Advancing the Myelofibrosis Treatment Paradigm

A Case-based Collaborative for the Advanced Practitioner in Oncology

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Learning Objectives

- Assess the pathogenesis and progression of myelofibrosis, including underlying pathophysiologic mechanisms and the most frequently related primary mutations
- Examine the patient burden of myelofibrosis, reviewing its prevalence, clinical manifestations, and evidence-supported risk stratification and diagnostic strategies
- Appraise the current treatment landscape for myelofibrosis, identifying healthcare disparities and inequities while focusing on areas of greatest unmet need for patients
- Explore therapeutic targets for myelofibrosis treatments
- Using a case-based approach, design individualized treatment plans for patients with myelofibrosis, highlighting clinical scenarios commonly encountered by the advanced practitioner, including recognition, mitigation, and management of adverse events

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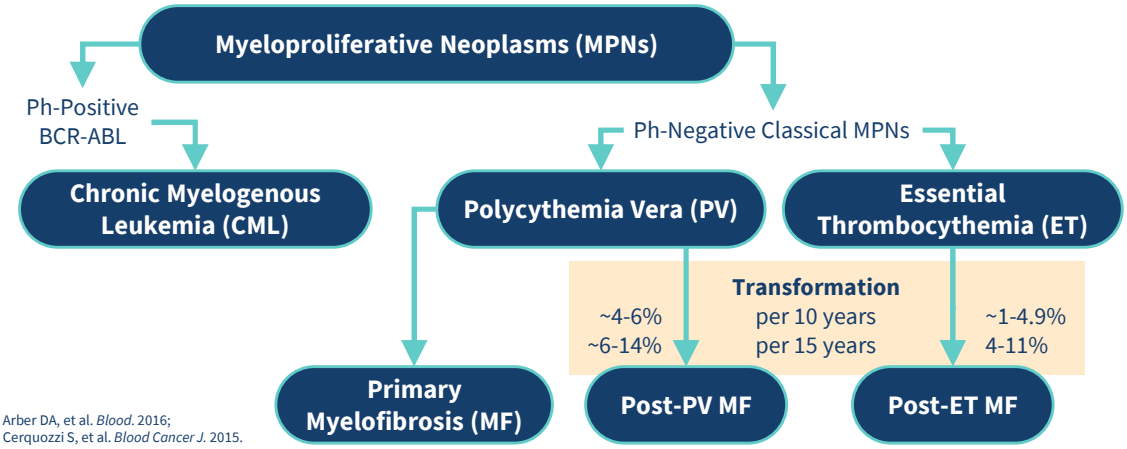
Foundations of Myelofibrosis

Assessing Physiologic Disease Processes, Clinical Manifestations, and Patient Burden

Lindsey Lyle, MS, PA-C, FAPO

Myelofibrosis is the Most Aggressive Myeloproliferative Neoplasm (MPN)



Arber DA, et al. *Blood.* 2016;
Cerquozzi S, et al. *Blood Cancer J.* 2015.

Prevalence and Risk for Myelofibrosis (MF)

- **Prevalence**
  - MF occurs in about 1.5 out of every 100,000 people in the United States annually
    - ~ 13,000 cases in the United States
  - Median age of diagnosis is 65 years
  - MF affects men and women equally
  - Increased prevalence among **Ashkenazi Jews**
- **Risk Factors**
  - **No major known risk factors** for the development of myelofibrosis
  - Prior history of **polycythemia vera or essential thrombocythemia puts one at an elevated risk of having secondary myelofibrosis**
  - Exposure to certain chemicals such as toluene and benzene as well as prolonged exposure to radiation has been observed in some cases

Tefferi A. *Am J Hematol.* 2023; https://rarediseases.org/rare-diseases/primary-myelofibrosis/; https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=EN&Expert=824.

Myelofibrosis Overview

Characterization	Clonal and pathologic proliferation of pluripotent stem and progenitor cells, release of pro-inflammatory cytokines, extramedullary hematopoiesis, splenomegaly, and progressive bone marrow fibrosis
Clinical Implications	Disruption of the physiologic medullary erythropoietic environment, leads to decreased erythropoiesis, progressive bone marrow failure and anemia
Cardinal Features	Splenomegaly Constitutional symptoms Anemia

Chifotides HT, et al. *J Hematol Oncol.* 2022.

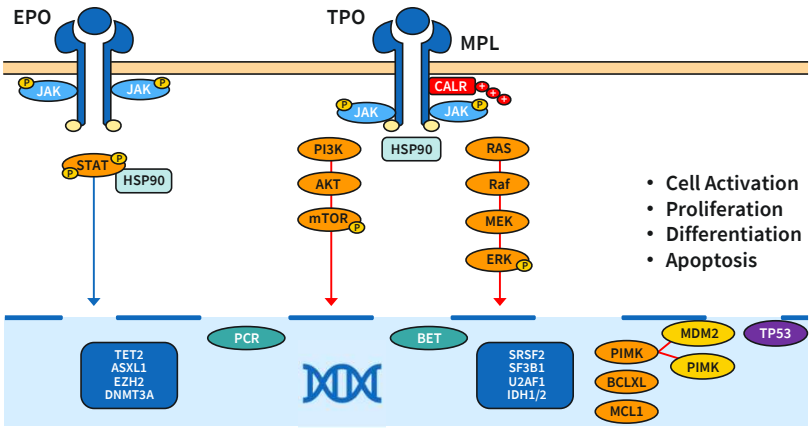
Driver Mutations and JAK-STAT Activation

Incidence of Driver Mutations:

Primary Myelofibrosis:
- *JAK2*^{V617F}(60%)
- *MPL* (5-10%)
- *CALR* (20-30%)
  - Type 1 most prevalent
- Triple Negative (10%)

Secondary Myelofibrosis:
- PPV-MF → *JAK2*^{V617F} (~95%)
- PET-MF → *JAK2*^{V617F} (50%), *CALR* (Type 1 most prevalent) (30%) and *MPL* (10%)

Overactive **JAK-STAT** Pathway Signaling is a Key Driver of MF



Morsia E, et al. *Int J Mol Sci.* 2022; Mascarenhas J, et al. *Leukemia.* 2023; Morris R, et al. *Protein Sci.* 2018.

Additional Biological Drivers of Disease

- Recent studies implicate additional biological drivers in the disease pathogenesis in MF including the TLR/Myddosome/IRAK1 inflammatory pathway and aberrant cytokine-driven signaling via activin receptor type 1 (ACVR1)
  - **ACVR1** a member of receptors that **controls iron storage** and also **upregulates hepcidin production**
- Overproduction of cytokines is thought to be one of the key factors leading to the clinical features of MF, including bone marrow fibrosis, extramedullary hematopoiesis and consequent splenomegaly, and anemia

Singer JW, et al. *Oncotarget*. 2018; Oh ST, et al. *Blood Adv*. 2020; Fisher DAC, et al. *Leukemia*. 2019.

Diagnosis: Primary Myelofibrosis

WHO Diagnosis of Primary MF	
Major Criteria	• Abnormal megakaryocytic proliferation and atypia with reticulin and/or collagen fibrosis grades 2 or 3 • No evidence of another myeloid malignancy with negative BCR-ABL PCR and not meeting criteria for ET, PV, or MDS • Mutation in JAK2, CALR, MPL, or other clonal markers including ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, and SF3B1
Minor Criteria	**Presence of *at least 1* of the following:** • Anemia not attributed to a comorbid condition • Leukocytosis with WBC (≥11×10^9/L) • Palpable splenomegaly • LDH > institutional ULN • Leukoerythroblastosis (presence of nucleated RBC and immature WBC in peripheral blood)

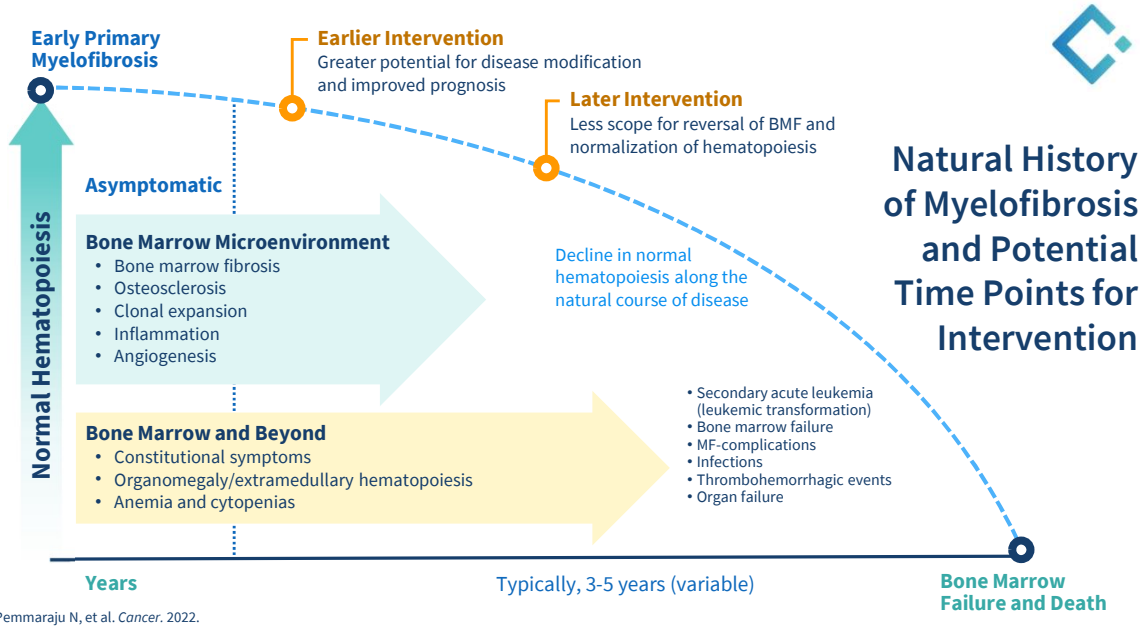
All 3 major and **at least 1 minor** required for diagnosis

Barbui T, et al. *Blood Rev*. 2016.

Diagnosis: Post-PV & Post-ET Myelofibrosis

	WHO Diagnosis of Post-ET MF	WHO Diagnosis of Post-PV MF
Required Criteria:	• Documentation of a **previous diagnosis of ET** as defined by the WHO criteria • Bone marrow fibrosis **grade 2–3** (on 0–3 scale) or **grade 3–4** (on 0–4 scale)	• Documentation of a **previous diagnosis of PV** as defined by the WHO criteria • Bone marrow fibrosis **grade 2–3** (on 0–3 scale) or **grade 3–4** (on 0–4 scale)
Additional Criteria (≥2 required)**:**	• **Anemia and ≥2 g/dL decrease from baseline hemoglobin level** • A leukoerythroblastic peripheral blood picture • Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly • **Increased LDH (above reference level)** • Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)	• **Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis** • A leukoerythroblastic peripheral blood picture • Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly • Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)

Barosi G, et al. *Leukemia*. 2008.



Natural History of Myelofibrosis and Potential Time Points for Intervention

Pemmaraju N, et al. *Cancer*. 2022.

Clinical Presentation

Heterogeneous with a highly variable disease course

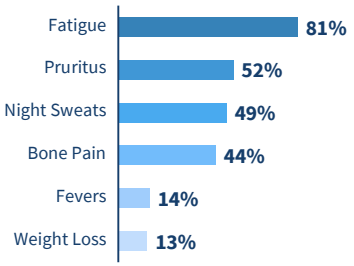
- Blood Count Abnormalities
  - Proliferative:
    - Leukocytosis, normal platelets or thrombocytosis, mild or no anemia
  - Non-proliferative/myelodepletive:
    - Leukopenia, thrombocytopenia, anemia
    - At diagnosis 25% pts with PLT <100,00 and 40% pts with anemia, Hgb <10 g/dL*
  - Peripheral blasts
- Varying degrees of splenomegaly
- Constitutional symptoms
- Thrombotic/hemorrhagic events

*During disease course 68% with PLT <100 and nearly all pts with some degree of anemia

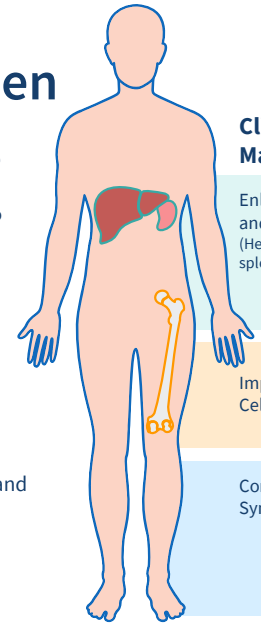
Pemmaraju N, et al. *Cancer* 2022;
Reynolds SB, et al. *Hematology Am Soc Hematol Educ Program.* 2022;
Masarova L, et al. *Eur J Haematol.* 2018.

Symptom Burden

MPN Symptom Incidence



*Validated MPN PROs allow for precise and rapid assessment of the MPN symptom burden in clinical and trial settings

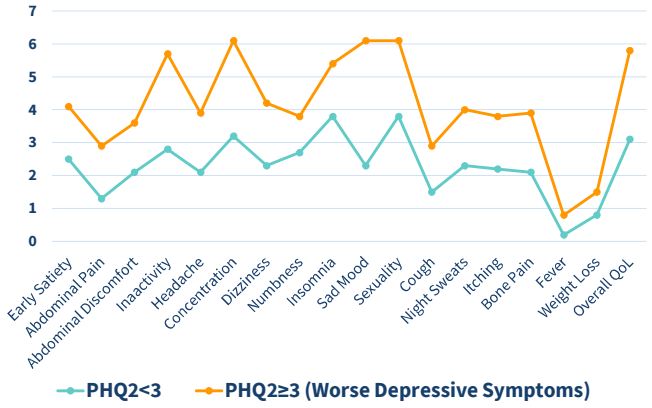


Clinical Manifestation	Symptomatology	Driver/Cause
Enlarged Liver and Spleen (Hepato-splenomegaly)	• Abdominal pain and/or fullness/ bloating • Portal hypertension • Pressure on the liver • Splenic infarction	• Abnormal trafficking of hematopoietic stem cell • Ineffective hepatosplenic extramedullary hematopoiesis (EMH)
Impaired Blood Cell Production	• Thrombocytopenia • Anemia • Leukopenia	• Build up of fibrosis in the BM leading to ineffective hematopoiesis
Constitutional Symptoms	• Fatigue • Night sweats • Fever • Weight loss (cachexia) • Bone pain • Pruritus • Thrombosis/bleeding	• Due to advancing fibrosis, accompanied with release of cytokines resulting in symptoms of inflammation

Tremblay D, et al. *Best Pract Res Clin Haematol*. 2022.

Constitutional Symptoms and Impact on Quality of Life (QoL) and Depressive Symptoms

- **QoL**
  - Inactivity, fatigue and depression were the most correlated with QoL decrement
  - Having **at least one severe symptom and having multiple symptoms of moderate intensity** are meaningfully predictive of QoL decrements
- **Depressive Symptoms**
  - Worse depressive symptoms (PHQ2≥3) were associated with higher MPN-SAF Total Symptom Score, higher worst fatigue score, and worse overall QoL
  - **Risk of depressive symptoms** were noted in approximately **20% of patients**
    - Consistent with the reports of depressive symptoms in other hematologic malignancies



Langlais BT, et al. *Leuk Lymphoma.* 2019; Padrnos L, et al. *Cancer Med.* 2020.

Symptom Assessment

- **MPN-SAF Total Symptom Score** (MPN-SAF TSS)
  - Compiled 10-item assessment of the **most representative MPN-SAF** (symptom assessment form) **symptoms**

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Myeloproliferative Neoplasms

NCCN Guidelines Index
Table of Contents
Discussion

MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS; MPN-10)[1]

(Recommended for monitoring symptoms during the course of treatment)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed November 2023.

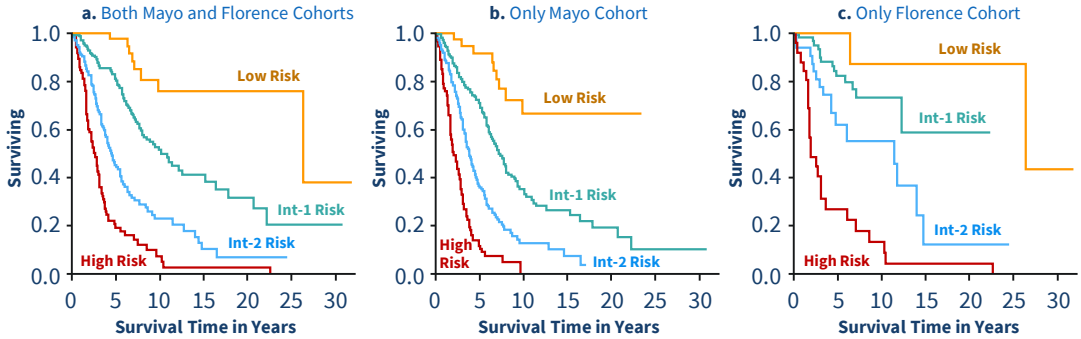
Risk Stratification in Primary Myelofibrosis

	DIPSS Plus	MIPSS70+ v2.0		GIPSS
Factors (points)	**Clinical** • Aged >65y • Hb <10 g/L • WBC >25×109/L • Circulating blasts ≥1% • Constitutional symptoms • Unfavorable karyotype[a] • Transfusion dependency • Platelets <100×109/L	**Clinical** • Severe anemia[b] • Moderate anemia[c] • Circulating blasts ≥2% • Constitutional symptoms	**Genetic** • VHR karyotype • Unfavorable karyotype • No CALR type 1/like • One HMR[d] mutation • ≥2 HMR[d] mutation	**Genetic** • VHR karyotype • Unfavorable karyotype • No CALR type 1/like • ASXL1 mutation • SRSF2 mutation • U2AF1Q157 mutation
Low Risk	0 Points	0-1 Points		0 Points
Int-1	1 Point	-		1 Point
Int	-	2-4 Points		-
Int-2	2-3 Points	-		2 Points
High	≥4 Points	≥5 Points		≥3 Points
Very High	-	≥5 Points		-

[a]Monosomal karyotype, isochromosome of the long arm of chromosome 17 and inversion of chromosome 3. [b,c] Hb <8 g/dL in women and <9 g/dL in men. d Hb 8-9.9 g/dL in women and 9-10.9 g/dL in men. [d]HMR mutations include ASXL1, SRSF2, EZH2, IDH1, and IDH2; for MIPSS70+ also U2AF1Q157. DIPSS, Dynamic International Prognostic Scoring System; GIPSS, genetically inspired prognostic scoring system; HMR, high molecular risk; MIPSS70+ version 2.0, mutation and karyotype enhanced international prognostic system; VHR, very high risk.

O'Sullivan JM, et al. *Clin Adv Hematol Oncol*. 2018; Tefferi A. *Am J Hematol*. 2021.

Prognostic Scoring Systems and Associated Overall Survival



HR (95% CI)			
	Low Risk: Reference	**Int-2 Risk: 8.8** (4.5-19.9)	
	Int-1 Risk: 3.5 (1.8-7.9)	**High Risk: 17.7** (9.0-40.3)	
	Low Risk: Reference	**Int-2 Risk: 7.7** (4.0-15.9)	
	Int-1 Risk: 3.5 (1.9-7.4)	**High Risk: 16.8** (8.9-36.2)	
	Low Risk: Reference	**Int-2 Risk: 9.2** (1.9-166.0)	
	Int-1 Risk: 3.7 (0.74-67.7)	**High Risk: 28.4** (5.9-510)	

a Genetically inspired prognostic scoring system (GIPSS)-stratified survival data in 485 patients with primary myelofibrosis and age 70 years or younger, including both Mayo and Florence cohorts. **b** GIPSS-stratified survival data in 488 Mayo Clinic patients with primary myelofibrosis, including Mayo cohort only. **c** GIPSS-stratified survival data in 153 Italian patients with primary myelofibrosis, including Florence cohort only

Tefferi A, et al. *Leukemia*. 2018.

Driver Mutations Impact Phenotype and Overall Survival

***JAK2* V617F**	• Older age, higher Hgb level, leukocytosis, and lower platelet count
CALR	• Younger age, higher platelet count, less frequent leukocytosis, anemia, and transfusion requirements, and (DIPSS-plus) scores compared with *JAK2*-mutated disease
***CALR* type 2**	• Higher risk DIPSS-plus scores, marked leukocytosis, and higher circulating blast percentage compared with type 1 variants
Triple-negative	• Older, with lower Hb levels, platelet and leukocyte counts • Highest risk of transformation to blast phase

- *Risk of thrombosis is higher in JAK2 mutated compared to CALR mutated, despite higher platelet count associated with CALR*
- *Anemia and leukopenia were associated with a low JAK2 V617F allele burden (<25%) and inferior survival*

Rumi E, et al. *Int J Mol Sci*. 2020; Chifotides HT, et al. *Cancers*. 2023.

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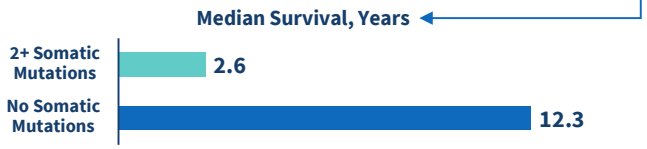
Non-Driver Mutations Impact Prognosis

- **Somatic mutations** (ASXL1, SRSF2, EZH2, RAS, IDH1, and IDH2) → **commonly associated with disease progression, occur randomly, and identify primary MF patients at high risk for leukemic transformation or premature death**

- *ASXL1* mutations tended to cluster with normal karyotype and predict a worse prognosis in patients classified as intermediate-1 and intermediate-2 risk
- The presence of *SRSF2* or *IDH1* mutations appeared to predict leukemic transformation independent of currently known risk factors including thrombocytopenia and unfavorable karyotype
- Presence of *TP53* is strongly associated with leukemic transformation

- **2 or more somatic mutations predicted worse outcomes**
- 3 or more somatic mutations contributes to the presence of myelodysplastic features and increases risk of evolution to blast phase



Rumi E, et al. *Blood*. 2014; Gangat N, et al. *J Clin Oncol*. 2011; Shammo JM. *Hematology*. 2016; Zhou A, *Best Pract Res Clin Haematol*. 2014; Chifotides HT, et al. *Cancers*. 2023.

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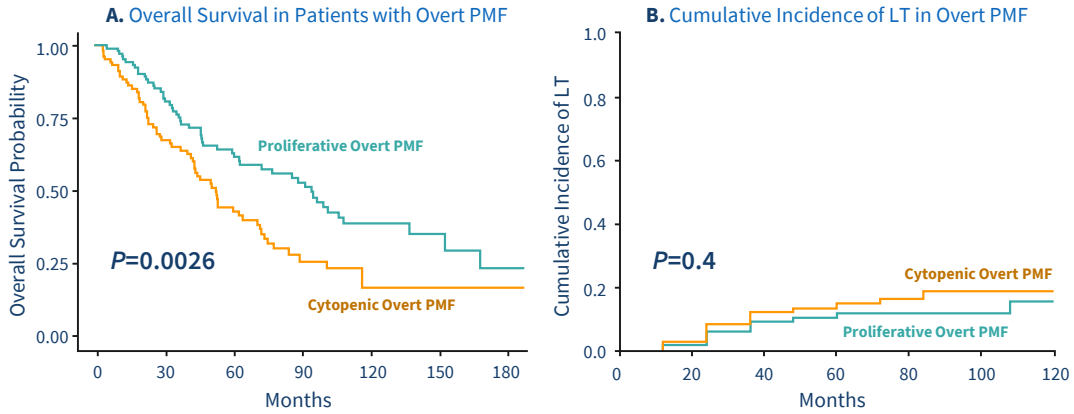
Overall Survival Differences by Phenotype



A. Kaplan-Meier estimates of overall survival in patients with overt PMF according to disease phenotype (cytopenic vs proliferative).
B. Competing risks-adjusted estimates of cumulative incidence of leukemic transformation in overt PMF according to disease phenotype (cytopenic vs proliferative).
Abbreviations: CI confidence interval, OS overall survival

Coltro G, et al. *Blood Cancer*. 2022.

Approach to Treatment

Leveraging Therapeutic Targets and Algorithms to Maximize Outcomes

Shawn Griffin, PharmD, BCOP

Treatment Algorithm

High/Intermediate Risk?

Considerations
- Past therapy
- Blood counts
- Age/fitness/comorbidities

Yes

- **If PLT <50 x 10^9/L**
  - **Pacritinib** (category 1)
  - **Momelotinib** (category 2B)
  - Clinical trial
  - ASCT
- **If PLT ≥50 x 10^9/L**
  - **Ruxolitinib** (category 1)
  - **Fedratinib** (category 1)
  - **Momelotinib**
  - **Pacritinib** (category 2B)
  - Clinical trial
  - ASCT
- Treatment of symptomatic anemia

No

Symptomatic?

Yes

- Clinical trial
- Hydroxyurea
- Peginterferon alfa-2a
- Ruxolitinib
- Momelotinib (category 2B)

No

- Clinical trial
- Observation

All recommendations are category 2A unless otherwise indicated.
ASCT, allogeneic stem cell transplant; PLT, platelets.

National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

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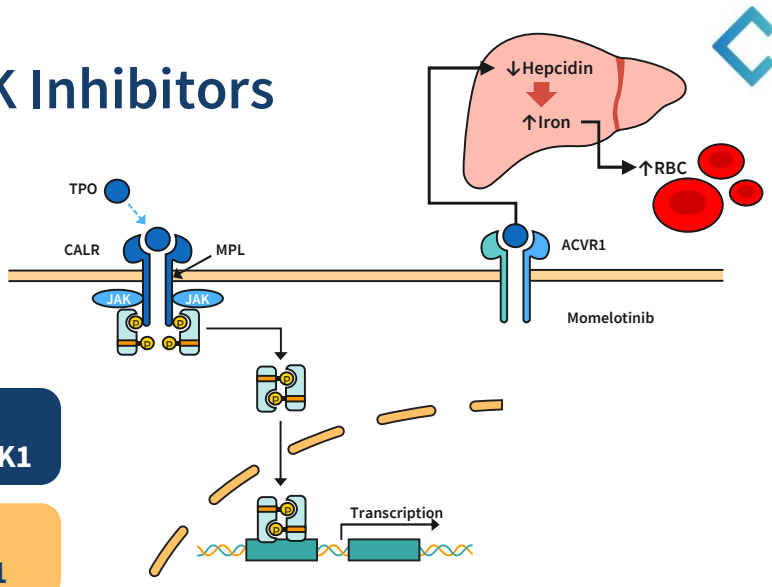
Approved JAK Inhibitors

Ruxolitinib
JAK1, JAK2

Fedratinib
JAK2, FLT3

Pacritinib
JAK2, FLT3, and IRAK1

Momelotinib
JAK1, JAK2, ACVR1



Garmezy B, et al. *Blood Rev.* 2021; National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023); Chifotides H, et al. *J Hematol Oncol.* 2022.

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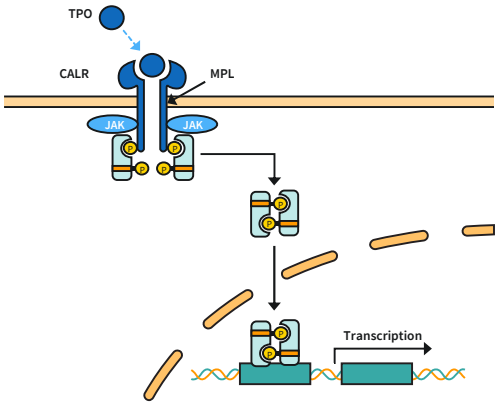
Pivotal JAK Inhibitor Studies

Ruxolitinib **JAK1, JAK2**	**COMFORT-1 COMFORT-2**
Fedratinib **JAK2, FLT3**	**JAKARTA JAKARTA-2 FREEDOM-1**
Pacritinib **JAK2, FLT3, and IRAK1**	**PERSIST-1 PERSIST-2**
Momelotinib **JAK1, JAK2, ACVR1**	**SIMPLIFY MOMENTUM**

National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

JAK Inhibitors: Summary

- Improve symptoms and spleen size
- Worsen cytopenias
- *Minimal effects* on survival
- **Unmet needs:**
  - ✓ Shrink spleen *without* worsening blood counts
  - ✓ Decrease transfusion requirements
  - ✓ Prevent leukemic transformation
  - ✓ Prolong survival



Garmezy B, et al. *Blood Rev.* 2021; National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

Emerging Agents

Momelotinib (JAKi)
FDA Approved
SIMPLIFY: phase 3
MOMENTUM: phase 3

Navitoclax (BCL-2i) + Ruxolitinib
Phase 3
REFINE: phase 2
Symptom, spleen, and marrow fibrosis improvements
TRANSFORM: ongoing phase 3

Luspatercept (inhibition of TGF-β) + Ruxolitinib
Phase 3
INDEPENDENCE: Phase 3 to improve anemia

Imetelstat (telomerase inhibitor)
Phase 2
Phase 2, relapsed after JAKi
N = 107; 4.7 mg or 9.4 mg/kg IV q3w
24-week SVR35 in 10.2% (9.4 mg/kg arm)
OS 29.9 months

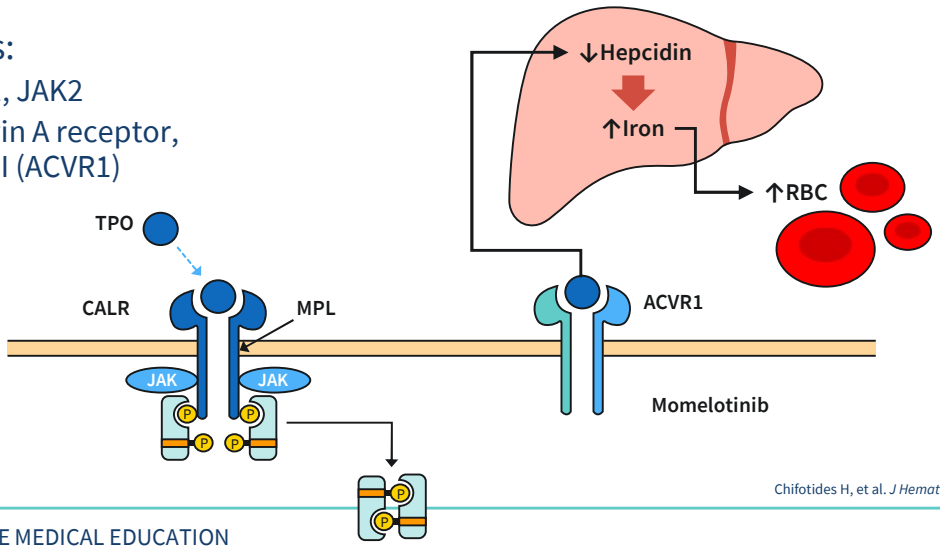
Pelabrisib (BETi) + Ruxolitinib
Phase 2
MANIFEST: Phase 2, JAKi naive
N = 84
24-week SVR35 of 68%
Marrow fibrosis improvement in 31%

INCA033989 (CALR inhibitor)
Pre-Clinical
Preclinical inhibition of mutant CALR with synergism in combination with ruxolitinib

Reis E, et al. *Blood*. 2022; Mascarenhas J, et al. *J Clin Oncol*. 2023; Chifotides H, et al. *J Hematol Oncol*. 2022; Mascarenhas J, et al. *J Clin Oncol*. 2021; INDEPENDENCE. ClinicalTrials.gov identifier: NCT04717414; Harrison C, et al. *J Clin Oncol*. 2022; Potluri J, et al. *Blood*. 2020.

Momelotinib Mechanism

- Inhibits:
  - JAK1, JAK2
  - Activin A receptor, type I (ACVR1)



Chifotides H, et al. *J Hematol Oncol*. 2022.

SIMPLIFY Trials (1 and 2)

- **SIMPLIFY 1**
  - vs. ruxolitinib in JAK-inhibitor naïve patients with high risk, intermediate 2 risk or symptomatic intermediate-1 risk disease
  - Primary endpoint: SR35 at 24 weeks
    - Non-inferior: 26.5% vs 29%
  - Secondary endpoints: ≥50% reduction in TSS and transfusion outcomes
    - Not non-inferior: 28.4% vs 42.2%
    - Transfusion rate, independence, and dependence were improved with momelotinib
- **SIMPLIFY 2**
  - vs. best available therapy in patients previously treated with ruxolitinib
  - Primary endpoint: SR35 at 24 weeks
    - Not superior: 7% vs 6%

Mesa RA, et al. *J Clin Oncol.* 2017; Harrison CN, et al. *Lancet Haematol.* 2018.

MOMENTUM Trial

- Primary end point: 50% reduction in symptoms at week 24

Phase 3, randomized, **previously received JAK inhibitor**
- Intermediate- to high-risk MF
- Included patients with cytopenias

(N = 195)

Randomized **2:1**

Momelotinib
200 mg orally once daily

Danazol
300 mg orally twice daily

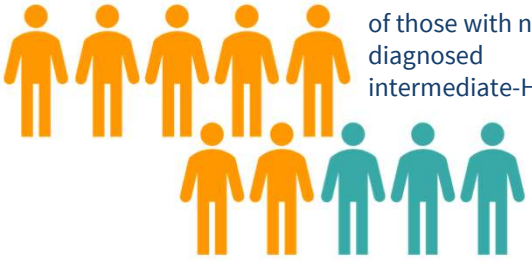
Takeaways
- 25% vs 9% had a 50% reduction in symptoms
- 30% vs 20% achieved transfusion independence
- 22% vs 3% had a SVR35
- AEs: anemia, thrombocytopenia, GI toxicity, infections
- Overall: improvements in symptoms, spleen size, and transfusion independence

Verstovesk S, et al. *Lancet.* 2023.

FDA Approval of Momelotinib

- Approved on September 15, 2023
- Intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF in adults with anemia
- *Both* treatment naïve and pretreated patients

7 out of **10**



of those with newly diagnosed intermediate-HR MF

are **anemic** at diagnosis.

FDA Prescribing Information.

Treatment-Related Supportive Care

- Infection Prophylaxis
- Growth Factors
- Anemia
- CV risk Factors
- Dosing

National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

Infection Prophylaxis

JAK inhibitors increase the risk for bacterial, fungal, and viral opportunistic infections.
Patient-specific factors such as ANC and asplenia should be considered.

Bacterial	• Consider fluoroquinolone • Screen for latent TB, treat as indicated
Fungal	• Consider fluconazole, posaconazole, or voriconazole
***Pneumocystis jirovecii* pneumonia (PJP)**	• Consider trimethoprim/ sulfamethoxazole
Viral	• Consider valacyclovir or acyclovir, recombinant zoster vaccine • Screen for latent HBV, treat as indicated

Patients with asplenia should receive:

- Quadrivalent meningococcal conjugate (MenACWY) vaccine series
- Monovalent meningococcal serogroup B (MenB) vaccine series
- Pneumococcal vaccine
- Penicillin prophylaxis

National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections (Version 1.2023).

Associated Anemia

Rule out coexisting causes

Treat Coexisting Causes:
- Replete iron, folate, B_{12}
- Treat hemolysis
- Red blood cell transfusions
- Supportive care

Serum EPO <500 mU/mL
- Erythropoiesis-stimulating agents
- Clinical trial

Serum EPO ≥500 mU/mL
- Clinical trial
- **Momelotinib**
- Consider:
  - Danazol
  - Lenalidomide/ thalidomide
  - Luspatercept (category 3)

National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

JAK Inhibitors: Class Toxicities

Secondary Malignancies

- Monitor for development of secondary malignancies, particularly in patients who are current or past smokers
- Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients with ruxolitinib

Thrombosis*

- Deep venous thrombosis, pulmonary embolism, and arterial thrombosis may occur
- JAK2 mutation confers an approximately 2-fold increased risk for arterial thrombotic events compared with non-JAK2 driver mutations in primary MF

Major Adverse Cardiac Events (MACE)*

- Assess for and decrease CV risk factors such as smoking, diet, exercise, hypertension, diabetes mellitus, lipid management

*Denotes toxicities seen only in JAK inhibitors used for inflammatory conditions.

FDA Prescribing Information; Leiva O, et al. *J Am Coll C Cardiol CardioOnc.* 2022; National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

Ruxolitinib Dosing

Baseline Platelet Count	Starting Dose
>200 × 10^9/L	**20 mg BID**
100 × 10^9/L to 200 × 10^9/L	**15 mg BID**
50 × 10^9/L to <100 × 10^9/L	**5 mg BID**

- Increase dose in 5-mg BID increments to maximum of to a maximum of 10 mg twice daily (if <100 x 10^9/L) or 25 mg BID (if ≥100 x 10^9/L)
- Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks

Alternate Dosing: REALISE Study, **if Hgb <10 g/dL...**

Initial dose: **10 mg BID** × 12 weeks → If PLT ≥100 and no response,* **↑ 15 mg BID** → If PLT ≥200 and no response, **↑ to 20 mg BID** → If PLT ≥200 and no response, **↑ to 25 mg BID**

*Response defined as ≥50% reduction in spleen length vs baseline.

Cervantes F, et al. *Leukemia*. 2021; National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

Ruxolitinib Discontinuation Syndrome

Symptoms **may return to pretreatment levels** over **approximately 1 week**

Some may experience **clinical findings suggestive of an inflammatory response**

- Fever, respiratory distress, hypotension, coagulation disorders, or multiorgan failure
- Prompt treatment with systemic glucocorticoids

Doses should **not be abruptly stopped** for reasons other than thrombocytopenia or neutropenia

Consider a **gradual taper** although there is no standardized approach

- Typically, over 1-2 weeks (5-mg dose reductions every 2-3 days)
- Consider use of prophylactic steroids in patients with higher disease burden

FDA Prescribing Information; Ibrahim U, et al. *Biol Blood Marrow Transplant*. 2020;
National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

Fedratinib Dosing and AEs

- Recommended dose: 400 mg once daily with or without food in patients with a platelet count ≥50 x 10^9/L
  - Decrease starting dose to 200 mg once daily when co-administered with a strong CYP3A4 inhibitor or in cases of severe renal impairment (CrCL 15-29 mL/min)

Obtain at baseline and periodically during treatment:

- Thiamine level
- Complete blood count
- Creatinine and BUN
- Hepatic panel
- Amylase/lipase

High Emetic Potential	• 62% nausea and 39% vomiting • Provide antiemetic prior to starting 5-HT3 receptor antagonists
Diarrhea	• 66% • Promptly manage diarrhea with antidiarrheal medications at the first onset of symptoms
Wernicke's Encephalopathy*	• Assess thiamine levels in ALL patients prior to starting • Replete thiamine prior to treatment initiation • If encephalopathy is suspected, immediately discontinue fedratinib and initiate parenteral thiamine

*FDA Black Box Warning

FDA Prescribing Information.

Fedratinib Encephalopathy

Serious and fatal encephalopathy, including Wernicke encephalopathy, has occurred in **fedratinib-treated patients**

Serious cases were reported in **1.3% of patients in clinical trials** and **0.16% of cases were fatal**

Wernicke encephalopathy is a **neurologic emergency** resulting from **thiamine (vitamin B1) deficiency**

Signs and symptoms of Wernicke encephalopathy may include **ataxia, mental status changes, and ophthalmoplegia** (eg, nystagmus, diplopia)

Any **change in mental status**, confusion, or memory impairment should **raise concern for potential encephalopathy**

If encephalopathy is suspected, **immediately discontinue fedratinib and initiate parenteral thiamine**

FDA Prescribing Information.

Pacritinib Dosing

- **Recommended dose:** 200 mg twice daily with or without food in patients with a platelet count <50 x 10^9/L
- **Contraindicated with strong CYP3A4 inhibitors or inducers**

Obtain at baseline and clinically indicated during treatment:

- Complete blood count
- Coagulation testing
- Hepatic panel
- Electrocardiogram

FDA Prescribing Information.

Pacritinib AEs

Discontinue pacritinib in patients unable to tolerate 100 mg daily

QTc Prolongation

- Obtain baseline EKG
- Avoid in patients with active bleeding or a baseline QTc of >480 msec
- QTc prolongation >500 msec or >60 msec from baseline→ HOLD therapy
- If QTc prolongation resolves to ≤480 msec or baseline within 1 week, resume

Thrombocytopenia

- Monitor platelet count prior to treatment and as clinically indicated
- For clinically significant worsening of thrombocytopenia that lasts >7 days
- Hold pacritinib, restart at 50% of the last dose once resolved

Nausea

- Consider providing antiemetic to have on hand

Diarrhea

- Initiate antidiarrheal medications and ensure adequate hydration
- Grade 3 or 4: Hold pacritinib until diarrhea resolves to grade ≤1 or baseline, then resume at the last dose
- If diarrhea recurs, hold pacritinib until resolves to grade ≤1 or baseline, then resume at 50% of last dose

FDA Prescribing Information.

Momelotinib Dosing and Safety

Dosing

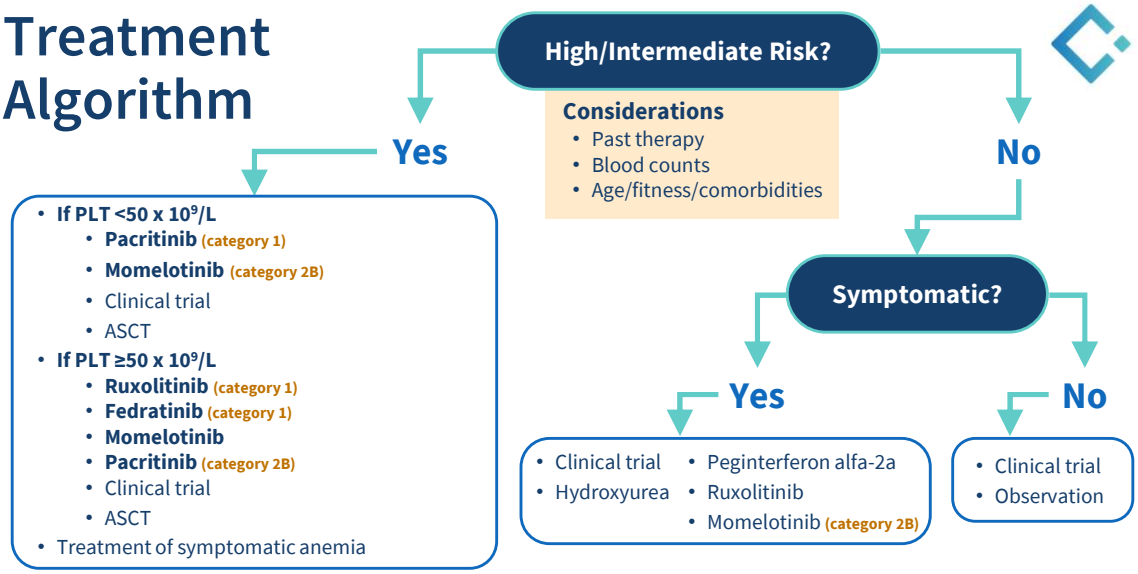
- 200 mg once daily with or without food
  - Decrease to 150 mg in severe hepatic impairment
  - Caution with OATP inhibitors and BCRP substrates

Adverse Events

- Thrombocytopenia
  - <50 x 10^9/L in 20%
- Neutropenia
  - <0.5 x 10^9/L in 2%
- Hepatotoxicity
  - All grades ALT/AST elevations: 23%/24%
  - Grade 3/4 ALT/AST elevations: 1%/0.5%

FDA Prescribing Information.

Treatment Algorithm



All recommendations are category 2A unless otherwise indicated.
ASCT, allogeneic stem cell transplant; PLT, platelets.

National Comprehensive Cancer Network. Myeloproliferative Neoplasms (Version 3.2023).

Patient Cases

Advanced Practitioner Insights and Real-World Strategies for Optimizing Therapeutic Management of Myelofibrosis

All Faculty; Moderated by: Ashley Leak Bryant, PhD, RN, OCN, FAAN

Cornerstone Medical Education
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Case #1: Frontline Treatment

DS is a 68-year-old woman with primary MF diagnosed in 2021 who hasn't required treatment but presents to clinic today with a total symptom score of 35. The clinic team would like to start her on first-line treatment with a JAK inhibitor.

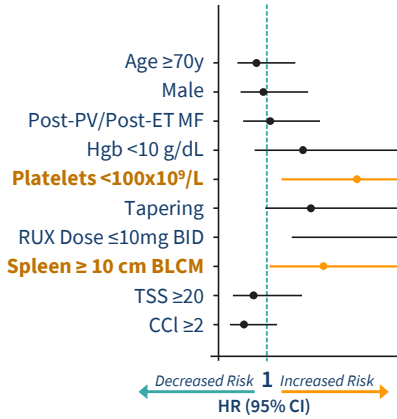
- PMH: GERD, HTN
- Current medications: omeprazole, lisinopril
- **Pertinent labs:**
  - Platelets: 105,000/mm^3
  - Hgb: 9.5 g/dL
  - CrCl: 73 mL/min

Therapy Considerations

- **Fedratinib:** prophylactic therapy for GI toxicity and thiamine supplementation
- **Ruxolitinib:** dose ramp-up?, counseling on withdrawal syndrome
- How often would you monitor this patient? What lab values would you monitor? Who should perform this monitoring?
- Where does **momelotinib** fit into therapy?

Switching JAK Inhibitors

- Should a taper be used for ruxolitinib?
- Should prophylactic steroids be used?
- Should there be overlap with pacritinib?



	UNIVARIATE HR (95% CI)	*P*	MULTIVARIABLE HR (95% CI)	*P*
Age ≥70y	0.79 (0.41-1.56)	0.51		
Male	0.92 (0.46-1.83)	0.83		
Post-PV/Post-ET MF	1.05 (0.53-2.07)	0.89		
Hgb <10 g/dL	1.73 (0.75-3.99)	0.19		
Platelets <100x10⁹/L	**2.83 (1.28-6.23)**	**0.01**	**2.98 (1.29-6.90)**	**0.01**
Tapering	1.89 (0.96-3.71)	0.06		
RUX Dose ≤10mg BID	4.95 (1.51-16.20)	0.01		
Spleen ≥ 10 cm BLCM	**2.15 (1.06-4.37)**	**0.03**	**2.03 (1.01-4.17)**	**0.04**
TSS ≥20	0.73 (0.31-1.69)	0.46		
CCl ≥2	0.53 (0.24-1.19)	0.13		

Palandri F, et al. *Blood Cancer J.* 2021.

Case #2

- MG is 59 y/o male with fatty liver disease who was referred to hematology/oncology due to thrombocytopenia
- Initial work-up
  - **Labs**
  - Abdominal Ultrasound: hepatic steatosis and mild splenomegaly
  - Symptom Assessment: Fatigue, inactivity, bone pain and easy bruising
  - ECOG Performance status: 1

Laboratory Parameter	Value
White blood cells (WBCs)	4.1 x 10^9/L
Hemoglobin (Hgb)	8.9 g/dL
Mean corpuscular volume	102.4 fl
Platelets	35 x 10^9/L
Peripheral blasts	2%
Total serum iron	116 ug/dL
Lactate dehydrogenase	251 IU/L
Erythropoietin	340 mU/mL

Case #2

- **Bone marrow biopsy:**
  - Markedly hypercellular bone marrow (80-90%) with patchy collagen fibrosis and grade 3/3 reticulin fibrosis and megakaryocyte atypia, no increase in blasts.
  - *JAK2*+, no other molecular mutations
  - Cytogenetics diploid

- **DIPSS+ Score: 3, Intermediate-2**
  - Age <65
  - **Constitutional symptoms**
  - WBC >25
  - **Hgb <10**
  - **Blasts >1%**
  - Diploid karyotype
  - Transfusion dependency
  - **Platelets <100,000**

Diagnosis: Primary MF, JAK2+

Case #2: Therapeutic/Shared Decision-Making

- **Discuss main clinical problems:** anemia, thrombocytopenia, splenomegaly and symptoms
- Given severe thrombocytopenia, intermediate-2 risk disease, young age and good performance status, the patient was referred for transplant consultation
- While awaiting transplant, **pacritinib 200 mg BID was initiated** with the goals of therapy being improvement in symptoms, spleen size reduction, and improvement in anemia while maintaining current platelet count

Case #2: Adverse Events

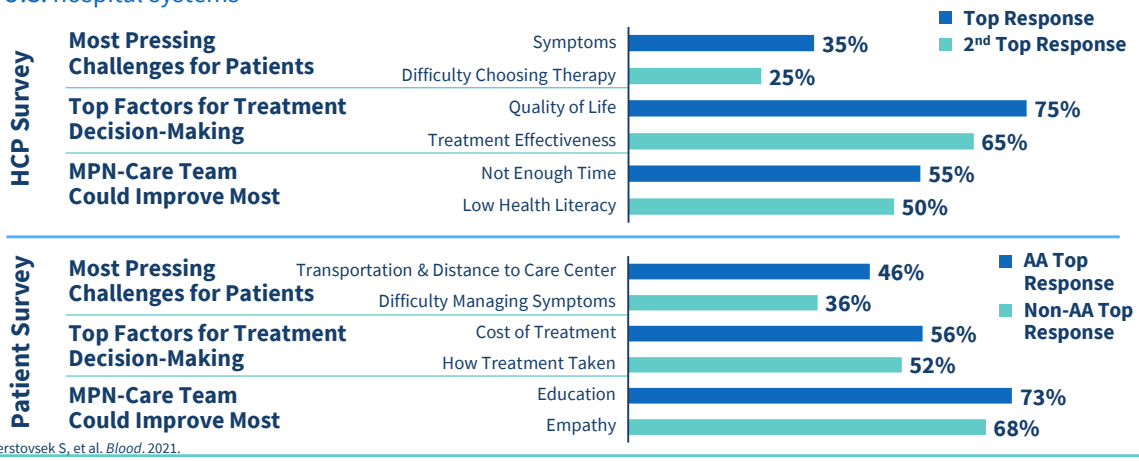
- Patient called triage RN with **a new "rash" and swelling in the left lower extremity**, after discussion with on call APP, patient was seen over telehealth and then directed to local ER due to concern for deep vein thrombosis (DVT)
- Doppler ultrasound was **positive for a DVT**
- Anticoagulation with 50% dose low-molecular weight heparin was initiated

Case #2: Ongoing Monitoring

- Complete blood count (CBC) weekly with special attention to hemoglobin and transfusion needs and platelet count given fluctuation between 30 – 50 $x10^9$/L and the ongoing need for anticoagulation
- Bi-monthly APP visit for symptom assessment, AE monitoring, physical exam
- Every-other-month MD visit

Barriers to Care

Quality improvement (QI) initiative assessing barriers to patient-centered MPN care in 2 large U.S. hospital systems

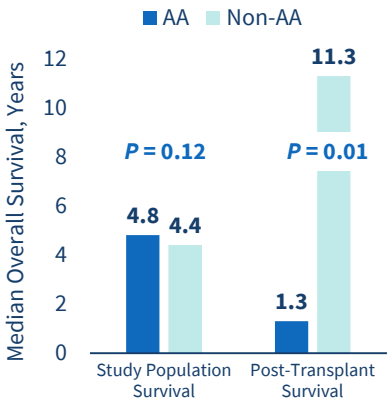


Verstovsek S, et al. *Blood*. 2021.

Sources of Outcome Disparity

Surveillance, Epidemiology, and End Results (SEER) Comparative Analysis of Phenotype and Survival

- Medicare database analysis of 3364 patients with myeloproliferative neoplasms (MPNs)
  - Included 10% non-White patients with primary MF
- AA vs Non-AA
  - Overall survival: not inferior
  - At presentation, AA patients: younger, predominantly female, and more likely DIPSS-plus lower risk category
  - Similar driver and other mutation distributions
  - **Posttransplant outcomes: inferior in the AA cohort**



Gangat N, et al. *Blood Adv*. 2023.

Sources of Outcome Disparity

Surveillance, Epidemiology, and End Results (SEER) Comparative Analysis of Phenotype and Survival

- Insights from SEER database between 2000 and 2020[2]
  - Overall patient population: White (82.0%), Black (8.4%), and Asian or from the Pacific Islands (7.7%)
  - **Worse survival was correlated with higher age, male sex, and black race**
  - Similar distribution of genetic mutations in patients regardless of race
  - No observed differences in rates of treatment modalities between Black and non-Black patients treated at Montefiore

Variable	Overall Survival HR (95% CI)	*P*-value
Age	**1.042** (1.038-1.046)	**<0.001**
Male Sex	**1.399** (1.277-1.533)	**<0.001**
Black Race	**1.202** (1.016-1.422)	**<0.032**

Protective Factors
Being married (all-cause mortality): ***P*=0.001**
Diagnosed before 2011 (cause-specific and all-cause mortality): ***P*=0.001**

Hammami MB, et al. Abstract MPN-470. Presented at: 2023 Society of Hematologic Oncology (SOHO).

Conclusions

- Myelofibrosis is a rare hematological malignancy with heterogeneity in patient presentation and variable disease course
- Symptom burden can be severe, affect QOL, and is a negative prognostic feature
- JAK inhibitor therapies have greatly improved symptoms and quality of life for patients with MF
- Novel therapies and recent MF regulatory approvals allow for efficacious and safe treatment in patients with thrombocytopenia and other comorbidities
- Advanced practice providers have an integral role in complex supportive care management, including close monitoring of drug- and disease-related effects in patients with MF

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