What is new in the treatment of MPNs in 2022

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Disclosure

Research support from Novartis, Bristol Myers Squibb and Incyte,
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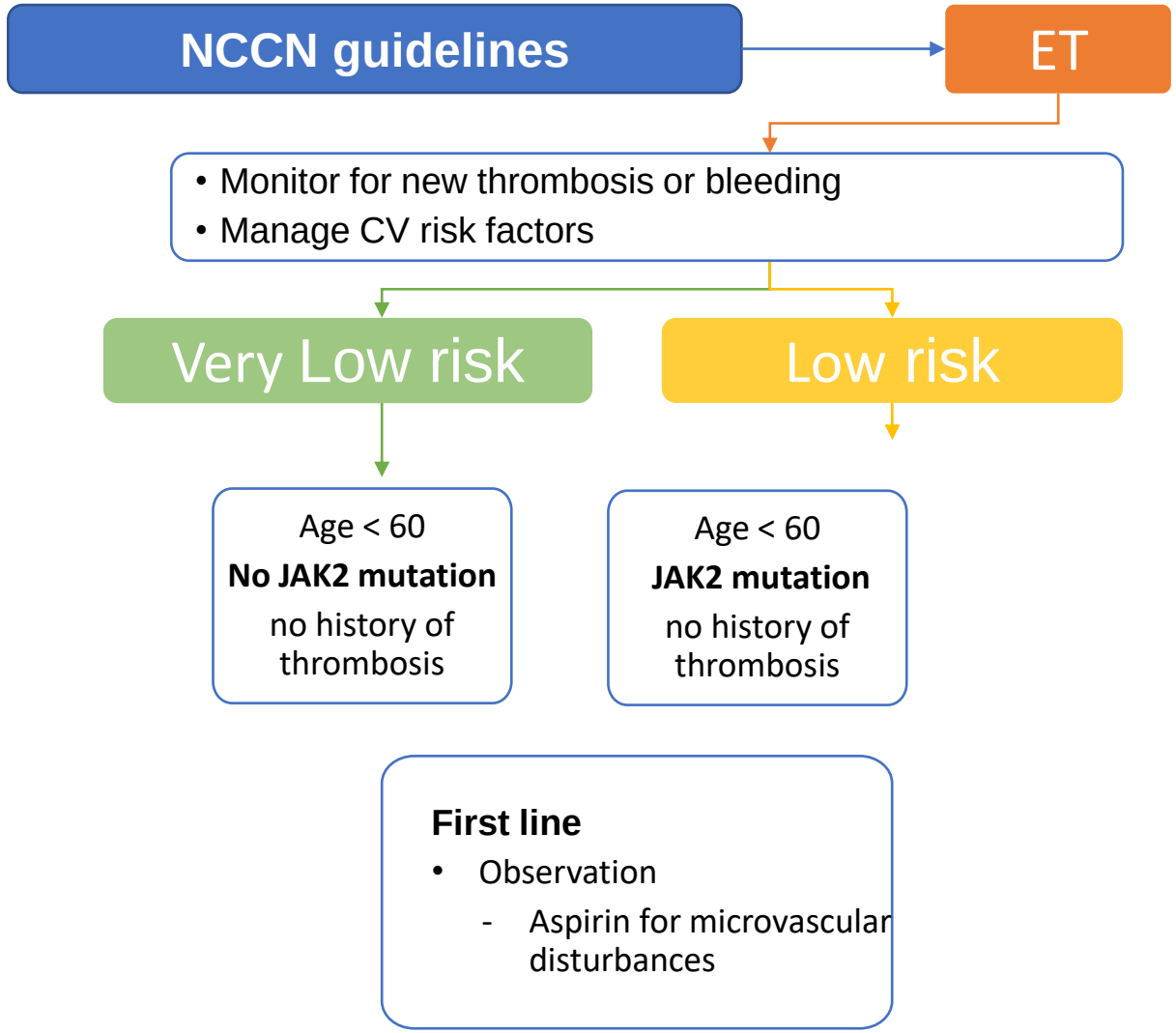
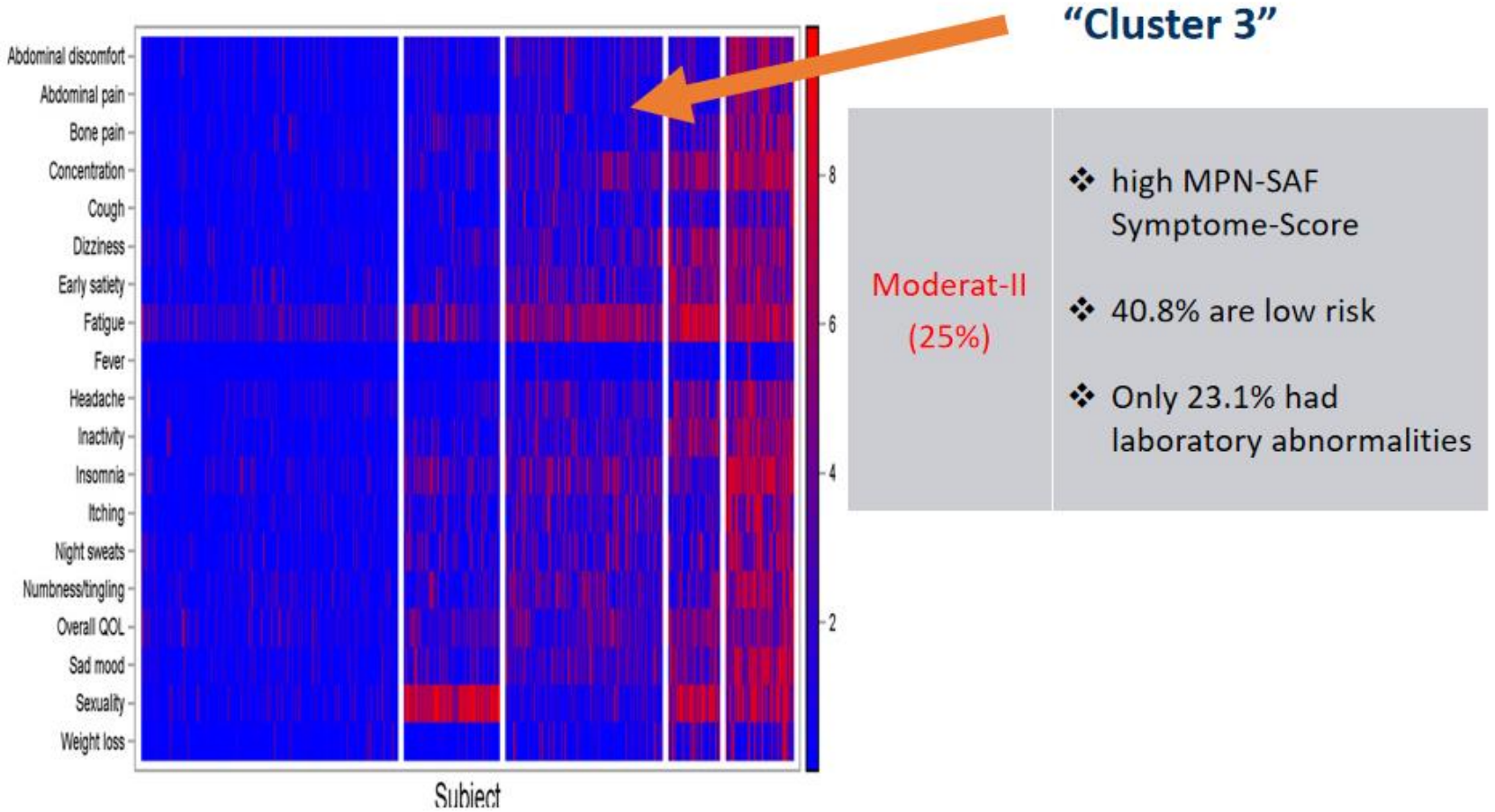
Risk stratification in ET



NCCN guidelines 2022

Is it possible to have severe symptomes in low risk ET?

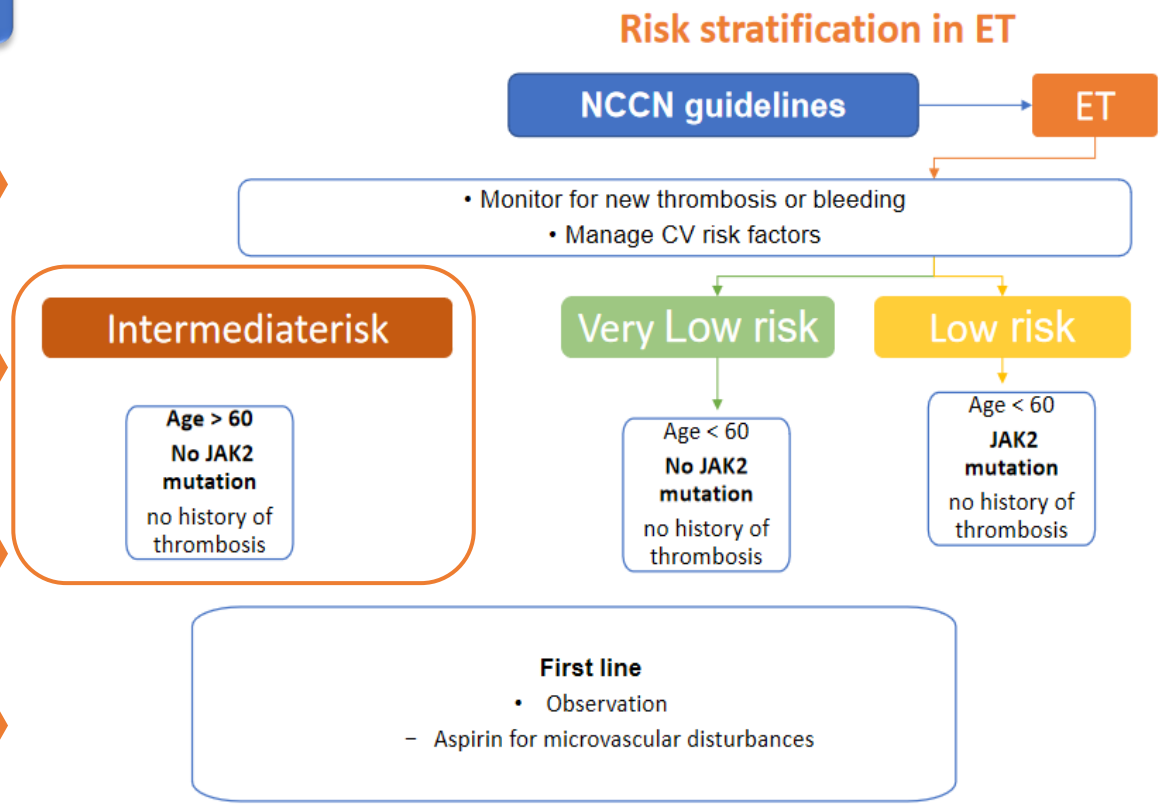


Geyer HL et al. *Blood* 2014; Emmanuel R et al. *Blood* 2013.

Should every patient above 60 years with ET automatically receive cytoreductive therapy?

Indications for cytoreductive therapy

- **High risk** (History of thrombosis at any age; Age > 60 & JAK2 mutation)
- Thrombosis; Bleeding; aquired VWD
- Splenomegaly and/or constitutional symptomes
- Progressive thrombocytosis and/or leukocytosis
- Microvascular symptomes not responsive to aspirin



NCCN guidelines 2022

Cytoreductive therapy in ET

HU

Anagrelide

IFN

NCCN guidelines 2022

Is anagrelide also effictive in patients with thrombosis?

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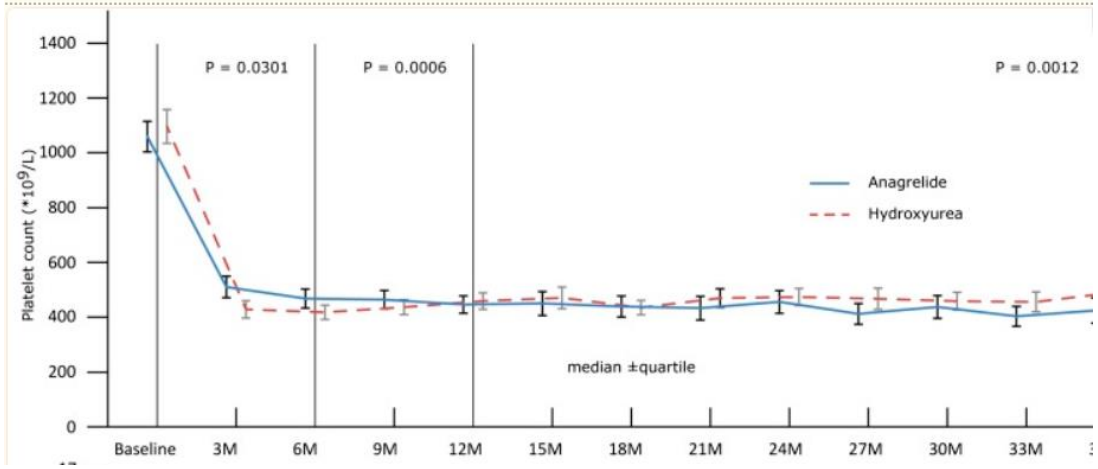
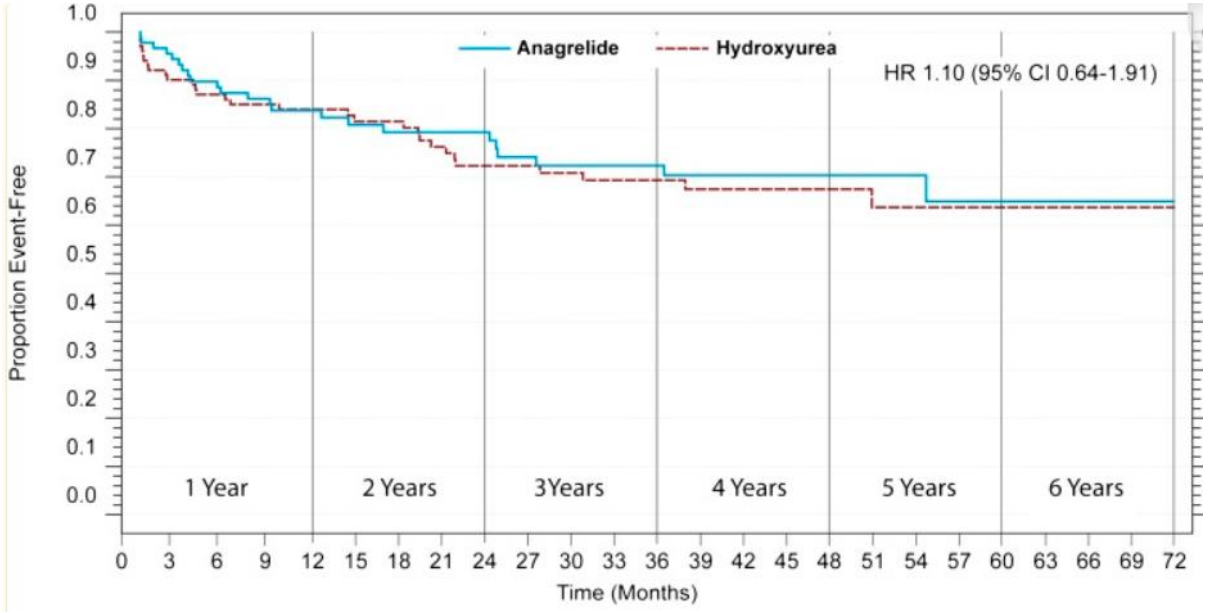
Blood. 2013 Mar 7; 121(10): 1720–1728.
Prepublished online 2013 Jan 11. doi: 10.1182/blood-2012-07-443770
PMCID: PMC3591796
PMID: 23315161

Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial

Heinz Gisslinger,[1] Mirjana Gotic,[2] Jerzy Holowiecki,[3] Miroslav Penka,[4] Juergen Thiele,[5] Hans-Michael Kvasnicka,[6] Robert Kralovics,[1,7] and Petro E. Petrides[8], for all members of the ANAHYDRET Study Group





What are the data to IFN in ET?

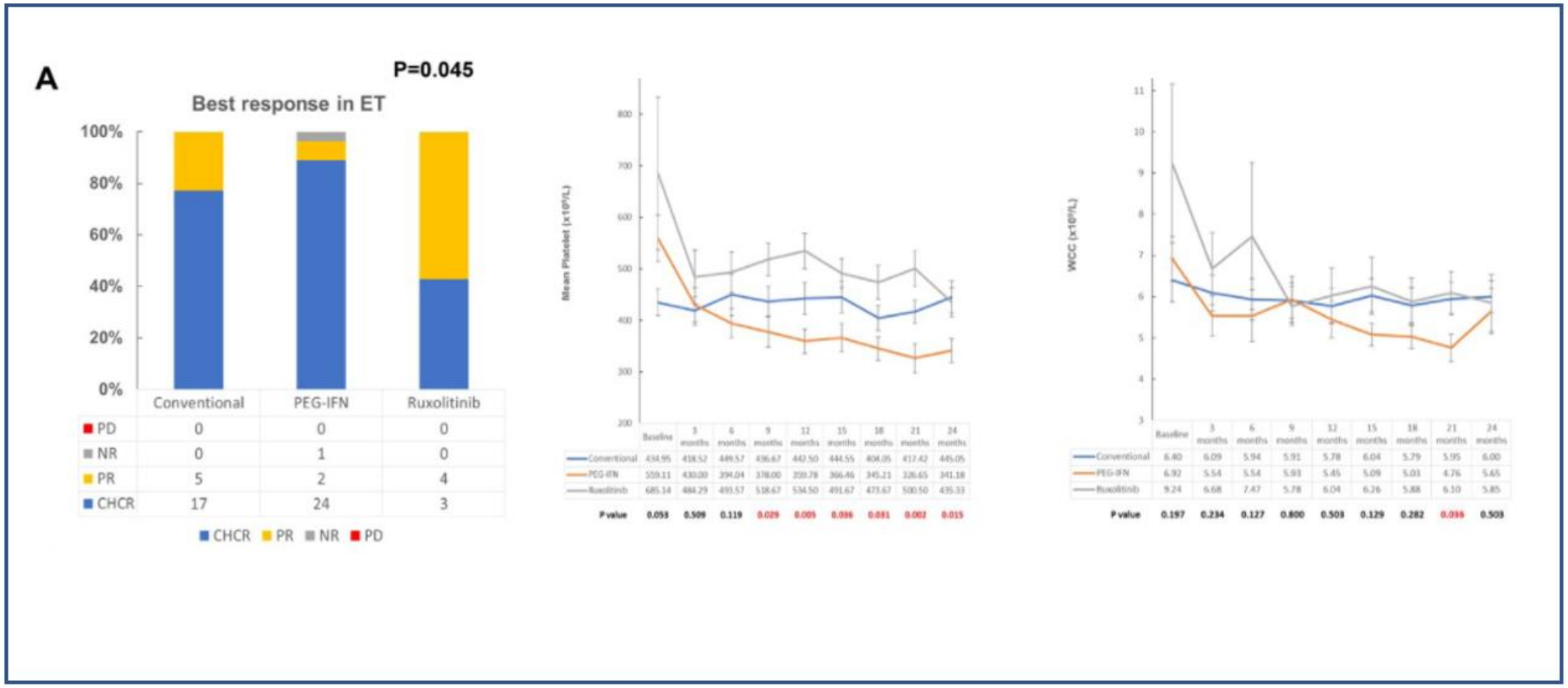
› Cancer Chemother Pharmacol. 2003 Jan;51(1):81-6. doi: 10.1007/s00280-002-0533-4.
Epub 2002 Nov 21.

Pilot study of pegylated interferon-alpha 2b in patients with essential thrombocythemia

› Hematology. 2020 Dec;25(1):247-257. doi: 10.1080/16078454.2020.1780755.

Myeloproliferative neoplasms treated with hydroxyurea, pegylated interferon alpha-2A or ruxolitinib: clinicohematologic responses, quality-of-life changes and safety in the real-world setting

What are the data to IFN in ET?



Gill H et al. Hematology 2020

IFN versus Anagelide in ET

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Ropeginterferon Alfa-2b (P1101) vs. Anagrelide in Essential Thrombocythemia Patients With Hydroxyurea Resistance or Intolerance (SURPASS ET)

⚠ The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT04285086

Recruitment Status ⓘ : Recruiting
First Posted ⓘ : February 26, 2020
Last Update Posted ⓘ : October 11, 2021

See **Contacts and Locations**

PV

Patient 1

April 2006

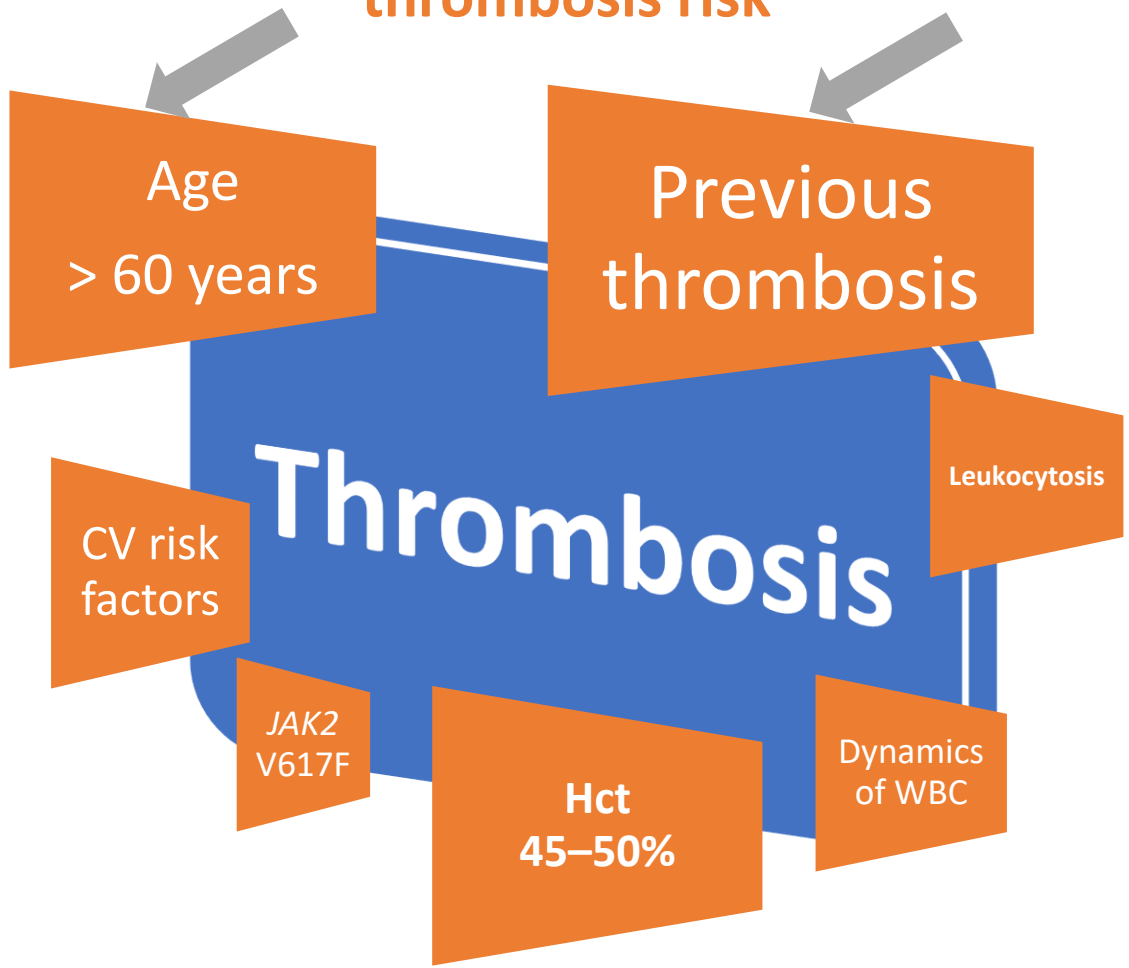
70 y, male
Fatigue
Splenomegaly 6 cm BCM

WBC 12.6 × 10^9/L
Differential normal
Hb **21.3** g/dL
Hct **62.5**%
PLT 591 × 10^9/L

JAK2 V617F-positive PV

BCM, below costal margin; CV, cardiovascular; Hb, hemoglobin; Hct, hematocrit; PLT, platelet; PV, polycythemia vera; WBC, white blood cell.

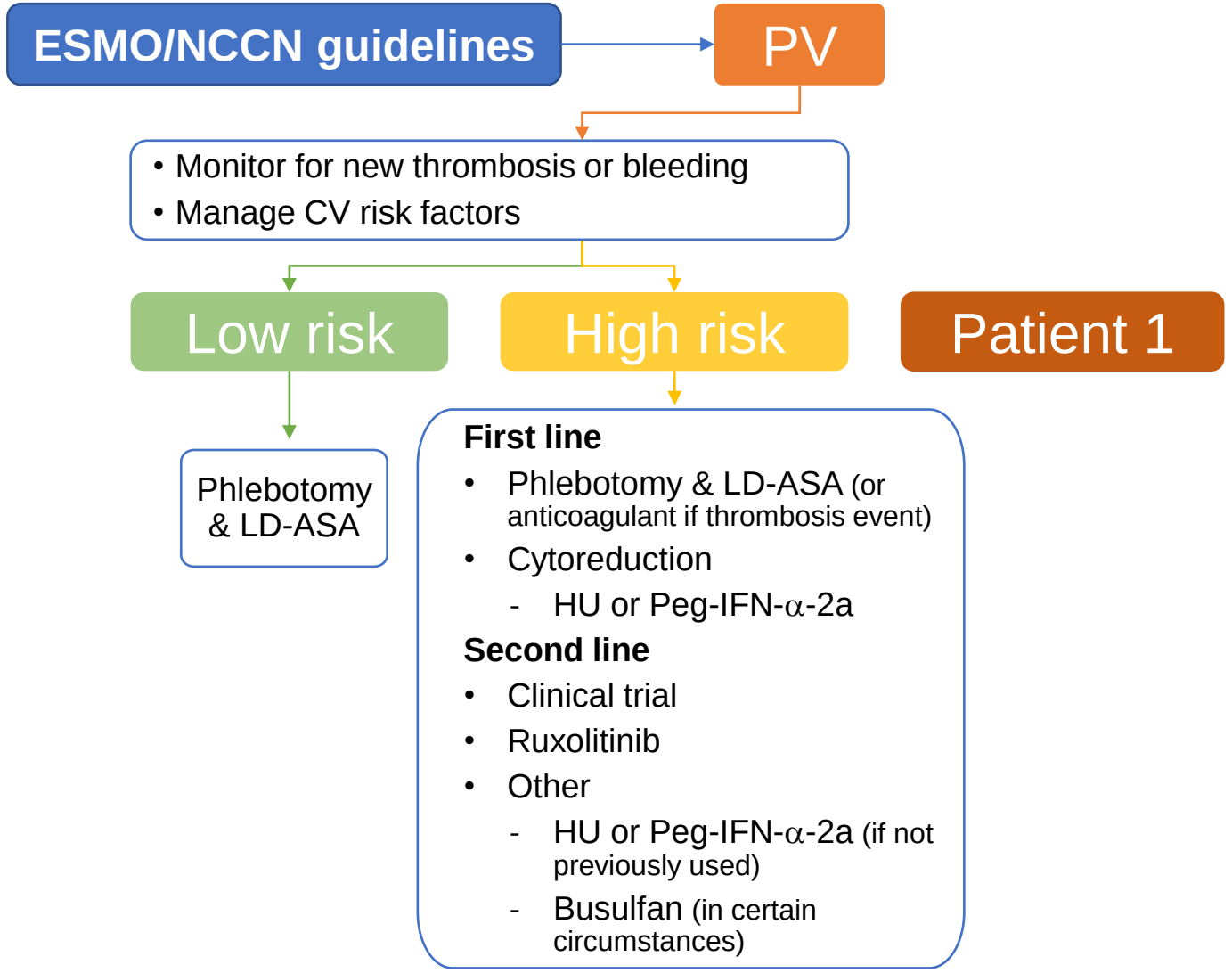
Treatment guidelines are based on thrombosis risk



Barbui T, et al. J Clin Oncol. 2011;29:761-70. Barbui T, et al. Blood. 2012;120:5128-33. Carobbio A, et al. Blood. 2008;112:3135-7. Carobbio A, et al. J Clin Oncol. 2008;26:2732-6. Landolfi R, et al. N Engl J Med. 2004;350:114-24. Marchioli R, et al. J Clin Oncol. 2005;23:2224-32. Marchioli R, et. al. N Engl J Med. 2013;368:22-33. Passamonti F, et al. J Thromb Haemost. 2009;7:1587-9.

How should I treat this patient?

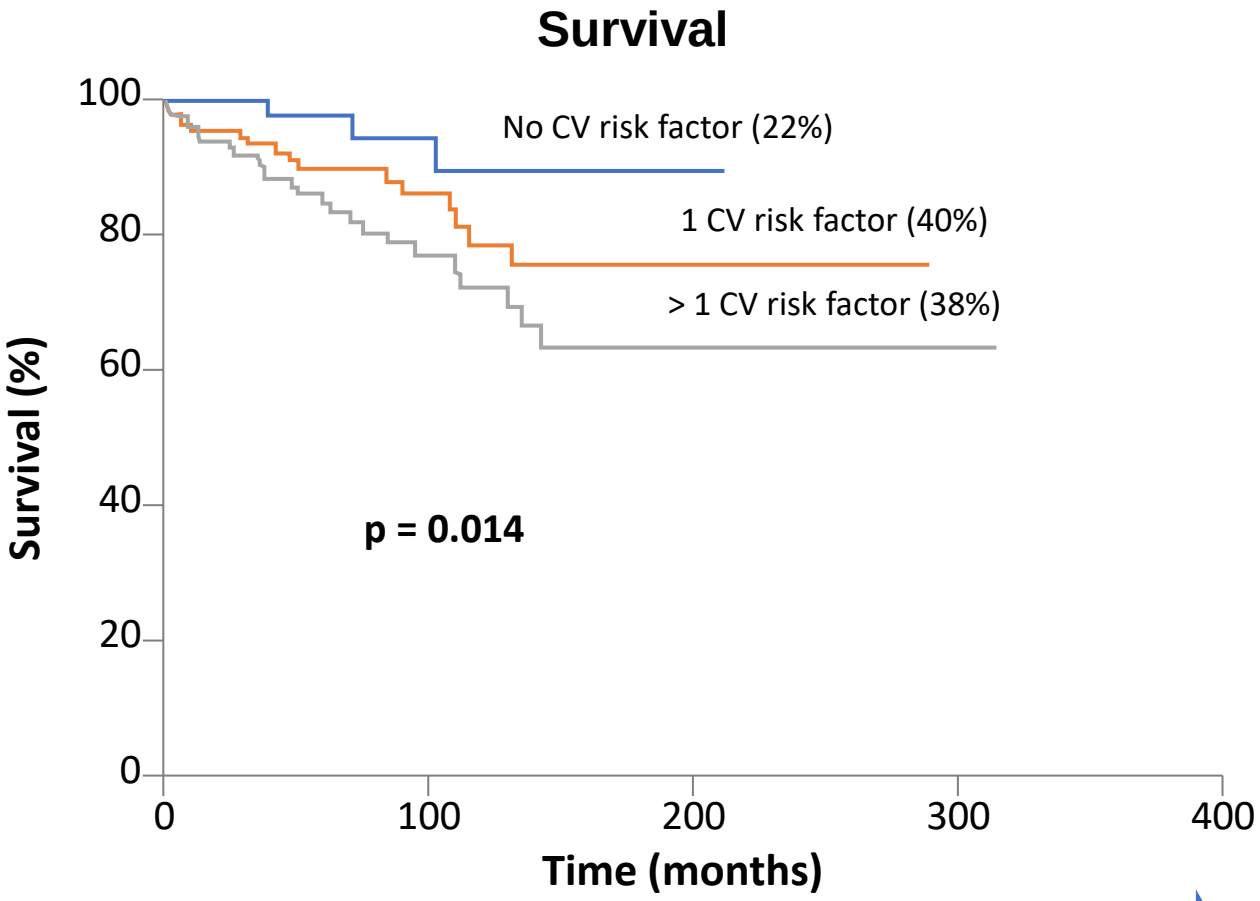
Patient 1	Therapy
2006 75 y, male **Therapy** Phlebotomy q4wk ASS 100 mg QD & HU (**age > 60 y**)	



ESMO, European Society for Medical Oncology; HU, hydroxyurea; IFN, interferon; LD-ASA, low-dose aspirin; NCCN, National Comprehensive Cancer Network; q4wk, every 4 weeks.

NCCN. Guidelines for Myeloproliferative neoplasms 2022; Vannucchi AM, et al. Ann Oncol. 2015;26 Suppl 5:v85-99.

Cardiovascular risk factors affect survival and thrombotic events in patients with polycythemia vera



CV risk factors in 165 PV patients

CV risk factor	n (%)
Smoke	25 (15.0)
Hypertension	105 (63.8)
Obesity	12 (7.5)
Dyslipidemia	47 (28.8)
Diabetes	28 (16.9)

The number of CV risk factors negatively correlates with survival

Has the patient developed HU resistance?

Patient 1	Therapy
75 y, male	
2006–2011	
ASS 100 mg QD	
Phlebotomy q4wk	
HU (age > 60 y)	
2011	
Headache; pruritus; fatigue	
WBC 15.8 × 10^9/L	
Hb 13.7 g/dL	
Hct 44%	
PLT 454 × 10^9/L	

HU resistance (modified ELN criteria)

McMullin MF, et al. Br J Haematol 2016;172:337-49.

HU resistance

HU resistance (modified ELN criteria)[5]

Thrombosis or bleeding

Thrombotic events in PV patients, (%)[1]	Known HU treatment N=1306		Known Phlebotomy treatment N=1314	
	YES	NO	YES	NO
	24.7	24.8	21.8	27.7

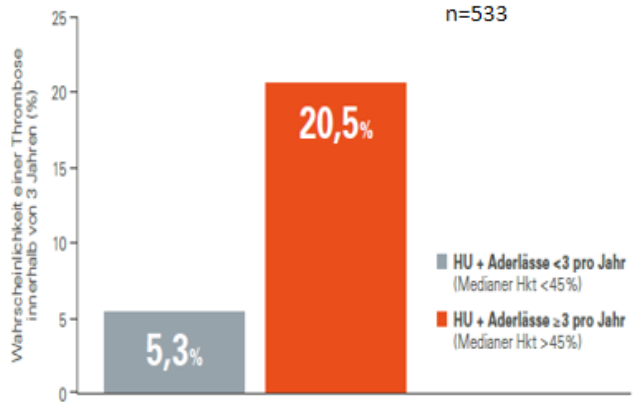
Recurrent thrombosis per 100 pt-years in MPN is 5.3 among patients on long-term vitamin K antagonists and 12.8 after discontinuation (P=0.008)

Geyer H, et al. JCO 2016; De Stefano V, et al. Leukemia 2016.

McMullin MF, et al. Br J Haematol 2016;172:337-49.

HU resistance

3 years probability of thrombosis within 3 years under HU + phlebotomy



Frequent phlebotomies under HU reflect a badly controlled Hct and may indicate an aggressive biology.

Alvarez Larran A, et al. Haematologica 2017.

HU resistance (modified ELN criteria)[5]

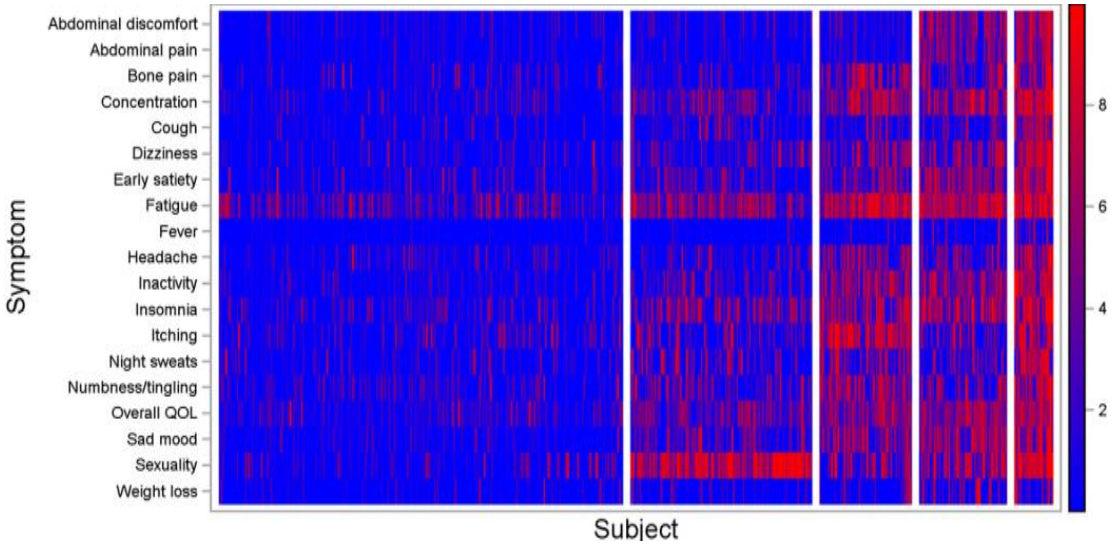
Thrombosis or bleeding

Frequent phlebotomies to keep Hct < 45%

McMullin MF, et al. Br J Haematol 2016;172:337-49.

Has the patient developed HU resistance?

Symptom burden in PV



HU resistance (modified ELN criteria)

Thrombosis or bleeding

Frequent phlebotomies to keep Hct < 45%

Symptoms Patient 1

Geyer HL, et al. Blood. 2014;123:3803-10. Emmanuel R, et al. Blood. 2013;112:4067. Meyers CA, et al. Cancer. 2005;104:788-93. McMullin MF, et al. Br J Haematol. 2016;172:337-49.

Has the patient developed HU resistance?

ECLAP Study

WBC, × 10^9/L	HR (95% CI)	p value
≤ 10 (n = 990)	1	
10.1–15 (n = 365)	1.06 (0.7–1.6)	0.80
> 15 (n = 241)	**1.71 (1.1–2.6)**	**0.02**

Platelet count is not a risk factor for thrombosis, but for bleeding!

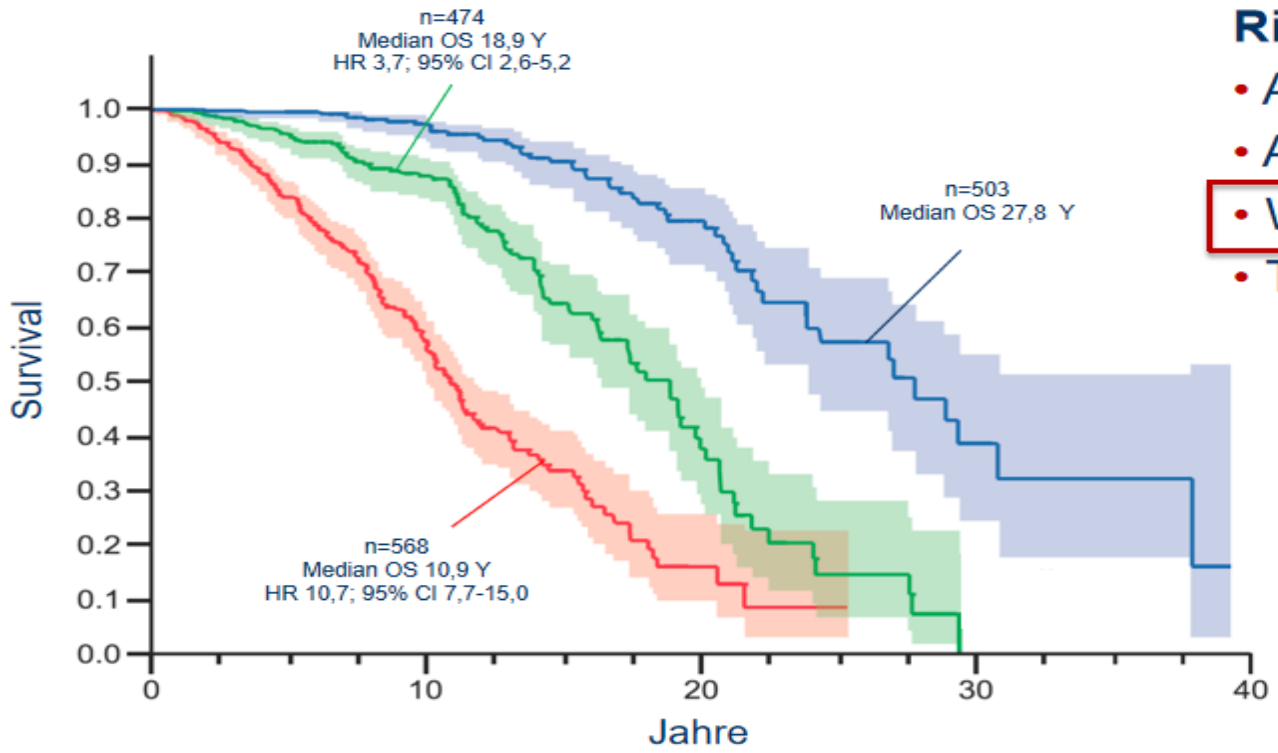
HU resistance (modified ELN criteria)[5]

- Thrombosis or bleeding
- Frequent phlebotomies to keep Hct < 45%
- **Symptoms**
- Platelets > 400 × 10^9/L and/or **leukocytes > 10 × 10^9/L**

Patient 1

Landolfi R, et al. Blood. 2007;109:2446-52. 5. McMullin MF, et al. Br J Haematol. 2016;172:337-49.

Survival in PV is not related to Hb



Risk Factors:

- Age ≥67 y (5 points)
- Age 57–66 y (2 points)
- WBC ≥15 x10^9/l (1 point)
- Thrombosis (1 point)

- **Low Risk** (0 points)
- **Intermediate Risk** (1 - 2 points)
- **High Risk** (≥3 Punkte)

Tefferi A, et al. *Leukemia.* 2013;27:1874-1881.

Has the patient developed HU resistance?

HU resistance (modified ELN criteria)

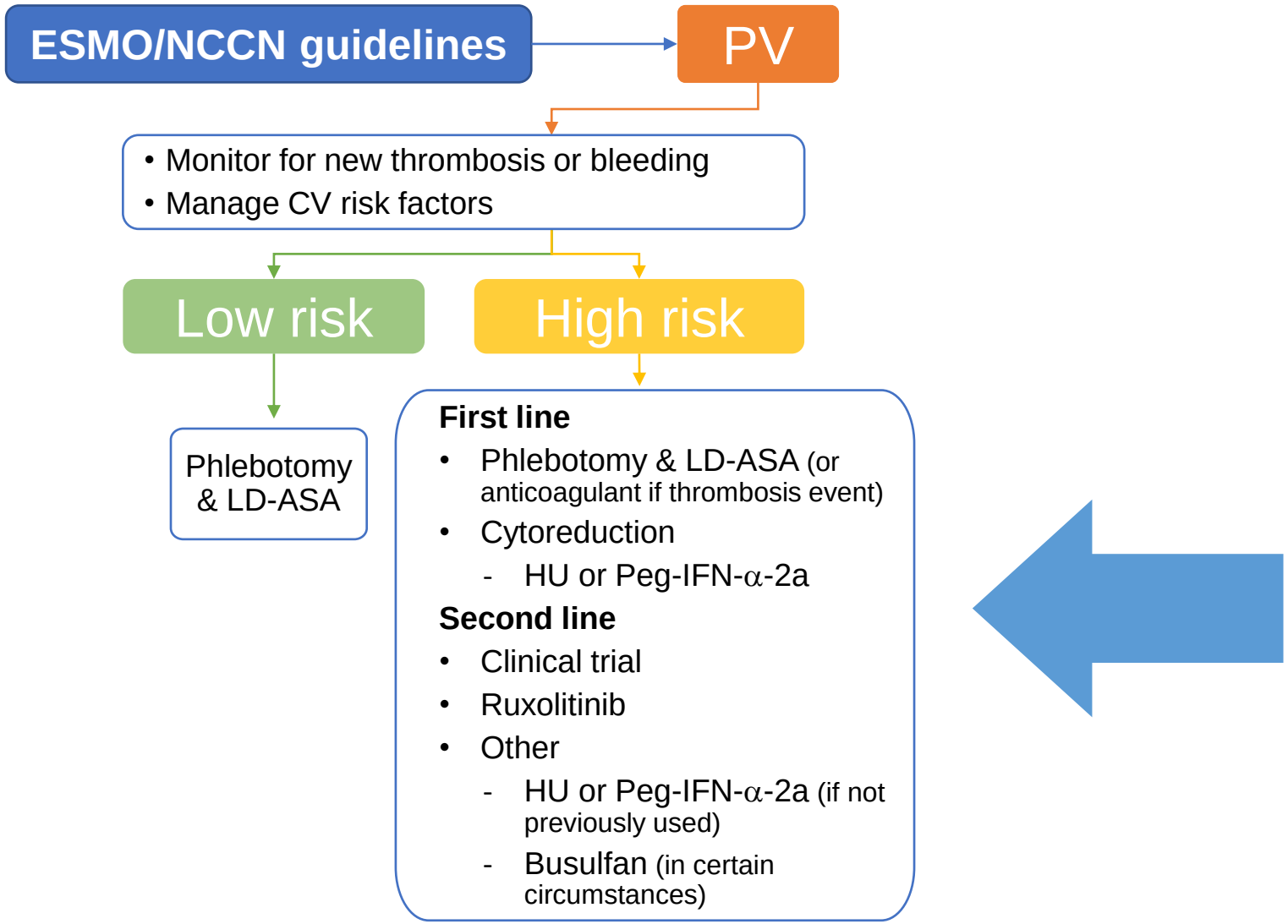
- Thrombosis or bleeding
- Frequent phlebotomies to keep Hct < 45%
- **Symptoms**

Patient 1

- Platelets > 400 × 10^9/L and/or **leukocytes > 10 × 10^9/L**
- No reduction in splenomegaly

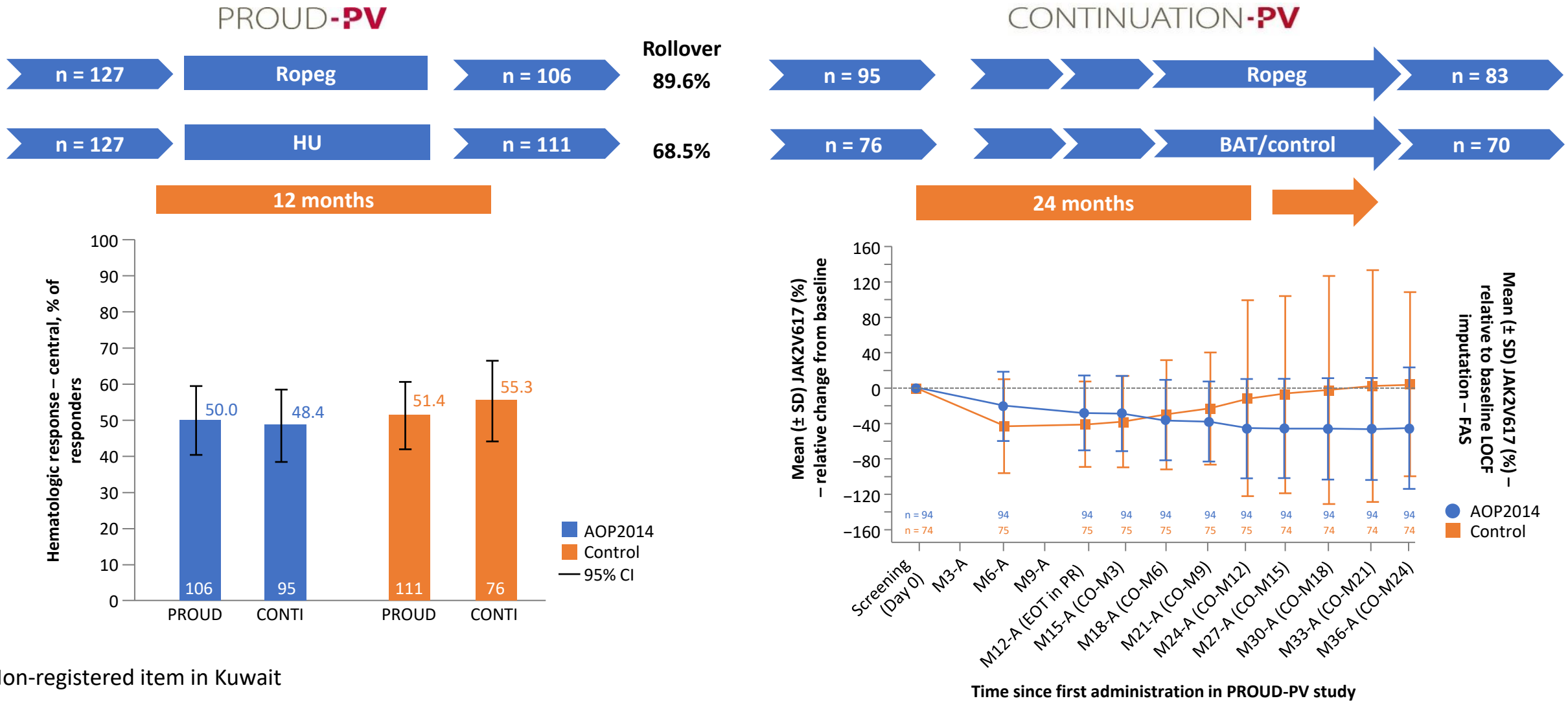
McMullin MF, et al. Br J Haematol. 2016;172:337-49.

What alternatives are available for patient 1?



NCCN. Guidelines for Myeloproliferative neoplasms 2022; Vannucchi AM, et al. Ann Oncol. 2015;26 Suppl 5:v85-99.

A) Interferon (ropeginterferon alfa-2b)



*Non-registered item in Kuwait

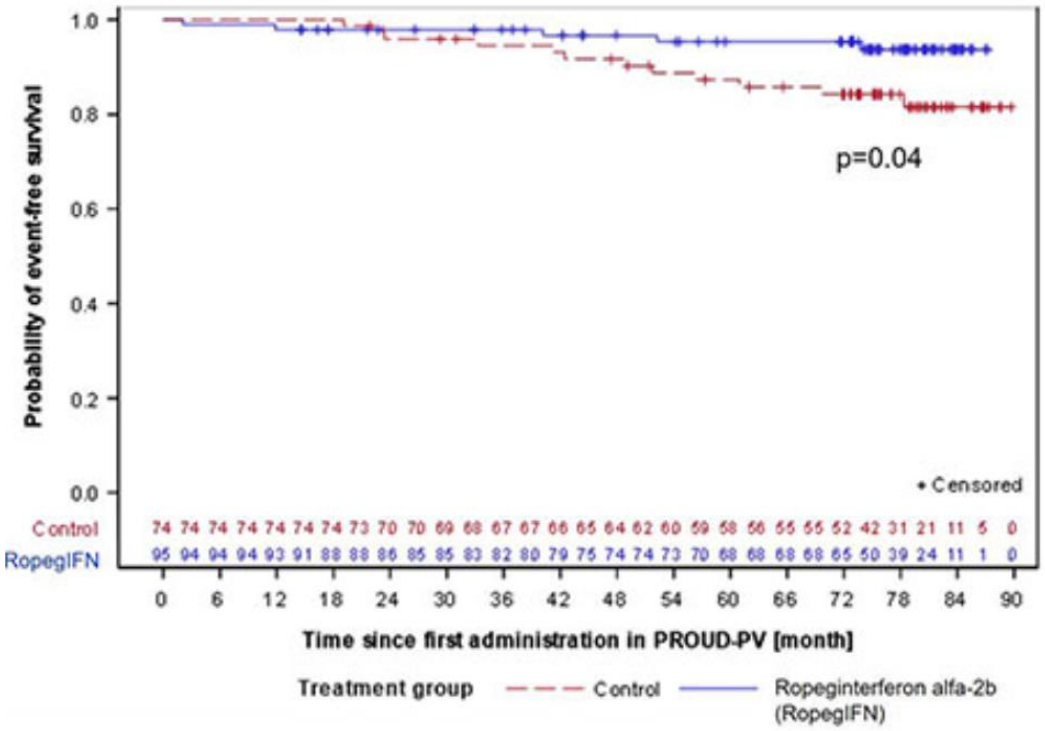
BAT, best available therapy; CONTI, CONTINUATION; FAS, full analysis set; LOCF, last observation carried forward; ropeg, ropeginterferon alfa-2b; SD, standard deviation.

Gisslinger H, et al. Presentation at ASH 2018. Blood. 2018;132 Suppl 1: abstract 579.

A) Interferon (ropeginterferon alfa-2b)

FINAL RESULTS FROM THE PROUD-PV/CONTINUATION-PV STUDIES

6th year of treatment	Ropeginterferon N=95	HU N=74
No phlebotomies (p=0.005)	81.4%	60.0%
JAK2V617F allele burden <1% (p=0.0001).	19/92 (20.7%)	1/70 (1.4%)
PV risk events reported (p=0.04)	5/95 (5.3%)	12/74 (16.2%)



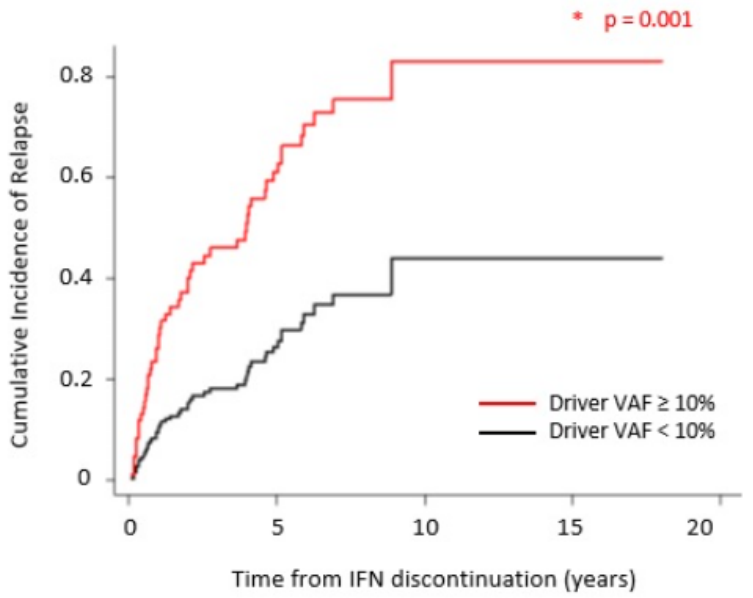
Giesslinger H, et al. EHA 2022; S196

Is TFR possible after IFN in Patients with Complete hematologic Remission (CHR)?

Median follow-up 72.4 months

Therapy IFN	N/ %
Yes (131)	131
No	250
Reasons for discontinuation	
Toxicity	50%
CHR	29.9%
Failure	6.3%
Others	11.8%

Long CHR (p=0.024) & VAF < 10% (p=0.004) are associated with a higher probability of TFR

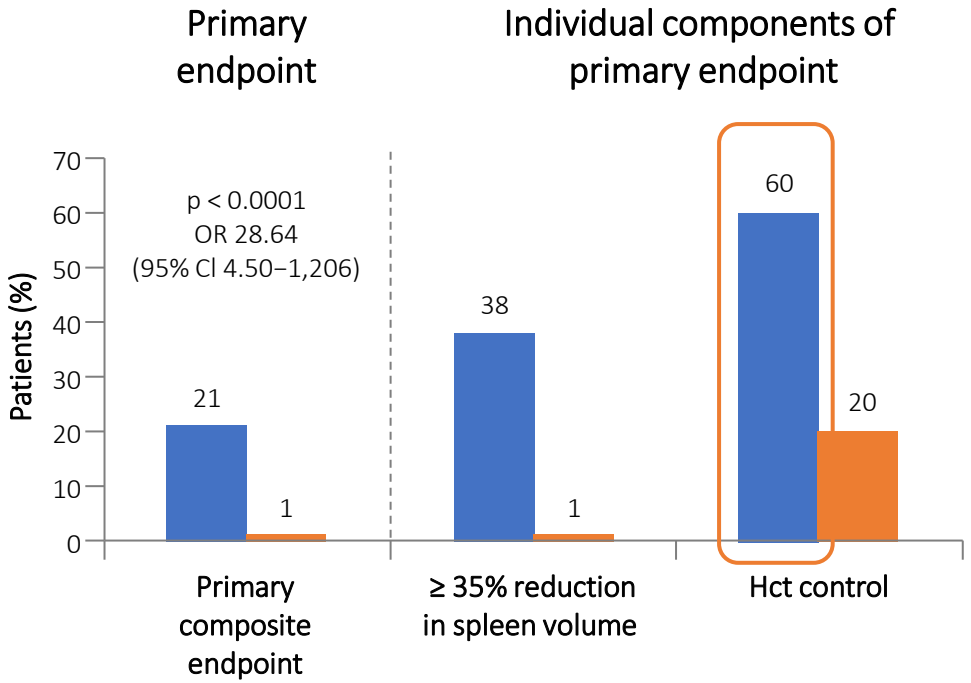


* 61 Patients needed a restart of therapy; 2. CHR: 83.6%

De Oliveira RD, et al; ASH 2020.

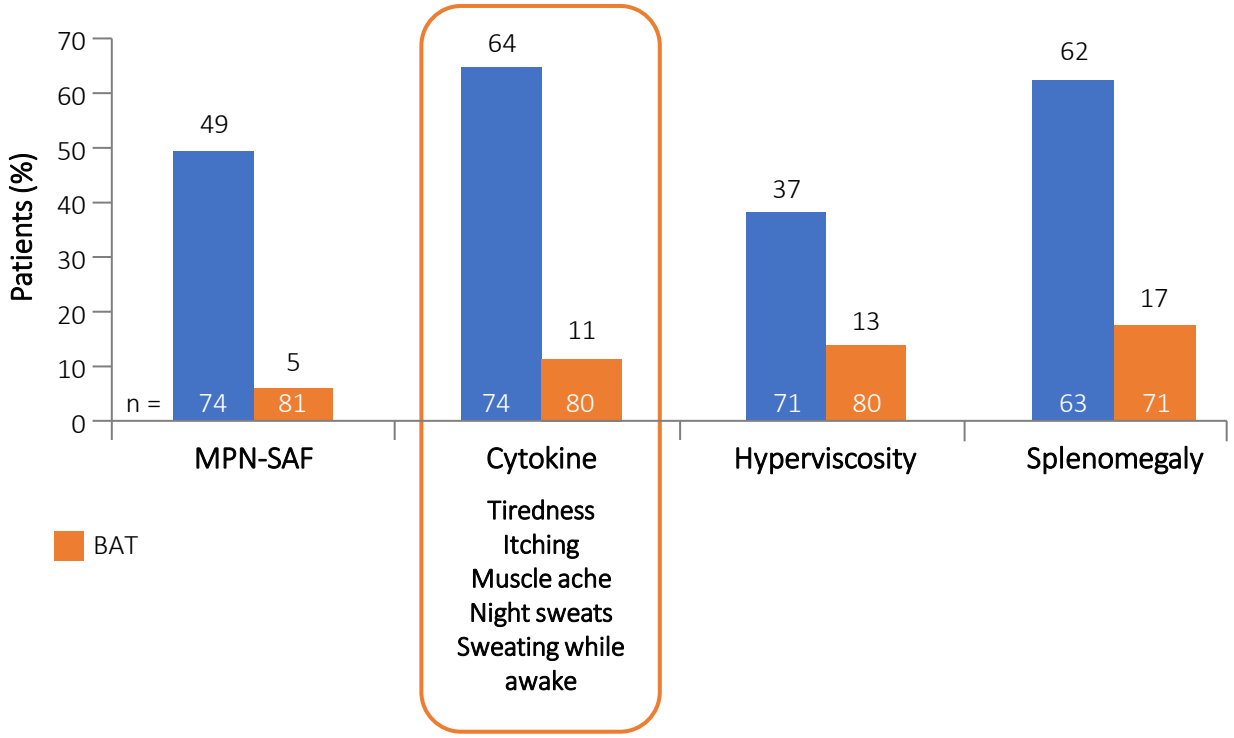
B) Ruxolitinib

Primary response at Week 32



77% of patients randomized to ruxolitinib met at least 1 component of the primary endpoint

Symptom assessment at Week 32

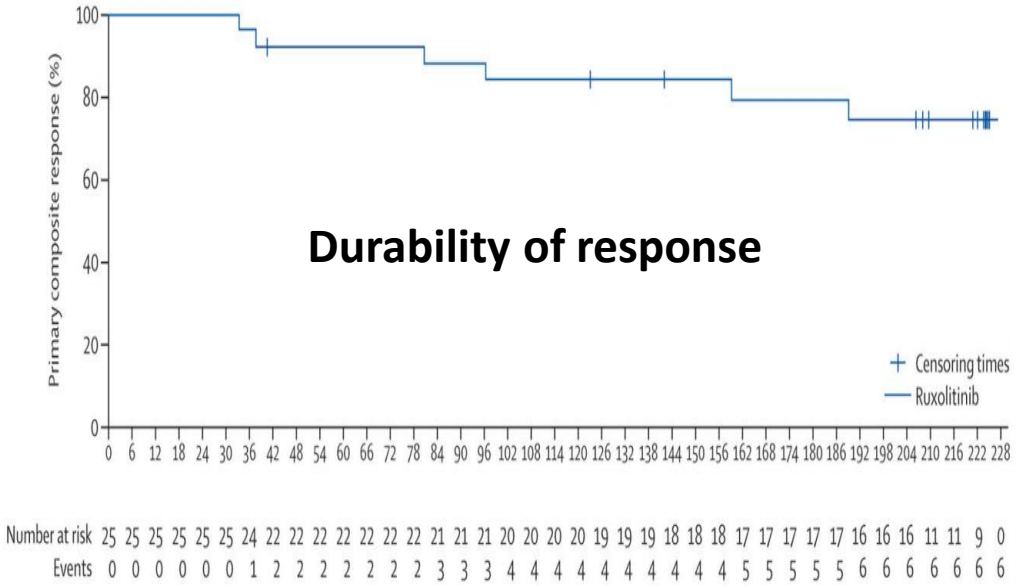


MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; OR, odds ratio.

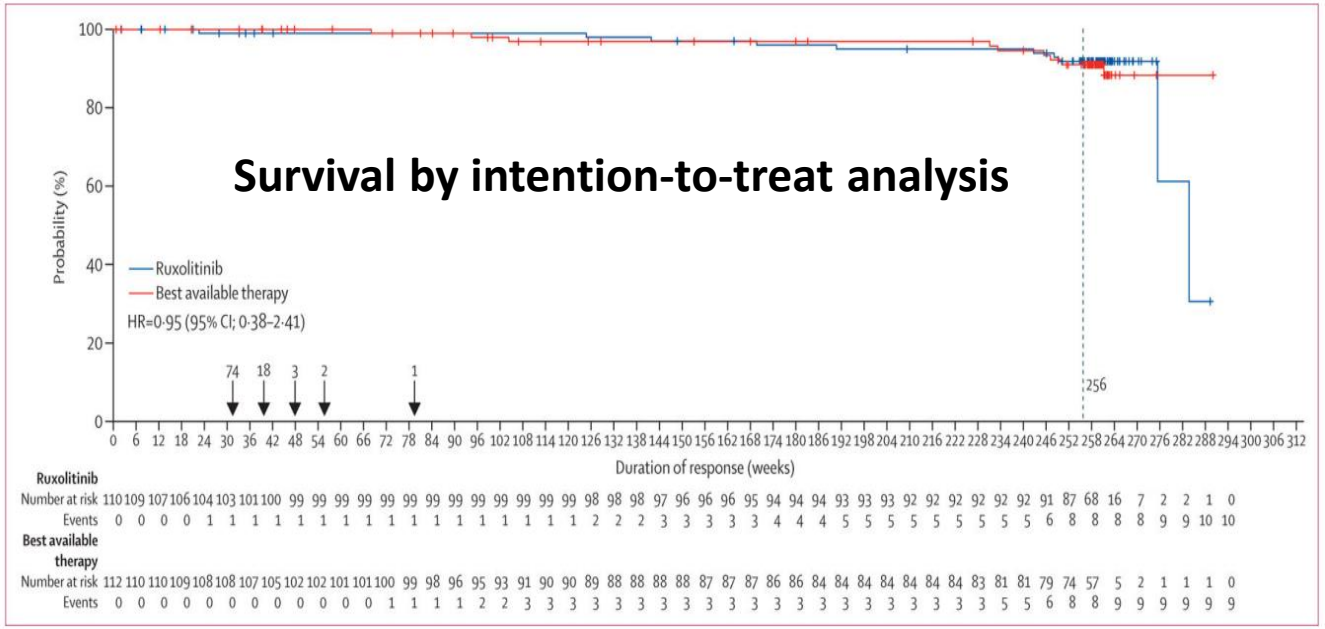
Vannucchi AM, et al. N Engl J Med. 2015;372:426-35.

B) Ruxolitinib

5-year follow up of ruxolitinib versus best available therapy in PV (RESPONSE)



Durability of response



Survival by intention-to-treat analysis

Kiladjian JJ, et al. Lancet Haematol. 2020;7:e226-37.

What about the tolerability of available drugs?

HU

Cytopenia at the lowest dose of HU for a response of **1.7%**

Unacceptable non-hematologic AEs 9% (leg ulcers [6%], mucocutaneous [3%])

"Manageable" toxicity 8% (mucocutaneous [4.4%], digestive [1.6%])

NMSC risk is increased by 20% in ET and PV

IFN-α

AEs are well known

(Flu-like symptoms, fatigue, neuropsychiatric symptoms, thyroiditis)

25–40% of patients with PV and 20–50% of patients with ET discontinued within 1–2 years due to AEs

Ruxolitinib

Anemia 8.9%

All infections 18.9%

(Herpes zoster 4.7%)

NMSC 5.1%

(428.4 patient-years)

	Ruxolitinib		BAT		Crossover	
Prior history of NMSC	No n = 97	Yes n = 13	No n = 105	Yes n = 6	No n = 92	Yes n = 6
Patient-years of exposure	385.3	43.0	70.1	3.5	307.5	22.4
Total NMSC events[a]	14	8	1	1	6	3
Rate per 100 patient-years of exposure	3.6	18.6	1.4	28.5	2.0	13.4

Alvarez-Larrán A, et al. Br J Haematol. 2016;172:786-93. Gómez M, et al. Eur J Haematol. 2016;96:285-90. Kiladjian JJ, et al. Blood. 2008;112:3065-72. Kiladjian JJ, et al. Leukemia. 2008;22:1990-8. Kiladjian JJ, et al. Lancet Haematol. 2020;7:e226-37. Sever M, et al. Leuk Lymphoma. 2014;55:2685-90.

PTG-300 (rusfertide)

Injectable hepcidin mimetic which traps iron within macrophages via ferroportin inhibition

PTG-300-04 study: PV diagnosis & ≥3 phlebotomies with/without concurrent cytoreductive therapy in the 24 weeks before enrollment.

Characteristic	N = 63
Age, mean (range)	56.3 (27–76)
Male, %	71.4
Risk, %	
Low	44.4
High	55.6
Therapy, %	
TP only	49.2
TP + cytoreductive therapy	50.8
Number of phlebotomies 28 weeks prior, %	
2–3	23.8
4–5	52.3
≥6	23.8
Days between phlebotomies, median	35

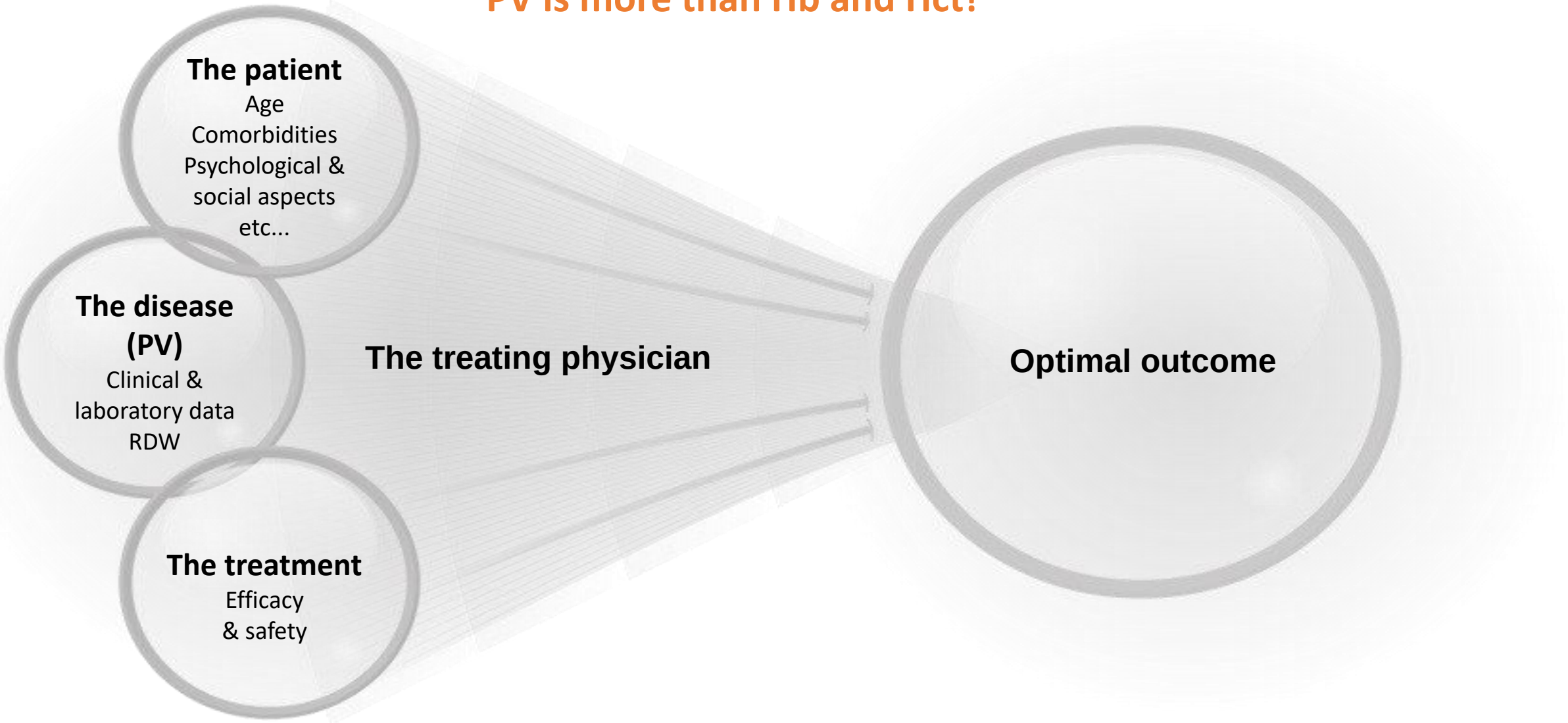
- 84% of patients did not require a phlebotomy, 14% required one, and 2% required two
- iron stores were normalized [increase in serum ferritin levels by Week 4 ($p < 0.01$)]
- reduction in MPN-TSS from baseline to Week 28 (16.3 vs 11.4). Symptomatic reductions were most marked in the level of fatigue, and problems with concentration ($p = 0.04$)
- increase in platelet count ($p < 0.01$) by Week 4, which persisted until Week 28 (the increase did not exceed 20% in platelet numbers)

- **During the brief clinical hold (FDA; NMSC), all patients had significant ($p<0.01$) increase in TPs, HCT, and RBC count; and reported increase in PV-related symptoms.**

Hoffman R, et al. Blood. 2021; Kuykendall A, et al EHA 2022

Conclusions to PV

PV is more than Hb and Hct!



MF
JAK2 Inhibitors (JAKi) in MPN

JAKi revolutionized the therapeutic landscape of MPN - particularly for patients with myelofibrosis (MF) with their efficacy in controlling disease-related symptoms and splenomegaly

Agent	JAK family target	Non-JAK target	Approved	Current/ future indication
Ruxolitinib	JAK1/2	TYK2, JAK3	Yes	1st-line MF; 2nd-line PV
Fedratinib	JAK2	FLT3	Yes (FDA/EMA)	1st- and 2nd-line MF
Momelotinib	JAK1/2	JNK1, CDk2, ACVR1/ALK2*	No	2nd-line MF
Pacritinib	JAK2	FLT3, CSF1R, IRAK1, TNK1, and ROS1**	No	2nd-line MF

* activin A receptor type 1 is a bone morphogenic protein receptor (BMPR) kinase that regulates hepcidin expression (Asshoff M, et al. Blood 2017.)

** This accounts for potent anti-proliferative effects and limited myelo- and immunosuppressive activities (Singer JW, et al. C J Exp Pharmacol. 2016.)

ry

Treatment in Myelofibrosis

NCCN guidelines for treatment of MF

Lower-risk

- Asymptomatic ➔ observation or clinical trial
- **Symptomatic** ➔ clinical trial or observation or **ruxolitinib** or peginterferon α-2a or HU

Higher-risk

- Transplant eligible ➔ allo-HSCT

or

- Transplant ineligible ➔ **ruxolitinib** or **fedratinib** or clinical trial

AND/OR

- Transplant ineligible/anemia ➔ anemia prescription or clinical trial

Lower-risk: MIPSS-70 ≤ 3; DIPSS-Plus ≤ 1; DIPSS ≤ 2

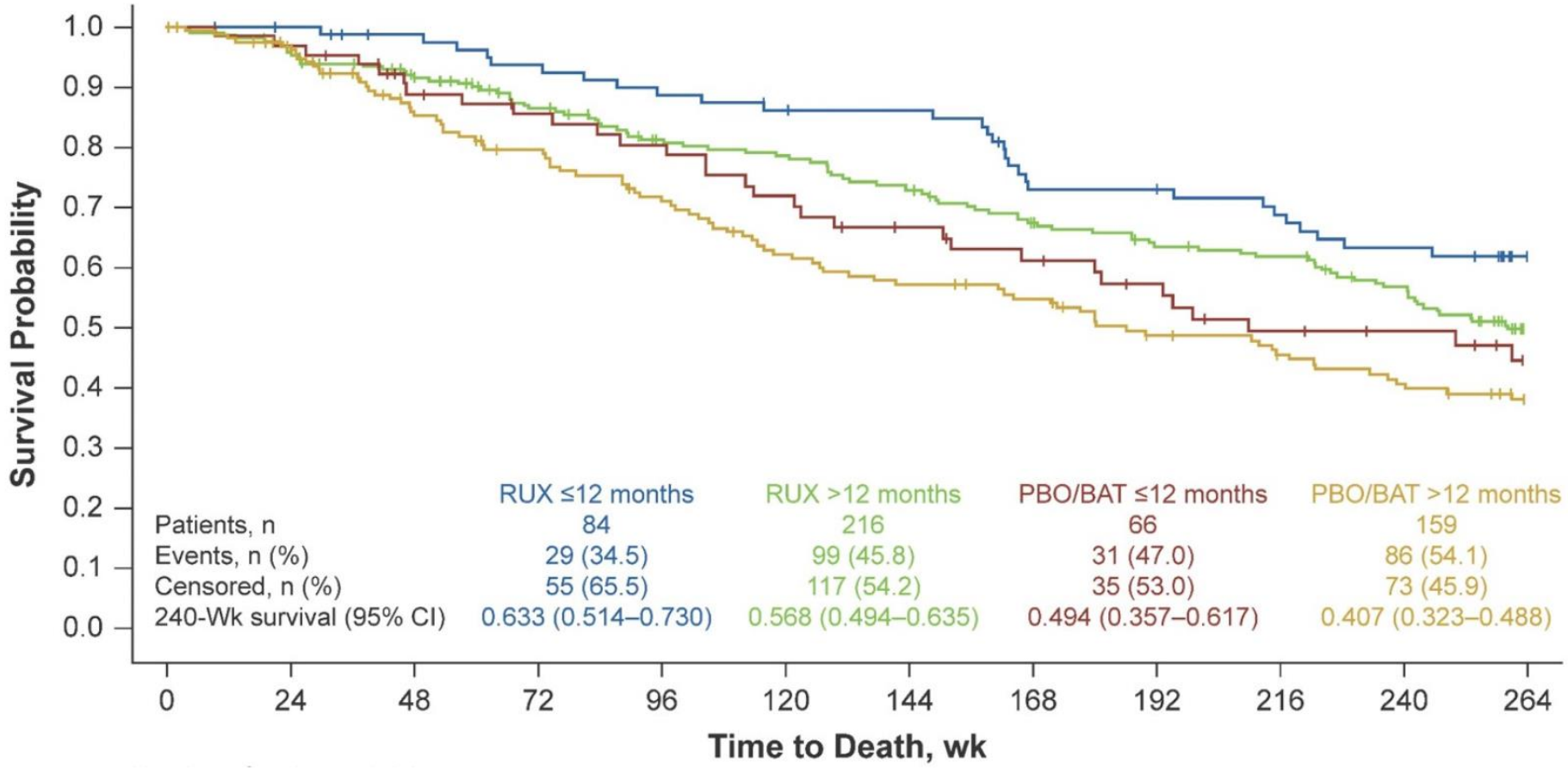
Higher-risk: MIPSS-70 ≥ 4; DIPSS-Plus > 1; DIPSS > 2

- Myeloproliferative Neoplasms. www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

Long-term Survival Data under Ruxolitinib

Early Intervention & Impact on outcomes. A Pooled Analysis of the Comfort I and II Studies

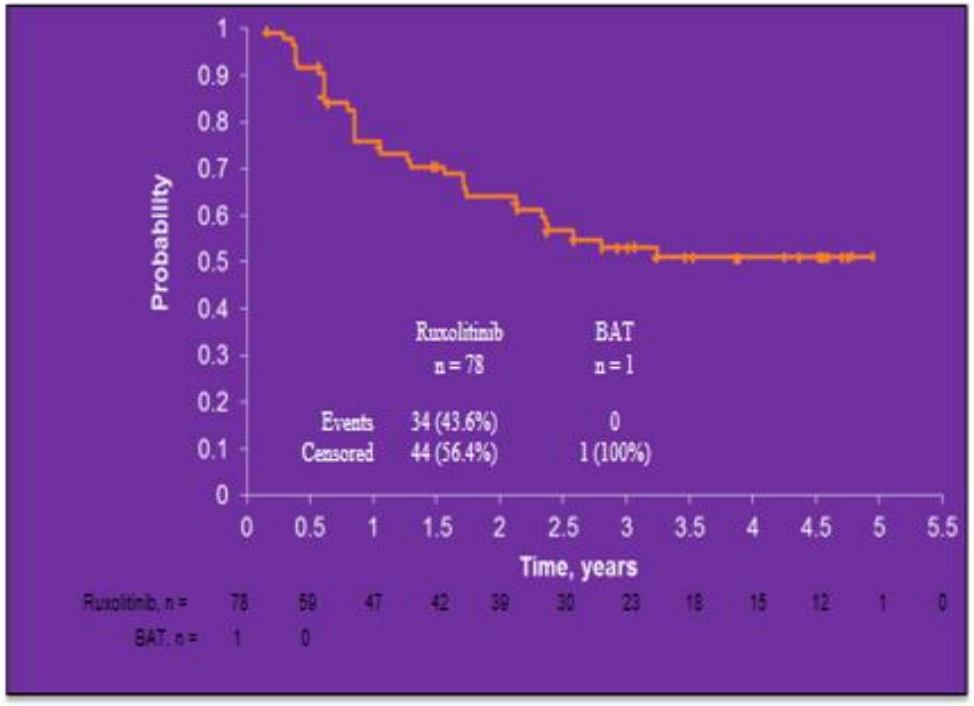
Figure. OS of Patients with MF Stratified by Disease Duration before RUX Initiation



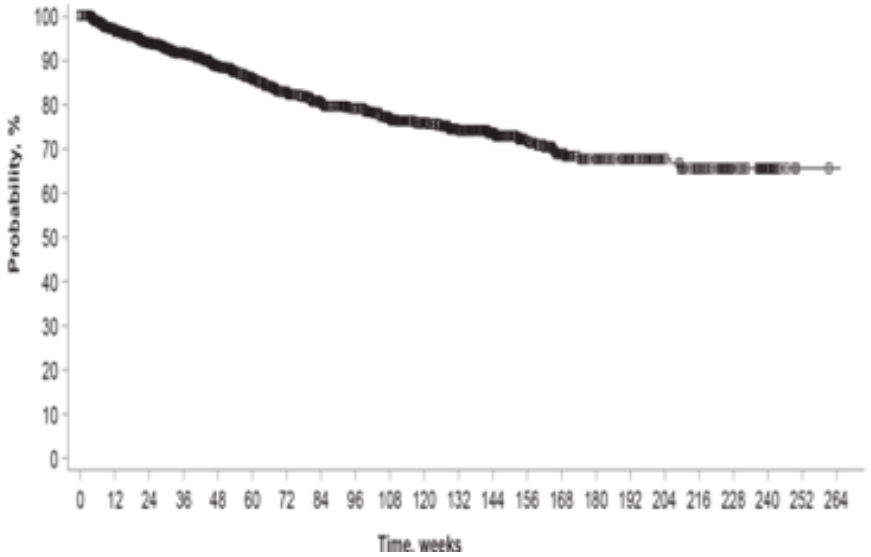
Verstovsek S, et al. *Blood* 2021; Harrison C, et al. EHA 2022.

A) Loss of Response to Ruxolitinib

COMFORT II : Median duration of spleen response is 3,2 years



JUMP: The Kaplan-Meier–estimated probability of maintaining a spleen response by IWG-MRT criteria was **60%** at two years



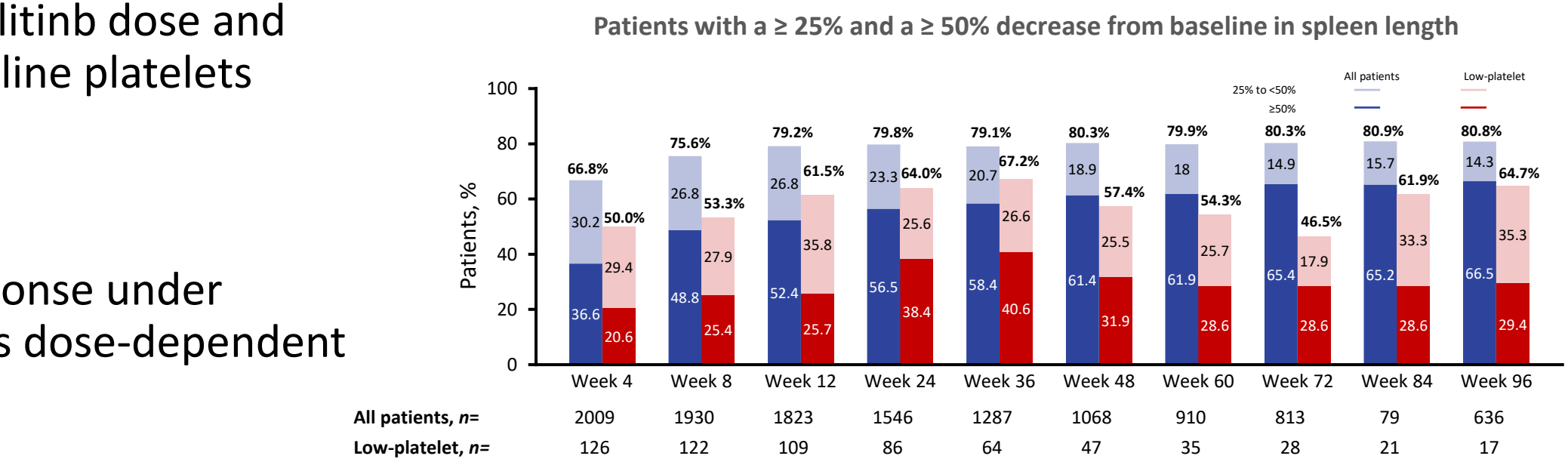
Al-Ali HK, et al. Br J Haematol. 2020; Verstovsek S, et al. Haematologica 2015; Cervantes F, et al. Blood 2013; Harrison C, et al. Leukemia 2016;

B) Ruxolitinib-related thrombocytopenia and dose-dependent response

- Thrombocytopenia is more frequent in patients with low baseline platelets (≥ 50 to < 100 × 10^9/L) despite only 5 mg BID compared to patients with higher ruxolitinb dose and higher baseline platelets

- Spleen response under ruxolitinib is dose-dependent

Preferred term	Platelet count < 100 × 10^9/L (n = 138)		Platelet count ≥ 100 × 10^9/L (n = 2087)	
	All grades	Grade 3/4	All grades	Grade 3/4
Thrombocytopenia, n (%)	101 (73.2)	75 (54.3)	1089 (52.2)	356 (17.1)



Al-Ali HK, et al. Br J Haematol. 2020;189:888–903.

B) Anemia- Ruxolitinib Based Treatment in Myelofibrosis

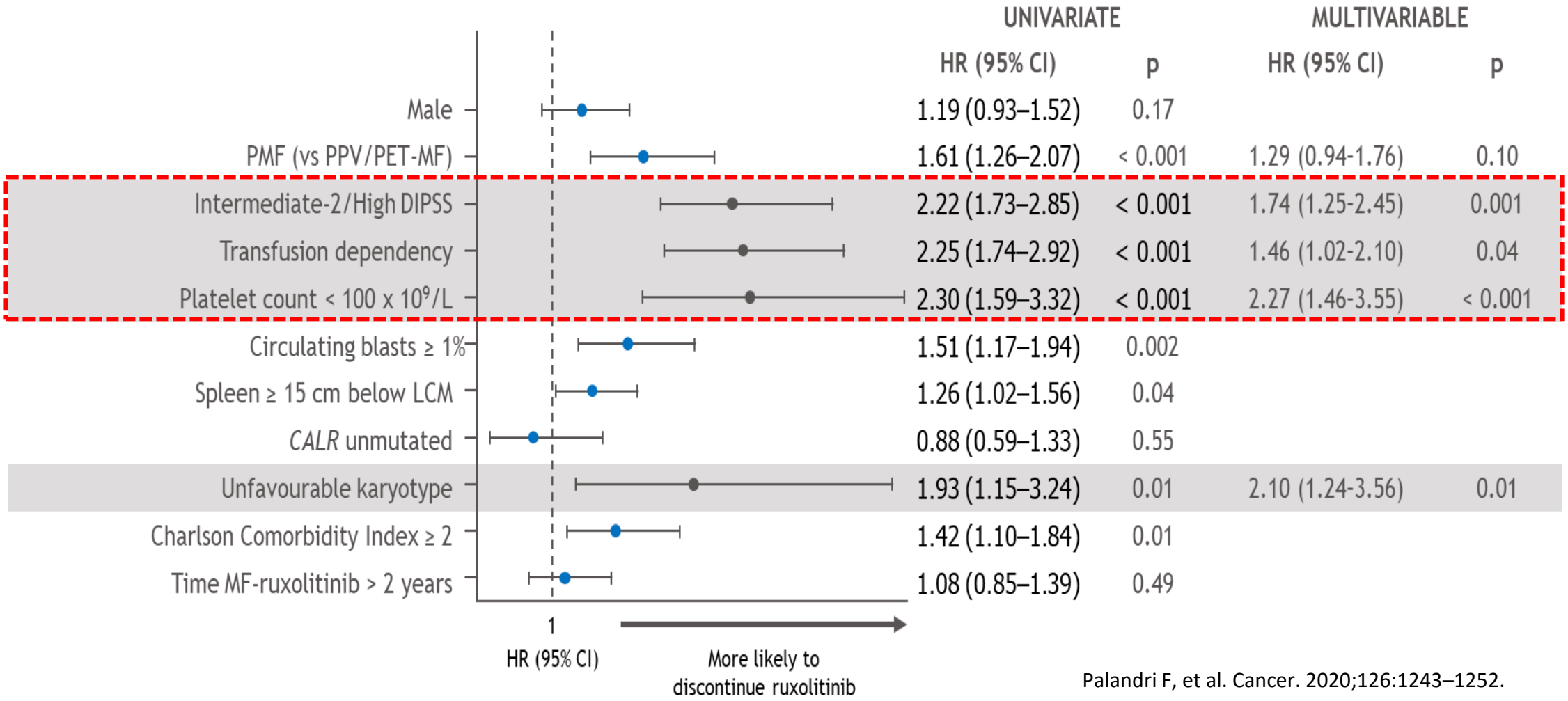
Ruxolitinib in IPSS-1 patients: higher response rate and lower toxicities

Clinical trial[a]	Spleen response at Week 24, %	Incidence of anemia Grade 3/4, %	Incidence of thrombocytopenia Grade 3/4, %	Incidence of infections, %	Discontinuation rate, %
Int-2- and High-risk patients					
COMFORT-I (n = 155)	41.9	45.0	13.0	~ 50.0	21.0
COMFORT-II (n = 146)	32.0	42.0	8.0	~ 50.0	38.0
Int-1-risk patients					
JUMP (n = 163)	63.8	24.5	11.0	40.0	19.6
ROBUST (n = 14)	50.0	N/A	N/A	N/A	N/A
Italian study (n = 70)	54.7	21.7	2.9	17.1	17.1

Verstovsek S, et al. N Engl J Med. 2012;366:799-807. Harrison C, et al. N Engl J Med. 2012;366:787-98. Al-Ali HK, et al. Haematologica. 2016;101:1065-73. Mead AJ, et al. Br J Haematol. 2015;170:29-39. Palandri F, et al. Hematol Oncol. 2018;36:285-90.

Ruxolitinib Based Treatment in Myelofibrosis

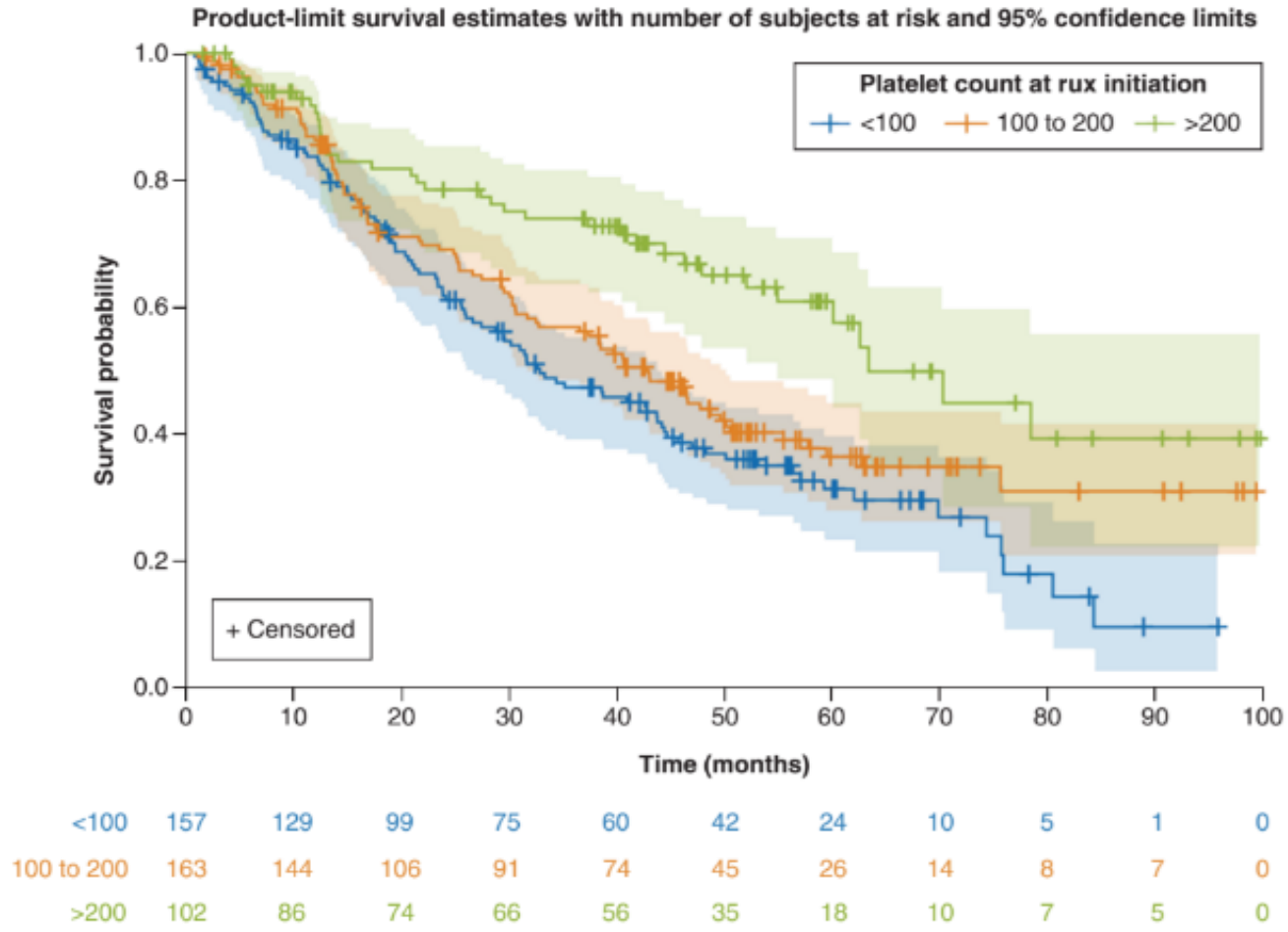
Disease stage is a predictive factor for ruxolitinib discontinuation



Palandri F, et al. Cancer. 2020;126:1243–1252.

Survival under ruxolitinib based on baseline platelet count

- Median OS under ruxolitinib in patients with a platelet count between 100 × 10^9/L and 200 x 10^9/L was 42.9 months compared with 32.9 months in patients with a platelet count < 100 × 109/L

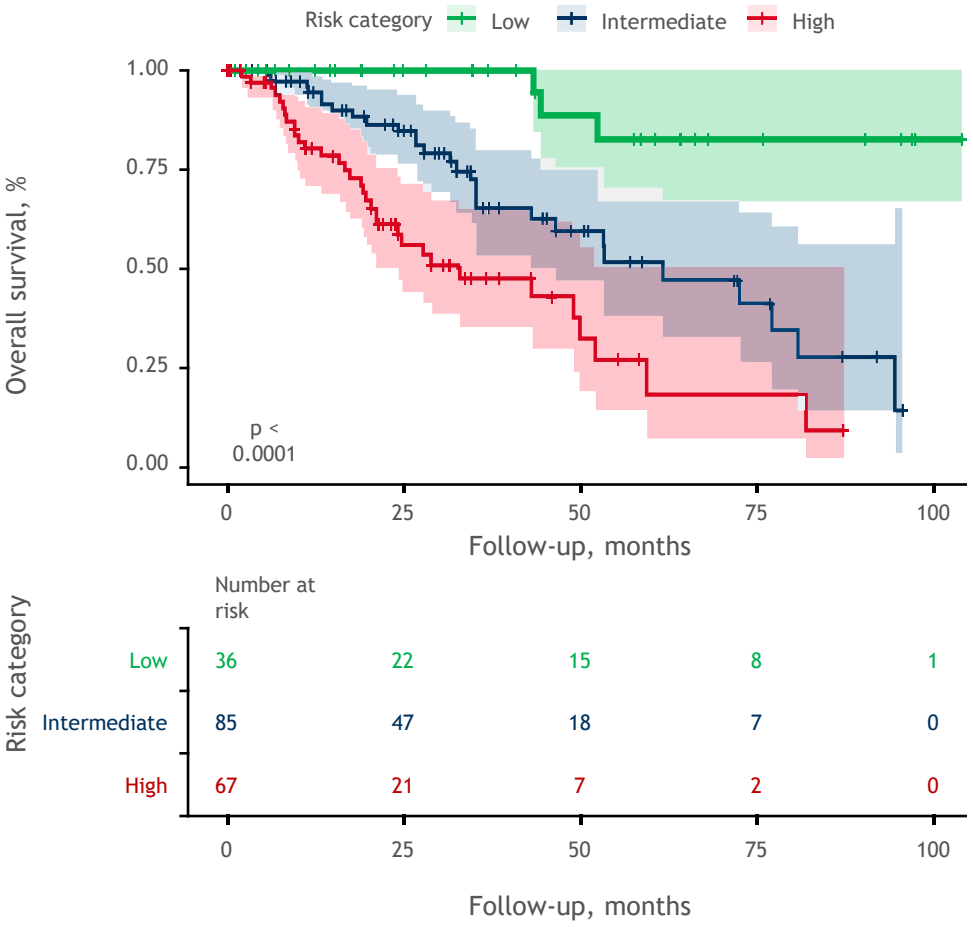


Passamonti F et al.Hematological Oncology 2021

Transfusion dependency during ruxolitinib treatment is associated with worse OS

A prognostic model to predict survival after 6 months of ruxolitinib in patients with MF

Variable	Univariate, HR (95% CI); P value	Multivariate, HR (95% CI); P value
Hb decrease at 6 mo vs baseline[a]	1.02 (0.87–1.21); 0.77	-
WBC count increase to > 25 x10^9/L at 6 mo vs baseline[b]	1.20 (0.38-3.84); 0.76	-
PLT count decrease at 6 mo vs baseline		-
Worsening of 1 grade[c]	0.81 (0.44-1.47); 0.48	
Worsening of 2 grades[c]	2.57 (1.25-5.25); 0.01	
Worsening of ≥ 2 grades[c] at 3 mo and/or 6 mo	1.07 (0.67-1.73); 0.77	
Circulating blast cell increase at 6 mo vs baseline	1.42 (0.85-2.37); 0.18	-
Acquisition of constitutional symptoms at 6 mo[d]	Not feasible[e]	-
Splenomegaly reduction ≤ 30% by palpation at 3 and 6 mo	2.54 (1.58-4.08); < 0.0001	2.26 (1.40-3.65); 0.0009
RBC transfusion need only at baseline	0.42 (0.10-1.75); 0.23	
RBC transfusion need at 3 and/or 6 mo	1.80(1.05-3.09); 0.03	1.66 (0.95-2.88); 0.07
RBC transfusion need at all time points (baseline, 3 mo and 6 mo)	2.88 (1.49-5.54); 0.002	2.32 (1.19-4.54); 0.02
RUX dose < 20 mg BID at all time points (baseline, 3 mo and 6 mo)	2.18 (1.31-3.63); 0.003	1.79 (1.07-3.00); 0.03



Maffioli M, et al. Blood Adv. 2022;6:1855–1864.

Treatment in Myelofibrosis

NCCN guidelines for treatment of MF

Lower-risk

- Asymptomatic ➔ observation or clinical trial
- **Symptomatic** ➔ clinical trial or observation or **ruxolitinib** or peginterferon α-2a or HU

Higher-risk

- Transplant eligible ➔ allo-HSCT

or

- Transplant ineligible ➔ **ruxolitinib** or **fedratinib** or clinical trial

AND/OR

- Transplant ineligible/anemia ➔ anemia prescription or clinical trial

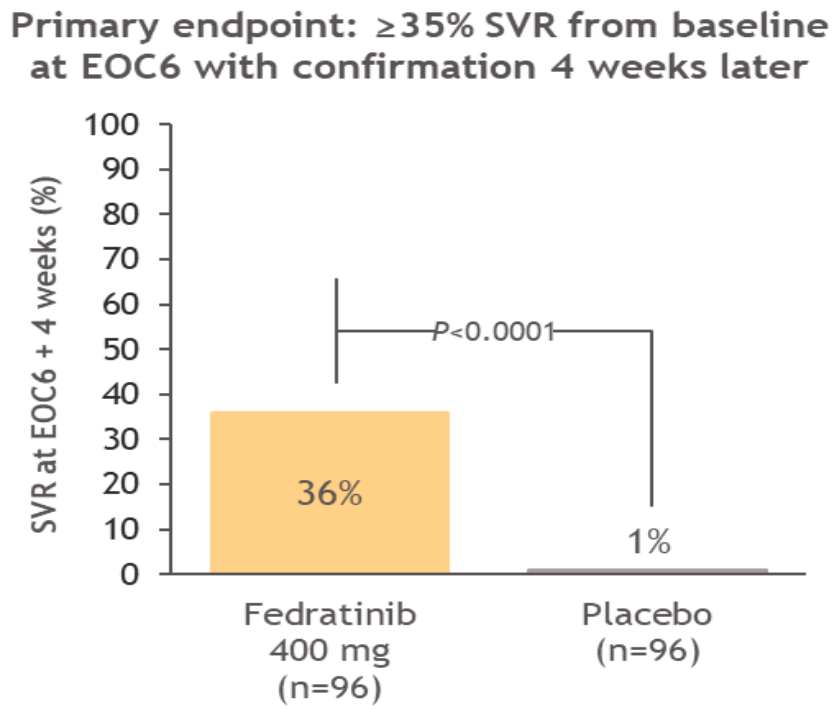
Lower-risk: MIPSS-70 ≤ 3; DIPSS-Plus ≤ 1; DIPSS ≤ 2

Higher-risk: MIPSS-70 ≥ 4; DIPSS-Plus > 1; DIPSS > 2

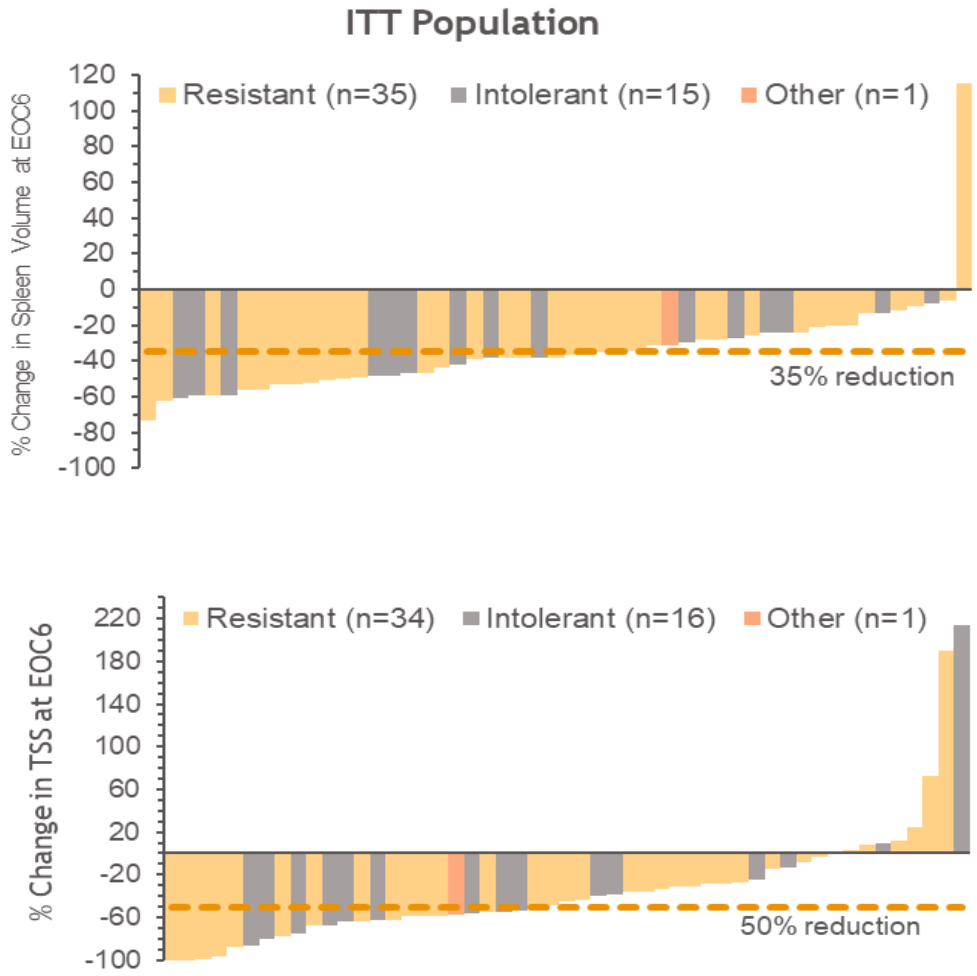
- Myeloproliferative Neoplasms. www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

Fedratinib Efficacy Data

JAKARTA



JAKARTA2

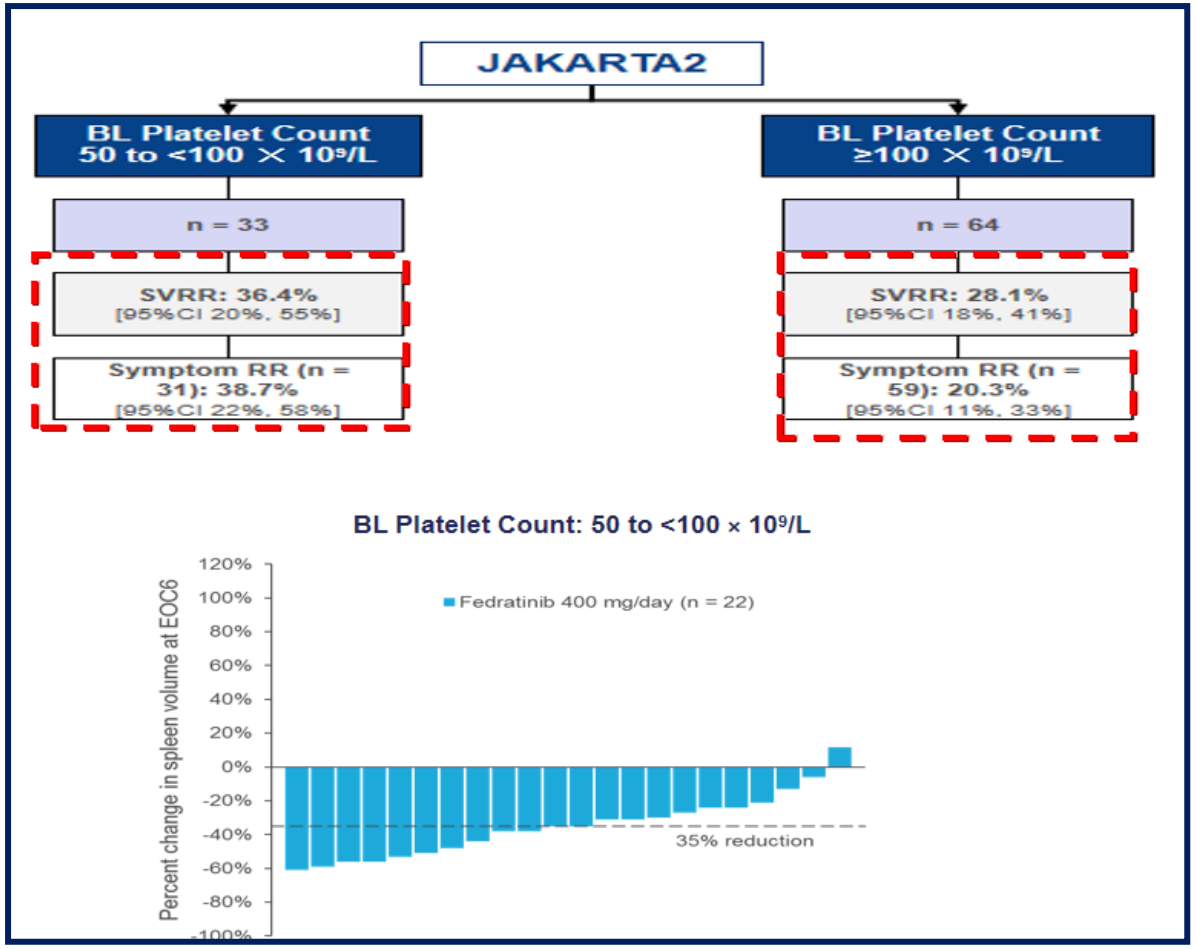


- **≥ 50% reductions in TSS** at the EOC6 was reported for **40%** (36/89) and 9% (7/81) of patients in the **fedratinib 400 mg** arm and placebo arm, respectively[2]

Talpaz et al. *Leukemia* 2020; Harrison et al. Am J Hematol 2020

2. Line Fedratinib (JAKARTA 2)

Response



Harrison C et al., Am J Hematol. 2020

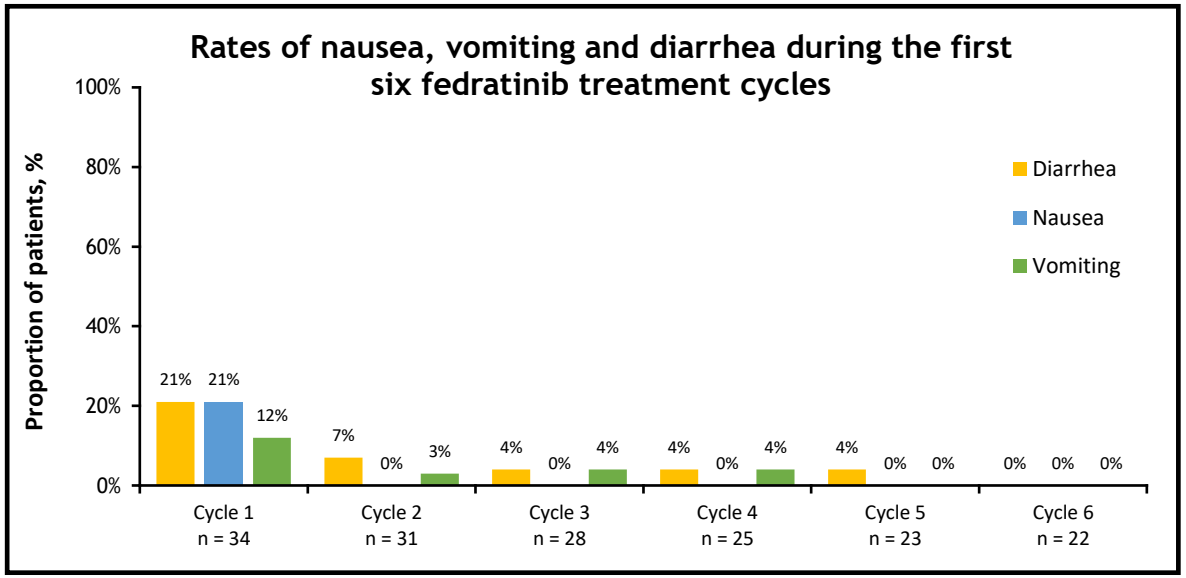
Management of AEs

- GI safety mitigation strategies
  - Prophylactic and symptomatic use of anti-nausea, anti-vomiting, and anti-diarrheal treatments
  - Fedratinib dosing modifications
  - Administration of fedratinib with food
- Screen for Encephalopathy (Wernicke) during treatment
- Thiamine monitoring and correction

Management of GI AEs under fedratinib

- The ongoing single-arm, Phase IIIb FREEDOM study (FEDR-MF-001; NCT03755518) is evaluating the long-term safety and efficacy of second-line fedratinib in MF
- Unlike previous studies, the FREEDOM study prospectively requires mitigation strategies to manage GI events
- GI safety mitigation strategies include:
  - prophylactic and symptomatic use of anti-nausea, anti-vomiting and anti-diarrheal treatments
  - fedratinib dosing modifications
  - administration of fedratinib with food

Medications	N (%)
Ondansetron	22 (65%)
Loperamide	11 (32%)



Gupta V, et al. Blood. 2021;138:389 . Gupta V, et al. EHA 2022

Further JAK Inhibitors as 2nd line therapy in MS

Agent	JAK family target	Non-JAK target	Remarks
Momelotinib	JAK1/2	JNK1 CDk2	An option for anemic patients (second-line): Momentum Trial
Pacritinib	JAK2	FLT3	An option for thrombocytopenic patients (second-line) Approved by FDA
Fedratinib	JAK2	FLT3	Approved by FDA and EMA

MOMENTUM: PHASE 3 RANDOMIZED STUDY OF MOMELOTINIB (MMB) VERSUS DANAZOL (DAN) IN SYMPTOMATIC AND ANEMIC MF PATIENTS PREVIOUSLY TREATED WITH A JAKi

Primary endpoint: TSS response (≥ 50% reduction in mean TSS over the 28 days immediately prior to the end of week 24 compared to baseline).

Endpoint at Week 24	MMB (N=130)	DAN (N=65)	P-value
TSS response rate, n (%)	32 (24.6%)	6 (9.2%)	p=0.0095 (superior)
TI rate, n (%)	40 (30.8%)	13 (20.0%)	p=0.0064 (non-inferior)
SRR (25% reduction), n (%)	52 (40.0%)	4 (6.2%)	p<0.0001 (superior)
Rate of zero transfusions to week 24	46 (35.4%)	11 (16.9%)	p=0.0012 (superior)

Verstovsek S, et al. *EHA* 2022

Pacritinib: A therapeutic option for patients with severe thrombocytopenia

- Pacritinib has demonstrated clinical benefit at the recommended dose of 200 mg BID in patients with cytopenias in the Phase 2 dose-finding PAC203 and Phase 3 PERSIST-2 studies
- Patients with baseline platelets < 50 x 10^9/L treated with pacritinib 200 mg BID in PERSIST-2 and PAC203 or BAT in PERSIST-2 were included in a retrospective analysis

Baseline characteristics (pacritinib 200 mg BID)	N = 71
Median platelet count, 10^9/L	30
Platelet transfusion dependent, n (%)	13 (18)
Prior JAKi, n (%)	45 (63)

Some AEs (all grades)	N (%)
Thrombocytopenia	23 (32)
Any grade bleeding	49 (58)
Grade ≥ 3 bleeding	11 (16)
Grade ≥ 3 cardiac AE	6 (9)

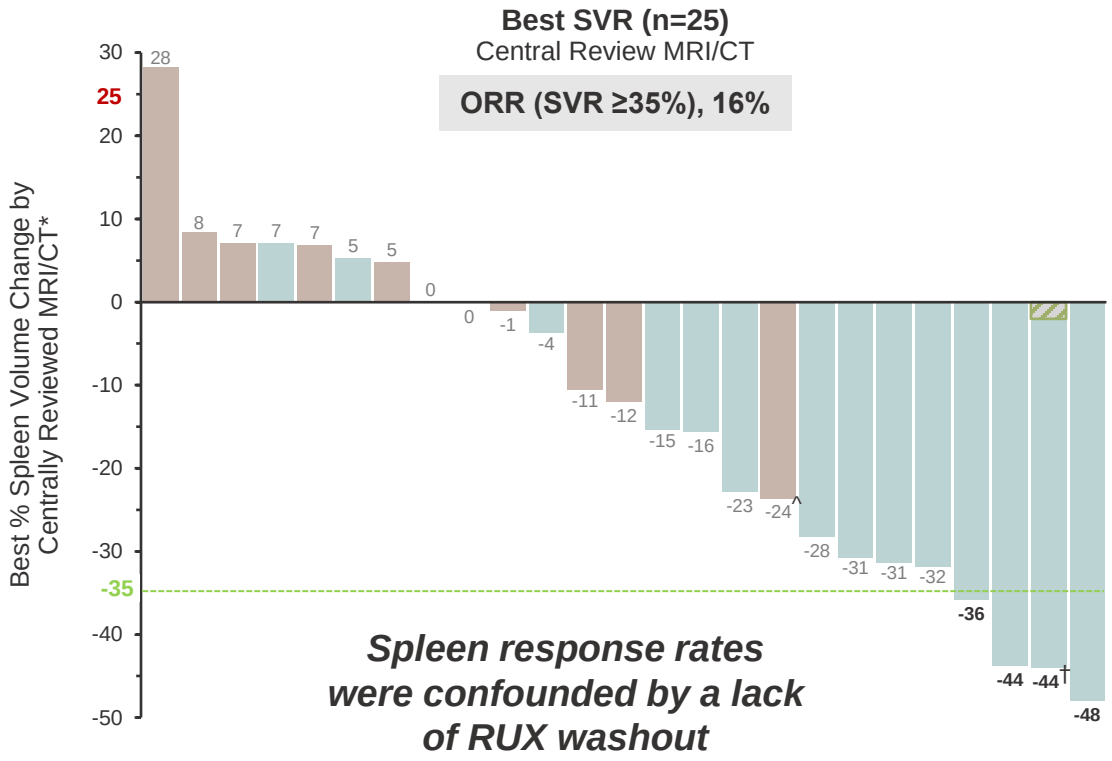
Mascarenhas J, et al. Blood. 2021; Vannucchi A, et al. EHA 2022

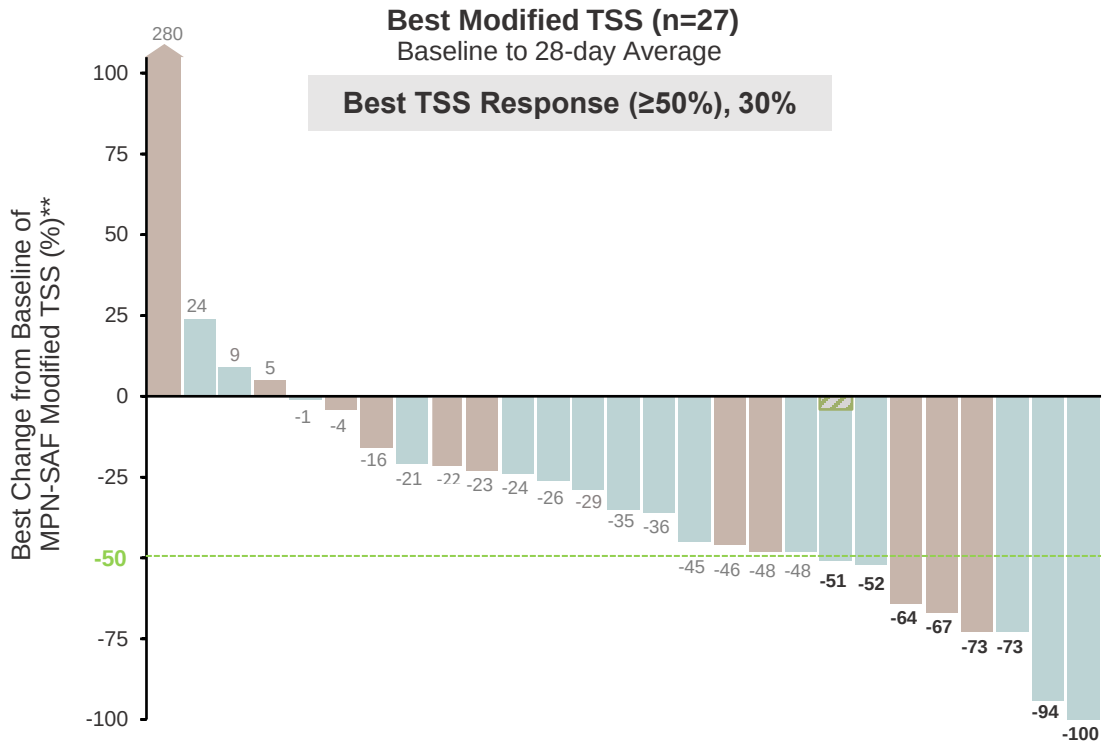
Some Non-JAKi therapies as 2.nd line in MF (phase III trials)

Agent	Class	Remarks	Trial(s)	Status
KRT-232	**MDM2i**	Only for TP53wt, Plt ≥ 50 /mm^3	KRT-232-101, Phase 2/3	open
Imetelstat	**Telomerase inhibitor**	Survival as Primary Endpoint, Plt ≥ 75 /mm^3	MYF3001, Phase 3	open

Navtemadlin (KRT232), Clinical Proof of Concept in R/R MF

240mg QD, D1-7/28-day cycle





Functional *TP53*^{MUT}
ON Rux at Baseline Scan
OFF Rux at Baseline Scan

*SVR Evaluable: Patients must have baseline and at least one pre-planned post-baseline spleen MRI/CT (Week -12, -24, -36).
^MRI out of window (Wk-37); †MRI out of window (Wk-38), -39% at Week-24.
**TSS Evaluable: Requires patients to have a baseline TSS and >20-days within a 28-day period reported for post-baseline assessments.
Best Modified TSS: Best change from baseline to trailing 28-day average at end of Week -4, -8, -12, -16, -20, -24, etc.
Modified MPN-SAF Total Symptom Score (TSS) includes early satiety, abdominal discomfort, night sweats, itching, bone pain, and rib pain.

Al-Ali HK et al. HemaSphere 4 65. Abstract S215 2020.

Navtemadlin (KRT232), Clinical Proof of Concept in R/R MF

MPNHub
Clinical Trial Club

live
WEBINAR

Clinical trial club | Novel agents for the treatment of advanced myelofibrosis

An EBAC Accredited Educational Programme

July 19, 2022 | 08:00 CST (15:00 CEST)

REGISTER YOUR PLACE

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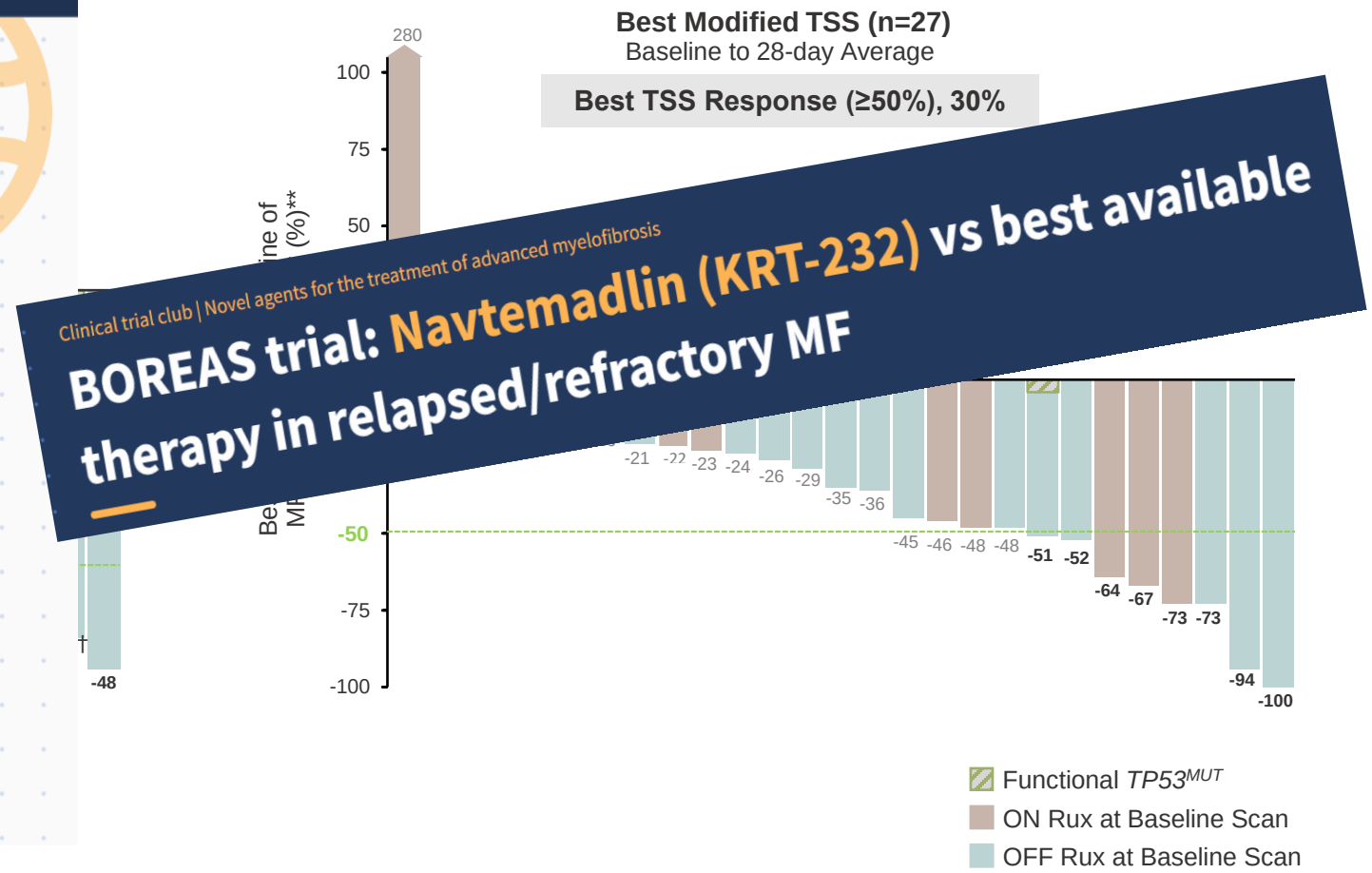
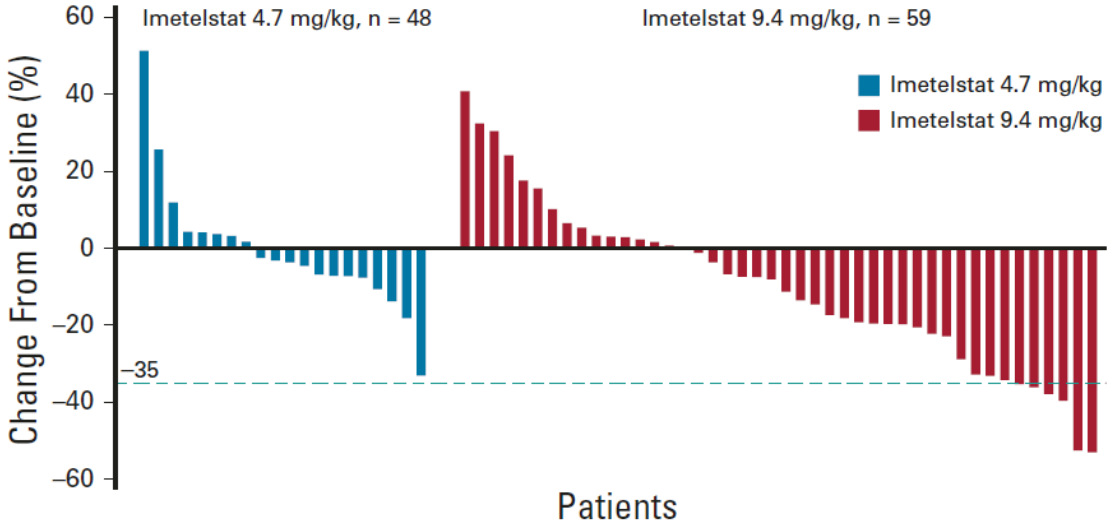


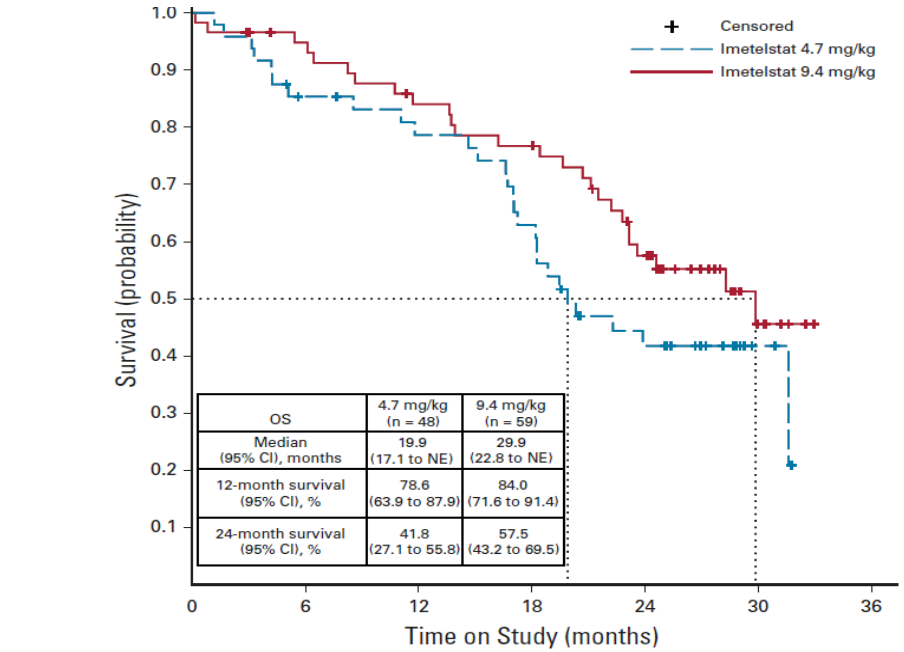
Imetelstat in relapsed or refractory MF

Waterfall plot of maximum percent change in SVR at Week 24 in patients with MF treated with imetelstat



Spleen Response	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)
≥ 10% SVR at week 24, No. (%)	4 (8.3)	22 (37.3)
≥ 20% SVR at week 24, No. (%)	1 (2.1)	13 (22)
≥ 35% SVR at week 24, No. (%)	0	6 (10.2)

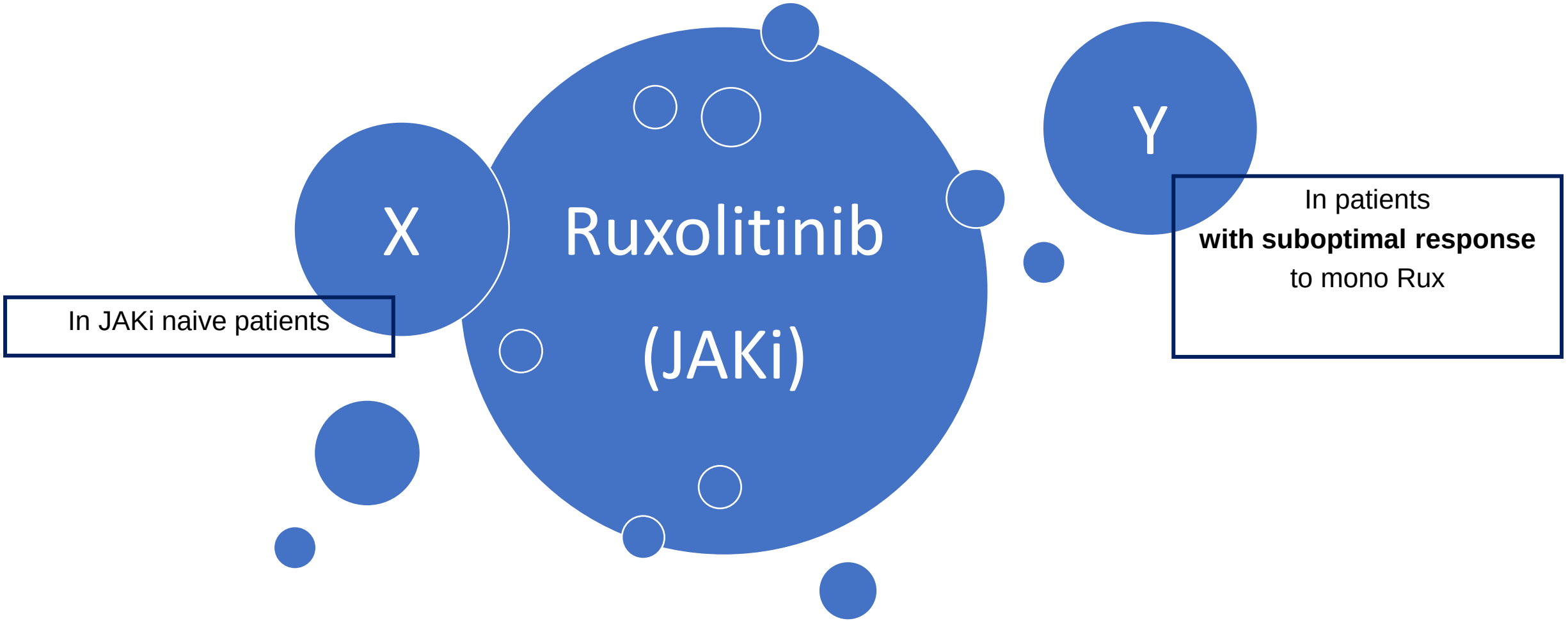
Kaplan-Meier ITT analysis of OS. All patients on study by random assignment arm



Mascarenhas J, et al. J Clin Oncol. 2021;39:2881–2892.

Future Perspectives

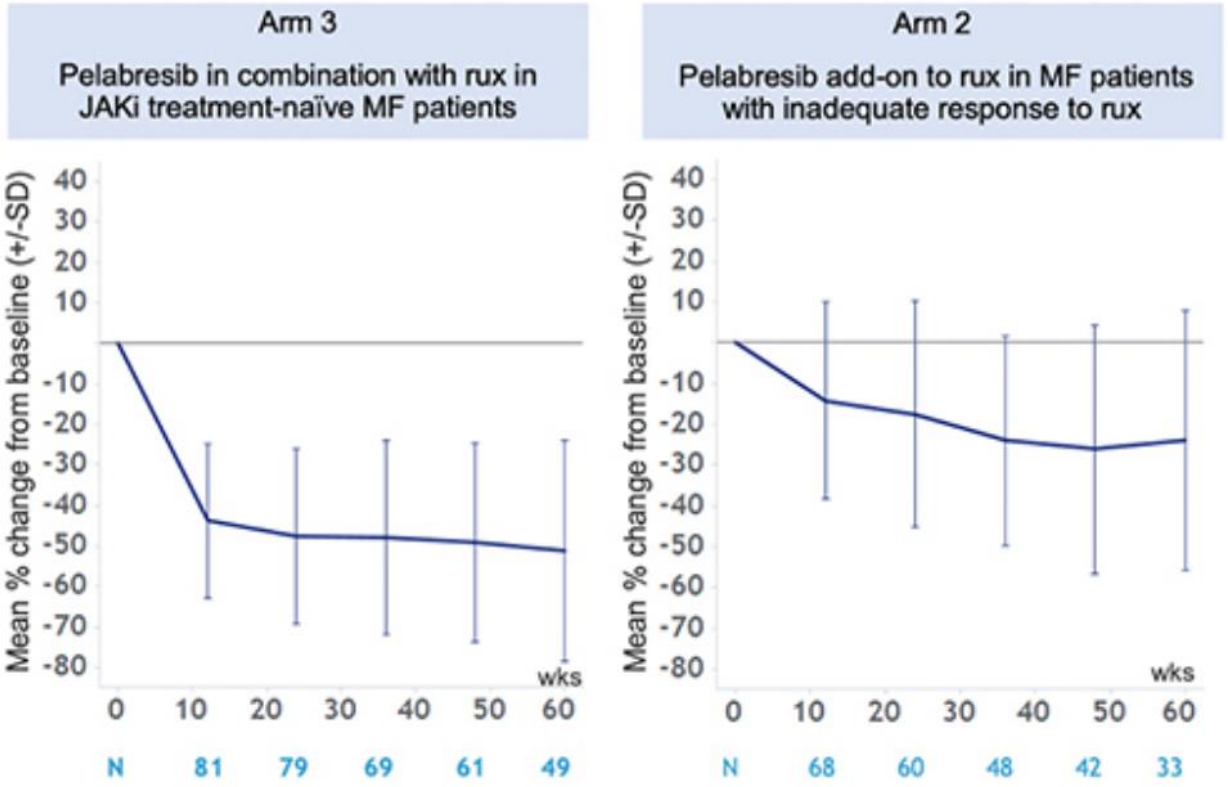
Combination or Add-on Strategies



Combination/Add-on Therapy Trials 2022

JAKi	2nd Agent	Class	Combination/ Add-on		Remarks	Trial(s)
			Combi	Add-on		
Rux	KRT-232	**MDM2i** (Murine Double Minute 2)	-	yes	Only for TP53wt, Plt ≥ 100 /mm^3	KRT-232-109, Phase 1b/2
Rux	CPI-0610 (PELABRESIB)	**BETi** (Bromodomain and Extraterminal Domain)	yes	--	Platelet count ≥ 100 /mm^3	MANIFEST-2, Phase 3
Rux or Fed	Luspatercept	**TGF-beta protein ligand**	-	yes	Patients who require red blood cell transfusions	INDEPENDENCE, Phase 3
Rux	Parsaclisib	**PI3Kδi**	yes	yes	Platelet count ≥ 50 /mm^3	Limber-304 und 313, Phase 3
Rux	Navitoclax	**BCL-2i**	yes	yes	Platelet count ≥ 100 /mm^3	Transform, Phase 3

Pelabresib (CPI-0610) has shown single-agent and combination activity in MFSVR35



Wk 24	JAKi naive	Add-on to ruxolitinib
Spleen response (SVR35)	68%	20%
TSS50	56%	37%
Mean Hb increase (1.5 g/dl) over 12 weeks	24%	
Achievement of TI ≥ 12 weeks	–	16%

Mascarenhas J, et al. EHA 2022.

Luspatercept and sotatercept have shown potential for anemia responses in MF

- Luspatercept

	Cohort 1 NTD, no Rux (n = 20)	**Cohort 2** NTD + Rux (n = 14)	**Cohort 3A** TD, no Rux (n = 21)	**Cohort 3B** TD + Rux (n = 19)
Hb increase ≥ 1.5 g/dL at every assessment	2 (10)	3 (21)	–	–
Mean Hb increase of ≥ 1.5 g/dL	3 (15)	8 (57)	–	–
Achievement of RBC-TI ≥ 12 wks	–	–	2 (10)	6 (32)
≥ 50% reduction in RBC transfusion burden	–	–	8 (38)	**10 (53)**

- Sotatercept

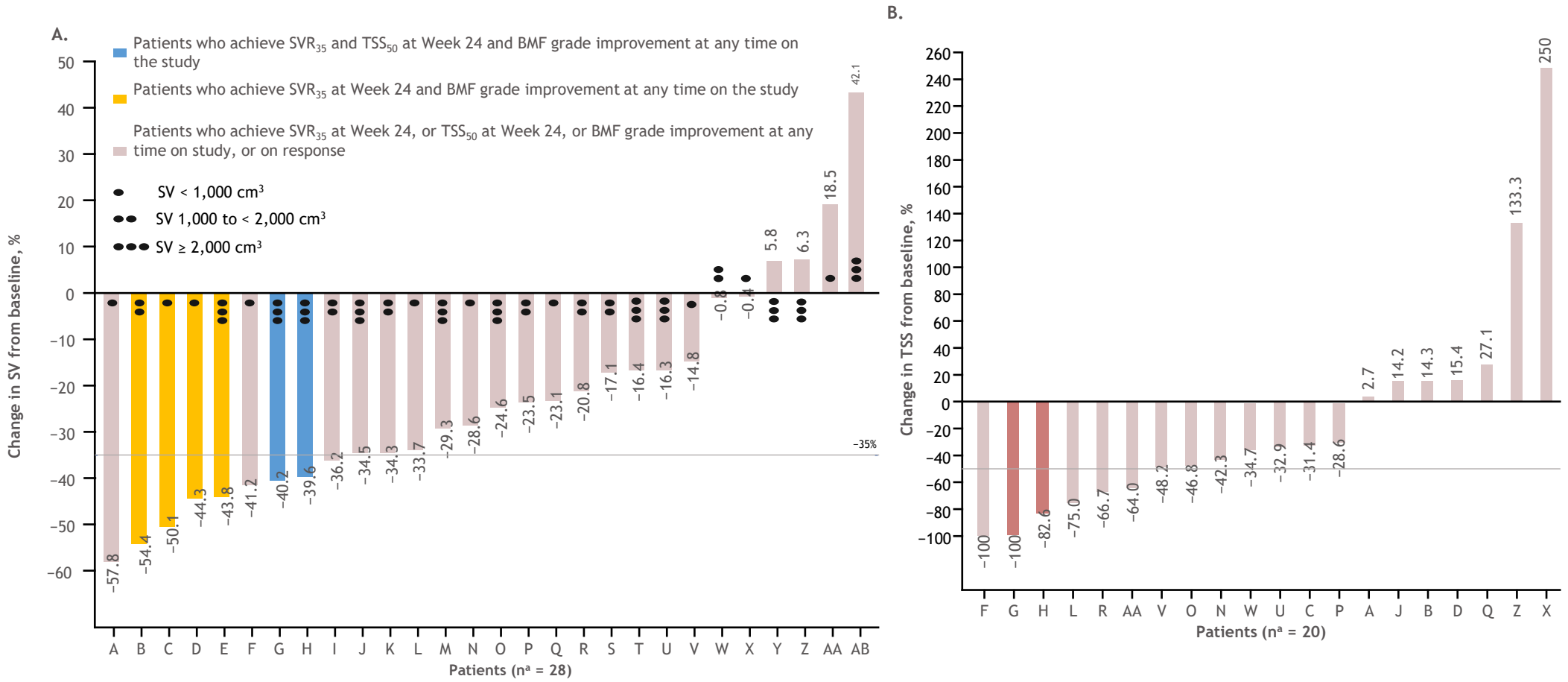
	Combination with ruxolitinib	**Single agent**
Responses, n/N (%)	**6/19 (32)**	**8/27 (30)**
Median time to response, days	14	19
Median duration of response, months	18.2	23.3

Clinical Trial ID	**Trial Name**	**Study Design**	**Treatment Details**
NCT04717414	INDEPENDENCE	Phase 3 Randomized, placebo-controlled	Combination with JAKi

Gerds AT, et al. Blood. 2019; Bose P, et al. Blood. 2021

Navitoclax + ruxolitinib for patients with progression or suboptimal response on ruxolitinb

Percentage change from baseline in (A) spleen volume and (B) TSS at Week 24



Harrison CN, et al. J Clin Oncol. 2022

Conclusions to MF

The influence of disease stage & duration on quality of response to ruxolitinib

- Spleen/symptom responses are lower if
  - Time interval between MF diagnosis and start of ruxolitinib > 2 years
  - Larger splenomegaly/higher total symptom score
  - Transfusion dependency/lower PLT count
  - IPSS Int-2/High risk

The influence of ruxolitinib dose

- Early MF patients may tolerate a higher ruxolitinib dose
- Patients starting with higher doses have a higher rate of spleen response
- Use of lower ruxolitinib doses (< 10mg BID) may also result in reduced efficacy

Novel treatments (mono and combination) could be new options for unmet medical needs and are being tested in clinical trials

Palandri F, et al. Oncotarget. 2017.

Thank you very much

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