



Guidelines for the Management of Myelofibrosis in Adults

An Educational Slide Set

American Society of Hematology 2026 Guidelines for the Management of Myelofibrosis in Adults

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How were these guidelines generated?

PANEL FORMATION

Guideline panel was formed following these key criteria:

- Balance of expertise (including disciplines beyond hematology, & inclusive of patients)
- Close attention to minimization & management of conflicts of interest

CLINICAL QUESTIONS

10 clinically-relevant questions generated in PICO format (population, intervention, comparison, outcome)

Example: PICO question

“In individuals with higher-risk myelofibrosis receiving JAK inhibitor therapy, should we refer early on for allogeneic hematopoietic cell transplantation or delay post JAK inhibitor therapy failure?”

EVIDENCE SYNTHESIS

Evidence summary generated for each PICO question via systematic review of health effects plus:

- Resource use
- Feasibility
- Acceptability
- Equity
- Patient values and preferences

MAKING RECOMMENDATIONS

Recommendations made by guideline panel members based on evidence for all factors.

ASH guidelines are reviewed annually by expert work groups convened by ASH. Resources, such as this slide set, derived from guidelines that require updating are removed from the ASH website.

How patients and clinicians should use these recommendations

STRONG Recommendation		CONDITIONAL Recommendation	
	“The panel recommends...”	“The panel recommends against...”	“The panel suggests...” “The panel suggests against...”
			 
For patients	Most individuals would want the intervention.		A majority would want the intervention, but many would not.
For clinicians	Most individuals should receive the intervention.		Different choices will be appropriate for different patients, depending on their values and preferences. Use shared decision making .

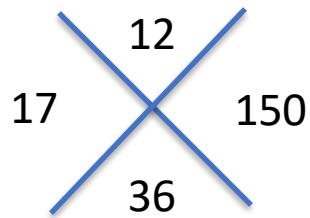
Objectives

By the end of this session, you should be able to

- Recognize scenarios in which extended molecular testing and interferon-based approaches should be considered in myelofibrosis (MF).
- Select initial treatment strategies for JAK inhibitor–naïve MF across different clinical phenotypes.
- Individualize management of disease-related anemia, JAK inhibitor–associated anemia, iron overload, and thrombosis prevention.
- Apply transplant referral and pre-transplant treatment recommendations in higher-risk MF.

Case 1: Extended molecular mutation testing in myelofibrosis (PICO 1)

- 66-year-old man, no significant PMH
- Denies fevers, night sweats
- Early satiety, no significant weight loss
- Active, ECOG PS 0
- Physical exam: palpable splenomegaly, 5 cm below left costal margin



Peripheral blasts 2%
Nucleated RBC and dacrocytes noted

- **Peripheral blood tested for *CALR*, *MPL* and *JAK2* mutations:** *JAK2 V617F mutation present*
- **Bone marrow biopsy:** megakaryocytic clustering and reticulin fibrosis (MF-2) present consistent with primary myelofibrosis
- **Karyotype:** 46, XY



Case 1: Extended molecular mutation testing in myelofibrosis (PICO 1)

- Patient requests comprehensive education on primary myelofibrosis, including prognosis and a review of all available interventions, including aggressive options
- Patient has Intermediate-1 risk disease by IPSS, DIPSS, and DIPSS PLUS
- Estimated overall survival based on these risk models was discussed with the patient

Question 1

Should extended molecular mutation testing be performed on this patient, and why?

- A. Yes, because it reliably predicts response to JAK inhibitors.
- B. Yes, because extended molecular testing refines prognostic risk stratification and may inform management decisions such as transplant referral.**
- C. No, because a patient's prognosis will not change from one scoring system to the next, even if the scoring system incorporates extended molecular mutation data.

Prognostic models in myelofibrosis that do not incorporate molecular mutations

Prognostic model	Variables (Scoring)	Risk groups (Median OS)
IPSS	Age >65 (1) Hb <10 g/dL (1) Circulating blasts $\geq 1\%$ (1) Constitutional symptoms (1)	0 = Low (11.3 years) 1 = Intermediate-1 (7.9 years) 2 = Intermediate-2 (4.0 years) ≥ 3 = High (2.3 years)
DIPSS (applicable anytime during disease course)	Age >65 (1) Hb <10 g/dL (2) WBC $>25 \times 10^9/L$ (1) Circulating blasts $\geq 1\%$ (1) Constitutional symptoms (1)	0 = Low (not reached) 1-2 = Intermediate-1 (14.2 years) 3-4 = Intermediate-2 (4.0 years) 5-6 = High (1.5 years)
DIPSS PLUS (applicable anytime during disease course)	DIPSS Low (0) DIPSS Int-1 (1) DIPSS Int-2 (2) DIPSS High (3) Unfavorable karyotype (1) Red cell transfusion dependency (1) Platelets $<100 \times 10^9/L$ (1)	0 = Low (15.4 years) 1 = Intermediate-1 (6.5 years) 2-3 = Intermediate-2 (2.9 years) 4-6 = High (1.3 years)

High molecular risk (HMR) non-driver mutations in myelofibrosis

- *ASXL1, EZH2, SRSF2, U2AF1 Q157, IDH1/2, multi-hit TP53, N/K RAS*
- Associated with shorter overall survival and shorter leukemia-free survival
- Number of HMR mutations affects prognosis
- Incorporating molecular data can result in an upgrade in risk assignment

Prognostic models in myelofibrosis that do incorporate molecular mutations

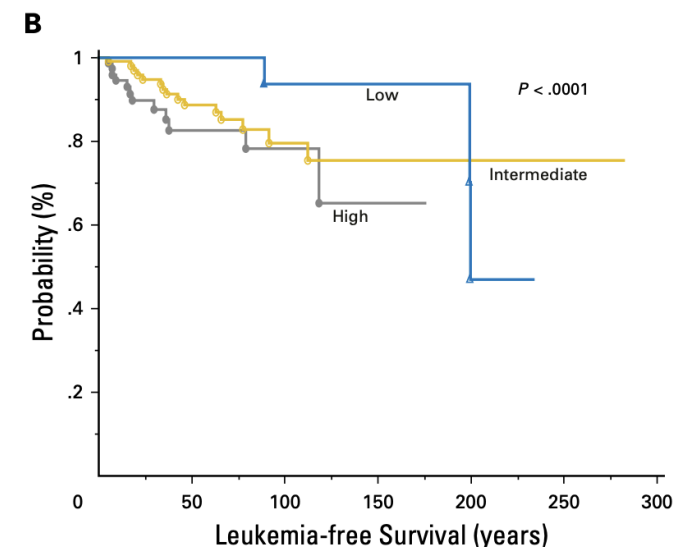
Prognostic model	Variables (Scoring)	Risk group (Median OS)
MIPSS70	Hb <10 g/dL (1) WBC >25×10 ⁹ /L (1) Circulating blasts ≥2% (1) Constitutional symptoms (1) Platelets <100×10 ⁹ /L (1) Bone marrow fibrosis grade ≥2 (1) 1 HMR mutation (1) ≥2 HMR mutations (2) Type 1/like <i>CALR</i> absent (1)	0-1 = Low (27.7 years) 2-4 = Intermediate (7.1 years) ≥5 = High (2.3 years)
MIPSS70 Plus	Hb <10 g/dL (1) Circulating blasts ≥2% (1) Constitutional symptoms (1) 1 HMR mutation (1) ≥2 HMR mutations (2) Type 1/like <i>CALR</i> absent (1) Unfavorable karyotype (3)	0-2 = Low (20 years) 3 = Intermediate (6.3 years) 4-6 = High (3.9 years) ≥7 = Very high (1.7 years)
GIPSS	Very high-risk karyotype (2) Unfavorable karyotype (1) Type 1/like <i>CALR</i> absent (2) <i>ASXL1</i> (1) <i>SRSF2</i> (1) <i>U2AF1</i> Q157 (1)	0 = Low (26.4 years) 1 = Intermediate-1 (8.0 years) 2 = Intermediate-2 (4.2 years) ≥3 = High (2.0 years)

Prognostic models in myelofibrosis that do incorporate molecular mutations (cont.)

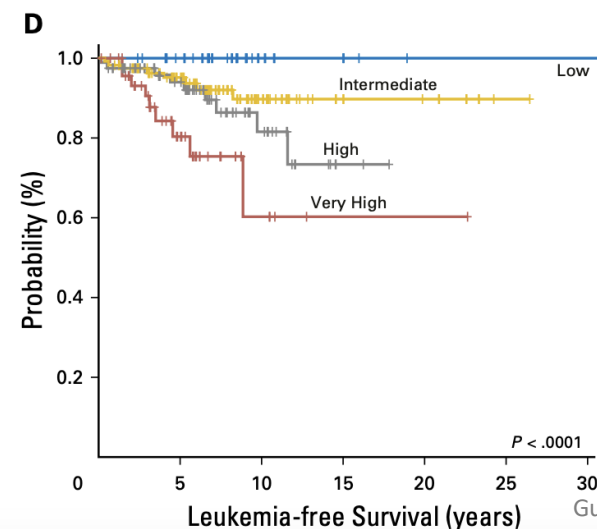
Prognostic model	Variables (Scoring)	Risk group (Median OS)
MIPSS70 Plus v2.0	Very high-risk karyotype (4) Unfavorable karyotype (3) 1 HMR mutation (2) ≥2 HMR mutations (3) Type 1/like <i>CALR</i> absent (2) Severe anemia (2) --Hb <8 g/dL in women, <9 g/dL in men Moderate anemia (1) --Hb 8-9.9 g/dL in women, 9-10.9 g/dL in men Circulating blasts ≥2% (1) Constitutional symptoms (2)	0 = Very low (not reached) 1-2 = Low (16.4 years) 3-4 = Intermediate (7.7 years) 5-8 = High (4.1 years) ≥9 = Very high (1.8 years)
MYSEC-PM	Age (0.15 per yr of age) Hb <11 g/dL (2) Platelets <150×10 ⁹ /L (1) Circulating blasts ≥3% (2) <i>CALR</i> absent (2) Constitutional symptoms (1)	<11 = Low (Not reached) 11-13 = Intermediate-1 (9.3 years) 14-16 = Intermediate-2 (4.4 years) >16 = High (2.0 years)

- Molecularly enhanced prognostic scoring systems can also predict Leukemia-free survival

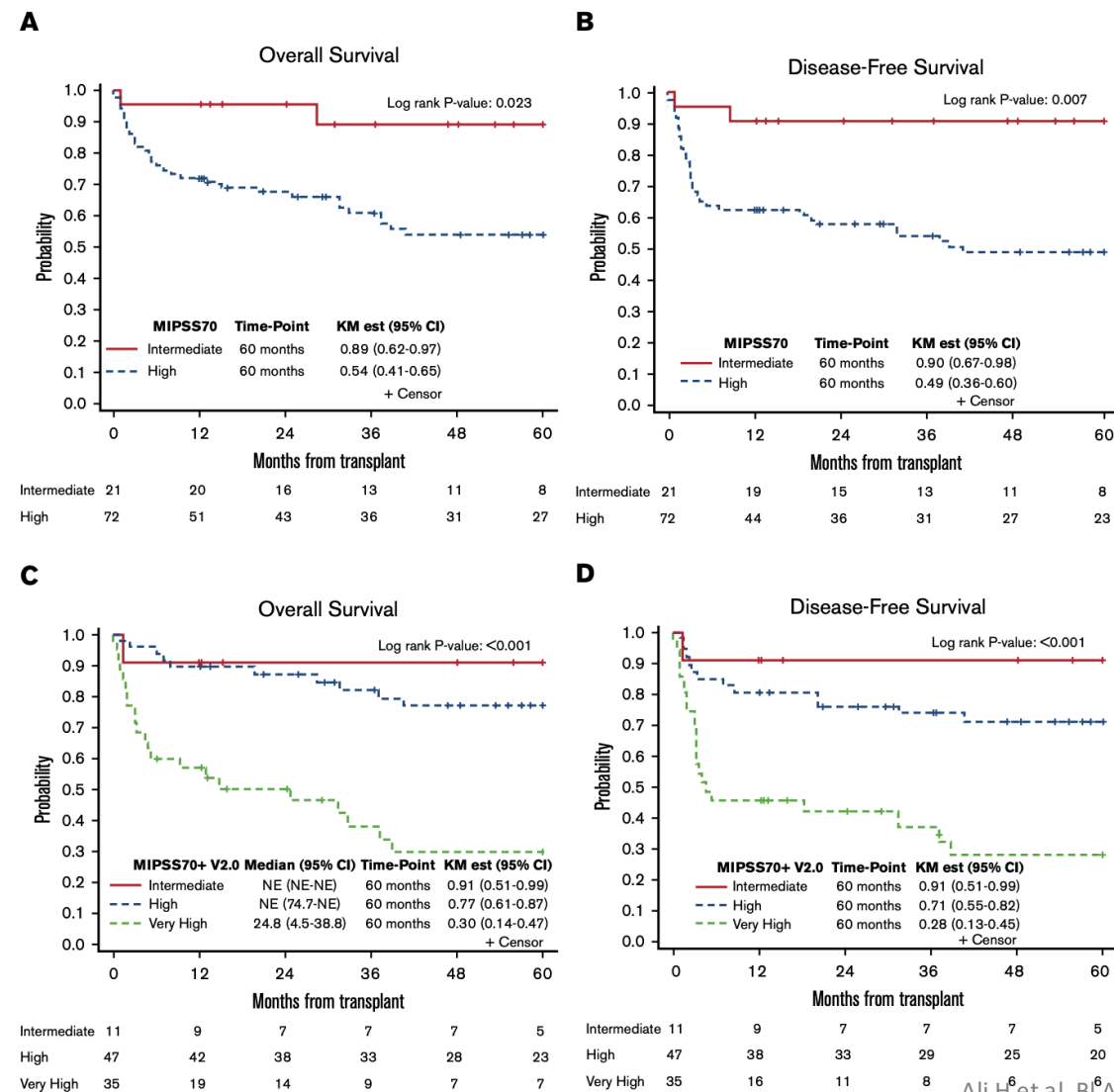
MIPSS



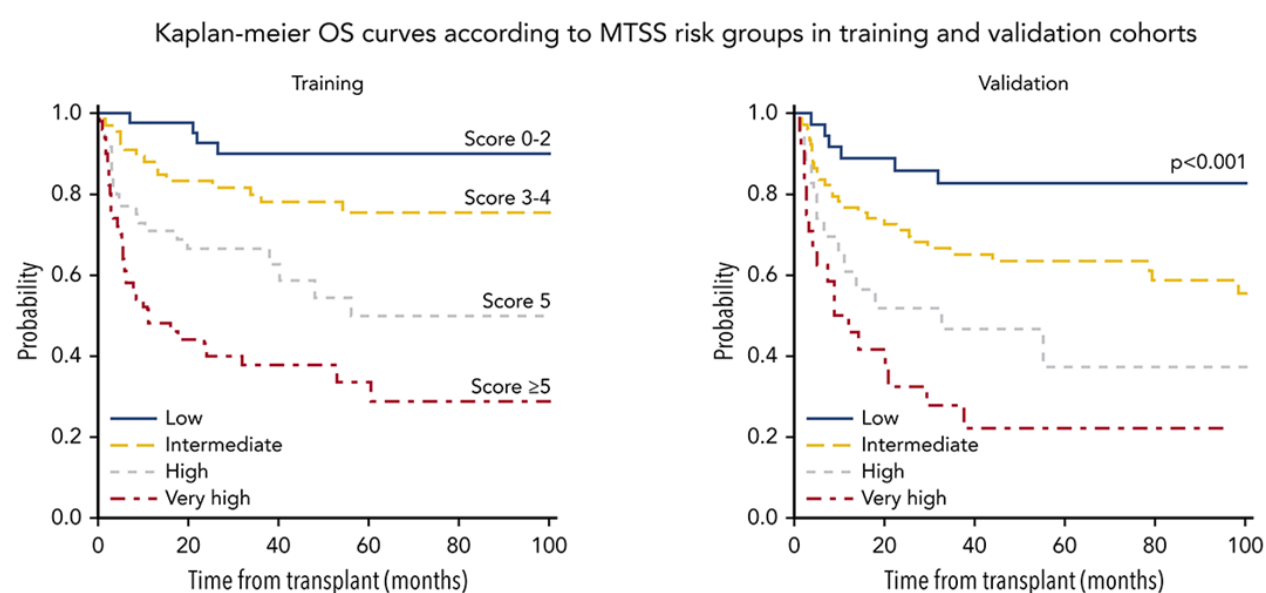
MIPSS PLUS



- Driver mutation and HMR mutation status have been shown to play a role in outcomes after alloSCT



MTSS: Myelofibrosis Transplant Scoring System



- Uses molecular, clinical, and transplant-specific factors to predict post-transplant outcomes

Variable							
	Platelets <150 x 10 ⁹ /L	Leukocytes >25 x 10 ⁹ /L	Karnofsky performance status <90%	Age ≥57 years	Non-CALR/MPL driver mutation genotype	ASXL1 mutation	HLA-mismatched unrelated donor
HR	1.67	1.57	1.50	1.65	2.40	1.42	2.08
Score	1	1	1	1	2	1	2

Case 1: Back to our patient...

- Extended molecular mutation panel obtained from peripheral blood
- *ASXL1 and EZH2 mutations detected, both HMR mutations*
- High-risk disease by MIPSS70, MIPSS70-Plus, and MIPSS70-Plus v2.0
- Transplant referral made to initiate discussion



Recommendation 1

Recommendation	Strength	Certainty of evidence
In all patients with myelofibrosis, we suggest extended molecular genetic testing compared to limited testing from MPN driver mutations.	Conditional	Moderate

Remarks:

- Extended molecular genetic testing should be performed at diagnosis. It may be repeated at key clinical decision points, such as disease progression, pre-transplant evaluation, or when making new treatment decisions, to identify acquisition of new mutations.
- Extended testing is less compelling for patients that are transplant-ineligible with poor extended longevity, or among patients that do not want to know prognosis if there is no impact on their treatment.

Case 2a: Use of interferon in myelofibrosis (PICO 2)

A 56-year-old, non-smoking man with no significant past medical history (including no prior thrombotic events) was incidentally found to have an elevated platelet count by his primary care physician. He feels well, is active, and reports no complaints, including no microvascular symptoms. Physical examination shows no hepatosplenomegaly.

14.8
6.2 956
43.6

No leukoerythroblastosis noted

LDH normal

•Peripheral blood tested for *CALR*, *MPL* and *JAK2* mutations: type 1 *CALR* mutation present

•Bone marrow biopsy: slightly hypercellular, slight myeloid predominance, megakaryocytic hyperplasia with atypia, megs arranged in clusters, grade 0-1 fibrosis noted, most consistent with prefibrotic MF

•Karyotype: 46, XY

Question 2a

In this newly diagnosed prefibrotic MF patient, what is the most appropriate management?

A. Observation alone.

B. Ruxolitinib.

C. Pegylated interferon.

Prefibrotic MF

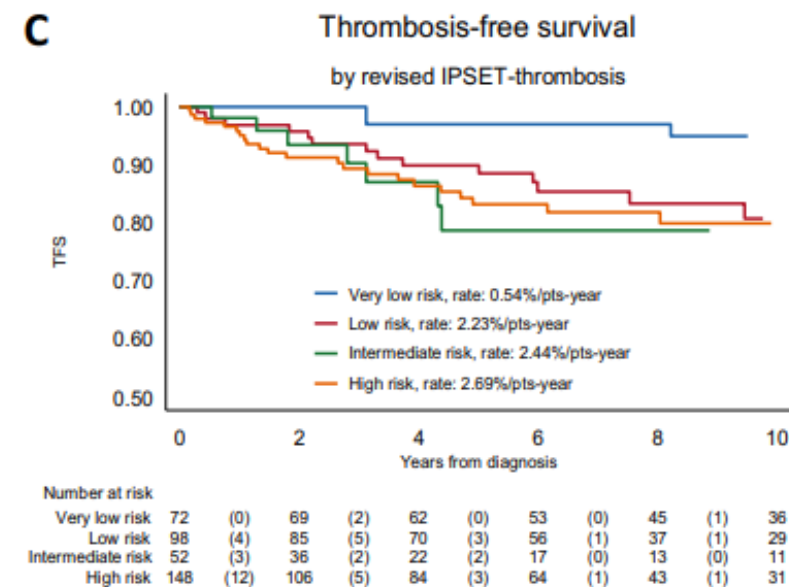
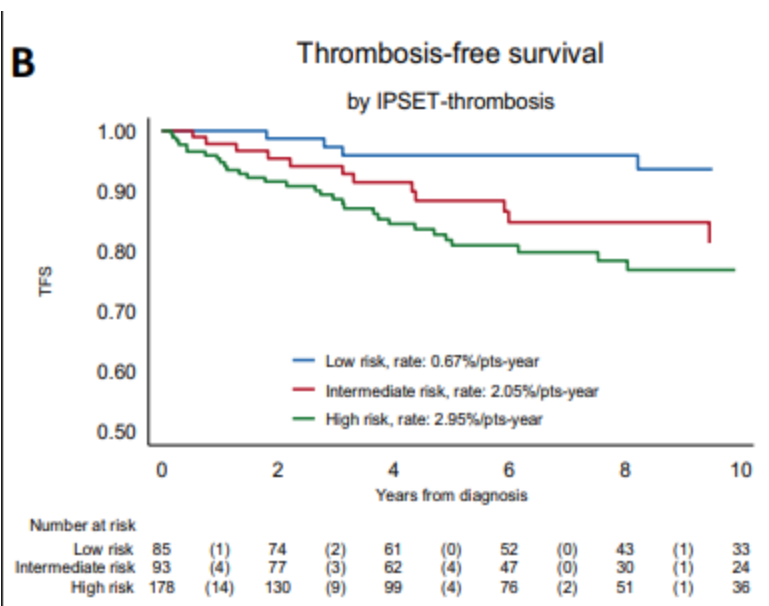
- Recognized as a distinct clinicopathologic entity in 2016 WHO classification
- Continues to be recognized in 2022 International Consensus Classification (ICC)

	Prefibrotic MF (2022 ICC)
MAJOR	Bone marrow biopsy --Increased age-adjusted bone marrow cellularity --Megakaryocytic proliferation and atypia --Granulocytic proliferation and (often) decreased erythropoiesis --Bone marrow fibrosis grade 0-1 Diagnostic criteria for BCR::ABL1-positive CML, PV, PMF, or other myeloid neoplasms are not met Presence of <i>JAK2</i>, <i>CALR</i>, or <i>MPL</i> mutation or presence of another clonal marker or absence of reactive bone marrow reticulin fibrosis
MINOR	Anemia not attributed to a comorbid condition Leukocytosis $\geq 11 \times 10^9/L$ Palpable splenomegaly LDH above reference range Leukoerythroblastosis
ALL 3 MAJOR AND 1 MINOR	

Prefibrotic MF and Goals of treatment

- Currently, no standard-of-care treatment algorithm for prefibrotic MF
- Variable clinical presentation that may not benefit from treatment with JAK inhibitors
- **Goals of treatment**
 - Control symptoms if present
 - Prevent thrombotic or hemorrhagic complications
 - 10 yr cumulative incidence of thrombosis in preMF 17.9%
 - 10 yr cumulative incidence of bleeding in preMF 14.9%
 - Prevent progression to overt MF, prevent transformation to AML, and prolong overall survival
 - 10 yr risk of progression to overt MF 12.3%
 - 5-year risk of leukemic transformation 5%; 10 yr risk of leukemic transformation 12%
 - Median overall survival 14.7 years

Thrombosis-free survival: (Revised) IPSET-Thrombosis validated in Prefibrotic MF



Prefibrotic MF: Antiplatelet treatment

- It is reasonable to consider initiating an antiplatelet agent in preMF patients, using the same criteria as in ET patients.

Revised IPSET-Thrombosis Risk Group	Characteristics	Antiplatelet treatment?
Very low	- Age ≤ 60 - No JAK2 mutation - No hx of thrombosis	Only if microvascular symptoms
Low	- Age ≤ 60 +JAK2 mutation - No hx of thrombosis	Yes
Intermediate	- Age > 60 - No JAK2 mutation - No hx of thrombosis	Yes
High	- Age > 60 +JAK2 mutation OR - Hx of thrombosis at any age	Yes

Prefibrotic MF: Cytoreductive treatment

- It is reasonable to consider initiating a cytoreductive agent in preMF patients using the same criteria as in ET patients.

Revised IPSET-Thrombosis Risk Group	Characteristics	Cytoreductive treatment?
Very low	- Age <60 - No <i>JAK2</i> mutation - No Hx of thrombosis	Only if refractory symptoms
Low	- Age <60 +<i>JAK2</i> mutation - No Hx of thrombosis	Only if refractory symptoms
Intermediate	- Age >60 - No <i>JAK2</i> mutation - No Hx of thrombosis	If no cardiovascular risk factors present: only if refractory symptoms If cardiovascular risk factors present: consider use
High	- Age >60 +<i>JAK2</i> mutation OR - Hx of thrombosis	Yes

Case 2a: Back to our patient...

- 56-year-old with type 1 *CALR*+ prefibrotic MF, no prior thrombotic event, asymptomatic
- Very low risk by Revised IPSET-Thrombosis score, validated in prefibrotic MF
- No indication for aspirin or cytoreductive agent
- No signs or symptoms warranting JAK inhibitor initiation
- Observation is most appropriate

Case 2b: Use of interferon in myelofibrosis (PICO 2)

A 45-year-old man with no significant past medical history presents with right arm weakness and is found to have a cerebrovascular accident (CVA). He has no other symptoms, and physical examination shows no hepatosplenomegaly.

14.8
6.2 654
43.6

No leukoerythroblastosis noted

LDH elevated

•Peripheral blood tested for *CALR*, *MPL* and *JAK2* mutations: *JAK2 V617F* mutation present

•Bone marrow biopsy: slightly hypercellular, slight myeloid predominance, megakaryocytic hyperplasia with atypia, megas arranged in clusters, grade 0-1 fibrosis noted, most consistent with prefibrotic MF

•Karyotype: 46, XY

Question 2b

What is an appropriate initial treatment for this newly diagnosed prefibrotic MF patient?

A. Observation alone.

B. Ruxolitinib.

C. Pegylated interferon.

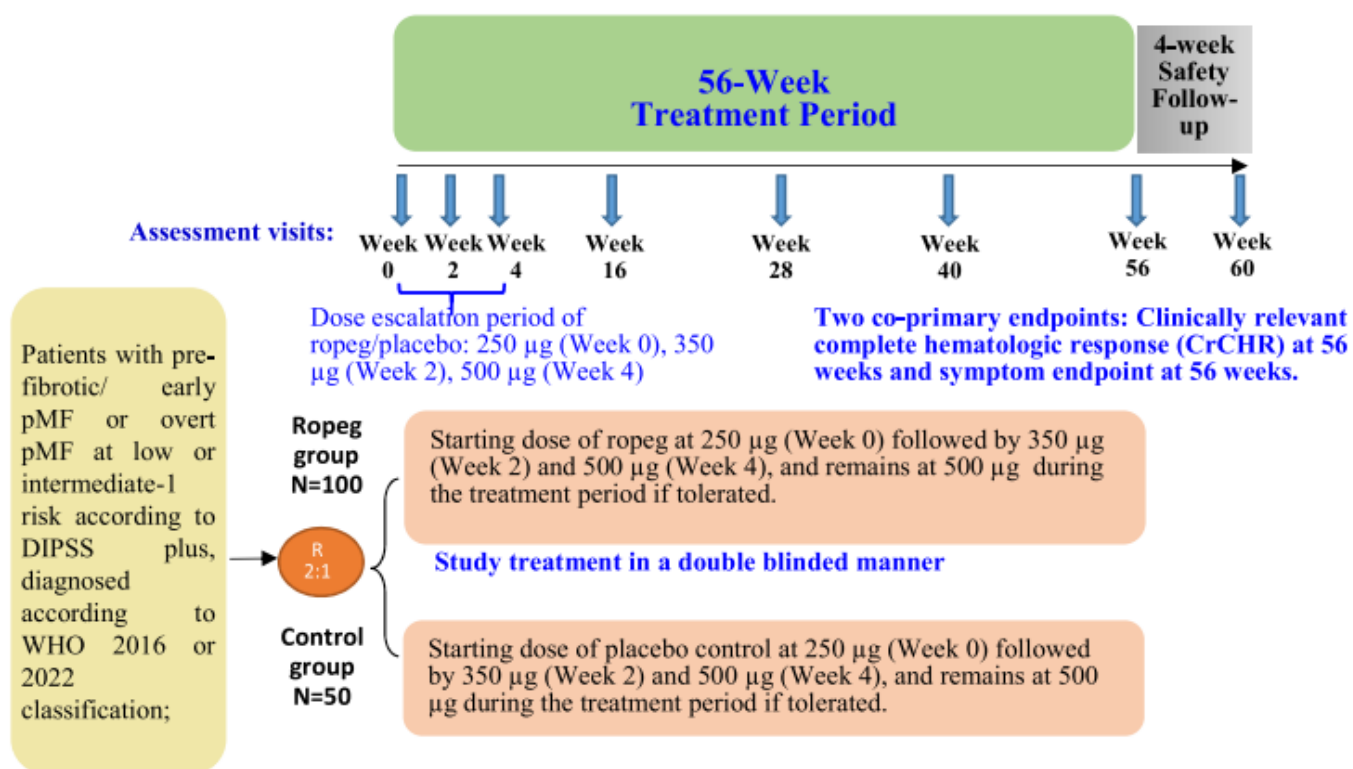
Interferon in MPNs

- Interferons thought to act at the level of the mutant MPN stem cell
- Interferons have a long history of efficacy and safety in MPNs
 - PV
 - ET
 - Myelofibrosis

Interferon in prefibrotic myelofibrosis

Clinical trial	Phase	Patients	Agent(s)	Clinical response			Molecular response	Toxicity
Silver et al	Retrospective	N=30 MF -low-INT-1 DIPSS	IFN-2b or PEG-IFNa-2a	CR 7% PR 30% CI 13% SD 23% 5-year PFS 88% 5-year OS 91.5%			28% VAF reduction of 23% and reduction in marrow cellularity	Mostly grade 1/2 toxicity
Ianotto et al	Retrospective	N=62 MF -42.6% low-INT-1 IPSS -53.2% low-INT-1 DIPSS	PEG-IFNa-2a	Median OS 7.4 years Median LFS NR			>10% VAF reduction 63% >20% VAF reduction 55.6% >50% VAF reduction 37%	AE-related tx discontinuation 44.4%
Gill et al	2 Prospective	N=51 preMF N=6 PMF (low-INT-1 DIPSS) N=5 SMF (low-INT-1 DIPSS)	RoPEG-IFNa-2b	preMF: W104 CHCR 78.4%	PMF: W104 CHCR 33.3%	SMF: W104 CHCR 50%	W104 JAK2 VAF reduction 67.6% W104 CALR VAF reduction 40%	AE-related tx discontinuation 4.2%
				Entire cohort: W104 TSS50 40% W104 SVR 50%				

Interim ropeginterferon alfa-2b data in preMF and low/intermediate-1 risk overt MF



Interim analysis: N=66; median follow-up 69 weeks

- PreMF cohort: no progression to overt MF or leukemia after 48 weeks of therapy
- No deaths reported in preMF cohort at median follow-up of 69 weeks

Five-year OS estimates apply to separate overt MF interferon cohorts, not the interim preMF analysis.

Recommendation 2

Recommendation	Strength	Certainty of evidence
In patients with prefibrotic myelofibrosis (preMF) and no indication for cytoreduction, the panel suggests against routine use of pegylated interferons.	Conditional	Very low

Remarks:

- There is a paucity of evidence to suggest routine use of pegylated interferons in preMF, but this body of literature is growing.
- Conversely, for patients with an indication for cytoreduction, which may include high risk disease by the International Prognostic Score of Thrombosis in Essential Thrombocythemia (IPSET-Thrombosis) score, profound leukocytosis or thrombocytosis, or symptomatic splenomegaly, the use of pegylated interferons could be considered.

Case 3: Asymptomatic Higher-Risk MF (PICO 3)

A 67-year-old dentist presents for evaluation of anemia, incidentally identified by his primary care physician. He denies fevers, night sweats, weight loss, and pruritus, and reports an excellent appetite without early satiety. Physical examination shows no palpable splenomegaly.

~~9.8~~
~~26.1~~ 167
~~29.6~~

Peripheral blasts: 2%

Nucleated RBC and dacrocytes noted

Bone marrow biopsy: megakaryocytic clustering and bone marrow fibrosis (MF-2) consistent with myelofibrosis

Karyotype: 46, XY

NGS: *JAK2 V617F* (32%) and *SF3B1* (18%)

Question 3

What is the appropriate initial treatment for a newly diagnosed, asymptomatic patient with DIPSS Intermediate-2 risk MF?

- A. Initiate JAK inhibitor therapy.
- B. Closely monitor for the development of spleen or constitutional symptoms.**
- C. Hypomethylating agent therapy.

Recommendation 3

Recommendation	Strength	Evidence Certainty
In JAK inhibitor–naïve patients with higher-risk overt myelofibrosis without symptomatic splenomegaly and/or disease-related symptoms, the ASH guideline panel suggests against the initiation of JAK inhibitors.	Conditional	Very low

Good practice statement. Use dynamic, structured symptom assessment during observation, as higher-risk patients under observation are increasingly likely to need treatment during their disease course.

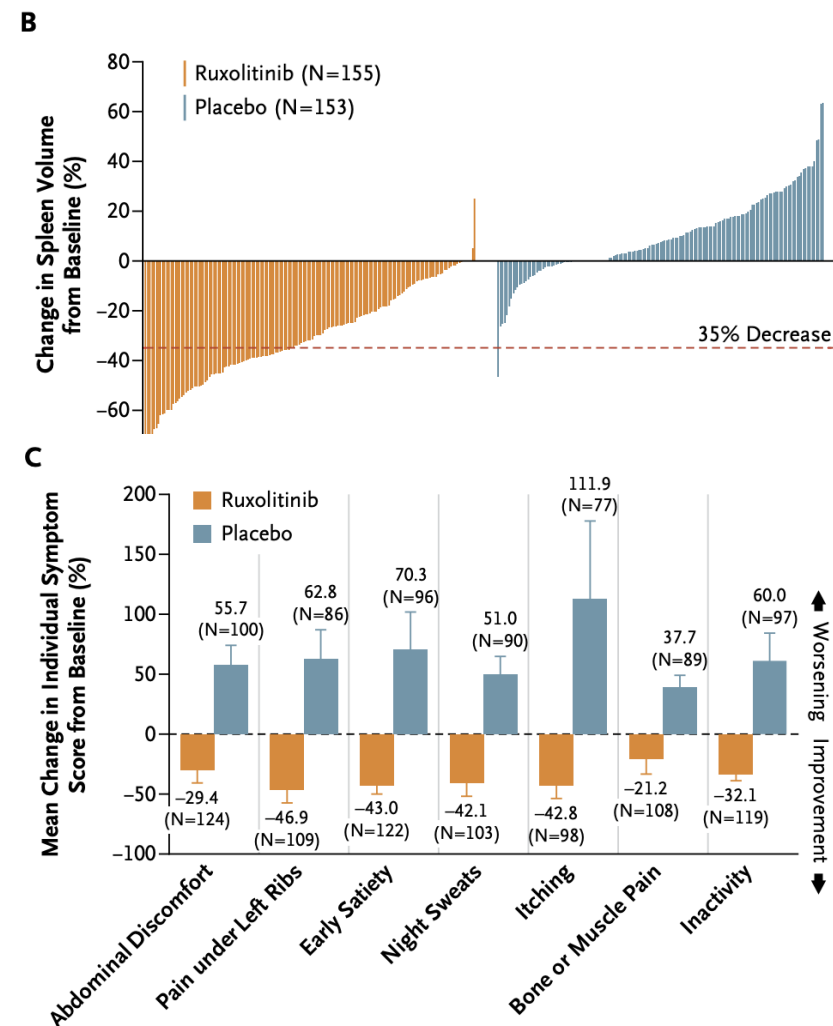
Case 3: Asymptomatic Higher-Risk MF

Why observation is important

- JAK inhibitors reduce spleen size and improve symptoms.
- Evidence in asymptomatic patients without splenomegaly is limited.

<https://pubmed.ncbi.nlm.nih.gov/22375971/>

Verstovsek et al NEJM 2012



Case 3: Asymptomatic Higher-Risk MF

JAK inhibitor	Upfront Study	Inclusion criteria		
		Risk score	Spleen size	Symptom burden
Ruxolitinib	COMFORT-I	IPSS intermediate-2 or high	Spleen >5 cm below LCM	Active symptoms of MF
	COMFORT-II			-
Fedratinib	JAKARTA	IPSS intermediate-2 or high	Spleen >5 cm below LCM	-
Pacritinib	PERSIST-I	DIPSS intermediate-1, intermediate-2 or high	Spleen >5 cm below LCM	MPN-SAF TSS ≥ 13
	PERSIST-II	DIPSS intermediate-1, intermediate-2 or high	Spleen >5 cm below LCM	MPN-SAF TSS ≥ 13
Momelotinib	SIMPLIFY-1	IPSS intermediate-2 or high	Spleen >5 cm below LCM	-

- In asymptomatic higher-risk MF without splenomegaly, benefit is uncertain and treatment-related toxicity remains relevant.
- Monitor symptoms and spleen size over time.

Verstovsek et al NEJM 2012; Harrison et al NEJM 2012; Pardanani et al JAMA Onc 2015; Mesa et al Lancet Haem 2017; Mascarenhas et al JAMA Onc 2018; Mesa et al JCO 2017

Case 4: Disease-Related Anemia (PICO 5)

After 2 years, the patient develops worsening fatigue that limits his activity and ability to practice dentistry. Physical examination reveals the spleen palpable 5 cm below the left costal margin (LCM). Labs and bone marrow biopsy are repeated.

~~7.9~~
~~32.2~~ 89
~~24.4~~

Peripheral blasts: 2%

Nucleated RBC and dacrocytes noted

Bone marrow biopsy: megakaryocytic clustering and bone marrow fibrosis (MF-3)

Karyotype: 46, XY

NGS: *JAK2 V617F* (37%) and *SF3B1* (43%)

Question 4

What is the appropriate initial treatment for a JAK inhibitor-naïve MF patient whose primary symptom burden is disease-related anemia?

A. Transfusion support alone.

B. Erythropoiesis-stimulating agent (ESA) or danazol.

C. Momelotinib or pacritinib.

Recommendation 5

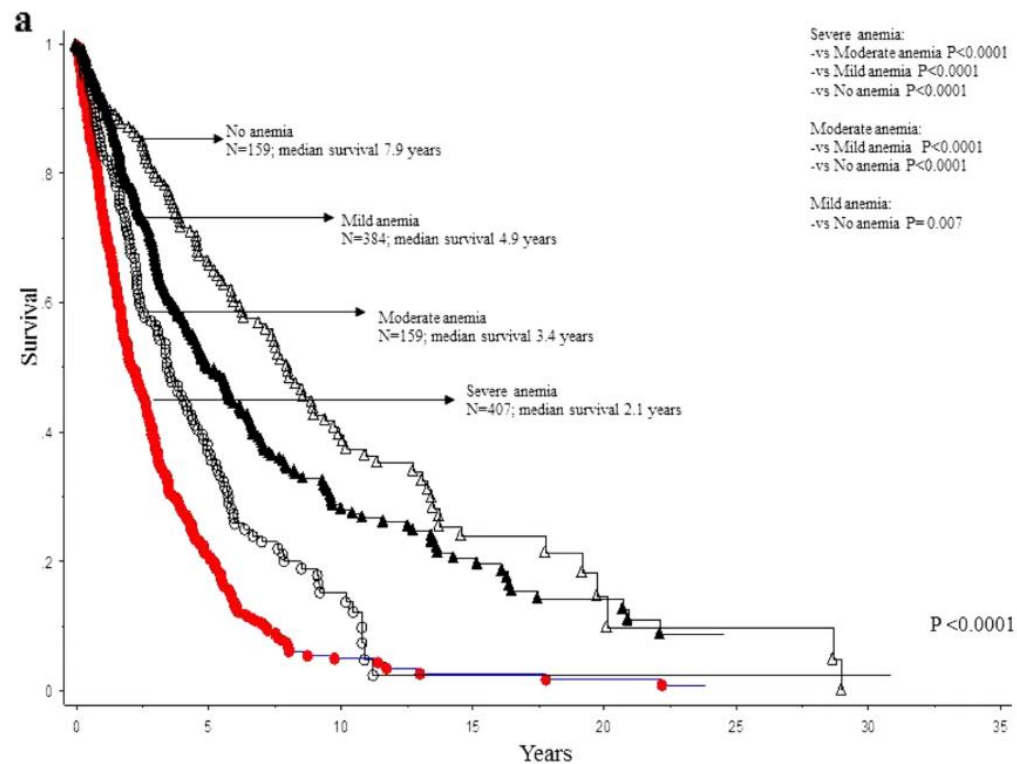
Recommendation	Strength	Evidence Certainty
In JAK inhibitor–naïve patients with myelofibrosis whose primary indication for treatment is disease-related anemia, the ASH guideline panel suggests either JAK inhibitor therapy (mometotinib or pacritinib) or non-JAK inhibitor anemia-directed therapies.	Conditional	Low

Remarks

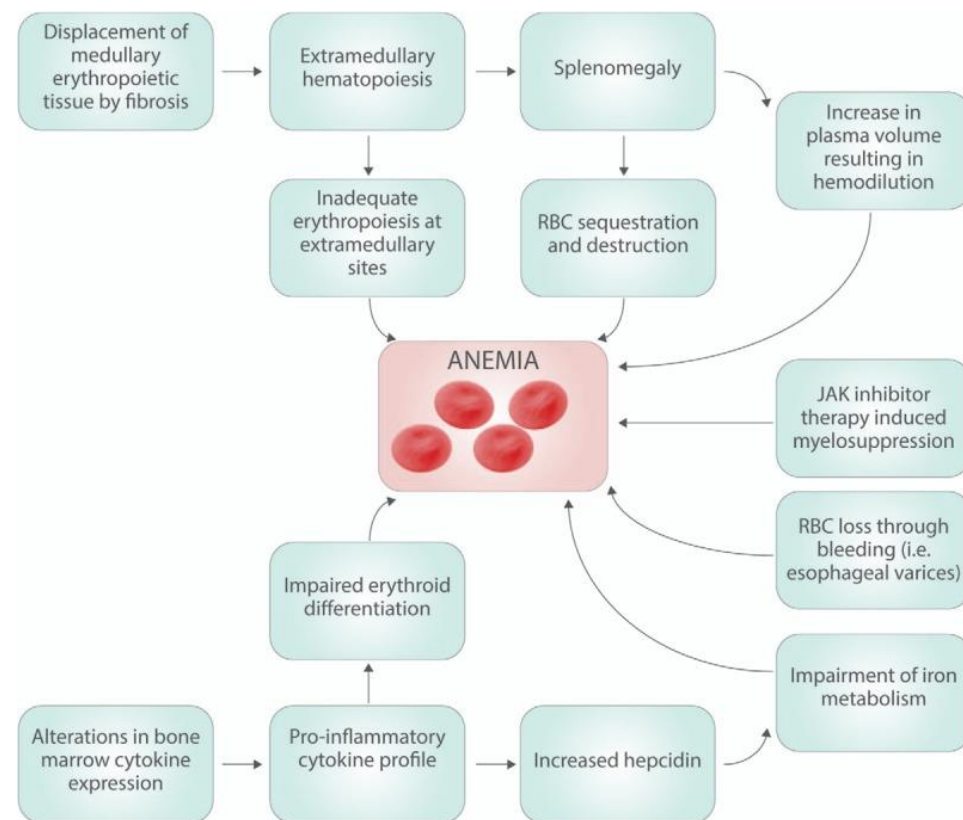
Severity of anemia influences decision-making. Some transfusion-dependent patients can become transfusion-independent when treated with momelotinib or pacritinib; in this context, these JAK inhibitors would be the preferred strategy compared to non-JAK inhibitor anemia-directed therapies. Pacritinib can be considered in patients with concurrent anemia and thrombocytopenia.

Alternatively, non-transfusion dependent patients may start with a non-JAK inhibitor directed therapy (e.g erythropoiesis-stimulating agent (if eligible), luspatercept, or danazol).

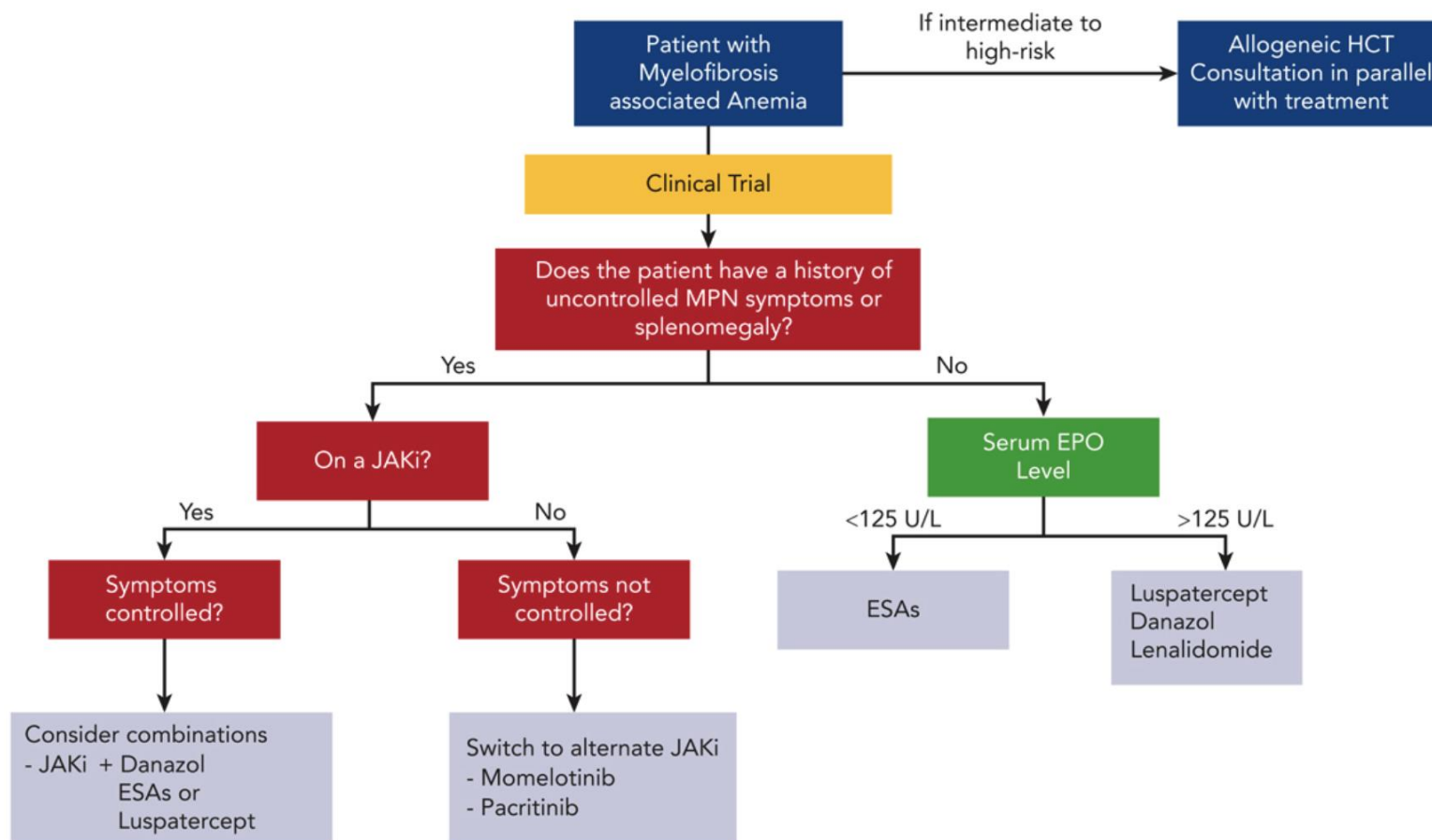
Anemia is a poor prognostic marker in MF and has multifactorial causes



- Anemia affects symptoms, quality of life, and transfusion burden.



Non-JAK inhibitor anemia directed therapies may also improve hemoglobin levels



- Momelotinib and pacritinib may improve anemia/transfusion dependence.
- ESA, danazol, and other non-JAK anemia-directed options may be appropriate.
- Access and resource considerations may influence treatment choice.



Case 5: Symptomatic Lower-Risk MF (PICO 4)

A 54-year-old marketing executive with no significant past medical history is seen by her primary care physician for unintentional weight loss (7% of baseline body weight) driven by early satiety. She has pruritus but no unexplained fevers or night sweats. Physical examination reveals the spleen palpable 12 cm below the left costal margin (LCM). Labs and bone marrow biopsy are repeated.

~~13.1~~
~~17.1~~ 124
42.0

Peripheral blasts: 0%

Nucleated RBC and dacrocytes noted

Bone marrow biopsy: megakaryocytic atypia with clustering and bone marrow fibrosis (MF-2)

Karyotype: 46, XY

NGS: *JAK2 V617F* (61%) and *ASXL1* (11%)

Question 5

In a newly diagnosed, low-risk, JAK inhibitor-naïve, overt MF patient with spleen-related complaints and constitutional symptoms, what is the most appropriate management?

A. Active monitoring.

B. Allogeneic stem cell transplantation referral.

C. Initiate JAK inhibitor therapy.

Recommendation 4

Recommendation	Strength	Evidence Certainty
In JAK inhibitor–naïve patients with lower-risk overt myelofibrosis with symptomatic splenomegaly and/or disease-related symptoms, the ASH guideline panel suggests the use of JAK inhibitors.	Conditional	Very low

Takeaways

- Treat the Patient, Not the Score: Symptomatic presentation should override prognostic scoring when deciding whether to initiate JAK inhibitor therapy.
- Specifically, we suggest JAK inhibitor therapy for low-risk patients with disease-related symptoms and/or splenomegaly. Conversely, we suggest against JAK inhibitor therapy in asymptomatic high-risk patients without splenomegaly.
- Anemia in MF is a poor prognostic marker. Momelotinib, pacritinib, and non-JAK inhibitor therapies can be utilized.

Case 6: Anemia With Ongoing Disease Control (PICO 6)

A 68-year-old man has primary overt MF. Symptoms include fatigue, early satiety, and night sweats. Exam reveals the spleen palpable 10 cm below the LCM. CBC shows Hb 10.4 g/dL, WBC $18 \times 10^9/\text{L}$, platelets $145 \times 10^9/\text{L}$, and 1% peripheral blasts. Bone marrow shows MF-2 fibrosis; karyotype is 46,XY. NGS shows *JAK2* V617F and *ASXL1* mutations. Ruxolitinib was started for symptomatic splenomegaly and constitutional symptoms.

At 12-week follow-up, symptoms had improved significantly and the spleen was now 4 cm below the LCM. However, hemoglobin declined to 7.8 g/dL, and intermittent RBC transfusions are now needed.

Question 6

How should JAK inhibitor–associated anemia be managed?

- A. Switch to an alternative JAK inhibitor.
- B. Maintain current therapy and implement an anemia-optimization strategy.**
- C. Discontinue JAK inhibitor.
- D. Observation.

Recommendation 6B

Recommendation	Strength	Evidence Certainty
In MF patients who experience JAK inhibitor–associated anemia but maintain adequate symptoms and spleen control on the current dose of first-line JAK inhibitor, the ASH guideline panel suggests implementing anemia optimization strategies.	Conditional	Low

Remarks:

- Options include RBC transfusion, ESA, luspatercept, and androgens.
- Pacritinib may be considered in patients with concurrent anemia and thrombocytopenia.
- Early-onset anemia may be drug-related.
- Late-onset or progressive anemia may indicate disease progression.

Good practice statement. In patients with myelofibrosis receiving first-line JAK inhibitor, anemia management should be guided by its timing and impact on disease control, using optimization strategies when benefit is maintained and switching therapy when anemia limits effective dosing.

Case 7: Anemia Limiting Effective JAK Inhibitor Dosing (PICO 6)

In the same clinic, you evaluate a similar case: a 68-year-old man with primary overt, *JAK2*-mutated MF. Bone marrow shows MF-2 fibrosis, karyotype is normal, and NGS is negative for additional mutations.

He started ruxolitinib 4 months ago for constitutional symptoms and symptomatic splenomegaly (12 cm below LCM). Shortly after initiation, he developed anemia (Hb 6.9 g/dL) requiring weekly transfusions, which he finds difficult to sustain. Ruxolitinib could not be titrated above 10 mg twice daily, and symptom and splenomegaly control remain suboptimal.

Question 7

How should JAK inhibitor–associated anemia be managed?

- A. Switch to an alternative JAK inhibitor.
- B. Maintain current therapy and implement an anemia-optimization strategy.
- C. Discontinue JAK inhibitor.
- D. Observation.

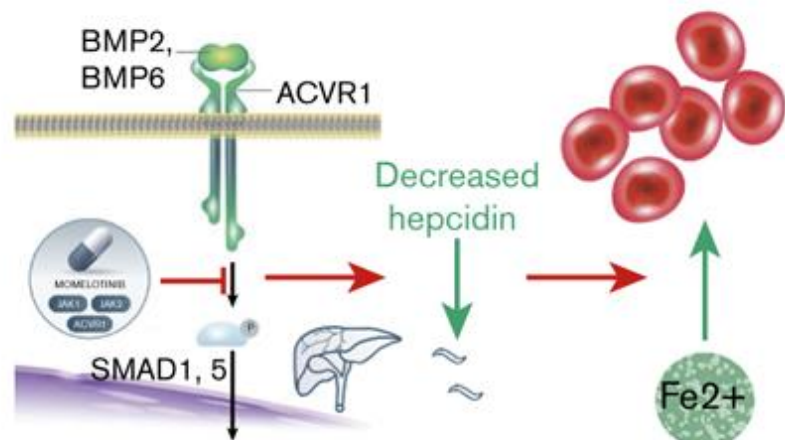


Recommendation 6A

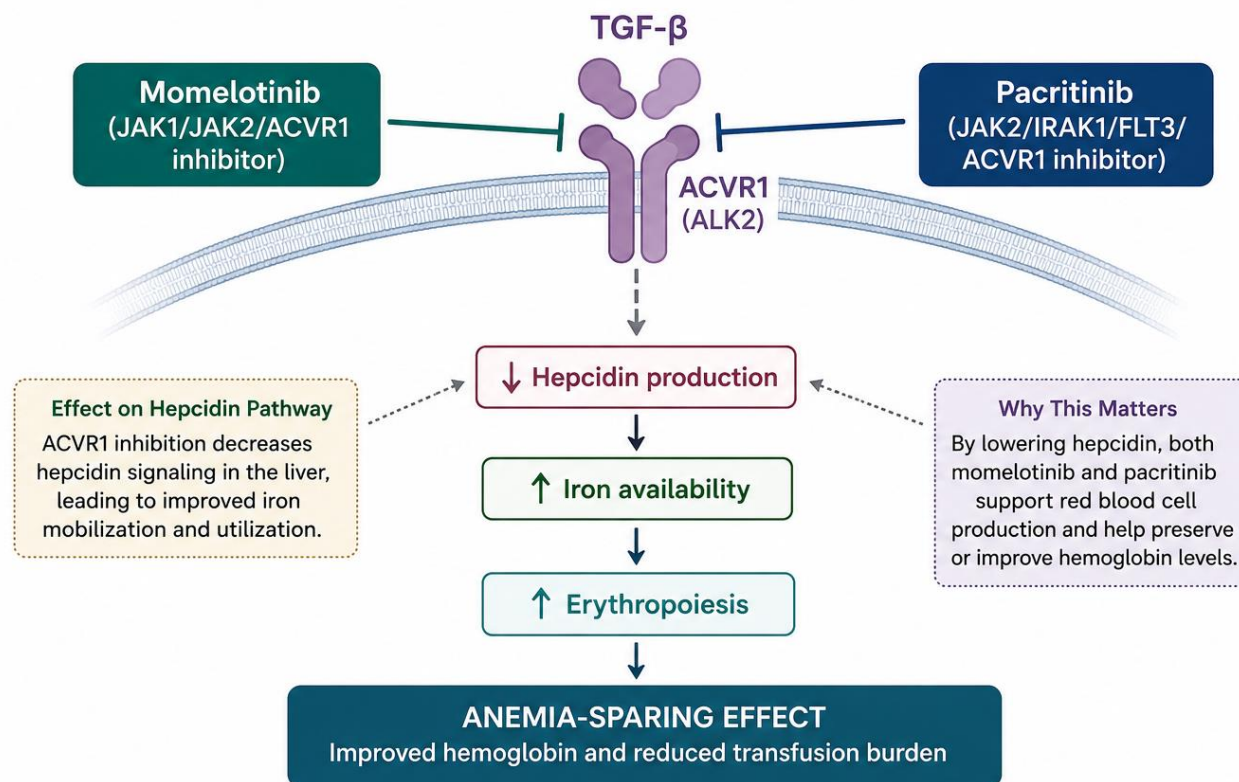
Recommendation	Strength	Evidence Certainty
In patients with myelofibrosis who experience JAK inhibitor–associated anemia that prevents the use of an optimal dose of first-line JAK inhibitor for symptoms and spleen control, the ASH guideline panel suggests switching to momelotinib or pacritinib.	Conditional	Low

Case 7: Anemia Limiting Effective JAK Inhibitor Dosing

Newer JAK inhibitors may reduce anemia and improve anemia and achieve transfusion independence in some patients while controlling splenomegaly and disease-related symptoms



Momelotinib and pacritinib inhibit ACVR1 and may improve anemia. Pacritinib is particularly relevant when anemia coexists with thrombocytopenia.



Case 8: Transfusional Iron Overload (PICO 10)

The patient from Case 7 remains transfusion-dependent. After sustained transfusions, ferritin has risen to 1,500 ng/mL. He is not a transplant candidate.

Question 8

Should iron chelation be started?

- A. Yes, routinely.
- B. Yes, if ferritin >1,000 ng/mL.
- C. No, individualized decision.
- D. Never.

Recommendation 10

Recommendation	Strength	Evidence Certainty
In patients with overt myelofibrosis and transfusional iron overload, the ASH guideline panel suggests against routine iron chelation therapy.	Conditional	Very low

Remark: Special considerations might apply for patients planned for hematopoietic stem cell transplant.

Case 8: Transfusional Iron Overload

Balance of benefits and harms

Potential benefits

- Overall survival*
- Leukemic transformation/ leukemia-related mortality*
- Hematologic benefits

*very low certainty



Adverse events

Present in up to 50% of patients

Primarily:

- Renal
- Gastrointestinal
- Cardiac

Overall insufficient data to routinely suggest

Case 9a: Aspirin Use in Secondary Myelofibrosis (PICO 9)

A 66-year-old man with *JAK2 V617F*-mutated essential thrombocythemia (ET), diagnosed in 2000, has no history of thrombosis. He is Revised IPSET-Thrombosis high risk and has been managed with aspirin 80 mg daily and cytoreduction with hydroxyurea. In 2024, he developed elevated lactate dehydrogenase, splenomegaly, and leukocytosis ($30 \times 10^9/L$); bone marrow biopsy confirmed myelofibrotic transformation. He has no bleeding history or major bleeding risk factors.

Question 9a

How would you manage aspirin?

- A. Maintain aspirin, since the patient is *JAK2 V617F*-mutated, at high thrombotic risk, and tolerating it well.
- B. Discontinue aspirin, as it is no longer required now that the disease has transformed to MF (lower thrombosis risk) and unduly increases bleeding risk.

Case 9b: Aspirin Use in Primary Myelofibrosis (PICO 9)

A 66-year-old man has newly diagnosed primary myelofibrosis (PMF) with *CALR* type 2 mutation. He has no comorbidities, no history of thrombosis, and is asymptomatic. WBC is $15\text{--}20 \times 10^9/\text{L}$, with no significant anemia and a normal platelet count. MIPSS70+ version 2.0 score is low risk.

Question 9b

How would you manage aspirin?

- A. Recommend aspirin, given the higher thrombotic risk in PMF compared with the general population.
- B. No aspirin; favor observation through shared decision-making, given *CALR* mutation, no cardiovascular risk factors or thrombosis history, normal platelet count, and no bleeding risk factors.

Balance of effects: thrombosis

- Prefibrotic MF: higher risk of thrombosis than general population and $\geq$ vascular risk than those with ET and overt MF
- Overt MF: thrombosis incidence ~7%–12%*
 - Subgroup consideration: highest risk in *JAK2* V617F-mutated, age >60 years, cardiovascular risk factors, and lower-risk IPSS*
- Post-PV/ET MF: thrombosis incidence MYSEC cohort ~11%**
 - Post-PV MF consistently demonstrated as being at higher risk (nearly universally *JAK2* V617F-mutated)

*Barbui T et al. Blood Cancer J, 2022/Blood, 2010; Finazzi G et al. Leukemia, 2015; Hernandez-Boluda J-C et al. BJH, 2022; Lussana F et al. Thromb Res, 2009 **Mora B et al. Leukemia, 2022

Balance of effects: bleeding

- Baseline risk:
 - Prefibrotic MF: higher than or comparable to ET*
 - Overt and post-PV/ET MF: potentially increased vs other MPNs**
- Impact of ASA:
 - Extrapolating from PV and ET (indirect evidence):
 - Increased incidence of bleeding in *CALR*-mutated ET patients (vs no effect in *JAK2 V617F*-mutated)
 - No increased major bleeding in PV
 - In MF: potentially increased risk with ASA, but conflicting data***

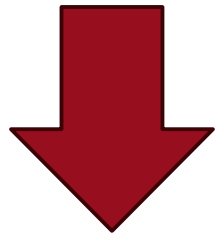
*Finazzi G et al. Leukemia, 2012; Rumi E et al. Oncotarget, 2017; **Larsson AE et al. Blood, 2024; ***Finazzi G et al. Leukemia, 2012; Larsson AE et al. Blood, 2024; Kander EM et al. Int J Hematol, 2015; Kaifie A et al. J Hematol Oncol, 2016

Recommendation 9

Recommendation	Strength	Evidence Certainty
In patients with <i>JAK2 V617F</i>-positive myelofibrosis, the ASH guideline panel suggests primary prevention with low-dose aspirin over no aspirin*. <i>*in the absence of contraindications</i> <i>*panel members emphasized the very low certainty in the evidence</i>	Conditional	Very Low
- In all other MF patients, we suggest a shared decision-making process that incorporates: - MF subtype - Thrombotic risk factors (age >60, cardiovascular risk factors) - Bleeding risk factors (extreme thrombocytosis, acquired von Willebrand disease, thrombocytopenia [platelets $<50 \times 10^9/L$], prior bleeding history)	Conditional	Very Low

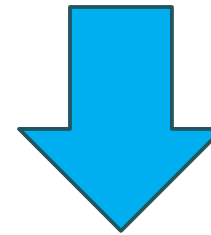
Summary of Decision-Making Regarding Aspirin use in MF

- 66 year-old man
- *JAK2*-mutated post-ET MF
- No previous thrombosis
- Revised IPSET-thrombosis: high risk
- Previously on ASA 80 die and hydroxyurea
- No risk factors for bleeding



PURSUE ASA

- 66 year-old man
- PMF
- *CALR*-mutated
- No CV risk factors, no history of thrombosis
- WBC $15\text{--}20 \times 10^9/\text{L}$, Hb/PLT normal
- MIPSS70+v2.0 = low risk



Watch-and-wait > ASA

(shared decision-making)

Case 10: Higher-Risk MF and Transplant Timing (PICO 7)

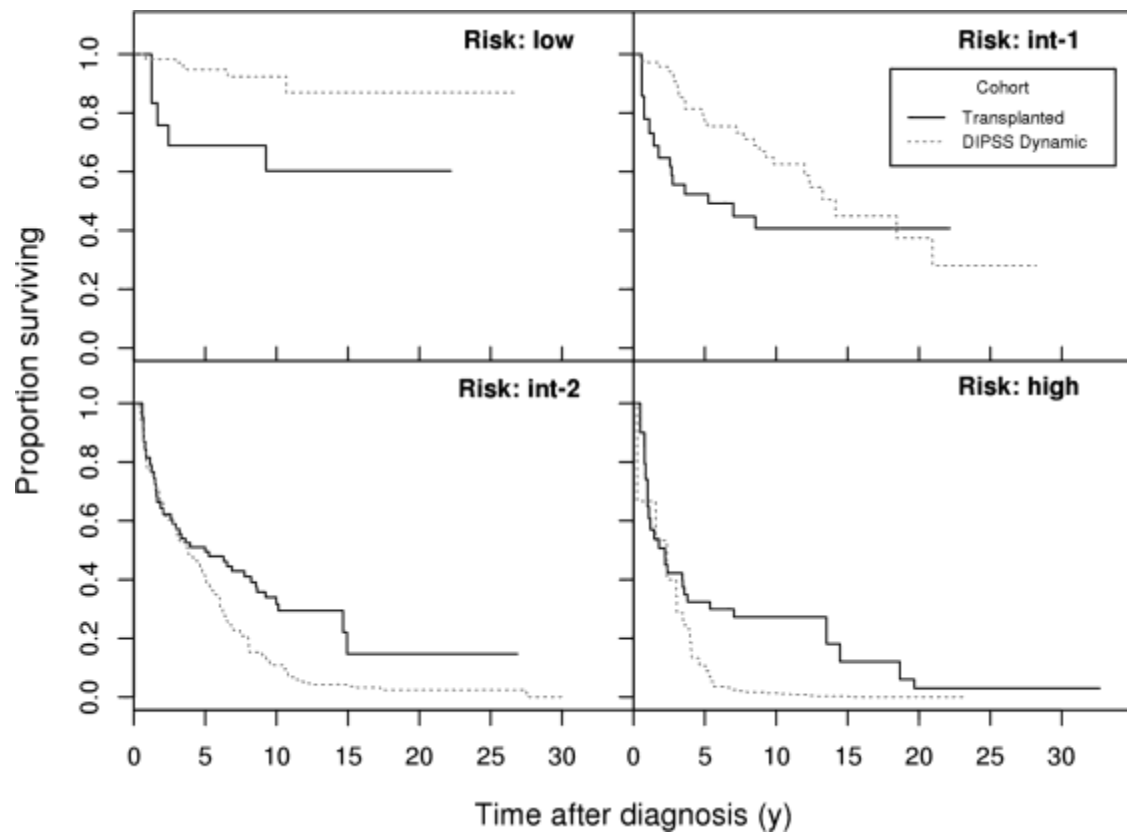
A 62-year-old man has post-ET myelofibrosis with symptomatic splenomegaly (21.5 cm at baseline). WBC is $5.3 \times 10^9/\text{L}$, hemoglobin 7.7 g/dL, and platelet count $87 \times 10^9/\text{L}$, with no blasts. Karyotype is normal. NGS shows *JAK2* 29%, *TET2* 12%, *U2AF1* Q157 23%, *IDH2* 17%, and *SH2B3* 48% (variant of uncertain significance, VUS). Risk stratification: DIPSS-Plus Intermediate-2; MIPSS70+ version 2.0, very high risk. He started ruxolitinib and has had a good spleen and symptom response.

Question 10

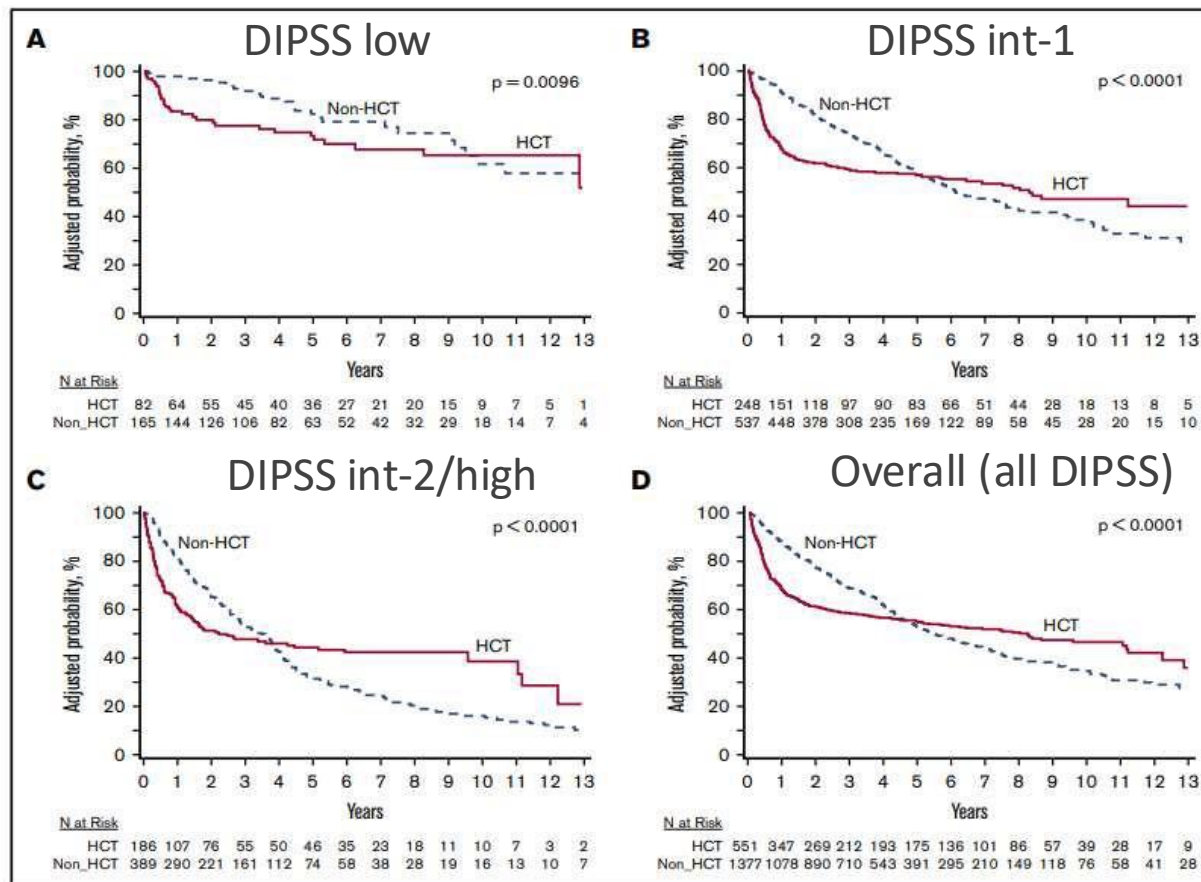
When should this patient be referred for transplant consultation?

- A. Refer now, while response to JAK inhibitor therapy is maintained.
- B. Wait until JAK inhibitor failure or suboptimal response.
- C. Refer only after disease progression.
- D. Do not refer, because the patient is currently responding.

Evidence: Timing of transplant and outcomes



HCT is associated with higher early mortality but may improve longer-term survival in higher-risk MF.



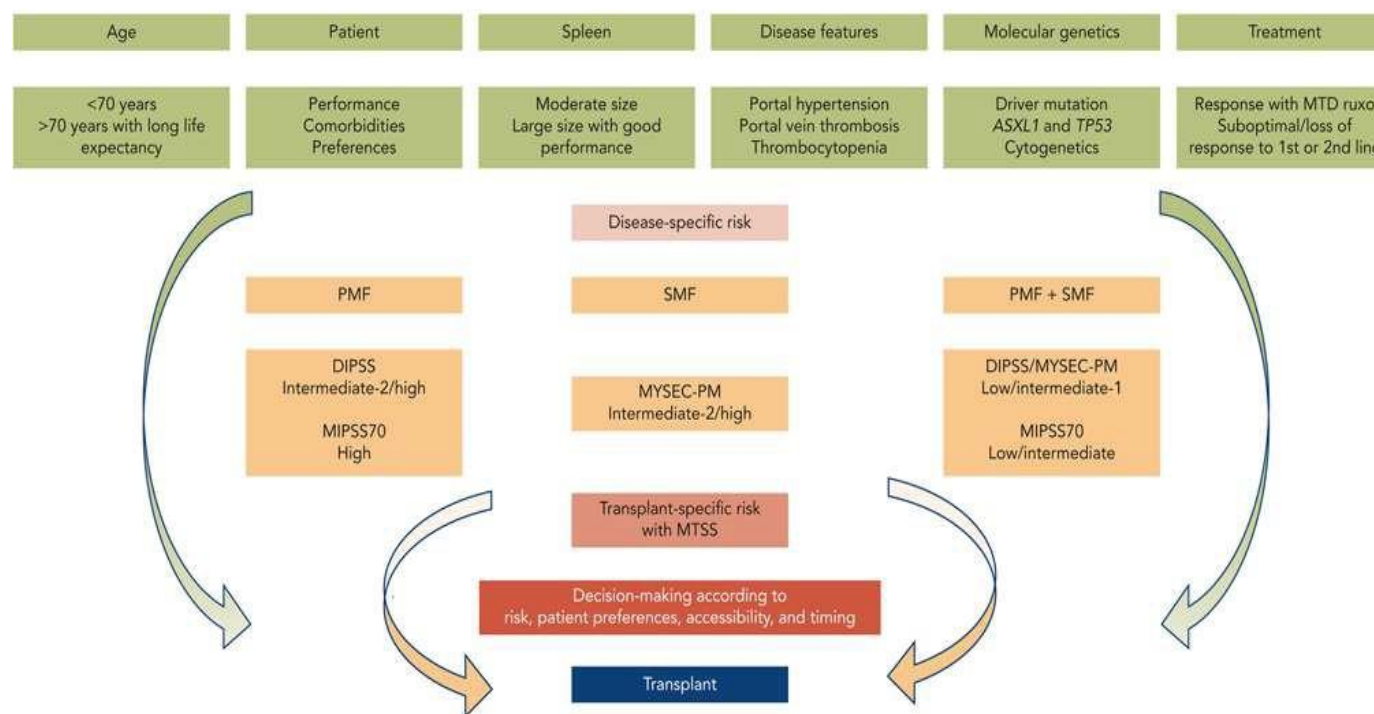


Recommendation 7

Recommendation	Strength	Evidence Certainty
In patients with higher-risk myelofibrosis receiving JAK inhibitor therapy, and responding to therapy, the ASH guideline panel suggests early referral for allogeneic hematopoietic cell transplantation consultation compared to delayed referral after failure of response to JAK inhibitor therapy.	Conditional	Low

Recommendation 7: Good Practice Statements

- **Early referral does not mean immediate transplant** and does not mean transplant will necessarily occur.
- **Prioritize early transplant consultation** for high-risk molecular or cytogenetic features, even with optimal JAK inhibitor response.
- **The final decision regarding transplant should be individualized** based on risks, benefits, patient preferences, and values.





Case 11: Asymptomatic Higher-Risk MF (PICO 8)

Question 11

In a JAK inhibitor–naïve patient scheduled for transplantation, should JAK inhibitor therapy be routinely initiated before transplantation?

- A. Yes, in all transplant candidates.
- B. Yes, but only with marked splenomegaly or disease-related symptoms.
- C. No, routine pre-transplant JAK inhibitor therapy is not recommended.
- D. Never use JAK inhibitors before transplant.

Recommendation 8

Recommendation	Strength	Evidence Certainty
In JAK inhibitor–naïve patients planned for transplantation, the ASH guideline panel suggests against the routine use of pre-transplant JAK inhibitors, except for patients with marked splenomegaly or disease-related symptoms.	Conditional	Very Low

Practical takeaways

- Do not require pre-transplant JAK inhibitor therapy for every patient.
- Consider a JAK inhibitor when marked splenomegaly or disease-related symptoms require treatment.
- Do not delay transplant solely to give routine JAK inhibitor therapy.
- Evidence is very low certainty, and practice should be individualized.

Future Priorities for Research

- Better evidence for extended molecular testing at serial clinical decision points.
- Prospective trials in prefibrotic MF and asymptomatic higher-risk MF.
- Direct comparisons of JAK inhibitor versus non-JAK anemia-directed therapy.
- Better evidence on optimal transplant timing and peri-transplant JAK inhibitor use.
- Prospective studies of aspirin and iron chelation in MF.

In Summary: Back to our Objectives

- Recognize scenarios in which extended molecular testing and interferon-based approaches should be considered in myelofibrosis (MF).
- Select initial treatment strategies for JAK inhibitor–naïve MF across different clinical phenotypes.
- Individualize management of disease-related anemia, JAK inhibitor–associated anemia, iron overload, and thrombosis prevention.
- Apply transplant referral and pre-transplant treatment recommendations in higher-risk MF.



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Learn more about the **ASH myelofibrosis guidelines** at hematology.org/myelofibrosis-guidelines