National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Myeloproliferative Neoplasms

Version 1.2021 — April 13, 2021

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National Comprehensive Cancer Network®

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Myeloproliferative Neoplasms

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial.
Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

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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Updates in Version 1.2021 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 1.2020 include:

MPN-1

Suspicion of MPN

- ***Footnote added: See Workup in the NCCN Guidelines for Systemic Mastocytosis and Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes***

Workup:

- **Fourth bullet, modified: FISH (~~if RT-PCR is not available~~) or multiplex RT-PCR (if available) (~~preferred~~) for *BCR-ABL1* to exclude the diagnosis of CML; if *BCR-ABL1*-positive, See NCCN Guidelines for Chronic Myeloid Leukemia.**
- **Sixth bullet modified: Bone marrow aspirate *with iron stain*; bone marrow biopsy with trichrome *and* reticulin stain**
- **Seventh bullet modified: Bone marrow cytogenetics (blood, if bone marrow is inaspirable) (karyotype~~±~~ *with or without* FISH) (Also for MF-4)**
- **Ninth bullet, new: *If there is evidence of mast cell aggregates in the bone marrow, see NCCN Guidelines for Systemic Mastocytosis for diagnostic workup***

MPN-2

- **Add new header to second column: *PROGNOSTIC RISK MODEL***
- **Significant edits made to define risk for ~~thrombohemorrhagic~~ *Conventional risk* model and IPSET-thrombosis.**

MF-1

- **Fourth column, deleted: Observation**
- **Sixth column, modified:**
  - ***Continue observation (if asymptomatic) and monitor for disease progression (MPN-10;* MPN-E 2 of 2) (Also for MF-2)**
  - ***Symptomatic patients should be managed as noted below***
- **Response, seventh column modified:**
  - **Continue treatment *and monitor for disease progression (MPN-10;* MPN-E 2 of 2)**
- **No Response or loss or response, seventh column modified:**
  - ***Alternate option not used for initial treatment and monitor for disease progression (MPN-10; MPN-E 2 of 2)***

MF-2

- **Second and third columns flipped**
  - **Platelets <50: *Transplant candidate to Allogeneic HCT* and *Not a transplant candidate* to Consider clinical trial.**
- **Reponse, eighth column modified: *..and monitor for disease progression (MPN-10; MPN-E 2 of 2).***
- **No Response or loss or response, eighth column modified:**
  - ***Clinical trial or Alternate* JAK *inhibitor not used before and monitor for disease progression (MPN-10; MPN-E 2 of 2)***

Footnote:

- **"i", modified to include the following: *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.* (Also for MF-4).**
- **"j" modified to include: *see* (MPN-G, 1 of 5). See Discussion *for the use of JAK inhibitors prior to transplant*. (Also for MF-3 and MF-4).**

MF-3

- ***Luspatercept* is a *category 3* recommendation for Serum EPO ≥500 with the following corresponding footnote, *A clinical trial of luspatercept is preferred (if available).***

Footnote:

- **"m" modified to include: ...statins are recommended *over concerns for increased risk of rhabdomyolysis.***
- ***Start as a combination followed by tapering of prednisone over 3 months* is a new footnote corresponding to Lenalidomide or Thalidomide ± prednisone**

MF-4

Workup:

- **Second bullet, modified: Bone marrow *evaluation* (blood, if bone marrow is inaspirable).**
  - **Cytogenetics (karyotype *with or without* FISH).**

Treatment:

- **Transplant candidate:**
  - ***Induction therapy followed by allogeneic HCT (for patients in remission)***
- **Induction therapy options include:**
  - **Hypomethylating agents *(HMA) ± JAK~~2~~ inhibitors* (~~azacitidine or decitabine~~)**
  - **Intensive induction chemotherapy (See NCCN Guidelines for AML) ~~followed by allogeneic HCT~~**
- **Not a candidate for transplant:**
- ***HMA ± JAK~~2~~ inhibitor* (~~azacitidine or decitabine~~) or**
- **Low-intensity ~~induction~~ chemotherapy**

Continued
UPDATES

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Updates in Version 1.2021 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 1.2020 include:

MF-4 (continued)

Footnote:

- "t" is new corresponding to transplant candidate and not a candidate for transplant: *JAK inhibitor (ruxolitinib or fedratinib) can be used in combination with HMA (azacitidine or decitabine) for the palliation of splenomegaly or other disease-related symptoms.*

MF-A (4 of 5)

- *Absence* or *CALR*-1 type *mutation* ~~unmutated genotype~~ (Also for MF-A, 5 of 5)
- *Unfavorable* ~~Complex~~ karyotype

Footnote:

- Preferred regimens:
  - "a" modified to included: *Q157*
  - "b" modified as follows: *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.

MF-B (1 of 4)

- "*Patients undergoing HCT may be evaluated for response assessment using other response criteria*" is a new footnote corresponding to the title, 2013 IWG-MRT and ELN Response Criteria for Myelofibrosis (MF).

MF-B (3 of 4)

- Molecular remission: removed "granulocytes"

PV-1

- Third column, modified: Monitor for new thrombosis or bleeding, moved from the 2nd column. (Also for PV-2).
- Fifth column, fourth bullet, modified: *Progressive* thrombocytosis *and/or* leukocytosis. (Also for PV-2, ET-1 and ET-2).

Footnote:

- "*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)*" is a new footnote corresponding to the second column, second bullet: Aspirin (81–100 mg/day). (Also for PV-2, ET-1, ET-2, and ET-3).

PV-2

- Second column, modified to include: Preferred regimens *for Cytoreductive therapy*
  - Peginterferon alfa-2a (~~based on age and other patient-specific variables~~)

Footnote:

- "I," modified: While normalization of blood counts after initiation of treatment is usually *a goal* ~~done~~ in clinical practice...(Also for ET-3)

ET-1

- For low-risk patients modified second bullet: Aspirin (81–100 mg/ day) *for low-risk patients with vasomotor/microvascular disturbances and/or JAK2-positive patients* ~~vascular symptoms~~
- Third column, modified: *Monitor for new thrombosis, acquired VWD, and/or disease-related major bleeding*, moved from the second column. (Also for ET-2 and ET-3)

Footnote:

- "a" added to Aspirin, sending the reader to "Special considerations in the treatment of PV and ET (MPN-H)." (Also for ET-2)
- "c" modified third sentence: 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. (Also for ET-2)

ET-2

- Intermediate-risk, modified second bullet: Aspirin (81–100 mg/ day) for *vasomotor/microvascular disturbances* ~~vascular symptoms~~

ET-3

- Second column, modified to include: *Cytoreductive therapy f*or Preferred and Other recommended regimens

ET-4

- *Plateletpheresis (for emergent situations, eg, severe thrombocytosis-related neurologic complications)* is new to the third column under Useful in certain circumstances, with the following reference: *Padmanabhan A, et al. J Clin Apher 2019;34:171-354.*

MPN-D (1 of 4)

Prognostic Significance of Mutations in MPN

- Primary Myelofibrosis (PMF)
  - *RAS: Associated with decreased OS,* with the corresponding reference; *Santos FPS, Getta B, Masarova, et al. Prognostic impact of RAS-pathway mutations in patients with myelofibrosis. Leukemia 2020;34:799-810.*

MPN-D (3 of 4)

Prognostic Significance of Mutations in MPN

- Polycythemia Vera (PV)
  - Updated reference: *Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythemia and polycythemia vera. Br J Haematol 2020;189:291-302.* (Also for MPN-D, 4 of 4)
  - *"SRSF2 and SF3B1 mutations remain significant predictors in the context of the clinical outcomes"* is a new footnote. (Also for MPN-D, 4 of 4)

Continued

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Updates in Version 1.2021 of the NCCN Guidelines for Myeloproliferative Neoplasms from Version 1.2020 include:

MPN-F (1 of 3)
Myelofibrosis
- **Fifth bullet, first sub-bullet: *Consider recombinant (killed) zoster vaccine for patients on ruxolitinib and fedratinib* is a new sub-bullet under Vaccinations.**

MPN-F (2 of 3)
Symptom Management in Patients with MPN
- **Second sentence modified: While JAK~~2 inhibition~~ *inhibitors* have been shown to broadly improve disease-related symptoms...**

MPN-G (2 of 5)
Special Considerations For The Use of JAK Inhibitors/Ruxolitinib
- **First bullet, second sentence, modified: *Consider monitoring uric acid and LDH.***

MPN-G (3 of 5)
Special Considerations for the Use of JAK Inhibitors/Ruxolitinib
- **Non-Melanoma Skin Cancer**
  - **Perform *annual* ~~periodic~~ skin examinations.**

MPN-G (5 of 5)
Lymphoma risk with JAK inhibitors in patients with MPN
- **First sentence, modified: Both low-and high-grade *lymphoid* neoplasms....**
- **Second sentence, modified: *Other studies found no evidence of increased lymphoma risk in patients treated with a JAK inhibitor* ~~additional studies are required to validate these observations~~**

References (New to the page):

- ***Rumi E, Zibellini S, Boveri E, et al. Ruxolitinib treatment and risk of B-cell lymphomas in myeloproliferative neoplasms. Am J Hematol 2019;94:E185-E188.***
- ***Barbui T, Ghirardi A, Masciulli A, et al. Second cancer in Philadelphia negative myeloproliferative neoplasms (MPN-K). A nested case-control study. Leukemia 2019;33:1996-2005.***
- ***Polverelli N, Elli EM, Abruzzese E, et al. Second Primary malignancy in myelofibrosis in patients treated with ruxolitinib. Br J Haematol 2020 Nov 21. doi: 10.1111/bjh.17192. Online ahead of print.***

MPN-H (1 of 3)
Special Considerations in the Treatment of Polycythemia Vera (PV) and Essential Thrombocythemia (ET)
- **Management of Vascular Events/Thrombosis**
  - **First bullet, second sub-bullet, new: *Consider aspirin for patients with other cardiovascular risk factors (refers to all subtypes) (See ET-1 and ET-2).***

MPN-H (2 of 3)
- **Pregnancy**
  - **Third bullet modified: "Low-risk disease (~~pregnancy~~) ... ~~(to maintain hematocrit <45% in patients with PV)~~"**
  - **Fifth bullet modified: *High-risk disease and history of thrombosis (~~pregnancy~~):* ~~Prior thrombotic event:~~**

Suspicion of myeloproliferative neoplasms (MPN)[a]

WORKUP

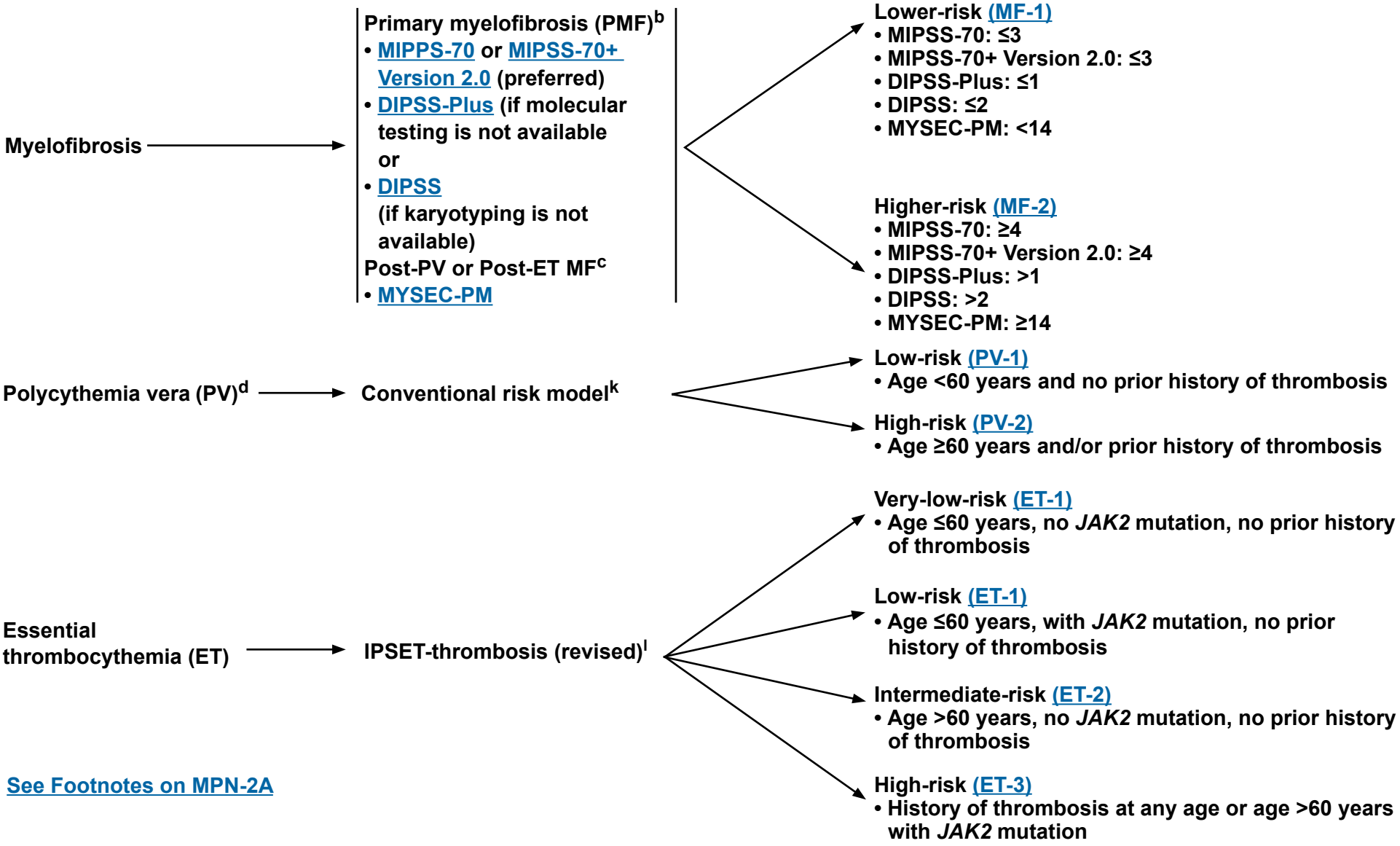
- **H&P, including spleen size by palpation, evaluation of thrombotic/hemorrhagic events and cardiovascular risk factors**
- **CBC with differential**
- **Comprehensive metabolic panel with uric acid, lactate dehydrogenase (LDH), and liver function tests (LFTs)**
- **FISH or multiplex RT-PCR (if available) for *BCR-ABL1* to exclude the diagnosis of 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,d]**
- **Bone marrow cytogenetics (blood, if bone marrow is inaspirable) (karyotype with or without FISH)[b,c,d]**
- **Molecular testing (blood) for *JAK2* V617F mutation; if negative, test for *CALR* and *MPL* mutations (for patients with ET and MF) and *JAK2* exon 12 mutations (for patients with PV) or molecular testing using multigene NGS panel that includes *JAK2, CALR,* and *MPL*[e]**
- **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-10; MPN-E 2 of 2)**
- **Documentation of transfusion/medication history**
- **Human leukocyte antigen (HLA) testing, if considering allogeneic hematopoietic cell transplant (HCT)[f]**
- **Serum erythropoietin (EPO) level**
- **Serum iron studies**
- **Coagulation tests to evaluate for acquired von Willebrand disease (VWD) and/or other coagulopathies in selected patients[g]**
  - **Prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen**
  - **Plasma von Willebrand Factor Antigen (VWFA) measurement**
  - **Von Willebrand Ristocetin Cofactor (VWF:RCo) activity[h]**

Diagnosis
and
Risk stratification

→ **See MPN-2**

[a]See Workup in the NCCN Guidelines for Systemic Mastocytosis and Myeloid/Lymphoid Neoplasms with Eosinophilia and Tyrosine Kinase Fusion Genes.
[b]See 2017 WHO Diagnostic Criteria for Primary Myelofibrosis (PMF). See (MPN-A).
[c]Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).
[d]See 2017 WHO Diagnostic Criteria for PV and ET. See (MPN-C).
[e]Prognostic models incorporating other mutations have been proposed to identify patients with myelofibrosis (MF) who may be at risk of leukemic transformation. Next-generation sequencing (NGS) may be useful to establish clonality in selected circumstances (eg, triple-negative non-mutated *JAK2*, *MPL*, and *CALR*). See MPN-D for a list of somatic mutations with prognostic significance in patients with MPN.
[f]See MF-2 and MF-3.
[g]Patients undergoing high-risk surgical procedures and those with elevated platelet count and/or splenomegaly or unexplained bleeding.
[h]An expanded panel including von Willebrand factor (VWF) antigen, Factor VIII activity, and VWF multimers may be useful under certain circumstances.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



See Footnotes on MPN-2A

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

FOOTNOTES

[b]See 2017 WHO Diagnostic Criteria for Primary Myelofibrosis. See (MPN-A).
[c]Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).
[d]See 2017 WHO Diagnostic Criteria for PV and ET. See (MPN-C).
[i]The diagnosis of MPN is based on the 2017 WHO Criteria and requires a combination of clinical, laboratory, cytogenetic, and molecular testings.
[j]Referral to specialized centers with expertise in the management of MPN is strongly recommended for all patients diagnosed with MF, PV, or ET.
[k]Marchioli R, et al. J Clin Oncol 2005;23:2224-2232.
[l]The revised International Prognostic Score of Thrombosis for ET (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).

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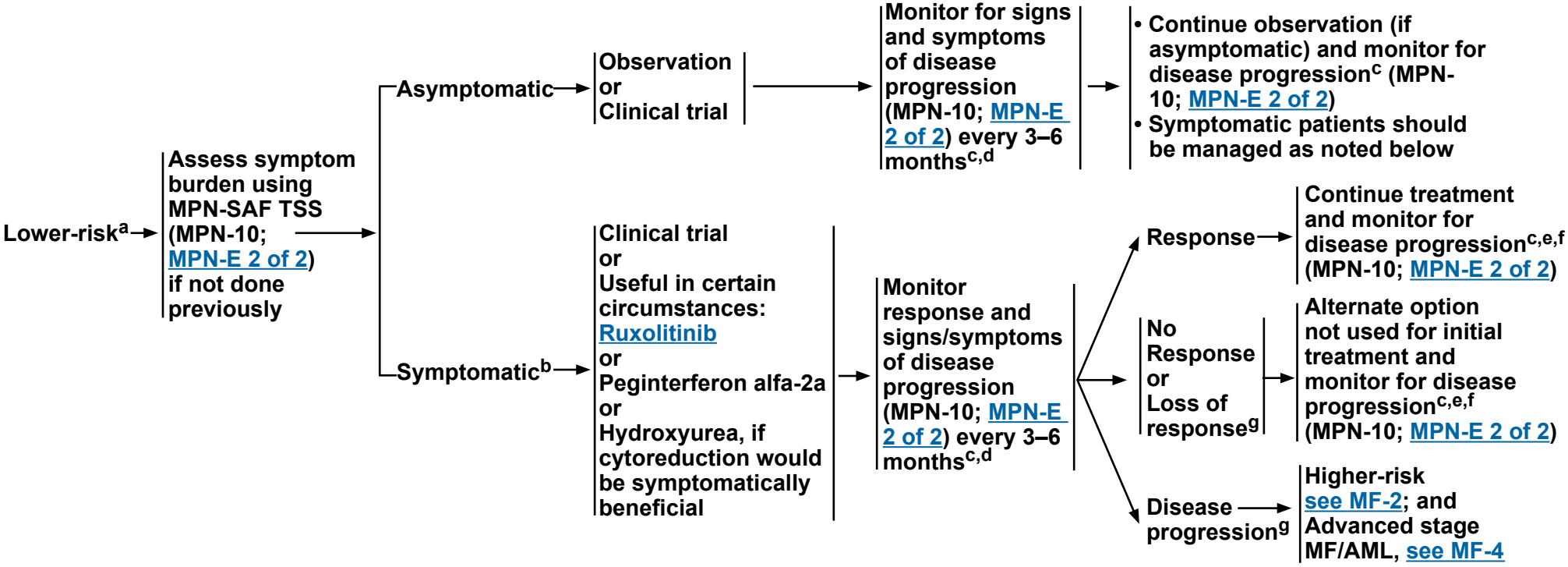
TREATMENT FOR LOWER-RISK MYELOFIBROSIS



[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 PMF. See Prognostic Significance of Mutations in MPN (MPN-D).

[b]See Supportive Care for Patients with MPN (MPN-F).

[c]Bone marrow aspirate and biopsy should be performed at diagnosis and as clinically indicated (if supported by increased symptoms and signs of progression).

[d]See 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). 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.

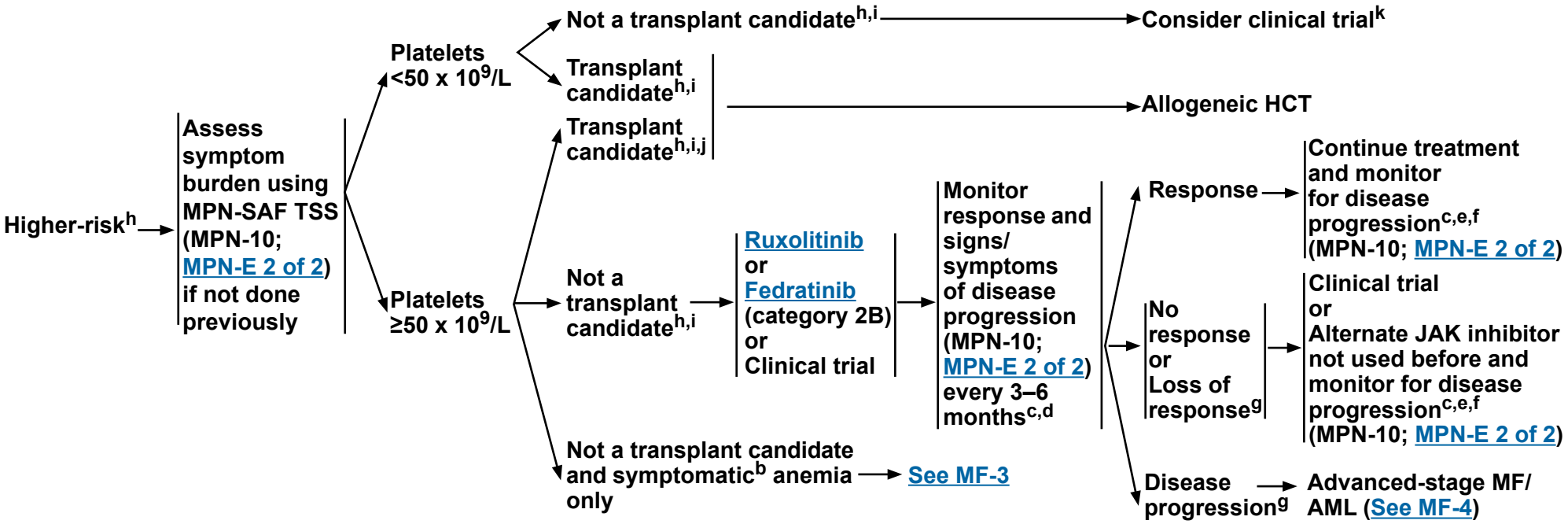
[e]See Special Considerations for the Use of JAK Inhibitors (MPN-G).

[f]Clinical benefit may not reach the threshold of the IWG Response Criteria and continuation of ruxolitinib is recommended based on the discretion of the clinician. See 2013 IWG-MRT and ELN Response Criteria for MF (MF-B).

[g]Additional molecular testing using multi-gene NGS panel should be considered to evaluate for higher-risk mutations associated with disease progression in patients with primary PMF. See Prognostic Significance of Mutations in MPN (MPN-D).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

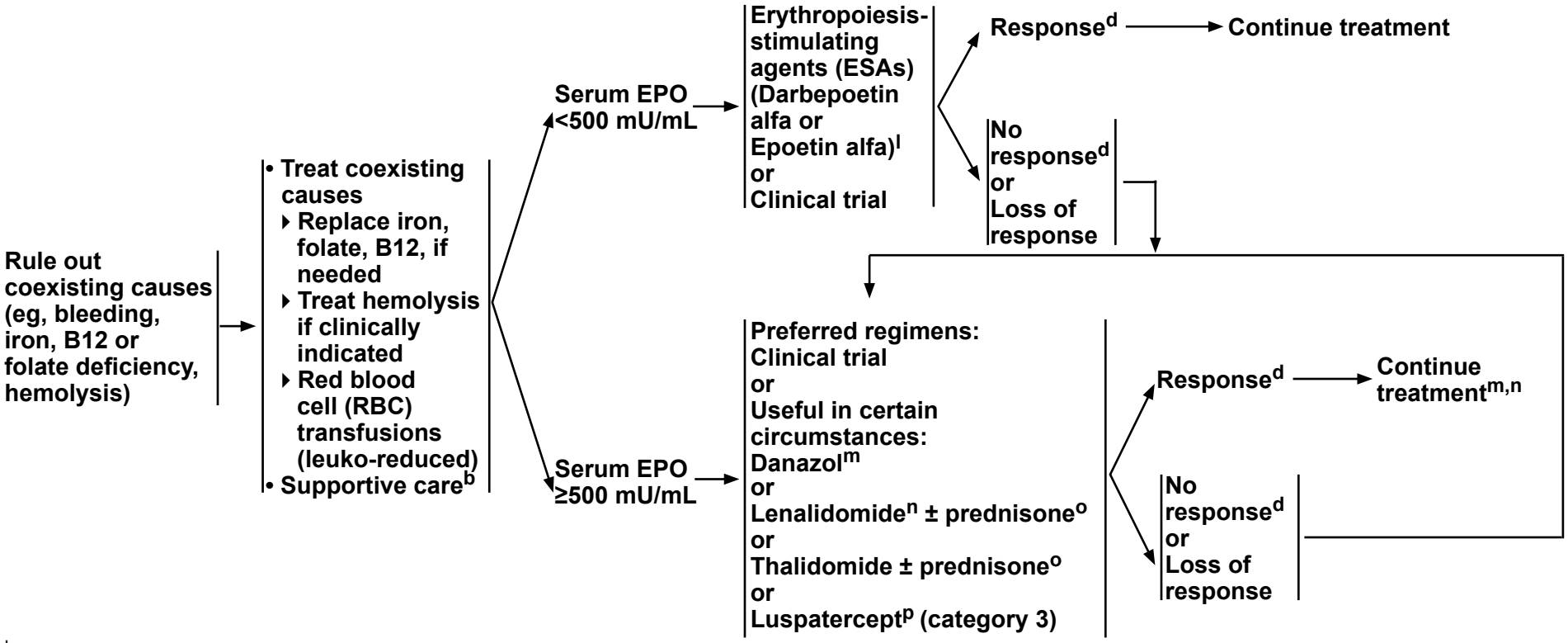
TREATMENT FOR HIGHER-RISK MYELOFIBROSIS



[b] See Supportive Care for Patients with MPN (MPN-F).
[c] Bone marrow aspirate and biopsy should be performed at diagnosis and as clinically indicated (if supported by increased symptoms and signs of progression).
[d] See 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). 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.
[e] See Special Considerations for the Use of JAK Inhibitors (MPN-G).
[f] Clinical benefit may not reach the threshold of the IWG Response Criteria and continuation of ruxolitinib or fedratinib is recommended based on the discretion of the clinician. See 2013 IWG-MRT and ELN Response Criteria for MF (MF-B).
[g] Additional molecular testing using multi-gene NGS panel should be considered to evaluate for higher-risk mutations associated with disease progression in patients with primary PMF. See Prognostic Significance of Mutations in MPN (MPN-D).
[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 PMF. See Prognostic Significance of Mutations in MPN (MPN-D).
[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] Ruxolitinib or fedratinib may be continued near to the start of conditioning therapy for the improvement of splenomegaly and other disease-related symptoms, see (MPN-G, 1 of 5). See Discussion for the use of JAK inhibitors prior to transplant.
[k] If a clinical trial is not available, other options should be considered. See Discussion for further details.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MANAGEMENT OF MF-ASSOCIATED ANEMIA[j]



[b] See Supportive Care for Patients with MPN (MPN-F).
[d] See 2013 IWG-MRT and ELN Response Criteria for MF (MF-B). 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.
[j] Ruxolitinib or fedratinib may be continued for the improvement of splenomegaly and other disease-related symptoms.
[l] An FDA-approved biosimilar is an appropriate substitute for epoetin alfa.
[m] Prostate cancer screening for men 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.
[n] Presence of del(5q) is associated with better response rates with lenalidomide.
[o] Start as a combination followed by tapering of prednisone over 3 months.
[p] A clinical trial of luspatercept is preferred (if available).

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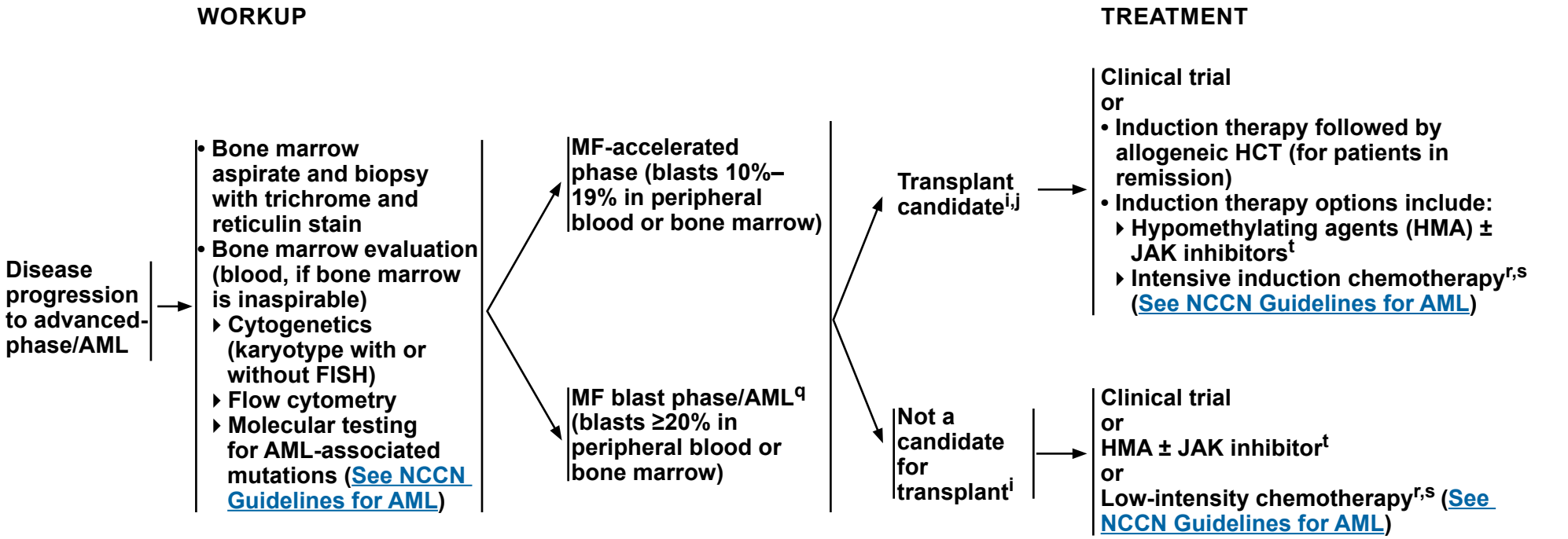
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



[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]Ruxolitinib or fedratinib may be continued near to the start of conditioning therapy for the improvement of splenomegaly and other disease-related symptoms, see (MPN-G, 1 of 5). See Discussion for the use of JAK inhibitors prior to transplant.

[q]The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

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

[s]AML-type induction chemotherapy regimens are generally used for the management of disease progression of MPN. However, these regimens typically result in poor responses.

[t]JAK inhibitor (ruxolitinib or fedratinib) can be used in combination with HMA (azacitidine or decitabine) for the palliation of splenomegaly or other disease-related symptoms.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

RISK STRATIFICATION FOR PATIENTS WITH MYELOFIBROSIS (MF)

PRIMARY 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.
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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.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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/.

Footnotes
[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.

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Note: All recommendations are category 2A unless otherwise indicated.
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RISK STRATIFICATION FOR PATIENTS WITH PMF

MUTATION AND KAROTYPE-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*-1 type mutation	2
HMR mutations[a]	2
≥2 HMR mutations	3
Unfavorable karyotype[b]	3
Very-high-risk (VHR) karyotype[c]	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
[a]Presence of a mutation in any of the following genes: *ASXL1*, *EZH2*, *SRSF2*, *U2AF1, Q157*, or *IDH1/2.*
[b]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.
[c]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;32:1189-199.

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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*-1 type mutation	2
Platelets <150 x 10^9/L	1
Constitutional symptoms	1

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

Online calculator for MYSEC 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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS (MF)[a,1,2]

Response Categories	Required Criteria (for all response categories, benefit must last for ≥12 wk to qualify as response)	
CR	Bone marrow:[a] Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF[b] AND Peripheral blood: Hemoglobin ≥10 g/dL and <upper normal limit (UNL); Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells[c]	Clinical: Resolution of disease symptoms; Spleen and liver not palpable; No evidence of extramedullary hematopoiesis (EMH)
PR	Peripheral blood: Hemoglobin ≥10 g/dL and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥100 x 10^9/L and <UNL; <2% immature myeloid cells[c] OR Bone marrow:[a] Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF[b] AND Peripheral blood: Hemoglobin ≥8.5, but <10 g/dL and <UNL; Neutrophil count ≥1 x 10^9/L and <UNL; Platelet count ≥50, but <100 x 10^9/L and <UNL; <2% immature myeloid cells[c]	Clinical: Resolution of disease symptoms; Spleen and liver not palpable; No evidence of EMH

See Footnotes on MF-B (4 of 4)

[a]Patients undergoing HCT may be evaluated for response assessment using other response criteria.

[1]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(8):1395-1398.

[2]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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS (MF)[1,2]

Response Categories	Required Criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
Progressive disease[d]	Appearance of a new splenomegaly that is palpable at least 5 cm below the left costal margin (LCM) or A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5–10 cm or A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or Leukemic transformation confirmed by a bone marrow blast count of ≥20% or A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 x 10^9/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least clinical improvement (CI) after achieving complete response (CR), partial response (PR), or CI or Loss of anemia response persisting for at least 1 month or Loss of spleen response persisting for at least 1 month
Clinical improvement (CI)	The achievement of anemia, spleen, or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia[e]
Anemia response	Transfusion-independent patients: a ≥2 g/dL increase in hemoglobin level[f] Transfusion-dependent patients: becoming transfusion-independent[g]
Spleen response[g,h]	A baseline splenomegaly that is palpable at 5–10 cm, below the LCM, becomes not palpable[i] or A baseline splenomegaly that is palpable at >10 cm below the LCM, decreases by ≥50%[i] A baseline splenomegaly that is palpable at <5 cm below the LCM, not eligible for spleen response A spleen response requires confirmation by MRI or CT showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS[j]

See Footnotes on MF-B (4 of 4)

[1]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(8):1395-1398.
[2]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.

Continued

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2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS (MF)[1,2]

RECOMMENDATIONS FOR ASSESSING TREATMENT-INDUCED CYTOGENETIC AND MOLECULAR CHANGES

Cytogenetic remission	**At least 10 metaphases must be analyzed for cytogenetic response evaluation and requires confirmation by repeat testing within 6-month window** **CR: Eradication of a pre-existing abnormality** **PR: ≥50% reduction in abnormal metaphases** **(partial response applies only to patients with at least 10 abnormal metaphases at baseline)**
Molecular remission	**Molecular response evaluation must be analyzed in peripheral blood and requires confirmation by repeat testing within 6-month window** **CR: Eradication of a pre-existing abnormality** **PR: ≥50% decrease in allele burden** **(partial response applies only to patients with at least 20% mutant allele burden at baseline)**
Cytogenetic/molecular relapse	**Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing**

See Footnotes on MF-B (4 of 4)

[1]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(8):1395-1398.
[2]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.

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Continued

FOOTNOTES

[a]Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

[b]Grading of MF is according to the European classification. (Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128.) It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

[c]Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

[d]Progressive disease assignment for splenomegaly requires confirmation by MRI or CT showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

[e]See definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥2 g/dL decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25 000 x 10^9/L and absolute neutrophil count of ≥0.5 x 10^9/L.

[f]Applicable only to patients with baseline hemoglobin of <10 g/dL. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but in those who have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

[g]Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBCs), in the 12 weeks prior to study enrollment, for a hemoglobin level of <8.5 g/dL, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥8.5 g/dL.

[h]In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

[i]Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

[j]Symptoms are evaluated by the MPN-SAF TSS. The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. 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). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

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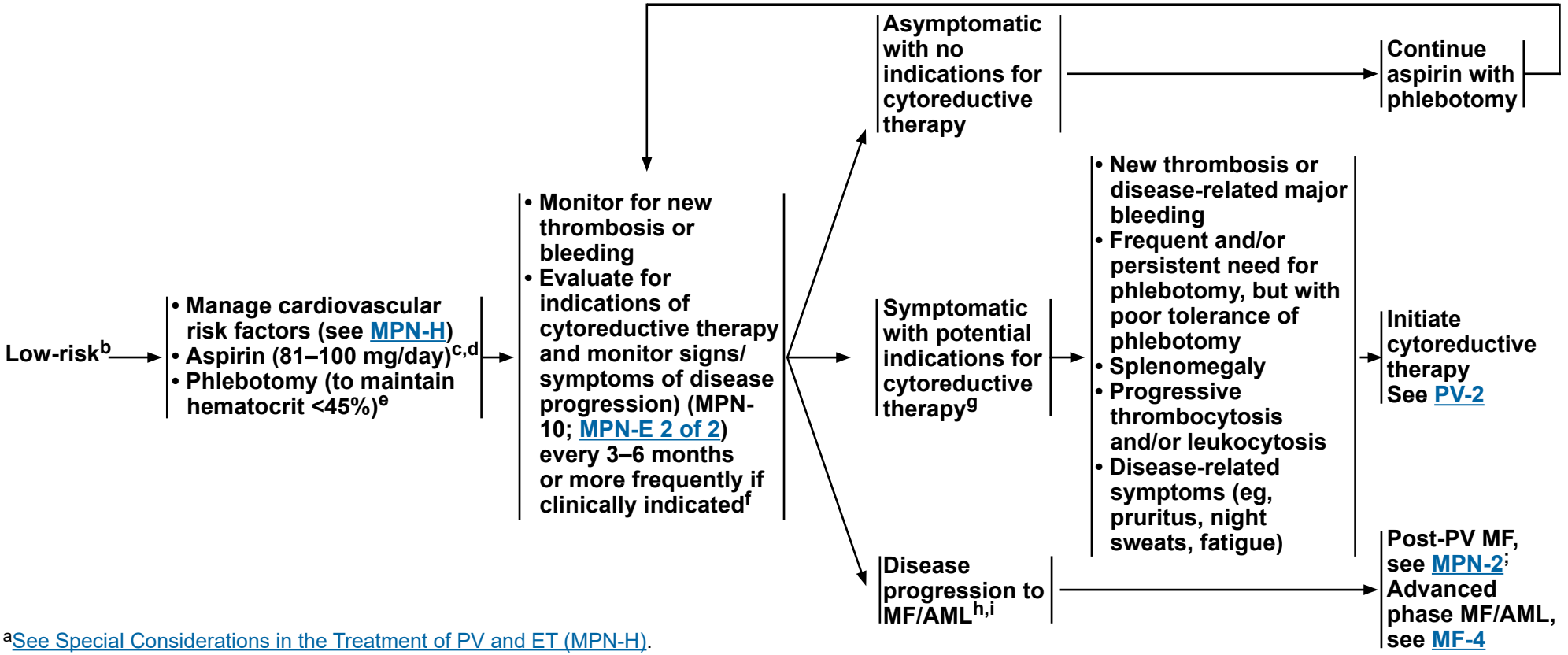
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT FOR LOW-RISK POLYCYTHEMIA VERA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).

[b] Cytoreductive therapy is not recommended as initial treatment.

[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.

[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al.Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).

[e] Hematocrit <45% is based on the data from the CYTO-PV Study (Marchioli R, et al. N Engl J Med 2013;368:22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized (eg, 42% for female patients and/or progressive symptoms).

[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.

[g] Barbui T, et al. Leukemia 2018;32:1057-1069.

[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).

[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

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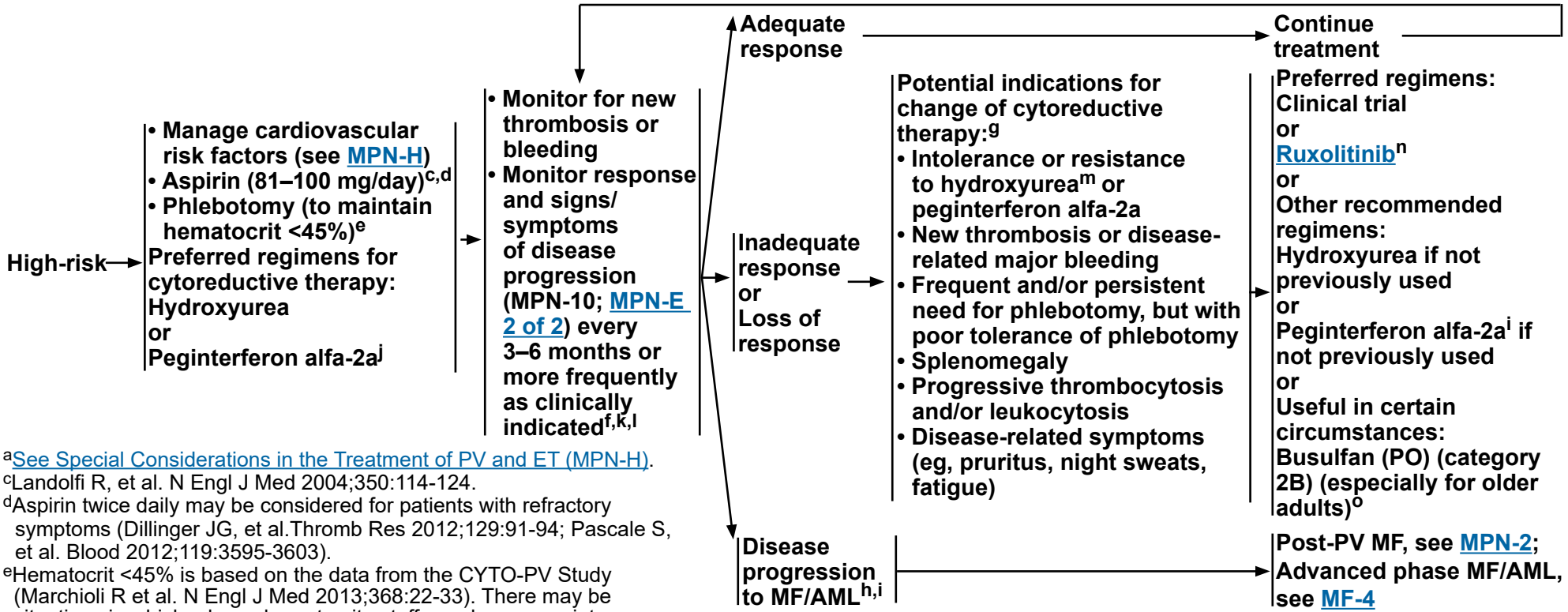
TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).

[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.

[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al.Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).

[e] Hematocrit <45% is based on the data from the CYTO-PV Study (Marchioli R et al. N Engl J Med 2013;368:22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized (eg, 42% for female patients and/or progressive symptoms).

[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.

[g] Barbui T, et al. Leukemia 2018;32:1057-1069.

[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).

[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

[j] Peginterferon alfa-2a can be considered for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy that defer hydroxyurea.

[k] See 2013 IWG-MRT and ELN Response Criteria for PV (PV-A). 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.

[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.

[m] Definition of intolerance/resistance to hydroxyurea (MPN-I).

[n] Ruxolitinib is FDA approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea.

[o] Alvarez Larran A, et al. Ann Hematol 2014;93:2037-2043.

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2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR POLYCYTHEMIA VERA (PV)[1,2]

Complete remission	
A	**Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,† AND**
B	**Durable* peripheral blood count remission, defined as: hematocrit lower than 45% without phlebotomies; platelet count ≤400 x 10^9/L, WBC count <10 x 10^9/L, AND**
C	**Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND**
D	**Bone marrow histologic remission defined as the presence of age-adjusted normocellularity and disappearance of trilineage hyperplasia, and absence of >grade 1 reticulin fibrosis.**
Partial remission	
A	**Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,† AND**
B	**Durable* peripheral blood count remission, defined as: hematocrit lower than 45% without phlebotomies; platelet count ≤400 x 10^9/L, WBC count <10 x 10^9/L, AND**
C	**Without progressive disease, and absence of any hemorrhagic or thrombotic event, AND**
D	**Without bone marrow histologic remission defined as persistence of trilineage hyperplasia.**
No response	**Any response that does not satisfy partial remission.**
Progressive disease	**Transformation into post-PV myelofibrosis, myelodysplastic syndrome, or acute leukemia.**

WBC: White blood cell
*Lasting at least 12 weeks
†Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.

[1]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(23):4778-4781.
[2]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.

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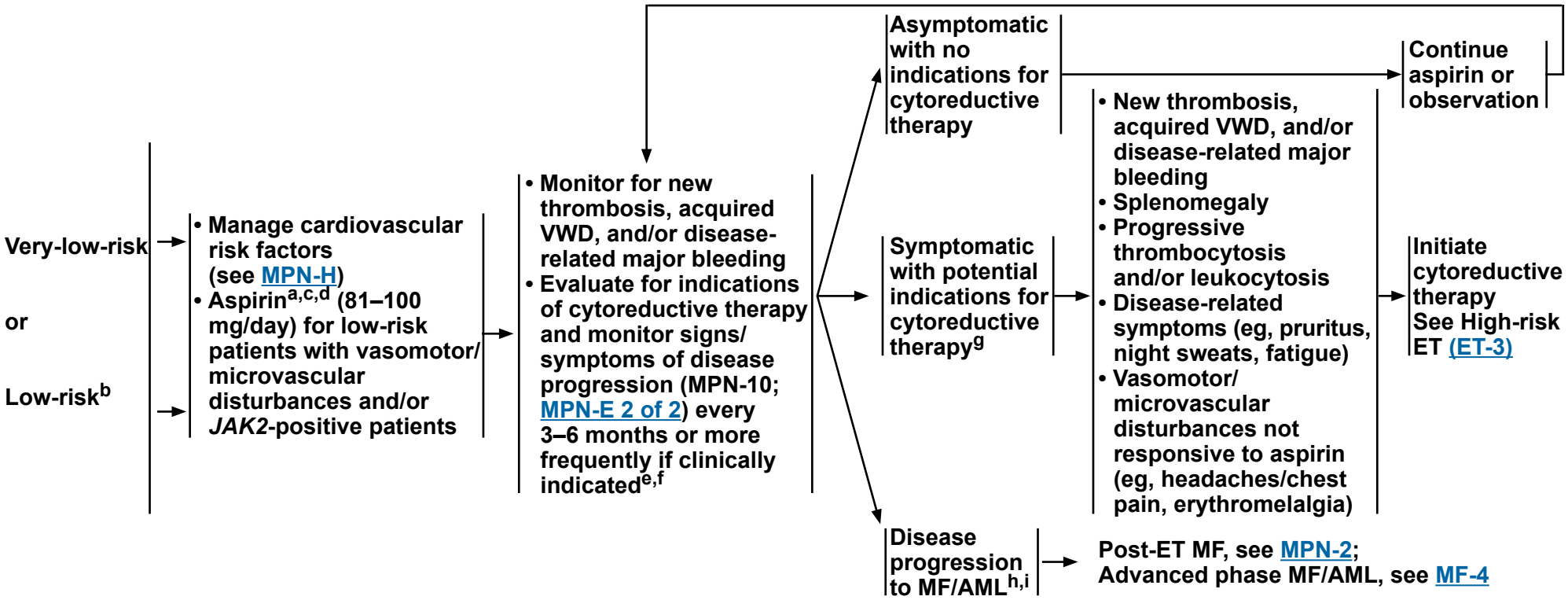
TREATMENT FOR VERY-LOW-RISK OR LOW-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[b] Harrison CN, et al. N Engl J Med 2005;353:33-45.
[c] Aspirin should be used with caution in patients with acquired VWD. 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] See Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).
[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

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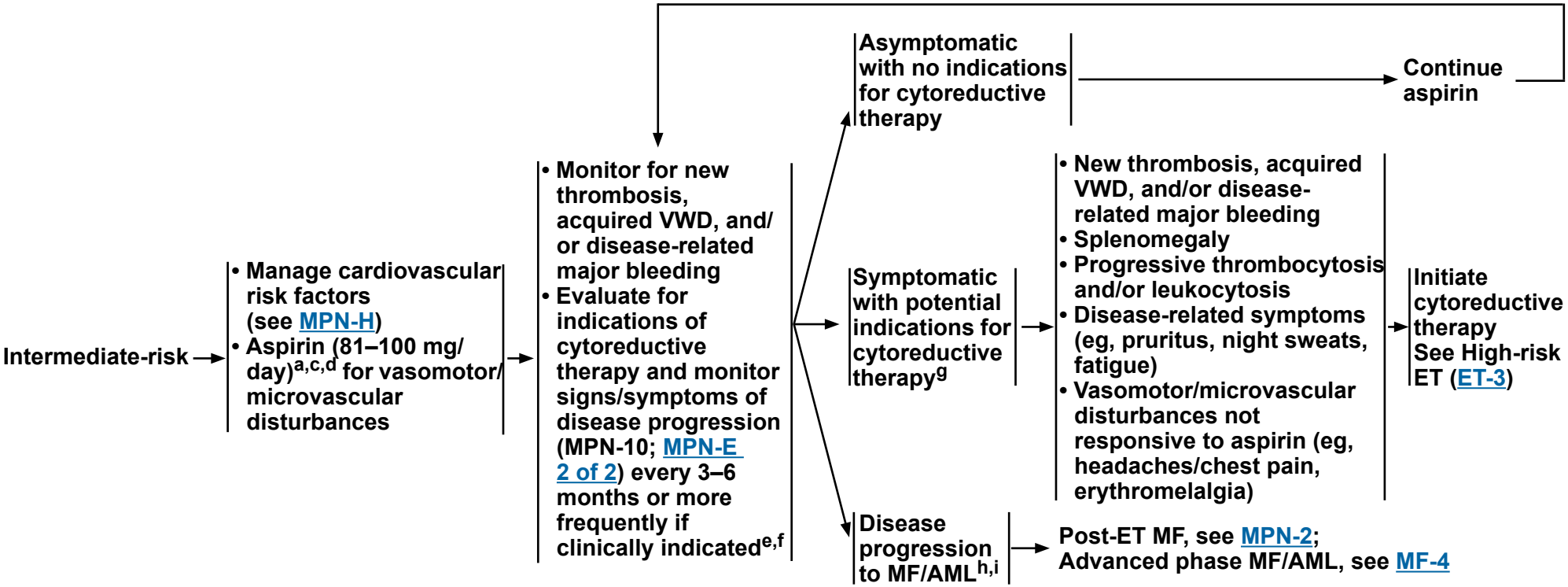
TREATMENT FOR INTERMEDIATE-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[c] Aspirin should be used with caution in patients with acquired VWD. 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] See Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).
[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].

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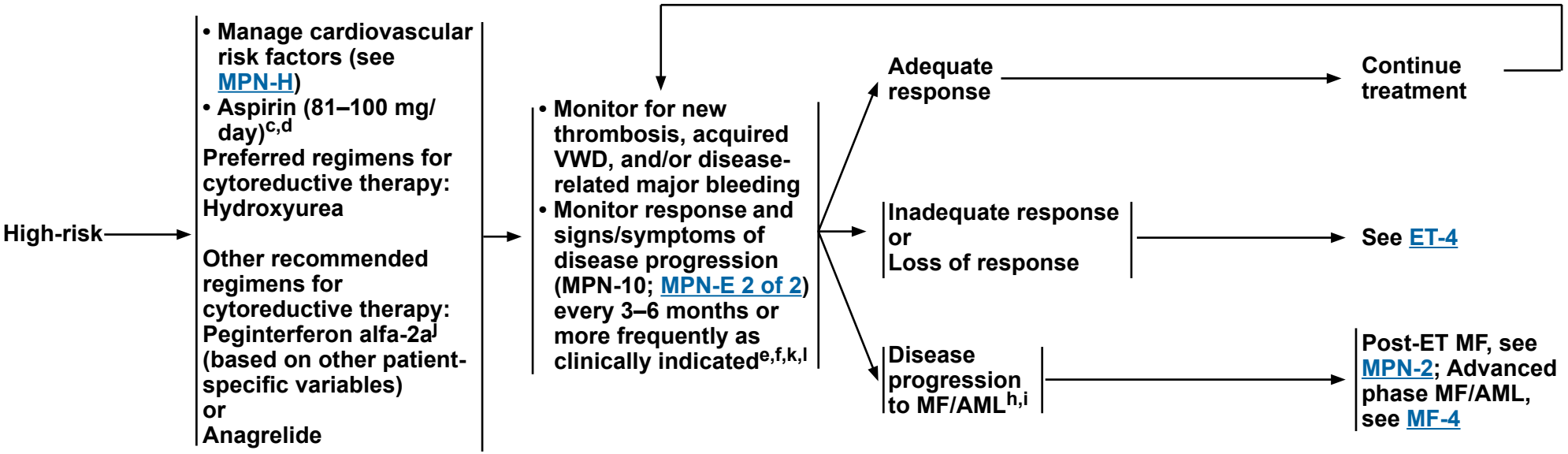
TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]



[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[c] Aspirin should be used with caution in patients with acquired VWD. Higher-dose aspirin may be appropriate in selected patients as clinically indicated. The risks and benefits of higher-dose aspirin 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] See Supportive Care for Patients with MPN (MPN-F).
[f] Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.
[h] Diagnostic criteria for post-ET or post-PV MF. See (MPN-B).
[i] The WHO classification defines acute leukemia as ≥20% blasts in the marrow or blood. A diagnosis of AML may be made with less than 20% in patients with recurrent cytogenetic abnormalities [eg, t(15;17), t(8;21), t(16;16), inv(16)].
[j] Peginterferon alfa-2a can be considered for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy that defer hydroxyurea.
[k] See 2013 IWG-MRT and ELN Response Criteria for ET (ET-A). 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.
[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.

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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**
- **New thrombosis, acquired VWD 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[j]
or
Anagrelide if not previously used

Useful in certain circumstances:
Ruxolitinib
or
Busulfan (PO) (especially for older adults)[n]
or
Plateletpheresis (for emergent situations, eg, severe thrombocytosis-related neurologic complications)[o]

[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[j] Peginterferon alfa-2a can be considered for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy who defer hydroxyurea.
[m] Definition of intolerance/resistance to hydroxyurea (MPN-I).
[n] Alvarez Larran A, et al. Ann Hematol 2014;93:2037-2043.
[o] Padmanabhan A, et al. J Clin Apher 2019;34:171-354.

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2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR ESSENTIAL THROMBOCYTHEMIA (ET)[1,2]

Complete remission	
A	**Durable* resolution of disease-related signs including palpable hepatosplenomegaly, large symptoms improvement,† AND**
B	**Durable* peripheral blood count remission, defined as: platelet count ≤400 x 10^9/L, WBC count <10 x 10^9/L, absence of leukoerythroblastosis, AND**
C	**Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND**
D	**Bone marrow histologic remission defined as disappearance of megakaryocyte hyperplasia and absence of >grade 1 reticulin fibrosis.**
Partial remission	
A	**Durable* resolution of disease-related signs including palpable hepatosplenomegaly, and large symptoms improvement, AND**
B	**Durable* peripheral blood count remission, defined as: platelet count ≤400 x 10^9/L, WBC count <10 x 10^9/L, absence of leukoerythroblastosis, AND**
C	**Without signs of progressive disease, and absence of any hemorrhagic or thrombotic events, AND**
D	**Without bone marrow histologic remission, defined as the persistence of megakaryocyte hyperplasia**
No response	**Any response that does not satisfy partial remission**
Progressive disease	**Transformation into PV, post-ET myelofibrosis, myelodysplastic syndrome, or acute leukemia**

WBC: White blood cell
*Lasting at least 12 weeks
†Large symptom improvement (≥10-point decrease) in MPN-SAF TSS.

[1]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(23):4778-4781.
[2]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.

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2017 WHO DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS[1]

WHO prePMF Criteria
(Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion)

- **Major criteria**
  - **Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1,[2] accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis**
  - **Not meeting WHO criteria for *BCR-ABL1*+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms**
  - **Presence of *JAK2, CALR,* or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,[3] or absence of minor reactive BM reticulin fibrosis[4]**

- **Minor criteria**
  - **Presence of at least one of the following, confirmed in 2 consecutive determinations:**
    - ◊ **Anemia not attributed to a comorbid condition**
    - ◊ **Leukocytosis ≥11 x 10^9/L**
    - ◊ **Palpable splenomegaly**
    - ◊ **LDH increased to above upper normal limit of institutional reference range**

WHO Overt PMF Criteria
(Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion)

- **Major criteria**
  - **Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3[2]**
  - **Not meeting WHO criteria for ET, PV, *BCR-ABL1*+ CML, myelodysplastic syndromes, or other myeloid neoplasms**
  - **Presence of *JAK2, CALR, or MPL* mutation or in the absence of these mutations, presence of another clonal marker,[3] or absence of reactive myelofibrosis[5]**

- **Minor criteria**
  - **Presence of at least one of the following, confirmed in 2 consecutive determinations:**
    - ◊ **Anemia not attributed to a comorbid condition**
    - ◊ **Leukocytosis ≥11 x 10^9/L**
    - ◊ **Palpable splenomegaly**
    - ◊ **LDH increased to above upper normal limit of institutional reference range**
    - ◊ **Leukoerythroblastosis**

[1]Adapted with permission Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon, 2017.
[2]See Grading of Myelofibrosis (MPN-A 2 of 2).
[3]In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (eg, *ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*) are of help in determining the clonal nature of the disease.
[4]Minor (grade 1) reticulin fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.
[5]BM fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

Continued

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GRADING OF MYELOFIBROSIS[6]

Myelofibrosis Grading

- **MF-0**
  - **Scattered linear reticulin with no intersections (crossovers) corresponding to normal BM**
- **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(8):1128-1132.
*In grades MF-2 or MF-3 an additional trichrome stain is recommended.

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IWG-MRT DIAGNOSTIC CRITERIA FOR POST-POLYCYTHEMIA VERA (PV) AND POST-ESSENTIAL (ET) 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) 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 left costal margin) 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]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.

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2017 WHO DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA[1]

Polycythemia Vera (PV)
(Diagnosis requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion[2])

- **Major criteria**
  - **Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women**
    OR
    Hematocrit >49% in men, >48% in women
    OR
    Increased red cell mass (RCM)[3]
  - **Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)**
  - **Presence of *JAK2* V617F or *JAK2* exon 12 mutation**

- **Minor criteria**
  - **Subnormal serum EPO level**

Essential Thrombocythemia (ET)
(Diagnosis requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion)

- **Major criteria**
  - **Platelet count ≥450 x 10^9/L**
  - **Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers**
  - **Not meeting WHO criteria for CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms**
  - **Presence of *JAK2, CALR,* or *MPL* mutation**

- **Minor criterion**
  - **Presence of a clonal marker or absence of evidence for reactive thrombocytosis**

[1]Adapted with permission Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon, 2017.
[2]Criterion number 2 (BM biopsy) may not be required in cases 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%) if major criterion 3 and the minor criterion are present. However, initial myelofibrosis (present in up to 20% of patients) can only be detected by performing a BM biopsy; this finding may predict a more rapid progression to overt myelofibrosis (post-PV MF).
[3]More than 25% above mean normal predicted value.

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PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

Mutated Gene	Primary Myelofibrosis (PMF)
***JAK2* V617F**	**Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]**
***MPL* W515L/K**	**Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]**
CALR	**Improved survival compared to *JAK2* mutation and "triple-negative" PMF[1-4] Lower risk of thrombosis compared to *JAK2* mutation[1]**
***CALR* Type 1/Type 1-like**	**Improved overall survival (OS) compared to *CALR* type 2/type 2-like and *JAK2* V617F mutation[5-8]**
"Triple Negative" (non-mutated *JAK2, MPL, and CALR*)	**Inferior leukemia-free survival compared to patients with *JAK2*- and/or *CALR*-mutated PMF[1-3] Inferior OS compared to patients with *CALR*-mutated PMF[2]**
ASXL1	**Independently associated with inferior OS* and leukemia-free survival as well as lower progression-free survival (PFS) following HCT [9,10]**
EZH2	**Independently associated with inferior OS[9]**
RAS	**Associated with decreased OS[11]**

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[1]Rumi E, Pietra D, Pascutto C, et al. Clinical effect of driver mutations of JAK2, CALR, or MPL in primary myelofibrosis. Blood 2014;124:1062-1069.
[2]Tefferi A, Lasho TL, Finke CM, et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia 2014;28:1472-1477.
[3]Tefferi A, Guglielmelli P, Larson DR, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood 2014;124:2507-2513.
[4]Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 2013;369:2379-2390.
[5]Guglielmelli P, Rotunno G, Fanelli T, et al. Validation of the differential prognostic impact of type 1/type-1 like versus type 2/type 2-like CALR mutations in myelofibrosis. Blood Cancer J 2015;5:e360.
[6]Tefferi A, Lasho TL, Tischer A, et al. The prognostic advantage of calreticulin mutations in myelofibrosis might be confined to type 1 or type 1-like CALR variants. Blood 2014;124:2465-2466.
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[8]Li B, Xu J, Wang J, et al. Calreticulin mutations in Chinese with primary myelofibrosis. Haematologica 2014;99:1697-1700.
[9]Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. Leukemia 2013;27:1861-1869.
[10]Kröger N, Panagiota V, Badbaran A, et al. Impact of molecular genetics on outcome in myelofibrosis patients after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2017;23:1095-1101.
[11]Santos FPS, Getta B, Masarova, et al. Prognostic impact of RAS-pathway mutations in patients with myelofibrosis. Leukemia 2020;34:799-810.

**ASXL1* mutation retains prognostic significance for inferior overall survival independent of IPSS or DIPSS-Plus risk score.

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PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

Mutated Gene	Primary Myelofibrosis (PMF)
IDH1/2	**Independently associated with inferior leukemia-free survival as well as lower PFS following HCT [9,10]**
SRSF2	**Independently associated with inferior OS and leukemia-free survival[9]**
Combined *CALR* and *ASXL1* status	**Survival longest for *CALR*(+)*ASXL1*(-) patients (median 10.4 years) and shortest in *CALR*(-) *ASXL1*(+) patients (median 2.3 years)[**12]** **Intermediate survival (median 5.8 years) for *CALR*(+)*ASXL1*(+) or *CALR*(-)*ASXL1*(-) patients[12]**
TP53	**Associated with leukemic transformation[13]**
***U2AF1* Q157**	**Inferior OS compared to patients with *U2AF1* S34 mutated or *U2AF1* unmutated PMF. The effect was most evident in younger patients[14]**
U2AF1* or *DNMT3A* or *CBL	**Associated with worse OS in patients with MF undergoing allogeneic HCT[15,16]**

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[9]Vannucchi AM, Lasho TL, Guglielmelli P, et al. Mutations and prognosis in primary myelofibrosis. Leukemia 2013;27:1861-1869.
[10]Kröger N, Panagiota V, Badbaran A, et al. Impact of molecular genetics on outcome in myelofibrosis patients after allogeneic stem cell transplantation. Biol Blood Marrow Transplant 2017;23(7):1095-1101.
[12]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.
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**The *CALR/ASXL1* mutation status was DIPSS-Plus independent ($P < .0001$) and effective in identifying low-/intermediate-1-risk patients with shorter (median, 4 years) or longer (median 20 years) survival and high-/intermediate-2-risk patients with shorter (median, 2.3 years) survival.

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PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN[17]

Mutated Gene	Polycythemia Vera (PV)
ASXL1/SRSF2/*** ***IDH1/2/RUNX1***	**The presence of at least 1 of these "adverse variants/mutations" is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age, IWG prognostic model for PV, and karyotype.[18,19] Adverse variants/mutations also affected myelofibrosis-free survival (*ASXL1*) and leukemia-free survival (*IDH2* and *RUNX1*)[18,19]**
***JAK2* exon 12 mutation**	**Patients with *JAK2* exon 12-mutated PV exhibit younger age, increased mean hemoglobin/hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared to those with *JAK2* V617F-mutated PV. However, both *JAK2* mutations are associated with similar rates of thrombosis, evolution to myelofibrosis or leukemia, and death.[20,21]**

[17]Next-generation sequencing (NGS) remains a research tool in many situations. However, it may be useful to establish clonality in selected circumstances (eg, "triple negative" non-mutated *JAK2, MPL*, and *CALR*).

[18]Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Advances 2016;1(1):21-30.
[19]Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythemia and polycythemia vera. Br J Haematol 2020;189:291-302.
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***SRSF2* and *SF3B1* mutations remain significant predictors in the context of the clinical outcomes.

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PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN[4]

Mutated Gene	Essential Thrombocythemia (ET)
CALR	**Lower risk of thrombosis compared to *JAK2*-mutated ET[22-24]** **No difference in overall survival or myelofibrotic or leukemic transformation compared to *JAK2*-mutated ET[22-24]** ***CALR* mutation does not modify the IPSET score for predicting thrombosis in patients with ET[13]**
TP53	**Associated with inferior leukemia-free survival in multivariate analysis[17]**
SH2B3/IDH2/U2AF1/ SRSF2/SF3B1/ *** ***EZH2/TP53/RUNX1***	**The presence of at least 1 of these "adverse variants/mutations" is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age and karyotype[18,19]** **Adverse variants/mutations also affect myelofibrosis-free survival (*U2AF1* and *SF3B1*)*** and leukemia-free survival (*EZH2* and *RUNX1*)[18,19]**

[4]Klampfl T, Gisslinger H, Harutyunyan AS, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. N Engl J Med 2013 Dec 19;369(25):2379-90.
[13]Rampal R, Ahn J, Abdel-Wahab O, et al. Genomic and functional analysis of leukemic transformation of myeloproliferative neoplasms. Proc Natl Acad Sci USA 2014;111:E5401-E5410.
[17]NGS remains a research tool in many situations. However, it may be useful to establish clonality in selected circumstances (eg, "Triple Negative" non-mutated *JAK2, MPL*, and *CALR*).
[18]Tefferi A, Lasho TL, Guglielmelli P, et al. Targeted deep sequencing in polycythemia vera and essential thrombocythemia. Blood Adv 2016;1(1):21-30.
[19]Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythemia and polycythemia vera. Br J Haematol 2020;189:291-302.
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[23]Rumi E, Pietra D, Ferretti V, et al. *JAK2* or *CALR* mutation status defines subtypes of essential thrombocythemia with substantially different clinical course and outcomes. Blood 2014 Mar 6;123:1544-1551.
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****SRSF2* and *SF3B1* mutations remain significant predictors in the context of the clinical outcomes.**

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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; MPN-10) is recommended for the assessment of symptom burden at baseline and monitoring symptom status during the course of treatment (See MPN-E, 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 ruxolitinib.**
- **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.**

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MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS; MPN-10)[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.

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SUPPORTIVE CARE FOR PATIENTS WITH MPN

MYELOFIBROSIS

- Transfusion support
  - 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 splenectomized patients, 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 ruxolitinib and fedratinib.
- 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 G-CSF or 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.
  - Hydration and/or diuresis
  - Consider management of hyperuricemia with allopurinol or rasburicase.
  - Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, and evidence of impaired renal function.
- Counseling at baseline and throughout disease course for assessment for, identification of, and decreasing cardiovascular risk factors (eg, smoking, diet, exercise, thrombotic and hemorrhagic risk factors).

Continued

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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, its 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 oral antihistamine therapy (ie, cetirizine, diphenhydramine), and topical steroids.**
  - **Ruxolitinib was shown to improve pruritus in patients with ET, PV, and MF patients in the MAJIC-ET, RESPONSE, and COMFORT-I trials, respectively.**
  - **Small pilot studies have shown SSRIs and narrow-band UVB 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 MF patients in the COMFORT-1 study.**
  - **Loratadine and 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 HCT 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.**

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Continued

SUPPORTIVE CARE FOR PATIENTS WITH MPN

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SPECIAL CONSIDERATIONS FOR THE USE OF JAK INHIBITORS

RUXOLITINIB (MPN-G 2 OF 5)

FEDRATINIB (MPN-G 4 OF 5)

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Continued

SPECIAL CONSIDERATIONS FOR THE USE OF JAK INHIBITORS[1]

RUXOLITINIB

- **CBC with differential and comprehensive metabolic panel must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. Consider monitoring uric acid and LDH.**
- **A baseline MPN-SAF TSS (MPN-10) (prior to initiation of therapy) is recommended to monitor symptoms during the course of therapy.**
- **Symptoms may return to pretreatment levels over a period of approximately one week following discontinuation or interruption of ruxolitinib. Consider tapering the dose of ruxolitinib gradually, when discontinuing or interrupting therapy with ruxolitinib for reasons other than thrombocytopenia or neutropenia.**
- **Monitor spleen size either by palpation or imaging.**

Myelofibrosis (MF)

Dosing and administration:
The recommended initial dosing of ruxolitinib (as described in the full prescribing information) is dependent on the patient's baseline platelet counts. However, certain clinical situations may support initiation of ruxolitinib at a lower dose with subsequent dose adjustments.

- **50 X 10^9/L to less than 100 X 10^9/L: 5 mg twice daily**
- **100 X 10^9/L - 200 X 10^9/L: 15 mg twice daily**
- **>200 X 10^9/L: 20 mg twice daily**

Dose modifications based on insufficient response:

- **Increase dose as tolerated, at 4-week intervals, in 5 mg twice daily increments to a maximum of 10 mg twice daily (if <100 x 10^9/L)/ 25 mg twice daily (if >100 x 10^9/L).**
- **Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks.**
- **Consider dose increases in patients who meet all of the following conditions. Discontinue if no response or improvement of symptoms after 6 months.**
  - **Failure to achieve a 50% reduction in palpable splenomegaly or symptom improvement or a 35% reduction in spleen volume as measured by CT or MRI. Inadequate reduction in splenomegaly is determined by the treating clinician. Less than 50% reduction in palpable splenomegaly may be clinically meaningful and justify continued use of ruxolitinib.**
  - **Platelet count >125 X 10^9/L at 4 weeks and platelet count never <100 X 10^9/L; ANC levels greater than 0.75 X 10^9/L.**

Polycythemia Vera (PV)

Dosing and administration:
The recommended initial dosing of ruxolitinib (as described in the full prescribing information) is 10 mg twice daily. Doses may be titrated based on safety and efficacy.

Dose modifications based on insufficient response:

- **Dose modification should be based on the efficacy of ruxolitinib (eg, improving phlebotomy burden, symptom burden, and splenomegaly) versus toxicity.**
- **Doses may be increased as tolerated in 5-mg twice-daily increments to a maximum of 25 mg twice daily.**
- **Doses should not be increased during the first 4 weeks of therapy and not more frequently than every 2 weeks.**

[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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Continued

SPECIAL CONSIDERATIONS FOR THE USE OF JAK INHIBITORS[1]
RUXOLITINIB

Dose Modifications for Adverse Reactions:

Hematologic Toxicities

Thrombocytopenia should be managed by dose reduction or dose interruption (at the discretion of treating clinician based on clinical parameters). Platelet transfusions may be necessary. Management of anemia may require blood transfusions and/or dose modifications. Severe neutropenia (ANC less than 0.5 X 10^9/L) was generally reversible by withholding ruxolitinib. Ruxolitinib may be restarted at prior dose or with subsequent modifications if necessary after recovery of the hematologic parameter(s) to acceptable levels. Monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated. See prescribing information for dose modifications for hematologic toxicities.

Non-Hematologic Toxicities

Lipid Elevations

Ruxolitinib has been associated with increases in lipid parameters, including total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. Assess lipid parameters approximately 8–12 weeks following initiation of ruxolitinib. Monitor and treat according to clinical guidelines for the management of hyperlipidemia.

Renal Impairment

Dose reduction is recommended for patients with moderate creatinine clearance [CrCl] (CrCl 30–59 mL/min) or severe renal impairment (CrCl 15–29 mL/min) with a platelet count between 50 X 10^9/L and 150 X 10^9/L. See prescribing information for dose adjustments related to renal impairment.

Hepatic Impairment

Dose reduction is recommended for patients with any degree of hepatic impairment and platelet count between 50 X 10^9/L and 150 X 10^9/L. See prescribing information for dose adjustments related to hepatic impairment.

Infections

Ruxolitinib is associated with a potentially increased risk of opportunistic infections. Patients should be assessed for the risk of developing serious bacterial, mycobacterial, fungal, and viral infections. Patients receiving ruxolitinib should be carefully observed for signs and symptoms of infections. Appropriate treatment should be initiated promptly to resolve active serious infections before initiating ruxolitinib therapy.

Tuberculosis

Tuberculosis infection has been reported in patients receiving ruxolitinib. Patients should be evaluated for tuberculosis risk factors, and those at higher risk should be tested for latent infection. Consultation with a physician with expertise in the treatment of tuberculosis is recommended prior to initiating ruxolitinib for patients with evidence of active or latent tuberculosis.

Hepatitis B

Increases in Hepatitis B viral load (HBV-DNA titer) with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic HBV infections treated with ruxolitinib. Patients with chronic HBV infection should be treated and monitored according to clinical guidelines.

PML and Herpes Zoster

Progressive multifocal leukoencephalopathy (PML) and herpes zoster virus (HZV) infection have been reported in patients treated with ruxolitinib. If PML is suspected, ruxolitinib should be discontinued. Patients with suspected HZV infection should be treated and monitored according to clinical guidelines. Consider the use of non-live, subunit herpes zoster vaccine for patients receiving ruxolitinib.

Non-Melanoma Skin Cancer

Non-melanoma skin cancers including basal cell, squamous cell, and Merkel cell carcinoma have occurred in patients treated with ruxolitinib. Perform annual skin examinations.

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Continued

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SPECIAL CONSIDERATIONS FOR THE USE OF JAK INHIBITORS[1]
FEDRATINIB

- **Serious and fatal encephalopathy, including Wernicke's encephalopathy, has occurred in patients treated with fedratinib. Wernicke's encephalopathy is a neurologic emergency.**
- **Thiamine (vitamin B1) level, CBC with platelets, and nutritional status should be assessed in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated.**
- **Fedratinib should not be started in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If Wernicke's encephalopathy is suspected, discontinue fedratinib immediately and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize.**

Myelofibrosis (MF)

Dosing and administration:
The recommended initial dosing of fedratinib (as described in the full prescribing information) is 400 mg once daily for patients with a baseline platelet count ≥50 x 10^9/L.
- **Fedratinib may be taken with or without food. Administration with a high-fat meal may reduce the incidence of nausea and vomiting.**
- **For patients who are on treatment with ruxolitinib: taper and discontinue ruxolitinib according to the ruxolitinib prescribing information before initiation of fedratinib.**

Dose modifications for concomitant use of strong CYP3A4 inhibitors:
Reduce fedratinib dose to 200 mg once daily. In cases where co-administration with a strong CYP3A4 inhibitor is discontinued, fedratinib dose should be increased to 300 mg once daily during the first 2 weeks after discontinuation of the CYP3A4 inhibitor, and then to 400 mg once daily thereafter as tolerated.

Dose modifications for adverse reactions:
Hematologic Toxicities
Grade 4 neutropenia or grade 4 thrombocytopenia or grade 3 thrombocytopenia with active bleeding should be managed with dose interruption until resolved to grade ≤2 or baseline. Fedratinib should be restarted at 100 mg daily below the last given dose. Dose reductions should be considered for patients who become transfusion-dependent during treatment with fedratinib.

Non-Hematologic Toxicities
Renal impairment
Reduce fedratinib dose to 200 mg once daily for patients with severe renal impairment (CrCl 15–29 mL/min as estimated by Cockcroft-Gault equation).
Hepatic toxicity
Monitor hepatic function at baseline, periodically during treatment, and as clinically indicated. Grade ≥3 elevations in ALT, AST, or bilirubin should be managed with dose interruption until resolved to grade ≤1 or baseline. Fedratinib should be restarted at 100 mg daily below the last given dose. Monitor ALT, AST, and bilirubin (total and direct) more frequently following the dose reduction. If there is reoccurrence of a grade ≥3 elevation, discontinue treatment with fedratinib.
Gastrointestinal toxicity
Grade ≥3 nausea, vomiting, or diarrhea not responding to supportive measures within 48 hours should be managed with dose interruption until resolved to grade ≤1 or baseline. Fedratinib should be restarted at 100 mg daily below the last given dose. Consider providing appropriate prophylactic antiemetic therapy during treatment with fedratinib.
Amylase and lipase elevation
Monitor amylase and lipase at baseline, periodically during treatment, and as clinically indicated. Grade ≥3 amylase and/or lipase elevations should be managed with dose interruption until resolved to grade ≤1 or baseline. Fedratinib should be restarted at 100 mg daily below the last given dose.
Other grade ≥3 non-hematologic toxicities
Manage with dose interruption until resolved to grade ≤1 or baseline. Fedratinib should be restarted at 100 mg daily below the last given dose.

[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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Continued

SPECIAL CONSIDERATIONS FOR THE USE OF JAK INHIBITORS[1]

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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SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA (PV) AND ESSENTIAL THROMBOCYTHEMIA (ET)

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 other cardiovascular risk factors (refers to all subtypes) (See ET-1 and ET-2).
  - 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 thrombotic disorders 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 a prospective, randomized, controlled trial.
  - 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 normalize platelet counts.
  - Coagulation tests to evaluate for acquired VWD 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 (see 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.
- 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.

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Continued
References

SPECIAL CONSIDERATIONS IN THE TREATMENT OF POLYCYTHEMIA VERA (PV) AND ESSENTIAL THROMBOCYTHEMIA (ET)

Surgery (continued)

- 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[4-10]

- Pregnancy pre-conception meeting and evaluation by high-risk obstetrician is recommended.
- All women with PV should maintain hematocrit, ideally, below the gestational range (<41% trimester 1, <38% trimester 2, <39% trimester 3).
- Low-risk disease: Low-dose aspirin (50–100 mg/day) is recommended throughout pregnancy; consult with obstetrician and obstetric anesthesiologist to determine timing of aspirin discontinuation prior to delivery/epidural.
- Prophylactic dose LMWH can be used for 6 weeks postpartum, especially in women who have undergone C-section.
- High-risk disease and history of thrombosis: For women with prior history of thrombosis and on long-term treatment doses of anticoagulant therapy, recommend therapeutic dosing of LMWH throughout pregnancy and in the postpartum period. For women not already receiving long-term anticoagulant therapy who have a history of VTE, recommend prophylactic LMWH with low-dose aspirin in both the antepartum and postpartum period.[11,12]
- In patients taking LMWH and aspirin, consultation with a high-risk obstetrician and obstetric anesthesiologist is recommended regarding the optimal timing of discontinuation in preparation for an epidural prior to delivery.
- Patients on hydroxyurea prior to pregnancy should be switched to peginterferon alfa-2a. If cytoreductive therapy is needed during pregnancy, peginterferon alfa-2a should be used. 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 (risk category C) in pregnancy. It should be used only if benefits outweigh potential risk to the fetus.[12]
- Direct oral anticoagulants should be avoided in breastfeeding women. Unfractionated heparin, LMWH, warfarin, and fondaparinux are all safe options in women who require anticoagulation and are breastfeeding.[13]
- Hydroxyurea is excreted in breastmilk and should be avoided in women who are breastfeeding.

References

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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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]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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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

All recommendations are category 2A unless otherwise indicated.

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.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Discussion

This discussion corresponds to the NCCN Guidelines for Myeloproliferative Neoplasms. Last updated 09/04/2019.

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 more recent survey that assessed the incidence rates (IRs) of different subtypes of MPN in the United States (2001–2012), the IRs were highest for PV (IR = 11) and ET (IR = 10).[2]

MPN are characterized by a complicated symptom profile; the symptom profile varies within and between each MPN subtype, but often includes constitutional symptoms, fatigue, pruritus, weight loss, symptoms from splenomegaly, and variable lab abnormalities, including erythrocytosis, thrombocytosis, and leukocytosis.[3-6] 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) and acute myeloid leukemia (AML), both of which are associated with poor prognosis.[8,9]

The diagnosis and the management of patients with MPN has evolved since the identification of “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 to provide 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.

Literature Search Criteria and Guidelines Update Methodology

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; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 146 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel’s review of lower-level evidence and expert opinion.

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

Molecular Abnormalities in MPN

JAK2 V617F mutations account for the majority of patients with PV (more than 90%) and 60% of patients with ET or MF.[13-15] The V617F mutation occurs in exon 14; however, rare insertions and deletions have been found in exon 12. *JAK2* exon12 mutations have been described in 2% to 3% of patients with PV.[16,17]

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.[18-20]

Mutations in exon 9 of the calreticulin gene (*CALR*) are reported in approximately 20% to 35% of all patients with ET and MF (accounting for about 60%–80% of patients with *JAK2/MPL*-negative ET and MF).[21,22] *Type 1* (52 base pair deletions) and *Type 2* (5 base pair insertions) mutations are the most frequent variants. *CALR*-Type 1 mutations are more frequent in patients with MF and *CALR*-Type 2 mutations are preferentially associated with ET.[23-25]

Mutations in several other genes that are involved in signal transduction (*CBL, LNK/SH2B3*), chromatin modification (*TET2, EZH2, IDH1/2, ASXL1, DNM3TA*), RNA splicing (*SF3B1, SRSF2, U2AF1),* and tumor suppressor function (*TP53*) have also been reported in patients with MPN.[26,27]

Myelofibrosis

CALR mutation is associated with better overall survival (OS) than *JAK2* V617F or *MPL* W515 mutation and the survival advantage is significant in patients with type 1/type 1-like mutation.[9,24,28,29] In a study of 617 patients with primary MF (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.[28] *CALR* mutations retained their prognostic significance for better OS compared to *JAK2* V617F mutation ($P = .19$) 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 who were triple negative. In the 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 (26 years; $P < .0001$) versus 7 years for those with type 2/type 2-like mutation or *JAK2* V617F mutation. 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.[29]

MPL mutations are associated with lower hemoglobin levels at diagnosis and increased risk of transfusion dependence in patients with MF.[30] The "triple-negative" mutation status (lack of all 3 "driver" mutations — *JAK2, CALR, or MPL)*, which occurs in approximately in 10% of patients, is associated with a worse prognosis in patients with MF.[31,32]

ASXL1, EZH2, SRSF2, TP53, IDH1, *or IDH2* mutations are considered as "high-molecular-risk" (HMR) mutations, associated with significantly shorter OS and leukemia-free survival (LFS) in patients with PMF.[33-36] *ASXL1, EZH2, and SRSF2* mutations are predictive of OS, while *ASXL1, SRSF2*, *and IDH1 or IDH2* are predictive of leukemic transformation in patients with PMF.[33-36] *TET2* or *TP53* mutations have also been associated with a worsened overall prognosis and an increased rate of leukemic transformation.[27,37] *U2AF1* mutations have also been associated with inferior survival in patients with PMF.[38] OS was significantly shorter for patients with *U2AF1* Q157 mutations, compared to those

with *U2AF1* S34 mutations or unmutated *U2AF1* and the survival effect was most evident in younger patients.

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.[35] 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 in patients with no mutations but also in those presenting with only one HMR mutation.[36] 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 risk factor for survival.[39] *CALR(+)/ASXL1(-)* was associated with the longest median OS (10 years) and *CALR(-)/ASXL1(+)* was associated with shortest median OS, and 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.[40]

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*-mutated PV.[41] However, both *JAK2* V617F and *JAK2* exon 12 mutations are associated with similar rates of thrombosis, transformation to MF or leukemia, and death.

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*- or *MPL*-mutated ET, whereas the presence of *MPL* mutations might be associated with a higher risk of fibrotic transformation.[42-44] However, *CALR* mutations have no impact on OS or myelofibrotic or leukemic transformation.[44,45] *CALR* mutation status also did not have a significant impact on the International Prognostic Score for ET (IPSET)-thrombosis prognostic score for predicting the risk of thrombosis.[46]

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.[32,47,48] In one report, the presence of at least one of the 3 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.[47] 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, for MF-free survival, and 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 a more recent report, myelofibrotic transformation was more frequent in patients with *SF3B1* and *IDH1/2* mutation, 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.[48]

Diagnostic Classification

The WHO classification of myeloid neoplasm was first published in 2001 and was updated in 2008 to refine the diagnostic criteria for previously described neoplasms based on the new scientific and clinical information and to introduce newly recognized disease entities.[49,50] It was revised again in 2017 to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the publication of the 2008 WHO classification.[51,52]

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.[52] 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.[35,36]

MF can either present as a de novo disorder (PMF) or it can develop from the transformation of PV and ET (post-PV MF or post-ET MF).[53] 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.[54] The revised 2017 WHO diagnostic criteria also 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.[52] The revised 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.[55,56]

In the International Working Group for MPN 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.[54] 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.

The diagnostic criteria for PV have also 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).[52] In an international study of 397 patients with *JAK2* V617F or a *JAK2* exon12 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 men (range 16.0–18.4 g/dL) and <16.5 g/dL in women (range 15.0–16.4 g/dL) and frequent presence of subnormal erythropoietin (EPO) levels.[57] 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 more recent 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.[58] 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.[52] However, bone marrow biopsy may not be required 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.

The diagnosis of MPN should be based on the 2017 WHO diagnostic criteria and requires a combination of clinical, laboratory, cytogenetic, and molecular testing.[52] The diagnosis of PMF requires meeting all 3 major criteria and at least one minor criterion as outlined in the revised 2017 WHO criteria.[52] The diagnosis of PV requires meeting either all 3 major criteria or the first 2 major criteria and the minor criterion, whereas the diagnosis of ET requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion as outlined in the revised 2017 WHO criteria.[52] See *2017 WHO Diagnostic Criteria for PMF, PV, and ET* in the algorithm for a list of major and minor criteria. The diagnosis of post-PV MF or post-ET MF is based on the 2008 IWG-MRT diagnostic criteria, requiring the documentation of a previous diagnosis of PV or ET as defined by the WHO criteria and the development of bone marrow fibrosis of grade 2–3 (or 3–4, depending on the scale) and at least 2 minor criteria.[59]

Workup of Suspected MPN

Initial evaluation of patients with suspected MPN should include a history and physical exam, palpation of spleen, evaluation of thrombotic/hemorrhagic events, cardiovascular risk factors, and documentation of transfusion/medication history. Laboratory evaluations should include complete blood count (CBC), 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 HCT would be considered.

Fluorescence in situ hybridization (FISH) or a multiplex reverse transcriptase polymerase chain reaction (RT-PCR) 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.[52] Molecular testing for *JAK2* V617F mutations is recommended as part of initial workup for all patients.[52] If *JAK2* V617F mutation testing is negative, molecular testing for *MPL* and *CALR* mutations should be performed for patients with MF and ET; molecular testing for the *JAK2* exon12 mutation should be done for those with suspected PV and negative for the *JAK2* V617F mutation.[16,17] Alternatively, molecular testing using the multi-gene NGS panel that includes *JAK2, CALR*, and *MPL* can be used as part of initial workup for all patients. 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.[60] 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 and biopsy with trichrome and reticulin stain and bone marrow cytogenetics (karyotype, with or without FISH; blood, 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).[52,54,57] 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.[52,61] Progression of PV or ET to MF can only be detected by performing a bone marrow biopsy; however, in patients with PV, bone marrow biopsy may not be required 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%]), *JAK2V617F* or *JAK2 exon12* mutations, and subnormal EPO level.[52]

MPN are associated with an increased risk of major bleeding and thrombosis/thromboembolism compared to the general population, and these events contribute considerably to morbidity and mortality in patients with MPN.[62,63] Acquired von Willebrand disease (VWD) is associated with a variety of hematologic disorders, being particularly frequent in lymphoproliferative (48%) and myeloproliferative disorders (15%). Among MPN, the frequency of acquired VWD is more common among patients with ET (11%–17%) but can also be seen in patients with PV.[64] Coagulation tests to evaluate for acquired VWD (plasma von Willebrand factor antigen measurement, von Willebrand ristocetin cofactor activity, von Willebrand multimer analysis, and Factor VIII level)[65] and/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 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 year before diagnosis in 49% of patients with MF, 61% of patients with PV, and 58% of patients with ET.[4] In a recent 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.[66-70]

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.[66]

MF-SAF was subsequently expanded to a 27-item tool, MPN 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).[68]

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.[69]

All 3 symptom assessment tools are coadministered with Brief Fatigue Inventory and the 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.[68,69]

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

The International Prognostic Scoring System (IPSS), dynamic International Prognostic Scoring System (DIPSS), and DIPSS-Plus are the 3 most common prognostic scoring systems used for the risk stratification of patients with MF.[71-73]

Other prognostic models incorporating cytogenetic information and mutational status such as mutation-enhanced international prognostic scoring system for (MIPSS70 and MIPSS70-plus) and genetically inspired prognostic scoring system (GIPSS) have been developed to further refine the risk stratification.[74,75] Further validation is essential before these models can be widely adopted for risk stratification of patients with MF.

IPSS should be used for the risk stratification at time of diagnosis.[71] DIPSS-Plus is preferred for the risk stratification during the course of treatment.[73] DIPSS can be used if karyotyping is not available.[72]

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% or greater at the time of diagnosis were identified as independent predictors of inferior survival.[71] IPSS stratifies patients at the time of diagnosis into 4 different risk groups based on the presence of 0, 1, 2, and 3 or more adverse factors: low-risk, intermediate-1-risk (INT-1-risk), intermediate-2-risk (INT-2-risk), and high-risk with the median survival of 135 months, 95 months, 48 months, and 27 months, respectively (P < .001).

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, development of anemia over time significantly affected survival (hazard ratio [HR] was approximately double than that of other adverse factors).[72] 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% at the time of diagnosis), 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 4 different risk groups: low-risk (0 adverse points), INT-1-risk (1 or 2 points), INT-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.[72]

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.[76-79] 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 2 additional risk factors.[73] Similarly, the median survival was <1.5 years for DIPSS high-risk patients with one or more of these additional prognostic factors compared to approximately 3 years for those patients without these prognostic factors.[73]

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), del5/5q, del12p, inv(3), or 11q23 rearrangement].[73] DIPSS-Plus also stratifies patients into 4 risk groups based on the aforementioned 8 risk factors: low-risk (no risk factors), INT-1-risk (one risk factor), INT-2-risk (2 or 3 risk factors), and high-risk (4 or more risk factors) with respective median survival rates of 15.4, 6.5, 2.9, and 1.3 years.

MIPSS70 and MIPSS70-plus

In a study of 805 patients with PMF (≤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 ≥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.[74] The MIPSS70 prognostic model (without the cytogenetic information) stratified patients into 3 risk categories (low-risk, intermediate-risk, and high-risk) with the median OS of 28 years, 7 years, and 2 years, respectively. The 5-year OS rates were 95%, 70%, and 29%, respectively. The MIPSS70-plus prognostic model, which included cytogenetic information, stratified patients into 4 risk categories (low-risk, intermediate-risk, high-risk, and very high-risk) with the 5-year OS rates of 91%, 66%, 42%, and 7%, respectively.

GIPSS

In an analysis of 641 patients with PMF for whom both cytogenetic information and mutational status were available, in a multivariate analysis, “very high-risk" (VHR) karyotype, unfavorable karyotype, absence of type 1/like *CALR* mutation, and the presence of *ASXL1*, *SRSF*2, or *U2AF1* Q157 mutations were identified as inter-independent predictors of inferior survival.[75] GIPSS stratified patients into 4 risk categories (low-risk, INT-1 and INT-2, and high-risk) based exclusively on genetic factors described above. The median 5-year survival rates were 94%, 73%, 40%, and 14%, respectively. However, the authors point out that this prognostic model should not be considered as a finished product but rather a template for incorporating additional genetic information, as it becomes available.

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.[80] Myelofibrosis Secondary to PV and ET-Prognostic Model (MYSEC-PM) is a novel prognostic model that stratifies patients with post-PV or post-ET MF into 4 risk groups, with distinct survival outcomes (low, INT-1, INT-2, and high risk) based on the hemoglobin level (<11 g/dL), circulating blasts (≥3%), *CALR* mutation status, platelet count (<150 × 10^9/L), and constitutional symptoms.[81] The median survival was not reached at 9 years, 4 years, and 2 years, respectively. Further validation studies are necessary to confirm these findings.

Treatment Options

Interferons

Interferon alfa, peginterferon alfa-2a, and peginterferon alfa-2b have been evaluated in a small series of patients with MF.[82,83]

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.[82]

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 (CI), and 23% of patients had stable disease [SD]).[83] 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 PFS and OS rates were 88% and 92%, respectively.

Ruxolitinib

Ruxolitinib is a potent and selective *JAK2* inhibitor approved for the treatment of intermediate-risk or high-risk MF, based on the results of phase III studies (COMFORT-I and COMFORT-II).[84,85] The COMFORT studies did not include patients with low-risk or INT-1-risk MF, and the use of ruxolitinib in this patient population is based on the evidence from retrospective analysis and non-randomized studies discussed below.

Low-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.[86] In this retrospective analysis of 108 patients (25 patients with low-risk MF and 83 patients with INT-1-risk MF) treated with ruxolitinib, patients with low-risk MF experienced a substantial improvement in splenomegaly and constitutional symptoms.[86] 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.

Intermediate-1-risk MF

The safety and efficacy of ruxolitinib in patients with INT-1-risk MF has been demonstrated in a retrospective analysis and nonrandomized studies.[86-89]

In the retrospective analysis (discussed above), among the 83 patients with INT-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.[86]

The ROBUST trial is an open-label phase II trial that evaluated the efficacy of ruxolitinib in patients with INT-1-risk MF (48 patients; 14 patients with INT-1-risk MF along with 13 patients with INT-2-risk MF and

21 patients had high-risk MF).[87] 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 INT-1-risk, 37% of patients with INT-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 (INT-1-risk, 21%; INT-2-risk, 23%; high-risk, 19%). Improvements in MF-SAF were seen in 80%, 73%, and 72% of patients with INT-1-risk, INT-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 INT-2-risk or high-risk MF with or without splenomegaly or INT-1-risk MF with a palpable spleen (≥5 cm from the costal margin).[88] Among 163 evaluable patients with INT-1-risk MF, at 24 and 48 weeks 64% and 61% of patients achieved a ≥50% reduction from baseline in palpable spleen length, respectively, and an additional 20% and 21% of patients had a 25% to <50% reduction in palpable spleen length, respectively. The median time to a ≥50% reduction in palpable spleen length was 5 weeks and the estimated probability of maintaining a response was 91% at 48 weeks and 88% at 60 weeks.

In another study that evaluated efficacy and safety of ruxolitinib in 70 patients with INT-1-risk MF, at 6 months the rates of spleen and symptom response were 55% and 80%, respectively. The majority of patients (83%) were still on therapy after a median follow-up of 27 months.[89]

Intermediate-2-risk/High-risk MF

The results of COMFORT-I[84,90,91] and COMFORT-II[85,92,93] 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 INT-2-risk or high-risk MF (PMF, post-PV MF, or post-ET MF).

The COMFORT-I trial randomized 259 patients with INT-2-risk or high-risk MF to twice-daily ruxolitinib (n = 155) or placebo (n = 154).[84] The starting dose of ruxolitinib was based on the baseline platelet count (15 mg twice daily for a platelet count of 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 INT-2-risk or high-risk MF.[90,91] 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; P = .025). 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.[91] 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 nonsignificant trend toward longer OS for patients with IPSS INT-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.[91,94]

In the COMFORT-II study, 219 patients with INT-2-risk or high-risk MF were randomized to ruxolitinib (n = 146) or best available therapy (n = 73).[85] 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 < .0001). 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.[85] 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 INT-2-risk or high-risk MF.[92,93] At the time of 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).[93] 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 INT-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 INT-2-risk MF in the control group.[95] 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.

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.[84,85] 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.[84,85] In general, the incidences of nonhematologic toxicities decreased with long-term therapy.[90,93]

Ruxolitinib is associated with a potentially increased risk of opportunistic infections.[96,97] In particular, tuberculosis, progressive multifocal leukoencephalopathy, reactivation of hepatitis B virus, and herpes simplex virus have been reported in patients treated with ruxolitinib.[91,98-102] Patients should be monitored for signs and symptoms of infections. Serious infections should be resolved prior to initiation of ruxolitinib. Ruxolitinib is contraindicated in patients with evidence of active or latent tuberculosis. Viral reactivations should be treated and monitored according to clinical guidelines.

Non-melanoma skin cancers have been reported in patients treated with ruxolitinib; periodic skin examinations are recommended.[103] Lymphoid neoplasms may be diagnosed concurrently with MPN or may develop during the natural history of MF, PV, or ET.[104-107] Although one report indicated that *JAK* inhibitor therapy is associated with an increased risk

of aggressive B-cell lymphomas in patients with MF, additional studies are required to validate these observations.[108]

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.[109] HMR mutations (*ASXL1, EZH2, SRSF2, IDH1, or IDH2)* were identified in 33%, 7%, 4%, 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 a hazard ratio of 0.57.[109]

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 ≥1 mutations in *ASXL1, EZH2, or IDH1/2* had shorter time to treatment discontinuation and OS.[110] 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, a selective *JAK2* inhibitor, has been evaluated as an initial treatment in patients with INT-2-risk/high-risk MF (JAKARTA trial) and as a second-line treatment for patients with ruxolitinib-resistant or ruxolitinib-intolerant INT-1-risk or INT-2-risk/high-risk MF (JAKARTA-2 trial).[111,112]

The phase III JAKARTA trial randomized 289 patients with INT-2-risk or high-risk MF (PMF, post-PV MF, or post-ET MF) to once-daily fedratinib 400 mg (n= 96) or 500 mg (n = 97) or placebo (n = 96) for at least 6 consecutive 4-week cycles.[111] Patients had palpable splenomegaly (≥5 cm below the left costal margin) and platelet count at least 50 × 10^3/μL. Patients with protocol defined progressive disease 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 < .001) in the fedratinib group (36% for 400 mg and 40% for 500 mg) than in the placebo group (1%). The confirmed spleen response rates at 24 weeks were higher for patients randomized to fedratinib 400 mg and 500 mg regardless of baseline platelet count, disease type (PMF, post-ET MF or post-PV MF), risk status and *JAK* mutation status. The symptom response rates at 24 weeks (≥50% reduction in the MF-SAF-TSS from baseline) were 36%, 34% and 7%, respectively for fedratinib 400 mg, fedratinib 500mg and placebo groups. At the time of this analysis, a total of 70 patients (10 patients before the end of 24 weeks and 60 patients after week 24) from the placebo group had crossed over to fedratinib.

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 INT-1-risk or INT-2-risk/high-risk MF (PMF, post-PV MF, or post-ET MF, palpable splenomegaly [≥5 cm below the left costal margin] and a platelet count of >50 x 10^9/L).[112] This study had no standard criteria to define ruxolitinib resistance or intolerance and 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.

Toxicity

Anemia and thrombocytopenia were the most common hematologic toxicities associated with fedratinib.[111,112] In the JAKARTA trial, grade 3 or 4 anemia and thrombocytopenia were reported in 43% and 17% of patients respectively in the fedratinib 400 mg group and the corresponding rates were 60% and 27% in the fedratinib 500 mg group.[111] In the reanalysis of JAKARTA-2 trial, grade 3 or 4 anemia and thrombocytopenia were reported in in 46% and 24% of patients respectively.[112]

Diarrhea, vomiting, and nausea were the most common nonhematologic toxicities.[111,112] The incidence of hyperbilirubinemia and elevations in creatinine, alanine aminotransferase, aspartate aminotransferase, lipase and amylase were more frequent with fedratinib than with placebo.[111] Fedratinib was also associated with a higher rate of infections (42% and 39% respectively for fedratinib 400 mg and 500 mg compared 27% in the placebo group).[111]

In 2013, the FDA placed a clinical hold on the development of fedratinib after 8 patients treated in several fedratinib trials experienced symptoms suggestive of Wernicke's encephalopathy (a neurological disorder that develops in the setting of thiamine deficiency) that resulted in the early termination of the aforementioned clinical trials evaluating fedratinib. Subsequent reports 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.[113,114] The reanalysis of the JAKARTA-2 study reported the efficacy data in 3 different cohorts of patients (intent-to treat population, n =97; ruxolitinib failure cohort, n = 79; and sensitivity cohort, 66 patients treated with 6 cycles of fedratinib or discontinued before cycle 6 for reasons other than study closure) by employing a more stringent criteria for ruxolitinib failure and intolerance.[113] The spleen response rates were 31%, 30% and 36% respectively for these 3 cohorts. The corresponding symptom response rates were 27%, 27% and 32% respectively. In this study, only one case of encephalopathy was reported, which was subsequently determined to be related to hepatic encephalopathy and inconsistent with Wernicke's encephalopathy. In another analysis of 670 patients enrolled in clinical trials evaluating fedratinib in patients with MPN or solid tumors, the overall prevalence of Wernicke's encephalopathy was observed only in 3 to 5 patients (<1% of treated patients).[114]

In August 2017, the FDA removed the clinical hold on the fedratinib development program. In August 2019, the FDA approved fedratinib for the treatment of patients with INT-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 risk of serious and fatal encephalopathy, including Wernicke's encephalopathy. Thiamine (Vitamin B1) level, CBC with platelets and nutritional status should be assessed in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated. Fedratinib should not be started in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If Wernicke's encephalopathy is suspected, discontinue fedratinib should be discontinued immediately and parenteral thiamine should be initiated. Patients should be monitored until the resolution of symptoms resolve or improvement and normalization of thiamine levels.

Allogeneic Hematopoietic Cell Transplant

Allogeneic hematopoietic cell transplant (HCT) is the only potentially curative treatment option resulting in long-term remissions for patients with MF. However, the use of myeloablative conditioning is associated with higher rates of non-relapse mortality (NRM). The estimated OS rates and NRM rates at 3 to 5 years range from 30% to 61% and 24% to

43%, respectively.[115] In a retrospective registry analysis of 289 patients with MF, allogeneic HCT resulted in long-term OS in about a third of patients, but the probability of long-term survival and NRM was dependent on the source of stem cells.[116] 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).

The use of reduced-intensity conditioning (RIC) has lowered the rates of NRM but it is also associated with a higher risk of relapse compared to myeloablative conditioning.[117-124] In a prospective, multicenter study that evaluated the 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%.[118] The estimated 5-year event-free survival 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.[121,122] 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 progression-free survival (PFS) at 5 years were 47% and 27%, respectively.[121] 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.[122]

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.[121] 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).[122]

DIPSS risk score has been shown to predict outcome after transplant.[121,125] In the aforementioned CIBMTR analysis, there was a trend towards lower mortality rates in patients with low-risk/INT-1-risk disease and higher NRM in patients with INT-2-risk/high-risk disease.[121] In another retrospective analysis of 170 patients with MF who received HCT, DIPSS risk score significantly correlated with mortality risk and NRM (hazard ratio for post-transplant mortality was 4.11 for high-risk disease compared to 3.15, 1.97, and 1, respectively, for INT-2-risk, INT-1-risk, and low-risk disease; the corresponding hazard ratios for NRM were 3.41, 3.19, 1.41, and 1, respectively).[125] 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.[121,126,127] However, in one retrospective

analysis, the differences in OS between patients with INT-1-risk and INT-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.[126] In another retrospective analysis that evaluated the impact of allogeneic HCT on survival in patients <65 years of age at the time of diagnosis of PMF (n = 438; 190 patients received allogeneic HCT and 248 patients received conventional therapy), the relative risk of death after allogeneic HCT was 5.6 for patients with DIPSS low-risk disease, 1.6 for INT-1-risk disease, 0.55 for INT-2-risk disease, and 0.37 for high-risk disease.[127]

These findings suggest that outcomes following allogeneic HCT are better for patients with low-risk or INT-1-risk MF.[121,125] However, it is also associated with high transplant-related morbidity and mortality in this group of patients. Allogeneic HCT is associated with a clear benefit in patients with INT-2-risk/high-risk PMF.

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.[128,129] Identification of HMR mutations (*ASXL1, EZH2, SRSF2, TP53, IDH1*, *or IDH2* mutations) may be helpful in decision-making regarding allogeneic HCT in patients with PMF.[27,35,36,129]

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* mutation (*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).[128]

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), in a multivariate analysis, *CALR* mutation was an independent factor for lower NRM, and improved PFS, and OS.[129] *ASXL1* and *IDH2* mutations were independent risk factors for lower PFS, whereas no impact was observed for triple-negative patients.

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 with should be considered for allogeneic HCT earlier in the disease course.[39]

Treatment Recommendations Based on Symptom Assessment and Risk Stratification

The selection of appropriate treatment should be based on the risk score and the presence of symptoms. Enrollment in clinical trial is recommended for all patients with the aim of reducing bone marrow fibrosis, improving cytopenias and symptom burden, restoring transfusion independence, and preventing/delaying progression to AML.

Low-risk or INT-1-risk MF

Asymptomatic patients with low-risk or INT-1-risk MF should be observed. Ruxolitinib[86-88] or interferons (interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b)[82,83] are included as options for symptomatic patients. Hydroxyurea has been shown to be an effective treatment option for the hyperproliferative manifestations of 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/d, subsequently adjusted to the individual efficacy and tolerability) resulted in CI in 40% of patients.[130] Anemia induced by hydroxyurea was manageable with concomitant treatment. The panel has included

hydroxyurea as an option for low-risk MF, if the use of cytoreductive therapy would be symptomatically beneficial in selected patients with high platelet counts.

Allogeneic HCT is included as an option for patients with INT-1-risk MF. Although the outcomes following allogeneic HCT are better for patients with low-risk or INT-1-risk MF, due to the high transplanted-related morbidity and mortality, treatment decisions regarding allogeneic HCT should be individualized for patients with INT-1-risk MF.[121,125,127] Allogeneic HCT should be considered for low-risk or INT-1-risk MF in patients with either refractory, transfusion-dependent anemia; circulating blast cells >2% in peripheral blood; or adverse cytogenetics.[127] Evaluation for allogeneic HCT is recommended for patients with low platelet counts or complex cytogenetics.

INT-2-risk or High-risk MF

Evaluation for allogeneic HCT is recommended for all patients with INT-2-risk and high-risk MF. 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.

Allogeneic HCT is recommended for patients with INT-2-risk or high-risk MF if they are candidates for transplant.[125] Patients may be taken immediately to allogeneic HCT or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to allogeneic HCT.

In patients who are not candidates for transplant, treatment options are based on the platelet count. Ruxolitinib[84,85,90-92] or clinical trial are included as options for patients with a platelet count ≥50K. Based on the recent FDA approval, fedratinib is included as an alternate treatment option with a category 2B recommendation.[111]

Patients with a platelet count <50K experience a greater symptom burden and might benefit from symptomatically guided treatment options.[131] However, at the present time, there are no effective treatment options for this group of patients since the majority of clinical trials evaluating treatment options for MF have excluded this group of patients.

The use of ruxolitinib at a lower dose (5 mg twice daily) has been shown to be effective, resulting in 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).[132] While ruxolitinib could be considered in symptomatic patients with platelet count <50K, it is not FDA approved for this indication. Pacritinib (another *JAK2* inhibitor) has also demonstrated significant activity resulting in ≥35% spleen volume reductions and symptom improvement, even in patients with severe baseline cytopenias.[133] Pacritinib could be an appropriate treatment option for patients with low platelet counts; however, it is not yet FDA approved. Therefore, enrollment in an appropriate clinical trial should be considered for patients with a platelet count <50K.

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.[84,85] Patients enrolled in the COMFORT trials were required to have a baseline platelet count of ≥100 x 10^9/L, and the initial starting dose of ruxolitinib was dependent on the patient's baseline platelet counts.[84,85] Preliminary results of the phase II study suggest that a lower initial dose of ruxolitinib (5 mg twice daily) with escalation to 10 mg BID may be appropriate in patients with baseline platelet counts of 50–100 x 10^9/L.[132]

The guidelines recommend that the initial dosing of ruxolitinib should be based on the patient's baseline platelet counts (as described in the full prescribing information). However, certain clinical situations may support

initiation of ruxolitinib at a lower dose (5 mg twice daily) with subsequent dose modifications based on CBC, which must be performed before initiating ruxolitinib and monitored every 2 to 4 weeks until the dose is stabilized, and then as clinically indicated.[132,134]

See *Special Considerations for the Use of JAK Inhibitors* in the algorithm for dose modifications for the management of hematologic toxicities.

Treatment Response Criteria

In 2006, the IWG-MRT first published the response criteria for MF, and the responses were categorized as CR, PR, CI, progressive disease (PD), SD, and relapse.[135] In 2013, these response criteria were revised by IWG-MRT and European LeukemiaNet (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.[136] These response criteria were developed mainly for use in clinical trials.

In addition to CR, PR, and CI, 3 other response categories (anemia response, spleen response, and symptoms response) have been 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.[136] The revised response criteria recommend that symptoms should be evaluated by the MPN-SAF TSS, and symptom response requires ≥50% reduction in the TSS.[69] 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. 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

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.[136]

The guidelines recommend monitoring response (anemia response, spleen response, and symptom response), signs, and symptoms of disease progression every 3 to 6 months during the course of treatment. Bone marrow aspirate and biopsy should be performed as clinically indicated (if supported by increased symptoms and signs of progression). Additional molecular testing using multi-gene NGS panel to evaluate for high-molecular-risk mutations associated with disease progression should be considered for patients with INT-1-risk or INT-2-risk/high-risk disease.[35,36]

Continuation of ruxolitinib or fedratinib 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.[70] The panel acknowledges that clinical benefit may not reach the threshold of the 2013 IWG-ELN Response Criteria (ie, symptom response requires ≥50% reduction in the MPN-SAF TSS) in patients receiving treatment with ruxolitinib or fedratinib. Continuation of ruxolitinib or fedratinib is recommended based on the discretion of the clinician, since a symptom response of <50% may be clinically meaningful and justify the continued use of ruxolitinib.

Ruxolitinib should be discontinued if there is no response or improvement of symptoms after 6 months. Gradually tapering the dose of ruxolitinib should be considered, when discontinuing or interrupting ruxolitinib for reasons other than thrombocytopenia or neutropenia. See *Special Considerations for the Use of JAK inhibitors* in the guidelines.
Disease-related symptoms may return to pretreatment levels over a period of approximately one week following discontinuation or interruption of ruxolitinib.[137] 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.[138] 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).[138] 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.

Fedratinib is recommended as a treatment option for INT-2-risk or high-risk MF resistant to ruxolitinib in patients with platelet count ≥50K or for those with intolerance to ruxolitinib.[112,113] Tapering and discontinuation ruxolitinib according to the prescribing information is recommended prior to the initiation of fedratinib.

JAK2 V617F *Allele Burden*

Long-term ruxolitinib therapy is associated with reductions in *JAK2* V617F allele burden.[93,139] In the COMFORT-I study, >50% reductions 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 6 patients had *JAK2* V617F allele burden values below quantifiable limit, meeting the criteria for complete molecular response (CMR).[139] 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.[140,141]

However, at the present time, the utility of *JAK2* V617F allele burden reduction as a predictor of treatment efficacy is not well established. In the 2013 IWG-MRT and ELN response criteria, cytogenetic and molecular responses are not required for CR assignment.[136] Therefore, measurement of the *JAK2* V617F allele burden is not currently recommended for use in routine clinical practice to guide treatment decisions.

Management of MF-Associated Anemia

Anemia is considered a negative prognostic risk factor for survival in patients with MF.[71] Symptomatic anemia is observed in more than 50% of patients at the time of diagnosis.[142] It is essential to rule out and treat (if necessary) the most common causes of anemia (eg, bleeding; hemolysis;

iron deficiency; vitamin B12; and folic acid) before considering other treatment options.

Leukoreduced RBC transfusion support is recommended for symptomatic anemia. EPO-stimulating agents (ESAs), danazol, and immunomodulatory agents (lenalidomide, thalidomide, and pomalidomide) have also been evaluated for the management of MF-associated anemia.

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.[143-145] 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 are less frequent in patients with transfusion dependency (19% compared to 44% in patients without transfusion requirements).[146] Prostate cancer screening and monitoring of liver function tests are recommended for patients receiving danazol for the management of MF-associated anemia.

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.[147-153] Lower dose of thalidomide (50 mg/d) 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).[154] 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 hematologic toxicity.[155-158] Lenalidomide is more likely to induce better response rates in patients with isolated 5q deletion.[159]

In an analysis that reassessed the efficacy of thalidomide and lenalidomide in 125 patients with MF treated in 3 consecutive phase 2 trials, the combination of lenalidomide and prednisone was more effective and safer than single-agent thalidomide or lenalidomide.[160] 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.[161,162] 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.[161] 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.[162]

Enrollment in a clinical trial should be considered for all patients with MF-associated anemia. Additional treatment options for the management of MF-associated anemia are based on the serum EPO levels as described below.

Serum EPO <500 mU/mL

EPO or darbepoetin alfa are recommended for the treatment of anemia in patients with serum EPO levels <500 mU/mL.

In the COMFORT-II study, anemia was managed with packed RBC transfusions and only a small number of patients (13 out of 146 patients) received both ruxolitinib and an ESA. The concomitant use of an ESA with ruxolitinib was well tolerated and did not affect the efficacy of ruxolitinib.[163] Additional studies are warranted to evaluate the efficacy of ESAs for the management of anemia in patients receiving ruxolitinib. ESAs are not effective for the management of transfusion-dependent anemia.[164]Continuation of treatment with ESA is recommended in patients achieving anemia response; those with no response or loss of response should be managed with androgens or immunomodulatory agents as described below for patients with serum EPO ≥500 mU/mL.

Serum EPO ≥500 mU/mL

Immunomodulatory agents (lenalidomide or thalidomide) with or without prednisone or danazol are recommended for the treatment of anemia in patients with serum EPO levels >500 mU/mL. Continuation of prior treatment is recommended in patients achieving anemia response, and those with no response or loss of response should be managed with another trial of treatment (danazol or immunomodulating agent) that has not been used before.

Disease Progression to Advanced Phase or Transformation to Acute Myeloid Leukemia

MF in accelerated phase (MF-AP) is characterized by the presence of ≥10% (10%–19%) blasts in the peripheral blood or bone marrow, platelets <50 x 10^9/L, and chromosome 17 aberrations.[165] MF in blast phase (MF-BP) is defined by the presence of ≥20% myeloid blasts in either the bone marrow or peripheral blood.[53]

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.[165,166] Among patients who present with chronic phase MF, development of accelerated phase features during follow-up was associated with short median survival times.[165]

Treatment with hydroxyurea has been associated with increased risk of transformation to AML in some studies.[167,168] These findings, however, were not confirmed in subsequent reports.[169-171] In a large cohort analysis (n = 11,039; 162 patients with transformation to AML/myelodysplastic syndrome [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 —but not treatment with hydroxyurea alone—was significantly associated with an increased risk of transformation to AML.[169] 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.[171] Hydroxyurea, however, was not an independent risk factor for transformation to AML.

Mutations in several genes (*ASXL1, TET2, TP53, SRSF2*, *and IDH1 or IDH2)* and other chromosomal abnormalities (eg, aberrations in chromosomes 1q and 9p) have been associated with transformation to AML.[27,35,37,172] Molecular testing for AML-associated mutations is recommended as part of initial workup of patients with disease progression to advanced-phase MF or transformation to AML.

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.[173] 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 (azacytidine or decitabine) have been evaluated in few small studies as a treatment option for MPN that has transformed to AML.[174-176] 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.[174] 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 azacytidine 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).[175] 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.[176] The median OS was significantly higher in patients with disease that responded to decitabine (12 months vs. 5 months, respectively, for patients with MPN-AP; 11 months vs. 4 months, respectively, for patients with MPN-BP/AML).

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.[177-180] In one retrospective analysis of 75 patients with MPN-BP/AML, 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).[179] 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; $P = .03$).[179] In another retrospective analysis of 46 patients who received allogeneic HCT for MF-BP/AML, 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; $P = .02$).[180] 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 the availability of caregiver. Patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.

Disease control/reduction in blast counts with hypomethylating agents (azacytidine or decitabine) or intensive AML-type induction chemotherapy followed by allogeneic HCT is recommended for patients who are candidates for transplant.[174,179,180] Enrollment in a clinical trial or treatment with hypomethylating agents (azacytidine or decitabine) or low-intensity AML-type induction chemotherapy is recommended for those who are not candidates for transplant. AML-type induction chemotherapy regimens are generally used for the management of disease progression to advanced phase or transformation to AML. However, these regimens typically result in poor responses.

The results of recent retrospective analyses suggest that prior exposure to ruxolitinib does not adversely affect outcomes after allogeneic HCT and that ruxolitinib should be continued near to the start of conditioning therapy.[181,182] The guidelines recommend continuation of ruxolitinib or fedratinib near to the start of conditioning therapy for all patients for the improvement of splenomegaly and other disease-related symptoms.

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 symptom status, counseling for the identification, and assessment and management of cardiovascular risk factors (eg, smoking, diet, exercise, thrombotic and hemorrhagic risk factors).

Transfusion support should include platelet transfusions for thrombocytopenic bleeding or a platelet count <10,000 m^3 and RBC transfusions for symptomatic anemia.[183] 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 low-risk or INT-1-risk disease.[183] However, the role of iron chelation remains unclear. Cytoreductive therapy (eg, hydroxyurea) is recommended for thrombocytosis or leukocytosis.

Serious bacterial, fungal, and viral infections have been reported in patients receiving ruxolitinib. 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. In splenectomized patients, antibiotic prophylaxis should be given per Infectious Diseases Society of America (IDSA) Guidelines. Growth factor support should be considered for recurrent infections with neutropenia. Cytoreductive therapy with hydroxyurea could be considered for the management of hyperproliferative manifestations of PMF (thrombocytosis or leukocytosis).[130]

Prophylaxis for tumor lysis syndrome (ie, hydration and/or diuresis, management of hyperuricemia with allopurinol or rasburicase) should be considered for patients undergoing induction chemotherapy for advanced-stage MF or leukemic transformation. Rasburicase should be considered as initial treatment in patients with rapidly increasing blast counts, high uric acid, and evidence of impaired renal function.

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

Retrospective studies have shown that leukocytosis at diagnosis is associated with higher risk of thrombosis and major hemorrhage in patients with PV and ET.[184-188] 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,[189,190] and other studies have reported that leukocytosis at diagnosis is not associated with the risk of subsequent thrombosis.[185] 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.[188] 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.[186,187] 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.[191] 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 2 different risk groups: low-risk (age <60 years and no prior history of thrombosis) and high-risk (age >60 years and/or prior history of thrombosis).

In another retrospective study of 1545 patients with PV, age ≥67 years, leukocyte count ≥15 x 10^9/L, and venous thrombosis were identified as independent risk factors for LFS.[192] A prognostic model incorporating leukocytosis at the time of diagnosis in addition to age has been developed to stratify patients into 3 risk groups with different survival outcomes. However, this model has not been validated in prospective clinical trials.

Essential Thrombocythemia

In an analysis of 867 patients with ET, age ≥60 years or older, leukocyte count ≥11 x 10^9/L, and prior thrombosis were significantly associated with inferior survival.[193] Based on these findings, IPSET was developed to stratify patients at the time of diagnosis into 3 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.[194] 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 3 groups with significantly different thrombosis-free survival: 87% after 15-year follow-up for low-risk patients and 50% after 7-year follow-up for high-risk patients.[194] 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 low-risk patients, 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%).[195] 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 were 2% and 3%, respectively. These findings led to the development of revised IPSET-thrombosis that stratifies patients into 4 different risk groups: very low risk (age ≤60 years, no prior history of thrombosis, and no *JAK2* mutation); low risk (age ≤60 years, no prior history of thrombosis, and *JAK2* mutation); intermediate risk (age >60 years, no prior history of thrombosis, and no *JAK2* mutation); and high risk (prior history of thrombosis and/or age >60 years with *JAK2* mutation). The revised IPSET-thrombosis has also been validated in an independent cohort of 585 patients.[195,196]

CALR mutation status, however, did not have a significant impact on the IPSET-thrombosis prognostic score for predicting the risk of thrombosis.[46] 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.

Treatment Options

Antiplatelet Therapy

The safety and efficacy of low-dose aspirin for the prevention of thrombotic complications in PV was established in a multicenter trial in patients with no contraindication to aspirin therapy and no history of a thrombotic event (ECLAP study; 518 patients).[197] 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 <45% in patients receiving treatment was established in the CYTO-PV study.[198] 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%.[198] 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.[199,200] 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.[199] 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.[199]

Cytoreductive Therapy

Hydroxyurea,[168,198,201] interferon alfa,[202-204] and peginterferon alfa[205-208] 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.[201] 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 transformations (6% compared to 2% for phlebotomy).[209] However, an analysis from the ECLAP study identified older age and the use of other alkylating agents (eg, P32, busulphan, pipobroman) but not hydroxyurea alone as an independent risk factor for leukemic transformation.[210] In the randomized trial that compared hydroxyurea and pipobroman as first-line therapy in 285 patients with PV <65 years, the cumulative incidence of leukemic transformation was significantly higher with pipobroman than with hydroxyurea.[168] At a median follow-up of 15 years the incidences of leukemic transformation were 17% and 34%, respectively, for hydroxyurea and pipobroman.

In a randomized, prospective, observational study that included 136 patients with *JAK2*-mutated PV, interferon alfa-2b resulted in greater molecular response rate (55% and 19%, respectively; $P < .01$) and 5-year PFS rate (66% and 47%, respectively; $P < .01$) than hydroxyurea.[204] 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.[206] At a median follow-up of 31 months, 36 patients with a response remained phlebotomy free. A more recent 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.[208] 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 failure to achieve CMR.[207] 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.

Hydroxyurea,[211-213] interferon alfa,[202,204,214,215] peginterferon alfa,[205,207,208,216] and possibly anagrelide[212,213] 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) or no myelosuppressive therapy (n = 58), the incidences of thrombotic episodes were significantly lower in patients treated with hydroxyurea (3.6% compared to 24%; $P = .003$).[211] In another randomized study of 809 patients with high-risk ET, hydroxyurea plus low-dose aspirin was superior to anagrelide plus low-dose aspirin. 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 ($P = .006$).[212] 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 more recent 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.[213] In this study, 259 patients were randomized to either hydroxyurea (n = 122) or anagrelide (n = 137). 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.

Interferon alfa-2b has been shown to be effective for patients with *JAK2*-mutated and *CALR*-mutated ET.[204,215] In a randomized, prospective, observational study that included 123 patients with ET, the 5-year PFS rate was 76% for those with *JAK2*-mutated ET compared to 48% for those without *JAK2* mutation ($P < .05$).[204] In another study of 31 patients, interferon alfa induced high rates of hematologic and molecular responses in *CALR*-mutated ET. However, the presence of additional mutations (*TET2, ASXL1, IDH2*, and *TP53*) was associated with poorer molecular response.[215] 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.[208] The presence of *TET2, ASXL1, EZH2, DNMT3A,* and *IDH1/2* mutations was associated with failure to achieve CMR.[207] 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.

Ongoing randomized clinical trials are evaluating hydroxyurea versus peginterferon alfa-2a or ropeginterferon alfa-2b as initial treatment for high-risk PV and ET.

Ruxolitinib

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.[217-219]

In this study, 222 phlebotomy-dependent patients with splenomegaly and an inadequate response to or intolerance of hydroxyurea were randomized to receive ruxolitinib (110 patients) or best available therapy (112 patients). 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%.[218] 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).[218]

Ruxolitinib has also been shown to be effective for the treatment of PV with an inadequate response to hydroxyurea in patients without splenomegaly.[220] 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.[221]

Treatment Recommendations Based on Risk Stratification

Treatment options should be individualized based on age and history of thrombosis for patients with PV,[191] and the revised IPSET-thrombosis is preferred for the risk stratification of patients with ET.[195,196]

Polycythemia Vera

Low-risk (age <60 years and no prior history of thrombosis)
Aspirin (81–100 mg/d) and phlebotomy (to maintain hematocrit <45%) are recommended for all patients with low-risk PV.[197,198] Cytoreductive therapy is not recommended as initial treatment. In the CYTO-PV study, the hematocrit target was the same for both men and women. No thrombotic event was observed in the 66 women with hematocrit of <45% compared to 9 events reported in the 72 women with a hematocrit target of 45% to 50%.[198] However, normal hematocrit levels vary in men (42%–54%) and women (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 for patients with high-risk PV. Cytoreductive therapy (hydroxyurea) with aspirin (81–100 mg/d) for vascular symptoms and phlebotomy (to maintain hematocrit <45%) is recommended as initial treatment. Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b could be considered for younger patients, in pregnant patients requiring cytoreductive therapy, or in those patients requiring cytoreductive therapy that defer hydroxyurea.

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) 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 recent systematic review also suggest that the risks and benefit of antiplatelet therapy in patients with ET remains highly uncertain.[222] Observation is appropriate for patients with very-low-risk or low-risk ET. Aspirin (81–100 mg/d) could be considered to reduce the risk of thrombotic complications for patients with very-low-risk, low-risk, or intermediate-risk ET. Aspirin should be used with caution in patients with acquired VWD who have an increased risk of bleeding.

A report from a more recent retrospective analysis suggests that the use of low-dose aspirin may not be beneficial in patients with low-risk *CALR*-mutated ET.[200] In an analysis that evaluated the benefit-to-risk ratio of low-dose aspirin in 433 patients with low-risk ET (271 patients with *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.[200] These findings have to be confirmed in prospective clinical trials. Therefore, at present, the panel feels that there is not enough evidence to recommend withholding aspirin for patients with *CALR*-mutated ET.

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.[223,224] The safety and efficacy of different aspirin dosing regimens in patients with ET is being evaluated in a phase II randomized trial.[225] At the present time, the risk and benefits of higher dose aspirin must be weighed based on the

presence of vasomotor symptoms and the risk of bleeding. It may be appropriate in carefully selected patients as clinically indicated.

High-risk (History of thrombosis at any age or >60 years with JAK2 mutation)
Cytoreductive therapy (hydroxyurea or anagrelide) with aspirin (81–100 mg/d) is recommended as initial treatment. Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b could be considered for younger patients, in pregnant patients requiring cytoreductive therapy, or in those patients requiring cytoreductive therapy that 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.[226] 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 4 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.[227] 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.[228-230] These findings suggest that monitoring *JAK2* V617F allele burden could be useful to identify patients at higher risk of myelofibrotic transformation. 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 *JAK2* mutation, a remission of one mutated clone is not always accompanied by remission of other mutated clones.[226] Therefore, measurement of the *JAK2* V617F allele burden is not currently recommended for use in routine clinical practice to guide treatment decisions.

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 or bleeding, management of cardiovascular risk factors, and monitoring of acquired VWD 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 symptom status using MPN-SAF TSS, signs/symptoms of disease progression, and evaluation for potential indications for cytoreductive therapy every 3 to 6 months or more frequently if clinically indicated. Bone marrow aspirate and biopsy should be performed as clinically indicated (if supported by increased symptoms and signs of progression).

The development of new thrombosis or disease-related major bleeding, frequent or persistent need for phlebotomy, splenomegaly, thrombocytosis, leukocytosis, or disease-related symptoms are considered as potential indications for cytoreductive therapy. In one recent 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; $P < .0001$).[231] However, these findings could not be confirmed by other investigators.[232,233] 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.[234,235] Patients with high-risk PV or ET treated with cytoreductive therapy as initial treatment should also be monitored for intolerance or resistance to hydroxyurea.[236]

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.[234,237-239] 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 done in clinical practice, it is not associated with long-term clinical benefit and there is 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 asymptomatic patients (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 symptomatic patients with potential indications for cytoreductive therapy.

Ruxolitinib is FDA approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea. Switching to ruxolitinib (for patients with PV) or alternate cytoreductive therapy (not used before) is recommended for patients with intolerance or with disease that is resistant to hydroxyurea or interferon. Busulfan has also been effective in the treatment of PV and ET that is refractory to hydroxyurea resulting in a CHR rate of 83% and a PMR rate of 33%.[240] However, it is also associated with a significant rate of transformation to AML, and the sequential use of busulphan and hydroxyurea has also been reported to significantly increase the risk of second malignancies.[210,241] Therefore, the panel does not recommend the use of busulfan as a treatment option.

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 anticoagulant, warfarin) is recommended for patients with active thrombosis.[242-244] 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.[242] 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.[243] 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 normalize platelet counts. Coagulation tests to evaluate for acquired VWD (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).[245]

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.[246] The presence of *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.[247-250] The use of aspirin has been reported to be effective in reducing pregnancy complications, especially in patients with *JAK2*-mutated ET.[251,252] 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. In another study of 63 pregnancies among 36 women 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).[252] The results of a recent 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.[253] The majority of women (88%) received aspirin and 38% of women 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. Aggressive intervention for the

control of hematocrit, the use of aspirin, and LMWH were associated with significantly better pregnancy outcome in patients with PV.[254]

Evaluation by a high-risk obstetrician should be considered prior to conception. In low-risk pregnancy (no prior ET-related complications, absence of hereditary thrombophilic factors, age <35 years, and platelet count <1000 x 10^9/L), low-dose aspirin (50–100 mg/d) is recommended throughout pregnancy and for 6 weeks postpartum. Aspirin could be stopped and substituted by LMWH about 2 weeks before labor is expected. In high-risk pregnancy (previous microcirculatory disturbances, presence of 2 or more hereditary thrombophilic factors, severe complications in a previous pregnancy, or age >35 years and platelet count >1000 x 10^9/L), the use of prophylactic LMWH (subcutaneously) with low-dose aspirin should be considered throughout pregnancy and for 6 weeks postpartum.

Low-dose aspirin should be stopped 1 to 2 weeks prior to delivery and LMWH should be stopped 12 hours to 24 hours before labor is expected.[246] In patients taking LMWH, consultation with a high-risk obstetrician and obstetric anesthesiologist is recommended to determine the optimal timing of discontinuation in preparation for an epidural prior to delivery. In patients without prior bleeding or thrombotic complications, the use of LMWH instead of low-dose aspirin should be considered in the last 2 weeks of pregnancy and continued until 6 weeks postpartum. Interferon alfa-2b, peginterferon alfa-2a, or peginterferon alfa-2b should be considered, if cytoreductive therapy is necessary.[248,255,256] Hydroxyurea is excreted in breastmilk and should be avoided in women who are breast-feeding. Patients on hydroxyurea prior to pregnancy should be switched to interferons.

Summary

MPN are characterized by a significant symptom burden and a propensity for disease transformation to blast phase and then AML. 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 to rule out disease progression should be an integral part of management of patients with MPN.

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