Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2025-B-223 Momelotinib

Stand: Oktober 2025

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Momelotinib
[zur Behandlung der Splenomegalie oder Symptome bei Erwachsenen mit Myelofibrose mit moderater bis schwerer Anämie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	- Allogene Stammzelltransplantation - Milzbestrahlung - Splenektomie
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	**Beschlüsse über die Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a SGB V:** • Fedratinib: Beschlüsse vom 2. September 2021 und vom 21. August 2025 • Momelotinib: Beschluss vom 15. August 2024 • Ruxolitinib: Beschluss vom 6. November 2014 **Beschlüsse über die Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen nach § 35a Absatz 3b SGB V:** • Fedratinib: Beschluss vom 3. November 2022 und 1. Juni 2023
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Momelotinib L01EJ04 Omjjara®	<u>Zugelassenes Anwendungsgebiet:</u> Omjjara wird angewendet zur Behandlung von krankheitsbedingter Splenomegalie oder Symptomen bei erwachsenen Patienten mit moderater bis schwerer Anämie, die an primärer Myelofibrose, Post-Polycythaemia Vera-Myelofibrose oder Post-Essentieller Thrombozythämie-Myelofibrose erkrankt sind, und die nicht mit einem Januskinase (JAK)-Inhibitor vorbehandelt sind oder die mit Ruxolitinib behandelt wurden.
Fedratinib L01EJ02 Inrebic®	Inrebic wird angewendet für die Behandlung krankheitsbedingter Splenomegalie oder Symptome bei erwachsenen Patienten mit primärer Myelofibrose, Post-Polycythaemia Vera-Myelofibrose oder Post-Essentielle Thrombozythämie-Myelofibrose, die nicht mit einem Janus-assoziierten Kinase (JAK)-Inhibitor vorbehandelt sind oder die mit Ruxolitinib behandelt wurden.
Ruxolitinib L01XE18 Jakavi®	Myelofibrose (MF) Jakavi ist angezeigt für die Behandlung von krankheitsbedingter Splenomegalie oder Symptomen bei Erwachsenen mit primärer Myelofibrose (auch bekannt als chronische idiopathische Myelofibrose), Post-Polycythaemia-vera-Myelofibrose oder Post-Essentieller-Thrombozythämie-Myelofibrose.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-223 (Beratung nach § 35a SGB V) Momelotinib

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	5. September 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

ATG	Anti-thymocyte Globulin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
BSH	British Society for Haematology
EBMT	European Blood and Marrow Transplantation Group
ECRI	Emergency Care Research Institute
ELN	European LeukemiaNet
ESA	Erythropoiesis-stimulating agents
ET	Essentielle Thrombozythämie
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCT	hematopoietic cell transplantation
HR	Hazard Ratio
HSCT	haemopoietic stem cell transplant
IK	Interessenkonflikt
IMiDs	Immunomodulatory Drugs
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
JAK	Januskinase
k.A.	keine Angabe
LCM	Left Costal Margin
LoE	Level of Evidence
MAC	Myeloablative Conditioning
MF	Myelofibrose
MPN	Myeloproliferative Neoplasm
MRD	Measurable Residual Disease
NCCN	National Comprehensive Cancer Network
NICE	National Institute for Health and Care Excellence
PMF	Primäre Myelofibrose
PV	Polycythaemia Vera
RIC	Reduced Intensity Conditioning
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von krankheitsbedingter Splenomegalie oder Symptomen bei erwachsenen Patienten mit moderater bis schwerer Anämie, die an primärer Myelofibrose, Post-Polycythaemia Vera-Myelofibrose oder Post-Essentieller Thrombozythämie-Myelofibrose erkrankt sind, und die nicht mit einem Januskinase (JAK)-Inhibitor vorbehandelt sind oder die mit Ruxolitinib behandelt wurden.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation *Myelofibrose* durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (*https://www.google.com/*) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 26.02.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 313 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, ein Publikationszeitraum von 2 Jahren und für Leitlinien von 5 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Am 15.08.2025 erfolgte eine zusätzliche Aktualisierung der iterativen Handsuche. Sie ergab zwei neue Referenzen [2,3]. Basierend darauf, wurden insgesamt vier Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine systematischen Reviews identifiziert.

3.3 Leitlinien

National Comprehensive Cancer Network (NCCN), 2025 [2,3].

Myeloproliferative neoplasms, Version 2.2025 — July 8, 2025

Zielsetzung/Fragestellung

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms were developed as a result of meetings convened by a multidisciplinary Panel with expertise in MPN, with the aim of providing recommendations for the management of adults with these diseases. The NCCN Guidelines® for Myeloproliferative Neoplasms include recommendations for the diagnostic workup, risk stratification, treatment, and supportive care strategies for the management of MF, PV, and ET.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, und aufgrund ihrer Aktualität, wird die LL jedoch ergänzend dargestellt.

** NCCN – Development and Update of Guidelines:*

https://www.nccn.org/guidelines/guidelines-process/development-and-update-of-guidelines

Grundlage der Leitlinie

Update von Version 2025.1

- Repräsentatives Gremium: **Trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft teilweise zu** – Interessenkonflikte der involvierten Experten und die finanzielle Unabhängigkeit der NCCN Gremien werden dargelegt, allerdings ist unklar, wie mit Interessenkonflikten umgegangen wird.
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft teilweise zu** – Eine systematische Recherche wurde durchgeführt, aber Angaben zu den Auswahlkriterien und der kritischen Bewertung der Literatur fehlen (siehe Recherche/Suchzeitraum).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft teilweise zu** – Konsensusprozesse werden dargelegt, aber es gibt kein externes Begutachtungsverfahren.*
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft teilweise zu** – In den Therapiealgorithmen werden

die Evidenzgrade der Empfehlungen angegeben und es gibt einen Hintergrundtext. Jedoch fehlt eine konkrete Beschreibung der Empfehlungen.

- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu** – The NCCN Guidelines are reviewed and updated on an ongoing basis to ensure that the recommendations reflect the most current evidence and clinical practice. All NCCN Guidelines are reviewed and updated at least annually.*

Recherche/Suchzeitraum:

- Prior to the update of this version of the NCCN Guidelines for Myeloproliferative Neoplasms, an electronic search of the PubMed database was performed to obtain key literature in Myeloproliferative Neoplasms published since the previous Guidelines update using the following search terms: myeloproliferative neoplasms, myelofibrosis, polycythemia vera, and essential thrombocythemia. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.12
- The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines as discussed by the Panel during the Guidelines update have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the Panel's review of lower-level evidence and expert opinion.

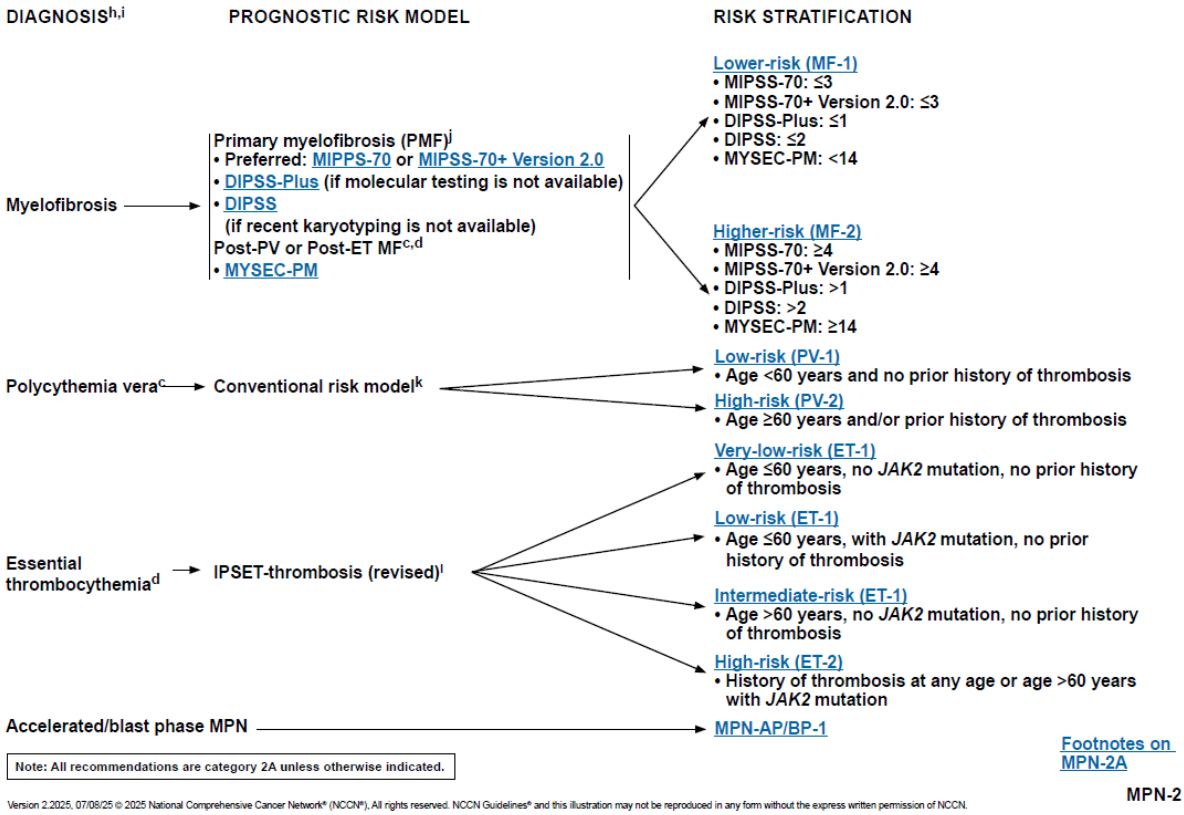
LoE/GoR*

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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.

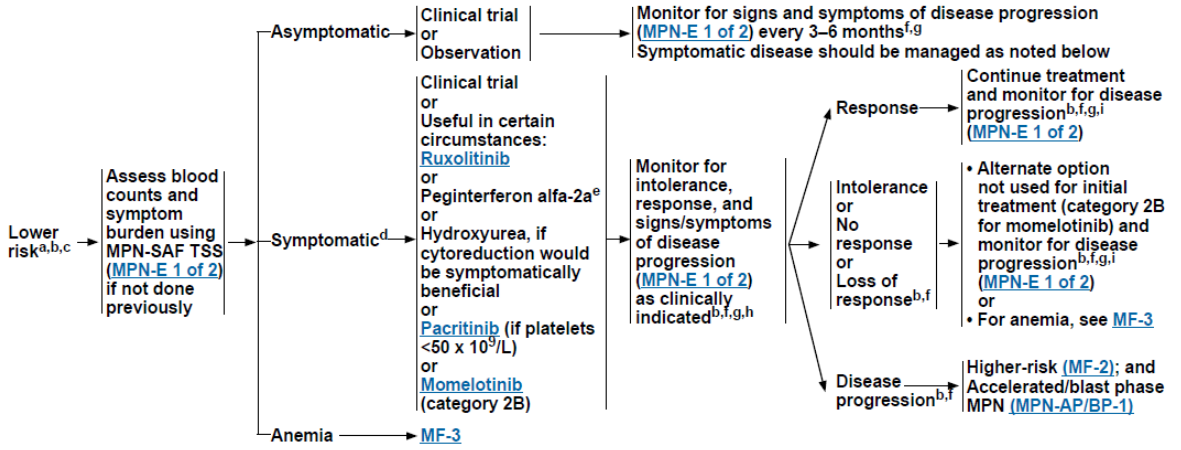


MPN-2

FOOTNOTES

[c] WHO and ICC diagnostic criteria for PV and Post-PV MF. See MPN-B.
[d] WHO and ICC diagnostic criteria for ET and Post-ET MF. See MPN-C.
[h] The diagnosis of MPN is based on the 2022 WHO criteria and ICC criteria.
[i] Referral to specialized centers with expertise in the management of MPN is strongly recommended for all patients diagnosed with MF, PV, or ET.
[j] See WHO and ICC diagnostic criteria for PMF (MPN-A).
[k] Marchioli R, et al. J Clin Oncol 2005;23:2224-2232.
[l] The revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) is preferred for the risk stratification of ET (Haider M, et al. Am J Hematol 2016;91:390-394. Barbui T, et al. Blood Cancer J 2015;5:e369).

TREATMENT FOR LOWER-RISK MYELOFIBROSIS

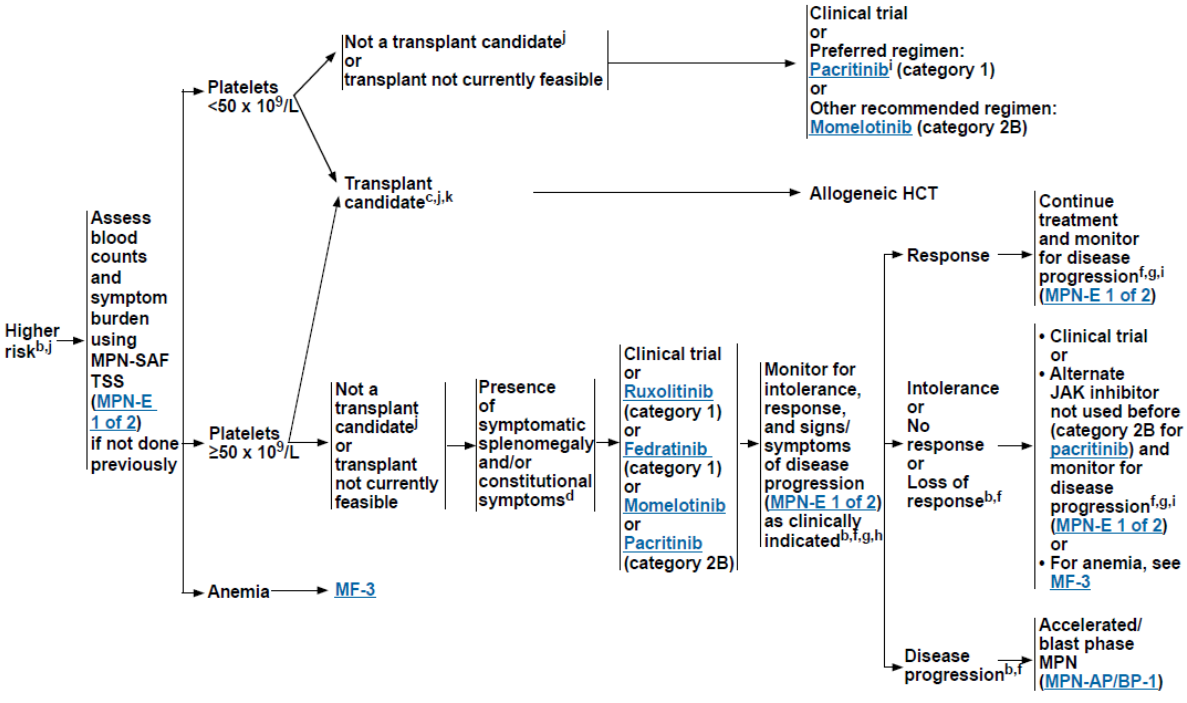


[a] Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics. Identification of higher-risk mutations may be helpful in the decision-making regarding allogeneic HCT for patients with MF.
[b] Prognostic Significance of Mutations in Myelofibrosis (MPN-D).
[c] When counseling patients about transplant, the myelofibrosis transplant scoring system (MTSS) can be helpful in predicting post-transplant survival.
[d] Supportive Care for Patients with MPN (MPN-F).
[e] In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.
[f] Bone marrow aspirate and biopsy with NGS and karyotyping should be performed at diagnosis and as clinically indicated (if supported by increased symptoms and signs of progression). Additional molecular testing using multigene NGS panel should be considered to evaluate for higher-risk mutations associated with disease progression in patients with MF.
[g] Response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician. RR6 may also be used to gauge response. Continuation of JAK inhibitors is recommended based on the discretion of the clinician.
[h] For ruxolitinib, use RR6 model to assess. Maffioli M, et al. Blood Adv 2022;6:1855-1864.
[i] Special Considerations for the Use of JAK Inhibitors (MPN-G).

Note: All recommendations are category 2A unless otherwise indicated.

MF-1

TREATMENT FOR HIGHER-RISK MYELOFIBROSIS



Note: All recommendations are category 2A unless otherwise indicated.

Footnotes on MF-2A

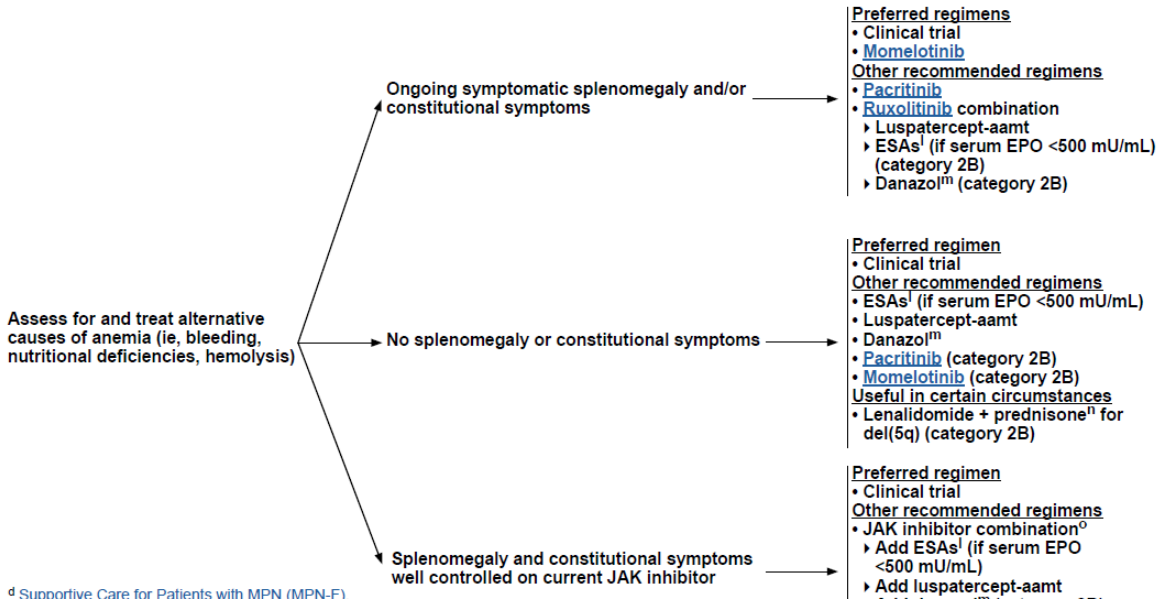
MF-2

TREATMENT FOR HIGHER-RISK MYELOFIBROSIS

FOOTNOTES

[b] Prognostic Significance of Mutations in Myelofibrosis (MPN-D).
[c] When counseling patients about transplant, the MTSS can be helpful in predicting post-transplant survival.
[d] Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy with NGS and karyotyping should be performed at diagnosis and as clinically indicated (if supported by increased symptoms and signs of progression). Additional molecular testing using multigene NGS panel should be considered to evaluate for higher-risk mutations associated with disease progression in patients with MF.
[g] Response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician. RR6 may also be used to gauge response. Continuation of JAK inhibitors is recommended based on the discretion of the clinician.
[h] For ruxolitinib, use RR6 model to assess. Maffioli M, et al. Blood Adv 2022;6:1855-1864.
[i] Special Considerations for the Use of JAK Inhibitors (MPN-G).
[j] Special Considerations for Allogeneic Hematopoietic Cell Transplant (MF-C).
[k] Donor selection and conditioning should be evaluated on a case-by-case basis. See NCCN Guidelines for Hematopoietic Cell Transplant (HCT).

MANAGEMENT OF MF-ASSOCIATED ANEMIA[d]



[d] Supportive Care for Patients with MPN (MPN-F).
[l] ESAs include epoetin alfa and darbepoetin alfa. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines.
[m] Prostate cancer screening and monitoring of LFTs as well as the use of concomitant medications such as statins are recommended over concerns for increased risk of rhabdomyolysis.
[n] Start as a combination followed by tapering of prednisone over 3 months.
[o] JAK inhibitors may be continued for the improvement of splenomegaly and other disease-related symptoms.

Note: All recommendations are category 2A unless otherwise indicated.

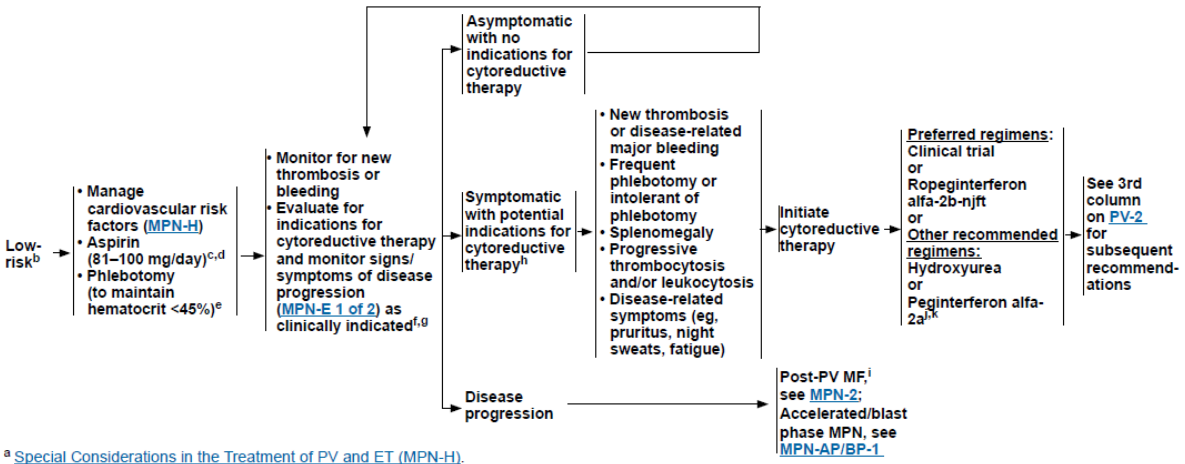
SPECIAL CONSIDERATIONS FOR ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANT[1,2]

- Referral to an HCT expert for allogeneic HCT evaluation is recommended for all patients stage DIPSS-Plus Int-1 or MIPSS-intermediate or higher.
- The selection of patients for allogeneic HCT is based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.
- Transplant is recommended for patients with DIPSS-Plus or MYSEC Int-2 or high risk disease or MIPSS70 or MIPSS 70+ high risk.
- Transplant can also be considered in selective cases – RBC transfusion dependence, high risk mutations (ie, ASXL1, RAS, TP53), or loss of response to JAK inhibitor therapy.
- The MTSS can be used to optimize patient selection, low and intermediate risk being optimal.[3]
- JAK inhibitors should be considered for use in patients for at least 2 months prior to transplant in patients with splenomegaly and/or constitutional symptoms even if the patient would otherwise be already transplant eligible.
- JAK inhibitors can be tapered prior to or during conditioning to be completed before cell infusion.
- In patients with massive splenomegaly not responding to JAK inhibition, alternative measures to reduce spleen size may be considered prior to transplant (eg splenic radiation, splenic artery embolization, or splenectomy).
- For MF with >10% blasts in the peripheral blood, consider azacitidine with or without a JAK inhibitor prior to allogeneic HCT to reduce the blast percentage.
- HLA matched siblings is the preferred donor, however, HLA matched unrelated donor, 7/8- mismatched unrelated donor and haploidentical donor are also appropriate.
- When counseling patients about transplant, the MTSS can be helpful in predicting post-transplant survival.

[1] Kröger N, Bacigalupo A, Barbui T,et al. Indication and management of allogeneic haematopoietic stem-cell transplantation in myelofibrosis: updated recommendations by the EBMT/ELN International Working Group. Lancet Hematol 2024;11:e62-e74 .
[2] Polverelli N, Hernández-Boluda JC, Czerw T, et al. Splenomegaly in patients with primary or secondary myelofibrosis who are candidates for allogeneic hematopoietic cell transplantation: a Position Paper on behalf of the Chronic Malignancies Working Party of the EBMT. Lancet Haematol 2023;10:e59-e70.
[3] Gagelmann N, Ditschkowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. Blood 2019;133:2233-2242.

Note: All recommendations are category 2A unless otherwise indicated.

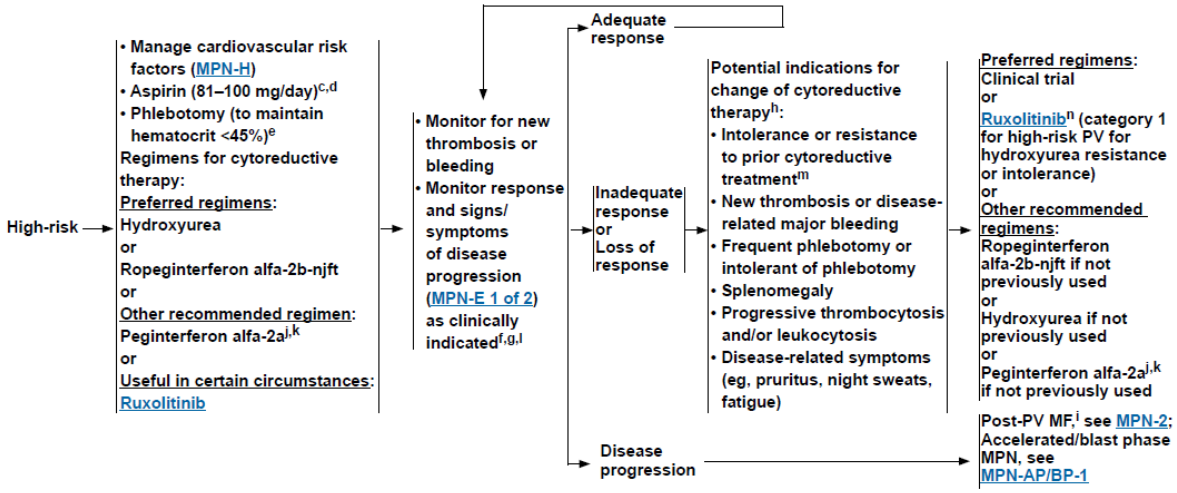
TREATMENT FOR LOW-RISK POLYCYTHEMIA VERA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-H).
[b] Cytoreductive therapy is not recommended as initial treatment.
[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] Hematocrit <45% is based on the data from the CYTO-PV study (Marchioli R, et al. N Engl J Med 2013;368:22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized (eg, progressive symptoms).
[f] Supportive Care for Patients with MPN (MPN-F).
[g] While normalization of blood counts after initiation of treatment is usually a goal in clinical practice, it is not associated with long-term clinical benefit and there are no evidence-based data to recommend a target white blood cell (WBC) or platelet count for patients receiving cytoreductive therapy. In selected patients with a severe thrombotic event or other disease-related symptoms, normalization of blood counts might be a goal of treatment.
[h] Barbui T, et al. Leukemia 2018;32:1057-1069.
[i] WHO and ICC diagnostic criteria for post-PV MF (MPN-B).
[j] Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy.
[k] In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.

Note: All recommendations are category 2A unless otherwise indicated.

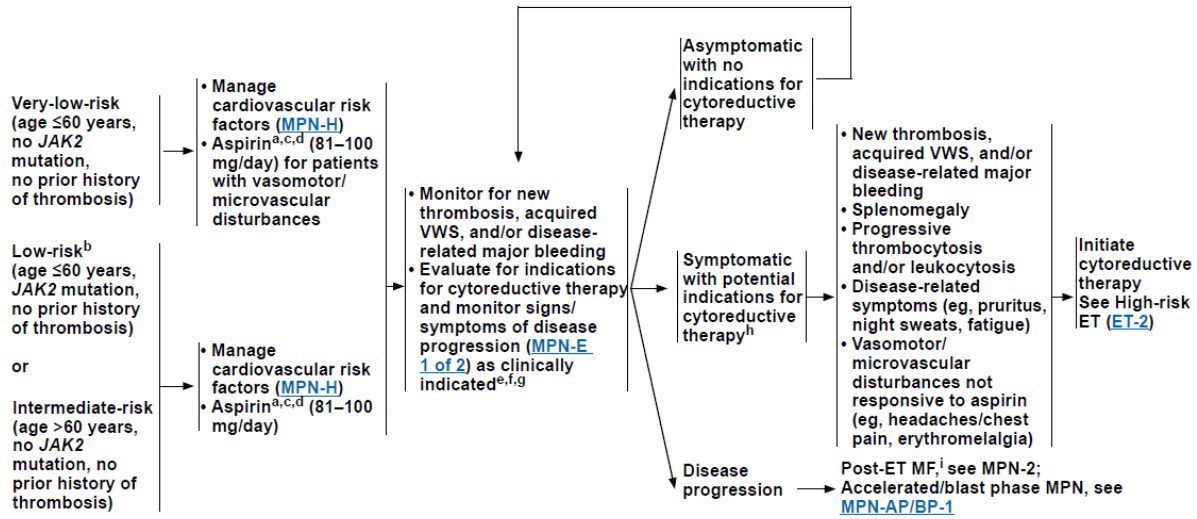
TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-H).
[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] Hematocrit <45% is based on the data from the CYTO-PV study (Marchioli R, et al. N Engl J Med 2013;368:22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized (eg, progressive symptoms).
[f] Supportive Care for Patients with MPN (MPN-F).
[g] While normalization of blood counts after initiation of treatment is usually a goal in clinical practice, it is not associated with long-term clinical benefit and there are no evidence-based data to recommend a target WBC or platelet count for patients receiving cytoreductive therapy. In selected patients with a severe thrombotic event or other disease-related symptoms, normalization of blood counts might be a goal of treatment.
[h] Barbui T, et al. Leukemia 2018;32:1057-1069.
[i] WHO and ICC diagnostic criteria for post-PV MF (MPN-B).
[j] Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy.
[k] In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.
[l] Response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria for PV (PV-A). Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.
[m] Definition of intolerance/resistance to hydroxyurea (MPN-I).
[n] Ruxolitinib is FDA approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea. Ruxolitinib may have activity after inadequate response or loss of response to other agents besides hydroxyurea. See Discussion.

Note: All recommendations are category 2A unless otherwise indicated.

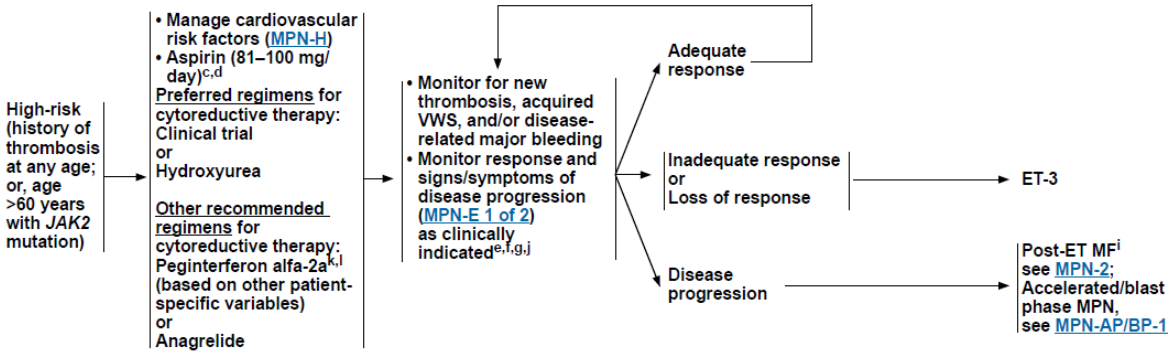
TREATMENT FOR VERY-LOW-RISK OR LOW-RISK OR INTERMEDIATE-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-H).
[b] Harrison CN, et al. N Engl J Med 2005;353:33-45.
[c] Aspirin should be used with caution in patients with acquired VWS. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risks and benefits of higher-dose aspirin (>100 mg) must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to MF prior to the initiation of cytoreductive therapy.
[g] While normalization of blood counts after initiation of treatment is usually a goal in clinical practice, it is not associated with long-term clinical benefit and there are no evidence-based data to recommend a target WBC or platelet count for patients receiving cytoreductive therapy. In selected patients with a severe thrombotic event or other disease-related symptoms, normalization of blood counts might be a goal of treatment.
[h] Barbui T, et al. Leukemia 2018;32:1057-1069.
[i] WHO and ICC diagnostic criteria for post-ET MF (MPN-C).

Note: All recommendations are category 2A unless otherwise indicated.

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]

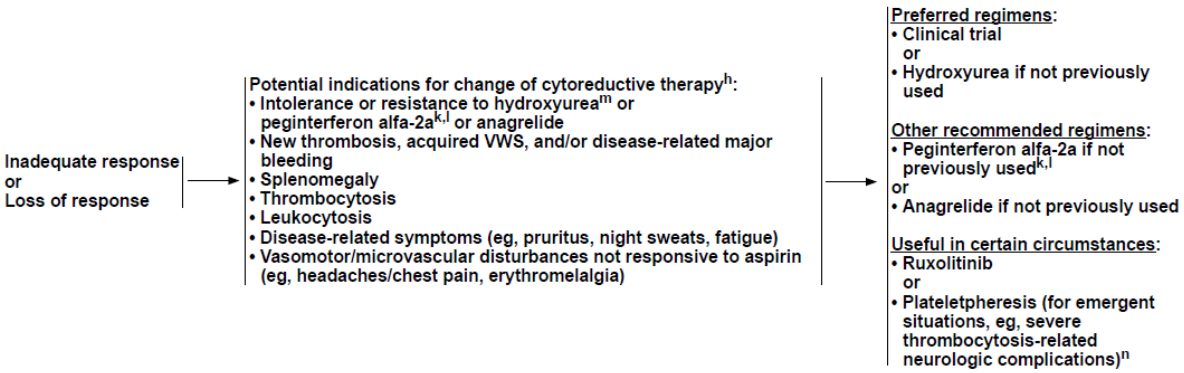


[a] Special Considerations in the Treatment of PV and ET (MPN-H).
[c] Aspirin should be used with caution in patients with acquired VWS. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risks and benefits of higher-dose aspirin (>100 mg) must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to MF if clinical/laboratory suspicion of MF.
[g] While normalization of blood counts after initiation of treatment is usually a goal in clinical practice, it is not associated with long-term clinical benefit and there are no evidence-based data to recommend a target WBC or platelet count for patients receiving cytoreductive therapy. In selected patients with a severe thrombotic event or other disease-related symptoms, normalization of blood counts might be a goal of treatment.
[i] WHO and ICC diagnostic criteria for post-ET MF (MPN-C).
[j] Response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria for ET (ET-A). Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.
[k] Peginterferon alfa-2a can be considered for patients in need of cytoreductive therapy who are younger or pregnant or who defer hydroxyurea.
[l] In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.

Note: All recommendations are category 2A unless otherwise indicated.

ET-2

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-H).
[h] Barbui T, et al. Leukemia 2018;32:1057-1069.
[k] Peginterferon alfa-2a can be considered for patients in need of cytoreductive therapy who are younger or pregnant or who defer hydroxyurea.
[l] In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.
[m] Definition of Resistance/Intolerance to Hydroxyurea (MPN-I).
[n] Padmanabhan A, et al. J Clin Apher 2019;34:171-354.

Note: All recommendations are category 2A unless otherwise indicated.

ET-3

SUPPORTIVE CARE FOR PATIENTS WITH MPN

MYELOFIBROSIS

- Transfusion support
  - Red blood cell (RBC) transfusions for symptomatic anemia
  - Platelet transfusions for thrombocytopenic bleeding or a platelet count <10,000/mm^3
  - In transplant candidates, use leukocyte-reduced blood products to prevent HLA alloimmunization and reduce the risk of cytomegalovirus (CMV) transmission.
- Consider antifibrinolytic agents for bleeding that is refractory to transfusions.
- Iron chelation could be considered for patients who have received >20 transfusions and/or ferritin >2500 ng/mL in patients with lower-risk MF. However, the role of iron chelation remains unclear.
- In patients who have had a splenectomy, vaccinations and antibiotic prophylaxis should be given per IDSA Guidelines.
- Vaccinations: See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
  - Consider recombinant (killed) zoster vaccine for patients on, or prior to, treatment with a JAK inhibitor.
- Hematopoietic growth factor support
  - ESAs: See (MF-3) for the management of MF-associated anemia. ESAs are generally less effective for patients with transfusion-dependent anemia.
  - Consider granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) for recurrent infections in patients with neutropenia. However, these should be used with caution in patients with an enlarged spleen since the use of G-CSF or GM-CSF has been associated with splenic rupture. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
- Consider cytoreductive therapy (eg, hydroxyurea) for hyperproliferative manifestations of PMF (thrombocytosis or leukocytosis).
- Consider prophylaxis for tumor lysis syndrome (TLS) for patients undergoing induction therapy for advanced-stage MF or disease progression to AML. See NCCN Guidelines for Acute Myeloid Leukemia.
- Counseling at baseline and throughout disease course for assessment for, identification of, and decreasing cardiovascular risk factors (eg, smoking, diet, exercise, hypertension, diabetes mellitus, lipid management), and thrombotic and hemorrhagic risk factors.

Continued

Note: All recommendations are category 2A unless otherwise indicated.

SUPPORTIVE CARE FOR PATIENTS WITH MPN

SYMPTOM MANAGEMENT IN PATIENTS WITH MPN

Disease-related symptoms commonly contribute to decreased quality of life in patients with MPN.[1] While JAK inhibitors have been shown to broadly improve disease-related symptoms, their use is not indicated in all patients with symptomatic MPN, and the presence of specific symptoms often requires a targeted approach. Pruritus, bone pain, and headaches/tinnitus occur across all MPN (albeit with some disease preference) and greatly impact quality of life. The optimal management of these symptoms in the setting of MPN has not been established and is based on subset analysis of large trials, small pilot studies, anecdotal evidence, extrapolation from other disease states, and expert opinion.

MPN are a chronic blood cancer that typically progress over time. The stress of uncertainty and of long-term care should be acknowledged. Referral to a mental health professional and other supportive services can be invaluable, including integrative health specialists.

- Pruritus[2-11]
  - Initial efforts to improve pruritus should include sensitive skin care practice (ie, short showers, mild soap, moisturizing), optimized antihistamine therapy (ie, cetirizine, diphenhydramine), and topical steroids.
  - Ruxolitinib was shown to improve pruritus in patients with ET, PV, and MF in the MAJIC-ET, RESPONSE, and COMFORT-I trials, respectively.
  - Small pilot studies have shown selective serotonin reuptake inhibitors and narrow-band ultraviolet B to be effective in treating pruritic symptoms.
  - Additional options include peginterferon alfa-2a, gabapentin, aprepitant, and immunosuppressant agents such as cyclosporine, methotrexate, azathioprine, mycophenolate mofetil, or dupilumab. In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.
  - A risk-stratified, step-wise approach should be utilized with the specific therapeutic option chosen based on strength of evidence, side effect profile, cost/benefit analysis, and concomitant disease-related symptoms.
- Bone Pain[12-14]
  - Close evaluation to distinguish disease-related bone pain from arthralgias should be undertaken in order to identify symptoms that may be amenable to local therapies.
  - Ruxolitinib was shown to stabilize bone/muscle pain in patients with MF in the COMFORT-1 study.
  - Loratadine and nonsteroidal anti-inflammatory drugs (NSAIDs) (naproxen) have been used in MPN-associated bone pain due to their efficacy in the treatment of growth-factor–related bone pain.
  - Single-fraction radiation has been effective in temporarily relieving MPN-associated bone pain.
- Headache/Tinnitus[15-22]
  - Given the increased risk of vascular complications in patients with MPN (ie, stroke, retinal artery or vein thrombosis, cerebral venous thrombosis), all patients with new onset of neurologic symptoms including headache and tinnitus or with progressive refractory symptoms should undergo appropriate and indicated workup to assess for thrombosis.
  - Low-dose aspirin (80–100 mg/day) has been shown to improve vasomotor symptoms including headache in patients with MPN. In patients with aspirin-resistant symptoms, consider a twice-daily rather than once-daily regimen of low-dose aspirin or alternative anti-platelet agents (clopidogrel 75 mg/day) as monotherapy or in combination with aspirin.
  - Cytoreduction or phlebotomy if PV with elevated hematocrit when aspirin is ineffective at relieving symptoms.
  - The use of ruxolitinib improves headache in patients with PV and associated iron deficiency, more so in patients with baseline iron deficiency.
  - NSAIDs should be used with caution (given concurrent aspirin use).
  - Consider treatment/prophylaxis with triptans or topiramate for migraine headaches.

References on MPN-F (3 of 3)

Note: All recommendations are category 2A unless otherwise indicated.

SUPPORTIVE CARE FOR PATIENTS WITH MPN

REFERENCES

[1] Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international internet-based survey of 1179 MPD patients. Cancer 2007;109:68-76.
[2] Saini KS, Patnaik MM, Tefferi A. Polycythemia vera-associated pruritus and its management. Eur J Clin Invest 2010;40:828-834.
[3] Vaa BE, Wolanskyj AP, Roeker L, et al. Pruritus in primary myelofibrosis: Clinical and laboratory correlates. Am J Hematol 2012;87:136-138.
[4] Teferri A, Fonseca R. Selective serotonin reuptake inhibitors are effective in the treatment of polycythemia vera-associated pruritus. Blood 2002;99:267.
[5] Baldo A, Sammarco E, Plaitano R, et al. Narrowband (TL-01) ultraviolet B phototherapy for pruritus in polycythaemia vera. Br J Dermatol 2002;147:979-981.
[6] Vaa BE, Teferri A. Pruritus in primary myelofibrosis: Treatment attempts, response and outcomes. Blood 2013;122:4081.
[7] Vaa BE, Tefferi A, Gangat N, et al. Pruritus in primary myelofibrosis: management options in the era of JAK inhibitors. Ann Hematol 2016;97:1185-1189.
[8] Diehn F, Tefferi A. Pruritus in polycythaemia vera: prevalence, laboratory correlates and management. Br J Haematol 2001;115:619-621.
[9] Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 2015;372:426-435.
[10] Ishii T, Wang J, Zhang W, et al. Pivotal role of mast cells in pruritogenesis in patients with myeloproliferative disorders. Blood 2009;113:5942-5950.
[11] Harrison CN, Mead AJ, Panchal A, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. Blood 2017;130:1889-1897.
[12] Kirshner JJ, McDonald MC, Kruter F, et al. NOLAN: a randomized, phase 2 study to estimate the effect of prophylactic naproxen or loratadine vs no prophylactic treatment on bone pain in patients with early-stage breast cancer receiving chemotherapy and pegfilgrastim. Support Care Cancer 2018;26:1323-1334.
[13] Verstovesk S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807.
[14] Neben-Wittich MA, Brown PD, Tefferi A. Successful treatment of severe extremity pain in myelofibrosis with low-dose single-fraction radiation therapy. Am J Hematol 2010;85:808-810.
[15] Frewin R, Dowson A. Headache in essential thrombocythaemia. Int J Clin Pract 2012;66:976-983.
[16] Michiels JJ, Berneman Z, Schroyens, et al. Platelet-mediated erythromelalgic, cerebral, ocular and coronary microvascular ischemic and thrombotic manifestations in patients with essential thrombocythemia and polycythemia vera: a distinct aspirin-responsive and coumadin-resistant arterial thrombophilia. Platelets 2006;17:528-544.
[17] Pascale S, Petrucci G, Dragani A, et al. Aspirin-insensitive thromboxane biosynthesis in essential thrombocythemia is explained by accelerated renewal of the drug target. Blood 2012;119:3595-3603.
[18] Tefferi A, Barbui T. Essential thrombocythemia and polycythemia vera: Focus on clinical practice. Mayo Clin Proc 2015;90:1283-1293.
[19] Michiels JJ. Erythromelalgia and vascular complications in polycythemia vera. Semin Thromb Hemost 1997;23:441-454.
[20] Verstovsek S, Harrison CN, Kiladjian JJ, et al. Markers of iron deficiency in patients with polycythemia vera receiving ruxolitinib or best available therapy. Leuk Res 2017;56:52-59.
[21] Mesa R, Verstovsek S, Kiladjian JJ, et al. Changes in quality of life and disease-related symptoms in patients with polycythemia vera receiving ruxolitinib or standard therapy. Eur J Haematol 2016;97:192-200.
[22] Billot S, Kouroupi EG, Le Guilloux J, et al. Neurological disorders in essential thrombocythemia. Haematologica 2011;96:1866-1869.

Note: All recommendations are category 2A unless otherwise indicated.

SPECIAL CONSIDERATIONS FOR THE USE OF JAK INHIBITORS[1]

- **JAK inhibitors are ruxolitinib, fedratinib, pacritinib, and momelotinib.**

Lymphoma Risk with JAK Inhibitors in Patients with MPN:
Both low- and high-grade lymphoid neoplasms may be diagnosed concurrently with MPNs or may develop during the natural history of PV, ET, or MF. Although one report indicated an increased risk of lymphomas with JAK inhibitor therapy,[2] other studies found no evidence of increased lymphoma risk in patients treated with a JAK inhibitor.[3-6]

[1] Please refer to package insert for full prescribing information available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.
[2] Porpaczy E, Tripolt S, Hoelbl-Kovacic A, et al. Aggressive B-cell lymphomas in patients with myelofibrosis receiving JAK1/2 inhibitor therapy. Blood 2018;132:694-706.
[3] Pemmaraju N, Kantarjian H, Nastoupil L, et al. Characteristics of patients with myeloproliferative neoplasms with lymphoma, with or without JAK inhibitor therapy. Blood 2019;133:2348-2351.
[4] Rumi E, Zibellini S, Boveri E, et al. Ruxolitinib treatment and risk of B-cell lymphomas in myeloproliferative neoplasms. Am J Hematol 2019;94:E185-E188.
[5] Barbui T, Ghirardi A, Masciulli A, et al. Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study. Leukemia 2019;33:1996-2005.
[6] Polverelli N, Elli EM, Abruzzese E, et al. Second primary malignancy in myelofibrosis in patients treated with ruxolitinib. Br J Haematol 2021;193:356-368.

Note: All recommendations are category 2A unless otherwise indicated.

Version 2.2025, 07/08/25 © 2025 National Comprehensive Cancer Network® (NCCN®), All rights reserved. NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN.

Backgroundinfos aus Leitlinie

Symptom Management in Patients with MPN

Disease-related symptoms commonly contribute to decreased quality of life in patients with MPN.85 While JAK inhibitors have been shown to broadly improve disease-related symptoms,86-94 their use is not indicated in all patients with symptomatic MPN, and the presence of specific symptoms often requires a targeted approach. Pruritus, bone pain,

headaches, and tinnitus occur across all MPN, albeit with some disease preference, and greatly impact quality of life. The optimal management of these symptoms in the setting of MPN has not been established and recommendations for symptom management as outlined in the guidelines (see Supportive Care for Patients with MPN: Symptom Management in Patients with MPN in the algorithm) are based on the subset analysis of

large trials, small pilot studies, anecdotal evidence, extrapolation from other disease states, and expert opinion.

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.

Risk Stratification

Primary Myelofibrosis

DIPSS, DIPSS-Plus, Mutation-Enhanced International Prognostic Scoring System 70 (MIPSS-70), and MIPSS-70-Plus are prognostic scoring systems used for the risk stratification of patients with MF.95-98 MIPSS-70 and MIPSS-70-Plus incorporate cytogenetic information and mutational status and have been developed to refine the risk stratification.98 DIPSS is a dynamic model and has been validated for use at any point over the course of disease.96 MIPSS-70 or MIPSS-70-Plus version 2.0 is preferred for the prognostic risk stratification of patients with PMF.98,99 Additionally, DIPSS-Plus is recommended for risk stratification at the time of treatment if molecular testing is not available97 and DIPSS can be used if recent karyotyping is not available.96 Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) is recommended for the risk stratification of post-PV or post-ET MF.100,101

DIPSS

In a subsequent analysis that evaluated the impact of each adverse factor on survival during follow-up after treatment, all variables retained statistical significance. However, the development of anemia over time significantly affected survival (hazard ratio [HR] was approximately double that of other adverse factors).96 Thus, a modified risk stratification system (DIPSS) was developed using the same prognostic variables as in IPSS (age >65 years, presence of constitutional symptoms, hemoglobin level <10 g/dL, leukocyte count >25 x 109/L, and circulating blast cells ≥1%), but two points were assigned for hemoglobin <10 g/dL. The DIPSS can be applied at any point during the disease course to stratify patients into four different risk groups: low risk (0 adverse points), intermediate-1 risk (1 or 2 points), intermediate-2 risk (3 or 4 points), and high risk (5 or 6 points) with the median survival rates of not reached, 14 years, 4 years, and 1.5 years, respectively.96

DIPSS-Plus

In subsequent reports, the need for red blood cell (RBC) transfusion, platelet count, and unfavorable karyotype have been identified as additional IPSS- and DIPSS-independent prognostic factors for inferior OS and LFS in patients with PMF.102-105 The median survival of patients with DIPSS low-risk disease with thrombocytopenia or unfavorable karyotype

was 6.5 years compared to >15 years in the absence of these two additional risk factors.97 Similarly, the median survival was <1.5 years for patients with DIPSS high-risk disease with ≥1 of these additional prognostic factors compared to approximately 3 years for those patients without these prognostic factors.97 DIPSS was modified into DIPSS-Plus by the incorporation of platelet count <100 x 109/L, RBC transfusion need, and unfavorable karyotype [complex karyotype or one or two abnormalities that include trisomy 8, del(7/7q), i(17q), del(5/5q), del(12p), inv(3), or 11q23 rearrangement].97 DIPSS-Plus also stratifies patients into four risk groups based on the aforementioned

eight risk factors: low risk (no risk factors), intermediate-1 risk (one risk factor), intermediate-2 risk (two or three risk factors), and high risk (≥4 risk factors) with respective median survival rates of 15.4, 6.5, 2.9, and 1.3 years, respectively. To calculate the DIPSS-Plus score, clinicians must first calculate the DIPSS score. Points are assigned as follows: 0 for DIPSS low risk, 1 for DIPSS intermediate-1 risk, 2 for DIPSS intermediate-2 risk, and 3 for DIPSS high risk. One point each is then added for platelets <100 x 109/L, RBC transfusion need, and unfavorable karyotype.

MIPSS-70 and MIPSS-70-Plus

In a study of 805 patients with PMF (aged ≤70 years), in a multivariate analysis, hemoglobin level <10 g/dL, leukocyte count >25 x 109/L, platelet count <100 x 109/L, circulating blast cells ≥2%, bone marrow fibrosis grade ≥MF-2, constitutional symptoms, absence of CALR type-1 mutation, and presence of ≥2 HMR mutations (ASXL1, EZH2, SRSF2, and IDH1/2) were identified as independent predictors of inferior OS.98 This mutationinformed (MIPSS-70) prognostic model (without the cytogenetic information) stratified patients into three risk categories (low risk, intermediate risk, and high risk) with a median OS of 28 years, 7 years, and 2 years, respectively. The 5-year OS rates were 95%, 70%, and 29%, respectively. The MIPSS-70-Plus prognostic model, which included cytogenetic information but omitted bone marrow fibrosis grade and leukocyte and platelet counts, stratified patients into four risk categories (low risk, intermediate risk, high risk, and very high risk) with 5-year OS rates of 91%, 66%, 42%, and 7%, respectively. The MIPSS-70-Plus version 2.0 prognostic model accounted for very-high-risk (VHR) karyotype, included U2AF1 Q157 as an HMR mutation, and specified new hemoglobin thresholds with adjustments for sex and severity.99 It stratified patients into five risk categories (very low risk, low risk, intermediate risk, high risk, and very high risk) with a median OS of not reached, 10.3 years, 7.0 years, 3.5 years, and 1.8 years, respectively, for patients of all ages. The 10-year survival rates were 86%, 50%, 30%, 10%, and <3%, respectively.

Post-PV MF and Post-ET MF

The prognostic scoring systems described above have been studied and validated only in patients with PMF. Although these prognostic scoring systems have been clinically used for the risk stratification of patients with post-PV or post-ET MF, they are not effective for the risk stratification of patients with post-PV or post-ET MF.106 The MYSEC-PM is a prognostic

model that stratifies patients with post-PV or post-ET MF into four risk groups, with distinct survival outcomes (low risk, intermediate-1, intermediate-2, and high risk) based on age, hemoglobin level (<11 g/dL), circulating blasts (≥3%), CALR mutation status, platelet count (<150 x 109/L), and constitutional symptoms.100 The median survival was not reached, 9 years, 4 years, and 2 years, respectively. Palandri et al101 validated the MYSEC-PM model in post-PV and post-ET MF. The model was successfully used to stratify patients into different risk categories, while the IPSS could not. Spleen responses and hematologic toxicities also differed based on the predicted risk. In a retrospective analysis of cytogenetic data from 376 patients with post-PV and post-ET MF, a significant association was uncovered between abnormal karyotypes and higher MYSEC-PM risk categories (P = .006).107 However, patients with a monosomal karyotype had a lower chance of survival that was independent of the MYSEC-PM stratification.

Treatment Options

Interferons

Interferons may demonstrate activity in low-risk MF108-110 but they are generally not recommended for higher-risk disease. In a retrospective study of 62 patients with early MF treated with peginterferon alfa-2a, improvement in constitutional symptoms and complete resolution of thrombocytosis and leukocytosis were observed in 82%, 83%, and 69% of patients, respectively, and a reduction of splenomegaly was seen in 47% of patients.108 Ianotto et al109 reported an improved OS compared to the reference cohorts used to determine DIPSS scores (intermediate-2: 6.9 vs. 4 years and high risk: 4.58 vs. 1.5 years). A reduction of >50% in the JAK2 V617F allele burden was observed in 58.8% of patients; the presence of ≥1 additional mutation(s) was associated with worse OS and LFS. In a prospective trial of 30 patients (21 patients with PMF, 7 patients with post-PV MF, and 2 patients with post-ET MF), treatment with interferon alfa-2b or peginterferon alfa-2a resulted in an overall response rate (ORR) of 73% (7% complete response [CR], 30% partial response [PR], 13% clinical improvement, and 23% of patients had stable disease [SD]).110 The corresponding response rates were 3%, 27%, 6%, and 13%, respectively, for patients with low-risk disease. Among patients with marked splenomegaly, spleen response (≥50% reduction in spleen size) was observed in 40% of patients (4 out of 10) and 60% of patients (6 out of 10) had either a slight decrease in spleen size or stable spleen size. Among the 25 patients with evaluable bone marrow biopsies, reduction in bone marrow cellularity and reductions of reticulin fibrosis were observed in 12 patients and 5 patients, respectively, after a median treatment duration of 6 years. The presence of HMR mutations or ≥3 mutations was associated with inferior response rates and the survival rates were better for patients without ASXL1 mutation; the 5-year progression-free survival (PFS) and OS rates were 88% and 92%, respectively.

The combination of interferons with JAK inhibitors is under investigation in clinical trials. The phase II COMBI study, which evaluated the efficacy of combined ruxolitinib and low-dose pegylated interferon alfa-2 in 32 patients with PV and 18 patients with primary or secondary MF, reported a remission rate of 31% in patients with PV and 44% in patients with primary or secondary MF at 2 years, as determined by the 2013 European LeukemiaNet (ELN) and IWG-MRT response criteria.111 Fortysix patients previously had disease that was intolerant of, or refractory to pegylated interferon alfa-2. Reductions in symptom burden (22 to 15) as assessed by the MPN-SAF TSS and in the median JAK2 V617F allele burden (47% to 12%) were also obtained. The main grade 3–4 hematologic adverse events reported were anemia (14.0%), thrombocytopenia (4.0%),

and leukopenia (2.0%) and the main grade 3– 4 nonhematologic adverse events were pneumonia (12.0%), hypertension (6%), and gastrointestinal bleeding (6%). Data from the phase I/II RUXOPEG trial demonstrated reduction of ≥50% in spleen length in 70% of patients within 24 weeks in the intention-to-treat population in patients with MF treated with ruxolitinib and pegylated interferon alfa-2a.112 A reduction in the JAK2 V617F allele burden was also reported (mean of 84% at baseline to 65% and 53% after 6 and 12 months, respectively).

Ruxolitinib

Ruxolitinib is a potent and selective JAK1 and JAK2 inhibitor that is U.S. Food and Drug Administration (FDA)-approved for the treatment of intermediate-risk or high-risk MF as determined by IPSS, based on the results of phase III studies (COMFORT-I and COMFORT-II).86,113 The COMFORT studies did not include patients with low-risk or intermediate-1-risk MF, and the use of ruxolitinib in this patient population is based on the evidence from retrospective analysis and non-randomized clinical studies as discussed below.114-117

Lower-Risk MF

The efficacy of ruxolitinib in low-risk MF has not been evaluated in prospective clinical trials. The results from a retrospective analysis suggest that ruxolitinib may be an appropriate treatment option for symptomatic patients with low-risk MF.114 In this retrospective analysis of 108 patients (25 patients with low-risk MF and 83 patients with

intermediate-1-risk MF) treated with ruxolitinib, patients with low-risk MF experienced a substantial improvement in splenomegaly and constitutional symptoms. The proportion of patients with moderate to severe splenomegaly reduced from 64% at the time of diagnosis to 16% at the time of best response to ruxolitinib. The proportion of patients with moderate or severe fatigue decreased from 90% at the time of diagnosis to 37% at the time of best response to ruxolitinib. The safety and efficacy of ruxolitinib in patients with intermediate-1-risk MF have been demonstrated in a retrospective analysis114 and nonrandomized studies.115-117 In the retrospective analysis (discussed above), among the 83 patients with intermediate-1-risk MF, the proportion of patients with moderate or severe splenomegaly decreased from 53% at the time of diagnosis to 10% at the time of best response to ruxolitinib, and the proportion of patients with moderate or severe fatigue decreased from 76% at the time of diagnosis to 42% at the time of best response to ruxolitinib.114

The ROBUST trial is an open-label phase II trial that evaluated the efficacy of ruxolitinib in patients with intermediate-1-risk MF (48 patients; 14 patients with intermediate-1-risk MF along with 13 patients with intermediate-2-risk MF and 21 patients with high-risk MF).115 The primary composite endpoint was the achievement of treatment success at 48 weeks after ruxolitinib therapy (≥50% reduction in palpable spleen length and/or a ≥50% decrease in MF-SAF). At 48 weeks, 47% of the overall population achieved a reduction in mean palpable spleen length and the effect was seen across all risk groups (52% of patients with

intermediate-1-risk, 37% of patients with intermediate-2-risk, and 49% of patients with high-risk disease). A ≥50% reduction in MF-SAF at 48 weeks was achieved in 20.8% of patients in the overall population and across all risk groups (intermediate-1 risk, 21%; intermediate-2 risk, 23%; high risk, 19%). Improvements in MF-SAF were seen in 80%, 73%, and 72% of patients with intermediate-1-risk, intermediate-2-risk, and high-risk disease, respectively.

JUMP is an expanded-access phase III study designed to assess the safety and efficacy of ruxolitinib in patients with intermediate-2-risk or high-risk MF with or without splenomegaly or intermediate-1-risk MF with a palpable spleen (≥5 cm from the costal margin).118 The JUMP study comprised 2087 patients with platelet count ≥100 x 109/L and 138 patients with platelet count <100 x 109/L. A primary analysis revealed that at 24, 48, and 96 weeks, 56.5%, 61.4%, and 66.5% of evaluable patients achieved a ≥50% reduction from baseline in palpable spleen length, respectively. At the same time points, 23.3%, 18.9%, and 14.3% of patients had a 25% to <50% reduction from baseline in palpable spleen

length, respectively. Of evaluable patients with platelet count <100 x 109/L, 38.4% and 31.9% achieved a ≥50% reduction from baseline in palpable spleen length at 24 and 48 weeks, respectively. The most common grade 3 or 4 hematologic adverse events were anemia and thrombocytopenia in patients with platelet count ≥100 x 109/L (34.7% and 17.1%, respectively) and in patients with platelet count <100 x 109/L (35.5% and 54.3%, respectively). The most common grade 3 or 4 non-hematologic adverse events were pneumonia (4.6%), pyrexia (2.3%), and asthenia (2.2%) in patients with platelet count ≥100 x 109/L and pneumonia (5.8%), pyrexia (3.6%), and dyspnea (3.6%) in patients with platelet count <100 x 109/L. At 96 weeks, the estimated OS and PFS (per IWG-MRT criteria) probabilities were 87% (95% CI, 85%–89%) and 81% (95% CI, 78%–83%), respectively. Treatment with ruxolitinib also led to the amelioration of symptoms. A multivariate analysis determined that IPSS low/intermediate-1 risk category (43.1% vs. 30.6% for IPSS intermediate-2/high-risk category; adjusted odds ratio [AOR], 0.65; 95% CI, 0.44–0.95), use of ruxolitinib in the first-line setting (40.2% vs. 31.5% for use in subsequent-line setting; AOR, 0.53; 95% CI, 0.38–0.75), and a total daily dose of >20 mg/day at 12 weeks (41.3% vs. 30.4% for <20 mg/day; AOR, 0.47; 95% CI, 0.33–0.68) were

associated with a higher spleen response rate.119 However, no association was found with symptom response rate.

In another study that evaluated efficacy and safety of ruxolitinib in 70 patients with intermediate-1-risk MF, the rates of spleen and symptom response at 6 months were 55% and 80%, respectively. The majority of patients (83%) were still on therapy after a median follow-up of 27 months.117

Higher-Risk MF

The results of COMFORT-I86,120,121 and COMFORT-II113,122,123 studies demonstrated that continuous ruxolitinib therapy was associated with significant clinical benefits in patients with MF in terms of reduction in spleen size, amelioration of disease-related symptoms, and improvement in quality of life and OS compared to either placebo or best available therapy for patients with intermediate-2-risk or high-risk MF (PMF, post-PV MF, or post-ET MF).

The COMFORT-I trial randomized 259 patients with intermediate-2-risk or high-risk MF to twice-daily ruxolitinib (n = 155) or placebo (n = 154).86 The starting dose of ruxolitinib was based on the baseline platelet count (15 mg twice daily for a platelet count 100 x 109/L to 200 x109/L and 20 mg twice daily for >200 x 109/L) and patients with protocol-defined worsening splenomegaly were permitted to cross over from placebo to ruxolitinib. The primary endpoint (≥35% reduction in spleen volume as assessed by MRI at 24 weeks) was reached in 42% of patients in the ruxolitinib group as compared with 0.7% in the placebo group (P < .001). An improvement of ≥50% in the MF-SAF at 24 weeks was seen in 46% of patients treated with ruxolitinib as compared with 5% of patients who received placebo (P < .001). Long-term follow-up results confirmed the safety and durable efficacy of ruxolitinib for the treatment of patients with intermediate-2-risk or high-risk MF.120,121 The 5-year follow-up data showed that patients treated with ruxolitinib had prolonged median OS compared to placebo (not reached compared to 200 weeks for patients randomized to placebo; HR, 0.69; 95% CI, 0.50–0.96; P = .025).121 Spleen response (≥35% reduction from baseline in spleen volume) was achieved in 59% of patients randomized to ruxolitinib and the median duration of spleen response was 168 weeks. At the time of this analysis, 111 patients from the placebo group had crossed over to ruxolitinib (median time to crossover was 40 weeks). The subgroup analyses showed that clinical benefit of ruxolitinib was seen across all patient subgroups including PMF, post-ET MF or post-PV MF, IPSS risk groups, and JAK mutation status (positive or negative), and there was also a non-significant trend toward longer OS for patients with IPSS intermediate-2-risk and high-risk MF treated with ruxolitinib. However, this study was not designed or powered to detect treatment efficacies between treatment arms within each subgroup.121,124

In the COMFORT-II study, 219 patients with intermediate-2-risk or high-risk MF were randomized to ruxolitinib (n = 146) or best available therapy (n = 73).113 The primary endpoint was at least a 35% reduction in spleen volume as assessed with MRI or CT scan at 48 weeks. The starting dose of ruxolitinib was based on the baseline platelet count (15 mg twice daily if the platelet count was ≤200 x 109/L and 20 mg twice daily if the platelet count was >200 x 109/L). A total of 28% of the patients in the ruxolitinib arm had a ≥35% reduction in spleen volume at 48 weeks compared with 0% in the group receiving the best available therapy (P <.001). The median duration of response among patients treated with ruxolitinib was not reached, with 80% of patients still having a response at a median follow-up of 12 months.113 Patients receiving ruxolitinib had improved quality of life and role functioning as well as significant reductions in disease-related symptoms compared to those receiving best available therapy. Long-term follow-up results confirmed that ruxolitinib is associated with durable efficacy and survival benefit compared to best available therapy for patients with intermediate-2-risk or high-risk MF.122,123 At the time of the 5-year final analysis, 53% of patients in the ruxolitinib arm achieved a ≥35% reduction in spleen volume at any time on treatment, and spleen volume reductions of ≥35% were sustained with long-term therapy (median duration, 3 years).123 The median OS was not reached for patients in the ruxolitinib arm, and it was 4 years for those in the best available therapy arm. The pooled analysis of COMFORT-I and COMFORT-II studies showed that patients with intermediate-2-risk or high-risk MF treated with ruxolitinib had prolonged OS, and the OS of patients with high-risk disease in the ruxolitinib group was similar to that of patients with intermediate-2-risk MF in the control group.125 Larger spleen size at baseline was associated with shortened survival, whereas any spleen volume reductions (>10% reduction in spleen size) and a palpable spleen length reduction of ≥25% correlated with longer survival. Verstovsek et al126 also determined that compared to patients who had a decrease of <25% in spleen length, those with a ≥50% decrease had significantly improved survival (HR, 0.223; 95% CI, 0.097–0.512; P = .0001).

The European Registry for Myeloproliferative Neoplasms: Toward a Better Understanding of Epidemiology, Survival, and Treatment (ERNEST) study enrolled patients with PMF or post-PV/ET MF.127 At enrollment, 10.7% of patients had received treatment with ruxolitinib and 48.2% of patients had received treatment with hydroxyurea only. Sixty-four percent of patients treated with ruxolitinib had received treatment with hydroxyurea. Analysis of the real-world data revealed an improved median OS with ruxolitinib compared to those treated with hydroxyurea (6.7 vs. 5.1 years; P = .001). A propensity score matching analysis also

demonstrated an improved median OS in patients treated with ruxolitinib (7.7 years) as first-line therapy or second-line therapy after hydroxyurea compared to those treated with hydroxyurea only (3.4 years; P = .002).

Toxicity

Anemia and thrombocytopenia were the most common hematologic toxicities associated with ruxolitinib, consistent with its mechanism of action, and the incidences of grade 3/4 anemia or thrombocytopenia were higher during the first 8 to 12 weeks of treatment.86,113,116 In the COMFORT-I study, ecchymosis, dizziness, and headache were the most frequent nonhematologic toxicities associated with ruxolitinib, and diarrhea was the most frequent nonhematologic adverse event associated with ruxolitinib in the COMFORT-II study.86,113 In general, the incidences of nonhematologic toxicities decreased with long-term therapy.120,123 Anemia associated with ruxolitinib treatment may not share the inferior prognosis of disease-related anemia as ruxolitinib can overcome the inferior prognosis of disease-induced anemia.128 A study by Cervantes et al129 suggests that an alternative dosing strategy for ruxolitinib consisting of a dose of 10 mg twice daily for 12 weeks and titrating up to a dose of 25 mg twice daily was well-tolerated and effective in patients with PMF or post-PV/ET MF and anemia.

Management of Treatment-Related Anemia and Thrombocytopenia

In the COMFORT-I and COMFORT-II studies, anemia and thrombocytopenia were managed with dose modifications and RBC transfusions.86,113 Patients enrolled in the COMFORT trials were required to have a baseline platelet count ≥100 x 109/L, and the initial starting dose of ruxolitinib was dependent on the patient's baseline platelet counts.86,113 The results of a phase II study suggest that a lower initial dose of ruxolitinib (5 mg twice daily with optional escalation up to 15 mg twice a day) may be appropriate in patients with baseline platelet count 50 to 100 x 109/L.130 In the dose-finding phase Ib EXPAND study, ruxolitinib was tolerated at a maximum safe starting dose of 10 mg twice daily in patients with MF with platelet count 50 to 74 x 109/L or 75 to 99 x 109/L.131 Patients with platelet count of 75 to 99 x 109/L displayed higher tolerability. At 48 weeks, 33.3% of patients with platelet count 75 to 99 x 109/L demonstrated a spleen response compared to 30% of patients with platelet count 50 to 74 x 109/L. See the prescribing information for dose modifications for the management of hematologic toxicities.

Other Toxicities

Ruxolitinib is associated with a potentially increased risk of opportunistic infections and viral reactivations.132,133 Non-melanoma skin cancers and pre-cancerous lesions have been reported in patients treated with ruxolitinib.134 Lymphoid neoplasms may be diagnosed concurrently with MPN or may develop during the natural history of MF, PV, or ET.135-138 Although one report indicated that JAK inhibitor therapy may be associated with an increased risk of aggressive B-cell lymphomas in patients with MF,139 other studies found no evidence of increased lymphoma risk in patients treated with a JAK inhibitor.140-143

Impact of Mutational Status and Response to Ruxolitinib

In the COMFORT-II study, ruxolitinib was associated with clinical efficacy and survival improvement across different molecular subsets of patients with MF.144 HMR mutations (ASXL1, EZH2, SRSF2, IDH1, or IDH2) were identified in 33%, 7%, 3%, <1%, and 0% of patients, respectively, and these frequencies were comparable in ruxolitinib and best available therapy arms. Responses in splenomegaly (>35% spleen volume reduction), symptomatic improvement, and the risk of ruxolitinib-associated anemia and thrombocytopenia were observed at similar frequencies across different mutation profiles. Ruxolitinib improved survival and reduced the risk of death in patients harboring HMR mutations (ASXL1, EZH2, SRSF2, IDH1, or IDH2) with an HR of 0.57.144 The use of ruxolitinib did not appreciably influence the acquisition of additional mutations during treatment compared to the use of hydroxyurea.145 A decrease in the JAK2 V617F variant allele frequency was associated with the duration of the spleen volume response. An increase in the variant allele frequency of any initial mutation or the acquisition of ≥1 non-driver mutations during treatment was associated with increased rates of treatment discontinuation.

The results of another analysis of 95 patients with MF treated with ruxolitinib in a single institution also showed that ASXL1, EZH2, and IDH1/2 mutations are associated with poor outcomes and patients with ≥3 mutations in ASXL1, EZH2, or IDH1/2 had shorter time to treatment discontinuation and OS.146 However, in contrast to the findings of the COMFORT-II study, patients with ≥1 mutations in ASXL1, EZH2, or IDH1/2 were significantly less likely to have a spleen response. Patients with ≥3 mutations had the worst outcomes, suggesting that multigene profiling may be useful for treatment planning in patients with MF.

Response Prediction to Ruxolitinib

The response to ruxolitinib after 6 months (RR6) model can be used to gauge response to ruxolitinib. This prognostic model takes into account the ruxolitinib dose, spleen response, and RBC transfusion needs for 6 months following the initiation of ruxolitinib therapy in order to predict OS.147 The results of a multivariable analysis revealed several risk factors: a ruxolitinib dose of <20 mg twice a day at baseline and at 3 and 6 months, a ≤30% reduction in spleen length from baseline at 3 and 6 months, an RBC transfusion requirement at 3 and/or 6 months, and an RBC transfusion requirement at baseline and at 3 and 6 months. The model

stratified patients into 3 risk categories: low-risk (median OS, not reached), intermediate-risk (median OS, 61 months; 95% CI, 43–80 months), and high-risk (median OS, 33 months; 95% CI, 21–50 months). The model's predictive potential was validated and confirmed in an external cohort of 40 patients with MF.

Fedratinib

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, based on the results of the randomized phase III JAKARTA trial, as well as the non-randomized phase II JAKARTA-2 trial, which evaluated efficacy in patients with ruxolitinib-resistant or ruxolitinib-intolerant intermediate-1, intermediate-2, or high-risk MF.89,94

The phase III JAKARTA trial randomized patients with intermediate-2-risk or high-risk MF (PMF, post-PV MF, or post-ET MF) with platelet counts ≥50 x 109/L to once-daily fedratinib 400 mg (n = 96) or placebo (n = 96).94 Patients with progressive disease (PD) were permitted to cross over from placebo to fedratinib. The proportion of patients achieving the primary endpoint (spleen response; ≥35% reduction in spleen volume as assessed by MRI or CT scan at 24 weeks and confirmed 4 weeks later) was significantly higher (P < .0001) in the 400 mg fedratinib group (37% [95% CI, 27%–46%]) than in the placebo group (1% [95% CI, 0%–3%]). The symptom response rates at 24 weeks (≥50% reduction in the MF-SAF-TSS from baseline) in evaluable patients were 40% (95% CI, 30%–51%) and 9% (95% CI, 3%–15%), respectively, for the 400 mg and placebo groups.

Seventy-four percent of patients initially in the placebo group crossed over to fedratinib during the study.148 The median OS was not reached in either group (HR, 0.57; 95% CI, 0.30–1.10; P = .094). The survival rates at 1 year and 18 months were 92% and 87%, respectively, for the fedratinib group, and 86% and 80%, respectively, for the placebo group. Patients treated with fedratinib had significantly longer median PFS (23.2 vs. 17.5 months) (HR, 0.42; 95% CI, 0.23–0.76; P = .004). The PFS rates were 83% for the fedratinib group and 67% for the placebo group at 1 year. A subsequent analysis of the JAKARTA study showed that the baseline platelet count did not significantly impact the rate of spleen response (P = .37), which was 36% in patients with platelet count 50 to <100 x 109/L (N = 14) and 49% in patients with platelet count ≥100 x 109/L (N = 82) who were treated with 400 mg daily fedratinib at 24 weeks.149 Similar results were obtained for the rates of symptom response (33% in the first group and 42% in the second group; P = .57).

The phase II non-randomized JAKARTA-2 trial (n = 97) showed that fedratinib 400 mg was also effective in reducing splenomegaly and symptom burden in patients with ruxolitinib-resistant or ruxolitinib-intolerant intermediate-1-risk or intermediate-2-risk/high-risk MF (PMF, post-PV MF, or post-ET MF, palpable splenomegaly [≥5 cm below the left costal margin], and platelet count ≥50 x 109/L).89 Patients were assigned by treating investigators as resistant or intolerant to ruxolitinib. Spleen response (≥35% reduction in spleen volume as assessed by MRI or CT scan at 24 weeks; 83 evaluable patients) and symptom response (≥50% reduction in the MF-SAF-TSS at 24 weeks; 90 evaluable patients) were achieved in 55% (53% in the ruxolitinib-resistant group and 63% in the ruxolitinib-intolerant group) and 26% (21% in the ruxolitinib-resistant group and 32% in the ruxolitinib-intolerant group) of patients, respectively. Another analysis of the JAKARTA-2 study reported the efficacy data in three different cohorts of patients (intent-to-treat population, n = 97; stringent criteria cohort, n = 79; and sensitivity analysis cohort, 66 patients treated with 6 cycles of fedratinib or discontinued before cycle 6 for reasons other than study closure) by using updated criteria for ruxolitinib failure and intolerance.150 The spleen response rates were 31%, 30%, and 36%, respectively, for these three cohorts. The corresponding symptom response rates were 27%, 27%, and 32%, respectively. At the end of the study, 81% of patients were censored for survival.148 The median OS was not reached (95% CI, 17.1 months–not reached) and the survival rates at 1 year and 18 months were 84% and 67%, respectively. The median PFS was 13.3 months (95% CI, 8.4–17.1 months) and the PFS rate at 1 year was 59%. A subgroup analysis of the JAKARTA2 study showed the baseline platelet count did not significantly impact the rate of spleen response (P = .41), which was 36% in patients with platelet count 50 to <100 x 109/L (N = 33) and 28% in patients with platelet count ≥100 x 109/L (N = 64) at 24 weeks.149 The rate of symptom response was 39% in the former group and 20% in the latter group (P = .06). Post hoc analyses from the JAKARTA and JAKARTA2 trials determined that treatment with fedratinib (400 mg daily) was not associated with clinically significant weight gain or an increase in the body mass index.151

Toxicity

Anemia and thrombocytopenia were the most common hematologic toxicities associated with fedratinib.89,94 In the JAKARTA trial, ≥grade 3 anemia was reported in 30% of patients.94 In an analysis of the JAKARTA-2 trial, grade 3 or 4 anemia was reported in 46% of patients and thrombocytopenia in 24% of patients.89 A pooled analysis of the JAKARTA/JAKARTA2/ARD11936 cohorts revealed a higher percentage of grade 3–4 treatment-emergent thrombocytopenia (40% for platelet count 50 to <100 x 109/L [N = 48] and 5% for platelet count ≥100 x 109/L [N = 155]) in patients treated with 400 mg daily fedratinib.149 Diarrhea, vomiting, and nausea were the most common nonhematologic toxicities and usually abated after the first 28-day cycle.89,94 Fedratinib has demonstrated inhibition of FLT3, which has been implicated in the occurrence of these gastrointestinal toxicities.152,153 Elevation of liver enzymes or creatinine levels were more frequent with fedratinib than with placebo.94 Fedratinib was also associated with a higher rate of infections (42% for

fedratinib 400 mg compared to 27% in the placebo group).154 The phase IIIb FREEDOM trial evaluated the efficacy and safety of fedratinib at a dose of 400 mg daily in patients with DIPSS intermediate-risk or high-risk PMF or post-PV/ET MF who were previously treated with ruxolitinib.155 At the end of cycle 6, 25.7% of evaluable patients achieved the primary endpoint of ≥35% reduction in spleen volume and 44.4% achieved the secondary endpoint of ≥50% reduction in total symptom score. Grade 3/4 anemia and thrombocytopenia occurred in 39.5% and 23.7% of patients, respectively. Grade 3 gastrointestinal adverse events were also reported in 15.8% of patients. Data also suggest that early treatment with gastrointestinal prophylactic agents may help to mitigate the rates of gastrointestinal adverse events. No cases of Wernicke encephalopathy (WE) were observed.

In August 2017, the FDA removed the clinical hold on the fedratinib development program, which was initially placed in 2013 because eight out of 670 patients in fedratinib clinical trials experienced symptoms suggestive of WE, which is a neurological disorder that develops in the setting of thiamine deficiency.156 A subsequent report showed that fedratinib does not increase the risk of thiamine deficiency beyond its potential to worsen malnutrition, which could be due to poor management of preventable gastrointestinal adverse events.156 In the JAKARTA2 study, only one case of encephalopathy was reported, which was subsequently determined to be related to hepatic encephalopathy and inconsistent with WE.150 In 670 patients enrolled in clinical trials evaluating fedratinib in patients with MPN or solid tumors, the overall prevalence of WE was observed in <1% of treated patients,156 and thus was not found to be clearly different than the 1% to 2% prevalence of WE in the general U.S. population.157

As a result of these updated analyses, the FDA approved fedratinib in 2019 for the treatment of patients with intermediate-2-risk or high-risk MF (PMF, post-PV MF, or post-ET MF). The prescribing information for fedratinib includes a boxed warning regarding the potential risk of encephalopathy, including WE. See the prescribing information for monitoring of thiamine levels.

Pacritinib

Pacritinib, a JAK2, FLT3, and IRAK1 inhibitor, was evaluated in patients with intermediate-1, intermediate-2, and high-risk MF.92,93,158 Pacritinib is FDA-approved for the treatment of intermediate or high-risk MF with a platelet count <50 x 109/L.93,158 The phase II PAC203 trial reported that 200 mg pacritinib twice daily showed clinical activity and had a manageable safety profile in patients with ruxolitinib-resistant or ruxolitinib-intolerant intermediate-1, intermediate-2, or high-risk MF with platelet count <50 x 109/L.158 At 24 weeks, the spleen response rate (≥35% reduction in spleen volume) was 9.3% in the overall cohort versus 16.7% in those with platelet count <50 x 109/L and the total symptom score response rate (≥50% reduction in total symptom score based on the MPN-SAF TSS 2.0) was 7.4% in the overall cohort versus 8.3% in those with platelet count <50 x 109/L. In the phase III PERSIST-1 trial, patients with intermediate-1, intermediate-2, or high-risk MF with palpable splenomegaly (≥5 cm below the left costal margin) were randomized 2:1 to receive pacritinib (n = 220), 400 mg once daily, or best available therapy (n = 107) (excluding JAK2 inhibitors).92 Patients were allowed to cross over to pacritinib at 24 weeks or if their disease progressed. In the best available therapy group, 84% of the patients crossed over to the pacritinib group at a median time point of 6.3 months. Nineteen percent of patients receiving pacritinib met the primary endpoint (≥35% spleen volume reduction, as determined by MRI or CT, in the intention-to-treat population) compared to 5% of patients receiving best available therapy (P = .0003) at 24 weeks. At the same time point, the percentage of patients with a total symptom score reduction of ≥50%, as determined using the MPN-SAF TSS 2.0, was similar in the pacritinib and best available therapy study arms (19% vs. 10%; P = .24). At 48 weeks, a significantly higher percentage of patients in the pacritinib study arm achieved this reduction (15% vs. 0%; P = .0027). OS did not differ between the two groups (HR, 1.36; 95% CI, 0.89–2.09; P = .16) prior to week 24.

The phase III PERSIST-2 trial randomized patients with intermediate-1, intermediate-2, or high-risk MF with platelet count ≤100 x 109/L 1:1:1 to receive once-daily pacritinib 400 mg, twice-daily pacritinib 200 mg, or best available therapy.93 Patients had palpable splenomegaly (≥5 cm below the left costal margin) and platelet count ≤100 x 109/L. Forty-eight percent of patients were previously treated with ruxolitinib. Among the best available therapy group, 45% of patients received ruxolitinib. Patients were allowed to cross over to pacritinib at 24 weeks or if splenomegaly progressed. At 24 weeks, in the intention-to-treat population, the proportion of patients achieving the co-primary endpoint of ≥35% reduction in spleen volume, as assessed by MRI/CT, was significantly higher in the pacritinib groups (15% [95% CI, 7.6%–24.7%; P = .02] for 400 mg once daily and 22% [95% CI, 12.9%–32.7%; P = .001] for 200 mg twice daily) than in the best available therapy group (3% [95% CI, 0.3%–9.7%]). Seventeen percent (95% CI, 9.6%–27.8%; P = .65) of patients receiving once-daily 400 mg pacritinib and 32% (95% CI, 22.0%–44.3%; P = .01) of patients receiving twice-daily 200 mg pacritinib met the co-primary endpoint of ≥50% reduction in total symptom score (MPN-SAF TSS 2.0), as opposed to 14% (95% CI, 6.9%–24.1%) of patients receiving best available therapy. OS was similar across all three groups (HR, 1.18; 95% CI, 0.57–2.44; and HR, 0.68; 95% CI, 0.30–1.53 for pacritinib 400 mg once daily and 200 mg twice daily, respectively, when compared to best available therapy).

Toxicity

The phase II PAC203 trial reported thrombocytopenia (33.3%), anemia (20.4%), and neutropenia (5.6%) as 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.158 Pneumonia (9.3%) as well as diarrhea, abdominal pain, and hyperuricemia (5.6% each) were the most common nonhematologic grade 3 or 4 treatment-emergent adverse events. Like fedratinib, pacritinib also exhibits FLT3 inhibition, which has been implicated in gastrointestinal toxicity.152,153

In the PERSIST-1 trial, the most frequent grade 3 or 4 adverse events in the pacritinib study arm were anemia (17%), thrombocytopenia (12%), and diarrhea (5%) and in the best available therapy arm, they were anemia (15%), thrombocytopenia (11%), dyspnea (3%), and hypotension (3%).92 One percent of patients in the pacritinib group had an infection compared to none in patients receiving best available therapy. In the PERSIST-2 trial, the most frequent grade 3 or 4 treatment-emergent adverse events in patients receiving once-daily pacritinib 400 mg, twice-daily pacritinib 200 mg, or best available therapy were thrombocytopenia (31%, 32%, and 18%, respectively) and anemia (27%, 22%, and 14%, respectively).93

In 2016, the FDA placed a clinical hold on the development of pacritinib while evaluating deaths related to intracerebral hemorrhage and cardiovascular events. In 2017, the FDA lifted the clinical hold and in 2022, the drug was approved for the treatment of intermediate- or high-risk MF (PMF, post-PV MF, or post-ET MF) for patients with platelet count <50 x 109/L.

Momelotinib

Momelotinib, a potent and selective JAK1/2 inhibitor and ACVR1/ALK2 inhibitor, is FDA-approved for the treatment of intermediate- or high-risk MF in patients with anemia based on the results of the randomized phase III MOMENTUM trial, as well as subgroup data from the randomized phase III SIMPLIFY-1 trial.90,91,159 Momelotinib was also evaluated in randomized phase III studies in patients with intermediate-1 (symptomatic), intermediate-2, or high-risk MF who were not previously treated with a JAK inhibitor, as well as in those who were previously treated with ruxolitinib.159,160 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 or danazol.90 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% (25% vs. 9%; P = .0095). Following week 24, all patients who remained in the study were treated with momelotinib.91 At 48 weeks, among those who were evaluable for total symptom score, 45% of patients treated with momelotinib from the start of the study had a response, compared to 50% of patients treated with danazol who crossed over.

The phase III SIMPLIFY-1 study randomized 432 patients with intermediate-1 (symptomatic), intermediate-2, or high-risk MF with no prior treatment with a JAK inhibitor to receive momelotinib 200 mg once daily or ruxolitinib 20 mg twice daily (or according to the label) for 24 weeks.159 Following this time period, all patients could cross over to the momelotinib arm. At 24 weeks, the data showed that momelotinib was noninferior to ruxolitinib. 26.5% of patients in the momelotinib arm achieved the primary endpoint of a spleen response, defined as a ≥35% decrease in the spleen volume, compared to 29% of patients in the ruxolitinib arm (P = .011). While momelotinib treatment led to an improvement in transfusion burden (transfusion rate, nominal P < .001; transfusion independence, nominal P < .001; transfusion dependence, P = .019), it did not improve the total symptom score response rate (P = .98). At 2 years, the OS and LFS were 81.6% (HR, 1.02; 95% CI, 0.73–1.43) and 80.7% (HR, 1.08; 95% CI, 0.78–1.50), respectively, in patients treated with momelotinib compared to 80.6% and 79.3%, respectively, in patients initially treated with ruxolitinib who crossed over to the momelotinib group.161

The phase III SIMPLIFY 2 trial randomized patients with intermediate-1 (symptomatic), intermediate-2, or high-risk MF who received prior ruxolitinib treatment 2:1 to receive momelotinib or best available therapy for 24 weeks.160 In an intention-to-treat analysis, 7% of patients in the momelotinib group met the primary endpoint of a ≥35% reduction in spleen volume, compared to 6% of patients in the best available therapy group (P = .90). At 2 years, the OS and LFS were 65.8% (HR, 0.98; 95% CI, 0.59–1.62) and 64.2% (HR, 0.97; 95% CI, 0.59–1.60), respectively, in patients treated with momelotinib compared to 61.2% and 59.7%, respectively, in patients initially treated with best available therapy who crossed over to the momelotinib group.161 Data from both SIMPLIFY trials showed that treatment with momelotinib led to a clinically meaningful symptomatic benefit in patients with MF.162

Toxicity

In the MOMENTUM study, at 24 weeks, anemia and thrombocytopenia were the most common grade 3 or higher treatment-emergent hematologic adverse events and were observed in 61% and 28%, respectively, of patients receiving momelotinib, and in 75% and 26%, respectively, in patients receiving danazol.90 At 48 weeks, anemia and thrombocytopenia were reported in 11% and 19% of patients treated with momelotinib,

including those who crossed over.91 Acute kidney injury (momelotinib, 3%; danazol, 9%) and pneumonia (momelotinib, 2%; danazol, 9%) were the most common grade 3 or higher nonhematologic treatment-emergent adverse event at 24 weeks.90 Asthenia (momelotinib, 3%; danazol, 2%), dyspnea (momelotinib, 3%; danazol, 0%), and fatigue (momelotinib, 3%; danazol, 7%) were the most common grade 3 or higher nonhematologic adverse events at 48 weeks.91 In the SIMPLIFY-1 trial, anemia and thrombocytopenia were the most frequent hematologic abnormalities in both groups.159 Seven percent of patients in the momelotinib group and 3% of patients in the ruxolitinib group had grade 3 or higher infections. Similarly, anemia (momelotinib group: 14%; best available therapy group: 14%) and thrombocytopenia (momelotinib group: 7%; best available therapy group: 6%) were the most frequent grade 3 or higher treatment-emergent adverse events in the SIMPLIFY-2 trial, with the most common nonhematologic treatment-emergent adverse events being asthenia (5%) in the momelotinib group and abdominal pain (6%) in the best available therapy group.160

Allogeneic Hematopoietic Cell Transplant

Allogeneic HCT is the only potentially curative treatment option resulting in long-term remissions for patients with MF. Donor selection and conditioning should be evaluated on a case-by-case basis (See NCCN Guidelines for Hematopoietic Cell Transplant, available at www.NCCN.org). Myeloablative conditioning and reduced-intensity conditioning (RIC) are relatively similar in terms of OS.163 The use of RIC is associated with a lower rate of non-relapse mortality (NRM), but it is also associated with a higher risk of relapse compared to myeloablative conditioning.164-171 Comparison studies of RIC also do not show a difference in OS,171,172 although one study reported a trend towards lower NRM (HR, 0.52; 95% CI, 0.26–1.05; P = .068) and a higher relapse rate (HR, 9.21; 95% CI, 1.81–46.9; P = .008) with regimens that use the combination of busulfan and fludarabine.171 Another study also determined a higher relapse rate but the difference was not statistically significant (P = .21).172 No statistically significant difference was obtained for NRM (P = .32). Patients with MPN are at particularly high risk for hepatobiliary toxicities related to transplant, including sinusoidal obstructive syndrome (SOS). Approaches to reduce SOS and NRM using specialized myeloablative conditioning have been used and may be helpful.173,174 The estimated OS and NRM rates for myeloablative conditioning at 3 to 5 years range from 30% to 61% and 35% to 50%, respectively.175 In a retrospective registry analysis of 289 patients with MF, allogeneic HCT resulted in long-term OS in approximately one third of patients, but the probability of long-term survival and NRM was dependent on the source of stem cells.176 The 5-year post-transplant OS rates were 37%, 40%, and 30%, respectively, for HLA-matched sibling donor transplant, other related donor transplant, and unrelated donor (URD) transplant, respectively. The corresponding 5-year disease-free survival rates were 33%, 22%, and 27%, respectively. The NRM rate at 5 years was higher for URD transplant (50% compared to 35% and 38% for HLA-matched sibling donor transplant and other related donor transplant, respectively). In a prospective, multicenter study that evaluated allogeneic HCT with RIC in 103 patients with MF, the cumulative incidence of NRM at 1 year was 16% and the cumulative incidence of relapse at 3 years was 22%.165 The estimated 5-year event-free survival (EFS) and OS rates were 51% and 67%, respectively. The NRM was significantly lower for patients with a completely matched donor (12% vs. 38%; P = .003). Other large retrospective registry analyses have also reported similar outcomes.168,169 In the Center for International Blood and Marrow Transplant Research (CIBMTR) analysis that included 233 patients who underwent allogeneic HCT using RIC for PMF, the probabilities of OS and PFS at 5 years were 47% and 27%, respectively.168 The cumulative incidence of NRM and relapse/progression at 5 years were 24% and 48%, respectively. In the European Bone Marrow Transplantation Registry (EBMTR) analysis that included 193 patients who underwent transplantation for post-PV or post-ET MF, the 3-year OS rate, incidence of relapse, and NRM were 55%, 32%, and 28%, respectively.169 Another study that included 2459 patients with MF who underwent allogeneic HCT reported an OS rate of 41% (95% CI, 39%–44%) and a disease-free survival rate of 32% (95% CI, 30%–35%) at 10 years.177 In 1055 patients who were disease-free at 2 years, the 10-year OS and disease-free survival rates were 74% (71%–78%) and 64% (60%–68%), respectively. Age (>55 years) and donor type (HLA-identical sibling donor transplant vs. HLA-well-matched URD transplant or partially/mismatched URD transplant) have been the most important prognostic factors of OS and NRM. Among patients who underwent allogeneic HCT with RIC for PMF, the 5-year survival rates following HLA-identical sibling donor transplant, HLA-well-matched URD transplant, and partially/mismatched URD transplant were 56%, 48%, and 34%, respectively (P = .002) and the relative risk of NRM was also the lowest for HLA-identical sibling donor transplant (1%) compared to 3% and 9% for HLA-well-matched URD transplant and partial/mismatched URD transplant, respectively.168 In patients who underwent allogeneic HCT with RIC for post-PV MF or post-ET MF, the overall 3-year cumulative incidence of NRM was significantly higher in patients >55 years (35% vs. 20% for younger patients; P = .032) and in those who underwent URD transplant (34% vs. 18% for those who had a related donor transplant; P = .034).169 The results of a retrospective study by the European Society for Blood and Marrow Transplantation with patients with MF who underwent allogeneic HCT from an HLA-identical sibling or an URD identified age ≥60 years, Karnofsky performance status of <90% at the time of transplant, graft failure, acute graft-versus-host disease (GVHD) (grades III–IV), and disease progression or relapse as factors that were independently

associated with a higher mortality rate.178 These factors, along with HCT-specific Comorbidity Index ≥3 and extensive chronic GVHD, were associated with higher NRM. The DIPSS risk score was not a prognostic factor.

Another retrospective multicenter study of 69 patients with chronic phase MF who were treated with allogeneic blood or marrow transplantation from a haploidentical donor and received cyclophosphamide post-transplantation reported an OS of 72% (95% CI, 59%–81%), a relapse-free survival (RFS) of 44% (95% CI, 29%–59%), and a GVHD-free RFS of 30% (95% CI, 17%–43%) at 3 years.179 A cumulative incidence of 10% was obtained for grade 3–4 acute GVHD and 8% for extensive chronic GVHD.

A few studies have shown that larger spleen size may be associated with inferior outcomes after transplant, possibly reflecting an aggressive disease biology.179-181 A spleen size ≥22 cm or a prior splenectomy (HR, 6.37; 95% CI, 2.02–20.1; P = .002) and bone marrow grafts (HR, 4.92; 95% CI, 1.68–14.4; P = .004) were associated with a higher incidence of relapse.179 A univariate analysis determined that a spleen size ≥17 cm or a prior splenectomy was associated with worse RFS (HR, 3.50; 95% CI, 1.18–10.37; P = .02) and a higher relapse rate (subdistribution HR not calculable; P = .01).180 The results of a multivariate analysis by Polverelli et al181 demonstrated that splenectomy was associated with reduced NRM (HR, 0.64; 95% CI, 0.44–0.93; P = .018) and a higher risk of relapse (HR, 1.43; 95% CI, 1.01–2.02; P = .042), but no effect on OS (HR, 0.86; 95% CI, 0.67–1.12; P = .274).

In another study, DIPSS risk score has been shown to predict outcome after transplant.168,182 In the aforementioned CIBMTR analysis, there was a trend towards lower mortality rates in patients with low- or intermediate-1-risk disease, and higher NRM in patients with intermediate-2 or high-risk disease.168 In another retrospective analysis of 170 patients with MF who received HCT, DIPSS risk score significantly correlated with mortality risk and NRM (HR for post-transplant mortality was 4.11 for high-risk disease compared to 3.15, 1.97, and 1, respectively, for intermediate-2, intermediate-1, and low-risk disease; the corresponding HRs for NRM were 3.41, 3.19, 1.41, and 1, respectively).182 The association of DIPSS risk score with relapse was not significant, although patients with higher-risk disease experienced more relapses than those with lower-risk disease. DIPSS risk scores prior to HCT have also been shown to correlate with OS following allogeneic HCT.168,183,184 However, in one retrospective analysis, the differences in OS between patients with intermediate-1 and intermediate-2-risk disease were not significantly different. In a multivariate analysis, only JAK2 wild-type, age ≥57 years, and the presence of constitutional symptoms were independent predictors of OS. The 5-year OS rates were 90%, 74%, and 50% for the presence of 0, 1, and 2 risk factors.183 In another retrospective analysis that evaluated the impact of allogeneic HCT on survival in patients <65 years of age at the time of diagnosis of PMF (n = 438; 190 patients received allogeneic HCT and 248 patients received conventional therapy), the relative risk of death after allogeneic HCT was 5.6 for patients with DIPSS low-risk disease, 1.6 for patients with intermediate-1-risk disease, 0.55 for patients with intermediate-2-risk disease, and 0.37 for patients with high-risk disease.184

These findings suggest that outcomes following allogeneic HCT are better for patients with low- or intermediate-1-risk MF.168,182 However, since HCT is associated with a significant rate of transplant-related complications and morbidity that may not otherwise occur with nontransplant therapies in this group of patients, the overall benefit may be with non-transplant therapies.185 Allogeneic HCT is associated with a clear benefit in patients with intermediate-2 or high-risk MF. A retrospective study of 544 patients with MF investigated the different prognostic models (IPSS, DIPSS, and DIPSS-Plus) and determined that the IPSS and DIPSS-plus models were most able to differentiate between the intermediate-1 and intermediate-2-risk categories.186

The Myelofibrosis Transplant Scoring System (MTSS) is a model that takes into account clinical (age ≥57 years, Karnofsky performance status <90%, platelet count <150 x 109/L, and leukocyte count >25 x 109/L), molecular (presence of ASXL1 mutation and absence of CALR and MPL mutations), and transplant-specific factors (HLA-mismatched URD), and is designed to assess prognosis after allogeneic transplant in patients with primary and post-ET/PV MF.187 It stratifies patients into four risk categories: low, intermediate, high, and very high. Validated in a cohort of 156 patients, the survival rates for these categories were 83% (95% CI, 71%–95%), 64% (95% CI, 53%–75%), 37% (95% CI, 17%–57%), and 22% (95% CI, 4%–39%), respectively (P < .001). Another study evaluating the performance of the MTSS model concluded that it may need to be refined as it did not distinctly stratify patients into four risk categories.188 However, the authors note that it still has clinical value. When the risk levels were combined to give two new categories, standard (low and intermediate) and high (high and very high), the MTSS was better able to distinguish risk (P < .001). The OS at 3 years for the standard- and highrisk levels were 62% (95% CI, 49%–72%) and 25% (95% CI, 9%–45%), respectively. Further validation studies are needed to confirm these findings.

Impact of Mutational Status

CALR mutation is associated with higher OS rates and lower rate of NRM following allogeneic HCT in patients with PMF as well as post-PV or post-ET MF.189,190 Identification of HMR mutations (ASXL1, EZH2, SRSF2, TP53, IDH1, or IDH2 mutations) may be helpful in decision-making regarding allogeneic HCT in patients with MF.29,37-39,190 CBL, DNMT3A, and U2AF1 were associated with worse OS in patients with MF undergoing

allogeneic HCT.191,192 The results from another study also suggest inferior OS with ASXL1 mutations (subdistribution HR, 2.36; 95% CI, 0.85–6.6; P = .09).180

In a study of 133 patients who underwent allogeneic HCT for PMF (n = 97) or post-ET/post-PV MF (n = 36), the 4-year OS rate was 82% for patients with CALR mutations compared to 56% for patients without CALR mutations (CALR wild-type). The NRM rate was also significantly lower in patients with CALR mutations compared with those who were CALR wild-type (4-year NRM rates were 7% and 31%, respectively; P = .024).189 In another study that evaluated the impact of molecular genetics on the outcome after allogeneic HCT in patients with MF (PMF, n = 110; post-PV or ET MF, n = 46; and MF in transformation, n = 13), the results of a multivariate analysis showed that CALR mutation was an independent factor for lower NRM and improved PFS and OS.190 ASXL1 and IDH2 mutations were independent risk factors for lower PFS, whereas no impact was observed for patients with triple-negative disease. As discussed earlier, CALR(-)/ASXL1(+) is associated with a poor prognosis (independent of the DIPSS-Plus risk score) in patients with PMF and this subset of patients should be considered for allogeneic HCT earlier in the disease course.43

A small study with 18 patients with primary or post-ET MF found that MPL mutations were associated with a favorable outcome following allogeneic HCT with an OS rate and an RFS rate of 83.5% (95% CI, 65.9%–100%) at 5 years and a relapse rate of 5.5%.193 The addition of mutational status to DIPSS-Plus can help improve the prediction of transplantation outcome.194 Patients with ≥3 mutations along with CALR or JAK2 mutations had higher NRM and risk of relapse following transplant compared to those with fewer mutations.

Treatment Recommendations Based on Symptom Assessment and Risk Stratification

The selection of appropriate treatment should be based on the risk score, the presence of symptoms, and the disease stage. A clinical trial or consideration of a clinical trial is recommended for all patients with MF who require treatment with the aim of reducing bone marrow fibrosis, improving cytopenias and symptom burden, restoring transfusion independence, and/or preventing/delaying progression to AML.

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). Enrollment in a clinical trial is also an option. Ruxolitinib,114-116 peginterferon alfa-2a,110 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). In a small study of 40 patients with symptomatic MF (constitutional symptoms, splenomegaly, thrombocytosis, leukocytosis, pruritus, and bone pain), treatment with hydroxyurea (500 mg/day, subsequently adjusted to the individual efficacy and tolerability) resulted in clinical improvement in 40% of patients.195 Anemia induced by hydroxyurea was manageable with concomitant treatment. The Panel has included hydroxyurea as an option for symptomatic lower-risk MF, if the use of cytoreductive therapy would be symptomatically beneficial in selected patients with high platelet counts. Ruxolitinib, peginterferon alfa-2a, hydroxyurea, pacritinib (if platelets <50 x 109/L), and momelotinib (category 2B) are listed as useful in certain circumstances options for the first-line treatment of patients with symptomatic lower-risk MF. In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate. For patients with anemia, see *Management of MF-Associated Anemia in the algorithm*.

Although the outcomes following allogeneic HCT are better for patients with lower-risk MF, due to the high transplantation-related morbidity and mortality, treatment decisions regarding allogeneic HCT should be individualized.168,182,184 Allogeneic HCT should be considered for lower-risk MF in patients with refractory, transfusion-dependent anemia, circulating blast cells >2% in peripheral blood, adverse cytogenetics, or molecular abnormalities.196 Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics. The MTSS can be helpful in predicting post-transplant survival when counseling patients about transplant.187

Higher-Risk MF

Referral to an HCT expert for allogeneic HCT evaluation is recommended for all patients with higher-risk MF that is DIPSS-Plus Int-1 or MIPSSintermediate or higher. Transplant is recommended for patients with higher-risk MF that is DIPSS-Plus or MYSEC Int-2 or high-risk disease or MIPSS70 or MIPSS 70+ high-risk.182 Transplant can also be considered in selective cases: RBC transfusion dependence, high-risk mutations (ie, ASXL1, RAS, TP53), or loss of response to JAK inhibitor therapy. The selection of patients for allogeneic HCT should be based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver. The MTSS can be helpful in predicting post-transplant survival when counseling patients about transplant and can be used to optimize patient selection, with low- and intermediate-risk being optimal.187 For patients with >10% blasts in the peripheral blood, azacitidine with or without a JAK inhibitor may be considered prior to allogeneic HCT to reduce the blast percentage.197 The results of several studies suggest that prior exposure to ruxolitinib may improve outcomes after allogeneic HCT.174,198-200 The guidelines recommend that JAK inhibitors should be considered for use in patients for at least 2 months prior to transplant in patients with splenomegaly and/or constitutional symptoms even if

the patient would otherwise be transplant eligible.174,198,199 JAK inhibitors can be tapered prior to or during conditioning to be completed before cell infusion. In patients with massive splenomegaly that does not respond to JAK inhibitors, alternative measures to reduce spleen size may be considered prior to transplant (eg, splenic radiation, splenic artery embolization, or splenectomy).201,202

In a prospective phase II trial, 28 patients with MF were treated with ruxolitinib for at least 8 weeks prior to HCT and followed a taper schedule that ended 4 days before donor cell infusion.174 Twenty-three patients underwent myeloablative conditioning while the remaining five underwent RIC. After termination of treatment with ruxolitinib, cytokine release syndrome was not observed, and engraftment was successful in all patients. Following transplant, the 2-year OS was 86% (95% CI, 61%–96%). Shanavas and colleagues199 examined data from 100 patients with MF who were treated with JAK inhibitors prior to HCT. Sixty-six patients continued ruxolitinib therapy until transplant. Most of the observed symptoms were consistent with symptoms associated with MF and were mild or moderate. Two patients had a severe adverse occurrence and, as a result, HCT was delayed. Patients who displayed clinical improvement with the use of a JAK inhibitor also had more favorable outcomes posttransplant. At 2 years, the OS was 61% (95% CI, 49%–71%).

Similarly, a study by Chhabra et al198 reported that treatment with ruxolitinib and management of splenomegaly with splenic irradiation prior to transplant, along with fludarabine/busulfan-based conditioning, led to more favorable outcomes. At 3 years, the OS was 81.1% (95% CI, 64.4%– 90.5%) and the RFS was 78.4% (95% CI, 61.4%–88.5%). Another study assessing the use of ruxolitinib prior to RIC and transplant in patients with MF found that treatment with ruxolitinib significantly reduced symptom burden.200 Patients did not experience significant side effects while tapering off ruxolitinib and HCT was not delayed. A retrospective study with 551 patients with MF who underwent HCT determined that the NRM at 1 year (HR, 0.80; P = .32), and the EFS (HR, 0.81; P = .19) and OS (HR, 0.81; P = .21) rates at 2 years did not differ between patients who received ruxolitinib prior to transplant versus those who did not.203 However, patients with ruxolitinib pretreatment who had an ongoing spleen response at the time of transplant had a decreased risk of relapse (HR, 0.34; P = .04) and an improved 2-year EFS (HR, 0.61; P = .02).

Pacritinib has demonstrated significant activity resulting in ≥35% spleen volume reductions and symptom improvement, even in patients with severe baseline cytopenias,92,93 and is a category 1, preferred option for patients with higher-risk MF with platelet count <50 x 109/L who are not transplant candidates or for whom transplant is not currently feasible.

Momelotinib is a category 2B, other recommended regimen for these patients.159 Enrollment in an appropriate clinical trial is also an option. The use of ruxolitinib at a lower dose (5 mg twice daily) has shown some efficacy, resulting in some reductions in spleen volume and improvement in total symptom score even in patients with low platelet counts at baseline (50–100 x 109/L).130 Enrollment in a clinical trial, ruxolitinib86,113,120-122 (category 1), fedratinib94 (category 1), momelotinib,159 or pacritinib92,93 (category 2B) are options for patients with higher-risk MF with symptomatic splenomegaly and/or constitutional symptoms and with platelet count ≥50 x 109/L who are not candidates for transplant or for whom transplant is not currently feasible. A study by Hernandez-Boluda204 reported that patients with severe thrombocytopenia (platelet count <50 x 109/L) were in a higher risk category and had more instances of anemia and leukopenia. Patients with platelet count <50 x 109/L experience a greater symptom burden and might benefit from symptomatically guided treatment options.205 For patients with anemia, see Management of MF-Associated Anemia in the algorithm.

Management of MF-Associated Anemia

Anemia is considered a negative prognostic risk factor for survival in patients with MF.95 Symptomatic anemia is observed in >50% of patients at the time of diagnosis.206 It is essential to assess for, and treat the most common alternative causes of anemia (ie, bleeding, nutritional deficiencies, hemolysis) before considering other treatment options. EPO-stimulating agents (ESAs), momelotinib, danazol, luspatercept-aamt, and immunomodulatory agents (lenalidomide, thalidomide, and pomalidomide) have also been evaluated for the management of MF-associated anemia. Because MF can be characterized by increased transforming growth factor beta (TGF-β) signaling and anemia related to increased TGF-β can be alleviated by inhibition of TGF-β signaling,207 luspatercept has garnered significant attention in the MF field and is the subject of a randomized phase lll clinical trial for patients with RBC transfusion-dependent MF on JAK2 inhibitor therapy (NCT04717414). The phase II open-label ACE-536-MF-001 clinical trial assessed the safety and efficacy of luspatercept for MF-related anemia.208 Patients were divided into four groups: no transfusion dependence and no ruxolitinib treatment; transfusion dependence and no ruxolitinib treatment; no transfusion dependence and ruxolitinib treatment; and transfusion dependence and ruxolitinib treatment. Anemia response rate, defined as a ≥1.5 g/dL rise in hemoglobin from baseline in the non-transfusion dependent group and transfusion independence in the transfusion-dependent group, over 12 consecutive weeks in the primary treatment period was the primary endpoint. In the group with no transfusion dependence, 13.6% of patients who did not receive ruxolitinib achieved an anemia response (defined as a ≥1.5 g/dL hemoglobin increase from baseline), while 14.3% of patients who received ruxolitinib achieved an

anemia response. In the group with transfusion dependence, 9.5% of patients with no ruxolitinib treatment achieved an anemia response, while 26.3% of patients who received ruxolitinib achieved an anemia response. All groups had a decrease in the total symptom score; patients with no transfusion dependence who received ruxolitinib had the highest decrease. Overall, hypertension was the most common treatment-related adverse event. Luspatercept-aamt is FDA-approved for the treatment of anemia without previous ESA use in adults with very low- to intermediate-risk MDS who may require regular RBC transfusions; and for the treatment of anemia refractory or intolerant to prior ESA treatment that requires ≥2 RBC transfusions over 8 weeks in adults with very-low- to intermediate-risk myelodysplastic syndromes (MDS) with ring sideroblasts or with myelodysplastic/MPN with ring sideroblasts and thrombocytosis. The use of recombinant human EPO or darbepoetin alfa has resulted in anemia responses (transfusion independence with normal haemoglobin levels, sustained increase in hemoglobin levels [>2 g/dL] within 12 weeks, or >50% reduction in transfusion requirements within 12 weeks) in 45% to 60% of patients with MF.209-211 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 to 44% in patients without transfusion requirements).212 Prostate cancer screening and monitoring of liver function tests, as well as the use of concomitant medications such as statins, are recommended over concerns for increased risk of rhabdomyolysis in patients receiving danazol for the management of MF-associated anemia.

In a post hoc analysis of the phase III SIMPLIFY-1 trial, treatment with momelotinib led to a greater transfusion independence rate at 24 weeks in both the subgroup with moderate/severe anemia (<10 g/dL) (momelotinib, 46.5%; ruxolitinib, 26.6%) and the subgroup with mild anemia (≥10 to <12 g/dL) (momelotinib, 80.8%; ruxolitinib, 50.7%).213 Among patients with moderate/severe anemia who did not require transfusions at baseline, 72.0% of those treated with momelotinib maintained transfusion independence at 24 weeks, compared to 34.1% of those treated with ruxolitinib. In the subgroup with mild anemia, 86.4% of those treated with momelotinib maintained transfusion independence, compared to 57.9% of those treated with ruxolitinib.

Data from the phase III MOMENTUM trial showed that at 24 weeks, treatment with momelotinib resulted in a significantly higher transfusion independence rate (31% vs. 20%; one-sided P = .0064), and a spleen volume reduction of ≥35% (23% vs. 3%; P = .0006) compared to treatment with danazol.90 At 48 weeks, the transfusion independence rate and spleen volume reduction of ≥35% were 57% and 43%, respectively, in the momelotinib group and 60% and 13%, respectively, in the danazol group who crossed over.91

Thalidomide (in escalating daily doses of 100–800 mg) has demonstrated very minimal efficacy, resulting in anemia response rates of 0% to 29%, and is also poorly tolerated.214-220 A lower dose of thalidomide (50 mg/day), when used in combination with prednisone, is better tolerated, leading to improved anemia response rates (62%) compared to high-dose thalidomide monotherapy in the management of MF-associated symptomatic anemia (hemoglobin level <10 g/dL or symptomatic splenomegaly).221 Lenalidomide, alone or in combination with prednisone, has also demonstrated modest efficacy in the management of MF-associated anemia, resulting in response rates of 19% to 32% with myelosuppression being the most common grade 3 or higher hematologic toxicity.222-225 Lenalidomide is more likely to induce better response rates in patients with isolated 5q deletion.226 In an analysis that reassessed the efficacy of thalidomide and lenalidomide in 125 patients with MF treated in three consecutive phase 2 trials, the combination of lenalidomide and prednisone was more effective and safer than single-agent thalidomide or lenalidomide.227 After a median follow-up of 42 months, the ORR was 38% for the combination of lenalidomide and prednisone compared to 34% and 16%, respectively, for lenalidomide and thalidomide. There was also a trend for a higher efficacy in patients receiving lenalidomide-based therapy (P = .06), and in a multivariate analysis the lenalidomide-based regimen was the only factor independently associated with a higher response rate.

Pomalidomide has also been evaluated as a treatment option for MF-associated anemia.228,229 In one phase II study, pomalidomide (with or without prednisone) resulted in similar response rates (39%) in patients with MF and anemia and/or thrombocytopenia and/or neutropenia, with a median response duration of 13 months.228 However, in another randomized study that evaluated pomalidomide in patients with MF and RBC transfusion dependence, the RBC transfusion independence response rates were similar for patients treated with pomalidomide and placebo.229

Studies are ongoing to evaluate the combination treatment of ruxolitinib with thalidomide or pomalidomide in patients with MF (NCT03069326 and NCT01644110).230,231 A response rate of 55% was obtained in a phase II study investigating the combination of ruxolitinib and lenalidomide in patients with PMF or post-PV/ET MF with anemia.232 However, a dose interruption was needed in 75% of patients due to toxicity and the study was terminated early due to lack of efficacy.

In the COMFORT-II study, anemia was managed with packed RBC transfusions.233 In a small number of patients (13 out of 146 patients) who received both ruxolitinib and an ESA, the use of an ESA with ruxolitinib was well tolerated and did not impact the effectiveness of ruxolitinib. Another study that assessed the use of ESAs along with ruxolitinib (n = 9) or the addition of ESAs after treatment with ruxolitinib for a median of 4 months (n = 50) in patients with MF also showed that the concomitant use of an ESA with ruxolitinib was effective for the management of anemia in patients with MF.234 Fifty-four percent of patients achieved an anemia response (per IWG-MRT criteria) and, at 5 years, a response was observed in 76% of patients. Spleen reduction was reported in 78% of patients. These findings support the feasibility of administration of ESAs for the management of anemia in patients receiving ruxolitinib. However, ESAs are less effective for the management of transfusion-dependent anemia.235

For patients with MF-associated anemia and ongoing symptomatic splenomegaly and/or constitutional symptoms, enrollment in a clinical trial and momelotinib are preferred regimens. Pacritinib, as well as ruxolitinib combination, are listed as other recommended regimens. Luspaterceptaamt, ESAs (epoetin alfa or darbepoetin alfa) (if serum EPO <500 mU/mL) (category 2B), or danazol (category 2B) can be added to ruxolitinib.

For patients with MF-associated anemia and no symptomatic splenomegaly or constitutional symptoms, a clinical trial is preferred. ESAs (if serum EPO <500 mU/mL), luspatercept-aamt, danazol, pacritinib (category 2B), and momelotinib (category 2B) are other recommended regimens. Lenalidomide with prednisone for del(5q) is a category 2B, useful in certain circumstances option. This regimen should start as a combination followed by tapering of prednisone over 3 months. For patients with MF-associated anemia and splenomegaly and constitutional symptoms that are well controlled on a current JAK inhibitor, enrollment in a clinical trial is preferred. JAK inhibitor combinations are other recommended regimens. ESAs (if serum EPO <500 mU/mL), luspatercept-aamt, or danazol (category 2B) can be added to JAK inhibitors. Changing to pacritinib or momelotinib may be useful in certain circumstances. An FDA-approved biosimilar is an appropriate substitute for any recommended systemic biologic therapy in the NCCN Guidelines. JAK inhibitors (ruxolitinib, fedratinib, momelotinib, or pacritinib) may be continued for the improvement of splenomegaly and other disease-related symptoms.

Treatment Response Criteria

In 2006, the IWG-MRT first published the response criteria for MF, and the responses were categorized as CR, PR, clinical improvement, PD, SD, and relapse.236 In 2013, these response criteria were revised by IWG-MRT and ELN to include MPN-SAF TSS as a quantifiable tool to assess changes in disease-related symptoms and stricter definitions of RBC transfusion dependency and independency.237 These response criteria were developed mainly for use in clinical trials. In addition to CR, PR, and clinical improvement, three other response categories (anemia response, spleen response, and symptoms response) were included in the revised 2013 IWG-MRT and ELN response criteria to quantify treatment-induced improvements in symptom burden, particularly anemia, splenomegaly, and constitutional symptoms.237 The revised response criteria recommend that symptoms should be evaluated by the MPN-SAF TSS and that symptom response requires ≥50% reduction in the TSS.82 The revised 2013 IWG-MRT and ELN response criteria also require that a ≥35% reduction in spleen volume should be confirmed by MRI or CT scan; volumetric imaging of the spleen is typically included in clinical trials to adjudicate this endpoint.237 In addition, a ≥35% reduction in spleen volume by MRI or CT scan constitutes a spleen response regardless of that reported by physical examination. Additional criteria are also included for PD, SD, and relapse.

Morphologic response in bone marrow is required for CR. The criteria for PR require morphologic response in the peripheral blood (but not necessarily in the bone marrow). Patients meeting criteria for CR with inadequate blood count recovery are also included in the PR category to capture those patients who have achieved CR with persistent drug-induced cytopenia despite a morphologically normal bone marrow. The revised response criteria also include response categories for cytogenetic and molecular response. However, these are not required for CR assignment.

Monitoring Response and Follow-up Therapy for Lower-Risk and Higher-Risk MF

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.237

The guidelines recommend monitoring for intolerance, response (anemia response, spleen response, and symptom response), signs, and symptoms of disease progression as clinically indicated during the course of treatment. Bone marrow aspirate and biopsy with NGS and karyotyping should be performed as clinically indicated (if supported by increased symptoms and signs of progression). Additional molecular testing using a multi-gene NGS panel to evaluate for HMR mutations associated with disease progression should be considered for patients with MF.37,38

Continuation of JAK inhibitors is recommended for patients achieving response to initial treatment. In the COMFORT-I study, the majority of patients (91%) treated with ruxolitinib experienced significant improvements in individual MF-related symptoms (≥50% improvement in total symptom score as assessed by MF-SAF) and quality of life; most importantly, patients with a lesser degree of symptom improvement (<50% improvement in total symptom score) also achieved improvements over placebo on these measures and other patient-reported outcomes.83 The Panel acknowledges that clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria (ie, symptom response requires ≥50% reduction in the MPN-SAF TSS) in patients receiving treatment with JAK inhibitors. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician. The RR6 model may also be used to gauge response to ruxolitinib.147 Continuation of JAK inhibitors is also recommended based on the discretion of the clinician, since a symptom response of <50%, as well as spleen volume reduction that does not meet the threshold of >35% (reduction in palpable splenomegaly of <50%), may be clinically meaningful.

Disease-related symptoms may return to pretreatment levels over a period of approximately 1 week following discontinuation or interruption of ruxolitinib.238 Low platelet counts (at initiation or completion of therapy) and clonal evolution (acquisition of new mutations while on treatment with ruxolitinib) were associated with a significantly shorter survival after discontinuation of ruxolitinib.239 In a study that evaluated the outcomes of ruxolitinib discontinuation in patients with MF, after a median follow-up of 32 months, the median survival was 14 months among 42 patients who had molecular data at baseline; during follow-up, clonal evolution was seen in 14 patients (33%; ASXL1 mutation in 60% of patients).239 RBC transfusion dependence at baseline was the only clinical variable associated with clonal evolution; survival after discontinuation of ruxolitinib was 6 months for patients with clonal evolution compared to 16 months for those without clonal evolution. A population-based analysis of 290 patients with MF found that 50% of patients developed cytopenias after terminating treatment with ruxolitinib.240 The median OS after discontinuation was 11.1 months (95% CI, 8.4–14.5 months) and the median PFS was 6.0 months (95% CI, 4.4–8.3 months).

For patients with symptomatic lower-risk MF with intolerance, 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, hydroxyurea [if cytoreduction would be symptomatically beneficial], pacritinib [if platelets <50 x 109/L], or momelotinib [category 2B]). In the event that peginterferon alfa-2a is unavailable, the use of other available pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate. If anemia is present, see Management of MF-Associated Anemia in the algorithm.

For patients with higher-risk MF with platelet count ≥50 x 109/L who are not candidates for transplant and who have intolerance, no response or loss of response following initial treatment, enrollment in a clinical trial or an alternate JAK inhibitor (ruxolitinib, fedratinib, momelotinib, or pacritinib [category 2B]) not used before is recommended.89,93,150,160 If anemia is present, see Management of MF-Associated Anemia in the algorithm.

JAK2 V617F Allele Burden

Reductions in JAK2 V617F allele burden have been observed in patients with MF with long-term fedratinib241 or ruxolitinib therapy.123,242 In the COMFORT-I study, a >50% reduction in JAK2 V617F allele burden were observed in 12% of patients (28 patients); 20 of these patients met the criteria for partial molecular response (PMR) and six patients had JAK2 V617F allele burden values below the quantifiable limit, meeting the criteria for complete molecular response (CMR).242 The median times to PMR and CMR were 22 months and 28 months, respectively. JAK2 V617F allele burden reductions also correlated with spleen volume reductions. Achievement of JAK2 V617F negativity or JAK2 V617F allele burden reduction after allogeneic HCT has also been associated with a decreased incidence of relapse.243,244

However, at the present time, the utility of JAK2 V617F allele burden reduction as a predictor of treatment efficacy remains unclear. In the 2013 IWG-MRT and ELN response criteria, cytogenetic and molecular responses are not required for CR assignment.237 Therefore, measurement of the JAK2 V617F allele burden is not currently recommended for use in routine clinical practice to guide treatment decisions.

Supportive Care

Supportive care for disease-related symptoms should be an integral part of clinical management during the course of treatment. This should include assessment and monitoring of symptom status and counseling for identification, assessment, and management of cardiovascular risk factors (eg, smoking, diet, exercise, hypertension, diabetes mellitus, lipid management) and thrombotic and hemorrhagic risk factors.

Transfusion support should include platelet transfusions for thrombocytopenic bleeding or platelet count <10 x 109/L and RBC transfusions for symptomatic anemia.245 The use of leukocyte-reduced blood products is recommended in transplant candidates to prevent HLA alloimmunization and reduce the risk of cytomegalovirus transmission. Antifibrinolytic agents should be considered for bleeding that is refractory to

transfusions. Iron chelation could be considered for patients who have received >20 transfusions and/or ferritin >2500 ng/mL in patients with lower-risk disease. However, the role of iron chelation remains unclear.

Specific warnings and precautions regarding serious bacterial, mycobacterial, fungal, and viral infections, including herpes zoster and John Cunningham virus (JCV), which is the causative agent of progressive multifocal leukoencephalopathy, have been reported in patients receiving ruxolitinib and are described in the prescribing information. Patients should be monitored for signs and symptoms of infections. Serious infections should be resolved prior to initiation of ruxolitinib. Vaccinations are recommended as outlined in the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections (available at www.NCCN.org). A recombinant (killed) zoster vaccine may be considered for patients on, or prior to, treatment with a JAK inhibitor. In patients who have had a splenectomy, vaccinations and antibiotic prophylaxis should be given per the Infectious Diseases Society of America (IDSA) Guidelines. Growth factor support (granulocyte colony-stimulating factor [G-CSF] or granulocyte-macrophage colony-stimulating factor [GM-CSF]) should be considered for recurrent infections with neutropenia. However, these should be used with caution in patients with an enlarged spleen since the use of G-CSF or GM-CSF has been associated with splenic rupture.246 Cytoreductive therapy (eg, hydroxyurea) could be considered for the management of hyperproliferative manifestations of PMF (thrombocytosis or leukocytosis).195 Prophylaxis for tumor lysis syndrome should be considered for patients undergoing induction chemotherapy for advanced-stage MF or disease progression to AML.

Management of Polycythemia Vera and Essential Thrombocythemia

Referral to specialized centers with expertise in the management of MPN is strongly recommended for all patients diagnosed with PV or ET.

Risk Stratification

Studies have shown that leukocytosis at diagnosis is associated with higher risk of thrombosis and major hemorrhage in patients with PV and ET.247-252 Data from some studies suggest that the prognostic significance of leukocytosis for the risk of recurrent thrombosis may be significant only in patients <60 years of age,253,254 and other studies have reported that leukocytosis at diagnosis is not associated with the risk of subsequent thrombosis.248 Thrombocytosis (platelet count >1000 x 109/L) has been associated with an immediate risk of major hemorrhage but not with the risk of thrombosis in patients with ET.251 In fact, some studies have reported that elevated platelet counts at diagnosis (>1000 x 109/L) are associated with significantly lower rate of thrombosis; this association was significant even in patients with JAK2-mutated ET.249,250 The potential benefit of initiation of cytoreductive therapy based on elevated blood counts (leukocytosis or thrombocytosis) at the time of diagnosis has not been evaluated in prospective studies.

Arterial/Venous Thrombosis Score

In a multivariable analysis of 1057 patients with MPN (training cohort), prior arterial thrombosis, age >60 years, presence of cardiovascular risk factors, and presence of TET2 or DNMT3A mutations were identified as independent predictors of arterial thrombosis and were used to calculate an arterial thrombosis score.255 This model stratified patients into two risk categories: low risk (0.37% patients-year) and high risk (1.19% patients-year), and was deemed to be superior when compared to the two-tiered conventional risk model in the training cohort, regardless of the MPN subtype. The arterial thrombosis score model was also validated in two external cohorts. A prior history of venous thrombosis and the presence of JAK2 V617F mutation with VAF ≥50% were identified as independent predictors of venous thrombosis and were used to calculate a venous thrombosis score. This model stratified patients into three risk categories: low risk, intermediate risk, and high risk. However, this model had a low prediction potential and was found to be similar to the two-tiered conventional risk model.

Polycythemia Vera

Conventional Risk Model

Advanced age (ie, >60 years) and history of thrombosis are the most consistent risk factors associated with the risk of thrombosis.256 In a cohort of 1638 patients with PV who were screened for inclusion in the ECLAP trial, age >65 years and a previous history of thrombosis were the two most important prognostic factors associated with an increasing risk of cardiovascular events resulting in the identification of three different risk groups: low risk (age <65 years and no prior history of thrombosis), intermediate risk (age <65 years with prior thrombosis or age ≥65 years without prior thrombosis), and high risk (age ≥65 years with prior thrombosis). There is a consensus to use age ≥60 years or history of thrombosis as prognostic factors for the risk of thrombosis.257,258

MIPSS-PV

In a study of 336 patients with PV, the presence of SRSF2 mutation, age >67 years, leukocyte count ≥15 x 109/L, and history of thrombosis were identified as independent risk factors for survival.259 Based on these findings, MIPSS-PV was developed. Patients were stratified into three risk categories: low risk, intermediate

risk, and high risk, with a median OS of 24 years, 13.1 years, and 3.2 years, respectively. Further studies are needed to validate these findings.

Essential Thrombocythemia

IPSET-Thrombosis

In an analysis of 867 patients with ET, age ≥60 years, leukocyte count ≥11 x 109/L, and prior thrombosis were significantly associated with inferior survival.260 Based on these findings, IPSET was developed to stratify patients at the time of diagnosis into three risk categories: low risk, intermediate risk, and high risk. The median survival was not reached for the low-risk group and the median survival was 24 years and 14 years, respectively, for the intermediate-risk and high-risk groups. In a subsequent analysis of 891 patients with ET, age >60 years, history of thrombosis, cardiovascular risk factors, and presence of JAK2 V617F mutation retained their prognostic significance regarding thrombosis risk in multivariable analysis.261 Thus, a modified prognostic model (IPSET-thrombosis) including cardiovascular risk factors and presence of JAK2 V617F mutation status as additional risk factors was developed to stratify patients into the same three groups with significantly different thrombosis-free survival: 87% after 15-year follow-up for patients with low-risk disease and 50% after 7-year follow-up for patients with high-risk disease.261 In the intermediate-risk group, the thrombosis-free survival rate for the first 10 years was closer to that of the low-risk group and then progressively reached the high-risk survival rate in the subsequent 5 years.

Further analysis of the IPSET-thrombosis showed that among the patients with low-risk disease, the risk of thrombosis was significantly lower in patients with JAK2-negative/unmutated ET in the absence of cardiovascular risk factors (0.44%) compared to the risk of thrombosis in patients with JAK2 unmutated ET in the presence of cardiovascular risk factors (1%).262 The risk of thrombosis in the presence of JAK2 mutation without cardiovascular risk factors and in the presence of both JAK2 mutation and cardiovascular risk factors was 2% and 3%, respectively. These findings led to the development of revised IPSET-thrombosis that stratifies patients into four different risk groups: very low risk (age ≤60 years, no JAK2 mutation, and no prior history of thrombosis); low risk (age ≤60 years, JAK2 mutation, and no prior history of thrombosis); intermediate risk (age >60 years, no JAK2 mutation, and no prior history of thrombosis); and high risk (history of thrombosis at any age; or age >60 years with JAK2 mutation). The revised IPSET-thrombosis has also been validated in an independent cohort of 585 patients.262,263

CALR mutation status, however, did not have a significant impact on the IPSET-thrombosis prognostic score for predicting the risk of thrombosis.54 While the incidences of thrombosis were slightly lower in patients with CALR-mutated ET than in those with JAK2-mutated ET, in multivariable analysis, CALR mutation status did not retain the association with the risk of thrombosis in low-risk and intermediate-risk groups. In part, this may be explained by the fact that CALR mutation status tended to cluster with other lower-risk features. The significance of CALR mutations and the risk of thrombosis could not be evaluated in the high-risk group since there was a lower proportion of patients with the CALR mutation in this group.

MIPSS-ET

In a study of 451 patients with ET, the presence of adverse mutations (ie, SF3B1, SRSF2, TP53, U2AF1), age >60 years, male sex, and leukocyte count ≥11 x 109/L were identified as independent risk factors for survival.259 Based on these findings, MIPSS-ET was developed. Patients were stratified into three risk categories: low risk, intermediate risk, and high risk, with a median OS of 34.4 years, 14.1 years, and 7.9 years, respectively. Further studies are needed to validate these findings.

"Triple A" Risk Model

The prognostic AAA risk model for ET is based on age, absolute neutrophil count, and absolute lymphocyte count. Data from 598 patients were used and this model was validated in an external cohort of 485 patients. Four risk categories were identified: low risk (47-year median survival), intermediate-1 risk (20.7-year median survival; HR, 3.8), intermediate-2 risk (13.5-year median survival; HR, 12.7), and high risk (8-year median survival; HR, 30.1). Age ≥50 years, ANC ≥8 x 109/L, absolute lymphocyte count <1.7 x 109/L were identified as independent predictors of survival.

Treatment Options

Antiplatelet Therapy

The safety and efficacy of low-dose aspirin for the prevention of thrombotic complications in PV were established in a multicenter trial in patients with no contraindication to aspirin therapy and no history of a thrombotic event (ECLAP study; 518 patients).264 The use of aspirin resulted in a significant reduction (60%) of combined risk of nonfatal myocardial infarction, nonfatal stroke, pulmonary embolism, major venous thrombosis, or death from cardiovascular causes (P = .03) and the incidence of major bleeding was not significantly increased in the aspirin group. The role of maintaining the hematocrit level below 45% in patients receiving treatment was established in the CYTO-PV study.265 In this randomized study of 365 patients with PV treated with phlebotomy and/or hydroxyurea, the hematocrit target of <45% resulted in a significantly lower rate of cardiovascular death and major thrombotic events (primary endpoint) than a hematocrit target

of 45% to 50%.265 After a median follow-up of 31 months, death from cardiovascular causes or major thrombotic events was recorded in 3% (5 of 182 patients) of patients with a hematocrit level of <45% compared to 10% (18 of 183 patients) of patients with a haematocrit level of 45% to 50% (P = .007).

The efficacy of low-dose aspirin for the prevention of thrombosis in patients with ET has not been evaluated in randomized clinical trials. The data supporting the use of aspirin in patients with ET is based on the extrapolation of results from the ECLAP study that evaluated the efficacy of aspirin in patients with PV and the results of retrospective analyses.266,267 Results from one retrospective analysis suggest that aspirin may be effective for the prevention of thrombosis in patients with low-risk JAK2-mutated ET and in those with cardiovascular risk factors.266 Observation may be appropriate for all other patients with low-risk ET. In this retrospective analysis of 300 patients with low-risk ET managed with aspirin (n = 198) or observation (n = 102), the incidences of venous thrombosis were higher for those with JAK2 V617F-positive ET not receiving any antiplatelet therapy; patients with cardiovascular risk factors had increased rates of arterial thrombosis while on observation.266

Cytoreductive Therapy

Hydroxyurea,265,268,269 peginterferon alfa,270-273 and ropeginterferon alfa-2bnjft274,275 have been shown to be effective for the prevention of thrombotic complications in patients with PV. In a nonrandomized study of 51 patients with PV, the use of hydroxyurea along with phlebotomy as needed significantly reduced the risk of thrombosis compared to a historical control of patients treated with phlebotomy alone.268 Long-term follow-up of this study (after a median follow-up of 9 years) showed that prolonged use of hydroxyurea was associated with leukemic transformation (6% compared to 2% for phlebotomy).276 However, an analysis from the ECLAP study identified older age and the use of other alkylating agents (eg, P32, busulfan, pipobroman) but not hydroxyurea alone as an independent risk factor for leukemic transformation.277 In the randomized trial that compared hydroxyurea and pipobroman as first-line therapy in 285 patients with PV <65 years of age, the cumulative incidence of leukemic transformation was significantly higher with pipobroman than with hydroxyurea.269 At a median follow-up of 15 years the incidences of leukemic transformation were 17% and 34%, respectively, for hydroxyurea and pipobroman.

In a phase II multicenter study of 40 patients with PV, peginterferon alfa-2a resulted in high rates of complete hematologic response (CHR; 95%) and CMR (24%) with limited toxicity.271 At a median follow-up of 31 months, 36 patients with a response remained phlebotomy free. A phase II trial that included 43 patients with PV reported a CHR rate of 77% and a CMR rate of 20% after a median follow-up of 83 months.273 The duration of response was longer among patients with CMR (70 months) than for those with CHR (65 months). The presence of TET2, ASXL1, EZH2, DNMT3A, and IDH1/2 mutations was associated with non-achievement of CMR.272 Patients with both JAK2 V617F and TET2 mutations at initiation of treatment had a less significant reduction in JAK2 V617F allele burden compared to those with JAK2-mutated/TET2 wild-type disease.

A phase III study comparing hydroxyurea to peginterferon alf-2a in patients with high-risk PV or ET reported no significant difference in CR rates at 12 months (37% vs. 35%; P = .80).278 However, the authors note that with prolonged treatment, hydroxyurea elicited a greater number of histopathologic responses, while peginterferon-afa-2a resulted in a greater reduction in the JAK2 V617F mutation burden. Grade 3 or higher adverse events, irrespective of cause, also occurred more frequently with peginterferon alfa-2a treatment (46% vs. 28% for hydroxyurea).

Hydroxyurea,279-281 peginterferon alfa-2a,272,273 and possibly anagrelide280-283 have been shown to be effective for the prevention of venous thrombotic complications in patients with high-risk ET.

In a study of 114 patients with high-risk ET (>60 years and high risk of thrombosis) randomized to receive hydroxyurea (n = 56), which was administered to maintain the platelet count <600 x 109/L or no myelosuppressive therapy (n = 58), the incidences of thrombotic episodes were significantly lower in patients treated with hydroxyurea (3.6% compared to 24% in patients with no myelosuppressive therapy; P = .003).279 In another randomized study of 809 patients with high-risk ET, hydroxyurea plus low-dose aspirin was superior to anagrelide plus low-dose aspirin.280 Patients in the hydroxyurea arm initially received the drug at a dose of 0.5 to 1 g daily, while those in the anagrelide arm received the drug at a dose of 0.5 mg twice daily. The dose of the drugs was adjusted subsequently to keep the platelet count at <400 x 109/L. After a median follow-up of 39 months, the long-term control of platelet counts was equivalent in both groups and anagrelide plus aspirin was better in the prevention of venous thrombosis (P = .006). However, the incidences of arterial thrombosis (P = .004), serious hemorrhage (P = .008), and transformation to MF (P = .01) were higher with anagrelide plus aspirin. In addition, treatment discontinuation rate was also significantly higher with anagrelide plus aspirin. The diagnosis of ET in this trial was based on the Polycythemia Vera Study Group criteria. A phase III randomized study showed that anagrelide was not inferior to hydroxyurea as first-line therapy for the prevention of thrombotic complications in patients with high-risk ET diagnosed according to the WHO criteria.281 In this study, 259 patients were randomized to either hydroxyurea (n = 122) or anagrelide (n = 137). The dose of the drugs was increased until platelet counts were maintained at a normal level (≤450 x 109/L) or close to it (>450 x 109/L to 600 x 109/L). After a total observation time of 730 patient-

years, there was no significant difference between anagrelide and hydroxyurea in the incidences of arterial or venous thrombotic events, severe bleeding, or rates of discontinuation. Another study showed that over a median period of 10 years, patients taking anagrelide experienced fewer minor arterial events (P < .001), had more major arterial events (P = .049), and had improved OS (P = .001) and PFS (P = .004) compared to patients taking hydroxyurea and aspirin.283

In a phase II trial that included 40 patients with ET, peginterferon alfa-2a induced a CHR rate of 73% and a CMR rate of 9% after a median follow-up of 83 months.273 The presence of TET2, ASXL1, EZH2, DNMT3A, and IDH1/2 mutations was associated with non-achievement of CMR.272 Patients with both JAK2 V617F and TET2 mutations at initiation of treatment had a less significant reduction in JAK2 V617F allele burden compared to those with JAK2-mutated or TET2 wild-type disease. The phase II Myeloproliferative Disorders Research Consortium-111 study consisted of patients with high-risk ET (n = 65) or PV (n = 50) that is resistant or intolerant to hydroxyurea. Treatment with peginterferon alfa-2a resulted in a 12-month ORR of 69% and 60%, respectively.284 Patients with ET who have a CALR mutation had increased CHR rates compared to those without a CALR mutation. Fourteen percent of patients discontinued treatment due to adverse events.

In the phase II Low-PV trial comprising 127 patients, a higher proportion of patients treated with ropeginterferon-alfa2b-njft in addition to phlebotomy achieved the primary endpoint, defined as the maintenance of a median hematocrit level of ≤45% over 12 months in the absence of disease progression, when compared to those treated with phlebotomy alone (81% vs. 51%; P < .001).275 At 24 months, the response rates were maintained (ropeginterferon-alfa-2b-njft with phlebotomy, 83%; phlebotomy alone, 59%; P = .02).

In the phase III PROUD-PV trial, patients received either ropeginterferon alfa-2b-njft (n = 127) or hydroxyurea (n = 127).274 The composite primary endpoint was the achievement of CHR and normal spleen size by imaging. At 12 months, noninferiority was not demonstrated (P = .23) with 21% of patients in the ropeginterferon alfa-2b-njft group and 28% in the hydroxyurea group achieving the composite primary endpoint. Not accounting for the spleen, 43% of patients achieved CHR in the ropeginterferon alfa-2b-njft group compared to 46% in the hydroxyurea group (P = .63). At the end of the 12-month PROUD-PV trial, patients were eligible to enter the CONTINUATION-PV extension study. Patients taking ropeginterferon alfa-2b-njft (n = 95) remained on the drug and those taking hydroxyurea received best available therapy (n = 76), chosen by the investigator. The co-primary endpoints were the achievement of CHR and normal spleen size as well as CHR accompanied by improved disease burden. Patient response to ropeginterferon alfa-2b-njft improved over time and, at 36 months, was significantly higher as CHR with improved disease burden was reported in 53% of patients, compared to 38% in the hydroxyurea group (P = .044). However, there was no significant difference at 36 months in terms of CHR with normal spleen size, with a response rate of 42% in the ropeginterferon alfa-2b-njft group and 30% in the hydroxyurea group (P = .16). Not accounting for the spleen, CHR was reported in 71% of patients in the ropeginterferon alfa-2b-njft group and in 51% of patients in the hydroxyurea group (P = .012). Across both studies, the most common grade 3 and 4 adverse occurrences for patients on ropeginterferon alfa-2b-njft were increased γ-glutamyltransferase and alanine aminotransferase and for those on hydroxyurea were leucopenia and thrombocytopenia.

Data from the PROUD-PV and CONTINUATION-PV trials at 5 years revealed a CHR rate and molecular response rate of 55.8% and 69.1%, respectively, in patients treated with ropeginterferon alfa-2b-njft compared to 44.0% (rate ratio, 1.30; P = .0974) and 21.6% (rate ratio, 3.04; P < .0001), respectively, in patients treated with best available therapy, which was mostly hydroxyurea.285 In the ropeginterferon alfa-2b-njft group, the median JAK2 V617F allele burden decreased from 37.3% at baseline to 8.5% at 60 months whereas in the best available therapy group, a decrease was observed at 12 months (38.1% at baseline to 18.2%) but at 60 months, the percentage was at 44.4% (P < .0001). The rates of treatment-related adverse events were similar in both groups, irrespective of prior treatment with hydroxyurea. At 72 months, patients treated with ropeginterferon alfa-2b-njft maintained a higher CHR rate compared to those treated with best available therapy (54.5% vs. 34.9%; P = .02).286 After 6 years, 66.0% of patients in the ropeginterferon alfa-2b-njft arm had a molecular response compared to 19.4% in the control arm (P < .0001), with a median JAK2 V617F allele burden of 8.5% and 50.4%, respectively (P < .0001), at 72 months. Patients in the former group also had a significantly higher probability of EFS (0.94 vs. 0.82 in the control group; P = .04), with 5.3% of patients in the former group having a risk event (thromboembolic event, 2; MF, 1; death, 2) versus 16.2% in the control group (thrombotic event, 5; MF, 2; acute leukemia, 2; death, 2). Ropeginterferon alfa-2b-njft was FDA-approved in 2021 for the treatment of adult patients with PV.

Ruxolitinib

A futility analysis of the phase IIb RuxoBEAT study showed that in patients with PV with no prior treatment, ruxolitinib resulted in a decrease in the median hematocrit, the median number of phlebotomies received per year, and the median pruritus scores at 6 months.287 Adverse events were reported in 24 out of 28 patients. The results of the phase III randomized trial (RESPONSE) confirmed that ruxolitinib is superior to best available therapy (hydroxyurea, interferon or pegylated interferon, pipobroman, anagrelide,

lenalidomide, thalidomide, or observation with the use of aspirin) at controlling hematocrit and improving splenomegaly and symptoms in patients with PV.87,288,289 In this study, 222 patients with PV who are phlebotomy-dependent with splenomegaly and whose disease had an inadequate response to or was intolerant of hydroxyurea were randomized to receive ruxolitinib (110 patients) or best available therapy (112 patients).87 The primary endpoint was hematocrit control without phlebotomy and at least a 35% reduction in spleen volume (as assessed by imaging) by 32 weeks. Patients randomized to best available therapy were eligible to cross over to ruxolitinib after 32 weeks if the primary endpoint was not met or if there were signs of disease progression. After 32 weeks, hematocrit control was achieved in 60% of patients treated with ruxolitinib compared to 20% of patients treated with best available therapy. A reduction in spleen volume (≥35%), CHR, and at least a 50% reduction in symptom burden were achieved in 38%, 24%, and 49% of patients, respectively, in the ruxolitinib group and in 1%, 9%, and 5% of patients, respectively, in the best available therapy group. The incidences of grade 3/4 anemia and herpes zoster infection were higher among patients treated with ruxolitinib (occurring in 2% and 6% of patients, respectively, compared to 0% of patients treated with best available therapy). The 80-week follow-up data confirmed the long-term efficacy of ruxolitinib, and the probability of maintaining CHR for ≥80 weeks was 69%.288 Ruxolitinib was also associated with a lower rate of thromboembolic events (1.8% and 4.1%, respectively, for patients originally randomized to ruxolitinib and for those receiving ruxolitinib after crossover compared to 8.2% for those receiving best available therapy). The 5-year follow-up of the RESPONSE study further confirmed the safety and efficacy of ruxolitinib as a long-term option for patients with PV that is resistant to or intolerant of hydroxyurea.290 By week 80, patients who did not cross over to the ruxolitinib arm discontinued the study. The probability of maintaining the primary endpoint response, complete hematologic remission, and overall clinicohematologic response at 5 years was 74% (95% CI, 51%–88%), 55% (95% CI, 32%–73%), and 67% (95% CI, 54%–77%), respectively. Compared to the best available therapy study arm, the patients in the ruxolitinib study arm experienced fewer thromboembolic and nonhematologic adverse events.

In a subsequent phase IIIb study (RESPONSE-2), ruxolitinib was shown to be effective for the treatment of PV with an inadequate response to hydroxyurea in patients without splenomegaly.291 A follow-up study performed 80 weeks later revealed sustained CHR in 24% of patients receiving ruxolitinib compared to 3% of patients receiving best available therapy.292 Of those receiving best available therapy, 77% crossed over to the ruxolitinib arm after week 28. At 80 weeks, patients discontinued best available therapy.293 At 5 years, durable hematocrit control was reported in 22% of patients in the ruxolitinib group.293 The results of another phase III study showed that ruxolitinib was also effective and resulted in improvements in symptoms (although non-significant) compared to hydroxyurea in patients with well-controlled PV; however, other disease-associated symptoms were reported.294

Results from the phase II MAJIC-PV study demonstrated the benefit of ruxolitinib over best available therapy in patients with PV that is resistant or intolerant to hydroxyurea.295 Forty-three percent of patients treated with ruxolitinib achieved a CR within 1 year compared to 26% of patients treated with best available therapy (OR, 2.12; 90% CI, 1.25–3.60; P = .02). Ruxolitinib treatment also led to more frequent molecular responses, which were associated with improved PFS, EFS, and OS. The presence of additional driver mutations negatively impacted EFS. The phase II MAJIC-ET trial investigated the efficacy of ruxolitinib versus best available therapy in patients with ET that is resistant or intolerant to hydroxyurea.88 The CR rates at 1 year, as well as occurrence of thrombosis, hemorrhage, and disease transformation at 2 years were similar in both groups. Ruxolitinib use was associated with a decrease in some disease-related symptoms, with a median total symptom score reduction of 32%, compared to 0% for patients receiving best available therapy (P = .03). An expanded analysis of the trial revealed that the presence of TP53 and splicing factor mutations led to poorer transformation-free survival.296 Treatment with ruxolitinib did not alleviate disease transformation. Another phase II study found that long-term treatment with ruxolitinib in patients with ET that is refractory to or intolerant of hydroxyurea led to lasting reductions in platelet counts and amelioration of ET-related symptoms.297

Treatment Recommendations Based on Risk Stratification

Treatment options should be individualized based on age and history of thrombosis for patients with PV,256 and the revised IPSET-thrombosis is recommended for the risk stratification of patients with ET.262,263

Polycythemia Vera

Low Risk (Age <60 years and no prior history of thrombosis)

Aspirin (81–100 mg/day), phlebotomy (to maintain hematocrit <45%), and the management of cardiovascular risk factors are recommended for all patients with low-risk PV.264,265 In the CYTO-PV study, the haematocrit target was the same for both males and females. No thrombotic event was observed in the 66 females with hematocrit of <45% compared to nine events reported in the 72 females with a hematocrit target of 45% to 50%.265 However, normal hematocrit levels vary in males (42%–54%) and females (38%–46%). While the target hematocrit level of <45% may be adequate for the majority of patients, there may be situations in

which a lower hematocrit cutoff may be appropriate and it should be individualized (eg, for patients with progressive symptoms).

High Risk (Age ≥60 years and/or prior history of thrombosis)

In addition to aspirin and phlebotomy, cytoreductive therapy is also used to reduce the risk of thrombotic complications in patients with high-risk PV. Management of cardiovascular risk factors is recommended. Cytoreductive therapy with aspirin (81–100 mg/day) for vascular symptoms and phlebotomy (to maintain hematocrit <45%) is recommended. Cytoreductive therapy options comprise hydroxyurea (preferred regimen), ropeginterferon alfa-2b-njft (preferred regimen), peginterferon alfa-2a (other recommended regimen), and ruxolitinib (useful in certain circumstances). Peginterferon alfa-2a is an option for younger patients or in pregant patients in need of cytoreductive therapy. In the event that peginterferon alfa-2a is unavailable, the use of other pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.

Essential Thrombocythemia

Very-Low Risk (Age ≤60 years without JAK2 mutation and no prior history of thrombosis), Low Risk (age ≤60 years with JAK2 mutation and no prior history of thrombosis), or Intermediate Risk (>60 years, no JAK2 mutation, and no prior history of thrombosis)

As discussed above, the efficacy and safety of low-dose aspirin in patients with ET has not been evaluated in randomized clinical trials. The results of a systematic review also suggest that the risks and benefits of antiplatelet therapy in patients with ET remain highly uncertain.298 Observation is appropriate for patients with very-low-risk, low-risk, and intermediate-risk ET. Aspirin (81–100 mg/day) is an option for patients with very-low-risk (with vasomotor/microvascular disturbances), low-risk, or intermediate-risk ET. Aspirin should be used with caution in patients with acquired VWS who have an increased risk of bleeding. In one study, patients with ET and no high-risk factors for thrombosis or extreme thrombocytosis were given either aspirin alone (n = 176) or aspirin with hydroxyurea (n = 182).299 The dose of hydroxyurea was adjusted in order to maintain platelet count between 200 x 109/L to 400 x 109/L. The results showed that this combination did not decrease the incidence of vascular events and myelofibrotic or leukemic transformation.

A report from a retrospective analysis suggests that the use of low-dose aspirin may not be beneficial in patients with low-risk CALR-mutated ET.267 In an analysis that evaluated the benefit-to-risk ratio of low-dose aspirin in 433 patients with low-risk ET (271 patients with a CALR mutation and 162 patients with a JAK2 V617F mutation) who were on antiplatelet therapy or observation, low-dose aspirin did not affect the risk of thrombosis but was associated with a higher incidence of bleeding in patients with CALR-mutated ET.267 These findings have to be confirmed in prospective clinical trials.

In carefully selected patients, twice-daily aspirin at a 100-mg dose has been found to be more effective than once-daily aspirin (100 mg), a finding that has yet to be confirmed in randomized controlled studies.300,301 One randomized trial found that a dosing interval of 12 hours heightened the effectiveness of low-dose aspirin as an antiplatelet drug.302 A study that compared once-daily aspirin (75 mg) to twice-daily aspirin (37.5 mg per dose) found that the twice-daily schedule led to improved platelet inhibition.303 Aspirin twice daily may be considered for patients with refractory symptoms.300,301 At the present time, the risks and benefits of higher dose aspirin (>100 mg) must be weighed based on the presence of vasomotor symptoms versus the risk of bleeding. It may be appropriate in carefully selected patients as clinically indicated.

High Risk (History of thrombosis at any age; or age >60 years with JAK2 mutation)

Cytoreductive therapy (clinical trial [preferred regimen], hydroxyurea [preferred regimen], peginterferon alfa-2a (based on other patient-specific variables) [other recommended regimen], or anagrelide [other recommended regimen]) with aspirin (81–100 mg/day) is recommended as initial treatment. Peginterferon alfa-2a can be considered for patients in need of cytoreductive therapy who are younger or pregnant or who defer hydroxyurea. In the event that peginterferon alfa-2a is unavailable, the use of other pegylated interferons (eg, ropeginterferon alfa-2b-njft) is appropriate.

Treatment Response Criteria

The IWG-MRT and ELN treatment response criteria for PV and ET were first published in 2009 and were revised in 2013.304 Responses are categorized as CR, PR, no response, and PD. The revised response criteria recommend that symptoms should be evaluated by the MPN-SAF TSS. The evaluation of CR or PR includes four categories: 1) resolution of disease-related signs and symptoms including palpable splenomegaly and large symptom improvement (≥10 point decrease in MPN-SAF TSS); 2) peripheral blood count response (platelet count ≤400 x 109/L, white blood cell [WBC] count <10 x 109/L, absence of leukoerythroblastosis, and hematocrit <45% without phlebotomies); 3) absence of signs of PD and absence of any hemorrhagic or thrombotic events; and 4) histologic response in bone marrow. Molecular response is not required for the assignment of CR or PR and the revised IWG-MRT and ELN treatment response criteria do not provide a definition of molecular response.

JAK2 V617F Allele Burden

Long-term ruxolitinib therapy has been shown to reduce JAK2 V617F allele burden in patients with PV that is resistant to hydroxyurea.305 High JAK2 V617F allele burden has also been reported as a risk factor for myelofibrotic transformation and higher incidences of thrombotic events in patients with PV and ET.306-308 These findings suggest that monitoring JAK2 V617F allele burden could be useful to identify patients at higher risk of myelofibrotic transformation. It could also be a useful adjunctive evaluation to assess the impact of cytoreduction on molecular response. However, the utility of JAK2 V617F allele burden reduction as a predictor of clinical outcome is not well-established. In addition, in patients with other mutations in addition to a JAK2 mutation, a remission of one mutated clone is not always accompanied by remission of other mutated clones.304

Referenzen aus Leitlinie

12. PubMed Overview. Available at: https://pubmed.ncbi.nlm.nih.gov/about/. Accessed July 26, 2022.
85. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): An international Internet-based survey of 1179 MPD patients. Cancer 2007;109:68-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17123268.
86. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebocontrolled trial of ruxolitinib for myelofibrosis. N Engl J Med 2012;366:799-807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22375971.
87. Vannucchi AM, Kiladjian JJ, Griesshammer M, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med 2015;372:426-435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25629741.
88. Harrison CN, Mead AJ, Panchal A, et al. Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide. Blood 2017;130:1889-1897. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29074595.
89. Harrison CN, Schaap N, Vannucchi AM, et al. Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): A single-arm, open-label, non-randomised, phase 2, multicentre study. Lancet Haematol 2017;4:e317-e324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28602585.
90. Verstovsek S, Gerds AT, Vannucchi AM, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis (MOMENTUM): Results from an international, double-blind, randomised, controlled, phase 3 study. Lancet 2023;401:269-280. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36709073.
91. Gerds AT, Verstovsek S, Vannucchi AM, et al. Momelotinib versus danazol in symptomatic patients with anaemia and myelofibrosis previously treated with a JAK inhibitor (MOMENTUM): An updated analysis of an international, double-blind, randomised phase 3 study. Lancet Haematol 2023;10:e735-e746. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37517413.
92. Mesa RA, Vannucchi AM, Mead A, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): An international, randomised, phase 3 trial. Lancet Haematol 2017;4:e225-e236. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28336242.
93. Mascarenhas J, Hoffman R, Talpaz M, et al. Pacritinib vs best available therapy, including ruxolitinib, in patients with myelofibrosis: A randomized clinical trial. JAMA Oncol 2018;4:652-659. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29522138.
94. Pardanani A, Tefferi A, Masszi T, et al. Updated results of the placebo-controlled, phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis. Br J Haematol 2021;195:244-248. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34331348.
95. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 2009;113:2895-2901. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18988864.
96. Passamonti F, Cervantes F, Vannucchi AM, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood 2010;115:1703-1708.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008785.
97. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: A refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol 2011;29:392-397.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/21149668.
98. Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for transplantation-age patients with primary myelofibrosis. J Clin Oncol 2018;36:310-318. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29226763.

99. Tefferi A, Guglielmelli P, Lasho TL, et al. MIPSS70+ Version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for primary myelofibrosis. J Clin Oncol 2018;36:1769-1770. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29708808.
100. Passamonti F, Giorgino T, Mora B, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia 2017;31:2726-2731. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28561069.
101. Palandri F, Palumbo GA, Iurlo A, et al. Differences in presenting features, outcome and prognostic models in patients with primary myelofibrosis and post-polycythemia vera and/or post-essential thrombocythemia myelofibrosis treated with ruxolitinib. New perspective of the MYSEC-PM in a large multicenter study. Semin Hematol 2018;55:248-255.
Available at: https://www.ncbi.nlm.nih.gov/pubmed/30502854.
102. Patnaik MM, Caramazza D, Gangat N, et al. Age and platelet count are IPSS-independent prognostic factors in young patients with primary myelofibrosis and complement IPSS in predicting very long or very short survival. Eur J Haematol 2010;84:105-108. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/19895568.
103. Tefferi A, Siragusa S, Hussein K, et al. Transfusion-dependency at presentation and its acquisition in the first year of diagnosis are both equally detrimental for survival in primary myelofibrosis—prognostic relevance is independent of IPSS or karyotype. Am J Hematol 2010;85:14-17. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20029953.
104. Hussein K, Pardanani AD, Van Dyke DL, et al. International Prognostic Scoring System-independent cytogenetic risk categorization in primary myelofibrosis. Blood 2010;115:496-499. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19901264.
105. Caramazza D, Begna KH, Gangat N, et al. Refined cytogenetic-risk categorization for overall and leukemia-free survival in primary myelofibrosis: A single center study of 433 patients. Leukemia 2011;25:82-88. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20944670.
106. Masarova L, Bose P, Daver N, et al. Patients with post-essential thrombocythemia and post-polycythemia vera differ from patients with primary myelofibrosis. Leuk Res 2017;59:110-116. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28601551.
107. Mora B, Giorgino T, Guglielmelli P, et al. Value of cytogenetic abnormalities in post-polycythemia vera and post-essential thrombocythemia myelofibrosis: A study of the MYSEC project. Haematologica 2018;103:e392-e394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29622658.
108. Ianotto JC, Boyer-Perrard F, Gyan E, et al. Efficacy and safety of pegylated-interferon alpha-2a in myelofibrosis: A study by the FIM and GEM French cooperative groups. Br J Haematol 2013;162:783-791.
Available at: http://www.ncbi.nlm.nih.gov/pubmed/23848933.
109. Ianotto JC, Chauveau A, Boyer-Perrard F, et al. Benefits and pitfalls of pegylated interferon-alpha2a therapy in patients with myeloproliferative neoplasm-associated myelofibrosis: A French Intergroup of Myeloproliferative neoplasms (FIM) study. Haematologica 2018;103:438-446. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29217781.
110. Silver RT, Barel AC, Lascu E, et al. The effect of initial molecular profile on response to recombinant interferon-alpha (rIFNalpha) treatment in early myelofibrosis. Cancer 2017;123:2680-2687. Available at:
https://www.ncbi.nlm.nih.gov/pubmed/28518222.
111. Sorensen AL, Mikkelsen SU, Knudsen TA, et al. Ruxolitinib and interferon-alpha2 combination therapy for patients with polycythemia vera or myelofibrosis: A phase II study. Haematologica 2020;105:2262-2272. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33054051.
112. Kiladjian JJ, Ianotto JC, Soret J, et al. Final results of RUXOPEG, a phase 1/2 adaptive randomized trial of ruxolitinib (rux) and pegylated interferon alpha (IFNa) 2a in patients with myelofibrosis (MF) [abstract]. Blood 2022;140:577-578. Available at:
https://ashpublications.org/blood/article/140/Supplement%201/577/488443/Final-Results-of-Ruxopeg-a-Phase-1-2-Adaptive.
113. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med 2012;366:787-798. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/22375970.
114. Davis KL, Cote I, Kaye JA, et al. Real-world assessment of clinical outcomes in patients with lower-risk myelofibrosis receiving treatment with ruxolitinib. Adv Hematol 2015;2015:848473. Available at:
https://www.ncbi.nlm.nih.gov/pubmed/26635878.
115. Mead AJ, Milojkovic D, Knapper S, et al. Response to ruxolitinib in patients with intermediate-1-, intermediate-2-, and high-risk myelofibrosis: results of the UK ROBUST Trial. Br J Haematol 2015;170:29-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25824940.
116. Al-Ali HK, Griesshammer M, le Coutre P, et al. Safety and efficacy of ruxolitinib in an open-label, multicenter, single-arm phase 3b expanded access study in patients with myelofibrosis: a snapshot of 1144 patients in the JUMP trial. Haematologica 2016;101:1065-1073. Available at:
https://www.ncbi.nlm.nih.gov/pubmed/27247324.

117. Palandri F, Tiribelli M, Benevolo G, et al. Efficacy and safety of ruxolitinib in intermediate-1 IPSS risk myelofibrosis patients: Results from an independent study. Hematol Oncol 2018;36:285-290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28512865.
118. Al-Ali HK, Griesshammer M, Foltz L, et al. Primary analysis of JUMP, a phase 3b, expanded-access study evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis, including those with low platelet counts. Br J Haematol 2020;189:888-903. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32017044.
119. Gupta V, Griesshammer M, Martino B, et al. Analysis of predictors of response to ruxolitinib in patients with myelofibrosis in the phase 3b expanded-access JUMP study. Leuk Lymphoma 2021;62:918-926. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33210570.
120. Verstovsek S, Mesa RA, Gotlib J, et al. Efficacy, safety, and survival with ruxolitinib in patients with myelofibrosis: results of a median 3-year follow-up of COMFORT-I. Haematologica 2015;100:479-488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25616577.
121. Verstovsek S, Mesa RA, Gotlib J, et al. Long-term treatment with ruxolitinib for patients with myelofibrosis: 5-year update from the randomized, double-blind, placebo-controlled, phase 3 COMFORT-I trial. J Hematol Oncol 2017;10:55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28228106.
122. Cervantes F, Vannucchi AM, Kiladjian JJ, et al. Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis. Blood 2013;122:4047-4053. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24174625.
123. Harrison CN, Vannucchi AM, Kiladjian JJ, et al. Long-term findings from COMFORT-II, a phase 3 study of ruxolitinib vs best available therapy for myelofibrosis. Leukemia 2016;30:1701-1707. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27211272.
124. Verstovsek S, Mesa RA, Gotlib J, et al. The clinical benefit of ruxolitinib across patient subgroups: analysis of a placebo-controlled, Phase III study in patients with myelofibrosis. Br J Haematol 2013;161:508-516. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23480528.
125. Vannucchi AM, Kantarjian HM, Kiladjian JJ, et al. A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase III trials of ruxolitinib for the treatment of myelofibrosis. Haematologica 2015;100:1139-1145. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26069290.
126. Verstovsek S, Kantarjian HM, Estrov Z, et al. Long-term outcomes of 107 patients with myelofibrosis receiving JAK1/JAK2 inhibitor ruxolitinib: Survival advantage in comparison to matched historical controls. Blood 2012;120:1202-1209. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22718840.
127. Guglielmelli P, Ghirardi A, Carobbio A, et al. Impact of ruxolitinib on survival of patients with myelofibrosis in the real world: Update of the ERNEST Study. Blood Adv 2022;6:373-375. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34753179.
128. Gupta V, Harrison C, Hexner EO, et al. The impact of anemia on overall survival in patients with myelofibrosis treated with ruxolitinib in the COMFORT studies. Haematologica 2016;101:e482-e484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27587385.
129. Cervantes F, Ross DM, Radinoff A, et al. Efficacy and safety of a novel dosing strategy for ruxolitinib in the treatment of patients with myelofibrosis and anemia: The REALISE phase 2 study. Leukemia 2021;35:3455-3465. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34017073.
130. Talpaz M, Prchal J, Afrin L, et al. Safety and efficacy of ruxolitinib in patients with myelofibrosis and low platelet counts (50 - 100 x 109/L): Final analysis of an open-label phase 2 study. Clin Lymphoma Myeloma Leuk 2022;22:336-346. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34911667.
131. Vannucchi AM, Te Boekhorst PAW, Harrison CN, et al. EXPAND, a dose-finding study of ruxolitinib in patients with myelofibrosis and low platelet counts: 48-week follow-up analysis. Haematologica 2019;104:947-954. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30442723.
132. Heine A, Brossart P, Wolf D. Ruxolitinib is a potent immunosuppressive compound: is it time for anti-infective prophylaxis? Blood 2013;122:3843-3844. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24288410.
133. Wysham NG, Sullivan DR, Allada G. An opportunistic infection associated with ruxolitinib, a novel janus kinase 1,2 inhibitor. Chest 2013;143:1478-1479. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23648912.
134. Blechman AB, Cabell CE, Weinberger CH, et al. Aggressive skin cancers occurring in patients treated with the janus kinase inhibitor ruxolitinib. J Drugs Dermatol 2017;16:508-511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28628689.
135. Palandri F, Derenzini E, Ottaviani E, et al. Association of essential thrombocythemia and non-Hodgkin lymphoma: A single-centre experience. Leuk Lymphoma 2009;50:481-484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19241208.
136. Vannucchi AM, Masala G, Antonioli E, et al. Increased risk of lymphoid neoplasms in patients with Philadelphia chromosome-negative myeloproliferative neoplasms. Cancer Epidemiol Biomarkers Prev 2009;18:2068-2073. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19531676.

137. Rumi E, Passamonti F, Elena C, et al. Increased risk of lymphoid neoplasm in patients with myeloproliferative neoplasm: A study of 1,915 patients. Haematologica 2011;96:454-458. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21109692.
138. Masarova L, Newberry KJ, Pierce SA, et al. Association of lymphoid malignancies and Philadelphia-chromosome negative myeloproliferative neoplasms: Clinical characteristics, therapy and outcome. Leuk Res 2015;39:822-827. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26012362.
139. Porpaczy E, Tripolt S, Hoelbl-Kovacic A, et al. Aggressive B-cell lymphomas in patients with myelofibrosis receiving JAK1/2 inhibitor therapy. Blood 2018;132:694-706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29907599.
140. Pemmaraju N, Kantarjian H, Nastoupil L, et al. Characteristics of patients with myeloproliferative neoplasms with lymphoma, with or without JAK inhibitor therapy. Blood 2019;133:2348-2351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30796023.
141. Rumi E, Zibellini S, Boveri E, et al. Ruxolitinib treatment and risk of Bcell lymphomas in myeloproliferative neoplasms. Am J Hematol 2019;94:E185-E188. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30972817.
142. Barbui T, Ghirardi A, Masciulli A, et al. Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study. Leukemia 2019;33:1996-2005. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31142846.
143. Polverelli N, Elli EM, Abruzzese E, et al. Second primary malignancy in myelofibrosis patients treated with ruxolitinib. Br J Haematol 2021;193:356-368. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33222197.
144. Guglielmelli P, Biamonte F, Rotunno G, et al. Impact of mutational status on outcomes in myelofibrosis patients treated with ruxolitinib in the COMFORT-II study. Blood 2014;123:2157-2160. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24458439.
145. Pacilli A, Rotunno G, Mannarelli C, et al. Mutation landscape in patients with myelofibrosis receiving ruxolitinib or hydroxyurea. Blood Cancer J 2018;8:122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30467377.
146. Patel KP, Newberry KJ, Luthra R, et al. Correlation of mutation profile and response in patients with myelofibrosis treated with ruxolitinib. Blood 2015;126:790-797. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26124496.
147. Maffioli M, Mora B, Ball S, et al. A prognostic model to predict survival after 6 months of ruxolitinib in patients with myelofibrosis. Blood Adv 2022;6:1855-1864. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35130339.
148. Harrison C, Kiladjian JJ, Verstovsek S, et al. Overall and progressionfree survival in patients treated with fedratinib as first-line myelofibrosis (MF) therapy and after prior ruxolitinib (RUX): Results from the JAKARTA and JAKARTA2 trials [abstract]. EHA Congress 2021:Abstract S203. Available at: https://library.ehaweb.org/eha/2021/eha2021-virtualcongress/ 324611/.
149. Harrison CN, Schaap N, Vannucchi AM, et al. Safety and efficacy of fedratinib, a selective oral inhibitor of Janus kinase-2 (JAK2), in patients with myelofibrosis and low pretreatment platelet counts. Br J Haematol 2022;198:317-327. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35476316.
150. Harrison CN, Schaap N, Vannucchi AM, et al. Fedratinib in patients with myelofibrosis previously treated with ruxolitinib: An updated analysis of the JAKARTA2 study using stringent criteria for ruxolitinib failure. Am J Hematol 2020;95:594-603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32129512.
151. Tremblay D, Cavalli L, Sy O, et al. The effect of fedratinib, a selective inhibitor of janus kinase 2, on weight and metabolic parameters in patients with intermediate- or high-risk myelofibrosis. Clin Lymphoma Myeloma Leuk 2022;22:e463-e466. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35120852.
152. Vainchenker W, Leroy E, Gilles L, et al. JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders. F1000Res 2018;7:82. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29399328.
153. Tefferi A. JAK inhibitors for myeloproliferative neoplasms: Clarifying facts from myths. Blood 2012;119:2721-2730. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22279053.
154. Pardanani A, Harrison C, Cortes JE, et al. Safety and efficacy of fedratinib in patients with primary or secondary myelofibrosis: A randomized clinical trial. JAMA Oncol 2015;1:643-651. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26181658.
155. Gupta V, Yacoub A, Mesa RA, et al. Safety and efficacy of fedratinib in patients with myelofibrosis previously treated with ruxolitinib: Primary analysis of FREEDOM trial. Leuk Lymphoma 2024:1-11. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38838026.
156. Harrison CN, Mesa RA, Jamieson C, et al. Case series of potential wernicke's encephalopathy in patients treated with fedratinib [abstract]. Blood 2017;130:Abstract 4197. Available at: http://www.bloodjournal.org/content/130/Suppl_1/4197.abstract.

157. National Organization for Rare Disorders. Wernicke-Korsakoff Syndrome. 2021. Available at: https://rarediseases.org/rarediseases/ wernicke-korsakoff-syndrome/. Accessed June 6, 2022.
158. Gerds AT, Savona MR, Scott BL, et al. Determining the recommended dose of pacritinib: results from the PAC203 dose-finding trial in advanced myelofibrosis. Blood Adv 2020;4:5825-5835. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33232476.
159. Mesa RA, Kiladjian JJ, Catalano JV, et al. SIMPLIFY-1: A phase III randomized trial of momelotinib versus ruxolitinib in janus kinase inhibitornaive patients with myelofibrosis. J Clin Oncol 2017;35:3844-3850. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28930494.
160. Harrison CN, Vannucchi AM, Platzbecker U, et al. Momelotinib versus best available therapy in patients with myelofibrosis previously treated with ruxolitinib (SIMPLIFY 2): a randomised, open-label, phase 3 trial. Lancet Haematol 2018;5:e73-e81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29275119.
161. Mesa R, Harrison C, Oh ST, et al. Overall survival in the SIMPLIFY-1 and SIMPLIFY-2 phase 3 trials of momelotinib in patients with myelofibrosis. Leukemia 2022;36:2261-2268. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35869266.
162. Hudgens S, Verstovsek S, Floden L, et al. Meaningful symptomatic change in patients with myelofibrosis from the SIMPLIFY studies. Value Health 2024;27:607-613. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38311180.
163. McLornan D, Szydlo R, Koster L, et al. Myeloablative and reduced intensity conditioned allogeneic hematopoietic stem cell transplantation in myelofibrosis: A retrospective study by the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant 2019;25:2167-2171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31284069.
164. Snyder DS, Palmer J, Stein AS, et al. Allogeneic hematopoietic cell transplantation following reduced intensity conditioning for treatment of myelofibrosis. Biol Blood Marrow Transplant 2006;12:1161-1168. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17085309.
165. Kroger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: A prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Blood 2009;114:5264-5270. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19812383.
166. Patriarca F, Bacigalupo A, Sperotto A, et al. Outcome of allogeneic stem cell transplantation following reduced-intensity conditioning regimen in patients with idiopathic myelofibrosis: The G.I.T.M.O. Experience. Mediterr J Hematol Infect Dis 2010;2:e2010010. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21415963.
167. Snyder DS, Palmer J, Gaal K, et al. Improved outcomes using tacrolimus/sirolimus for graft-versus-host disease prophylaxis with a reduced-intensity conditioning regimen for allogeneic hematopoietic cell transplant as treatment of myelofibrosis. Biol Blood Marrow Transplant 2010;16:281-286. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19786111.
168. Gupta V, Malone AK, Hari PN, et al. Reduced-intensity hematopoietic cell transplantation for patients with primary myelofibrosis: A cohort analysis from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant 2014;20:89-97. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24161923.
169. Lussana F, Rambaldi A, Finazzi MC, et al. Allogeneic hematopoietic stem cell transplantation in patients with polycythemia vera or essential thrombocythemia transformed to myelofibrosis or acute myeloid leukemia: A report from the MPN Subcommittee of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation. Haematologica 2014;99:916-921. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24389309.
170. Rondelli D, Goldberg JD, Isola L, et al. MPD-RC 101 prospective study of reduced-intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. Blood 2014;124:1183-1191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24963042.
171. Robin M, Porcher R, Wolschke C, et al. Outcome after transplantation according to reduced-intensity conditioning regimen in patients undergoing transplantation for myelofibrosis. Biol Blood Marrow Transplant 2016;22:1206-1211. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26970380.
172. Jain T, Kunze KL, Temkit M, et al. Comparison of reduced intensity conditioning regimens used in patients undergoing hematopoietic stem cell transplantation for myelofibrosis. Bone Marrow Transplant 2019;54:204- 211. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29795431.
173. Rezvani AR, McCune JS, Storer BE, et al. Cyclophosphamide followed by intravenous targeted busulfan for allogeneic hematopoietic cell transplantation: Pharmacokinetics and clinical outcomes. Biol Blood Marrow Transplant 2013;19:1033-1039. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23583825.
174. Salit RB, Scott BL, Stevens EA, et al. Pre-hematopoietic cell transplant Ruxolitinib in patients with primary and secondary myelofibrosis. Bone Marrow Transplant 2020;55:70-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30962501.
175. Deeg HJ, Bredeson C, Farnia S, et al. Hematopoietic cell transplantation as curative therapy for patients with myelofibrosis: Longterm success in all age groups. Biol Blood Marrow Transplant

2015;21:1883-1887. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26371371.
176. Ballen KK, Shrestha S, Sobocinski KA, et al. Outcome of transplantation for myelofibrosis. Biol Blood Marrow Transplant 2010;16:358-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19879949.
177. Robin M, de Wreede LC, Wolschke C, et al. Long-term outcome after allogeneic hematopoietic cell transplantation for myelofibrosis. Haematologica 2019;104:1782-1788. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30733269.
178. Hernandez-Boluda JC, Pereira A, Kroger N, et al. Determinants of survival in myelofibrosis patients undergoing allogeneic hematopoietic cell transplantation. Leukemia 2021;35:215-224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32286544.
179. Kunte S, Rybicki L, Viswabandya A, et al. Allogeneic blood or marrow transplantation with haploidentical donor and post-transplantation cyclophosphamide in patients with myelofibrosis: A multicenter study. Leukemia 2022;36:856-864. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34663912.
180. Jain T, Tsai HL, DeZern AE, et al. Post-transplantation cyclophosphamide-based graft- versus-host disease prophylaxis with nonmyeloablative conditioning for blood or marrow transplantation for myelofibrosis. Transplant Cell Ther 2022;28:259.e251-259.e211. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35158092.
181. Polverelli N, Mauff K, Kroger N, et al. Impact of spleen size and splenectomy on outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis: A retrospective analysis by the chronic malignancies working party on behalf of European society for blood and marrow transplantation (EBMT). Am J Hematol 2021;96:69-79. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33064301.
182. Scott BL, Gooley TA, Sorror ML, et al. The Dynamic International Prognostic Scoring System for myelofibrosis predicts outcomes after hematopoietic cell transplantation. Blood 2012;119:2657-2664. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22234678.
183. Alchalby H, Yunus DR, Zabelina T, et al. Risk models predicting survival after reduced-intensity transplantation for myelofibrosis. Br J Haematol 2012;157:75-85. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22280409.
184. Kroger N, Giorgino T, Scott BL, et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. Blood 2015;125:3347-3350. Available at: http://www.ncbi.nlm.nih.gov/pubmed/25784679.
185. Gowin K, Ballen K, Ahn KW, et al. Survival following allogeneic transplant in patients with myelofibrosis. Blood Adv 2020;4:1965-1973. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32384540.
186. Hernandez-Boluda JC, Pereira A, Correa JG, et al. Prognostic risk models for transplant decision-making in myelofibrosis. Ann Hematol 2018;97:813-820. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29396714.
187. Gagelmann N, Ditschkowski M, Bogdanov R, et al. Comprehensive clinical-molecular transplant scoring system for myelofibrosis undergoing stem cell transplantation. Blood 2019;133:2233-2242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30760453.
188. Hernandez-Boluda JC, Pereira A, Alvarez-Larran A, et al. Predicting survival after allogeneic hematopoietic cell transplantation in myelofibrosis: Performance of the myelofibrosis transplant scoring system (MTSS) and development of a new prognostic model. Biol Blood Marrow Transplant 2020;26:2237-2244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32717433.
189. Panagiota V, Thol F, Markus B, et al. Prognostic effect of calreticulin mutations in patients with myelofibrosis after allogeneic hematopoietic stem cell transplantation. Leukemia 2014;28:1552-1555. Available at: http://www.ncbi.nlm.nih.gov/pubmed/24504025.
190. Kroger N, Panagiota V, Badbaran A, et al. Impact of molecular genetics on outcome in myelofibrosis patients after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2017;23:1095-1101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28389256.
191. Tamari R, Rapaport F, Zhang N, et al. Impact of high-molecular-risk mutations on transplantation outcomes in patients with myelofibrosis. Biol Blood Marrow Transplant 2019;25:1142-1151. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30625392.
192. Ali H, Aldoss I, Yang D, et al. MIPSS70+ v2.0 predicts long-term survival in myelofibrosis after allogeneic HCT with the Flu/Mel conditioning regimen. Blood Adv 2019;3:83-95. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30622146.
193. Mannina D, Gagelmann N, Badbaran A, et al. Allogeneic stem cell transplantation in patients with myelofibrosis harboring the MPL mutation. Eur J Haematol 2019;103:552-557. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31446640.
194. Stevens EA, Jenkins IC, Beppu LW, et al. Targeted sequencing improves DIPSS-Plus prognostic scoring in myelofibrosis patients undergoing allogeneic transplantation. Biol Blood Marrow Transplant 2020;26:1371-1374. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32194289.
195. Martinez-Trillos A, Gaya A, Maffioli M, et al. Efficacy and tolerability of hydroxyurea in the treatment of the hyperproliferative manifestations of myelofibrosis: Results in 40 patients. Ann Hematol 2010;89:1233-1237. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20567824.

196. Kroger NM, Deeg JH, Olavarria E, et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: A consensus process by an EBMT/ELN international working group. Leukemia 2015;29:2126-2133. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26293647.
197. Masarova L, Verstovsek S, Hidalgo-Lopez JE, et al. A phase 2 study of ruxolitinib in combination with azacitidine in patients with myelofibrosis. Blood 2018;132:1664-1674. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30185431.
198. Chhabra S, Narra RK, Wu R, et al. Fludarabine/busulfan conditioning-based allogeneic hematopoietic cell transplantation for myelofibrosis: Role of ruxolitinib in improving survival outcomes. Biol Blood Marrow Transplant 2020;26:893-901. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31982543.
199. Shanavas M, Popat U, Michaelis LC, et al. Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibrosis with prior exposure to janus kinase 1/2 inhibitors. Biol Blood Marrow Transplant 2016;22:432-440. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26493563.
200. Gupta V, Kosiorek HE, Mead A, et al. Ruxolitinib therapy followed by reduced-intensity conditioning for hematopoietic cell transplantation for myelofibrosis: Myeloproliferative Disorders Research Consortium 114 Study. Biol Blood Marrow Transplant 2019;25:256-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30205231.
201. Kroger N, Bacigalupo A, Barbui T, et al. Indication and management of allogeneic haematopoietic stem-cell transplantation in myelofibrosis: Updated recommendations by the EBMT/ELN International Working Group. Lancet Haematol 2024;11:e62-e74. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38061384.
202. Polverelli N, Hernandez-Boluda JC, Czerw T, et al. Splenomegaly in patients with primary or secondary myelofibrosis who are candidates for allogeneic hematopoietic cell transplantation: A position paper on behalf of the Chronic Malignancies Working Party of the EBMT. Lancet Haematol 2023;10:e59-e70. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36493799.
203. Kroger N, Sbianchi G, Sirait T, et al. Impact of prior JAK-inhibitor therapy with ruxolitinib on outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis: A study of the CMWP of EBMT. Leukemia 2021;35:3551-3560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34023851.
204. Hernandez-Boluda JC, Correa JG, Alvarez-Larran A, et al. Clinical characteristics, prognosis and treatment of myelofibrosis patients with severe thrombocytopenia. Br J Haematol 2018;181:397-400. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28419426.
205. Scotch AH, Kosiorek H, Scherber R, et al. Symptom burden profile in myelofibrosis patients with thrombocytopenia: Lessons and unmet needs. Leuk Res 2017;63:34-40. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29096334.
206. Tefferi A, Lasho TL, Jimma T, et al. One thousand patients with primary myelofibrosis: the mayo clinic experience. Mayo Clin Proc 2012;87:25-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22212965.
207. Fenaux P, Kiladjian JJ, Platzbecker U. Luspatercept for the treatment of anemia in myelodysplastic syndromes and primary myelofibrosis. Blood 2019;133:790-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30602619.
208. Gerds AT, Harrison CN, Kiladjian JJ, et al. Safety and efficacy of luspatercept for the treatment of anemia in patients with myelofibrosis. Blood Adv 2024. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38820422.
209. Cervantes F, Alvarez-Larran A, Hernandez-Boluda JC, et al. Erythropoietin treatment of the anaemia of myelofibrosis with myeloid metaplasia: results in 20 patients and review of the literature. Br J Haematol 2004;127:399-403. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15521916.
210. Cervantes F, Alvarez-Larran A, Hernandez-Boluda JC, et al. Darbepoetin-alpha for the anaemia of myelofibrosis with myeloid metaplasia. Br J Haematol 2006;134:184-186. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16740139.
211. Tsiara SN, Chaidos A, Bourantas LK, et al. Recombinant human erythropoietin for the treatment of anaemia in patients with chronic idiopathic myelofibrosis. Acta Haematol 2007;117:156-161. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17159338.
212. Cervantes F, Isola IM, Alvarez-Larran A, et al. Danazol therapy for the anemia of myelofibrosis: Assessment of efficacy with current criteria of response and long-term results. Ann Hematol 2015;94:1791-1796. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26122869.
213. Gupta V, Oh S, Devos T, et al. Momelotinib vs. ruxolitinib in myelofibrosis patient subgroups by baseline hemoglobin levels in the SIMPLIFY-1 trial. Leuk Lymphoma 2024;65:965-977. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38501751.
214. Barosi G, Elliott M, Canepa L, et al. Thalidomide in myelofibrosis with myeloid metaplasia: a pooled-analysis of individual patient data from five studies. Leuk Lymphoma 2002;43:2301-2307. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12613516.
215. Elliott MA, Mesa RA, Li CY, et al. Thalidomide treatment in myelofibrosis with myeloid metaplasia. Br J Haematol 2002;117:288-296. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11972510.
216. Merup M, Kutti J, Birgergard G, et al. Negligible clinical effects of thalidomide in patients with myelofibrosis with myeloid metaplasia. Med Oncol 2002;19:79-86. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/12180484.
217. Marchetti M, Barosi G, Balestri F, et al. Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: A phase II trial. J Clin Oncol 2004;22:424-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14752066.
218. Strupp C, Germing U, Scherer A, et al. Thalidomide for the treatment of idiopathic myelofibrosis. Eur J Haematol 2004;72:52-57. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14962263.
219. Thomas DA, Giles FJ, Albitar M, et al. Thalidomide therapy for myelofibrosis with myeloid metaplasia. Cancer 2006;106:1974-1984. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16583431.
220. Abgrall JF, Guibaud I, Bastie JN, et al. Thalidomide versus placebo in myeloid metaplasia with myelofibrosis: A prospective, randomized, doubleblind, multicenter study. Haematologica 2006;91:1027-1032. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16885042.
221. Mesa RA, Steensma DP, Pardanani A, et al. A phase 2 trial of combination low-dose thalidomide and prednisone for the treatment of myelofibrosis with myeloid metaplasia. Blood 2003;101:2534-2541. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12517815.
222. Tefferi A, Cortes J, Verstovsek S, et al. Lenalidomide therapy in myelofibrosis with myeloid metaplasia. Blood 2006;108:1158-1164. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16609064.
223. Quintas-Cardama A, Kantarjian HM, Manshouri T, et al. Lenalidomide plus prednisone results in durable clinical, histopathologic, and molecular responses in patients with myelofibrosis. J Clin Oncol 2009;27:4760-4766. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19720904.
224. Mesa RA, Yao X, Cripe LD, et al. Lenalidomide and prednisone for myelofibrosis: Eastern Cooperative Oncology Group (ECOG) phase 2 trial E4903. Blood 2010;116:4436-4438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20651074.
225. Chihara D, Masarova L, Newberry KJ, et al. Long-term results of a phase II trial of lenalidomide plus prednisone therapy for patients with myelofibrosis. Leuk Res 2016;48:1-5. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27416326.
226. Santana-Davila R, Tefferi A, Holtan SG, et al. Primary myelofibrosis is the most frequent myeloproliferative neoplasm associated with del(5q): Clinicopathologic comparison of del(5q)-positive and -negative cases. Leuk Res 2008;32:1927-1930. Available at: https://pubmed.ncbi.nlm.nih.gov/18538839/.
227. Jabbour E, Thomas D, Kantarjian H, et al. Comparison of thalidomide and lenalidomide as therapy for myelofibrosis. Blood 2011;118:899-902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21622644.
228. Schlenk RF, Stegelmann F, Reiter A, et al. Pomalidomide in myeloproliferative neoplasm-associated myelofibrosis. Leukemia 2017;31:889-895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27774990.
229. Tefferi A, Al-Ali HK, Barosi G, et al. A randomized study of pomalidomide vs placebo in persons with myeloproliferative neoplasmassociated myelofibrosis and RBC-transfusion dependence. Leukemia 2017;31:896-902. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27773929.
230. Rampal RK, Verstovsek S, Devlin SM, et al. Safety and efficacy of combined ruxolitinib and thalidomide in patients with myelofibrosis: A phase II study [abstract]. Blood 2019;134:Abstract 4163. Available at: https://ashpublications.org/blood/article/134/Supplement_1/4163/425729/Safety-and-Efficacy-of-Combined-Ruxolitinib-and.
231. Stegelmann F, Jahn E, Koschmieder S, et al. Clinical and genetic results of the phase IB/II trial MPNSG-0212: Ruxolitinib plus pomalidomide in myelofibrosis with anemia [abstract]. HemaSphere 2022;6:945-946. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9429480/.
232. Daver N, Cortes J, Newberry K, et al. Ruxolitinib in combination with lenalidomide as therapy for patients with myelofibrosis. Haematologica 2015;100:1058-1063. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26088933.
233. McMullin MF, Harrison CN, Niederwieser D, et al. The use of erythropoiesis-stimulating agents with ruxolitinib in patients with myelofibrosis in COMFORT-II: An open-label, phase 3 study assessing efficacy and safety of ruxolitinib versus best available therapy in the treatment of myelofibrosis. Exp Hematol Oncol 2015;4:26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26380150.
234. Crisa E, Cilloni D, Elli EM, et al. The use of erythropoiesis-stimulating agents is safe and effective in the management of anaemia in myelofibrosis patients treated with ruxolitinib. Br J Haematol 2018;182:701-704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29984826.
235. Huang J, Tefferi A. Erythropoiesis stimulating agents have limited therapeutic activity in transfusion-dependent patients with primary myelofibrosis regardless of serum erythropoietin level. Eur J Haematol 2009;83:154-155. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19366369.
236. Tefferi A, Barosi G, Mesa RA, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). Blood 2006;108:1497-1503. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16675707.
237. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. Blood 2013;122:1395-1398. Available at:

http://www.ncbi.nlm.nih.gov/pubmed/23838352.
238. Tefferi A, Pardanani A. Serious adverse events during ruxolitinib treatment discontinuation in patients with myelofibrosis. Mayo Clin Proc 2011;86:1188-1191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22034658.
239. Newberry KJ, Patel K, Masarova L, et al. Clonal evolution and outcomes in myelofibrosis after ruxolitinib discontinuation. Blood 2017;130:1125-1131. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28674026.
240. Mascarenhas J, Mehra M, He J, et al. Patient characteristics and outcomes after ruxolitinib discontinuation in patients with myelofibrosis. J Med Econ 2020;23:721-727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32159402.
241. Pardanani A, Gotlib JR, Jamieson C, et al. Safety and efficacy of TG101348, a selective JAK2 inhibitor, in myelofibrosis. J Clin Oncol 2011;29:789-796. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21220608.
242. Deininger M, Radich J, Burn TC, et al. The effect of long-term ruxolitinib treatment on JAK2p.V617F allele burden in patients with myelofibrosis. Blood 2015;126:1551-1554. Available at: http://www.ncbi.nlm.nih.gov/pubmed/26228487.
243. Alchalby H, Badbaran A, Zabelina T, et al. Impact of JAK2V617F mutation status, allele burden, and clearance after allogeneic stem cell transplantation for myelofibrosis. Blood 2010;116:3572-3581. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20489052.
244. Lange T, Edelmann A, Siebolts U, et al. JAK2 p.V617F allele burden in myeloproliferative neoplasms one month after allogeneic stem cell transplantation significantly predicts outcome and risk of relapse. Haematologica 2013;98:722-728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23300178.
245. Cervantes F. How I treat myelofibrosis. Blood 2014;124:2635-2642. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25232060.
246. Kaur A, Wang S, Jayarangaiah A, et al. Real world risk of splenic rupture with G-CSF/GM-CSF therapy: A pharmacovigilance assessment using FDA Adverse Event Reporting System (FAERS) database [abstract]. Blood 2020;136:32-33. Available at: https://ashpublications.org/blood/article/136/Supplement%201/32/473386/Real-World-Risk-of-Splenic-Rupture-with-G-CSF-GM.
247. Landolfi R, Di Gennaro L, Barbui T, et al. Leukocytosis as a major thrombotic risk factor in patients with polycythemia vera. Blood 2007;109:2446-2452. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17105814.
248. Gangat N, Wolanskyj AP, Schwager SM, et al. Leukocytosis at diagnosis and the risk of subsequent thrombosis in patients with low-risk essential thrombocythemia and polycythemia vera. Cancer 2009;115:5740-5745. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19806641.
249. Carobbio A, Finazzi G, Antonioli E, et al. Thrombocytosis and leukocytosis interaction in vascular complications of essential thrombocythemia. Blood 2008;112:3135-3137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18587010.
250. Carobbio A, Thiele J, Passamonti F, et al. Risk factors for arterial and venous thrombosis in WHO-defined essential thrombocythemia: an international study of 891 patients. Blood 2011;117:5857-5859. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21490340.
251. Campbell PJ, MacLean C, Beer PA, et al. Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort. Blood 2012;120:1409-1411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22709688.
252. Carobbio A, Ferrari A, Masciulli A, et al. Leukocytosis and thrombosis in essential thrombocythemia and polycythemia vera: a systematic review and meta-analysis. Blood Adv 2019;3:1729-1737. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31175128.
253. De Stefano V, Za T, Rossi E, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica 2008;93:372-380. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18268279.
254. De Stefano V, Za T, Rossi E, et al. Leukocytosis is a risk factor for recurrent arterial thrombosis in young patients with polycythemia vera and essential thrombocythemia. Am J Hematol 2010;85:97-100. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20052743.
255. Pasquer H, Daltro de Oliveira R, Vasseur L, et al. Distinct clinicomolecular arterial and venous thrombosis scores for myeloproliferative neoplasms risk stratification. Leukemia 2024;38:326-339. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38148396.
256. Marchioli R, Finazzi G, Landolfi R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol 2005;23:2224-2232. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15710945.
257. Passamonti F, Caramazza D, Mora B, et al. It is time to change thrombosis risk assessment for PV and ET? Best Pract Res Clin Haematol 2014;27:121-127. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25189723.

258. Cervantes F, Passamonti F, Barosi G. Life expectancy and prognostic factors in the classic BCR/ABL-negative myeloproliferative disorders. Leukemia 2008;22:905-914. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18385755.
259. Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera. Br J Haematol 2020;189:291-302. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31945802.
260. Passamonti F, Thiele J, Girodon F, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: A study by the International Working Group on Myelofibrosis Research and Treatment. Blood 2012;120:1197-1201.
Available at: https://www.ncbi.nlm.nih.gov/pubmed/22740446.
261. Barbui T, Finazzi G, Carobbio A, et al. Development and validation of an International Prognostic Score of thrombosis in World Health Organization-essential thrombocythemia (IPSET-thrombosis). Blood 2012;120:5128-5133. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23033268.
262. Barbui T, Vannucchi AM, Buxhofer-Ausch V, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer J 2015;5:e369. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26617062.
263. Haider M, Gangat N, Lasho T, et al. Validation of the revised International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) in 585 Mayo Clinic patients. Am J Hematol 2016;91:390-394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26799697.
264. Landolfi R, Marchioli R, Kutti J, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med 2004;350:114-124. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14711910.
265. Marchioli R, Finazzi G, Specchia G, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med 2013;368:22-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23216616.
266. Alvarez-Larran A, Cervantes F, Pereira A, et al. Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. Blood 2010;116:1205-1210. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20508163.
267. Alvarez-Larran A, Pereira A, Guglielmelli P, et al. Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. Haematologica 2016;101:926-931. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27175028.
268. Kaplan ME, Mack K, Goldberg JD, et al. Long-term management of polycythemia vera with hydroxyurea: a progress report. Semin Hematol 1986;23:167-171. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3749925.
269. Kiladjian JJ, Chevret S, Dosquet C, et al. Treatment of polycythemia vera with hydroxyurea and pipobroman: Final results of a randomized trial initiated in 1980. J Clin Oncol 2011;29:3907-3913. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21911721.
270. Samuelsson J, Hasselbalch H, Bruserud O, et al. A phase II trial of pegylated interferon alpha-2b therapy for polycythemia vera and essential thrombocythemia: feasibility, clinical and biologic effects, and impact on quality of life. Cancer 2006;106:2397-2405. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16639737.
271. Kiladjian JJ, Cassinat B, Chevret S, et al. Pegylated interferon-alfa-2a induces complete hematologic and molecular responses with low toxicity in polycythemia vera. Blood 2008;112:3065-3072. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18650451.
272. Quintas-Cardama A, Abdel-Wahab O, Manshouri T, et al. Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon alpha-2a. Blood 2013;122:893-901. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23782935.
273. Masarova L, Patel KP, Newberry KJ, et al. Pegylated interferon alfa- 2a in patients with essential thrombocythaemia or polycythaemia vera: a post-hoc, median 83 month follow-up of an open-label, phase 2 trial. Lancet Haematol 2017;4:e165-e175. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28291640.
274. Gisslinger H, Klade C, Georgiev P, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): A randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol 2020;7:e196-e208. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32014125.
275. Barbui T, Vannucchi AM, De Stefano V, et al. Ropeginterferon versus standard therapy for low-risk patients with polycythemia vera. NEJM Evid 2023;2:EVIDoa2200335. Available at: https://www.ncbi.nlm.nih.gov/pubmed/38320126.
276. Fruchtman SM, Mack K, Kaplan ME, et al. From efficacy to safety: a Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. Semin Hematol 1997;34:17-23. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9025158.
277. Finazzi G, Caruso V, Marchioli R, et al. Acute leukemia in polycythemia vera: an analysis of 1638 patients enrolled in a prospective observational study. Blood 2005;105:2664-2670. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/15585653.
278. Mascarenhas J, Kosiorek HE, Prchal JT, et al. A randomized phase 3 trial of interferon-α vs hydroxyurea in polycythemia vera and essential thrombocythemia. Blood 2022;139:2931-2941. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35007321.
279. Cortelazzo S, Finazzi G, Ruggeri M, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med 1995;332:1132-1136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7700286.
280. Harrison CN, Campbell PJ, Buck G, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med 2005;353:33-45. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16000354.
281. Gisslinger H, Gotic M, Holowiecki J, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: The ANAHYDRET study, a randomized controlled trial. Blood 2013;121:1720-1728. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23315161.
282. Kanakura Y, Shirasugi Y, Yamaguchi H, et al. A phase 3b, multicenter, open-label extension study of the long-term safety of anagrelide in Japanese adults with essential thrombocythemia. Int J Hematol 2018;108:491-498. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30121892.
283. Kellner A, Dombi P, Illes A, et al. Anagrelide influences thrombotic risk, and prolongs progression-free and overall survival in essential thrombocythaemia vs hydroxyurea plus aspirin. Eur J Haematol 2020;105:408-418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32557810.
284. Yacoub A, Mascarenhas J, Kosiorek H, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. Blood 2019;134:1498-1509. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31515250.
285. Kiladjian JJ, Klade C, Georgiev P, et al. Long-term outcomes of polycythemia vera patients treated with ropeginterferon Alfa-2b. Leukemia 2022;36:1408-1411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35210530.
286. Gisslinger H, Klade C, Georgiev P, et al. Event-free survival in patients with polycythemia vera treated with ropeginterferon alfa-2b versus best available treatment. Leukemia 2023;37:2129-2132. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37634011.
287. Koschmieder S, Isfort S, Wolf D, et al. Efficacy and safety of ruxolitinib in patients with newly-diagnosed polycythemia vera: Futility analysis of the RuxoBEAT clinical trial of the GSG-MPN study group. Ann Hematol 2023;102:349-358. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36564535.
288. Verstovsek S, Vannucchi AM, Griesshammer M, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow-up from the RESPONSE trial. Haematologica 2016;101:821-829. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27102499.
289. Kiladjian JJ, Guglielmelli P, Griesshammer M, et al. Efficacy and safety of ruxolitinib after and versus interferon use in the RESPONSE studies. Ann Hematol 2018;97:617-627. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29396713.
290. Kiladjian JJ, Zachee P, Hino M, et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study. Lancet Haematol 2020;7:e226-e237. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31982039.
291. Passamonti F, Griesshammer M, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. Lancet Oncol 2017;18:88-99. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27916398.
292. Griesshammer M, Saydam G, Palandri F, et al. Ruxolitinib for the treatment of inadequately controlled polycythemia vera without splenomegaly: 80-week follow-up from the RESPONSE-2 trial. Ann Hematol 2018;97:1591-1600. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29804268.
293. Passamonti F, Palandri F, Saydam G, et al. Ruxolitinib versus best available therapy in inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): 5-year follow up of a randomised, phase 3b study. Lancet Haematol 2022;9:e480-e492. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35597252.
294. Mesa R, Vannucchi AM, Yacoub A, et al. The efficacy and safety of continued hydroxycarbamide therapy versus switching to ruxolitinib in patients with polycythaemia vera: a randomized, double-blind, doubledummy, symptom study (RELIEF). Br J Haematol 2017;176:76-85. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27858987.
295. Harrison CN, Nangalia J, Boucher R, et al. Ruxolitinib versus best available therapy for polycythemia vera intolerant or resistant to hydroxycarbamide in a randomized trial. J Clin Oncol 2023;41:3534-3544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37126762.
296. O'Sullivan JM, Hamblin A, Yap C, et al. The poor outcome in high molecular risk, hydroxycarbamide-resistant/intolerant ET is not ameliorated by ruxolitinib. Blood 2019;134:2107-2111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31578205.
297. Verstovsek S, Passamonti F, Rambaldi A, et al. Ruxolitinib for essential thrombocythemia refractory to or intolerant of hydroxyurea: longterm phase 2 study results. Blood 2017;130:1768-1771. Available at:

https://www.ncbi.nlm.nih.gov/pubmed/28827411.
298. Chu DK, Hillis CM, Leong DP, et al. Benefits and risks of antithrombotic therapy in essential thrombocythemia: a systematic review. Ann Intern Med 2017;167:170-180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28632284.
299. Godfrey AL, Campbell PJ, MacLean C, et al. Hydroxycarbamide plus aspirin versus aspirin alone in patients With essential thrombocythemia age 40 to 59 years without high-risk features. J Clin Oncol 2018;36:3361-3369. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30153096.
300. Dillinger JG, Sideris G, Henry P, et al. Twice daily aspirin to improve biological aspirin efficacy in patients with essential thrombocythemia. Thromb Res 2012;129:91-94. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22014557.
301. Pascale S, Petrucci G, Dragani A, et al. Aspirin-insensitive thromboxane biosynthesis in essential thrombocythemia is explained by accelerated renewal of the drug target. Blood 2012;119:3595-3603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22234683.
302. Rocca B, Tosetto A, Betti S, et al. A randomized double-blind trial of 3 aspirin regimens to optimize antiplatelet therapy in essential thrombocythemia. Blood 2020;136:171-182. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32266380.
303. Larsen ML, Pedersen OH, Hvas AM, et al. Once- versus twice-daily aspirin treatment in patients with essential thrombocytosis. Platelets 2019;30:322-328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29442537.
304. Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013;121:4778-4781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/23591792.

McLornan DP et al., 2024 [1].

British Society for Haematology

The management of myelofibrosis: A British Society for Haematology Guideline

Zielsetzung/Fragestellung

This document represents an update of the British Society for Haematology guideline on Myelofibrosis first published in 2012 and updated in 2015.1 These guidelines aim to provide healthcare professionals with clear guidance on stratified management for primary myelofibrosis (PMF), as well as postpolycythaemia myelofibrosis (post-PV MF) and postessential thrombocythaemia myelofibrosis (post-ET MF). A separate BSH guideline covers the diagnosis and prognostic evaluation of myelofibrosis and is published alongside this guideline.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz und aufgrund ihrer Aktualität, wird die LL jedoch ergänzend dargestellt.

* *British Society for Haematology Guidelines Committee – BSH Guidelines Process 2018 https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf*

Grundlage der Leitlinie

Update der Version von 2015 (Erstausgabe: 2012)

- Repräsentatives Gremium: **Unklar** – *The Task Force will discuss the composition of the writing group to ensure that all areas of the Guidance will be written by an appropriate expert and that relevant professional and patient bodies are represented or consulted during the scoping/writing/review process*.*
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Unklar** – *All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. All conflict of interest statements have been registered with the British Society of Haematology.*
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft teilweise zu** – Eine systematische Recherche wurde durchgeführt, aber Angaben zu den Auswahlkriterien und der kritischen Bewertung der Literatur fehlen (siehe Recherche/Suchzeitraum).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft teilweise zu** – Konsensusprozesse werden dargelegt, aber es gibt kein externes Begutachtungsverfahren.*
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft zu**
- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft zu** – *At each Task Force meeting members should consider whether any current guideline needs an update. Every three years all BSH Guidelines must have the literature search re-run as a check for new evidence. If there is no substantial new evidence the guideline should be approved by the task force and the BSH administrator should note this on the website*.*

Recherche/Suchzeitraum:

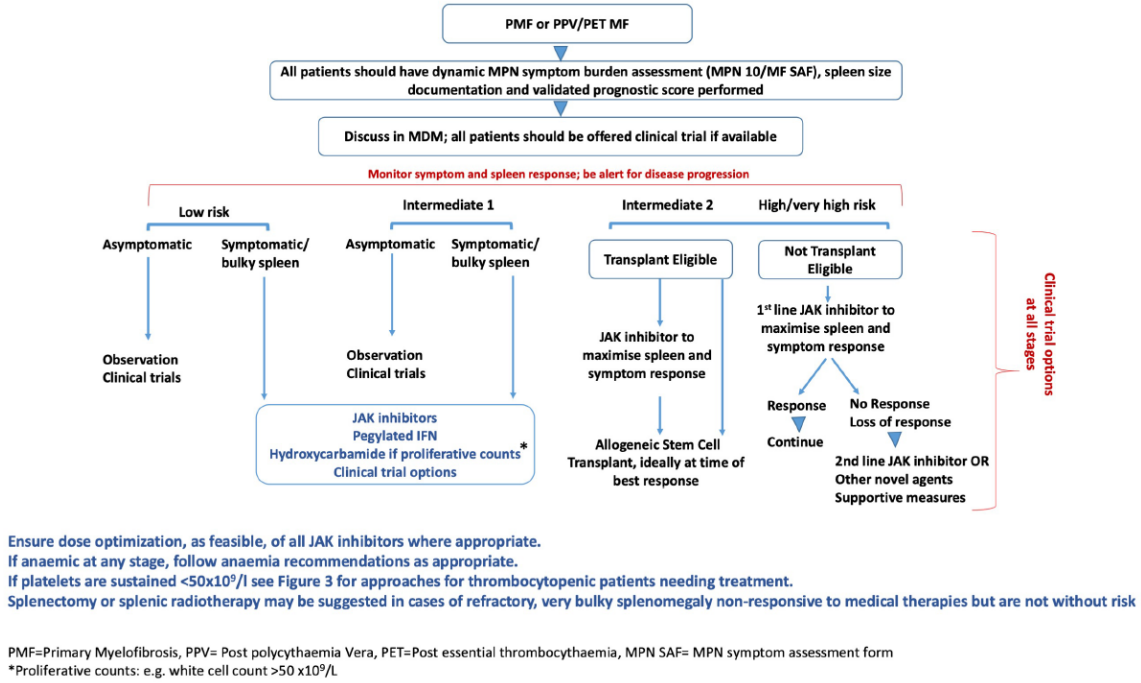
- Recommendations are based on a review of the relevant myelofibrosis-related literature using Medline, PubMed/Medline and Cochrane searches beginning from 2012 up to

mid-2022. Filters were applied to include only publications written in English, studies carried out in humans, clinical conferences, congresses, clinical trials, clinical studies, meta-analyses, multicentre studies and randomised controlled trials. Exclusion criteria included papers published in non-English journals and those publications without an abstract.

LoE/GoR

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and assess the strength of recommendations.

Empfehlungen



Ensure dose optimization, as feasible, of all JAK inhibitors where appropriate.
If anaemic at any stage, follow anaemia recommendations as appropriate.
If platelets are sustained <50x10^9/l see Figure 3 for approaches for thrombocytopenic patients needing treatment.
Splenectomy or splenic radiotherapy may be suggested in cases of refractory, very bulky splenomegaly non-responsive to medical therapies but are not without risk

PMF=Primary Myelofibrosis, PPV= Post polycythaemia Vera, PET=Post essential thrombocythaemia, MPN SAF= MPN symptom assessment form
*Proliferative counts: e.g. white cell count >50 x10^9/L

Empfehlung 1

- Ruxolitinib is indicated in the treatment of myelofibrosis-related splenomegaly or symptoms (Grade 1A).
- Ruxolitinib is associated with a potentially increased risk of opportunistic infections. Hepatitis B and C and HIV status should be assessed prior to commencement. Risk factors for mycobacterial infection and herpes zoster reactivation should be evaluated (Grade 1B).
- Individual consideration should be given to prophylactic strategies directed to herpes virus family reactivation (Grade 2C).
- Initial dosing is based upon the platelet count, and dosing should be regularly optimised by clinical assessment and blood count monitoring (Grade 1B).
- Assessment of response by objective symptom monitoring and spleen size assessment via palpation is recommended (Grade 1B).

- Ruxolitinib is associated with an increased risk of non-melanoma skin cancers. Consideration should be given to skin surveillance in selected high-risk patients (those with a previous history of skin cancer and those who have actinic keratosis) (Grade 2C).
- Ruxolitinib should not be stopped abruptly to avoid the possibility of a SIRS (Grade 1C).

Empfehlung 2

1. Fedratinib can be considered for patients with myelofibrosis for the treatment of disease-related splenomegaly or for those who are resistant to or intolerant of ruxolitinib (Grade 1B).
2. Blood thiamine levels should be measured prior to starting fedratinib and monitored during treatment, with replacement given if levels are lower than the local normal range. Pragmatic thiamine replacement is recommended if concerns exist (Grade 2B).
3. Care should be taken if patients transition from ruxolitinib to fedratinib to avoid a withdrawal reaction. Discuss transition from one agent to the other with a MPN specialist centre (Grade 2B).

Empfehlung 3

- Momelotinib is effective in the treatment of myelofibrosis-related splenomegaly or symptoms. In particular, we recommend consideration for those with myelofibrosis and anaemia, irrespective of being used in first, second or higher lines of therapy (Grade 2A).

Empfehlung 4

- Initial management of anaemia should address any deficiencies of iron, folate or vitamin B12 and/or autoimmune haemolysis (Grade 1B).
- A trial of erythropoiesis-stimulating agents (ESAs), including in combination with ruxolitinib, is recommended for patients with anaemia associated with inadequate erythropoietin levels (Grade 1B).
- A trial of danazol, with or without ruxolitinib, can be considered initially for a period of 6 months including in patients who have failed a trial of ESA (Grade 1C).
- For those failing ESA and/or danazol, a trial of immunomodulatory drugs (IMiDs; thalidomide, lenalidomide or pomalidomide) either alone or in combination with prednisolone may be merited, but access is difficult, response rates overall remain low and toxicity is not inconsiderable (Grade 2B).
- Transfusion may be required in the short term for symptomatic relief and while optimising other strategies. Once the above strategies have been exhausted or fail, the patient may become transfusion dependent (Grade 1B).
- Oral iron chelation should be considered in transfusion-dependent and/or iron-overloaded patients who are likely to be considered for allo-HSCT (Grade 2B).

Empfehlung 5

1. Splenic irradiation can be considered in symptomatic splenomegaly or splenic pain refractory to medical therapies in those not suitable for splenectomy (Grade 2C).
2. Regular haematological monitoring during and following the course is required due to the risk of significant cytopenia requiring blood product support (Grade 1C).

3. Dose and fractionation should depend on initial blood parameters and discussion with clinical oncology experts. A weekly or twice weekly low-dose regimen may result in less complications (Grade 1C).
4. Combination with agents such as JAK inhibitors remains experimental (Grade 2C).

Empfehlung 6

- In general, consideration of allo-HSCT in myelofibrosis should be in line with current EBMT-ELN guidelines (Grade 1B).
- All transplant-eligible patients should be discussed early with a transplant centre as regards suitability and donor options (Grade 1C).
- Pretransplant therapy with JAKi or enrolment in a suitable clinical trial to maximise spleen response is warranted prior to allo-HSCT in those with bulky splenomegaly (Grade 1C).
- For patients with iron overload, consideration should be given to iron chelation, if time permits (Grade 1C).
- For older patients or those with significant comorbidities, a RIC regimen is appropriate, whereas for fit, younger patients (<45 years) with good performance status, a non-TBI-based MAC regimen could be considered (Grade 1B).
- A variety of RIC regimens have demonstrated acceptable outcomes. Most commonly these are fludarabine and either busulphan or melphalan-based. T-cell depletion should preferentially be with ATG rather than with alemtuzumab (Grade 1B).
- Where possible, allo-HSCT should be performed at the time of best response to a JAK inhibitor (Grade 1C).
- Post-transplant measurable residual disease monitoring (MRD) is recommended. MRD monitoring can guide immunosuppressive therapy and use of adoptive immunotherapy with donor lymphocyte infusions where appropriate (Grade 1B).

Referenzen aus Leitlinien

1. Reilly JT, McMullin MF, Beer PA, Butt N, Conneally E, Duncombe AS, et al. Use of JAK inhibitors in the management of myelofibrosis: a revision of the British Committee for Standards in Haematology Guidelines for Investigation and management of myelofibrosis 2012. Br J Haematol. 2014;167(3):418–20.

Polverelli N et al., 2023 [4].

European society for Blood and Marrow Transplantation (EBMT)
Splenomegaly in patients with primary or secondary myelofibrosis who are candidates for allogeneic hematopoietic cell transplantation: a Position Paper on behalf of the Chronic Malignancies Working Party of the EBMT

Zielsetzung/Fragestellung

Currently, there are no standardised guidelines to assist transplantation physicians in deciding optimal management of splenomegaly before HCT. Therefore, the aim of this Position Paper is to offer a shared position statement on this issue.

Methodik

Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz und aufgrund ihrer Aktualität, wird die LL jedoch ergänzend dargestellt.

Grundlage der Leitlinie

- Repräsentatives Gremium: **Trifft teilweise zu** – *Haematologists, transplantation physicians, gastroenterologists, surgeons, radiotherapists, and radiology experts in the field of myelofibrosis*; es werden jedoch keine Patientenvertretung und keine Methodikberatung erwähnt.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **Trifft teilweise zu** – Interessenkonflikte werden angegeben, aber es fehlen Angaben zur Finanzierung/finanziellen Unabhängigkeit.
- Systematische Suche, Auswahl und Bewertung der Evidenz: **Trifft teilweise zu** – Eine systematische Recherche wurde durchgeführt, aber Angaben zu den Auswahlkriterien und zur kritischen Bewertung der eingeschlossenen Evidenz fehlen (siehe Recherche/Suchzeitraum).
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **Trifft teilweise zu** – Konsensusprozess werden beschrieben, aber es gibt kein externes Begutachtungsverfahren
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: **Trifft teilweise zu** – Es erfolgte keine Graduierung der Empfehlungen in der Leitlinie.
- Regelmäßige Überprüfung der Aktualität gesichert: **Trifft nicht zu** – Es werden keine Angaben zur Aktualisierung gemacht.

Recherche/Suchzeitraum:

- For this Position Paper, a comprehensive review of the scientific literature was performed with PubMed and EMBASE. Searches were performed monthly from Nov 1, 2021, to June 30, 2022, to collect the latest studies on this topic. The searched article dates spanned from January, 1975, to June, 2022, and only papers published in English were considered. The MESH search terms used were: “Primary Myelofibrosis”, “transplantation”, “spleen”, “splenomegaly”, “splenectomy”, “radiotherapy”, and “COVID-19”. The final reference list reflects the relevance to the scope of this Position Paper.

LoE

- GRADE

GoR

- k.A.

Medical management of splenomegaly

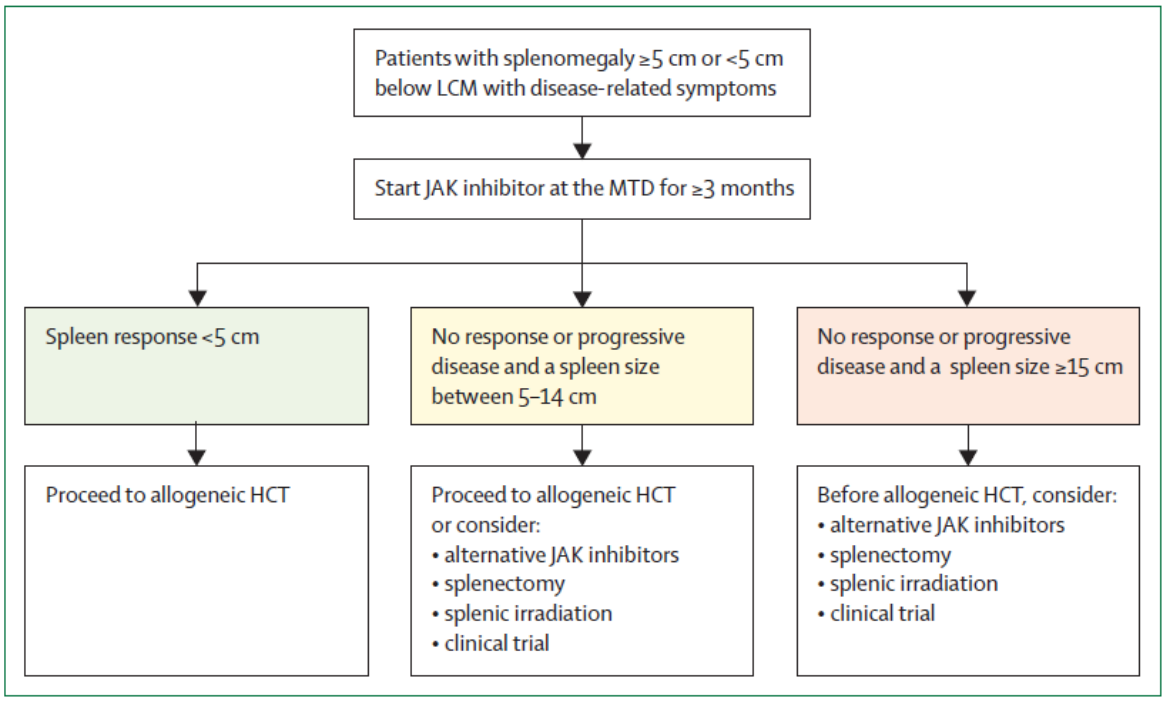


Figure 2: **Flowchart for managing myelofibrosis candidates for transplantation with splenomegaly**
HCT=haematopoietic cell transplantation. LCM=left costal margin. MTD=maximum tolerated dose.

JAK inhibitors

If available, patients with myelofibrosis and splenomegaly more than 5 cm below the LCM or with disease-related symptoms should receive JAK inhibitors rather than hydroxyurea, interferon, or immunomodulating drugs before allogeneic HCT to maximise spleen responses and improve performance status. Ruxolitinib could be the preferred first-line option based on more robust data available before HCT. However, in selected patients (ie, patients who are thrombocytopaenic or at high risk for infectious complications), alternative JAK inhibitors can be considered first. For example, in patients with splenomegaly or disease-related symptoms, in the presence of platelet count lower than 50 × 10^9 platelets per L, pacritinib could be used. Fedratinib might be preferred in thrombocytopaenic patients (ie, 50–100 × 10^9 platelets per L) where ruxolitinib-titrated dose is expected to be less effective.

Allogeneic HCT

The panel agreed to perform allogeneic HCT at the time of best splenic response to JAK inhibitors (ie, ideally with a spleen palpable less than 5 cm from the LCM), which has been associated with improvement of disease-related symptoms. 3 months of JAK inhibitor treatment can be sufficient to achieve a spleen response in patients who are naive to JAK inhibitors, but it is recommended that the spleen response be maximised whenever possible. Although relatively high frequency of haematological toxicity (in particular,

anaemia and thrombocytopenia) is seen with JAK inhibitor administration, the best splenic response should be prioritised before allogeneic HCT. Titration of JAK inhibitors to the maximum tolerated dose at the expense of short-term haematological toxicity is acceptable to reach the minimum splenomegaly in preparation for transplantation. For patients with suboptimal response (spleen >5 cm below the LCM), second-line options (eg, alternative JAK inhibitors, splenectomy, splenic irradiation, or experimental strategies) might be considered, as guided by the clinical scenario, patient fitness, and transplantation urgency, especially when spleen size exceeds 15 cm. A JAK inhibitor dose interruption attempted 3–5 days before or after the start of the conditioning regimen is suggested to avoid withdrawal syndrome. Corticosteroids or JAK inhibitor rechallenge can be used to reduce symptom rebound when needed. The continued use of JAK inhibitors during the peri-transplantation period until haematological recovery or as a post-transplantation maintenance strategy is of great interest, but remains investigational. Current evidence is too preliminary to recommend the routine use of novel compounds for the management of myelofibrosis-related splenomegaly in candidates for allogeneic HCT.

When medical treatment fails

Splenectomy

Splenectomy might be considered, with careful evaluation of the risk to benefit ratio, in candidates for allogeneic HCT who have myelofibrosis with splenic progression exceeding 15 cm below the LCM by palpation, despite medical treatment at the maximum tolerated dose. Vaccinations against encapsulated bacteria are required to be administered at least 2 weeks before a planned splenectomy. Cytoreductive treatment should be evaluated in a case-by-case method to reduce the incidence of post-surgery vascular events. Open splenectomy is still the preferred surgical modality but is clearly surgeon dependent and patient dependent.

Splenic irradiation

Splenic irradiation is an alternative option for managing non-responsive splenomegaly in allogeneic HCT myelofibrosis candidates with contraindications for surgery (eg, severe thrombocytopenia or high surgical risks). More information is necessary to recommend this strategy as a primary option in patients who did not respond to medical treatment, given the more robust data regarding splenectomy in this setting. Treatment schedules are variable, however, in the bridge to a transplantation setting, doses ranging from 2–3 Gy to 10 Gy seem to be effective with a positive risk to benefit ratio. The conditioning regimen should be started early after splenic irradiation, possibly within 30 days, to limit radiation-related haematological side-effects and to maximise the benefit from the induced spleen reduction.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 02 of 12, February 2025) am 24.02.2025

#	Suchschritt
1	MeSH descriptor: [Splenomegaly] explode all trees
2	(splenomegal* OR spleenomegal*):ti,ab,kw
3	((spleen OR spleens) AND enlarg*):ti,ab,kw
4	MeSH descriptor: [Primary Myelofibrosis] explode all trees
5	(myelofibros* OR (bone NEXT marrow NEXT fibros*)):ti,ab,kw
6	MeSH descriptor: [Polycythemia Vera] explode all trees
7	((polycythemi* OR polycythaemi* OR postpolycythemi* OR postpolycythaemi*) AND (vera OR rubra OR ruba)):ti,ab,kw
8	MeSH descriptor: [Thrombocythemia, Essential] explode all trees
9	(thrombocythemia* OR thrombocythaemia*):ti,ab,kw
10	MeSH descriptor: [Anemia, Myelophthisic] explode all trees
11	(myelophthis*):ti,ab,kw
12	MeSH descriptor: [Myeloproliferative Disorders] explode all trees
13	(myeloproliferativ* OR MPN):ti,ab,kw
14	((philadelphia AND chromosome AND negative) OR ph-neg OR ph-negative):ti,ab,kw
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 with Cochrane Library publication date from Feb 2020 to present
16	#15 with Cochrane Library publication date from Feb 2023 to present
17	#15 NOT #16

Leitlinien und systematische Reviews in PubMed am 24.02.2025

verwendeter Suchfilter für Leitlinien ohne Änderung:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	splenomegaly[mh]
2	(splenomegal*[tiab] OR spleenomegal*[tiab])
3	((spleen[tiab] OR spleens[tiab])) AND enlarg*[tiab]

#	Suchschritt
4	primary myelofibrosis[mh]
5	(myelofibros*[tiab]) OR bone marrow fibros*[tiab]
6	polycythemia vera[mh]
7	(polycythemi*[tiab] OR polycythaemi*[tiab] OR postpolycythemi*[tiab] OR postpolycythaemi*[tiab]) AND (vera[tiab] OR rubra[tiab] OR ruba[tiab])
8	thrombocythemia, essential[mh]
9	thrombocythemia*[tiab] OR thrombocythaemia*[tiab]
10	Anemia, Myelophthisic[mh]
11	myelophthis*[tiab]
12	"Myeloproliferative Disorders"[Mesh:NoExp]
13	myeloproliferativ*[tiab] OR MPN[tiab]
14	(Philadelphia[tiab] AND chromosome[tiab] AND negative[tiab]) OR ph-neg[tiab] OR ph-negative[tiab]
15	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
16	(#15) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
17	(#16) AND ("2020/02/01"[PDAT] : "3000"[PDAT])
18	(#17) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews
19	(#15) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR ((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR

#	Suchschritt
	ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
20	(#19) AND ("2020/02/01"[PDAT] : "3000"[PDAT])
21	(#20) NOT "The Cochrane database of systematic reviews"[Journal]
22	(#21) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
23	#22 NOT #18
24	(#23) AND ("2023/02/01"[PDAT] : "3000"[PDAT])
25	#23 NOT #24

Iterative Handsuche nach grauer Literatur, abgeschlossen am 15.08.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Alberta Health Service (AHS)
- European Society for Medical Oncology (ESMO)
- National Comprehensive Cancer Network (NCCN)
- American Society of Clinical Oncology (ASCO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **McLornan DP, Psaila B, Ewing J, Innes A, Arami S, Brady J, et al.** The management of myelofibrosis: A British Society for Haematology Guideline. Br J Haematol 2024;204(1):136-150.

2. **National Comprehensive Cancer Network (NCCN).** Myeloproliferative neoplasms, version 2.2025 [online]. Plymouth Meeting (USA): NCCN; 2025. [Zugriff: 06.08.2025]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

3. **National Comprehensive Cancer Network (NCCN).** Myeloproliferative neoplasms; NCCN evidence blocks, version 2.2025 [online]. Plymouth Meeting (USA): NCCN; 2025. [Zugriff: 06.08.2025]. (NCCN Clinical Practice Guidelines in Oncology). URL: https://www.nccn.org/professionals/physician_gls/pdf/mpn_blocks.pdf.

4. **Polverelli N, Hernandez-Boluda JC, Czerw T, Barbui T, D'Adda M, Deeg HJ, et al.** Splenomegaly in patients with primary or secondary myelofibrosis who are candidates for allogeneic hematopoietic cell transplantation: a Position Paper on behalf of the Chronic Malignancies Working Party of the EBMT. Lancet Haematol 2023;10(1):e59-e70.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021

Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO