National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myeloproliferative Neoplasms

Version 2.2024 — August 8, 2024

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Myeloproliferative Neoplasms

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Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

NCCN Categories of Evidence and Consensus:
All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference:
All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 2.2024 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 1.2024 include:

MS-1

• The discussion has been updated to reflect the changes in the algorithm.

Updates in Version 1.2024 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 3.2023 include:

Global

• Removed MPN-10 throughout the guidelines.
• von Willebrand disease (VWD) was revised to von Willebrand syndrome (VWS) throughout the guidelines.

MPN-1

Footnotes

• Deleted: ICC Diagnostic Criteria for PV and Post-PV MF See (MPN-C).
• b: modified: See International Consensus Classification (ICC) and WHO diagnostic criteria for primary myelofibrosis (PMF) (MPN-A), *PV* (*MPN-C*), *and ET* (*MPN-D*).
• c: modified: See IWG-MRT (MPN-B), *ICC, and WHO* diagnostic criteria for post-PV *MF* (MPN-C) and post-ET MF (MPN-D), (Also for MPN-2A).
• d: modified: last sentence, ...in patients with *MF* ~~MPN.~~

MPN-2

• Accelerated/blast phase MPN: removed from risk stratification for myelofibrosis and added under Diagnosis.

MPN-2A

Footnotes

• k, New: ICC and WHO diagnositic criteria for ET and Post-ET MF. See MPN-D.
• l, New: See ICC and WHO diagnostic criteria for PMF (MPN-A).

MF-1

• Removed: Continue observation (if asymptomatic).
• 4th column, added: Pacritinib (if platelets <50 x 10^9/L) as a first-line therapy option for symptomatic lower-risk myelofibrosis.
• 5th column, 2nd row:
  ▸ removed every 3-6 months; added: as clinically indicated (Also for MF-2).

Footnotes

• a, modified: 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 ~~PMF~~ MF. See Prognostic Significance of Mutations in MPN (MPN-E).
• b, Added: Prognostic Significance of Mutations in Myelofibrosis (MPN-E) (Also for MF-2A).
• d, modified: *Additional molecular testing using multigene NGS panel should be considered to evaluate for higher-risk mutations associated with disease progression in patients with MF*. ~~See Prognostic Significance of Mutations in MPN (MPN-E).~~ (Also for MF-2A).
• Footnote removed: Consider pacritinib for patients with platelet counts <50 x 10^9/L.

MF-2

• 4th column, top and bottom pathways, modified to include: ...*or transplant not currently feasible.*
• 5th column, bottom pathway, following not a transplant candidate or transplant not currently feasible, New: Presence of symptomatic splenomegaly and/or constitutional symptoms.
• 9th column, bottom pathway, modified: Accelerated/blast phase ~~MF~~ (~~MF-4~~) *MPN (MPN-AP/BP-1).*

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 3.2023 include:

MF-2A

Footnotes

- h, modified: Evaluation...for patients with ~~PMF~~ *MF*. ~~See prognostic significance of mutations in MPN (MPN-E)~~.
- k, New: Donor selection and conditioning should be evaluated on a case-by-case basis. See NCCN Guidelines for Hematopoietic Cell Transplant (HCT).

MF-3

- The previous MF-3 page was removed and a new page added for Management of MF-Associated Anemia.
- For anemia and symptomatic splenomegaly and/or constitutional symptoms currently controlled on a JAK inhibitor:
  - Preferred regimen:
    - Clinical trial
  - Other recommended regimens:
    - Ruxolitinib combination:
      - Add luspatercept-aamt
      - Add ESAs (if serum EPO <500 mU/mL)
      - Add danazol (category 2B)
  - Useful in certain circumstances:
    - Change to momelotinib
    - Change to pacritinib
- For anemia and symptomatic splenomegaly and/or constitutional symptoms not controlled:
  - Preferred regimens
    - Clinical trial
    - Momelotinib
  - Other recommended regimens:
    - Pacritinib
    - Ruxolitinib in combination with:
      - luspatercept-aamt
      - ESAs (if serum EPO <500 mU/mL) (category 2B)
      - danazol (category 2B)
- For anemia and no symptomatic splenomegaly and/or constitutional symptoms:
  - Preferred regimen:
    - Clinical trial
  - Other recommended regimens:
    - Luspatercept-aamt
    - ESAs (if serum EPO <500 mU/mL)
    - Danazol
    - Momelotinib (category 2B)
    - Pacritinib (category 2B)
  - Useful in certain circumstances
    - lenalidomide + prednisone for del(5q) (category 2B).

Continued

Updates in Version 1.2024 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 3.2023 include:

MF-4
Updated page name: Accelerated/blast phase ~~MF~~ *MPN,* now page *MPN-AP/BP-1.*

MF-B
- Previous content removed; page modified to include the following:
  - 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.
  - These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.
  - Patients undergoing HCT may be evaluated for response assessment using other response criteria.

PV-1
- 3rd column, bullet 2, modified: ~~every 3–6 months or more frequently if~~ as clinically indicated (Also for PV-2, ET-2).
- 4th column, bottom pathway, modified: Disease progression ~~to MF~~ (Also for PV-2, ET-1, ET-2).
- 6th column, bottom pathway, modified: Accelerated/blast phase *MPN* ~~MF~~ (Also for PV-2, ET-1, ET-2).
- 7th column, *Clinical trial* added under Preferred regimens.
  - Hydroxyurea and peginterferon alfa-2a are now listed as Other recommended regimens.

Footnotes
- h, modified: See IWG-MRT (MPN-B), *ICC, and WHO* diagnostic criteria for post-PV *MF* (MPN-C) ~~and post-ET MF~~ (MPN-D) (Also for PV-2).

PV-2
- Column 2:
  - Peginterferon alfa-2a is now listed as Other recommended regimens.
  - New: Ruxolitinib, Useful in certain circumstances.
- 5th column, modified: Intolerance or resistance to *prior cytoreductive treatment* ~~hydroxyurea~~, ~~or interferons~~

PV-A
- Previous content removed; page modified to include the following:
  - 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.
  - These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.

ET-1
- Updated page title to include *Intermediate-risk.*

Footnotes
- h, modified: See IWG-MRT (MPN-B), *ICC, and WHO* diagnostic criteria for ~~post-PV (MPN-C) and~~ post-ET MF (MPN-D) (Also for ET-2).

ET-2
- The previous ET-2 page was removed and "Intermediate-risk" was added to ET-1 with Low-risk ET.

Footnotes
- i, modified: Peginterferon alfa-2a can be considered for ~~younger~~ patients ~~or in pregnant patients~~ in need of cytoreductive therapy *who are younger* or *pregnant* ~~in those in need of cytoreductive therapy~~ *or* who defer hydroxyurea (Also for ET-3)
- k, modified: ~~2013 IWG-MRT and ELN Response Criteria for ET (ET-A). These~~ Response criteria were developed mainly for use in clinical trials.

ET-A
- Previous content removed; page modified to include the following:
  - 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.
  - These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.

Updates in Version 1.2024 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 3.2023 include:

MPN-AP/BP-1
- 1st column, modified: Accelerated/blast phase ~~MF~~ *MPN*
- 2nd column, 3rd sub-bullet modified: *Broad-based NGS panels that include* ~~*Molecular testing for*~~ *acute myeloid leukemia (AML)-associated mutations*
  3rd column, top and bottom pathways modified:*MPN* ~~MF~~ accelerated phase and blast phase....
- 5th column, bullet 2, for transplant candidate modified: ~~Induction~~ *Bridging* therapy followed by allogeneic HCT ~~(for patients in remission)~~
- 1st sub bullet, modified: ~~Induction~~ *Bridging* therapy options include:
  - Added: HMA + venetoclax
- Not a candidate for transplant arm added, HMA + venetoclax

Footnotes
- a, modified: ...Early referral to transplant is recommended for planning purposes *and to discuss the role of* bridging therapy. ~~can be used to decrease marrow blasts to an acceptable level prior to transplant.~~ *Some patients in accelerated phase may proceed to transplant directly without bridging therapy (Gagelmann N, et al. Blood Adv 2022;6:1222-1231).*
- d, modified: AML-type induction chemotherapy regimens and *HMA + venetoclax* ~~are generally~~ *may be* used for the management of disease progression of MPN. However, these regimens typically result in poor responses *and are associated with significant toxicities*. Based on NGS panel results, low-intensity or targeted therapy *alone or in combination with HMAs* can be considered.

MPN-A, 1 of 2
- Updated: *And WHO* to the title of the page. (Also for MPN-C, MPN-D)

Footnotes
- a, modified: ~~These criteria are the same in the 2022 WHO Classification~~*. The WHO 2022 criteria are the same as the WHO 2017 criteria. Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017*; Khoury JD, et al. Leukemia 2022;36:1703-1719 (Also for MPN-C, MPN-D)

MPN-E
- The table was updated for MF and the tables for PV and ET were removed.
- Deleted reference: Tefferi A, Guglielmelli P, Lasho TL, et al. CALR and ASXL1 mutations-based molecular prognostication in primary myelofibrosis: an international study of 570 patients. Leukemia 2014;28:1494-1500.
- Added reference: Guglielmelli P, Lasho TL, Rotunno G, et al. The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: An international study of 797 patients. Leukemia 2014;28:1804-1810.

MPN-F, 1 of 2
- Bullet 4, modified: ...and justify continued use of *JAK inhibitors* ~~ruxolitinib~~.

MPN-G, 2 of 3
- Bullet 1, sub-bullet 1, deleted ~~oral~~.

MPN-H
- Removed special considerations for ruxolitinib, fedratinib, pacritinib, momelotinib (MPN-H, 1-7)
- Added: JAK inhibitors are ruxolitinib, fedratinib, pacritinib, and momelotinib.

MPN-I, 2 of 4
- Bullet 3, 4th sentence under Pregnancy, deleted risk category C

MPN-I 4 of 4
- Updated reference: Maze D, Kazi S, Gupta V, et al. Association of treatments for myeloproliferative neoplasms during pregnancy with birth rates and maternal outcomes. JAMA Netw Open 2019;2:e1912666. ~~Pregnancy outcomes in patients with myeloproliferative neoplasms: A systematic review and meta-analysis. 2018;132(Suppl 1):3046-3046.~~

WORKUP

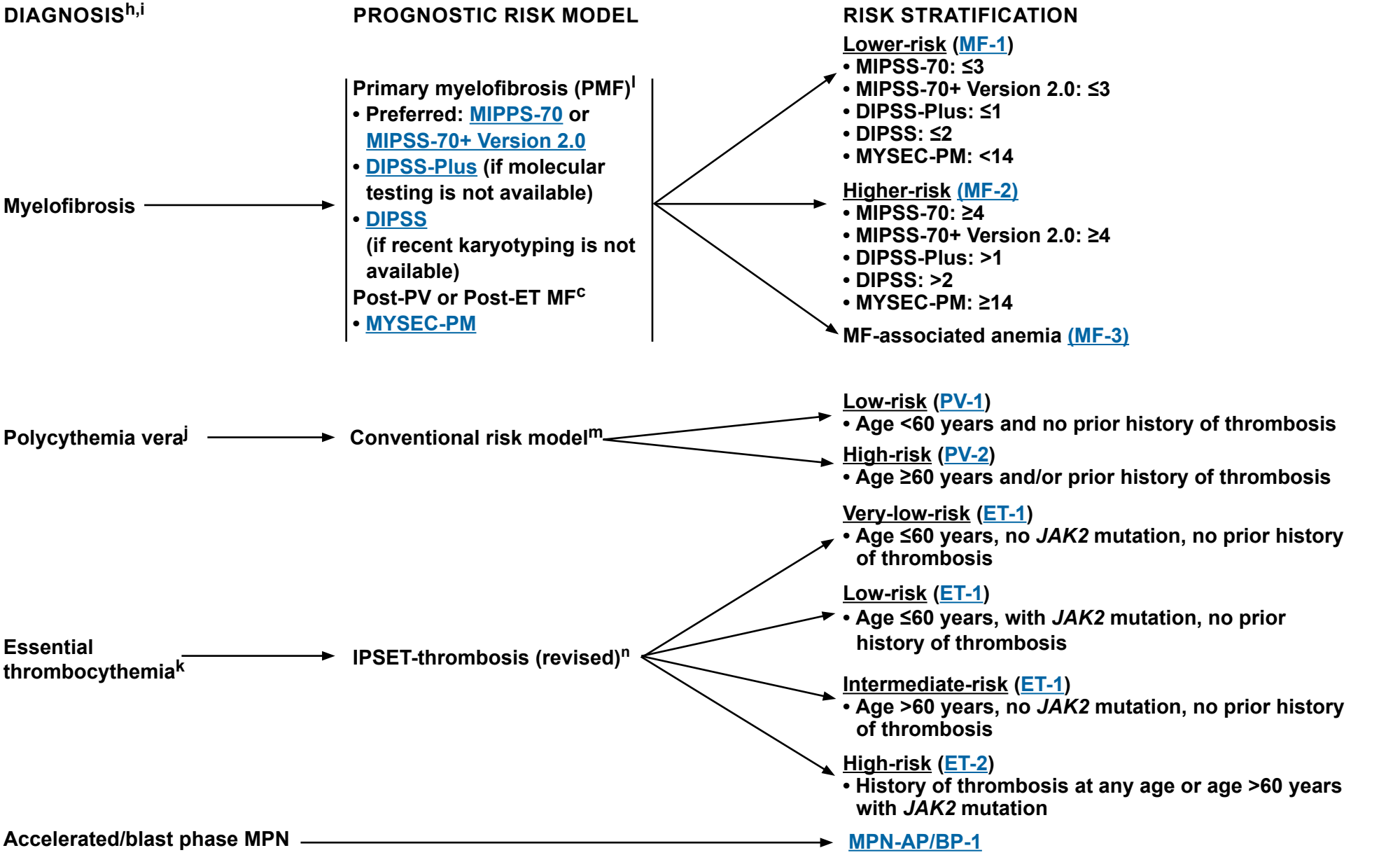
Suspicion of myeloproliferative neoplasms (MPN)[a] →

- **History and physical (H&P), including spleen size by palpation, evaluation of thrombotic/hemorrhagic events and cardiovascular risk factors**
- **Complete blood count (CBC) with differential**
- **Comprehensive metabolic panel with uric acid, lactate dehydrogenase (LDH), and liver function tests (LFTs)**
- **Fluorescence in situ hybridization (FISH) or multiplex reverse transcriptase polymerase chain reaction (RT-PCR) (if available) for *BCR::ABL1* to exclude the diagnosis of chronic myeloid leukemia (CML); if *BCR::ABL1*-positive, see NCCN Guidelines for Chronic Myeloid Leukemia**
- **Examination of blood smear**
- **Bone marrow aspirate with iron stain; bone marrow biopsy with trichrome and reticulin stain[b,c]**
- **Bone marrow cytogenetics (blood, if bone marrow is inaspirable) (karyotype with or without FISH)[b,c]**
- **Molecular testing (blood or bone marrow) for *JAK2* V617F mutation; if negative, test for *CALR* and *MPL* mutations (for patients with essential thrombocythemia [ET] and myelofibrosis [MF]) and *JAK2* exon 12 mutations (for patients with polycythemia vera [PV]); or molecular testing using multigene next-generation sequencing (NGS) panel that includes *JAK2, CALR,* and *MPL*[d]**
  - **Once an MPN diagnosis is confirmed, NGS is recommended for mutational prognostication[d]**
- **If there is evidence of mast cell aggregates in the bone marrow, see NCCN Guidelines for Systemic Mastocytosis for diagnostic workup**
- **Assessment of symptom burden using MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS; MPN-F 2 of 2)**
- **Documentation of transfusion/medication history**
- **Human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplant (HCT)[e]**
- **Serum erythropoietin (EPO) level**
- **Serum iron studies**
- **Coagulation tests to evaluate for acquired von Willebrand syndrome (VWS) or other coagulopathies in selected patients[f]**
- **Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen**
  - **Plasma von Willebrand factor antigen (VWFA) measurement**
  - **Von Willebrand ristocetin cofactor (VWF:RCo) activity[g]**

→ **Diagnosis and Risk stratification** → **MPN-2**

[a] See Workup in the NCCN Guidelines for Systemic Mastocytosis and Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Gene Fusions.
[b] See International Consensus Classification (ICC) and WHO diagnostic criteria for primary myelofibrosis (PMF) (MPN-A), PV (MPN-C), and ET (MPN-D).
[c] See IWG-MRT (MPN-B), ICC, and WHO diagnostic criteria for post-PV MF (MPN-C) and post-ET MF (MPN-D).
[d] Prognostic models incorporating other mutations have been proposed to identify patients with MF as well as PV and ET to better estimate overall survival (OS), MF-free survival (PV and ET), and rates of leukemic transformation. NGS may be useful to establish clonality in selected circumstances (eg, triple-negative non-mutated *JAK2*, *MPL*, and *CALR*). See MPN-E for a list of somatic mutations with prognostic significance in patients with MF.
[e] See MF-1 and MF-2.
[f] Patients undergoing high-risk surgical procedures and those with elevated platelet count or splenomegaly or unexplained bleeding.
[g] An expanded panel including VWFA, factor VIII activity, and VWF multimers may be useful under certain circumstances.

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



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

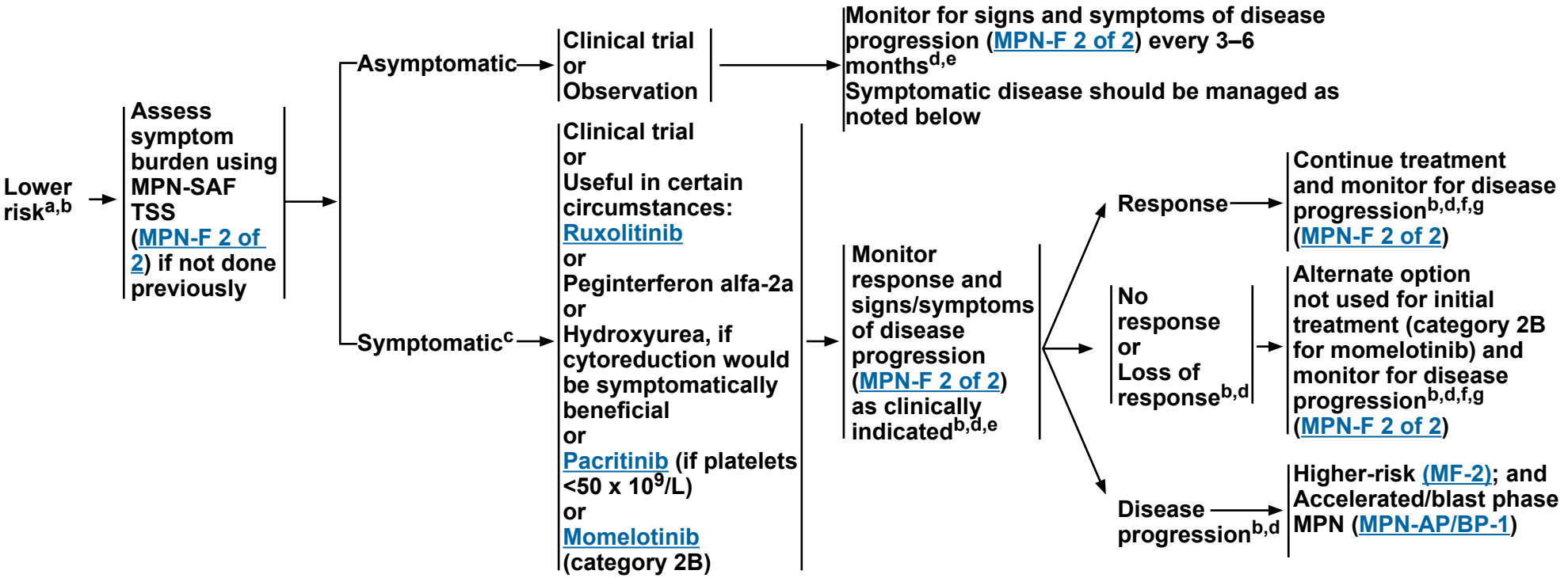
Footnotes on MPN-2A

FOOTNOTES

[c] See IWG-MRT (MPN-B), ICC, and WHO diagnostic criteria for post-PV MF (MPN-C) and post-ET MF (MPN-D).
[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] ICC and WHO diagnostic criteria for PV and Post-PV MF. See MPN-C.
[k] ICC and WHO diagnostic criteria for ET and Post-ET MF. See MPN-D.
[l] See ICC and WHO diagnostic criteria for PMF (MPN-A).
[m] Marchioli R, et al. J Clin Oncol 2005;23:2224-2232.
[n] 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).

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

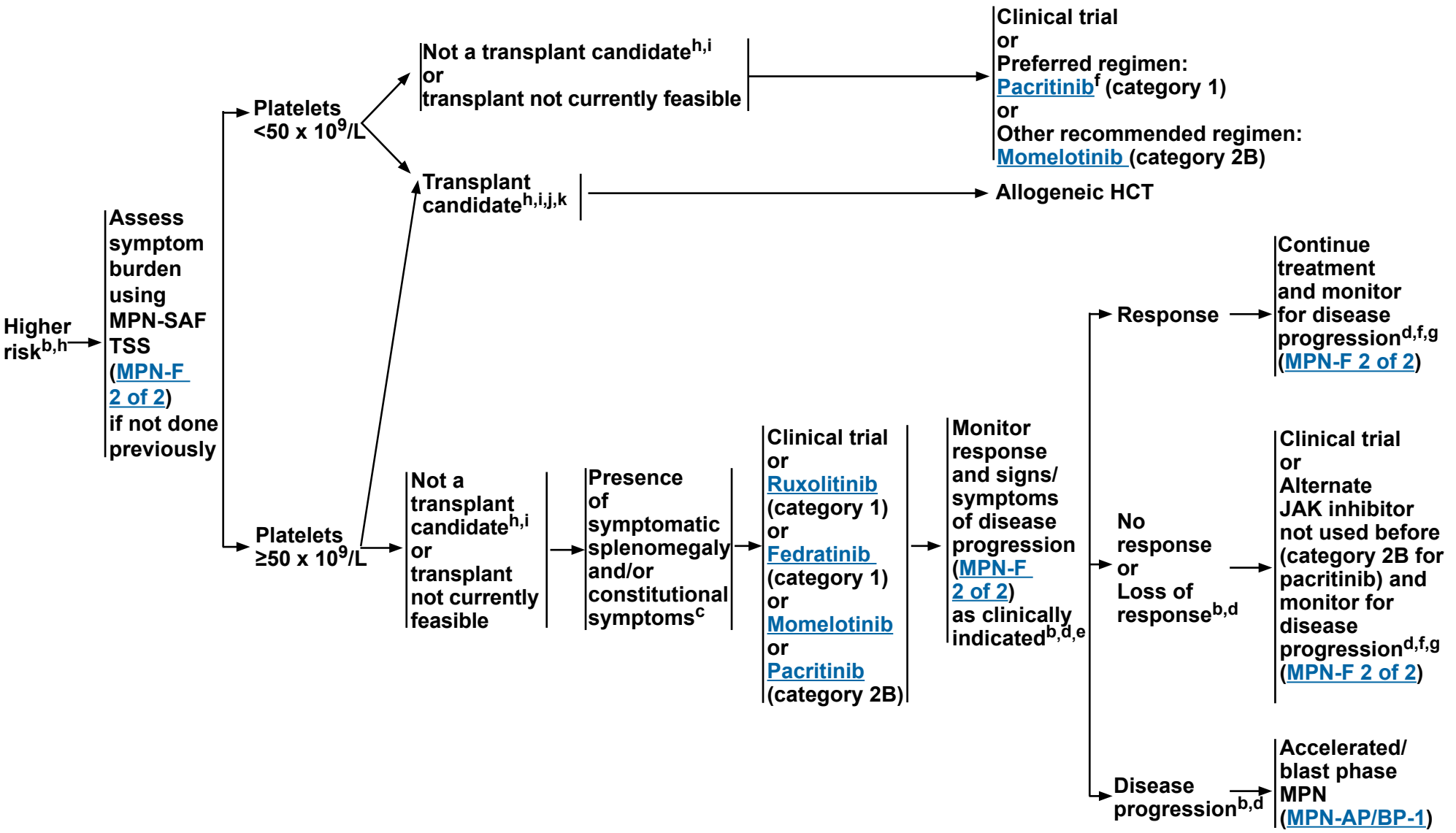
TREATMENT FOR LOWER-RISK MYELOFIBROSIS



[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-E).
[c] Supportive Care for Patients with MPN (MPN-G).
[d] 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.
[e] 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.
[f] Special Considerations for the Use of JAK Inhibitors (MPN-H).
[g] Clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria for MF (MF-B).Continuation of JAK inhibitors is recommended based on the discretion of the clinician.

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

TREATMENT FOR HIGHER-RISK MYELOFIBROSIS



Footnotes on the next page

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

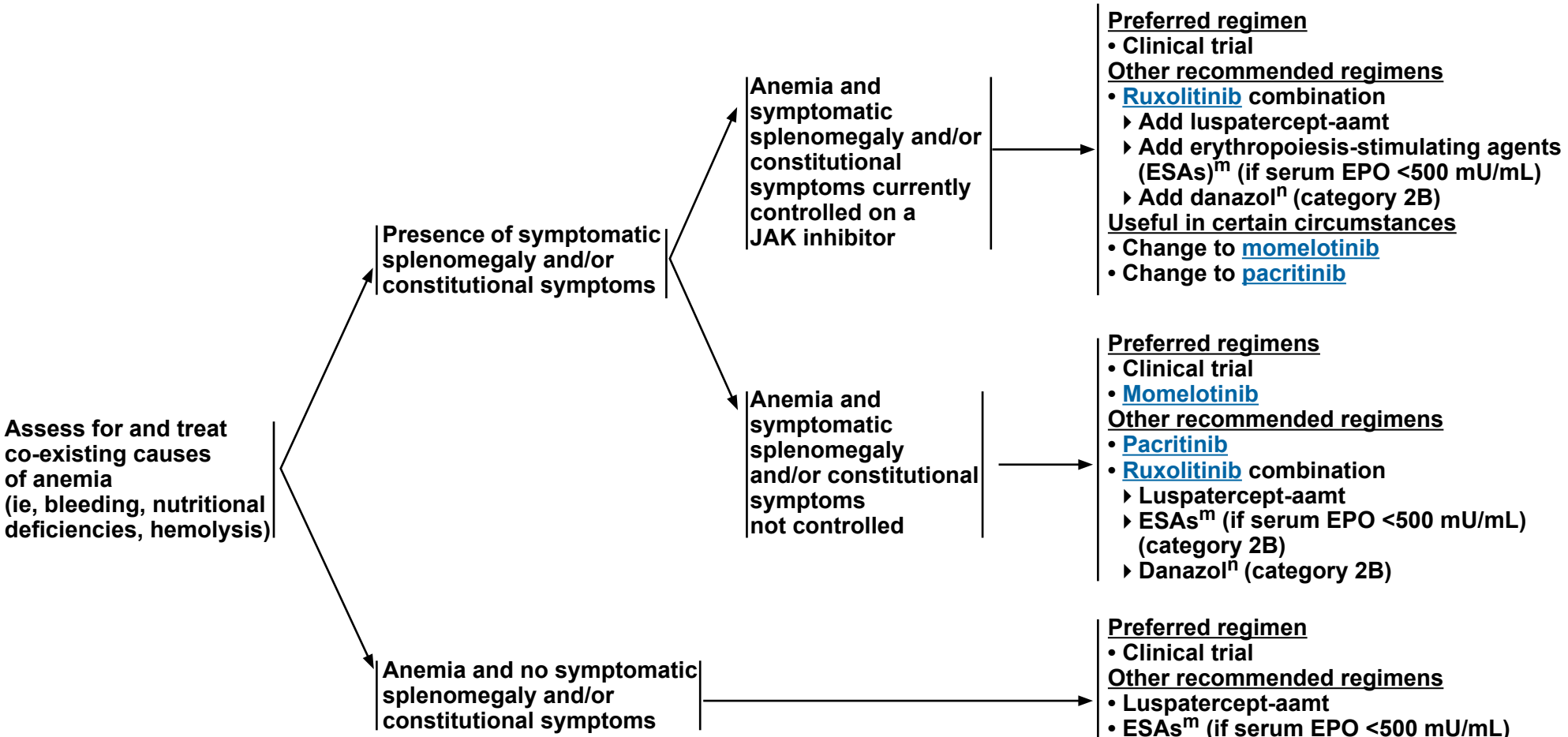
TREATMENT FOR HIGHER-RISK MYELOFIBROSIS

FOOTNOTES

[b] Prognostic Significance of Mutations in Myelofibrosis (MPN-E).
[c] Supportive Care for Patients with MPN (MPN-G).
[d] 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.
[e] 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.
[f] Special Considerations for the Use of JAK Inhibitors (MPN-H).
[g] Clinical benefit may not reach the threshold of the 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). Continuation of JAK inhibitors is recommended based on the discretion of the clinician.
[h] Evaluation for allogeneic HCT is recommended for all patients. Identification of higher-risk mutations may be helpful in the decision-making regarding allogeneic HCT for patients with MF.
[i] 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. Early referral to transplant is recommended for planning purposes. Bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.
[j] JAK inhibitors may be continued near to the start of conditioning therapy for the improvement of splenomegaly and other disease-related symptoms; see MPN-H. See Discussion for the use of JAK inhibitors prior to transplant.
[k] Donor selection and conditioning should be evaluated on a case-by-case basis. See NCCN Guidelines for Hematopoietic Cell Transplant (HCT).

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

MANAGEMENT OF MF-ASSOCIATED ANEMIA[c,l]



[c] Supportive Care for Patients with MPN (MPN-G).
[l] JAK inhibitors may be continued for the improvement of splenomegaly and other disease-related symptoms.
[m] ESAs include epoetin alfa and darbepoetin alfa. An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.
[n] 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.
[o] Start as a combination followed by tapering of prednisone over 3 months.

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

RISK STRATIFICATION FOR PATIENTS WITH MYELOFIBROSIS

PMF

DIPSS	(MF-A, 2 of 5)
DIPSS-PLUS	(MF-A, 2 of 5)
MIPSS-70	(MF-A, 3 of 5)
MIPSS-70+ Version 2.0	(MF-A, 4 of 5)

POST-PV AND POST-ET MF

MYSEC-PM	(MF-A, 5 of 5)

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

RISK STRATIFICATION FOR PATIENTS WITH PMF

DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)[1]

Prognostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10^9/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

Online calculator for DIPSS score can be found at https://qxmd.com/calculate/calculator_187/dipss-prognosis-in-myelofibrosis

DIPSS-PLUS[2]

Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), or 11q23 rearrangement.

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

Online calculator for DIPSS-PLUS score can be found at https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis

[1] 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.
[2] 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.

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

RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION-ENHANCED IPSS (MIPSS-70) FOR PATIENTS WITH PMF AGE ≤70 YEARS[3]

Prognostic Variable	Points
Hemoglobin <10 g/dL	1
Leukocytes >25 x 10^9/L	2
Platelets <100 x 10^9/L	2
Circulating blasts ≥2%	1
Bone marrow fibrosis grade ≥2	1
Constitutional symptoms	1
CALR type-1 unmutated genotype	1
High-molecular-risk (HMR) mutations[a]	1
≥2 HMR mutations	2

Risk Group	Points
Low	0–1
Intermediate	2–4
High	≥5

Online calculator for MIPSS-70 can be found at http://www.mipss70score.it/.

Footnote
[a] Presence of a mutation in any of the following genes: *ASXL1*, *EZH2*, *SRSF2*, or *IDH1/2*.

References
[3] Guglielmelli P, Lasho TL, Rotunno G, et al. MIPSS-70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients with Primary Myelofibrosis. J Clin Oncol 2018,36:310-318.

Continued

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

RISK STRATIFICATION FOR PATIENTS WITH PMF
MUTATION AND KARYOTYPE-ENHANCED IPSS (MIPSS-70+ VERSION 2.0) FOR PATIENTS WITH PMF[4,5]

Prognostic Variable	Points
Severe anemia (Hemoglobin <8 g/dL in women and <9 g/dL in men)	2
Moderate anemia (Hemoglobin 8–9.9 g/dL in women and 9–10.9 g/dL in men)	1
Circulating blasts ≥2%	1
Constitutional symptoms	2
Absence of *CALR* type 1 mutation	2
HMR mutations[b]	2
≥2 HMR mutations	3
Unfavorable karyotype[c]	3
Very-high-risk (VHR) karyotype[d]	4

Risk Group	Points
Very low	0
Low	1–2
Intermediate	3–4
High	5–8
Very high	≥9

Online calculator for MIPSS-70+ Version 2.0 can be found at http://www.mipss70score.it/.

Footnotes
[b] Presence of a mutation in any of the following genes: *ASXL1*, *EZH2*, *SRSF2*, *U2AF1* Q157, or *IDH1/2.*
[c] Unfavorable karyotype: any abnormal karyotype other than normal karyotype or sole abnormalities of 20q-, 13q-, +9, chromosome 1 translocation/duplication, or -Y or sex chromosome abnormality other than –Y.
[d] VHR karyotype: single/multiple abnormalities of −7, i(17q), inv(3)/3q21, 12p−/12p11.2, 11q−/11q23, or other autosomal trisomies not including + 8/+9 (eg, +21, +19).

References
[4] 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.
[5] Tefferi A, Nicolosi M, Mudireddy M, et al. Revised cytogenetic risk stratification in primary myelofibrosis: analysis based on 1002 informative patents. Leukemia 2018;32:1189-1199.

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

RISK STRATIFICATION FOR PATIENTS WITH POST-PV AND POST-ET MF

MYELOFIBROSIS SECONDARY TO PV AND ET-PROGNOSTIC MODEL (MYSEC-PM)[6]

Prognostic Variable	Points
Age at diagnosis	0.15 per patient's year of age
Hemoglobin <11 g/dL	2
Circulating blasts ≥3%	2
Absence of *CALR* type 1 mutation	2
Platelets <150 x 10^9/L	1
Constitutional symptoms	1

Risk Group	Points
Low	<11
Intermediate-1 (INT-1)	≥11 and <14
Intermediate-2 (INT-2)	≥14 and <16
High	≥16

Online calculator for MYSEC-PM can be found at http://mysec-pm.eu/.

[6] 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.

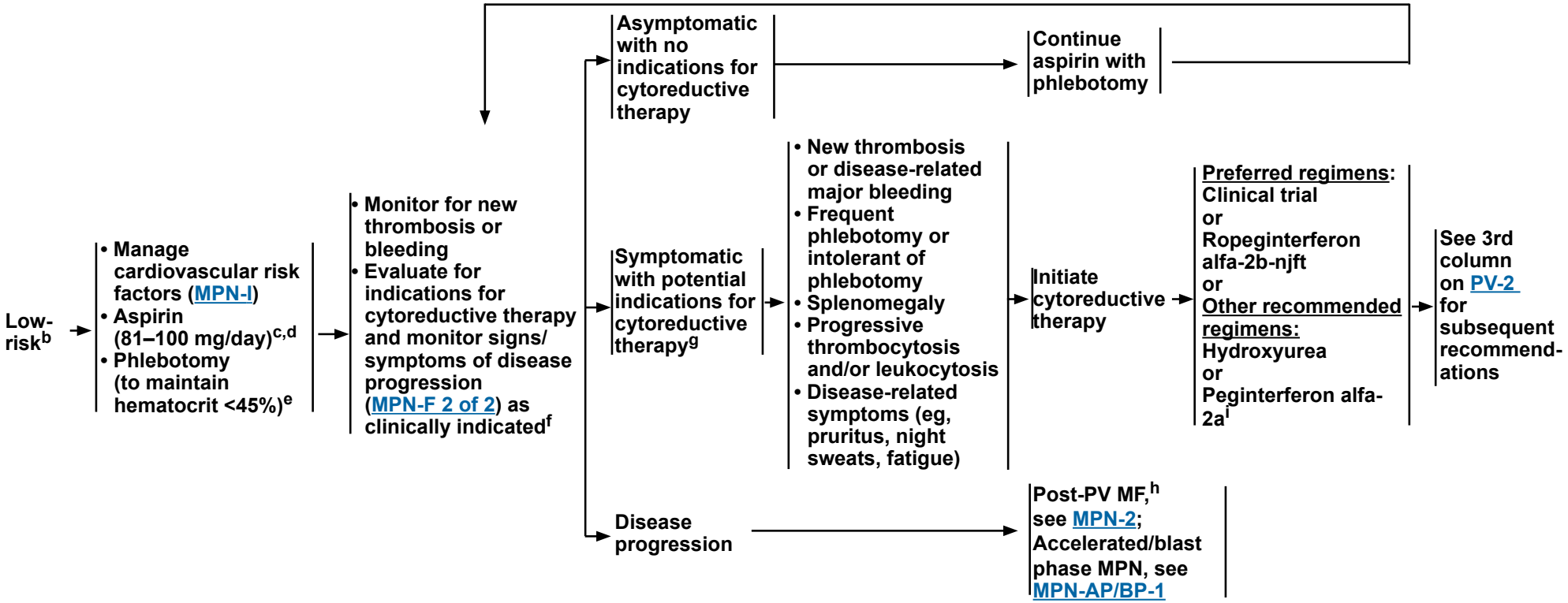
Note: All recommendations are category 2A unless otherwise indicated.

2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS

- **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.**
- **These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.**
- **Patients undergoing HCT may be evaluated for response assessment using other response criteria.**

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

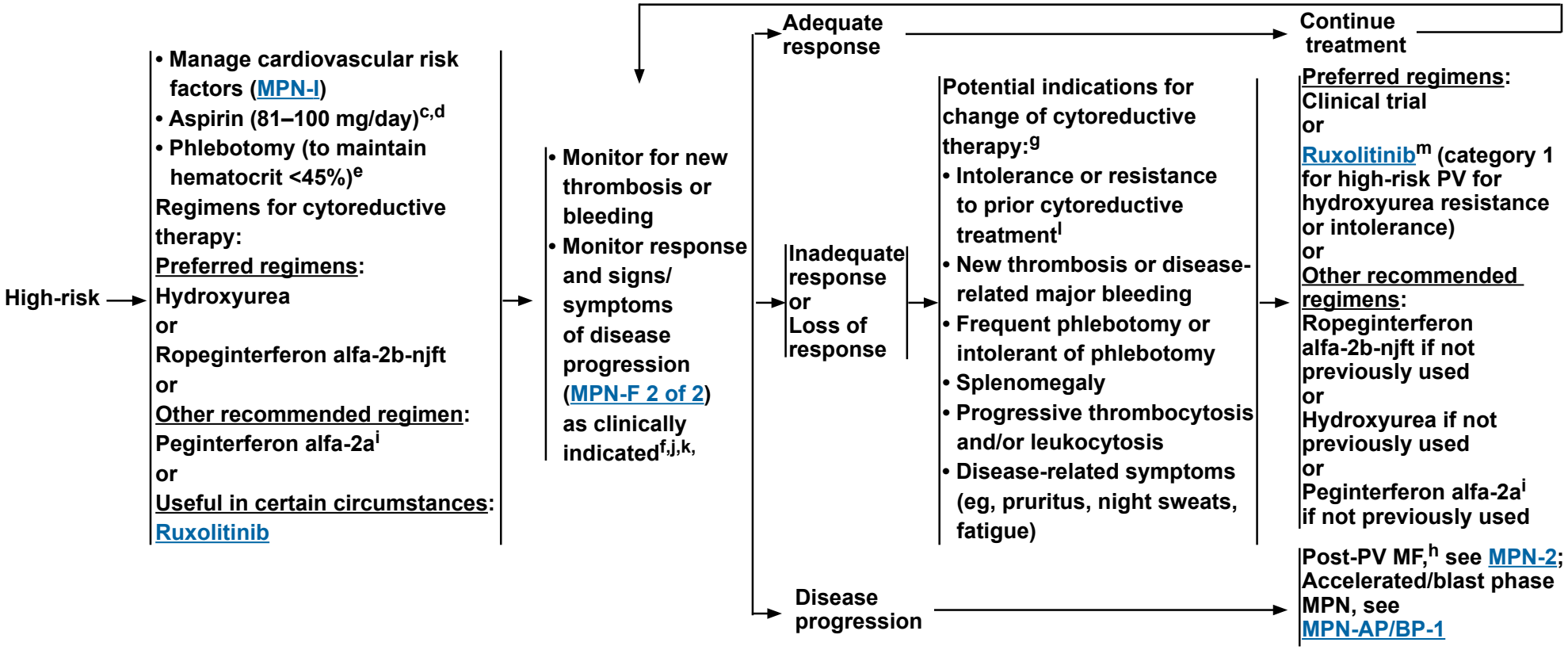
TREATMENT FOR LOW-RISK POLYCYTHEMIA VERA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-I).
[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, 42% for female patients and/or progressive symptoms).
[f] Supportive Care for Patients with MPN (MPN-G).
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] See IWG-MRT (MPN-B), ICC, and WHO diagnostic criteria for post-PV MF (MPN-C).
[i] Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy.

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-I).
[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, 42% for female patients and/or progressive symptoms).
[f] Supportive Care for Patients with MPN (MPN-G).
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] See IWG-MRT (MPN-B), ICC, and WHO diagnostic criteria for post-PV MF (MPN-C).
[i] Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy.
[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 PV (PV-A). Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.
[k] 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 an essential goal of treatment.
[l] Definition of intolerance/resistance to hydroxyurea (MPN-J).
[m] 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.

2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR POLYCYTHEMIA VERA

- **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.**
- **These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.**

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

RISK STRATIFICATION FOR PATIENTS WITH POLYCYTHEMIA VERA[a]

MIPSS-PV

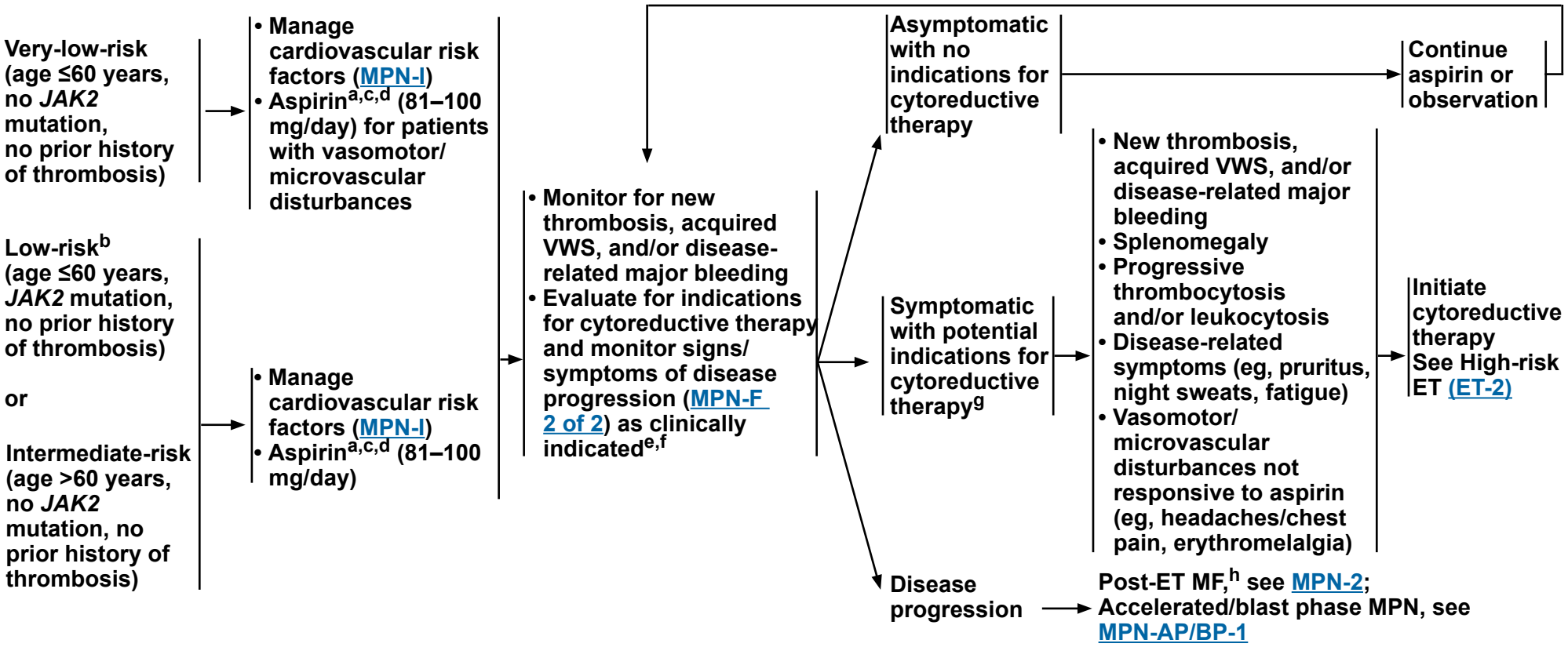
Prognostic Variable	Points
Thrombosis history	1
Leukocyte count ≥15x10^9/L	1
Age >67	2
Adverse mutations (*SRSF2*)	3

Risk Group	Points
Low	0–1
Intermediate	2–3
High	≥4

[a] 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.

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

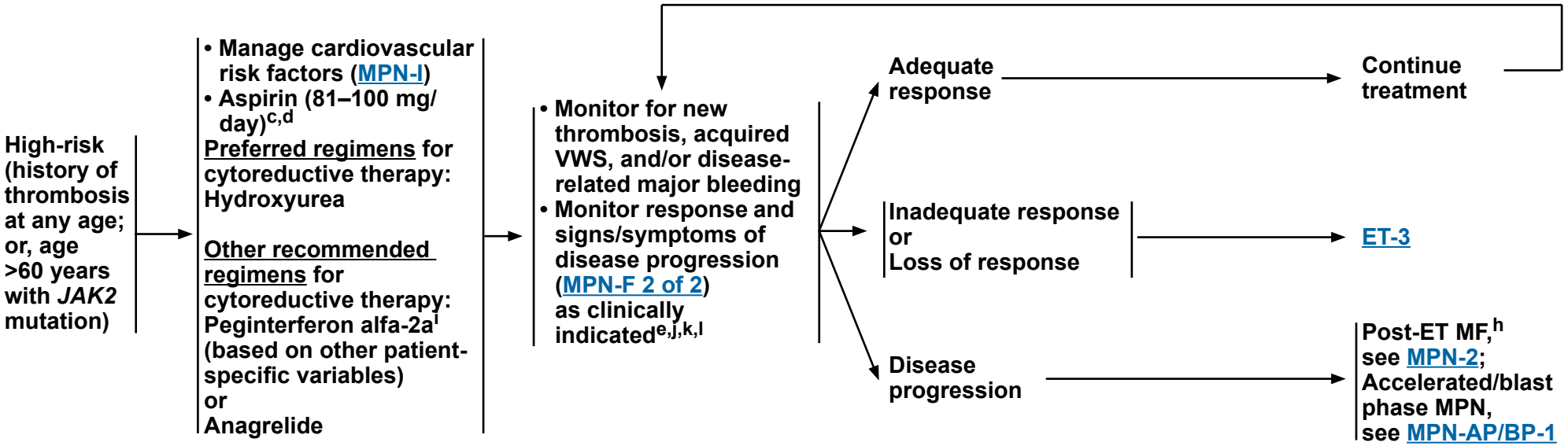
TREATMENT FOR VERY-LOW-RISK OR LOW-RISK OR INTERMEDIATE-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-I).
[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-G).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to MF prior to the initiation of cytoreductive therapy.
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] See IWG-MRT (MPN-B), ICC, and WHO diagnostic criteria for post-ET MF (MPN-D).

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-I).
[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-G).
[h] See IWG-MRT (MPN-B), ICC, and WHO diagnostic criteria for post-ET MF (MPN-D).
[i] Peginterferon alfa-2a can be considered for patients in need of cytoreductive therapy who are younger or pregnant or who defer hydroxyurea.
[j] Bone marrow aspirate and biopsy should be performed to rule out disease progression to MF if clinical/laboratory suspicion of MF.
[k] 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.
[l] 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 an essential goal of treatment.

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

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]

Inadequate response or Loss of response →

Potential indications for change of cytoreductive therapy:[g]
- **Intolerance or resistance to hydroxyurea[m] or peginterferon alfa-2a or anagrelide**
- **New thrombosis, acquired VWS, and/or disease-related major bleeding**
- **Splenomegaly**
- **Thrombocytosis**
- **Leukocytosis**
- **Disease-related symptoms (eg, pruritus, night sweats, fatigue)**
- **Vasomotor/microvascular disturbances not responsive to aspirin (eg, headaches/chest pain, erythromelalgia)**

→

Preferred regimens:
- **Clinical trial**

or
- **Hydroxyurea if not previously used**

Other recommended regimens:
- **Peginterferon alfa-2a if not previously used[i]**

or
- **Anagrelide if not previously used**

Useful in certain circumstances:
- **Ruxolitinib**

or
- **Plateletpheresis (for emergent situations, eg, severe thrombocytosis-related neurologic complications)[n]**

[a] Special Considerations in the Treatment of PV and ET (MPN-I).
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[i] Peginterferon alfa-2a can be considered for patients in need of cytoreductive therapy who are younger or pregnant or who defer hydroxyurea.
[m] Definition of intolerance/resistance to hydroxyurea (MPN-J).
[n] Padmanabhan A, et al. J Clin Apher 2019;34:171-354.

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

2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA

- **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.**
- **These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.**

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

RISK STRATIFICATION FOR PATIENTS WITH ESSENTIAL THROMBOCYTHEMIA[a]

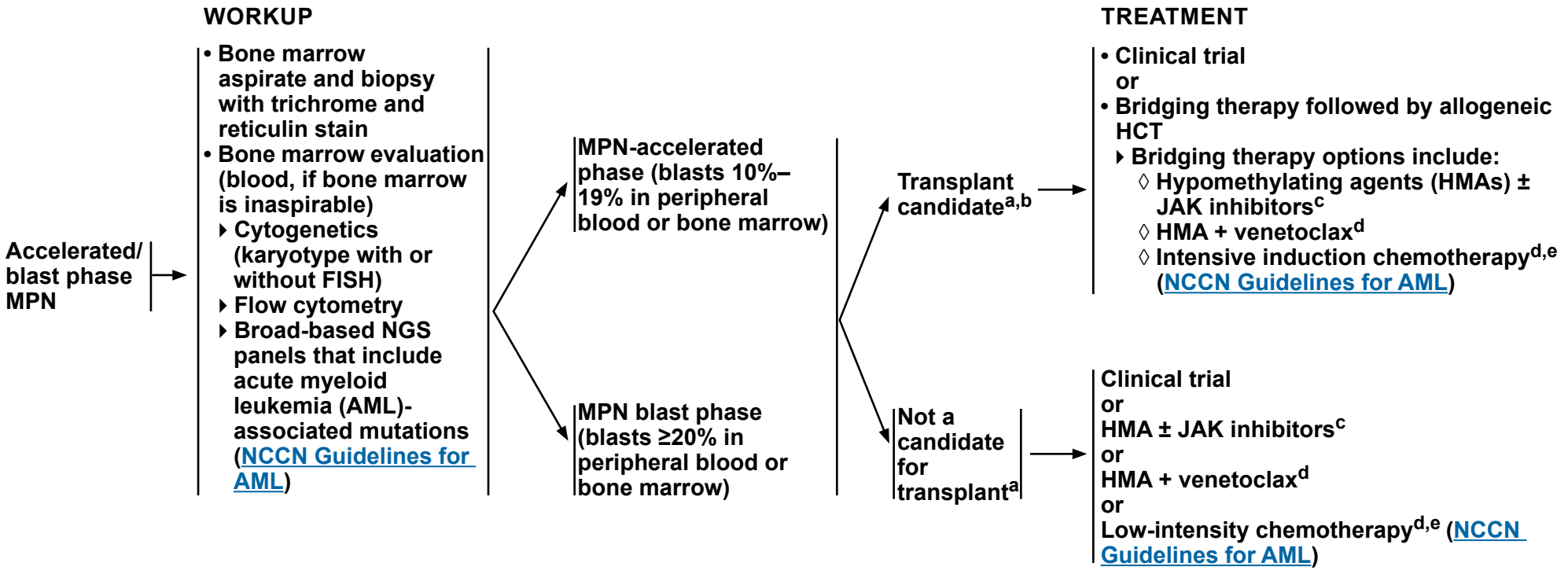
MIPSS-ET

Prognostic Variable	Points
Male sex	1
Leukocyte count ≥11 x 10^9/L	1
Adverse mutations (*SRSF2*, *SF3B1*, *U2AF1*, *TP53*)	2
Age >60	4

Risk Group	Points
Low	0–1
Intermediate	2–5
High	≥6

[a] 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.

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



[a] 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. Early referral to transplant is recommended for planning purposes and to discuss the role of bridging therapy. Some patients in accelerated phase may proceed to transplant directly without bridging therapy (Gagelmann N, et al. Blood Adv 2022;6:1222-1231).

[b] JAK inhibitors may be continued near to the start of conditioning therapy for the improvement of splenomegaly and other disease-related symptoms (MPN-H). See Discussion for the use of JAK inhibitors prior to transplant.

[c] JAK inhibitors can be used in combination with HMA (azacitidine or decitabine) for the palliation of splenomegaly or other disease-related symptoms. There are very limited data regarding the use of fedratinib, momelotinib, or pacritinib with HMAs.

[d] AML-type induction chemotherapy regimens and HMA + venetoclax may be used for the management of disease progression of MPN. However, these regimens typically result in poor responses and are associated with significant toxicities. Based on NGS panel results, low-intensity or targeted therapy alone or in combination with HMAs can be considered.

[e] Consider prophylaxis for tumor lysis syndrome (TLS). See Supportive Care for Patients with MPN (MPN-G).

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

INTERNATIONAL CONSENSUS CLASSIFICATION (ICC) AND WHO DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS[1,a]

PMF, early/prefibrotic stage (pre-PMF)	PMF, overt fibrotic stage
Major criteria **1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* bone marrow fibrosis grade <2, increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis** **2. *JAK2, CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive bone marrow reticulin fibrosis§** **3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met**	**Major criteria** **1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3** **2. *JAK2, CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§** **3. Diagnostic criteria for ET, PV, *BCR::ABL1*-positive CML, myelodysplastic syndrome, or other myeloid neoplasms‖ are not met**
Minor criteria **• Anemia not attributed to a comorbid condition** **• Leukocytosis ≥11 x 10^9/L** **• Palpable splenomegaly** **• LDH level above the above reference range**	**Minor criteria** **• Anemia not attributed to a comorbid condition** **• Leukocytosis ≥11 x 10^9/L** **• Palpable splenomegaly** **• LDH level above the above reference range** **• Leukoerythroblastosis**
The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations	

* Morphology of megakaryocytes in pre-PMF and overt PMF usually demonstrates a higher degree of megakaryocytic atypia than in any other MPN subtype; distinctive features of megakaryocytes include small to giant megakaryocytes with a prevalence of severe maturation defects (cloud-like, hypolobulated, and hyperchromatic nuclei) and presence of abnormal large dense clusters (mostly >6 megakaryocytes lying strictly adjacent).

† It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level <1%) and *CALR* and *MPL* (sensitivity level 1% to 3%); in negative cases, consider searching for noncanonical *JAK2* and *MPL* mutations.

‡ Assessed by cytogenetics or sensitive NGS techniques; detection of mutations associated with myeloid neoplasms (eg, *ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2,* and *TET2* mutations) supports the clonal nature of the disease.

§ Minimal reticulin fibrosis (grade 1) secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

‖ Monocytosis can be present at diagnosis or develop during the course of PMF; in these cases, a history of MPN excludes chronic myelomonocytic leukemia (CMML), whereas a higher variant allelic frequency for MPN-associated driver mutations is supporting the diagnosis of PMF with monocytosis rather than CMML.

[a] The WHO 2022 criteria are the same as the WHO 2017 criteria. Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017; Khoury JD, et al. Leukemia 2022;36:1703-1719.

[1] Adapted with permission from Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical and genomic data. Blood 2022;140:1200-1228. from Arber DA, et al. Blood 2022;140:1200-1228.

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

GRADING OF MYELOFIBROSIS[6]

Myelofibrosis Grading

- **MF-0**
  - **Scattered linear reticulin with no intersections (crossovers) corresponding to normal bone marrow**
- **MF-1**
  - **Loose network of reticulin with many intersections, especially in perivascular areas**
- **MF-2**
  - **Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis***
- **MF-3**
  - **Diffuse and dense increase in reticulin with extensive intersections and course bundles of thick fibers consistent with collagen, usually associated with osteosclerosis***

[6] Reproduced with permission ©2018 Ferrata Storti Foundation. Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128-1132.

*In grades MF-2 or MF-3 an additional trichrome stain is recommended.

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

IWG-MRT DIAGNOSTIC CRITERIA FOR POST-POLYCYTHEMIA VERA AND POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS[1]

Criteria for Post-PV Myelofibrosis

Required criteria:

- **Documentation of a previous diagnosis of PV as defined by the WHO criteria[2]**
- **Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,5]**

Additional criteria (two are required):

- **Anemia[6] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis**
- **A leukoerythroblastic peripheral blood picture**
- **Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin [LCM]) or the appearance of a newly palpable splenomegaly**
- **Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)**

Criteria for Post-ET Myelofibrosis

Required criteria:

- **Documentation of a previous diagnosis of ET as defined by the WHO criteria[2]**
- **Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,5]**

Additional criteria (two are required):

- **Anemia[6] and ≥2 g/dL decrease from baseline hemoglobin level**
- **A leukoerythroblastic peripheral blood picture**
- **Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the LCM) or the appearance of a newly palpable splenomegaly**
- **Increased LDH (above reference level)**
- **Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)**

[1] Reproduced with permission from Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the international working group for myelofibrosis research and treatment. Leukemia 2008;22:437-438.
[2] Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 2007;110:1092-1097.
[3] Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128-1132.
[4] Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukaemia in adults. Br J Haematol 1979;43:185-190.
[5] Grade 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.
[6] Below the reference range for appropriate age, sex, gender, and altitude considerations.

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

ICC AND WHO DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA AND POST-PV MYELOFIBROSIS[1,a]

PV	Post-PV MF
Major criteria 1. Elevated hemoglobin concentration or elevated hematocrit or increased red blood cell mass[b] 2. Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia[c] 3. Presence of *JAK2* V617F or *JAK2* exon 12 mutation[d] **Minor criterion** • Subnormal serum erythropoietin level	**Required criteria** 1. Previous established diagnosis of PV 2. Bone marrow fibrosis of grade 2 or 3 **Additional criteria** 1. Anemia (ie, below the reference range given age, sex, and altitude considerations) or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis 2. Leukoerythroblastosis 3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly 4. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)
The diagnosis of PV requires either all 3 major criteria or the first 2 major criteria plus the minor criterion	**The diagnosis of post-PV MF is established by all required criteria and at least 2 additional criteria**

[a] The WHO 2022 criteria are the same as the WHO 2017 criteria. Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017; Khoury JD, et al. Leukemia 2022;36:1703-1719.

[b] Diagnostic thresholds: hemoglobin: >16.5 g/dL in men and >16.0 g/dL in women; hematocrit: >49% in men and >48% in women; red blood cell mass: >25% above mean normal predicted value.

[c] A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (hemoglobin concentrations of >18.5 g/dL in men or >16.5 g/dL in women and hematocrit values of >55.5% in men or >49.5% in women) and the presence of a *JAK2* V617F or *JAK2* exon 12 mutation.

[d] It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level <1%) and *CALR* and *MPL* (sensitivity level 1%–3%) in negative cases, consider searching for non-canonical or atypical *JAK2* mutations.

[1] Adapted with permission from Thiele J, Kvasnicka HM, Orazi A, et al. The International Consensus Classification of myeloid neoplasms and acute leukemias: Myeloproliferative neoplasms. Am J Hematol 2023;98:544-545. Erratum for: Am J Hematol 2023;98:166-179.

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

ICC AND WHO DIAGNOSTIC CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA AND POST-ET MYELOFIBROSIS[1,a]

ET	Post-ET MF
Major criteria **1. Platelet count ≥450 × 10^9/L** **2. Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated staghorn-like nuclei, infrequently dense clusters*; no significant increase or left shift in neutrophil granulopoiesis or erythropoiesis; no relevant bone marrow fibrosis†** **3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, PMF, or other myeloid neoplasms are not met** **4. *JAK2, CALR*, or *MPL* mutation‡** **Minor criteria** **• Presence of a clonal marker§ or absence of evidence of reactive thrombocytosis‖**	**Required criteria** **1. Previous established diagnosis of ET** **2. Bone marrow fibrosis of grade 2 or 3** **Additional criteria** **1. Anemia (ie, below the reference range given age, sex, and altitude considerations) and a >2 g/dL decrease from baseline hemoglobin concentration** **2. Leukoerythroblastosis** **3. Increase in palpable splenomegaly of >5 cm from baseline or the development of a newly palpable splenomegaly** **4. Elevated LDH level above the reference range** **5. Development of any 2 (or all 3) of the following constitutional symptoms: >10% weight loss in 6 mo, night sweats, unexplained fever (>37.5°C)**
The diagnosis of ET requires either all major criteria or the first 3 major criteria plus the minor criteria	**The diagnosis of post-ET MF is established by all required criteria and at least 2 additional criteria**

* Three or more megakaryocytes lying adjacent without other bone marrow cells in between; in most of these rare clusters ≤6 megakaryocytes may be observed, increase in huge clusters (>6 cells) accompanied by granulocytic proliferation is a morphological hallmark of pre-PMF (Table 5).
† Very rarely a minor increase in reticulin fibers may occur at initial diagnosis (grade 1).
‡ It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level <1%) and CALR and *MPL* (sensitivity level 1% to 3%); in negative cases, consider a search for noncanonical *JAK2* and *MPL* mutations.
§ Assessed by cytogenetics or sensitive NGS techniques.
‖ Reactive causes of thrombocytosis include a variety of underlying conditions like iron deficiency, chronic infection, chronic inflammatory disease, medication, neoplasia, or history of splenectomy.

[a] The WHO 2022 criteria are the same as the WHO 2017 criteria. Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017; Khoury JD, et al. Leukemia 2022;36:1703-1719.

[1] Adapted with permission from Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of myeloid neoplasms and acute leukemias: Integrating morphologic, clinical and genomic data. Blood 2022;140:1200-1228.

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

PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MYELOFIBROSIS
To be used in conjunction with the prognostic scoring systems[a]

Mutated Gene	Driver Mutations[b]
JAK2 V617F	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* type 1 mutation[1]
MPL W515L/K	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* type 1 mutation[1]
CALR type 1	Improved overall survival (OS) and lower risk of thrombosis compared to *JAK2* mutation and "triple-negative" PMF.[1-4] Improved OS compared to *CALR* type 2 mutation[5-8]
CALR type 2	Decreased OS compared to *CALR* type 1 mutation[5-8]
Mutated Gene	**Other Somatic Mutations**
ASXL1	Associated with inferior OS[c] and leukemia-free survival (LFS) and LFS following HCT[9,10]
EZH2	Associated with inferior OS[9]
RAS	Associated with inferior OS[11]
IDH1/2	Associated with inferior LFS and lower PFS following HCT[9,10]
SRSF2	Associated with inferior OS and LFS[9]
TP53	Associated with increased risk of leukemic transformation[12]
U2AF1	Associated with inferior OS following HCT[13-15] *U2AF1* Q157 is associated with inferior OS compared to patients with *U2AF1* S34 mutated or *U2AF1* unmutated MF
DNMT3A	Associated with inferior OS following HCT[14,15]
CBL	Associated with inferior OS following HCT[14,15]

[a] Various clinical outcomes are worse with multiple versus one somatic mutation identified.[16]
[b] Driver mutation negative "triple negative" MF is associated with inferior OS and LFS.[1-3]
[c] *ASXL1* mutation retains prognostic significance for inferior OS independent of IPSS or DIPSS-Plus risk score.

Continued

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

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

ASSESSMENT OF SYMPTOM BURDEN

- **Assessment of symptoms (in provider's office) at baseline and monitoring symptom status (stable, improved, or worsening) during the course of treatment is recommended for all patients.**
- **Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) is recommended for the assessment of symptom burden at baseline and monitoring symptom status during the course of treatment (MPN-F, 2 of 2).**
- **MPN-SAF TSS is assessed by the patients themselves. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0–100 scale).**
- **Symptom response requires ≥50% reduction in the MPN-SAF TSS. A symptom response <50% may be clinically meaningful and justify continued use of JAK inhibitors.**
- **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.**

Continued

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

MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS)[1]

(Recommended for monitoring symptoms during the course of treatment)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

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

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

[1] Reproduced with permission from Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012;30:4098-4103.

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

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.**
- **Antibiotic prophylaxis for recurrent infections is recommended. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections. In patients who have had a splenectomy, 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.

- **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.**
  - **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.**

Continued

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

SUPPORTIVE CARE FOR PATIENTS WITH MPN

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

SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA

Management of Vascular Events

- **Thrombosis**
  - The use of clinically appropriate anticoagulant therapy (eg, low-molecular-weight heparin [LMWH], direct oral anticoagulant, warfarin) is recommended for patients with active thrombosis. The initial use of anticoagulant therapy for the prevention and treatment of thrombosis should be based on the current American College of Chest Physicians (ACCP) Guidelines.[1,2]
  - Consider aspirin for patients with cardiovascular risk factors. The risks and benefits of aspirin plus anticoagulation need to be individualized on a case-by-case basis.
  - There are no data to guide the selection or appropriate duration of anticoagulation with or without antiplatelet therapy in patients with PV or ET. The use of anticoagulant therapy in combination with aspirin is associated with an increased risk of bleeding compared with aspirin alone. Caution is required when using antiplatelet agents with anticoagulants for the treatment of thrombosis in patients with PV.[3] The duration of anticoagulant therapy is dependent on the severity of the thrombotic event (eg, abdominal vein thrombosis vs. deep vein thrombosis), degree of disease control, and assessment of likelihood of recurrence after cessation of anticoagulant therapy.
  - Assess the need for cytoreductive therapy (if not done before) and initiate cytoreductive therapy (to maintain hematocrit <45% in patients with PV) if necessary. In the presence of inadequate response, consider intensification of therapy or switch to an alternate agent. The value of cytoreduction in reducing future vascular events has not been studied in prospective, randomized controlled trials in PV.
  - Plateletpheresis may be indicated in patients with ET presenting with acute life-threatening thrombosis or severe bleeding.
- **Bleeding**
  - Rule out other potential causes and treat coexisting causes as necessary.
  - Aspirin should be withheld until bleeding is under control. Consider the use of appropriate cytoreductive therapy to optimize platelet counts while minimizing hematologic and non-hematologic toxicities; see Discussion.
  - Coagulation tests to evaluate for acquired VWS and/or other coagulopathies are recommended for patients undergoing high-risk surgical procedures and those with elevated platelet count and/or splenomegaly or unexplained bleeding (MPN-1).
  - In unanticipated gastrointestinal (GI) bleeding, particularly in the setting of splenomegaly, portal hypertension, and gastric varices, special consultation (for endoscopic evaluation) with a hepatologist or a GI specialist is recommended.

Surgery

- Multidisciplinary management with surgical and perioperative medical teams (eg, review of bleeding and thrombosis history; medication list) is recommended.
- Emergency surgery should be performed as necessary with close postoperative surveillance for the symptoms of arterial or venous thrombosis and bleeding.
- Patients with PV and ET are at higher risk for bleeding despite optimal management. The thrombotic and bleeding risk of the surgical procedure (eg, orthopedic and cardiovascular surgery) should be strongly considered prior to elective surgery.

Continued
References

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

SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA[a]

Surgery (continued)

- **Thrombosis and bleeding risk should be well controlled (normalization or near-normalization CBC without causing prohibitive cytopenias) prior to performing elective surgery (particularly for orthopedic surgeries or any surgical procedures associated with prolonged immobilization) with the use of appropriate anticoagulant prophylaxis and cytoreductive therapy. If surgery is associated with a high risk for venous thromboembolism (VTE) (eg, cancer surgery, splenectomy, orthopedic and cardiovascular surgery), extended prophylaxis with LMWH should be considered. Prophylaxis with aspirin may be considered following vascular surgery.**
- **In patients with PV, hematocrit should be controlled for 3 months before elective surgery (normalization or near-normalization of CBC). Additional phlebotomy may also be necessary to maintain hematocrit <45% prior to performing elective surgery.**
- **Aspirin should be discontinued one week prior to surgical procedure and restarted 24 hours after surgery or when considered acceptable depending on the bleeding risk.**
- **Anticoagulant therapy should be withheld (based on the half-life/type of agent) prior to surgery and restarted after surgery when considered acceptable depending on the bleeding risk.**
- **Cytoreductive therapy could be continued throughout the perioperative period, unless there are unique contraindications expressed by the surgical team.**

Pregnancy

General Pregnancy-Related Recommendations

- **Pregnancy pre-conception meeting and evaluation by high-risk obstetrician is recommended.**
- **All females with PV should maintain hematocrit, ideally, below the gestational range (<41% trimester 1, <38% trimester 2, <39% trimester 3).**
- **Hydroxyurea should be discontinued in anticipation or in the event of pregnancy. If cytoreductive therapy is needed during pregnancy, peginterferon alfa-2a could be considered.[4] Potential indications include those with prior pregnancy loss or complications (pre-eclampsia), or uncontrolled leukocytosis/thrombocytosis. There are no sufficient data to establish the use of peginterferon alfa-2a in pregnancy. It should be used only if benefits outweigh potential risk to the fetus.[4]**
- **Direct oral anticoagulants should be avoided in breastfeeding females. Unfractionated heparin, LMWH, warfarin, and fondaparinux are all safe options in females who require anticoagulation and are breastfeeding.[5]**
- **Hydroxyurea is excreted in breastmilk and should be avoided in females who are breastfeeding.**

[a] NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

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

Continued
References

SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA

Recommendations for the Management of Standard-Risk Pregnancy

- **Patients with PV or ET who become pregnant and do not have the high-risk features (standard-risk pregnancy, listed below) should take low-dose aspirin daily throughout the pregnancy and should receive prophylactic LMWH alone during the first 6 weeks of the postpartum period (unless there are patient-specific contraindications). If they were taking low-dose aspirin prior to pregnancy, it can be resumed once the postpartum course of LMWH is complete.**

Definition of High-Risk Pregnancy in PV or ET[6]

Pregnancy in the setting of PV or ET is considered high risk if any of the following is present:

- **Previous venous and/or arterial thrombosis with/without pregnancy**
- **Previous hemorrhage due to PV or ET (see management section)**
- **Previous pregnancy complications:**
  - **Unexplained death of a morphologically normal fetus ≥10 weeks of gestation. Premature delivery of a morphologically normal fetus at <34 weeks of gestation due to:**
    - ◊ **Severe preeclampsia or eclampsia defined according to standard criteria**
    - ◊ **Recognized features of placental insufficiency**
  - **≥3 unexplained consecutive miscarriages at <10 weeks of gestation, without anatomic, hormonal, or chromosomal abnormalities**
  - **Unexplained intrauterine growth restriction**
  - **Significant antepartum or postpartum hemorrhage**

Recommendations for the Management of High-Risk Pregnancy[7-14]

Treatment to start (continue) when pregnancy test is positive, and pregnancy is considered high risk:

- **Low-dose aspirin daily**
- **Prophylactic LMWH throughout pregnancy and for 6 weeks postpartum[b]**
- **Cytoreductive therapy with interferon or peginterferon alfa-2a. See Table 1. Mastocytosis Treatments and Pregnancy/Lactation Risk in the NCCN Guidelines for Systemic Mastocytosis.**

[b] Administration of LMWH should be modified based on renal function, body weight, and medical history. Prophylactic LMWH should be avoided among patients with a history of MPN-related bleeding. Therapeutic anticoagulation with LMWH should be continued during pregnancy by patients receiving anticoagulation therapy after venous and/or arterial thrombotic events prior to pregnancy. Timing of LMWH and aspirin discontinuation prior to epidural and delivery and re-initiation of medications after delivery should be discussed with a high-risk obstetrician and obstetric anesthesiologist.

References

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

SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA

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

DEFINITION OF RESISTANCE/INTOLERANCE TO HYDROXYUREA[1]

Myeloproliferative Neoplasm	Definition of Resistance/Intolerance to Hydroxyurea
Polycythemia vera	**1. Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/d of hydroxyurea, OR** **2. Uncontrolled myeloproliferation (ie, platelet count >400 x 10^9/L AND WBC count >10 x 10^9/L) after 3 months of at least 2 g/d of hydroxyurea, OR** **3. Failure to reduce massive* splenomegaly by >50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/d of hydroxyurea, OR** **4. Absolute neutrophil count <1.0 x 10^9/L OR platelet count <100 x 10^9/L OR hemoglobin <10 g/dL at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response,† OR** **5. Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of hydroxyurea**
Essential thrombocythemia	**1. Platelet count >600 x 10^9/L after 3 months of at least 2 g/d of hydroxyurea (2.5 g/d in patients with a body weight >80 kg), OR** **2. Platelet count >400 x 10^9/L and WBC count <2.5 x 10^9/L at any dose of hydroxyurea, OR** **3. Platelet count >400 x 10^9/L and hemoglobin <10 g/dL at any dose of hydroxyurea, OR** **4. Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxyurea, OR** **5. Hydroxyurea-related fever**

*Organ extending by >10 cm from the costal margin.
†Complete response is defined as hematocrit less than 45% without phlebotomy, platelet count ≤400 x 10^9/L, WBC count ≤10 x 10^9/L, and no disease-related symptoms. Partial response is defined as hematocrit less than 45% without phlebotomy or response in three or more of other criteria.

[1] Reproduced with permission from Barbui T, Barosi G, Birgegard G, et al. Philadelphia-negative classical myeloproliferative neoplasms: Critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol 2011;29:761-770.

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

ABBREVIATIONS

ACCP	American College of Chest Physicians
AML	acute myeloid leukemia
CBC	complete blood count
CML	chronic myeloid leukemia
CMML	chronic myelomonocytic leukemia
CMV	cytomegalovirus
ESA	erythropoiesis-stimulating agent
ET	essential thrombocythemia
DIPSS	Dynamic International Prognostic Scoring System
FISH	fluorescence in situ hybridization
G-CSF	granulocyte colony-stimulating factor
GI	gastrointestinal
GM-CSF	granulocyte-macrophage colony-stimulating factor
HCT	hematopoietic cell transplant
H&P	history and physical
HLA	human leukocyte antigen
HMA	hypomethylating agent
HMR	high molecular risk
ICC	International Consensus Classification
IPSET	International Prognostic Score of Thrombosis for Essential Thrombocythemia
LCM	left costal margin
LDH	lactate dehydrogenase
LFT	liver function test
LFS	leukemia-free survival
LMWH	low-molecular-weight heparin
MF	myelofibrosis
MIPSS	Mutation-Enhanced International Prognostic Scoring System
MPN	myeloproliferative neoplasm(s)
MPN-SAF TSS	Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score
MYSEC-PM	Myelofibrosis Secondary to Polycythemia Vera and Essential Thrombocythemia-Prognostic Model
NGS	next-generation sequencing
NSAID	nonsteroidal anti-inflammatory drug
OS	overall survival
PCR	polymerase chain reaction
PFS	progression-free survival
PMF	primary myelofibrosis
PT	prothrombin time
PTT	partial thromboplastin time
PV	polycythemia vera
RBC	red blood cell
RT-PCR	reverse transcriptase polymerase chain reaction
TLS	tumor lysis syndrome
VHR	very high risk
VTE	venous thromboembolism
VWFA	von Willebrand factor antigen
VWF:RCo	von Willebrand ristocetin cofactor
VWS	von Willebrand syndrome
WBC	white blood cell

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analyses), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) 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.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

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

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2024
Myeloproliferative Neoplasms

Discussion

This discussion corresponds to the NCCN Guidelines for Myeloproliferative Neoplasms. Last updated: August 8, 2024.

Table of Contents

Overview

Myelofibrosis (MF), polycythemia vera (PV), and essential thrombocythemia (ET) are a group of heterogeneous disorders of the hematopoietic system collectively known as Philadelphia chromosome-negative myeloproliferative neoplasms (MPN). The prevalence of MF, ET, and PV in the United States is estimated to be approximately 13,000, 134,000, and 148,000, respectively.[1] In a survey that assessed the incidence rates (IRs) of different subtypes of MPN in the United States (2002–2016), the age-adjusted IRs per 100,000 person-years were highest for PV (IR = 1.57) and ET (IR = 1.55) and was 0.44 for primary MF (PMF).[2]

MPN are characterized by a complicated symptom profile; the symptom profile varies within and between each MPN subtype, but often includes fatigue, pruritus, weight loss, and symptoms from splenomegaly.[3-6] Variable laboratory abnormalities are observed depending on the type of MPN, including erythrocytosis, thrombocytosis, and leukocytosis, and sometimes myeloid immaturity, especially in progressive MF.[6] A SEER-Medicare database analysis showed that patients with MPN have substantially inferior survival compared to matched controls, and the survival for patients with MF is worse than that of patients with ET or PV and significantly worse than matched controls.[7] In addition, MPN also have the propensity for disease transformation into blast phase (MPN-BP), which is akin to acute myeloid leukemia (AML), which is associated with a poor prognosis.[8,9]

The diagnosis and comprehensive care of patients with MPN has evolved since the identification of JAK-STAT “driver” mutations (*JAK2, CALR*, and *MPL* mutations), and the development of targeted therapies has resulted in significant improvements in disease-related symptoms and quality of life.[10] However, certain aspects of clinical management regarding the diagnosis, assessment of symptom burden, and selection of appropriate symptom-directed therapies continue to present challenges for hematologists and oncologists.[11]

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 MPN in adults. 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.

Guidelines Update Methodology

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

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.

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[13] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Molecular Abnormalities in MPN

JAK2 V617F mutations account for the majority of patients with PV (>90%) and 60% of patients with ET or MF.[14-16] *JAK2* V617F can be identified in hematopoietic stem and progenitor cells.[17] The V617F mutation occurs in exon 14; however, rare insertions and deletions have been found in exon 12. *JAK2* exon 12 mutations have been described in 2% to 3% of patients with PV.[18,19]

Activating mutations in the thrombopoietin receptor gene (*MPL* W515L/K) are reported in approximately 5% to 8% of all patients with MF and 1% to 4% of all patients with ET.[20-22]

Frameshift mutations in exon 9 of *CALR* are reported in approximately 20% to 35% of all patients with ET and MF (accounting for approximately 60%–80% of patients with *JAK2/MPL*-negative ET and MF).[23,24] Type 1 (52 base pair deletions) and type 2 (5 base pair insertions) mutations are the most frequent *CALR* variants. *CALR* type 1 mutations are more frequent in patients with MF and *CALR* type 2 mutations are preferentially associated with ET.[25-27]

Mutations in several other genes that are involved in signal transduction (*CBL* and *LNK/SH2B3*), chromatin modification (*TET2, EZH2, IDH1/2, ASXL1,* and *DNM3TA*), RNA splicing (*SF3B1, SRSF2, U2AF1,* and *ZRSR2),* and tumor suppressor function (*TP53*) have also been reported in patients with MPN.[28,29]

Myelofibrosis

Mutations in *CALR* are associated with better overall survival (OS) than the *JAK2* V617F or *MPL* W515 mutations and the survival advantage is more pronounced in patients with a type 1/type 1-like mutation.[9,26,30,31] In a study of 617 patients with PMF, the median OS was 18 years for those with *CALR* mutations versus 9 years for those with *JAK2* V617F mutation or *MPL* mutation and 3 years for patients with triple-negative MF.[30] *CALR* mutations retained their prognostic significance for better OS compared to *JAK2* V617F mutation ($P = .019$) or triple-negative status ($P < .001$) in a multivariate analysis corrected for age. The 10-year cumulative incidence of leukemic transformation was also lower (9%) for patients with *CALR* mutation compared to 19% for those with *JAK2* V617F mutation, 17% for

those with *MPL* mutation, and 34% for those with triple-negative disease. In a study that evaluated the prognostic impact of the two different types of *CALR* mutations in 396 patients with PMF, the median survival was significantly higher for patients with type 1/type 1-like mutation than for those with type 2/type 2-like mutation or *JAK2* V617F mutation (26 vs. 7 years; $P < .0001$).[31] The rate of leukemic transformation was also higher among patients with type 2/type 2-like mutation than for those with type 1/type 1-like and *JAK2* V617F mutation.

MPL mutations are associated with lower hemoglobin levels at diagnosis and increased risk of transfusion dependence in patients with MF.[32] The triple-negative mutation status (lack of all three "driver" mutations—*JAK2, CALR, or MPL)*, which occurs in approximately 10% of patients, is associated with a worse prognosis in patients with MF.[33,34]

ASXL1, EZH2, SRSF2, TP53, IDH1, *IDH2, or U2AF1* mutations are considered as high-molecular-risk (HMR) mutations and are associated with significantly shorter OS and leukemia-free survival (LFS) in patients with PMF.[35-40] *ASXL1, EZH2, SRSF2, and RAS* mutations are predictive of OS, while *ASXL1, SRSF2*, *and IDH1 or IDH2* are predictive of leukemic transformation in patients with PMF.[35-38,41,42] *TET2* or *TP53* mutations have also been associated with a worsened overall prognosis and an increased rate of leukemic transformation.[29,39] *U2AF1* mutations have also been associated with inferior survival in patients with PMF.[40]

In a study that evaluated the prognostic significance of somatic mutations in 879 patients with PMF, the median survival was significantly shorter (81 vs. 148 months; $P < .0001$) in patients with at least one mutation in the prognostically significant genes (*ASXL1, EZH2, SRSF2, IDH1*, *or IDH2*) compared with those with no mutation in any of these genes.[37] However, only *ASXL1* mutations retained prognostic significance after accounting for known prognostic factors. The results of a subsequent analysis that evaluated the additional prognostic value of the "number" of mutated genes in 797 patients with PMF confirmed that patients harboring ≥2 HMR mutations had significantly reduced OS and LFS compared not only to patients with no mutations but also to those presenting with only one HMR mutation.[38] The median OS was 3 years for patients with ≥2 HMR mutations compared to 7 years and 12 years, respectively, for those with one HMR mutation and no mutations. The corresponding LFS was 7 years, 11 years, and 27 years, respectively.

An analysis that assessed the impact of both *CALR* and *ASXL1* mutations on OS in 570 patients with PMF identified *CALR(-)/ASXL1(+)* mutational status as the most significant adverse risk factor for survival.[43] *CALR(+)/ASXL1(-)* was associated with the longest median OS (10.4 years) and *CALR(-)/ASXL1(+)* was associated with shortest median OS (2.3 years); this prognostic significance was independent of the Dynamic International Prognostic Scoring System (DIPSS)-plus risk score.

The prognostic significance of these HMR mutations, perhaps with the exception of *SRSF2* mutations, has not yet been established in patients with post-PV or post-ET MF.[44]

Polycythemia Vera and Essential Thrombocythemia

JAK2 exon 12-mutated PV is characterized by significantly higher hemoglobin level and lower platelet and leukocyte counts at diagnosis compared to *JAK2* V617F-mutated PV.[45,46] However, both *JAK2* V617F and *JAK2* exon 12 mutations are associated with similar rates of thrombosis, transformation to MF or leukemia, and death.[45] Another study reported similar findings but found no difference in hemoglobin level.[47] The number of deaths was also significantly higher in patients with *JAK2* V617V mutation.

CALR-mutated ET is characterized by younger age, male sex, higher platelet count, lower hemoglobin, lower leukocyte count, and lower risk of

thrombosis than *JAK2*-mutated ET, whereas the presence of *MPL* mutations might be associated with a higher risk of fibrotic transformation.[48-52] Compared to patients with *MPL*-mutated ET, patients with CALR-mutated ET had a lower risk of thrombosis but similar hemoglobin levels and leukocyte and platelet counts.[48]

However, *CALR* mutations have no impact on OS or myelofibrotic or leukemic transformation.[50,53] *CALR* mutation status also did not have a significant impact on the International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) prognostic score for predicting the risk of thrombosis.[54]

Next-generation sequencing (NGS) has identified adverse variants/mutations in several other genes and may be useful to identify a minority of patients with PV and ET with increased risk of leukemic transformation.[34,55-57] In one report, the presence of at least one of the three non-driver mutations (*ASXL1, SRSF2*, and *IDH2)* was associated with inferior OS and MF-free survival but it did not significantly affect the LFS in patients with PV.[55] In the multivariable analysis, *ASXL1* and *SRSF2* retained the prognostic significance for OS and *ASXL1* was prognostic of MF-free survival. *SH2B3, IDH2, U2AF1, SF3B1, EZH2, and TP53* mutations were identified as significant risk factors for inferior OS, MF-free survival, and LFS in patients with ET. Multivariable analysis confirmed the individual prognostic significance of *U2AF1* mutation for OS and MF-free survival and *TP53* mutation for LFS. In one report, myelofibrotic transformation was more frequent in patients with *SF3B1* and *IDH1/2* mutations, although a persistently high or a progressive increase of the *JAK2* V617F allele burden while receiving cytoreductive therapy was the strongest predictor of myelofibrotic transformation.[56]

Diagnostic Classification

The World Health Organization (WHO) classification of myeloid neoplasms was first published in 2001 and was updated in 2008 to refine the diagnostic criteria for previously described neoplasms based on new scientific and clinical information and to introduce newly recognized disease entities.[58,59] It was revised in 2017 and once again in 2022 to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the publication of the 2008 WHO classification.[60-63]

The 2017 WHO diagnostic criteria include molecular testing for *JAK2, CALR*, and *MPL* mutations for PMF and ET and molecular testing for *JAK2* V617F or *JAK2* exon 12 mutations for PV.[61] In the absence of *JAK2, CALR,* and *MPL* mutations, the presence of another clonal marker is included as one of the major diagnostic criteria for PMF. Additional mutations in *ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2,* and *SF3B1* genes are noted to be of use in determining the clonal nature of the disease.[37,38]

MF can present as a de novo disorder (PMF) or it can develop from the progression of PV and ET (post-PV MF or post-ET MF).[64] Prefibrotic/early-stage PMF is characterized by an increase in atypical megakaryocytes, reduced erythropoiesis, and increased age-matched bone marrow cellularity. However, overt bone marrow fibrosis might be absent in early-stage/prefibrotic PMF, leading to a diagnosis of ET.[65] The revised 2017 WHO and the 2022 International Consensus Criteria (ICC) diagnostic criteria include separate criteria for prefibrotic/early-stage PMF and overt fibrotic-stage PMF in order to differentiate true ET from prefibrotic/early PMF by the morphologic findings of the bone marrow biopsy, including the lack of reticulin fibrosis at onset.[61,62] The 2017 WHO diagnostic criteria for prefibrotic/early-stage PMF and overt fibrotic-stage PMF have also been validated in a large series of patients with pre-PMF and overt PMF.[66-68]

In the International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) study that reevaluated 1104 patients with a diagnosis of ET, central pathology review revealed a diagnosis (as defined by the WHO criteria) of ET in 891 patients (81%) and early/prefibrotic PMF in 180 patients (16%). The remaining 33 patients (3%) were unevaluable.[65] The frequency of grade 1 bone marrow fibrosis was greater in patients with early/prefibrotic PMF. In addition, leukocyte count, platelet count, serum lactate dehydrogenase (LDH) level, and the incidence of palpable splenomegaly were greater in patients with early/prefibrotic PMF, whereas hemoglobin level was greater in patients with ET. The long-term clinical outcomes were significantly worse for patients with early-stage/prefibrotic PMF. The 15-year rates of OS, leukemic transformation, and fibrotic progression were 59%, 12%, and 17%, respectively, for patients with early-stage/prefibrotic PMF. The corresponding rates were 80%, 2%, and 9%, respectively, for patients with ET. In a multivariate analysis, bone marrow histopathology remained prognostically significant for survival (*P* = .03), leukemic transformation (*P* = .007), and overt fibrotic progression *(P* = .019). Therefore, accurate evaluation of bone marrow morphology is essential to distinguish early-stage/prefibrotic PMF from ET, especially since the long-term clinical outcomes are significantly better for patients with ET than for those with prefibrotic MF.

In the 2017 WHO criteria, the diagnostic criteria for PV have been refined to differentiate masked PV from ET (recognizing the utility of bone marrow biopsy in patients with hemoglobin levels <18.5 g/dL in men and <16.5 g/dL in women).[61] In an international study of 397 patients with *JAK2* V617F or a *JAK2* exon 12 mutation and WHO-defined PV morphology, 257 patients were diagnosed with overt PV that met the full 2008 WHO diagnostic criteria for PV. The remaining 140 patients were classified as having masked PV with hemoglobin levels at diagnosis of <18.5 g/dL in males (range, 16.0–18.4 g/dL) and <16.5 g/dL in females (range, 15.0–16.4 g/dL) and frequent presence of subnormal erythropoietin (EPO) levels.[69] In a multivariate analysis, the diagnosis of masked PV was an independent predictor of poor survival in patients aged >65 years with a leukocyte count >10 x 10^9/L. In the absence of these risk factors, the outcome of patients with masked PV was similar to that of patients with overt PV, suggesting that a fraction of patients with lower hemoglobin levels should still be considered as overt PV. The results of a study also showed that the OS, rates of thrombosis and major bleeding, and probability of transformation were similar among patients with masked and overt PV.[70] Thus, the major diagnostic criteria for PV have been refined to include hemoglobin levels (>16.5 g/dL in men and >16.0 g/dL in women) or hematocrit >49% in men and >48% in women and a bone marrow biopsy to confirm the age-matched hypercellularity.[61] Bone marrow biopsy may not be required to make the diagnosis in patients with sustained absolute erythrocytosis (hemoglobin levels >18.5 g/dL in men [hematocrit >55.5%] or >16.5 g/dL in women [hematocrit >49.5%]) and *JAK2* V617F or *JAK2* exon 12 mutations and subnormal EPO levels. However, a bone marrow biopsy in these patients can still provide helpful prognostic information.

The diagnosis of MPN should be based on the 2022 WHO and ICC diagnostic criteria.[61-63] The diagnosis of PMF requires meeting all three major criteria and at least one minor criterion confirmed in two consecutive determinations as outlined in the 2022 WHO or ICC criteria.[61-63] The diagnosis of PV requires meeting either all three major criteria or the first two major criteria and the minor criterion, whereas the diagnosis of ET requires meeting all four major criteria or the first three major criteria and the minor criterion as outlined in the 2022 WHO or ICC criteria.[61-63,71] See *International Consensus Classification and WHO Diagnostic Criteria for Primary Myelofibrosis* and *ICC and WHO Diagnostic Criteria for Polycythemia Vera and Post-PV Myelofibrosis* in the algorithm for the lists

of major and minor criteria. The diagnosis of post-PV MF or post-ET MF is based on the 2008 IWG-MRT, 2022 ICC, and 2022 WHO diagnostic criteria. The 2008 IWG-MRT and 2022 ICC criteria require the documentation of a previous diagnosis of PV or ET as defined by the WHO criteria and the development of European bone marrow fibrosis grade MF-2 to MF-3 (or 3–4+, depending on the scale) and at least two minor criteria.[62,72]

Workup of Suspected MPN

Initial evaluation of patients with suspected MPN should include a history and physical examination, palpation of spleen, evaluation of thrombotic and hemorrhagic events, cardiovascular risk factors, as well as transfusion and medication history. Laboratory evaluations should include complete blood count (CBC) with differential, microscopic examination of the peripheral smear, comprehensive metabolic panel with serum uric acid, serum LDH, liver function tests, serum EPO level, and serum iron studies. Human leukocyte antigen (HLA) typing should be performed for patients with MF for whom allogeneic hematopoietic cell transplant (HCT) would be considered.

Fluorescence in situ hybridization (FISH) or a multiplex reverse transcriptase polymerase chain reaction (RT-PCR), if available, on peripheral blood to detect *BCR::ABL1* transcripts and exclude the diagnosis of CML is especially recommended for patients with left-shifted leukocytosis and/or thrombocytosis with basophilia.[61] FISH may have better specificity than RT-PCR in the detection of unusual breakpoints. Some institutions prefer FISH to detect cryptic translocations while others prefer RT-PCR. The preferred method may vary based on institutional expertise. Molecular testing on blood or bone marrow for *JAK2* V617F mutations is recommended as part of initial workup for all patients.[61] If *JAK2* V617F mutation testing is negative, molecular testing for *CALR* and *MPL* mutations should be performed for patients with suspected ET and MF; molecular testing for the *JAK2* exon 12 mutation should be done for those with suspected PV and negative for the *JAK2* V617F mutation.[18,19] Alternatively, molecular testing using the multigene NGS panel that includes *JAK2, CALR*, and *MPL* can be used as part of initial workup for all patients. Once an MPN diagnosis is confirmed, NGS is recommended for mutational prognostication. The application of an NGS-based 28-gene panel in patients with MPN identified significantly more mutated splicing genes (*SF3B1, SRSF2*, and *U2AF1*) in patients with PMF compared to those with ET, and no mutations in splicing genes were found in patients with PV.[73] NGS may also be useful to establish the clonality in selected circumstances (eg, triple-negative MPN with non-mutated *JAK2, MPL,* and *CALR*). It can also identify second, third, and fourth mutations that may hold prognostic relevance.

Bone marrow aspirate with iron stain and biopsy with trichrome and reticulin stains and bone marrow cytogenetics (karyotype, with or without FISH; peripheral blood for FISH, if bone marrow is inaspirable) are necessary to accurately distinguish the bone marrow morphologic features between the disease subtypes (early or prefibrotic PMF, ET, and masked PV).[61,65,69] Bone marrow histology shows hypercellularity and megakaryocytic proliferation. In the case of MF, bone marrow fibrosis is demonstrated on the reticulin stain and an additional trichrome stain is recommended to distinguish grade MF-1 from MF-2 or MF-3, as outlined in the 2017 WHO diagnostic criteria.[61,74] Progression of PV or ET to MF can only be detected by performing a bone marrow biopsy. If there is evidence of mast cell aggregates, the diagnostic workup should be performed according to the NCCN Guidelines for Systemic Mastocytosis (available at www.NCCN.org).

MPN are associated with an increased risk of major bleeding and thrombosis compared to the general population, and these events contribute considerably to morbidity and mortality in patients with MPN.[75,76]

Acquired von Willebrand syndrome (VWS) is associated with a variety of hematologic disorders, being particularly frequent in lymphoproliferative (48%) and myeloproliferative disorders (15%). Among MPN, the frequency of acquired VWS is more common among patients with ET (11%–17%) but can also be seen in patients with PV.[77] Coagulation tests to evaluate for acquired VWS (plasma von Willebrand factor antigen measurement, ristocetin cofactor activity [also referred to as von Willebrand factor activity], von Willebrand multimer analysis, and Factor VIII level)[78] or other coagulopathies (prothrombin time, partial thromboplastin time, and fibrinogen activity) are recommended for patients undergoing high-risk surgical procedures and those with elevated platelet count or splenomegaly or unexplained bleeding.

Assessment of Symptom Burden

MPN are characterized by a complicated symptom profile resulting in reductions in quality of life, functional status, and activities of daily living.[3-5] Constitutional symptoms (fever, night sweats, and weight loss) are more frequently reported in patients with MF compared to those with PV or ET.[3,5] In a landmark survey that evaluated the symptom burden experienced by patients with MPN, disease-related symptoms were reported ≥1 years before diagnosis in 49% of patients with MF, 61% of patients with PV, and 58% of patients with ET.[4] In an online survey of 669 patients with MPN, fatigue was the most frequent symptom observed in 54% of patients with MF, 45% of patients with PV, and 64% of patients with ET.[5] Abdominal discomfort, night sweats, difficulty sleeping, shortness of breath, pruritus, bruising, loss of concentration, and dizziness were the other common symptoms and the incidences varied by disease type.

Various tools have been developed and validated in a large cohort of patients with MPN for the assessment of symptom burden.[79-83]

The Myelofibrosis Symptom Assessment Form (MF-SAF) is a 20-item tool used for the assessment of MF-associated symptoms, including fatigue, symptoms associated with splenomegaly (early satiety, abdominal pain or discomfort, inactivity, and cough), constitutional symptoms (night sweats, itching, bone pain, fever, and weight loss), and quality of life.[79] MF-SAF was subsequently expanded to a 27-item tool, Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF), to include the assessment of additional symptoms that are relevant to ET and PV (insomnia, headaches, concentration, dizziness, vertigo, lightheadedness, numbness or tingling, depression, and sexual desire dysfunction).[81]

MPN-SAF was further simplified to a concise and abbreviated tool, MPN-SAF Total Symptom Score (MPN-SAF TSS; MPN-10), which is used for the assessment of the 10 most relevant symptoms in patients with MPN (fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fever) in both clinical practice and clinical trial settings.[82] The MPN-10 score is influenced by *JAK2*, *CALR*, and triple-negative mutation status, which can be helpful for predicting survival and disease progression in patients with MPN.[84]

All three symptom assessment tools are co-administered with the Brief Fatigue Inventory and symptom severity is rated by patients on a scale of 1 to 10. Assessment of symptom burden at baseline and during the course of treatment with MPN-SAF TSS (MPN-10) is recommended for all patients.[81,82]

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 available[97] 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 10^9/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 DIPSS low-risk patients 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 10^9/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 10^9/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 10^9/L, platelet count <100 x 10^9/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 mutation-informed (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 10^9/L), and constitutional symptoms.[100] The median survival was not reached, 9 years, 4 years, and 2 years, respectively. Palandri et al[101] 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 MF[108-110] 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 al[109] 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] Forty-six 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 analysis[114] 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 10^9/L and 138 patients with platelet count <100 x 10^9/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 10^9/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 10^9/L (34.7% and 17.1%, respectively) and in patients with platelet count <100 x 10^9/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 10^9/L and pneumonia (5.8%), pyrexia (3.6%), and dyspnea (3.6%) in patients with platelet count <100 x 10^9/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-I[86,120,121] and COMFORT-II[113,122,123] 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 10^9/L to 200 x10^9/L and 20 mg twice daily for >200 x 10^9/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 10^9/L and 20 mg twice daily if the platelet count was >200 x 10^9/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 al[126] 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 al[129] 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 10^9/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 10^9/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 10^9/L or 75 to 99 x 10^9/L.[131] Patients with platelet count of 75 to 99 x 10^9/L displayed higher tolerability. At 48 weeks, 33.3% of patients with platelet count 75 to 99 x 10^9/L demonstrated a spleen response compared to 30% of patients with platelet count 50 to 74 x 10^9/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.

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 10^9/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.[147] 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 10^9/L (N = 14) and 49% in patients with platelet count ≥100 x 10^9/L (N = 82) who were treated with 400 mg daily fedratinib at 24 weeks.[148] 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 10^9/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.[149] 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.[147] 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 10^9/L (N = 33) and 28% in patients with platelet count ≥100 x 10^9/L (N = 64) at 24 weeks.[148] 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.[150]

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 10^9/L [N = 48] and 5% for platelet count ≥100 x 10^9/L [N = 155]) in patients treated with 400 mg daily fedratinib.[148]

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.[151,152] 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). [153]

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.[154] 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.[155] 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.[155] 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.[149] 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,[155] and thus was not found to be clearly different than the 1% to 2% prevalence of WE in the general U.S. population.[156]

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.[92,93,157] Pacritinib is FDA-approved for the treatment of intermediate or high-risk MF with a platelet count <50 x 10^9/L.[93,157]

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 10^9/L.[157] 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 10^9/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 10^9/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 10^9/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 10^9/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.[157] Pneumonia (9.3%) as well as diarrhea, abdominal pain, and hyperuricemia (5.6% each) were the most common non-hematologic grade 3 or 4 treatment-emergent adverse events. Like fedratinib, pacritinib also exhibits FLT3 inhibition, which has been implicated in gastrointestinal toxicity.[151,152]

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 10^9/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.[90,91,158] 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.[158,159]

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.[158] 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.[160]

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.[159] 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.[160]

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.[158] 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.[159]

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). Myeloablative conditioning and reduced-intensity conditioning (RIC) are relatively similar in terms of OS.[161] 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.[162-169] Comparison studies of RIC also do not show a difference in OS,[169,170] 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.[169] Another study also determined a higher relapse rate but the difference was not statistically significant (*P* = .21).[170] 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.[171,172] The estimated OS and NRM rates for myeloablative conditioning at 3 to 5 years range from 30% to 61% and 35% to 50%, respectively.[173] 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.[174] 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%.[163] 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.[166,167] 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.[166] 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.[167] 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.[175] 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.[166] 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).[167]

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.[176] 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.[177] 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.[177-179] 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.[177] 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).[178] The results of a multivariate analysis by Polverelli et al[179] 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.[166,180] 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.[166] 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).[180] 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.[166,181,182] 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.[181] In another retrospective analysis that evaluated the impact of allogeneic HCT on survival in patients <65 years 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.[182]

These findings suggest that outcomes following allogeneic HCT are better for patients with low- or intermediate-1-risk MF.[166,180] However, since HCT is associated with a significant rate of transplant-related complications and morbidity that may not otherwise occur with non-transplant therapies in this group of patients, the overall benefit may be with non-transplant therapies.[183] 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.[184]

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 10^9/L, and leukocyte count >25 x 10^9/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.[185] 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.[186] 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 high-risk 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.[187,188] 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.[29,37-39,188] *CBL*, *DNMT3A*, and *U2AF1* were associated with worse OS in patients with MF undergoing allogeneic HCT.[189,190] The results from another study also suggest inferior OS with *ASXL1* mutations (subdistribution HR, 2.36; 95% CI, 0.85–6.6; *P* = .09).[178]

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).[187] 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.[188] *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%.[191]

The addition of mutational status to DIPSS-Plus can help improve the prediction of transplantation outcome.[192] 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.[193] 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 10^9/L), and momelotinib (category 2B) are listed as useful in certain circumstances options for patients with symptomatic lower-risk MF.

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.[166,180,182] 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.[194] Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics.

Higher-Risk MF

Evaluation for allogeneic HCT is recommended for all patients with higher-risk MF and allogeneic HCT is recommended for patients who meet transplant eligibility criteria.[180] 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(s).

Early referral to transplant is recommended for planning purposes. Bridging therapy can be used to decrease marrow blasts to an acceptable level prior to allogeneic HCT. The results of several studies suggest that prior exposure to ruxolitinib may improve outcomes after allogeneic HCT.[172,195-197] The guidelines recommend continuation of JAK inhibitors near to the start of conditioning therapy for the improvement of splenomegaly and other disease-related symptoms.[172,195,196] 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.[172] 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 colleagues[196] 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 post-transplant. At 2 years, the OS was 61% (95% CI, 49%–71%).

Similarly, a study by Chhabra et al[195] 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.[197] 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.[198] 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 10^9/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.[158] 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 10^9/L).[130]

Enrollment in a clinical trial, ruxolitinib[86,113,120-122] (category 1), fedratinib[94] (category 1), momelotinib,[158] or pacritinib[92,93] (category 2B) are options for patients with higher-risk MF with symptomatic splenomegaly and/or constitutional symptoms and with platelet count ≥50 x 10^9/L who are not candidates for transplant or for whom transplant is not currently feasible. A study by Hernandez-Boluda[199] reported that patients with severe thrombocytopenia (platelet count <50 x 10^9/L) were in a higher risk category and had more instances of anemia and leukopenia. Patients with platelet count <50 x 10^9/L experience a greater symptom burden and might benefit from symptomatically guided treatment options.[200]

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.[201] It is essential to assess for and treat (if necessary) the most common co-existing 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 fueled 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,[202] luspatercept has garnered significant attention in the MF field and is the subject of a randomized phase III 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.[203] 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 hemoglobin 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.[204-206] 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).[207] 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.

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.[208-214] 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).[215] 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.[216-219] Lenalidomide is more likely to induce better response rates in patients with isolated 5q deletion.[220]

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.[221] 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.[222,223] 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.[222] 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.[223]

Studies are ongoing to evaluate the combination treatment of ruxolitinib with thalidomide or pomalidomide in patients with MF (NCT03069326 and NCT01644110).[224,225] 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.[226] 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.[227] 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.[228] 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.[229] The guidelines recommend continuation of JAK inhibitors (ruxolitinib, fedratinib, momelotinib, or pacritinib) for the improvement of splenomegaly and other disease-related symptoms.

Treatment options for the management of MF-associated anemia are based on the presence or absence of symptomatic splenomegaly and/or constitutional symptoms. For patients with anemia and symptomatic splenomegaly and/or constitutional symptoms that are currently controlled on a JAK inhibitor, enrollment in a clinical trial is preferred. Ruxolitinib combinations are other recommended regimens. Luspatercept-aamt, ESAs (epoetin alfa or darbepoetin alfa) (if serum EPO <500 mU/mL), or danazol (category 2B) can be added to ruxolitinib. An FDA-approved biosimilar is an appropriate substitute for epoetin alfa. Changing to momelotinib or pacritinib may be useful in certain circumstances.

For patients with anemia and symptomatic splenomegaly and/or constitutional symptoms not controlled, enrollment in a clinical trial and momelotinib are preferred regimens. Pacritinib, as well as ruxolitinib combination, are other recommended regimens. Luspatercept-aamt, ESAs (if serum EPO <500 mU/mL) (category 2B), or danazol (category 2B) can be added to ruxolitinib. In the absence of symptomatic splenomegaly and/or constitutional symptoms, a clinical trial is preferred for patients with anemia. Luspatercept-aamt, ESAs (if serum EPO <500 mU/mL), danazol, momelotinib (category 2B), and pacritinib (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.

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.[230] 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.[231] 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.[231] 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.[231] 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.[231]

The guidelines recommend monitoring 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. Continuation of JAK inhibitors is 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.[232] 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.[233] 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).[233] 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.[234] 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 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 10^9/L], or momelotinib [category 2B]).

For patients with higher-risk MF with platelet count ≥50 x 10^9/L who are not candidates for transplant and who have 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.[89,93,149,159]

JAK2 V617F Allele Burden

Reductions in *JAK2* V617F allele burden have been observed in patients with MF with long-term fedratinib[235] or ruxolitinib therapy.[123,236] 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).[236] 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.[237,238]

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.[231] 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 10^9/L and RBC transfusions for symptomatic anemia.[239] 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 (JC) virus, 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. Antibiotic prophylaxis and vaccinations for recurrent infections are recommended as outlined in the NCCN Guidelines for the Prevention and Treatment of Cancer-Related Infections. 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, 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.[240] Cytoreductive therapy (eg, hydroxyurea) could be considered for the management of hyperproliferative manifestations of PMF (thrombocytosis or leukocytosis).[193] 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.[241-246] 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,[247,248] and other studies have reported that leukocytosis at diagnosis is not associated with the risk of subsequent thrombosis.[242] Thrombocytosis (platelet count >1000 x 10^9/L) has been associated with an immediate risk of major hemorrhage but not with the risk of thrombosis in patients with ET.[245] In fact, some studies have reported that elevated platelet counts at diagnosis (>1000 x 10^9/L) are associated with significantly lower rate of thrombosis; this association was significant even in patients with *JAK2*-mutated ET.[243,244] 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.

Polycythemia Vera

Advanced age (ie, >60 years) and history of thrombosis are the most consistent risk factors associated with the risk of thrombosis.[249] 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.[250,251]

In a study of 336 patients with PV, the presence of *SRSF2* mutation, age >67 years, leukocyte count ≥15 x 10^9/L, and history of thrombosis were identified as independent risk factors for survival.[252] 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

In an analysis of 867 patients with ET, age ≥60 years, leukocyte count ≥11 x 10^9/L, and prior thrombosis were significantly associated with inferior survival.[253] 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.[254] 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.[254] 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%).[255] 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.[255,256]

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.

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.[252] 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.

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).[257] 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.[258] 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%.[258] 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 hematocrit 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.[259,260] 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.[259] 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.[259]

Cytoreductive Therapy

Hydroxyurea,[258,261,262] interferon alfa,[263-265] peginterferon alfa,[266-269] and ropeginterferon alfa-2b-njft[270,271] 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.[261] 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).[272] 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.[273] 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.[262] 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.[267] 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.[269] 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.[268] 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).[274] 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,[275-277] peginterferon alfa-2a,[268,269] and possibly anagrelide[276-279] 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 below 600 x 10^9/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).[275] In another randomized study of 809 patients with high-risk ET, hydroxyurea plus low-dose aspirin was superior to anagrelide plus low-dose aspirin.[276] Patients in the hydroxyurea arm initially received the drug at a dose of 0.5 g 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 10^9/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.[277] 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 10^9/L) or close to it (>450 x 10^9/L to 600 x 10^9/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.[279]

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.[269] The presence of *TET2, ASXL1, EZH2, DNMT3A,* and *IDH1/2* mutations was associated with non-achievement of CMR.[268] 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.[280] 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).[271] 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).[270] The composite primary endpoint was the achievement of CHR and normal spleen size by imaging. At 12 months, non-inferiority 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.[281] 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).[282] 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.[283] 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.[87,284,285]

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%.[284] 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.[286] 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 non-hematologic 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.[287] 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.[288] Of those receiving best available therapy, 77% crossed over to the ruxolitinib arm after week 28. At 80 weeks, patients discontinued best available therapy.[289] At 5 years, durable hematocrit control was reported in 22% of patients in the ruxolitinib group.[289] 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.[290]

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.[291] 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.[292] 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.[293]

Treatment Recommendations Based on Risk Stratification

Treatment options should be individualized based on age and history of thrombosis for patients with PV,[249] and the revised IPSET-thrombosis is preferred for the risk stratification of patients with ET.[255,256]

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.[257,258] In the CYTO-PV study, the hematocrit 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%.[258] 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, 42% for female patients and/or for patients with progressive or residual vascular 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 pregnant patients in need of cytoreductive therapy.

Essential Thrombocythemia

Very Low Risk (Age ≤60 years without JAK2 mutation and no prior history of thrombosis) or Low Risk (age ≤60 years with JAK2 mutation and no prior history of thrombosis) or Intermediate Risk (age >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.[294] 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).[295] The dose of hydroxyurea was adjusted in order to maintain platelet count between 200 x 10^9L to 400 x 10^9/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.[260] 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.[260] 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.[296,297] One randomized trial found that a dosing interval of 12 hours heightened the effectiveness of low-dose aspirin as an antiplatelet drug.[298] 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.[299] Aspirin twice daily may be considered for patients with refractory symptoms.[296,297] 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 (hydroxyurea [preferred regimen], peginterferon alfa-2a [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.

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.[300] 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 10^9/L, white blood cell [WBC] count <10 x 10^9/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.[301] 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.[302-304] 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.[300]

Monitoring Response and Follow-up Therapy

The goal of therapy is to prevent thrombotic and hemorrhagic complications without increasing the risk of bleeding. Monitoring for new thrombosis, acquired VWS, and/or disease-related major bleeding (in patients with ET) is recommended for all patients. After initiation of low-dose aspirin (and phlebotomy for patients with PV), the guidelines recommend monitoring for new thrombosis or bleeding, symptom status using MPN-SAF TSS, signs/symptoms of disease progression, and evaluation for potential indications for cytoreductive therapy as clinically indicated. For ET, bone marrow aspirate and biopsy should be performed to rule out disease progression to MF if there is clinical and/or laboratory suspicion of MF. The development of new thrombosis or disease-related major bleeding, frequent phlebotomy or intolerance to phlebotomy, splenomegaly, progressive thrombocytosis and/or leukocytosis, or disease-related symptoms are considered as potential indications for cytoreductive therapy.

In one retrospective study, the need for ≥3 phlebotomies per year was associated with a significantly higher rate of thrombosis in patients with PV treated with hydroxyurea (21% at 3 years compared to 5% at 3 years for those receiving ≤2 phlebotomies per year; $P < .0001$).[305] However, these findings could not be confirmed by other investigators.[306,307] The development of cytopenia (one of the ELN-defined criteria for resistance or intolerance to hydroxyurea) at the lowest dose of hydroxyurea is an adverse prognostic factor associated with higher risk of death and transformation to AML.[308,309] Patients with high-risk PV or ET treated with cytoreductive therapy as initial treatment should also be monitored for intolerance or resistance to hydroxyurea.[310]

The Panel acknowledges that the IWG-MRT and ELN treatment response criteria were developed mainly for use in clinical trials and that clinical benefit may not reach the threshold of the IWG-MRT and ELN response criteria. Response criteria are not defined for patients treated with low-dose aspirin. Available evidence from retrospective studies that have evaluated these response criteria in patients with PV and ET treated with cytoreductive therapy suggests that achievement of CR as outlined in the response criteria did not correlate with a lower incidence of thrombosis or improvement in thrombosis-free survival.[308,311-313] In selected patients with a severe thrombotic event, normalization of blood counts might be an essential goal of treatment. 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. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician, and target WBC or platelet counts should be individualized to prevent new thrombosis or bleeding in each patient depending on the presence of risk factors.

Continuation of prior treatment is recommended for patients with asymptomatic disease (low-risk PV and very-low-risk, low-risk, or intermediate-risk ET) with no potential indications for cytoreductive therapy and for patients with high-risk PV or ET with adequate response to initial cytoreductive therapy. Initiation of cytoreductive therapy is recommended for patients with symptomatic disease with potential indications for cytoreductive therapy. For symptomatic low-risk PV, enrollment in a

clinical trial and ropeginterferon alfa-2b-njft are preferred regimens, while hydroxyurea and peginterferon alfa-2a are other recommended regimens. Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy. Subsequent recommendations are the same as those for high-risk PV. The cytoreductive therapy regimens for symptomatic very-low-risk, low-risk, and intermediate-risk ET are the same as for those with high-risk ET.

Potential indications for change of cytoreductive therapy for patients with PV include intolerance or resistance to prior cytoreductive treatment, new thrombosis or disease-related major bleeding, frequent phlebotomy or intolerance to phlebotomy, splenomegaly, progressive thrombocytosis and/or leukocytosis, and disease-related symptoms (eg, pruritus, night sweats, fatigue).[314] For patients with an inadequate response or a loss of response, a clinical trial and ruxolitinib[87,284,285,287,290] (category 1 for high-risk PV for hydroxyurea resistance or intolerance) are preferred regimens. Ruxolitinib is FDA approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea.[87,284,287,290] and may have activity after inadequate response or loss of response to other agents besides hydroxyurea.[285] If not previously used, hydroxyurea,[258,261,262] peginterferon alfa-2,[266-269] and ropeginterferon alfa-2b-njft[270,271] are other recommended regimens. Ropeginterferon alfa-2b-njft is FDA approved for the treatment of patients with PV.[270,271]

Potential indications for change of cytoreductive therapy for patients with ET include intolerance or resistance to hydroxyurea, peginterferon alfa-2a, or anagrelide; new thrombosis; acquired VWS and/or disease-related major bleeding; splenomegaly; thrombocytosis; leukocytosis; disease-related symptoms; and vasomotor/microvascular disturbances not responsive to aspirin (eg, headaches, chest pain, erythromelalgia).[314] For patients with an inadequate response or a loss of response, a clinical trial and hydroxyurea,[275-277] if not previously used, are preferred regimens. If not previously used, peginterferon alfa-2a[266,268,269] and anagrelide[276-278] are other recommended regimens. Peginterferon alfa-2a can be considered for patients in need of cytoreductive therapy who are younger or pregnant or who defer hydroxyurea. Ruxolitinib[88,293] and plateletpheresis[315] (for emergent situations such as severe thrombocytosis-related neurologic complications) are options that are useful in certain circumstances.

Special Considerations in the Management of PV and ET

Management of Thrombosis

The use of clinically appropriate anticoagulant therapy (eg, low-molecular-weight heparin [LMWH], direct oral anticoagulants [DOACs], warfarin) is recommended for patients with active thrombosis.[316-318] The initial use of anticoagulant therapy for the prevention and treatment of thrombosis should be based on the current American College of Chest Physicians Guidelines.[316] Aspirin may be considered for patients with cardiovascular risk factors. There are no evidence-based data to guide the selection or appropriate duration of anticoagulation with or without antiplatelet therapy in patients with PV or ET. The duration of anticoagulant therapy is dependent on the severity of the thrombotic event, degree of disease control, and assessment of likelihood of recurrence after cessation of anticoagulant therapy.[317] The risks and benefits of aspirin plus anticoagulation need to be individualized on a case-by-case basis. Plateletpheresis may be indicated in patients with ET presenting with acute life-threatening thrombosis or severe bleeding.

Management of Bleeding

It is essential to rule out other potential causes and treat any coexisting causes as necessary. Aspirin should be withheld until bleeding is under control and the use of appropriate cytoreductive therapy should be considered to optimize platelet counts while minimizing hematologic and

non-hematologic toxicities. Coagulation tests to evaluate for acquired VWS (von Willebrand factor activity level) and/or other coagulopathies are recommended for patients undergoing high-risk surgical procedures and those with elevated platelet count and/or splenomegaly or unexplained bleeding. In unanticipated gastrointestinal bleeding, particularly in the setting of splenomegaly, portal hypertension, and gastric varices, special consultation (for endoscopic evaluation) with a hepatologist or a gastrointestinal specialist is recommended.

Surgery

The thrombotic and bleeding risk of the surgical procedure should be strongly considered prior to elective surgery since patients with PV and ET are at higher risk for bleeding despite optimal management. In a retrospective analysis that evaluated the post-surgery outcomes in patients with PV (n = 105) and ET (n = 150), although the majority of patients (74%) were treated with cytoreductive therapy and phlebotomy prior to surgery and antithrombotic prophylaxis, a significant proportion of surgeries was complicated by vascular occlusion (8%) or major hemorrhage (7%). Arterial thrombotic events were more frequent in patients with ET (5% vs. 2%; *P* = .08) and venous thrombotic events were more frequent in PV (8% vs. 1%; *P* = .002).[319]

Multidisciplinary management with careful review of bleeding and thrombosis history is recommended prior to surgery for all patients. Emergency surgery should be performed as necessary with close postoperative surveillance for the symptoms of arterial or venous thrombosis and bleeding. Thrombosis and bleeding should be well-controlled without causing prohibitive cytopenias prior to performing elective surgery (particularly for orthopedic surgeries or any surgical procedures associated with prolonged immobilization) with the use of appropriate antiplatelet therapy, anticoagulant prophylaxis, and cytoreductive therapy. In patients with PV, hematocrit should be controlled for 3 months before elective surgery with the use of additional phlebotomy if necessary to maintain hematocrit <45% prior to performing elective surgery. Prophylaxis with aspirin may be considered following vascular surgery. Extended prophylaxis with LMWH should be considered, if surgery is associated with a high risk for venous thromboembolism.

Pregnancy

Pregnancy is considered a high-risk clinical situation in patients with PV and ET.[320] The presence of a *JAK2* V617F mutation is an adverse prognostic factor for pregnancy outcome, and pregnancy complications are associated with a higher risk of subsequent thrombotic events in patients with ET.[321-324] The use of aspirin has been reported to be effective in reducing pregnancy complications, especially in patients with *JAK2*-mutated ET.[325-327] In a study that investigated 129 pregnancies in 78 patients with ET, among patients with *JAK2*-mutated ET, complications occurred in 36% of patients receiving aspirin compared to 68% of patients not receiving aspirin.[326] In another study of 63 pregnancies among 36 females with ET, the rate of pregnancy loss was 21% among patients receiving aspirin during the first trimester compared to 75% among those not receiving aspirin (*P* = .002).[325] The results of a UK prospective cohort study (58 women with a diagnosis of MPN; 47 had a diagnosis of ET) suggest that maternal MPN is associated with higher incidences of maternal complications, preterm delivery, and small-for-gestational-age infants compared to the general population.[328] The majority of women (88%) received aspirin and 38% of females additionally received a prophylactic dose of LMWH. Preeclampsia was the most common antenatal complication reported in 9% of women, and 22% of neonates were below the 10th percentile for growth. A systematic review and meta-analysis of pregnant patients with MPN also reported preeclampsia as the most common adverse occurrence (3.1% incidence). Aspirin and interferon use were linked to increased odds of a successful pregnancy.[329] Aggressive intervention for the control of hematocrit, the use of aspirin,

and LMWH were associated with significantly better pregnancy outcome in patients with PV.[330]

Evaluation by a high-risk obstetrician is recommended prior to conception. Hydroxyurea should be discontinued in anticipation or in the event of pregnancy. Peginterferon alfa-2a should be considered if cytoreductive therapy is needed during pregnancy.[331] Potential indications include those with prior pregnancy loss or complications (pre-eclampsia) or uncontrolled leukocytosis/thrombocytosis. There are no sufficient data to establish the use of peginterferon alfa-2a in pregnancy and it should be used only if benefits outweigh potential risk to the fetus.[331] DOACs should be avoided in breastfeeding females. Although large studies do not exist, there have been some reports that show that DOACs are in the breastmilk of patients who are taking them.[332] Unfractionated heparin, LMWH, warfarin, and fondaparinux are all safe options in patients who require anticoagulation and are breastfeeding as they are unlikely to transfer into milk in clinically significant amounts, and are not absorbed from the infant's gastrointestinal tract due to large molecular weight.[333] Hydroxyurea is excreted in breastmilk and should be avoided in females who are breastfeeding. Patients with PV or ET who become pregnant and do not have high-risk features (standard-risk pregnancy) should take low-dose aspirin daily throughout the pregnancy and should receive prophylactic LMWH alone during the first 6 weeks of the postpartum period, unless there are patient-specific contraindications. If they were taking low-dose aspirin prior to pregnancy, it can be resumed once the postpartum course of LMWH is complete.

For patients with PV or ET whose pregnancies are considered high risk, the recommended treatments to start or continue once a positive pregnancy test is obtained are: 1) low-dose aspirin daily; 2) prophylactic LMWH throughout pregnancy and for 6 weeks postpartum; and 3) cytoreductive therapy with interferon or peginterferon alfa-2a.[314,320,328,329,334-337] The administration of LMWH should be modified based on renal function, body weight, and medical history. Prophylactic LMWH should be avoided among patients with a history of MPN-related bleeding. Therapeutic anticoagulation with LMWH should be continued during pregnancy by patients receiving anticoagulation therapy after venous and/or arterial thrombotic events prior to pregnancy. The timing of LMWH and aspirin discontinuation prior to the epidural and delivery and the re-initiation of medications after delivery should be discussed with a high-risk obstetrician and obstetric anesthesiologist.

Accelerated/Blast Phase MPN

MPN in accelerated phase is characterized by the presence of 10%–19% blasts in the peripheral blood or bone marrow, while blast phase is defined as the presence of ≥20% blasts.[62]

Patients with a blast percentage of 5% to 9% in the peripheral blood or bone marrow and those with 10% to 19% share similar clinical characteristics.[338] In patients with <10% blasts in the peripheral blood or bone marrow, treatment with ruxolitinib improved survival.[338,339] Patients with a blast percentage of ≥4% in the peripheral blood or ≥5% in the bone marrow have unfavorable outcomes. OS was not significantly different in patients with 5% to 9% blasts in the peripheral blood or bone marrow and in patients with 10% to 19% blasts (24 vs. 13 months; $P = .19$).[338] Similarly, OS was comparable in patients with 5% to 9% blasts in the bone marrow and in patients with ≥10% blasts (22 vs. 14 months; $P = .73$).[339]

The incidence of transformation to AML is significantly higher for patients with MF than for those with PV and ET, although the risk is very low in patients who remain in chronic phase MF.[340,341] Among patients who present with chronic phase MF, development of accelerated phase features during follow-up was associated with short median survival times.[340]

Treatment with hydroxyurea has been associated with increased risk of transformation to AML in some studies.[262,342] These findings, however, were not confirmed in subsequent reports.[343-345] In a large cohort analysis (n = 11,039; 162 patients with transformation to AML/ MDS) that evaluated treatment-related risk factors for transformation to AML/MDS in patients with MPN, the use of alkylating agents or a combination of ≥2 cytoreductive agents—but not treatment with hydroxyurea alone—was significantly associated with an increased risk of transformation to AML.[343] The results of another large analysis (649 patients with PMF, post-PV MF, or post-ET MF) identified bone marrow blasts ≥10% and high-risk karyotypes as independent prognostic factors for the transformation to AML.[345] Hydroxyurea, however, was not an independent risk factor for transformation to AML.

Mutations in several genes (*ASXL1, EZH2, TP53, SRSF2*, and *IDH1* or *IDH2*) and other chromosomal abnormalities (eg, aberrations in chromosomes 1q and 9p) have been associated with transformation to AML.[29,37,39,346] Broad-based NGS testing that includes AML-associated mutations is recommended as part of initial workup for patients with accelerated/blast phase MPN (MPN-AP/BP).

Treatment Options

In a retrospective analysis of 91 patients with MF that had transformed to AML, the median OS after transformation to AML was 3 months. Among patients who were treated with AML-type induction chemotherapy, reversal to chronic phase without an increase in the blast percentage occurred in 41% of patients.[347] However, it was also associated with a treatment-related mortality (TRM) rate of 33%. The median OS was 4 months, which was comparable to that observed in patients treated with supportive care or low-intensity chemotherapy (2 months and 3 months, respectively).

Hypomethylating agents (HMAs) (azacitidine or decitabine) have been evaluated in a few small studies as a treatment option for MPN that has transformed to AML.[348-350] In a small series of 11 patients with MF-BP/AML, decitabine was associated with improved survival in patients who were not eligible for allogeneic HCT.[348] At a median follow-up of 9 months, 67% of the patients treated with decitabine were alive. In another series of 54 patients with MPN-BP/AML (21 patients with ET, 21 patients with PV, 7 patients with PMF, and 5 patients with unclassified MPN), first-line therapy with azacitidine resulted in an ORR of 52% (24% CR, 11% PR, 8% bone marrow CR or CR with incomplete recovery of cytopenias, and 9% hematologic improvement).[349] The median duration of response and the median OS were 9 months and 11 months, respectively. In a retrospective analysis of 21 patients with MPN-BP/AML and 13 patients with MPN-AP treated with decitabine, the ORRs were 62% (8 out of 13 patients) and 29% (6 out of 21 patients), respectively, for patients with MPN-AP and MPN-BP/AML.[350] The median OS was significantly higher in patients with disease that responded to decitabine (12 vs. 5 months, respectively, for patients with MPN-AP; 11 vs. 4 months, respectively, for patients with MPN-BP/AML).

In a small study of 21 patients with MPN-AP/BP, decitabine in combination with dose-escalated ruxolitinib resulted in an ORR (by protocol-defined criteria) of 53% (95% CI, 27.8%–77.0%) and a median OS of 7.9 months (95% CI, 4.1 months–not reached).[351] The results of a phase II study with 25 patients with MPN-AP/BP demonstrated an ORR of 44% (95% CI, 24.4%–65.1%) and a median OS of 9.5 months (95% CI, 4.3–12.0 months) in patients treated with the combination of ruxolitinib and decitabine.[352] A phase 1/2 trial investigating the combination of ruxolitinib and decitabine in patients with post-MPN AML reported an ORR of 45% in the intention-to-treat population and 61% in patients who received the recommended phase II dose.[353] A phase II study (NCT04282187) is

examining the combination of decitabine with ruxolitinib or fedratinib in patients with MPN-AP/BP prior to HCT.

The role of venetoclax combinations has not yet been established in MPN-BP/AML. In one study, the complete remission rate (with or without count recovery) was 44% in patients with MPN-BP treated with venetoclax in combination with azacitidine or decitabine.[354] The authors note that 6 patients with complete remission (with or without count recovery) proceeded to transplant. In another study, venetoclax-based combination therapy resulted in an ORR of 50% and 53%, respectively, in MPN-AP/BP.[355] However, significant toxicities were also reported.

There is a paucity of data regarding the use of targeted therapies for MPN-AP/BP. In a retrospective analysis of 8 patients with MPN-AP/BP with *IDH2* mutations treated with enasidenib, an ORR of 37.5% was obtained based on the 2017 ELN criteria.[356] Another study also demonstrated the clinical benefit of IDH1/2 inhibitor-based combinations in patients with post-MPN AML with *IDH1/2* mutations.[357] Of the 12 patients that were evaluated, 3 achieved CR, with a median OS of 10 months. The addition of midostaurin, a FLT3 inhibitor, to chemotherapy resulted in improved median OS (74.7 months vs. 25.6 months; HR, 0.78; $P = .009$) in patients with AML with a *FLT3* mutation, when compared to placebo.[358] Similarly, the use of quizartinib, another FLT3 inhibitor, in combination with chemotherapy led to higher median OS (31.9 months vs. 15.1 months for placebo; HR, 0.78; $P = .032$) in patients with *FLT3*-ITD AML.[359]

Allogeneic HCT remains the only curative option resulting in long-term disease control in selected transplant-eligible patients who achieve a CR to induction chemotherapy.[360-363] Early referral to transplant is recommended for planning purposes and to discuss the role of bridging therapy. Some patients in accelerated phase may proceed to transplant directly without bridging therapy.[364] In one retrospective analysis of 75 patients with MPN-BP, patients who were treated with curative intent (induction chemotherapy with or without allogeneic HCT) had significantly improved survival compared with those treated with non-curative intent (non-intensive chemotherapy or supportive care).[362] The 2-year OS rates were 26% and 3%, respectively, and the median survival was 9 months and 2 months, respectively ($P < .0001$). Among patients treated with curative intent, the ORR to induction chemotherapy was 46% and reversal to chronic phase was observed in 31% of patients, with 17 patients undergoing allogeneic HCT. The OS rate was significantly higher for patients who underwent allogeneic HCT following induction chemotherapy (2-year OS rate was 47% compared with 15% for those who did not undergo allogeneic HCT; $P = .03$). In another retrospective analysis of 46 patients who received allogeneic HCT for MF-BP, the 3-year PFS and OS rates following transplant were 26% and 33%, respectively. The response status prior to transplant (CR vs. no CR) was a significant predictor of OS (69% for CR vs. 22% for no CR; $P = .008$) and PFS (55% and 19%, respectively; $P = .02$).[363] The cumulative incidence of TRM was 28% at 1 year and the absence of CR before allogeneic HCT was also associated with significantly increased TRM (35% vs. 0%; $P = .053$).

Treatment Recommendations Based on Eligibility for Transplant

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(s). Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

Enrollment in a clinical trial or bridging therapy followed by allogeneic HCT are treatment options for patients who are candidates for transplant. Bridging therapy options include HMAs (azacitidine or decitabine) with or without a JAK inhibitor (ruxolitinib, fedratinib, momelotinib, or pacritinib), HMAs with venetoclax, or intensive AML-type induction chemotherapy.[348,362,363] Enrollment in a clinical trial, HMAs (azacitidine or

decitabine) with or without a JAK inhibitor (ruxolitinib, fedratinib, momelotinib, or pacritinib), HMAs with venetoclax, or low-intensity AML-type chemotherapy is recommended for those who are not candidates for transplant. AML-type induction chemotherapy regimens and HMAs in combination with venetoclax may be used for the management of disease progression of MPN. However, these regimens typically result in poor responses and are associated with significant toxicities. Based on NGS panel results (eg, if NGS shows particular mutations such as *IDH1*, *IDH2*, or *FLT3*), low intensity or targeted therapy alone or in combination with HMAs can be considered.[356,357] HMAs (azacitidine or decitabine) can be used in combination with a JAK inhibitor (ruxolitinib, fedratinib, momelotinib, or pacritinib) for the palliation of splenomegaly or other disease-related symptoms.[351,353] However, the Panel notes that there are very limited data regarding the use of fedratinib, momelotinib, or pacritinib with HMAs. While the combination of an HMA and pacritinib has been evaluated in AML and chronic myelomonocytic leukemia (CMML),[365,366] the combination has not been evaluated in MPN-AP/BP. Ruxolitinib, fedratinib, momelotinib, or pacritinib may be continued near to the start of conditioning therapy for the improvement of splenomegaly and other disease-related symptoms in patients who are transplant candidates.[172,195-197]

Summary

MPN are characterized by a significant symptom burden and a propensity for disease transformation to accelerated and blast phases. The goal of treatment is to reduce symptom burden and the risk of developing thrombotic and hemorrhagic complications. Regular monitoring of disease-related symptoms, assessment of need for cytoreductive therapy, and appropriate evaluation for disease progression should be an integral part of the comprehensive care of patients with MPN.

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