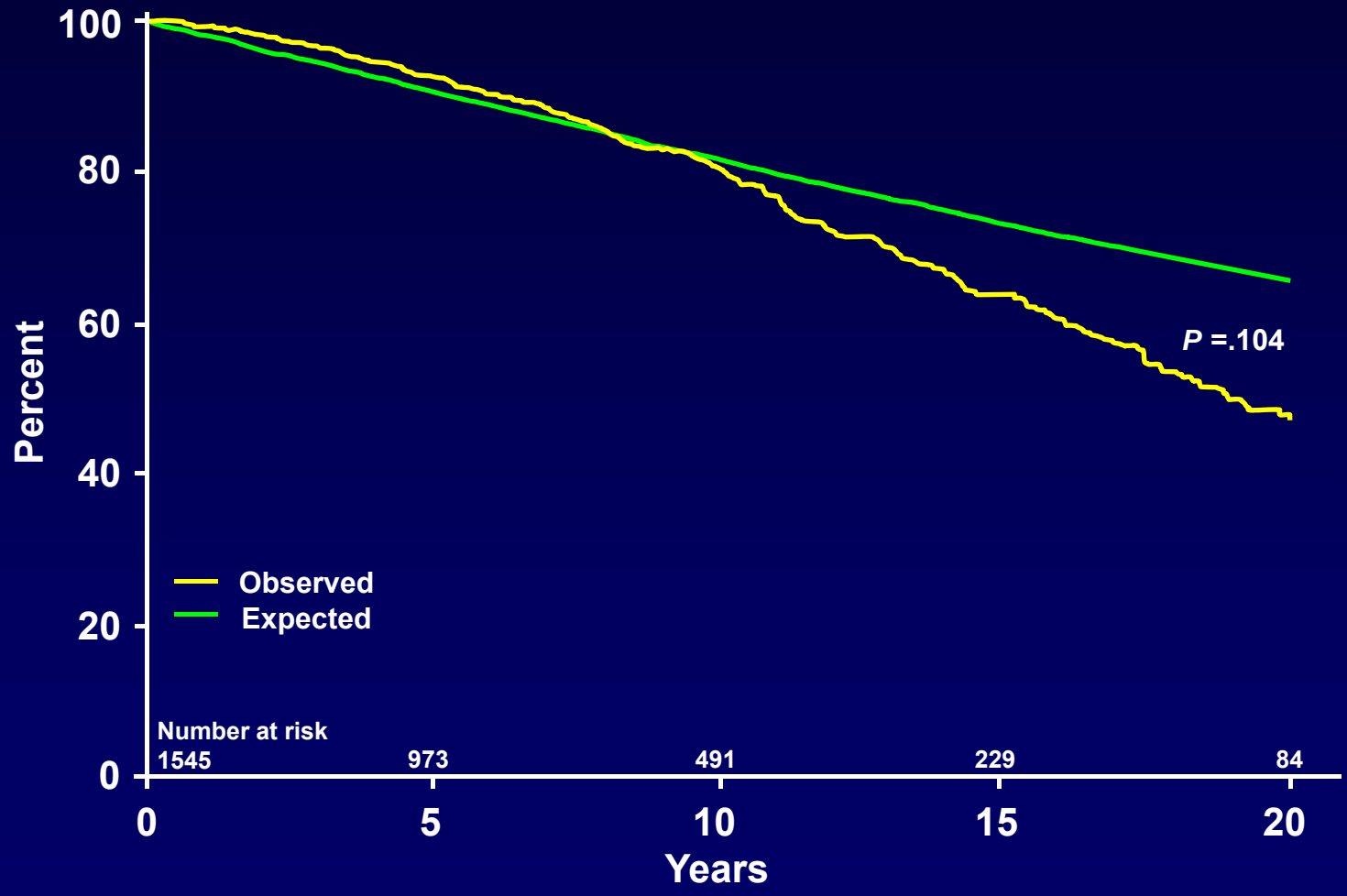
Do We Really Know the Best Initial Therapy for Polycythemia Vera (PV)?

Mary Frances McMullin, MD, FRCPath
Belfast City Hospital
Belfast, United Kingdom

m.mcmullin@qub.ac.uk

Survival in Patients With PV



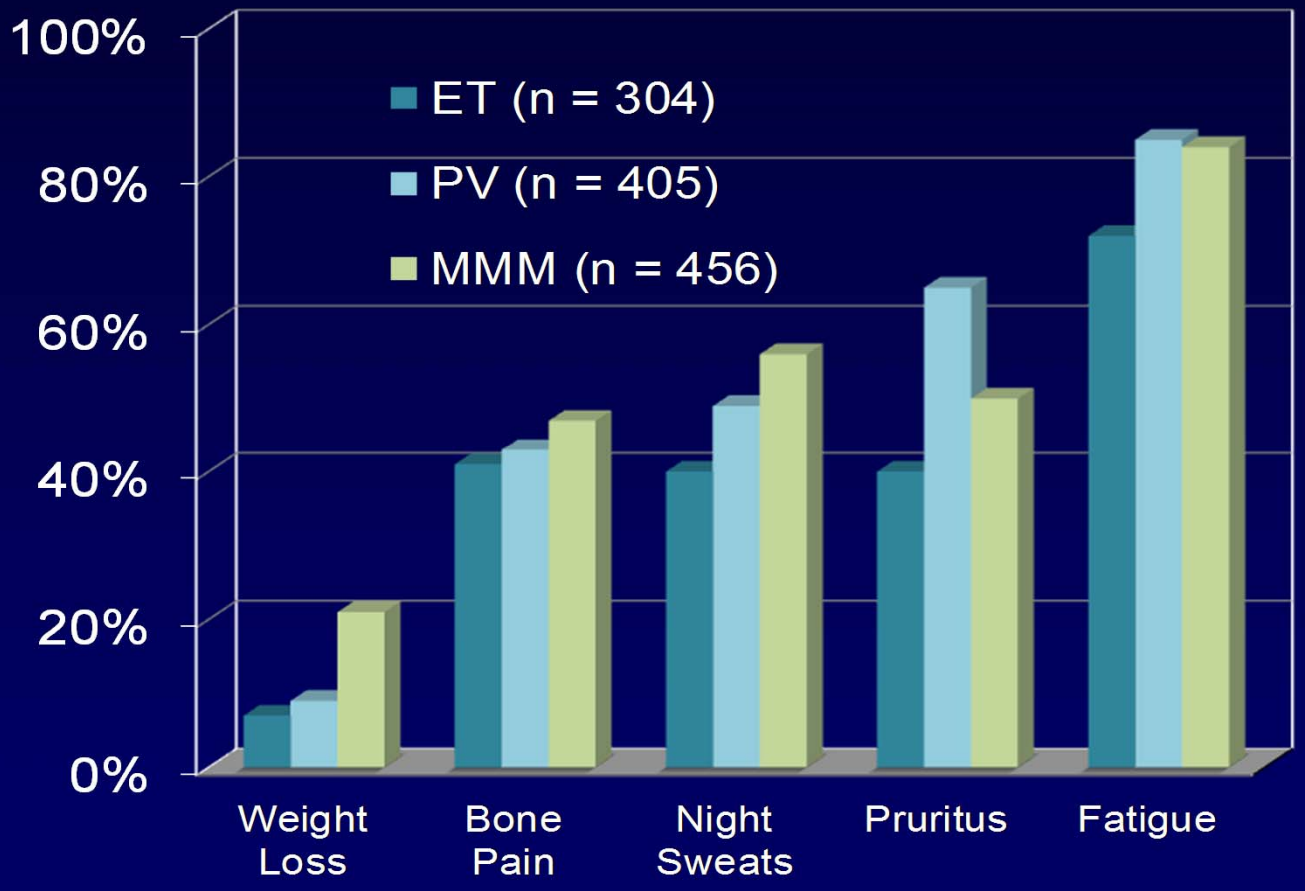
Tefferi A, et al. *Leukemia*. 2013;27(9):1874-1881.

Goals of Therapy

- Control blood counts
- Prevent thromboembolic events
- Prevent hemorrhagic events
- Remove or reduce MPN associated symptoms
- Prevent progression to myelofibrosis (MF) or acute leukemia
- Reduce or eliminate *JAK2* mutant clone
- “Cure” the disease

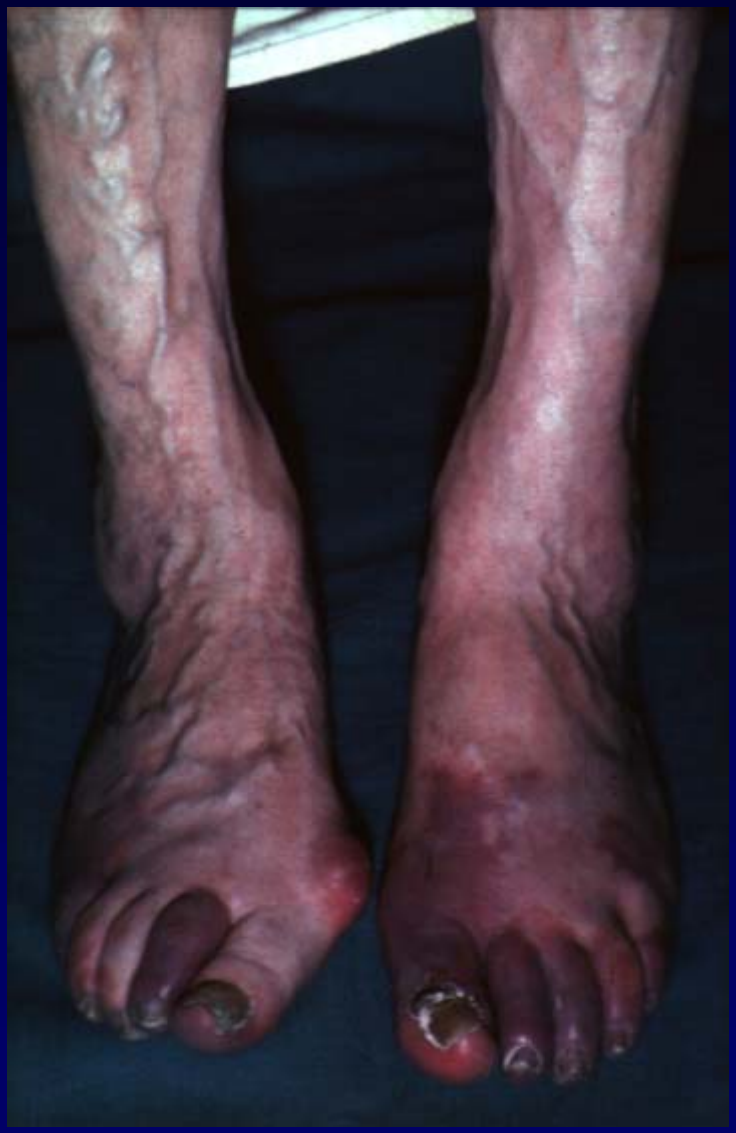
MPN, myeloprofilerative neoplasms

Symptoms in 1179 MPN Patients



ET, essential thrombocythemia; MMM, myeloid metaplasia

Mesa RA, et al. *Cancer.* 2007;109(1):68-76.

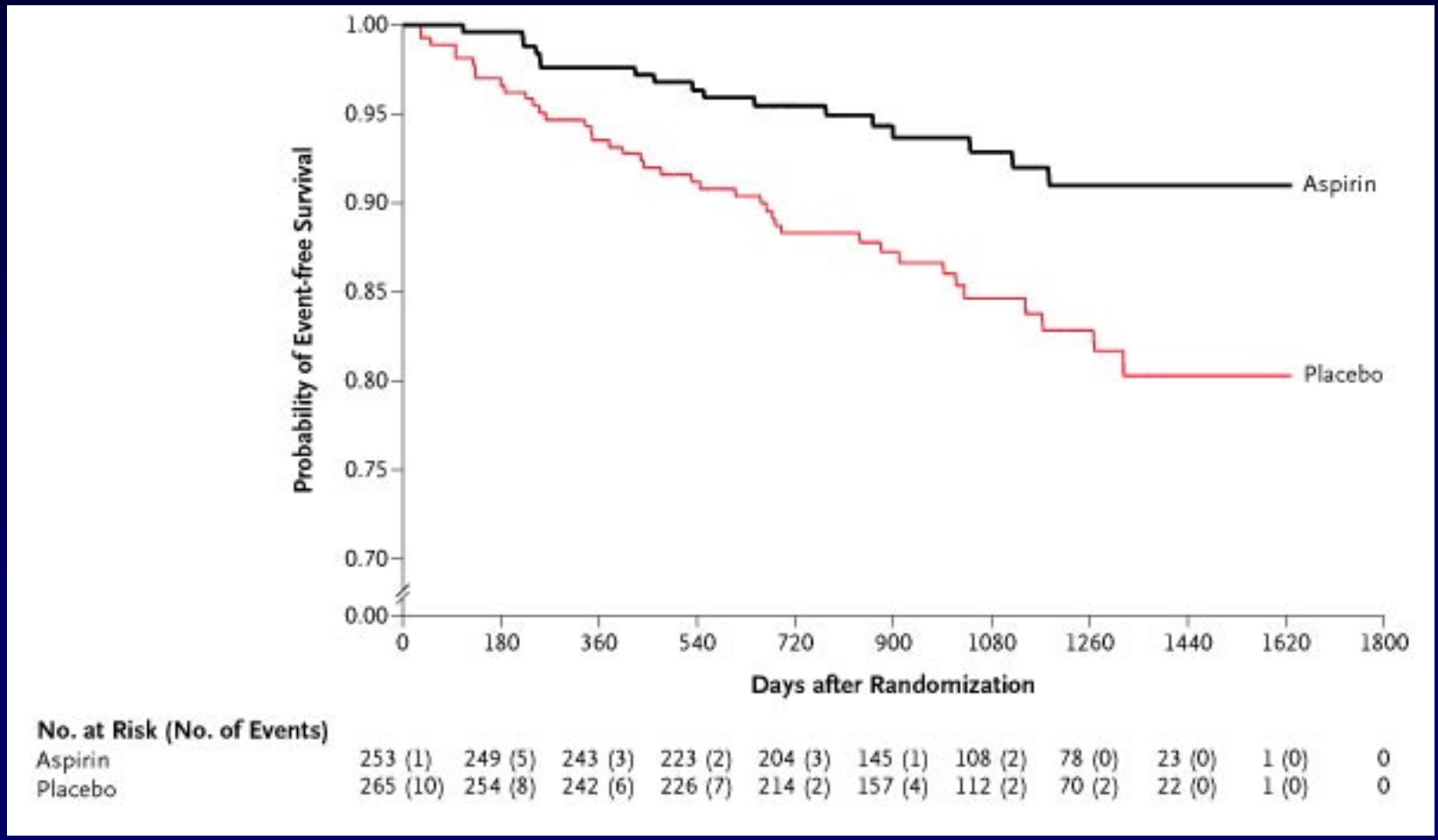


PV: Management Agents

- Aspirin
- Venesection
- Hydroxycarbamide
- Interferons
- Radioactive phosphorus-32
- Busulfan
- Anagrelide

Hydroxycarbamide = hydroxyurea

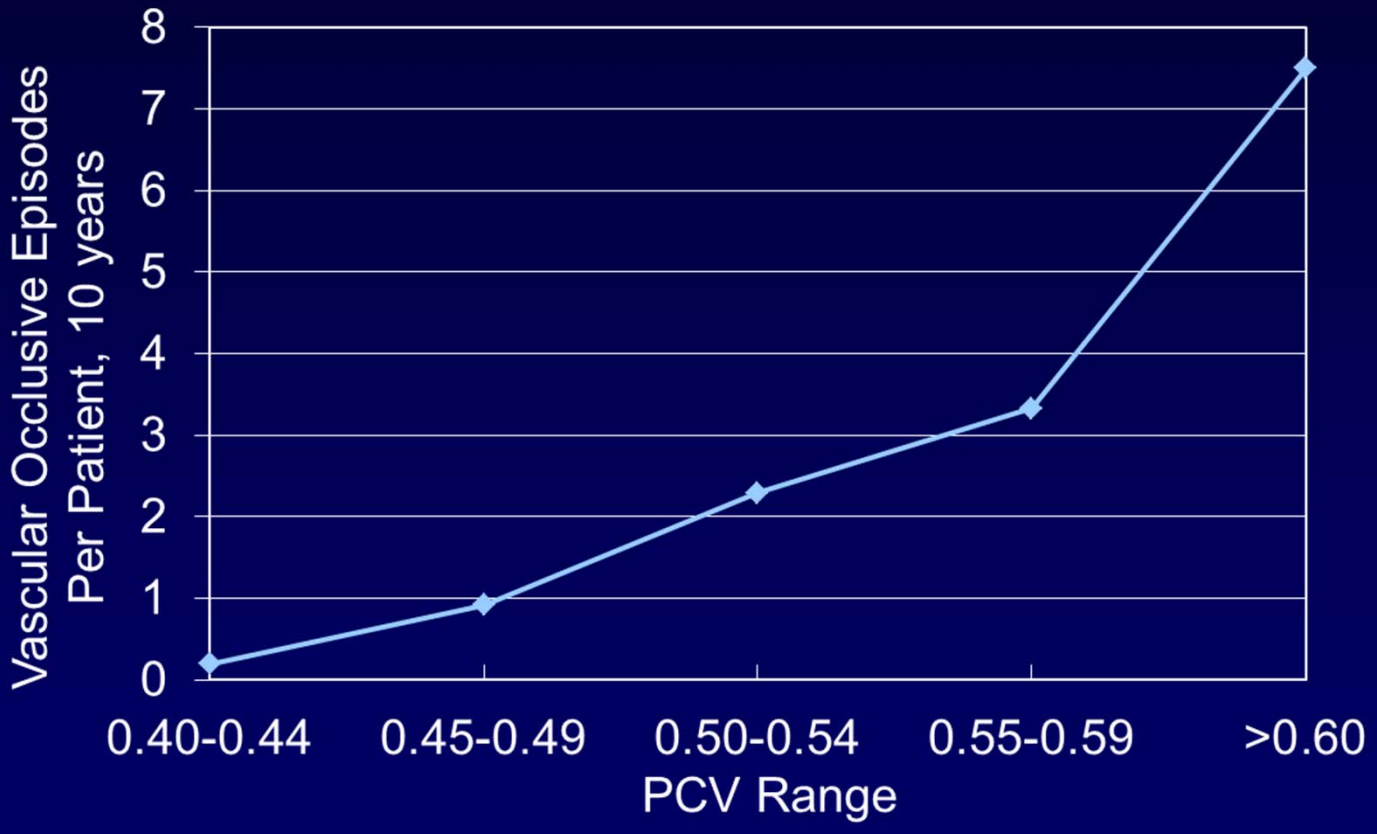
Probability of Survival Free of a Thrombotic Event



Landolfi R, et al. *N Engl J Med.* 2004;350(2):114-124.

“Bloodletting”
18th century Persian manuscript illustration

Relationship Between PCV Range and Vascular Occlusive Episodes

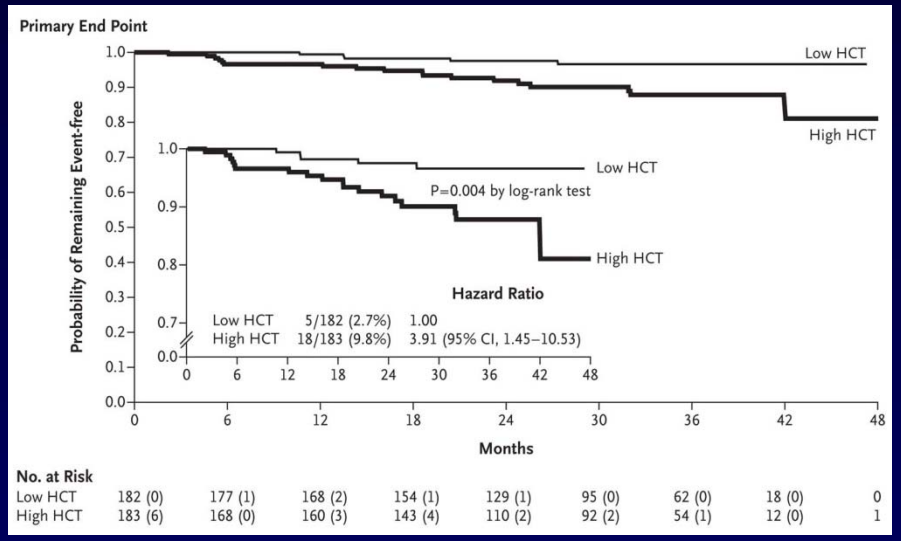


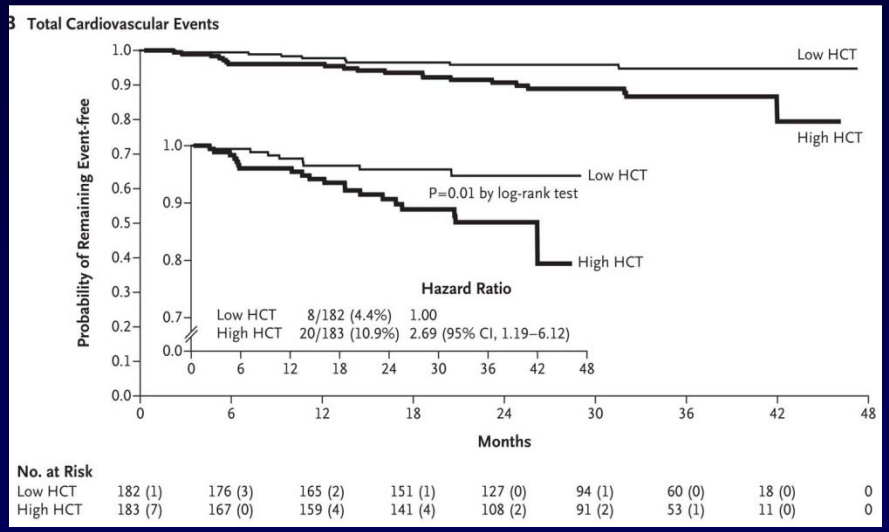
In patients with primary proliferative polycythemia

PCV, packed cell volume

Adapted from Pearson TC, et al. Lancet. 1978;2(8102): 1219-1222

Kaplan-Meier Curves for the Primary End Point and Total Cardiovascular Events





Primary endpoint

- **Time until death from cardiovascular causes or major thrombotic event**

Secondary endpoint

- **Total rate of cardiovascular events, defined as the primary endpoint plus superficial-vein thrombosis**

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

Hydroxycarbamide

Trial	Patients	Follow-up	Outcomes	Treatments		*P* value
				Previously treated	Previously untreated	
PSVG-08	118		1 year failure free survival	59%	73%	
Donovan, 1984	59 untreated					
				Hydroxycarbamide	Controls	
PSVG-08	51	795	Overall survival	68.60%	60.00%	.07
Kaplan, 1986 and	(134 PSVG-01	weeks	Thrombosis	9.80%	32.80%	.018
Fructman, 1997	controls)		Acute leukemia	5.90%	1.50%	.25
			Myelofibrosis	7.80%	12.70%	.37
West, 1987	100	1963-1986	Thrombosis	1.00%		
			Acute leukemia	1.00%		
			Myelofibrosis	6.00%		
Löfvenberg, 1988	59	1981-1986	5-year survival	86.00%		
	(24 PV)		Thrombosis	8.40%		
			Acute leukemia and MDS	3.00%		
Weinfeld, 1994	50	5 years	Thrombosis	12.00%		
	(30 PV)	minimum	Acute leukemia and MDS	10.50%		
Nand, 1996	42	1993-1995	Acute Leukemia	6.00%		
	(16 on HU alone)					
Tartarsky and	71	10.9 years	Thrombosis	5.60%		
Sharon, 1997		median	Acute leukemia	5.60%		
			Myelofibrosis	2.80%		
Nielsen, 2003	58 (29 PV)	7.8 years	Acute leukemia and MDS	14%		

Donovan PB, et al. *Am J Hematol*. 1984;17(4):329-334. Kaplan ME, et al. *Semin Hematol*. 1986;23(3):167-171. Fruchtman SM, et al. *Semin Hematol*. 1997;34(1):17-23. West WO, et al. *South Med J*. 1987;80(3):323-327. Löfvenberg E, et al. *Eur J Haematol*. 1988;41(4):375-381. Weinfeld A, et al. *Eur J Haematol*. 1994;52(3):134-139. Nand S,et al. Am J Hematol. 1996;52(1):42-46. Tatarsky I, et al. *Semin Hematol*. 1997;34(1):24-28. Nielsen I, et al. *Am J Hematol*. 2003;74(1):26-31.

Hydroxycarbamide

- PVSG -08: Showed efficacy of hydroxycarbamide
- Acute leukemia and MDS: 0% to 14%
- Extensive experience in sickle cell anemia: No increase in leukemia
- Hydroxycarbamide: Leukemogenicity not proven, prevents thrombosis and possibly progression to myelofibrosis

PVSG, Polycythemia Vera Study Group

Donovan PB, et al. *Am J Hematol.* 1984;17(4):329-334.

^{32}P and Busulfan

- EORTC trial (1981)
- Comparing ^{32}P and busulfan and venesection to maintain the hematocrit (Hct)
- Better overall survival with busulfan than ^{32}P (70% vs 55% at 10 years)
- No differences in leukemia, non-hematologic malignancy, or myelofibrosis rates between arms

European Organization for Research on Treatment of Cancer (EORTC). *Br J Cancer,* 1981;44(1):75-80

Acute Myeloid Leukemia (AML)/MDS Transformation According to Treatment

Treatment	Odds ratios	95% CI
None	1.0	Ref
^{32}P only	1.5	0.8-2.8
Alkylating agent only	0.9	0.4-2.1
Hydroxyurea (HU) only	1.2	0.6-2.4
Mixed treatment (2 or more)	2.9	1.4-5.9

Björkholm M, et al. *J Clin Oncol.* 2011;29(17): 2410-2415.

Recommendation: Management of PV

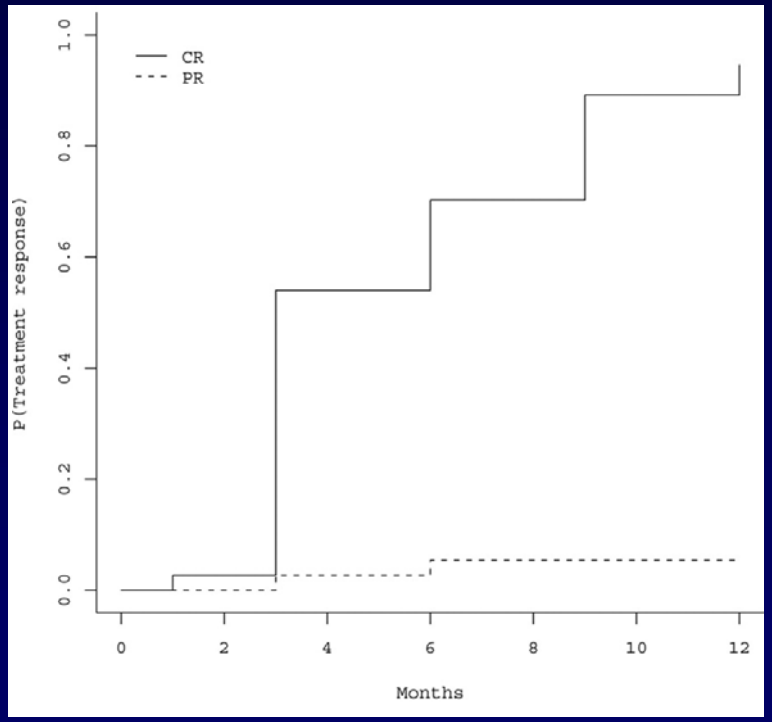
1. Venesection to maintain the Hct at <0.45
2. Aspirin 75 mg/day unless it is contraindicated
3. Cytoreduction should be considered if:
   - Poor tolerance of venesection
   - Symptomatic or progressive splenomegaly
   - Other evidence of disease progression (eg, weight loss and nights sweats)
   - Thrombocytosis
4. Choice of cytoreductive therapy, if indicated:
   - <40 years: First-line interferon, second-line hydroxycarbamide or anagrelide
   - 40-75 years: First-line hydroxycarbamide, second-line interferon or anagrelide
   - >75 years: First-line hydroxycarbamide, second-line ^{32}P or intermittent low dose busulfan

Grade C recommendation; Evidence level IV

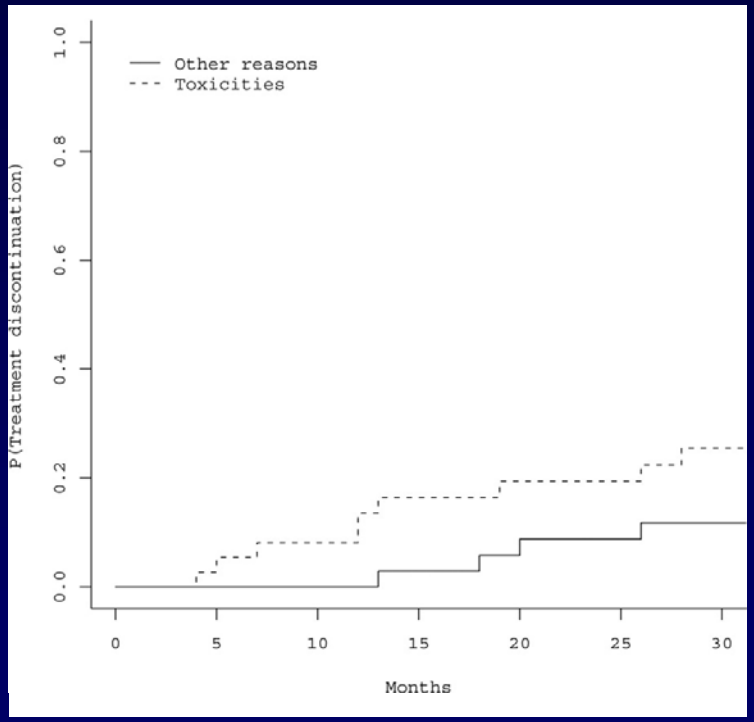
McMullin MF, et al. *Br J Haematol.* 2005;130(2):174-195.

Pegylated Interferon-Alpha-2a: Hematological Responses and Treatment Discontinuations

Estimated cumulative incidence of treatment response

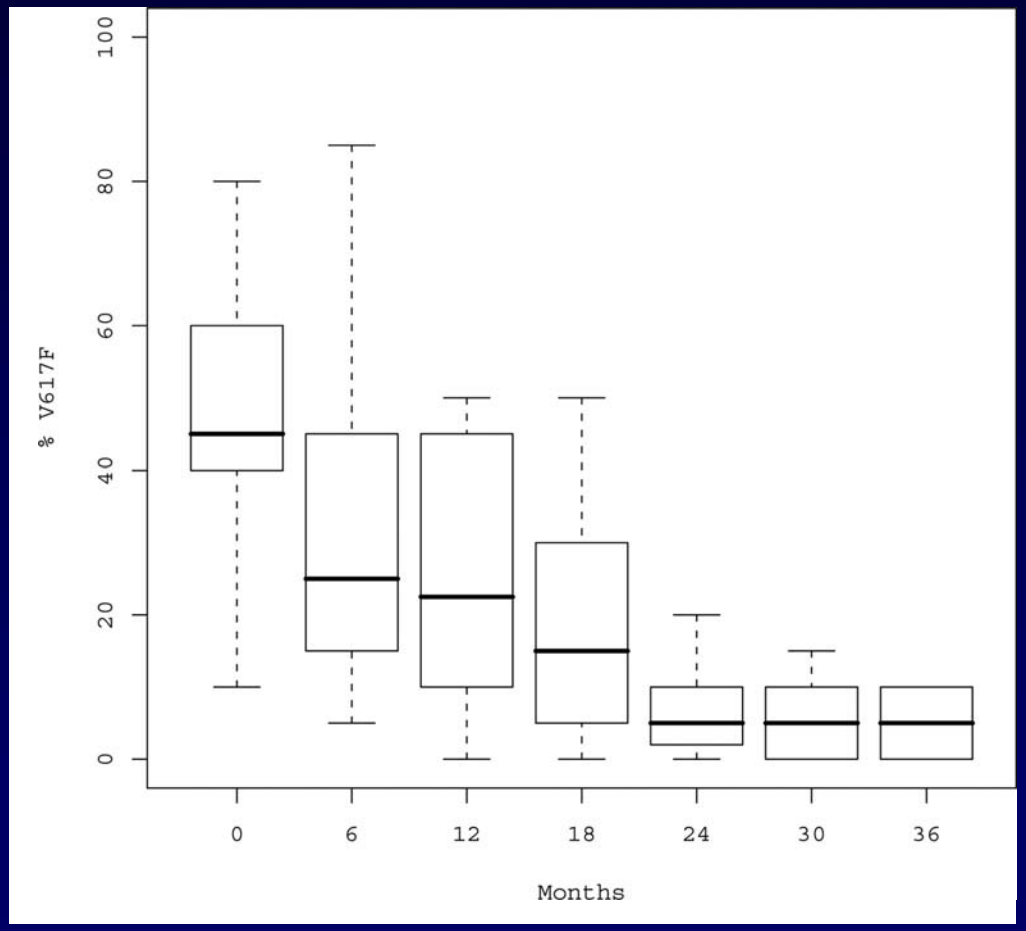


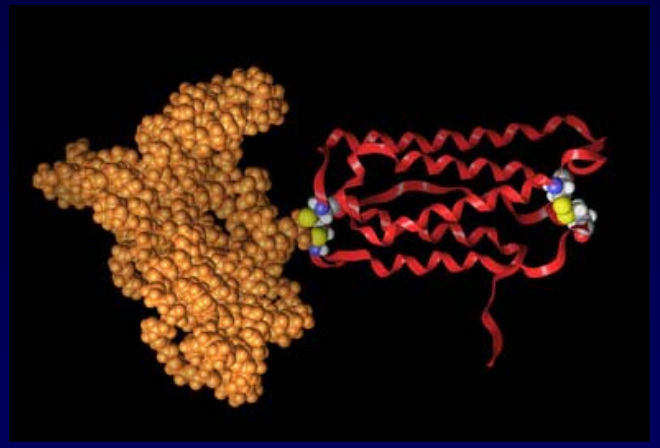
Cumulative incidence of treatment discontinuation



Kiladjian JJ, et al. *Blood*. 2008;112(8):3065-3072.

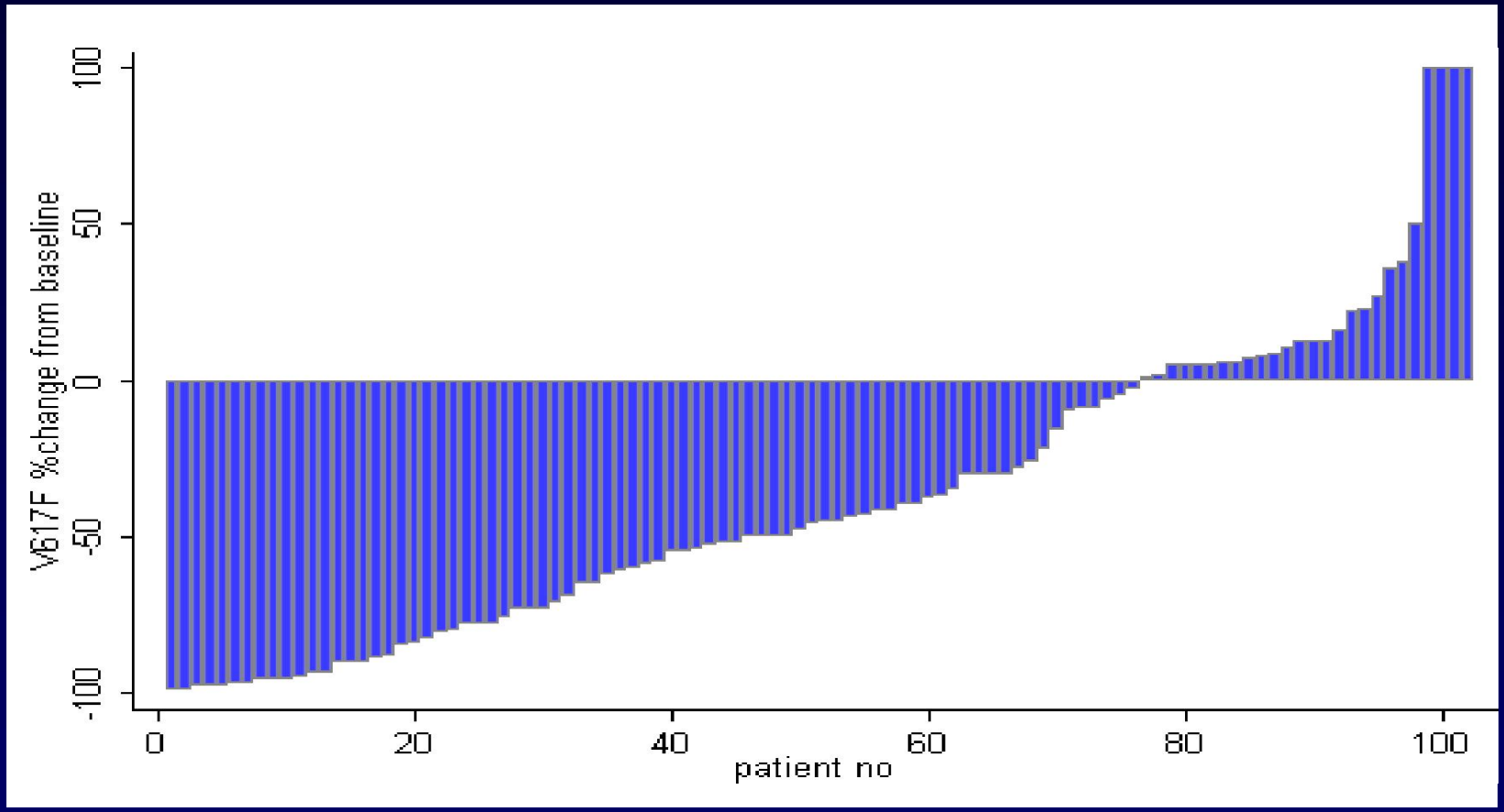
Pegylated Interferon-Alpha-2a Is Able to Induce Molecular Remission in Patients With PV





Kiladjian JJ, et al. *Blood*. 2008;112(8):3065-3072.

Cohort of Danish Patients With ET, PV, and MF Treated With Recombinant Interferon Alpha



Change from baseline in JAK2 V617F mutant allele burden in the 102 individual patients with a median follow-up of 42 months (range 12–146 months)

Stauffer Larsen T, et al. *Leuk Res.* 2013;37(9):1041-1045.

The ELN Criteria for Response

- Endpoints that are capable of measuring the effects of drugs on clinically relevant benefit for patients
- Symptomatology
  - Patient-reported quality-of-life instrument (MPN-SAF TSS)
- Disease complications
- Bone marrow histological remission

ELN, European LeukemiaNet; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score

Definition of Response in PV

CR	A	Durable* resolution of disease-related signs, including palpable hepatosplenomegaly, large symptom improvement,† AND
	B	Durable* PB count remission, defined as Hct lower than 45% without phlebotomies platelet count <400 x10^9/L, WBC count <10 x10^9L, AND
	C	Without progressive disease, and no hemorrhagic or thrombotic events, AND
	D	Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of greater than grade 1 reticulin fibrosis
PR	A	Durable* resolution of disease-related signs, including palpable hepatosplenomegaly, and large symptoms improvement, AND
	B	Durable* PB count remission, defined as: Hct lower than 45% without phlebotomies, platelet count <400 x10^9/L, WBC count <10 x10^9L, AND
	C	Without progressive disease, and absence of hemorrhagic or thrombotic events, AND
	D	Without bone marrow histological remission defined as persistence of trilineage hyperplasia
NR		Any response that does not satisfy partial remission
PD		Transformation into post-PV myelofibrosis, myelodysplastic syndrome or AML

*Lasting for at least 12 weeks; †Large symptom improvement (≥ 10-point decrease) in MPN-SAF TSS.
CR, complete resonse; PR, partial response
Barosi G, et al. *Blood.* 2013;121(23):4778- 4781

Molecular Response

- Not required for assignment as complete or partial response
- Molecular response evaluation requires analysis in peripheral blood granulocytes
- CR: Eradication of a preexisting abnormality
- PR: >50% decrease in allele burden, assessable only if baseline mutant burden >20%

MPD-RC Pegylated Interferon-Alpha-2a Studies

MPD-RC 111[1]
Phase II

168 patients

ET/PV patients HU resistant/refractory

and

20 patients with splanchnic vein thrombosis

MPD-RC 112[2]
Phase III

612 patients

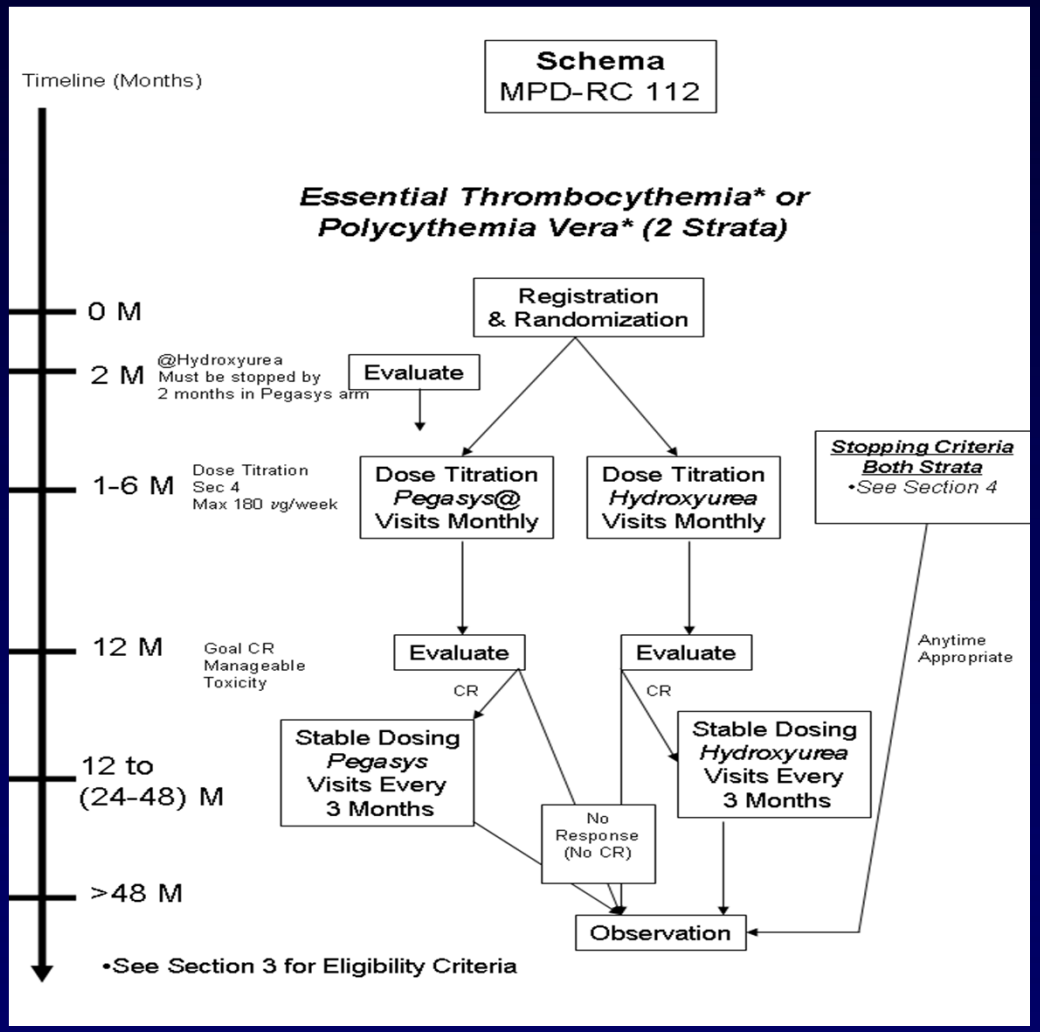
ET/PV patients diagnosed within three years of trial entry

Randomized between pegylated interferon-alpha-2a plus aspirin and HU plus aspirin

MPD-RC, Myeloproliferative Disorders Research Consortium

1. National Institutes of Health. Available at: http://clinicaltrials.gov/show/NCT01259817. Assessed on October 21, 2014. 2. National Institutes of Health. Available at: http://clinicaltrials.gov/show/NCT01259856. Assessed on October 21, 2014.

MPD-RC 112 Study Design



National Institutes of Health. Available at: http://clinicaltrials.gov/show/NCT01259856. Assessed on October 21, 2014.