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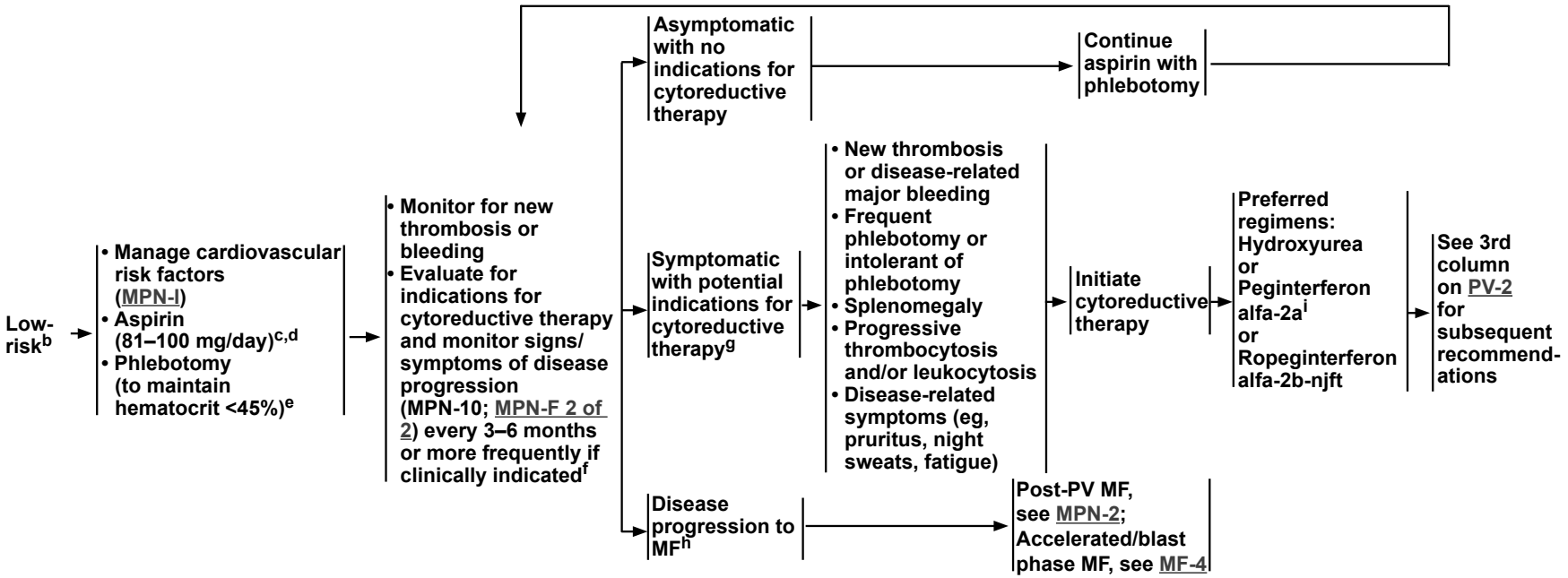
NCCN Clinical Practice Guidelines in Oncology
(NCCN Guidelines®)

Myeloproliferative Neoplasms

Overall management of Myeloproliferative Neoplasms is described in the full NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms. Visit NCCN.org to view the complete library of NCCN Guidelines®.

NCCN National Comprehensive Cancer Network®

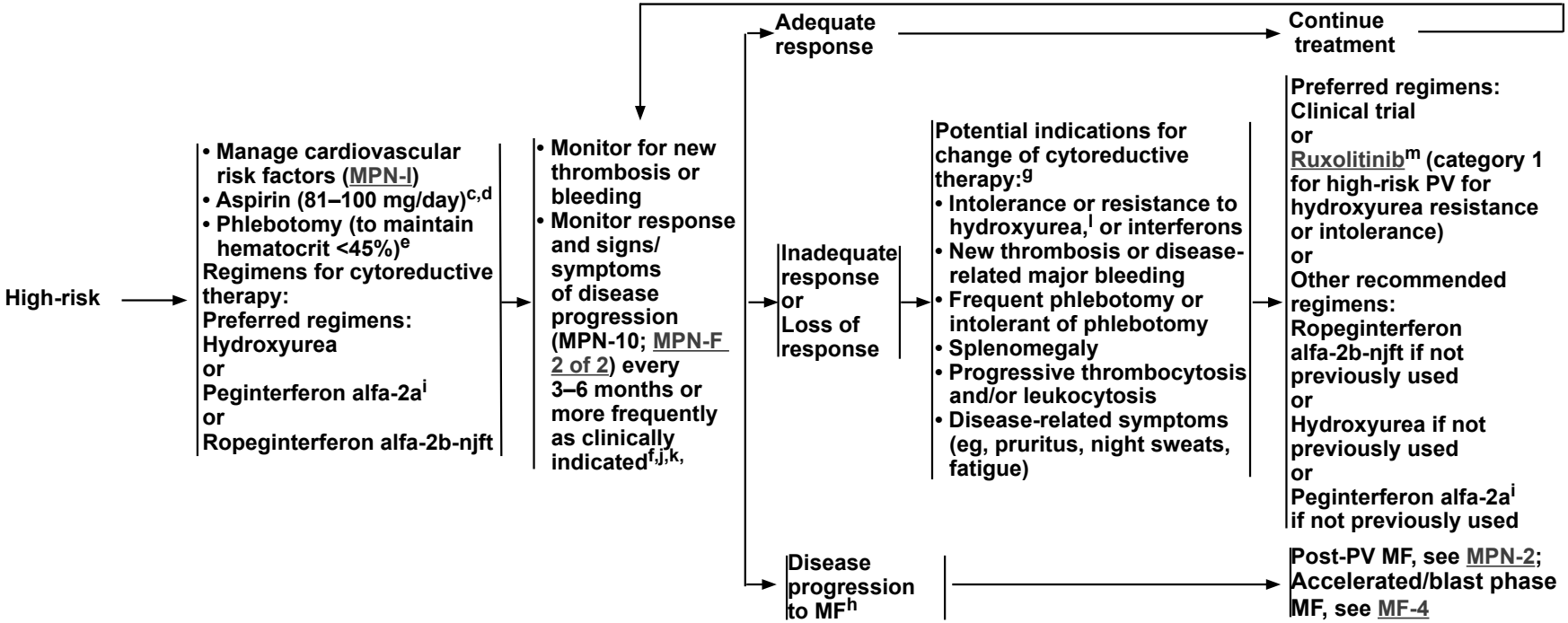
TREATMENT FOR LOW-RISK POLYCYTHEMIA VERA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-I).
[b] Cytoreductive therapy is not recommended as initial treatment.
[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al. Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] Hematocrit <45% is based on the data from the CYTO-PV study (Marchioli R, et al. N Engl J Med 2013;368:22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized (eg, 42% for female patients and/or progressive symptoms).
[f] Supportive Care for Patients with MPN (MPN-G).
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] See IWG-MRT Diagnostic Criteria for Post-PV and Post-ET Myelofibrosis (MPN-B)
[i] Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy.

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

TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA[a]



[a] Special Considerations in the Treatment of PV and ET (MPN-I).
[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.
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[f] Supportive Care for Patients with MPN (MPN-G).
[g] Barbui T, et al. Leukemia 2018;32:1057-1069.
[h] See IWG-MRT Diagnostic Criteria for Post-PV and Post-ET Myelofibrosis (MPN-B).
[i] Peginterferon alfa-2a is an option for younger patients or in pregnant patients in need of cytoreductive therapy.
[j] 2013 IWG-MRT and ELN Response Criteria for PV (PV-A). These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.
[k] While normalization of blood counts after initiation of treatment is usually a goal in clinical practice, it is not associated with long-term clinical benefit and there are no evidence-based data to recommend a target white blood cell (WBC) or platelet count for patients receiving cytoreductive therapy. In selected patients with a severe thrombotic event or other disease-related symptoms, normalization of blood counts might be an essential goal of treatment.
[l] Definition of intolerance/resistance to hydroxyurea (MPN-J).
[m] Ruxolitinib is FDA approved for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea. Ruxolitinib may have activity after inadequate response or loss of response to other agents besides hydroxyurea. See Discussion.

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

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

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

[1] Reproduced with permission from Barosi G, Mesa R, Finazzi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood 2013;121:4778-4781.
[2] These response criteria were developed mainly for use in clinical trials. Clinical benefit may not reach the threshold of the IWG-MRT Response Criteria. Response assessment should be done based on the improvement of disease-related symptoms at the discretion of the clinician.

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RISK STRATIFICATION FOR PATIENTS WITH POLYCYTHEMIA VERA[a]

MIPSS-PV

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

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

[a] Tefferi A, Guglielmelli P, Lasho TL, et al. Mutation-enhanced international prognostic systems for essential thrombocythaemia and polycythaemia vera. Br J Haematol 2020;189:291-302.

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National Comprehensive Cancer Network®

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IMPORTANT SAFETY INFORMATION

WARNING: RISK OF SERIOUS DISORDERS

Interferon alfa products may cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Patients should be monitored closely with periodic clinical and laboratory evaluations. Therapy should be withdrawn in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy.

CONTRAINDICATIONS

- Existence of, or history of severe psychiatric disorders, particularly severe depression, suicidal ideation, or suicide attempt
- Hypersensitivity to interferons including interferon alfa-2b or any of the inactive ingredients of BESREMi.
- Moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment
- History or presence of active serious or untreated autoimmune disease
- Immunosuppressed transplant recipients

WARNINGS AND PRECAUTIONS

- Depression and Suicide: Life-threatening or fatal neuropsychiatric reactions have occurred in patients receiving interferon alfa-2b products, including BESREMi. These reactions may occur in patients with and without previous psychiatric illness.

  Other central nervous system effects, including suicidal ideation, attempted suicide, aggression, bipolar disorder, mania and confusion have been observed with other interferon alfa products.

  Closely monitor patients for any symptoms of psychiatric disorders and consider psychiatric consultation and treatment if such symptoms emerge. If psychiatric symptoms worsen, it is recommended to discontinue BESREMi therapy.

- Endocrine Toxicity: These toxicities may include worsening hypothyroidism and hyperthyroidism. Do not use BESREMi in patients with active serious or untreated endocrine disorders associated with autoimmune disease. Evaluate thyroid function in patients who develop symptoms suggestive of thyroid disease during BESREMi therapy. Discontinue BESREMi in patients who develop endocrine disorders that cannot be adequately managed during treatment with BESREMi.

- Cardiovascular Toxicity: Toxicities may include cardiomyopathy, myocardial infarction, atrial fibrillation and coronary artery ischemia. Patients with a history of cardiovascular disorders should be closely monitored for cardiovascular toxicity during BESREMi therapy. Avoid use of BESREMi in patients with severe or unstable cardiovascular disease, (e.g., uncontrolled hypertension, congestive heart failure (≥ NYHA class 2), serious cardiac arrhythmia, significant coronary artery stenosis, unstable angina) or recent stroke or myocardial infarction.

- Decreased Peripheral Blood Counts: These toxicities may include thrombocytopenia (increasing the risk of bleeding), anemia, and leukopenia (increasing the risk of infection). Monitor complete blood counts at baseline, during titration and every 3-6 months during the maintenance phase. Monitor patients for signs and symptoms of infection or bleeding.

- Hypersensitivity Reactions: Toxicities may include serious, acute hypersensitivity reactions (e.g., urticaria, angioedema, bronchoconstriction, anaphylaxis). If such reactions occur, discontinue BESREMi and institute appropriate medical therapy immediately. Transient rashes may not necessitate interruption of treatment.

- Pancreatitis: Pancreatitis has occurred in 2.2% of patients receiving BESREMi. Symptoms may include nausea, vomiting, upper abdominal pain, bloating, and fever. Patients may experience elevated lipase, amylase, white blood cell count, or altered renal/hepatic function. Interrupt BESREMi treatment in patients with possible pancreatitis and evaluate promptly. Consider discontinuation of BESREMi in patients with confirmed pancreatitis.

- Colitis: Fatal and serious ulcerative or hemorrhagic/ischemic colitis have occurred in patients receiving interferon alfa products, some cases starting as early as 12 weeks after start of treatment. Symptoms may include abdominal pain, bloody diarrhea, and fever. Discontinue BESREMi in patients who develop these signs or symptoms. Colitis may resolve within 1 to 3 weeks of stopping treatment.

- Pulmonary Toxicity: Pulmonary toxicity may manifest as dyspnea, pulmonary infiltrates, pneumonia, bronchiolitis obliterans, interstitial pneumonitis, pulmonary hypertension, and sarcoidosis. Some events have resulted in respiratory failure or death. Discontinue BESREMi in patients who develop pulmonary infiltrates or pulmonary function impairment.

- Ophthalmologic Toxicity: These toxicities may include severe eye disorders such as retinopathy, retinal hemorrhage, retinal exudates, retinal detachment and retinal artery or vein occlusion which may result in blindness. During BESREMi therapy, 23% of patients were identified with an eye disorder. Eyes disorders ≥5% included cataract (6%) and dry eye (5%). Advise patients to have eye examinations before and during BESREMi therapy, specifically in those patients with a retinopathy-associated disease such as diabetes mellitus or hypertension. Evaluate eye symptoms promptly. Discontinue BESREMi in patients who develop new or worsening eye disorders.

- Hyperlipidemia: Elevated triglycerides may result in pancreatitis. Monitor serum triglycerides before BESREMi treatment and intermittently during therapy and manage when elevated. Consider discontinuation of BESREMi in patients with persistently, markedly elevated triglycerides.

- Hepatotoxicity: These toxicities may include increases in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT) and bilirubin. Liver enzyme elevations have also been reported in patients after long-term BESREMi therapy. Monitor liver enzymes and hepatic function at baseline and during BESREMi treatment. Discontinue BESREMi in patients who develop evidence of hepatic decompensation (characterized by jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome or variceal hemorrhage) during treatment

- Renal Toxicity: Monitor serum creatinine at baseline and during therapy. Avoid use of BESREMi in patients with eGFR <30 mL/min. Discontinue BESREMi if severe renal impairment develops during treatment.

- Dental and Periodontal Toxicity: These toxicities may include dental and periodontal disorders, which may lead to loss of teeth. In addition, dry mouth could have a damaging effect on teeth and mucous membranes of the mouth during long-term treatment with BESREMi. Patients should have good oral hygiene and regular dental examinations.

- Dermatologic Toxicity: These toxicities have included skin rash, pruritus, alopecia, erythema, psoriasis, xeroderma, dermatitis acneiform, hyperkeratosis, and hyperhidrosis. Consider discontinuation of BESREMi if clinically significant dermatologic toxicity occurs.

- Driving and Operating Machinery: BESREMi may impact the ability to drive and use machinery. Patients should not drive or use heavy machinery until they know how BESREMi affects their abilities. Patients who experience dizziness, somnolence or hallucination during BESREMi therapy should avoid driving or using machinery.

- Embryo-Fetal Toxicity: Based on the mechanism of action, BESREMi can cause fetal harm when administered to a pregnant woman. Pregnancy testing is recommended in females of reproductive potential prior to treatment with BESREMi. Advise females of reproductive potential to use an effective method of contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

ADVERSE REACTIONS

The most common adverse reactions reported in > 40% of patients in the PEGINVERA study (n=51) were influenza-like illness, arthralgia, fatigue, pruritis, nasopharyngitis, and musculoskeletal pain. In the pooled safety population (n=178), the most common adverse reactions greater than 10%, were liver enzyme elevations (20%), leukopenia (20%), thrombocytopenia (19%), arthralgia (13%), fatigue (12%), myalgia (11%), and influenza-like illness (11%).

DRUG INTERACTIONS

Patients on BESREMi who are receiving concomitant drugs which are CYP450 substrates with a narrow therapeutic index should be monitored to inform the need for dosage modification for these concomitant drugs. Avoid use with myelosuppressive agents and monitor patients receiving the combination for effects of excessive myelosuppression. Avoid use with narcotics, hypnotics or sedatives and monitor patients receiving the combination for effects of excessive CNS toxicity.

USE IN SPECIFIC POPULATIONS

- Pregnancy: Based on mechanism of action and the role of interferon alfa in pregnancy and fetal development, BESREMi may cause fetal harm and should be assumed to have abortifacient potential when administered to a pregnant woman. There are adverse effects on maternal and fetal outcomes associated with polycythemia vera in pregnancy. Advise pregnant women of the potential risk to a fetus.

- Lactation: There are no data on the presence of BESREMi in human or animal milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed children from BESREMi, advise women not to breastfeed during treatment and for 8 weeks after the final dose.

- Females of Reproductive Potential: BESREMi may cause embryo-fetal harm when administered to a pregnant woman. Pregnancy testing prior to BESREMi treatment is recommended for females of reproductive potential. Advise female patients of reproductive potential to use effective contraception during treatment with BESREMi and for at least 8 weeks after the final dose.

- Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

- Geriatric Use: In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function and of concomitant disease or other therapy.

Please see accompanying full Prescribing Information, including Boxed Warning.

INDICATION

BESREMi is indicated for the treatment of adults with polycythemia vera