



# Understanding Myeloproliferative Neoplasm

**Idoroenyi Amanam, MD**

Assistant Professor, Division of Leukemia

Hematology & Hematopoietic Cell Transplantation

City of Hope

# Disclosures

- I have no relevant financial relationships.

*This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.*

# Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

## STATE LAW:

The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

*The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.*

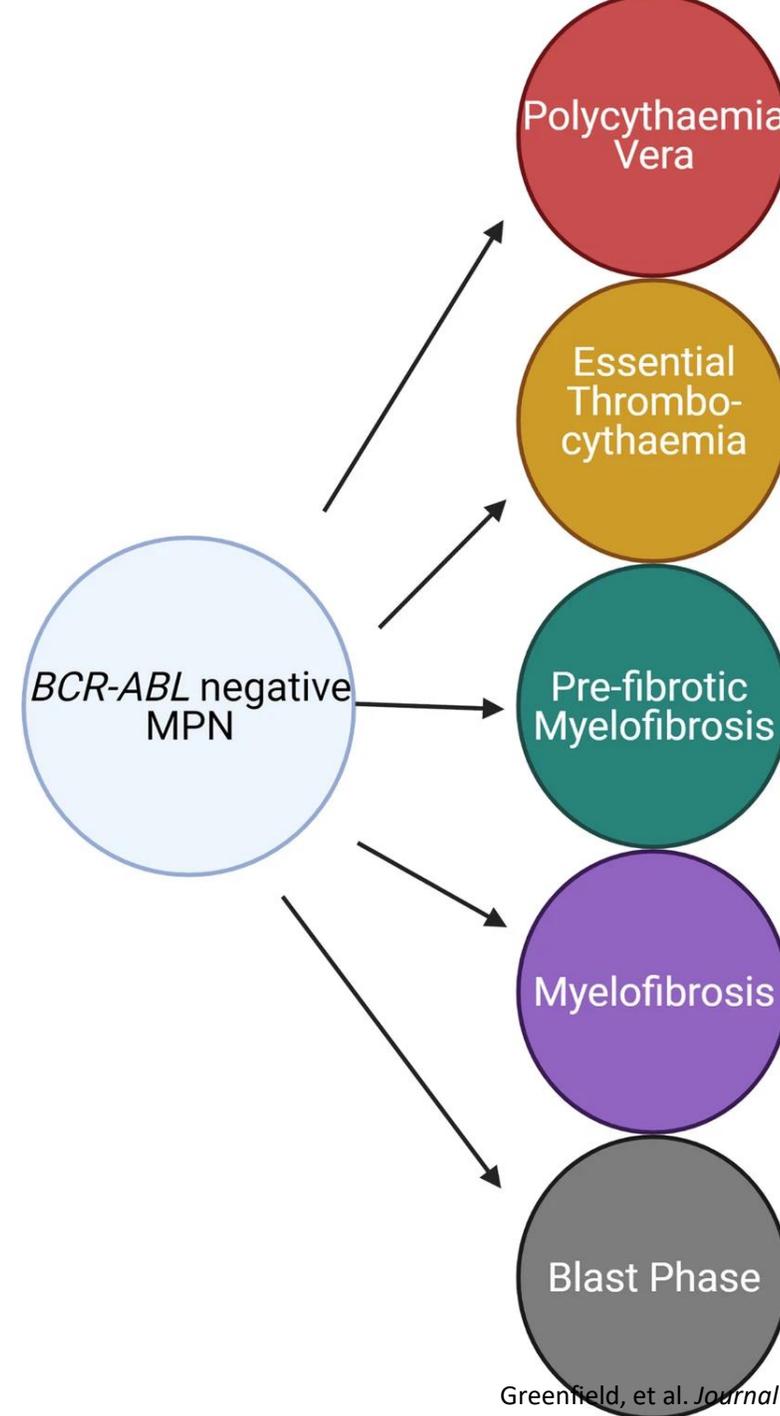
## **EXEMPTION:**

Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

***This presentation is dedicated solely to research or other issues that do not contain a direct patient care component.***

# Myeloproliferative Neoplasms

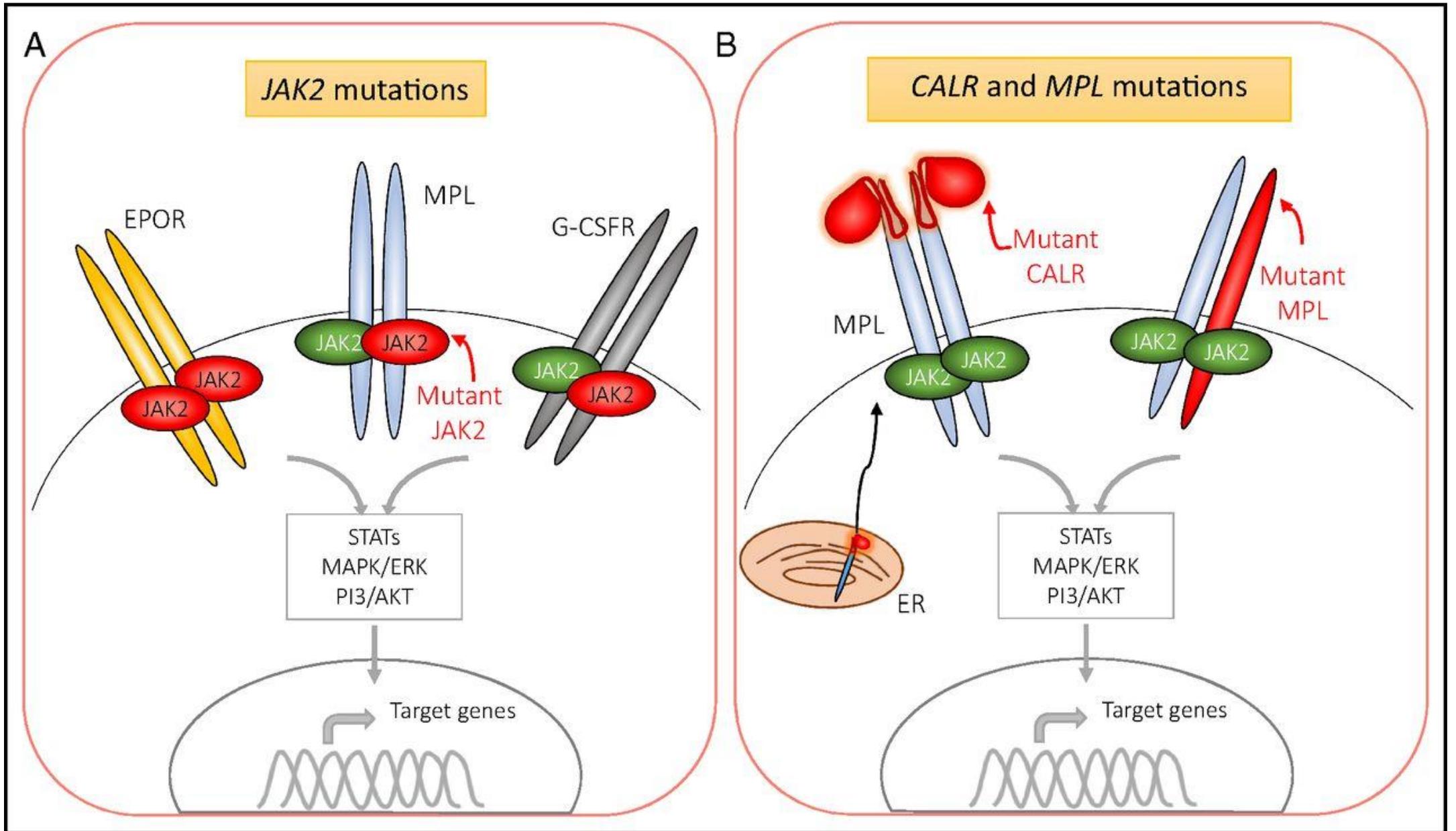
- Classic (BCR-ABL negative)
  - Essential Thrombocythemia
  - Polycythemia Vera
  - Myelofibrosis



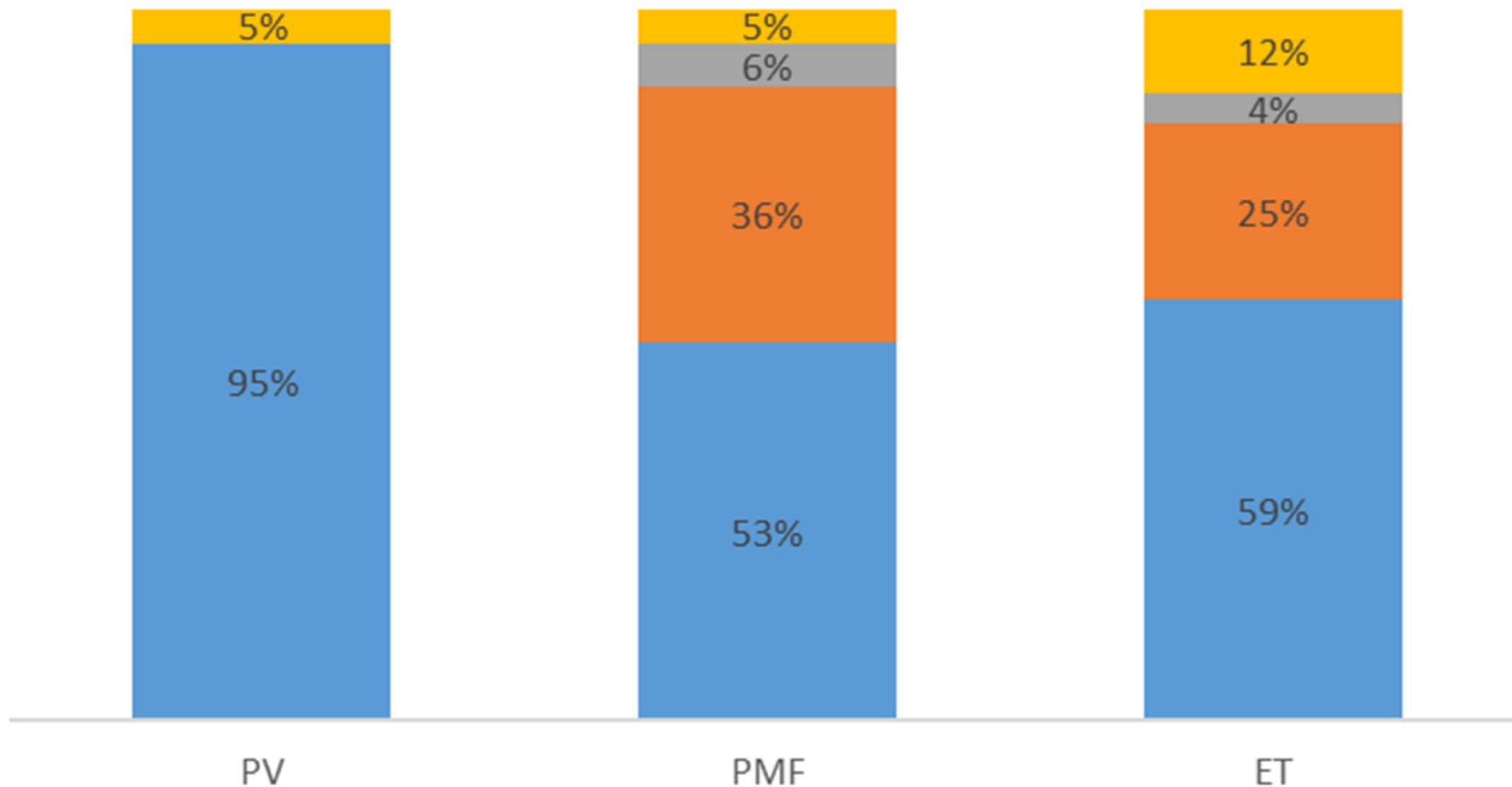
# Objectives

- Background
- Diagnosis
- Prognostication
- Treatment

Background



■ JAK2 ■ CALR ■ MPL ■ Triple Negative



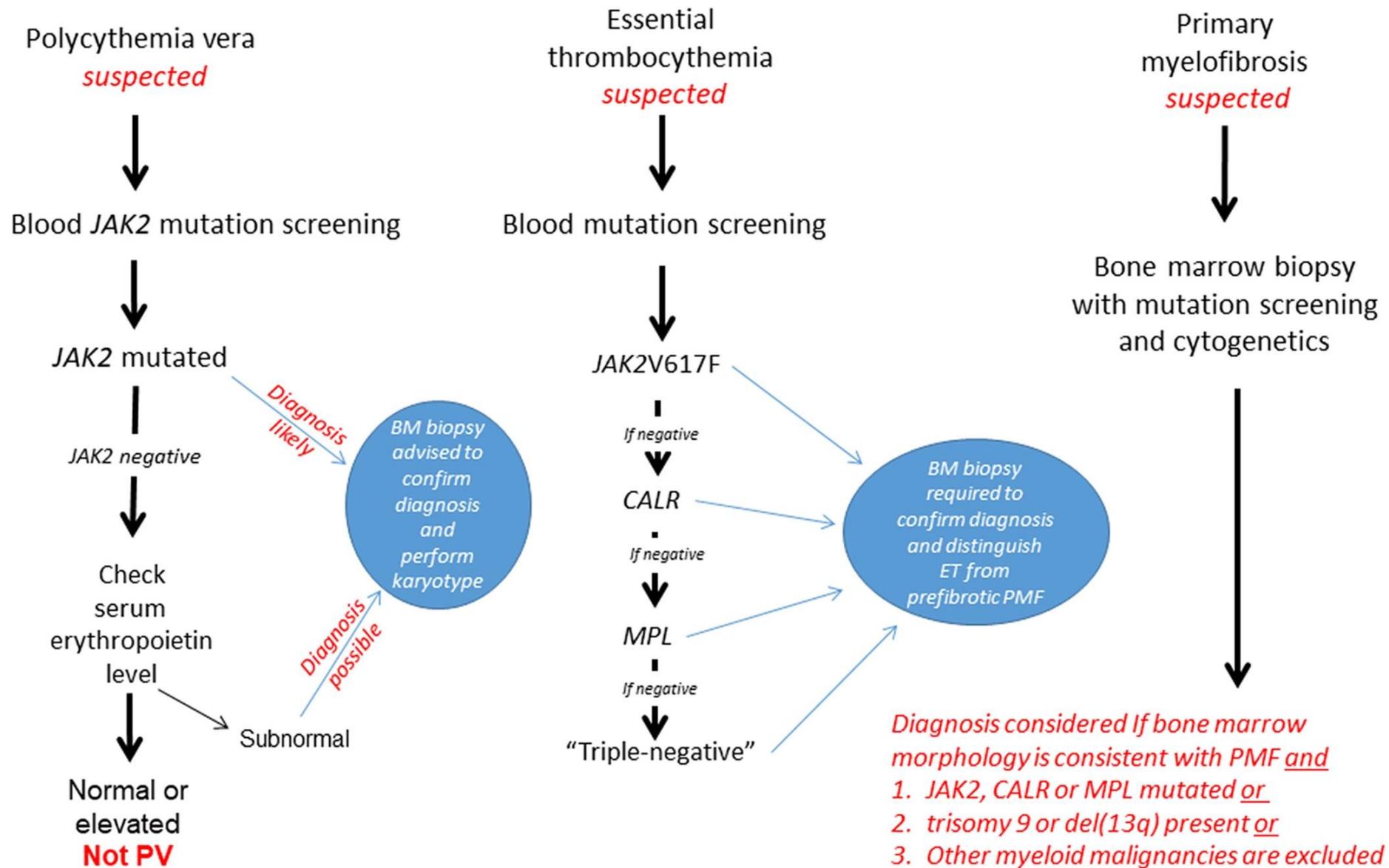
# Co-occurring Mutations

Class	Mutated Gene	Frequency (%)		
		PV	ET	PMF
Epigenetic regulation	DNMT3A	2–7	0–9	3–15
	TET2	19–22	5–16	10–18
	IDH1/2 <sup>a</sup>	2	1	0–6
	ASXL1 <sup>a</sup>	3–12	1–11	13–37
	EZH2 <sup>a</sup>	0–3	1–3	1–9
	SUZ12	2–3	<1	2
Messenger RNA splicing	SRSF2 <sup>a</sup>	3	2	8–18
	U2AF1	<1	1	6–16
	SF3B1	3	5	6–10
	ZRSR2	5	3	4–10
Signaling	N/KRAS	0–1	<1	3–4
	CBL	1	1	4–7
	SH2B3 (LNK)	9	3	3–6
	PTPN11	<1	0–2	0–2
Transcriptional regulation	RUNX1	0–2	0–2	3–4
	NFE2	2–3	<1	0–3
DNA repair	TP53	1	2–6	1
	PPM1D	1	2	1

# Objectives

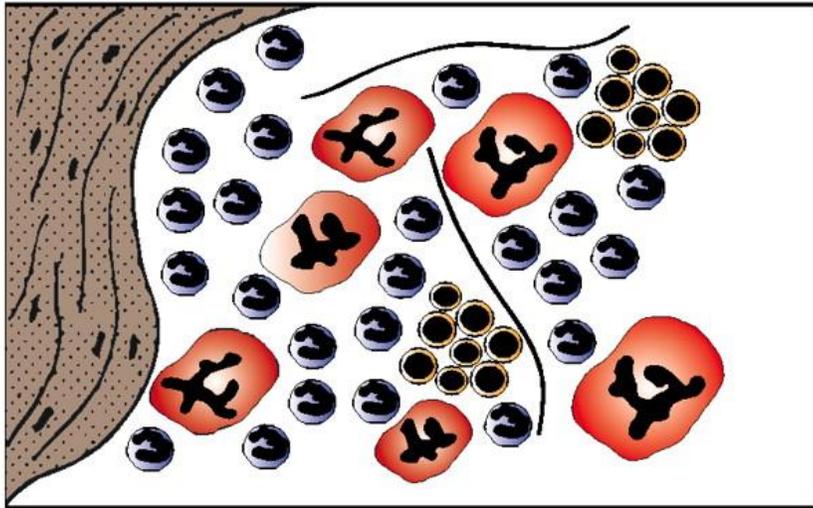
- Background
- **Diagnosis**
- Prognostication
- Treatment

Diagnosis



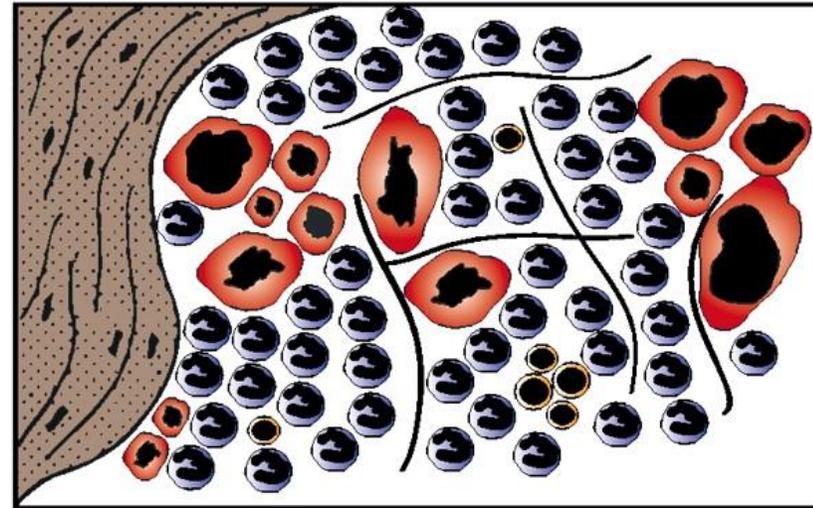
## ET

- no or only slight increase in age-matched cellularity
- no significant increase in granulo- and erythropoiesis
- prominent large to giant mature megakaryocytes with hyperlobulated or deeply folded nuclei, dispersed or loosely clustered in the marrow space
- no or very rarely minor increase in reticulin fibers

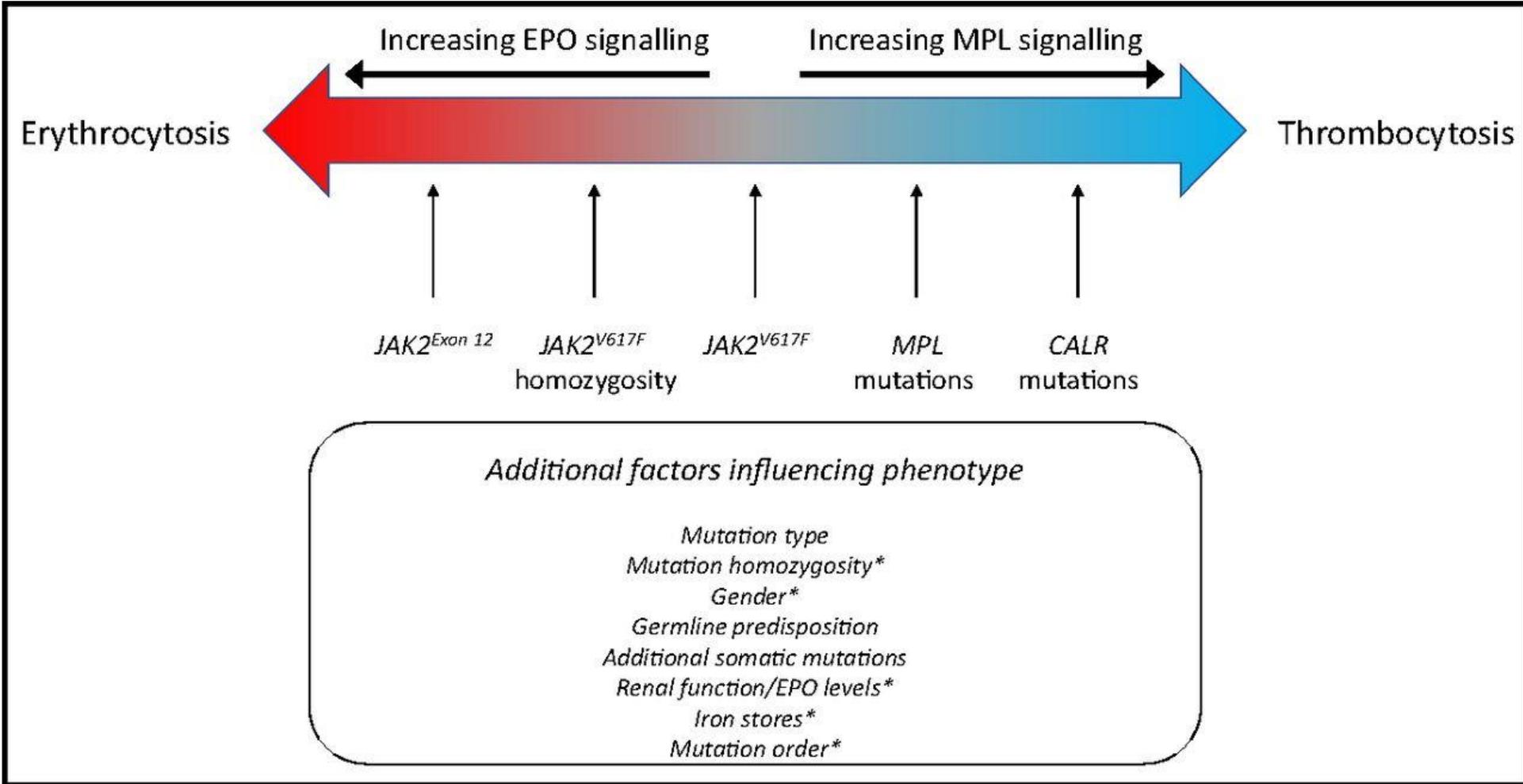


## PMF (early-prefibrotic stage)

- marked increase in age-matched cellularity
- pronounced proliferation of granulopoiesis and reduction of erythroid precursors
- dense or loose clustering and frequent endosteal translocation of medium sized to giant megakaryocytes showing hyperchromatic, hypolobulated, bulbous, or irregularly folded nuclei and an aberrant nuclear/cytoplasmic ratio
- no or no significant increase in reticulin fibers



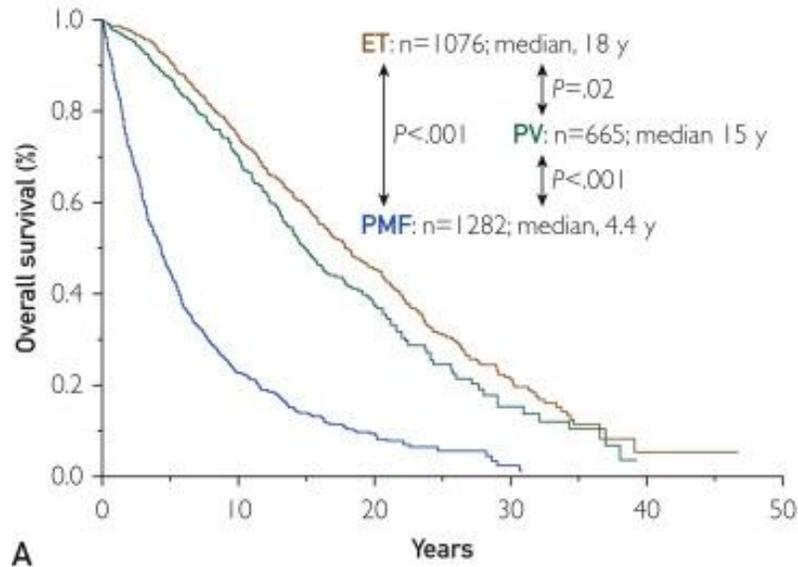
🔴 Megakaryopoiesis; 🔵 Granulopoiesis; 🟡 Erythropoiesis; ⚫ Reticulin fibers



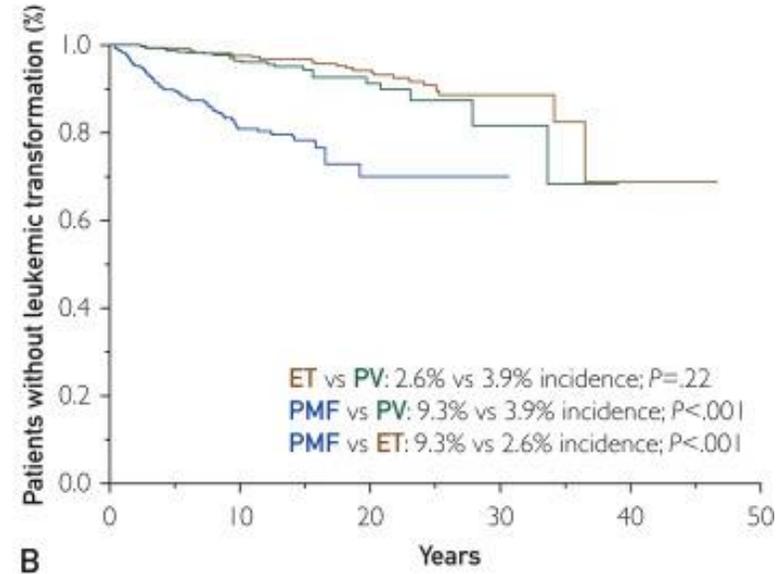
# Objectives

- Background
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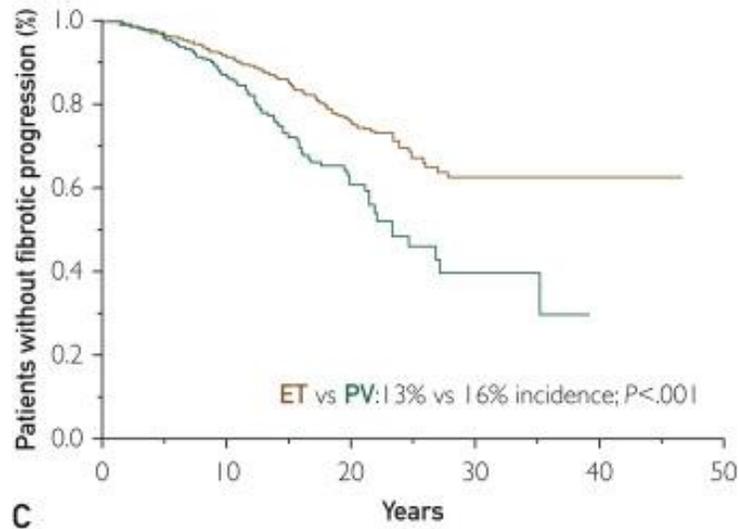
# Prognostication



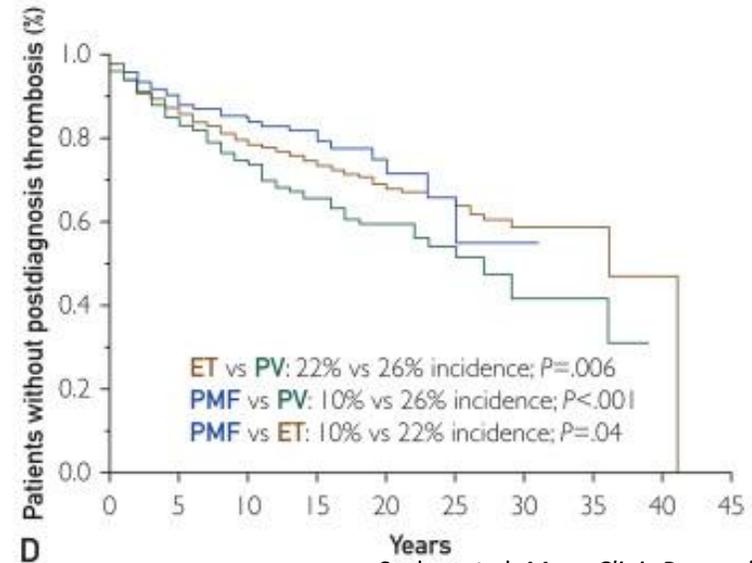
**A**



**B**



**C**

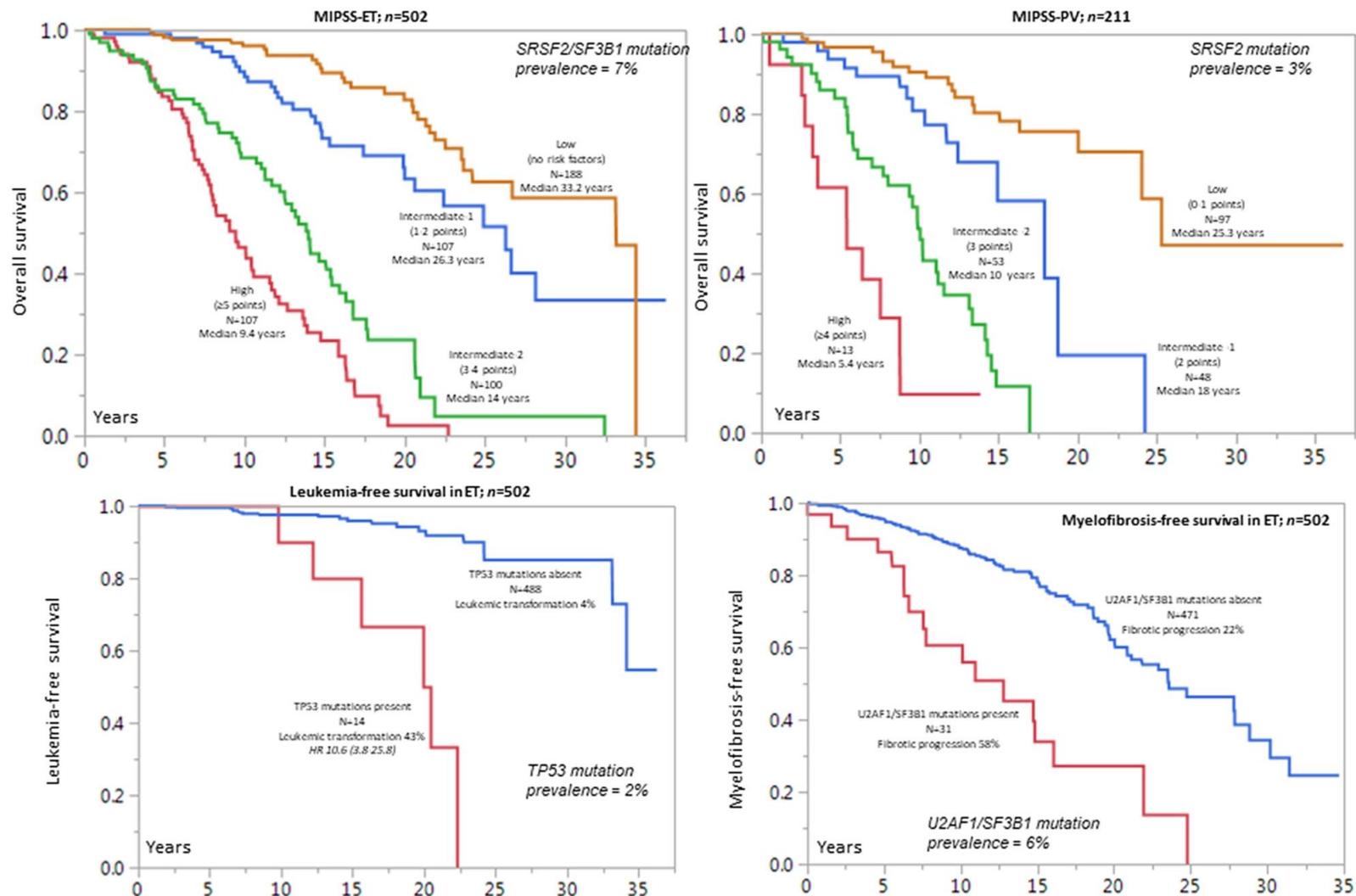


**D**

## Mutation-enhanced international prognostic scoring system (MIPSS) for essential thrombocythemia (ET) and polycythemia vera (PV)

**ET survival risk factors:** *SRSF2/SF3B1* mutations (2 points), age >60 years (4 points) and male sex (1 point)

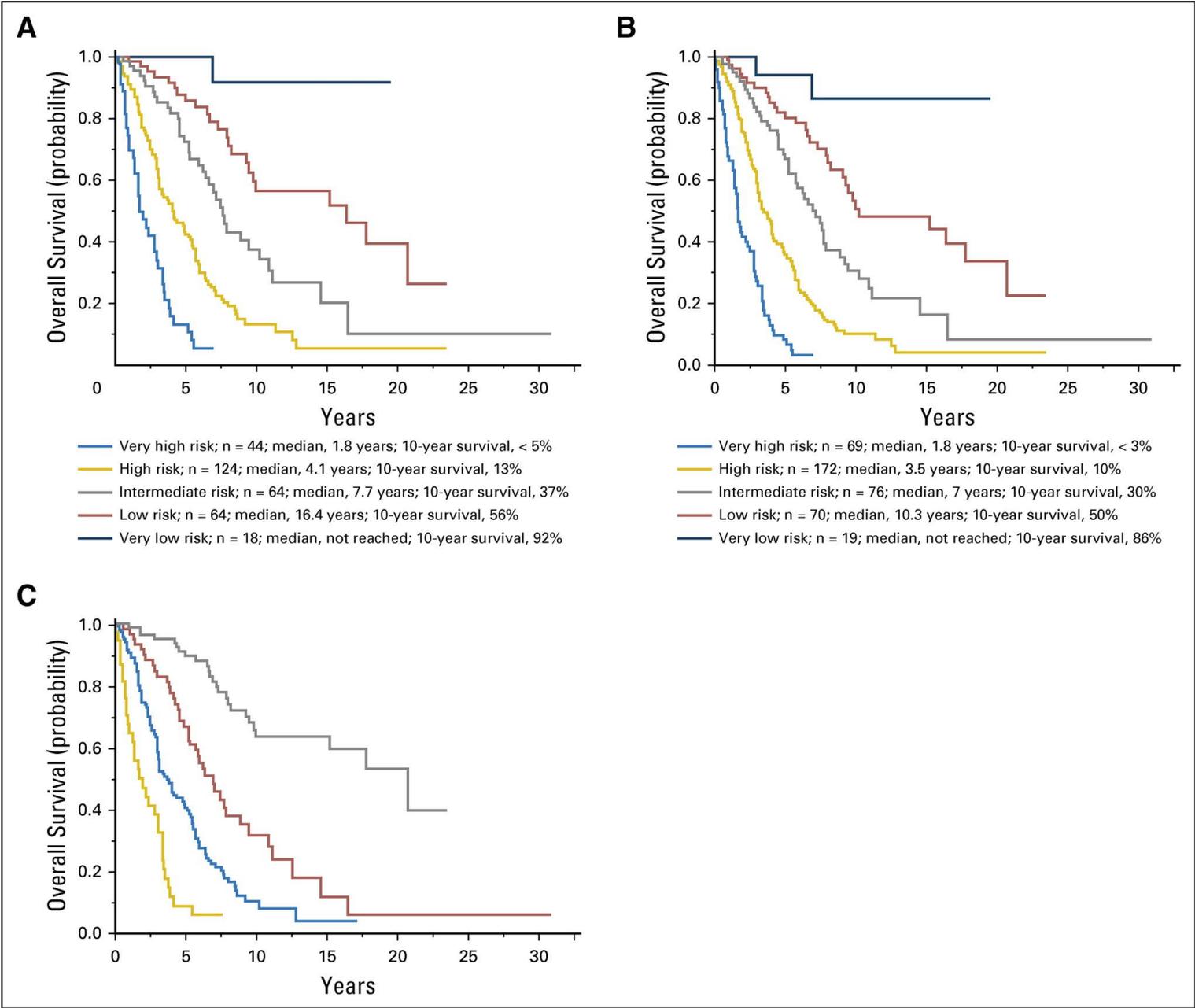
**PV survival risk factors:** *SRSF2* mutations (2 points), age >60 years (2 points), leukocyte count  $\geq 11 \times 10^9/l$  (1 point) and abnormal karyotype (1 point)



Adapted from Tefferi et al. *BJH* 2020;180:201

# Prognosis PMF

- DIPSS
- DIPSS-Plus
- GIPSS
- MIPSS70+ v2.0



# Objectives

- Background
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Treatment



**DIAGNOSIS<sup>l,j</sup>**

**PROGNOSTIC RISK MODEL**

**RISK STRATIFICATION**

Myelofibrosis →

Primary myelofibrosis (PMF)<sup>b</sup>  
 • [MIPSS-70](#) or [MIPSS-70+ Version 2.0 \(preferred\)](#)  
 • [DIPSS-Plus](#) (if molecular testing is not available)  
 or  
 • [DIPSS](#) (if karyotyping is not available)  
 Post-PV or Post-ET MF<sup>c</sup>  
 • [MYSEC-PM](#)

**Lower-risk (MF-1)**

- MIPSS-70: ≤3
- MIPSS-70+ Version 2.0: ≤3
- DIPSS-Plus: ≤1
- DIPSS: ≤2
- MYSEC-PM: <14

**Higher-risk (MF-2)**

- MIPSS-70: ≥4
- MIPSS-70+ Version 2.0: ≥4
- DIPSS-Plus: >1
- DIPSS: >2
- MYSEC-PM: ≥14

Polycythemia vera (PV)<sup>d</sup> →

Conventional risk model<sup>k</sup>

**Low-risk (PV-1)**

- Age <60 years and no prior history of thrombosis

**High-risk (PV-2)**

- Age ≥60 years and/or prior history of thrombosis

Essential thrombocythemia (ET) →

IPSET-thrombosis (revised)<sup>l</sup>

**Very-low-risk (ET-1)**

- Age ≤60 years, no *JAK2* mutation, no prior history of thrombosis

**Low-risk (ET-1)**

- Age ≤60 years, with *JAK2* mutation, no prior history of thrombosis

**Intermediate-risk (ET-2)**

- Age >60 years, no *JAK2* mutation, no prior history of thrombosis

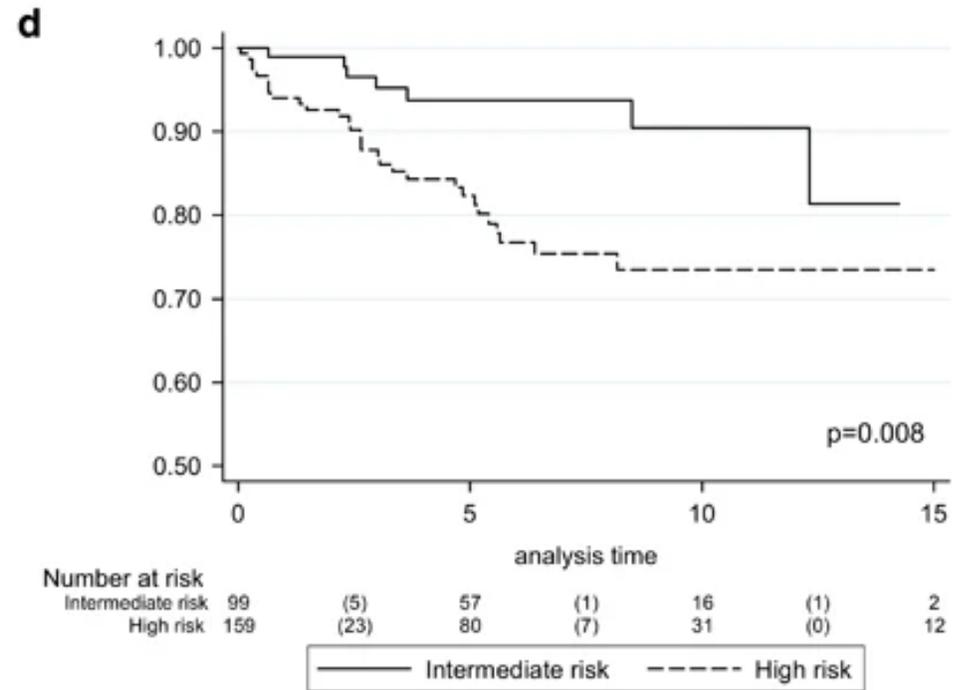
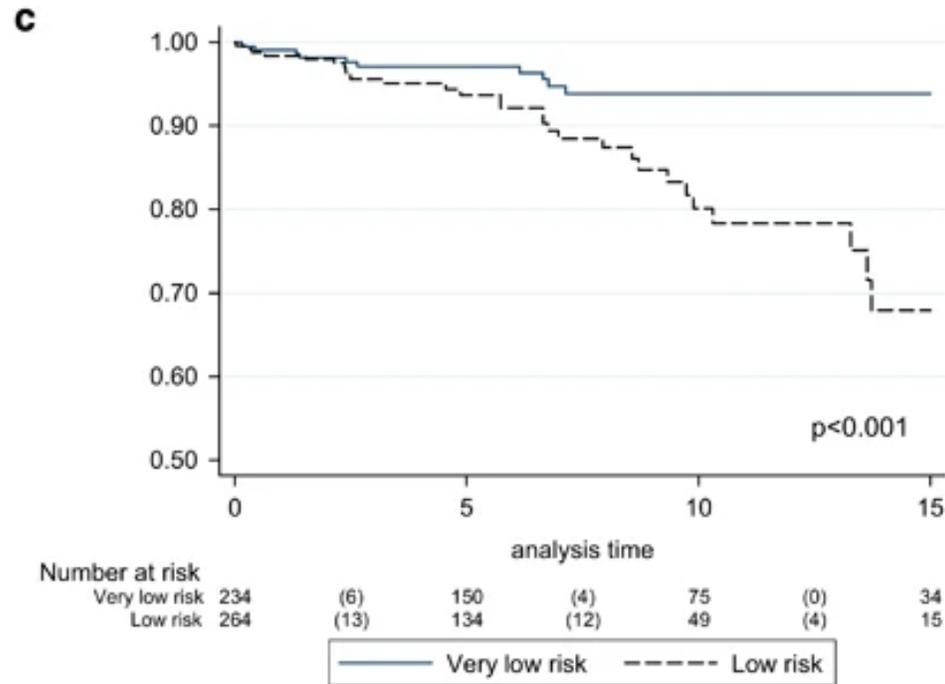
**High-risk (ET-3)**

- History of thrombosis at any age or age >60 years with *JAK2* mutation

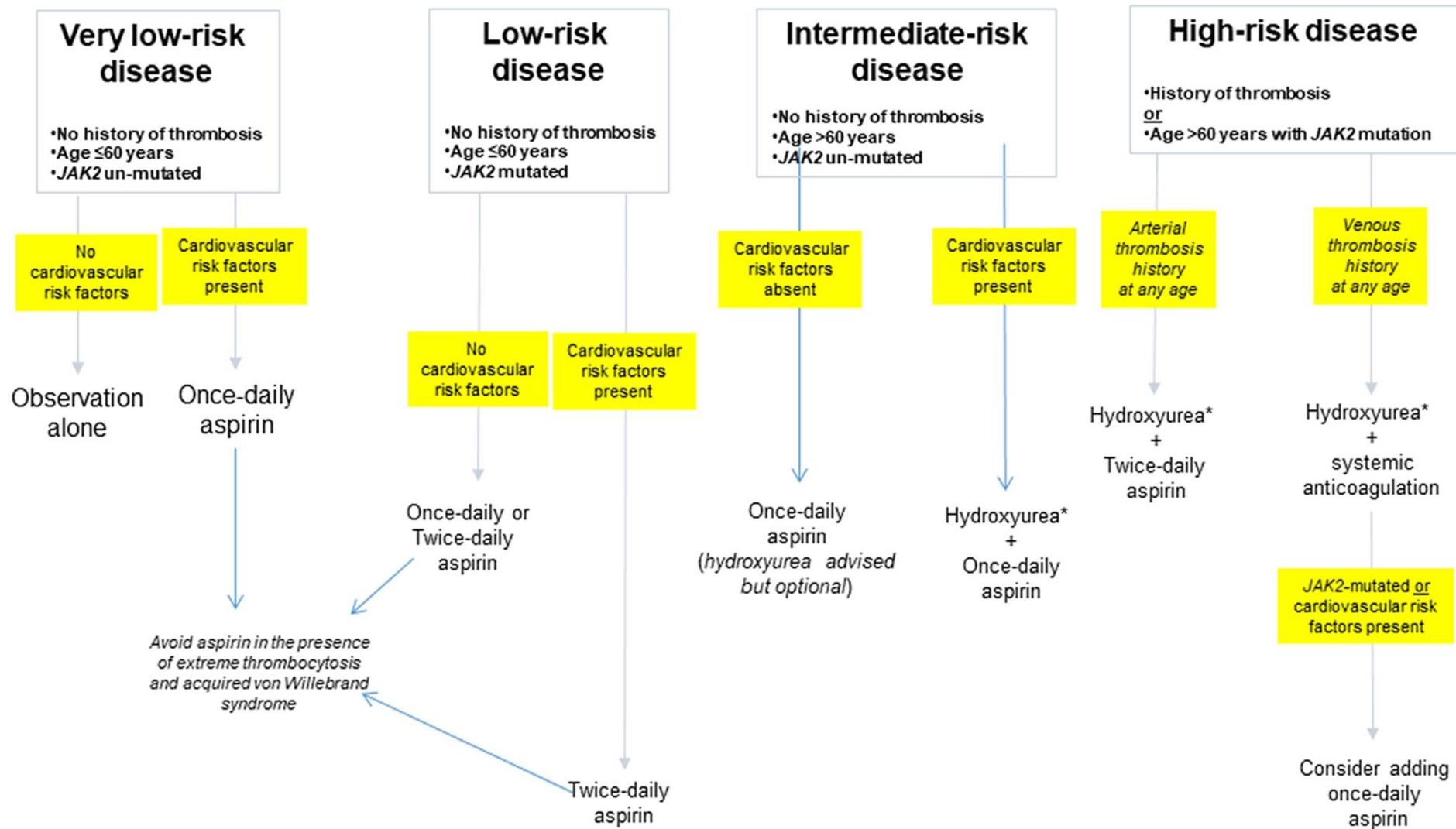
[See Footnotes on MPN-2A](#)

# Treatment- Essential Thrombocythemia

# Thrombosis Risk in ET



# Current Treatment Recommendations in Essential Thrombocythemia



\*Second-line treatment in hydroxyurea intolerant or refractory patients is pegylated IFN-alpha or busulfan

# Cytoreduction in ET

## Hydroxyurea

- HU vs Placebo – Cortelazzo NEJM 1995
- HU vs Anagrelide– Harrison NEJM 2005

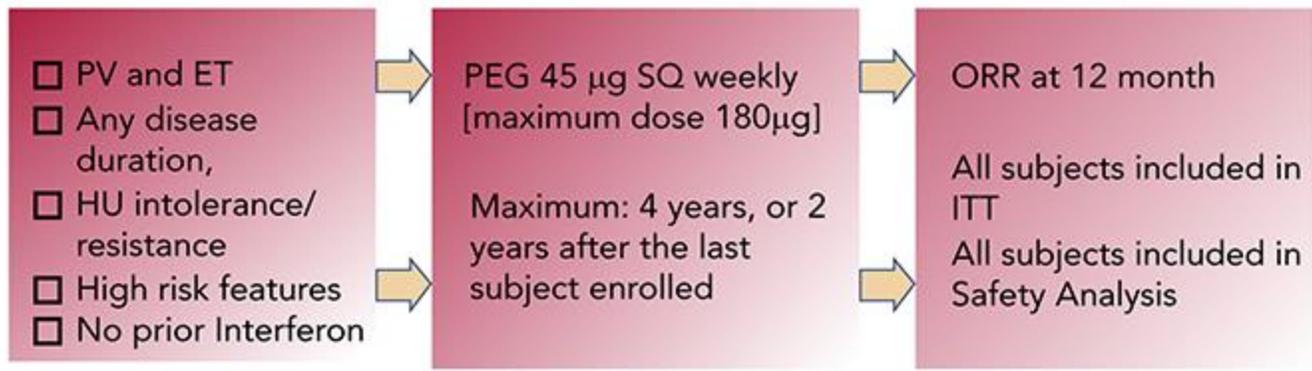
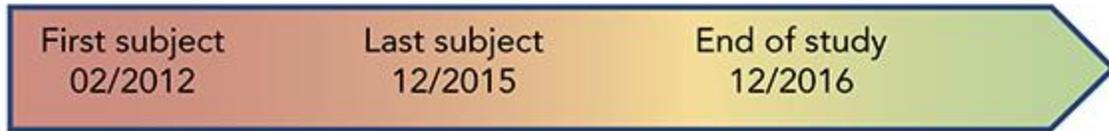
## Pegylated Interferon

- Single-arm studies
  - Phase II trial– Masarova et al, Lancet Onco. 2017
- Langer et al., Haematologica 2005
- Cassinat et al., NEJM 2014

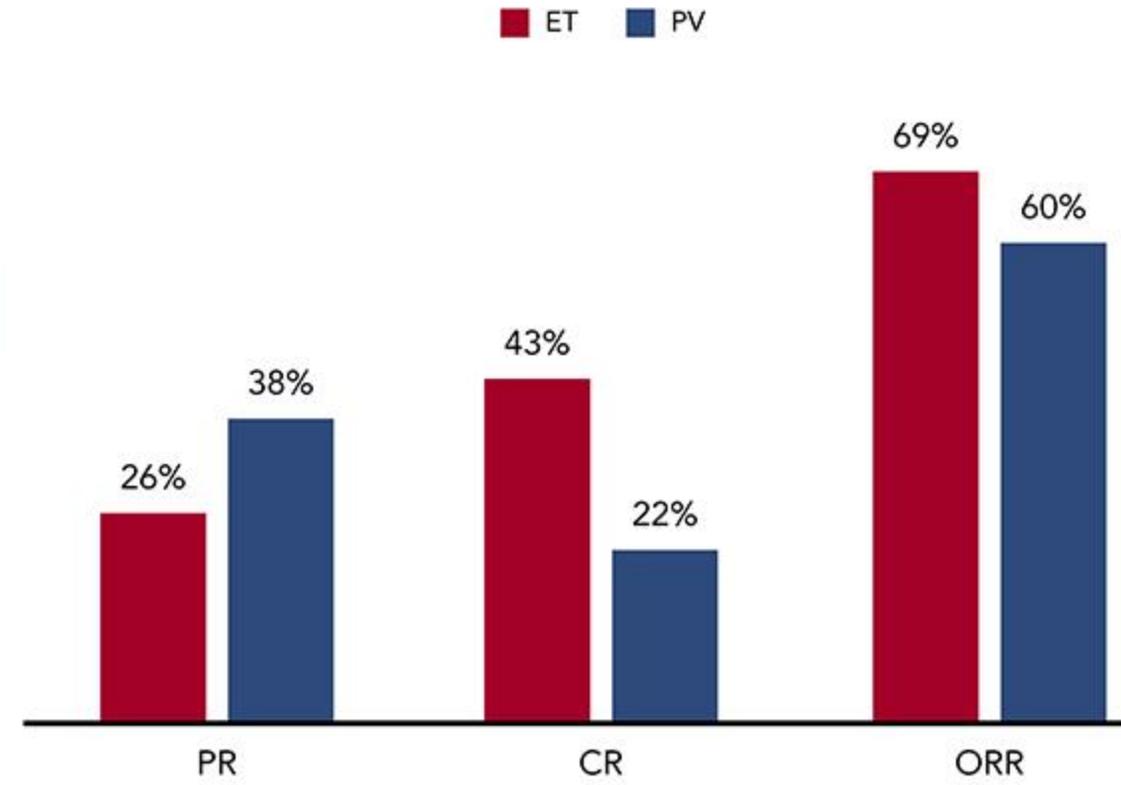
## Anagrelide

- HU vs Anagrelide – Gisslinger Blood 2013

## Study Procedures



## Primary End Point at 12 Months



Pegylated Interferon Alfa-2a for Polycythemia Vera or Essential Thrombocythemia Resistant or Intolerant to Hydroxyurea

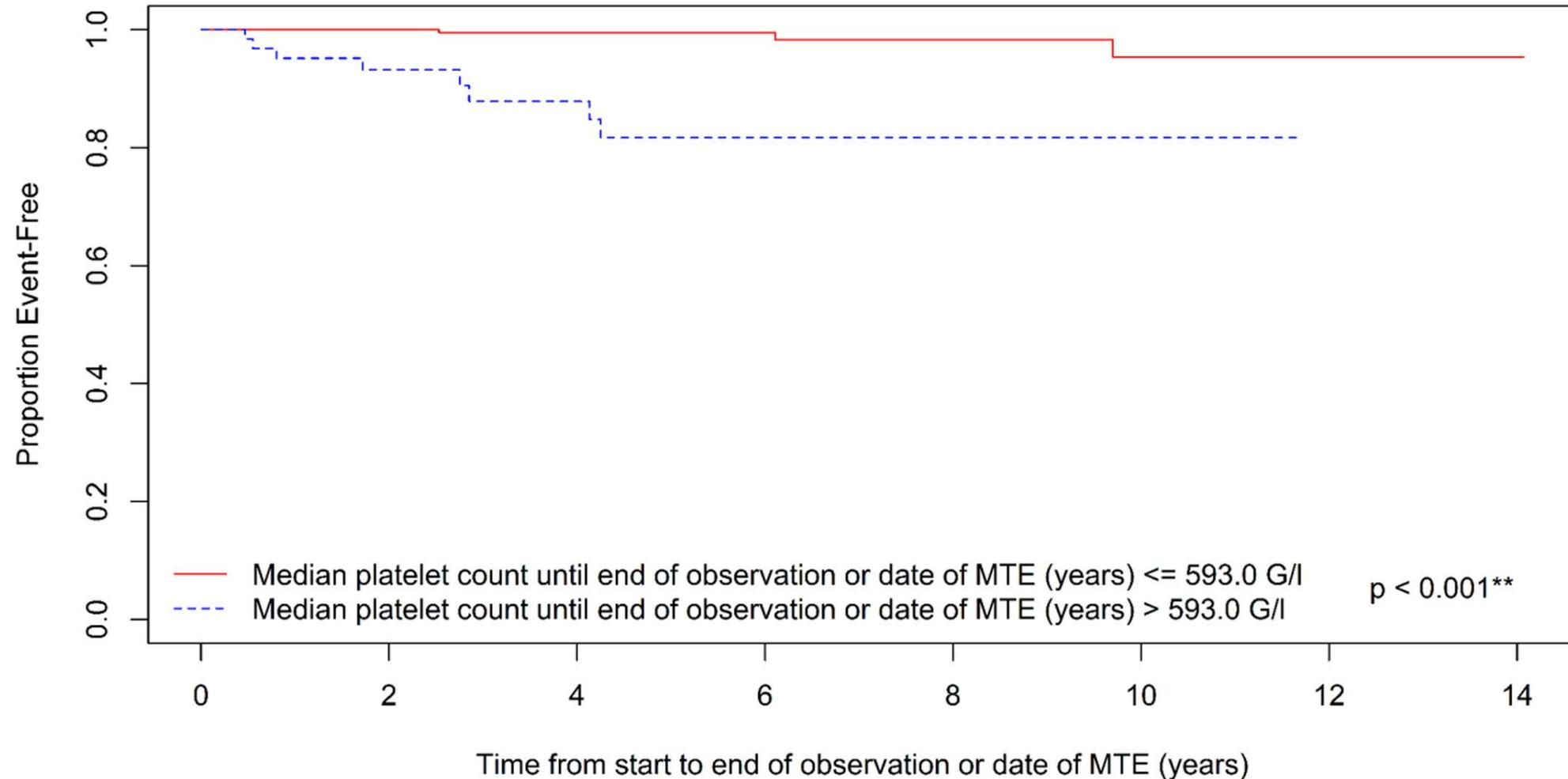
**Table 1. Listing of clinical studies evaluating the role of interferon in the treatment and management of myeloproliferative neoplasms. (Table view)**

First study (year)	ET patients (n)	Response rate (%)	Discontinuation, n (%)	Type of IFN
Giles (1988)	18	100	0	2a and 2b
Bellucci (1988)	12	NA	4 (33)	2a
Gugliotta (1989)	10	100	NA	2a
Lazzarino (1989)	26	86	9 (35)	2b
Gisslinger (1991)	20	85	10 (50)	2c
Kasparu (1992)	14	86	0	2b
Berte (1996)	12	83	NA	2a/2b
Alvarado (2003)	11	100	2 (18)	PEG-2b
Saba (2005)	20	75	3 (15)	2a
Langer (2005)	36	75	13 (36)	PEG-2b
Samuelsson (2006)	21	70	11 (55)	PEG-2b
Jabbour (2007)	13	70	NA	PEG-2b
Quintás-Cardama (2009 and 2013)	39	81	NA	PEG-2a
Verger (2015)	31	100	39%	PEG-2b
Mascarenhas <i>et al.</i> (2016)	31	80	NR	PEG-2a
Gowin (2017)	20	65	NA	PEG-2a

ET: Essential thrombocythemia; IFN: Interferon; MPN: Myeloproliferative neoplasms; NA: Not applicable; NR: Not reported.

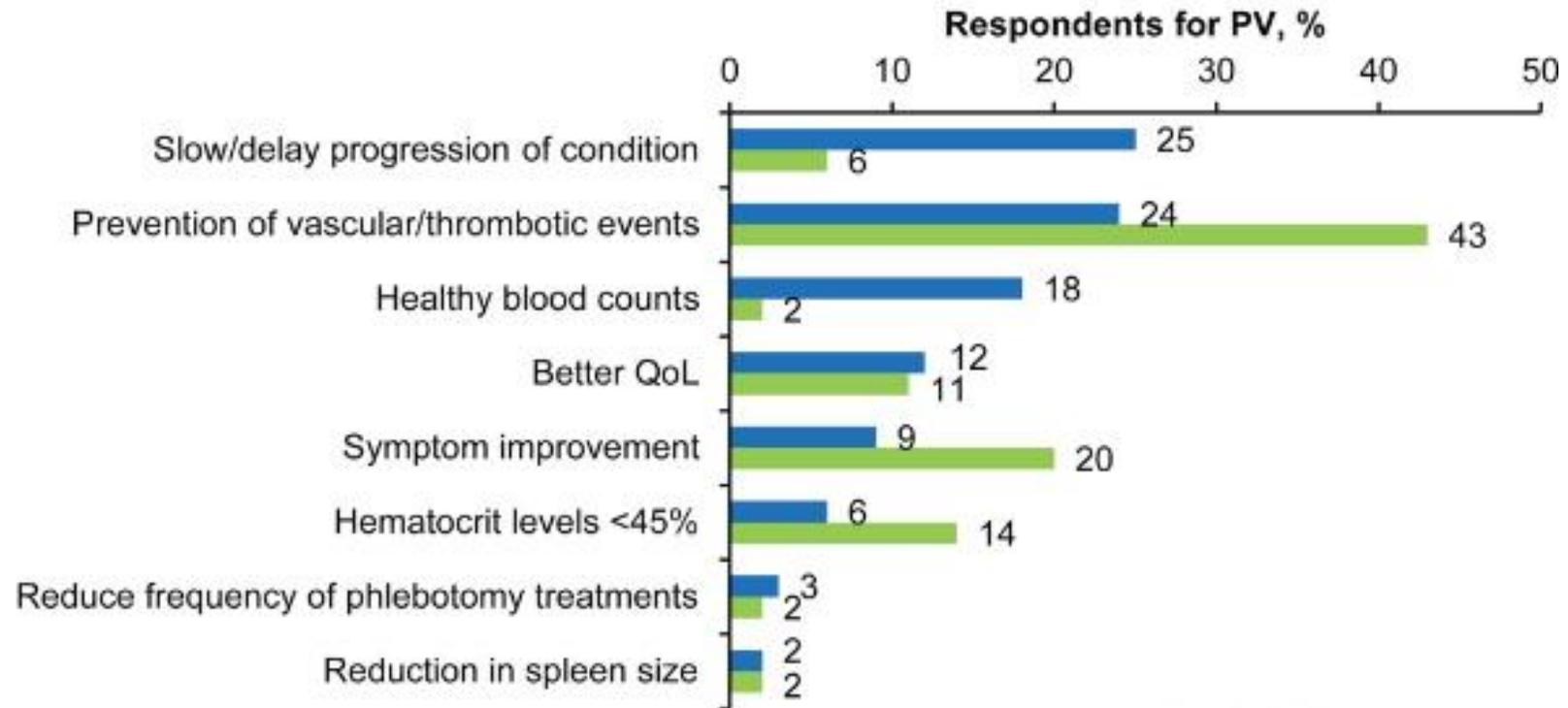
# Impact of platelets on major thrombosis in patients with a normal white blood cell count in

**Kaplan-Meier Plot**



Treatment- Polycythemia Vera

# Goals for PV therapy



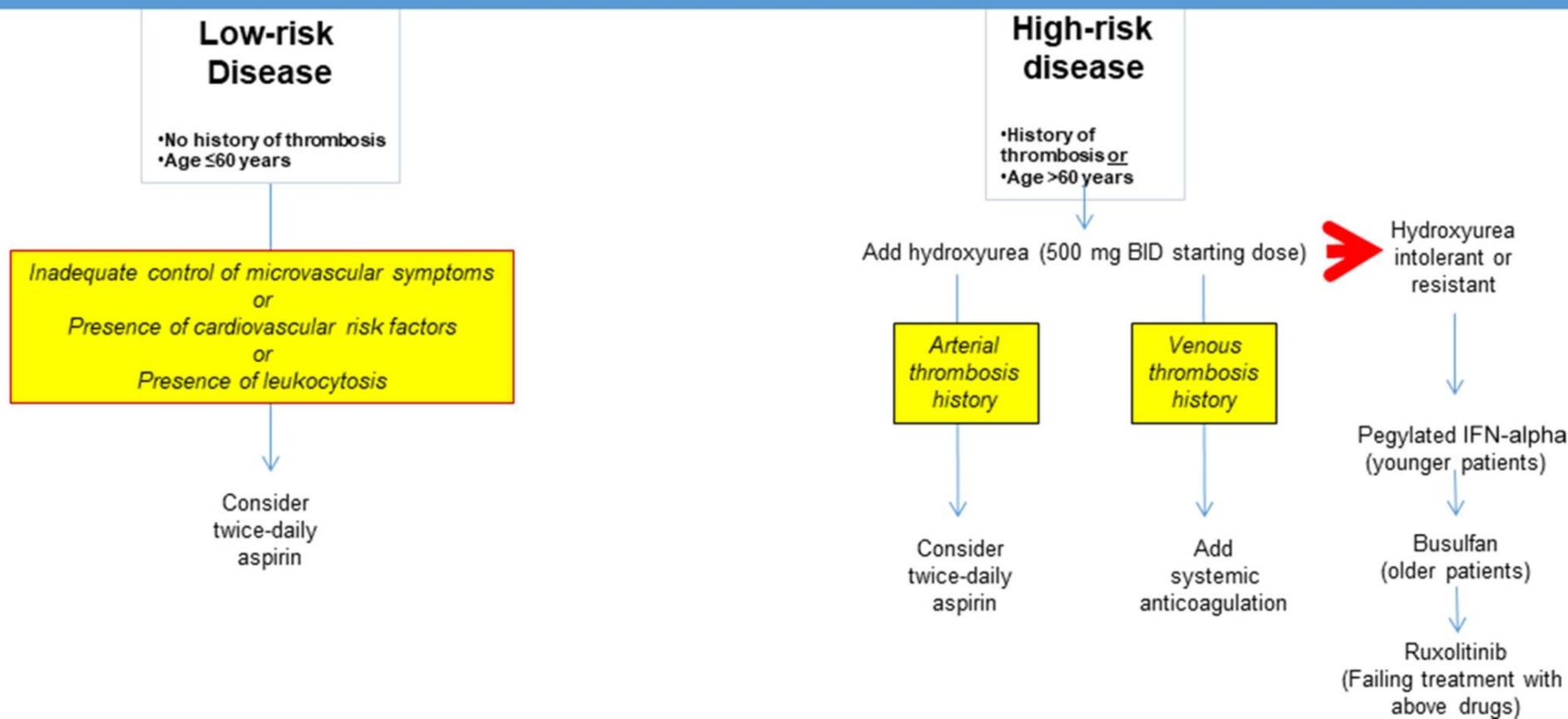
# Current Treatment Recommendations in Polycythemia Vera



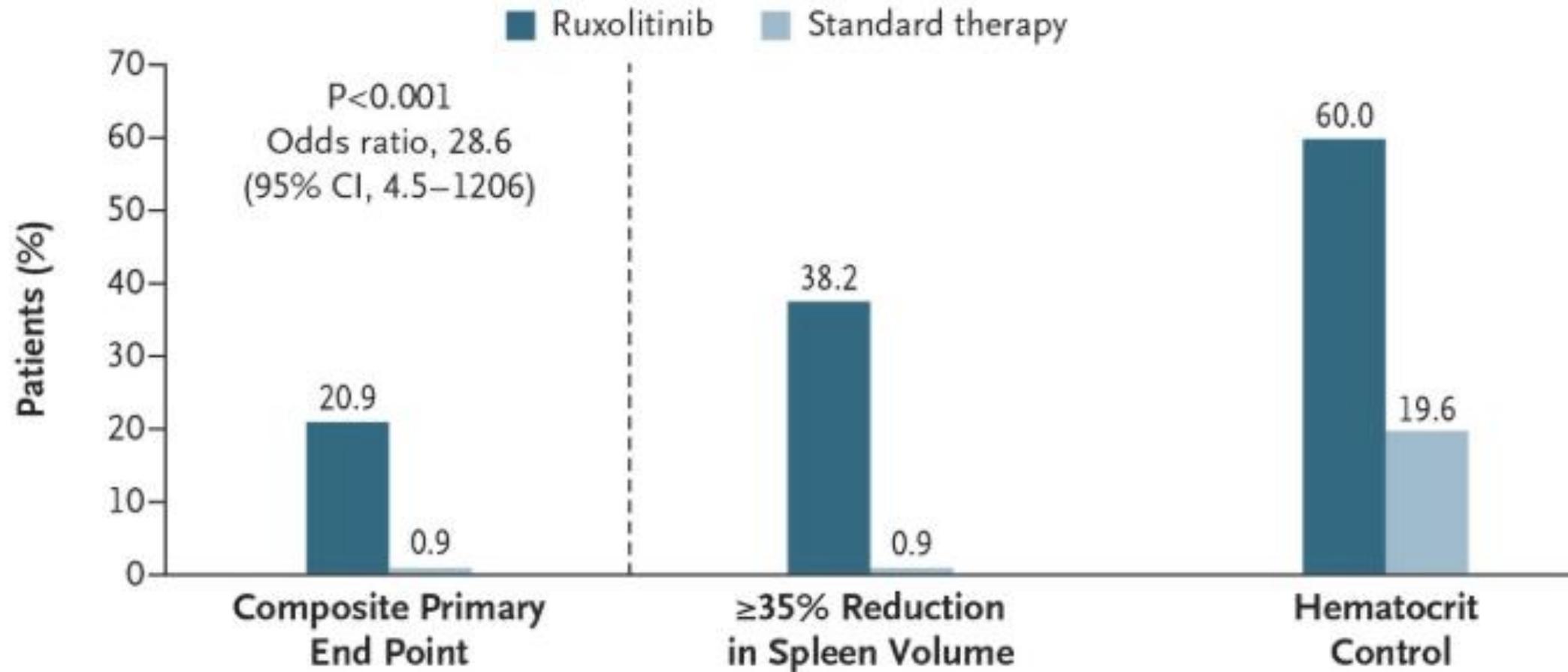
Phlebotomy to hematocrit <45% in both males and females

+

Once-daily low-dose aspirin (40-100 mg)

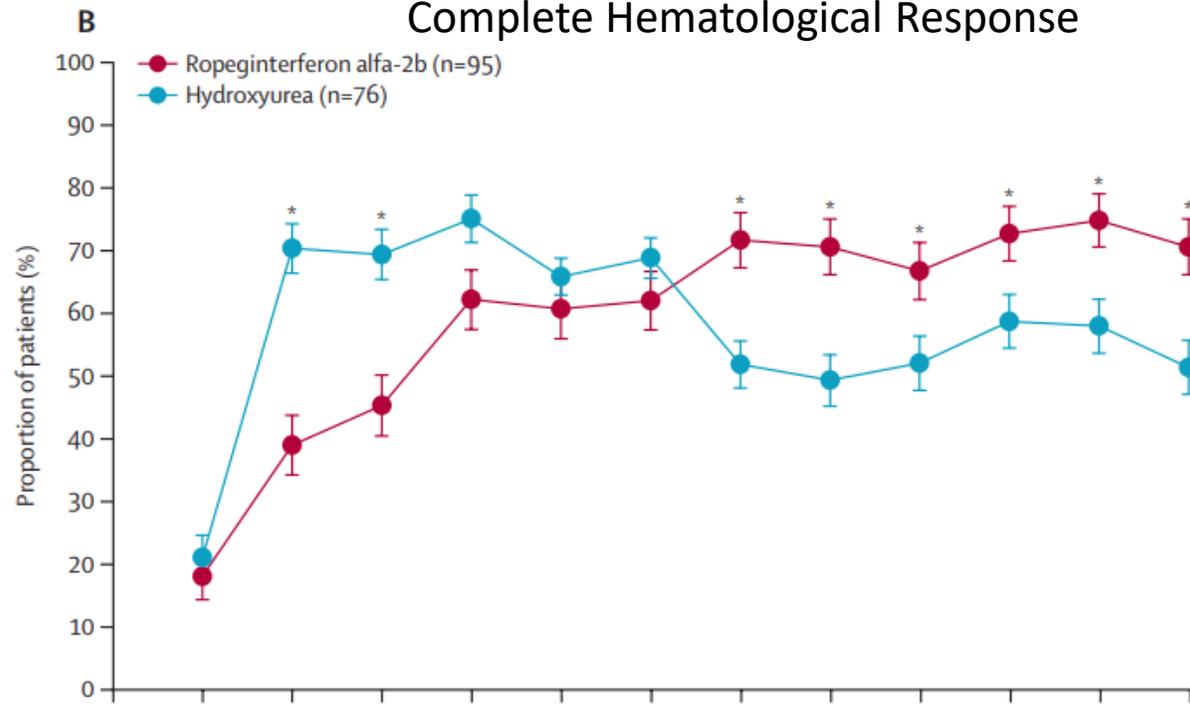


# RESPONSE

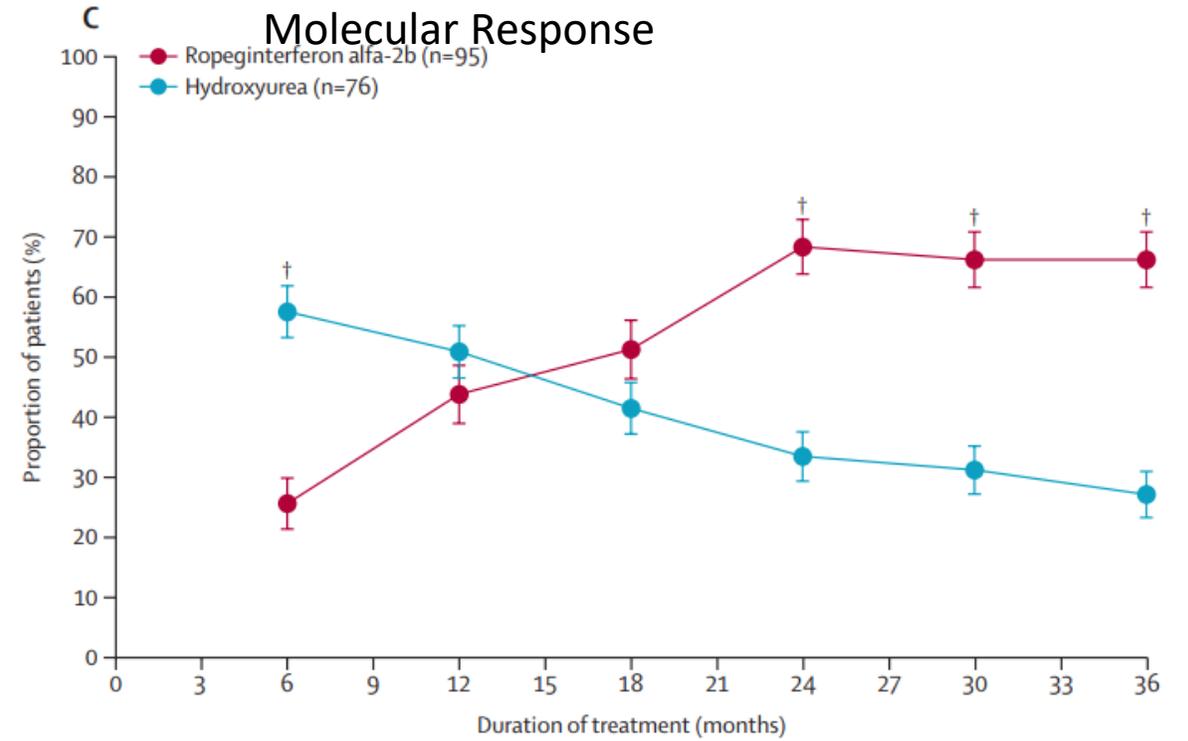


# Proud-PV

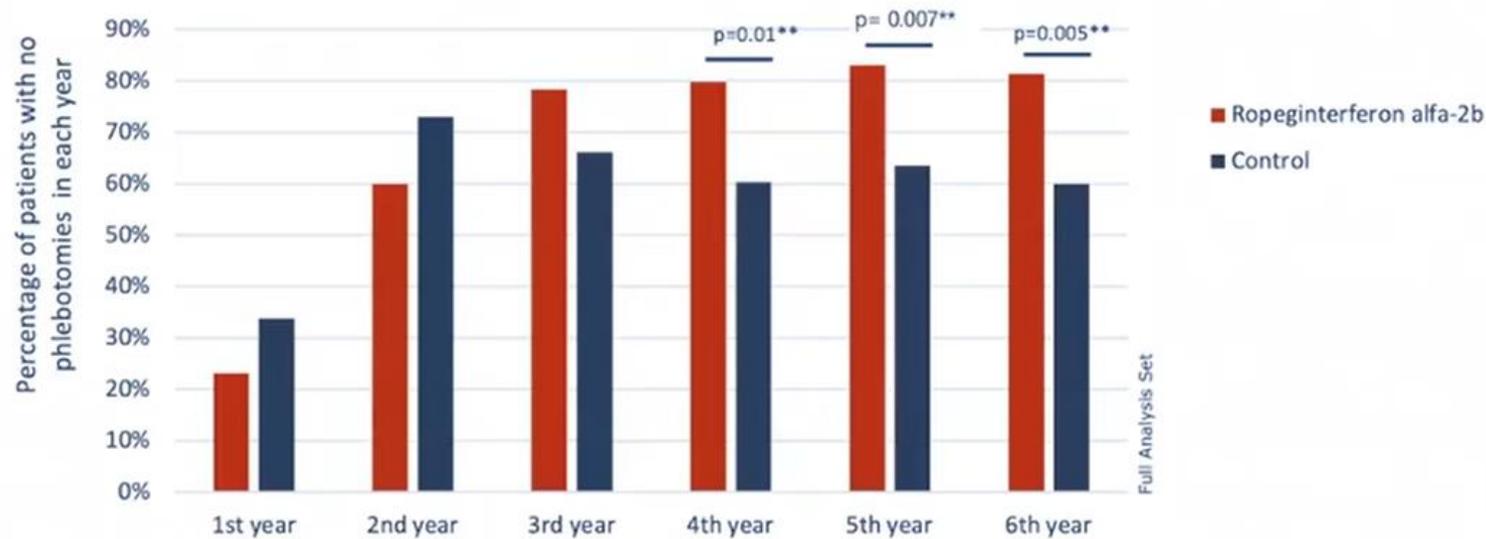
## B Complete Hematological Response



## C Molecular Response



## Freedom from phlebotomy



In the 6<sup>th</sup> year of treatment, no phlebotomies were required to maintain hematocrit <45% in 81.4% of patients receiving ropeginterferon alfa-2b compared with 60.0% of patients in the control arm (p=0.005).

\*Among patients with available data for each treatment year \*\*Likelihood of ratio test (incidence ratio for no phlebotomy vs at least 1 phlebotomy)

Treatment- Myelofibrosis

# Myelofibrosis

DIPSS and DIPSS-Plus Risk Score = 0  
MIPSS70 = 0 or 1  
MIPSS70+ v2 = ≤2  
MYSEC-PM = <11

DIPSS-Plus = 1 and DIPSS = 1 or 2  
MIPSS70 = 2 - 4  
MIPSS+ v2 = 3 or 4  
MYSEC-PM = 11 - <14

DIPSS-Plus = ≥2 and DIPSS = ≥3  
MIPSS70 = ≥5  
MIPSS70+ v2 = ≥5  
MYSEC-PM = ≥14

Clinical trial if available

**Low-Risk**

**Intermediate-risk**

**High-risk**

*Symptomatic*

*Asymptomatic*

Cytogenetic and molecular studies

*High-risk features present\**

*No high-risk features or anemia, asymptomatic*

*No high-risk features or anemia, symptomatic*

*Anemia alone, asymptomatic*

*Serum EPO <500*

*Serum EPO >500*

Transplant candidate

Ruxolitinib

Allo-HCT

Ruxolitinib or Interferons

Observation

Ruxolitinib

Erythropoiesis stimulating agent

Danazol or Lenalidomide

Platelets >50

Ruxolitinib

Platelets <50

Clinical trial

Gerds, A., et al. Hematology 2019.

# Approved Myelofibrosis Therapy

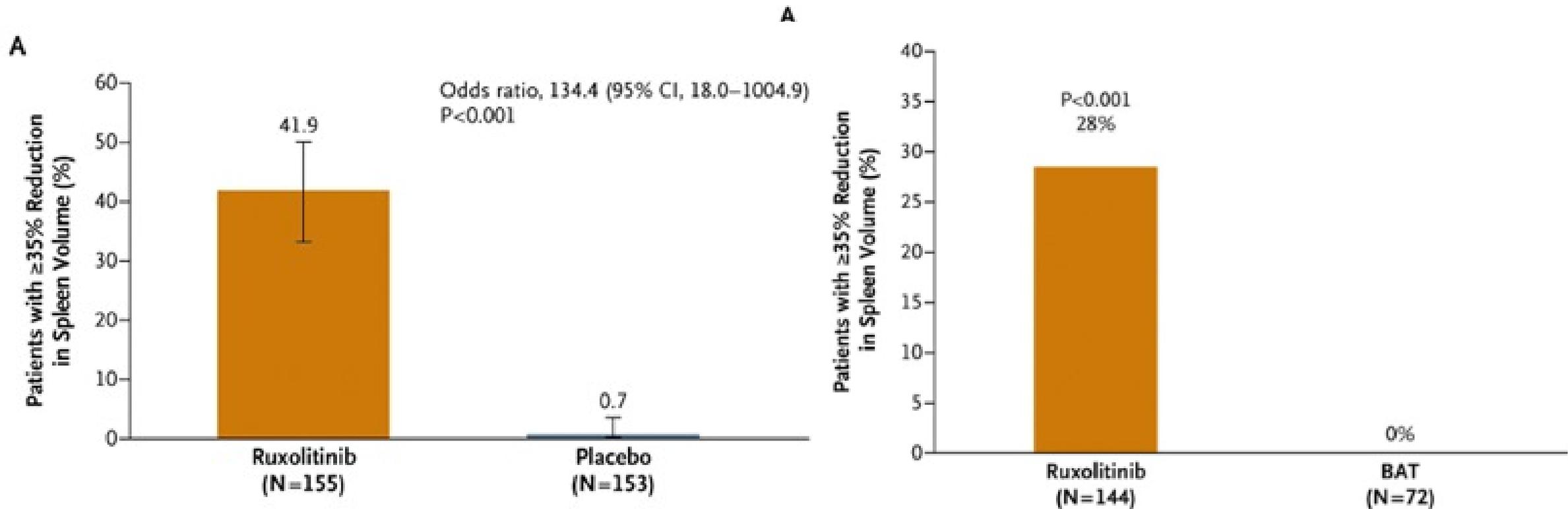
## Approved

- Ruxolitinib
  - 1<sup>st</sup> Line
- Fedratinib
  - 1<sup>st</sup> Line, 2<sup>nd</sup> line
- Pacritinib
  - 1<sup>st</sup> Line Low PLT, 2<sup>nd</sup> Line

## Seeking Approval

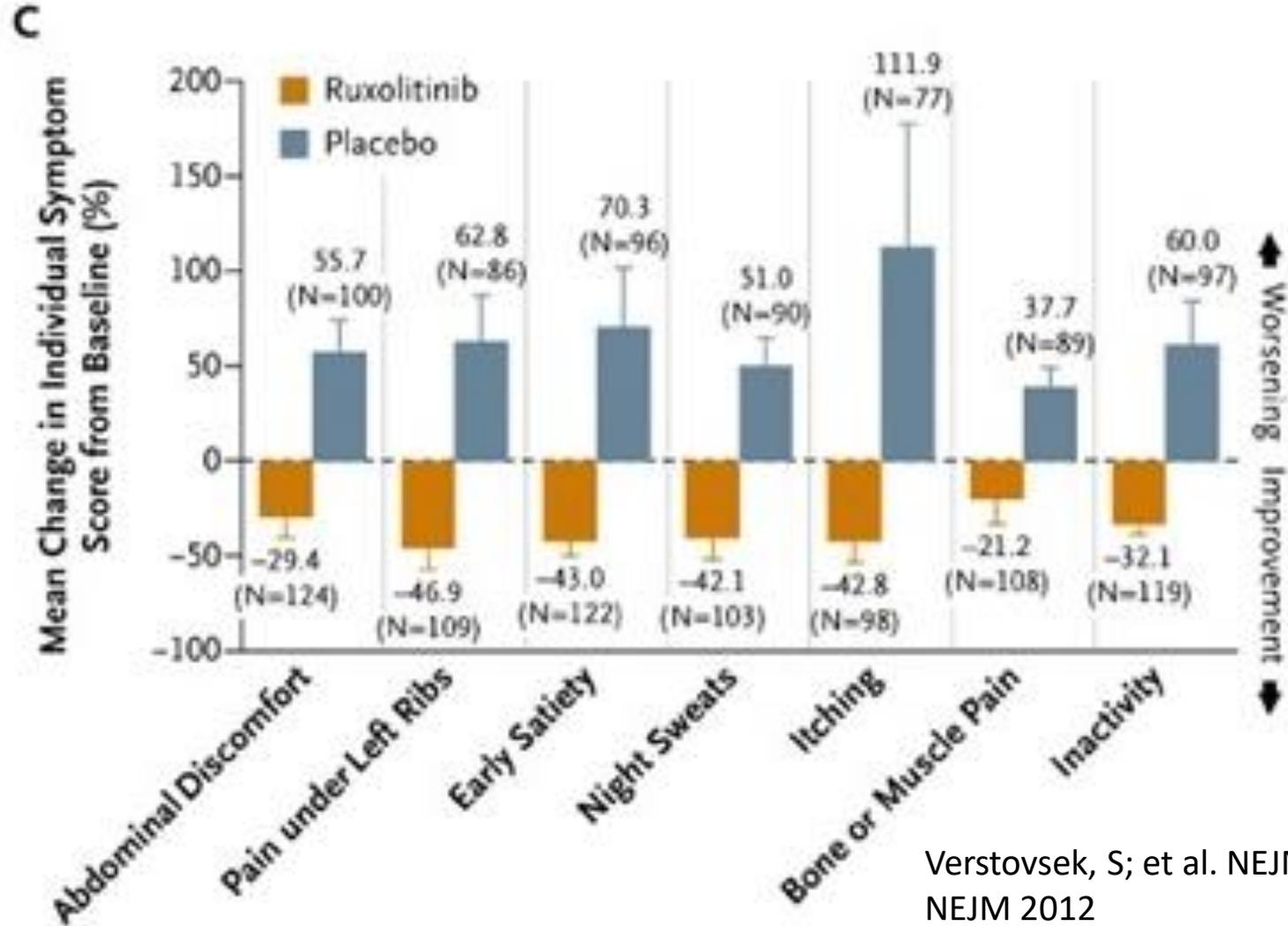
- Momelotinib
- Ruxolitinib Combinations

# JAK Inhibitor: COMFORT-1 and COMFORT-2



Verstovsek, S; et al. NEJM 2012. Harrison, C; et al. NEJM 2012

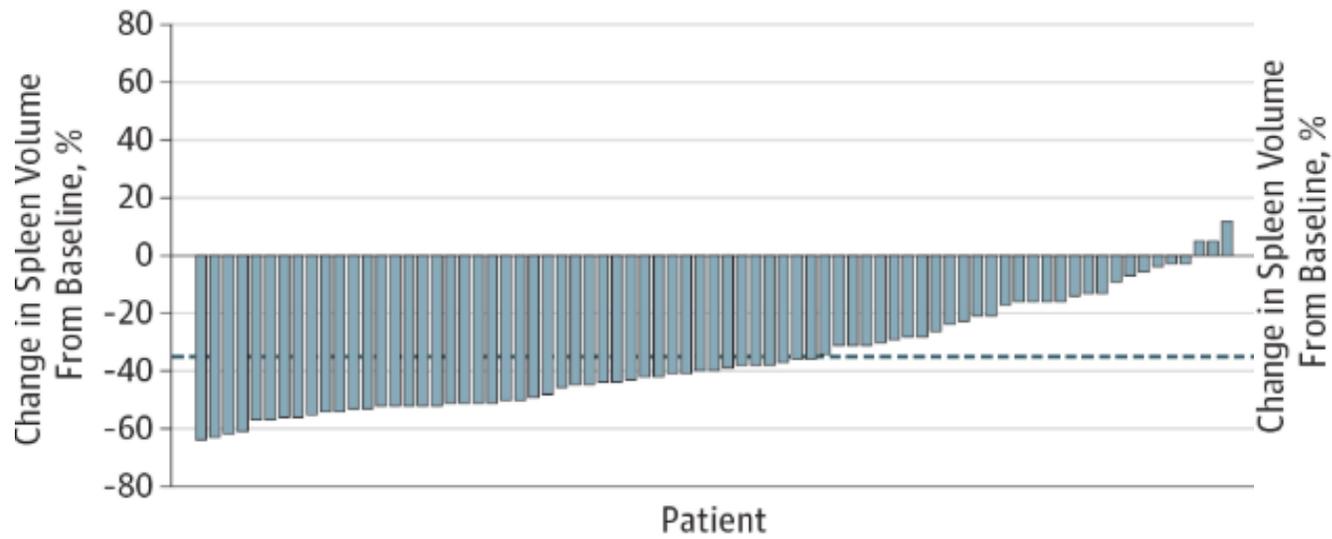
# COMFORT-1



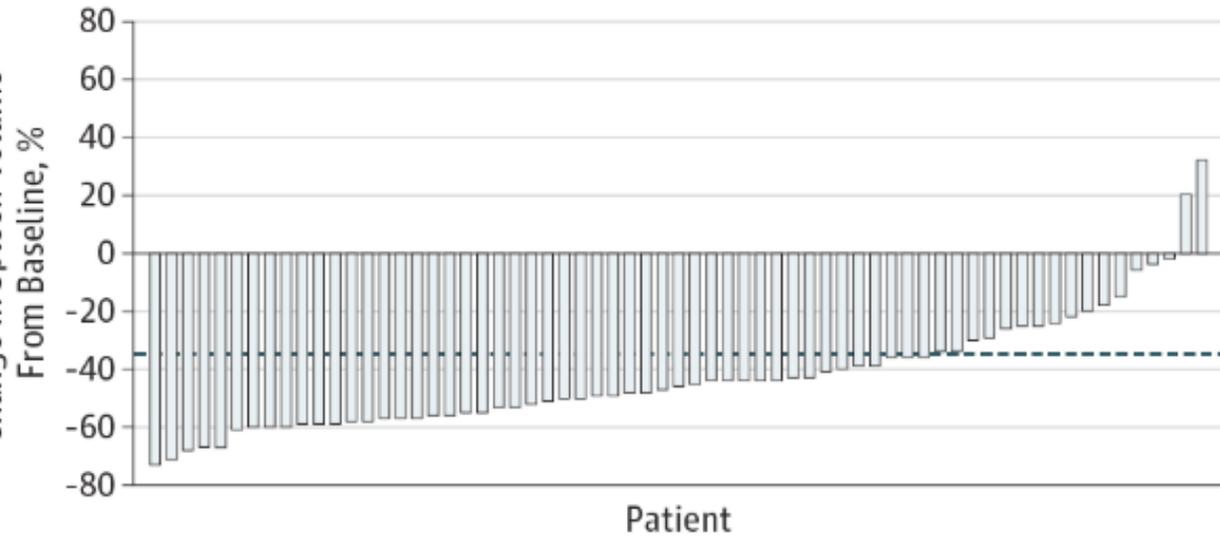
Verstovsek, S; et al. NEJM 2012. Harrison, C; et al. NEJM 2012

# JAKARTA

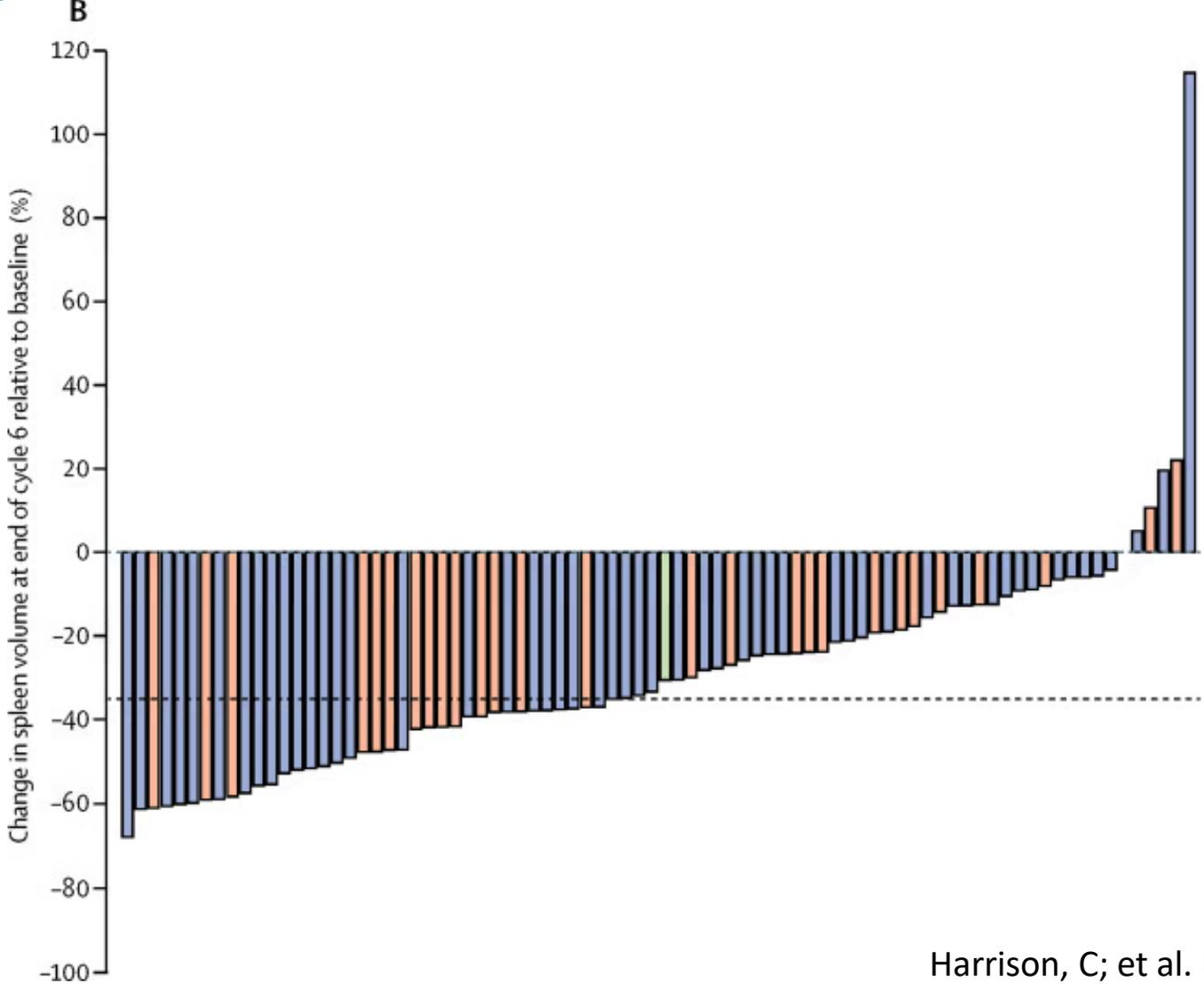
Fedratinib 400 mg



Fedratinib 500 mg

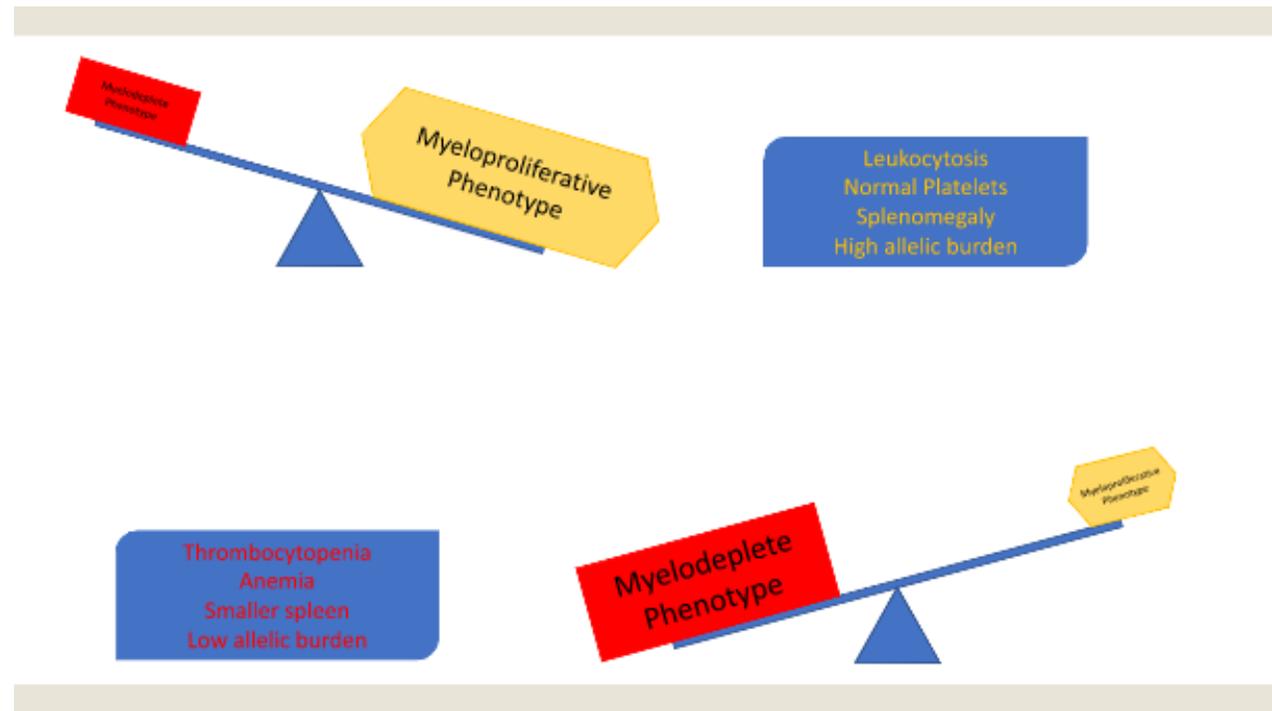


# JAKARTA-2



Harrison, C; et al. Lancet 2017.

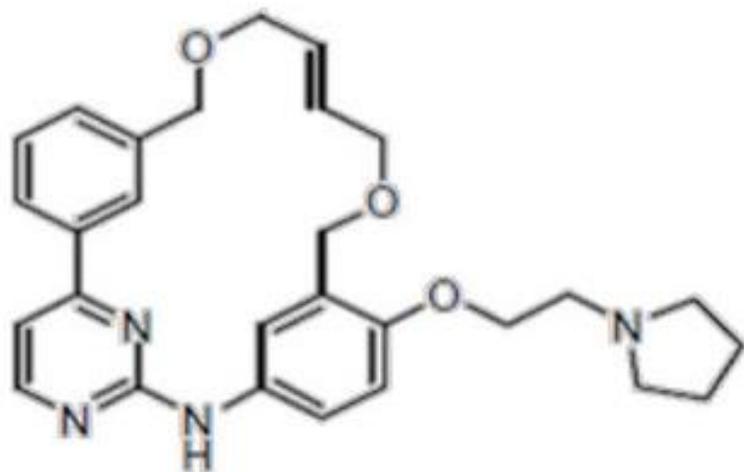
# Proliferative MF vs Cytopenic MF



Parameter	Prognostic Significance	Supporting Data
Platelet count $< 100 \times 10^9/L$ ; PMF	Decreased survival (1.8 vs. 11.2 y)	Patnaik et al <sup>4</sup>
Platelet count $< 150 \times 10^9/L$ ; PPV/PET-MF	Decreased survival	Passamonti et al <sup>5</sup>
Platelet count $< 50 \times 10^9/L$ ; PMF	Increased leukemic transformation; decreased survival	Ahmad et al, <sup>6</sup> Hernandez-Boluda et al, <sup>7</sup> Masarova et al <sup>8</sup>
Platelet count $< 50 \times 10^9/L$ ; PPV/PET-MF	Increased leukemic transformation; decreased survival	Ahmad et al, <sup>6</sup> Hernandez-Boluda et al, <sup>7</sup> Masarova et al <sup>8</sup>

# Pacritinib

An oral kinase inhibitor with selectivity for JAK2 and FLT3

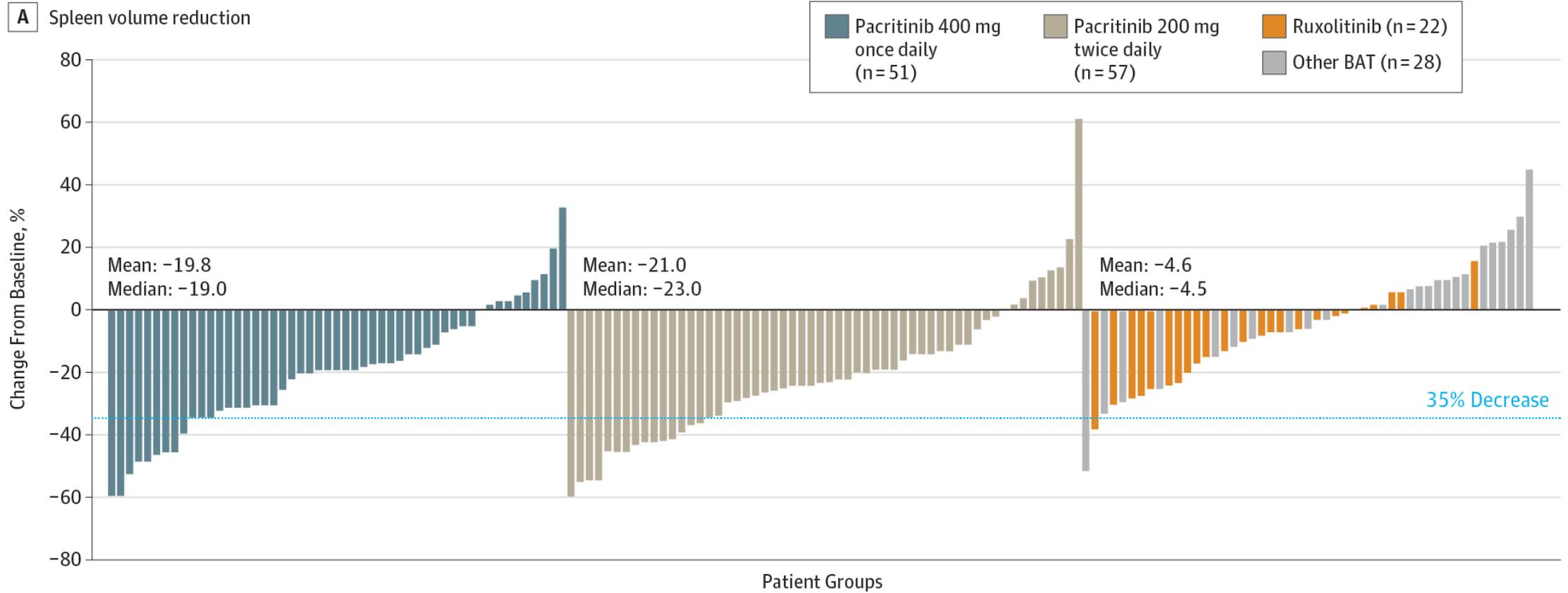


Kinase <sup>1</sup>	IC <sub>50</sub> (nM)
JAK1	1280
JAK2 <sup>wt</sup>	6.0
JAK2 <sup>V617F</sup>	9.4
JAK3	18.3
TYK2	27.0
FLT3-ITD	13.4
FLT3 <sup>D835Y</sup>	4.7
CSF1R	39.5
IRAK1	13.6

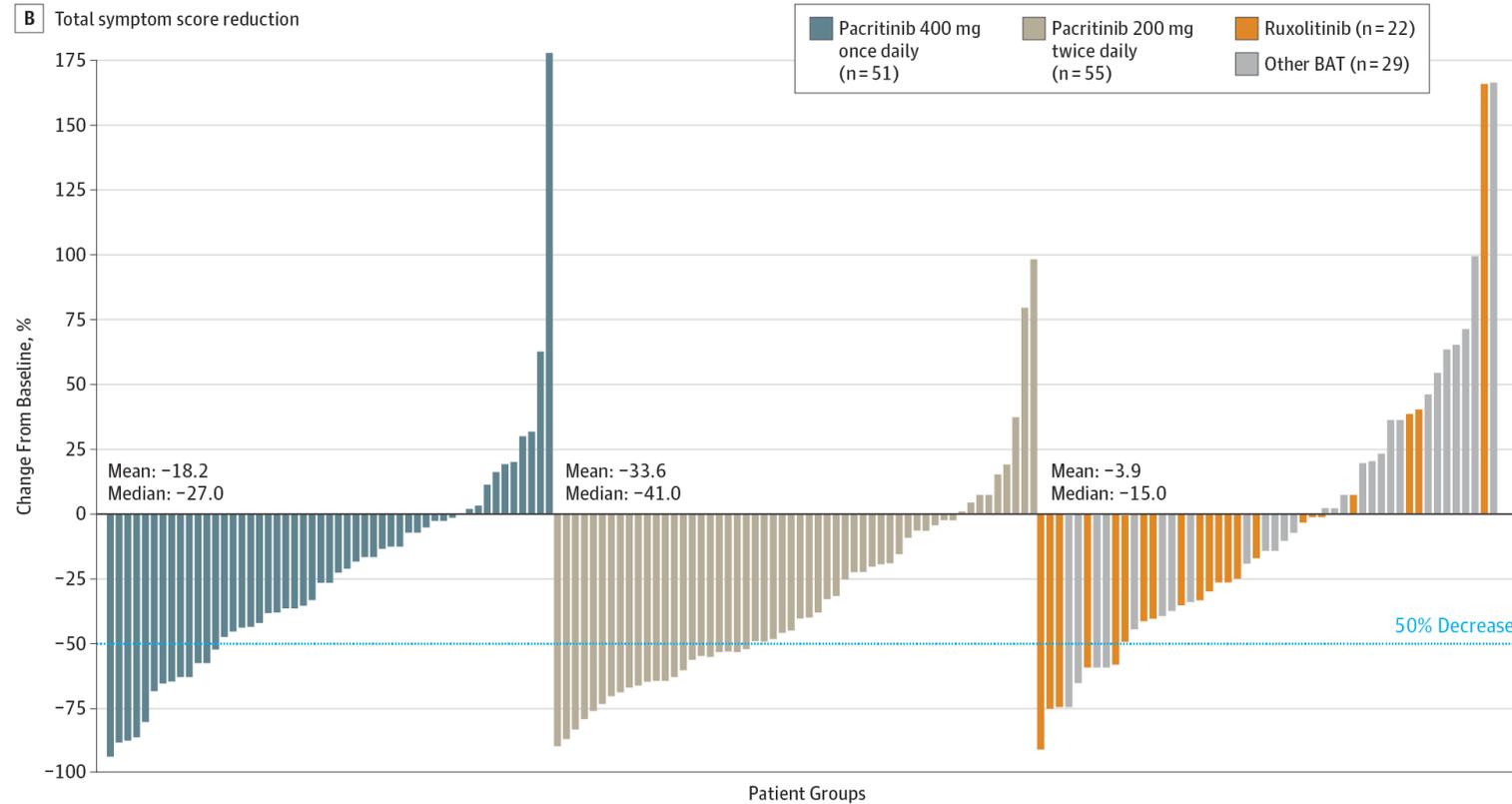
1. Singer J, et al. ASH, 2014, Abstract 1874.

CSF1R, colony stimulating factor 1 receptor; FLT, FMS-like tyrosine kinase; IC<sub>50</sub>, half-maximal inhibitory concentration; IRAK, interleukin-1 receptor-associated kinase; ITD, internal tandem duplication; JAK, Janus kinase; TYK, tyrosine kinase.

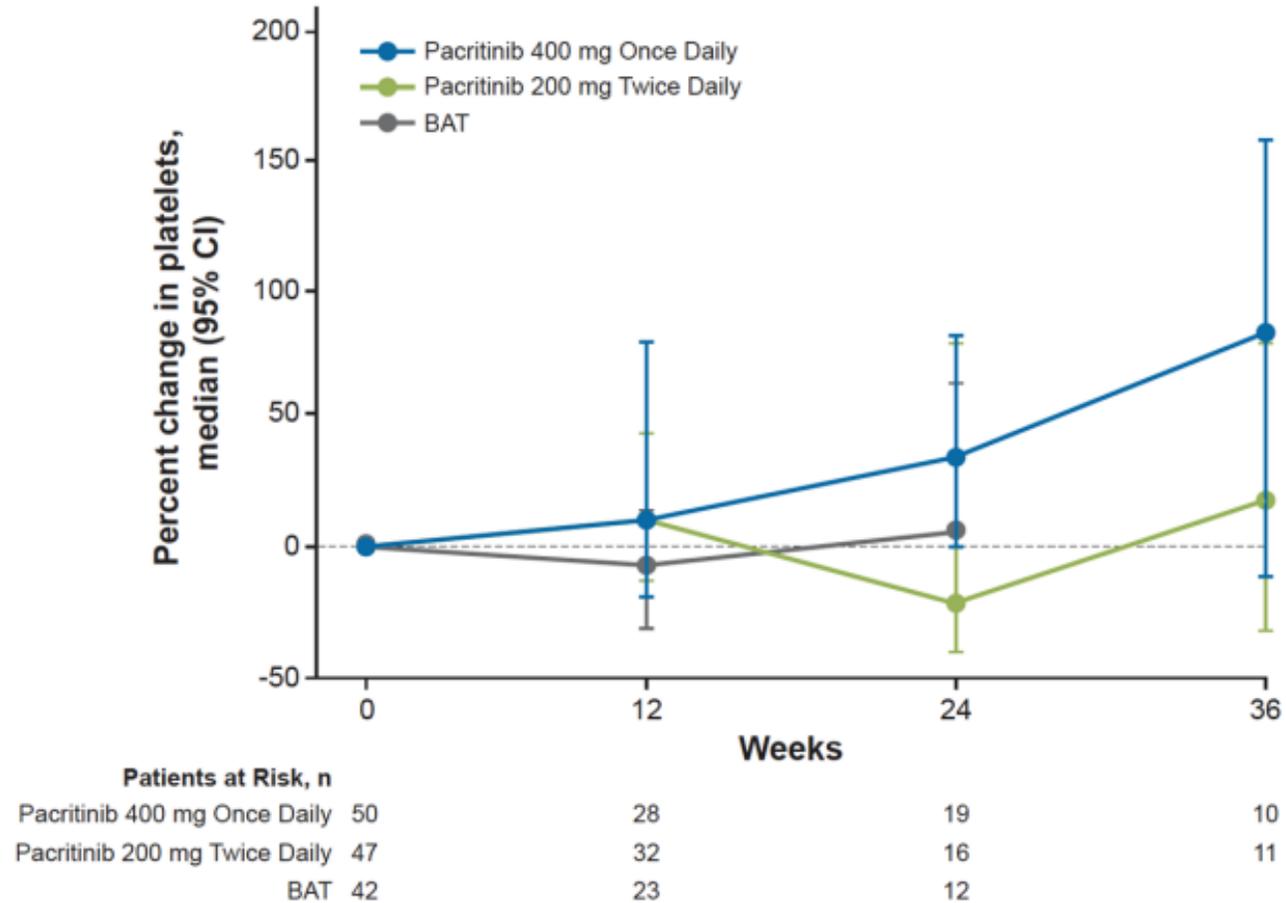
# PERSIST-2 SVR > 35%



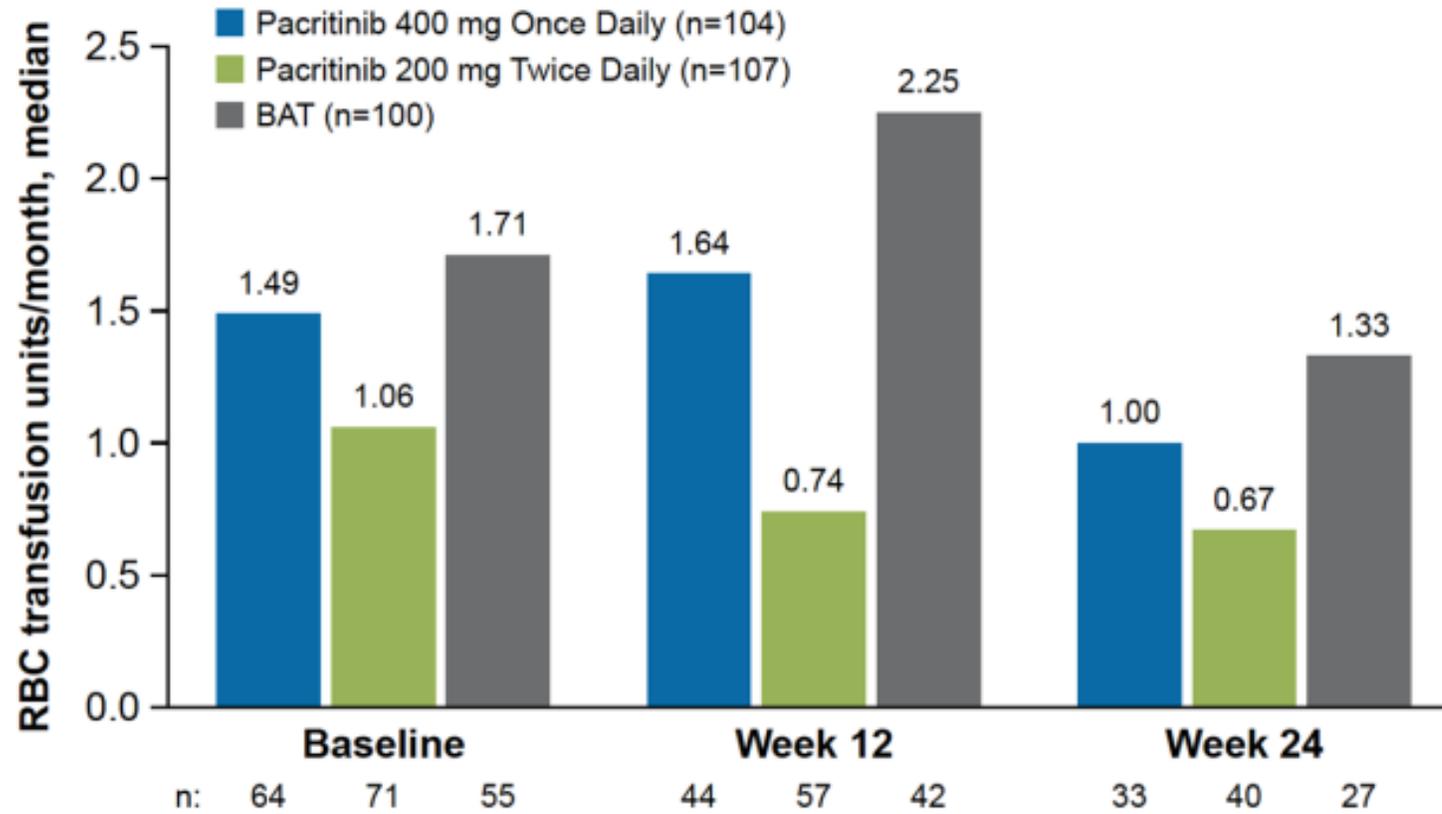
# PERSIST-2 TSS Reduction > 50%



# PERSIST-2 Baseline Change in PLT Count

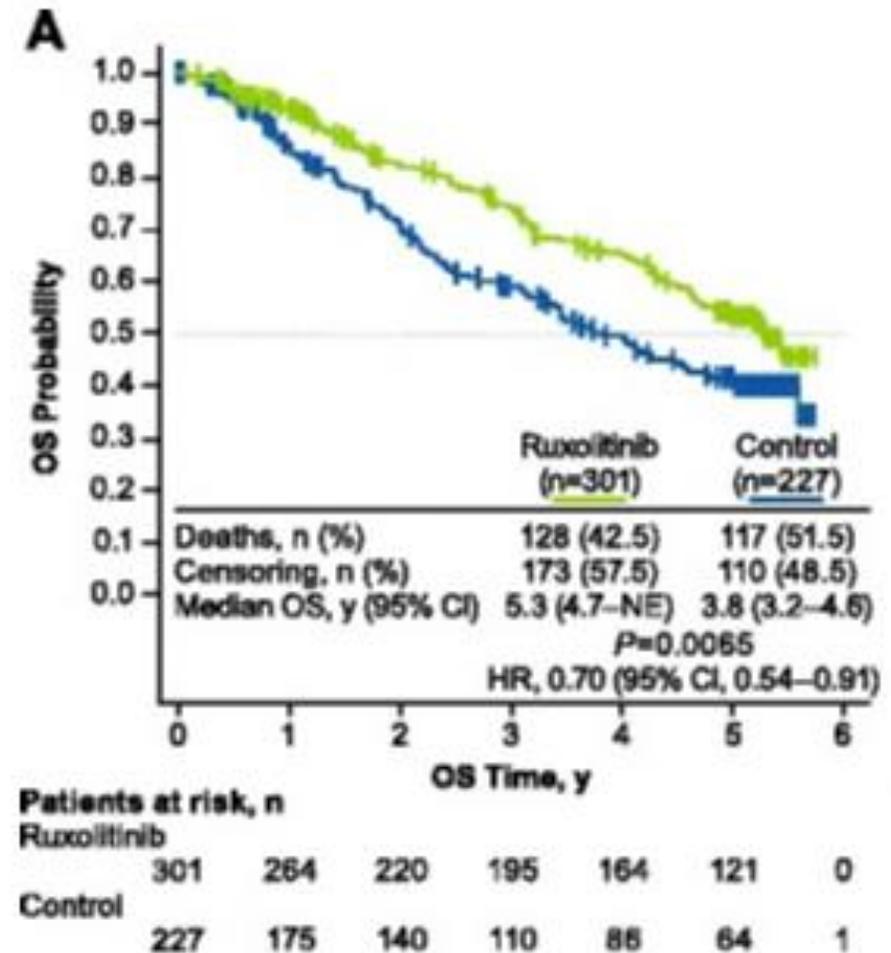


# PERSIST-2 improvement in transfusions

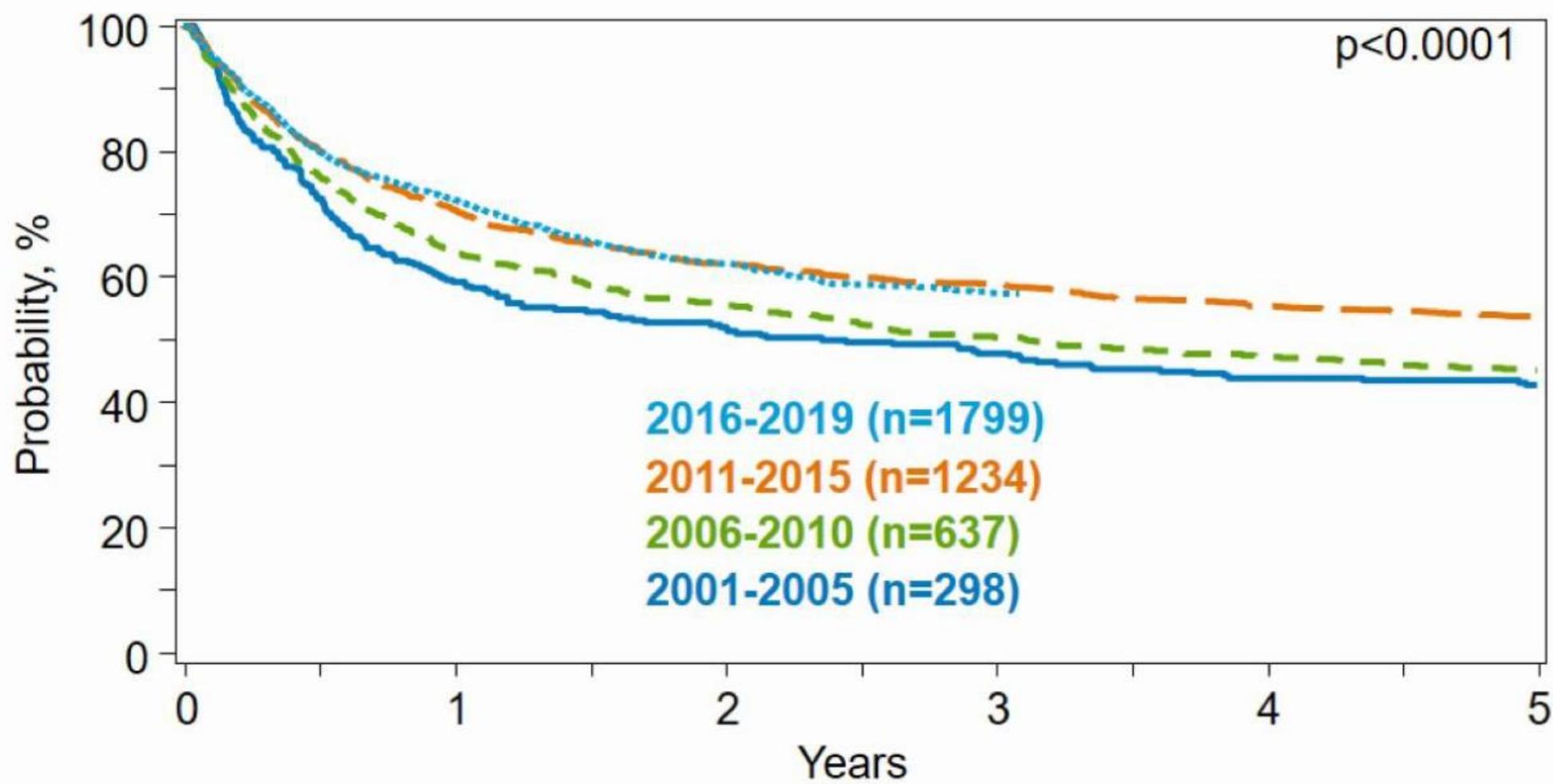


# Survival on Ruxolitinib

- Median time on ruxolitinib in COMFORT ~ 3 years

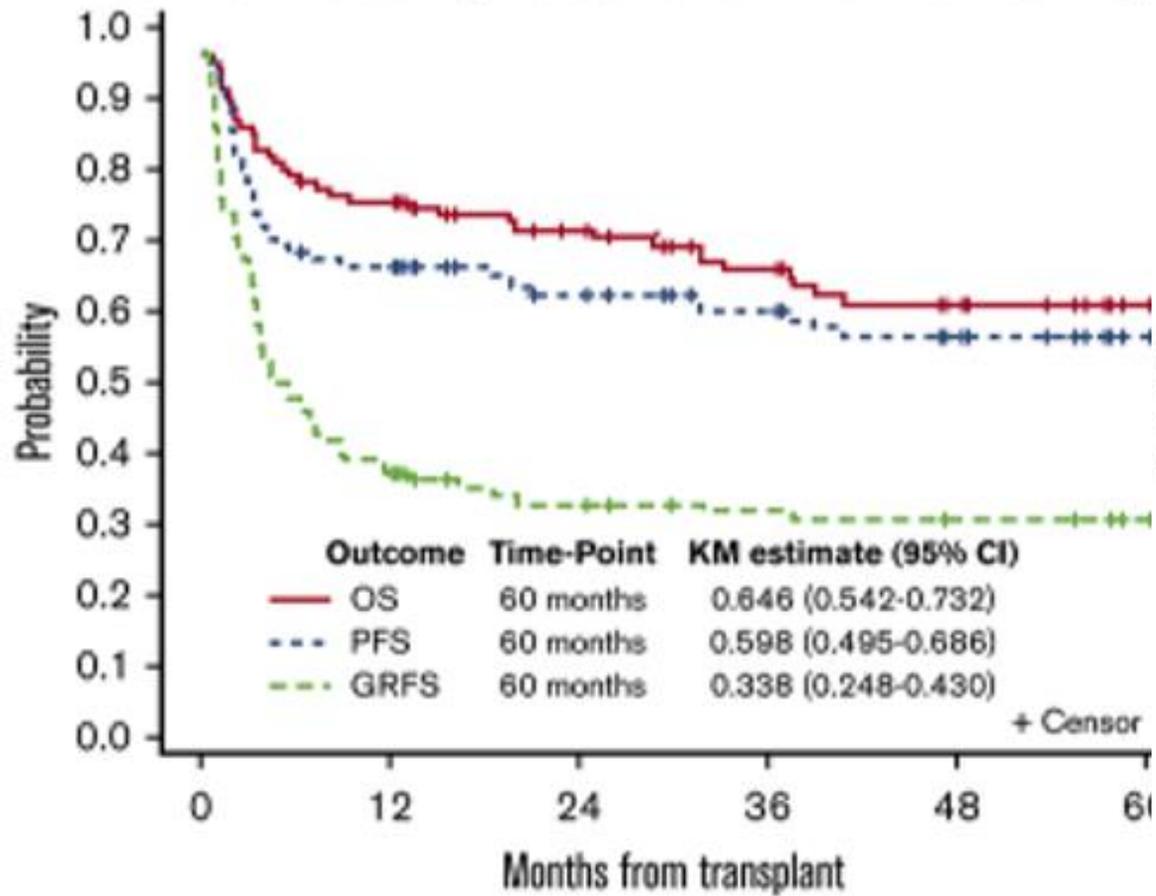


# Trends in Survival after Allogeneic HCTs for Myeloproliferative Neoplasms (MPN), in the US, 2001-2019

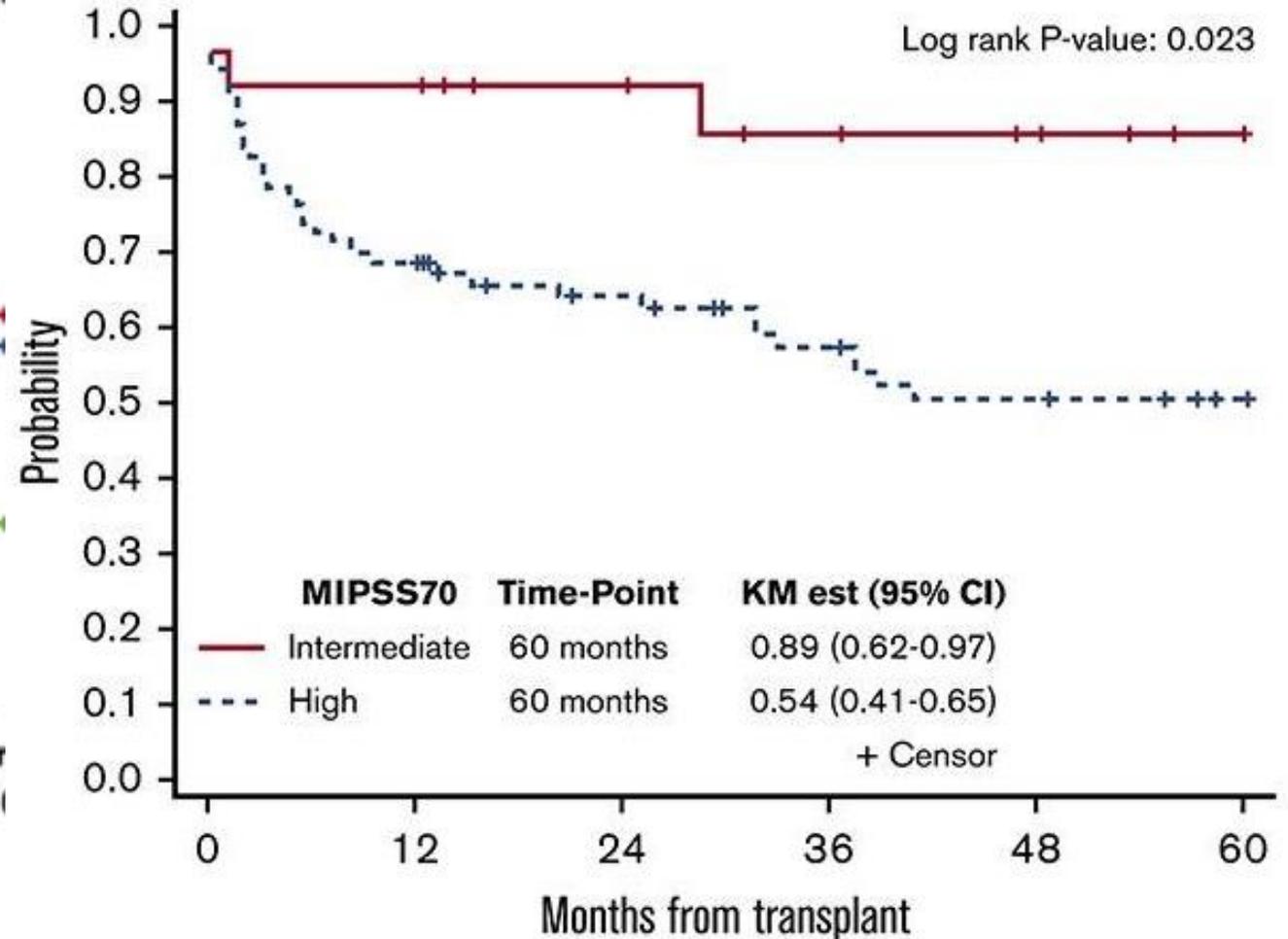


# Survival after alloHCT

Survival Probability Post-alloHCT with Flu/Mel Regi

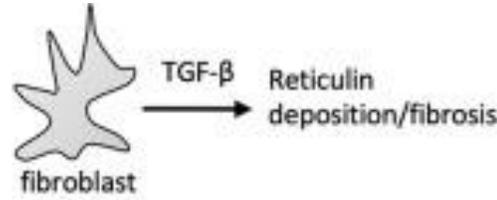


Overall Survival Based on MIPSS70



Microenvironment and Fibrosis

- TGF-β inhibition
- Fibroblast differentiation inhibition
- TGF-β ligand traps
- Sympathomimetics
- Aurora Kinase-A Inhibition

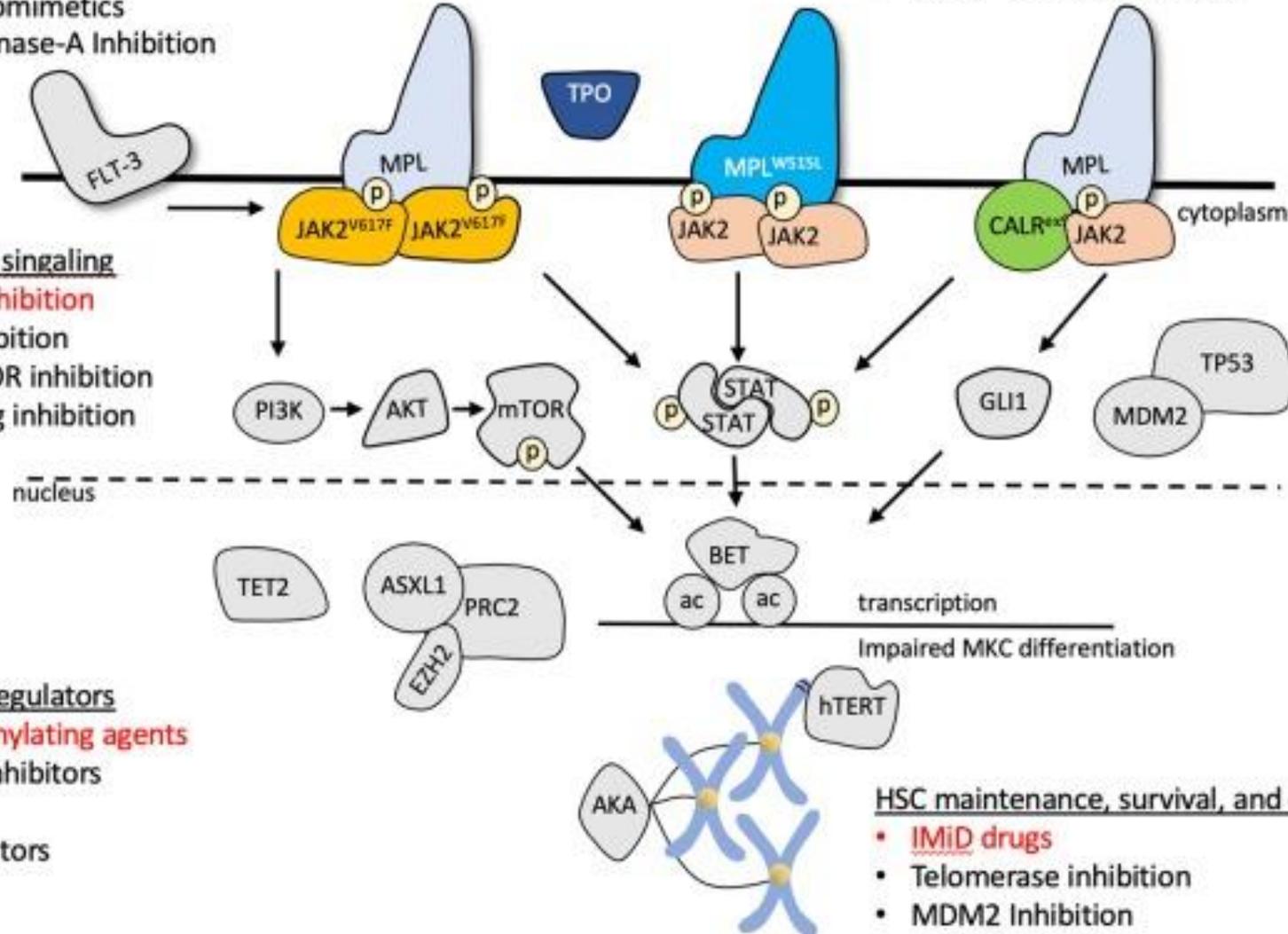


Immunotherapy

- Interferons
- PD-1/PD-L1 Inhibition
- CALR<sup>ex9</sup> peptide vaccination, cell transfer
- CALR<sup>ex9</sup> antibody therapy

Proliferative signaling

- JAK1/2 Inhibition
- FLT-3 inhibition
- PI3K/mTOR inhibition
- Hedgehog inhibition



Epigenetic Regulators

- Hypomethylating agents
- IDH 1/2 inhibitors
- HDACs
- BET inhibitors

HSC maintenance, survival, and differentiation

- IMiD drugs
- Telomerase inhibition
- MDM2 Inhibition

# Thank You

[iamanam@coh.org](mailto:iamanam@coh.org)

Twitter **@amyeloidpersona**

Idoroenyi Amanam, MD

Assistant Professor

Division of Leukemia

Hematology/HCT

City of Hope

Duarte, CA