GIORNATE EMATOLOGICHE VICENTINE

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Presente e futuro del trattamento della mielofibrosi

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Disclosures of MASSIMILIANO BONIFACIO

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen						X	
Ascentage Pharma						X	
Blueprint Medicines						X	
Bristol Myers Squibb						X	
Glaxo Smith Kline						X	
Incyte						X	
Novartis						X	
Pfizer						X	

Myelofibrosis is a personalized disease

Thrombosis

Thrombocytopenia 20%

Bleedings

Extramedullary hemopoiesis

Risk of leukemia

Leukopenia Leukocytosis

Infections

Splenomegaly 86%

Abdominal pain
Early satiety
Splancnic vein thrombosis

Systemic symptoms 80%

Reduced QoL
Reduced work capacity

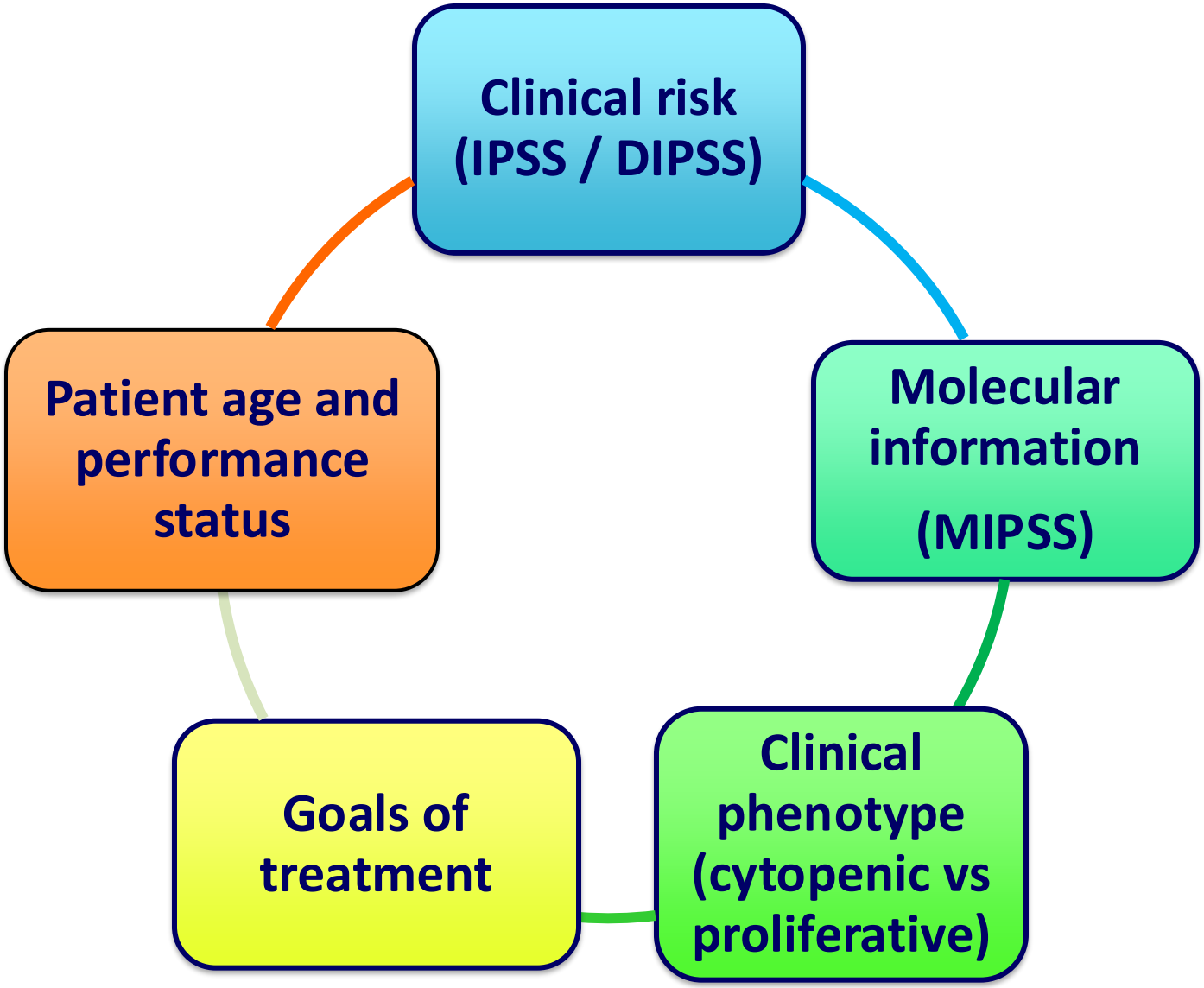
Anemia 40-60%

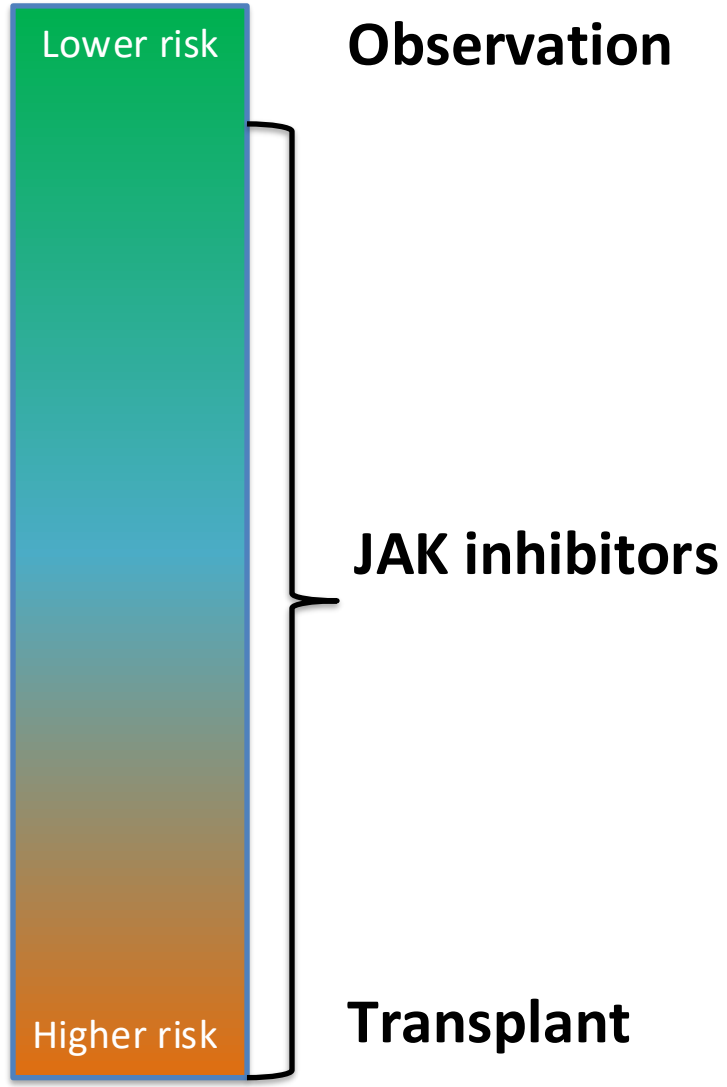
Need for RBC transfusion

- A patient may present more than one clinical need at the same time
- Prioritization of clinical needs may be necessary and may change over time
- Addressing one clinical need may worsen other clinical needs.

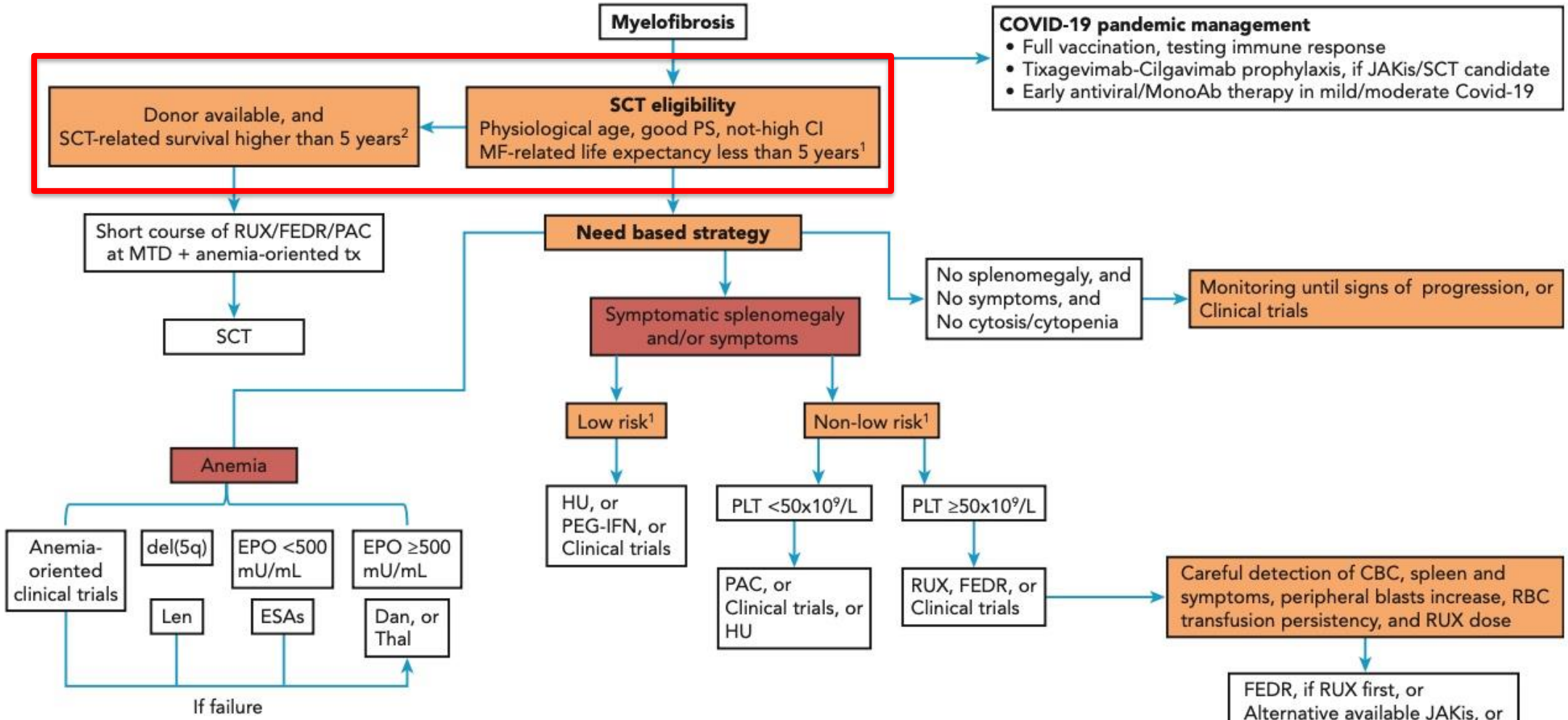
Courtesy of Francesca Palandri

Factors to consider for treatment's choice





Current management of myelofibrosis



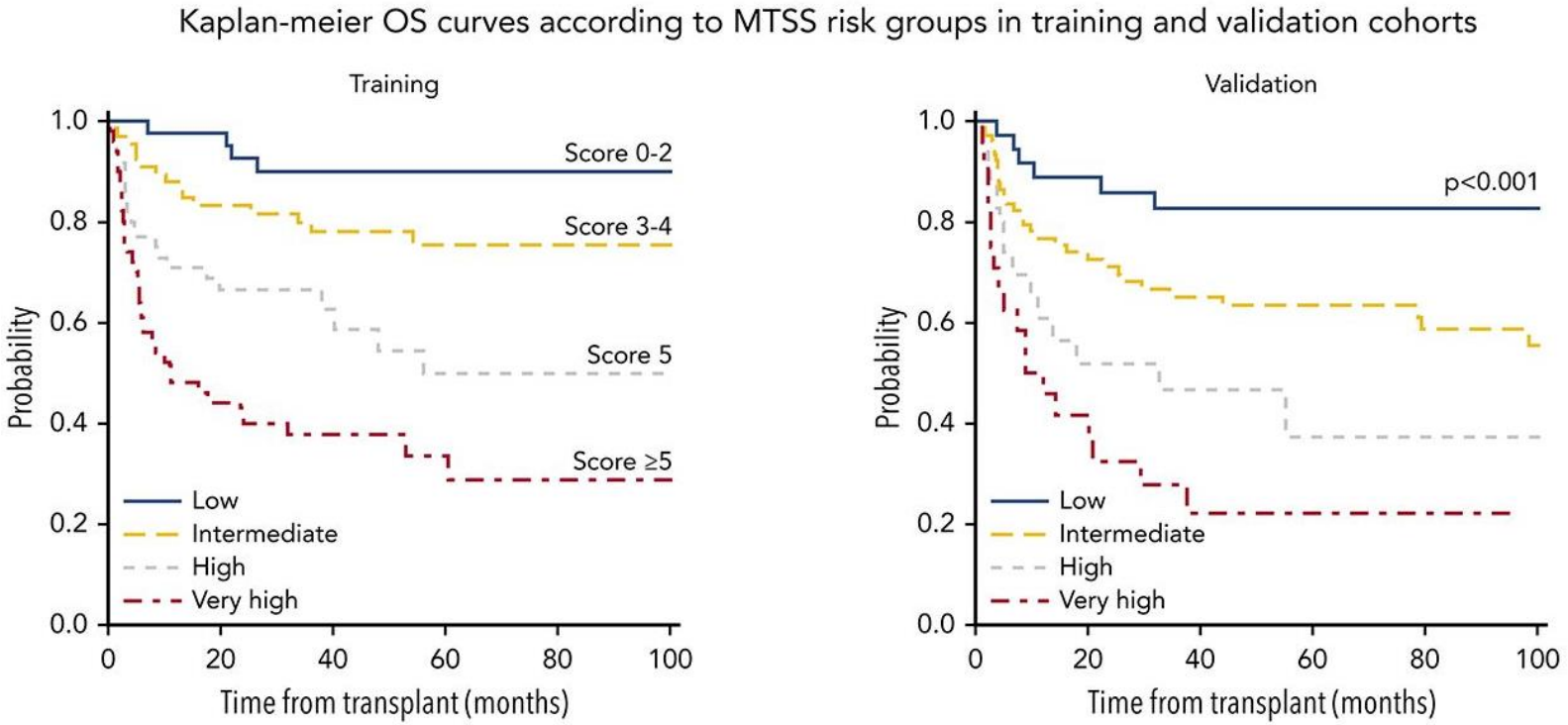
Passamonti and Mora. *Blood* **2023**;141:1954-1970.

Prognostic models to predict survival in myelofibrosis

	DIPSS	DIPSS+	MIPSS-70	MIPSS-70+ version 2.0	MYSEC-PM
Patients' characteristics (score)	Age > 65 y (1) Constitutional symptoms (1)	Age > 65 y (1) Constitutional symptoms (1) RBC transfusions need (1)	Constitutional symptoms (1)	Constitutional symptoms (2)	Age (0.15 × y) Constitutional symptoms (1)
Laboratory values (score)	Hb < 10 g/dl (2) WBC > 25 × 10^9/l (1) Blasts ≥ 1% (1)	Hb < 10 g/dl (1) WBC > 25 × 10^9/l (1) Blasts ≥ 1% (1) PLT < 100 × 10^9/l (1)	Hb < 10 g/dl (1) WBC > 25 × 10^9/l (2) Blasts ≥ 2% (1) PLT < 100 × 10^9/l (2)	Severe anemia[2] (2) Moderate anemia[3] (1) Blasts ≥ 2% (1)	Hb < 11 g/dl (2) Blasts ≥ 3% (2) PLT < 150 × 10^9/l (1)
Driver mutation (score)			Absence of type 1/like *CALR* (1)	Absence of type 1/like *CALR* (2)	Absence of *CALR* (2)
Myeloid-gene variants (score)			1 HMR (1) ≥ 2 HMR (2)	1 HMR included *U2AF1*Q157 (2) ≥ 2 HMR included *U2AF1*Q157 (3)	
Karyotype (score)		Unfavourable[1] (1)		Unfavourable[4] (3) Very high-risk[5] (4)	
Bone marrow (score)			BMF grade ≥ 2 (1)		
Risk (score), median survival	*Low (0)*, NR *Int-1 (1–2)*, 14.2 y *Int-2 (3–4)*, 4 y *High (5–6)*, 1.5 y	*Low (0)*, 15.4 y *Int-1 (1)*, 6.5 y *Int-2 (2–3)*, 2.9 y *High (≥ 4)*, 1.3 y	*Low (0–1)*, NR *Int (2–4)*, 6.3 y *High (≥ 5)*, 3.1 y	*Very low (0)*, NR *Low (1–2)*, 16.4 y *Int (3–4)*, 7.7 y *High (5–8)*, 4.1 y *Very high (≥ 9)*, 1.8 y	*Low (< 11)*, NR *Int-1 (11–13)*, 9.3 y *Int-2 (14–15)*, 4.4 y *High (≥ 16)*, 2 y

Mora et al. *Curr Hematol Malign rep* **2024**;19:223-235.

Prognostic models to predict survival after transplant (1)

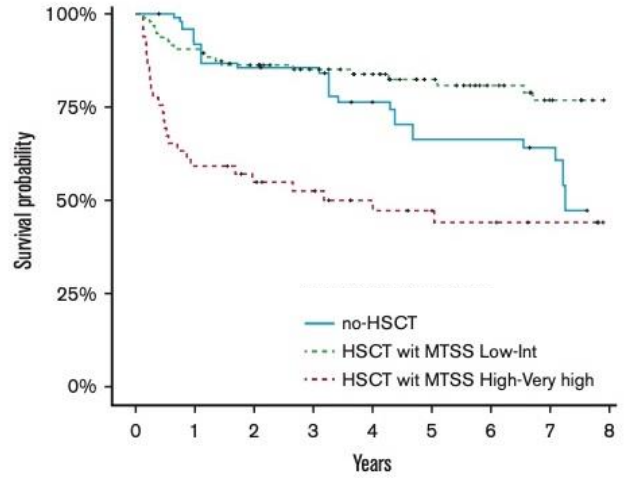


Variable	Platelets <150 x 10^9/L	Leukocytes >25 x 10^9/L	Karnofsky performance status <90%	Age ≥57 years	Non-*CALR*/*MPL* driver mutation genotype	*ASXL1* mutation	HLA-mismatched unrelated donor
HR	1.67	1.57	1.50	1.65	2.40	1.42	2.08
Score	1	1	1	1	2	1	2

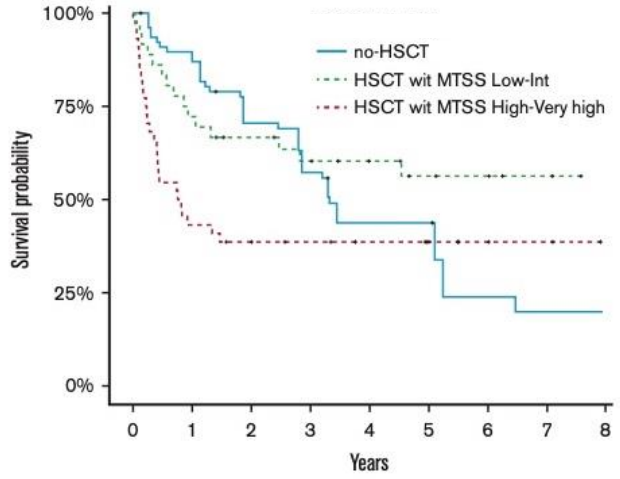
Gagelmann et al. *Blood* **2019**;133:2233-2242.

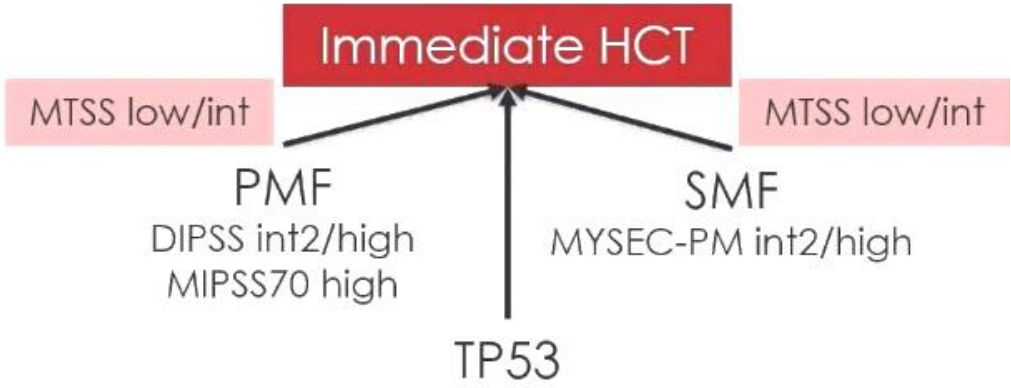
Integration of prognostic models for personalized transplant decision making

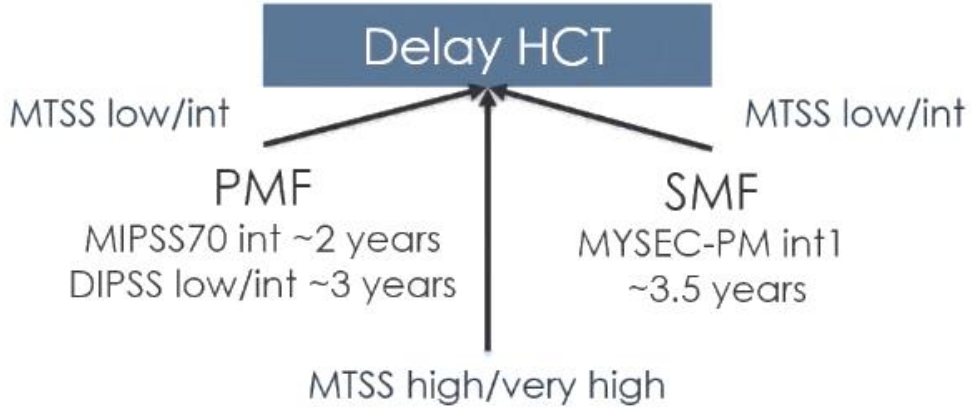
MIPSS70: Intermediate



MIPSS70: High

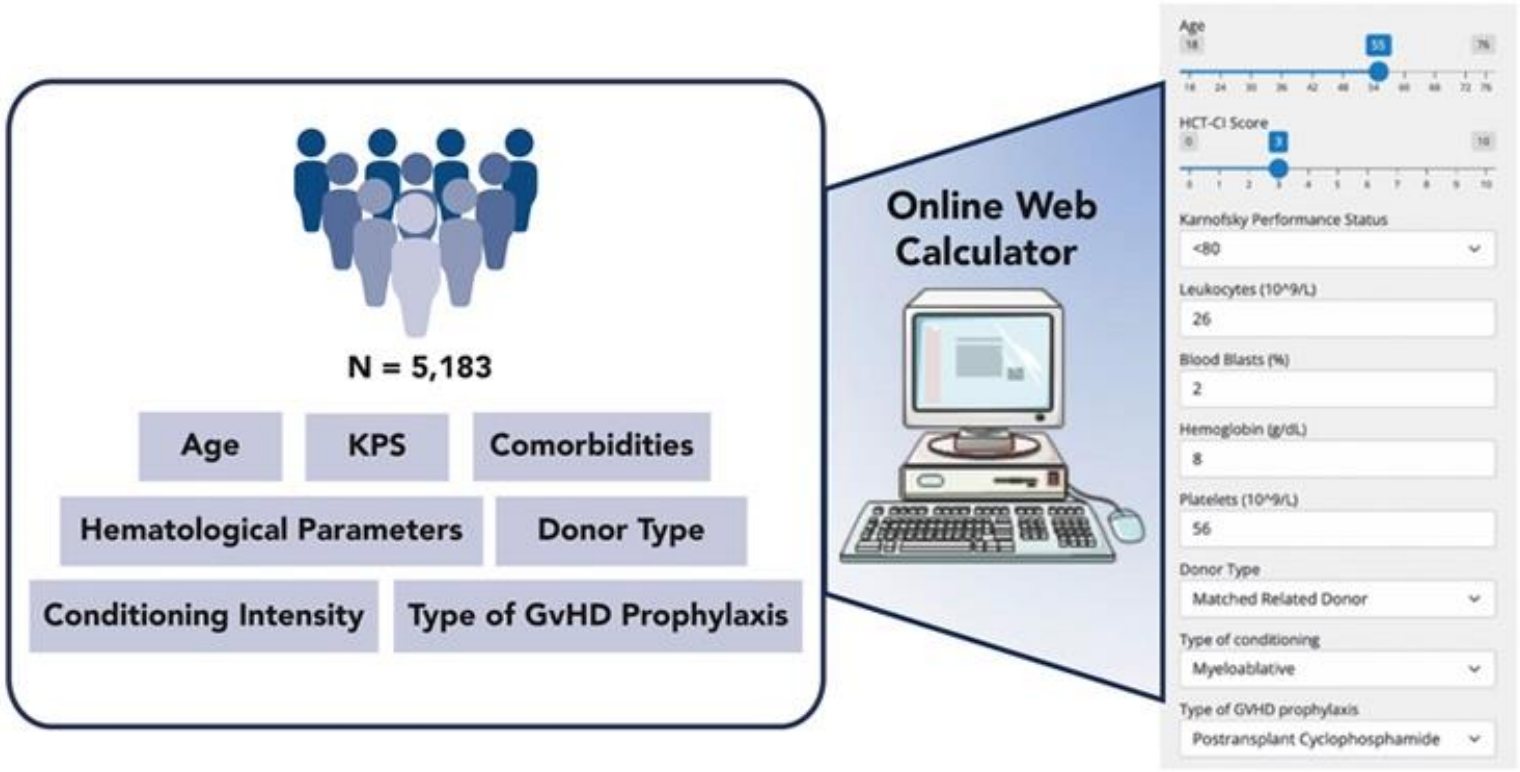






Luque-Paz et al. *Blood Adv* **2024**;9:797-807. Gagelmann et al. *Blood (ASH annual meeting)* **2024**;abs#245.

Prognostic models to predict survival after transplant (2)



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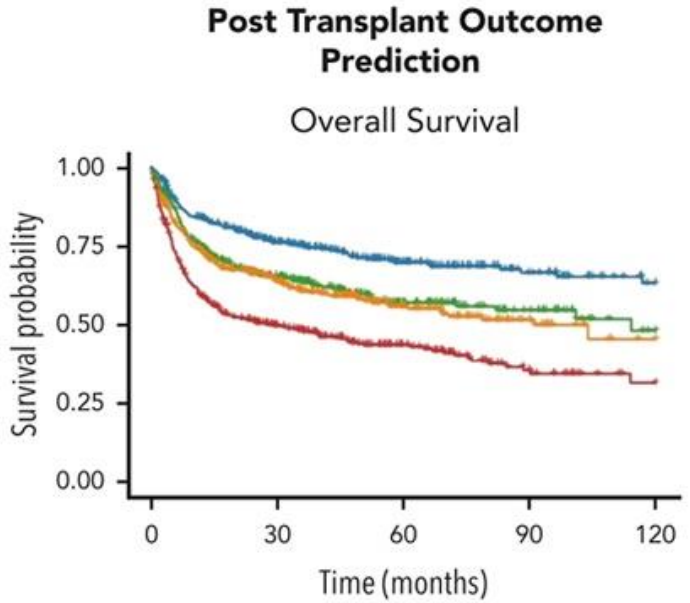
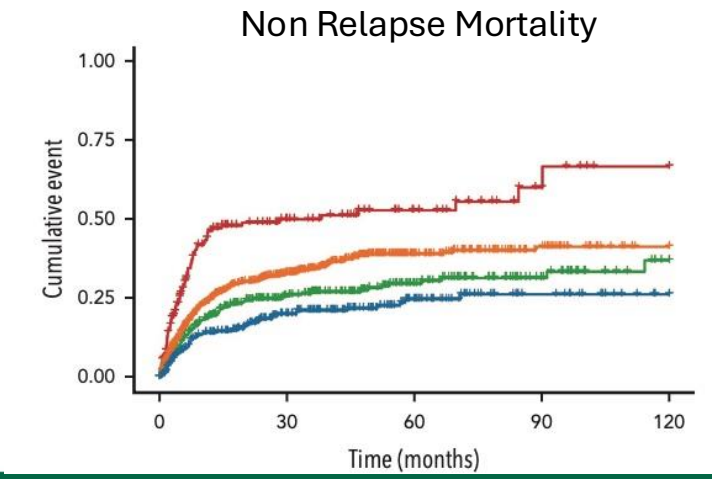




Hernandez-Boluda et al. *Blood* **2025**;145:3139-3152.

Overview of JAK inhibitors in myelofibrosis

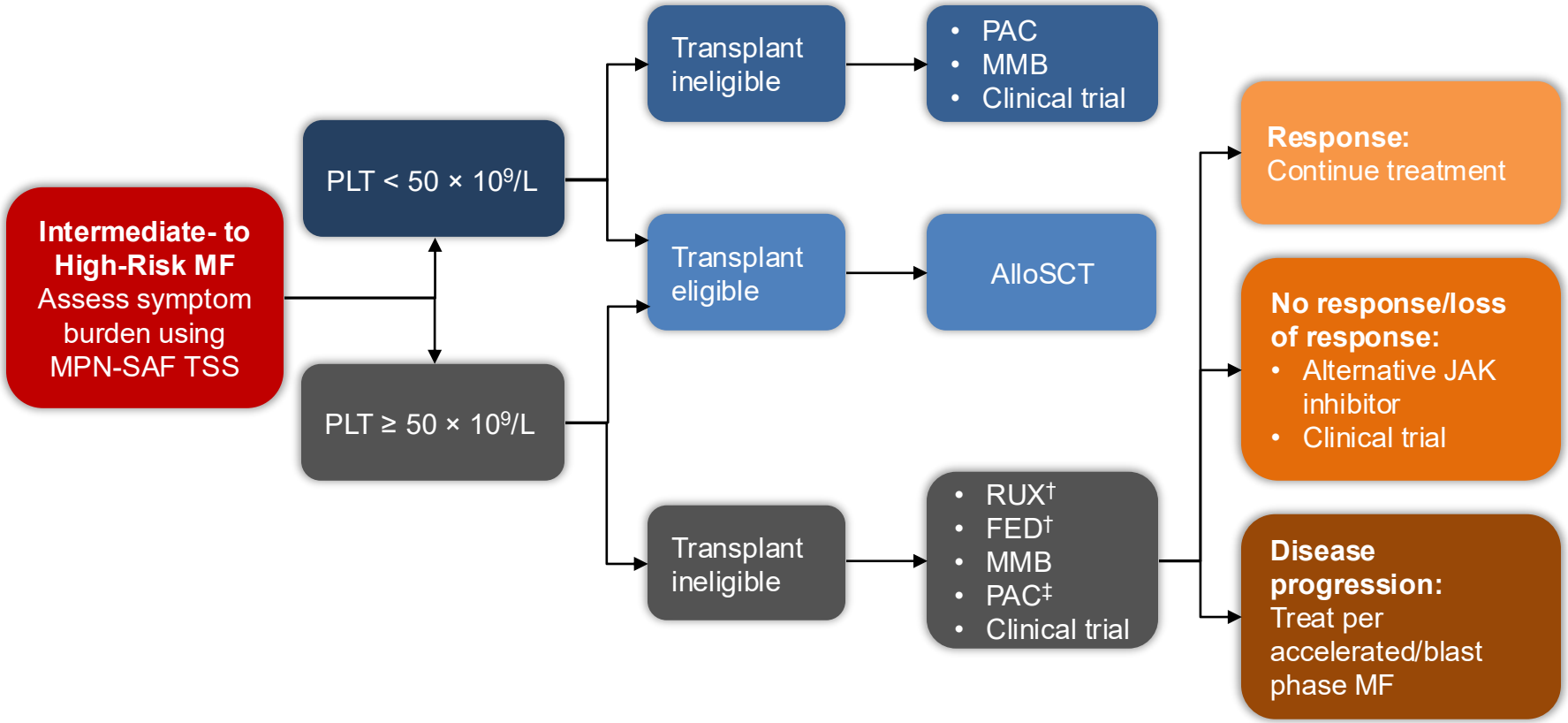
JAK-inhibitors

Potential mechanism of action:

1. Suppresses the growth of malignant cells (*JAK2* inhibition)
2. Down-regulate the cytokines (*JAK1* & JAK2 inhibition) that contribute to hyperinflammation and hypermetabolic state

Not selective for *JAK2V617F* mutation

1. Benefit for patients with and without mutation
2. On-target side effects related to
   - *JAK2* inhibition (decreased erythropoiesis and thrombocytopoiesis)
   - *JAK1* inhibition (decreased immune surveillance)



*All recommendations are category 2A unless otherwise indicated. †Category 1 recommendation.‡Category 2B recommendation.

AlloSCT, allogeneic stem cell transplantation; AML, acute myeloid leukemia; FED, fedratinib; HCT, hematopoietic cell transplant; JAK, Janus kinase; MF, myelofibrosis; MPN, myeloproliferative neoplasms; MPN-SAF-TSS, Myeloproliferative Neoplasms Symptom Assessment Form: Total Symptom Score. PAC, pacritinib; PLT, platelet; RUX, ruxolitinib.

NCCN Clinical Practice Guidelines in Oncology: Myeloproliferative Neoplasms. Version 2.**2025**

What are the benefits of ruxolitinib in myelofibrosis?

- **Splenomegaly:** Evidence of therapeutic benefit based on SVR35
- **Symptoms:** Evidence of therapeutic benefit based on TSS50
- **Survival:** Evidence of survival benefit for ruxolitinib

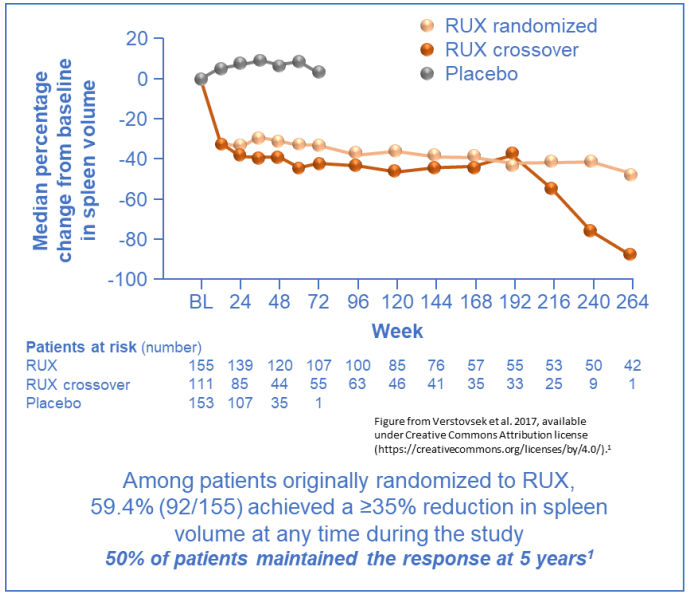


Figure from Verstovsek et al. 2017, available under Creative Commons Attribution license (https://creativecommons.org/licenses/by/4.0/).[1]

Among patients originally randomized to RUX, 59.4% (92/155) achieved a ≥35% reduction in spleen volume at any time during the study

50% of patients maintained the response at 5 years[1]

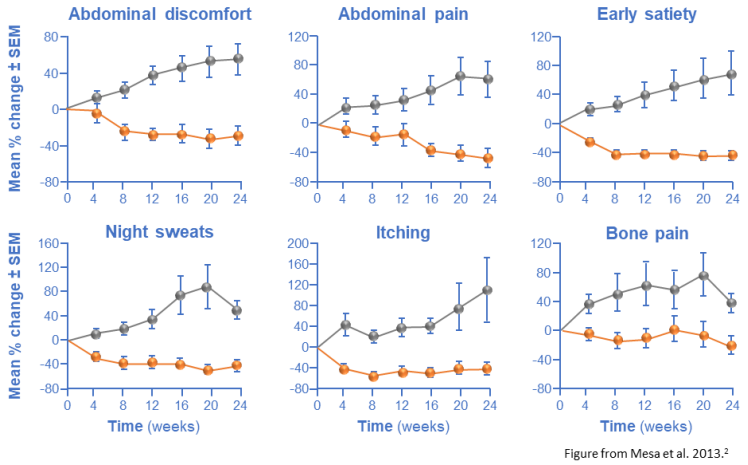
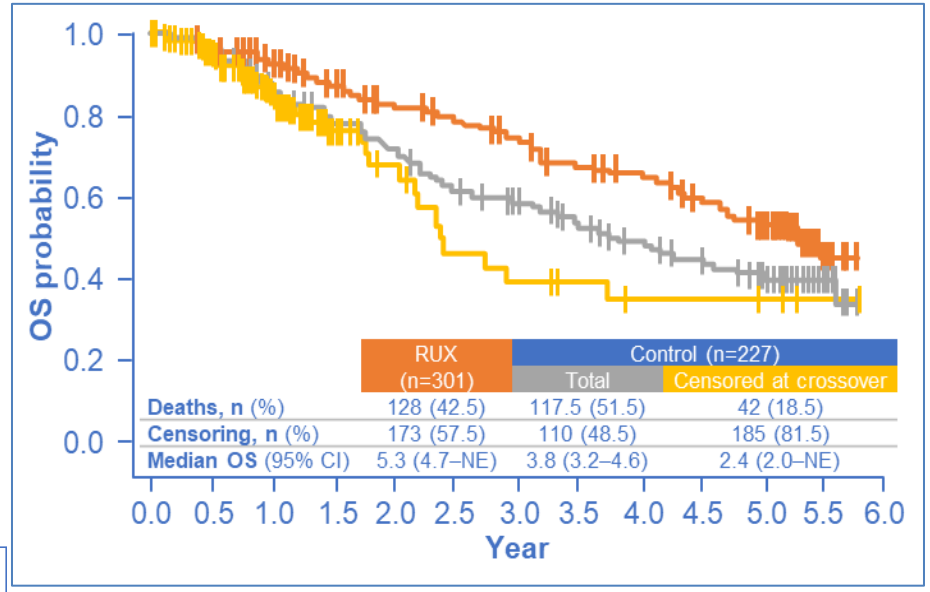


Figure from Mesa et al. 2013.[2]

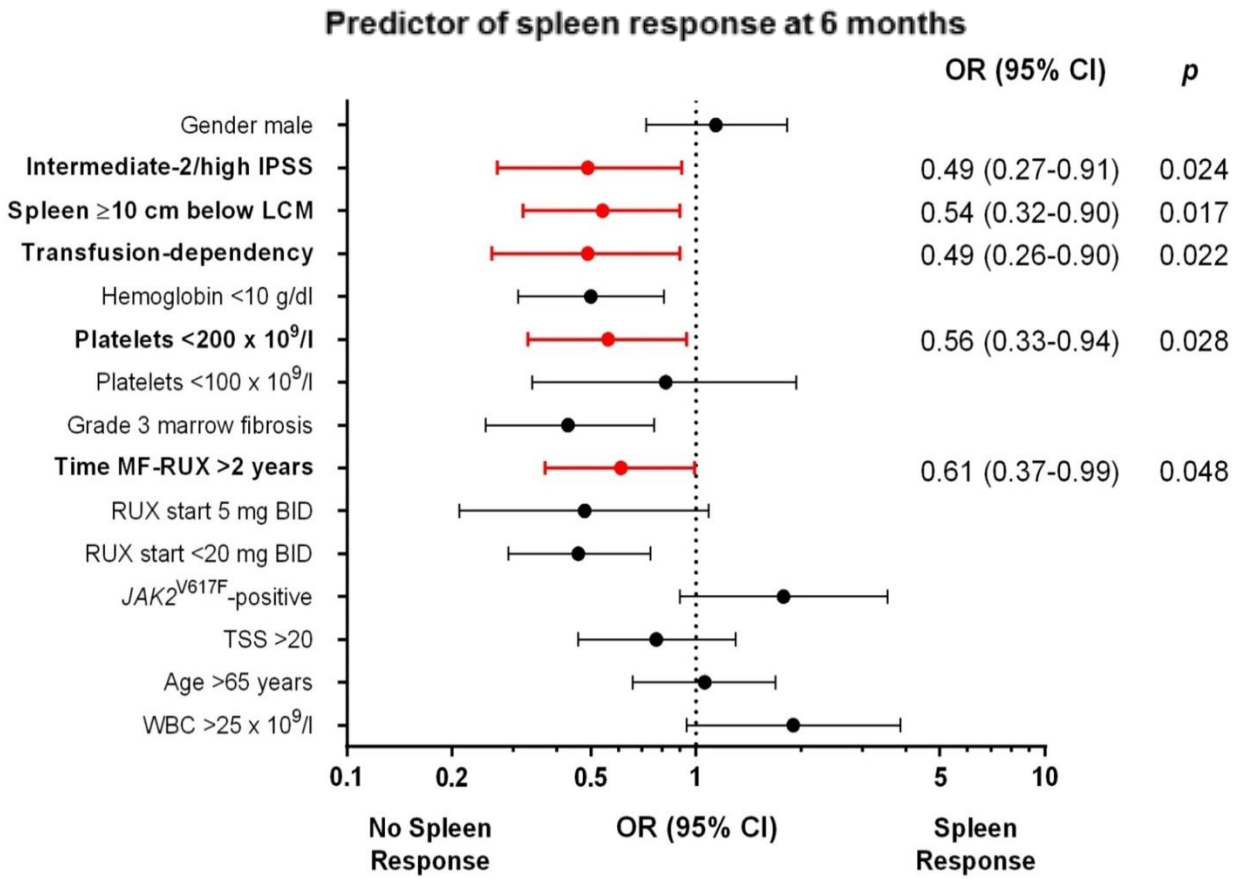
Individual symptom scores, as assessed by the modified MFSAF v2.0 at each 4-week timepoint in patients receiving RUX, showed **improvement relative to baseline[2]**

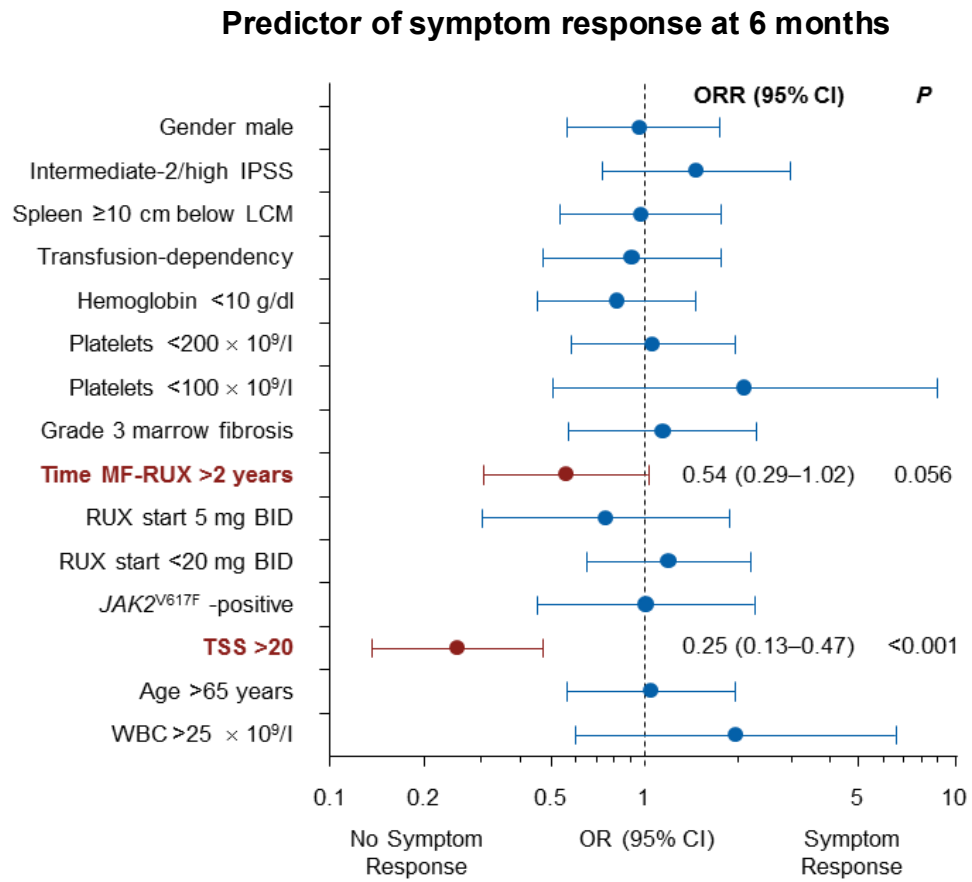
RUX
Placebo



Verstovsek et al. *J Hematol Oncol* **2017**;10:55. Mesa et al. *J Clin Oncol* **2013**;31:1285-1292.

Early intervention with ruxolitinib results in higher rates of response





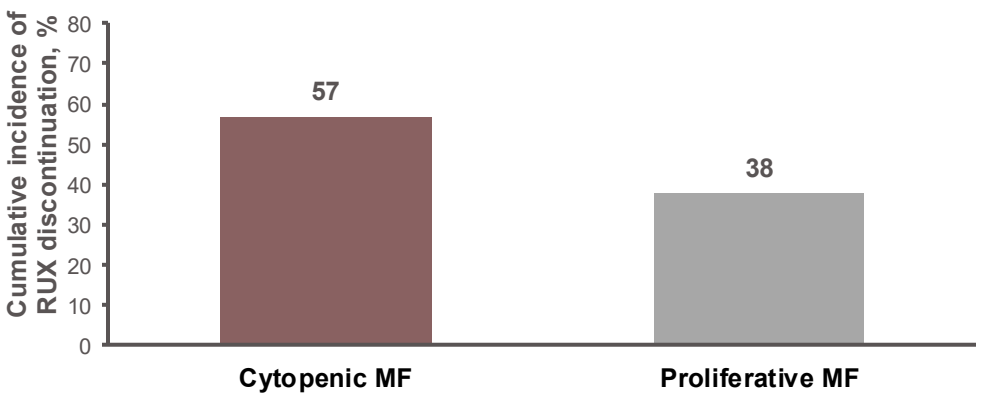
Delaying treatment from MF diagnosis to ruxolitinib start >2 years reduces probability of response by 40-50%

Palandri, Palumbo, Bonifacio et al. *Oncotarget* **2017**;8:79073-79086.

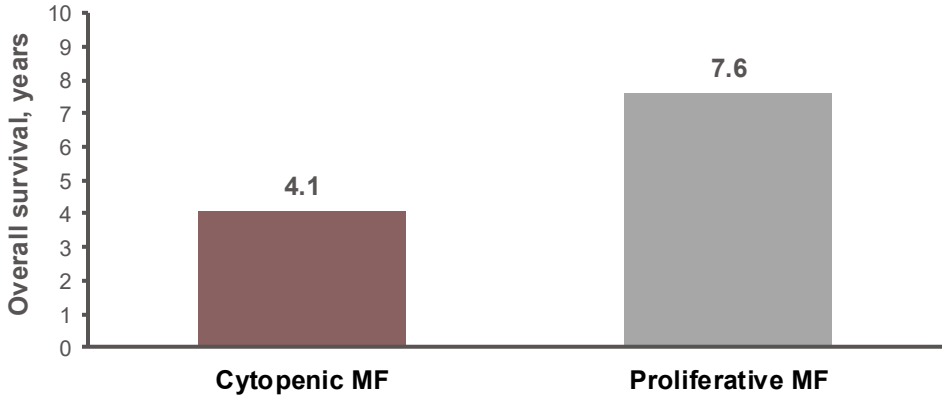
Ruxolitinib has a lower efficacy in cytopenic myelofibrosis

- The RUX-MF retrospective study evaluated 886 RUX-treated chronic-phase patients in 26 hematology centers.
- At ruxolitinib start, a cytopenic phenotype was present in 407 (45.9%) patients. Anemia was present in over 80% of the patients

Rates of spleen response at Week 24 was significantly lower in patients with cytopenic MF (**34.1%**) compared with those with proliferative MF (**26.5%**; P = 0.04)



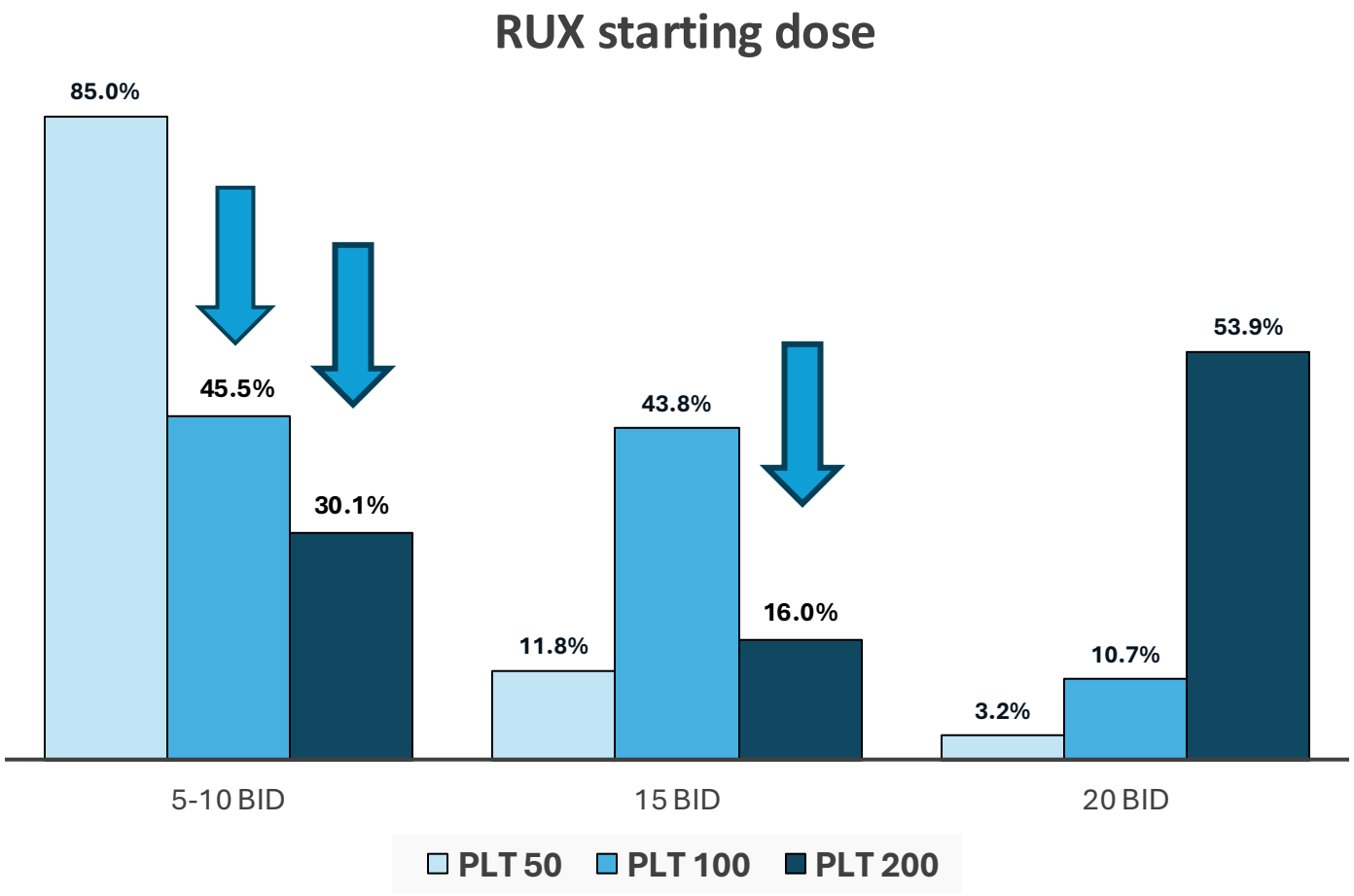
Cumulative incidence of RUX discontinuation at 5 years was 57% and 38% in patients with cytopenic and proliferative MF, respectively



Overall survival was significantly shorter in patients with cytopenic (4.1 years) versus proliferative MF (7.6 years; P < 0.001)

Palandri et al. *Cancer* **2023**;129:1704-1713.

Ruxolitinib is underdosed in almost 50% of patients (Italy, real-life)



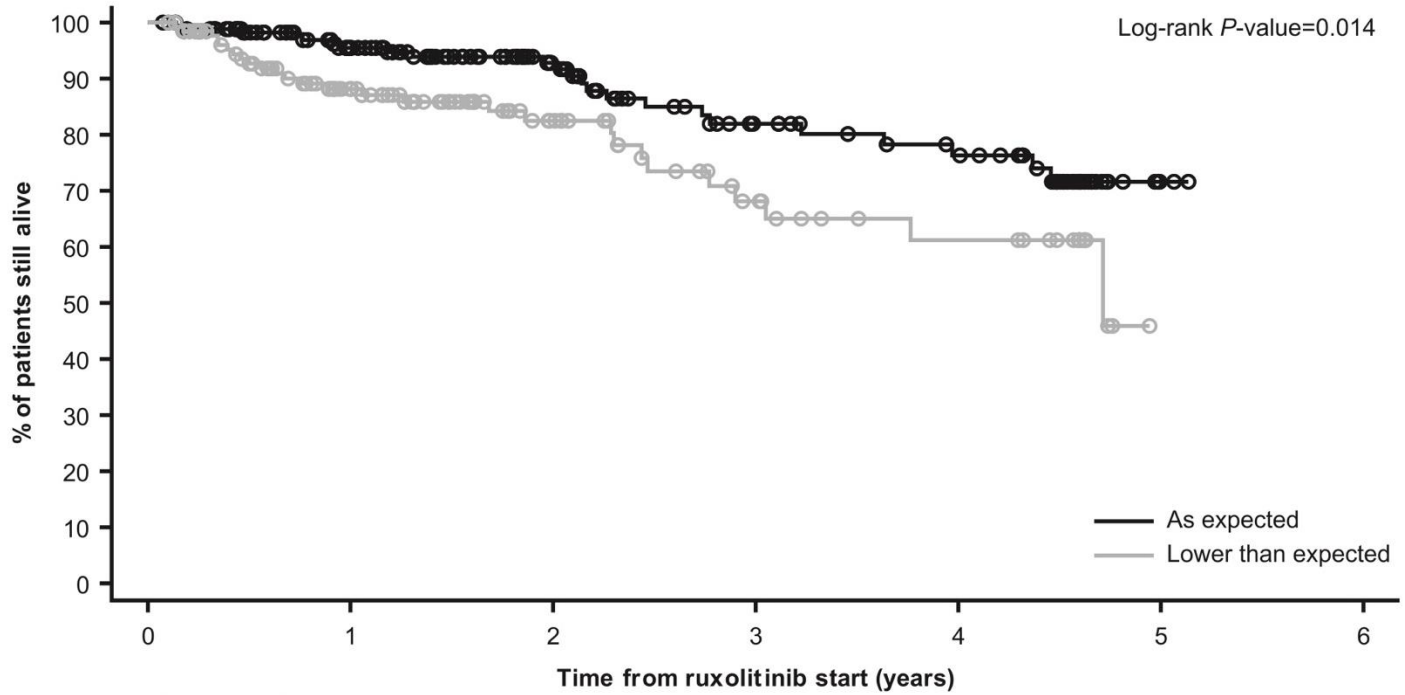
In the real-world "RUX-MF" study including >1000 MF patients treated with ruxolitinib in a real-life context:

- 45.5% of PLT-100 and 46.1% of PLT-200 patients started with lower doses than expected, mainly 10 mg BID.
- Among the 365 (41.2%) patients who started with lower-than-expected ruxolitinib dose, 177 (48.5%) had anemia and/or leukopenia.

Palandri et al. *Cancer* **2023**;129:1704-1713.

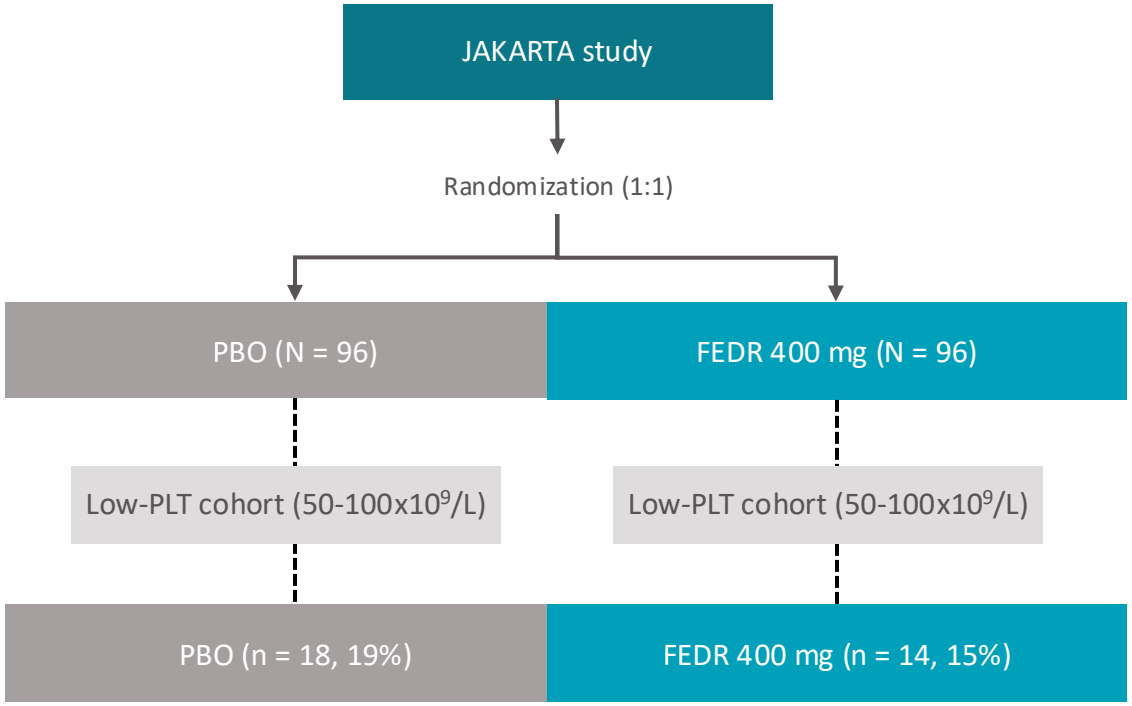
Use of lower ruxolitinib doses has a strong impact on survival

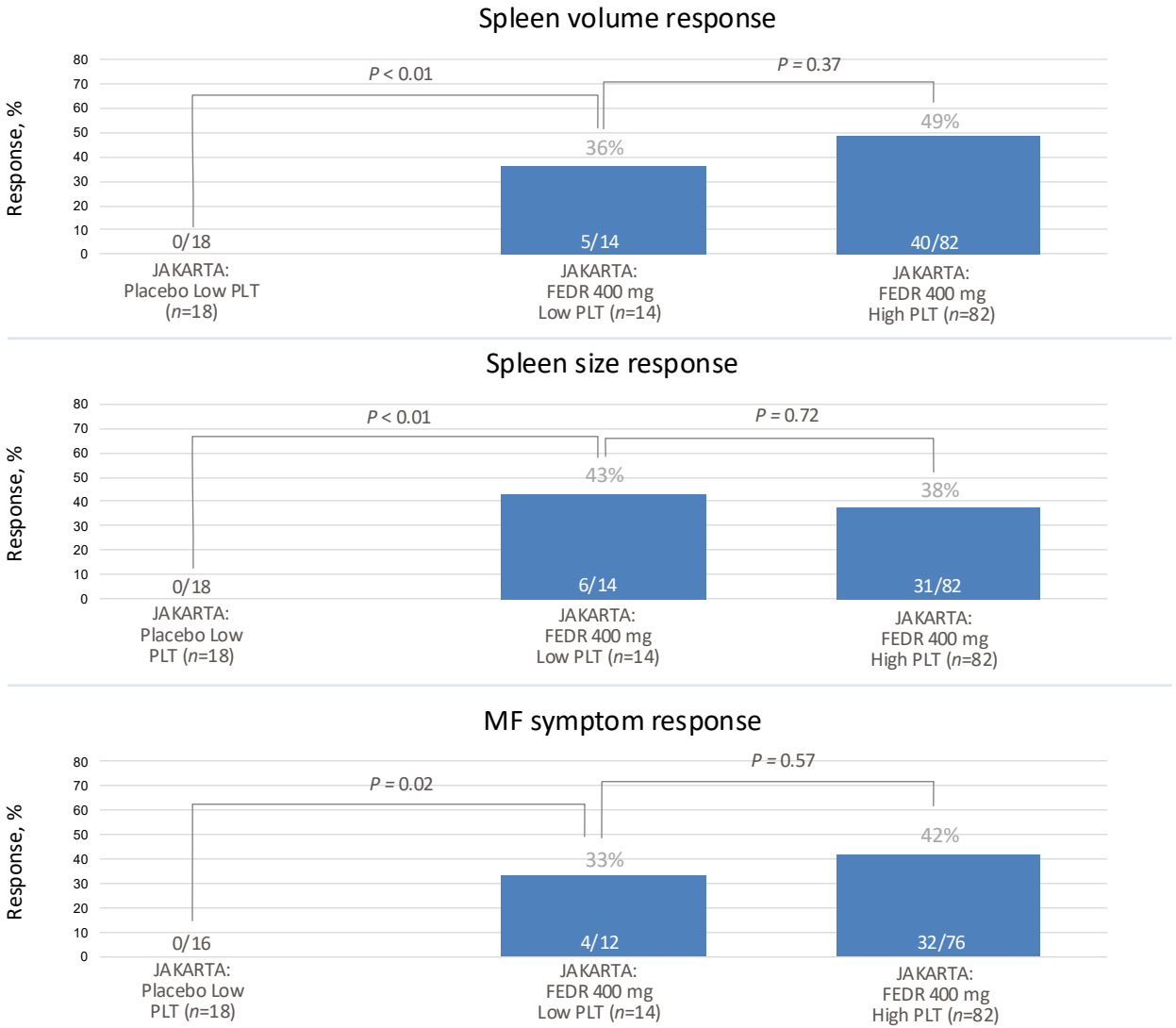
Compared to patients treated as-expected, patients treated with lower-than-expected ruxolitinib doses were older (p=.001), with lower hemoglobin baseline levels (p=.009) and with lower platelets at baseline (p=.021).



Breccia et al. *Cancer* **2025**;131:e35801.

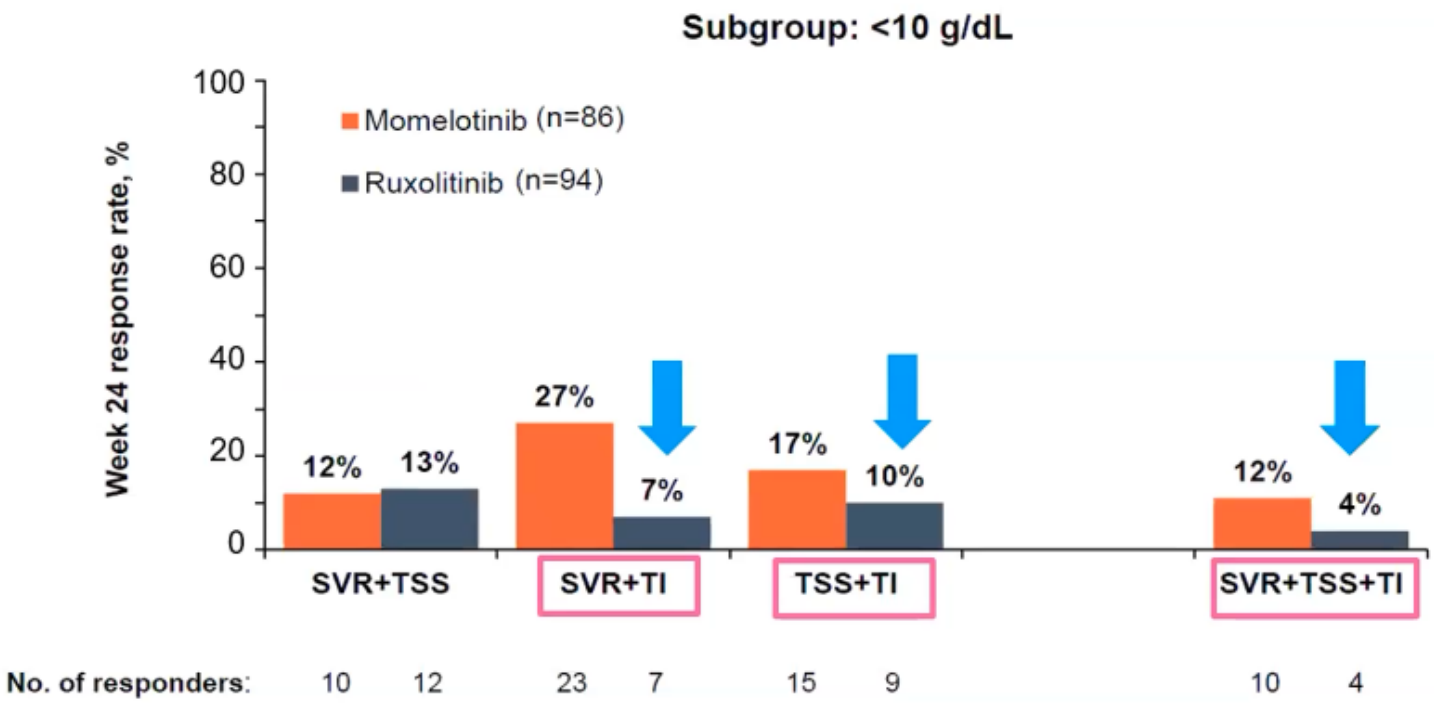
Front-line fedratinib: analysis of efficacy per platelet count





Harrison et al. *Br J Haematol* **2022**;198:317-327.

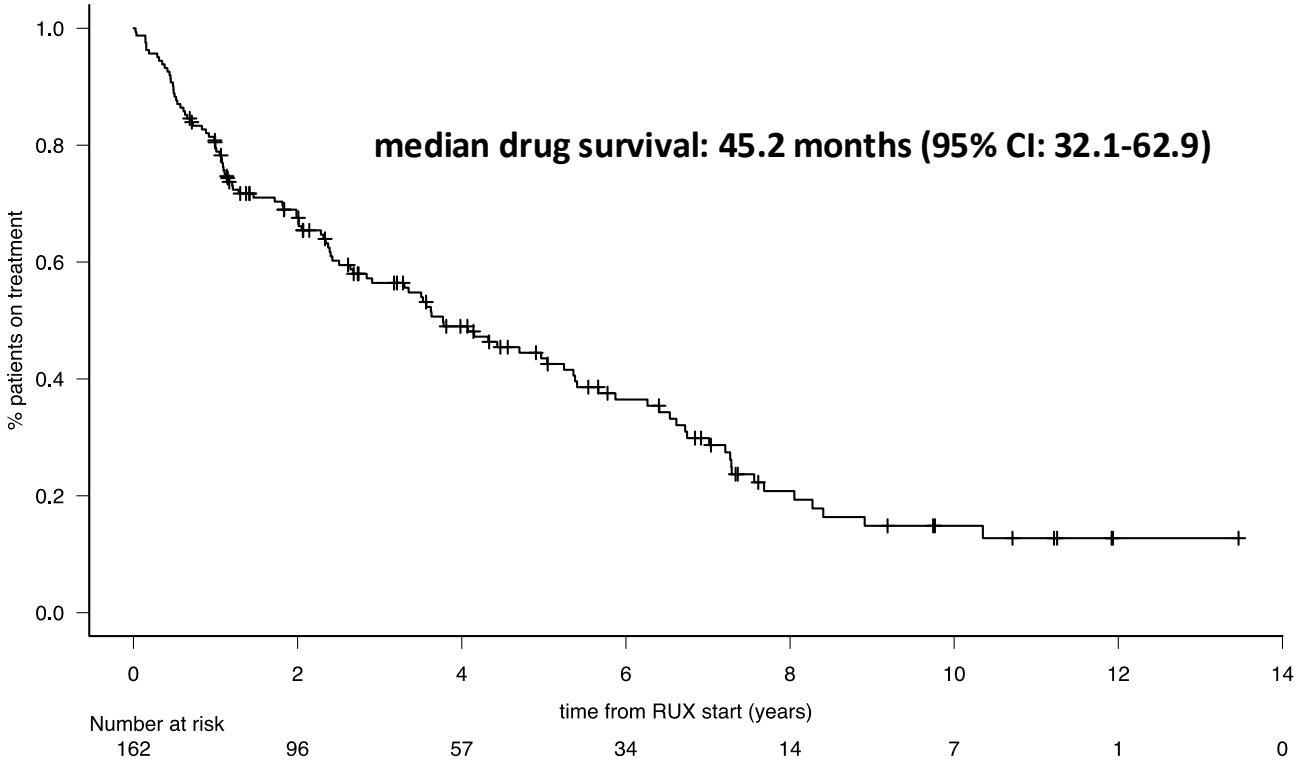
Front-line momelotinib in patients with moderate/severe anemia

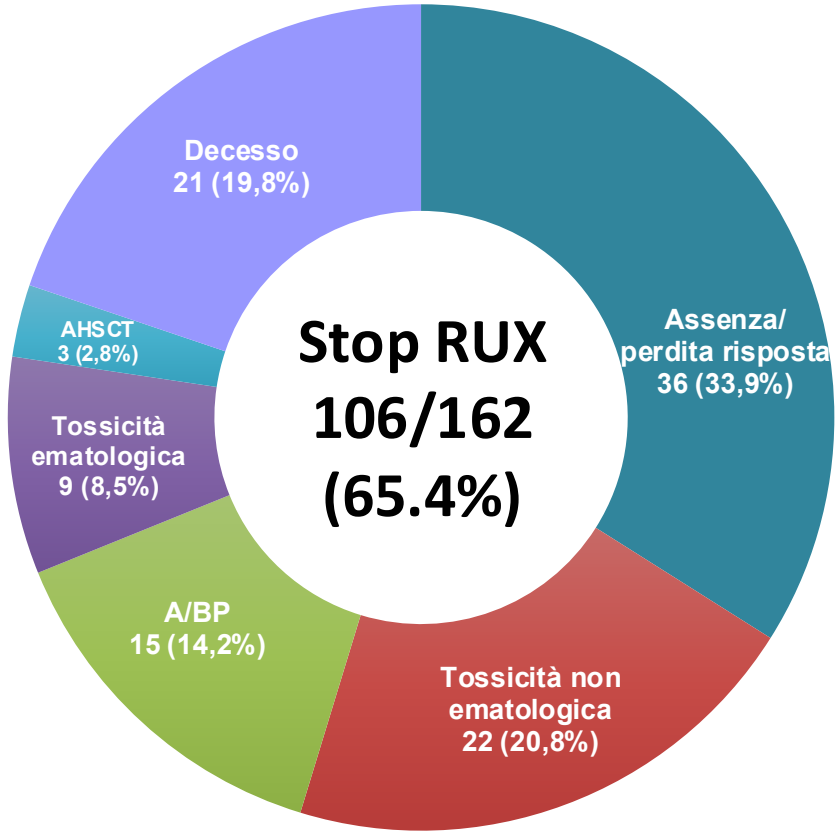


- In the **moderately/severely anemic subgroup**
- In the MMB group a dual endpoint of TI was achieved by 23 of 27 (85.2%) splenic responders and 15 of 21 (71.4%) TSS responders
- Dual endpoint rates were lower with RUX in the anemic subgroups;
- TI was achieved by 7 of 31 (22.6%) splenic responders and 9 of 33 (27.3%) TSS responders
- Triple responses (SVR, TSS, and TI) were more frequent with MMB vs RUX

Gupta et al. *Leuk Lymhpoma* **2024;65:965-977.**

Rates and reasons for ruxolitinib discontinuation





Personal data. Thanks to Dr. Alda Strazimiri

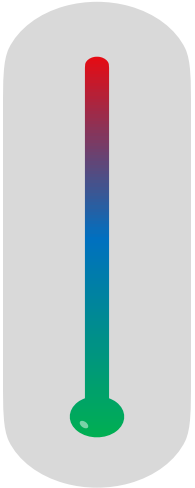
A prognostic model to predict survival with ruxolitinib and guide treatment switch

- RUX at a dose <20 mg twice daily at all time points
- RBC transfusion requirement at 3 and/or 6 months

→ 1 point

- RBC transfusions at all time points
- Palpable spleen length reduction ≤30% respect to baseline at 3 and 6 months

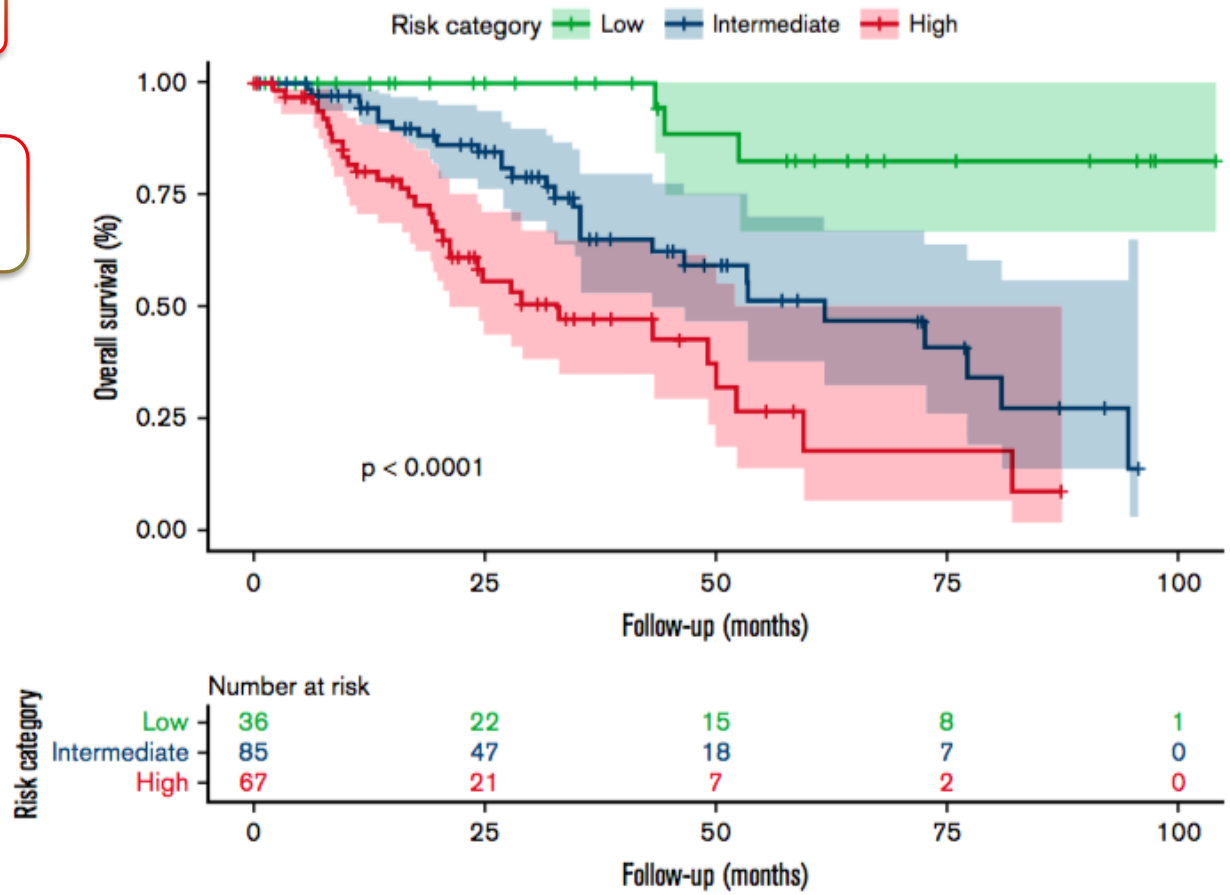
→ 1.5 points



High Risk: >2 — median OS 33 months

Intermediate Risk: 1-2 — median OS 61 months

Low Risk: 0 — median OS not reached



Maffioli et al. *Blood Adv* **2022**;6:1855-1864.

Efficacy of fedratinib in second-line treatment: the FREEDOM-2 trial

Adult patients with int-2/high–risk MF with Plt ≥50 x 10^9/L; relapsed, refractory, or intolerant to ruxolitinib; normal baseline thiamine; prophylactic antiemetics and thiamine supplementation, symptomatic antidiarrheals as required (N = 201)

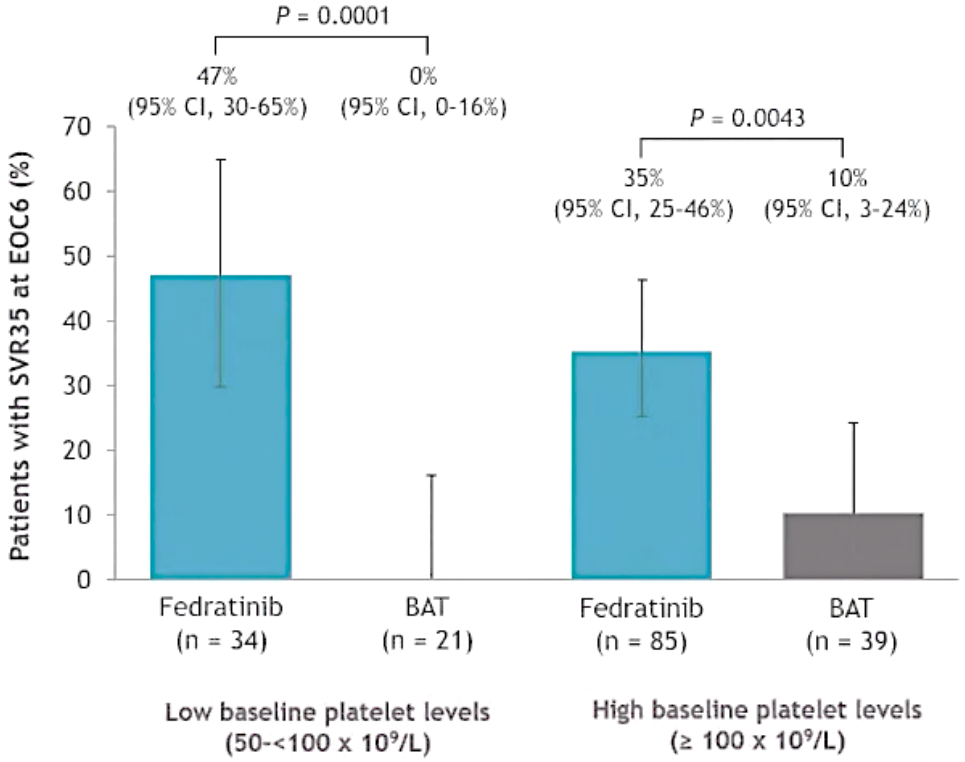
Fedratinib 400 mg daily

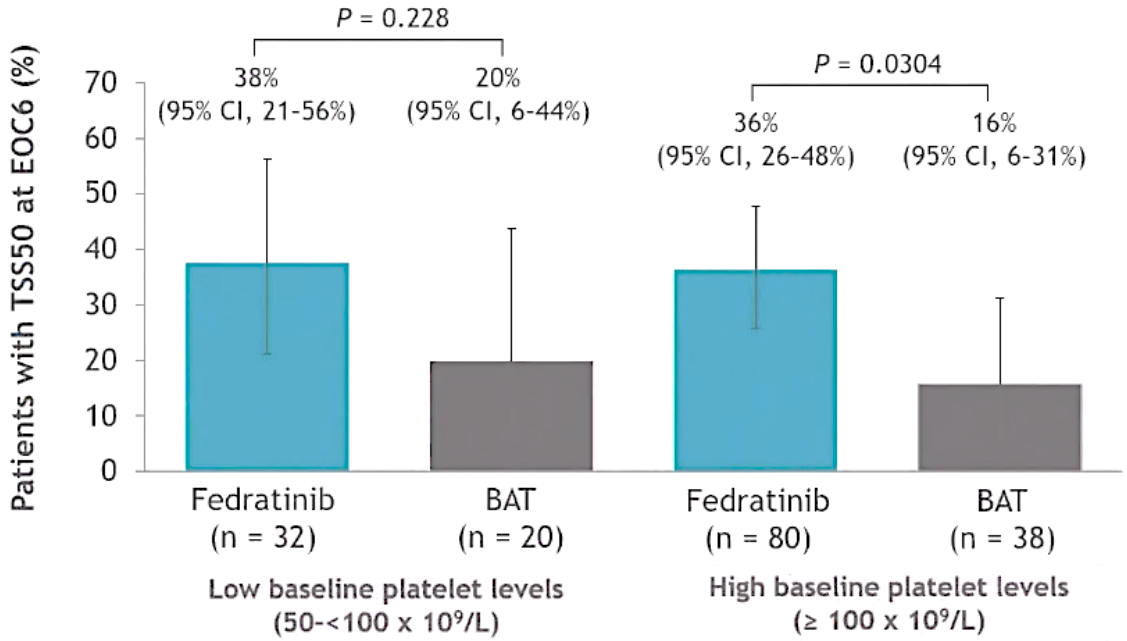
BAT (78% received RUX as BAT)

Crossover permitted

Primary EP: SVR35 at EOC6

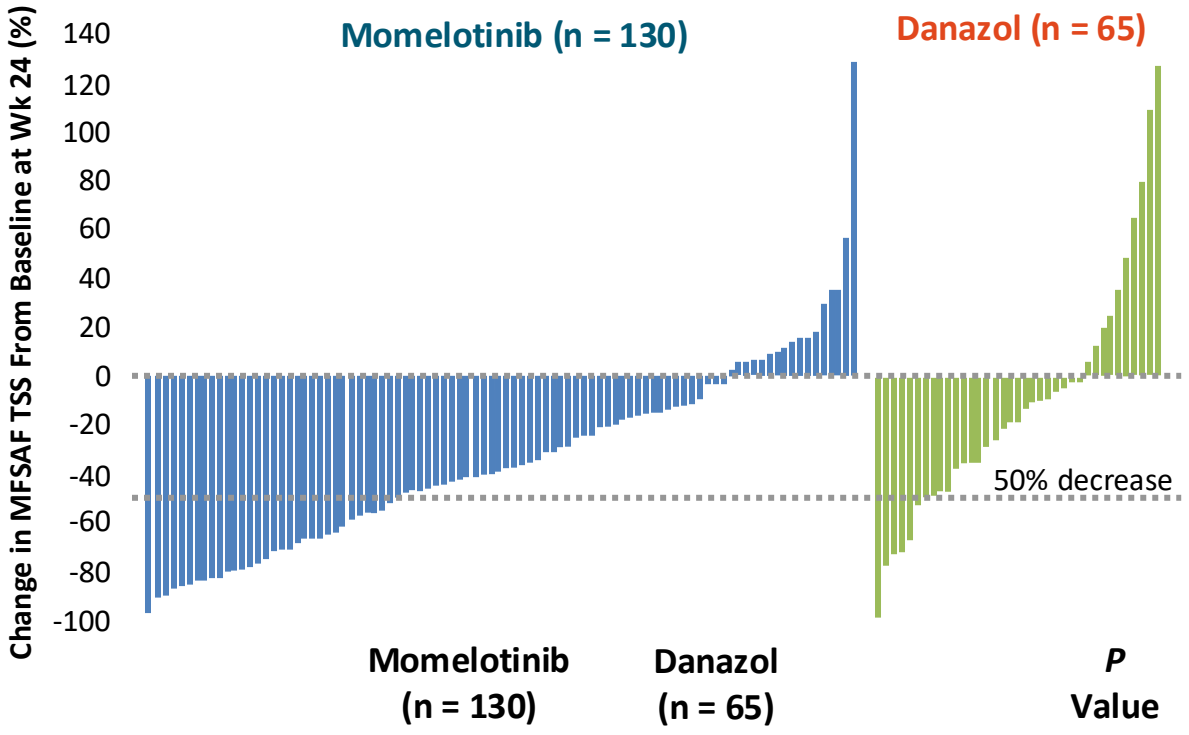
Key Secondary EP: TSS50 and SVR25 at EOC6, Safety



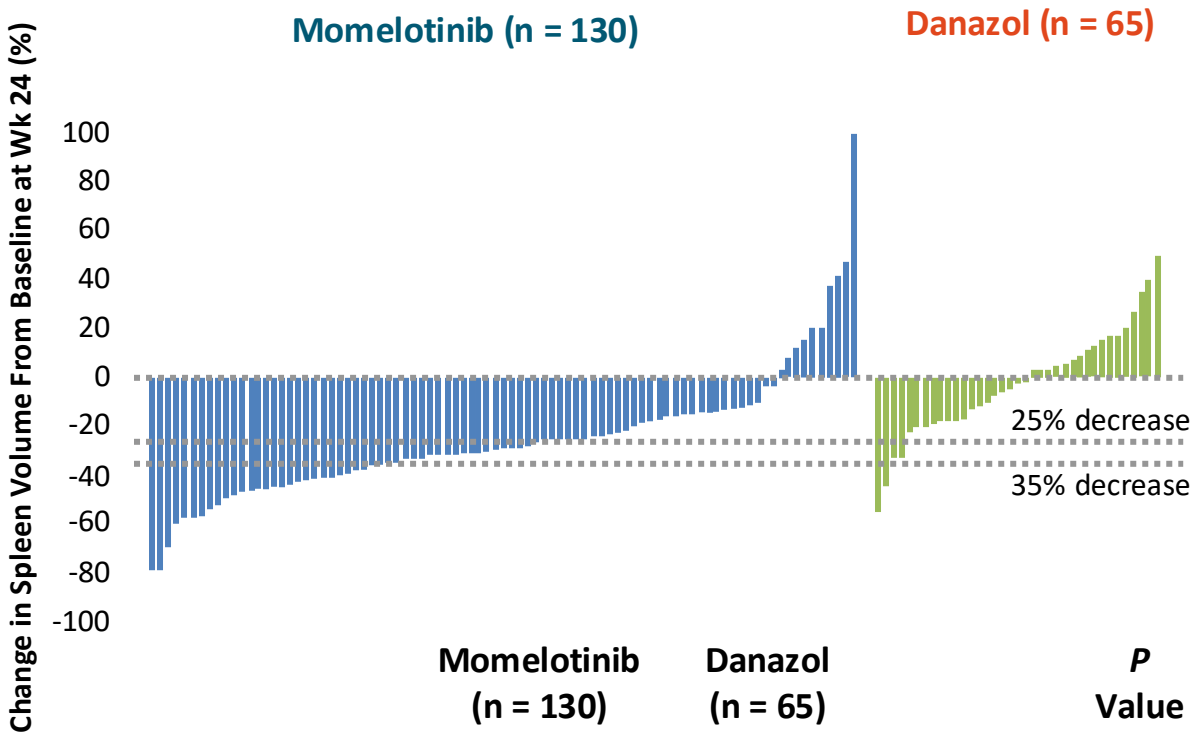


Harrison et al. *Lancet Hematol* **2024**;11:e729-e740.

Efficacy of momelotinib in second-line treatment: the MOMENTUM trial



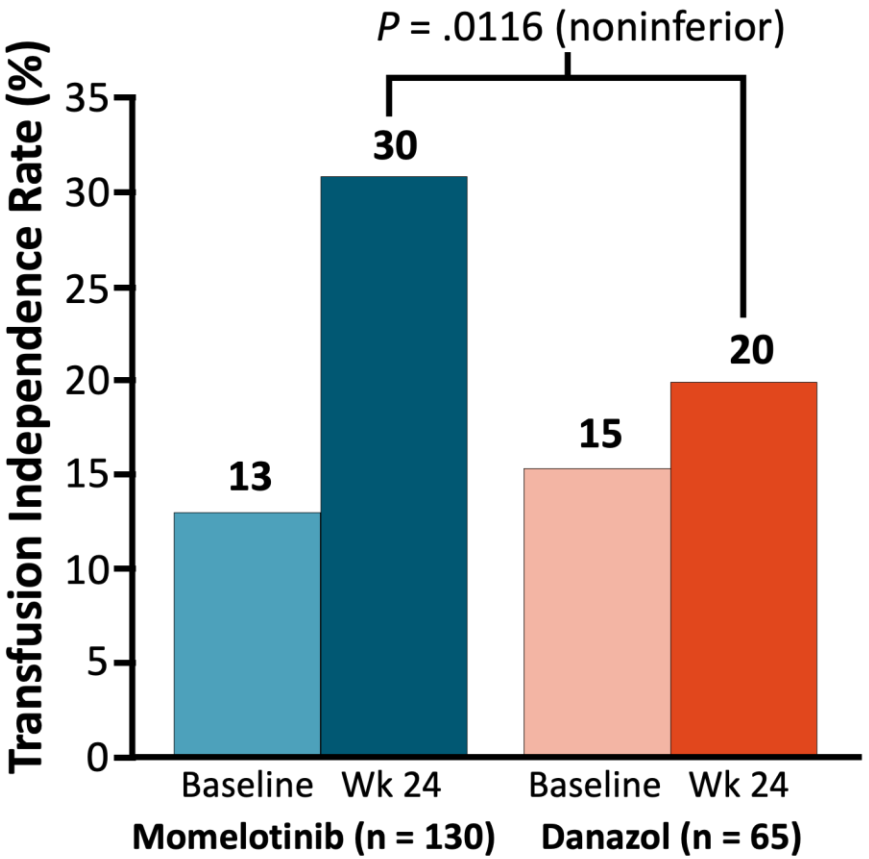
	Momelotinib (n = 130)	Danazol (n = 65)	*P* Value
≥50% MSAF TSS reduction at Wk 24, n (%) [95% CI]	32 (25) [17-33]	6 (9) [4-19]	.0095

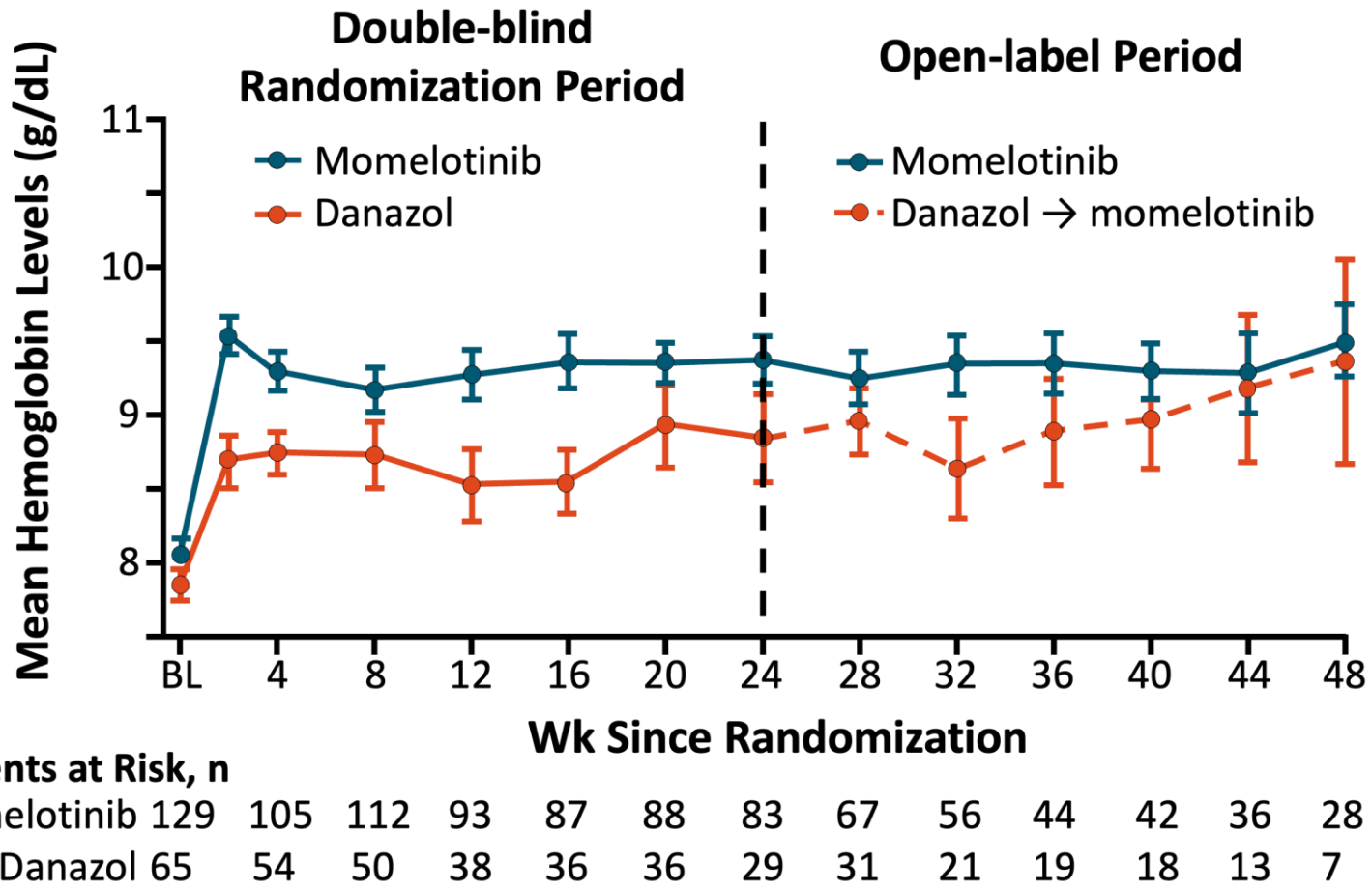


	Momelotinib (n = 130)	Danazol (n = 65)	*P* Value
≥25% SVR, n (%) [95% CI]	51 (39) [31-48]	4 (6) [2-15]	<.0001
≥35% SVR , n (%) [95% CI]	29 (22) [15-30]	2 (3) [0-11]	.0011

Verstovsek et al. *Lancet* **2023**;401:269-280.

Momelotinib leads to a superior transfusion independence rate



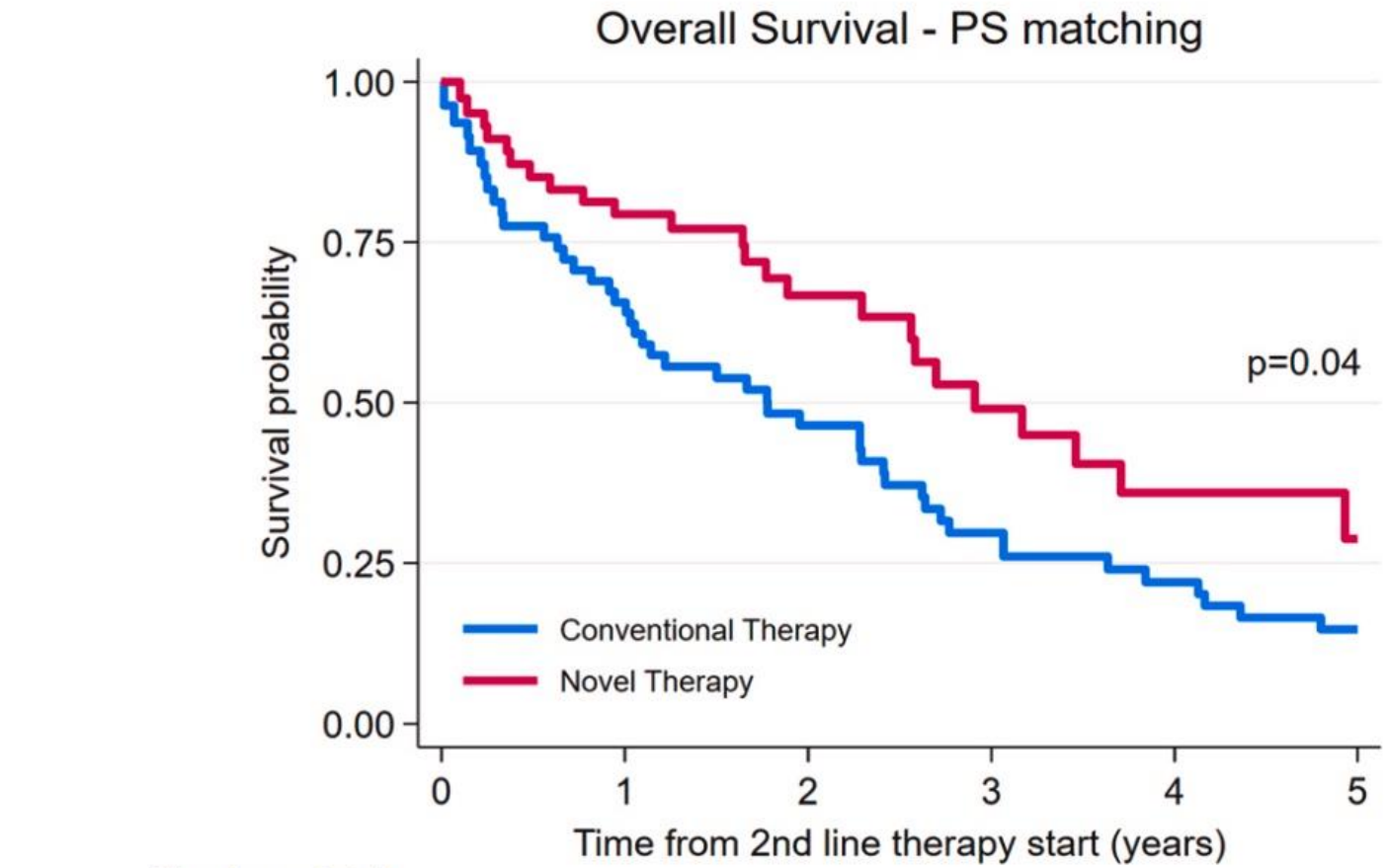


Patients at Risk, n

Momelotinib	129	105	112	93	87	88	83	67	56	44	42	36	28
Danazol	65	54	50	38	36	36	29	31	21	19	18	13	7

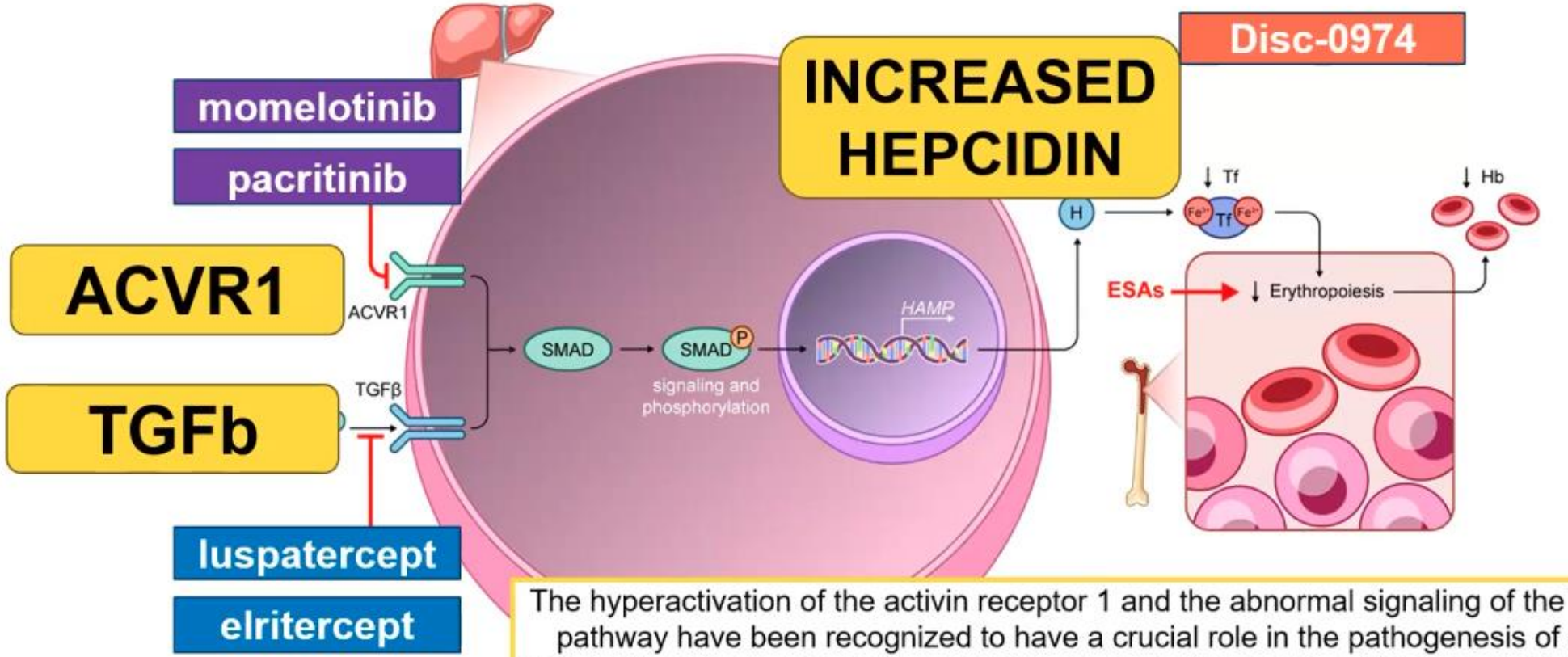
Verstovsek et al. *Lancet* **2023**;401:269-280.

Benefit of switching to effective 2L therapies



Palandri et al. *Leuk Res* **2025**;154:107719.

Other options for treating myelofibrosis-associated anemia

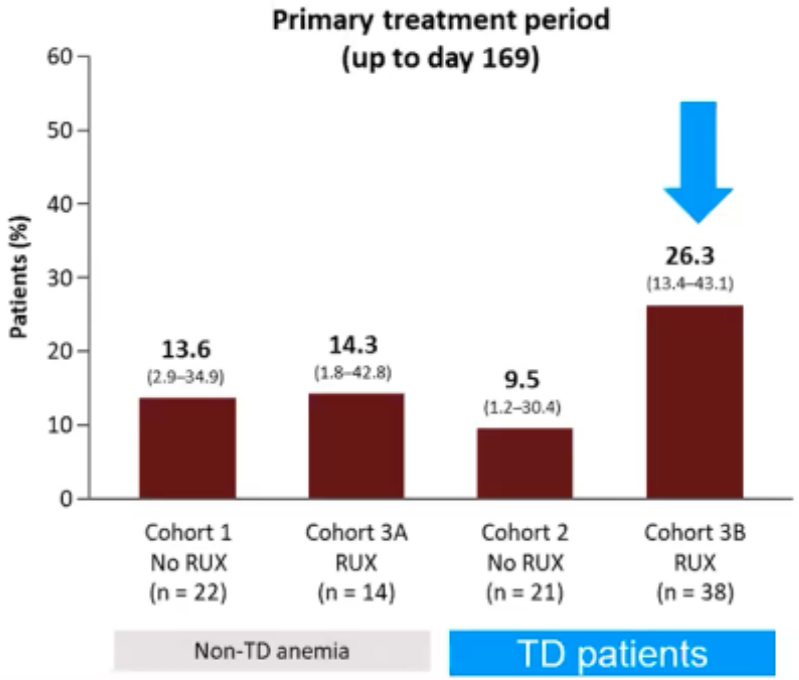


The hyperactivation of the activin receptor 1 and the abnormal signaling of the TGF-beta pathway have been recognized to have a crucial role in the pathogenesis of anemia. Both pathways are responsible for increased hepcidin levels, which leads to impaired iron metabolism and unavailability of iron deposits for erythropoiesis

ACVR1, Activin A receptor, type 1; ESA, erythropoietin stimulating agent; MF, myelofibrosis; Hb, hemoglobin; RBC, red blood cell; SMAD, small mothers against decapentaplegic; Tf, transferrin; TGFβ, transforming growth factor beta.

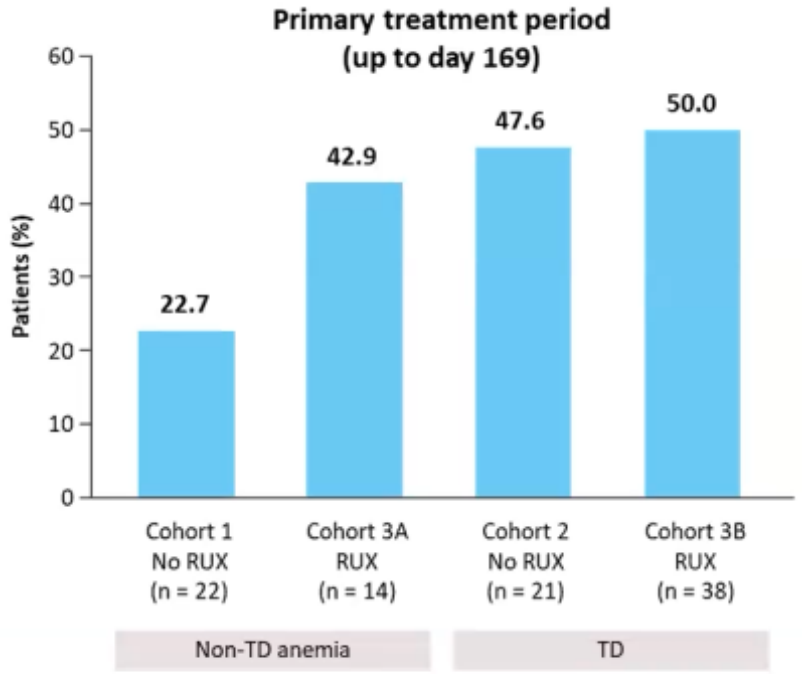
Anemia response and transfusion independency to luspatercept

Anemia response seen across all cohorts, with greatest responses seen in pts who received the combination with RUX



Primary endpoint: anemia response
TD patients: 84 consecutive days without RBC transfusion
Non-TD patients: 84 consecutive days with ≥ 1.5 g/dL Hb increase from BL without transfusion

Approximately half of TD patients receiving luspatercept achieved a 50% reduction in transfusion burden

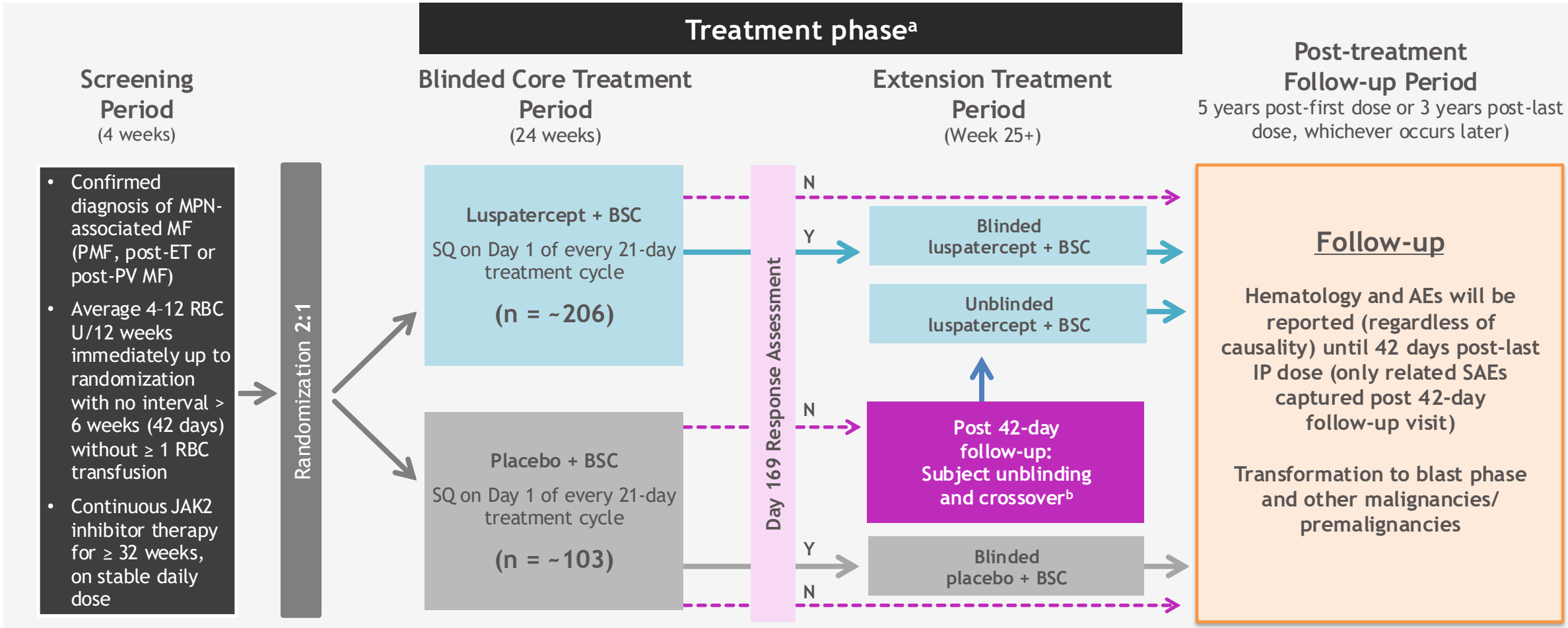


Primary endpoint: anemia response
TD patients: ≥ 50% reduction in RBC transfusion burden from baseline
Non-TD patients: mean Hgb increase ≥ 1.5 g/dL from baseline

Most pts continued RUX at stable dose

Gerds et al. *Blood Adv* **2024**;8:4511-4522.

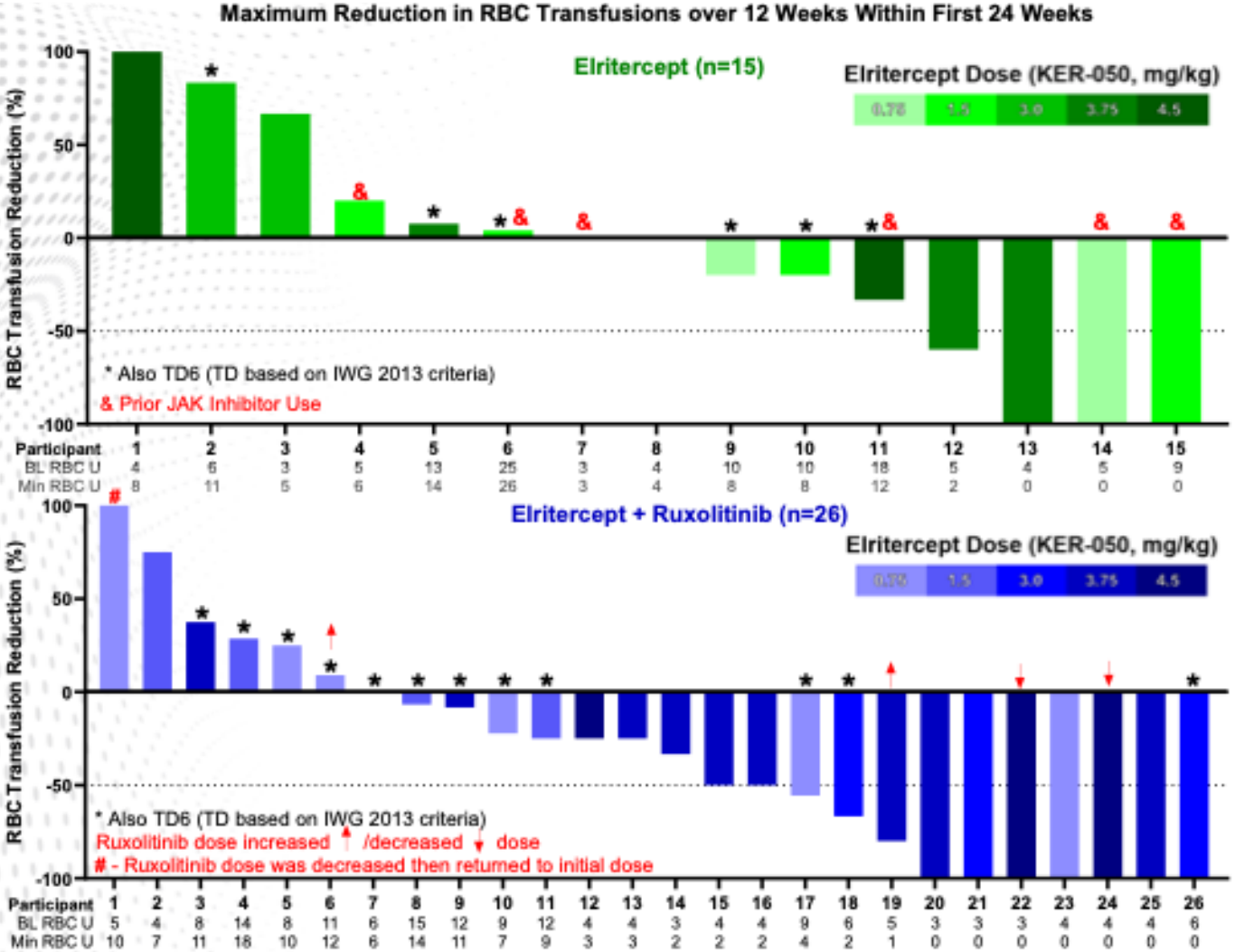
Phase 3 randomized, placebo-controlled trial of luspatercept in myelofibrosis



[a] Study unblinding will occur after analysis of the primary endpoint and with DMC consultation; [b] Subjects who do not meet any of the clinical benefit criteria (defined in the Day 169 Response Assessment as "no") will have the option to unblind. If the subject is on placebo, they may crossover into the Open-label Extension Treatment Period and have the opportunity to receive luspatercept after meeting the safety-related eligibility criteria (all inclusion and exclusion criteria are met except inclusion criteria 1 through 4). Unblinding can only occur after completion of the Day 169 Response Assessment, EOT visit, and 42-day Follow-up Period. Those subjects on placebo have the opportunity to receive luspatercept treatment and be treated for at least 24 weeks in the Open-label Extension Treatment Period as long as they continue to demonstrate clinical benefit from treatment, or they experience transformation to blast phase, unacceptable toxicities, or meet any other criteria for treatment discontinuation.

AE, adverse event; BSC, best supportive care; DMC, Data Monitoring Committee; EOT, end of treatment; IP, investigational product; n, number of subjects; N, Patient did not meet Day 169 Response Assessment criteria; SAE, serious adverse event; SQ, subcutaneously; Y, Patient met Day 169 Response Assessment criteria.

Hemoglobin responses and transfusion-independence with elritercept treatment



- Overall, in both arms, reductions in transfusion burden were observed in evaluable** TD3 participants over the first 24 weeks of treatment
  - 16/41 (39%) had reduction ≥ 50%
  - 10/41 (24%) achieved transfusion independence (TI)

- For evaluable** TD3 participants in the combination arm treated with a starting dose of elritercept of 3 mg/kg or higher:
  - 10/16 (62.5%) had reduction ≥ 50%
  - 6/16 (37.5%) achieved TI

Reductions in transfusion burden observed in both arms further support potential to address ruxolitinib-associated anemia as well as anemia due to underlying MF

RESTORE

BL RBC U = baseline RBC U/12 weeks; Min RBC U = minimum postbaseline RBC U/12 weeks; TD = transfusion dependent, TD3 = received ≥ 3 RBC U/12 weeks at baseline; TI = transfusion independence.
*Denotes TD3 participants who also qualified as transfusion dependent based on IWG 2013 criteria (TD6); **Evaluable = TD3 with at least 12 consecutive weeks of postbaseline RBC transfusion data in the first 24 weeks. Participants without 12 consecutive weeks of transfusion data (n = 10; 6 monotherapy, 4 combination) were excluded from the analysis.

Data as of 30Aug2024

Harrison et al. *Blood (ASH annual meeting)* **2024**;abs#997.

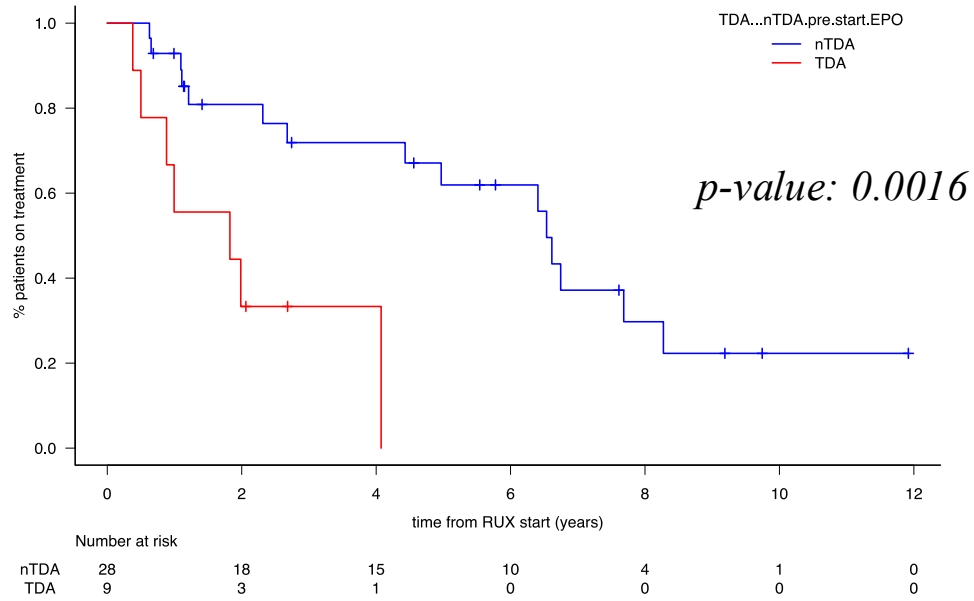
Predictive factors of erythroid response to standard anemia-directed therapies

	Patients N (%)	TDA baseline n (%)	nTDA baseline n (%)	ΔT startRUX-startADT, months (range)	Duration of concomitant treatment, months (range)
rhEPO	**37 (57,8)**	9 (24,3)	28 (75,7)	**6 (0-138)**	**8 (0-83)**
Steroids	20 (31,3)	11 (55)	9 (45)	14,5 (0-52)	7 (2-50)
Danazol	13 (20,3)	7 (53,8)	6 (46,2)	20 (3-87)	6 (2-74)
IMiDs	4 (6,3)	2 (50)	2 (50)	44,5 (24-55)	10,5 (2-26)

	On treatment n (%)	Discontinued n (%)	MAJOR RESPONSE n (%)	MINOR RESPONSE n (%)	NO RESPONSE n (%)
rhEPO (n=37, 57.8%)					
3m	34 (91,9)	3 (8,1)	11 (32,4)	5 (14,7)	18 (52,9)
6m	24 (64,9)	13 (35,1)	9 (37,5)	8 (33,3)	7 (29,2)
9m	15 (40,5)	22 (59,5)	5 (33,3)	4 (26,7)	6 (40)
12m	14 (37,8)	23 (62,2)	5 (35,7)	2 (14,3)	7 (50)

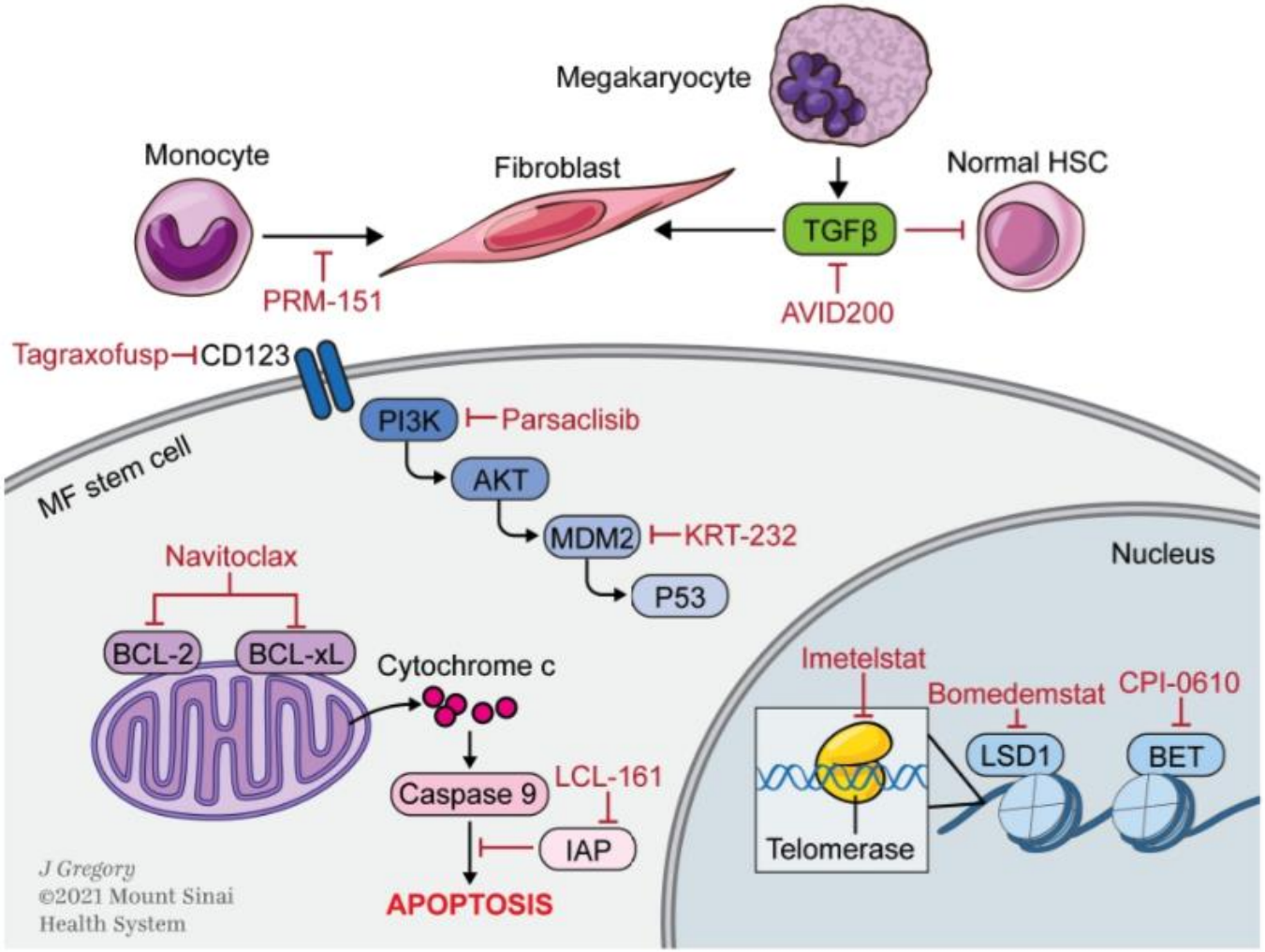
	rhEPO Major Response (A)	rhEPO minor response (B)	rhEPO no response (C)	*p* A vs (B+C)
Pz = 37	20 (54,1)	6 (16,2)	11 (29,7)	
RR6, n (%)			N=10	
LOW	**6 (30)**	0	1 (10)	***0,0123***
INT	**14 (70)**	4 (66,7)	6 (60)	
HIGH	0	2 (33,3)	3 (30)	

	Other ADT Major Response (A)	Other ADT minor response (B)	Other ADT no response (C)	*p* A vs (B+C)
Pz tot	8	4	21	
JAKi reduction anytime, n (%)	**7 (87,5)**	0	11 (52,4)	***0,046***
TDA, n (%)	1 (12,5)	2 (50)	14 (66,7)	***0,016***
nTDA, n (%)	**7 (87,5)**	2 (50)	7 (33,3)	



Bonifacio, Strazimiri et al. *Blood (ASH annual meeting)* **2025;abs#3820**.

Beyond JAK inhibition: novel therapies and combinations



Apoptosis
- BCL-2/xL inhibitors (navitoclax)
- SMAC mimetics (LCL-161)
- MDM2 antagonists (idasanutlin, navtemadlin, siremadlin)

Epigenetic modulation
- BET inhibitors (pelabresib, BMS-986158, INCB-57643)
- LSD1 inhibitors (bodememstat)

Microenvironment
- TGFβ-1 and -3 traps (AVID200)
- Activin receptor ligand traps (luspatercept, elritercept)
- Aurora kinase Ainhibitors (alisertib)

Signaling pathways
- PI3K inhibitors (buparlisib, parsaclisib)

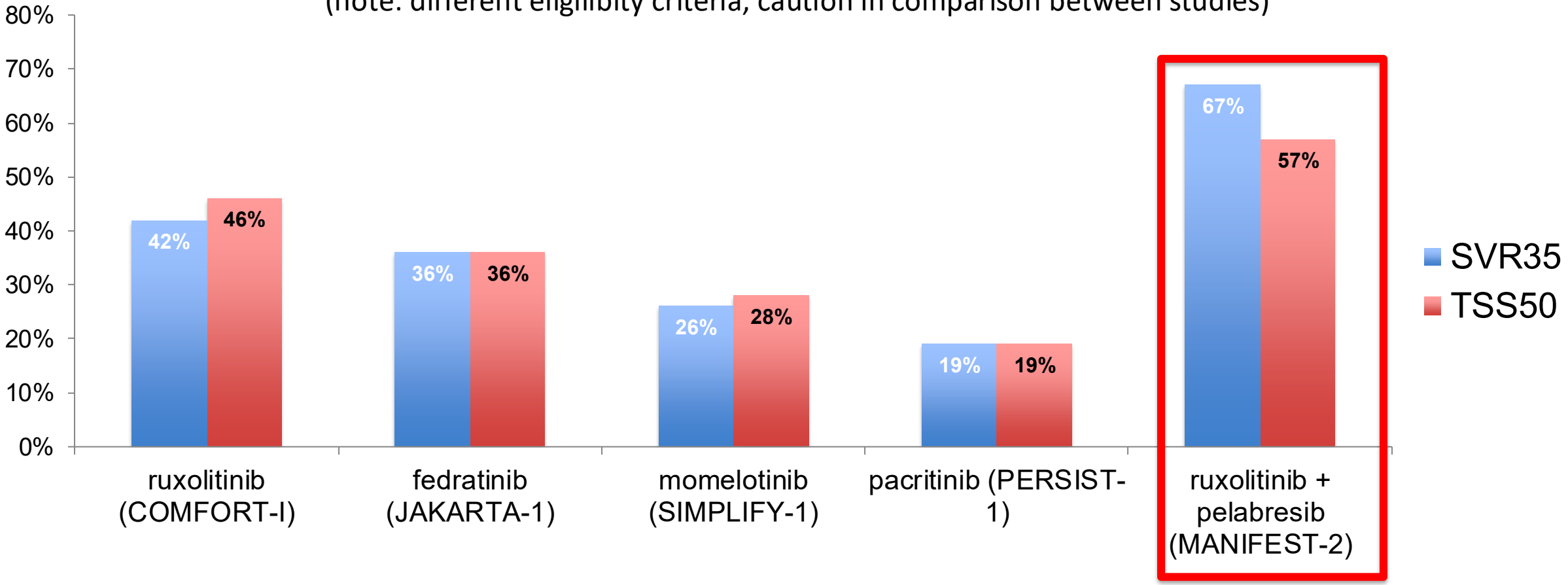
Other targets
- Anti-CD123 antibodies (tagraxofusp)
- Telomerase inhibitors (imetelstat)
- Checkpoint inhibitors (MBG453)

Tremblay and Mascarenhas. *Cells* **2021;10:1034**.

Pelabresib plus ruxolitinib in front-line treatment

1L studies in patients with MF

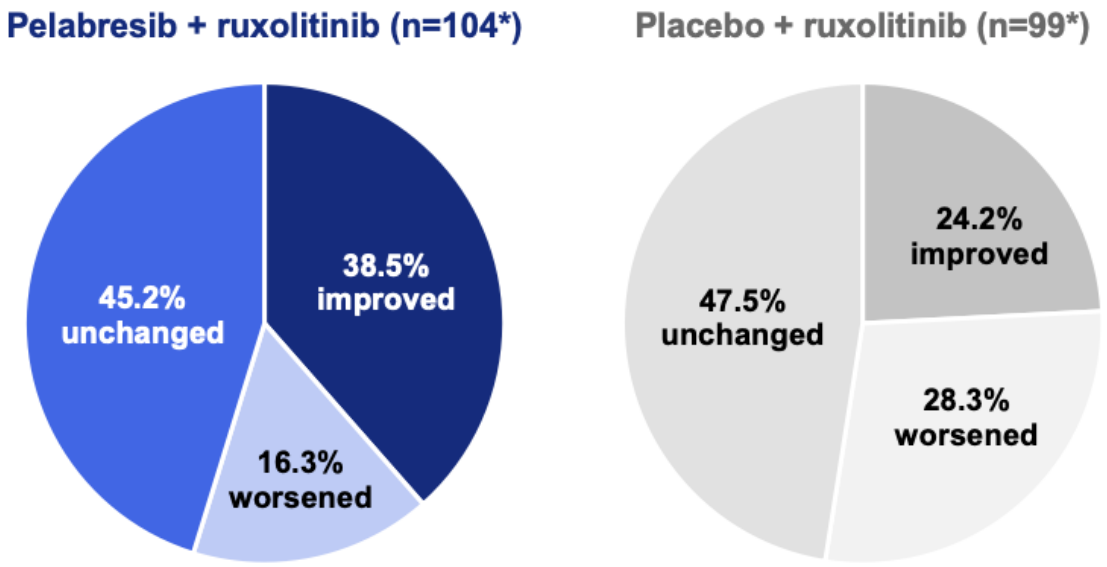
(note: different eligibity criteria, caution in comparison between studies)



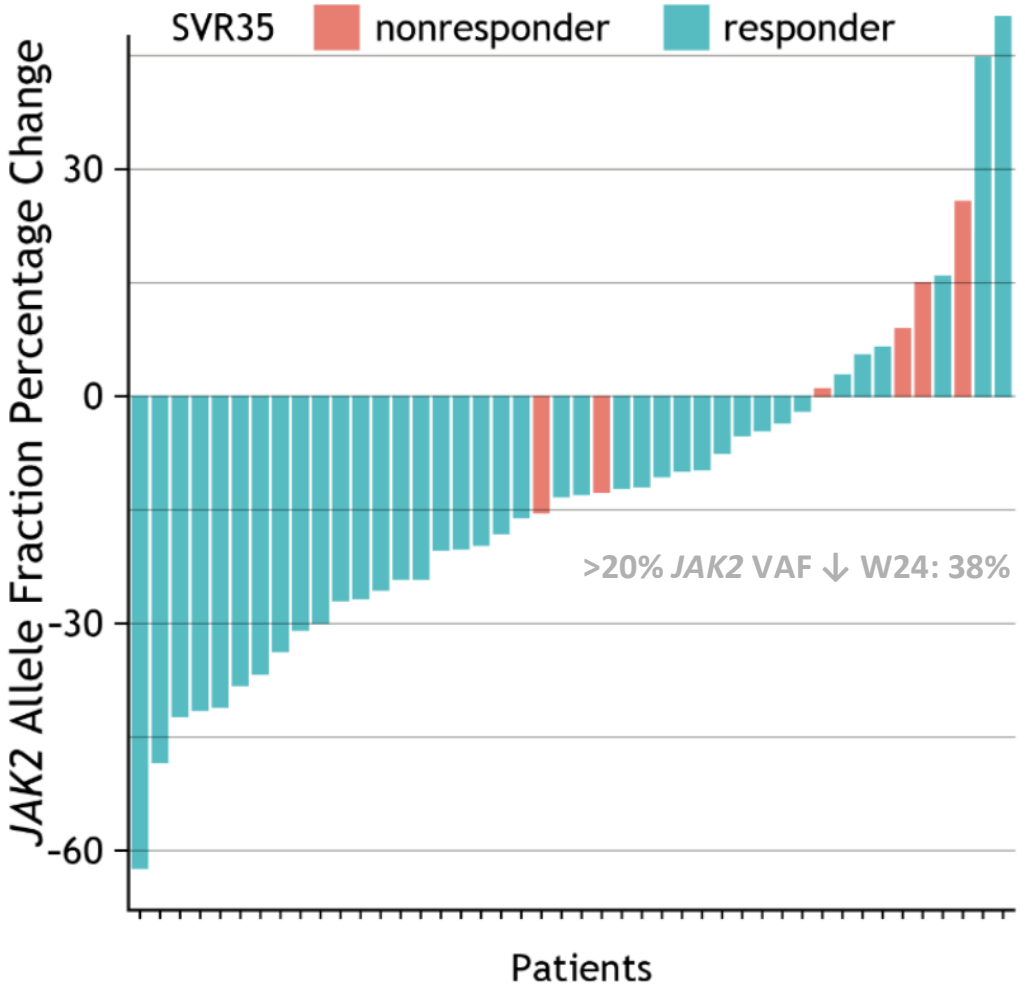
Rampal et al. *Nat Med* **2025;31:1531-1538**.

Potential disease modification with pelabresib

BMF grade changes W24



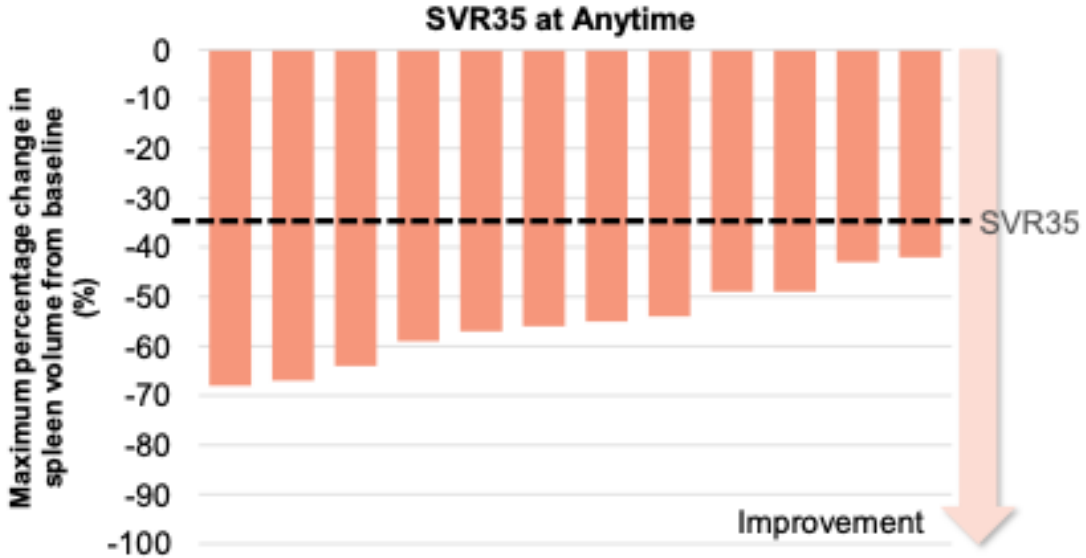
IMPROVED OR: 2.09 (1.14-3.93)



Rampal et al. *Nat Med* **2025;31:1531-1538**.

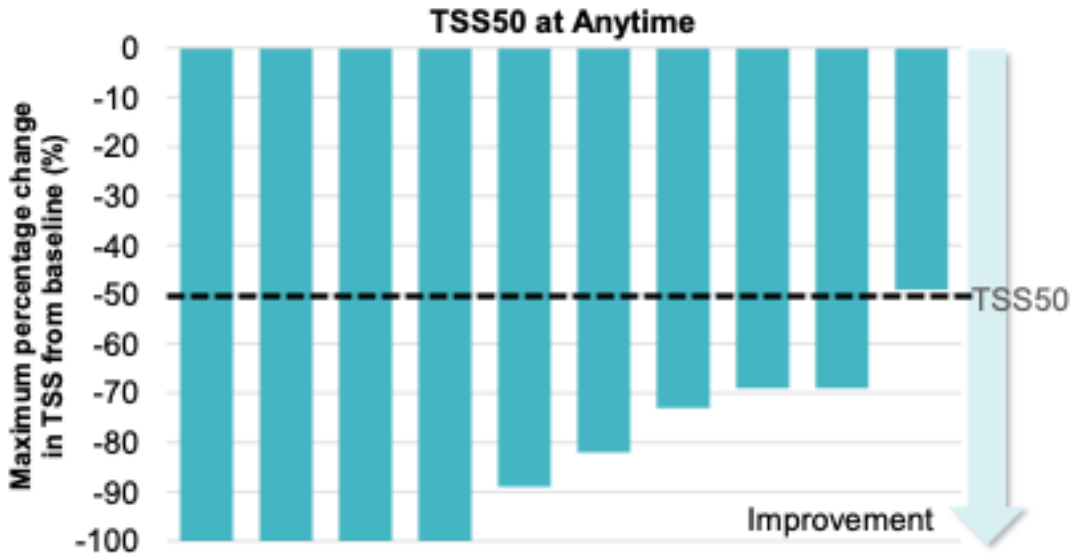
Responses with selinexor (60 mg QW) plus ruxolitinib

		SVR35
Population	Timepoint	Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	10/12† (83)
	Week 24	**11/12 (92)**
Intent-to-treat	Week 12	10/14 (71)
	Week 24	**11/14 (79)**



All patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved an SVR35 at anytime

		TSS50
Population	Timepoint	Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	8/10‡ (80)
	Week 24	**7/9§ (78)**
Intent-to-treat	Week 12	8/12 (67)
	Week 24	**7/12 (58)**

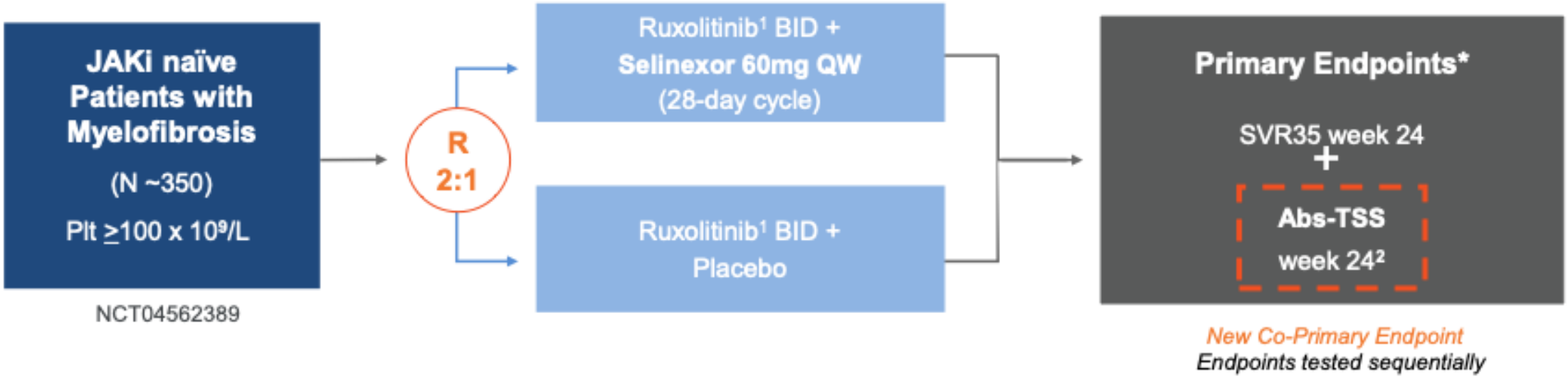


90% of patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved an TSS50 at anytime

Tantravahi et al. *Blood (ASH annual meeting abstract)* **2023;abs#622**.

SENTRY (XPORT-MF-034) phase 3 trial of selinexor plus ruxolitinib in JAKi naïve MF

Abs-TSS is Replacing TSS50 as a Co-Primary Endpoint*



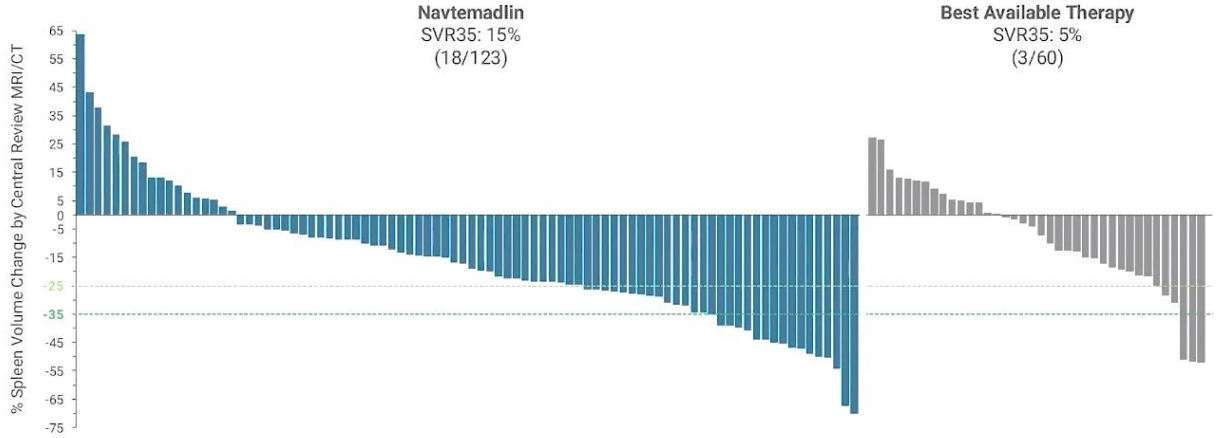
Randomization stratified by:

- Dynamic International Prognostic Scoring System (DIPSS) risk category intermediate -1 vs. intermediate -2 or high-risk
- Spleen volume <1800 cm^3 vs. ≥1800 cm^3 by MRI/CT scan
- Baseline platelet counts 100-200 x 10^9/ L vs. >200 x 10^9/L

BID: Twice daily; Plt: Platelet; QW: Once weekly; SVR 35: Spleen volume reduction ≥ 35%:
*Pending submission of protocol amendment to FDA

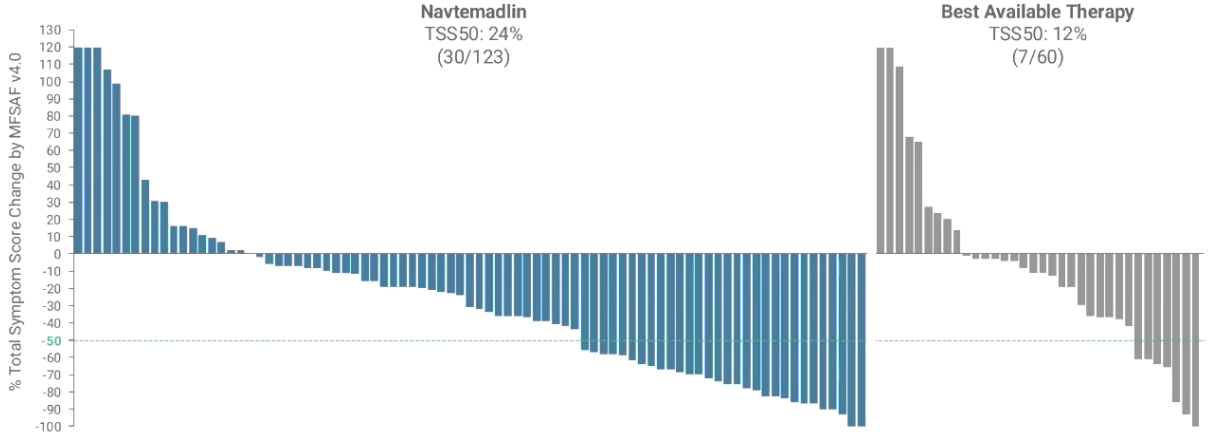
Navtemadlin in TP53$^{wild\text{-}type}$ patients relapsed or refractory after JAK inhibitors

Spleen Volume Reduction by Central Review MRI/CT – Baseline to Week 24



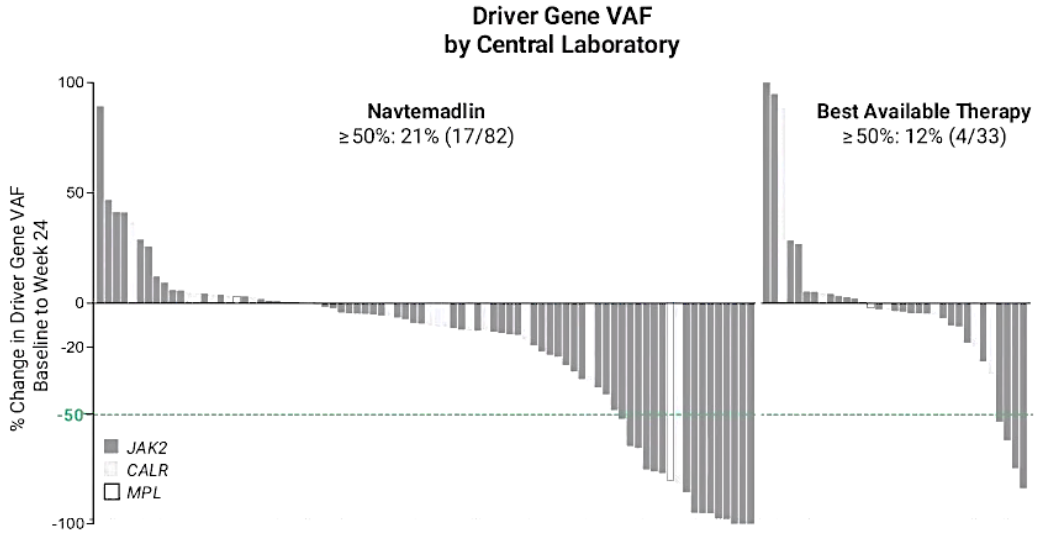
Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). ITT is all randomized subjects. Figure represents subjects with baseline and Week 24 data.
Navtemadlin vs BAT, p=0.0815. SVR25. Navtemadlin, 27% (33/123); BAT, 10% (6/60). BAT SVR35 responders received hydroxyurea (2) and lenalidomide (1).

Total Symptom Score Reduction by MFSAF v4.0 – Baseline to Week 24

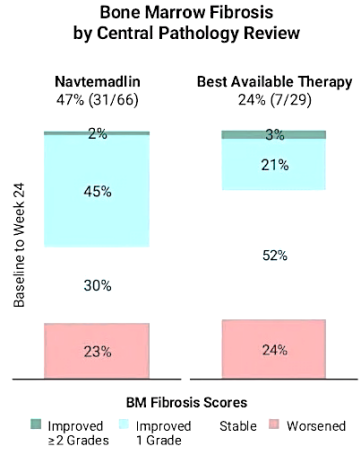


Data cut-off: 30 Sep 2024.
Note: Navtemadlin dosed at 240 mg QD (Days 1-7/28-day cycle). ITT is all randomized subjects. Figure represents subjects with baseline and Week 24 data. Navtemadlin vs BAT, p=0.0507.
Week 24 TSS assessment includes Week 23 scores for subjects who stopped TSS at the start of Week 24 (n=2).
Abbreviations: BAT, best available therapy; ITT, intention-to-treat; MFSAF, myelofibrosis symptom assessment form; TSS, total symptom score; TSS50, total symptom score reduction ≥50%.

Driver Gene VAF Reduction and Bone Marrow Fibrosis Improvement



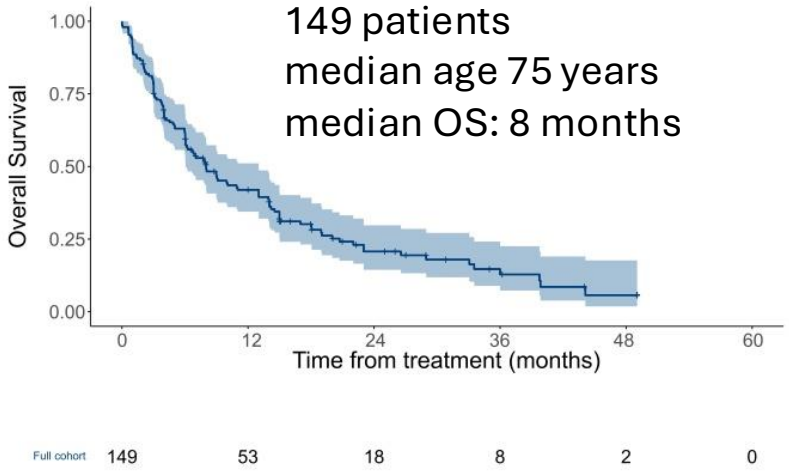
Data cut-off: 30 Sep 2024.
Note: Week 24 evaluable subjects shown.
Abbreviations: BM, bone marrow; *CALR*, calreticulin; *JAK2*, Janus kinase 2; *MPL*, myeloproliferative leukemia virus oncogene; VAF, variant allele frequency.



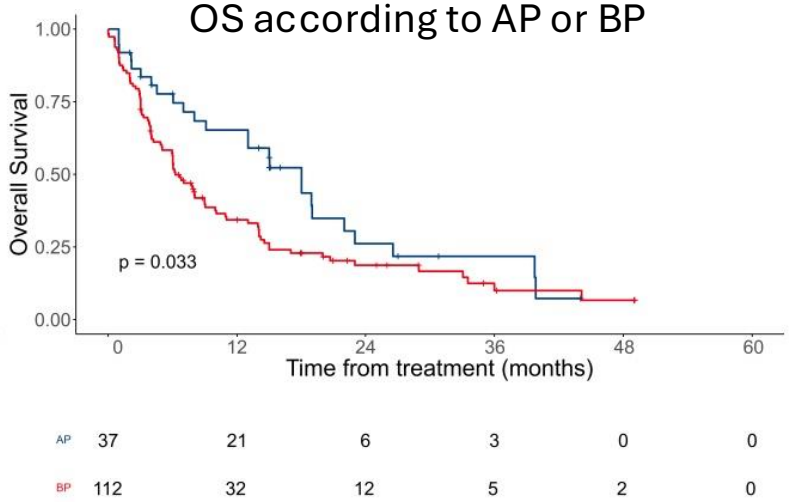
Mascarenhas et al. *Blood (ASH annual meeting abstract)* **2024;abs#1000**.

Accelerated and blast phase MPN still represent a high unmet need

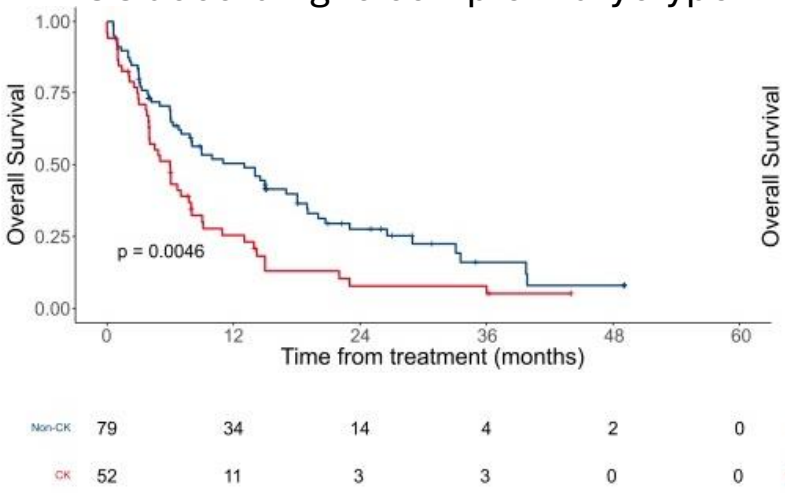
149 patients
median age 75 years
median OS: 8 months



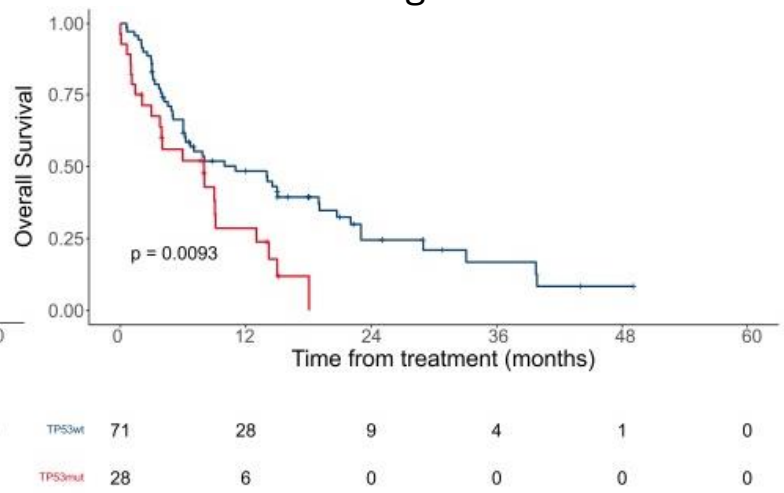
OS according to AP or BP

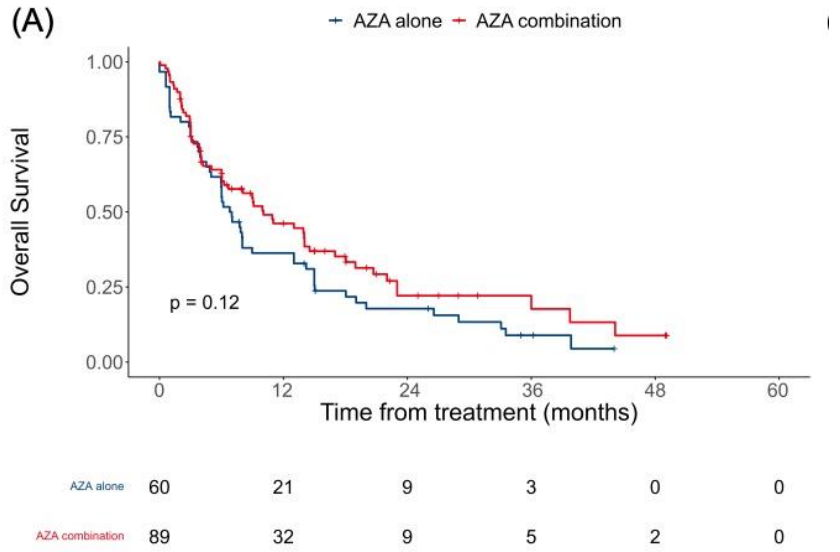


OS according to complex karyotype



OS according to TP53 mutation





Orvain et al. *HemaSphere* **2025;9:e70202**.

Conclusions

- JAK inhibition marked a revolutionary breakthrough in the treatment of myelofibrosis.
- Most patients treated with JAKi have consistent spleen and symptoms response, ameliorating quality of life and possibly exteding OS; however, many of them lose their response in the long-term.
- Different potency and selectivity against JAK1 vs JAK2 vs other kinases (e.g. ACVR1) may explain different levels of response and drug-associated toxicities
    - Cytokine reduction, symptoms control and immunosuppression are more related to JAK1 inhibition
    - Control of myeloproliferation and myelosuppression are more related to JAK2 inhibition
- Drug combinations including a JAK inhibitor and non JAK-targeting drugs have the potential of improving quality and duration of response, including disease-modifying effects (reduction of fibrosis, molecular responses).
- All young and fit patients must be evaluated integrating information from prognostic tools which predict survival with JAKi treatment, survival according to response to ruxolitinib, and survival after transplant.