Management of Ruxolitinib-Refractory Myelofibrosis.

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Objectives

- Review the epidemiology, pathophysiology, clinical presentation, and diagnostic criteria for primary myelofibrosis (PMF)
- Identify ruxolitinib's current role in therapy, as well as considerations when evaluating ruxolitinib responsiveness
- Identify and summarize literature of alternative FDA approved JAK inhibitor therapies for myelofibrosis
- Explore the role of pharmacists in monitoring and supporting patients with myelofibrosis

Historical Review

1879

- First description of myelofibrosis

'Two cases of leukemia with peculiar blood and bone marrow findings'
-- Gustav Heuck (1854 – 1940)

1905 – 1930

- Published reports describing massive splenomegaly, myeloid metaplasia, and osteosclerosis

1951

- William Damashek coins the term 'myeloproliferative disorders'

Suggested PV, CML, and myeloid metaplasia are closely related

1975

- Silverstein establishes idiopathic myelofibrosis as a chronic MPN

2005

- ***Discovery of JAK2^{V617F}***

PV: polycythemia vera
CML: chronic myelogenous leukemia
MPN: myeloproliferative neoplasm

Tefferi A. *Leukemia*. 2008;22(1):3-13.
Weinstein IM. *Blood Rev*. 1991;5(2):98-104.

Slide originally created by: Carissa Ganihong, PharmD – 2023

Epidemiology: Myelofibrosis

~13,000 cases in the United States

Can either be primary myelofibrosis (PMF) or secondary myelofibrosis

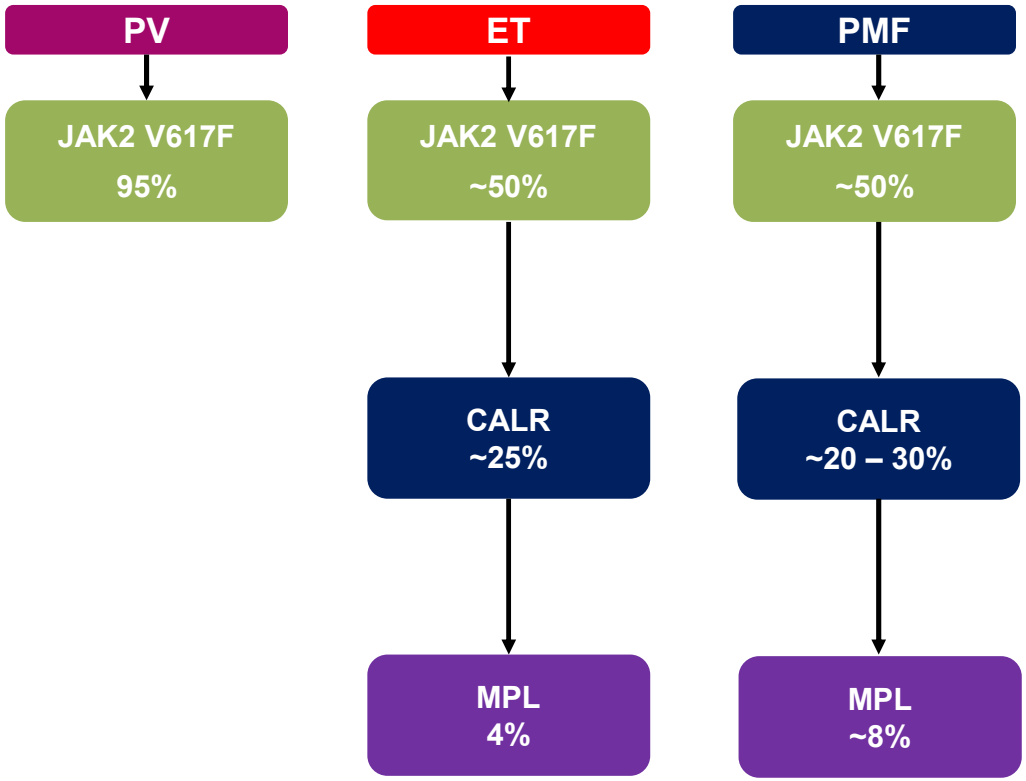
- Transformation from polycythemia vera
- Transformation from essential thrombocythemia

Morbidity and mortality

- Cardiovascular complications
- Infectious complications
- Bleeding/hemorrhaging
- Transformation to acute leukemia (MPN-blast phase (BP))

NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated December 2023
Tefferi A. *Am J Hematol*. 2021;96(1):145-162.

Driver Mutations in Myelofibrosis and MPNs



- Three primary somatic function mutations associated with MPNs
  - *JAK2*
  - *CALR*
  - *MPL*
- Estimated that 90% of patients with myelofibrosis will have a mutation in at least one of the 3 driver mutations
- Importance of mutations
  - Diagnostics
  - Prognosis
  - Does **not** impact treatment decisions

Dysregulated JAK/STAT Pathways

- Overactivation of the JAK/STAT pathway leads to an overproduction of inflammatory cytokines and increased clonal proliferation of inflammatory cells
- Overtime, persistent inflammation leads to bone marrow fibrosis and, ultimately, bone marrow failure

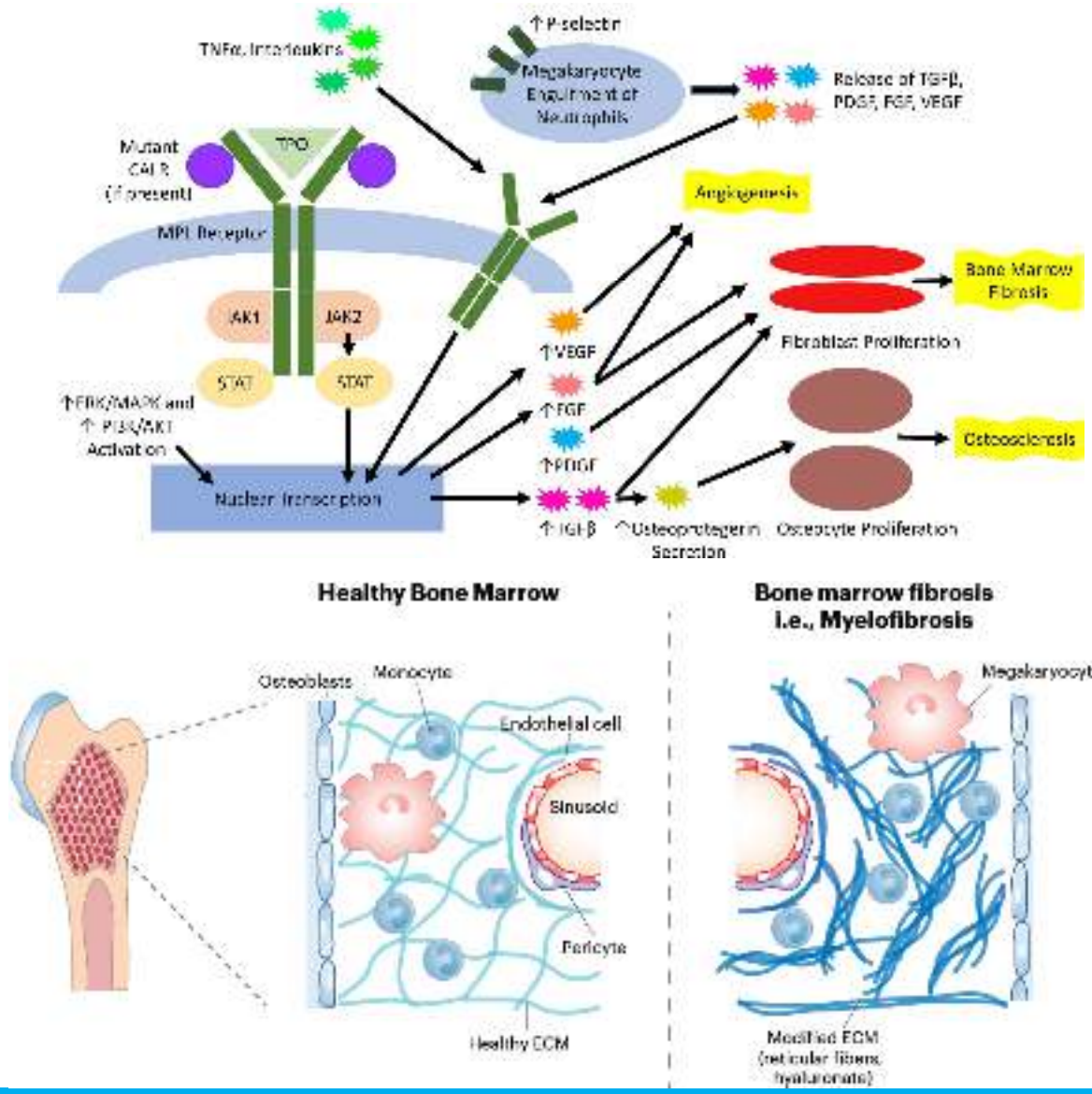
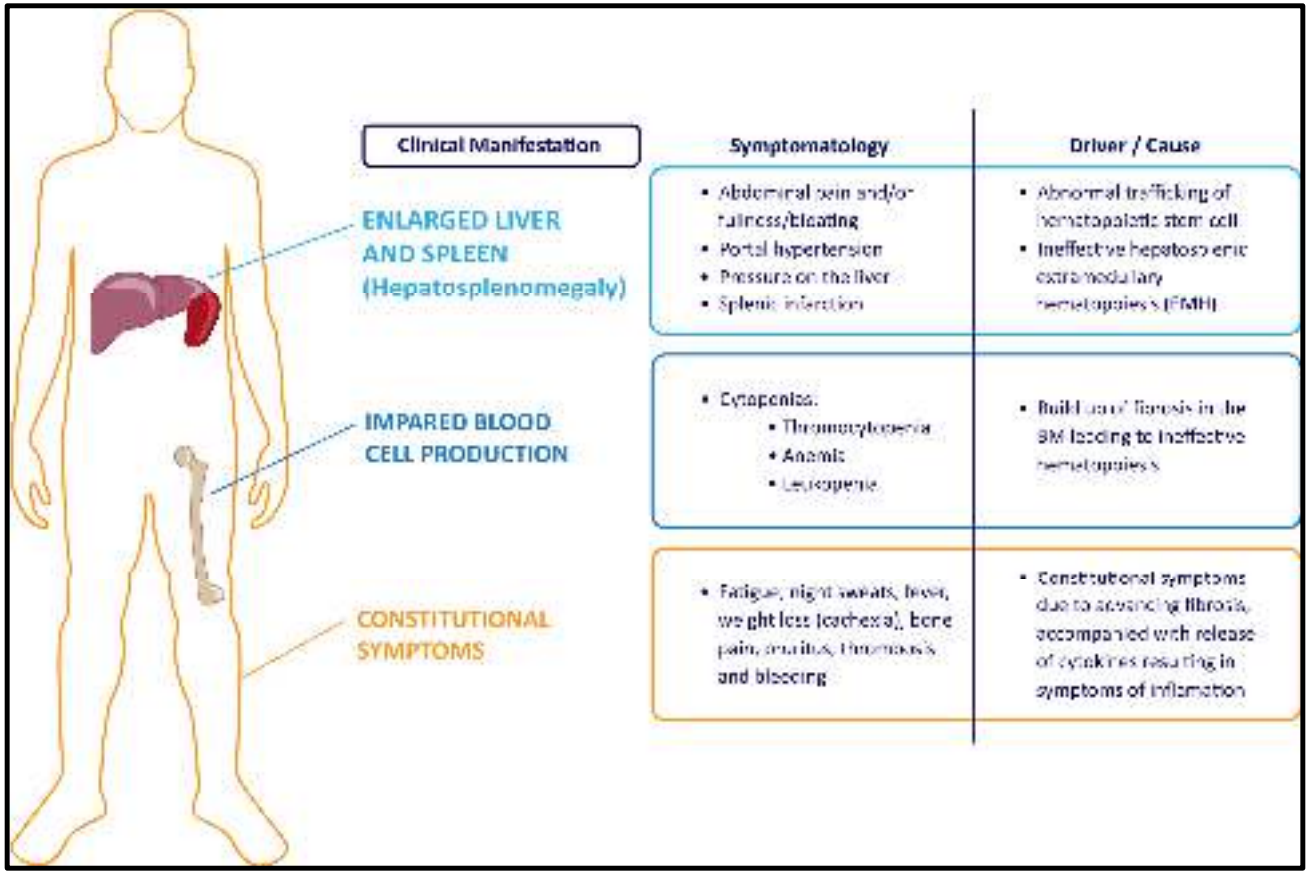


Image retrieved from: Garmezy B, Schaefer JK, Mercer J, Talpaz M. *Blood Rev*. 2021;45:100691.
Image retrieved from: https://penntoday.upenn.edu/news/deconstructing-mechanics-bone-marrow-disease,

Clinical Presentation of Myelofibrosis



- The primary presenting symptom of myelofibrosis is **splenomegaly**, in the presence or absence of other **constitutional symtoms**
- It is estimated that ~30% of patients may be asymptomatic at presentation
  - Abnormal lab work
  - Abnormal scan/imaging

NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated: December 2023
Image retrieved from: https://abbviescience.com/oncology/tumor-types/myelofibrosis.

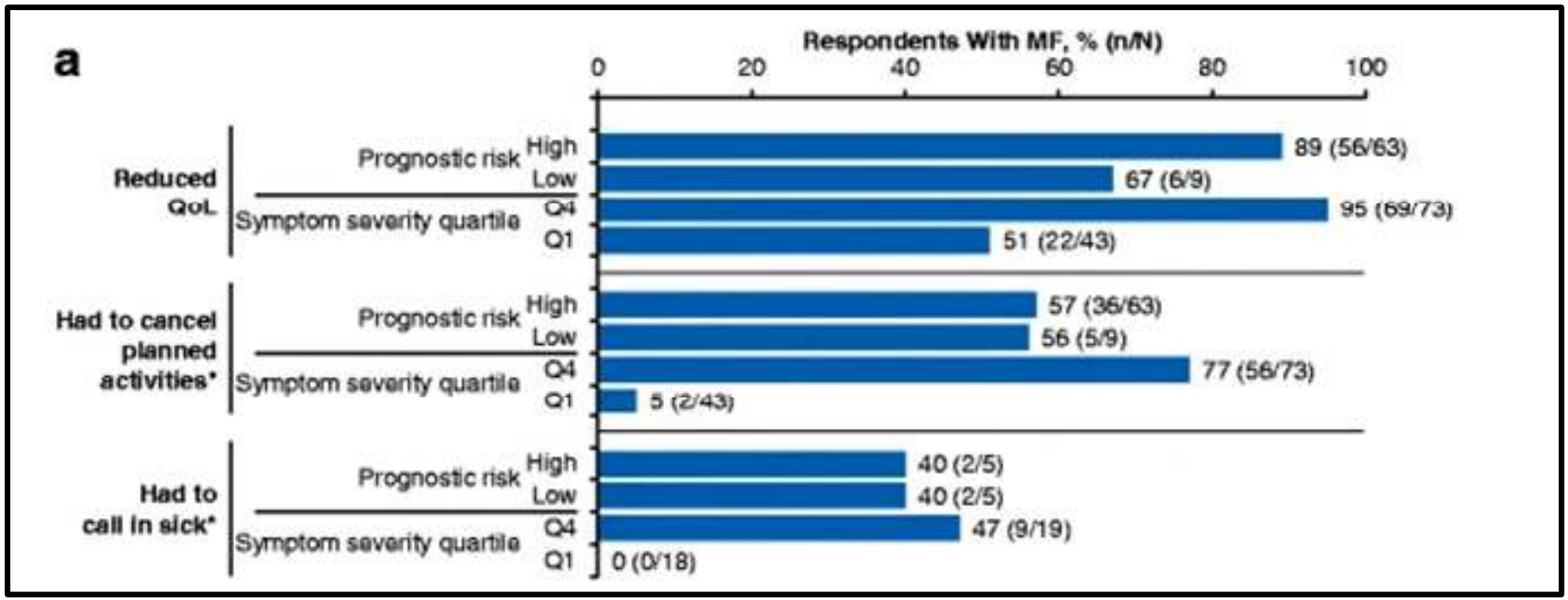
Morbidity Associated with Myelofibrosis

MPN Landmark Survey in MPN/Myelofibrosis Patients:

- **47%** Fatigue as the #1 symptom patients wanted resolved
- **81%** Symptoms reduced their quality of life (QoL)
- **53%** Disease interfered with daily activities
- **31%** Voluntarily terminated job
- **75%** Reported feeling depressed and/or 43% reported feeling angry

Mesa R, Miller CB, Thyne M, et al *BMC Cancer*. 2016;16:167. Published 2016 Feb 27.

Impact on Patient Quality of Life



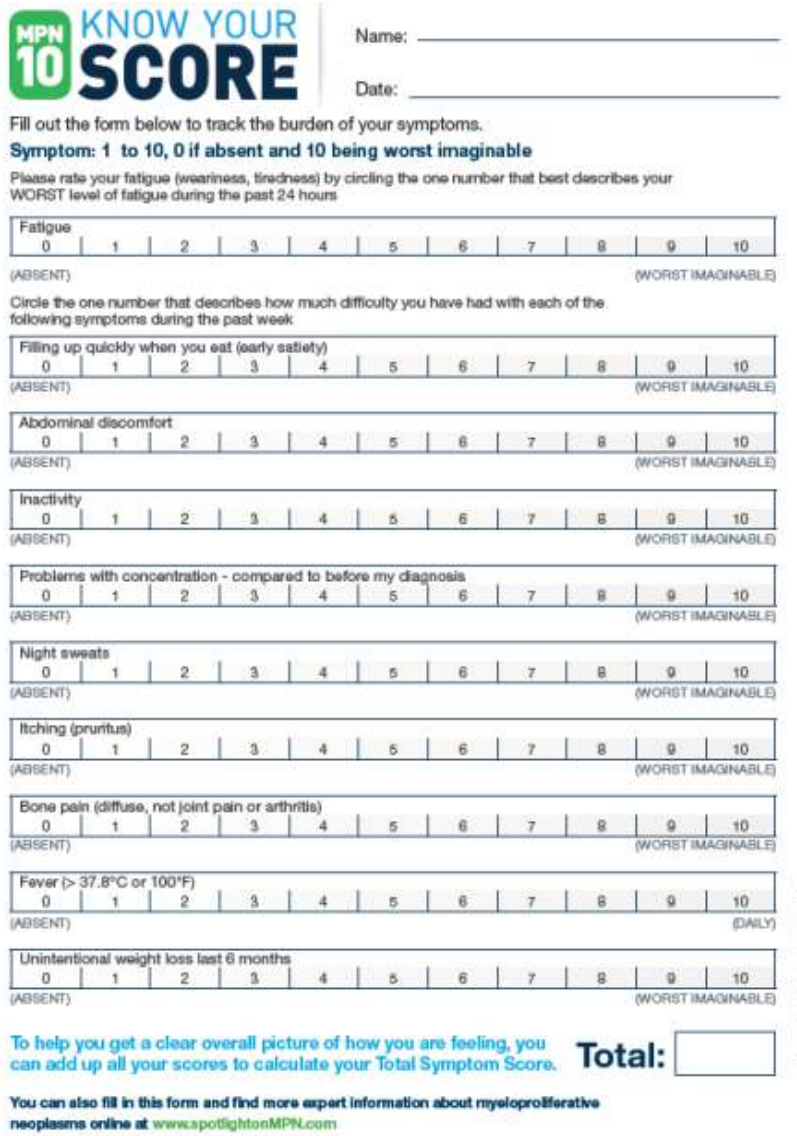
Mesa R, Miller CB, Thyne M, et al *BMC Cancer*. 2016;16:167. Published 2016 Feb 27.

Symptom Assessment in Myelofibrosis

- Several models have been developed as a means of standardizing symptom assessment in patients with MF
  - MFSAF
  - MPN-SAF TSS (pictured to right)

- **<u>MPN-SAF TSS</u>**
  - 10 item-questionnaire which evaluates the most common symptoms with MF
  - Fatigue, inactivity, early satiety, itching, fevers, etc.

- Important to check which scoring tool patients are using/previously using!



MPN 10 KNOW YOUR SCORE

Name: _____

Date: _____

Fill out the form below to track the burden of your symptoms.

Symptom: 1 to 10, 0 if absent and 10 being worst imaginable

Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during the past 24 hours

Fatigue											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

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

Filling up quickly when you eat (early satiety)											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

Abdominal discomfort											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

Inactivity											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

Problems with concentration - compared to before my diagnosis											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

Night sweats											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

Itching (pruritus)											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

Bone pain (diffuse, not joint pain or arthritis)											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

Fever (> 37.8°C or 100°F)											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(DAILY)	

Unintentional weight loss last 6 months											
0	1	2	3	4	5	6	7	8	9	10	
(ABSENT)										(WORST IMAGINABLE)	

To help you get a clear overall picture of how you are feeling, you can add up all your scores to calculate your Total Symptom Score. **Total:** _____

You can also fill in this form and find more expert information about myeloproliferative neoplasms online at www.spotlightonMPN.com

Image retrieved from: https://mpninfo.org/wp-content/uploads/2019/03/05_Ruben-Mesa-MD-PhD-Guidelines-and-Gaps-in-MPNs.pdf

Initial Work-Up of Myeloproliferative Neoplasms

H&P
- Spleen size by palpation
- Thrombotic/hemorrhagic events
- CV risk factors
- Transfusion history

Symptom burden
- MPN-SAF TSS/ MPN-10

Labs
- CBC including differential
- CMP + uric acid, LDH
- EPO level
- Serum iron studies

Diagnostics
- FISH/RT-PCR for BCR-ABL1 (exclude CML diagnosis)
- Bone marrow biopsy/aspirate, blood smear examination
  - Cytogenetics
  - Molecular testing
    - JAK2V617F mutation -- If negative, then test for CALR and MPL mutations

Tefferi A. *Am J Hematol*. 2023;98(5):801-821

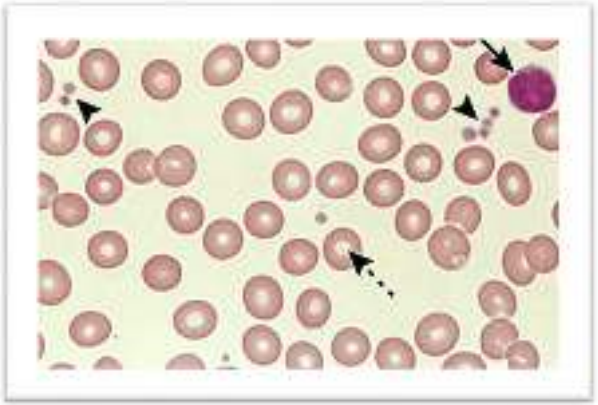
Diagnostic Criteria for Myelofibrosis

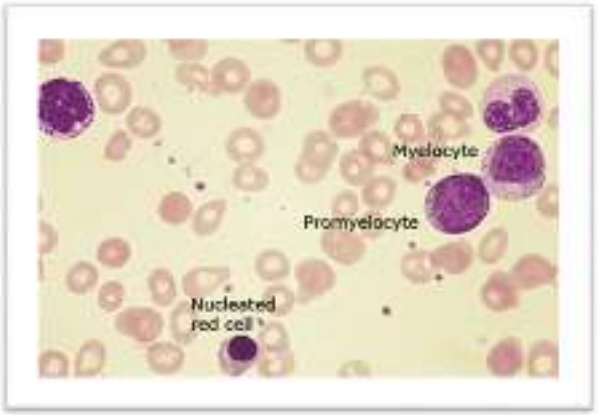
World Health Organization (WHO) Major Criteria (must meet ALL major criteria)

- Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3
- NOT meeting WHO criteria for other MPN, MDS, or other myeloid neoplasms
- Presence of JAK2, CALR, or MPL mutation or in the absence, presence of another clonal marker, or absence of reactive MF

Minor Criteria (≥ 1, confirmed in 2 consecutive determinations)

- Anemia not attributed to comorbid condition
- Leukocytosis ≥ 11 x 10^9/L
- Palpable splenomegaly
- LDH > ULN
- Leukoerythroblastosis





Tefferi A. *Am J Hematol*. 2023;98(5):801-821.
Images retrieved from: https://www.uptodate.com/contents/image/print?imageKey=HEME%2F68110

Prognostic Scoring Tools
DIPSS and DIPSS-Plus

Model	Variables Included	Risk Category and Associated Overall Survival (OS; years)			
		Low	Int-1	Int-2	High
DIPSS	• Age >65 years (1 point) • Constitutional symptoms (1 point) • Hemoglobin <10 g/dL (2 point) • Leukocytes >25 x10^9 cells/L (1 point) • Circulating blasts ≥1% (1 point)	0 points NR	1 to 2 points 14.2 years	3 to 4 points 4 years	5 to 6 points 1.5 years
DIPSS-Plus	• Age >65 years (1 point) • Constitutional symptoms (1 point) • Hemoglobin <10 g/dL (1 point) • Leukocytes >25 x10^9 cells/L (1 point) • Circulating blasts ≥1% (1 point) • Unfavorable Karyotype (1 point) • Platelet count <100x10^9 cells/L (1 point) • Transfusion needs at baseline (1 point)	0 points 15.4 years	1 point 6.5 years	2 to 3 points 2.9 years	≥4 points 1.3 years

Tefferi A/ *Am J hematol.* 2023 Mat;98(5):801-821

Treatment Principles

Current available therapies are *palliative* for myelofibrosis

- Symptom management
- Improvements in spleen volume/spleen volume response (SVR)

Allogenic stem cell transplant (AlloSCT) is the only potential cure at this time

- Associated with ~50% transplant-related morbidity/mortality
- Potential decreased patient quality of life
- Several barriers: patient comorbidities, financial, donor

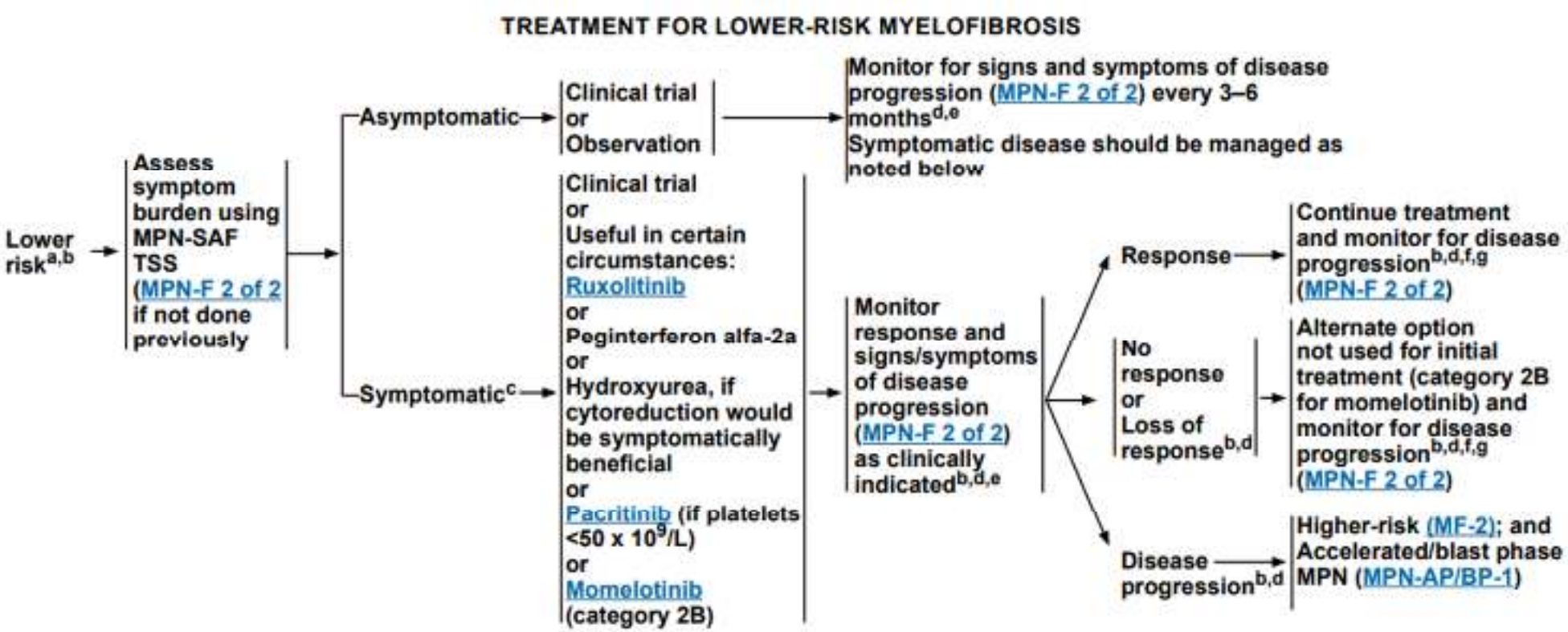
Tefferi A. *Am J Hematol*. 2021;96(1):145-162.

Supportive Care

- Transfusion Support
- Iron Overload/ Iron Chelation
- Hematopoietic Growth Factor Support
- Antimicrobial Prophylaxis
- Splenectomy Vaccines
- Cytoreductive Therapy

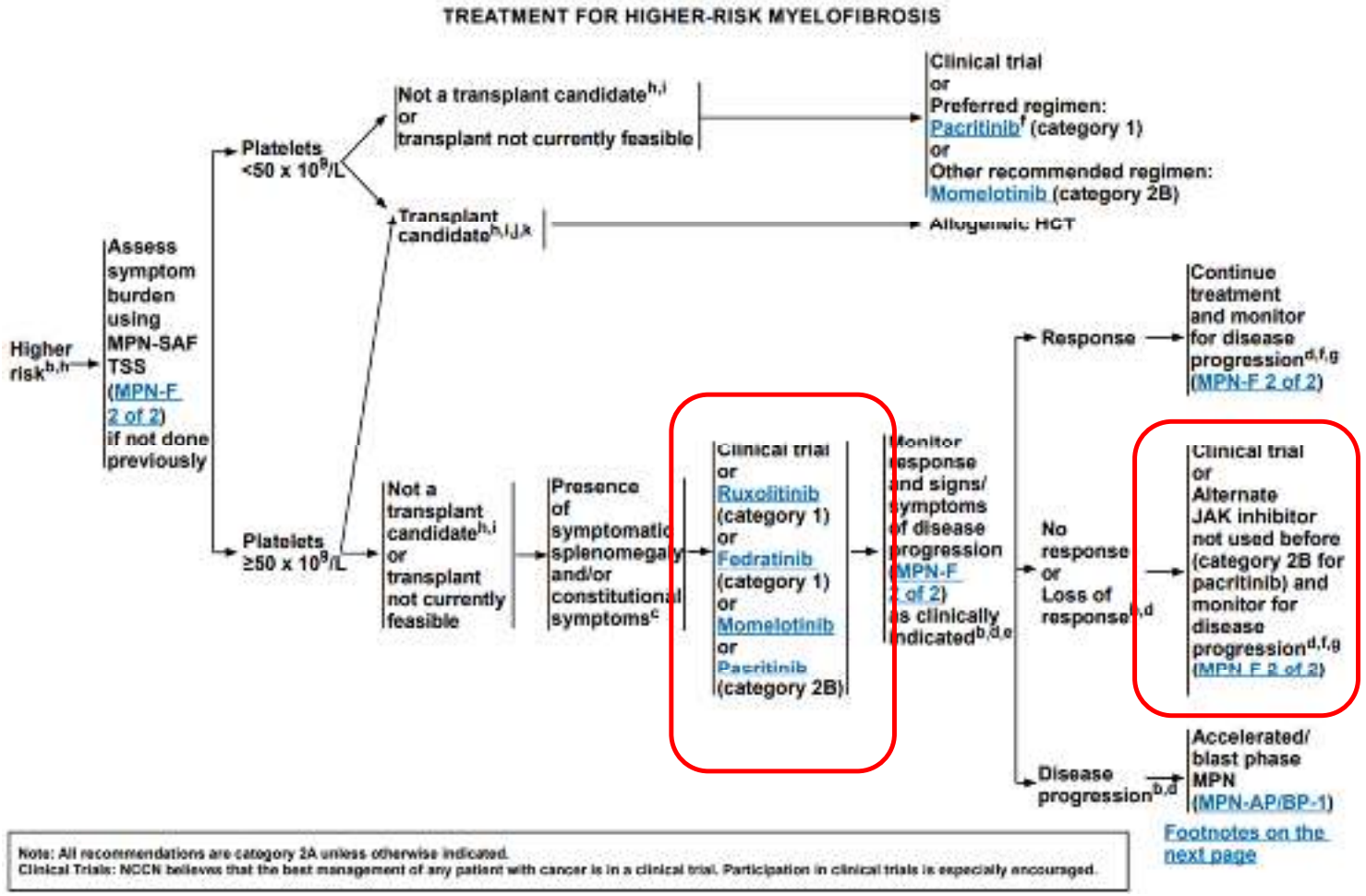
NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated December 2023

Lower Risk Myelofibrosis Recommendations



NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated: December 2023

Higher Risk Myelofibrosis Treatment Recommendations



NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated: December 2023

Ruxolitinib in Myelofibrosis

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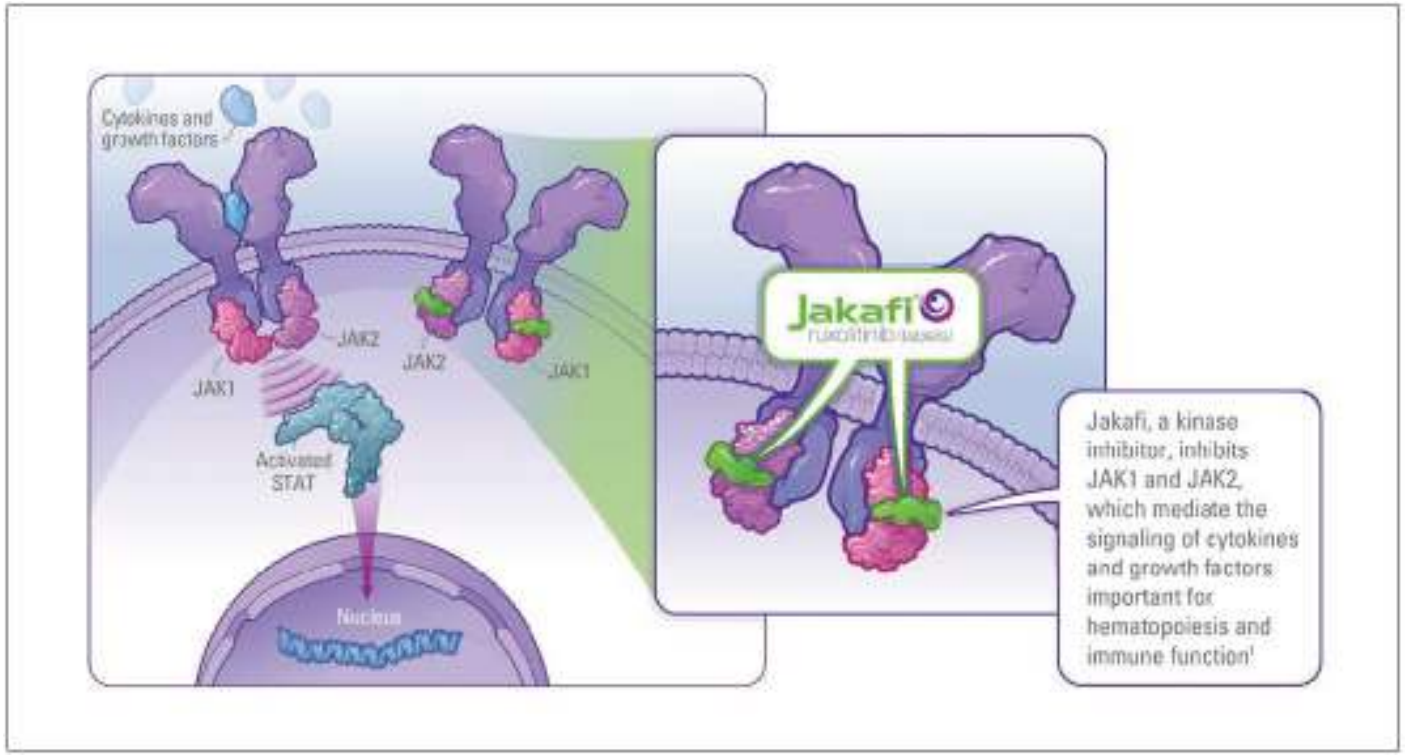
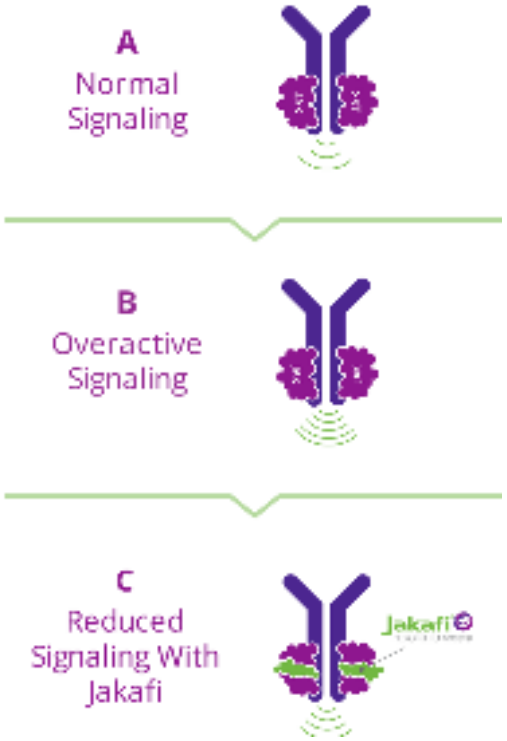
Ruxolitinib (Jakafi®)

JAK1/JAK2 Inhibitor





Images retrieved from: https://www.valuebasedcancer.com/special-issues/mechanism-of-action-magnifier-2016-desk-reference/1318-ruxolitinib-a-kinase-inhibitor-that-inhibits-overactive-jak-pathway-signalling, https://www.jakafi.com/myelofibrosis/mf-treatment

Ruxolitinib Overview

Indications	Int1-, Int-2 or high risk-myelofibrosis (including PMF, post-PV MF and post-ET MF) in adults
Dose	Initial dosing based on **platelet** count at diagnosis (Max Dose: ruxolitinib 25 mg PO twice daily) • *≥200 x 10^9/L:* 20 mg PO BID • *100 – 200 x 10^9/L*: 15 mg PO BID • *50 -- <100 x 10^9/L*: 10 mg BID
Monitoring	• CBC every 2 to 4 weeks until doses are stabilized (more frequently as clinically indicated) • Modifications and interruptions for thrombocytopenia are recommended • Lipid panel 8 to 12 weeks from start of therapy
Warnings	• Thrombocytopenia, anemia, and neutropenia • Infections (CMV, HBV, opportunistic fungal infections, PJP, PML, TB, VZV) • Ruxolitinib withdrawal syndrome (RDS) • Lipid elevations • Major adverse cardiovascular events (MACE) • Thrombosis • Secondary malignancies
Interactions	Strong CYP3A4 inhibitors
ADEs (≥15%)	Thrombocytopenia, anemia, bruising, dizziness, headache, diarrhea

Jakafi [package insert]. Wilmington, DE: Incyte Corporation; 2011.

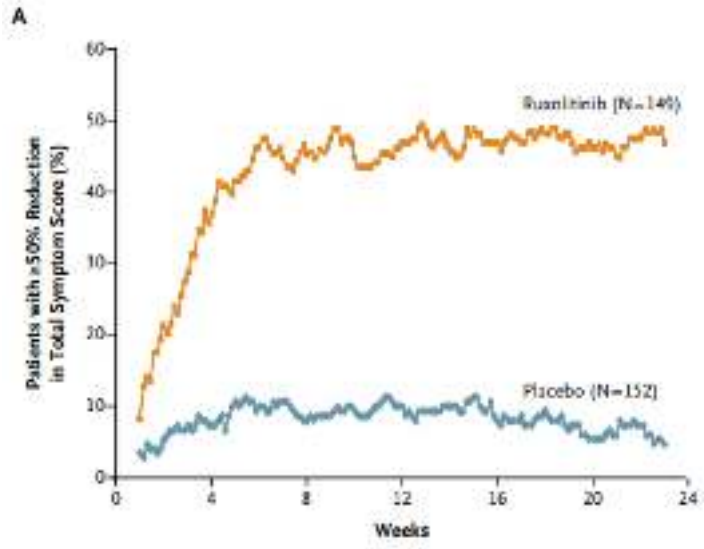
COMFORT-I – Ruxolitinib vs. Placebo

Study Design

- Phase 3, double-blind, placebo-controlled, multicenter, international study (crossover allowed)

Patient population (n=306)

- High or intermediate-2 risk
- PMF (45.2%), post-PV or post-ET MF
- Platelets > 100 x 10^9/L
- Refractory to or not candidates for available therapies



Outcomes (ruxolitinib v. placebo)

- ***≥ 35% reduction in spleen size*** **41.9%** v. 5.3%, p <0.001
- ***≥ 50% reduction of total symptom score*** **45.9%** v. 5.3%, p <0.001
- ***Improved overall survival*** **8.4%** v. 15.6% deaths , p = 0.04
- *If ruxolitinib was discontinued, symptoms returned to baseline over ~1 week*

Verstovsek S, Mesa RA, Gotlib J, et al. *N Engl J Med*. 2012;366(9):799-807

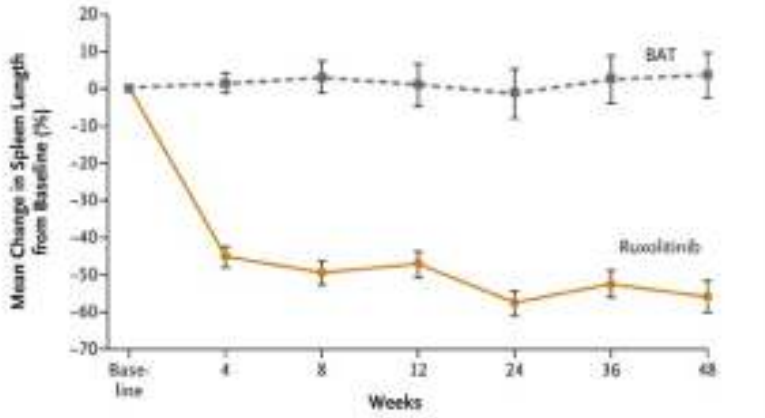
COMFORT-II – Ruxolitinib vs. Best Available Therapy (BAT)

Study Design

- Phase 3, open-label, multicenter, international study comparing ruxolitinib to best available therapy (BAT)
- crossover allowed in extension phase

Patient population (n=219)

- High or intermediate-2 risk
- PMF (53%), post-PV or post-ET MF
- Platelets > 100 x 10^9/L



Outcomes (ruxolitinib v. BAT)

- ***≥ 35% reduction in spleen size at 48-weeks*** **28% v. 0%,** p <0.001
- ***35% reduction in spleen size at 24-weeks*** **32% v. 0%,** p <0.001
- *Median time to ≥ 35% spleen reduction on MRI/CT = 12 weeks*

Harrison C, Kiladjian JJ, Al-Ali HK, et al.. *N Engl J Med*. 2012;366(9):787-798.

Ruxolitinib: Adverse Events

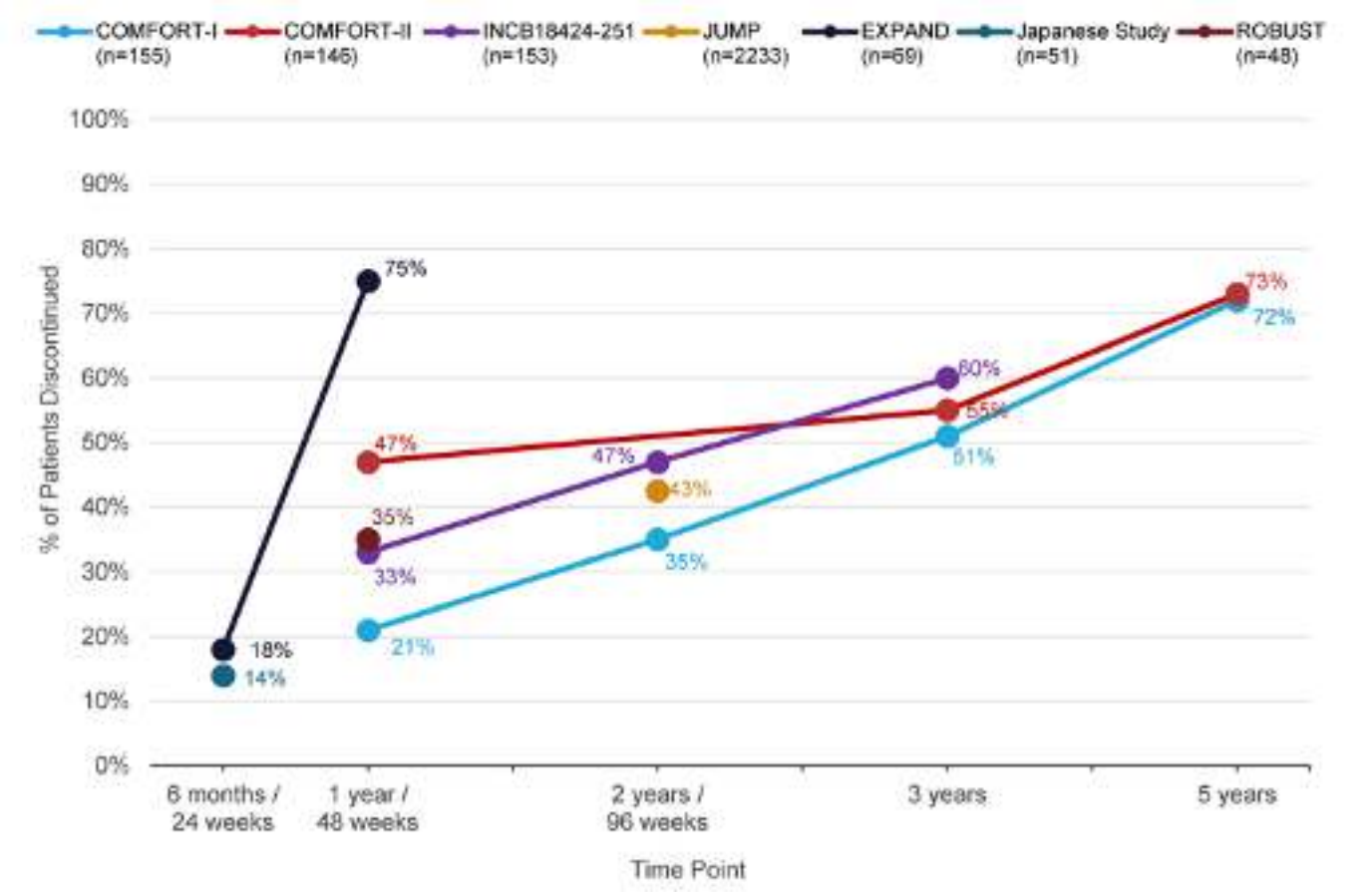
	COMFORT-I (n=155)		COMFORT-II (n=146)	
	All Grade (%)	Grade 3/4 (%)	All Grade (%)	Grade 3/4 (%)
Anemia	96.1	45.2	96	42
Thrombocytopenia	69.7	12.9	68	8
Diarrhea	23.2	1.9	23	1
Bruising	18.7	0	NR	NR
Dizziness	14.8	0.6	NR	NR
Headache	14.8	0	10	1

NR: not reported

Verstovsek S, Mesa RA, Gotlib J, et al. *N Engl J Med*. 2012;366(9):799-807
Harrison C, Kiladjian JJ, Al-Ali HK, et al.. *N Engl J Med*. 2012;366(9):787-798.

Ruxolitinib Discontinuation in COMFORT Studies

- Many patients in clinical trials permanently discontinued ruxolitinib after even just 1 year of therapy
  - Comfort-I: 21%
  - Comfort-II: 47%
- Median survival after ruxolitinib discontinuation is poor
  - ~6 months to 1 year



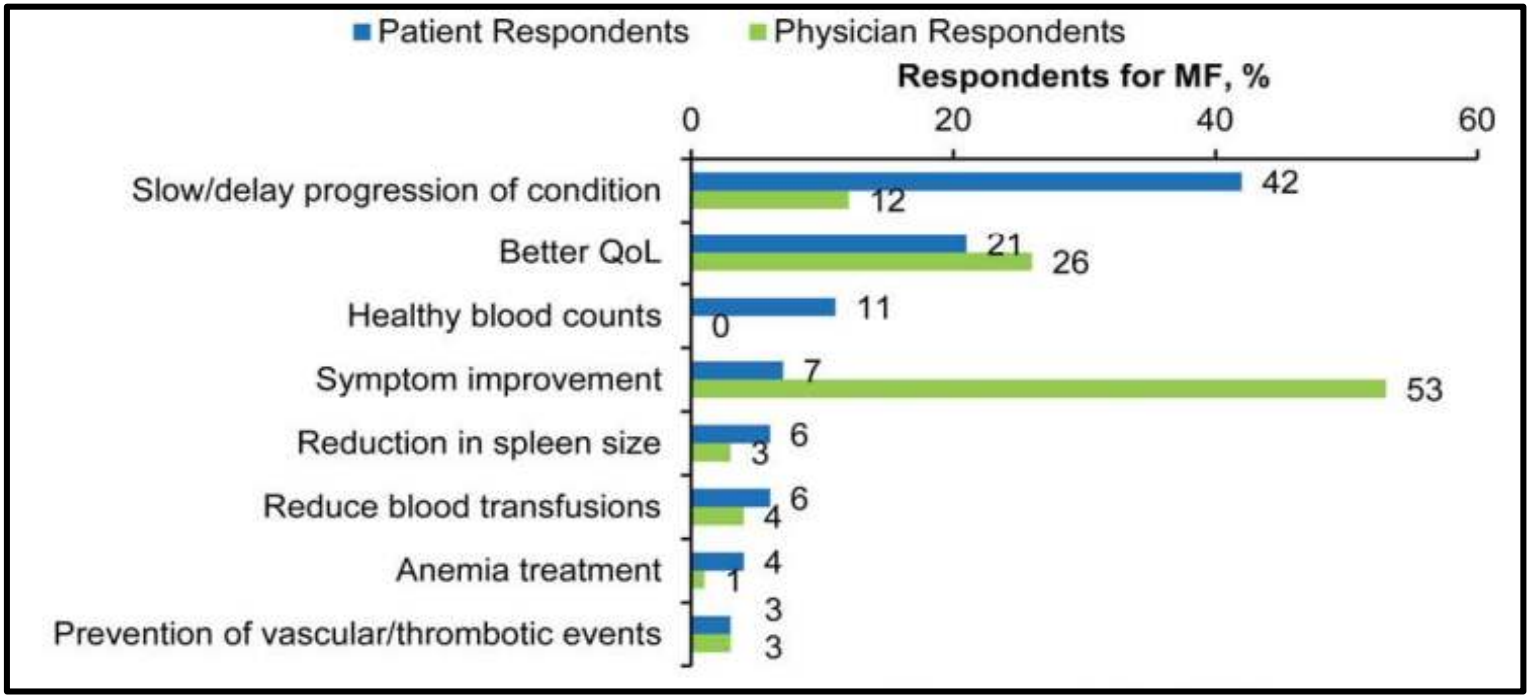
Harrison CN, Schaap N, Mesa RA. *Ann Hematol*. 2020;99(6):1177-1191

Potential Causes of Ruxolitinib Discontinuation

- **Primary resistance (Refractoriness)**
- **Secondary resistance (Splenic relapse)**
- **Disease progression**
- **Treatment-related toxicities (intolerance)**

Pardanani A, Tefferi A *Blood Cancer J*. 2014;4(12):e268. Published 2014 Dec 12.

Discordant Perceptions of Treatment Goals



- >77% of MF physician respondents reported patients “sometimes” or “often did not want to comply with physician’s primary treatment recommendations
- 30% of MF patients did not believe their physician had a treatment plan or was not providing updates on new treatments

Mesa RA, Miller CB, Thyne M, et al. *Cancer*. 2017;123(3):449-458.

Ruxolitinib Intolerance – Real-World Survey of Physician Practices

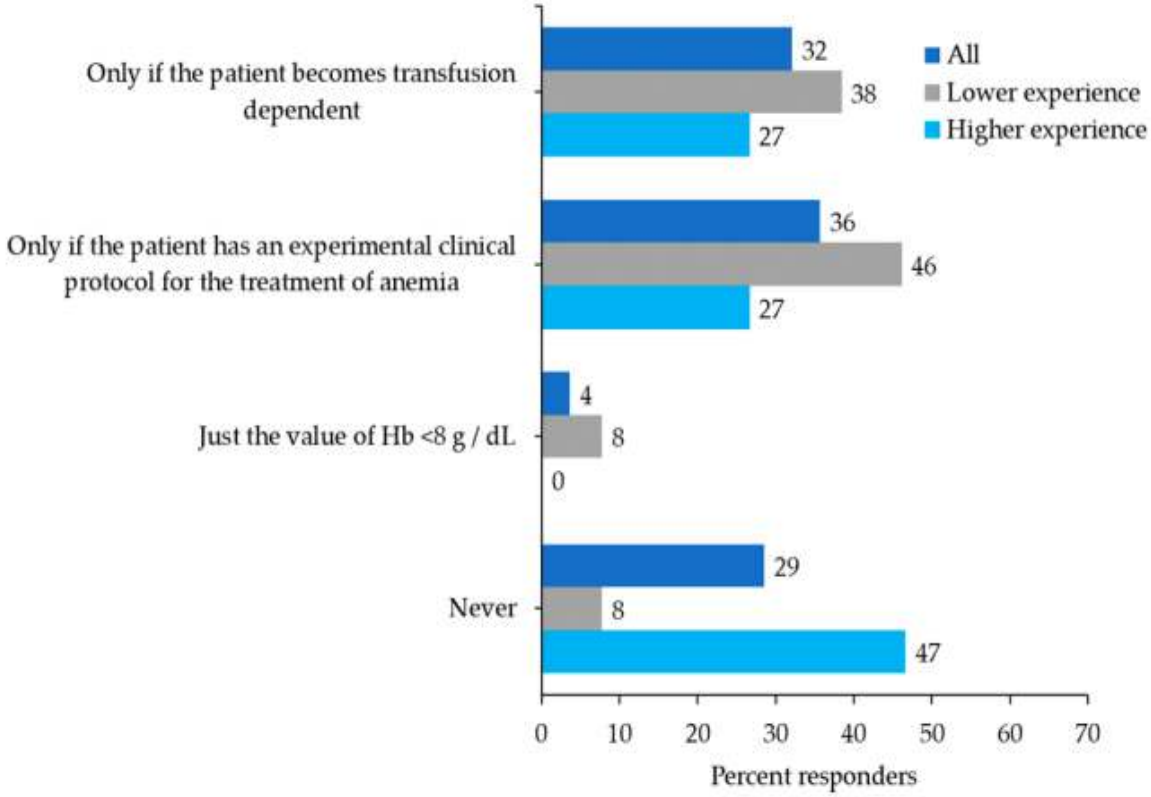
Anemia

- *In a patient with MF receiving ruxolitinib and clinical response but with anemia, when do you feel it is necessary to stop or reduce the dose of treatment?*

Thrombocytopenia

- 64% would discontinue or reduce ruxolitinib dose in patients with hemorrhagic events

Physicians' Responses to Ruxolitinib-Induced Anemia



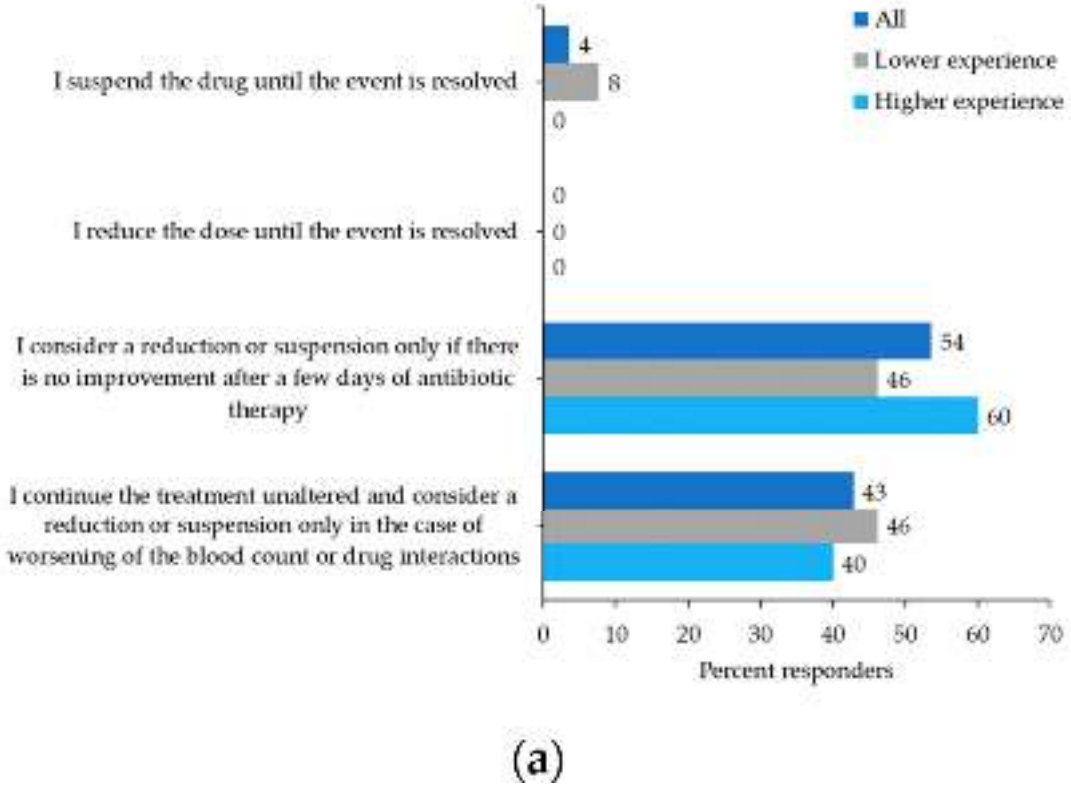
Breccia M, Palandri F, Guglielmelli P, et al *Curr Oncol*. 2022;29(7):4970-4980. Published 2022 Jul 15.

Ruxolitinib Intolerance – Real-World Survey of Physician Practices

Bacterial Infection

- *How to you manage treatment in patients with MF on stable doses of ruxolitinib who have intercurrent infectious events*

Physicians Responses to Bacterial Infection during Ruxolitinib Treatment



Breccia M, Palandri F, Guglielmelli P, et al *Curr Oncol*. 2022;29(7):4970-4980. Published 2022 Jul 15.

Ruxolitinib Failure?

No Consensus At This Time!

Source	Timeframe	Requirement
PI, NCCN	6 months	Insufficient response: failure to achieve reduction from pretreatment baseline in either palpable spleen length of 50% or a 35% reduction in spleen volume as measured by CT or MRI
Clinical Trials		
JAKARTA-2	14 days	Physician/investigator judgment
MOMENTUM	28 days	Requirement for RBC transfusions while on ruxolitinib treatment or a need to adjust dose of ruxolitinib to < 20mg BID for either > grade 3 thrombocytopenia or anemia or hematoma

Harrison CN, Schaap N, Mesa RA. *Ann Hematol*. 2020;99(6):1177-1191
NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated December 2023.

Predictors of Ruxolitinib Failure – Spleen Response

Higher risk MF	**Massive Splenomegaly**	**Transfusion-Dependency**	**Platelet count <200 x 10^9/L**
Time-interval between MF diagnosis and ruxolitinib start (> 2 years)	**Ruxolitinib ≥ second-line treatment**	**Any genotype other than JAK2V617F with ≥ 50% allele burden**	**≥ 3 mutations identified by next-generation sequencing**

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

IWG-MRT and ELN 2013 Response Criteria

Category	Required Criteria (all categories, lasting ≥12 weeks to qualify as response
Complete Response (CR)	• Bone marrow: normocellularity, <5% blasts, ≤ grade 1 MF + peripheral blood (Hgb ≥ 10 g/dL, neutrophils ≥1000 x 10^6/L, platelets > 100 x 10^9/L and <ULN + clinical resolution of symptoms
Partial Response (PR)	Complete response, except: • Hgb: 8.5 g/dL to <10 g/dL; ANC: 1000 x 10^6/L to <ULN; platelets: 50 to 100 x 10^9/L
Progressive Disease	• New splenomegaly • Increase in palpable distance of splenomegaly (based on baseline) • Leukemic transformation confirmed by bone marrow/peripheral blood blast count
Relapse	• No longer meeting criteria for CR or PR or clinical improvement • Loss of anemia response ≥1 month • Loss of spleen response ≥1 month

ANC: absolute neutrophil count; ULN: upper limit of normal

Tefferi A, Cervantes F, Mesa R, et al. *Blood*. 2013;122(8):1395-1398.

IWG-MRT and ELN 2013 Response Criteria – Symptoms

Category	Required Criteria (all categories, lasting ≥12 weeks to qualify as response
Clinical Improvement	Achievement of anemia, spleen, or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia
Symptoms response	≥ 50% reduction in MPN-SAF TSS
Spleen Response	If baseline is palpable: • 5 to 10 cm becomes not palpable OR • >10 cm decreases by ≥ 50% OR • <5 cm not eligible for spleen response Required confirmation by MRI or CT showing ≥ 35% spleen volume reduction
Anemia response	Transfusion-independent patients: ≥ 2 g/dL increase in Hgb level Transfusion-dependent: becoming transfusion-independent

Tefferi A, Cervantes F, Mesa R, et al. *Blood*. 2013;122(8):1395-1398.

Predictors of Response to Ruxolitinib After 6 Months Model (RR6)

Criteria	Points
Ruxolitinib < 20 mg BID at all time points	1
RBC transfusion requirement at 3 or 6 months	1
Palpable spleen length reduction ≤ 30% with respect to baseline at months 3 and 6	1.5
Requirement of RBC transfusion at all time points	1.5

Score	Risk	Median OS
0	Low	Not reached
1 – 2	Intermediate	61 months
3 – 4	High	33 months

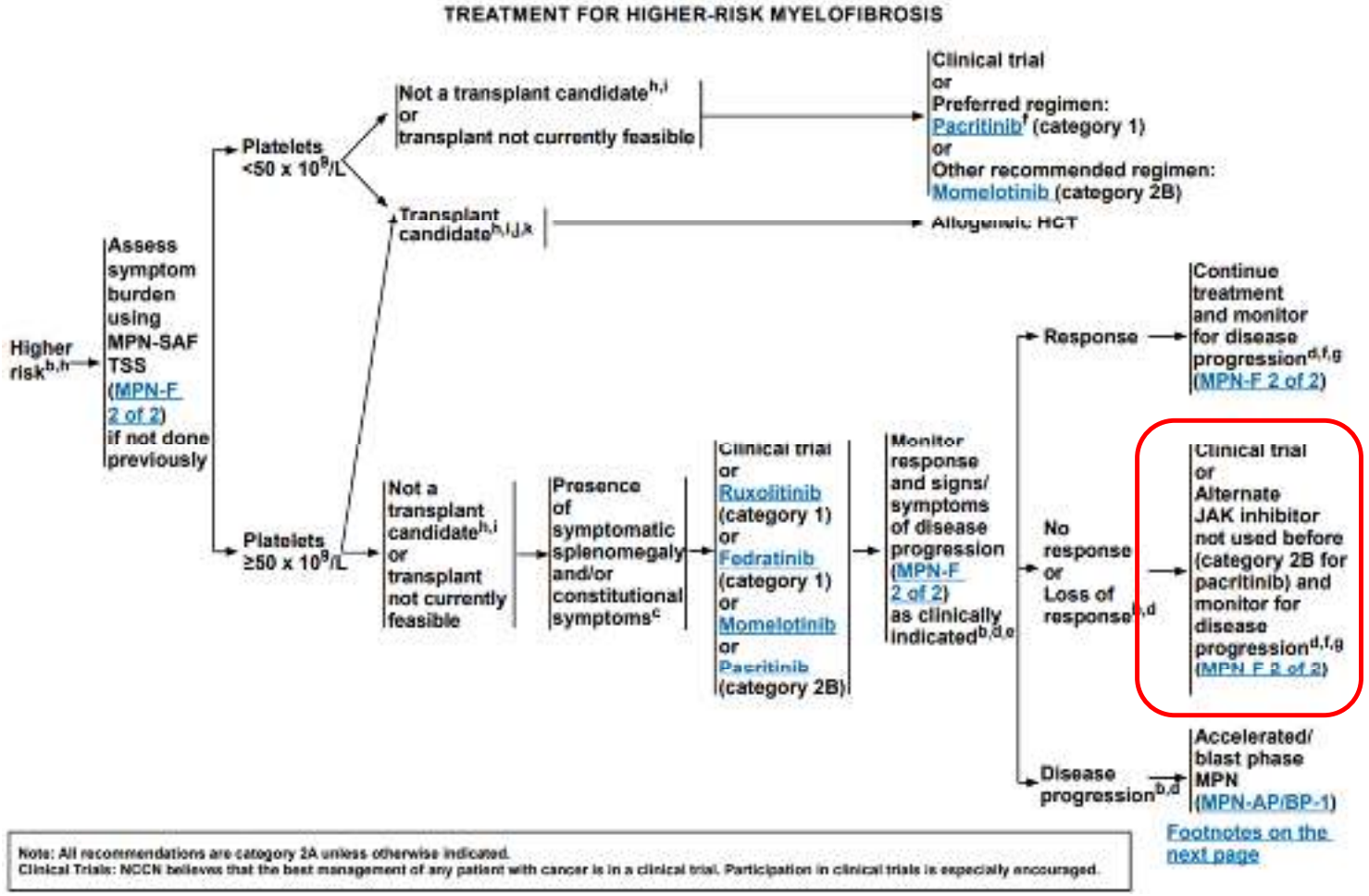
- Consider switching therapy in high risk, ideally to disease-modifying therapy (i.e transplant, clinical trial)

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

Treatment Options in The Setting of Ruxolitinib "Failure"

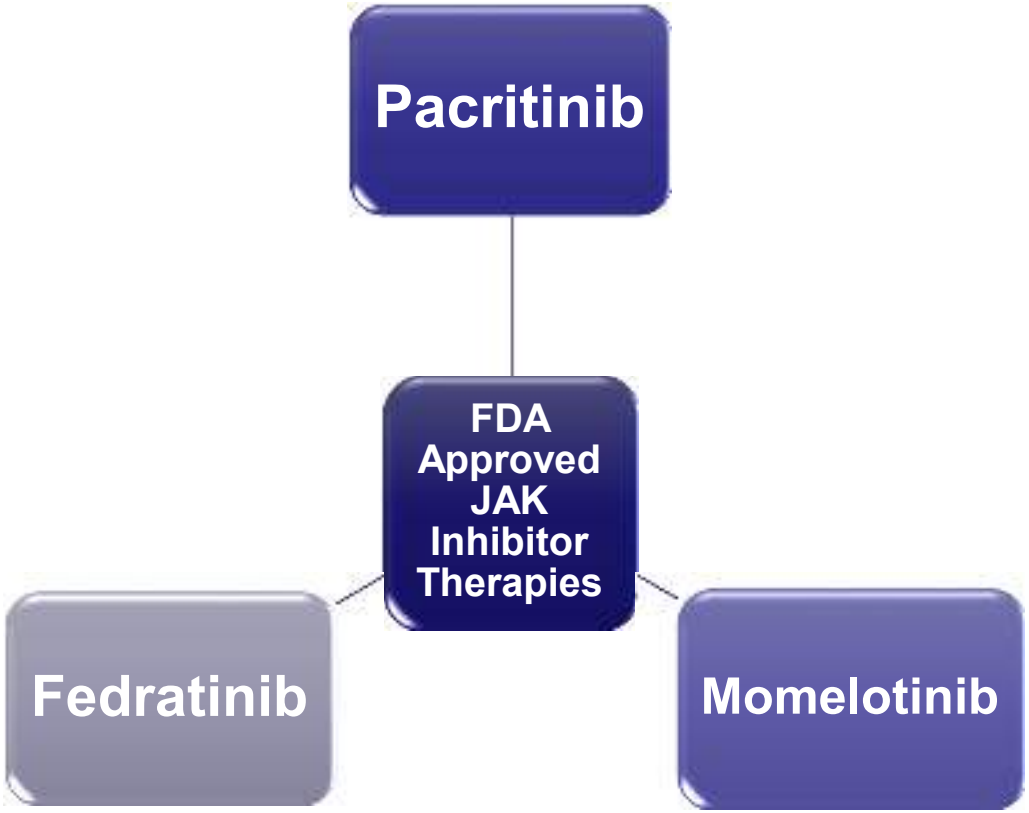
Mount Sinai Hospital

Higher Risk Myelofibrosis Treatment Recommendations



NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated: December 2023

Three FDA Approved Ruxolitinib-Alternative JAK-Inhibitors for Patients with Myelofibrosis



Fedratinib (Inrebic®)

MOA	JAK-Inhibitor (JAK-2 Selective)
Indications	INT-2 or high-risk MF (including PMF, post-PV MF and post-ET MF) in adults with myelofibrosis
Dose	400 mg PO once daily for patients with platelets > 50 x 10^9/L
Monitoring	• **Thiamine levels in all patients at baseline, periodically during treatment, and clinically as indicated. Replete thiamine prior to initiation** • CBC, creatinine and BUN, hepatic panel, amylase lipase at baseline and periodically during treatment
Warnings	• **BBW: Encephalopathy including Wernicke's** • **Gastrointestinal toxicity** • Hepatic toxicity • Amylase and lipase elevation • Thrombocytopenia, anemia • Major adverse cardiovascular events (MACE) • Thrombosis • Secondary malignancies
Interactions	• Affected by CYP3A4, CYP2C19 • Affects CYP3A4, 2C19, 2D6, OC2, MATE1/2-K
ADEs (≥20%)	• **Diarrhea, nausea, anemia, vomiting**

Fedratinib [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2019.

JAKARTA-1 (2015)

Study Design

- Ph3, double-blind, ***placebo-controlled***, multicenter (94), international study, randomized 1:1, crossover allowed after 24 weeks

Protocol

- ***Fedratinib 400 mg OR Fedratinib 500 mg OR placebo once daily***
- **Duration*:*** **≥** 6 consecutive 4-week cycles until disease progression or relapse, excess toxicity, or other criteria

Inclusion

- Adults with INT-2 or high-risk MF
- ECOG 0 – 2
- ***Platelet ≥ 50 x 10^9/L***

Exclusion

- ***Prior JAK2 inhibitor***
- Concomitant mod-severe CYP3A4 inhibitors/inducers

Primary Endpoint

- ***≥ 35% reduction in spleen volume (SVR)*** on MRI/CT from baseline to week 24 and confirmed 4 weeks later

Pardanani A, Harrison C, Cortes JE, et al. *JAMA Oncol*. 2015;1(5):643-651.

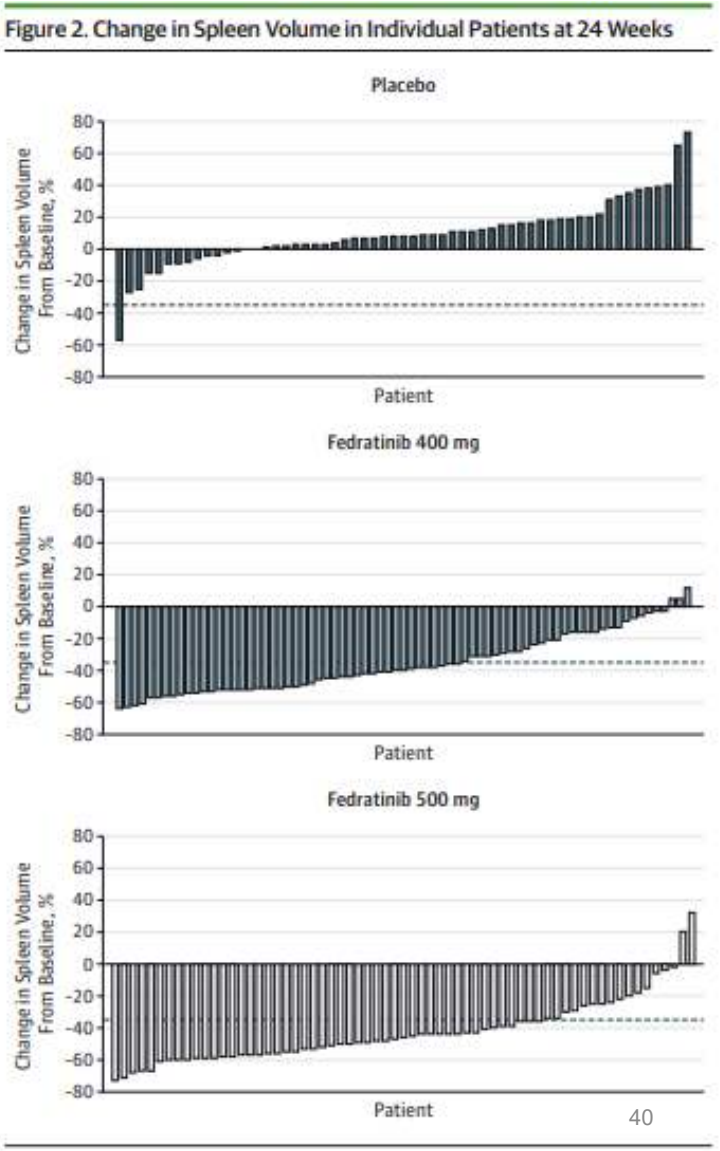
JAKARTA-1 Results

Primary Endpoint (≥ *35% SVR)*

- **Fedratinib 400mg: 35%**
- **Fedratinib 500 mg: 39%**
- **Placebo: 1%**
- P<0.001

Symptom Response – ≥ *50%* ↓Total Symptom Score (TSS)

- **Fedratinib 400mg: 36%** (95% CI, 26% – 46%)
- **Fedratinib 500 mg: 34%** (95% CI, 24% – 44%)
- **Placebo: 7%** (95% CI, 2% – 12%)
- P<0.001



Pardanani A, Harrison C, Cortes JE, et al. *JAMA Oncol*. 2015;1(5):643-651.

Safety Data/Conclusions

Grade 3-4 ADEs	Fedratinib 400 mg (n=96)	Fedratinib 500 mg (n = 97)	Placebo (n=95)
Any TEAE Grade 3 or 4, n (%)	52 (54)	68 (70)	30 (32)
Anemia, n (%)	41 (43)	58 (60)	24(25)
Thrombocytopenia, n (%)	16 (17)	26 (27)	9(9)

TEAE: treatment-emergent adverse event

- 14% discontinuation rate due to ADEs:
  - Thrombocytopenia (7), cardiac failure (4), vomiting (4), diarrhea (4)
- High frequency of Grade 1-2 GI side effects (66%, 42%, 64% for diarrhea, vomiting, and nausea)
- ***7 cases of Wernicke's Encephalopathy (WE) in women who received fedratinib 500 mg***

Due to inability to identify mechanism of WE at this time, sponsor terminated clinical development (risk > benefit)

Pardanani A, Harrison C, Cortes JE, et al. *JAMA Oncol*. 2015;1(5):643-651.

JAKARTA-2 (2017)

Study Design

- Ph2, multicenter, international, single-arm, open-label

Protocol

- **Fedratinib 400 mg PO once daily x 6 cycles (28 days)**
- May ↑ to 600 mg/day if did not achieve ≥ 50% spleen reduction or ↓ to minimum 200 mg/day for toxicity
- ***All patients required to initiate thiamine supplementation + safety follow-up x 90 days***

Inclusion

- Adults with INT-2 or high-risk MF or INT-1 with symptoms
- ***Prior ruxolitinib use ≥ 14 days***
- ECOG 0 – 2

Exclusion

- ***Platelet count < 50 x 10^9/L***
- Receive chemo/ruxolitinib within 14 days (except hydroxyurea)

Primary Endpoint

- ≥ *35%* SVR on MRI/CT at the end of cycle 6 (24 weeks)

Harrison CN, Schaap N, Vannucchi AM, et al.. Lancet Haematol. 2017;4(7):e317-e324.

JAKARTA-2 Results

- Median follow-up: 6 months (early study termination)

Primary Endpoint (≥ *35% SVR)*

- ***55%*** (46/83) (95% CI 44-66) overall
  - 53% (29/55) of patients resistant to ruxolitinib
  - 63% (17/27) of patients intolerant to ruxolitinib

Symptom Response – ≥ *50%* ↓TSS

- ***26% overall (23/90)***
  - 21% (13/90) of patients resistant to ruxolitinib
  - 32% (9/28) of patients intolerant to ruxolitinib

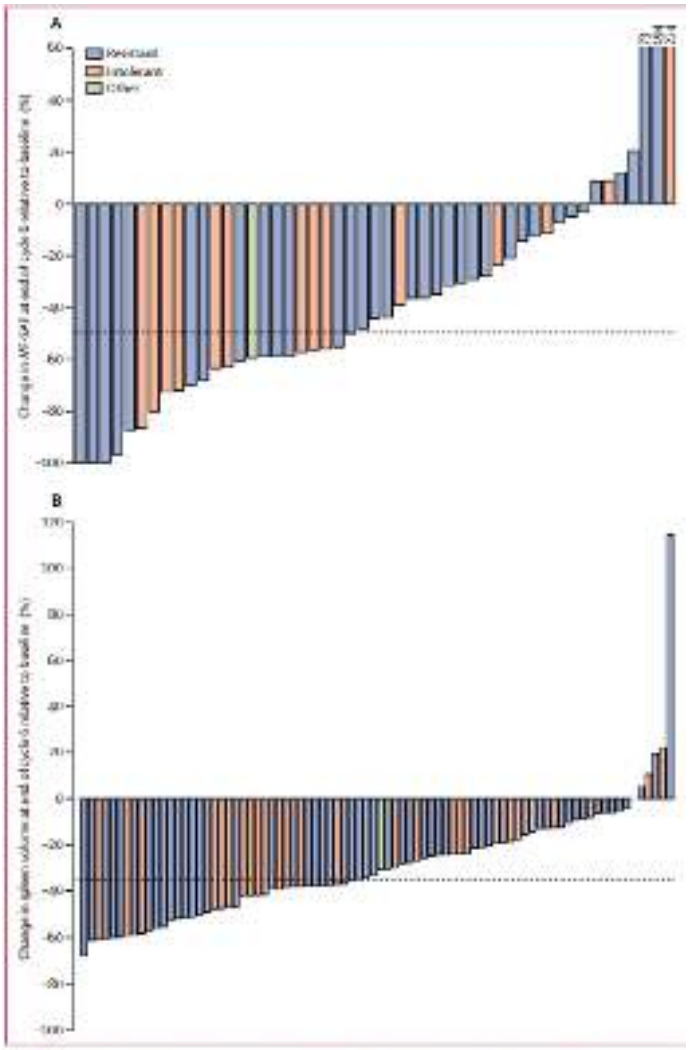


Figure 2: Change in total symptom score (A) and spleen volume (B) from baseline to end of cycle 6, according to reason for ruxolitinib discontinuation
MF-SAF = modified myeloid-specific symptom assessment form.

Harrison CN, Schaap N, Vannucchi AM, et al.. Lancet Haematol. 2017;4(7):e317-e324.

JAKARTA-2 Safety/Conclusions

Safety

- 18 patients (19%) discontinued due to ADEs, most commonly Grade 3 to 4 thrombocytopenia
- At study discontinuation, 63 patients remained on active treatment **and no encephalopathy or cardiac failure reported during extended safety follow-up**

Limitations

- No control
- Early study termination (USA)
- "Per protocol" population
- **Ruxolitinib failure = investigator judgment**

Conclusions

- Wernicke's is preventable with thiamine supplementation
- Fedratinib might achieve significant clinical benefit in those who are intolerant or resistant to ruxolitinib

Harrison CN, Schaap N, Vannucchi AM, et al.. Lancet Haematol. 2017;4(7):e317-e324.

Updated JAKARTA-1 and JAKARTA-2 Data

FDA approval based on updated JAKARTA analysis

JAKARTA-1 (2021)

- Similar responses to original analysis
- ***No Wernicke's occurred in fedratinib 400 mg group***

JAKARTA-2 (2020)

- ITT population with stringent definition of ruxolitinib failure
- Spleen volume response rate = 30%
- Symptom response = 27%

Definition	Stringent Criteria
Relapsed	≥ 3 months with spleen regrowth, • <10% SVR or <30% ↓ in size from baseline, after initial response
Refractory	≥ 3 months with spleen regrowth, • <10% SVR or <30% ↓ in size from baseline
Intolerant	≥ 28 days • RBC transfusion requirement (≥2 units per months x 2 months), ≥ Gr3 thrombocytopenia, anemia, hematoma +/- hemorrhage

Pardanani A, Tefferi A, Masszi T, et al. *Br J Haematol*. 2021;195(2):244-248.
Harrison CN, Schaap N, Vannucchi AM, et al. *Am J Hematol*. 2020;95(6):594-603.

Pacritinib (Vonjo®)

MOA	Selective JAK2 and FLT3 inhibitor
Indications	Int-1, Int-2, or high-risk primary or secondary MF **with a platelet count <50 x 10^9/L** in adults
Dose	200 mg PO **twice daily** with or without food
Monitoring	• CBC, **coagulation testing**, **baseline ECG**, and monitor as clinically indicated
Warnings	• **Hemorrhage: Hold for planned surgical procedures** • Diarrhea • Thrombocytopenia • **Prolonged QT interval: Do NOT use if baseline QTc >480 msec** • Major adverse cardiovascular events (MACE) • **Thrombosis** • Secondary malignancies • Infections
Interactions	• Avoid use with moderate CYP3A4 inhibitors or inducers • Avoid with sensitive Pgp, BCRP, OCT1 substrates
ADEs (≥20%)	• Diarrhea, nausea, thrombocytopenia, bleeding, peripheral edema

Pacritinib [package insert]. Seattle, WA: CTI BioPharma Corp; 2022.

PERSIST-1 (2017)

Study Design

- Ph3, multicenter, international, randomized 2:1

Protocol

- Pacritinib 400 mg once daily vs. **BAT**
- Cross-over from BAT allowed at disease progression OR without progression after 24 weeks

BAT: Best Available Therapy
- Ruxolitinib (45%)
- Hydroxyurea (19%)
- Other (15%)

Inclusion

- Adults with intermediate or high risk MF
- ECOG 0 – **3**
- MPN-SAF TSS score ≥ 3 x 2 symptoms, or ≥ 4 x 1 symptom other than fatigue

Exclusion

- **Prior treatment with other JAK2 inhibitors**

Primary Endpoint

- ≥ *35% SVR* on MRI/CT at 24 weeks

Mesa RA, Vannucchi AM, Mead A, et al. *Lancet Haematol*. 2017;4(5):e225-e236.

PERSIST-1 Results

- Median follow-up: 23 months
- Median treatment duration: 15.6 months (IQR 5.6 – 23.7)

Primary Endpoint (≥ *35% SVR)*

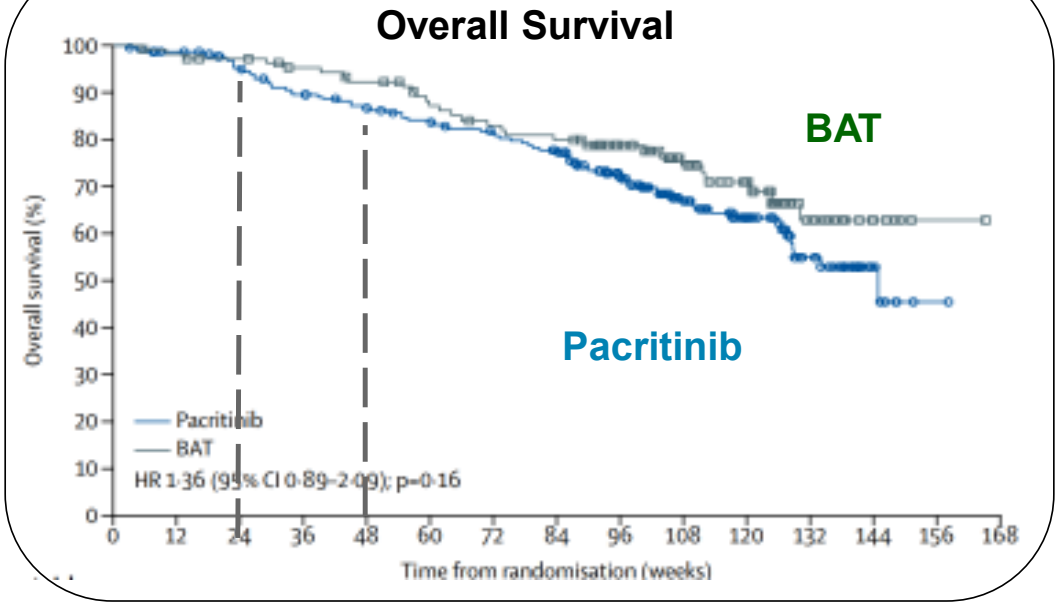
- Pacritinib 400mg (n=220): **19%**
- BAT (n=107)**: 5%**
  - P<0.0003
- Crossed over from BAT to pacritinib (n=90): 12%

Symptom Response – ≥ *50%* ↓TSS

24 weeks
- Pacritinib vs. BAT: 19% v. 10%, p = 0.24

48 weeks *(p = 0.0027)*
- Pacritinib vs. BAT: 15% v. 0%, p = 0.0027

Baseline Characteristics
- Mostly ECOG 0-1: 90%
- Fewer patients with INT-2 in pacritinib v. BAT group: 29% vs. 40%
- **Platelet count <50 x 10^9/L: 15%**
- Platelet count 50– 99 x 10^9/L: 17%



Mesa RA, Vannucchi AM, Mead A, et al. *Lancet Haematol*. 2017;4(5):e225-e236.

PERSIST-1 Safety/Conclusions

Adverse event(s)	Pacritinib 400 mg (n=220)		Best Available Therapy (n=106)	
Adverse event, %	**Grade 1/2**	**Grade 3/4**	**Grade 1/2**	**Grade 3/4**
Diarrhea	50	3	10	0
Nausea	36	1	7	0
Anemia	7	17	5	15
Thrombocytopenia	5	11	3	11
Vomiting	15	1	6	0
QTc prolongation	4	1	1	0
Cardiac failure	<1	2	0	1

Conclusion

Pacritinib induces significant reduction in splenomegaly and improvement in symptoms in patients with MF, **regardless of presence of severe cytopenias, and is minimally myelosuppressive**

Mesa RA, Vannucchi AM, Mead A, et al. *Lancet Haematol*. 2017;4(5):e225-e236.

PERSIST-2 (2018)

Study Design

- Ph3, multicenter, international, randomized 1:1:1

Protocol

- Pacritinib 400 mg once daily vs. pacritinib 200 mg BID v. **BAT (including JAK inhibitors)**
- Cross-over from BAT allowed at disease progression OR without progression after 24 weeks

BAT: Best Available Therapy

- Ruxolitinib (45%)
- Hydroxyurea (19%)
- Watchful waiting (19%)
- Prednisone and/or prednisolone (13%)

Inclusion

- Adults with intermediate or high risk MF
- ECOG 0 – 3
- **Platelet count < 100 x 10^9/L**
- TSS ≥ 13 on MPN-SAF TSS 2.0

Exclusion

- Active bleeding requiring hospitalization
- Significant cardiac abnormalities (including QTc prolongation)

Primary Endpoint

- Efficacy of pooled pacritinib arms v. BAT
- ≥ 35% SVR and ≥ 50% ↓ TSS at 24 weeks

Secondary Endpoint

- Pacritinib once daily vs. twice daily vs. BAT

Mascarenhas J, Hoffman R, Talpaz M, et al. *JAMA Oncol*. 2018;4(5):652-659

PERSIST-2: Results

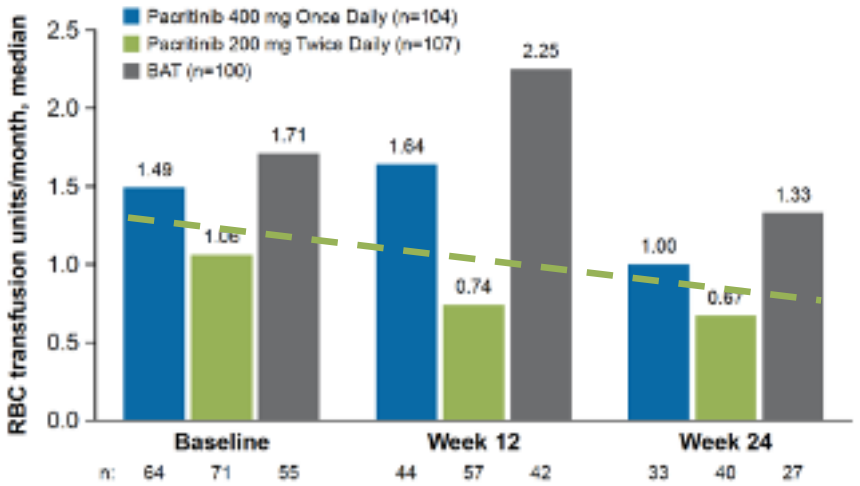
Outcomes/Endpoint	Pacritinib 400 mg once daily (n=75)	Pacritinib 200 mg twice daily (n=74)	BAT (n=72)
Patients with ≥ 35% SVR, n (%)	11 (15)	16 (22)	2 (3)
p-value vs. BAT	0.02	0.001	N/A
≥ 50% ↓ TSS	13 (17)	24 (32)	10 (14)
p-value vs. BAT	0.65	0.01	N/A
Prior ruxolitinib therapy, n	31	31	33
Patients with ≥ 35% SVR, n (%)	2 (6)	4 (13)	1 (3)
≥ 50% ↓ TSS	3 (10)	10 (32)	5 (15)
TSS with PLTs< 50 x 10^9/L, n	38	31	32
Patients with ≥ 35% SVR, n (%)	7 (18)	9 (29)	1 (3)
≥ 50% ↓ TSS	6 (16)	7 (23)	4 (13)

- Improved outcomes in pacritinib 200mg BID group across various subgroups
- Pacritinib 200 mg BID was associated with higher systemic exposure

Mascarenhas J, Hoffman R, Talpaz M, et al. *JAMA Oncol*. 2018;4(5):652-659

PERSIST-2 – Safety and Conclusions

	Pacritinib 400 mg once daily (n=104)	Pacritinib 200 mg BID (n=106)
Remained on treatment at time of clinical hold, n (%)	61 (59)	76 (71)
Dose interruptions due to ADEs, n (%)	39 (38)	29 (27)
Thrombocytopenia	4 (4)	2 (2)
Anemia	2 (2)	3 (3)
Disease progression	2 (2)	1 (1)
Deaths due to ADEs	11 (11)	3 (3)
Cardiac events	3 (3)	0
Bleeding events	1 (1)	2 (2)



eFigure 6. RBC Transfusions Over Time (Intention-to-Treat).
Median RBC transfusion requirements (units/month) are shown at baseline, week 12, and week 24 for patients on the 3 treatment arms who received ≥1 RBC unit while on study. Patients treated with pacritinib had lower RBC transfusion requirements than those treated with BAT at week 12 and week 24.
Abbreviation: BAT, best available therapy; RBC, red blood cell.

Conclusion

Pacritinib 200 mg PO twice daily significantly improved outcomes compared to best available therapy, with a favorable efficacy and safety profile to pacritinib 400 mg PO once daily

- Modest improvements in transfusion burden/requirements with twice daily dosing
- Less deaths due to adverse drug reactions?

Mascarenhas J, Hoffman R, Talpaz M, et al. *JAMA Oncol*. 2018;4(5):652-659

Momelotinib (Ojjaara®)

MOA	JAK1/2 Inhibitor and ACVR1 Inhibitor
Indications	Int-1, Int-2, or high-risk primary or secondary MF in adults **with anemia**
Dose	200 mg PO once daily with or without food
Monitoring	• CBC, • Hepatic function panel (baseline and as clinically indicated)
Warnings	• Risk of infections • Thrombocytopenia • Neutropenia • Hepatotoxicity • Major adverse cardiovascular events (MACE) • Thromboses • Risk of secondary malignancies
Interactions	• BCRP/ABCG2, PATP1B1/1B3; minor metabolism via CYP pathway • Inhibits BCRP/ABCG2
ADEs (≥20%)	• Diarrhea, nausea, thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness

Momelotinib [package insert]. Durham,NC: Glakosmithkline; 2023.

SIMPLIFY Trials

	SIMPLIFY-1	SIMPLIFY-2
Study Design	Ph3, randomized, double-blind, non-inferiority vs. ruxolitinib	Ph3, randomized, open-label, superiority study (vs. BAT, which could include ruxolitinib)
Inclusion	Intermediate or high-risk MF, JAK inhibitor naïve, platelet ≥ 50 x 10^9/L	• Intermediate or high-risk MF • Previously treated with ruxolitinib • Requiring dose adjustment to < 20 mg BID • Anemia, Gr3 thrombocytopenia/bleeding
Primary Endpoint	24-week SVR ≥35%	24-week SVR ≥35%
Intervention	Momelotinib 200 mg daily vs. ruxolitinib	Momelotinib 200 mg daily vs. BAT, which could include ruxolitinib (89%)
Results	Momelotinib vs. ruxolitinib: • SVR≥35% - non-inferior: 27% vs. 29%, p = 0.011 • TSS ↓ 50% - NOT non-inferior: 28% vs. 42%, p = 0.98 • More RBC transfusion independence – 67% vs. 49%, p <0.001 • Median OS: not reached	Momelotinib vs. BAT: • SVR≥35%- 7% vs. 6%, p = 0.90 • More TSS ↓ 50% = 26% vs. 6%, p = 0.0006 • Fewer RBC transfusion dependent: 50% vs. 64%, p = 0.1
Gr3/4 ADEs	Thrombocytopenia (7%), anemia (5.6%), diarrhea (2.8%), hypertension (2.8%), neutropenia (2.8%)	Anemia (14%), thrombocytopenia (7%), abdominal pain (1%)
Other ADEs	Peripheral neuropathy (10%)	Peripheral neuropathy (11%)

Tremblay D, Mesa R. *Future Oncol*. 2022;18(20):2559-2571.

MOMENTUM Trial

Study Design

- Ph3, randomized (2:1), double-blind, crossover allowed after 24 weeks

Protocol

- Momelotinib 200 mg daily vs. danazol 600 mg daily
- Ongoing JAKi therapy must be tapered, followed by 2-week non-treatment interval

Inclusion

- Prior JAKi therapy ≥ 90 days OR
- Prior JAKi therapy ≥ 28 and
  - RBC transfusion requirement of ≥ 4 units in 8 weeks
  - Gr3/4 thrombocytopenia, anemia, or hematoma
- **Symptomatic with anemia (Hgb < 10 g/dL)**
- Platelet ≥ 25 x 10^9/L
- Baseline TSS ≥ 10

Primary Endpoint

- TSS ↓ 50% at week 24 (MFSAF TSS response rate)

Secondary Endpoints

- SVR35%, RBC transfusion dependence at week 24

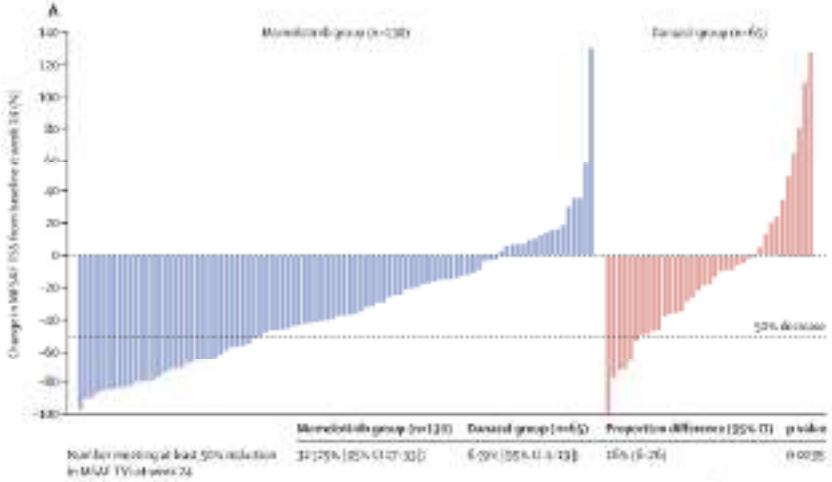
Verstovsek S, et al. *Lancet. 223 Jan 28;401(10373):269-280*

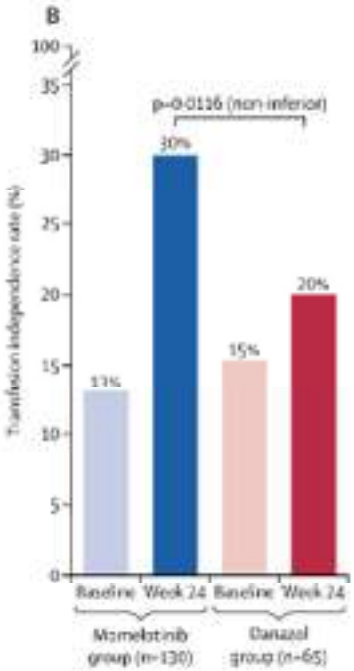
MOMENTUM Efficacy Results

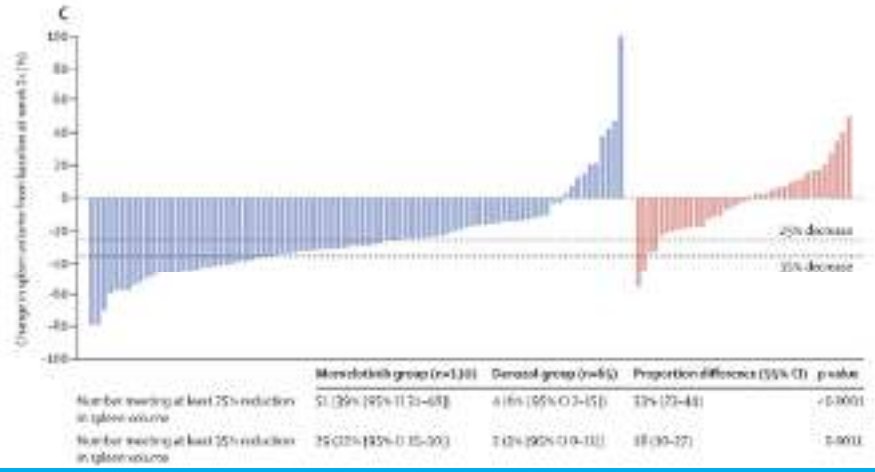
Outcomes/Endpoint	Momelotinib 200 mg PO once daily (n=130)	Danazol (n=65)	P-Value
Primary Endpoint			
Total Symptom Score Response Rate (MFSAS-TSS)	32 (25%)	6 (9%)	0.0095 (superior)
Secondary Endpoints			
Transfusion independence at week 24, n	39 (30%)	13 (20%)	0.0064 (non-inferior)
≥25% SVR at week 24, n	51 (39%)	4 (6%)	<0.0001 (superior)
≥35% SVR at week 24, n	29 (22%)	2 (3%)	0.006 (superior)
Change in MFSAF-TSS at week 24, n	-11.5	-3.9	0.0014 (superior)
Zero transfusions at week 24, n	46 (35%)	11 (17%)	0.0012 (superior)

Verstovsek S, et al. *Lancet. 223 Jan 28;401(10373):269-280*

Change in TSS (A), Transfusion Independence (B), and Spleen Volume (C)







MOMENTUM Safety/Conclusions

Outcomes/Endpoint	Momelotinib 200 mg PO once daily (n=130)		Danazol (n=65)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Hematologic, n (%)				
Anemia	129 (99%)	79 (61%)	65 (100%)	49 (75%)
Thrombocytopenia	99 (76%)	36 (28%)	49 (62%)	17 (26%)
Neutropenia	38 (29%)	16 (12%)	17 (26%)	6 (9%)
Non-Hematologic				
Nausea	21 (16%)	3 (2%)	6 (9%)	2 (3%)
Diarrhea	29 (22%)	0	6 (9%)	1 (2%)
Pruritus	14 (11%)	2 (2%)	7 (11%)	0
Peripheral Edema	10 (8%)	2 (2%)	9 (14%)	10
Acute Kidney Injury	6 (5%)	4 (3%)	8 (12%)	6 (9%)

Conclusions

- Momelotinib significantly improved key primary and secondary endpoints in the ruxolitinib refractory setting when compared to danazol therapy
- Significant limitations when comparing data to other JAK inhibitor therapies, including primary outcome and comparator arm

Verstovsek S, et al. *Lancet. 223 Jan 28;401(10373):269-280*

Three FDA Approved Ruxolitinib-Alternative JAK-Inhibitors for Patients with Myelofibrosis

Fedratininb

- Approval for intermediate/high-risk myelofibrosis patients
- Associated with significant cytopenias and gastrointestinal toxicities
- Potential benefit in patients with larger spleens?

Pacritinib

- Approval for intermediate/high-risk myelofibrosis patients **with thrombocytopenia (platelet counts <50k x 10^9 cells/L)**
- Can be used in the 1st line or 2nd line settings (PERSIST I-II)
- Concern for QTc prolongation, GI upset, and bleed risk

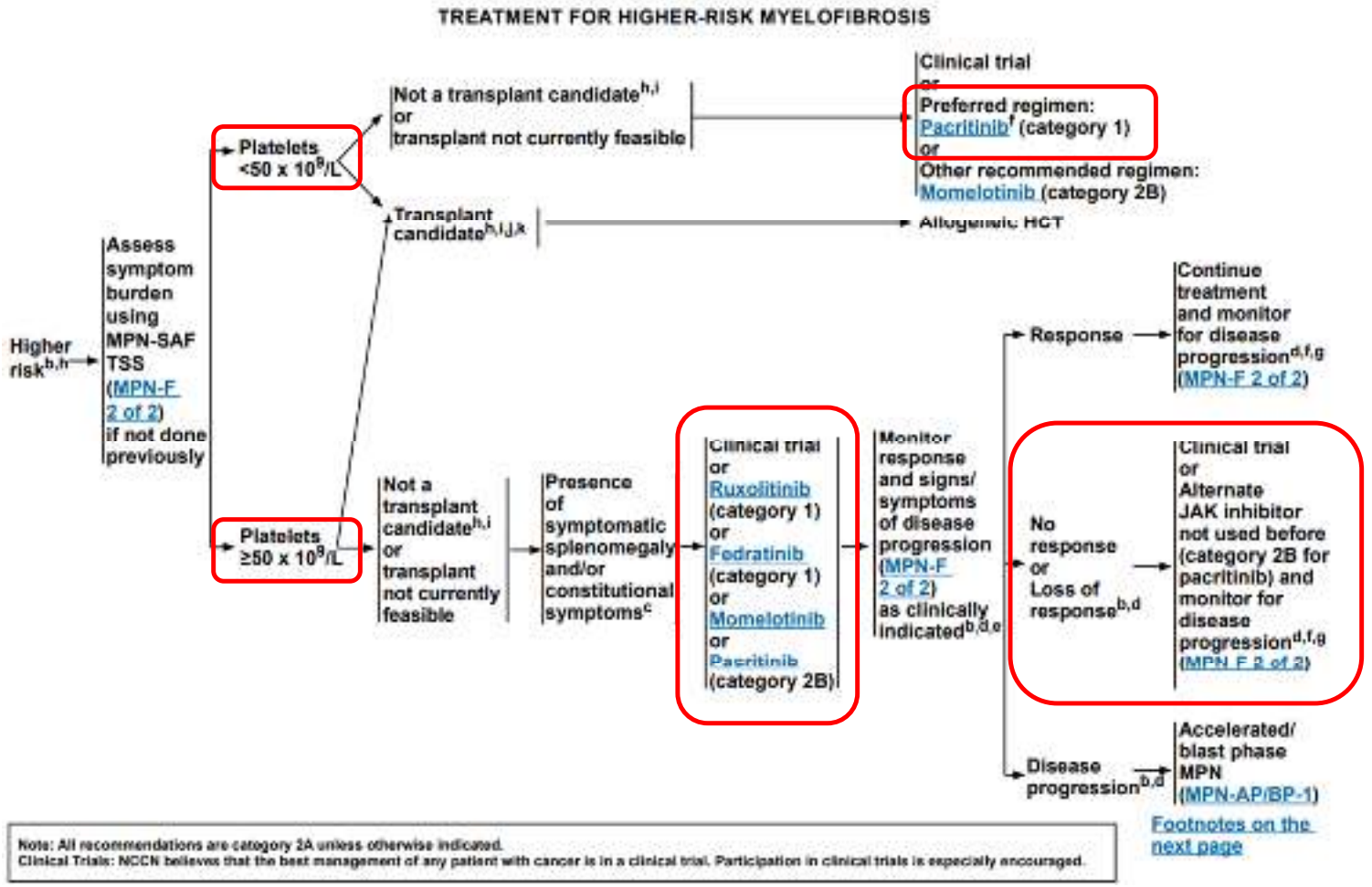
Momelotinib

- Approval for intermediate/high-risk myelofibrosis patients **with anemia**
- Can be used 1st or 2nd line settings (SIMPLIFY, MOMENTUM)
- Potentially not as impactful on spleen volume?

Concluding Thoughts

Mount Sinai Hospital

Higher Risk Myelofibrosis Treatment Recommendations



NCCN. Myeloproliferative Neoplasms. Ver 1.2024. Updated: December 2023

JAK Inhibitors Comparison

	Ruxolitinib (Jakafi®)	Fedratinib (Inrebic®)	Pacritinib (Vonjo®)	Momelotinib (Ojjara®)
Dose/Admin	10 mg – 25 mg BID ± food	400 mg once daily ± high fat meal to reduce N/V	200 mg BID ± food	200 mg daily ± food
ADEs	**Thrombocytopenia Anemia**	Diarrhea, nausea, vomiting **Thrombocytopenia Anemia**	Peripheral edema Diarrhea, nausea, Anemia, thrombocytopenia	Thrombocytopenia, anemia, **hepatotoxicity,** peripheral neuropathy?
Unique Warnings	**Withdrawal symptom exacerbation** lipid elevations	**Wernicke's encephalopathy Gastrointestinal toxicity** hepatotoxicity amylase/lipase elevations	**QT prolongation** diarrhea, hemorrhage	Risk of bacterial infections? **hepatotoxicity**
Monitoring	CBC, lipid panel	CBC, **thiamine**, creatinine/BUN, LFTs, amylase/lipase	CBC, coagulation testing, baseline ECG	CBC, hepatic function panel (baseline)
Supportive Care	Infection prophylaxis?	Thiamine supplementation Antiemetics, antidiarrheal Infection prophylaxis?	Infection prophylaxis? Antidiarrheal	Infection prophylaxis?
DDI	CYP3A4	CYP3A4, CYP2C19	CYP3A4	BCRP, OAT1A1/1B3
DDI (other drug)	**N/A**	CYP3A4, 2C19, 2D6, OCT2, MATE1/2K	Pgp, BCRP, OCT1	BCRP

Fedratinib [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2019.
Jakafi [package insert]. Wilmington, DE: Incyte Corporation; 2011.
Pacritinib [package insert]. Seattle, WA: CTI BioPharma Corp; 2022.
Momelotinib [package insert]. Durham,NC: Glakosmithkline; 2023

Key Takeaways

- Myelofibrosis is a rare malignancy, characterized by JAK/STAT pathway dysregulation and progressive bone marrow failure
- Ruxolitinib is the first JAK inhibitor and commonly utilized in the front-line setting for initial treatment of intermediate/high-risk myelofibrosis
- Fedratinib, pacritinib and momelotinib are all approved to be used in patients with myelofibrosis
- Pharmacists play a large role in optimization of care for myelofibrosis patients, including symptom assessment, assessment of drug therapy, and mitigation of AEs/DDIs

Management of Ruxolitinib-Refractory Myelofibrosis.

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