
Lymphoma · Leukemia
& Myeloma Congress
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New York City
lymphomaandmyeloma.com

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Updates in Evolving Standards in PV and ET: Applying Next-Generation Diagnostics and Targeted Therapies

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Disclosures

- **Ghaith Abu-Zeinah, MD:** Consultant – Cogent, Incyte, PharmaEssentia; Silence Therapeutics, Takeda; speaker's bureau – AOP Orphan, PharmaEssentia, Sobi; research/grant support – PharmaEssentia, Pharma&; other material support – AOP Orphan, Incyte, PharmaEssentia, Sobi
- **Raajit Rampal, MD, PhD:** Consultant – Abbvie, Blueprint, Caltryx, Celgene/BMS, Cogent, Galecto, Incyte, Jubilant, Kartos, Karyopharm, Merck, Novartis/Morphosys, Opna, Pharmaessentia, Protagonist, Servier, Sierra Oncology/GSK, Silence Therapeutics, Sobi/CTI, Stemline, Sumitomo Dainippon, Takeda, Zentalis; research/grant support – Biomed Valley Discoveries, Incyte, Novartis, Ryvu, Stemline, Sumitomo Dainippon, Zentalis

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Learning Objectives

- Evaluate and integrate recent clinical trial data, evolving real-world evidence, and updated practice guidelines to improve accurate differentiation, molecular diagnosis, and risk-adapted management of ET and PV within the spectrum of MPNs
- Assess mechanisms of action, clinical utility, and comparative safety and efficacy of emerging targeted and disease-modifying therapies—such as interferon formulations, JAK inhibitors, hepcidin mimetics, and *CALR*-directed antibodies—to inform precision-based treatment strategies that prevent disease transformation and optimize long-term outcomes
- Implement multidisciplinary, patient-centered strategies that incorporate validated PROs and cardiovascular risk reduction frameworks to manage treatment-related adverse events, address symptom burden, and enhance QoL in patients with ET and PV

PV = polycythemia vera; EV = essential thrombocythemia; MPN = myeloproliferative neoplasm; JAK = Janus kinase; QoL = quality of life; PRO = patient-reported outcomes.

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Updates in Polycythemia Vera (PV)

Ghaith Abu-Zeinah, MD

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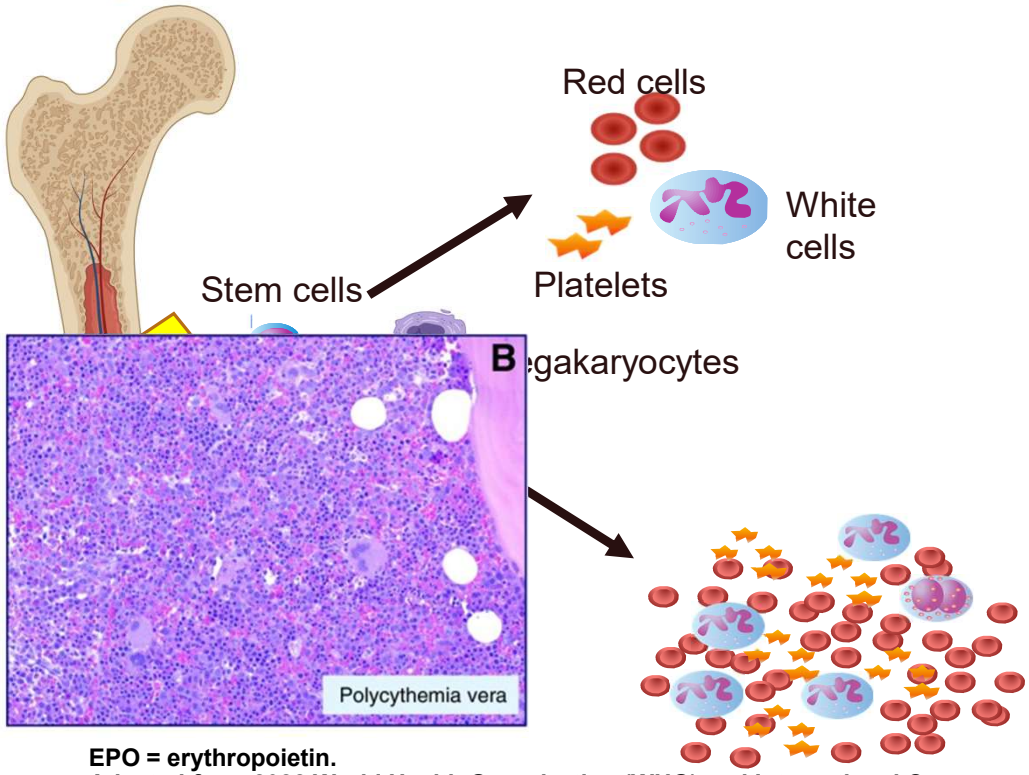
Agenda

- Review diagnosis standards, prognosis, and risk-adapted management of PV
- Review MOA, clinical utility, and comparative safety/ efficacy from trials/RWE of
  - Established therapies (interferon, JAKi, HU)
  - New/emerging therapies (hepcidin modulators, other)

MOA = mechanism of action; RWE = real world evidence.

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PV Is Characterized by *JAK2mut* Clonal Erythrocytosis + Panmyelosis



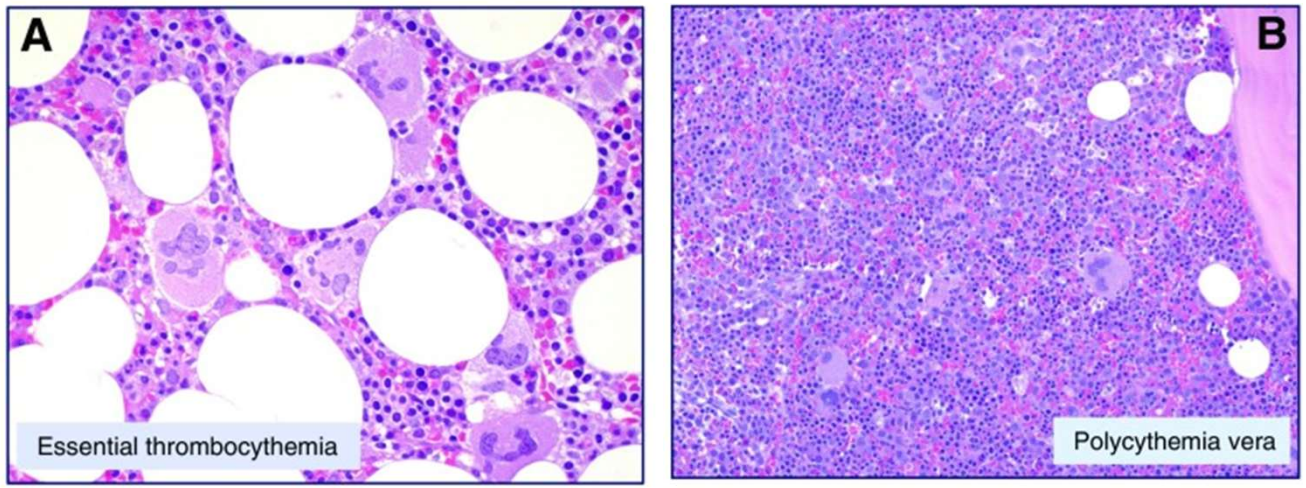
PV
Major criteria 1. **Hgb** >16.5 (M), >16 g/dL (F), OR **Hct** >49% (M), >48% (F), OR increased Red Cell Mass 2. **BMbx** ; hypercellularity for age with panmyelosis, and pleomorphic mature MgK 3. **JAK2V617F** or **JAK2 exon 12** mutations
Minor criterion Subnormal EPO
Diagnosis requires all **3 major** 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. Rumi E, Cazzola M. *Blood*. 2017;129(6):680-692.

Bone Marrow Biopsy Is Essential

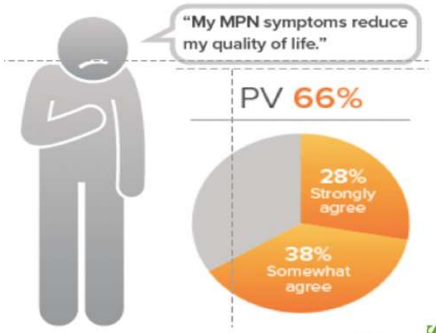


- *JAK2* MPN with borderline or lower H/H (*JAK2* ET vs early or masked PV)
- *JAK2* MPN with borderline or higher H/H (PV from *JAK2* ET or prefibrotic PMF with secondary erythrocytosis)

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

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Pts with PV Experience High Morbidity (Symptom Burden, Risks of Thrombosis, Progression)

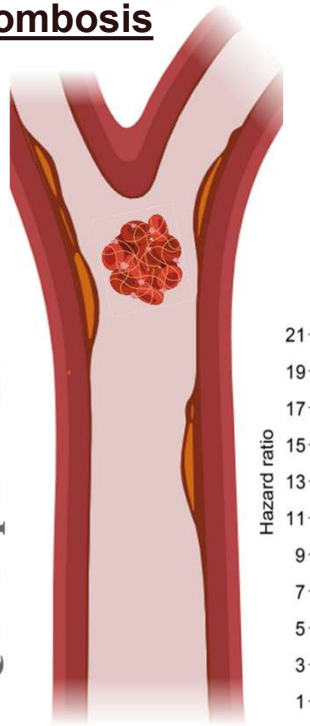


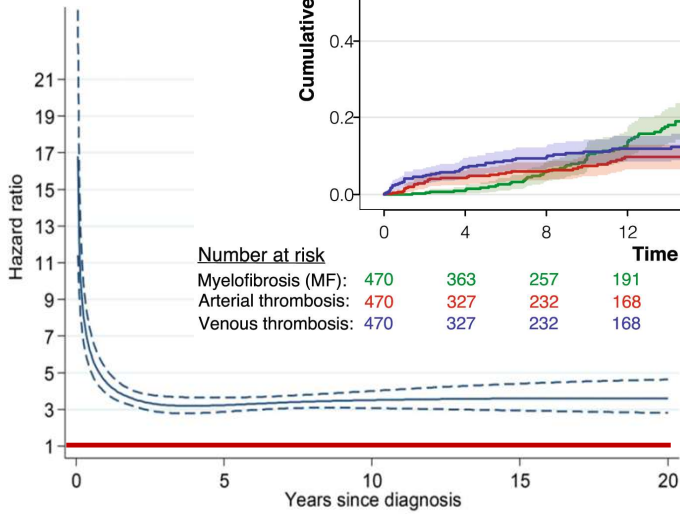




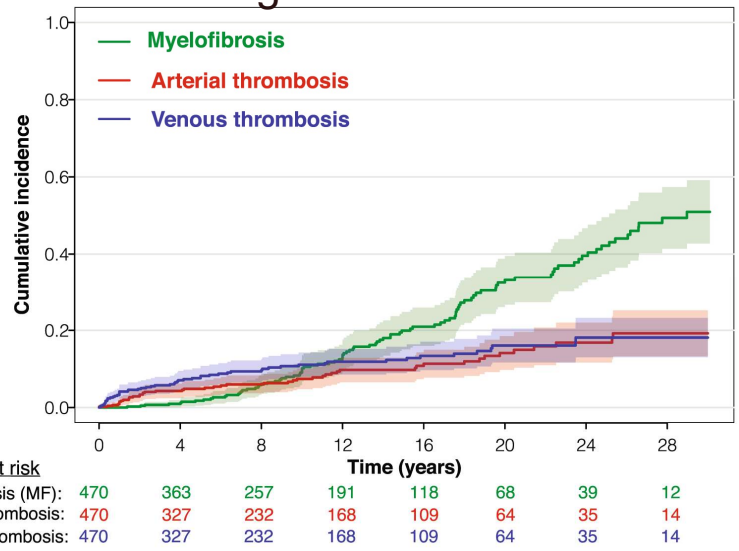


Thrombosis





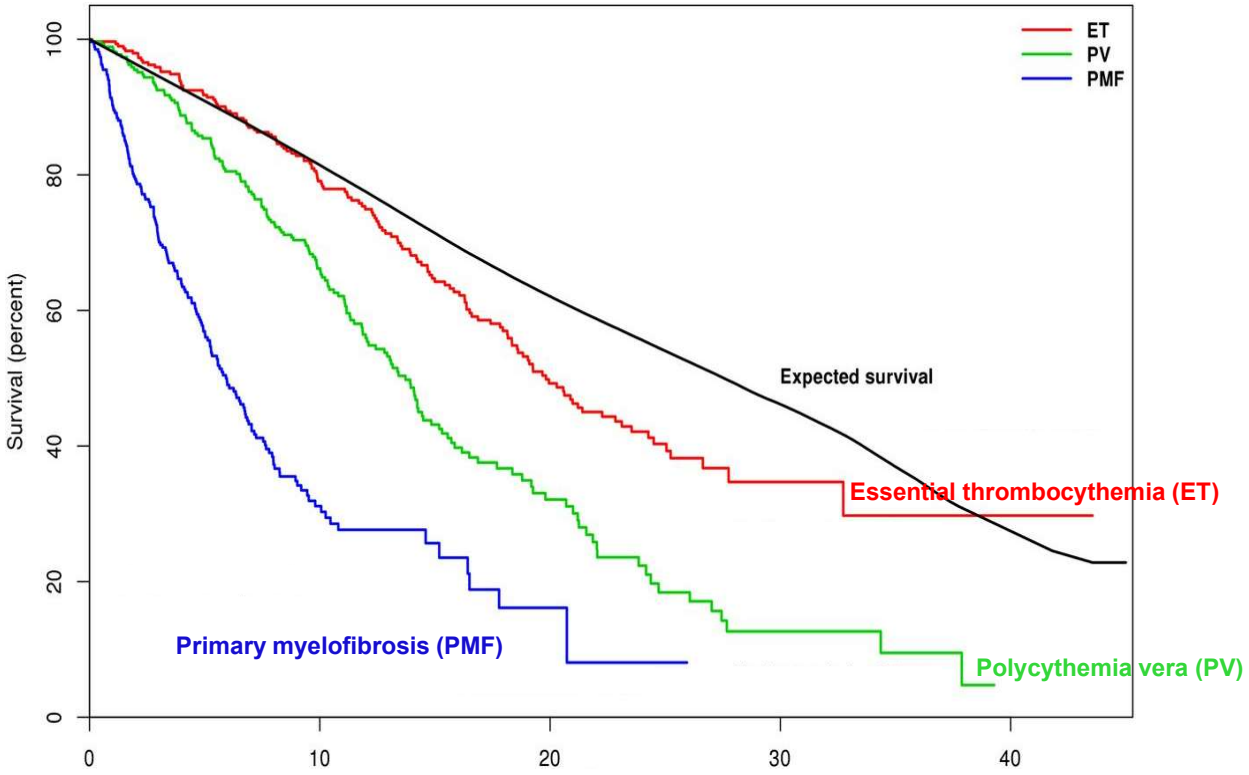
~50% progress to MF…a bigger threat long-term than thrombosis

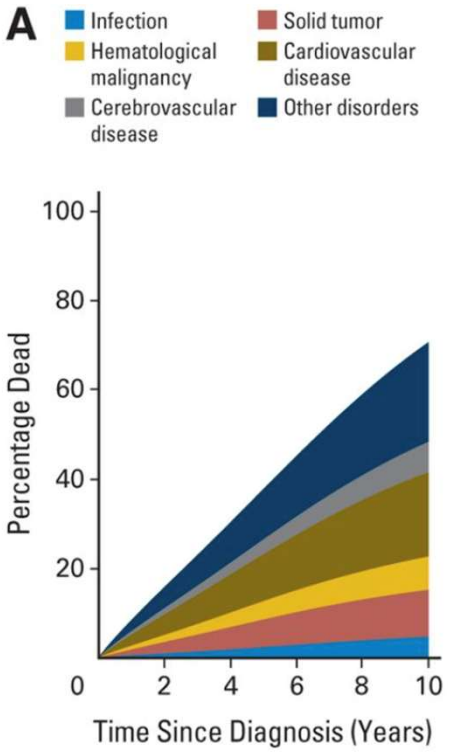


Scherber R, et al. *Blood*. 2011;118(2):401-408. Hultcrantz M, et al. *Ann Intern Med*. 2018;168(5):317-325. Abu-Zeinah G, et al. *Leukemia*. 2022;36(2):569-572. Figures adapted from Mesa RA, et al. *Cancer*. 2017;123(3):449-458. Lipsker D. *N Engl J Med*. 2010;363(15):1463.

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Pts with PV Have Shortened Survival





	PV
Infection	4.6 (3.5 to 5.8)
Solid tumor	10.5 (8.6 to 12.5)
Hematological malignancy	7.4 (5.4 to 9.5)
Cardiovascular disease	18.9 (16.5 to 21.3)
Cerebrovascular disease	6.9 (5.4 to 8.4)
Other disorders	22.3 (19.7 to 25.0)
Total	70.7

Tefferi A, et al. *Blood*. 2014;124(16):2507-2513. Hultcrantz M, et al. *J Clin Oncol*. 2015;33(20):2288-2295.

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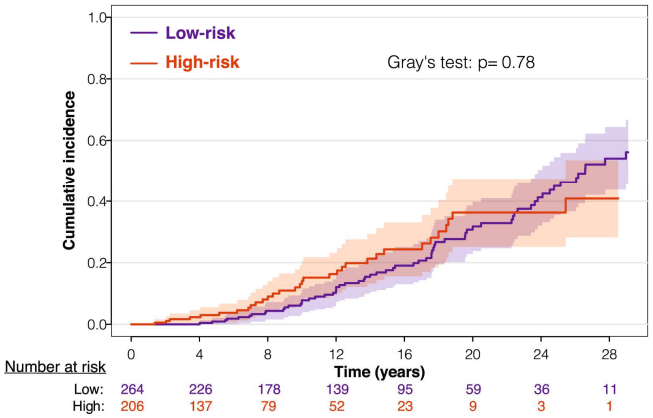
Prognosis: We Don't Have Good Risk-Stratification Models

ELN risk **Relevant for thrombosis only**

Risk Category	Criteria	~Thrombosis Risk
Low	Age ≤60, no prior thrombosis	~2% /yr
High	Age >60 **or** prior thrombosis	~5-6% /yr

Not relevant for progression risk, no progression model

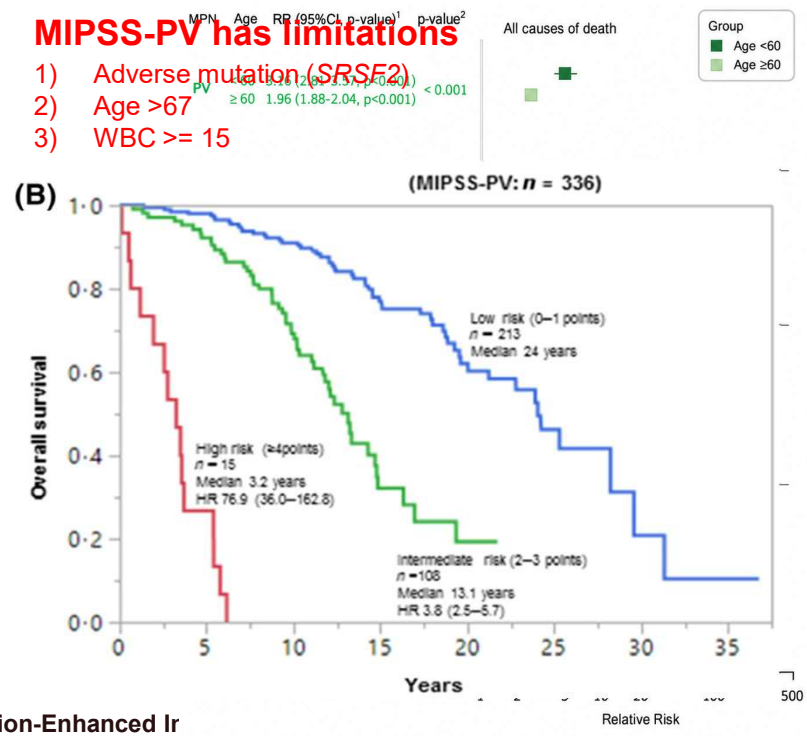
Cumulative incidence of MF progression in ELN low- and high-risk PV-WCM patients.



Age is only relative, disease duration is probably more relevant

MIPSS-PV has limitations

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

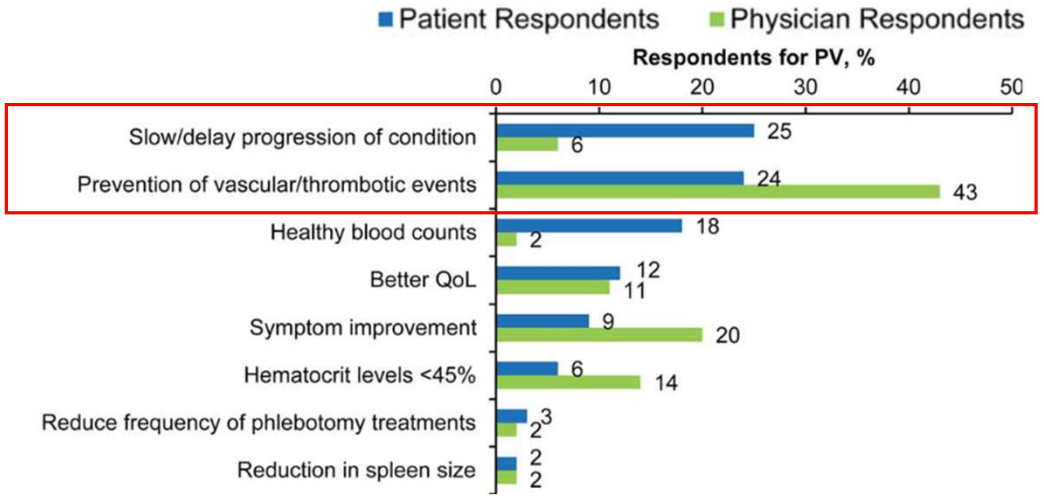


OS = overall survival; WBC = white blood cell; ELN = European LeukemiaNet; MIPSS PV = Mutation-Enhanced Ir

Landolfi R, et al. *N Engl J Med.* 2004;350(2):114-124. Abu-Zeinah G, et al. *Leukemia* 2022. Abu-Zeinah K, et al. *Leuk & Lymph.* 2023 64:3, 725-729. Tefferi A, et al. *Br J Haematol.* 2020;189(2):291-302.

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Current Risk-Adapted Treatment Goals and Future Direction



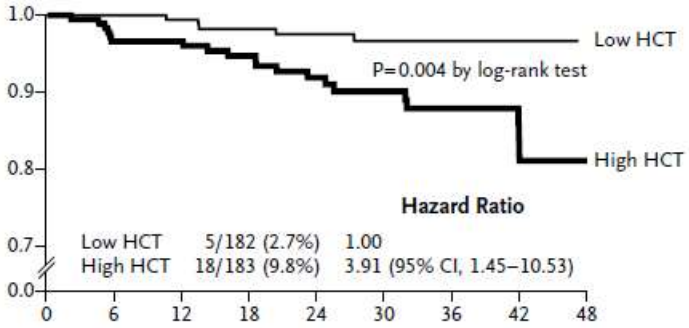
PERSPECTIVE OPEN

Check for updates

Defining and predicting disease progression in myeloproliferative neoplasms: a proposed biomarker-driven approach

Traditional treatment goals: Thrombosis risk reduction

- **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:** OR low-risk patients with symptoms, high phlebotomy requirements
- **HCT control < 45%.** ~4x risk of major thrombotic event or cardiovascular death compared to HCT 45-50



MI = myocardial infarction; PE = pulmonary embolism; DVT = deep vein thrombosis; CV = cardiovascular; HCT = hematopoietic cell transplantation.

Mesa RA, et al. *Cancer*. 2017;123(3):449-458. Rampal RK, et al. *Leukemia*. 2026. [Epub ahead of print.] PMID: 42680822. Barbui T, et al. *Leukemia*. 2018;32(5):1057-1069. Marchetti M, et al. *Lancet Haematol*. 2022;9(4):e301-e311.

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RWE of Non-Adherence to Standard Practice in PV

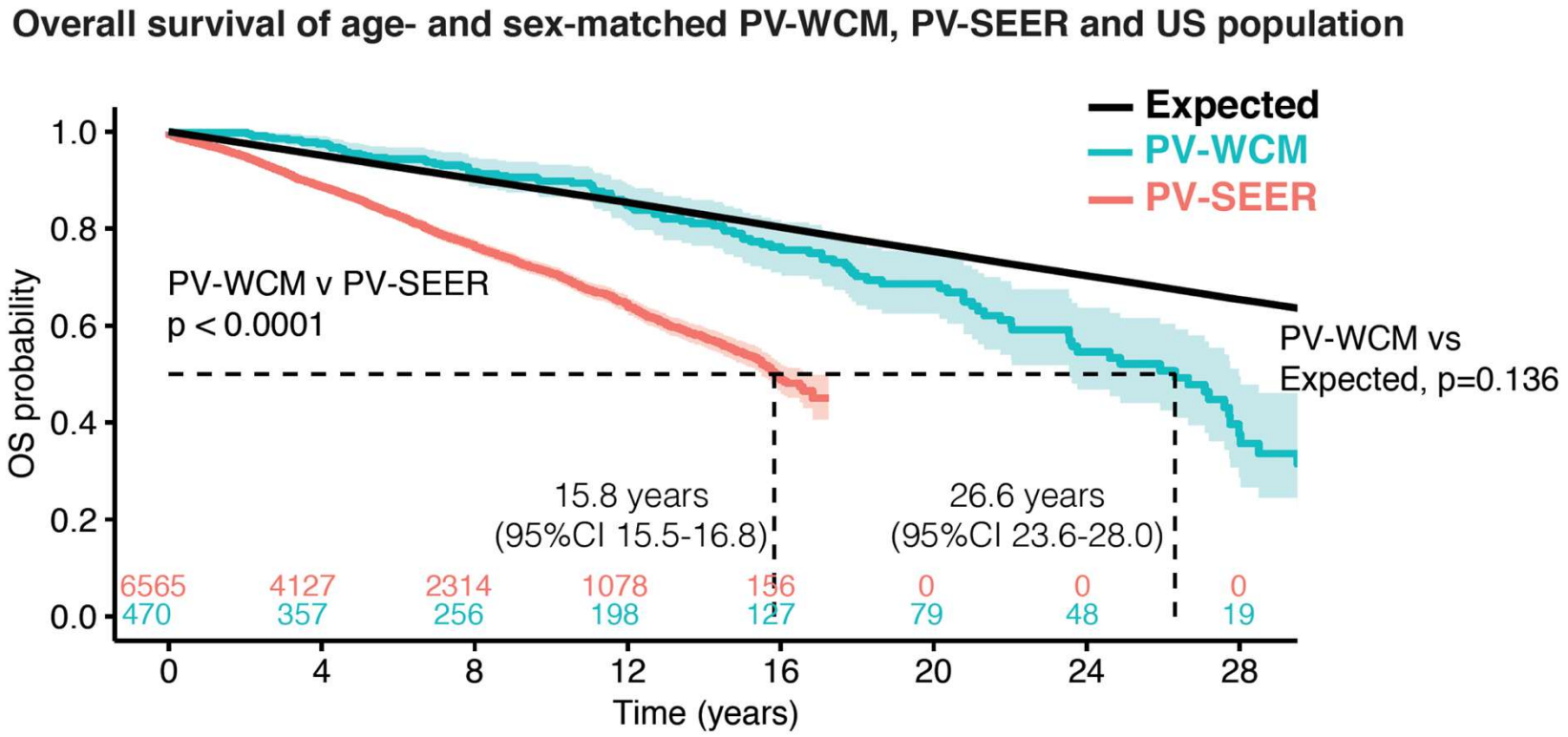
	Low-risk PV **N=503**	High-risk PV **N=1768**
Disease duration	3.2 y	4.3 y
Watchful waiting	25 (5.0%)	107 (6.1%)
PHL	273 (54%)	478 (27%)
HU	91 (18%)	654 (29%)
PHL + HU	79 (16%)	549 (24%)
Other **(IFN = 1.5%)**	45 (7.0%)	150 (9.1%)

- **REVEAL prospective observation study (2014-2016)**
  - ~33% of high-risk pts had no cytoreductive Rx
  - ~30-33% not on aspirin at time of enrollment
  - ~50% had HCT >45% at enrollment
  - ~1.5% only received IFN (preferred 1st line for younger pts)
- **RWE retrospective registry study (2016-2024)**
  - ~27% of high-risk pts had no cytoreductive Rx
  - <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

IFN = interferon; PHL = phlebotomy; HU = hydroxyurea; FDA = Food and Drug Administration,
Adapted from: Gerds AT, et al. *Blood*. 2024;143(16):1646-1655. Abu-Zeinah G, et al. *Blood Neoplasia*. 2025;2(4):100167.

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Optimizing Available Therapy May Improve Survival in PV



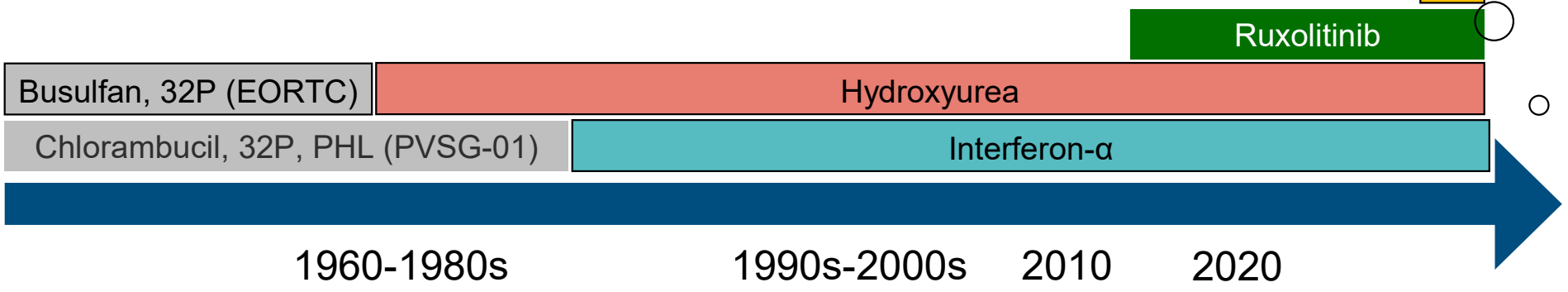
SEER = Surveillance, Epidemiology and End Results; WCM = Weill Cornell Medicine.
Abu-Zeinah G, et al. *Leukemia*. 2022;36(2):569-572.

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PV Drugs: Past, Present, and Future

- FDA approvals for PV
  - 2014: Ruxolitinib for PV 2nd line after HU failure
  - 2021: Ropeginterferon alfa-2b 1st line for PV
  - 2026: Rusfertide for PV erythrocytosis

Novel MOA/agents
- Hepcidin (divesiran, sapablursen, DISC-3405)
- LSD1i (bomedemstat)
- HDACi (givinostat)
- Next-gen *JAK* inhibitors



Drugs@FDA: FDA-Approved Drugs. Accessed Oct 5, 2026. https://www.accessdata.fda.gov/scripts/cder/daf/. FDA. Accessed Oct 5, 2026. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-its-kind-polycythemia-vera-rare-blood-disorder.

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First-Line CytoRx in High-Risk 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 or event-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.

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Decades of IFN in PV: Old Is Gold, Thanks to Silver

1988

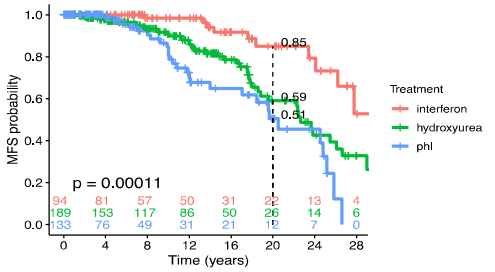


LETTERS TO THE EDITOR | VOLUME 332, ISSUE 8607, P403, AUGUST 13, 1988

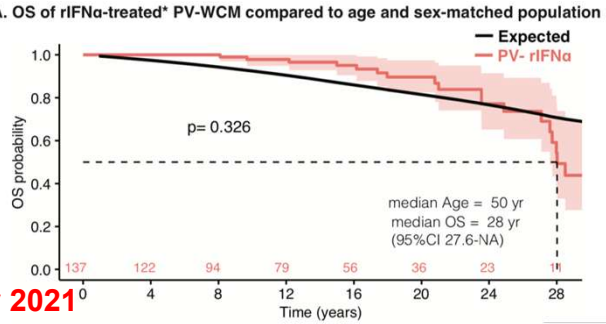
RECOMBINANT INTERFERON-ALPHA FOR TREATMENT OF POLYCYTHAEMIA VERA

RichardT. Silver

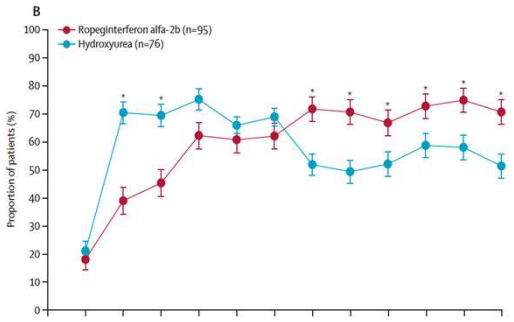
2019-2022



IFN improved MFS/OS



Ropeg v HU durable CR –

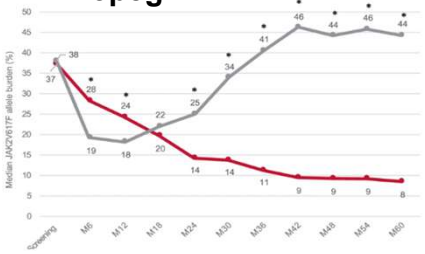


MPD-RC112: pegIFN v HU

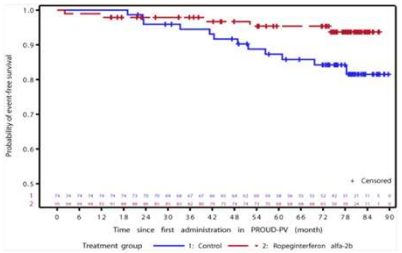
Low PV: Ropeg > PHL.

Ropeg FDA approved Nov 2021

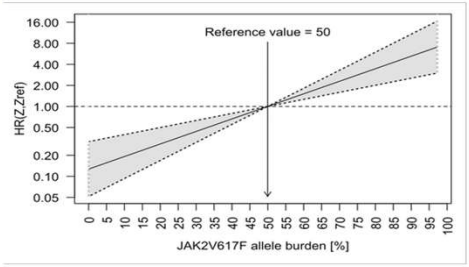
2023-2026



Ropeg deep MR



Ropeg improved EFS



Ropeg MR correlates w EFS

EFS = event-free survival.

Barbui T, et al. *NEJM Evid*. 2023;2(6):EVIDoa2200335. Gisslinger H, et al. *Lancet Haematol*. 2020;7(3):e196-e208. Abu-Zeinah G, et al. *Leukemia*. 2021;35(9):2592-2601. Mascarenhas J, et al. *Blood*. 2022;139(19):2931-2941. Kiladjian JJ, et al. *Leukemia*. 2022;36(5):1408-1411. Gisslinger H, et al. *Leukemia*. 2023;37(10):2129-2132. Kiladjian JJ, et al. *Hemasphere*. 2025;9(5):e70137.

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Ropeg Is Well Tolerated and May Improve QoL

PROUD/CONTI-PV adverse events: Ropeg vs HU

	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%)					
Alanine aminotransferase increased	16 (13%)					
Arthralgia	15 (12%)					
Hypertension	5 (4%)					
Nasopharyngitis	7 (6%)					
Nausea	4 (3%)					
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%)

Low-PV symptom burden: Ropeg 100 mcg q2wk vs PHL

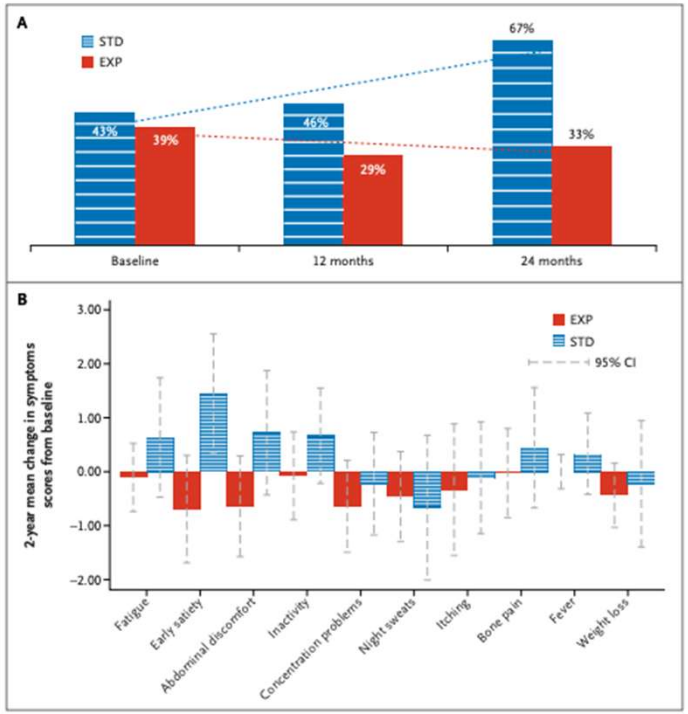


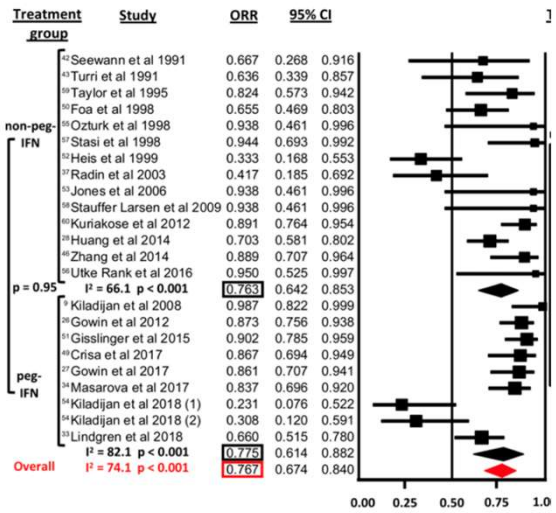
Figure 2. Change in Quality of Life over Time by Study Group.

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

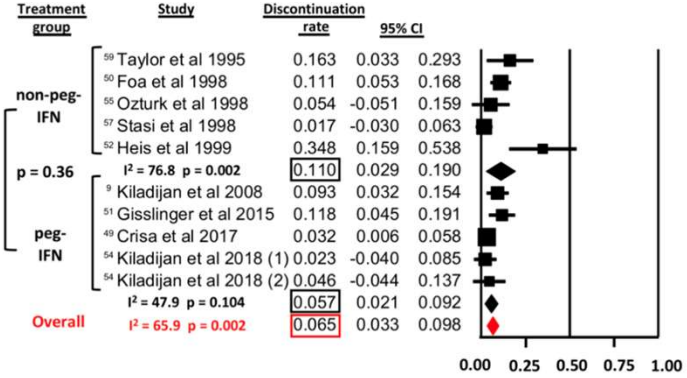
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rIFN -> pegIFN -> ropegIFN: What's Different?

Non-peg vs peg IFN (ORR)



(Discontinuation)



Peg vs ropeg IFN

Leuk Res. Author manuscript; available in PMC: 2026 May 1.

Published in final edited form as: Leuk Res. 2025 Sep 19;158:108110. doi: 10.1016/j.leukres.2025.108110

Low-dose ropeginterferon alfa-2b and peginterferon alfa-2a have comparable efficacy and tolerability in polycythemia vera

Neville Lee Jr [1], Katie Erdos [1], Aqib Abdul Rahman [2], Richard T Silver [1], Joseph M Scandura [1], Ghaith Abu Zeinah [1]

Annals of Hematology (2026) 105:302
https://doi.org/10.1007/s00277-026-07143-5

CORRESPONDENCE

Between the classic hit and the modern sequel: transition dosing between peginterferon alfa-2a and ropeginterferon alfa-2b for myeloproliferative neoplasms

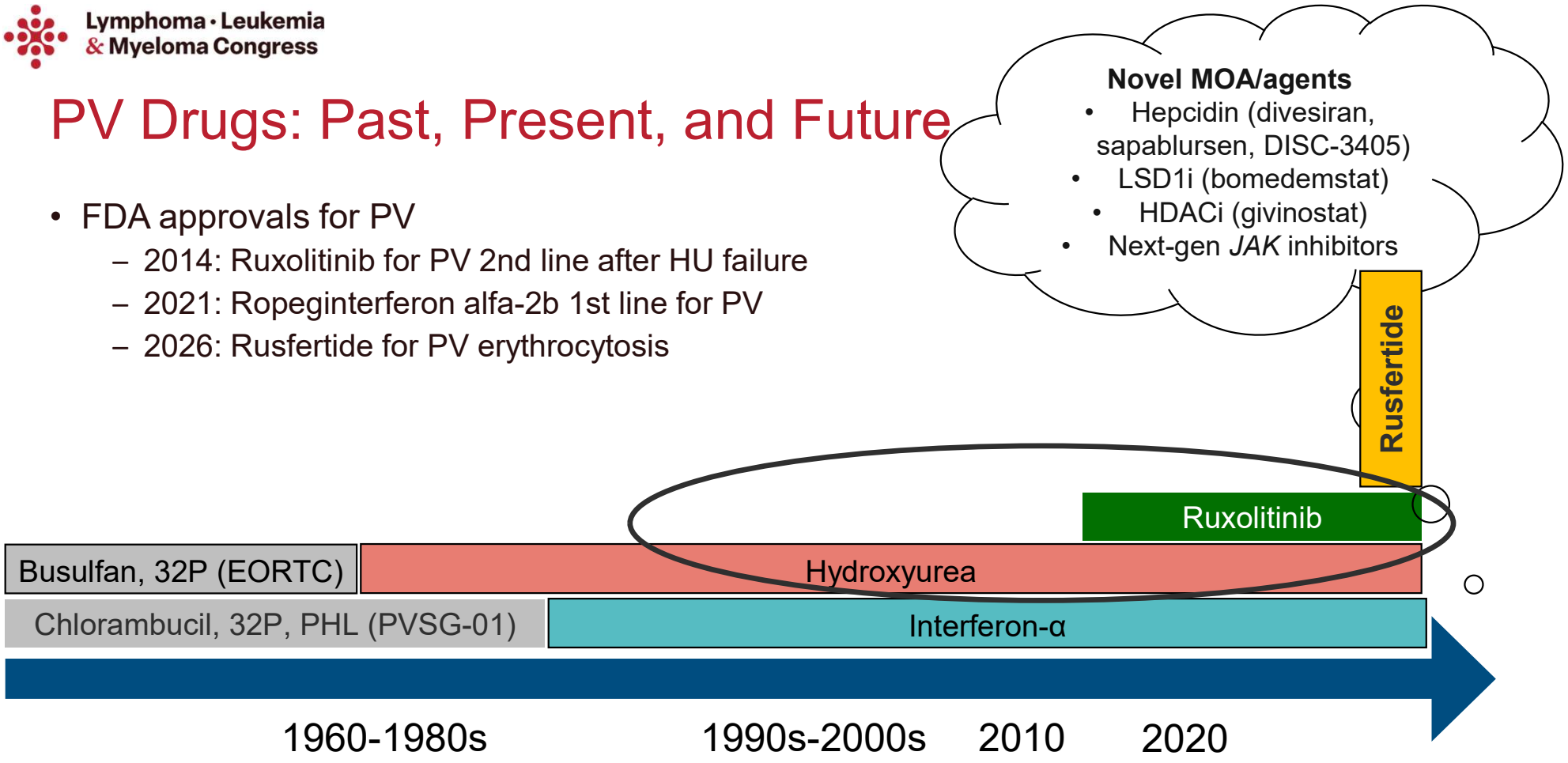
Ghaith Abu-Zeinah[1] · Gabriela Hobbs[2] · Brandi N. Reeves[3] · Abdulraheem Yacoub[4] · Joseph M. Scandura[1]

ORR = overall response rate.
Bewersdorf JP, et al. *Transplant Cell Ther*. 2021;27(12):997.e1-997.e11.

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PV Drugs: Past, Present, and Future

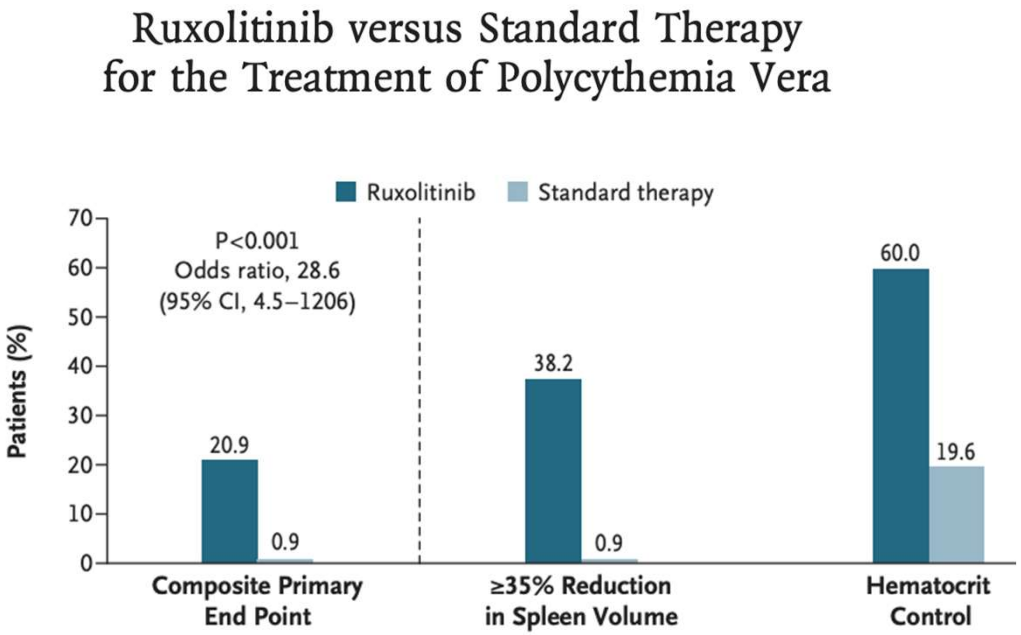
- FDA approvals for PV
  - 2014: Ruxolitinib for PV 2nd line after HU failure
  - 2021: Ropeginterferon alfa-2b 1st line for PV
  - 2026: Rusfertide for PV erythrocytosis

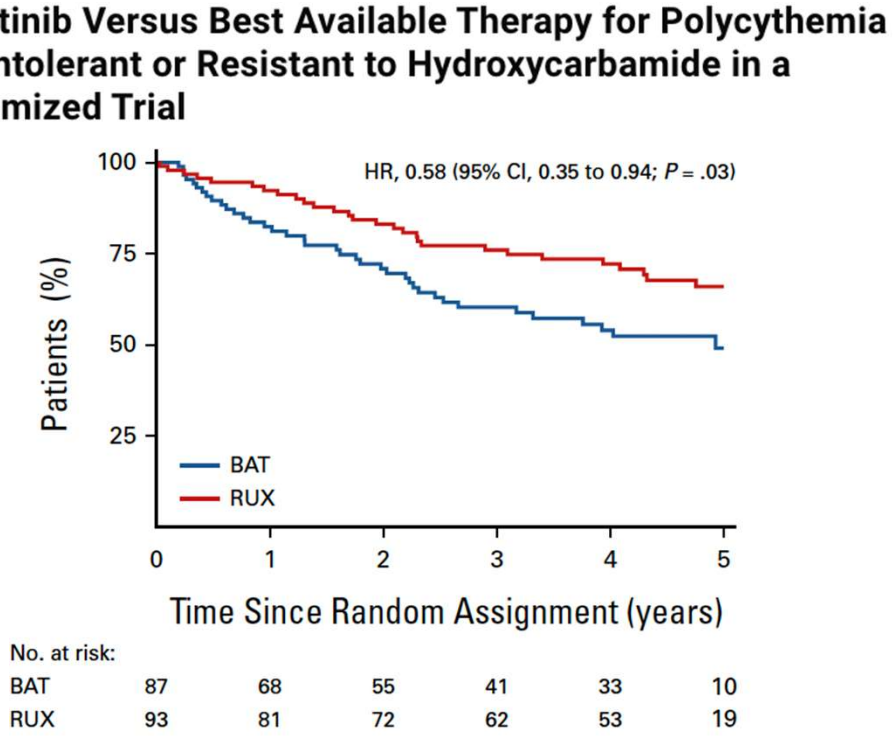


Drugs@FDA: FDA-Approved Drugs. Accessed Oct 5, 2026. https://www.accessdata.fda.gov/scripts/cder/daf/. FDA. Accessed Oct 5, 2026. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-its-kind-polycythemia-vera-rare-blood-disorder.

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2nd-Line Ruxolitinib > BAT: RESPONSE & MAJIC-PV Trials



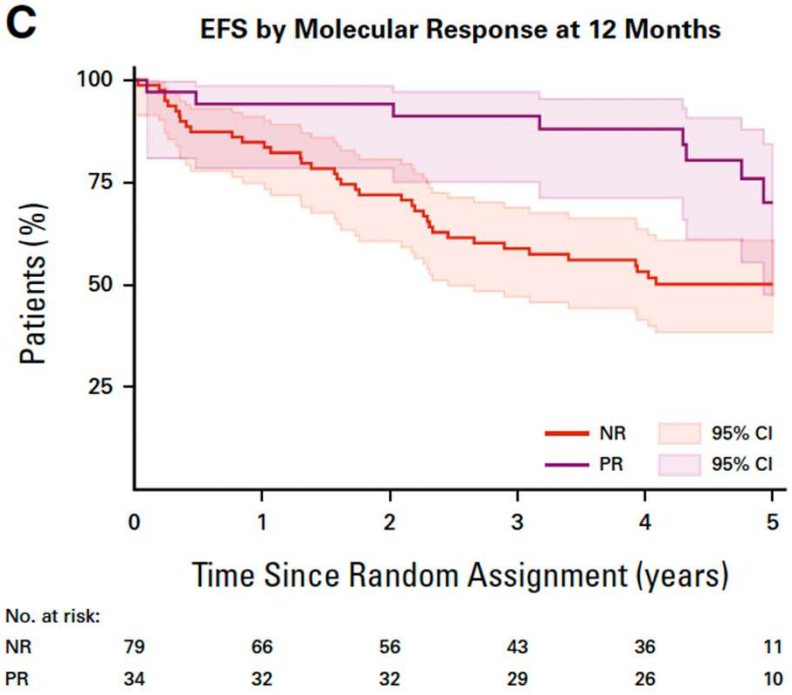


BAT = best available therapy.

Vannuchi AM, et al. *N Eng J Med*. 2015;372(5):426-435. Harrison CN, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

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Ruxolitinib Was Associated with Molecular Response and EFS in MAJIC-PV

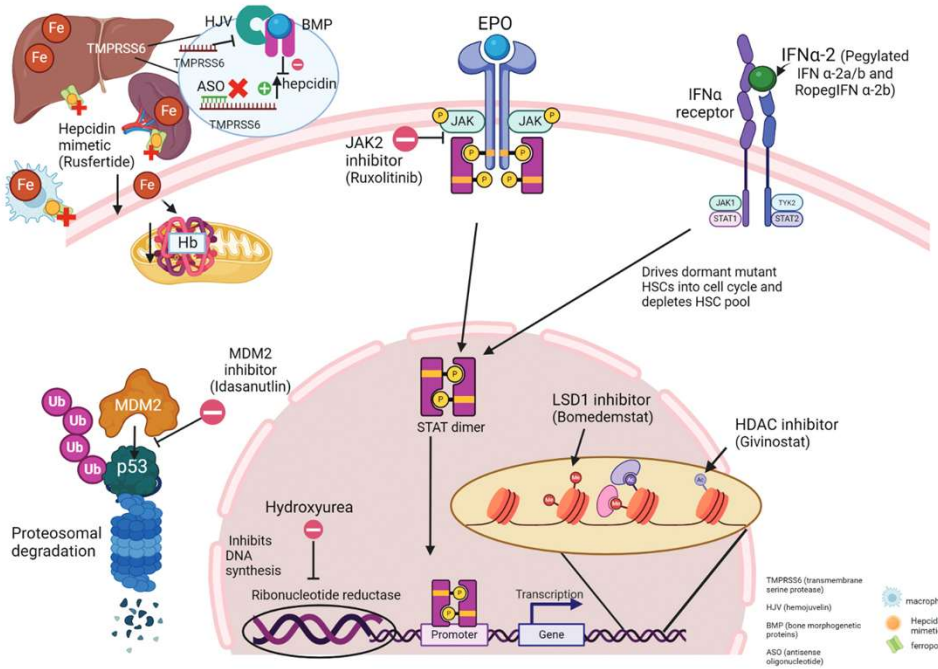


Outcome	Ruxolitinib			BAT		
	NR[a] (n = 31), Events, No. (%)	PR[b] (n = 39), Events, No. (%)	*P*	NR[a] (n = 43), Events, No. (%)	PR[b] (n = 14), Events, No. (%)	*P*
Thromboembolic event[c]	10 (32)	7 (18)	.17	18 (42)	3 (21)	.17
Hemorrhagic event[c]	9 (29)	4 (10)	.04	14 (33)	1 (7)	.06
Progression-free 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.
Harrison CN, et al. *J Clin Oncol*. 2023;41(19):3534-3544.

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PV Drugs: Past, Present, and Future



Novel MOA/agents

- Hepcidin (divesiran, sapablursen, DISC-3405)
- LSD1i (bomedemstat)
- HDACi (givinostat)
- Next-gen *JAK* inhibitors

failure

FDA NEWS RELEASE

FDA Approves First Drug of Its Kind for Polycythemia Vera, a Rare Blood Disorder

First-in-class therapy targets the biology driving red blood cell overproduction in polycythemia vera

For Immediate Release: August 28, 2026

Rusfertide

Ruxolitinib

Hydroxyurea

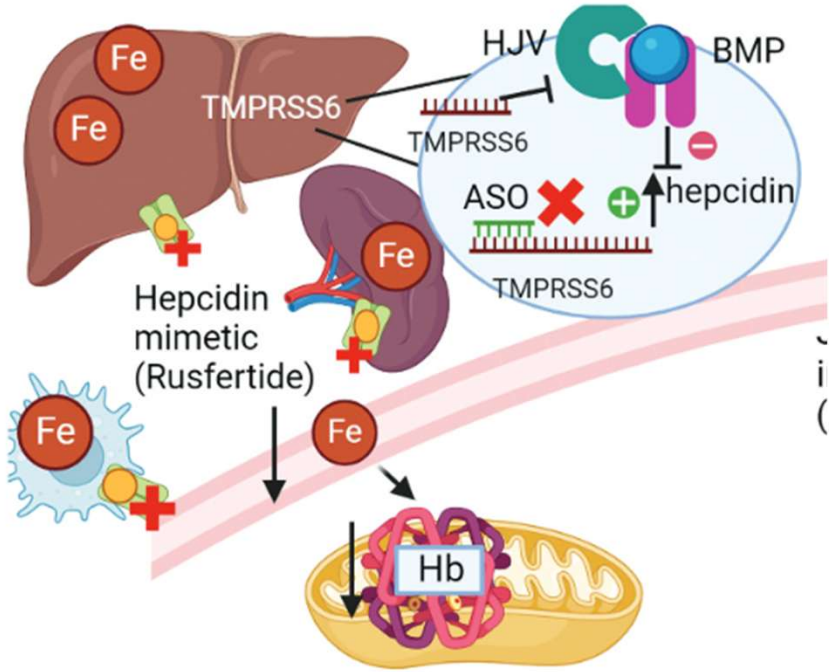
Interferon-α

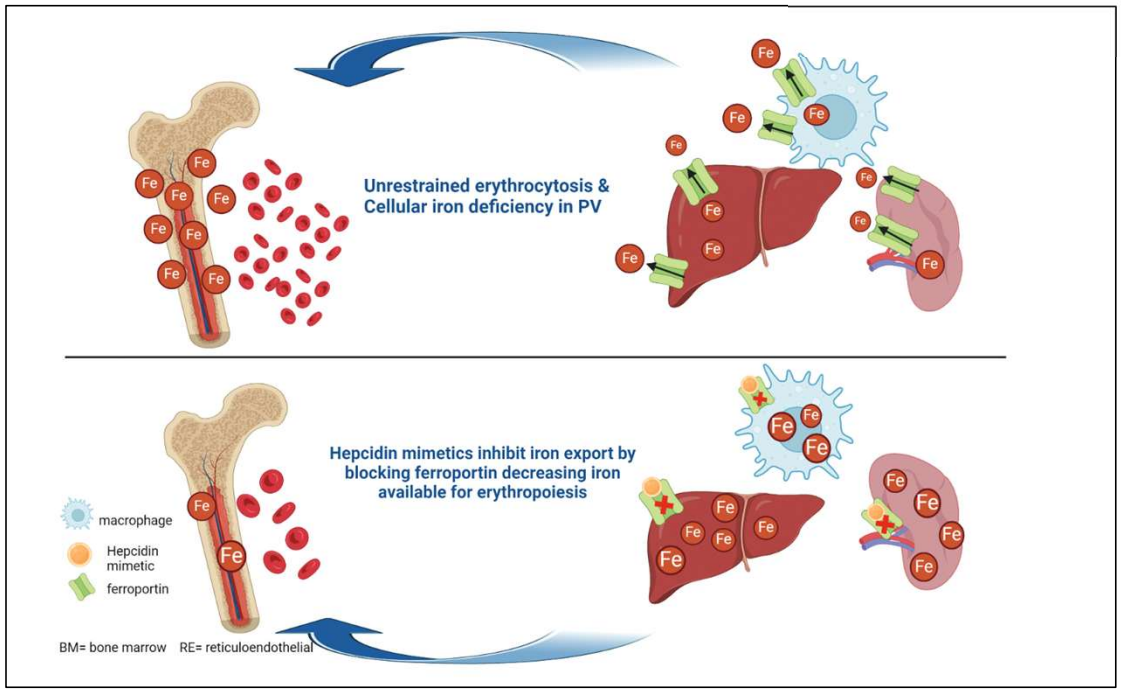
1960-1980s 1990s-2000s 2010 2020

Drugs@FDA: FDA-Approved Drugs. Accessed Oct 5, 2026. https://www.accessdata.fda.gov/scripts/cder/daf/. FDA. Accessed Oct 5, 2026. https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-its-kind-polycythemia-vera-rare-blood-disorder. Martinez J, et al. *Expert Opin Pharmacother*. 2024;25(11):1439-1452

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Rusfertide MOA, Other Hepcidin Modulators



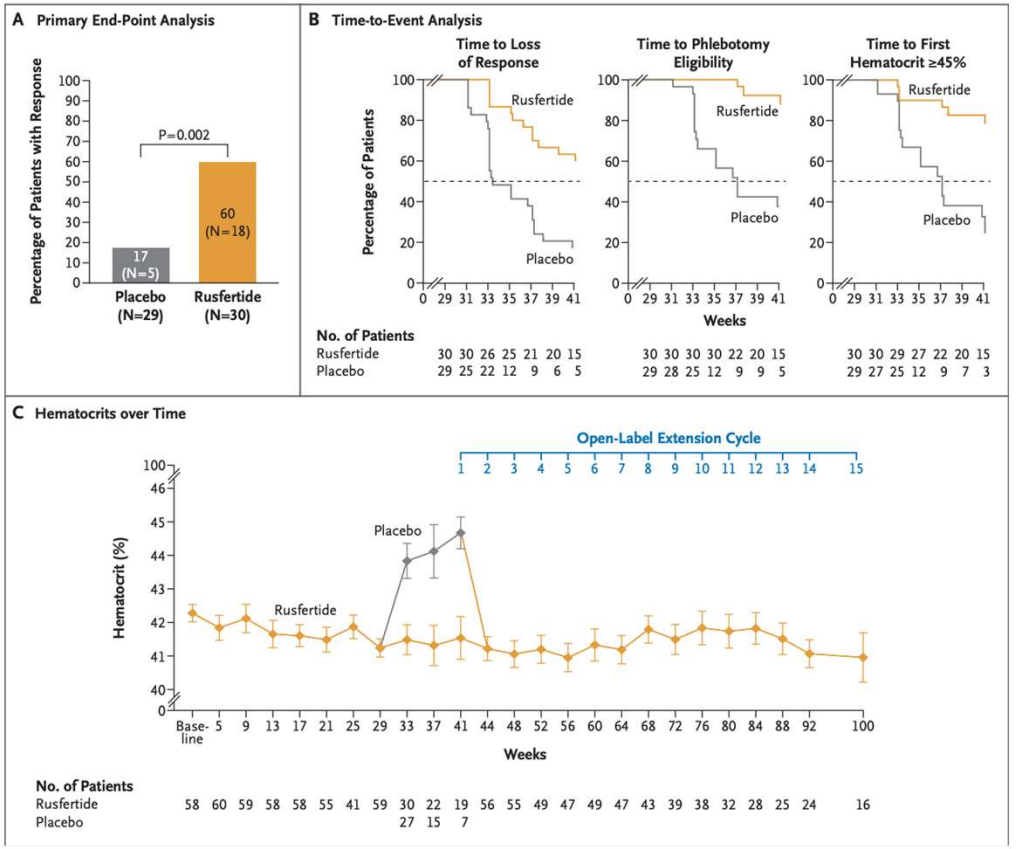


Martinez J, et al. *Expert Opin Pharmacother*. 2024;25(11):1439-1452.

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Rusfertide for HCT Control in REVIVE (Phase 2) Study

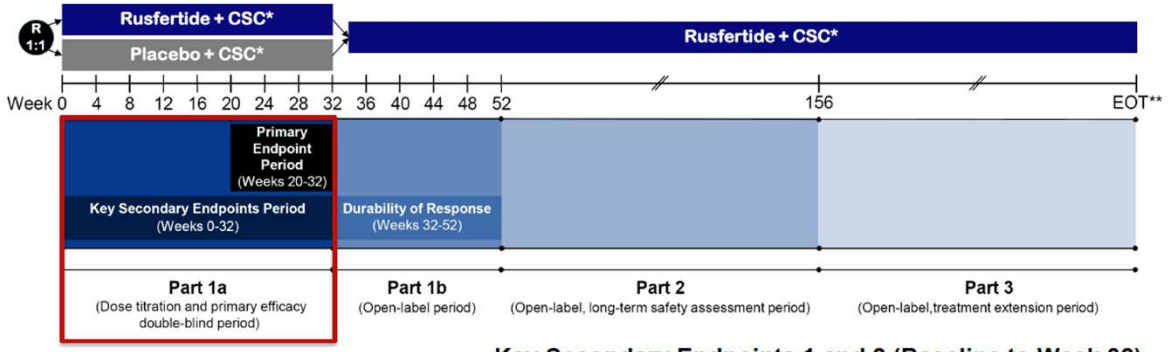
- Single-arm Phase 2 PV study with placebo-controlled randomized withdrawal phase, part 2 (59 patients)
- Both low/high-risk, with or w/o cytoRx allowed
- Phlebotomy dependent (3+ PHL ~29w)
- Primary endpoint = response during the randomized withdrawal period



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

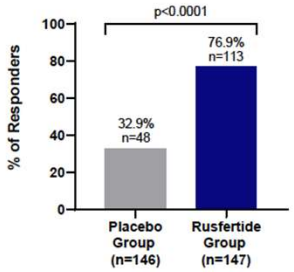
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Rusfertide in VERIFY Phase 3 Met Its Primary and 4 Secondary Endpoints



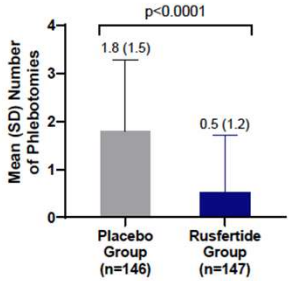
Primary Endpoint (Weeks 20-32)

More Responders With Rusfertide vs Placebo

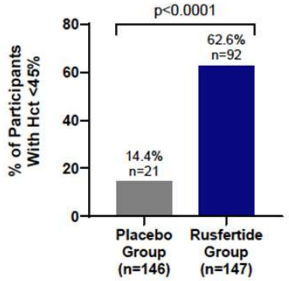


Key Secondary Endpoints 1 and 2 (Baseline to Week 32)

Fewer PHLs With Rusfertide vs Placebo

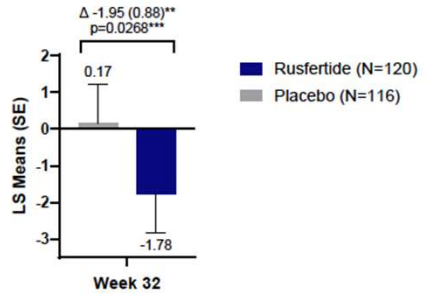


More Patients Maintained Hct <45% With Rusfertide vs. Placebo



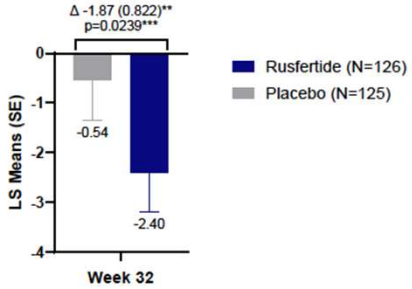
Improvement in PROMIS Fatigue SF-8a T-Score With Rusfertide vs Placebo

LS Means Difference at Week 32:



Improvement in MFSAF TSS7 With Rusfertide vs Placebo

LS Means Difference at Week 32:

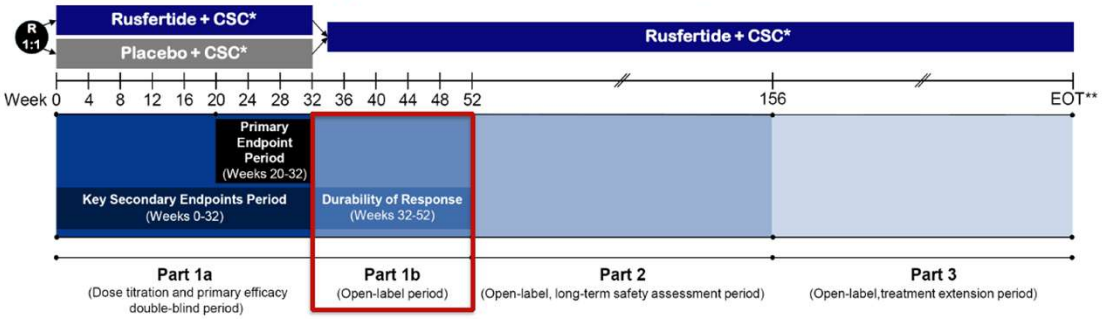


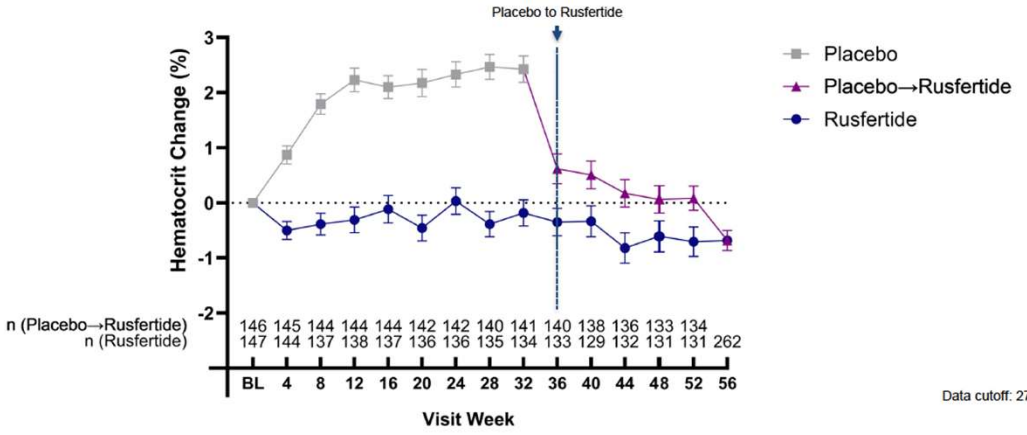
MFSAF TSS = Myelofibrosis Symptom Assessment Form Total Symptom Score; PROMIS = Patient-Reported Outcomes Measurement Information System.

Kuykendall A, et al. *J Clin Oncol*. 2025;43(17_suppl):LBA3. Kuykendall AT, et al. *Blood.* 2025;146(Suppl 1):81.

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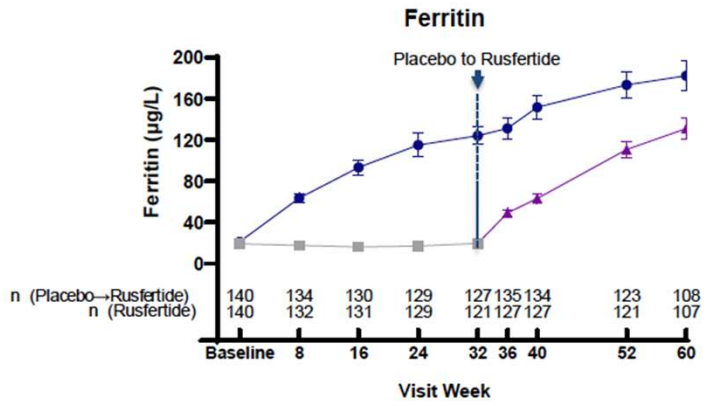
Rusfertide Led to Rapid, Durable HCT Control (VERIFY 1b) with Improved Iron, and a Favorable Safety Profile





Data cutoff: 27 May 2025

Most Frequent TEAEs (≥10% in either group), n (%)	Part 1a Baseline to Week 32 PBO Group (n=146)	Part 1a Baseline to Week 32 RUS Group (n=145)	Part 1b Weeks 32-52 PBO to RUS (n=140)	Part 1b Weeks 32-52 RUS to RUS (n=134)
Patients with at least 1 TEAE	126 (86.3)	131 (90.3)	107 (76.4)	101 (75.4)
Injection site reactions[a]	48 (32.9)	81 (55.9)	46 (32.9)	13 (9.7)
Fatigue	23 (15.8)	23 (15.9)	13 (9.3)	12 (9.0)
Anemia	6 (4.1)	22 (15.2)	14 (10.0)	15 (11.2)
Headache	18 (12.3)	16 (11.0)	4 (2.9)	5 (3.7)
COVID-19	16 (11.0)	14 (9.7)	3 (2.1)	4 (3.0)
Pruritus	15 (10.3)	15 (10.3)	3 (2.1)	5 (3.7)

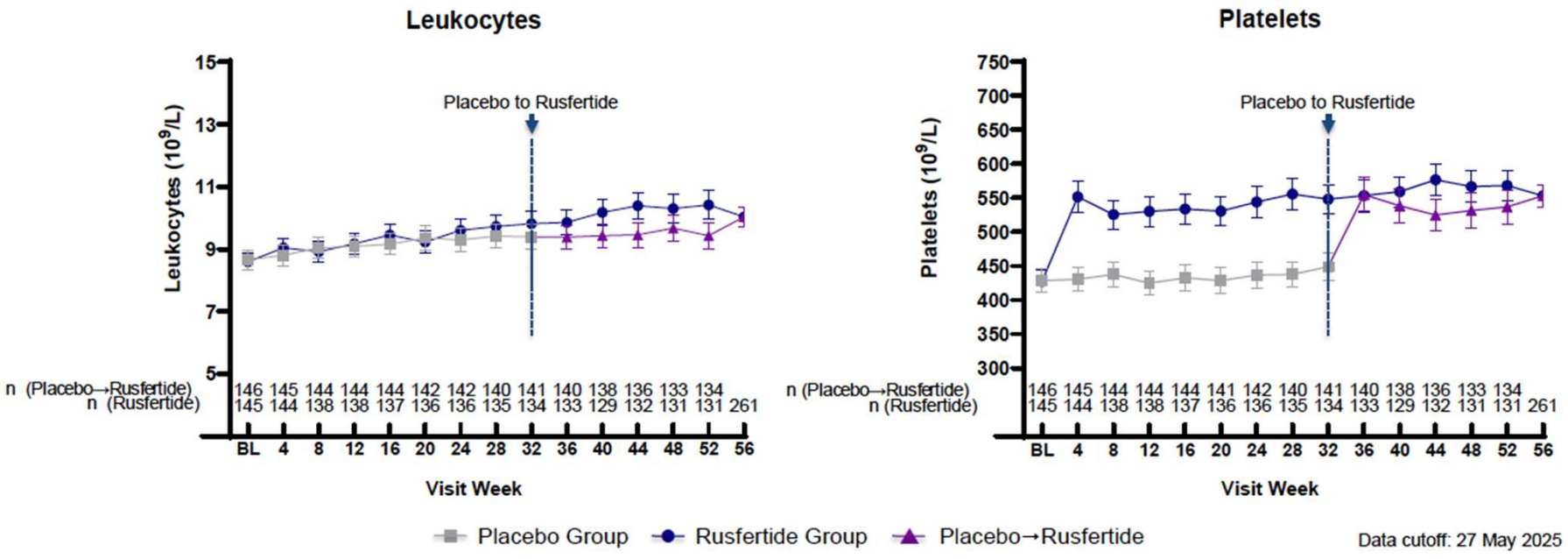


TEAE = treatment-emergent adverse event.

Kuykendall AT, et al. *Blood.* 2025;146(Suppl 1):81.

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Rusfertide (and Hepcidin Class) Do Not Leuko/Thrombo Reduce, and Initial Platelet Increase Is Observed

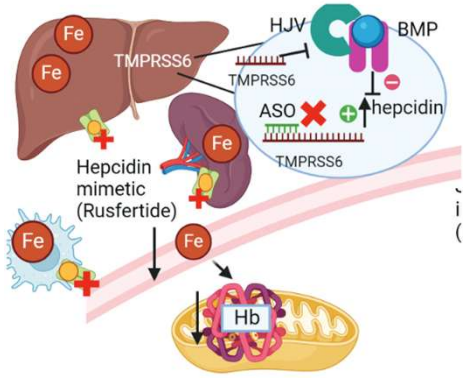


All values on the y-axis are mean ± standard error of measurement. Data are reported for the safety analysis set.
BL, baseline; n (Placebo→Rusfertide), number of patients treated with placebo from baseline to Week 32 followed by rusfertide (Weeks 32 to 52); n (rusfertide), number of patients who received rusfertide from baseline to week 32 and weeks 32 to 52.

Kuykendall AT, et al. *Blood.* 2025;146(Suppl 1):81.

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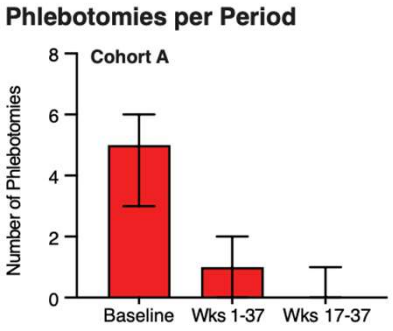
Sapablursen, Divesiran: Longer Acting Hepcidin Modulators in Development (TMPRSS6-Targeting Therapies)





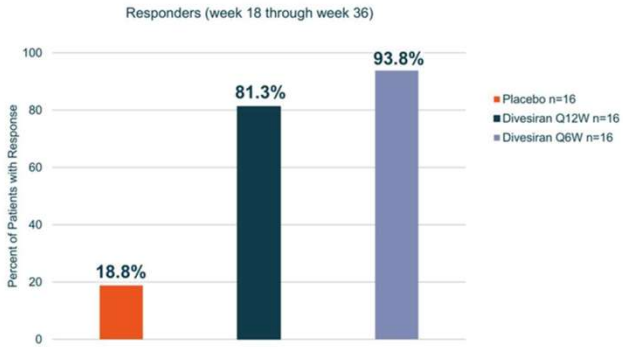
Sapablursen IMPRSSION ph2

1st endpoint: Reduction in phlebotomy frequency from baseline.



Divesiran SANRECO ph2:

1st endpoint: % who maintain HCT <45%



Martinez J, et al. *Expert Opin Pharmacother*. 2024;25(11):1439-1452. Palmer JM, et al. *Blood*. 2026:blood.2026033792. BusinessWire. Accessed Oct 5, 2026. https://shorturl.at/SDjGA.

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Key Learning Points



- Appropriate **PV diagnosis and stratification** is important to understand disease-related risks, prognosis and inform individualized treatment decisions. **Optimizing and implementing standard/ available therapy improves survival**
- **Interferon alfa** is disease-modifying and associated with clinical, molecular response and EFS in the first-line setting. Ruxolitinib in PV may also induce molecular response and EFS benefit in HU resistant/ intolerant patients
- **Rusfertide**, a recently approved hepcidin mimetic, and hepcidin modulators in development (sapablursen, divesiran) are highly efficacious in achieving HCT control and reducing phlebotomy requirements with tolerable safety profile

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Essential Thrombocythemia: Clinical Updates

Raajit Rampal, MD, PhD

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A 55 y/o Male with High-Risk ET

- Patient was diagnosed with *JAK2*V617F mutant ET 2 years ago. Presented with LLE DVT and PE
- Other medical diagnoses: Hypertension, dyslipidemia
- Patient was initially started on ASA and hydroxyurea
- Ongoing symptoms: Fatigue and headaches
- Since starting hydrea, no substantial improvement in symptoms
- He has learned to live with his fatigue and headaches, but it troubles him

- What are the treatment goals for this patient?
- What are the options to address this patients needs?

LLE = left lower extremity; ASA = aminosalicylic acid.

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Clinical Characteristics of ET

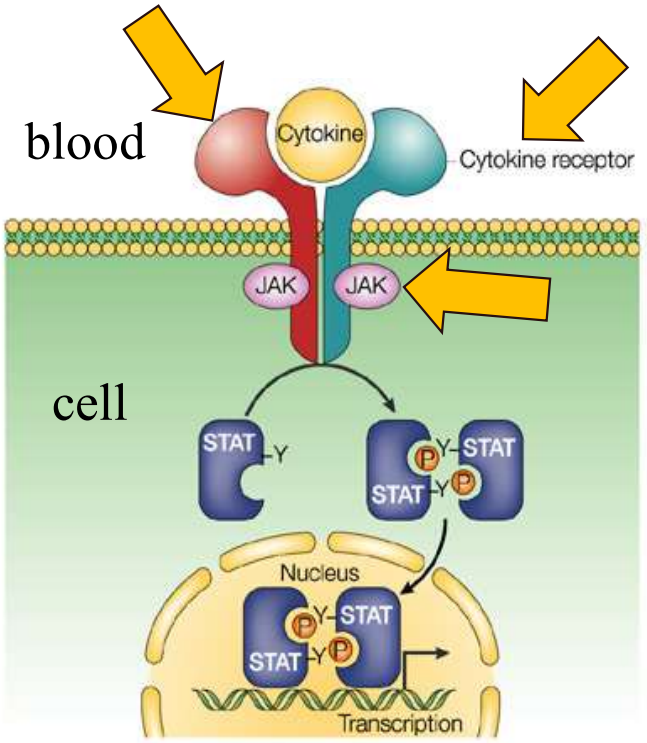
- Symptoms are variable and may be due to
  - Microvascular complications (eg. headache, dizziness, paresthesia, erythromelalgia, blurred vision)
  - Constitutional symptoms (eg. fatigue, night sweats, itching [pruritus], weight loss)
  - Splenomegaly and associated symptoms
- Cardiovascular complications
  - Bleeding
- Sequelae
  - 15-year leukemia risk=2%
  - 15-year myelofibrosis risk=4%
  - 15-year thrombosis risk=17%

Vardiman JW, et al. *Blood*. 2009;114:937-951. Vannucchi AM, et al. *CA Cancer J Clin*. 2009;59:171-191. Gowin K, Mesa R. *F1000Res*. 2014;3:227-237. Passamonti F, et al. *Am J Med*. 2004;117(10):755-61.

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Activation of *JAK/STAT* Signaling Plays a Central Role in MPN Pathogenesis

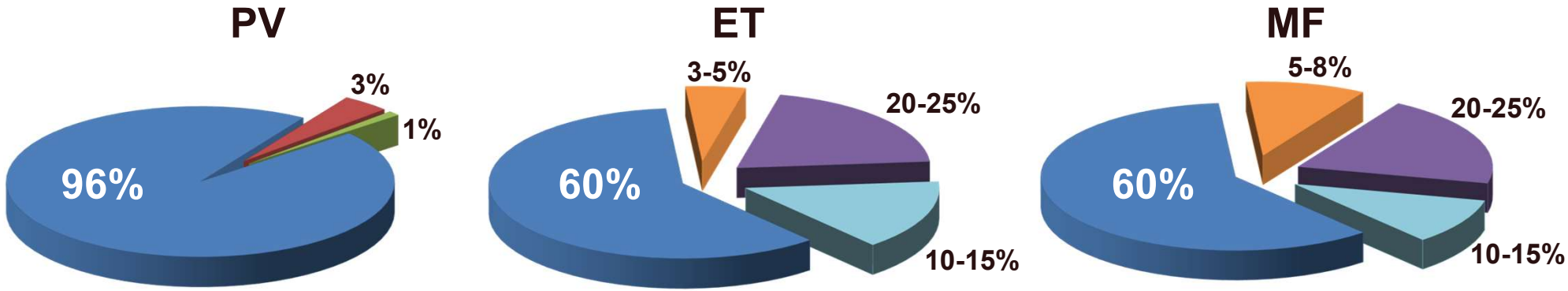
- A well characterized signaling pathway involved in normal hematopoiesis, inflammation, and immune function
- Four members of JAK family
  - *JAK1, JAK2, JAK3*, and *Tyk2*
- *JAK2* **specifically** mediates cytokine signaling for red blood cells and platelets (its inhibition causes anemia and low platelets)
- JAK-STAT is hyperactive in MPN due to different mutations
- (*JAK2, MPL, CALR*)



Shuai K, Liu B. *Nat Rev Immunol.* 2003;3(11):900-911.

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Phenotypic Driver Mutations (Activate JAK-STAT Pathway) in MPNs



- *JAK2* V617F
- *JAK2* Exon12
- Others (*SH2B3*)
- *MPL* (W515x)
- *CALR* mut
  - Type1/Type1-like
  - Type2/Type2-like
- Unknown (Triple Negative)

***CALR*-mutated ET is generally associated with lower thrombotic risk but greater risk of progression to myelofibrosis than JAK2-mutated ET**

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WHO Criteria for ET and Prefibrotic Primary Myelofibrosis

	ET	prePMF
Major Criteria	• **PLT ≥ 450 × 10^9/L** • **BM biopsy** with predominent proliferation of megakaryocytes (normocellular), **fibrosis grade 0-1** • Not meeting WHO criteria for other MPN subtype or MDS, or other • ***JAK2, CALR,* or *MPL* mutation**	• **BM biopsy** with megakaryocytic proliferation and atypia, (hypercellular) **fibrosis grade 0-1** • Not meeting WHO criteria for other MPN subtype or MDS, or other • ***JAK2, CALR,* or *MPL* mutation** or presence of other clonal markers[a] or absence of reactive myelofibrosis[b]
Minor Criteria	• Presence of a clonal marker or absence of evidence for reactive thrombocytosis	**At least one of the following**: a. Anemia b. Leukocytosis >11 x 10^9/L c. Splenomegaly d. LDH increase above ULN
Diagnosis	All four major criteria or the first three major criteria and one minor criterion	All three major criteria, and one minor criterion

[a]In the absence of any of the 3 major clonal mutations, the search for the most frequent accompanying mutations (*ASXL1, EZH2, TET2, IDH1/IDH2, SRSF2, SF3B1*) is of help in determining the clonal nature of the disease; [b]Bone marrow fibrosis secondary to infection, autoimmune disorder or other chronic inflammatory condition, hairy cell leukemia or other lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.
WHO = World Health Organization; BM = bone marrow; PLT = platelet.
Arber DA, et al. *Blood.* 2016;127:2391-2405. Swerdlow SH, et al. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Fourth edition, volume 2. IARC Publications; 2017.

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Therapeutic Goals in ET

- **Goals of therapy**
  - Decrease risk of thrombotic events
  - Reduce symptoms burden
  - Ideally, reduce risk of disease progression

- **Therapeutic modalities**
  - Cytoreductive therapies
  - Antithrombotic modalities: Aspirin, lifestyle modification

Yoon SY, et al. *Blood Res.* 2023;58(Suppl 1):S83-S89.

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ET: Traditional Thrombosis Risk Stratification

Category	Characteristics	Therapy
Low risk	Age < 60 years and no history of thrombosis	Aspirin
High risk	Age ≥ 60 years or history of thrombosis	Aspirin and cytoreductive agent: 1. Hydroxyurea 2. Anagrelide (AG) 3. Interferon

Additional cardiovascular risk factors to consider

- Congestive heart failure
- Smoking
- Hyperlipidemia
- Diabetes mellitus
- Obesity

Platelet number is not a risk factor for thrombosis!!!

Extreme thrombocytosis (PLT count > 1,500 x109/L) is associated with increased risk of bleeding (acquired vW factor deficiency)

Barbui T, et al. *J Clin Oncol*. 2011;29:761-770.

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ET: Revised IPSET-Thrombosis Prognostic Score

	Risk Factors
	Age ≥60 years
	Previous thrombosis
	JAK2V617F mutation positive
	Risk Categories
"OLD" low risk	Very low-risk: No risk factors ---------- NO aspirin?
	Low-risk: *JAK2V617F only* ---------- aspirin
"OLD" high risk	**Intermediate-risk: Age ≥60 years only ---------- aspirin, NO cytoreduction**
	High-risk: Previous thrombosis OR ≥60 years and *JAK2V617F* ---------- aspirin and cytoreduction

Platelet number is not a risk factor for thrombosis!!!

IPSET = International Prognostic Score of thrombosis in Essential Thrombocythemia.
Barbui T, et al. *Blood Cancer.* 2015;5:e369. Haider M, et al. *Am J Hematol.* 2016;91(4):390-394.

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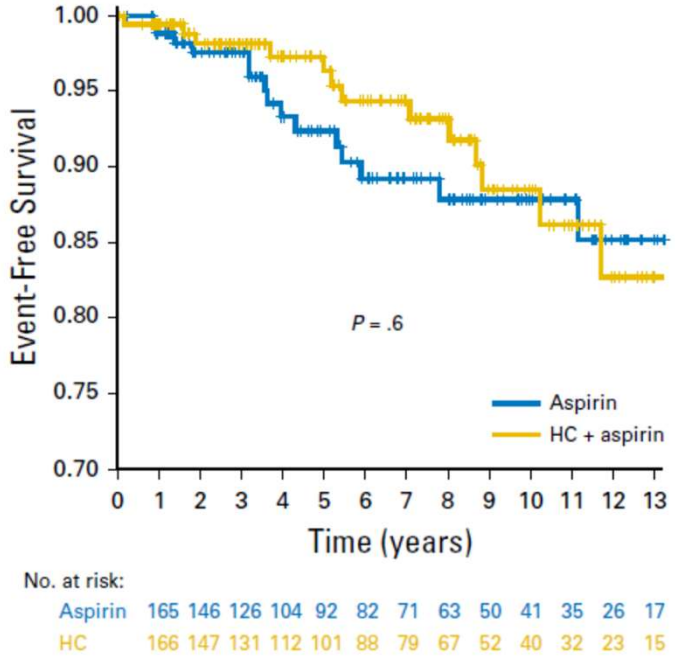
Agent	Comment
Hydroxyurea	Utilized in clinical practice
Anagrelide	FDA approved
Peginterferon-alpha-2a	Utilized in clinical practice
Ropeginterferon-alpha-2b	FDA approved 2026
Ruxolitinib	Studied in Phase II trials; not FDA approved
Busulfan	Sometimes used in refractory cases

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HU + Aspirin vs Aspirin Alone in Patients with ET Age 40 to 59 Years without High-Risk Features

- Preemptive addition of HU to aspirin did not reduce the risk of vascular events, myelofibrotic progression, or leukemic transformation in this patient subset
- Patients age 40 to 59 years without other indications for treatment (ie. previous thrombosis or hemorrhage) and platelet count <1,500 x 109/L should not receive cytoreductive therapy

Composite end point: Any major disease-related complication (arterial thrombosis, venous thromboembolism, major hemorrhage, transformation to AML, MDS, MF, or death from any of these causes.



AML = acute myeloid leukemia; MF = myelofibrosis.
Godfrey AL, et al. *J Clin Oncol.* 2018;36:3361-3369.

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Current Considerations in the Management of ET

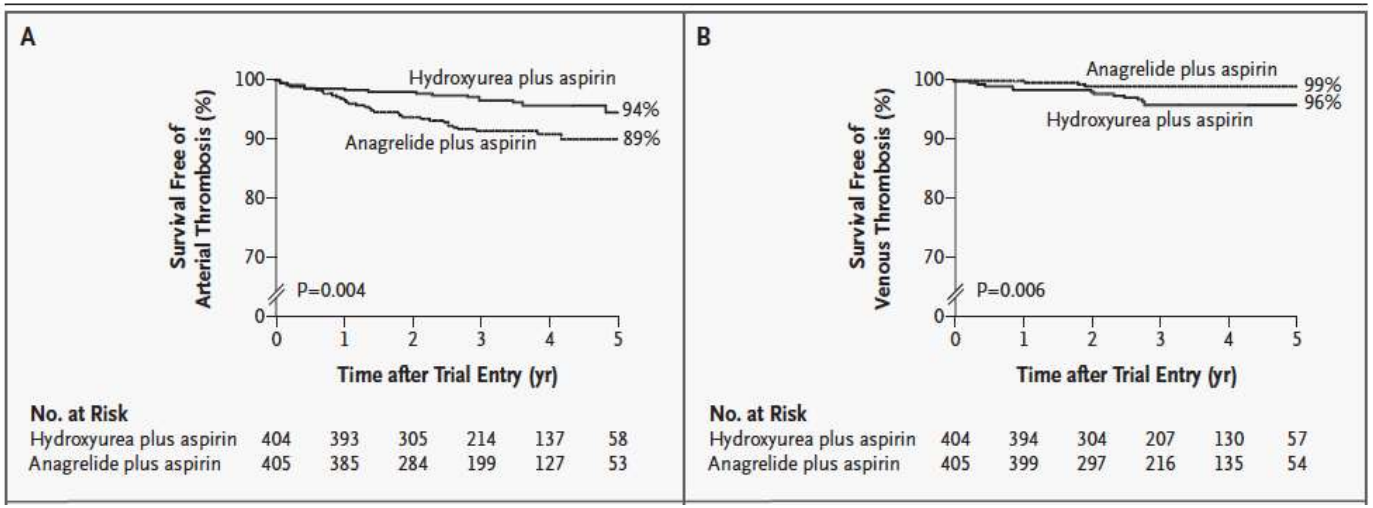


Table 4. ET-related events after long-term observation

	Anagrelide group (n=122)	Hydroxyurea group (n=131)	*P* value
A) Major events (total)	No. of events	No. of events	.86
	14	16	
Major arterial thrombosis	7	8	.90
Claudication	1	-	
Myocardial infarction	3	2	
Peripheral arterial disease	-	2	
Coronary arterial disease (bypass surgery)	1	-	
Obstruction of subclavian artery	-	1	
Cerebrovascular event/stroke	2	2	
Carotid artery stenosis	-	1	
Major venous thrombosis	2	6	.18
Thrombosis of mesenteric venocaval shunt	1	-	
Thrombosis of V. ileofemoralis	1	4	
Pulmonary embolism	-	1	
Lower limb thrombosis	-	1	
Severe bleeding events	5	2	.21
Rectal bleeding	1	-	
Bleeding into gluteal muscle	1	-	
Severe hypermenorrhea	1	-	
Bleeding of esophageal varices	-	1	
Metrorrhagia	-	1	
Severe bleeding after cyst puncture	1	-	
Other major bleeding events	1	-	

Harrison CN, et al. *N Engl J Med*. 2005;353(1):33-45. Gisslinger H, et al. *Blood*. 2013;121(10):1720-1728.

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Study Design of SURPASS-ET (NCT04285086)

Randomized, phase 3, multicenter, active-controlled, open-label study

Enrollment criteria

- Male or female ≥18 years
- Diagnosis of high-risk ET (WHO 2016 criteria)
- Resistant or intolerant to hydroxyurea
- IFN-α treatment naïve or anti-ropeg antibody–negative

Stratification factors

- Baseline platelet count ≥800 × 10^9/L vs. <800 × 10^9/L
- Baseline TSS (<10, 10-14, 15-19, ≥20)
- Country

R 1:1

Investigational arm: Ropeg, Q2W, SC (N=91)

Wk 0-2 **250 µg** → Wk 2-4 **350 µg** → **Fixed dose (500 µg)** → **Follow-up**

Reference arm: Anagrelide, PO (N=83)

Labeled dose → **Maintain optimal blood counts control at acceptable toxicity** → **Follow-up**

Dose escalation | **Treatment (52 weeks)** | **4 weeks**

Baseline | **Week 4** | **Primary Analysis (Months 9 and 12)**

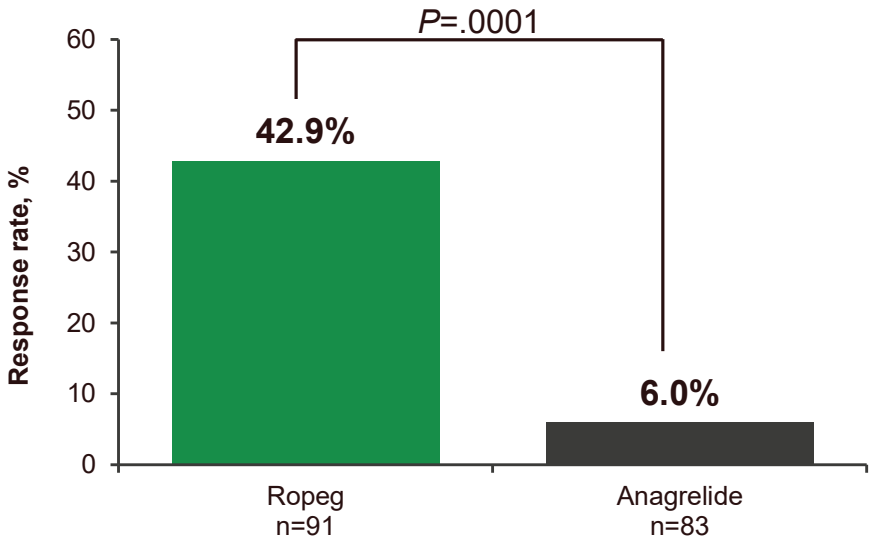
Primary Endpoint

- Modified ELN response rate at months 9 and 12
  - Platelet count of ≤400 × 10^9/L and WBC count of <9.5 × 10^9/L
  - Improvement or no progression in disease-related signs (eg, splenomegaly control)
  - Improvement or no progression in large symptoms based on the MPN-SAF TSS
  - Absence of hemorrhagic or thrombotic events

Mesa RA, et al. *J Clin Oncol*. 2025;43(16_suppl):6500.

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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]

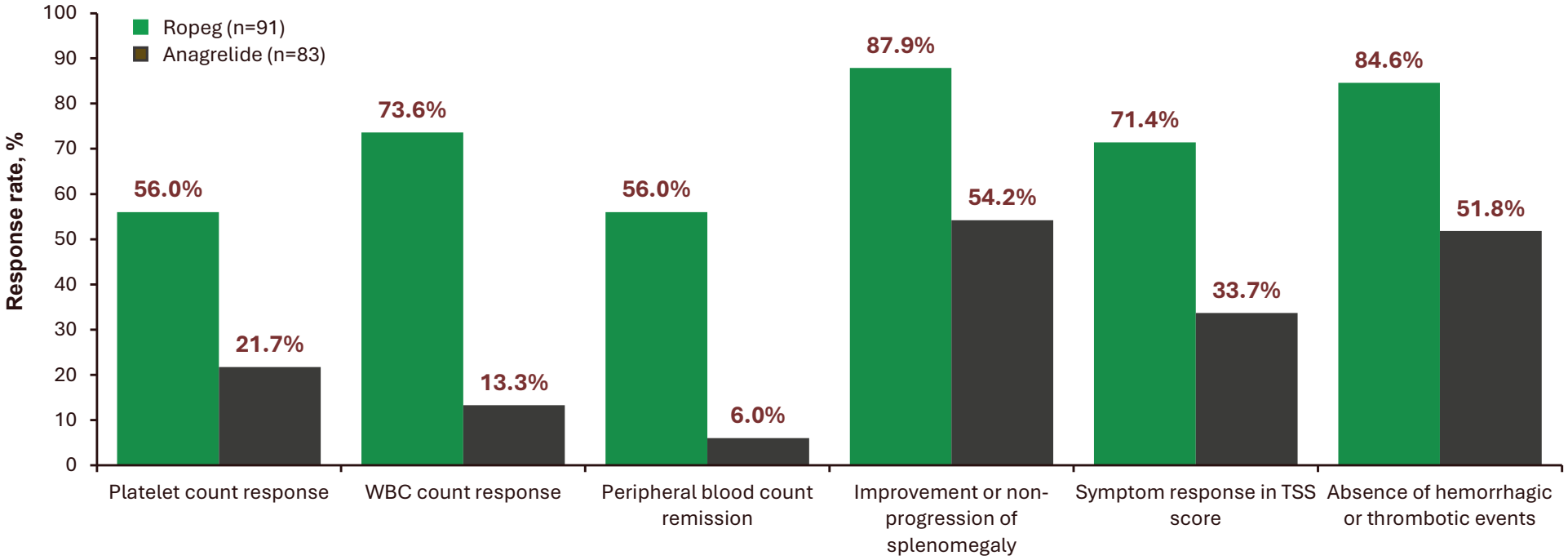
Modified ELN response criteria component endpoints

- ≥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.
MPN-SAF TSS = Myeloproliferative Neoplasms Symptom Assessment Form Total Symptom Score.
Mesa RA, et al. *J Clin Oncol*. 2025;43(16_suppl):6500.

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Primary Endpoint: Response Rate for Individual Modified ELN Parameters

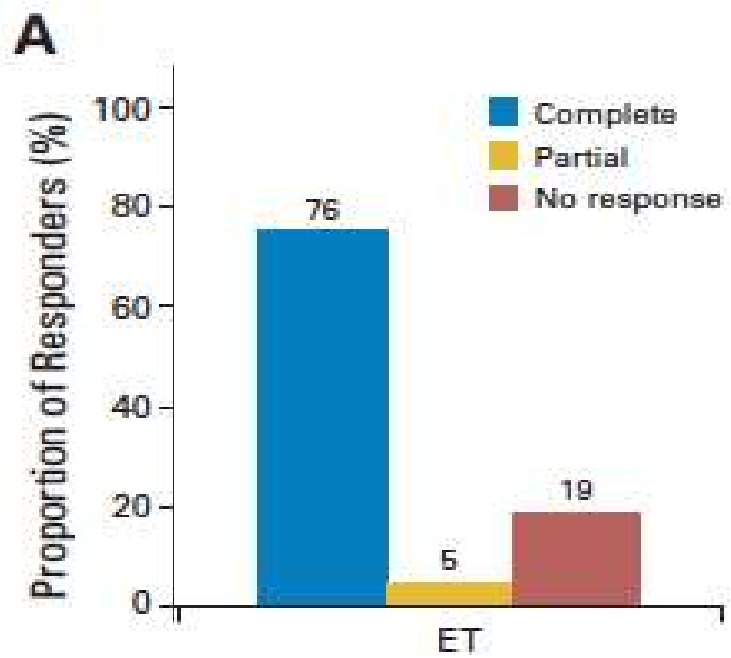


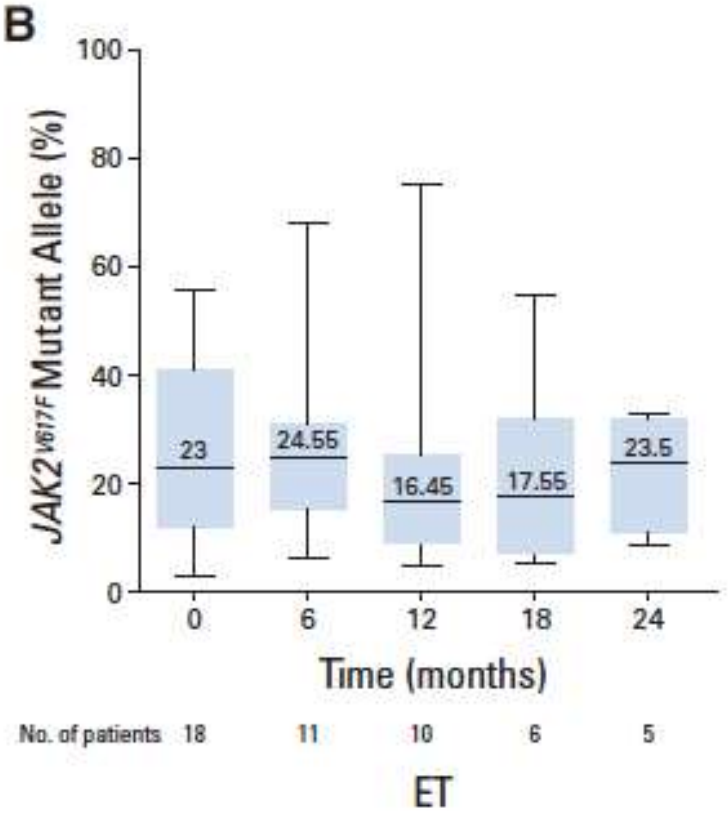
****P*<0.0001. Response defined as meeting the following criteria at months 9 and 12: Hematologic control, spleen and symptom improvement or stability (MPN-SAF TSS), and no thrombotic/hemorrhagic events.**

Mesa RA, et al. *J Clin Oncol*. 2025;43(16_suppl):6500.

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Phase II Study of PEG-IFN-Alpha-2a





Quintás-Cardama A, et al. *J Clin Oncol*. 2009;27(32):5418-5424.

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MPN-RC 112 Response

12 MONTHS

168 pts randomized
Polycythemia Vera: 87
Essential Thrombocytopenia: 81

Arm A (HU): 86 pts
PV: 44, ET: 42

Arm B (PEG): 82 pts
PV: 43, ET: 39

Response at 12 months

	ET	PV	Total
CR	19 (45.2%)	13 (29.5%)	32 (37.2%)
PR	11 (26.2%)	17 (38.6%)	28 (32.6%)
NR	1	2	3
UE*	11 (3 **)	12 (3 **)	23 (6 **)
TOTAL	42	44	86

ORR= 69.8%

***Unevaluable (n=23) at 12 mos due to:**
Adverse events: 7
Pt withdrew prior to starting trt: 6
Pt refused further trt: 5
Investigator decision: 2
Death: 1
Unknown: 2

75.0% accounting for withdrawals

	ET	PV	Total
CR	17 (43.6%)	12 (27.9%)	29 (35.4%)
PR	10 (25.6%)	25 (58.1%)	35 (42.7%)
NR	3	2	5
UE*	9	4	13
TOTAL	39	43	82

ORR= 78.0%

***Unevaluable (n=13) at 12 mos due to:**
Adverse events: 5
Pt refused further trt: 3
Pt did not respond to trt: 1
Lost to follow-up: 1
Investigator decision: 2
Unknown: 1

CR = complete response; PR = partial response.
Mascarenhas J, et al. *Blood.* 2022;139(19):2931-2941.

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Symptom Burden and Quality of Life in Patients with High-Risk ET and PV Receiving Hydroxyurea or Pegylated Interferon Alfa-2a: Results of MPN-RC 111 and 112 Trials

Mazza GL, et al. *Blood*. 2020;136(suppl 1):19-21.

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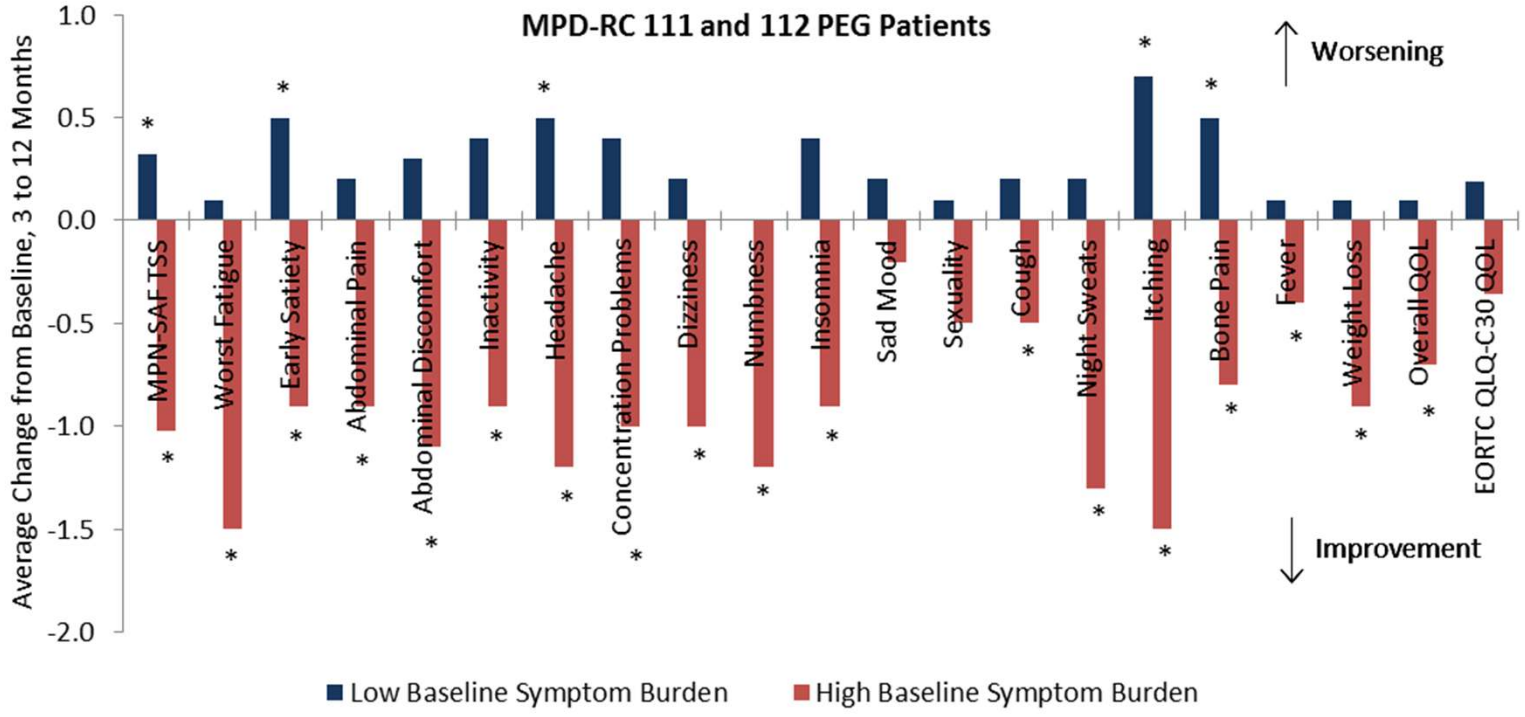
Results: Patients

Characteristic	MPN-RC 111		MPN-RC 112	
	ET (*n* = 64)	PV (*n* = 50)	ET (*n* = 79)	PV (*n* = 87)
Sex (% Female)	51%	48%	50%	33%
Age in Years (Median, Range)	65 (20 – 85)	64 (26 – 84)	60 (18 – 83)	62 (20 – 88)
Months Since Dx (Median, Range)	38 (0 – 291)	55 (1 – 394)	3 (0 – 48)	3 (0 – 84)
Prior Thrombosis (%)	31%	22%	25%	29%
Splenomegaly (%)	19%	56%	11%	37%

Mazza GL, et al. *Blood*. 2020;136(suppl 1):19-21.

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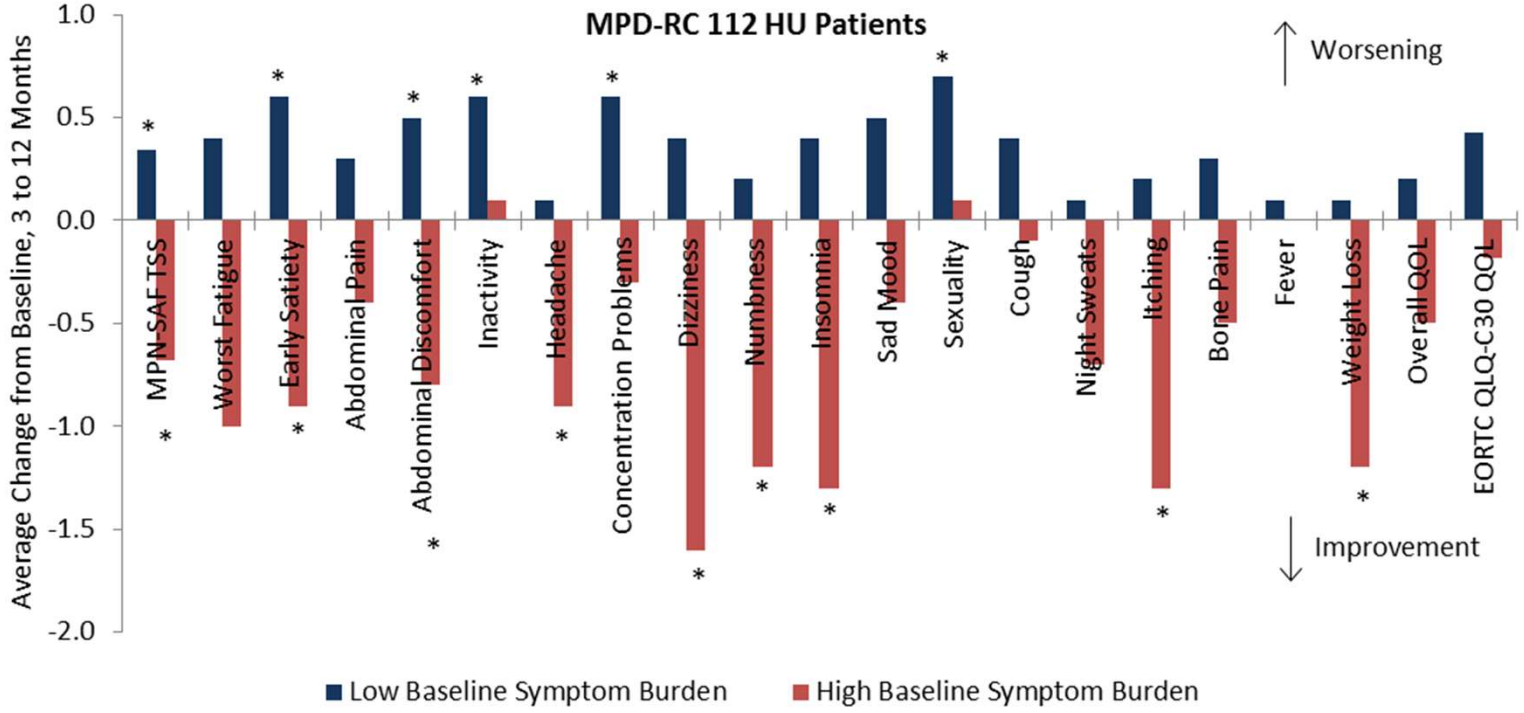
Change in Symptoms for Patients with MPN Treated with PEG INF on Trials MPN-RC 111 and 112



Mazza GL, et al. *Blood*. 2020;136(suppl 1):19-21.

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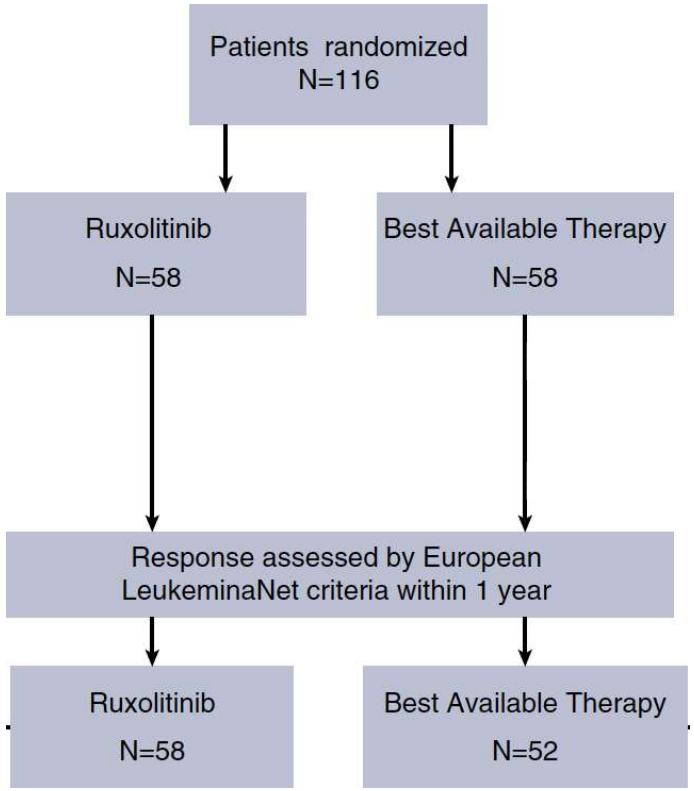
Change in Symptoms for Patients with MPN Treated with HU on Trials MPN-RC 111 and 112



Mazza GL, et al. *Blood*. 2020;136(suppl 1):19-21.

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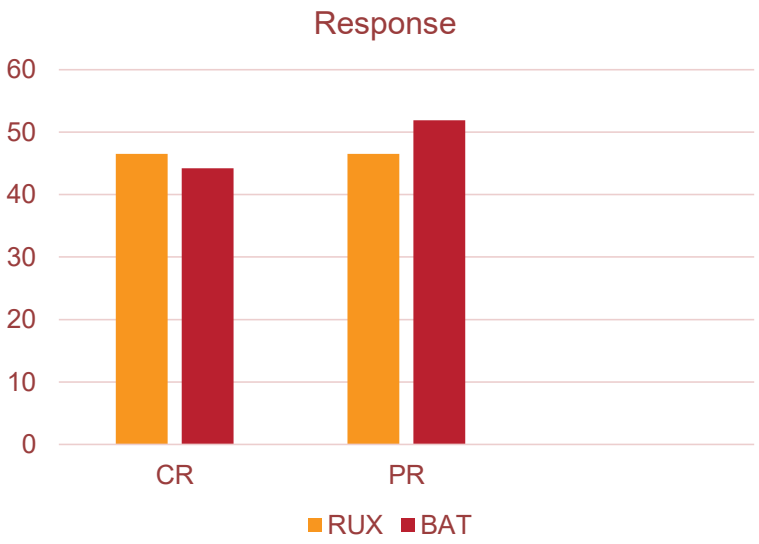
Ruxolitinib vs BAT in HU Resistant/Refractory Patients (MAJIC Trial – Randomized Phase II)



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

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Ruxolitinib vs BAT in HU Resistant/Intolerant ET (MAJIC-ET)



N=116; mITT N=110

BAT
HU 37/52 (71.1%)
Anagrelide 25/52 (48.1%)
IFN 21/52 (40.4%)

- There was no evidence of improvement in complete response within 1 year reported in 27 (46.6%) patients treated with ruxolitinib vs 23 (44.2%) with BAT (*P* = .40)
- At 2 years, rates of thrombosis, hemorrhage, and transformation were not significantly different; however, some disease-related symptoms improved in patients receiving ruxolitinib relative to BAT
- Grade 3 and 4 anemia occurred in 19% and 0% of ruxolitinib vs 0% (both grades) in the BAT arm, and grade 3 and 4 thrombocytopenia in 5.2% and 1.7% of ruxolitinib vs 0% (both grades) of BAT-treated patients
- Rates of discontinuation or treatment switching did not differ between the 2 trial arms
- Ruxolitinib significantly improved some disease-related symptoms, but rates of thrombosis, hemorrhage, or transformation were not different

CR = plt ≤400x10^9/L, normal spleen size on imaging, WBC ≤ 10x109/L; PR = per ELN criteria within 1 year of treatment.
Harrison CN, et al. *Blood*. 2017;130(17):1889-1897.

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INCA033989 is a mut*CALR*-Targeted Therapy for Patients with ET and MF

- INCA033989 has a unique mechanism of action compared with other available therapies
  - INCA033989 is a novel, fully human, high-affinity, Fc-silenced, immunoglobulin G1 monoclonal antibody that selectively targets mut*CALR* in complex with thrombopoietin receptor to inhibit oncogenic signaling and proliferation of cells

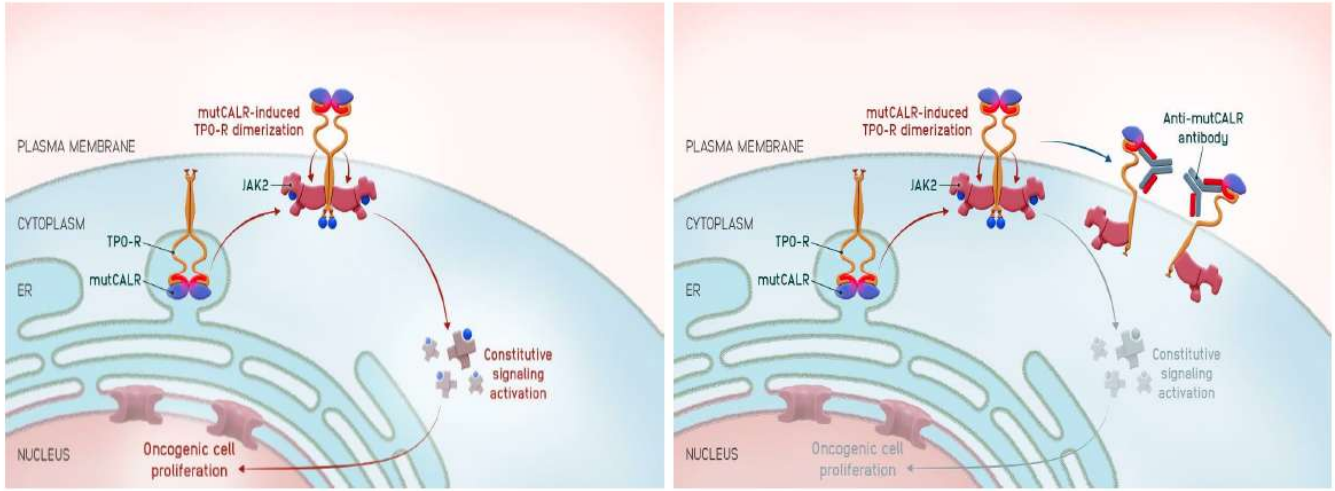


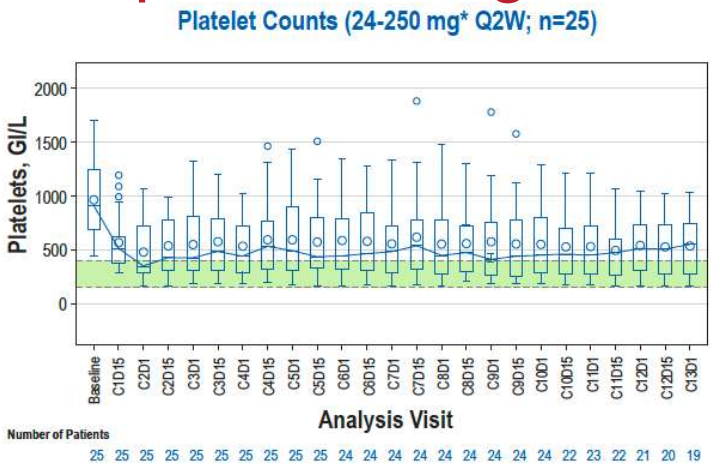
Figure reprinted from Reis E, et al. *Blood*. 2024;144:2336-2348 [visual abstract] with permission of Elsevier Inc. Copyright © 2024 American Society of Hematology.

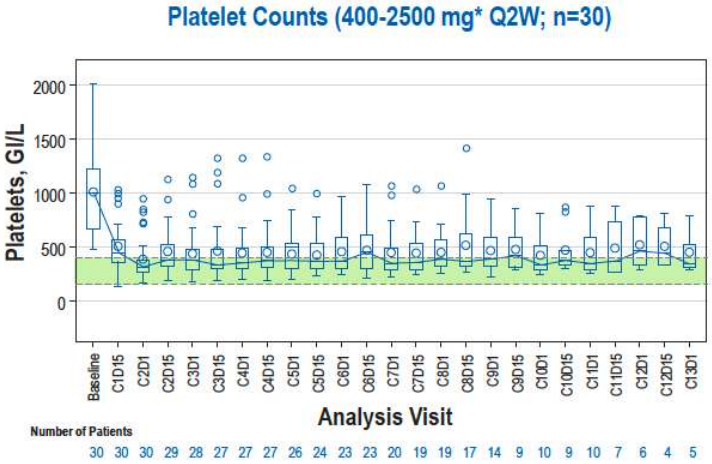
1. Reis ES, et al. *Blood*. 2024;22:2336-2348.

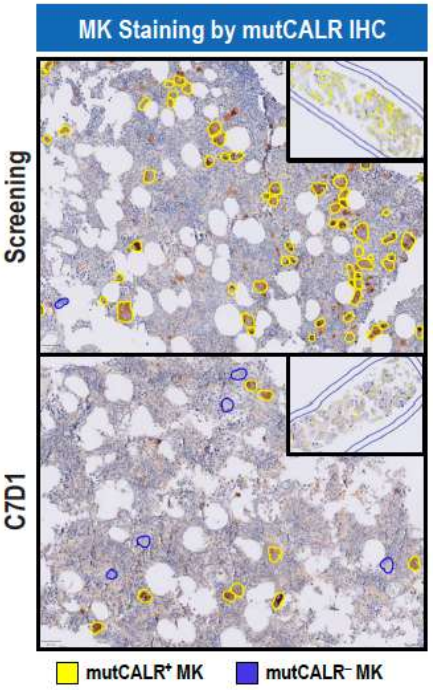
CALR, calreticulin; ER, endoplasmic reticulum; ET, essential thrombocythemia; JAK2, Janus kinase 2; MF, myelofibrosis; mut*CALR*, mutations of calreticulin; TPO-R, thrombopoietin receptor (myeloproliferative leukemia protein).

Gupta V, et al. *Blood*. 2025;146(suppl 1):1024.

Rapid and Durable Platelet Normalization with Optimal Response at Higher Doses of INCA033989







- Median (range) duration of exposure was 45.0 (4.0, 94.1) weeks
- Of the 34 patients who enrolled with concomitant cytoreductive therapy (HU [n=27] or anagrelide [n=7]), most (71%) discontinued and remained on study
  - Median (range) time to discontinuation of cytoreductive therapy (HU and anagrelide) was 23.0 (1.0-322.0) days

Dotted lines indicate upper (400 G/L) and lower limit (150 G/L) 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.*Starting dose.

Gupta V, et al. *Blood*. 2025;146(suppl 1):1024.

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A 55 y/o Male with High-Risk ET

- Patient was diagnosed with *JAK2*V617F mutant ET 2 years ago. Presented with LLE DVT and PE
- Other medical diagnoses: Hypertension, dyslipidemia
- Patient was initially started on ASA and hydroxyurea
- Ongoing symptoms: Fatigue and headaches
- Since starting hydrea, no substantial improvement in symptoms
- He has learned to live with his fatigue and headaches, but it troubles him
- What are the treatment goals for this patient? > Reduce thrombotic risk, attenuate risk of disease progression, reduce symptom burden
- What are the options to address this patients needs? > Could consider Ropeg-INF as a second line agent, or possibly anagrelide

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Key Learning Points



- The use of cytoreductive therapy in ET is risk-adapted
- Driver mutation and clinical factors (like cardiovascular risk factors inform the need to give cytoreductive therapy
- Ropeg-INF has been recently FDA approved for the treatment of ET
- *CALR*-targeting agents are showing early evidence of clinical efficacy