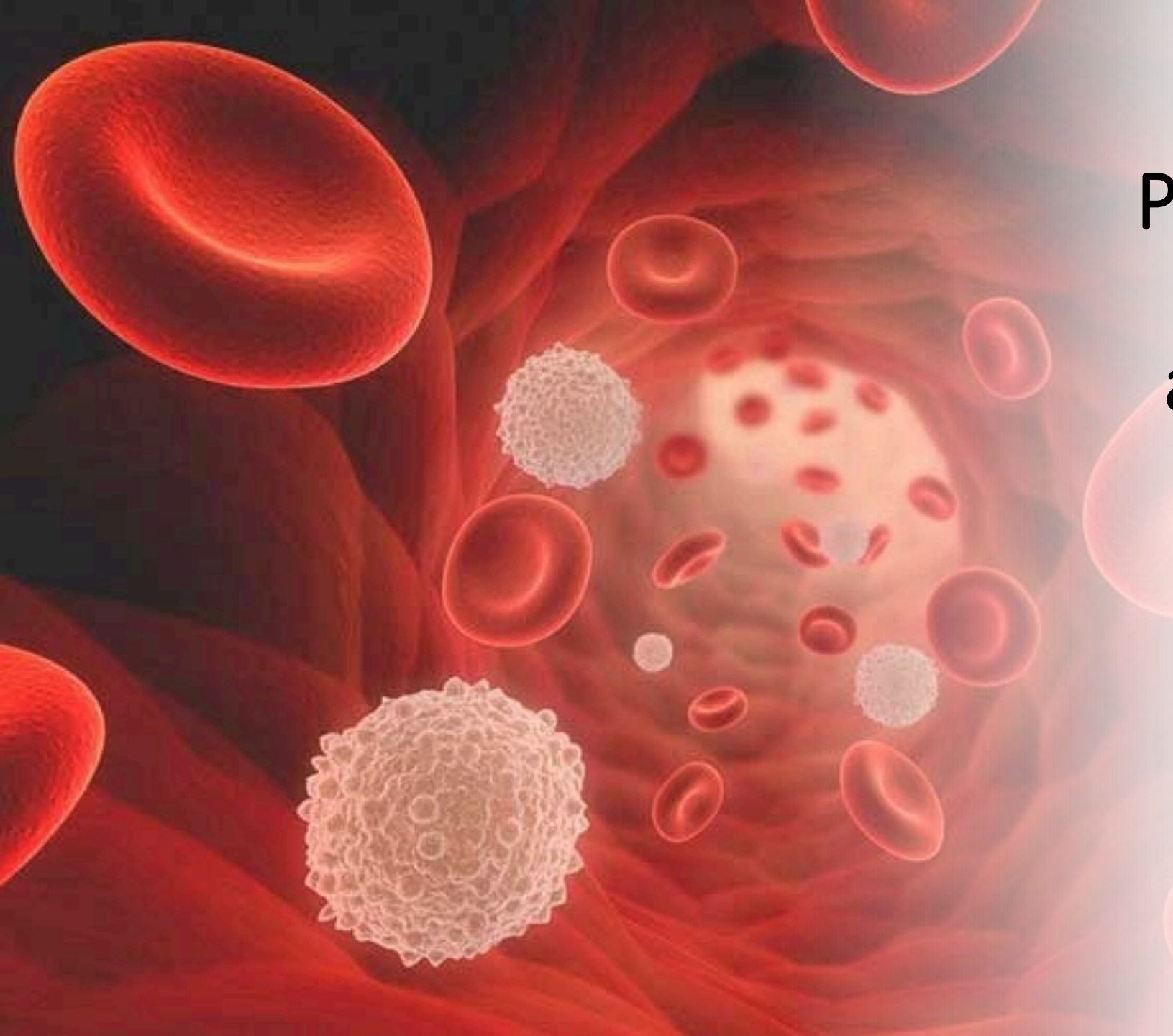


Polycythemia Vera, Ph-negative MPN, and FGFR Myeloid Neoplasms

Angela Fleischman MD PhD

Associate Professor

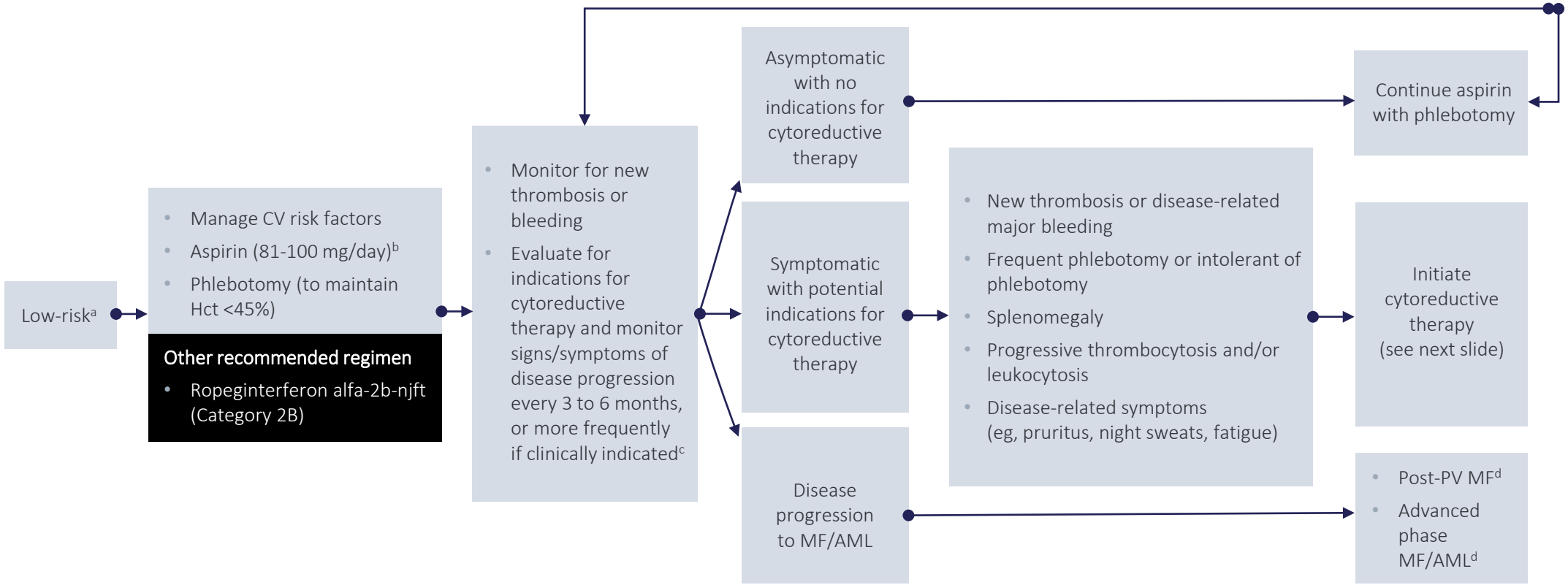
University of California, Irvine

Disclosures

- CTI – Advisory Board, Speakers Bureau
- Pharmaessentia – Speakers Bureau
- Sierra/GSK – Advisory Board

2022 NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Treatment Recommendations for Patients With Low-risk PV



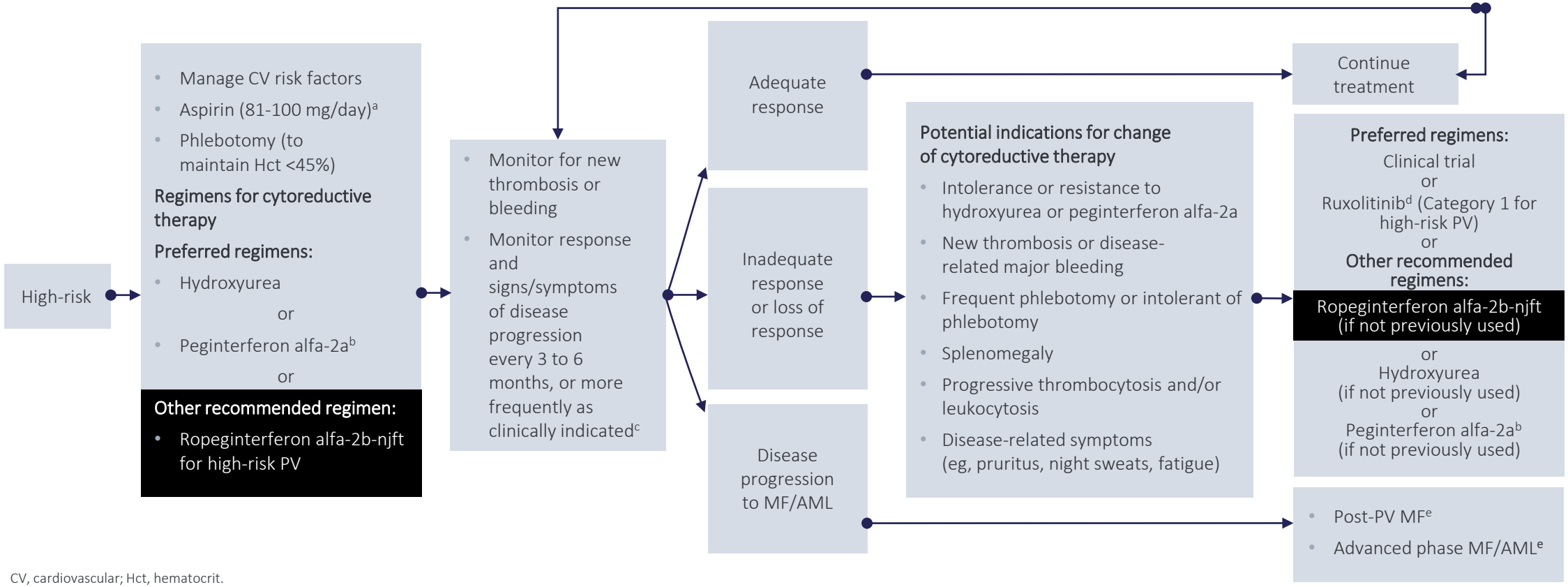
CV, cardiovascular; Hct, hematocrit.

For the complete clinical practice guidelines, please visit https://www.nccn.org.

[a]Cytoreductive therapy is not recommended as initial treatment.
[b]Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG et al. *Thromb Res.* 2012;129[1]:91-94; Pascale S et al. *Blood.* 2012; 119[15]:3595-3603).
[c]Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.
[d]See www.NCCN.org for additional recommendations.

2022 NCCN Guidelines®

Treatment Recommendations for Patients With High-risk PV



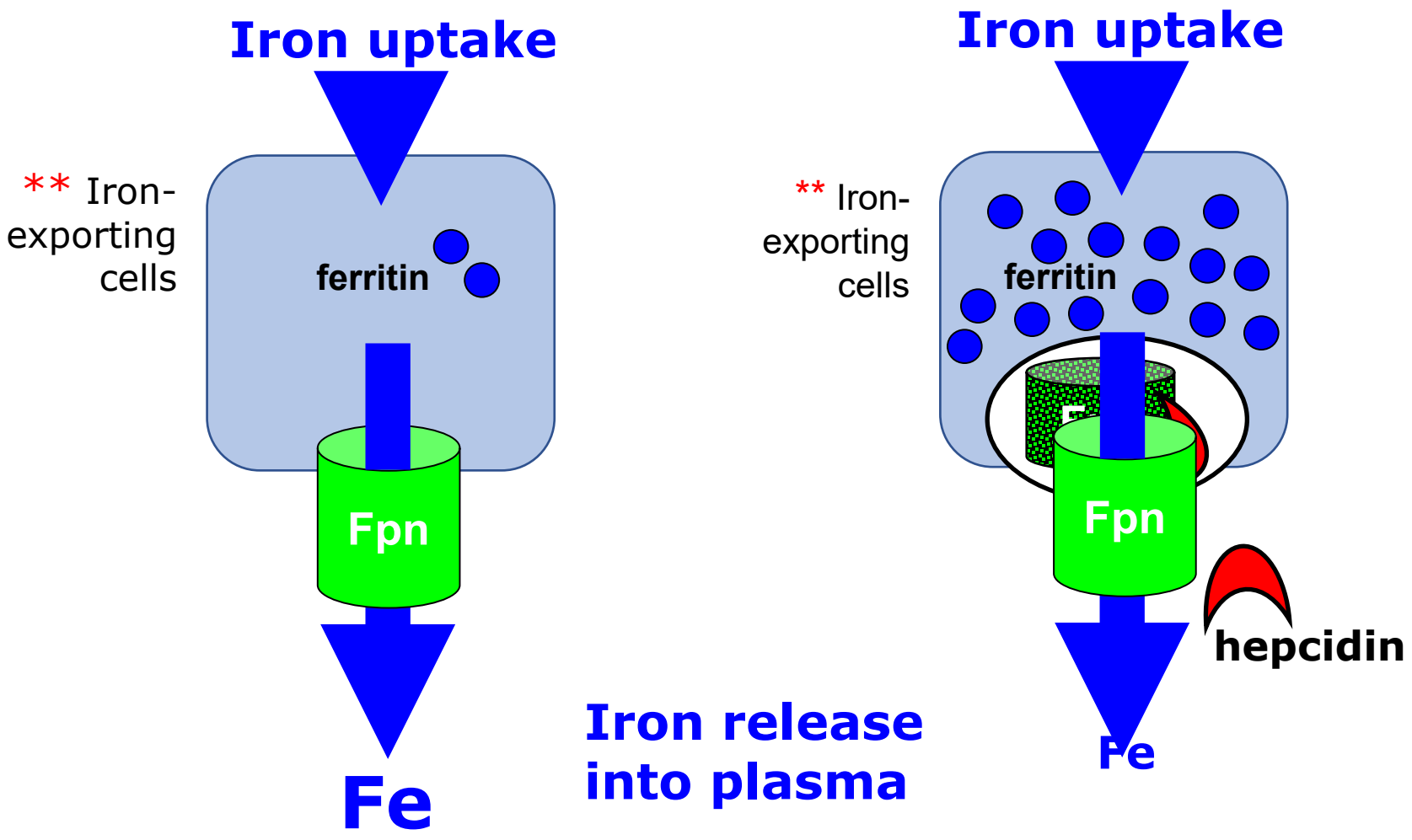
CV, cardiovascular; Hct, hematocrit.

For the complete clinical practice guidelines, please visit https://www.nccn.org.

[a]Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG et al. *Thromb* Res. 2012;129[1]:91-94; Pascale S et al. *Blood*. 2012;119[15]:3395-3603).
[b]Peginterferon alfa-2a can be considered for younger patients or in pregnant patients in need of cytoreductive therapy or in those in need of cytoreductive therapy that defer hydroxyurea or ropeginterferon alfa-2b-njft.
[c]Bone marrow aspirate and biopsy should be performed to rule out disease progression to myelofibrosis prior to the initiation of cytoreductive therapy.
[d]Ruxolitinib is FDA approved for the treatment of patients with PV who have had inadequate response to or are intolerant of hydroxyurea.
[e]See www.NCCN.org for additional recommendations.

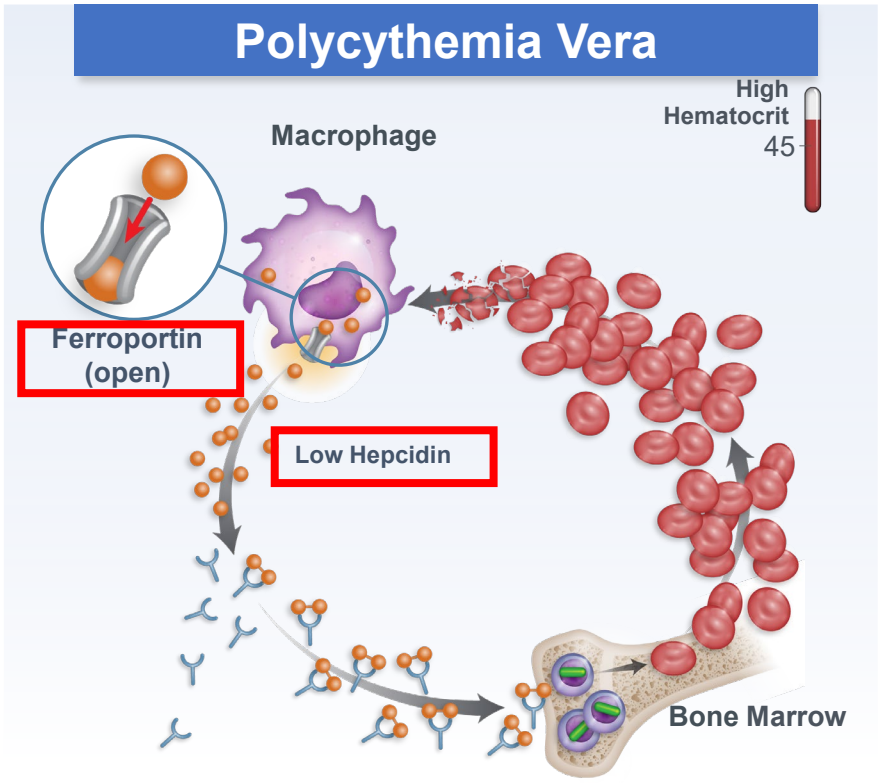
Low hepcidin

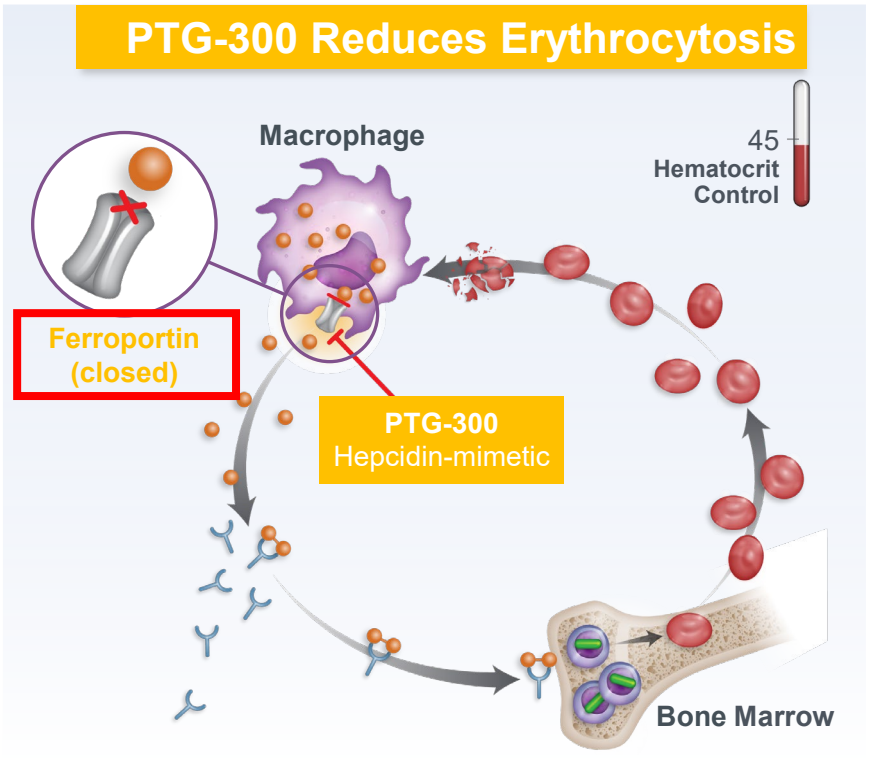
High hepcidin



** e.g. duodenal enterocytes, macrophages, hepatocytes

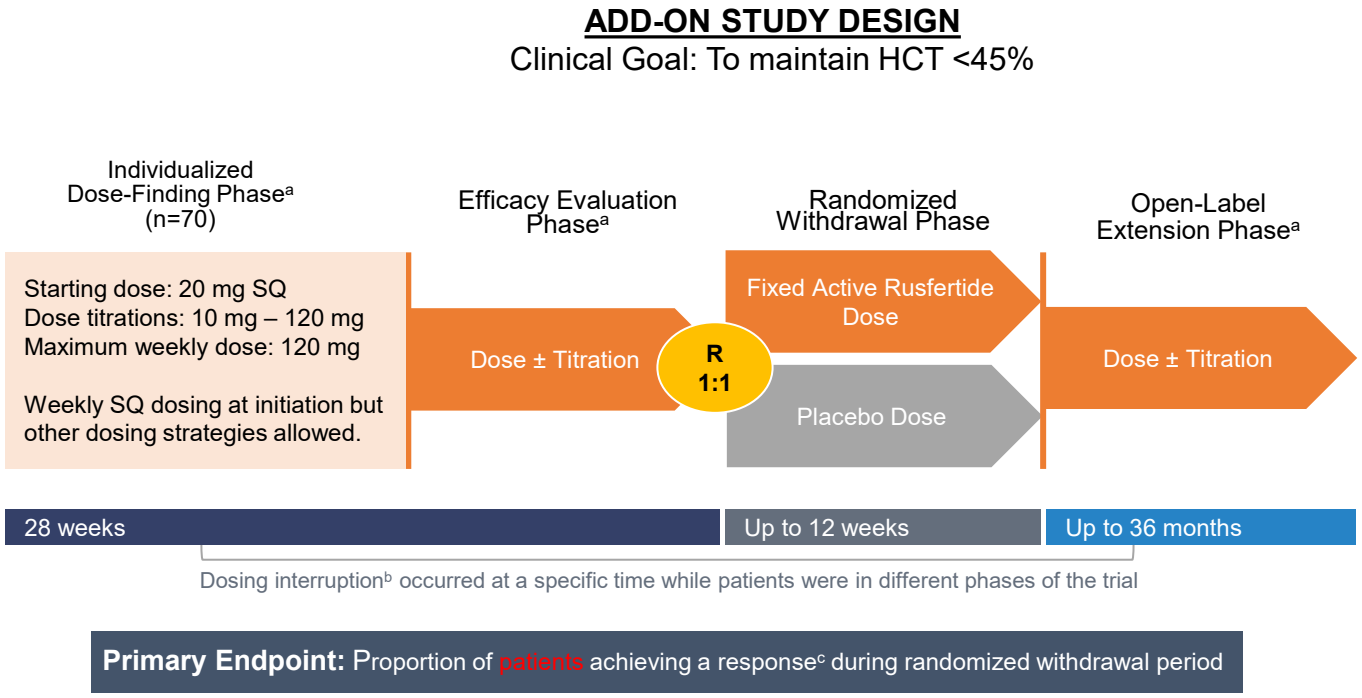
PTG-300 (Hepcidin-mimetic) Mechanism of Action in PV





REVIVE Study Design

- *First patient enrolled in October 2019, and last patient enrolled March 2022*
- **ELIGIBILITY REQUIREMENTS:**
  - Phlebotomy-dependent PV patients diagnosed per 2016 WHO criteria
  - ≥3 phlebotomies in 6 months with or without concurrent cytoreductive therapy
  - All patients prior to first rusfertide dose were phlebotomized to HCT <45% to standardize the starting HCT
  - Rusfertide doses of 10–120 mg administered subcutaneously added to prior standard therapy



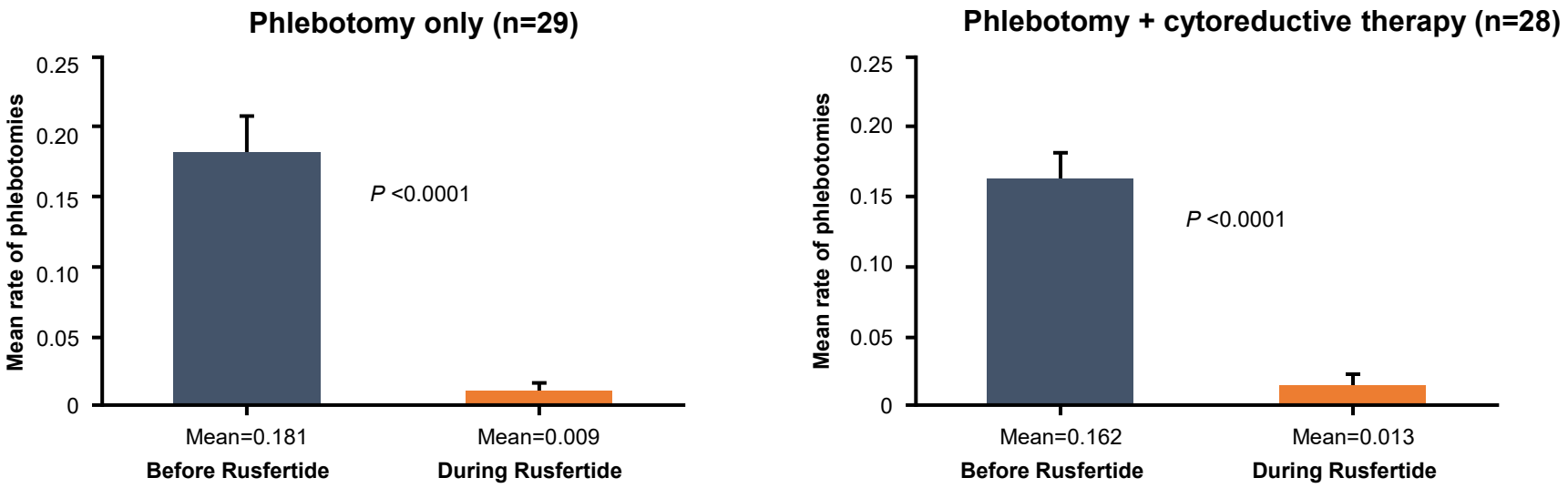
[a]Titrate every 4 weeks to maintain HCT <45%. [b]Dosing interruptions were due to clinical hold and not protocol defined. [c]Response defined as having achieved the absence of "phlebotomy eligibility", or HCT >45% that was ≥3% higher than baseline or HCT >48%, during the efficacy evaluation phase beginning Week 17 and continuing to Week 29.

CRT, cytoreductive therapy; HCT, hematocrit; PV, polycythemia vera; SQ, subcutaneous; WHO, World Health Organization. ClinicalTrials.gov Identifier: NCT04057040

Rusfertide Significantly Decreased Phlebotomy Requirements in Patients Treated With Phlebotomy Only or Cytoreductive Therapy Plus Phlebotomy

- Mean number of phlebotomies in 28 weeks before treatment with rusfertide: 4.81 (range 2–10)
- Mean number of phlebotomies after starting rusfertide: 0.3 (range 0–2)

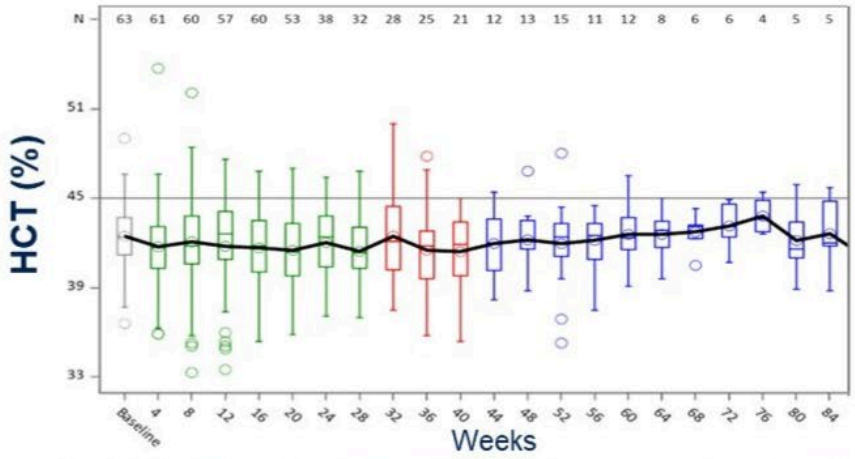
Mean rate of phlebotomies before and during Part 1



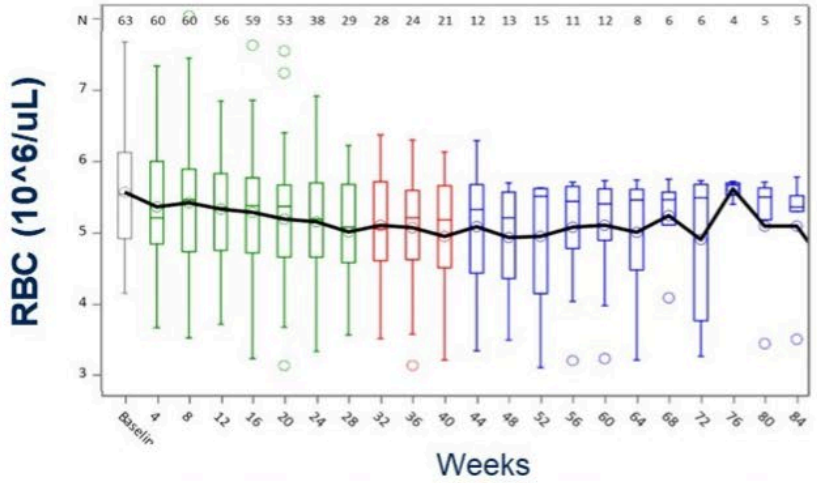
N. Pemmaraju et al SOHO 2022

Effect of Rusfertide on HCT, RBC, WBC, Platelet Counts

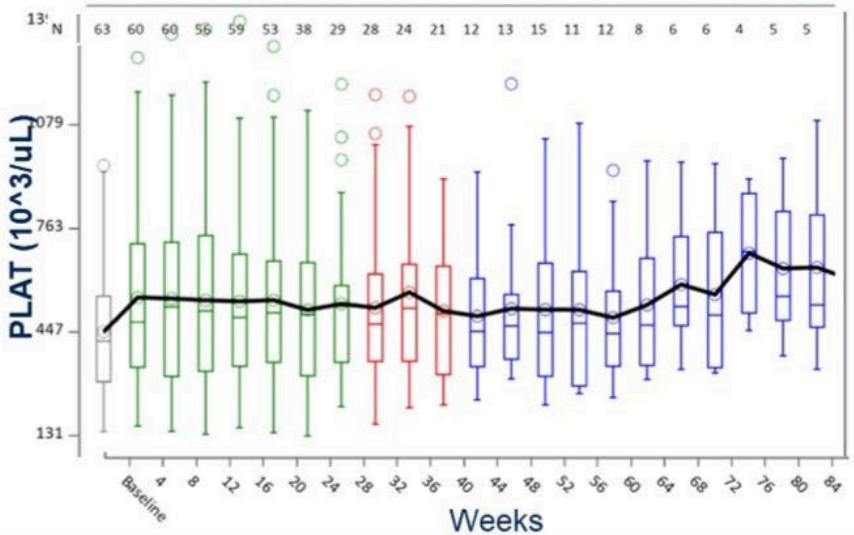
RUSFERTIDE CONTROLS HCT



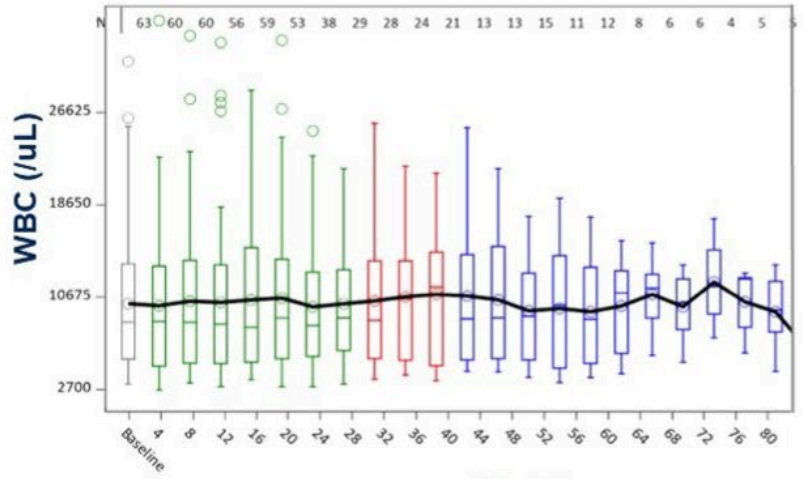
RUSFERTIDE REDUCES RBC COUNT



NO CLINICALLY SIGNIFICANT CHANGES IN PLATELETS



NO CLINICALLY SIGNIFICANT CHANGES IN WBC



Screening

Part 1 – Dose Finding

Part 2/3 – Blinded Withdrawal/OLE

Part 3 – Open Label Extension

Data cut off Sept 30, 2021

Safety: Rusfertide (PTG-300)

- ***Most treatment-emergent adverse events (TEAEs) were grade 1- 2***
  - *Injection site reaction (ISRs) were the most common AE and occurred in 85.6% of patients. All ISRs were transient, and no patient discontinued due to an ISR*
- ***No grade 3 events related to rusfertide***
- ***No grade 4 or 5 TEAEs***
- ***2 withdrawals due to TEAEs***
  - *1 popliteal aneurysm, 1 pulmonary embolism identified on study*
- ***Secondary malignancies***
  - *5 patients (5.5%) had secondary malignancies (6 skin cancers, 1 AML) in all rusfertide-treated patients in phase 2 trials (N=90)*
  - *All skin cancers were in situ or stage 1*
  - *All newly developed cancers were in patients with previous rux and/or HU. The patient with AML had also experienced radioactive iodine exposure*

Any-grade TEAE in ≥10% (preferred term)	n (%)
Total number of patients	**70**
Injection site reaction	77 (85.6)
Fatigue	20 (28.6)
Headache	17 (24.3)
Pruritus	17 (24.3)
Arthralgia	16 (22.9)
Dizziness	15 (21.4)
Nausea	15 (21.4)
Anemia	12 (17.1)
COVID-19	9 (12.9)
Dyspnea	9 (12.9)
Hyperhidrosis	9 (12.9)
Diarrhea	8 (11.4)
Insomnia	8 (11.4)
Myalgia	8 (11.4)
Pain in extremity	7 (10.0)
Paresthesia	7 (10.0)

Additional Hepcidin-mimetic Agents Currently in Trials for PV Patients

A Phase 2a, Randomized, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of ISIS 702843 Administered to Patients with Phlebotomy Dependent Polycythemia Vera (PD-PV)

Liver-targeted ASO against TMPRSS6, sapablursen (NCT05143957), SQ monthly

Tmprss6-ASO as a tool for the treatment of Polycythemia Vera mice

Carla Casu[1]*, Alison Liu[1], Gianluca De Rosa[1], Audrey Low[2], Aae Suzuki[3], Sayantani Sinha[1], Yelena Z. Ginzburg[4], Charles Abrams[3], Mariam Aghajan[2], Shuling Guo[2], Stefano Rivella[1,3,5,6,7]

PLOS ONE | https://doi.org/10.1371/journal.pone.0251995 December 10, 2021

SLN124, a GalNAc-siRNA Conjugate Targeting TMPRSS6, Efficiently Prevents Iron Overload in Hereditary Haemochromatosis Type 1

Sandro Altamura[1,2], Ute Schaeper[3], Sibylle Dames[3], Kathrin Löffler[3], Mona Eisermann[3], Christian Frauendorf[3], Katja Müdder[1,2], Joana Neves[1], Martina U. Muckenthaler[1,2]

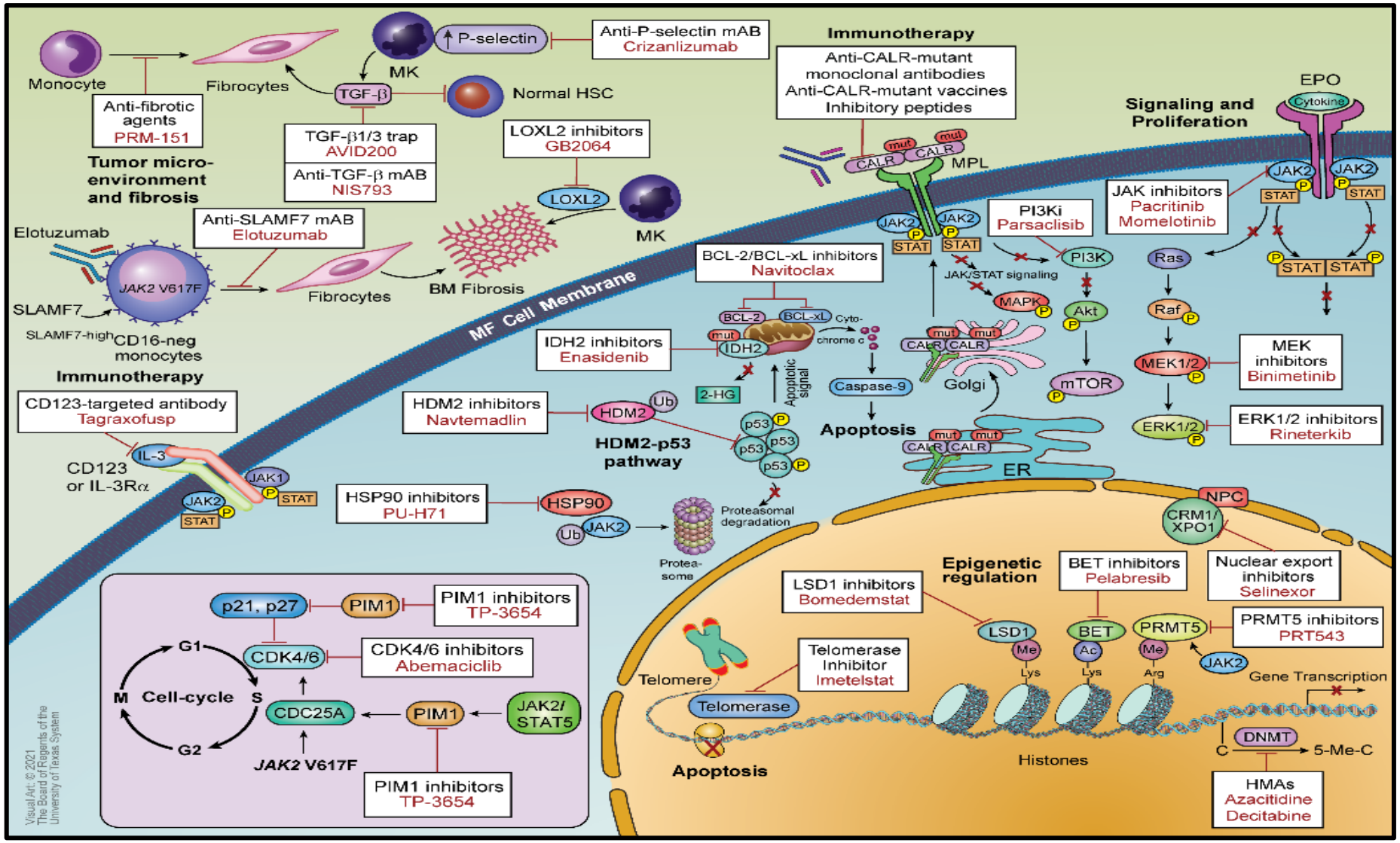
HemaSphere (2019) 3:6 www.hemaspherejournal.com

Liver-targeted double-stranded siRNA against TMPRSS6, SQ every 6 weeks

SLN124-004

Phase 1/2 study with an open-label dose escalation phase followed by a randomized, double-blind phase of SLN124 in patients with Polycythemia Vera.

Therapeutic Targets in Myelofibrosis



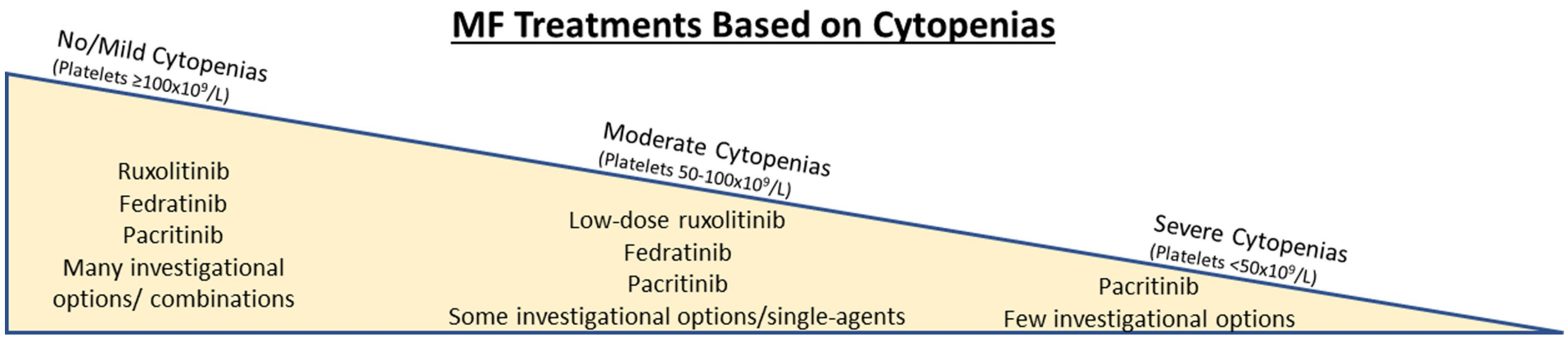
Not all MF is the same

Proliferative MF

Leukocytosis, normal platelets, mild or no anemia
More likely post-ET/PV MF
Lower risk scores
Fewer blasts
Less marrow fibrosis
More splenomegaly
Higher JAK2 VAF
Better outcomes
More treatment options

Cytopenic MF

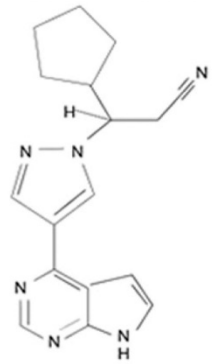
Low platelets, anemia, normal to low WBC
More likely primary MF
Higher risk scores
More blasts
More marrow fibrosis
Lower JAK2 VAF
High molecular risk (U2AF1 mutations)
Worse OS
Higher leukemic transformation risk
Fewer treatment options



Reynolds and Pettit, New approaches to tackle cytopenic myelofibrosis, Hematology Am Soc Hematol Educ Program, 2022,

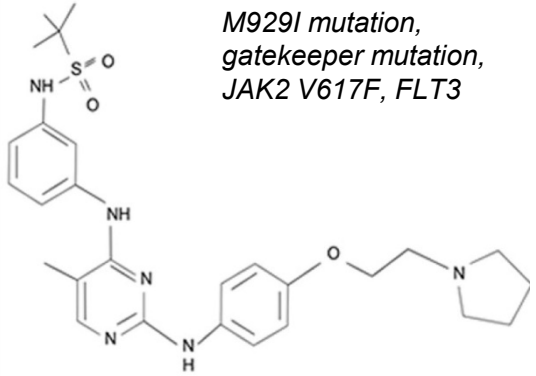
JAK Inhibitors for Myelofibrosis

Ruxolitinib



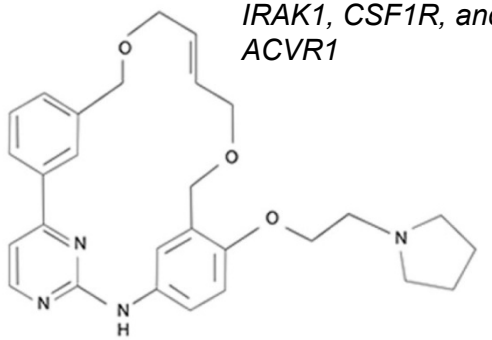
Fedratinib

M929I mutation, gatekeeper mutation, JAK2 V617F, FLT3



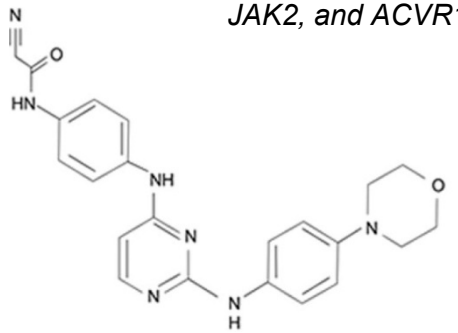
Pacritinib

Inhibits JAK2, FLT3, IRAK1, CSF1R, and ACVR1



Momelotinib

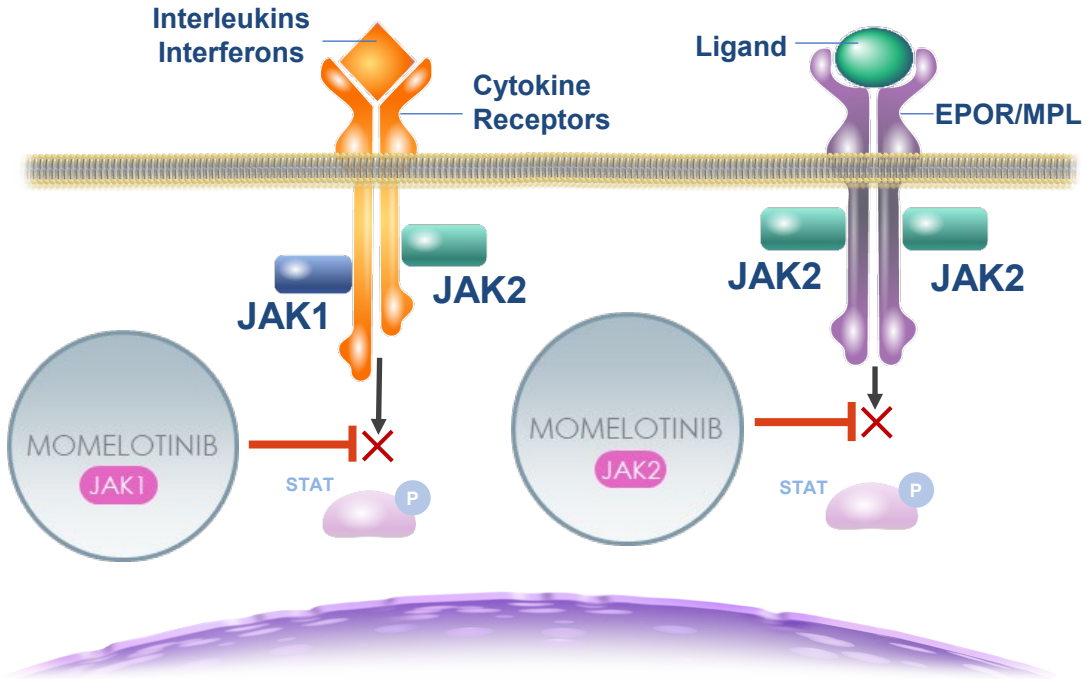
Inhibits JAK1, JAK2, and ACVR1



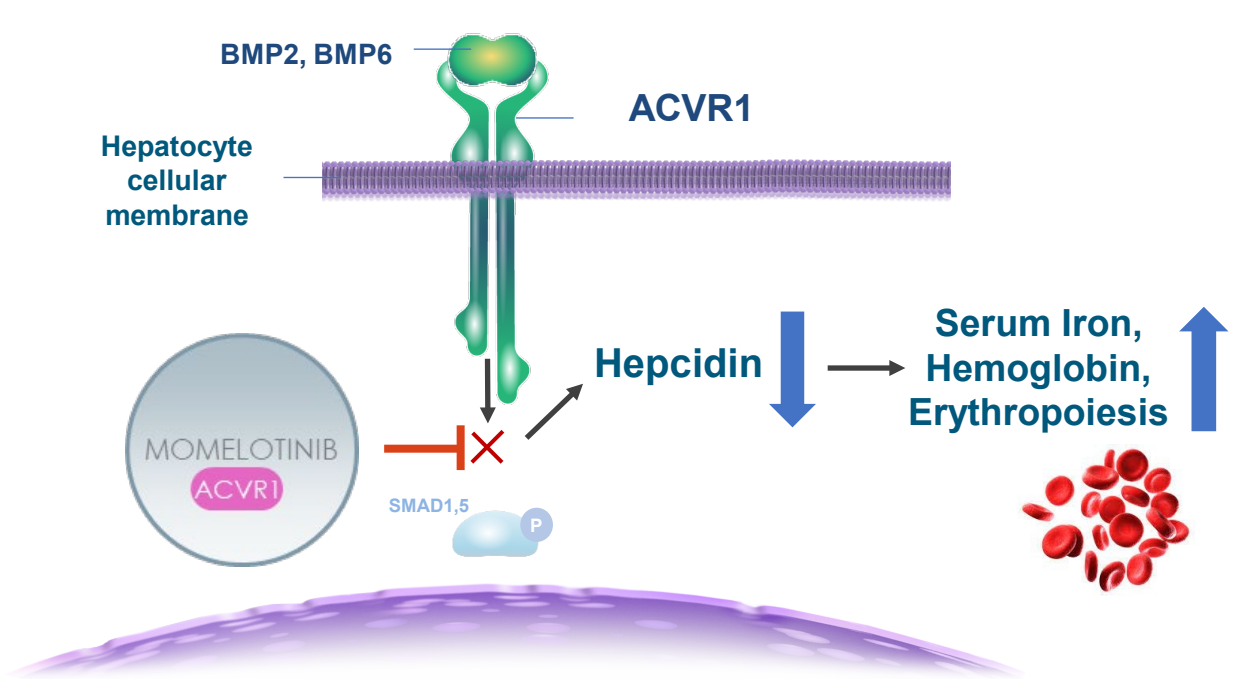
	IC_{50} (nanomolar)				AEs
	JAK1	JAK2	JAK3	TYK2	
Ruxolitinib	2.8	4.5	322	30	Cytopenias (anemia, thrombocytopenia), infection
Fedratinib	105	3	>1000	405	Wernicke encephalopathy
Pacritinib	1280	6	18.3	27	GI (diarrhea, nausea)
Momelotinib	11	18	155	17	Increased amylase/lipase, thrombocytopenia, PN

Duenas-Perez AB, Mead AJ. *Ther Adv Hematol*. 2015;6:186-201.

Momelotinib Mechanism of Action



Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation, resulting in extramedullary hematopoiesis and **splenomegaly**.[1,2]



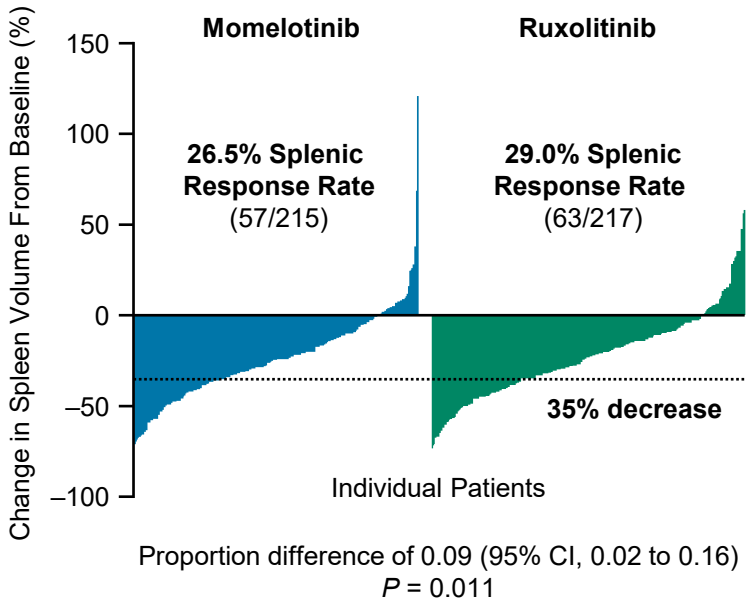
Chronic inflammation also drives hyperactivation of **ACVR1**, elevated **hepcidin**, dysregulated iron metabolism, and **anemia** of MF.[3,4]

ACVR1=activin A receptor type 1; BMP=bone morphogenic protein; EPOR=erythropoietin receptor; JAK=Janus kinase; MPL=myeloproliferative leukemia protein; STAT=signal transducer and activator of transcription.

1. Chifotides HT, et al. J Hematol Oncol. 2022;15(1):7; 2. Verstovsek S, et al. Future Oncol. 2021;17(12):1449-1458; 3. Asshoff M, et al. Blood. 2017;129(13):1823-1830; 4. Oh S, et al. Blood Adv. 2020;4(18):4282-4291.

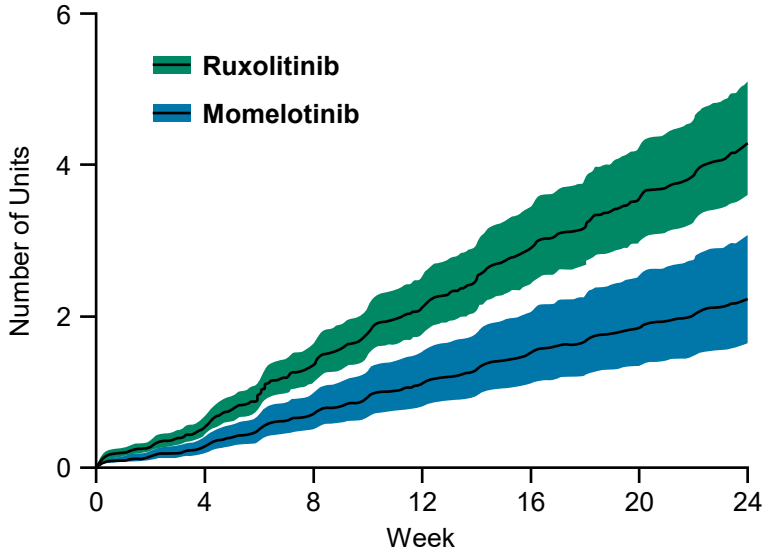
Momelotinib: Prior Evidence of Clinical Benefit in Completed Trials

SIMPLIFY-1: Splenic Response

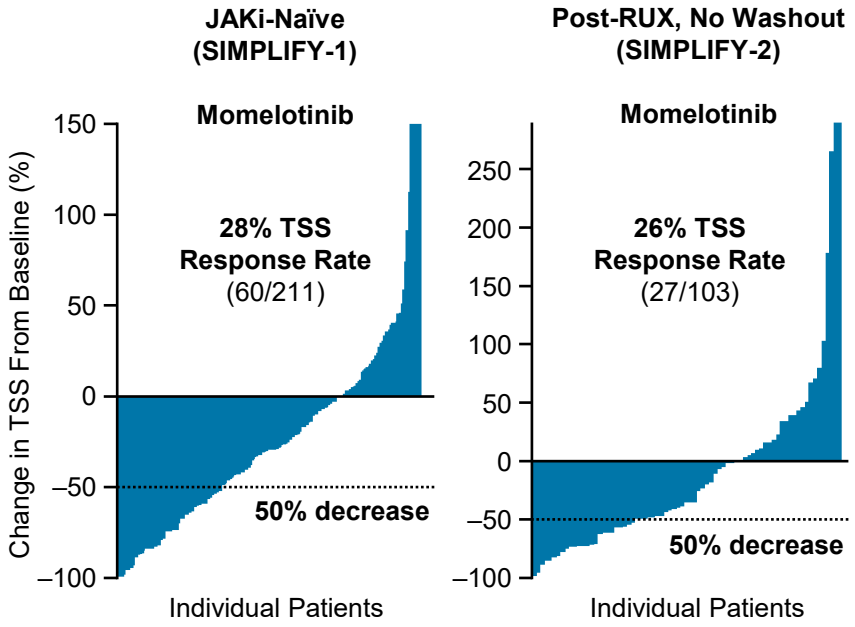


Proportion difference of 0.09 (95% CI, 0.02 to 0.16)
P = 0.011

SIMPLIFY-1: Transfusion Requirement



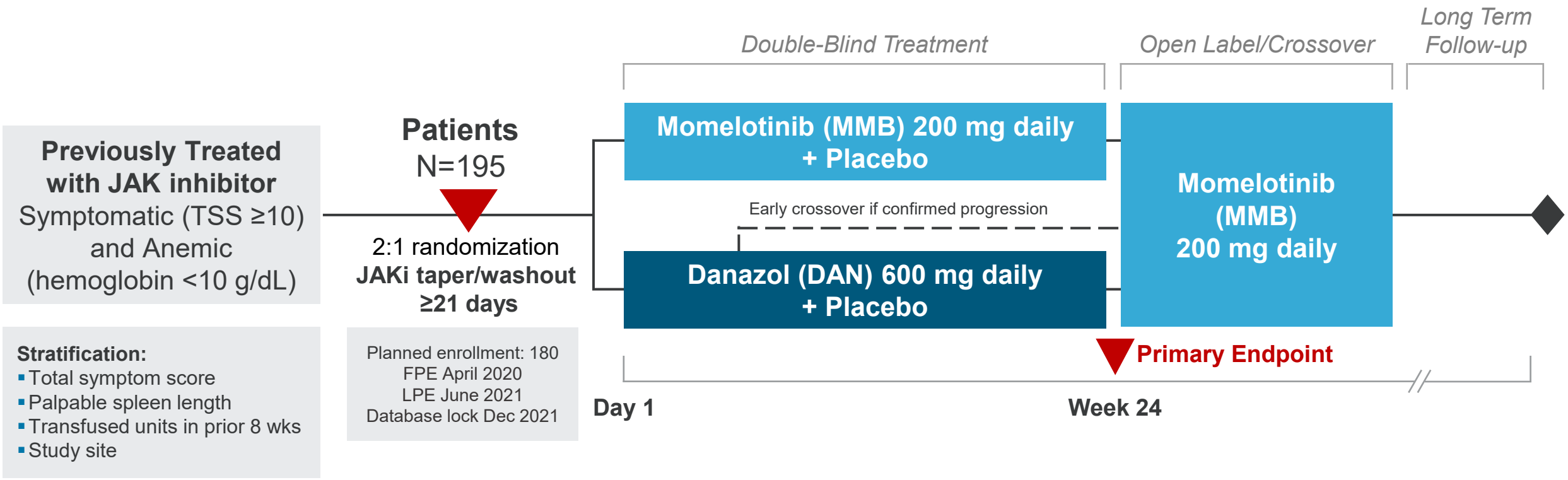
SIMPLIFY-1 and -2: Total Symptom Score Response



Phase 3 SIMPLIFY studies in JAKi-naïve and post-RUX patients with MF demonstrated momelotinib benefits on symptoms, spleen, and anemia.

Mesa R, et al. J Clin Oncol. 2017;35(34):3844–3850. Harrison CN, et al. Lancet Haematol. 2018;5(2):e73–e81. Mesa R, et al. Leuk Lymphoma. 2022;7:1–5.

MOMENTUM Study Design



Primary Endpoint

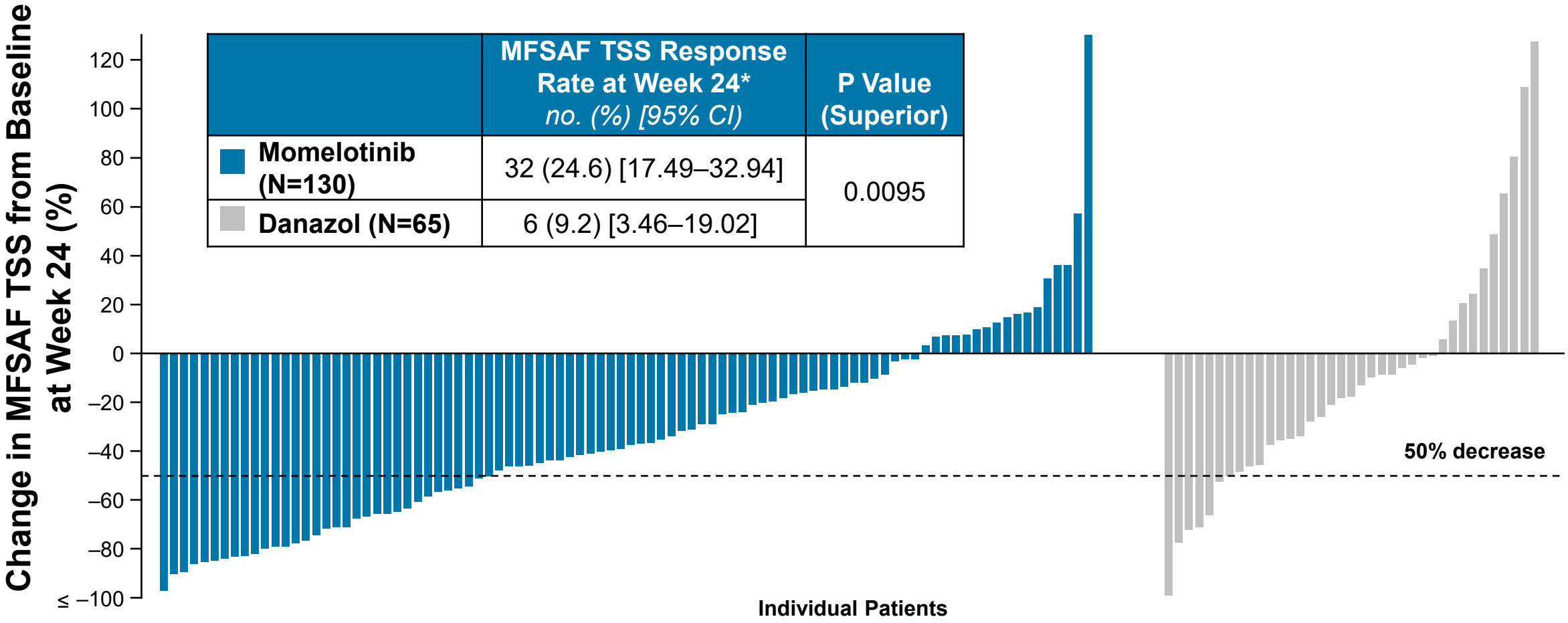
- **Total symptom score (TSS) response rate at Week 24** (defined as achieving ≥50% reduction in TSS over the 28 days immediately prior to the end of week 24 compared to baseline.)

Key Secondary Endpoints

- **Transfusion independence (TI) rate at Week 24** (defined as not requiring red blood cell transfusion in the last 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.)
- **Splenic response rate (SRR) at Week 24** (defined as achieving a ≥25% or ≥35% reduction in spleen volume from baseline.)

Mesa RA, et al. Journal of Clinical Oncology. 2022;40(16_suppl):7002.

MFSAF Total Symptom Score Response Rate at W24



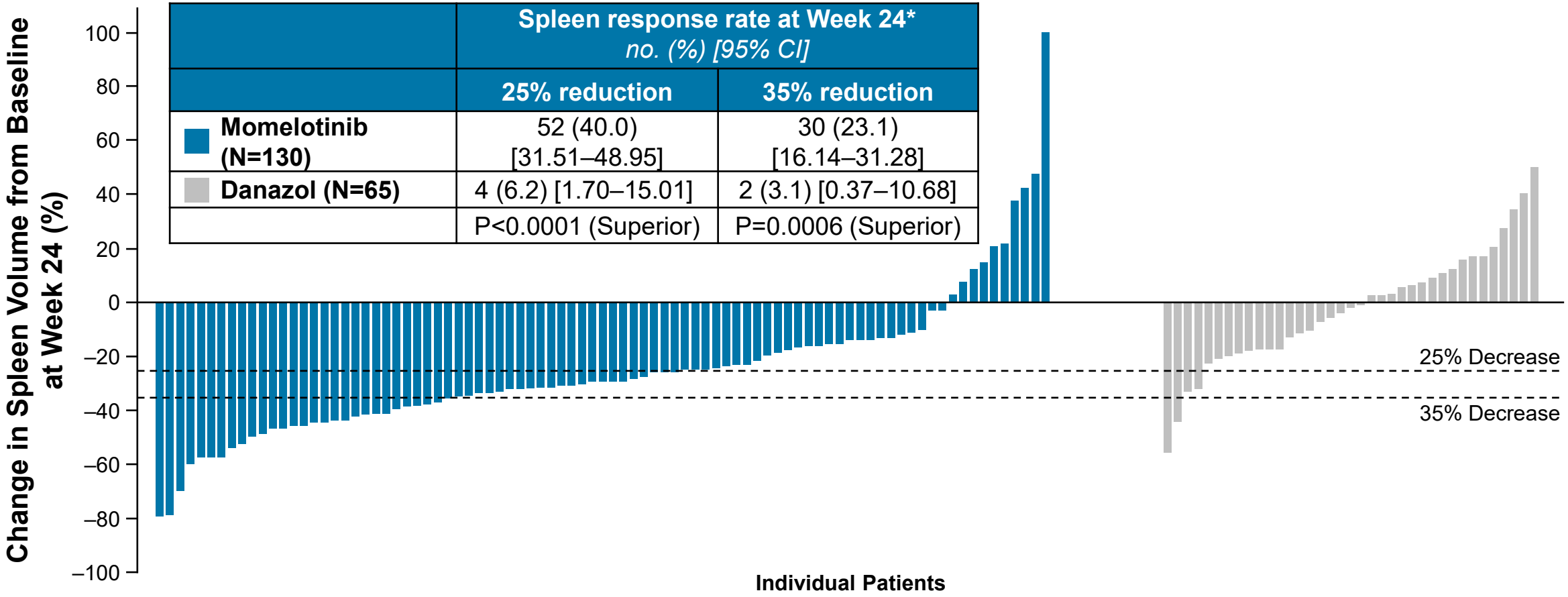
	MFSAF TSS Response Rate at Week 24* *no. (%) [95% CI)*	P Value (Superior)
Momelotinib (N=130)	32 (24.6) [17.49–32.94]	0.0095
Danazol (N=65)	6 (9.2) [3.46–19.02]	

*Defined as the proportion of patients who achieve ≥50% reduction in TSS over the 28 days immediately prior to the end of Week 24 compared to baseline.

Mesa RA, et al. Journal of Clinical Oncology. 2022;40(16_suppl):7002.

Spleen Response Rate at Week 24

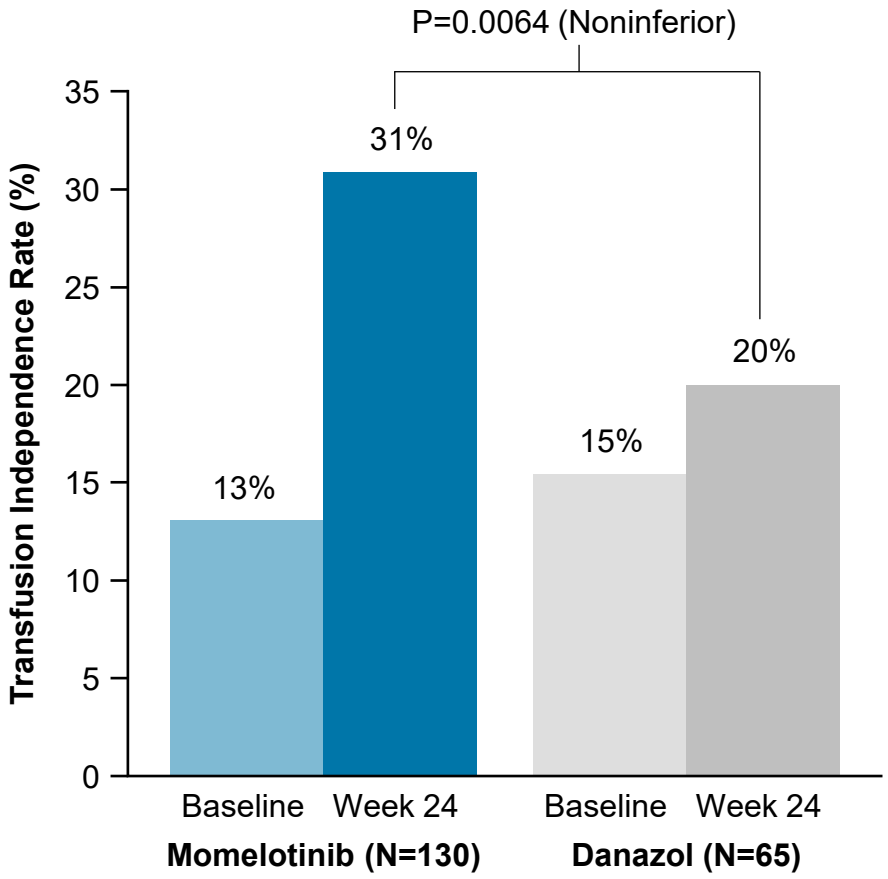
	Spleen response rate at Week 24* *no. (%) [95% CI]*	
	25% reduction	**35% reduction**
Momelotinib (N=130)	52 (40.0) [31.51–48.95]	30 (23.1) [16.14–31.28]
Danazol (N=65)	4 (6.2) [1.70–15.01]	2 (3.1) [0.37–10.68]
	P<0.0001 (Superior)	P=0.0006 (Superior)

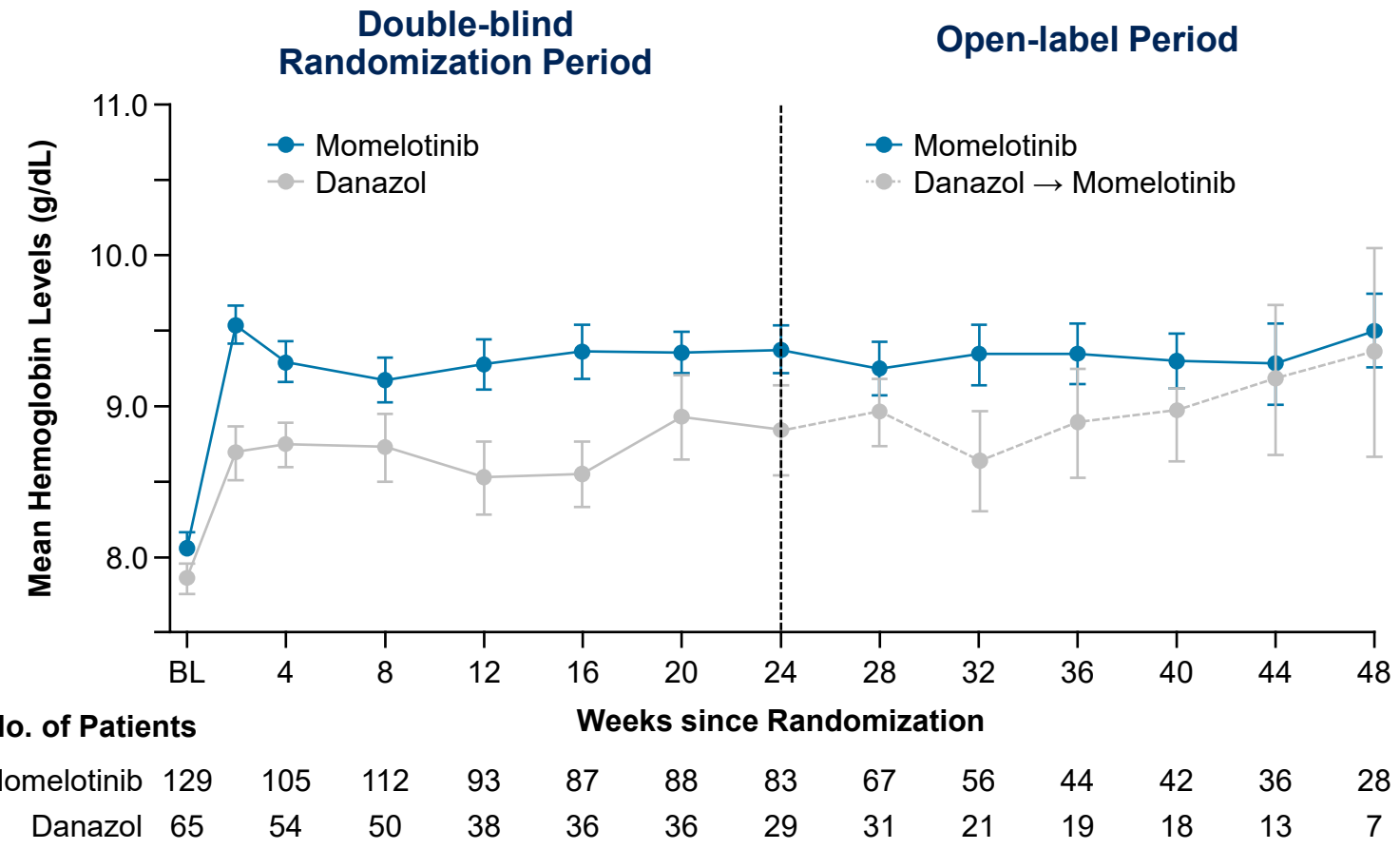


*Defined as the proportion of patients who have a reduction in spleen volume of ≥25% or ≥35% from baseline.

Mesa RA, et al. Journal of Clinical Oncology. 2022;40(16_suppl):7002.

Transfusion Independence Rate at W24 and Mean Hemoglobin Over Time





*Defined as not requiring red blood cell transfusion in the terminal 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.

Mesa RA, et al. Journal of Clinical Oncology. 2022;40(16_suppl):7002.

Pacritinib: Phase 3 Trial PERSIST-2

Key Eligibility Criteria

- PMF, PET-MF, PPV-MF
- Intermediate- or high-risk disease
- Moderate-to-severe thrombocytopenia at baseline (≤100x10^9/L)
- No exclusion for Hgb levels or RBC-TD
- Prior JAK1/2 inhibitors allowed

1:1:1 Randomization N=311

Stratification at randomization

- Rebound platelet count
- DIPSS risk category
- Geographic region

Pacritinib 400 mg QD

Pacritinib 200 mg BID

BAT; including JAK1/2 inhibitors

Coprimary endpoints

Pooled pacritinib arms vs BAT

- SVR ≥35% by MRI/CT
- ≥50% reduction in TSS

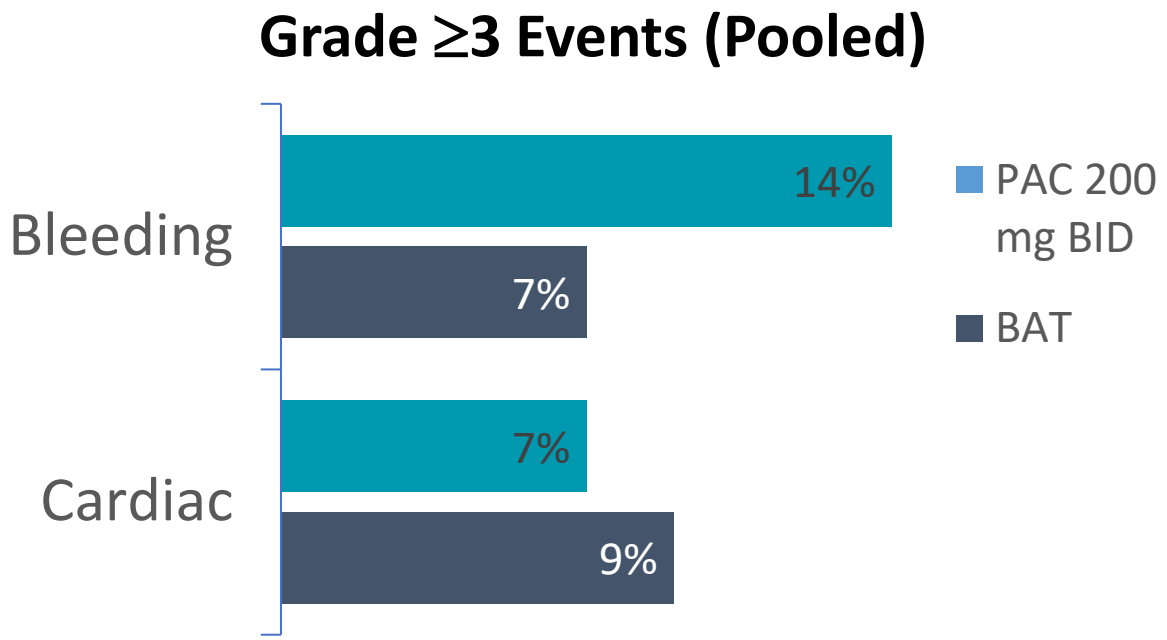
ITT-efficacy population, baseline to week 24

Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659., Al-Fayoumi S, et al. *Blood*. 2013;122;4080.

PERSIST-2: Adverse Event Profile

Adverse Reactions	PAC 200 mg BID (n=106)	BAT (n=98)
Any-grade AEs in >15% of patients in either arm, %		
Diarrhea	48	15
Thrombocytopenia	34	24
Nausea	32	11
Anemia	24	15
Peripheral edema	20	15
Vomiting	19	5
Fatigue	17	16
Grade ≥3 AEs in >5% of patients in either arm, %		
Thrombocytopenia	32	18
Anemia	22	14
Neutropenia	7	5
Pneumonia	7	3
Serious AEs in >3% of patients in either arm, %		
Anemia	8	3
Thrombocytopenia	6	2
Pneumonia	6	4
Congestive heart failure	4	2

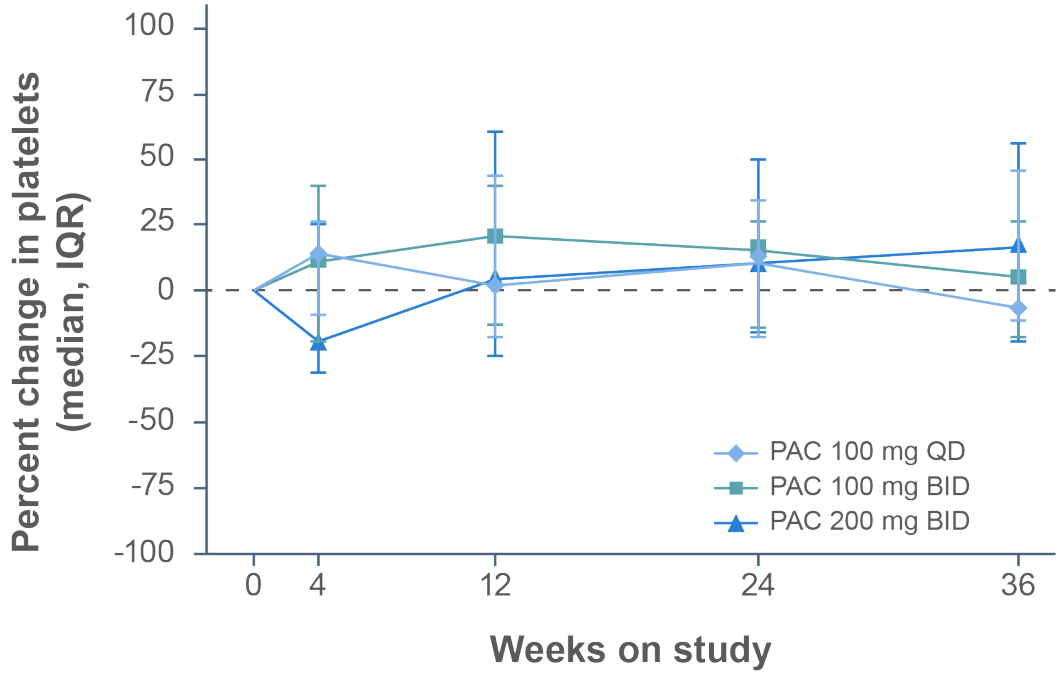
- Diarrhea with pacritinib most often occurred during weeks 1-8, was manageable, and resolved within 1-2 weeks



Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

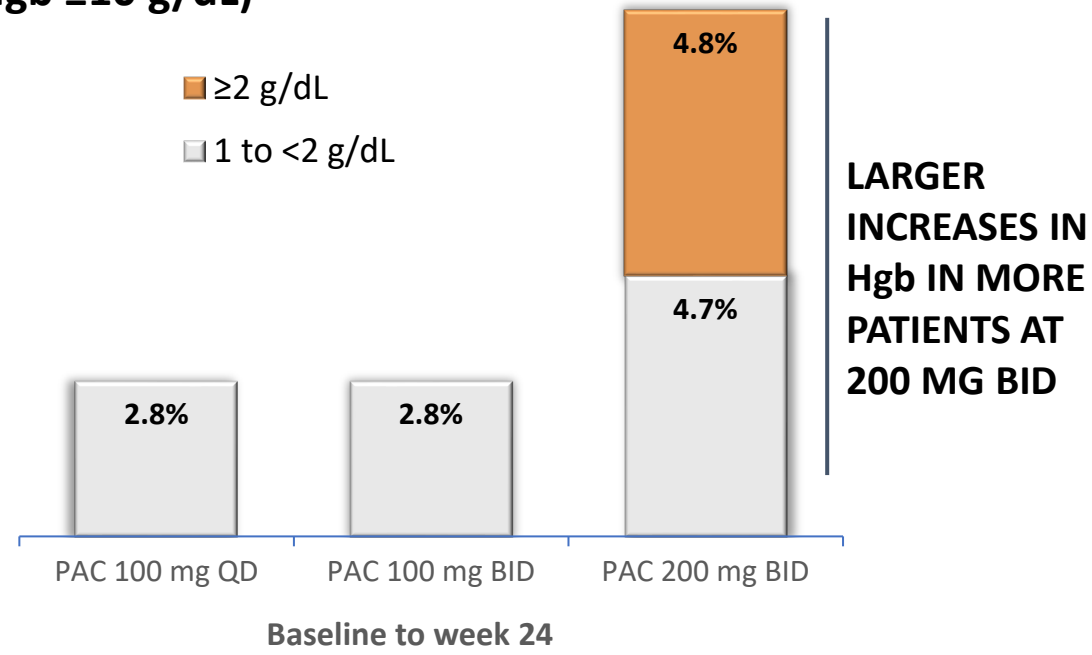
PAC203: Hematologic Stability

Percent Change in Platelet Count From Baseline



Number of Patients					
PAC 100 mg QD	52	44	37	22	11
PAC 100 mg BID	55	49	42	24	16
PAC 200 mg BID	53	49	38	26	14

Hgb Increases in Patients With Baseline Anemia (Hgb ≤10 g/dL)

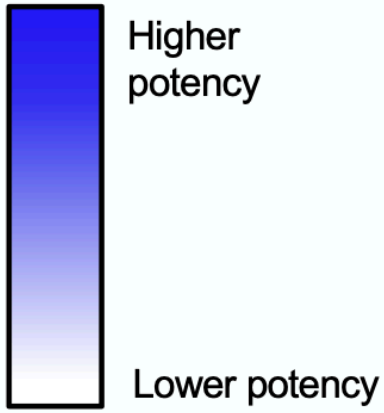


Gerds AT, et al. *Blood Adv*. 2020;4:5825-5835.

Pacritinib Is a Potent ACVR1 Inhibitor

- **Pacritinib is ~4x more potent** than momelotinib against ACVR1

	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Replicate 1 ACVR1 IC_{50} (nM)	20.4	22.6	70.2	312.0	>1000
Replicate 2 ACVR1 IC_{50} (nM)	32.4	10.8	34.9	235.0	>1000
Mean ACVR1 IC_{50} (nM)	26.4	16.7	52.6	273.5	>1000
Potency[b] (C_{max}:IC_{50})	N/A	12.7	3.2	1.0	<0.01



[a]LDN 193189 is an ACVR1 inhibitor.
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

Oh ST, et al. ASH Annual Meeting Dec 11, 2022, #628

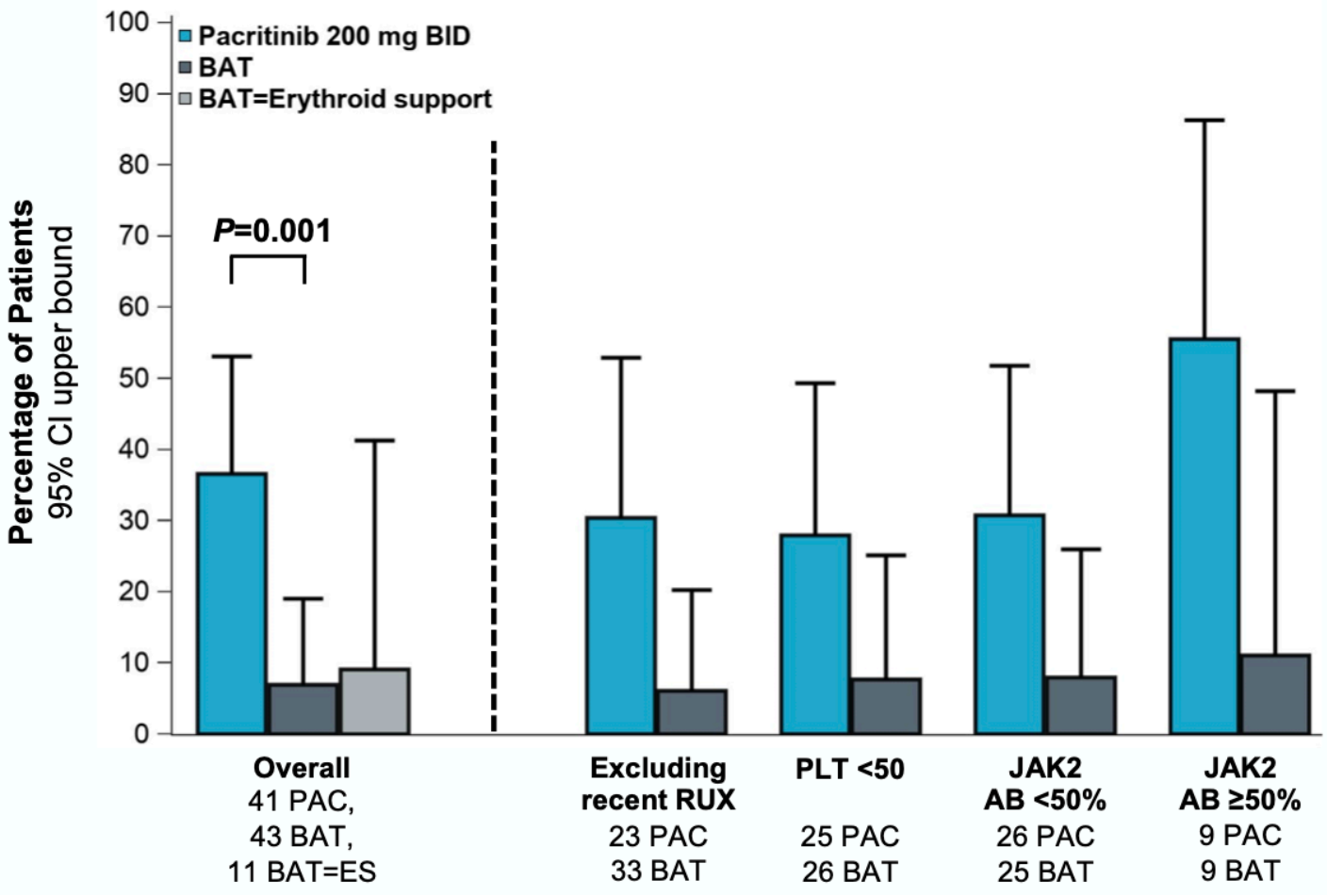
Transfusion Independence per Gale Criteria

TI Conversion Rate

Pacritinib N=41	BAT N=43	*P*-value
37%	7%	0.001

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
  - Erythroid support agents were prohibited on the pacritinib arm

Rate of TI (Gale criteria) through Week 24



Oh ST, et al. ASH Annual Meeting Dec 11, 2022, #628

Discontinuation of JAK inhibitors

Intolerance | Treatment Failure

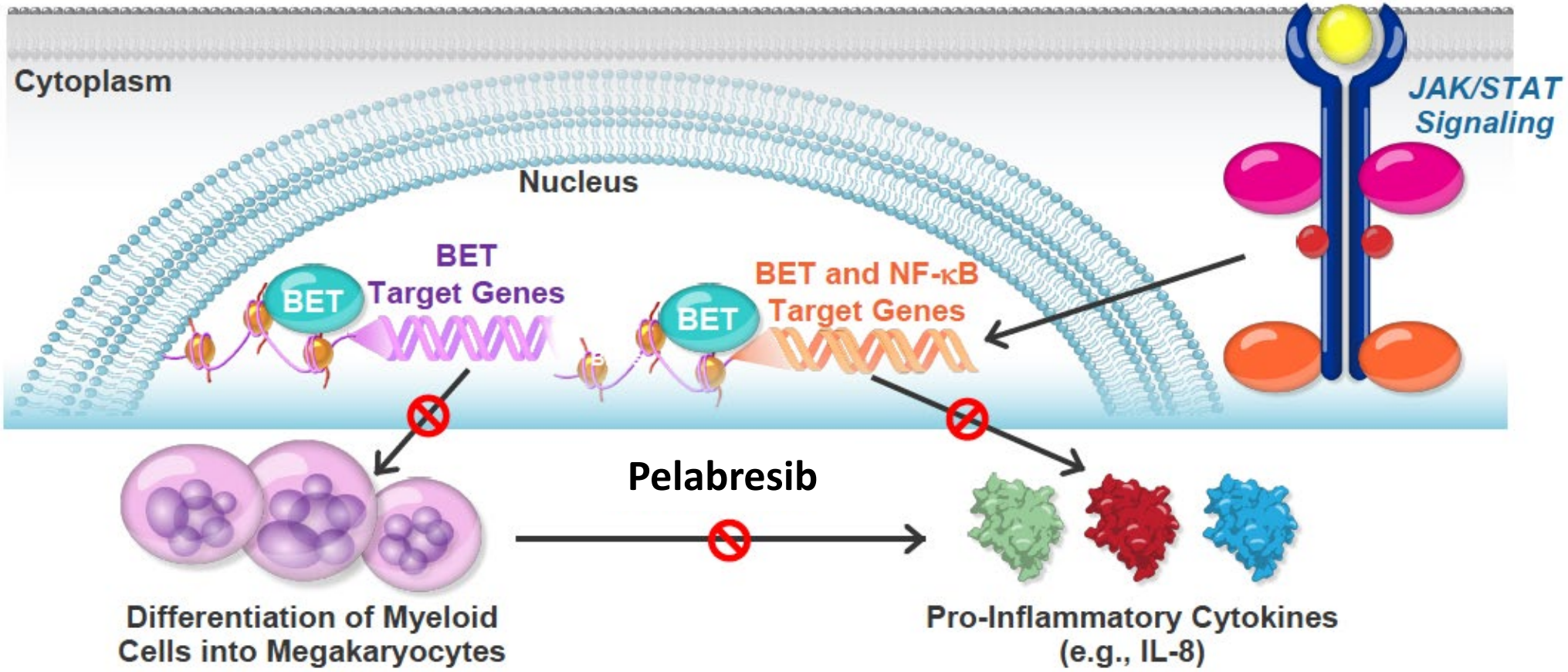
Toxicity
- Gastrointestinal
- Cytopenia(s)
- Neurologic
- Others

Lack of Efficacy
- No initial improvement in spleen size or symptom burden

Disease Progression
- Worsening cytopenia(s)
- Leukemia/hyperleukocytosis
- Worsening symptoms
- Increasing spleen size

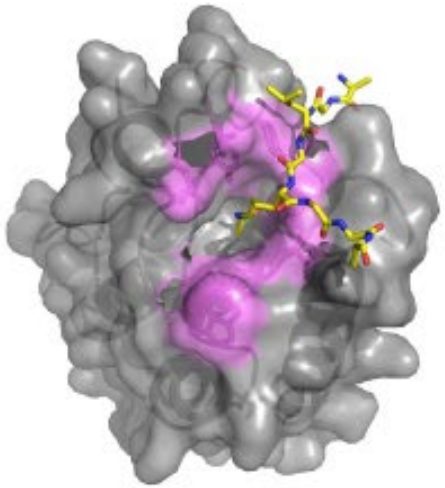
Mechanism of Potential Disease Modification in MF

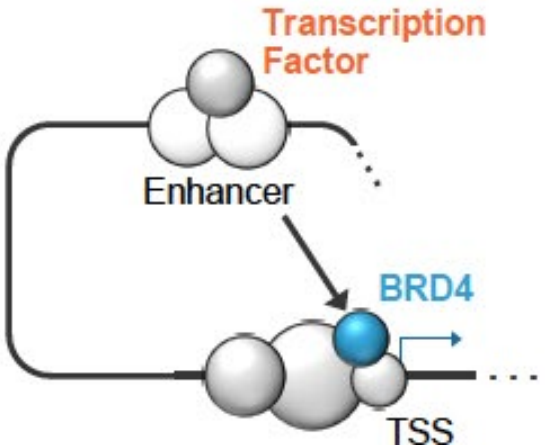
Pelabresib is an **oral inhibitor of bromodomain and extraterminal domain (BET) proteins**, which modifies the expression of genes involved in NFκB and TGFβ signaling in MF



Mascarenhas J, et al. Blood. 2019;134(Supplement_1):670. Kremyanskaya M, et al. Blood. 2021;138(Suppl 1):141.

BET Family of Proteins





Immune Signaling
- NF-κB target genes

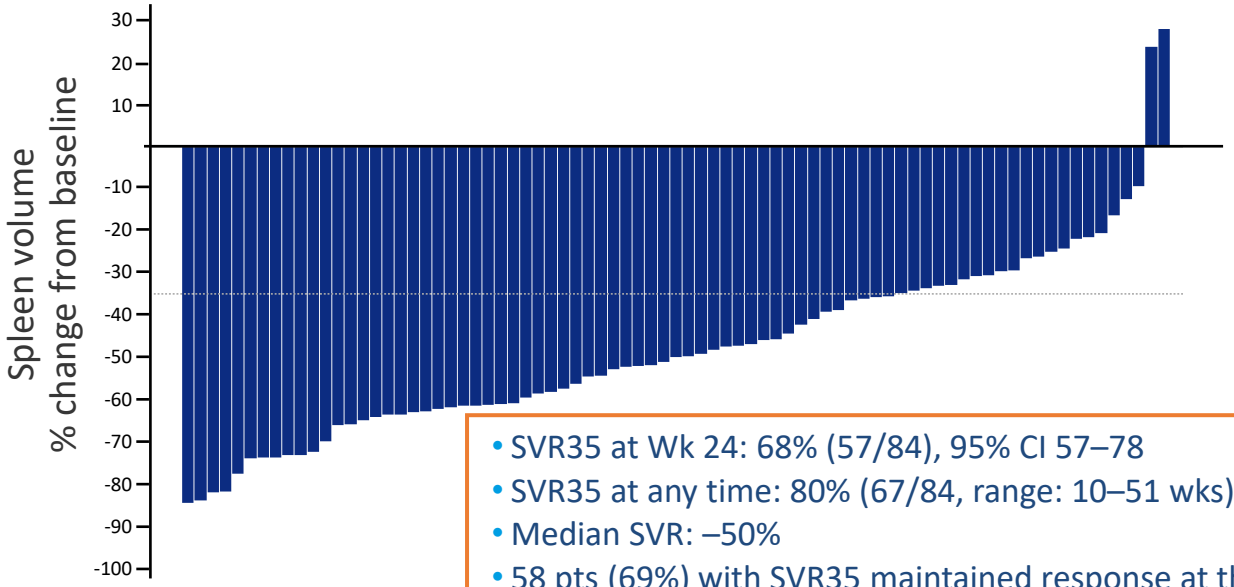
Fibrosis
- TGF-β target genes

Cancer Genetics
- MYC, BCL2

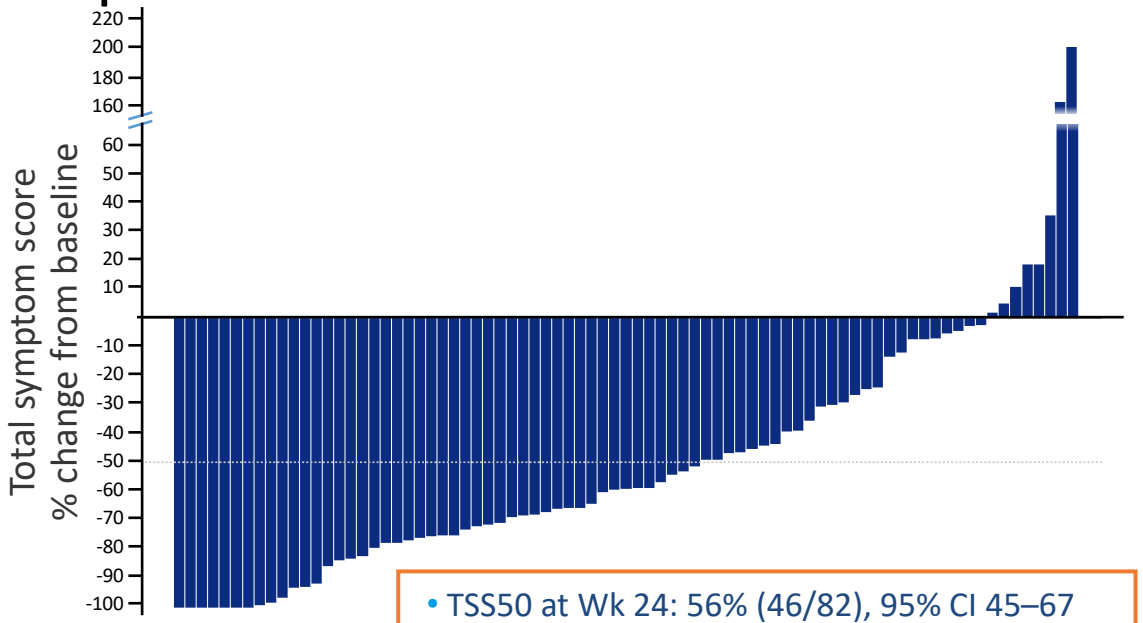
Mascarenhas J, et al. Blood. 2019;134(Supplement_1):670. Kremyanskaya M, et al. Blood. 2021;138(Suppl 1):141.

Preliminary Data From the MANIFEST Study

- Pelabresib with ruxolitinib in patients with MF
  - JAK inhibitor-naïve or with suboptimal response to ruxolitinib



- SVR35 at Wk 24: 68% (57/84), 95% CI 57–78
- SVR35 at any time: 80% (67/84, range: 10–51 wks)
- Median SVR: –50%
- 58 pts (69%) with SVR35 maintained response at the time of data cut-off
- Median follow-up* for SVR35 response: 37 wks



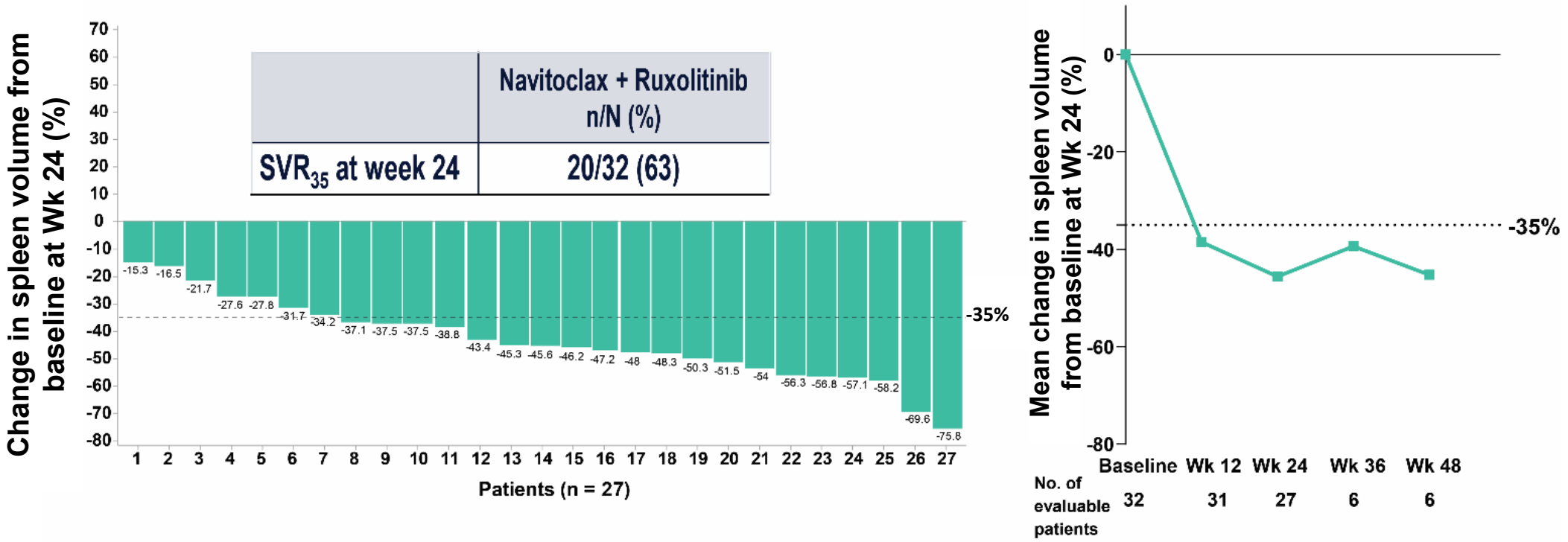
- TSS50 at Wk 24: 56% (46/82), 95% CI 45–67
- Median TSS % change: –59%

Patients are evaluable for SVR35 or TSS50 at Wk 24 if they have had Wk 24 assessment by the data cut-off date or discontinued without Wk 24 assessment at any time.

SVR, spleen volume reduction; SVR35, ≥35% reduction in spleen volume from baseline; TSS, total symptom score; TSS50, ≥50% reduction in total symptom score from baseline

Mascarenhas J, et al. Clin Lymphoma Myeloma Leuk. 2022 Oct;22 Suppl 2:S335-S336.

Navitoclax Plus Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis

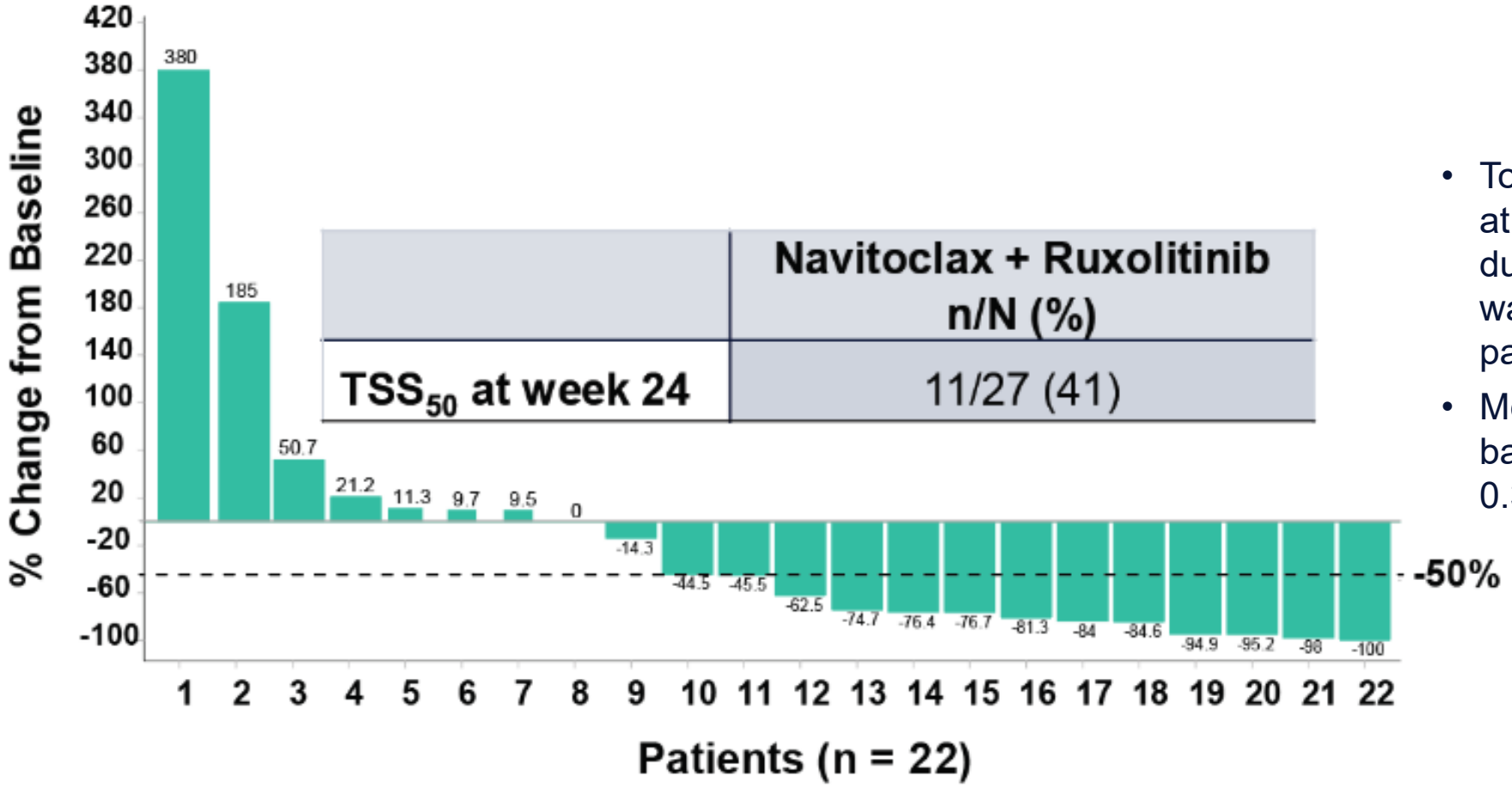


- All patients experienced reduction in spleen volumes; 20/32 (63%) achieved spleen volume reduction of at least 35% (SVR_{35}) at week 24
- SVR_{35} obtained anytime during the post-baseline period was observed in 25/32 (78%) patients
- Median time to first SVR_{35} was 12.3 weeks (range, 11.1 to 47.3)
- Estimated rate of maintaining SVR_{35} at 12 months was 92.9% (95% CI, 59.1 to 99.0)

Patients treated with navitoclax and ruxolitinib achieved spleen volume reductions

Passamonti F, et al. Journal of Clinical Oncology. 2022;40(16_suppl):7015.

Navitoclax + Ruxolitinib in JAK Inhibitor-Naïve Patients With Myelofibrosis

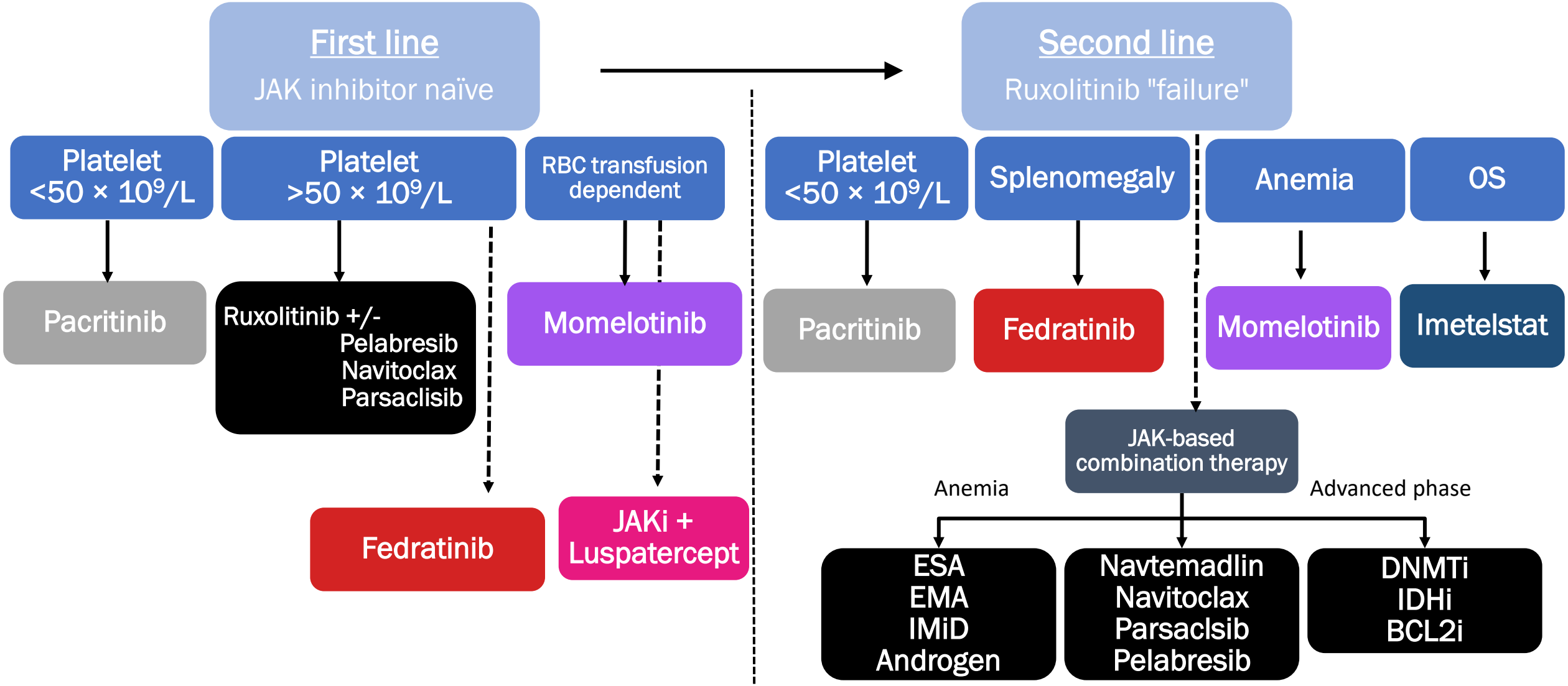


- Total symptom score reduction of at least 50% (TSS_{50}) at anytime during the post-baseline period was observed in 18/27 (67%) patients
- Median time to first TSS_{50} from baseline was 3.2 weeks (95% CI, 0.3 to 16.3)

Patients treated with navitoclax and ruxolitinib reported reduction in disease symptom burden

Passamonti F, et al. Journal of Clinical Oncology. 2022;40(16_suppl):7015.

3-5-Year Outlook for Myelofibrosis



Pemigatinib approved for relapsed or refractory myeloid/lymphoid neoplasm with FGFR1 rearrangement

MLN^{FGFR1} are rare hematologic neoplasms typically associated with eosinophilia

Diagnosis requires t(8;13)(p11;q12) or another translocation involving 8p11 that results in constitutive activation of FGFR1

Hydroxyurea or other inhibitors often lead to partial or short-lived complete responses

FIGHT-203 Trial demonstrated that in all 28 patients the complete cytogenetic RR was 79%