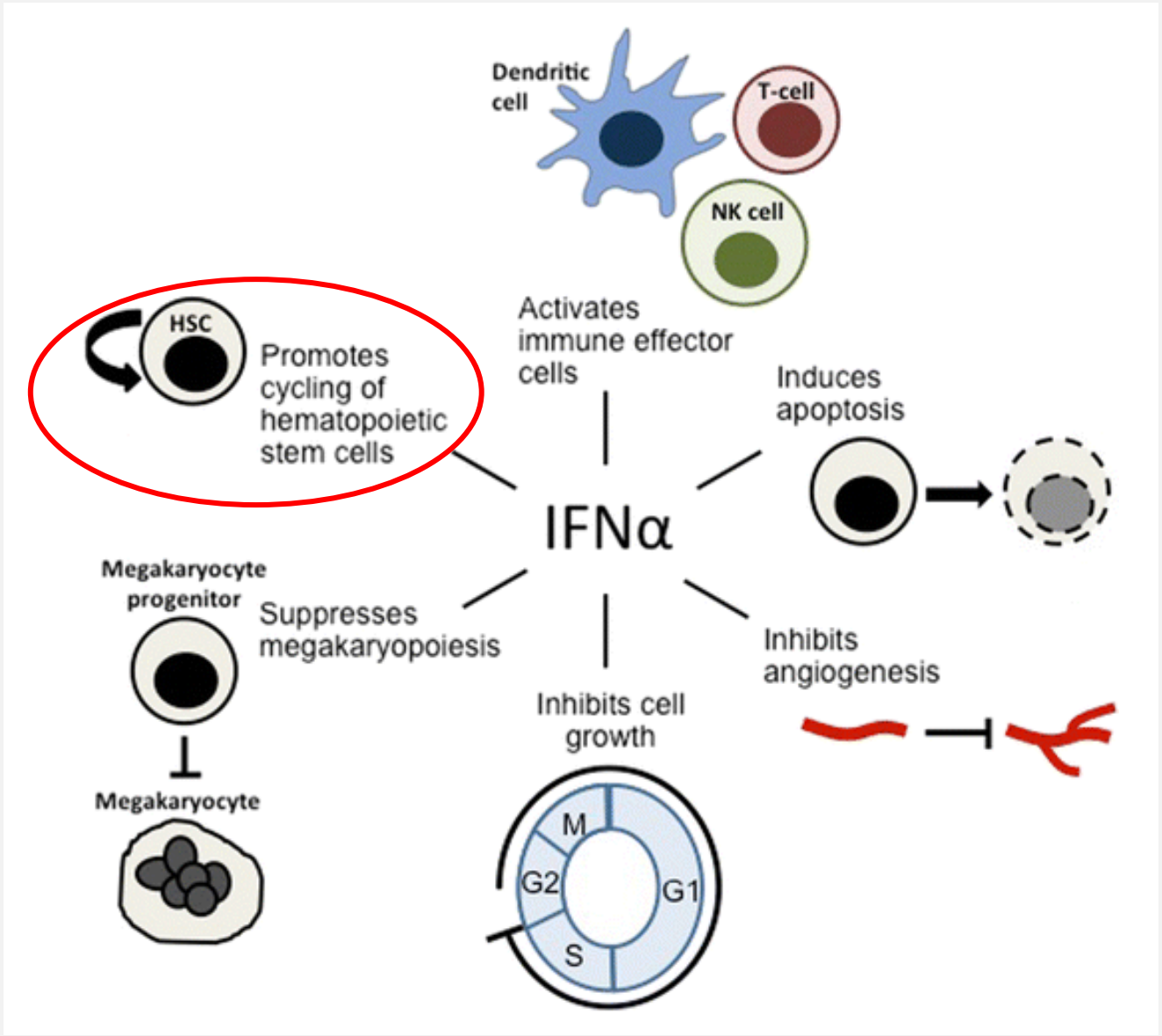
Interferon-alpha therapy for myeloproliferative neoplasms (MPN)

Auszüge aus wissenschaftlichen Vorträgen der Jahre 2022 bis 2024

Prof. Dr. med. Eva Lengfelder
III. Medizinische Klinik
Universitätsmedizin Mannheim,
Universität Heidelberg

IFN-alpha antitumor effects

Mechanisms of antitumor effects of Interferon-alpha affecting several biologic processes in hematologic malignancies



Talpaz et al, Ann Hematol 2015

Multiple and complex effects of IFN-alpha on hematopoietic stem (HSC) and progenitor cells (HPC) in MPN

Selection of effects:

Transient induction of proliferation of HSC (acute effect)

Suppressive effects of chronic exposure

Direct pro-apoptotic effect on myeloid progenitors

Higher activity against mutant than wild type cells

Nonspecific effects on any genetic alterations (e.g. cytogenetic remissions)

Some genetic alterations in HSC and HPC may be associated with resistance.

Does IFN alpha have the potential to eradicate the disease initiating cells ?

Reviewed in: Talpaz et al, Ann Hematol 2015, Kliladjian et al, Leukemia 2016

blood
Plenary Paper

MYELOID NEOPLASIA

JAK2-V617F and interferon-α induce megakaryocyte-biased stem cells characterized by decreased long-term functionality

Tata Nageswara Rao,[1] Nils Hansen,[1] Jan Stetka,[1,2] Damien Luque Paz,[1] Milena Kalmer,[3] Julian Hilfiker,[1] Max Endele,[4] Nouraiz Ahmed,[4] Lucia Kubovcakova,[1] Margareta Rybarikova,[1] Hui Hao-Shen,[1] Florian Geier,[1,5] Christian Beisel,[4] Stefan Dirnhofer,[6] Timm Schroeder,[4] Tim H. Brümmendorf,[3] Dominik Wolf,[7] Steffen Koschmieder,[3] and Radek C. Skoda[1]

Blood. 2021;137(16):2139-2151

Anticlonal activity of IFN-α:

Investigations leading to a model of how IFN-a, in combination with JAK2-V617F, could selectively reduce the JAK2 mutant clone
(possible mechanisms of anticlonal activity of IFN-α).

blood
Brief Report

MYELOID NEOPLASIA

Germline genetic factors influence the outcome of interferon-α therapy in polycythemia vera

Roland Jäger,[1] Heinz Gisslinger,[2] Elisabeth Fuchs,[3] Edith Bogner,[3] Jelena D. Milosevic Feenstra,[4] Jakob Weinzierl,[1] Fiorella Schischlik,[3] Bettina Gisslinger,[2] Martin Schalling,[2] Michael Zörer,[5] Kurt Krejcy,[5] Christoph Klade,[5] and Robert Kralovics[1,3]

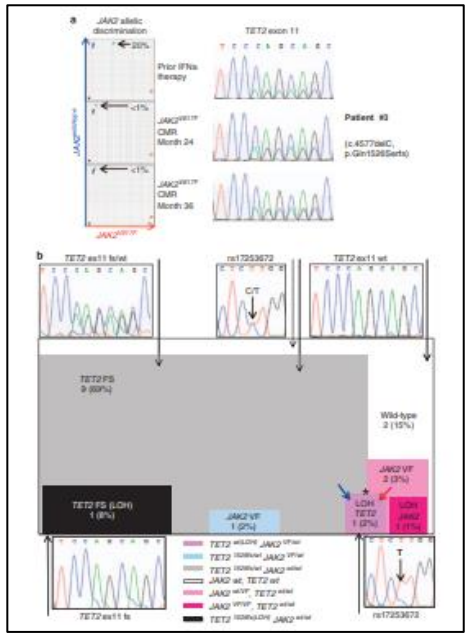
Blood. 2021;137(3):387-391

A diplotype spanning the coding region of the IFNL4 gene influences molecular response to IFN-a therapy in polycythemia vera.

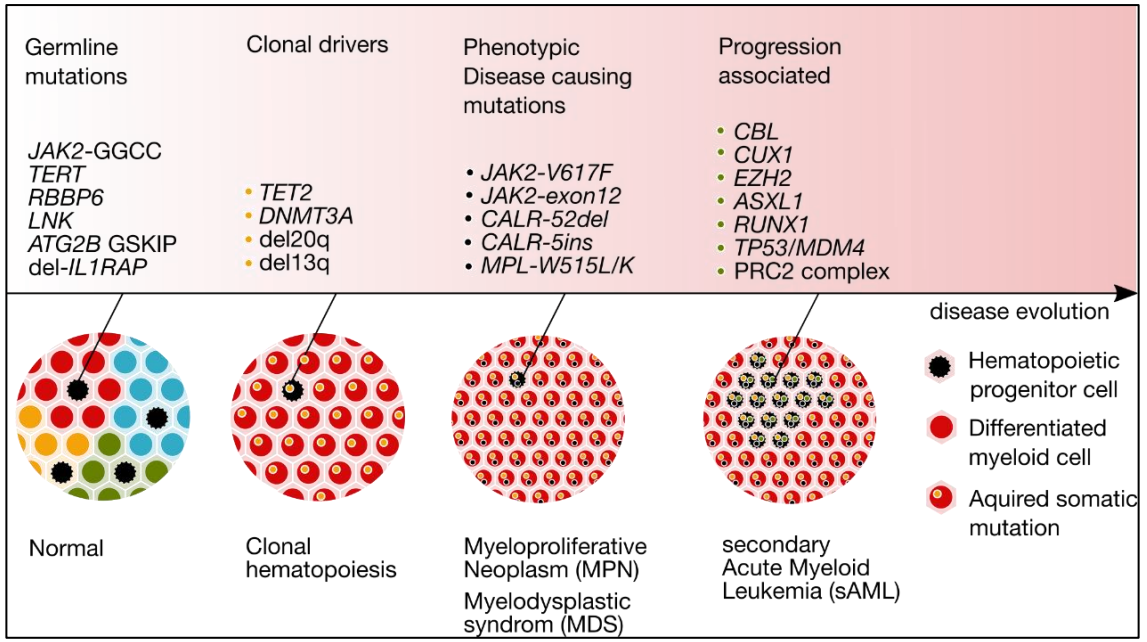
Clonal analysis of erythroid progenitors suggests that pegylated interferon α-2a treatment targets *JAK2*^{V617F} clones without affecting *TET2* mutant cells

Kiladjian JJ et al.

Leukemia (2010) **24**, 1519–1523; doi:10.1038/leu.2010.120; published online 3 June 2010



Mutations in Myeloproliferative Neoplasms - Hypothesis in Disease Evolution and Pathogenesis



Schischlik and Kralovics, Expert Reviews of Hematology, 2017;10:961-972

Earlier studies and clinical observations

First Clinical Report on Interferon in CML

Leukocyte Interferon-Induced Myeloid Cytoreduction in Chronic Myelogenous Leukemia

By Moshe Talpaz, Kenneth B. McCredie, Giora M. Mavligit, and Jordan U. Gutterman

Blood 1983;62:689-692

Basis:

- Antitumor effect of IFNα against several cancers
- Significant anti-cellular effect on normal and CML progenitor cells.

Main results:

- Hematologic remission in 5 of 7 patients
- Decrease of white blood cell count, platelet count and spleen enlargement
- Durable remissions on IFN up to 35+ weeks

Summarized results of 32 reports on recombinant IFN-alpha in ET and PV in the eighties and nineties of the last century

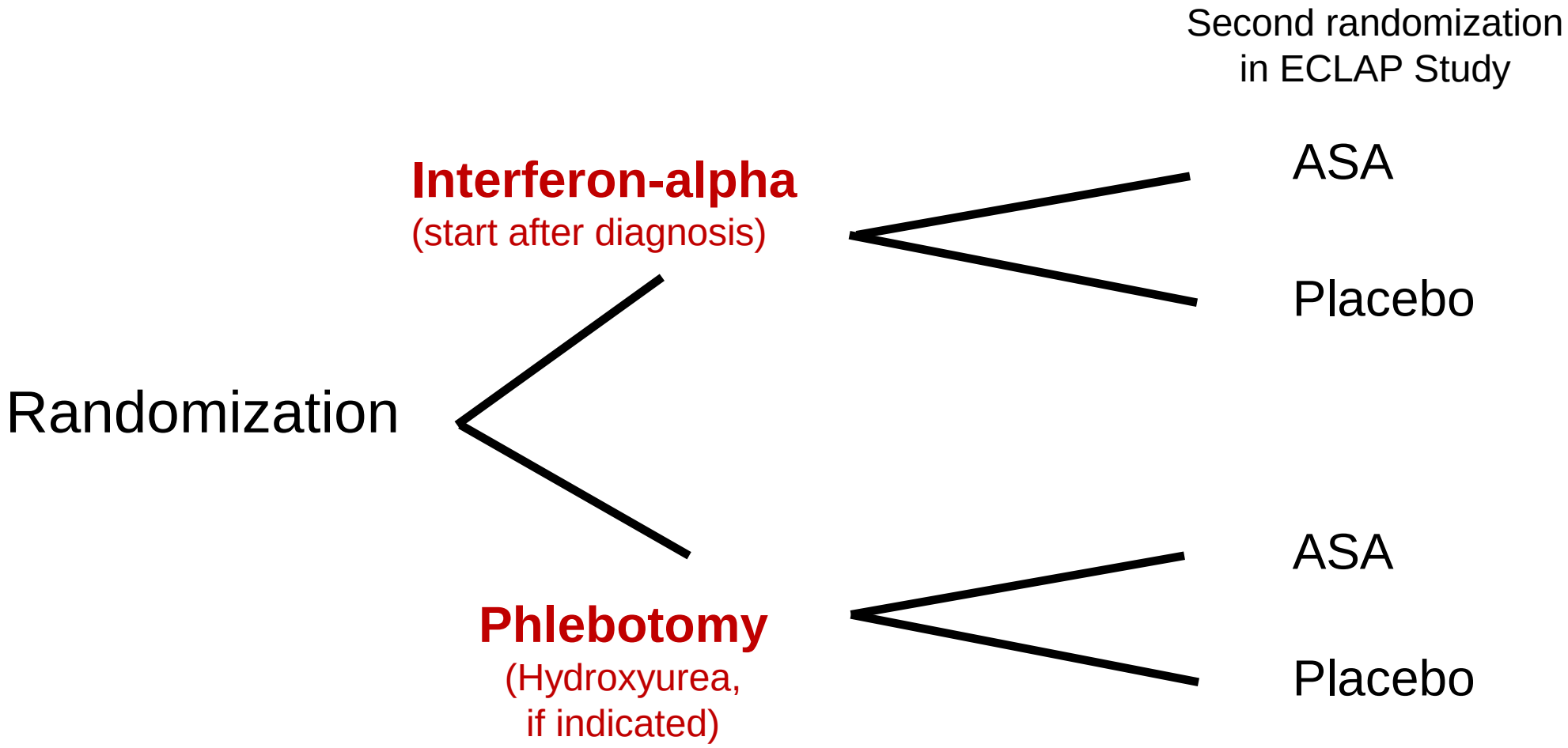
	Number of patients	Response rate (Average non-pegylated IFN dose: 3 Mill/day)	Discontinuation	Unmaintained remission	Duration of unmaintained remission
ET	273	87% (platelets)	25%	12%	up to 3+ years
PV	279	82% (blood counts) (50% phlebotomy free) (77% of splenomegaly) (81% of pruritus)	21% (of these 56% in the first year)	8%	up to 4.8+ years; second responses after relapse

Reviewed in: Lengfelder, Leuk Lymph 1996; Ann Hematol 1999

Further observations:
Restoration of polyclonal Hematopoiesis,
Cytogenetic remissions,
More benefit of IFN in early stages of CML *(Kantarjian 1986)*, occasional suggestive observations in ET and PV.

(Historical) German Study Protocol for newly diagnosed PV*

(certified by the German Cancer Society, started in the year 1999, prematurely closed after one year due to changed laws and to non-approval of IFN for MPN)



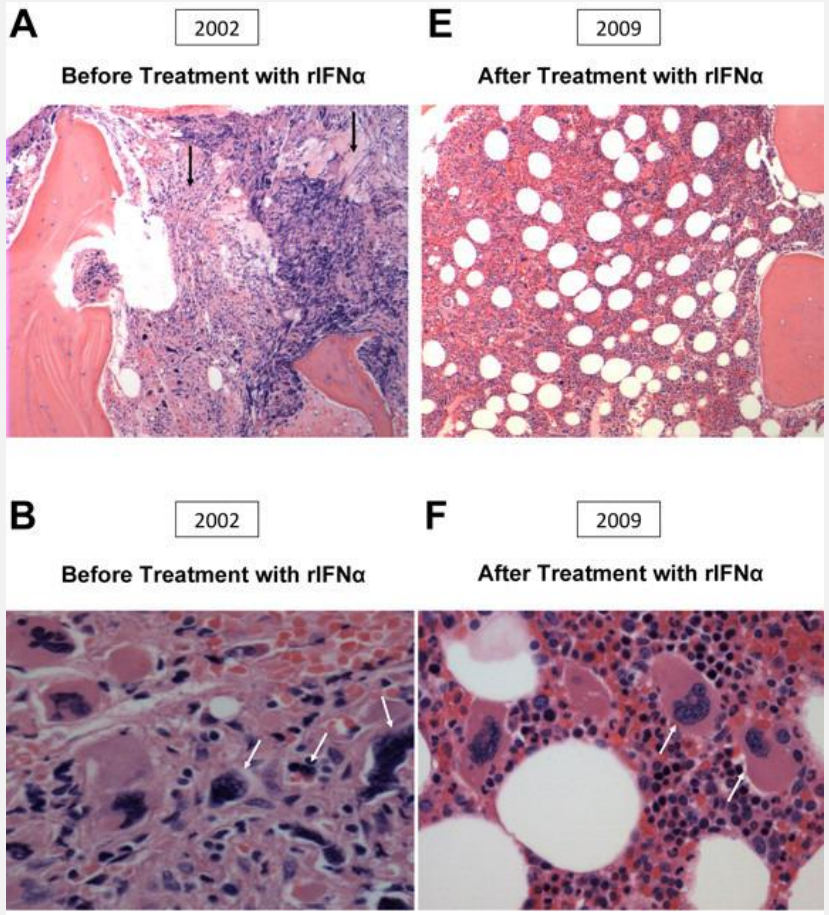
* No previous cytoreductive therapy

Results of larger Phase-II Studies with PegIFN-alpha in PV and ET

Author	n	Pretreated	Follow up	ORR (%)	CHR (%)	Mol. R (%)	Mol. CR (%)	Discontinuation due to IFN toxicity
Kiladjian, 2008	40 PV	no	31 mo	100	95	90	24	24%
Gisslinger, 2015	51 PV	no/yes	80 wk	90	47	68	21	20%
Masarova, 2017	83 40 ET 43 PV	no/yes	7 years	80	75	63	18	22%
Yacoub, 2019	65 ET 50 PV	yes	12 mo	64	34	41		14%

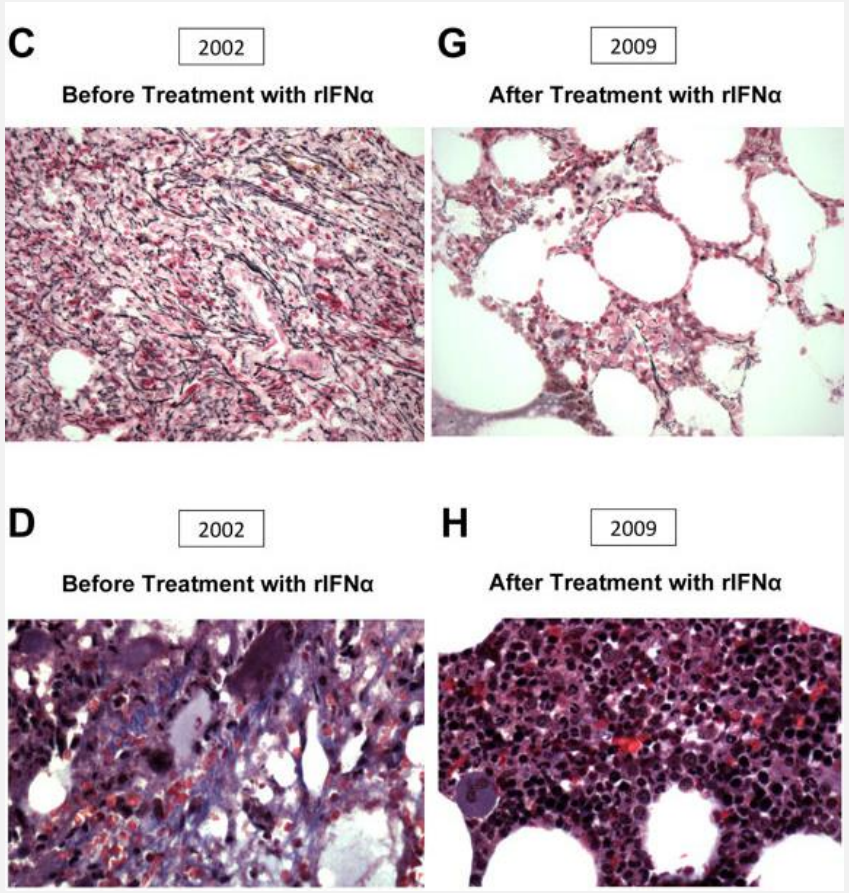
Most frequent grad 3-4 adverse events: neuropsychiatric, autoimmune, endocrine, cytopenia.
CR rates higher in CALR-mutated ET than in subjects lacking the mutation (Yacoub 2019)

Recombinant Interferon-alpha may retard progression of early primary myelofibrosis: a preliminary report (n=11)



Improved bone marrow architecture, hematopoiesis, and megakaryocyte morphology

Improved megakaryocyte morphology and increased normoblastic erythropoiesis

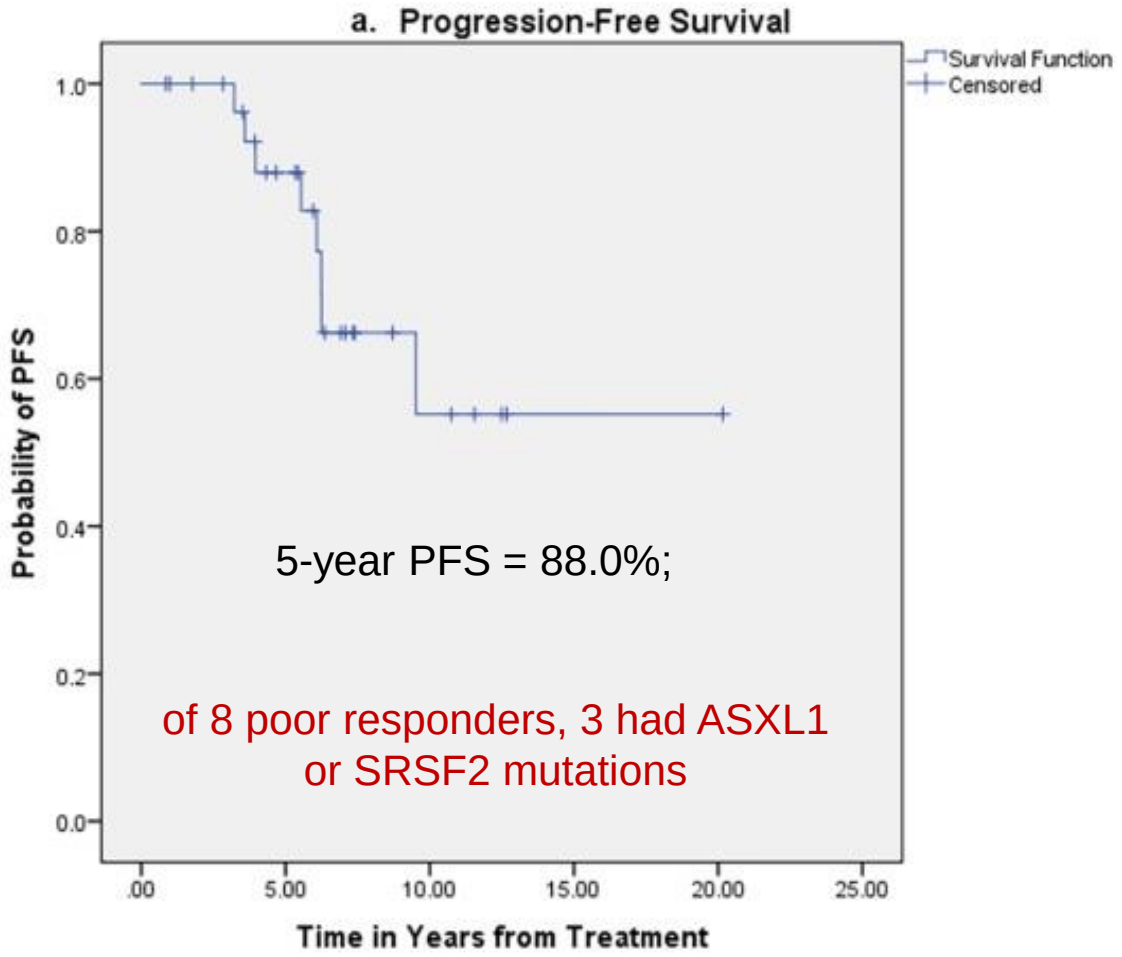


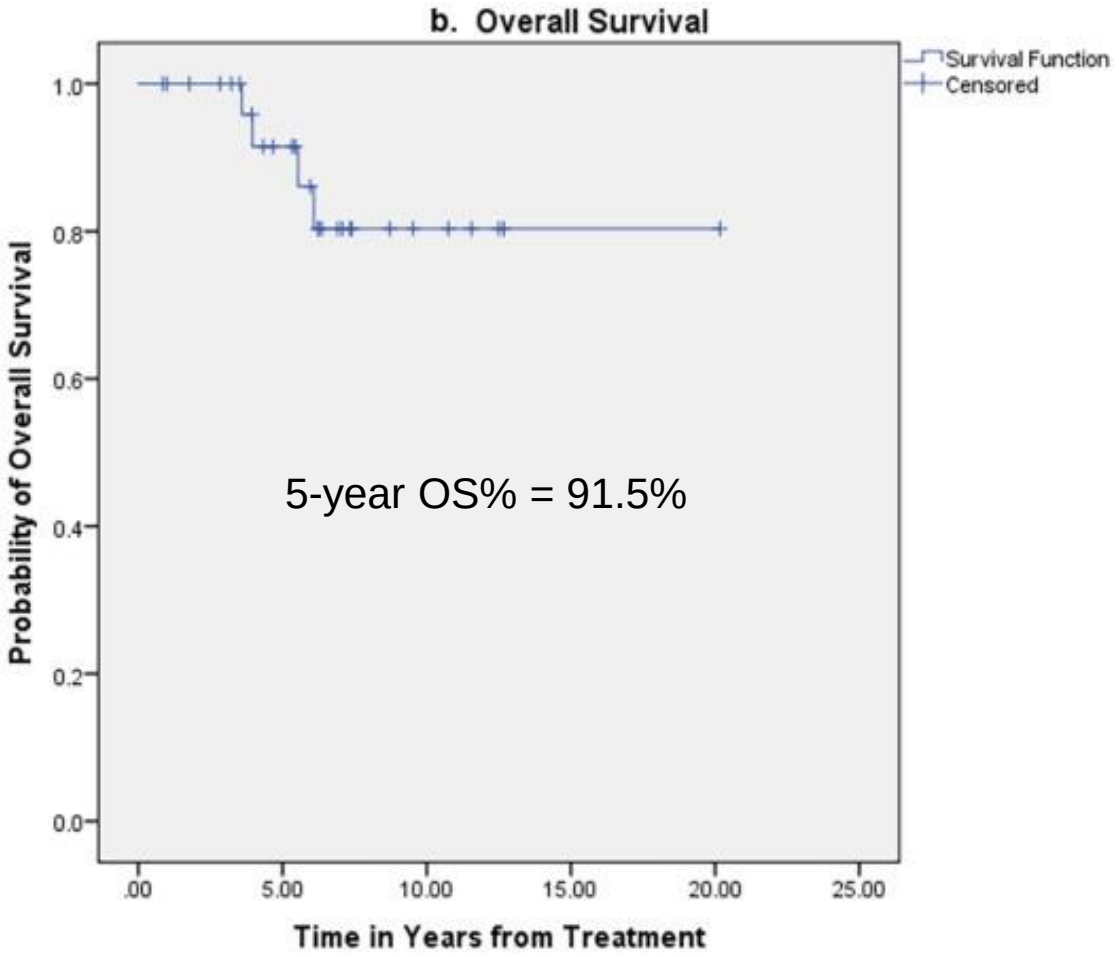
Minimal reticulin fibrosis

Absent collagen fibrosis

Silver et al, Blood 2011;117:6669-6672

Results of recombinant interferon-alpha* treatment in early myelofibrosis (n=30; DIPPS low or intermediate 1)

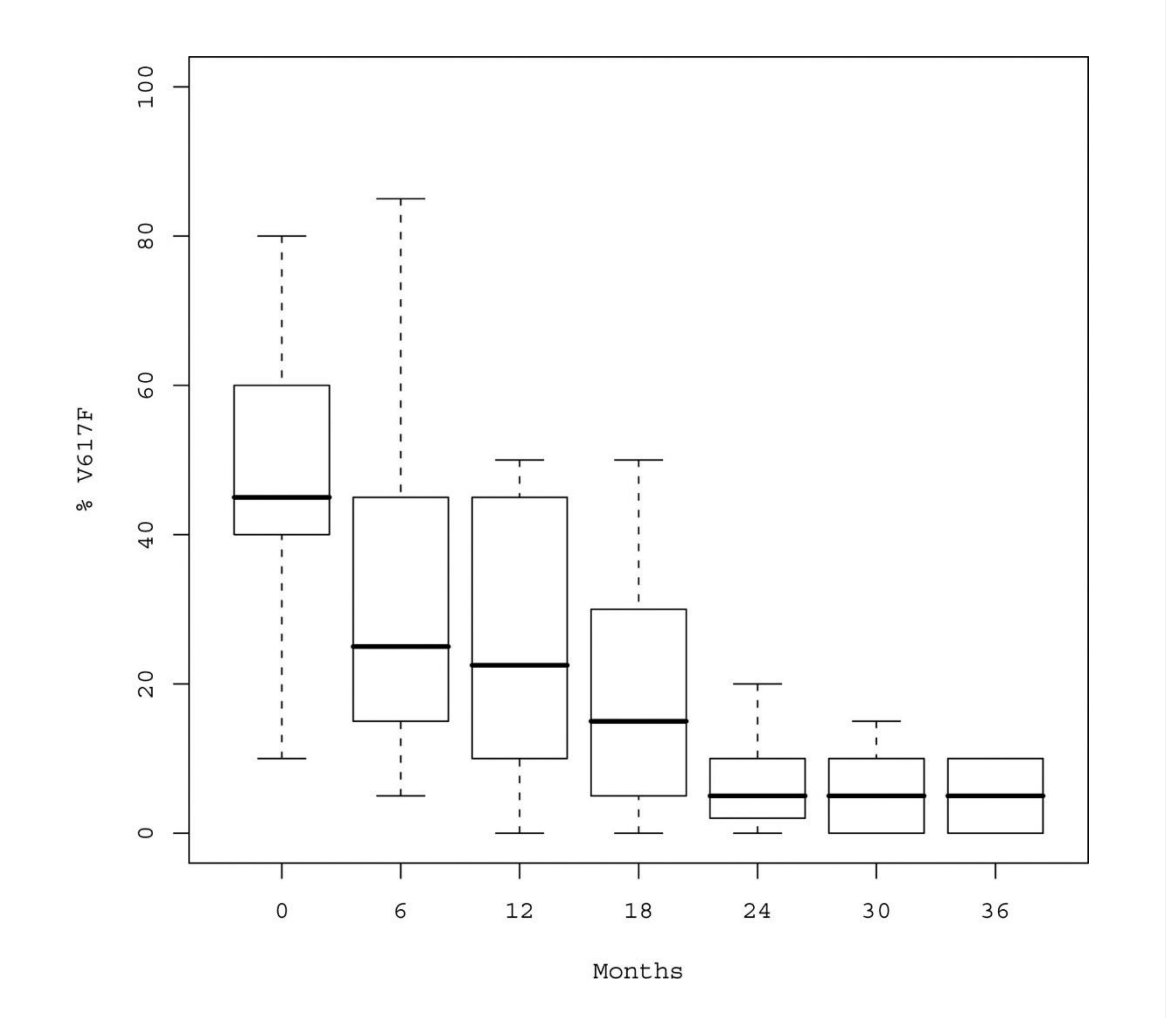




*pegylated or unpegylated recombinant interferon-alpha

Silver et al, Cancer 2017;123:2680-2687

Decrease of *JAK2* V617F allele burden over time in PV patients treated with pegylated IFN-alpha-2a

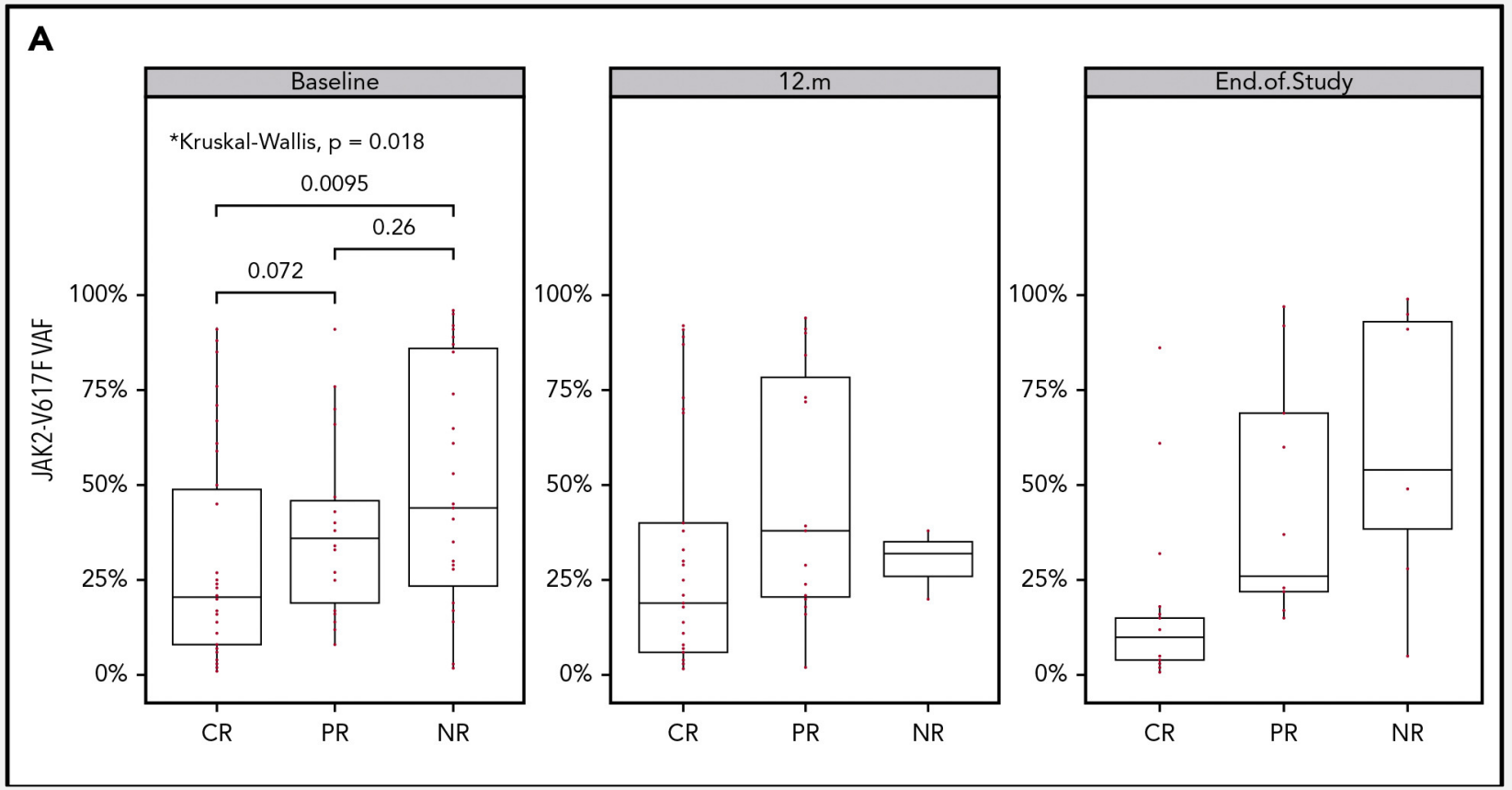


Median %V617F was 45%, 22%, 5%, and 3% at baseline, 12, 24, and 36 months, respectively.

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

Molecular response in correlation to the quality of hematological response and treatment duration with PegIFN-alpha in PV or ET

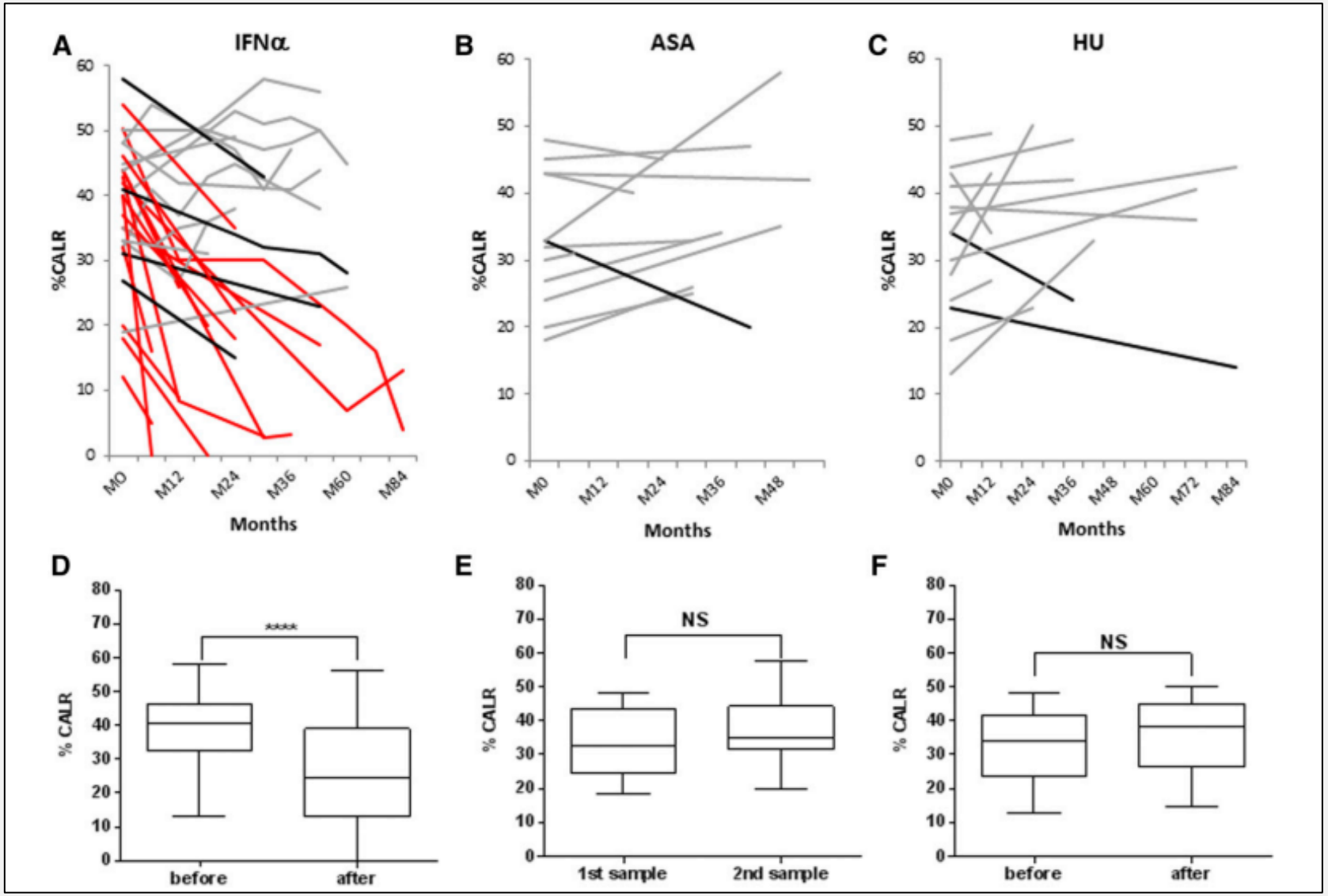
(baseline, 12 months, end of study)



CR only in 3 of 11 pts with *TP53*-mutation and in 3 of 8 pts with ASXL1-mutation (ET or PV pts)

Yacoub et al, Blood 2019;134:1498-1509

Evolution of CALR mutant allele burden (%CALR) with time, Comparison of PegIFN-alpha, ASA and HU in ET



red: **CMR/ PMR**
black: **mMR**
gray: **no response**

Verger et al, Blood 2015;126:2585-2591

Serial mutational analysis of genes outside of JAK2 during therapy with PegIFN-alpha-2a in patients with PV and ET

A

JAK2V617F response	Patient	Days between serial samples	*JAK2V617F* allele-burden Initial	*JAK2V617F* allele-burden Serial[1]	*TET2*	*DNMT3A*	*ASXL1*	*IDH1/2*	*EZH2*
CMR	1	577	82.4%	0.01%					
	2	524	63.4%	2.5%					
	3	885	58.7%	0%	Mutation lost				Mutation lost
	4	1,292	68.4%	0.01%					
	5	550	5.8%	0.01%		Mutation lost			
	6	356	45.8%	0.01%					
	7	723	11.8%	0%			Mutation lost		
	8	259	9.1%	0.02%					
	9	2,554	8.1%	0.02%					
PMR	10	1,084	82.1%	19.8%	Mutation acquired				
	11	1,462	86.1%	23.8%		Mutation retained			
	12	1,462	45.4%	14.1%					
	13	1,462	41.9%	14.7%	Mutation retained				
	14	1,462	98.8%	25.9%		Mutation acquired			
	15	564	89.6%	7.0%					
	16	363	71.8%	55%					
	17	1,462	77.7%	18.5%	Mutation acquired				
mMR	18	373	92.6%	89.8%					
	19	1,857	87.7%	71.4%	Mutation acquired	Mutation acquired	Mutation acquired	Mutation lost	
No response	20	366	83.0%	79.2%		Mutation acquired			
	21	749	68.2%	78%		Mutation acquired			
	22	400	52.4%	82.3%	Mutation acquired	Mutation acquired	Mutation acquired		
	23	780	99.2%	94.6%					

[1] All CMR patients found to have sustained undetectable quantitative *JAK2*V617F allele burden coicident or following these values

Mutation lost in serial sample

Mutation acquired in serial sample

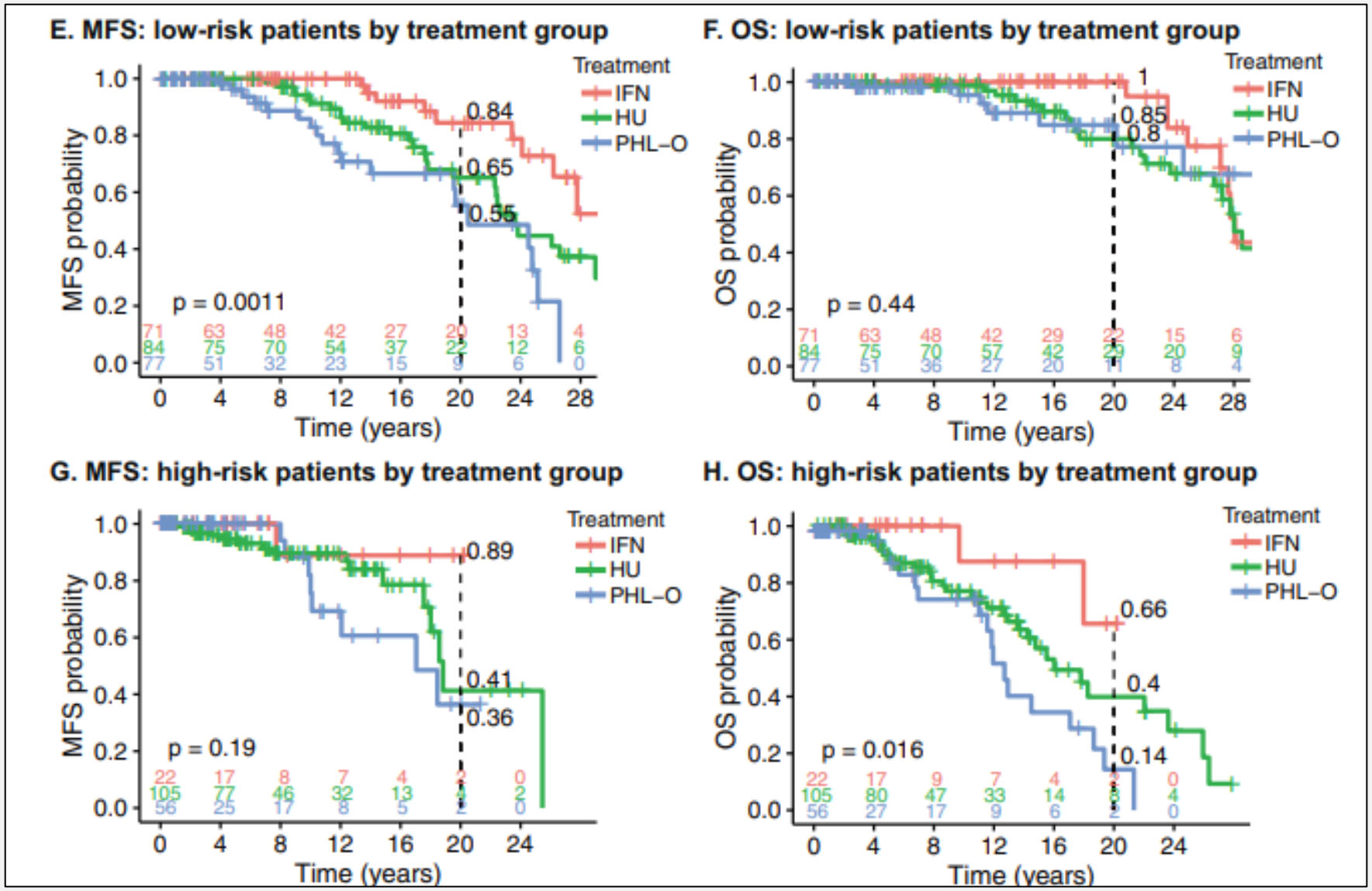
Mutation retained in serial sample

No mutation in genes sequenced (other than possibly *JAK2*)

Quintás-Cardama Blood 2013;122:893-901

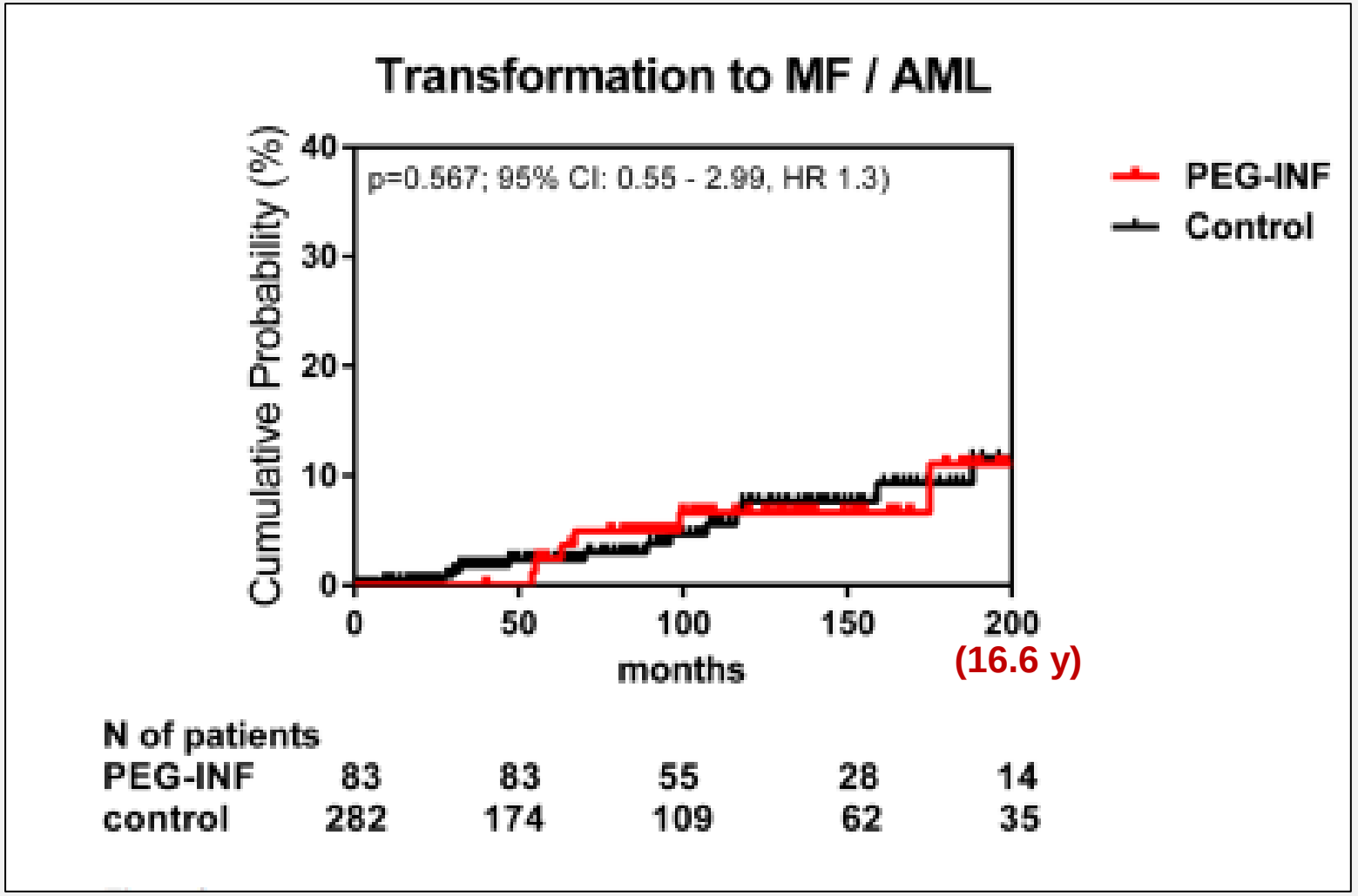
Current results of IFN-therapy in MPN

Myelofibrose-freies und Gesamtüberleben bei PV (IFN vs HU vs Aderlässe)



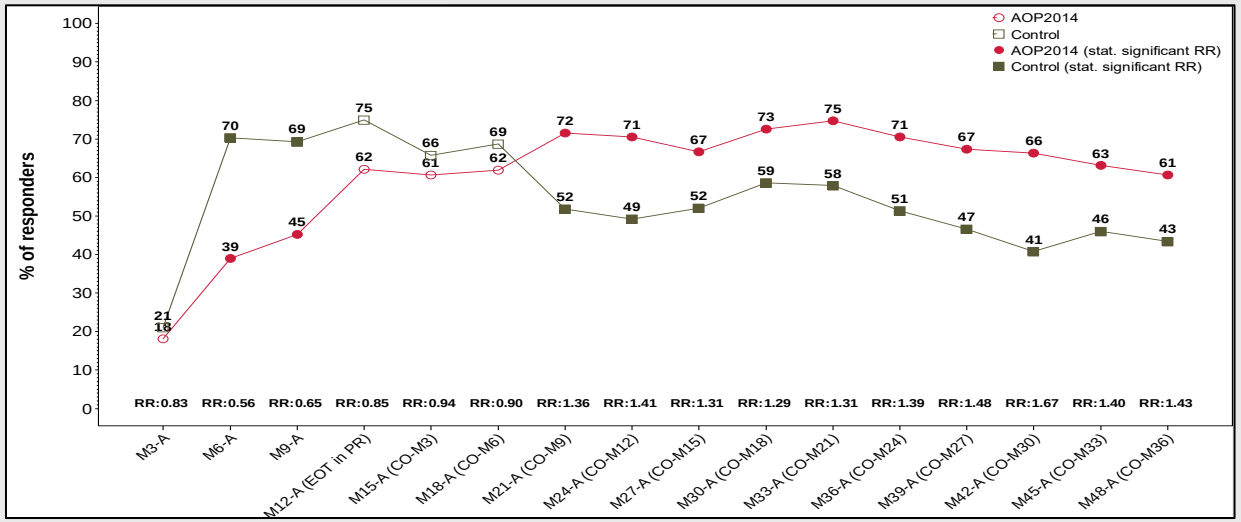
Abu-Zeinah et al, Leukemia 2021;35,2592–2601

Cumulative probability of transformation to MF/AML, phase 2 study with Peg-IFN vs historical control after 7 years median follow up

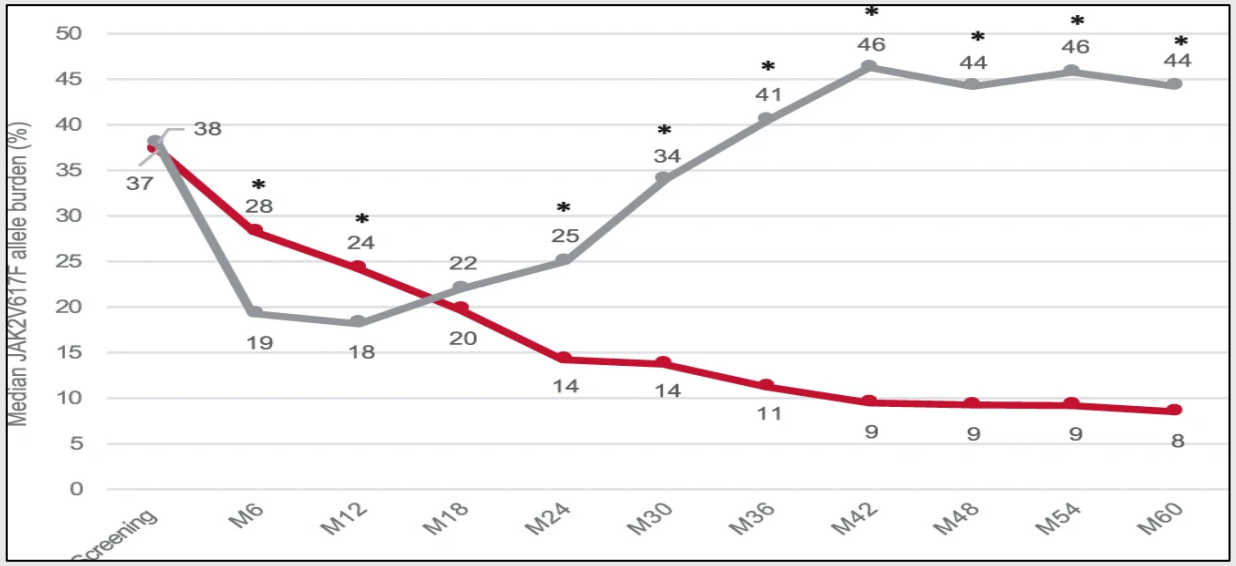


Masarova et al, Lancet Haematol 2017;4:e165-e175

Randomisierte IFN-Studie (n=254): (PROUD-PV und CONTINUATION-PV)
Ropeg-IFN (rot) vs. best verfügbare Therapie (BAT) (grau)



Komplettes hämatologisches Ansprechen nach 48 Monaten



Molekulares Ansprechen (*JAK2*) nach 5 Jahren IFN:
69,1% (vs. 21,6% BAT)

JAK2 <10%: 54,3%
JAK2 <1%: 19,6% (p=0.0002)

IFN-Abbrüche: 10,2%

Gisslinger et al, Lancet Haematol 2020;7:e196-e208; Kiladjian, Leukemia 2022;36:1408-1411

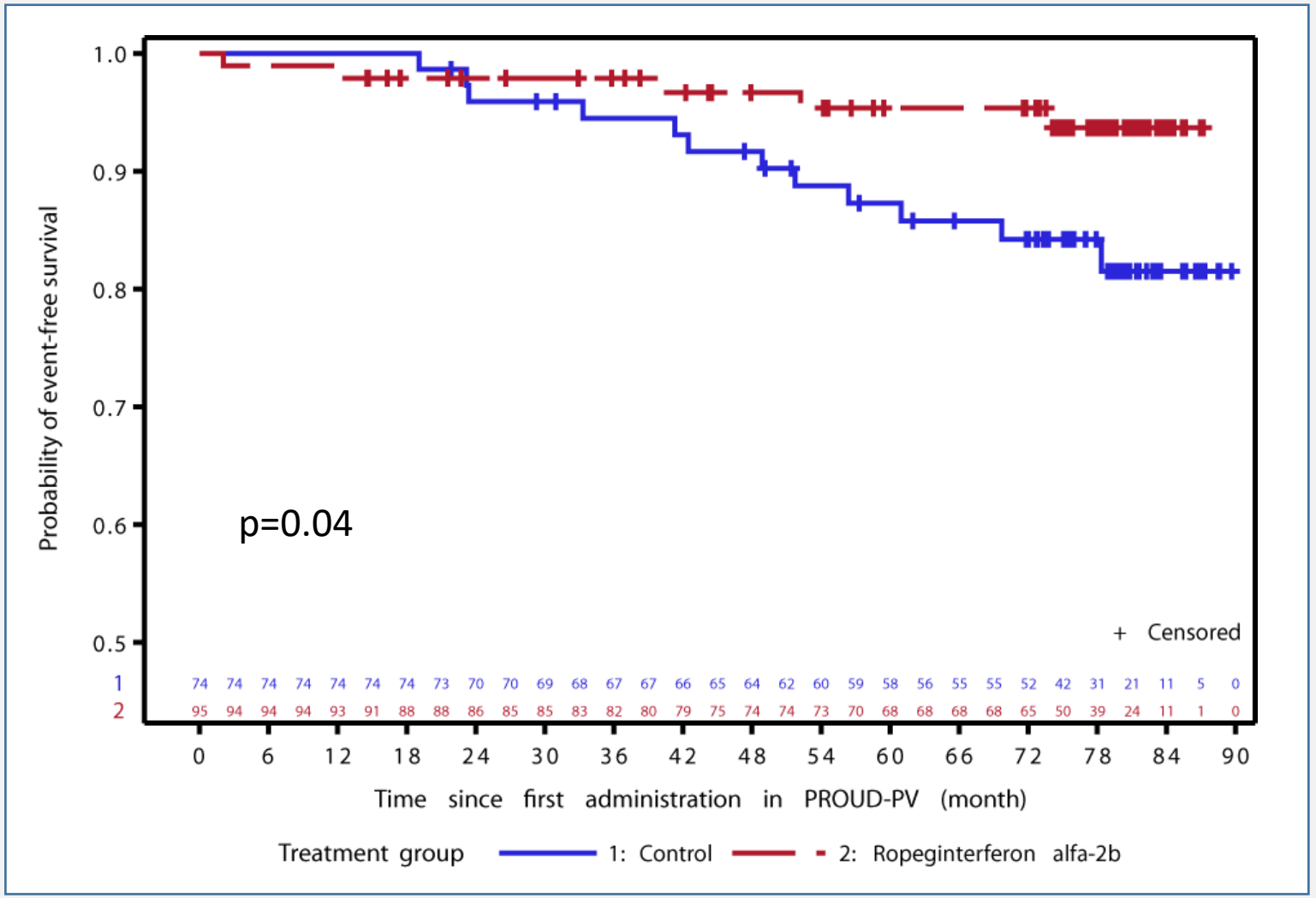
PROUD-PV and CONTINUATION-PV Studien: ≥ 6 Jahre unter IFN-Therapie

	Ropeg-IFN	BAT	p-Wert
Therapieergebnisse (CONTI)			
Kompl. hämatol. Remission (LOCF)	72,6%	47,3	0,001
Molekulares Ansprechen	66%	19,4%	<0,0001
Mediane *JAK2* V617F-Allellast	8,5%	50,4%	<0,0001
JAK2 V617F-Allellast >50%	11,6%	50,0%	<0,0001
Toxizität (PROUD und CONTI)			
Therapieabbrüche (wegen Med.-Tox.)	11,0%	2,4%	
AEs ≥ Grad 3	15,7%	16,6%	
PV-assoz. AEs im 6. Therapiejahr	7,1%	12,1%	

Gisslinger et al, Leukemia 2023;37:2129–2132

PROUD-PV and CONTINUATION-PV Studies: over ≥6 years of treatment

Event-free survival (risk events: disease progression, death and thromboembolic events)

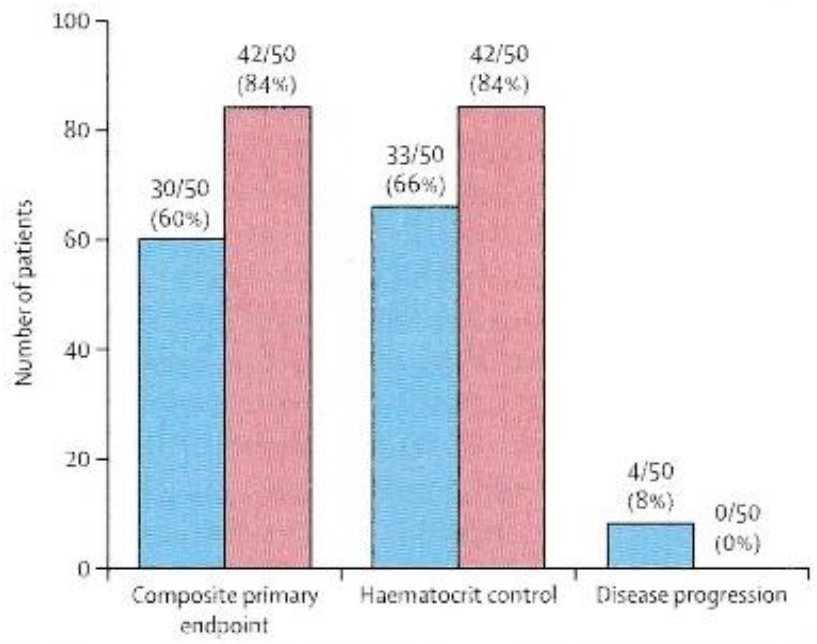


Gisslinger et al, Leukemia 2023;37:2129–2132

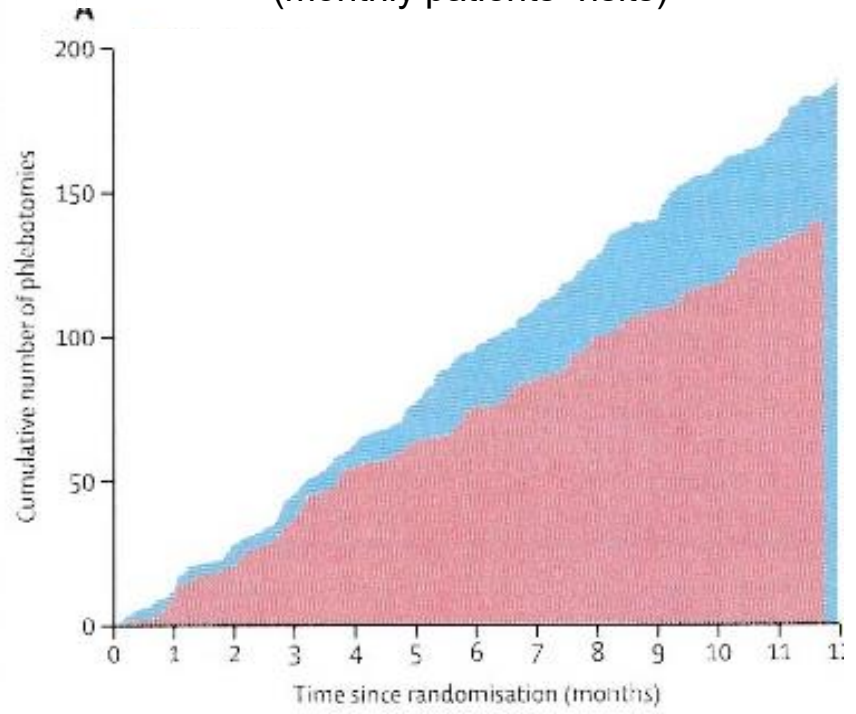
Low-PV study: Ropeg-IFN (100 µg every two weeks) vs. phlebotomy in low-risk patients with PV

Primary composite endpoint: response to treatment
(maintenance of Hkt <45% over 12 months without disease progression)

Primary response



Cumulative number of phlebotomies in each group (monthly patients' visits)



Standard group

Experimental group (ropeginterferon alfa-2b)

Results after 24 months:

Ropeg more effective than standard treartment:
(Hkt consistently <45% (p=0.02), reduction of phlebotomy need without thrombotic complications)

Barbui et al, Lancet Haematol 2021;8:e1875-184
NEJM Evidence 2023;2(6)

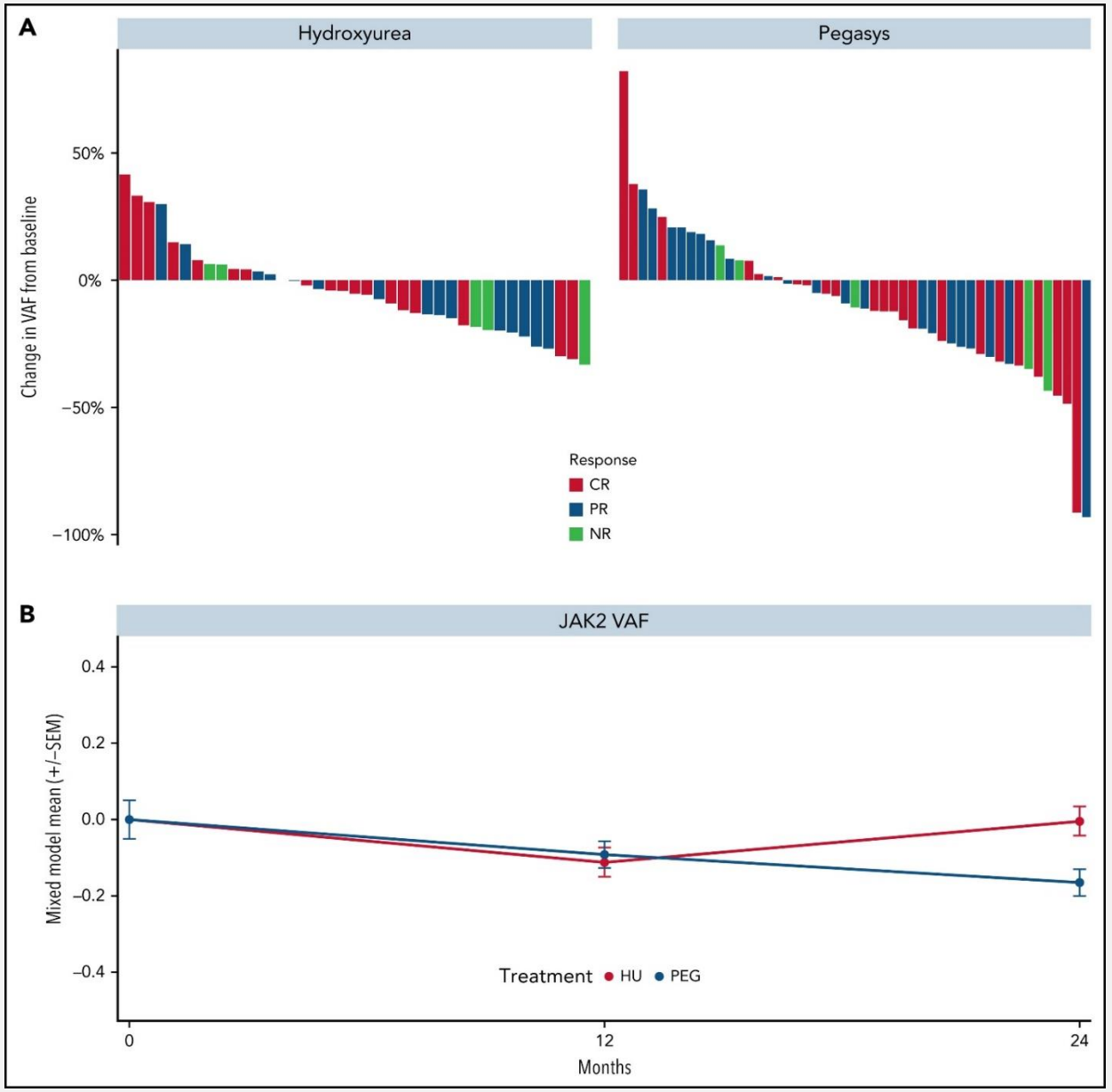
Low-PV study: finale Resultate nach 5 Jahren

Core Study, Jahr 1 und 2
Extensions-Studie, Jahr 3 bis 5

Ropeg-IFN Arm	n=64
Abbruchrate nach 2 Jahren	33%
Reponsekriterien nicht erfüllt	19% (nach 5 Jahren 22%)
IFN-Nebenwirkungen	10% (nach 5 Jahren 14%)
Fortsetzung Ropeg, Jahr 3 bis 5	n=36 (nur Therapieansprecher)
Erhalt des Ansprechens	nach 5 Jahren 94% (davon 60% Phlebotomie-frei)
Phlebotomie-Arm	n=63
Coss-over zu Ropeg bei Nichtansprechen	n=31
	Ropeg-IFN um 30% weniger effizient (deutlich mehr Aderlässe in den ersten 6 Monaten unter IFN im Vergleich zur primär mit Ropeg-IFN behandelten Gruppe)

Barbui et al, Ann Hematol 2023
Published online: 07 December

Randomized phase III trial of PegIFN-alpha vs Hydroxyurea in PV and ET



Patients n=168,
median treatment duration 81 weeks.

A
Maximum change in JAK2V617F allele burden by response status.

B
JAK2V617F allele burden over time ($p<0.05$);

(ASXL1 mutation associated with decreased probability of hematological CR).

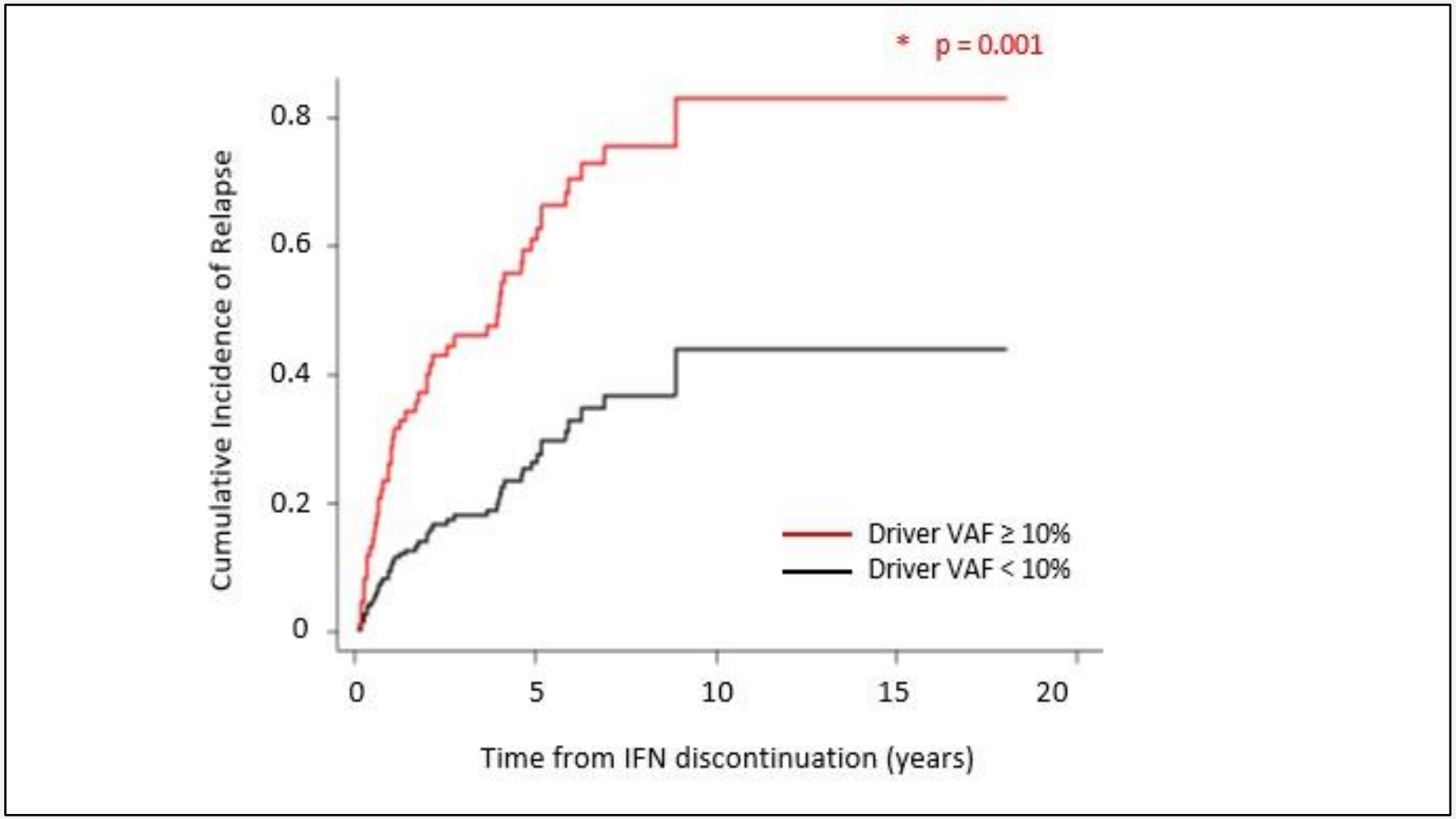
Mascarenhas et al, Blood 2022;139:2931-2941

Interferon-alpha therapy in essential thrombocythemia and polycythemia vera: a systematic review and meta-analysis

Metaanalysis of 44 studies Period of more than three decades	PV n=629	ET n=730
Overall response rate	80.1%	76.7%
Complete hematologic response	59.0%	48.5%
Annual rate of thrombotic complications	1,2%	0.5%
Annual rate of treatment discontinuation	8.8%	6.5%
Freedom from phlebotomy	58.1%	

Bewersdorf et al, 2021;35:1643-1660

Rezidivwahrscheinlichkeit in Abhängigkeit von der Allel-Last bei Absetzen der Interferontherapie (<10% vs ≥10%)



De Oliveira et al, ASH 2020, #483

Weitere mögliche Vorteile von IFN-alpha bei MPN

Splanchnic vein thrombosis:

N=20: ORR of 70% (15% CR, 55% PR at 12 months of therapy)
No recurrence during a median follow up of 2.2 years
Mascarenhas et al, Leukemia 2019;33:2974-2978

HU no preventive effect (pooled analysis: 258 of 1500 MPN cases in atypical locations)
De Stefano, Blood Cancer J. 2018;8,112.

PV and ET in 278 adolescents and young adults:

Ten and 20 year myelofibrosis free survival with IFN was 100%.
Beauverd et al, ASH 2023, Abstr. 748

Interferon-alpha in der Schwangerschaft bei PV und ET

- PV: bei 129 Schwangerschaften von 69 Patientinnen Gesamt-Lebendgeburtenrate von 68,2%.

  Bei PV-spezifischer Therapie Lebendgeburtenrate 78,2%, gegenüber nur 47,8% bei Fällen ohne PV-spezifische Therapie (ASS, niedermolekulares Heparin, IFN-alpha jeweils als Monotherapie oder in verschiedenen Kombinationen).

- Hochrisiko ET (n=34): 74% erfolreiche Schwangerschaften ohne signifikante Nebenwirkungen.

Wille et al, HemaSphere 2023;7:5(e882)
Schrickel et al, J Cancer Res Clin Oncol 2021;147:1481-1491

Zusammenfassung

- Klinische Wirksamkeit von Interferon-alpha (IFN) bereits seit über drei Dekaden bekannt.
- Genauer Wirkmechanismus nicht im Detail aufgeklärt.
- Quantifizierung der Allellast von *JAK2* V617F als möglicher Parameter des molekularen Ansprechens.
- Komplette molekulare Remissionen möglich:
  den Krankheitsverlauf modifizierendes Potenzial von IFN?
- Bisher noch keine Korrelation von molekularer Remissionsqualität und Gesamtüberleben.
- Abbruchrate durch Medikamententoxizität zwischen 10% und 14% bei IFN der neuen Generation.
- Noch viele offene Fragen hinsichtlich Einfussfaktoren auf die allgemeine und individuelle Wirksamkeit.