Recognizing the Profound Impact on Quality of Life:

Emerging Therapy Options for Patients with Myelofibrosis

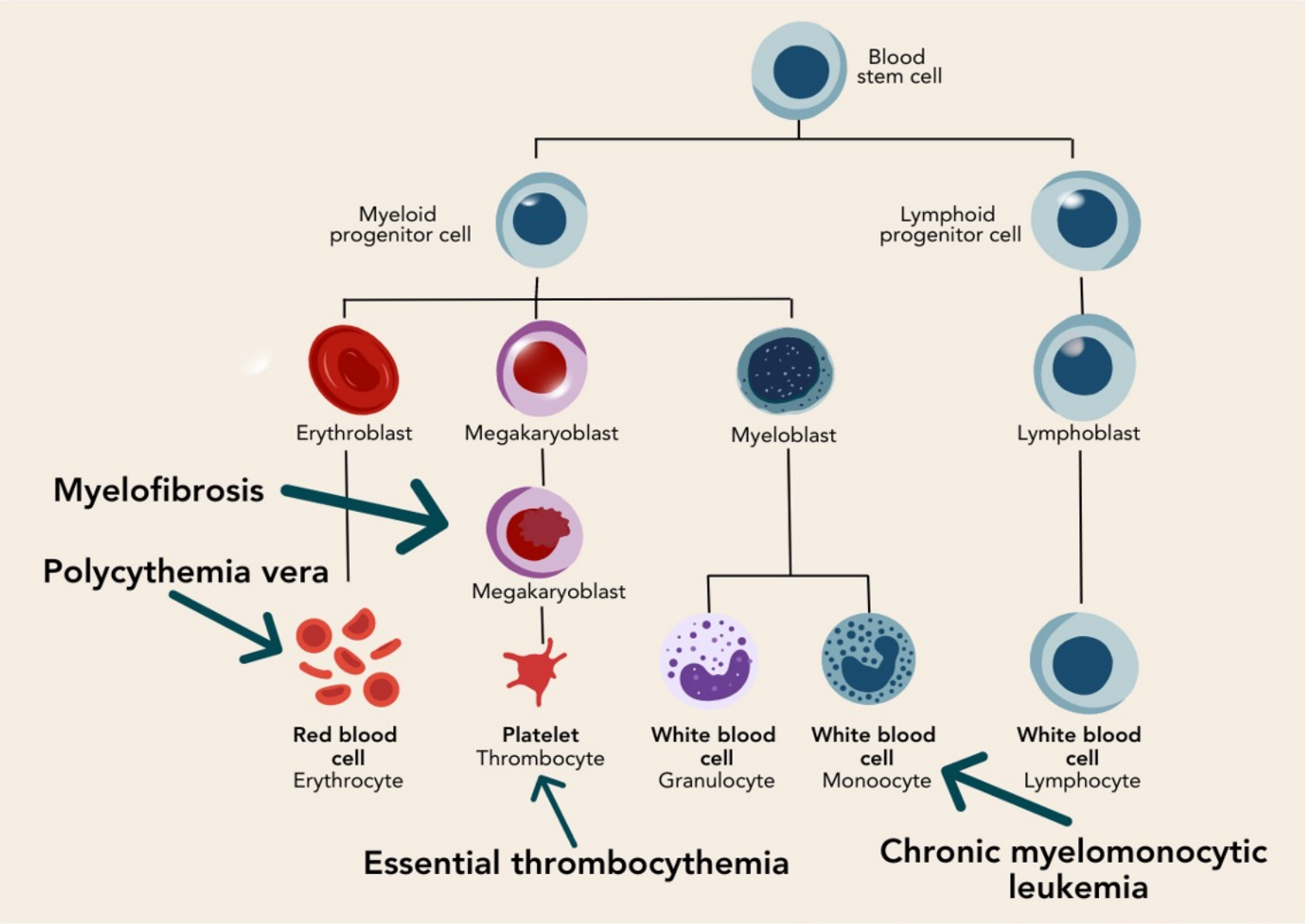
Learning Objectives

- Correctly evaluate the alignment of JAK inhibitors and emerging treatment options with evidence-based clinical guidelines for patients diagnosed with MF
- Appropriately assess patient symptoms and potential adverse events related to JAK inhibitors and emerging treatment options to effectively address patient QOL
- Consistently implement shared decision-making strategies to create a personalized care plan that alleviates QOL burdens associated with MF

Making an Appropriate Treatment Selection for Patients with MF:

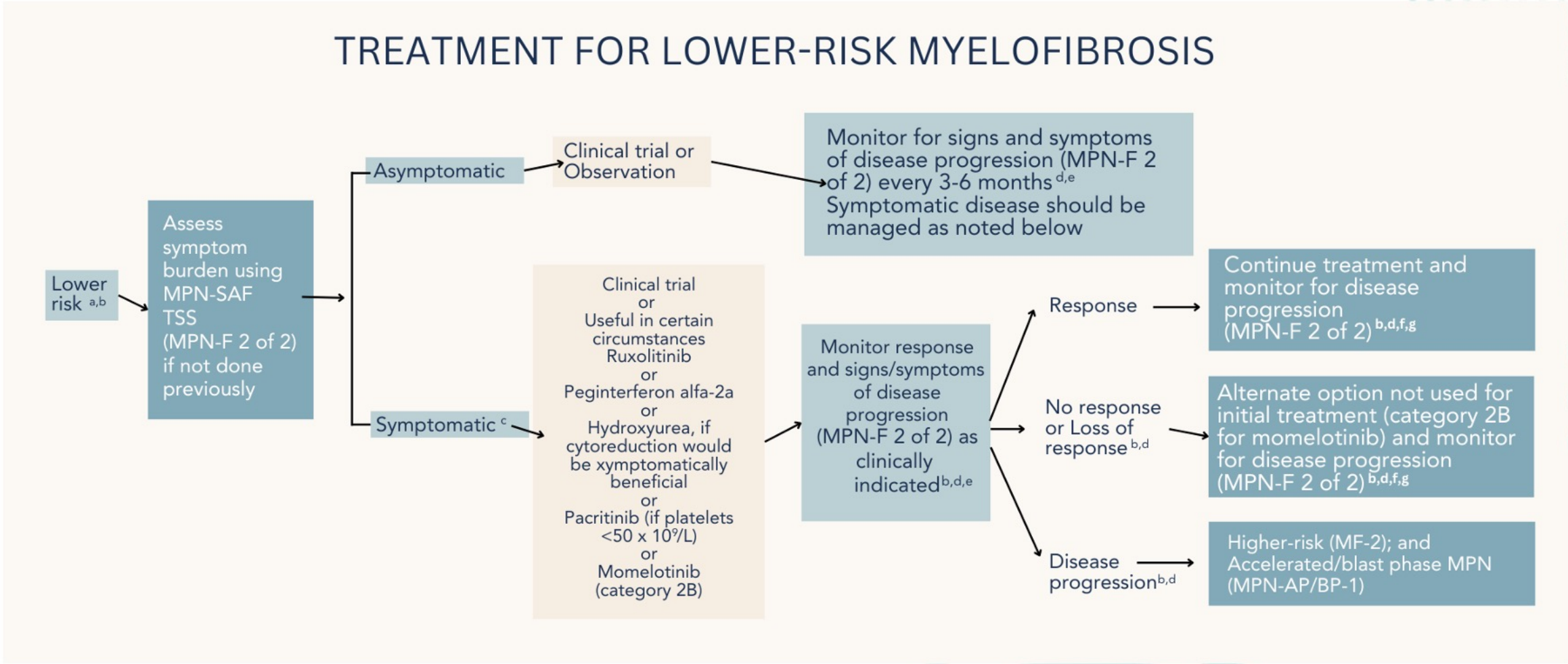
Understanding How Patient Risk and Drug Mechanism of Action Leads to Effective Treatment and Management Decisions

Myeloproliferative Neoplasms



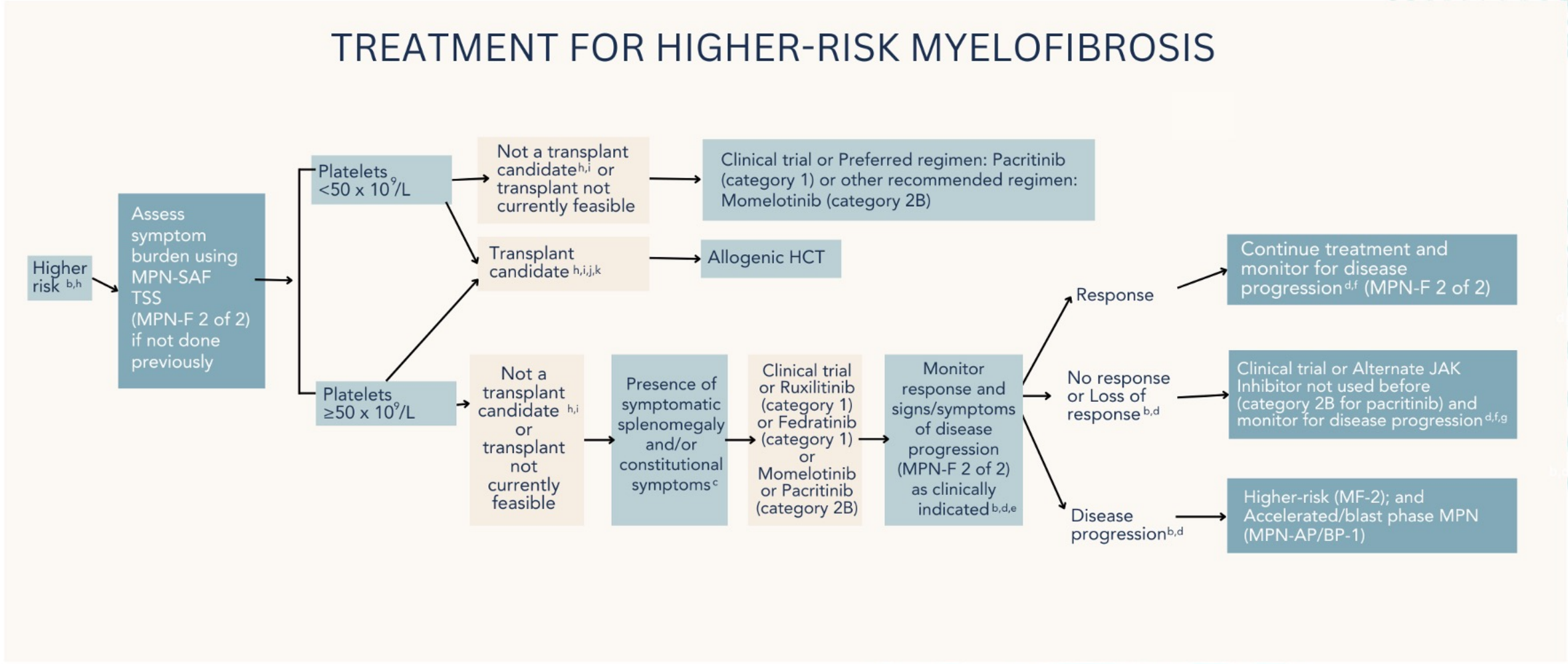
NCCN Guidelines for Patients. Myeloproliferative Neoplasms 2024.

Treatment Algorithm for Lower-Risk Myelofibrosis



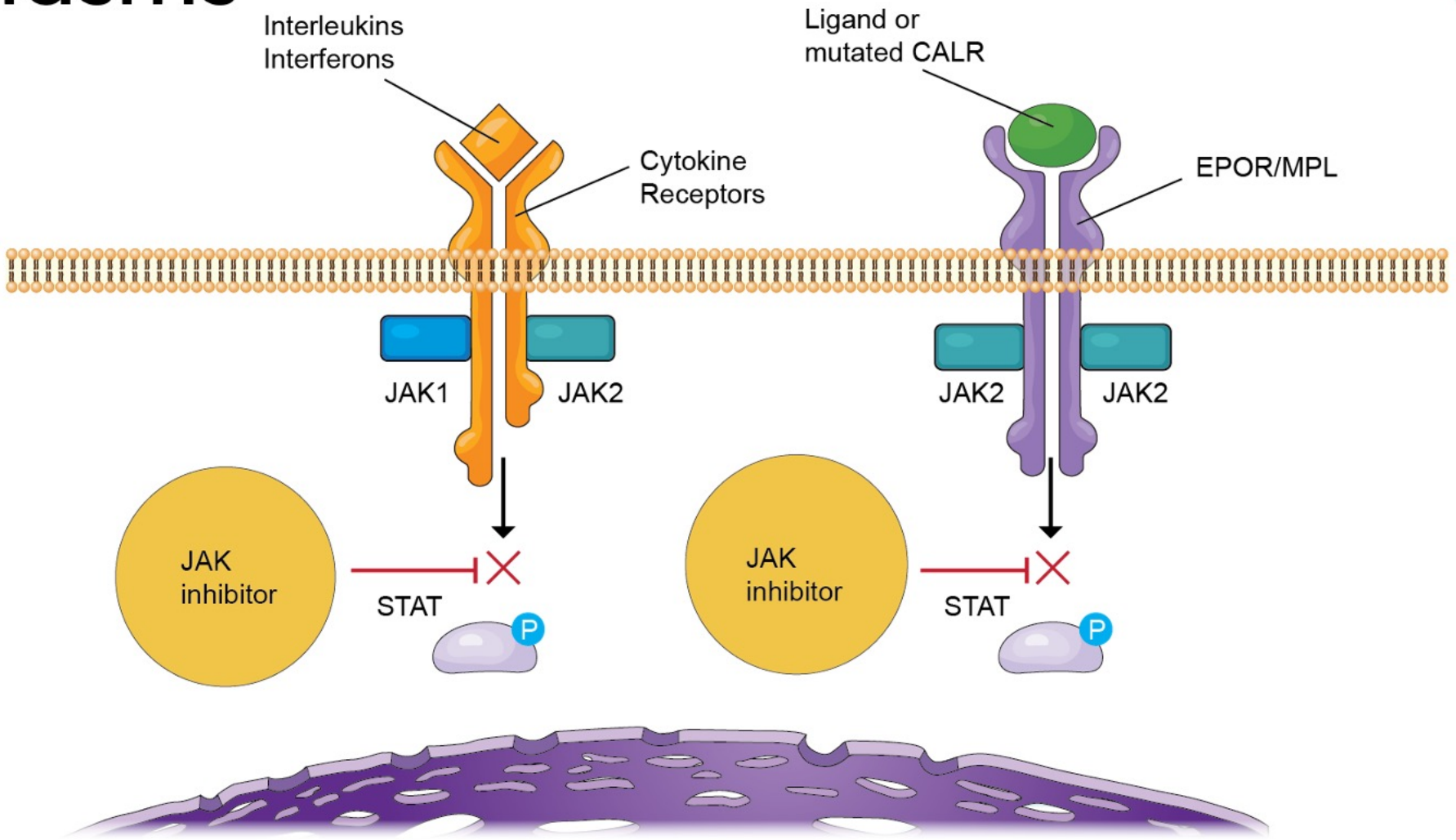
NCCN Guidelines Version 1.2024. Myelofibrosis.

Treatment Algorithm for Higher-Risk Myelofibrosis



NCCN Guidelines Version 1.2024. Myelofibrosis.

Pathophysiology of Myeloproliferative Neoplasms



CALR, calreticulin; EPOR, erythropoietin receptor; JAK, Janus kinase; MPL, myeloproliferative leukemia protein; STAT, signal transducer and activator of transcription.
Redrawn from Mesa RA, et al. ASCO 2022. Oral Presentation 7002.

Predictors of Inferior OS Following JAK Inhibitors

- Age > 65
- Absence of spleen and anemia responses
- Emergent mutations in RAS pathway genes (KRAS, NRAS, CBL and PTPN11) and ASXL1 (associated with AP/BP disease)
- Transfusion-dependence
- Presence of ASXL1/SRSF2 mutations

Gangat N, et al. Blood Cancer J. 2023;13(1):3.England JT, et al. Leukemia. 2022;36(6):1689-1692.

DIPSS and DIPPS+ to Assess Patient Risk

DIPSS/DIPSS-plus Scoring

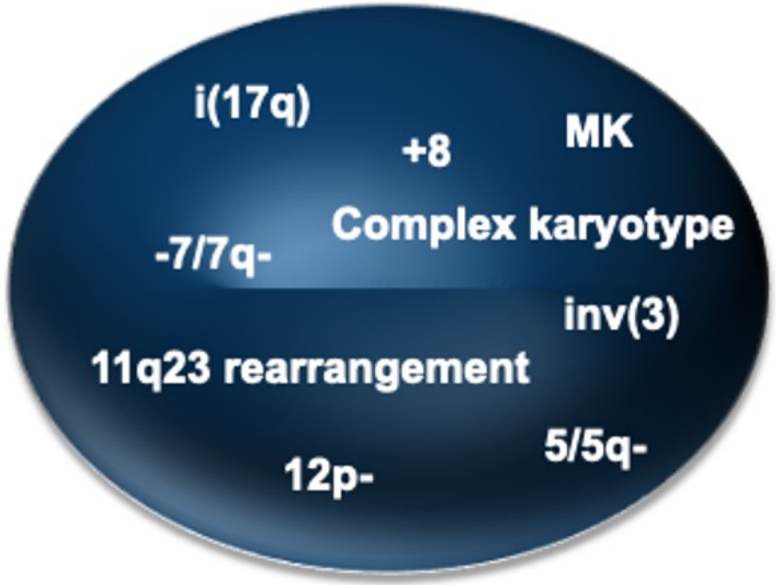
DIPSS Factors	Points
Age >65 ys	1
Symptoms	1
WBC >25,000	1
Hgb <10	2
Blood Myeloblasts >1%	1

DIPSS Risk Category	Points	Value for DIPSS *plus* risk
Low	0	0
Intermediate 1	1	1
Intermediate 2	2-3	2
High	≥4	3

DIPSS plus Factors	Points
Adv. Karyotype	1
Platelets <100k	1
RBC Transf.	1

DIPSS plus Risk	Points	Median survival (ms)
Low	0	185
Intermediate 1	1	78
Intermediate 2	2-3	35
High	4-6	16

Adverse Karyotypes



Tefferi A, et al. *Leukemia*. 2012;26:1439-1441.; Gangat N, et al. *J Clin Oncol*. 2011;29:392-397.; Caramazza D, et al. *Leukemia*. 2011;25:82-88. Passamonti F, et al. *Blood*. 2010;115:1703-1708.

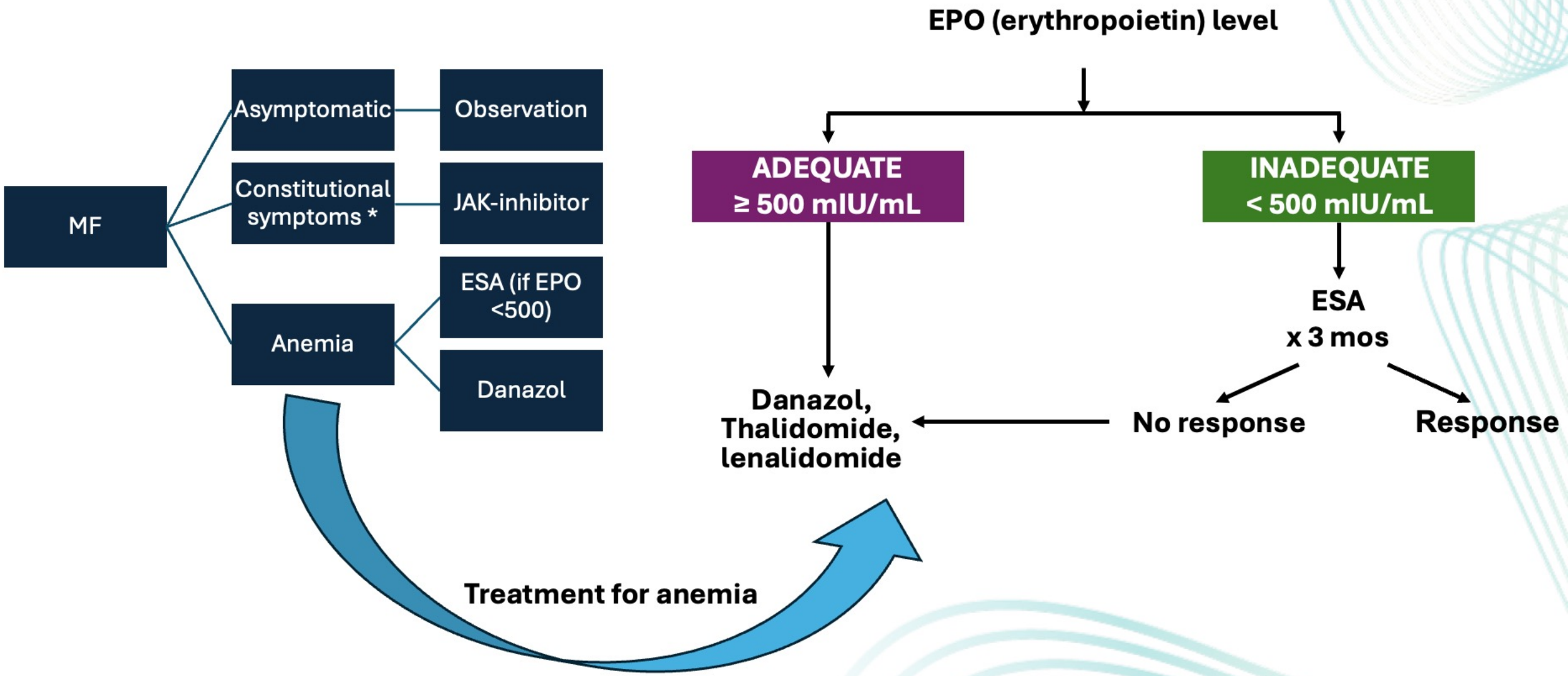
Non-JAK Inhibitor Emerging Therapeutics for MF

Novel Agent	MOA	Study Indication	Pivotal Trial(s)
ESAs	Darbopoeitin alpha Epoetin alpha	Anemia, if endogenous Epo level < 500 mU/mL	Retrospective, multicenter study
Pelabresib	BET inhibitor	• Spleen reduction and symptom responses • Single agent in JAK inhibitor refractory settings, • Combination with ruxolitinib in both up-front and JAK inhibitor refractory MF	MANIFEST MANIFEST-2
Navitoclax	BCL2 inhibitor	• Clinical responses • Navitoclax + ruxolitinib vs ruxolitinib alone • Navitoclax + ruxolitinib vs physician's choice therapy in the 2L setting, with exclusion criteria for platelet counts ($<100 \times 10^9$/L)	REFINE TRANSFORM-1 TRANSFORM-2
AVID200 Luspatercept Sotatercept	TGF-β inhibitor	Anemia	NCT04717414
Thalidomide Lenalidomide Pomalidomide	IMiDs	Severe anemia, thrombocytopenia	Phase 2 and pooled data
Danazol	Androgen	Anemia, thrombocytopenia	Small study population
Eltrombopag	TPO RA	Thrombocytopenia	Small study population

2L, second-line setting; BCL2, B-cell lymphoma 2; BET, bromodomain and extraterminal; MF, myelofibrosis; RA, receptor agonist; TO, thrombopoietin.

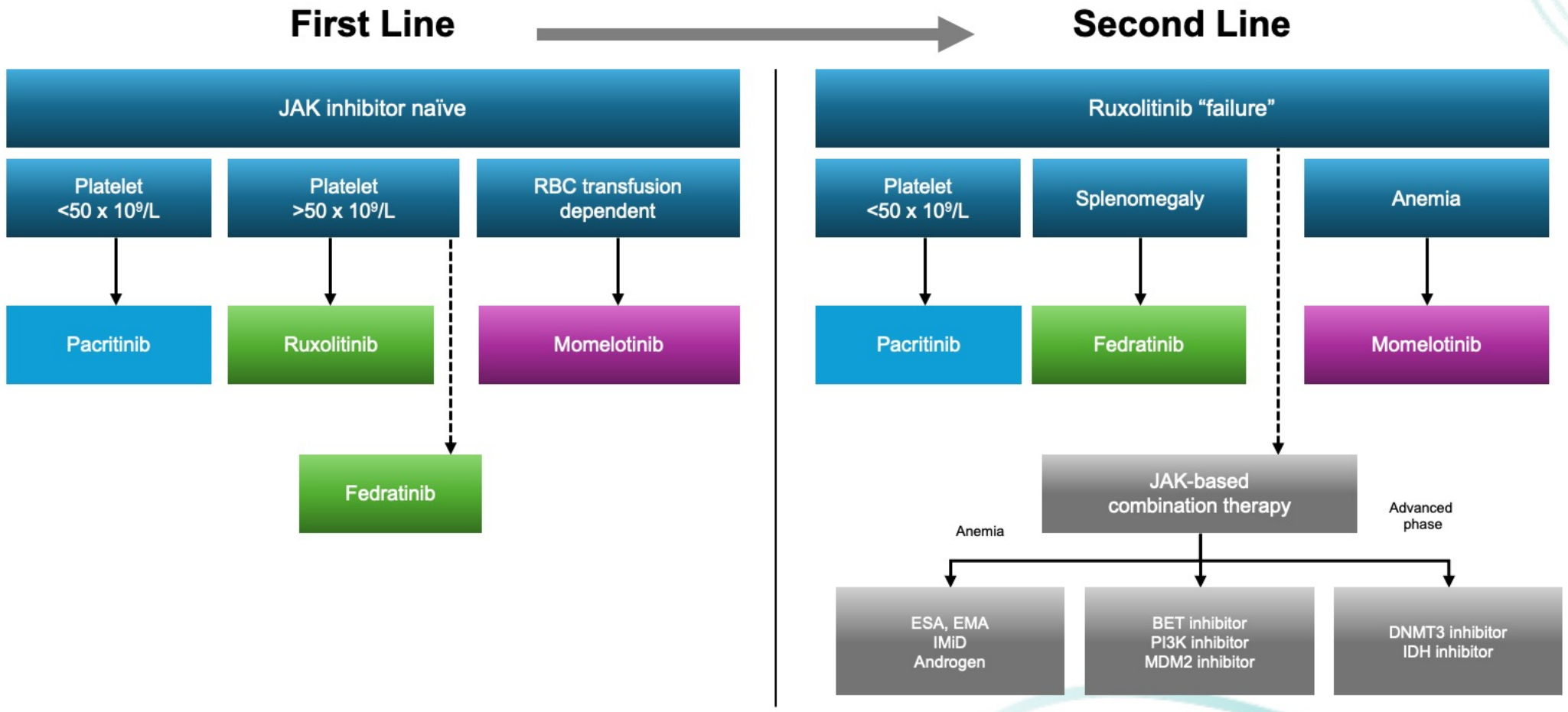
Reynolds SB & Pettit K. *Hematology Am Soc Hematol Educ Program* 2022; 2022 (1): 235–244.

Treatment Approach for Myelofibrosis



NCCN Guidelines Version 1.2024. Myelofibrosis.

Positioning of JAK Inhibitors for Treatment of MF



Venugopal S & Mascarenhas J. *J Hematol Oncol.* 2020;13:162.

Making an Appropriate Treatment Selection for Patients with MF:

Recognizing the Gaps in MF Care that Influence Patient Quality of Life

Symptoms of Myelofibrosis Affecting Patient Quality of Life

Baseline Health
Age
Medical Comorbidities
Psychological
Medications
Nutritional Status

Vascular Events
- Clots, bleeding
- Elevated blood counts
- Abdominal Vein Thrombosis

Cytopenias
- Transfusions
- Medication-related
- As a result of disease

Progression
- Transformation into another blood cancer
- Worsening of the current disease state

Inflammation
- Constitutional Symptoms
- Cachexia
- Anemia
- Cognitive dysfunction

Organ Dysfunction
- Spleen enlargement
- Liver issues
- Pulmonary extramedullary hematopoiesis

Symptoms Burden is Significant Compared to the General Population

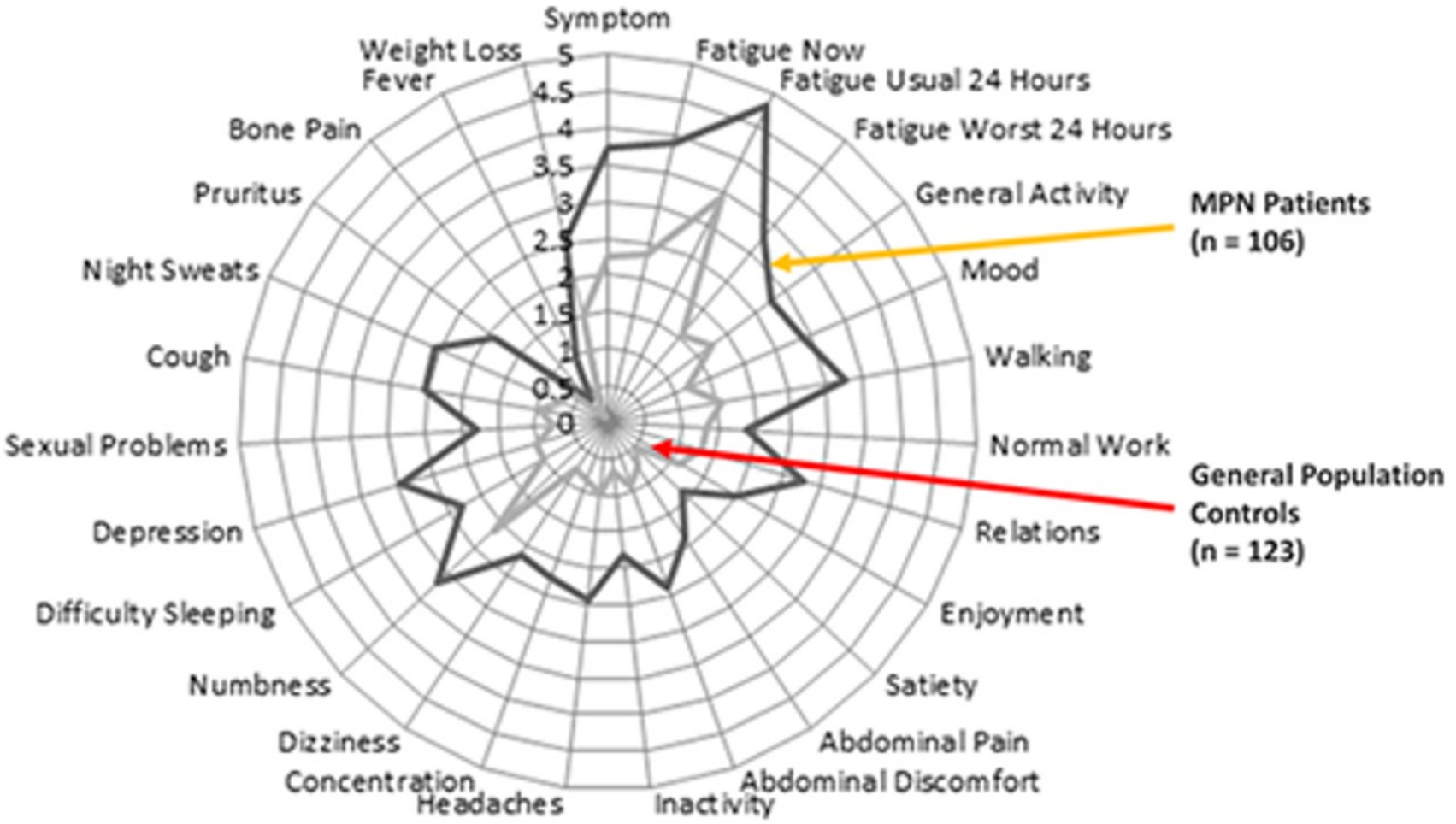


Image courtesy of Ruben A. Mesa, MD.

MPN Total Symptom Score (MPN-SAF TSS)

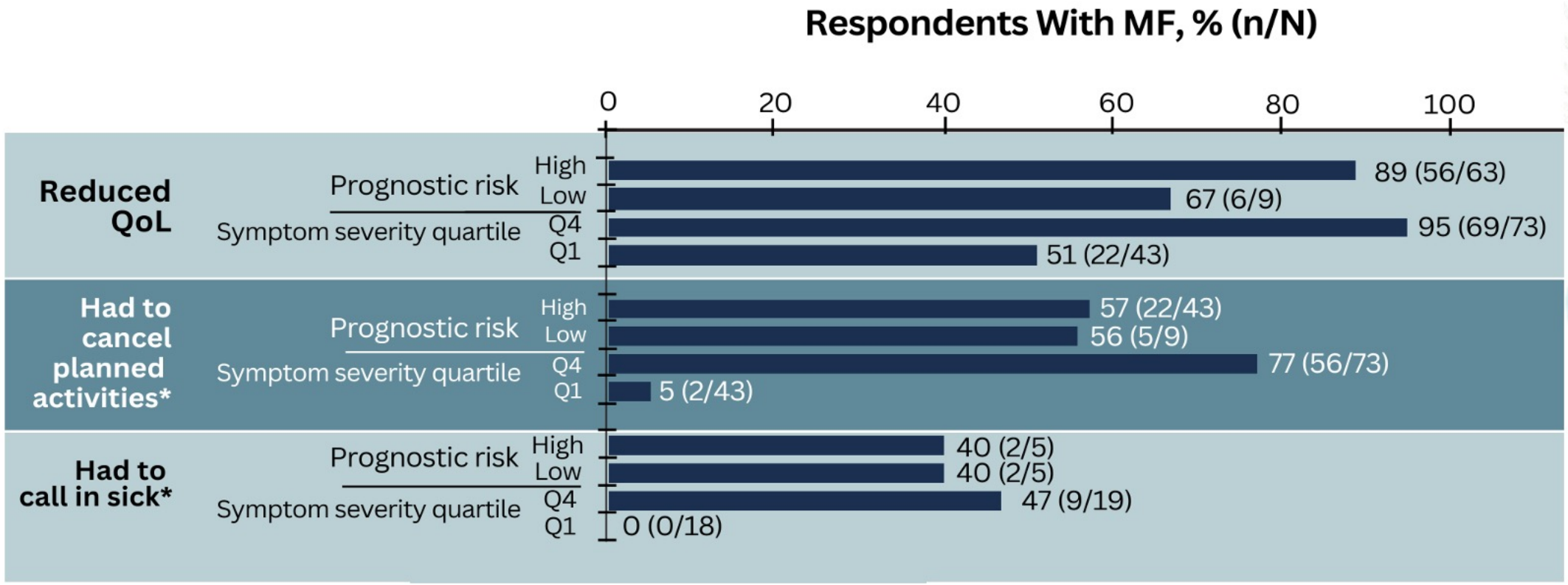
MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS; MPN-10)

(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)

NCCN Guidelines Version 1.2024. Myelofibrosis.

Clinical Burden of Myelofibrosis



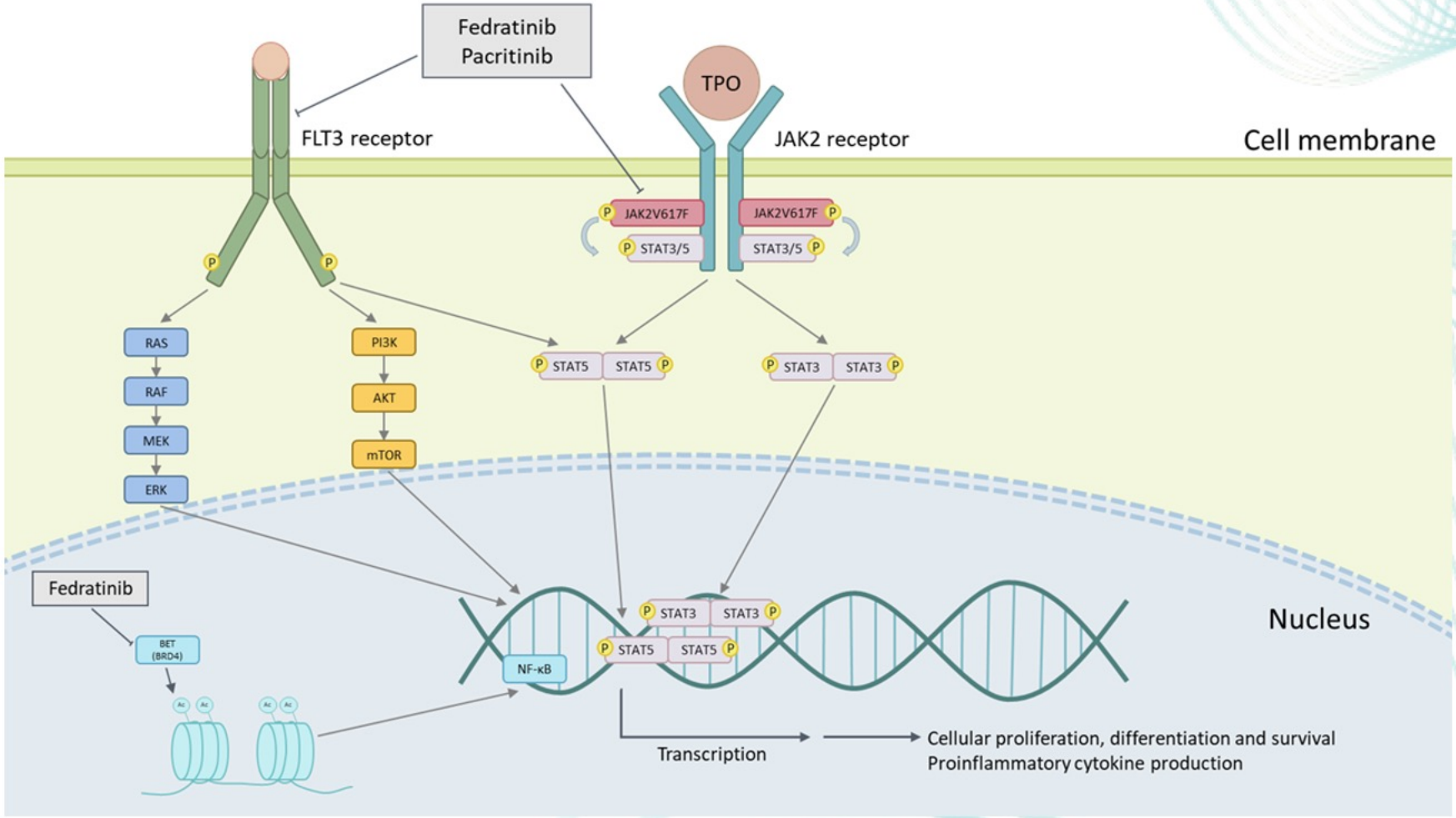
- Patients with DIPSS low-risk MF were moderately to highly symptomatic in 44% of the cases
- The reduction of quality of life and social/working activity was similar in low- and high-risk categories

Petruk C & Mathias J. *Adv Ther*. 2020 May;37(5):2050-2070.

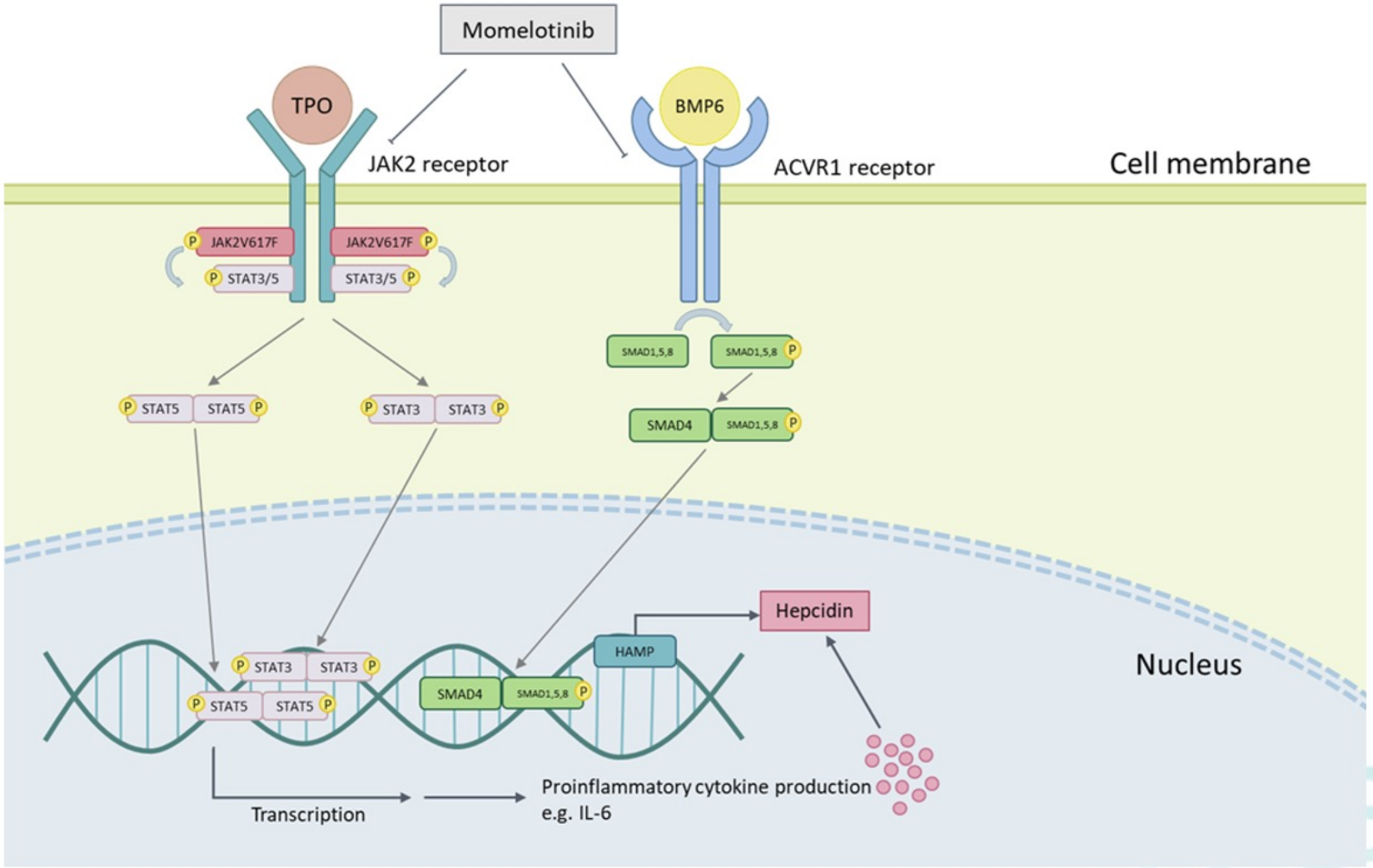
New Generations of JAK Inhibitors

Fedratinib
- Potent JAK2/ FLT3/ BRD4 inhibitor
- Combined inhibition of the JAK/STAT pathway and BRD4 synergistically suppresses NF-kB hyperactivation and cytokine production

Pacritinib
- JAK2/FLT3 inhibitor
- Off-target inhibitory action against interleukin-1 receptor-associated kinase 1 (IRAK1) and colony-stimulating factor 1 receptor (CSF1R) 18,36-38 promotes rapid suppression of inflammatory pathways
- With minimal JAK1 inhibition, pacritinib is less myelosuppressive and immunosuppressive

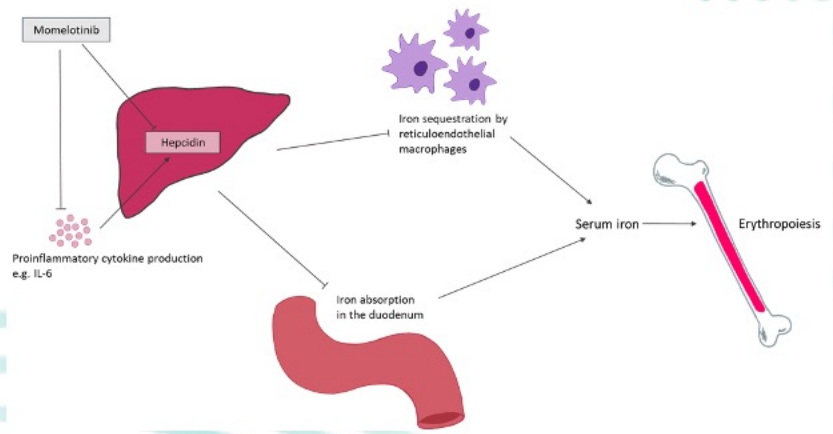


New Generations of JAK Inhibitors



Momelotinib

- JAK1/JAK2 inhibitor that has additional inhibitory effect against activin A receptor type I (ACVR1)
- ACVR1 is an important mediator of SMAD2/3 signalling that upregulates hepcidin production and results in iron-restricted erythropoiesis.



Key Efficacy Data of JAK Inhibitors for Treatment of MF

Generic (Brand Name)	Key efficacy findings (based off primary endpoint)	Pivotal Trial(s)
Ruxolitinib (JAKAFI)	At week 48, 28% (41/146) of patients randomized to ruxolitinib achieved ≥ 35% decrease in spleen volume compared with no patients on BAT (P< 0.001)	COMFORT-1 COMFORT-2
Fedratinib (INREBIC)	Nine (25.7%; 95% confidence interval 12.5–43.3) patients achieved primary endpoint of ≥ 35% spleen volume reduction at EOC 6	JAKARTA JAKARTA2 FREEDOM FREEDOM2
Pacritinib (VONJO)	Pacritinib (arms combined) was more effective than BAT for 35%or more spleen volume reduction (27 patients [18%] vs 2 patients [3%]; P= .001)	PERSIST-1 PERSIST-2 PACIFICA PAC203
Momelotinib (OJJAARA)	Median OS of 2.9 years in MMB crossover to MMB arm Median OS of 3.1 years in BAT/RUX crossover to MMB arm	SIMPLIFY-1 SIMPLIFY-2 MOMENTUM

BAT, best available therapy; EOC, end of cycle; MMB, momelotinib; OS, overall survival; RUX, ruxolitinib.

Harrison CN, et al. Leukemia. 2016 Aug;30(8):1701-7. Gupta V, et al. Leuk Lymphoma. 2024 Jun 5:1-11. Verstovsek S, et al. Lancet. 2023 Jan 28;401(10373):269-280. Mascarenhas J, et al. JAMA Oncol. 2018 May 1;4(5):652-659

Adverse Events of JAK Inhibitors for MF

Generic (Brand Name)	Common AEs	Serious AEs	Contraindication(s)	DDI(s)
Ruxolitinib (JAKAFI)	Hematologic: thrombocytopenia, anemia Nonhematologic: bruising, dizziness, headache, diarrhea	Thrombocytopenia, risk of infection, symptom exacerbation following interruption or discontinuation, risk of non-melanoma skin cancer, lipid elevations, MACE, thrombosis, secondary malignancies	None	Avoid concomitant use with fluconazole doses > 200 mg. Reduce dosage with fluconazole doses ≤ 200 mg Strong CYP3A4 Inhibitors: Reduce, interrupt, or discontinue Jakafi doses as recommended
Fedratinib (INREBIC)	Diarrhea, nausea, anemia, vomiting	Anemia and thrombocytopenia, GI toxicity, hepatic toxicity, amylase and lipase elevation, MACE, thrombosis, secondary malignancies	None	Strong CYP3A4 Inhibitors: Reduce fedratinib dose as recommended Strong and Moderate CYP3A4 Inducers: Avoid use of fedratinib CYP3A4, CYP2C19, or CYP2D6 substrates: Dose modifications of substrates drugs may be needed OCT2 and MATE1/2-K substrates: Dose modifications of substrate drugs may be needed
Pacritinib (VONJO)	Thrombocytopenia, nausea, anemia, peripheral edema	Hemorrhage, diarrhea, thrombocytopenia, prolonged QT interval, MACE, thrombosis, secondary malignancies, risk of infection	Concomitant use of strong CYP3A4 inhibitors or inducers	Avoid use with moderate CYP3A4 inhibitors or inducers, which can alter the concentration of drugs that are P-gp, BCRP, or OCT1 substrates. Avoid use with sensitive substrates
Momelotinib (OJJAARA)	Thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, nausea	Risk of infection, thrombocytopenia and neutropenia, hepatotoxicity, MACE, thrombosis, secondary malignancies	None	OATP1B1/B3 inhibitors: Monitor for adverse reactions BCRP substrates: Reduce rosuvastatin dosage and follow approved product information recommendations for other BCRP substrates

BCRP, breast cancer resistance protein; GI, gastrointestinal; MACE, major adverse cardiovascular events; OATP, Organic Anion Transporting Polypeptide.
U.S. Prescribing Information.

Treatment Failure

- Approximately 50% of patients discontinue ruxolitinib after 3 years, mostly due to disease progression, suboptimal response or cytopenia
- Definitions of “ruxolitinib failure” include:
  - Disease progression to accelerated or blast phase
  - Suboptimal response of spleen or constitutional symptoms
  - Increases in splenomegaly or constitutional symptoms after initial response
  - Development of transfusion-dependent anemia or grade 3/4 thrombocytopenia or hemorrhagic events
- Outcome after ruxolitinib discontinuation is poor with a median OS of approximately 14 months
- Patients with ≥ 3 non-driver gene mutations generally have a shorter time-to-discontinuation

Kvasnicka H. *Lancet Haematol*. 2017;4(7):e305-e306. Harrison CN, et al. *Annals of Hematology*. 2020;99(6):1177-1191. Gupta V, et al. *JCO Oncology Practice*. 2020;16(7):351-359. Newberry KJ, et al. *Blood*. 2017;130(9):1125-1131. Palandri F, et al. *Cancer*. 2020;126(6):1243-1252. Patel KP, et al. *Blood*. 2015;126(6):790-797.

MANIFEST: Pelabresib in Combination With Ruxolitinib for JAK Inhibitor Treatment-Naïve MF

- JAK inhibitors can result in spleen response rates of 30%-40%, high discontinuation rates, and a lack of disease modification
- Combination of the BET inhibitor pelabresib with ruxolitinib in JAK inhibitor-naïve patients with MF was well tolerated with durable improvements in spleen and symptom burden, with associated biomarker findings of potential disease-modifying activity
  - At 24 weeks, 68% (57/84) achieved SVR35
  - Additionally, 56% (46/82) achieved a TSS50
- Grade 3 or 4 toxicities seen in ≥ 10% patients
  - Thrombocytopenia (12%)
  - Anemia (35%)

SVR35, spleen volume reduction of ≥ 35%; TSS50 , total symptom score reduction of ≥ 50% .
Mascarenhas J, et al. *J Clin Oncol.* 2023 Nov 10;41(32):4993-5004.

Combination of Navitoclax and Ruxolitinib in JAK Inhibitor-Naïve Patients with MF

- Ruxolitnib improves splenomegaly and disease symptoms but has limited impact on disease biology
- Combination of navitoclax and ruxolitinib reduced splenomegaly in several high-risk groups known to confer poor prognosis
  - SVR35 at week 24 was observed in all subgroups known to confer poor prognosis
    - Age (≥75 years, 50% [n = 4/8])
    - High DIPSS score (Intermediate-2, 63% [n = 12/19]; high, 33% [n = 1/3])
    - HMR mutations (47% [n = 9/19]
  - Complete resolution of BMF was observed in 2/9 (22%) patients
  - Reduction in JAK2V617 mutation VAF > 20% from baseline at week 12 or 24 was observed in 50% (14/28) of patients

BMF, bone marrow fibrosis; SVR35, spleen volume reduction of ≥ 35%; VAF, variant allele frequency.

Passamonti F, et al. *Blood* 2022; 140 (Supplement 1): 583–585.

Accounting for Patient Quality of Life Based on MF- and Treatment-Related Factors:

Increasing Familiarity with Disease- and Treatment-Related Adverse Events

Considerations of JAK inhibitors

JAK inhibitors have led to significant advances in MF symptom control but have limitations

- These agents have limited tolerability
- They do not modify the natural history of MF for most patients
  - Concern for leukemia transformation remains
- Hematologic side effects are often dose-limiting and lead to discontinuation
  - Cytopenias, disease progression, and unsatisfactory therapeutic effect

There is a need to identify patients who could benefit from other treatments such as clinical trials or transplant

- Other JAK inhibitors in clinical trials include itacitinib, jaktinib

Bose P & Verstovsek S. *Hemasphere*. 2020 Jul 21;4(4):e424. National Library of Medicine. ClinicalTrials.gov. https://clinicaltrials.gov/.

Burden of Anemia in Myelofibrosis

Anemia may be influenced by primary versus secondary MF

- Prevalence of 35–38% in patients with MF
- In a study of patients after the 1st year after diagnosis, 64% were anemic and 45% required RBC transfusions

JAK inhibitors may induce or worsen related anemia

Multiple factors contribute to the development of anemia in MF

Anemia profoundly impacts patient quality of life

- Red blood cell transfusion dependence
- Chronic anemia associated with fatigue, excess morbidity, cardiovascular mortality, and iron overload

Presence of anemia can be used to determine patient prognosis

- Red blood cell transfusion dependence
- Chronic anemia associated with fatigue, excess morbidity, cardiovascular mortality, and iron overload

Passamonti F, et al. *Crit Rev Oncol Hematol*. 2022 Dec;180:103862.

Burden of Splenomegaly in Myelofibrosis

Symptoms resulting from splenomegaly include abdominal pain, left subcostal pain, abdominal fullness, and early satiety

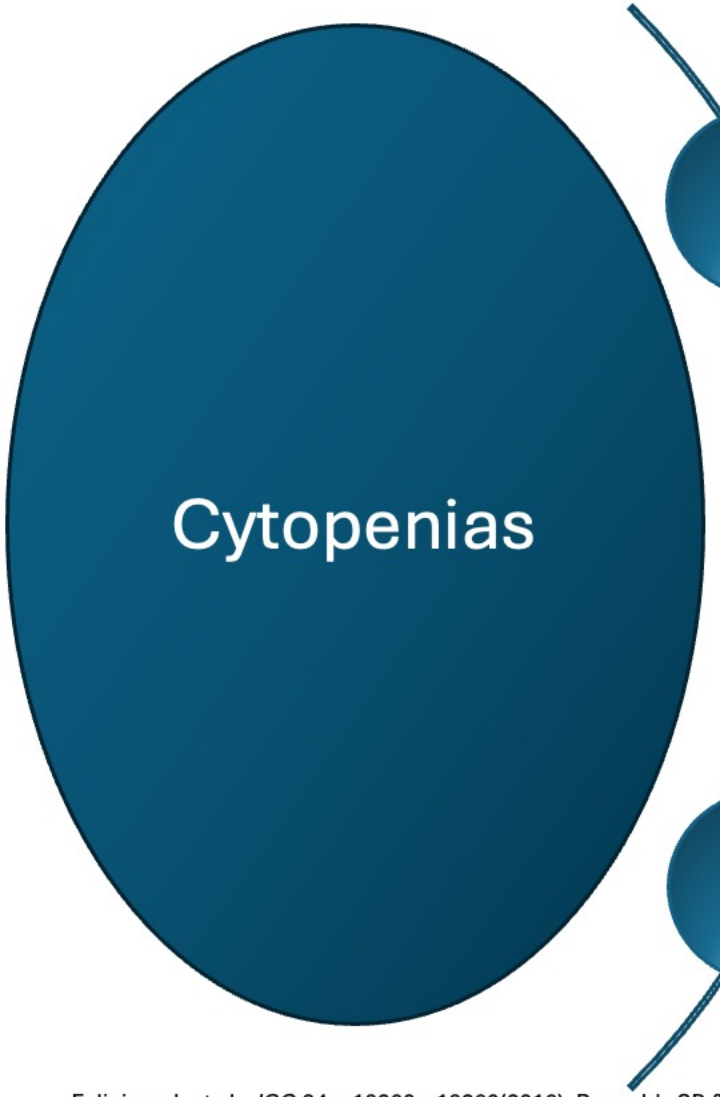
- Complications can lead to clinical manifestations of portal hypertension and bleeding from esophageal varices
- The bulk of the spleen can result in areas of ischemia and painful episodes of splenic infarction
- Splenomegaly can result in development (or exacerbation) of cytopenias from splenic sequestration

In one study, palpable splenomegaly was observed in 80% of asymptomatic patients

- About 10% of patients with MF showed severe symptomatic splenomegaly

Song MK, et al. Int J Mol Sci. 2018 Mar 18;19(3):898. Mitra D, et al. Cancer Med. 2013 Dec;2(6):889-98. Ruben A. Mesa. Blood 2009; 113 (22): 5394–5400.

Burden of Cytopenias in Myelofibrosis



Presence of cytopenias in MF can lead to the following outcomes:

- Low platelets, anemia, normal to low WBC
- High risk scores and molecular risk
- Increased blasts and marrow fibrosis
- Worse overall survival
- High leukemic transformation risk
- Fewer treatment options the more severe the cytopenias

Emerging non–JAK inhibitors carry a risk of hematologic toxicities and tend to exclude patients with baseline thrombocytopenia

High prevalence of cytopenias in MF force a significant resource burden to the healthcare system

- Inpatient costs are the major cost driver

Feliciano J, et al.. *JCO* 34, e18260-e18260(2016). Reynolds SB & Pettit K. *Hematology Am Soc Hematol Educ Program* 2022; 2022 (1): 235–244.

Accounting for Patient Quality of Life Based on MF- and Treatment-Related Factors:

Establishing Trust with Patients to Improve Outcomes and Quality of Life

Goals of Myelofibrosis Therapy

Curative

Allogeneic stem cell Transplantation

•

Based on prognostic scores and patient eligibility

•

Psychosocial Evaluation
Institutional criteria

Symptomatic

FDA approved JAK inhibitors

Cytopenia directed

Improve blood counts

Ali H, Bacigalupo A. *Am J Hematol*. 2021 Nov 1;96(11):1532-1538.

Effective Strategies for Shared Decision-Making in MF Care:

Finding Value in Shared Decision-Making and the Unique Role of Multidisciplinary Teams

Shared Decision-Making Between Clinical Staff and the Patient

Joint process between healthcare providers and patients based on evidence-based information and a patient's preferences, beliefs, and values

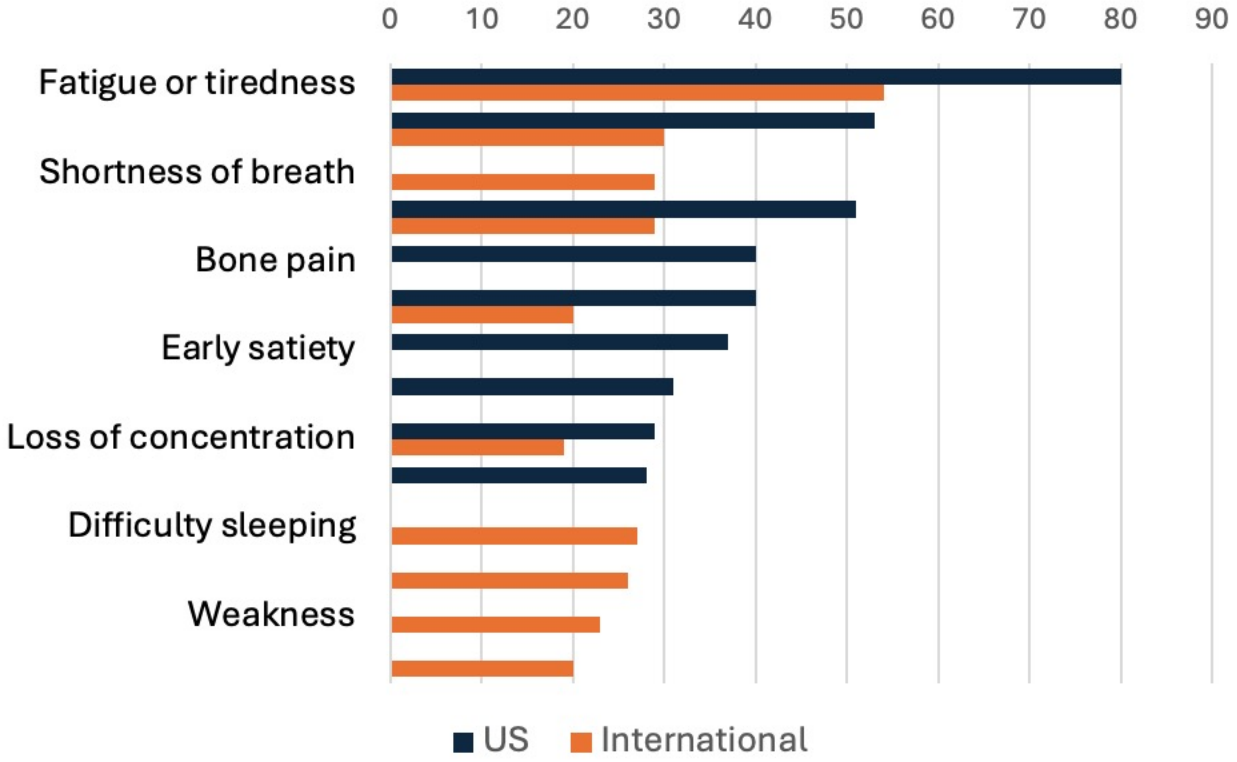
- Outcomes
- Benefits
- Harms
- Uncertainties

Empowers patients to make decisions about the treatment and care that is right for them at that time, including choosing to continue with their current treatment or choosing no treatment at all

Truglio-Londrigan M, Slyer JT. *Open Nurs J*. 2018 Jan 22;12:1-14.

High Burden of MF Symptoms Impacts Patient Quality of Life

Symptom prevalence (%) among patients with MF in the US[1] and International MPN Landmark Surveys[2]



Characteristics of Patients with MF

- **US survey[1]**
  - Patients (n = 207) surveyed May-July 2014
  - Median age: 66 years (range 28-90)
  - Median disease duration: 4 years (range 0-36)
  - Most patients (71%) had intermediate-2 or high-risk disease by DIPSS
- **International survey[2]**
  - Patients (n = 174) from Australia, Canada, Germany, Italy, Japan, and the UK surveyed April-October 2016
  - Median age: 59.6 years (range 28-89)
  - Median disease duration: 4 years (range 0-81)
  - 42% intermediate or high risk respondents; risk status unknown in 43%

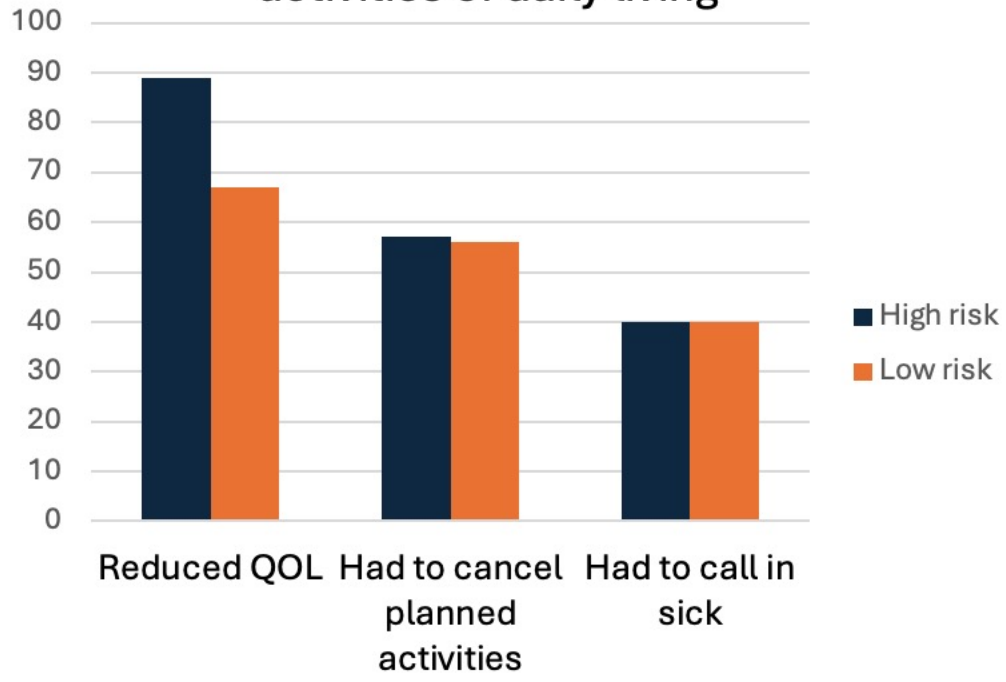
MPN, myeloproliferative neoplasms

1. Mesa R, et al. *BMC Cancer*. 2016;16:167. 2. Harrison CN, et al. *Ann Hematol*. 2017;96(10):1653-1665.

MF Impact on Quality of Life and Employment

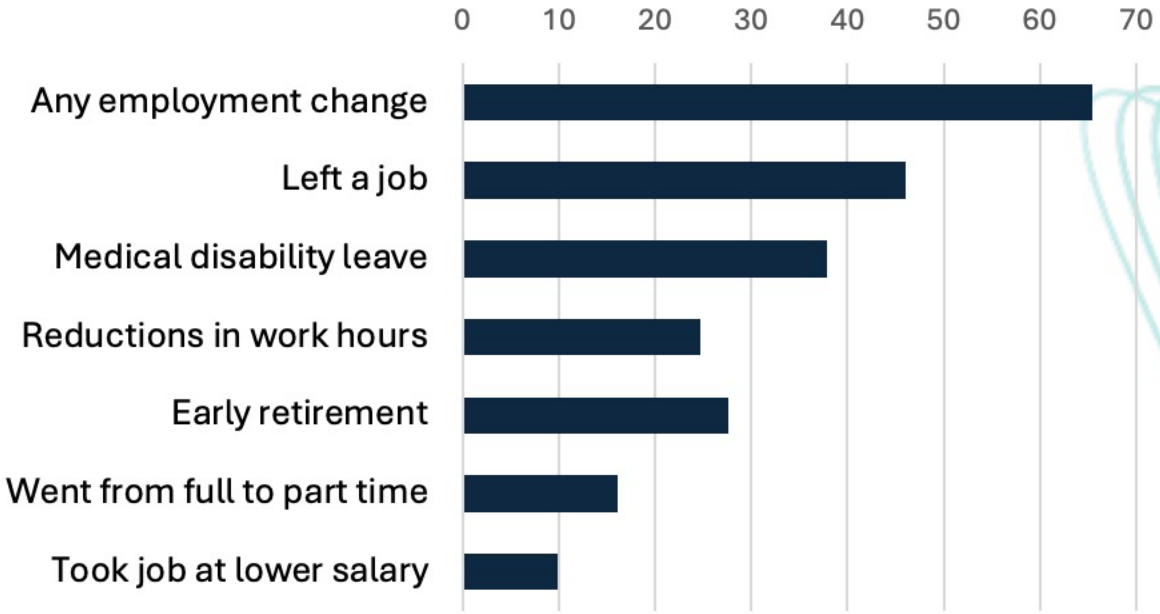
MPN Landmark Survey (US)[1]

Even low risk disease has an impact on QoL and activities of daily living



Living with MPNs Survey (US)[2]

MF has a high impact on employment status and work productivity



MPN, myeloproliferative neoplasms; QOL, quality of life.

1. Mesa R, et al. *BMC Cancer*. 2016;16:167. 2. Yu J, et al. *BMC Cancer*. 2018;18(1):420.

Patient and Provider Perspectives on Treatment Goals

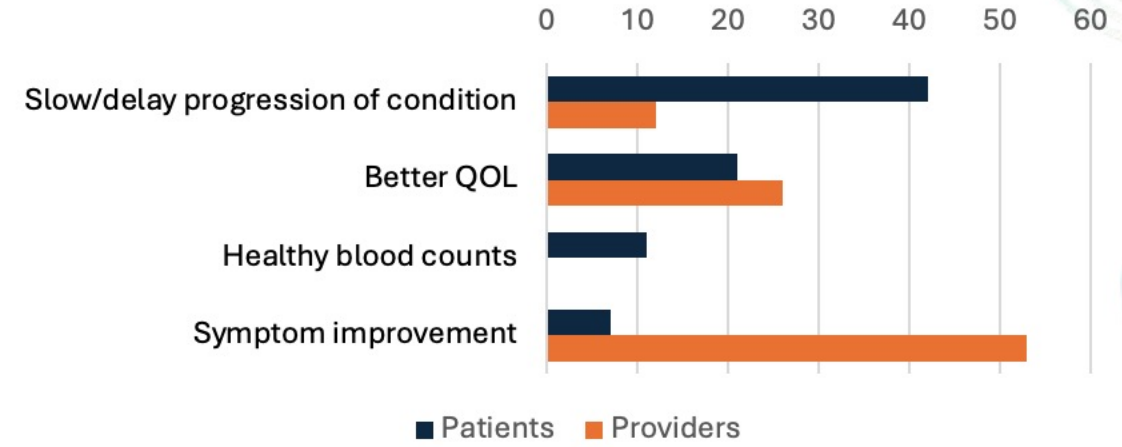
Patient and provider goals are discordant

- Patients' top goal is to slow or delay disease progression
- Providers' top goal is to improve symptoms

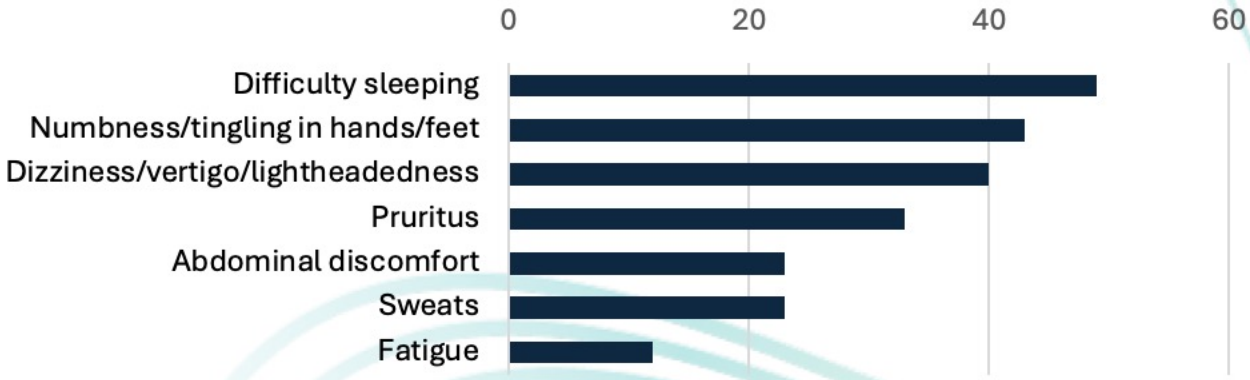
Patients often fail to recognize symptoms related to their MF

- Suggests a need for improved patient education and formal shared decision-making

"Other than a cure, what is your most important treatment goal for therapy?"



Proportion of patients who selected each goal (%)



QOL, quality of life.
Mesa R, et al. *BMC Cancer*. 2016;16:167.

Use of Interdisciplinary Teams to Address Healthcare Barriers and Quality of Life

SDOH and healthcare inequities considerations

Patient symptoms and treatment-emergent adverse events

SHARE Model for Shared Decision-Making

Seek your patient's participation

Help your patient explore and compare treatment options

Assess your patient's values and preferences

Reach a decision with your patient

Evaluate your patient's decision

Hargraves IG, et al. *Patient Educ Couns*. 2020;103(10):2192-2199.

Advocating for Patients as the Nursing Professional

Nurses are uniquely positioned to enhance the quality of health care for patients with MF in the following ways:

- Guide patients through all facets of the healthcare system
- Offer continuous monitoring and follow-up throughout the care continuum
- Provide effective care management
- Ensure person-centered approaches

- Address holistic needs of individuals
- Deliver culturally respectful and appropriate care
- Break down barriers to quality care including structural inequities and implicit bias

National Academies of Sciences, Engineering, and Medicine; National Academy of Medicine; Committee on the Future of Nursing 2020–2030; Flaubert JL, Le Menestrel S, Williams DR, et al., editors. The Future of Nursing 2020-2030: Charting a Path to Achieve Health Equity. Washington (DC): National Academies Press (US); 2021 May 11. 4, The Role of Nurses in Improving Health Care Access and Quality. Available from: https://www.ncbi.nlm.nih.gov/books/NBK573910/.