MYELOFIBROSIS

CHI Formulary Development Project

مجلس الضمان الصحي
Council of Health Insurance

INDICATION UPDATE

ADDENDUM- October 2023

To the CHI Original Myelofibrosis Clinical Guidance- Issued July 2020

Contents

Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

List of Tables

List of Figures

Abbreviations

AHSCT	Allogeneic Hematopoietic Stem Cell Transplant
BCR-ABL1	Breakpoint cluster region/Abelson murine leukemia viral oncogene homolog 1
BCRP	Breast Cancer Receptor Protein
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
DIPSS	Dynamic International Prognostic Scoring System
EPO	Erythropoietin
ET	Essential Thrombocythemia
FISH	Fluorescence in situ hybridization
GIPSS	Genetically Inspired Prognostic Scoring System
HCT	Hematopoietic Cell Transplant
HLA	Human leukocyte Antigen
HTA	Health Technology Assessment
IDF	CHI Drug Formulary
IPSS	International Prognostic Scoring System
IWG-MRT	International Working Group for MPN Research and Treatment
MF	Myelofibrosis
MF-AP	MF in Accelerated Phase
MF-SAF	Myelofibrosis Symptom Assessment Form
MPN	Myeloproliferative Neoplasms
MPN-SAF TSS; MPN 10	MPN-SAF Total Symptom Score
MYSEC-PM	Myelofibrosis Secondary to PV and ET Prognostic Model
NCCN	National Comprehensive Cancer Network
OCT1	Organic Cation Transporter 1
Pgp	P-Glycoprotein
PMF	Prefibrotic/early-stage Myelofibrosis
PV	Polycythemia Vera
RT-PCR	Reverse Transcription Polymerase Chain Reaction

Executive Summary

Myelofibrosis (MF) is one of the heterogeneous disorders of the hematopoietic system collectively known as Philadelphia chromosome–negative myeloproliferative neoplasms (MPN)[1]. More specifically, myelofibrosis is a Breakpoint cluster region/Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL1)-negative chronic myeloproliferative neoplasm that includes primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis[2].

The World Health Organization (WHO) classification system currently recognizes four variants of myeloproliferative neoplasms (MPN) associated with JAK2, CALR or MPL mutations: primary myelofibrosis (PMF), prefibrotic PMF (pre-PMF), essential thrombocythemia (ET) and polycythemia vera (PV)[3]. Literatures showed that 5–30% patients with ET or PV experience fibrotic progression of their disease over time, referred to as post-ET and post-PV myelofibrosis, respectively[4,5]. At the same time, all the mentioned MPN variants might evolve into blast phase disease (MPN-BP), operationally defined by the presence of ≥ 20% blasts in the blood or bone marrow[WHO 32022]. The current diagnosis of PMF is based on the 2022 International Consensus Classification (ICC) which differs from the World Health Organization (WHO) classification system; however, both are similar in subclassification of MPN. The ICC subclassifies PMF into “prefibrotic” and “overtly fibrotic” stages[6].

Clinical manifestations in PMF include severe anemia, marked hepatosplenomegaly and constitutional symptoms like fatigue, night sweats and fever. Other manifestations include cachexia, bone pain, splenic infarct, pruritus, thrombosis, and bleeding[7,8]. Moreover, ineffective erythropoiesis and hepatosplenic Extramedullary hematopoiesis (EMH) are the main causes of anemia and organomegaly in MF patients, respectively[9].

Data on prevalence of MF and its economic burden in Saudi Arabia remains limited. Yet, the economic impact of MF has been studied in individual real-world settings, and MF was associated with significant economic burden and work productivity loss to the health system, patients, and their families. studies conducted in the USA showed that total medical healthcare costs associated with MF ranged from USD 21,000 to USD 66,000 per patient[10–12]. Three other European studies reported that the annual productivity losses per patient ranged from EUR 7,774 to EUR 11,000, with total annual productivity losses as high as EUR 217,975[13,14].

Selection of appropriate treatment of PMF is based on presence of symptoms and a prognostic modeling that started with the development of the International Prognostic Scoring System (IPSS) in 2009 and then evolved to the dynamic prognostic model (DIPSS) in 2010, and the DIPSS-plus in 2011. More recently, mutations were considered in the development of three new prognostic models in PMF: MIPSS70, MIPSS70+ version 2.0 (MIPSSv2), and GIPSS[9,15,16].

According to the relevant sources, this report gathers all the clinical and economic evidence pertaining to MF. The primary goal of the Council of Health Insurance

(CHI) in issuing MF guidelines is to incorporate the most up-to-date clinical and economic evidence regarding drug therapies into the IDF (CHI Drug Formulary). This objective aims to ensure that patients with MF in Saudi Arabia have timely and secure access to appropriate treatments while prioritizing their safety. The focus of the review was on Saudi, American, European and England guidelines issued within the last three years.

All recommendations are well supported by reference guidelines, Grade of Recommendation (GoR), Level of Evidence (LoE) and Strength of Agreement (SoA) reflecting specific drug class role in the management of bipolar disorder.

This report functions as an addendum to the prior CHI Myelofibrosis disease report and seeks to offer guidance for the effective management of MF.

Regarding the management of MF, two new drugs were extensively mentioned in updated guidelines, however, both were approved by the FDA for treatment, yet not registered by SFDA. No changes or modifications were made to existing drugs and no drugs were withdrawn from Saudi FDA.

Below is a table summarizing the major changes based on the different MF guidelines used to issue this report:

Table 1. General Recommendations for the Management of Myelofibrosis

Management of Myelofibrosis		
General Recommendations	**Level of Evidence/Grade of Recommendation**	**Reference**
The WHO classification of myeloid neoplasms was revised in 2022 to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since 2008.	Not graded	Myeloproliferative Neoplasms, NCCN Clinical Practice Guidelines in Oncology, (Version 2.2023)

Current diagnosis of PMF is based on the 2022 ICC criteria and involves a composite assessment of clinical and laboratory features. Subclassification into overtly fibrotic and early/pre-fibrotic stages is to be noted and the distinction from other MPNs required.	Not graded	Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management; American Journal of Hematology
The selection of appropriate treatment should be based on the risk score and the presence of symptoms.	Not graded	Myeloproliferative Neoplasms, NCCN Clinical Practice Guidelines in Oncology, (Version 2.2023) The 2020 revision of the guidelines for the management of myeloproliferative neoplasms; The Korean Association of Internal Medicine.
Prognostic scoring used evolved from the International Prognostic Scoring System in 2009 to the DIPSS in 2010, and the DIPSS-plus in 2011	Not graded	The 2020 revision of the guidelines for the management of myeloproliferative neoplasms; The Korean Association of Internal Medicine.
Patients with asymptomatic lower-risk MF should be observed and monitored for signs and symptoms of disease progression with MPN-SAF TSS (MPN-10). Ruxolitinib, peginterferon alfa-2a, or a clinical trial are included as options for	Not graded	Myeloproliferative Neoplasms, NCCN Clinical Practice Guidelines in Oncology, (Version 2.2023)

patients with symptomatic disease. Hydroxyurea has been shown to be an effective treatment option for the hyperproliferative manifestations of lower-risk MF (thrombocytosis or leukocytosis).		
Evaluation for allogeneic HCT is recommended for all patients with higher-risk MF and allogeneic HCT is recommended for patients who meet transplant eligibility criteria. Prior exposure to Ruxolitinib may improve outcomes after allogeneic HCT.	Not Graded	Myeloproliferative Neoplasms, NCCN Clinical Practice Guidelines in Oncology, (Version 2.2023)
Ruxolitinib, Fedratinib, or clinical trial are options for patients with higher-risk MF with platelet count > $50x10^9$/L who are not candidates for transplant.	(Category 1 recommendations).	Myeloproliferative Neoplasms, NCCN Clinical Practice Guidelines in Oncology, (Version 2.2023)

Section 3 lists the key recommendations synthesis for the treatment of myelofibrosis.

Section 1.0 Summary of Reviewed Clinical Guidelines and Evidence

This section is divided into two parts: the first includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Myelofibrosis report, and the second includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This part contains the updated versions of the guidelines mentioned in the 2020 CHI myelofibrosis report and the corresponding recommendations:

Two guidelines were used in the last version of myelofibrosis. Updates were only found for NCCN Clinical Practice Guidelines in Oncology, Myelofibrosis version 3, published in 2022 in comparison with NCCN Guidelines on Myeloproliferative neoplasms 2020.

Table 2. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
ESMO Guidelines on Philadelphia chromosome-negative chronic myeloproliferative neoplasms (**2015**)	N/A*
NCCN Guidelines on Myeloproliferative neoplasms (**v.1 2020**)	Myeloproliferative Neoplasms, **Version 2.2023**, **NCCN** Clinical Practice Guidelines in Oncology

**: No updated version available:* the existing version is the most recent one and no further updates or revisions have been made or released.

1.1.1 National Comprehensive Care Network (NCCN) Myeloproliferative Neoplasms (Version 2.2023)

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MPN were developed with the goal of providing recommendations for the management of MPN in adults. The Guidelines include recommendations for the diagnostic workup, risk stratification, treatment, and supportive care strategies for the management of myelofibrosis, polycythemia vera, and essential thrombocythemia[1].

Definition: Myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET) are a group of heterogeneous disorders of the hematopoietic system collectively known as Philadelphia chromosome–negative myeloproliferative neoplasms (MPN).

MPN are characterized by a complicated symptom profile.

Variable laboratory abnormalities are observed depending on the type of MPN, including erythrocytosis, thrombocytosis, and leukocytosis, and sometimes myeloid immaturity, especially in progressive myelofibrosis.

Molecular Abnormalities in MF:

The diagnosis and management of patients with MPN has evolved since the identification of JAK-STAT "driver" mutations (JAK2, CALR, and MPL mutations)

The development of targeted therapies has resulted in significant improvements in disease-related symptoms and quality of life.

JAK2 V617F mutations account for 60% of patients MF. It can be identified in hematopoietic stem and progenitor cells.

Activating mutations in the thrombopoietin receptor gene (MPL W515L/K) are reported in approximately 5%–8% of all patients with MF.

Frameshift mutations in exon 9 of the calreticulin gene (CALR) are reported in approximately 20%–35% of all patients with ET and MF (accounting for approximately 60%–80% of patients with JAK2/MPL-negative ET and MF).

Table 3. Prognostic Significance of Mutations

Mutated Gene	Primary Myelofibrosis (PMF)
JAK2 V617F	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation
MPL W515L/K	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation
CALR	Improved survival compared to *JAK2* mutation and "triple-negative" PMF Lower risk of thrombosis compared to JAK2 mutation
CALR Type 1/Type 1-like	Improved overall survival (OS) compared to *CALR* type 2/type 2-like and *JAK2 V617F* mutation
"Triple Negative" (non-mutated *JAK2*, *MPL*, and *CALR*)	Inferior leukemia-free survival compared to patients with *JAK2*- and/or *CALR*-mutated PMF Inferior OS compared to patients with *CALR*-mutated PMF
ASXL1	Independently associated with inferior OS and leukemia-free survival as well as lower progression-free survival (PFS) following HCT

EZH2	Independently associated with inferior OS
RAS	Associated with decreased OS
IDH1/2	Independently associated with inferior leukemia-free survival as well as lower PFS following HCT
SRSF2	Independently associated with inferior OS and leukemia-free survival
Combined *CALR* and *ASXL1* status	Survival longest for *CALR*(+)*ASXL1*(-) patients (median 10.4 years) and shortest in *CALR*(-) *ASXL1*(+) patients (median 2.3 years) Intermediate survival (median 5.8 years) for *CALR*(+)*ASXL1*(+) or *CALR*(-)*ASXL1*(-) patients
TP53	Associated with leukemic transformation
U2AF1 Q157	Inferior OS compared to patients with *U2AF1* S34 mutated or *U2AF1* unmutated PMF. The effect was most evident in younger patients.
U2AF1 or *DNMT3A* or *CBL*	Associated with worse OS in patients with MF undergoing allogeneic HCT

Diagnostic Classification

The WHO classification of myeloid neoplasms was first published in 2001 and was updated in 2008. It was revised in 2017 and once again in 2022 to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since 2008.

MF can present as a de novo disorder (PMF) or it can develop from the progression of PV and ET (post-PV MF or post-ET MF).

- Prefibrotic/early-stage PMF is characterized by an increase in atypical megakaryocytes, reduced erythropoiesis, and increased age-matched bone marrow cellularity.
- However, overt bone marrow fibrosis might be absent in early-stage/prefibrotic PMF, leading to a diagnosis of ET.
- The diagnosis of PMF requires meeting all 3 major criteria and at least one minor criterion as outlined in the revised 2017 WHO criteria.
- The diagnosis of post-PV MF or post-ET MF is based on the 2008 International Working Group for MPN Research and Treatment (IWG-MRT) diagnostic criteria, requiring the documentation of a previous diagnosis of PV or ET as defined by the WHO criteria and the development of European bone marrow fibrosis grade MF-2 to MF-3 (or 3–4+, depending on the scale) and at least 2 minor criteria.

Workup of Suspected MPN

Initial evaluation of patients with suspected MPN should include a history and physical examination, palpation of spleen, evaluation of thrombotic and hemorrhagic events, cardiovascular risk factors, as well as transfusion and medication history.

Laboratory evaluations: CBC with differential, microscopic examination of the peripheral smear, comprehensive metabolic panel with serum uric acid, serum lactate dehydrogenase, liver function tests, serum erythropoietin (EPO) level, and serum iron studies.

Human leukocyte antigen (HLA) typing should be performed for patients with MF for whom allogeneic hematopoietic cell transplant (HCT)would be considered.

Fluorescence in situ hybridization (FISH) or a multiplex reverse transcription polymerase chain reaction (RT-PCR), if available, on peripheral blood to detect BCR::ABL1 transcripts and exclude the diagnosis of CML is especially recommended for patients with left-shifted leukocytosis and/or thrombocytosis with basophilia.

Molecular testing on blood or bone marrow for JAK2 V617F, CALR and MPL mutations is recommended as part of the workup for all patients.

Bone marrow aspirate with iron stain and biopsy with trichrome and reticulin stains and bone marrow cytogenetics are necessary to accurately distinguish the bone marrow morphologic features between the disease subtypes (early or prefibrotic PMF, ET, and masked PV).

Assessment of Symptom Burden

MPN are characterized by a complicated symptom profile resulting in reductions in quality of life, functional status, and activities of daily living.

Constitutional symptoms: fever, night sweats, and weight loss, are frequently reported in patients with MF.

The Myelofibrosis Symptom Assessment Form (MF SAF): 20-item tool used for the assessment of MF-associated symptoms, including fatigue, symptoms associated with splenomegaly (early satiety, abdominal pain or discomfort, inactivity, and cough), constitutional symptoms and quality of life.

MPN-SAF Total Symptom Score (MPNSAF TSS; MPN 10): a simplified tool used for the assessment of the 10 most relevant symptoms in patients with MPN (fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever) in both clinical practice and clinical trial settings.

Management of Myelofibrosis

The treatment approach is currently identical for PMF and post-PV or post-ET MF. Referral to specialized centers with expertise in the management of MPN is strongly recommended for all patients diagnosed with MF.

Primary Myelofibrosis:

The International Prognostic Scoring System (IPSS), DIPSS, and DIPSS-Plus are the 3 most common prognostic scoring systems used for the risk stratification of patients with MF.

Myelofibrosis Secondary to PV and ET Prognostic Model (MYSEC-PM) is recommended for the risk stratification of post-PV or post-ET MF.

Treatment Options:

- **Interferons** may demonstrate activity in low-risk MF, but they are generally not recommended for higher-risk disease.
- The combination of interferons with JAK inhibitors is under investigation in clinical trials.
- **Ruxolitinib**: a potent and selective JAK1 and JAK2 inhibitor FDA-approved for the treatment of intermediate-risk or high-risk MF as determined by IPSS.
- The use of Ruxolitinib in Low-risk MF patients is based on the evidence from retrospective analysis and nonrandomized clinical studies: it may be an appropriate treatment option for symptomatic patients with low-risk MF.
- Anemia and thrombocytopenia were the most common hematologic toxicities associated with Ruxolitinib.
- **Fedratinib** is a potent and selective JAK2 and FLT3 inhibitor approved by the FDA for the treatment of intermediate- 2 or high-risk MF as determined by IPSS.
- Anemia and thrombocytopenia were the most common hematologic toxicities associated with Fedratinib. Diarrhea, vomiting, and nausea were the most common nonhematologic toxicities and usually abated after the first 28-day cycle.
- **Pacritinib**: a JAK2, FLT3, and IRAK1 inhibitor, was evaluated in patients with intermediate-1, intermediate-2, and high-risk MF. It was approved for the treatment of intermediate or high-risk MF with a platelet count < $50x10^9$/L.
- Thrombocytopenia, anemia, and neutropenia were the most common grade 3 or 4 treatment-emergent hematologic events in patients with MF resistant to or intolerant of Ruxolitinib who received twice-daily Pacritinib 200 mg.
- **Allogeneic HCT** is the only potentially curative treatment option resulting in long-term remissions for patients with MF and can be considered for high-risk patients.

Treatment Recommendations Based on Symptom Assessment and Risk Stratification

The selection of appropriate treatment should be based on the risk score and the presence of symptoms:

1. **Lower-risk MF**

- Patients with asymptomatic lower-risk MF should be observed and monitored for signs and symptoms of disease progression with MPN-SAF TSS (MPN-10).
- Ruxolitinib, peginterferon alfa-2a, or a clinical trial are included as options for patients with **symptomatic** disease.
- Hydroxyurea has been shown to be an effective treatment option for the hyperproliferative manifestations of lower-risk MF (thrombocytosis or leukocytosis).
- Treatment decisions regarding allogeneic HCT should be individualized in low-risk MF due to the high transplantation- related morbidity and mortality.

2. **Higher-Risk MF**

- Evaluation for **allogeneic HCT** is recommended for all patients with higher-risk MF and allogeneic HCT is recommended for patients who meet transplant eligibility criteria.
- Bridging therapy can be used to decrease marrow blasts to an acceptable level prior to allogeneic HCT.
- Prior exposure to Ruxolitinib may improve outcomes after allogeneic HCT.
- Guidelines recommend continuation of JAK inhibitors near to the start of conditioning therapy for the improvement of splenomegaly and other disease related symptoms.
- Ruxolitinib, Fedratinib, or clinical trial are options for patients with higher-risk MF with platelet count > $50x10^9$/L who are not candidates for transplant (category 1 recommendations).

Monitoring Response and Follow-up Therapy

The goal of treatment is to reduce symptom burden and minimize the risk of leukemic transformation.

Changes in symptom status could be a sign of disease progression. Therefore, change in symptom status should prompt evaluation of treatment efficacy and/or disease status.

Evaluation of treatment efficacy should include CBC to assess normalization of blood counts, monitoring symptom status using MPN-SAF TSS, and monitoring spleen size either by palpation or imaging.

Continuation of JAK inhibitors is recommended for patients achieving response to initial treatment.

Ruxolitinib should be discontinued if there is no response or improvement of symptoms after 6 months.

For patients with symptomatic lower-risk MF with no response or loss of response following initial treatment, an alternate option not used for initial treatment is recommended (clinical trial, ruxolitinib, peginterferon alfa-2a, or hydroxyurea [if cytoreduction would be symptomatically beneficial]).

Pacritinib may also be considered for patients with platelet count < $50x10^9$/L.

For patients with higher-risk MF with platelet count ≥ $50x10^9$/L who are not transplant candidates and with no response or loss of response after initial treatment, enrollment in a clinical trial or an alternate JAK inhibitor (ruxolitinib, fedratinib, or pacritinib [category 2B]) not used before is recommended.

Tapering and discontinuation of Ruxolitinib according to the prescribing information is recommended prior to the initiation of Fedratinib or another therapy.

Management of MF-Associated Anemia

Anemia is considered a **negative prognostic risk factor** for survival in patients with MF.

The use of recombinant human EPO or darbepoetin alfa has resulted in anemia responses (transfusion independence with normal hemoglobin levels, sustained increase in hemoglobin levels [>2 g/dL] within 12 weeks, or > 50% reduction in transfusion requirements within 12 weeks) in 45%–60% of patients with MF.

Lower serum EPO levels (<125 mU/mL), smaller spleen size, and low RBC transfusion requirements have been associated with favorable responses.

In a study of 50 patients with MF and anemia, danazol therapy resulted in an anemia response in 30% of patients, and responses were less frequent in patients with transfusion dependency (19% compared with 44% in patients without transfusion requirements).

In the phase III MOMENTUM trial, patients with PMF or post-PV/ET MF with DIPSS intermediate-1, intermediate-2, or high-risk disease were randomized 2:1 to receive treatment with momelotinib, a JAK1/2 and ACVR1/ALK2 inhibitor, or danazol. The patients had symptomatic disease, anemia, and had previously received treatment with a JAK inhibitor. At 24 weeks, a significantly higher percentage of patients in the momelotinib arm had a total symptom score response rate of 50% or greater (25% vs. 9%; P = .0095), transfusion independence rate (31% vs. 20%; one-sided P = .0064), and a spleen volume reduction of 35% or greater (23% vs. 3%; P = .0006) compared to patients in the danazol arm.

1.2 Additional Guidelines

This part includes the added guidelines to the previous CHI Myelofibrosis report, along with their recommendations.

Table 4. List of Additional Guidelines

List of additional guidelines
American Journal of Hematology (Review Article) - Primary Myelofibrosis: **2023** Update on Diagnosis, Risk-Stratification, and Management
European LeukemiaNet Philadelphia Chromosome-Negative Classical Myeloproliferative Neoplasms: Revised Management Recommendations (**2018**)
Korean Association of Internal Medicine: The **2020** Revision of the Guidelines for the Management of Myeloproliferative Neoplasms

1.2.1 American Journal of Hematology (Review Article) - Primary Myelofibrosis: 2023 Update on Diagnosis, Risk-Stratification, and Management

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by stem cell-derived clonal myeloproliferation that is often but not always accompanied by JAK2, CALR, or MPL mutations[9].

Additional disease features include bone marrow reticulin/collagen fibrosis, aberrant inflammatory cytokine expression, anemia, hepatosplenomegaly, extramedullary hematopoiesis (EMH), constitutional symptoms, cachexia, leukemic progression, and shortened survival.

Diagnosis:

Current diagnosis of PMF is based on the 2022 ICC criteria and involves a composite assessment of clinical and laboratory features; subclassification into overtly fibrotic and early/pre-fibrotic stages is to be noted (Table4) and the distinction from other MPNs required.

Table 5. International Consensus Classification (ICC) Diagnostic Criteria for Primary Myelofibrosis (PMF), Overt and Pre-Fibrotic

Primary myelofibrosis (overtly fibrotic) (diagnosis requires meeting all three major criteria and one minor criterion)	Primary myelofibrosis (Pre-fibrotic/early stage) (diagnosis requires meeting all three major criteria and one minor criterion)
MAJOR CRITERIA	
1. Megakaryocyte proliferation and atypia[a] accompanied by≥grade 2 reticulin/collagen fibrosis[b]	1. Megakaryocyte proliferation and atypia[a] accompanied by≤grade 1

	reticulin/collagen fibrosis, granulocyte proliferation/decreased erythropoiesis
2. Presence of JAK2, CALR or MPL mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis.	2. Presence of JAK2, CALR or MPL mutations, or presence of other clonal markers, or absence of evidence for reactive bone marrow fibrosis.
3. Not meeting ICC criteria for other myeloid neoplasms	3. Not meeting ICC criteria for other myeloid neoplasms
MINOR CRITERIA	
Anemia not otherwise explained	Anemia not otherwise explained
Leukocytosis ≥ 11 × 109/L	Leukocytosis ≥ 11 × 109/l
Palpable splenomegaly	Palpable splenomegaly
Increased serum lactate dehydrogenase	Increased serum lactate dehydrogenase
A leukoerythroblastic blood smear	

b Diffuse often coarse fiber network with or without evidence of collagenization (trichrome stain).

a Aberrant nuclear/cytoplasmic ratio; hyperchromatic and irregularly folded nuclei; dense megakaryocyte clustering; these changes are often accompanied by increased cellularity, granulocytic proliferation and decreased erythropoiesis.

The diagnosis of post-PV or post-ET MF should adhere to criteria published by the International Working Group for MPN Research and Treatment (IWG-MRT) (table 5).

Table 6. International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) Recommended Criteria for Post-Polycythemia Vera and Post-Essential Thrombocythemia Myelofibrosis

Post-polycythemia vera myelofibrosis (post-PV MF)	**Post-essential thrombocythemia myelofibrosis (post-ET MF)**
REQUIRED	
Prior documentation of ICC defined PV	Prior documentation of ICC defined ET
Bone marrow fibrosis grade ≥ 2b	Bone marrow fibrosis grade ≥ 2b
ADDITIONAL CRITERIA (TWO REQUIRED)	
Anemia or loss of phlebotomy requirement.	Anemia and≥2 g/dl decrease in hemoglobin level.
A leuko-erythroblastic blood smear	A leuko-erythroblastic blood smear
Increasing splenomegaly	Increasing splenomegaly
Development of constitutional symptoms	Development of constitutional symptoms

	Increased serum lactate dehydrogenase

a ICC, International consensus classification. b Diffuse often coarse fiber network with or without evidence of collagenization (trichrome stain).

Prefibrotic PMF with thrombocytosis can mimic ET in its presentation and mutation profile (both can express JAK2, CALR, or MPL mutations) and, therefore, careful morphologic examination is necessary for distinguishing the two.

Risk Stratification:

Contemporary prognostic modeling in PMF started with the development of the International Prognostic Scoring System (IPSS) in 2009.

The **IPSS** for PMF was designed for use at time of initial diagnosis and applies five independent predictors of inferior survival: age > 65 years, hemoglobin <10 g/dL, leukocyte count >25 × 109/L, circulating blasts ≥1%, and presence of constitutional symptoms.

The presence of 0, 1, 2, and ≥ 3 adverse factors defined low, intermediate-1, intermediate-2, and high-risk disease, respectively.

The IWG-MRT subsequently developed a dynamic prognostic model (DIPSS) that utilizes the same prognostic variables used in IPSS but can be applied at any time during the disease course.

DIPSS assigned two, instead of one, adverse points for hemoglobin <10 g/dL, and risk categorization was accordingly modified: low (0 adverse points), intermediate-1 (1 or 2 points), intermediate-2 (3 or 4 points), and high (5 or 6 points).

The incorporation of three additional DIPSS-independent risk factors (platelet count <100 × 109/L, red cell transfusion need, and unfavorable karyotype) to DIPSS led to the development of **DIPSS-plus**.

The four DIPSS-plus risk categories based on the aforementioned eight risk factors are low (no risk factors), intermediate-1 (one risk factor), intermediate-2 (two or 3 risk factors), and high (four or more risk factors)

More recently, mutations were considered in the development of three new prognostic models in PMF: MIPSS70, MIPSS70+ version 2.0 (MIPSSv2), and GIPSS.

Table 7. Contemporary Prognostic Scoring Systems for Primary Myelofibrosis

Models	Variables	Risk Category					
		Very low	**Low**	**Intermediate -1**	**Intermediate -2**	**High**	**Very High**
IPSS[d] International Prognostic Scoring System	Age >65 years (1 point) Constitutional symptoms[a] (1 point) Hemoglobin <10 g/dl (1 point) Leukocytes >25x10^9/L (1 point) Circulating blasts≥1% (1 point)	NA	0 points 11.3 years	1 point 7.9 years	2 points 4 years	≥3 points 2.3 years	NA
DIPSS[e] Dynamic International Prognostic Scoring System	Age >65 years (1 point) Constitutional symptoms (1 point) Hemoglobin <10 g/dl (2 points) Leukocytes >25x10^9/L (1 point) Circulating blasts≥1% (1 point)	NA	0 point Not reached	1-2 points 14.2 years	3-4 points 4 years	5-6 points 1.5 years	NA
DIPSS-plus[e]	Age > 65 years (1 point) Constitutional symptoms[a] (1 point) Hemoglobin <10 g/dl (1 point) Leukocytes >25x10^9/L (1 point) Circulating blasts≥1% (1 point) Unfavorable karyotype[h] (1 point) Platelet count <100x10^9/L (1 point) Transfusion needs (1 point)	NA	0 point 15.4 years	1 point 6.5 years	2-3 points 2.9 years	≥4 points 1.3 years	NA
MIPSS70[d] Mutation-enhanced International Prognostic Scoring System (Age≤70 year	≥2 HMR mutations[b] (2 points) Leukocytes >25x10^9/L (2 points) Platelets <100x10/L (2 points) Hemoglobin <10 g/dl (1 point) Circulating blasts≥2% (1 point) BM fibrosis grade≥2 (1 point) Constitutional symptoms[a] (1 point) Type 1/like CALR absent (1 point) One HMR mutation[b] (1 point)	NA	0-1 point Not reached	2-4 points 6.3 years	-	≥5 points 3.1 years	NA
MIPSS70+v2[e]	Very high-risk karyotype[f] (4 points) Unfavorable karyotype[g] (3 points)	0 point Not reached	1-2 points 16.4 years	3-4 points 7.7 years	-	5-8 points 4.1 years	≥9 points 1.8 years

	≥2 HMR mutations[c] (3 points) One HMR mutation[c] (2 points) Type 1/like CALR absent (2 points) Constitutional symptoms[a] (2 points) Severe anemia[i] (2 points) Moderate anemia[j] (1 point) Circulating blasts≥2% (1 point)						
GIPSS[e] Genetics-inspired International Prognostic Scoring System	Very high-risk karyotype[f] (2 points) Unfavorable karyotype[g] (1 point) ASXL1mutation (1 point) SRSF2mutation (1 point) U2AF1Q157 mutation (1 point) Type 1/like CALR absent (1 point)	NA	0 point 26.4 years	1 point 8 years	2 points 4.2 years	≥3 points 2 years	NA

[a] ***Constitutional symptoms****=weight loss, fever, drenching night sweats.*
[b] ***High molecular risk (HMR)*** *mutations for MIPSS70 include ASXL1, SRSF2, EZH2, IDH1, IDH2.*
[c] ***HMR for MIPSSv2 and GIPSS*** *include ASXL1 .SRSF2 and U2AF1 Q157.*
[d] *Parameters used at time of diagnosis.*
[e] *Parameters used at any time in the clinical course.*
[f] *Very high-risk (VHR) karyotype=single/multiple abnormalities of_7, inv (3)/3q21, i(17q), 12p-/12p11.2 or 11q-/11q23, single/multiple autosomal trisomies other than+9 and+8.*
[g] *Unfavorable karyotype in the context of GIPSS/MIPSSv2=any abnormal karyotype other than VHR karyotype, normal karyotype or sole abnormalities of 20q-, 13q-,+9, chr. 1 translocation/duplication,–Y, or sex chromosome abnormality other than–Y.*
[h] *Unfavorable karyotype in the context of DIPSS-plus=complex karyotype or sole or two abnormalities that include+8,_7/7q-, i(17q), inv (3),5/5q-,12p- or 11q23 rearrangement any*
[j] *Severe anemia: Hemoglobin <8 g/dl in women and <9 g/dl men.jModerate anemia: Hemoglobin 8–9.9 g/dl in women and 9–10.9 g/dl men*

Treatment:

The only treatment modality that is currently capable of prolonging survival or potential cure in MF is allogeneic hematopoietic stem cell transplant (AHSCT).

For the individual patient, the risk of AHSCT must be balanced against expected survival without AHSCT.

Current drug therapy for PMF is mostly palliative in scope and has not been shown to favorably modify the disease natural history or prolong survival.

JAK2 inhibitor (JAKi) therapy in MF has not been shown to reverse bone marrow fibrosis or induce complete or partial remissions; instead, its value is limited to symptoms relief and reduction in spleen size. Recently introduced JAKi (i.e., Momelotinib and Pacritinib) might also possess erythropoietic benefit.

Clinical trial participation or symptom-directed therapy is considered in treatment-requiring MIPSSv2 intermediate-risk dis-ease and in higher risk patients that are not eligible for AHSCT (figure1).

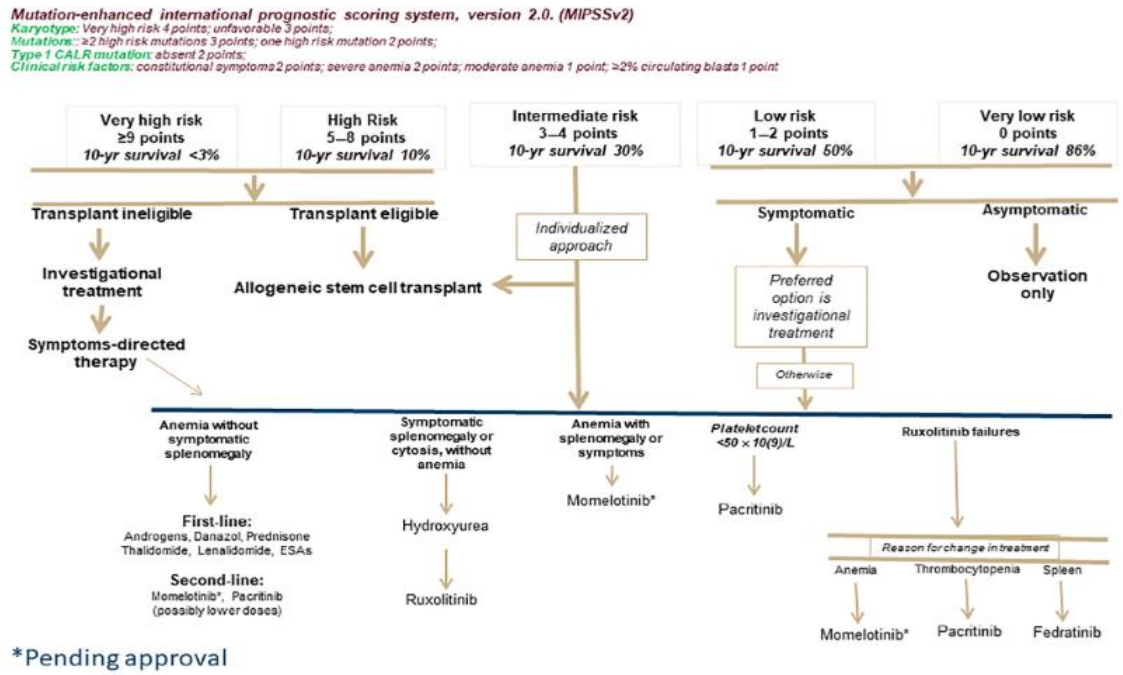

Figure 1. *Risk-adapted treatment approach in primary myelofibrosis using the mutation- and karyotype-enhanced international prognostic system, version 2.0. (MIPSS v2); Adapted from the American Journal of Hematology 2023.*

Allogeneic hematopoietic stem cell transplant in myelofibrosis

At present, AHSCT is the only treatment modality in MF with the potential to cure the disease or prolong survival.

Pre-transplant management of marked splenomegaly in MF includes splenectomy, use of JAKi therapy, or involved-field radiotherapy.

SYMPTOMS DIRECTED THERAPY

Management of anemia in the absence of symptomatic splenomegaly

Non-JAKi drugs are preferred as first-line therapy for MF-associated anemia that is not accompanied by symptomatic splenomegaly or constitutional symptoms.

These include androgens: testosterone enanthate 400–600 mg IM weekly, oral fluoxymesterone 10 mg TID, prednisone (0.5 mg/kg/day), danazol (600 mg/day), thalidomide (50 mg/day) ± prednisone or lenalidomide (10 mg/day) ± prednisone (10 mg/day).

Erythropoiesis stimulating agents (ESAs) are often ineffective in transfusion-dependent patients and could exacerbate splenomegaly.

Luspatercept, a recombinant activin receptor type IIB fusion protein which was recently approved for the treatment anemia associated with transfusion-requiring beta thalassemia and low/intermediate-risk MDS with ring sideroblasts without (MDS-RS) or with (MDS-RS-T) thrombocytosis, was largely ineffective in patients with MF.

Emerging information suggests the possibility of using certain JAKi (i.e., Momelotinib and Pacritinib), at lower dose levels, as second-line therapy in anemic patients with MF who are otherwise not disabled by symptomatic splenomegaly or constitutional symptom.

Management of anemia associated with symptomatic splenomegaly or constitutional symptoms

Among the currently available JAKi, activity against all three major complications in MF, including anemia, splenomegaly, and constitutional symptoms, was most apparent for Momelotinib.

A substantial minority of Momelotinib-treated patients develop a potentially irreversible sensory peripheral neuropathy, which at a minimum should be fully discussed with the patient prior to its administration.

Management of splenomegaly in the absence of anemia

In the absence of anemia or constitutional symptoms, the first-line drug of choice for MF-associated splenomegaly, leukocytosis or thrombocytosis is hydroxyurea.

Spleen response to hydroxyurea lasts for an average of 1 year and treatment side effects include myelosuppression and painful mucocutaneous ulcers.

Interferon (IFN)-α is of limited value in the treatment of MF-associated splenomegaly.

In hydroxyurea-refractory MF patients with symptomatic splenomegaly that is not accompanied by anemia: Ruxolitinib offers an effective alternative and also has the capacity to alleviate constitutional symptoms.

JAKi choices during Ruxolitinib failure or thrombocytopenia

In general, Ruxolitinib-intolerant, as opposed to ruxolitinib-resistant, patients are more likely to respond to an alternative JAKi.

Considering its above-elaborated value in alleviating anemia, it is reasonable to consider Momelotinib as the first-line drug of choice in patients failing treatment with Ruxolitinib.

Fedratinib might be considered in patients who are intolerant to Ruxolitinib while increasing the dose of Ruxolitinib is initially preferred for those resistant to Ruxolitinib.

Pacritinib is approved in patients with platelet count $<50x10^9$/L and recent observations suggest additional value in combating anemia through ACRV1 inhibition.

JAKi associated side effects are delignated in the Annex D.

New drugs under investigation

New agents, alone or in combination with Ruxolitinib, are currently under investigation.

These include PI3Kδ inhibitors (e.g., parsaclisib), LSD1 (histone demethylase specific for H3K4) inhibitor omedemstat), bromodomain and extraterminal domain (BET) inhibitor (e.g., CPI-0610/pelabresib), telomerase inhibitor (e.g., imetelstat), pegylated interferon alpha, luspatercept (binds to TGF-▫super-family ligands), BCL-2/BCL-XL inhibitors (e.g., navitoclax), and others.

Overall, the preliminary results so far suggest less than impressive single-agent activity for any one of these drugs whereas controlled studies are needed to decipher added value (or added toxicity) when these agents were coupled with Ruxolitinib.

Splenectomy: Symptomatic splenomegaly in MF that is refractory to drugs is often managed by splenectomy.

Indications for splenectomy in MF include splenic abdominal pain and discomfort, symptomatic portal hypertension, severe thrombocytopenia, and frequent red blood cell transfusion.

Involved-field radiation treatment: Splenic irradiation induces transient reduction in spleen size but can be associated with severe and protracted pancytopenia, and can be considered in carefully selected patients.

With the now well-established value of JAKi therapy in reducing spleen size in MF, the need for palliative splenic radiation is becoming less certain and splenectomy is preferred in JAKi-refractory cases.

Trans-jugular intrahepatic portosystemic shunt: Trans-jugular intrahepatic portosystemic shunt (TIPS) might be considered to alleviate symptoms of portal hypertension associated with MPN or other conditions.

Blast phase myeloproliferative neoplasm

Blastic transformation is the most dreaded complication in MPN, including PV, ET, and PMF.

Post-MPN AML is operationally designated as blast-phase MPN (MPN-BP) and requires the presence of≥20% circulating or bone marrow blasts while blast count of 10–19% constitutes “accelerated phase” disease (MPN-AP).

Neither intensive nor less intensive chemotherapy, by itself, secures long-term survival in MPN-BP. Patients with post-MPN AML are treated based on the guidelines of secondary acute leukemia.

1.2.2 European LeukemiaNet Philadelphia Chromosome-Negative Classical Myeloproliferative Neoplasms: Revised Management Recommendations (2018)

The European LeukemiaNet consortium published in 2018 an update on the previous 2011 clinical guidelines for the management of Philadelphia chromosome-negative classical myeloproliferative neoplasms (Ph-neg MPNs)[17]. The main recommendations are detailed below:

1. **Diagnosis**

In all three categories of Ph-neg MPNs, i.e., PV, ET, and MF, strict adherence to the **2016 revised WHO diagnostic criteria** is recommended.

Bone marrow (BM) biopsy is a necessary diagnostic test in any patient suspected of a Ph-neg MPN, except for patients with PV with a hemoglobin greater than 18.5 g/dL in males and greater than 16.5 g/dl in females.

Peripheral blood or BM screening for driver mutations, i.e., JAK2V617F, CALR, and MPL, is recommended in any patient who may have a Ph-neg MPN. **JAK2V617F** should be the first test in patients suspected of any of the three diseases; in the case of JAK2V617F negativity, CALR and MPL, in that order, should then be tested in ET and MF.

2. **Risk stratification**

In MF, the IPSS, based on hematological and clinical variables, is the recommended prognostic system and should be scored in all patients at diagnosis.

DIPSS, based on hematological and clinical variables, or DIPSS-plus, based on hematological, clinical, and cytogenetic variables, are the recommended systems for prognostic reassessment during the disease course.

Molecular assessment during the course of the disease, mainly ASXL1 mutation, is recommended for therapeutic decisions in selected MF patients, such as to decide a transplant in those who have an intermediate-1 risk category according to the DIPSS/DIPSS-plus score.

3. **Management**

    a. **Asymptomatic patients with low- or intermediate-1 risk disease**

Observation alone is recommended for IPSS/DIPSS/DIPSSplus low- or intermediate-1 MF risk patients who lack significant symptoms, and who do not display significant anemia (hemoglobin < 10 g/dl), splenomegaly (palpable spleen size > 10 cm), leukocytosis (leukocyte count > 25 × 109 /l), or marked thrombocytosis (platelet count > 1000 × 109 /l).

If cytoreductive treatment for the reduction of leukocytosis or thrombocytosis is indicated, the first-line drug of choice is **hydroxyurea**.

b. Treatment of MF-associated anemia

The choice of a specific drug for MF-associated anemia should be based on overall toxicity profile and its expected risk in the individual patient.

Thalidomide and its analogs should be avoided in patients with documented peripheral neuropathy grade 2, and its use should be strictly monitored in those with grade 1 neuropathy or who are at risk for such complications such as diabetics.

In patients with transfusion dependency, a low rate of response to epoetins is expected, therefore the risk/benefit of a therapeutic use with epoetins is questionable.

Lenalidomide use is justified in cases with the presence of del(5q31).

There is currently not enough evidence to recommend combination therapy for MF-associated anemia, other than the addition of a short course of prednisone therapy to treatment with thalidomide.

c. Treatment of MF-associated splenomegaly

Ruxolitinib is recommended as first-line approach for MF-associated splenomegaly in patients with intermediate-2 or high-risk disease.

Ruxolitinib is also recommended as first-line therapy in patients with intermediate-1 risk disease and highly symptomatic splenomegaly, i.e., with the presence of local symptoms, or impairment of food intake.

Hydroxyurea is recommended as first-line therapy in other patients with intermediate-1 risk disease, and in those with low-risk disease in need of therapy for MF-associated splenomegaly.

Ruxolitinib is also recommended for reducing splenomegaly in patients with splenomegaly not responding to or intolerant to hydroxyurea.

d. Allogeneic stem cell transplantation

Allogeneic stem cell transplant should be considered for all transplant-eligible patients with IPSS/DIPSS/DIPSSplus high or intermediate-2 risk.

It may also be considered in IPSS/DIPSS/DIPSS-Plus intermediate-1 risk score who present with either refractory, transfusion-dependent anemia, a percentage of blasts in peripheral blood > 2% in at least two repeated manual measurements, adverse cytogenetics, or high-risk mutations.

e. Splenectomy

Splenectomy is a viable palliative treatment option for drug-refractory symptomatic splenomegaly and may be considered when drug-induced anemia hampers the effective use of hydroxyurea or ruxolitinib.

1.2.3 Korean Association of Internal Medicine: The 2020 Revision of the Guidelines for the Management of Myeloproliferative Neoplasms

In 2016, the World Health Organization revised the diagnostic criteria for myeloproliferative neoplasms (MPNs) based on the discovery of disease-driving genetic aberrations and extensive analysis of the clinical characteristics of patients with MPNs.

Based on these changes, the Korean Association of Internal Medicine have revised the guidelines and presented the diagnosis, treatment, and risk stratification of MPNs encountered in Korea[16].

Profibrotic (early stage) primary myelofibrosis:

Previously, PMF had been diagnosed as ET according to the 2008 WHO diagnostic criteria for MPNs, because it shares characteristics with overt PMF, such as atypical megakaryocytes, reduced erythropoiesis, high lactate dehydrogenase level, and anemia.

A bone marrow aspirate and biopsy with trichrome and reticulin staining are critical for differentiating ET from prefibrotic PMF.

The main diagnostic difference between prefibrotic and overt PMF is the grade of reticulin fibrosis in the bone marrow.

Compared with overt PMF, pre-PMF causes a higher hemoglobin level and platelet count, a lower circulating blast percentage, and a lower incidence of splenomegaly.

No treatment guidelines have been established for patients with pre-PMF because of the absence of long-term observations and treatment validation for this disease entity.

Primary myelofibrosis:

The Myeloproliferative Neoplasm Symptom Assessment Form total symptom score is a simple assessment tool for checking a patient's constitutional symptoms, splenomegaly related symptoms, and quality of life at diagnosis and during the course of treatment.

The majority of patients with PMF harbor one of three driver mutations: JAK2, CALR, or MPL.

Patients with PMF harboring CALR type1/type1-like mutations show improved median OS (8.2 to 10.3 years) compared with those harboring CALR type 2/type 2-like (3.1 years), JAK2 (4.3 years), or MPL (4.1 years) mutations.

Risk stratification and treatment of PMF:

Prognostic scoring evolved from the International Prognostic Scoring System in 2009 to the DIPSS in 2010, and the DIPSS-plus in 2011 (Appendix D).

The current treatment algorithm using the risk stratification in Korea is depicted in figure 2.

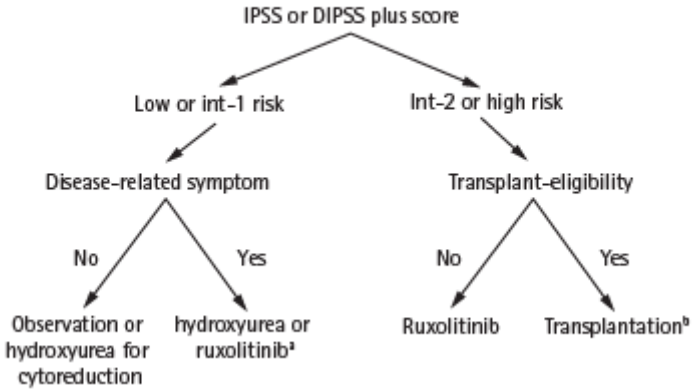

Figure 2. *Recommended algorithm for the treatment of primary myelofibrosis. Retrieved from Korean J Intern Med 2021;36:45-62.*

IPSS, International Prognostic Scoring System; DIPSS, Dynamic International Prognostic Scoring System. a Ruxolitinib for low or intermediate-1 risk patients is approved by the Ministry of Food and Drug Safety but not currently covered by National Health Insurance system of Korea, b Ruxolitinib treatment before transplantation to alleviate symptoms and splenomegaly can be considered.

Treatment of splenomegaly and constitutional symptoms

Hydroxyurea can improve splenomegaly, bone pain, constitutional symptoms, and pruritus. But improvements are temporary and the myelosuppressive toxicity of this agent hampers continued therapy.

Ruxolitinib was the first JAK inhibitor approved for patients with intermediate- to high-risk MF, in 2011.

Fedratinib, Pacritinib, and Momelotinib are new JAK inhibitors that have recently shown potential for patients resistant to or intolerant to Ruxolitinib.

Response evaluation

No drug modifying the disease activity of PMF is available. Thus, current treatment is aimed at improving anemia, reducing splenomegaly, and relieving disease-related symptoms.

Recent trials using JAK inhibitors, IFNs, and other emerging drugs have attempted to demonstrate effects on molecular and cytogenetic responses, and marrow fibrosis. Therefore, the response criteria were revised to evaluate hematologic, clinical, molecular, and cytogenetic responses.

Treatment of anemia

Erythropoiesis-stimulating agents have been shown to improve anemia in 45% to 60% of MF patients.

Plasma erythropoietin levels < 125 U/L have been associated with a higher probability of a response.

Androgenic steroids, such as danazol, may stimulate bone marrow function and improve hemoglobin concentrations in 30% to 40% of patients with MF.

Thalidomide or lenalidomide, in combination with low dose prednisone, can increase hemoglobin levels and decrease spleen size.

Hematopoietic cell transplantation in PMF:

Despite the advent of JAK inhibitors, allogeneic hematopoietic cell transplantation remains the only curative treatment for PMF.

Allogeneic hematopoietic cell transplantation is recommended in patients with an intermediate-2 or high-risk classification, according to the DIPSS or DIPSS-plus at diagnosis or during follow-up.

For patients with intermediate-1 risk classification, individual counseling is necessary, and MIPSS70 or GIPSS are recommended to assess the need for transplantation.

Pre-transplant use of Ruxolitinib may improve transplant outcomes by improving splenomegaly and performance status. Several recent trials have demonstrated the potential benefit of this strategy.

Section 2.0 Drug Therapy

2.1 Additions

There have been no new SFDA-registered drugs for the treatment of myelofibrosis.

Several drugs are under review for primary myelofibrosis. Fedratinib, Pacritinib, and Momelotinib are new JAK inhibitors that have recently shown potential for patients resistant to or intolerant to Ruxolitinib. Pacritinib and momelotinib were recently approved for the treatment of myelofibrosis. They are not yet registered by the SFDA and are detailed in section 2.4 below.

2.2 Modifications

There are no new modifications regarding the prescribing edits mentioned in the previous CHI report.

2.3 Delisting

None of the previous medications were withdrawn from Saudi FDA.

2.4 Other Drugs

2.4.1 Pacritinib

Vonjo® (Pacritinib) is an oral kinase inhibitor with specificity for JAK2, IRAK1 and CSF1R, approved by FDA in 2022 for the treatment of adults with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 109/L. Main characteristics are listed in the table below:

Table 8. Pacritinib Drug Information

SCIENTIFIC NAME PACRITINIB	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	Yes, 2022
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D75.81
Drug Class	Kinase inhibitor

Drug Sub-class	Macrocyclic protein kinase inhibitor
ATC Code	L01EJ03
Pharmacological Class (ASHP)	Selective JAK2, fms-like tyrosine kinase 3 (FLT3), interleukin-1 receptor-associated kinase 1 (IRAK1) inhibitor
DRUG INFORMATION	
Dosage Form	**Hard Capsule**
Route of Administration	Oral use
Dose (Adult) [DDD]*	Recommended dosage is 200 mg orally twice daily· May be taken with or without food
Maximum Daily Dose Adults*	400 mg
Dose (pediatrics)	Not recommended for children and adolescents under 18 years.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	Hepatic Impairment: avoid use in moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C). Renal impairment: avoid use in patients with eGFR <30 mL/min.
Prescribing edits*	AGE, MD, PA, ST
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a hematologist.	
PA (Prior Authorization): Approved for patients intolerant or non-responding to Ruxolitinib with a platelet count < $50x10^9$/L.	
QL (Quantity Limit): N/A	
ST (Step Therapy): To be used after a trial with Ruxolitinib	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	The most common (≥20% of patients) adverse reactions are diarrhea, thrombocytopenia, nausea, anemia, and peripheral edema.
Drug Interactions*	Avoid use with moderate CYP3A4 inhibitors or inducers. Coadministration of VONJO can alter the concentration of drugs that are

	Pgp, BCRP, or OCT1 substrates. Avoid use with sensitive substrates
Special Population	Lactation: Advise not to breastfeed. Hepatic Impairment: Avoid use in moderate (Child-Pugh B) and severe hepatic impairment (Child-Pugh C). Renal Impairment: Avoid use in patients with eGFR <30 mL/min.
Pregnancy	The background risk of major birth defects and miscarriage for the indicated population is unknown.
Lactation	Advise not to breastfeed.
Contraindications	Concomitant use of strong CYP3A4 inhibitors or inducers.
Monitoring Requirements	Complete blood count (CBC; including white blood cell count differential and platelet count) Coagulation testing (prothrombin time, partial thromboplastin time, thrombin time, and international normalized ratio). Baseline electrocardiogram (ECG), prior to starting VONJO, and monitor as clinically indicated while the patient is on treatment.
Precautions	Hemorrhage: Avoid use in patients with active bleeding and hold VONJO prior to any planned surgical procedures. May require dose interruption, dose reduction or permanent discontinuation depending on severity. Diarrhea: Manage significant diarrhea with anti-diarrheals, dose reduction, or dose interruption· Thrombocytopenia: Manage by dose reduction or interruption. Prolonged QT Interval: Avoid use in patients with baseline QTc >480 msec. Interrupt and reduce VONJO dosage in patients who have a QTcF >500 msec. Correct hypokalemia prior to and during VONJO administration.

	Major Adverse Cardiac Events (MACE): Risk may be increased in current/past smokers and patients with other cardiovascular risk factors. Monitor for signs, evaluate and treat promptly. Thrombosis: Including deep venous thrombosis, pulmonary embolism, and arterial thrombosis may occur. Monitor for signs, evaluate and treat promptly. Secondary Malignancies: Lymphoma and other malignancies may occur. Past/current smokers may be at increased risk. Risk of Infection: Delay starting VONJO until active serious infections have resolved. Observe for signs and symptoms of infection and manage promptly.
Black Box Warning	None
REMS*	Not Applicable

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The below table lists the health technology Assessment recommendations of VONJO® (Pacritinib) by the following agencies/institutes/authorities: both National Institute for Health and Care Excellence (NICE) and the Canadian Agency for Drugs and Technologies in Health (CADTH) were discontinued or suspended. Key conclusions are listed verbatim from their original source.

Table 9. Pacritinib HTA Analysis

Medication	Agency	Date – HTA Recommendation
Pacritinib	CADTH	N/A
	NICE	Assessment was discontinued in Nov 2022. Following on from information provided to NICE by the company in January 2019, the appraisal of Pacritinib for treating myelofibrosis was suspended from NICE's work program. As no further information has been received from the company the topic has been discontinued.
	HAS	N/A
	IQWIG	N/A
	PBAC	N/A

None of the health technology assessment agencies/institutes/authorities provided a recommendation for Pacritinib for treatment of Myelofibrosis.

Conclusion Statement – Pacritinib

Pacritinib is an oral kinase inhibitor with specificity for JAK2, IRAK1 and CSF1R, that was approved by FDA in 2022 for the treatment of adults with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 109/L. This indication was approved under accelerated approval based on spleen volume reduction. HTA recommendations by Nice for Pacritinib were suspended. Yet, based on the above guideline's recommendations, Pacritinib may be considered in patients with platelet count < $50x10^9$/L with one prior JAK inhibitor. Thus, **we recommend adding Pacritinib with prior authorization for patients intolerant or non-responding to Ruxolitinib with platelet count < $50x10^9$/L.**

2.4.2 Momelotinib

Momelotinib (OJJAARA®) is a kinase inhibitor indicated for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia. Momelotinib was approved by the FDA in September 2023.

Table 10. Momelotinib Drug Information

SCIENTIFIC NAME OJJAARA® (MOMELOTINIB)	
SFDA Classification	Prescription
SFDA Approval	No
US FDA	Yes, 2023
EMA	No
MHRA	No
PMDA	No
Indication (ICD-10)	D75.81
Drug Class	kinase inhibitor
Drug Sub-class	Macrocyclic protein kinase inhibitor
ATC Code	L01EJ04
Pharmacological Class (ASHP)	Antineoplastics JAK Inhibitor
DRUG INFORMATION	
Dosage Form	**Tablet**
Route of Administration	Oral use

Dose (Adult) [DDD]*	Recommended dosage: 200 mg orally once daily with or without food.
Maximum Daily Dose Adults*	200 mg
Dose (pediatrics)	Not recommended for children and adolescents under 18 years.
Maximum Daily Dose Pediatrics*	Not applicable
Adjustment	Hepatic Impairment: Severe hepatic impairment (Child-Pugh Class C): Reduce the starting dose to 150 mg orally once daily Renal impairment: avoid use in patients with eGFR <30 mL/min.
Prescribing edits*	AGE, MD, PA
AGE (Age Edit): Safety and effectiveness in pediatric patients have not been established.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): To be prescribed by a hematologist.	
PA (Prior Authorization): For the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF (post-polycythemia vera [PV] and post-essential thrombocythemia [ET]), in adults **with anemia**.	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	The most common adverse reactions (≥20% in either study) are thrombocytopenia, hemorrhage, bacterial infection, fatigue, dizziness, diarrhea, and nausea.
Drug Interactions*	Organic Anion Transporting Polypeptide (OATP)1B1/B3 inhibitors: Monitor for adverse reactions. Breast Cancer Resistance Protein (BCRP) substrates: Reduce rosuvastatin (BCRP substrate) dosage. Follow approved product information

	recommendations for other BCRP substrates.
Special Population	Lactation: Advise not to breastfeed. Pregnancy: May cause fetal harm.
Pregnancy	OJJAARA should only be used during pregnancy if the expected benefits to the mother outweigh the potential risks to the fetus.
Lactation	Advise not to breastfeed.
Contraindications	None
Monitoring Requirements	Obtain the following blood tests prior to starting treatment with OJJAARA, periodically during treatment, and as clinically indicated: - Complete blood count (CBC) with platelets. - Hepatic panel
Precautions	Risk of Infections: Do not initiate OJJAARA in patients with an active infection. Monitor for signs and symptoms of infection, including reactivation of hepatitis B, and initiate appropriate treatment promptly. Thrombocytopenia and Neutropenia: Manage by dose reduction or interruption. Hepatotoxicity: Obtain liver tests before initiation of and periodically throughout treatment with OJJAARA. Major Adverse Cardiovascular Events (MACE): Monitor for symptoms, evaluate and treat promptly. Thrombosis: Evaluate and treat symptoms of thrombosis promptly. Malignancies: Monitor for development of secondary malignancies, particularly in current or past smokers.
Black Box Warning	None
REMS*	Not Applicable

HEALTH TECHNOLOGY ASSESSMENT (HTA)

None of the health technology Assessment agencies/institutes/authorities including the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorite de Sante (HAS), Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC), provided a recommendation for Momelotinib for treatment of Myelofibrosis. Only the National Institute for Health and Care Excellence (NICE) posted that appraisal of Momelotinib is in progress but expected to be published in March 2024.

Conclusion Statement – Momelotinib

Momelotinib is a kinase inhibitor approved in 2023 by the FDA for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia. None of the health technology Assessment agencies/institutes/authorities provided a recommendation for Momelotinib for treatment of Myelofibrosis. Yet, Momelotinib was mentioned in most guidelines. At the same time, a meta-analysis comparing Momelotinib, Pacritinib and Ruxolitinib showed that Momelotinib has the best potential therapeutic value in patients with MPN among the three drugs, but further clinical studies are needed to prove it[18]. Thus, **we do not recommend against adding Momelotinib for the above indication once it is registered by SFDA.**

Section 3.0 Key Recommendations Synthesis

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) characterized by stem cell-derived clonal myeloproliferation that is often but not always accompanied by JAK2, CALR, or MPL mutations.

Current diagnosis of PMF is based on the 2022 ICC criteria and involves a composite assessment of clinical and laboratory features.

Subclassification into overtly fibrotic and early/pre-fibrotic stages is to be noted and the distinction from other MPNs required.

One new drug was approved by the FDA for treatment of Myelofibrosis. However, this medication is still not registered by Saudi FDA. No changes or modifications were made to existing drugs. And no drugs previously used in Saudi Arabia were withdrawn from SFDA.

Pacritinib is an oral kinase inhibitor with specificity for JAK2, IRAK1 and CSF1R, that was approved by FDA in 2022 for the treatment of adults with intermediate- or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 109/L. This indication was approved under accelerated approval based on spleen volume reduction. HTA recommendations by Nice for Pacritinib were suspended. Yet,

based on the above guideline's recommendations, Pacritinib may be considered in patients with platelet count < $50x10^9$/L with one prior JAK inhibitor.

Based on the above, we recommend for adding Pacritinib with prior authorization for patients intolerant or non-responding to Ruxolitinib with platelet count < $50x10^9$/L.

Momelotinib a kinase inhibitor approved in 2023 by the FDA for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF or secondary MF [post-polycythemia vera (PV) and post-essential thrombocythemia (ET)], in adults with anemia. None of the health technology Assessment agencies/institutes/authorities provided a recommendation for Momelotinib for treatment of Myelofibrosis. Yet, Momelotinib was mentioned in most guidelines. At the same time, a meta-analysis comparing Momelotinib, Pacritinib and Ruxolitinib showed that Momelotinib has the best potential therapeutic value in patients with MPN among the three drugs, but further clinical studies are needed to prove it. Thus, **the addition of Momelotinib for the above indication is warranted once it is registered by SFDA.**

Section 4.0 Conclusion

This report serves as **an annex to the previous myelofibrosis report** and aims to provide recommendations to aid in the management of dementia. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with myelofibrosis. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

Section 5.0 References

1. Ali H, Castells M, Dunbar A, et al. NCCN Guidelines Version 2.2023 Myeloproliferative Neoplasms. Published online 2023. Accessed September 29, 2023. https://www.nccn.
2. Genthon A, Killian M, Mertz P, et al. [Myelofibrosis: A review]. *Rev Med Interne*. 2021;42(2):101-109. doi:10.1016/J.REVMED.2020.08.018
3. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues – IARC. Accessed August 30, 2023. https://www.iarc.who.int/news-events/who-classification-of-tumours-of-haematopoietic-and-lymphoid-tissues-2/
4. Tefferi A, Saeed L, Hanson CA, Ketterling RP, Pardanani A, Gangat N. Application of current prognostic models for primary myelofibrosis in the setting of post-polycythemia vera or post-essential thrombocythemia myelofibrosis. *Leukemia*. 2017;31(12):2851-2852. doi:10.1038/LEU.2017.268

5. Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment. *Leukemia*. 2008;22(2):437-438. doi:10.1038/SJ.LEU.2404914

6. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. *Blood*. 2022;140(11):1200-1228. doi:10.1182/BLOOD.2022015850

7. Tefferi A. Primary myelofibrosis: 2021 update on diagnosis, risk-stratification and management. *Am J Hematol*. 2021;96(1):145-162. doi:10.1002/AJH.26050

8. Lock G, Kendrick C. Myelofibrosis with Myeloid Metaplasia. *https://doi.org/101056/NEJM200004273421706*. 2000;60(1):3-6. doi:10.1056/NEJM200004273421706

9. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2023;98(5):801-821. doi:10.1002/AJH.26857

10. Gerds AT, Harrison C, Thompson S, Snopek F, Pemmaraju N. The Burden of Illness and the Incremental Burden of Transfusion Dependence in Myelofibrosis in the United States. *Blood*. 2022;140(Supplement 1):3974-3975. doi:10.1182/BLOOD-2022-162657

11. Wang H, Mehta J, Iqbal U, Mesa RA. Analysis of the Impact and Burden of Illness of Myelofibrosis in the US. *Blood*. 2012;120(21):972-972. doi:10.1182/BLOOD.V120.21.972.972

12. Copher R, Kee A, Gerds A. Treatment Patterns, Health Care Resource Utilization, and Cost in Patients with Myelofibrosis in the United States. *Oncologist*. 2022;27(3):228-235. doi:10.1093/ONCOLO/OYAB058

13. Tang D, Taneja A, Rajora P, Patel R. Systematic Literature Review of the Economic Burden and Cost of Illness in Patients with Myelofibrosis. *Blood*. 2019;134(Supplement_1):2184-2184. doi:10.1182/BLOOD-2019-122919

14. Gimenez E, Besses C, Boque C, et al. Indirect and non-medical economic burden, quality-of-life, and disabilities of the myelofibrosis disease in Spain. *J Med Econ*. 2014;17(6):435-441. doi:10.3111/13696998.2014.903257

15. Gerds AT, Gotlib J, Ali H, et al. Myeloproliferative Neoplasms, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network*. 2022;20(9):1033-1062. doi:10.6004/JNCCN.2022.0046

16. Kim SY, Bae SH, Bang SM, et al. The 2020 revision of the guidelines for the management of myeloproliferative neoplasms. *Korean J Intern Med*. 2021;36(1):45. doi:10.3904/KJIM.2020.319

17. Barbui T, Tefferi A, Vannucchi AM, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management

recommendations from European LeukemiaNet. *Leukemia*. 2018;32(5):1057-1069. doi:10.1038/s41375-018-0077-1

18. Ye W, Wu X, Zheng X. Comparison of Momelotinib, Pacitinib and Ruxolitinib in patients with Myeloproliferative Neoplasm: An Indirect-Comparison Meta-Analysis of Randomized Controlled Trials. Published online June 2, 2020. doi:10.21203/RS.3.RS-29345/V1

19. Clair JS. A New Model of Tracheostomy Care: Closing the Research–Practice Gap. In: Henriksen K, Battles JB, Marks ES, et al., editors. Advances in Patient Safety: From Research to Implementation (Volume 3: Implementation Issues). Rockville (MD): Agency fo.

Section 6.0 Appendices

Appendix A. Prescribing Edits

Some covered drugs may have additional requirements, rules or limits on coverage. These requirements and limits may include:

Prescribing edits Tools	Description
AGE (Age Edit):	Coverage may depend on patient age
CU (Concurrent Use Edit):	Coverage may depend upon concurrent use of another drug
G (Gender Edit):	Coverage may depend on patient gender
MD (Physician Specialty Edit):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limit):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another Drug
EU (Emergency use only):	This drug status on Formulary is only for Emergency use.
PE (Protocol edit)	Use of drug is dependent on protocol combination, doses and sequence of therapy

Examples:
Age edit: Desmopressin in Nocturnal Enuresis should not be prescribed for children < 5 years.
Concurrent Use Edit: Flavoxate in Nocturnal Enuresis should be used as add on to desmopressin after desmopressin failure and cannot be used alone.
Gender Edit: Exemestane in Endometriosis should be used only by Females.
Physician Specialty Edit: Fentanyl in Endometriosis should be prescribed by a gynecologist or pain management specialist.
Prior Authorization: Desmopressin in Nocturnal Enuresis: The prescriber must check the following before prescribing:

- Failure of combination of behavioral and alarm therapy.

Quantity Limit: Idarubicin in Acute Leukemia: Cumulative dose should not exceed 150 mg/m2. Please note that this Quantity Limit is different than the one based on maximum daily dose as this is not necessary based on Maximum Daily Dose
Step Therapy: Aripiprazole in Social Anxiety: should be used as third line after:
First-line: Escitalopram, fluvoxamine, fluvoxamine CR, paroxetine, paroxetine CR, pregabalin, sertraline, venlafaxine XR
Second-line: Alprazolam, bromazepam, citalopram, clonazepam, gabapentin
Emergency use only: Furosemide IV form in Hypertension is used only in emergency setting.
Protocol edit: Bendamustine Hydrochloride, Cyclophosphamide, Ifosfamide, Dacarbazine should be used in Lymphoma as per the following protocol

I. Adult and Pediatric Quantity Limit?

This is either the adult or pediatric maximum amount of a drug that can be administered per day based on a maximum daily dose.
If there is no clinical evidence supporting the quantity limit for that relevant indication, this column will be left as Blank.

II. What information are available in the notes?

"Notes" section provides details of the prescribing edits, extra important drug information and special warning and precautions.

III. Drug interactions

- A: No known interaction
- B: No action needed
- C: Monitor therapy
- D: Consider therapy modification
- X: Avoid combination

IV. Defined Daily Dose

The Defined Daily Dose (DDD) is to be set based on the WHO recommendations https://www.whocc.no/ddd/definition_and_general_considera/

V. REMS

A Risk Evaluation and Mitigation Strategy (REMS) is a drug safety program that the U.S. Food and Drug Administration (FDA) can require for certain medications with serious safety concerns to help ensure the benefits of the medication outweigh its risks.

Appendix B. Level of Evidence Adopted

Grade of research[19]	
A	Strongly recommend; Good evidence
B	Recommend; At least fair evidence
C	No recommendation for or against; Balance of benefits and harms too close to justify a recommendation
D	Recommend against; Fair evidence is ineffective, or harm outweighs the benefit
E	Evidence is insufficient to recommend for or against routinely; Evidence is lacking or of poor quality; Benefits and harms cannot be determined.
Level of evidence	
Level I	Meta-analysis of multiple studies
Level II	Experimental studies
Level III	Well-designed, quasi-experimental studies

Level IV	Well-designed, non-experimental studies
Level V	Case reports and clinical examples

Appendix C. PubMed Search

The following is the result of the PubMed search conducted for MF guideline search:

Query	Filters	Search Details	Results
((Myelofibrosis) AND (management)) AND (Guidelines)	Guideline, in the last 5 years	(("primary myelofibrosis"[MeSH Terms] OR ("primary"[All Fields] AND "myelofibrosis"[All Fields]) OR "primary myelofibrosis"[All Fields] OR "myelofibrosis"[All Fields]) AND ("manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR "managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]) AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	1
((Myelofibrosis) AND (management)) AND (Guidelines)	in the last 5 years	(("primary myelofibrosis"[MeSH Terms] OR ("primary"[All Fields] AND "myelofibrosis"[All Fields]) OR "primary myelofibrosis"[All Fields] OR "myelofibrosis"[All Fields]) AND ("manage"[All Fields] OR "managed"[All Fields] OR "management s"[All Fields] OR	29

		"managements"[All Fields] OR "manager"[All Fields] OR "manager s"[All Fields] OR "managers"[All Fields] OR "manages"[All Fields] OR "managing"[All Fields] OR "managment"[All Fields] OR "organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]) AND ("guideline"[Publication Type] OR "guidelines as topic"[MeSH Terms] OR "guidelines"[All Fields])) AND (y_5[Filter])	
JAK inhibitors	in the last 5 years	("janus kinase inhibitors"[Pharmacological Action] OR "janus kinase inhibitors"[MeSH Terms] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitors"[All Fields]) OR "janus kinase inhibitors"[All Fields] OR ("jak"[All Fields] AND "inhibitors"[All Fields]) OR "jak inhibitors"[All Fields]) AND (y_5[Filter])	5,379
JAK inhibitors	Guideline, in the last 5 years	("janus kinase inhibitors"[Pharmacological Action] OR "janus kinase inhibitors"[MeSH Terms] OR ("janus"[All Fields] AND "kinase"[All Fields] AND "inhibitors"[All Fields]) OR "janus kinase inhibitors"[All Fields] OR ("jak"[All Fields] AND "inhibitors"[All Fields]) OR "jak inhibitors"[All Fields]) AND ((y_5[Filter]) AND (guideline[Filter]))	12
(Primary) AND (Myelofibrosis)	Guideline, in the last 5 years	(("primaries"[All Fields] OR "primary"[All Fields]) AND ("primary myelofibrosis"[MeSH	1

		Terms] OR ("primary"[All Fields] AND "myelofibrosis"[All Fields]) OR "primary myelofibrosis"[All Fields] OR "myelofibrosis"[All Fields])) AND ((y_5[Filter]) AND (guideline[Filter]))	
(Primary) AND (Myelofibrosis)	Guideline	(("primaries"[All Fields] OR "primary"[All Fields]) AND ("primary myelofibrosis"[MeSH Terms] OR ("primary"[All Fields] AND "myelofibrosis"[All Fields]) OR "primary myelofibrosis"[All Fields] OR "myelofibrosis"[All Fields])) AND (guideline[Filter])	8
(Primary) AND (Myelofibrosis)		("primaries"[All Fields] OR "primary"[All Fields]) AND ("primary myelofibrosis"[MeSH Terms] OR ("primary"[All Fields] AND "myelofibrosis"[All Fields]) OR "primary myelofibrosis"[All Fields] OR "myelofibrosis"[All Fields])	8,292
myelofibrosis	Guideline, in the last 5 years	"primary myelofibrosis"[MeSH Terms] OR ("primary"[All Fields] AND "myelofibrosis"[All Fields]) OR "primary myelofibrosis"[All Fields] OR "myelofibrosis"[All Fields]	10,230

Appendix D. MIPSS, MIPSS-plus, and GIPSS Models for Primary Myelofibrosis

Table 7. MIPSS, MIPSS-plus, and GIPSS models for primary myelofibrosis

Prognostic model and risk factors (weight)		Risk groups and median survival
MIPSS70		
Genetic variables	• Clinical variables	
One HMR mutation (1 point)	Hemoglobin < 10 g/dL (1 point)	Low risk: 0–1 point (not reached)
≥ 2 HMR mutations (2 points)	Leukocytes > 25×10^9/L (2 points)	Intermediate risk: 2–4 (6.3 yr)
Type 1/like CALR absent (1 point)	Platelet < 100×10^9/L (2 points)	High risk: ≥ 5 (3.1 yr)
	Circulating blast ≥ 2% (1 point)	
	Constitutional symptom (1 point)	
	Marrow fibrosis grade ≥ 2 (1 point)	
MIPSS70+ version 2.0		
• Genetic variables	• Clinical variables	
VHR karyotype (4 points)	Severe anemia[a] (2 points)	Very low risk: 0 point (not reached)
Unfavorable karyotype (3 points)	Moderate anemia[b] (1 point)	Low risk: 1–2 (16.4 yr)
≥ 2 HMR mutations (3 points)	Circulating blasts ≥ 2% (1 point)	Intermediate-1 risk: 3-4 (7.7 yr)
One HMR mutation (2 points)	Constitutional symptoms (2 points)	High risk: 5–8 (4.1 yr)
Type 1/like CALR absent (2 points)		Very high risk: ≥ 9 (1.8 yr)
GIPSS		
• Genetic variables		
VHR karyotype (2 points)		Low risk: 0 point (26.4 yr)
Unfavorable karyotype (1 point)		Intermediate-1 risk: 1 point (8 yr)
Type 1/like CALR absent (1 point)		Intermediate-2 risk: 2 points (4.2 yr)
ASXL1 mutation (1 point)		High risk: ≥ 3 points (2 yr)
SRSF2 mutation (1 point)		
U2AF1Q157 mutation (1 point)		

Adapted from Tefferi, with permission from John Wiley and Sons.
MIPSS70 for transplant-age patients (age ≤ 70 years); MIPSS70+ version 2.0: mutation and karyotype enhanced international prognostic system. Survival quotes are for age ≤ 70 years. Survival quotes are for all age groups; HMR mutations include ASXL1, SRSF2, EZH2, IDH1, IDH2, and in addition, for GIPSS and MIPSS70+ version 2.0, U2AF1Q157.
MIPSS, mutation-enhanced international prognostic scoring system; GIPSS, genetically inspired prognostic scoring system; HMR, high molecular risk; CALR, calreticulin; VHR, very high risk.
a Severe anemia: Hemoglobin < 8 g/dL in women and < 9 g/dL in men.
b Moderate anemia: Hemoglobin 8 to 9.9 in women and 9 to 10.9 in men.

Appendix E. Efficacy and Toxicity Details for Ruxolitinib, Fedratinib, Pacritinib, and Momelotinib, in JAK Inhibitor-Naïve Patients with Myelofibrosis

	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Myelofibrosis symptom-relevant targets	JAK1/2	JAK2	JAK2 ACRV1	JAK1/2 ACRV1
FDA-approved indication	IPSS* High/intermediate risk	IPSS* High/Intermediate-2 risk First-line and Second-line	DIPSS** High/Intermediate risk First-line and Second-line for platelet count <50 × 10^9/L	Approval pending
FDA-approved dose and schedule	20 mg twice-daily (Platelet count >200 × 10^9/L) 15 mg twice-daily (Platelet count 150–200 × 10^9/L)	400 mg twice-daily (Platelet count ≥50 × 10^9/L)	200 mg twice-daily (Platelet count <50 × 10^9/L)	Approval pending (Expected 200 mg once-daily)
Spleen volume reduction ≥35% (radiographic)	42%% (COMFORT-1) 29% (COMFORT-2) 29% (SIMPLIFY-1)	36% (JAKARTA-1)	19% (PERSIST-1)	27% (SIMPLIFY-1)
Spleen response by palpation	32% (Mayo study)	83% (Mayo study)	Not reported	47% (Mayo study)
Anemia response in transfusion-dependent patients	30% (Mayo study)	10% (Mayo study)	25% (PERSIST-1)	51% (Mayo study)
Symptom response	57% (Mayo study) 46% (COMFORT-1) 42% (SIMPLIFY-1)	65% (Mayo study) 36% (JAKARTA-1)	19% (PERSIST-1)	48% (Mayo study) 28% (SIMPLIFY-1)
Adverse effects	Anemia Thrombocytopenia Withdrawal syndrome Opportunistic infections Poor response to COVID vaccines	Anemia Thrombocytopenia GI symptoms ↑Liver function tests ↑Amylase/lipase Wernicke's encephalopathy (Rare event)	GI symptoms (substantial) Peripheral edema Pneumonia Cardiac failure	Thrombocytopenia ↑Liver function tests ↑Amylase/lipase Peripheral neuropathy First-dose effect (Dizziness, Hypotension, Flushing, Nausea)

Abbreviations: **DIPSS, dynamic international prognostic scoring system; *IPSS, international prognostic

Appendix F. Treatment Algorithm for Lower-Risk Myelofibrosis

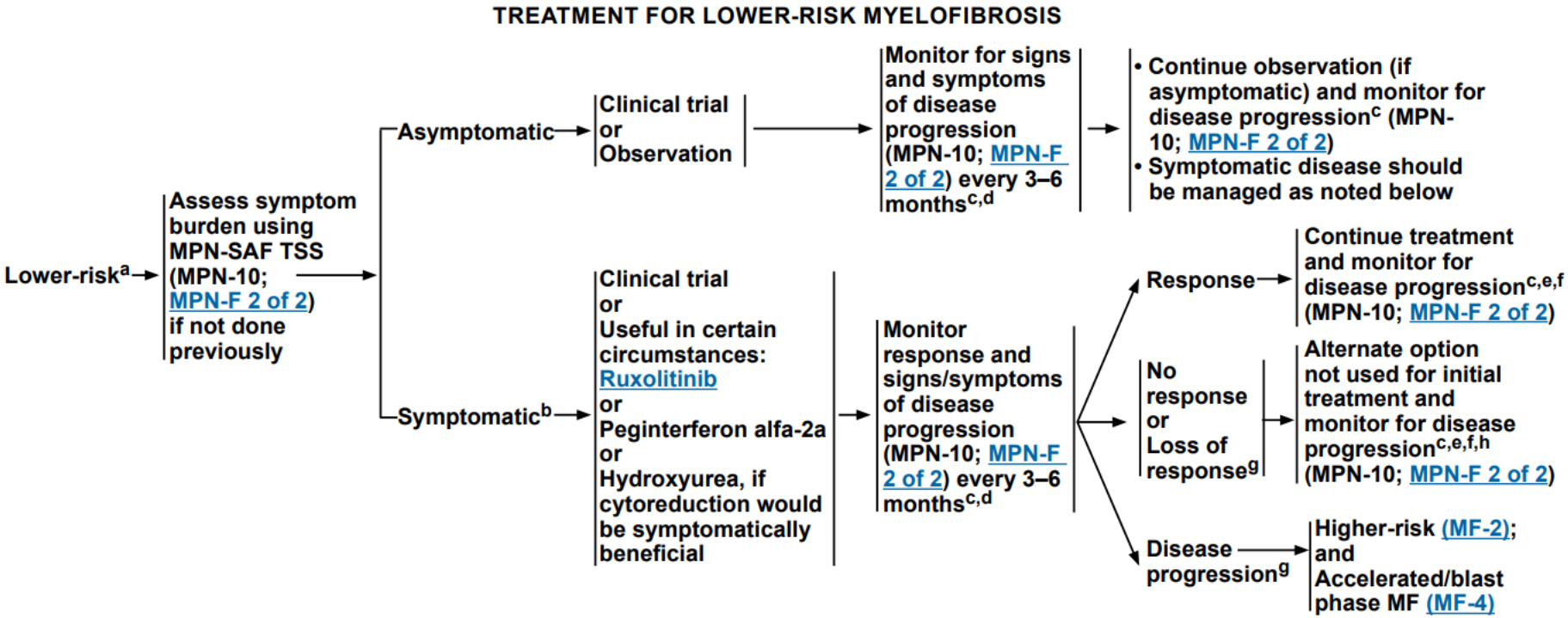

Figure adapted from NCCN Clinical Practice Guidelines in Oncology (Myeloproliferative Neoplasms, Version 2.2023)

Appendix G. Treatment Algorithm for Higher-Risk Myelofibrosis

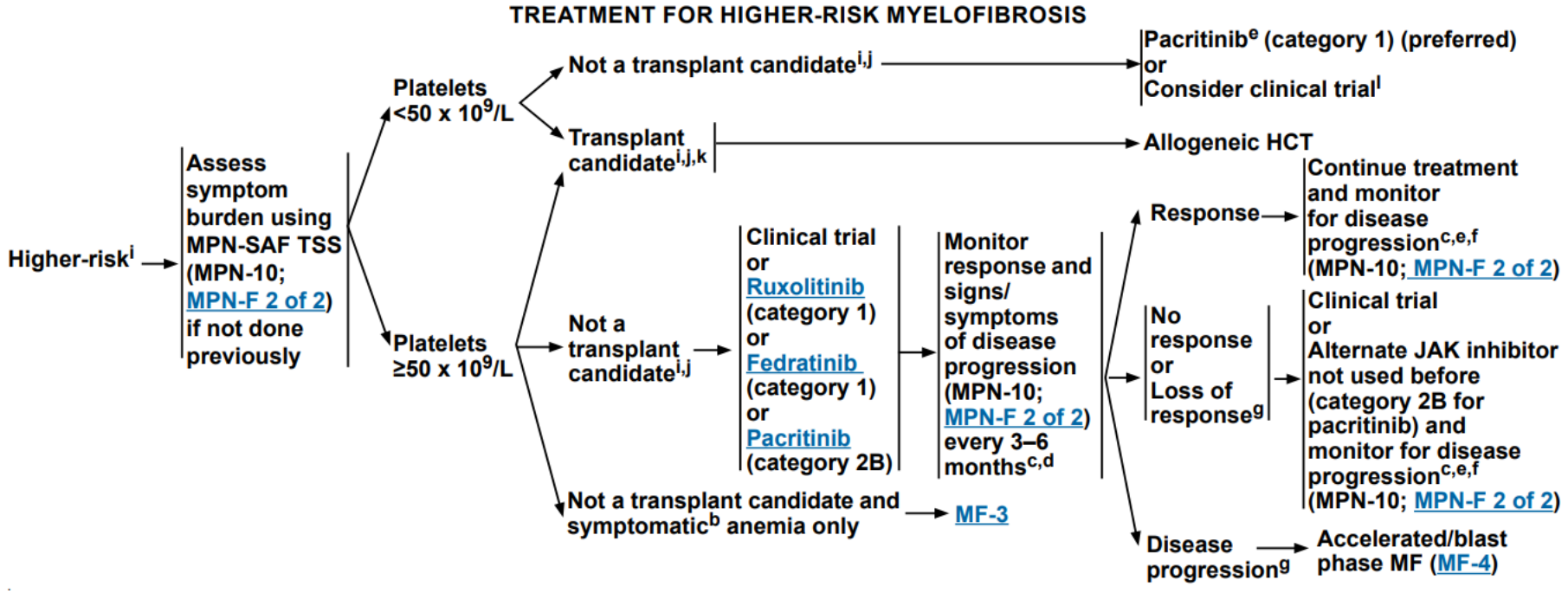

Figure adapted from NCCN Clinical Practice Guidelines in Oncology (Myeloproliferative Neoplasms, Version 2.2023)

Appendix H. Management of MF-Associated Anemia

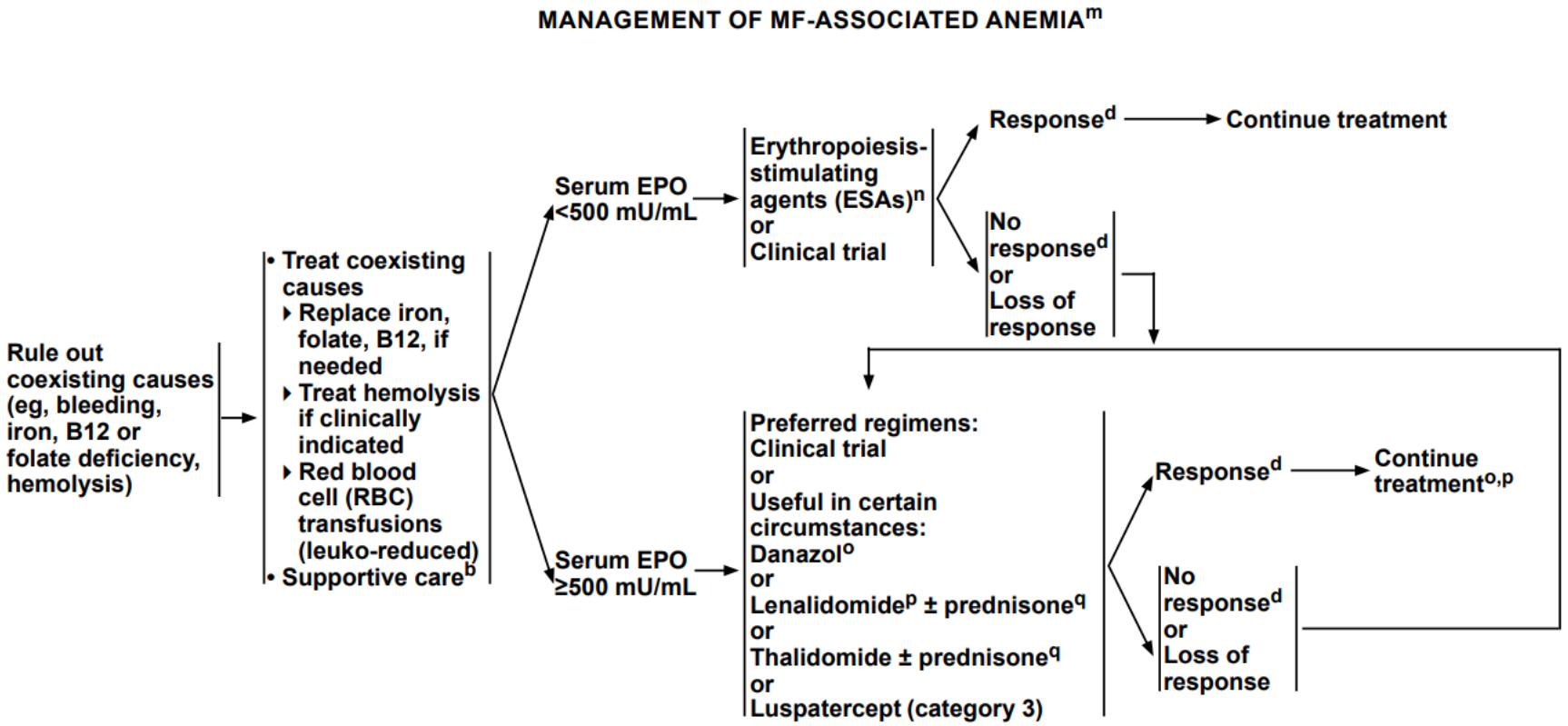

Figure adapted from NCCN Clinical Practice Guidelines in Oncology (Myeloproliferative Neoplasms, Version 2.2023)

Appendix I. Myelofibrosis Workup and Treatment

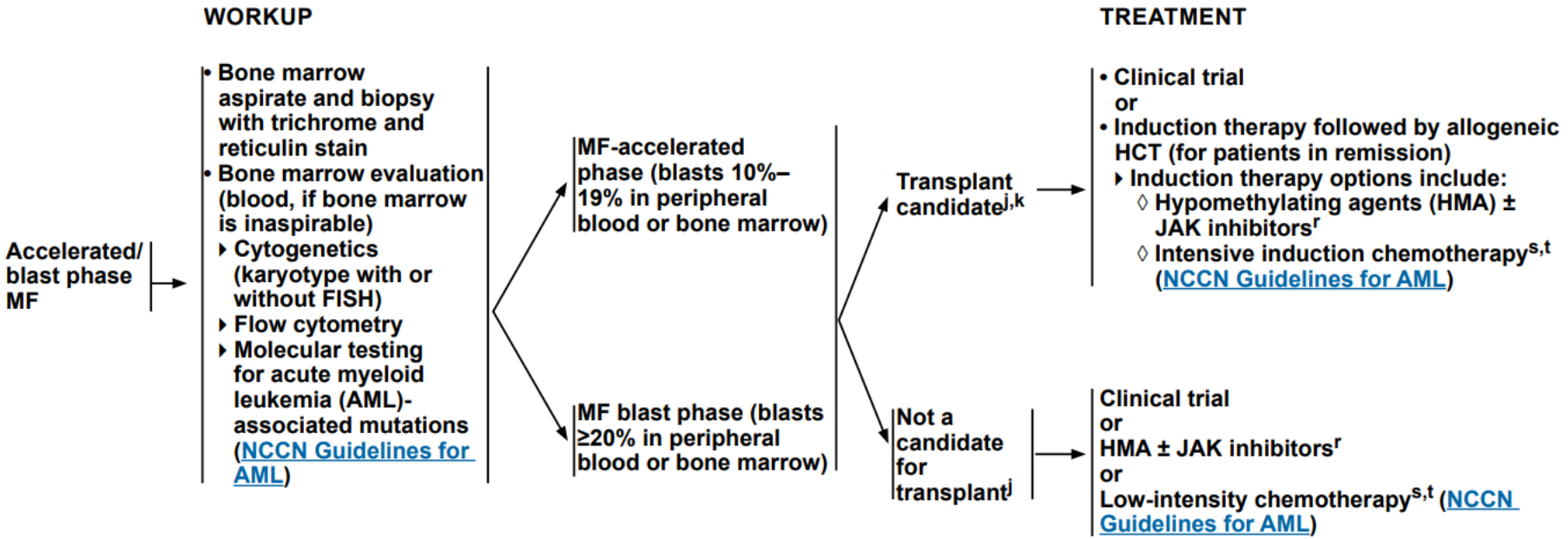

Figure adapted from NCCN Clinical Practice Guidelines in Oncology (Myeloproliferative Neoplasms, Version 2.2023)

Appendix J. Scope

2020 Version	Changes Performed	2023 (Current version)	Rationale/Description
Not available	New section	Scope	Summarize the main changes and updates between the 2020 and 2023 versions
Executive Summary	New section	Background	A general overview covering pathophysiological and epidemiological aspects was added.
Section 1. Myelofibrosis CLINICAL GUIDELINES			
NCCN Guidelines on Myeloproliferative neoplasms (v.1 2020)	**Updated**	Myeloproliferative Neoplasms, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology	Kerds AT, Gotlib J, Ali H, Bose P, Dunbar A, Elshoury A, George TI, Gundabolu K, Hexner E, Hobbs GS, Jain T, Jamieson C, Kaesberg PR, Kuykendall AT, Madanat Y, McMahon B, Mohan SR, Nadiminti KV, Oh S, Pardanani A, Podoltsev N, Rein L, Salit R, Stein BL, Talpaz M, Vachhani P, Wadleigh M, Wall S, Ward DC, Bergman MA, Hochstetler C. Myeloproliferative Neoplasms, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022 Sep;20(9):1033-1062. doi: 10.6004/jnccn.2022.0046. PMID: 36075392.
Not available	New section	The 2020 revision of the guidelines for the management of myeloproliferative	Kim SY, Bae SH, Bang SM, Eom KS, Hong J, Jang S, Jung CW, Kim HJ, Kim HY, Kim MK, Kim SJ, Mun YC, Nam SH, Park J, Won JH, Choi CW. The 2020 revision of the guidelines for the management of myeloproliferative neoplasms. Korean J Intern Med.

		neoplasms, Korean Journal of Internal Medicine	2021 Jan;36(1):45-62. doi: 10.3904/kjim.2020.319. Epub 2020 Dec 4. PMID: 33147902; PMCID: PMC7820646.
Not available	New section	Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management	Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023 May;98(5):801-821. doi: 10.1002/ajh.26857. Epub 2023 Feb 6. PMID: 36680511.
Section 2. DRUG THERAPY FOR Myelofibrosis			
oral kinase inhibitor with specificity for JAK2, IRAK1 and CSF1R	Addition of a medication	Pacritinib (Vonjo®)	Approved by FDA in 2021 for treatment of Myelofibrosis Not SFDA registered NICE, Nov 2022: Discontinued. Following on from information provided to NICE by the company in January 2019, the appraisal of Pacritinib for treating myelofibrosis was suspended from NICE's work programme. As no further information has been received from the company the topic has been discontinued. CADTH 2022:

Not existing	**New section**	**Section 4. Key Recommendations Synthesis**	
Not existing	**New section**	**Section 5. Conclusion**	
References	Updated	**Section 6. References**	
Appendices	Updated	**Section 7. Appendices**	