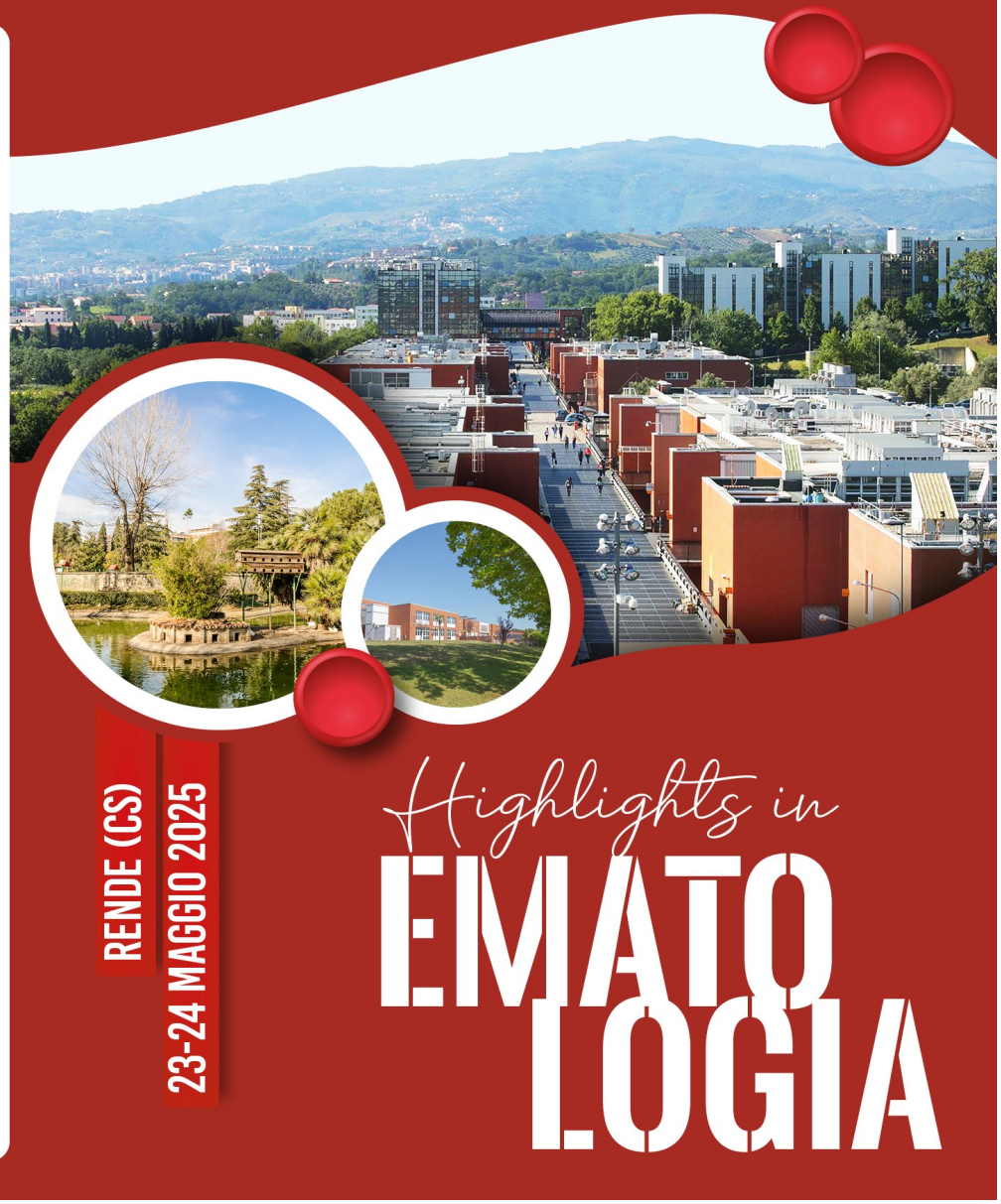
Highlights
nelle sindromi mieloproliferative croniche

ph negative

Alessandra Iurlo
Fondazione IRCCS Ca' Granda Policlinico-Milano



Conflitti di interessi di ALESSANDRA IURLO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
AOP Health						X	
BMS					X	X	
GSK					X		
Incyte					X	X	
Novartis					X	X	
Pfizer					X		

The NEW ENGLAND JOURNAL of MEDICINE

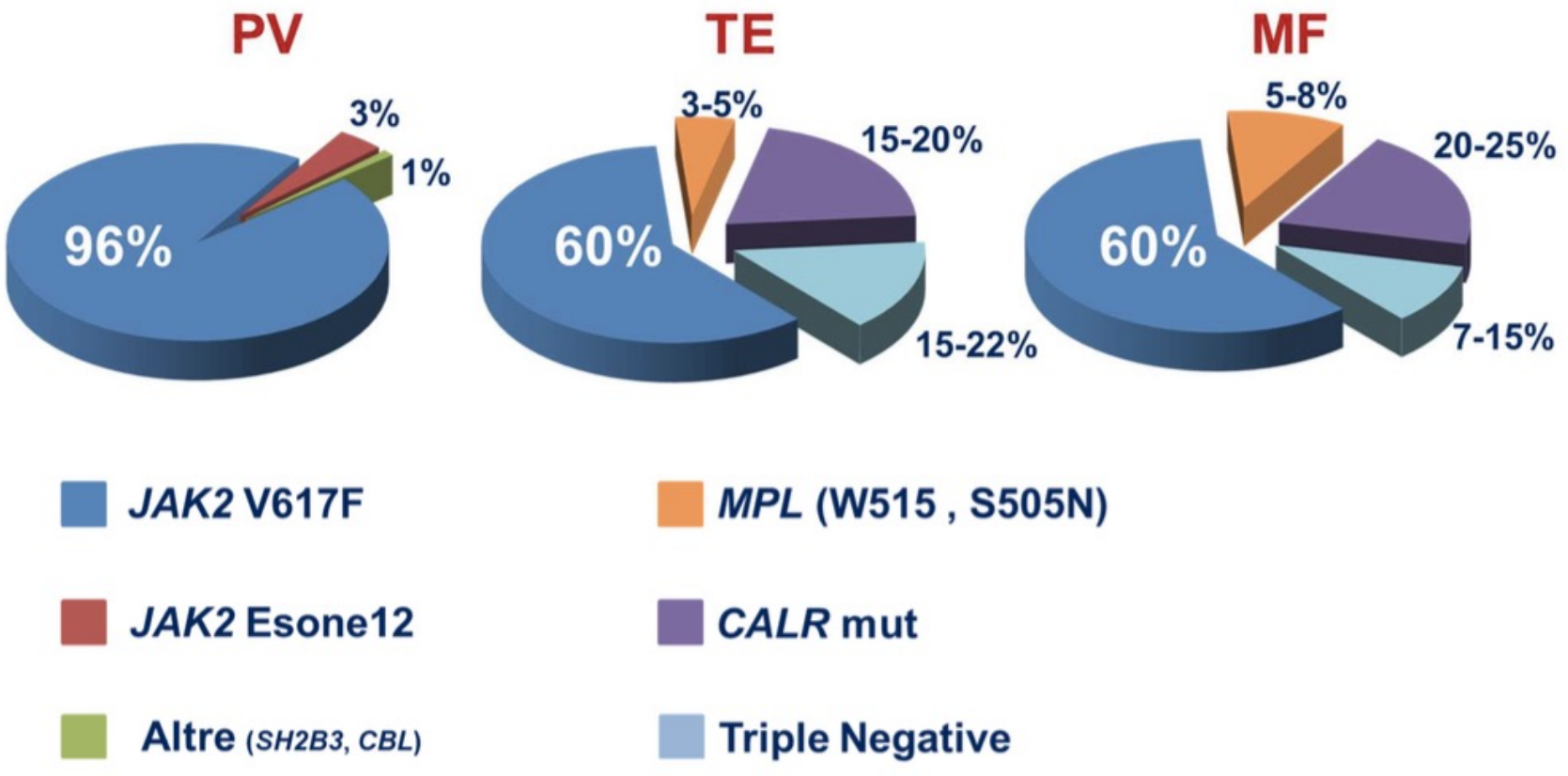
ORIGINAL ARTICLE

A Gain-of-Function Mutation of *JAK2* in Myeloproliferative Disorders

Robert Kralovics, Ph.D., Francesco Passamonti, M.D., Andreas S. Buser, M.D., Soon-Siong Teo, B.S., Ralph Tiedt, Ph.D., Jakob R. Passweg, M.D., Andre Tichelli, M.D., Mario Cazzola, M.D., and Radek C. Skoda, M.D.

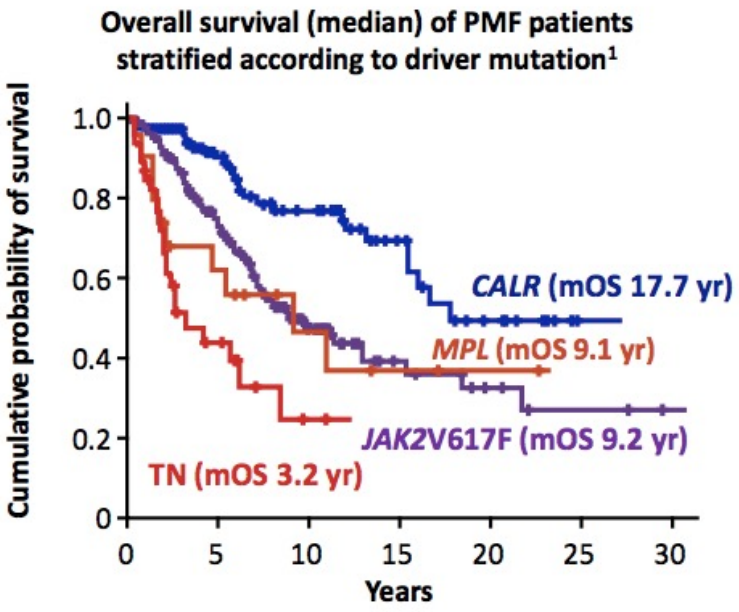
2005

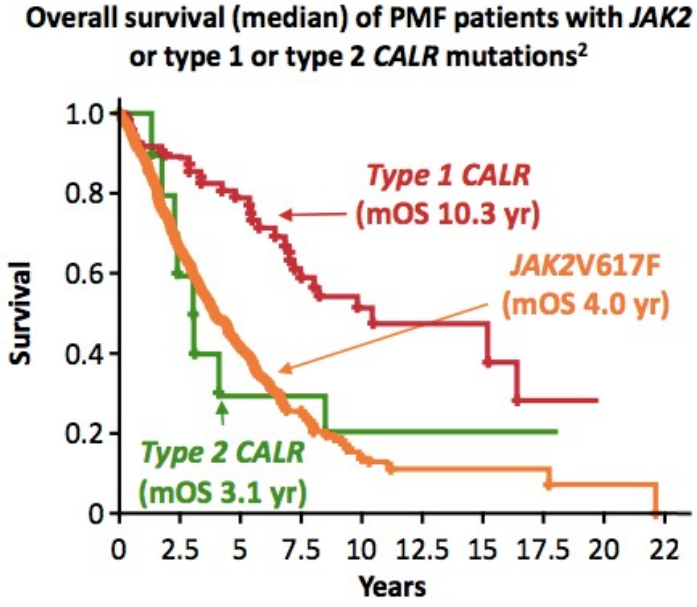
Phenotipic driver mutations in MPN

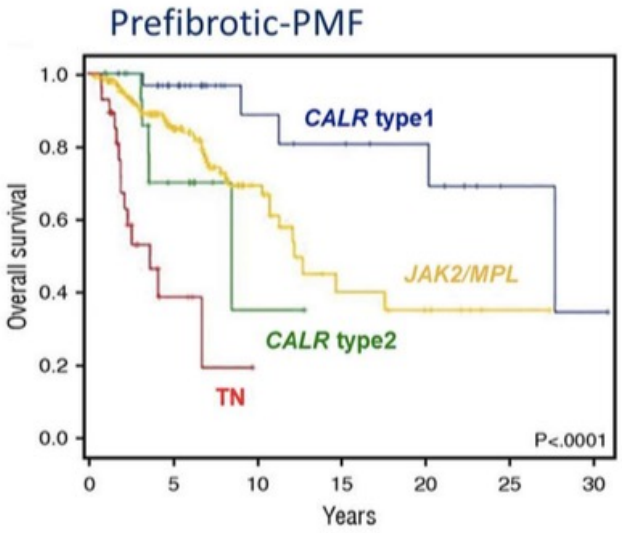


Klampfl T, et al. *NEJM* 2013;369(25):2379-90; Nangalia J, et al. *NEJM* 2013;369(25):2391-405; Milosevic JD et al. Blood 2016;127:325-332; Cabagnols J et al. Blood 333-342

Prognostic significance of phenotype driver mutations in MF







Patients with triple negative PMF or with mutations in *JAK2V617F* or type 1 *CALR* mutations have poorer survival outcomes[1,2]

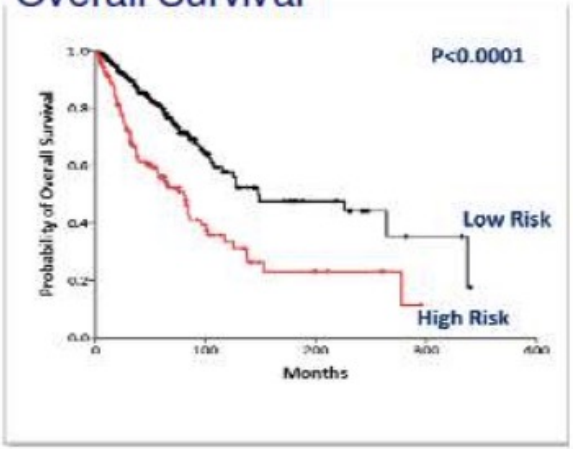
Rumi E et al. Blood 2014; Tefferi A et al. Leukemia 2014; Guglielmelli P et al. Blood 2017

Additional mutations

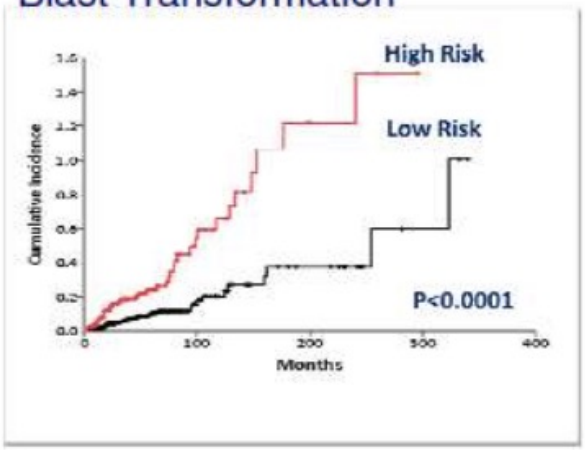
High Molecular Risk Prognostic Category

harboring ≥1 mutation in any one of ***ASXL1, EZH2, SRSF2, IDH1/2***

Overall Survival



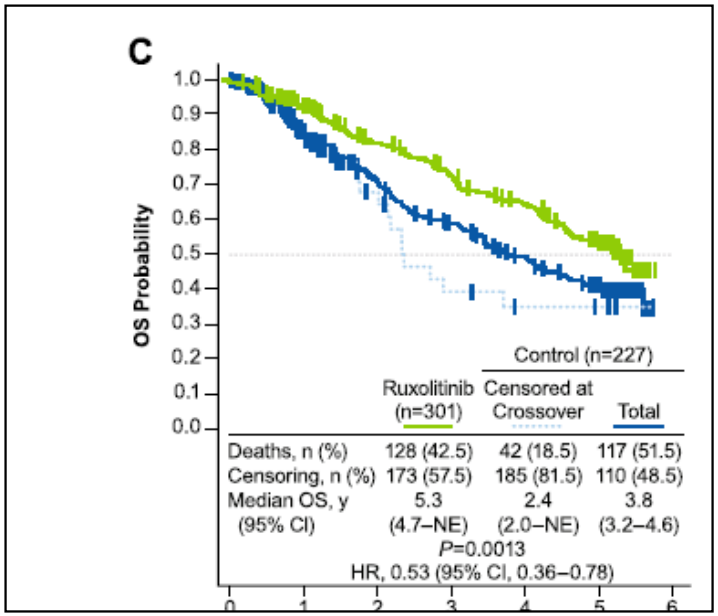
Blast Transformation



- A HMR status is associated with reduced OS and increased risk of blast transformation in PMF patients independent of IPSS/DIPPS-plus scores

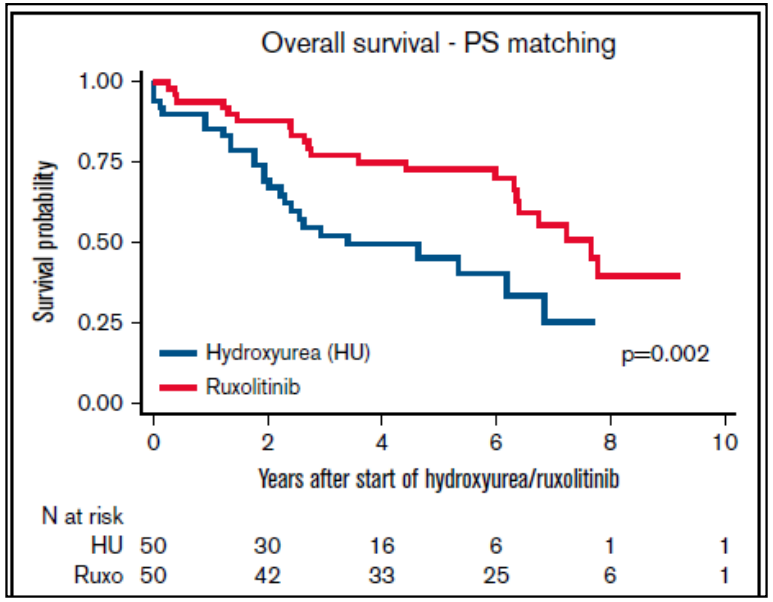
Vannucchi AM et al. Leukemia 2013

Ruxolitinib



The survival was more pronounced in ruxo *vs* crossover, suggesting better outcome with earlier treatment

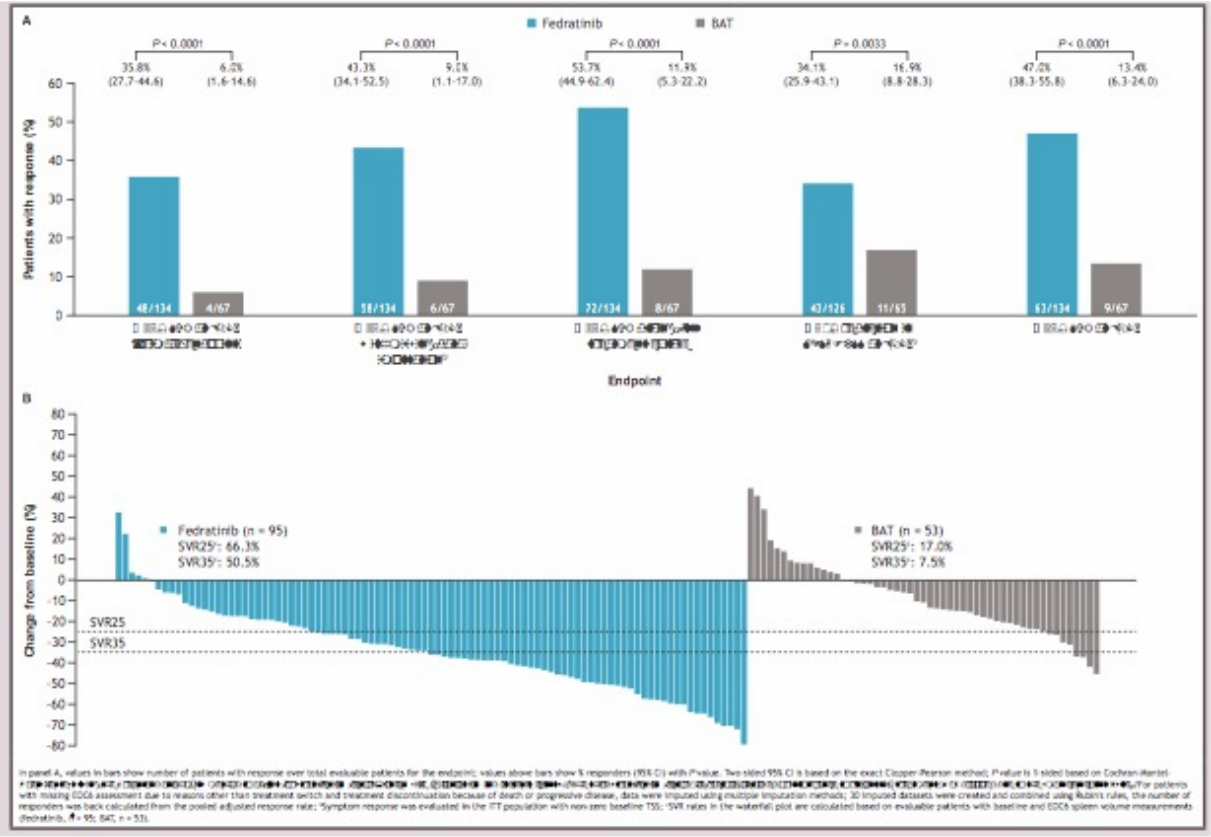
Verstovsek S et al. J Hematol Oncol 2018



Mortality rate was reduced by 38% with ruxo *vs* HU and PS matching analysis demostrated 73% reduced risk of death in the ERNEST EU registry

Guglielmelli P et al Blood Adv 2022

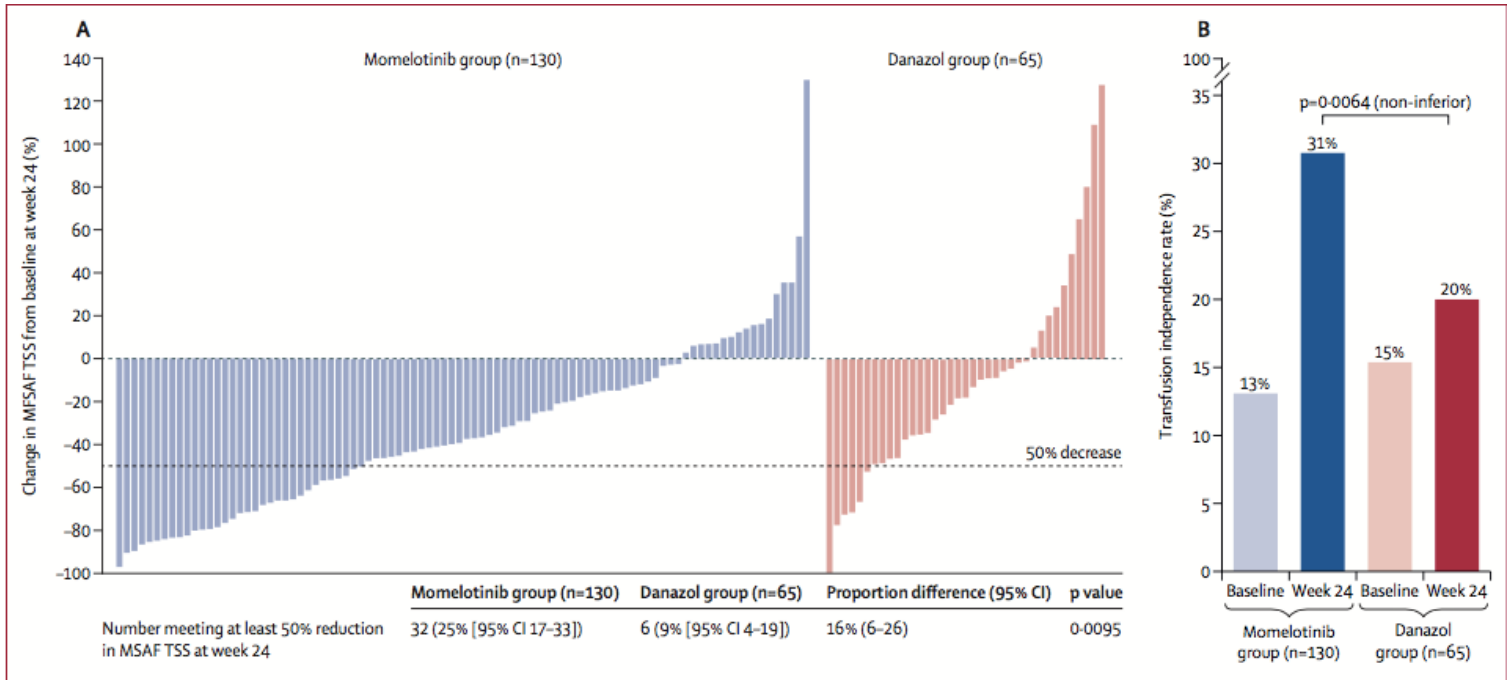
Fedratinib



- The primary endpoint of SVR35 at EOC6 was met by 35.8% of patients treated with FEDR vs. 6.0% of BAT-treated patients
- Most patients treated with FEDR showed a reduction in spleen volume from baseline at EOC6
- FEDR-treated patients experienced higher rates of symptom response vs. BAT-treated ones

Harrison C et a. Lancet Hematol 2024

Momelotinib

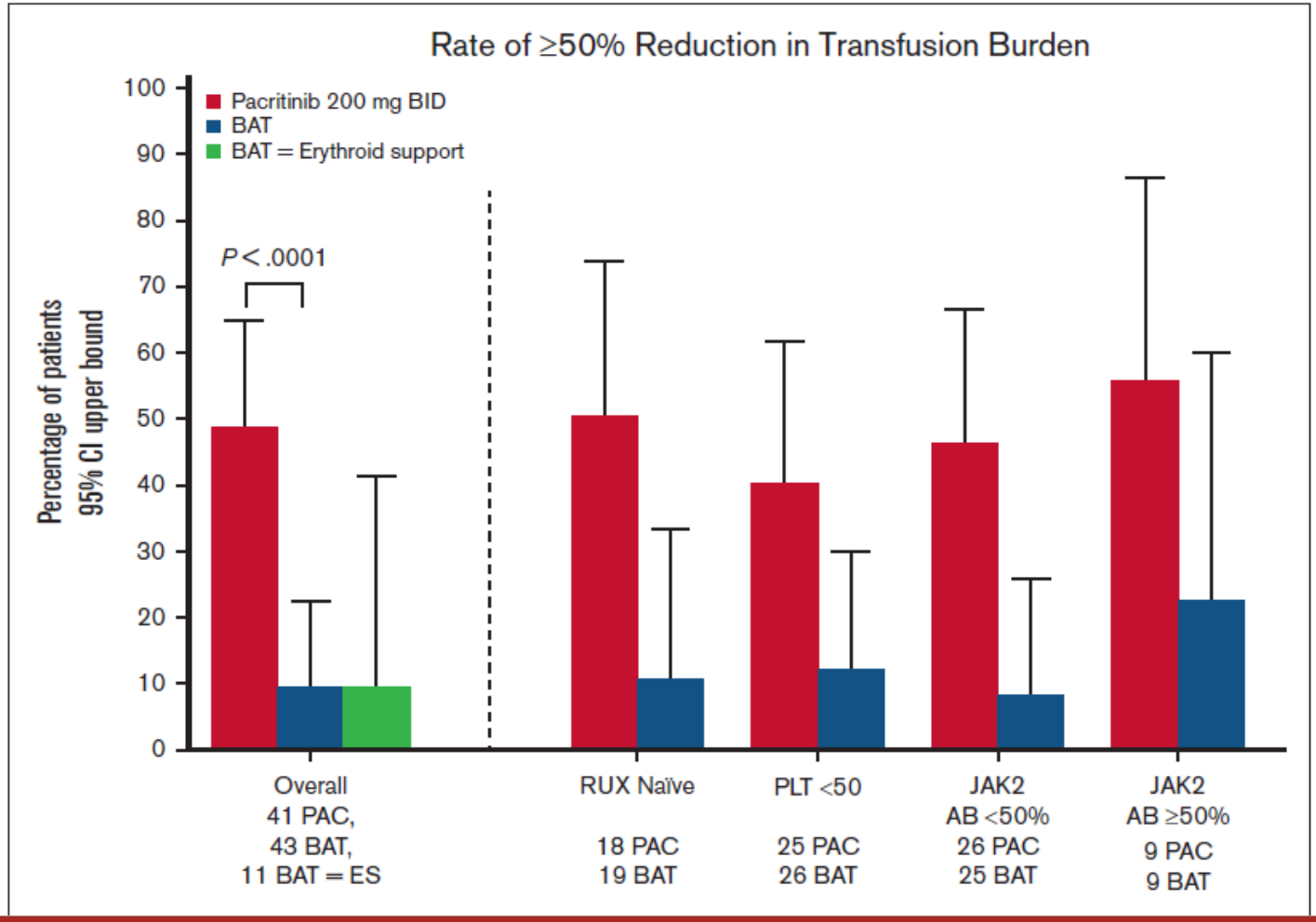


	Momelotinib group (n=130)	Danazol group (n=65)	Proportion difference (95% CI)	p value
Number meeting at least 50% reduction in MSAF TSS at week 24	32 (25% [95% CI 17–33])	6 (9% [95% CI 4–19])	16% (6–26)	0·0095

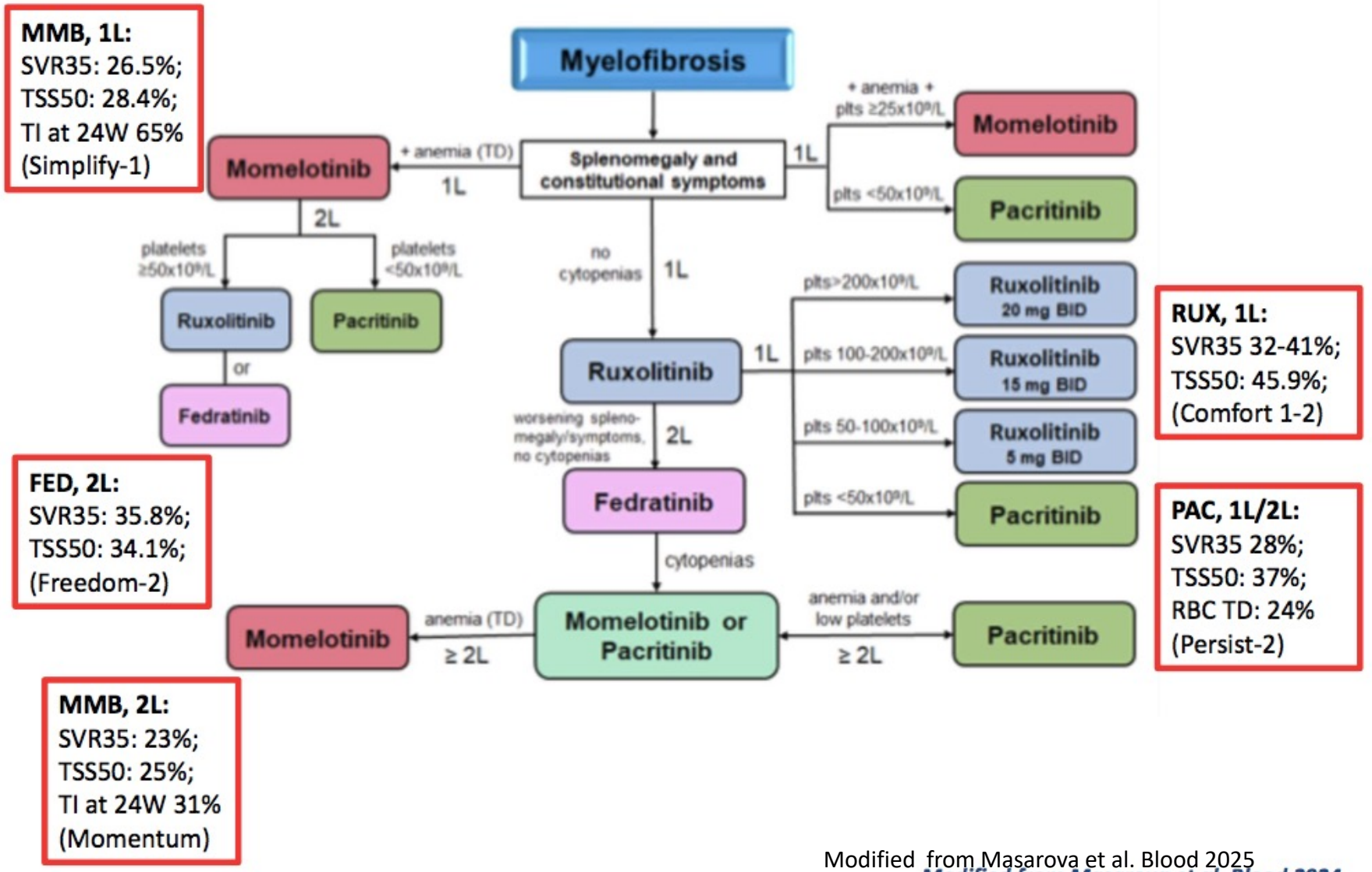
	Momelotinib group (n=130)	Danazol group (n=65)	Proportion difference (95% CI)	p value
Number meeting at least 25% reduction in spleen volume	52 (40% [95% CI 32–49])	4 (6% [95% CI 2–15])	34% (24–45)	<0·0001
Number meeting at least 35% reduction in spleen volume	30 (23% [95% CI 16–31])	2 (3% [95% CI 0–11])	19% (11–28)	0·0006

Verstovsek S et al.
Lancet 2023

Pacritinib



Oh ER al. Blood Adv 2023



Modified from Masarova et al. Blood 2025

ASH 2024

997 Hematological Improvement and Other Clinical Benefits of Elritercept As Monotherapy and in Combination with Ruxolitinib in Participants with Myelofibrosis from the Ongoing Phase 2 Restore Trial

Claire Harrison, Lynette C.Y. Chee, Timothy Devos, Maria Laura Fox, Alessandra Iurlo, Francesca Palandri, David M Ross, Shuhying Tan, Alessandro Maria Vannucchi, Marielle Wondergem, Michael Pace, Hongying Wang, Ming Yang, Ying Jiang, Suresh Bobba, Montagu Hankin, Chris Materna, Christine Graham, Sanjay Thamak, Christopher Rovaldi, Dena Grayson and Jen L. Salstrom

634 The Efficacy and Safety of Selinexor in Combination with Ruxolitinib in Ruxolitinib-Treated Myelofibrosis Patients: The Interim Analysis of a Prospective, Open-Label, Multicenter, Parallel-Cohort, Phase 2 Study

Minghui Duan, Lan Ma, Qiuling Wu, Hong Liang, Wei Wang, Lijun Mu, Hai Lin, Hebing Zhou, Hong-xia Shi, Jinghua Wang, Hongmei Jing

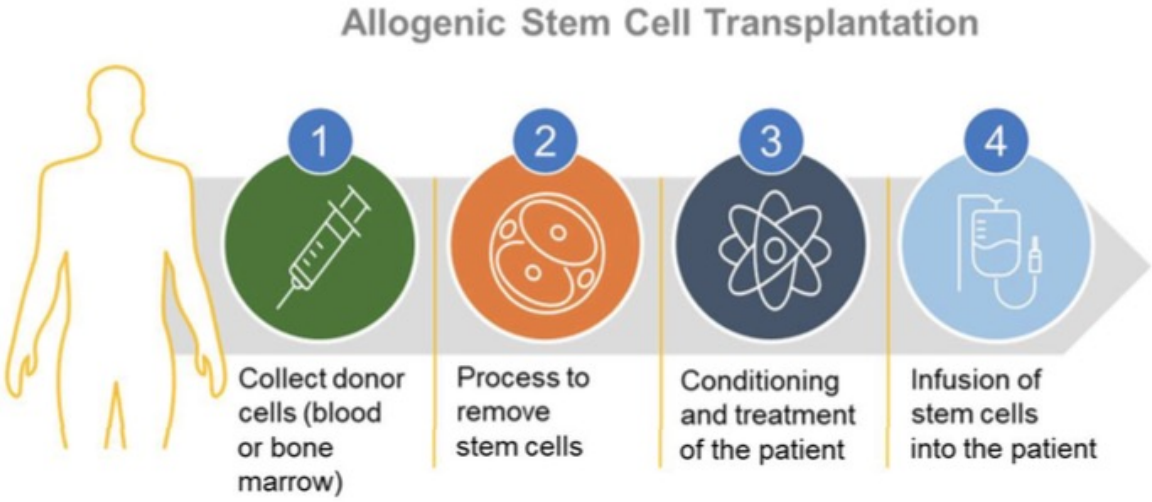
ASH 2024

58 Safety and Efficacy of Bromodomain and Extra-Terminal Inhibitor INCB057643 in Patients with Relapsed or Refractory Myelofibrosis and Other Advanced Myeloid Neoplasms: A Phase 1 Study
Justin M. Watts, Anthony M. Hunter, Alessandro Vannuchhi, Vikas Gupta, Srinivas K Tantravahi, Alessandra Iurlo, Brandon McMahon, Francesca Palandri, María Teresa Gómez Casares, Junichiro Yuda, Emma Searl, Anna B. Halpern, Rosa Ayala, Akihiro Tomita, Blanca Xicoy, Prithviraj Bose, Brandi N. Reeves, Xuejun Chen, Lea M Burke, Feng Zhou, Fred Zheng and Pankit Vachhani

655 Nuvisertib (TP-3654), an Investigational Selective PIM1 Kinase Inhibitor, Showed Durable Clinical Response and Sustained Hematological Improvement in Relapsed/Refractory Myelofibrosis Patients
Firas El Chaer, Lindsay A.M. Rein, Junichiro Yuda, Kazuya Shimoda, Akiyoshi Takami, Michiko Ichii, James McCloskey, Joseph M. Scandura, Alessandra Iurlo, Prithviraj Bose, Tamanna Haque, Alessandro Lucchesi, MD, Shuichi Shirane, Giulia Benevolo, Idoroenyi Amanam, Jean-Jacques Kiladjian, Pankit Vachhani, Srinivas K Tantravahi, Yasushi Onishi, Ciro Rinaldi, Marcello Rotta, Nikki Granacher, Anand Ashwin Patel, Michael Loschi, Samah Alimam, MD, Terrence Bradley, Stanley Cheung, Vincent Ribrag, Sujan Kabir, Karen Ansaldo, Masataka Seki, Vincent Loksa, Zhonggai Li, Jason M. Foulks, Jatin Shah and Raajit Rampal

HCT is recommended when possible
However, the majority of patients with myelofibrosis do not undergo HCT

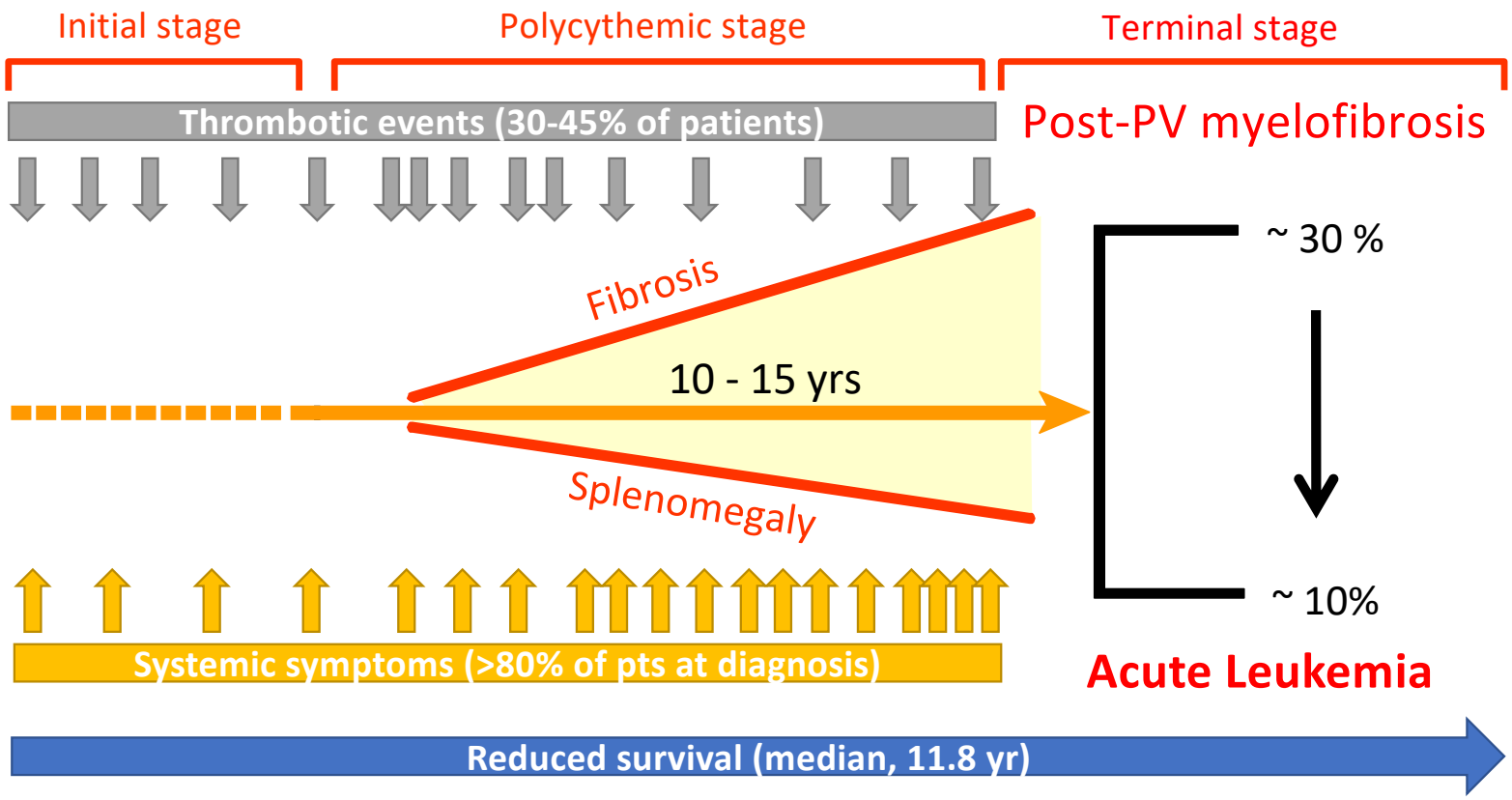
- Both the ELN guidelines and the NCCN Guidelines recommend HCT for patients with MF that are candidates[1,2]
- Most patients with MF do not undergo HCT due to precluding factors, such as older age (median age at MF diagnosis is >65 years), poor performance status, significant comorbidities, and patient choice[3-5]
- Morbidity associated with HCT in patients with myelofibrosis includes graft-versus-host disease (GVHD), infection, organ failure, and secondary cancers; 1-year transplant-related mortality in patients with MF aged <50 years ranges from 27% to 43%[6,7]



1. Barbui T, et al. Leukemia. 2018;32(5):1057-1069. 2. NCCN Clinical Practice Guidelines: Myeloproliferative Neoplasms. Version 1.2020. Published May 21, 2020. Accessed August 14, 2020. 3. Kröger N. Curr Hematol Malig Rep. 2015. 4. Kröger N, et al. Leukemia. 2015. 5. Tefferi A, et al. Mayo Clin Proc. 2012. 6. Ballen K. Blood Cancer J. 2012. 7. Tanaka Y, et al. Blood. 2015.

Polycythemia Vera

- Erythrocytosis is the clinical hallmark of PV
- The excess production of RBC is caused by hyper-activation of the JAK-STAT signaling



Srour et al. Br J Haematol 2016; Tefferi et al. Blood 2014; Marchioli et al, J Clin Oncol. 2005; Tefferi et al, Leukemia. 2013; Harrison et al. Ann Hematol. 2017; Mesa et al. BMC Cancer 2016. Figure modified from Barbui T et al, Leukemia 2013

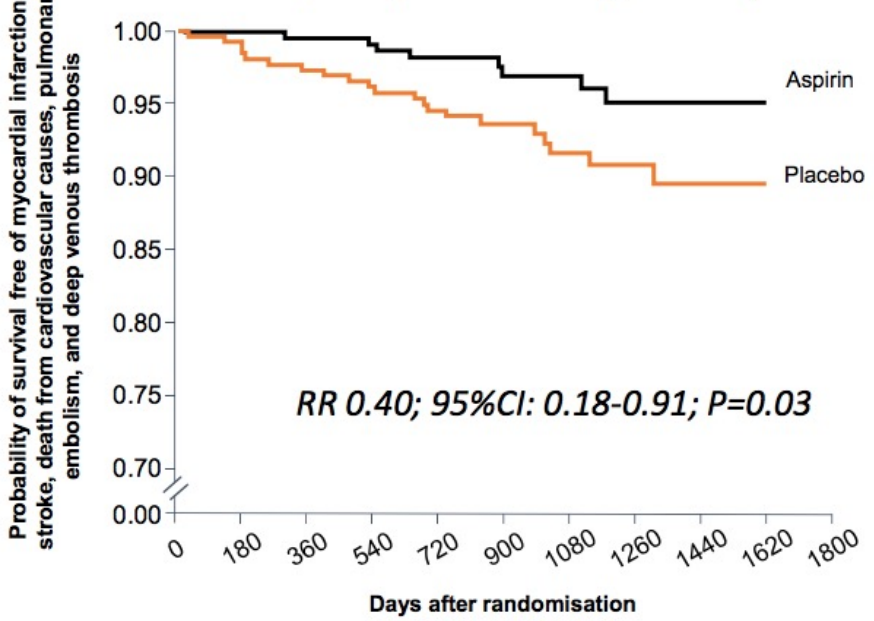
Prognostic stratification

	Risk Factors	
Currently Used	Low-risk	High-risk
	Age < 60 years [52] and no previous thrombosis [52]	Age > 60 years [52] and/or previous thrombosis [52]
Proposed	Hypertension [54] Smoking habit Leukocytosis (>15 × 10^9/L [55] or >11 × 10^9/L [56])	
Emerging	Platelet count [57] Abnormal karyotype [53] RDW [57,58] Lymphocyte percentage [57] Leuko-erythroblastosis [34]	

Iurlo A et al. Int J Mol Sci 2020

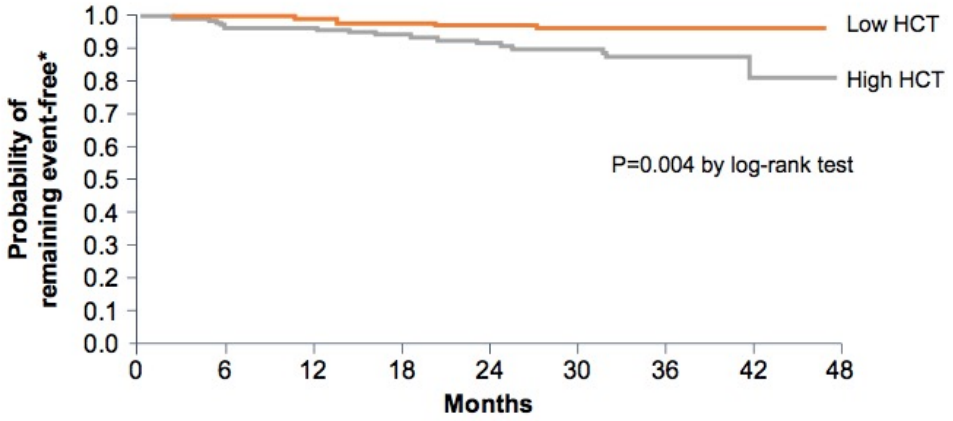
Backbone of care in PV

LD Aspirin (ECLAP study, N=518)



LD Aspirin also effective on microvascular symptoms

Hct target <45% (CYTO-PV study, N=365)



*death for cardiovascular causes or major thrombotic events.

At a median FUP of 31 mts, **9.8%** of the **high HCT** group (45-50%) met the primary endpoint* vs. **2.7%** in the **low HCT** group (<45%, *P = 0.007*)

Response Trials: main results with RUXO

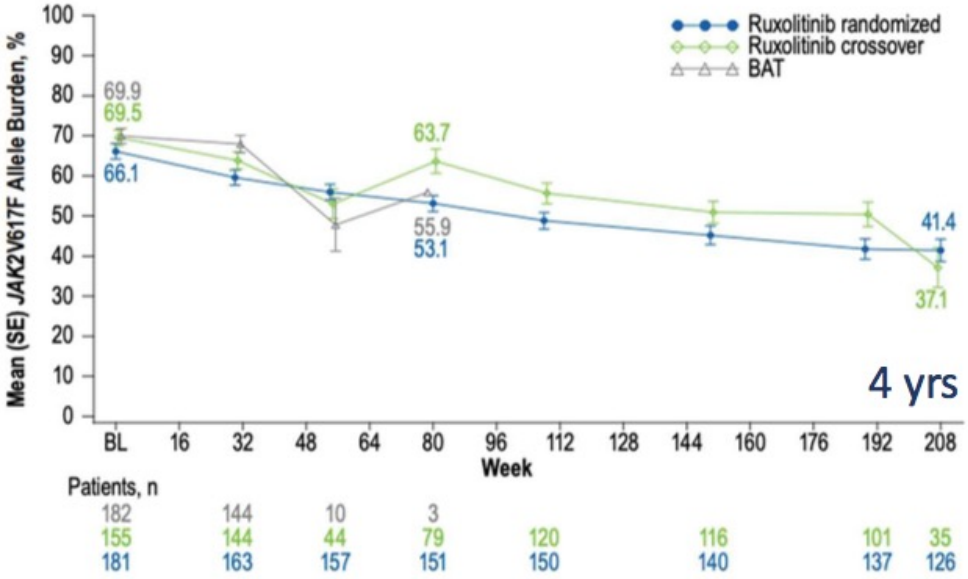
Endpoint, %	RESPONSE-2 phase III (*without* splenomegaly) 28-week analysis		RESPONSE phase III (*with* splenomegaly) 32-week analysis	
	Ruxolitinib n=74	BAT n=75	Ruxolitinib n=110	Standard therapy n=112
HCT control	62[a]	19	60	20
≥35% Reduction in spleen volume	NA	NA	38	1
Complete hematologic remission	23[c]	5	24[d]	9
≥1 Phlebotomy	19	60	20	62
≥50% Reduction in MPN-SAF TSS	45	23	49	5

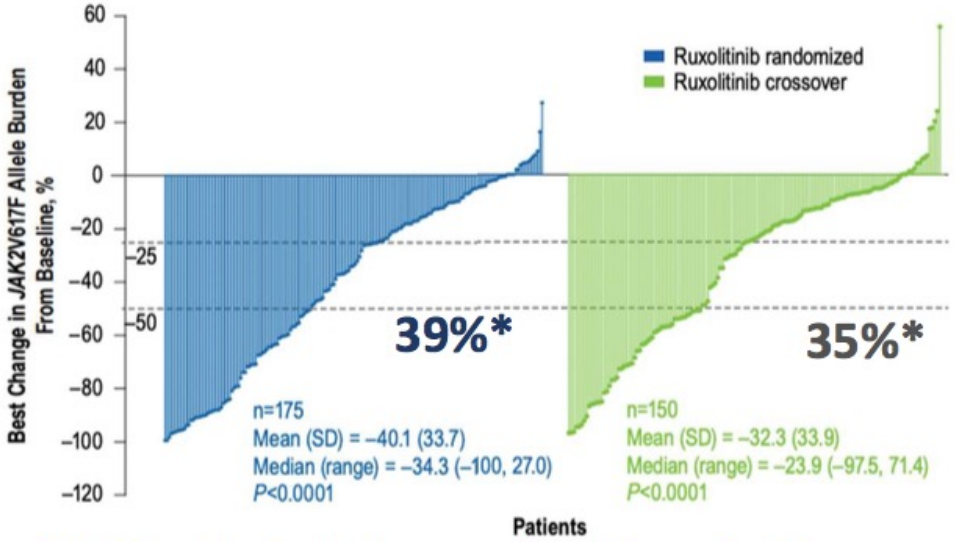
[a] OR, 7.8; 95% CI, 3.43-15.45; *P*<.0001; [c] OR, 5.58; 95% CI, 1.73-17.99; *P*=.0019; [d] *P*=.003 vs SOC

Durable responses at the 5 years-update

Vannucchi AM et al. NEJM 2015 ; Passamonti F et al Lancet Oncol 20217

Response trials: molecular responses in a pooled analysis





PMR* obtained at a median time of ~2 years

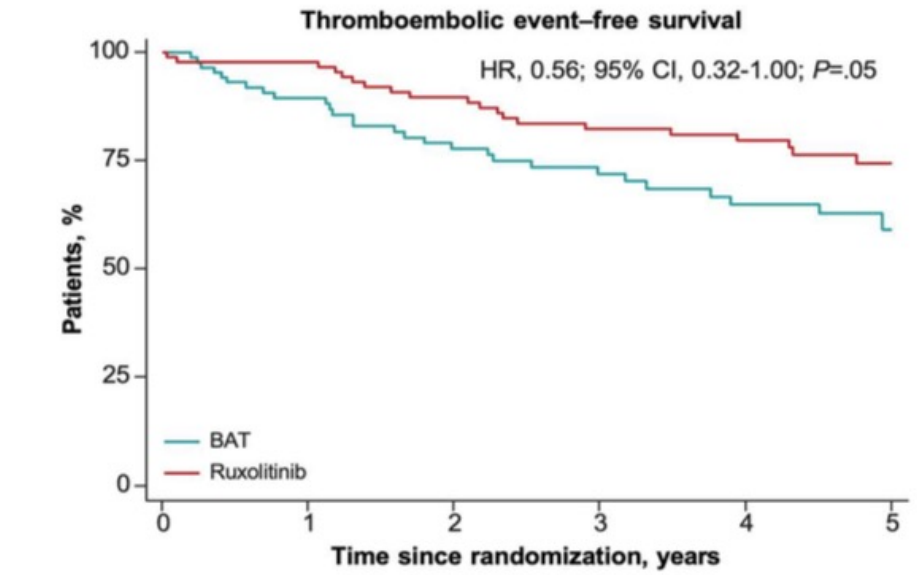
*= ≥50% ↓ in *JAK2* VAF if absolute VAF ≥20% at BL

***JAK2* VAF <1%:** 2.2% of RUX randomized patients (median time: 3y)

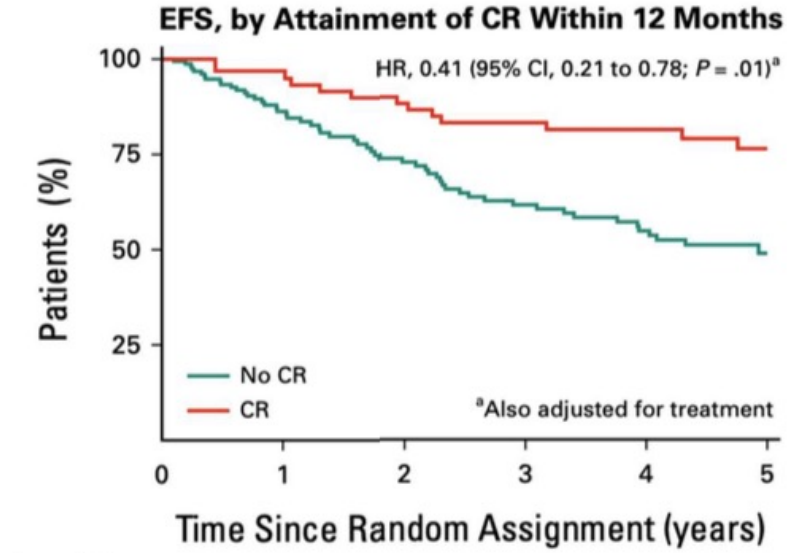
Harrison C et al ASH 2023

MAJIC-PV: key efficacy results

1year CR* (primary endpoint): 43% RUX vs. 26% BAT (*p 0.02*)



No. at risk						
BAT	87	74	59	45	36	10
Ruxolitinib	93	85	76	65	56	20



No. at risk:						
No CR	180	101	74	57	46	14
CR	0	50	53	46	40	15

*Hct<45% no Phls for >3 mts, PLT <400 x 10^9/L, WBC <10 x 10^9/L, normal spleen

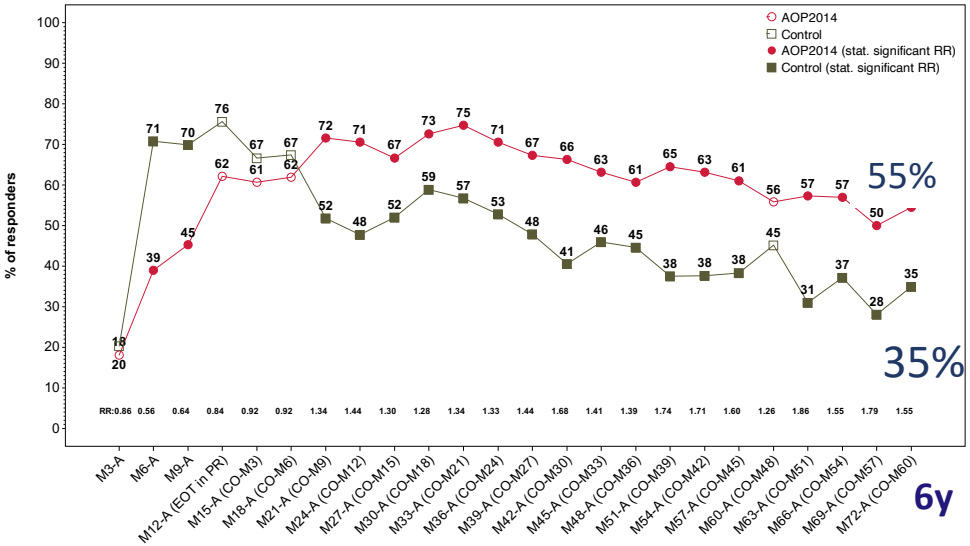
EFS= time to first event (N=38 thrombosis, N=28 bleedings, N=20 PD, N=32 death)

Harrison C et al. J Clin Oncol. 2023

RopegIFNα-2b *vs* BAT in PV: PROUD/CONTINUATION study

N=254 PV, 10% splenomegaly, 70% tx naïve, ~90%BAT=HU

Complete Hematologic Response (CHR)



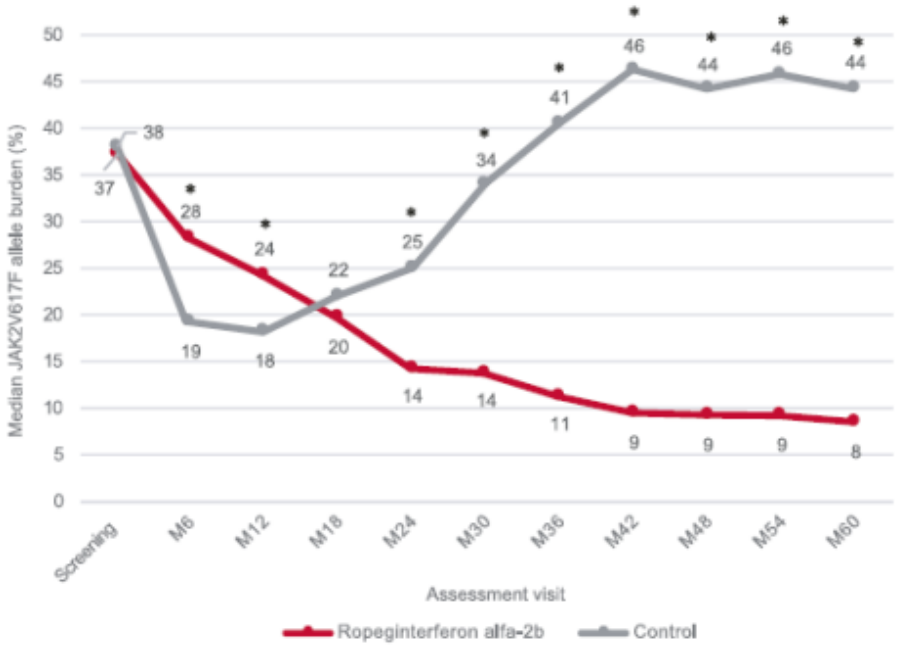
CHR & normal spleen size:
~50% rate at 3 years

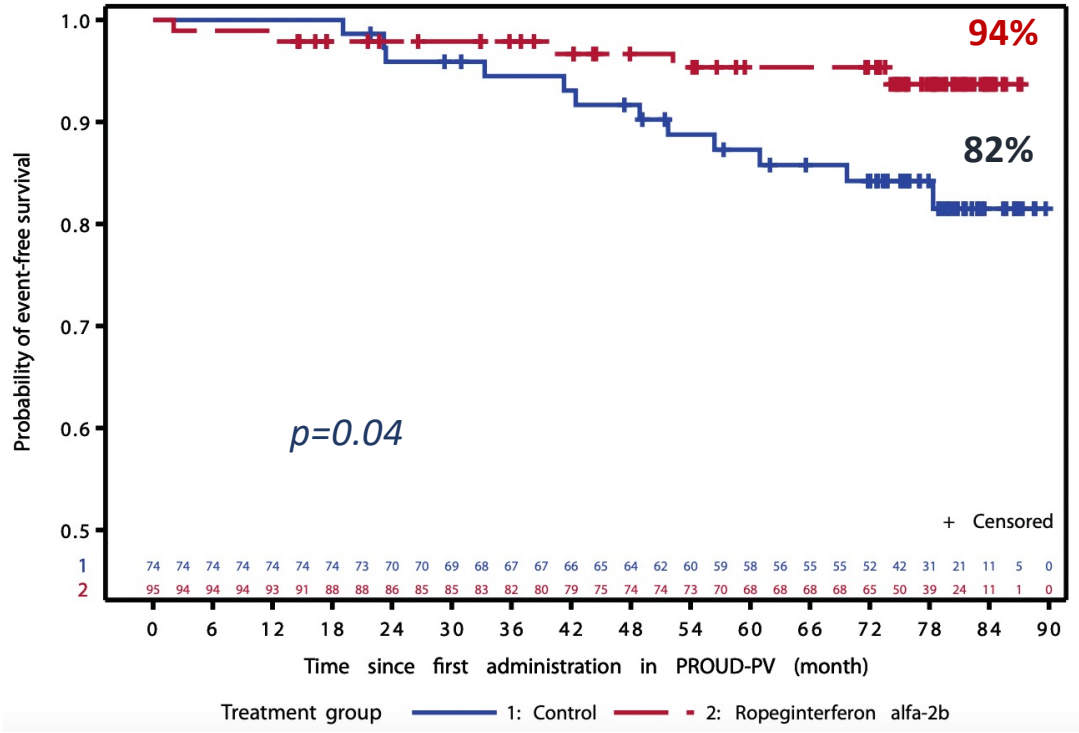
Discontinuation due to TrAEs:
11% (ropeg) and 2.4% (BAT)

CHR: Hct<45% & no Phls for ≥3 month & PLT <400 x 10^9/L & WBC <10 x 10^9/L

Gisslinger et al. Lancet Haematol 2020; Kiladjian et al. Leukemia 2022; Gisslinger et al. Leukemia 2023

PROUD/CONTINUATION study





Risk events: N=3 (4%) if MR, N=14 (16%) if no MR

Kiladjian JJ et al. Leukemia 2022

Gisslinger et al. Leukemia 2023

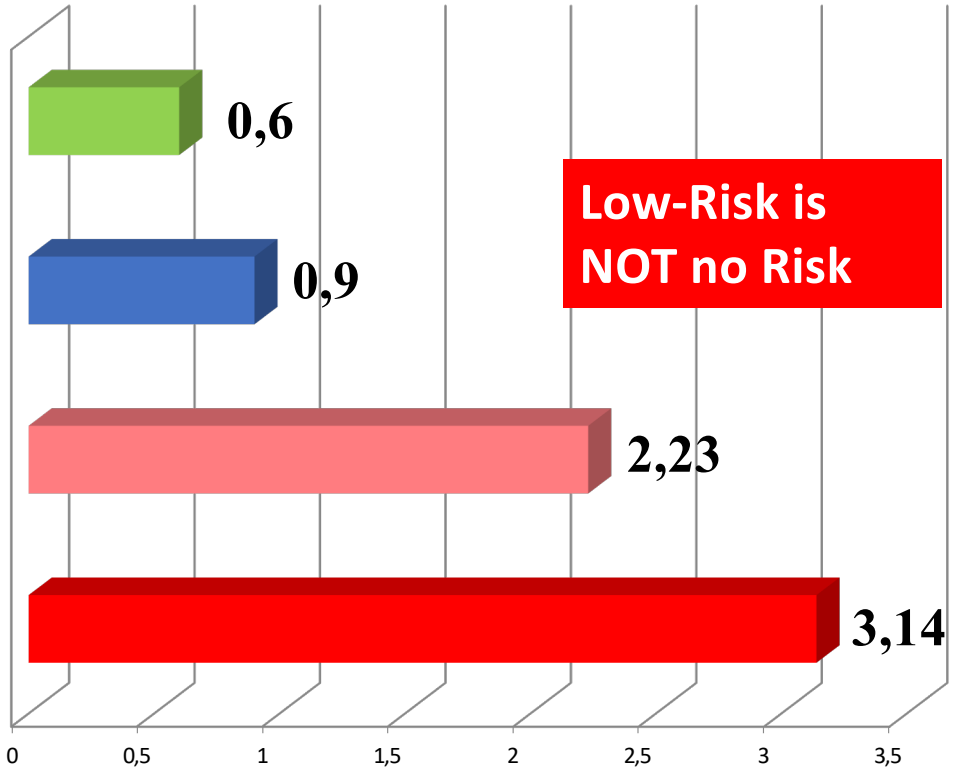
Annual rate of thrombosis in contemporary patients with PV and in general population

General Population without CV risk factors

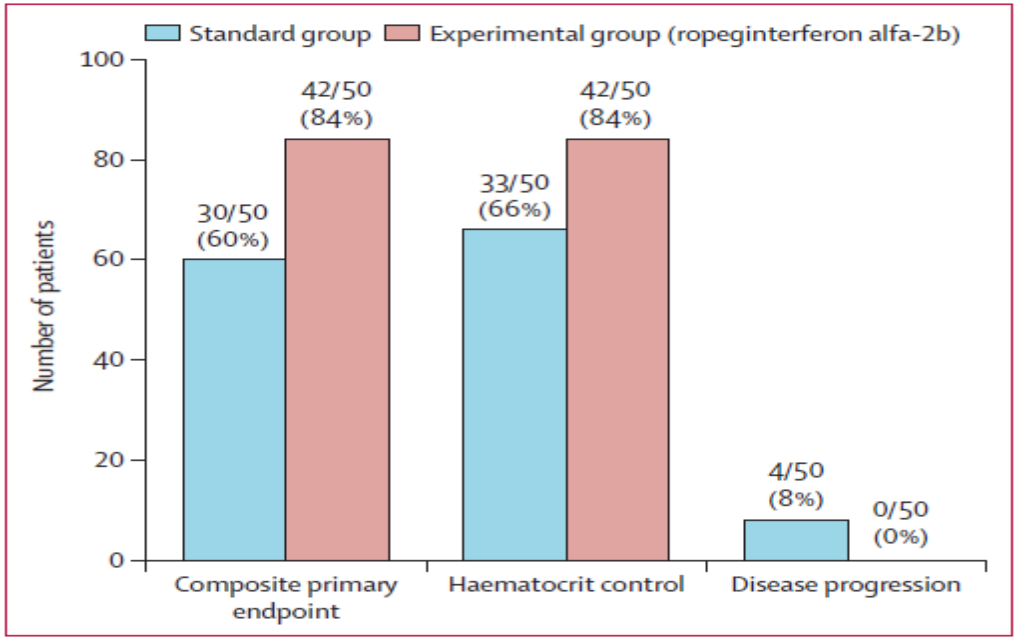
General Population with multiple CV risk factors

PV patients Low-Risk

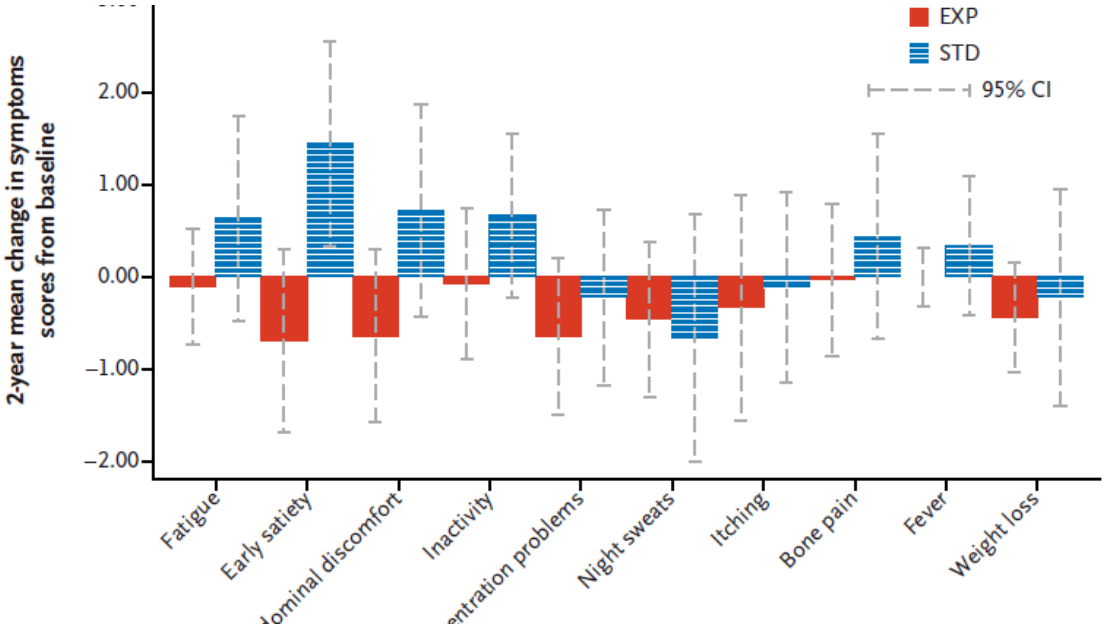
PV patients High-Risk



Low-PV study



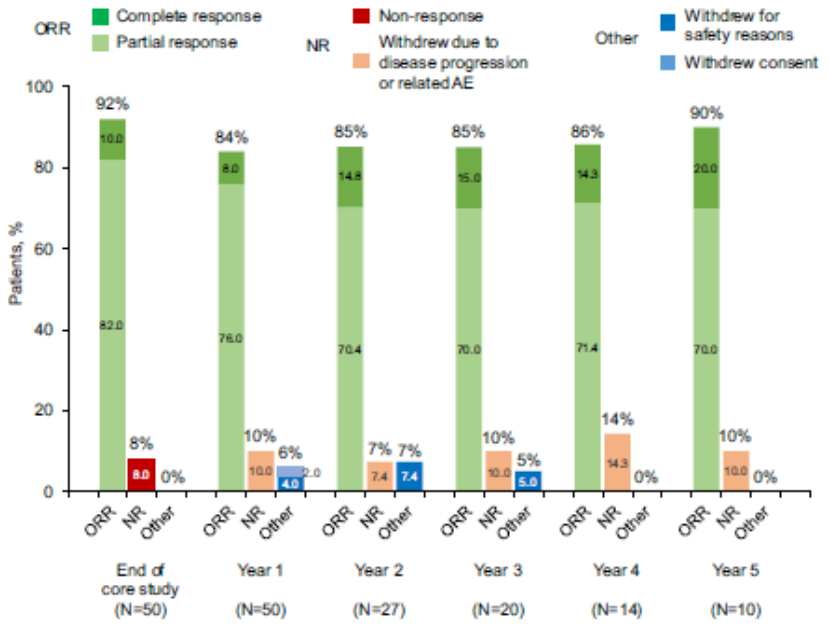
Barbui T et al. Lancet Hematol 2021



Barbui T et al. NEJM Evid 2023

Long-term safety and efficacy of givinostat in polycythemia vera: 4-year mean follow up of three phase 1/2 studies and a compassionate use program

Alessandro Rambaldi[1], Alessandra Iurlo[2], Alessandro M. Vannucchi[3], Bruno Martino[4], Attilio Guarini[5], Marco Ruggeri[6], Nikolas von Bubnoff[7,8], Marianna De Muro[9], Mary Frances McMullin[10], Stefania Luciani[11], Vincenzo Martinelli[12], Axel Nogai[13], Vittorio Rosti[14], Alessandra Ricco[15], Paolo Bettica[16], Sara Manzoni[16] and Silvia Di Tollo[16]



Rambaldi A et al. Blood Cancer J 2021

ONGOING

Randomized, open-label, multicenter **phase 3 study** to assess the efficacy and safety of **Givinostat versus hydroxyurea in JAK2V617F-positive high-risk Polycythemia Vera patients**: the GIV-IN PV TRIAL

TRIAL OBJECTIVE

To compare the efficacy, safety and tolerability of givinostat versus HU after 48 weeks of treatment in HR patients affected by polycythemia vera

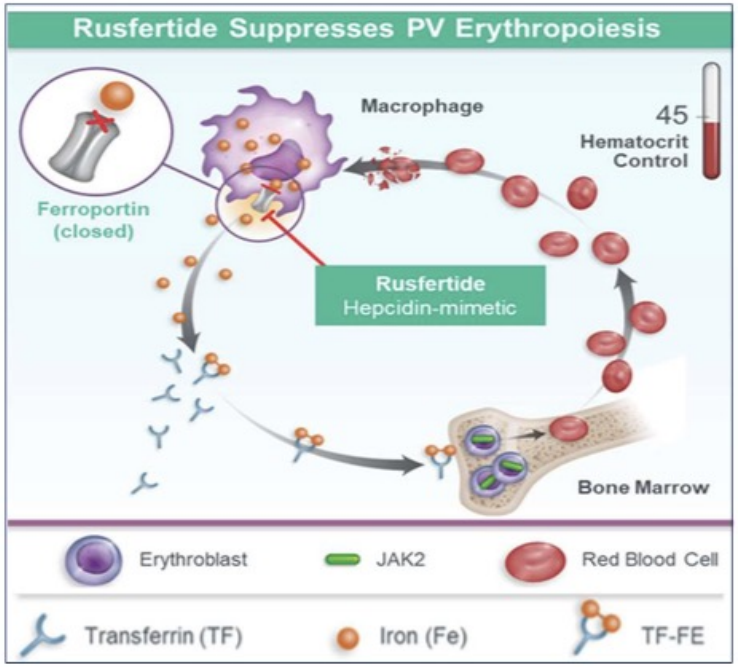
PRIMARY ENDPOINT

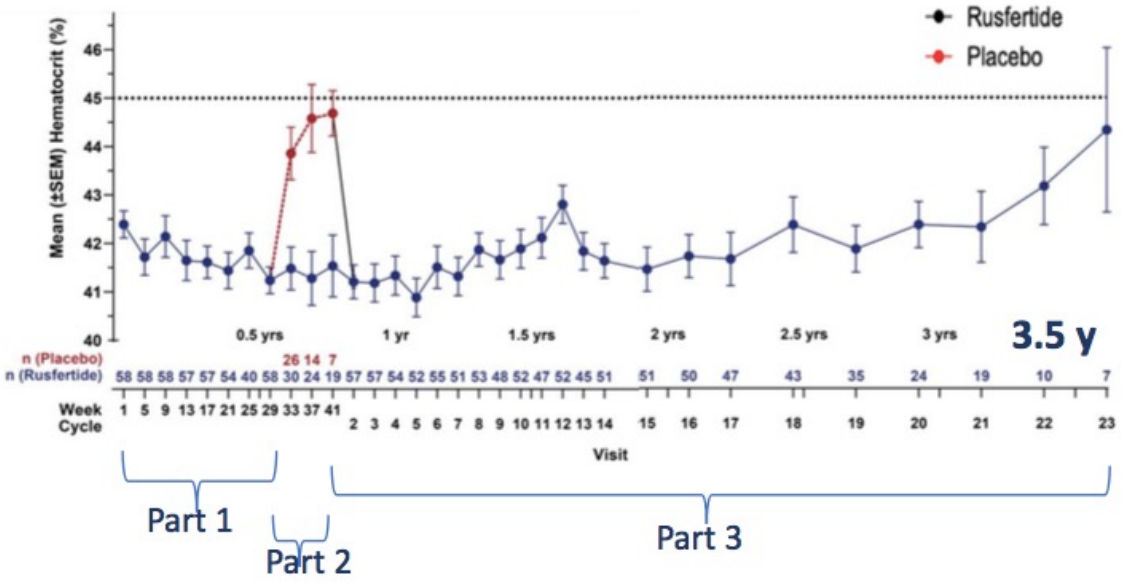
- HCT < 45% without phlebotomy in the prior 3 months,
- White blood cell (WBC) ≤10 × 109/L,
- PLT≤ 400 × 109/L,
- Normal spleen size

Rusfertide

N=58 PHLs dependent (≥3/28W)

44% Low Risk, 47% CT

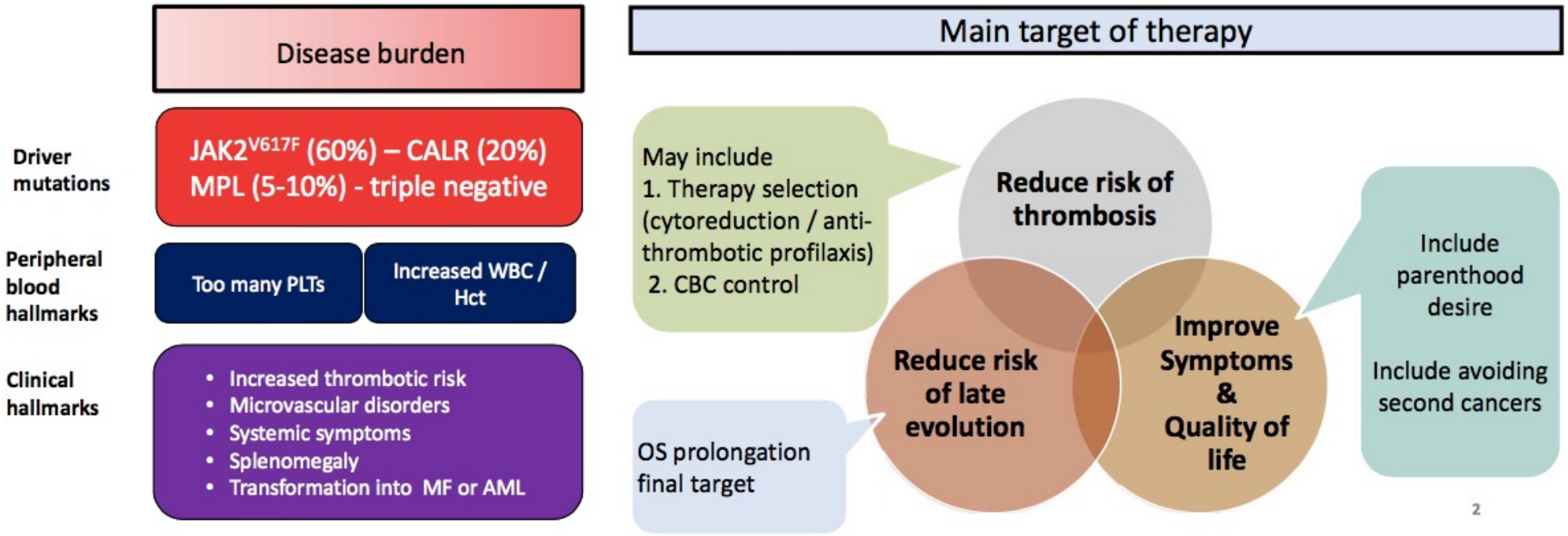




- ↓ Phl.s (<1/y) and symptoms, mean WBC count stable
- After rising by ~30%, PLT count stable over time
- N=9 NMSC; N=7 thrombosis in High-Risk pts within W100

Kremayanska et al, NEJM 2024; Gerds et al, ASH 2024 Poster 4559

Essential Thrombocythemia



Evolution of prognostic models in ET

ELN guidelines [44] Risk factors	IPSET-Thrombosis [45]	Revised IPSET [46]	MIPSS-ET [48•]
1. Age > 60 2. Previous thrombosis	1. Age > 60 (1 point) 2. CV risk factors* (1 point) 3. Previous thrombosis (2 points) 4. *JAK2*V617F (2 points)	1. Age > 60 2. Previous thrombosis 3. *JAK2*V617F	1. Age > 60 (4 points) 2. Male sex (1 point) 3. Adverse mutations# (2 points) 4. WBC count ≥ 11×10^9/L (1 point)
(a) Low risk: none of the above (b) High risk: at least one of the above	(a) Low risk: 0–1 point (b) Intermediate risk: 2 points (c) High risk: ≥ 3 points	(a) Very low risk: none of the above (b) Low risk: no thrombosis history, age ≤ 60 and *JAK2*-mutated (c) Intermediate risk: age > 60, no thrombosis history, and *JAK2*-unmutated (d) High risk: thrombosis history or age > 60 with *JAK2* mutation	(a) Low risk: 0–1 point (b) Intermediate risk: 2–5 points (c) High risk: ≥ 6 points

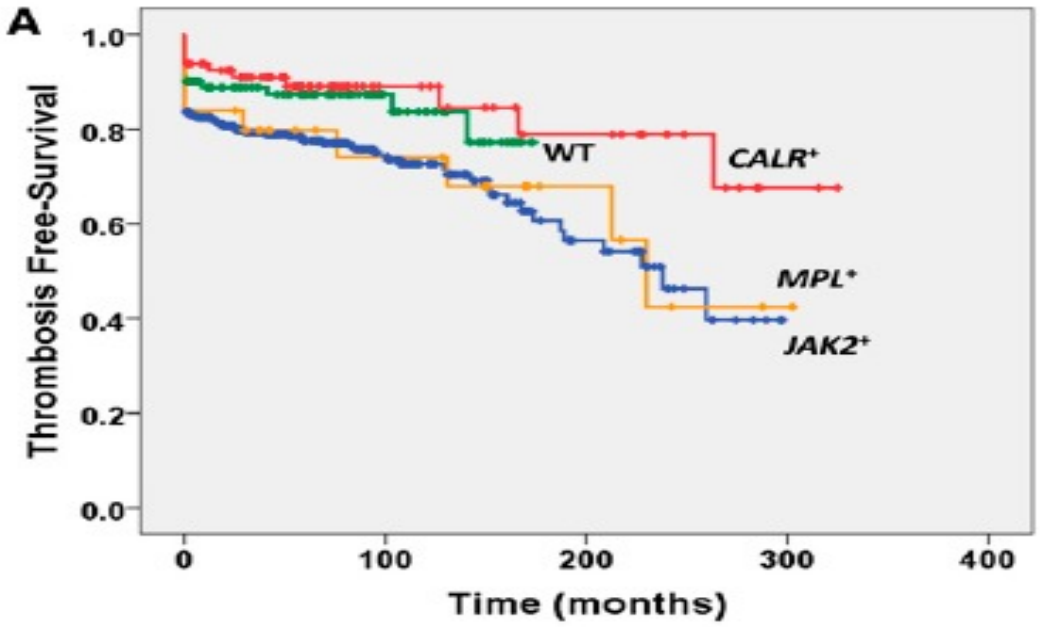
CV, cardiovascular; *WBC*, white blood cells

*CV risk factors: hypertension, diabetes, and active tobacco use

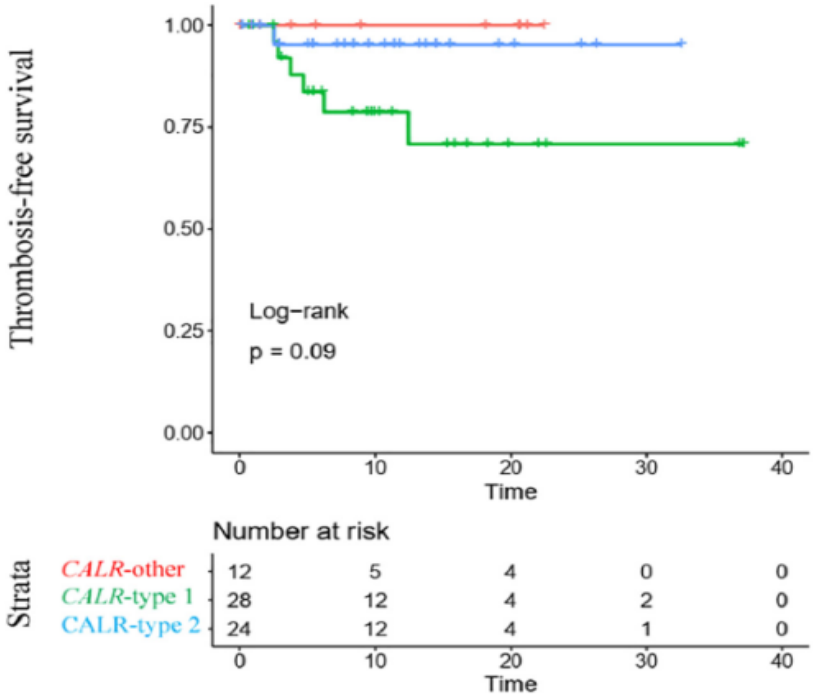
#Adverse mutations: any mutation in *SRSF2*, *SF3B1*, *U2AF1*, *TP53*

Iurlo A et al. Curr Treat Options Oncol 2023

Impact on thrombotic risk of canonical and atypical *CALR* mutations in ET



Rotunno G et al. Blood 2014



Fabris S et al. Thromb Res 2022

ARES trial

The **currently recommended aspirin regimen of 75 to 100 once daily for cardiovascular prophylaxis appears to be largely inadequate** in reducing platelet activation in the vast majority of patients with ET.

Rocca et al. Blood 2020

- The antiplatelet response to low-dose aspirin can be markedly improved by shortening the dosing interval to 12 hours, with no improvement with further reductions.

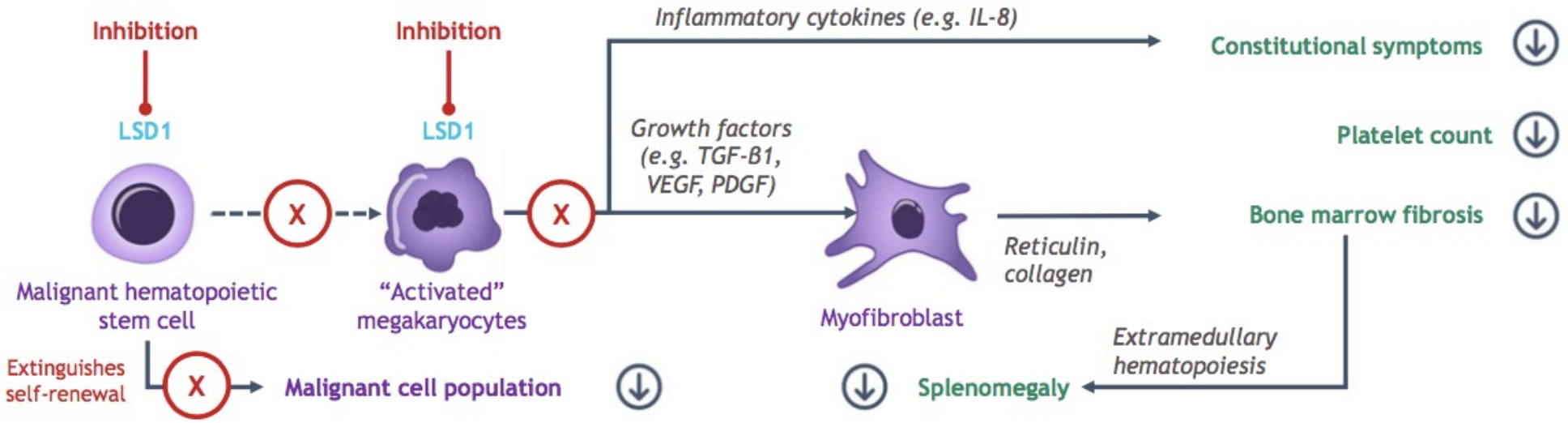
Twice-daily low-dose aspirin was consistently and persistently superior to the standard once-daily regimen in suppressing platelet TXA_2 production in patients with ET and reduced microvascular symptoms with no detectable excess of bleeding complications and gastrointestinal discomfort.

Rocca et al. AJH 2024

- Twice-daily ASA may be considered in selected cases

Bomedemstat

- LSD1 inhibition impairs function of both “activated” megakaryocytes and malignant stem cells
- Megakaryocytes produce cytokines and growth factors that drive bone marrow remodeling (MF)



LSD1 inhibition reduces production of megakaryocytes, growth factors and cytokines = symptom improvement
Potential to extinguish self-renewal of malignant stem cells = potential to improve OS

GRAZIE PER L'ATTENZIONE!

alessandra.iurlo@policlinico.mi.it