PharmaEssentia™

Understanding Myeloproliferative Neoplasms (MPNs)

MED-US-RPEG-2300012 (v1.0) 06/2023

Content Outline

- **Overview of MPNs**
  - Disease state overview
  - Pathogenesis and allele burden of MPNs
  - Symptoms of MPNs
- **IFN Use in MPNs**
  - Overview of IFNs
  - History of IFNs
  - Role of IFNs
- **Understanding MPNs Summary**

IFN, interferon; MPN, myeloproliferative neoplasm.

For Educational Purposes Only

- **This deck is intended for disease state education only and should not be considered a comprehensive resource on myeloproliferative neoplasms**
- **PharmaEssentia Corporation does not endorse the off-label use of its approved products. Healthcare professionals are encouraged to use their clinical judgment when treating patients with myeloproliferative neoplasms**

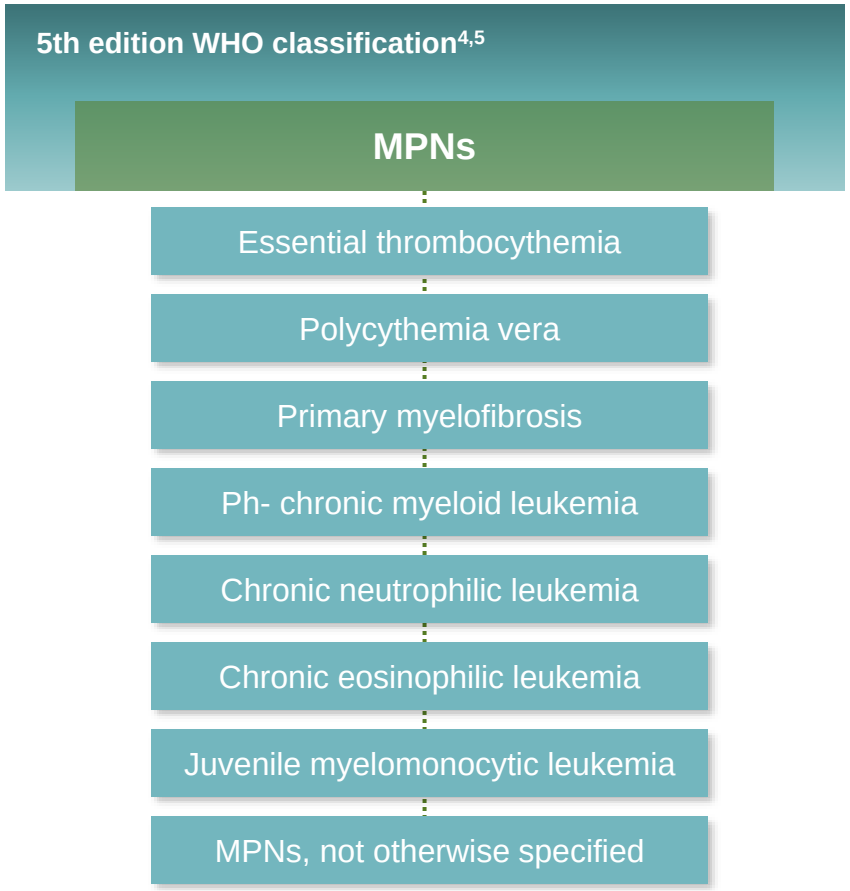
Overview of MPNs

Myeloproliferative Neoplasms (MPNs) Are Rare, Chronic Myeloid Neoplasms[1,2]

MPNs are characterized by an abnormal proliferation of myeloid cells caused by gain-of-function somatic mutations of specific genes in hematopoietic stem cells (HSCs)[3]

Overproduction of one or more mature, non-lymphoid cell lineages may result in erythrocytosis, thrombocytosis, and/or myeloproliferation[2]

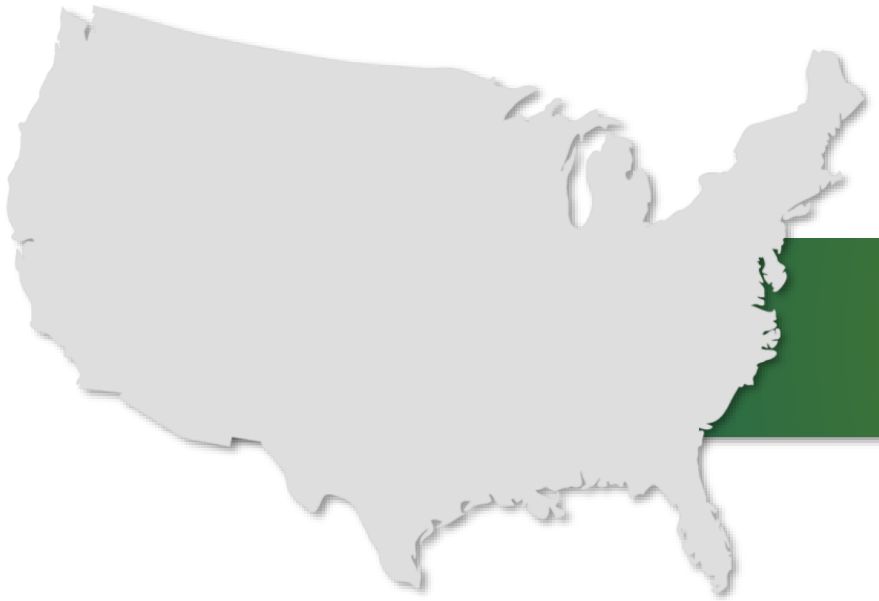
Inflammation in the bone marrow can contribute to clonal dominance and disease progression, including fibrotic transformation of the bone marrow and suppression of benign hematopoiesis[2]



Ph-, Philadelphia chromosome–negative; WHO, World Health Organization.

1. Greenfield G et al. *J Hematol Oncol*. 2021;14(1):103. **2.** Fisher DAC et al. *Front Immunol.* 2021;12:683401. **3.** Hermange G et al. *Proc Natl Acad Sci U S A.* 2022;119(37):e2120374119. **4.** Khoury JD et al. *Leukemia.* 2022;36(7):1703-1719. **5**. Diamantopoulos PT, Viniou NA. *Front Oncol*. 2021;11:722507.

The Most Common MPNs Are PV, ET, and MF[1]



Incidence rates for common MPNs in the United States*[1,2]

PV:	ET:	MF:
1.57 per 100,000 person-years	1.55 per 100,000 person-years	0.44 per 100,000 person-years

The prevalence of **PV cases** (44-57 per 100,000 people) and **ET cases** (38-57 per 100,000 people) is **higher than MF cases** (0.3-5.7 per 100,000 people)†[3]

Although most patients are a median age of ~60 years at diagnosis, **young adults aged ≤40 years** as well as **pediatric patients** can also be diagnosed with MPNs[4]

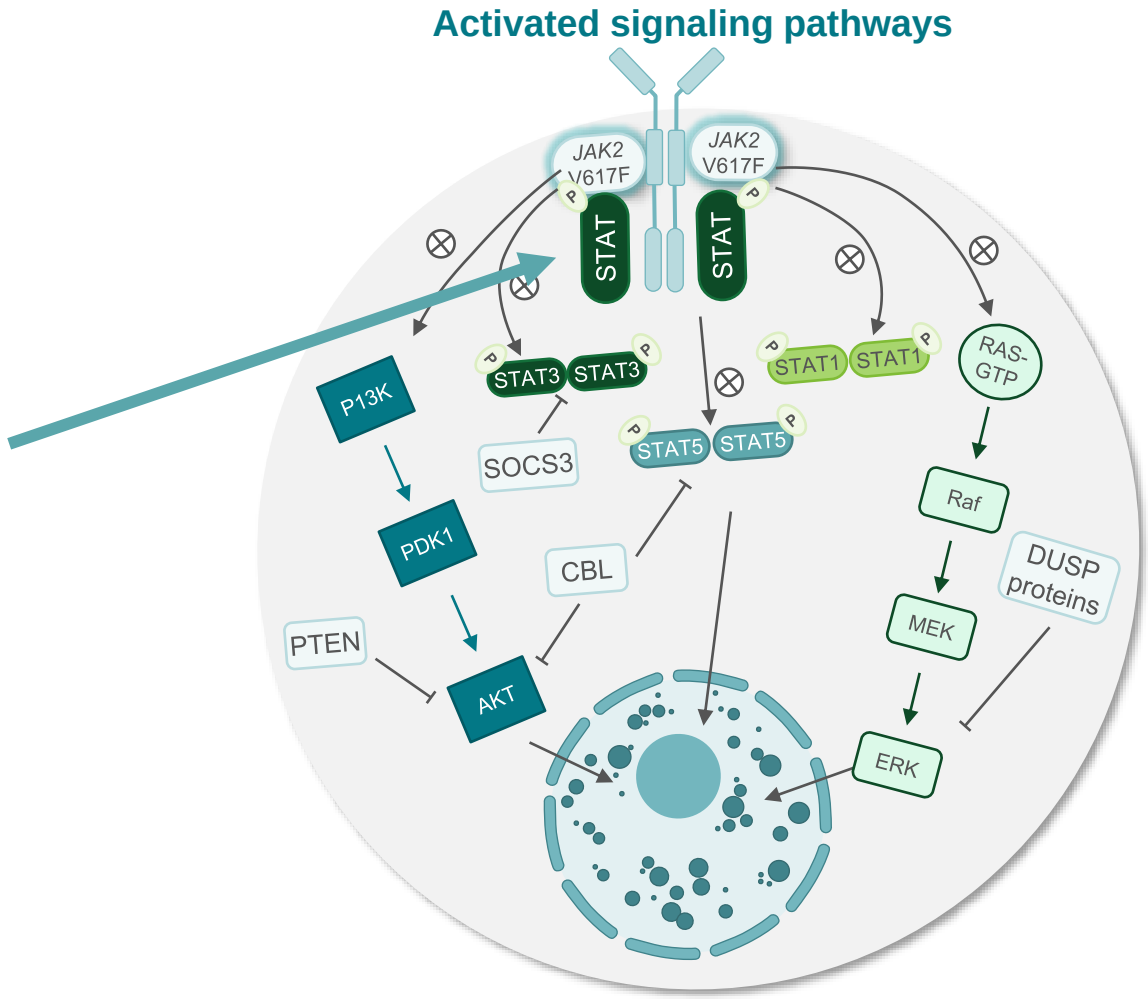
*Based on data through 2016 from the Surveillance, Epidemiology, and End Results database.[2] †Based on data from two large US healthcare data providers, the IBM MarketScan Commercial Claims and Encounters database and the Medicare Supplemental and Coordination of Benefits database.[3]

ET, essential thrombocythemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera.

1. Allegra A et al. *Antioxidants (Basel)*. 2020;9(11):1037. **2.** Verstovsek S et al. *Leuk Lymphoma.* 2022;63(3):694-702. **3.** Mehta J et al. *Leuk Lymphoma***.** 2014;55(3):595-600. **4.** Kucine N. *Curr Hematol Malig Rep.* 2020;15(2):141-148.

The Pathogenesis of MPNs May Include Various Signaling Pathways

The constitutive activation of the JAK/STAT signaling pathway is a central feature of MPN pathogenesis

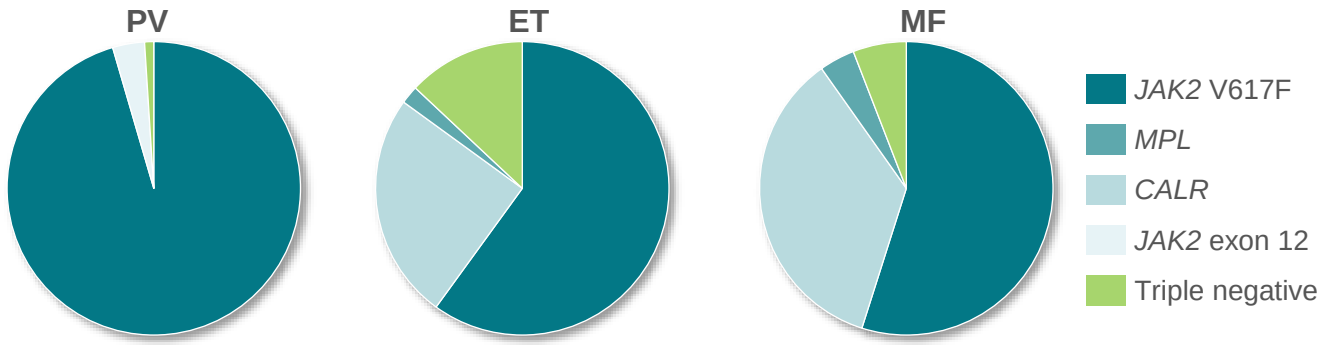


AKT, protein kinase B; CBL, Cbl proto-oncogene; DUSP, dual-specificity phosphatase; ERK, extracellular signal-related kinase; JAK, Janus kinase; JAK2, Janus kinase 2; MPN, myeloproliferative neoplasm; PI3K, phosphoinositide 3-kinase; PTEN, phosphatase and tensin homolog; SOCS3, suppressor of cytokine signaling 3; STAT, signal transducer and activator of transcription.

Greenfield G et al. *J Hematol Oncol*. 2021;14(1):103.

The Majority of Patients With MPNs Carry Mutations in *JAK2*, *CALR*, or *MPL*[1]

Driver mutations in classical MPNs[2]



JAK2 V617F mutations are most commonly seen in ≥95% of PV cases and in 60% of cases of ET and MF[3]

Most patients with ET and MF who are *JAK2* V617F-negative have detectable mutations in *CALR* or *MPL*[4]

- A proportion of patients with MPNs (specifically ET and MF) do not have mutations in *JAK2*, *CALR*, or *MPL*, and are considered triple negative[5]
- Mutations in genes such as *ASXL1*, *SRSF2*, *EZH2*, *IDH1*, and *IDH2* are considered high-molecular-risk mutations that have an adverse prognostic impact and association with disease progression[3,5]
- Mutations associated with sporadic MPNs are typically not inherited[6]

ASXL1, additional sex combs-like 1; CALR, calreticulin; ET, essential thrombocythemia; EZH2, enhancer of zeste 2 polycomb repressive complex 2 subunit; IDH1, isocitrate dehydrogenase 1; IDH2, isocitrate dehydrogenase 2; JAK2, Janus kinase 2; MF, myelofibrosis; MPL, myeloproliferative leukemia virus oncogene; MPN, myeloproliferative neoplasm; PV, polycythemia vera; SRSF2, serine/arginine-rich splicing factor 2.

1. Fisher DAC et al. *Front Immunol.* 2021;12:683401. **2.** Jia R, Kralovics R. *Int J Hematol*. 2020;111(2):182-191. **3.** Palumbo GA et al. *Front Oncol*. 2019;9:321. **4.** Greenfield G et al. *J Hematol Oncol*. 2021;14(1):103. **5.** Brkic S, Meyer SC. *Hemasphere*. 2020;5(1):e516. **6.** Jones AV, Cross NC. *Ther Adv Hematol.* 2013;4(4):237-253.

Allele Burden of Driver Mutations in MPNs Is a Highly Variable Factor[1]

The allele burden of mutations such as *JAK2* V617F is associated with[2]:

- Phenotypic presentation of MPNs
- Severity of MPNs
- Risk of thrombotic events
- Progression to secondary MF

In PMF, a low *JAK2* V617F allele burden is associated with shorter overall survival[3]

In PV, a higher *JAK2* V617F allele burden is associated with more frequent thrombotic complications, pruritus, and fibrotic transformation[2]

CALR allele burden is associated with higher hemoglobin levels and lower white blood cell and platelet counts[2]

CALR, calreticulin; JAK2, Janus kinase 2; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera.

1. Baumeister J et al. *Cells.* 2021;10(12):3551. **2.** Palumbo GA et al. *Front Oncol*. 2019;9:321. **3**. Rozovski U et al. *Haematologica*. 2017;102(1):79-84.

Symptom Burden Can Negatively Affect Quality of Life Among Patients With MPNs[1]

Symptoms of MPNs may include[1]:

Fever | Night sweats | Fatigue | Weight loss | Headaches | Difficulty concentrating | Abdominal pain

- Quantifying symptoms in patients with MPNs can be difficult due to substantial heterogeneity in the type and severity of symptoms[1]
- Patients with MPNs are at variable risk of vascular complications, including arterial or venous thrombosis and bleeding[2]
- Life expectancy is reduced overall, with the relative survival rates lower in PMF compared with PV, and in PV compared with ET[2]

ET, essential thrombocythemia; MPN, myeloproliferative neoplasm; PMF, primary myelofibrosis; PV, polycythemia vera.

1. Tremblay D, Mesa R. *Best Pract Res Clin Haematol*. 2022;35(2):101372. **2.** Rumi E, Cazzola M. *Blood*. 2017;129(6):680-692.

IFN Use in MPNs

PharmaEssentia™

IFN Alfa Has Been Used for Years in Multiple Oncologic Diseases[1]

- IFNs are a group of cytokines with immunomodulatory, antiproliferative, and antiangiogenic properties[1]

There are 3 types of IFNs:

Type I

- **IFNs have been used in MPNs for more than 30 years[2]**
- IFN alfa belongs to the Type I IFN group, and IFN alfa-2 is the predominant form used as a therapeutic agent[1]
- Pegylated forms of IFNs include pegylated IFN alfa-2a, pegylated IFN alfa-2b, and ropeginterferon alfa-2b-njft[3]

Type II

- Type II IFN (IFN gamma) inhibits viral replication and is essential for the regulation of several immune responses[4]

Type III

- Type III IFN (IFN lambda) provides supplementary antiviral protection at epithelial surfaces for the body's front-line defense[4,5]

The wide array of antitumor properties of IFNs led to the testing of IFN alfa in hematologic malignancies, and the strongest responses were observed in patients with MPNs[6]

IFN, interferon; MPN, myeloproliferative neoplasm.

1. How J, Hobbs G. *Cancers (Basel)*. 2020;127(7):1954. **2.** Verstovsek S et al. *Future Oncol.* 2022;18(27):2999-3009. **3**. How J, Hobbs G. *J Natl Compr Canc Netw*. 2022;20(9):1063-1068. **4**. Green DS et al. *J Biol Chem*. 2017;292(34):13925-13933. **5.** Lazear HM et al. *Immunity*. 2019;50(4):907-923. **6**. Swaroop A et al. *Bioessays*. 2023;45(3):e2200203.

Type I IFNs Activate Signaling Through the JAK/STAT Pathway by Binding to IFN Alfa Receptors[1]

The JAK/STAT signaling pathway is one of the major pathways that IFN alfa-2 engages

Type I IFN-dependent signaling pathways are activated by Type I IFN alfa receptor chains 1 and 2[2]

JAK is activated when IFN alfa-2 binds to its receptors[2]

The phosphorylation of JAK activates STAT proteins, which translocate to the nucleus and activate gene expression[2]

The action of IFNs on megakaryocyte proliferation likely accounts for its effects on thrombocytosis[1]

Inhibition of thrombopoietin activation is achieved by suppressing *JAK2* substrate phosphorylation[1]

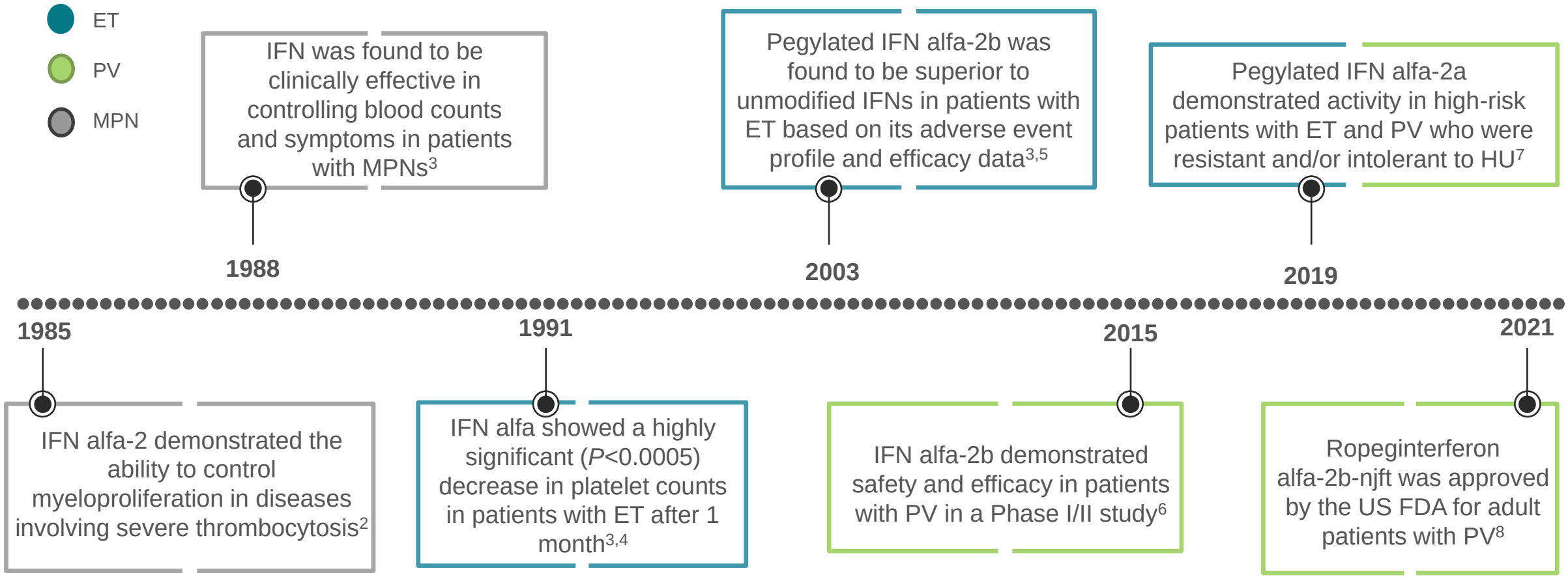
IFNs may cause apoptosis of hematopoietic progenitors, particularly those with a mutated clone[1]

By stimulating the immune system, IFNs can enhance surveillance and mutant clone targeting[1]

IFN, interferon; JAK, Janus kinase; JAK2, Janus kinase 2; STAT, signal transducer and activator of transcription.

1. How J, Hobbs G. *Cancers (Basel)*. 2020;12(7):1954. **2.** Hasselbalch HC, Holmström MO. *Semin Immunopathol*. 2019;41(1):5-19.

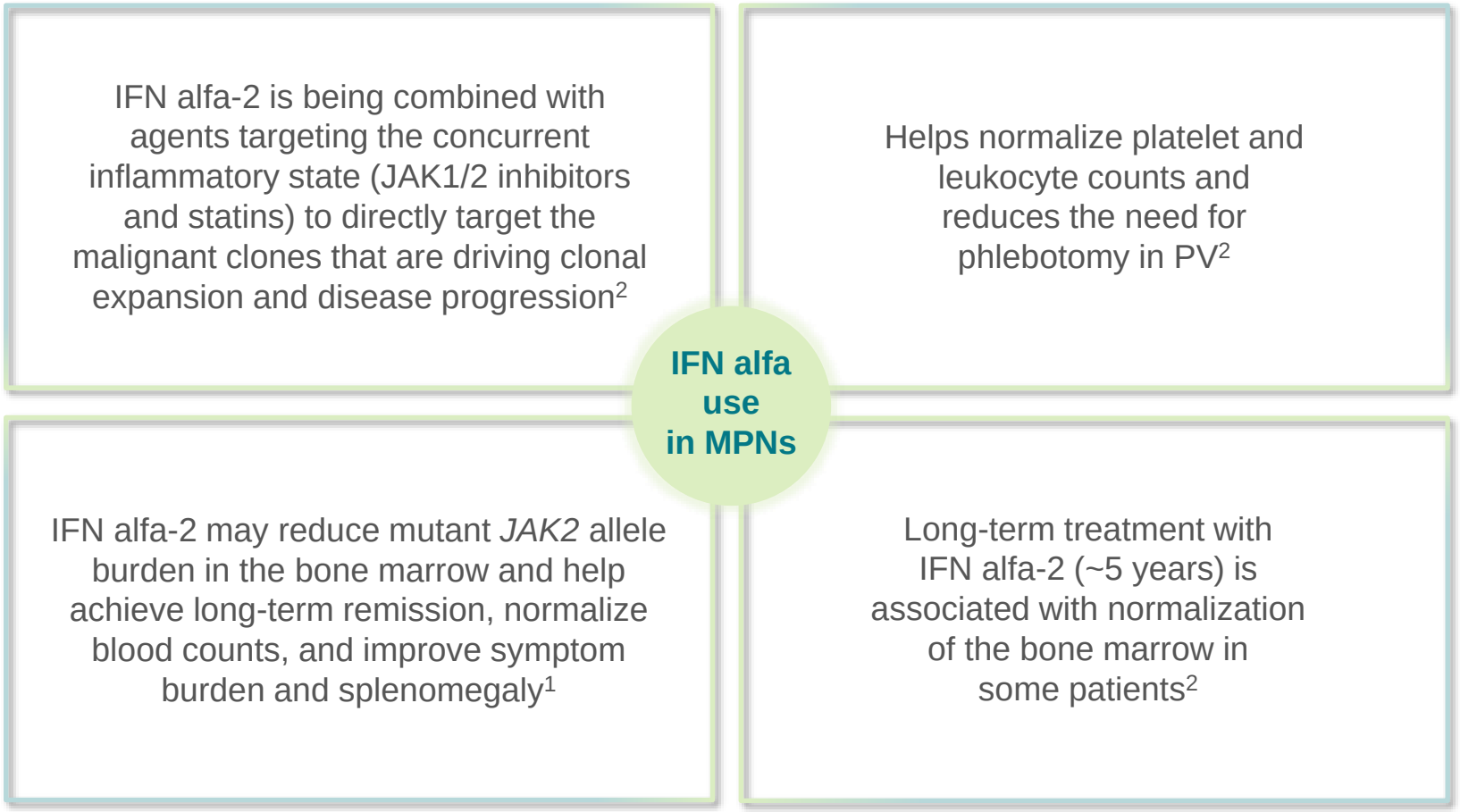
The Efficacy of IFN Alfa Was First Demonstrated in PV and ET in the 1980s[1]



ET, essential thrombocythemia; HU, hydroxyurea; IFN, interferon; MPN, myeloproliferative neoplasm; PV, polycythemia vera.

1. Swaroop A et al. *Bioessays*. 2023;45(3):e2200203. **2.** Hasselbalch HC, Holmström MO. *Semin Immunopathol*. 2019;41(1):5-19. **3.** Verstovsek S et al. *Future Oncol.* 2022;18(27):2999-3009. **4**. Gisslinger H et al. *Br J Haematol*. 1991;79(1):42-47. **5**. Alvarado Y et al. *Cancer Chemother Pharmacol*. 2003;51(1):81-86. **6**. Gisslinger H et al. *Blood*. 2018;132(suppl 1):3030. **7**. Yacoub A et al. *Blood*. 2019;134(18):1498-1509. **8**. BESREMi. Prescribing Information. PharmaEssentia Corporation; 2021.

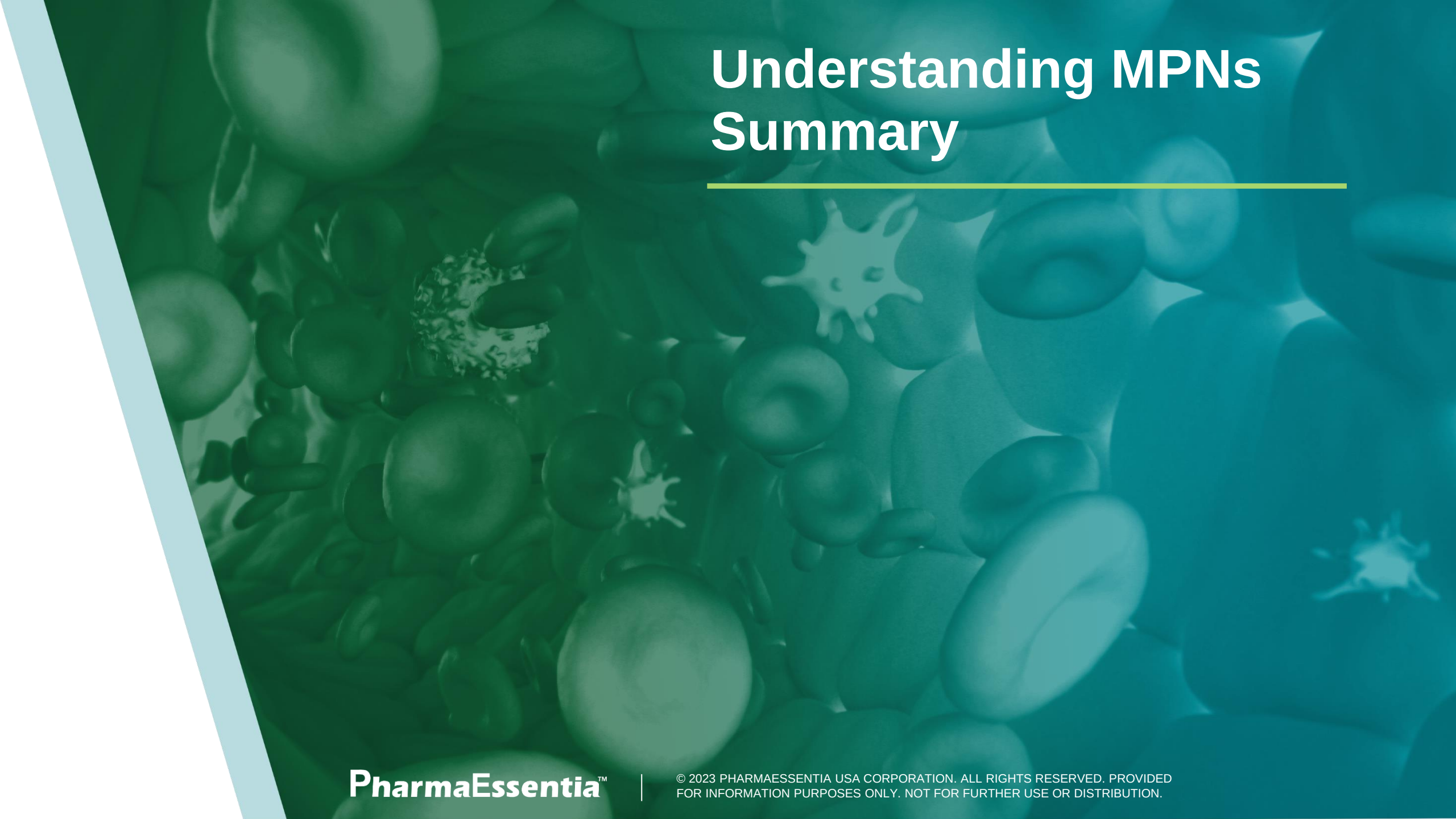
IFN Alfa Can Have Beneficial Effects on HSCs in MPNs[1]



HSC, hematopoietic stem cell; IFN, interferon; JAK1, Janus kinase 1; JAK2, Janus kinase 2; MPN, myeloproliferative neoplasm; PV, polycythemia vera.

1. Swaroop A et al. *Bioessays*. 2023;45(3):e2200203. **2.** Hasselbalch HC, Holmström MO. *Semin Immunopathol*. 2019;41(1):5-19.

Understanding MPNs Summary



PharmaEssentia™

Understanding MPNs Summary

MPNs are rare, chronic myeloid neoplasms characterized by the excessive production of mature blood cells, which can result in erythrocytosis, thrombocytosis, and/or myeloproliferation[1-3]

Patients with MPNs may harbor any of the 3 driver mutations, including *JAK2, CALR,* or *MPL*; a higher mutant allele burden has been associated with a more unfavorable disease prognosis in PV and ET[2,4]

IFNs play a continued role in the treatment of BCR-ABL–negative MPNs[5]

ABL, Abelson gene; BCR, breakpoint cluster region; CALR, calreticulin; IFN, interferon; JAK2, Janus kinase 2; MPL, myeloproliferative leukemia virus oncogene; MPN, myeloproliferative neoplasm.

1. Greenfield G et al. *J Hematol Oncol*. 2021;14(1):103. **2.** Fisher DAC et al. *Front Immunol.* 2021;12:683401. **3.** Jia R, Kralovics R. *Int J Hematol.* 2020;111(2):182-191. **4.** Palumbo GA et al. *Front Oncol*. 2019;9:321. **5.** Swaroop A et al. *Bioessays*. 2023;45(3):e2200203.