Oncology
Learning Network

REDEFINING THERAPEUTIC
PATHWAYS IN PV AND ET

Interferons and the Future of Cytoreduction

Faculty

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Disclosures

- **Ghaith Abu-Zeinah, MD:** Speaker—PharmaEssentia; Advisory Board/consultancy—PharmaEssentia, Silence Therapeutics, Takeda; research funding to institution—PharmaEssentia, Pharma&

Program Information

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- Supported by an educational grant from PharmaEssentia USA Corporation

Learning Objectives

- Apply contemporary risk-stratification and guideline-based criteria to determine when cytoreductive therapy is indicated in patients with PV or ET
- Evaluate the efficacy, safety, long-term tolerability, and clinical utility of interferon-based strategies compared with hydroxyurea, JAK inhibition, and other cytoreductive options to inform treatment selection and sequencing and improve long-term patient outcomes

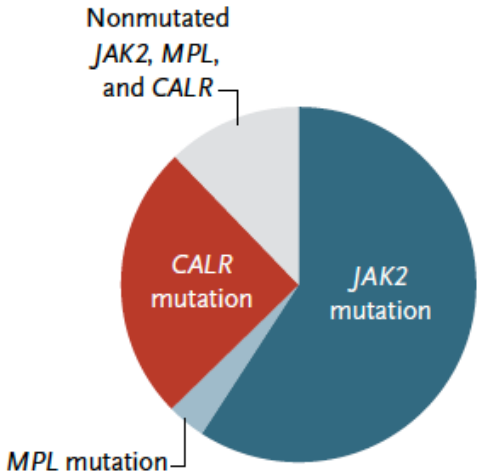
ET = essential thrombocythemia; PV = polycythemia vera.

Differentiating ET/PV Diagnoses and Risk Assessment

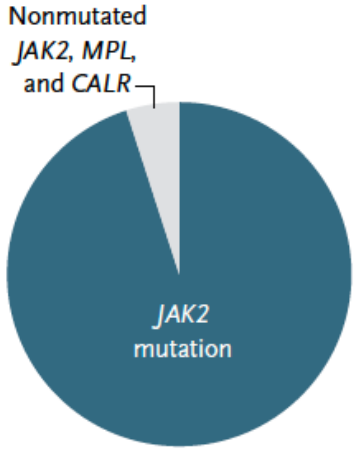
What Are ET and PV Anyway?

- Classical, Philadelphia chromosome-negative myeloproliferative neoplasms…OR chronic blood cancers
- Initiated by driver mutations in hematopoietic stem cells

Essential Thrombocythemia (ET)



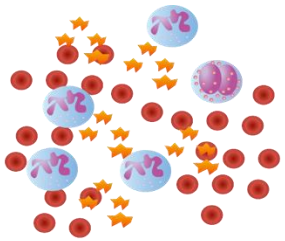
Polycythemia Vera (PV)



Klampfl T, et al. *N Engl J Med*. 2013;369(25):2379-2390.

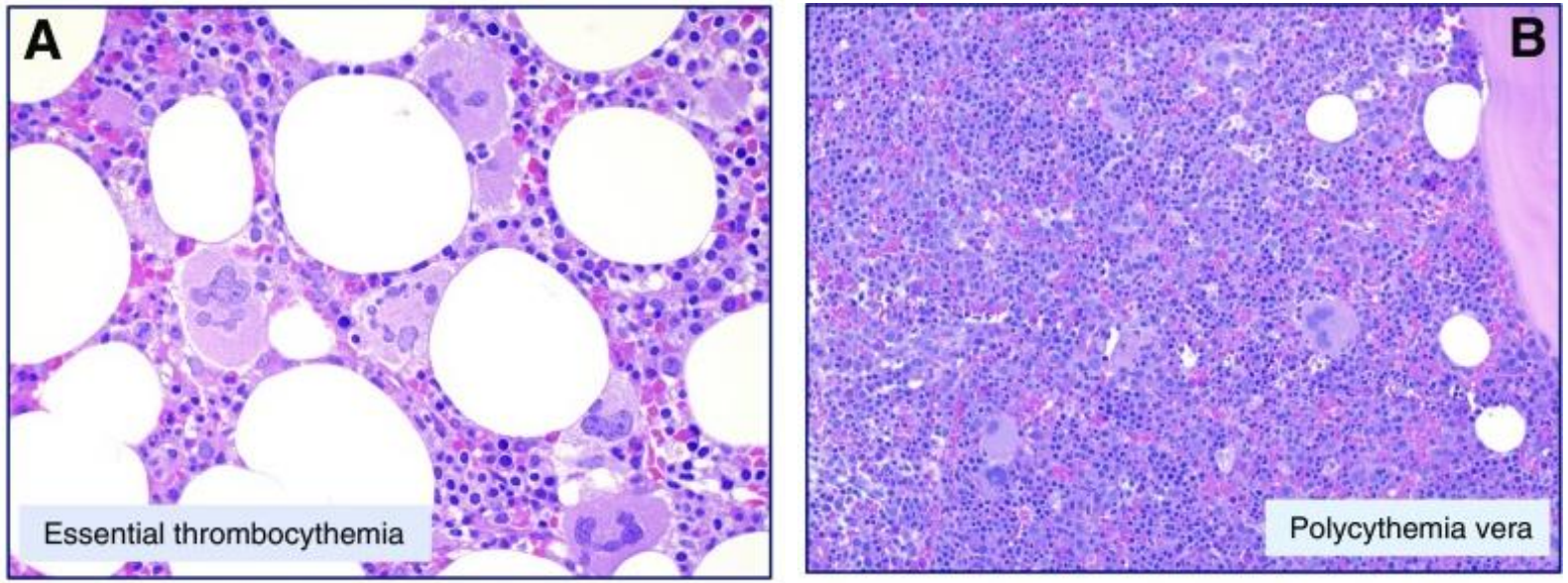
Diagnostic Criteria for ET and PV

ET	PV
Major criteria 1. **Plt** ≥ 450 x 10^9/L 2. **BMbx** ; proliferation mainly of Megakaryocytic (MgK) lineage with increased number of large, mature MgK with hyperlobated nuclei 3. Not meeting WHO criteria for other myeloid neoplasms 4. **JAK2, CALR, or MPL** mutations	**Major criteria** 1. **Hgb** >16.5 (M), >16 g/dL (F), OR **Hct** >49% (M), >48% (F), OR increased Red Cell Mass 2. **BMbx** ; hypercellularity for age with panmyelosis, and pleomorphic mature MgK 3. **JAK2V617F** or **JAK2 exon 12** mutations
Minor criterion Presence of a clonal marker or absence of evidence for reactive thrombocytosis	**Minor criterion** Subnormal EPO
Diagnosis requires all **4 major** OR the **first 3 major and the minor**	Diagnosis requires all **3 major** OR **first 2 major and the minor**



Plt = platelet count; BMbx = bone marrow biopsy; EPO = erythropoietin; Hgb = hemoglobin; Hct = hematocrit.
Adapted from 2022 World Health Organization (WHO) and International Consensus Classification (ICC) classification.
Arber DA, et al. *Blood*. 2022;140(11):1200-1228. Khoury JD, et al. *Leukemia*. 2022;36(7):1703-1719.

Bone Marrow Biopsy Is Essential

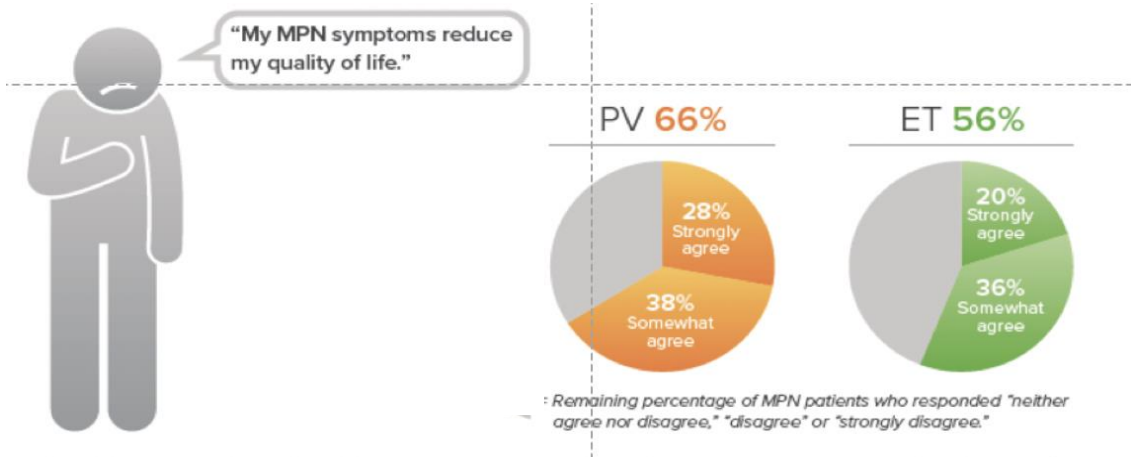


- Distinguish *JAK2* ET from early or masked PV
- Distinguish ET from prefibrotic PMF

PMF = primary myelofibrosis.
Rumi E, Cazzola M. *Blood*. 2017;129(6):680-692.

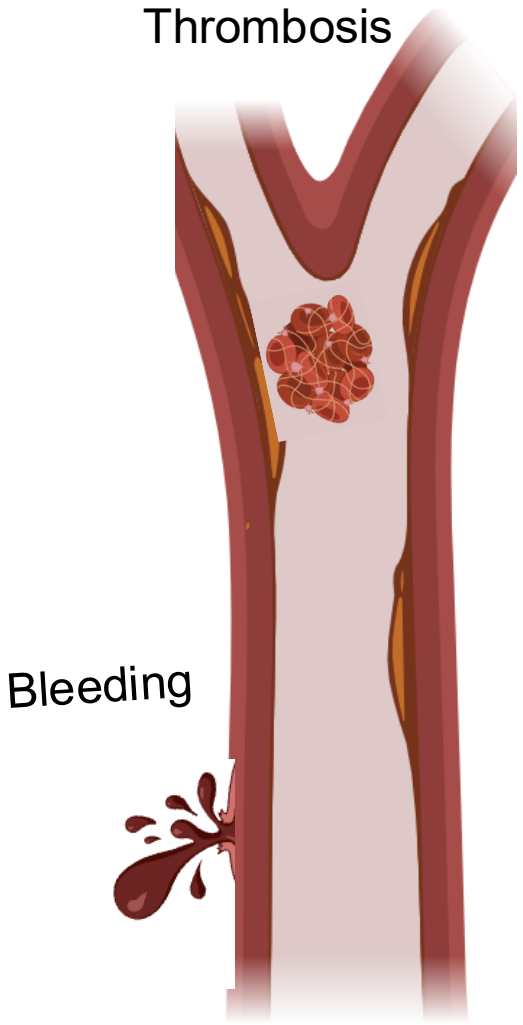
Clinical Presentation—Symptoms

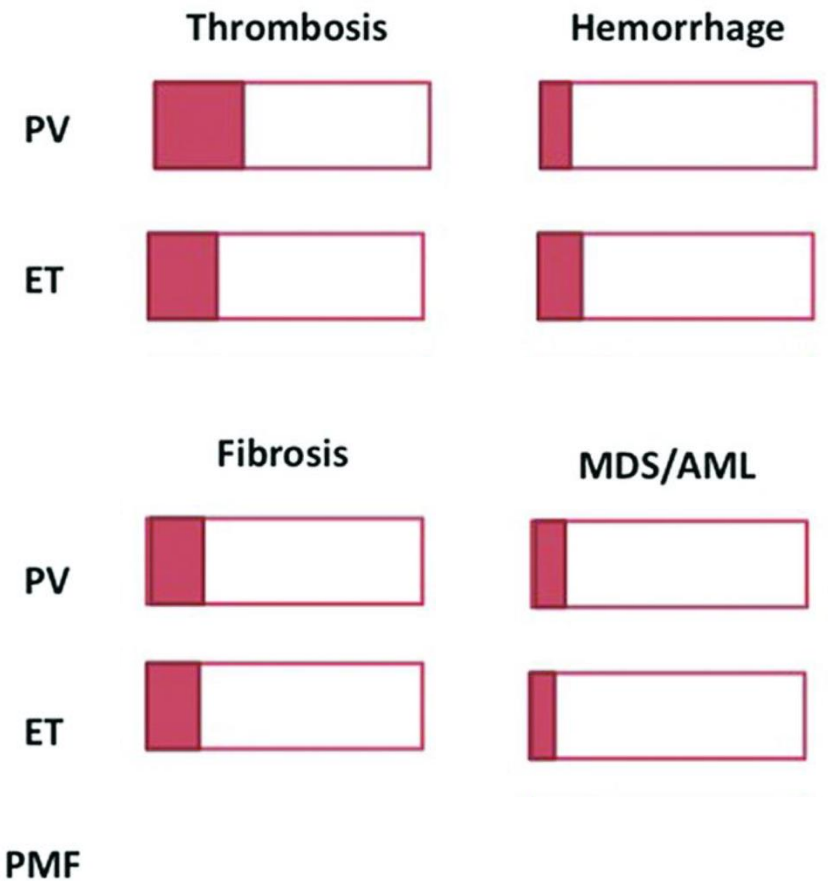
High symptom burden in many



QoL = quality of life.
Modified from Thyne M. Mesa R, et al. *Cancer*. 2017;123(3):449-458. Image of hands: Lipsker D. *N Engl J Med*. 2010;363(15):1463.
Data adapted from: Scherber R, et al. *Blood*. 2011;118(2):401-408.

Complications of ET/PV: Thrombosis, Bleeding, and Progression



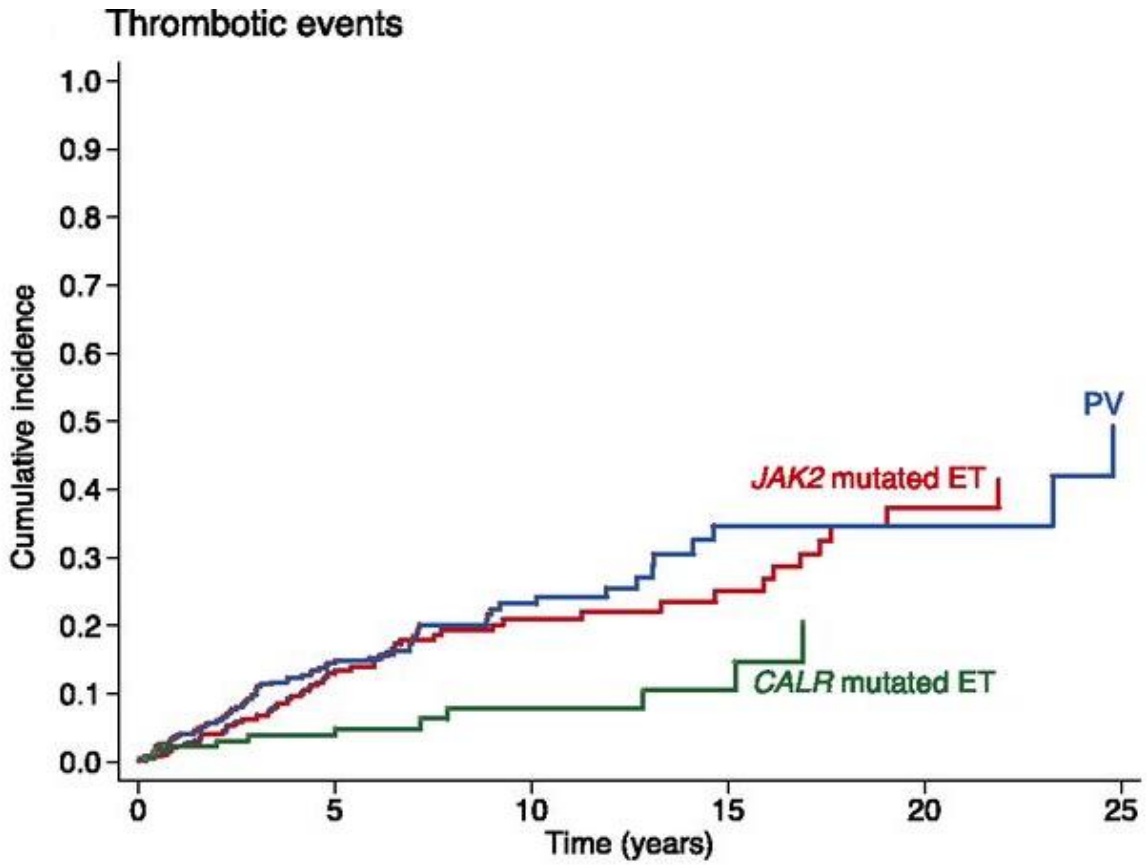


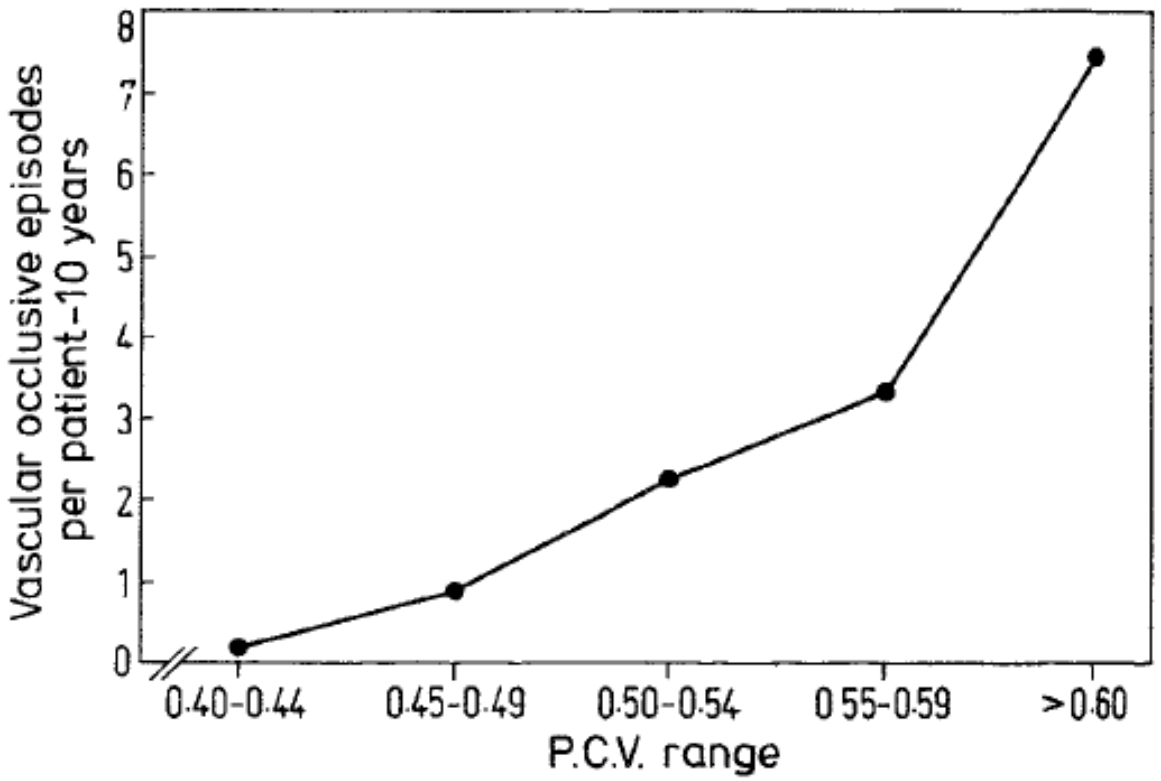
- 15-20% present with thrombosis, including venous: DVT/PE, SVT/PVT, Budd-Chiari, and arterial: MI, CVA
- Progression to MF increasingly common with longer duration of ET/PV

DVT = deep vein thrombosis; PE = pulmonary embolism; SVT = splanchnic vein thrombosis; PVT = portal vein thrombosis; MI = myocardial infarction; CVA = cerebrovascular accident; MF = myelofibrosis.

Kiladjian JJ. *Hematology Am Soc Hematol Educ Program*. 2012;2012:561-566.

Thrombosis in PV > ET: Driven by JAK2V617F and High Blood Viscosity



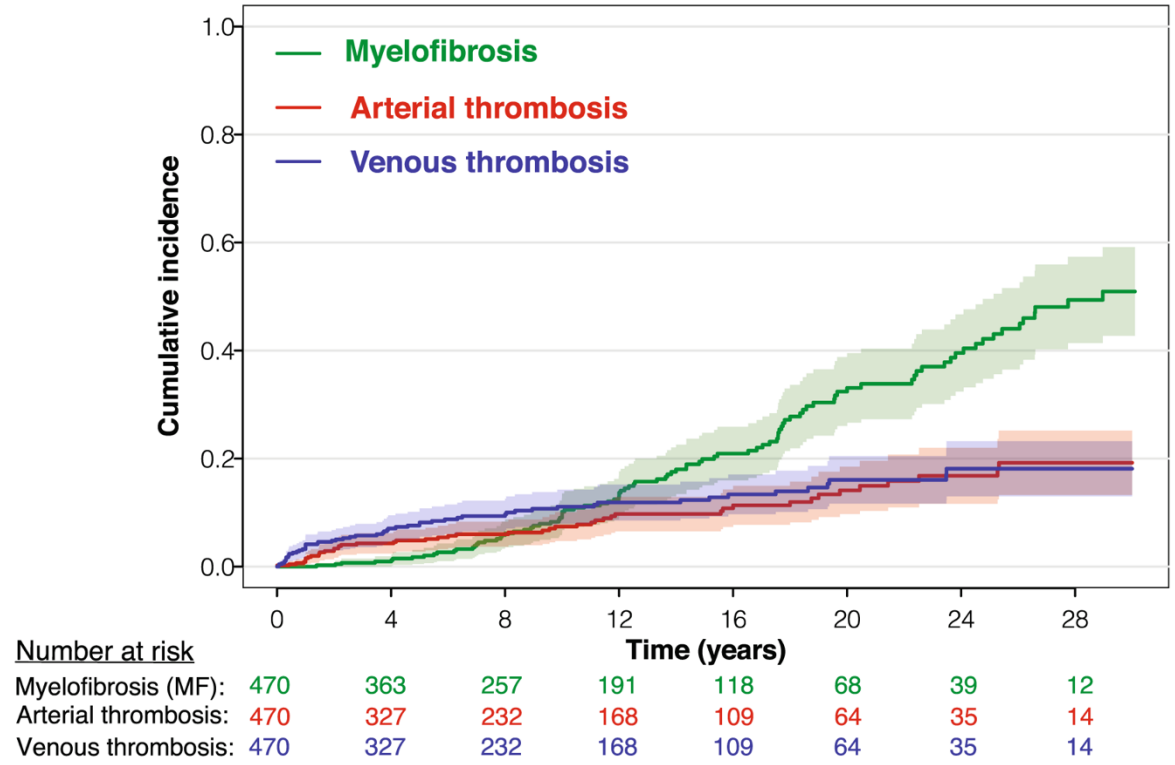


PCV = packed cell volume.

Rumi E, et al. *Blood*. 2014;123(10):1544-1551. Pearson TC, Wetherley-Mein G. *Lancet*. 1978;2(8102):1219-1222.

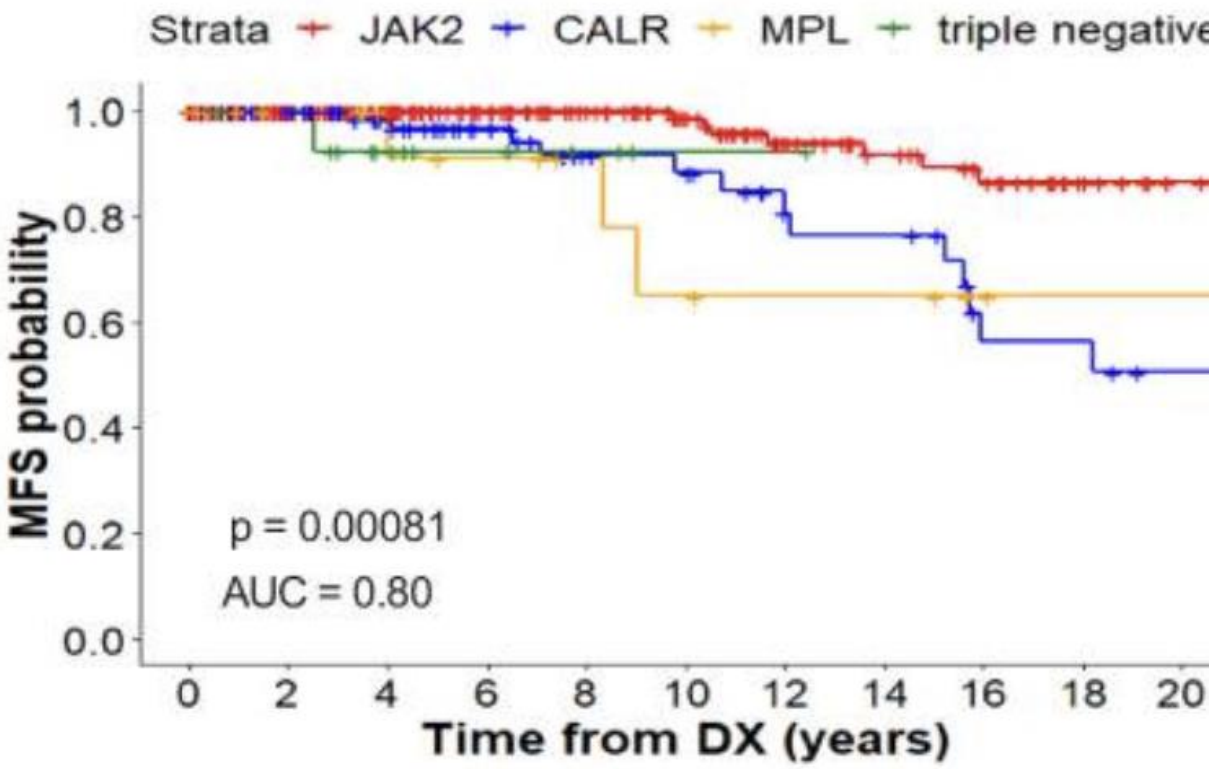
But Progression to Myelofibrosis Is Increasingly More Problematic in PV

~50% of PVs progress to MF…a bigger threat long-term than thrombosis



Abu-Zeinah G, et al. *Leukemia*. 2022;36(2):569-572.

In ET, Progression to MF Is More Common with CALR, MPL Mutations (>10x)



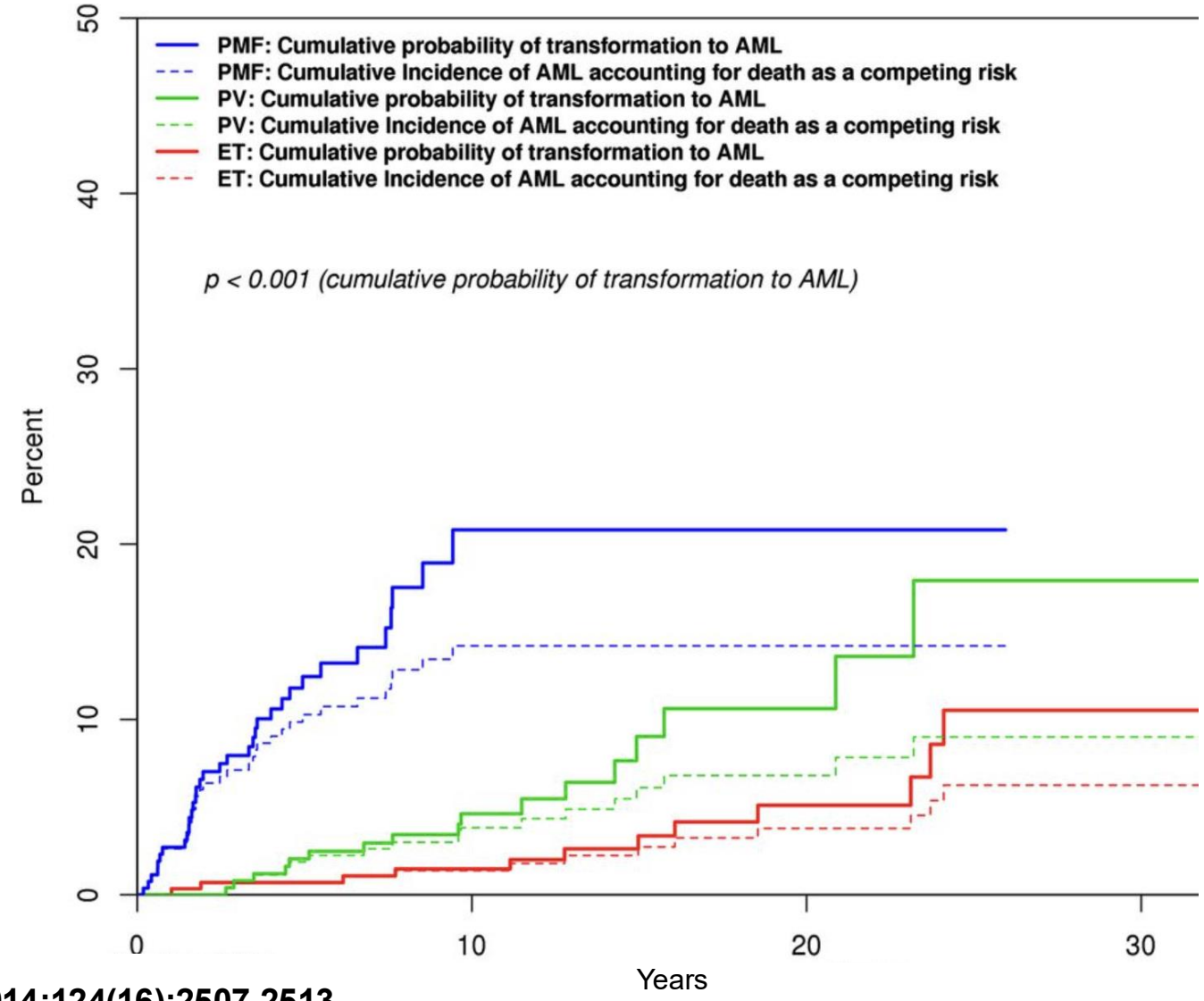
2 large studies of 1000 patients with ET show similar results

- Mayo Clinic
- Italy

MFS = metastasis-free survival; DX = diagnosis.

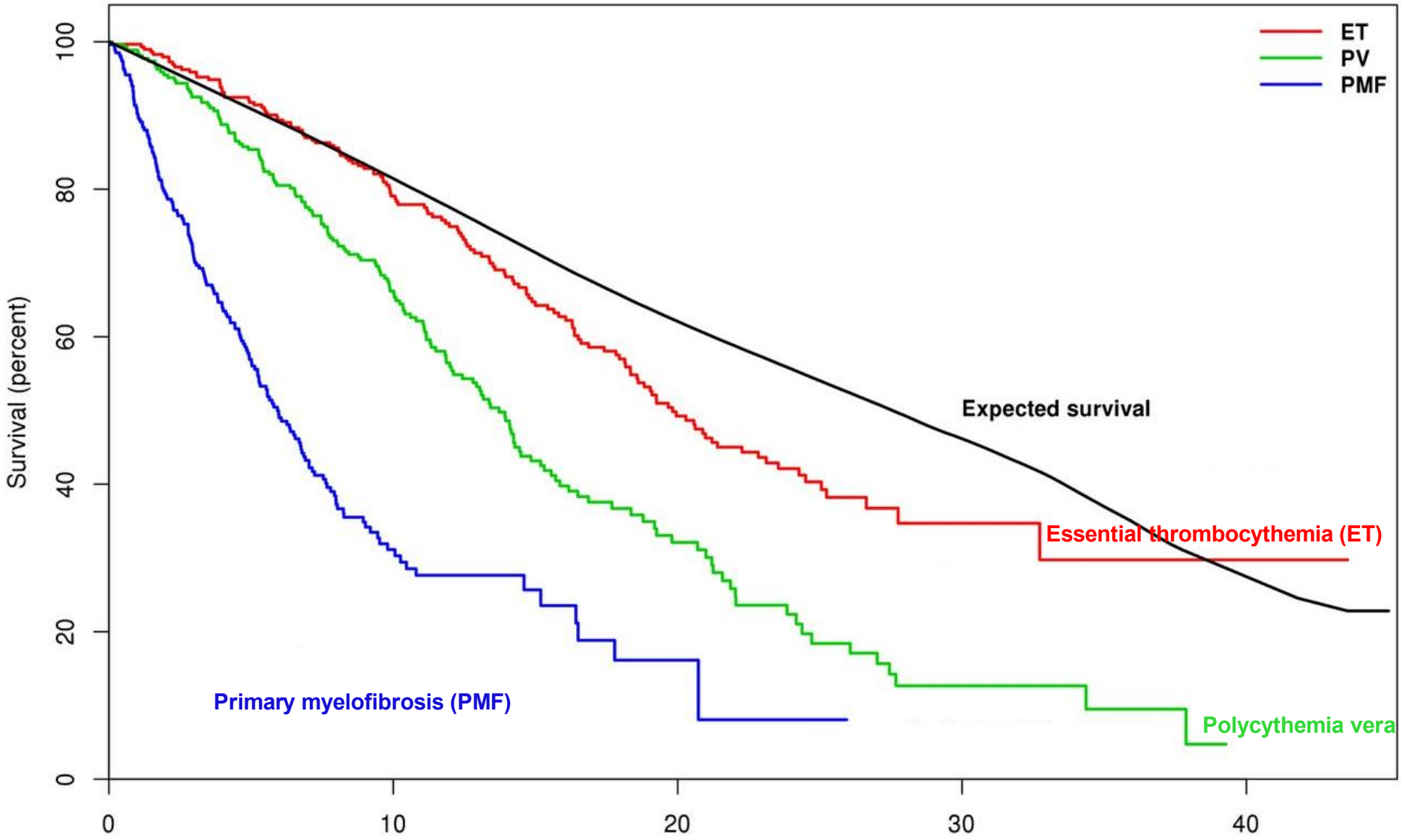
Abu-Zeinah G, et al. *Blood Cancer J*. 2024;14(1):103. Gangat N, et al. *Blood Cancer J*. 2024;14(1):11. Loscocco GG, et al. *Blood Cancer J*. 2024;14(1):10.

Lifetime Risk of ET/PV Transformation to AML ~10-20%



Tefferi A, et al. *Blood*. 2014;124(16):2507-2513.

MPNs Shorten Survival

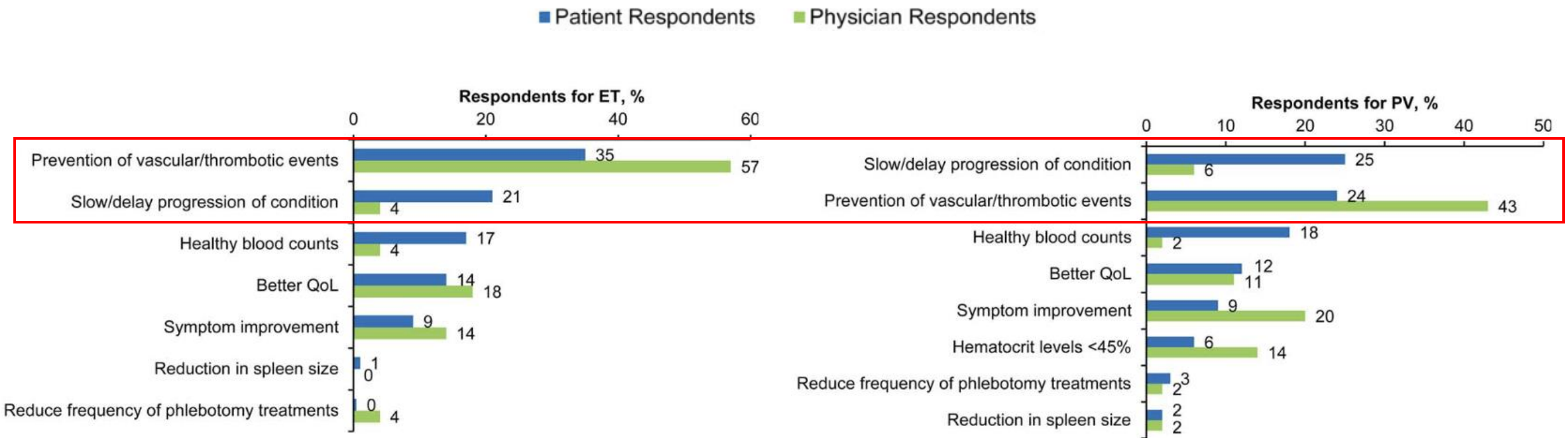


	Age at diagnosis (median)
Essential thrombocythemia (ET)	55
Polycythemia vera (PV)	64

MPN = myeloproliferative neoplasm.
Tefferi A, et al. *Blood*. 2014;124(16):2507-2513.

Risk Assessment and Treatment in ET

Discordance in ET and PV Treatment Goals between Physicians and Patients



Mesa RA, et al. *Cancer*. 2017;123(3):449-458.

Risk Stratification and Treatment in ET Is Primarily Driven by Thrombosis Risk (Revised IPSET-Thrombosis)

Risk Category	Criteria	~Annual Thrombosis Risk
Very Low	Age ≤60, no thrombosis history, *JAK2*-negative	~1% per year
Low	Age ≤60, no thrombosis history, *JAK2*-positive	~1.5% per year
Intermediate	Age >60, no thrombosis history, *JAK2*-negative	~2-3% per year
High	Prior thrombosis at any age **OR** age >60 with *JAK2*-positive	~3-4% per year

IPSET = International Prognostic Score for Essential Thrombocythemia.
Barbui T, et al. *Blood Cancer J*. 2015;5(8):e337.

Thrombosis-Directed Treatment Approach Ignores Progression Risk

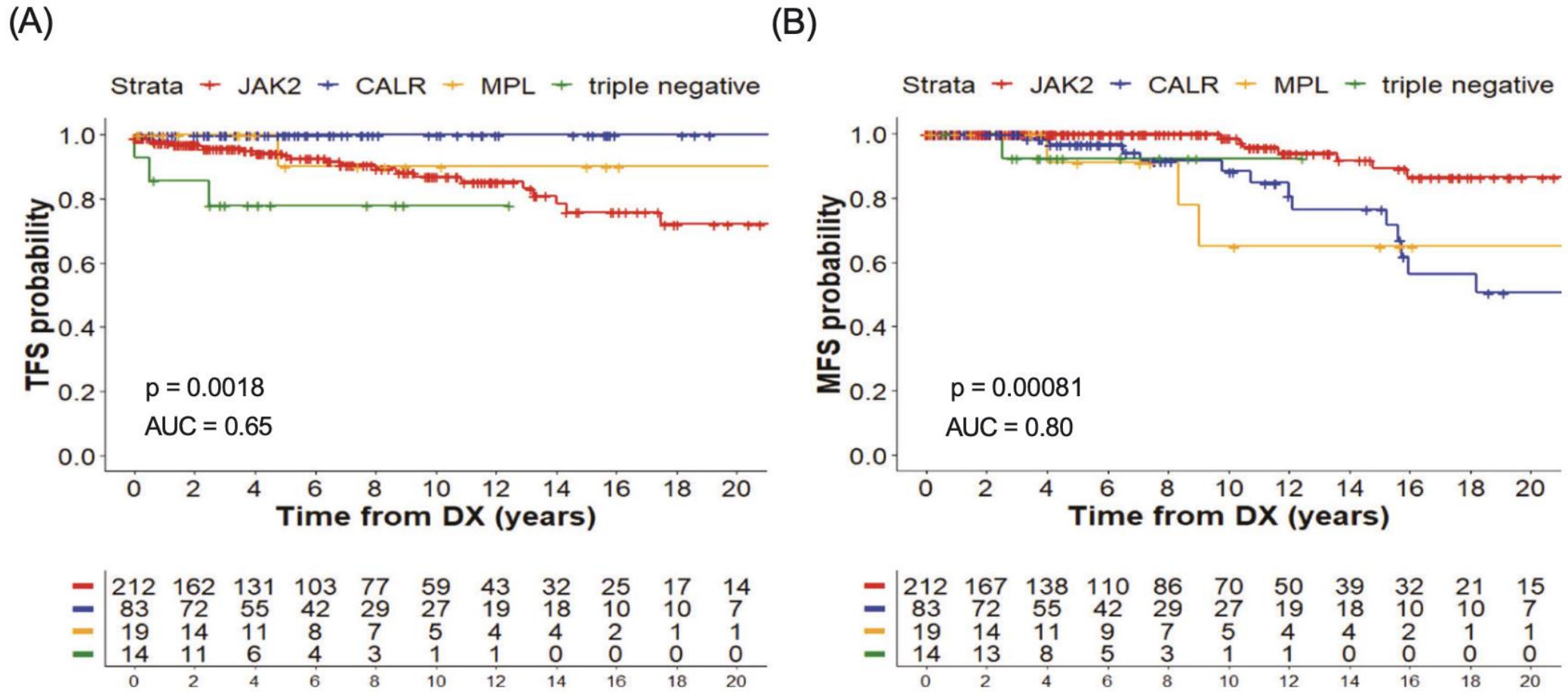


Fig. 1 Thrombosis-free (TFS) and myelofibrosis-free survival (MFS) by driver mutation. A TFS of ET patients stratified by driver n
B MFS of ET patients stratified by driver mutation.

Abu-Zeinah G, et al. *Blood Cancer J*. 2024;14(1):103.

Thrombosis Risk-Adapted Treatment of ET: Very Low, Low, or Intermediate Risk

Treatment for Very-Low-Risk or Low-Risk or Intermediate-Risk Essential Thrombocythemia

Manage CV risk factors for all

Very-low-risk (age ≤60 years, no *JAK2* mutation, no prior history of thrombosis)

cardiovascular risk factors (MPN-H)
• Aspirin (81-100 mg/day) for patients with vasomotor/ microvascular disturbances

Low-risk (age ≤60 years, *JAK2* mutation, no prior history of thrombosis)

OR

Intermediate-risk (age [illegible] *JAK2* mutation, no prior history of thrombosis)

• Manage cardiovascular risk factors (MPN-H)
• Aspirin (81-

Asymptomatic with no indications for cytoreductive therapy

ASA for most (eg, asymptomatic, very-low risk/non-*JAK2*)

disease-related major bleeding
• Evaluate for indications for cytoreductive therapy and monitor signs/symptoms of disease progression (MPN-E 1 of 2) as clinically indicated

Symptomatic with potential indications for cytoreductive therapy

• New thrombosis, acquired VWS, and/or disease-related major bleeding
• Splenomegaly
• Progressive thrombocytosis and/or leukocytosis
• Disease-related symptoms (eg, pruritus, night sweats, fatigue)
• Vasomotor/microvascular disturbances not responsive to aspirin (eg, headaches/chest pain, erythromelalgia)

Initiate cytoreductive therapy, see high-risk ET (ET-2)

Cytoreductive therapy for some (eg, symptomatic)

Disease progression

Post-ET MF, see MPN-2; Accelerated/blast phase MPN, see MPN-AP/BP-1

CV = cardiovascular; VWS = von Willebrand syndrome; ASA = acetylsalicylic acid.

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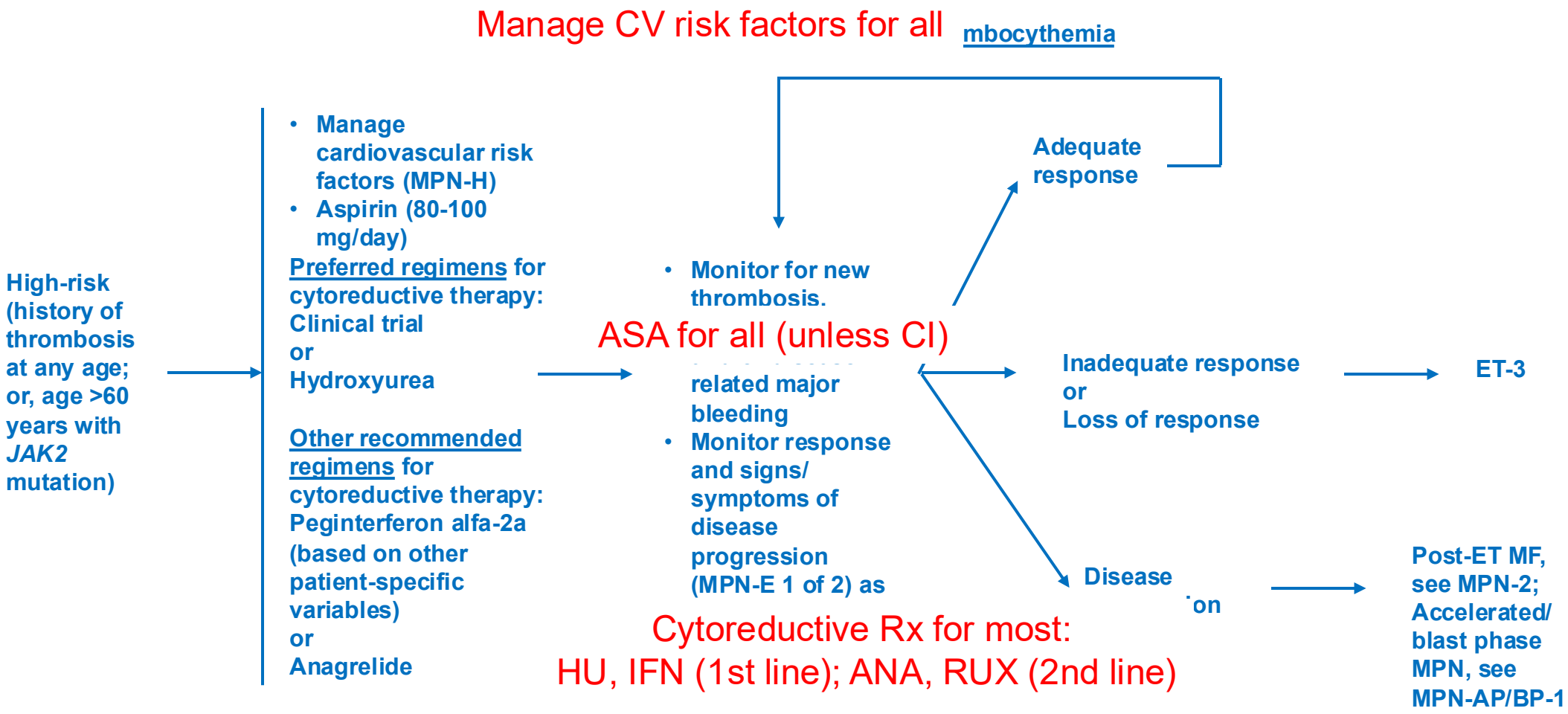
Thrombosis Risk-Adapted Treatment of ET: High-Risk



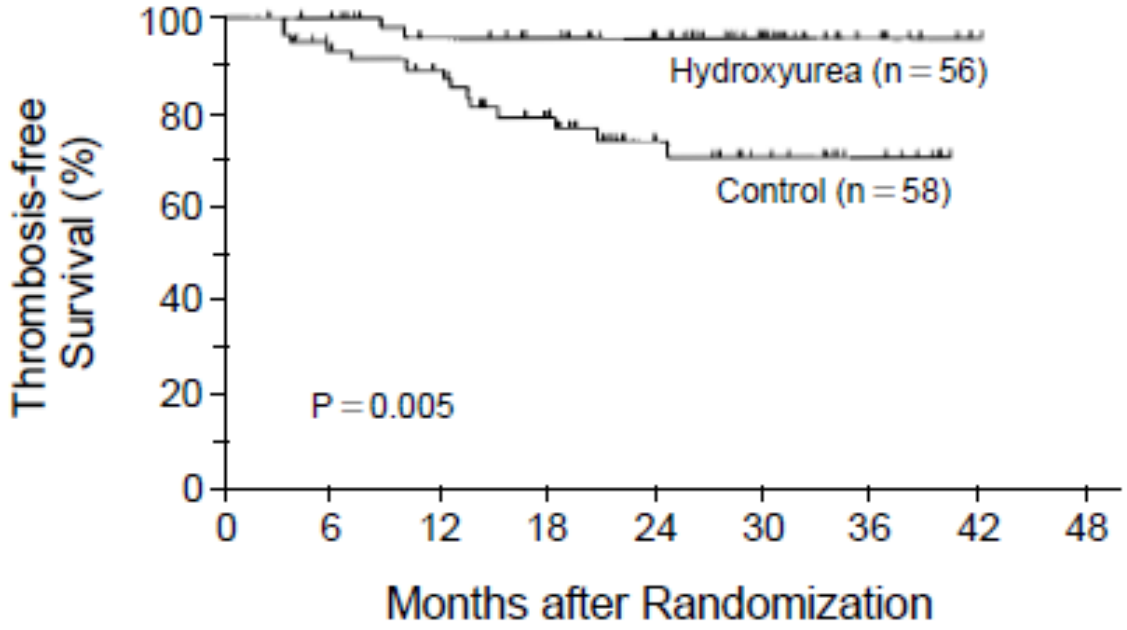
CI = contraindicated; HU = hydroxyurea; IFN = interferon; ANA = anagrelide; RUX = ruxolitinib.

Adapted from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Myeloproliferative Neoplasms V.2.2025. © 2025 National Comprehensive Cancer Network, Inc. All rights reserved. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available.

Cytoreduction in ET May Improve Thrombosis-Free Survival: Results of RCT from 1995

Hydroxyurea (HU) targeting plt <600K vs observation

- Significant reduction in thrombotic events in the treatment arm (3.6% vs 24%)



RCT = randomized controlled trial.
Cortelazzo S, et al. *N Engl J Med*. 1995;332(17):1132-1136.

Special Considerations for Cytoreduction in ET

- Extreme thrombocytosis: if plt count >1.5x10^6/uL (? >1x10^6/uL)
- Acquired VWD: typically with extreme thrombocytosis
- Symptoms: microvascular or otherwise
- Pregnancy: particularly with risk factors for thrombosis, miscarriage

VWD = von Willebrand disease.

CASE 1: A 35-Year-Old Man with Abdominal Pain

Presentation

- 3 weeks of progressive abdominal pain
- Found to have acute PVT with extension into the splenic vein
- **Imaging:** Marked splenomegaly (up to 20.5 cm), periportal lymphadenopathy, patent hepatic veins
- **Endoscopy:** Erythematous gastric and duodenal mucosa
- **Laboratory findings**
  - Thrombocytosis (platelets 600K)
  - Mild leukocytosis (WBC 10-11)
  - Mild anemia (Hgb 13.9)
  - Normal ATIII, protein C/S, APC resistance
  - Negative lupus anticoagulant
  - *JAK2*V617F-positive (17.8% allele frequency)
- No prior primary care or recent blood work

Diagnostic workup

- Bone marrow biopsy: 60-70% cellularity (normocellular for age), increased megakaryocytes with atypical morphology and clustering, no significant reticulin fibrosis (MF0)

Diagnosis

- Essential thrombocythemia with *JAK2*V617F mutation

Current management

- Started on apixaban for PVT

APC = activated protein C; ATIII = antithrombin III.

CASE 1: A 35-Year-Old Man with ET and SVT

- **What is the best next step in management for this patient with newly diagnosed *JAK2*V617F-positive essential thrombocythemia and acute portal vein thrombosis?**

❑ **A**. Continue anticoagulation alone

❑ **B**. Add cytoreductive therapy (eg, hydroxyurea or interferon)

❑ **C**. Switch to low molecular weight heparin

❑ **D**. Consider splenectomy

- **What additional monitoring or workup is indicated after 6 months of treatment (pain has resolved)?**

❑ **A**. Repeat bone marrow biopsy

❑ **B**. Molecular response assessment and testing for additional mutations

❑ **C**. Serial abdominal imaging

❑ **D**. Routine blood count monitoring

❑ **E**. All of the above

1st-Line CytoRx in High-Risk ET and PV: The HU vs IFNα Saga

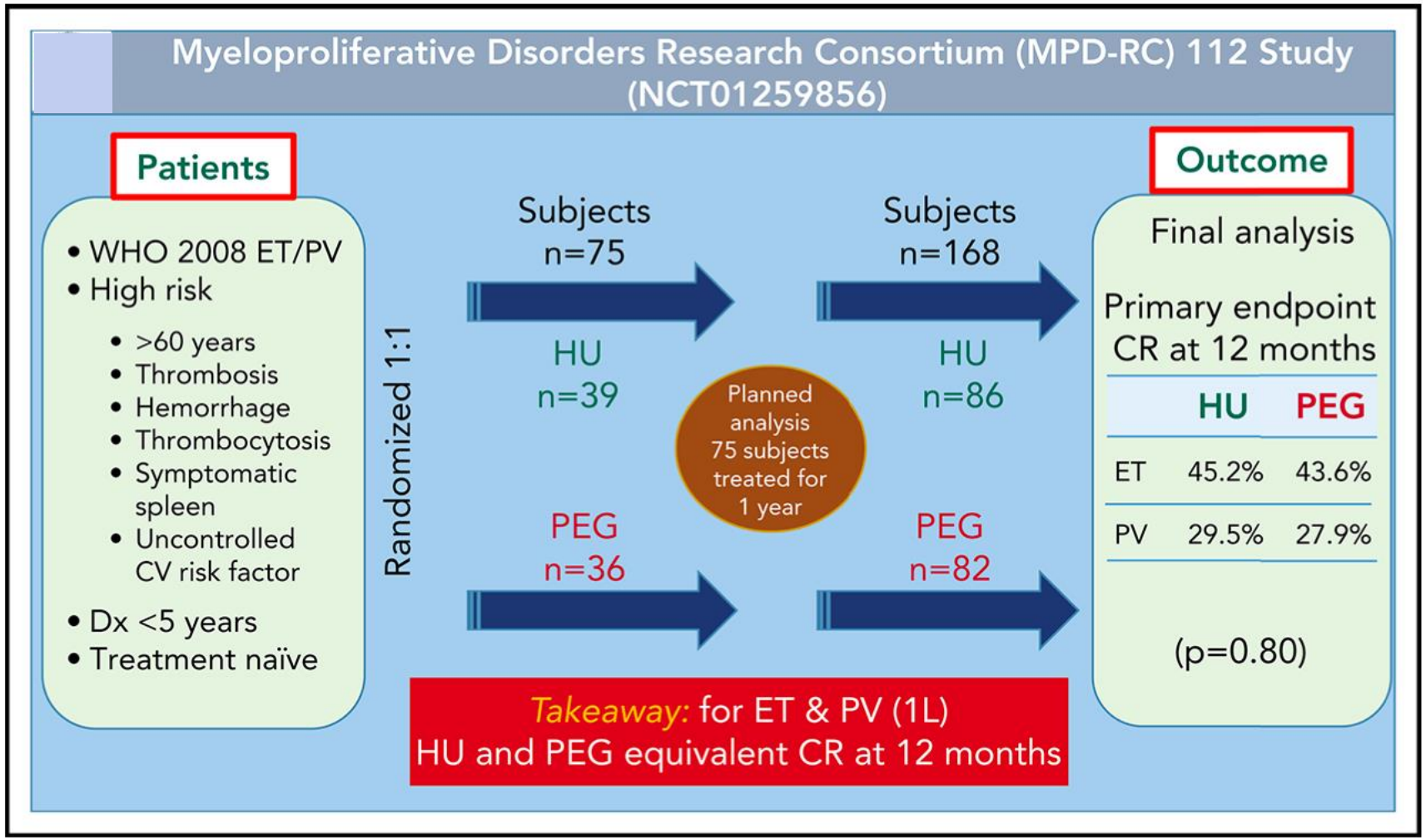
- MPD-RC 112: Phase 3 multi-center study (US) of high-risk patients with PV or ET randomized to PEG-IFN vs HU
- PROUD/CONTI-PV: Phase 3 randomized, multi-center study of non-inferiority of ropegIFN to HU in newly diagnosed high-risk patients with PV

Note: NONE of the RCTs use thrombosis-free survival as endpoint. Primary endpoint is clinical response.

PEG = pegylated IFN-α.

Mascarenhas J, et al. *Blood*. 2022;139(19):2931-2941. ClinicalTrials.gov. Accessed October 10, 2025. https://www.clinicaltrials.gov/study/NCT01387763. ClinicalTrials.gov. Accessed October 10, 2025. https://www.clinicaltrials.gov/study/NCT02218047.

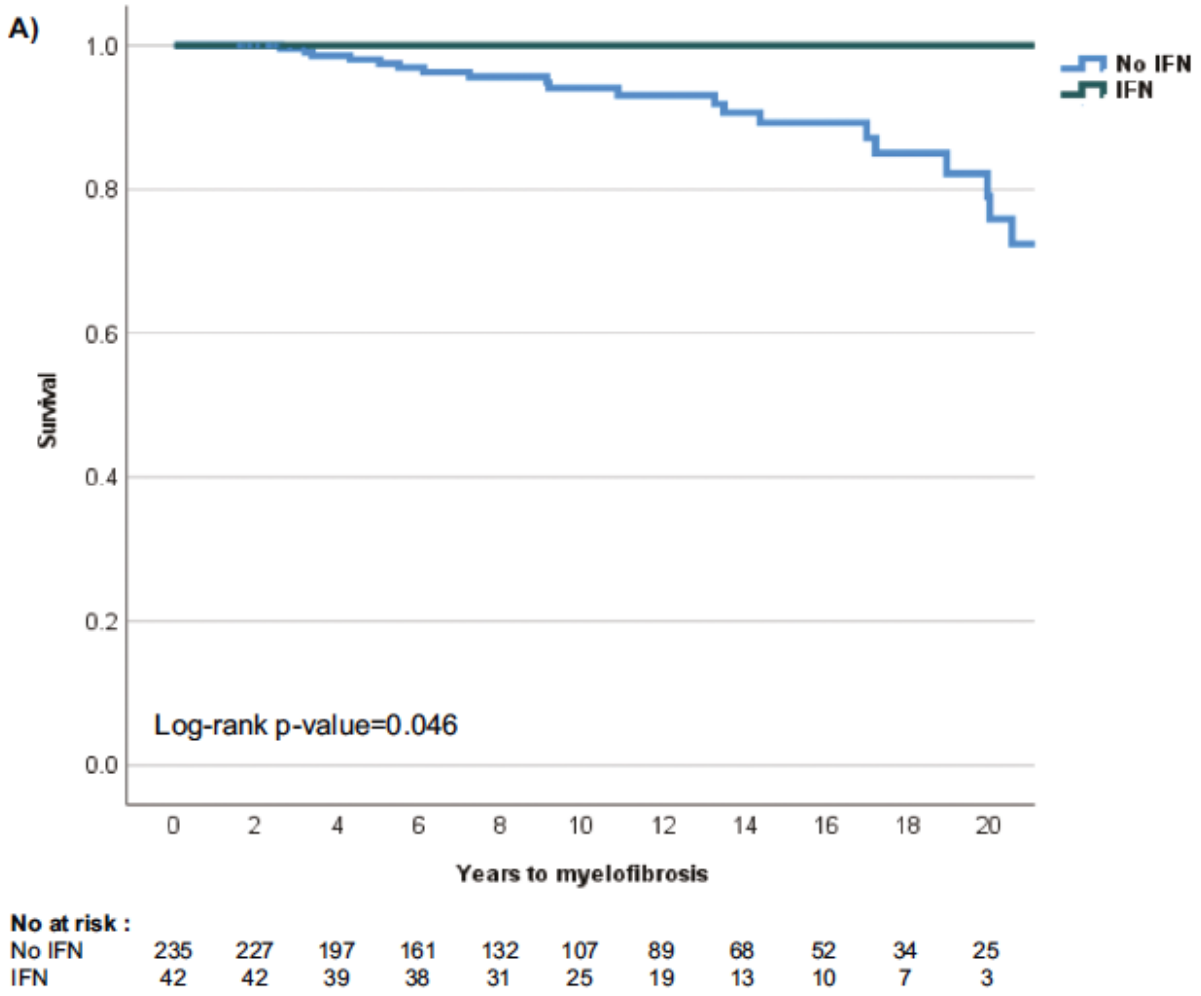
MPD-RC112: HU vs PEG
CR Rate Similar at 1 Year



CR = complete response.

Mascarenhas J, et al. *Blood*. 2022;139(19):2931-2941.

Long-Term Survival Outcomes May Support IFN Use in AYA Patients with ET



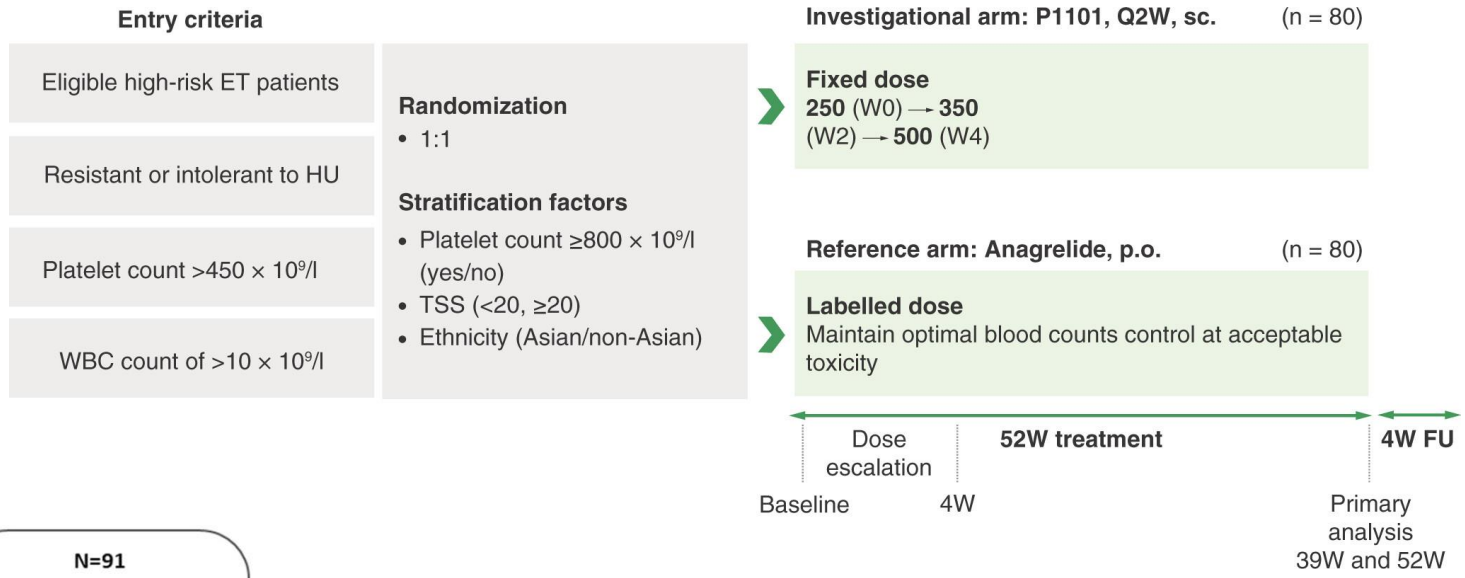
- Median age ~20 y
- Mostly ET
- 348 patients (278 ET, 70 PV)

AYA = adolescent and young adult.

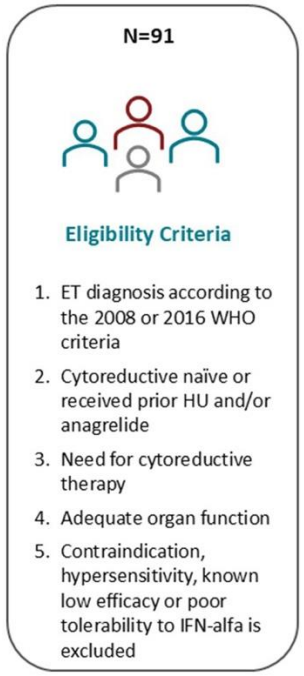
Beauverd Y, et al. *Leukemia*. 2025;39(5):1135-1145.

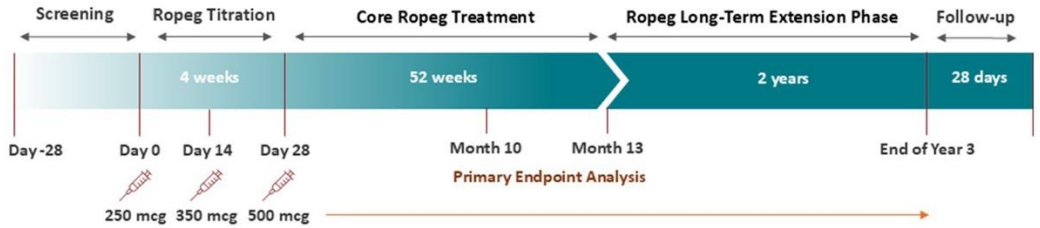
Ropeginterferon Alfa-2b in ET

SURPASS ET



EXCEED ET



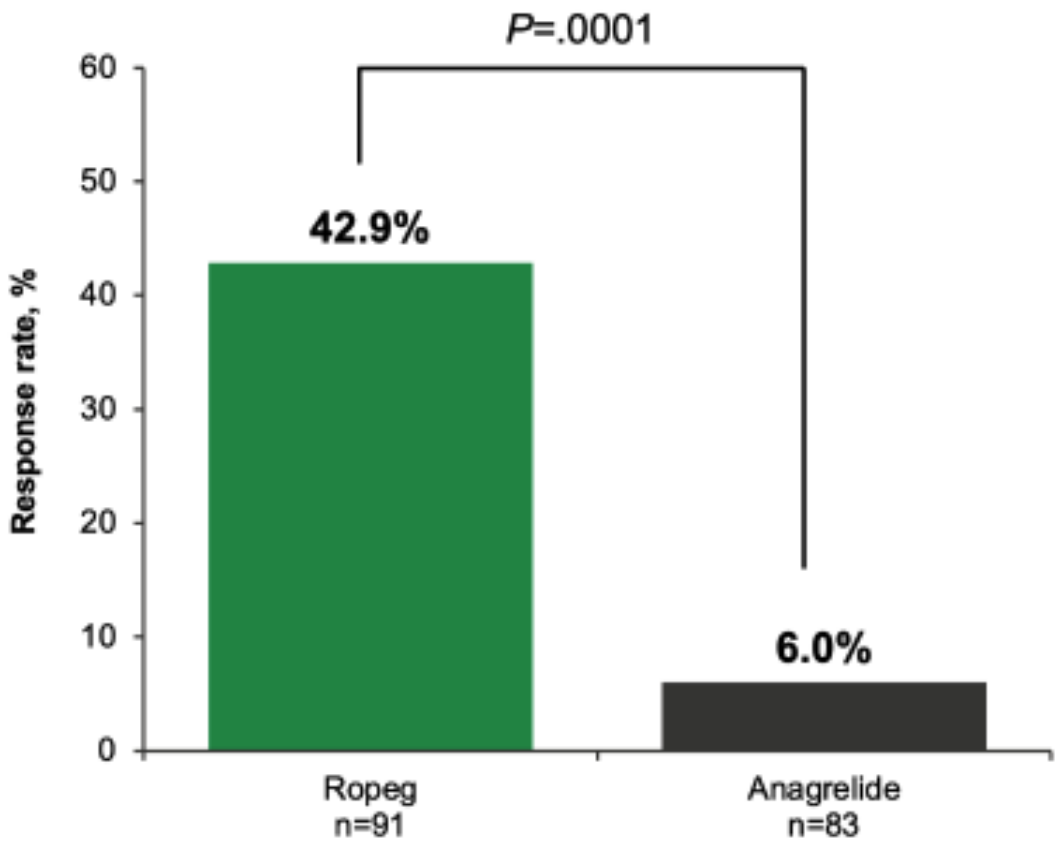


Primary Endpoint: platelets ≤400 x 10^9/L, white blood cells <10 x 10^9/L, improvement or non-progression of disease-related signs (splenomegaly) and major symptoms, and absence of hemorrhagic or thrombotic events, at both Month 10 and Month 13 (corresponding to 9 and 12 months of ropeg core treatment)

Ropeg; Ropeginterferon alfa-2b-nɨ jft

Verstovsek S, et al. *Future Oncol*. 2022;18(27):2999-3009.
Masarova L, et al. *Front Med (Lausanne)*. 2025:12:1548590.

Primary Endpoint: Modified ELN Response Rate



Significantly more participants in the ropeg arm achieved durable modified ELN criteria response rate at months 9 and 12, compared with those in the anagrelide arm[a,b]

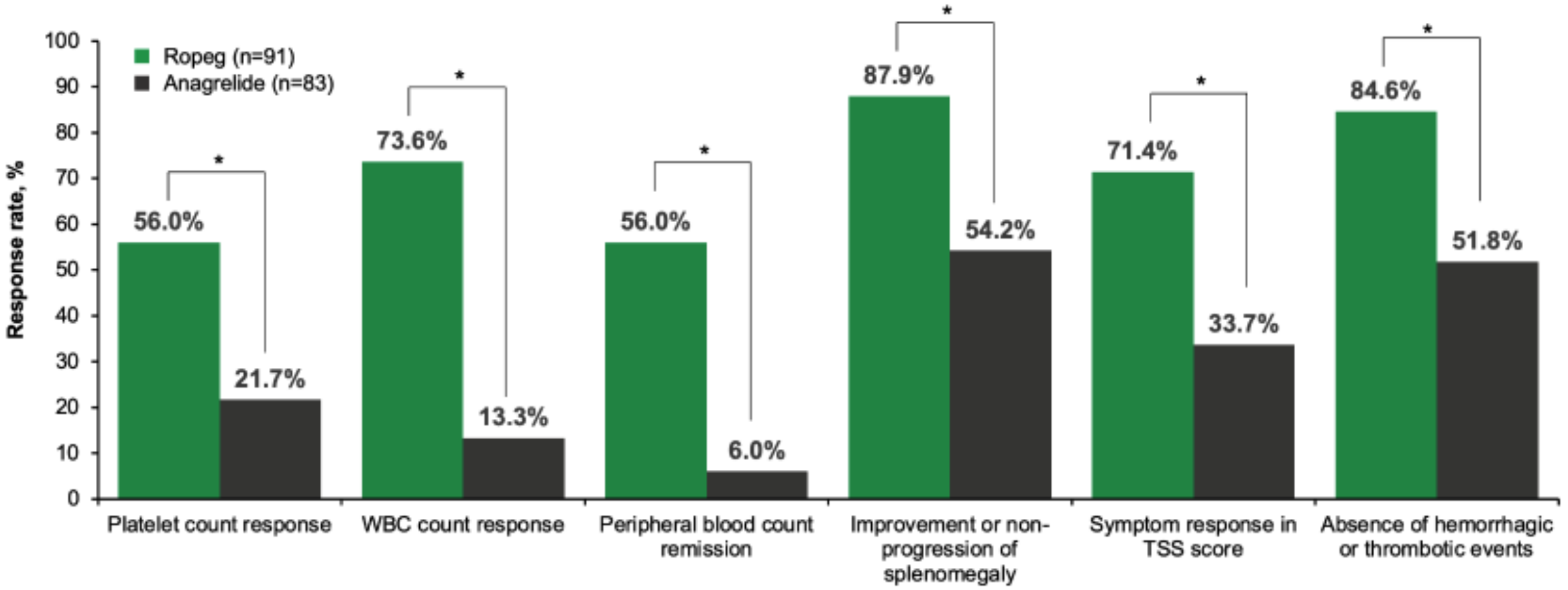
Modified ELN response criteria component endpoints

- ≥10-point decrease in the MPN-SAF TSS for at least 12 weeks
- Normalization of peripheral blood counts for at least 12 weeks
- Absence of vascular events and disease progression

[a]The median dose of ropeg over the 12-months was 448.6 µg (range 225 µg, 487 µg) once every 2 weeks.
[b]The median dose of anagrelide over the 12 months was 2.0 mg (range 0.3 mg, 4.6 mg) daily.
ELN, European LeukemiaNet; MPN-SAF TSS, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score.

Slide courtesy of Mesa RA.

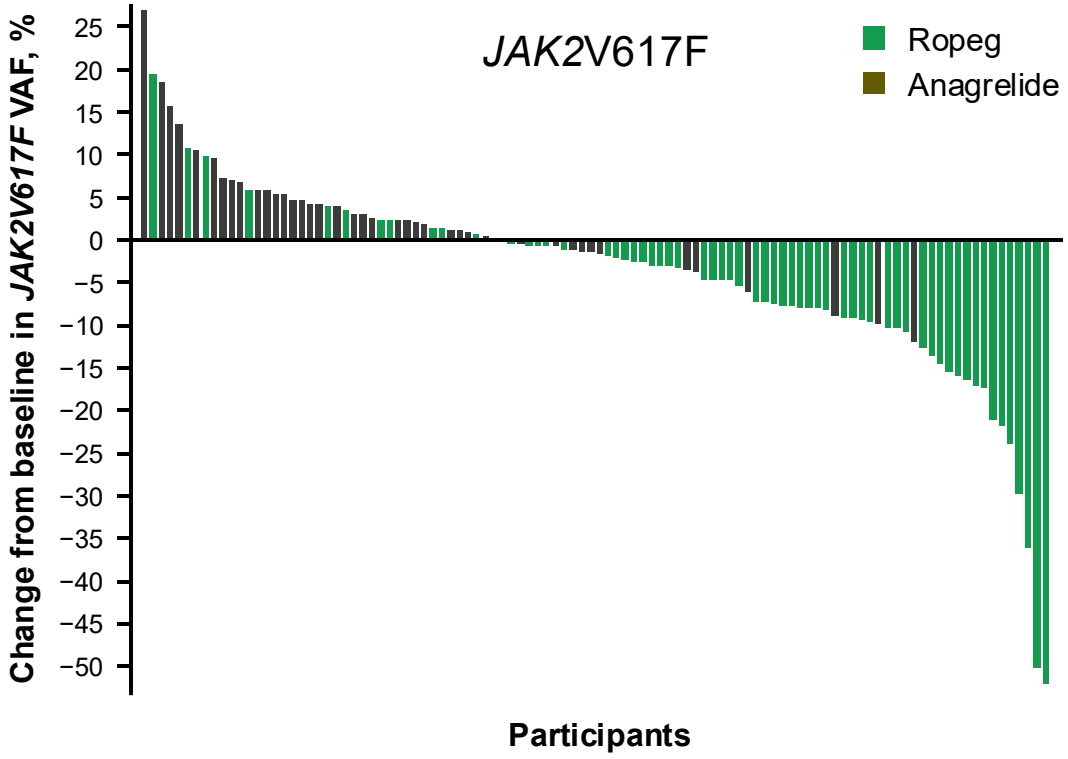
Primary Endpoint: Response Rate for Individual Modified ELN Parameters

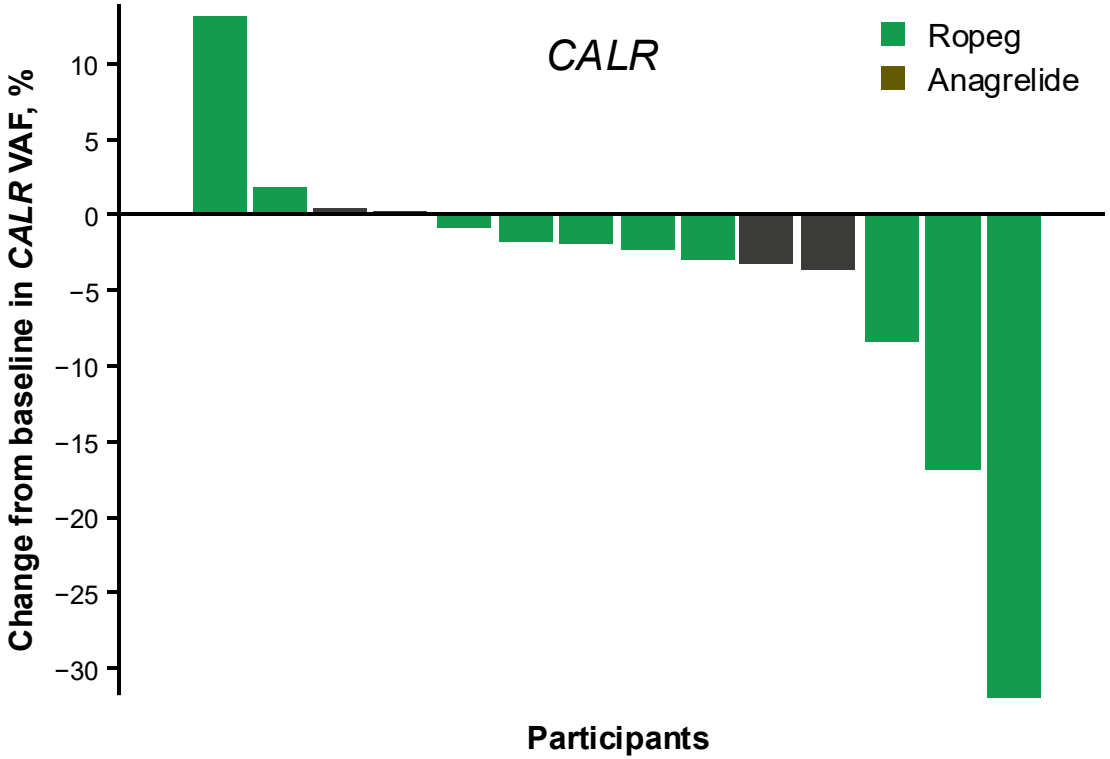


*P<0.0001.
Response defined as meeting the following criteria at months 9 and 12: hematologic control, spleen and symptom improvement or stability (MPN-SAF TSS), and no thrombotic/hemorrhagic events.
MPN-SAF TSS, Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score; WBC, white blood cell.

Slide courtesy of Mesa RA.

Change in *JAK2*V617F and *CALR* Variant Allele Burden in Individual Participants





VAF = variant allele frequency.
Slide courtesy of Mesa RA.

Risk Assessment and Treatment in PV

Risk Stratification and Treatment in PV Is Also Primarily Driven by Thrombosis Risk

Risk Category	Criteria	Approx. Annual Thrombosis Risk
Low	Age ≤60, no prior thrombosis	~2% per year
High	Age >60 **or** prior thrombosis	~5-6% per year

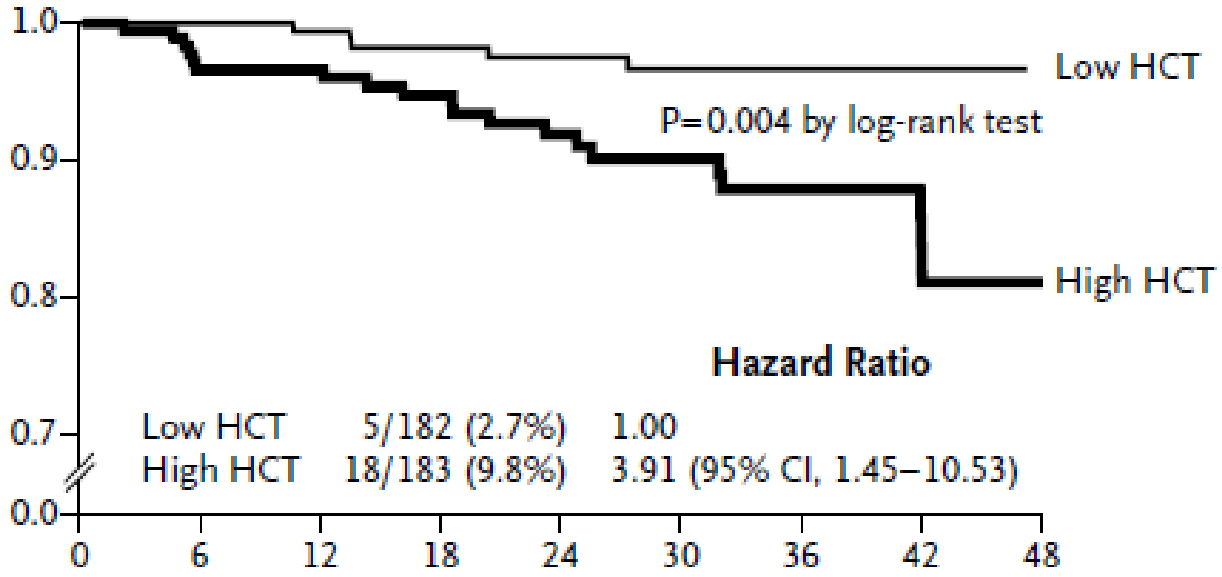
- **Low-dose aspirin for all except** if contraindicated or on therapeutic anticoagulation; ECLAP trial showed 60% significant decrease in risk of combined primary endpoint of MI, stroke, PE, DVT, and death from CV cause
- **Cytoreduction for high-risk patients** OR low-risk patients with symptoms, high phlebotomy requirements

Landolfi R, et al. *N Engl J Med*. 2004;350(2):114-124. Barbui T, et al. *Leukemia*. 2018;32(5):1057-1069. Marchetti M, et al. *Lancet Haematol*. 2022;9(4):e301-e311.

HCT Control <45% Is a Standard Goal of Treatment to Reduce Thrombosis Risk

CYTO-PV trial

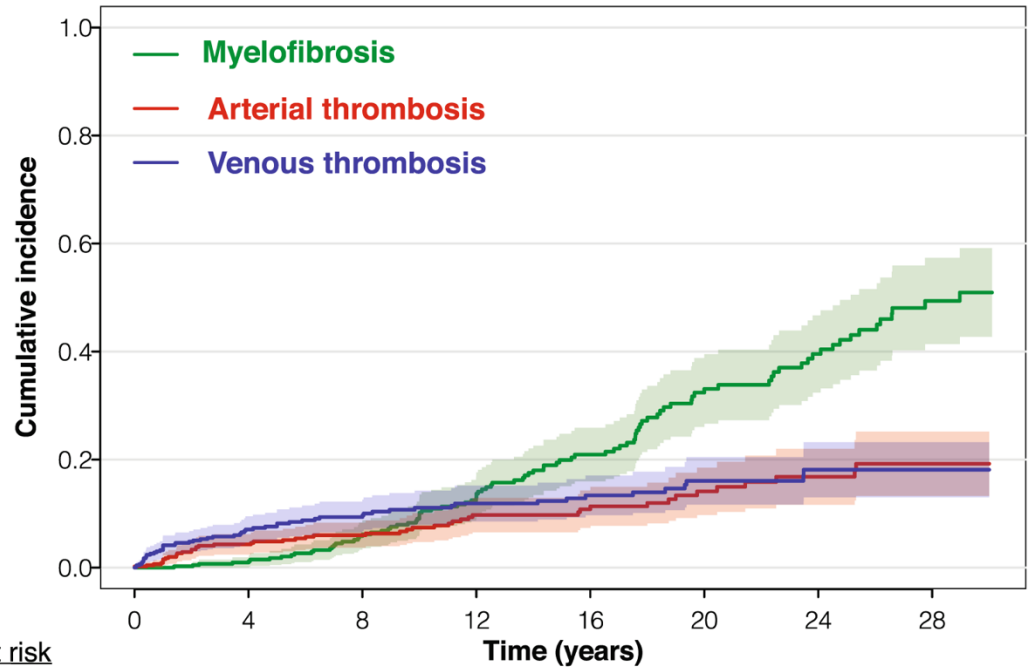
- Approximately 4-fold increase in risk of major thrombotic event or cardiovascular death in the group with HCT 45-50



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

But Thrombosis Risk-Based Approach Ignores Progression Threat

~50% of PV progress to MF…a bigger threat long-term than thrombosis

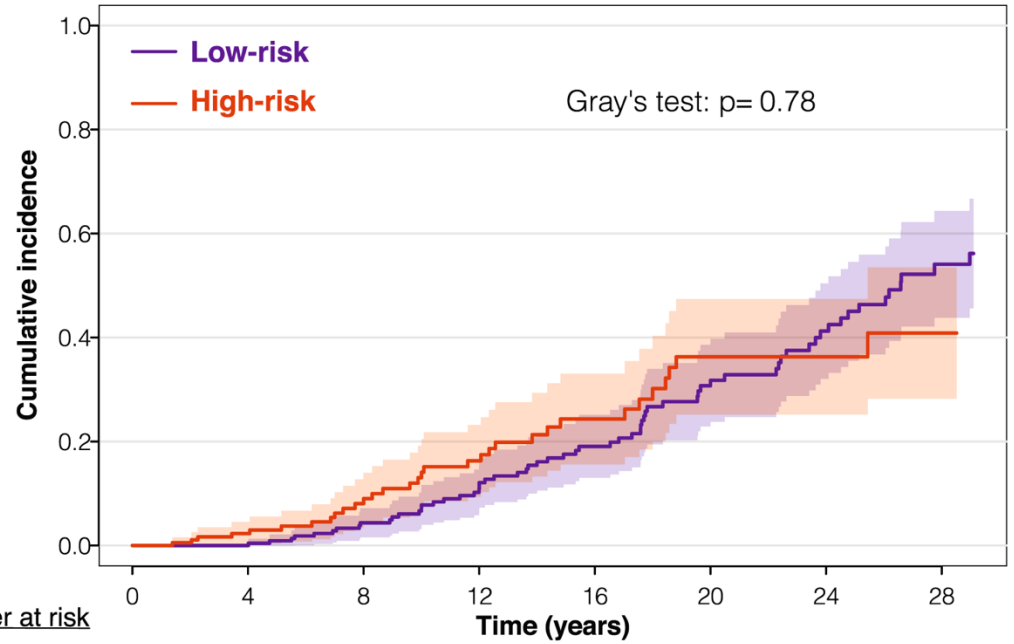


Number at risk

Myelofibrosis (MF):	470	363	257	191	118	68	39	12
Arterial thrombosis:	470	327	232	168	109	64	35	14
Venous thrombosis:	470	327	232	168	109	64	35	14

Patients with "low-risk" PV are at equally high risk of progression

Cumulative incidence of MF progression in ELN low- and high-risk PV-WCM patients.



Number at risk

Low:	264	226	178	139	95	59	36	11
High:	206	137	79	52	23	9	3	1

Abu-Zeinah G, et al. *Leukemia*. 2022;36(2):569-572.

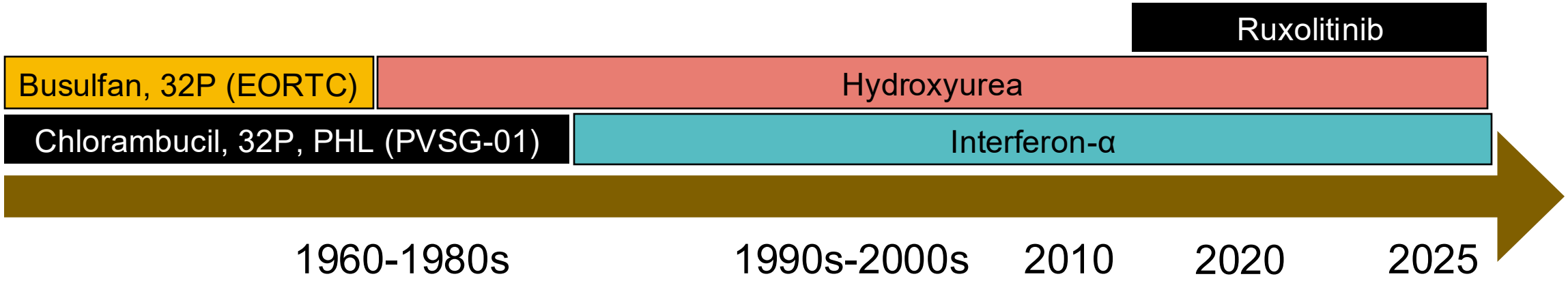
CASE 2: A 58-Year-Old Man with Asymptomatic Polycythemia

- 58M presented in 2002 with asymptomatic elevation in HCT (51%) and PLT (720K)
- No splenomegaly (SPML) on exam
- A BMB confirmed diagnosis of PV
- Phlebotomy (PHL) and low-dose ASA initiated. Required 12 PHL 1st year and 10 PHL 2nd year to maintain HCT <45%.

BMB = bone marrow biopsy.

Cytoreductive Treatments in PV

FDA approvals for PV:
2014: ruxolitinib for PV after HU failure
2021: ropeginterferon alfa 2a for PV



EORTC = European Organisation for Research and Treatment of Cancer.
Raedler LA. *Am Health Drug Benefits*. 2015;8(Spec Feature).75-79. MPNHub [www.mpn-hub.com]. Last updated November 15, 2021. https://mpn-hub.com/medical-information/m.

CASE 2: A 58-Year-Old Man with PV + High PHL Needs

- At ~3 years, started hydroxyurea (HU) and dose uptitrated to 1000 mg daily
- At ~6 years → disease progression on HU
  - CBC: WBC 16.3, HGB 14.7, HCT 47.6, RBC 6.71, PLT 942
  - SPML on exam 17 cm below LCM
  - JAK2V617F allele frequency 93%
  - BMBx: markedly hypercellular >95% with MF-2 to 3 fibrosis (trace collagen)
- HU discontinued due to disease progression and severe oral ulcers
- Switched to pegylated interferon alfa-2a (IFN)

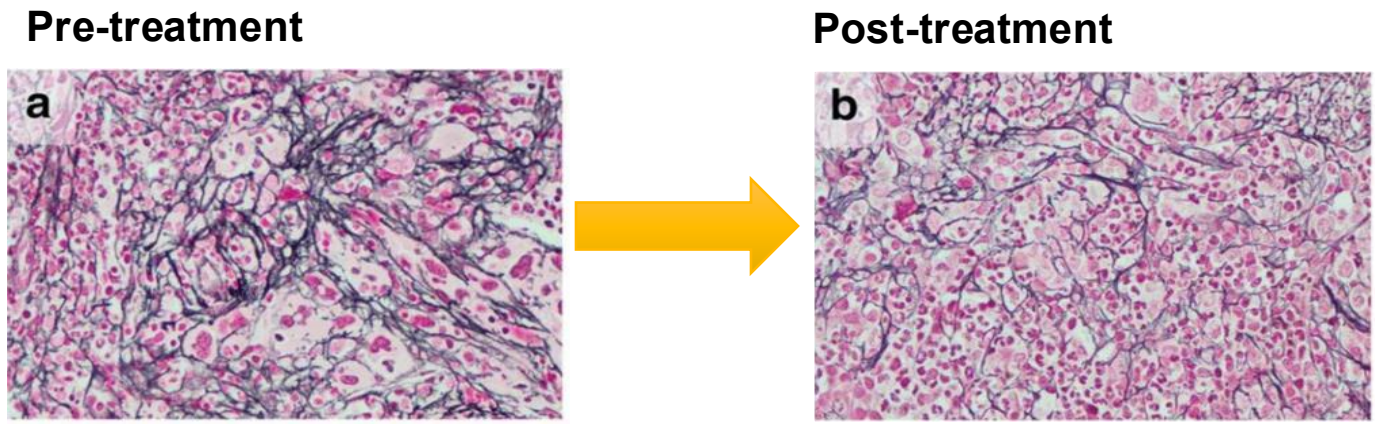
CBC = complete blood count; RBC = red blood cell count; LCM = left costal margin.

CASE 2: A 58-Year-Old Man with PV Progression on HU

- At ~3 years, started hydroxyurea (HU) and dose uptitrated to 1000 mg daily
- At ~6 years → disease progression on HU
  - CBC: WBC 16.3, HGB 14.7, HCT 47.6, RBC 6.71, PLT 942
  - SPML on exam 17 cm below LCM
  - JAK2V617F allele frequency 93%
  - BMBx: markedly hypercellular >95% with MF-2 to 3 fibrosis (trace collagen)
- HU discontinued due to disease progression and severe oral ulcers
- Switched to pegylated interferon alfa-2a (IFN)

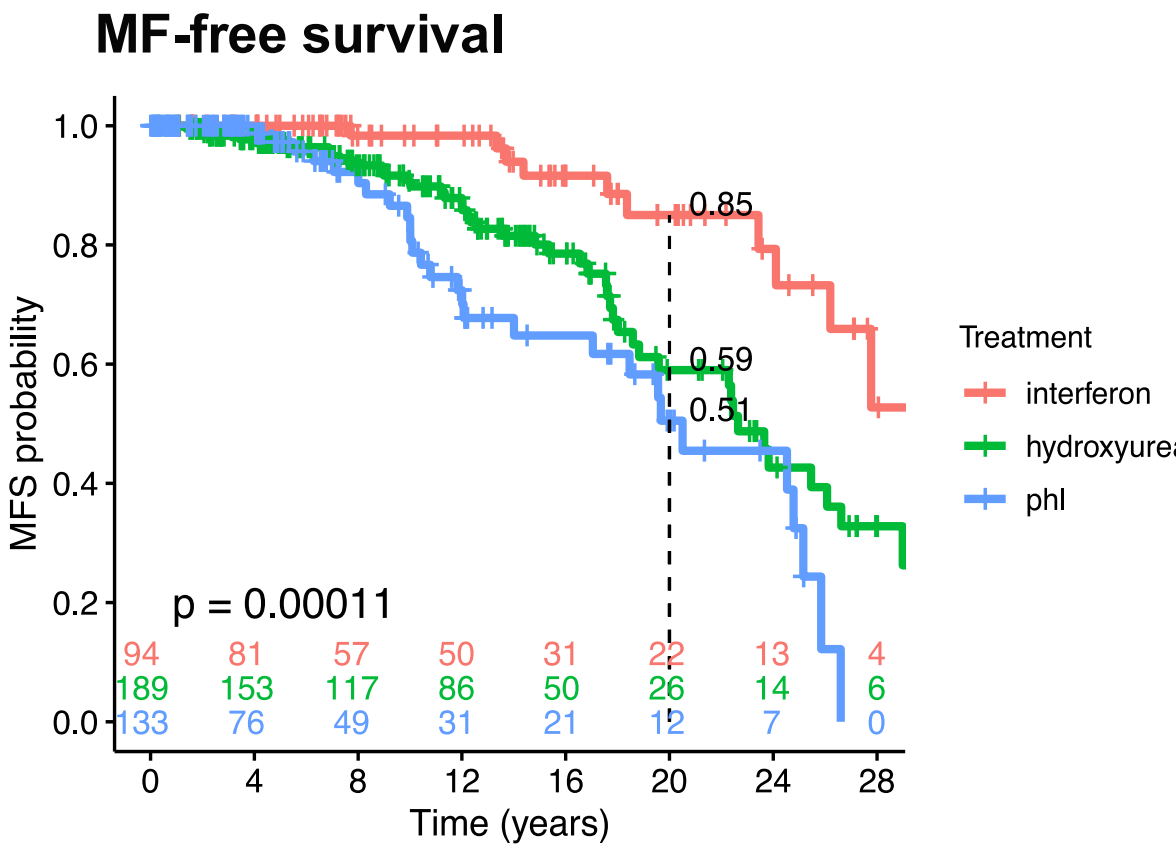
CASE 2: A 58-Year-Old Man with Post-PV MF on IFN

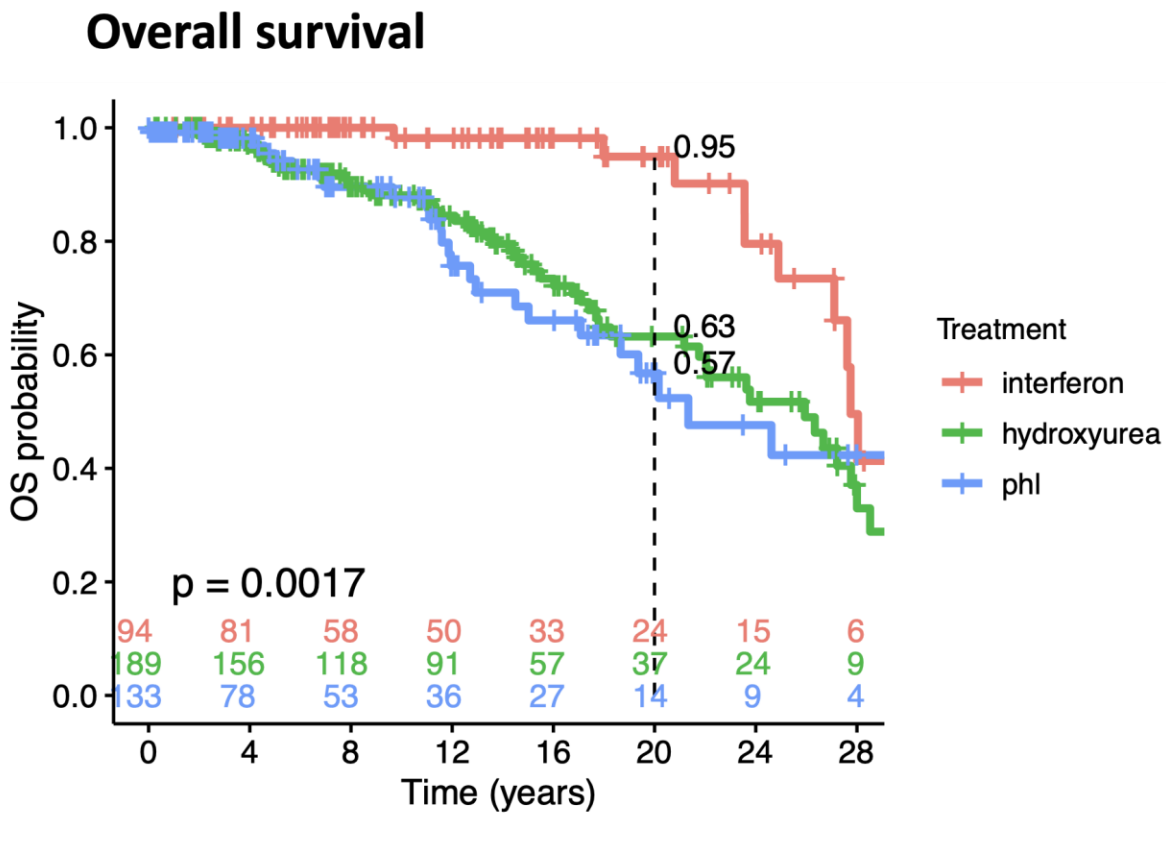
- ~10 years on IFN; CBC: WBC 12.1, HGB 14.1, HCT 44%, RBC 5.1, PLT 326
- BMBx: hypercellular 80% with mild MF-1 fibrosis, no collagen



Pizzi M, et al. *Mod Pathol*. 2015;28(10):1315-1323.

Long-Term Survival Outcomes Support IFN Use in "Low-Risk" Patients with PV





MVA: 9% MF risk reduction/yr of IFNα

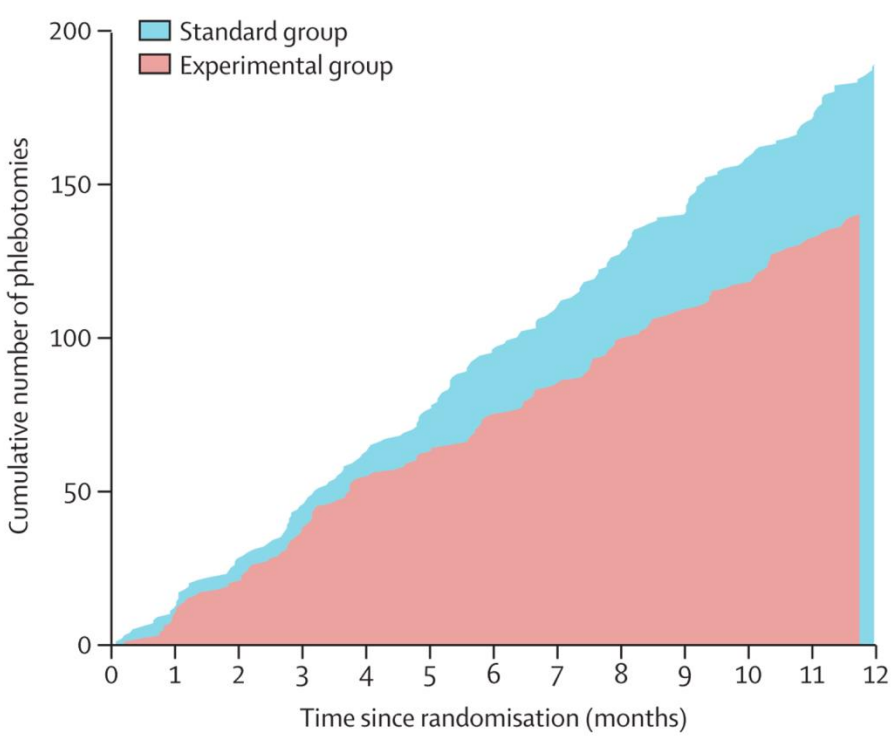
MVA: 6% mortality risk reduction/yr of IFNα

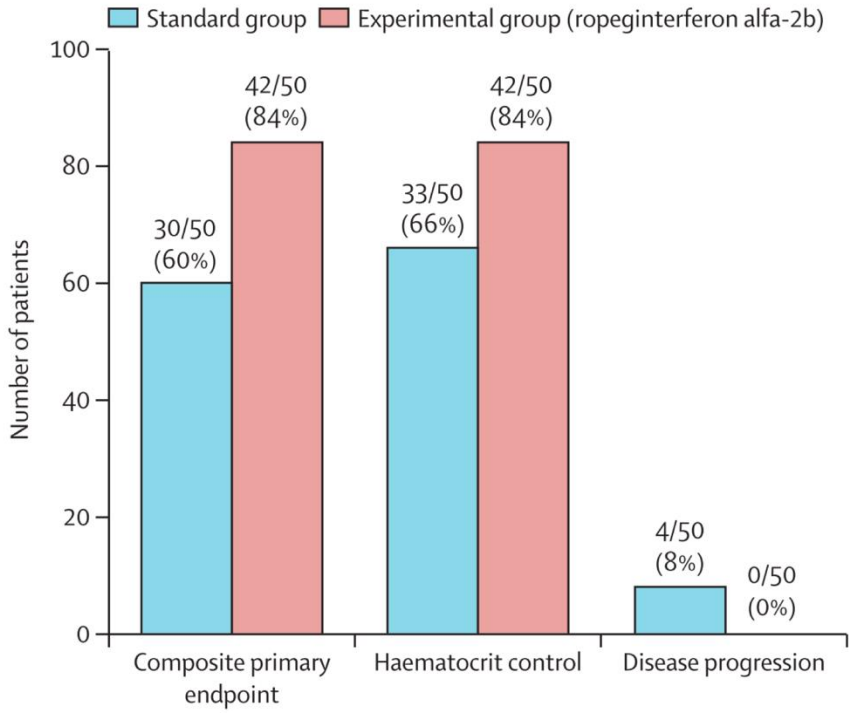
MVA = multivariable analysis; MFS = myelofibrosis-free survival; OS = overall survival.

Abu-Zeinah G, et al. *Leukemia*. 2021;35(9):2592-2601.

1st-Line CytoRx in Low-Risk ET and PV: IFN or No IFN??

Low-PV study is the only RCT: 64 ropeg vs 63 phlebotomy-only controls





Barbui T, et al. *Lancet Haematol*. 2021;8(3):e175-e184.

Low PV Study: RopegIFN Improved Disease Control and QoL in "Low-Risk" PV

Table 2. Main Efficacy Results of the Core Study.*

Core Study (12 Months)	Randomized Groups: EXP (n=64)	STD (n=63)	P Value	Effect Estimate† (95% CI)
Treatment response — n (%)	52 (81.3)	32 (50.8)	<0.001	4.20 (1.77–10.23)
Hematocrit control	52 (81.3)	37 (58.7)		3.05 (1.28–7.50)
Disease progression	0 (0.0)	8 (12.7)		—‡
No. of phlebotomies per patient year — mean (SD)	2.9 (2.4)	4.2 (3.2)		1.27 (0.27–2.26)
	EXP (n=55)	**STD (n=43)**		
Absolute *JAK2*V617F VAF change from baseline — %, mean (SD)	−11.9 (20.7)	1.8 (9.0)		13.73 (7.00–20.46)
Partial molecular response — n (%)	16 (29.1)	0 (0.0)		—‡

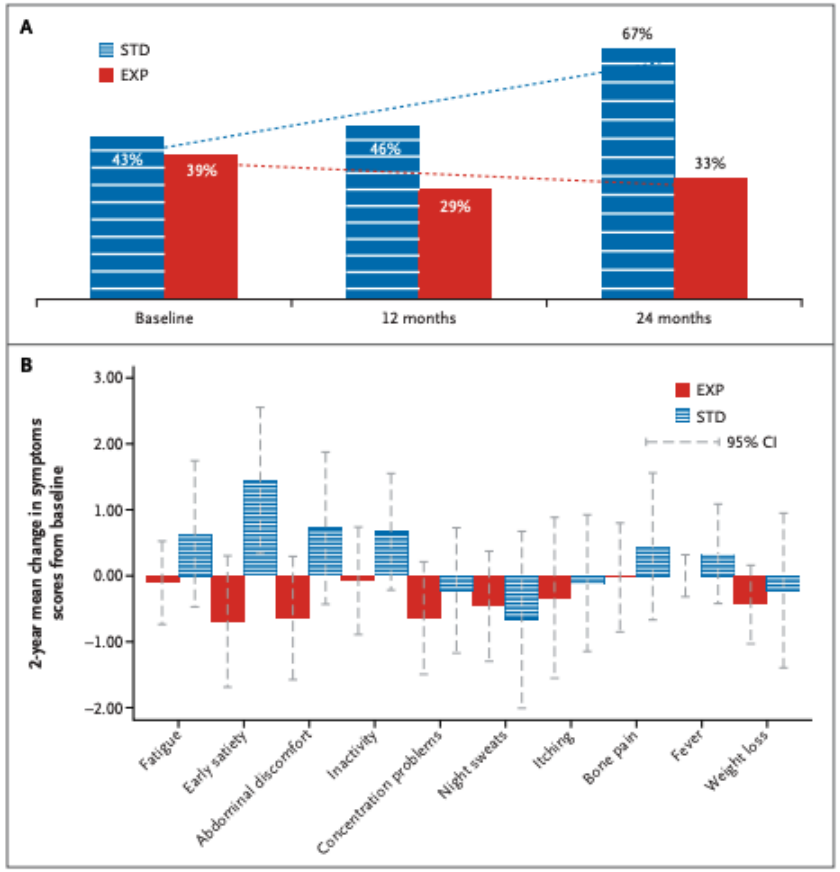


Figure 2. Change in Quality of Life over Time by Study Group.

Barbui T, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200335.

Low PV Study: Low-Dose RopegIFN Well-Tolerated; ~8% Discontinued

Table 4. Adverse Events by Treatment Received and Severity Regardless of Causality.*

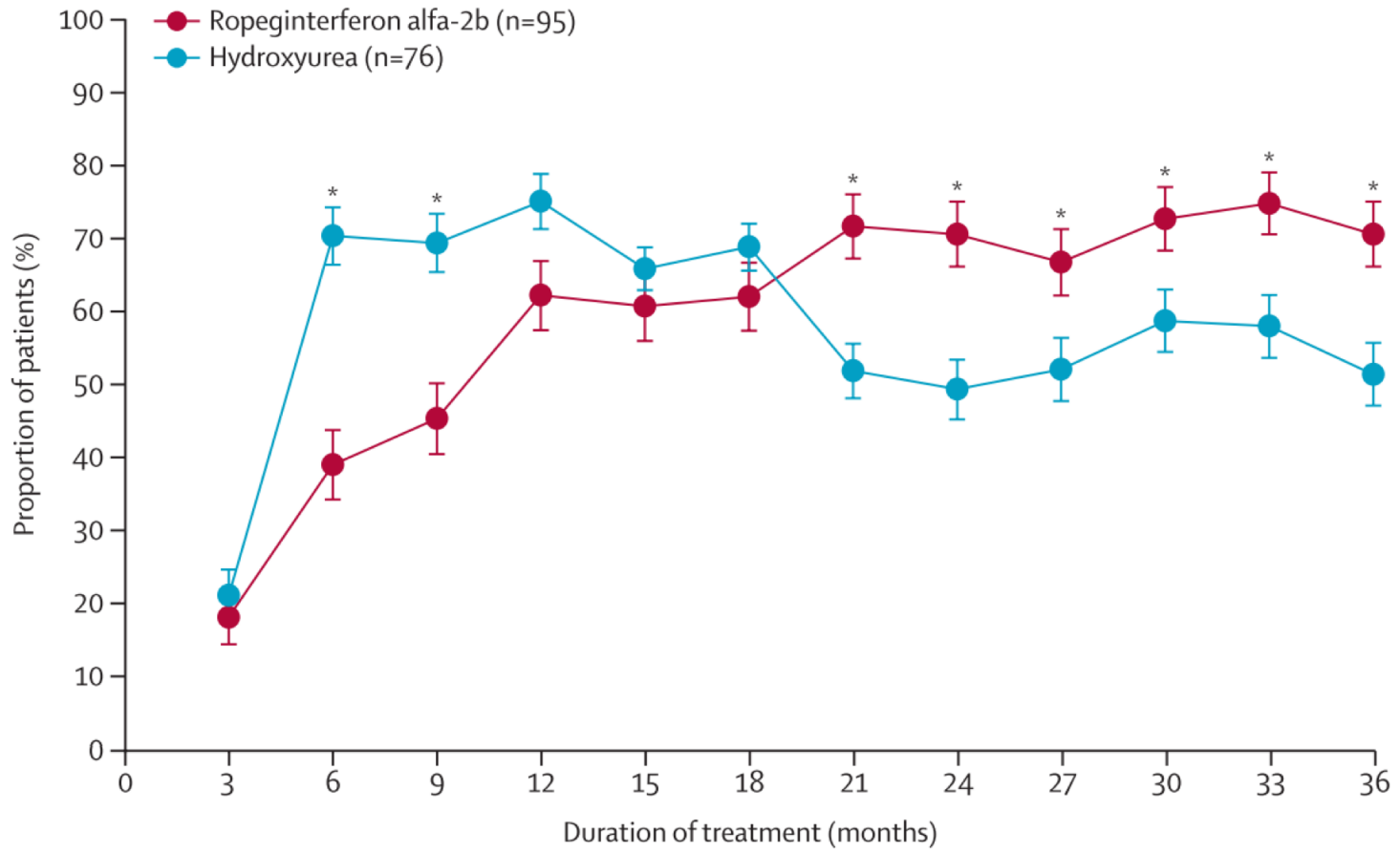
	Experimental (n=87)		Standard (n=72)	
Adverse Event	Grade 1 and 2	Grade 3 and 4	Grade 1 and 2	Grade 3 and 4
Neutropenia	13 (14.9)	8 (9.2)	0 (0.0)	0 (0.0)
Hypertransaminasemia	6 (6.9)	2 (2.3)	0 (0.0)	0 (0.0)
Hypertriglyceridemia	4 (4.6)	2 (2.3)	0 (0.0)	0 (0.0)
Pruritus	3 (3.4)	1 (1.1)	1 (1.4)	0 (0.0)
Fatigue	1 (1.1)	1 (1.1)	1 (1.4)	0 (0.0)
Carditis pericardium myocardium	0 (0.0)	1 (1.1)	0 (0.0)	0 (0.0)
Skin symptoms	0 (0.0)	0 (0.0)	2 (2.8)	3 (4.2)
Thrombosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Acute appendicitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Knee impingement syndrome	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)
Pain not otherwise specified	0 (0.0)	0 (0.0)	2 (2.8)	1 (1.4)
Flu-like symptoms	11 (12.6)	0 (0.0)	1 (1.4)	0 (0.0)
Leucopenia	10 (11.5)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	8 (9.2)	0 (0.0)	1 (1.4)	0 (0.0)
Nausea	8 (9.2)	0 (0.0)	0 (0.0)	0 (0.0)
Asthenia	7 (8.0)	0 (0.0)	3 (4.2)	0 (0.0)
Fever	6 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperpyrexia	6 (6.9)	0 (0.0)	0 (0.0)	0 (0.0)
Hypertension	6 (6.9)	0 (0.0)	1 (1.4)	0 (0.0)
Amylase increased	5 (5.7)	0 (0.0)	1 (1.4)	0 (0.0)
Back pain	5 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperthermia	4 (4.6)	0 (0.0)	2 (2.8)	0 (0.0)
Vertigo	4 (4.6)	0 (0.0)	1 (1.4)	0 (0.0)
Anemia	0 (0.0)	0 (0.0)	4 (5.6)	0 (0.0)

* Values are presented as n (%). Adverse events are reported under the treatment actually received (i.e., 87 patients received ropeginterferon alfa-2b: 64 since randomization and 23 after crossover; 72 patients received phlebotomy only: 63 since randomization and 9 after crossover). All grade 3 or 4 adverse events are reported. Grade 1 or 2 adverse events that occurred in at least 5% of patients are reported.

Barbui T, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200335.

PROUD/CONTI-PV: Comparing IFN vs HU as First-Line Treatment for High-Risk PV

Complete hematologic response



Gisslinger H, et al. *Lancet Haematol*. 2020;7(3):e196-e208.

PROUD/CONTI-PV: HU vs Ropeg Similarly Tolerable, but AEs Differ

	Ropeginterferon alfa-2b (n=127)			Control (n=127)		
	Grade 1–2*	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any adverse event	113 (89%)	40 (32%)	3 (2%)	114 (90%)	33 (26%)	1 (1%)
Thrombocytopenia	27 (21%)	3 (2%)	0	36 (28%)	5 (4%)	0
Leucopenia	23 (18%)	3 (2%)	0	28 (22%)	6 (5%)	0
Anaemia	16 (13%)	1 (1%)	0	31 (24%)	2 (2%)	0
Fatigue	17 (13%)	0	0	17 (13%)	1 (1%)	0
γ-glutamyltransferase increased	20 (16%)	9 (7%)	1 (1%)	2 (2%)	2 (2%)	0
Headache	15 (12%)	0	0	16 (13%)	0	0
Diarrhoea	12 (9%)	0	0	14 (11%)	1 (1%)	0
Dizziness	14 (11%)	0	0	10 (8%)	0	0
Alanine aminotransferase increased	16 (13%)	5 (4%)	0	2 (2%)	0	0
Arthralgia	15 (12%)	1 (1%)	0	5 (4%)	0	0
Hypertension	5 (4%)	4 (3%)	0	6 (5%)	5 (4%)	0
Nasopharyngitis	7 (6%)	0	0	13 (10%)	0	0
Nausea	4 (3%)	0	0	15 (12%)	0	0
Aspartate aminotransferase increased	13 (10%)	3 (2%)	0	2 (2%)	0	0

Discontinuation for toxicity

- Ropeg 11 of 127 (8%)
- HU 3 of 127 (2.4%)

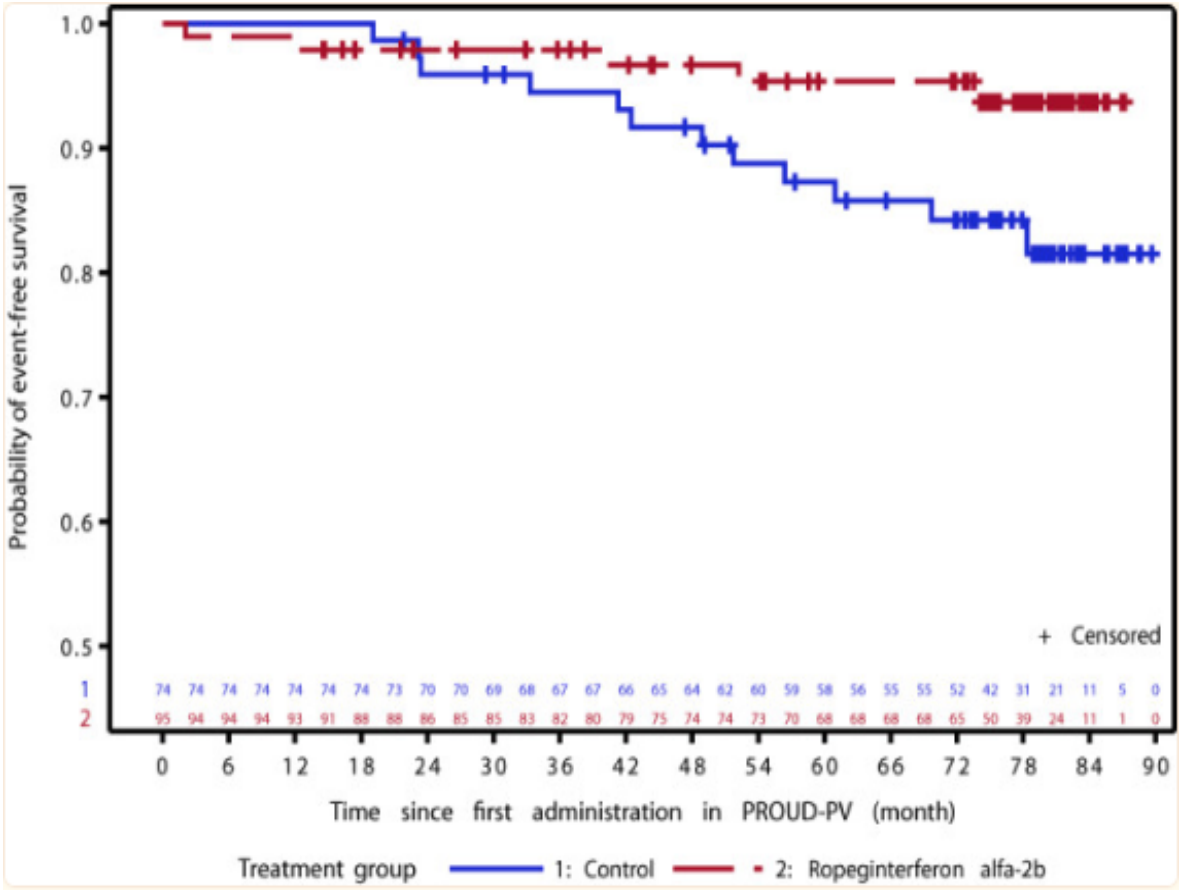
AE = adverse event.

Gisslinger H, et al. *Lancet Haematol*. 2020;7(3):e196-e208.

Long-Term PROUD/CONTI-PV Results: IFN Yields Higher, Durable Molecular Response and Event-Free Survival

Molecular response: Ropeg > HU

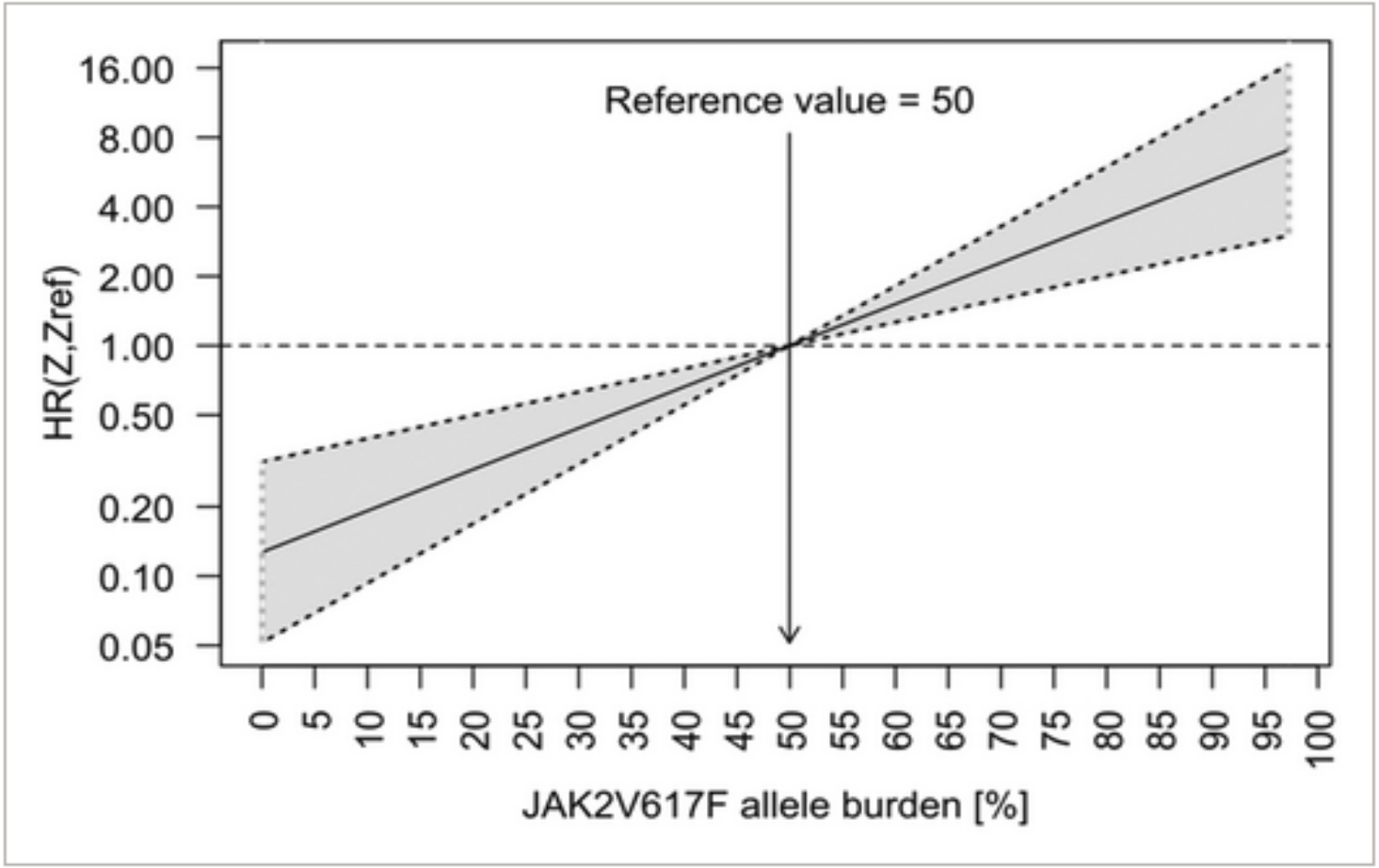
Event-free survival: Ropeg > HU



Gisslinger H, et al. *Leukemia*. 2023;37(10):2129-2132. Kiladjian JJ, et al. *Leukemia*. 2022;36(5):1408-1411.

JAK2V617F Molecular Response Correlates with Event-Free Survival

HR of events vs *JAK2* VAF over time



Gisslinger H, et al. *Leukemia*. 2023;37(10):2129-2132. Kiladjian JJ, et al. *Hemasphere*. 2025;9(5):e70137.

Real-World Evidence REVEALs Non-Adherence to Standard Practice in PV (2014-2016)

	Low-risk PV **N=503**	High-risk PV **N=1768**
Disease duration	3.2 y	4.3 y
Watchful waiting	25 (5.0%)	107 (6.1%)
PHL	273 (54%)	478 (27%)
HU	91 (18%)	654 (29%)
PHL + HU	79 (16%)	549 (24%)
Other **(IFN = 1.5%)**	45 (7.0%)	150 (9.1%)

Issues

- ~27-33% of high-risk patients were treated without cytoreductive therapy
- ~30-33% not on aspirin at time of enrollment
- ~50% of patients at enrollment had HCT >45%
- ~1.5% only received IFN (a preferred 1st line for younger patients)

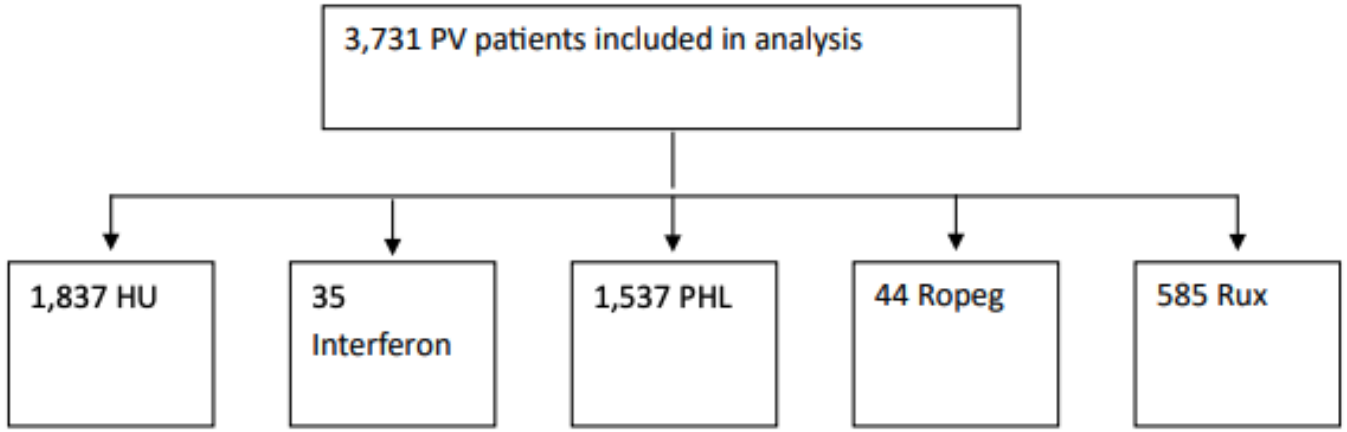
Adapted from: Gerds AT, et al. *Blood*. 2024;143(16):1646-1655.

Real-World Evidence Still Reveals Nonadherence to Standard Practice in PV (2016-2024)

TO THE EDITOR:

Real-world analysis of polycythemia vera treatment reveals nonadherence to NCCN guidelines in a large proportion of patients

Ghaith Abu-Zeinah,[1] Anthony M. Hunter,[2] Joseph J. Shatzel,[3] Abdulraheem Yacoub,[4] Albert Qin,[5] Hung-Lun Chien,[5] and Ruben A. Mesa[6]



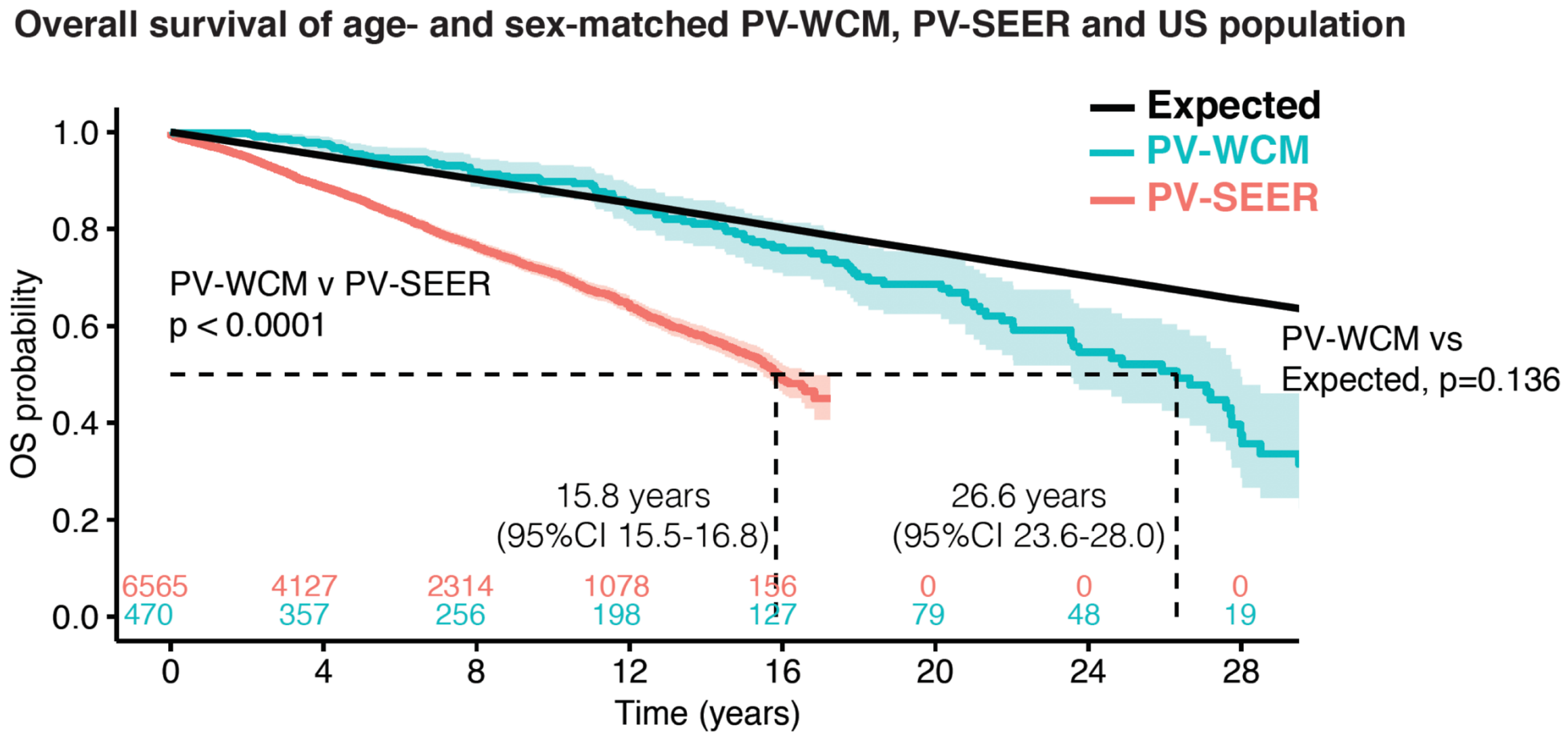
Issues

- Again, ~27% of high-risk patients were treated with phlebotomy only
- <2% received IFN, despite 1st-line designation by guidelines and FDA approval of ropeg for PV
- Ruxolitinib used as 1st line (~32% of rux use), more commonly than IFN

FDA = US Food and Drug Administration.

Abu-Zeinah G, et al. *Blood Neoplasia*. 2025;2(4):100167.

Optimizing Standard of Care May Improve Survival in PV

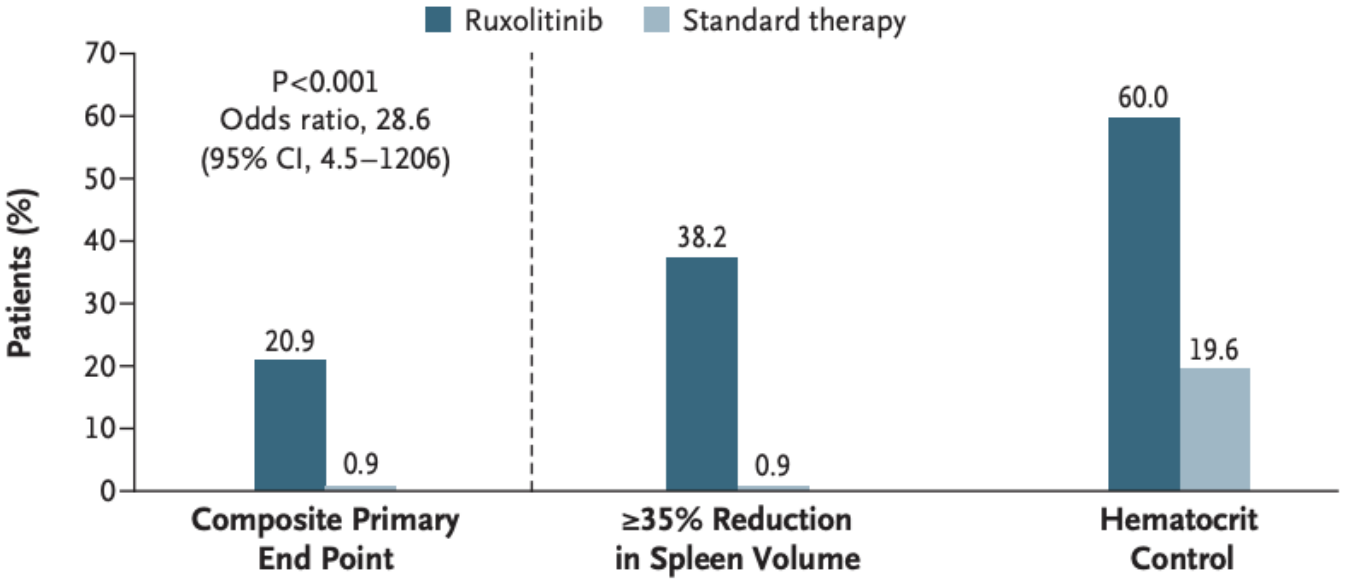


WCM = Weill Cornell Medicine; SEER = National Cancer Institute Surveillance, Epidemiology and End Results program.
Abu-Zeinah G, et al. *Leukemia*. 2022;36(2):569-572.

2nd-Line CytoRx in PV: Ruxolitinib, RESPONSE Trial

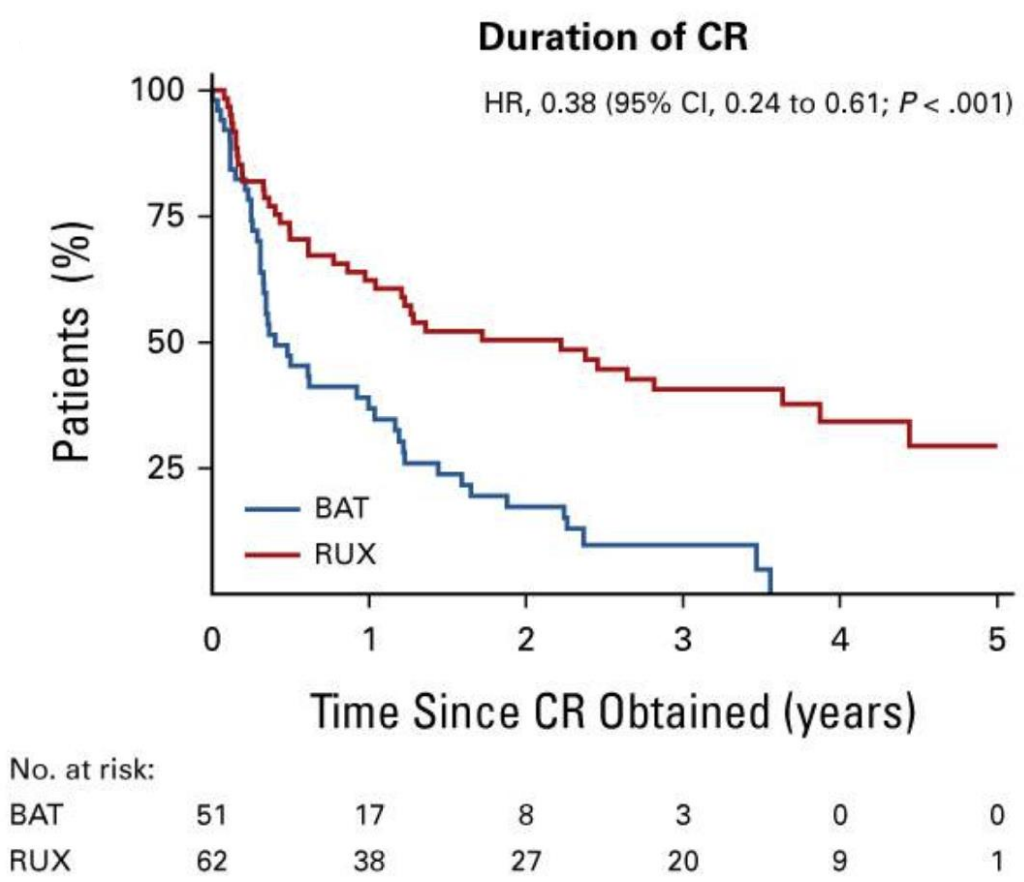
Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

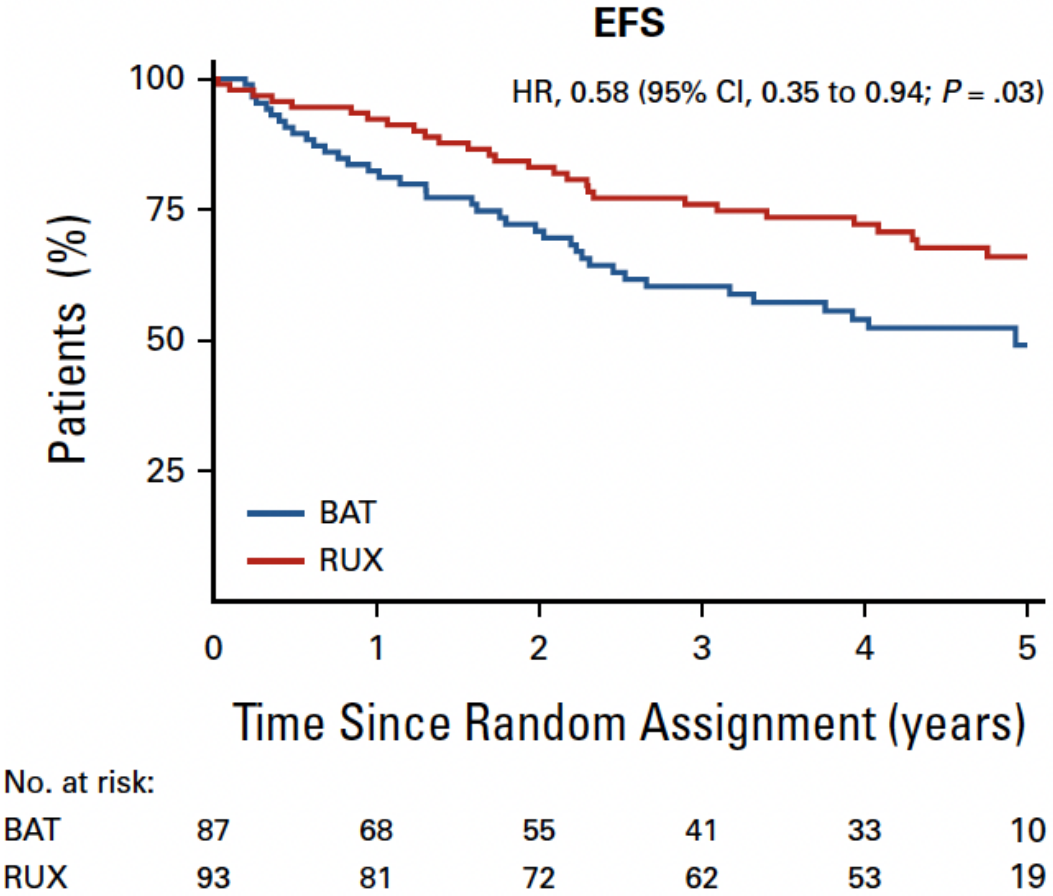
Alessandro M. Vannucchi, M.D., Jean Jacques Kiladjian, M.D., Ph.D., Martin Griesshammer, M.D., Tamas Masszi, M.D., Ph.D., Simon Durrant, M.D., Francesco Passamonti, M.D., Claire N. Harrison, D.M., Fabrizio Pane, M.D., Pierre Zachee, M.D., Ph.D., Ruben Mesa, M.D., Shui He, Ph.D., Mark M. Jones, M.D., William Garrett, M.B.A., Jingjin Li, Ph.D., Ulrich Pirron, Ph.D., Dany Habr, M.D., and Srdan Verstovsek, M.D., Ph.D.



Vannuchi AM, et al. *N Eng J Med*. 2015;372(5):426-435.

2nd-Line CytoRx in PV: Ruxolitinib, MAJIC-PV Study

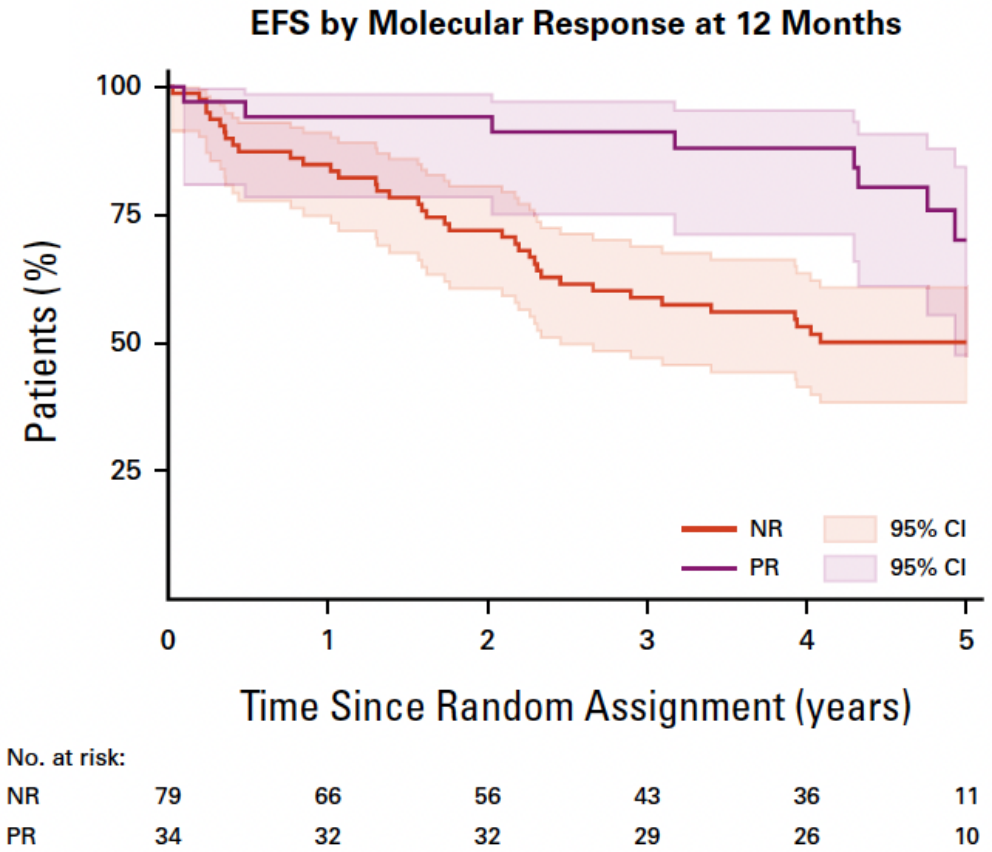




CR = complete response; EFS = event-free survival; BAT = best available therapy.

Harrison CN, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

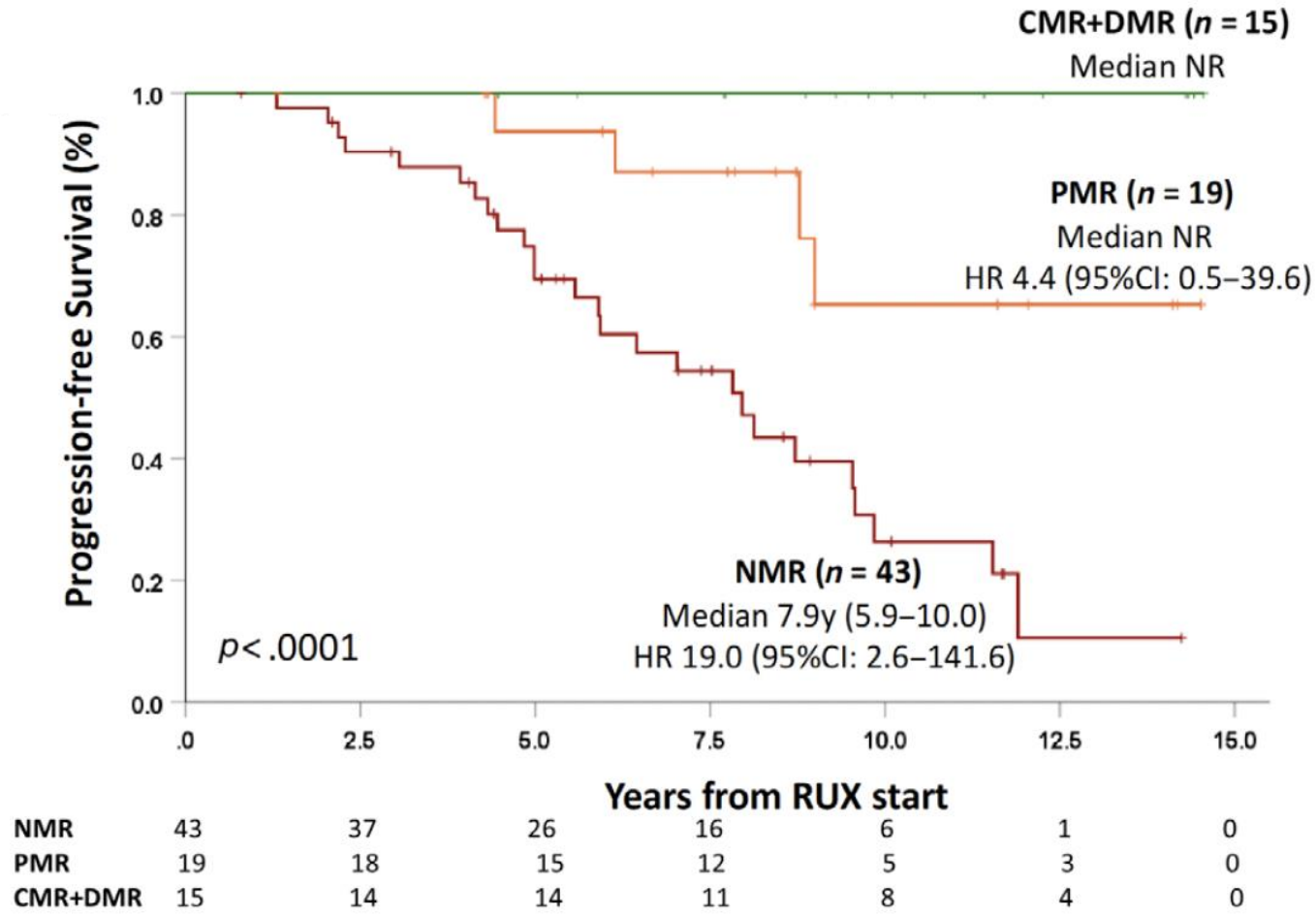
Ruxolitinib in PV Associated with Molecular Response and Event-Free Survival



Outcome	Ruxolitinib			BAT		
	NR[a] (n = 31), Events, No. (%)	PR[b] (n = 39), Events, No. (%)	*P*	NR[a] (n = 43), Events, No. (%)	PR[b] (n = 14), Events, No. (%)	*P*
Thromboembolic event[c]	10 (32)	7 (18)	.17	18 (42)	3 (21)	.17
Hemorrhagic event[c]	9 (29)	4 (10)	.04	14 (33)	1 (7)	.06
Progression-free survival[c]	13 (42)	3 (8)	.001	16 (37)	3 (21)	.28
EFS[c]	16 (52)	8 (21)	.006	24 (56)	5 (36)	.19
OS[c]	8 (26)	3 (8)	.04	10 (23)	1 (7)	.18
CR achieved at 1 year	10 (32)	22 (56)	.04	12 (28)	5 (36)	.58

[a]No molecular response defined as <50% reduction in *JAK2* variant allele fraction. [b]Partial molecular response defined as ≥50% response in *JAK2* variant allele fraction. [c]These comparisons include any event that contributes to EFS outcome.
NR = not reached; PR = partial response.
Harrison CN, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

Ruxolitinib in PV + ET Associated with Molecular Response and Myelofibrosis-Free Survival



CR = complete response; EFS = event-free survival; BAT = best available therapy; NMR = no molecular response; PMR = partial MR; CMR = complete MR; DMR = durable MR.

Harrison CN, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

Key Learning Points

- Differentiating ET/PV diagnoses and their clinical courses is important
- Thrombosis risk assessment is important, but progression risk should be considered
- Evidence-based standard of care is the least we can do to optimize outcomes; newer evidence involving EFS, MFS, and OS with IFN and rux should be considered for early treatment; monitoring molecular response may serve as a surrogate for EFS

Thanks for Your Attention!