Polycythemia Vera: Disease State Overview

MI-DIS-US-0079 03/26

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BACK

MPN Epidemiology and Overview

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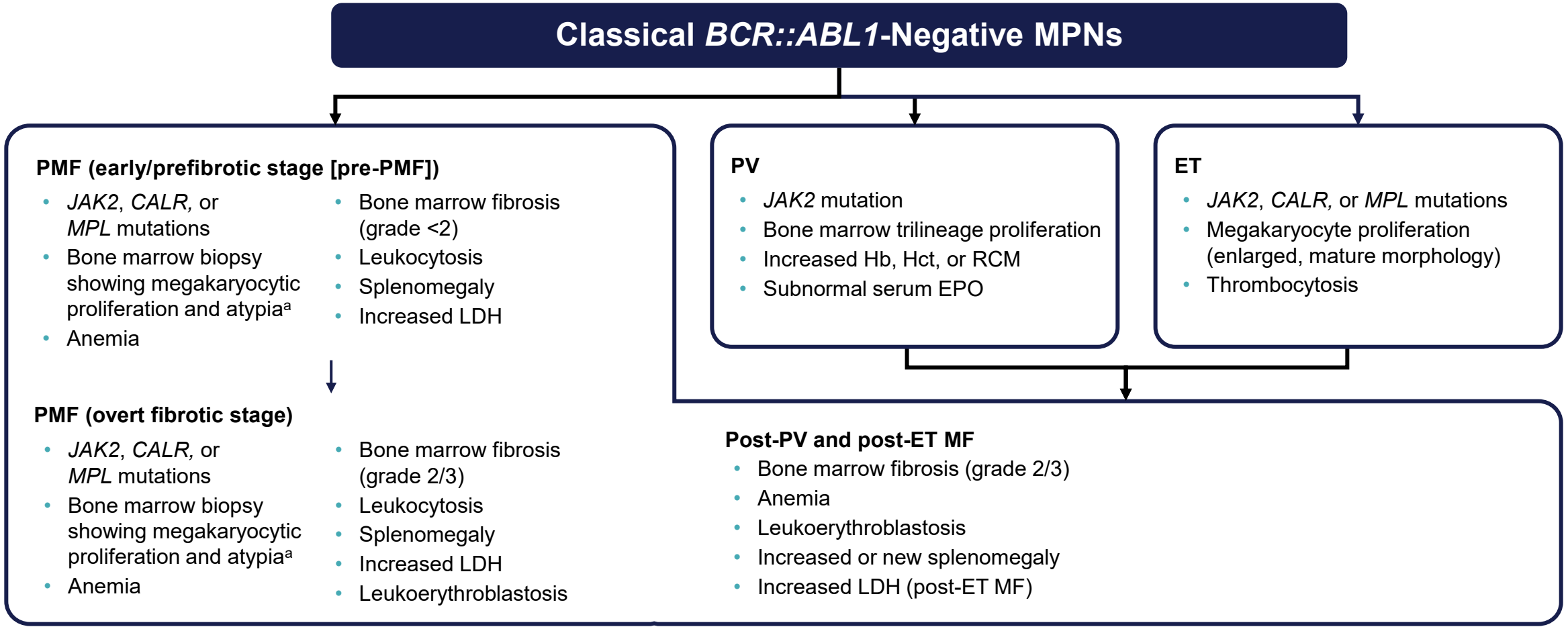
MF, PV, and ET Are *BCR::ABL1*-Negative MPNs



[a] Morphology of megakaryocytes in pre-PMF and overt PMF usually demonstrates a higher degree of megakaryocytic atypia than in any other MPN subtype.
ABL1, Abelson murine leukemia viral oncogene homolog 1; BCR, breakpoint cluster region; CALR, calreticulin; EPO, erythropoietin; ET, essential thrombocytopenia; Hb, hemoglobin; Hct, hematocrit; JAK, Janus kinase; LDH, lactate dehydrogenase; MF, myelofibrosis; MPL, myeloproliferative leukemia proto-oncogene, thrombopoietin receptor; MPN, myeloproliferative neoplasm; PMF, primary MF; PV, polycythemia vera; RCM, red blood cell mass.
Arber DA, et al. *Blood.* 2022;140:1200-1228.

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MPNs Are Rare and Usually Develop Later in Life

	MF	PV	ET
Prevalence	4-6 cases per 100,000[1]	44-57 cases per 100,000[1]	38-57 cases per 100,000[1]
Incidence	2-3 cases per 100,000 patient-years[1]	1.57 cases per 100,000 patient-years[2]	1.55 cases per 100,000 patient-years[2]
Median age at diagnosis	65 years; slightly more common in men than in women, with men making up ≈60% of patients[3]	61-62 years; similar frequency in men and women[4-6]	58 years[4]
Bone marrow abnormalities	Excess fibrous tissue, megakaryocytes proliferation and atypia[7]	Bone marrow trilineage proliferation and pleomorphic megakaryocytes[7]	Increased megakaryocytes[7]
Blood cell abnormalities	Reduced RBCs, increased WBCs[7]	Elevated Hb, evelated Hct, increased RCM[7]	Elevated platelets[7]
% with *JAK2* mutation	*JAK2*V617F mutation: ≈60% of patients[8]	*JAK2*V617F mutation: ≈96% of patients[9] *JAK2* exon 12 mutation: ≈3% of patients[9]	*JAK2*V617F mutation: ≈55% of patients[9]
% with *CALR* mutation[a]	≈35% of patients[10]	Not observed[10]	≈25% of patients[10]
Median survival	3.6-7.4 years[2,4,11,12]	11.9-14.1 years[2,4,5,11,12]	12.0-20.6 years[2,4,11-13]

[a] Based on an MPN cohort of 896 patients.[10]

RBC, red blood cell; WBC, white blood cell.

1. Mehta J, et al. *Leuk Lymphoma*. 2014;55:595-600. 2. Verstovsek S, et al. *Leuk Lymphoma.* 2022;63:694-702. 3. Gangat N, et al. *J Clin Oncol*. 2010;29:392-397. 4. Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610. 5. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. 6. Tefferi A, et al. *Am J Hematol.* 2023; 98(9):1465-1487. 7. Arber DA, et al. *Blood.* 2022;140:1200-1228. 8. Rafati M, et al. *Blood Adv.* 2023;7(24):7506-7515. 9. Tefferi A. *Am J Hematol*. 2021;96:145-162. 10. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390. 11. Tefferi A, et al. *Blood*. 2014;124:2507-2513. 12. Smith CJ, et al. *Am J Hematol*. 2021;96:E464-E468. 13. Gangat N, et al. *Blood Cancer J*. 2024;14:11.

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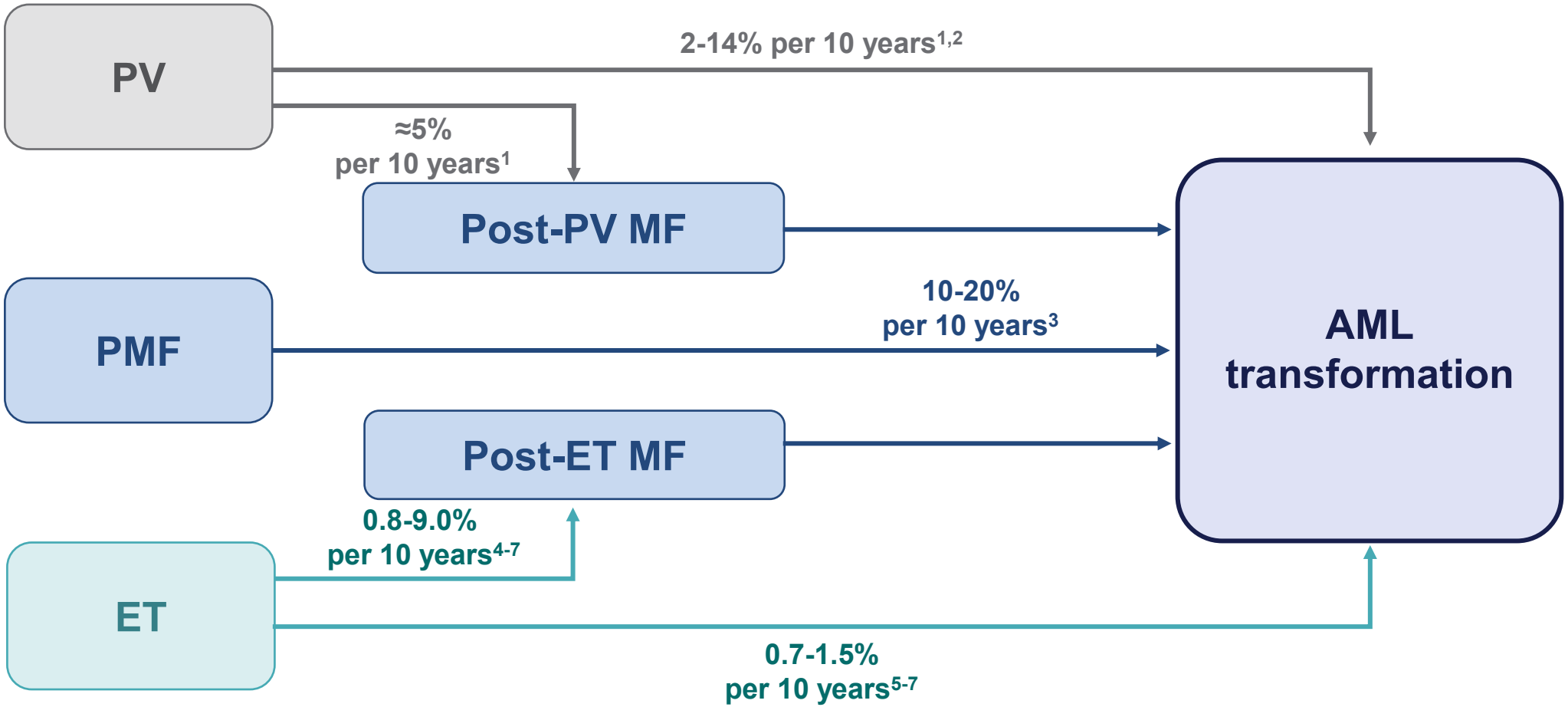
MPN Disease Progression and Transformation



AML, acute myeloid leukemia.

1. Cerquozzi S, Tefferi A. *Blood Cancer J*. 2015;5:e366. 2. Tefferi A, et al. *Leukemia.* 2013;27(9):1874-1881. 3. Yogarajah M, Tefferi A. *Mayo Clin Proc*. 2017;92(7):1118-1128. 4. Arber DA, et al. *Blood.* 2022;140:1200-1228. 5. Tefferi A, et al. *Am J Hematol.* 2024;99:697-718. 6. Gangat N, et al. *Blood Cancer J*. 2024;14:11. 7. Barbui T, et al. *J Clin Oncol*. 2011;29(23):3179-3184.

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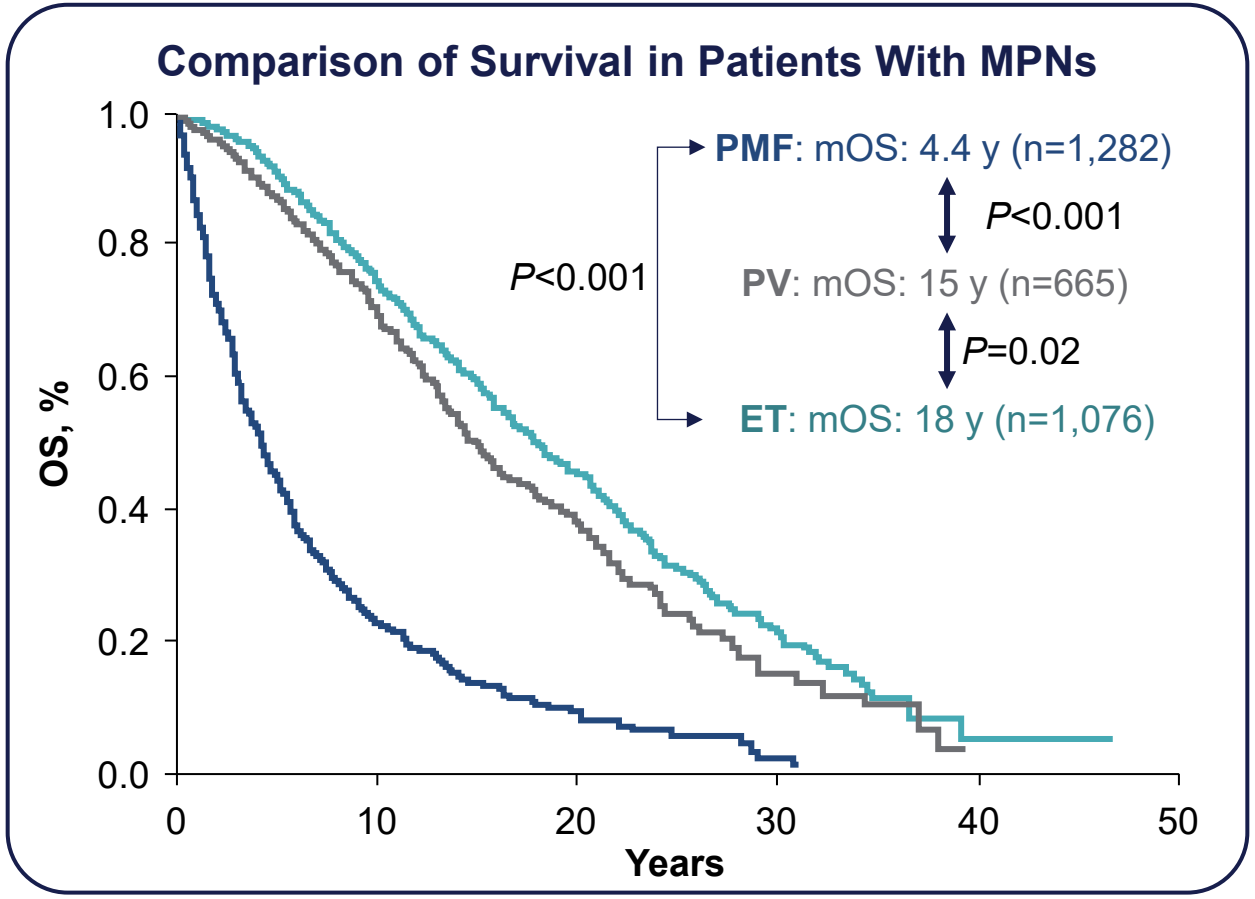
MPN Survival Outcomes



MPN	Median survival (all patients)
PMF	4.4 years
PV	15 years
ET	18 years

MPN	Median survival (high-risk patients)
PMF	1.5 years
PV	9.6 years
ET	10.2 years

mOS, median OS; OS, overall survival.

Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610.

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BACK

Polycythemia Vera

- Mechanism of Disease
- Disease Characteristics
- Clinical Work-Up, Diagnosis, and Stratification

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BACK

Mechanism of Disease

Polycythemia Vera

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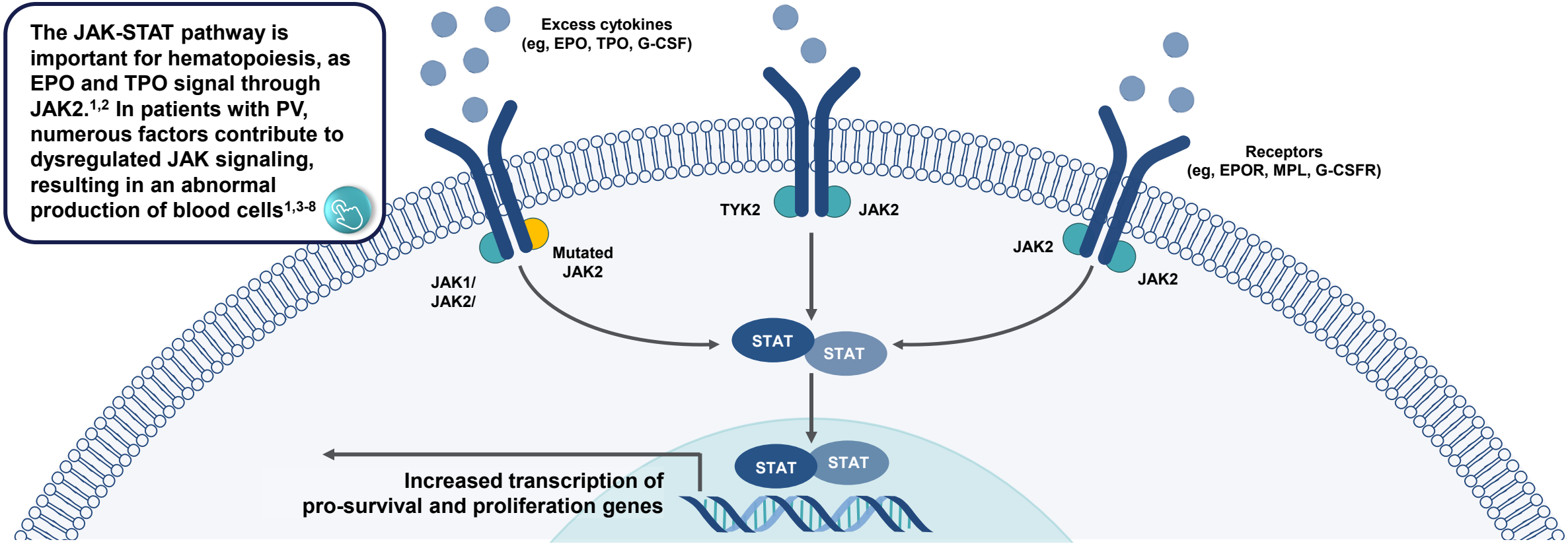
Overactive JAK Signaling Contributes to the Pathogenesis of PV, Leading to Abnormal Blood Cell Production

The JAK-STAT pathway is important for hematopoiesis, as EPO and TPO signal through JAK2.[1,2] In patients with PV, numerous factors contribute to dysregulated JAK signaling, resulting in an abnormal production of blood cells[1,3-8]



EPO, erythropoietin; EPOR, erythropoietin receptor; G-CSF, granulocyte colony-stimulating factor; G-CSFR, granulocyte colony-stimulating factor receptor; JAK, Janus kinase; MPL, MPL proto-oncogene thrombopoietin receptor; PV, polycythemia vera; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TYK2, tyrosine protein kinase 2.

1. Quintás-Cardama A, et al. *Nat Rev Drug Discov.* 2011;10:127-140. 2. JAKAFI® (ruxolitinib). Prescribing information. Incyte Corporation; Jan 2023. 3. Meyer SC, Levine RL. *Clin Cancer Res*. 2014;20:2051-2059. 4. Vainchenker W, et al. *Blood.* 2011;118:1723-1735. 5. Schafer AI. *Blood*. 2006;107:4214-4222. 6. Mascarenhas J, et al. *Curr Med Chem*. 2012;19:4399-4413. 7. Vannucchi AM, et al. *CA Cancer J Clin*. 2009;59:171-191. 8. Spivak JL. *Ann Intern Med*. 2010;152:300-306. 9. Barosi G, et al. *Blood*. 2009;113:4829-4833. 10. Baxter EJ, et al. *Lancet*. 2005;365:1054-1061.

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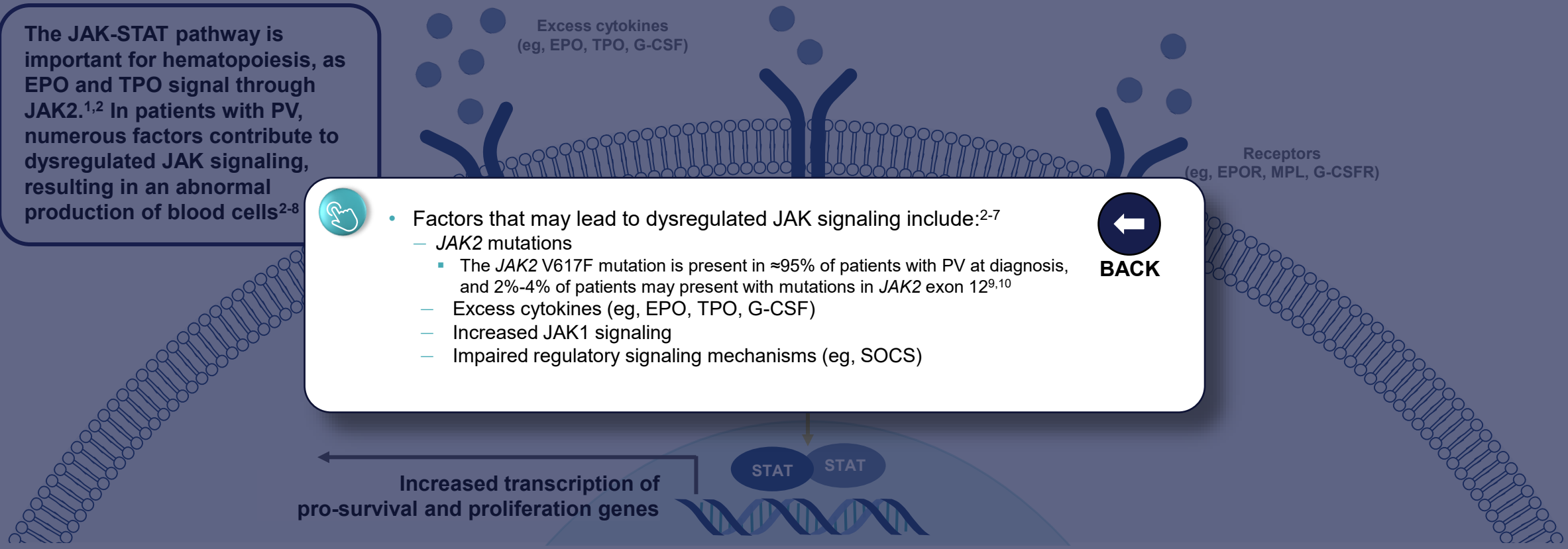
Overactive JAK Signaling Contributes to the Pathogenesis of PV, Leading to Abnormal Blood Cell Production

The JAK-STAT pathway is important for hematopoiesis, as EPO and TPO signal through JAK2.[1,2] In patients with PV, numerous factors contribute to dysregulated JAK signaling, resulting in an abnormal production of blood cells[2-8]



- Factors that may lead to dysregulated JAK signaling include:[2-7]
  - *JAK2* mutations
    - The *JAK2* V617F mutation is present in ≈95% of patients with PV at diagnosis, and 2%-4% of patients may present with mutations in *JAK2* exon 12[9,10]
  - Excess cytokines (eg, EPO, TPO, G-CSF)
  - Increased JAK1 signaling
  - Impaired regulatory signaling mechanisms (eg, SOCS)

BACK

EPO, erythropoietin; EPOR, erythropoietin receptor; G-CSF, granulocyte colony-stimulating factor; G-CSFR, granulocyte colony-stimulating factor receptor; JAK, Janus kinase; MPL, MPL proto-oncogene thrombopoietin receptor; PV, polycythemia vera; SOCS, suppressor of cytokine signaling; STAT, signal transducer and activator of transcription; TPO, thrombopoietin; TYK2, tyrosine protein kinase 2.

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BACK

Disease Characteristics

Polycythemia Vera

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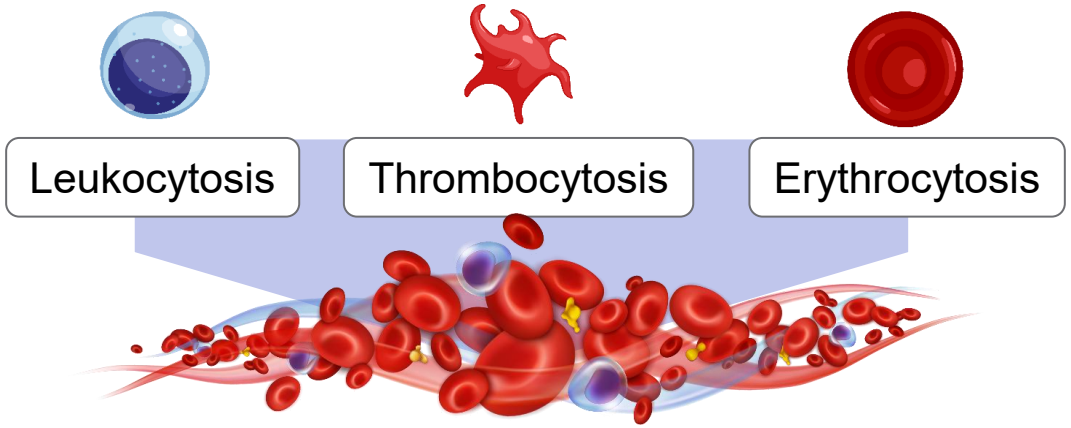
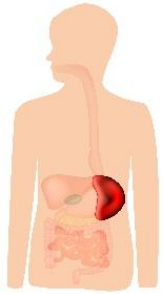
PV Is Characterized by Elevated Blood Counts, Splenomegaly, and Numerous Nonspecific Symptoms

Increased Myeloproliferation[1]



Splenomegaly[1]



Substantial Symptom Burden[2,a]

- Fatigue
- Early satiety
- Abdominal discomfort
- Inactivity
- Concentration problems
- Night sweats
- Itching
- Bone pain
- Weight loss

[a] This list is based on the 10 symptoms used to assess and validate the MPN-SAF TSS in 1,433 patients with MPNs.
MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, Total Symptom Score.

1. Spivak JL. *Ann Intern Med*. 2010;152:300-306. 2. Emanuel RM, et al. *J Clin Oncol*. 2012;30:4098-4103.

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Patients Typically Present With 1 of 3 Clinical Scenarios[1]

Asymptomatic	Symptomatic	Thrombotic Event
Some patients are asymptomatic and are diagnosed because of incidental findings on laboratory blood tests[1,2]	Approximately half of patients present with PV-related symptoms at diagnosis, resulting from erythrocytosis or thrombocytosis[3,4]	Approximately one-third of patients are diagnosed after experiencing a thrombotic event[5]

Over the course of the disease, many patients can develop new or progressive symptoms[4,6,7]

1. Raedler LA. *Am Health Drug Benefits*. 2014;7:S36-S47. 2. Passamonti F, et al. *Haematologica*. 2000;85:1011-1018. 3. Stein B, et al. ASH 2015. Abstract 2813. 4. Mesa R, et al. *BMC Cancer*. 2016;16:167. 5. Falanga A, Marchetti M. *Semin Thromb Hemost*. 2014;40:348-358. 6. Reiter A, Harrison C. *Curr Hematol Malig Rep*. 2016;11:356-367. 7. Scherber R, et al. *Blood*. 2011;118:401-408.

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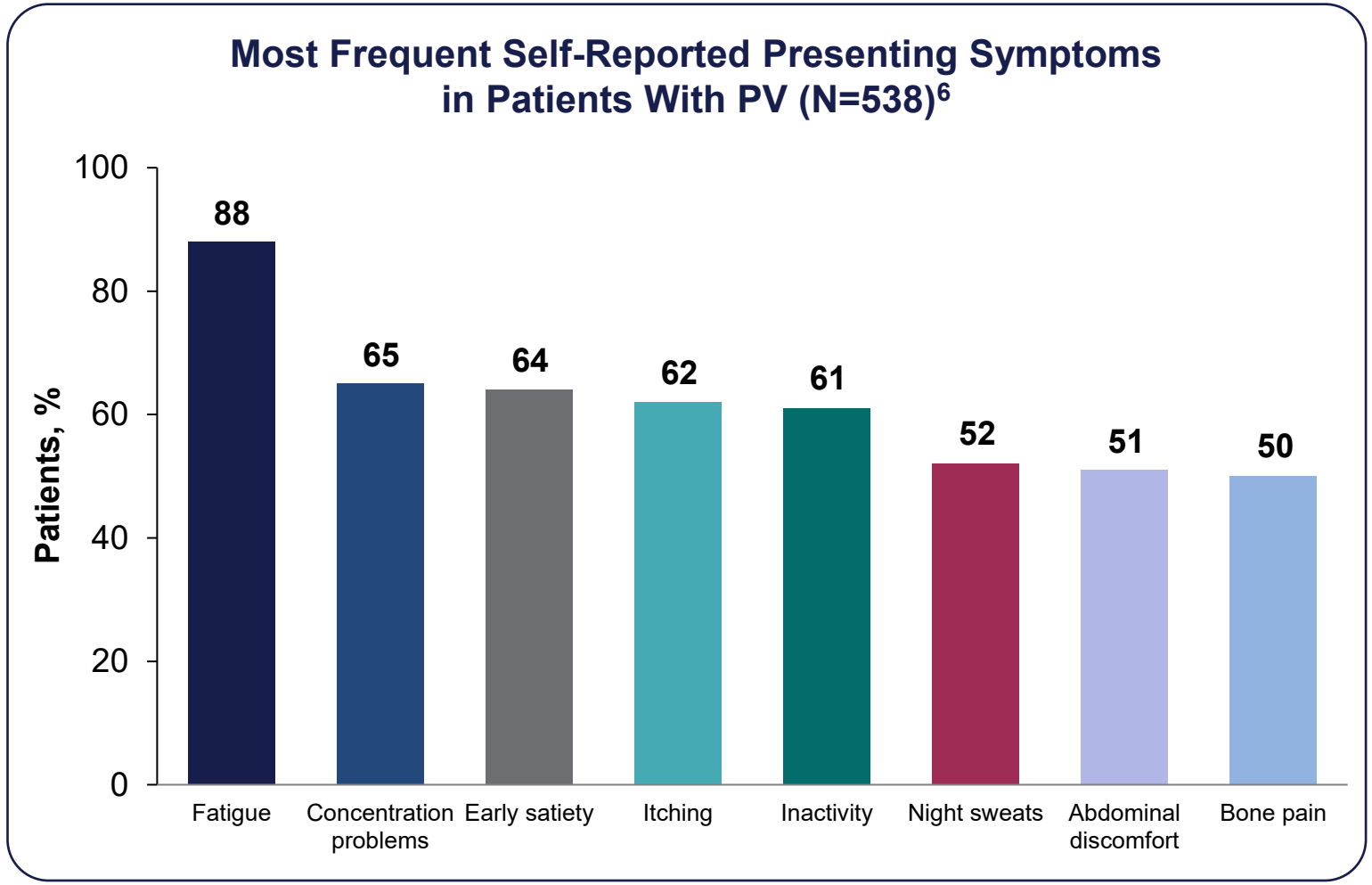
Symptom Presentation May Vary From Patient to Patient

- Some patients are asymptomatic or have vague symptoms at diagnosis[1-3]
- Types of symptoms and their severity:[4,5]
  - Vary among patients
  - Can evolve over time
  - Occur independently of blood counts, duration of disease, and treatment
- Across a number of studies, the most common symptoms of PV include fatigue and pruritus[1,4-10]



1. Stein B, et al. ASH 2015. Abstract 2813. 2. Raedler LA. *Am Health Drug Benefits*. 2014;S36-S47. 3. Passamonti F, et al. *Haematologica*. 2000;85:1011-1018. 4. Reiter A, Harrison C. *Curr Hematol Malig Rep*. 2016;11:356-367. 5. Scherber R, et al. *Blood*. 2011;118:401-408. 6. Emanuel RM, et al. *J Clin Oncol*. 2012;30:4098-4103. 7. Mesa R, et al. *BMC Cancer*. 2016;16:167. 8. Mesa RA, et al. *Cancer*. 2007;109:68-76. 9. Geyer HL, et al. *Blood*. 2014;123:3803-3810. 10. Geyer H, et al. *J Clin Oncol*. 2016;34:151-159.

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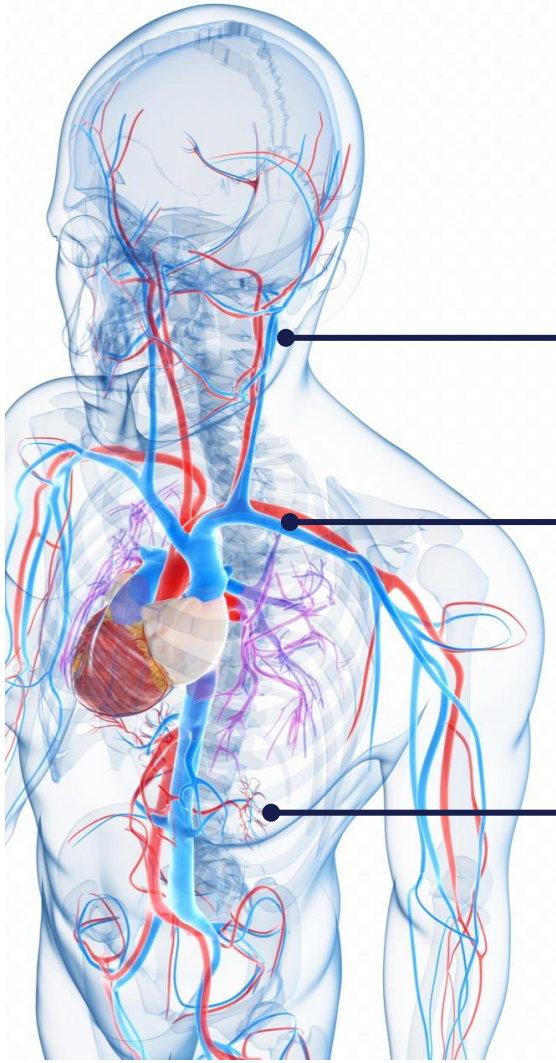
Thrombosis Is a Common Complication of PV and Is Associated With Significant Morbidity and Mortality[1,2]



Venous Thrombosis

Clinical Manifestations

- Deep venous thrombosis (legs and arms)
- Pulmonary embolism
- Superficial venous thrombosis
- Unusual sites of venous thrombosis (visceral vein thrombosis and cerebral sinus)

>12% of patients[3]

Arterial Thrombosis

Clinical Manifestations

- Myocardial infarction
- Unstable angina
- Ischemic stroke
- Transient ischemic attack
- Acute peripheral and visceral thromboembolism

>17% of patients[3]

Microcirculatory Disturbances

Clinical Manifestations

- Erythromelalgia
- Seizures
- Migraine
- Vertigo
- Tinnitus
- Scintillating scotomas
- Amaurosis fugax

1. Falanga A, Marchetti M. *Hematology Am Soc Hematol Educ Program*. 2012;2012:571-581. 2. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881.
3. Marchioli R, et al. *N Engl J Med*. 2013;368:22-33.

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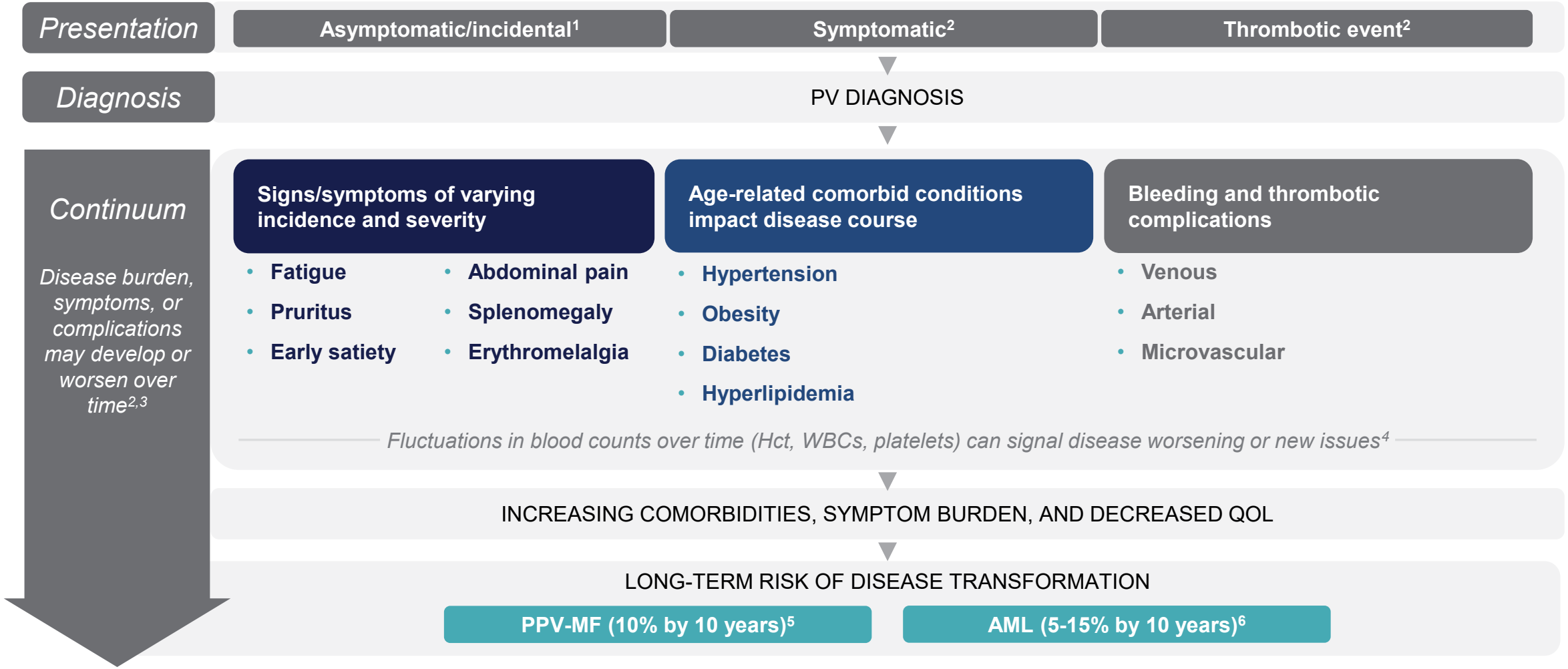
Disease Evolution and Principal Morbidities



AML, acute myeloid leukemia; PPV-MF, post–polycythemia vera myelofibrosis; QOL, quality of life; WBC, white blood cell.

1. Spivak JL. *Blood*. 2002;100:4272-4290. 2. Elliott MA, Tefferi A. *Br J Haematol*. 2005;128:275-290. 3. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881.
4. Stein BL, et al. *J Clin Oncol*. 2015;33:3953-3960. 5. Tefferi A. *Am J Hematol*. 2008;83:491-497. 6. Finazzi G, et al. *Blood*. 2005;105:2664-2670.

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BACK

Clinical Work-Up, Diagnosis, and Stratification

Polycythemia Vera

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PV Diagnosis Requires a Comprehensive Evaluation and Work-Up

History and physical[1,2]

- Asymptomatic or presenting with symptoms, including:
  - Fatigue
  - Early satiety
  - Inactivity
  - Pruritus
  - Problems with concentration
  - Abdominal discomfort
  - Night sweats
  - Bone pain
  - Thrombosis
  - Bleeding
  - Headache

Blood tests[2-4]

- Various blood tests can show:
  - Elevated Hb, Hct, RCM
  - Elevated WBCs and PLT
  - Low EPO
  - *JAK2* mutation at V617F or exon 12

Bone marrow biopsy[3]

- Evaluates presence and degree of hypercellularity with trilineage proliferation

PLT, platelet; RCM, red blood cell mass.

1. Tefferi A, Barbui T. *Am J Hematol.* 2023;98:1465-1487. 2. Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk.* 2019;19:579-584.e1. 3. Arber DA, et al. *Blood.* 2022;140:1200-1228. 4. Pemmaraju N, et al. *Expert Rev Hematol.* 2025;18:529-536.

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Diagnostic Criteria for PV

International Consensus Classification of Myeloid Neoplasms and Acute Leukemias

☑ Must meet either 3 major criteria or the first 2 major criteria plus the minor criterion[a]

Major

- ☐ Elevated Hb concentration or elevated Hct or increased RCM[b]
- ☐ Presence of *JAK2*V617F or *JAK2* exon 12 mutation[c]
- ☐ Bone marrow biopsy showing age-adjusted hypercellularity with trilineage proliferation (panmyelosis), including prominent erythroid, granulocytic, and increase in pleomorphic, mature megakaryocytes without atypia

Minor

- ☐ Subnormal sEPO level

[a] A bone marrow biopsy may not be required in patients with sustained absolute erythrocytosis (Hb concentrations of >18.5 g/dL in men or >16.5 g/dL in women and Hct values of >55.5% in men or >49.5% in women) and the presence of a *JAK2*V617F or *JAK2* exon 12 mutation. [b] Diagnostic thresholds: Hb: 16.5 g/dL in men and 16.0 g/dL in women; hematocrit: 49% in men and 48% in women; RCM: 25% above mean normal predicted value. [c] It is recommended to use highly sensitive assays for *JAK2*V617F (sensitivity level <1%); in negative cases, consider searching for noncanonical or atypical *JAK2* mutations in exons 12 to 15.

sEPO, serum erythropoietin.

Arber DA, et al. *Blood.* 2022;140:1200-1228.

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Risk Stratification With the Goal of Controlling Hct and Reducing the Risk of Thrombotic Events[1]

Traditional risk factors for thrombosis in PV include advanced age and a previous history of thrombosis[1]

Low risk[1]

- NO HISTORY OF THROMBOSIS
- ≤60 YEARS OF AGE

High risk[1]

HISTORY OF THROMBOSIS

OR

>60

>60 YEARS OF AGE

Studies suggest that more than 70% of patients diagnosed with PV may be considered high risk[3,4]

Additional considerations[1,2]

- Leukocytosis
- *JAK2*V617F allele burden
- Intensity of phlebotomy
- Elevated Hct
- CV risk factors, including prior arterial event, hypertension, hyperlipidemia, and diabetes

Failure to maintain an Hct <45% has been associated with a significantly increased risk of major thrombosis or CV-related death[2]

CV, cardiovascular.

1. Tefferi A, Barbui T. *Am J Hematol.* 2023;98(9):1465-1487. 2. Marchioli R, et al. *N Engl J Med*. 2013;368:22-33. 3. Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk.* 2020;20:219-225. 4. Kuykendall A, et al. *Expert Rev Hematol.* 2025;18(11):979-986.

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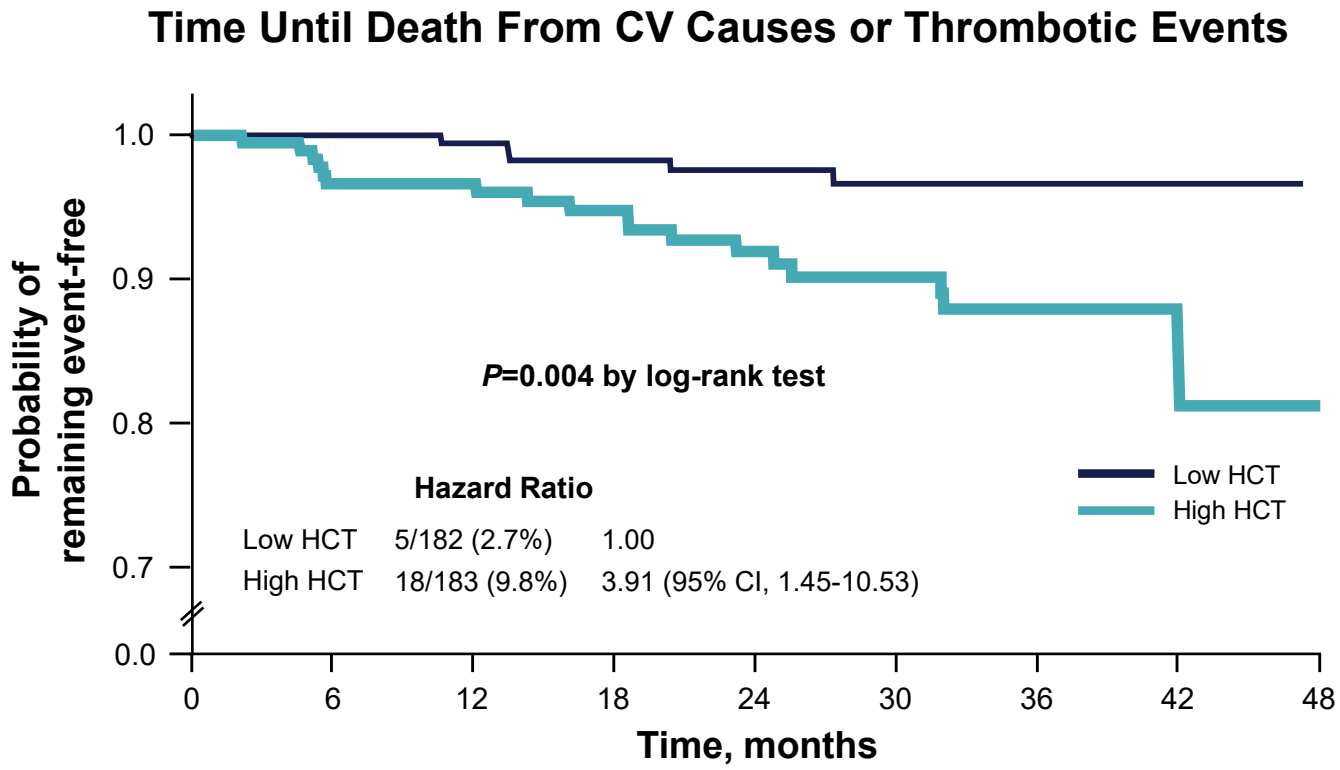
CYTO-PV: Study Findings Helped Establish an Hct Target of <45%



The rate of major thrombosis or death from CV events was **4-fold lower in patients who maintained an Hct target of <45%** compared with those with a target of 45-50%

CI, confidence interval; CYTO-PV, Cytoreductive Therapy in Polycythemia Vera.
Marchioli R, et al. *N Engl J Med*. 2013;368:22-33.

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PV Management Goals

Control Hct <45%[1,2]

Maintaining Hct <45% may lower CV mortality or major thrombosis[3,4]

Reduce risk of thrombotic events[1,5]

12-13% or 15-17% of patients with PV may have a history of venous or arterial thrombotic events at diagnosis, respectively[3,6]

Manage PV disease–related symptoms[1,5]

Symptoms and their severity vary among patients, can evolve over time, and may persist despite control of blood counts[7,8]

Modification of CV risk factors[2]

CV risk factors are taken into consideration when determining risk stratification and treatment[1,2]

1. Tefferi A, Barbui T. *Am J Hematol.* 2023;98:1465-1487. 2. Kuykendall AT, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24:512-522. 3. Marchioli R, et al. *N Engl J Med*. 2013;368:22-33. 4. Parasuraman S, et al. *Ann Hematol.* 2019;98:2533-2539. 5. Spivak JL. *Blood.* 2019;134:341-352. 6. Szuber N, et al. *Mayo Clin Proc.* 2019;94:599-610. 7. Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:219-225. 8. Cuthbert D, Stein BL. *J Blood Med.* 2019;10:359-371.

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PV Summary

- Patients with PV can present with a heterogeneous constellation of clinical features and symptoms, complicating diagnosis[1,2]
  - Fatigue, early satiety, inactivity, pruritus, and problems with concentration are some of the common symptoms[3]
  - Bone marrow biopsy is included in the International Consensus Classification of Myeloid Neoplasms and Acute Leukemias as one of the major diagnostic criteria for PV, as it may facilitate diagnosis and provide a baseline assessment of the disease[2,4,5]
- PV is associated with a substantial symptom burden and increased risk of thrombotic and bleeding complications, which can substantially impact QOL and survival[2,6-8]
- PV management goals are centered around the following:
  - Maintaining Hct <45%[2,9]
  - Reducing the risk of thrombotic events[2,10]
  - Managing disease-related symptoms[2,10]
  - Modifying CV risk factors[9]

1. Raedler LA. *Am Health Drug Benefits*. 2014;7:S36-S47. 2. Tefferi A, Barbui T. *Am J Hematol.* 2023;98:1465-1487. 3. Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk.* 2020;20:219-225. 4. Arber DA, et al. *Blood.* 2022;140:1200-1228. 5. Thiele J, et al. *Am J Hematol.* 2023;98:166-179. 6. Mesa R, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:590-596. 7. Tremblay D, et al. *JAMA*. 2025;333:153-160. 8. Pemmaraju N, et al. *Leuk Res.* 2022;115:106809. 9. Kuykendall AT, et al. *Clin Lymphoma Myeloma Leuk*. 2024;24:512-522. 10. Spivak JL. *Blood.* 2019;134:341-352.

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