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Myeloproliferative Neoplasms, Version 2.2017

Clinical Practice Guidelines in Oncology

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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]

Abstract

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 (MPNs). The diagnosis and the management of patients with MPNs have evolved since the identification of mutations that activate the JAK pathway (*JAK2, CALR*, and *MPL* mutations) and the development of targeted therapies has resulted in significant improvements in disease-related symptoms and quality of life. This manuscript discusses the recommendations outlined in the NCCN Guidelines for the diagnostic workup of MPN (MF, PV, and ET), risk stratification, treatment, and supportive care strategies for the management of MF.

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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 noted.

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

Please Note

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Disclosures for the NCCN Myeloproliferative Neoplasms Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Myeloproliferative Neoplasms Panel members can be found on page 1611. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

MPNs are characterized by a complicated symptom profile and a risk of transformation to acute myeloid leukemia (AML), which is associated with a poor response to therapy and short survival.[2–4] 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.[5] A SEER-Medicare database analysis showed that patients with MPN have substantially inferior survival compared with matched controls, and survival for patients with MF is worse than that of patients with ET or PV and significantly worse than matched controls.[6]

The diagnosis and management of patients with MPN has evolved since the identification of mutations that activate the JAK pathway (*JAK2*, *CALR*, and *MPL* mutations) and since the development of targeted therapies, which have resulted in significant improvements in disease-related symptoms and quality of life.[7,8] However, certain aspects of clinical management regarding diagnosis, assessment of symptom burden, and selection of appropriate symptom-directed therapies continue to present challenges for clinicians.[9]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for MPNs were developed as a result of meetings convened by a multidisciplinary panel of MPN experts, with the goal to provide recommendations for the management of MPNs in adults. The first version of the NCCN Guidelines focuses on the recommendations for the diagnostic workup of MPNs (MF, PV, and ET), risk

Text cont. on page 1594.

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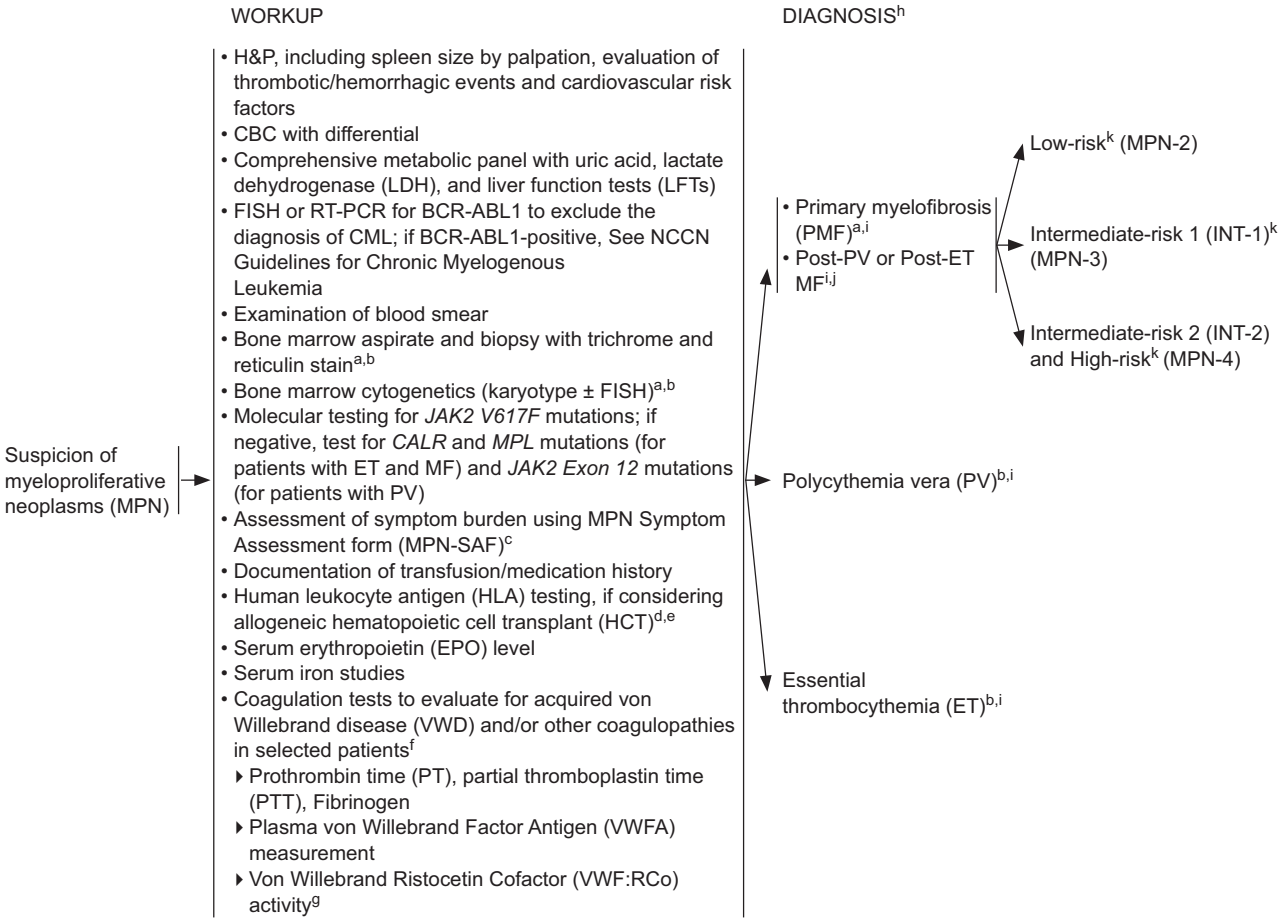

[a]See 2016 WHO Diagnostic Criteria for Primary Myelofibrosis (PMF). See (MPN-A).

[b]See 2016 WHO Diagnostic Criteria for PV and ET. See (MPN-B).

[c]Assessment of symptoms (in provider's office) at baseline using MPN Symptom Assessment form (MPN-SAF-20 items) is recommended for all patients. See Assessment of Symptom Burden (MPN-C 1 of 3).

[d]Prognostic models incorporating other mutations have been proposed to identify patients who may be at risk of leukemic transformation. However, the role of next-generation sequencing (NGS) to identify high-risk mutations and the use of the Molecular International Prognostic Scoring System (MIPSS) is less well-established.

[e]Evaluation for allogeneic HCT is recommended for all patients with intermediate-2-risk (INT-2) and high-risk disease and for patients with intermediate-1-risk (INT-1) disease with low platelet counts and complex cytogenetics. Identification of "higher-risk" mutations may be helpful in the decision-making regarding allogeneic HCT. See Prognostic Significance of Mutations in MPN (MPN-D).

[f]Patients undergoing high-risk surgical procedures and those with elevated platelet count and/or splenomegaly or unexplained bleeding.

[g]An expanded panel including von Willebrand factor (VWF) antigen, Factor VIII activity, and VWF multimers may be useful under certain circumstances.

[h]The diagnosis of MPN is based on the 2016 WHO Criteria and requires a combination of clinical, laboratory, cytogenetics, and molecular testings.

[i]Referral to specialized centers with expertise in the managment of MPN is strongly recommended for all patients diagnosed with MF, PV, or ET. These guidelines pertain to the treatment of myelofibrosis. Guidelines are forthcoming for PV and ET.

[j]Diagnostic criteria for Post-ET or Post-PV MF. See (MPN-E).

[k]Dynamic International Prognostic Scoring System (DIPSS)-Plus is preferred for the risk stratification of myelofibrosis; however, IPSS should be used at diagnosis. DIPSS can be used for risk stratification, if karyotyping is not available. See Risk Stratification for Patients with Myelofibrosis (MPN-F).

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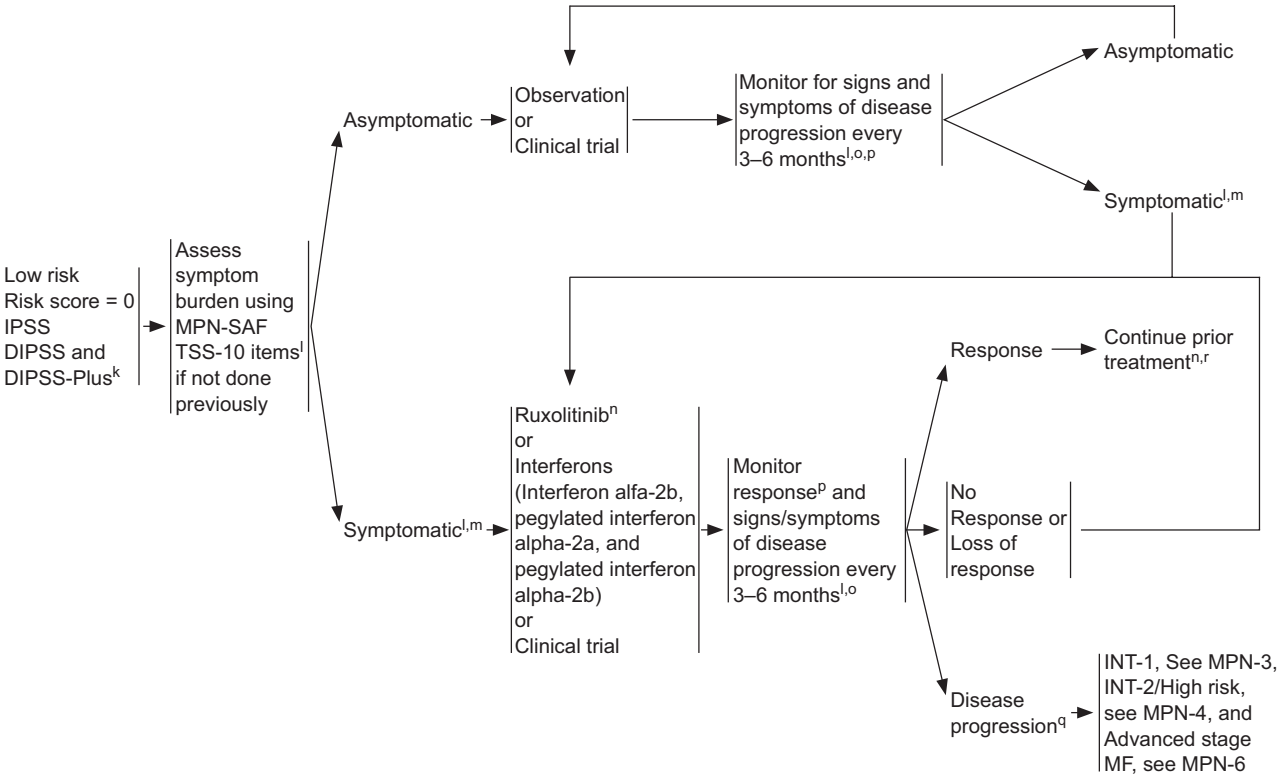
TREATMENT FOR LOW-RISK MYELOFIBROSIS



[k]Dynamic International Prognostic Scoring System (DIPSS)-Plus is preferred for the risk stratification of myelofibrosis; however, IPSS should be used at diagnosis. DIPSS can be used for risk stratification, if karyotyping is not available. See Risk Stratification for Patients with Myelofibrosis (MPN-F).

[l]See Assessment of Symptom Burden (MPN-C 3 of 3).

[m]See Supportive Care (MPN-G).

[n]See Special Considerations for the Use of Ruxolitinib (MPN-H).

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

[p]See 2013 IWG-MRT and ELN Response Criteria for MF (MPN-I).

[q]Disease progression to intermediate-risk 1 (INT-1) or intermediate-risk 2 (INT-2)/high-risk should be managed as outlined on MPN-3 and MPN-4. See MPN-6 for disease progression to accelerated or blast phase MF or AML.

[r]Clinical benefit may not reach the threshold of the 2013 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 (MPN-I).

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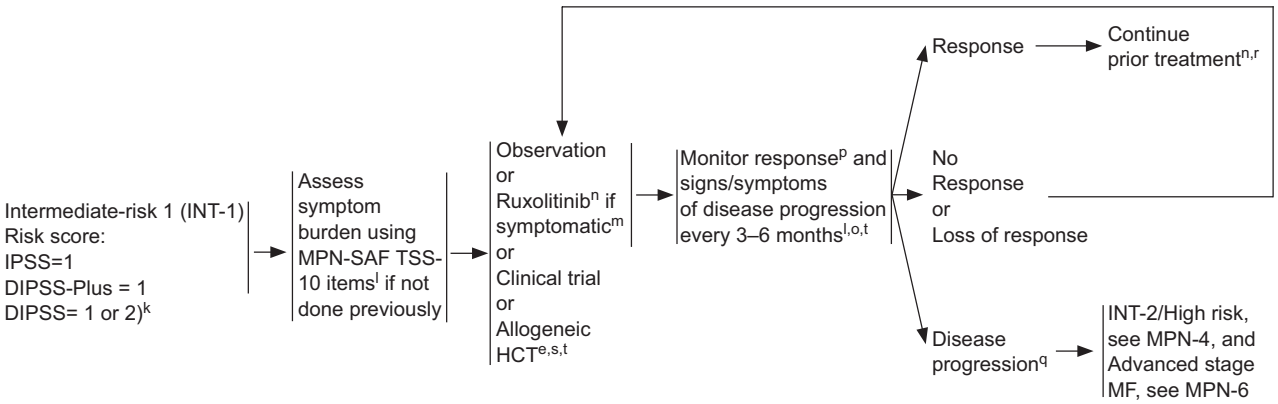
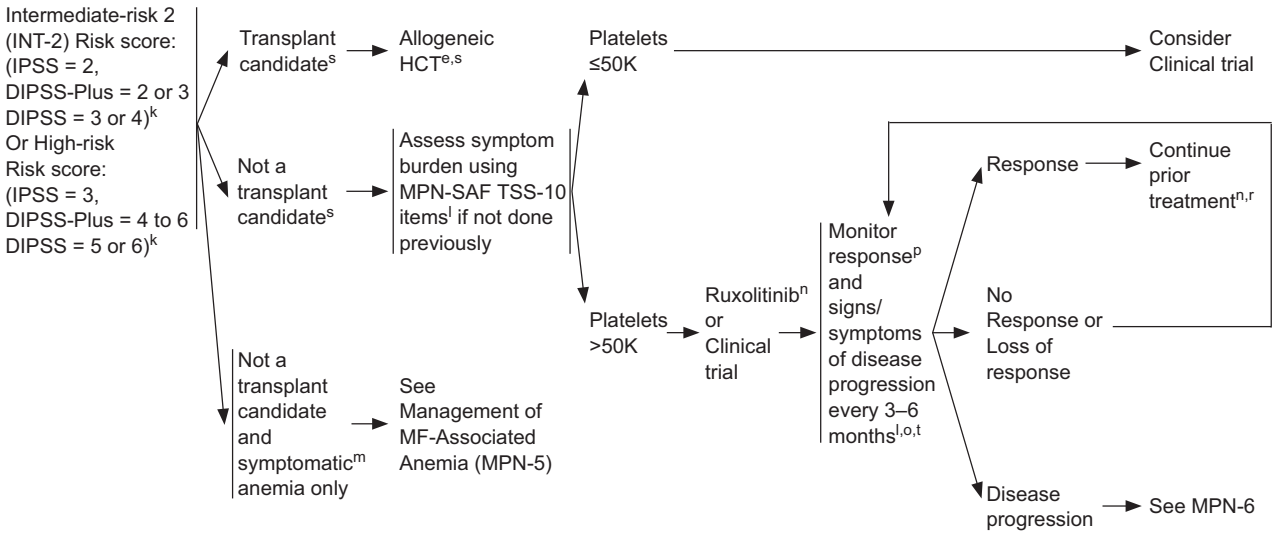
TREATMENT FOR INTERMEDIATE-RISK 1 (INT-1) MYELOFIBROSIS



TREATMENT FOR INTERMEDIATE-RISK 2 (INT-2) OR HIGH-RISK MYELOFIBROSIS



[e]Evaluation for allogeneic HCT is recommended for all patients with intermediate-2 risk (INT-2) and high-risk disease and for patients with intermediate-1 (INT-1) disease with low platelet counts and complex cytogenetics. Identification of "higher-risk" mutations may be helpful in the decision-making regarding allogeneic HCT. See Prognostic Significance of Mutations in MPN (MPN-D).

[k]Dynamic international prognostic scoring system (DIPSS)-Plus is preferred for the risk stratification of myelofibrosis; however, IPSS should be used at diagnosis. DIPSS can be used for risk stratification, if karyotyping is not available. See Risk Stratification for Patients with Myelofibrosis (MPN-F).

[l]See Assessment of Symptom Burden (MPN-C 3 of 3).

[m]See Supportive Care (MPN-G).

[n]See Special Considerations for the Use of Ruxolitinib (MPN-H).

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

[p]See 2013 IWG-MRT and ELN Response Criteria for MF (MPN-I).

[q]Disease progression to intermediate-risk 2 (INT-2)/high-risk should be managed as outlined on MPN-3 and MPN-4. See MPN-6 for disease progression to accelerated or blast phase MF or AML.

[r]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 (MPN-I).

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

[t]Additional molecular marker monitoring is recommended for higher-risk patients including next-generation DNA sequencing (NGS). See Prognostic Significance of Mutations in MPN (MPN-D).

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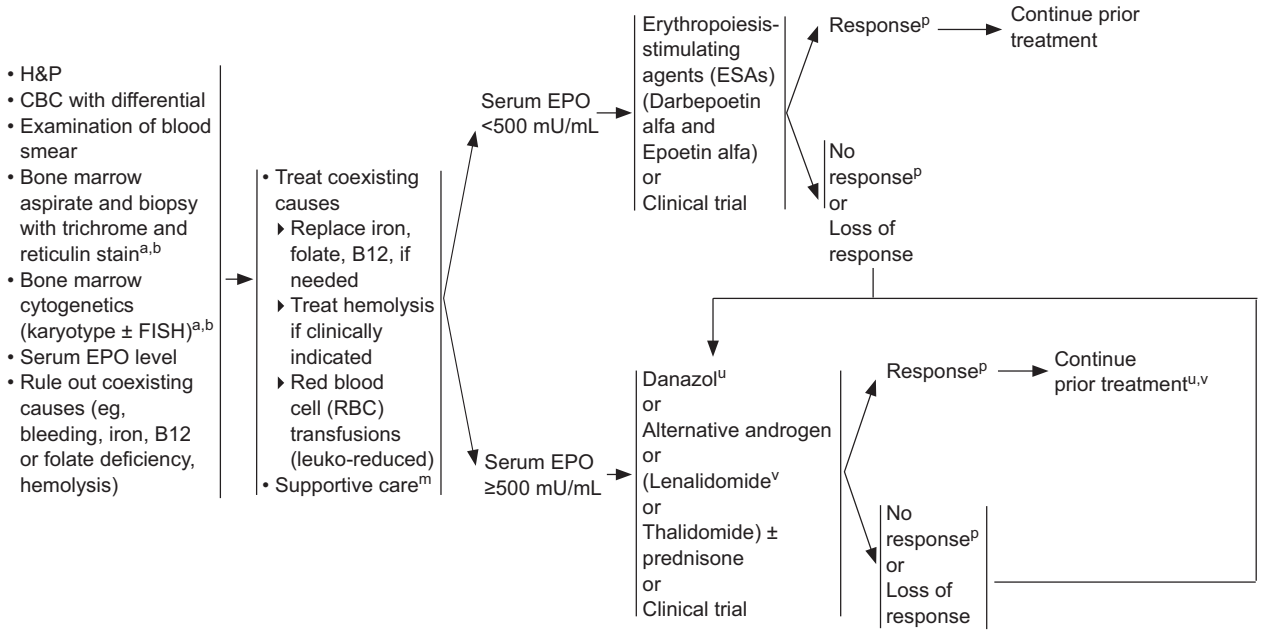
MANAGEMENT OF MF-ASSOCIATED ANEMIA



[a]See 2016 WHO Diagnostic Criteria for Primary Myelofibrosis (PMF). See (MPN-A).

[b]See 2016 WHO Diagnostic Criteria for PV and ET. See (MPN-B).

[m]See Supportive Care (MPN-G).

[p]See 2013 IWG-MRT and ELN Response Criteria for MF (MPN-I).

[u]Prostate cancer screeing for men and monitoring of liver function tests are recommended.

[v]Presence of del(5q) is associated with better response rates with lenalidomide.

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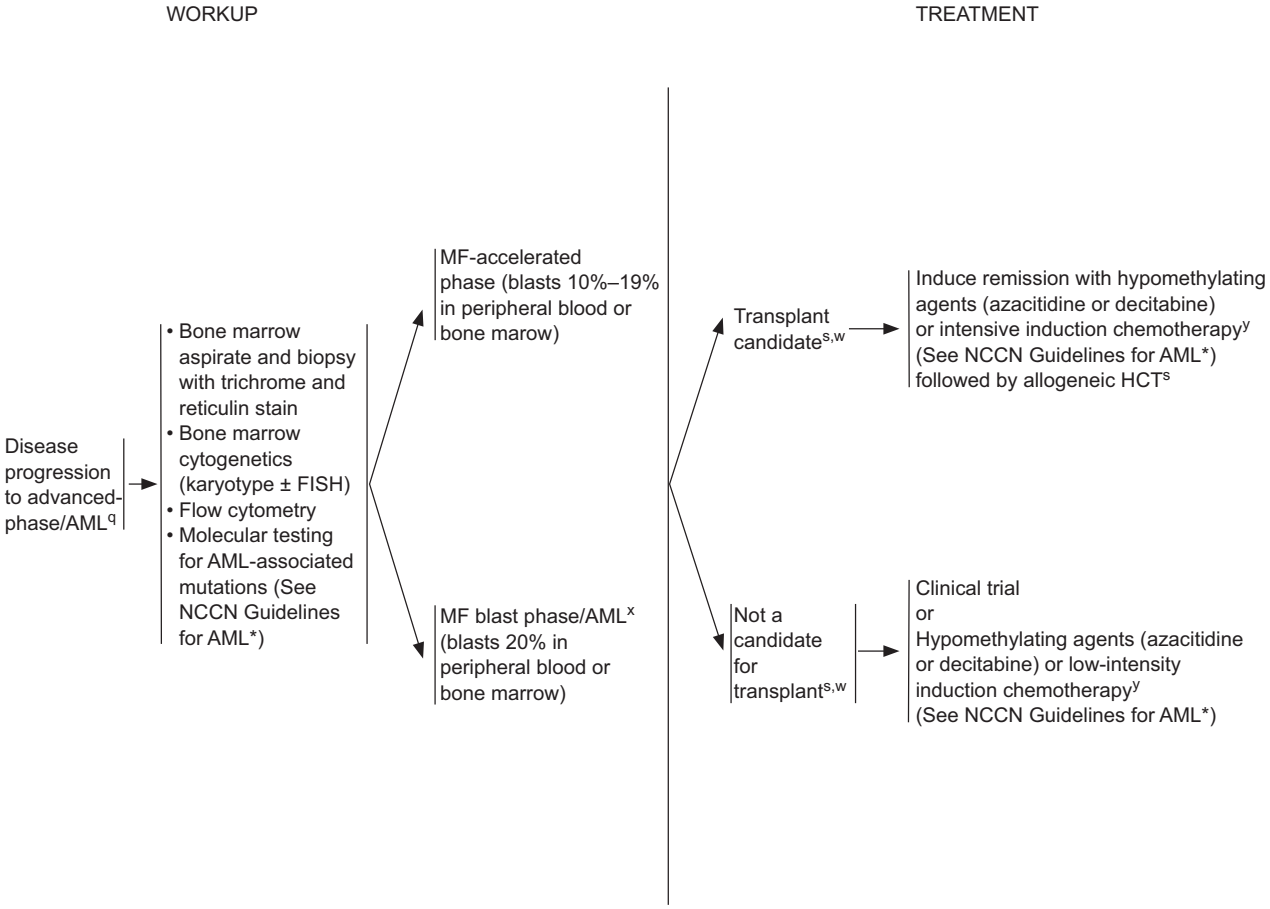

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[q]Disease progression to intermediate-risk 1 (INT-1) or intermediate-risk 2 (INT-2)/high-risk should be managed as outlined on MPN-3 and MPN-4. See MPN-6 for disease progression to accelerated or blast phase MF or AML.

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

[w]Ruxolitinib may be continued for the improvement of splenomegaly and other disease-related symptoms.

[x]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)].

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

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2016 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]Arber D, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405.

[2]See 2016 WHO 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.

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2016 WHO DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS[1]

2016 WHO GRADING OF MYELOFIBROSIS

WHO 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*

[1]Arber D, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405.

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

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2016 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 *BCR-ABL1*+ 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]Arber D, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405.

[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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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 (MPN-SAF) is recommended for the assessment of symptom burden at baseline (See MPN-C, 2 of 3).
- The 2013 IWG-MRT and ELN Response Criteria for MF recommend the use of MPN-SAF Total Symptom Score (MPN-SAF TSS) for monitoring symptom status during the course of treatment (See MPN-C 3 of 3).
- 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 idividual 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.

MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM (MPN-SAF)[1]
(Recommended for assessment of symptom burden at baseline)

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 pain	(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 headaches	(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)
Dizziness/Vertigo/Lightheadedness	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Difficulty sleeping	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Depression or sad mood	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with sexual desire or function	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Cough	(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)
What is your overall quality of life?	(As good as it can be) 0 1 2 3 4 5 6 7 8 9 10 (As bad as it can be)

[1]Scherber R, Dueck AC, Johansson P, et al. The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF): international prospective validation and reliability trial in 402 patients. Blood 2011;118:401-408.

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MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM
TOTAL SYMPTOM SCORE (MPN-SAF TSS-10 ITEMS)[2]

(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)
Numbness/Tingling (in my hands and feet)	(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)

[2]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.

MPN-C
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PROGNOSTIC SIGNIFICANCE OF MUTATIONS IN MPN

Mutated Gene	Primary Myelofibrosis (PMF)
JAK2V617F	Intermediate prognosis and higher risk of thrombosis compared to patient with *CALR* mutation[1]
MPLW515L/K	Intermediate prognosis and higher risk of thrombosis compared to patient 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 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 overall survival compared to patients with *CALR*-mutated PMF[2]
ASXL1	Independently associated with inferior overall survival* and leukemia-free survival[9]
EZH2	Independently associated with inferior overall survival[9]
IDH1/2	Independently associated with inferior leukemia-free survival[9]
SRSF2	Independently associated with inferior overall survival 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)**[10] Intermediate survival (median 5.8 years) for *CALR*(+)*ASXL1*(+) or *CALR*(-)*ASXL1*(-) patients[10]
TP53	Associated with leukemic transformation[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.

[7]Tefferi A, Lasho TL, Finke CM, et al. Type 1 vs type 2 calreticulin mutations in primary myelofibrosis: differences in phenotype and prognostic impact. Leukemia 2014;28:1568-1570.

[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]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.

[11]Rampal et al. Genomic and functional analysis of leukemic transformation of myeloproliferative neoplasms. Proc Natl Acad Sci U S A 2014;111:E5401-5410.

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

**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.

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

IWG-MRT DIAGNOSTIC CRITERIA FOR POST ESSENTIAL (ET) AND POST-POLYCYTHEMIA VERA (PV) 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 a ≥2 mg mL^2 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, Kvasnicka HM, Barbui T, Hanson CA 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, Franco V, van der Walt J, Orazi A. 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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RISK STRATIFICATION FOR PATIENTS WITH MYELOFIBROSIS

INTERNATIONAL PROGNOSTIC SCORING SYSTEM (IPSS)[1]

PROGNOSTIC VARIABLE	POINTS	
	0	1
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
Intermediate-2 (INT-2)	2
High	≥3

[1]Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood 2009;113:2895-2901.

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RISK STRATIFICATION FOR PATIENTS WITH MYELOFIBROSIS

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

DIPSS-PLUS[2]

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	
Platelets, x10^9/L	≥100	<100	
Transfusion need	N	Y	
Unfavorable karyotype*	N	Y	

RISK GROUP	POINTS
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

*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.

[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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20008785.

[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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21149668. www.qxmd.com/calculate/dipss-plus-score-for-prognosis-in-myelofibrosis.

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SUPPORTIVE CARE

- Transfusion support
  - RBC transfusions for symptomatic anemia; platelet transfusions for thrombocytopenic bleeding or a platelet count <10,000 m^3. In transplant candidates, use leukocyte-reduced blood products to prevent HLA alloimmunization and reduce the risk of (CMV) transmission.
- Consider antifibrionolytic agents for bleeding that is refractory to transfusions.
- Iron chelation could be considered for patients that have received >20 transfusions and/or ferritin >2500 ng/mL in low/intermediate-1-risk patients. However, the role of iron chelation remains unclear.
- Antibotic 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*.
- Hematopoietic growth factor therapy
  - ESA: See "Management of MF-Associated Anemia" (MPN-5). Not effective for patients with transfusion-dependent anemia.
  - Consider G-CSF or GM-CSF for recurrent infections in patients with neutropenia. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections*.
- Consider cytoreductive therapy (eg, hydroxyurea) for 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 imparied 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).

*To view the most recent version of these guidelines, visit NCCN.org.

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SPECIAL CONSIDERATIONS FOR THE USE OF RUXOLITINIB[1]

- A CBC and comprehensive metabolic panel with uric acid and LDH must be performed before initiating therapy, every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- A baseline MPN-SAF TSS-10 items (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.

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.

See MPN-H (2 of 2) for Hematologic Toxicities

[1]Please refer to package insert for full prescribing information available at www.fda.gov.

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SPECIAL CONSIDERATIONS FOR THE USE OF RUXOLITINIB[1]

Dose Modifications for Hematologic and Non-Hematologic Toxicities:

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 (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.

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 periodic skin examinations.

[1]Please refer to package insert for full prescribing information available at www.fda.gov.

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

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)	
CR	Bone marrow:[2] Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF[3] and Peripheral blood: Hemoglobin ≥100 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[4]	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 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[4] OR Bone marrow:[2] Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF[3] and Peripheral blood: Hemoglobin ≥85, but <100 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[4]	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH

EMH - extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH)
LCM - left costal margin
UNL - upper normal limit

See Footnotes on MPN-I 3 of 3

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2013 IWG-MRT AND ELN RESPONSE CRITERIA FOR MYELOFIBROSIS[1]

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
Progressive disease[11]	Appearance of a new splenomegaly that is palpable at least 5 cm below the 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 confidence interval (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[5]
Anemia response	Transfusion-independent patients: a ≥20 g/dL increase in hemoglobin level[6] Transfusion-dependent patients: becoming transfusion-independent[7]
Spleen response[8]	A baseline splenomegaly that is palpable at 5–10 cm, below the LCM, becomes not palpable[9] or A baseline splenomegaly that is palpable at >10 cm below the LCM, decreases by ≥50%[9] 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[10]

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 granulocytes 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

EMH - extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH)
LCM - left costal margin
UNL - upper normal limit

See Footnotes on MPN-I 3 of 3

FOOTNOTES

[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]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.

[3]Grading of MF is according to the European classification. (Thiele 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.

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

[5]See definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 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 109/L and absolute neutrophil count of ≥0.5 x 109/L.

[6]Applicable only to patients with baseline hemoglobin of <100 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.

[7]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 <85 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 ≥85 g/dL.

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

[9]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.

[10]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.

[11]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.

Text cont. from page 1573.

stratification, treatment, and supportive care strategies for the management of MF.

Molecular Abnormalities in MPN

JAK2 V617F mutations account for the majority of patients with PV (>90%) and 60% of those with ET or MF.[10–12] Most of these mutations occur in exon 14 with rare insertions and deletions in exon 12; *JAK2* exon 12 mutations have been described in 2% to 3% patients with PV.[13,14] 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 those with ET.[15–17] *MPL* mutations are associated with lower hemoglobin levels at diagnosis and an increased risk of transfusion dependence in patients with MF.[18]

Mutations in exon 9 of the calreticulin (*CALR*) gene are reported in approximately 20% to 35% of all patients with ET and MF (approximately 60%–80% of all patients with *JAK2/MPL*-negative ET and MF)[19,20]; *CALR* 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 are associated with a significantly higher risk of myelofibrotic transformation in ET.[21] *CALR* type 2 mutations are preferentially associated with ET, have a low risk for thrombosis, and have an indolent clinical course.[21–23] The *CALR* mutation is associated with a lower hemoglobin level, lower white blood cell count, higher platelet count, and lower incidences of thromboembolic complications than the *JAK2* V617F mutation.[19,24,25]

Approximately 10% of patients with MF and ET lack *JAK2*, *CALR*, or *MPL* mutations (ie, triple-negative MPN) and are associated with a worse prognosis in patients with MF.[25,26] Mutations in several other genes that are involved in signal transduction (*CBL, LNK*), 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.[27,28]

Diagnostic Classification

The WHO classification of myeloid neoplasm incorporates criteria previously published by other cooperative groups to classify myeloid neoplasms into specific subtypes. The WHO classification was first published in 2001 and was updated in 2008 to refine the diagnostic criteria for previously described neoplasms based on new scientific and clinical information and to introduce newly recognized disease entities.[29,30] It was revised again in 2016 to incorporate new clinical, prognostic, morphologic, immunophenotypic, and genetic data that have emerged since the 2008 publication.[7,31]

The 2016 WHO diagnostic criteria now includes molecular testing for *JAK2, CALR,* and *MPL* mutations for primary MP (PMF) and ET, and molecular testing for *JAK2* V617F or *JAK2* exon 12 mutations for patients with PV.[7] 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.[7] Additional mutations in *ASXL1, EZH2, TET2, IDH1, IDH2, SRSF2,* and *SF3B1* are noted to be of help in determining the clonal nature of the disease.[32,33]

MF can either present as a de novo disorder known as PMF, or it can develop from the transformation of PV and ET (post-PV MF or post-ET MF).[34] Prefibrotic/early-stage PMF is characterized by increased megakaryopoiesis of atypical megakaryocytes, reduced erythropoiesis, and increased age-matched bone marrow cellularity. However, overt bone marrow fibrosis may be absent in early-stage/prefibrotic PMF, leading to a diagnosis of ET.[35] The revised 2016 WHO diagnostic criteria also includes separate criteria for prefibrotic/early-stage and overt fibrotic-stage PMF to differentiate true ET from prefibrotic/early-stage PMF by the morphologic findings of the bone marrow biopsy, including the lack of reticulin fibrosis at onset.[7]

In the International Working Group for MPN Research and Treatment (IWG-MRT) study that re-evaluated 1,104 patients with a diagnosis of ET, central pathology review revealed a diagnosis (as defined by the WHO criteria) of ET in 891 patients (81%), early/prefibrotic PMF in 180 patients (16%), and the remaining 33 patients (3%) were unevaluable.[35] The frequency of grade 1 bone marrow fibrosis was higher in patients with early/prefibrotic PMF. In addition, leukocyte count, platelet count, serum lactate dehydrogenase level, and the incidence of palpable splenomegaly were higher in patients with early/prefibrotic PMF; however, hemoglobin levels were higher in those with ET. Long-term clinical outcomes were significantly worse

for patients with early-stage/prefibrotic PMF. The 15-year rates of overall survival (OS), leukemic transformation, and fibrotic progression were 59.0%, 11.7%, and 16.9%, respectively, for patients with early-stage/prefibrotic PMF; corresponding rates for patients with ET were 80.0%, 2.1%, and 9.3%, respectively. In 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 because long-term clinical outcomes are significantly better for patients with ET than for those with prefibrotic MF.

Diagnostic criteria for PV was also 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).[7] In an international study of 397 patients with *JAK2* V617F exon 12 mutation and WHO-defined PV morphology, 257 patients were diagnosed with overt PV that met the full 2008 WHO diagnostic criteria for PV; the remaining 140 patients were classified as having masked PV with hemoglobin levels at diagnosis ranging from 16.0 to 18.4 g/dL in men and 15.0 to 16.4 g/dL in women and a frequent presence of subnormal erythropoietin (EPO) levels.[36] In multivariate analysis, the diagnosis of masked PV was an independent predictor of poor survival as was those aged more than 65 years and a leukocyte count higher than 10 x 10^9/L. Progression to MF and AML were reported in 10.0% of patients with masked PV and 5.8% of patients overt PV. There was also a trend towards worsening OS in patients with masked PV, and the annual rate of death due to transformation to MF and AML was almost twice that of patients with overt PV. Based on these findings, the major diagnostic criteria for PV have been refined to include bone marrow biopsy to confirm age-matched hypercellularity and lower hemoglobin levels (>16.5 g/dL in men; >16.0 g/dL in women) or hematocrit greater than 49% in men and greater than 48% in women.[7] However, bone marrow biopsy may not be required in patients with sustained erythrocytosis and *JAK2* V617F or *JAK2* V617F exon 12 mutations and subnormal EPO levels.

A diagnosis of MPN should be based on the 2016 WHO diagnostic driteria and requires a combination of clinical, laboratory, cytogenetic, and molecular testing. A diagnosis of PMF requires meeting all 3 major criteria and at least one minor criteria as outlined in the revised 2016 WHO criteria.[7] A 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 WHO criteria.[7] See *2016 WHO Diagnostic Criteria for PMF, PV and ET* in the NCCN Guidelines for a list of major and minor criteria (see MPN-A and MPN-B; pages 1579–1581 and online at NCCN.org). A diagnosis of post-PV MF or post-ET MF is based on the 2008 IWG-MRT diagnostic criteria, which requires documentation of a previous diagnosis of PV or ET as defined by the WHO criteria and development of bone marrow fibrosis of grade 2 or 3 (or 3–4, depending on the scale) and at least 2 minor criteria.[37]

Workup of Suspected MPN

The initial evaluation of patients with suspected MPN should include a history and physical, palpation of spleen, evaluation of thrombotic/hemorrhagic events, cardiovascular risk factors, and documentation of transfusion/medication history. Laboratory evaluations should include a complete blood count, microscopic examination of the peripheral smear, comprehensive metabolic panel with serum uric acid, serum lactate dehydrogenase, liver function tests, serum EPO level, and serum iron studies.

Fluorescence in situ hybridization (FISH) or a reverse transcriptase polymerase chain reaction on a peripheral blood specimen to detect *BCR-ABL1* transcripts and exclude the diagnosis of chronic myelogenous leukemia (CML) is recommended for all patients, especially those with left-shifted leukocytosis and/or thrombocytosis with basophilia.[7] Molecular testing for *JAK2* V617F mutations should be performed in all patients.[7] If *JAK2* V617F mutation is negative, molecular testing for *MPL* and *CALR* mutations should be performed for patients with MF and ET; molecular testing for *JAK2* exon 12 mutations should be performed for those with PV.[13,14]

Bone marrow aspirate and biopsy with trichrome and reticulin stain and bone marrow cytogenetics (karyotype, ± FISH) is necessary to accurately distinguish bone marrow morphological features between disease subtypes (early/prefibrotic PMF, ET, and masked PV).[7,35,36] Bone marrow histology shows

hypercellularity, age-matched hypercellularity, and megakaryocytic proliferation in most myeloproliferative disorders. For MF, bone marrow fibrosis is demonstrated on the reticulin stain and an additional trichrome stain is recommended for grades MF-2 or MF-3, as outlined in the 2016 WHO diagnostic criteria.[7] Initial MF can only be detected by performing a bone marrow biopsy, which may predict a more rapid progression to overt MF in patients with PV and ET; however, in patients with PV, bone marrow biopsy may not be required in those with sustained absolute erythrocytosis, hemoglobin levels more than 18.5 g/dL in men (hematocrit, 55.5%) or more than 16.5 g/dL in women (hematocrit, 49.5%), *JAK2* V617F or *JAK2* exon 12 mutations, and subnormal EPO level.[7]

Human leukocyte antigen (HLA) typing should be performed in patients with MF for whom allogeneic hematopoietic cell transplantation (HCT) would be considered. Identification of high-molecular risk mutations (*ASXL1*, *EZH2*, *TET2*, *IDH1*, *IDH2*, *SRSF2*, and *TP53*) may be helpful in determining whether to undergo allogeneic HCT.[28,32,33]

MPNs are associated with an increased risk of major bleeding and thrombosis/thromboembolism compared with the general population, and these events contribute considerably to morbidity and mortality in this patient population.[38,39] Acquired von Willebrand disease (VWD) is associated with a variety of hematologic disorders, and is particularly frequent in lymphoproliferative (48%) and myeloproliferative disorders (15%). Among MPNs, the frequency of acquired VWD is more common among patients with ET (11%–17%), but can also be seen in those with PV.[40] Coagulation tests to evaluate for acquired VWD (plasma von Willebrand factor antigen measurement and von Willebrand ristocetin cofactor activity)[41] 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. An expanded panel including factor VIII activity and von Willebrand factor multimers may be useful under certain circumstances.[41]

Assessment of Symptom Burden

MPNs are characterized by a complicated symptom profile resulting in reductions in quality of life, functional status, and activities of daily living.[2,3] Constitutional symptoms (fever, night sweats, and weight loss) are more frequently reported in patients with MF compared with those with PV or ET.[2,42] In a recent landmark survey that evaluated the symptom burden experienced by patients with MPN, disease-related symptoms were reported 1 year or more before diagnosis in 49% of patients with MF, 61% of patients with PV, and 58% of patients with ET.[3] In an online survey of 1,179 patients with MPN, fatigue was the most frequent symptom observed in 84% of patients with MF, 85% of patients with PV, and 72% of patients with ET.[42] Additional symptoms included pruritus (52%), night sweats (49%), bone pain (44%), fever (14%), and weight loss (13%).

Various tools have been developed and validated in large cohorts of patients with MPNs for the assessment of disease-related symptoms.[43–47] The MF 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.[43] The MF-SAF was subsequently expanded to a 27-item tool, MPN Symptom Assessment Form (MPN-SAF), to include an assessment of additional symptoms relevant to ET and PV (insomnia, headaches, concentration, dizziness, vertigo, lightheadedness, numbness or tingling, depression, and sexual desire dysfunction).[45] The MPN-SAF was further simplified to a concise and abbreviated tool, MPN-SAF Total Symptom Score (MPN-SAF TSS; MPN 10), 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 fevers) in both clinical practice and clinical trial settings.[46] All 3 symptom assessment tools are coadministered with the Brief Fatigue Inventory, and symptom severity is rated by patients on a scale of 1 to 10.

Assessment of symptoms at baseline and symptom monitoring during treatment is recommended for all patients. MPN-SAF is recommended for the assessment of symptom burden at baseline, and MPN-SAF TSS is recommended for monitoring symptom status during treatment.[45,46]

Management of MF

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

Prognostic Significance of Mutations

JAK2, *CALR*, and *MPL* mutational status provide prognostic information in terms of OS and leukemic transformation.[24] The *CALR* mutation is associated with better OS than either *JAK2* V617F or *MPL* W515.[24] The survival advantage is significant in patients with type 1/type 1–like mutations.[23,48,49] In a study of 617 patients with PMF, the median OS was 17.7 years for those with *CALR* mutations versus 9.2, 9.1, and 3.2 years for those with *JAK2* V617F mutations, *MPL* mutations, and triple-negative PMF, respectively.[24] *CALR* mutations retained their prognostic significance for a better OS compared with *JAK2* V617F mutations (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 (9.4%) for patients with *CALR* mutations compared with 19.4% for those with *JAK2* V617F mutations, 16.9% for *MPL* mutations, and 34.4% for those who were triple negative. In a study that evaluated the prognostic impact of *CALR* type 1 and 2 mutations in 396 patients with PMF, median survival was significantly higher for patients with type 1/type 1–like mutations at 26.4 years (P<.0001) versus 7.4 and 7.2 years, respectively, for those with type 2/type 2-like and *JAK2* V617F mutations. The rate of leukemic transformation was also higher among patients with type 2/type 2–like mutations than those with type 1/type 1–like and *JAK2* V617F mutations.[49]

CALR mutations are also associated with higher OS rates and lower rates of nonrelapse treatment-related mortality (NRM) after allogeneic HCT in patients with PMF and post-PV or post-ET MF.[50] 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 with 56% for those without *CALR* mutations (*CALR* wild-type); NRM was also significantly lower in patients with *CALR* mutations compared with those who were *CALR* wild-type (4-year NRM 7% and 31%, respectively; P=.024).[50]

ASXL1, *EZH2*, *SRSF2*, *TP53*, *IDH1*, or *IDH2* mutations are considered high-molecular risk mutations, and are associated with significantly shorter OS and leukemia-free survival. *ASXL1*, *EZH2*, and *SRSF2* mutations are predictive of OS, although *ASXL1*, *SRSF2*, and *IDH1/2* are predictive of leukemic transformation in patients with PMF.[32,33,51,52] *TET2* or *TP53* mutations have also been associated with a worsened overall prognosis and an increased rate of leukemic transformation.[28,53] 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 mutations in any of these genes.[32] However, only *ASXL1* mutations retained prognostic significance after accounting for known prognostic factors. Results of a subsequent analysis that evaluated the additional prognostic value of the number of mutated genes in 797 patients with PMF confirmed that those harboring 2 or more high-molecular risk mutations had significantly reduced OS and leukemia-free survival compared with patients with no mutations and those presenting with only one high-molecular risk mutation.[33] Median OS was 2.6 years for patients with 2 or more high-molecular risk mutations compared with 7.0 and 12.2 years for those with one high-molecular risk mutation and no mutations, respectively; leukemia-free survival was 6.6, 11.1, and 26.7 years, respectively.

An analysis that assessed the impact of both *CALR* and *ASXL1* mutations on OS in 570 patients with PMF identified *CALR*-negative/*ASXL1*-positive mutational status as the most significant risk factor. The median OS was the longest in patients who were *CALR*-positive/*ASXL1*-negative (10.4 years) and shortest in those with *CALR*-negative/*ASXL1*-positive mutations; OS was similar for patients who were *CALR*-positive/*ASXL1*-positive and *CALR*-negative/*ASXL1*-negative (5.8 years).[54]

Risk Stratification

International Prognostic Scoring System (IPSS), dynamic IPSS (DIPSS), and DIPSS-plus are the 3 most common prognostic scoring systems used for the risk stratification of patients with MF.[55–57] These prognostic scoring systems were developed using data from patients with PMF, but still often used for the risk

stratification of patients with post-PV MF or post-ET MF. Other prognostic models incorporating mutational status (Mutation-Enhanced IPSS [MIPSS] and Genetics-Based Prognostic Scoring System [GPSS]) have been developed to further refine the risk stratification.[58,59] Further validation is essential before these models can be widely adopted for risk stratification of patients with MF.

IPSS should be used for risk stratification at the time of diagnosis.[55] DIPSS-plus is preferred for risk stratification of MF during treatment.[57] DIPSS can be used, if karyotyping is not available.[56]

IPSS: Patients aged greater than 65 years, the presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count more than 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.[55] IPSS stratifies patients at 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-1–risk (INT-2–risk), and high-risk with median survivals of 135, 95, 48, 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, the acquisition of anemia over time significantly affected survival (hazard ratio was approximately double that of other adverse factors).[56] Thus, a modified risk stratification system was developed using the same prognostic variables as the 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 diagnosis), but 2 points were assigned for hemoglobin less than 10 g/dL. 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 of not reached, 14.2 years, 4 years, and 1.5 years, respectively.[56]

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 leukemia-free survival in patients with PMF.[60–63] The median survival of DIPSS low-risk patients with thrombocytopenia or unfavorable karyotype was 6.5 years compared with more than 15 years in the absence of these 2 additional risk factors.[57] Similarly, the median survival was less than 1.5 years for DIPSS high-risk patients with one or more of these additional prognostic factors compared with approximately 3 years for patients without these prognostic factors.[57]

DIPSS was modified into DIPSS-plus by the incorporation of platelet count less than 100 x 10^9/L, RBC transfusion need, and unfavorable karyotype (complex karyotype or 1–2 abnormalities that include trisomy 8, del 7/7q, i(17q), del5/5q, del12p, inv(3), or 11q23 rearrangement).[57] DIPSS-plus also stratifies patients into 4 risk groups based on the aforementioned 8 risk factors: low-risk (no risk factors), INT-1–risk (1 risk factor), INT-2–risk (2–3 risk factors), and high-risk (≥4 risk factors) with median survivals of 15.4, 6.5, 2.9, and 1.3 years, respectively.

MF Treatment Response Criteria

In 2006, the IWG-MRT first published the response criteria for MF, and the responses were categorized as complete remission (CR), partial remission (PR), clinical improvement, progressive disease, stable disease, and relapse.[64] In 2013, these response criteria were revised by IWG-MRT and European Leukemia Net (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.[65] These response criteria were developed mainly for use in clinical trials.

In addition to CR, PR, and clinical improvement, 3 other response categories (anemia, spleen, and symptoms response) have been included in the revised 2013 IWG-MRT/ELN response criteria to quantify treatment-induced improvements in symptom burden, particularly anemia, splenomegaly, and constitutional symptoms.[65] The revised response criteria recommend that symptoms should be evaluated by the MPN-SAF TSS, and symptom response requires a 50% or greater reduction in the TSS.[46] The revised 2013 IWG-MRT/ELN response criteria also require that a 35% or greater reduction in spleen volume should be confirmed by MRI or CT scan. If confirmed via CT or MRI, this constitutes a spleen response regardless of report via physical examination. Additional criteria are also included for progressive disease, stable disease, and relapse.

Morphologic remission in bone marrow is required for CR; criteria for PR require morphologic remission in the peripheral blood (but not necessarily the bone marrow). Patients meeting CR criteria 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 remission. However, these are not required for CR assignment.

Treatment Options

Interferons: Interferon-alfa (IFN-alfa), pegylated interferon alfa-2a (PEG-IFN-alf-2a), and pegylated interferon alfa-2b (PEG-IFN-alfa-2b) have been evaluated in small series of patients with MF.[66–69]

In a prospective trial of 32 patients (12 patients with PMF, 7 with post-PV MF, 11 with post-ET MF, and 2 with PV), IFN-alfa or PEG-IFN-alfa resulted in an overall response rate (ORR) of 78% (9.4% experienced CR, 37.5% experienced PR, 9.4% experienced clinical improvement, and 21.8% had stable disease)[68]; corresponding response rates were 9.1%, 50%, 9.1%, and 18%, respectively, for patients with low-risk disease. Among the 15 patients with a reduction in splenomegaly and evaluable bone marrow biopsies, reduction in bone marrow cellularity was observed in 7 and a significant improvement in megakaryocyte morphology, marrow architecture, and reductions of reticulin and collagen fibrosis were observed in 3. Among the 22 patients with follow-up bone marrow biopsies, a reduction in cellularity was observed in 12 after a median treatment duration of 2 years.

In another retrospective study of 62 patients with early MF treated with PEG-IFN-alfa-2a, improvement in constitutional symptoms, complete resolution of thrombocytosis, and leucocytosis were observed in 82%, 83%, and 69% of patients, respectively, and a reduction of splenomegaly was seen in 46.5% of patients.[69]

Ruxolitinib: Ruxolitinib is a potent and selective JAK2 inhibitor approved for the treatment of intermediate- or high-risk MF. The safety and efficacy of ruxolitinib in patients with INT-2–risk or high-risk MF were evaluated in 2 phase III studies (COMFORT-I and -II).[70,71] The COMFORT studies did not include patients with INT-1–risk MF; the safety and efficacy of ruxolitinib in these patients have been demonstrated in nonrandomized studies.[72,73] Results from a retrospective analysis suggest that ruxolitinib may be an appropriate treatment option for symptomatic patients with low-risk MF.[74] However, the efficacy of ruxolitinib in low-risk MF has not been evaluated in prospective clinical trials.

Low-Risk MF: In a retrospective study of 108 patients (25 patients with low-risk MF, 83 patients with INT-1–risk MF) treated with ruxolitinib, patients with low-risk MF experienced a substantial improvement in splenomegaly and constitutional symptoms.[74] The proportion of patients with moderate to severe splenomegaly was reduced from 64% at diagnosis to 16% at time of best response to ruxolitinib. The proportion with moderate or severe fatigue decreased from 90% at diagnosis to 37% at time of best response to ruxolitinib. Similar findings were observed for patients with INT-1–risk MF. The proportion of patients with moderate or severe splenomegaly decreased from 53% at diagnosis to 10% at time of best response to ruxolitinib, and the proportion of patients with moderate or severe fatigue decreased from 76% at diagnosis to 42% at time of best response to ruxolitinib.

INT-1–Risk MF: 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 with INT-1–risk, 13 with INT-2–risk, and 21 with high-risk MF).[72] The primary composite end point was achievement of treatment success at 48 weeks after ruxolitinib therapy (≥50% reduction in palpable spleen length and/or ≥50% decrease in MF-SAF). At 48 weeks, 46.7% achieved a reduction in mean palpable spleen length and the effect was seen across all risk groups (51.6% with INT-1–risk, 37% with INT-2–risk, and 48.6% with high-risk disease). A 50% or greater reduction in MF-SAF at 48 weeks was achieved in 20.8% of patients and across all risk groups (21.4% with INT-1–risk, 23.1% with INT-2–risk, and 19.0% with high-risk disease). Improvements in MF-SAF were seen in 80.0%, 72.7%, and 72.2% 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).[73] Re-

cent data from 1,869 patients on ruxolitinib therapy for one year (median duration of treatment, 13.6 months) showed that at 48 weeks, 62.0% of evaluable patients achieved a 50% reduction in palpable spleen length and an additional 19.0% had a 25% to 50% reduction in palpable spleen length; 70.5% of patients experienced a 50% or greater reduction at any time and 23.3% had complete resolution of splenomegaly.

INT-2–Risk/High-Risk MF: Results of COMFORT-I[70,75,76] and COMFORT-II[71,77,78] 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 with either placebo or best available therapy for patients with INT-2–risk or high-risk MF (PMF, post-PV MF, or post-ET MF).

COMFORT-I randomized 259 patients with INT-2–risk or high-risk MF to twice-daily ruxolitinib (n=155) or placebo (n=154).[70] 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–200 x10^9/L; 20 mg twice daily for >200 x 10^9/L) and patients with protocol-defined worsening splenomegaly were permitted to crossover from placebo to ruxolitinib. The primary end point (≥35% reduction in spleen volume as assessed by MRI at 24 weeks) was reached in 41.9% of patients in the ruxolitinib group compared with 0.7% in the placebo group (*P*<.001). An improvement of 50% or greater in the MF-SAF at 24 weeks was seen in 45.9% of patients treated with ruxolitinib compared with 5.3% of those 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.[75,76] At the median follow-up of 268 weeks, OS was favorable for patients treated with ruxolitinib (69 and 82 deaths among patients originally randomized to ruxolitinib and placebo, respectively; hazard ratio, 0.69; *P*=.025).[76] The mean spleen volume reduction at 264 weeks was 37.6%, and median duration of 35% or greater spleen volume reduction was 168.3 weeks. At the time of this analysis, 111 patients from the placebo group had crossed over to ruxolitinib (median time to crossover, 41.1 weeks). The subgroup analyses showed that the 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); however, this study was not designed or powered to detect treatment efficacies between treatment arms within each subgroup.[79]

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).[71] The primary end point was at least a 35% reduction in spleen volume as assessed by MRI or CT scan at 48 weeks. The starting dose of ruxolitinib was based on the baseline platelet count (15 mg twice daily for platelet counts ≤200 x 10^9/L; 20 mg twice daily for platelet counts >200 x 10^9/L). A total of 28% of the patients in the ruxolitinib arm had at least a 35% reduction in spleen volume at 48 weeks compared with 0% in the best available therapy group (*P*<.0001). The median duration of response among patients treated with ruxolitinib was not reached, with 80% of patients still experiencing response at a median follow-up of 12 months.[71] Patients receiving ruxolitinib experienced improved quality of life and role functioning, as well as significant reductions in disease-related symptoms compared with those receiving best available therapy. Long-term follow-up results confirmed that ruxolitinib is associated with durable efficacy and survival benefit compared with best available therapy for patients with INT-2–risk or high-risk MF.[77,78] At the time of 5-year final analysis, 53.4% of patients in the ruxolitinib arm achieved a 35% or greater reduction in spleen volume at any time on treatment, and spleen volume reductions of 35% or greater were sustained with long-term therapy (median duration, 3.2 years).[78] Median OS was not reached for patients in the ruxolitinib arm, and was 4.1 years for those in the best available therapy arm.

The pooled analysis of COMFORT-I and COMFORT-II 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.[80] Larger spleen size at baseline was associated with shortened survival whereas any spleen volume reductions (>10% reduction) and palpable spleen length reductions of 25% or greater with ruxolitinib correlated with longer survival.

Toxicity: Anemia and thrombocytopenia were the most common hematologic toxicities associated with ruxolitinib, consistent with its mechanism of action, and incidences of grade 3/4 anemia or thrombocytopenia were higher during the first 8 to 12 weeks of treatment.[70,71] In the COMFORT-I study, ecchymosis, dizziness, and headache were the most frequent nonhematologic toxicities associated with ruxolitinib; diarrhea was the most frequent nonhematologic adverse event associated with ruxolitinib in the COMFORT-II study.[70,71] In general, the incidences of nonhematologic toxicities decreased with long-term therapy[75,78]

Ruxolitinib is associated with a potentially increased risk of opportunistic infections.[81,82] In particular, tuberculosis, progressive multifocal leukoencephalopathy, reactivation of hepatitis B virus, and herpes simplex virus have been reported in patients treated with ruxolitinib.[83–87] Patients should be monitored for signs and symptoms of infections. Serious infections should be resolved before 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.

Impact of Mutational Status and Response to Ruxolitinib: In the COMFORT-II study, ruxolitinib was associated with clinical efficacy and a survival improvement across different molecular subsets of patients with MF.[88] High-molecular risk mutations (*ASXL1*, *EZH2*, *SRSF2*, *IDH1*, or *IDH2)* were identified in 32.5%, 7.2%, 4.4%, 3.0%, 0.7%, and 0.0% of patients, respectively, and these frequencies were comparable in the 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 high-molecular risk mutations (*ASXL1*, *EZH2*, *SRSF2*, *IDH1*, or *IDH2*) with a hazard ratio of 0.57.[88]

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 one or more mutations in *ASXL1*, *EZH2*, or *IDH1/2* had shorter time to treatment discontinuation and OS.[89] However, in contrast to the findings of the COMFORT-II study, patients with one or more mutations in *ASXL1*, *EZH2*, or *IDH1/2* were significantly less likely to have a spleen response. Patients with 3 or more mutations experienced the worst outcomes, suggesting that multigene profiling may be useful for treatment planning in patients with MF.

Allogeneic HCT: Allogeneic HCT is the only treatment that is potentially curative resulting in long-term remission for patients with MF. However, the use of myeloablative conditioning is associated with higher rates of NRM; estimated OS and NRM rates at 3 to 5 years range from 30% to 61% and 24% to 43%, respectively.[90] In a retrospective registry analysis of 289 patients with MF, allogeneic HCT resulted in long-term OS in approximately one-third of patients, but the probability of long-term survival and NRM was dependent on the source of stem cells.[91] The 5-year posttransplant OS rates were 37%, 40%, and 30% for HLA-matched sibling donor transplant, other related donor transplant, and unrelated donor (URD) transplant, respectively; 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% vs 35% and 38% for HLA-matched sibling donor and other related donor transplant, respectively).

Use of reduced-intensity conditioning (RIC) has lowered the NRM rates but it is associated with a higher risk of relapse compared with myeloablative conditioning.[92–99] In a prospective multicenter study that evaluated allogeneic HCT with RIC in 103 patients with MF, the cumulative incidence of NRM at 1 year was 16% and the cumulative incidence of relapse at 3 years was 22%.[93] The estimated 5-year event-free survival and OS rates were 51% and 67%, respectively. 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.[96,97] In the Center for International Blood & Bone 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 at 5 years were 47% and 27%, respectively.[96] The cumulative incidence of NRM and relapse/progression at 5-years was 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 was 55%, 32%, and 28%, respectively.[97]

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, 5-year survival rates after HLA-identical sibling donor transplant, HLA–well-matched URD transplant, and partially/mismatched URD transplant were 56%, 48%, and 34%, respectively (P=.002). The relative risk of NRM was lowest for HLA-identical sibling donor transplant (1%) compared with 3.02% and 9.37% for HLA–well-matched URD transplant and partially/mismatched URD transplant, respectively.[96] 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 aged greater than 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).[97]

DIPSS risk score has been shown to predict outcome after transplant.[96,100] In the previously discussed CIBMTR analysis, there was a trend toward lower mortality rates in patients with low-risk/INT-1–risk disease and higher NRM in those with INT-2–risk/high-risk disease.[96] 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 posttransplant mortality was 4.11 for high-risk disease vs 3.15, 1.97, and 1.0 for INT-2–risk, INT-1–risk, and low-risk disease, respectively; corresponding hazard ratios for NRM were 3.41, 3.19, 1.41, and 1.0, respectively).[100] 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 after allogeneic HCT.[96,101,102] 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 or greater 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, respectively.[101] In another retrospective analysis that evaluated the impact of allogeneic HCT on survival in patients aged less than 65 years at PMF diagnosis (n=438; 190 patients received allogeneic HCT, 248 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, and 0.37 for high-risk disease.[102]

These findings suggest that outcomes after allogeneic HCT are better for patients with low-risk or INT-1–risk MF.[96,100] However, allogeneic HCT is also associated with high transplant-related morbidity and mortality in this population.[102] Allogeneic HCT is associated with a clear benefit in patients with INT-2–risk/high-risk PMF.

Treatment Recommendations Based on Symptom Assessment and Risk Stratification

The selection of appropriate treatment should be based on the risk score and presence of symptoms. Enrollment on clinical trials is recommended for all patients with the goal of reducing bone marrow fibrosis, improving cytopenias and symptom burden, restoration of 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[72–74] or interferons (IFN-alfa-2b, PEG-IFN-alfa-2a, or PEG-IFN-alfa-2b)[68,69] are included as options for symptomatic patients.

Allogeneic HCT is included as an option for patients with INT-1–risk MF. Evaluation for allogeneic HCT is recommended for patients with low platelet counts and identification of potentially high-molecular risk mutations may be helpful in the decision-making process regarding allogeneic HCT.[32,33] Although outcomes after 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.[96,100,102]

INT-2–Risk or High-Risk MF: Evaluation for allogeneic HCT is recommended for all patients with INT-2–risk and high-risk MF. Patient selection patients for allogeneic HCT should be based on age, performance status, major comorbid conditions, psy-

chosocial status, patient preference, and 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. Identification of high-molecular risk mutations may be helpful in the decision-making process regarding allogeneic HCT.[32,33]

Allogeneic HCT is recommended for patients with INT-2–risk or high-risk MF if they are candidates for transplant.[100] For those who are not candidates, treatment options are based on the platelet count. Enrollment on clinical trials should be considered for patients with platelet counts of 50 x 10^9/L or less. Ruxolitinib[70,71,75–77] or a clinical trial are included as options for patients with platelet counts greater than 50 x 10^9/L.

Management of Treatment-Related Anemia and Thrombocytopenia

In COMFORT-I and COMFORT-II studies, anemia and thrombocytopenia were managed with dose modifications and RBC transfusions.[70,71] Patients enrolled on the COMFORT trials were required to have a baseline platelet count of 100 x 10^9/L or greater, which the initial starting dose of ruxolitinib was dependent on.[70,71] Preliminary results of phase II study that evaluated the efficacy of ruxolitinib in patients with baseline platelet counts of between 50 x 10^9/L and 100 x 10^9/L suggest that a lower initial dose (5 mg, twice daily) with escalation to 10 mg, twice daily may be appropriate in those with low platelet counts.[103]

The NCCN Guidelines recommend that the initial dosing of ruxolitinib should be based on the patient's baseline platelet count (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 complete blood count, which must be performed before ruxolitinib initiation and monitored every 2 to 4 weeks until the dose is stabilized, and then as clinically indicated.[103,104] See the section "Special Considerations for the Use of Ruxolitinib" in the guidelines algorithm (MPN-H; pages 1589 and 1590) for dose modifications for the management of hematologic toxicities.

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 a complete blood count to assess normalization of blood counts, monitoring symptom status using MPN-SAF TSS, and monitoring spleen size either by palpation or imaging.[65]

The NCCN Guidelines recommend monitoring response (anemia, spleen, and symptom response), signs, and symptoms of disease progression every 3 to 6 months during treatment. Bone marrow aspirate and biopsy should be performed as clinically indicated (if supported by increased symptoms and signs of progression). Additional molecular monitoring is recommended for patients with INT-1–risk or INT-2–risk/high-risk disease because the identification of high-molecular risk mutations may be helpful in the decision-making process regarding allogeneic HCT.[32,33]

Continuation of prior treatment 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 TSS via MF-SAF) and quality of life; most importantly, however, patients with a lesser degree of symptom improvement (<50% improvement in TSS) also achieved improvements compared with placebo on these measures and other patient-reported outcomes.[47] The NCCN Guidelines Panel acknowledges that clinical benefit may not reach the threshold of the 2013 IWG-MRT/ELN response criteria (ie, symptoms response requires ≥50% reduction in the MPN-SAF TSS) for patients undergoing treatment with ruxolitinib. Continuation of ruxolitinib is recommended based on the discretion of the clinician, because a symptom response or less than 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. However, disease-related symptoms may return to pretreatment levels over a period of approximately one week after discontinuation or interruption of ruxolitinib.[105] Gradual dose tapering should be considered when discontinuing or interrupting ruxolitinib for reasons other than thrombocytopenia or neutropenia. See "Special Considerations for

the Use of Ruxolitinib" in the guidelines algorithm (MPN-H; pages 1589 and 1590).

JAK2 V617F Allele Burden: Long-term ruxolitinib therapy is associated with reductions in *JAK2* V617F allele burden.[78,106] In the COMFORT-I study, more than a 50% reduction in the *JAK2* V617F allele burden was observed in 12% of patients (28 patients); of these 20 met the criteria for partial molecular remission and 6 had *JAK2* V617F allele burden values below the quantifiable limit, meeting the criteria for complete molecular remission.[106] Median times to partial and complete molecular remission were 22.2 and 27.5 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.[107,108]

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/ELN response criteria, although cytogenetic and molecular remissions are included in response categories, these are not required for CR assignment.[65] 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.[55] Symptomatic anemia is observed in more than 50% of patients at diagnosis.[109] It is essential to rule out and treat (if necessary) the most common causes of anemia (eg, bleeding, hemolysis, deficiency of iron, vitamin B12, and folic acid) before considering other treatment options. Enrollment on clinical trials should be considered for all patients with MF-associated anemia. Leucoreduced RBC transfusion support is recommended for symptomatic anemia. Additional treatment options for the management of MF-associated anemia are based on serum EPO levels.

Serum EPO Less Than 500 mU/mL: Erythropoietin stimulating agents (ESAs; darbepoetin alfa or epoetin alfa) are recommended for the treatment of anemia for patients with serum EPO levels less than 500 mU/mL. 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 of >2 g/dL within 12 weeks or >50% reduction in transfusion requirements within 12 weeks) in 45% to 60% of patients with MF.[110–112] Lower serum EPO levels (<125 mU/mL), smaller spleen size, and low RBC transfusion requirements have been associated with favorable responses. In the COMFORT-II study, anemia was managed with packed RBC transfusions and only a small number of patients (13 of 166 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.[113] Additional studies are warranted to evaluate the efficacy of ESAs to alleviate anemia in patients receiving ruxolitinib. ESAs are not effective for the management of transfusion-dependent anemia.[114]

Continuation of treatment with ESAs is recommended in patients achieving anemia response. Those with no response or loss of response should be managed with androgens or immunomodulating agents as described in the following section.

Serum EPO of 500 mU/mL or Greater: Danazol (or alternative androgens) or immunomodulating agents (lenalidomide or thalidomide) with or without prednisone are recommended for patients with serum EPO levels 500 mU/mL or greater.

In a study of 50 patients with MF and anemia, danazol therapy resulted in an anemia response in 30% of patients, and responses were less frequent in patients with transfusion dependency (18.5% vs 43.5% in those without transfusion requirements).[115] Prostate cancer screening and monitoring of liver function tests are recommended for patients receiving danazol therapy for anemia.

Thalidomide (in escalating daily doses of 100–800 mg) has demonstrated very minimal efficacy resulting in anemia responses rates of 0% to 29% and is poorly tolerated.[116–122] A lower dose of thalidomide (50 mg/d) when used in combination with prednisone is better tolerated, leading to improved anemia response rates (62%) compared with high-dose thalidomide monotherapy in the management of MF-associated symptomatic anemia (hemoglobin level <10 g/dL or symptomatic splenomegaly).[123] Lenalidomide alone or in combination with prednisone has also demonstrated modest efficacy in the management of MF-associated anemia, resulting in response rates of 19% to 32% with myelosuppression

being the most common grade 3 or higher hematologic toxicity.[124–127]

In an analysis that reassessed the efficacy of thalidomide and lenalidomide in 125 patients with MF treated in 3 consecutive phase II trials, combination lenalidomide and prednisone was more effective and safer than single-agent thalidomide or lenalidomide.[128] After a median follow-up of 42 months, the ORR was 38% for combination lenalidomide and prednisone compared with 34% and 16% for lenalidomide and thalidomide, respectively. There was also a trend for higher efficacy in patients receiving lenalidomide-based therapy (P=.06), and in a multivariate analysis, lenalidomide-based regimen was the only factor independently associated with a higher response rate. The presence of del(5q) is associated with better response rates with lenalidomide.[129]

Continuation of prior treatment is recommended in patients achieving anemia response. Those with no response or loss of response should be given another trial of an alternative androgen or immunomodulating agent not previously used.

Disease Progression to Advanced Phase or Transformation to AML

MF in accelerated phase (AP) is characterized by the presence of 10% or greater blasts in the peripheral blood or bone marrow, platelet count of less than 50 x 10^9/L, and chromosome 17 aberrations.[130] In a cohort of 293 patients who presented with chronic-phase MF, development of AP features during follow-up was associated with short median survival times (12, 15, and 6 months for ≥10% blasts, platelets <50 x 10^9/L, and chromosome 17 aberrations, respectively).[130]

MF in blast phase or transformation to AML (MF-BP/AML) is defined by the presence of 20% or greater myeloid blasts in either the bone marrow or peripheral blood. The incidence of transformation to AML is significantly higher for patients with MF (1.09% vs 0.38% for PV and 0.37% for ET).[131] However, the risk of transformation is very low in patients who remain in chronic-phase MF (3% risk at 10 years).[130] In some studies, treatment with hydroxyurea has been associated with an increased risk of transformation to AML.[132,133] These findings were not confirmed in subsequent reports.[134–136] The results of a large cohort analysis (n=11,039; 162 patients with transformation to AML/myelodysplastic syndromes) showed that the use of alkylating agents or a combination of 2 or more cytoreductive treatments (but not treatment with hydroxyurea alone) was associated with an increased risk of transformation to AML.[134] In another large analysis of 649 patients with either PMF or post-PV MF or post-ET MF, bone marrow blasts of 10% or greater and high-risk karyotypes were identified as independent poor prognostic factors for the transformation to AML.[136] Hydroxyurea, however, was not an independent risk factor for transformation to AML, although it was found to be associated with shorter OS.

Bone marrow aspirate and biopsy with trichrome and reticulin stain and bone marrow cytogenetics (karyotype, ± FISH), flow cytometry, and molecular testing for AML-associated mutations is recommended as part of the initial work up. Mutations in several genes (*ASXL1*, *TET2*, *TP53*, *SRSF2*, and *IDH1/2*) and other chromosomal abnormalities (eg, aberrations in chromosomes 1q and 9p) have been associated with transformation to AML.[28,32,53,137]

Treatment Options: Transformation to AML is associated with a poor prognosis and poor response to standard treatment options.[138–140] In a retrospective analysis of 91 patients with MF that had transformed to AML, the median OS after transformation to AML was 2.6 months. Among patients treated with AML-type induction chemotherapy, reversal to chronic phase without an increase in the blast percentage occurred in 41% of patients.[138] However, it was also associated with a treatment-related mortality rate of 33%. Median OS was 3.9 months and was comparable to that observed in patients treated with supportive care or low-intensity chemotherapy (2.0 and 2.9 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.[141–143] 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.[141] At a median follow-up of 9 months, 67% of patients treated with decitabine were alive. In another series of 54 patients with MPN-BP/AML (21 patients with ET, 21 with PV, 7 with PMF, and 5 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).[142] The median duration of response was 9 months and the median OS was 11 months. In a retrospective analysis of 21 patients with MPN-BP/AML and 13 patients with MPN-AP treated with decitabine, the ORR was 62% (8 of 13 patients) and 29% (6 of 21 patients) for patients with MPN-AP and MPN-BP/AML, respectively.[143] The median OS was significantly higher in patients who responded to decitabine (11.8 vs 4.7 months for patients with MPN-AP; 10.5 vs 4 months for patients with MPN-BP/AML).

Allogeneic HCT remains the only curative option resulting in long-term disease control for select transplant-eligible patients who achieve a complete response to induction chemotherapy.[140,144–146] In one retrospective analysis of 75 patients with MPN-BP/AML, patients treated with curative intent (induction chemotherapy ± allogeneic HCT) had significantly improved survival compared with those treated with noncurative intent (nonintensive chemotherapy or supportive care).[140] The 2-year OS rates were 25.6% and 3.1%, respectively, and the median survival was 9.4 and 2.3 months, respectively ($P<.0001$). Among those treated with curative intent, the ORR to induction chemotherapy was 46% and reversal to chronic phase was observed in 31%, 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, 47% vs 15% for those who did not undergo allogeneic HCT; $P=.03$).[140] In another retrospective analysis of 46 patients who received allogeneic HCT for MF-BP/AML, the 3-year progression-free survival and OS rates after transplant were 26% and 33%, respectively. The remission 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 progression-free survival (55% and 19%, respectively; $P=.02$).[146] The cumulative incidence of treatment-related mortality was 28% at 1 year, and the absence of CR before allogeneic HCT was also associated with significantly increased treatment-related mortality (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 before 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 transplant candidates.[140,141,146] Enrollment on a clinical trial or treatment with hypomethylating agents (azacytidine or decitabine) or low-intensive AML-type induction chemotherapy is recommended for those who are not transplant candidates.

The results of a recent retrospective analysis suggest that prior exposure to ruxolitinib did not adversely affect posttransplantation outcomes, and that ruxolitinib should be continued near to the start of conditioning therapy.[147] The NCCN Guidelines recommend continuation of ruxolitinib 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 treatment, and should include assessment and monitoring symptom status and counseling for the identification, assessment, and management of cardiovascular risk factors (eg, smoking, diet, and exercise; thrombotic and hemorrhagic risk factors).

Transfusion support should include platelet transfusions for thrombocytopenic bleeding or a platelet count of less than 10,000 m^3 and RBC transfusions for symptomatic anemia.[148] The use of leukocyte-reduced blood products is recommended in transplant candidates to prevent HLA alloimmunization and to 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 more than 20 transfusions and/or ferritin levels of greater than 2500 ng/mL in patients with low-risk or INT-1–risk disease.[148] 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

before initiation of ruxolitinib. Antibiotic prophylaxis and vaccinations for recurrent infections is recommended as outlined in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections (to view the most recent version of these guidelines, visit NCCN.org). In splenectomized patients, antibiotic prophylaxis should be given per the Infectious Diseases Society of America (IDSA) guidelines. Growth factor support should be considered for recurrent infections with neutropenia.

Prophylaxis for tumor lysis syndrome (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.

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Individual Disclosures of the Myeloproliferative Neoplasms Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Date Completed
Ravi Bhatia, MD	None	None	None	9/27/16
Michael W. Deininger, MD, PhD	Bristol-Myers Squibb Company; Celgene Corporation; Gilead Sciences, Inc.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	ARIAD Pharmaceuticals, Inc.; CTI BioPharma Corp.; Novartis Pharmaceuticals Corporation; and Pfizer Inc.	None	8/31/16
Aaron T. Gerds, MD, MS	None	Cell Therapeutics, Inc.; and Incyte Corporation	None	9/8/16
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Gabriela Hobbs, MD	Incyte Corporation	None	None	10/28/16
Catriona Jamieson, MD, PhD	Cell Therapeutics, Inc.; GlaxoSmithKline; and Janssen Pharmaceutica Products, LP	None	None	6/17/16
Rebecca B. Klisovic, MD	Gilead Sciences, Inc.; and Novartis Pharmaceuticals Corporation	Novartis Pharmaceuticals Corporation; Pfizer Inc.; and Spectrum Pharmaceuticals, Inc.	None	10/5/16
Patricia Kropf, MD	None	Astex Pharmaceuticals, Inc.	Celgene Corporation; and Millennium Pharmaceuticals, Inc.	10/26/16
Ruben Mesa, MD	Cell Therapeutics, Inc.; Eli Lilly and Company; Gilead Sciences, Inc.; Incyte Corporation; NS Pharma, Inc.; Pfizer Inc.; PharmaEssentia Corp.; and Promedior, Inc.	ARIAD Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; and Shire plc	None	6/5/16
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Daniel A. Pollyea, MD, MS	AbbVie Inc.; Agios Pharmaceuticals; Celgene Corporation; FLX Bio, Inc.; Genentech, Inc.; GlycoMimetics, Inc.; and Pfizer Inc.	Alexion Pharmaceuticals, Inc.; ARIAD Pharmaceuticals, Inc.; Celgene Corporation; Karyopharm Therapeutics Inc.; and Pfizer Inc.	None	5/31/16
Raajit Rampal, MD, PhD	None	None	Cell Therapeutics, Inc.; and Incyte Corporation	6/5/16
Lindsay A. M. Rein, MD	None	None	None	6/17/16
Bart Scott, MD, MS	Alexion Pharmaceuticals, Inc.; Celgene Corporation; Genentech, Inc.; and Novartis Pharmaceuticals Corporation	Celgene Corporation	Alexion Pharmaceuticals, Inc.; Celgene Corporation; and Novartis Pharmaceuticals Corporation	6/14/16
David S. Snyder, MD	ARIAD Pharmaceuticals, Inc.; Bristol-Myers Squibb Company; Cell Therapeutics, Inc.; Janssen Pharmaceutica Products, LP; and Roche Laboratories, Inc.	ARIAD Pharmaceuticals, Inc.; and Incyte Corporation	None	4/19/16
Brady L. Stein, MD, MHS	Cell Therapeutics, Inc.; Incyte Corporation; and NS Pharma, Inc	UBC Late Stage	Incyte Corporation	4/7/16
Srdan Verstovsek, MD, PhD	AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Celgene Corporation; Cell Therapeutics, Inc.; Eli Lilly and Company; Galena BioPharma, Inc.; Genentech, Inc.; Geron Corporation; Gilead Sciences, Inc.; Incyte Corporation; NS Pharma, Inc; Pfizer Inc.; Promedior, Inc.; Roche Laboratories, Inc.; and Seattle Genetics	None	None	11/7/16
Martha Wadleigh, MD	None	None	None	5/9/16
Eunice S. Wang, MD	Immunogen Pharmaceuticals	Amgen Inc.; Seattle Genetics; and Spectrum Pharmaceuticals, Inc.	Incyte Corporation	10/11/16

The NCCN Guidelines Staff have no conflicts to disclose.