



Medical University of Vienna

Long-term Treatment of PVs and IFNs

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Disclosure Information

Advisory honoraria: Novartis, AOP Orphan, Celgene, CTI

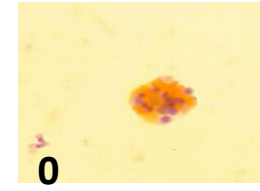
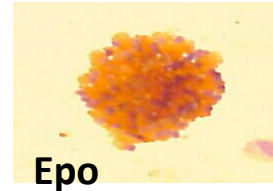
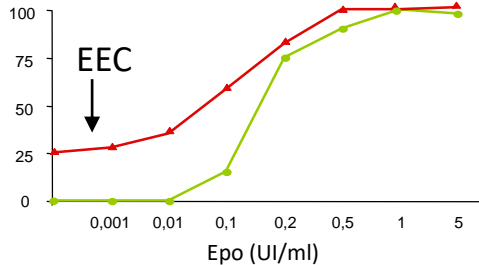
Research grants: Novartis, AOP Orphan

- **Pathogenesis of PV**
- **Effect of IFN on hematopoietic cells**
 - Essers et al, Nature 2013
 - Mullaly et al, Blood 2013
- **Clinical development program of RopegIFN**
- **Very long-term treatment of PV with IFN alpha**

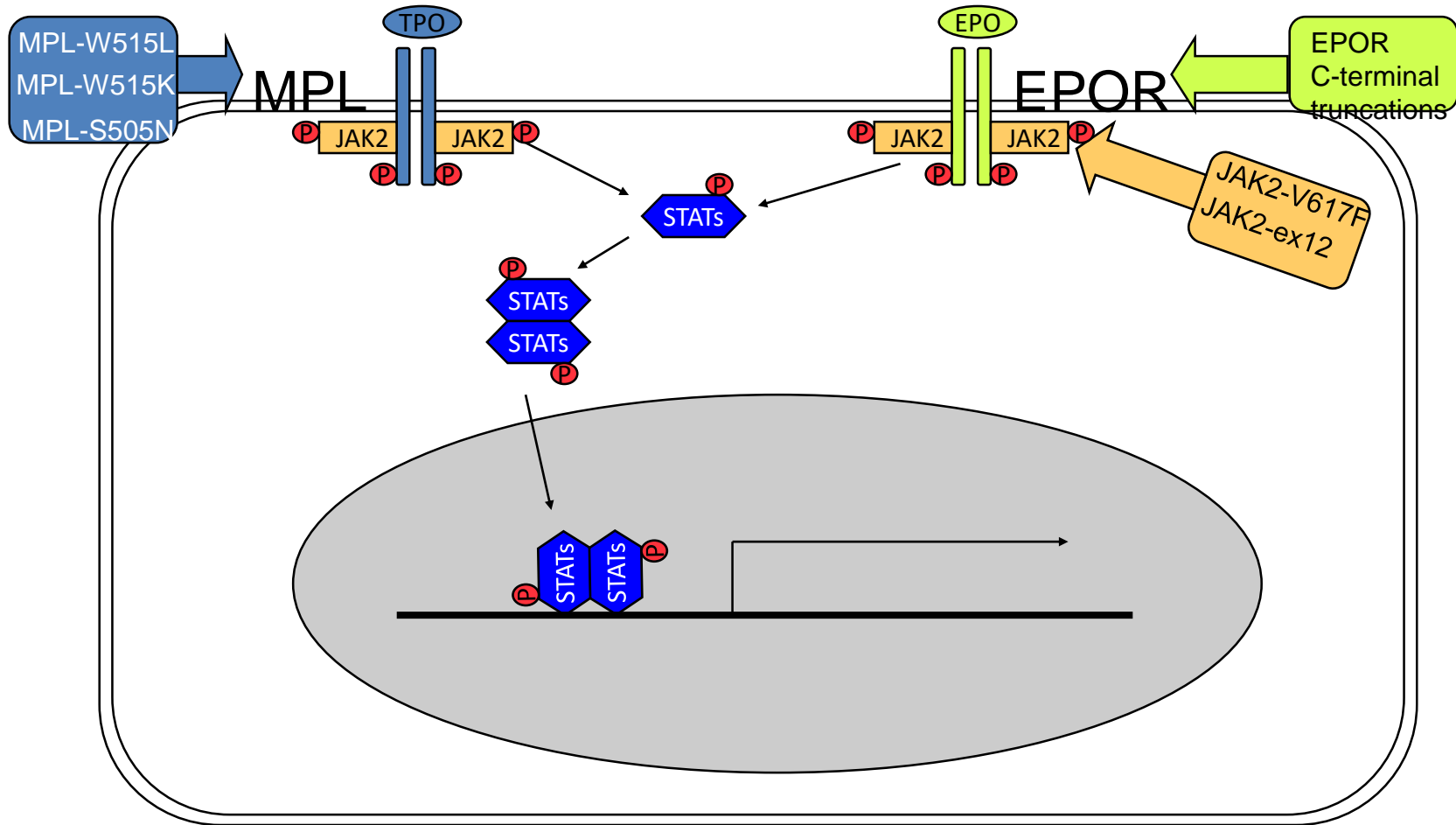
Hypersensitivity of PV hematopoietic progenitors to cytokines

PV erythroid progenitors are Epo hypersensitive

- Presence of endogenous erythroid colonies called EEC
- They are also found in some ET and some IMF

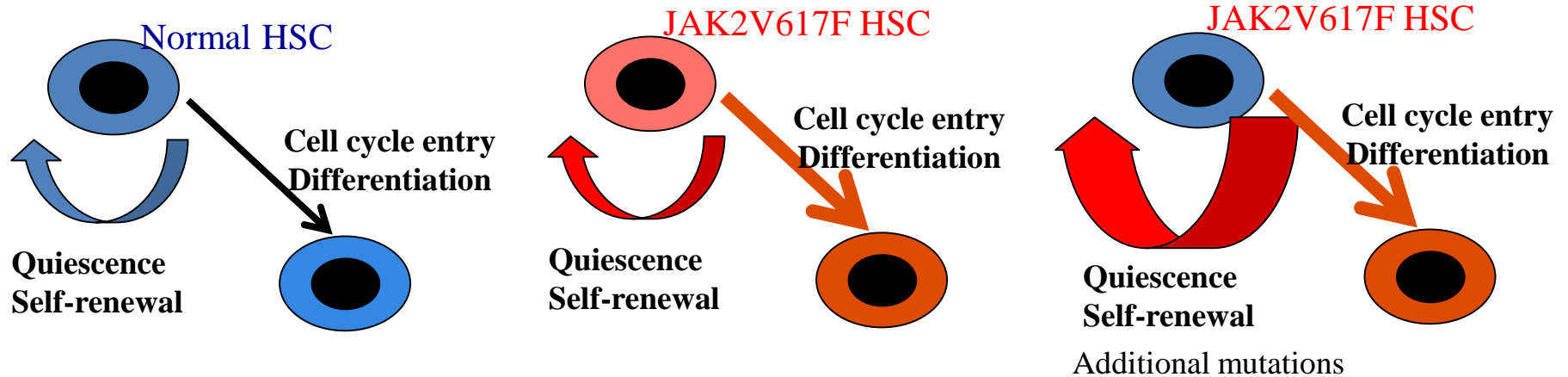


- **This abnormal response involves other cytokines**
 - Abnormal response to SCF, GM-CSF, IL3, IGF-1, and TPO (ET, IMF)
 - Hypersensitivity > true independence



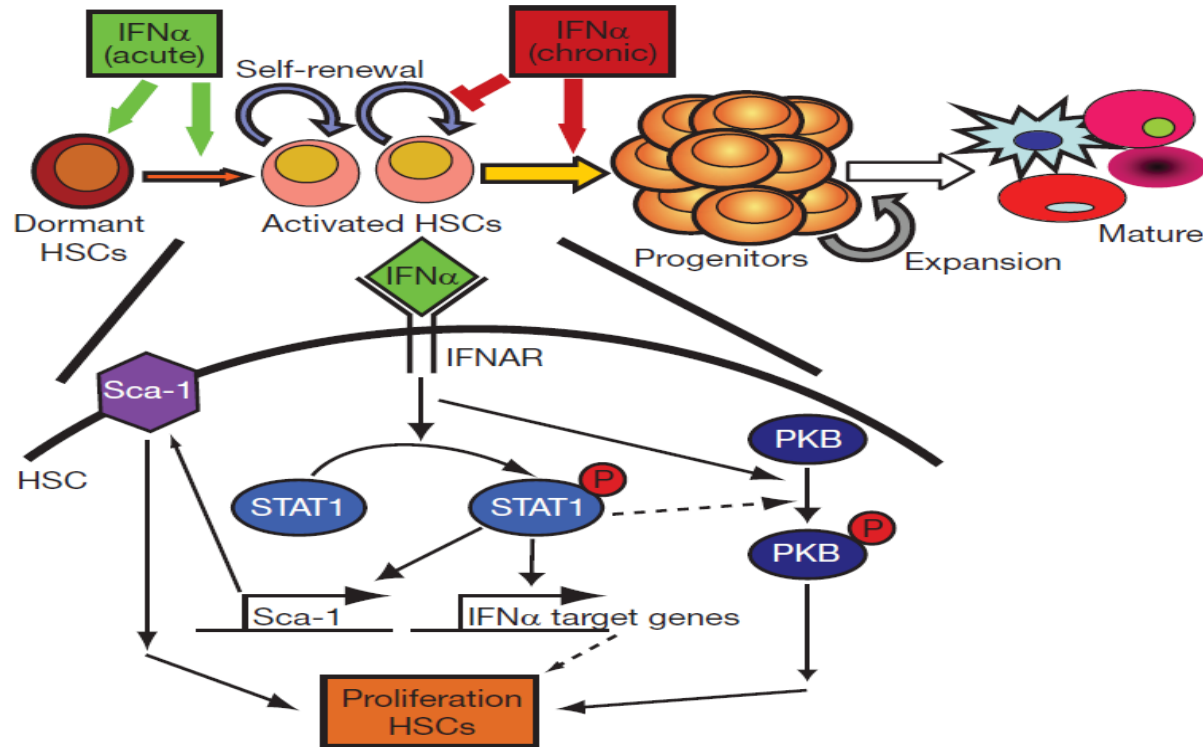
Why the need for several mutations

Working hypothesis

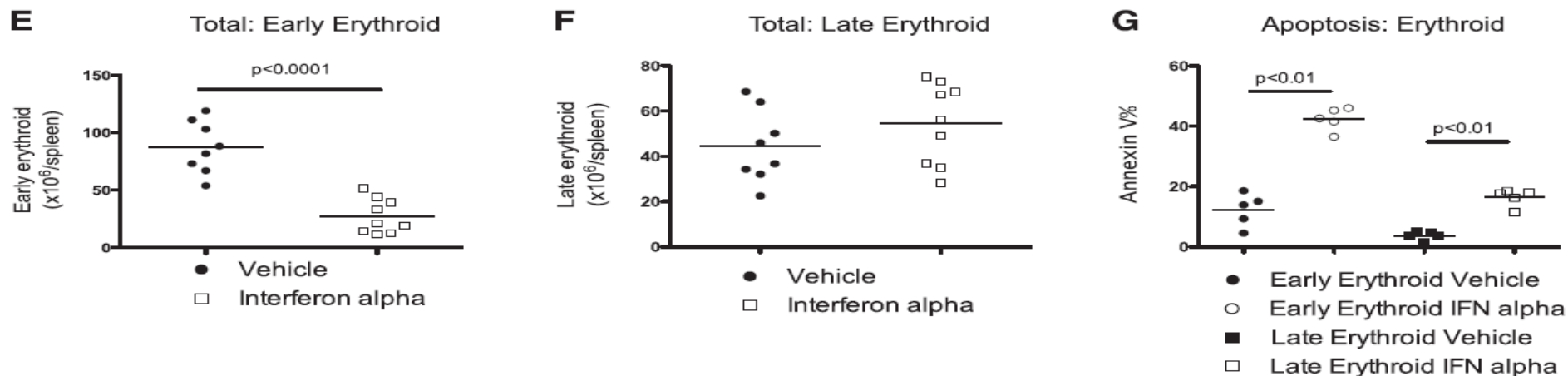


- Pathogenesis of PV
- **Effect of IFN on hematopoietic cells**
 - Essers et al, Nature 2013
 - Mullaly et al, Blood 2013
- Effect of IFN treatment vs BAT/HU
- Long-term treatment with IFN in PV

Model showing the activating effects of short-term (acute) IFN α stimulation on dormant/quiescent HSCs, and the inhibitory effects of chronic IFN α treatment on HSC self-renewal



Effects on extramedullary hematopoiesis of 4 weeks of daily IFNa on Jak2^{VF} chimeric mice



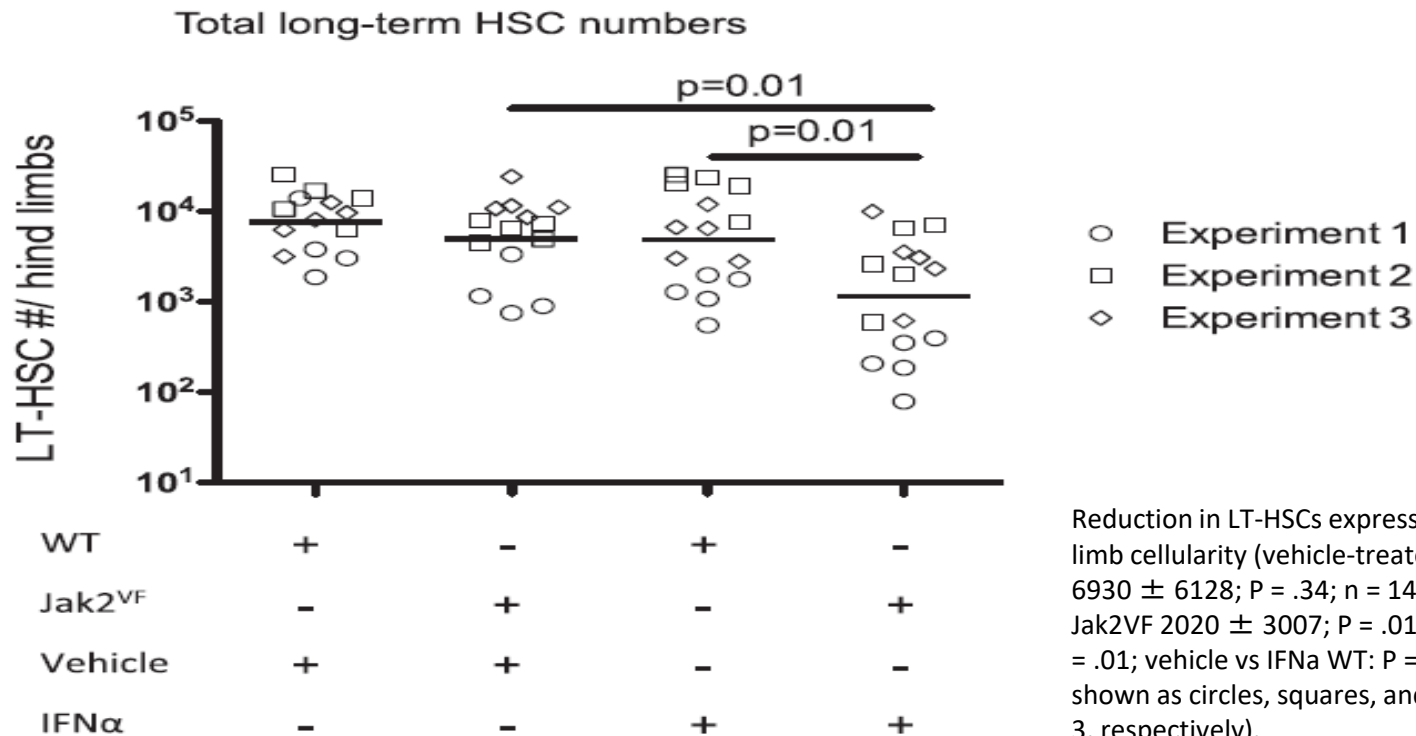
(E) Total early erythropoiesis reduced in IFNa-treated mice (vehicle $87.2 \pm 8.0 \times 10^6/\text{spleen}$ vs IFNa $27.6 \pm 5.0 \times 10^6/\text{spleen}$; $P, .01$; n 5 9-10)

(F) No change in total late erythropoiesis (vehicle $44.3 \pm 5.7 \times 10^6/\text{spleen}$ vs IFNa $54.4 \pm 6.0 \times 10^6/\text{spleen}$; P 5 .24; n 5 9-10). Each data point represents an individual mouse. Data shown are pooled results from 2 independent experiments.

(G) Apoptosis in early erythroid precursors increased after IFNa treatment (vehicle $12.3 \pm 2.4\%$ vs IFNa 42.4 ± 1.7 ; $P, .01$; n 5 5). Apoptosis in late erythroid precursors increased after IFNa treatment (vehicle $3.7 \pm 0.6\%$ vs IFNa 16.4 ± 1.3 ; $P, .01$; n 5 5).

Results given are mean \pm standard deviation.

Effect on HSPC populations of 4 weeks of daily IFNa on Jak2^{VF} chimeric mice



Reduction in LT-HSCs expressed as absolute number per lower limb cellularity (vehicle-treated WT: 8896 ± 6612 vs Jak2VF 6930 ± 6128 ; $P = .34$; $n = 14$; IFN α -treated WT: 6503 ± 8885 vs Jak2VF 2020 ± 3007 ; $P = .01$; $n = 15$; vehicle vs IFN α WT: $P = .78$). Experimental replicates are shown as circles, squares, and diamonds (experiments 1, 2, and 3, respectively).

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- Effect of IFN on hematopoietic cells
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- **Clinical development program of RopegIFN**
- Very long-term treatment of PV with IFN alpha

Ropeginterferon alfa-2b (AOP2014/P1101)

- A novel monopegylated interferon alfa-2b, composed of only one single isoform due to an innovative pegylation technology
- Administration frequency once every 14 days (once monthly in long-term maintenance) with a pre-filled, dose-adjustable pen suitable for self-administration

AOPs clinical development program ongoing since 2010

- **PROUD-PV Study (Phase III)**: demonstrated non-inferiority of complete hematological response of Ropeginterferon alfa-2b to HU after 12 months of treatment ²⁾
- **CONTINUATION-PV Study (Phase III, extension study)**: Ropeginterferon alfa-2b appears more efficacious than HU in the long run, showing high and durable hematological response and symptom improvement (i.e. after 18 months). The Safety/Tolerability profile of Ropeginterferon alfa-2b remains excellent beyond the second year of treatment. ³⁾
- **Ropeginterferon alfa-2b is equal effective** in patients <60 years and > 60 years of age
- **PEGINVERA Study (Phase II)**: showed that long-term maintenance treatment of PV patients is feasible, efficacious and well tolerated ¹⁾

COMPARISON OF LONG-TERM EFFICACY AND SAFETY OF ROPEGINTERFERON ALFA-2B VS. HU IN POLYCYTHEMIA VERA PATIENTS AGED BELOW OR ABOVE 60 YEARS: TWO-YEAR ANALYSIS FROM THE PROUD/CONTINUATION PHASE III TRIALS

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Rossiev, Petr Dulicek, Arpad Illes, Halyna Pylypenko, Lylia Sivcheva, Jiri Mayer,
Vera Yablokova, Barbara Grohmann-Izay, Gabriele Maurer, Hans Hasselbalch,
Robert Kralovics and Jean-Jacques Kiladjian

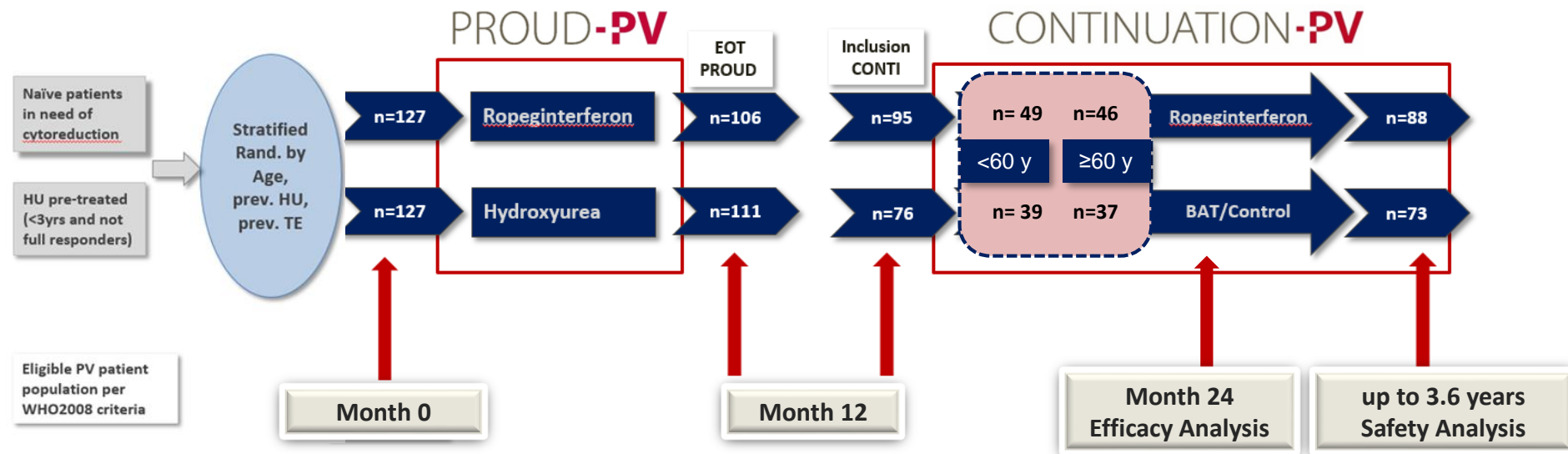
Background

- Hydroxyurea (HU) is the only licensed first-line therapy in high-risk patients with PV of all ages.
- Off-label IFN α as first-line therapy is primarily used in patients of younger age, partly because of the misconception that the risk-benefit ratio is not so favorable in elderly patients.

Aim:

To analyze the efficacy and safety of Ropeginterferon alfa-2b and HU in two age cohorts (<60 years and ≥ 60 years).

Patient Disposition



Patient Characteristics at Treatment Start

	Ropeg		Control	
	< 60 years N = 49	≥ 60 years N = 46	< 60 years N = 39	≥ 60 years N = 37
Age [year] <i>Mean</i> <i>Median (range)</i>	49.3 (±7.04) 51.0 (30.0 -59.0)	66.0 (±6.00) 64.0 (60.0- 85.0)	48.4 (±7.45) 50.0 (32.0- 59.0)	67.2 (±5.25) 66.0 (61.0 - 79.0)
Duration of PV [month] <i>Mean (±SD)</i> <i>Median (range)</i>	11.3 (±25.27) 1.9 (0.0 - 145.5)	12.9 (±26.64) 1.7 (0.1 / 102.4)	10.9 (±19.86) 1.6 (0.0 / 91.6)	9.4 (±14.38) 1.7 (0.0 / 65.6)
Female	26 (53.1%)	22 (47.8%)	22 (56.4%)	18 (48.6%)
Previous TE event	8 (16.3%)	13 (28.3%)	5 (12.8%)	9 (24.3%)
HU pretreated <i>Duration of prev. HU treatment [month]*</i>	17 (34.7%) 11.3 (±10.76)	14 (30.4%) 14.8 (±11.46)	12 (30.8%) 16.0 (±11.59)	13 (35.1%) 11.2 (±12.02)
JAK2V617F allele burden [%]*	38.4 (±21.15)	47.4 (±24.96)	38.1 (±21.98)	48.1 (±23.27)
Hematocrit [%]*	48.5 (±5.38)	48.1 (±5.26)	49.6 (±6.17)	50.3 (±4.80)
Normal spleen size*	18 (36.7%)	21 (45.7%)	17 (43.6%)	19 (51.4%)
Splenomegaly present**	2 (4.1%)	5 (10.9%)	4 (10.3%)	4 (10.8%)
Disease-related symptoms present	5 (10.2%)	10 (21.7%)	4 (10.3%)	13 (35.1%)

*Displayed as mean +/- SD; **per Investigator assessment

Efficacy Assessment

Hematologic assessment

- Complete Hematologic Response (CHR) - ELN
 - Hematocrit <45% without phlebotomy (at least 3 months since the last phlebotomy),
 - Platelets <400 x 10⁹/L,
 - WBCs <10 x 10⁹/L
- CHR & Improvement in Disease Burden
 - Disease-related signs (clinically significant splenomegaly reported as AE by the Investigator) and
 - Disease-related symptoms
- CHR Response Maintenance (from first occurrence to 24 months assessment)

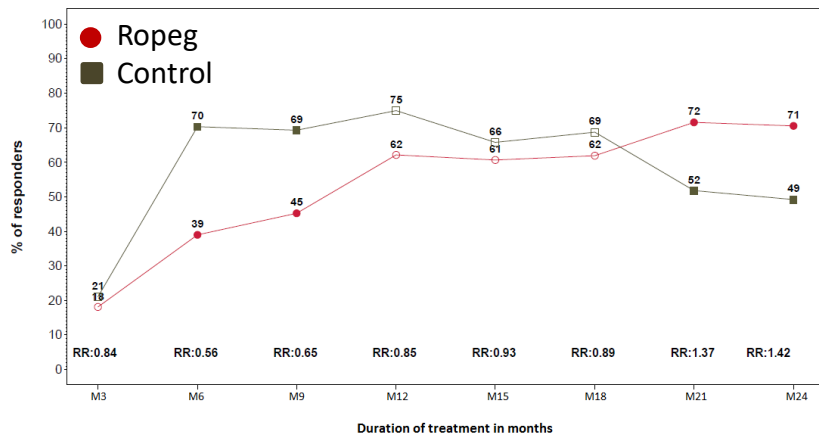
Molecular assessment

- Molecular Response – ELN
- JAK2V617F Allele Burden

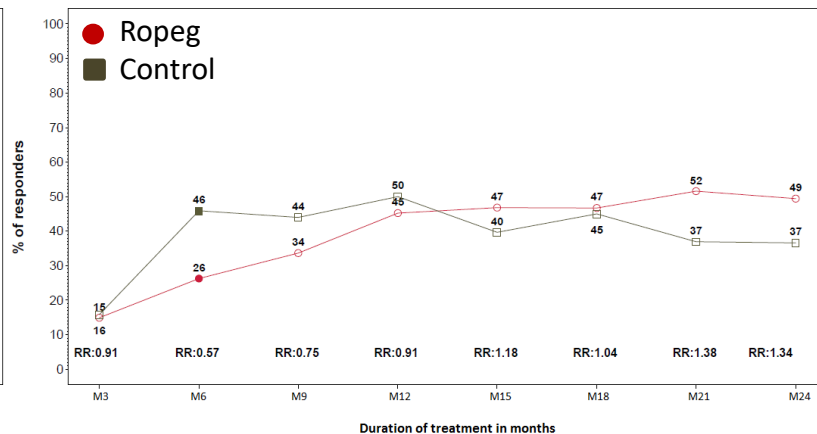
Efficacy Results 24 Months

	Ropeg	Control	RR [95% CI] (Ropeg/Control)	P-value
Complete Hematologic Response (CHR)	70.5% (67/95)	49.3% (33/67)	1.42 [1.09-1.87]	<0.05
CHR & Improvement in Disease Burden	49.5% (47/95)	36.6% (26/71)	1.34 [0.93-1.92]	0.118

CHR

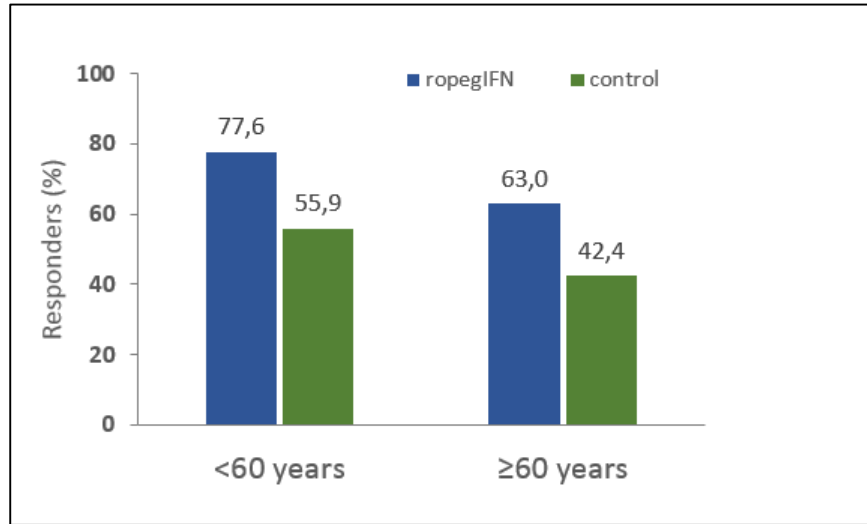


CHR & Improvement in Disease Burden

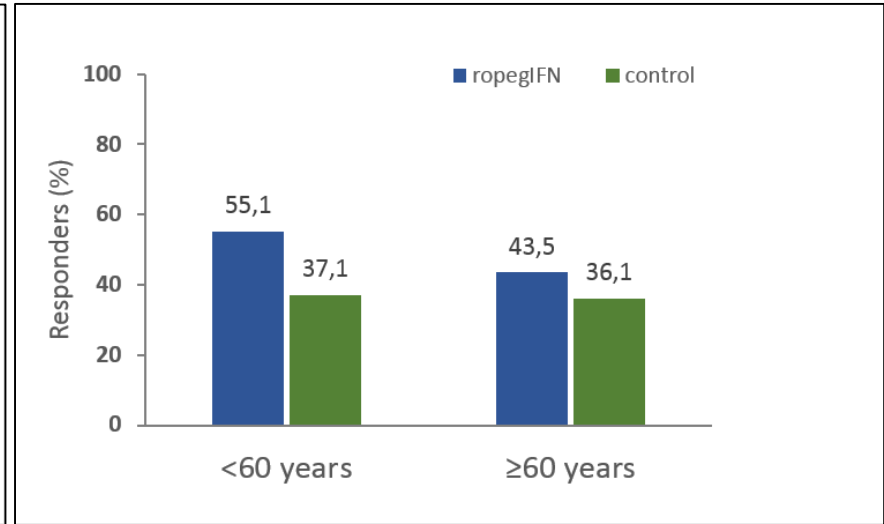


Efficacy Results 24 Months – by age group

CHR



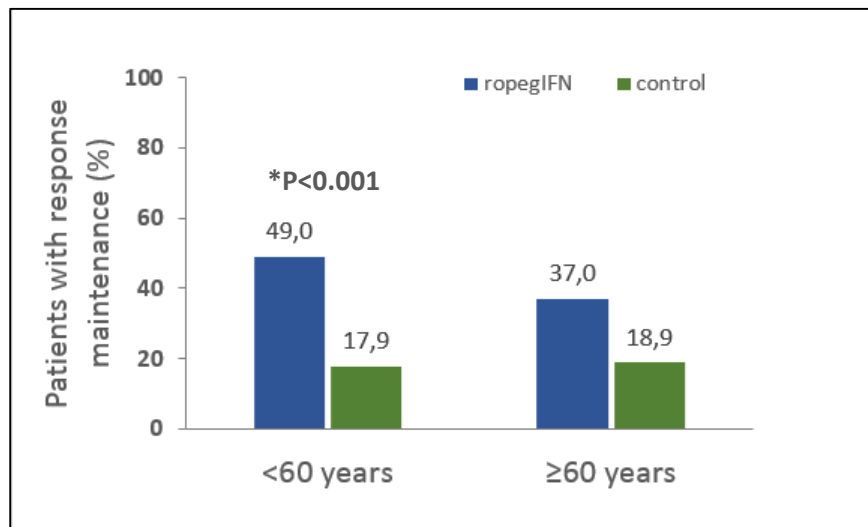
CHR & improvement in disease burden



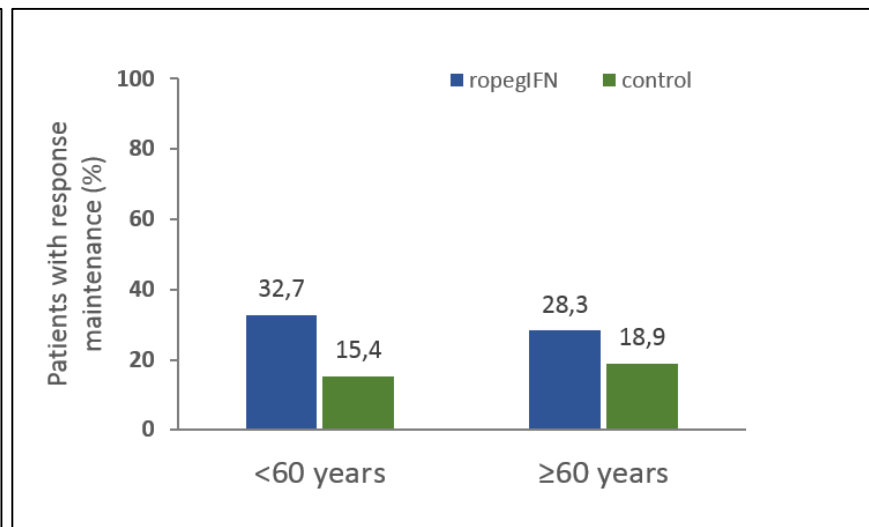
Ropeginterferon alfa-2b induced higher CHR rates compared to control, irrespective of age.

Efficacy Results 24 Months – by age group

Maintenance of CHR



Maintenance of CHR & improvement in disease burden



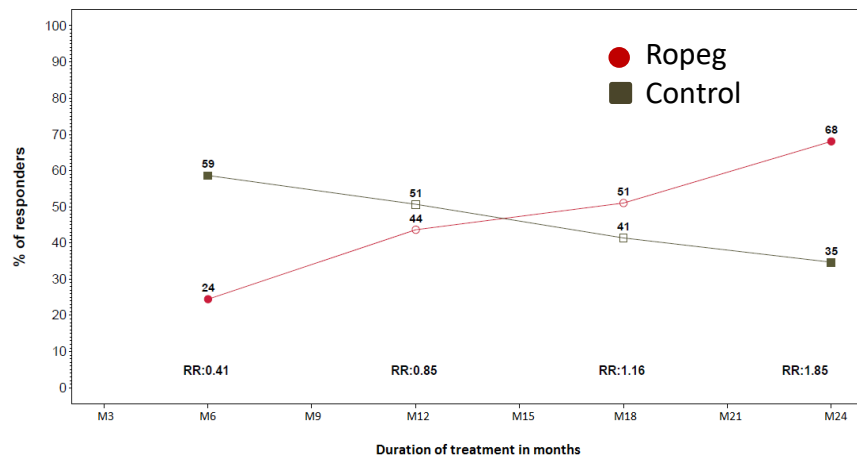
*RR Ropeg/control [95% CI]: 2.82 [1.37-5.79]

Ropeginterferon alfa-2b induced higher maintenance rates of CHR compared to control, irrespective of age.

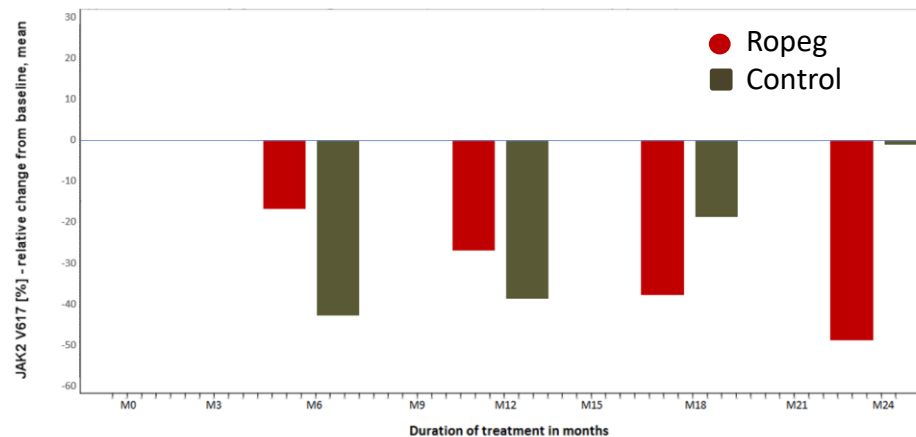
Efficacy Results 24 Months

	Ropeg	Control	Ropeg/Control	P-value
Molecular Response (LOCF)	68.1% (64/94)	34.7% (26/75)	RR [95% CI] 1.85 [1.33-2.56]	<0.01

Molecular Response

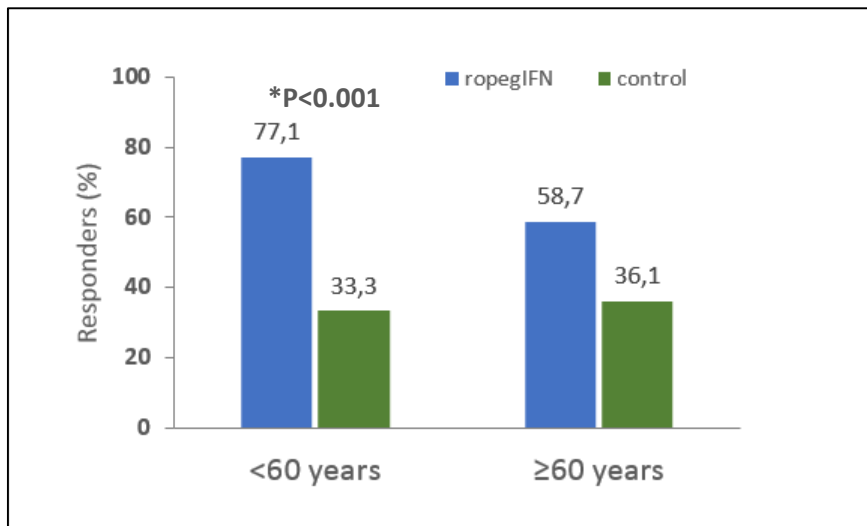


JAK-2 allele burden relative change from baseline over time



Efficacy Results 24 Months – by age group

Molecular response (LOCF)



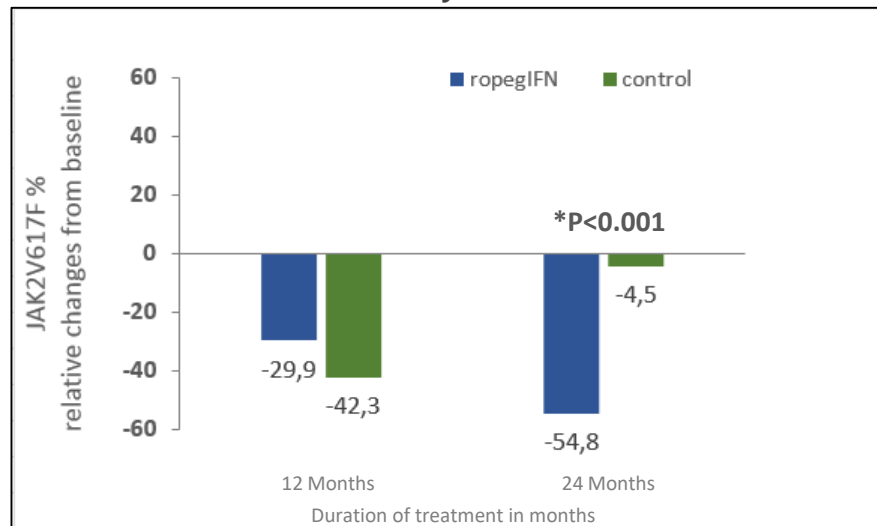
*RR Ropeg/control [95% CI]: 2.17 [1.38 to 3.42]

Ropeginterferon alfa-2b induced a higher molecular response compared to control, irrespective of age

Efficacy Results 24 Months – by age group

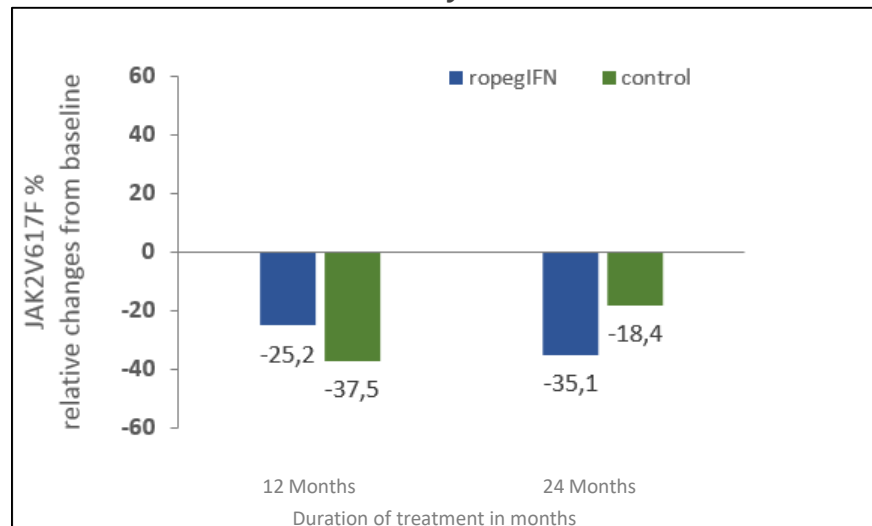
JAK2V617F (%) relative changes from baseline (LOCF)

<60 years



LS mean [95% CI] of difference Ropeg/control: *-15.49 [-22.07 to -8.90]

≥ 60 years



Ropeginterferon alfa-2b induced a higher reduction in *JAK2V617F* allele burden compared to control after 24 months of treatment

Long-term Safety: up to 3.6 years of treatment; mean 2.7 years

	Ropeg		Control	
	<60 years N=49	≥60 years N=46	<60 years N=39	≥60 years N=37
Patients with AE	44 (89.8%)	43 (93.5%)	36 (92.3%)	34 (91.9%)
Patients with serious AE	3 (6.1%)	10 (21.7%)	4 (10.3%)	9 (24.3%)
Patients with adverse drug reaction (ADR)	38 (77.6%)	29 (63.0%)	29 (74.4%)	33 (89.2%)
Patients with serious ADR	0 (0.0%)	0 (0.0%)	0 (0.0%)	4 (10.8%)*
Patients with ≥ Grade 3 AE	10 (20.4%)	16 (34.8%)	10 (25.6%)	14 (37.8%)

- Comparable numbers of AEs and serious AEs in the treatment arms, irrespective of age.
- Number of ADRs was comparable in the patients <60 years but a trend towards a lower number of ADRs (serious and non-serious) was evident for Ropeginterferon alfa-2b vs. control in patients ≥60 ys

*Acute Leukemia, Anemia, Leukopenia, Granulocytopenia

Long-term Safety: up to 3.6 years of treatment; mean 2.7 years

	Ropeg		Control	
	<60 years N=49	≥60 years N=46	<60 years N=39	≥60 years N=37
Patients with outcome death	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.7%)
Patients recovered from AE	43 (87.8%)	40 (87.0%)	35 (89.7%)	34 (91.9%)
Adverse event of special interest (PI definition)	3 (6.1%)	6 (13.0%)	1 (2.6%)	4 (10.8%)
Endocrine disorders	Hyper-, hypothyreosis	-	-	Autoimmune thyroiditis
Psychiatric disorders	-	Irritability, Anxiety/Depression	Depression	-
Ocular events	-	Retinal injury	-	-
Tissue disorders	Psoriasis	Dermatitis acneiform, Sjogren's S.	-	-
Cardiac/Vascular disorders	-	Thrombotic event, stroke	-	Thrombotic event, pericardial effusion, haematoma

- There was no difference between Ropeginterferon alfa-2b and control, regarding AEs of special interest including autoimmune, mood-disorder or thrombotic events.

* Adverse events of special interest (Irritability, retinal injury) occurred in the same patient.

Adverse Events of Special Interest (IFNs)

Long-term Safety (up to 3.6 years of treatment; mean 2.7 years)		
	AOP2014 (n=127)	Control (n=127)
Endocrine disorders*	5 (3.9%)	1 (0.8%)
Psychiatric disorders**	3 (2.4%)	1 (0.8%)
Cardiac/Vascular disorders	13 (10.2%)	7 (5.5%)
Stroke	2 (1.6%)	0 (0.0%)
Thrombotic event	2 (1.6%)	2 (1.6%)
Cardiac failure	0 (0.0%)	2 (1.6%)
Atrial fibrillation	5 (3.9%)	3 (2.4%)
Others [§]	4 (3.2%)	0 (0.0%)
Tissue disorders***	2 (1.6%)	0 (0.0%)

* Autoimmune thyroiditis, Hypo-/Hyperthyroidism

** Anxiety, Depression, Mood altered

*** Rheumatoid arthritis, Sjogren's Syndrom

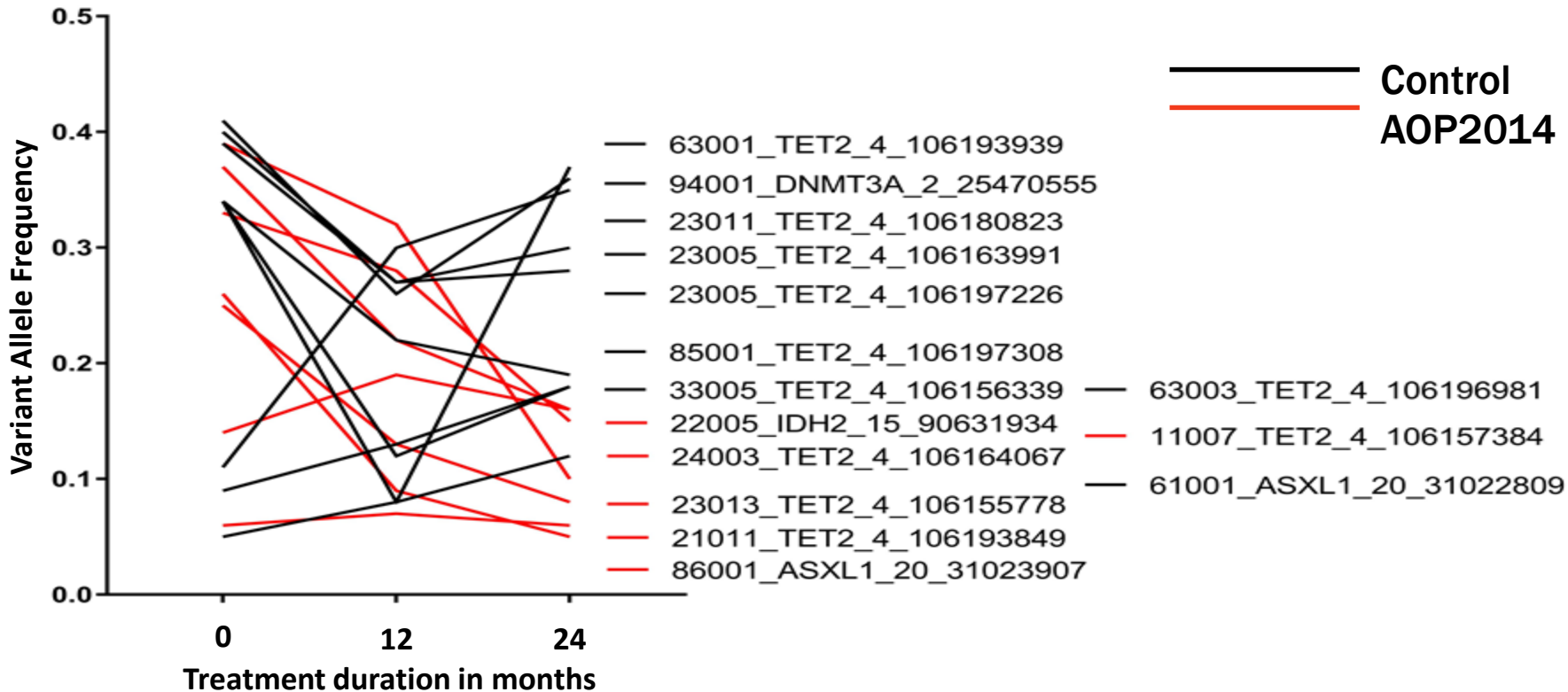
[§] additional events reported: peripheral arterial occlusive disease (presented already in medical history), hematemesis, phlebitis

Malignancies

Long-term Safety (up to 3.6 years of treatment; mean 2.7 years)		
	AOP 2014 (n=127)	Control (n=127)
Acute leukemia		2
Basal cell carcinoma		2
Malignant melanoma		1
Adrenal neoplasm*	1	
Glioblastoma	1	
Spermatocytic seminoma	1	

* No additional information on type of neoplasm available

Burden changes of non-JAK2 mutations



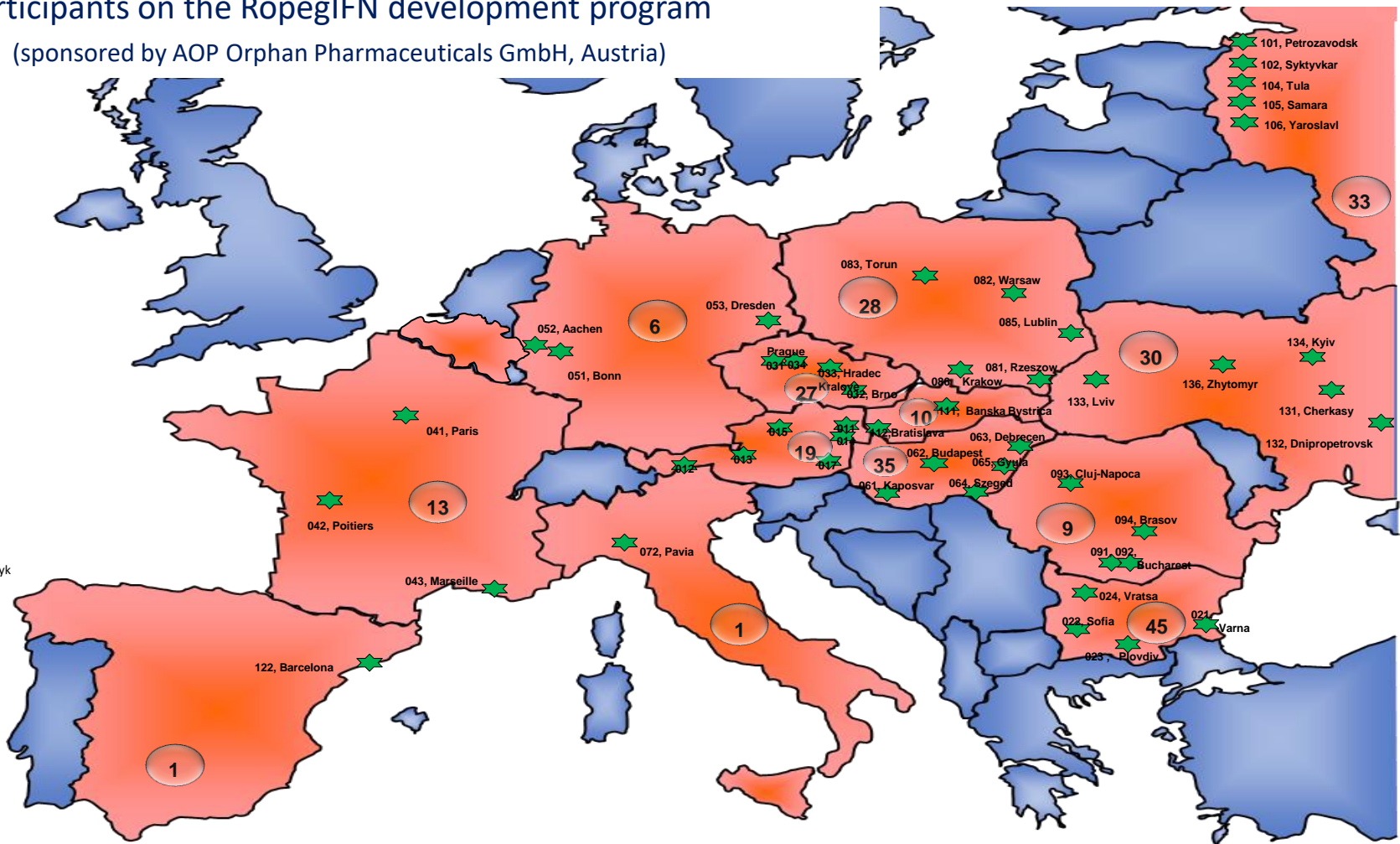
Summary - Conclusion

- A high CHR, symptom improvement and molecular response (*JAK2V617F*) as well as maintenance of response achieved by long-term treatment with Ropeginterferon alfa-2b was shown, with an advantage over HU independent of age.
 - Ropeginterferon alfa-2b was well tolerated in all age groups. The safety analysis in patients ≥ 60 years also showed a positive trend regarding less ADRs and less serious ADRs for Ropeginterferon alfa-2b vs. HU.
 - **These data confirms that Ropeginterferon alfa-2b provides a valuable, efficacious and safe new treatment option for PV patients of all ages including elderly.**
-

Participants on the RopegIFN development program

(sponsored by AOP Orphan Pharmaceuticals GmbH, Austria)

011 Wien, Gisslinger
 012 Innsbruck, Willenbacher
 013 Salzburg, Greil
 014 Wien, Schloegl
 015 Linz, Buxhofer-Ausch
 017 Graz, Bauer
 021 Varna, Gercheva
 022 Sofia, Mihaylov
 023 Plovdiv, Georgiev
 024 Vratsa, Sivcheva
 031 Prague, Schwarz
 032 Brno, Mayer
 033 Hradec Kralove, Dulicek
 034 Prague, Cerna
 041 Paris, Kiladjian
 042 Poitiers, Roy
 043 Marseille, Rey
 051 Bonn, Wolf
 052 Aachen, Koschmieder
 053 Dresden, Platzbecker
 061 Kaposvar, Egyed
 062 Budapest, Masszi
 063 Debrecen, Illes
 064 Szeged, Borbenyi
 065 Gyula, Jakucs
 072 Pavia, Cazzola
 081 Rzeszow, Starzak-Gwozdz
 082 Warsaw, Warzocha
 083 Torun, Calbecka
 085 Lublin, Soroka-Wojtaszko
 086 Krakow, Skotnicki/Krochmalcyk
 091 Bucharest, Berbec
 092 Bucharest, Bumba
 093 Cluj-Napoca, Cucuianu
 094 Brasov, Gheorghita
 101 Petrozavodsk, Myasnikov
 102 Syktyvkar, Sokolova
 104 Tula, Volodicheva
 105 Samara, Rossiev
 106 Yaroslavl, Yablokova
 111 Banska Bystrica, Vallova
 112 Bratislava, Hrubisko
 122 Barcelona, Besses
 131 Cherkasy, Pylypenko
 132 Dnipropetrovsk, Kaplan
 133 Lviv, Masliak
 134 Kyiv, Klymenko
 136 Zhytomyr, Lysa



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- Administration frequency once every 14 days (once monthly in long-term maintenance) with a pre-filled, dose-adjustable pen suitable for self-administration

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- **PEGIVERA Study (Phase II)**: showed that long-term maintenance treatment of PV patients is feasible, efficacious and well tolerated ¹⁾

1) Gisslinger et al. Blood 2015, Gisslinger et al. EHA 2017 2) Gisslinger et al. ASH 2016 3) Gisslinger et al. ASH 2017

Long-term RopegIFN alfa 2b

PEGINVERA-study (phase I/II) (MUW-cohort only)

Patient characteristics (n=19)	
Age* [years]	62 (41-80)
No. of pts. started [m/f]	19 (11/8)
Ongoing treatment [m/f]	10 (8/2)
Time on study drug* [months]	68
Withdrawals [m/f]	9 (3/6)
Median time until withdrawal [months]	9 (4-12)

*Numbers describe median values

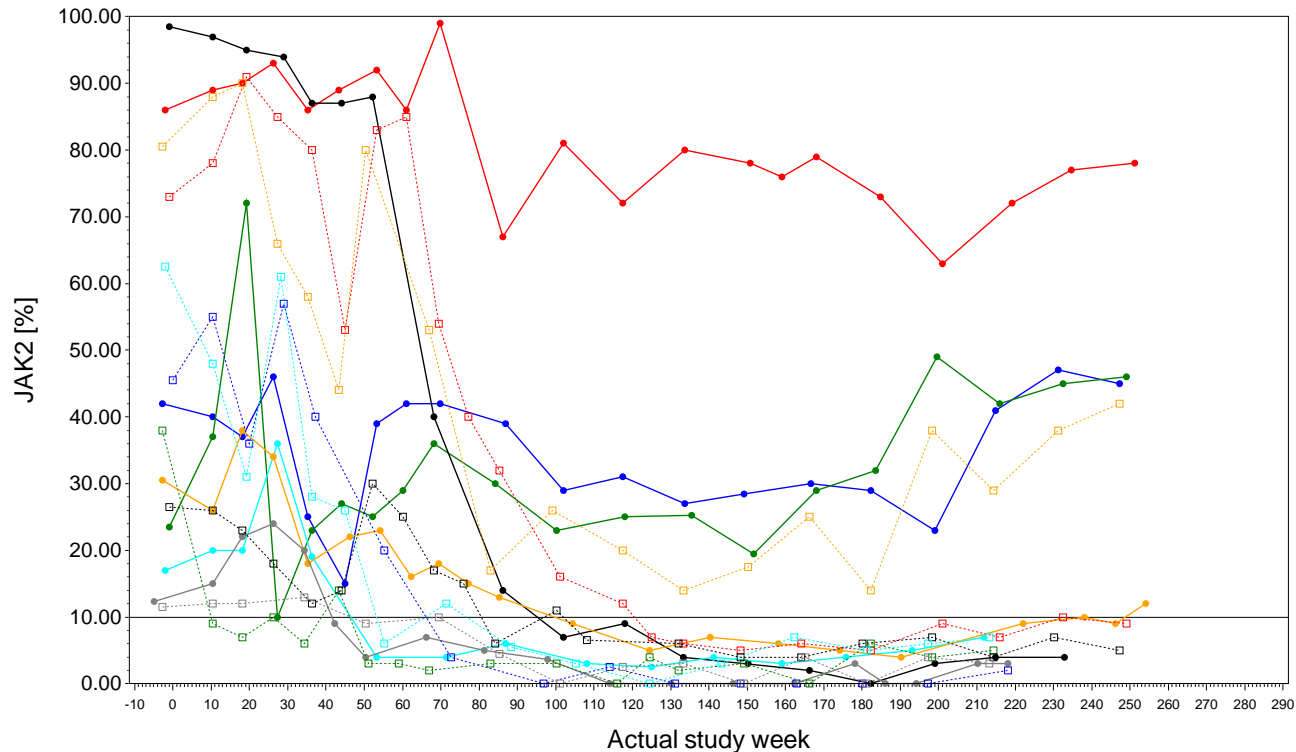
Reasons for withdrawal from IFN treatment

(by the example of the MUW PegInvera cohort, n=19)

Median observation time of the total cohort was 61 months

Symptom	N
Worsening of general constitution	3
Arthritis	2
Diagnosis of (pre-existing) N.coli	1
Interferon antibodies	1
Neuropathy	1
Frontal fibrosing alopecia	1

Pattern of molecular genetic response during ropeginterferon alfa-2b therapy in PV

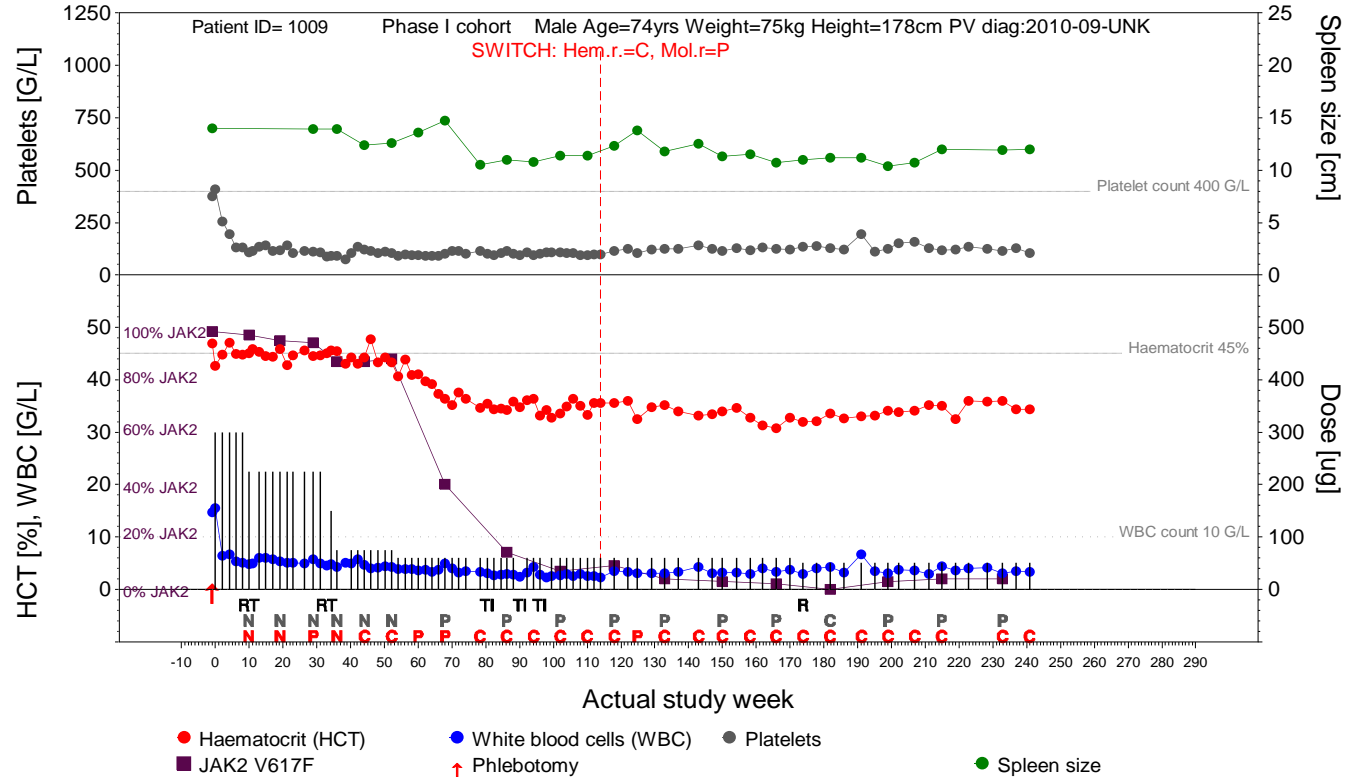


Case No 1:

- Male patient (B.A), age: 81 years
- Diagnose PV in 2010 (JAK2 pos)
- Initial therapy: phlebotomy only, no history of VTE/AT
- Start with IFN-alfa 2b (PEGINVERA) 2011 – ongoing
starting dose 300µg every 2 weeks – continuous dose reduction
currently 35µg 1x/month
- Complete hematologic response
- Complete molecular genetic response
 - DESPITE A VERY LOW IFN DOSE!!!

Case No. 1 (switch Ropeg-IFN 2-weekly - 4 weekly after 112 weeks)

complete hematologic and complete molecular response



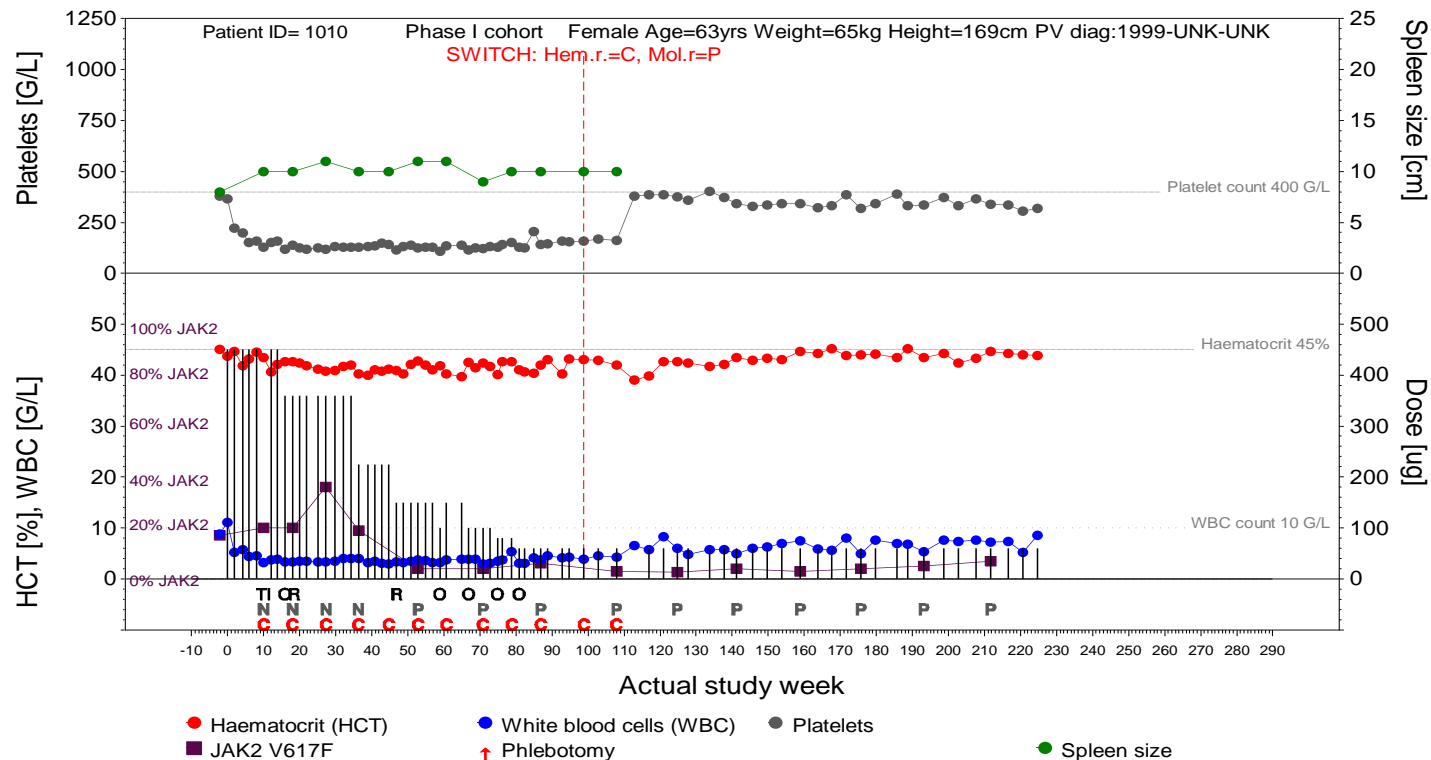
Haematological response (complete, partial, none): C, P, N Molecular response - derived (complete, partial, none): C, P, N

Occurrence of AEs leading to dose change: R = Reduction, TI = Temporarily Interrupted, RT = Reduction+Temp. Interruption, W = Withdrawn
O = Other reason for dose change without AE (with action taken leading to dose change) starting at date of dose change.

Case No. 2:

- Female patient (P.I.), 69 years
- Diagnosed PV in 1999 (JAK2 pos), the first time at our institution in 2010
- Initial therapy with phlebotomies, St.p. cerebral palsy, St.p. PE, bleeding tendency
- Start with IFN- α 2b (PEGINVERA) 2011 – ongoing
starting dose 450 μ g every 2 weeks – continuous dose reduction
currently 100 μ g 1x/month
- Complete hematologic response
- Partial molecular response (>50% reduction of allele burden)

Case No. 2 (switch Ropeg-IFN 2-weekly - 4 weekly after 100 weeks)



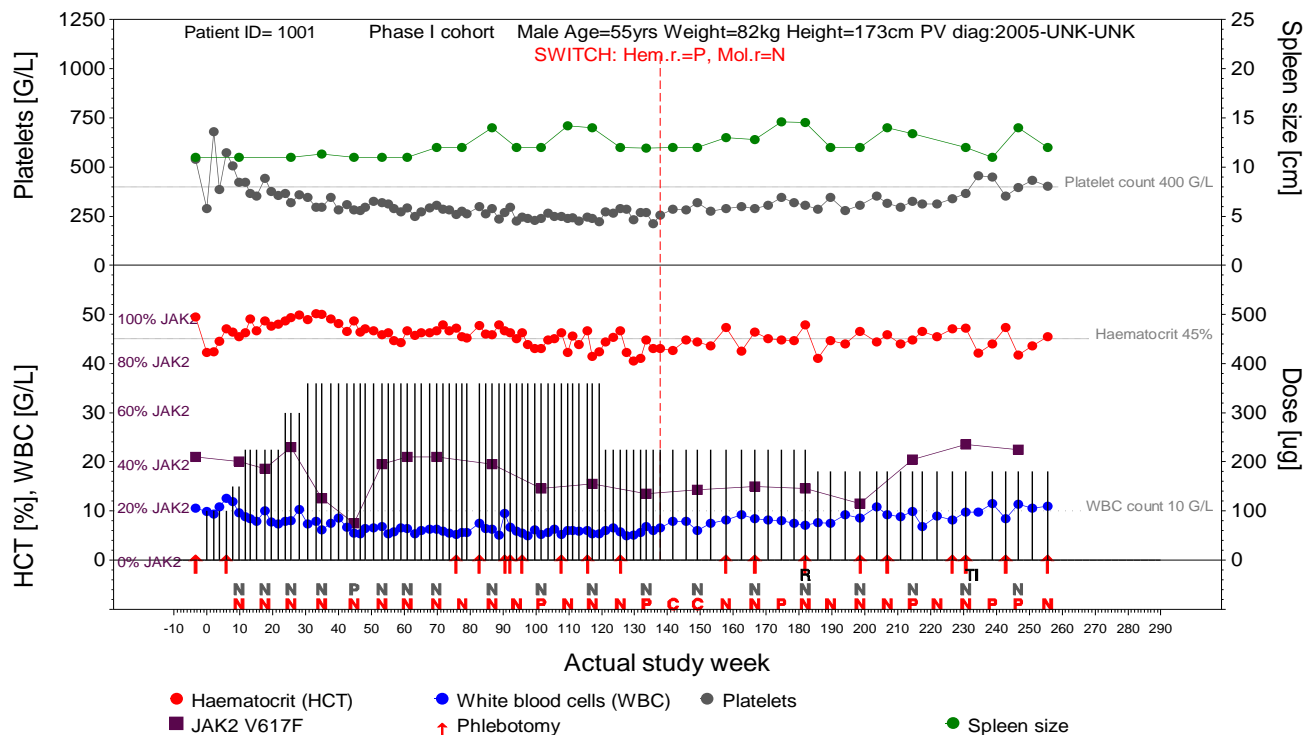
Haematological response (complete, partial, none): C, P, N Molecular response - derived (complete, partial, none): C, P, N

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O = Other reason for dose change without AE (with action taken leading to dose change) starting at date of dose change.

Case No. 3:

- Male patient (H.F.), age: 62 years
- Diagnosis PV in 2005 (JAK2 pos), the first time at our institution in 2010
- Initial treatment hydroxyurea, phlebotomy, previously no VTE/AT
- Start IFN-alfa 2b (PEGINVERA) 2010 – until now
Start Dose 300µg every other week – continuous reduction
derzeit 150 µg 1x/Monat
- partial hematologic response
- partial molecular response
 - Advantage from IFN therapy without complete response!

Case No. 3 (switch Ropeg-IFN 2-weekly - 4 weekly after 136 weeks)



Haematological response (complete, partial, none): C, P, N Molecular response - derived (complete, partial, none): C, P, N

Occurrence of AEs leading to dose change: R = Reduction, TI = Temporarily Interrupted, RT = Reduction+Temp. Interruption, W = Withdrawn
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 - Mullaly et al, Blood 2013
- Clinical development program of RopegIFN
- **Very long-term treatment of PV with IFN alpha**

Very long-term treatment of PV with IFN (MUW PV cohort)

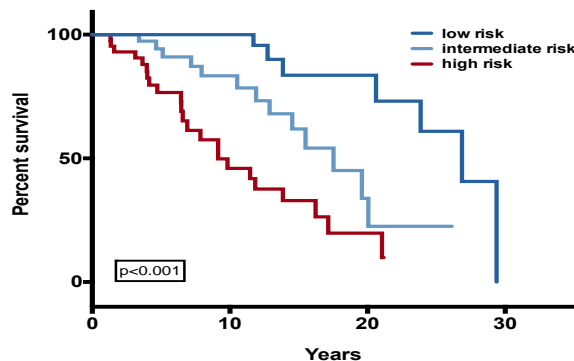
	IFN-treated (N=90)	BAT (N=56)
Age* [years]	52,4	66,7
Sex [m/f]	44/36	31/25
Observ. Time* [years]	13,4	6,0

*Numbers describe median values

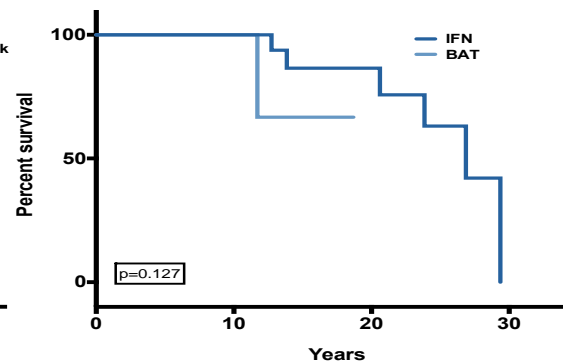
Overall survival in high-risk PV

A retrospective analysis of 129 patients

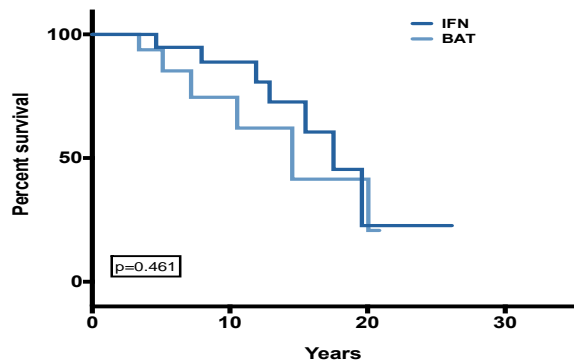
Survival stratified by risk groups



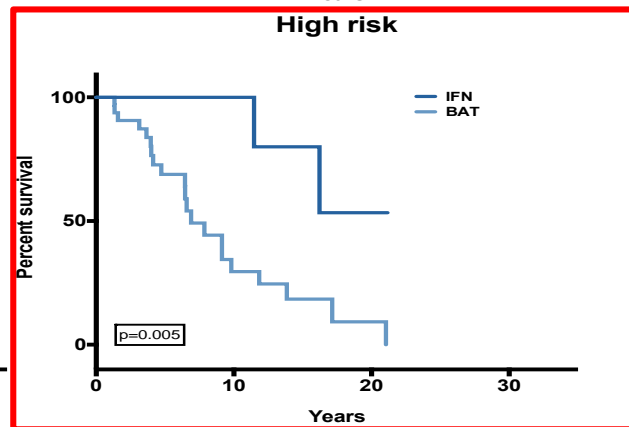
Low risk



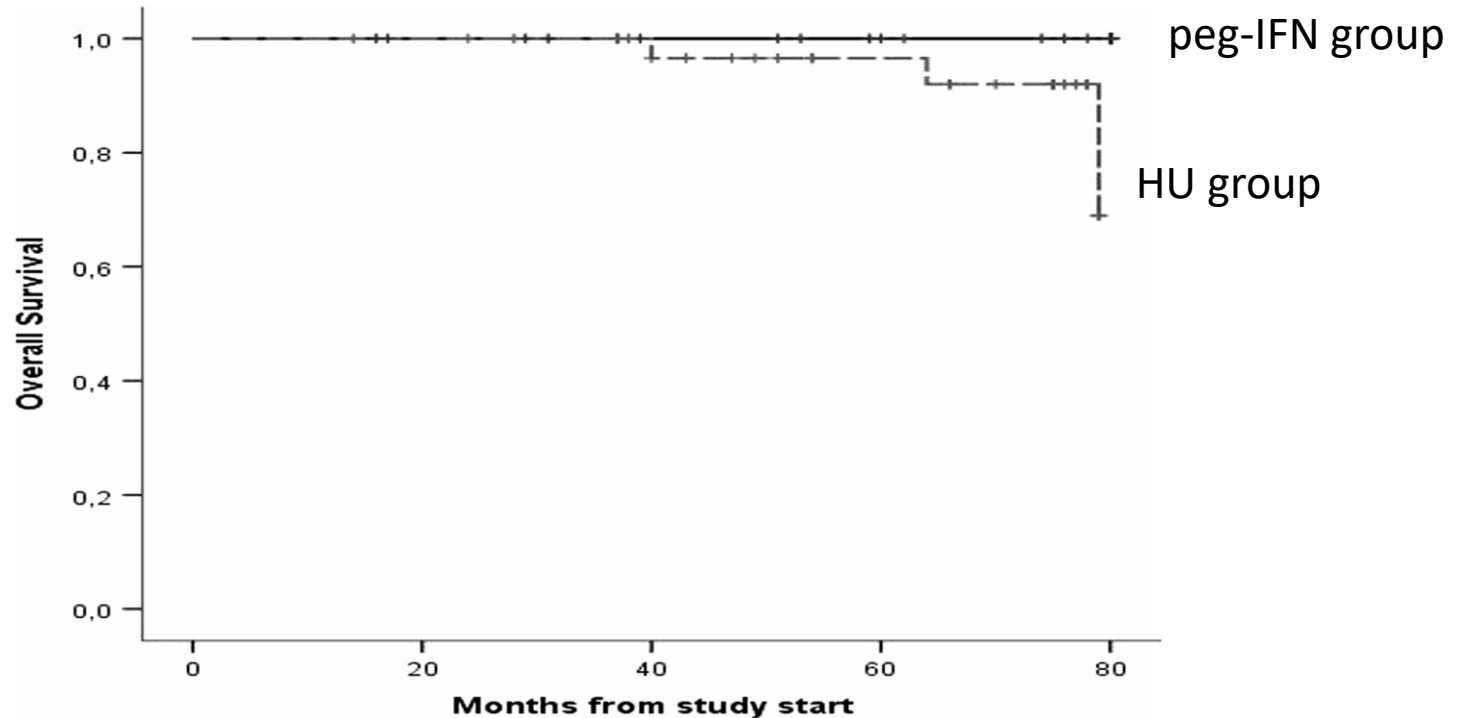
Intermediate risk



High risk



Overall survival from study start by intention to treat principle

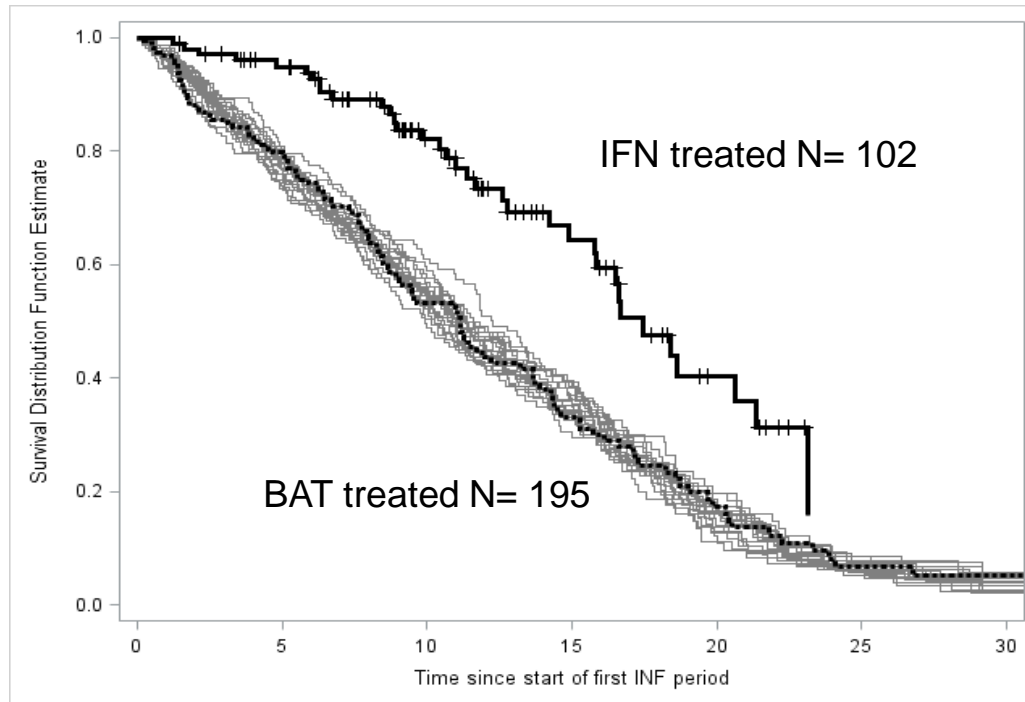


Overall survival IFN alpha vs. Long term BAT in PV

(updated MUW cohort, 2018)

Total cohort (N=297)	IFN-treated (N=102)	BAT (N=195)
Age* [years]	52,6 (28,7-86,5)	66,8 (27,9-92,5)
Sex [m/f]	58/44	96/99
Observ. Time* [years]	12,9 (1,5-30,7)	7,72 (0,5-35,25)

Overall survival IFN alpha vs. Long term BAT in PV (updated MUW cohort, 2018)



IFN vs. BAT
HR = 0.59
(CI 0.40-0.88, p=0.010)

Summary

IFN treatment in PV

- Who should be treated with Interferon?
 - Patients without signs of autoimmunity
 - Patients without signs of mood disorders
- Who should be withdrawn from Interferon?
 - Only patients with IFN-intolerance
- In all other patients, **IFN should be continued**

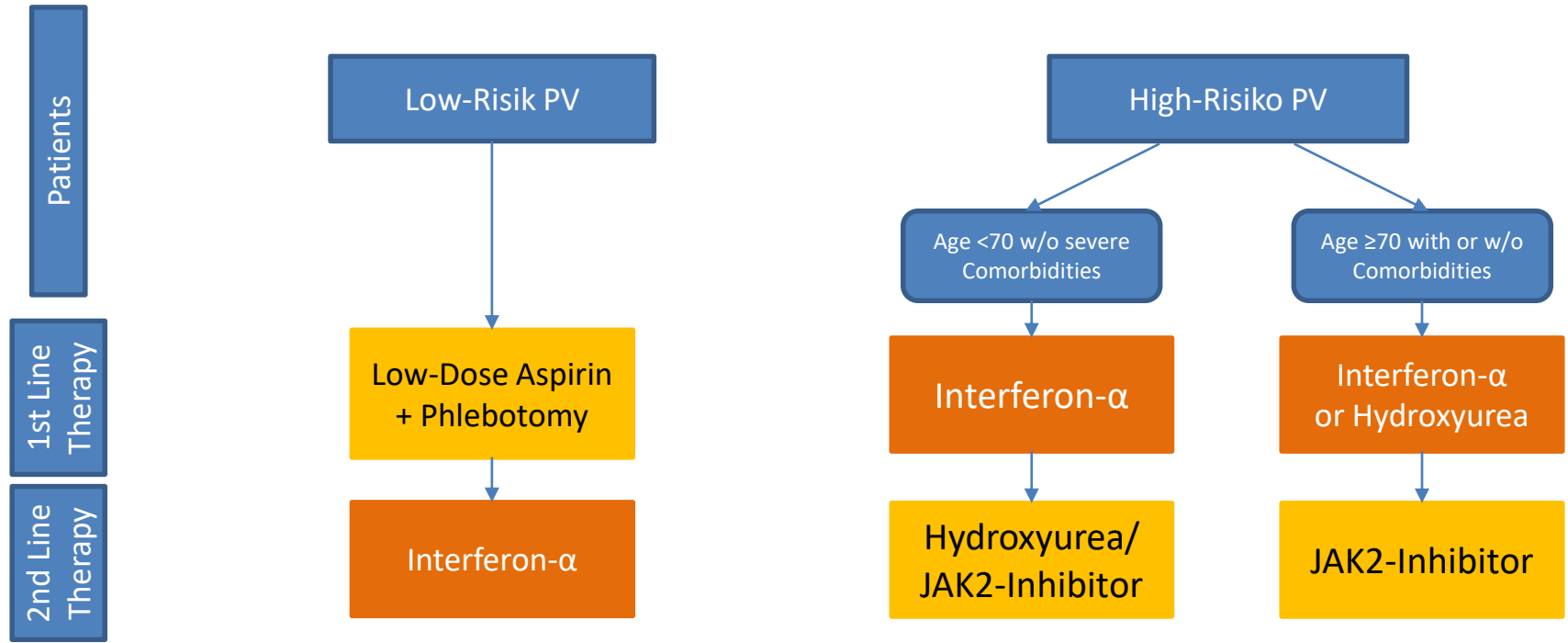
When should PV patients be treated with Interferon?

- Interferon should be considered as first-line therapy in PV
- Start with lower IFN doses in elderly

Reasons for exclusion from IFN treatment

- Comorbidities
 - Pre-existing autoimmunity
 - Mood disorders
- Age (relative contraindication)
- No consent for IFN treatment
- Objections for other reasons

CEMPO Treatment Guidelines for PV



Thank you for your attention