PV Treatment in 2017: Is it curable?

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Outline

- What are we treating?
  - WHO Criteria 2016
  - Distinguishing between PV and JAK2(+) ET
- Treatment
  - Phlebotomy
  - Hydroxyurea
  - Interferon
  - Ruxolitinib
- Is PV curable?

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. "The 2016 revision to the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia." Blood (2016): blood-2016.

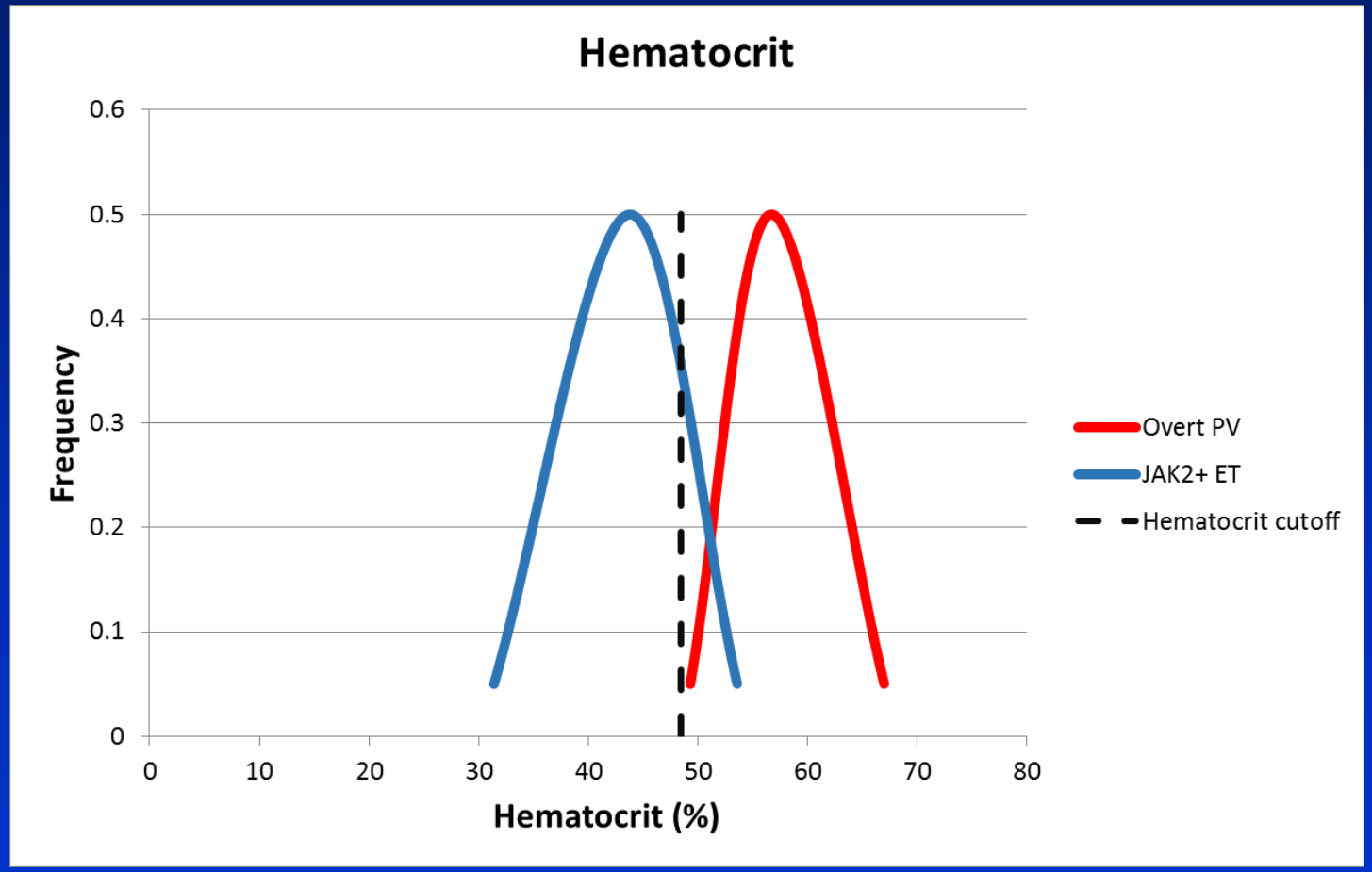
Two main points regarding diagnosis of PV:

A single hematocrit or hemoglobin value is not a substitute for measuring red cell mass!!

EPO Levels may be normal (~15 %).

Ancochea, Àgueda, et al. Brit J Haem 167;3 (2014): 411-417.
Silver, Krichevsky, Gjoni. Lymph and Hem. 2016, in press.

Hematocrit ranges in JAK2(+) ET and PV patients

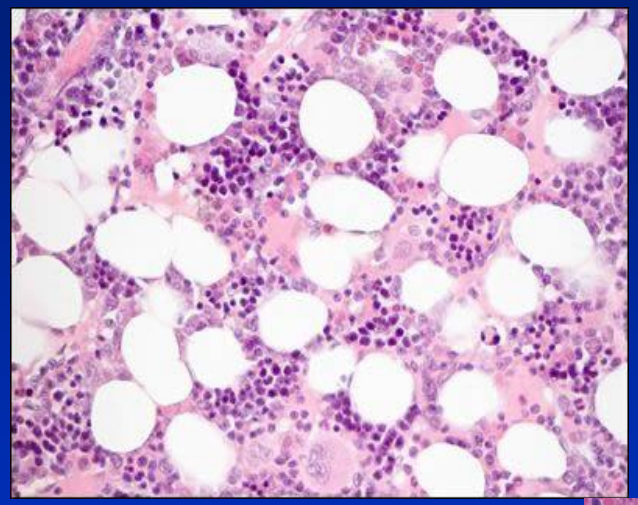


Potential error when using hematocrit to distinguish JAK2+ ET and PV.

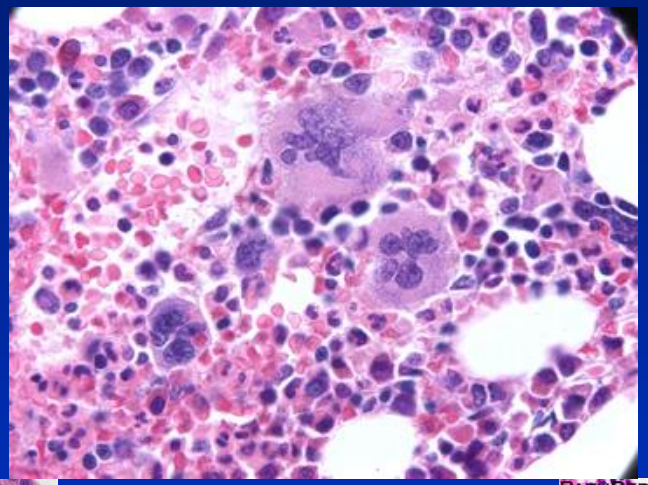
Barbui T et. al., "Masked polycythemia vera (mPV): Results of an international study." Am. J. Hematol. 89:52-54

Bone Marrow Examination is Helpful

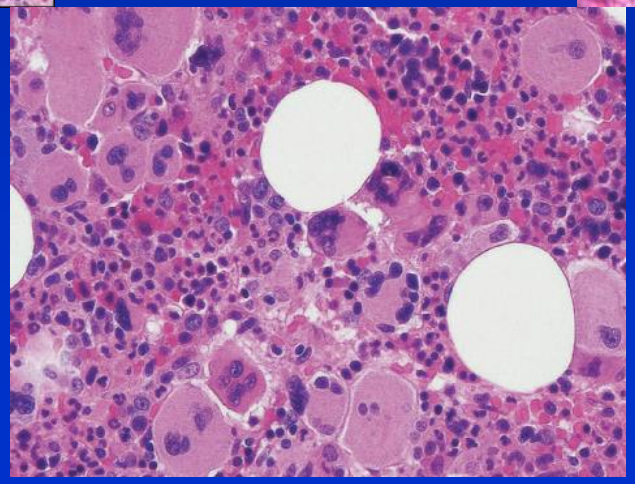
Normal



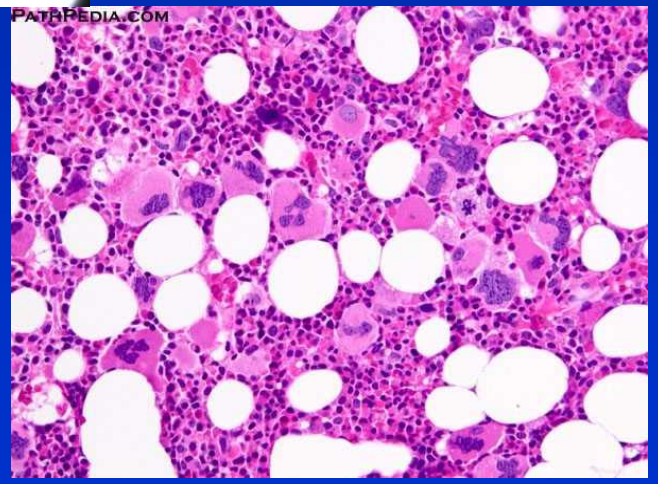
PV



Cellular PMF



ET



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Phlebotomy

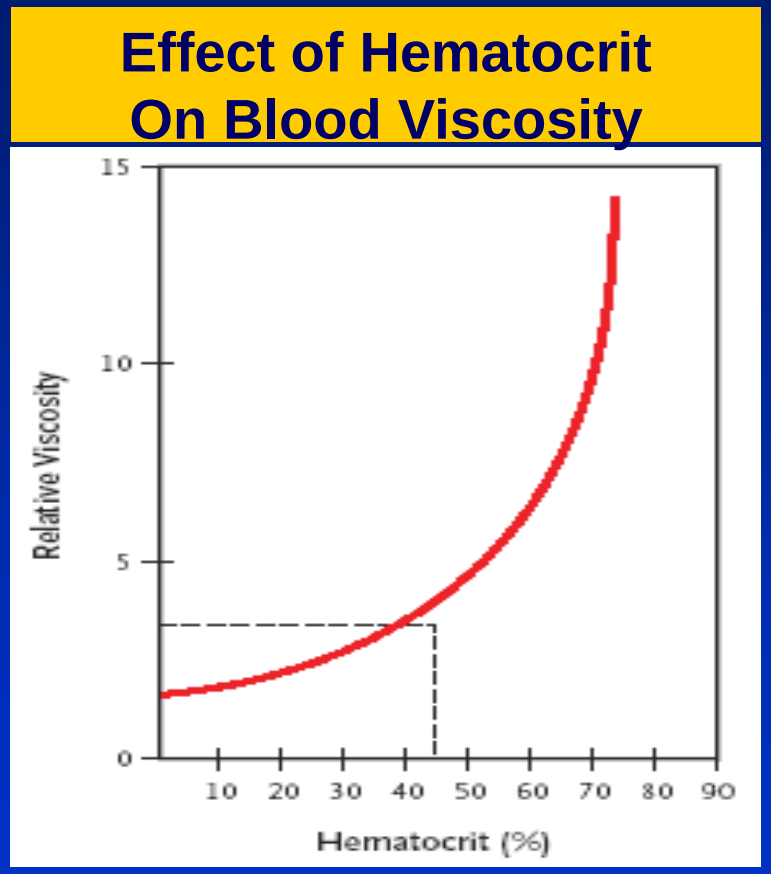
All agree must phlebotomize patients

However, must adjust for gender difference

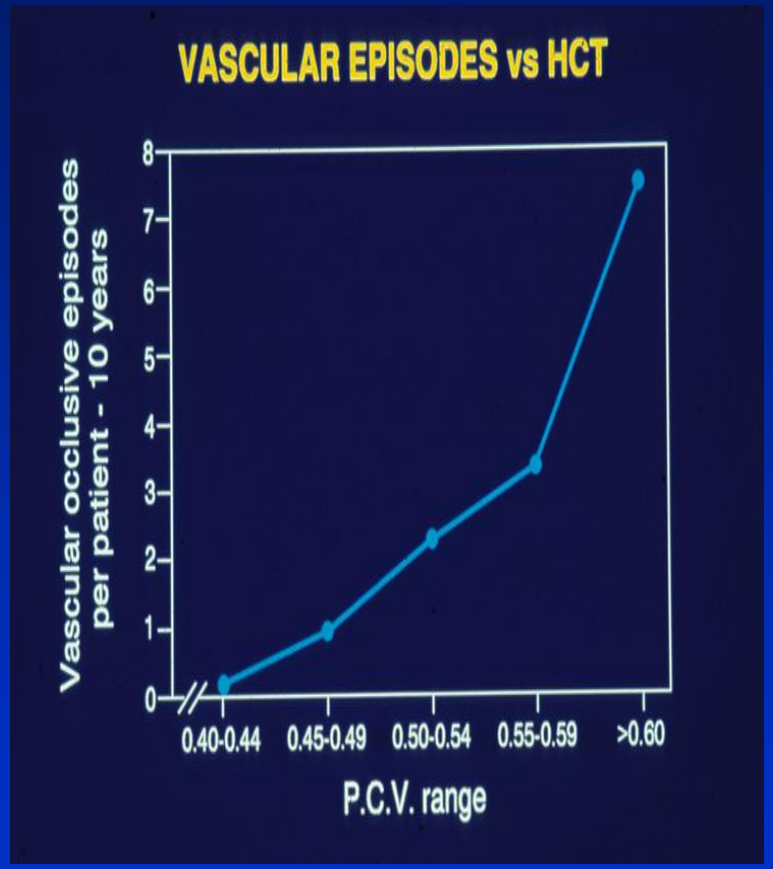
- **Men: Hct ≤ 45% (RBC = 5.0×10^6/mm)**
- **Women: Hct ≤ 42% (RBC = 4.5×10^6 /mm)**

Marchioli, Roberto, et al. *New England Journal of Medicine* 368.1 (2013): 22-33

Phlebotomy: 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

Initial Treatment

Must assess phlebotomy

requirements first.

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; 107:451-58

Myth of Phlebotomy Only:
Phlebotomy Unacceptable as Sole Treatment

1. Poor clinical tolerance
2. Frequency of vascular complications
3. Development of iron-deficiency anemia
4. Risk of early progression to myelofibrosis (?)
5. Cardiac toxicity

The hematocrit value in polycythemia vera: caveat utilitor

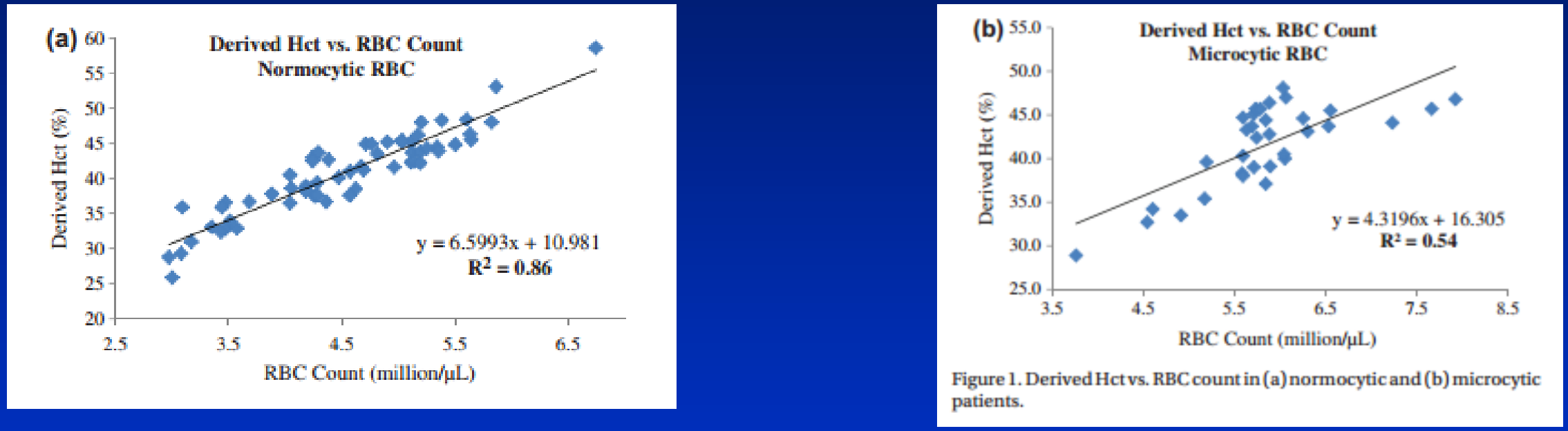


Figure 1. Derived Hct vs. RBC count in (a) normocytic and (b) microcytic patients.

With iron deficiency anemia , there is a poor correlation (right graph) between derived hematocrit and red cell count.

Silver and Gjoni, *Leukemia Lymphoma*, 2014

Effect of MCV on Derived HCT

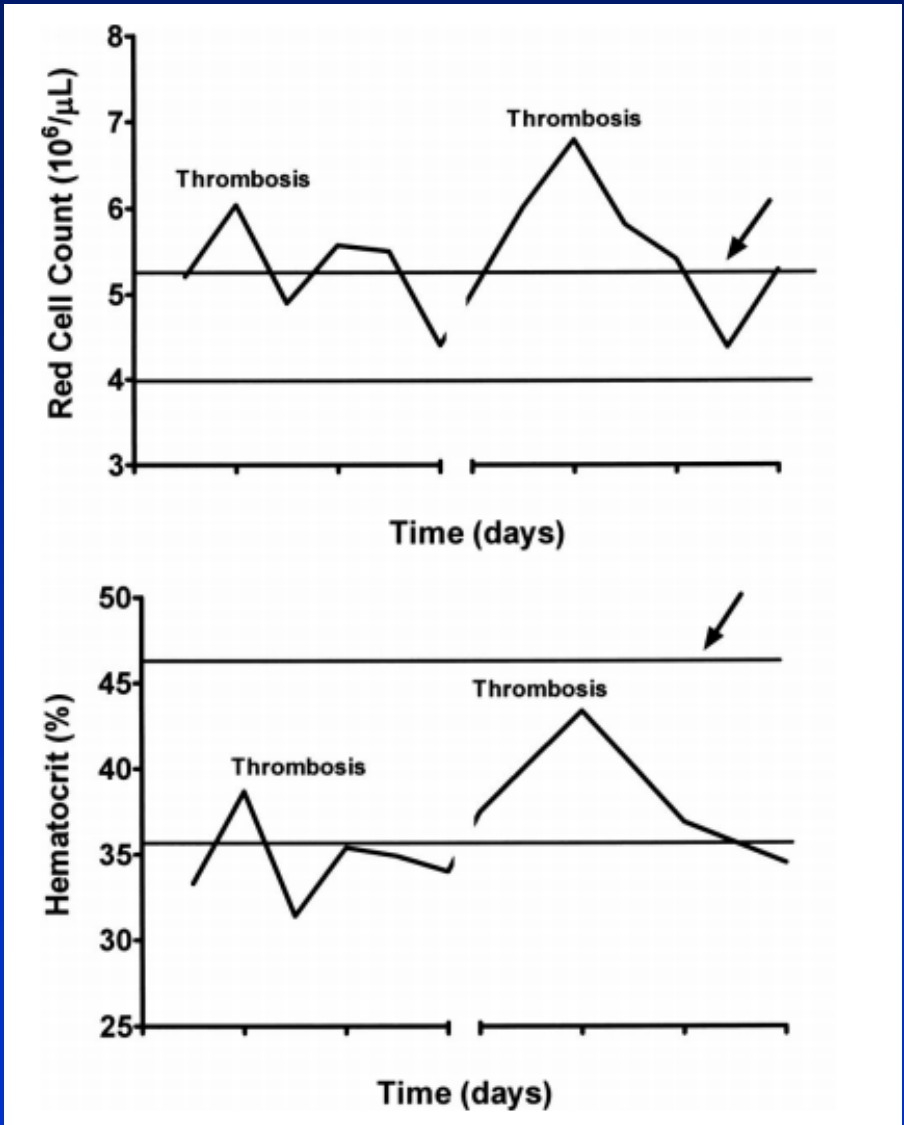
Remember, simple arithmetic is still important!

Phlebotomy: low MCV

Chemotherapy: high MCV

RBC	X	MCV	=	HCT
5.0	X	90	=	45
5.0	X	110	=	55
5.0	X	75	=	37.5
6.4	X	70	=	45

Dangers of hematocrit values ignoring RBC



Spivak, Jerry L., and Richard T. Silver. "The revised World Health Organization diagnostic criteria for polycythemia vera, essential thrombocytosis, and primary myelofibrosis: an alternative proposal." Blood 112.2 (2008): 231-239.

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**

Fructman. Sem Hem. 1997. 34(17).

Hydroxyurea

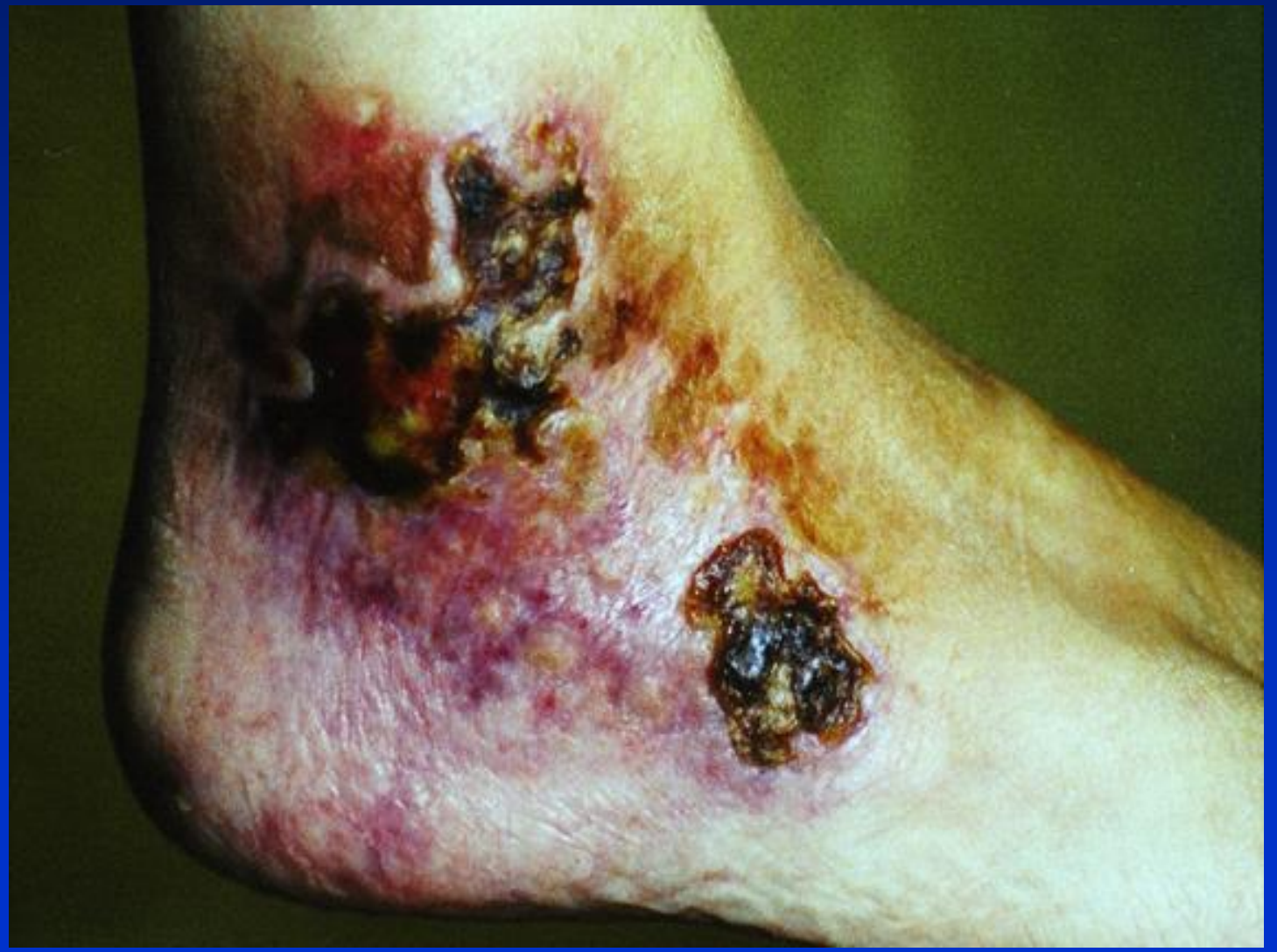
- **Worldwide, the majority of hematologists still use hydroxyurea (HU) as a cytoreductive agent**
- **Predisposition to cancers and leukemia?**

Comparative incidence of thrombosis (PVSG study)

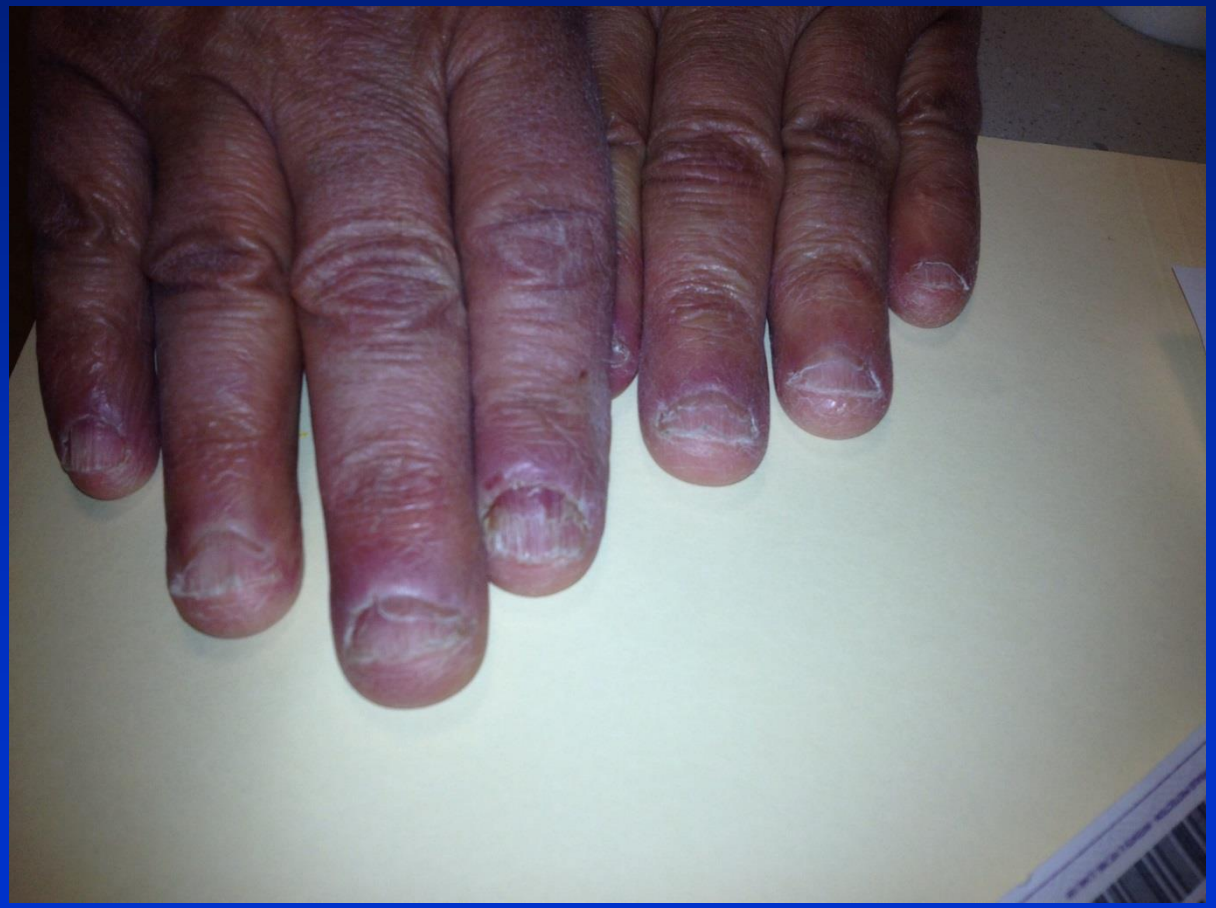
All events, first 378 weeks of study (7.3 years)

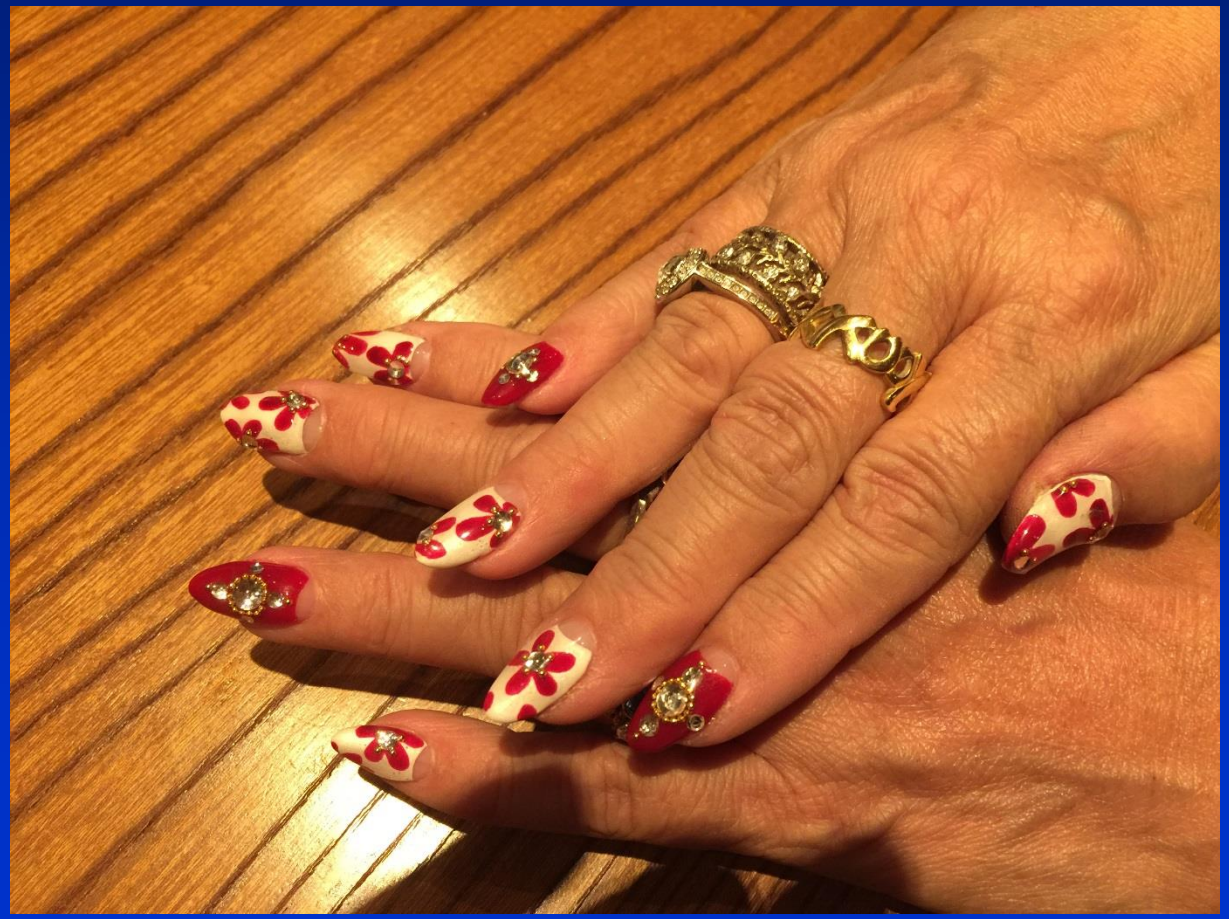
Treatment	Total patients	No. events	%
Hydrea + phlebotomy	51	7	13.7
Phlebotomy-only	134	51	38.1

Toxicities of hydroxyurea



Toxicities of hydroxyurea





Specific Activities of interferon-alpha (rIFN-α) of interest in PV

- **rIFN specifically affects JAK2(+) stem cells in mice (Mullaly, *et al.* ASH, 2013)**
- **Affects intracellular signaling related to JAK-STAT and other pathways**
- **Inhibits early red cell and megakaryocyte development**
- **Inhibits blood vessel formation**

Treatment of PV with low-dose rIFNa (N= 55)

Start {rIFNα-2b 1 million unts 3 X wk
{Peg rifn α-2b 45 mgm/wk

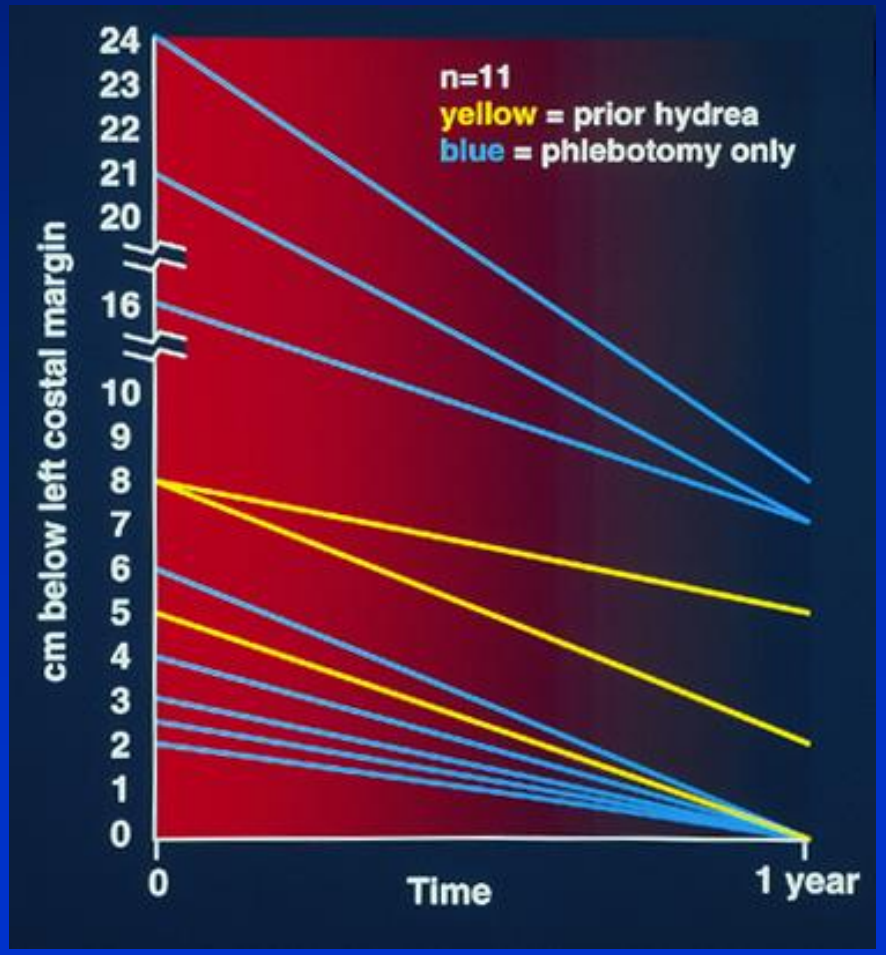
According to the PVSG criteria (HCT ≤ 45%, no phlebotomy requirements, and platelets ≤ 600,000/µL):

- **All 55 patients had clinical responses**
- **No thrombohemorrhagic episodes**
- **Previous treatment with HU in 30%**

Silver RT. *Sem Hem*. 1997; 34:40-50
Silver RT. *Cancer*. 2006; 107:451-58

Change in Spleen Size

1 year after rIFN-α



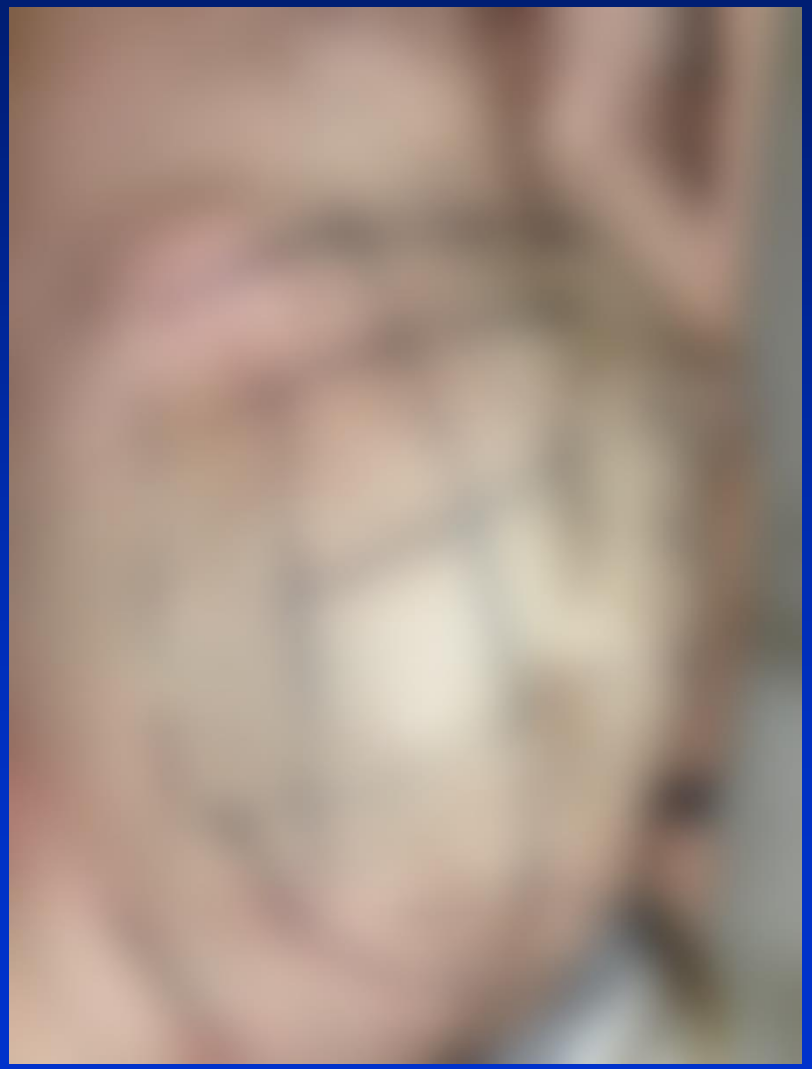
2 years after rIFN- α

- **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**

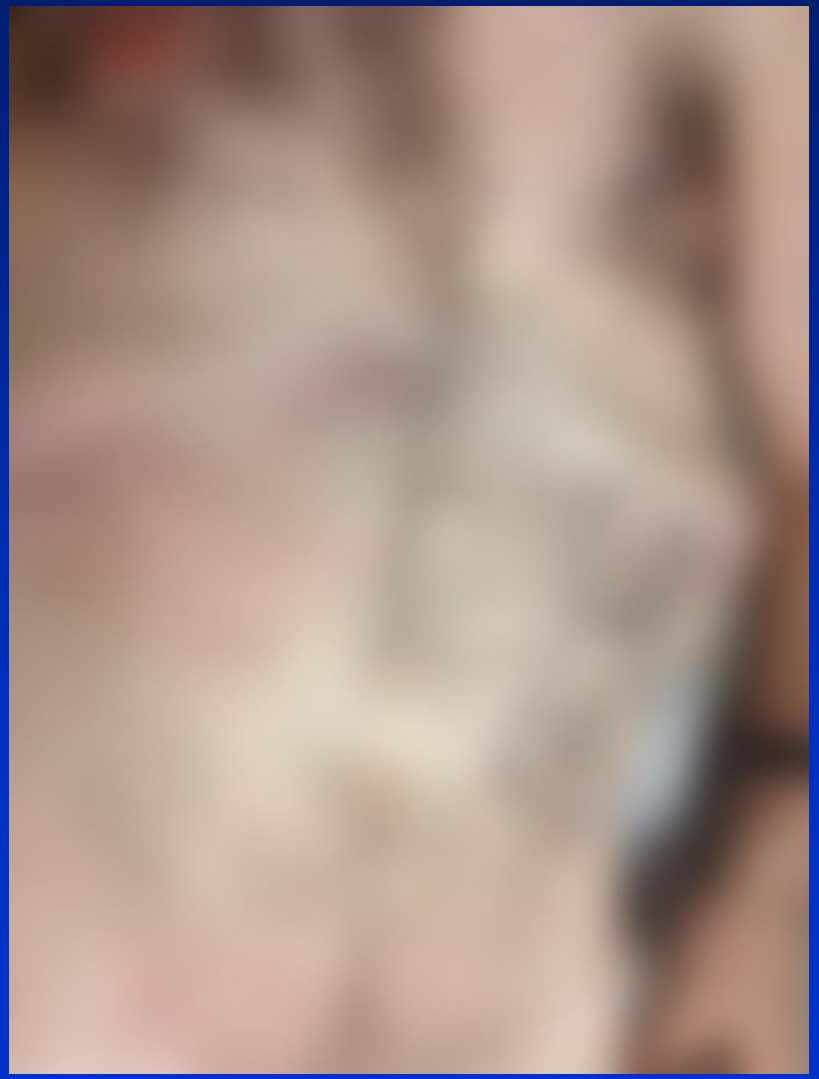
Silver, RT, *Cancer*, 2006

Effect of interferon treatment on spleen size

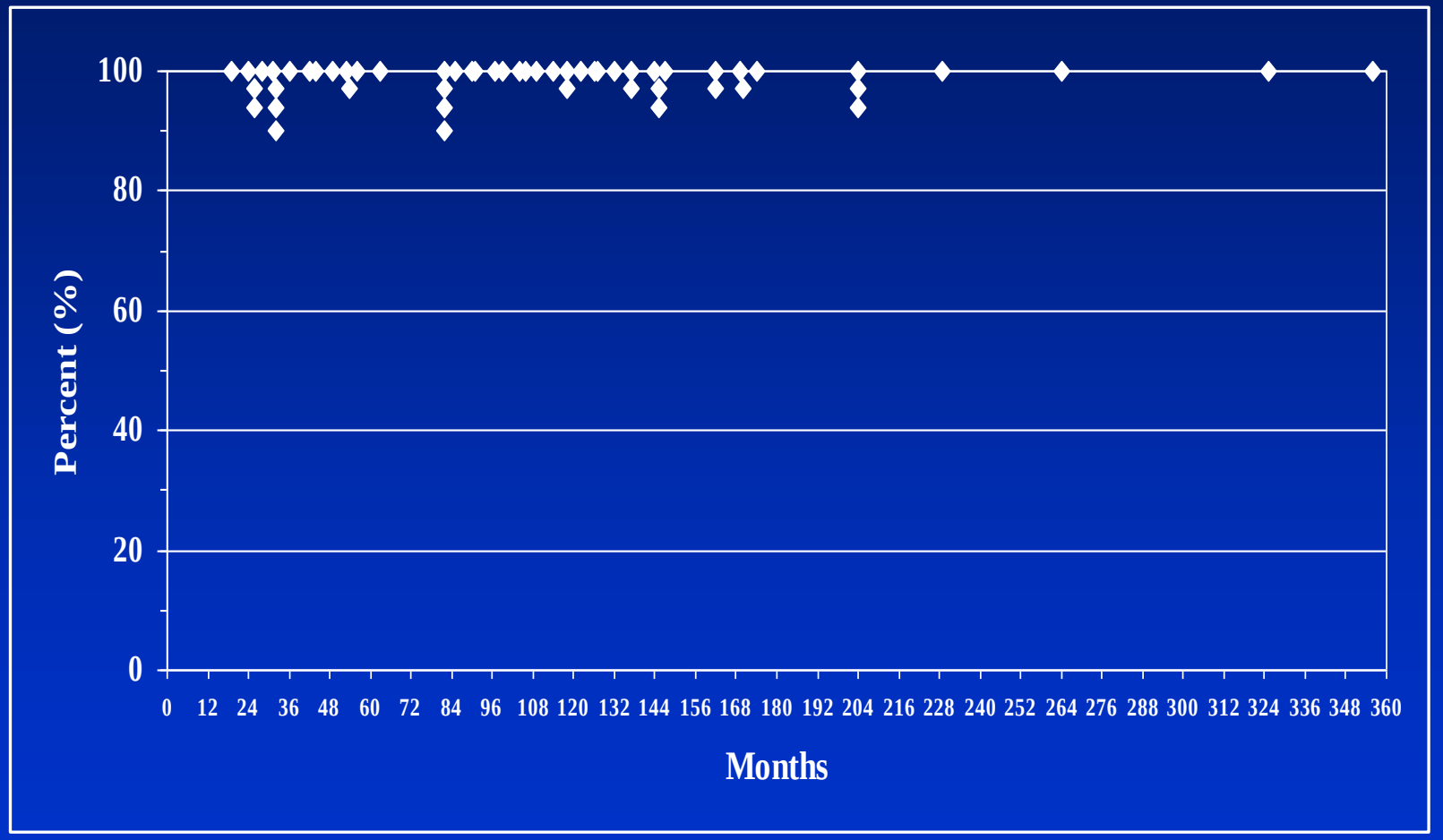
BEFORE rIFN RX



Two years AFTER



Progression-Free Survival from Thrombohemorrhagic Events, 55 PV Patients



All 55 patients had CR or PR

Silver, RT. Cancer 107:451-58, 2006

Limitations of rIFN therapy

Side effects are mainly dose dependent; perhaps less with single isomer interferon, RO-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 dysfuntion, bilateral lower extremity neuritis

Ropeginterferon alpha 2b (RoPEGα2b)

- **51 patients, treated every 2 weeks**
  - **33% treated with hydroxyurea at time of screening**
  - **Prior to therapy, 22% of patients suffered major cardiovascular events**

- **Response rate: 90%**
  - CR: 47%
  - PR: 43%
  - CMR: 31%

Gisslinger, et. al.;Blood, 2015

Significant Decreases in JAK2 Allele Burden After Peg-rIFNα

(a quantitative number from 0 – 100%)

- **First reported by Kiladjian, then Quintas-Cardama, Verstovsek**
- **Not by Silver and Kuriakose**
- **May be related to dose, duration, degree of toxicity**

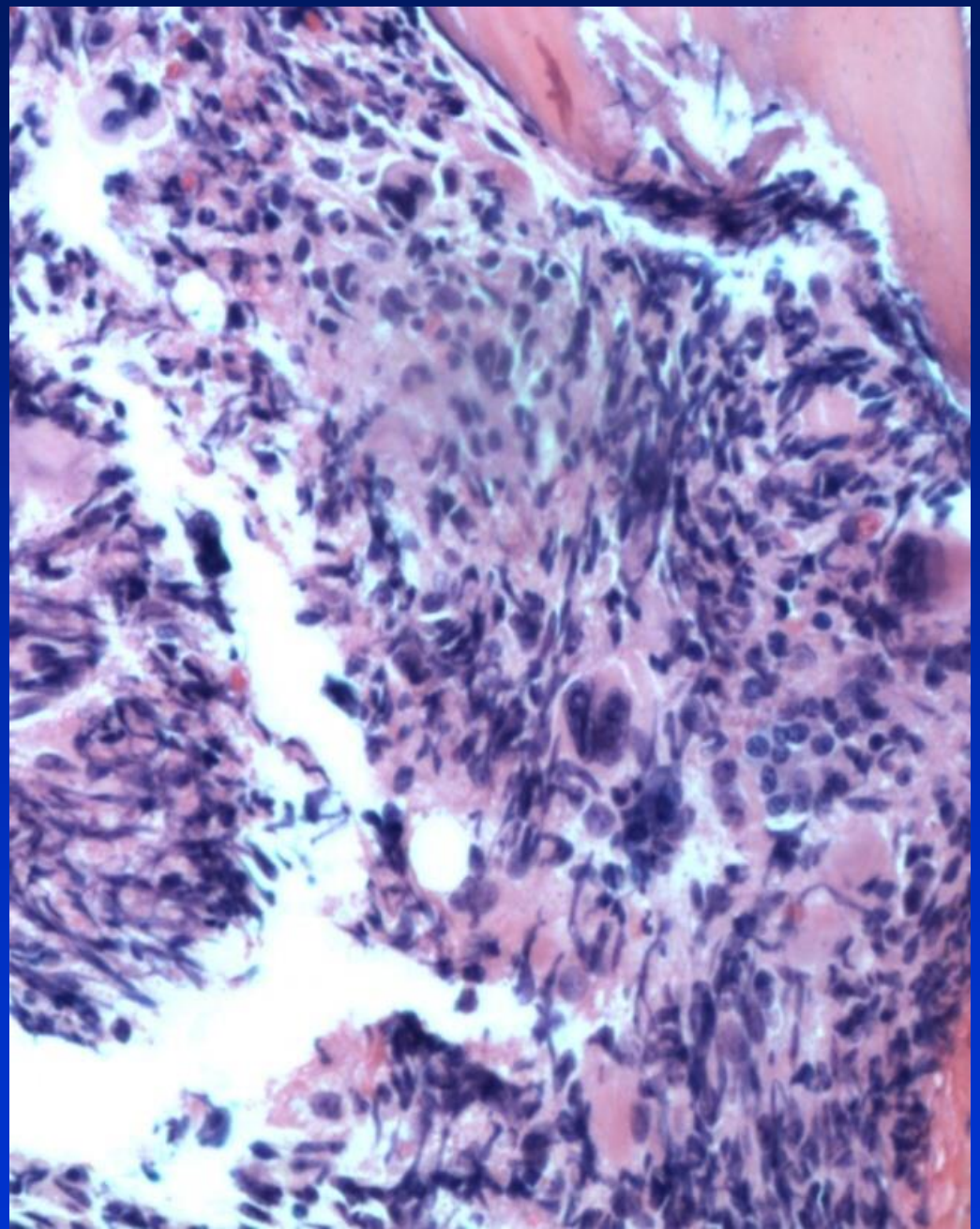
Therapeutic Conundrum

Is it preferable to maintain complete hematologic response with lowest interferon dose rather than to aim for *JAK2* negativity?

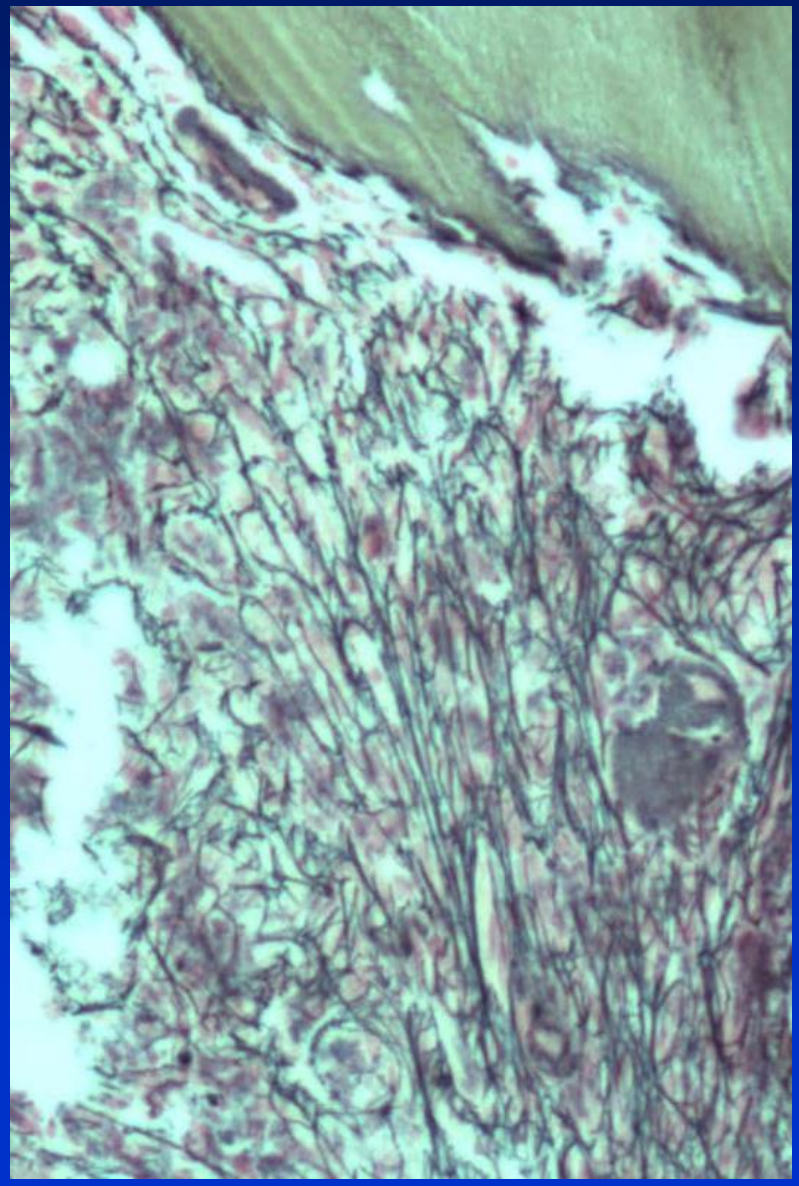
Interferon is effective in treating the fibrosis that occurs in polycythemia vera in the absence of leukoerythroblastosis.

This provided the basis for its use in treating “early” myelofibrosis.

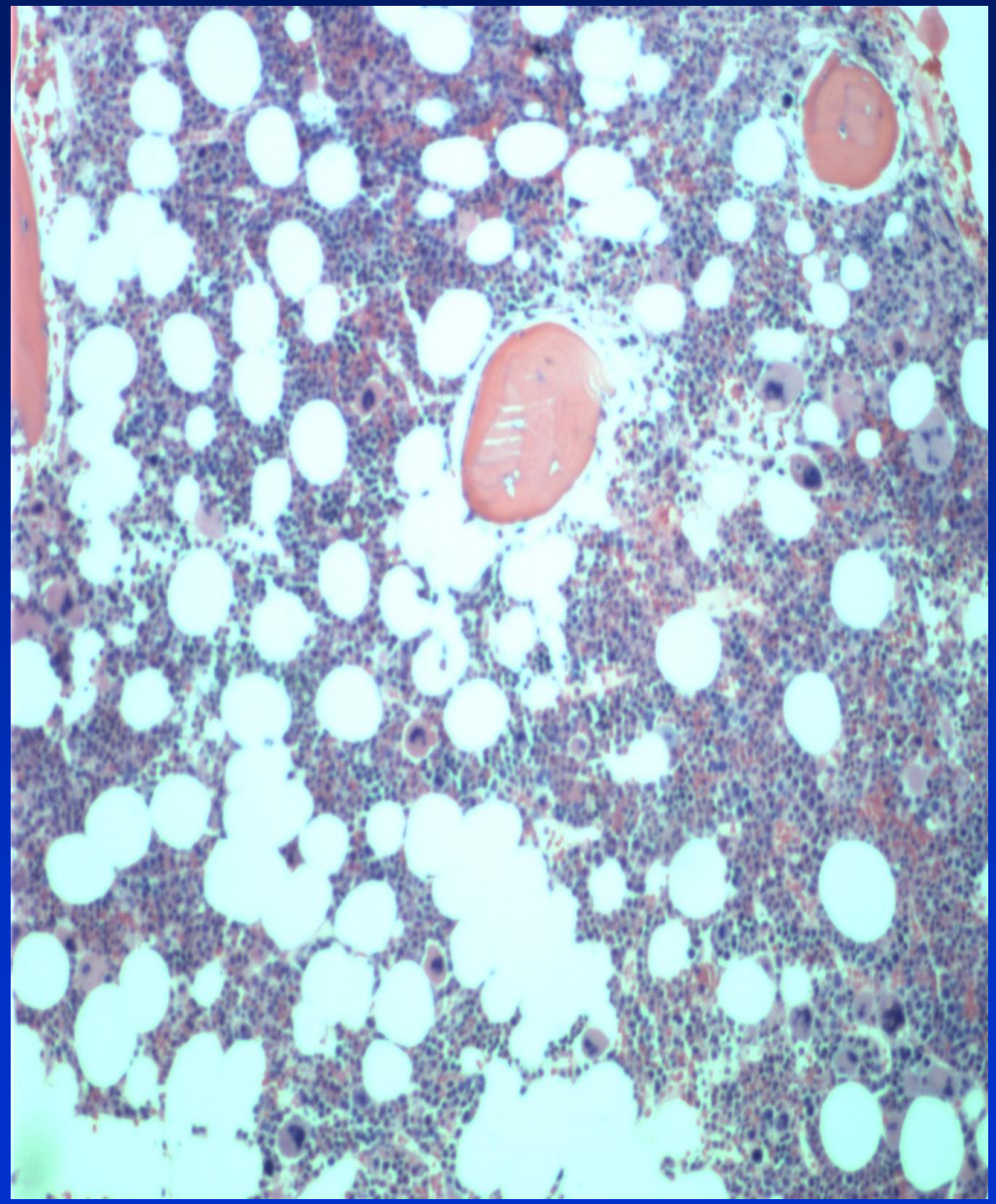
2/11/2009: H&E section (20X): increased fibrosis and increased atypical megakaryocytes



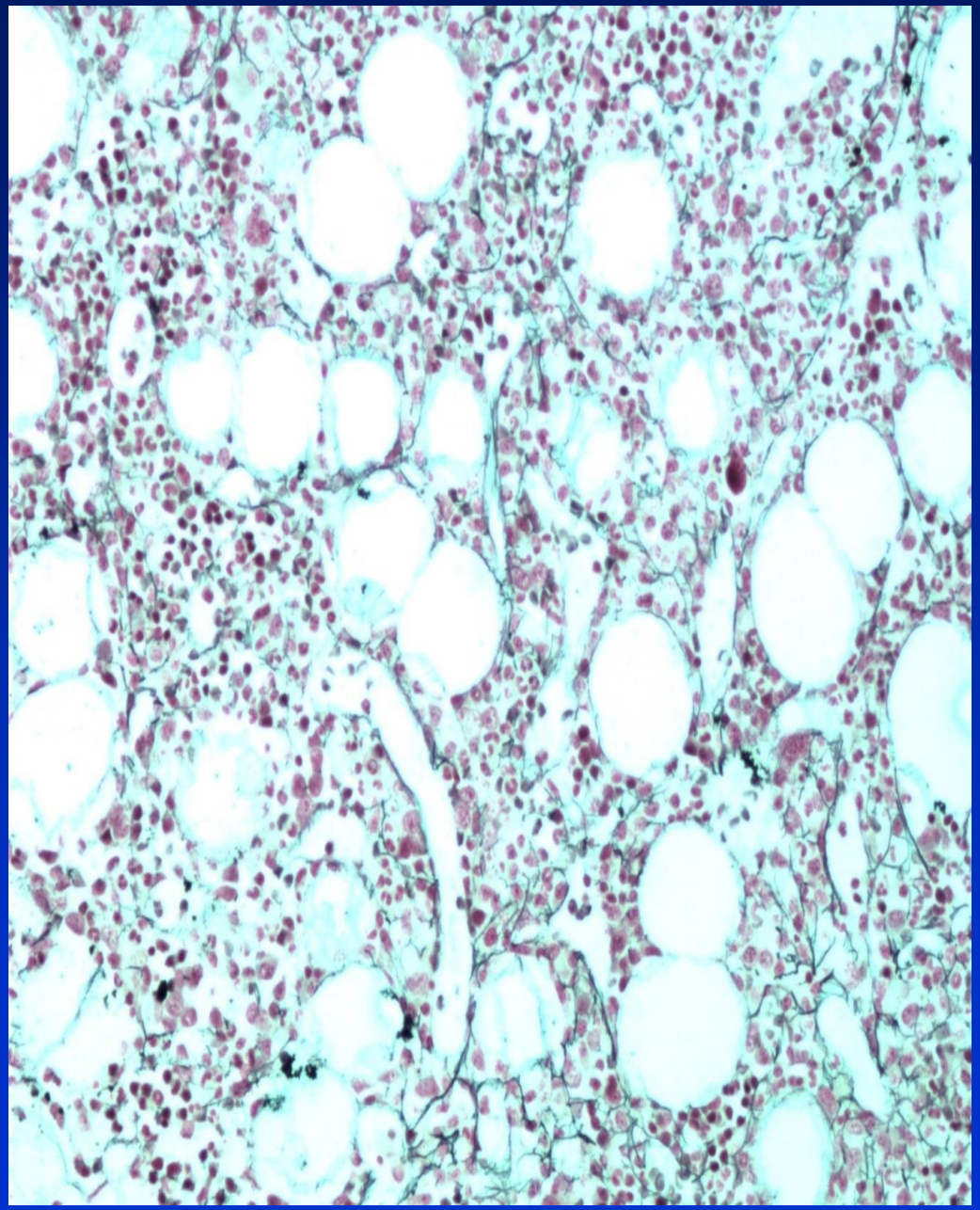
2/11/2009: 20X reticulin special stain: Markedly increased fibrosis – diffuse thick reticulin fibers



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



7/27/2011: 20X, reticulin special stain: mild increase in fibers (1+)



Response to treatment in primary, post-PV, and post-ET myelofibrosis: all patients (N=30)

Response	No
CR	2
PR	9
CI	4
Stable	7
PD	4
Death	4

73% improved or remained stable, with 50% achieving CI or better

Silver et al, Proceedings American Society of Hematology 2016
Silver et al, Cancer *{In Press}*

Ruxolitinib in PV
N=322

Patients: inadequate response/unacceptable toxicity after HU treatment

Results: 21% of patients in ruxolitinib group achieved end point of Hct control, 35% reduction in spleen size at 32 weeks

Rux + other drugs (rIFN, azacytadine) undergoing evaluation

Vannucchi et. al.; NEJM 2015

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Basis for Early Treatment

1) PV, $JAK2^{V617}$ HSC clone is small

2) Minimum $JAK2^{V617F}$ tumor burden preferentially sensitive to rIFNα

↓

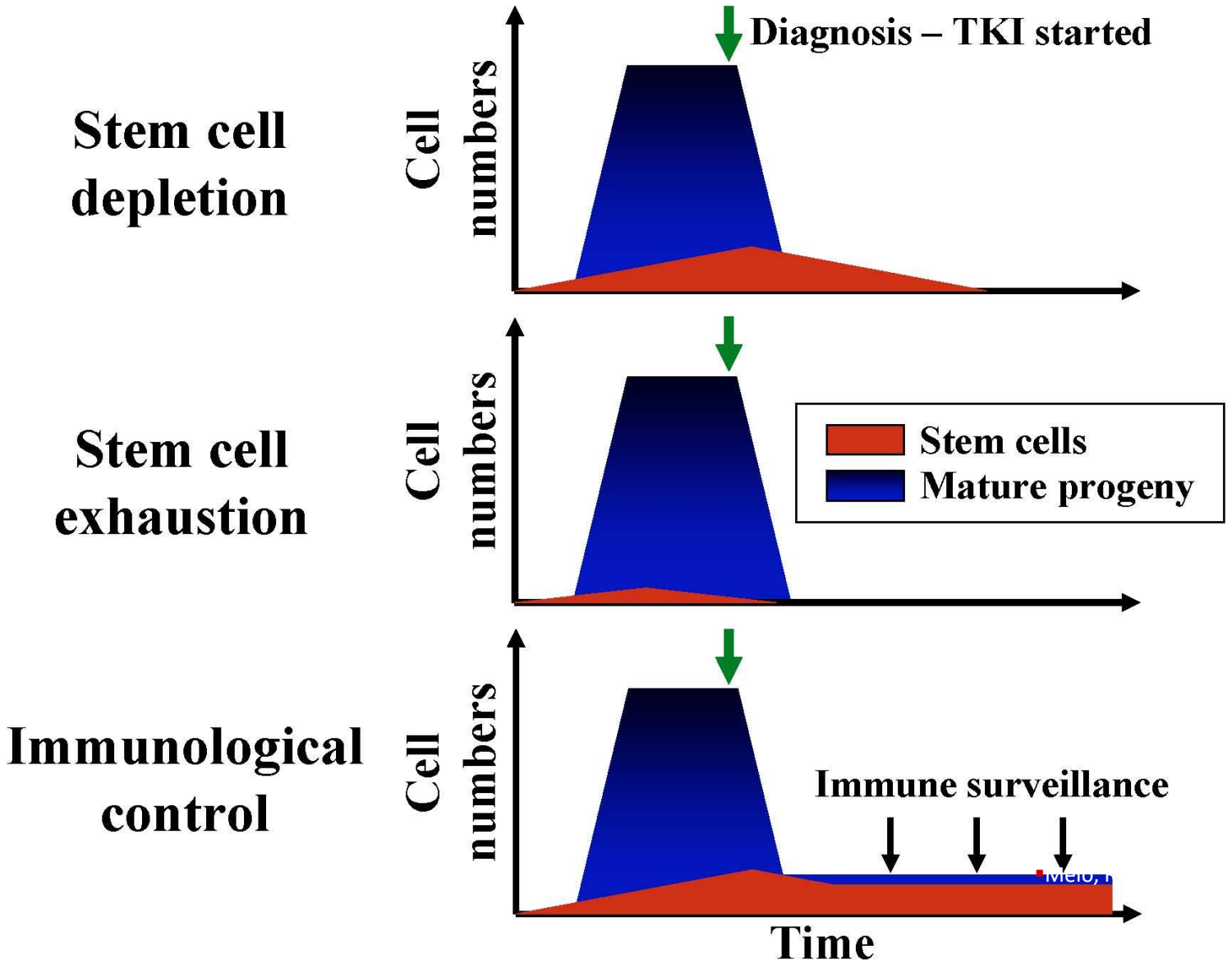
3) Activate cell cycle within HSC compartment

↓

Preferential depletion of $JAK2^{V617F}$ HS

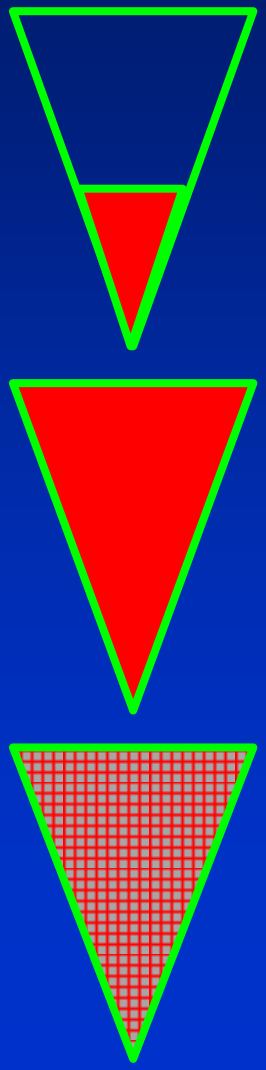
Chen E, Mullally A: How does JAK2V617F contribute to the pathogenesis of myeloproliferative neoplasms? *Hematology Am Soc Hematol Educ Program*. 2014 Dec 5;2014(1):268-76

Conceptual models for drug-free remission ('cure')



Melo, JV and Ross, DM, 2011

Model for Early Treatment of MPNs with rIFN



Early — **rIFN effective**

Advanced — **rIFN less effective**

Sclerotic — **rIFN not effective**

Myeloproliferative Neoplasms (MPNs)

Mutation	PV (%)	ET (%)	MF (%)	post- MPN AML (%)
JAK2^{V617F}	95-99	50-70	40-50	
JAK2 exon 12	Rare	None	None	
MPL exon 10	Rare	4	11	
TET2	15	4-11	19	26
CBL	Rare	Rare	6	
IDH	1.9	0.8	4.2	21.6
IKZF1	Rare	Rare	Rare	21
EZH2	3	None	13	
ASXL1 exon 12	<7	<7	19-40	19

PV: Polycythemia Vera, ET: Essential Thrombocythemia, MF: Myelofibrosis, AML: Acute Myeloid Leukemia

Vainchenker W, et al. Blood 118:1723-1735, 2011

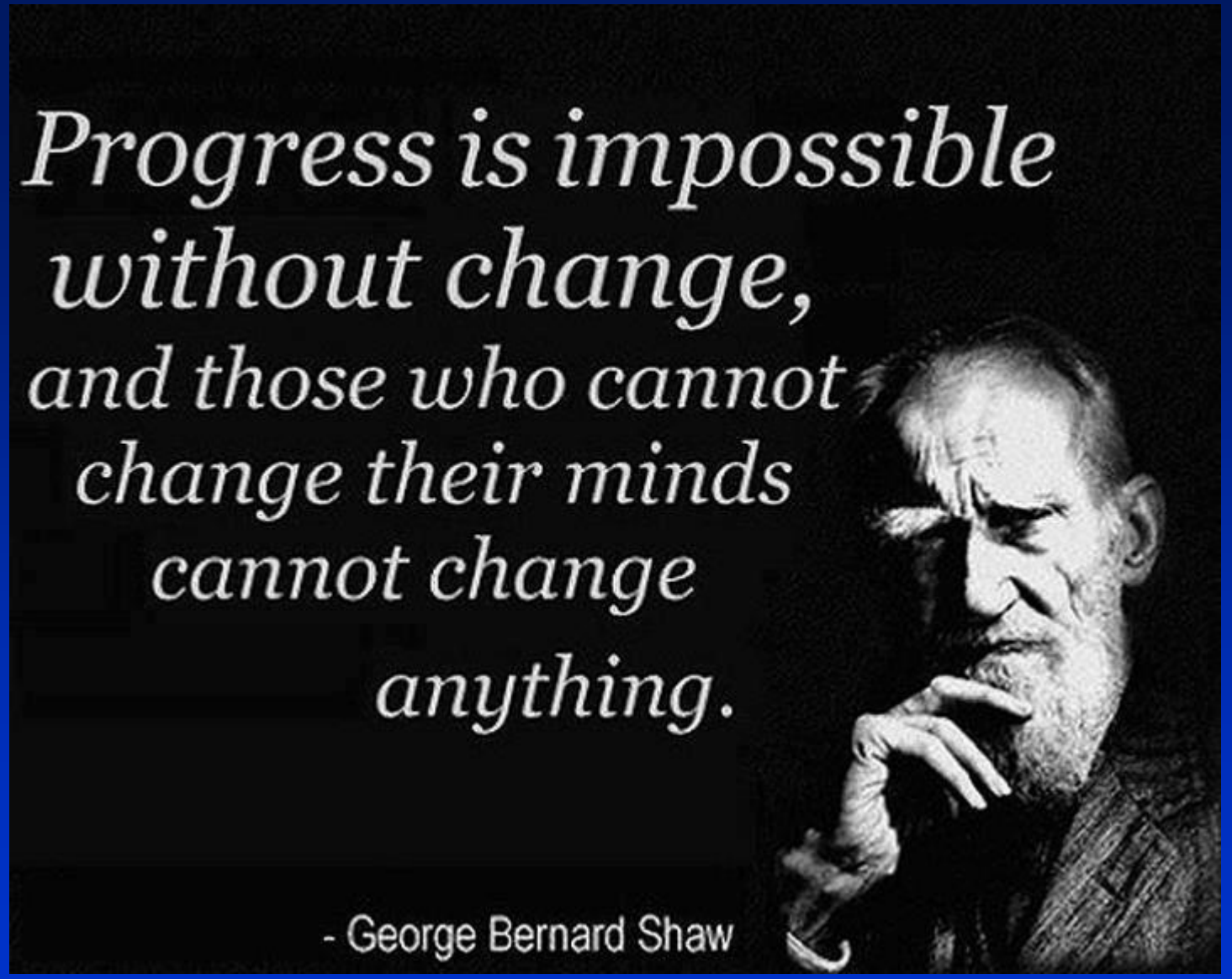
Change in Biopsy and JAK2V617 Value

No apparent correlation between hematologic response, complete molecular response, and change in cellularity or fibrosis.

Margolskee, Krichevsky, Orazi, Silver. Haemotologica, 2017.

Is PV Curable?

• **"Absolute" cure**	Not now
• **"Biologic" cure**	Possible
• **Hematologic/molecular remission**	Most likely


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