Issues I am concerned with regarding polycythemia vera, 2019

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Disclosures

(Past 12 months)

- **Speaker's Bureau**

  AOP Orphan

  PharmEssentia

- **No conflict of interest**

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Outline:

Diagnostic Criteria

- WHO 2016 criteria
- Distinguishing ET^{JAKV617F} from PV

Treatment issues

- Risk categories
- Treatment with ruxolitinib
- Treatment with phlebotomy-only

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Outline:

Diagnostic Criteria

WHO 2016 criteria

Distinguishing ET^{JAKV617F} from PV

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Definition

Polycythemia vera (PV) should be defined by an absolute increase in red blood cells. (red cell volume or red cell mass, RCM)

Should not be based on hemoglobin concentration since 95% of PV patients are iron-deficient at the time of diagnosis. Varying Hgb values are characteristic of PV.

Red cell mass (RCM) >125% of mean expected volume

Nearly always accompanied by other evidence of myeloproliferation (WBC, platelets, splenomegaly)

***JAK2*^{V617F} or exon12 mutation virtually always present, thus excluding "secondary" polycythemias.**

Silver RT, et. al. Blood. 2013

Major Molecular Abnormalities in Myeloproliferative Neoplasms

Molecular Abnormality	PV	ET	PM
	Approximate %		
JAK2^{V617F}	97	60	50
EXON12	2	0	0
CALR	0	25	35
MPL	0	5	5
Triple Neg	0	10	10

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WHO Criteria 2016

Major Criteria:

1. Presence of JAK2 mutation(s)
2. ♂ Hb > 16.5 g/dl ♀ Hb > 16 g/dl or

   ♂ Hct > 49% ♀Hct > 48% or

   Increased red cell volume > 125%
3. Marrow biopsy hypercellular for age with trilineage hyperplasia and megarkaryocytic variability in size

Minor Criterion (in the case of JAK2 negativity):

Subnormal serum EPO level

Arber, Daniel A., et al. Blood. 2016

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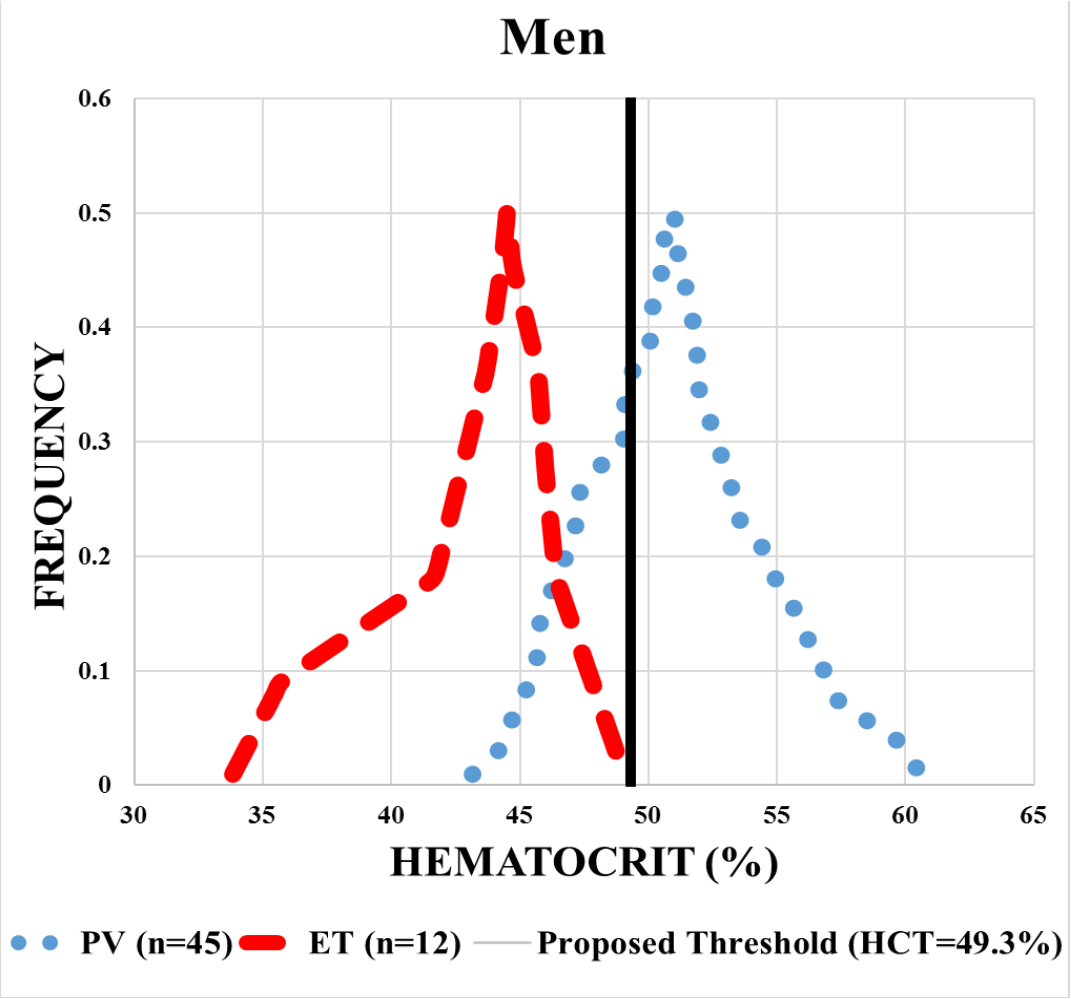
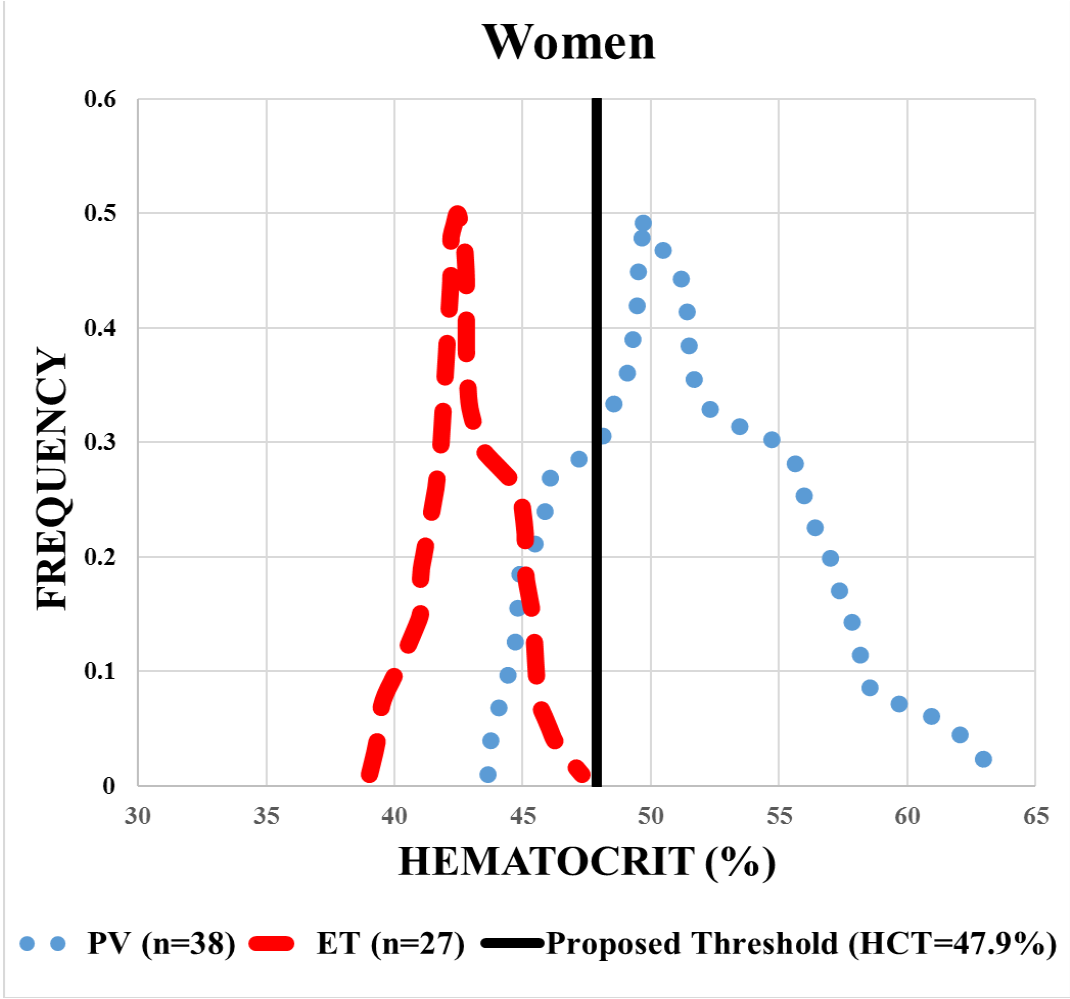
Initially, make the correct diagnosis

- In approximately 15% of patients, the diagnosis of JAK2+ ET, PV, or early MF may be incorrect

- This has obvious therapeutic and prognostic implications

Overlap Values for HCT in PV and ET^{JAKV617F}





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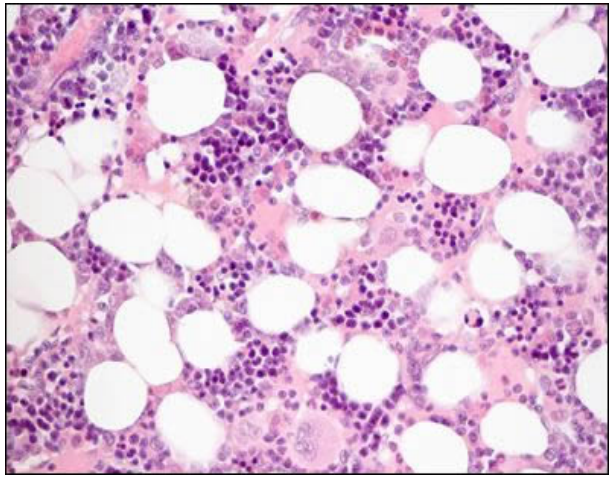
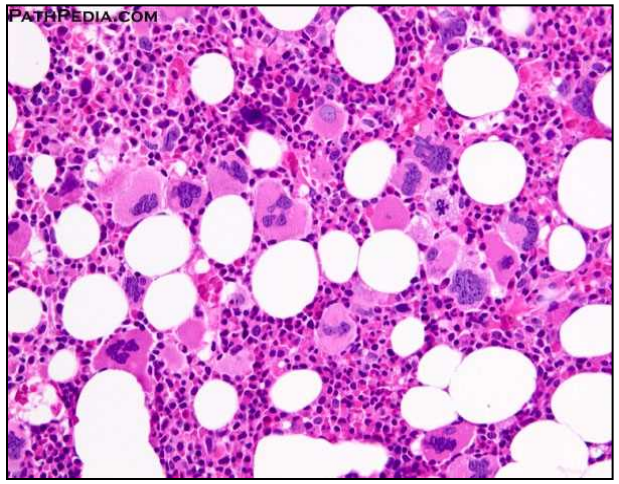
Bone Marrow Examination is Helpful

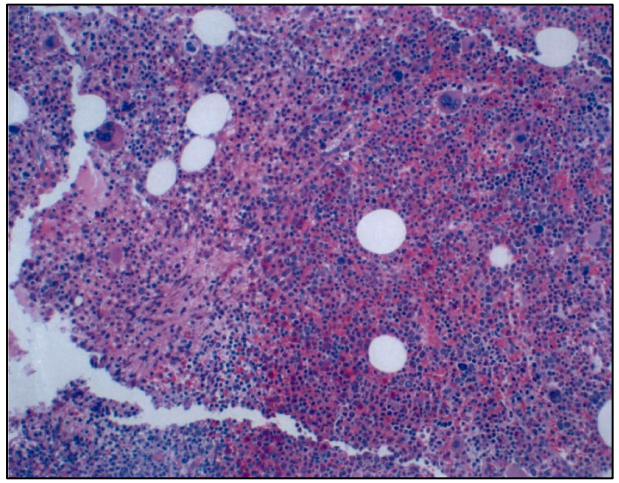
Normal bone marrow



ET bone marrow



PV bone marrow



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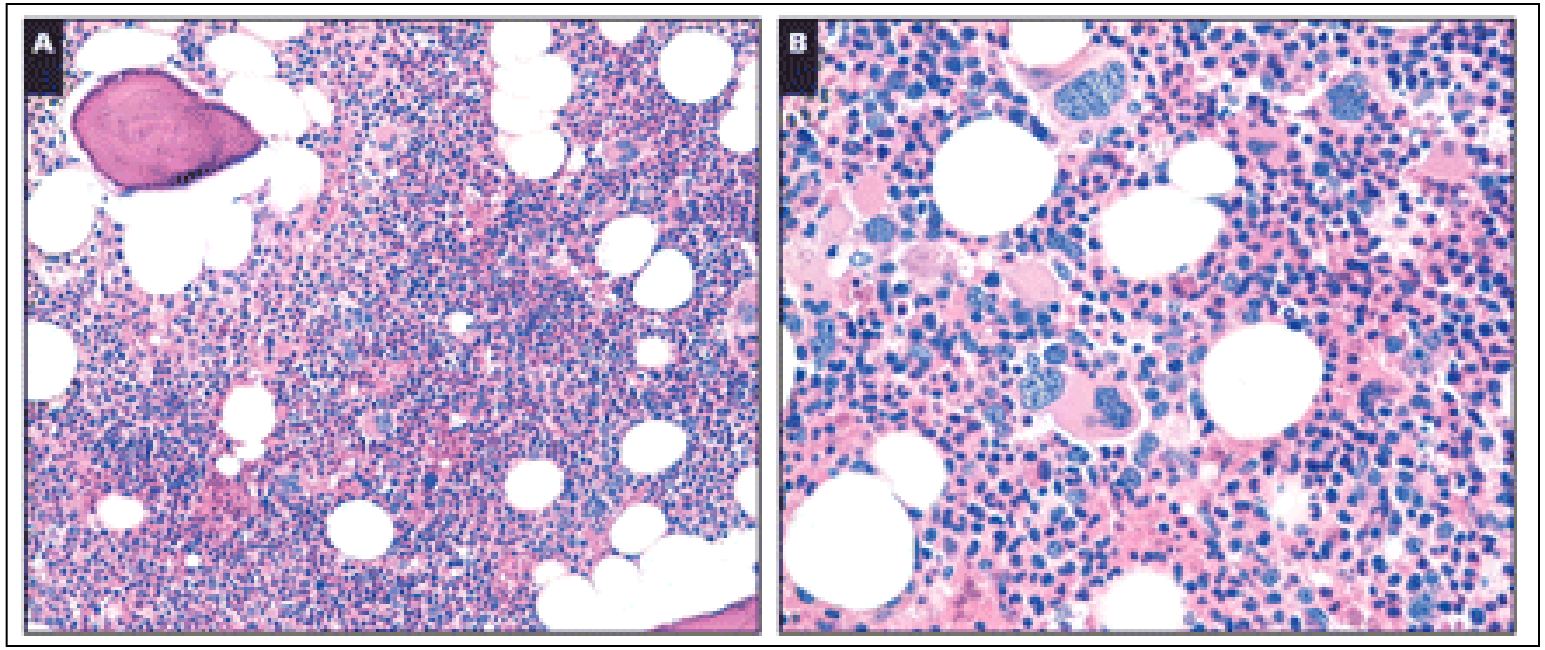
Polycythemia Vera: Bone Marrow Biopsy



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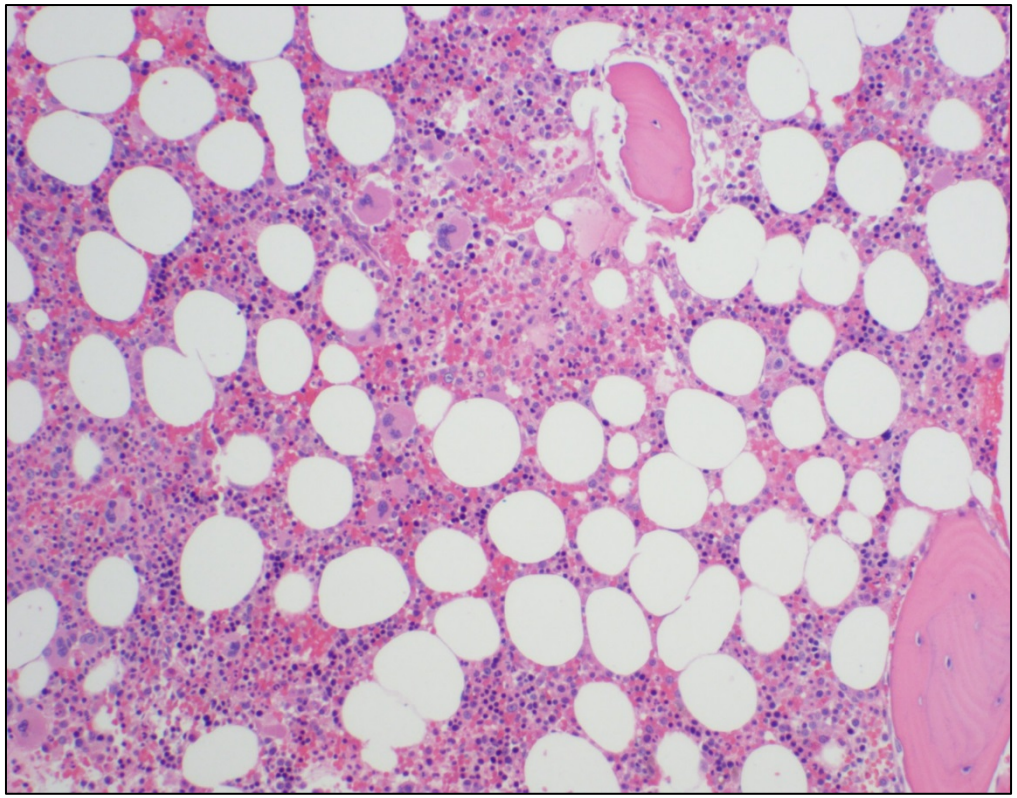
PV, 81 year old male



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Caveats

1. Not clear how many centers are performing at diagnosis a marrow biopsy or erythropoietin values.

2. Cannot rely only on peripheral counts to separate PV from ET^{JAKV617F}

3. Serum erythropoietin values normal in 15% of PV patients.

Laboratory Investigation of Myeloproliferative Neoplasms Recommendations of the Canadian MPN group

Busque L. et al. Am. J. Clin. Path, 2016, 146, 408

Cr-51 RBC – not available in Canada

> "Although both hemoglobin and hematocrit levels have some limitations, they are accepted as reasonable surrogates and indicators of red cell mass"

"Bone marrow provides limited additional value for diagnostic purposes"

Only about 25% of PV patients have had bone marrow biopsy at diagnosis at MPN centers in the US (courtesy of Incyte Corporation)

Initial Treatment

All agree must phlebotomize patients

Adjust for gender difference

- Men: Hct ≤ 45%
- Women: Hct ≤ 42%

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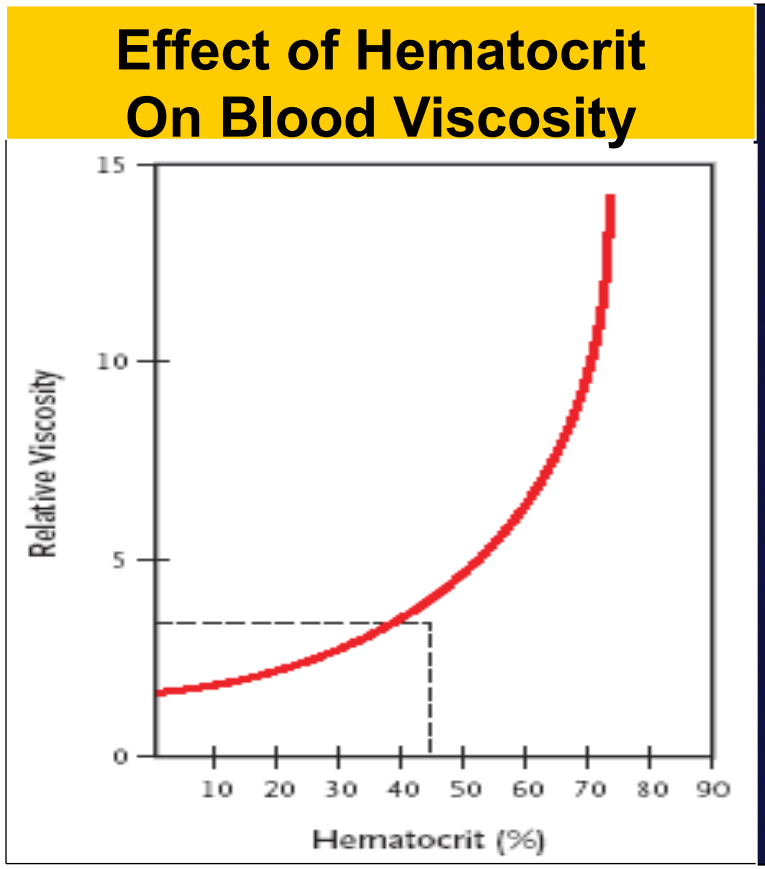
Outline of Lecture

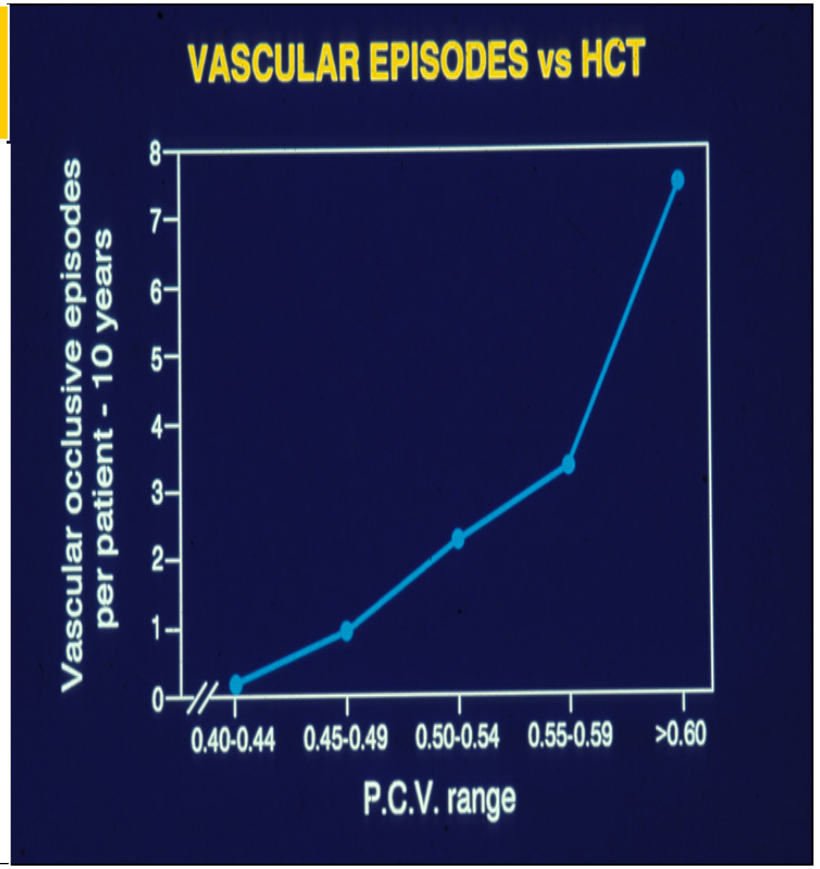
1. **DIAGNOSIS**
    - Definitions
    - What are we treating?

2. **ISSUES OF TREATMENT**
    - Phlebotomy
    - Hydroxyurea
    - Ruxolitinib
    - Interferon

Phlebotomy: Initially, Important Form of Treatment



Based on Chien S, Gallik S. American Physiological Society 1984; 217-249



Pearson TC, Wetherley-Mein G. *Lancet* 1978;1219-1222

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Treatment option in PV after initial phlebotomy to Hct ♂ 45%, ♀ 42%

Phlebotomy (continued)

Hydroxyurea

Interferon

Ruxolitinib after HU

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Risk Assessment
(Italian-derived studies)

	Treatment
Low Risk	
Under 60 years of age	Phlebotomy + Aspirin
No thrombotic events	HCT ≤ 45%
High Risk	
More than 60 years of age	Cytoreduction + Aspirin
History of thrombotic events	HCT ≤ 45%

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After Initial Phlebotomy Treatment

Must assess subsequent phlebotomy

requirements first.

Those who cannot remember the past are condemned to repeat it.

George Santayana

PHLEBOTOMY REQUIREMENTS DURING THE YEAR PRIOR TO rIFNα, ALL PATIENTS (CORNELL EXPERIENCE)

Quartile	# Patients	# PHL during the year prior to rIFNα	Median	Mean
1	9	1-4	3	2.8
2	9	5-7	5.5	5.7
3	8	8-12	9.5	9.6
4	8	12-25	15	16
Totals	34	Range: 1-25	7	8

Silver RT. Cancer. 2006

MPN Patients are highly symptomatic regardless of subset

Fatigue	61%
Trouble concentrating	61%
Loss of appetite	52%
Inactivity	52%
Weight loss	87%
Itching	62%

Geyer and Mesa, Blood, 2015

"Symptoms remain undermanaged in low risk patients not deemed candidates for cytoreductive therapy" (N=1334)

Gerber H, et al. J. Clin. Onc. 2016

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Low Risk Patient: Treatment

47 year old dentist

Hgb: 23.3 g/dL
HCT: 69%
Platelets: 145,000 x10^9/L
Low ferritin
Phlebotomies
Initial 13
Maintenance: 6 per year
"Complaints of increasing weakness that limits some activities ascribed to severe iron deficiency…"

Vannucchi, AM. Blood 2014

Phlebotomy-Only (PHL-O) is Unacceptable as Sole Treatment in PV

1. Poor Clinical Tolerance

2. Frequency of Vascular Complications

3. Risk of Early Progression to Myelofibrosis (probably an association)

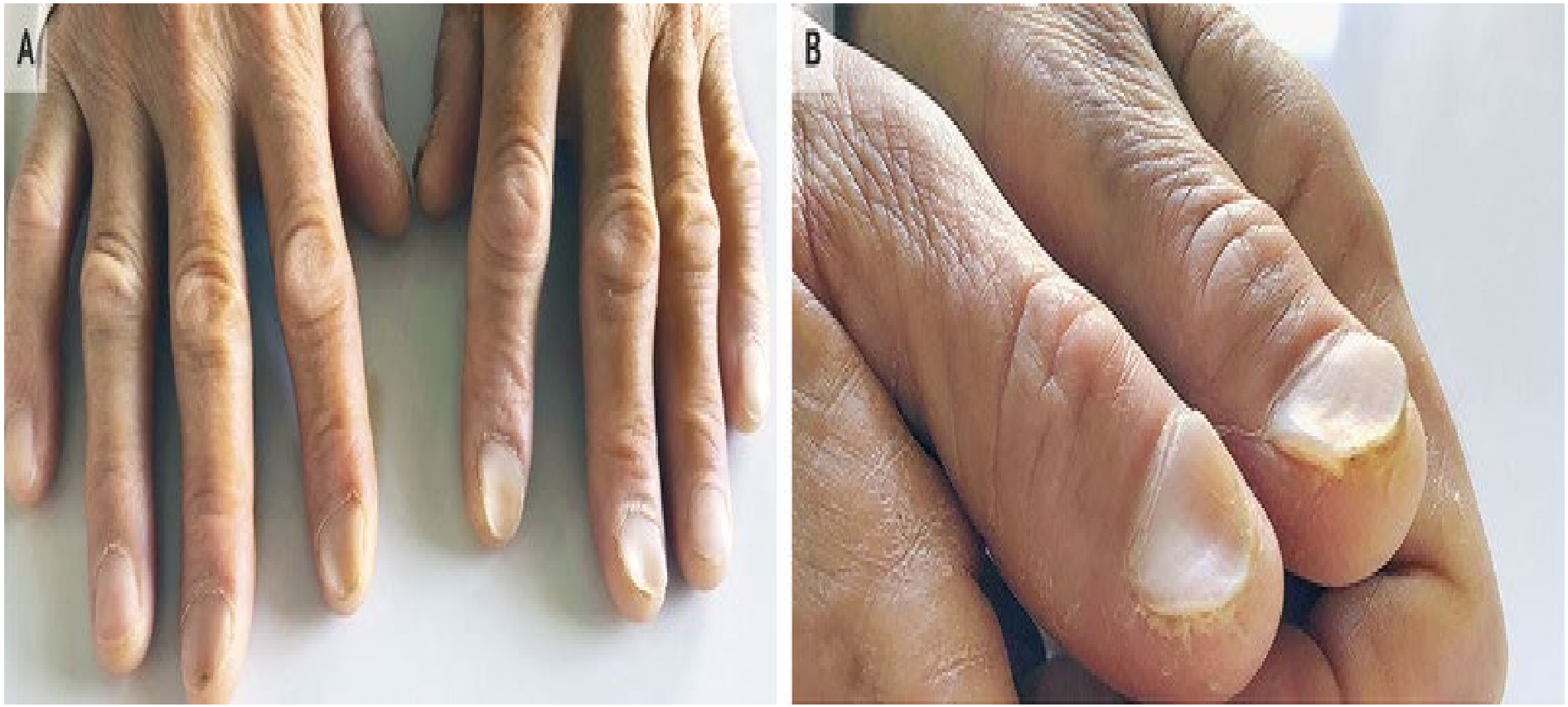
Najean Y, et al. Br J Haematol. 1994

Consequences of Iron Deficiency (clinical)

1) More Frequent Falls
2) Cognitive impairment
3) Dementia
4) Poor Exercise Tolerance
5) Impaired Results after chemotherapy
6) Impaired Results after Myocardial Infarction

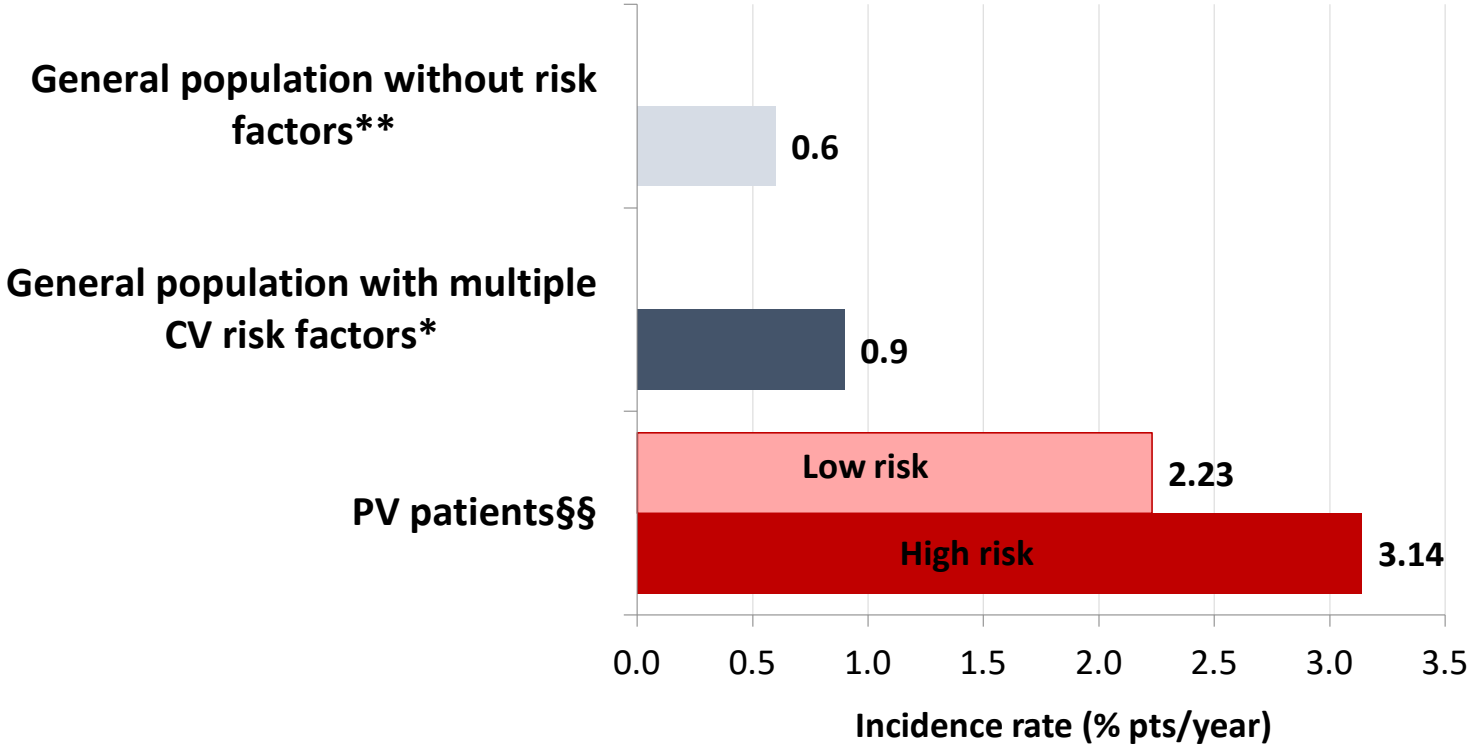
Stanley Schrier, MD, Hem Onc, January 2015
DeLoughery, New England Journal of Medicine, 2014

Koilonychia in iron-deficiency anemia



Ghaffari and Pourafkari, N Engl J Med 2018

Annual rate of thrombosis in contemporary patients with polycythemia vera and in general population



** Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual partecipant data from randomized trials, Lancet 2009; 373:1849-1860..* Yusef S et al Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease NEJM 2016

***The Risk and Prevention Study Collaborative Group. N−3 Fatty Acids in Patients with Multiple Cardiovascular Risk Factors. N Engl J Med 2013;368:1800-8.*

§ Barbui T, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer Journal. In press

§§ Barbui T, et al. In contemporary patients with polycythemia vera, rates of thrombosis and risk factors delineate a new clinical epidemiology. Blood 2014 124: 3021-3023

Courtesy: T. Barbui, MD

“Myelosupression is an important component of PV treatment”
PVSG

1. Control peripheral RBC, platelets, WBC
2. Diminish symptomatic splenomegaly
3. Relieves pruritis
4. Adjunct to phlebotomy

Fruchtman SM. Semin Hematol. 1997

Treatment

Worldwide, the majority of hematologists still use hydroxyurea (HU) for marrow suppression.

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Comparative incidence of thrombosis (PVSG study)

All events, first 378 weeks of study (7.3 years)

Treatment	Total patients	No. events	%
Hydrea + phlebotomy	**51**	**7**	**13.7**
Phlebotomy-only	**134**	**51**	**38.1**

Fruchtman S. PVSG Data. 1996

FAILURE, HU AT 1 YEAR, PVSG

(118 PTS)

Previously untreated:	**27%**
Previous myelosuppressives:	**41%**

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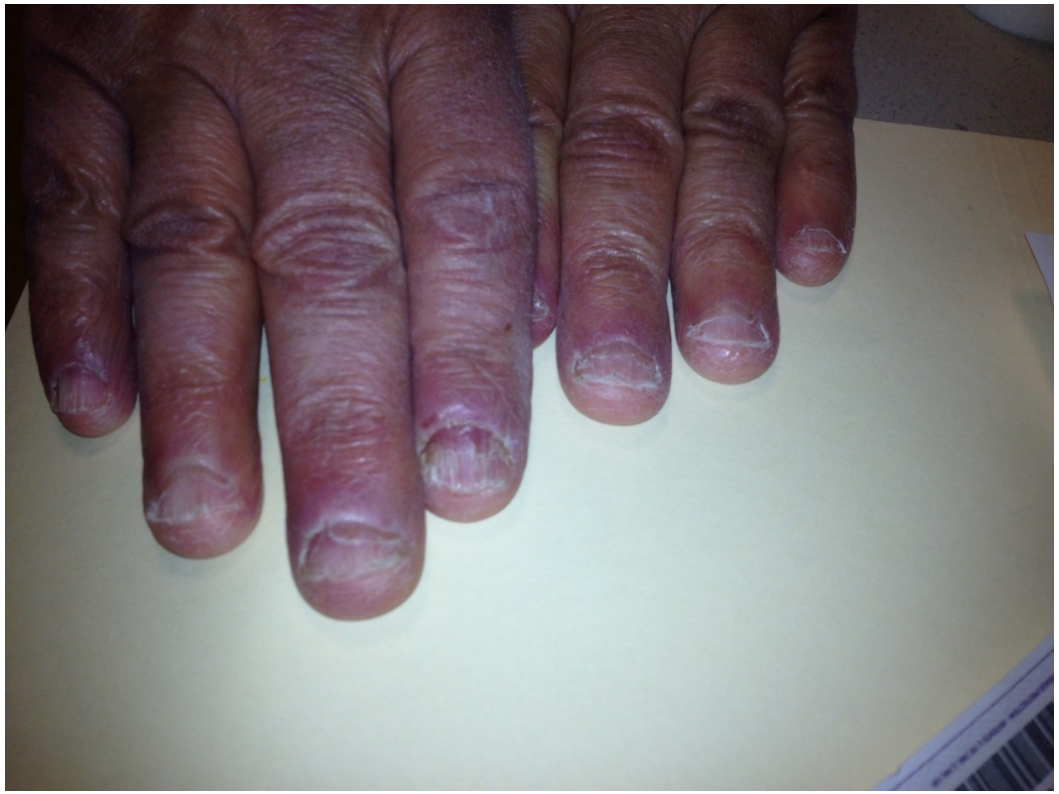
Toxicities of hydroxyurea



Nail Changes during Chemotherapy

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Ruxolitinib in PV
N=222

Patients: inadequate response or unacceptable toxicity after HU treatment

Phlebotomy dependant: 2 PHLs in prior 6 months

Control arm: resistant/intolerant to HU: 58.9%

Efficacy:	**1. HCT ≦ 45% :** **2. 35% spleen size reduction,**	**20%**
	HCT control only	**60%**

Safety: H. zoster in (6.4%) in the first 8 months

Vannucchi et. al.; NEJM 2015

Side effects of ruxolitinib

Anemia (43% vs. 31%) and thrombocytopenia	Initially, and usually mild
Infections urinary tract, lungs tuberculosis	Long-term use
Neoplasms B-cell lymphoma non-melanoma skin cancer other second cancers	Long-term use

Vannucchi et. al.; NEJM. 2015
Gisslinger et. al.; Blood. 2018
Pardanani, Tefferi; Blood 2018

When should ruxolitinib be used in PV? (RTS, 2019)

1. For symptomatic patients with:
   - pruritus
   - night sweats
   - early satiety, etc.

2. Symptomatic and/or persistent splenomeyaly

3. Patients resistant, refractory to HU, rIFNα

4. Frank myelofibrosis inappropriate for or not responsive to rIFN

5. Combination therapy with:
   - rIFNα – early stage (Hasselbach)
   - azacitidine – late stage (Verstovsek)

Specific activities of interferon-alpha (rIFN-a) of interest in PV

Suppresses megakaryopoiesis (Wang)

Antagonizes action of PDGF (Lin)

Inhibits erythroid progenitors in vitro (Means, Krantz)

Anti-angiogenic (Folkman)

Involved in *JAK*-STAT signaling

Affects PV stem cell (Mullaly)

Safe to use during pregnancy

Not leukemogenic

Basic principles for using IFN in PV (RTS et al.)

Most start with low dose

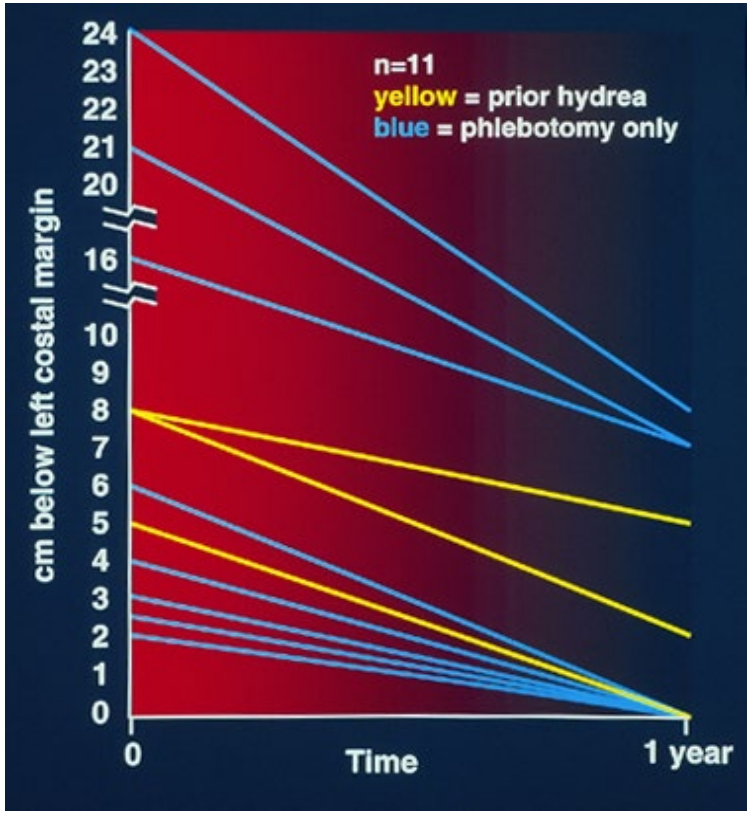
Increase dose slowly

End point: phlebotomy free

Silver RT. Cancer. 2006

CHANGE IN SPLEEN SIZE

1 year after rIFN-a



2 years after rIFN-a

- 27/30 (90%) patients with initial splenomegaly showed greater than 50 % reduction in spleen size whether or not they received prior HU
- In 23 (76.7%) patients, spleen became non-palpable

Silver RT. Cancer. 2006

Limitations of rIFN therapy

Side effects are mainly dose dependent; perhaps less with single isomer interferon, RHO-PEG.

Typically transient flu-like symptoms that occur shortly after injections

- Headache
- Myalgia
- Back/joint pain
- Fever
- Chills
- Mild skin reaction
- Fatigue

Less common (resolve upon rIFN discontinuation or decrease in dose):

- Chronic fatigue
- Depression
- Musculoskeletal pain
- Alopecia
- GI toxicity
- Confusion (elderly patients)
- Liver toxicity
- Cytopenias
- Autoimmune disease
- Pulmonary, cardiac, or renal dysfunction
- Neurological (gait disturbance, frontal lobe dysfunction, bilateral lower extremity neuritis

Summary: Drop-out rate 15-25% in reported studies depending on dose, enthusiasm of physician and patient.

Interferon is effective

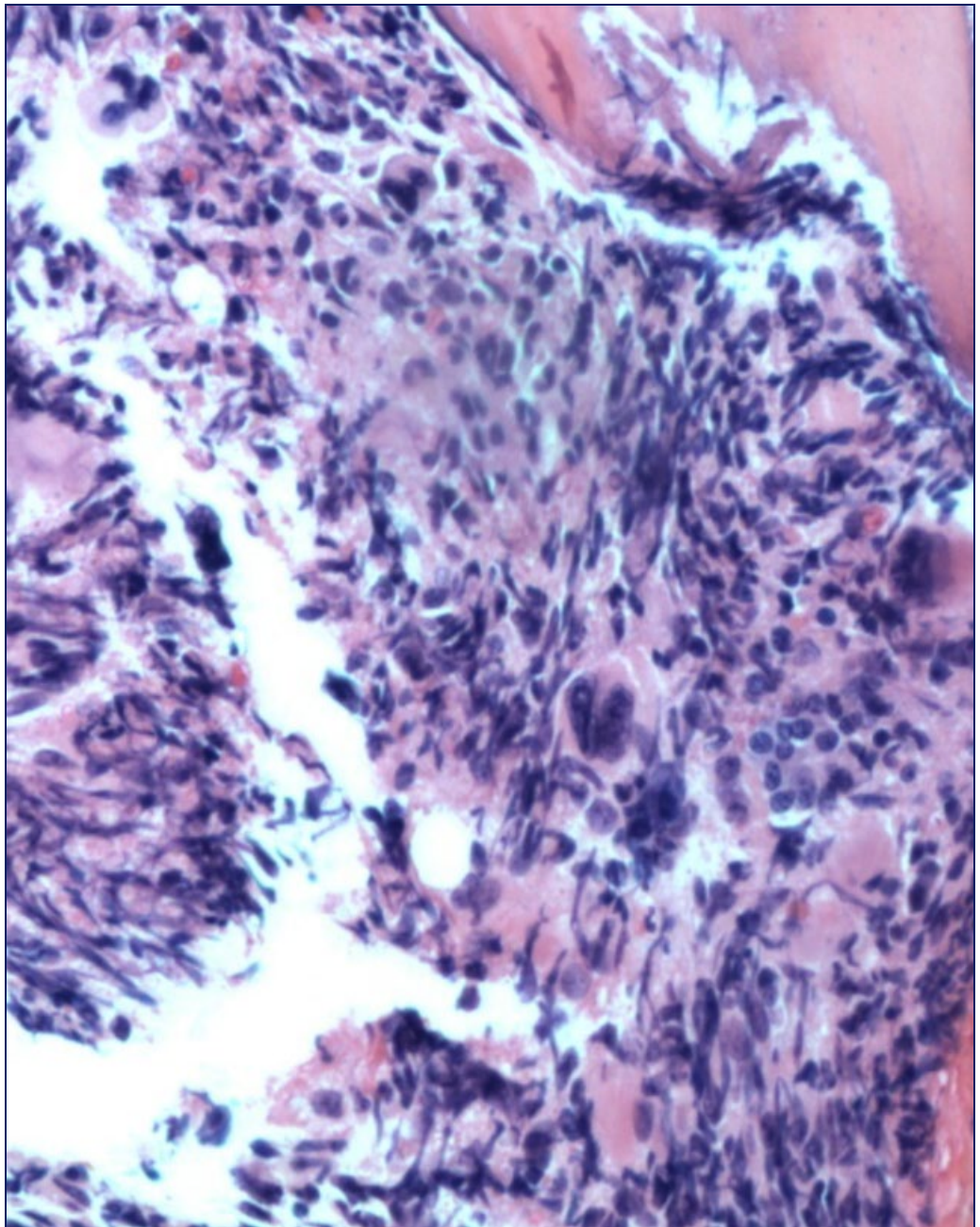
in treating the fibrosis

that occurs in

polycythemia vera in the absence of

leukoerythroblastosis

2/11/2009: H&E section (20X): increased fibrosis and increased atypical megakaryocytes



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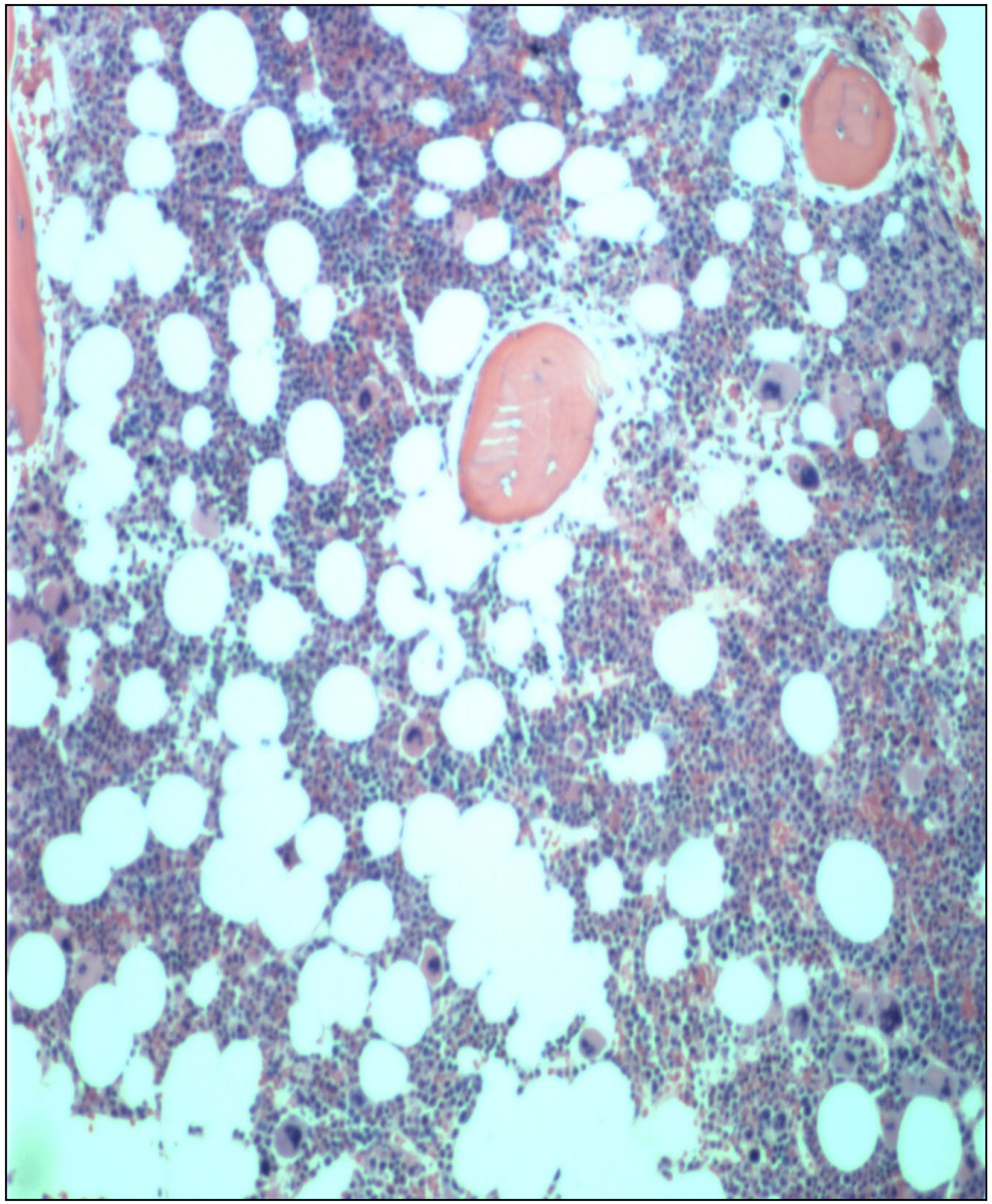
7/27/2011: H&E, 20X: Megakaryocytes form focal clusters



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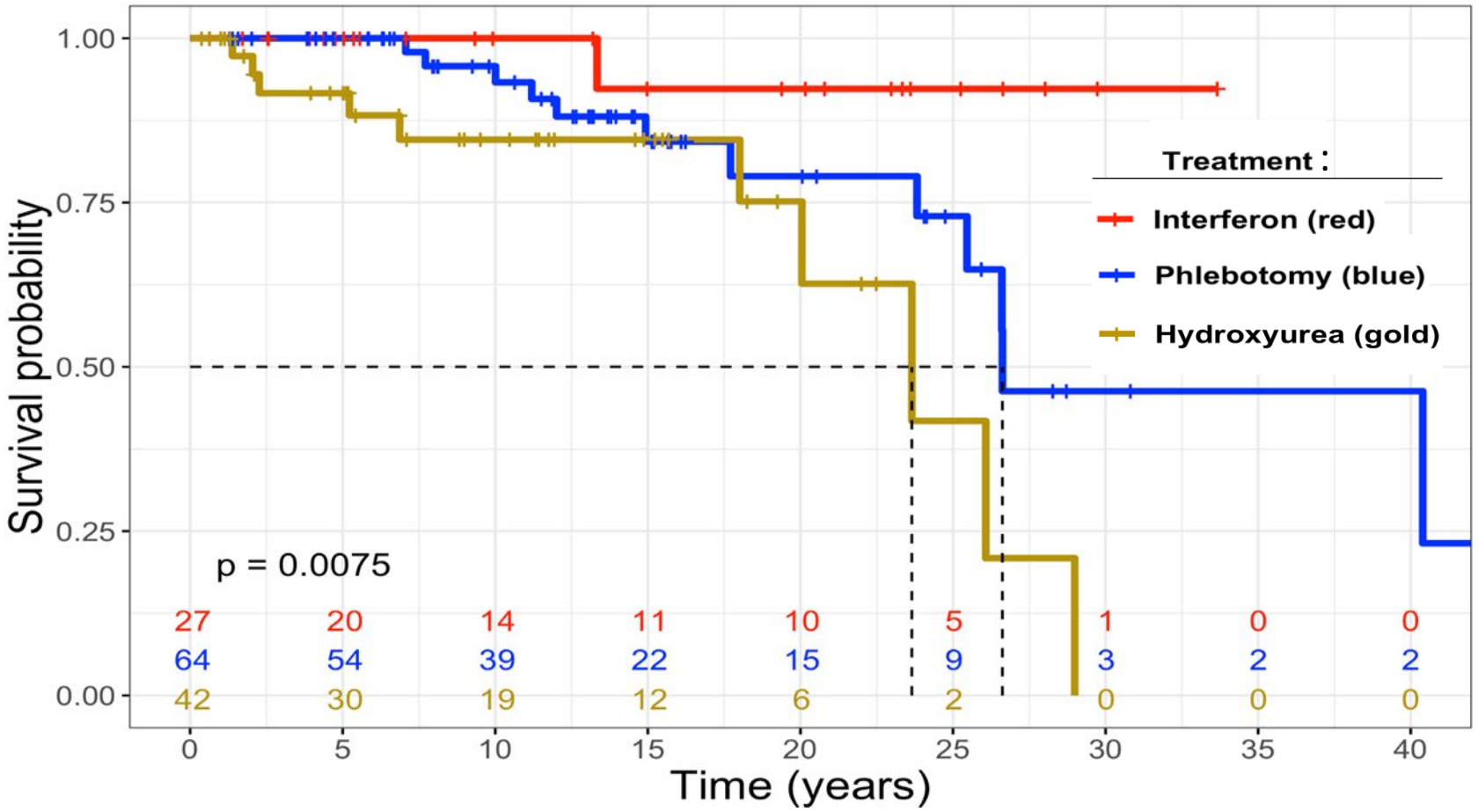
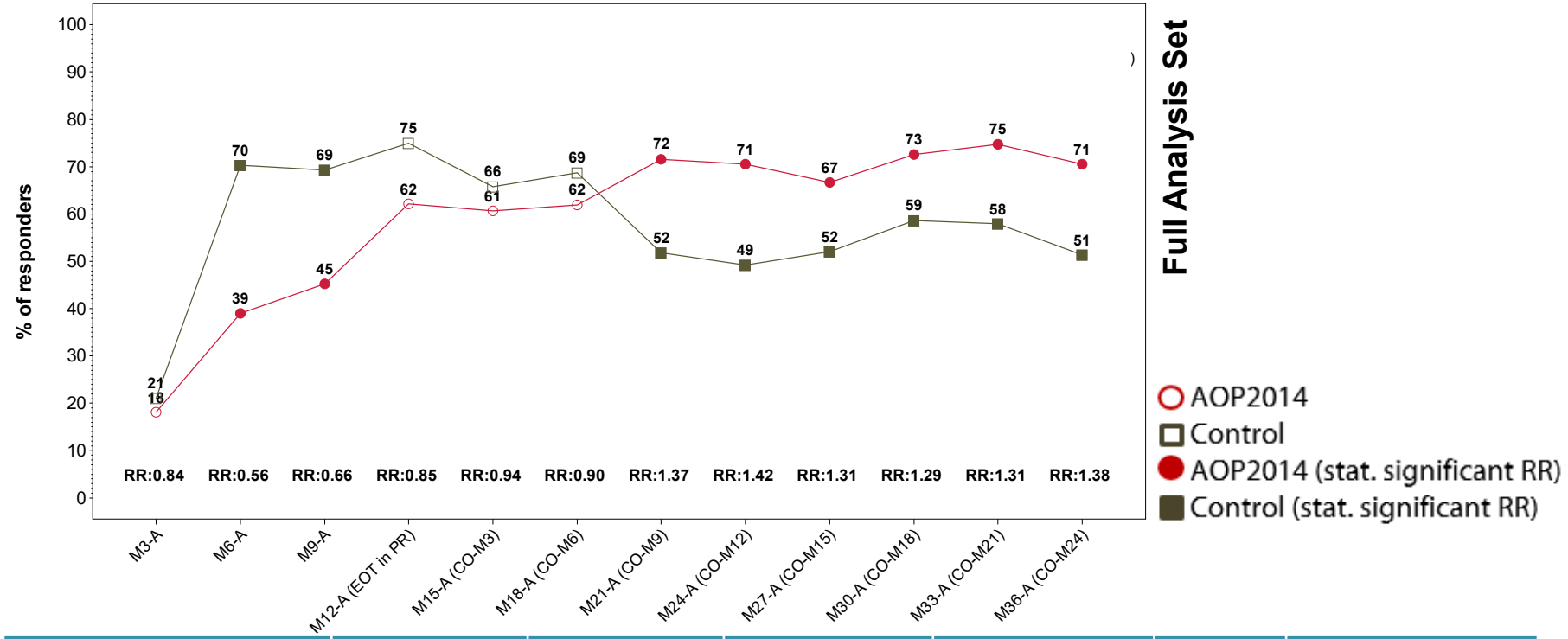
PV: Myelofibrosis-free survival, by treatment



Abu-Zeinah G, Kirchevsky S, Sosner C, Savage N, Scandura JM, Silver RT. ASH 2018

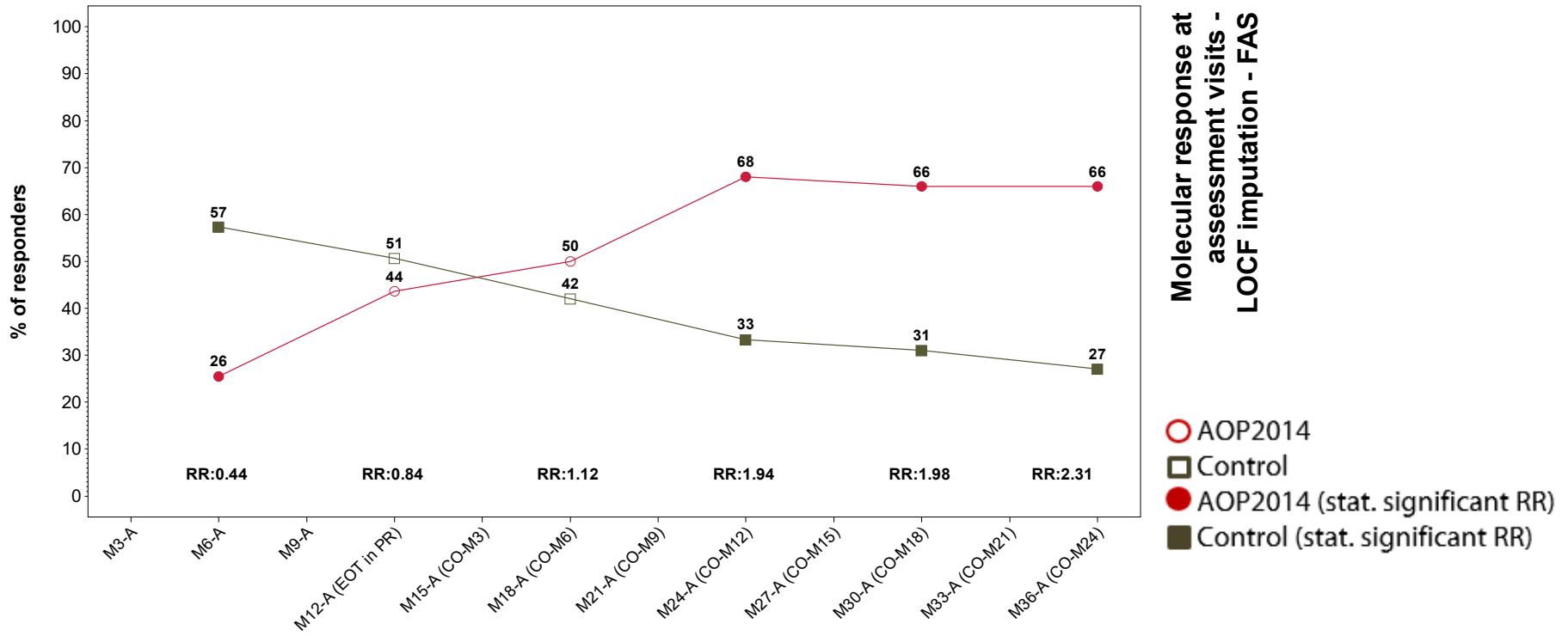
Complete hematologic response (CHR)



Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	59/95	62.1	57/76	75.0	0.1201	0.85 [0.70-1.04]
MONTH 24	67/95	70.5	33/67	49.3	0.0111	1.42 [1.08-1.87]
MONTH 36	67/95	70.5	38/74	51.4	0.0122	1.38 [1.07-1.79]

Courtesy of Gissingler H. ASH 2018

JAK2 (V617F) - Molecular response



Study Month	Responder/N	Responder %	Responder/N	Responder %	P-value	RR [95% CI] (AOP2014/Control)
	Ropeg (N=95)		Control (N=76)			
MONTH 12 (EOT in PR)	41/94	43.6	38/75	50.7	0.5001	0.84 [0.62-1.15]
MONTH 24 (LOCF)	64/94	68.1	25/75	33.3	0.0001	1.99 [1.40-2.84]
MONTH 36 (LOCF)	62/94	66.0	20/74	27.0	<0.0001	2.31 [1.56-3.42]

Courtesy of Gissingler H. ASH 2018

Conclusions

Diagnosis of PV vs. ET^{V617F} can be difficult, must have marrow

Phlebotomy only results in severe iron deficiency anemia; and allows the disease to progress unchecked.

Limitations in the use of ruxolitinib in PV

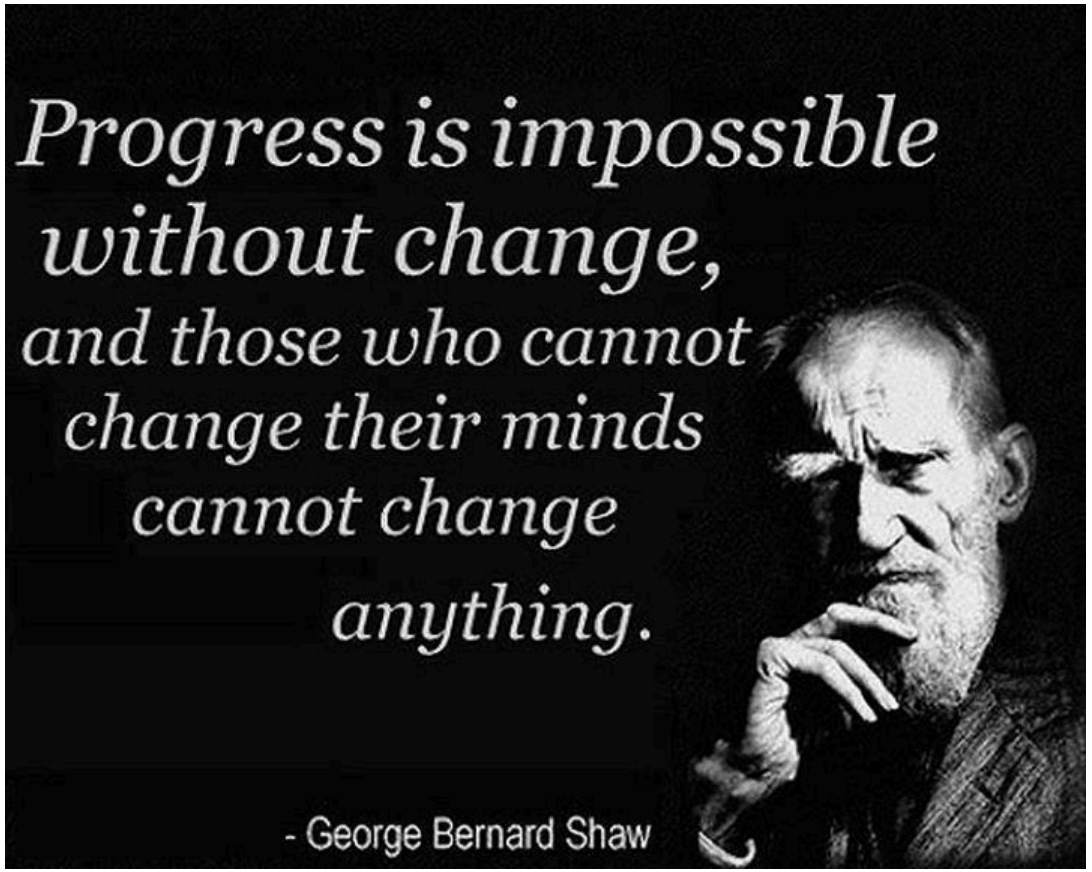
Interferon is probably the best treatment to control the proliferative aspects of polycythemia vera

- Biological basis for its use. Not leukemogenic.
- Able to induce clinical, hematological and some degree of molecular remission.
- Evidence of delayed onset of MF submitted

We use JAK2 allele burden and marrow biopsy to decide on discontinuing rIFN

JAK2 inhibitors in combination with interferon for symptomatic patients


Leeches


Progress is impossible
without change,
and those who cannot
change their minds
cannot change
anything.
- George Bernard Shaw