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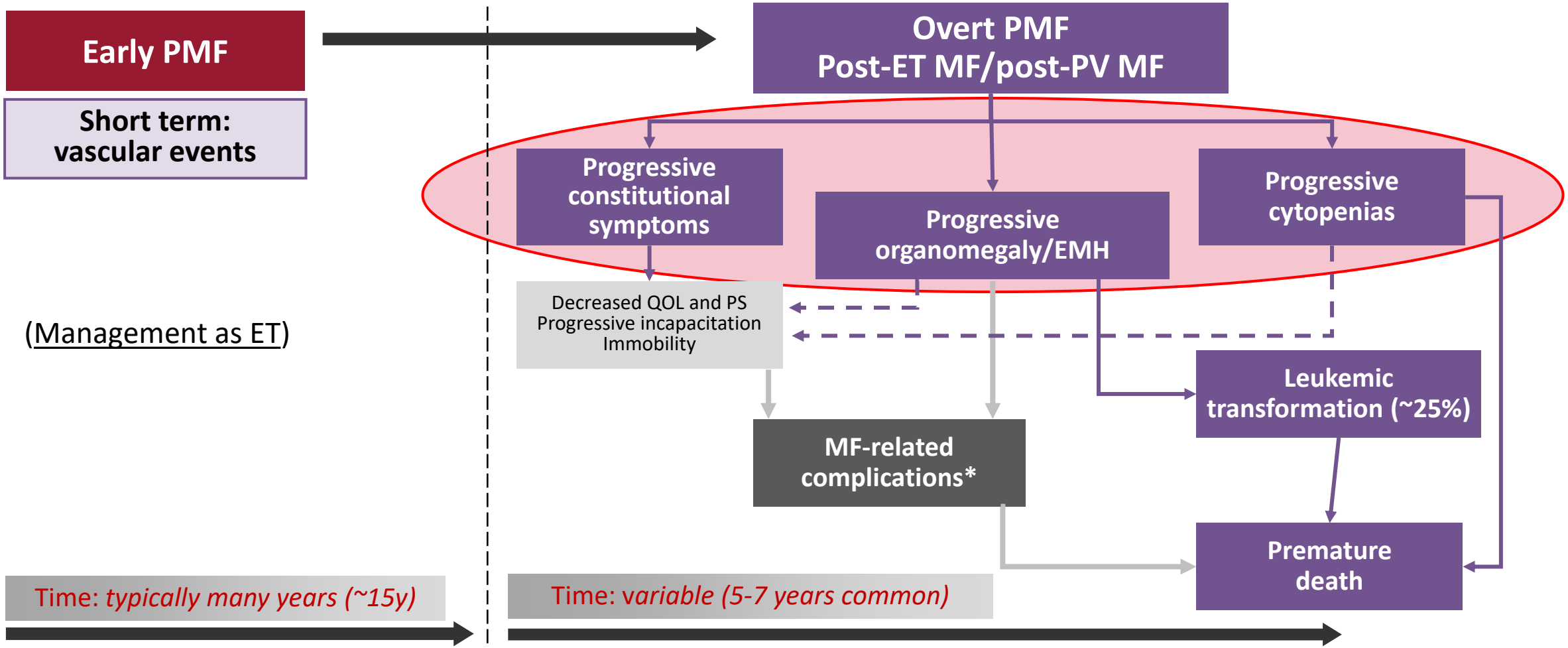
MD Anderson Cancer Center
Making Cancer History®

Myelofibrosis in 2023

Srdan Verstovsek, M.D., Ph.D.
Professor of Medicine, Department of Leukemia
University of Texas, MD Anderson Cancer Center
Houston, Texas, USA

Myelofibrosis: Disease Course and Complications



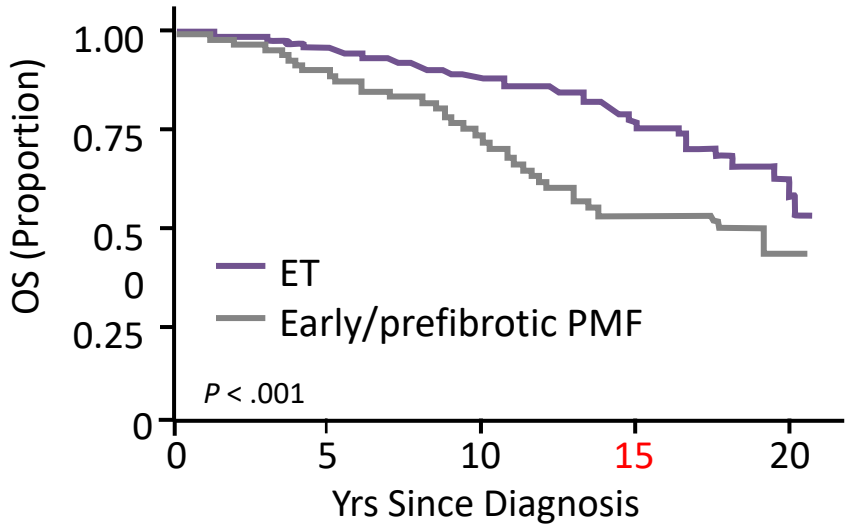
***Including cardiovascular events[2]**

Abbreviations: EMH, extramedullary hematopoiesis; ET, essential thrombocythemia; PMF, primary myelofibrosis; PS, performance status; PV, polycythemia vera; QOL, quality of life.

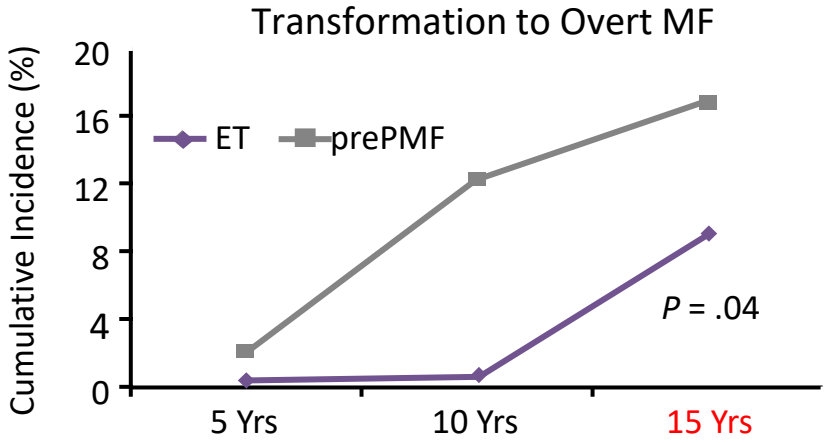
1. Mughal TI, et al. *Int J Gen Med.* 2014;7:89-101; 2. Haybar H, et al. *Cardiovasc Hematol Disord Drug Targets*. 2017;17(3):161-166.

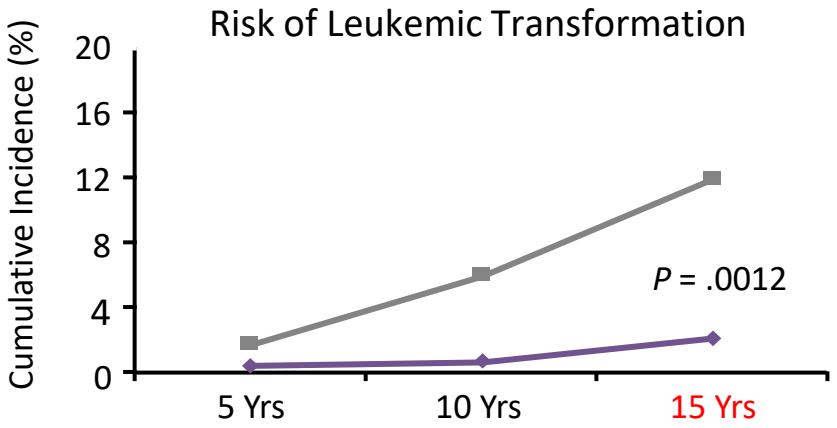
Early/Prefibrotic Primary Myelofibrosis

- International, observational study in which patients with ET or rediagnosed prePMF were followed for disease progression (N = 1,104)



Events	32	47	31	13
No. at risk	628	326	157	57





Simplified NCCN Guidelines for Treatment of MF: Based on Risk and Symptoms/Signs

Lower-risk

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

Higher-risk

- Transplant eligible ➔ allo-HSCT

  or
- Transplant ineligible ➔ **ruxolitinib** or **fedratinib** (either one for patients with platelets >50K) or **pacritinib** (for patients with platelets <50K) or clinical trial

  AND/OR
- Transplant ineligible/anemia ➔ anemia therapy or clinical trial

JAK inhibitors are not selective for mutated JAK2V617F protein

Lower-risk: MIPSS-70 ≤ 3; MIPPS-70+ ≤ 3; DIPSS-Plus ≤ 1; DIPSS ≤ 2; MYSEC-PM <14
Higher-risk: MIPSS-70 ≥ 4; MIPPS-70+ ≥ 4; DIPSS-Plus > 1; DIPSS > 2; MYSEC-PM ≥14

allo-HSCT, allogeneic hematopoietic stem cell transplantation; DIPSS, Dynamic International Prognostic Scoring System; Int, intermediate; MIPPS: Mutation-Enhanced International Prognostic Score System; MYSEC-PM, Myelofibrosis Secondary to PV and ET-Prognostic Model; NCCN, National Comprehensive Cancer Network.

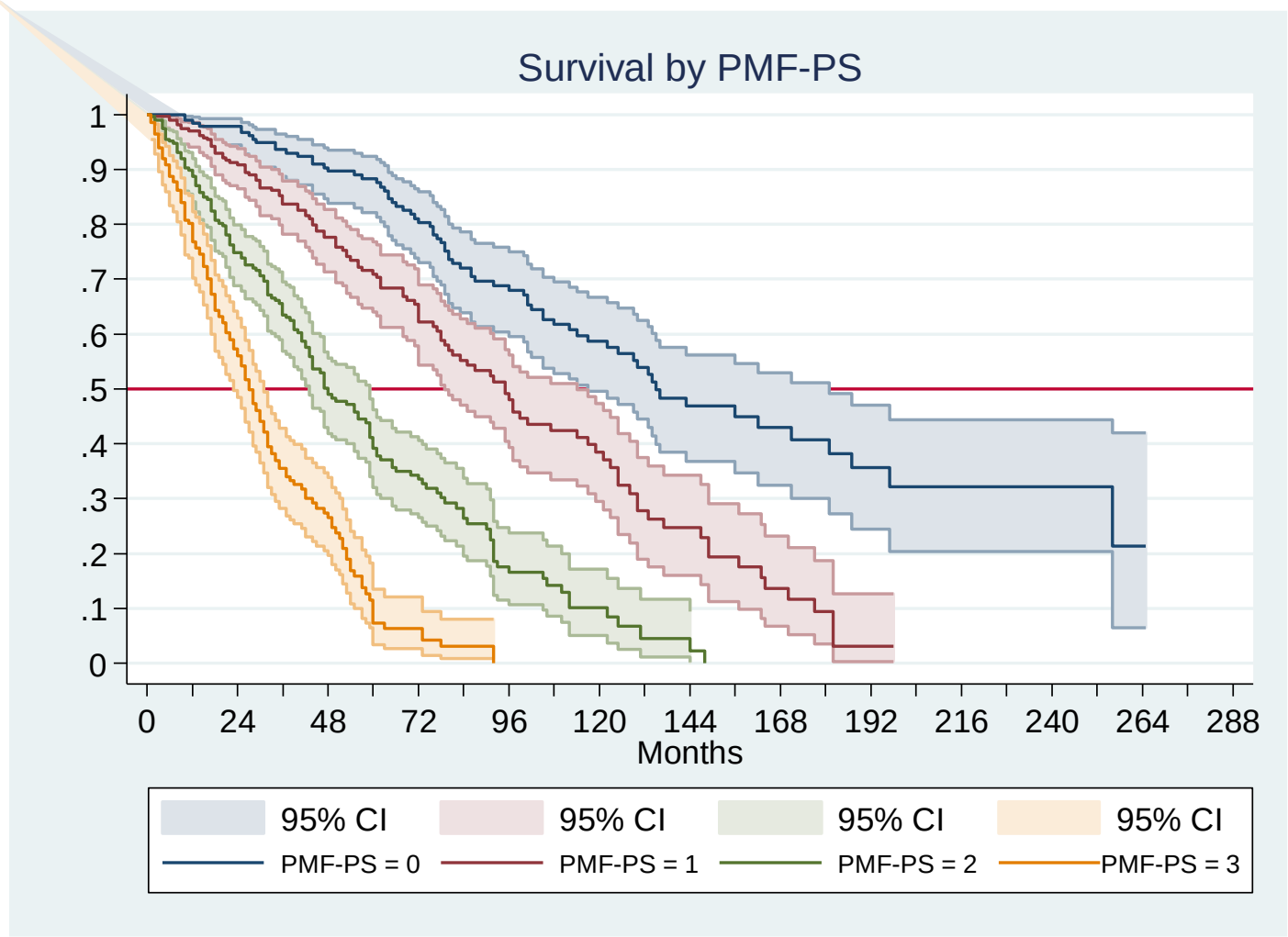
National Comprehensive Cancer Network (NCCN). Myeloproliferative Neoplasms (Version 1.2020). Available from: www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Last accessed August 2020.

International Prognostic Scoring System (IPSS) in Primary Myelofibrosis

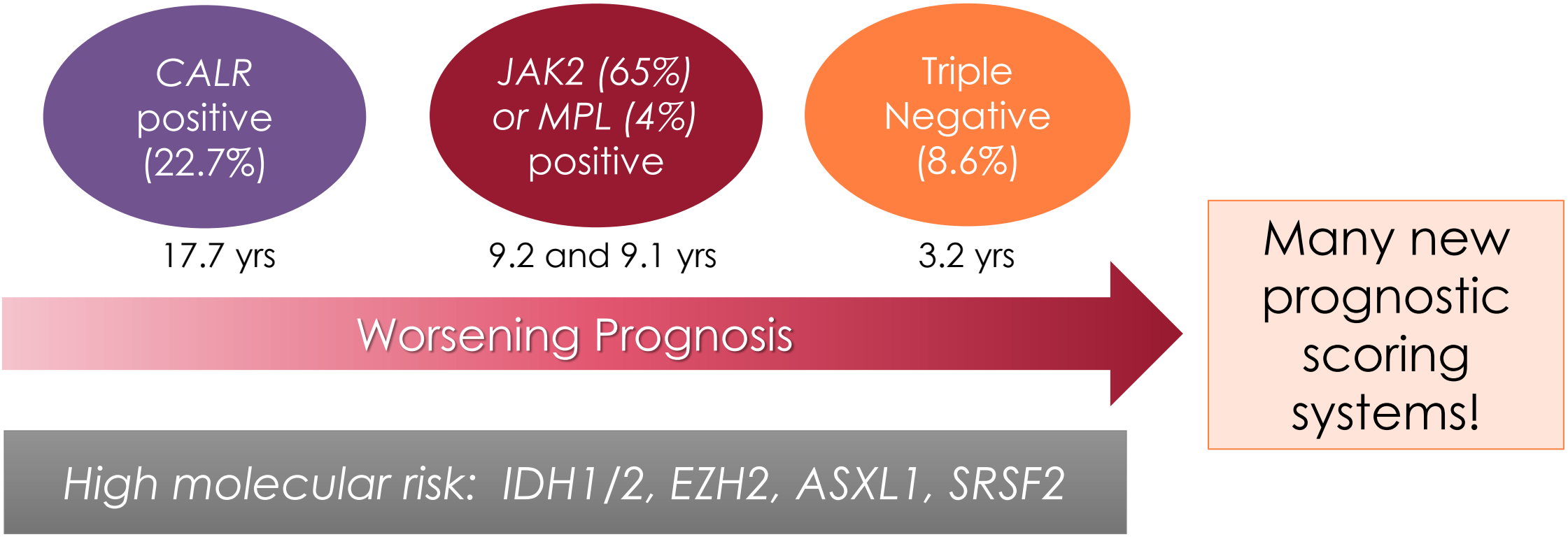
Prognostic factors

- Age > 65 years
- Constitutional symptoms
- Hb < 10 g/dL
- Leukocytes > 25 x 10^9/L
- Blood blasts ≥ 1%

Risk group	#factors	OS (y)
Low	0	11
Intermediate-1	1	8
Intermediate-2	2	4
High	≥ 3	2



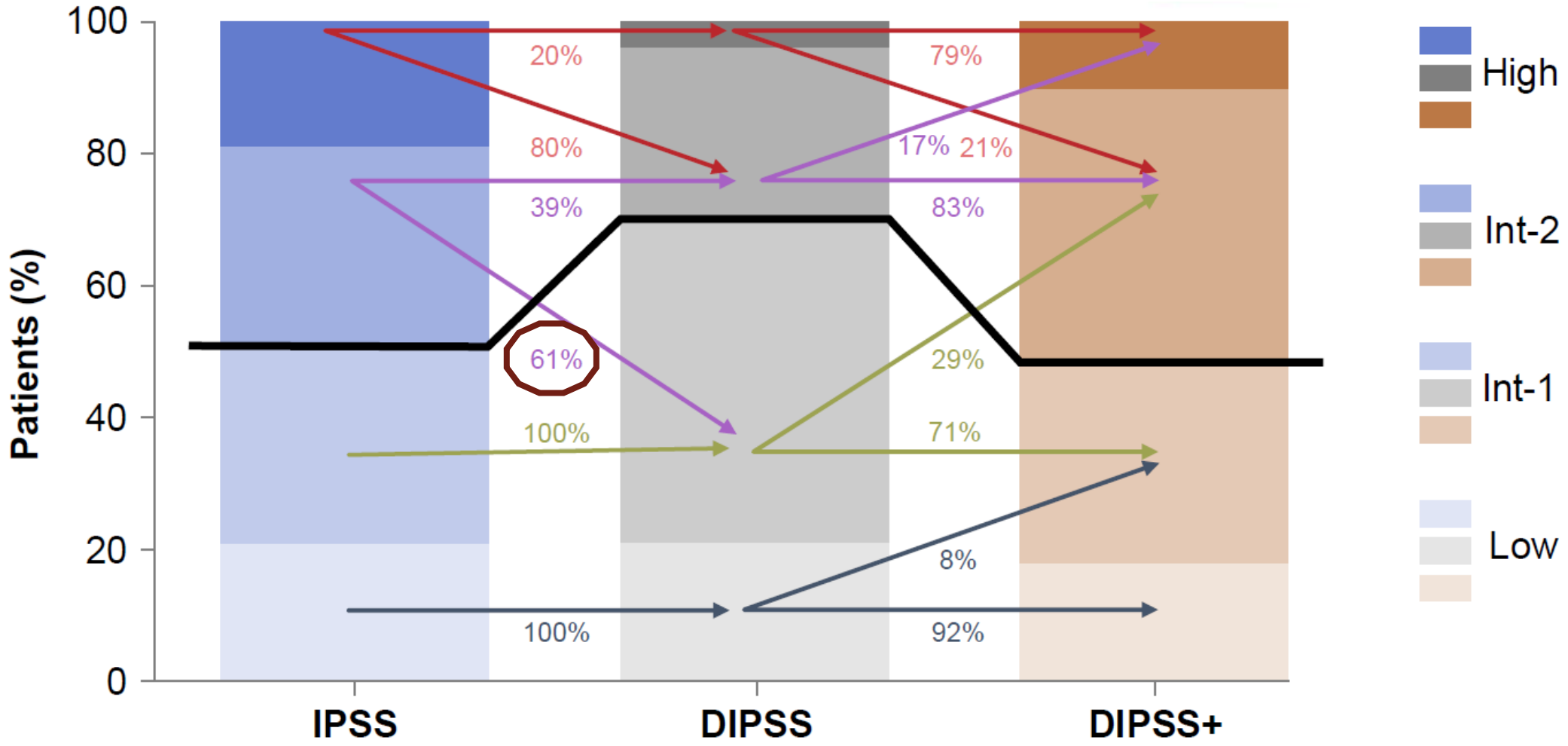
Impact of Driver and "High Molecular Risk" Mutations in Primary Myelofibrosis



- 2 or more HMR mutations also worsen survival

Rumi E et al. *Blood*. 2014;124:1062-1069; Vannucchi AM et al. *Leukemia*. 2013;27:1861-9; Guglielmelli P, et al. *Leukemia*. 2014;28:1804-10.

Distribution of Myelofibrosis Patients by Different Prognostic Models



Reproduced from Hernandez-Boluda JC, *Ann Hematol*. 2018;97(5):813-820.

MPN10

Total Symptom Score [MPN-SAF]

An easy tool to assess symptoms in MPNs

- Inflammation
- Splenomegaly
- Anemia

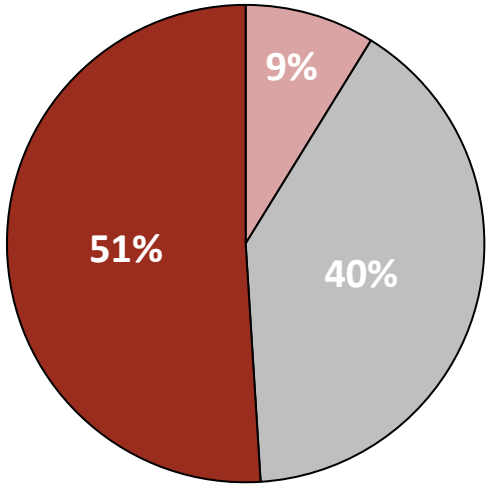
	Value	Prognostic variable
Fatigue	0	1 to 10 ranking (0 if absent; 1 most favorable; 10 least favorable)
Early satiety	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Unintentional weight loss last 6 months	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
MPN10 score	0	

Scherber R, et al. *Blood*. 2011;118:401-408.

MPN Patient Treatment-Watch and Wait
2016 International Landmark Study

- 23% of patients managed with watch and wait had high to moderate symptom burden
- Only 36% reported not currently experiencing symptoms

MF
(n = 194)

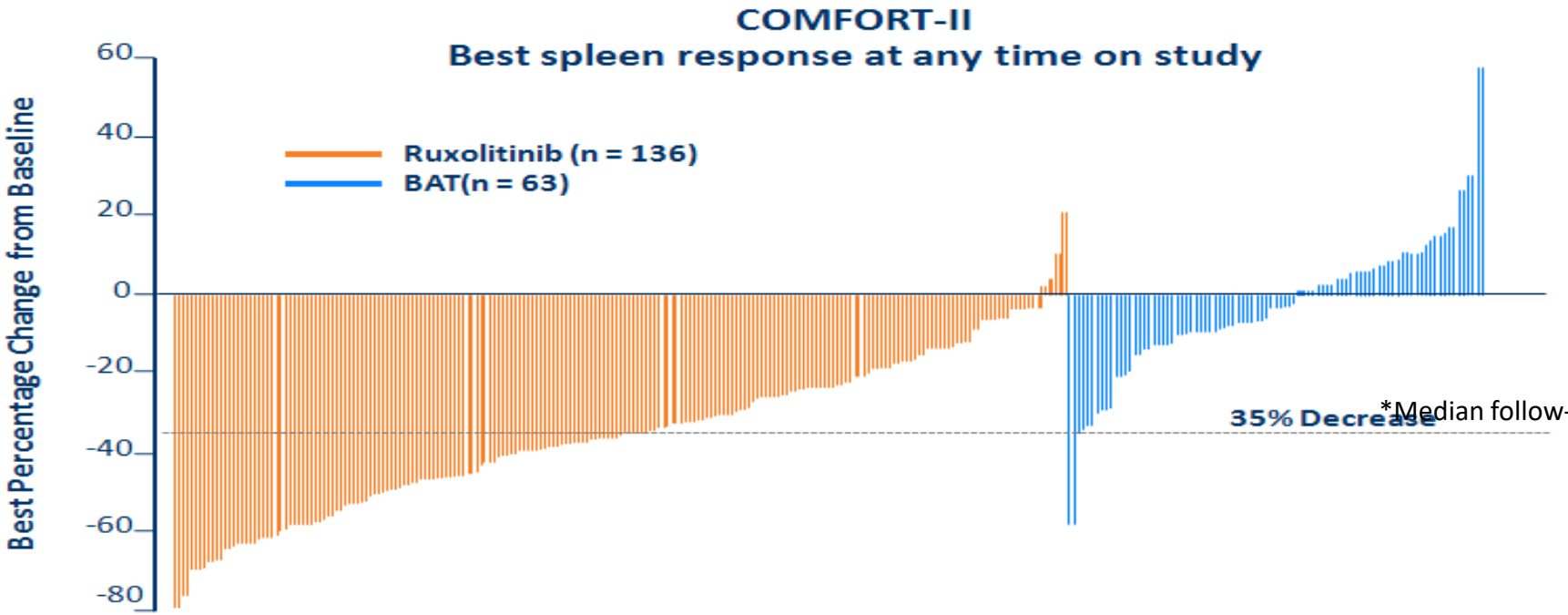


Despite a significant symptom burden in some untreated patients, around half of the physicians would still observe > 25% of patients at diagnosis

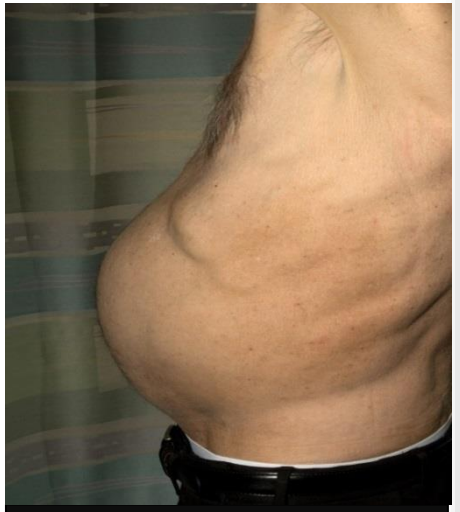
Observe > 25% of patients
Observe 1%-25% of patients
Active treatment

From Koschmieder S, et al. *Congress of the European Hematology Association*; June 22 - 25, 2017; Madrid, Spain [poster 706].

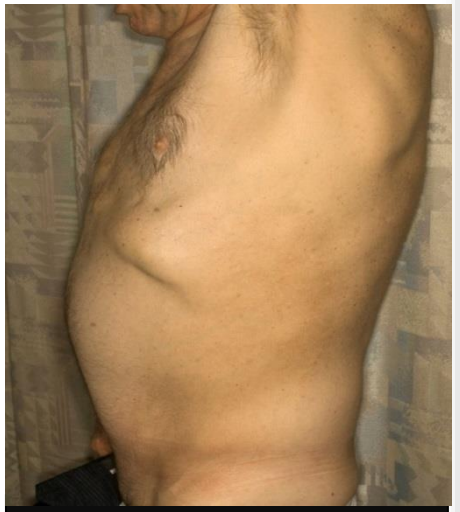
Myelofibrosis: What are JAK inhibitors for? Spleen and symptoms



*Median follow-up: 4.3 years



MF Patient Pre-Ruxolitinib Therapy

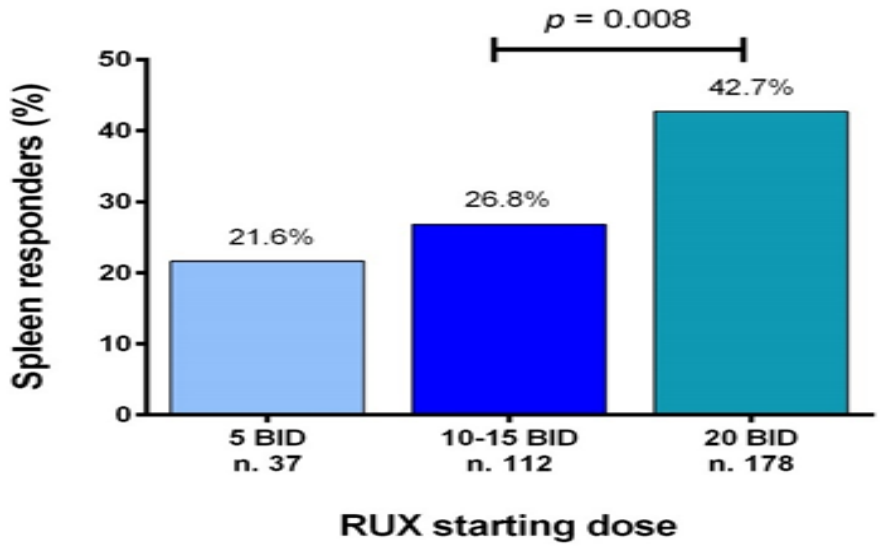


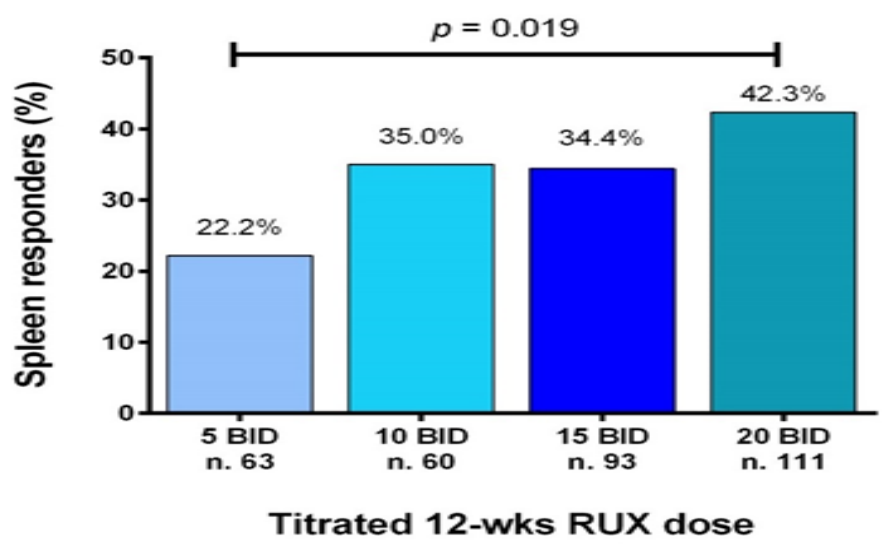
After 2 Months of Therapy

- Dosed based on platelet number (not recommended for platelets <50K)
- It can cause anemia and thrombocytopenia
- Long-term ruxolitinib therapy prolongs survival (earlier intervention and better the spleen response, longer the survival)

Harrison C, et al. *N Engl J Med*. 2012;366(9):787-798. *Images courtesy of Srdan Verstovsek, MD, PhD*

Ruxolitinib Efficacy by Titrated Dose: *real-word evidence*



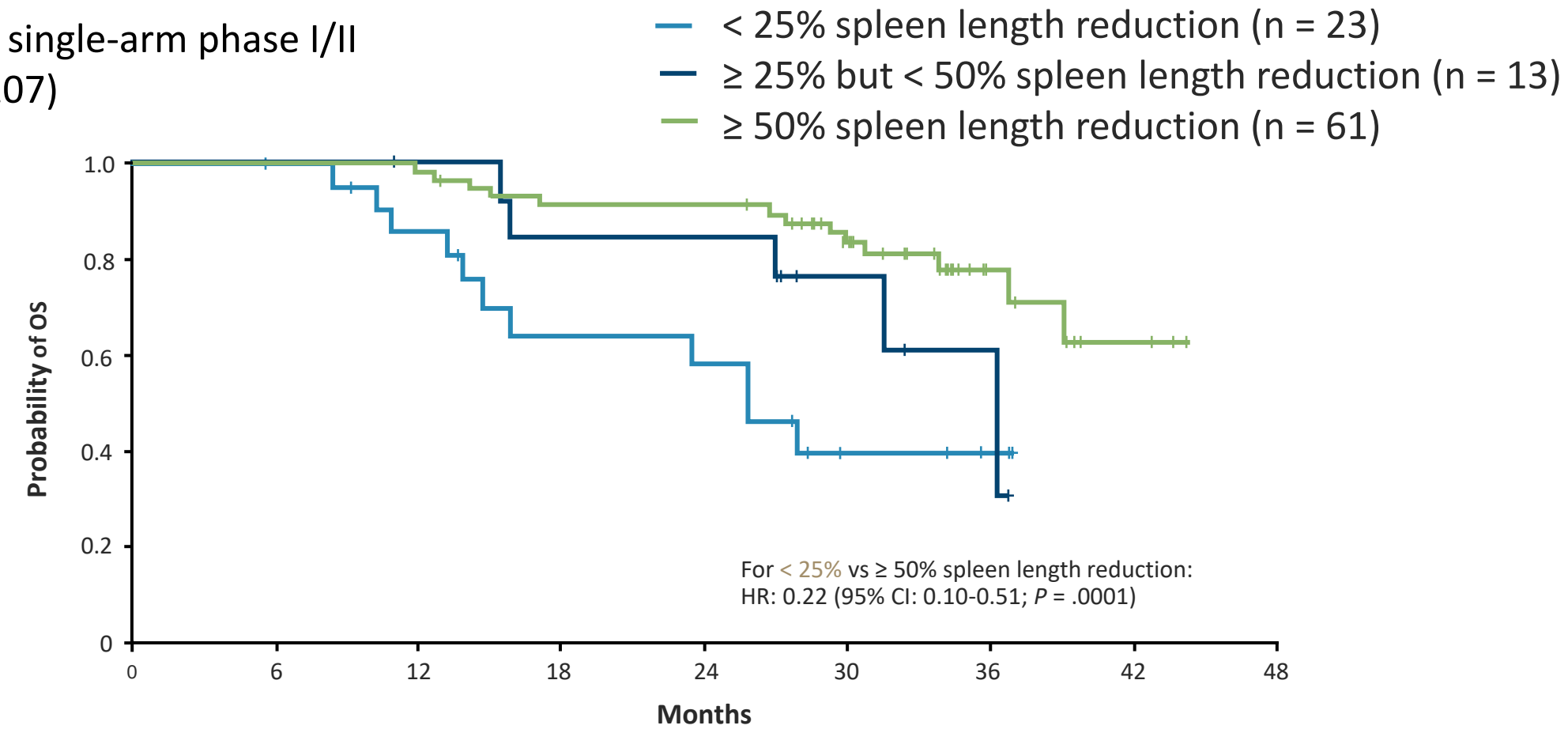


- Phase 2 study and real-world data showed that doses less than 10mg BID are not effective long term
- If starting low, ESCALATE quickly to maximum safe dose

Palandri F, et al. Oncotarget. 2017;8:79073–86.

Overall Survival Improves with Spleen Length Reduction in Patients Receiving Ruxolitinib

Open-label, single-arm phase I/II study (N = 107)



Verstovsek S, et al. *Blood*. 2012;120:1202-1209.

Early intervention: Ruxolitinib in IPSS-1 Patients

Higher Response Rate and Lower Toxicities

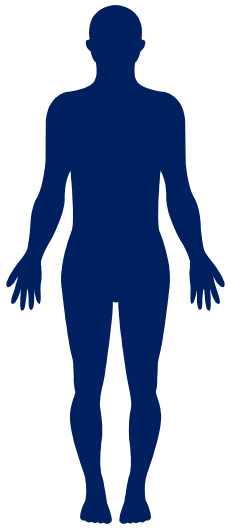
	Clinical Trial	Spleen Response at Week 24	Incidence of Anemia G3/G4	Incidence of Thrombocytopenia G3/G4	Incidence of Infections	Discontinuation rate
Int-2 and high-risk patients	COMFORT-I (n = 155)[1]	41.9%	45%	13%	≈ 50%	21%[6]
	COMFORT-II (n = 146)[2]	32%	42%	8%	≈ 50%	38%
Int-1- risk patients	JUMP INTM-1 (n = 163)[3]	56.9%	24.5%	11%	40%	19.6%
	ROBUST trial (n = 14)[4]	50%	NA	NA	NA	NA
	Italian study (n = 70)[5]	54.7%	21.7%	2.9%	17.1%	17.1%

IPSS intermediate-1 patients may possibly achieve higher reponse rates and experience lower toxicities than patients with higher-risk disease

1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807; 2. Harrison C, et al. N *Engl J Med.* 2012;366:787-98; 3. Al-Ali HK, et al. *Haematologica*. 2016;101:1065-73;
4. Mead AJ, et al. *Br J Haematol.* 2015;170:29-39; 5. Palandri F, et al. *Hematol Oncol.* 2018;36:285-290; 6. Verstovsek, et al. *Haematologica*. 2015;100:479-488.

Fedratinib in Myelofibrosis

Phase 3 JAKARTA Trial: Fedratinib vs. placebo in patients with Int-2/high-risk MF first line



N = 289

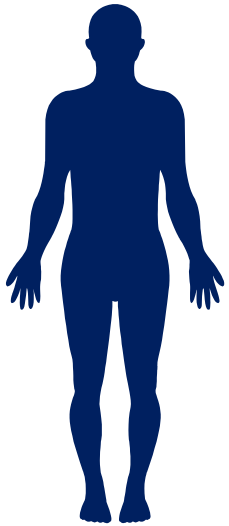
Fedratinib 400 mg

- 37% Spleen volume reduction ≥ 35%
- 40% Symptom burden reduction ≥ 50%
- 14% Discontinuation due to AEs

Fedratinib 500 mg

- 40% Spleen volume reduction ≥ 35%
- 34% Symptom burden reduction ≥ 50%
- 25% Discontinuation due to AEs

Phase 2 JAKARTA-2 Trial: Fedratinib in patients with Int-2/high-risk MF resistant or intolerant to ruxolitinib



N = 97
*N = 79

Primary analysis

- 55% Spleen volume reduction ≥ 35%
- 11.0% Discontinuation due to AEs

Reanalysis (2019)*

- 30% Spleen volume reduction ≥ 35%
- 27% Symptom burden reduction ≥ 50%

*More stringent criteria for relapse, refractory, and intolerance to ruxolitinib

AE = Adverse Event; Int-2 = Intermediate-2; Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643–651; Harrison CN, et al. *Lancet Haematol*. 2017;4(7):317–324; Harrison CN, et al. ASCO 2019. Abstract 7057.

Fedratinib Adverse Events

Adverse Event, %	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		Placebo (n = 95)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Nonhematologic						
Diarrhea	66	5	56	5	16	0
Vomiting	42	3	55	9	5	0
Nausea	64	0	51	6	15	0
Constipation	10	2	18	0	7	0
Asthenia	9	2	16	4	6	1
Abdominal pain	15	0	12	1	16	1
Fatigue	16	6	10	5	1	0
Hematologic						
Anemia	99	43	98	60	91	25
Thrombocytopenia	63	17	57	27	51	9
Lymphopenia	57	21	66	27	54	21
Leukopenia	47	6	53	16	19	3
Neutropenia	28	8	44	18	15	4

Black box warning

- Wernicke's encephalopathy (ataxia, altered mental status, ophthalmoplegia) occurred in 8 of 608 (1.3%) patients receiving fedratinib in clinical trials

Considerations

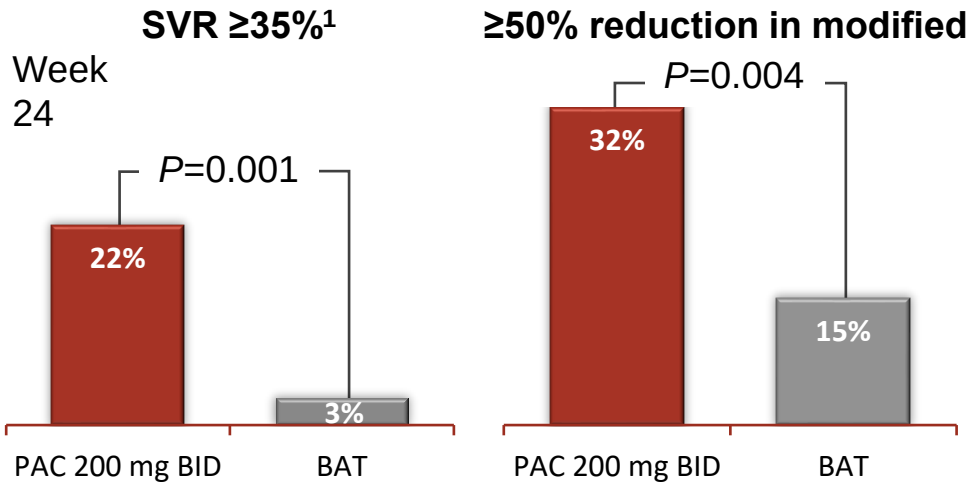
- Measure and address thiamine levels prior to treatment initiation
- Do not start fedratinib in patients with thiamine deficiency

Pardanani A, et al. *JAMA Oncol*. 2015;1(5):643–651.

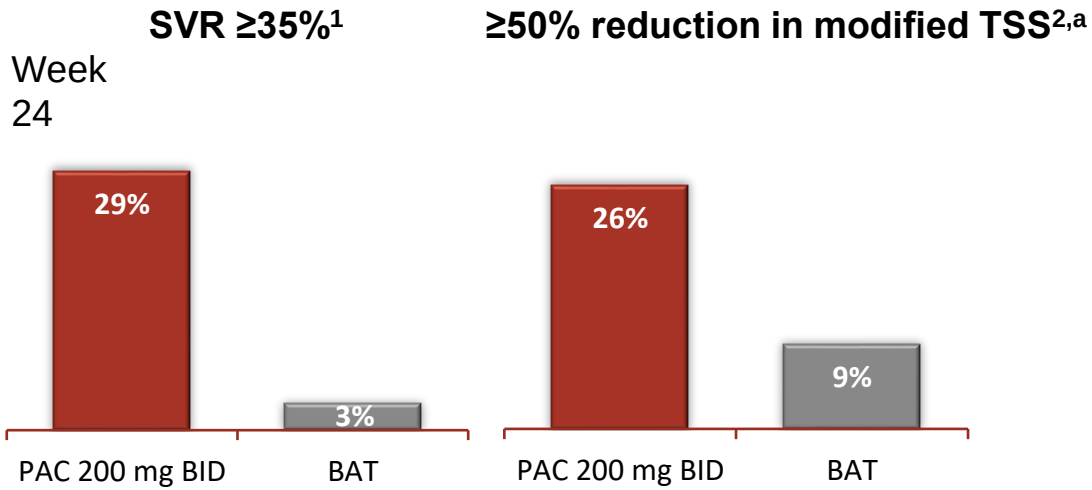
Pacritinib vs. BAT in Thrombocytopenic Patients (PERSIST-2)

Pacritinib received accelerated approval in the US on February 28th, 2022 as therapy for MF patients with platelets <50x109/L

ITT Population (plts <100x10^9/L)



Patients With Platelets <50x10^9/L

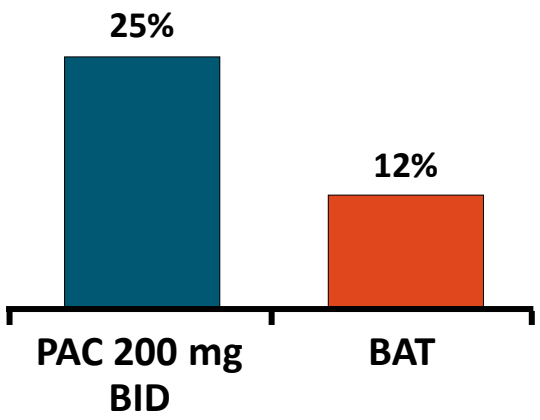


- PERSIST-2 study: prior JAK2 inhibitor allowed (48%), BAT included ruxolitinib (45%)
- Rarely myelosuppressive
- Causes GI side effects

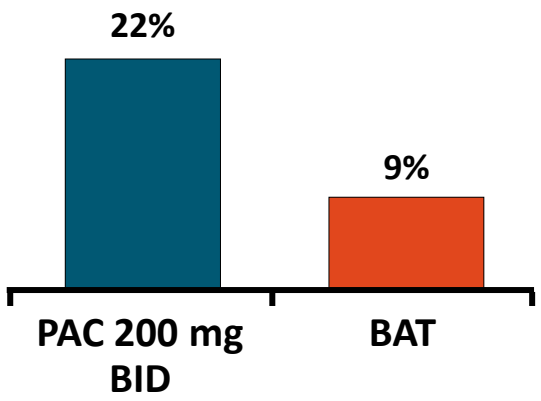
[a] Excludes individual symptom score for tiredness from MPN-SAF TSS v2.0; utilized in pivotal trials for other JAK inhibitors.
BAT, best available therapy; BID, twice daily; ITT, intention-to-treat; MPN-SAF, myeloproliferative symptom assessment form; PAC, pacritinib; SVR, spleen volume reduction; TSS, total symptom score.
1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659. 2. Data on File. CTI Biopharma Corp. Pacritinib Clinical Overview.

PERSIST-2: Hematologic Stability/Improvement

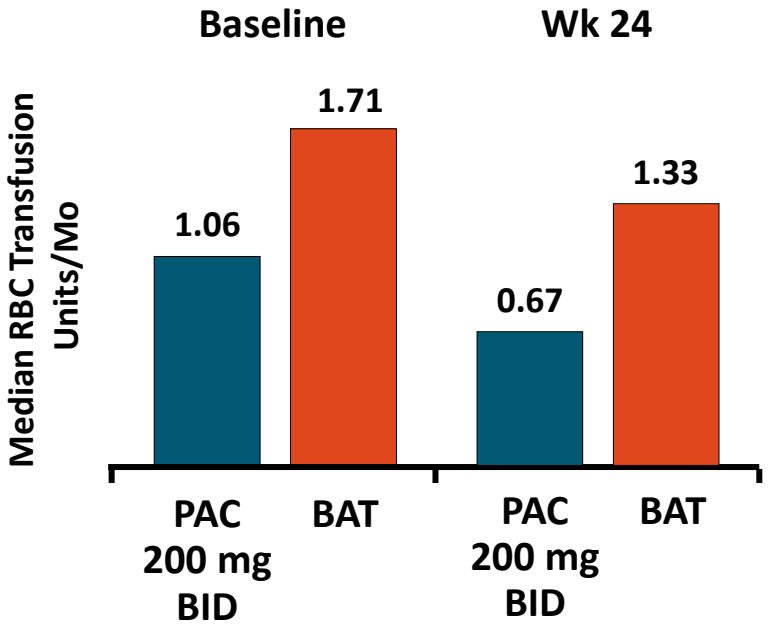
Clinical Improvement in Hemoglobin Levels in Patients With Baseline Anemia, Baseline to Wk 24*



Pacritinib Reduced Transfusion Burden in Patients Not TI at Baseline, Baseline to Wk 24



Transfusion Burden in Patients Who Received ≥1 RBC Transfusion on Study



TI defined according to Gale criteria (0 units over the course of 12 wk).
*International Working Group response criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 wk prior; anemia defined as hemoglobin <10 g/dL.

Mascarenhas. JAMA Oncol. 2018;4:652.

PERSIST-2: Adverse Events

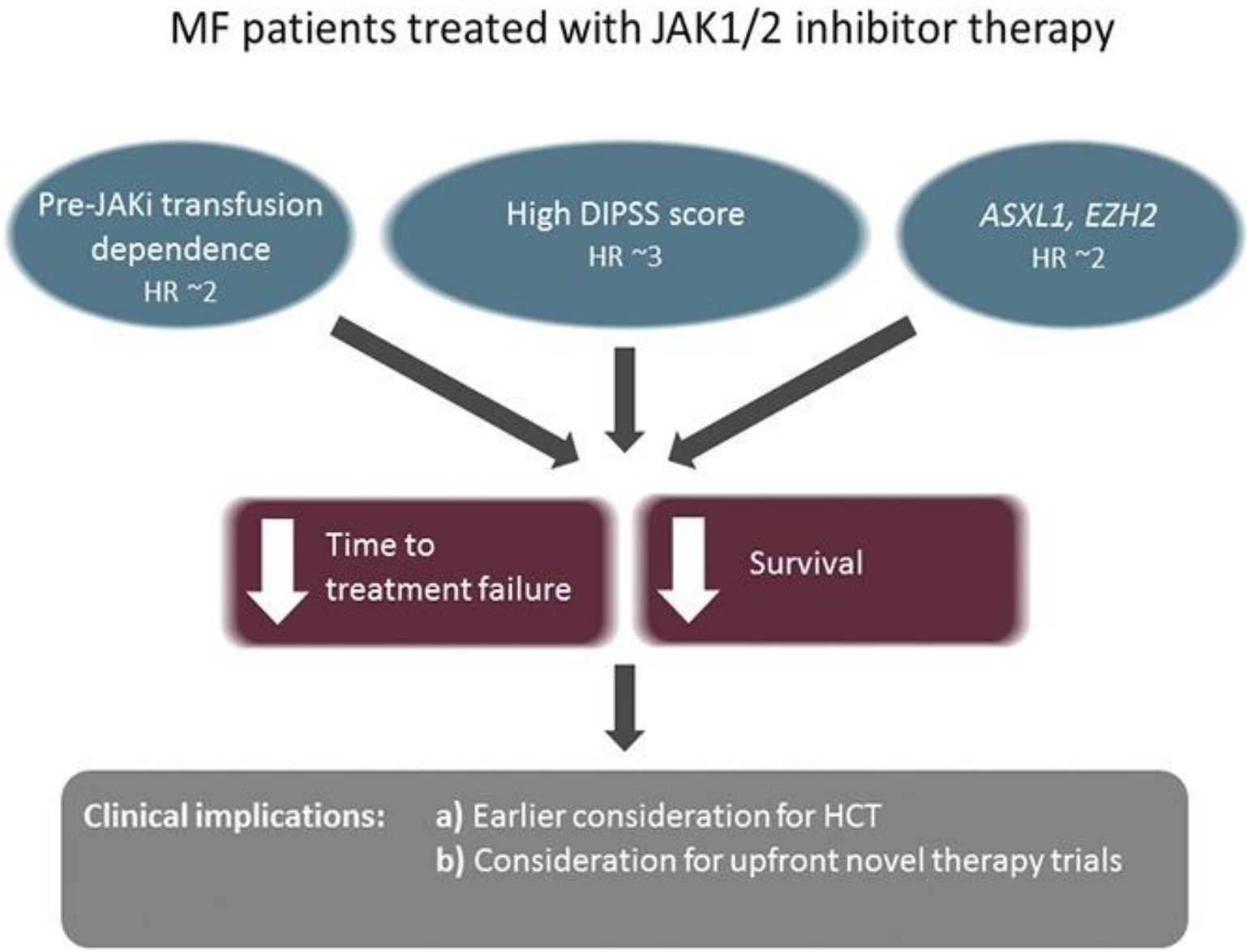
Adverse Reactions	PAC 200 mg BID (n = 106)	BAT (n = 98)
Any-grade AEs in ≥15% of patients in either arm, %		
Diarrhea	48	15
Thrombocytopenia	34	23
Nausea	32	11
Anemia	24	15
Peripheral edema	20	15
Vomiting	19	5
Fatigue	17	16

- Diarrhea with pacritinib most often occurred during Wk 1-8, was manageable, and resolved within 1-2 wk
- Neurologic AEs and opportunistic infections rarely reported with pacritinib
- Safety outcomes with pacritinib were similar for those with baseline platelets <50 x 10^9/L vs 50-100 x 10^9/L

Mascarenhas. JAMA Oncol. 2018;4:652.

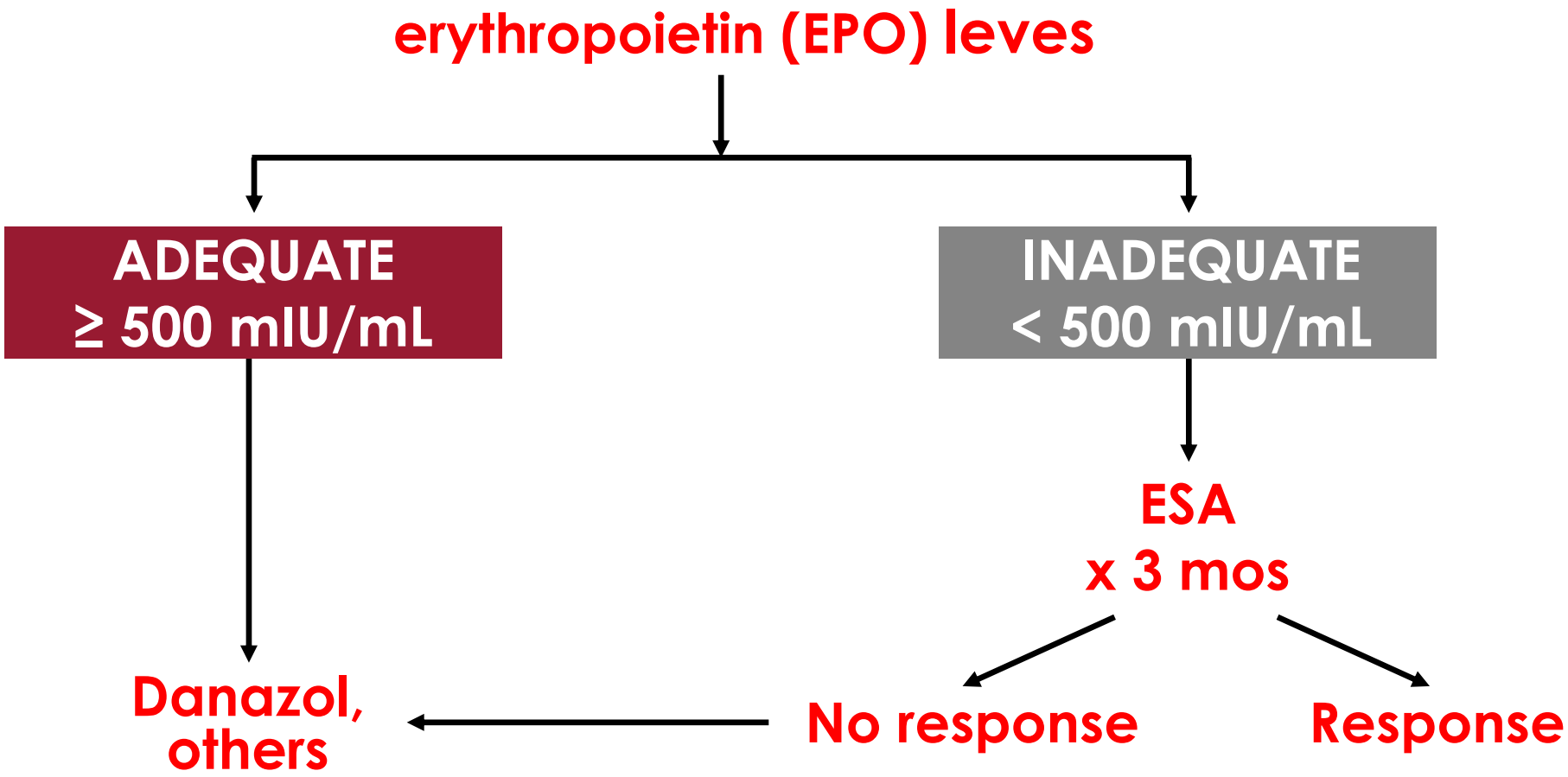
Impact of Patients Characteristics on Outcomes in Patients Treated With JAK1/JAK2 Inhibitor Therapy

Transfusion dependence, high risk score and ***ASXL1/EZH2*** mutations predict shorter time to failure in MF patients receiving JAK1/JAK2 inhibitor treatment.



Spiegel JY, et al. *Blood Adv.* 2017;1(20):1729-1738.

Approach to the Treatment of Anemia in MF



NCCN guidelines

Momelotinib Inhibits JAK1, JAK2, and ACVR1 to Address MF Symptoms, Spleen, and Anemia

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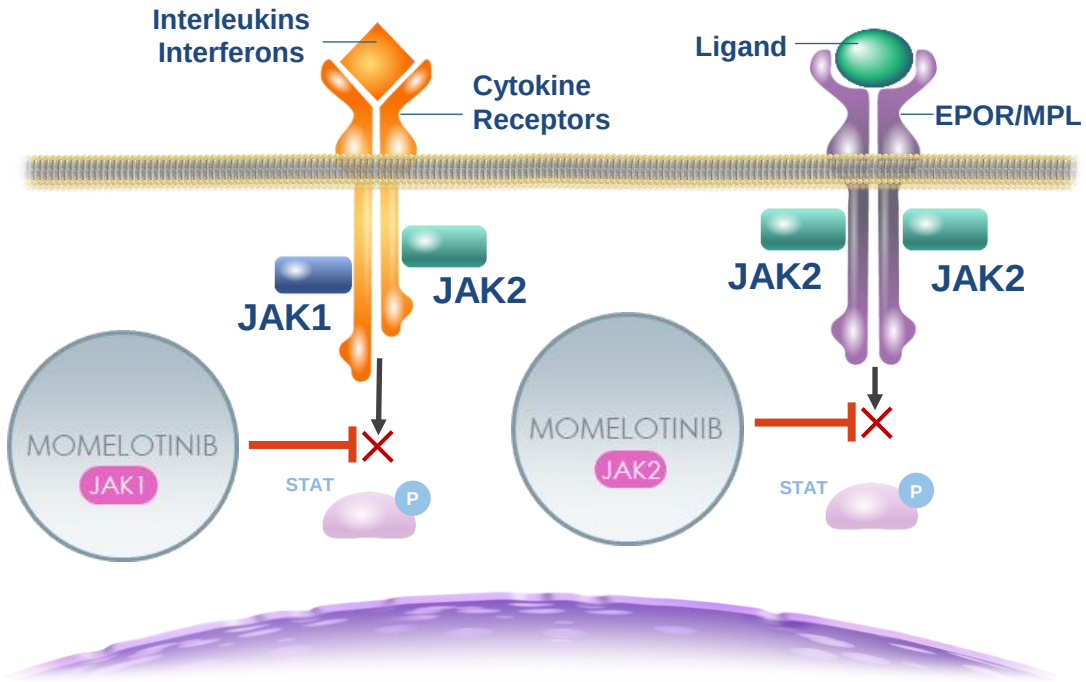
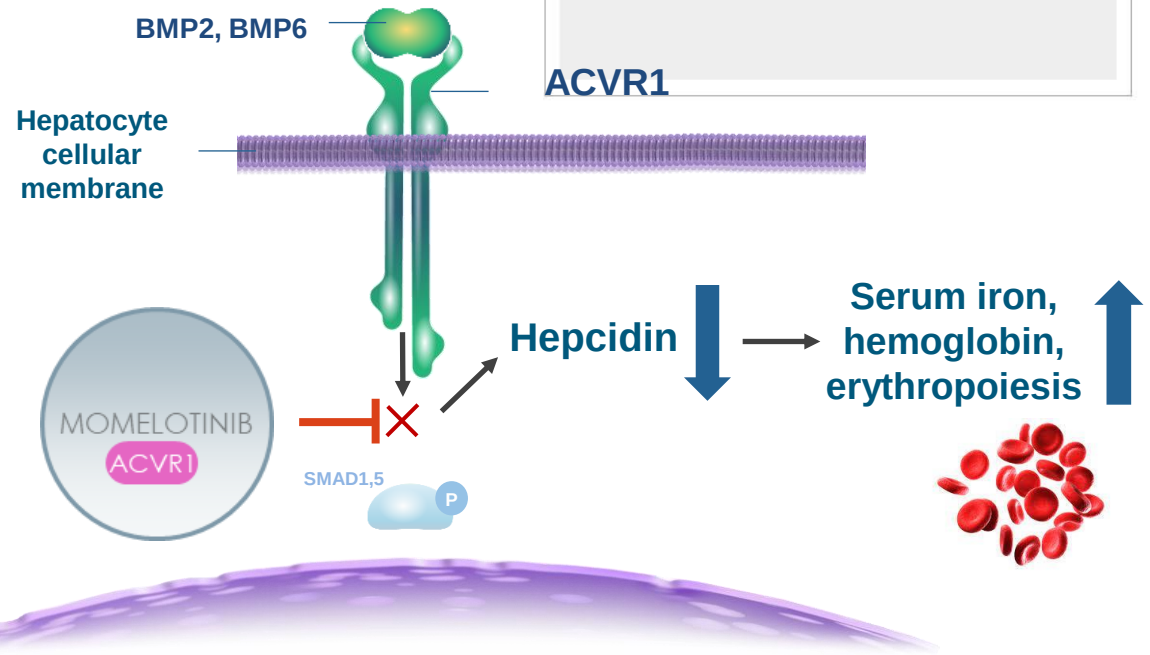


Dysregulated **JAK-STAT signaling** in MF drives overproduction of inflammatory cytokines, **bone marrow fibrosis, systemic symptoms,** and clonal proliferation resulting in extramedullary hematopoiesis and **splenomegaly**[1,2]



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 morphogenetic protein; EPOR, erythropoietin receptor; JAK, Janus kinase; MF, myelofibrosis; MPL, myeloproliferative leukemia protein; SMAD1/5, mothers against decapentaplegic homolog 1/5; STAT, signal transducer and activator of transcription.

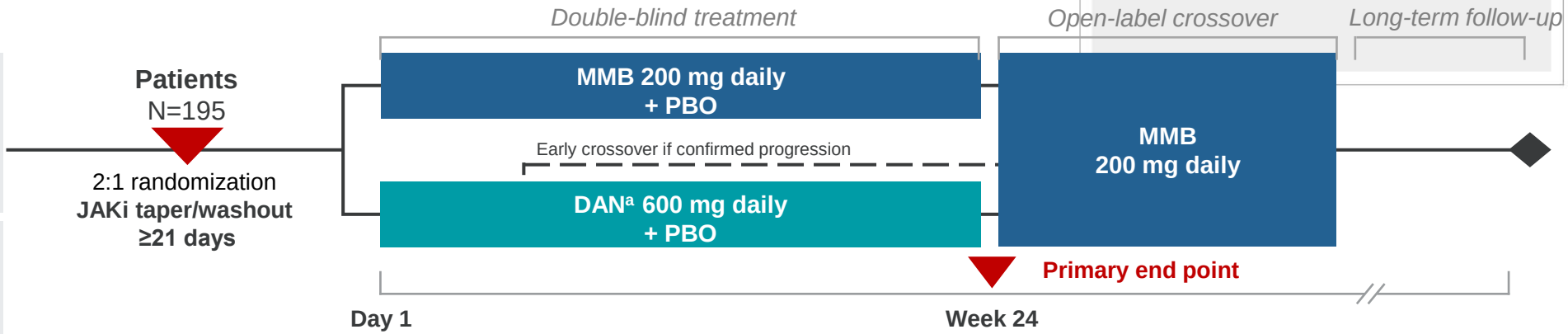
1. Chifotides HT, et al. *J Hematol Oncol*. 2022;15(1):7. 2. Verstovsek S, et al. *Future Oncol*. 2021;17(12):1449-1458. 3. Asshoff M, et al. *Blood*. 2017;129(13):1823-1830. 4. Oh ST, et al. *Blood Adv*. 2020;4(18):4282-4291.

MOMENTUM Is an Ongoing Phase 3 Study of Momelotinib Versus DAN in Symptomatic, Anemic, JAKi-Experienced Patients

Place video here

Previously treated with JAKi
Symptomatic (TSS ≥10)
Anemic (Hgb <10 g/dL)
Platelets ≥25×10^9/L

Stratification:
- TSS
- Palpable spleen length
- Transfused units in prior 8 weeks
- Study site



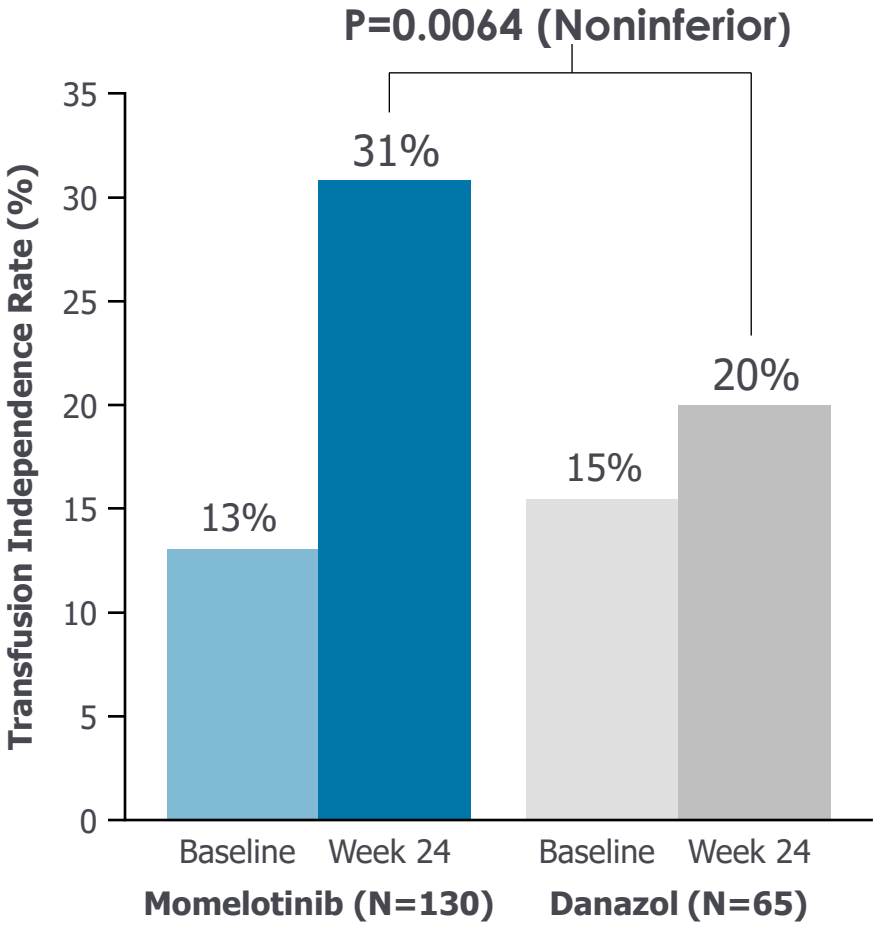
MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met[1,2]

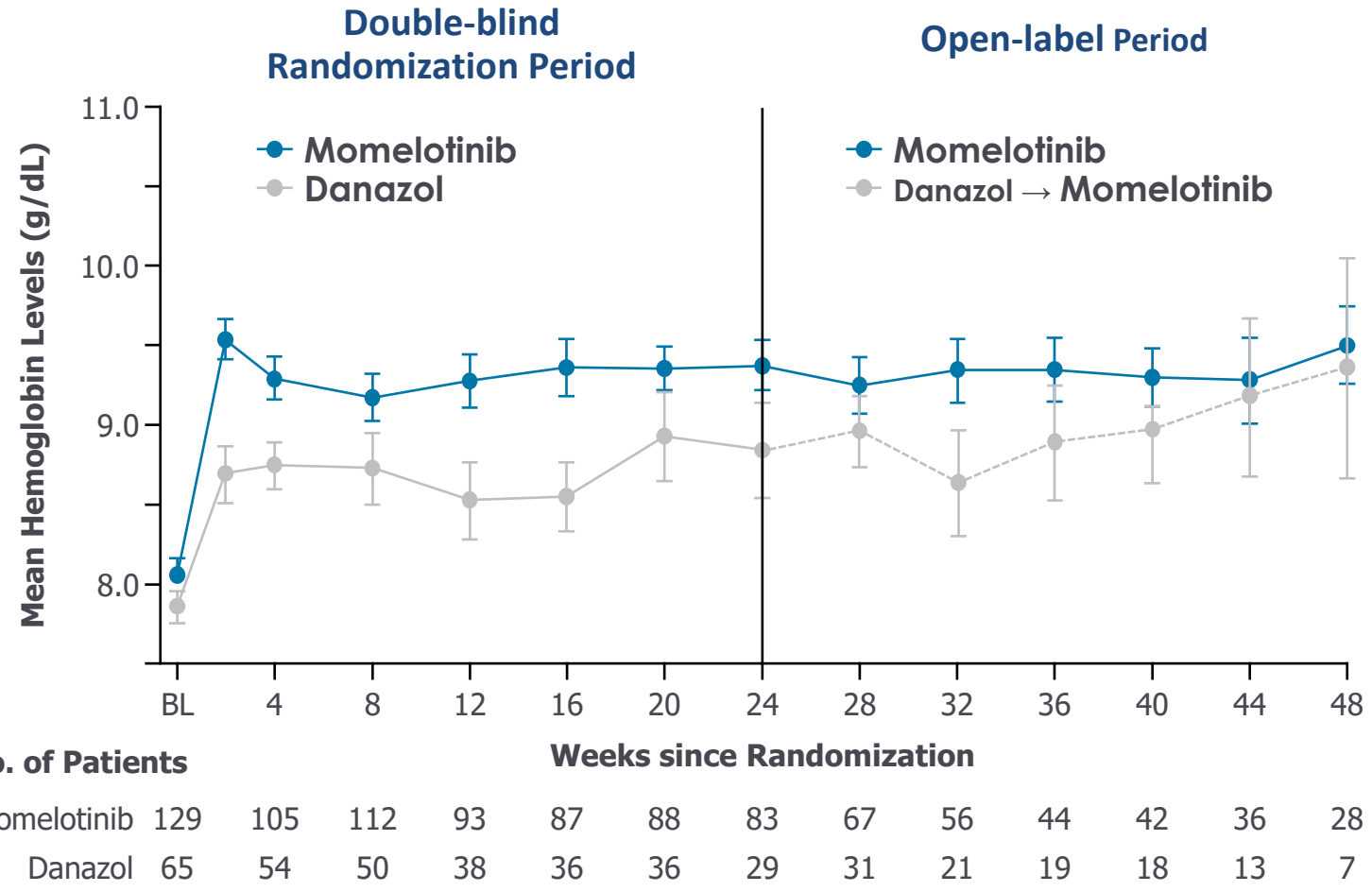
	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

ClinicalTrials.gov: NCT04173494.
[a]Danazol was selected as an appropriate comparator given its use to ameliorate anemia in patients with MF.[3-5] [b]TSS response defined as achieving ≥50% reduction in TSS over the 28 days immediately before the end of week 24 compared with baseline. [c]TI response defined as not requiring red blood cell transfusion in the last 12 weeks of the 24-week randomized period, with all Hgb levels during the 12-week interval of ≥8 g/dL. [d]SRR defined as achieving a ≥25% or ≥35% reduction in spleen volume from baseline.
DAN, danazol; FPE, first patient enrolled; Hgb, hemoglobin; JAKi, Janus kinase inhibitor; LPE, last patient enrolled; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; PBO, placebo; SRR, splenic response rate; TI, transfusion independence; TSS, total symptom score.
1. Mesa R, et al. Abstract presented at: 2022 ASCO Annual Meeting; June 3-6, 2022; Chicago, IL and Virtual. Abstract 7002. 2. Verstovsek S, et al. Abstract presented at: 2022 EHA Congress; June 9-12; 2022; Vienna, Austria and Virtual. Abstract S195. 3. Chifotides HT, et al. *J Hematol. Oncol.* 2022;15(1):7. 4. Naymagon L, et al. *Hemasphere*. 2017;1(1):e1. 5. Vannucchi AM, et al. *Ann Oncol*. 2015;26(suppl 5):v85-v99.

MOMENTUM: Momelotinib vs Danazol

Transfusion Independence at Week 24, Mean Hemoglobin Over Time





No. of Patients													
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

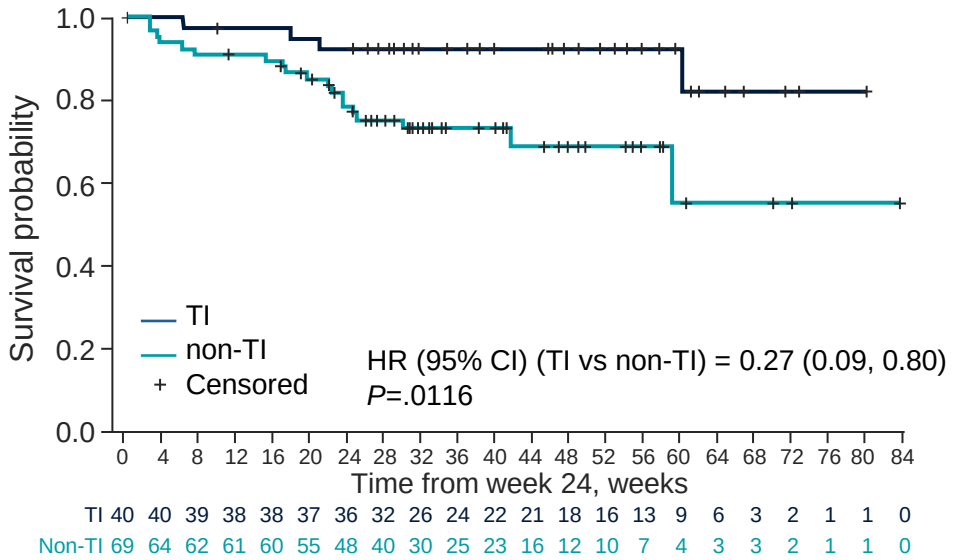
*Defined as not requiring red blood cell transfusion in the terminal 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥8 g/dL.

> Verstovsek S, et al. Presented at: 2022 EHA Congress; June 9-12, 2022. Vienna, Austria. Abstract S195.

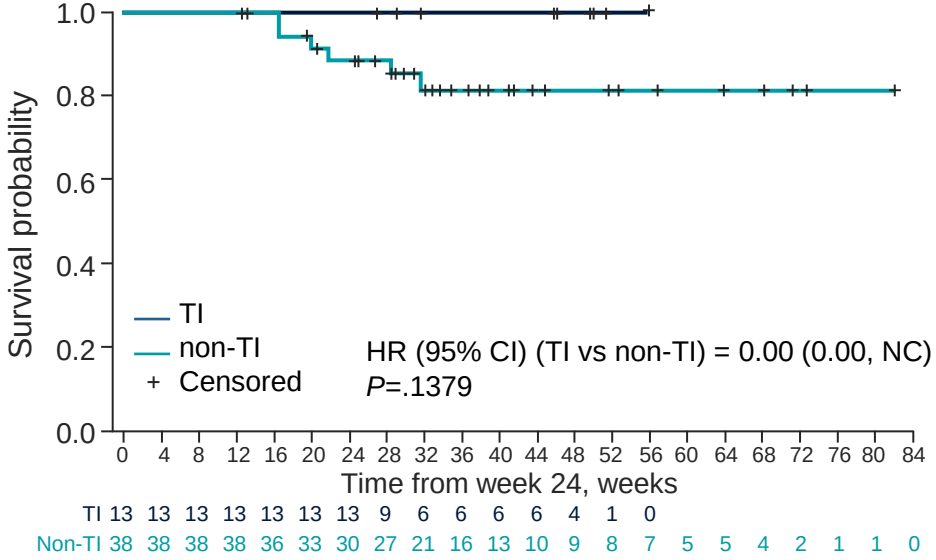
OS Was Improved in Patients Who Achieved Week 24 TI-R on Momelotinib, Including Those Randomized to DAN and Crossed Over to Momelotinib

Place video here

OS of patients originally randomized to momelotinib stratified by week 24 TI-R



OS of patients originally randomized to DAN stratified by week 24 TI-R



- For those patients randomized to momelotinib achieving week 24 TI-R, OS was significantly improved, consistent with observations in the SIMPLIFY studies
- Patients randomized to DAN achieving week 24 TI-R who then crossed over to momelotinib also trended toward longer OS

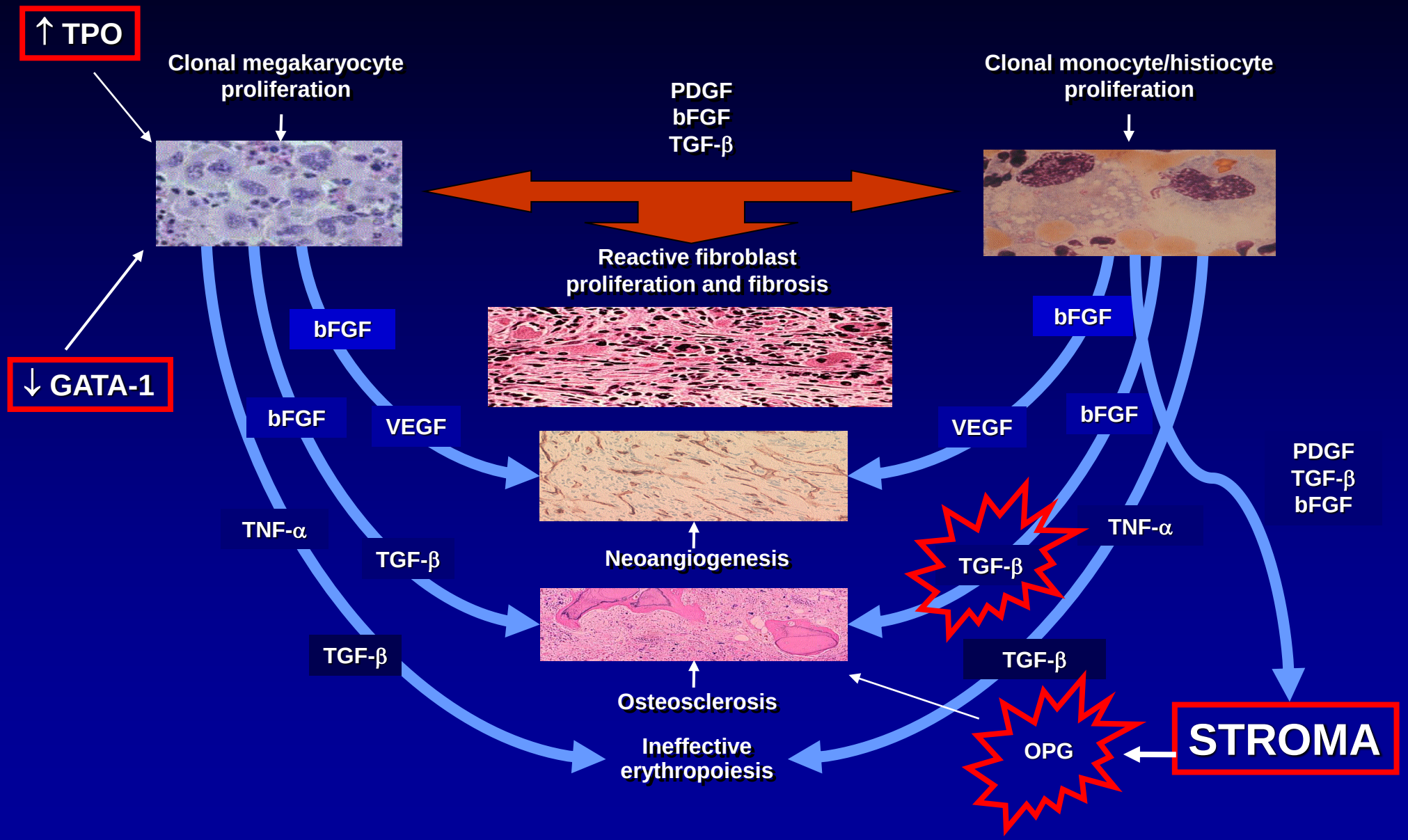
DAN, danazol; HR, hazard ratio; NC, not calculable; OL, open-label; OS, overall survival; TI, transfusion independence; TI-R, transfusion independence response; TR, transfusion-requiring.

2005

Novel Therapies for Myeloproliferative Diseases

Srdan Verstovsek, M.D., Ph.D.
Assistant Professor
Department of Leukemia
M. D. Anderson Cancer Center

MF: Treatment Targets



Future Directions in MPDs

- Thalidomide + prednisone based combinations (with etanercept, or imatinib, or cytoxan)
- Thalidomide analogs (CC-5013) +/- prednisone
- Proteasome inhibitors (bortezomib)
- Hypomethylation agents (decitabine, azacitidine)
- Gleevec and PEG Intron
- Tyrosine kinase inhibitors of c-kit, PDGFR A and B

4/2008

4/2021

Thank You

sverstov@mdanderson.org

Srdan Verstovsek, MD, PhD

Professor, Department of Leukemia

Division of Cancer Medicine

The University of Texas MD Anderson

Cancer Center

Houston, Texas