Myelofibrosis: new treatment strategies

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Mayo Clinic Arizona
Evolution of Myelofibrosis

Early MF

Overt MF/secondary MF

Terminal stage

EARLY DEATH

18% BM insufficiency
31% Acute Leukemia
13% Thrombosis
11% Infections
17% Second neoplasia
5% Bleedings

Years after diagnosis

Symptoms/Splenomegaly

Thrombocytopenia/Anemia
Leukoerythroblastosis
Peripheral blasts

Marrow fibrosis grade

MF0
MF1 RETICULUM
MF2 COLLAGEN FIBROSIS
MF3 OSTEOSCLEROSIS

PV/ET

## WHO Diagnostic Criteria: Prefibrotic MF vs Overt MF

### Primary MF Diagnosis

**Requirement for diagnosis**
- All 3 major criteria AND ≥ 1 minor criteria

**Major criteria**
1. Megakaryocytic proliferation and atypia, **without reticulin fibrosis > grade 1 (prefibrotic PMF)** or **with reticulin and/or collagen fibrosis grade 2/3 (overt fibrotic PMF)**
2. **JAK2, CALR, or MPL** mutation, presence of other clonal markers* OR absence of reactive MF
3. Not meeting WHO criteria for other myeloid malignancies

**Minor criteria**
1. Anemia not attributed to a comorbid condition
2. Leukocytosis ≥ 11 × 10⁹/L
3. Palpable splenomegaly
4. LDH increased above ULN
5. Leukoerythroblastosis (overt fibrotic PMF)

* eg, ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1.

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The heterogeneous clinical spectrum of prefibrotic myelofibrosis

Mimicking essential thrombocythemia

Progression towards overt myelofibrosis

Bleeding and thrombosis

Time

Symptoms of myelofibrosis

Life expectancy
Treatment algorithm in prefibrotic myelofibrosis for the thrombotic and bleeding risk

No previous thrombosis or bleeding

- Observation only, or Low-dose ASA in selected patients*

Previous thrombosis

- Low-dose ASA (if arterial) or Oral anticoagulation (if venous) and Cytoreduction** (if thrombocytosis or leukocytosis)

Previous bleeding

- Avoid ASA and use Cytoreduction** (if thrombocytosis or leukocytosis)

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* Age > 60 yrs., or CV risk factors, or JAK2V617F mutation, or leukocytosis or microvascular symptoms and low bleeding risk

** Hydroxyurea as first choice, rIFNα in HU resistant or intolerant patients
## Diagnosing PPV- or PET-MF

### PV

10% transformation rate per 10 years\(^2\)

### ET

<4% transformation rate per 10 years\(^2\)

### Post-PV or Post-ET Myelofibrosis\(^1\)

#### Diagnostic Criteria for Post-PV Myelofibrosis

<table>
<thead>
<tr>
<th>REQUIRED CRITERIA</th>
<th>IWG Diagnostic Criteria for Post-PV Myelofibrosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documentation of previous diagnosis of PV or ET as defined by WHO criteria</td>
<td></td>
</tr>
<tr>
<td>Grade 2 or 3 bone marrow fibrosis (0-3 scale) or grade 3 or 4 bone marrow fibrosis (0-4 scale)</td>
<td></td>
</tr>
</tbody>
</table>

#### Additional Criteria (2 Required)

<table>
<thead>
<tr>
<th>PV</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia or sustained loss of need for either phlebotomy or cytoreductive therapy</td>
<td>Anemia and a decrease of ≥2 mg/mL from baseline hemoglobin level</td>
</tr>
<tr>
<td>Leukoerythroblastosis</td>
<td>Leukoerythroblastosis</td>
</tr>
<tr>
<td>≥5 cm increase in palpable splenomegaly or new splenomegaly</td>
<td>≥5 cm increase in palpable splenomegaly or new splenomegaly</td>
</tr>
<tr>
<td>Development of ≥1 of 3 constitutional symptoms(^3)</td>
<td>Increased serum LDH level</td>
</tr>
<tr>
<td>Development of ≥1 of 3 constitutional symptoms(^3)</td>
<td>Development of ≥1 of 3 constitutional symptoms(^3)</td>
</tr>
</tbody>
</table>

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ET = essential thrombocythemia; IWG = International Working Group; LDH = lactate dehydrogenase; PET-MF = post-essential thrombocythemia myelofibrosis; PPV-MF = post-polycythemia vera myelofibrosis; PV = polycythemia vera; WHO = World Health Organization.

\(^1\)Constitutional symptoms include > 10% weight loss in 6 months, night sweats and unexplained fever (>37.5°C).

NCCN Guideline for Treatment of MF: Based on Risk and Symptoms/Signs

- **Low Risk**: Observation or ruxolitinib (if symptomatic) or clinical trial

- **Intermediate-1**
  - Observation or ruxolitinib (if symptomatic) or clinical trial or allogeneic HSCT (selected pts)
  - Transplant candidate $\Rightarrow$ Allogeneic HSCT
  - or

- **Intermediate-2**
  - Transplant ineligible/symptomatic $\Rightarrow$ ruxolitinib or clinical trial
  - AND/or

- **High Risk**
  - Transplant ineligible/anemia $\Rightarrow$ anemia rx or clinical trial

Low risk = 0 on IPSS, DIPSS-Plus, or DIPSS

INT-1 risk = IPSS = 1, DIPSS-Plus = 1, DIPSS = 1 or 2

INT-2 risk = IPSS = 2, DIPSS-Plus =2 or 3, DIPSS = 3 or 4

High risk = IPSS = 3, DIPSS-Plus =4 to 6, DIPSS = 5 or 6

HOW DO WE DEFINE RISK?
Dynamic International Prognostic Scoring System

DIPSS scores/risk:

- 0 pts: low risk
- 1-2 pts: Intermediate – 1
- 3-4 pts: Intermediate – 2

<table>
<thead>
<tr>
<th>DIPSS</th>
<th>DIPSS plus</th>
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</thead>
<tbody>
<tr>
<td>Anemia (hgb &lt;10) (2)</td>
<td>DIPSS score</td>
</tr>
<tr>
<td>WBC &gt;25 pts</td>
<td>Platelets &lt;100</td>
</tr>
<tr>
<td>Blasts &gt;1%</td>
<td>Transfusion dependant</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>poor risk cytogenetics: complex karyotype or any sole or two abnormalities including +8, -7/7q-, -5/5q-, inv(3), i(17q), 12p-, 11q23 rearrangement</td>
</tr>
<tr>
<td>Age &gt;60</td>
<td></td>
</tr>
</tbody>
</table>

DIPSS plus scores/risk

- 0 pts: low risk
- 1 pt: intermediate-1
- 2-3 pts: intermediate-2
Clarification of risks

- **Anemia**—low red blood cell count. Hemoglobin (hgb) is consistently less than 10.
- **Thrombocytopenia**—low platelet (plt) count, less than 100.
- **Leukocytosis**—high white blood cell count (WBC), consistently greater than 25.
- **Blasts**—immature white blood cells
  - Note this does not mean you have leukemia unless blast % greater than 20%.
Other factors that contribute to risk

• Driver mutation

• Cytogenetics

• Molecular mutations
Driver mutation

• Mutations that CAUSE the disease
  • JAK-2
  • MPL
  • CAL-R
• CAL-R is GOOD
• No mutations is unfavorable
Cytogenetics

- Cytogenetics (abnormal chromosomes found in your bone marrow)
  - complex karyotype (3 or more abnormalities) or sole or 2 abnormalities that include +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, or 11q23 rearrangement

These are not inherited... they are changes that occur only in disease cells
Molecular mutations
“next generation sequencing”

Prognostically important genes, other than JAK2/CALR/MPL, in essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF)
TREATMENT
EARLY FRONT LINE TREATMENT
IFN for First-Line MF Treatment: Consideration in Early Hyperproliferative Stage

Impact of Use

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
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<tbody>
<tr>
<td>• Blood count control</td>
<td>• Anticlonal activity</td>
</tr>
<tr>
<td>• Address splenomegaly, when modest</td>
<td>• Potential for regression of histologic changes and delayed transformation?</td>
</tr>
<tr>
<td>• Reduction in thrombosis risk</td>
<td></td>
</tr>
</tbody>
</table>

- Consider IFN use in selected pts
  - With preserved performance status and limited comorbidities
  - Who are earlier in disease course
  - When splenomegaly modest
  - Without additional non-JAK2 mutations (?)

- Limitations:
  - Potential for short-term negative impact on QoL
  - Tolerable in the long term?

Approach to the Treatment of Anemia in MF

EPO (erythropoietin) level

ADEQUATE ≥ 500 mIU/mL

- Danazol, Thalidomide, lenalidomide

INADEQUATE < 500 mIU/mL

- ESA x 3 mos

- No response

- Response

NCCN guidelines, 2017
Approach to symptomatic disease

- Ruxolitinib -- JAK2 inhibitor

- Works even if you DON’T have a JAK2 mutation

- Approved in 2011
MF: What does ruxolitinib do?

Patient Pre-Ruxolitinib Therapy

After 2 Months of Therapy

It is good for spleen and symptoms
Early-Stage MF May Have a Significant Clinical Burden

<table>
<thead>
<tr>
<th></th>
<th>Prognostic risk</th>
<th>Symptom severity quartile</th>
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<tbody>
<tr>
<td>Reduced QoL</td>
<td>High</td>
<td>Q4</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Q1</td>
</tr>
<tr>
<td>Respondents With MF, % (n/N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>89 (56/63)</td>
<td>67 (6/9)</td>
</tr>
<tr>
<td></td>
<td>95 (69/73)</td>
<td>51 (22/43)</td>
</tr>
<tr>
<td>Had to cancel planned activities*</td>
<td>High</td>
<td>Q4</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Q1</td>
</tr>
<tr>
<td>Respondents With MF, % (n/N)</td>
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<td>60</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>5 (2/43)</td>
<td>57 (36/63)</td>
</tr>
<tr>
<td></td>
<td>77 (56/73)</td>
<td>56 (5/0)</td>
</tr>
<tr>
<td>Had to call in sick*</td>
<td>High</td>
<td>Q4</td>
</tr>
<tr>
<td></td>
<td>Low</td>
<td>Q1</td>
</tr>
<tr>
<td>Respondents With MF, % (n/N)</td>
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<td>60</td>
</tr>
<tr>
<td></td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>47 (9/19)</td>
<td>40 (2/5)</td>
</tr>
</tbody>
</table>

- DIPSS low-risk MF patients are moderately to highly symptomatic in 44% of the cases
- The reduction of quality of life and social/working activity is similar in low and high risk categories

OK, these medications don’t work, now what?

- Anemia associated with MF
- Ruxolitinib failure
How to approach this

• Add agents to ruxolitinib

• Newer JAK inhibitors

• Anti-fibrotic agents

• Novel agents/pathway
How to approach this

• Add agents to ruxolitinib
  • Newer JAK inhibitors
  • Anti-fibrotic agents
  • Novel agents/pathway
Resurrecting response to ruxolitinib: A Phase I study of ruxolitinib and umbralisib (TGR-1202) in ruxolitinib-experienced myelofibrosis


June 15, 2018
23rd Congress of EHA
Study design and patient populations

Ruxolitinib-experienced Myelofibrosis (MF)
- PMF, post-PV MF or post-ET MF
- Grade ≥1 fibrosis
- Lost, suboptimal or no response on a stable dose of ruxolitinib for ≥ 8 weeks

EXPANSION COHORT 1
Ruxolitinib-experienced MF

EXPANSION COHORT 2
Treatment-naïve MF

EXPANSION COHORT 3
Polycythemia vera

EXPANSION COHORT 4
CMML

EXPANSION COHORT 5
Other MDS/MPNs

ESCALATION STAGE 1
Stable ruxolitinib + Escalating umbralisib

ESCALATION STAGE 2
Escalating ruxolitinib + Umbralisib MTD from ES1

23 patients in this analysis

Stable ruxolitinib (cleared ES2) + Umbralisib MTD from ES1
IWG-MRT & ELN responses to umbralisib + ruxolitinib

-30

Weeks on Study

120

Best IWG-MRT & ELN Response*

- Not Assessed
- Stable Disease
- Clinical Benefit
- Complete Remission

Status
Off-study
Continues on Treatment

Off Study Reason
Dose-limiting Toxicity (n=2)
Adverse Event (n=1)
Progressive Disease (n=3)
Physician or Patient Decision (n=6)
Transplant (n=1)

Two subjects achieved complete remission.

<table>
<thead>
<tr>
<th></th>
<th>Case 1</th>
<th>Case 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td></td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
<tr>
<td>Reticulin</td>
<td>Baseline</td>
<td>Follow-up</td>
</tr>
</tbody>
</table>
Newer JAK inhibitors

- Pacritinib
- Momolotenib
- Fedratinib
JAK Inhibitor Monotherapy (Phase 3 Programs - MF)

**Momelotinib (Gilead, USA)**

**JAK1/ JAK2 Inhibitor:** Phase II Program ↓ Spleen, ↓ MPN Sx, ↑ Hemoglobin

**MF**
- Int 1 & 2/ High Risk
- PLT ≥ 50 x 10^9/L

**Response**
- ≥35% SV ↓
- MPN-SAF
- Anemia

**NCT01969838**

**Momelotinib b**
- 200 QD

**Randomize**

**Ruxolitini b**
- (PI Dose)

**NCT02101268**

**Momelotinib b**
- 200 QD

**Randomize**

**BAT**
- (include Rux)

**Response**
- ≥35% SV ↓
- MPN-SAF
- Anemia

- No JAK excl.
Momelotinib Open Label Trial (N=61)

<table>
<thead>
<tr>
<th>Clinical Outcomes</th>
<th>Responder/Evaluable n/n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spleen response by MRI at 24 weeks</strong></td>
<td>27/50 (54)</td>
</tr>
<tr>
<td><strong>Anemic response any time on study</strong></td>
<td></td>
</tr>
<tr>
<td>8 weeks</td>
<td>18/40 (45)</td>
</tr>
<tr>
<td>12 weeks</td>
<td>10/40 (25)</td>
</tr>
<tr>
<td><strong>Transfusion response any time on study</strong></td>
<td></td>
</tr>
<tr>
<td>Response lasting ≥8 weeks</td>
<td>15/29 (52)</td>
</tr>
<tr>
<td>Response lasting ≥12 weeks</td>
<td>9/29 (31)</td>
</tr>
<tr>
<td><strong>Hgb response any time on study</strong></td>
<td></td>
</tr>
<tr>
<td>Response lasting ≥8 weeks</td>
<td>3/11 (27)</td>
</tr>
<tr>
<td>Response lasting ≥12 weeks</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td><strong>TSS improvement of 50% at 3 months</strong></td>
<td>14/60 (23)</td>
</tr>
</tbody>
</table>

*35% reduction from baseline; †Transfusion response and hemoglobin (Hgb) response; ‡No transfusion for patients who were transfusion dependent at baseline; where transfusion dependent is defined as receiving ≥2 units of red blood cells (RBC) ≤30 days prior to first dose of MMB; ‡‡≥2 g/dL Hgb increase from baseline for patients who were transfusion independent with Hgb <10 g/dL at baseline, where transfusion independent is defined as not receiving an RBC transfusion within 12 weeks prior to first dose of MMB. MRI, magnetic resonance imaging.
RESULTS OF THE PERSIST-2 PHASE 3 STUDY OF PACRITINIB (PAC) VERSUS BEST AVAILABLE THERAPY (BAT), INCLUDING RUXOLITINIB (RUX), IN PATIENTS WITH MYELOFIBROSIS (MF) AND PLATELET COUNTS ≤100,000/ML

John Mascarenhas¹, Ronald Hoffman¹, Moshe Talpaz², Aaron T. Gerds³, Brady Stein⁴, Vikas Gupta⁵, Anita Szoke⁶, Mark Drummond⁷, Alexander Pristupa⁸, Tanya Granston⁹, Robert Daly⁹, James P. Dean⁹, Suliman Al-Fayoumi⁹, Jennifer A. Callahan⁹, Jack W. Singer⁹, Jason Gotlib¹⁰, Catriona Jamieson¹¹, Claire Harrison¹², Ruben Mesa¹³, Srdan Verstovsek¹⁴

¹Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; ²University of Michigan, Comprehensive Cancer Center, Ann Arbor, MI, USA; ³Cleveland Clinic, Cleveland, OH, USA; ⁴Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; ⁵Princess Margaret Cancer Center, University of Toronto, Ontario, Canada; ⁶Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary; ⁷Beatson West of Scotland Cancer Centre, Glasgow, UK; ⁸Ryazan’s Clinical Hospital, Ryazan, Russia; ⁹CTI BioPharma Corp., Seattle, WA, USA; ¹⁰Stanford University Medical Center, Stanford, CA, USA; ¹¹University of California-San Diego, La Jolla, CA, USA; ¹²Guy’s and St Thomas’ NHS Foundation Trust, London UK; ¹³Mayo Clinic, Scottsdale, AZ, USA; ¹⁴MD Anderson Cancer Center, Houston, TX, USA.
**Key Eligibility Criteria**

- Primary/secondary

**Randomization (N = 311)**

- PAC 400 mg QD
- PAC 200 mg BID
- BAT (including)

**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 $C_{min}$ and lower $C_{max}$ than PAC 400 QD
- Crossover from BAT allowed after progression (any time) or at Wk 24
- Allowed previous JAK2 inhibitor use

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

PK, pharmacokinetics; PPV, post-polycythemia; PET, post-essential thrombocytemia.
Key Eligibility Criteria

- Primary/secondary

Eligibility Criteria

- Primary/secondary MF
- Platelets ≤100,000/µL
- Prior JAK2 inhibitors allowed

Randomization (N = 311)

1:1:1

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*

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How to approach this

• Add agents to ruxolitinib

• Newer JAK inhibitors

• **Anti-fibrotic agents**

• Novel agents/pathway
PRM-151: Recombinant Human Pentraxin-2 (PTX-2)

- PTX-2 (ぺんたけしん）is an endogenous regulator of tissue repair
- PTX-2 binds to damaged tissue (ダメージ）and monocytes/macrophages
- PTX-2 prevents and reverses fibrosis in pre-clinical models
- PTX-2 levels are low in MF patients
  - Also low in patients with renal, pulmonary and liver fibrosis

**Hypothesis:**
Reduction of bone marrow fibrosis will restore hematopoiesis and

Image courtesy of Ruben A. Mesa, MD.
PRM-151 Adaptive Phase 2 Trial Design: Myelofibrosis

Stage 1 Design Highlights:

- 24-week treatment period with days 1, 3, 5 loading dose in all arms
  - Patients with clinical benefit may continue beyond 24 weeks
- PRM-151 + RUX: stable RUX dose ≥3 months with no decrease in splenomegaly for ≥4 weeks
- No eligibility restrictions for anemia, thrombocytopenia, leukopenia, or spleen size

How to approach this

• Add agents to ruxolitinib

• Newer JAK inhibitors

• Anti-fibrotic agents

• Novel agents/pathway
Sotatercept (ACE-011) Alone and in Combination With Ruxolitinib in Patients (pts) With Myeloproliferative Neoplasm (MPN)-Associated Myelofibrosis (MF) and Anemia

Abstract 255

Sotatercept (ACE-011)

A fusion protein consisting of the extracellular domain of human activin receptor type IIA linked to the Fc portion of human IgG1. It “traps” ligands of the TGF-beta superfamily, thus relieving their suppressive effect on terminal erythropoiesis.
73-year-old female, PMF, MF-3, MPL W515L+, del7q, del13q, transfusion-dependent, DIPSS int-2, previous therapies pomalidomide and momelotinib (4 years).

Sotatercept (ACE-011) in MF and Anemia

ACE-011: Results and Future Directions

• Sotatercept (ACE-011) effective for anemia in MF, alone or in conjunction with ruxolitinib (~40% response; N= 35)

• Luspatercept (ACE-536) promising in anemia of lower-risk MDS; pivotal trial MEDALIST fully accrued

• Ongoing: Multicenter phase II trial of luspatercept in MF (NCT03194542 – clinicaltrials.gov)
## Ruxolitinib-Based Combination Therapy for MF: Selected Ongoing Clinical Trials

<table>
<thead>
<tr>
<th>Partner</th>
<th>MPN</th>
<th>Phase</th>
<th>ClinicalTrials.gov</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azacytidine</td>
<td>MF, MDS/MPN</td>
<td>II</td>
<td>NCT01787487</td>
</tr>
<tr>
<td>Danazol</td>
<td>MF</td>
<td>II</td>
<td>NCT01732445</td>
</tr>
<tr>
<td>Decitabine</td>
<td>MPN-AML</td>
<td>I/II</td>
<td>NCT02257138, NCT02076191</td>
</tr>
<tr>
<td>INC8050465</td>
<td>MF</td>
<td>II</td>
<td>NCT02718300</td>
</tr>
<tr>
<td>Idelalisib</td>
<td>MF</td>
<td>I</td>
<td>NCT02436135</td>
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<td>Itacitinib</td>
<td>MF</td>
<td>II</td>
<td>NCT03144687</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>MF</td>
<td>II</td>
<td>NCT01375140</td>
</tr>
<tr>
<td>Navitoclax</td>
<td>MF</td>
<td>II</td>
<td>NCT03222609</td>
</tr>
<tr>
<td>Panobinostat</td>
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<td>PegIFN α-2a</td>
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<td>I/I/II</td>
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<table>
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<td>Sotatercept</td>
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<td>Thalidomide</td>
<td>MF</td>
<td>II</td>
<td>NCT03069326</td>
</tr>
<tr>
<td>Umbralisib</td>
<td>PV, MF, MDS/MPN</td>
<td>I</td>
<td>NCT02493530</td>
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Summary

• Early MF: IFN-alpha
• Symptomatic MF: Ruxolitinib
• Up and coming therapies
  – Rux + other agents
  – New JAK-inhibitors
  – Anti-fibrotics
  – New pathways/approaches—ie anemia
THANK YOU FOR YOUR ATTENTION!!

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