Overcoming your MPN!

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Chair, Division of Hematology & Medical Oncology
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Arizona, USA
Symptomatic Burden in MPNs

- Why do symptoms matter in MPNs
- Development and testing of MPN Symptom Assessment
- Current and Future Management of MPN Symptoms
- Application in Clinical Trials and Next Steps
Symptoms in 1179 MPD Patients

- Weight Loss
- Bone Pain
- Night Sweats
- Pruritus
- Fatigue

ET (n=304)
PV (n=405)
MMM (n=456)

Burden of ET/PV

- Macrovascular Risk
- Microvascular Symptoms
- MPN Associated Symptoms
Clonal MPN cells

- Anemia
- Enlarged Spleen
- Fibrosis In Marrow

Symptoms:
- Fever
- Weight Loss
- Night Sweats
- Itching
- Bone pain
- Fatigue
Burden of Myelofibrosis

- Splenomegaly
- MF Associated Symptoms
- Anemia/Cytopenias
Femme Ivre Se Fatigue
1902
O. Huber Collection
Pablo Picasso (1881-1973)
Symptomatic Burden in MPNs

- Why do symptoms matter in MPNs
- Development and testing of MPN Symptom Assessment
- Current and Future Management of MPN Symptoms
- Application in Clinical Trials and Next Steps
## Current Medications for MF

### Medicines for MF Anemia
- Androgens
- EPO
- Thalidomide

### Medicines for MF Spleen
- Hydroxyurea
- Busulfan
- 2-CDA
- Splenectomy
- Splenic Radiation

### Medicines for MF Symptoms
- None

### Medicines for Anemia & Spleen
- Lenalidomide
Net Symptom Burden

Disease Sx

Rx Tox

Disease Sx

NET Effect

Time on a Medical Therapy
ENDPOINTS

- Cure
- Prolong Life
- Delay Progression
- Relieve Burden of MPN Suffering

Measured in the Eyes of the patient

Compared to?

Absence Of Dz

Compared to Controls?
MPN-SAF (N=1433)
Myeloproliferative Neoplasm Symptom Assessment Form

- English: 12%
- Spanish: 14%
- Italian: 13%
- German: 4%
- Swedish: 8%
- French: 33%
- Dutch: 16%

Scherber et al. 2011
All for measurement of the Validated Brief Fatigue Inventory

Scherber et al. 2011
6. Mark the one number that describes how, over the last week, the following symptoms have affected you.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filling up quickly when you eat (early satiety)</td>
<td>Absent</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>Absent</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>Absent</td>
</tr>
<tr>
<td>Inactivity</td>
<td>Absent</td>
</tr>
<tr>
<td>Problems with headaches</td>
<td>Absent</td>
</tr>
<tr>
<td>Problems with concentration - compared to prior to my MPD</td>
<td>Absent</td>
</tr>
<tr>
<td>Dizziness/vertigo/lightheadness</td>
<td>Absent</td>
</tr>
<tr>
<td>Numbness/tingling (in your hands and feet)</td>
<td>Absent</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>Absent</td>
</tr>
<tr>
<td>Depression or sad mood</td>
<td>Absent</td>
</tr>
<tr>
<td>Problems with sexual desire or function</td>
<td>Absent</td>
</tr>
<tr>
<td>Cough</td>
<td>Absent</td>
</tr>
<tr>
<td>Night sweats</td>
<td>Absent</td>
</tr>
<tr>
<td>Itching (pruritus)</td>
<td>Absent</td>
</tr>
<tr>
<td>Bone pain (diffuse not joint pain or arthritis)</td>
<td>Absent</td>
</tr>
<tr>
<td>Fever (greater than 100°F)</td>
<td>Absent</td>
</tr>
<tr>
<td>Unintentional weight loss last 6 months</td>
<td>Absent</td>
</tr>
</tbody>
</table>

6. What is your overall quality of life? As good as it can be. As bad as it can be. Thank you for your time!
### MPN- SAF

10 Item Total Symptom Score (TSS)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>1 to 10 (0 if absent) ranking*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours</td>
<td>(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms</td>
<td></td>
</tr>
<tr>
<td>Filling up quickly when you eat (Early satiety)</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
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<tr>
<td>Inactivity</td>
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<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
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<td>Itching (pruritus)</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
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<tr>
<td>Bone pain (diffuse not joint pain or arthritis)</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
<tr>
<td>Fever (&gt;100 F)</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)</td>
</tr>
<tr>
<td>Unintentional weight loss last 6 months</td>
<td>(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)</td>
</tr>
</tbody>
</table>

Scherber et. al. 2011
MPN-SAF (N=1433)
Myeloproliferative Neoplasm Symptom Assessment Form

Mean TSS (0-10 Point Scale)

- ET 1.9 (N=594)
- PV 2.2 (N=538)
- MF 2.5 (N=293)

P<0.001

Scherber et. al. 2011
TSS MF Subtypes (N=284)

Myeloproliferative Neoplasm Symptom Assessment Form

Mean TSS (0-10 Point Scale)

- PMF 2.5 (N=169)
- PPVMF 2.7 (N=64)
- PETMF 2.7 (N=51)

P = N.S. Between MF Subtypes

Scherber et. al. 2011
Prevalence of “Constitutional” Symptoms in 1433 MPN Patients

Scherber et. al. 2011

Fever
Wt loss
Itching
Night sweats
Fatigue

ET (N=594)
PV (N=538)
MF (N=293)

* - P<0.001
Severity of “Constitutional” Symptoms in 1433 MPN Patients

Scherber et al. 2011

- P<0.001

Severity of symptoms:
- Fever
- Weight loss
- Itching
- Night sweats
- Fatigue

ET (N=594)
PV (N=538)
MF (N=293)
Spleen Derived Symptoms in 1433 MPN Patients

Scherber et al. 2011

**Prevalence**

- Abdominal pain
- Abdominal discomfort
- Early satiety

ET (N=594)  
PV (N=538)  
MF (N=293)

**Severity**

- Abdominal pain
- Abdominal discomfort
- Early satiety

ET (N=594)  
PV (N=538)  
MF (N=293)

* - P<0.001

Scherber et al. 2011
Prevalence of “End Organ” Symptoms in 1433 MPN Patients

Scherber et al. 2011

* - P<0.001
Severity of “End Organ” Symptoms in 1433 MPN Patients

Scherber et al. 2011

* - P<0.001
Decreased QOL in 1433 MPN Patients

**Prevalence**

- ET (N=594)
- PV (N=538)
- MF (N=293)

P<0.001

**Severity**

- ET (N=594)
- PV (N=538)
- MF (N=293)

P<0.001

Scherber et. al. 2011
## EORTC ET Scales Comparison

<table>
<thead>
<tr>
<th>EORTC QLQ-C30 Scores (Mean ± SD)</th>
<th>Current Data</th>
<th>Samuelsson 2006 †</th>
<th>EORTC 2008*</th>
<th>EORTC 2008*</th>
<th>EORTC 2008*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ET (N=161)</td>
<td>Baseline values for PV and ET pts (N=1616)</td>
<td>General Population (N=7,802)</td>
<td>Cancer patients with recurrent or metastatic disease (N=4,812)</td>
<td>Patients with AML (N=155)</td>
<td></td>
</tr>
</tbody>
</table>

### EORTC Subscales

- **Physical Functioning**: 85.1 ± 16.9  
  - Samuelsson 2006 †: 90.6 ± 11.5  
  - EORTC 2008*: 89.8 ± 16.2 | 75.8 ± 23.1  
  - N/A
- **Role Functioning**: 85.0 ± 23.0  
  - Samuelsson 2006 †: 81.5 ± 24.5  
  - EORTC 2008*: 84.7 ± 25.4 | 60.7 ± 35.1  
  - N/A
- **Emotional Functioning**: 77.7 ± 22.9  
  - Samuelsson 2006 †: 82.4 ± 17.1  
  - EORTC 2008*: 76.3 ± 22.8 | 68.7 ± 24.8 | 82.2 ± 18.9  
  - N/A
- **Cognitive functioning**: 83.4 ± 19.4  
  - Samuelsson 2006 †: 86.7 ± 17.4  
  - EORTC 2008*: 86.1 ± 20.0 | 80.5 ± 23.2 | 86.1 ± 18.5  
  - N/A
- **Social Functioning**: 88.4 ± 19.7  
  - Samuelsson 2006 †: 89.6 ± 18.6  
  - EORTC 2008*: 87.5 ± 22.9 | 70.5 ± 30.7 | 66.1 ± 31.0  
  - N/A
- **Global Health Status/QOL**: 71.1 ± 24.9  
  - Samuelsson 2006 †: 72.1 ± 23.4  
  - EORTC 2008*: 71.2 ± 22.4 | 56.3 ± 25.6  
  - N/A

### EORTC Symptom Scales

- **Fatigue**: 26.9 ± 25.5  
  - Samuelsson 2006 †: 23.1 ± 24.1  
  - EORTC 2008*: 24.1 ± 24.0 | 41.8 ± 29.4 | 36.2 ± 22.7  
  - N/A
- **Nausea/ Vomiting**: 4.0 ± 9.7  
  - Samuelsson 2006 †: 2.6 ± 6.2  
  - EORTC 2008*: 3.7 ± 11.7 | 13.1 ± 22.5 | 9.0 ± 18.3  
  - N/A
- **Pain**: 14.3 ± 23.1  
  - Samuelsson 2006 †: 15.4 ± 25.2  
  - EORTC 2008*: 20.9 ± 27.6 | 33.7 ± 32.4 | 13.7 ± 20.4  
  - N/A
- **Dyspnea**: 18.5 ± 25.8  
  - Samuelsson 2006 †: 10.6 ± 15.7  
  - EORTC 2008*: 11.8 ± 22.8 | 23.4 ± 30.1 | 11.3 ± 17.1  
  - N/A
- **Insomnia**: 25.0 ± 27.4  
  - Samuelsson 2006 †: 19.3 ± 27.5  
  - EORTC 2008*: 21.8 ± 29.7 | 33.6 ± 33.4 | 20.4 ± 26.1  
  - N/A
- **Appetite loss**: 5.1 ± 14.7  
  - Samuelsson 2006 †: 2.6 ± 9.1  
  - EORTC 2008*: 6.7 ± 18.3 | 28.2 ± 34.9 | 18.0 ± 30.5  
  - N/A
- **Constipation**: 19.0 ± 29.0  
  - Samuelsson 2006 †: 4.4 ± 13.8  
  - EORTC 2008*: 6.7 ± 18.4 | 23.2 ± 32.3 | 7.9 ± 19.1  
  - N/A
- **Diarrhea**: 9.0 ± 18.3  
  - Samuelsson 2006 †: 4.4 ± 11.4  
  - EORTC 2008*: 7.0 ± 18.0 | 10.7 ± 22.4 | 12.6 ± 25.1  
  - N/A
- **Financial Difficulties**: 8.0 ± 19.3  
  - Samuelsson 2006 †: 7.2 ± 17.8  
  - EORTC 2008*: 9.5 ± 23.3 | 16.2 ± 27.7 | 18.7 ± 28.8  
  - N/A

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## EORTC PV Scales Comparison

<table>
<thead>
<tr>
<th>EORTC Subscales</th>
<th>Current Data PV (N=145)</th>
<th>Samuelsson 2006 † Baseline values for PV and ET pts (N=1616)</th>
<th>EORTC 2008 General Population (N=7,802)</th>
<th>EORTC 2008 Cancer patients with recurrent or metastatic disease (N=4,812)</th>
<th>EORTC 2008 Patients with AML (N=155)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Functioning</td>
<td>83.3 ± 17.7</td>
<td>90.6 ± 11.5</td>
<td>89.8 ± 16.2</td>
<td>75.8 ± 23.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>85.2 ± 22.7</td>
<td>81.5 ± 24.5</td>
<td>84.7 ± 25.4</td>
<td>60.7 ± 35.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>78.2 ± 20.8</td>
<td>82.4 ± 17.1</td>
<td>76.3 ± 22.8</td>
<td>68.7 ± 24.8</td>
<td>82.2 ± 18.9</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>83.0 ± 18.8</td>
<td>86.7 ± 17.4</td>
<td>86.1 ± 20.0</td>
<td>80.5 ± 23.2</td>
<td>86.1 ± 18.5</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>88.3 ± 20.1</td>
<td>89.6 ± 18.6</td>
<td>87.5 ± 22.9</td>
<td>70.5 ± 30.7</td>
<td>66.1 ± 31.0</td>
</tr>
<tr>
<td>Global Health Status/QOL</td>
<td>65.7 ± 24.8</td>
<td>72.1 ± 23.4</td>
<td>71.2 ± 22.4</td>
<td>56.3 ± 25.6</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### EORTC Symptom Scales

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Current Data</th>
<th>Samuelsson 2006 † Baseline values for PV and ET pts</th>
<th>EORTC 2008 General Population</th>
<th>EORTC 2008 Cancer patients with recurrent or metastatic disease</th>
<th>EORTC 2008 Patients with AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>29.3 ± 21.9</td>
<td>23.1 ± 24.1</td>
<td>24.1 ± 24.0</td>
<td>41.8 ± 29.4</td>
<td>36.2 ± 22.7</td>
</tr>
<tr>
<td>Nausea/ Vomiting</td>
<td>3.3 ± 8.2</td>
<td>2.6 ± 6.2</td>
<td>3.7 ± 11.7</td>
<td>13.1 ± 22.5</td>
<td>9.0 ± 18.3</td>
</tr>
<tr>
<td>Pain</td>
<td>14.6 ± 20.4</td>
<td>15.4 ± 25.2</td>
<td>20.9 ± 27.6</td>
<td>33.7 ± 32.4</td>
<td>13.7 ± 20.4</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>19.6 ± 24.2</td>
<td>10.6 ± 15.7</td>
<td>11.8 ± 22.8</td>
<td>23.4 ± 30.1</td>
<td>11.3 ± 17.1</td>
</tr>
<tr>
<td>Insomnia</td>
<td>26.6 ± 28.0</td>
<td>19.3 ± 27.5</td>
<td>21.8 ± 29.7</td>
<td>33.6 ± 33.4</td>
<td>20.4 ± 26.1</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>10.3 ± 21.7</td>
<td>2.6 ± 9.1</td>
<td>6.7 ± 18.3</td>
<td>28.2 ± 34.9</td>
<td>18.0 ± 30.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>13.4 ± 24.5</td>
<td>4.4 ± 13.8</td>
<td>6.7 ± 18.4</td>
<td>23.2 ± 32.3</td>
<td>7.9 ± 19.1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.3 ± 16.3</td>
<td>4.4 ± 11.4</td>
<td>7.0 ± 18.0</td>
<td>10.7 ± 22.4</td>
<td>12.6 ± 25.1</td>
</tr>
<tr>
<td>Financial Difficulties</td>
<td>6.4 ± 15.9</td>
<td>7.2 ± 17.8</td>
<td>9.5 ± 23.3</td>
<td>16.2 ± 27.7</td>
<td>18.7 ± 28.8</td>
</tr>
</tbody>
</table>
### EORTC MF Scales Comparison

<table>
<thead>
<tr>
<th>EORTC QLQ-C30 Scores (Mean ± SD)</th>
<th>Current Data</th>
<th>Samuelsson 2006 †</th>
<th>EORTC 2008*</th>
<th>EORTC 2008*</th>
<th>EORTC 2008*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EORTC Subscales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MF (N=96)</td>
<td></td>
<td>Baseline values for PV and ET pts (N=1616)</td>
<td>General Population (N=7,802)</td>
<td>Cancer patients with recurrent or metastatic disease (N=4,812)</td>
<td>Patients with AML (N=155)</td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>74.9 ± 20.7</td>
<td>90.6 ± 11.5</td>
<td>89.8 ± 16.2</td>
<td>75.8 ± 23.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Role Functioning</td>
<td>68.8 ± 28.9</td>
<td>81.5 ± 24.5</td>
<td>84.7 ± 25.4</td>
<td>60.7 ± 35.1</td>
<td>N/A</td>
</tr>
<tr>
<td>Emotional Functioning</td>
<td>76.5 ± 20.5</td>
<td>82.4 ± 17.1</td>
<td>76.3 ± 22.8</td>
<td>68.7 ± 24.8</td>
<td>82.2 ± 18.9</td>
</tr>
<tr>
<td>Cognitive Functioning</td>
<td>77.0 ± 20.4</td>
<td>86.7 ± 17.4</td>
<td>86.1 ± 20.0</td>
<td>80.5 ± 23.2</td>
<td>86.1 ± 18.5</td>
</tr>
<tr>
<td>Social Functioning</td>
<td>74.9 ± 24.1</td>
<td>89.6 ± 18.6</td>
<td>87.5 ± 22.9</td>
<td>70.5 ± 30.7</td>
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<tr>
<td>Global Health Status/QOL</td>
<td>59.9 ± 24.6</td>
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<td>71.2 ± 22.4</td>
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<td>N/A</td>
</tr>
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<td><strong>EORTC Symptom Scales</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>41.0 ± 25.1</td>
<td>23.1 ± 24.1</td>
<td>24.1 ± 24.0</td>
<td>41.8 ± 29.4</td>
<td>36.2 ± 22.7</td>
</tr>
<tr>
<td>Nausea/ Vomiting</td>
<td>6.3 ± 11.4</td>
<td>2.6 ± 6.2</td>
<td>3.7 ± 11.7</td>
<td>13.1 ± 22.5</td>
<td>9.0 ± 18.3</td>
</tr>
<tr>
<td>Pain</td>
<td>22.6 ± 27.8</td>
<td>15.4 ± 25.2</td>
<td>20.9 ± 27.6</td>
<td>33.7 ± 32.4</td>
<td>13.7 ± 20.4</td>
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<tr>
<td>Dyspnea</td>
<td>29.8 ± 29.0</td>
<td>10.6 ± 15.7</td>
<td>11.8 ± 22.8</td>
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<tr>
<td>Insomnia</td>
<td>33.7 ± 30.6</td>
<td>19.3 ± 27.5</td>
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<td>Appetite loss</td>
<td>15.1 ± 23.1</td>
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<tr>
<td>Constipation</td>
<td>16.8 ± 26.1</td>
<td>4.4 ± 13.8</td>
<td>6.7 ± 18.4</td>
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<tr>
<td>Financial Difficulties</td>
<td>17.5 ± 28.7</td>
<td>7.2 ± 17.8</td>
<td>9.5 ± 23.3</td>
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</tr>
</tbody>
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Martyrdom of Saint Sebastian
1473
National Gallery, London
Antonio del Pollaiuolo (1431-1498)
Symptomatic Burden in MPNs

• Why do symptoms matter in MPNs
• Development and testing of MPN Symptom Assessment
• Current and Future Management of MPN Symptoms
• Application in Clinical Trials and Next Steps
Managing MPN Fatigue

- Exercise
- Healthy Lifestyle and Diet
- Correction of Iron Deficiency When Possible
- Stimulants
  - Ritalin/Provigil/ Nuvigil
- JAK2 Inhibitors
Managing MPN Micro-vascular Sx

- Aspirin
- Smoking Cessation
- Management of Blood Counts
- ? Additional Anti-platelet therapy
Managing MPN Itching (Pruritus)

- Anti-histamines
- Therapeutic UV Light
- Physical Measures (avoiding hot baths, air drying)
- Interferon / Peg Interferon
- JAK2 Inhibitors
Managing MPN
Cachexia & Splenomegaly

• JAK 2 inhibitors (Both)

• Hydroxycarbamide (Spleen alone)

• Splenectomy (Spleen Alone)

• Splenic Radiation (Spleen Alone)

• Other Chemotherapy (Spleen Alone)
JAK2 Inhibitors in Development for MF

Ruxolitinib (INCB18424)
SAR302503 (TG101348)
Pacritinib (SB1518)
CEP701
CYT387
BMS-911543
LY2784544
NS018

Clinical Phase of Testing
Ruxolitinib Therapy Associated with Rapid and Durable Improvement In Symptoms Associated with Enlarged Spleen

Mesa et. al. Cancer 2011
Ruxolitinib Therapy Associated with Rapid and Durable Reduction of Symptoms Associated with Elevated Inflammatory Cytokines

Mesa et. al. Cancer 2011
Ruxolitinib Phase II

Mesa et. al. Cancer 2011
ET & PV

Short Term

Thrombosis & Bleeding

High and ? Int Risk = Cytoreduction
All Risk = ASA

Long Term

Post ET/PV MF & MPN Blast Phase

No Known Therapy
? JAK2 Inhibitors

High and ? Int Risk = Cytoreduction
All Risk = ASA
Management of PV

• ALL PV Patients
  – Maintain HCT <45% Men, 42% Women
  – Low Dose ASA
  – Aggressive control of CV risk factors

• Cytoreduction
  – High Risk or
  – Intol to Phlebotomy, Increasing Spleen, Severe Sx
    \[ Plt > 1500 \times 10^9/L, \text{ or prog WBC} \]
  – Medications
    • Hydroxyurea or Interferon alpha as Front line (or second)
    • Busulfan, pipobroman, P-32 as second line

Barbui et. al. LeukemiNET Consensus Guidelines JCO 2011 in press
Management of ET

• ALL ET Patients
  – Low Dose ASA
  – Aggressive control of CV risk factors

• Cytoreduction
  – High Risk
  – Medications
    • Hydroxyurea as Front line
    • Anagrelide second line
    • Interferon alpha third line
    • Busulfan, pipobroman, P-32 for elderly

Barbui et al. LeukemiNET Consensus Guidelines JCO 2011 in press
PEG-IFN is able to induce molecular remission in patients with PV

Kiladjian 2008
Morphologic change after IFN therapy in a patient with primary myelofibrosis (After Median 3 years of Rx).

Silver et. al. Blood 2011
• 17 “Early” PMF (MF<Grade 3)
• IWG (11 low, 6 Int 1)
• INFα2b or PEG Infα-2a
• IWG-MRT
  2 CR, 7 PR, 1 CI (59% Response)

Gowin et. al. ASH 2011
• 17 “Early” PMF (MF<Grade 3)
• PEG Infα-2a
• IWG-MRT
  1 CR, 2 PR, 1 CI (29% Response)
Pegylated Interferon Alpha–2a in Polycythemia Vera (PV) and Essential Thrombocythemia (ET) Myeloproliferative Disorders Research Consortium (MPD-RC)

High Risk
PV and ET
(N=780)

- **MPD-RC 111**
  Phase II Pegylated Interferon Alpha – 2a Salvage for Resistance/Intolerance to Hydroxyurea or Splanchnic Vein Thrombosis

- **MPD-RC 112**
  Phase III Randomized Trial Pegylated Interferon Alpha -2a Vs. Hydroxyurea

  Continuous Therapy for Up to 24 Months To Assess Maximal Confirmed Response To Pegylated Interferon Alpha – 2a (111 all, 112 half) or Hydroxyurea (112 half)

  *Primary Endpoint*
  - Complete Response by LeukemiaNet Criteria (Stratified by ET and PV)

  *Secondary Endpoints*
  - Partial Response Rate, Mutation Allele Burden, Rate of Vascular Events, Toxicity/Tolerability, Impact on Symptoms and QOL, Rates of progression and/or death
Phase II Study of INCB 18424 in Patients with Advanced ET and PV

Eligibility Criteria:
- Refractory or intolerant to hydroxyurea (HU) or HU contraindicated
- PV: Hct > 45% OR phlebotomy 2 times in last 6 months, with at least one phlebotomy in last 3 months
- ET: Platelets > 650 x 10^9/L unless on therapy
49% achieved normal platelet counts and 79% achieved <600,000 or a ≥50% reduction as of last follow-up visit

13 of 14 subjects with baseline platelet counts >1,000,000 have achieved a greater than 50% reduction
PV Results: Hematocrit Control (Hct ≤ 45%) without Phlebotomy

97% of patients have achieved hematocrit ≤ 45% without the use of phlebotomy

% Patients Achieving Hematocrit Control Without Phlebotomy

| Months of Treatment | Bar Graph
|--------------------|-----------
| 1                  | 60% (n=34) |
| 3                  | 80% (n=34) |
| 6                  | 100% (n=34) |
| 9                  | 100% (n=33) |
| 12                 | 100% (n=31) |
| 15                 | 100% (n=29) |
| 18                 | 100% (n=28) |
| 21                 | 100% (n=19) |

Verstovsek et. al. ASH 2010; Abstract 313
PV Results: Splenomegaly

Rapid and Durable Reductions in Palpable Spleen Length

- 80% of patients with palpable splenomegaly (n=25) achieved ≥ 50% reduction as of the last follow-up (68% achieved complete resolution of palpable splenomegaly)

Verstovsek et. al. ASH 2010; Abstract 313
PV Results: Symptoms

- Rapid improvements in patient reported symptom scores observed
- Responses have been durable in the majority of responding patients through the last follow-up visit
The Broken Column
1944
Museo Dolores Olmedo, Mexico
Frida Kahlo (1907-1954)
Symptomatic Burden in MPNs

- Why do symptoms matter in MPNs
- Development and testing of MPN Symptom Assessment
- Current and Future Management of MPN Symptoms
- Application in Clinical Trials and Next Steps
COMFORT-I: Study Design

- PMF or PPV-MF, or PET-MF
- INT-2 or high risk
- Palpable spleen ≥5 cm
- Platelet count ≥100 x10⁹/L
- JAK2 V617F positive or negative

Ruxolitinib
15 or 20 mg BID

Placebo

Spleen volume by MRI every 12 weeks
Daily assessment of symptoms from Day -7 through week 24
Cross over to ruxolitinib was possible

BID, twice daily; COMFORT: COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment; CT, computed tomography; ECOG PS, Eastern Cooperative Oncology Group Performance Status; INT-2, intermediate-2; MRI, magnetic resonance imaging; PET-MF, post-essential thrombocythemia-myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera-myelofibrosis.
Symptom Response COMFORT-1

Mesa et. al. EHA 2011

Ruxolitinib

Placebo

% Change From Baseline

-100
-50
0
50
100
150
200

50% DECREASE
Comfort I Symptom Response
Individual Symptom Scores

- Abdominal discomfort: Ruxolitinib -29.4, Placebo -46.9
- Pain under left ribs: Ruxolitinib -43.0, Placebo -42.8
- Early satiety: Ruxolitinib -42.1, Placebo -21.2
- Night sweats: Ruxolitinib -42.8, Placebo -37.7
- Itching: Ruxolitinib 111.9, Placebo 60.0
- Bone/muscle pain: Ruxolitinib -32.1, Placebo -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
PGIC Scores of Improvement at Week 24

Mesa et. al. EHA 2011
Relationship between Spleen volume Reduction and Symptom/QoL Outcomes

![Graph showing the relationship between Spleen volume reduction and symptom outcomes.](chart1.png)

- **Reduction in Spleen Volume**
  - N=99
  - N=20, p=0.0004
  - N=46, p<0.0001
  - N=60, p<0.0001

- **% Change in Total Symptom Score**
  - N=96
  - N=20, p=0.0304
  - N=44, p<0.0001
  - N=59, p<0.0001

- **% Change in Total Abdominal Symptom Score**
  - N=98
  - N=22, p=0.4176
  - N=46, p<0.0001
  - N=64, p<0.0001

- **Change in Global Health Status/QoL Score**
  - N=105
  - N=23, p=0.9206
  - N=50, p<0.0001
  - N=65, p<0.0001

- **Patient Global Impression of Change Score**
  - N=101
  - N=23, p=0.0058
  - N=50, p<0.0001
  - N=62, p<0.0001

![Graph showing the relationship between Spleen volume reduction and symptom outcomes.](chart2.png)
Change in EORTC QLQ-C30 Scores From Baseline to Week 48

- Patients in the ruxolitinib arm had more improvement in symptoms compared with patients in the BAT arm.
- Improvements were seen by week 8 and continued through week 48.

Scores selected represent symptoms relevant to MF patients.
### Symptomatic Change in Control Arms of the COMFORT Trials

**EORTC-QLQ-C30**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (Comfort 1)</th>
<th>BAT (Comfort II)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Mean change from baseline at week 24 (SD)</td>
</tr>
<tr>
<td>Global health status/QoL</td>
<td>104</td>
<td>-3.4 (21.53)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>107</td>
<td>1.8 (24.71)</td>
</tr>
<tr>
<td>Pain</td>
<td>104</td>
<td>8.3 (27.47)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>105</td>
<td>1 (27.53)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>105</td>
<td>-2.2 (32.12)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>107</td>
<td>0.6 (33.96)</td>
</tr>
</tbody>
</table>

“Meaningful” Change ≥ 10 Point Change
Values only shown for those with data at both baseline and after 24 weeks
Symptom Responses to TG101348 (SAR302503)

A) Early Satiety

B) Fatigue

C) Night Sweats

Pardanani et. al. JCO 2011;29(7):789-796
> 9 Months Sustained Improvement in MF-related Symptoms Observed Using MF-SAF

- Patients with baseline symptom score ≥ 4 were analyzed
- Numbers inside bars represent the number of patients with paired values for each symptom at each time point
- Durable improvement in most symptom scores was observed

*C* = No change in mean symptom score

- **Abdominal Pain**
  - C4D1
  - C7D1
  - C10D1

- **Bone Pain**
  - C4D1
  - C7D1
  - C10D1

- **Early Satiety**
  - C4D1
  - C7D1
  - C10D1

- **Fatigue (worst)**
  - C4D1
  - C7D1
  - C10D1

- **Inactivity**
  - C4D1
  - C7D1
  - C10D1

- **Night Sweats**
  - C4D1
  - C7D1
  - C10D1

- **Pruritus**
  - C4D1
  - C7D1
  - C10D1

Mesa et. al. EHA 2011 (a1022) Oral Sunday
Control of constitutional symptoms

### Night sweats (n=26)
- All: 100%
- 150 mg/d: 100%
- 300 mg/d: 100%

### Bone pain (n=25)
- All: 80%
- 150 mg/d: 80%
- 300 mg/d: 80%

### Pruritus (n=13)
- All: 90%
- 150 mg/d: 90%
- 300 mg/d: 90%

### Fever (n=5)
- All: 100%
- 150 mg/d: 100%
- 300 mg/d: 100%

---

### Pruritus

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>INCB018424</td>
<td>82%</td>
</tr>
<tr>
<td>TG101348</td>
<td>100%</td>
</tr>
<tr>
<td>CYT387</td>
<td>92%</td>
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</tbody>
</table>

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Pardanani A et al. JCO in press
Pardanani A et al. ASH 2010 abstract #460
# Comparing JAK2 Inhibitors

## Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Spleen</th>
<th>MF Symptoms</th>
<th>Anemia</th>
</tr>
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<tbody>
<tr>
<td><strong>Ruxolitinib</strong></td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td><strong>SAR302503</strong></td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td><strong>SB1518</strong></td>
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<td>X</td>
<td></td>
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<tr>
<td><strong>CYT387</strong></td>
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<td><strong>BMS-911543</strong></td>
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</table>

*Phase I Testing*
First Line Therapy of Myelofibrosis in 2012

N.B.
Consider Rx for Prevention of Vascular Events in Appropriate Patients (Aspirin & Cytoreduction)

Primary, Post ET or Post PV Myelofibrosis

Calculate DIPSS MF Score & Assess MF Symptoms (MPN-SAF)

Low Risk Med S = 185m
Asymptomatic

Low Risk Med S <185m
Symptomatic

Int-1 Med S = 78m

Int-2 & High Risk Med S = 16-35m

MPN-BP Med S <3m

Low Risk Med S = 185m
Asymptomatic

JAK2 Inhib (If Many Sx)

Observation Vs. Interferon

JAK2 Inhib

Int-1 Med S = 78m

JAK2 Inhib Vs. Allo SCT Vs. Anemia Rx

Int-2 & High Risk Med S = 16-35m

? Allo SCT Eligible

MPN-BP Med S <3m

Induction

JAK2 Inhib Vs. Anemia Rx

Allo SCT

Hypometh Vs. Trial Vs. Supp

JAK2 Inhib vs. Allo SCT vs. Anemia Rx

Response

YES

JAK2 Inhib Vs. Anemia Rx

Allo SCT

Hypometh Vs. Trial Vs. Supp

JAK2 Inhib

Clinical Trial JAK2 Inhib

Anemia Rx

IMID

Androgens

N.B.
Consider Rx for Prevention of Vascular Events in Appropriate Patients (Aspirin & Cytoreduction)

JAK2 Inhibitor

- Ruxolitinib (Jakifi)
- Clinical Trial JAK2 Inhib

Anemia Rx

- IMID
- Androgens
54 MPN Investigators
19 Countries

- North America
- EU
- Australasia
- South America
- Asia
MPN-QOL ISG Trial 1

Serial MPN Symptom Assessment on Standard Rx

Enroll

Physician Visit

On Therapy >30 but <180 days

MPN- SAF Diary for 7 days

Physician Assessment Day 1

Begin new non experimental intervention for MPN

MPN- SAF Diary for 7 days

Physician Assessment return
MPN-QOL ISG Trial 2
Serial MF Symptom Assessment in Patients Undergoing ASCT

Enroll

Physician Visit

ASCT vs. Standard RX Clinical Choice

MF Patient HLA Typed

MPN-SAF Diary/FACT BMT

Physician Assessment Day 1

Physician Assessment return

Physician Visit Day 0, 30, 100, 180, 365

Physician Visit

MPN-SAF Diary/FACT BMT
To Heal

• *To restore to health or soundness*

“www.thefreedictionary.com”
Medicine Wheel of Health
“Integrative Medicine”
The Race (with No Finish Line)

Illness

Surgery

Medicines

Transplant

Wellness

Exercise

Family

Spirituality

Nutrition
Patient Focused Strategy

Upfront Education

Care Teams

MPN Patient

Fostering Patient Communities

Team Based Care
State of the Art Care

Clinical Trial As appropriate

Integrative Care
Exercise and MPNs

• Optimize
  – Flexibility
  – Heart/ lung function
  – Muscle tone
  – Improve strength
  – Improve sleep
  – Improve fatigue
Range of Needs

• Early stage:
  – Define limitations (or perceived limitations)
  – Needs may mirror those of all adults

• Moderate stages:
  – Overcoming barriers related to disease
  – Overcoming medication side effects

• Advanced stage:
  – Maximize mobility
  – Maximize flexibility
Figure 1: Range of $\text{VO}_2\text{max}$ Across Various People—Marathoners would be in the 70 to 90 range; frail elderly people in the 10 to teens range.
Vicious Cycle

Fatigue

Loss of Muscle

Being Sedentary

Deconditioning
The goal

Physical Health ↔ Spirit/Soul Wellness
“In 5 years we will have regrets and remorse for the things we did not do, rather than what we did.”
What have I learned?

• Don’t wait to go to Alaska
Quotes from Erma Bombeck
Written as she was dying from Cancer

• If I had my life to live over I would…

• Have gone to bed when I was sick instead of pretending the earth would go into a holding pattern if I weren’t there for a day
I would have...

• Burned the pink candle sculpted like a rose before it melted in storage
I would have...

• Sat on the lawn with my grass stains
I would have...

• Talked less and listened more
I would have...

- Invited friends over for dinner even if the carpet was stained or the sofa faded
I would have...

- Shared more of the responsibility carried by my husband
I would have...

- Never have insisted the car windows be rolled up on a summer day because my hair had just been teased and sprayed.
I would have...

• Don’t worry about who doesn’t like you, who has more or who is doing what. Instead, cherish the relationships we have with those who do love us.
I would have...

• Never have bought anything just because it was practical, wouldn’t show soil, or was guaranteed to last a lifetime
I would have...

- Instead of wishing away nine months of pregnancy, I’d have cherished every moment and realized that the wonderment growing inside me was the only chance in life to assist God in a miracle.
I would have...

- Taken the time to listen to my grandfather ramble about his youth
I would have...

- Cried and laughed less while watching TV and more while watching life
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.
Carpe Diem

Seize the day!
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The Painters Honeymoon
1864
Museum of Fine Arts, Boston
Lord Frederic Leighton(1830-1896)