POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
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Policitemia Vera e Trombocitemia Essenziale

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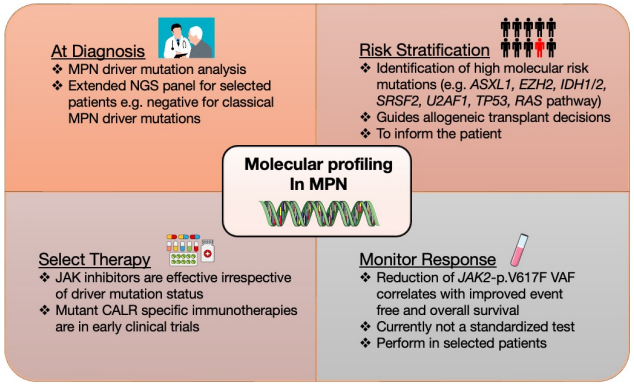
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other-Lectures
Novartis							x
Incyte						x	
Blueprint						x	x
AOP						x	x
GSK						x	x
Menarini Stemline							x
Otsuka							x

Educational: MPN Practice Pearls: Profiling, Pegylated IFN and Pregnancy



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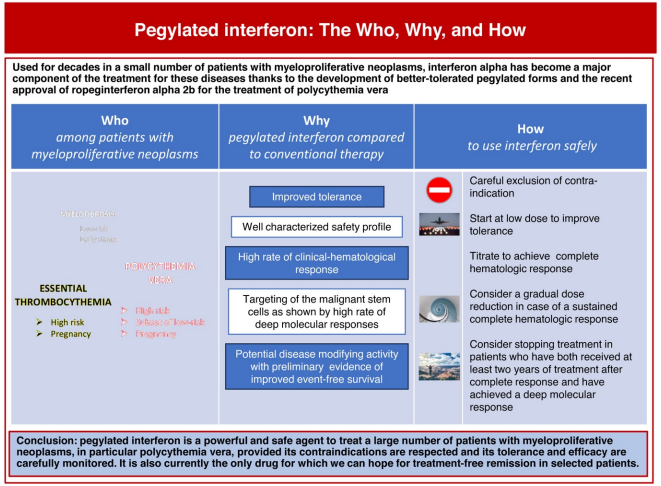
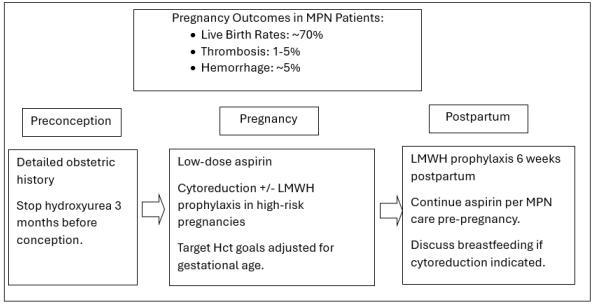


Kiladjian JJ.



How J.

Novità dal Meeting della Società Americana di Ematologia

Policitemia Vera e Trombocitemia Essenziale

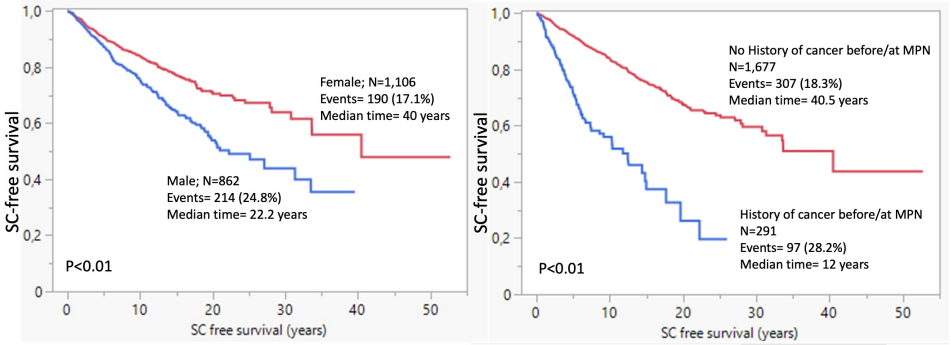
Topics

- Fenotipo di malattia e modelli predittivi.
- Terapie.
- Late breaking abstract: *Andean enriched NFKB1 haplotype.*

Second Cancers & Autoimmune Disorders in PV and ET

n=968 PV/ET pts Mayo

- History of cancer in 30%; 404 cancers after dx (SC).



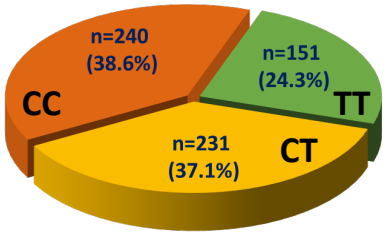
- Risk of SC significantly higher in older patients, men, if with pre-MPN cancer history and AID.
- Incidental venous thrombosis was associated with subsequent SC, not NMSC.

- AID was diagnosed in 157 (8%) pts, 121 (6%) before and 43 (4%) after.
- Pre-MPN history of AID did not affect OS, MFS, LFS, AT-FS or VT-FS (p=0.6).
- SC-FS, including (p<0.01) or excluding (p<0.01) NMSC, was negatively affected by pre-MPN history of AID.

- Increased risk of post-MPN AID and SC in patients with pre-MPN history of AID.
- Significant association between pre-MPN history of AID and venous thrombosis at MPN diagnosis (?role of tumor-extrinsic inflammation in thrombophilia and SC).

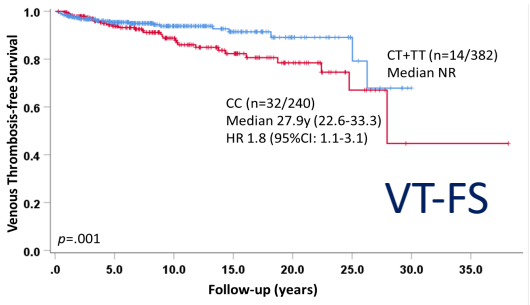
Homozygosity of JAK2 46/1 Haplotype is a Phenotypic Modifier in PV

- The JAK2 46/1, or GGCC, haplotype, spans a region of 250kb in chr9 including the JAK2 gene,. With 4 SPNs that are in complete linkage disequilibrium The GGCC haplo was found to confer susceptibility to *JAK2* mutated MPN.
- **AIM:** To assess the clinical correlates and the prognostic significance of GGCC haplo status in a large cohort of PV.

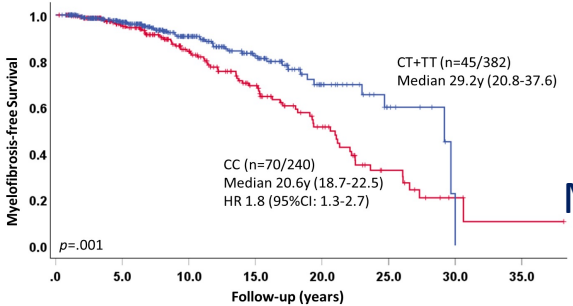


n= 662 PV pts

- The CC genotype was significantly enriched in patients with a *JAK2*VF VAF >50% (67.7% *vs* 22.0% VAF <50%; p<0.001).



VT-FS

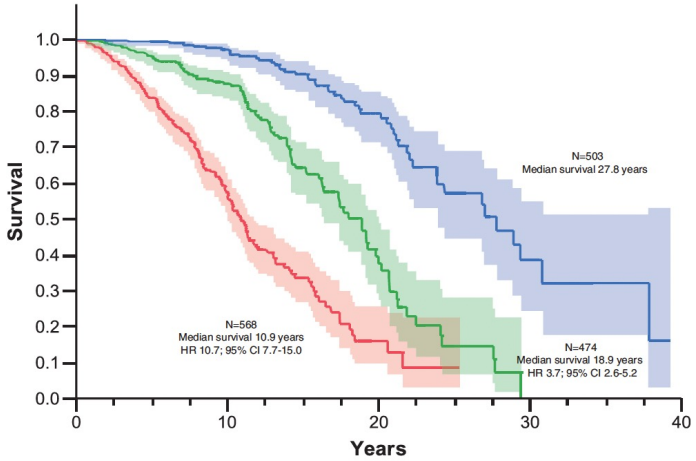


MF-FS

➢ Homozygosity for 46/1 (CC haplotype) is associated with shorter MF-FS and an increased risk of venous thrombosis, in part possibly mediated by associated higher *JAK2*V67F VAF.

Revised International Working Group Risk Model for Survival in PV

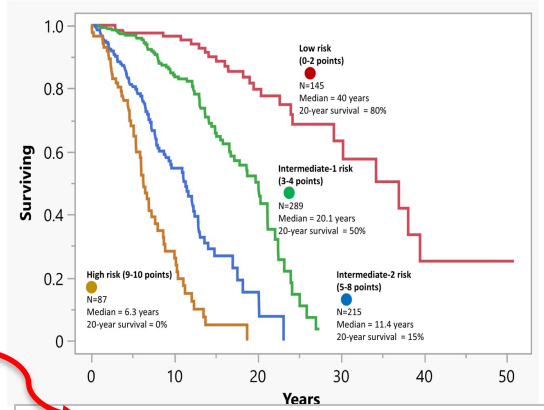
- **IWG-MRT model** for survival in PV.
- Includes 3-tiered age categories, leukocytosis (≥15x10^9/L), and venous thrombosis, as risk variables.



Tefferi A et al. 2013

AIM: to examine individual prognostic contribution from specific leukocyte components, to construct a more contemporary clinical risk model. N=736 PV patients.

(1) Age >70 years (7 points), 50-70 years (3 points)
(2) Absolute neutrophil count ≥8 x 10(9)/L (1 point)
(3) Absolute monocyte count ≥0.8 x 10(9)/L (1 point)
(4) Arterial thrombosis (1 point)



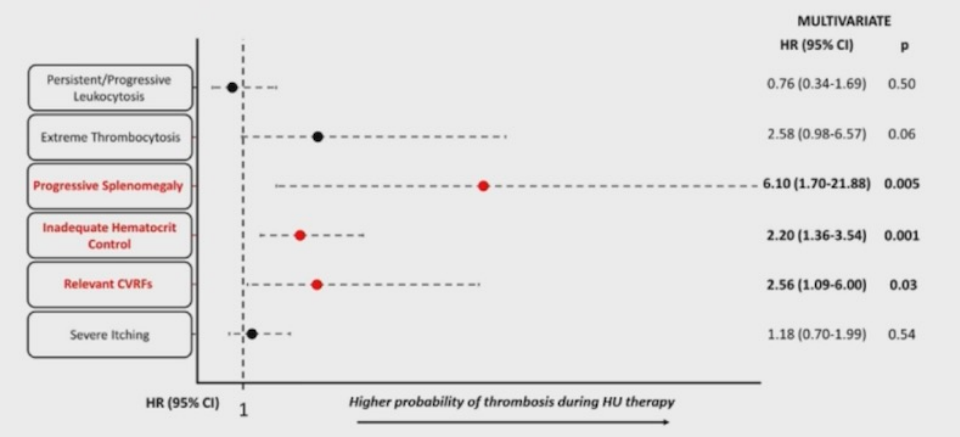
- MVA revealed adverse survival impact for **age >70y**, **age 50-70y**, **AMC ≥0.8x10^9/L**, **ANC ≥8x10^9/L**, **arterial thrombosis**, **diabetes**, **male sex**.
- Not in the model, *SRSF2* 4%, *IDH2* 2%, *TP53* 2%, *RUNX1* 1.4% were risk factors in MVA.

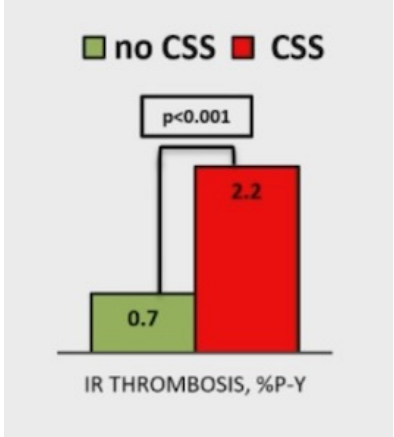
➢ The proposed revised IWG risk model for survival in PV is globally applicable and based on four easily accessible clinical variables.

Revised ELN Criteria in PV Identify an Increased Risk Phenotype for Thrombosis

- 739 PV treated with first line HU, 81.5% high-risk, 18.5% low-risk.
- **AIM:** impact of ELN-defined CCS on thrombosis risk.

CSS





CSS= Clinical Signs and Symptoms

➢ CSS identifies an increased thrombotic risk phenotype independent of conventional risk categories, supporting their incorporation in existing prognostic models.

Prognostic value of Response to First-Line HU, according to IPSET, in ET

- The prognostic value of attaining CHR according to ELN criteria in ET is unknown.
- **AIM:** to analyze impact of achieving CHR to first-line HU in 1,080 ET patients from the Spanish Registry of ET.

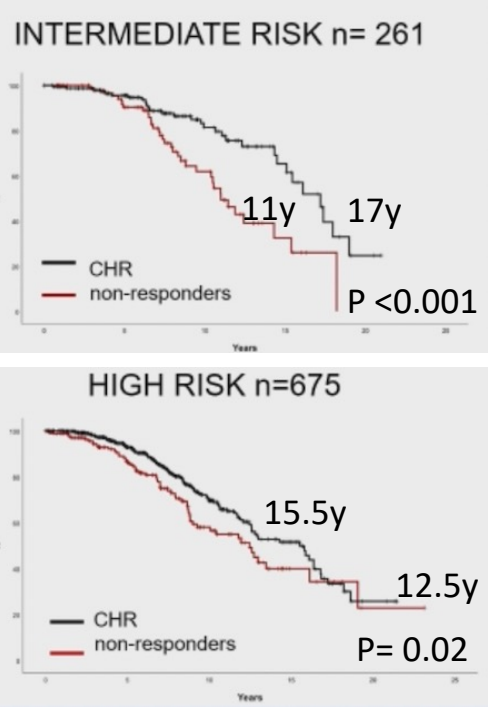
Risk	Adverse features	Management
Very low	None	Observation or low-dose aspirin
Low	JAK2V617F+ Age≤60 years, no prior thrombosis	Low-dose aspirin
Intermediate	Age>60 years *JAK2* wt, no prior thrombosis	Cytoreductive therapy plus low-dose aspirin
High	Age>60 years and JAK2V617F+ or Prior thrombosis	Cytoreductive therapy plus low-dose aspirin

IPSET-r

Complete Hematological Response (CHR) – ELN criteria

- Normalization of platelet count (<400x10^9/L)
- Leukocyte count <10x10^9/L
- Absence of disease-related symptoms
- Normal spleen size

SURVIVAL



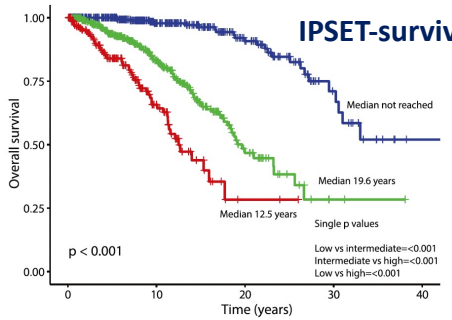
10y probability	CHR	Non-CHR	P
Arterial events	7.2%	27.9	<0.001
Venous events	3.7%	9.3%	0.035
Post-ET MF	6.0%	15.0%	0.003

*IPSETr high-risk category

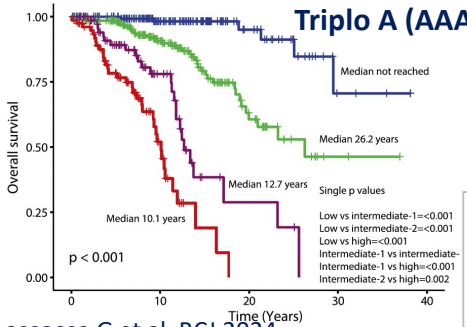
- Failure to achieve CHR in ET is associated with worse survival, higher thrombotic risk, higher rate of progression to MF.
- Failure to achieve CHR might be considered an eligibility criterion for second-line clinical trials.

Monocytosis is an Independent Risk Factor for Survival in ET: a Revised AAA+A Score

- 2 models for predicting survival in ET.



Age
Thrombosis history
Leukocyte count

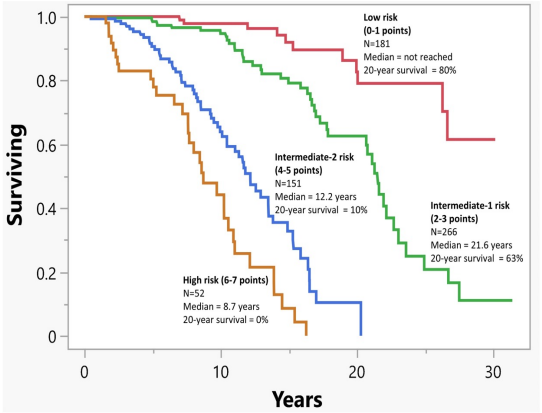


Age
Absolute N count
Absolute L count

Loscocco G et al, BCJ 2024

- 650 ET patients.
- In age-adjusted UVA, a ≥0.8x10^9/L AMC was associated with OS.
- **AAAv2.0** model: **Age**, ANC (>8x10^9/L), **ALC** (<1.7x10^9/L), **AMC** (>0.8x10^9/L), **Arterial thrombosis** history.

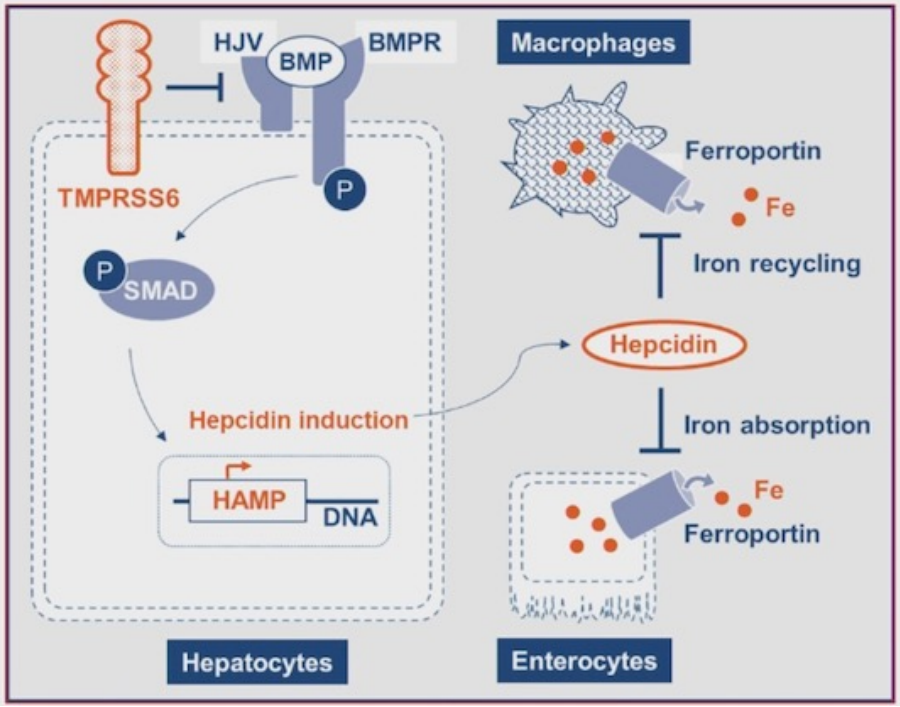
(1) Age >70 years (4 points), 50-70 years (2 points)
(2) Absolute neutrophil count ≥8 x 10(9)/L (1 point)
(3) Absolute monocyte count ≥0.8 x 10(9)/L (1 point)
(4) Absolute lymphocyte count <1.7 x 10(9)/L (1 point)



Monocytosis is an adverse prognostic factor in ET that enhances predictive value of the AAA model, that is equally simple to apply worldwide.

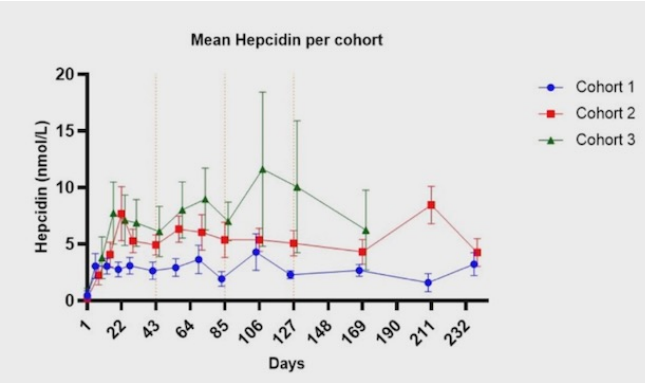
Tefferi A et al.

A Phase1/2 Study of Divesiran, a Novel GalNAc Conjugated siRNA, in PV (SANRECO)



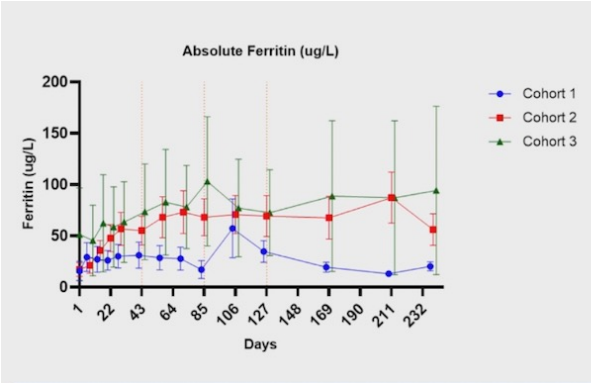
- **Hepcidin** reduces uptake of dietary iron and release of iron from storage cells.
- **HJV/BMP/SMAD** signaling pathway induces hepcidin expression. **TMPRSS6** is a **negative** regulator of this pathway. It is a serine protease which cleaves HJV
- **Hepcidin** levels are low to normal in patients with Polycythemia Vera
- **Therapeutic hypothesis:** inhibition of TMPRSS6 will raise hepcidin and reduce iron delivery to the bone marrow resulting in reduced erythropoiesis.

- Divesiran is a 19mer siRNA conjugate, with target sequence and high knock-down properties to *TMPRSS6.*
- Specific modifications to allow long duration action.
- Conjugated with tri-antennary GalNAc for specific targeting of hepatocytes via asialoglycoprotein receptor interaction. Liver is the target organ.
- Subcutaneous injection (Q6W x four doses in the study, followed by16w observation).
- 3 cohorts: 3mg/kg, 6 mg/kg, 9mg/kg. Participants: n=21.

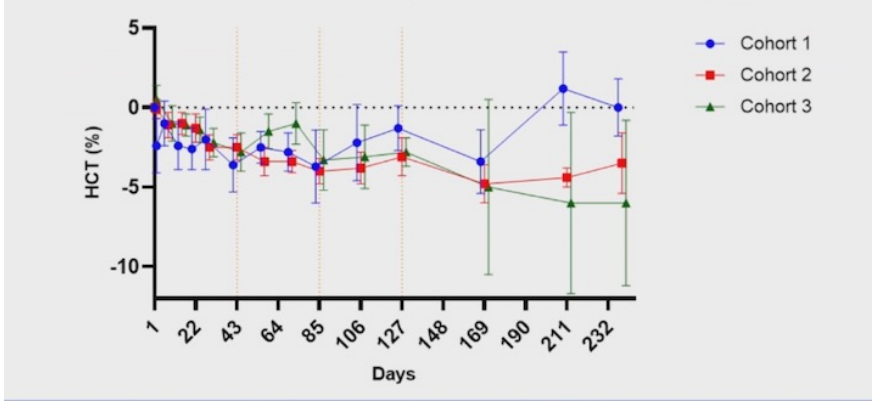


Increases of hepcidin

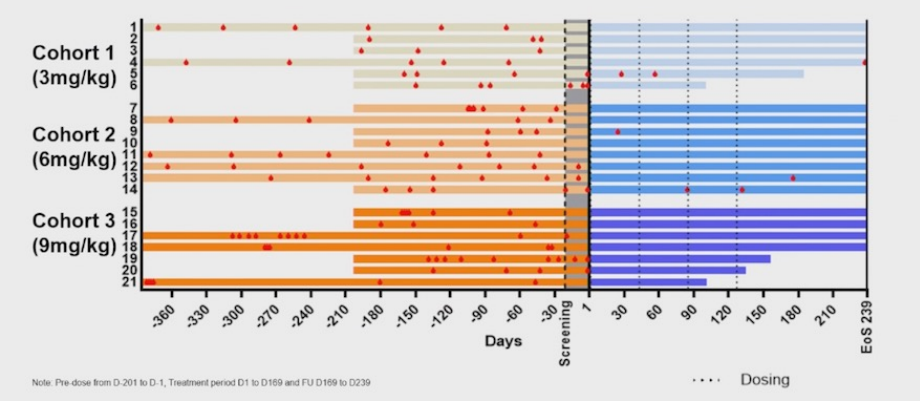
and ferritin



- Reduction of Hct levels over treatment



- Reduction of pHL requirement



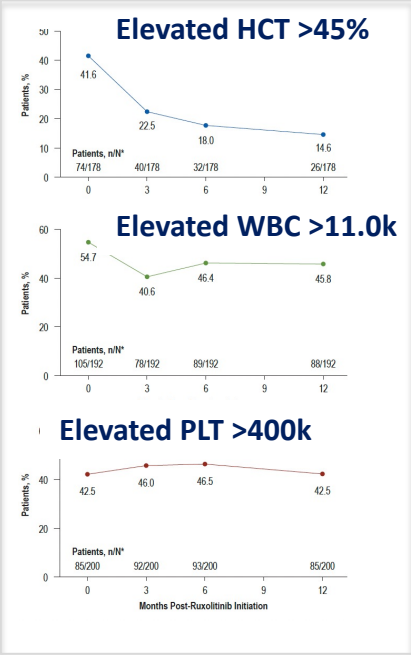
79 PHL prior to dosing, 5 in treatment period, 2 in FU

- Platelet count increased by day 29 w/o dose dependency, WBC unchanged.
- Few AEs, mainly injection site reaction.

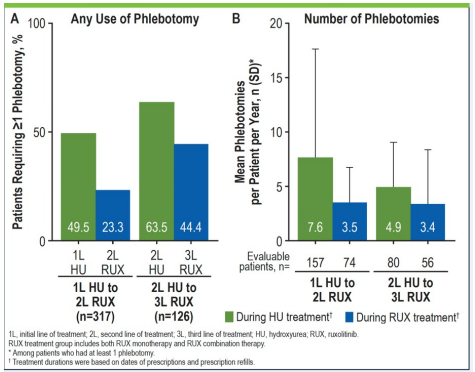
➢ These early results support further development of devesiran in PV.

RW Patterns and Blood Count Control in PV Patients who Switched from HU to Rux

AIM: To describe treatment patterns, blood count control, and use of PHL in PV patients who switched from HU to ruxolitinib at US community practices. N= 443 of 10,112 included.



	Overall (N=443)	1L HU to 2L RUX (n=317)	2L HU to 3L RUX (n=126)
Time from PV diagnosis to HU initiation, median (IQR), mo	1.4 (0.03–13.5)	0.4 (0–3.2)	19.2 (5.3–27.8)
Absolute duration of HU treatment,* median (IQR), mo	9.3 (3.7–26.4)	9.7 (3.6–27.5)	9.2 (3.9–25.0)
Patients continuing on RUX at end of study period, n (%)	170 (38.4)	118 (37.2)	52 (41.3)



Conclusions

- Patients switching from HU to ruxolitinib treatment had improved Hct and WBC count control
  - Differences in percentages of patients meeting treatment goals for Hct control compared with WBC and PLT may reflect current treatment guidelines in PV[4]
- Patients required fewer phlebotomies to maintain Hct when treated with ruxolitinib vs HU
- A strength of these real-world data is that they were collected from community oncology clinics across the United States
- These data suggest clinical benefits for patients switching to ruxolitinib following inadequate disease control with HU treatment

Ropeginterferon in Low-Risk Patients with PV

- **AIM:** efficacy and safety of Ropeg-IFN in low-risk PV patients (n=42) with rapid dose escalation (250→350→500 ug Q2w).

Figure 1. Complete hematologic response rates over time

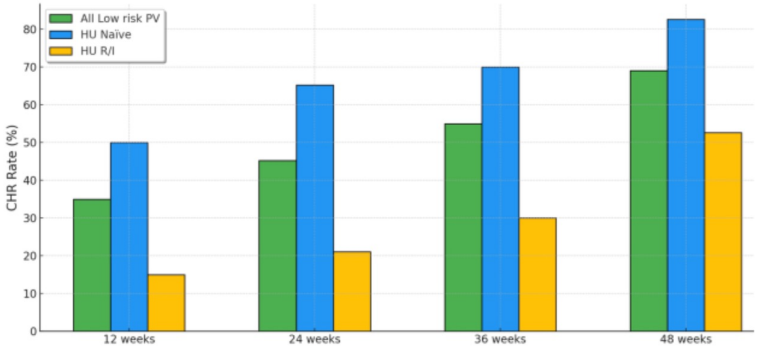
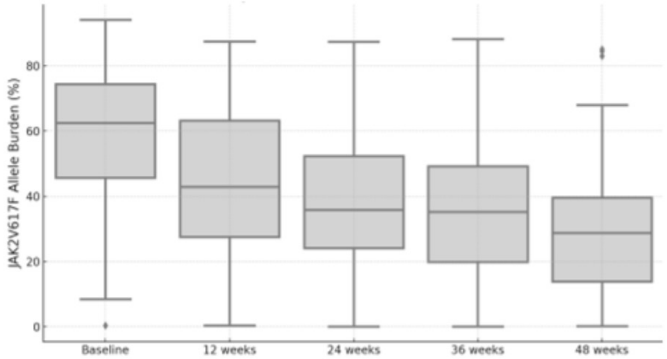


Figure 4. Change of JAK2V617F Allele Burden During Ropeg Treatment



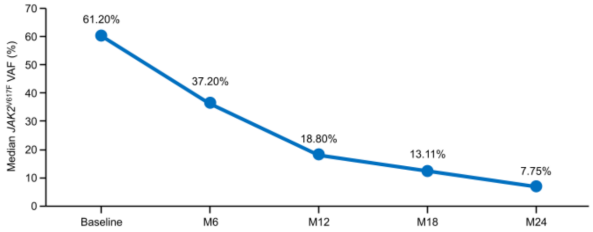
- 76% had ≥1 TEAE, mild or moderate, most common hepatobiliar function and alopecia.

Ropeginterferon in Low-Risk Patients with PV

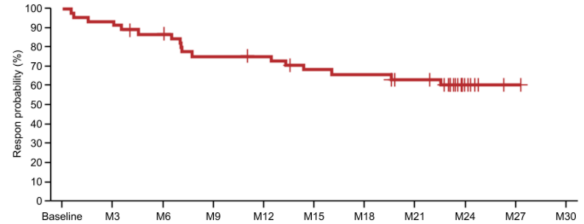
- **AIM:** effect of Ropeg-IFN on *JAK2*V617F VAF in PV patients (n=49) with rapid dose escalation (250→350→500 ug Q2w).

ITT population (N = 49)	n (%) or mean
Sex	
male	31 (63.3%)
female	18 (36.7%)
Age (years)	
Mean (SD)	53.0 (10.92)
Median (Min, Max)	56.0 (29,70)
PV diagnosis, months	
Mean (±SD)	44.44 (59.04)
Median (Min, Max)	15.5 (0.03,245.6)
HU pretreated, no. (%)	
HU resistance	0 (0%)
HU intolerance	49 (100%)
***JAK2* ^{V617F} mutation**	
Positive	49 (100%)
Negative	0 (0%)
Baseline parameters	
Hematocrit (%)	45.95
Platelets (10^9/L)	478.5
Leukocytes (10^9/L)	11.35
JAK2 ^{V617F} allele burden(%)	58.49

Median *JAK2*^{V617F} VAF at assessment visits



Kaplan-Meier plot showing the durability of CHR



Safety Results

Treatment Emergent Adverse Events occurring in ≥10% of patients

System Organ Class Preferred Term	Patients (N=44) Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Total n (%)
Metabolism and nutrition disorders						
Hyperuricaemia	12 (27.3%)	0	0	0	0	12 (27.3%)
Hypertriglyceridemia	6 (13.6%)	0	0	0	0	6 (13.6%)
Renal and urinary disorders						
Proteinuria	5 (11.4%)	0	0	0	0	5 (11.4%)
Investigations						
Alanine aminotransferase increased	13 (29.5%)	0	0	0	0	13 (29.5%)
Aspartate aminotransferase increased	7 (15.9%)	0	0	0	0	7 (15.9%)
Lymphocyte count decreased	1 (2.3%)	4 (9.1%)	0	0	0	5 (11.4%)
Neutrophil count decreased	5 (11.4%)	8 (18.2%)	1 (2.3%)	0	0	14 (31.8%)
White blood cell count decreased	6 (13.6%)	13 (29.5%)	0	0	0	19 (43.2%)
Anemia	6 (13.6%)	0	0	0	0	6 (13.6%)

Final Results from the Phase 2 REVIVE Study

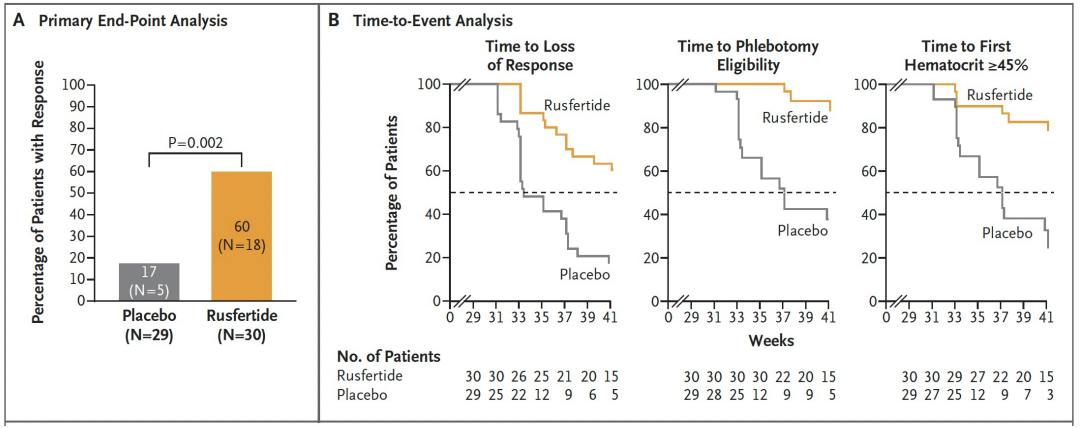
- The phase 2 REVIVE study, investigating rusfertide in patients with PV met its primary endpoint and demonstrated that rusfertide was superior to placebo in achieving Hct levels <45% and reducing or eliminating the need for PHL in patients who were PHL dependent prior to study entry.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

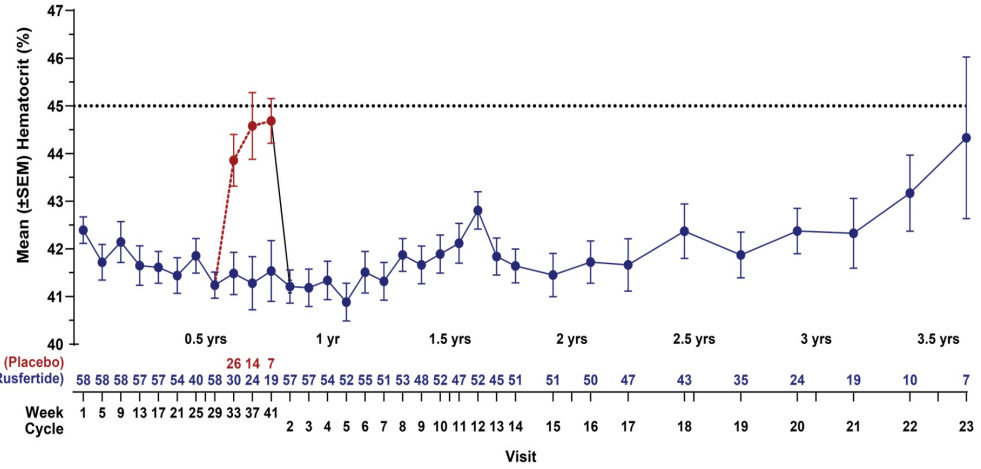
Rusfertide, a Hepcidin Mimetic, for Control of Erythrocytosis in Polycythemia Vera

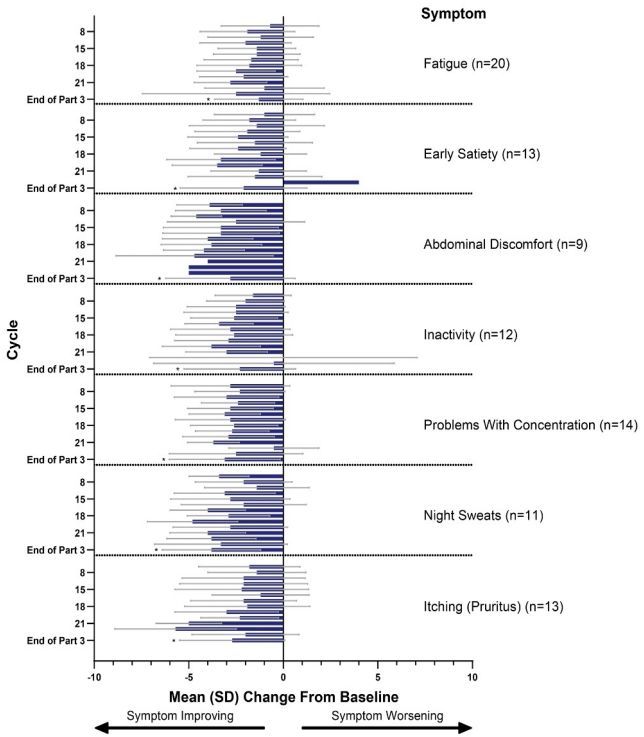
Kremyansakaya M et al, NEJM 390:723



- **AIM:** To present final results from REVIVE, including data from patients who received rusfertide for more than 3.5 years

- Rusfertide consistently maintained Hct <45% for ≥3y.





- Rusfertide improved several symptoms (MPN-SAF) throughout study duration.

Safety

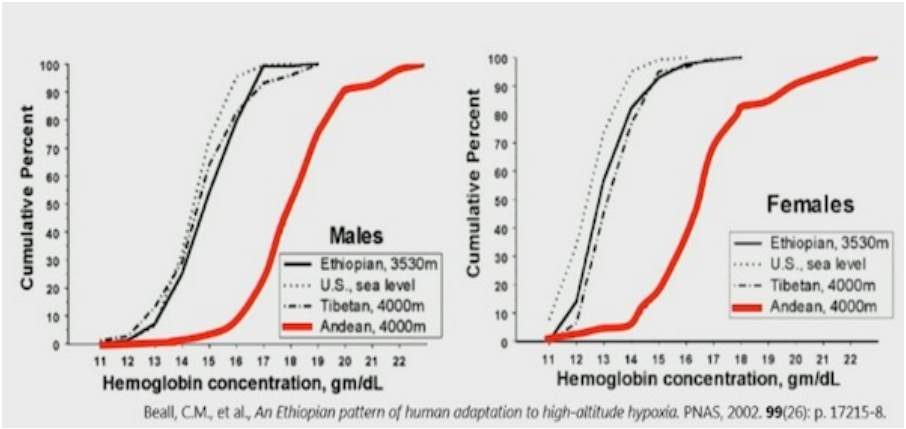
- There were no Grade 4 or 5 TEAEs.
- Most AE were injection site reaction.
- Overall, 18 (26%) patients experienced SAEs.
- After more than 150 patient-years of rusfertide exposure, **malignancies** were reported in 11 patients (9 patients had skin malignancies)
- Seven **thrombotic events** (6 arterial and 1 venous) occurred in 6 patients; all had high-risk PV.

Conclusions

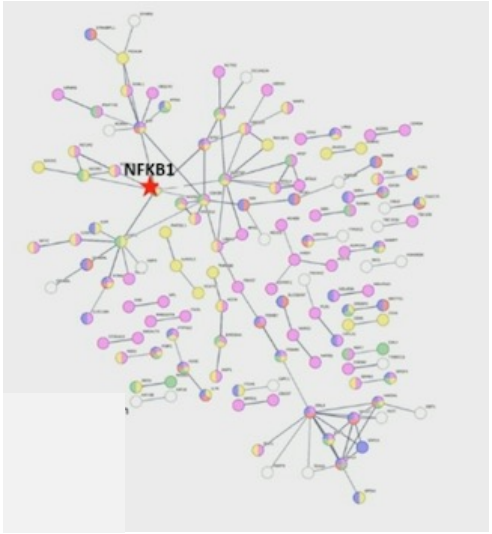
- In REVIVE, rusfertide added to PHL with or without CRT controlled erythrocytosis, provided long-term durable control of Hct, and decreased the need for PHL.
- Patients in REVIVE rolled over to the phase 2 THRIVE OLE study (n=46, 79%), which will continue to assess the long-term safety and efficacy of rusfertide for up to 2 additional years.
- The ongoing, randomized phase 3 VERIFY study (NCT05210790) is evaluating rusfertide + PHL ± CRT vs placebo + TP ± CRT in patients with PV.

Andean Enriched *NFKB1* Haplotype Reduces Inflammation and Improves Response to RopegIFN

- Aymara is a population that lives close to Titicaka lake (3812m slm) in Perù, Bolivia, Cile and Argentina that has adapted uniquely to high altitude.

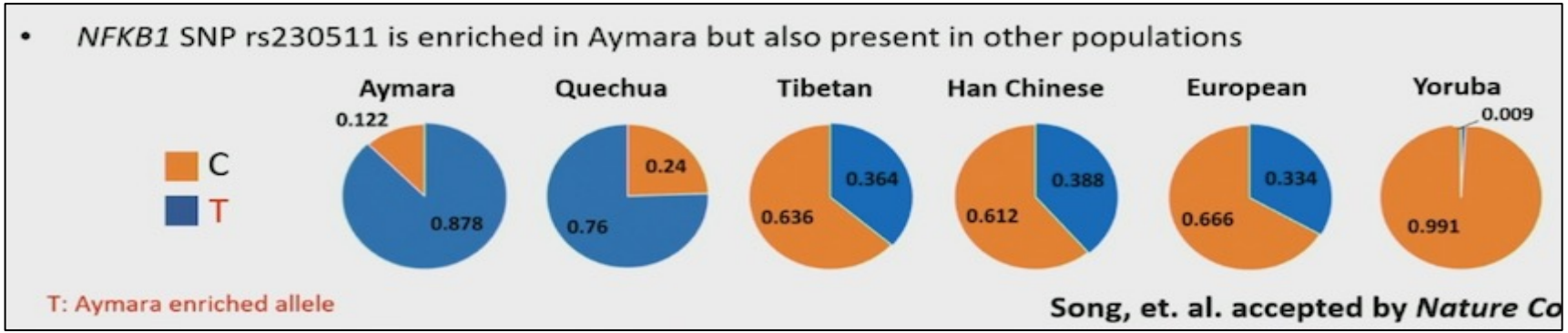


Beall, C.M., et al., *An Ethiopian pattern of human adaptation to high-altitude hypoxia.* PNAS, 2002. **99**(26): p. 17215-8.



- Whole transcriptome analysis of GN, compared to European descendant, discovered enhanced inflammatory pathways, particularly NF-kB pathw.

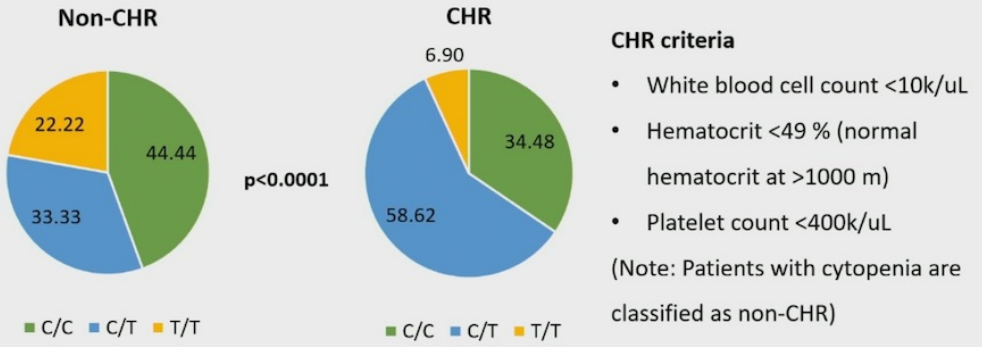
- Activation of NF-kB path is a primary driver of inflammation in MPN.
- Suppression of NF-kB pathway reduces disease burden in MPN.
- NFKB1 is the subunit 1 of NF-kB.
- *Nfkb1*$^{-/-}$ mice display increased inflammation.



- **AS-*NFKB1*** correlates with upregulation of HIFs and increased Aymara hemoglobin.
- In *in vitro* TNF-a stimulated Mo, **AS-NFKB1** showed paradoxical down-inflammatory regulation

NFKB1 haplotype enhances response to ropeginterferon Alfa-2b

- Ropeginterferon-α-2b (Ropeg) modulates inflammation through interferon signaling
- C/T genotype (58.6%) was more common in the patients who achieved complete hematological response (CHR) compared to the non-CHR cohort (33.3%) (p<0.0001)



CHR criteria

- White blood cell count <10k/uL
- Hematocrit <49 % (normal hematocrit at >1000 m)
- Platelet count <400k/uL

(Note: Patients with cytopenia are classified as non-CHR)

➢ Might serve as predictive variable of hematologic response to ropegIFN.

- The IFNL4 rs3682348 diplotype has been associated with molecular response to ropegIFN.
  Jager R et al. 2021

POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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