Polycythemia Vera: Disease State Overview

MI-DIS-US-0079 09/25

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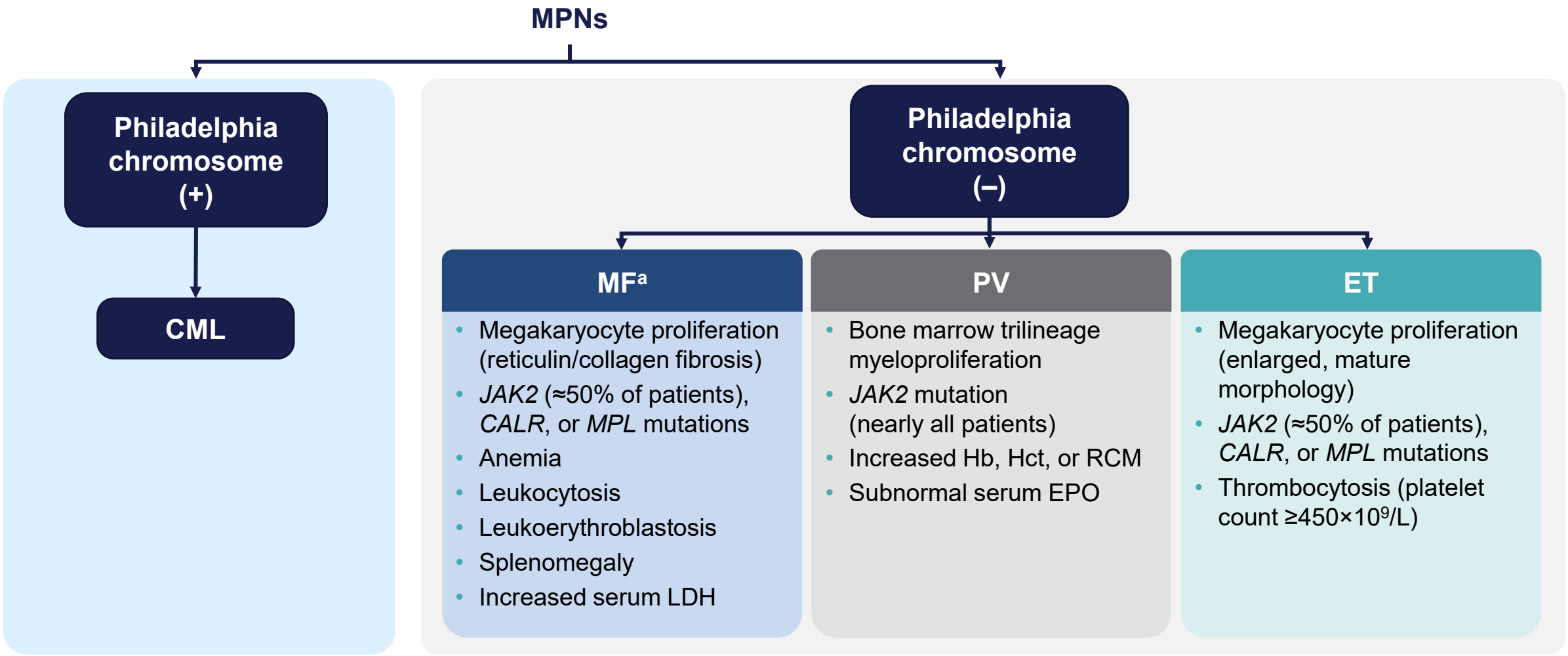
MPN Epidemiology and Overview

MF, PV, and ET Are Philadelphia-Negative MPNs



[a] MF includes primary MF, post-PV MF, and post-ET MF.

CALR, calreticulin; CML, chronic myeloid leukemia; EPO, erythropoietin; ET, essential thrombocythemia; Hb, hemoglobin; Hct, hematocrit; JAK2, Janus kinase 2; LDH, lactate dehydrogenase; MF, myelofibrosis; MPL, MPL proto-oncogene thrombopoietin receptor; MPNs, myeloproliferative neoplasms; PV, polycythemia vera; RCM, red cell mass.

Arber DA, et al. *Blood*. 2016;127:2391-2405.

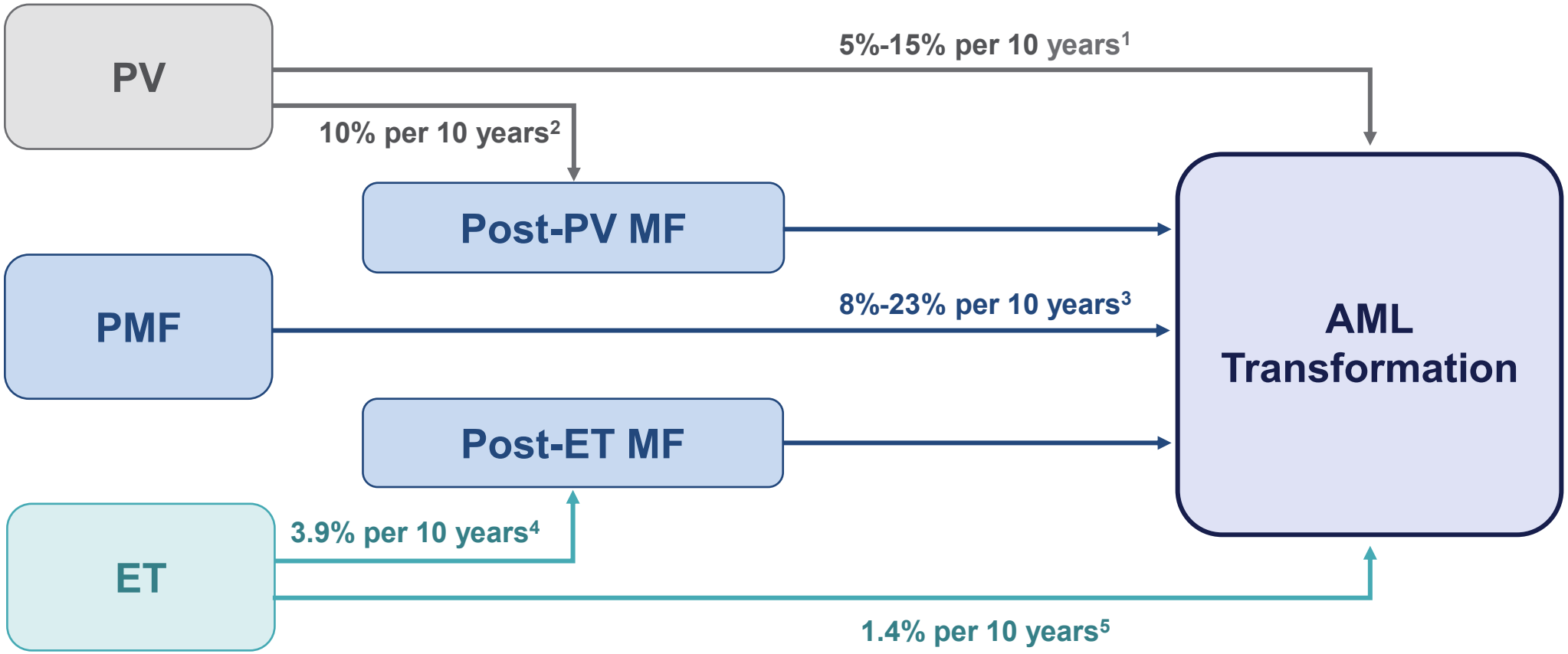
MPNs Are Rare and Usually Develop Later in Life

	MF	PV	ET
Prevalence	4-6 cases per 100,000[1,2]	44-57 cases per 100,000[1,3]	38-57 cases per 100,000[1]
Incidence	≈2-3 cases per 100,000[1,2]	≈1-3 cases per 100,000[4]	2.0-2.4 cases per 100,000[1,5]
Median age at diagnosis	>65 years and slightly more common in men than in women; ≈60% of affected patients are men[6]	60 years; similar frequency in men and women[7,8]	60 years[5]
Bone marrow abnormalities	Excess fibrous tissue and increase in megakaryocytes[9]	Trilineage myeloproliferation and pleomorphic megakaryocytes[10]	Increased megakaryocytes[9]
Blood cell abnormalities	Reduced RBCs;[9] variable/increased WBCs[9]	High Hct;[9] increased RCM[9]	Elevated platelets;[9] no or few WBCs or RBCs[9]
% with *JAK2* mutation[a]	≈50% of patients[10]	>99%[11,a]	≈50% of patients[10]
% with CALR mutation[b]	≈35% of patients[12]	Not observed[12]	≈25% of patients[12]
Median survival	4.4-7.4 years[13,14]	14-15 years after diagnosis[8,14]	15-20 years[14,15]

[a] *JAK2* alterations include *JAK2* V617F mutations and *JAK2* exon 12 mutations.
CALR, calreticulin; RBCs, red blood cells; WBCs, white blood cells. [b] Based on a MPN cohort of 896 patients.[12]

1. Mehta J, et al. *Leuk Lymphoma*. 2014;55:595-600. 2. Data on file, Incyte Corporation. 3. Stein B, et al. *J Clin Oncol*. 2015;33:3953-3960. 4. Johansson P. *Semin Thromb Hemost*. 2006;32:171-173. 5. Girodon F, et al. *Haematologica*. 2009;94:865-869. 6. Gangat N, et al. *J Clin Oncol*. 2010;29:392-397. 7. National Cancer Institute. Accessed Sep 2024. http://seer.cancer.gov/seertools/hemelymph/51f6cf57e3e27c3994bd538d/. 8. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. 9. Campbell PJ, Green AR. *N Engl J Med*. 2006;355:2452-2466. 10. Arber DA, et al. *Blood*. 2016;127:2391-2405. 11. Pardanani A, et al. *Leukemia*. 2007;21:1960-1963. 12. Klampfl T, et al. *N Engl J Med*. 2013;369:2379-2390 [supplementary appendix]. 13. Cervantes F, et al. *J Clin Oncol*. 2012;30:2981-2987. 14. Szuber N, et al. *Mayo Clin Proc*. 2019;94:599-610. 15. Barbui T, et al. *J Clin Oncol*. 2011;29:761-770.

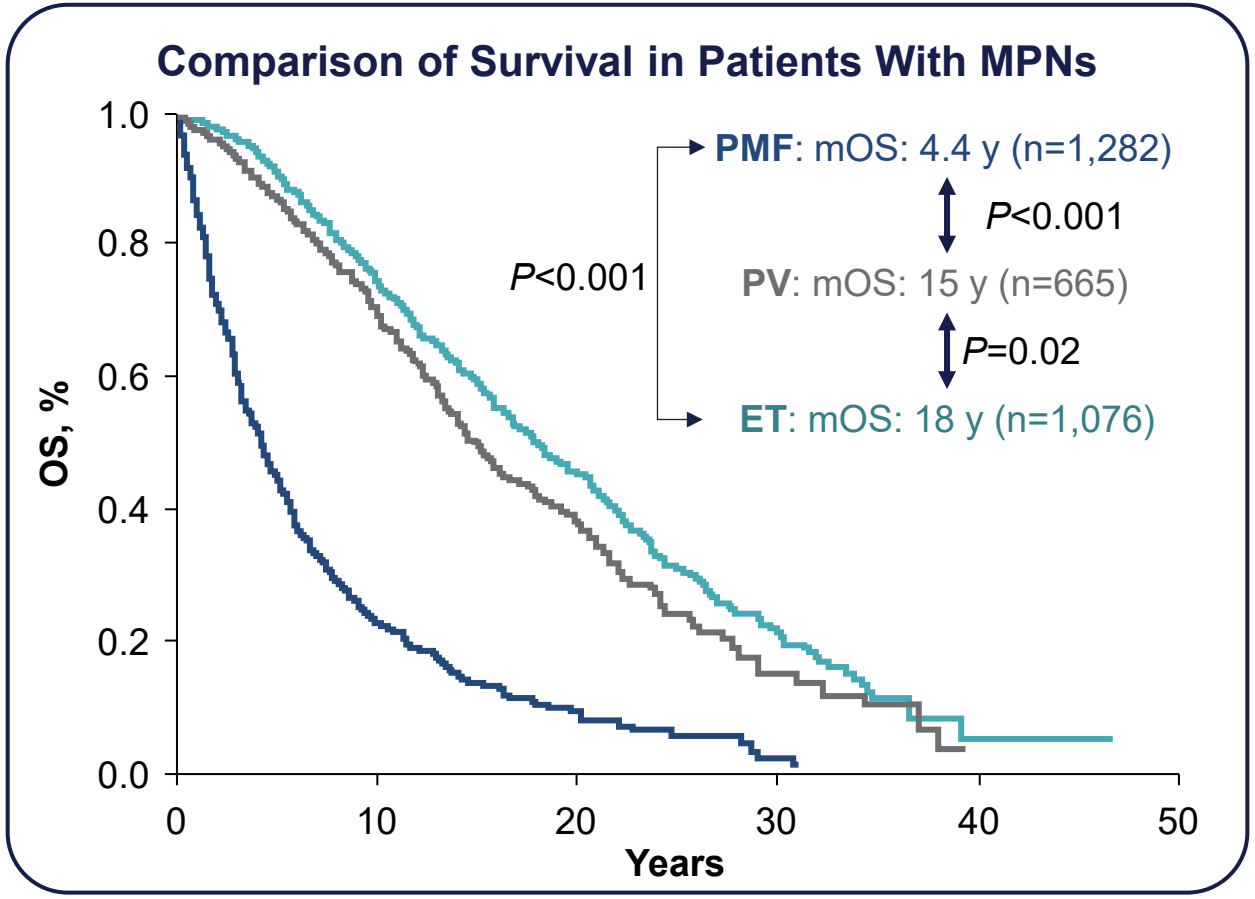
MPN Disease Progression and Transformation



AML, acute myeloid leukemia; PMF, primary myelofibrosis.

1. Finazzi G, et al. *Blood*. 2005;105:2664-2670. 2. Tefferi A. *Am J Hematol*. 2008;83:491-497. 3. Mesa RA, et al. *Blood*. 2005;105:973-977. 4. Cerquozzi S, Tefferi A. *Blood Cancer J*. 2015;5:e366. 5. Wolanskyj AP, et al. *Mayo Clin Proc*. 2006;81:159-166.

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 overall survival; OS, overall survival.

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

BACK

Polycythemia Vera

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

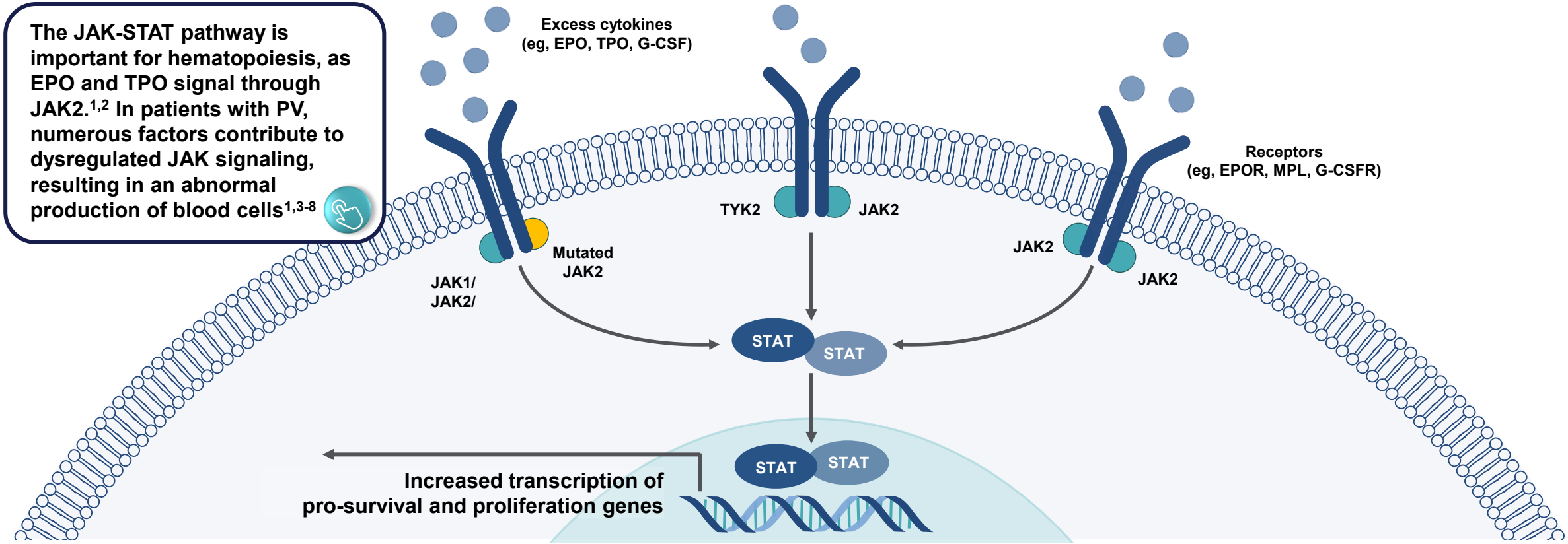
BACK

Mechanism of Disease

Polycythemia Vera

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]

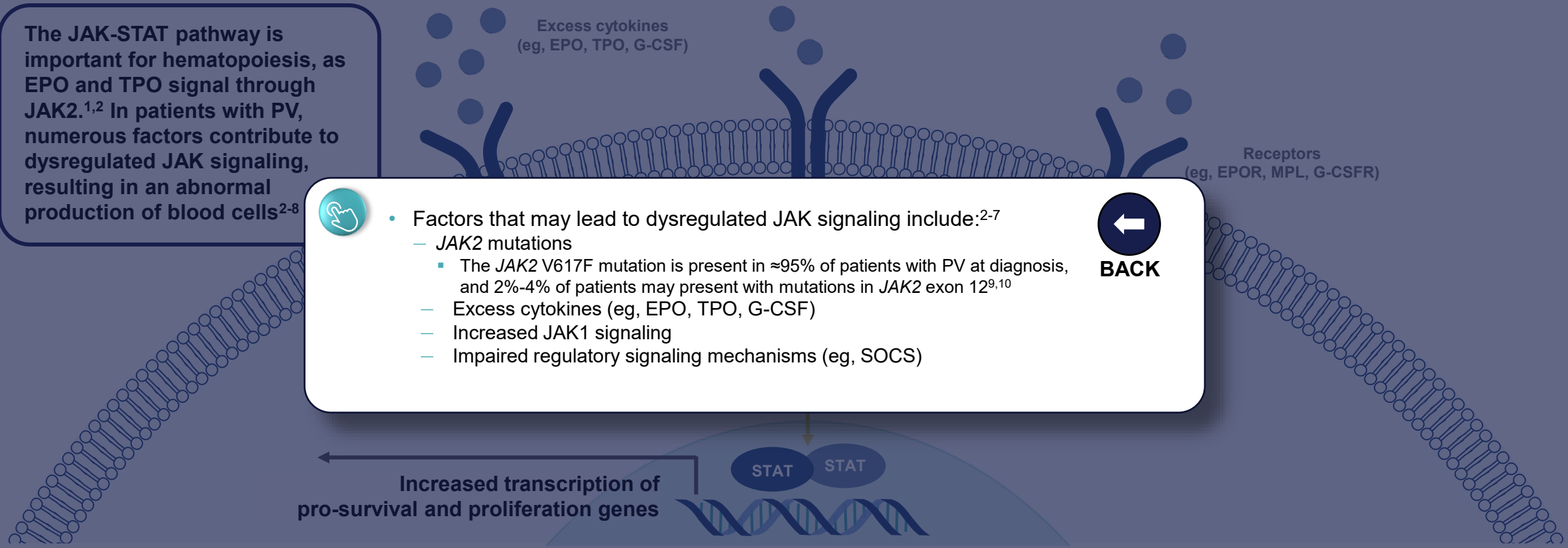


EPO, erythropoietin; EPOR, erythropoietin receptor; G-CSF, granulocyte colony-stimulating factor; G-CSFR, granulocyte colony-stimulating factor receptor; JAK, Janus kinase; MPL, MPL proto-oncogene thrombopoietin receptor; PV, polycythemia vera; SOCS, suppressor of cytokine signaling; STAT, signal transducer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

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.

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.

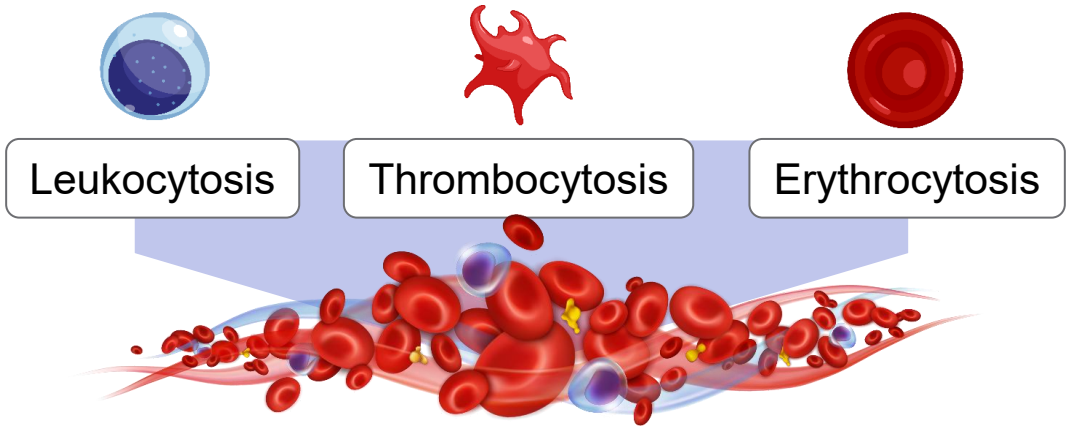
BACK

Disease Characteristics

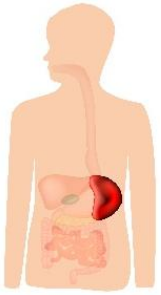
Polycythemia Vera

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.
MPNs, myeloproliferative neoplasms; 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.

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

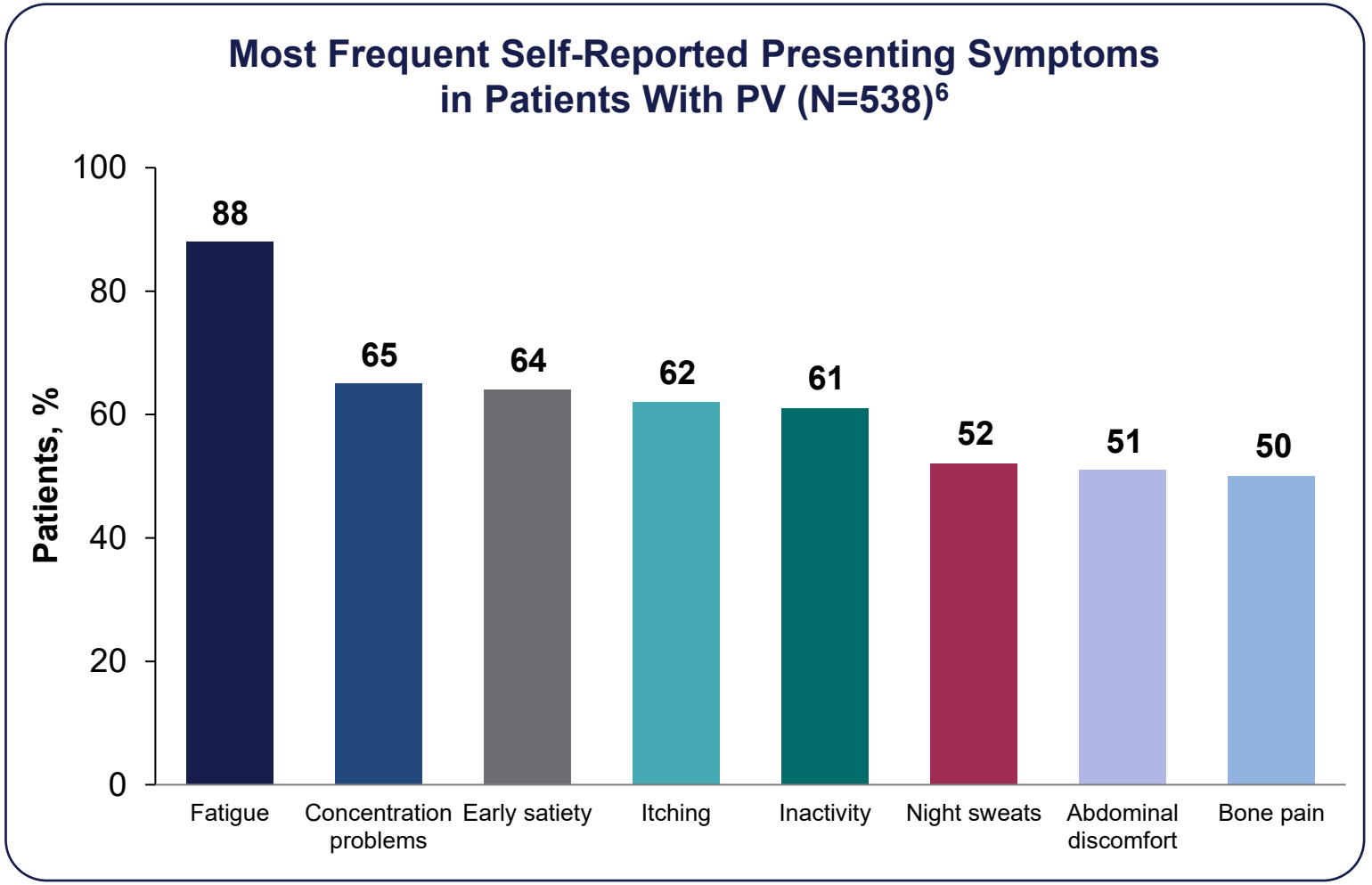
Asymptomatic	Symptomatic	Thrombotic Event
Some patients are asymptomatic and are diagnosed because of incidental findings on laboratory blood tests[1,2]	Approximately half of patients present with PV-related symptoms at diagnosis, resulting from erythrocytosis or thrombocytosis[3,4]	Approximately one-third 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(7 suppl 3):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;27;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.

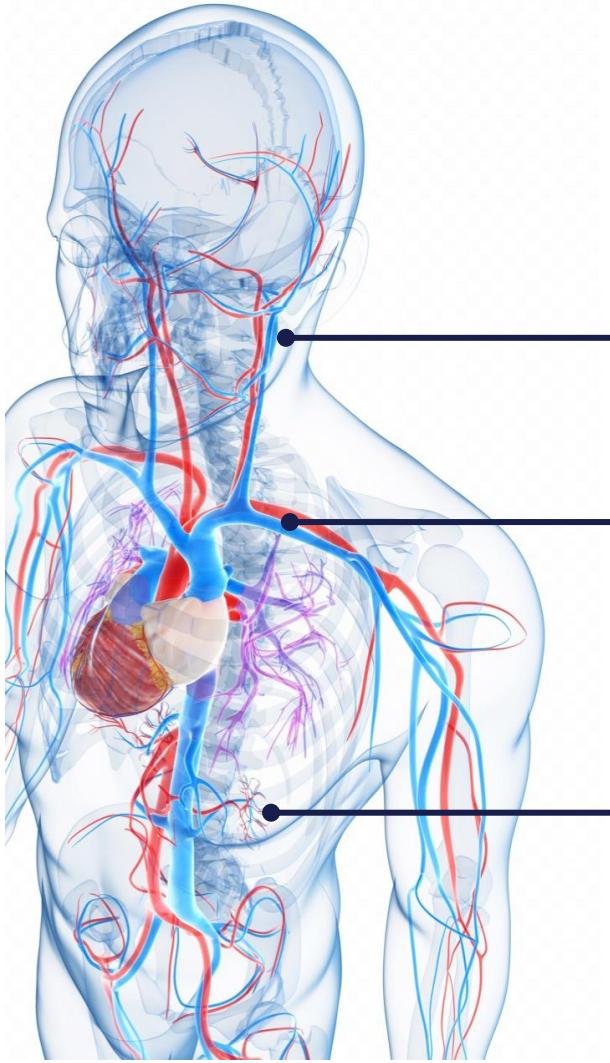
Symptom Presentation May Vary From Patient to Patient

- 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;7(7 suppl 3):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;27;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.

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]

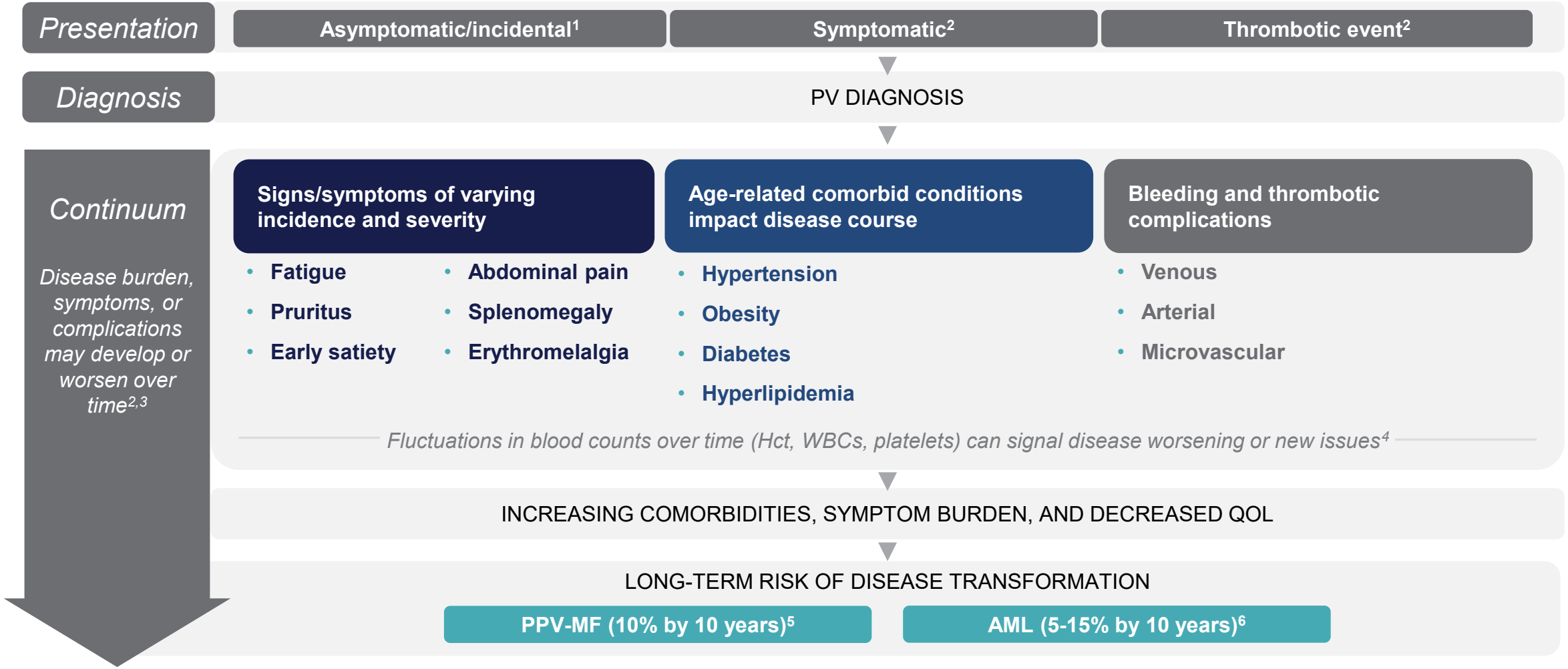
Microcirculatory Disturbances

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.

Disease Evolution and Principal Morbidities



AML, acute myeloid leukemia; Hct, hematocrit; PPV-MF, post–polycythemia vera myelofibrosis; QOL, quality of life; WBCs, white blood cells.

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.

BACK

Clinical Work-Up, Diagnosis, and Stratification

Polycythemia Vera

PV Diagnosis Requires a Comprehensive Evaluation and Work-Up

History and Physical[1,2]

- Common presentation includes:
  - Fatigue
  - Pruritus
  - Vasomotor disturbances
  - Abdominal pain
  - Early satiety
  - Thrombosis

Blood Tests[1,3]

- 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 trilineage hypercellularity

Hb, hemoglobin; PLT, platelets; RCM, red cell mass.

1. Arber DA, et al. *Blood*. 2016;127:2391-2405. 2. Reiter A, Harrison C. *Curr Hematol Malig Rep*. 2016;11:356-367. 3. Spivak JL. *Blood*. 2002;100:4272-4290.

2016 WHO Diagnostic Criteria: PV

2016 WHO Criteria: ☑ Must meet all 3 major OR the first 2 major and the minor[a]

Major

- ☐ Hb >16.5 g/dL in men, >16.0 g/dL in women; or Hct >49% in men, >48% in women; or increased RCM[b]
- ☐ Bone marrow biopsy showing trilineage myeloproliferation and pleomorphic megakaryocytes
- ☐ Presence of *JAK2* V617F or *JAK2* exon 12 mutation

Minor

- ☐ Subnormal sEPO level

[a] Bone marrow biopsy may not be required in cases with sustained absolute erythrocytosis: Hb levels >18.5 g/dL in men (Hct 55.5%) or >16.5 g/dL in women (Hct 49.5%) if major criterion 3 and minor criterion are present. However, initial MF (presented in ≤20% of patients) can be detected only by performing a bone marrow biopsy; this finding may predict a more rapid progression to overt MF (post-PV MF). [b] RCM >25% above mean normal predicted level.
sEPO, serum erythropoietin; WHO, World Health Organization.
Arber DA, et al. *Blood.* 2016;127:2391-2405.

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[1,2]
Median survival, 26 years

- NO HISTORY OF THROMBOSIS
- <60 YEARS OF AGE

High Risk[1,2]
Median survival, 8.3 years

HISTORY OF THROMBOSIS *OR* >60 YEARS OF AGE

Studies suggest that over 70% of patients diagnosed with PV may be considered high risk[5,6]

Additional Considerations[1,3,4]

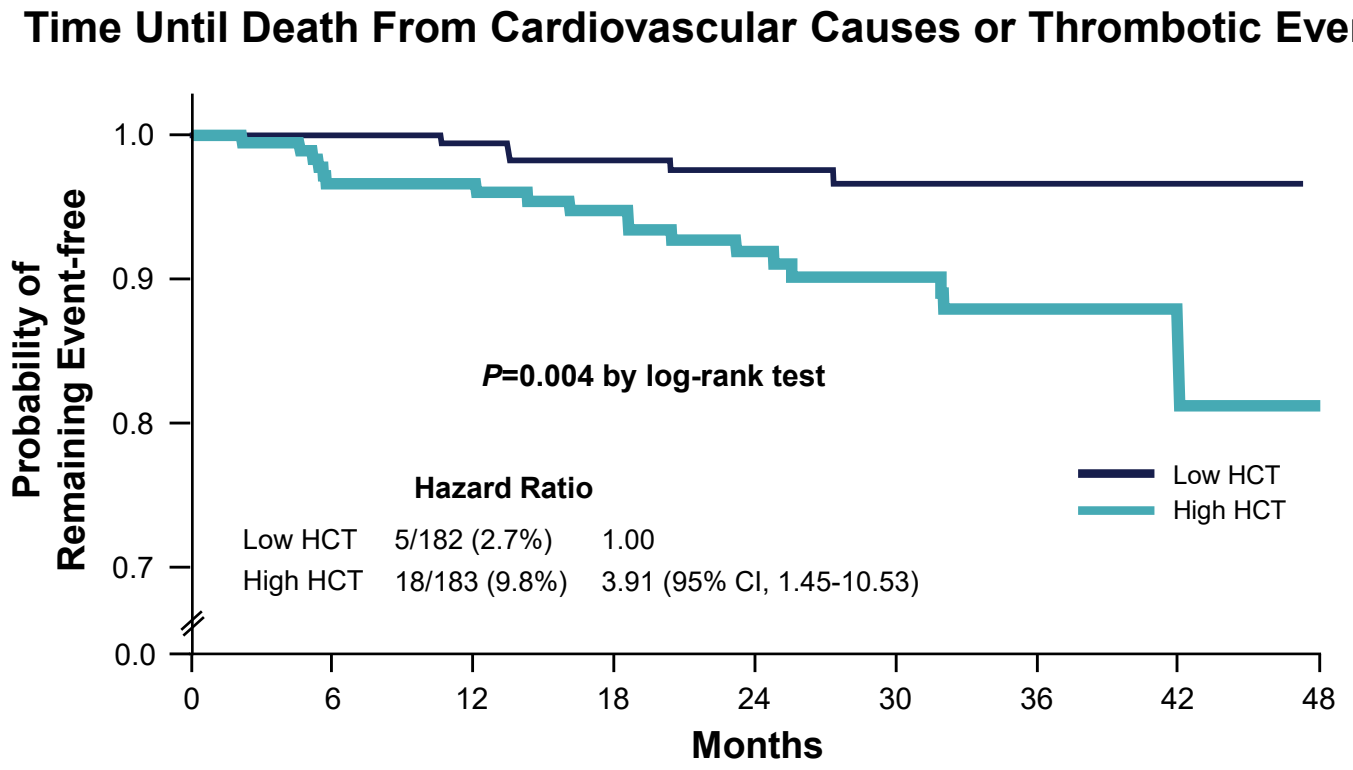
- Leukocytosis
- Elevated Hct
- CV risk factors
  - Hypertension
  - Hyperlipidemia
  - Diabetes
  - BMI
  - Tobacco use

Failure to maintain an Hct <45% has been associated with a significantly increased risk of major thrombosis or CV-related death[4]

BMI, body mass index; CV, cardiovascular.

1. Tefferi A, Barbui. *Am J Hematol*. 2020;95:1599-1613. 2. Tefferi A, et al. *Leukemia*. 2013;27:1874-1881. 3. Tefferi A, et al. *Leukemia*. 2021;35:3339-3351. 4. Marchioli R, et al. *N Engl J Med*. 2013;368:22-33. 5. Lyons RM et al. *Clin Lymphoma Myeloma Leuk*. 2022;Suppl 2:S325. 6. Grunwald MR, et al. Clin Lymphoma Myeloma Leuk. 2020;20:219-225

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



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

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

PV Management Goals

Control Hct <45%[1-4]

Maintaining Hct <45% may lower CV mortality or major thrombosis[5]

Reduce Risk of Thrombotic Events[1,2,6]

>12% or >17% of patients with PV may have a venous or arterial thrombotic event, respectively[5]

Manage PV Disease–Related Symptoms[1,6]

Symptoms and their severity vary among patients, can evolve over time, and occur independently of blood counts, duration of disease, and treatment[7,8]

Modification of CV Risk Factors[3]

CV risk factors are taken into consideration when determining risk stratification[5,9,10]

1. Tefferi A. *Am J Hematol*. 2013;88:507-516. 2. Vannucchi AM. *Blood*. 2014;124:3212-3220. 3. Barbui T, et al. *J Clin Oncol*. 2011;29:761-770. 4. Barosi G, et al. *Blood*. 2013;121:4778-4781. 5. Marchioli R, et al. *N Engl J Med*. 2013;368:22-33. 6. Patel AB, et al. *Clin Cancer Res*. 2016;22:1037-1047. 7. Reiter A, Harrison C. *Curr Hematol Malig Rep*. 2016;11:356-357. 8. Scherber R, et al. *Blood*. 2011;118:401-408. 9. Tefferi A, Barbui T. *Am J Hematol*. 2020;95:1599-1613. 10. Tefferi A, et al. *Leukemia*. 2021;35:3339-3351.

Summary

- Patients with PV can present with a heterogeneous constellation of clinical features and symptoms, complicating diagnosis[1]
  - Fatigue, bone pain, and itching are some of the common symptoms[2]
  - Bone marrow biopsy has been added to the WHO diagnostic criteria for PV because it may facilitate diagnosis and provide a baseline assessment of the disease[3,4]

- PV is associated with a substantial symptom burden and increased risk of thrombotic and bleeding complications, which can substantially impact QOL and survival[5-7]

- PV management goals are centered around:
  - Maintaining Hct <45%[8-11]
  - Reducing the risk of thrombotic events[8,9,12]
  - Managing disease-related symptoms[8,12]
  - Modifying CV risk factors[10]

1. Raedler LA. *Am Health Drug Benefits*. 2014;7(7 suppl 3):S36-S47. 2. Stein B, et al. ASH 2015. Abstract 2813. 3. Arber DA, et al. *Blood.* 2016;127:2391-2405. 4. Barbui T, et al. *Blood Cancer J*. 2015;5:e337. 5. Kaifie A, et al. *J Hematol Oncol*. 2016;9:18. 6. Scherber R, et al. *Blood*. 2011;118:401-408. 7. Mesa R, et al. *BMC Cancer.* 2016;27;16:167. 8. Tefferi A. *Am J Hematol*. 2013;88:507-516. 9. Vannucchi AM. *Blood.* 2014;124:3212-3220. 10. Barbui T, et al. *J Clin Oncol*. 2011;29:761-770. 11. Barosi G, et al. *Blood*. 2013;121:4778-4781. 12. Patel AB, et al. *Clin Cancer Res*. 2016;22:1037-1047.

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