On the "Curability" of Polycythemia Vera with Interferon

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On the Curability of Polycythemia Vera with Interferon

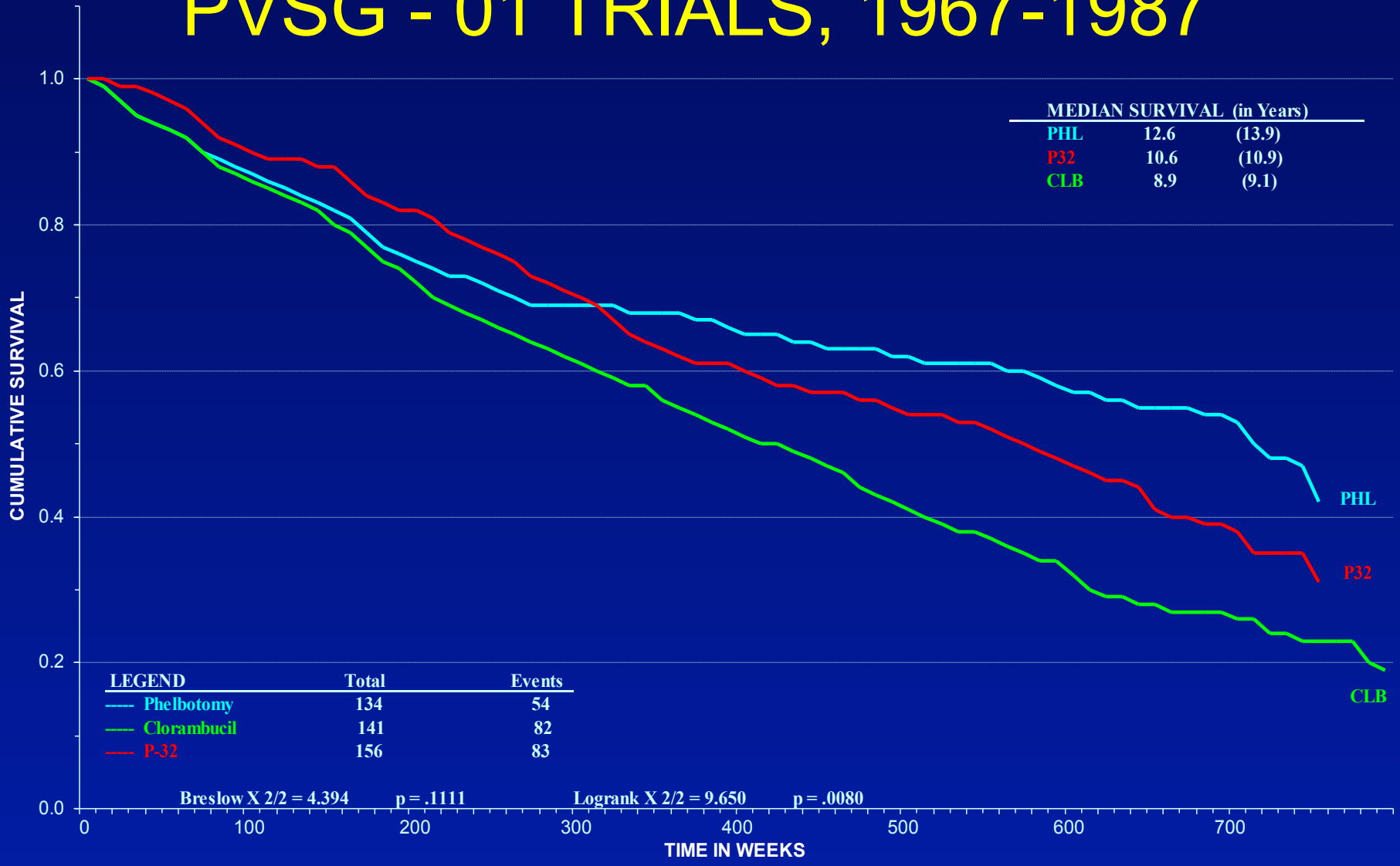
1) Brief history of treatment of PV

2) Types of IFNs and their activities

3) Clinical and Molecular results

4) Conclusion

CUMULATIVE SURVIVAL
PVSG - 01 TRIALS, 1967-1987



Wasserman LR, Berk PD, Berlin NI. Polycythemia Vera and the Myeloproliferative Disorders. 1995; (15):176.

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

1. Poor Clinical Tolerance

2. Frequency of Vascular Complications

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

* Najean Y, Dresch C, Rain JD. Br J Haematol. 1994 Jan; 86(1):233-5.

Treatment

- Worldwide, the majority of hematologists still use hydroxyurea (HU)

- However…

FAILURE, HU AT 1 YEAR, PVSG

(118 PTS)

Previously untreated:	27%
Previous myelosuppressives:	41%

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General Remarks about Interferons

- Discovered more than 50 years ago
- Interferons are proteins
- 3 types of interferons
  - TYPE 1 (α, β) – "viral interferon"
  - TYPE 2 – immune – "antigens"
  - TYPE 3 (λ, I, 2, 3) [Similar to type I]

Pegylated IFNs

- Peg-IFN α-2b: unstable urethane bond between Peg and IFN molecule; more likely to hydrolyze; more rapid release of IFN; shorter half-life
- Peg-IFN α-2a: more stable amide bond; longer half life; prolonged plasma concentration; ? prolonged efficacy;

  ? less toxicity
- No randomized controlled trials in Hep C.
- Similar results in one CML comparative trial
- Safety profiles similar

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

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Treatment of PV with rIFNα

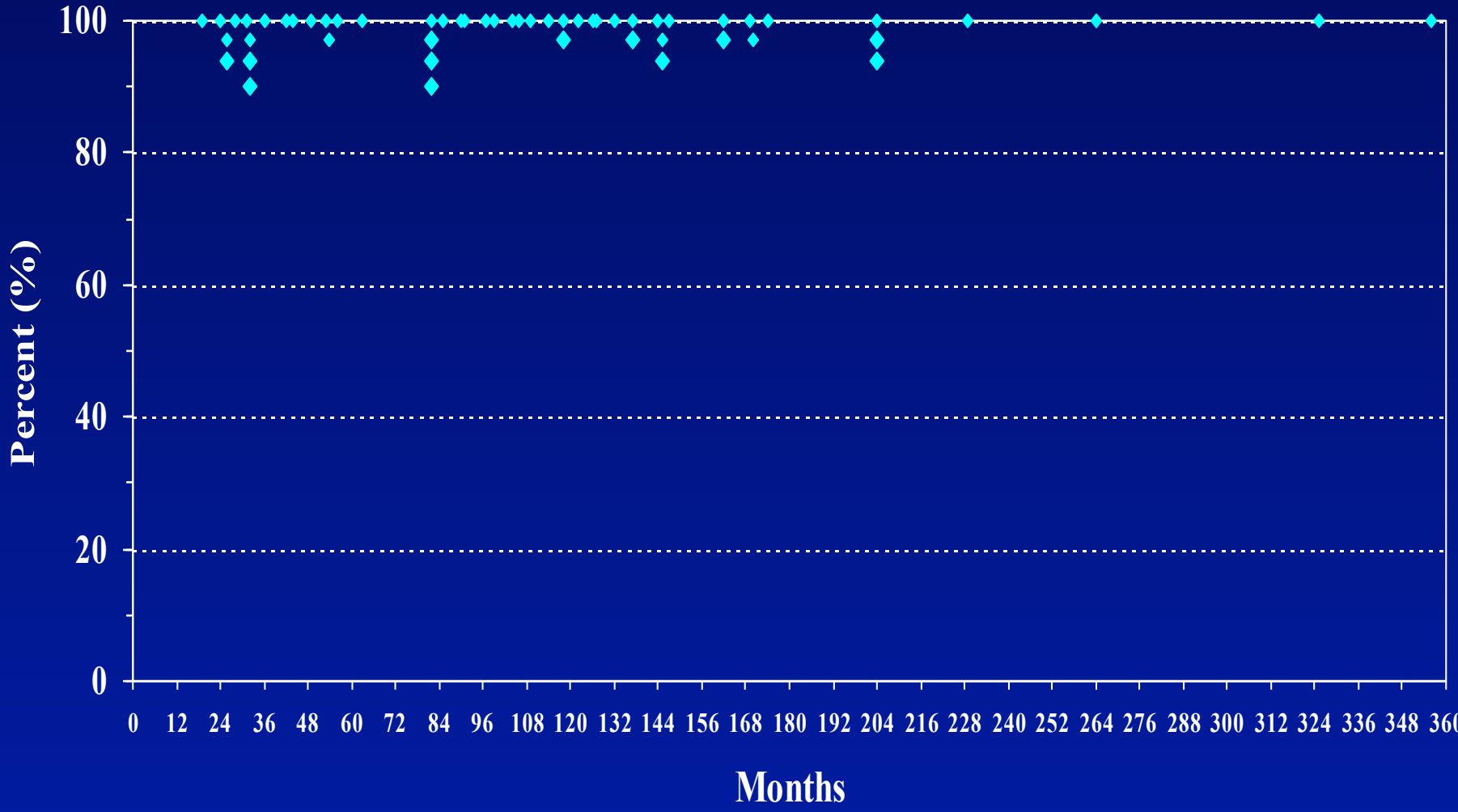
Must start and maintain low dose

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

- **All 55 patients have had clinical responses**
- **No thrombohemorrhagic episodes**

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

Progression-Free Survival from Thrombohemorrhagic Events, 55 Patients



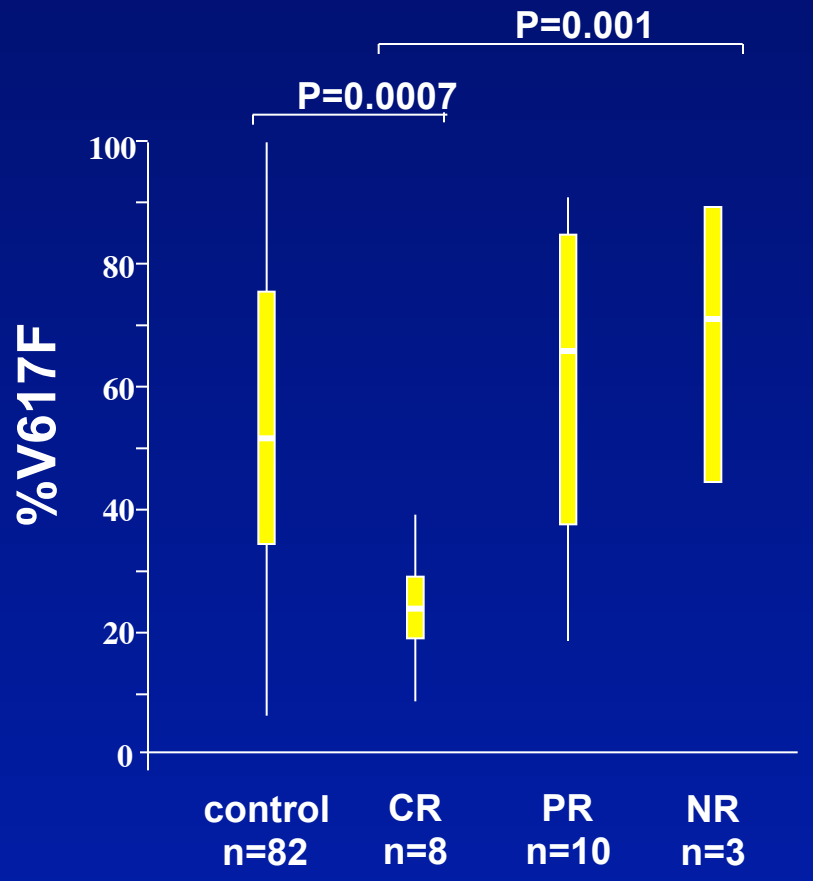
- All 55 patients have had clinical responses

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

RESPONSE OF PV PATIENTS TO INTERFERON OR IMATINIB

- All 21 cases on imatinib or rIFNα remained V617F positive

- Lower %V617F in CR patients on imatinib or rIFNα compared to controls
- Lower %V617F in treated patients who achieved CR compared to those who did not achieve CR



Jones, Silver, Cross, *et al.* Blood 107:3339-41, 2006

Molecular Changes with Peg-rIFNα

- Decrease in *JAK2*^{V617F} allele burden in 26 (90%) of patients (Kiladjian 2008)
- Undetectable in 24% - Kiladjian *et al* (2008)
- Undetectable in 14% - Quintas-Cardama (2009)
- Clinical response not correlated with molecular response. May be dose. Kuriakose *et al* (2011)

Kiladjian J-J, *et al.* Blood 112:3065-3072, 2008

Quintas-Cardama A, *et al.* J Clin Oncol 27:5418-5424, 2009

Kuriakose E, *et al.* Haematol 97(4):538-542, 2011

Clonality changes in PV Following Treatment with Interferon

- In addition to change in *JAK2*^{V617F} status, other changes in clonality have been reported:

  - Reversal of chromosome abnormalities

  - Restoration of polyclonal hematopoiesis

  - Normalization of PRV-1 expression

  - Suppression of endogeneous erythroid colony growth.

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

Some Reasons for Different Results

(1) More “advanced” cases. Much higher JAK2V617F allele burden (Silver)

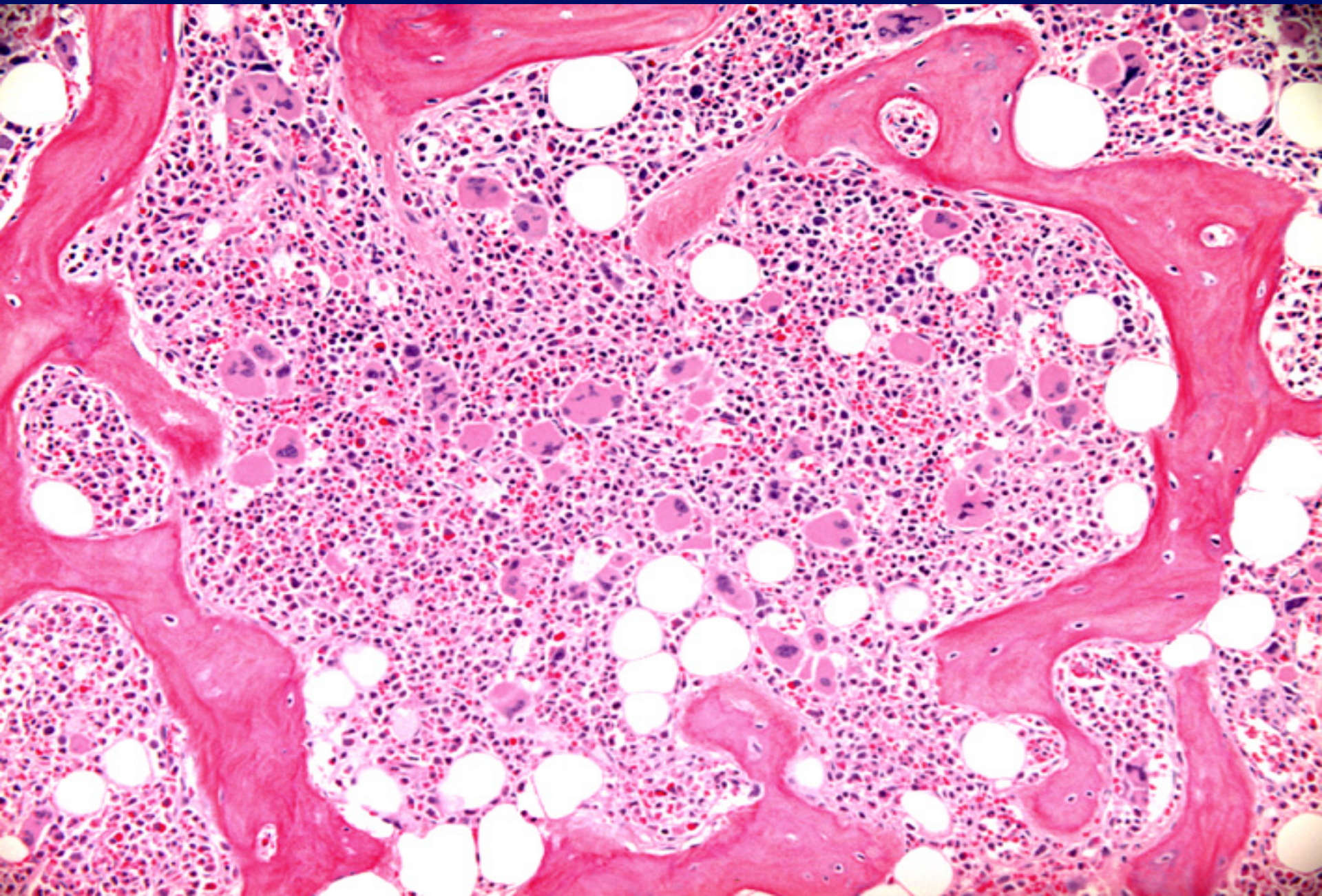
(2) More toxicity with better JAK2 results (Kiladjian, Quintas-Cardama)

(3) Shorter duration of therapy before toxicity (Kiladjian, Quintas-Cardama)

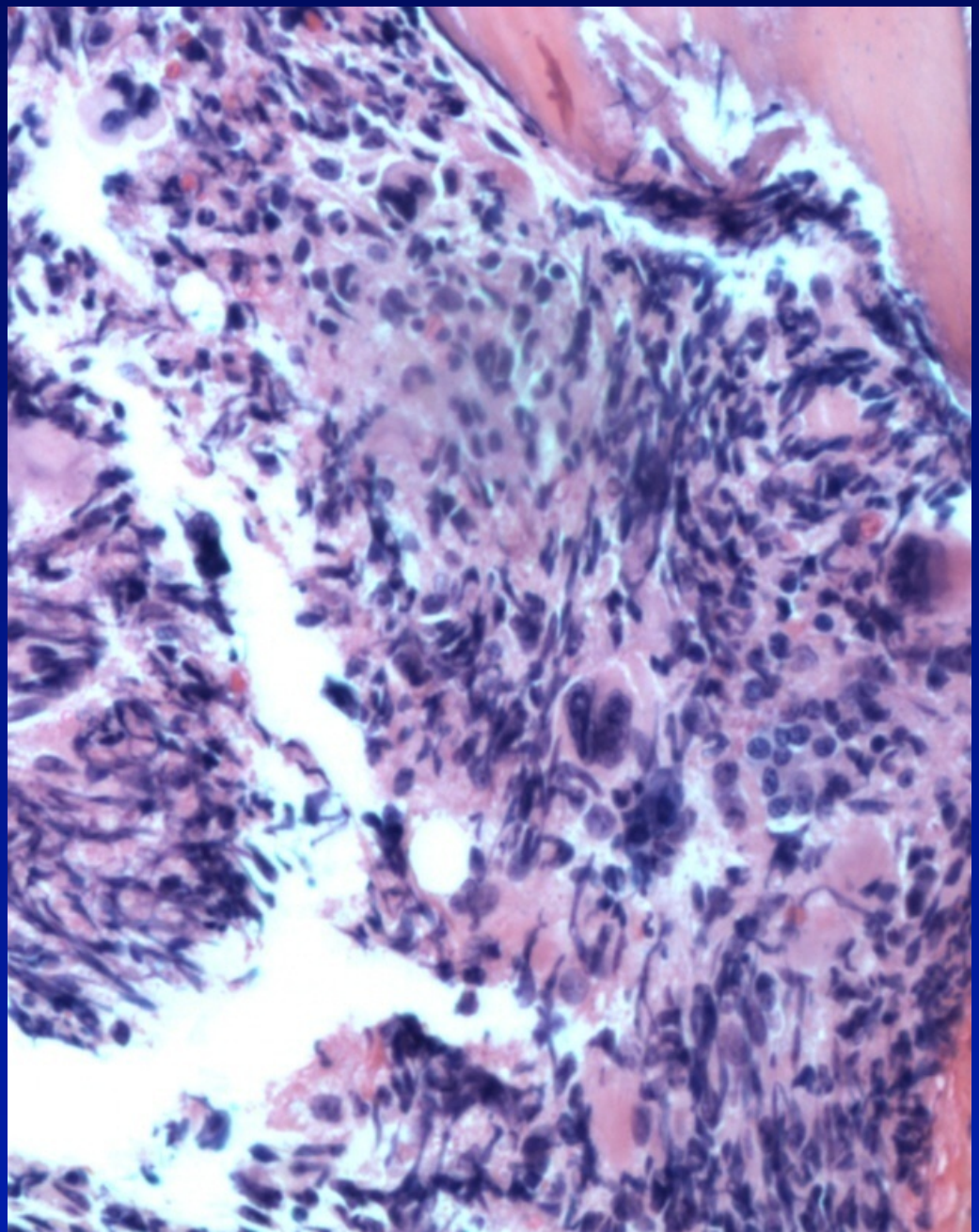
Therapeutic Conundrum

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

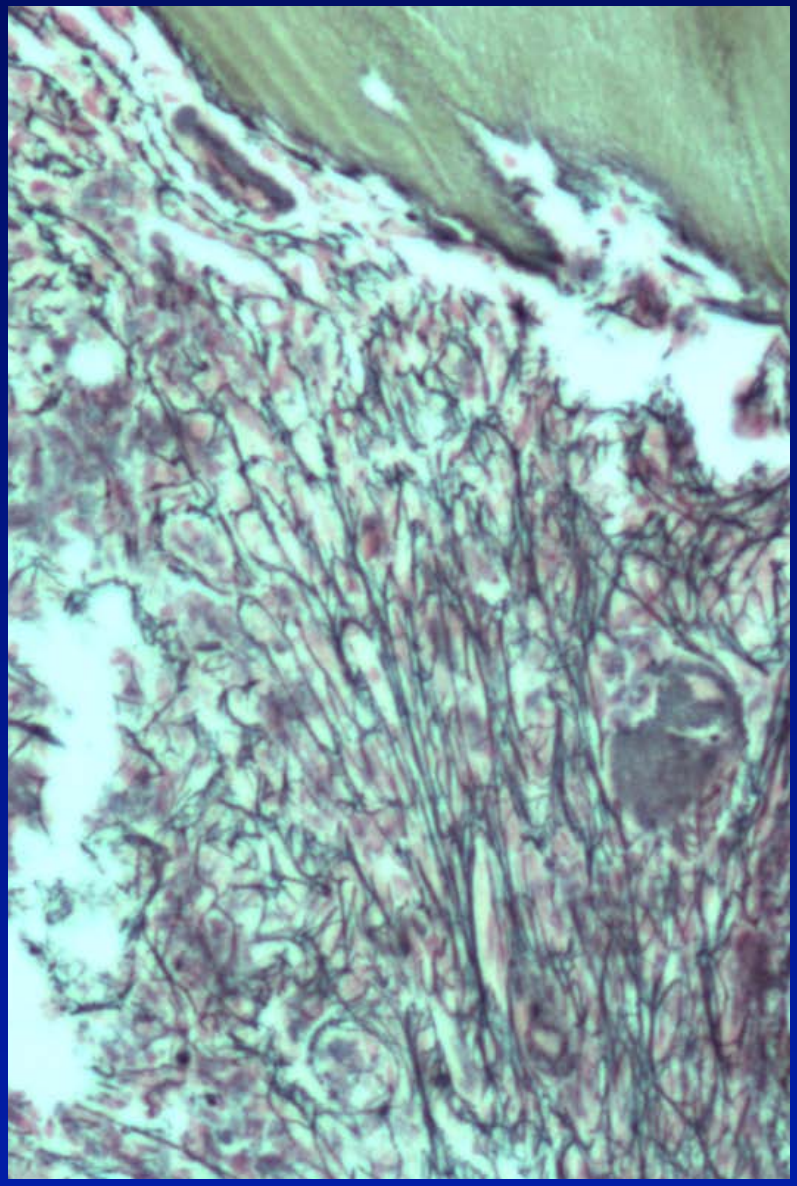
Interferon is effective in treating the fibrosis that occurs in Polycythemia Vera



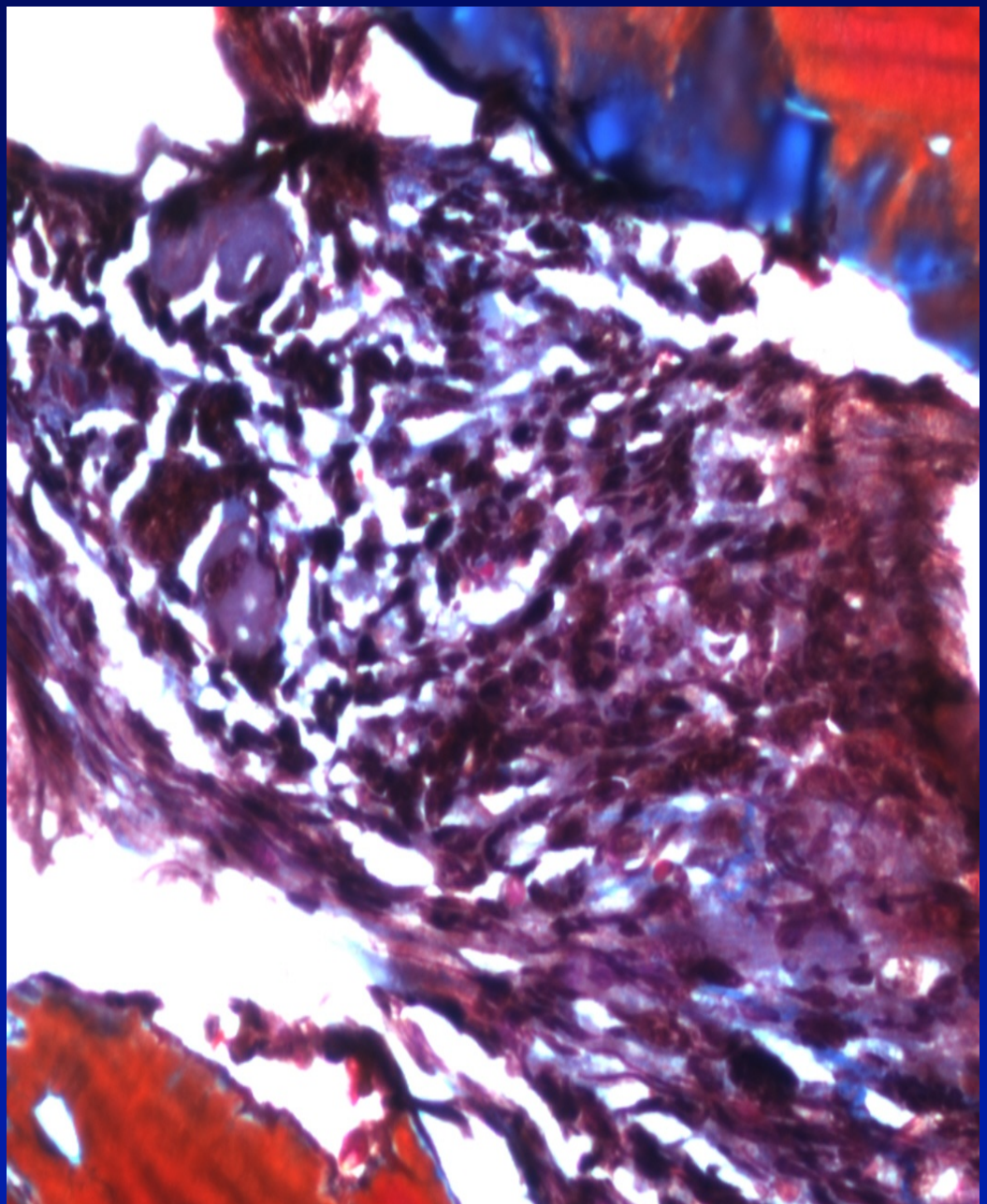
2/11/2009: H&E section (20X): increased fibrosis and increased atypical megakaryocytes



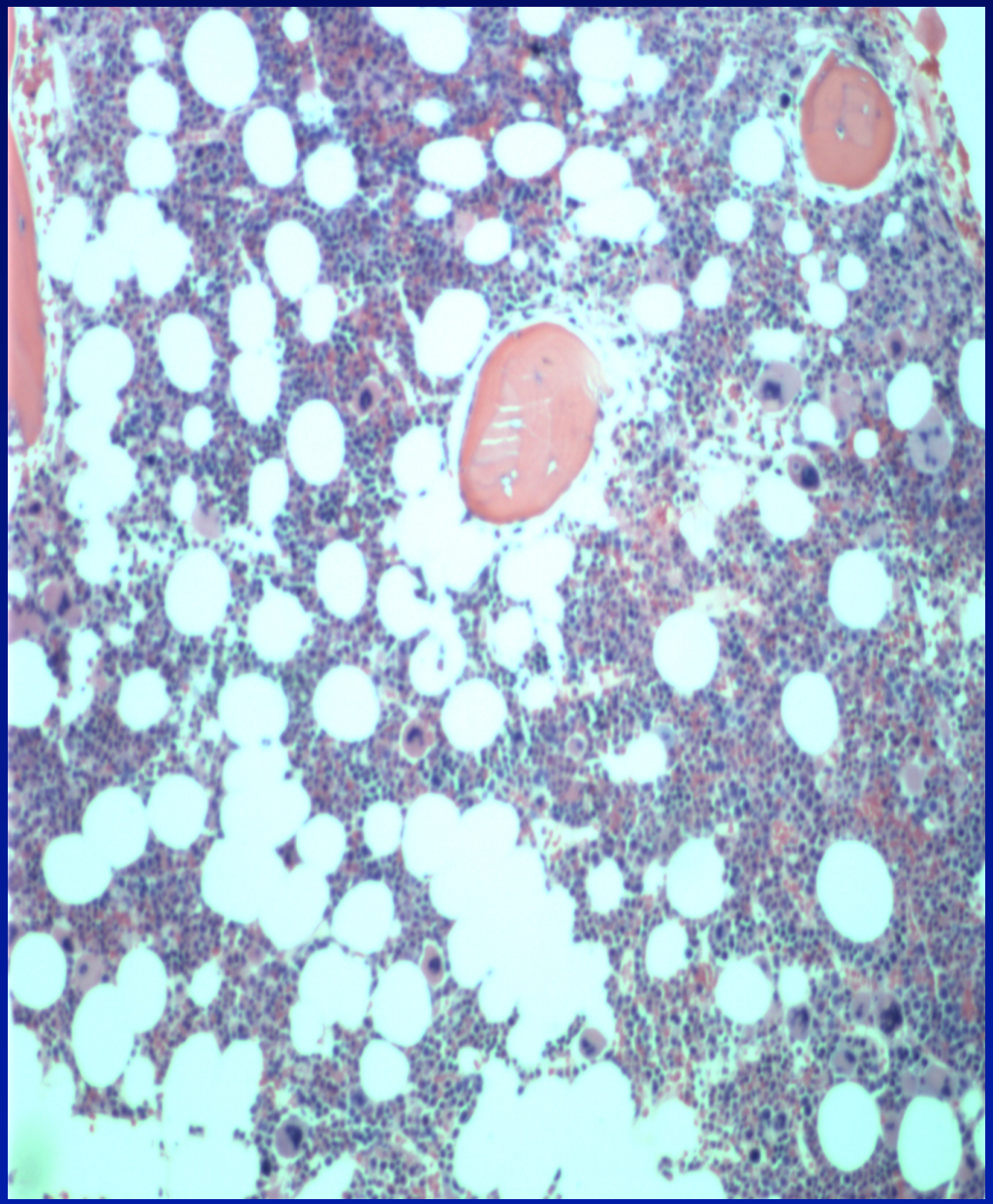
2/11/2009: 20X reticulin special stain: Markedly increased fibrosis – diffuse thick reticulin fibers



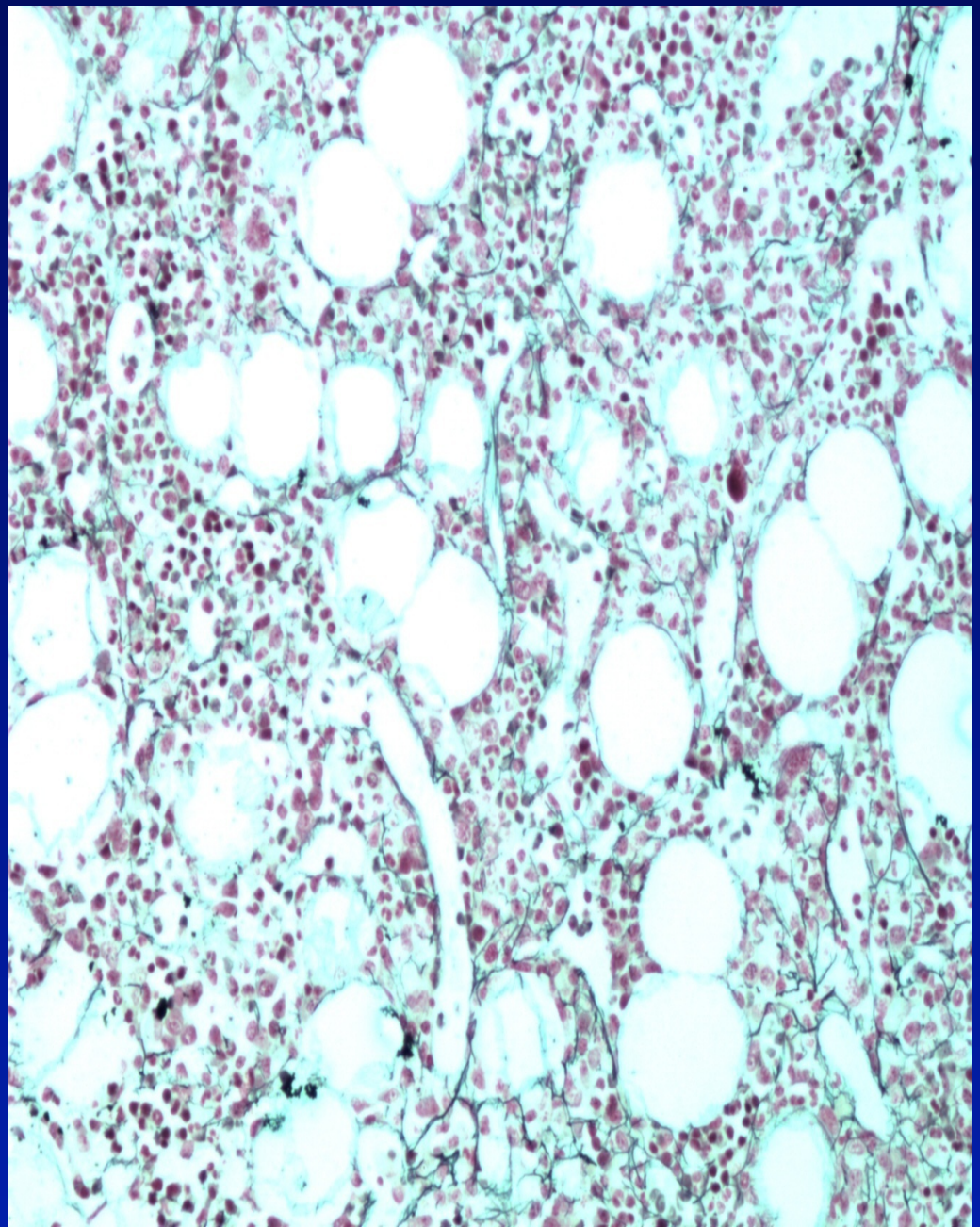
2/11/2009: 40X: Trichrome special stain: Increased type I collagen (blue)



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



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



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So,

Is Polycythemia Vera Curable?

Myeloproliferative Neoplasms (MPNs)
The State of Affairs re. Mutations in 2012

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

Role of Other Mutations

1. TET2 mutations persist despite eradication of *JAK2* (TET2 may precede *JAK2*)

2. In patients with complete molecular response, *JAK2*(+) cells in some EPO-independent colonies

3. Patients who evolve to acute leukemia lose *JAK2* positivity

4. More mutations seen in poor responders to Interferon alfa

1, 2: Kiladjian, et al. Leukemia 24:1519-1523, 2010

4. Quintas-Cardama et al. ASH Proceedings 2011 Abstract #281

Conclusion

- Interferon maybe the best treatment to control the proliferative aspects of polycythemia vera
  - Biological basis for its use
  - Able to induce clinical, hematological and some degree of molecular remission
  - Requires clinical trial
- Interferon in combination with *JAK2* inhibitors and other drugs for symptomatic relief
  - In the year 2012, treat for clinical response, not for molecular response to avoid toxicity (?)

Is polycythemia vera curable with Inteferon?

No!

Not at the present time.

But don't despair!

- Inducing clinical remission is possible and attainable.
- Quality of life can improve.


Leeches

Acknowledgement and Thanks to . . .

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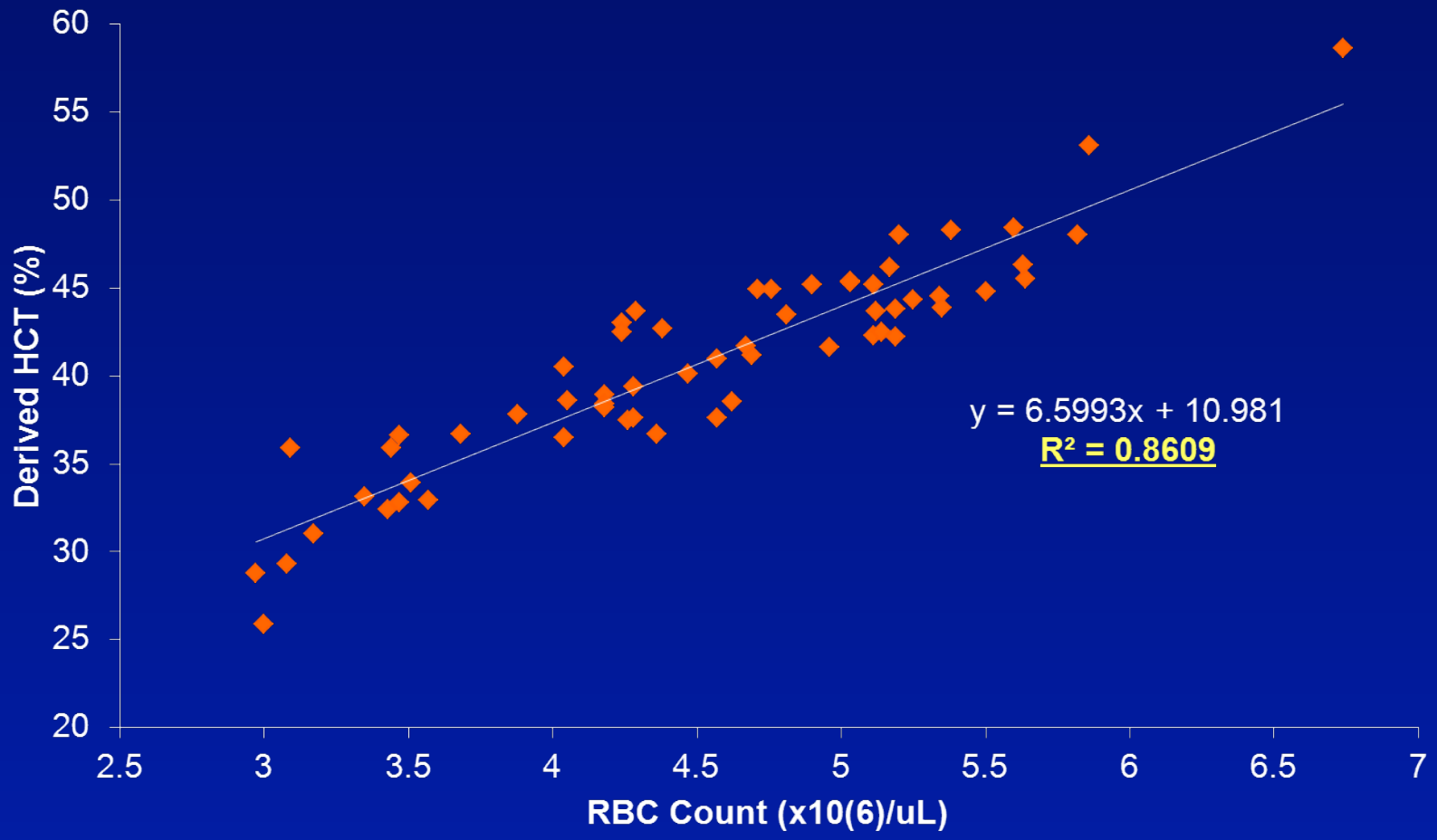
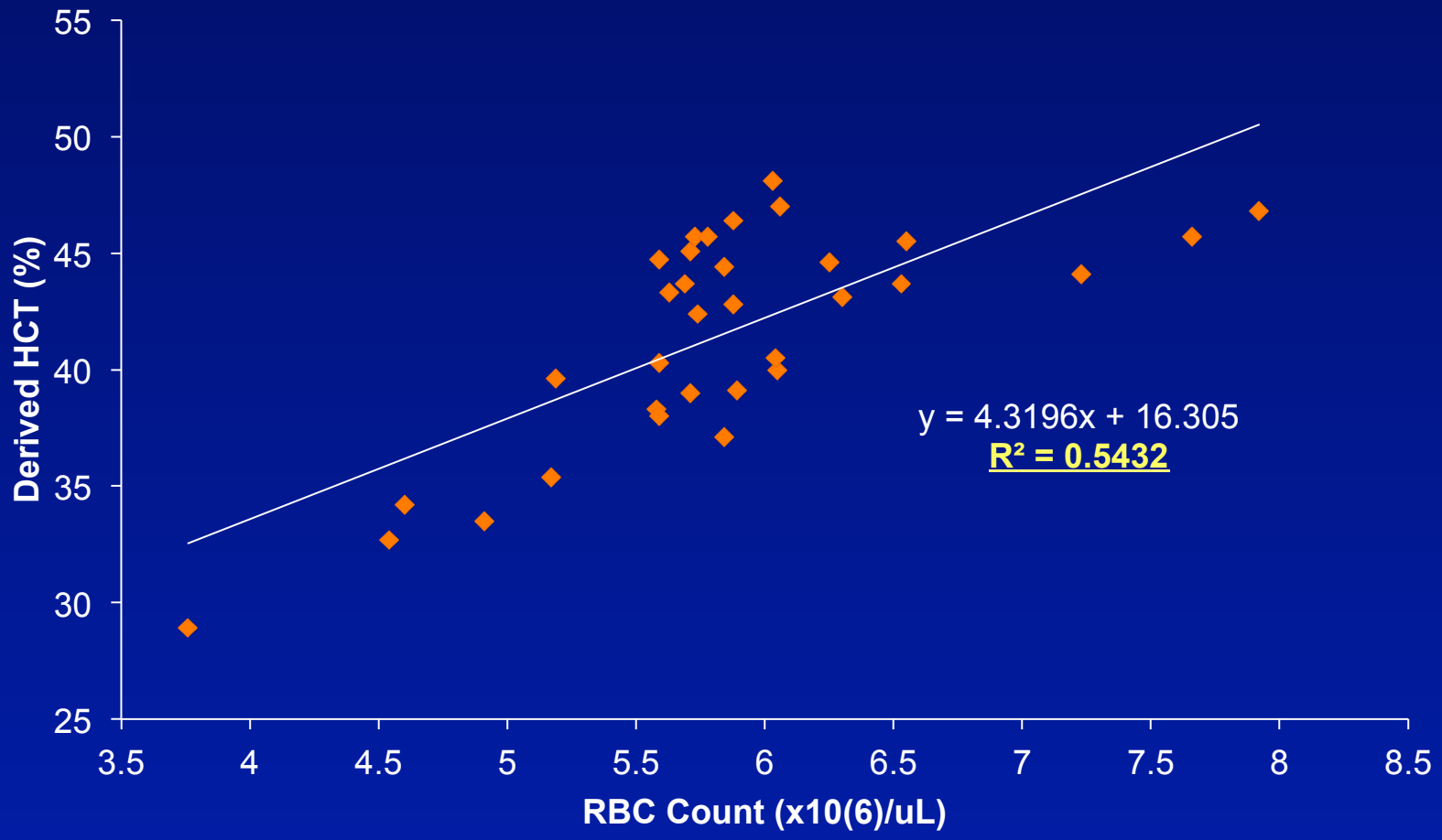
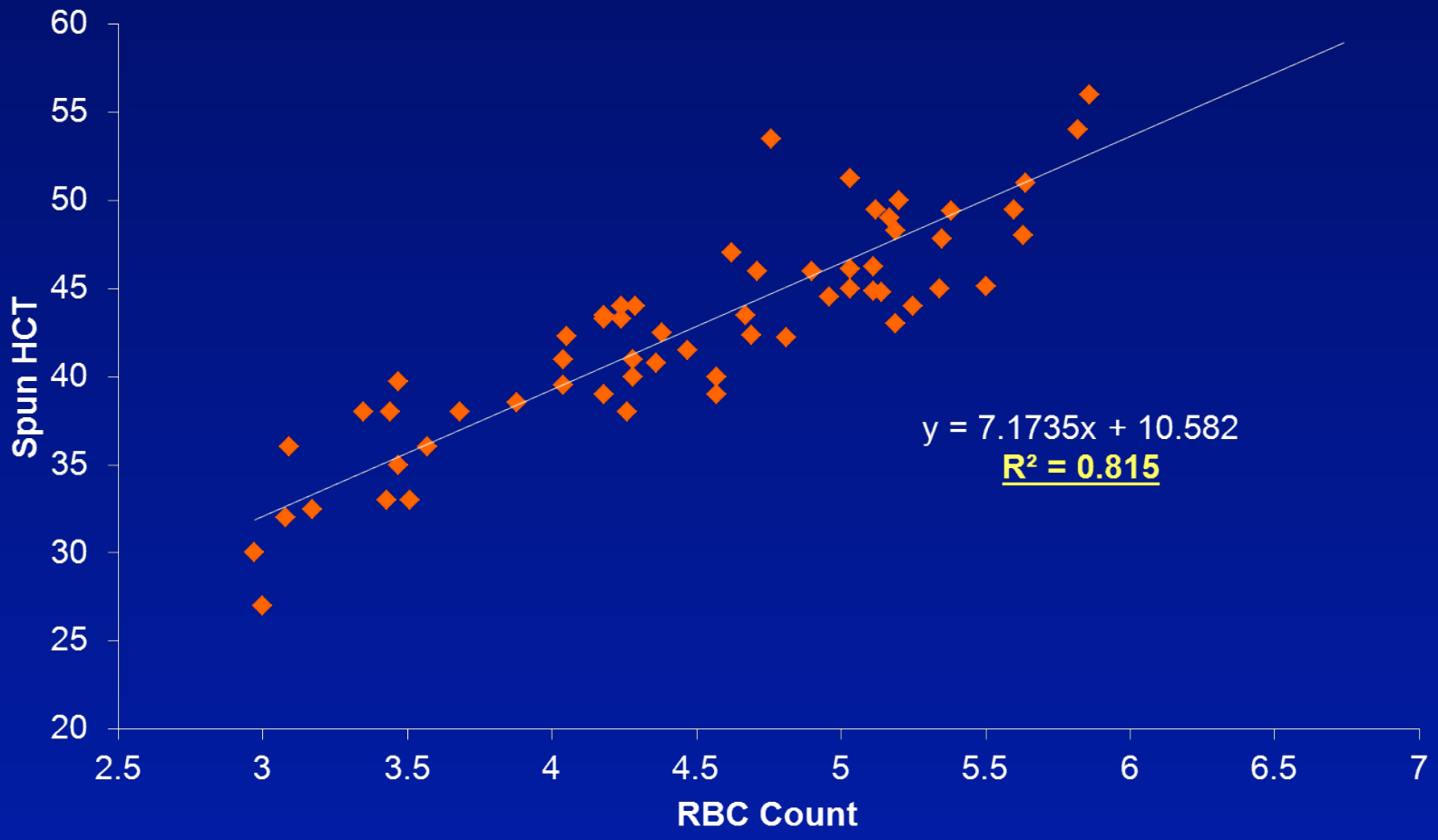
Derived HCT vs. RBC Count Normocytic



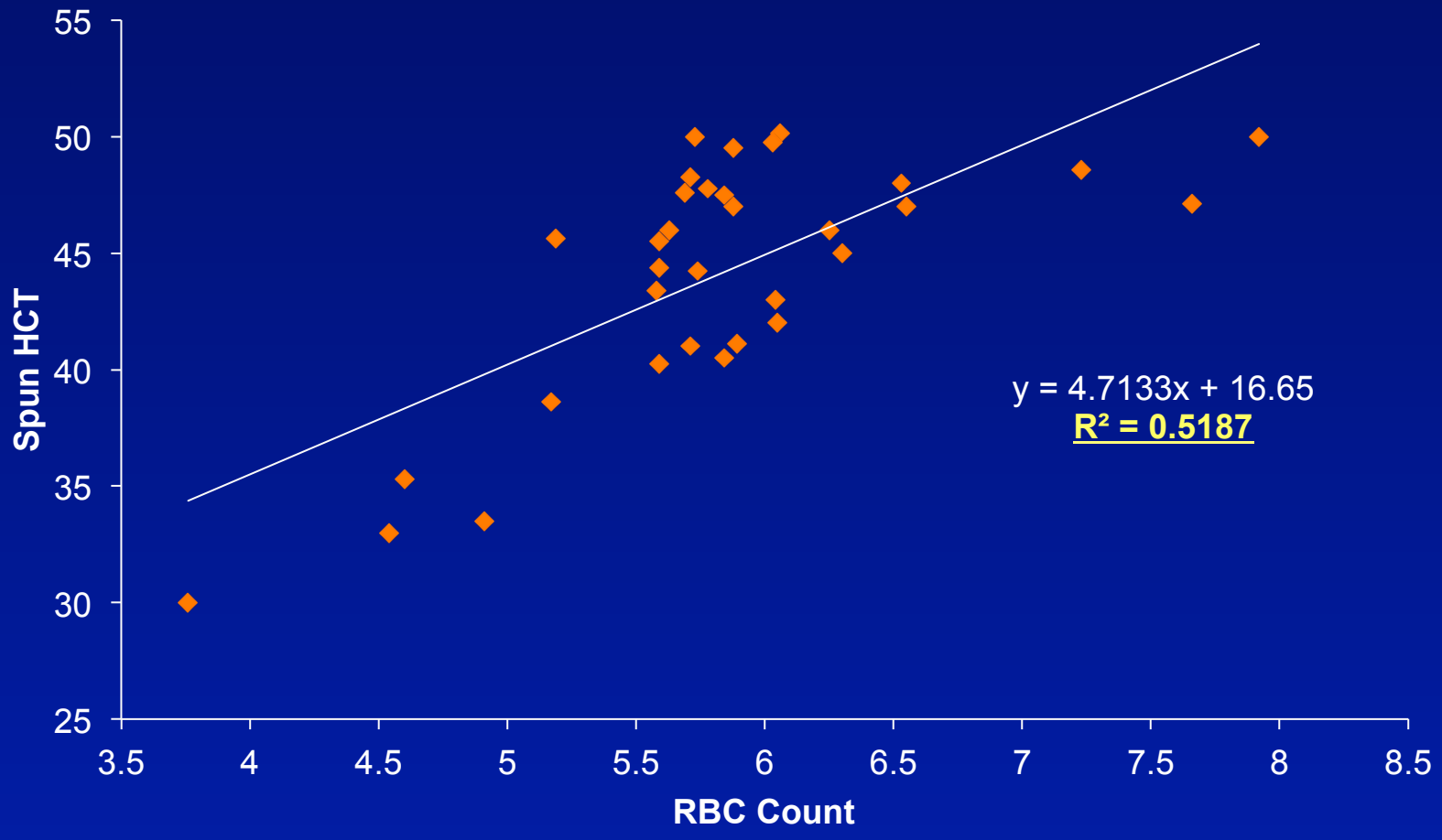
Derived HCT vs. RBC Count Microcytic



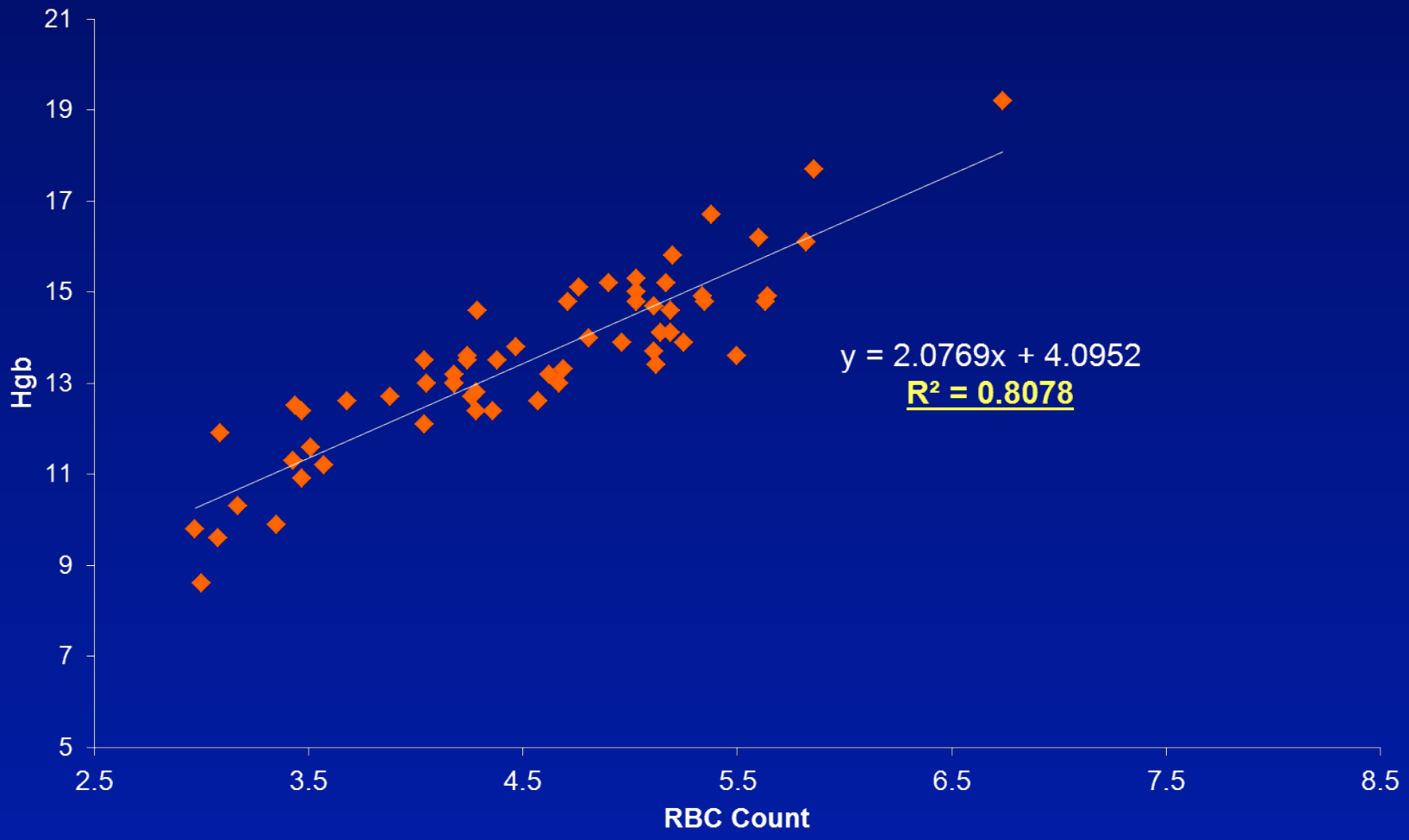
Spun HCT vs. RBC Count Normocytic



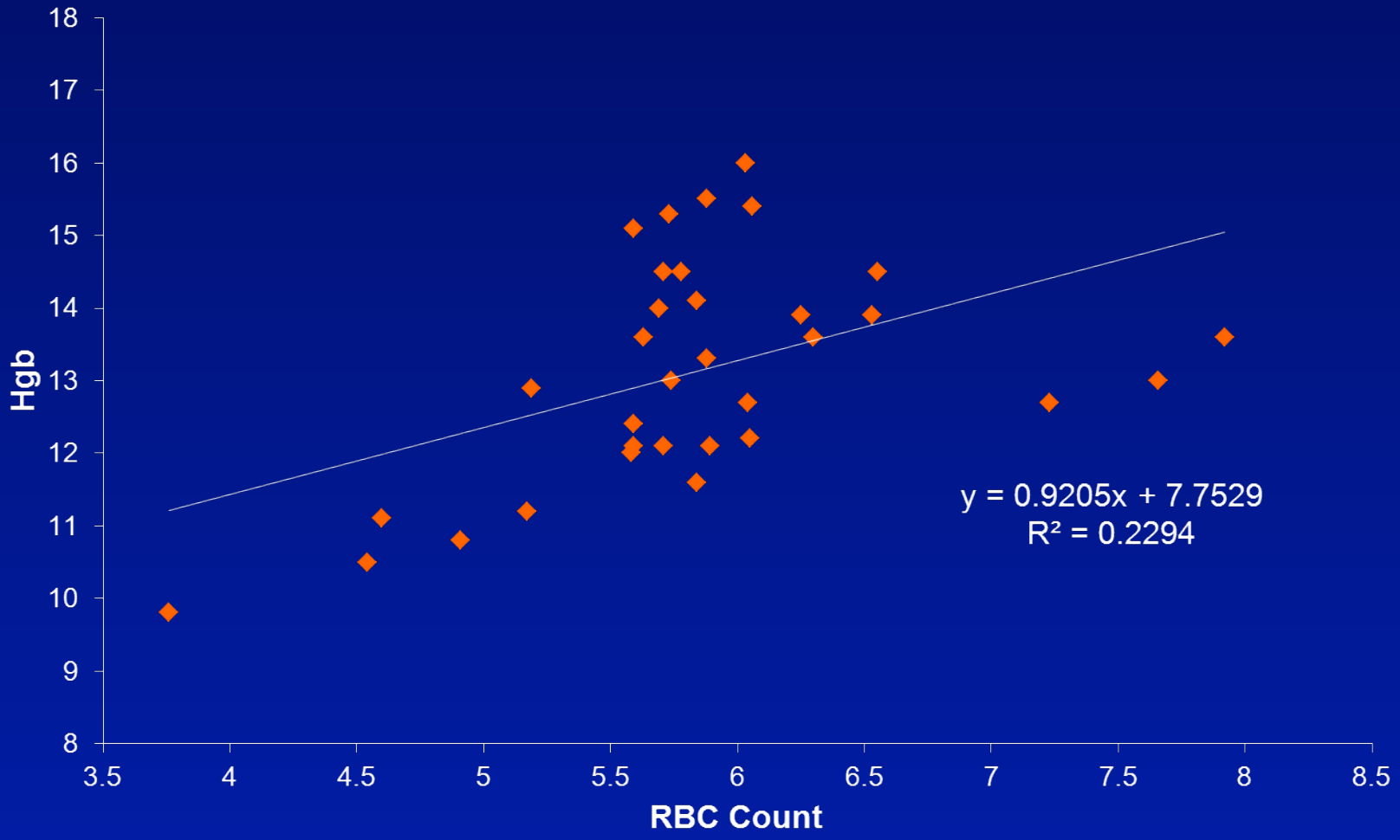
Spun HCT vs. RBC Count Microcytic



RBC vs. Hgb
Normocytic



RBC vs. Hgb
Microcytic



Is Polycythemia Vera Curable?

Major Questions

1) Is the disease properly defined (diagnosed)?

2) What is the best way to induce clinical remission?

3) Once remission is induced, can we target the major molecular abnormality (ie - *JAK2*^{V617F}) and "cure" the disease?

Outline of lecture

1) How is polycythemia vera defined?
   - Current clinical and laboratory definitions
   - Evaluation of major and minor criteria
   - Proposed new WHO criteria

2) Treatment
   - History of treatment of PV
   - Clinical trials using interferon

3) Effect on *JAK2*^{V617F}

4) Conclusion

Correct Diagnosis of PV in 2012

- Current WHO criteria do not distinguish between "early-stage" PV and ET

- Correct diagnosis requires increased Cr 51 RCM and *JAK2* mutation

  - In rare *JAK2*-negative patients, bone marrow findings can be helpful

  - I-125 plasma volume RCM: no value

WHO criteria for PV (2008)

Major criteria

1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume.*
2. Presence of JAK2V617F or other functionally similar mutation such as JAK2 exon 12 mutation.

Minor criteria

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.
2. Serum erythropoietin level below the reference range for normal.
3. Endogenous erythroid colony formation in vitro.

Diagnosis:

- both major criteria and 1 minor criterion

or

- if JAK(-), increased red cell volume with 2 minor criteria

First major criterion arbitrarily defined as:

- Hgb > 18.5 g/dL in men, 16.5 g/dL in women *or*
- Hct > 99th percentile of reference range *or*
- Elevated RCM > 25% above mean normal predicted value

CRITIQUE OF WHO CRITERIA: "THE STANDARD"

WHO has promulgated the 2008 WHO criteria for diagnosis of PV; *however*, these have never been prospectively tested.

RECENT Warnings

"An elevated venous hemoglobin concentration cannot be used as a surrogate marker for absolute erythrocytosis"
– Johansson PL, *et al.* British Journal of Hematology 129: 701-705, 2005

"RCM measurement is useful for proper MPD classification ……of Ph-negative MPD".
– Cassinat, *et al*. Leukemia 22:452-453, 2008

"Alternative proposal to revised WHO criteria for MPDs"
Spivak JL, Silver RT. Blood. 112:231-9, 2008

"Red cell mass measurement in patients with clinically suspected diagnosis of polycythemia vera or essential thrombocythemia"
-Alvarez-Larran A, Ancochea A, Angona A, et al. Haematologica. 2012 Jun 11. [Epub ahead of print]

"Prospective Evaluation of the World Health Organization Criteria for the Diagnosis of Polycythemia Vera"
-Silver RT, Chow W, Vandris K, et al. Blood (ASH Annual Meeting Abstracts). Nov 2011; 118: Abstract 3837

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

– George Santayana

(*Reason in Common Sense*, 1905)

Relation of Absolute Erythrocytosis (AE) to HCT

HCT (Hgb)	% with AE Using Cr^{51} RCM	Conclusion
50-52 (16.7-17.3)	18	82% DO NOT have PV
56-58 (18.7-19.3)	65	35% DO NOT have PV
>60	100	All have Polycythemia

■ Pearson ■ Silver

Pearson CT. Apparent Polycythaemia. *Blood Rev*. 1991 Dec;5(4):205-13.
Pearson CT *et al*. Interpretation of measured red cell mass and plasma volume in males with elevated venous PCV values. *Scand J. Hematol*. 1984 Jul;33(1):68-74.

An evaluation of 30 *JAK2*^{V617F}(+) patients

Indications for Cr^{51} red cell mass and I^{125} plasma volume determinations

Any combination of JAK2 positivity and one or more of the following:

- Hct between 45 and 55%
- Hgb > 14.0 g/dl
- Increased WBC, BCR(-)
- Platelet count > 400,000/uL
- Splenomegaly
- Bone marrow histology

Median 4 year follow up of all patients

Silver, *et al.* Blood 118:1639-40, 2011

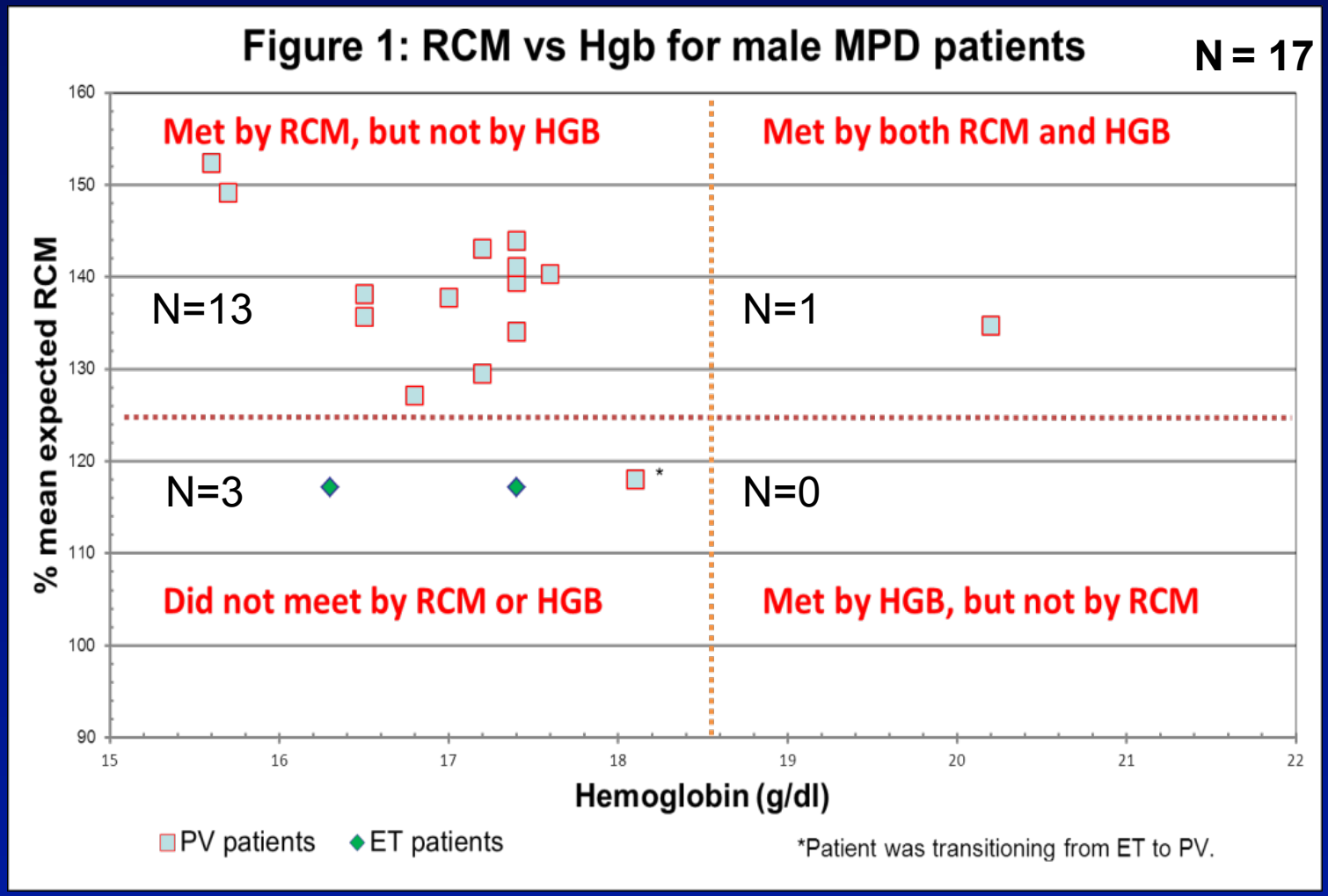


Figure 1: RCM vs Hgb for male MPD patients
N = 17
Met by RCM, but not by HGB
Met by both RCM and HGB
N=13
N=1
N=3
N=0
Did not meet by RCM or HGB
Met by HGB, but not by RCM
% mean expected RCM
160
150
140
130
120
110
100
90
15
16
17
18
19
20
21
22
Hemoglobin (g/dl)
PV patients
ET patients
*Patient was transitioning from ET to PV.

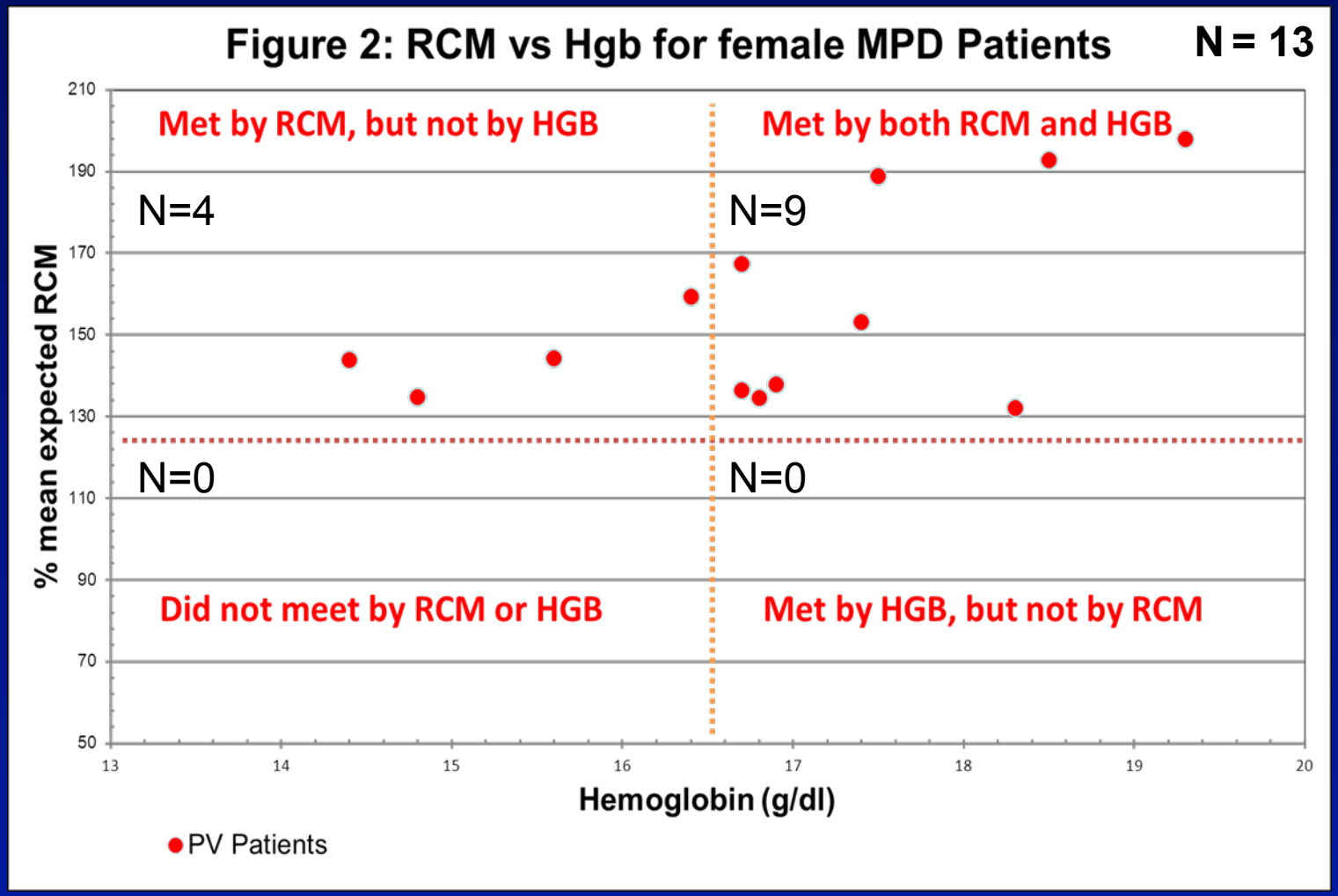


Figure 2: RCM vs Hgb for female MPD Patients
N = 13
Met by RCM, but not by HGB
Met by both RCM and HGB
N=4
N=9
N=0
N=0
Did not meet by RCM or HGB
Met by HGB, but not by RCM
% mean expected RCM
210
190
170
150
130
110
90
70
50
13
14
15
16
17
18
19
20
Hemoglobin (g/dl)
PV Patients

Evaluation of major criterion #1

	Male PV patients who met criterion (n=15)	Female PV patients who met criterion (n=13)
Using Hgb	7% (1/15)	69% (9/13)

RCM determination remains critical (using Cr 51)

Prospective Evaluation of the World Health Organization Criteria for the Diagnosis of Polycythemia Vera, Silver *et al*. ASH, 2011

Evaluation of Minor Criteria

Minor criteria

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation.

2. Serum erythropoietin level below the reference range for normal.

3. Endogenous erythroid colony formation in vitro.

- **PV patients**
  - **All patients with elevated RCM had marrow findings consistent with PV according to WHO criteria**
  - **2 patients had normal RCM consistent with ET, and 1 MPN not specified**
  - **Marrow interpretations by 3 observers were blinded**
- **Serum EPO levels were NOT diagnostic**
  - **Only 75% of patients diagnosed with PV had an EPO <5 U/mL**
- **EEC assays not performed at Cornell**

How should "early" PV be diagnosed? RBC remains preferable.

- Absolute increase in red blood cells (not Hgb), RBC determined by RCM using Cr 51.
- *JAK2*^{V617F} or Exon 12 mutation always present n = 292 (The Cornell experience)
- Virtually always accompanied by other evidence of myeloproliferation (confirmatory)

Study	Type of Interferon/ No. of Pts.	Median *JAK2*^{V617F} Allele Burden		Median Starting Dose	Duration of Treatment/ Follow-up (Months)	Discontinuation due to Toxicity No. (%)
		Before Tx.	After Tx.			
Kiladjian PV= 37	Peg-rIFNα-2a	45%	5%	109.0 mcg/week	TTR: 12.0 Overall: 31.4	9 (24.3%)
Quintas-Cardama PV + ET = 79 PV = 40	Peg-rIFNα-2a	64%	12%	180.0 mcg/week (Esimated)	21.0	8 (10.0%)
Silver PV= 49	rIFNα-2b: 31	42%	53%	1.0 MU 3x weekly	81.6†	5 (16.1%)
	Peg-rIFNα-2a: 18	72%	69%	90.0 mcg/week	19.2†	1 (5.6%)

Kiladjian J-J, et al. Blood. 2008;112:3065-3072.

Quintas-Cardama A, et al. J Clin Oncol. 2009;27:5418-5424

Kuriakose E, et al. Decrease in *JAK2*^{V617F} allele burden is not a prerequisite to clinical response in patients with polycythemia vera. Haematologica. 2011

†Ongoing