JADPRO CE
Regional Lectures

Clinical Management of Novel Therapies for Hematologic Malignancies: Targeted Therapies, CAR-T, and Beyond

Risk-Adapted Treatment of Ph- Myeloproliferative Neoplasms

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Faculty Financial Disclosures

- Ms. Kurtin has served as a consultant for AbbVie, Celgene, Genentech, and Pharmacyclics.
- Ms. Goodrich has served on the speakers bureau for Gilead.
- Dr. Kiel has served on speakers bureaus for Celgene, Genentech, Gilead, and Takeda.
- Ms. Ridgeway has served on the speakers bureau for Abbvie and Phamacyclics
- Ms. Rogers has served on advisory boards for Gilead, Merck, and Takeda, and has served on speakers bureaus for Bristol-Myers Squibb, Genentech, Seattle Genetics, and Teva Pharmaceuticals.

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Learning Objectives

- Describe the latest World Health Organization disease definitions for diagnosing myeloid malignancies
- Discuss the normal physiology of the JAK-STAT biochemical signaling pathway, as well as its dysregulation in myeloproliferative neoplasms
- Identify germline mutations in patients with predisposition for MPNs/MDS

MPNs = myeloproliferative neoplasms; MDS = myelodysplastic syndrome.

Myeloproliferative Neoplasms

- A group of clonal myeloid malignancies with unique clinicopathologic characteristics
- Somatic hematopoietic stem cell mutations
- Overactivation of JAK-STAT signaling
- Hyperproliferation of one or more hematologic cell lines
- Mutually exclusive Janus kinase 2 (JAK2), calreticulin (CALR), or thrombopoietin receptor gene mutation (MPL)
- Subdivided into classical and non-classical MPNs

Rumi E, Cazzola M. *British Journal of Haematology*. 2017;178(5):689-698.

Audience Response Question #13

Which of the following patient profiles requires initiation of cytoreductive therapy using a JAK2 inhibitor?

A. Confirmed diagnosis of ET, *JAK2* mutation, no prior thrombosis, age 58, platelets 750,000
B. New diagnoses of PV, *JAK2* mutation, no history of thrombosis, splenomegaly, on ASA, requiring phlebotomy to keep Hct < 45%
C. Age 58, confirmed diagnosis of myelofibrosis with asymptomatic splenomegaly, *JAK2, CALR, MPL+*
D. Diagnosis of PV, age 72, history of DVT, on hydroxyurea and ASA, requiring phlebotomy to keep Hct < 45%
E. Unsure

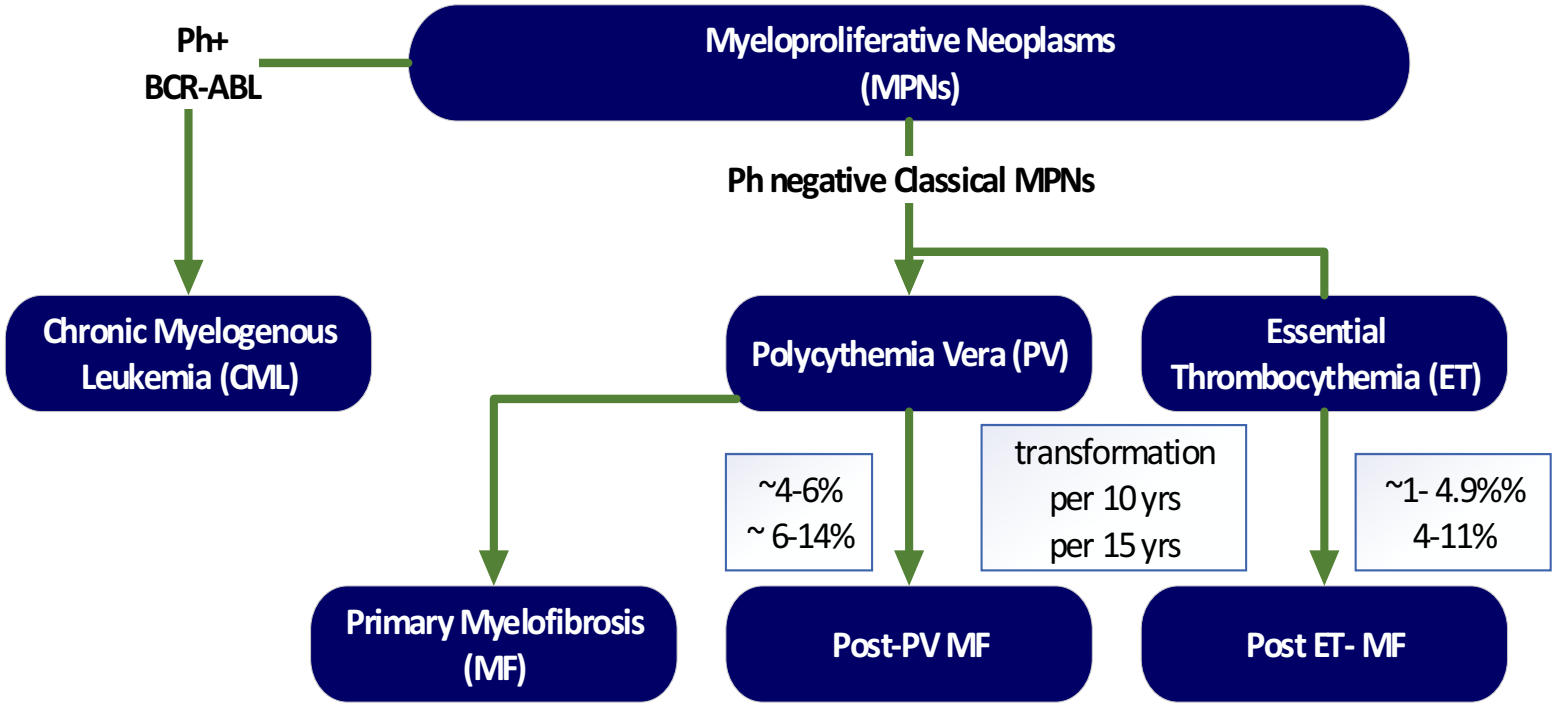
Hct = hematocrit; PV = polycythemia vera, DVT = deep-vein thrombosis; ASA = acetylsalicylic acid.

Audience Response Question #14

Which driver mutations are not present in patients with polycythemia vera?

A. JAK2 V617F and MPLW515L
B. JAK2 exon 12 and MPLW515K
C. CALR exon 9 and MPLW515L
D. JAK2 exon 12 and CALR exon 9
E. Unsure

Classification of MPNs



Arber DA, Orazi A, Hasserjian R, et al. *Blood*. 2016;127(20):2391-2405.
Cerquozzi S, Tefferi A. *Blood Cancer J* 2015; 5:e366.

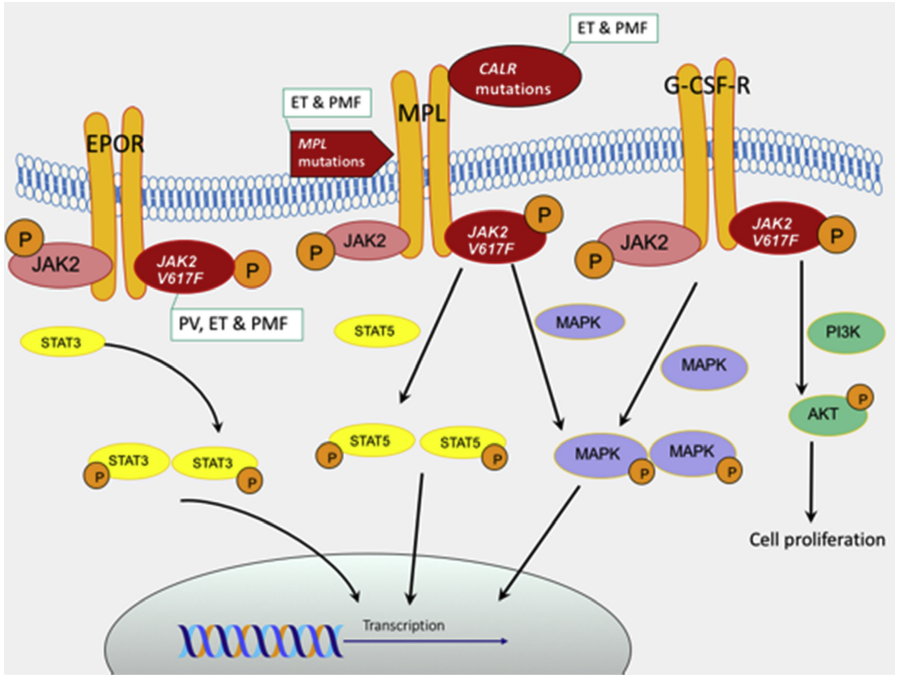
Risk Factors

- Aging: Older age is associated with abnormal clonal expansion. The average at diagnosis for MPNs is 67.
- Chemical exposure: Exposure to benzenes, certain solvents or pesticides, and heavy metals, such as mercury or lead have been associated with changes in bone marrow stem cells and/or the bone marrow microenvironment
- Hereditary MPNs are rare; however, germline mutations have been identified
- Acquired (somatic) driver

Shlush LI. *Blood.* 2018;131(5):496-504.
Harrison CN, Keohane C. *Medicine.* 2013;41(5):265-268.
Rumi E, Cazzola M. *British Journal of Haematology.* 2017;178(5):689-698.
Tashi T, Swierczek S, Prchal JT. *Current Hematologic Malignancy Reports.* 2017;12(5):442-447.

JAK-STAT Signaling Pathway and MPNs

- Well-characterized signaling pathway involved in hematopoiesis, inflammation, and immune function
- JAK2 (Janus kinase), MPL (myeloproliferative leukemia virus) and CALR (calreticulin)
- Mutation in JAK, MPL, CALR are gain of function mutations
- Upregulate JAK-STAT (Signal Transducer and Activator of Transcription) signaling with increase in downstream transcription and gene expression



Driver Mutations in Ph- MPNs

- **JAK2 V617F**
  - Present in ~90% of PV
  - Present in ~50% of ET and PMF
  - Activates erythropoietin receptor, thrombopoietin receptor, and granulocyte colony-stimulating factor receptor
  - Janus kinase (JAK)2 V617f mutation was first discovered in 2005
- **JAK2 exon 12**
  - A variant of the *JAK2* mutation
  - JAK2 V617F, exon 12 mutations are not seen in ET or MF
- **MPLW515l and MPLW515K**
  - Receptor for thrombopoietin which regulates megakaryopoiesis
  - Present in 3%–4% of ET and 6%–7% of PMF
  - MPL mutations are absent in PV
  - More common with older age, higher platelet counts and low hemoglobin levels
  - In PMF, it occurs more commonly in females
  - The MPL mutation was first discovered in 2006

ET = essential thrombocytopenia; PMF = primary myelofibrosis.

Schischlik F, Kralovics R. *Expert Rev Hematol.* 2017;10(11):961-973.
O'Sullivan JM, Harrison CN. *Molecular and Cellular Endocrinology*. 2017;451:71-79

Driver Mutations in Ph- MPNs (cont.)

- **CALR exon 9**
  - Calreticulin gene (CALR) mutations are present in 20%–35% of patients with JAK2 and MPL negative ET or PMF
  - Binds to the thrombopoietin receptor (MPL)
  - Type I (insertion associated with lower DIPSS risk) and type II (deletion associated with poor risk)
  - CALR is not found in PV
  - The CALR mutation was first discovered in 2013
- **Triple negative**
  - 5%–12% of MF, 5%–15% of ET
  - Very poor prognosis, higher risk of leukemic transformation, associated with a higher Dynamic International Prognostic Scoring System (DIPSS) risk
- **Other associated mutations with prognostic importance**
  - Epigenetics: TET2, ASXL1
  - Other: IDH1/2

Schischlik F, Kralovics R. *Expert Rev Hematol*. 2017;10(11):961-973.
O'Sullivan JM, Harrison CN. *Molecular and Cellular Endocrinology*. 2017;451:71-79

Goals of Care

- Prolongation of life
  - Reduce risk/incidence of leukemic transformation
  - Reduce risk/incidence of thrombosis
  - Reduce risk/incidence of bleeding
  - Reduce risk/incidence of infection
- Maintain or improve quality of life
  - Reduce symptom burden
  - Reduce splenomegaly

Besses C, Alvarez-Larran A. *Clinical Lymphoma, Myeloma & Leukemia.* 2016;16 Suppl:S114-123.
Bose P, Gotlib J, Harrison CN, Verstovsek S. *Clinical Lymphoma, Myeloma & Leukemia*. 2018;18(1):1-12.

Symptom Assessment

Symptoms related to overactive signaling pathway (JAK-STAT) with overproduction of inflammatory cytokines and splenomegaly

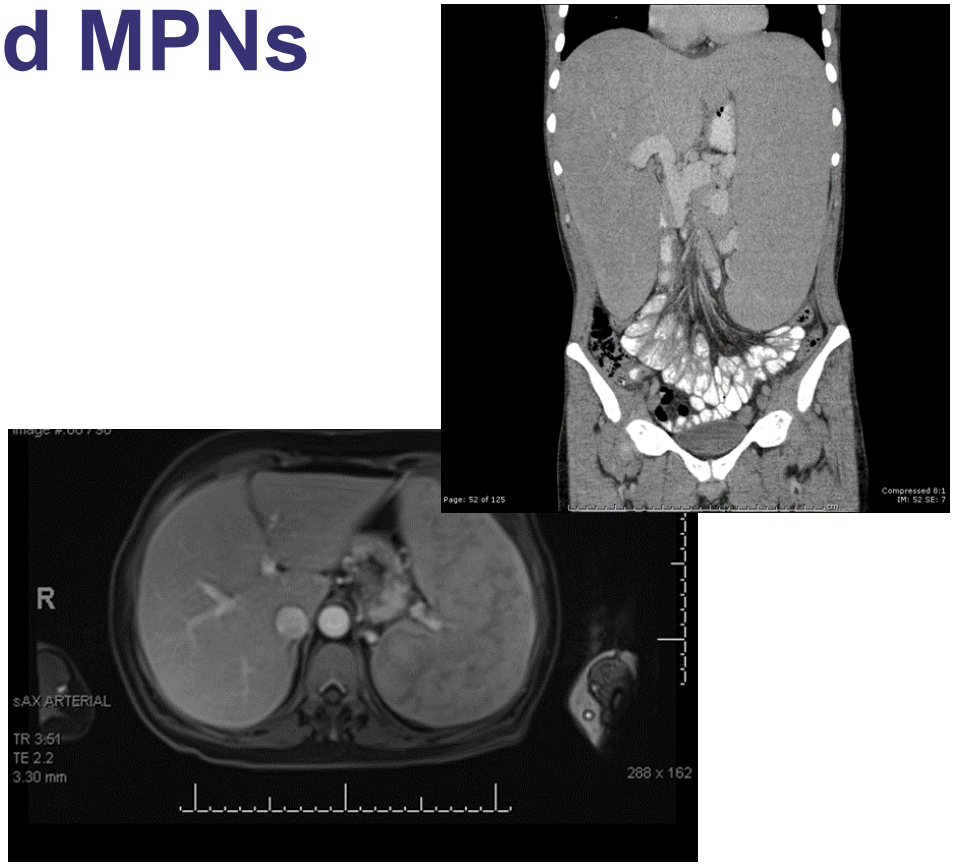
Fatigue	Dizziness	Night sweats
Early satiety	Numbness	Itching
Abdominal pain	Insomnia	Bone pain
Abdominal discomfort	Sad mood	Fever
Inactivity	Sexuality problems	Weight loss
Headache	Cough	Quality of life
Concentration problem	Erythromelalgia	

- Myeloproliferative Symptom Assessment Form (MPN-SAF)
- Includes Brief Fatigue Inventory
- Survey of Symptoms and Impact on Daily Activities

Symptom Burden and MPNs

Clinical findings

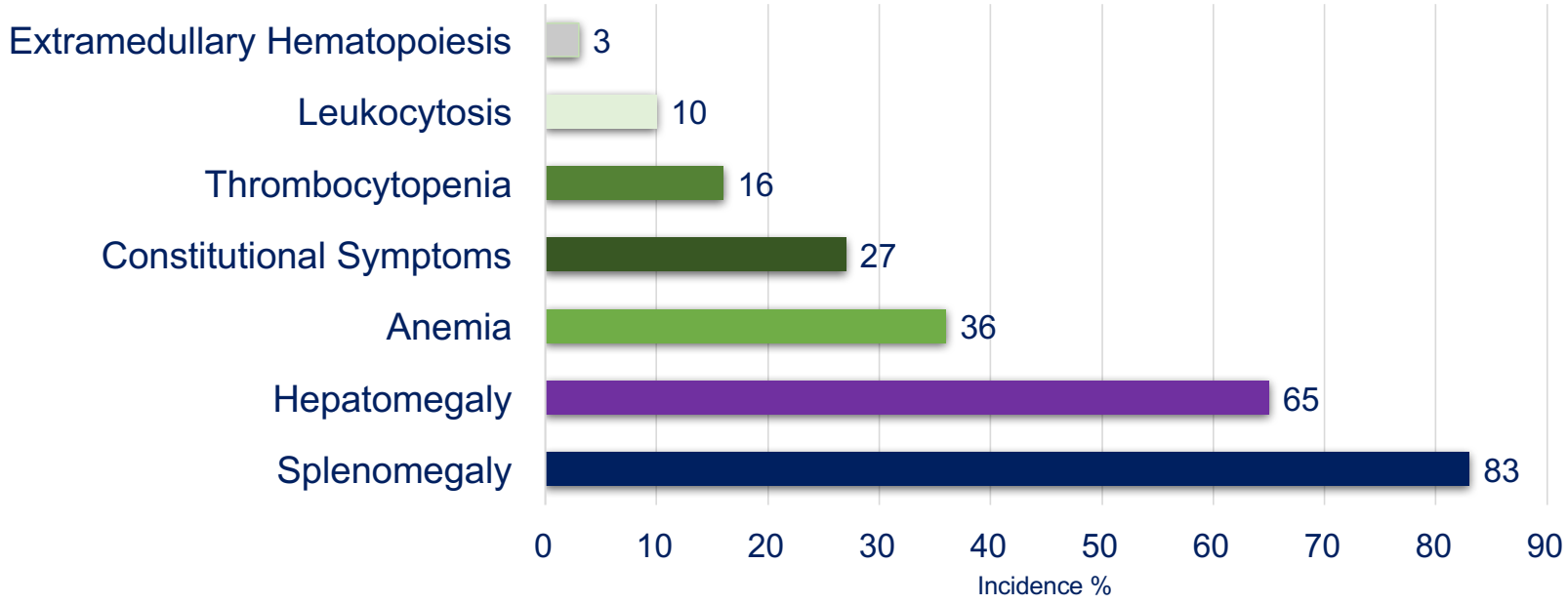
- Pan-myelopoiesis
- Thrombosis (venous or arterial)
  - DVT, PE
  - Stroke or MI
  - Splanchnic vein thrombosis
- Splenomegaly
  - 20%–30% in MF; 10% in PV, uncommon in ET
- Hepatomegaly (secondary)
- Portal hypertension
- Esophageal varices



PE = pulmonary embolism; MI = myocardial infarction

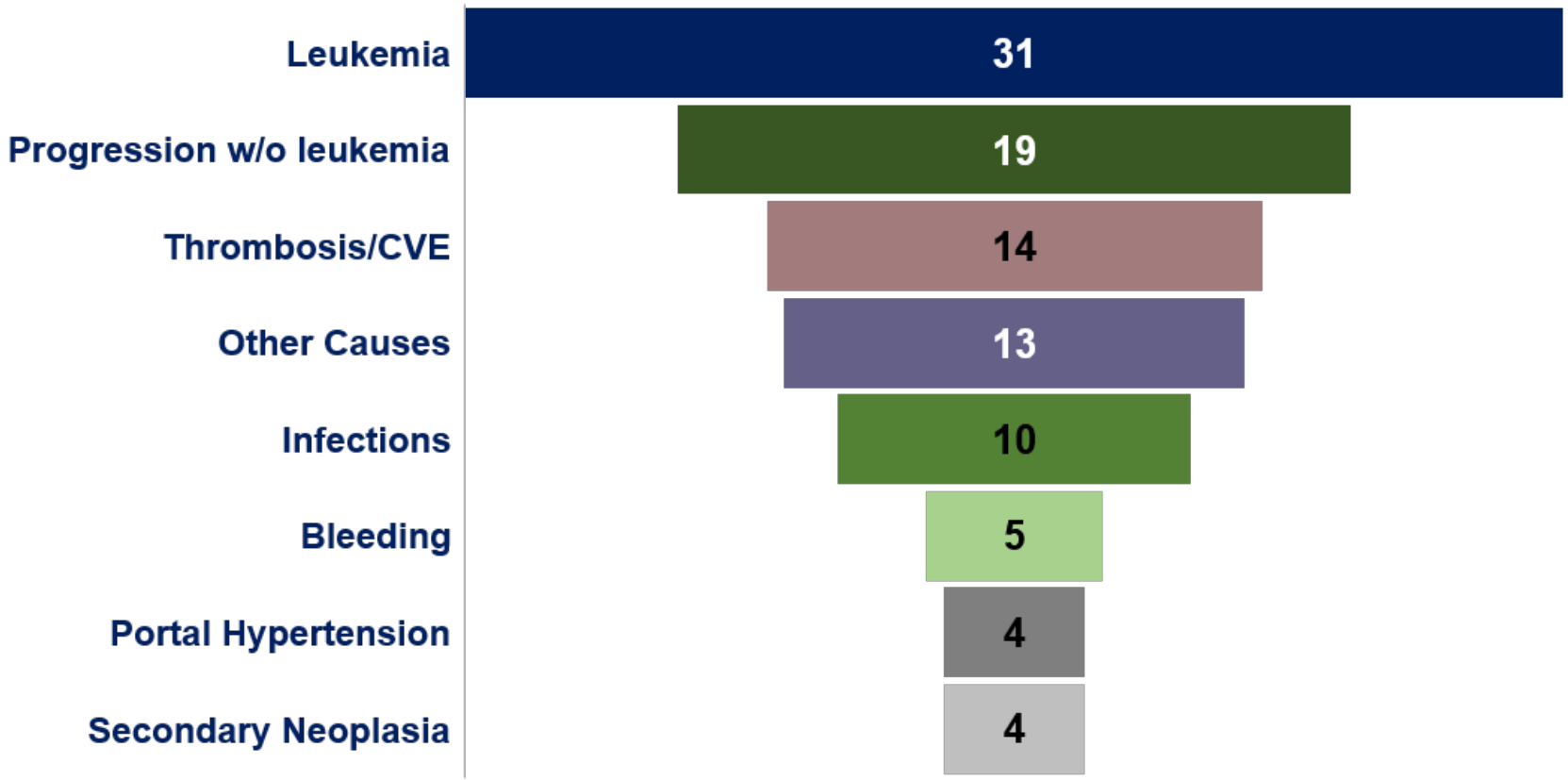
Ageno W, Dentali F, Squizzato A. *Blood.* 2014;124(25):3685-3691.
Mesa RA. *Blood.* 2009;113(22):5394-5400.
Hultcrantz M, Bjorkholm M, Dickman PW, et al. *Ann Intern Med.* 2018

Main Clinical Problems in MF



Barbui T et al. *Blood* 2010;115;778-82; Passamonti F et al. *Blood* 2010;116:2857-8

Cause of Death in MF



Barbui T et al. *Blood* 2010;115; 778-82; Passamonti F et al. *Blood* 2010;116:2857-8

Essential Thrombocythemia

WHO Criteria for the Diagnosis of ET

Diagnosis requires that all four major criteria are met, or the first three major criteria and the minor criteria are met.

	Major Criteria
1.	Platelet count > 450 x 10^9/L
2.	BM 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.
3.	Not meeting WHO criteria for BCR-ABL11 CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
4.	Presence of *JAK2*, *CALR*, or *MPL* mutation
	Minor Criteria
1.	Presence of a clonal marker or absence of evidence for reactive thrombocytosis

Arber DA, Orazi A, Hasserjian R, et al. *Blood.* 2016;127(20):2391-2405.

Characteristics of MPNs: ET

Clinical and morphologic features	Clinical outcomes
• Thrombocytosis • Normocellular bone marrow, proliferation of enlarged megakaryocytes • Microvascular symptoms • Thrombosis • Hemorrhage • Splenomegaly is rare	• Increased risk of thrombosis and bleeding • May progress to more aggressive myeloid neoplasms • JAK2 (V617F)-mutant ET: high risk of thrombosis, and higher risk of progression to post-ET MF • CALR-mutant ET: lower risk of thrombosis and higher risk of progression to myelofibrosis • Triple-negative ET is an indolent disease with low incidence of vascular events

Rumi & Cazzola, *Blood*. 2017;129(6):680-692
O'Sullivan JM, Harrison CN. *Molecular and Cellular Endocrinology*. 2017;451:71-79

Revised International Prognostic Score for Thrombosis in Essential Thrombocythemia

Risk category	Characteristics
Very low risk	No thrombosis history, age 60 yr or younger, and *JAK2* wild type
Low risk	No thrombosis history, age 60 yr or younger, with *JAK2* mutation
Intermediate risk	No thrombosis history, age older than 60 yr, and *JAK2* wild type
High risk	Thrombosis history or age older than 60 yr, with *JAK2* mutation

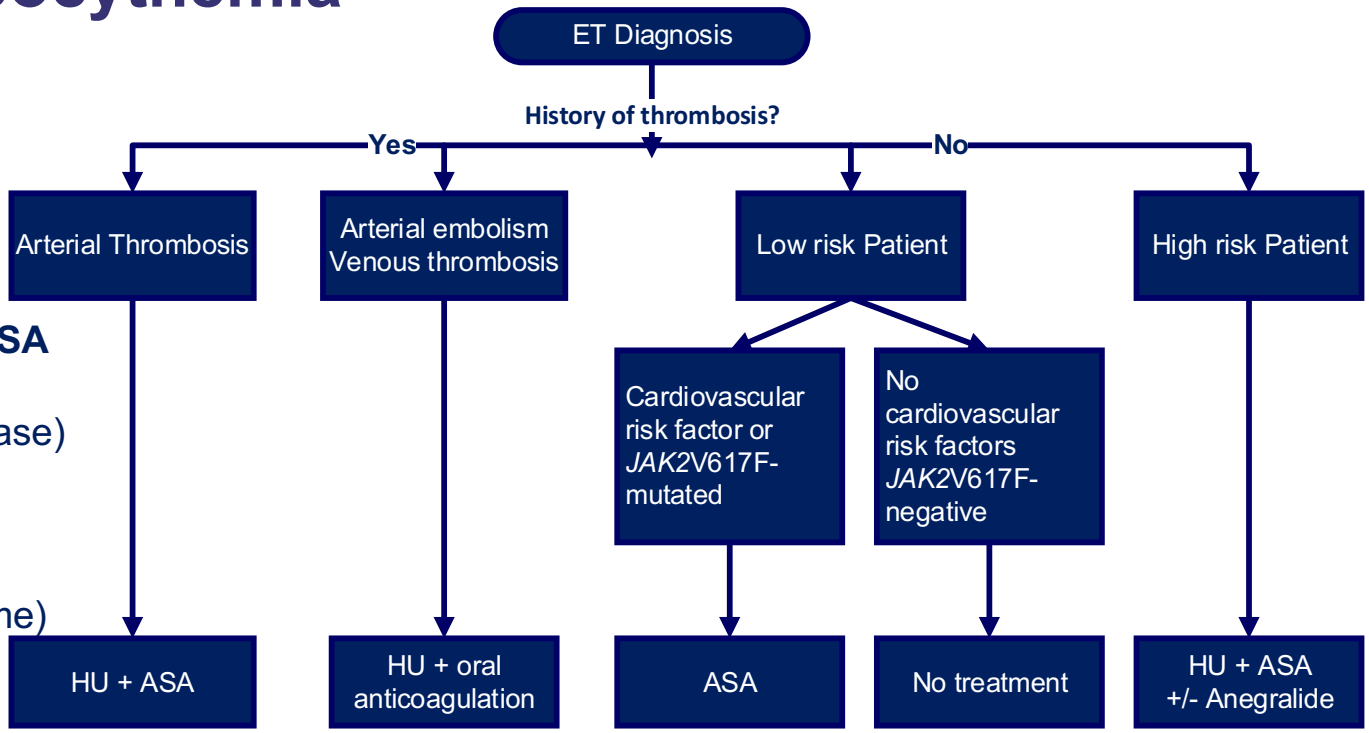
Treatment Decision-Making for Essential Thrombocythemia

Goal:

Platelets < 400 x 10^9/L and
Leukocytes <10 10^9/L

Contraindications to low-dose ASA

Platelets > 1,500 x 10^9/L
(acquired von Willebrand disease)
History of bleeding
Active bleeding
Allergy to ASA
Children < 12 years (Reye syndrome)



HU = hydroxyurea

Besses C, Alvarez-Larrán A. Clinical Lymphoma Myeloma and Leukemia. 2016;16, Supplement:S114-S123.

Polycythemia Vera

WHO Criteria for the Diagnosis of PV

Diagnosis requires meeting either all 3 major criteria or the first 2 major criteria and the minor criterion

	Major criteria	Minor criterion
1.	Elevation in red blood cell count Men: Hgb >16.5 or Hct > 49% Women: Hgb > 16 or Hct > 48%	Decrease in erythropoietin levels in blood
2.	Hypercellular bone marrow	
3.	Identification of a molecular mutation JAK2 V617F (95%) or JAK2 Exon 12 (3%)	

Key changes:
↓ Hct threshold to increase diagnosis of “masked PV”
Included requirement for bone marrow biopsy for differential diagnosis of PV vs. JAK2 mutated ET

Hgb = hemoglobin; Hct = hematocrit

Arber DA, Orazi A, Hasserjian R, et al. *Blood.* 2016;127(20):2391-2405.

Characteristics of MPNs: PV

Clinical and morphologic features	Clinical outcomes
• Erythrocytosis • May also have thrombocytosis and/or leukocytosis • Erythromelalgia • Aqueous pruritus • Splenomegaly (10%) • Suppressed endogenous erythropoietin • Hypercellularity bone marrow with panmyelopoeisis	• Increased risk of thrombosis • May progress to post-PV-MF (5%–10% over 10 years) • May progress to MDS, AML (2%–14%)

Rumi & Cazzola, *Blood*. 2017;129(6):680-692
O'Sullivan JM, Harrison CN. *Molecular and Cellular Endocrinology*. 2017;451:71-79

IPSS PV

Risk factor	Points
Age ≥ 67 y	5
Age 57–66 y	2
Leukocyte count ≥ 15 x 10^9/L	1
Previous venous thrombosis	1

Risk	Points	Median survival
Low	0	28 yr
Intermediate	1–2	19 yr
High	≥ 3	11 yr

IPSS = International Prognostic Scoring System.

Risk Stratification for Thrombosis in PV

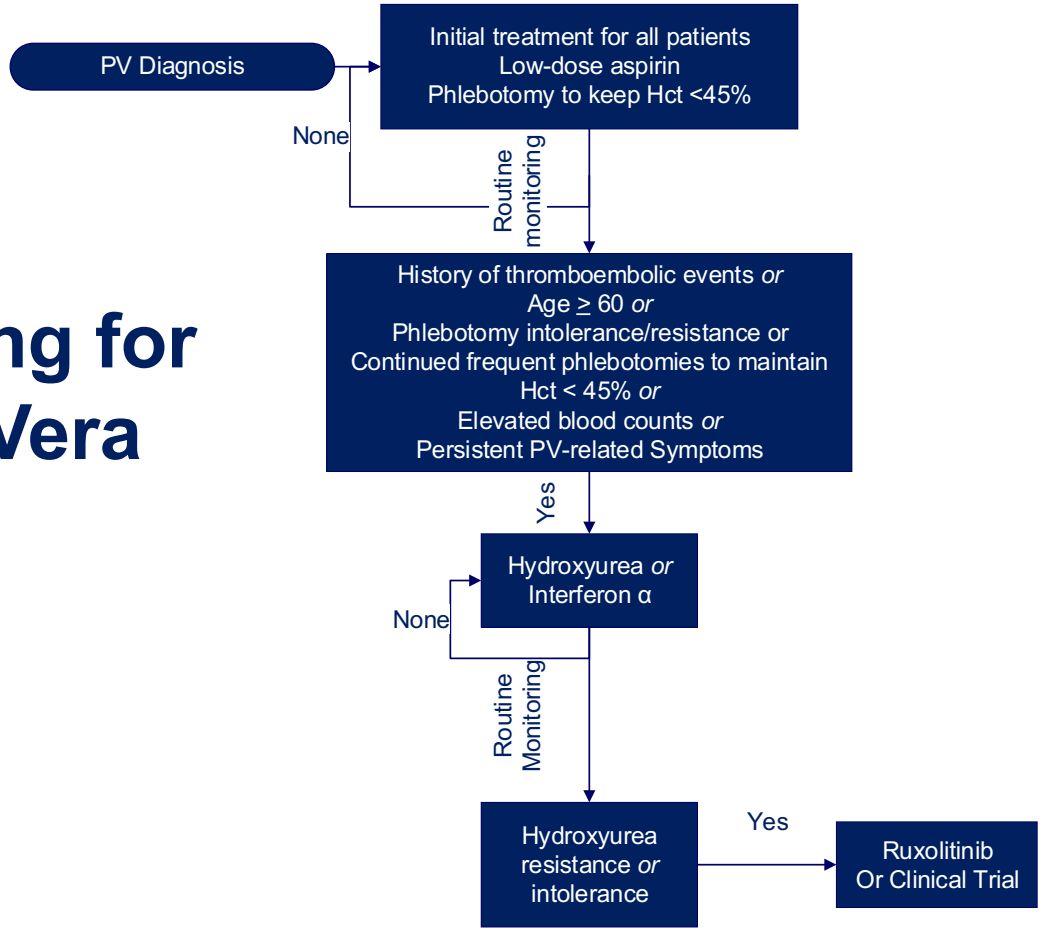
- High-risk PV: Age > 60 and/or a history of a blood clot
- Low-risk PV: Age < 60 and no history of a blood clot

Contributing factors

- Elevated white blood cell count
- Cardiovascular risk factors
  - Congestive heart failure
  - Arterial hypertension
  - Hypercholesterolemia
- Diabetes mellitus
- Tobacco use
- Obesity
- Immobility

Besses C, Alvarez-Larran A. *Clinical Lymphoma, Myeloma & Leukemia.* 2016;16 Suppl:S114-123.
Bose P, Gotlib J, Harrison CN, Verstovsek S. *Clinical Lymphoma, Myeloma & Leukemia*. 2018;18(1):1-12.

Treatment Decision-Making for Polycythemia Vera



Adapted from: Kurtin & Lyle, *J Adv Pract Oncol* 2018;9(1):56–66

European LeukemiaNet Definition of Resistance and Intolerance to HU in PV

1. Need for phlebotomy to keep hematocrit < 45% after 3 mo of 2 g/day of HU, or
2. Uncontrolled myeloproliferation (i.e., platelets > 400 x 10^9/L and leukocytes >10 x 10^9/L) after 3 mo of 2 g/day of HU, or
3. Failure to reduce massive (10 cm below the left costal margin) splenomegaly by 50% measured using palpation, or failure to completely relieve symptoms related to splenomegaly, after 3 mo of 2 g/day of HU, or
4. Absolute neutrophil count < 1 x 10^9/L or platelets < 100 x 10^9/L or hemoglobin < 10 g/dL at the lowest dose of HU required to achieve a complete or partial response, or
5. Presence of leg ulcers or other unacceptable HU-related nonhematologic toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of HU

Alvarez-Larrán et al *Blood* 2012;119:1363–1369. https://doi.org/10.1182/blood-2011-10-387787

Myelofibrosis

WHO Criteria for Overt Primary Myelofibrosis

Requires meeting all 3 major criteria, and at least 1 minor criterion

	Major Criteria
1.	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
3.	Presence of *JAK2*, *CALR*, or *MPL* mutation or in the absence of these mutations, presence of another clonal marker, or absence of reactive myelofibrosis
	Minor Criteria **Presence of at least 1 of the following, confirmed in 2 consecutive determinations**
1.	Anemia not attributed to a comorbid condition
2.	Leukocytosis ≥ 11 × 10^9/L
3.	Palpable splenomegaly
4.	LDH increased to above upper normal limit of institutional reference range
5.	Leukoerythroblastosis

LDH = lactate dehydrogenase

Arber DA, Orazi A, Hasserjian R, et al. *Blood.* 2016;127(20):2391-2405.

International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) Diagnostic Criteria for Post-Polycythemia Vera Myelofibrosis (Post-PV-MF)

	Required Criteria
1.	Documentation of a previous diagnosis of PV as defined by the WHO criteria
2.	Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)
	Additional Criteria: Presence of at least 2 are required
1.	Anemia or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis
2.	A leukoerythroblastic peripheral blood picture
3.	Increasing splenomegaly defined as either an increase in palpable splenomegaly or ≥ 5 cm (distance of the spleen from the left costal margin) or the appearance of newly palpable splenomegaly
4.	Development of ≥ 1 of three constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)

International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) Diagnostic Criteria for Post-Essential Thrombocythemia Myelofibrosis (Post-ET-MF)

Required Criteria	
1.	Documentation of a previous diagnosis of ET as defined by the WHO criteria
2.	Bone marrow fibrosis grade 2–3 (on 0–3 scale) or grade 3–4 (on 0–4 scale)
Additional Criteria: Presence of at least 2 are required	
1.	Anemia and ≥ 2 g/dL decrease from baseline hemoglobin level
2.	A leukoerythroblastic peripheral blood picture
3.	Increasing splenomegaly defined either as an increase in palpable splenomegaly or > 5 cm (distance of the spleen from the left costal margin) or the appearance of newly palpable splenomegaly
4.	Development of > 1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)

Characteristics of MPNs: MF

Clinical and morphologic features	Clinical outcomes
Pre-fibrotic • Various abnormalities of peripheral blood • Granulocytic and megakaryocytic proliferation in the bone marrow with lack of reticulin fibrosis *Fibrotic* • Various abnormalities of peripheral blood • Megakaryocytic proliferation with atypia, with either reticulin and/or collagen fibrosis grades 2/3 • Abnormal stem cell trafficking with myeloid metaplasia (extramedullary hematopoiesis in the liver and/or the spleen)	• Greatest symptom burden • Worst prognosis • Variable risk of progression to AML • CALR-mutant PMF: longer survival • JAK2 (V617F)- and MPL-mutant PMF: worse prognosis • Triple-negative PMF: an aggressive myeloid neoplasm characterized by prominent myelodysplastic features and high risk of leukemic evolution

Rumi & Cazzola, *Blood*. 2017;129(6):680-692
O'Sullivan JM, Harrison CN. *Molecular And Cellular Endocrinology*. 2017;451:71-79

DIPSS - PMF

Risk factor	Points
Age ≥ 67 yr	5
Age 57–66 yr	2
Leukocyte count ≥ 15 x 10^9/L	1
Previous venous thrombosis	1

Risk	Points	Median survival
Low	0	15 yr
Intermediate-1	1–2	6.6 yr
Intermediate-2	3–4	2.9 yr
High	5–6	1.3 yr

DIPSS = Dynamic International Prognostic Scoring System; PMF = primary myelofibrosis.

DIPSS-Plus - PMF

DIPSS-Plus can be applied anytime during clinical course

Risk factor	Points
DIPSS – Low	0
DIPSS – Int 1	1
DIPSS – Int 2	2
DIPSS – High	3
RBC transfusion dependent	1
Platelets < 100 x 10^9/L	1
Unfavorable karyotype	1

Risk	Points	Median survival
Low	0	> 15 yr
Intermediate-1	1	6.6 yr
Intermediate-2	2–3	2.9 yr
High	4–6	1.3 yr

DIPSS = Dynamic International Prognostic Scoring System; RBC = red blood cell.

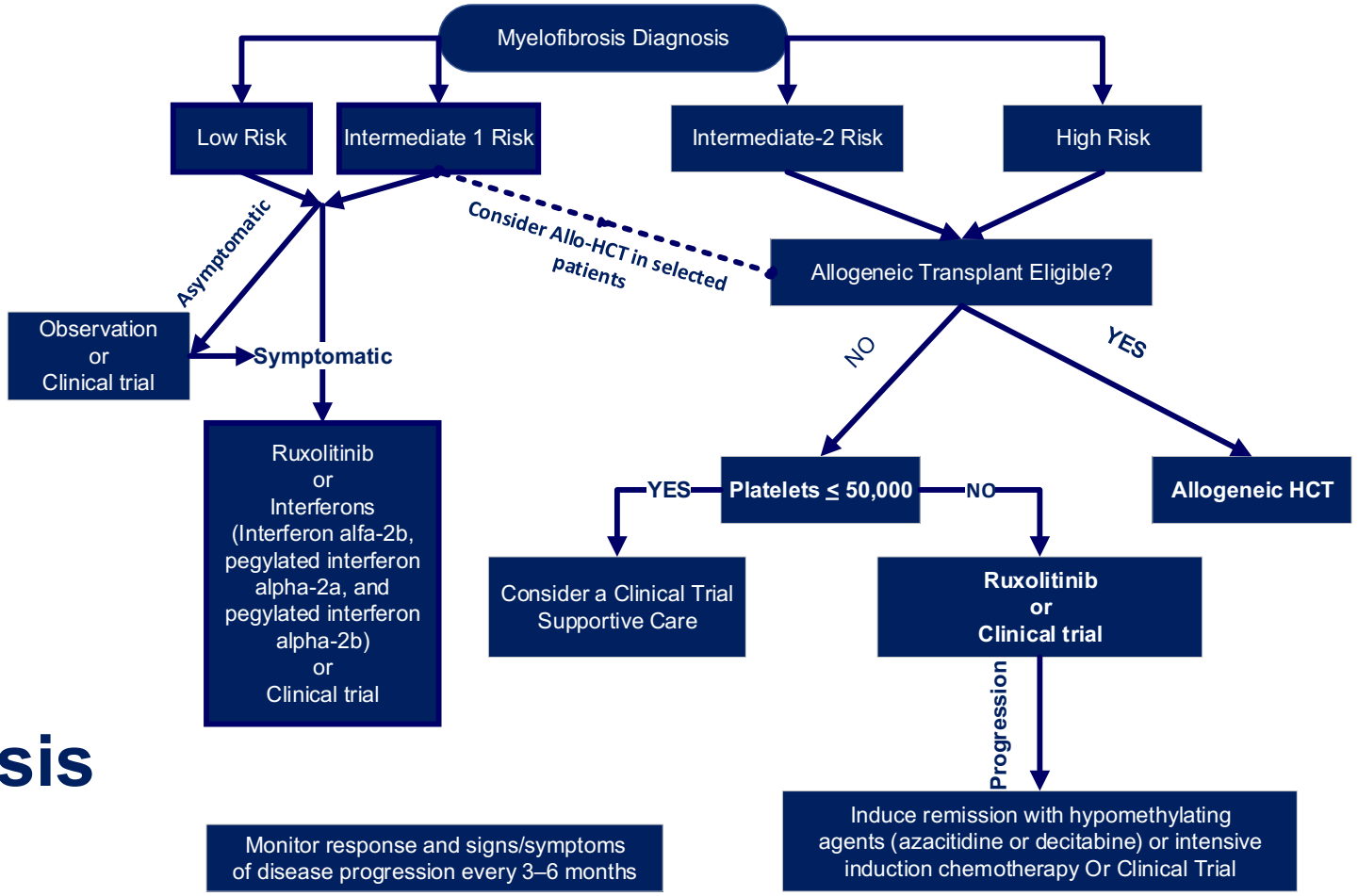
Gangat et al *J Clin Oncol*. 2010;29(4):392-397. doi:10.1200/jco.2010.32.2446

The Myelofibrosis Secondary to PV and ET Prognostic

Clinical variable	Points assigned
Hemoglobin < 11 g/dL	2
Circulating blasts 3%	2
CALR-unmutated genotype	2
Platelets < 150 x 10^9/L	1
Constitutional symptoms	1

Points total to be used along with patient age on published nomogram to identify risk category.

Treatment Decision-Making for Myelofibrosis



Mesa R, Jamieson C, Bhatia R, et al. *J Natl Compr Canc Netw.* 2016;14(12):1572-1611

JAK2 Inhibitors

- One of the most important developments in MPNs
- The first-in-class JAK1/2 inhibitor, ruxolitinib, was approved in 2011 for patients with MF
- Other JAK inhibitors are at various stages of clinical development, several pulled from development due to toxicity—possible off-target effects

Harrison et. al. *N Engl J Med* 2012;366:787-98.
Verstovsek et al. *N Engl J Med* 2012;366:799-807.

JAK2 Inhibitors: Ruxolitinib

- **Mechanism:** JAK1/2 inhibitor
  - FDA approved in November 2011 based on two phase III trials, COMFORT-I and COMFORT-II
- **Indication**
  - Treatment of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea
  - Treatment of patients with intermediate or high-risk myelofibrosis (MF), including primary MF, post–polycythemia vera MF and post–essential thrombocythemia MF
- **Clinical benefits**
  - Reduction in splenomegaly seen in almost all patients, 29%–42% (≥ 35% reduction in spleen volume)
  - Significant improvement in MF-associated symptoms, and improvement in self-reported QOL, marginal survival benefit in COMFORT-1, no survival benefit in COMFORT-II
  - Equally effective in unmutated JAK2 pts

JAK2 Inhibitors: Ruxolitinib (cont.)

Dosing and administration

- Dosing should be individualized based on platelet count to maximize efficacy and minimize toxicities
  - 5 mg bid for platelet count 50–100 x 10^9/L
  - 10 mg bid for platelet count > 100–200 x 10^9/L and moderate or severe renal impairment, any hepatic impairment or taking strong CYP3A4 inhibitor
  - 15 mg bid for platelet count 100–200 x 10^9/L
  - 20 mg bid for platelet count > 200 x 10^9/L
- Ruxolitinib should be tapered slowly if treatment is interrupted
- MF-related symptoms can return rapidly if drug is discontinued abruptly
- Treatment should continue until disease progression, allo-HST or unacceptable toxicity

JAK2 Inhibitors: Ruxolitinib (cont.)

Dosing and administration (cont.)

- May be taken with or without food
- May be given via nasogastric tube (8 French or greater)
- Should not be taken before dialysis
- Inform patient to report any
  - Bleeding
  - Signs and symptoms of infection
  - Report any changes in medications (Rx or OTC)
- Discuss need for frequent monitoring of blood counts, renal and hepatic function on the early days of treatment
- Dose adjustments may be required for cytopenias, renal or hepatic function

Ruxolitinib Safety: Warnings and Precautions

- **Infectious complications**
  - Serious bacterial, mycobacterial, fungal and viral infections have occurred; do not start in setting of active infection
  - Progressive multifocal leukoencephalopathy has occurred
  - Increases in hepatitis B viral load with or without associated elevations in alanine aminotransferase and aspartate aminotransferase have been reported in patients with chronic hepatitis B virus infections.
  - Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- Non-melanoma skin cancers including basal cell, squamous cell, and merkel cell carcinoma have occurred. Perform periodic skin examinations.
- Increases in total cholesterol, low-density lipoprotein cholesterol, and triglycerides have been reported. Assess lipid parameters 8-12 weeks after initiating treatment.

Ruxolitinib Safety

Common adverse events

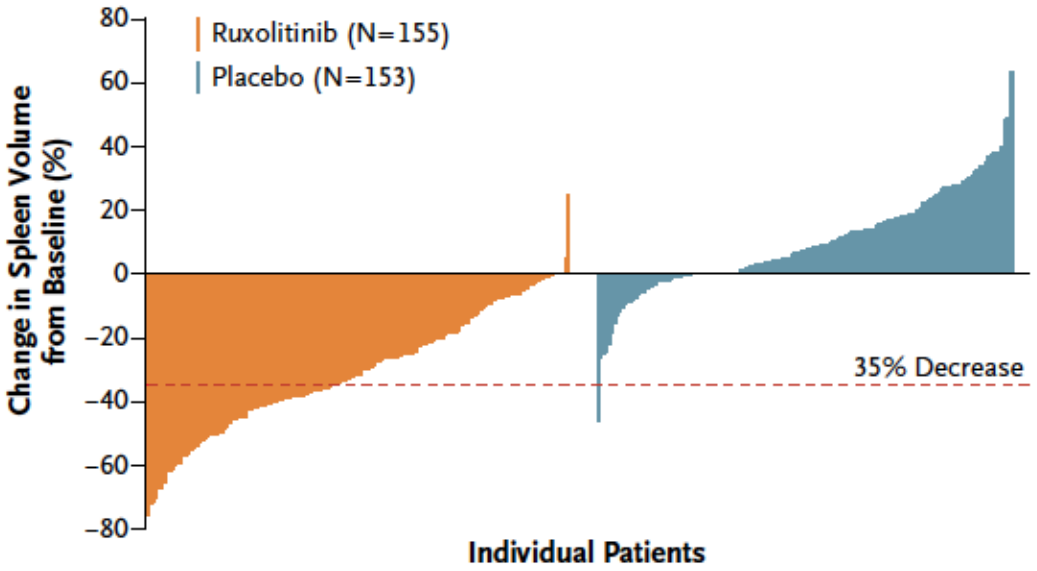
- Nonhematologic toxicities
  - The three most frequent nonhematologic adverse reactions (incidence >10%) were bruising, dizziness, and headache
  - No significant difference from placebo
- Hematologic toxicities
  - Compared with placebo (45% vs. 19%)
    - Thrombocytopenia (13% vs. 1%)

Ruxolitnib MF Clinical Trials: Spleen Volume

In COMFORT-II, at 48 weeks, 28.5% of patients receiving ruxolitinib achieved a ≥ 35% reduction in spleen volume vs. 0% of patients receiving best available therapy ($p < .0001$)

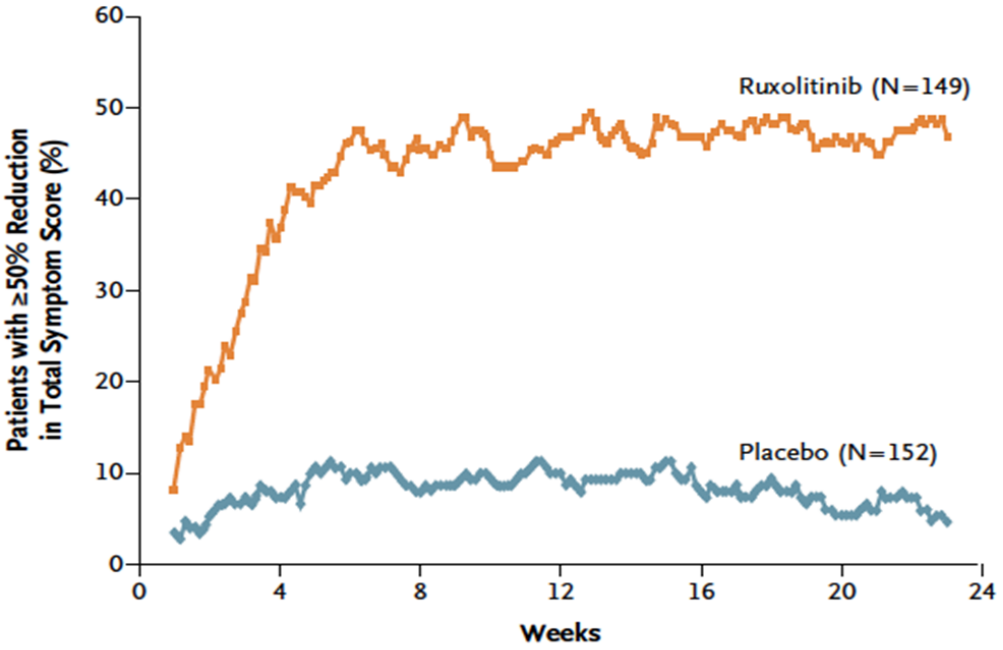
Patients in the lowest spleen volume quartile saw comparable reductions with ruxolitinib to those with more severe splenomegaly

~32% mean decrease in spleen volume was achieved at week 243



Verstovsek S et al. *N Engl J Med*. 2012;366:799-807.
Harrison CN, et al. *N Engl J Med*. 2012; 366: 787-798.
Deisseroth AB et al. *Clin Cancer Res*. 2012;18:3212-3217.

Improvement in Symptoms by TSS



Individual symptoms: abdominal discomfort, pain under left ribs, early satiety, night sweats, Itching, bone or muscle pain, inactivity

TSS = Total Symptom Score

COMFORT-I Trial: 3-Year Update

- Patient disposition
- Median follow-up of 149 weeks
  - 77/155 patients (49.7%) originally randomized to ruxolitinib were still receiving ruxolitinib therapy
  - 111/154 (72%) originally randomized to placebo crossed over to ruxolitinib therapy
  - 57/111 (51.4%) were still receiving ruxolitinib therapy
  - 42 patients randomized to ruxolitinib and 54 randomized to placebo had died
- Median time to crossover was 9 months
- Overall survival probability
  - At 3 years, survival probability was 70% for patients originally randomized to ruxolitinib and 61% for those originally randomized to placebo
- Median exposure to ruxolitinib was 145 weeks for patients originally randomized to ruxolitinib, mean dose remained stable after initial dose adjustments in first 8–12 weeks of therapy.

Verstovsek S et al. *Haematologica* 2015; 100(4).
Verstovsek S el al. *Blood*. 2013;122(21). Abstract 396.
Verstovsek S et al. *N Engl J Med*. 2012;366(9):799-807

COMFORT-II Trial: 3-Year Update (cont.)

- Patient disposition
  - 66/146 (45.2 %) still on treatment with ruxolitinib
  - 45/73 (61.6%) had crossed over and 48.9% of those who crossed over were still on treatment with ruxolitinib
- Most common reasons for discontinuation
  - Adverse event, disease progression, other reasons including transplant, study drug interruption, or withdrawal of consent
- Overall survival probability
  - Kaplan-Meier estimated probability of survival at 144 weeks was 81% in ruxolitinib arm and 61% in best available therapy arm
- Safety
  - Hematologic toxicity remained grades 1 and 2 and rarely lead to definitive treatment discontinuation
  - Increased frequency of infections in ruxolitinib arm, but rarely severe and decreased over time
  - No new safety signals
  - Durable reductions in splenomegaly

Cervantes F et al. *Blood*. 2013;122:4047-4053

COMFORT Trials: 5-Year Update

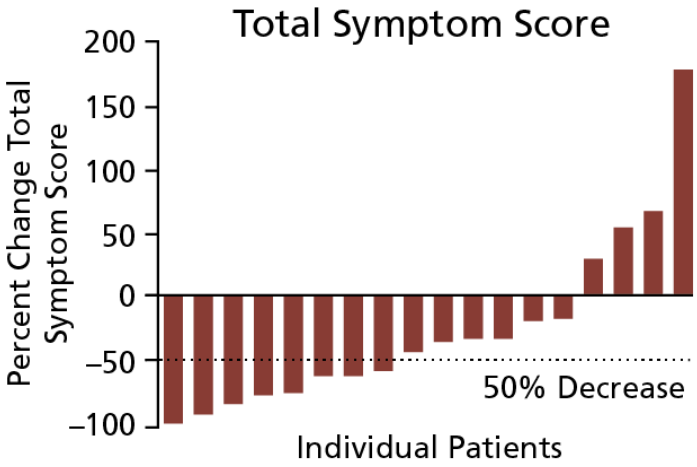
- Rates of best response improved over time
- No new safety signals emerged
- Median duration of spleen response ~3 years
- Patients originally assigned to ruxolitinib lived longer than those assigned to placebo or BAT, despite near-complete crossover, confirming the superior survival observed at earlier time points (trials not powered for overall survival)
- Benefit in MF greatest in patients with a JAK2V617F allele burden > 50%
- The presence of ≥ 3 non-driver mutations associated with ↓ probability of spleen response, shorter time to treatment discontinuation and inferior survival

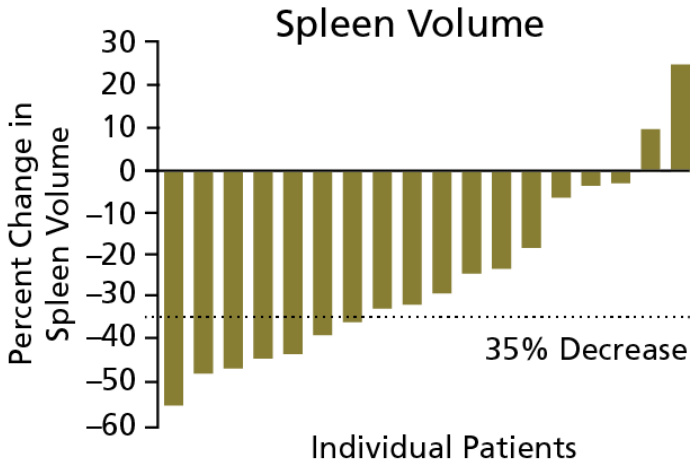
Verstovsek S, Mesa RA, Gotlib J, et al. *J Hematol Oncol* 2017; 10:55.
Harrison CN, Vannucchi AM, Kiladjian JJ, et al. *Leukemia* 2016; 30:1701-7.

JAK Inhibition in Patients With Low Platelet Counts

Starting dose of ruxolitinib 5 mg twice daily, with escalations to 15 mg twice daily in patients with MF and platelets 50–100 x 10^9/L

Pts with IPSS int-1/2 or high risk MF (evaluable N = 41)
At 24 wk, most pts optimized to ruxolitinib dose 10 mg bid or higher; spleen volume reduction and TSS reduction consistent with data reported in COMFORT-I





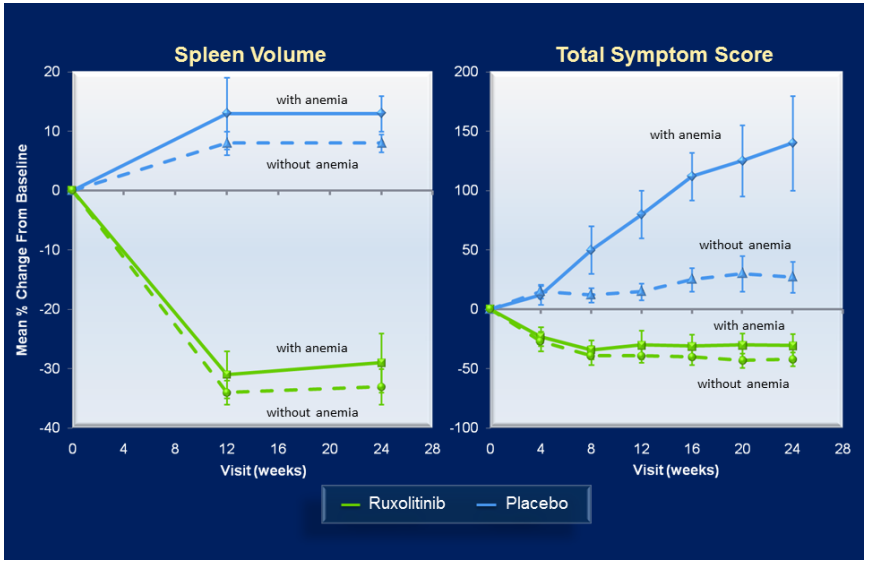
COMFORT-I: Reduction of JAK2V617F Allele Burden on Ruxolitinib

- Higher allele burden associated with higher leukocyte counts, hemoglobin levels and more profound splenomegaly
- Reduction in allele burden from baseline correlated with spleen volume reductions
- Changes in JAK2p.V617F allele burden did not correlate with changes in other clinical/hematologic parameters, bone marrow morphology, constitutional symptoms, or cytokines

Verstovsek S et al. *Haematologica* 2015; 100(4).
Verstovsek S el al. *Blood*. 2013;122(21). Abstract 396.
Verstovsek S et al. *N Engl J Med*. 2012;366(9):799-807

Development of Anemia Does Not Affect Response to Ruxolitinib Treatment

- Androgens, steroids, erythropoiesis-stimulating agents – limited overall benefit
- Immunomodulatory agents
  - Lenalidomide ~20% response
  - Pomalidomide ~30% response
  - Concomitant cytopenias when combined with ruxolitinib
  - Thalidomide–less myelosuppressive–clinical trial with ruxolitinib and thalidomide is ongoing
- Clinical trials
  - Activin receptor type II ligand traps – response ~40% when combined with ruxolitinib or as a single agent



Verstovsek S, et al. Oral presentation at ASCO Annual Meeting; June 3-7, 2011. Abstract 6500.

JAK Inhibitors in Clinical Trials for MPNs

Inhibitor	Selectivity	Diseases	Clinical phase
Ruxolitinib	JAK2>JAK1>JAK3	MF and hydroxyurea resistant or intolerant PV Refractory leukemia (post-MPN leukemia)	FDA-approved Phase II
Momelotinib (CYT-387)	JAK2>JAK1>JAK3 (off target - ALK-2 TBK1, IKKε)	PMF, Post PV/ET MF PV/ET	Phase III - SIMPLIFY-1/2 (Stopped) Phase II (terminated)
AZD1480	JAK2>JAK1 (off target - Aurora A, FGFR1, FLT4	PMF Post PV/ET MF	Phase I (completed)
Gandotinib (LY2784544)	Pan-JAK JAK2V617F>JAK2	JAK2V617F-positive MF, ET and PV patients	Phase I Phase II (in progress)

JAK Inhibitors in Clinical Trials for MPNs

Inhibitor	Selectivity	Diseases	Clinical phase
Pacritinib (SB11518)	JAK2 (off target – FLT3)	MF	Phase III: PERSIST-1, PERSIST-2 PAC203 study evaluating the effect of lower doses
NVP-BVB808	JAK2 (off target – FLT3)	MPN	Cell lines
TG101209	JAK2 (off target – FLT3)	MPN, systemic sclerosis	Cellular models
Fedratinib (TG101348)	JAK2 (off target – FLT3, BRD4)	MPN	Phase III: JAKARTA FDA removed the clinical hold August 2017
Itacitinib (INCB-039110)	JAK1	MF	Phase II (alone or in combination with low-dose of ruxolitinib)

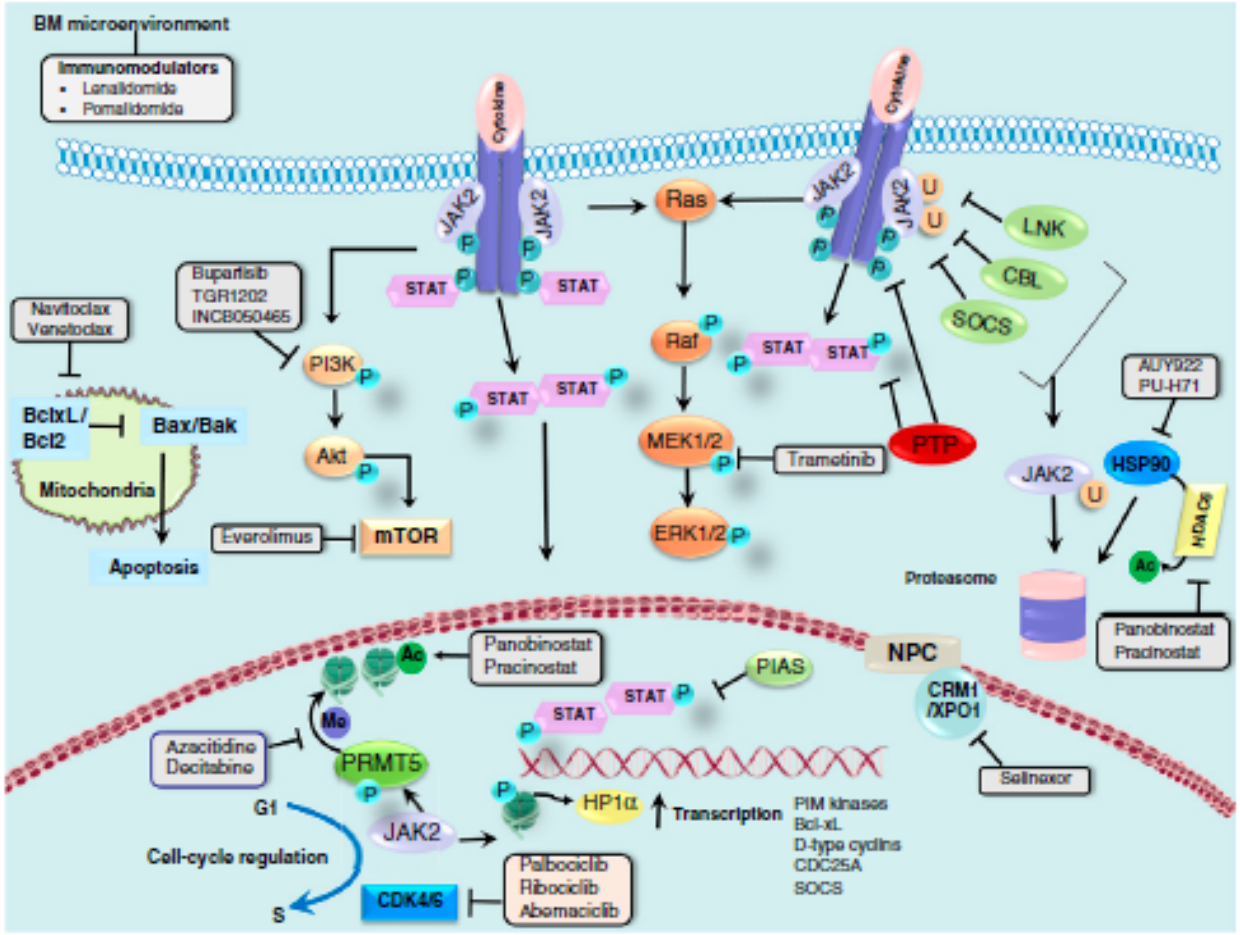
Vainchenker W, Leroy E, Gilles L, Marty C, Plo I, Constantinescu SN. F1000Research. 2018;7:82.

MDS/MPN Overlap Syndromes: CMML

- Aberrant signaling through the granulocyte-macrophage colony-stimulating factor pathway, JAK-STAT dependent
- JAK2 inhibition in CMML has been demonstrated preclinically in phase 1 trial (n= 520)
- Phase II trial: Ruxolitinib 20 mg twice per day
  - No dose-limiting toxicities were identified
  - Objective responses using MDS response criteria (mostly hematologic improvement) occurred in 5 patients
- Majority of patients had improvement or resolution in splenomegaly and disease related symptoms
- The combination of ruxolitinib and azacitidine seems promising in patients with unclassifiable MDS/MPNs

CMML = chronic myelomonocytic leukemia.

Molecular Pathways in MPNs: Opportunities for Future Treatment



Ruxolitinib Combinations in Clinical Trials

Partner drug class	Specific agent	Clinicaltrials.gov identifier
Histone deacetylase inhibitor	Panobinostat	NCT01693601
	Panobinostat	NCT01433445
	Pracinostat	NCT02267278
Phosphatidylinositol-3-kinase (delta isoform) inhibitor	INCB050465	NCT02718300
	Idelalisib	NCT02436135
	TGR1202	NCT02493530
Immunomodulatory agent	Thalidomide	NCT03069326
	Lenalidomide	NCT01375140
	Pomalidomide	NCT01644110
Janus kinase 1 inhibitor	Itacitinib	NCT03144687
BH3-mimetic	Navitoclax	NCT03222609

Ruxolitinib Combinations in Clinical Trials

Partner drug class	Specific agent	Clinicaltrials.gov identifier
Hedgehog (smoothened) inhibitor	Vismodegib	NCT02593760
	Sonidegib	NCT01787552
Cyclin-dependent kinase 4/6 inhibitor and PIM kinase inhibitor	Ribociclib and PIM447	NCT02370706
Androgen	Danazol	NCT01732445
Interferon	Pegylated interferon alfa 2a	NCT02742324
Hypomethylating agent	Azacitidine	NCT01787487
Activin receptor ligand trap	Sotatercept	NCT01712308
	Luspatercept	NCT03194542
Erythropoiesis stimulating agent	Any (observational study)	NCT03208803

Bose P, Verstovsek S. *Blood*. 2017;130(2):115-125.

Audience Response Question #13

Which of the following patient profiles requires initiation of cytoreductive therapy using a JAK2 inhibitor?

A. Confirmed diagnosis of ET, *JAK2* mutation, no prior thrombosis, age 58, platelets 750,000
B. New diagnoses of PV, *JAK2* mutation, no history of thrombosis, splenomegaly, on ASA, requiring phlebotomy to keep Hct < 45%
C. Age 58, confirmed diagnosis of myelofibrosis with asymptomatic splenomegaly, *JAK2, CALR, MPL+*
D. Diagnosis of PV, age 72, history of DVT, on hydroxyurea and ASA, requiring phlebotomy to keep Hct < 45%
E. Unsure

Hct = hematocrit; PV = polycythemia vera, DVT = deep-vein thrombosis; ASA = acetylsalicylic acid.

Audience Response Question #14

Which driver mutations are not present in patients with polycythemia vera?

A. JAK2 V617F and MPLW515L
B. JAK2 exon 12 and MPLW515K
C. CALR exon 9 and MPLW515L
D. JAK2 exon 12 and CALR exon 9
E. Unsure