Myeloproliferative Neoplasms (MPNs): Diagnosis, Treatment, and Side Effects Management

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LEARNING OBJECTIVES

- Describe the types of myeloproliferative neoplasms, including myelofibrosis, polycythemia vera, and essential thrombocythemia
- Identify tests used to diagnose disease and monitor treatment
- Explain the overarching goals of treatment for the various types of myeloproliferative neoplasms
- Explain approved and emerging treatment options for all myeloproliferative neoplasms, including stem cell transplantation, and the role of clinical trials
- Describe strategies to manage treatment side effects as well as potential long-term and late effects of treatments
- Identify resources for patients, caregivers and healthcare providers

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Myeloproliferative Neoplasms: Diagnosis, Treatment, and Side Effects Management

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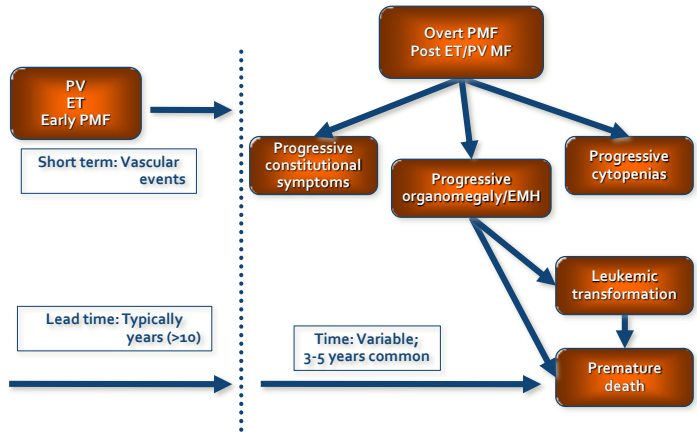
MPN Overview: Timeframes



EMH, extramedullary hematopoiesis; ET, essential thrombocythemia; MF, myelofibrosis; PMF, primary myelofibrosis, PV, polycythemia vera

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Pinilla-Ibarz J et al. (2016). Onco Targets Ther, 9:4937-4957; Lichtman M et al. (2011). Williams Manual of Hematology (8th ed). New York: McGraw Hill Medical.

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JAK2 V617F Mutation Discovery in MPNs: "The Other BCR-ABL"

March 18, 2005

Acquired mutation of the tyrosine kinase JAK2 in human myeloproliferative disorders

March 24, 2005

Activating mutation in the tyrosine kinase JAK2 in polycythemia vera, essential thrombocythemia, and myeloid metaplasia with myelofibrosis

April 28, 2005

letters to nature

A unique clonal *JAK2* mutation leading to constitutive signalling causes polycythaemia vera

THE NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Gain-of-Function Mutation of *JAK2* in Myeloproliferative Disorders

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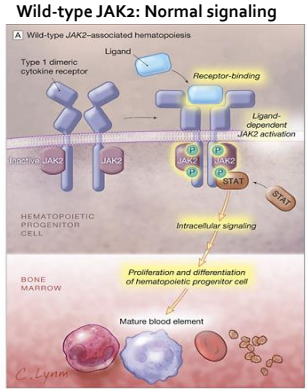
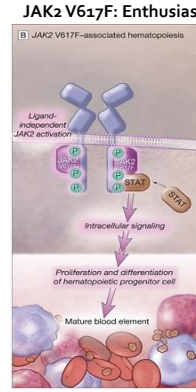
JAK2 Signaling in MPNs: Finding the "Driver"

Wild-type JAK2: Normal signaling



JAK2 V617F: Enthusiastic signaling



Disease	Frequency
PV	~95%
ET	~50-60%
PMF	~50-60%

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Stein B, *JAMA*. 2010;303(24):2513-2518.

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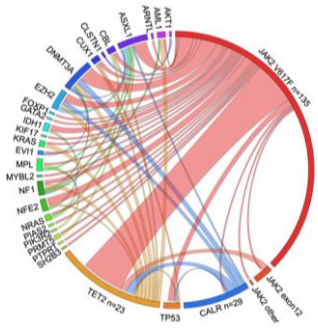
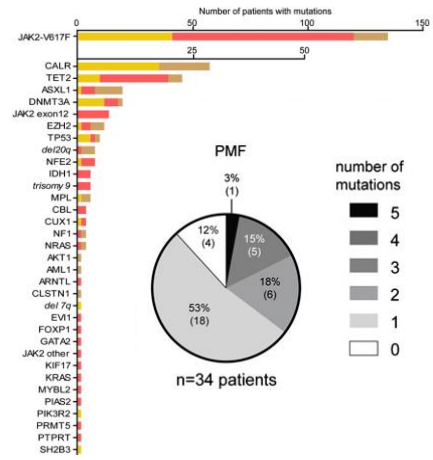
Frequency and Distribution of "Driver" and Other Mutations in Patients With MPNs





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Courtesy of J. Mascarenhas, modified from Lundbertg P et al. Blood. 2014;123(14):2220-8.

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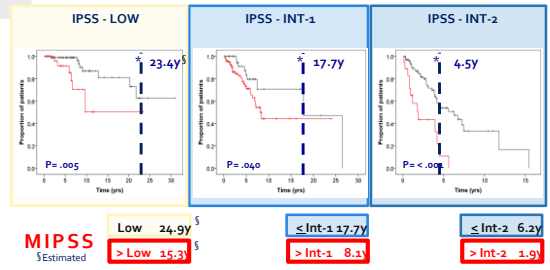
Molecular International Prognostic Scoring System[1] in Myelofibrosis

MULTIVARIATE ANALYSIS			Weighted value
Variables	HR (95% CI)	P	
Age >60 yrs	3.8 (2.60-5.51)	<0.0001	1.5
Hgb <100 g/L	1.4 (1.01-1.99)	0.04	0.5
Constitutional Symptoms	1.5 .(1.13-2.16)	0.007	0.5
PLT <200x10⁹/L	2.5 (1.77-3.42)	<0.0001	1.0
Triple Negativity	3.9 (2.20-6.80)	<0.0001	1.5
JAK2/MPL mutation	1.8 (1.11-2.90)	0.016	0.5
ASXL1 mutation	1.4 (1.06-1.99)	0.02	0.5
SRSF2 mutation	1.7 (1.08-2.58)	0.02	0.5

Refines prognostic stratification within the IPSS categories→

*, IPSS Median Survival



MIPSS §Estimated

Low 24.9y§	≤ Int-1 17.7y	≤ Int-2 6.2y
> Low 15.3y§	> Int-1 8.1y	> Int-2 1.9y

[1] Mutation-Enhanced International Prognostic Scoring System

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Vannucchi A et al. *Blood.* 2014;124:405.

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Molecular Prognosis in Myelofibrosis

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Mutated Gene	Primary Myelofibrosis (PMF)
JAK2 V617F	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]
MPL W515L/K	Intermediate prognosis and higher risk of thrombosis compared to patients with *CALR* mutation[1]
CALR	Improved survival compared to *JAK2* mutation and "triple-negative" PMF[1-4] Lower risk of thrombosis compared to *JAK2* mutation[1]
CALR Type 1/Type 1-like	Improved overall survival compared to *CALR* type 2/type 2-like and *JAK2* V617F mutation[5-8]
"Triple Negative" (non-mutated *JAK2, MPL, and CALR*)	Inferior leukemia-free survival compared to patients with *JAK2*- and/or *CALR*-mutated PMF[1-3] Inferior overall survival compared to patients with *CALR*-mutated PMF[2]
ASXL1	Independently associated with inferior overall survival* and leukemia-free survival[9]
EZH2	Independently associated with inferior overall survival[9]
IDH1/2	Independently associated with inferior leukemia-free survival[9]
SRSF2	Independently associated with inferior overall survival and leukemia-free survival[9]
Combined *CALR and ASXL1* status	Survival longest for *CALR*(+)*ASXL1*(-) patients (median 10.4 years) and shortest in *CALR*(-)*ASXL1*(+) patients (median 2.3 years)**[10] Intermediate survival (median 5.8 years) for *CALR*(+)*ASXL1*(+) or *CALR*(-)*ASXL1*(-) patients[10]
TP53	Associated with leukemic transformation[11]
U2AF1 Q157	Inferior overall survival compared to patients with *U2AF1* S34 mutated or *U2AF1* unmutated PMF. The effect was most evident in younger patients[12]

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NCCN Guidelines v3.2019. Myeloproliferative Neoplasms. Accessed November 6, 2019.

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Molecular Prognosis in Polycythemia Vera

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Myeloproliferative Neoplasms

Mutated Gene	Polycythemia Vera (PV)
ASXL1/ SRSF2/ IDH1/21	The presence of at least 1 of these "adverse variants/mutations" is associated with inferior overall survival (compared to other sequence variants/mutations, or none) independent of age, IWG prognostic model for PV, and karyotype.[2] Adverse variants/mutations also affected myelofibrosis-free survival.
JAK2 exon 12 mutation	Patients with *JAK2* exon 12-mutated PV exhibit younger age, increased mean hemoglobin/hematocrit, and lower mean white blood cell and platelet counts at diagnosis compared to those with *JAK2 V617F*-mutated PV. However, both *JAK2* mutations are associated with similar rates of thrombosis, evolution to myelofibrosis or leukemia, and death.[3,4]

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NCCN Guidelines v3.2019. Myeloproliferative Neoplasms. Accessed November 6, 2019.

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Molecular Prognosis in Essential Thrombocythemia

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Myeloproliferative Neoplasms

Mutated Gene	Essential Thrombocythemia (ET)
CALR	Lower-risk of thrombosis compared to *JAK2*-mutated ET[1-3] No difference in overall survival or myelofibrotic or leukemic transformation compared to *JAK2*-mutated ET[1-3] *CALR* mutation does not modify the IPSET score for predicting thrombosis in patients with ET[4]
TP53	Associated with inferior leukemia-free survival in multivariate analysis[5]
SH2B3/IDH2/U2AF1/ SF3B1/EZH2/TP53[6]	The presence of at least 1 of these "adverse variants/mutations" is associated with inferior overall survival (compared to other sequence variants/ mutations, or none) independent of age and karyotype[7] Adverse variants/mutations also affect myelofibrosis-free survival[7]

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NCCN Guidelines v3.2019. Myeloproliferative Neoplasms. Accessed November 6, 2019.

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Assessing MPN Patient Risk: Prognostic Models

	IPSET (ET—3 groups) *Survival thrombosis risk*	PV Risk (4 groups) *Survival leukemia rates*	DIPSS (PMF—4 groups) *Survival*
Age, years	≥ 60 (2 points) *vs* < 60	≥ 67 (5 points) 57-66 (2 points), < 60 (0)	≥ 65 (1 point) *vs* < 65
Leukocytes	≥ 11 (1 point) *vs* < 11 x 10^9/L	≥ 15 (1 point) *vs* < 15 x 10^9/L	> 25 (1 point) vs ≤ 25 x 10^9/L
Hemoglobin			< 10 (2 points) *vs* ≥ 10 g/dL
Constitutional symptoms			Present[a] (1 point) *vs* absent
Blasts			≥ 1% (1 point) *vs* < 1%
Prior thrombosis	Yes (1 point) *vs* No	Yes (1 Point) *vs* No	
Risk group point cutoffs	0; 1-2; 3-4 points	0; 1-2; 3; 4 points	0; 1-2; 3-4; ≥ 4 points

IPSET, International Prognostic Score of Thrombosis for Essential Thrombocythemia; DIPSS, Dynamic International Prognostic Scoring System

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Bose & Verstovsek. (2016). Cancer. 122:681-692.

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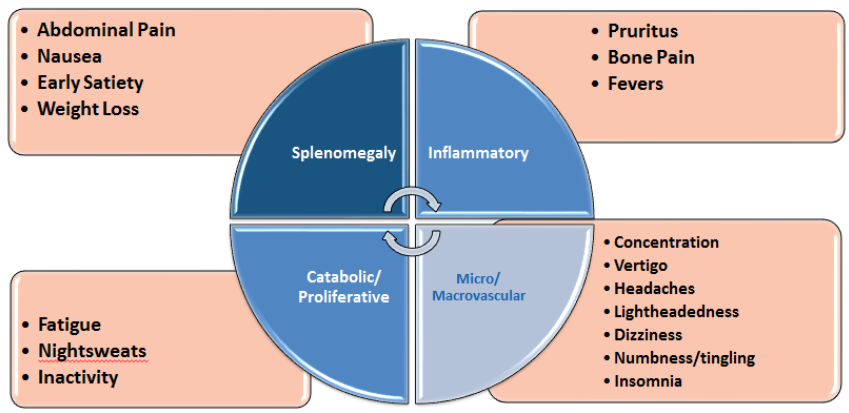
Symptom Burden in MPNs



Courtesy of R. Mesa, Mayo Clinic

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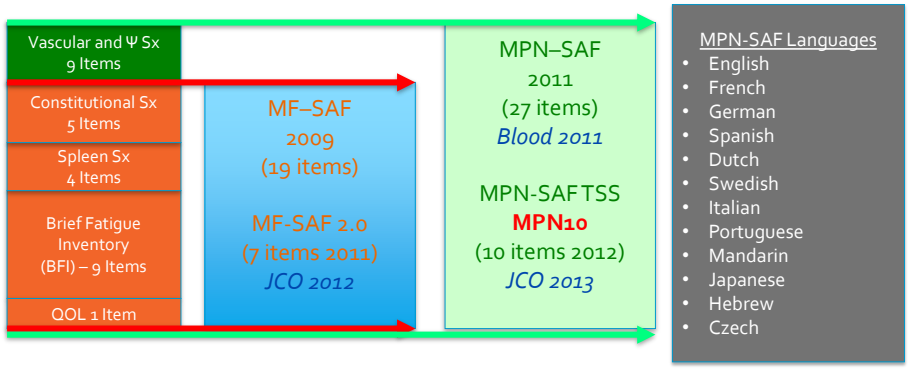
Formally Assessing MPN Symptom Burden: Symptom Assessment Form



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Courtesy of R. Mesa, Mayo Clinic.

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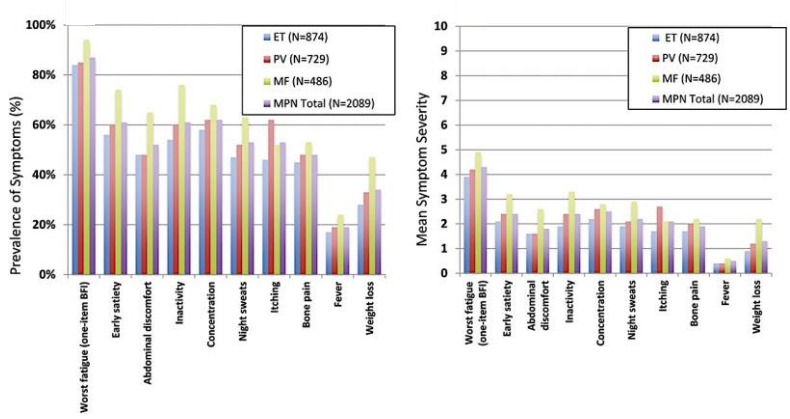
Signs and Symptoms of MPNs: Often Under-Queried…



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Geyer HL et al. *Blood*. 2014;124:3529-3537.

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MPN Symptom Assessment

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MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS; MPN-10)[1]

(Recommended for monitoring symptoms during the course of treatment)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

[1]Reproduced with permission from Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol 2012;30:4098-4103.

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NCCN Guidelines v3.2019. Myeloproliferative Neoplasms. Accessed November 6, 2019.

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Myelofibrosis

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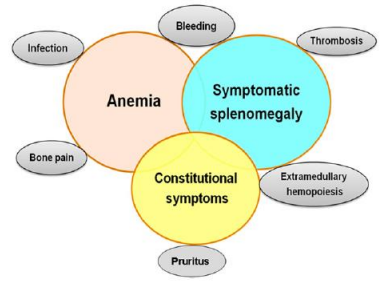
Clinical Features of Myelofibrosis

- **Bone marrow fibrosis**
- **Splenomegaly**
  - Splenomegaly-associated symptoms include abdominal pain/discomfort, early satiety
- **Cytopenias**
  - Anemia, thrombocytopenia
- **Constitutional symptoms**
  - Include fatigue, night sweats, pruritus (itching), bone aches, weight loss



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Cervantes F. *Blood*. 2014;124(17):2635-42.

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WHO Criteria for Diagnosis of Overt Primary Myelofibrosis

- **ALL 3 major criteria plus at least 1 minor criteria**

Major Criteria	Minor 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, MDS, 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	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

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

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MPN Fibrosis Grading

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Myelofibrosis Grading

- **MF-0**
  - **Scattered linear reticulin with no intersections (crossovers)corresponding to normal BM**
- **MF-1**
  - **Loose network of reticulin with many intersections, especially in perivascular areas**
- **MF-2**
  - **Diffuse and dense increase in reticulin with extensive intersections, occasionally with focal bundles of thick fibers mostly consistent with collagen, and/or focal osteosclerosis***
- **MF-3**
  - **Diffuse and dense increase in reticulin with extensive intersections and course bundles of thick fibers consistent with collagen, usually associated with osteosclerosis***

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NCCN Guidelines v3.2019. Myeloproliferative Neoplasms. Accessed November 6, 2019.

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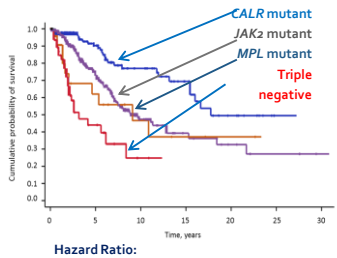
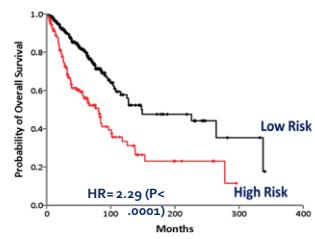
The "Driver" Mutation and Other Alterations Affect Outcome in MF

The mutational status of *JAK2*, *MPL* and *CALR* and the presence and number of other relevant mutations (*ASXL1*, *SRSF2*, *EZH2*, *IDH1/2*) provide IPSS/DIPSS-plus independent prognostic information



Hazard Ratio:
2.3 for *JAK2*V617F (P<.001)
2.6 for *MPL* (P=.009)
6.2 for Triple Negative (P<.001)



High risk:
any mutation in *ASXL1*, *EZH2*, *SRSF2*, *IDH1/2*

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Rumi E et al. *Blood.* 2014;124:1062-9.
Vannucchi AM et al. *Leukemia.* 2013;27:1861-9.

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Risk Stratification in Myelofibrosis

			Prognostic scoring system					
			Lille (1996)	IPSS (2009)	DIPSS (2010)	DIPSS+ (2011)	MIPSS (2014)	GPSS (2014)
Patient specific variable		Age		○	○	○	○	
Disease specific variables	clinic	Constitutional symptoms		○	○	○	○	
	laboratory	WBC	○	○	○	○		
		Hemoglobin <10 g/dL	○	○	○	○	○	
		Peripheral blood blasts >1%		○	○	○		
		Platelet count				○	○	
		RBC Transfusional support				○		
	genetic	Karyotype (-8, -7, -5, i17q, 12p-, inv3, 11q23 or complex)				○		○
		Mutational status					○	○

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Mascarenhas J. Hematology Am Soc Hematol Educ Program. 2015.

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2008 IWG-MRT Diagnostic Criteria for Post-PV MF and Post-ET MF

Diagnostic criteria for post-PV MF	Diagnostic criteria for post-ET MF
REQUIRED CRITERIA	
1. Documentation of a previous diagnosis of ET or PV as defined by the WHO criteria	
2. Bone marrow fibrosis grade 2/3 (on a 0-3 scale) or grade 3/4 (on a 0-4 scale)	
ADDITIONAL CRITERIA (2 are required)	**ADDITIONAL CRITERIA (2 are required)**
1. Anemia or sustained loss of requirement for either phlebotomy (in the absence of cytoreductive therapy) or for cytoreductive treatment for erythrocytosis	1. Anemia and a ≥ 2 mg/mL decrease from baseline hemoglobin level
	2. A leukoerythroblastic peripheral blood picture
2. A leukoerythroblastic peripheral blood picture	3. Increasing splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of newly palpable splenomegaly
3. Increasing splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly	4. Increased lactate dehydrogenase (above reference level)
4. Development of ≥ 1 of 3 constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)	5. Development of ≥ 1 of 3 constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)

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Barosi G et al. *Leukemia*. 2008;22:437-438.

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Risk-Adapted Treatment of Myelofibrosis

Low Risk
- Asymptomatic: Observation or clinical trial
- Symptomatic: JAK2 inhibitor, interferon, or clinical trial

INT-1
- Observation, JAK2 inhibitor, AlloSCT, anemia treatment, or clinical trial

INT-2 & High Risk
- Transplant candidates: AlloSCT
- Non-transplant candidate: Clinical trial or JAK2 inhibitor +/- anemia treatment

Anemia treatment may include: Immunomodulatory imide drugs (IMID), androgens, erythropoiesis stimulating agents; clinical trial, splenectomy

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Mesa RA. *Leuk Lymphoma.* 2013;54:242-51.
Geyer HL, Mesa RA. *Hematol.*2014 277-86.
NCCN Guidelines v3.2019. Myeloproliferative Neoplasms. Accessed November 6, 2019.

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Interferon for the Treatment of Myelofibrosis

Author, Year, study design	N	Intervention	CR/PR/ORR	Grade 3 – 4 ADRs
Jabbour E et al. 2007, Prospective	11	PEG-INF-α-2b (Peg-Intron®) 2-3 mcg/kg SC weekly (median dose: 1.5 mcg/kg weekly)	9%/0%/NR	Fatigue, myalgias, weakness, thrombocytopenia
Silver RT et al. 2013, Prospective single-arm trial	32	rIFN-α-2b (Intron A®) 500,000– 1 million units SC thrice weekly PEG-INF-α-2a (Pegasys®) 45 mcg SC weekly	9.4%/37.5%/78%	Thrombocytopenia
Ianotto JC et al. 2013, Retrospective	62	PEG-INF-α-2a (Pegasys®) 45 mcg SC weekly	ORR: 69 – 83% Spleen reduction: 46.5%	Anemia, thrombocytopenia, leukopenia

PEG-INF-α-2b (Peg-Intron®): Pegylated Interferon-alpha-2b (Peg-Intron®)
rIFN-α-2b (Intron A®): Interferon-alpha 2b
PEG-INF-α-2a (Pegasys®): Pegylated Interferon-alpha-2b (Peg-Intron®)

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Jabbour E et al. *Cancer*. 2007;110:2012-2018.
Silver RT et al. ASH 2013. Abstract 4053.
Ianotto JC et al. *Br J Haematol.* 2013;162(6):783-91.

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Interferon From a Pharmacist's Perspective

- Data supporting the use of 3 different formulations
  - PEG-INF-α-2b (Peg-Intron®), rIFN-α-2b (Intron A®), PEG-INF-α-2a (Pegasys®)
- Initial dosing
  - Dependent on formulation
- Dose adjustments
  - Renal impairment
  - Hematologic toxicity
- Drug interactions
  - No major interactions
- Warnings and precautions
  - Cytopenias, cognitive impairment, cutaneous reactions, GI hemorrhage, hepatotoxicity, hypersensitivity reactions, new or worsening depression, ophthalmic effects, pancreatitis, and pulmonary effects
- Administration
  - SC injection
- Dosage forms
  - Pre-filled syringes and solution for injection
- Storage
  - Store in the refrigerator
- Cost
  - $3,600 – $4,500/month
- Drug acquisition
  - Not FDA approved for any MPN
  - Will likely require prior authorization
- Disposal
  - Sharps container
  - Adhere to state laws

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Ruxolitinib (Jakafi®) in Myelofibrosis

COMFORT-I (N = 309) **Ruxolitinib (Jakafi®) vs. placebo in pts with intermediate- or high-risk MF**	• 41.9% (ruxolitinib [Jakafi®]) vs 0.7% (placebo) had ≥35% reduction in spleen volume at week 24 (P < 0.001)
COMFORT-II (N = 219) **Ruxolitinib (Jakafi®) vs. best available therapy (BAT) in pts with intermediate- or high-risk MF**	• 32% (ruxolitinib [Jakafi®]) vs 0% (BAT) had ≥ 35% reduction in spleen volume at week 24 (P < 0.001)

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Verstovsek S et al. *N Engl J Med.* 2012;366:799-807.
Harrison C et al. *N Engl J Med.* 2012;366:787-798.

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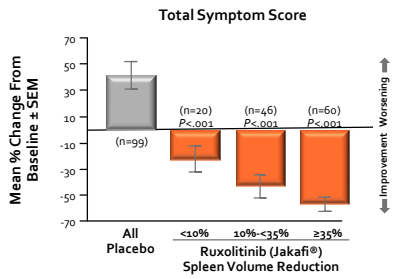
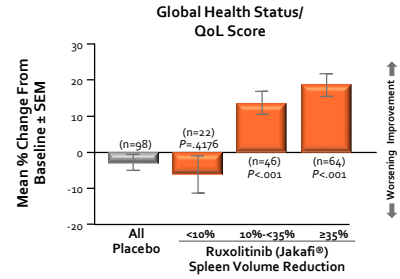
Effect of Spleen Volume Reduction on MF-Related Symptoms, QoL



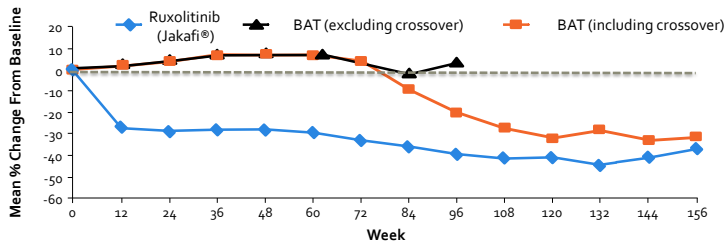


Memorial Sloan Kettering Cancer Center

Mesa RA et al. *J Clin Oncol.* 2013;31(10):1285-1292.

29

COMFORT-II: Mean Percentage Change in Spleen Volume Over Time



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Cervantes F et al. *Blood.* 2013;122(25):4047-53.

30

COMFORT-I: Non-Hematologic Adverse Events in ≥10%

Adverse Event	Ruxolitinib (Jakafi®), n = 155 % With Adverse Event		Placebo, n = 151 % With Adverse Event	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Fatigue	25	5	34	7
Diarrhea	23	2	21	0
Peripheral edema	19	0	23	1
Ecchymosis	**19**	**0**	**9**	**0**
Dyspnea	17	1	17	4
Dizziness	**15**	**1**	**7**	**0**
Nausea	15	0	19	1
Headache	**15**	**0**	**5**	**0**
Constipation	13	0	12	0
Vomiting	12	1	10	1
Pain in extremity	12	1	10	0
Insomnia	12	0	10	0
Arthralgia	11	2	9	1
Pyrexia	11	1	7	1
Abdominal pain	**10**	**3**	**41**	**11**

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

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Ruxolitinib (Jakafi®): Survival Data

COMFORT-I			COMFORT-II		
RUX (n=155) vs Placebo (n=154)			RUX (n=146) vs Best available therapy (n=73)		
Median follow-up	HR (95% CI)	*P* value*	Median follow-up	HR (95% CI)	*P* value*
OS at 1 year	0.50 (0.25–0.98)	0.04	OS at 1 year	0.70 (0.20–2.49)	
OS at 2 years	0.58 (0.36–0.95)	0.03	OS at 2 years	0.51 (0.27–0.99)	0.041
OS at 3 years	0.69 (0.46–1.03)	0.067	OS at 3 years	0.48 (0.28–0.85)	0.009

Combined Survival Data for COMFORT-I and COMFORT-II		
Median follow-up	HR (95% CI)	*P* value*
OS at 5 years	0.70 (0.54-0.91)	0.0065

Memorial Sloan Kettering Cancer Center

Harrison C et al. *N Engl J Med.* 2012;366(9):787–98.
Cervantes F et al. *Haematologica.* 2013;98(2):160–2.
Cervantes F et al. *Blood.* 2013;122(25):4047-53.

Verstovsek S et al. *N Engl J Med.* 2012;366(9):799–807.
Verstovsek S et al. *Haematologica.* 2013;98(12):1865–71.
Verstovsek S et al. *Haematologica.* 2015;100(4):479-88.
Verstovsek S et al. *J Hematol Oncol.* 2017;10:156.

32

Summary: Ruxolitinib (Jakafi®) in Patients With Myelofibrosis

- COMFORT-I and COMFORT-II phase III trials:
  - Efficacy
    - Spleen size reduction, significant improvement in symptoms, quality of life, performance status
    - Not selective for JAK2V617F (i.e., benefits patients with and without JAK2 mutation)
    - Possible prolongation of life in patients with advanced disease
  - Safety
    - Myelosuppression
    - Infection risk

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Ruxolitinib (Jakafi®) From a Pharmacist's Perspective

- Initial dosing
  - Dependent on platelet count and renal/hepatic function
- Dose adjustments
  - Renal impairment
  - Hepatic impairment
  - Hematologic toxicity
- Drug interactions
  - CYP_3A_4 and CYP2C9
- Warnings and precautions
  - Cytopenias, infection, discontinuation syndrome, non-melanoma skin cancers, & lipid elevations; Following discontinuation of Jakafi, symptoms from myeloproliferative neoplasms may return to pretreatment levels over a period of approximately one week. Some patients with MF have experienced one or more of the following adverse events after discontinuing Jakafi:
    - fever
    - respiratory distress
    - hypotension
    - DIC
    - multi-organ failure
- Administration
  - Regardless of food
  - Via nasogastric tube
- Dosage forms
  - 5, 10, 15, 20, and 25 mg tablets
- Cost
  - $12,703.20/month
- Drug acquisition
  - Specialty pharmacies only

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Jakafi (Ruxolitinib [package insert]. Wilmington, DE; 2016.

34

Fedratinib (Inrebic®): The Second Approved JAK Inhibitor for MF

- Phase II study of primary and secondary MF previously exposed to ruxolitinib (Jakafi®; n=97)
  - DIPSS INT-1 with constitutional symptoms
  - INT/High Risk
  - Splenomegaly ≥5cm below left CM
  - Platelets >50,000
- 1° endpoint: ≥35% reduction in spleen volume at 24 weeks
- 2° endpoint: ≥50% reduction in total symptom score at 24 weeks
- Fedratinib (Inrebic®) 400 mg QD

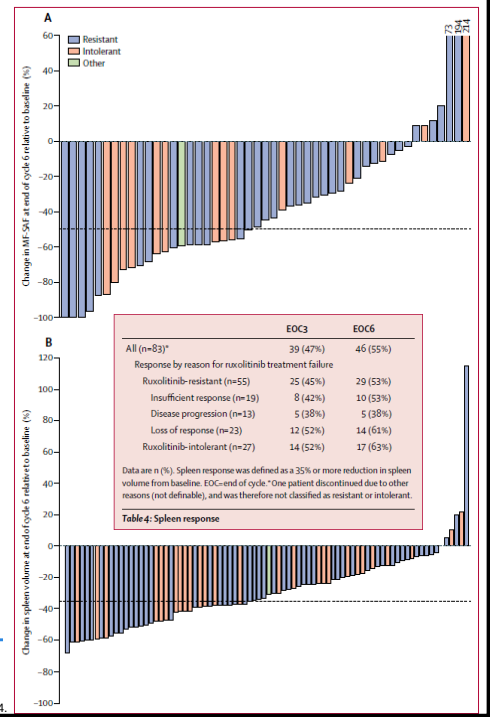
	Patients (n=97)
Initial daily ruxolitinib dose (mg)	
≤25	26 (27%)
30	39 (40%)
40	30 (31%)
50	2 (2%)
Cumulative dose administered (mg)	9040 (5075-13 005)
Duration of exposure (months)	10·25 (5·75-14·75)
Reduction in palpable spleen size at best response	
Ruxolitinib-resistant (n=53)	
≥50%	23/53 (43%)
<50%	30/53 (57%)
Ruxolitinib-intolerant (n=23)	
≥50%	10/23 (43%)
<50%	13/23 (57%)

Data are median (IQR), n (%), or n/N (%). Data are from the per-protocol population.

Table 3: Summary of previous ruxolitinib treatment

Prior RUX (Jakafi®) Response:

Fedratinib (Inrebic®) Response:



	EOC3	EOC6
All (n=83)*	39 (47%)	46 (55%)
Response by reason for ruxolitinib treatment failure		
Ruxolitinib-resistant (n=55)	25 (45%)	29 (53%)
Insufficient response (n=19)	8 (42%)	10 (53%)
Disease progression (n=13)	5 (38%)	5 (38%)
Loss of response (n=23)	12 (52%)	14 (61%)
Ruxolitinib-intolerant (n=27)	14 (52%)	17 (63%)

Data are n (%). Spleen response was defined as a 35% or more reduction in spleen volume from baseline. EOC=end of cycle. *One patient discontinued due to other reasons (not definable), and was therefore not classified as resistant or intolerant.

Table 4: Spleen response

Memorial Sloan Kettering Cancer Center

Harrison CN et al. *Lancet Haematol.* 2017;4:e317-24.

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Fedratinib (Inrebic®): The Second Approved JAK Inhibitor for MF

- Toxicity raised distinct novel AEs
  - 39% ≥ 1 dose reduction; most common for GI
  - 19% discontinuation for AEs
  - Most common AEs anemia, thrombocytopenia
- During study concern over risk of **Wernicke encephalopathy** (WE): acute neurological condition characterized by a clinical triad of ophthalmoparesis with nystagmus, ataxia, and confusion, generally caused by thiamine deficiency
- Grade 3 encephalopathy in one patient, adjudicated to be hepatic not Wernicke

FDA Label:

WARNING: ENCEPHALOPATHY INCLUDING WERNICKE'S
See full prescribing information for complete boxed warning.

Serious and fatal encephalopathy, including Wernicke's, has occurred in patients treated with INREBIC. Wernicke's encephalopathy is a neurologic emergency. Assess thiamine levels in all patients prior to starting INREBIC, periodically during treatment, and as clinically indicated. Do not start INREBIC in patients with thiamine deficiency; replete thiamine prior to treatment initiation. If encephalopathy is suspected, immediately discontinue INREBIC and initiate parenteral thiamine. Monitor until symptoms resolve or improve and thiamine levels normalize. (2.6, 5.1, 6.1).

	Grade 1–2	Grade 3–4	Grade 5
Haematological adverse events* (n=97)			
Anaemia	10 (10%)	37 (38%)	0
Thrombocytopenia	5 (5%)	21 (22%)	0
Lymphopenia	1 (1%)	3 (3%)	0
Non-haematological adverse events (n=97)			
Diarrhoea	56 (58%)	4 (4%)	0
Nausea	54 (56%)	0	0
Vomiting	40 (41%)	0	0
Constipation	19 (20%)	1 (1%)	0
Pruritus	16 (16%)	0	0
Fatigue	13 (13%)	2 (2%)	0
Headache	12 (12%)	1 (1%)	0
Cough	13 (13%)	0	0
Urinary tract infection	12 (12%)	0	0
Dyspnoea	11 (11%)	1 (1%)	0
Dizziness	11 (11%)	0	0
Abdominal pain	7 (7%)	2 (2%)	0
Alanine aminotransferase increased	3 (3%)	3 (3%)	0
Pneumonia	3 (3%)	2 (2%)	1 (1%)
Hyperlipasaemia	1 (1%)	3 (3%)	0
Hyperuricaemia	2 (2%)	2 (2%)	0
Dehydration	1 (1%)	2 (2%)	0
Tumour lysis syndrome	0	2 (2%)	0
Cardiac failure	1 (1%)	2 (2%)	0
Amylase increased	1 (1%)	2 (2%)	0
Blood bilirubin increased	0	2 (2%)	0
Cardiac failure	1 (1%)	2 (2%)	0
Respiratory failure	0	0	1 (1%)
Splenic rupture	0	0	1 (1%)

Data are n (%). Shown are any grade event occurring in more than 10% of patients, grade 3-4 events occurring in more than one patient, and all deaths (excluding four deaths due to disease progression). *Laboratory measurements.

Table 5: Adverse events

Memorial Sloan Kettering Cancer Center

Harrison CN et al. *Lancet Haematol.* 2017;4:e317-24.

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Fedratinib (Inrebic®) From a Pharmacist's Perspective

- Initial dosing
  - 400 mg PO daily
  - Baseline PLT >50
- Dose adjustments
  - Renal impairment
  - Hematologic toxicity
  - Non-hematologic toxicity
- Drug interactions
  - CYP3A4 and CYP2C19
- Warnings and precautions
  - Encephalopathy (Wernicke's), GI toxicity (N/V/D), cytopenias, hepatotoxicity
- Administration
  - Regardless of food
  - Take with high fatty meal to reduce N/V
- Dosage forms
  - 100 mg tablets
- Cost
  - $25,200/month
- Drug acquisition
  - Specialty pharmacies only

Check thiamine level prior to initiating treatment. Replete thiamine BEFORE starting fedratinib (Inrebic®)

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Inrebic® (fedratinib [package insert]). Summit, NJ; 2019.

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Patient Case: BP

- 60-year-old male with no major past medical history
- Presentation: Fatigue, pruritus, abdominal discomfort, 15-lb weight loss
- Physical exam: Splenomegaly by palpation (extends 8 cm below the left costal margin)

Diagnostics	
WBC	55x 10^9/L (reference range: 4.3-10.5 x 10^9/L)
Peripheral blasts	3%
Hgb	8.1 g/dL (reference range: Male, 13.8 to 17.2 g/dL)
Platelets	130 x 10^9/L (reference range: 150-400 x 10^9/L)
LDH	1000 IU/L (reference range: 105 - 333 IU/L)
Bone marrow	Atypical megakaryocytes and proliferation; grade 3 reticulin fibrosis
Cytogenetics	Normal karyotype
Diagnostic molecular pathology	BCR-ABL negative, JAK2V617F mutation

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Patient Case: BP

- Based on the patient's presentation, laboratory, and bone marrow biopsy findings, does the patient meet the criteria for PMF?
  - Yes
  - No

- **ALL 3 major criteria plus at least 1 minor criteria**

Major Criteria	Minor Criteria
1. Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3	At least 1 of the following, confirmed in 2 consecutive determinations:
2. Not meeting WHO criteria for ET, PV, BCR-ABL1+ CML, MDS, or other myeloid neoplasms	1. Anemia not attributed to a comorbid condition
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	2. Leukocytosis ≥ 11 x 10^9/L
	3. Palpable splenomegaly
	4. LDH increased to above upper normal limit of institutional reference range
	5. Leukoerythroblastosis

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BP's Risk Status

Patient Review: This 60-year-old man presented with constitutional symptoms and splenomegaly, WBC 55 x 10^9/L, peripheral blasts 3%, Hgb 8.1 g/dL, platelets 130 x 10^9/L, megakaryocyte atypia and grade 3 reticulin fibrosis, and *JAK2V617F* mutation.

What is the IPSS risk status of this newly-diagnosed PMF patient?

A. Low
B. Intermediate-1
C. Intermediate-2
D. High

IPSS Risk Assessment for PMF

Risk Factors	No. of Risk Factors	Risk Level	Median OS, mo.
❑ Age > 65 yrs	0	Low	135
Constitutional symptoms	1	Intermediate-1	95
Hgb <10 g/dL	2	Intermediate-2	48
WBC count > 25 x 10^9/L	≥ 3	High	27
Blood blasts ≥1%			

Memorial Sloan Kettering Cancer Center

Cervantes F et al. *Blood*. 2009;113:2895-2901.

40

Treatment Options for BP

- **Patient Review**: 60-year-old man presented with constitutional symptoms and splenomegaly, WBC 55 x 10^9/L, peripheral blasts 3%, Hgb 8.1 g/dL, platelets 130 x 10^9/L, megakaryocyte atypia and grade 3 reticulin fibrosis, a *JAK2V617F* mutation, and an IPSS score of 4

What is/are the best treatment options for BP?

A. Rituximab (Rituxan®)
B. Allogeneic stem cell transplant
C. Ruxolitinib (Jakafi®)
D. Interferon
E. Both B and C
F. None of the above

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Treatment for BP

- While allogeneic SCT would be a potentially curative option, BP opted against proceeding with transplant. As such, his hematologist would like to prescribe ruxolitinib (Jakafi®) and comes to you as the pharmacist to assist with dosing and acquisition of the drug.

Dosing Considerations	Drug Acquisition
• PLT count: 130 x 109/L • CrCL = 120 mL/hr • Hepatic function: Normal • Based on FDA labeling, the patient's dose would be 15 mg PO BID	• Insurance information • Specialty pharmacy • Consider starting with 5-mg tablets • Follow-up with specialty pharmacy • Assess financial feasibility • Identify co-pay assistance programs • Follow-up with patient

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Polycythemia Vera

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WHO Criteria for Diagnosis of PV

- **Diagnosis of PV requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion**

Major Criteria	Minor Criteria
1. Hgb >16.5 g/dL or HCT > 49% in men or Hgb > 16.0 or HCT > 48% in women or increased red cell mass 2. BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) 3. Presence of JAK2V617F or JAK2 exon 12 mutation	1. Subnormal serum erythropoietin level

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

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Risk-Adapted Management of Patients With PV

- Hematocrit (HCT) control is a key therapeutic goal
  - Maintaining HCT <45% significantly decreases the risk of cardiovascular death and major thrombotic events

Conventional Risk Category	Risk Variables	Therapy
Low	• Age < 60 years • No thrombosis history	• Phlebotomy, and • Correction of CV risk factors, and • Aspirin
High	• Age ≥ 60 years and/or • Thrombosis history	• Cytoreduction*, and • Correction of CV risk factors, and • Aspirin, and • Phlebotomy

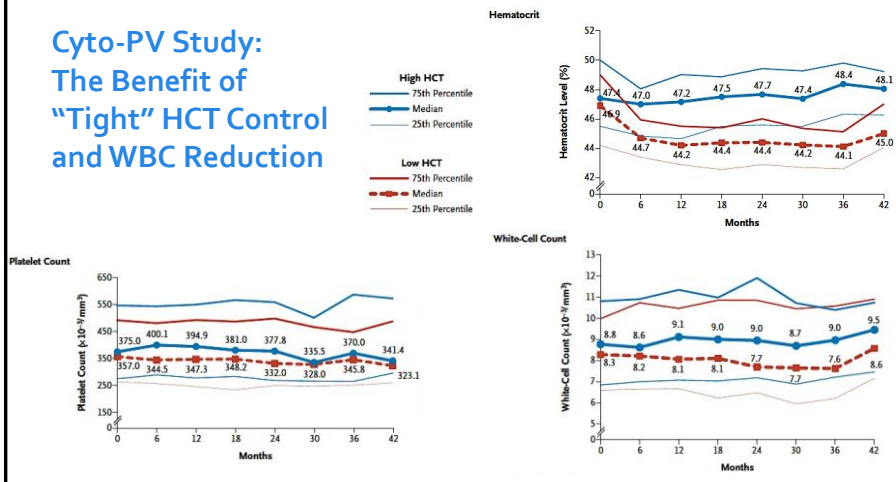
*Cytoreductive therapy includes hydroxyurea, interferon alfa, or busulfan for patients age >75 years

Memorial Sloan Kettering Cancer Center

Barbui T et al. *J Clin Oncol*. 2011;29(6):761-770.
Marchioli R et al. *N Engl J Med*. 2013;368(1):22-33.
Vannucchi AM. *Blood*. 2014;124(22):3212-3220.

45

Cyto-PV Study: The Benefit of "Tight" HCT Control and WBC Reduction



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Marchioli R et al. *N Engl J Med*. 2013;368:22-33.

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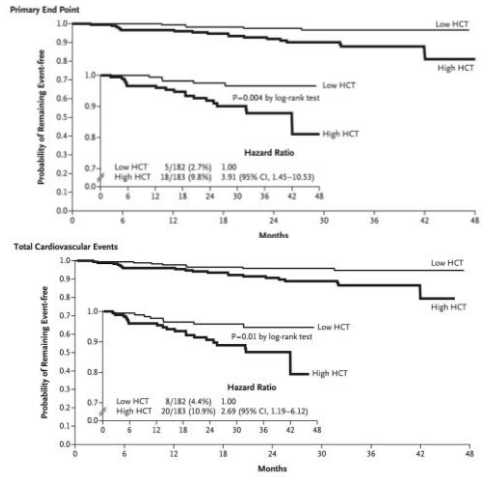
Cyto-PV Study: Events

Table 2. Primary and Secondary End Points.*

End Point	Low Hematocrit (N=182)	High Hematocrit (N=183)	All Patients (N=365)	Hazard Ratio (95% CI)	P Value
	number (percent)				
Primary end point†	5 (2.7)	18 (9.8)	23 (6.3)	3.91 (1.45–10.53)	0.007
Total cardiovascular events‡	8 (4.4)	20 (10.9)	28 (7.7)	2.69 (1.19–6.12)	0.02
Death					
All patients	3 (1.6)	6 (3.3)	9 (2.5)	2.16 (0.54–8.62)	0.28
Cardiovascular causes	0	4 (2.2)	4 (1.1)	NA	
Myocardial infarction	0	1 (0.5)	1 (0.3)	NA	
Stroke	0	2 (1.1)	2 (0.5)	NA	
Pulmonary embolism	0	1 (0.5)	1 (0.3)	NA	
Cancer	2 (1.1)	1 (0.5)	3 (0.8)	0.55 (0.05–6.02)	0.62
Nonfatal events					
Myocardial infarction	3 (1.6)	0	3 (0.8)	NA	
Stroke	0	4 (2.2)	4 (1.1)	NA	
Peripheral arterial thrombosis	0	3 (1.6)	3 (0.8)	NA	
Deep-vein thrombosis	1 (0.5)	4 (2.2)	5 (1.4)	4.11 (0.46–36.74)	0.21
Pulmonary embolism	0	1 (0.5)	1 (0.3)	NA	
Transient ischemic attack	1 (0.5)	4 (2.2)	5 (1.4)	4.24 (0.47–37.97)	0.20
Superficial thrombophlebitis	4 (2.2)	2 (1.1)	6 (1.6)	0.51 (0.09–2.79)	0.44
Bleeding	2 (1.1)	5 (2.7)	7 (1.9)	2.53 (0.49–13.06)	0.27
Hematologic progression or cancer					
Myelofibrosis	6 (3.3)	2 (1.1)	8 (2.2)	0.34 (0.07–1.67)	0.18
Myelodysplasia or acute leukemia	2 (1.1)	1 (0.5)	3 (0.8)	0.52 (0.05–5.71)	0.59
Other hematologic cancer	1 (0.5)	1 (0.5)	2 (0.5)	1.01 (0.06–16.23)	0.99
Solid cancer	7 (3.8)	5 (2.7)	12 (3.3)	0.74 (0.23–2.33)	0.60

* NA denotes not applicable.
† The primary end point was death from cardiovascular causes or thrombotic events (stroke, acute coronary syndrome, transient ischemic attack, pulmonary embolism, abdominal thrombosis, deep-vein thrombosis, or peripheral arterial thrombosis). The incidence of the primary end point was 1.1 per 100 person-years in the low-hematocrit group, as compared with 4.4 per 100 person-years in the high-hematocrit group.
‡ Total cardiovascular events consisted of the primary end point plus superficial-vein thrombosis. The incidence of total cardiovascular events was 1.9 per 100 person-years in the low-hematocrit group, as compared with 5.0 per 100 person-years in the high-hematocrit group.



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Marchioli R et al. *N Engl J Med*. 2013;368:22-33.

47

ECLAP Trial – Study Design

Prospective, multicenter, randomized, placebo-controlled trial

Inclusion Criteria

- Diagnosis of PV
- No contraindications of aspirin

N = 253 → Aspirin 100 mg PO daily

N = 265 → Placebo

Primary Endpoint:

- Cumulative rate of nonfatal MI, stroke, or death CV causes
- Cumulative rate of nonfatal MI, stroke, PE, major VTE, or death from CV causes

Secondary Endpoints:

- Fatal or nonfatal cerebrovascular events, fatal or nonfatal cardiac events, and major and minor thrombotic complications

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Landolfi R et al. *N Engl J Med*. 2004;350:114-24.

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ECLAP Trial – Results

End Point	Aspirin (N=253)	Placebo (N=265)	Relative Risk (95% CI)	P value
Nonfatal MI, nonfatal stroke, PE, major VTE, or death from CV causes	8 (3.2)	21 (7.9)	0.4 (0.18-0.91)	0.03
Nonfatal MI, nonfatal stroke, PE, DVT, or death from any cause	13 (5.1)	29 (10.9)	0.47 (0.25–0.91)	0.02
Major or minor thrombosis	17 (6.7)	41 (15.5)	0.42 (0.24–0.74)	0.003
Any Bleeding	23 (9.1)	14 (5.3)	1.82 (0.94–3.53)	0.08
Major Bleeding	3 (1.2)	2 (0.8)	1.62 (0.27–9.71)	0.60
Minor Bleeding	20 (7.9)	12 (4.5)	1.83 (0.90–3.75)	0.10

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Landolfi R et al. *N Engl J Med*. 2004;350:114-24.

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Summary

- Low-dose aspirin can safely prevent thrombotic complications in patients with PV who have no contraindications to aspirin therapy
- If patients encounter gastrointestinal discomfort with aspirin consider adding H_2-antagonist
- Patients with extreme thrombocytosis (i.e. platelets > 1,000 x10^9/L) should be screened for acquired Von Willebrand syndrome

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Hydroxyurea (Hydrea®, Droxia™, Mylocel™) in PV Management

- Usually used as a first-line cytoreductive treatment
  - Controls myeloproliferation
  - Reduces splenomegaly
  - May reduce risk of major thrombosis
- Side effects
  - Myelosuppression
  - Leg ulcers
  - Hyperpigmentation
  - Fever
  - Alopecia
  - Increased risk of squamous cell carcinoma
  - Longstanding controversy re: leukemogenic risk

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Sever M et al. *Leuk Lymphoma*. 2014;55(12):2685-90.
Mascarenhas J et al. *Haematologica*. 2014;99(6):945-49.
Fruchtman SM et al. *Semin Hematol*. 1997;34(1):17-23.

51

Definition of HU Resistance/Intolerance

1. Need for phlebotomy to keep HCT < 45% after 3 months of at least 2 g/day of HU
2. Uncontrolled myeloproliferation:
   - Platelet count > 400 x 10^9/L AND WBC > 10 x 10^9/L after 3 months of at least 2 g/day HU
3. Failure to reduce massive splenomegaly by more than 50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly, after 3 months of at least 2 g/day of HU
4. ANC < 1.0 x 10^9/L OR platelet count < 100 x 10^9/L or Hgb <10.0 g/dL at the lowest dose of HU required to achieve a CR or PR
5. Presence unacceptable HU non-hematological toxicities:
   - Leg ulcers
   - Mucocutaneous manifestations
   - Gastrointestinal symptoms
   - Pneumonitis
   - Fever at any dose of HU

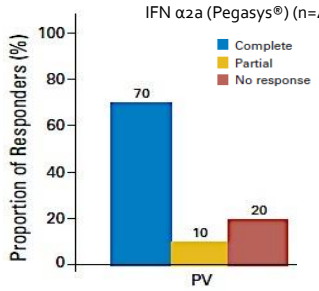
Memorial Sloan Kettering Cancer Center

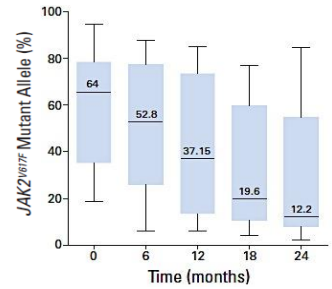
Barosi G et al. *Br J Haematol*. 2010;148(6):961-3.

52

Interferon in the Treatment of PV

Phase II studies: Treatment with PEG-IFN-α2a (Pegasys®) or α2b (Peg-Intron®) resulted in high rates of complete hematologic and molecular response, and low rates of thrombosis.





Memorial Sloan Kettering Cancer Center

Quintas-Cardama A et al. *J Clin Oncol*. 2009;27(32):5418-24.

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Interferon Tolerability in PV

All patients

Toxicity	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %
Neutropenia	3	8	0	0
Elevated LFTs	2	5	0	0
Fatigue	1	3	0	0
Pain	1	3	0	0
Infection	1	3	0	0
Depression	1	3	0	0
Diarrhea	1	3	0	0
Mucositis	0	0	0	0
Blurred vision	1	3	0	0
Dizziness	1	3	0	0
Anemia	0	0	0	0

Patients treated at 90 mcg/week

Toxicity	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %
Neutropenia	0	0	0	0
Diarrhea	0	0	0	0
Elevated LFTs	0	0	0	0

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Quintas-Cardama A et al. *J Clin Oncol*. 2009;27(32):5418-24.

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Ropeginterferon in the Treatment of PV

Author, Year, study design	N	Intervention	Response	ADRs
Gisslinger H et al. Blood. 2015 PEGINVERA Phase I/II	Phase I = 25 Phase II = 26	Phase I = rIFN-α-2b (Intron A®) 50-540 µg SC every 2 weeks (no MTD) Phase II = Response driven dosing up to 540 µg SC every 2 weeks (median dose: 250 µg SC every 2 weeks	Dose <300 µg (n=37): 43% (CR)/43% (PR) Dose ≥300 µg (n=14): 57% (CR)/43% (PR)	Common: Pruritus, arthralgia, fatigue, headache, diarrhea, influenza-like illness, vertigo Serious: Psychiatric ADR (31%), autoimmune thyroiditis (2 pts)
Gisslinger H et al. Blood. 2016 ASH Abstract PROUD-PV Phase III	254	rIFN-α-2b (Intron A®) with response driven dosing up to 540 µg SC every 2 weeks (median dose: 450 µg SC every 2 weeks HU with CBC driven dosing (median dose: 1250 mg) *Treatment for 12 months	*Met non-inferiority analysis CHR: 43.1% (rIFN-α-2b [Intron A®]) vs. 45.6% (HU), p = 00.28	No difference in endocrine disorders, psychiatric disorders, cardiac/vascular disorders, and tissue disorders. 5 secondary malignancies in HU group vs. 0 in rIFN-α-2b (Intron A®) group
Gisslinger H et al. Blood. 2017 Mature results from PROUD-PV called CONTINUATION-PV	171	rIFN-α-2b (Intron A®) with response driven dosing up to 540 µg SC every 2 weeks (median dose: 450 µg SC every 2 weeks BAT	CHR: 70.5% vs. 49.3%, p = 0.0101 Partial molecular response: 49.5% vs. 36.6%, p = 0.1183	Thrombocytopenia (19.7% vs. 26.8%), leukopenia (18.9% vs. 22%), anemia (9.4% vs. 22%), increased GGT (11% vs. 0%), endocrine (3.9% vs. 0.8%), and psychiatric (2.4% vs. 0.8%)

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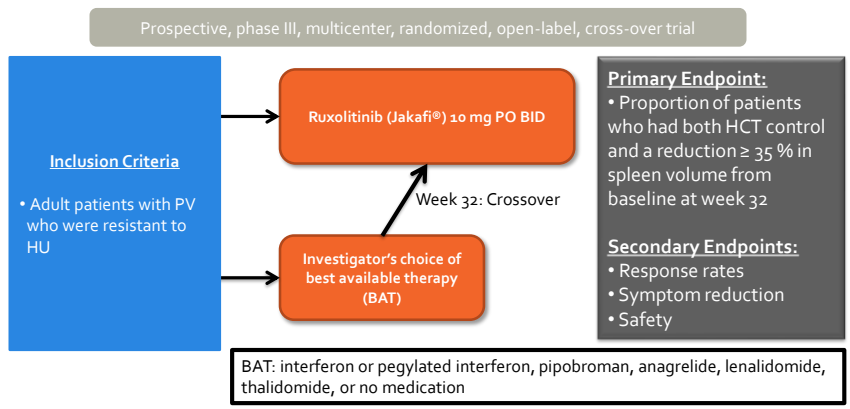
Gisslinger H et al. *Blood*. 2015;126 (15):1762-1769.
Gisslinger H et al. *Blood*. 2016;128(suppl 22).
Gisslinger H et al. *Blood*. 2017;130(suppl 1).

55

Ruxolitinib (Jakafi®) in PV – RESPONSE Trial



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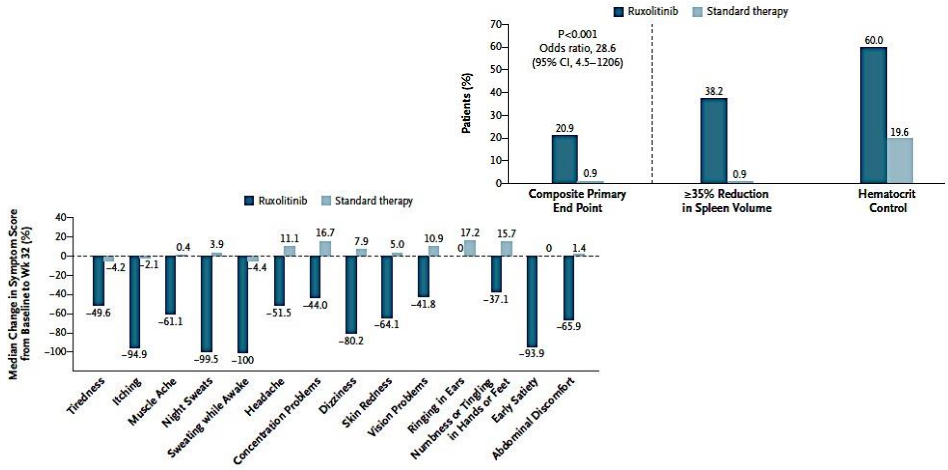
Marchioli R et al. *N Engl J Med*. 2013;368(1):22-33.

56

Response Trial – Results



Ruxolitinib- (Jakafi®)
Jakafi® is indicated for treatment of polycythemia vera (PV) in adults who have had an inadequate response to or are intolerant of hydroxyurea

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Marchioli R et al. *N Engl J Med.* 2013;368(1):22-33.
Jakafi® (Ruxolitinib) [package insert]. Wilmington, DE; 2016.

57

RESPONSE Trial – Safety Results

	Ruxolitinib (Jakafi®) (n = 110)		BAT (n = 111)	
Patients, %	All Grades	Grade 3/4	All Grades	Grade 3/4
Anemia	43.6	1.8	30.6	0.0
Thrombocytopenia	24.5	5.5	18.9	3.6
Neutropenia	1.8	0.9	8.1	0.9

- Most common grade 3/4 non-hematologic adverse events in the ruxolitinib (Jakafi®) arm: dyspnea (2.7%) and asthenia (1.8%)
- Rate of herpes zoster infection was higher in the ruxolitinib (Jakafi®) group (6.4% vs 0; all grade 1-2)
- Thromboembolic events occurred in 1 patient receiving ruxolitinib (Jakafi®) and in 6 patients receiving standard therapy

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Marchioli R et al. *N Engl J Med.* 2013;368(1):22-33.

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Treatment Summary

- Treatment for patients with PV combines:
  - Modification of CV risk factors
  - Phlebotomy (HCT target <45%)
  - Antiplatelet therapy
  - First-line cytoreductive therapy: HU or IFN-alfa
  - Second-line: Ruxolitinib (Jakafi®) for patients resistant to or intolerant of HU
    - Other options may include PEG-IFN or busulfan

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PV-Associated Pruritus

Feature	PV-associated pruritus	Idiopathic AP	AP of the elderly
Mean age (yrs)	59 (range 21–89)	29.4 (females), 34.5(males)	>60
Gender distribution (F:M)	~1:1	~1:1	3:1
Family history	None	33%	None
Relationship of pruritus to water	Usually follows contact with water at any temperature, but less frequently after contact with cold water	Hot water causes symptoms in 30% and cold water in 35% of patients	Itching is invariably absent during bathing, but starts soon after (during drying)
Clinical features	Distributed over torso and extensor surface of limbs, lower rate of arterial thrombosis, negative impact on QoL	Onset of itching is upon contact with water, duration averages 40 min, condition is usually unremitting, psychiatric symptoms may be present	Fair color, dry scaly skin, females have more severe symptoms, itching begins in lower extremities and spreads upwards, but spares head, symptoms are worse in winter, and are progressive
Histopathological features	Increased skin mast cells, mononuclear cells and eosinophils, itching correlates with homozygosity for the JAK2V617F mutation	Normal number of skin mast cells, acetylcholine mediated, increased cutaneous fibrinolytic activity	Non-specific lymphocytic perivenular infiltrate

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Saini KS et al. *Eur J Clin Invest*. 2010 Sep;40(9):828-34.

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Management of PV-Associated Pruritus

Typically Effective	Mixed Results	Typically Ineffective
• Interferon-α • Ruxolitinib (Jakafi®) • SSRIs • Phototherapy	• Anti-histamines	• Cytoreductive therapy • Phlebotomy

SSRIs, Selective Serotonin Reuptake Inhibitors

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Tefferi A et al. *Blood.* 2002;7:2627.
Sharon R et al. *Cancer*. 1986;4:718–20.
Mesa R et al. *Eur J Haematol*. 2016;97(2):192-200.
Diehn F et al. *Br J Haematol.* 2001;115:619-21.
Jackson N et al. *Br J Dermatol.* 1987;116:21-9.
de Wolf JT et al. *Lancet*. 1991;8735:241.
Baldo A et al. *Br J Dermatol*. 2002;147:979–81.

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Patient Case: SO

- 66 yo M with a history of a right lower extremity DVT
- Presentation: fatigue, persistent pruritus, and headaches
- Physical exam: No evidence of splenomegaly by palpation

Diagnostics 4/15/2008	
WBC	6.7 x 10^9/L (reference range: 4.3-10.5 x 10^9/L)
Peripheral blasts	0%
Hgb	18.1 g/dL (reference range: Male, 13.8 to 17.2 g/dL)
HCT	54% (reference range: Male, 38.8 to 52%)
Platelets	223 x 10^9/L (reference range: 150-400 x 10^9/L)
Bone Marrow Biopsy	Hypercellular, trilineage hematopoiesis with pleomorphic, mature megakaryocytes
Cytogenetics	Normal karyotype
Diagnostic molecular pathology	BCR-ABL negative, JAK2V617F mutation
Erythropoietin level	<1.0 mIU/mL (reference range: 2.6 – 18.5 mIU/mL)

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Patient Case: BP

- Based on the patient's presentation, laboratory, and molecular findings does the patient meet the criteria for PV?
  - Yes
  - No
    - **All 3 major criteria, or the first 2 major criteria and the minor criterion**

Major Criteria	Minor Criteria
Hgb >16.5 g/dL or HCT > 49% in men or Hgb > 16.0 or HCT > 48% in women or increased red cell mass BM biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size) Presence of JAK2V617F or JAK2 exon 12 mutation	Subnormal serum erythropoietin level

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BP's Risk Status

Patient Review: This 66-year-old man presented with fatigue, persistent pruritus, and headaches, WBC 6.7 x 10^9/L, Hgb 18.1 g/dL, HCT 54%, platelets 223 x 10^9/L, a *JAK2V617F* mutation, and a previous history of a DVT.

What is the risk status of this patient with newly-diagnosed PV?

A. Low

B. High

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Patient Case: BP

- **Patient Review**: This 66-year-old man presented with fatigue, persistent pruritus, and headaches, WBC 6.7 x 10^9/L, Hgb 18.1 g/dL, HCT 54%, platelets 223 x 10^9/L, a *JAK2V617F* mutation, and a previous history of a DVT.

What is/are the best treatment options for BP?

A. Hydroxyurea
B. Aspirin
C. Ruxolitinib (Jakafi®)
D. Interferon
E. Both A and B
F. None of the above

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Patient Case: BP

- **Patient Review**: This 66-year-old man presented with fatigue, persistent pruritus, and headaches, WBC 6.7 x 10^9/L, Hgb 18.1 g/dL, HCT 54%, platelets 223 x 10^9/L, a *JAK2V617F* mutation, and a previous history of a DVT. He was placed on hydroxyurea (Hydrea®, Droxia™, Mylocel™) and tolerated it well until today when he presented to clinic with leg ulcers, increasing Hgb and HCT, and a return of his constitutional symptoms.

What should we do now?

a. Continue hydroxyurea, but increase the dose
b. Consider starting ruxolitinib (Jakafi®)
c. Admit the patient to start 7+3 chemotherapy

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Essential Thrombocythemia

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Diagnosis of Essential Thrombocythemia

- WHO Diagnosis of ET requires ALL 4 major criteria or the first 3 major criteria and the minor criterion

Major Criteria

1. Platelet count ≥ 450 × 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-ABL1+ CML, PV, PMF, MDS, or other MPNs
4. Presence of JAK2, CALR, or MPL mutation

Minor Criteria

1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis

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

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ET Risk Assessment

- IPSET Prognostic Features
  - Age > 60 years (2 points)
  - Prior history of thrombosis (1 point)
  - Leukocytes >11 x 10^9/L (1 point)

IPSET Risk Group:
0 points: Low
1-2 points: Intermediate
3-4 points: High

IPSET-thrombosis			
Low	**Intermediate**	**High**	**Total**
n = 281	n = 277	n = 32	N = 590
48%	47%	5%	100%
0.59%pts/y	1.55%pts/y	1.77%pts/y	0.95%pts/y
n = 193	n = 194	n = 243	N = 630
31%	31%	39%	100%
1.27%pts/y	2.67%pts/y	3.71%pts/y	2.86%pts/y
n = 474	n = 471	n = 275	N = 1220
39%	39%	23%	100%
1.03%pts/y	2.35%pts/y	3.56%pts/y	1.77%pts/y

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Barbui T et al. *J Clin Oncol.* 2011;29:761-70;.

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ET Risk Assessment

- IPSET Prognostic Features
  - Age > 60 years (2 points)
  - Prior history of thrombosis (1 point)
  - Leukocytes >11 x 10^9/L (1 point)

IPSET Risk Group:
0 points: Low
1-2 points: Intermediate
3-4 points: High

Conventional Risk Category	Risk Variables	Therapy
Low	• None	• Observation • Correction of CV risk factors
High	• Age ≥ 60 years **OR** • Thrombosis history **OR** • Platelet count ≥1500 x 10^9/L	• Cytoreduction*, and • Correction of CV risk factors, and • Aspirin**

*Hydroxyurea (Hydrea®, Droxia™, Mylocel™) is the first-line treatment of choice. Anagrelide (Agrylin®) is generally 2nd-line therapy if resistant or intolerant to HU. IFN-a is used for young patients, pregnant women, or patients who are refractory/intolerant to HU
**Acquired Von Willebrand syndrome should be assessed if platelet count is ≥ 1000 x 10^9/L

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Rumi E et al. *Blood*. 2016 Aug 25 [epub ahead of print].
Beer PA et al. *Blood*. 2011;117(5):1472-1482.

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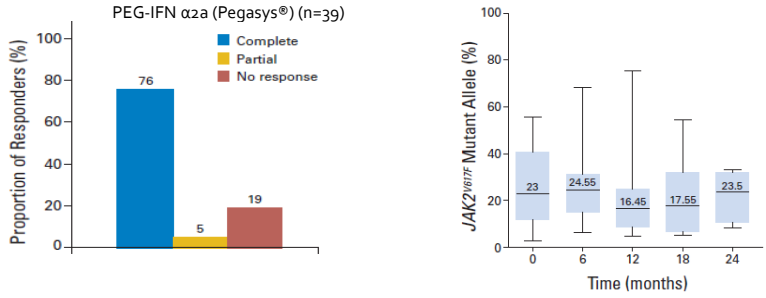
Interferon in the Treatment of ET

Treatment with PEG-IFN- α2a (Pegasys®) resulted in high rates of complete hematologic and molecular response, and low rates of thrombosis.



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Quintas-Cardama A et al. *J Clin Oncol*. 2009;27(32):5418-24.

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Interferon Tolerability in ET

All patients

Toxicity	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %
Neutropenia	12	31	1	3
Elevated LFTs	3	8	0	0
Fatigue	2	5	0	0
Pain	1	3	0	0
Infection	1	3	0	0
Depression	1	3	0	0
Diarrhea	0	0	0	0
Mucositis	1	3	0	0
Blurred vision	0	0	0	0
Dizziness	0	0	0	0
Anemia	1	3	0	0

Patients treated at 90 mcg/week

Toxicity	Grade 3 No.	Grade 3 %	Grade 4 No.	Grade 4 %
Neutropenia	2	13	0	0
Diarrhea	1	6	0	0
Elevated LFTs	1	6	0	0

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Quintas-Cardama A et al. *J Clin Oncol*. 2009;27(32):5418-24.

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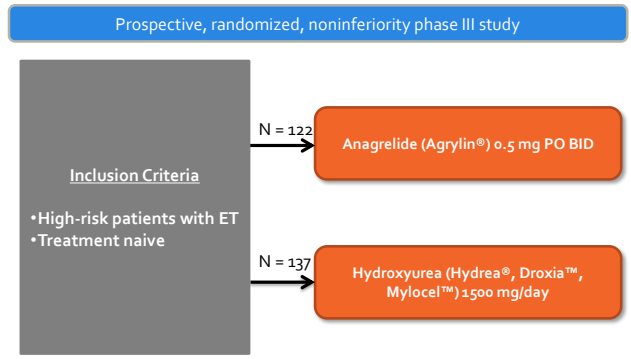
Anagrelide (Agrylin®) for Treatment of ET: ANAHYDRET Study



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Gisslinger H et al. *Blood*. 2013;121(10):1720-1728.

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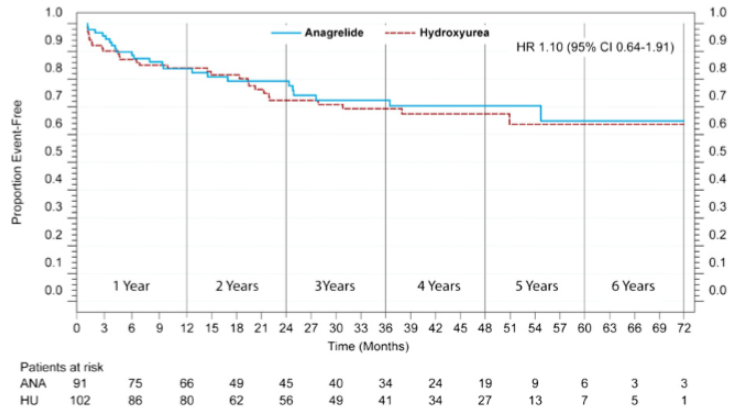
Anagrelide (Agrylin®) for Treatment of ET: ANAHYDRET Study

Figure 3. Event-free survival for ET-related events for patients who were rediagnosed as having WHO-ET ("true-ET"). The HR (95% CI) is presented after an observation time of 6 years.



Anagrelide- Agrylin®; Hydroxyurea (Hydrea®, Droxia™, Mylocel™)

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Gisslinger H et al. *Blood*. 2013; 121(10): 1720-1728.

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Safety of Anagrelide (Agrylin®) in ANAHYRDET Study

Table 5. Safety profile according to organ classes

Organ manifestations	Symptoms	No. of patients: Anagrelide group	No. of patients: Hydroxyurea group	*P* value
Infections and infestations	Herpes (simplex, labialis, zoster)	1	4	.37
	Infections (viral, influenza-like symptoms)	12	28	.01
Blood and lymphatic system disorders	Anemia	11	24	.04
	Epistaxis	6	15	.07
	Leukopenia	1	37	< .01
Nervous system disorders	Headache	29	22	.21
	Vertigo	6	14	.10
Ear and labyrinth disorders	Dizziness	7	2	.09
Cardiac disorders	Hypertension	14	4	.01
	Palpitations	30	3	< .01
	Tachycardia	13	3	.01
Respiratory, thoracic, and mediastinal disorders	Bronchitis	3	8	.22
Gastrointestinal disorders	Abdominal pain	11	11	1.00
	Diarrhea	17	10	.15
	Other gastrointestinal events	11	14	.83
Skin and subcutaneous tissue disorders	Alopecia	0	5	.06
	Skin disorders	7	16	.12

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Gisslinger H et al. *Blood*. 2013; 121(10): 1720-1728.

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Anagrelide (Agrylin®) From a Pharmacist's Perspective

- Initial dosing
  - 0.5 mg PO BID
  - Dose adjust to platelet count to <600, ideally between 150-400
- Dose adjustments
  - Hepatic impairment
  - Hematologic toxicity
- Drug interactions
  - Antiplatelet and anticoagulation
- Warnings and precautions
  - Bleeding risk, cardiovascular, pulmonary hypertension, pulmonary toxicity, renal abnormalities
- Administration
  - Regardless of food
- Dosage forms
  - 0.5 and 1 mg capsules
- Cost
  - $669.60/month
- Drug acquisition
  - Retail pharmacy

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Anagrelide (Agrylin® [package insert]) 2016.

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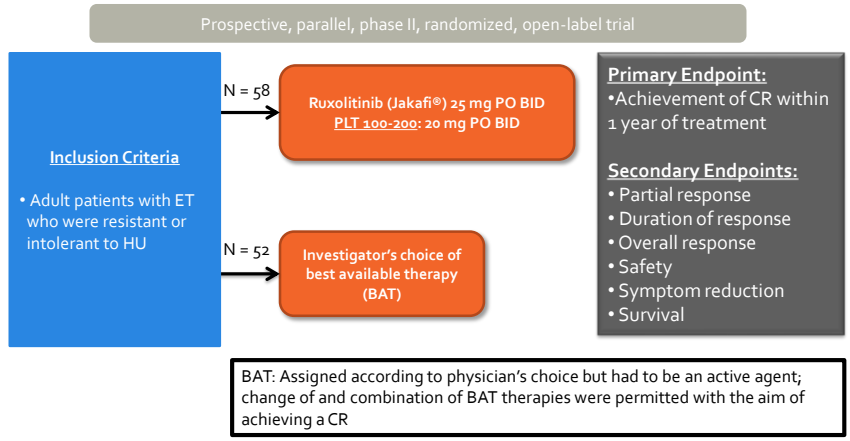
Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial



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Harrison CN et al. *Blood*. 2017;130(17):1889-1897.

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Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial

	Ruxolitinib (Jakafi®)	BAT	P-Value
CR	46.5%	44.2%	0.40
PR	46.5%	51.9%	*Not reported
OS	0.98	0.98	0.99
PFS	0.93	0.96	0.97
Thrombotic event	17.2%	5.8%	0.09
Hemorrhagic event	1.7%	8.9%	0.14
Maximum % TSS reduction at any point during first 12 months	32%	0%	**0.03**
Symptom response at 2 months	19%	3%	**0.04**

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Harrison CN et al. *Blood*. 2017;130(17):1889-1897.

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Ruxolitinib (Jakafi®) in ET: MAJIC-ET Trial

Grade 3/4	Ruxolitinib (Jakafi®)	BAT	P-value
Anemia	21%	0%	<0.005
Thrombocytopenia	3.4%	0%	0.32
Infection	15.5%	3.5%	0.03

Overview of assigned therapy switches and discontinuations per treatment arm

	Ruxolitinib	BAT	Total
Assigned therapy switches			
Patients that switched BAT therapy at least once	N/A	30	30
Total number of times BAT therapy was switched	N/A	86	86
Discontinuations			
Transformation	9	3	12
Loss of response	11	0	11
Lack of efficacy	5	1	6
Toxicity			
Anemia	2	0	2
Other	3	1	4
Other	3	3	6
Death	1	2	3
Withdrawal of consent	1	0	1
Total	35	10	45

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Harrison CN et al. *Blood*. 2017;130(17):1889-1897.

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Patient Case: MT

- 62-year-old man had elevated platelet count (780 x 10^9/L) was recently admitted for a DVT
- History, examination, and laboratory tests (iron status, inflammatory markers, rheumatoid disease and malignancy screening) did not reveal underlying cause

Diagnostics	
WBC	9.6 x 10^9/L (reference range: 4.3-10.5 x 10^9/L)
Hgb	14.3 g/dL (reference range: Male, 13.8 to 17.2 g/dL)
Platelets	775 x 10^9/L (reference range: 150-400 x 10^9/L)
Bone Marrow Biopsy	Increased megakaryocytes with prominent large hyperlobulated forms; reticulin is not increased
Cytogenetics	Normal karyotype
Diagnostic molecular pathology	BCR-ABL negative, JAK2V617F mutation present

DVT, Deep vein thrombosis

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Patient Case: MT

- Does MT meet the diagnostic criteria for ET?
  - A. Yes
  - B. No

Major Criteria	Minor Criteria
1. Platelet count ≥ 450 × 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-ABL1+ CML, PV, PMF, MDS, or other MPNs 4. Presence of JAK2, CALR, or MPL mutation	1. Presence of a clonal marker or absence of evidence for reactive thrombocytosis

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Patient Case: MT

- **Patient Review**: 62-year-old man had elevated platelet count (780 x 10^9/L), was found to have a DVT and subsequently diagnosed with ET.

What initial treatment should MT start to reduce the risk of thrombosis?

A. Rituximab (Rituxan®)
B. Hydroxyurea (Hydrea®, Droxia™, Mylocel™).
C. Aspirin
D. Busulfan (Busulfex® and Myleran®)
E. Both B and C

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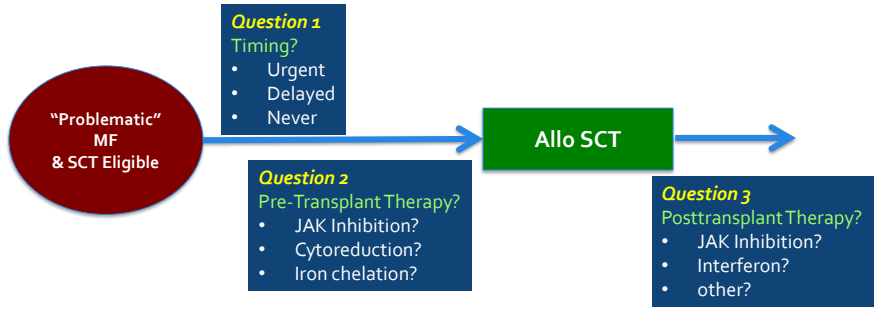
Stem Cell Transplant Use in MPNs

- SCT *almost* exclusively for MF/ MPN-BP
- In MF evolving risk/benefit analysis for use



MPN-BP, myeloproliferative neoplasms in blast phase

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Courtesy of R. Mesa, Mayo Clinic.

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MPN Conclusions

- MPNs are chronic and variably progressive, hematopoietic diseases with shared biology, clinical features, and molecular basis
- Proper diagnosis is essential given overlaps
- Patient-reported symptom burden is crucial and quantifiable through treatment
- Treatment strategies can vary depending on the individual's risk status and management needs
- Thrombosis is a shared risk and antiplatelet therapy a mainstay for a majority of patients

- Ruxolitinib (Jakafi®) represented a major paradigm shift and can significantly improve the outlook for many patients with MF or HU-resistant/intolerant PV, but it does not cure these diseases
- Interferon may offer significant benefit, but toxicity warrants careful patient selection and monitoring
- Novel therapies for MPNs are needed, and a number of strategies are in development
  - Novel JAK pathway inhibitors
  - Antifibrotics
  - Telomerase inhibitors
  - Combination approaches (hypomethylating agents + JAK inhibitors in BP, numerous in early disease)

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Resources

- The Leukemia & Lymphoma Society
- MPN Advocacy Network
- NCCN
- Patient Access Network
- Needymeds.org

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Nursing Care in the Treatment and Side Effect Management of Myeloproliferative Neoplasms

Carolanne Carini, BSN, RN, BMTCN
Office Practice Nurse, Medical Oncology
Memorial Sloan Kettering Cancer Center

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Treatment Goals

- Reduction in life-threatening disease sequelae
- Slow/reduce disease progression
- Improve quality of life

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Common Symptoms

- Vascular
  - Micro- and microvascular
    - Neurologic, Cognitive, Cardiac, Pulmonary
- Inflammation
- Proliferation
- Gastrointestinal

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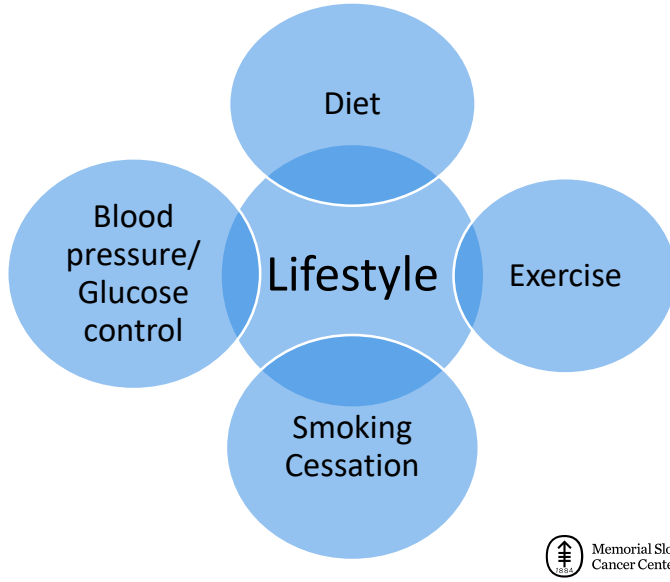
Cardiovascular Risk Reduction



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Splenomegaly

- Prevalent in MF, also common in PV and ET
- Symptoms:
  - Early satiety
  - Abdominal fullness
  - Nausea
  - Increased abdominal girth
- Nursing interventions

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Pruritus

- Most common in PV
- Related to increased number of mast cells
- Worse after showering
- Treatment

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Constitutional Symptoms

- Associated with inflammation in bone marrow and throughout the body
- Common symptoms:
  - Fatigue
  - Night sweats
  - Bone pain
  - Low-grade fevers
  - Weight loss

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Treatment: Therapeutic Phlebotomy

- Used in PV patients
- Remove approximately 450 cc of blood
- Target HCT<45%
- Nursing implications:
  - Monitor patient labs
  - Hydration
  - What to avoid
  - What to expect

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Treatment: ASA

- Low-dose aspirin to prevent thrombotic complications
- Nursing implications:
  - Review patient history
  - Monitor for sign of bleeding
  - Very high platelets and Von Willebrand disease

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Treatment: Hydroxyurea

- Cytoreductive agent, reduce risk of thrombotic events by managing blood levels

- Nursing Implications:
  - Monitor blood counts
  - Immune suppression
  - Dermatologic changes

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Treatment: Interferon

- Used to control erythrocytosis and thrombocytosis

- Nursing Implications:
  - Monitor labs
  - Administered subcutaneously
  - Local reactions
  - Side effects

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Conclusions

- Focus on symptom recognition and assessment
- Educate on lifestyle changes and strategies for cardiovascular risk reduction
- Collaborate with interdisciplinary team

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RESOURCES FOR YOU & YOUR PATIENTS

FROM THE LEUKEMIA & LYMPHOMA SOCIETY (LLS)

WWW.LLS.ORG

LEUKEMIA & LYMPHOMA SOCIETY

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LLS RESOURCES FOR HEALTHCARE PROFESSIONALS

Online and in-person CE/CME webinars, symposia & rounds

Free CME & CE **www.LLS.org/CE**

Podcast series for healthcare professionals
Conversations with experts about diagnosing & treating blood cancers **www.LLS.org/HCPpodcast**

HCP palm card – *User friendly links to resources for you & your patients*
www.LLS.org/CE

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LLS RESOURCES FOR PATIENTS AND CAREGIVERS

- **Information Specialists** – disease information, emotional support, financial, travel & co-pay assistance, local support through LLS patient access field team. Also send free materials to patients & HCPs.

- **Nutrition Consultations** – One-on-one consultations from certified dietitian

Specialists can serve as a resource for your HCP team
M - F, 9 am to 9 pm ET:
- Phone: (800) 955-4572
- Live chat: **www.LLS.org/InformationSpecialists**
- Email: **infocenter@LLS.org**

- **Additional support for patients & caregivers – www.LLS.org/Support**

- **Booklets on disease, treatment, & support - www.LLS.org/Booklets**
- **Webinars, videos, in-person programs - www.LLS.org/Programs & www.LLS.org/Educationvideos**

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CLINICAL TRIAL NURSE NAVIGATORS

Help patients find and enroll in clinical trials based on highly detailed individualized assessments

www.LLS.org/Navigation

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patients provided with in-depth clinical trial navigation and support in past year

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THANK YOU

We have one goal: A world without blood cancers

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