Myeloproliferative Neoplasms 2017

Leukemia and Lymphoma Society - Northern CA Blood Cancer Conference

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The Itch

I have an itch you cannot know, not the least hint will ever show
No bump no rash no insect bite provides a clue as to my plight
My clothes, a shower, the air I breathe make my skin prickle and seethe
Constant reminders it provides of the disease my body hides
Maddening tears the burning brings, no scratch, no pills can stop the stings
Life is good, it could be much worse
I can live with my itchy curse
I walk the dog to pass the time, take deep breaths and clear my mind
Pruritus is a small price for my wonderful blessed life

Paul Nudelman
Poet & PV Patient
Gurnee, IL, USA
MPNS 2017

• MPNs – spectrum of burden, risk, care needs
• Evolving Options for PV and ET
• Footprint of Ruxolitinib 4 years after MF Launch
• New JAK inhibitors
• JAKi combinations
• New Targets
• Future Directions
## Acute vs. Chronic Neoplasms

<table>
<thead>
<tr>
<th>ACUTE Neoplasm (AML, DLBCL, Some MF)</th>
<th>CHRONIC Neoplasm (ET, PV, Some MF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Life threatening in &lt; 2 years</td>
<td>• Survival ranges from normal to diminished but at least 5 years</td>
</tr>
<tr>
<td>• Disease eradication most critical goal</td>
<td>• Diminishment of disease morbidity a key goal</td>
</tr>
<tr>
<td>• Significant toxicity acceptable to extend life</td>
<td>• QOL and acceptability of toxicity a key issue</td>
</tr>
<tr>
<td>• Quality of life frequently a casualty of therapy</td>
<td>• Cure a goal, but not at any price</td>
</tr>
</tbody>
</table>
### Assessing MPN Patient Risk

<table>
<thead>
<tr>
<th></th>
<th>IPSET (ET—3 groups) Survival thrombosis risk</th>
<th>PV Risk (4 groups) Survival leukemia rates</th>
<th>DIPSS (PMF—4 groups) Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>≥ 60 (2 pts) vs &lt; 60</td>
<td>≥ 67 (5 pts)</td>
<td>≥ 65 (1 pt) vs &lt; 65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>57-66 (2 pts), &lt; 60</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(0)</td>
<td></td>
</tr>
<tr>
<td><strong>Leukocytes</strong></td>
<td>≥ 11 (1 pt) vs &lt; 11 x 10⁹/L</td>
<td>≥ 15 (1 point) vs &lt; 15 x 10⁹/L</td>
<td>&gt; 25 (1 pt) vs ≤ 25 x 10⁹/L</td>
</tr>
<tr>
<td><strong>Hemoglobin</strong></td>
<td></td>
<td></td>
<td>&lt; 10 (2 pts) vs ≥ 10 g/dL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Constitutional symptoms</strong></td>
<td></td>
<td></td>
<td>Present^{a} (1pt) vs absent</td>
</tr>
<tr>
<td><strong>Blasts</strong></td>
<td></td>
<td></td>
<td>≥ 1% (1pt) vs &lt; 1%</td>
</tr>
<tr>
<td><strong>Prior thrombosis</strong></td>
<td>Yes (1 point) vs No</td>
<td>Yes (1 Point) vs No</td>
<td></td>
</tr>
<tr>
<td><strong>Risk group point cutoffs</strong></td>
<td>0; 1-2; 3-4 pts</td>
<td>0; 1-2; 3; 4 pts</td>
<td>0; 1-2; 3-4; ≥ 4 pts</td>
</tr>
</tbody>
</table>

^{a} 10% weight loss over prior 6 months, night sweats, unexplained fever.

*Blood 2012* | *Leuk 2014* | *Blood 2010*
Test ID: NGSHM
OncoHeme Next Generation Sequencing (NGS), Hematologic Neoplasms

Testing Algorithm

This assay detects the following mutations:
ASXL1 (NM_015338.5) exons 11-14, BCOR (NM_001123385.1) exons 5-16, BRAF (NM_004333.4) exon 15, CALR (NM_004343.3) exon 9, CBL (NM_005188.3) exons 8-9, CEBPA (NM_004364.4) exon 1, CSF3R (NM_000760.3) exons 14 and 17, DNMT3A (NM_022552.4) exons 8-23, ETV6 (NM_001987.4) exons 3-8, EZH2 (NM_004456.4) exons 3-21, FLT3 (NM_004119.2) exons 14-20, GATA1 (NM_002049.3) exons 2 and 4, GATA2 (NM_001145661.1) exons 4-8, IDH1 (NM_005896.3) exon 4, IDH2 (NM_002168.3) exon 4, JAK2 (NM_004972.3) exons 12-16, KIT (NM_000222.2) exons 8-11 and 17, KRAS (NM_033360.3) exons 2 and 3, MPL (NM_005373.2) exons 10-11, MYD88 (NM_002468.4) exon 5, NOTCH1 (NM_017617.3) exons 26, 27, and 34, NPM1 (NM_002520.6) exons 9, 11, and 12, NRAS (NM_002524.4) exons 2 and 3, PHF6 (NM_001015877.1) exons 2-10, PTPN11 (NM_002834.3) exons 3-4 and 12-13, RUNX1 (NM_001001890.2) exons 4-10, SETBP1 (NM_015559.2) partial exon 6; amino acids 400 - 950, SF3B1 (NM_012433.2) exons 14-17, SRSF2 (NM_003016.4) exons 1 and 2, TERT (NM_198253.2) exons 2-16, TET2 (NM_001127208.2) exons 3-11, TP53 (NM_000546.4) exons 4-9, U2AF1 (NM_001025203.1) exons 2, 7, and 9, WT1 (NM_024426.4) exons 1-11, and ZRSR2 (NM_005089.3) exons 1-11.
NGS and Myeloid Mutations/Other Prognosis

- >80% of PMF patients have a non JAK2/CALR/MPL mutation
- The greater the number the worse the prognosis
- ASXL1, CBL, RUNX1, SRSF2 have independent adverse prognostic impact

- MF grades 2 and 3 worse prognosis than 0 and 1
- With allo outcomes may improve with SRSF2, EZH2, IDH1 mutations
  - May not improve with ASXL1, U2AF1, IDH2, DNMT3A

Tefferi et. al. ASH 2015; Guggliemi et. al. ASH 2015, Kroger et. al. ASH 2015
Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story

MPN Symptoms
- MF > PV > ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive rx frequently not effective

Vascular Events
- PV/ET > MF
- Counts matter
- Can be unrecognized

Progression
- PV/ET to MF
- PV/ET to AML
- MF to AML
- ? 2\textsuperscript{nd} MDS

Cytopenias
- MF > ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
  - TPN 30%

Baseline Health
AGE/ Medicines Comorbidities

Splenomegaly
- MF > ET/PV
- Pain not always a function of size

Baseline Health
- MF > ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
  - TPN 30%
Classic Signs and Symptoms of MPNs

Geyer H L, and Mesa R A Blood 2014;124:3529-3537
MPNS 2017

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Diagnosis of PV/ET

Assess PV/ET Risk Score & Assess MPN Symptoms (MPN 10)

Decide on need for concurrent cytoreduction based on PV Risk and Symptoms

YES

Front Line Cytoreduction HU, or HU vs INF Clinical Trial

Worsening symptom burden Vascular event, progression HU Resistance/Intolerance

Consider Ruxolitinib (PV) or INF (Trial)/HU if not previously received

NO

Monitor for symptom burden, vascular events, progression

Worsening symptom burden Vascular event, progression Phlebotomy intolerance

All PV/ET Patients

Control of Hematocrit (<45%)

Low dose aspirin
MPD-RC 112 Study Schema

- WHO 2008 ET/PV
- High Risk
  - >60 years
  - Thrombosis
  - Thrombocytosis
  - Symptomatic spleen
  - Uncontrolled CV risk factor
- Dx <5 years
- Treatment naïve

Randomized 1:1

n=168

HU n=39
PEG n=36

INTERIM ANALYSIS

HU n=86
PEG n=82

Planned analysis
75 subjects treated for 1 year

Modified protocol to include final analysis to be completed once all subjects enrolled for 1 year (n=168)

[anticipated date of 6/30/2017]
Ropeginterferon alfa-2b phase III development: PROUD/CONTI-PV

Naïve patients in need of cytoreduction

HU pre-treated (<3yrs and not full responders)

Stratified Randomization by Age, prev. HU, prev. TE

Eligible PV patient population per WHO2008 criteria

12 months treatment

Expected outcome: *) non-inferiority: Hematologic Response

** benefit: durable Hematologic Response, PFS, PV symptom relief

Ropeginterferon

Hydroxyurea

Efficacy analysis*)

Efficacy analysis**)
• Both treatments achieved robust hematologic control from week 12 on.

• Non-inferiority of Ropeginterferon vs. HU demonstrated: 12 month Complete Hematologic Response: 43.1 vs. 45.6% (p=0.0028).

• Safety and tolerability of Ropeginterferon showed benefits over HU.

• Five related secondary malignancies appeared in the HU cohort (long-term).
Final results from the Phase 3 trial ARETA comparing a novel, extended-release \textit{anagrelide} formulation to placebo in essential thrombocythemia patients with defined risk status

\textit{Heinz Gisslinger, Christoph Klade, Kudrat Abdulkadyrov, Sławomira Kyrcz-Krzemien, Elena Karyagina, Anait Melikyan, Kryztof Warzocha, Barbara Grohmann-Izay, Juri Hodisch, Rudolf Widmann, Robert Kralovics, Petro E. Petrides, Jiri Schwarz, and Jean-Jacques Kiladjian}
ARETA
Phase III, multicenter, randomised, subject- and sponsor-blinded, placebo-controlled study – early intervention in ET

Eligible patients
ET diagnosed according to WHO2008 with „at risk“ status

Stratification by JAK2 status

Randomization

1:1

Anagrelide ER
2-8 mg/day

Placebo

6 weeks titration weekly visits
1 year main study visits every 3 months
Up to 3 years extension period visits every 3 months

Primary endpoint:
ET-related cardiovascular events (as confirmed by independent blinded Endpoint Adjudication Committee), or disease progression or disease worsening (platelet increase >1000 G/l)
SUMMARY & CONCLUSION

- Primary Endpoint time to first ET related event met ($p=0.0008$).
- Platelet count normalization and delayed progression to high risk status.
- Safety profile consistent with conventional anagrelide formulations.
- More convenient dosing schedule compared to licensed immediate release formulations confirmed.

In conclusion data from ARETA support a “treat early concept” for all ET patients where platelet count or symptom reduction is a goal.
**RESPONSE Study Design**

- Resistance to or intolerance of HU (modified ELN criteria)
- Phlebotomy requirement
- Splenomegaly (spleen volume ≥450 cm³)

**Prerandomization (day −28 to day −1)**
Hct 40% to 45%

- Patients randomized to BAT were permitted to cross over to ruxolitinib at week 32 if they did not meet the primary endpoint or after week 32 in case of phlebotomy eligibility or splenomegaly progression

**Randomized 1:1**

- Ruxolitinib 10 mg twice daily
  - n=110

- Extended treatment phase
  - Week 256

- Crossover to ruxolitinib

- Week 80 (planned analysis)

- Week 256

ELN=European LeukemiaNet; Hct=hematocrit

Vannucchi et. al. NEJM 2014
Kiladjian et. al. EHA 2015
During MRI data review for the current 80-week analysis, 2 additional patients were identified that were primary responders in the ruxolitinib arm bringing the total number (%) of primary responders to 25 (22.7%). No additional responders were identified in the BAT group.

Vannucchi et al. NEJM 2014
Kiladjian et al. EHA 2015
Phlebotomy Procedures in the Ruxolitinib Arm

- Of the 98 patients who did not discontinue ruxolitinib at week 32, 88 (89.8%) had no phlebotomy between weeks 32 and 80.

- Of the 109 patients randomized to BAT who did not discontinue before week 8, 68 (62%) had ≥1 phlebotomy and 22 (20%) had ≥3 phlebotomies between week 8 and 32.

Vannucchi et al. NEJM 2014
Kiladjian et al. EHA 2015
Improvements in Blood Counts – Rux in PV

<table>
<thead>
<tr>
<th>Changes in WBC Counts and Platelet Counts in Ruxolitinib Arm</th>
<th>N</th>
<th>Week 32 % Patients</th>
<th>Week 80 % Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC ≤ 10x10⁹/L in patients with baseline WBC &gt; 10 x 10⁹/L</td>
<td>87</td>
<td>31.0</td>
<td>47.1</td>
</tr>
<tr>
<td>WBC ≤ 10x10⁹/L in patients with baseline WBC &gt; 15 x 10⁹/L</td>
<td>64</td>
<td>26.6</td>
<td>42.2</td>
</tr>
<tr>
<td>Platelets ≤ 400x10⁹/L in patients with baseline platelet count &gt;400x10⁹/L</td>
<td>54</td>
<td>44.4</td>
<td>59.3</td>
</tr>
</tbody>
</table>

Vannucchi et al. NEJM 2014
Kiladjian et al. EHA 2015
Thromboembolic Adverse Events

- At the week 80 analysis, the rates of thromboembolic events per 100 patient-years of exposure were 1.8 in the ruxolitinib arm vs 8.2 in the BAT arm.

<table>
<thead>
<tr>
<th>Exposure, Patient-Years</th>
<th>Ruxolitinib (n=110)</th>
<th>BAT (n=111*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate per 100 Patient-Years of Exposure</td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
</tr>
<tr>
<td>All thromboembolic events</td>
<td>1.8</td>
<td>0.9</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Retinal vascular thrombosis</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Splenic infarction</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombophlebitis</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*1 patient was randomized to BAT but did not receive study treatment
†1 patient in the BAT arm had both pulmonary embolism and deep vein thrombosis

Vannucchi et. al. NEJM 2014
Kiladjian et. al. EHA 2015
MPNS 2017

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Duration of ≥35% Reduction From Baseline in Spleen Volume*

- In the primary analysis, 41.9% of patients randomized to ruxolitinib vs 0.7% randomized to placebo had a ≥35% spleen volume reduction at Week 24 (odds ratio, 134.4 [95% CI, 18.0–1004.9]; \( P < 0.001 \))

- In the 5-year analysis, median duration of response was 168.3 weeks for the 92 patients who had a spleen response with ruxolitinib

\*The median time to loss of spleen response was defined as the interval from the first spleen response to the first spleen volume that was a <35% reduction from Baseline and a >25% increase from the nadir.

Gupta et al. ASCO 2016
Mean Percentage Change From Baseline in Spleen Volume Over Time*

- Mean percentage reductions from Baseline in spleen volume were rapid and durable in the ruxolitinib randomized and crossover arms.

For patients in the ruxolitinib crossover arm, Baseline represents the date of crossover to ruxolitinib.

**Patients, n**

<table>
<thead>
<tr>
<th>Patients, n</th>
<th>Ruxolitinib randomized</th>
<th>Ruxolitinib crossover</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>155</td>
<td>111</td>
<td>107</td>
</tr>
<tr>
<td>24</td>
<td>139</td>
<td>85</td>
<td>35</td>
</tr>
<tr>
<td>48</td>
<td>120</td>
<td>44</td>
<td>1</td>
</tr>
<tr>
<td>72</td>
<td>107</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>96</td>
<td>100</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>85</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>144</td>
<td>76</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>168</td>
<td>57</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>192</td>
<td>55</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>216</td>
<td>53</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>240</td>
<td>50</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>264</td>
<td>42</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Gupta et. al. ASCO 2016
Overall Survival as Assessed by the Kaplan-Meier Method

- Median follow-up was 268.4 weeks for ruxolitinib and 269.0 weeks for placebo
- Median OS was not reached for patients randomized to ruxolitinib and was 200 weeks for patients in the placebo arm
  - A sensitivity analysis censoring patients at crossover showed a median OS of 108 weeks for patients randomized to placebo

### Patients at risk, n

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>155</td>
<td>154</td>
</tr>
<tr>
<td>24</td>
<td>148</td>
<td>144</td>
</tr>
<tr>
<td>48</td>
<td>137</td>
<td>119</td>
</tr>
<tr>
<td>72</td>
<td>124</td>
<td>105</td>
</tr>
<tr>
<td>96</td>
<td>112</td>
<td>95</td>
</tr>
<tr>
<td>120</td>
<td>108</td>
<td>85</td>
</tr>
<tr>
<td>144</td>
<td>100</td>
<td>78</td>
</tr>
<tr>
<td>168</td>
<td>86</td>
<td>72</td>
</tr>
<tr>
<td>192</td>
<td>80</td>
<td>59</td>
</tr>
<tr>
<td>216</td>
<td>75</td>
<td>51</td>
</tr>
<tr>
<td>240</td>
<td>69</td>
<td>46</td>
</tr>
<tr>
<td>264</td>
<td>57</td>
<td>38</td>
</tr>
</tbody>
</table>

### Deaths, n/N (%)

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>69/155 (44.5)</td>
<td>82/154 (53.2)</td>
<td></td>
</tr>
</tbody>
</table>

### Censored, n/N (%)

<table>
<thead>
<tr>
<th></th>
<th>Ruxolitinib</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>86/155 (55.5)</td>
<td>72/154 (46.8)</td>
<td></td>
</tr>
</tbody>
</table>

### Hazard ratio, 0.69 (95%, CI, 0.50–0.96)

\[ P=0.025 \text{ (nominal)} \]

Gupta et. al. ASCO 2016
TREATMENT FOR LOW-RISK MYELOFIBROSIS

Low risk
Risk score = 0
IPSS
DIPSS and
DIPSS-Plus

Assess symptom burden using MPN-SAF TSS-10 items if not done previously

Asymptomatic
Symptomatic
TREATMENT FOR LOW-RISK MYELOFIBROSIS

Asymptomatic
- Observation or Clinical trial
  - Monitor for signs and symptoms of disease progression every 3–6 months
  - Asymptomatic
  - Symptomatic

Symptomatic
- Ruxolitinib or Interferons (Interferon alfa-2b, pegylated interferon alpha-2a, and pegylated interferon alpha-2b) or Clinical trial
  - Monitor response and signs/symptoms of disease progression every 3–6 months
  - Response → Continue prior treatment
  - No Response or Loss of response → Disease progression → INT-1, INT-2/High risk, and Advanced stage MF

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TREATMENT FOR INTERMEDIATE-RISK 1 (INT-1) MYELOFIBROSIS

Intermediate-risk 1 (INT-1)
Risk score:
IPSS=1
DIPSS-Plus = 1
DIPSS= 1 or 2

Assess symptom burden using MPN-SAF TSS-10 items if not done previously

Observation or Ruxolitinib if symptomatic or Clinical trial or Allogeneic HCT

Monitor response and signs/symptoms of disease progression every 3–6 months

Response
Continue prior treatment

No Response or Loss of response

Disease progression
INT-2/High risk, and Advanced stage MF

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TREATMENT FOR INTERMEDIATE-RISK 2 (INT-2) OR HIGH-RISK MYELOFIBROSIS

**Intermediate-risk 2 (INT-2) Risk score:**
(IPSS = 2, DIPSS-Plus = 2 or 3, DIPSS = 3 or 4)  
Or **High-risk Risk score:**  
(IPSS = 3, DIPSS-Plus = 4 to 6, DIPSS = 5 or 6)

- **Transplant candidate**  →  **Allogeneic HCT**
- **Not a transplant candidate**
- **Not a transplant candidate and symptomatic anemia only**  →  **See Management of MF-Associated Anemia**
- **Assess symptom burden using MPN-SAF TSS-10 items if not done previously**
NCCN Guidelines Version 1.2017
Myeloproliferative Neoplasms

TREATMENT FOR INTERMEDIATE-RISK 2 (INT-2) OR HIGH-RISK MYELOFIBROSIS

Platelets ≤50K → Consider Clinical trial

Platelets >50K → Ruxolitinib or Clinical trial

Monitor response and signs/symptoms of disease progression every 3–6 months

Response → Continue prior treatment

No Response or Loss of response

Disease progression
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**Key Eligibility Criteria**
- Primary/secondary MF
- Platelets ≤100,000/µL,
- Prior JAK2 inhibitors allowed

**Randomization (N=311)**
- PAC 400 mg QD
- PAC 200 mg BID
- BAT (including RUX)

**Co-Primary Endpoints (Wk 24)**
- % of pts achieving ≥35% SVR
- % of pts achieving ≥50% reduction in TSS*

*TSS, total symptom score by MPN-SAF 2.0

- In PK simulations, PAC 200 mg BID was predicted to have higher $C_{\text{min}}$ and lower $C_{\text{max}}$ than PAC 400 QD
- Crossover from BAT allowed after progression (any time) or at Wk 24

**Study Objectives:**
- Primary: efficacy of pooled QD and BID PAC vs BAT
- Secondary: efficacy of QD PAC or BID PAC separately vs BAT
Efficacy: Analysis by Arm

**SVR**

- **PAC QD (n=51)**
  - Mean: -19.8
  - Median: -19.0

- **PAC BID (n=57)**
  - Mean: -21.0
  - Median: -23.0

- **RUX (n=22)**
  - Other (n=28)
  - Mean: -4.6
  - Median: -4.5

% Change from Baseline

**TSS**

- **PAC QD (n=51)**
  - Mean: -18.7
  - Median: -27.0

- **PAC BID (n=55)**
  - Mean: -33.6
  - Median: -41.0

- **RUX (n=22)**
  - Other (n=29)
  - Mean: -3.9
  - Median: -15.0

% Change from Baseline

35% decrease

50% decrease
Patient Global Impression of Change Scores

![Bar chart showing improvement and no improvement categories with different groups.

- PAC QD (n=75)
- PAC BID (n=74)
- BAT (n=72)

- Very much improved
- Much improved
- Minimally improved
- No change
- Minimally worse
- Much worse
- Very much worse

Patients, %

MAYO CLINIC Cancer Center
Conclusions
Despite study truncation due to the clinical hold:

- PAC (QD+BID) was significantly more effective than BAT (including RUX) for SVR ($p=0.001$) and trended toward improved TSS ($p=0.079$)
- PAC BID appeared more effective than PAC QD versus BAT for SVR and TSS
- SVR and TSS responses to PAC BID were consistent across demographic and disease risk characteristics
- PAC BID appeared to have a better benefit/risk profile than BAT, which included RUX
Momelotinib Update 11/16/2016

Simplify 1

- Spleen Redux
- Symp (TSS)
- Anemia Improve

MOM non inferior to RUX
Superior

Simplify 2

- Spleen Redux
- Symp (TSS)
- Anemia Improve

MOM SUP to BAT (RUX)
Superior
MPNS 2017

- MPNs – spectrum of burden, risk, care needs
- Evolving Options for PV and ET
- Footprint of Ruxolitinib 4 years after MF Launch
- New JAK inhibitors
- JAKi combinations
- New Targets
- Future Directions
<table>
<thead>
<tr>
<th>Combination + Ruxolitinib</th>
<th>Authors</th>
<th>Spleen Response</th>
<th>Symptom Response</th>
<th>PLT Impact</th>
<th>HB Impact</th>
<th>Fibrosis Response</th>
<th>Other</th>
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<td>Danazol</td>
<td>Gowin Mascarenhas Mesa</td>
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<td>5- AZA</td>
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MPNS 2017

• MPNs – spectrum of burden, risk, care needs
• Evolving Options for PV and ET
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• New JAK inhibitors
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• New Targets
• Future Directions
A Phase 2, Prospective Study Of PRM-151 In Subjects With Primary Myelofibrosis (PMF), Post-Polycythemia Vera MF (post-PV MF), Or Post-Essential Thrombocythemia MF (post-ET MF)

Key Eligibility:
- Int-1, Int-2, or High Risk MF: Primary, Post-ET, or Post-PV
- WHO Grade 2 or 3 MF
- Not a candidate for ruxolitinib based on
  - EITHER Hgb <100 g/L, requiring transfusions, and intolerant of or inadequate response to RUX
  - OR Platelets <50 x 10^9/L

84 subjects

- 10 mg/kg PRM-151 Q4W
- 3 mg/kg PRM-151 Q4W
- 0.3 mg/kg PRM-151 Q4W
Imetelstat Phase 2 MF Study – Opened for Enrollment

A Randomized, Single-Blind, Multicenter Phase 2 Study to Evaluate the Activity of 2 Dose Levels of Imetelstat in Subjects With Intermediate-2 or High-Risk Myelofibrosis (MF) Relapsed/Refractory to Janus Kinase (JAK) Inhibitor

Co-Primary End Points
- To evaluate the spleen response rate at Week 24
  - The percentage of participants who achieve ≥ 35% reduction in spleen volume from baseline as measured by MRI
- To evaluate the symptom response rate at Week 24
  - The percentage of subjects who have ≥50% reduction in total symptom score as measured by modified MFSAF v2.0.

Secondary End Points
- To measure complete remission (CR) or partial remission (PR) per modified 2013 IWG-MRT criteria
- To measure clinical improvement (CI) per modified 2013 IWG-MRT criteria
- PK profile
- Safety profile
- Overall Survival

Key Eligibility Criteria*
- 18 years of age and older
- Diagnosis of PMF or PET-MF or PPV-MF
- DIPSS intermediate-2 or high risk MF
- Measurable splenomegaly
- Active symptoms of MF prior to study entry
- Documented progressive disease during or after JAK inhibitor
- ANC ≥ 1,500/µl
- Platelets ≥ 75,000/ mm³
- Peripheral blood and bone marrow blast count of <10%

*Not a complete list of inclusion and exclusion criteria
NCT02426086 – clinicaltrials.gov
New MPN Therapies – Possible Positioning

**Myelofibrosis**
- Front Line: Ruxolitinib
- Second Line: Momelotinib?
- Third Line: Momelotinib?

**Polycythemia Vera**
- Front Line: HU, ? INF
- Second Line: Ruxolitinib
- Third Line: Ruxolitinib

**Essential Thrombocythemia**
- Front Line: HU, ? INF
- Second Line: Anagrelide
- Third Line: Ruxolitinib
Non Transplant Care of MPN Patients

- MPNs – spectrum of burden, risk, care needs
- Evolving Options for PV and ET
- Footprint of Ruxolitinib 4 years after MF Launch
- New JAK inhibitors
- JAKi combinations
- New Targets
- Future Directions
CRISPR and MPNs: Collaborations – Advocacy by Patient Groups/Foundations and Scientists

- Patient groups have been at vanguard encouraging CRISPR scientists to explore MPNs as a target genetic disease
- Clinical trials first in HIV, now in hemophilia B
- CRISPR Editing of JAK2-V617F in vitro in patient samples

The MPN Yoga Study - Feasibility 1

**METHODS**

- Recruitment using Social Media
- Surveys evaluated at Wk 1, Wk 7 and Wk 12
- Participants completed 60 minutes online-streamed yoga/week
- After each session, patients complete the MPN-10

**RESULTS**

- 38 MPN Patients participated
  - PV (38%)
  - ET (37%)
  - MF (20%)
- 43% of participants completed >60min/wk
- Baseline MPN TSS: 34.6
- 68% were satisfied (32%) or very satisfied (36%) with online yoga
- Improved MPN-10 by 4.77 points, p<0.004
- Improved fatigue, anxiety, depression, sleep (all p=0.05)

M3 Team: Mayo Clinic: R. Mesa and K. Gowin
Arizona State University: Jennifer Huberty PhD
MPN Yoga II - Pilot

Online Registration & Randomization

At Home Yoga (N=30)
- Active Yoga
  - 12 Weeks
  - >/= 60 Min/ Week
  - Fitbit tracking (Blinded)
  - Daily Logs-Yoga and activity
  - Blood (2 Timepoints)
    - TNFa
    - IL6
  - Saliva (2 Timepoints, 4x each timpoint)
    - Cortisol
    - MPN Sx, QOL, Sleep

Wait List Control (N=30)
- Wait List
  - 12 Weeks
  - Fitbit tracking/Blinded
  - Usual Level of Activity
  - Daily Logs - Activity
  - MPN Sx, QOL, Sleep

Post 12 week Cross Over

Key Eligibility
- MPN Patient
- Not Depressed
- PS<3
- Not already doing yoga or Mindfullness
- <150 Min of weekly exercise

MPN Yoga Team:
Arizona State University: Jennifer Huberty PhD
Linda Larkey, PhD
Ryan Eckert, B.S.
Mayo Clinic Arizona
R. Mesa, MD
Amylou Dueck, PhD
K. Gowin, MD

Online Registration & Randomization
Acceptance and Commitment Therapy for MPNs - The Opportunity -

Psychological Intervention

Accept Value Be Present Action

Physical Emotional Mental Financial Relationships

ACT in Chronic Conditions
- Chronic Pain
  - ↓ anxiety
  - ↓ pain
  - ↓ pain disability
  - ↑ QOL

- Fibromyalgia
  - ↑ mental QOL
  - ↓ anxiety

- Chronic Fatigue
  - ↓ insomnia
  - ↓ anxiety
  - ↓ depression
  - ↓ fatigue

ACT in Cancer
- Breast Cancer
  - ↑ QOL
  - ↓ Depressive
  - ↓ Anxiety

- CNS Tumors
  - ↑ QOL brain tumor specific
  - Completed Cancer Treatment

Padrnos, Geda, Stonnington & Mesa: Mayo Clinic
Overcoming Blood Diseases – A Partnership

Top 10 List

10. Learn about your disease
April 23-25, 2010
The Sheraton Chicago Hotel & Towers
Chicago, Illinois

Course Director:
Ruben Mesa, MD

Course Co-Directors:
Timothy Call, MD
Phillip Greipp, MD
Thomas Hiebermann, MD
Joseph Mikhaeli, MD
Tait Shanafelt, MD
David Steensma, MD

Mayo Clinic Hematology
Arizona | Minnesota | Florida
Quality of life and disease understanding: impact of attending a patient-centered cancer symposium

Leslie Padrnos¹, Amylou C. Dueck², Robyn Scherber¹, Pamela Glassley³, Rachel Stigge³, Donald Northfelt³, Joseph Mikhai³, Annette Aguirre³, Robert M. Bennett⁴ & Ruben A. Mesa³

¹Internal Medicine Residency Program, Mayo Clinic, Scottsdale, Arizona
²Division of Health Sciences Research, Mayo Clinic, Scottsdale, Arizona
³Division of Hematology and Medical Oncology, Mayo Clinic, Scottsdale, Arizona
⁴Paradise Valley Community College, Phoenix, Arizona

- Sense of community
- Deeper understanding of my disease
- Better understanding of resources to help me
- Decrease in stress
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
Precise Knowledge of Your Disease

- Rest of Your Health
- Biological Features (Genes, Proteins, Other)
- Precise Options (including Clinical Trials)
- Your Beliefs and Choices
- Your Wellness
Classic Signs and Symptoms of MPNs

Geyer H L , and Mesa R A Blood 2014;124:3529-3537
Lesson 4 MPN Symptoms ASH 2015: 
**MPNs Have A Major Impact on Employment**

- Landmark (N = 813 MPN Patients): Impact on Employment

![Graph showing impact of MPNs on employment]

Quality of Life (QOL)

- Definitions
  - “net consequence of life characteristics on a person’s perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns.” (WHO, Soc Sci Med 1995)

- **Calman’s Gap**: “the gap between one’s life expectations and actual life experiences….a good quality of life can be said to be present when the hopes of an individual are matched and fulfilled by experience.” (Calman, J Med Ethics, 1984)

  **The narrower the gap the better.**
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
What is your plan? Do you understand it?

My Plan?

- How long till it works?
- What do I do next?
- How do we know it is working?
- Cure or Control?
LANDMARK Study in PV Goals (Patients (N=382) & Physicians)

Respondents for PV, %

- Slow/delay progression of condition
- Prevention of vascular/thrombotic events
- Healthy blood counts
- Better QoL
- Symptom improvement
- Hematocrit levels <45%
- Reduce frequency of phlebotomy treatments
- Reduction in spleen size

Mesa et. al. BMC Cancer 2016;16:167
LANDMARK Study in MF
Goals (Patients (N=207) & Physicians)
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
7. Harness the power of the immune system
Using your immune system to treat your disease

Humoral – B Cell Immunity

Cellular – T Cell Immunity

Bad Cell

T/ NK Cell

T/ NK Cell
Using your immune system to treat your disease

**Humoral – B Cell Immunity**
- Rituximab
- Bexxar
- Zevalin
- Blinatumomab
- Ofatumumab
- Daratumumab
- Pembrolizumab
- PRM151

**Cellular – T Cell Immunity**
- CART (Chimeric Antigen Receptor) T Cell Therapy
- Allogeneic Stem Cell Transplant
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
7. Harness the power of the immune system
6. Take care of the rest of your health
Medicine Wheel of Health
“Integrative Medicine”
Overcoming Blood Cancers – A Partnership

**Top 10 List**

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
7. Harness the power of the immune system
6. Take care of the rest of your health
5. Targeting key weaknesses in blood cancer cells
Targeting the weakness in blood cancer cells

Targeted Inhibitors in Heme Cancers (Partial List) ("-nibs")

- Imatinib
- Nilotinib
- Dasatinib
- Ponatinib
- Bosutinib
- Ruxolitinib
- Pacritinib
- Momelotinib
- Fedratinib
- Ibrutinib
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
7. Harness the power of the immune system
6. Take care of the rest of your health
5. Targeting key weaknesses in blood cancer cells
4. Eat in a healthy way (most of the time😊)
Eat healthy most of the time
Mayo Clinic – Cancer Wellness Program

Wellness

Cancer Post Therapy Care

Cancer Deficit/Therapy Recovery Care
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
7. Harness the power of the immune system
6. Take care of the rest of your health
5. Targeting key weaknesses in blood cancer cells
4. Eat in a healthy way (most of the time)
3. The complex healing power of Stem Cell transplant
What about Autologous Stem Cell Transplant?
Putting It All Together – MPNs and QOL

MPN Patient
- Disease Prognosis
- Vascular Risk
- Symptom Burden
- Impact of Disease on QOL
- Patient Choice and Input
- Treatment Options

Role of Stem Cell Transplant

Improving Symptom Burden & QOL

Avoiding Progression

Preventing Vascular Events

Reduction of Splenomegaly

Prolonging Survival
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
7. Harness the power of the immune system
6. Take care of the rest of your health
5. Targeting key weaknesses in blood cancer cells
4. Eat in a healthy way (most of the time😊)
3. The complex healing power of Stem Cell transplant
2. Live every moment
“In 5 years we will have regrets and remorse for the things we did not do, rather than what we did.”
Don’t wait to go to Alaska
Overcoming Blood Cancers – A Partnership

Top 10 List

10. Learn about your disease
9. Understand precisely your disease
8. Have a clear plan with your team that you understand
7. Harness the power of the immune system
6. Take care of the rest of your health
5. Targeting key weaknesses in blood cancer cells
4. Eat in a healthy way (most of the time😊)
3. The complex healing power of Stem Cell transplant
2. Live every moment
1. **Focus on relationships**
What is quality of life

Quality of Life

Increasing
I would have...

• But mostly, given another shot at life, I would seize every minute… look at it and really see it… live it and never give it back. Stop sweating the small stuff.

Erma Bombeck
1927-1996
Myeloproliferative Neoplasms
Multi-Disciplinary Team
Mayo Clinic, Arizona, USA

- MPN Burden/Symptom/QOL Assessment
- Improving Transplant Outcomes
- New MPN Drug/Genetic Therapies
- Physical Activity/Behavioral Therapies
Questions?