Update on the Biology and Treatment of Myeloproliferative Neoplasms

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University of Chicago
## Conflict of Interest Disclosure

<table>
<thead>
<tr>
<th>Company</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGI Pharma/Eisai</td>
<td>Research Support</td>
</tr>
<tr>
<td>Curagen/Topotarget</td>
<td></td>
</tr>
<tr>
<td>Incyte, Sanofi Aventis, Suneisis, Algeta, Spectrum Pharmaceuticals</td>
<td>Advisory Board/Consultancy</td>
</tr>
</tbody>
</table>
Objectives

• Describe the molecular genetic aberrations underlying the myeloproliferative neoplasms (MPNs)
• Discuss targeted therapeutic approaches for MPNs with a focus on JAK inhibitors in myelofibrosis (MF)
• Discuss ongoing challenges in treatment of MF and novel combination approaches
Myeloproliferative neoplasms

<table>
<thead>
<tr>
<th>Mast cell</th>
<th>Systemic mastocytosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red blood cells</td>
<td>Polycythaemia vera</td>
</tr>
<tr>
<td>Platelets</td>
<td>Essential thrombocythaemia</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>Chronic eosinophilic leukemia</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Chronic myeloid leukaemia</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Chronic myelomonocytic leukemia</td>
</tr>
<tr>
<td>Monocytes</td>
<td>Primary myelofibrosis</td>
</tr>
</tbody>
</table>

Activating mutation

- KITD816V
- FIP1L1–PDGFRA
- JAK2V617F JAK2 Exon 12
- JAK2V617F MPLW515L/K
- FIP1L1–PDGFRA
- BCR–ABL
- TEL–PDGFRB
- BCR–PDGFR
- TEL–JAK2
- other fusion TKs
- JAK2V617F MPLW515L/K

Levine et al. Nature Reviews Cancer 2007
Myeloproliferative neoplasms and JAK2

<table>
<thead>
<tr>
<th>Other Myeloid Neoplasms</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refractory anemia with ring sideroblasts and thrombocytosis (RARS-T)</td>
<td>~50</td>
</tr>
<tr>
<td>Chronic myelomonocytic leukemia (CMML)</td>
<td>~5-10</td>
</tr>
<tr>
<td>Chronic eosinophilic leukemia, atypical CML, systemic mastocytosis</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
**JAK2 Mutations in MPN**

- **JAK2 V617F mutation**
  - Single nucleotide substitution in JAK2 exon 14 sequence
  - Mutation occurs in the pseudokinase domain of the protein

- **JAK2 exon 12 abnormalities**
  - Mutations, deletions, insertions

  - Result in constitutive activation of JAK2 TK
JAK-2 mediated Signal Transduction Pathways

Ligand Bound Receptor (EPOR, MPL, GCSFR)

P13K

AKT

mTOR

RAS

MAPK

STAT

Survival

Differentiation

Proliferation

Target Gene Activation
Diagnostic algorithm for MPN in JAK2 Era

*JAK2V617F genotyping when a MPN is suspected*

Positive

PV, ET, PMF

Likely

Use additional WHO criteria

Negative

PV: unlikely; test for *JAK2* ex 12

ET or PMF: possible; test for *MPL*

Use additional WHO criteria

Adapted from Vannucchi AM et al, CA Cancer J Clin 2009
What is the mutational basis of JAK2 V617F-negative ET and PMF?

Calreticulin (CALR) mutations

Late Breaking Abstracts Session, ASH Meeting, 2013

LBA-1: Dr. Robert Kralovics and colleagues
   — Presented by Dr. Klampfl Thorsten

LBA-2: Dr. Tony Green and colleagues
   — Presented by Dr. Jyoti Nangalia
CALR mutations in JAK2V617F negative ET and MF

JAK2 exon 12 mutant

Polycythemia Vera

97% JAK2V617F mutant

Essential Thrombocytosis Primary Myelofibrosis

30-40% CALR mutant

50-60% JAK2V617F mutant

Late Breaking Abstract #1 and #2: Tuesday, December 10, 2013: Kralovics & Green labs
Within ER
- chaperone ensuring quality control of glycoprotein folding
- calcium homeostasis

Outside ER
- found in cytoplasmic, cell surface and extracellular compartments
- roles in: proliferation
  - apoptosis
  - phagocytosis
  - immunogenic cell death

Calreticulin (CALR)
Diagnostic algorithm for MPN in JAK2/CALR Era

**JAK2V617F genotyping when a MPN is suspected**

- **Positive**
  - PV, ET, PMF
  - Likely
  - Use additional WHO criteria

- **Negative**
  - PV: unlikely; test for JAK2 ex 12
  - ET or PMF: possible; test for MPL and CALR
  - Use additional WHO criteria

Adapted from Vannucchi AM et al, CA Cancer J Clin 2009
### Mutation Frequency in Chronic Phase and Post-MPN AML

<table>
<thead>
<tr>
<th>Gene</th>
<th>Chronic Phase</th>
<th>Blast Phase / AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>TET2</td>
<td>PV: 7-16%, ET: 4-11%, PMF: 8-17%</td>
<td></td>
</tr>
<tr>
<td>ASXL1*</td>
<td>PV: 2-5%; ET: 5-8%; PMF: 7-17%</td>
<td>19%</td>
</tr>
<tr>
<td>DNMT3A</td>
<td>PV: 7%, ET: 3%, PMF: 7-15%</td>
<td>17%</td>
</tr>
<tr>
<td>CBL</td>
<td>PMF: 6%</td>
<td></td>
</tr>
<tr>
<td>LNK</td>
<td>PV, ET, PMF: &lt;5%</td>
<td>~10%</td>
</tr>
<tr>
<td>IDH 1/2*</td>
<td>PMF: 4%</td>
<td>21%</td>
</tr>
<tr>
<td>IKZF1</td>
<td></td>
<td>19%</td>
</tr>
<tr>
<td>EZH2*</td>
<td>5-13% of MPNs</td>
<td></td>
</tr>
<tr>
<td>P53</td>
<td></td>
<td>27%</td>
</tr>
<tr>
<td>SRSF2*</td>
<td></td>
<td>19%</td>
</tr>
</tbody>
</table>

* Associated with worse leukemia-free or overall survival in PMF patients

Vannucchi et al, *Leukemia*, 2013
Therapeutic Implications of the Molecular Genetic Aberrations in MPNs?

Focus on Myelofibrosis
Survival in PMF

No. patients: 1,054
Median #months 69 (61 - 76)

Cervantes et al., Blood 2009
Causes of Mortality in MF

- **Transformation to acute leukemia**, 31%
- **PMF progression without transformation**, 18%
- **Thrombosis and cardiovascular complications**, 13%
- **Infection**, 11%
- **Bleeding**, 5%
- **Portal hypertension**, 4%
- **Other (including 12 cases second neoplasia)**, 17%
- **Transplant complications**, 1%
- **Other (including 12 cases second neoplasia)**, 17%

**Median survival** = 69 months (95% CI, 61-76 months)
- **517 of 1001 patients dead at time of analysis**
## JAK Inhibitors in Clinical Use or in Trials in MF

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial Name</th>
<th>Current Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruxolitinib (Jakafi)</td>
<td>COMFORT-I COMFORT-II</td>
<td>Approved</td>
</tr>
<tr>
<td>Fedratinib (SAR302503, formerly TG101348)</td>
<td>JAKARTA</td>
<td>Phase III *</td>
</tr>
<tr>
<td>Pacritinib (SB1518)</td>
<td>PERSIST-I PERSIST-2</td>
<td>Phase III</td>
</tr>
<tr>
<td>Momelotinib (GS-0387; formerly CYT387)</td>
<td></td>
<td>Phase III Momelotinib vs. Ruxolitinib</td>
</tr>
<tr>
<td>INCB039110</td>
<td></td>
<td>Phase II</td>
</tr>
<tr>
<td>BMS-911543</td>
<td></td>
<td>Phase I/II</td>
</tr>
<tr>
<td>LY2784544</td>
<td></td>
<td>Phase I</td>
</tr>
</tbody>
</table>

* Abstract 393, ASH 2013; Clinical development halted due to Wernicke’s encephalopathy
COMFORT-I: Study Design
COntrolled MyeloFibrosis Study With ORal JAK Inhibitor Treatment

**KEY INCLUSION CRITERIA**
- PMF, PPV-MF, or PET-MF
- Intermediate-2 or high risk by IWG-MRT (IPSS)
- Palpable spleen ≥5 cm
- Platelet count ≥100 × 10^9/L
- JAK2 V617F positive or negative

(N=309)

**RANDO M I Z E**

1:1

**Ruxolitinib**
- 15 mg or 20 mg (n=155)

**Placebo**
- (n=154)

**Patient population**
- Study only enrolled patients with MF who were refractory to or were not candidates for available therapy

**Starting doses of ruxolitinib:**
- 15 mg in patients with platelet counts 100-200 × 10^9/L
- 20 mg in patients with platelet counts >200 × 10^9/L
COMFORT-I
Primary Endpoint: % of Patients With ≥35% Decrease in Spleen Volume at Week 24 (ITT)

- Patients who discontinued prior to week 24 or crossed over prior to week 24 were counted as non-responders
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 ($P < 0.0001$)
COMFORT-I: Percent of Patients With $\geq 50\%$ Decrease in Total Symptom Score at Week 24 (ITT)

- **Total Symptom Score** = the sum of scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the ribs on the left, and early satiety
- **Patients who discontinued prior to week 24 or crossed over prior to week 24 were counted as failures**

Ruxolitinib (n = 148) vs Placebo (n = 152)

- **Odds ratio (95% CI)**: $15.28 (6.93-33.66)$
- **$P < 0.0001$**

**COMFORT-I** three-year survival analysis

**COMFORT-II** three-year survival analysis: patients randomized to ruxolitinib showed longer overall survival than those randomized to BAT (hazard ratio, 0.48; 95% CI, 0.28-0.85; log-rank $P = 0.009$)

The survival benefit observed with ruxolitinib is likely a composite of multiple treatment effects (e.g., spleen volume reduction, improvement in constitutional symptoms, improvement in nutritional status).

Mesa et al. ASH 2012; abstract 1733
JAK Inhibitors in MF: Key Points

- Core benefits: reduction of splenomegaly, MF-related symptoms/QOL, and inflammatory cytokines
- Inhibitors exert anti-JAK1/JAK2 activity or more selective anti-JAK2 activity
- Active in JAK2 V617F-mutated AND JAK2 wild-type patients
- No substantive effect on marrow fibrosis or JAK2 V617F allele burden in most patients
- Data support relative survival benefit of ruxolitinib (vs. placebo or best available therapy [BAT]) with 2-3 years of median follow-up
- Managing on-target effects: anemia and thrombocytopenia
Mean Hemoglobin and Red Blood Cell Products Over Time

Mean Hemoglobin ± SEM (g/L)

Ruxolitinib

Placebo

Percent of Patients Receiving RBC Products in Prior 4 Weeks

Ruxolitinib: Anemia & Thrombocytopenia

- Total & high grade anemia (and thrombocytopenia) were more common with ruxolitinib compared to placebo or BAT
- Primarily manifests in the first 8-12 weeks
- Rarely leads to drug discontinuation
- Symptomatic improvement with ruxolitinib is similar in patients with high grade anemia versus no anemia
- Management of anemia requires a patient-specific approach:
  1) Dose-reduction or close watchful waiting over the first 8-12 weeks
  2) RBC transfusions as needed
  3) ESAs and other agents (e.g. danazol, lenalidomide) are being evaluated in combination with JAK inhibitors
- Starting dose and dose modifications for the platelet count should be guided by the prescribing information
## Momelotinib: Transfusion Independence Response

### Response by Dose (Core Study)

<table>
<thead>
<tr>
<th>Response by Dose (Core Study)</th>
<th>150 mg QD (n=52)</th>
<th>300 mg QD (n=60)</th>
<th>150 mg BID (n=42)</th>
<th>Total¹ (n=166)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transfusion dependent at baseline (evaluable)</td>
<td>24</td>
<td>28</td>
<td>14</td>
<td>68</td>
</tr>
<tr>
<td>Transfusion independence rate (12 wks)</td>
<td>63%</td>
<td>75%</td>
<td>57%</td>
<td>68%</td>
</tr>
<tr>
<td>Minimum 2 g/dL increase in hemoglobin level (8 wks)</td>
<td>11%</td>
<td>8%</td>
<td>14%</td>
<td>13%</td>
</tr>
<tr>
<td>IWG-MRT anemia response rate</td>
<td>48%</td>
<td>55%</td>
<td>36%</td>
<td>48%</td>
</tr>
</tbody>
</table>

Of the transfusion dependent patients who did not achieve a full transfusion independence response, 23% achieved at least a 50% reduction in transfusion requirement in any 3-month period.

### Onset and Durability of Response (Core and Extension Study)

<table>
<thead>
<tr>
<th>Onset and Durability of Response (Core and Extension Study)</th>
<th>Median</th>
<th>Min-Max</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to confirmed response (12 weeks) (Core; days)³</td>
<td>85</td>
<td>85-353</td>
</tr>
<tr>
<td>Duration of transfusion-free period (12 weeks) (Core and Extension; days)³</td>
<td>Not yet reached</td>
<td>85-988*</td>
</tr>
</tbody>
</table>

- 3 additional subjects achieved 12 week transfusion independence response during the Extension Study

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³ Data based on responders

* Ongoing as of November 2012

Pardanani et al, ASH 2012

Update: Abstract 106
Pardanani et al, ASH 2013

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Not statistically significant vs. 300mg QD
Efficacy of JAK inhibitors in MF Patients with Thrombocytopenia (50-100 x 10^9/L)

Talpaz et al, ASH 2012

Ruxolitinib

Pacritinib

Combined Best Response up to Week 24 data from two pacritinib Phase 2 clinical trials in patients with myelofibrosis

Komrojki et al, ASH, 2011; Mesa et. al. EHA 2011
JAK Inhibition: Other Applications

- **Hydroxyurea refractory / intolerant PV and ET**
  - ‘RESPONSE’ Trial

- **MDS/ MPN with JAK2 V617F mutation (e.g. CMML, RARS-T)**

- **JAK2-rearranged myeloid neoplasms**
  - Cytogenetic remissions with ruxolitinib in *PCM1-JAK2*-positive disease

- **Chuvash Polycythemia**
  - R200W-mutated *VHL* fails to bind SOCS1 and degrade JAK2

- **Chronic Neutrophilic Leukemia / Atypical CML**
  - *CSF3R* mutations signal through JAK2

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2. Lierman et al, Blood, 2012
What are the unmet needs for MF in the JAK inhibitor era?

- Resistance/Disease Persistence to JAK inhibitors
- Lack of improvement in baseline cytopenias
- Lack of significant inhibition of the neoplastic clone
- Magnitude of the effects on natural history of disease unclear at this point
  - Leukemic transformation?
  - Survival benefit?
Other Novel Therapies in MF

• Epigenetic Modulators
• Immunomodulatory Agents
• Non-JAK kinase Inhibitors
• Antifibrosis agents
• Agents targeting the malignant megakaryocyte
• Telomerase Inhibitors
• Combination therapies
Mutations in Epigenetic Modifiers are an aspect of the Molecular Complexity of PMF

Chart adapted from analysis of all 10 markers in 483 patients with PMF: Vannucchi et al, Leukemia 2013
## Hypermethylated Genes in Ph- MPN

<table>
<thead>
<tr>
<th>Author</th>
<th>Gene</th>
<th>Function</th>
<th>N</th>
<th>Methy %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Capello D 2008</td>
<td>SOCS3</td>
<td>Signal Transduction</td>
<td>112</td>
<td>41</td>
</tr>
<tr>
<td>Jost 2007</td>
<td>SOCS1</td>
<td>Signal Transduction</td>
<td>39</td>
<td>15</td>
</tr>
<tr>
<td>Quentmeier 2007</td>
<td>SOCS2</td>
<td>Signal Transduction</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>Wang 2002</td>
<td>p15</td>
<td>Cell Cycle Regulation</td>
<td>10</td>
<td>40</td>
</tr>
<tr>
<td>Jones 2004</td>
<td>RARβ</td>
<td>Retinoic acid receptor</td>
<td>18</td>
<td>89</td>
</tr>
<tr>
<td>Bogani 2008</td>
<td>CXCR4</td>
<td>Chemokine receptor</td>
<td>18</td>
<td>100</td>
</tr>
</tbody>
</table>
Drugs that act on the Epigenome

DNA Methyltransferase Inhibitors

- 5-aza-2'-deoxy-cytidine (decitabine)
- 5-aza-cytidine (azacitidine)

Histone Deacetylase Inhibitors

- Vorinostat (SAHA)
- Trichostatin A
- Romidepsin (Depsipeptide, FK-228)
Epigenetic modulators correct the abnormal stem cell trafficking in MF

- Combined DNMT inhibitor plus HDAC inhibitor in MF led to
  - Decrease in numbers of MF progenitor CD34+ cells
  - Upregulation in CXCR4
  - Correction of the abnormal stem cell trafficking in a NOD/SCID mouse model
  - Elimination of JAK2V617F + clonogenic cells

The HDAC Inhibitor ITF2357 inhibits the clonogenic activity of JAK2V617F cells

## Clinical Relevance of DNMT Inhibition in MF?

<table>
<thead>
<tr>
<th>Agent</th>
<th>N</th>
<th>Response Rate</th>
<th>Comments</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacitidine</td>
<td>34</td>
<td>24%</td>
<td>PR=1 CI=7</td>
<td>Quintas-Cardama</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>10</td>
<td>0</td>
<td>Only 2 patients received &gt;3 cycles</td>
<td>Mesa</td>
</tr>
<tr>
<td>Decitabine</td>
<td>21</td>
<td>37%</td>
<td>PR=2 CI=6</td>
<td>Odenike</td>
</tr>
<tr>
<td>Azacitidine</td>
<td>50</td>
<td>52%</td>
<td>Focused on MPN-blast phase</td>
<td>Thepot</td>
</tr>
</tbody>
</table>

Quintas-Cardama et al, Leukemia 2008; 22:965-70  
Odenike O et al, ASH Annual Meeting abstracts, 2008, #2809  
Thepot S et al, Blood 2010; 116:3735-42
## HDAC inhibitor trials in MF

<table>
<thead>
<tr>
<th>Agent</th>
<th>Phase</th>
<th>N</th>
<th>Comments</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Givinostat</td>
<td>II</td>
<td>29</td>
<td>Included 16 pts with MF, 3 achieved major response in anemia</td>
<td>Rambaldi</td>
</tr>
<tr>
<td>Pracinostat</td>
<td>II</td>
<td>22</td>
<td>2 patients with anemia response</td>
<td>Quintas-Cardama</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>Ia/II</td>
<td>176</td>
<td>Included 13 pts with MF, CI in 4 patients</td>
<td>DeAngelo</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>II</td>
<td>35</td>
<td>Only 16 pts received &gt;2 cycles, IWG response=1</td>
<td>DeAngelo</td>
</tr>
<tr>
<td>Panobinostat</td>
<td>I</td>
<td>18</td>
<td>3 of 5 patients treated &gt;6 cycles responded</td>
<td>Mascarenhas</td>
</tr>
</tbody>
</table>

Rambaldi A et al, BJH, 2010; 150:446-455  
DeAngelo DJ, Leukemia 2013  
Mascarenhas J, BJH, 2008; 161:68-75  
DeAngelo DJ, BJH 2013
**Improved Efficacy of Combined Ruxolitinib and Panobinostat Treatment in murine model of JAK2V617F**

Enhanced efficacy was observed with a combination of RUX and PAN

- There was no major change in tolerability, as assessed by body weight, between panobinostat alone or in combination with ruxolitinib

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mice Count</th>
<th>Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAN 4 mg/kg</td>
<td>27% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAN 8 mg/kg</td>
<td>20% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAN 12 mg/kg</td>
<td>11% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUX 60 mg/kg</td>
<td>40% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUX 60 mg/kg + PAN 4 mg/kg</td>
<td>22% *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUX 60 mg/kg + PAN 8 mg/kg</td>
<td>15% *†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RUX 60 mg/kg + PAN 12 mg/kg</td>
<td>3% *† ‡</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P < 0.05 vs vehicle control  † P < 0.05 vs rux  ‡ P < 0.05 vs pan at same dose

Combination trials with Epigenetic Modulators

• Panobinostat and ruxolitinib
  - Phase I/II (PRIME) Study- NCT0169301 at Mt Sinai
  - Phase 1b study- NCT1433445 in Europe

• Azacitidine and ruxolitinib
  – Phase I/II Study- NCT01787487 at MDACC

• Future combinations
  – HDAC inhibitor + DNMT inhibitor
  – HDAC inhibitor +HSP90 inhibitor?
Non-JAK Kinase Inhibitors in MF

Combination trials of JAK Inhibitors and inhibitors of downstream signaling pathways
- Ruxolitinib plus the PI3K/mTOR inhibitor BKM120
- Clinicaltrials.gov-NCT01703248

Adapted from Odenike O, ASH Education Session 2013
Thalidomide and IMiD Analogs in Myelofibrosis

• Thalidomide
  – Antiangiogenic, anti-TNFα and T-cell co-stimulatory effects
  – Response rates in the 22% range for anemia, 8% for splenomegaly
  – Toxicities include sedation, neuropathy

• Lenalidomide (CC-5013)
  – Anemia response rates similar to Thalidomide
  – Active in del 5q

• Pomalidomide (CC-4047)

Mesa RA Blood 2010, 116:4436-38
Combination trials with Immunomodulatory Agents

• Ruxolitinib plus Pomalidomide
  – Phase I/II in Germany
  – Clinical trials.gov NCT01644110

• Ruxolitinib plus Lenalidomide
  – Clinical trials.gov NCT01375140
How I treat MF in the JAK Inhibitor era
DIPSS for Predicting Survival IN PMF

- Adverse prognostic Factors:
  - Age > 65
  - *Hb < 10 g/dl
  - WBC > 25K/μL
  - PB blasts ≥ 1%
  - Constitutional symptoms

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk Group</th>
<th>Median Survival (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Low</td>
<td>Not reached</td>
</tr>
<tr>
<td>1-2</td>
<td>Intermediate-1</td>
<td>9.8</td>
</tr>
<tr>
<td>3-4</td>
<td>Intermediate-2</td>
<td>4.8</td>
</tr>
<tr>
<td>&gt;4</td>
<td>High</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Low risk; Score = 0
Median survival: Not Reached

Int – 1 risk; Score = 1-2
Median Survival: 9.8 yrs.

Int – 2 risk: Score = 3-4
Median Survival: 4.8 yrs.

High Risk; Score = 5-6
Median Survival: 2.3 yrs.

- Asymptomatic: Observe
- Symptomatic or anemic:
  - JAK inhibitor if symptomatic
  - Clinical trial if cytopenic and / or prior JAK inhibitor exposure.
  - Consider ImiDs or androgens or ESAs for anemia

- Early referral for allogeneic SCT.
- JAK inhibitor if symptomatic
- Clinical trial if significant cytopenias and / or prior JAK inhibitor exposure

Adapted from Odenike O, ASH Education Session 2013