Managing Polycythemia Vera in 2021

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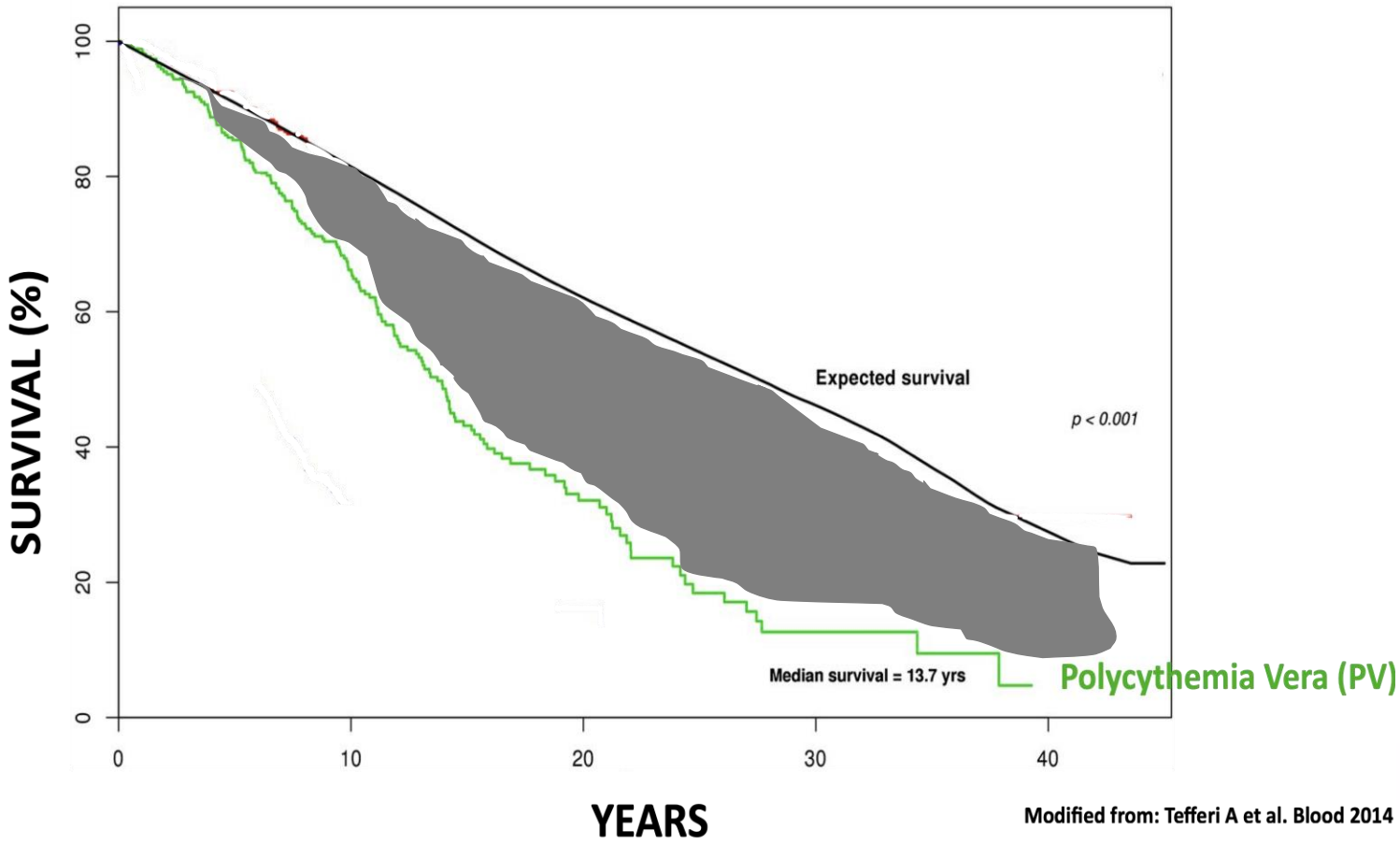
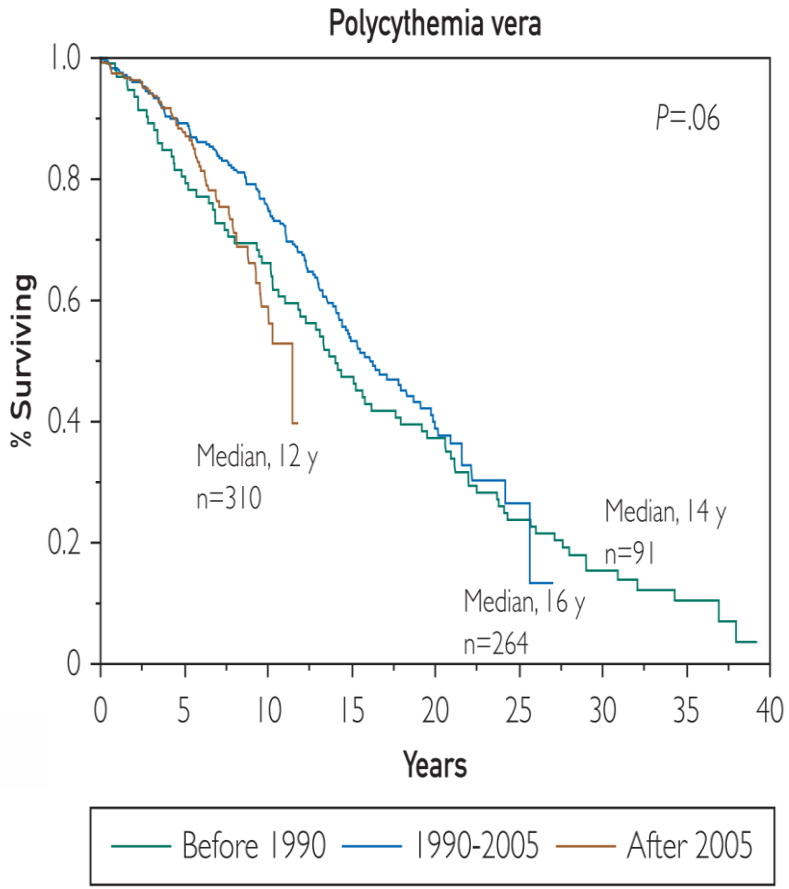
Disclosures

PharmaEssentia:	**Speakers Bureau**
	Consultant
Clinical Trials:	**Multiple**

PV patients have shortened survival



Modified from: Tefferi A et al. Blood 2014



Szuber N et al. Mayo Clin Proc. 2019

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Initial Treatment of PV

All agree we must phlebotomize patients

However, we should adjust for gender difference

- Men: Hct $\leq$ 45%
- Women: Hct $\leq$ 42%

After Initial Phlebotomy Treatment

Must assess subsequent phlebotomy requirements first.

Phlebotomy requirements during the year prior to rIFNa, 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

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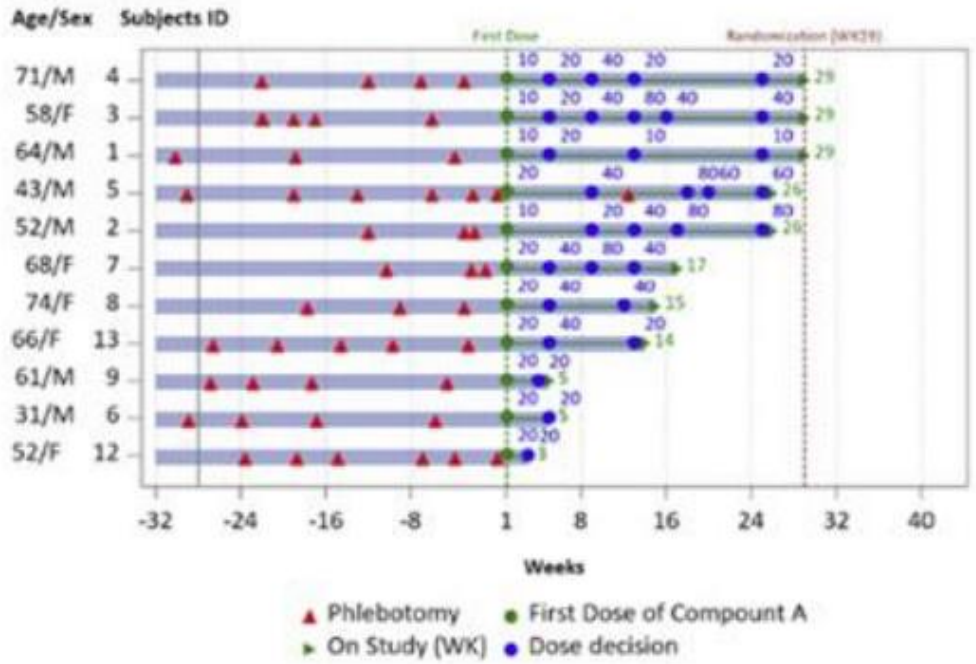
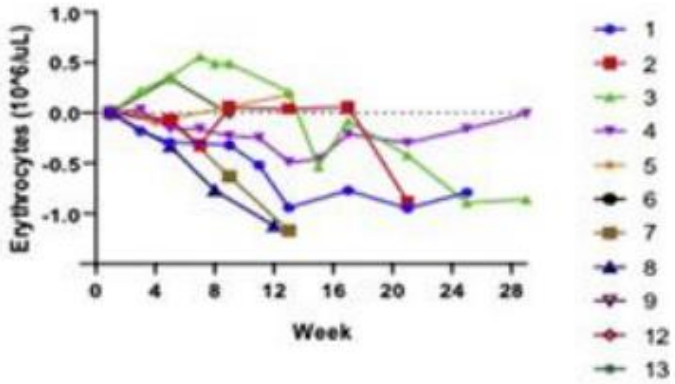
Second-line treatments and clinical trials in PV: PTG-300 hepcidin mimetic

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL | NOVEMBER 5, 2020

PTG-300 Eliminates the Need for Therapeutic Phlebotomy in Both Low and High-Risk Polycythemia Vera Patients

Marina Kremyanskaya, Yelena Ginzburg, MD, Andrew T. Kuykendall, MD, Abdulraheem Yacoub, MD, Jay Yang, MD, Suneel K Gupta, PhD, Frank Valone, MD, Sarita Khanna, PhD, Srdan Verstovsek, MD PhD, Ronald Hoffman, MD





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

Phlebotomy (continued)

Hydroxyurea

Interferon

Ruxolitinib after HU

Risk Assessment

(NCCN, ELN)

	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%

PV initial treatment approach:

What do guidelines recommend? What do we recommend?

National Guidelines

Initial Treatment by Risk Group	
Low Risk	• Assess for new blood clots and major bleeding • Manage cardiovascular risk factors • Aspirin • Phlebotomy
High Risk	• Assess for new blood clots and major bleeding • Manage cardiovascular risk factors • Aspirin • Hydroxyurea or interferons

NCCN Guidelines for Patients, Myeloproliferative Neoplasms, 2019

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+ INTERFERON (IFN)

IFN or Hydroxyurea (HU)

Related to Anemia

1) More frequent falls
2) Cognitive impairment
3) Dementia
4) Poor exercise tolerance
5) Impaired results after chemotherapy
6) Impaired results after myocardial infarction

Schrier S. Hem Onc. Jan 2015
DeLoughery, NEJM 2014

Myth of Phlebotomy-only: Phlebotomy is unacceptable as sole treatment

1. Poor Clinical Tolerance

2. Frequency of Vascular Complications

3. Risk of Early Progression to Myelofibrosis

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

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MPN Patients are highly symptomatic regardless of subset

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

Geyer and Mesa, *Blood* 2015

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Annual rate of thrombosis in general population and in contemporary patients with polycythemia vera
% pts/year

General population without risk factors	0.6
General population with multiple risk factors	0.9
PV patients with low risk	2.23
PV patients with high risk	3.14

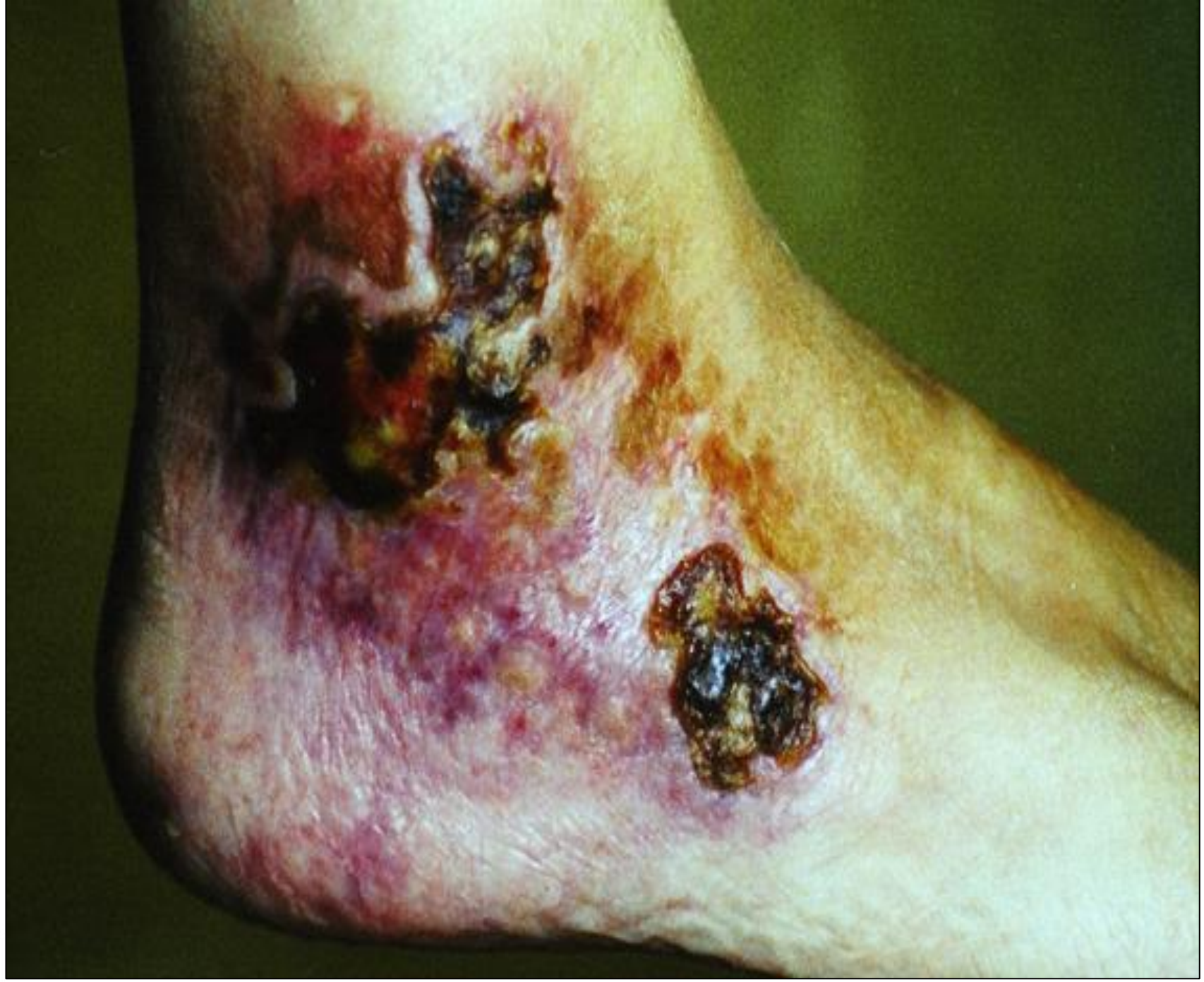
With permission and courtesy of T. Barbui MD
10th International Patient Symposium

Comparative incidence of thrombosis (PVSG study)

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

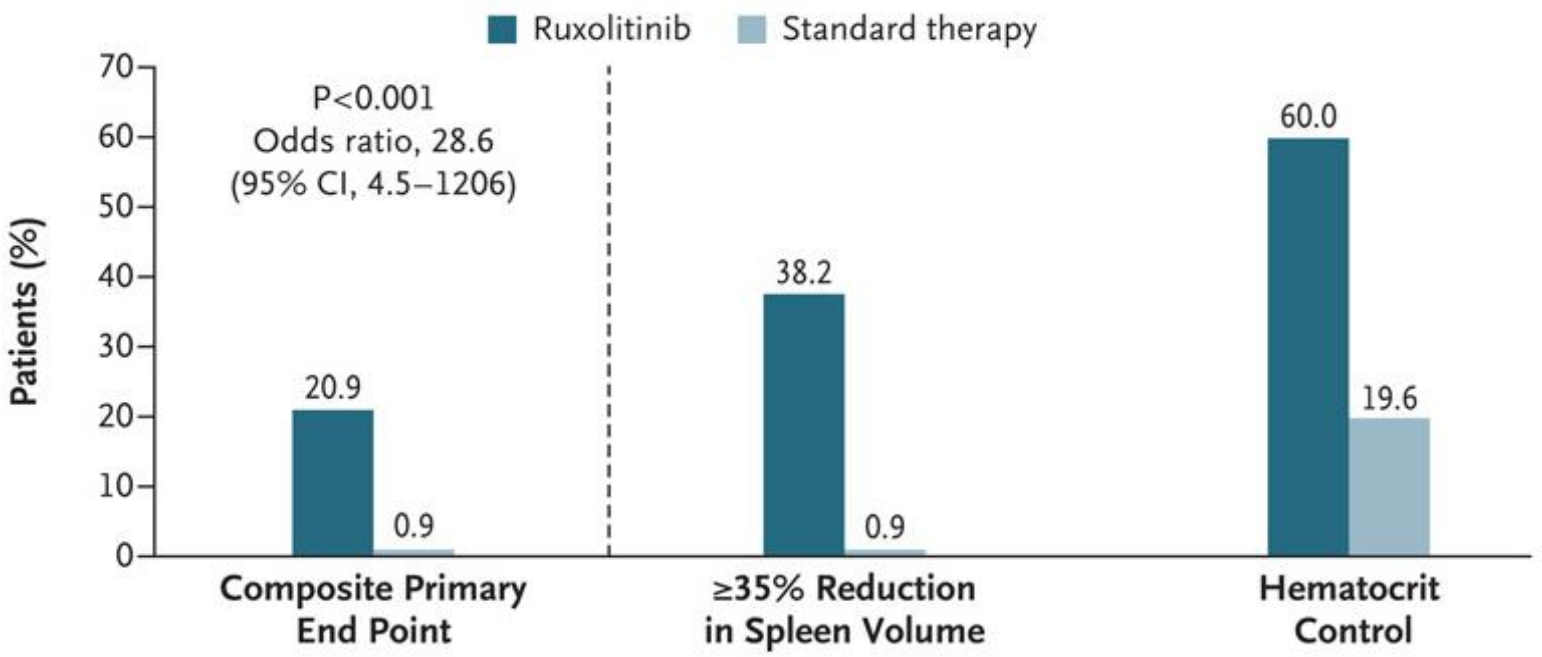
Treatment	Total patients	No. events	%
Hydrea + phlebotomy	**51**	**7**	**13.7**
Phlebotomy-only	**134**	**51**	**38.1**

Fruchtman S. PVSG Data. 1996



“Approved” Treatment for HU Resistance or Toxicity

RESPONSE Trial: Ruxolitinib vs. “Standard therapy”



Vannucchi, et al. N Engl J Med 2015

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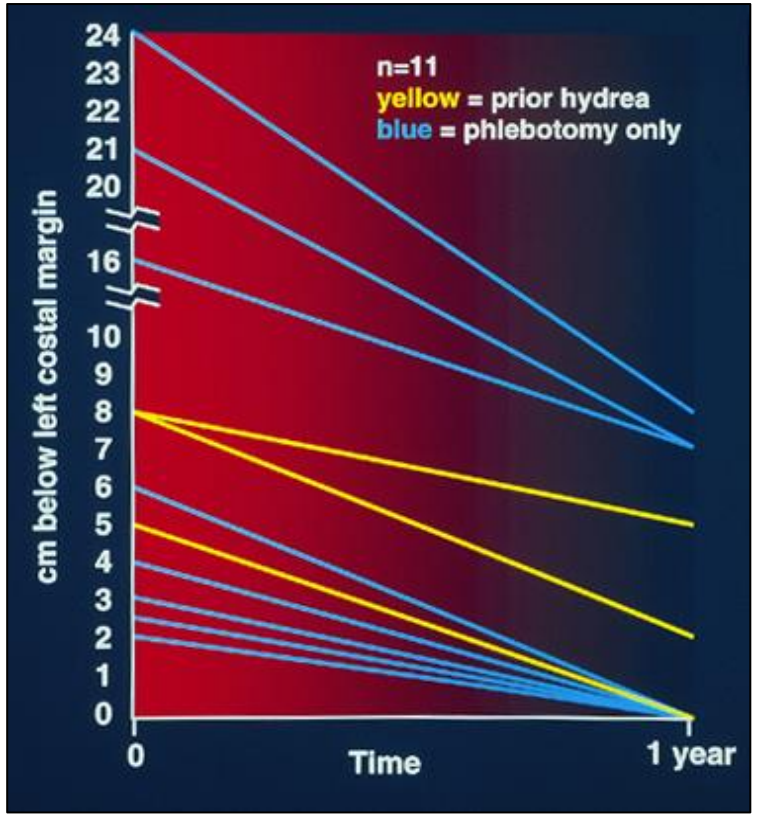
CHANGE IN SPLEEN SIZE

1 year after rIFN-a

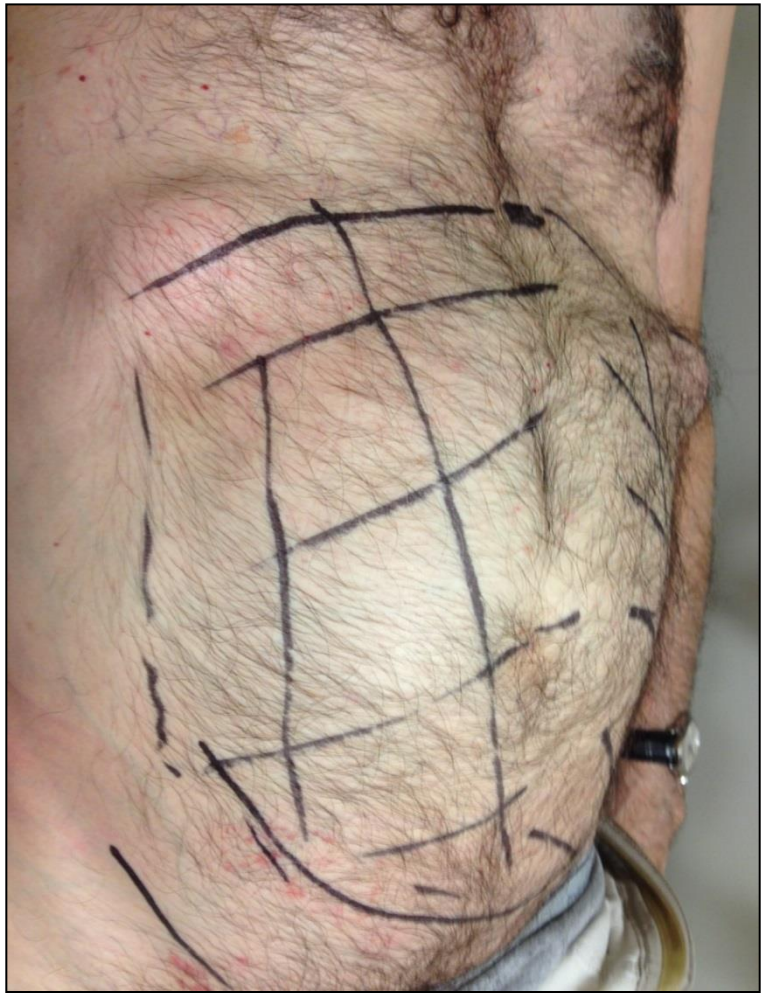


2 years after rIFN-a

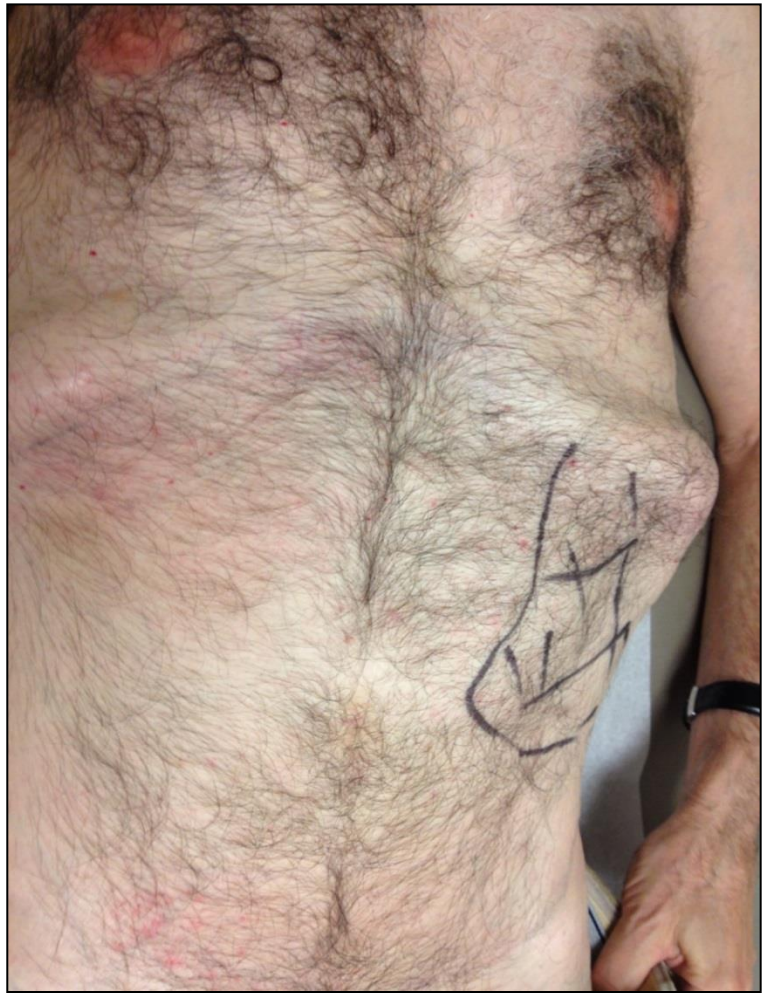
- 27/30 (90%) patients with initial splenomegaly showed greater than 50 % reduction in spleen size whether or not they received prior HU
- In 23 (76.7%) patients, spleen became non-palpable

Silver RT. Cancer. 2006

BEFORE rIFN RX



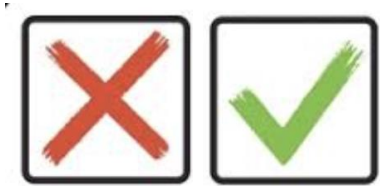
One year AFTER



Specific Activities of Interferon-alpha (rIFNa) 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

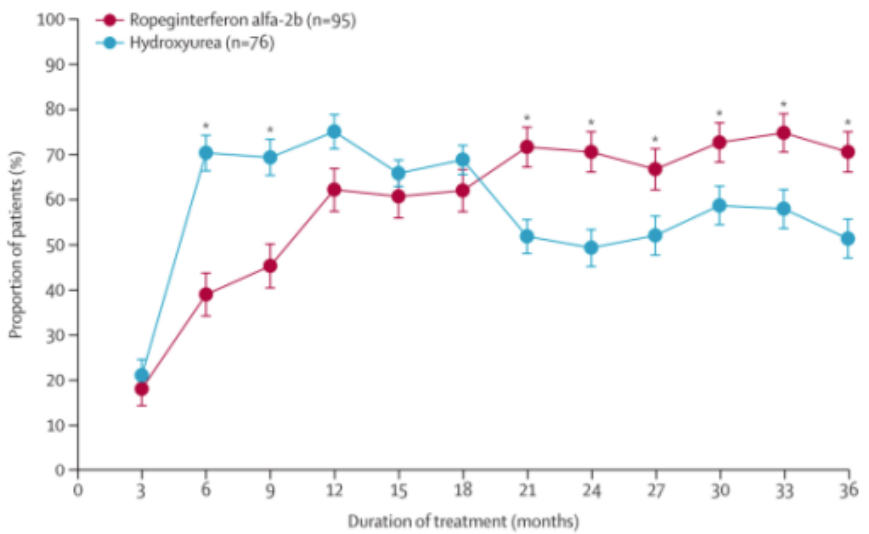
Does Interferon-alpha prolong survival of PV patients?

	Large study	Randomized, controlled	Long follow-up
MPN-RC 112 **DALIAH** **CONTI-PV** **Low-PV**	85-254 patients 		~1-3 years 
WCM (Cornell)	470 patients 		Median 10 years (up to 45) 

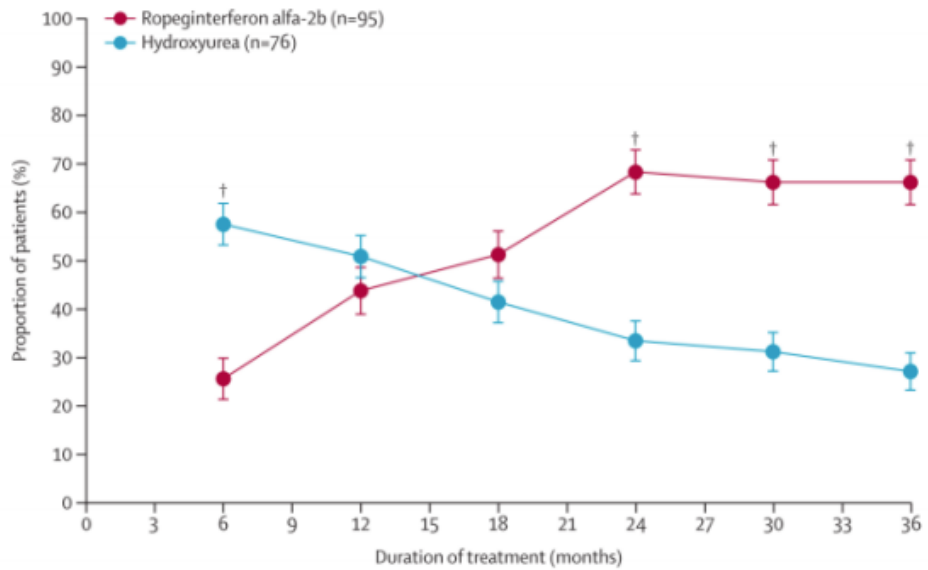
Ropeg-IFN is possibly better than HU in a randomized trial of high-risk PV (CONTI-PV)

Ropeginterferon α-2b (Ropeg-FN) is a longer-acting, biweekly dosed form of Interferon-alpha

Complete hematologic response

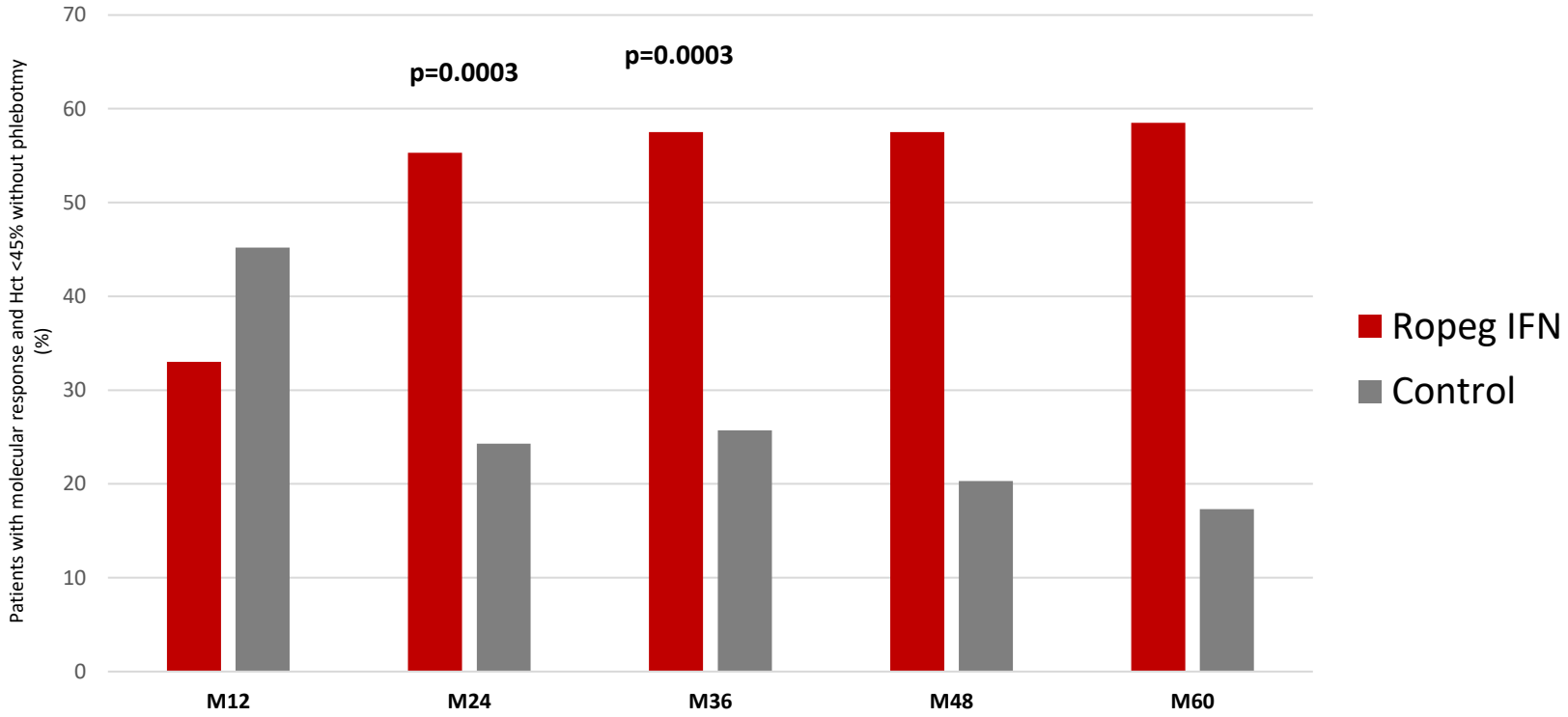


Partial molecular response



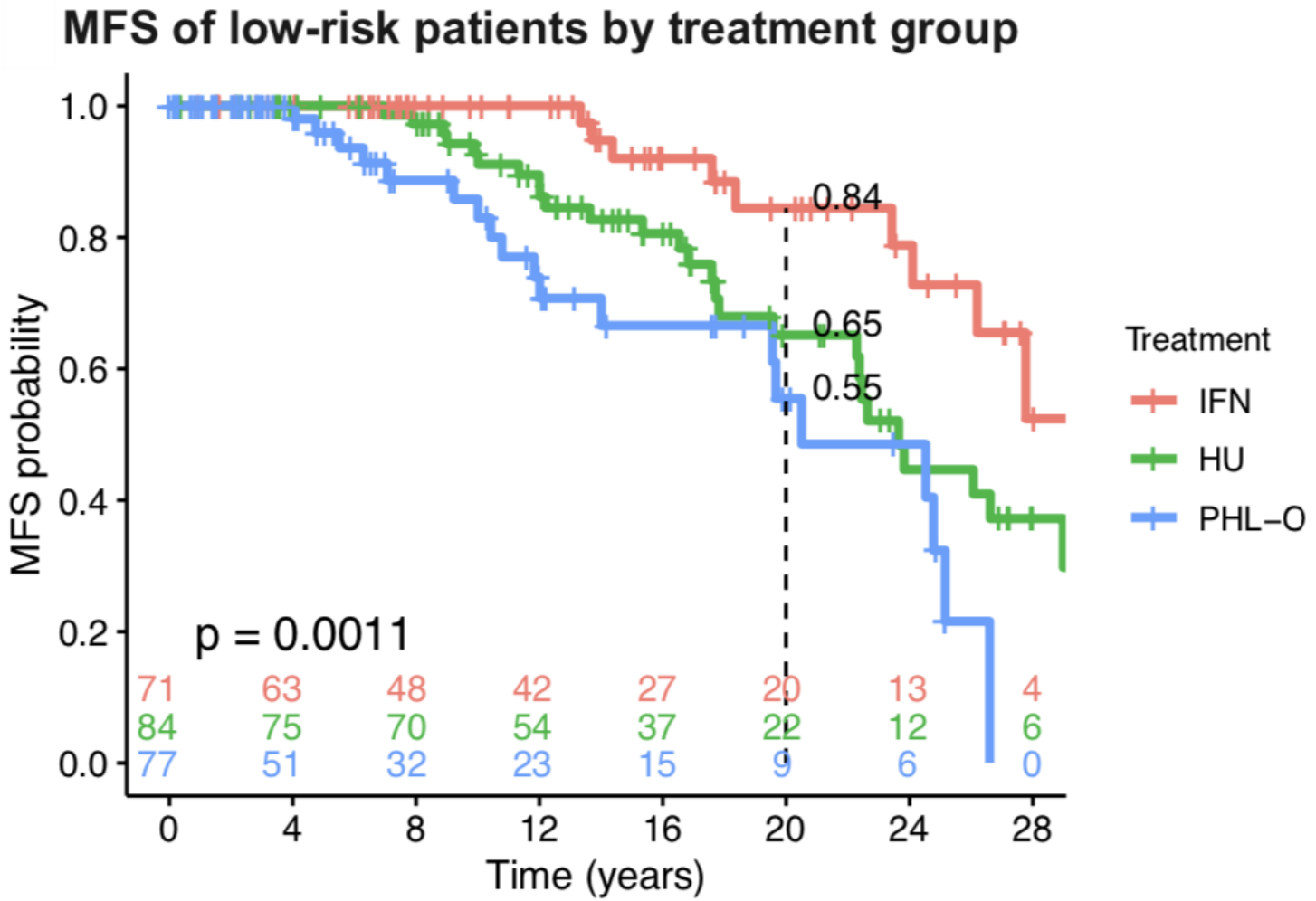
Gisslinger H et al. Lancet Hematology 2020

Combined analysis of Hct<45% without phlebotomy AND molecular response



Barbui et al. *Lancet Haematology* 2021

IFN is associated with improved MFS in low-risk PV



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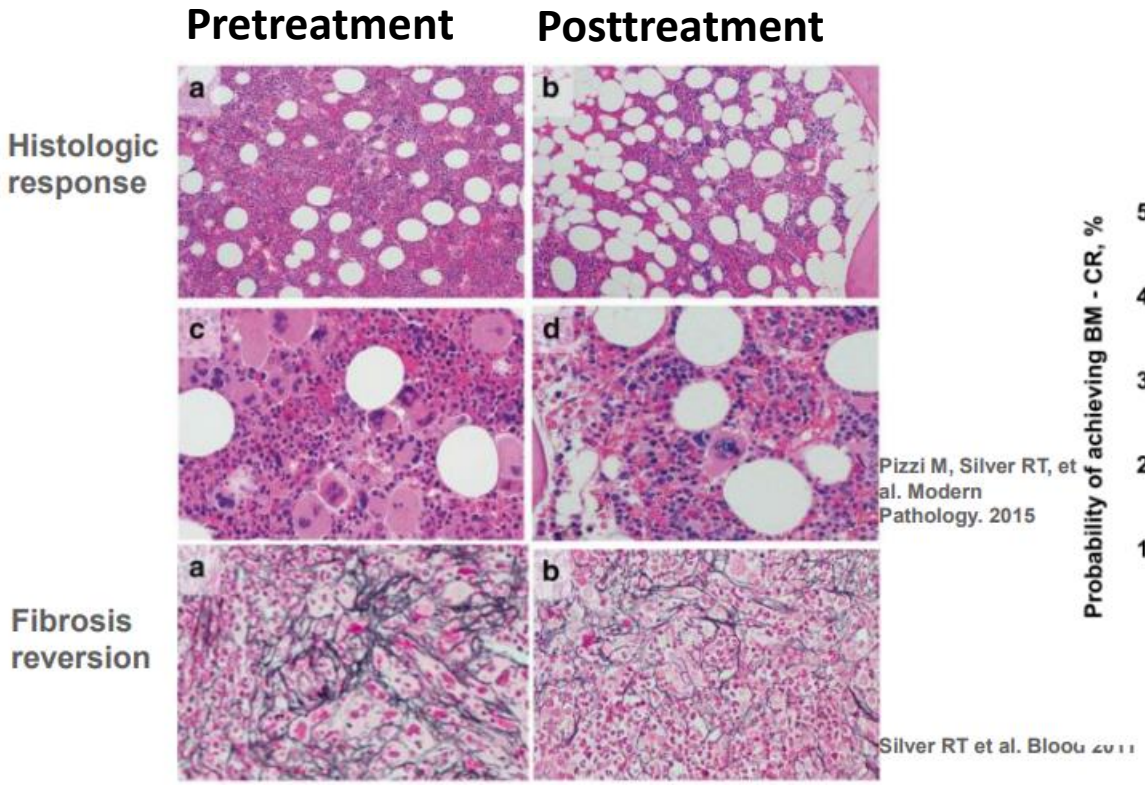
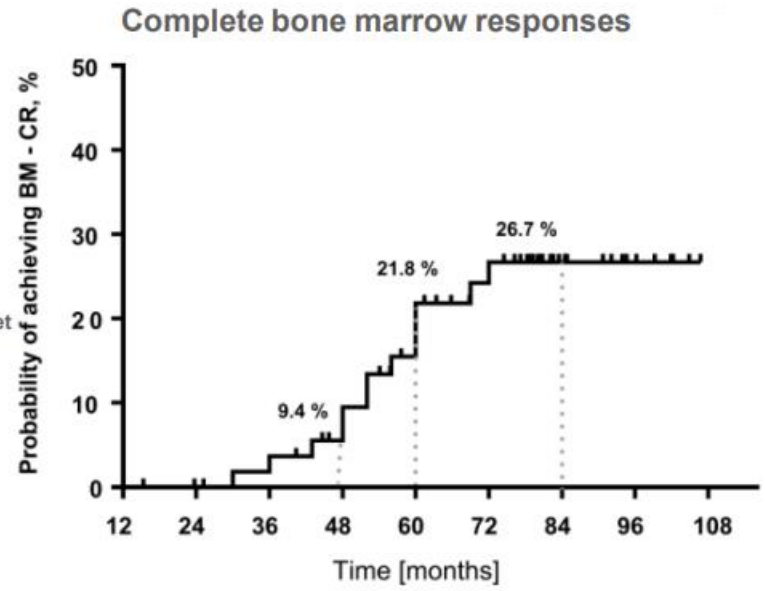
Abu-Zeinah G et al. Oral abstract at the 2020 annual meeting of the American Society of Hematology
Manuscript accepted to *Leukemia*

IFN in PV is disease-modifying



Pizzi M, Silver RT, et al. Modern Pathology. 2015

Silver RT et al. Blood 2011



Masarova L et al. Hematol Oncol. 2017

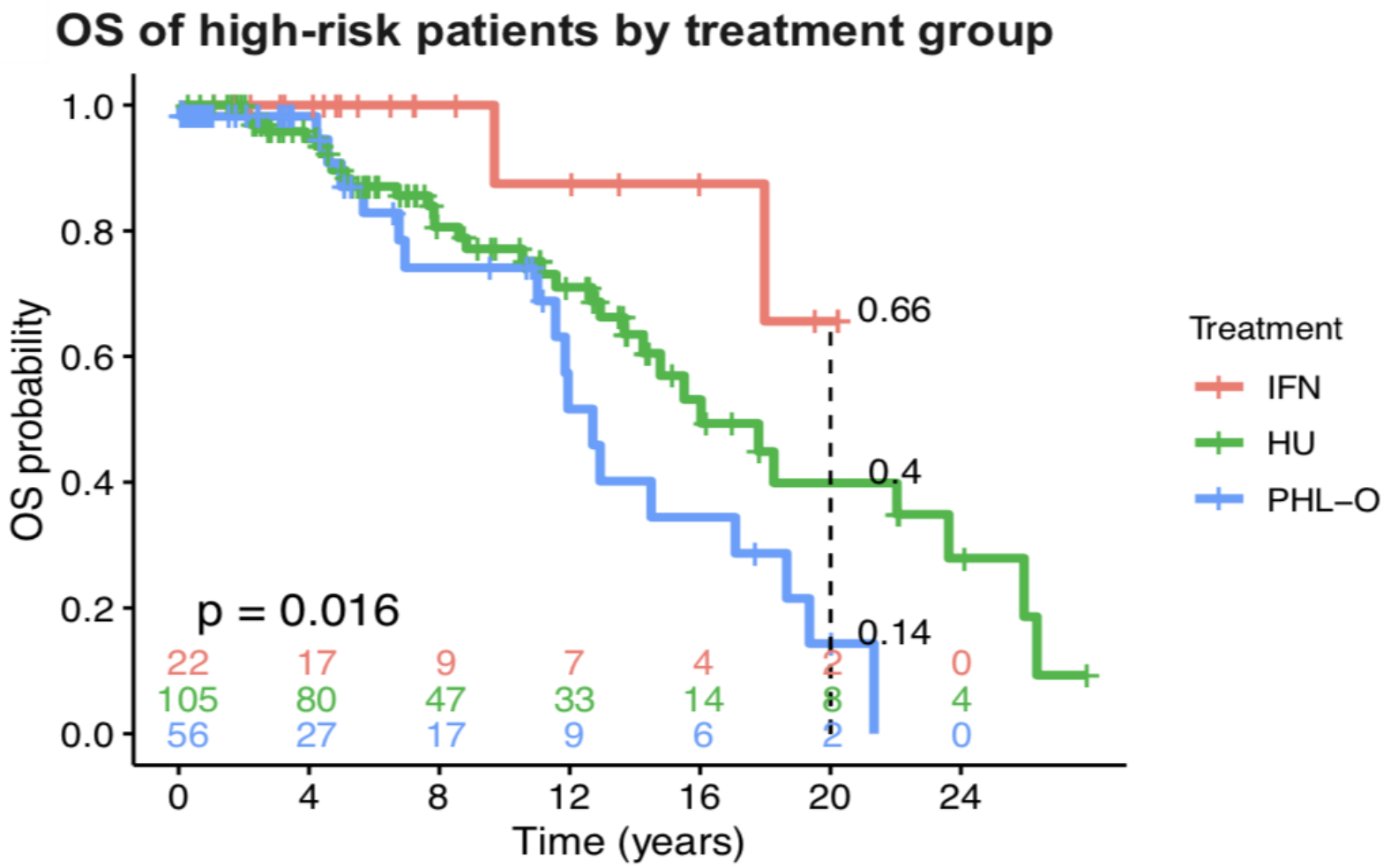
Longer time on IFN is associated with reduced MF

Variable	Myelofibrosis (MF) HR (95% CI, p-value)
Age	1.01 (0.99-1.03, NS)
Sex (Female/Male)	0.70 (0.46-1.07, NS)
Thrombosis history (Y/N)	1.18 (0.63-2.20, NS)
CV risk factors (Y/N)	0.81 (0.47-1.38, NS)
IFN (time on therapy)	0.91 (0.87-0.95, p<0.001)
HU (time on therapy)	0.98 (0.95-1.01, NS)
Other (time on therapy)	0.99 (0.94-1.05, NS)

9% MF risk reduction / year of IFN

Abu-Zeinah, Silver. *Leukemia*, in press, 2021

IFN is associated with improved OS in high-risk PV



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Abu-Zeinah G et al. Oral abstract at the 2020 annual meeting of the American Society of Hematology
Manuscript accepted to *Leukemia*

Longer time on IFN is associated with reduced mortality

Variable	Mortality HR (95% CI, p-value)
Age	1.10 (1.07-1.12, p<0.001)
Sex (Female/Male)	0.54 (0.36-0.83, p=0.005)
Thrombosis history (Y/N)	1.12 (0.61-2.04, NS)
CV risk factors (Y/N)	1.06 (0.67-1.68, NS)
IFN (time on therapy)	0.94 (0.90-0.99, p=0.012)
HU (time on therapy)	0.97 (0.94-1.00, NS)
Other (time on therapy)	1.00 (0.94-1.06, NS)

6% mortality risk reduction / year of IFN

Abu-Zeinah, Silver. *Leukemia*, in press, 2021

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):

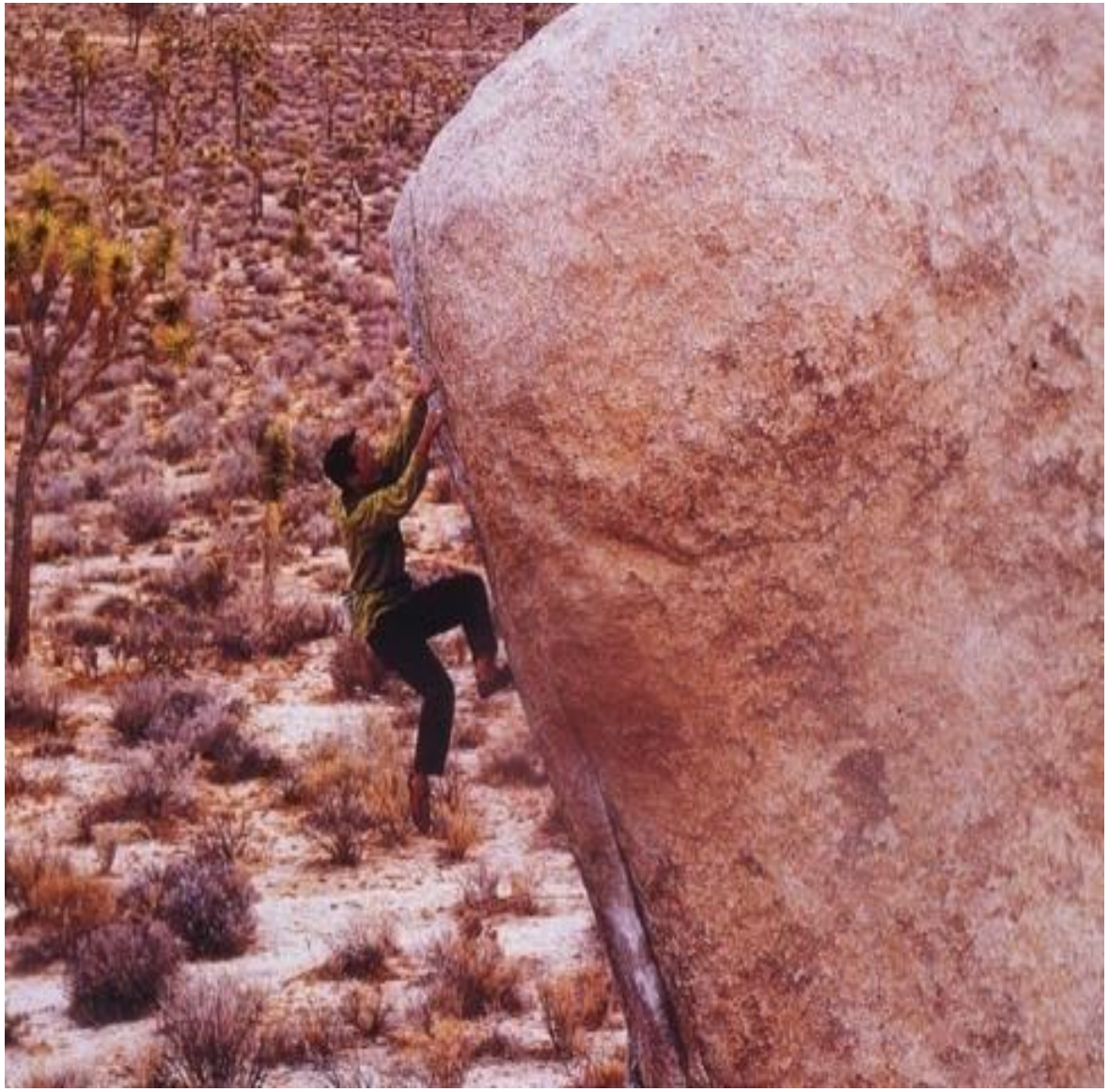
Chronic fatigue
Depression
Musculoskeletal pain
Alopecia
GI toxicity
Confusion (elderly patients)
Liver toxicity
Cytopenias
Autoimmune disease
Pulmonary, cardiac, or renal dysfunction
Neurological (gait disturbance, frontal lobe dysfunction, bilateral lower extremity neuritis)

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

IFN should be considered for both low and high risk patients

	Initial treatment by risk group	
	Low risk	**High risk**
NCCN	PHL-O	HU or IFN
ELN	PHL-O	HU or IFN
WCM	**IFN** > PHL-O	**IFN** > HU

Climbing the PV rock



Interferon

Hydroxyurea

Ruxolitinib

Fedratinib

Transplantation

etc., etc…

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WCM

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MPN Research Foundation CHANGE YOUR PROGNOSIS