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ALL HANDS ON DECK

Utilizing JAK Inhibitors in Myelofibrosis Care

Evidence, Timing, and Strategic Approaches

Presented by Creative Educational Concepts LLC
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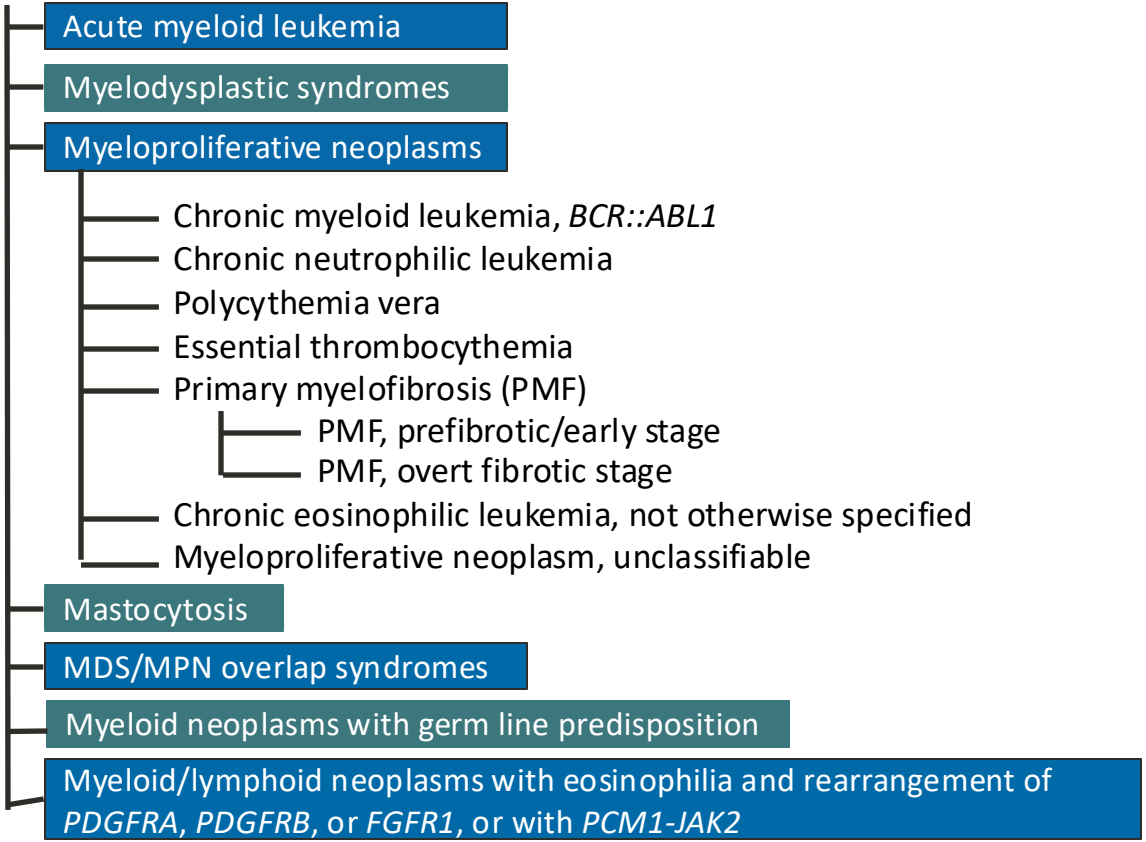
LO 1

Assess patients for MF therapy utilizing guideline-recommended risk-stratification algorithms as well as molecular indicators of disease prognosis, clinical features, and symptom burden.

2022 ICC Classification

Myeloid Neoplasms



ICC = International Consensus Classification; JAK = Janus kinase; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm.

Arber D, et al. *Blood.* 2022;140(11):1200-1228.

2022 ICC Criteria for Pre-PMF

- All 3 major criteria and ≥ 1 minor criterion

Major Criteria	Minor Criteria
1. Presence of megakaryocytic proliferation and atypia, bone marrow fibrosis grade < 2, increased cellularity	1. Anemia not attributed to a comorbid condition
	2. Leukocytosis ≥ 11 × 10^9/L
2. Not meeting WHO criteria for ET, PV, *BCR::ABL1*+ CML, MDS, or other myeloid neoplasms	3. Palpable splenomegaly
	4. Elevated LDH
3. Presence of *JAK2*, *CALR*, or *MPL* mutation, or in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis	

CALR = calreticulin; CML = chronic myeloid leukemia; ET = essential thrombocytosis; LDH = lactate dehydrogenase; pre-PMF = prefibrotic PMF; PV = polycythemia vera; WHO = World Health Organization.

Arber D, et al. *Blood*. 2022;140(11):1200-1228.

2022 ICC Criteria for Overt MF

- All 3 major criteria and ≥ 1 minor criterion

Major Criteria	Minor Criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grade 2 or 3	1. Anemia not attributed to a comorbid condition
	2. Leukocytosis ≥ 11 × 10^9/L
2. Not meeting WHO criteria for ET, PV, *BCR::ABL1*+ CML, MDS, or other myeloid neoplasms	3. Palpable splenomegaly
	4. Elevated LDH
3. Presence of *JAK2*, *CALR*, or *MPL* mutation, or in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis	5. Leukoerythroblastosis

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MF = myelofibrosis.

Arber D, et al. *Blood*. 2022;140(11):1200-1228.

Primary Treatment Goals in MF

The practical treatment goals for patients with MF are unusually well-aligned with the endpoints commonly used in clinical trials for new MF therapies

Treatment Goal		Clinical Trial Endpoint
Alleviate systemic/ constitutional symptoms		Reduction in total symptom score (TSS)
Reduce organomegaly (e.g., splenomegaly)		Spleen volume reduction (SVR)
Mitigate progressive cytopenias (anemia and thrombocytopenia)		Increase in Hgb and PLTs/ reduction in transfusion dependence

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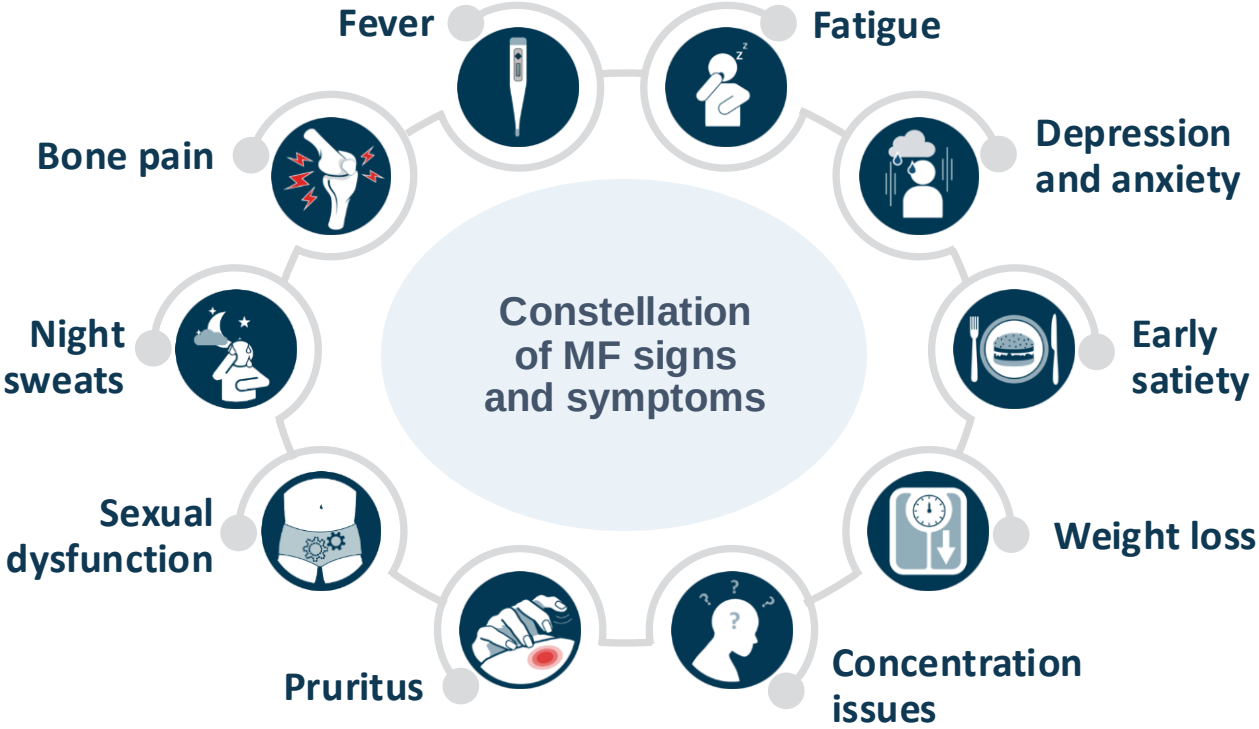
Hgb = hemoglobin; PLTs = platelets.

Yoon J, et al. *Expert Rev Hematol*. 2021;14:607-619. Verstovsek S, et al. *Leukemia*. 2016;30:1413-1415. Cervantes F, et al. *Expert Rev Hematol*. 2016;9:489-496.

Symptom Burden in MF: Wide Range of Constitutional Symptoms



Yoon J, et al. *Expert Rev Hematol*. 2021;14:607-619. Verstovsek S, et al. *Leukemia*. 2016;30:1413-1415. Cervantes F, et al. *Expert Rev Hematol*. 2016;9:489-496.

Myelofibrosis Takes a Toll Physically and Emotionally

"My husband does most of the cooking and a lot of the housework because *some days I just can't.*"

"It's causing me *problems with my driving and I have to get to my appointments and I don't always have a way to get there, and I'm having problems trying to find somebody that will drive me to get to them. It's affecting my eyesight.*"

"I get sick very easy and it takes me a long time to heal. *I get a lot of fatigue. I freeze all the time and I'm in excruciating pain.*"

"*It's just exhausting. Emotionally it's draining.* I got to the point where I was reading too much into it and it was overwhelming me. And I just had a discussion with my physician, and she just basically told me that *let's live day to day*. Let's think about the future, but don't dwell on the future. I know that this disease will progress and it will get worse, but I'm just looking day to day and enjoying my life as I can."

"*I would say that it has just slowed me down considerably.* Uh, I just don't move as fast. I don't seem to think as fast."

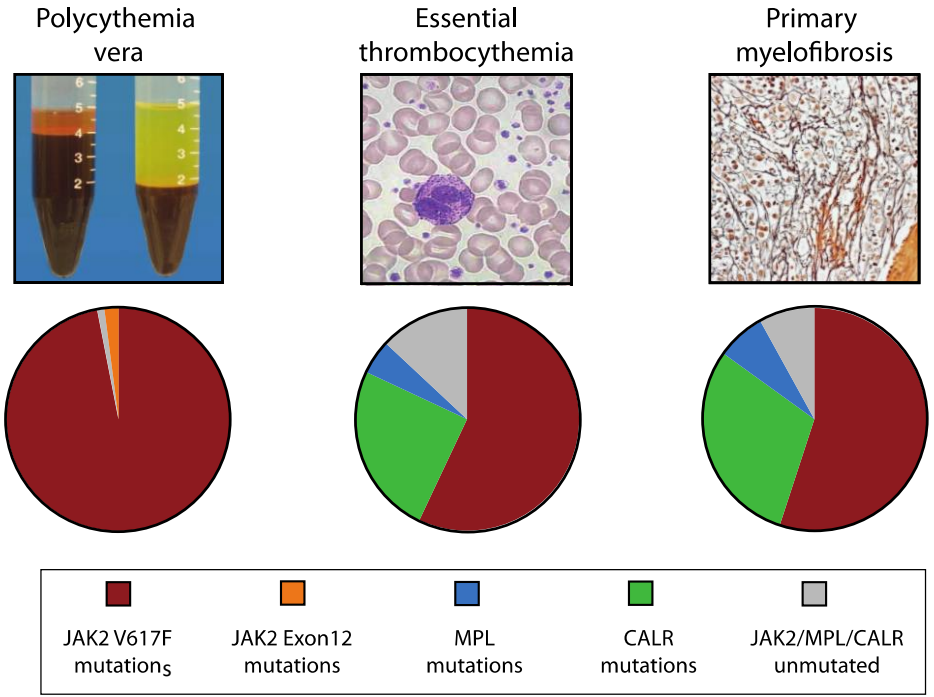
How has myelofibrosis changed your life?

WEGO patient survey, 2023.

Driver Mutations in MPN

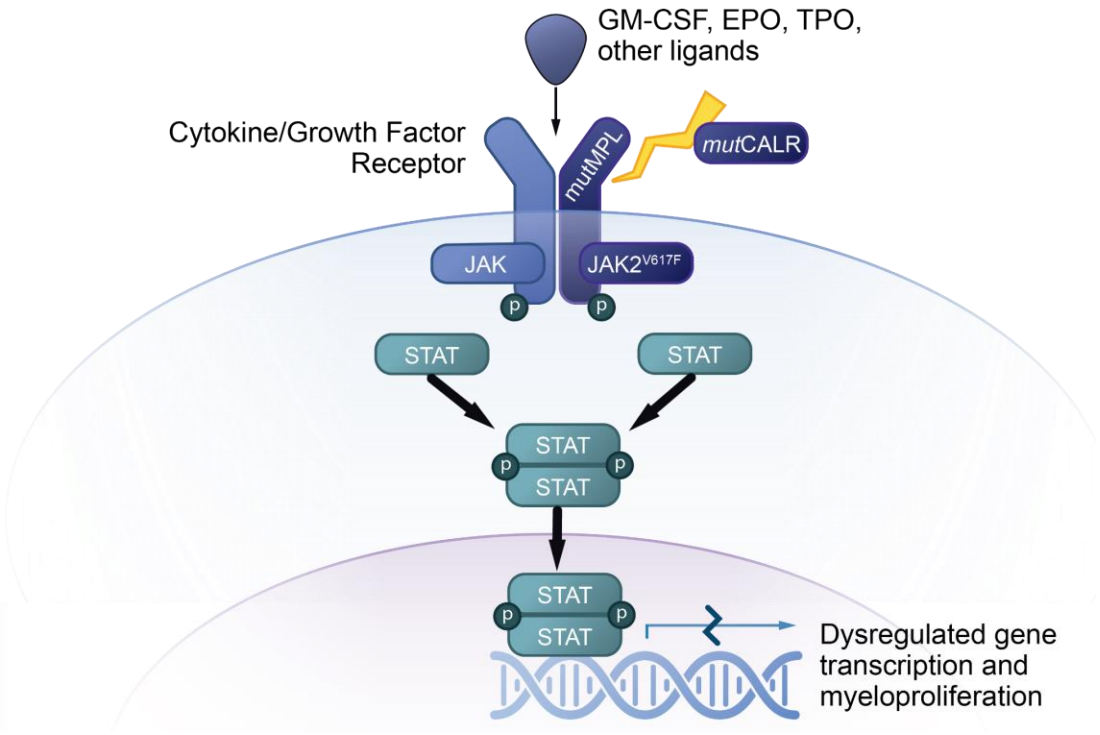
- JAK2
- CALR
- MPL

Allele burden = % of mutated JAK2 genes in sample



Cazzola M, Kralovics R. *Blood*. 2014;123(24):3714-3719. Nangalia J, Green TR. *Hematology Am Soc Hematol Educ Program*. 2014;2014:287-296.

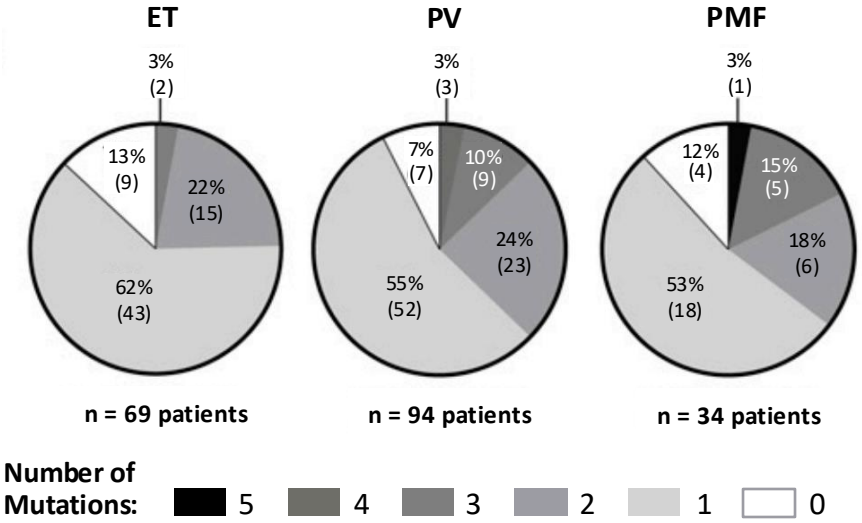
JAK/STAT Pathway



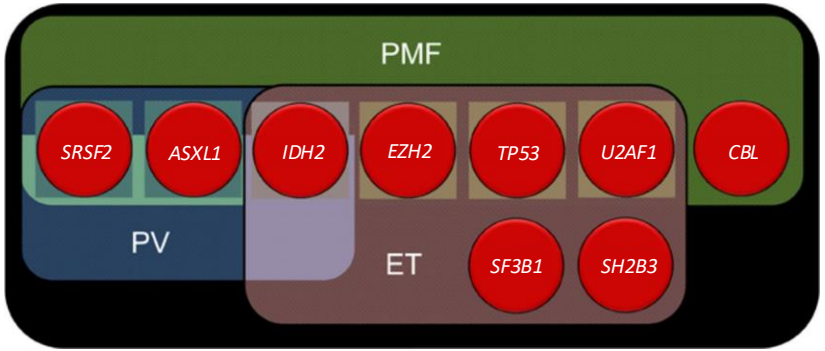
EPO = erythropoietin; GM-CSF = granulocyte-macrophage colony-stimulating factor; STAT = signal transducer and activator of transcription; TPO = thrombopoietin.

Adapted from Mascarenhas J. *Expert Rev Hematol*. 2022;15(8):671-684. Nangalia J, Green AR. *Hematology Am Soc Hematol Educ Program*.2017;1:470-479.

Mutational Landscape in MPNs

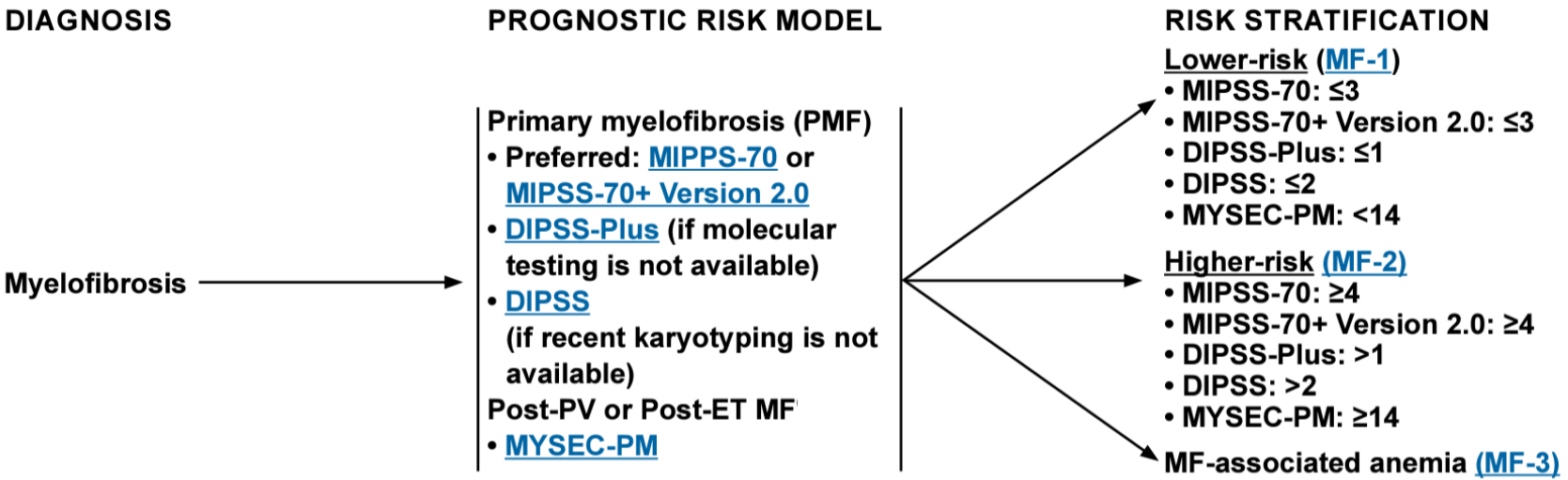


Prognostically important genes, other than *JAK2/CALR/MPL*, in ET, PV, and PMF



Lundberg P, et al. *Blood.* 2014;123:2220-2228. Tefferi A, et al. *Blood Advances.* 2016;1:21-30.

Prognostic Risk Models in MF



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NCCN Guidelines. Myeloproliferative Neoplasms (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

MIPSS70:

Mutation-Enhanced International Prognostic Score System for Patients of Transplantation Age with Primary Myelofibrosis

MIPSS70 Parameter	Points		
	0	1	2
Anemia	≥ 10 g/dL	< 10 g/dL	
Leukocytosis	< 25 x 10^9/L		≥ 25 10^9/L
Platelet Count	≥ 100 x 10^9/L		< 100 x 10^9/L
Circulating Blasts	< 2%	≥ 2%	
Bone Marrow Fibrosis Grade	< MF-2	≥ MF-2	
Constitutional Symptoms	Absent	Present	
Absence of *CALR* type 1/like mutation	No	Yes	
High-molecular risk (HMR) mutations*	No	Yes	
≥2 HMR mutations	No		Yes

Risk Group	Points	Median Survival (yr)	5-Year OS
Low	0-1	27.7 (95% CI, 22-34)	96%
Intermediate	2-4	7.1 (95% CI, 6.2-8.1)	67%
High	≥ 5	2.3 (95% CI, 1.9-2.7)	34%

Online calculator for MIPSS-70 can be found at http://www.mipss70score.it/

*ASXL1, EZH2, SRSF2, IDH1/2.
CI = confidence interval; OS = overall survival.
Guglielmelli P, et al. *J Clin Oncol*. 2018,36:310-318.

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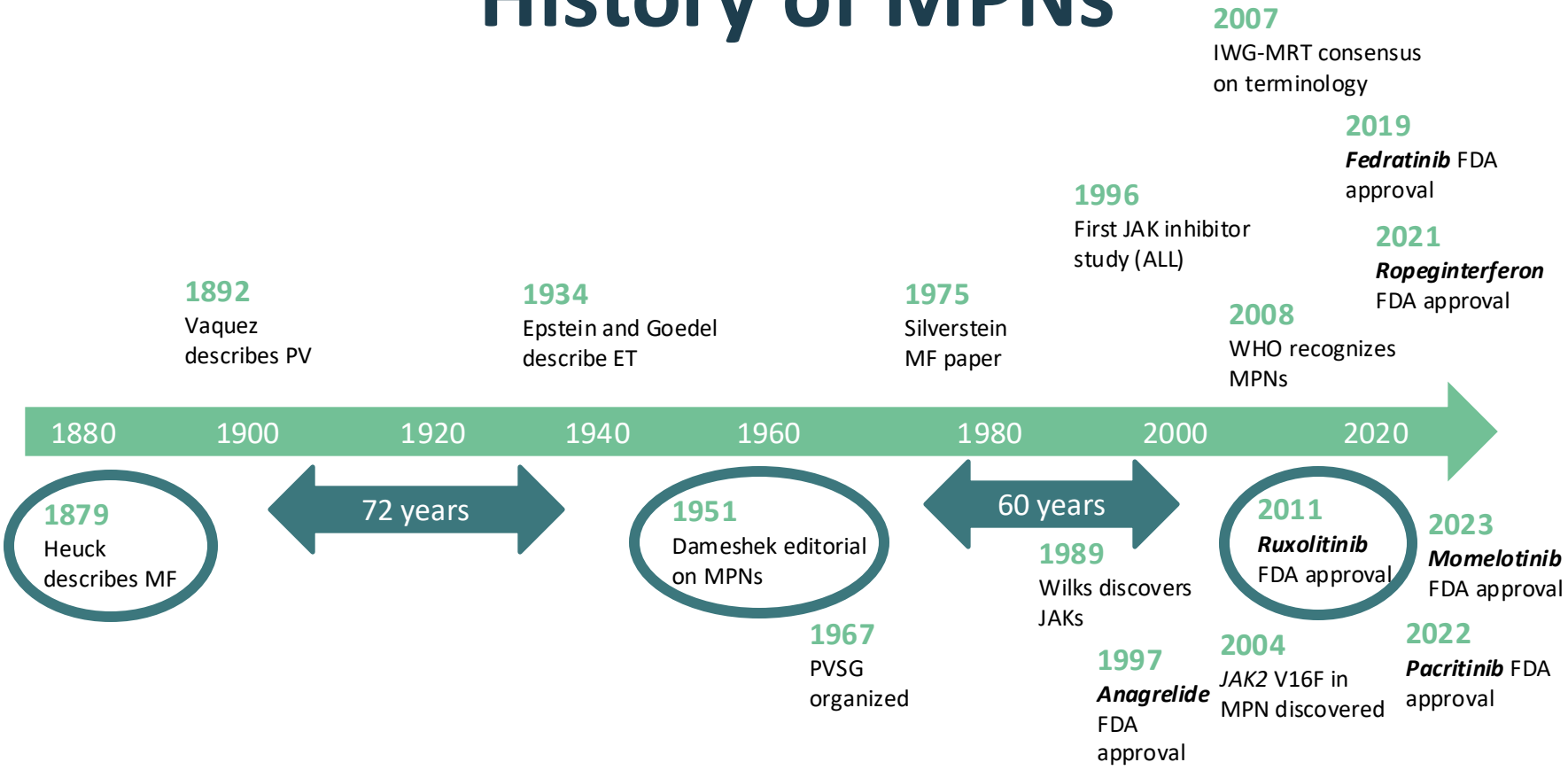
LO 2

Integrate current and emerging data on JAKis when choosing the most suitable MF treatment for each individual patient.

History of MPNs



FDA = U.S. Food and Drug Administration; IWG-MRT = International Working Group-Myeloproliferative Neoplasms Research and Treatment; PVSG = Polycythemia Vera Study Group.

Mahmud M, et al. *Int J Mol Sci.* 2023;24(24):17383. Wilks A. *Proc Natl Acad Sci U S A.* 1989;86(5):1603-1607. Meydan N, et al. *Nature.* 1996;379(6566):645-648.
Mughal TI, Barbui T. History of the myeloproliferative neoplasms. In: *Oxford specialist handbook: myeloproliferative neoplasms*. 1st ed. 2020: Online edition. https://academic.oup.com/book/29612/chapter-abstract/249509344?redirectedFrom=fulltext.

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JAK Inhibitors in MF: An Overview

JAK Inhibitor	Primary Targets	Major Clinical Trials in MF	Approval Date	Approved and Recommended Indications	Notable Side Effects
Ruxolitinib	JAK1, JAK2	COMFORT-I/II (phase III)	2011	**FDA:** frontline for intermediate- and high-risk MF	**Anemia, thrombocytopenia** Nonmelanoma skin cancers Infections Hyperlipidemia
Fedratinib	JAK2, FLT3	JAKARTA (phase III) JAKARTA-2 (phase II) FREEDOM (phase IIIb)	2019	**FDA:** frontline or second-line for intermediate-2 and high-risk MF	GI Low thiamine/WE **Cytopenias**
Pacritinib	JAK2, JAK3, TYK2, ACVR1, IRAK1, FLT3	PERSIST 1/2 (phase III) PAC203 (phase II)	2022	**FDA:** frontline for intermediate- and high-risk MF with PLT < 50 × 10^9 **NCCN:** Second-line with any PLT count	GI Adverse cardiac events QT interval ↑ Hemorrhage **Thrombocytopenia**
Momelotinib	JAK1, JAK2, TYK2, ACVR1	SIMPLIFY-1/2 (phase III) MOMENTUM (phase III)	2023	**FDA:** intermediate- or high-risk myelofibrosis, including primary or secondary myelofibrosis, and disease-related anemia **NCCN:** Category 2B	GI **Cytopenias**

GI = gastrointestinal; WE = Wernicke's encephalopathy.

Ruxolitinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202192s028lbl.pdf.
Fedratinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212327s006lbl.pdf.
Pacritinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208712s001lbl.pdf.
Momelotinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216873s000lbl.pdf.
NCCN Guidelines. Myeloproliferative Neoplasms (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

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Patient Case: JJ

- JJ is a 58-year-old male with newly diagnosed primary myelofibrosis. He presents with constitutional symptoms including fatigue, significant weight loss, and abdominal discomfort due to splenomegaly. He reports early satiety and a noticeable increase in abdominal girth.

- Bone marrow biopsy: megakaryocytic proliferation and atypia as well as grade 2 fibrosis
- Next-generation sequencing: *JAK2*^{V617f} mutation, *CALR* type-1 unmutated

- Labs: RBC 4.10 x 10^{12}/L, Hgb 12.0 g/dL, MCV 84 fL,
  WBC 22.0 x10^{9}/L, platelets 108 x 10^{9}/L, circulating blasts < 2%

MCV = mean corpuscular volume; RBC = red blood cells; WBC = white blood cells.

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- Labs: RBC 4.10 x 10^{12}/L, Hgb 12.0 g/dL, MCV 84 fL, WBC 22.0 x10^{9}/L, platelets 108 x 10^{9}/L, circulating blasts < 2%

- **Risk Assessment (MIPPS-70): 3 (Intermediate)**

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION-ENHANCED IPSS (MIPSS-70) FOR PATIENTS WITH PMF AGE ≤70 YEARS[3]

Prognostic Variable	Points
Hemoglobin <10 g/dL	1
Leukocytes >25 x 10^{9}/L	2
Platelets <100 x 10^{9}/L	2
Circulating blasts ≥2%	1
Bone marrow fibrosis grade ≥2	1
Constitutional symptoms	1
CALR type-1 unmutated genotype	1
High-molecular-risk (HMR) mutations[a]	1
≥2 HMR mutations	2

Risk Group	Points
Low	0–1
Intermediate	2–4
High	≥5

- Treatment: ruxolitinib

RUX Starting Dose is Based on Baseline Platelet Count	
Greater than 200 × 10^{9}/L	20 mg PO BID
100 × 10^{9}/L to 200 × 10^{9}/L	**15 mg PO BID**
50 × 10^{9}/L to less than 100 × 10^{9}/L	5 mg PO BID

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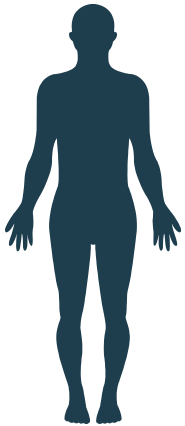
NCCN Guidelines. Myeloproliferative Neoplasms (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.
Ruxolitinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202192s028lbl.pdf.

Ruxolitinib in Myelofibrosis: COMFORT-I and COMFORT-II Trials

Phase III COMFORT-I Trial

Ruxolitinib vs placebo in patients with Int-2/high-risk MF and platelets ≥ 100 x 10^9/L



N = 309

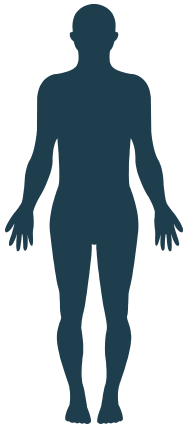
42%
Spleen volume reduction ≥ 35%

46%
Symptom burden reduction ≥ 50%

11%
Discontinuation due to AEs

Phase III COMFORT-II Trial

Ruxolitinib vs best available therapy in patients with Int-2/high-risk MF and platelets ≥ 100 x 10^9/L



N = 219

28%
Spleen volume reduction ≥ 35%

Not reported
Symptom burden reduction ≥ 50%

8%
Discontinuation due to AEs

Most common grade ≥ 3 AEs in the ruxolitinib arm:
- Anemia (45.2%)
- Thrombocytopenia (12.9%)
- Neutropenia (7.1%)
- Fatigue (5.2%)

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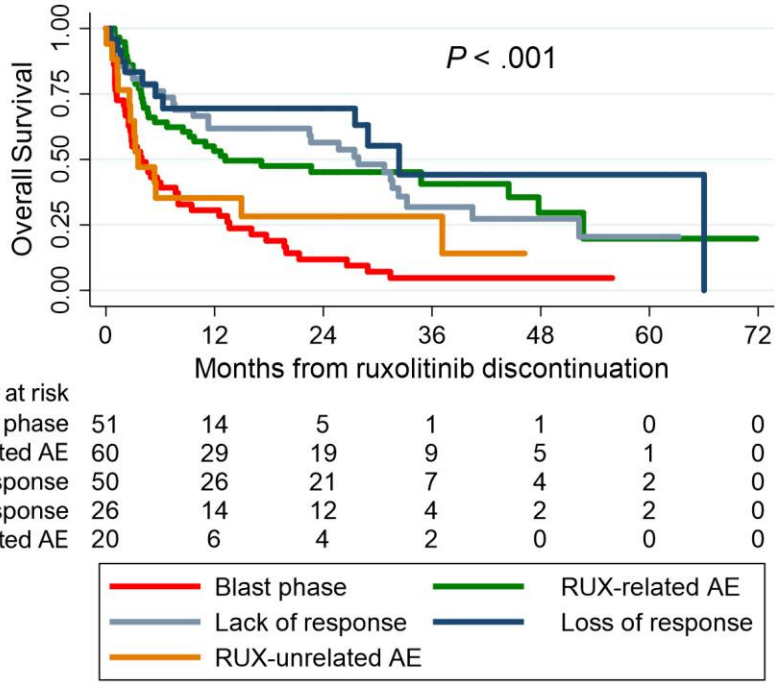
AEs = adverse events.

Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. Harrison C, et al. *N Engl J Med*. 2012;366:787-798.

Ruxolitinib in Myelofibrosis: Limitations in Long-term Efficacy

- High rates of ruxolitinib discontinuation in long-term analysis of COMFORT-I and COMFORT-II
- Survival following ruxolitinib discontinuation is poor



RUX = ruxolitinib.

Newberry KJ, et al. *Blood*. 2017;130(9):1125-1131. Palandri F, et al. *Cancer*. 2020;126(6):1243-1252. Verstovsek S, et al. *J Hematol Oncol*. 2017;10(1):55. Cervantes F, et al. *Blood*. 2013;122(25):4047-4053.

RR6 Model: Response to Ruxolitinib After 6 Months

- The RR6 model predicts survival in myelofibrosis based on clinical response after 6 months of ruxolitinib
- Risks for impaired survival among patients with MF treated with RUX:

RUX dose < 20 mg twice daily at *baseline*, *3 months*, and *6 months*

RBC transfusion need at *3 months and/or 6 months* **and** RBC transfusion at *all time points*

Spleen length reduction from baseline ≤ 30% at *3 months and 6 months*

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Maffioli M, et al. *Blood Adv*. 2022;6(6):1855-1864.

Fedratinib in Myelofibrosis: JAKARTA and JAKARTA-2 Trials

Phase III JAKARTA Trial

Fedratinib vs placebo in patients with Int-2/high-risk MF and platelets ≥ 50 x 10^9/L; N = 289

Fedratinib 400 mg*	Fedratinib 500 mg
36% Spleen volume reduction ≥ 35%	40% Spleen volume reduction ≥ 35%
36% Symptom burden reduction ≥ 50%	34% Symptom burden reduction ≥ 50%
14% Discontinuation due to AEs	25% Discontinuation due to AEs

Phase II JAKARTA-2 Trial

Fedratinib vs placebo in patients with Int-2/high-risk MF resistant or intolerant to ruxolitinib and platelets ≥ 50 x 10^9/L; N = 97(79*)

Primary Analysis	Reanalysis (2019)*
55% Spleen volume reduction ≥ 35%	30% Spleen volume reduction ≥ 35%
11% Discontinuation due to AEs	27% Symptom burden reduction ≥ 50%

Black box warning for Wernicke's encephalopathy (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

Most common grade ≥ 3 AEs:
- Anemia (25%)
- Thrombocytopenia (9%)
- Lymphopenia (21%)

**FDA-approved dose: 400 mg orally once daily with or without food for patients with a baseline platelet count of greater than or equal to 50 x 10^9/L.*

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643-651. Harrison CN, et al. *Lancet Haematol*. 2017;4(7):e317-e324. Harrison CN, et al. *J Clin Oncol*. 2019;37(15_suppl):7057. Fedratinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212327s006lbl.pdf.

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- Bone marrow biopsy: megakaryocytic proliferation and atypia as well as grade 2 fibrosis
- NGS: *JAK2*^{V617f} mutation, *CALR* type-1 unmutated

- Labs: RBC 4.10 x 10^{12}/L, Hgb 12.0 g/dL, MCV 84fL, WBC 22.0 x10^{9}/L, **↓plt 40 x 10^{9}/L**, Circulating blasts <2%

- Risk Assessment (MIPPS-70): 5 (High)

- Treatment: pacritinib

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION-ENHANCED IPSS (MIPSS-70) FOR PATIENTS WITH PMF AGE ≤70 YEARS[3]

Prognostic Variable	Points
Hemoglobin <10 g/dL	1
Leukocytes >25 x 10^{9}/L	2
Platelets <100 x 10^{9}/L	2
Circulating blasts ≥2%	1
Bone marrow fibrosis grade ≥2	1
Constitutional symptoms	1
CALR type-1 unmutated genotype	1
High-molecular-risk (HMR) mutations[a]	1
≥2 HMR mutations	2

Risk Group	Points
Low	0–1
Intermediate	2–4
High	≥5

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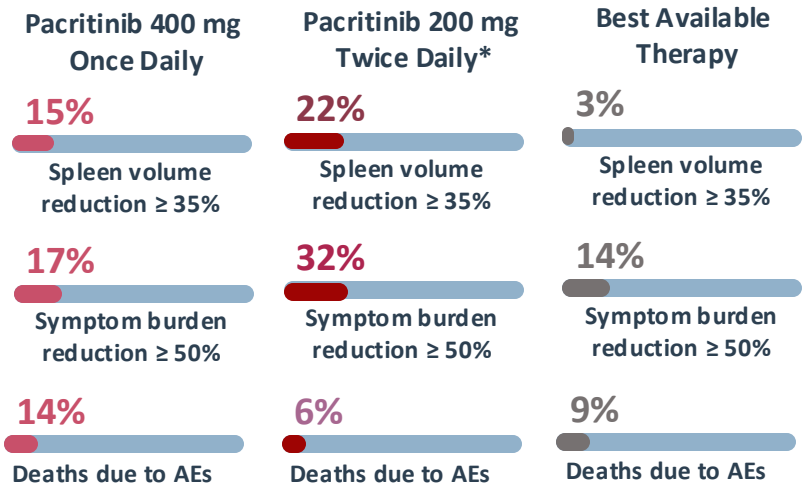
NCCN Guidelines. Myeloproliferative Neoplasms (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.
Pacritinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208712s001lbl.pdf.

Pacritinib in Myelofibrosis: PERSIST-2 Trial

Phase III PERSIST-2 Trial

Pacritinib vs best available therapy (including JAK inhibitors), N = 311 (N = 149 prior RUX)



- Enrollment criteria:
  - ≥ Intermediate-1 risk MF
  - Thrombocytopenia: platelets < 100 × 10^9/L
  - Previously treated or JAK inhibitor naïve

BAT Received in > 2 Patients, %	BAT (n = 98)
Ruxolitinib	45
Hydroxyurea	19
Watch-and-wait only	19
Prednisone/prednisolone	13
Danazol	5
Thalidomide	3

Most common grade ≥ 3 AEs:
- Anemia (14%)
- Thrombocytopenia (18%)
- Neutropenia (5%)

*FDA recommended dose: 200 mg orally twice daily.
BAT = best available therapy.
Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

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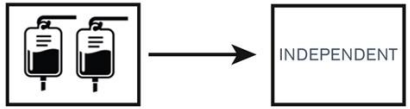
Pacritinib as an ACVR1 Inhibitor: PERSIST-2 Trial

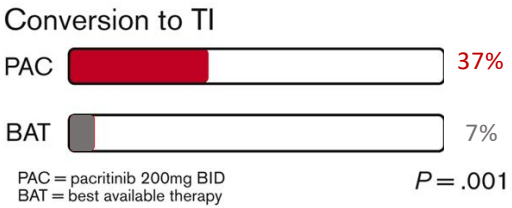
PAC is a potent inhibitor of ACVR1 (IC_{50} 16.7 nM)

- PAC potently inhibits the hepcidin regulator ACVR1 (IC_{50}16.7nM)
- PAC decreases *HAMP* (hepcidin) transcription *in vitro*
- Hepcidin reduction may result in improvement in inflammatory anemia associated with myelofibrosis

PAC improves RBC transfusion independence (37% vs. 7%, *P* = .001)

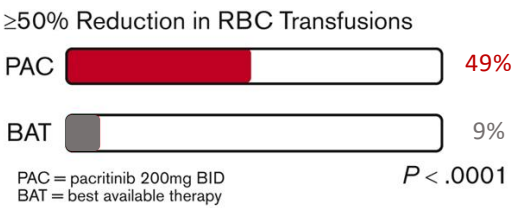


- A greater percentage of PAC vs. BAT-treated patients on PERSIST-2 achieved TI over any 12-week period through week 24 (among those requiring RBC transfusion at baseline)



PAC reduces RBC transfusion burden (49% vs. 9%, *P*< .0001)

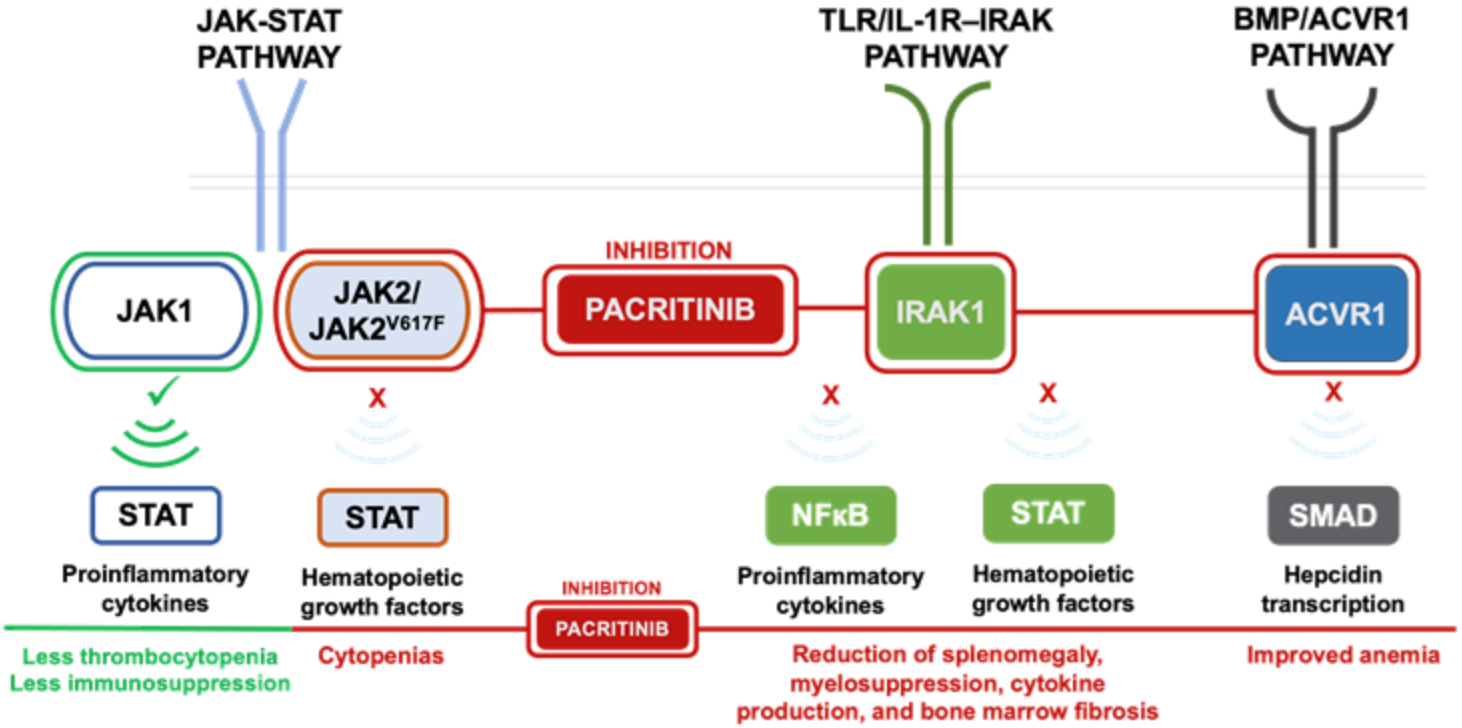
- A greater percentage of PAC vs. BAT-treated patients achieved ≥50% reduction in transfusions over any 12-week interval through week 24 in the same PERSIST-2 cohort.



PAC = pacritinib; TI = transfusion independence.

Oh S, et al. *Blood Adv.* 2023;7(19):5835-5842.

Pacritinib Inhibits JAK2, IRAK1, ACVR1, Sparing JAK1



Mascarenhas J, et al. *Haematologica*. 2017;102;327-335. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. Oh S, et al. *Blood Adv*. 2023;7(19):5835-5842.

Patient Case: JJ

- JJ is a 58-year-old male with newly diagnosed primary myelofibrosis. He presents with constitutional symptoms including fatigue, significant weight loss, and abdominal discomfort due to splenomegaly. He reports early satiety and a noticeable increase in abdominal girth.

- Bone marrow biopsy: megakaryocytic proliferation and atypia as well as grade 2 fibrosis
- Next-generation sequencing: *JAK2*^{V617f} mutation, *CALR* type-1 unmutated

- Labs: RBC 4.10 x 10^{12}/L, **↓Hgb 8.2 g/dL**, MCV 84 fL, WBC 22.0 x10^{9}/L, platelets 108 x 10^{9}/L, circulating blasts < 2%

- Risk Assessment (MIPPS-70): 4 (Intermediate)

- Treatment: momelotinib

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION-ENHANCED IPSS (MIPSS-70) FOR PATIENTS WITH PMF AGE ≤70 YEARS[3]

Prognostic Variable	Points
Hemoglobin <10 g/dL	1
Leukocytes >25 x 10^{9}/L	2
Platelets <100 x 10^{9}/L	2
Circulating blasts ≥2%	1
Bone marrow fibrosis grade ≥2	1
Constitutional symptoms	1
CALR type-1 unmutated genotype	1
High-molecular-risk (HMR) mutations[a]	1
≥2 HMR mutations	2

Risk Group	Points
Low	0–1
Intermediate	2–4
High	≥5

NCCN Guidelines. Myeloproliferative Neoplasms (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.
Momelotinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216873s000lbl.pdf.

Momelotinib in Myelofibrosis: SIMPLIFY-1 and SIMPLIFY-2 Trials

SIMPLIFY-1

Phase III trial, MMB vs RUX (N = 432)

ELIGIBILITY

- MF **untreated** with JAK inhibitors

RESULTS

- SVR35: **noninferior to RUX** (27% vs 29%, *p* = .011)
- TSS50: **inferior to RUX** (28% vs 42%, *p* = .98)
- TI: **67%** (vs 49% for RUX, *p* < .001)

SIMPLIFY-2

Phase III trial, MMB vs BAT (N = 156)

ELIGIBILITY

- MF **pretreated** with RUX

RESULTS

- SVR35: **not superior to BAT** (7% vs 6%, *p* = .89)
- TSS50: **superior to BAT** (26% vs 6%, *p* < .001)
- TI: **43%** (vs 21% for BAT, *p* = .0012)

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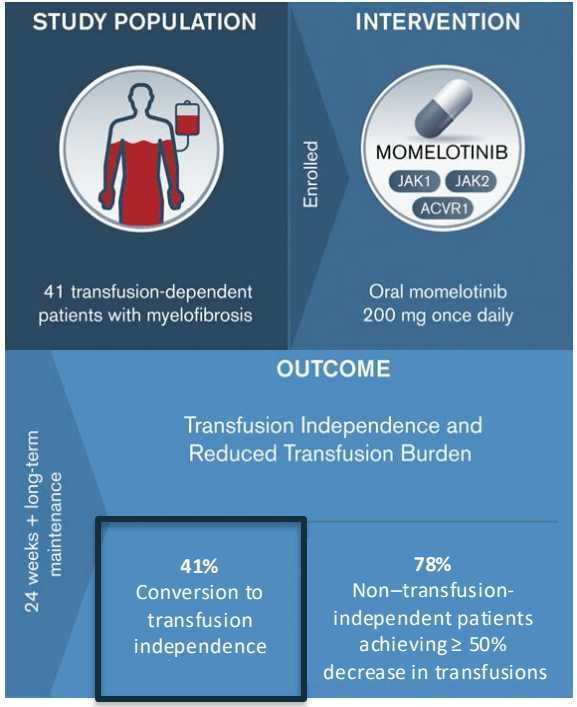
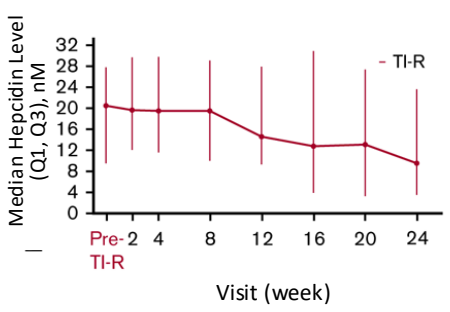
MMB = momelotinib.

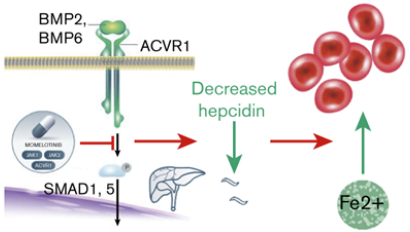
Mesa RA, et al. *J Clin Oncol*. 2017;35(34):3844-3850. Harrison CN, et al. *Lancet Haematol*. 2018;5(2):e73-e81.

Momelotinib in Myelofibrosis: Phase II Open-Label Study

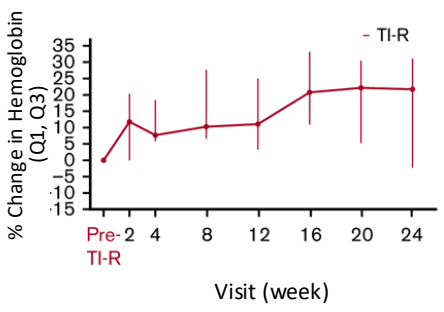




Median hepcidin over time for week 24 transfusion-independent responders



Decreased hepcidin transcription restores iron homeostasis and increases hemoglobin, leading to an array of anemia benefits



Change in hemoglobin over time for week 24 transfusion-independent responders

Momelotinib decreases hepcidin production, increasing serum iron and erythropoiesis

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TI-R = transfusion-independent response.

Oh ST, et al. *Blood Adv*. 2020;4(18):4282-4291.

Momelotinib in Anemia Management: MOMENTUM Trial

Phase III MENTUM Trial

JAK1/2 and ACVR Inhibitor

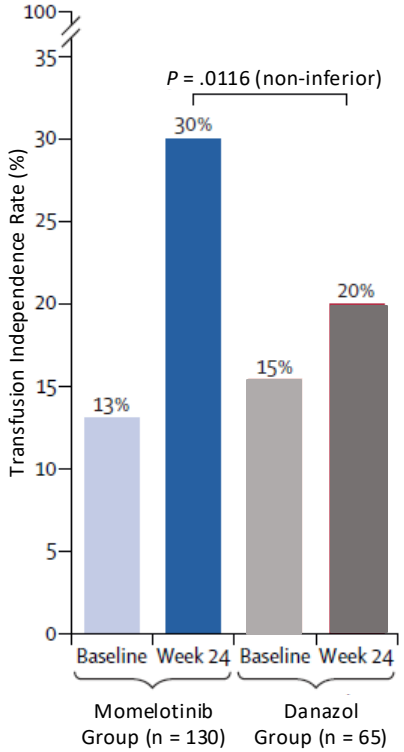
Patient Population

- ✓ *Int-1, Int-2, or high-risk MF*
- ✓ *Prior JAK inhibitor treatment for ≥ 90 days*
- ✓ *RBC transfusions ≥4 units in 8 weeks*

Most Common AEs Grade ≥ 3

Thrombocytopenia (22%)
Anemia (8%)
Infections (15%)

	Momelotinib ***N = 94***	***Danazol*** ***N = 38***
TSS response rate at week 24	25%	9%
Transfusion independence at week 24	31%	20%
SRR ≥ 35% at week 24	23%	3%



SRR = splenic response rate; TSS = Total Symptom Score.

Verstovsek S, et al. *Lancet*. 2023;401:269-280.

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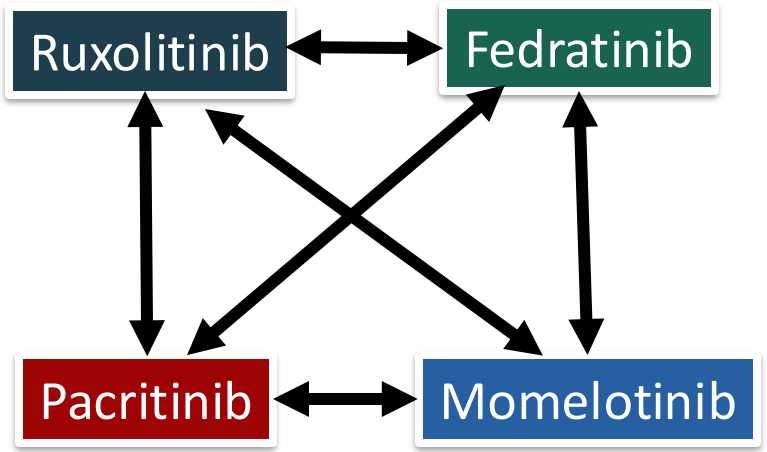
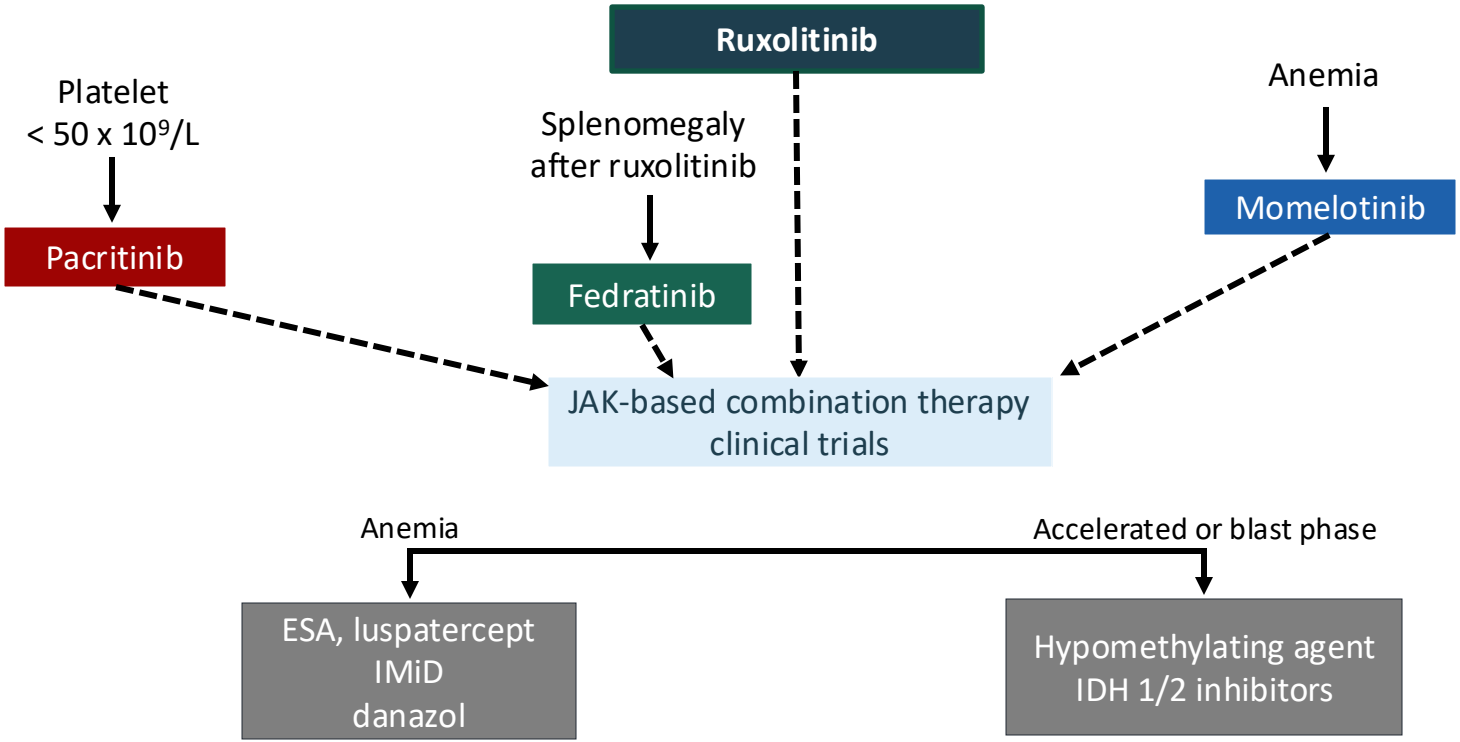
Direct Comparisons?

- Ruxolitinib vs fedratinib
  - *None*
- Ruxolitinib vs pacritinib
  - **Subset of PERSIST-2**
- Ruxolitinib vs momelotinib
  - **SIMPLIFY-1**
- Fedratinib vs pacritinib
  - *None*
- Fedratinib vs momelotinib
  - *None*
- Pacritinib vs momelotinib
  - *None*



Positioning of JAK Inhibitors in Myelofibrosis

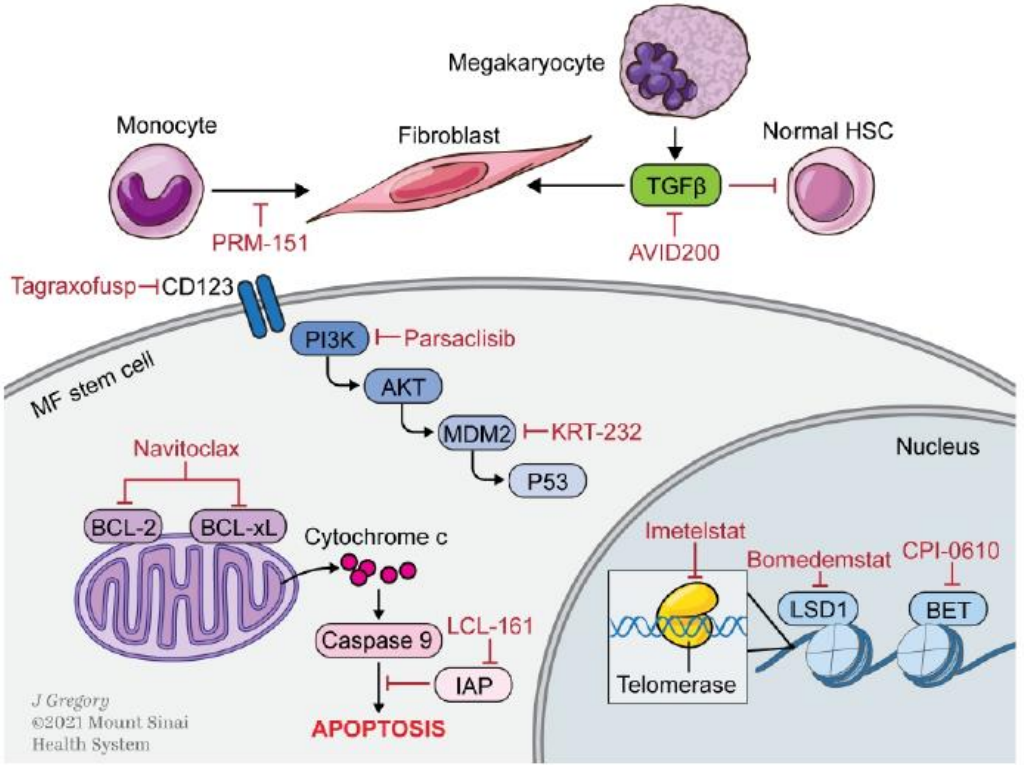


ESA = erythropoietin stimulating agents; IDH = isocitrate dehydrogenase; IMiD = immunomodulatory drug.

Slide Courtesy of Aaron Gerds, MD.

New Treatment Targets in MF

- Novel targets in clinical development include:
  - Apoptosis
  - Epigenetic modulation
  - Telomerase activity
  - Bone marrow microenvironment
  - Intracellular signaling pathways



Tremblay D, Hoffman R. Expert *Opin Emerg Drugs*. 2021;26(4):351-362.
Tremblay D, Mascarenhas J. *Cells*. 2021;10(5):1034. How J, et al. *Blood*. 2023;141(16):1922-1933.

New Therapies in Phase III Trials for MF

Agent/Target	Trial Name	Design	Patient Risk Levels	Setting
Imetelstat Telomerase	IMpactMF	Imetelstat vs BET	Intermediate-2 or high	Relapsed/refractory to JAK inhibitor
Luspatercept ACVR1, TGF-beta	INDEPENDENCE	Luspatercept vs placebo	---	Transfusion dependent on concomitant JAK2 inhibitor therapy
Navitoclax BCL-2/BCL-xl	TRANSFORM-1	Navitoclax + ruxolitinib vs ruxolitinib alone	Intermediate-2 or high	JAK inhibitor naive
Navitoclax BCL-2/BCL-xl	TRANSFORM-2	Navitoclax + ruxolitinib vs BAT	Intermediate-2 or high	Relapsed/refractory to ruxolitinib
Pelabresib BET	MANIFEST-2	Pelabresib + ruxolitinib vs placebo + ruxolitinib	Intermediate-1, -2 or high	JAK inhibitor naive
Selinexor XPO1	---	Selinexor + ruxolitinib vs placebo + ruxolitinib	Intermediate-1, -2 or high	JAK inhibitor naive

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Mascarenhas J, et al. *Hemasphere.* 2023;7(Suppl):e99899f4. Kiladjian JJ, et al. *Clin Lymphoma Myeloma and Leuk.* 2023; 23: S390. Pemmaraju N, et al. *Blood.* 2023; 142 (Supplement 1): 620. Dilley K, et al. *Blood.* 2020; 136 (Supplement 1): 8. Rampal RK, et al. *Blood.* 2023; 142 (Supplement 1): 628. Mascarenhas J, et al. *J Clin Oncol.* 2024; 42:TPS6594.

LO 3

Develop individualized strategies to reduce treatment toxicity and enhance treatment adherence for patients with MF.

Assessing Symptoms in MF: MPN-SAF TSS (MPN-10)

- Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)
  - 10-symptom assessment scale for MPNs
  - Each symptom is rated on a 0 to 10 scale from absent (0) to worst imaginable (10)
  - Total possible score: 100

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)

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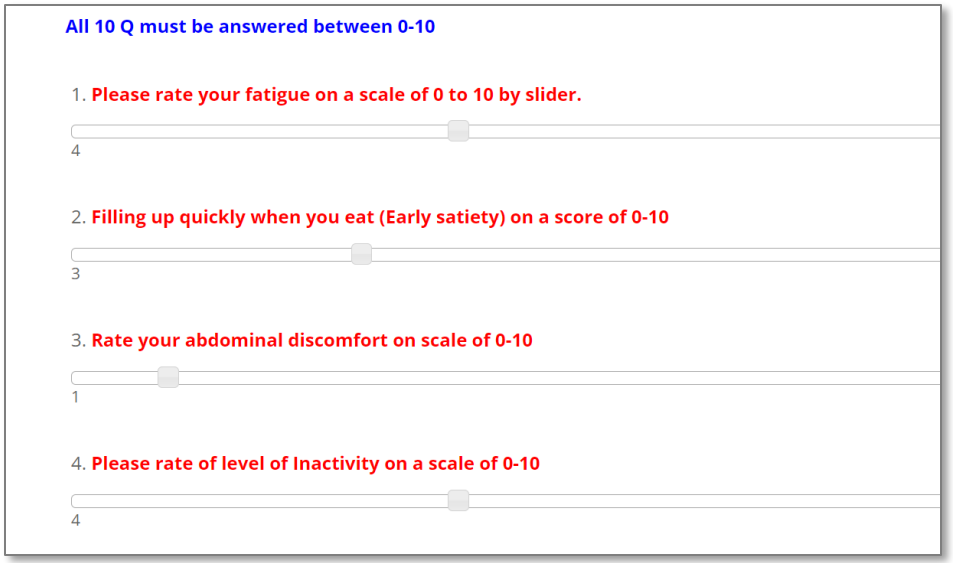
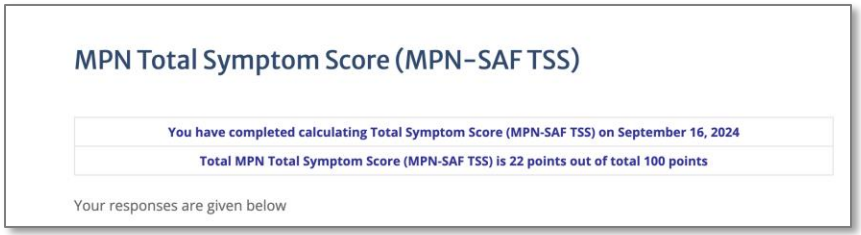
Emanuel RM, et al. *J Clin Oncol*. 2012;30:4098-4103.

Assessing Symptoms in MF: Online Tools for Patients

Slider bars allow numeric and/or visual rating of each symptom



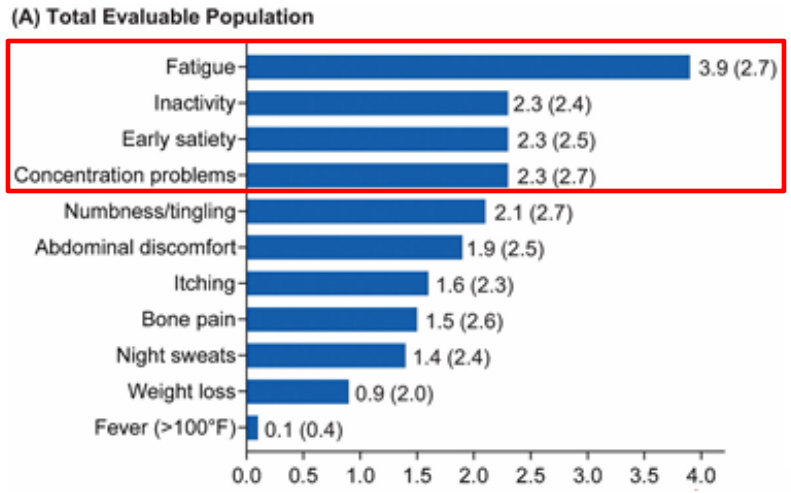
Total score is calculated automatically

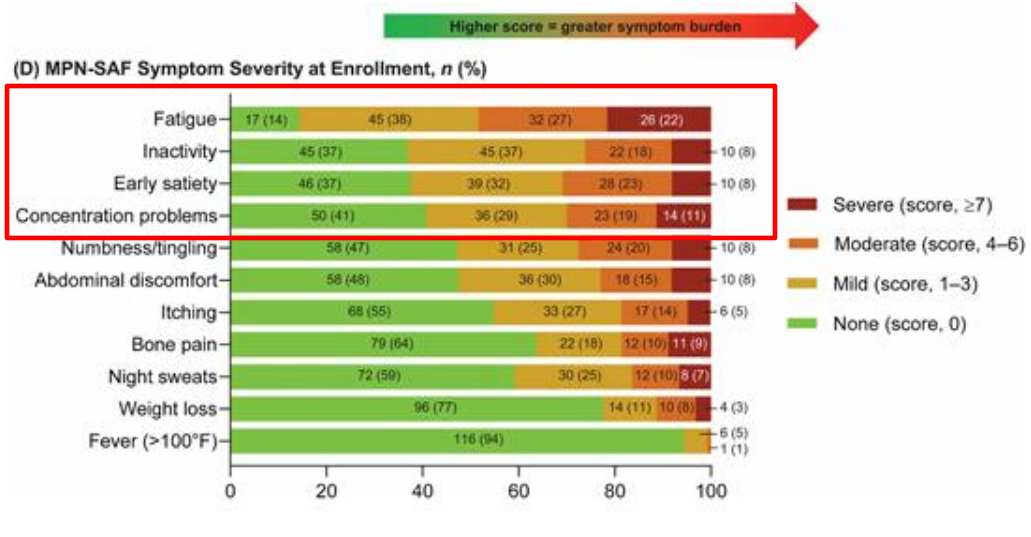


cec ONCOLOGY

Emanuel RM, et al. *J Clin Oncol*. 2012;30:4098-4103.
thehematologist.org. 2020. https://thehematologist.org/mpn-total-symptom-score.

PRO for Impact of MF-Associated Symptoms: The MOST Trial



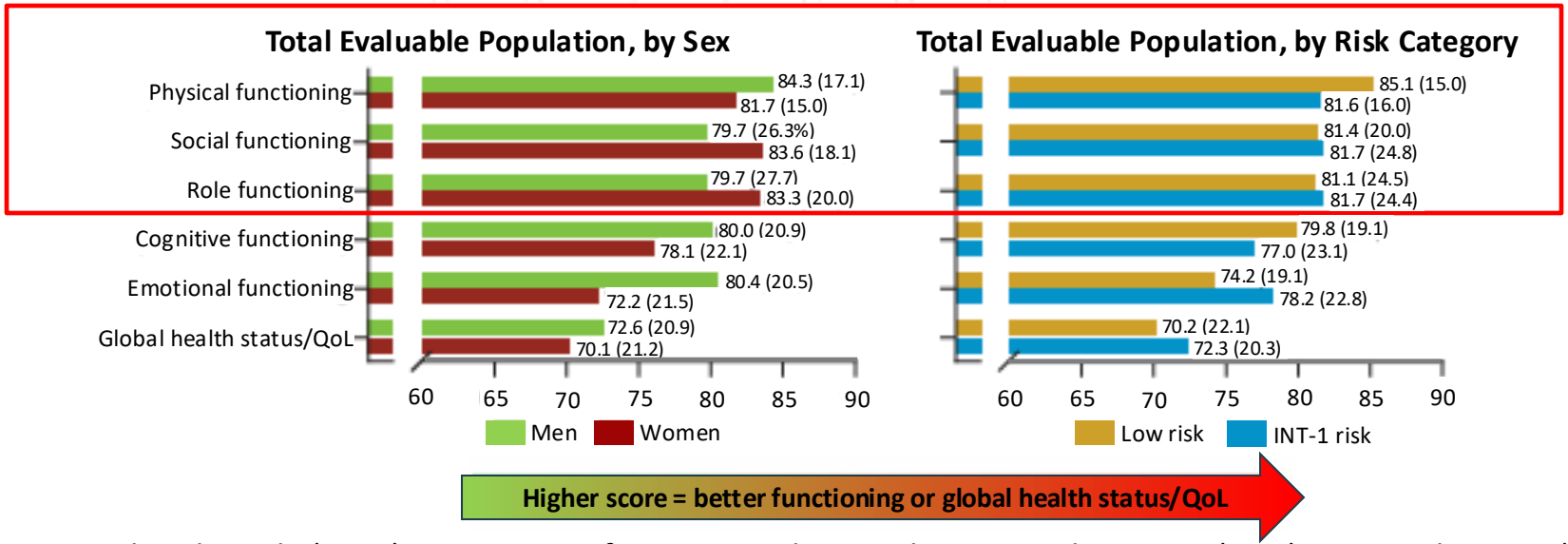


- Noninterventional study assessing clinical characteristics and PROs of patients with MF or essential thrombocythemia
- Patients with MF: mean (SD) MPN-SAF TSS PRO scores for (A) total evaluable population, and (D) MPN-SAF symptom severity at enrollment

PRO = patient-reported outcome; SAF = symptoms assessment form.

Ritchie E, et al. *Leuk Lymphoma*. 2022;63(13):3138-3153.

Symptoms and QoL in MF



- MPN Landmark Study (2016) – USA: 81% of patients with MF either somewhat agree (31%) or strongly agree (50%) with "My MPN symptoms reduce my quality of life"
- More recent measures across QoL domains regardless of sex or risk category in MF have not changed substantially (2022)

QoL = quality of life.

Ritchie E, et al. *Leuk Lymphoma*. 2022;63(13):3138-3153.

Assessing Symptom Burden Over Time

- Assessment of symptoms at each visit from baseline and then consistently over time is recommended for all patients
- Changes in symptom status could be a sign of disease progression
- Consistent use of validated tools and a workflow for documenting TSS at each visit is essential to communicate across the interdisciplinary team

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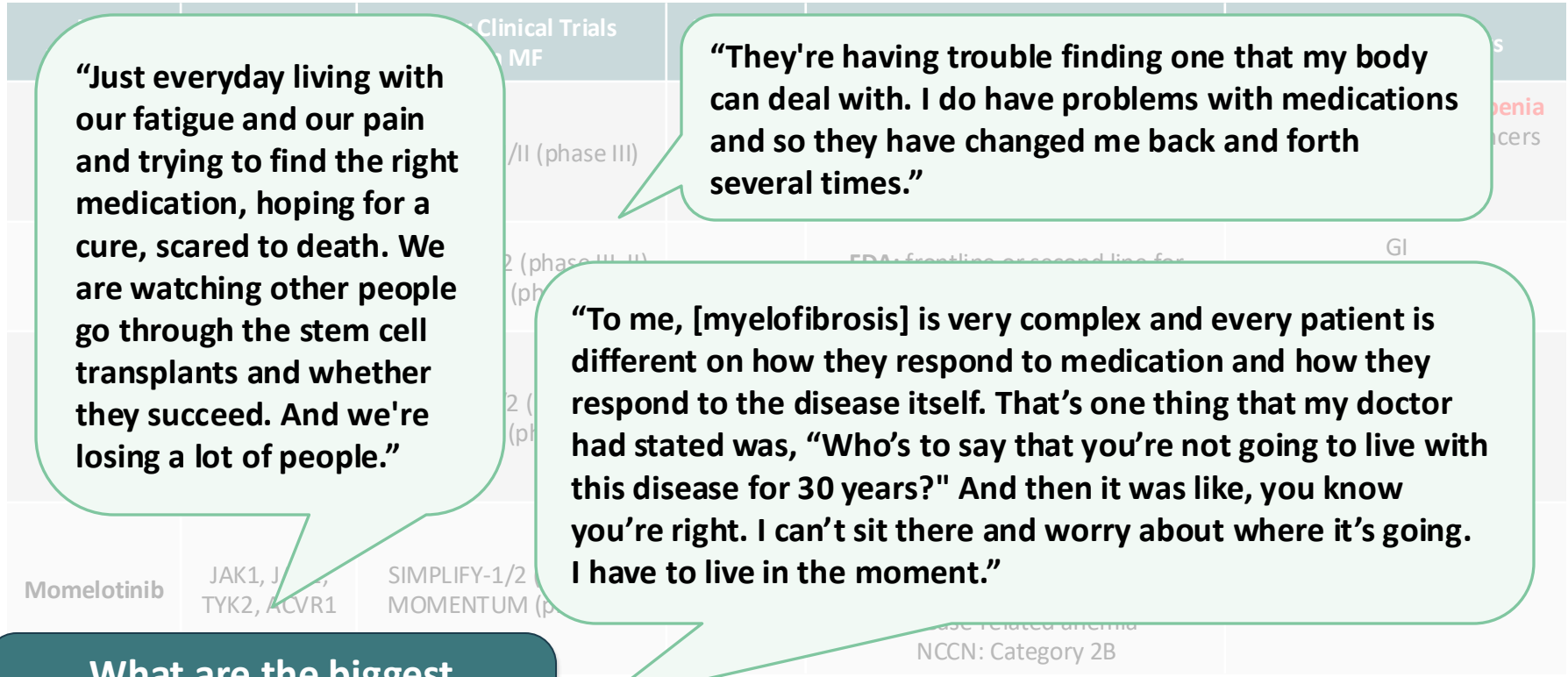
Yoon J, Pettit K. *Expert Rev Hematol*. 2021;14(7):607-619.

Treatment-Related AEs: JAK Inhibitors in MF

JAK Inhibitor	Primary Targets	Major Clinical Trials in MF	Approval Date	Approved and Recommended Indications	Notable Side Effects
Ruxolitinib	JAK1, JAK2	COMFORT-I/II (phase III)	2011	**FDA:** frontline for intermediate- and high-risk MF	**Anemia, thrombocytopenia** Nonmelanoma skin cancers Infections Hyperlipidemia
Fedratinib	JAK2, FLT3	JAKARTA-1/2 (phase III, II) FREEDOM (phase IIIb)	2019	**FDA:** frontline or second line for INT-2 and high-risk MF	GI Low thiamine/WE **Cytopenias**
Pacritinib	JAK2, JAK3, TYK2, ACVR1, IRAK1, FLT3	PERSIST 1/2 (phase III) PAC203 (phase II)	2022	**FDA:** frontline for intermediate- and high-risk MF with PLT < 50×10^9 **NCCN:** second line with any PLT count	GI Adverse cardiac events QT interval ↑ Hemorrhage **Thrombocytopenia**
Momelotinib	JAK1, JAK2, TYK2, ACVR1	SIMPLIFY-1/2 (phase III) MOMENTUM (phase III)	2023	**FDA:** intermediate- or high-risk myelofibrosis, including primary or secondary myelofibrosis, and disease-related anemia NCCN: Category 2B	GI **Cytopenias**

Ruxolitinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202192s028lbl.pdf.
Fedratinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212327s006lbl.pdf.
Pacritinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208712s001lbl.pdf.
Momelotinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216873s000lbl.pdf.
NCCN Guidelines. Myeloproliferative Neoplasms (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

Treatment-Related AEs: JAK Inhibitors in MF



"Just everyday living with our fatigue and our pain and trying to find the right medication, hoping for a cure, scared to death. We are watching other people go through the stem cell transplants and whether they succeed. And we're losing a lot of people."

"They're having trouble finding one that my body can deal with. I do have problems with medications and so they have changed me back and forth several times."

"To me, [myelofibrosis] is very complex and every patient is different on how they respond to medication and how they respond to the disease itself. That's one thing that my doctor had stated was, "Who's to say that you're not going to live with this disease for 30 years?" And then it was like, you know you're right. I can't sit there and worry about where it's going. I have to live in the moment."

What are the biggest challenges you face in staying on your medications?

WEGO patient survey, 2023.
Ruxolitinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/202192s028lbl.pdf.
Fedratinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/212327s006lbl.pdf.
Pacritinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/208712s001lbl.pdf.
Momelotinib [package insert]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/216873s000lbl.pdf.
NCCN Guidelines. Myeloproliferative Neoplasms (Version 2.2024). https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

Discontinuation of JAK Inhibitors

Toxicity

- Gastrointestinal
- Cytopenia(s)
- Neurologic
- Others

Lack of Efficacy

- No initial improvement in spleen size or symptom burden

Disease Progression

- Worsening cytopenia(s)
- AP/BP MPN (e.g., AML), hyperleukocytosis
- Worsening symptoms
- Increasing spleen size

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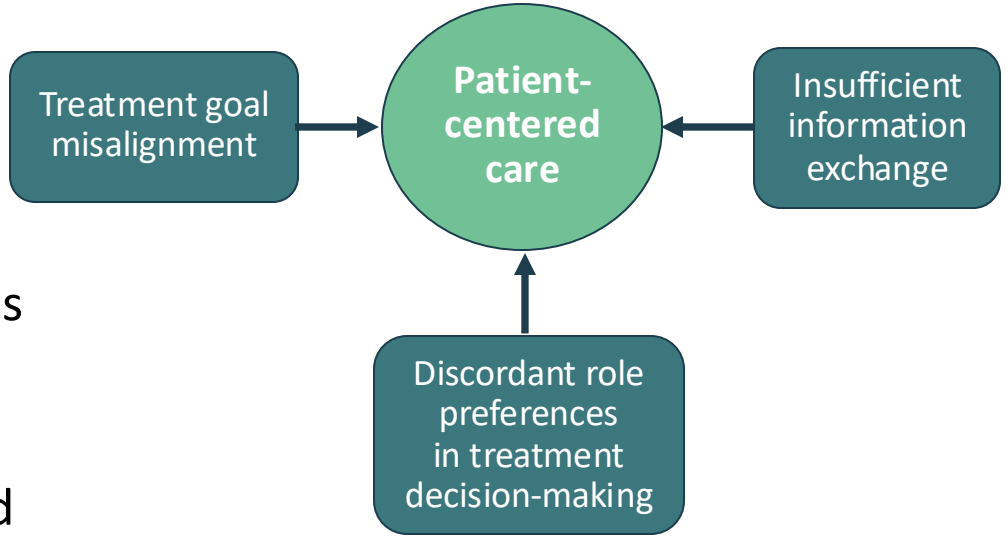
AML = acute myeloid leukemia; AP = accelerated phase; BP = blast phase.
Tefferi A. *Am J Hematol*. 2021;96(1):145-162.

LO 4

Evaluate current health disparities impacting treatment outcomes in MF, including consideration of clinical trial participation opportunities for patients in underserved populations.

Barriers to Patient-Centered Care

- Limited access to clinical trials
- Distance to a specialty center
- Lack of time during visits
- Symptom burden
- Inconsistent communication across team and with patient
- Transitions in care team over time
- Limited access to primary care and subspecialists



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LeBlanc TW, et al. *Patient Educ Couns*. 2019;102:1602-1612.

Access to Medications Can Be Challenging

"They're having trouble finding one that my body can deal with. I do have problems with medications and so they have changed me back and forth several times."

"I've done it for so long, twice a day meds, that it's just habit. Every once in a while things will get outta kilter in the morning. I'll get off schedule and not get one taken. I don't throw a three-time-a-day pill in there because the third time is hard to remember, you know, you get busy doing other stuff, you just don't think about it."

"In terms of my medications, I have a medication for my heart, and I have one medication for my myelofibrosis and several other medications that I take. And what I do is I write out a sheet of paper and I do it physically by hand, and every day I mark in the medications that I take, and I take them all at the same time in the morning."

What are the biggest challenges you face in staying on your medications?

"At first when I lost my benefits, it was a financial challenge because one medication was very expensive, something that we could not afford."

WEGO patient survey, 2023.

Clinicians Generally Encourage Participation in Treatment Planning, but Not Always

"I had a previous doctor that said I was intelligent, said, 'Pull your chair up next to me. Let's look at this together.' And we shared the information. The doctor that I have now does not do that."

"Everybody, [the hematologist/oncologist] and the nurse practitioners that work with her are very, very helpful. And in terms of treatment planning, the only thing we can do is watch my numbers, watch the results of the blood tests."

Do you feel your doctor listens to you and encourages your participation in your treatment planning?

"Unfortunately, my much-loved doctor just retired. His replacement's bedside manner is not nearly what the first one's was. He doesn't seem to be as vocal or is as involved, but he did answer some questions for me that I hadn't thought to answer earlier. My appetite has changed drastically, and my husband was going, 'Eat, eat, eat.' I'm going, 'I can't, I'm full.' He said, 'That's okay, just eat higher-calorie meals when you do eat.' Now, who's ever been lucky enough to have a doctor to tell him to eat lots of calories?"

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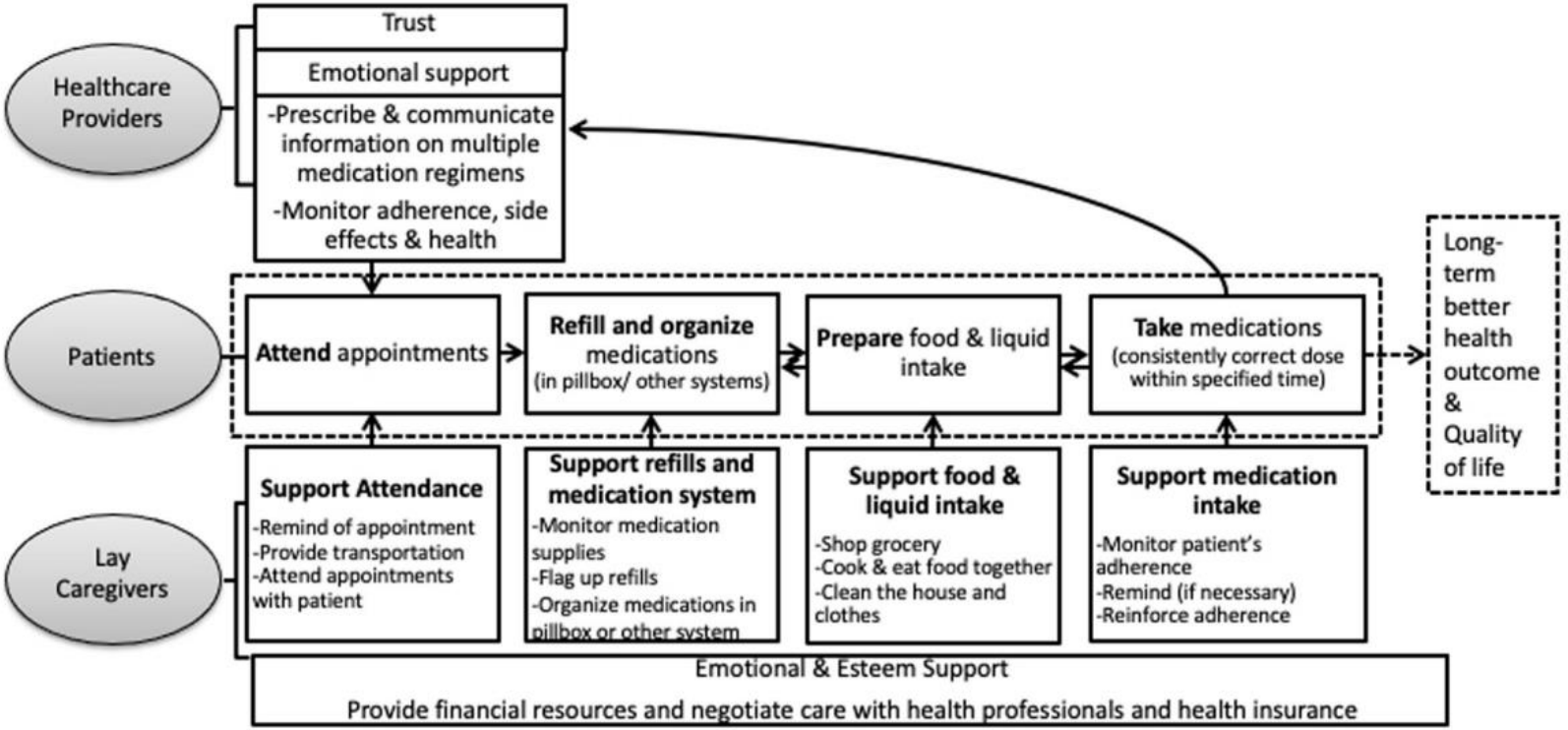
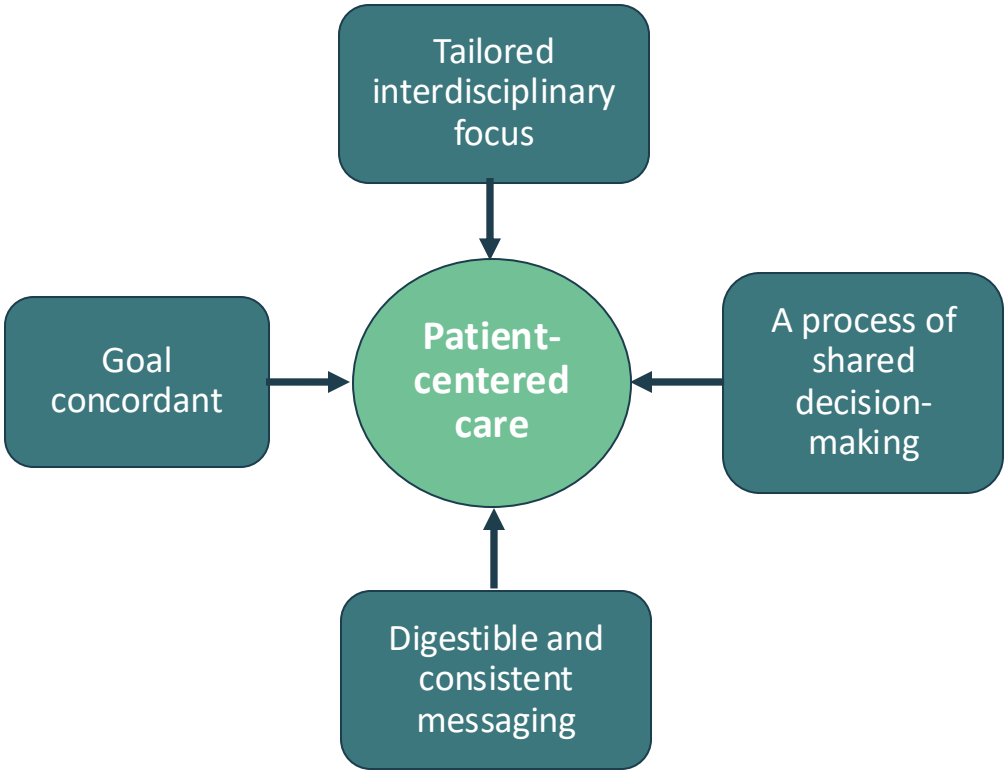
WEGO patient survey, 2023.

Patients and Caregivers as Partners in Care



Song Y, et al. *Front Psychol*. 2021;12:624906.

Patient-Centered Care



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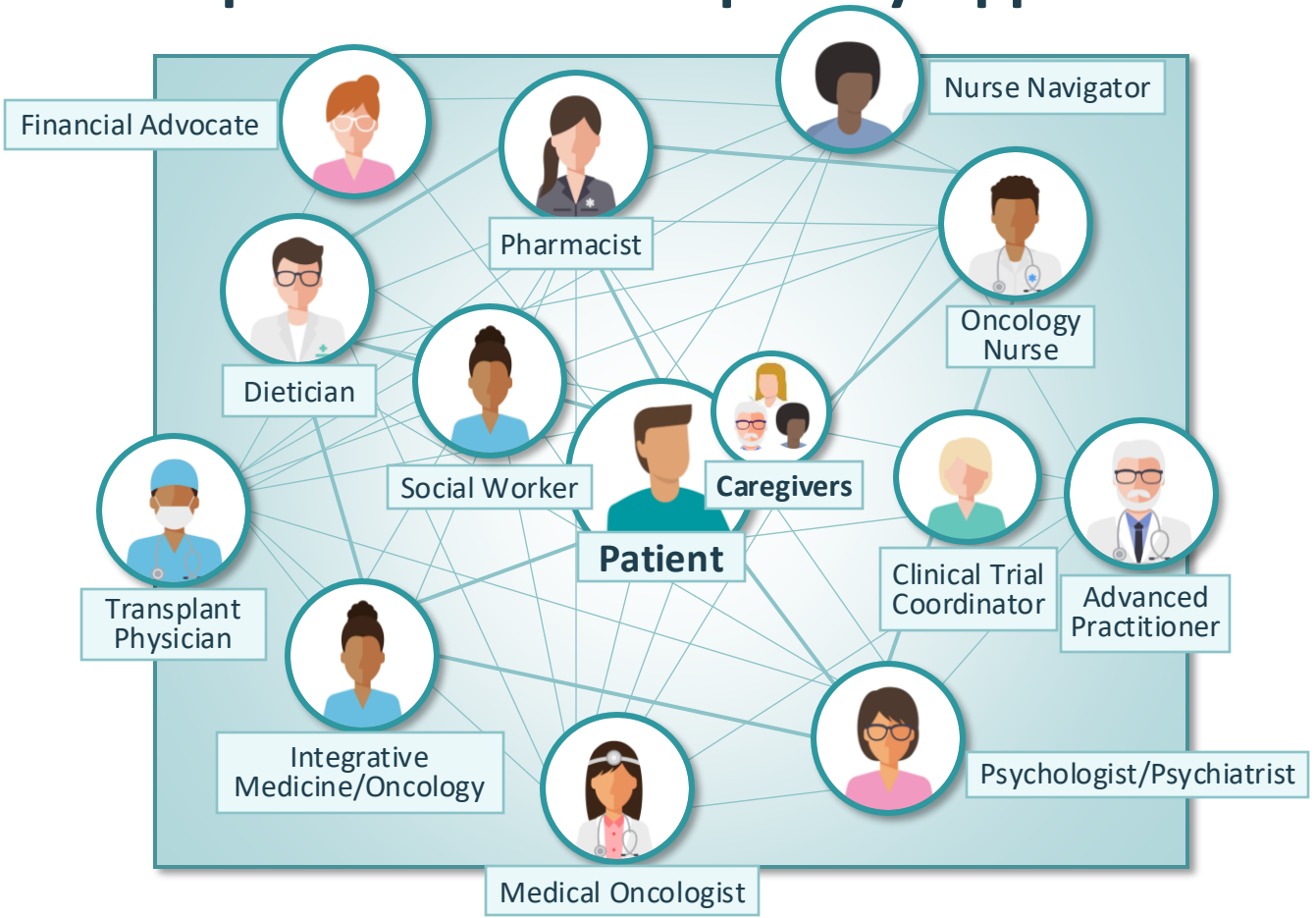
LeBlanc TW, et al. *Patient Educ Couns*. 2019;102:1602-1612.

Optimal Management of Myelofibrosis Requires a Multidisciplinary Approach



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MPN Patient Community

MPN Group	Focus	Website
MPN Research Foundation	RES-ED-ADV	www.Mpnresearchfoundation.org
Leukemia and Lymphoma Society	RES-ED-ADV	www.lls.org
MPN Advocacy & Education International	ED-ADV	www.mpnadvocacy.com
MPN Education Foundation	ED-COMM	www.mpninfo.org
AAMDS Foundation	ED	www.aamds.org
MPN Voice	ED	www.mpnvoice.org.uk
MPN HUB	ED	www.mpn-hub.com
MPN Advocates Network	ED-ADV	www.mpn-advocates.net
Global MPN Scientific Foundation	RES-ED-ADV	www.gmpnsf.org
MPN Forum Facebook Group	ED-COMM	https://www.facebook.com/groups/ourmpnforum/

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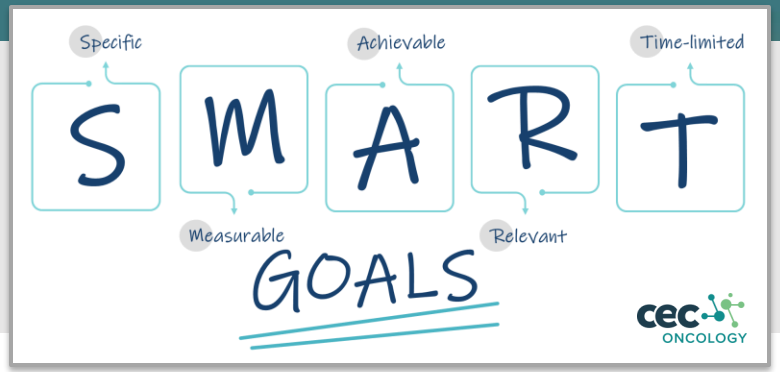

Put information into action!

Takeaways from this program can be implemented into your practice to improve patient care.

- ***Increase the percentage*** of patients who have treatment decisions made ***based on guideline-recommended risk stratification tools*** (such as MIPSS-70), integrating molecular indicators (e.g., *JAK2*, *CALR*, *MPL* mutations), clinical features (e.g., anemia, spleen size), and symptom burden.

- ***Improve adherence*** to myelofibrosis treatment guidelines through ***enhanced clinician education***, incorporating ***training on emerging therapies***, and establishing a standardized treatment protocol within your practice.

- ***Implement a comprehensive symptom assessment tool*** to regularly monitor fatigue, pain, and spleen-related discomfort in patients with myelofibrosis, and ***provide individualized care plans to address symptom management.***

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Click on the *Request Credit* tab to complete the process and print your certificate.