAEs, n (%)</td>
<td>3 (6.1)</td>
<td>3 (5.6)</td>
</tr>
</tbody>
</table>

- no report of “withdrawal syndrome”

- Percent of patients that **discontinued ruxolitinib** due to side effects was **11%**

- Percent of patient that **discontinued placebo** due to side effects was **11%**
JAK2 Inhibitors in MF

Can JAK2 inhibitors prolong life of patients with MF?
Overall Survival: ruxolitinib vs. placebo

- **Survival Probability**
- **Weeks**: 0, 12, 24, 36, 48, 60, 72, 84, 96, 108, 120, 132
- **Survival Probability**:
  - Placebo: 1.0, 0.8, 0.6, 0.4, 0.2, 0, 0
  - Ruxolitinib: 1.0, 0.8, 0.6, 0.4, 0.2, 0, 0

- **No. at risk**
  - Ruxolitinib: 155, 154, 148, 145, 136, 125, 121, 113, 96, 44, 6
  - Placebo: 154, 148, 142, 133, 117, 111, 102, 95, 74, 32, 7

- **Median follow-up**: 102 weeks.
- **No. of deaths**: Ruxolitinib = 27; Placebo = 41; HR = 0.58 (95% CI: 0.36, 0.95); \( P = .028 \)
Overall Survival: ruxolitinib vs. BAT

Suggests a relative reduction in the risk of death with ruxolitinib compared with BAT (HR = 0.51; 95% CI, 0.26-0.99), \( P = .041 \)

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>BAT</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>146</td>
<td>73</td>
</tr>
<tr>
<td>Events</td>
<td>20 (13.7%)</td>
<td>16 (21.9%)</td>
</tr>
</tbody>
</table>
Overall Survival: Ruxolitinib vs. matched historical control

Hazard ratio = 0.61
95% CI: 0.41–0.89
p-value = 0.022

Number of Patients at Risk—MDACC Study 251
- Ruxolitinib: 107
- Control: 310

Number of Patients at Risk—Historical Control
- 107: 300
- 257: 257
- 226: 226
- 180: 180
- 146: 146
- 118: 118
- 93: 93

Survival Probability vs. Months
JAK2 Inhibitors for Myelofibrosis

- Not selective for JAK2V617F (patients with and without JAK2 mutation benefit)

- Safety: lowering of blood count (not a cause for stopping therapy), others

- Efficacy:
  - spleen size reduction and significant improvement in quality of life and performance status = better control of MF
  - possible prolongation of life in patients with advanced disease
WHAT IS NEXT: combination trials with JAK2 inhibitors

- To **increase** benefits seen with JAK2 inhibitors (splenomegaly, symptoms) as well as to **bring additional** benefits (anemia, BM fibrosis, clone elimination)
- To **reduce** unwanted side effects (anemia, thrombocytopenia) but maintain clinical benefits
- To **improve** stem cell transplant result
### Ongoing/Planned Ruxolitinib-based Combinations

- plus Panobinostat  (USA: Mt Sinai Hospital NYC)
- plus Lenalidomide  (USA: MD Anderson)
- plus hedgehog inhibitor  (USA: MD Anderson, others)
- plus peg-Interferon-alpha2a  (France)
- plus Everolimus  (Italy)
- plus Pomalidomide  (Germany)
- plus erythropoietin  (Germany)
- plus Azacytidine  (USA: MD Anderson)
- plus Decitabine in MPN-related AML (USA: Mt Sinai Hospital NYC)
Clinical study: Feasibility of administering Ruxolitinib with reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (RIC-ASCT) in MF patients 

(Canada, USA, Italy, Germany, UK, Israel)
THANK YOU

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