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From Diagnosis to Disease Control: Integrating Next-Generation Therapies into ET and PV Management

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Disclosures

- **Ghaith Abu-Zeinah, MD:** Speaker – PharmaEssentia; Advisory Board/ Consultancy – PharmaEssentia, Silence Therapeutics, Takeda

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Learning Objectives

- Integrate the latest clinical trial data, real-world evidence, and practice guidelines to effectively differentiate, diagnose, and manage ET and PV
- Assess the MOAs and the safety and efficacy profiles of newer and emerging targeted therapies for managing ET and PV to prevent disease progression
- Implement multidisciplinary, patient-centered strategies that leverage PROs to manage TRAEs, assess symptoms, and reduce cardiovascular risk

ET = essential thrombocythemia; PV = polycythemia vera; MOAs = mechanisms of action; PROs = patient-reported outcomes; TRAEs = treatment-related adverse events.

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Differentiating ET/PV Diagnoses and Their Clinical Courses

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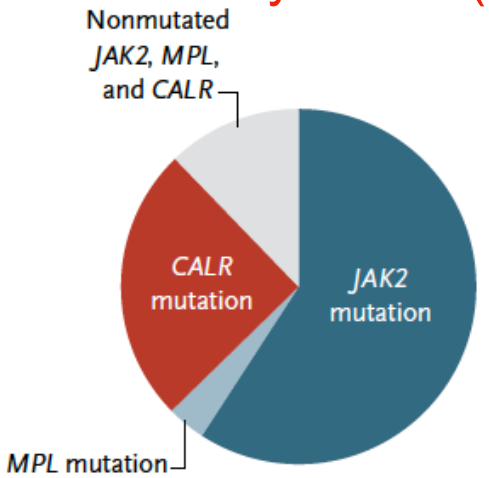
What Are ET and PV Anyway?

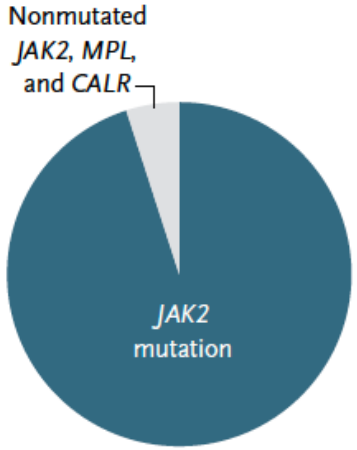
- Classical, Philadelphia chromosome-negative myeloproliferative neoplasms…OR chronic blood cancers

- Initiated by driver mutations in hematopoietic stem cells

Essential Thrombocythemia (ET)

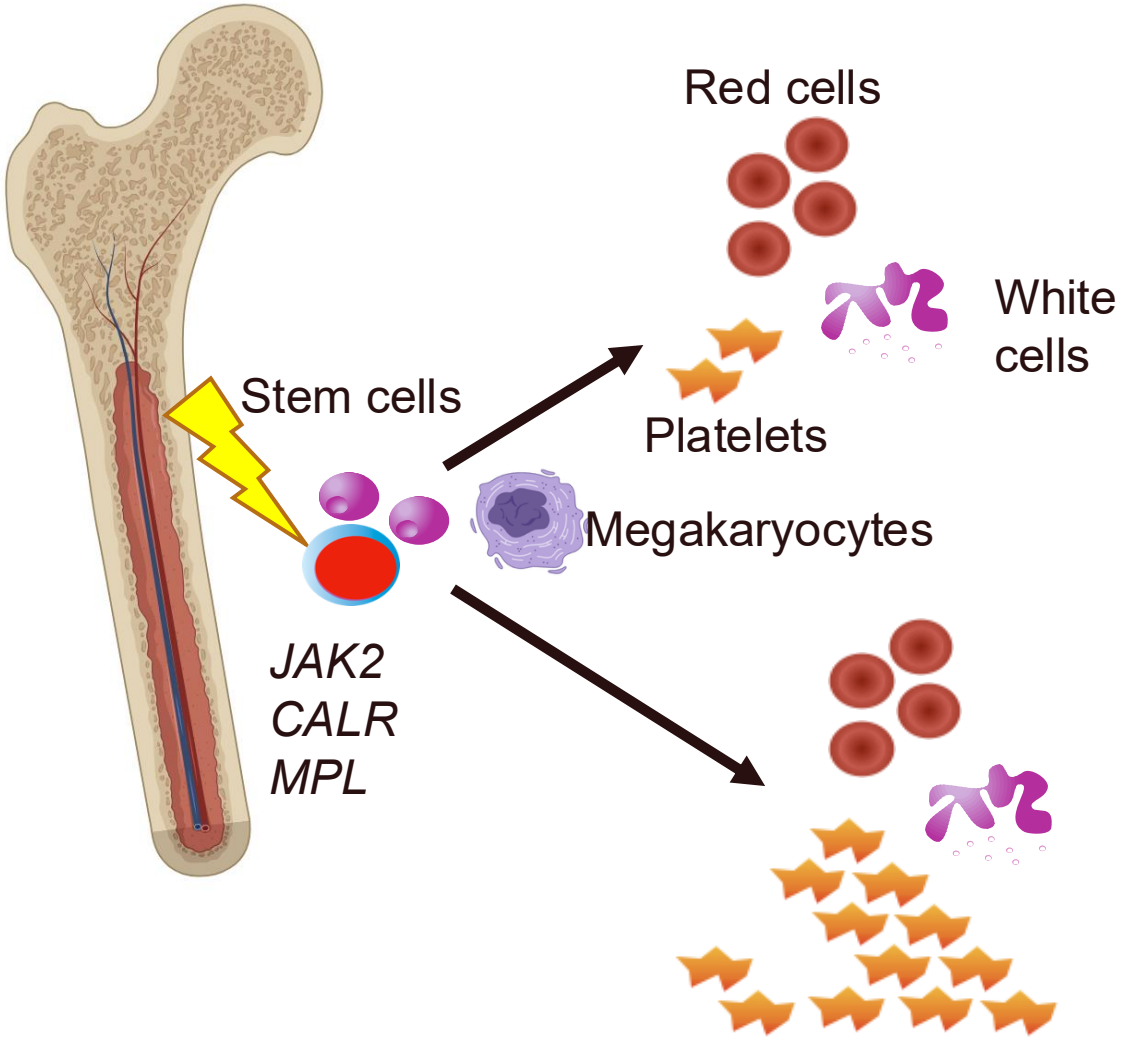


Polycythemia Vera (PV)

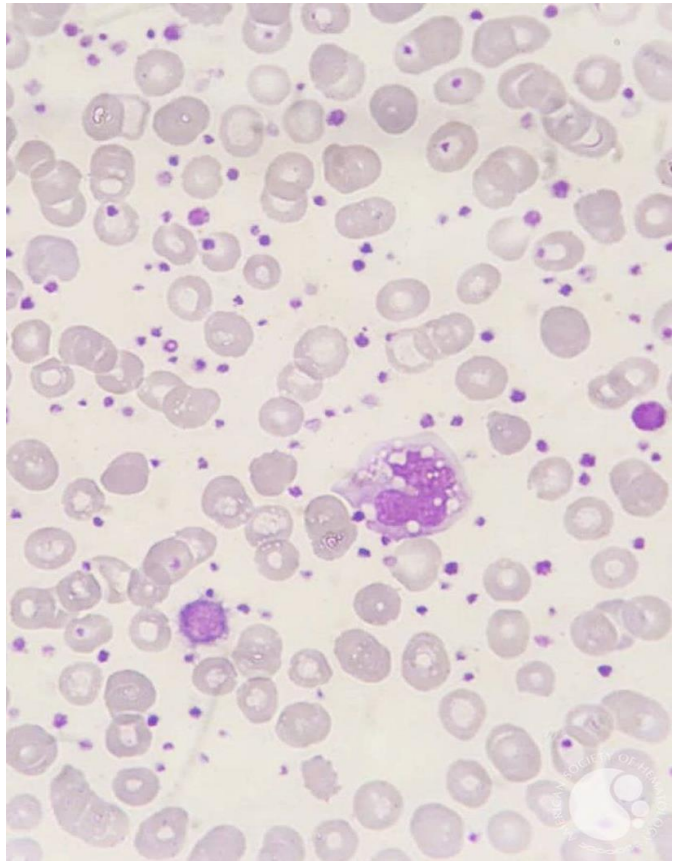


Klampfl T, et al. *N Engl J Med*. 2013;369(25):2379-2390.

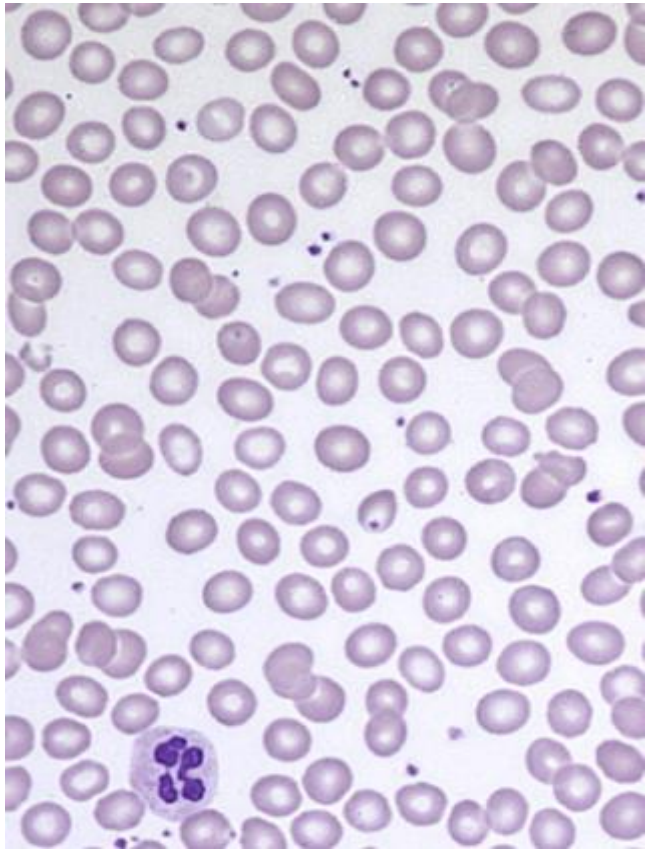
ET Is Characterized by Clonal Thrombocytosis



ET
2,500 x10^3/uL platelets

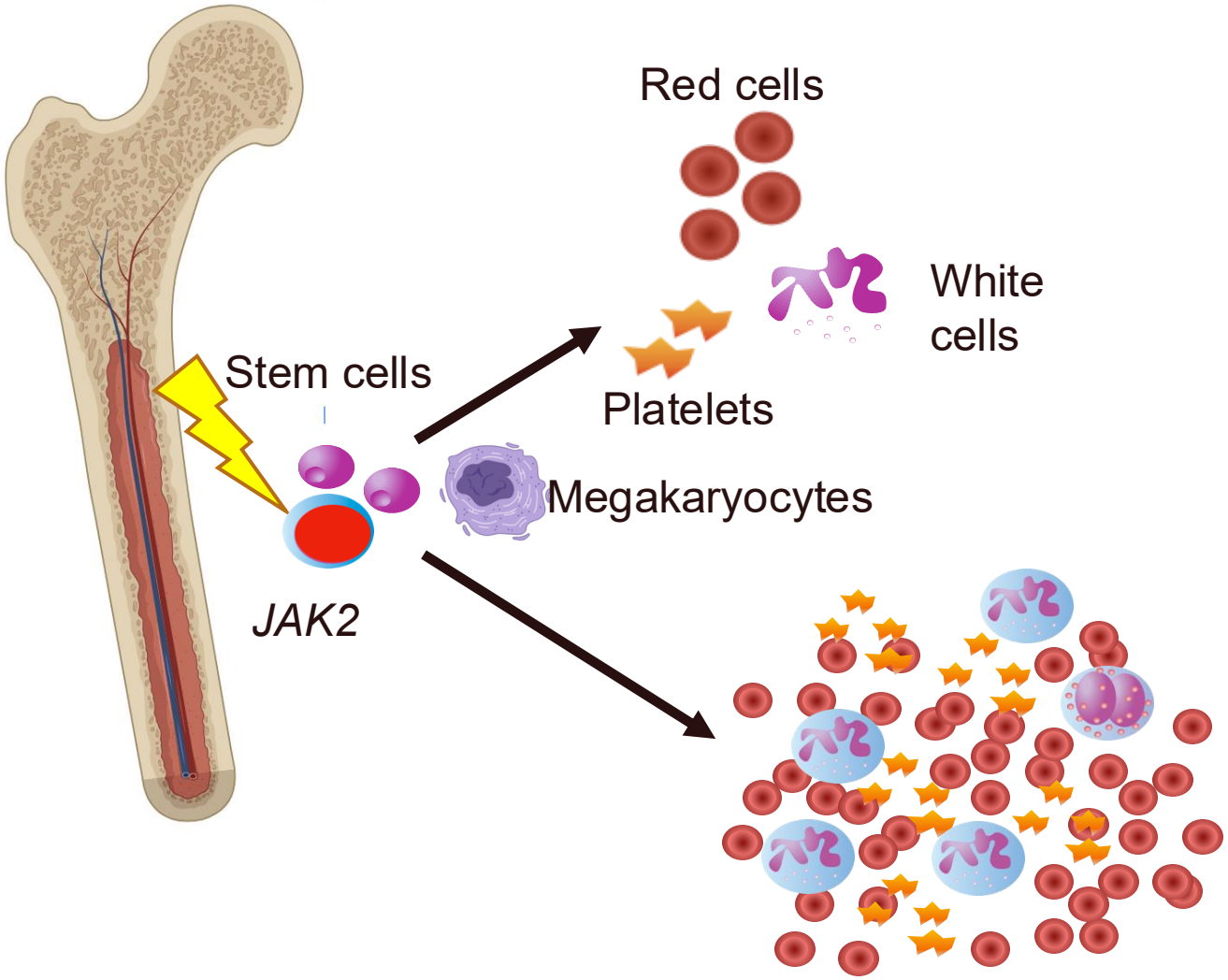


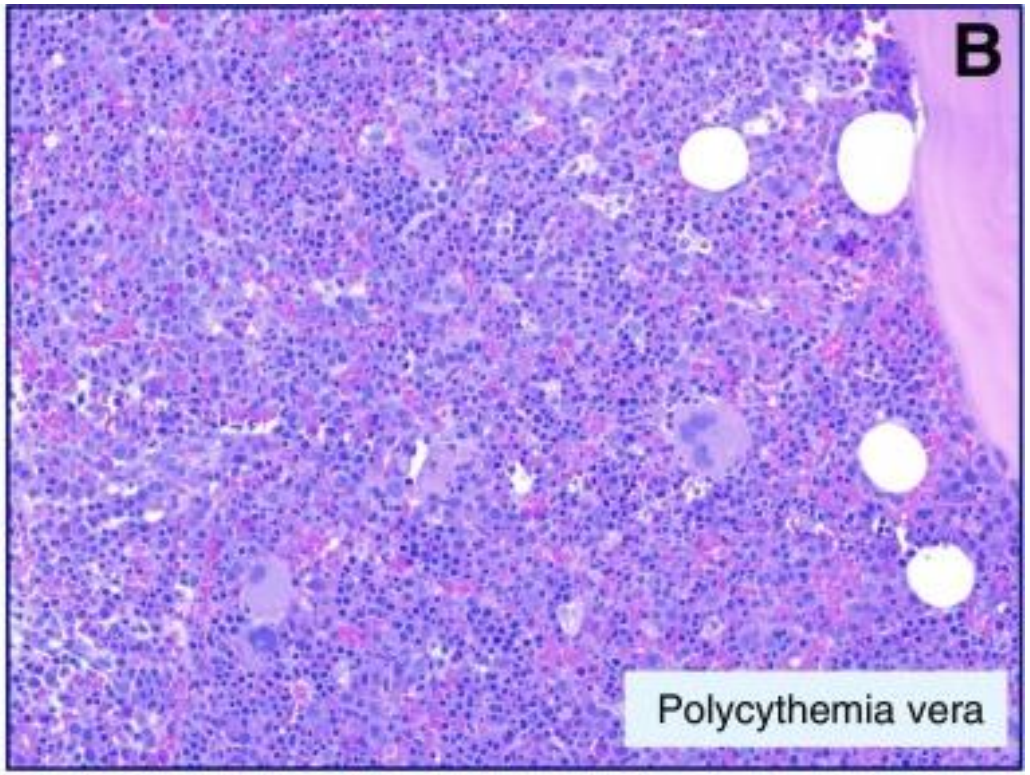
Normal
150-450 x10^3/uL



Leite LA, Costa JVM. American Society of Hematology (ASH) image bank; 2021. Maslak P. ASH image bank; 2008.

PV Is Characterized by *JAK2mut* Clonal Erythrocytosis + Panmyelosis





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

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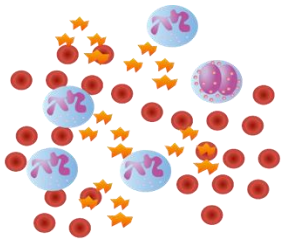
Diagnostic Criteria for ET and PV

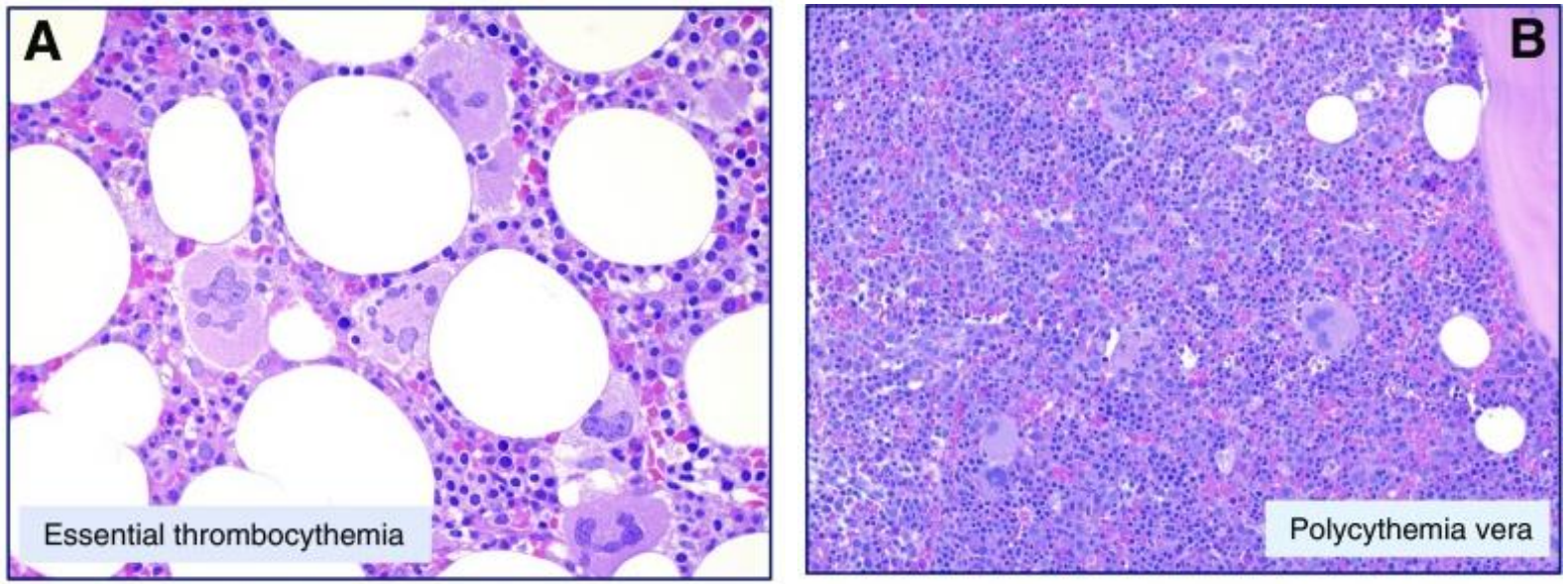
ET	PV
Major criteria 1. **Plt** ≥ 450 x 10^9/L 2. **BMbx** ; proliferation mainly of Megakaryocytic (MgK) lineage with increased number of large, mature MgK with hyperlobated nuclei 3. Not meeting WHO criteria for other myeloid neoplasms 4. **JAK2, CALR, or MPL** mutations	**Major criteria** 1. **Hgb** >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**



EPO = erythropoietin.

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.

Scenarios of Diagnostic Ambiguity: ET, PV, Pre-PMF, or CHIP?

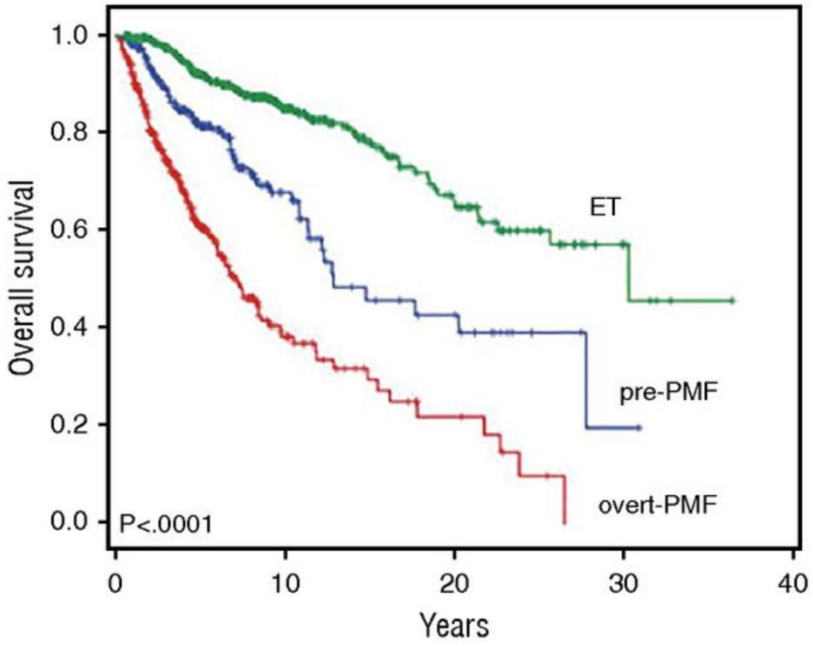
ET (*JAK2*) vs PV

- ET with secondary erythrocytosis (sleep apnea, smoking, lung disease, high altitude, testosterone use)
- PV with red cell parameters below WHO/ICC diagnosis cutoff (early or masked PV)

ET vs CHIP

- CHIP is having a mutation without blood abnormalities or MPN; CHIP can be detected during “reactive thrombocytosis”

ET vs prefibrotic MF



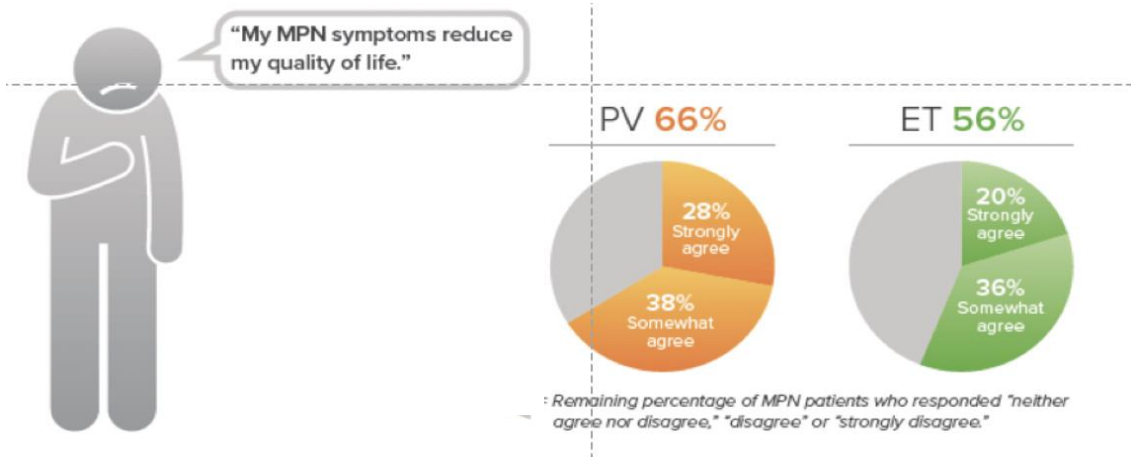
- Symptoms, spleen size, CBC, LDH, and, most importantly, marrow biopsy help

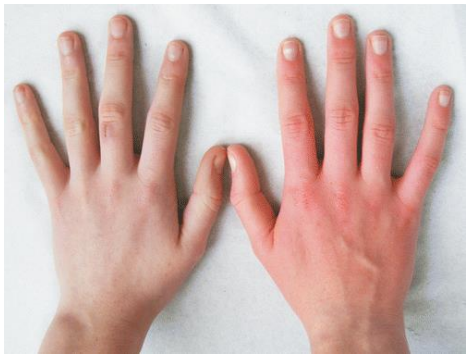
CHIP = clonal hematopoiesis of indeterminate potential; WHO = World Health Organization; ICC = International Consensus Classification; MPN = myeloproliferative neoplasm; CBC = complete blood count; LDH = lactate dehydrogenase.

Guglielmelli P, et al. *Blood*. 2017;129(24):3227-3236.

Clinical Presentation – Symptoms

- High symptom burden in many

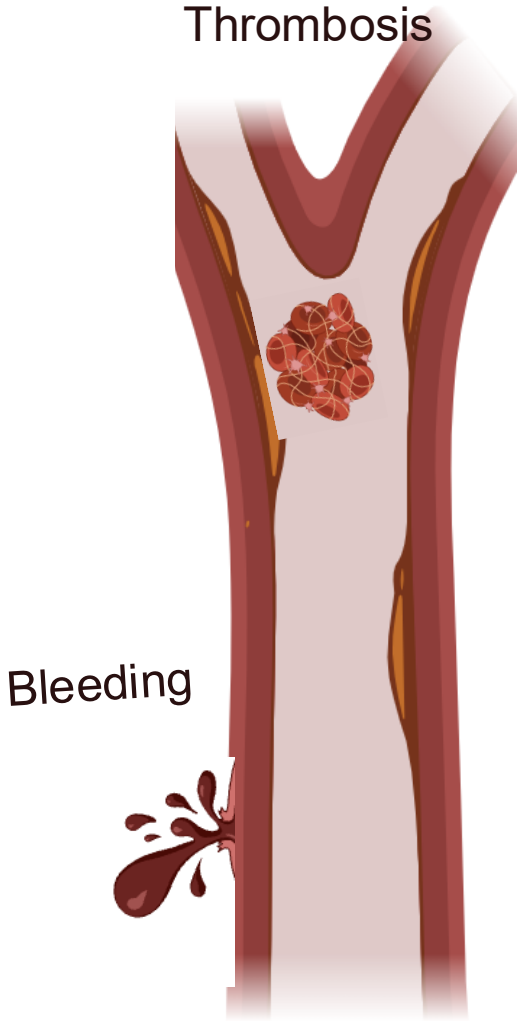


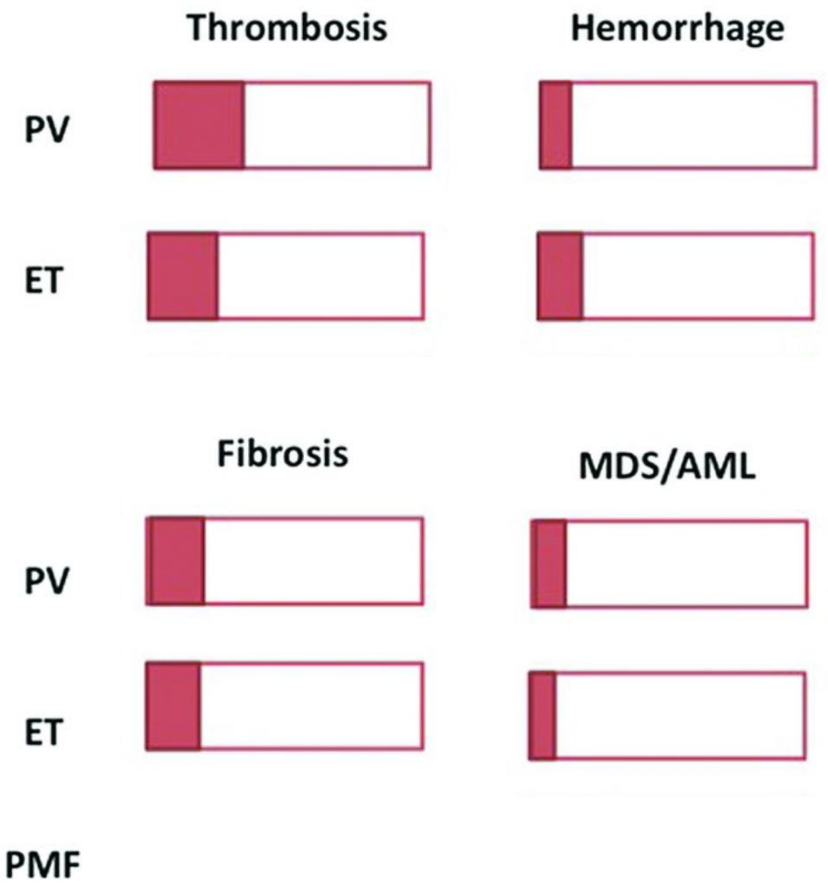


QoL = quality of life.

Modified from: Maureen Thyne. 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



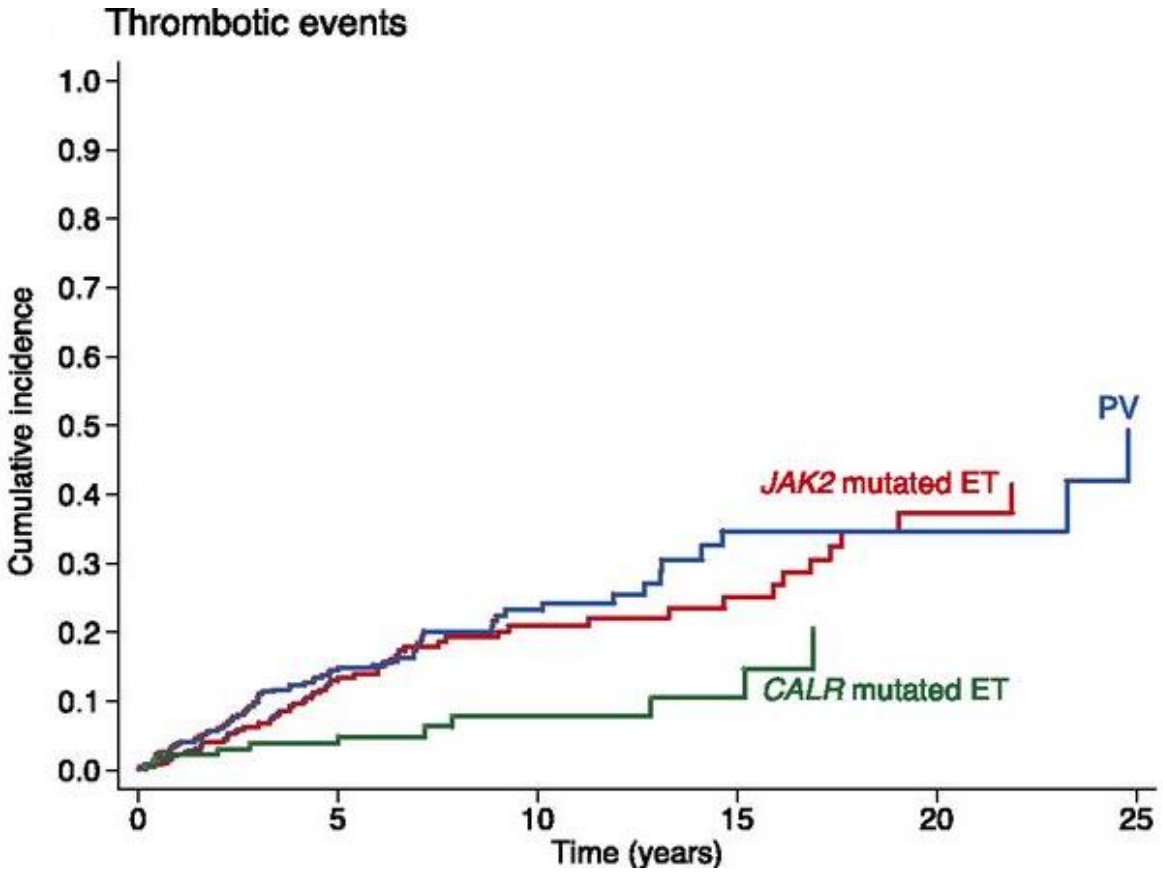


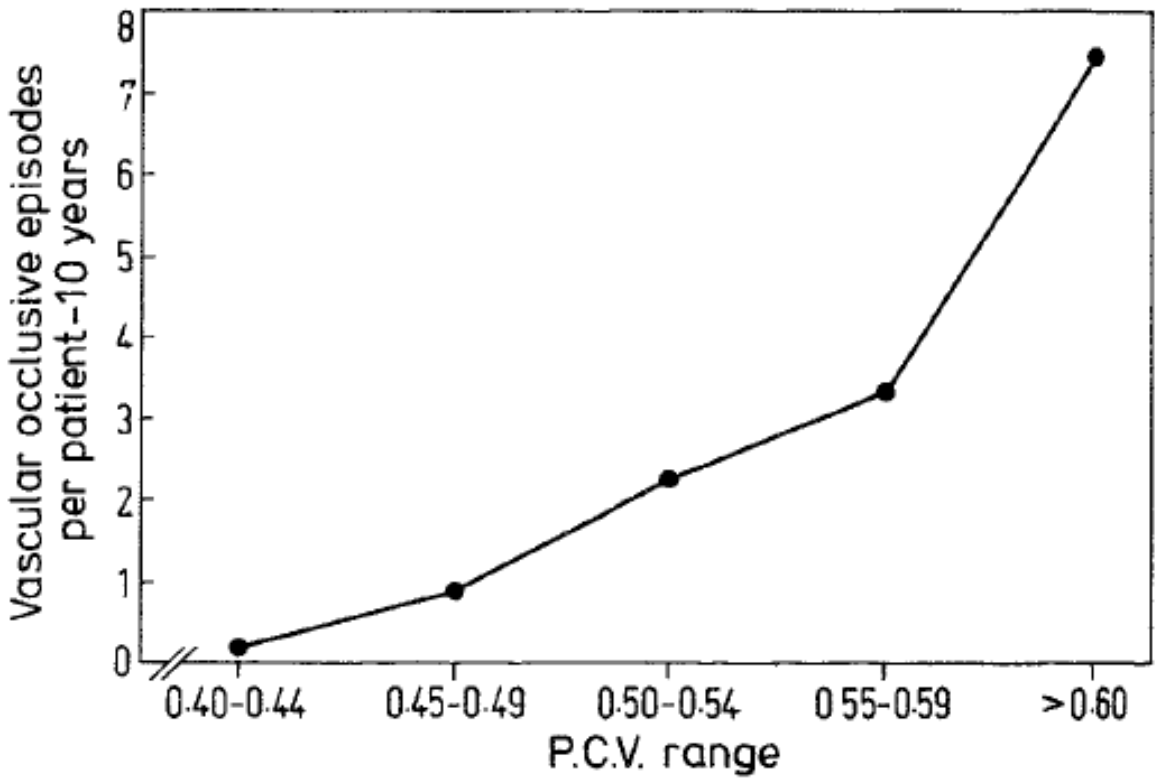
- 15-20% present with thrombosis, including venous: DVT/PE, SVT/PVT, Budd-Chiari, and arterial: MI, CVA
- Progression to MF increasingly more common with longer duration of ET/PV

MDS = myelodysplastic syndrome; AML = acute myeloid leukemia; DVT = deep vein thrombosis; PE = pulmonary embolism; SVT = splanchnic vein thrombosis; PVT = portal vein thrombosis; MI = myocardial infarction; CVA = cerebrovascular accident.

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

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





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

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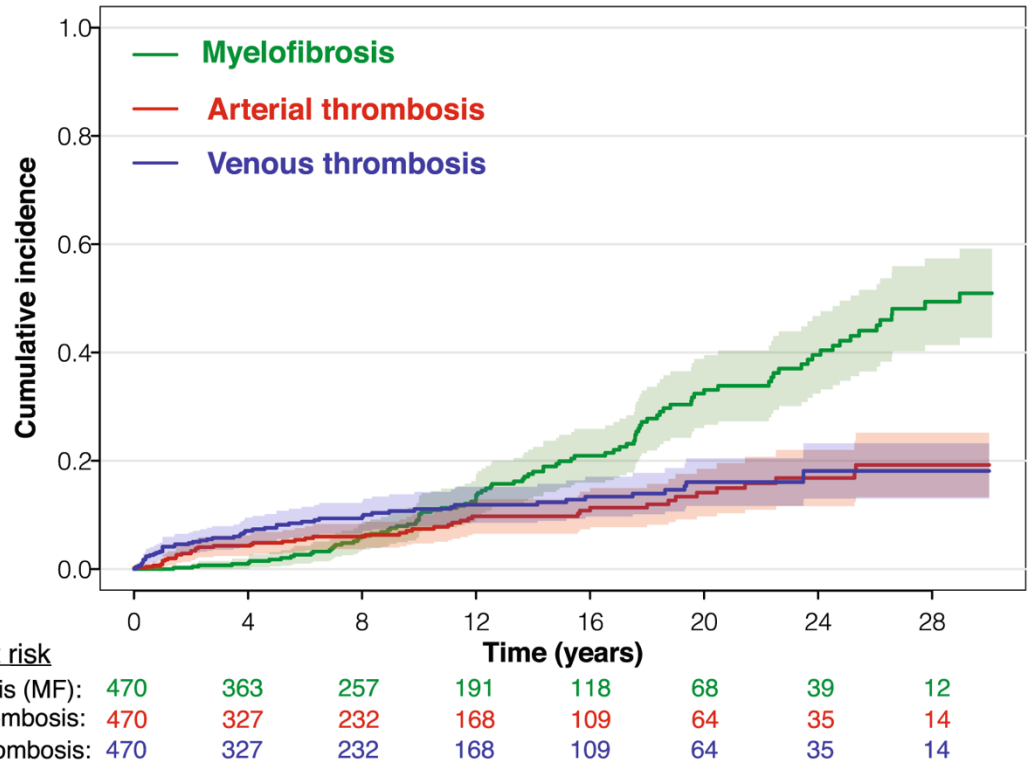
But Progression to Myelofibrosis Is Increasingly More Problematic in PV

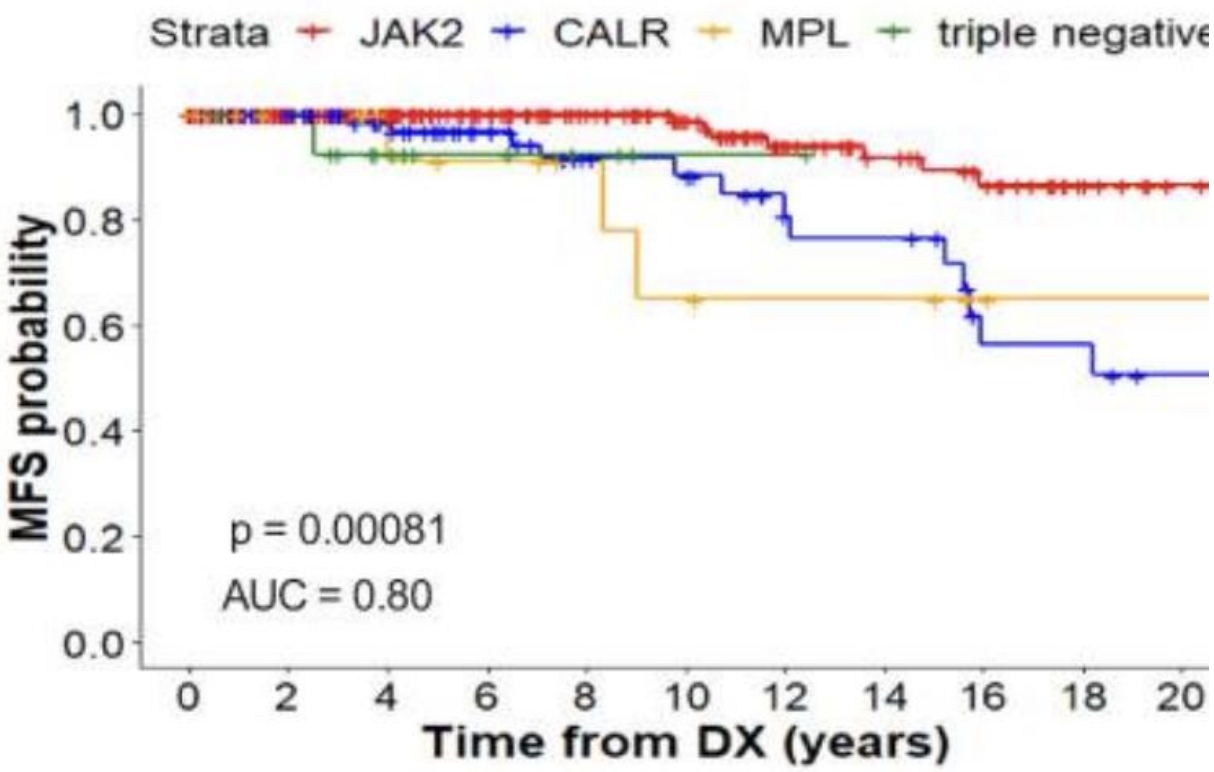
~~50% of PVs progress to MF~~…a bigger threat long-term than thrombosis



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

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

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

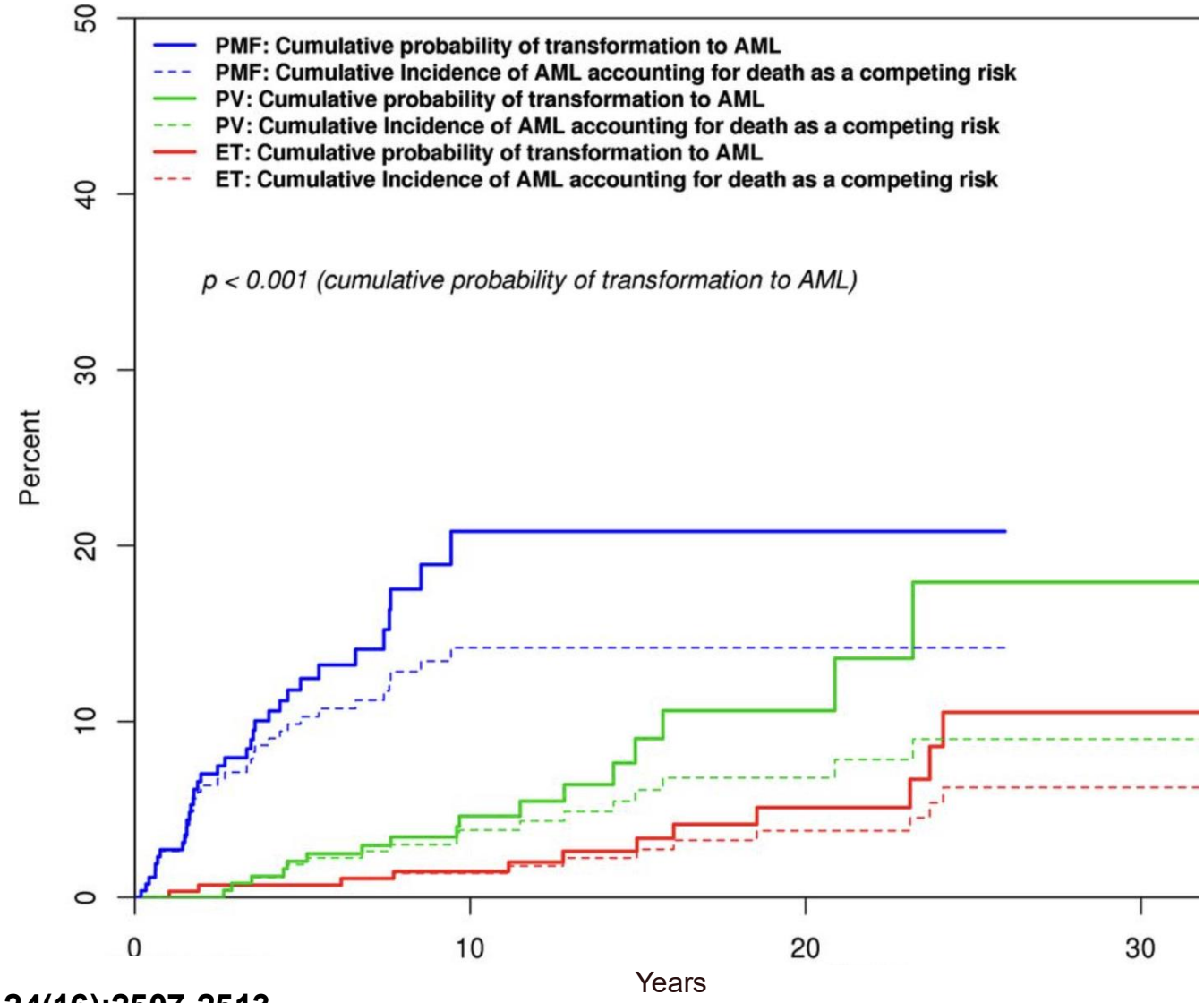


2 large studies of 1000 patients with ET show similar results

- Mayo Clinic
- Italy

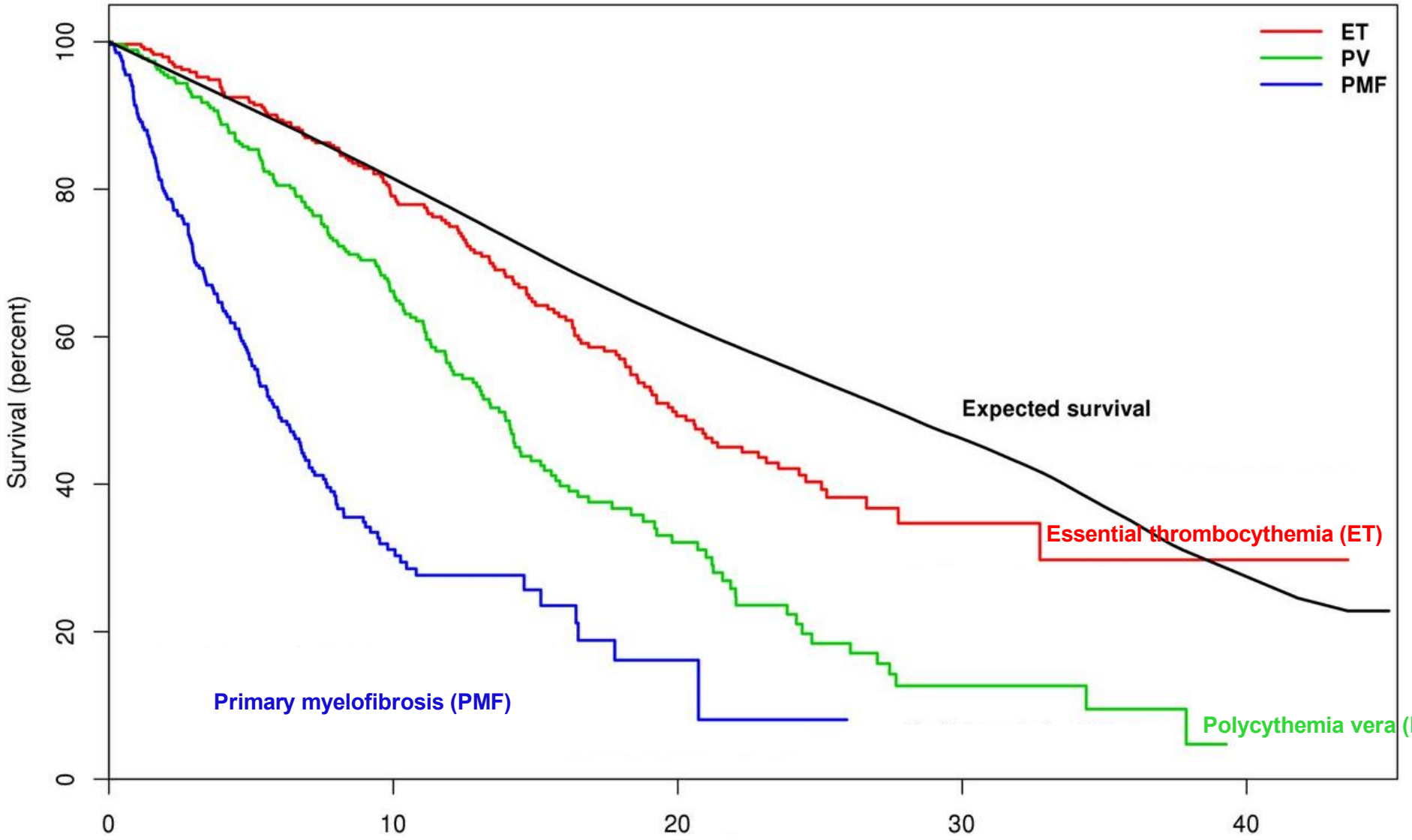
Abu-Zeinah G, et al. *Blood Cancer J*. 2024;14(1):103. Gangat N, et al. *Blood Cancer J*. 2024;14(1):11. Loscocco GG, et al. *Blood Cancer J*. 2024;14(1):10.

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)

55

64

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

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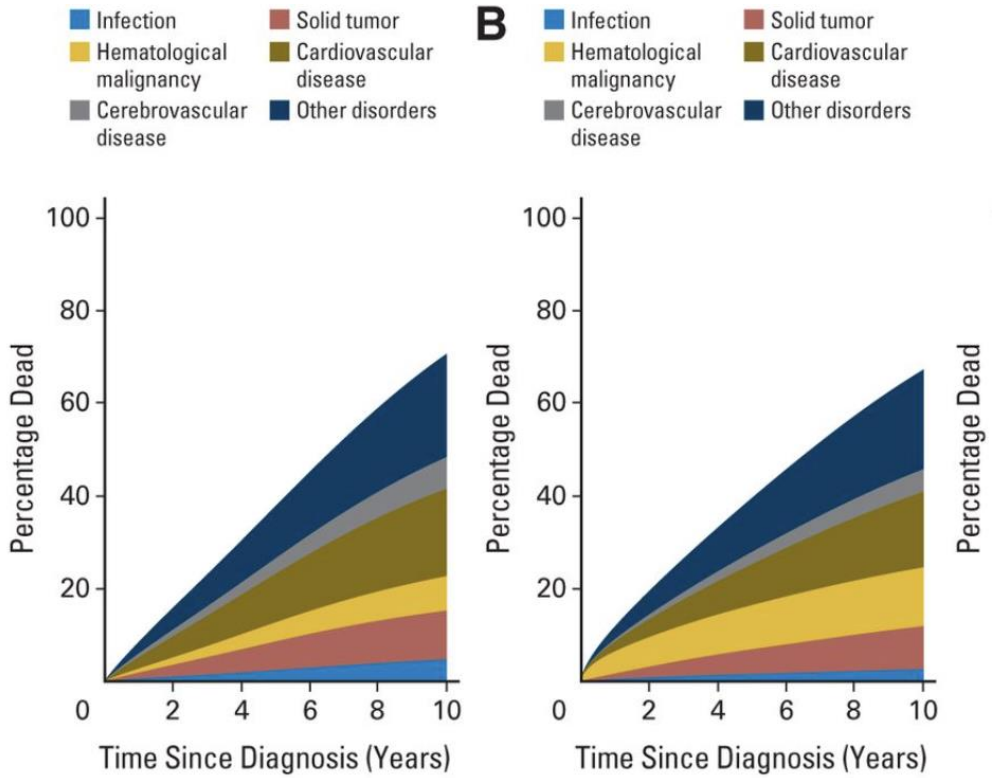
Excess Mortality Historically Linked to CV Events…

BUT…progression to MF, MDS, AML, and development of second cancers are also leading causes of death



	PV	ET
Infection	4.6 (3.5 to 5.8)	2.5 (1.6 to 3.5)
Solid tumor	10.5 (8.6 to 12.5)	9.3 (6.8 to 11.8)
Hematological malignancy	7.4 (5.4 to 9.5)	12.7 (9.5 to 15.8)
Cardiovascular disease	18.9 (16.5 to 21.3)	16.3 (13.1 to 19.5)
Cerebrovascular disease	6.9 (5.4 to 8.4)	4.9 (3.1 to 6.7)
Other disorders	22.3 (19.7 to 25.0)	21.5 (18.1 to 25.0)
Total	70.7	67.2

Hultcrantz M, et al. *J Clin Oncol*. 2015;33(20):2288-2295.

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Understanding Risk Assessment and Treatment Goals in ET/PV, and Current Limitations

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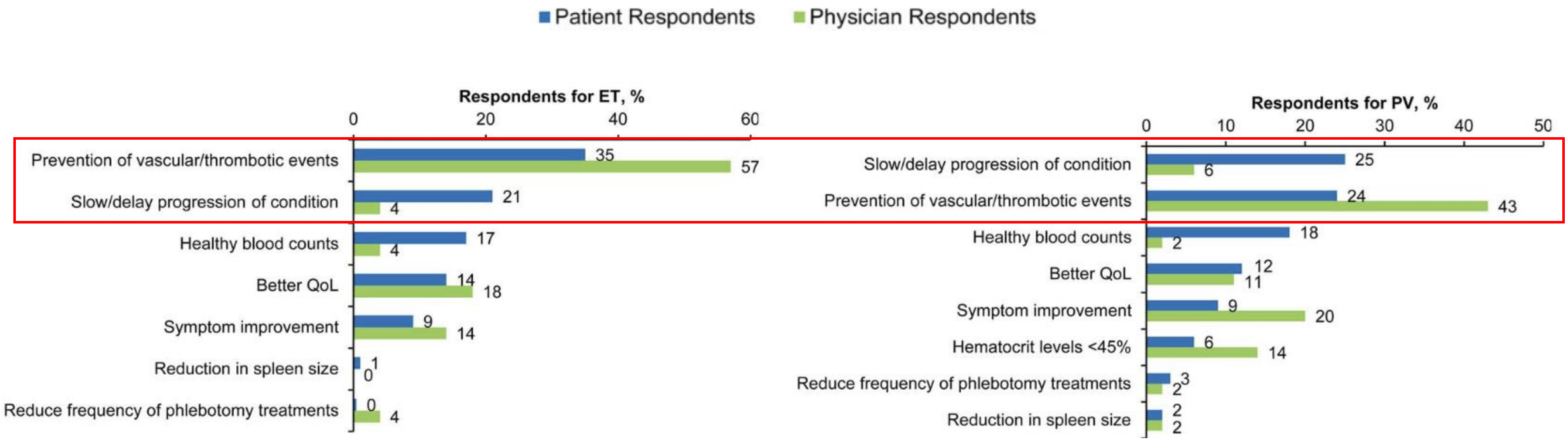
Discordance in ET and PV Treatment Goals between Physicians and Patients



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

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

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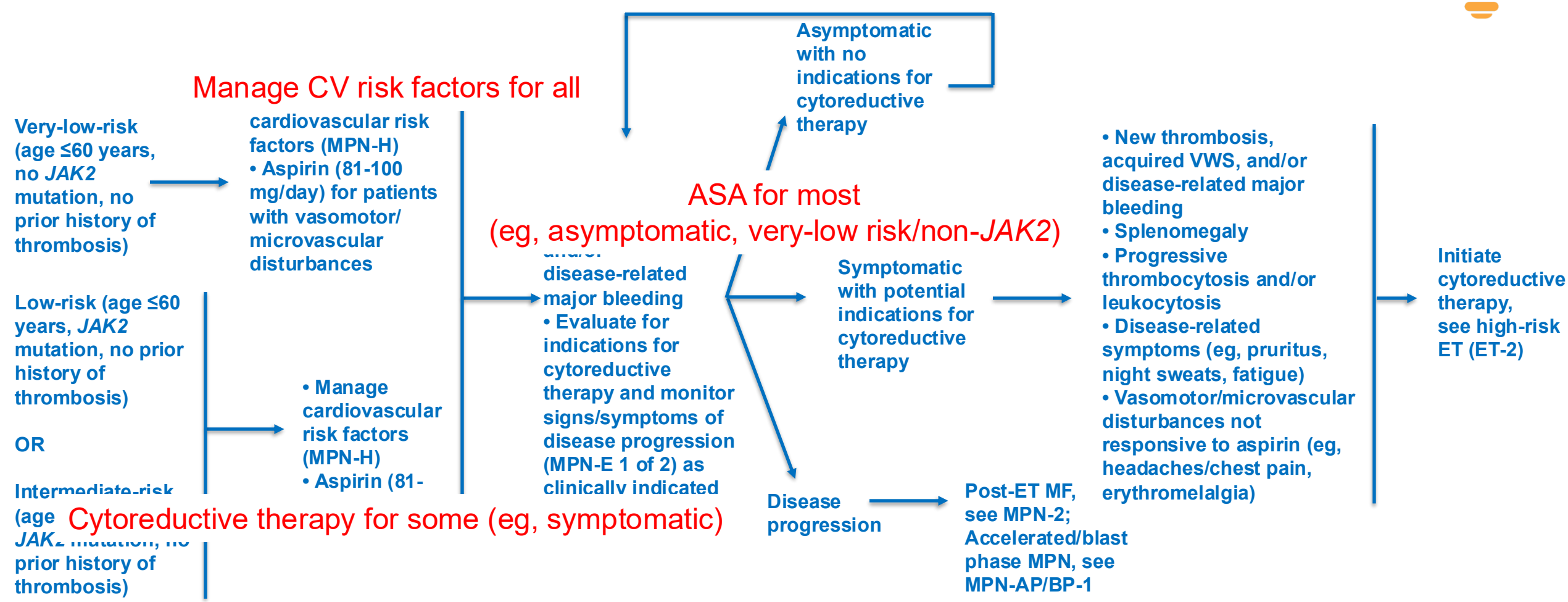
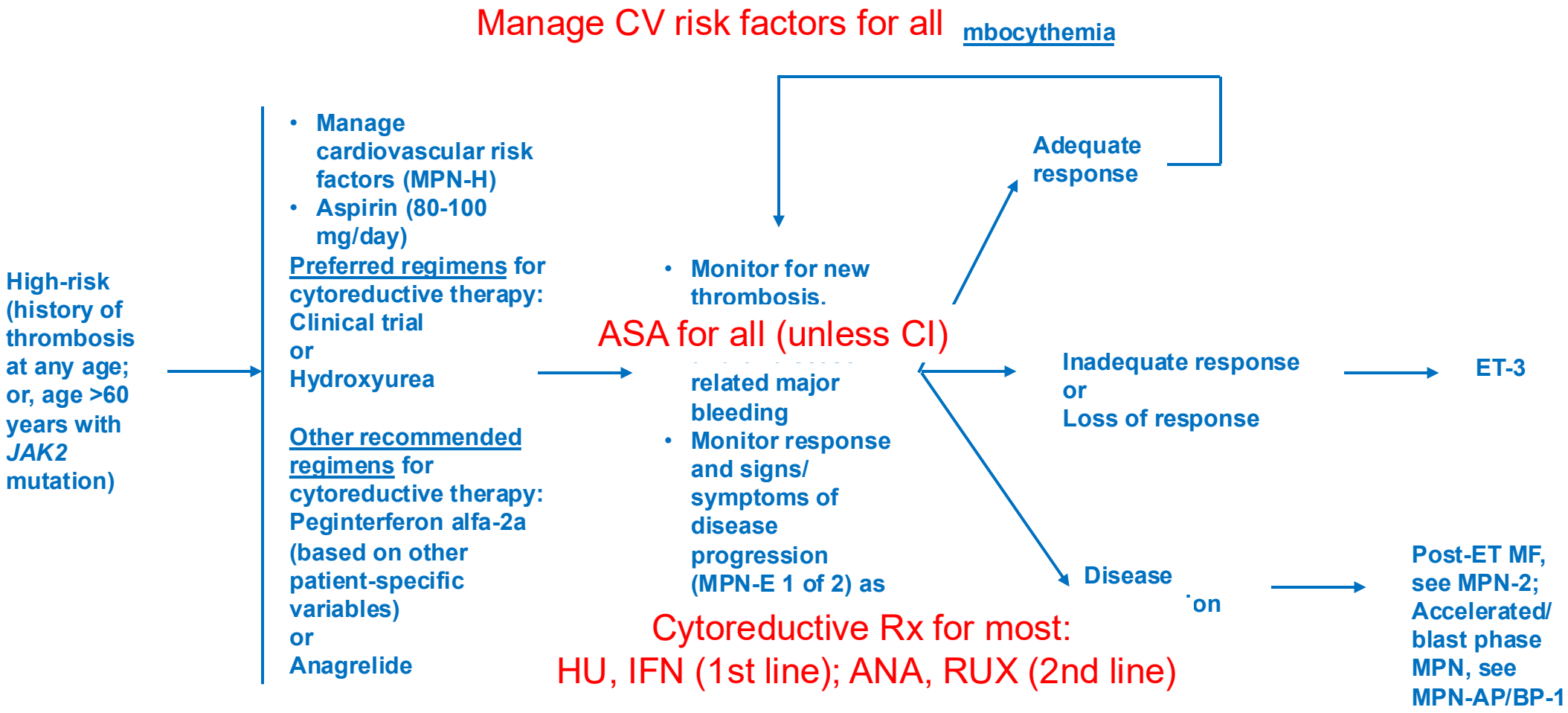
Treatment for Very-Low-Risk or Low-Risk or Intermediate-Risk Essential Thrombocythemia



VWS = von Willebrand Syndrome.

Thrombosis Risk-Adapted Treatment of ET: High Risk

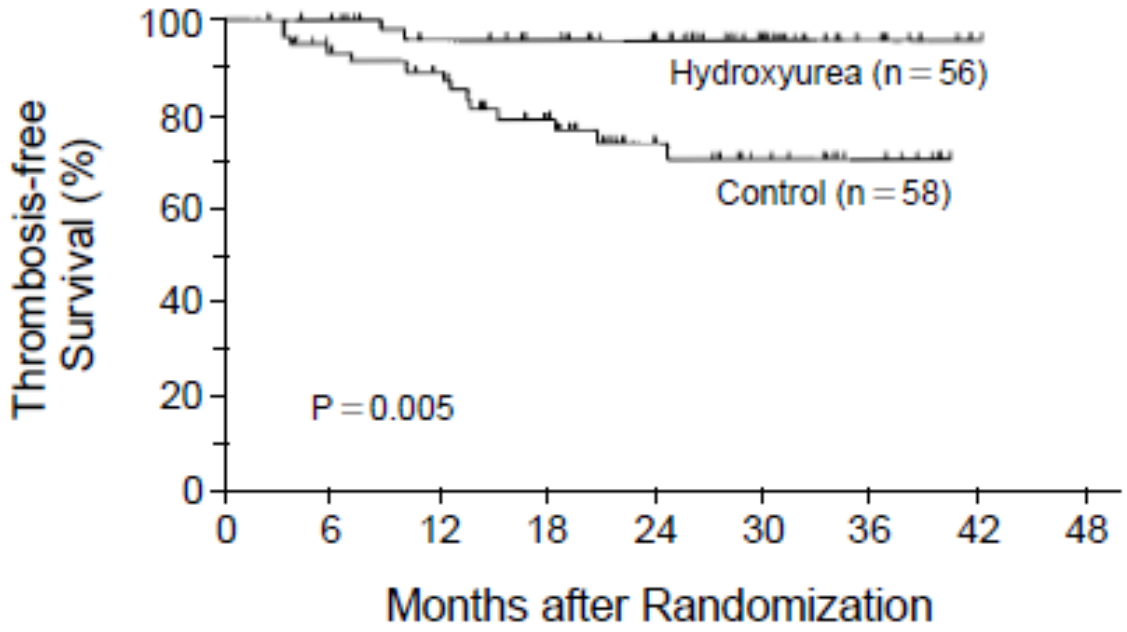


ASA = acetylsalicylic acid; CI = contraindicated; HU = hydroxyurea; IFN = interferon; ANA = anagrelide; RUX = ruxolitinib.

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.

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Thrombosis-Directed Treatment Approach Ignores Progression Risk

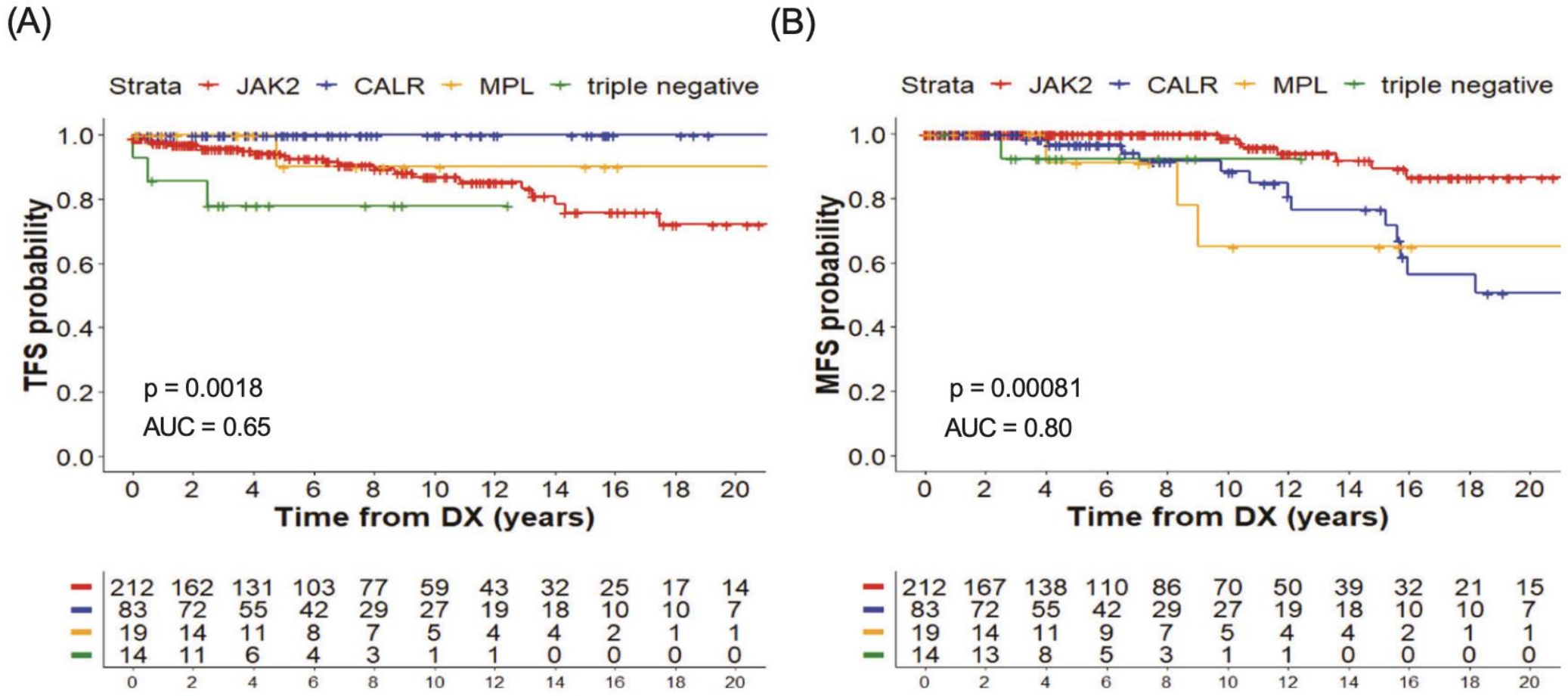

Fig. 1 Thrombosis-free (TFS) and myelofibrosis-free survival (MFS) by driver mutation. A TFS of ET patients stratified by driver n
B MFS of ET patients stratified by driver mutation.

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

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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

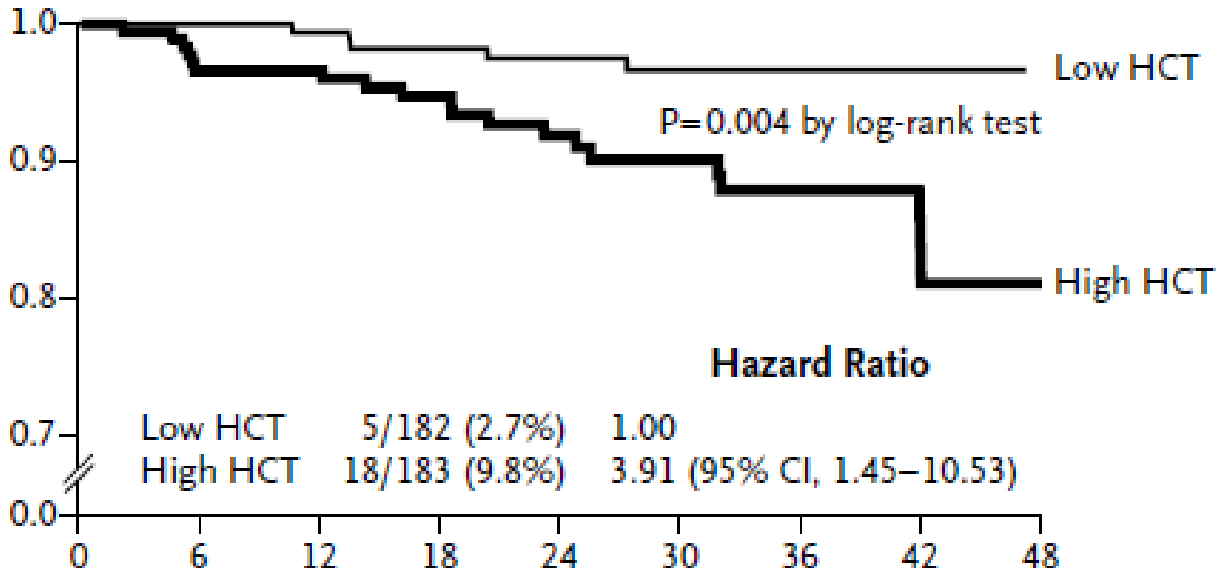
- **Cytoreduction for high-risk patients** OR low-risk patients with symptoms, high phlebotomy requirements

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



HCT = hematocrit.

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

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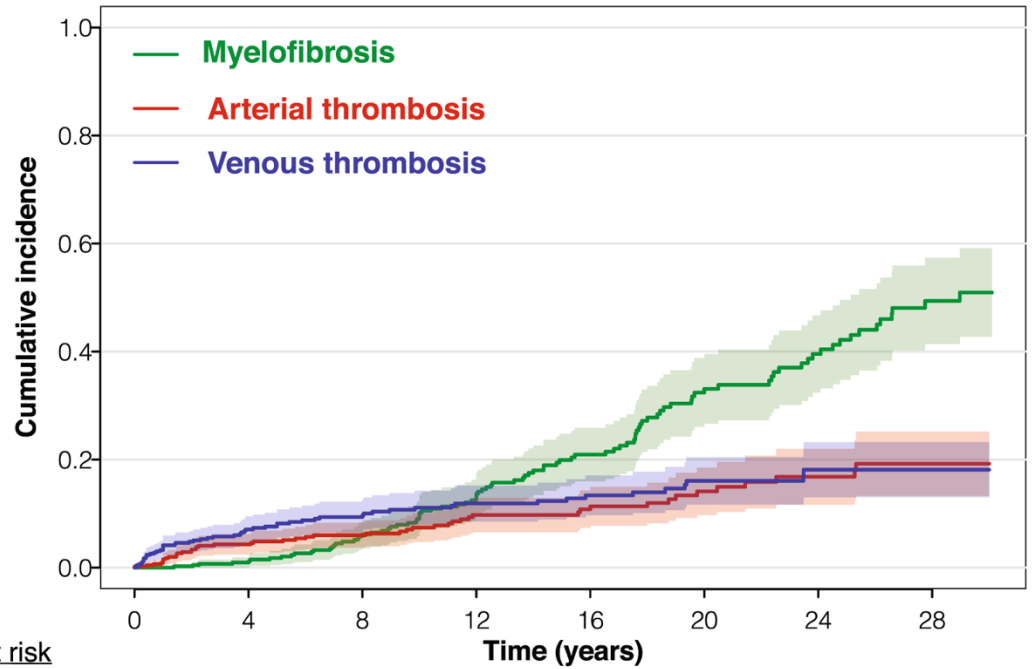
But Thrombosis Risk-Based Approach Ignores Progression Threat

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

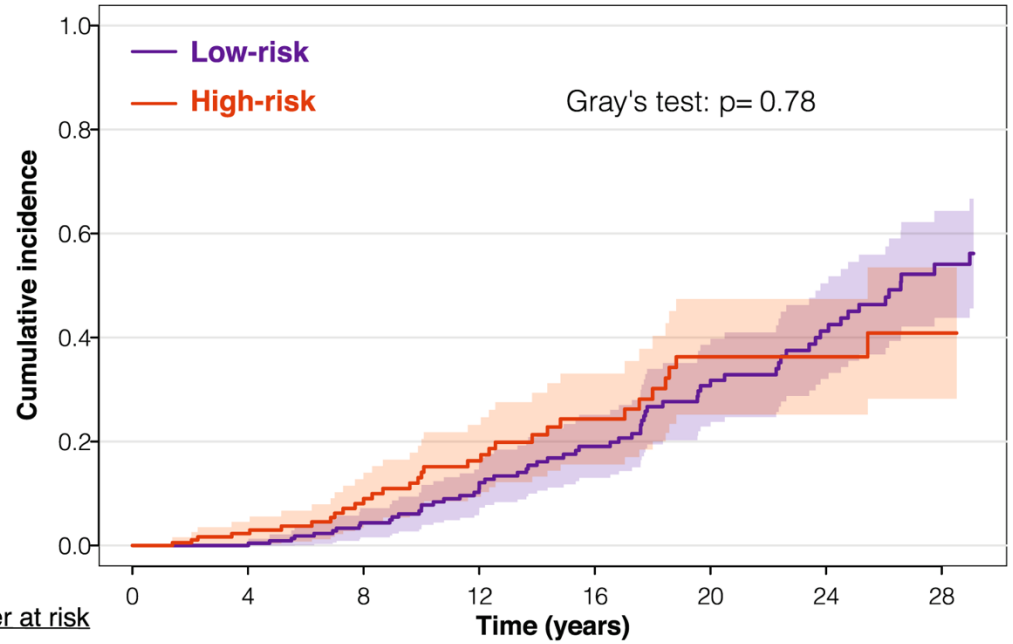


Number at risk

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.

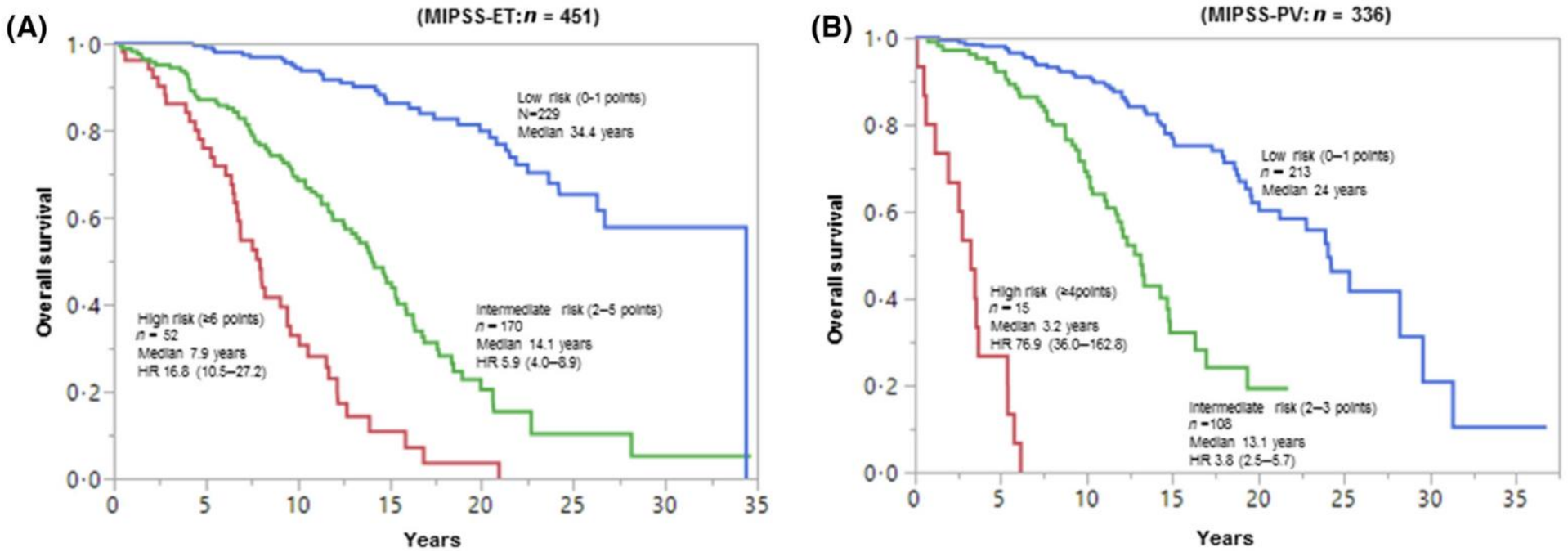
Molecularly Inspired Prognostic Scoring Systems for OS

MIPSS-ET

1) Adverse mutation (*SRSF2*, *SF3B1*, *U2AF1*, *TP53*)
2) Age >60
3) Male
4) WBC >= 11

MIPSS-PV

1) Adverse mutation (*SRSF2*)
2) Age >67
3) WBC >= 15



OS = overall survival; WBC = white blood cell.

Tefferi A, et al. *Br J Haematol*. 2020;189(2):291-302.

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Optimizing “Standard-of-Care” Evidence-Based Approaches in Management

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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)

PHL = phlebotomy.

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

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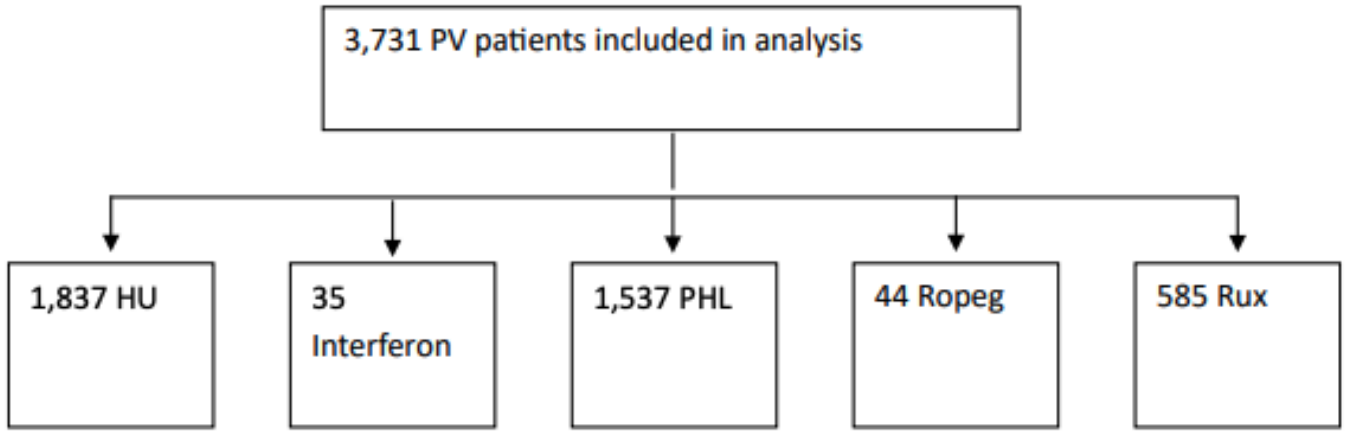
Real-World Evidence Still Reveals Non-Adherence to Standard Practice in PV (2016-2024)

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]

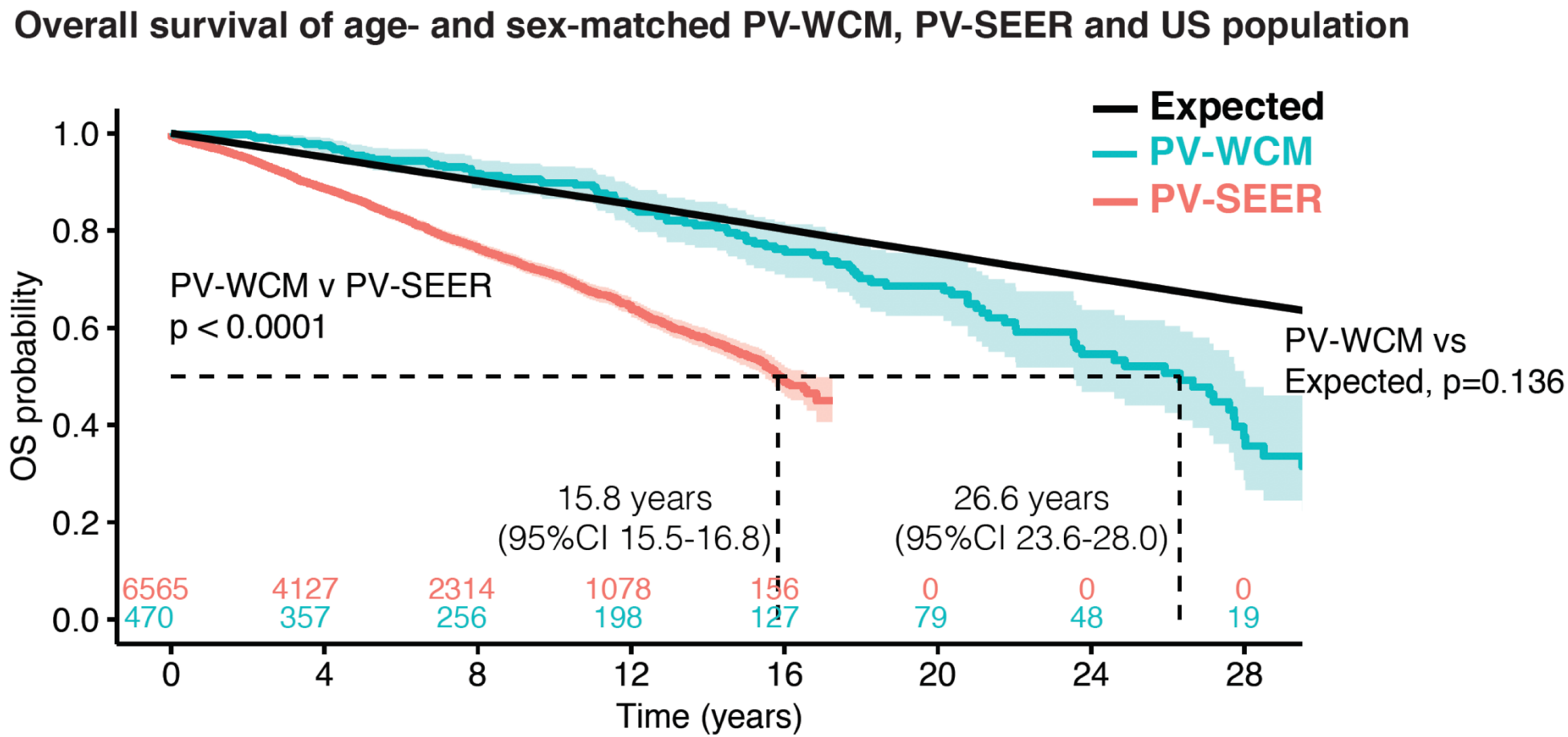


Issues

- 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

Abu-Zeinah G, et al. *Blood Neoplasia*. 2025 [Epub ahead of print].

Optimizing Standard of Care May Improve Survival in PV



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

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Cytoreductive Treatments in PV (and ET)

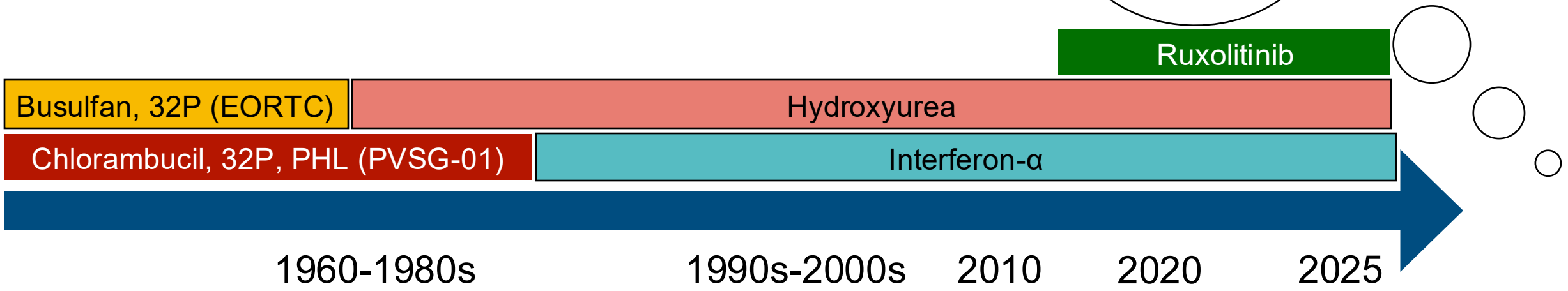
Novel MOA/agents

- Hepcidin (rusfertide, divesiran)
- LSD1i (bomedemstat)
- HDACi (givinostat)
- BETi (pelabrisib)
- CALR Ab (INCA033989)
- Next-gen *JAK* inhibitors

<u>FDA approvals for PV:</u>

2014: ruxolitinib for PV after HU failure

2021: ropeginterferon alfa 2a for PV



FDA. Accessed October 10, 2025. https://www.fda.gov.

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

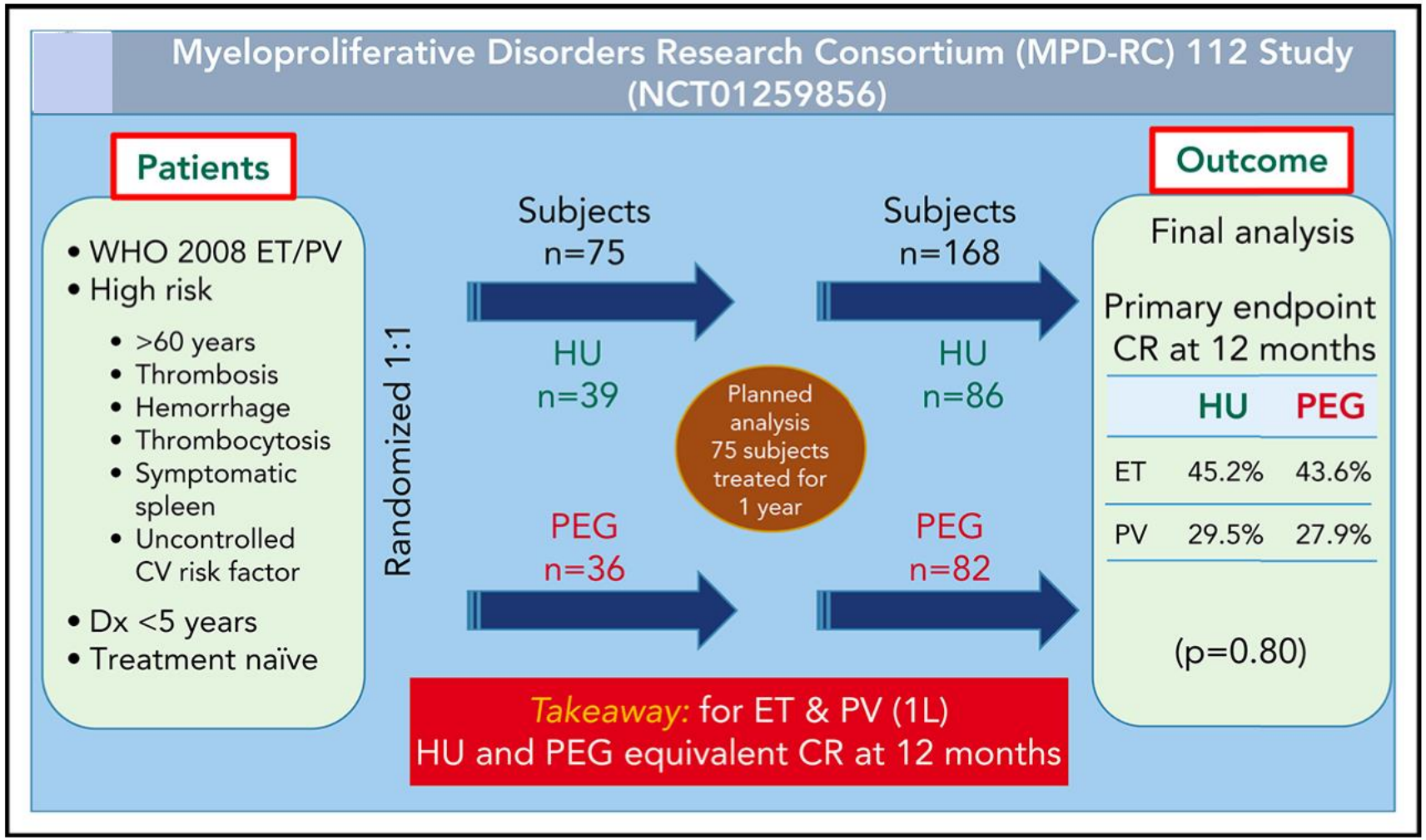
- MPD-RC 112: Phase 3 multi-center study (US) of high-risk patients with PV or ET randomized to PEG-IFN vs HU
- DALIAH: Phase 3 single-center (Denmark) study of high-risk patients with PV randomized to PEG-IFN vs HU
- PROUD/CONTI-PV: Phase 3 randomized, multi-center study of non-inferiority of ropegIFN 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; https://www.clinicaltrials.gov/study/NCT02218047.

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

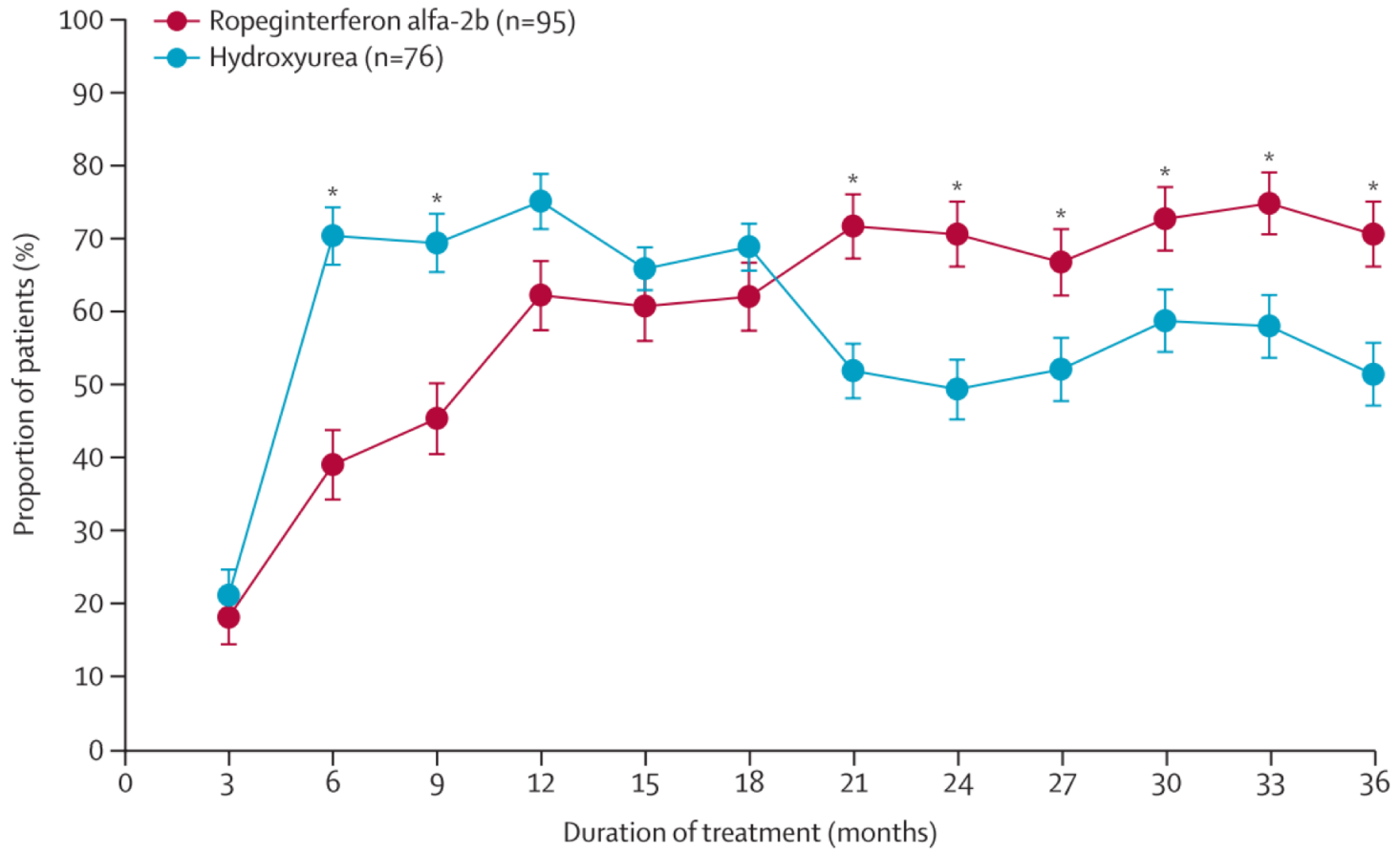


CR = complete response.

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

PROUD/CONTI-PV: HU vs Ropeg CR Rate Is Time-Dependent

Complete hematologic response



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

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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%)

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

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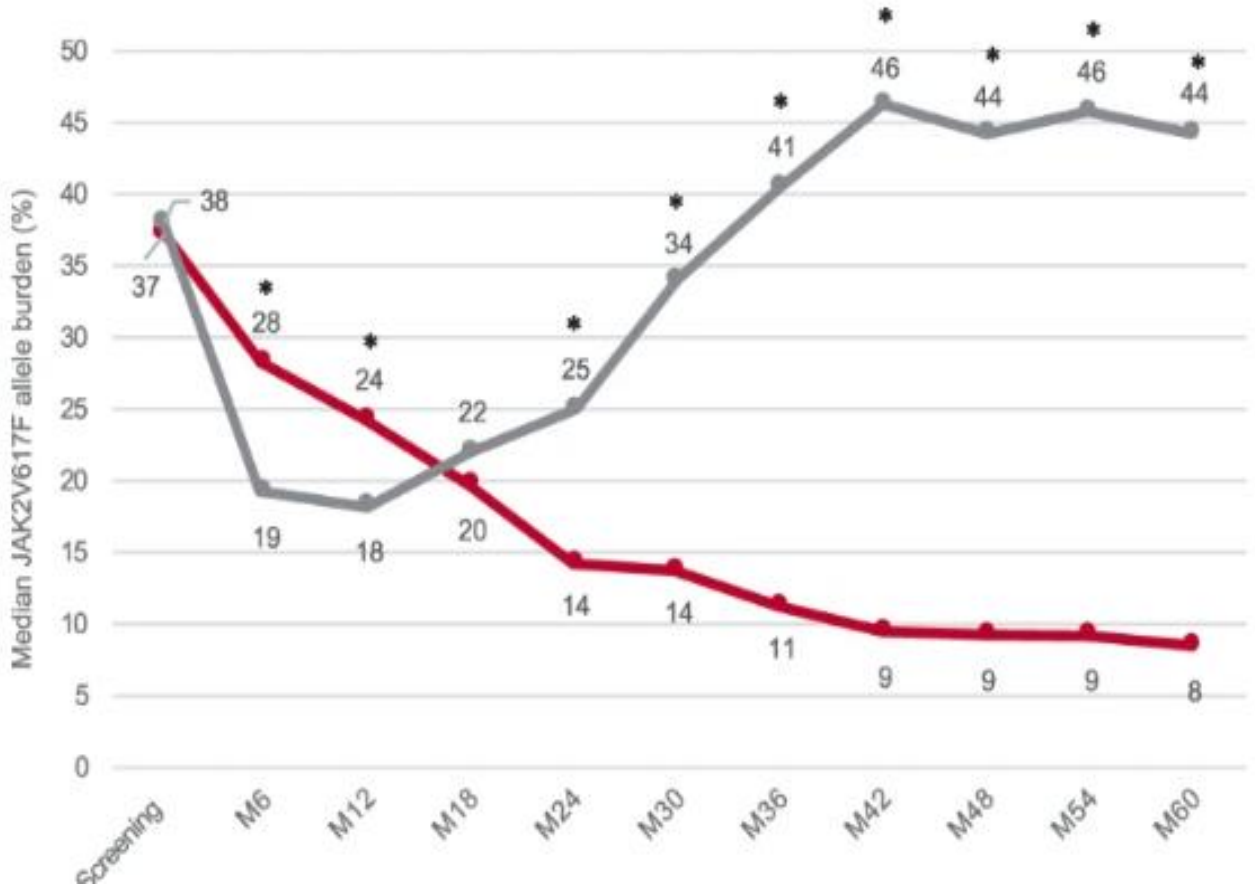
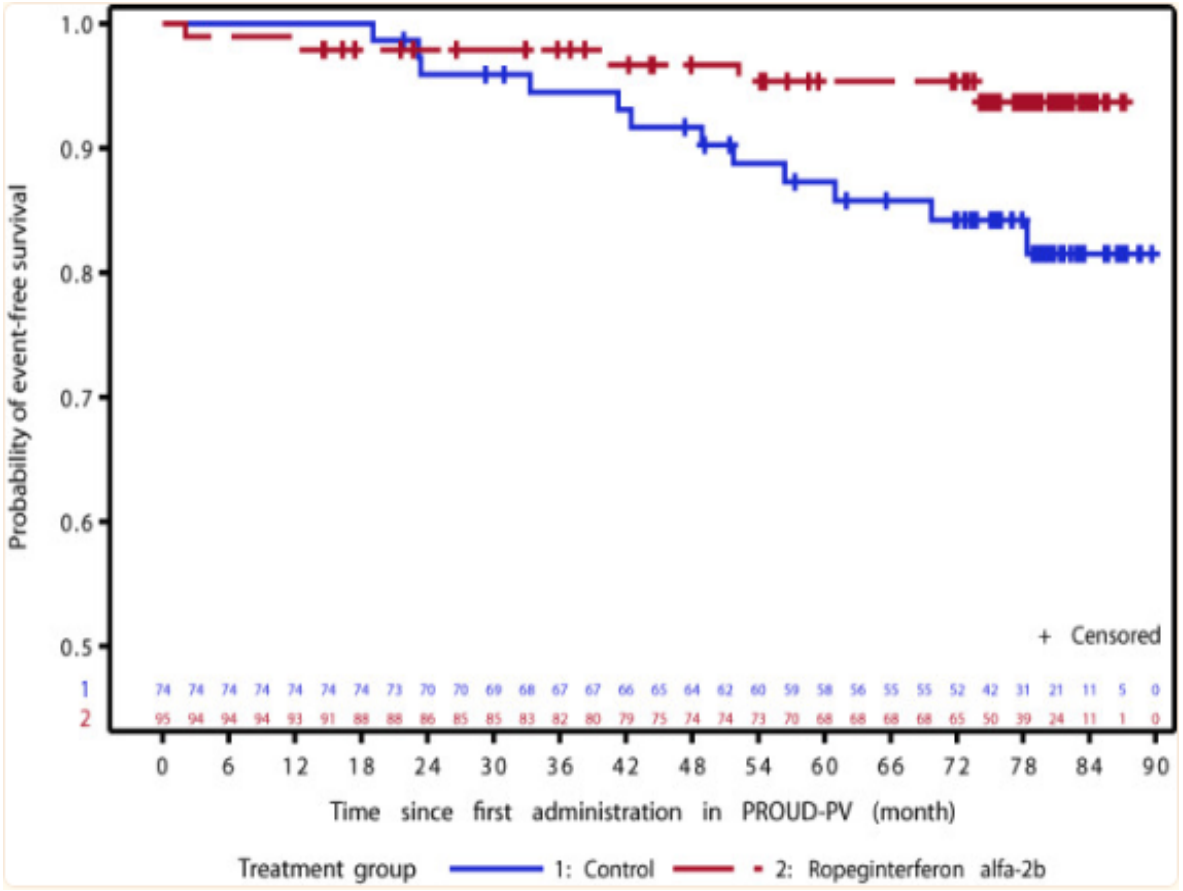
Long-Term PROUD/CONTI-PV Results: IFN Yields Higher, Durable Molecular Response and Event-Free Survival

Molecular response: Ropeg > HU



Event-free survival: Ropeg > HU



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

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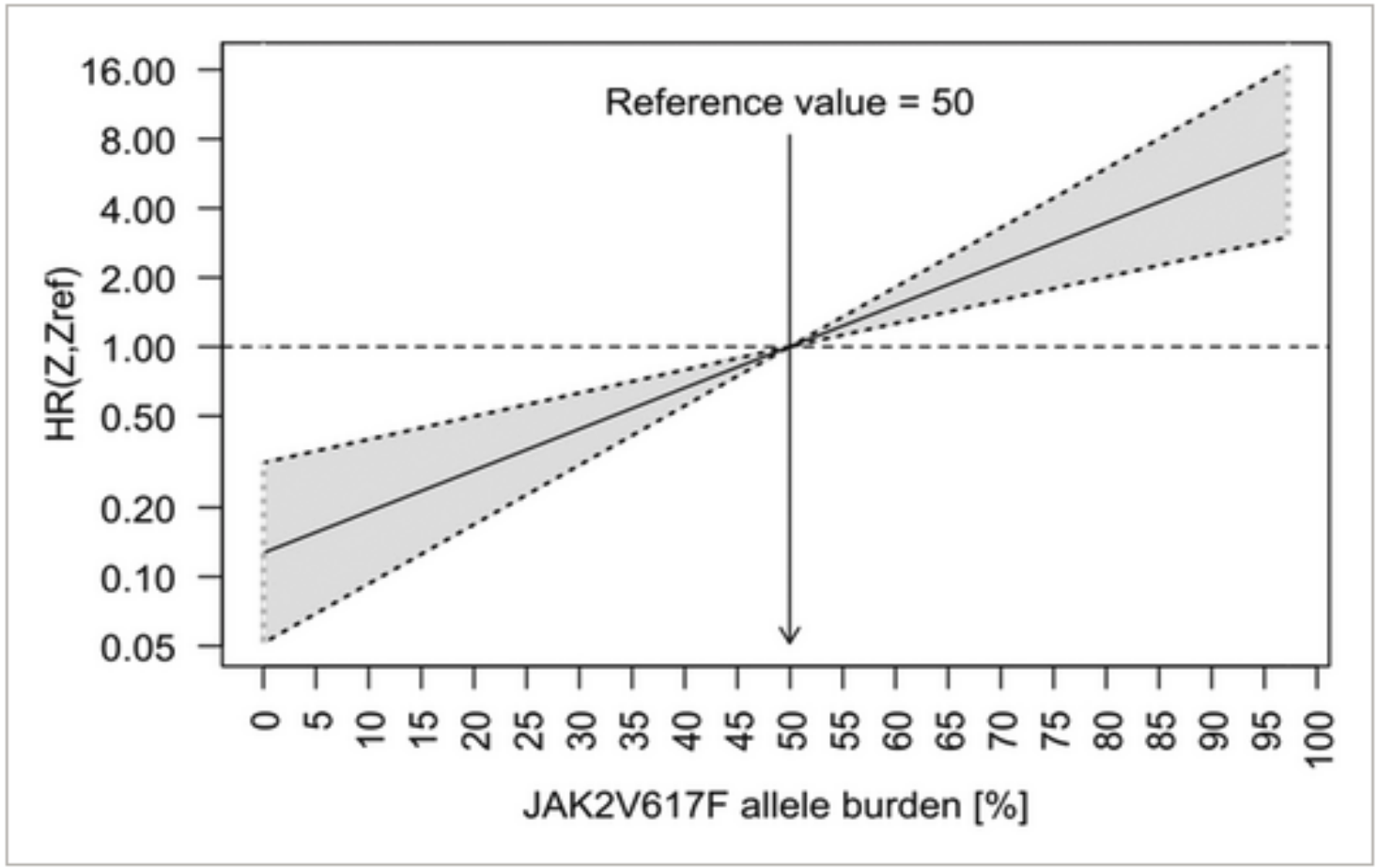
JAK2V617F Molecular Response Correlates with Event-Free Survival

HR of events vs *JAK2* VAF over time

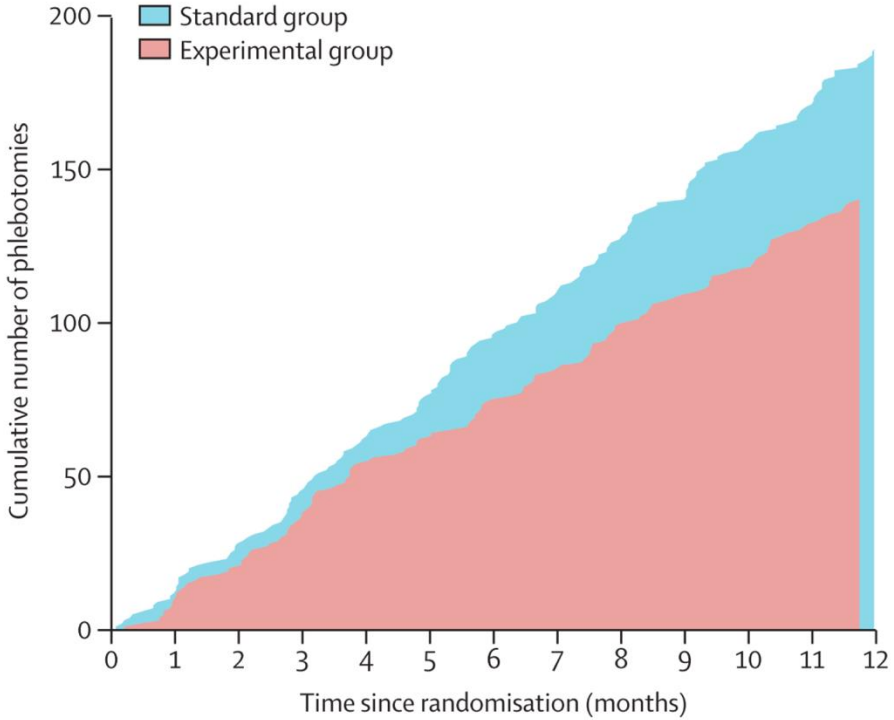


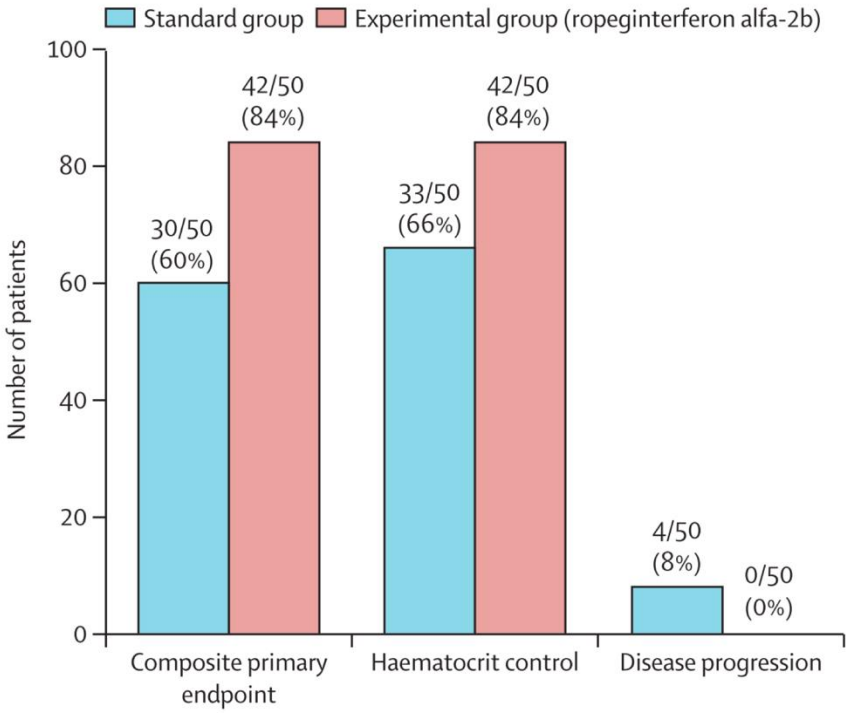
HR = hazard ratio; VAF = variant allele frequency.

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

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.

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

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

	Randomized Groups			
Core Study (12 Months)	**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)		—‡

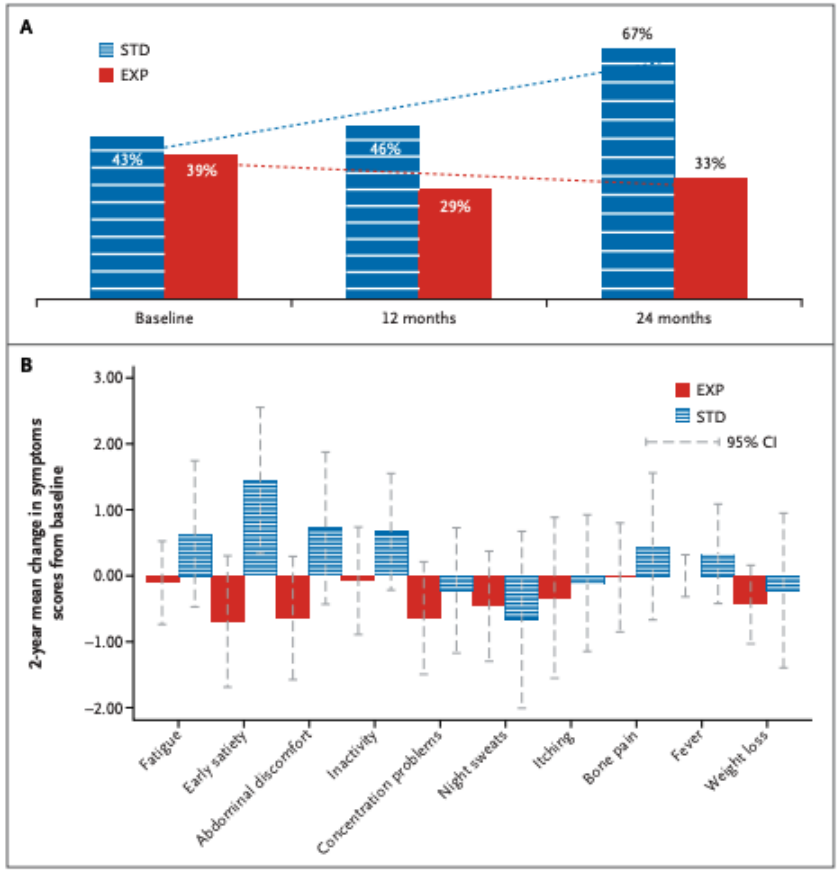

Figure 2. Change in Quality of Life over Time by Study Group.

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

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

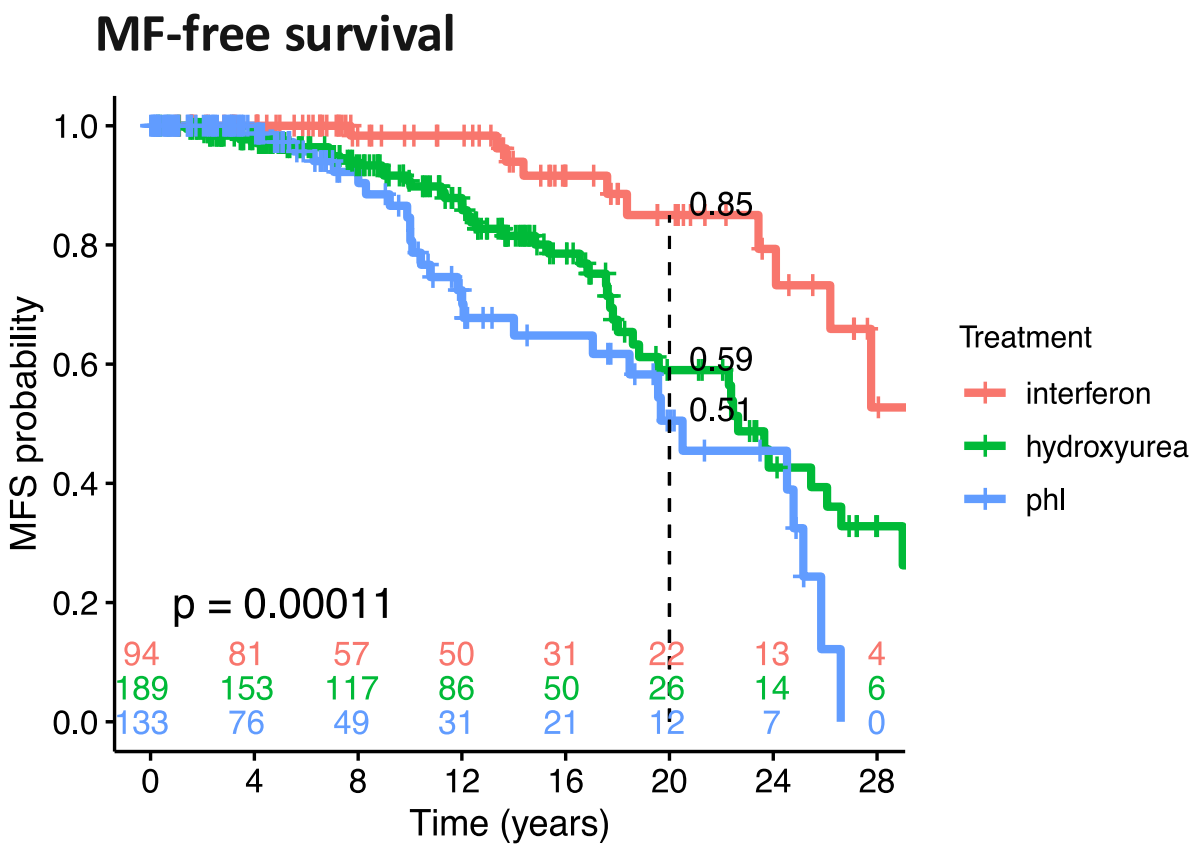
Table 4. Adverse Events by Treatment Received and Severity Regardless of Causality.*

	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)

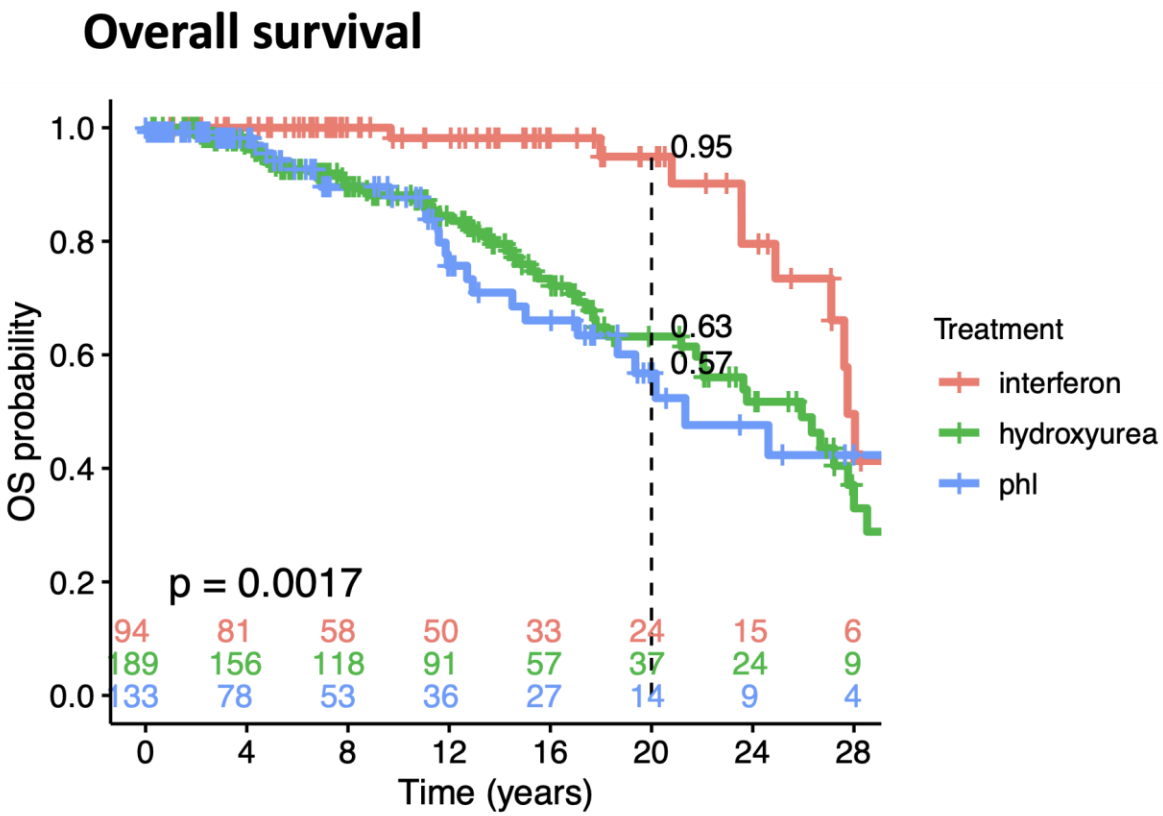
* Values are presented as n (%). Adverse events are reported under the treatment actually received (i.e., 87 patients received ropeginterferon alfa-2b: 64 since randomization and 23 after crossover; 72 patients received phlebotomy only: 63 since randomization and 9 after crossover). All grade 3 or 4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

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.

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

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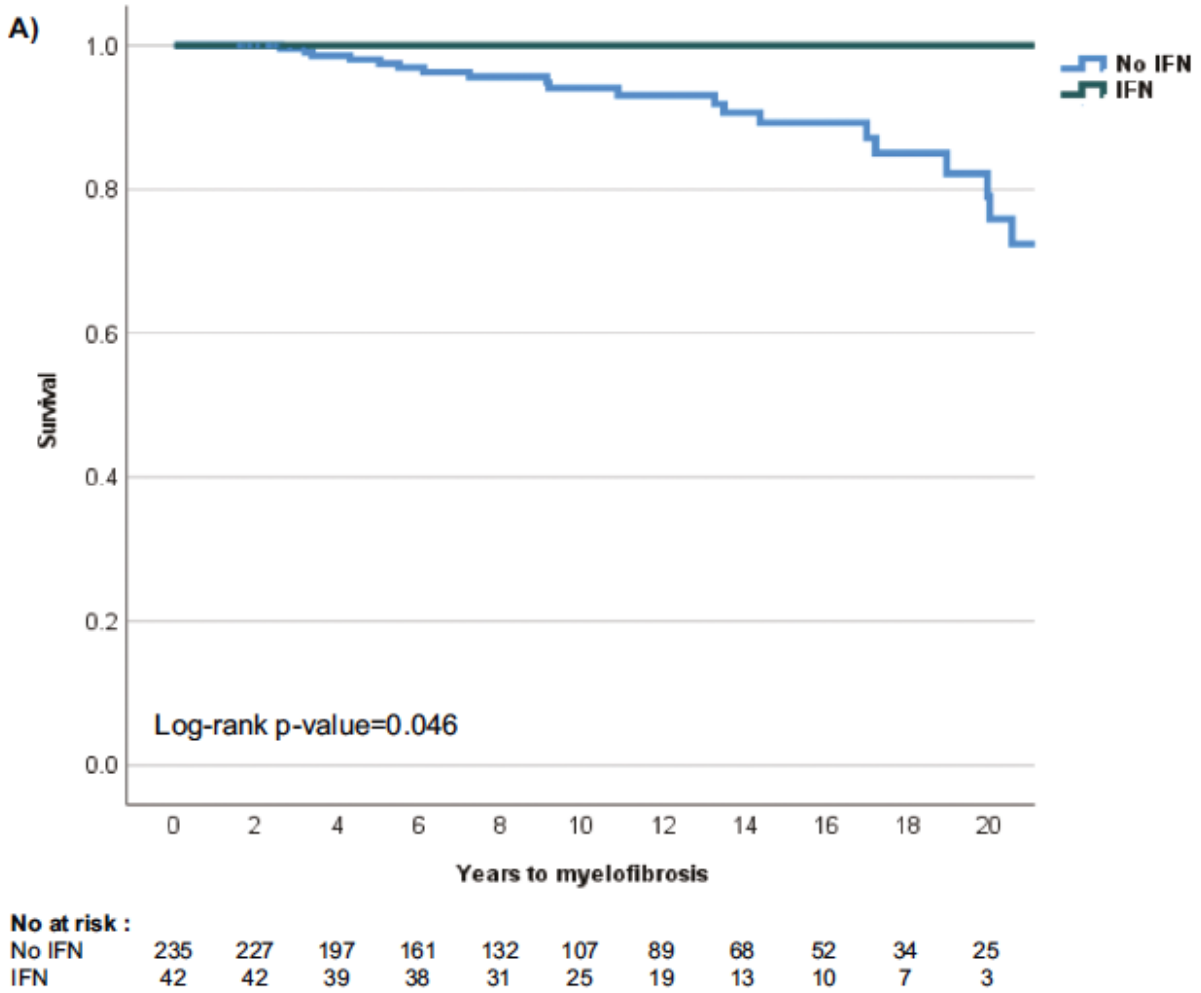
Long-Term Survival Outcomes May Support IFN Use in AYA Patients with ET



- 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.

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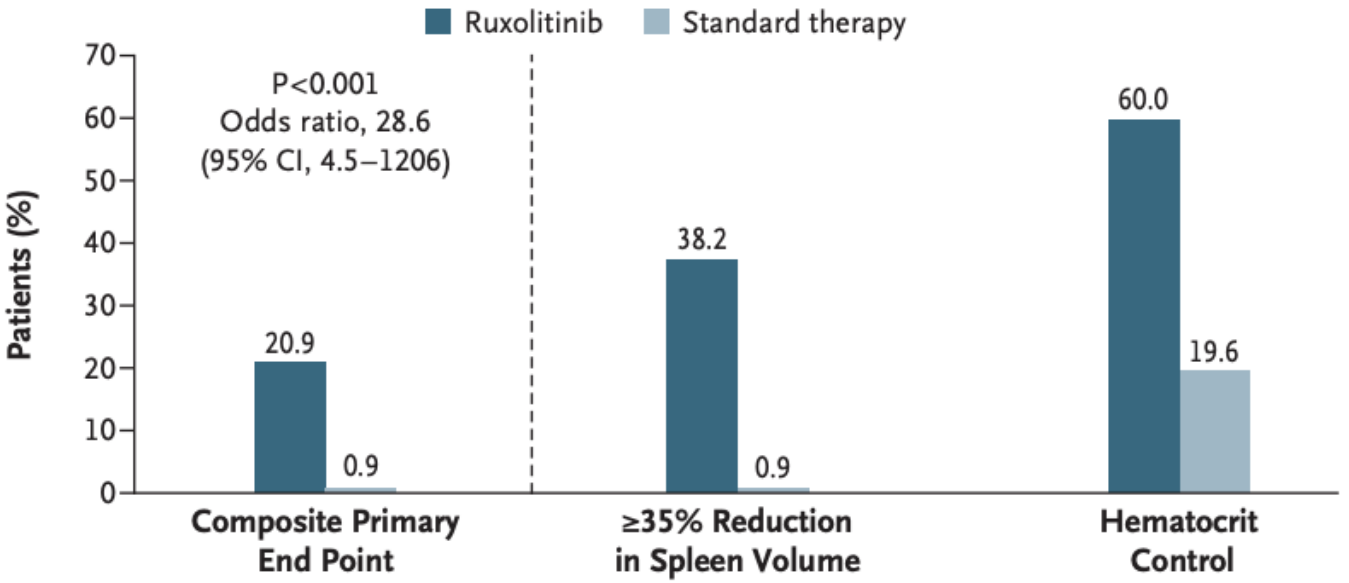
2nd-Line CytoRx in PV: Ruxolitinib, RESPONSE Trial

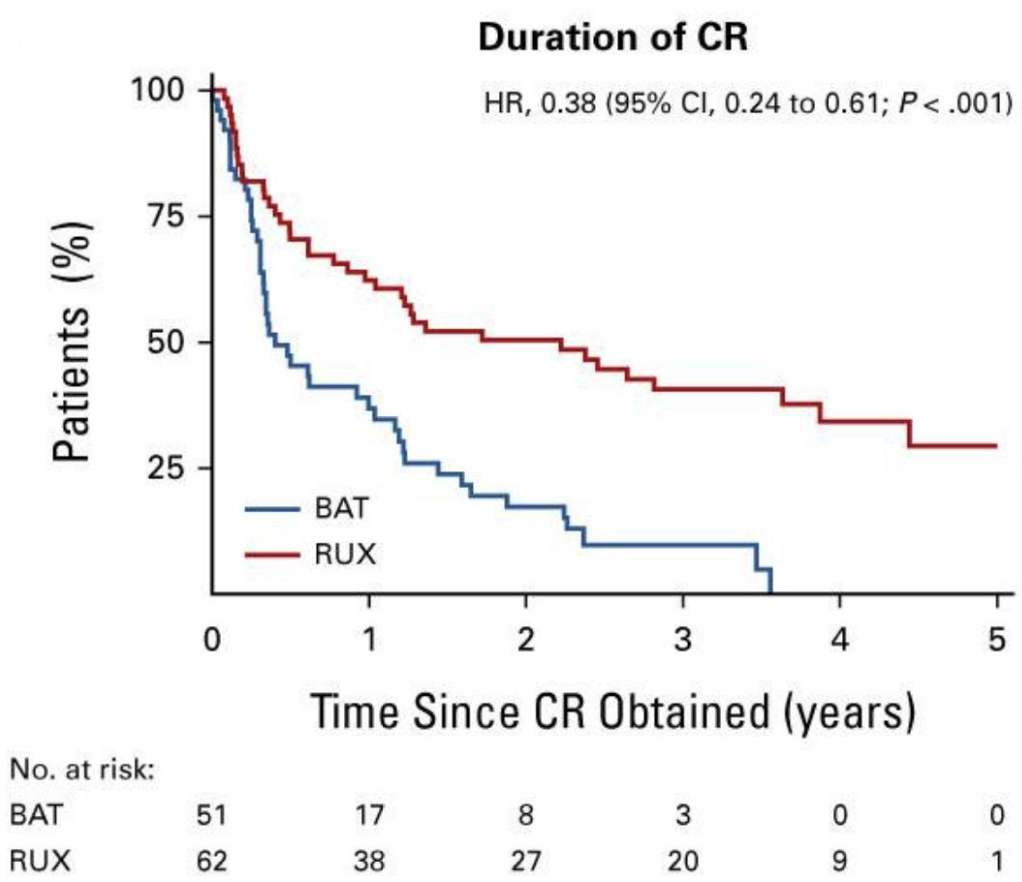
Ruxolitinib versus Standard Therapy for the Treatment of Polycythemia Vera

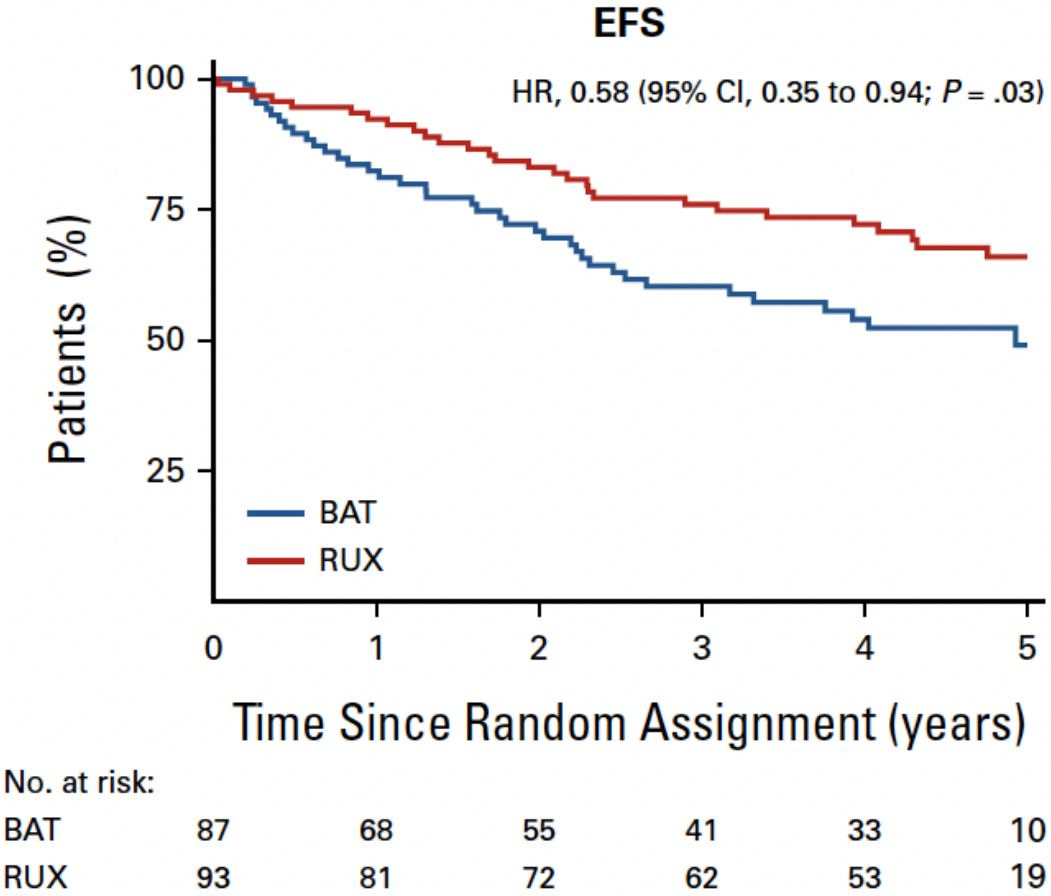
Alessandro M. Vannucchi, M.D., Jean Jacques Kiladjian, M.D., Ph.D., Martin Griesshammer, M.D., Tamas Masszi, M.D., Ph.D., Simon Durrant, M.D., Francesco Passamonti, M.D., Claire N. Harrison, D.M., Fabrizio Pane, M.D., Pierre Zachee, M.D., Ph.D., Ruben Mesa, M.D., Shui He, Ph.D., Mark M. Jones, M.D., 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





EFS = event-free survival.

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

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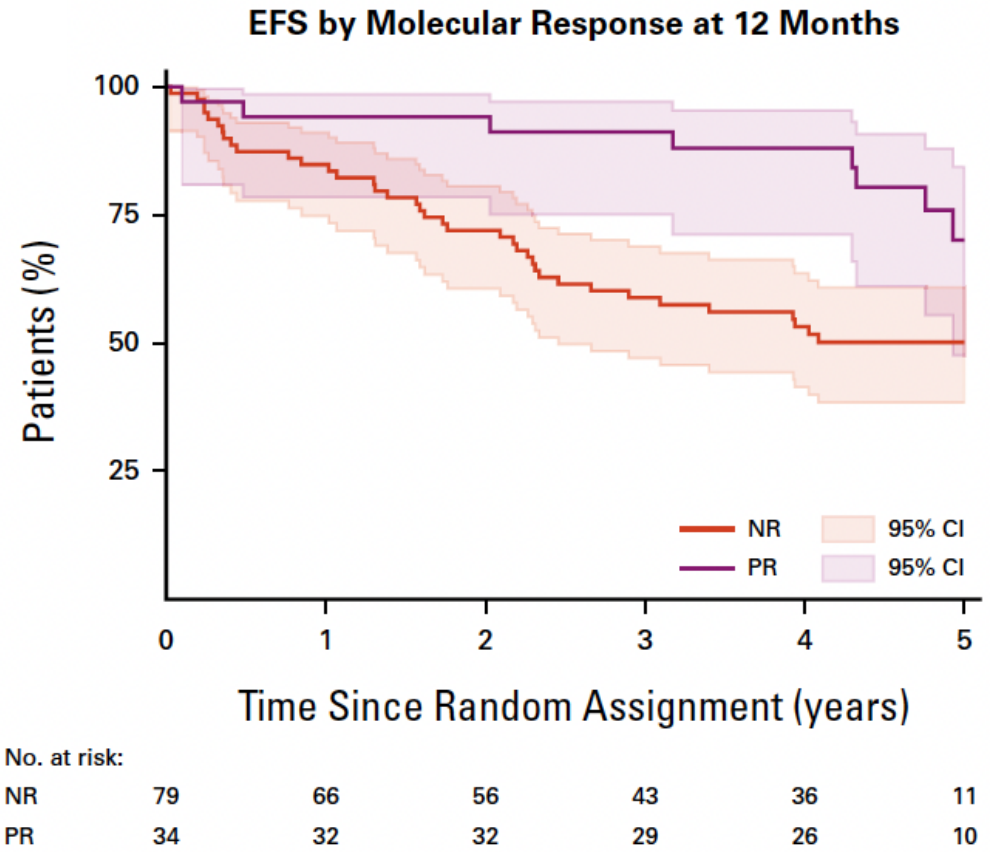
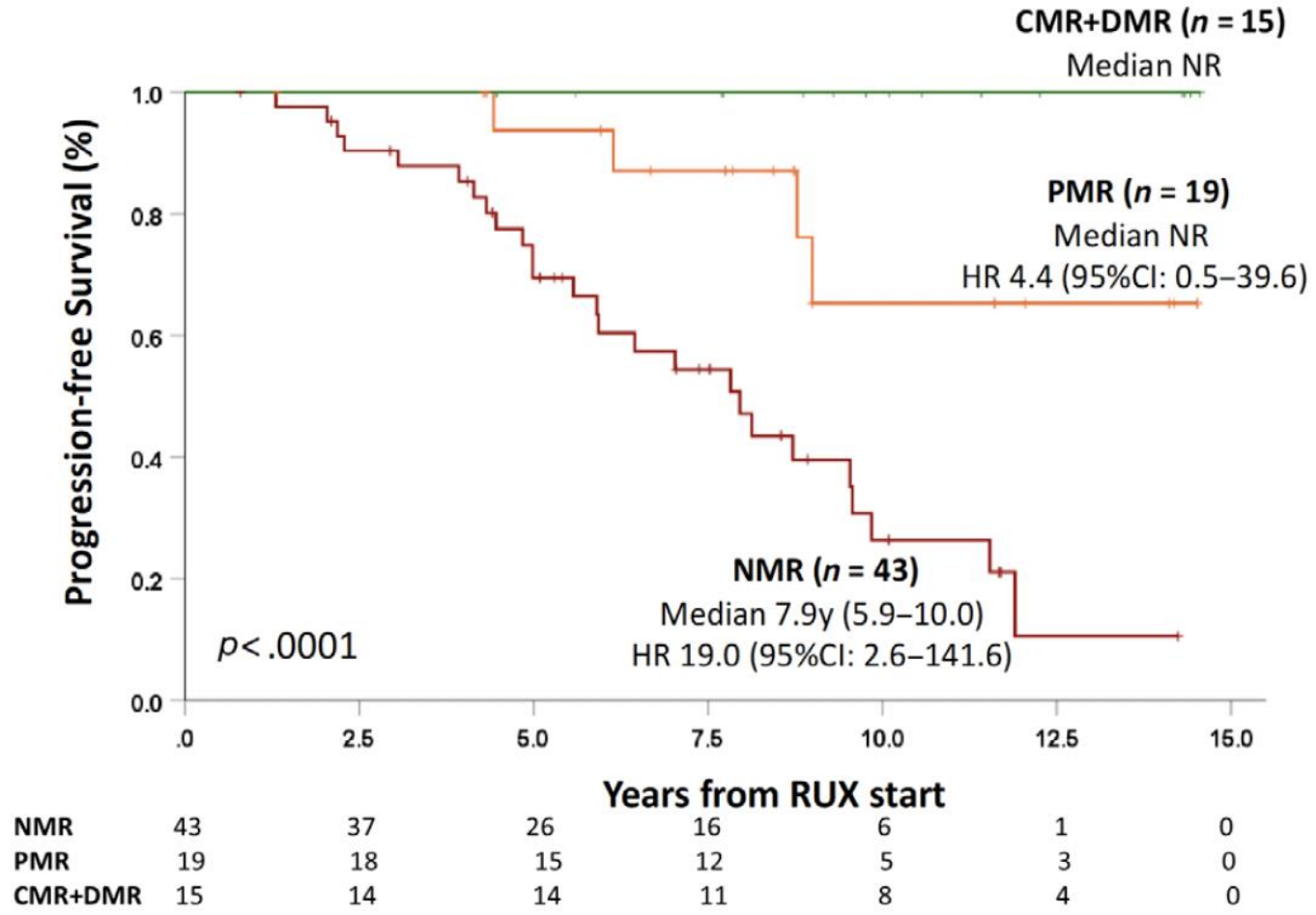
Ruxolitinib in PV Associated with Molecular Response and Event-Free Survival



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

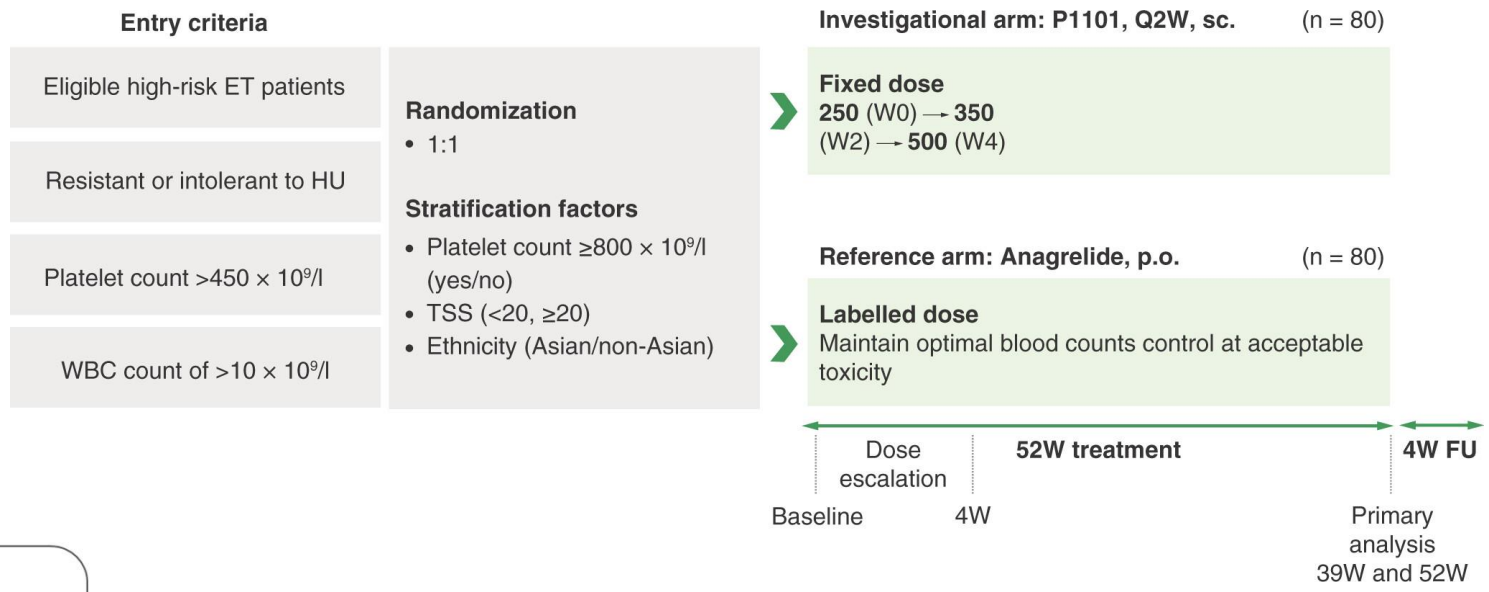
Ruxolitinib in PV + ET Associated with Molecular Response and Myelofibrosis-Free Survival



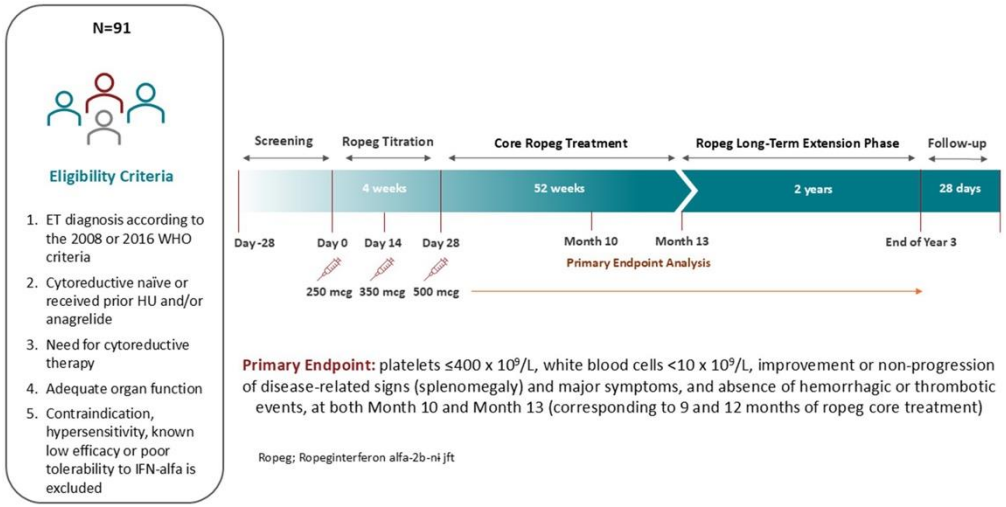
Guglielmelli P, et al. *Am J Hematol*. 2024;99(8):1550-1559.

In ET, IFN and Rux Remain Off-Label, but Ropeg Trials Recently Completed

SURPASS-ET



EXCEED-ET



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

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Familiarizing with Investigational Therapies: Their MOAs, Safety/Efficacy, and Potential

Novel Agents in ET and PV

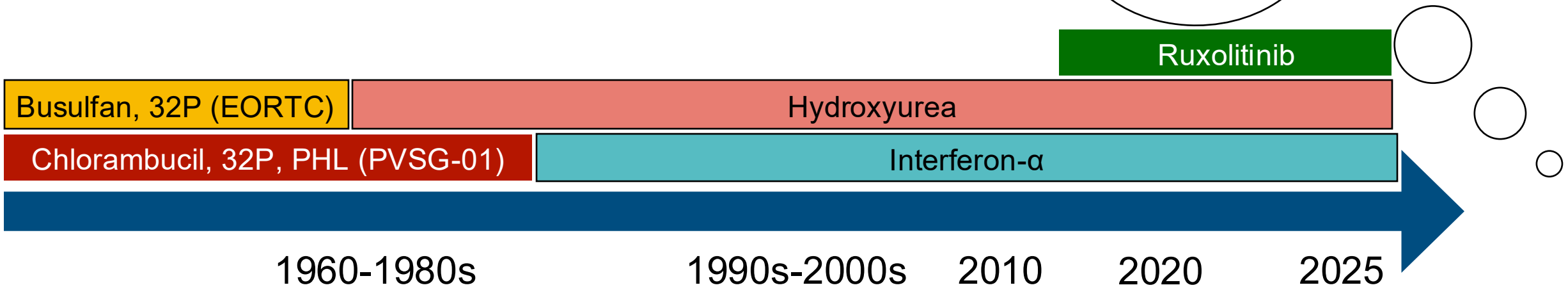
Novel MOA/agents

- Hepcidin (rusfertide, divesiran)
- LSD1i (bomedemstat)
- HDACi (givinostat)
- BETi (pelabrisib)
- CALR Ab (INCA033989)
- Next-gen *JAK* inhibitors

<u>FDA approvals for PV:</u>

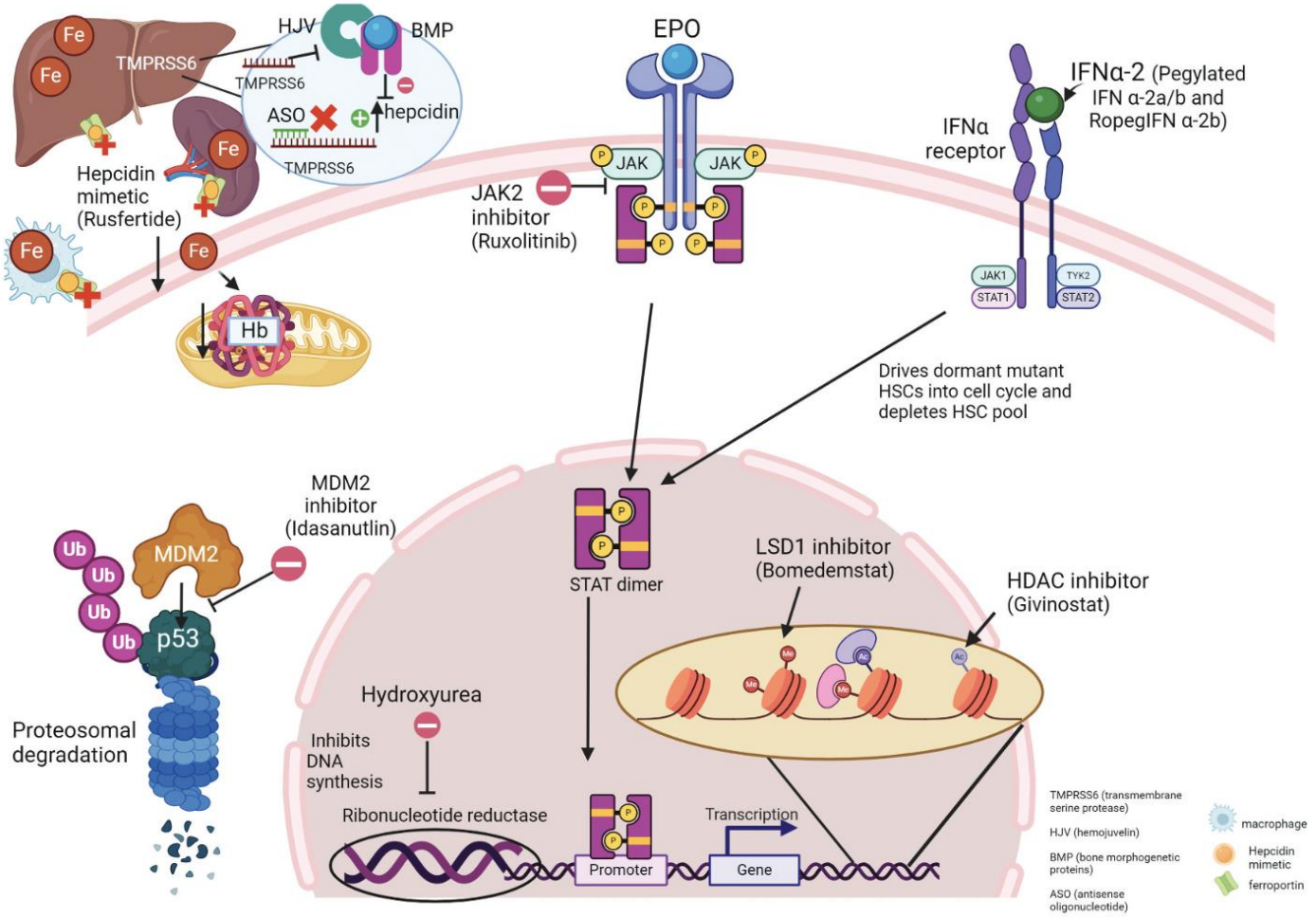
2014: ruxolitinib for PV after HU failure

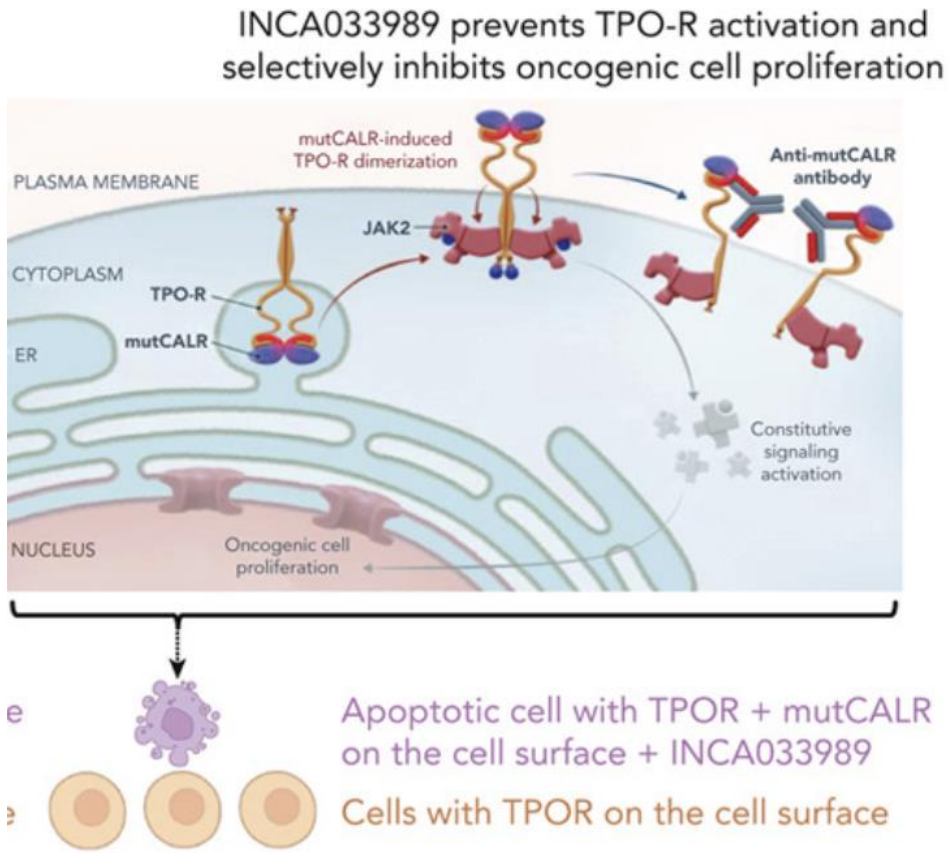
2021: ropeginterferon alfa 2a for PV



FDA. Accessed October 10, 2025. https://www.fda.gov.

Novel Agents in ET and PV





Martinez J, et al. *Expert Opin Pharmacother*. 2024;25(11):1439-1452. Reis ES, et al. *Blood*. 2024;144(22):2336-2348.

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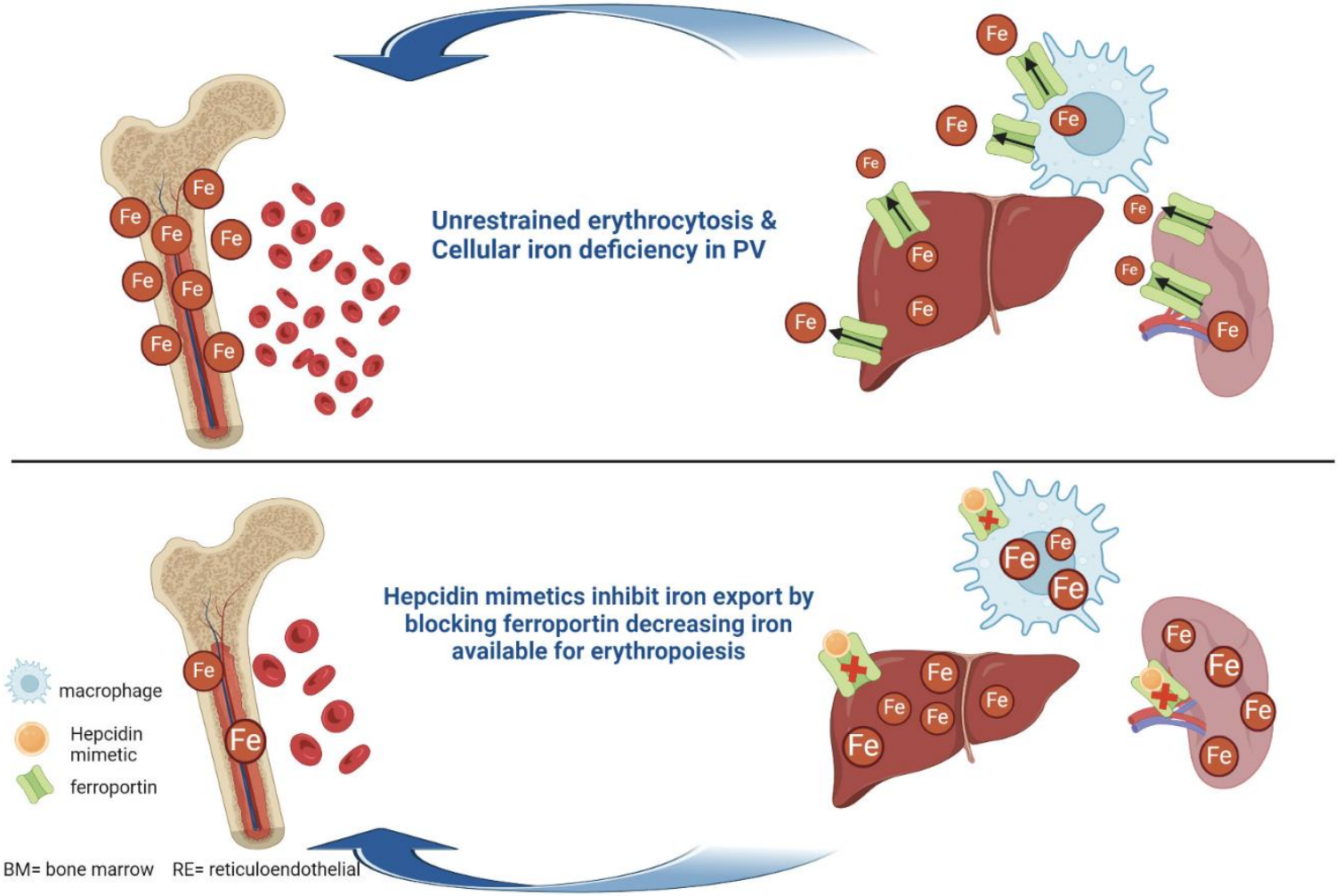
Role of Hepcidin and Hepcidin Mimetic (Rusfertide) in PV



Martinez J, et al. *Expert Opin Pharmacother*. 2024;25(11):1439-1452.

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Rusfertide in Phase 2 REVIVE Trial

Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera

M. Kremyanskaya, A.T. Kuykendall, N. Pemmaraju, E.K. Ritchie, J. Gotlib, A. Gerds, J. Palmer, K. Pettit, U.K. Nath, A. Yacoub, A. Molina, S.R. Saks, N.B. Modi, F.H. Valone, S. Khanna, S. Gupta, S. Verstovsek, Y.Z. Ginzburg, and R. Hoffman, for the REVIVE Trial Investigators*

- Single-arm Phase 2 PV study (70 patients)
- Both low/high-risk, with or w/o cytoRx allowed
- Phlebotomy dependent (>=3 PHL/28 weeks)
- If on cytoRx, stable dose for 8 weeks
- With placebo-controlled randomized withdrawal phase (part 2)
- Primary endpoint = response during the randomized withdrawal period

Kremyanskaya M, et al. *N Engl J Med*. 2024;390(8):723-735.

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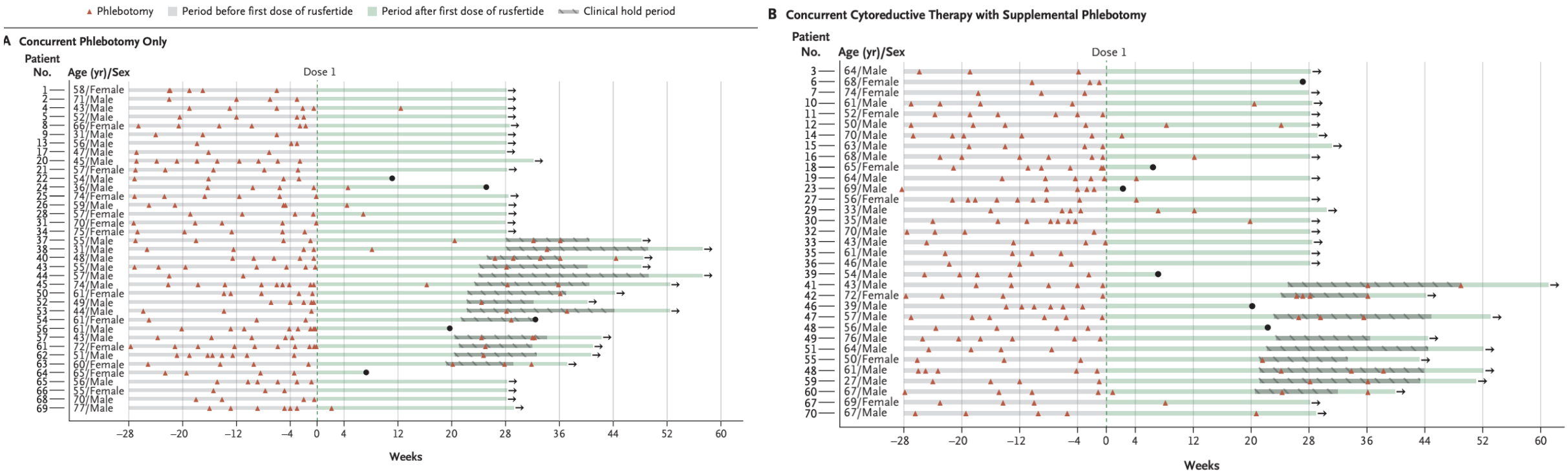
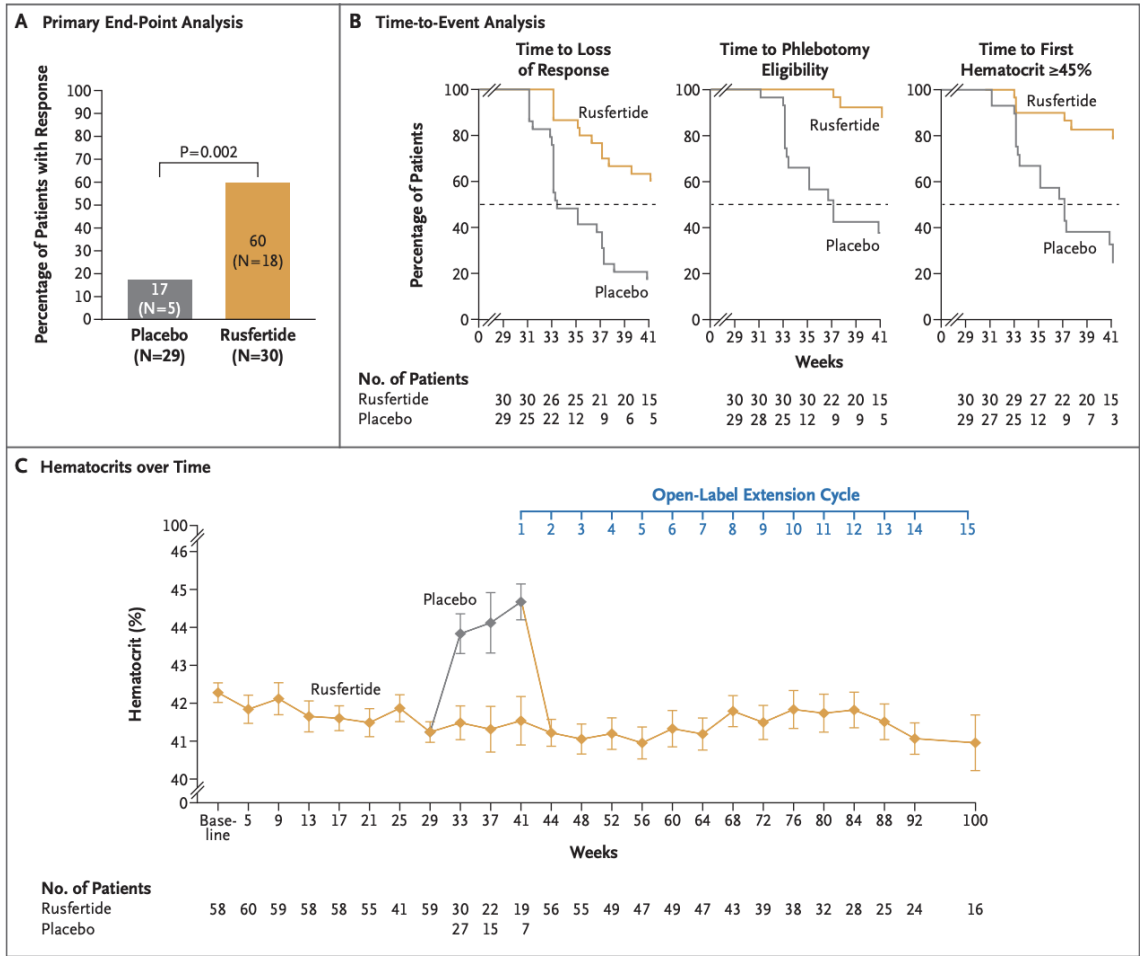
Rusfertide Eliminated Phlebotomy Dependency – Part 1



Kremyanskaya M, et al. *N Engl J Med*. 2024;390(8):723-735.

Rusfertide Met Primary Efficacy Endpoint of Response (Hematocrit Control, Absence of Phlebotomy, Completion of Part 2)



Kremyanskaya M, et al. *N Engl J Med*. 2024;390(8):723-735.

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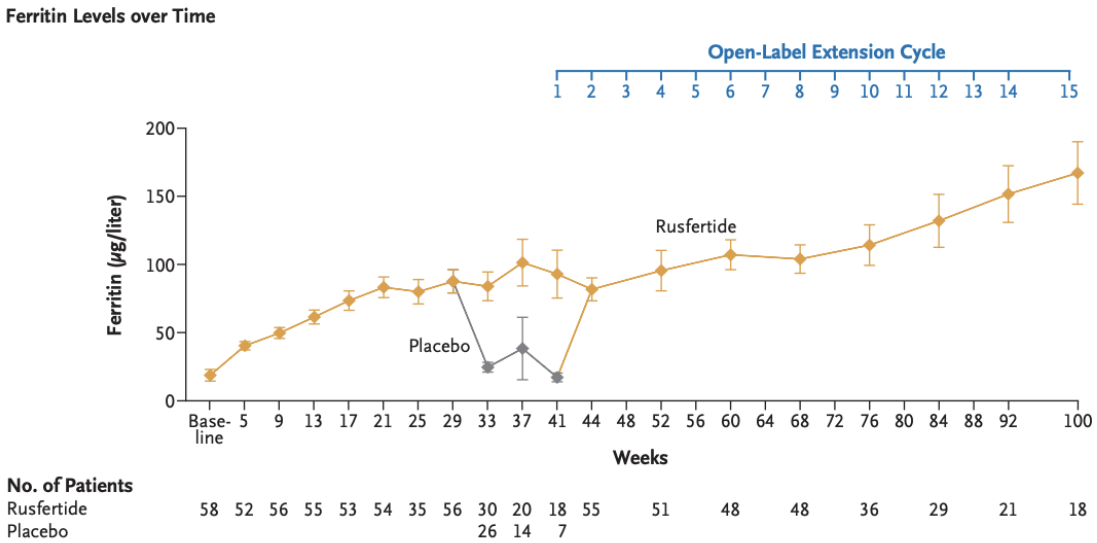
Rusfertide Was Well-Tolerated, Improved MPN-SAF Symptoms, and Corrected Iron Deficiency (as Measured by Ferritin)

Table 2. Adverse Events during Parts 1 and 2 of the Trial.*

Event	Part 1 (N=70)		Part 2				Overall (N=70)	
			Placebo (N=29)		Rusfertide (N=30)			
	Any	Grade 3	Any	Grade 3	Any	Grade 3	Any	Grade 3
	number of patients (percent)							
Any adverse event	69 (99)	7 (10)	16 (55)	2 (7)	24 (80)	0	70 (100)	9 (13)
Injection-site reaction†	60 (86)	0	3 (10)	0	13 (43)	0	60 (86)	0
Fatigue	16 (23)	1 (1)	1 (3)	0	1 (3)	0	18 (26)	1 (1)
Pruritus	14 (20)	0	3 (10)	0	2 (7)	0	17 (24)	0
Nausea	11 (16)	0	2 (7)	0	1 (3)	0	14 (20)	0
Arthralgia	13 (19)	0	0	0	0	0	13 (19)	0
Headache	11 (16)	0	2 (7)	0	0	0	13 (19)	0
Anemia	12 (17)	0	0	0	0	0	12 (17)	0
Dizziness	9 (13)	0	0	0	0	0	9 (13)	0
Dyspnea	6 (9)	0	2 (7)	0	1 (3)	0	9 (13)	0
Hyperuricemia	6 (9)	0	1 (3)	0	2 (7)	0	8 (11)	0
Diarrhea	7 (10)	0	1 (3)	0	0	0	7 (10)	0
Insomnia	7 (10)	0	0	0	0	0	7 (10)	0
Myalgia	4 (6)	0	1 (3)	0	2 (7)	0	7 (10)	0
Paresthesia	4 (6)	0	1 (3)	0	2 (7)	0	7 (10)	0

* Adverse events that occurred in at least 10% of the patients in the intention-to-treat population during parts 1 and 2 are presented according to *Medical Dictionary for Regulatory Activities*, version 25.0, preferred term. Patients with multiple occurrences of the same event are counted only once. No grade 4 or 5 events were reported.
† Injection-site reactions that occurred in at least 10% of the patients are listed in Table S13.

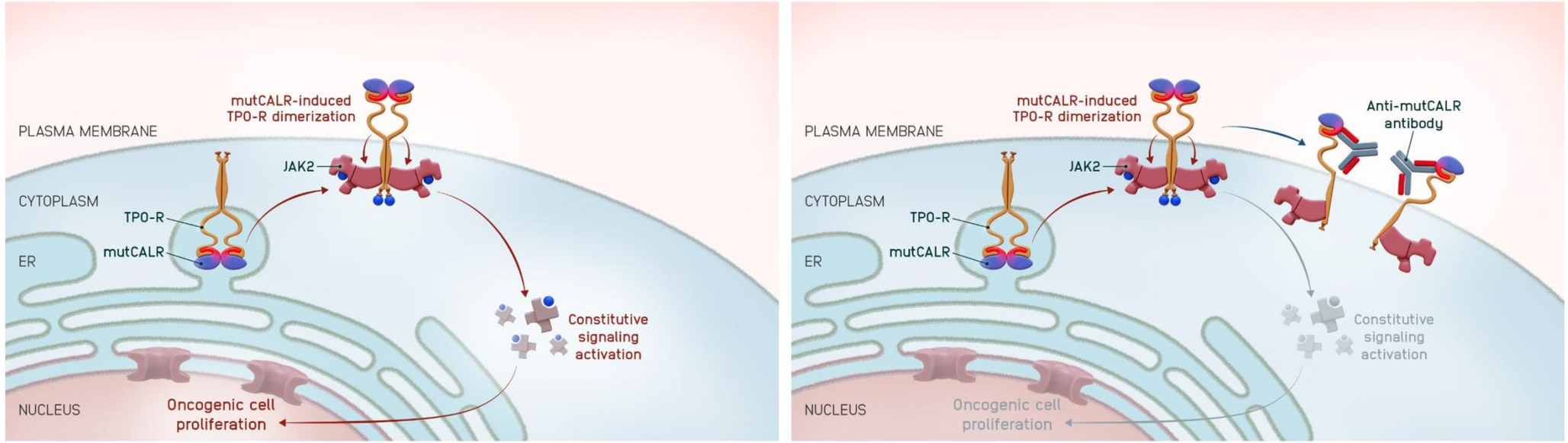


SAF = Symptom Assessment Form.

Kremyanskaya M, et al. *N Engl J Med.* 2024;390(8):723-735.

INCA33989 Is a Mutant-Specific Targeted Therapy for Patients with *CALR* Mutations

- INCA33989 has a unique mechanism of action compared with other available therapies
  - INCA33989 is a high-affinity, fully human IgG1 monoclonal antibody that selectively targets mutCALR in complex with TPO-R (MPL) to inhibit cell signaling and proliferation[1]



1. Reis, et al. *Blood.* 2024;22:2336-2348.

CALR, calreticulin; MPL, myeloproliferative leukemia protein; mut*CALR*, mutations of calreticulin; TPO-R, thrombopoietin receptor (MPL).

Slide courtesy of John Mascarenhas, MD.

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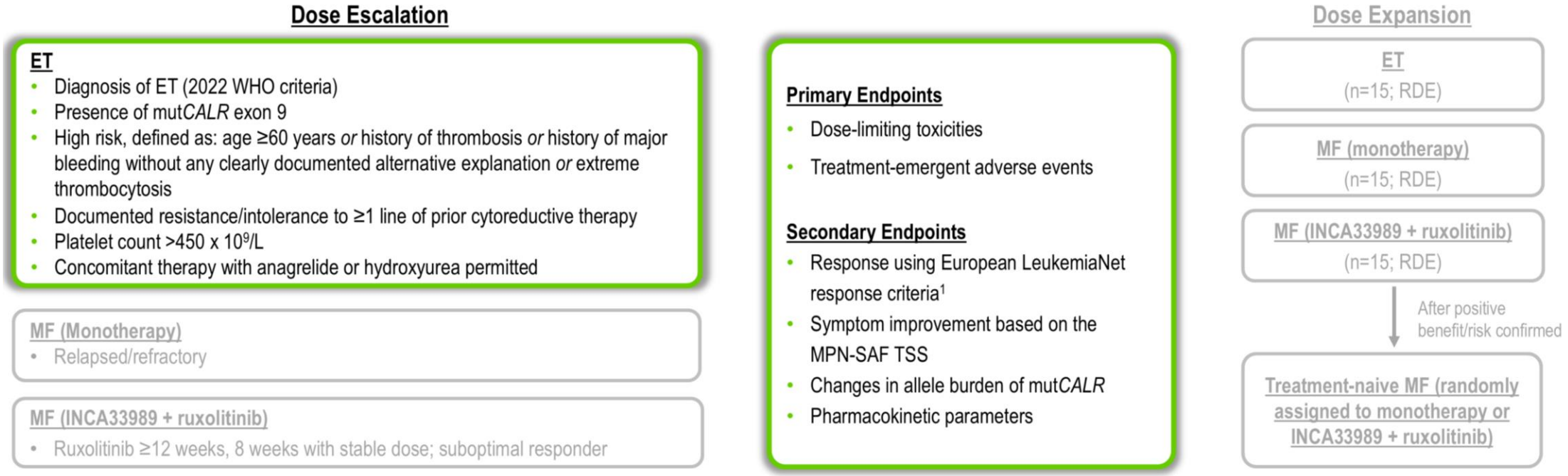
Study Design: INCA33989-101 and INCA33989-102



- **INCA33989-101** (NCT05936359; outside the US) and **INCA33989-102** (NCT06034002; US only) are phase 1, first-in-human, multicenter, open-label studies evaluating INCA33989 in patients harboring a *CALR* exon-9 mutation with high-risk ET or MF (as monotherapy or in combination with ruxolitinib)
- INCA33989 is administered intravenously every 2 weeks

1. Barosi et al. *Blood*. 2013;23:4778-4781.

CALR, calreticulin; ET, essential thrombocythemia; MF, myelofibrosis; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; mut*CALR*, mutations of calreticulin; RDE, recommended dose for expansion; TSS, total symptom score.

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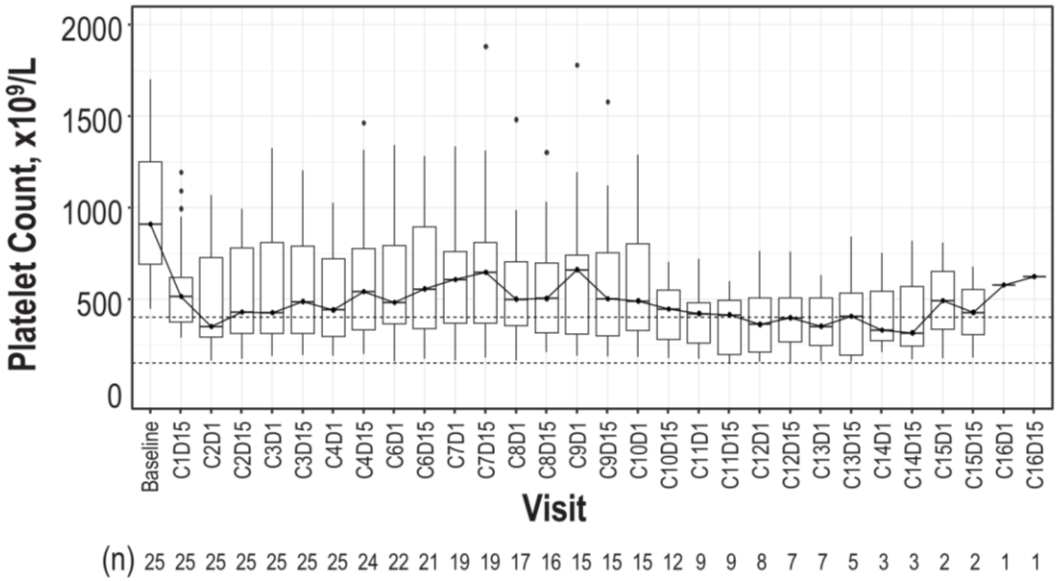
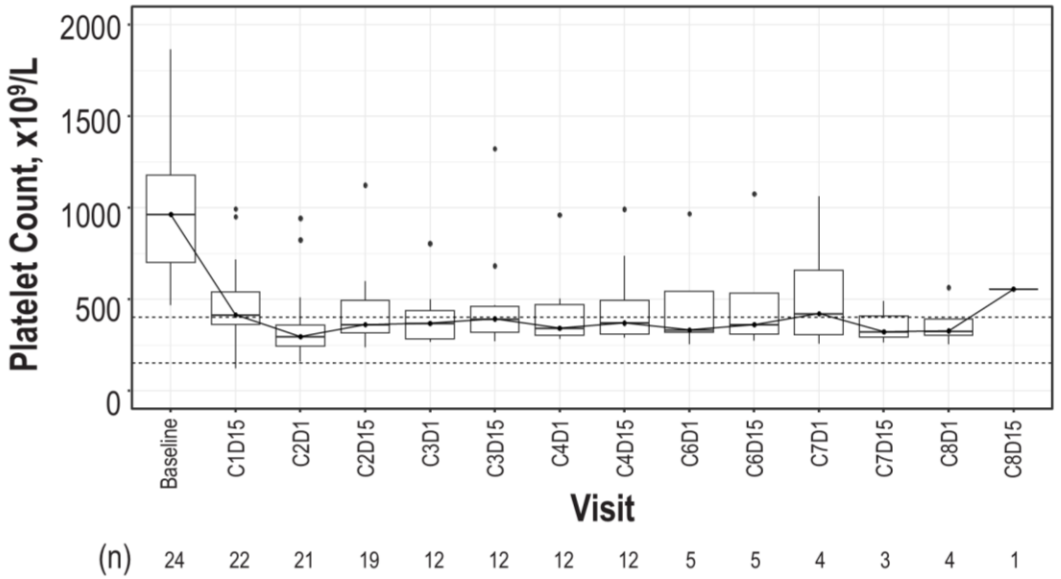
Rapid and Durable Normalization of Platelet Counts Observed in Most Patients

Doses 24-250 mg*



Doses 400-2500 mg†



- Of the 31 patients that enrolled with concomitant cytoreductive therapy (hydroxyurea or anagrelide), 20 (65%) discontinued it and remained on study
- Thrombocytopenia was not observed in any patient
- Doses of ≥400 mg produced higher frequency of platelet count normalization

Dotted lines indicate upper and lower limit of normal. Boxes denote the first and third quartiles, lines represent the median. Number of patients with available data at each visit is noted below the x axis.
*24 mg (n=3), 50 mg (n=3), 70 mg (n=3), 100 mg (n=3), 200 mg (n=5), 250 mg (n=8). †400 mg (n=5), 750 mg (n=9), 1500 mg (n=6), 2500 mg (n=4). C, cycle; D, day.

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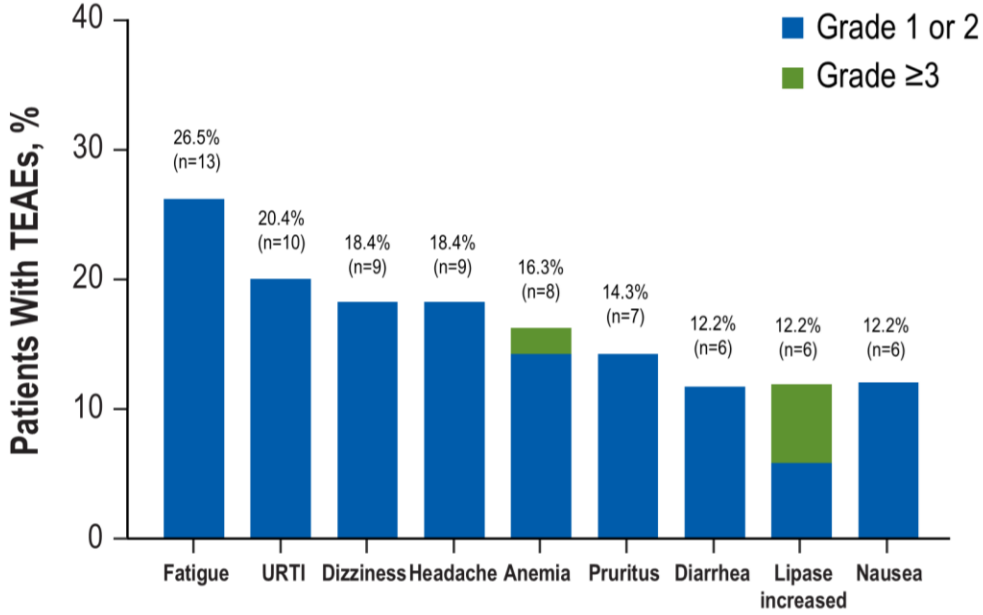
Safety: No Dose-Limiting Toxicities Were Observed

Summary of TEAEs

TEAE, n (%)	Total (N=49)
Any TEAE	42 (85.7)
Treatment-related	30 (61.2)
Grade ≥3*	13 (26.5)
Serious	3 (6.1)
Discontinuation due to TEAEs	1 (2.0)
Dose reduction due to TEAEs	1 (2.0)
Infusion interruption due to TEAEs	0
Dose-limiting toxicity	0

- A maximum tolerated dose was not reached
- Only 1 patient discontinued due to a treatment-emergent adverse event (TEAE)
- Serious TEAEs:
  - Asymptomatic lipase increase (n=1; 24 mg)
  - Visceral venous thrombosis† (n=1; 24 mg)
  - Diverticulitis (n=1; 400 mg)

Most Common TEAEs



- The majority of TEAEs were grade 1-2
- Most frequent grade ≥3 TEAE was transient, asymptomatic lipase increase (6.1%)
  - All resolved without clinical sequelae
  - No correlation to dose or onset post treatment

*One grade 4 TEAE was observed (transient neutropenia related to concomitant hydroxyurea). †Followed by melena (after anticoagulant initiation) and treatment discontinuation.
TEAE, treatment-emergent adverse event; URTI, upper respiratory tract infection

Slide courtesy of John Mascarenhas, MD.

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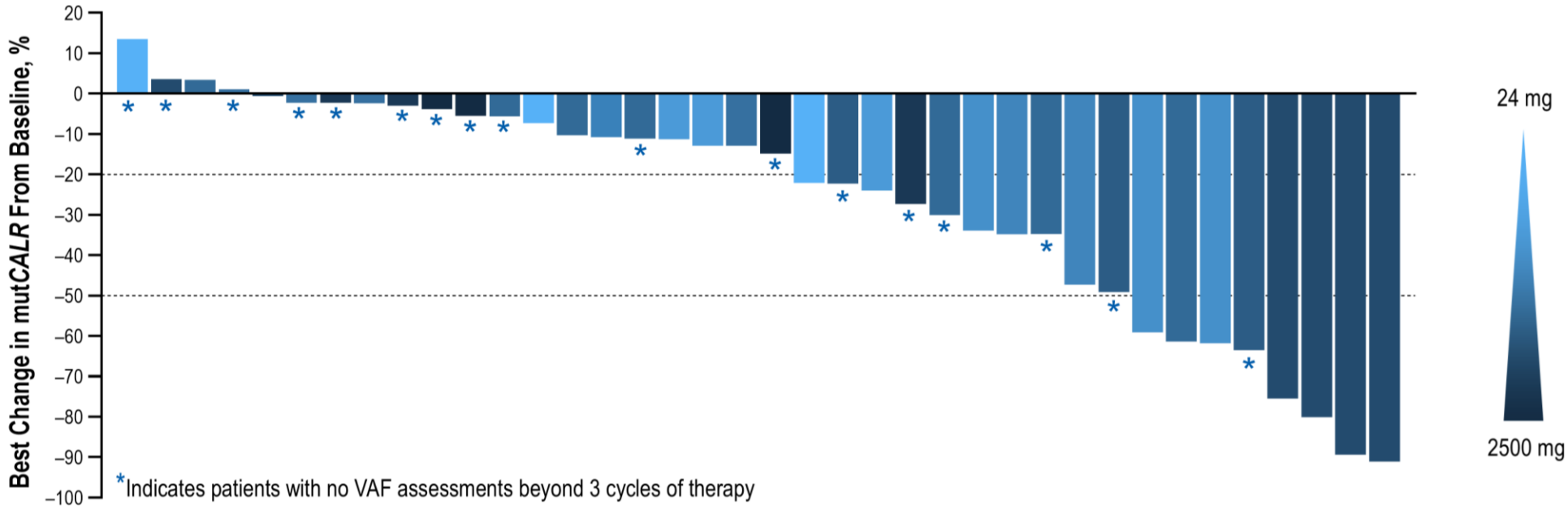
Molecular Responses Are Rapid and Frequent

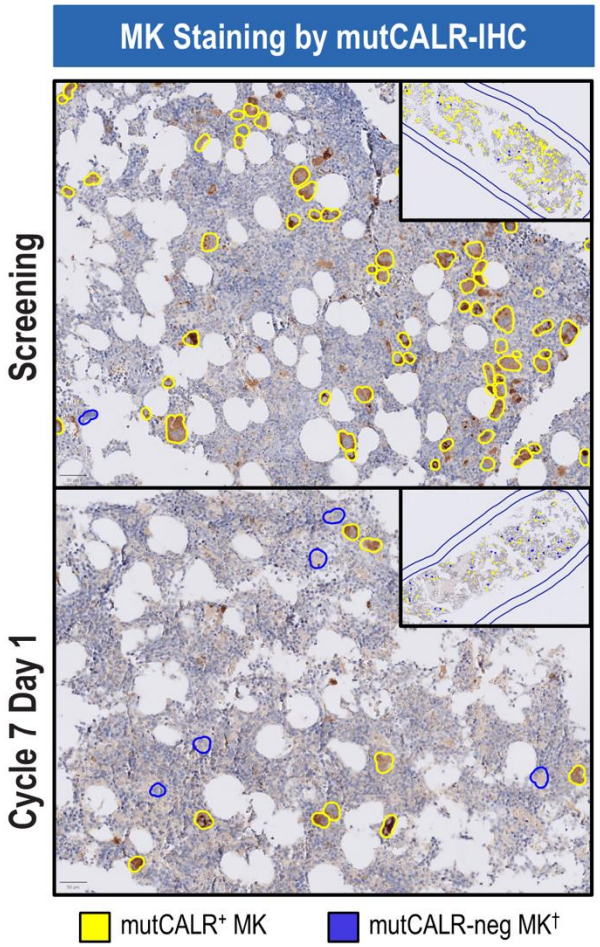
- A reduction in mut*CALR* VAF from baseline occurred in 34/38 (89%) evaluable patients
  - 18/38 (47%) achieved >20% best reduction in VAF
  - 8/38 (21%) achieved >50% best reduction in VAF
- A reduction of ≥20% VAF occurred within 6 cycles of therapy for all 18 responders
- All 18 molecular responders achieved a hematological response of CR or PR

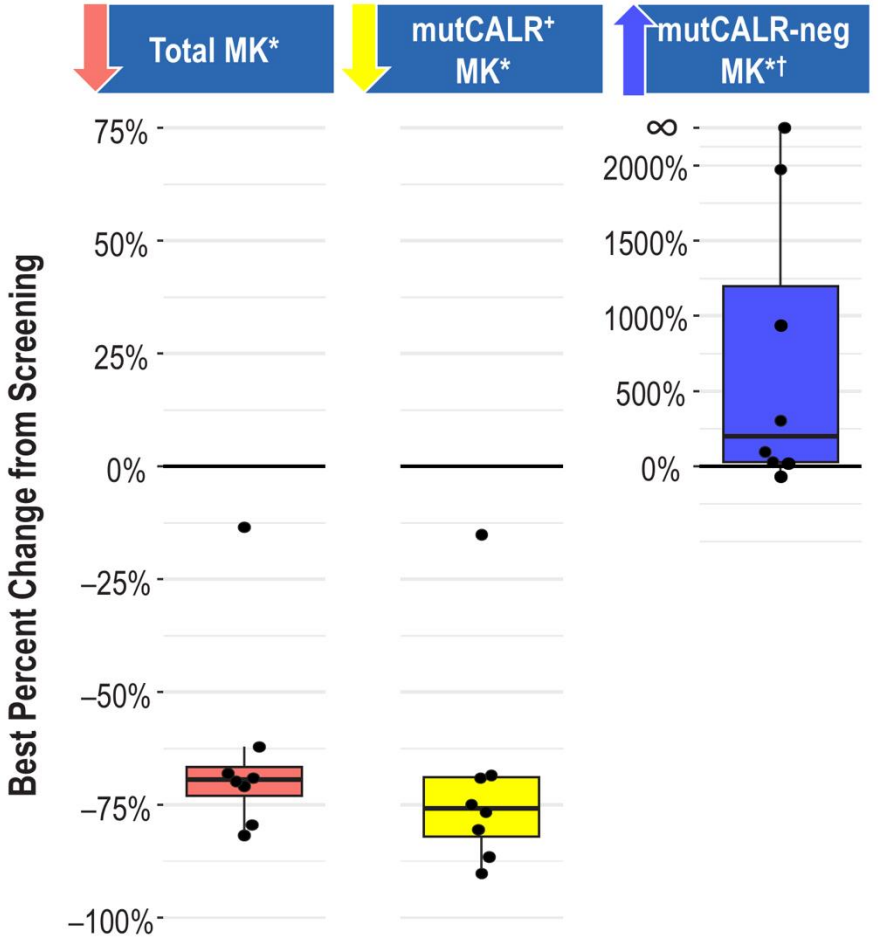


Dotted lines represent 20% and 50% VAF thresholds. 1 cycle = 28 days or 2 doses. CR, complete response; mut*CALR*, mutations in calreticulin; PR, partial response; VAF, variant allele frequency.

Slide courtesy of John Mascarenhas, MD.

Reduction in mutCALR⁺ Megakaryocytes in the Bone Marrow of Clinical Responders





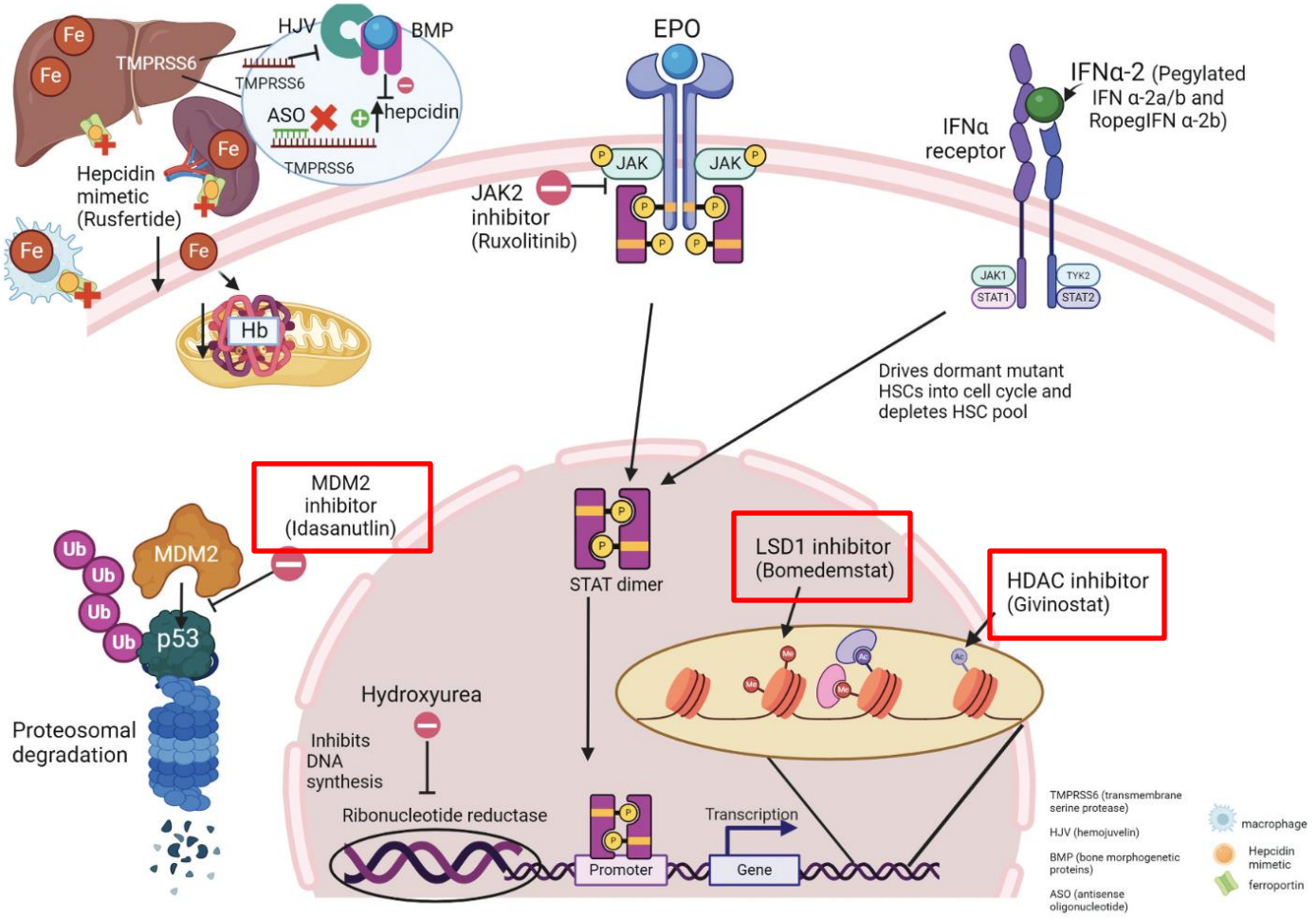
In 8 patients with hematologic response after 6 cycles of treatment

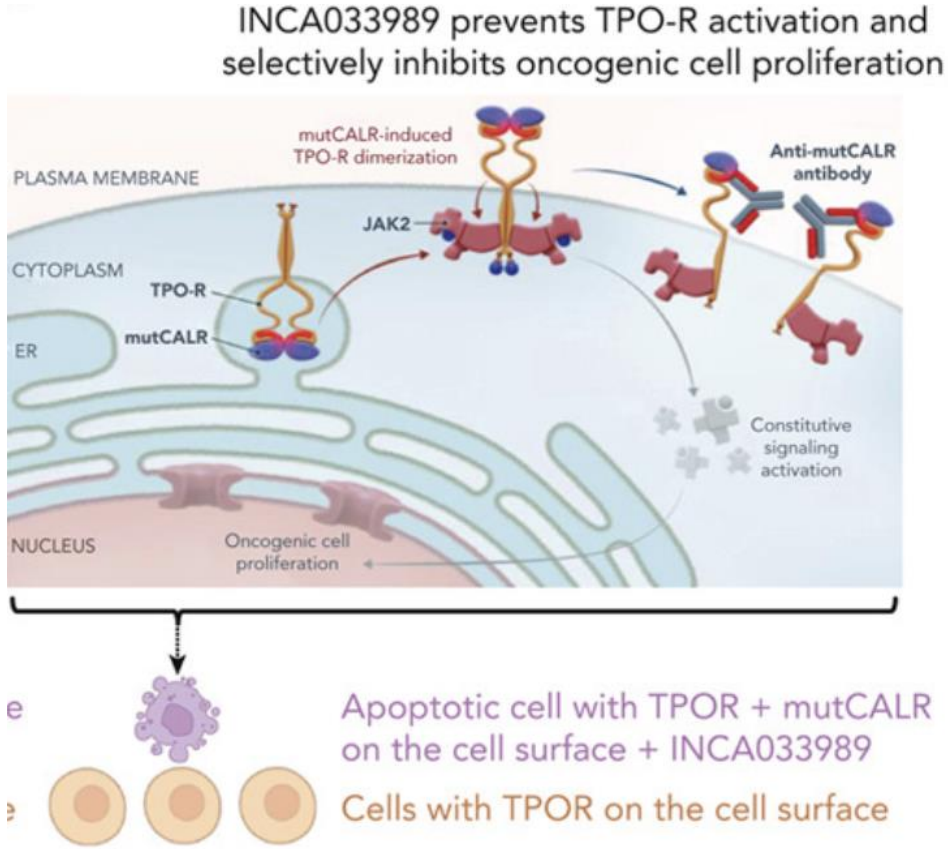
- Total number of megakaryocytes (MK) decreased
- Fraction of mutCALR⁺ MKs decreased
- Fraction of mutCALR negative MKs increased

*Best % change in total, mutCALR⁺, or mutCALR-neg MKs in hematologic responders with available data (n=8), dose range 24 mg-250 mg. †Undetectable mutCALR protein by IHC. Bone marrow biopsies stained for mutCALR using mutant-specific IHC. MKs quantified by semi-automated pathology scoring. CALR, calreticulin; IHC, immunohistochemistry; MK, megakaryocytes; mutCALR, mutations in calreticulin.

Slide courtesy of John Mascarenhas, MD.

Novel Agents in ET and PV





Martinez J, et al. *Expert Opin Pharmacother*. 2024;25(11):1439-1452. Reis ES, et al. *Blood*. 2024;144(22):2336-2348.

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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
- Clinical trials are ongoing for promising novel agents; pathways involved include hepcidin (rusfertide, divesiran), *LSD1i* (bomedemstat), and *CALR*-targeted mAb

MFS = metastasis-free survival; mAb = monoclonal antibody.

Thanks for Your Attention!

Q&A

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Please participate in our **polling** questions.

To participate: Scan QR code or Go to https://app.meet.ps/attendee/llm