JAK2 Inhibitors for Myelofibrosis

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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 MPD: 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 MPD: 2011

- Other mutations identified (about 10 so far); clonal hierarchy → “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 MPDs

Anand S, Blood 2011;118(6): 1610-21
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
Evaluation of JAK2 Inhibitors in MF

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

Toxicity:
- Lowering of blood count, other?
Evaluation of JAK2 Inhibitors in MF

Splenomegaly
Splenomegaly in MF Patient Pre-Therapy
Splenomegaly after 2 Months of Therapy
15 of 34 (44%) patients had response of ≥ 50% reduction
Spleen Response to CYT387

Maximal Change in Spleen Size from Baseline (to Date)

46% had 50% reduction
Spleen Response to SAR302503 (TG101348)

Pardanani et. al. JCO 2011;29(7):789-796
Rapid and Durable Impact on Spleen Size in Patients With and Without JAK2V617F Mutation

Ruxolitinib phase I/II

JAK mutation POSITIVE; N = 33
JAK mutation NEGATIVE; N = 6
Ruxolitinib phase III (COMFORT-1 study): at week 24, ruxolitinib-treated patients had a median 33.0% decrease in spleen volume, and placebo-treated patients had a median 8.5% increase ($P < 0.0001$).
Evaluation of JAK2 Inhibitors in MF

Quality of life/ Performance status
Symptom Response to CYT387

- Night sweats (n=26)
- Bone pain (n=25)
- Pruritus (n=13)
- Fever (n=5)

[Bar chart showing symptom response to CYT387 at different dosages]
Symptom Response to SAR302503 (TG101348)

A) Early Satiety

B) Fatigue

C) Night Sweats

Pardanani et. al. JCO 2011;29(7):789-796
Comfort I Symptom Response
Individual Symptom Scores

- Abdominal discomfort: -29.4
- Pain under left ribs: -46.9
- Early satiety: -43.0
- Night sweats: -42.1
- Itching: -42.8
- Bone/muscle pain: -21.2
- Inactivity: -32.1

For all individual symptoms above, comparisons between ruxolitinib- and placebo-treated groups were highly statistically significant ($P < 0.01$)

Verstovsek et. al. ASCO 2011 a6500
Mesa et. al. EHA 2011 (a912) Poster Saturday
Improved Exercise Capacity and Body Weight

- 6-minute walk test (6MWT) is well established measure of exercise capacity
- MF patients walk **60-90 meters less** than age-matched healthy volunteers

![Graph showing change in 6MWT performance and body weight over time.](attachment:image.png)
Evaluation of JAK2 Inhibitors in MF

Anemia
### Red Blood Cell Transfusions

**CONCLUSION:** response criteria is not good

<table>
<thead>
<tr>
<th></th>
<th>JAK2 inhibitor #1</th>
<th>JAK2 inhibitor #2</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Newly transfusion independent by IWG criteria*</td>
<td>41%</td>
<td>58%</td>
<td>47%</td>
</tr>
</tbody>
</table>

*Patients receiving at least 2 units PRBC during the 4 weeks prior to therapy and no transfusions for at least 8 weeks while receiving treatment*
Hemoglobin improvement

- In general no significant improvement

YM/Cytopia phase I/II
Impact on Blood and Bone Marrow

In general:

- High white blood cells and high platelets decrease to normal levels
- Percent blast in blood stays stable
- Bone marrow fibrosis does not change, stays stable
- JAK2V617F allele burden may decrease
JAK2 Inhibitor Side Effects from Phase II Studies

<table>
<thead>
<tr>
<th></th>
<th>GI</th>
<th>Anemia</th>
<th>Platelets</th>
<th>Liver</th>
<th>Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAR302503</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>SB1518</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CYT387</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</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>
<tr>
<td>Febrile neutropenia</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>GI hemorrhage</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Urosepsis</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (2.0)</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Pulmonary edema</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
<tr>
<td>Gout</td>
<td>0</td>
<td>1 (1.9)</td>
</tr>
</tbody>
</table>

Overall:
- 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 for MF

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

• Toxicity profiles differ

• Efficacy:
  • MF: spleen size reduction and significant improvement in quality of life = better control of MF
  • improved survival – YES! (retrospective and prospective analyses)
Overall Survival: MDACC Phase 1-2 Study Cohort vs. 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: N = 107
- Control: N = 310

Number of Patients at Risk—Historical Control
- N = 300
- 60 months: 257
- 24 months: 226
- 12 months: 180
- 6 months: 146
- 3 months: 118
- 1 month: 93

Months
Survival Probability
Overall survival analysis conducted at the time of a preplanned safety update with data cutoff 4 months after primary analysis cutoff date

- After a median follow up of 51 weeks, 13 (8.4%) deaths in ruxolitinib group and 24 (15.7%) deaths in placebo group

**HR = 0.50 (0.25–0.98)**  
**P = 0.04**
### Clinical Trials in MPD at MD Anderson

<table>
<thead>
<tr>
<th>Agent</th>
<th>(Company)</th>
<th>Diseases and studies</th>
<th>Type of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAR302503</td>
<td>(Sanofi)</td>
<td>MF: phase III</td>
<td>JAK2 inhibitor</td>
</tr>
<tr>
<td>LY2784544</td>
<td>(Lilly)</td>
<td>ET/PV/MF: phase I</td>
<td>JAK2 inhibitor</td>
</tr>
<tr>
<td>CYT387</td>
<td>(Cytopia/YM)</td>
<td>MF: phase I</td>
<td>JAK2 inhibitor</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>(Incyte/Novartis)</td>
<td>MF low platelets: phase I</td>
<td>JAK1 and JAK2 inhibitor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MF: combination with revlimid</td>
<td></td>
</tr>
<tr>
<td>NS-018</td>
<td>(NS Pharma)</td>
<td>MF: phase I</td>
<td>JAK2 inhibitor</td>
</tr>
<tr>
<td>BMS911543</td>
<td>(BMS)</td>
<td>MF: phase I</td>
<td>JAK2 inhibitor</td>
</tr>
<tr>
<td>AB0024</td>
<td>(Gilead)</td>
<td>MF: phase II</td>
<td>LOXL2 antibody</td>
</tr>
<tr>
<td>IPI-926</td>
<td>(Infinity)</td>
<td>MF: phase II</td>
<td>Hedgehog inhibitor</td>
</tr>
<tr>
<td>Pomalidomide + pred</td>
<td></td>
<td>MF: phase II</td>
<td>IMID</td>
</tr>
</tbody>
</table>
SAR302503 Phase III Study Design

Multinational, multicenter, double blind, placebo-controlled randomized study

- Intermediate-2 or High risk Primary MF
- Post-Polycythemia Vera Myelofibrosis
- Post-Essential Thrombocythemia Myelofibrosis

No Stratification factor
Randomization 1/1/1

- 75 pts
- Q 4 weeks SAR302503 500mg Daily oral doses
- 75 pts
- Q 4 weeks SAR302503 400mg Daily oral doses
- Cross over 1/1
- End of C6
- 75 pts
- Q 4 weeks Placebo Daily oral doses
- End of C6 or PD
- EOT

- 225 pts, Sites ~125, Recruitment: 9 months, 25 countries
- Safety data monitored by DMC (~Q 6 months)
- Cross over possible
Phase II study of ruxolitinib in PV (n=34)

- Response Criteria - European LeukemiaNet:
  - CR:
    - Hct < 45% without phlebotomy
    - platelet count < 400,000
    - WBC < 10,000
    - normal spleen
    - no disease-related symptoms
  - PR: Hct < 45% OR response in ≥ 3 of the other criteria

- 97% overall response
  - 50% CR
  - 47% PR

- Phase 3 study for approval of ruxolitinib for PV is underway