Current and Future Myelofibrosis Treatments

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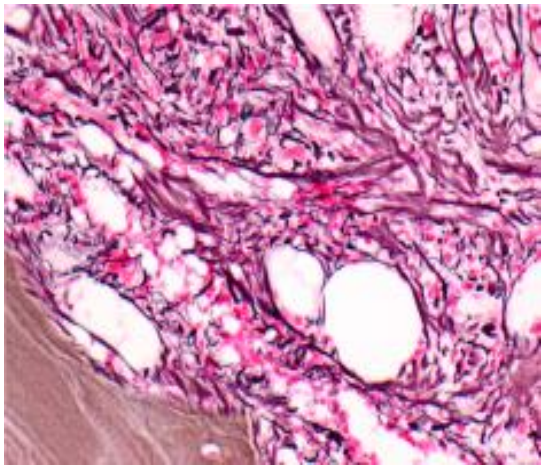
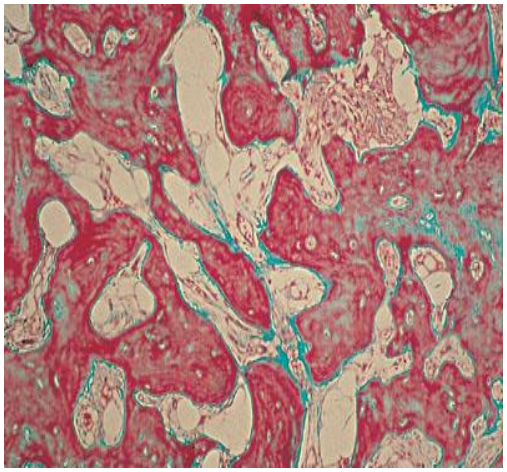
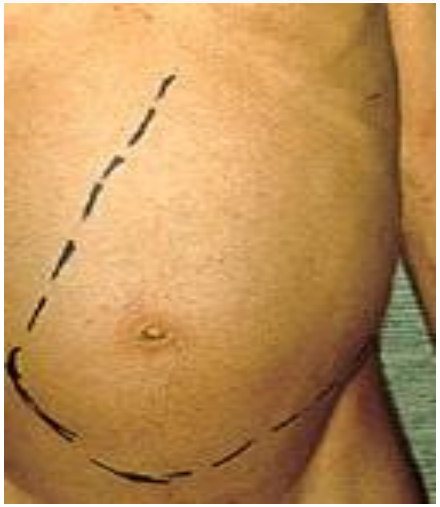
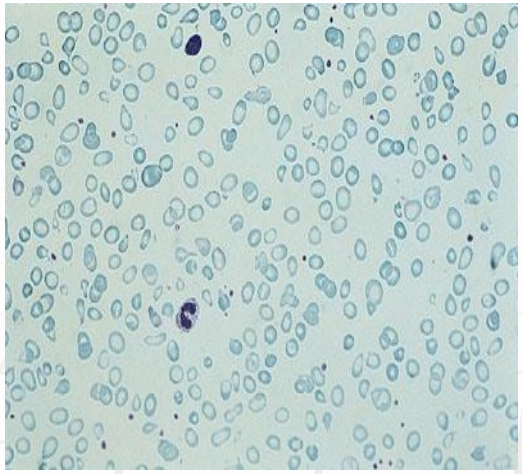
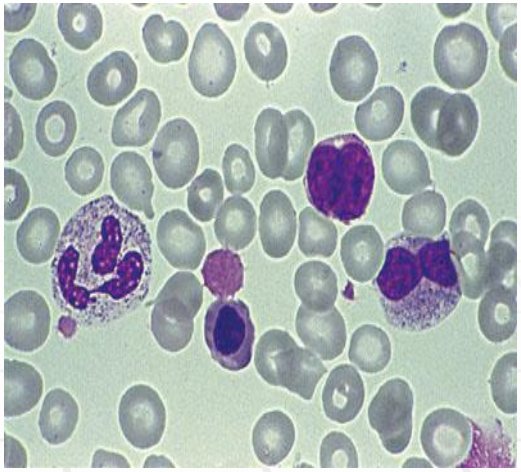
Myelofibrosis



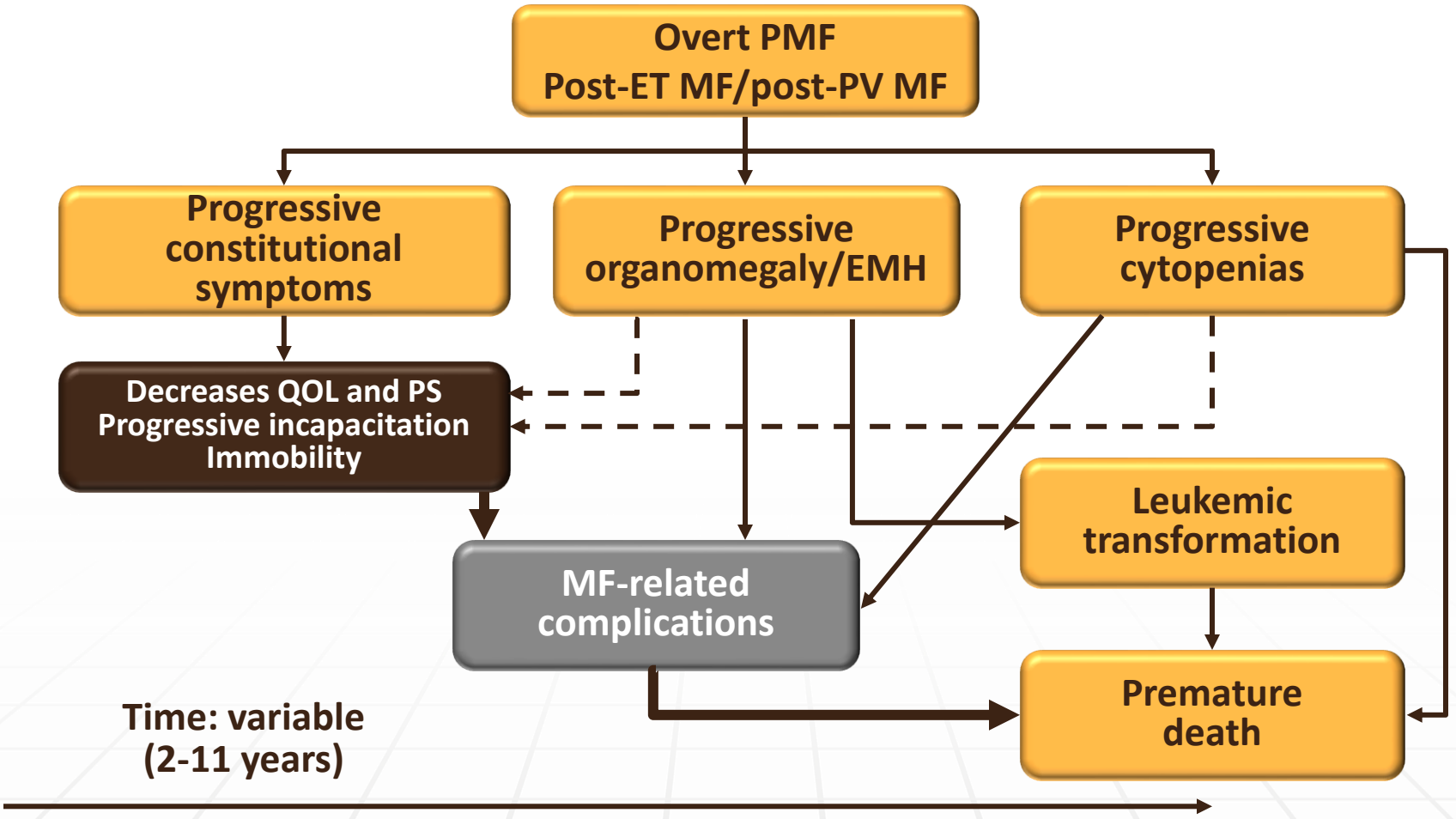








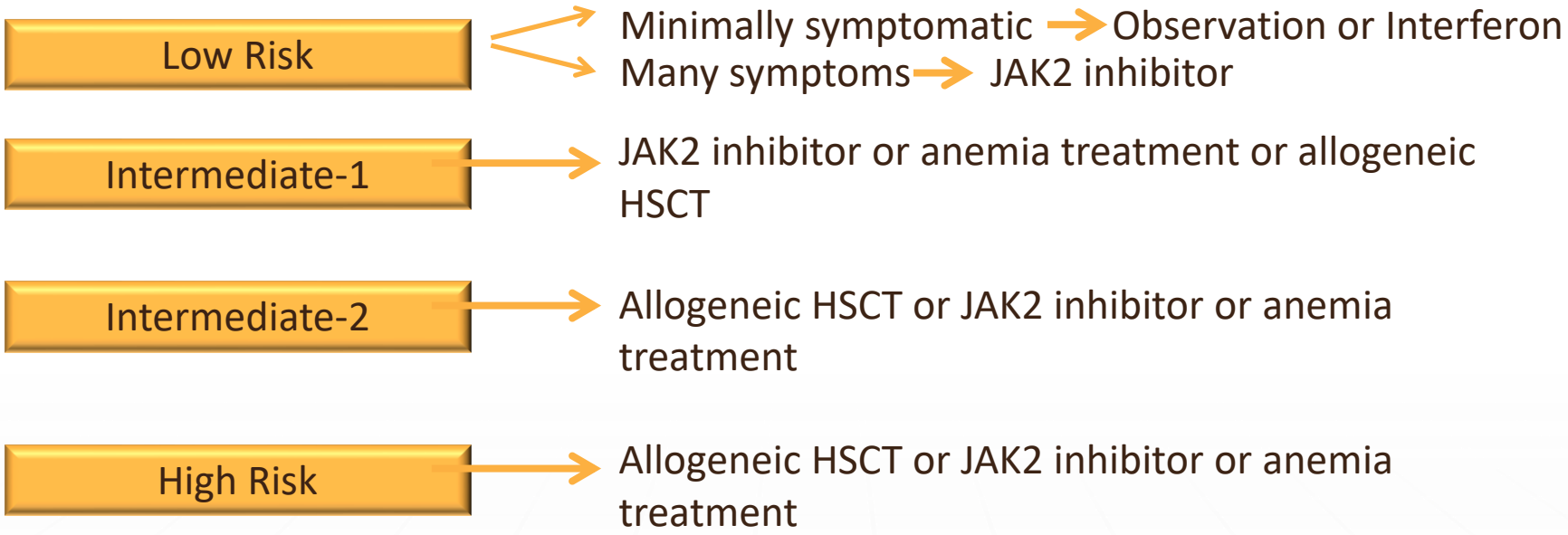
Disease Course and Complications in Patients with Myelofibrosis



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

Mughal TI ,et al. *Int J Gen Med.* 2014;7:89-101.

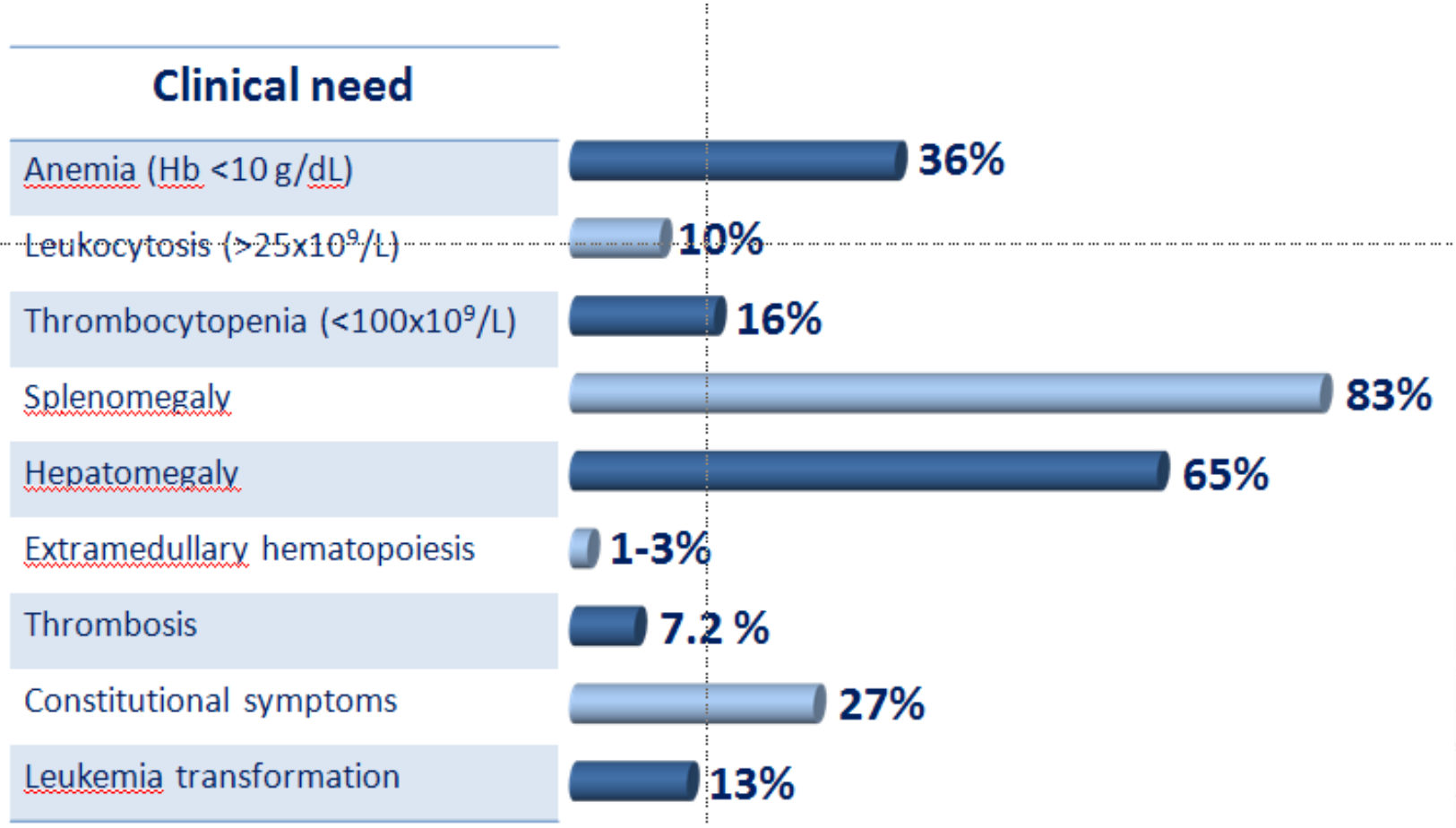
Current MF Treatment is Based on Risk and MF-related Symptoms/Signs



HSCT, hematopoietic stem cell transplantation.

1. Mesa RA. *Leuk Lymphoma.* 2013;54:242-51; 2. Geyer HL, Mesa RA. *Hematol.*2014 277-86.

Main Clinical Problems in Myelofibrosis



Passamonti F et al. Blood 2010;115:1703-8;
Barbui T et al. Blood 2010; 115;778-82; Passamonti F et al. Blood 2010; 116:2857-8

Patients are treated for specific problems, not based on prognosis

Medicines for Anemia

- *Prednisone*
- *Androgens (danazol)*
- *EPO*
- *Thalidomide or Lenalidomide +/- prednisone*

Medicines for Spleen

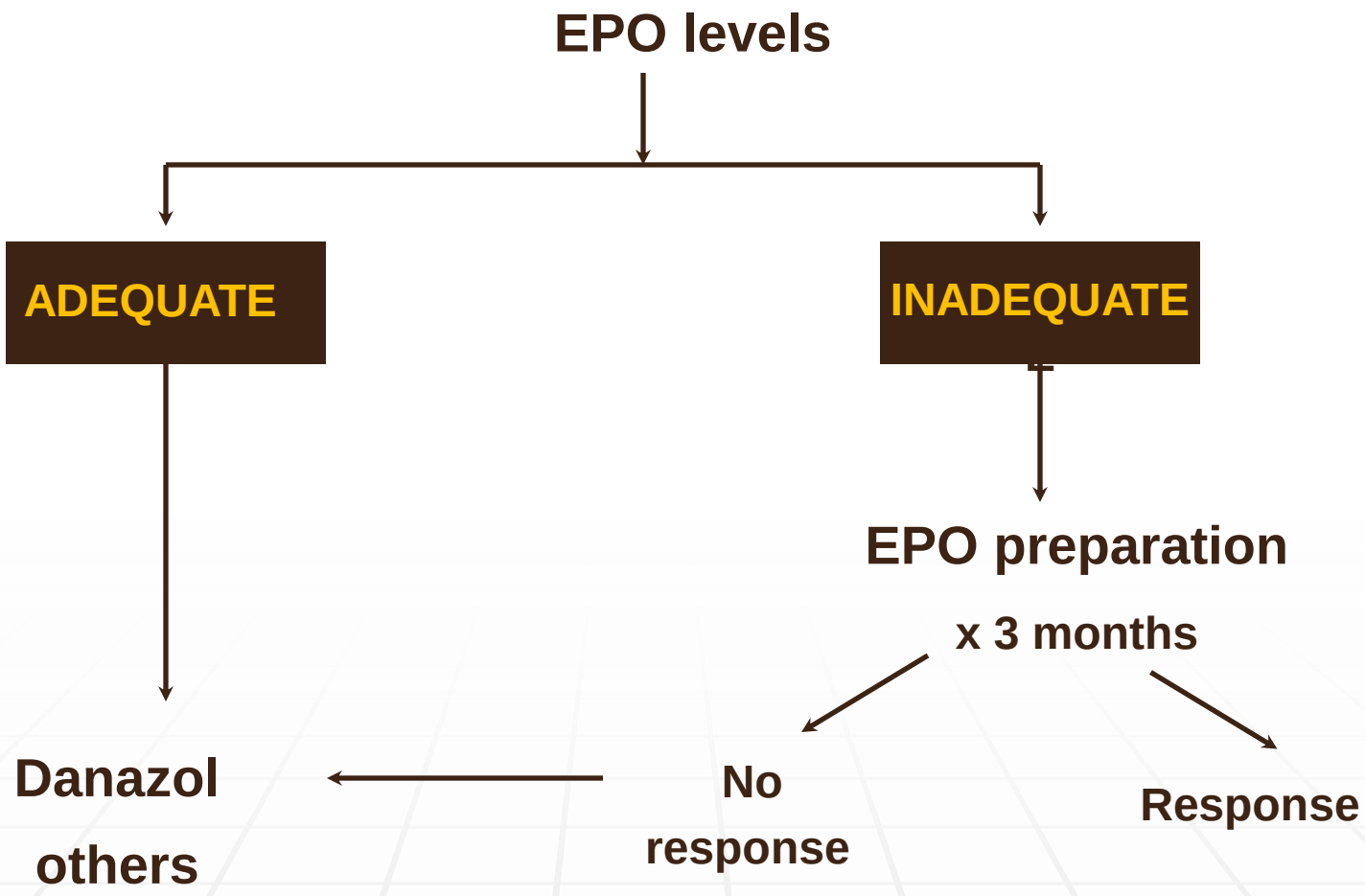
- *Ruxolitinib*
- *Hydroxyurea*
- *Busulfan*
- *Cladribine*

- *Splenectomy*
- *Splenic Radiation*

Medicines for Symptoms

- *Ruxolitinib*
- *Prednisone*

Initial Approach to the Treatment of Anemia of Myelofibrosis



1. Mesa RA. *Leuk Lymphoma.* 2013;54:242-51; 2. Geyer HL, Mesa RA. *Hematol.*2014 277-86.

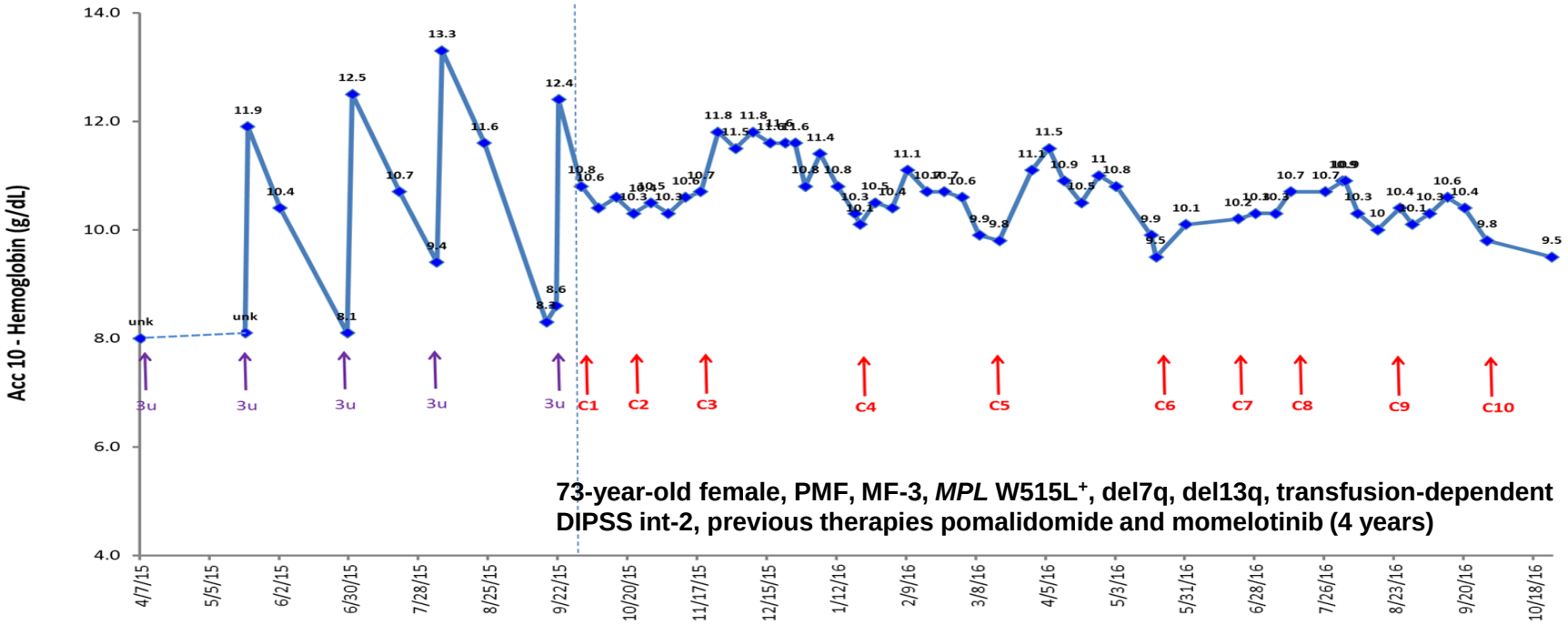
Phase II Study of Sotatercept (ACE-011) in Myeloproliferative Neoplasm-Associated Myelofibrosis and Anemia

ASH Abstract 478

Bose P, Daver N, Jabbour EJ, Pike A, Newberry KJ, Zhou L, Pierce S, Wang X, Kantarjian HM, Verstovsek S

Sotatercept in MF

- Efficacy: ~40% response rate using 0.75 mg/kg dose Q3W



Bose P, et al. *Blood.* 2016;128: Abstract 478.

Splenectomy in Myelofibrosis

ASSOCIATED RISKS

- up to 40% morbidity
- up to 10% mortality
- Liver enlargement and failure
- Higher acute transformation rate?
- Average survival post splenectomy: 18 months

CONTRAINDICATION

Thrombocytosis

MAIN INDICATIONS

- Symptomatic splenomegaly unresponsive to treatment
- Severe refractory anemia and thrombocytopenia
- Unresponsive constitutional symptoms
- Uncontrollable hemolysis
- Portal hypertension

Splenic Irradiation in Myelofibrosis

INDICATIONS

- Symptomatic splenomegaly in poor candidates to surgery

- Severe pain from splenic infarction

RESULTS

- Dose: variable, median 2.8 Gy, fractioned

- Effect duration: median 6 mos.

CONTRAINDICATION

As preparation for splenectomy

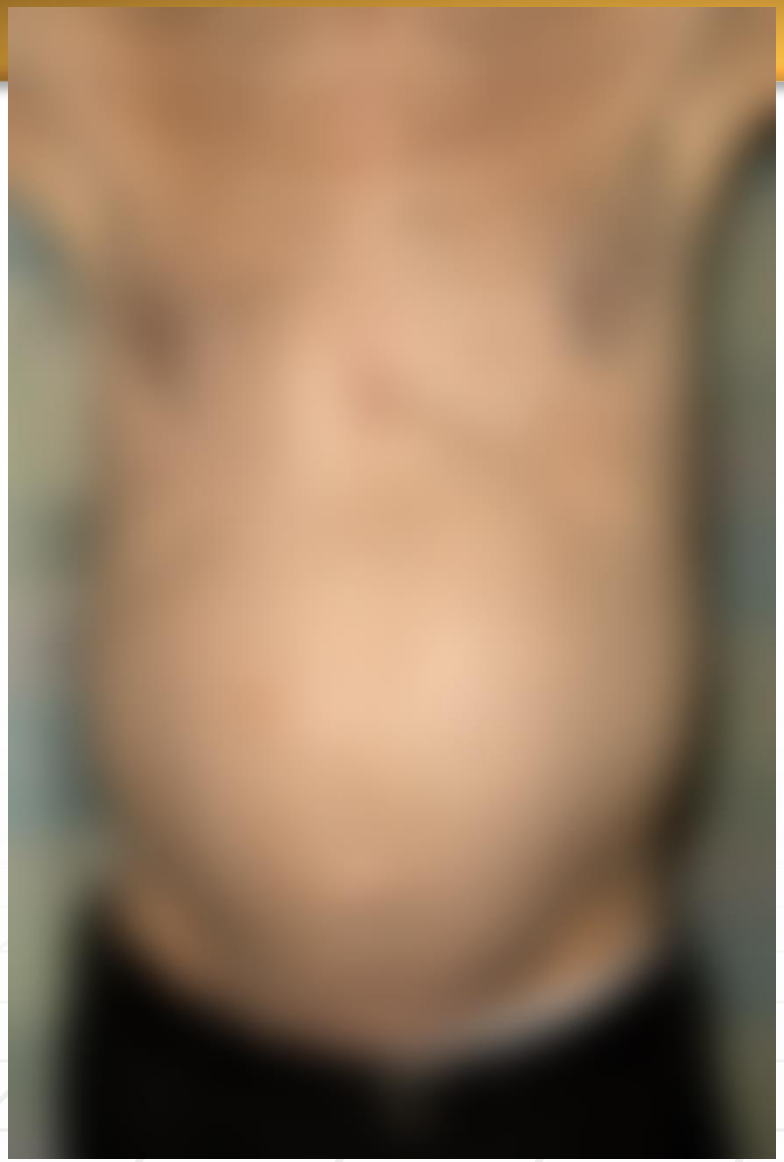
ASSOCIATED RISK

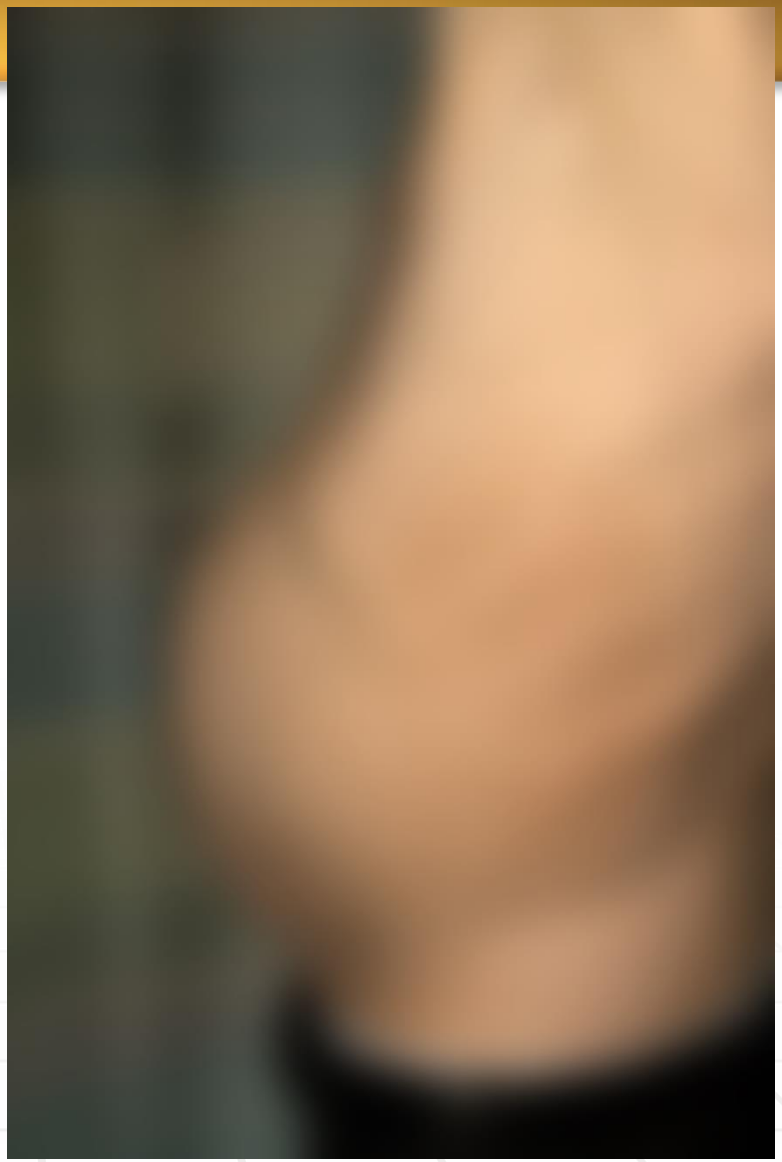
Long-lasting cytopenias (43%)

Ruxolitinib

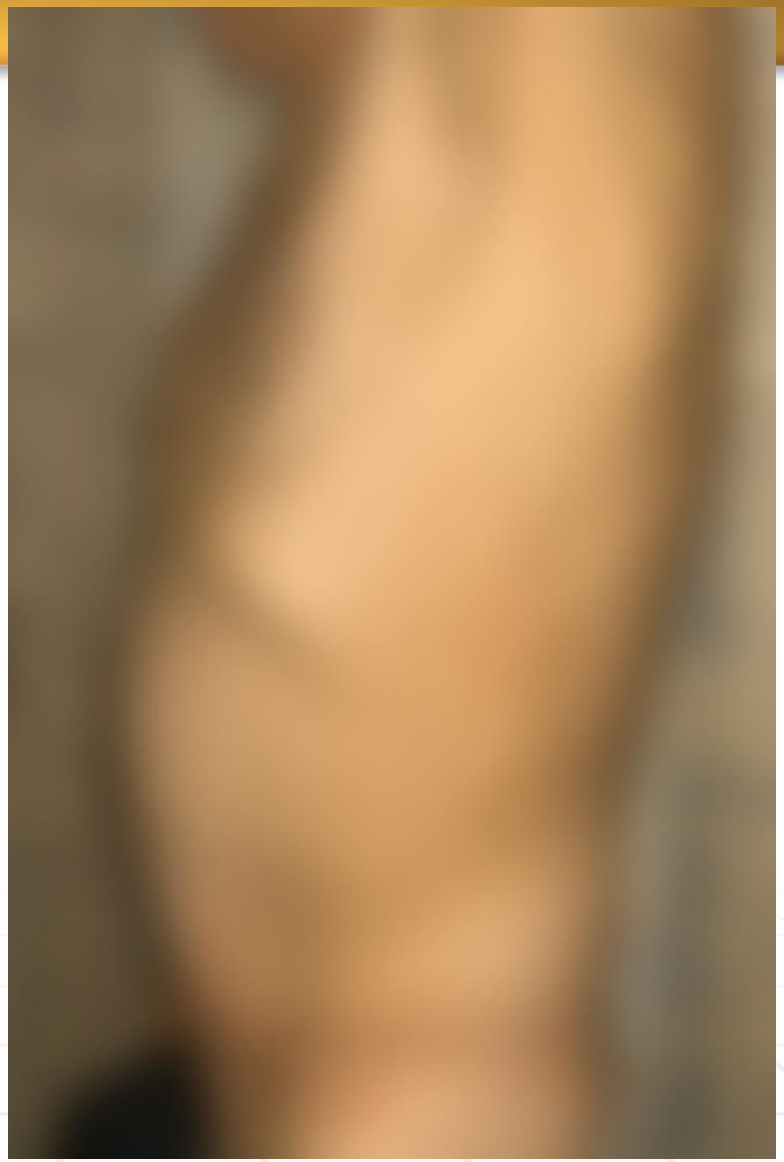
- Not selective for mutated JAK2V617F enzyme (ATP binding inhibitors)
- Inhibit JAK-STAT pathway
- Lowering of platelets and red blood cells is expected side effect due to inhibition of wild type (normal) JAK2
- Elimination of the disease very unlikely

Patient with Myelofibrosis



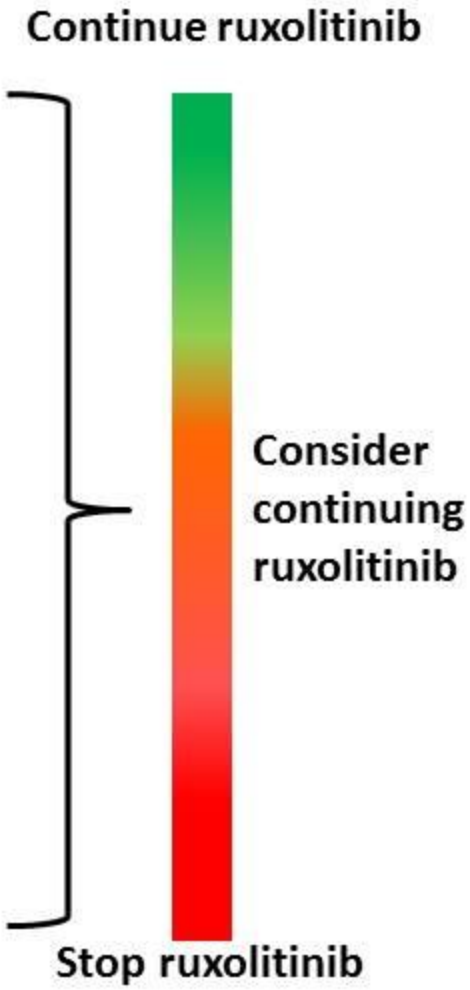


MF Patient after 2 Months of Therapy



British Guidelines for myelofibrosis & use of JAK inhibitors

Symptoms	Spleen	Haematological toxicity
Clear	Clear	No
		Yes
	Suboptimal	No
		Yes
Suboptimal		No
		Yes
Minimal	Equivocal	No
		Yes
None	None	No
		Yes

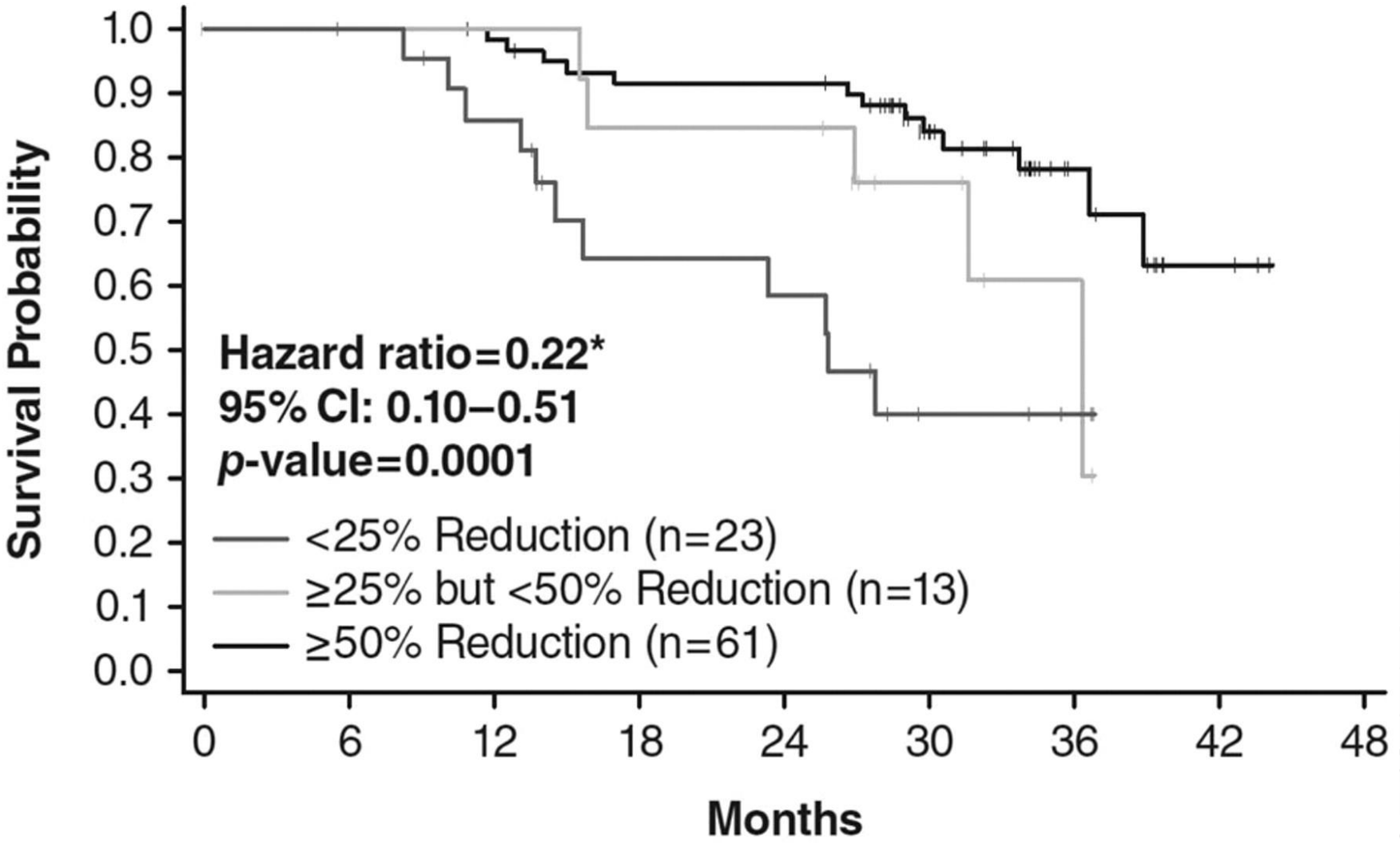


Reilly JT, et al. British Journal of Haematology. 2014; 167 (3): 418-420

British guidelines for Myelofibrosis & use of JAK Inhibitors

- Target spleen and symptom reduction will be **individual** for each patient
- Starting dose selected based on platelet number; anemia is NOT contraindication for use of JAK2 inhibitors
- Dose should be modified to the **maximum** tolerated where response is not adequate, and treatment should be continued for 6 months
- Decision to stop ruxolitinib will depend upon a **combination** of different factors, including benefit and presence or absence of toxicity
- Avoid abrupt interruption of ruxolitinib in patients responding well to therapy
- Development of anemia DOES NOT affect benefits of JAK2 inhibitor

Overall survival of patients by degree of spleen length reduction on ruxolitinib



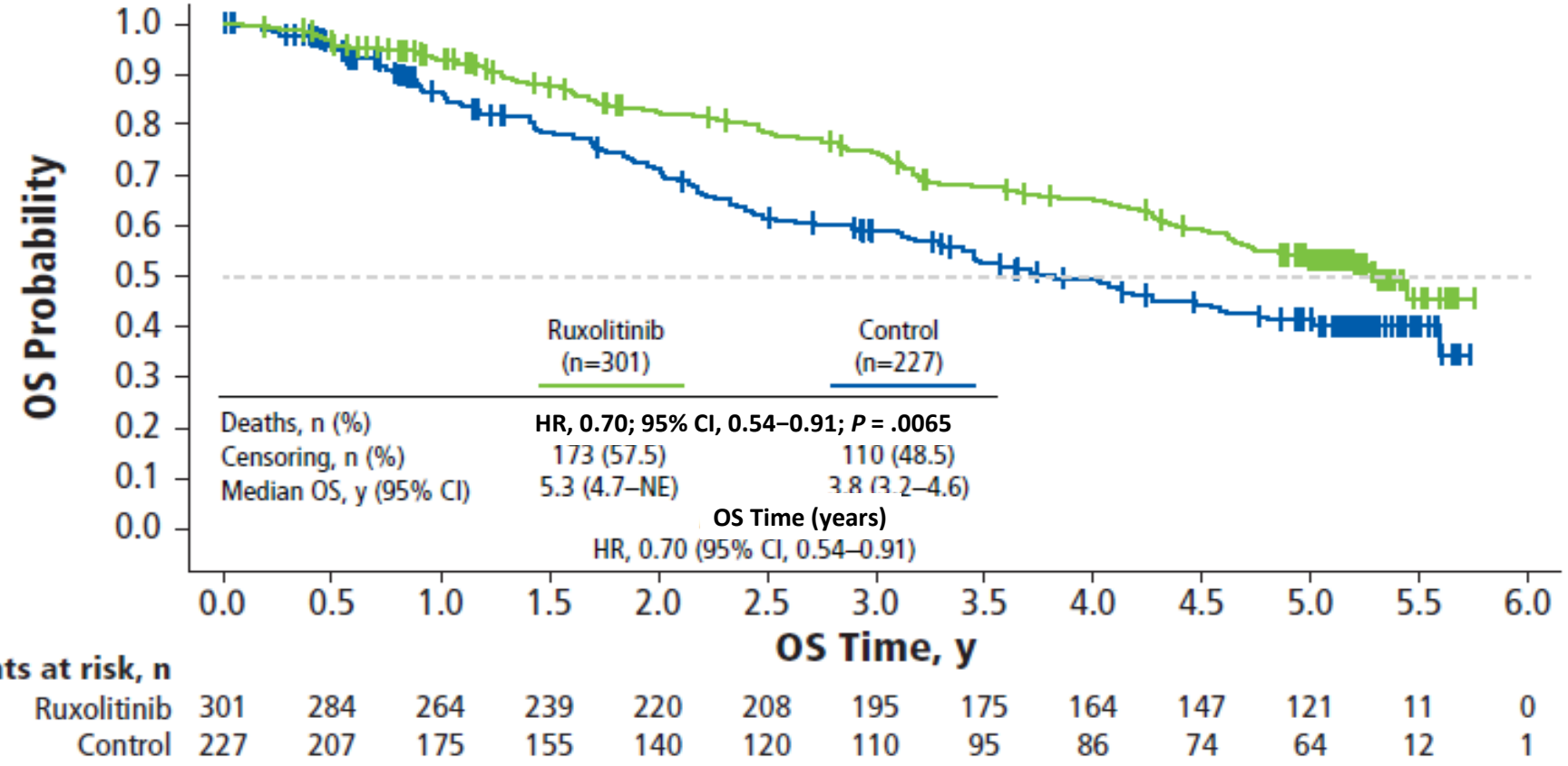
Verstovsek S et al. Blood 2012; 120(6):1202-1209

Present time

Almost 9 years

Ruxolitinib Randomized Trials: Overall Survival

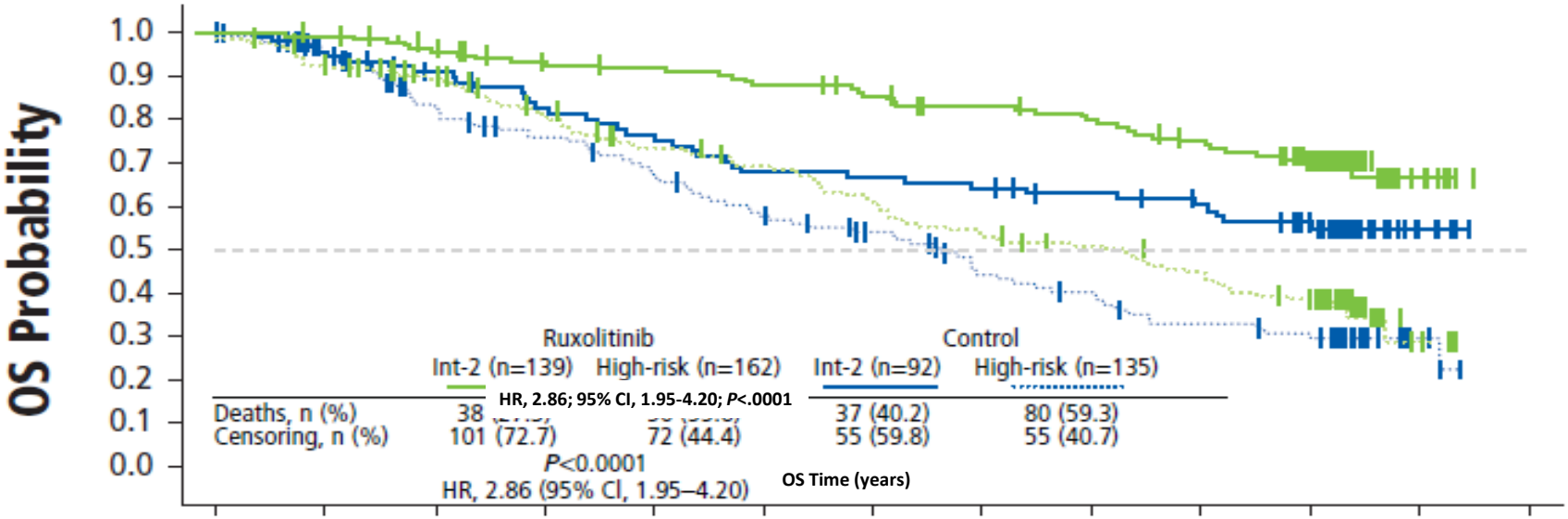
The risk of death was reduced by 30% among patients randomized to ruxolitinib compared with control patients (median overall survival (OS): ruxolitinib, 5.3 years; control, 3.8 years; HR (ruxolitinib vs control), 0.70; 95% CI, 0.54-0.91; *P* = .0065)



Verstovsek S, et al. *Blood.* 2016;128: Abstract 3110.

Results: OS Among Ruxolitinib-Treated Patients, Stratified by IPSS Risk Status

Among patients randomized to ruxolitinib, intermediate-2 (int-2) patients had longer median OS than those with high-risk disease (median OS: int-2, not reached, estimated, 8.5 years; high-risk, 4.2 years; HR (high risk vs int-2), 2.86; 95% CI, 1.95-4.20; *P*<.0001)



Patients at risk, n

Ruxolitinib int-2	139	137	129	120	117	114	110	101	98	89	73	7	0
Ruxolitinib high-risk	162	147	135	119	103	94	85	74	66	58	48	4	0
Control int-2	92	84	75	67	62	55	54	52	48	44	37	7	0
Control high-risk	135	123	100	88	78	65	56	43	38	30	27	5	1

Verstovsek S, et al. *Blood.* 2016;128: Abstract 3110.

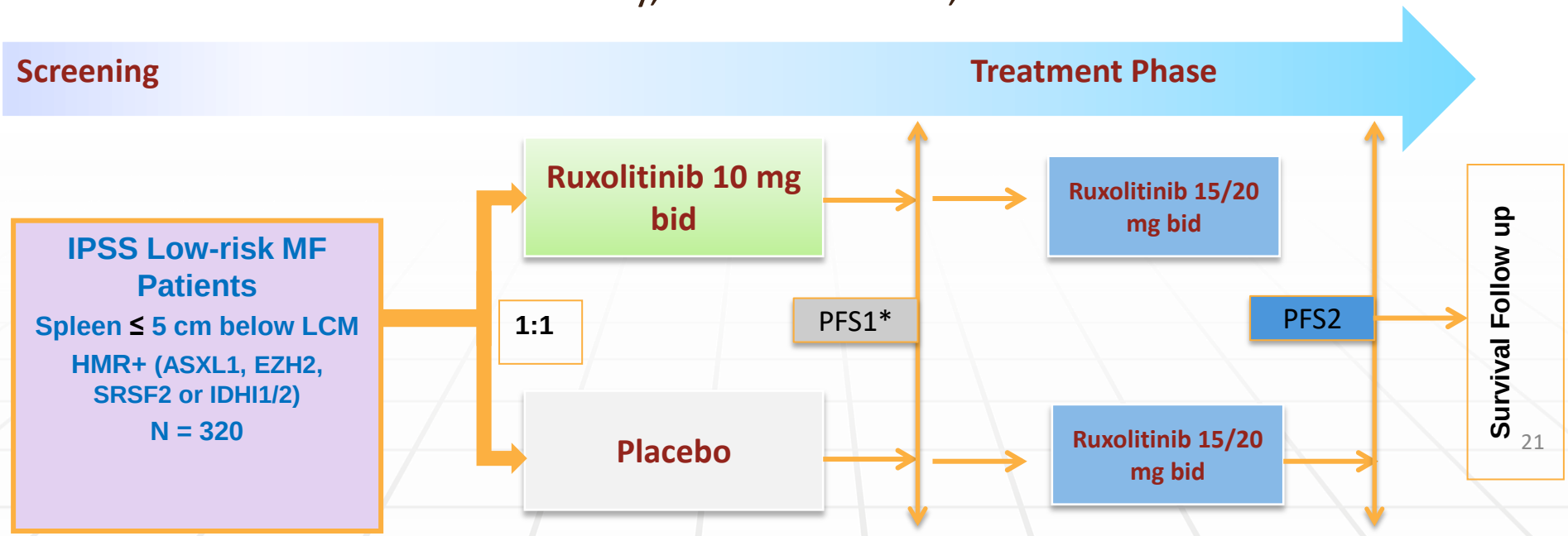
IPSS, International Prognostic Scoring System

ReTHINK: prevention study in early MF

Objectives & Study design

Primary Objective : Progression-free survival

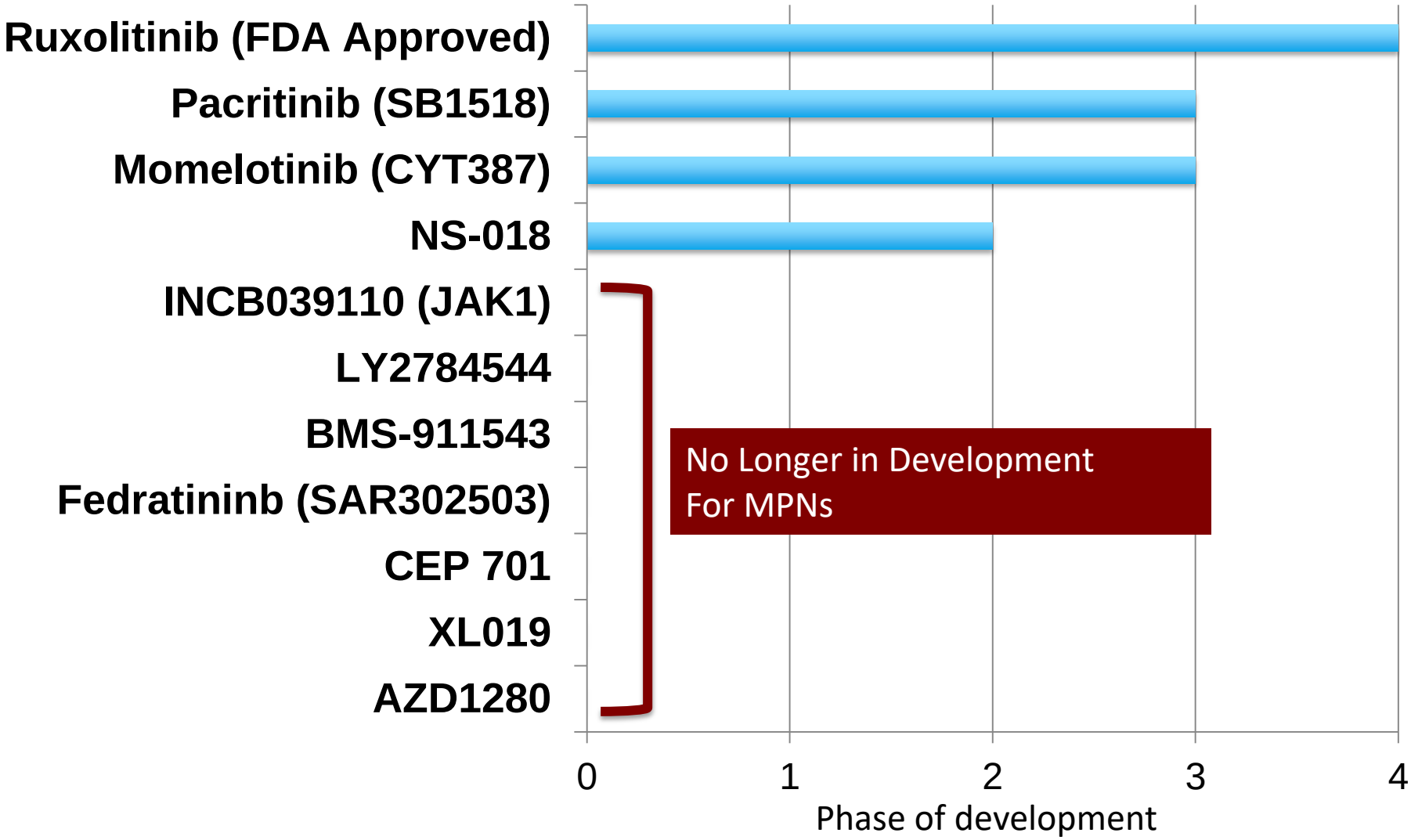
Secondary Objectives :Time to progression in spleen/symptoms, Safety, Overall Survival,



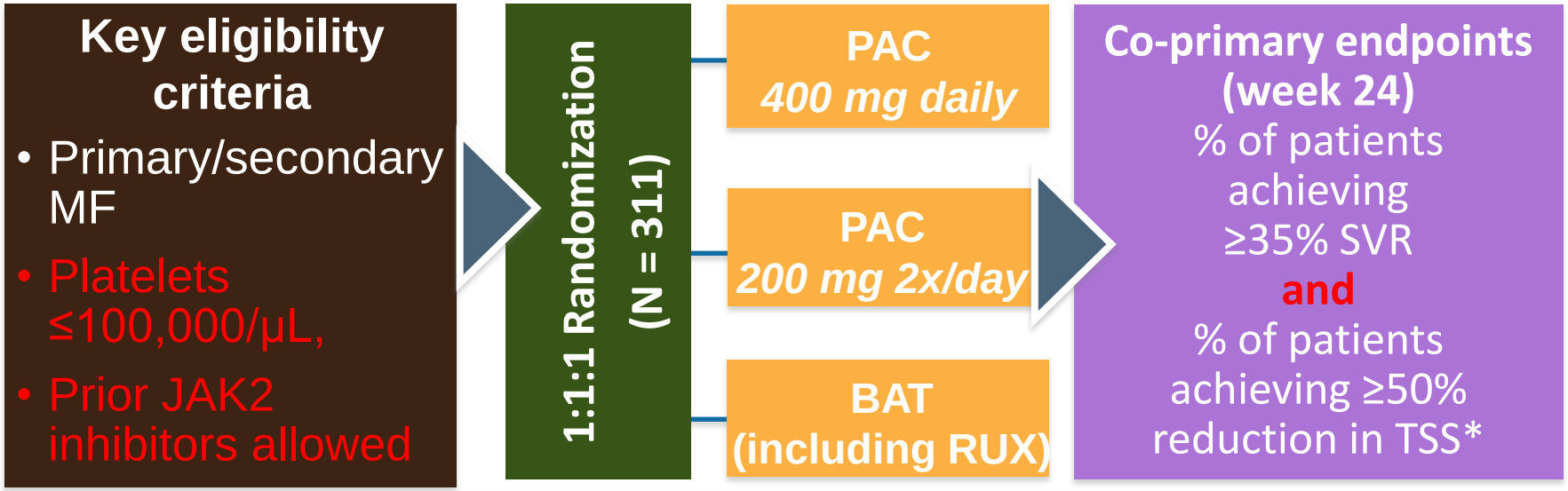
Myelofibrosis: "Clinical needs"-oriented current therapy

Clinical need	Drugs / Intervention	
Anemia	• Prednisone • Danazol • erythropoietin	• Thalidomide • Lenalidomide
Symptomatic splenomegaly	• Ruxolitinib • Hydroxyurea	• Cladribine, IMIDs • Splenectomy
Extramedulary hematopoiesis	• Radiation therapy	
Hyperproliferative (early) disease	• Interferon	
Risk of thrombosis	• Low-dose ASA	
Constitutional symptoms/ QoL	• Ruxolitinib • Prednisone	
Accelerated/blastic Phase	• Hypomethylating agents	
Improved survival	• Allo SCT • Ruxolitinib	

JAK Inhibitors and Status of Development: *Myelofibrosis as lead indication*



Pacritinib
PERSIST-2 Phase III Study Design



*TSS, total symptom score by MPN-SAF 2.0
SVR, spleen volume reduction;

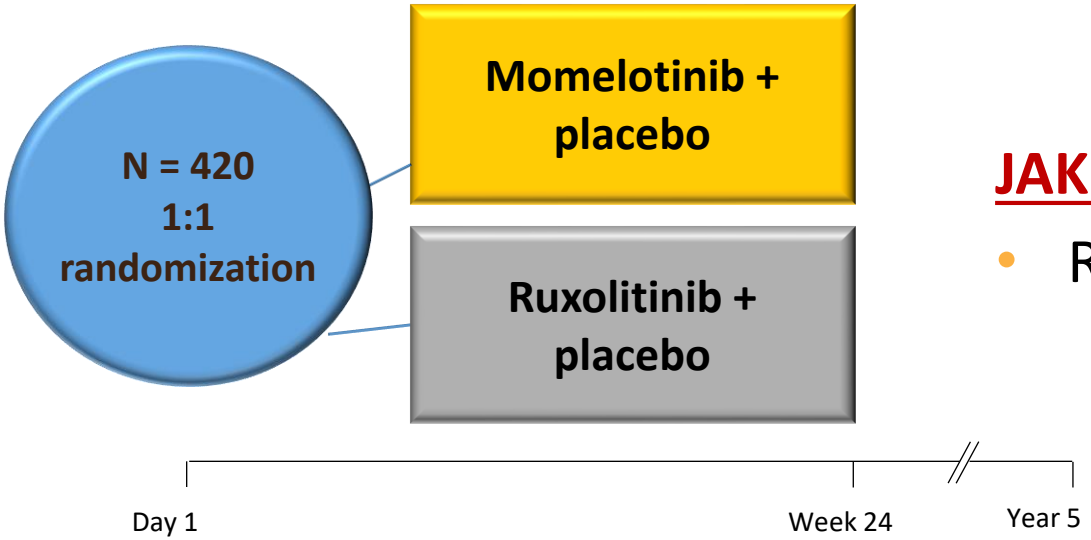
- Crossover from BAT (best available therapy) allowed after progression (anytime) or at week 24
- **Study objectives:**
  - **Primary: Efficacy of pooled PAC arms vs. BAT**

Mascarenhas J, et al. *Blood.* 2016;128: Abstract LBA-5.

Key Efficacy Results From PERSIST-2 *Phase 3*

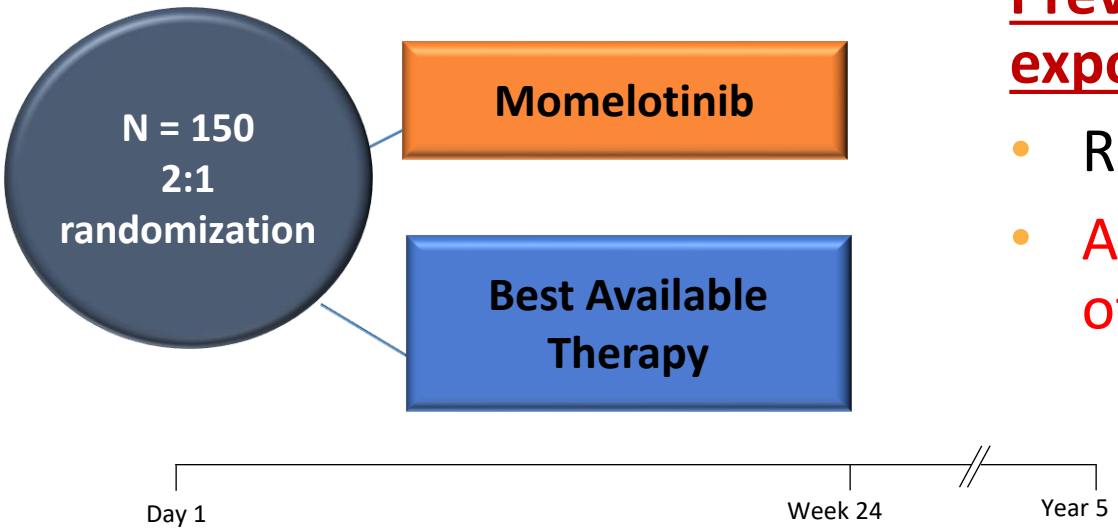
- PERSIST-2 trial met one of its two primary endpoints
  - Patients treated with pacritinib demonstrated a statistically significant response rate in spleen volume reduction in patients with myelofibrosis treated with pacritinib compared with BAT, including ruxolitinib
  - The primary endpoint of ≥ 50 percent reduction in total symptom score was not met
  - HOWEVER: PAC 2x/day appeared more effective than PAC daily versus BAT for BOTH spleena nd symptom control
  - Plan for more studies to define proper dose and schedule of PAC

Phase 3 SIMPLIFY Studies of Momelotinib for Myelofibrosis



JAK inhibitor naïve

- Randomized, Double Blind



Previous JAK inhibitor exposure

- Randomized, Open Label
- Allows continuation/restart of ruxolitinib on BAT arm

Phase 3 SIMPLIFY Studies (Momelotinib): Top-line Results, November 2016

- SIMPLIFY-1: Momelotinib vs ruxolitinib
  - Met primary endpoint of splenic response BEING SIMILAR between two treatments
  - Did not meet secondary endpoint: was LESS effective for symptom control
  - Improvement in anemia-related endpoints with momelotinib

- SIMPLIFY-2: Momelotinib vs BAT
  - Did not meet primary endpoint: was NOT better for spleen than BAT

Gilead, Nov 2016 press release

Thank You

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