12th Joyce Niblack MPN Conference

Gaps and Guidelines

Ruben A. Mesa, MD
Executive Director, Mays Cancer Center
Mays Family Foundation Distinguished University Presidential Chair
mesar@uthscsa.edu
Twitter: @mpdrc
Disclosures

Consulting: Novartis, La Jolla, Samus, Sierra Oncology, Blueprint, Abbvie, BMS, Genentech, Roche

Research Support: Incyte, Celgene, CTI, Promedior, Genentech, Abbvie, Imago
What is a treatment guideline?

Guideline – Guardrails

The science of medicine

How applied to an individual

The art of medicine
MPNs 2021

• Burden of Having an MPN
• Essential Thrombocythemia
• Polycythemia Vera
• Myelofibrosis
• Complementary Approaches
Assessing MPN Burden

WHO Diagnosis Does Not Tell Whole Story

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

Progression
- PV/ET to MF
- PV/ET to AML
- MF to AML
- ? 2nd MDS

Baseline Health
Age/Medicines
Comorbidities

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

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

Splenomegaly
- MF > ET/PV
- Pain not always a function of size
Evolution of MPN Symptom Assessment Tools

- **Vascular and Ŷ symptoms** 9 Items
- **Constitutional symptoms** 5 Items
- **Spleen symptoms** 4 Items
- **Brief Fatigue Inventory** 9 Items
- **Quality of life** 1 Item

**MF-SAF 2009**
- (19 items)

**MF-SAF 2.0**
- 2011
- (7 items)

**MPN-SAF 2011**
- (27 items)*

**MPN-SAF TSS 2012**
- (10 items)*

**MPN-SAF Languages**
- Albanian
- Czech
- Chinese
- Danish
- Dutch
- English
- French
- German
- Hebrew
- Hungarian
- Italian
- Japanese
- Portuguese
- Romanian
- Swedish
- Spanish
- Urdu

MF: myelofibrosis; MPN, myeloproliferative neoplasm; QOL, quality of life; SAF, symptom assessment tool; TSS, total symptom score.

*Scherber et al. *Blood* 2011;118:401-408.
MPN Symptom Burden

A Diverse, Disabling Constellation of Symptoms

- Fatigue: 92% (3.2)
- Insomnia: 65% (2.8)
- Sad Mood: 62% (2.2)
- Concentration Difficulties: 61% (2.2)
- Early Satiety: 61% (2.3)
- Inactivity: 60% (2.1)
- Sexual Problems: 57% (3.0)
- Night Sweats: 56% (2.3)
- Dizziness: 55% (1.9)
- Abdominal Discomfort: 53% (2.0)
- Bone Pain: 48% (2.0)
- Headache: 48% (1.4)
- Abdominal Pain: 48% (1.4)
- Cough: 46% (1.5)
- Weight Loss: 34% (1.2)

- Fevers: 20% (0.4)
## MPN Recent Phase 3 Trials

### MPN Symptom Assessment

<table>
<thead>
<tr>
<th>Disease</th>
<th>Drug (Trial)</th>
<th>MPN Symptom Tool</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td>Ruxolitinib (COMFORT 1)</td>
<td>MF-SAF 2.0</td>
</tr>
<tr>
<td>MF</td>
<td>Ruxolitinib (COMFORT 2)</td>
<td>FACT-LYM</td>
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<tr>
<td>MF</td>
<td>Fedratinib (JAKARTA)</td>
<td>MF-SAF</td>
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<tr>
<td>MF</td>
<td>Pacritinib (PERSIST 1&amp;2)</td>
<td>MPN-SAF</td>
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<tr>
<td>MF</td>
<td>Momelotinib (SIMPLIFY 1&amp;2)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>MF</td>
<td>Pomalidomide (RESUME)</td>
<td>FACT-AN</td>
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<tr>
<td>MF</td>
<td>Ruxolitinib (RETHINK)</td>
<td>MPN-10</td>
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<tr>
<td>PV</td>
<td>Ruxolitinib (RESPONSE)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>PV</td>
<td>Ruxolitinib (RELIEF)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>PV</td>
<td>PEG INFa2a (MPD-RC 112)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>ET</td>
<td>Ruxolitinib (MAGIC)</td>
<td>MPN-SAF</td>
</tr>
<tr>
<td>ET</td>
<td>PEG INFa2a (MPD-RC 112)</td>
<td>MPN-SAF</td>
</tr>
</tbody>
</table>

ET, essential thrombocytopenia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PEG INFa2a, Pegylated interferon alfa-2a; PV, polycythemia vera; SAF, symptom assessment tool.
Symptoms Change During the Natural History of MPNs

- Cytoreduction
- Symptomatic iron deficiency
- Thrombosis
- Medication Side Effects
- Disease Progression
- Worsened Baseline Health
- Organ Dysfunction
- Psychological Comorbidities
- Further Disease Progression
- Severe Cytopenias
- Transfusions
- Baseline Health Status
- Inflammation
- Vascular Events

Therapies

Normal Hematopoiesis

Premature Death
Inflammation in MPNs

**Inflammation Drives Clonal Proliferation**

- **Effect of Inflammation**
  - Auto-production of inflammatory cytokines
  - Induce bystander cell production of inflammatory cytokines
  - Production of IL-6, IL-8, IL-1B
  - Production of IL-6, bFGF, LCN2
  - Production of TNF-a, VEGF, TGF-b, BMP2, RUNX2, osteoprogerin, collagen type I

- **Suppressed growth WT**

- **Acquisition of the JAK2v617f mutation**

Koschmieder *et al.* Leukemia 2016

CALR mutated cells secrete mutant CALR that acts in an autocrine fashion similar to cytokines.
What do symptoms tell us about MPN Biology?

MPN Symptoms

Mood Disorders
Anxiety over Uncertainty

Cytokine Driven Symptoms
Spleen/Inflammation
Fatigue

Cytokines

Pathways

Symptom

Fatigue

Hypocortisolism

HPA Axis Dysregulation

Cytopenias

Depressed Mood

IL4, IL6, IL8, IL10 TNFa

IL1, IL6

IL1, IL6, TNFa

IL6

Abdominal Symptoms

Symptom Category
- Abdominal Symptoms

Symptom
- Abdominal Pain
- Abdominal Discomfort
- Early Satiety

Pathways
- Splenomegaly, (Hematopoietic Expansion)
- Abdominal Thrombosis
- Portal HTN
- Cytokine-Induced Nerve Hyperstimulation

Cytokines
- TNF-α
- MIG, HGF, IL-1RA
- IL1b, IL6, IL8, hsCRP, IL-12, TNFa
- hs-CRP and PTX3
- TNF-α, IL-1, and IL-6
- IL-2 mRNA and TNF-α mRNA
Constitutional Symptoms

Overview

Symptom
- Fevers
- Chills
- Night Sweats
- Weight Loss

Pathways
- Direct Activation
- Portal HTN/Thrombosis
- Cancer Cachexia
- Microbiome
- Splenomegaly/ Early Satiety
- Appetite Loss

Cytokines
- IL-1, IL-2, IL-6, TNF-α, and IFN
- Leptin, CD40L
- TNFa
- Other pathways as mentioned
Microvascular Symptoms

### Symptom Category
- Microvascular Symptoms

### Symptom
- Itching
- Cognitive Symptoms (Headaches, Dizziness, memory changes, N/T, Vertigo)
- Sexual Dysfunction

### Pathways
- Basophil and Mast Cell Activation, prostaglandin
- Iron Deficiency
- Altered Neurotransmitter Function
- Blood Brain Barrier Permeability
- Depression
- Thrombosis

### Cytokines
- Leukotriene, Histamine, Tryptase
- Low Ferritin
- RANTES and Pal1
- IL-1, TNF-α, IL-6, and CRP
- IL1b
- As detailed prior
- As detailed prior
Treatment Goals

• Avoiding thrombosis and bleeding?
• Improving MPN associated symptoms?
• Increase activity?
• Decreasing splenomegaly?
• Improving anemia?
• Improving low platelets?
• Decreasing progression?
• Preventing progression?
• Live longer?
MPNs 2021

- Burden of Having an MPN
- Essential Thrombocytemia
- Polycythemia Vera
- Myelofibrosis
- Complementary Approaches
PV/ET: When Do Problems Occur?

- Diagnosis
- Counts
- Symptoms
- Progression
- Vascular
Management of ET 2021

1. Diagnosis of ET
2. Assess Survival & Disease Burden
3. Develop Treatment Plan
4. Front Line ET Medical Management
   - Progression to MF
   - Second Line & Beyond ET Medical Management
   - Progression to AML
Treatment Gaps - ET

1. What is the optimal front line therapy for ET?

2. How do we prevent disease progression?

3. What is the role of JAK inhibition?
Pipeline – PV and ET

**PV**
- Hepcidin Agonists (PTG-300)
- HDAC Inhibition (Givinostat)
- MDM2 Inhibitors Idasanutlin-KRT232
- Other?

**ET**
- RoPEG vs ANAG
- IMG7289
- Other?
MPNs 2021

- Burden of Having an MPN
- Essential Thrombocythemia
- Polycythemia Vera
- Myelofibrosis
- Complementary Approaches
Symptom Burden and Quality of Life in High-Risk ET and PV Patients Receiving Hydroxyurea or Pegylated Interferon Alfa-2a: Results of MPN-RC 111 and 112 Trials

Gina L. Mazza

on behalf of
Carolyn Mead-Harvey, John Mascarenhas, Abdulraheem Yacoub, Ronald Hoffman, Heidi E. Kosiorek, Josef T. Prchal, Richard T. Silver, Tiziano Barbui, Amylou C. Dueck, Ruben A. Mesa
## Results – Patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>MPN-RC 111</th>
<th>MPN-RC 112</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ET (n = 64)</td>
<td>PV (n = 50)</td>
</tr>
<tr>
<td>Sex (% Female)</td>
<td>51%</td>
<td>48%</td>
</tr>
<tr>
<td>Age in Years (Median, Range)</td>
<td>65 (20 – 85)</td>
<td>64 (26 – 84)</td>
</tr>
<tr>
<td>Months Since Dx (Median, Range)</td>
<td>38 (0 – 291)</td>
<td>55 (1 – 394)</td>
</tr>
<tr>
<td>Prior Thrombosis (%)</td>
<td>31%</td>
<td>22%</td>
</tr>
<tr>
<td>Splenomegaly (%)</td>
<td>19%</td>
<td>56%</td>
</tr>
</tbody>
</table>
Results – Symptoms

• MPN-RC 111 patients had significant **improvement** of TSS, fatigue, abdominal pain, abdominal discomfort, dizziness, numbness, night sweats, and fever
• MPN-RC 112 PEG patients had significant **worsening** of fever
• MPN-RC 112 HU patients had significant **worsening** of inactivity
• MPN-RC 111 and 112 PEG patients had significant **worsening** of PEG-related symptoms
Conclusions

• Although no statistical comparisons were made across trials, overall improvements were seen in MPN-RC 111 but not MPN-RC 112

• Patients with high baseline symptom burden experienced the greatest improvements in symptom burden and quality of life during treatment with PEG or HU
  – These results may explain the improvements seen in the more advanced MPN-RC 111 patients compared to MPN-RC 112 patients
MPNs 2021

• Burden of Having an MPN
• Essential Thrombocythemia
• Polycythemia Vera
• Myelofibrosis
• Complementary Approaches
Management of Myelofibrosis 2021

1. Diagnosis of Myelofibrosis (Primary/Post ET/Post PV)
2. Assess Survival & Disease Burden
3. Develop Treatment Plan
4. Stem Cell Transplant Soon
5. Front Line MF Medical Management
6. Second Line MF Medical Management
7. "Salvage" Transplant
8. AP/ Blast Phase Management
JAK Inhibitor Landscape 2021

Approved
- Ruxolitinib
  1L - MF, 2L PV
- Fedratinib
  MF-1L

NOW
Approved
INREBIC

Seeking Approval
- Pacritinib
  MF (Low PLT)
- Momelotinib
  MF
- Ruxolitinib Combinations
- NS-018
  MF

CTI
PAC203
NCT03165734

Sierra Oncology
NCT04173494

Inactive
- XL019
- BMS-911543
- AZD-1480
- LY-2784544
A selection of novel agents/targets being developed in MPN particularly MF

Cell-cycle Checkpoint
- Imetelstat | Telomerase Inhibitor (Geron)
- Alisertib | Aurora Kinase Inhibitor (Takeda)

Anti-fibrotic
- PRM-151 | Pentraxin-2 (Promedior)

Receptor Ab / ADC
- SL-401 | CD123-toxin (Stemline)

Signaling / TKI
- Glasdegib | Hedgehog (Pfizer)
- Sonidegib | Hedgehog (Sun)
- INCB'465 | PI3Ki (Incyte)
- LCL1 | SMAC/IAP (Novartis)

Next-gen JAKi
- Fedratinib | JAK2 (Celgene)
- Pacritinib | JAK2/FLT3 (CTI Bio)
- Momelotinib | JAK2/1/ACVR1 (Sierra)
- Itacitinib | JAK1 (Incyte)

Apoptosis/MDM2/BCL
- KRT-232 (Kartos Therapeutics)
- Idasanutlin / RG7388 (Roche)
- Navitoclax | BCL2 inhibition (Abbvie)

Immuno-modulator / CPI
- Pegasys | IFN-α2a (ESR/Roche)
- Ropeg-IFN-α2b (PharmaEssentia)
- Nivolumab / Pembrolizumab | PD-1 (BMS / MRK)

HDAC / Epigenetic
- Azacytidine | HMA (ESR/Celgene)
- Panobinostat | HDAC (Novartis)
- Givinostat | HDAC (Italfama)
- IMG-7289 | LSD1 (Imago)
- CPI-0610 | BETi (Constellation)
- PU-H71 | HSP90i (Samus)

PHASE OF DEVELOPMENT (IN MPN):
- P1
- P2
- P3

Slide Courtesy of Prof Claire Harrison
Takeaway 1:
Effective MF Therapies May Prolong Overall Survival
Questions? MF and Survival

1. Is survival benefit across all responders to JAKi?

2. Do all patients who experience clear response for splenomegaly and/or symptoms have improved survival? Mechanism?

3. What might be better surrogates of OS benefit? What thresholds of clinical benefit will predict OS benefit?
Takeaway 2:

What is successful front line therapy for MF?
Comparison for 1L MF Therapy

1L Data in Myelofibrosis
(N.B. Non-Randomized (Between Drugs), Different Elig Criteria)

- SVR35%
- TSS50%

RUX COMFORT 1
FEDR JAKARTA
MOM SIMPLIFY 1
PAC PERSIST 1
CPI-0610 PLUS
RUX PH II

Reference:
- Verstovsek et. al. NEJM 2012
- Pardanani et. al. JAMA Inc 2015
- Mesa et. al. JCO 2017
- Mesa et. al. Lancet Hematology 2017
- Mascarenhas et. al. ASH 2020
Questions? Front Line and MF

1. Does OS benefits to medical therapy alter decision for transplant in certain candidates?

2. Would a lower rate of response to spleen or symptoms be a good exchange for expanded additional areas of efficacy?

3. To justify 2 agent front line approach is a broader response needed? Deeper? In certain subsets?
Takeaway 3:

Second line – Add on to JAKi or Switch Gears All Together?
Comparison for 2L Therapy

Second Line MF Therapy

ADD ON TO RUX

SVR35%  TSS50%

Navitoclax PLUS RUX  CPI0610 PLUS RUX  FEDR JAKARTA II (2019 Analysis)  MOM SIMPLIFY 2  PAC PERSIST 2  IMG 7289 Bone demstat  Imetelstat  CPI-0610 Single Agent

Pemmaraju et. al. ASH 2020
Verstovsek et. al. ASH 2020
Harrison et. al. ASH 2019
Verstovsek et. al.
Mascarenhas et. al.
Yacoub et. al. ASH 2020
Mascarenhas et. al. ASH 2020
Talpaz et. al ASH 2020
## Treatment Efficacy Observed/ ENDPOINTS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Spleen</th>
<th>Symptoms</th>
<th>Anemia</th>
<th>Fibrosis</th>
<th>Molecular</th>
<th>PFS</th>
<th>OS</th>
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<td>Ruxolitinib</td>
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<tr>
<td>Momelotinib</td>
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<td>Pacritinib</td>
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<td>CPI-0610</td>
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<td>Navitoclax</td>
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<td>IMG-7289</td>
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<td>Imetelstat</td>
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<td>Luspatercept</td>
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MPNs 2021

- Burden of Having an MPN
- Essential Thrombocythemia
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- Myelofibrosis
- Complementary Approaches
Non Pharmacological Approaches for MPN Burden Relief

- Yoga: Phase 2 trials ASH 2017
- Physical Activity: In development
- Meditation: Ongoing and Accrued
- Nutrition: Scherber ASH 2017
- Diet Intervention: In Preparation
- ACT Therapy: Ongoing
Yoga In MPNs

Initial Investigation Efforts

MPN Patients Completing the Yoga Study (N=38)

12 Week Online Yoga Course

Yoga participation averaged 50.8 min/week.

Patient Satisfaction:
- 68% of participants were either satisfied or very satisfied
- 75% felt that it was helpful for coping

Subsequent Investigation Efforts

Online Registration & Randomization

Intervention Online Yoga (N=30)
- 12 Weeks
- >/= 60 Min/Week
- Fitbit tracking (Blinded)
- Daily Logs-Yoga and activity
- Blood (2 Timepoints)
- Salivary cortisol (2 Timepoints)
- MPN Sx, QOL, Sleep

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

Cytokine analysis: Significant decrease in TNF-α from wk 0 to wk 12 (-1.3±1.5; p=0.005) but no significant differences in CBC or IL-6.

PROs analysis: Significant decrease in depression from wk 0 to wk 12 and wk 16 (figure 3 below)

Huberty et al., Blood 2016 128:5478
Huberty et al., BMC CAM 2019 19(1)
Cognitive/Mindfulness Interventions in MPNs

Meditation App Study:
- **Calm Meditation** OR **10% Happier Meditation**
  - 10 min/day of meditation using Calm app for 4 weeks
  - 10 min/day of meditation using 10% Happier app for 4 weeks

MyACT Study:
- 190 MPN patient Baseline Surveys and FitBit Delivered
  Randomization: Age and Brief Fatigue Index Score (4-6, 7-10)
- 95 patients Intervention Group
  - Weeks 1-8 Weekly ACT videos
  - Surveys at week 4 and 8
  - FitBit Assessed Weekly
- 95 patients Wait List Control Group
  - Surveys at week 4 and 8
  - FitBit Assessed Weekly
- Washout Period
  - Survey at week 12
  - FitBit Assessed Weekly
- Wait List Crossover
  - Weekly ACT Videos
  - Surveys at week 20
  - FitBit Assessed week 20

Outcomes:
- Emotional distress (i.e., anxiety, depression)
- Sleep disturbance
- Fatigue
- Quality of life
- MPN10 Score change

Findings:
- Small/moderate improvements in anxiety, depression, fatigue, sleep disturbance, physical health, and MPN10 TSS in all participants
- Calm users reported greater participation, use, and satisfaction

Huberty et. al., JMIR Form Res 2019
### Nutrition in MPNs

#### Initial Investigation Efforts

<table>
<thead>
<tr>
<th>Correlate</th>
<th>Mean symptom burden (MPN-10)</th>
<th>P-value</th>
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<tbody>
<tr>
<td>Diet</td>
<td>Not Following Diet</td>
<td>Following Diet</td>
</tr>
<tr>
<td>Diabetic diet</td>
<td>3.33</td>
<td>4.67</td>
</tr>
<tr>
<td>Lactose Intolerant</td>
<td>3.35</td>
<td>3.87</td>
</tr>
<tr>
<td>Food Intake (Dichotomous)</td>
<td>Never</td>
<td>At Least Once Per Week</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3.62</td>
<td>3.11</td>
</tr>
<tr>
<td>Fast Food</td>
<td>3.24</td>
<td>3.59</td>
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<tr>
<td>Fried Foods</td>
<td>3.22</td>
<td>3.46</td>
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<tr>
<td>Rice</td>
<td>3.57</td>
<td>3.30</td>
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<tr>
<td>Soda</td>
<td>3.22</td>
<td>3.72</td>
</tr>
</tbody>
</table>

#### Subsequent Investigation Efforts

- **Nutritional Ketosis Collaboration**
  - Enrollment N=30
  - Baseline
  - 5 weeks
  - 12 weeks
  - Primary Endpoint: combined >70% Dietary Adherence and >50% patient reported feasibility

- **Nutrient Study Collaboration**
  - Blood draw
  - BMI
  - 24-Hour Diet recall
  - Diet education

**Foods associated with worsened symptom score in red, foods associated with improved score in green**
Calm for Cancer Sleep

Online Registration & Randomization

Calm App #1
- Use the Calm app for ~10 min/day for 12 weeks
- Listen to a meditation before bed
- Primary outcome: sleep disturbance

Calm App #2
- Use the Calm app for ~10 min/day for 12 weeks
- Listen to a sleep story before bed
- Primary outcome: sleep disturbance

Educational Podcast App
- Listen to ~10 min/day of educational, cancer-related podcasts
- Primary outcome: sleep disturbance

Calm for Cancer App Development

STTR grant

Recently funded by NIH – 1 year grant to develop and beta-test a cancer-specific version of the Calm meditation app

Phase 1
- Advisory board consisting of 10 cancer patients/survivors and 10 healthcare professionals uses the app for a week and participates in a focus group to give feedback on app

Phase 2
- Calm developers utilize feedback and additional available evidence from the literature to develop cancer-specific prototype of Calm app

Phase 3
- 30 cancer patients/survivors will test the cancer-specific Calm app prototype and provide feedback for further refinement of the app to be tested again in a future RCT

Current Enrollment:
- 36 enrolled in Calm app #1 group
- 23 enrolled in Calm app #2 group
- 22 enrolled in podcast control group

Target Enrollment:
- 100 enrolled in Calm app #1 group
- 100 enrolled in Calm app #2 group
- 100 enrolled in podcast control group
Conclusions

Improving Outcomes

1) Adequately assess the burden on the MPN and develop appropriate therapy and goals

2) If therapy is not beneficial change to alternative therapy or clinical trial

3) JAK inhibitors and interferons do have a benefit for many subsets of MPN patients, yet opportunities exist

4) Multiple additional pathway targeted agents are undergoing parallel testing – primarily in 2nd line MF and 3rd line PV or ET

5) Non pharmacological therapies may augment treatment options for MPNs