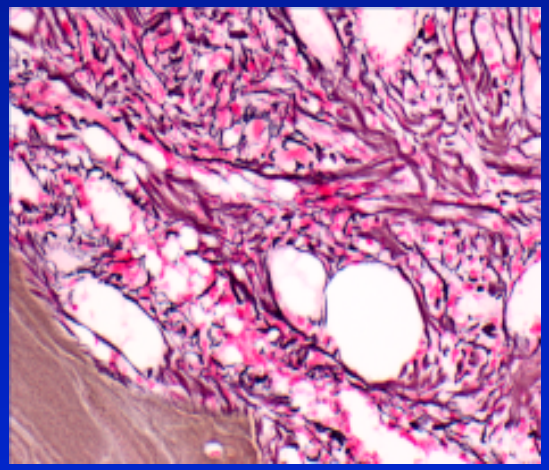
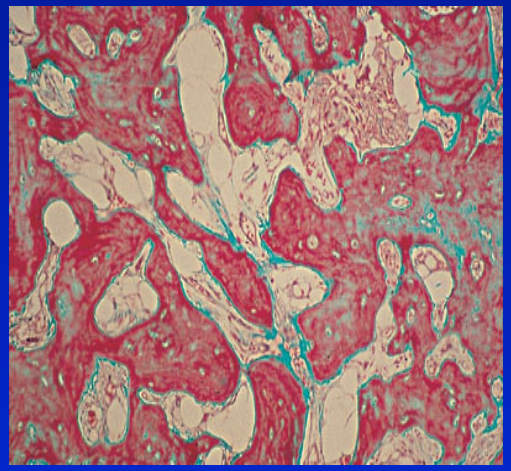
Primary myelofibrosis and new treatment

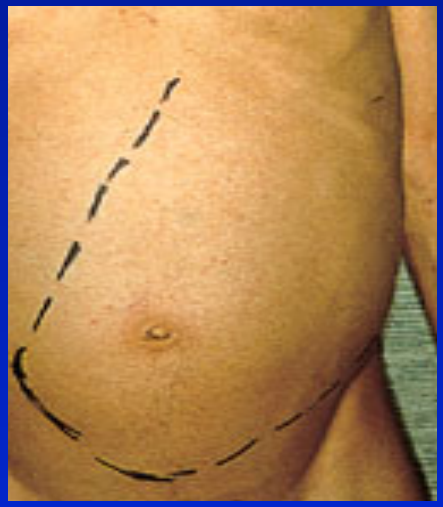
- Clonal myeloproliferative neoplasm characterized by a proliferation of predominantly megekariocytes and granulocytes in the bone marrow.
- Prefibrotic phase-
- Fibrotic phase

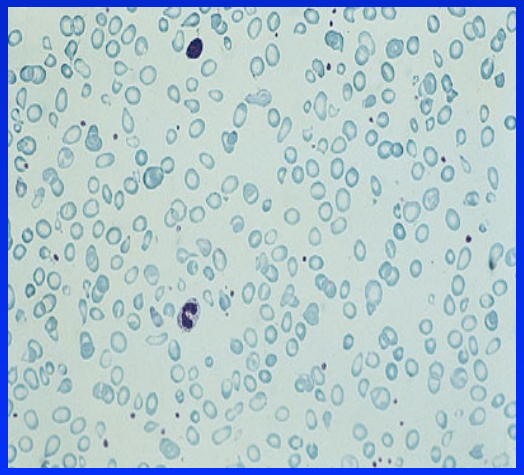
- Major criteria
- Presence of megakaryocyte proliferation and atypia, with reticulin and/or collagen fibrosis
- Not meeting WHO criteria WHO BCR-ABL + chronic myeloid leukemia, PV, myelodysplastic syndrome or other myeloid neoplasms.
  Demonstration of JAK2V617F or other clonal markers
- Minor criteria
  Leukoerytroblastosis
  Increase in serum lactate dehydrogenase level,
  Anaemia,
  Splenomegaly

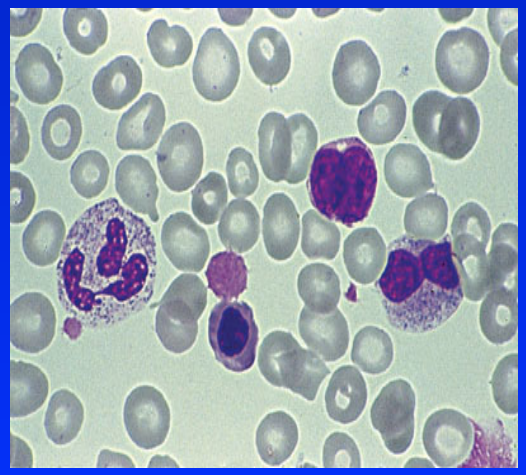
Myelofibrosis











Diagnosis of myelofibrosis

Physical exam	Bone marrow biopsy	Blood analysis
Palpable splenomegaly	Fibrotic or hypercellular bone marrow	Anemia
	Clonal marker or absence of reactive fibrosis	Leukoerythroblastosis
	Does not meet criteria for other myeloid disorder	Increased serum lactate dehydrogenase (LDH)

- Major WHO diagnostic criteria[3]
- Minor WHO diagnostic criteria[3]

Diagnosis requires meeting all 3 major criteria and at least two minor criteria.

1. Barbui T, et al. *J Clin Oncol*. 2011; 29: 761-770;
2. Chou JM, et al. *Leuk Res*. 2003; 27: 499-504;
3. 2008 WHO Diagnostic Criteria for PMF (Vardiman JW, et al. *Blood*. 2009; 114: 937-951).

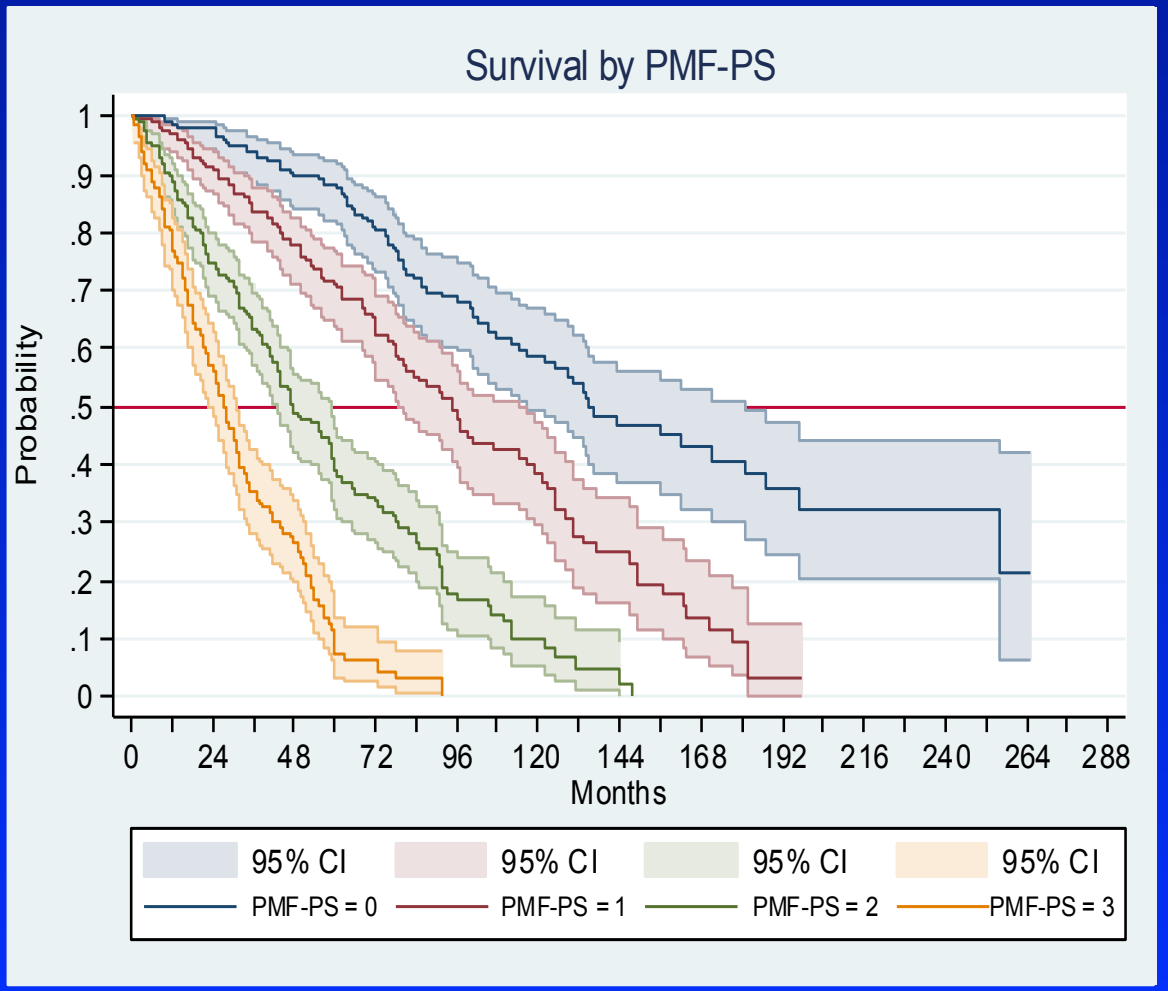
International Prognostic Scoring System (IPSS): Risk classification of PMF at presentation

Prognostic factors

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

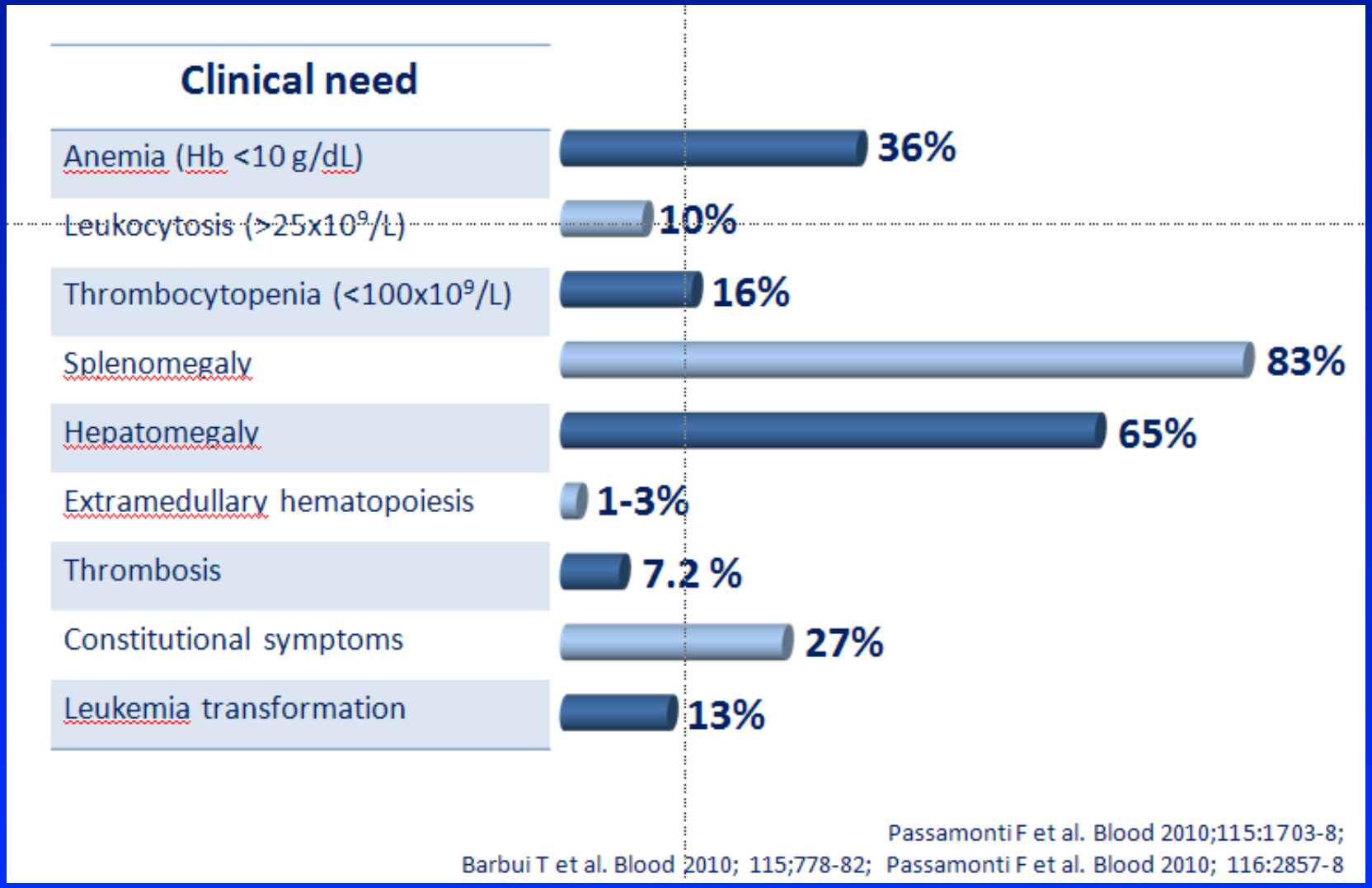
Risk groups #factors

• Low	0
• Intermediate-1	1
• Intermediate-2	2
• High	≥ 3



Cervantes et al., Blood 2009;113:2895-2901

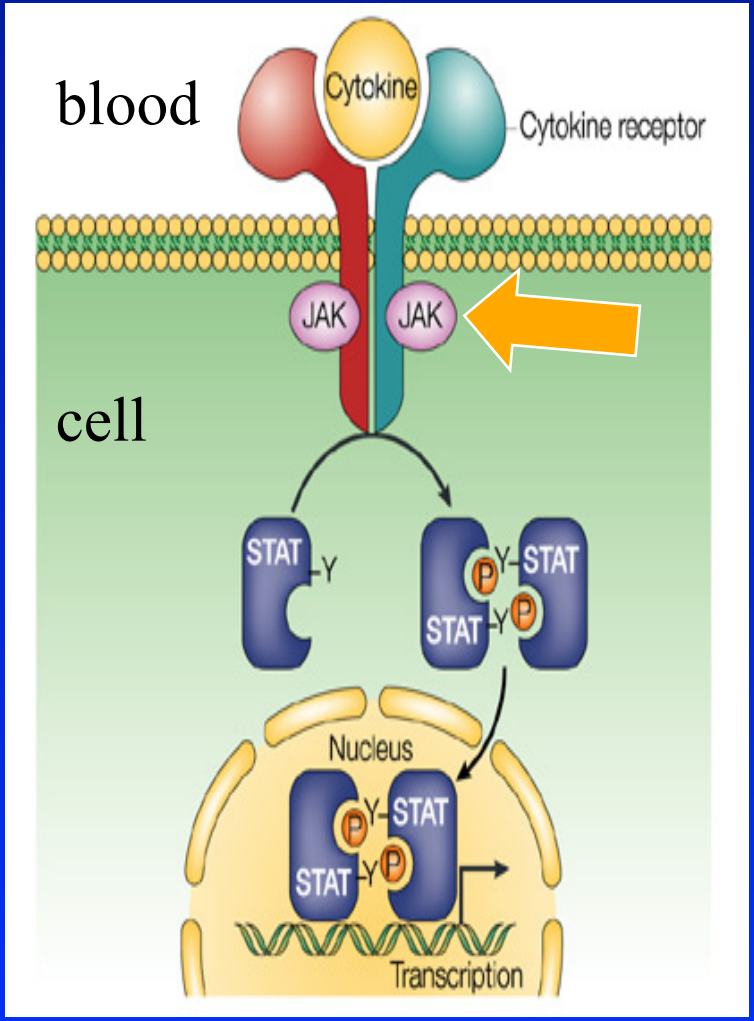
Main Clinical Problems in MF



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

JAK-STAT Signaling

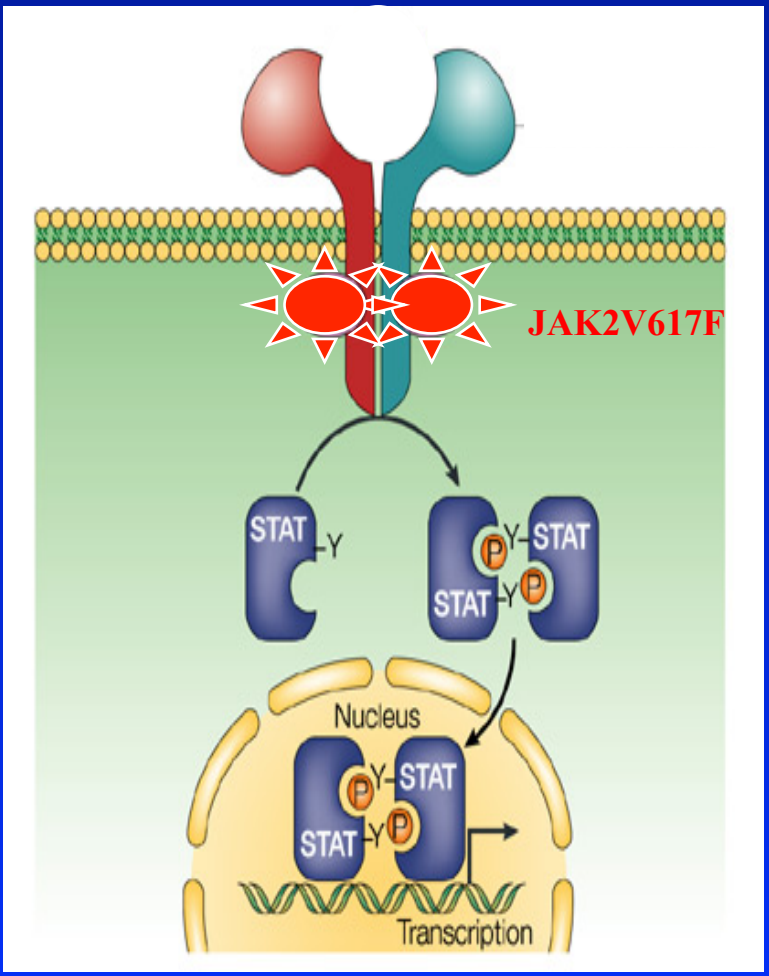
- A well characterized signaling pathway involved in normal hematopoiesis (blood making), inflammation, and immune function
- Four members of JAK family
  - JAK1, JAK2, JAK3 and Tyk2
  - Promiscuous signaling (!)
- JAK2 specifically mediates cytokine signaling for red blood cells and platelets (its inhibition causes anemia and low platelets)



Shuai, K. & Liu,B. (2003) Nature Reviews Immunology 3:900

JAK2 V617F Mutation in MPN

- Acquired
- Arises in multipotent progenitors
- Results in constitutively active JAK2 tyrosine kinase
- Causes disease (PV → MF) in mice
- Present in ~50% of ET and MF patients, ~97% PV



Quintás-Cardama A, Nat Rev Drug Discov. 2011 Feb;10(2):127-40.

JAK2V617F in MPN: 2013

- Other mutations identified (about 25 so far); clonal hyerarchy → "multiclonal" state
- JAK2 mutation is unlikely a cause for the disease in humans, but main contributor to clinical phenotype
- JAK-STAT pathway dysregulation, regardless of JAK2 mutational status, is a key pathologic feature of MPNs

Quintás-Cardama A, Nat Rev Drug Discov ;10(2):127-40.
Anand S, Blood 2011;118(6): 1610-21

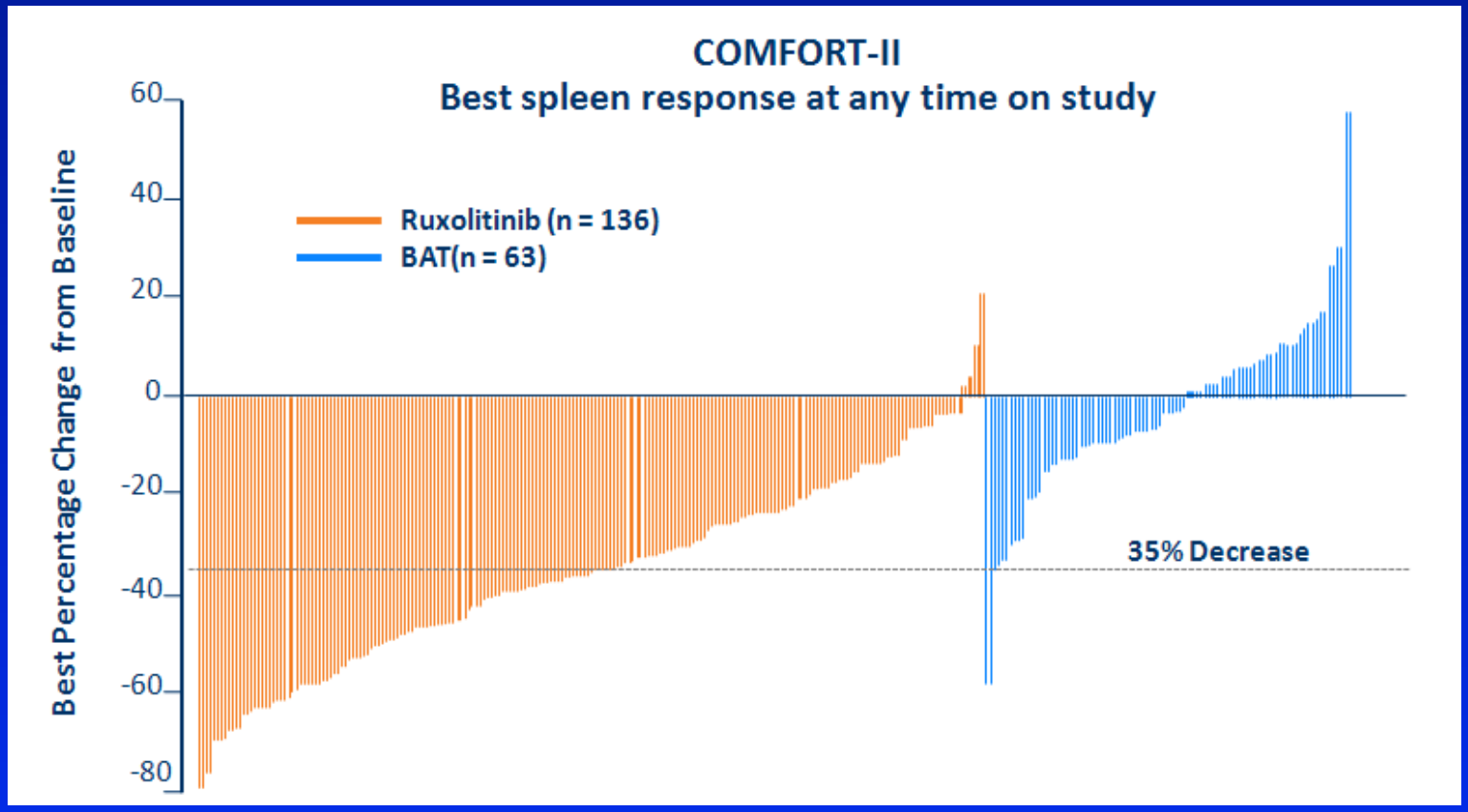
JAK2 Inhibitors

- Not selective for mutated JAK2V617F enzyme (ATP binding inhibitors)
- Lowering of platelets and red blood cells is expected side effect due to inhibition of normal JAK2
- Elimination of the disease unlikely
- However: may benefit patient with and without JAK2V617F mutation

Benefits of a JAK Inhibitor Therapy in MF

Splenomegaly

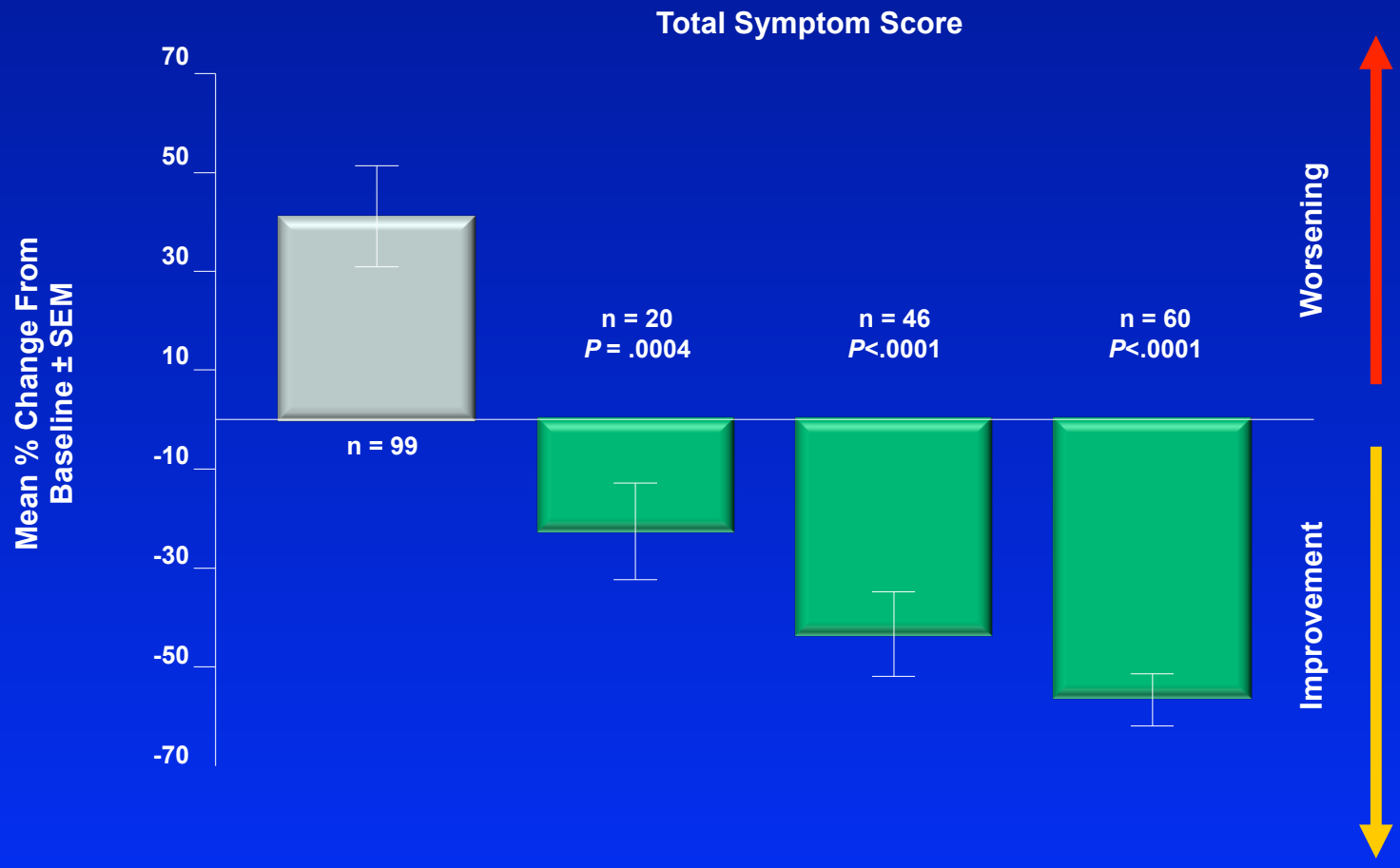
Spleen Volume Response: Ruxolitinib vs. best available drug (BAT)



	Ruxolitinib	BAT
↓ Spleen volume	132 (97%)	35 (56%)
↑ Spleen volume	4 (3%)	28 (44%)

Harrison CN, et al. *N Engl J Med.* 2012;366:787-798.

Reduction in MF-Related Symptoms by Spleen Volume Reduction at Week 24



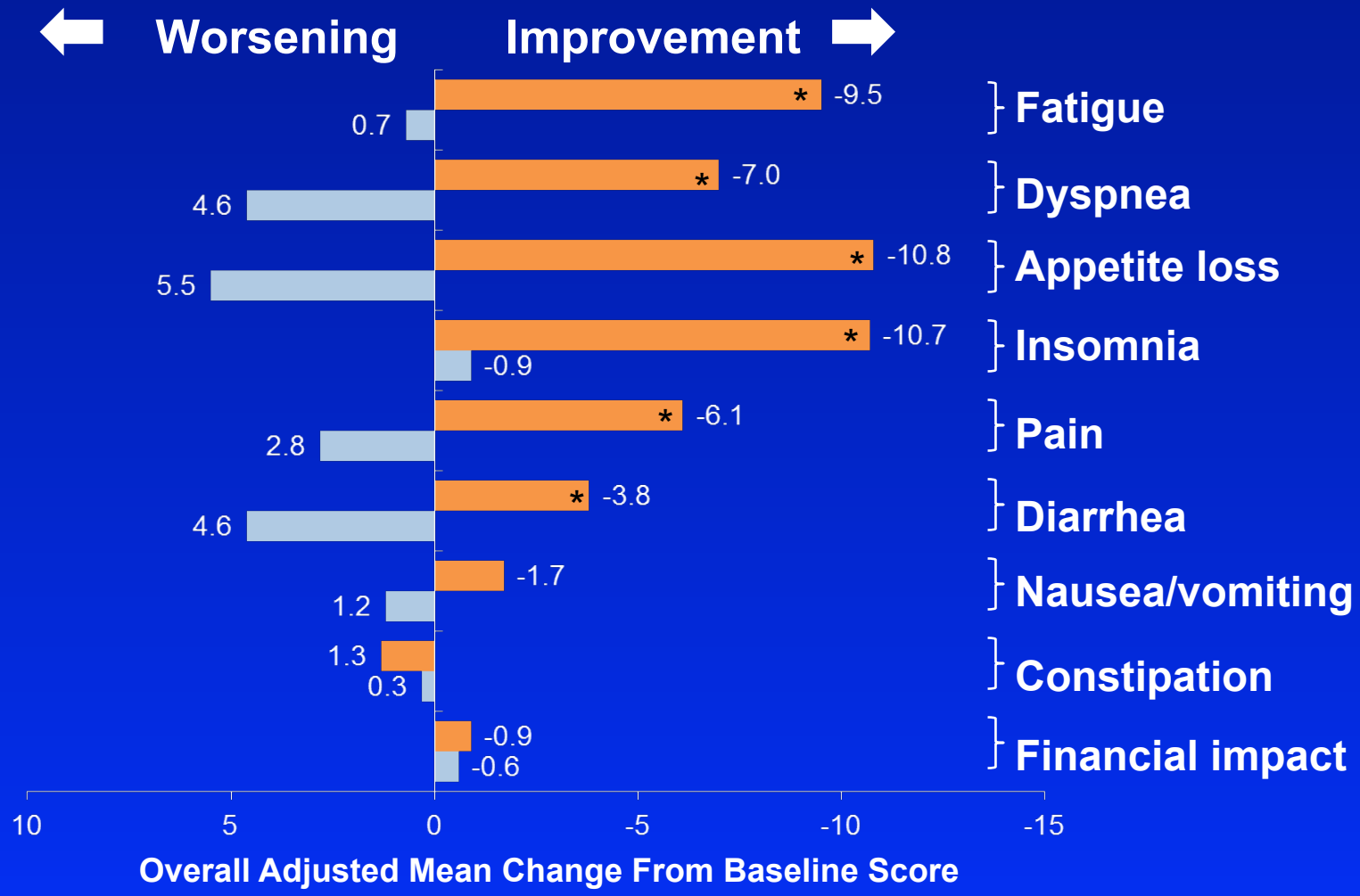
P value vs all placebo.

Mesa et J Clin Oncol. 2013 Apr 1;31(10):1285-92.

Benefits of a JAK Inhibitor Therapy in MF

Quality of life / Performance status

Improvement in Symptoms



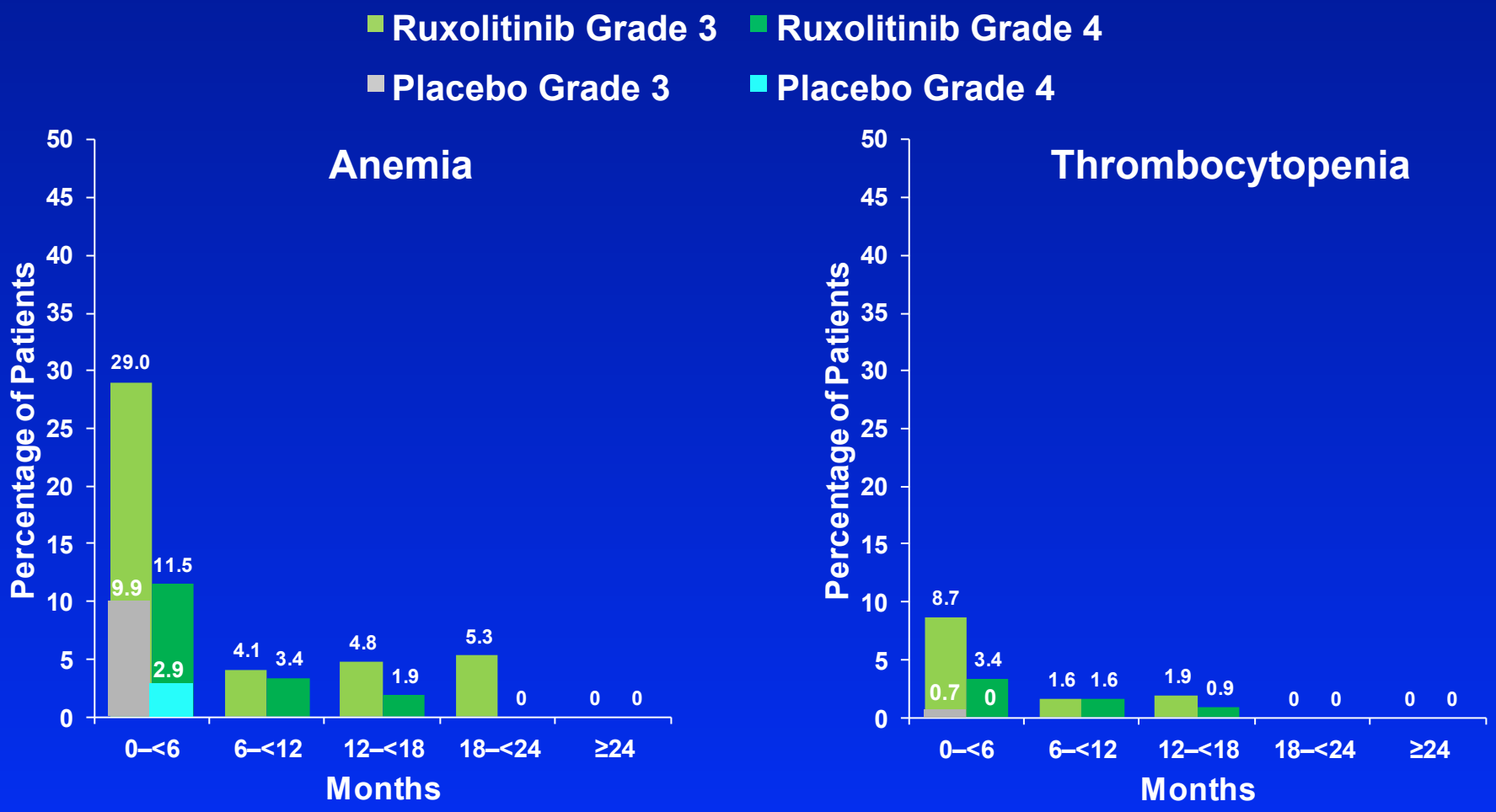
Harrison CN, et al. Oral presentation at ASH Annual Meeting; December 10-13, 2011. Abstract 279.

Proportion of Patients with ≥50% Reduction in Total Symptom Score Over Time

- Patients who discontinued or had missing data were considered non-responders

Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807.

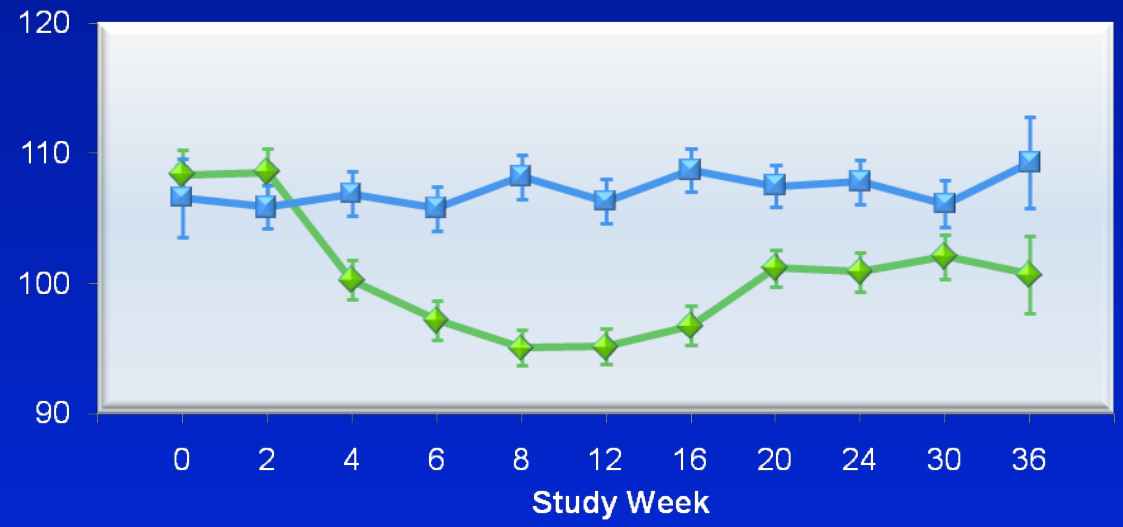
Incidence of New Onset Grade 3 or 4 Anemia and Thrombocytopenia Over Time

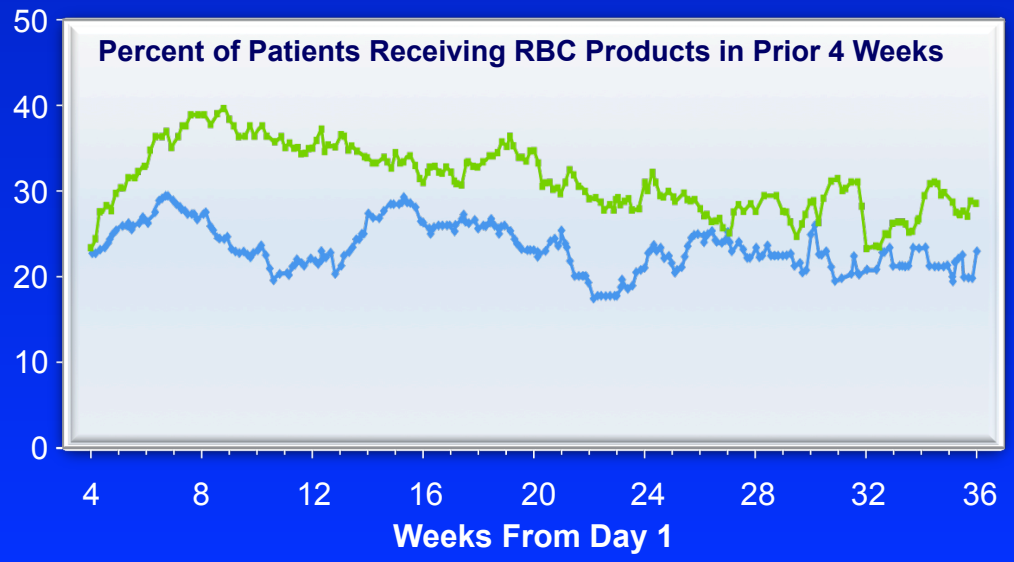


- All patients receiving placebo at the primary analysis crossed over or discontinued within 3 months of the primary analysis; therefore, data for patients receiving placebo is shown for 0–<6 months only

Verstovsek S, et al. *Blood.* 2012;120: Abstract 800.

Mean Hemoglobin and Red Blood Cell Products Over Time



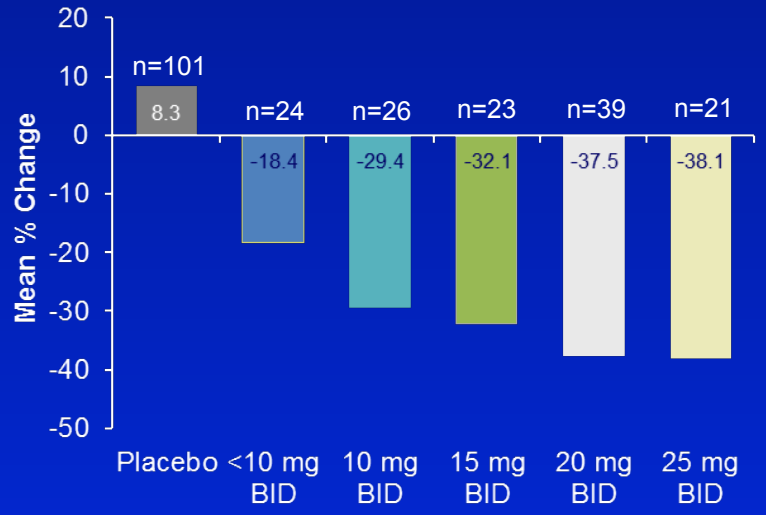


Verstovsek et al. Haematologica 2011;96(s2):213 (abstract 0505).

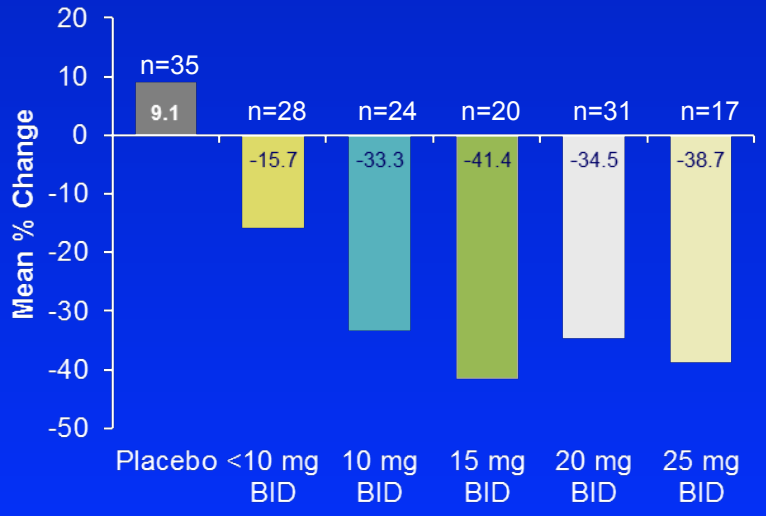
Efficacy by Titrated Dose

Spleen Volume

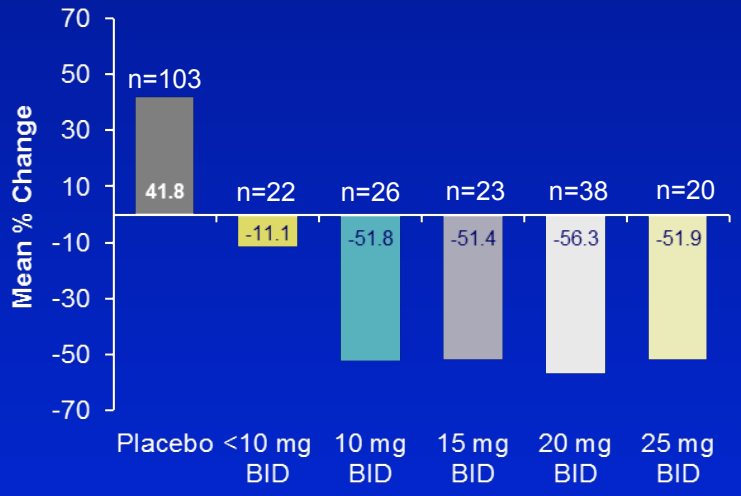
Week 24



Week 48



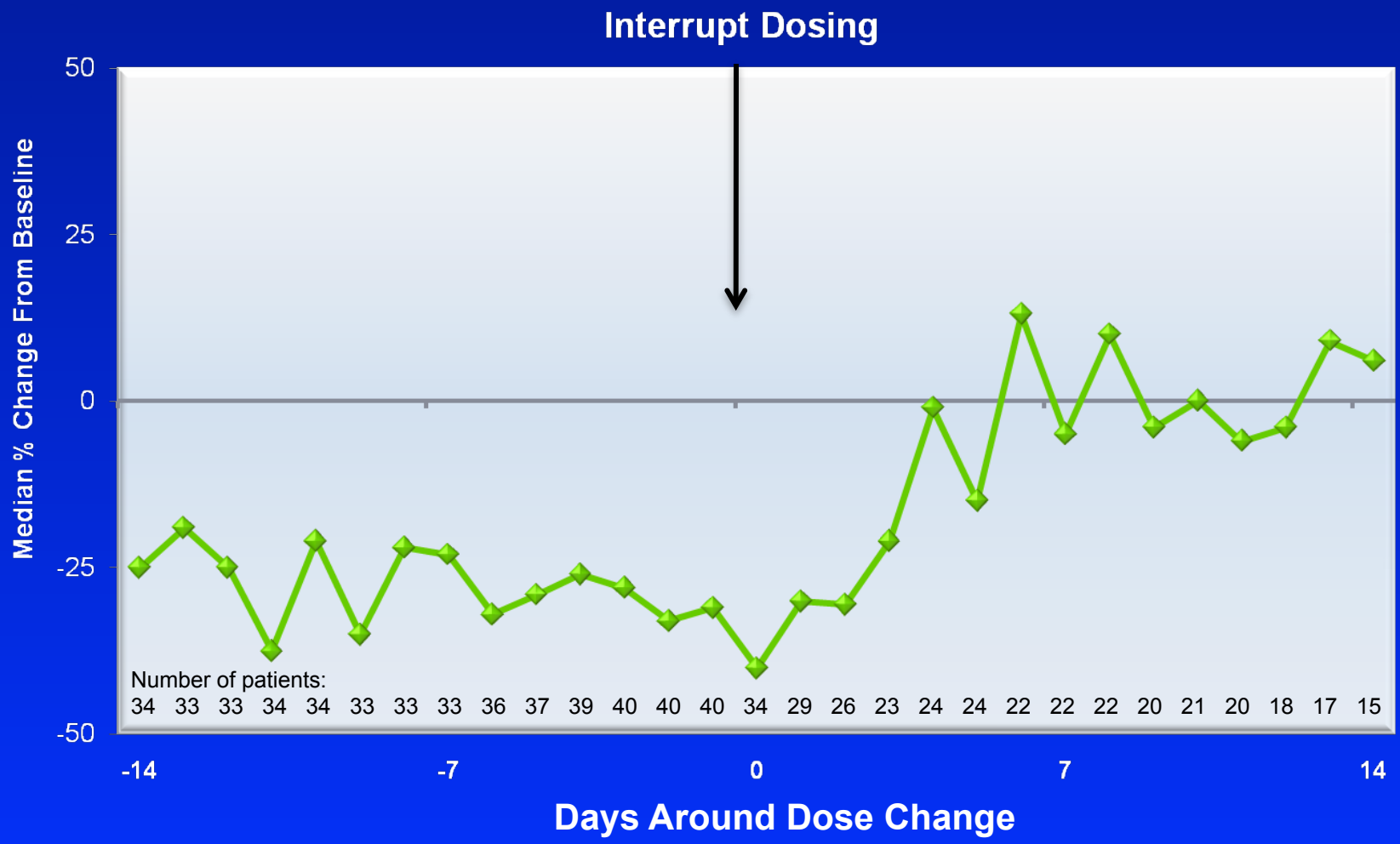
Total Symptom Score



Titrated dose is defined as the average dose patients received in the last 4 weeks before assessment.

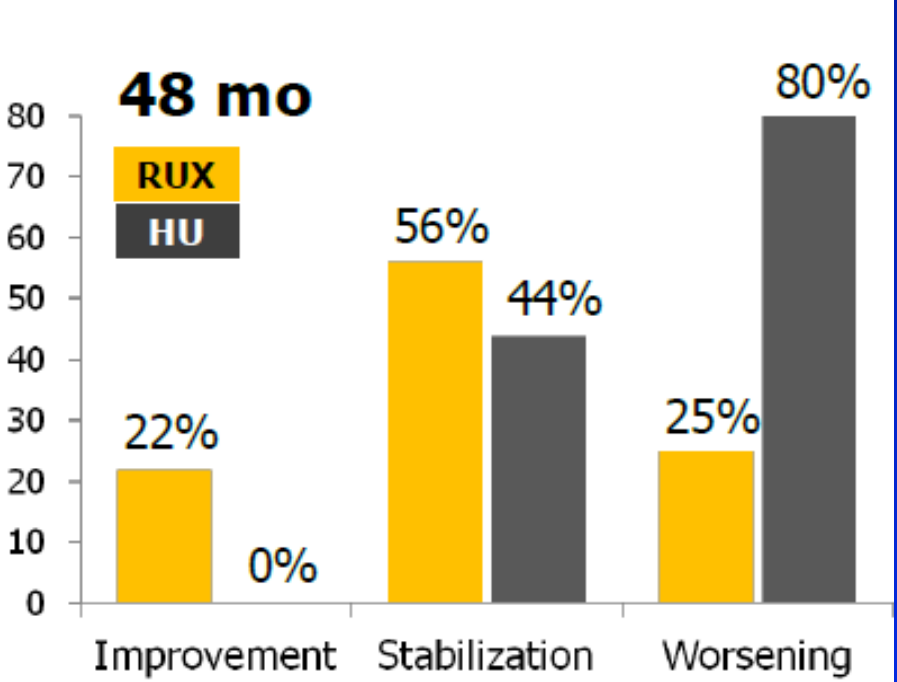
Verstovsek S, et al. *Blood.* 2012;120: Abstract 800.

What happens if therapy with ruxolitinib is interrupted?



- Return of the symptoms within 7 days: avoid interruptions!

Change in BM Fibrosis Over Time*



Odds Ratio [95% CI]** for worsening BM fibrosis at 48 mo
Rux 0.12 [0.03 – 0.50]

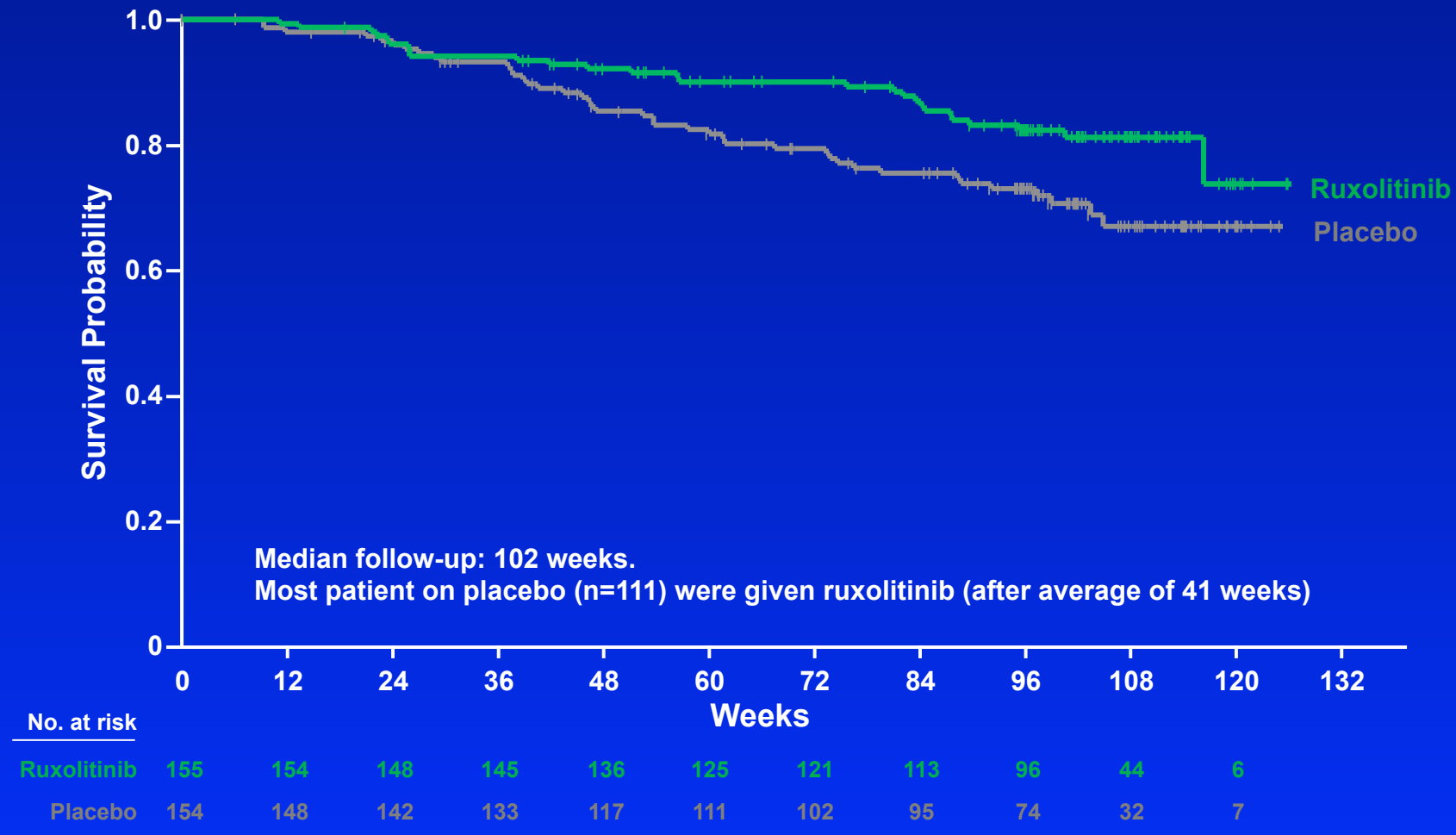
* Compilation of data - not a formal comparison

Kvasnicka et al, ASCO 2013

JAK2 Inhibitors in MF

Can JAK2 inhibitors prolong life of patients with MF?

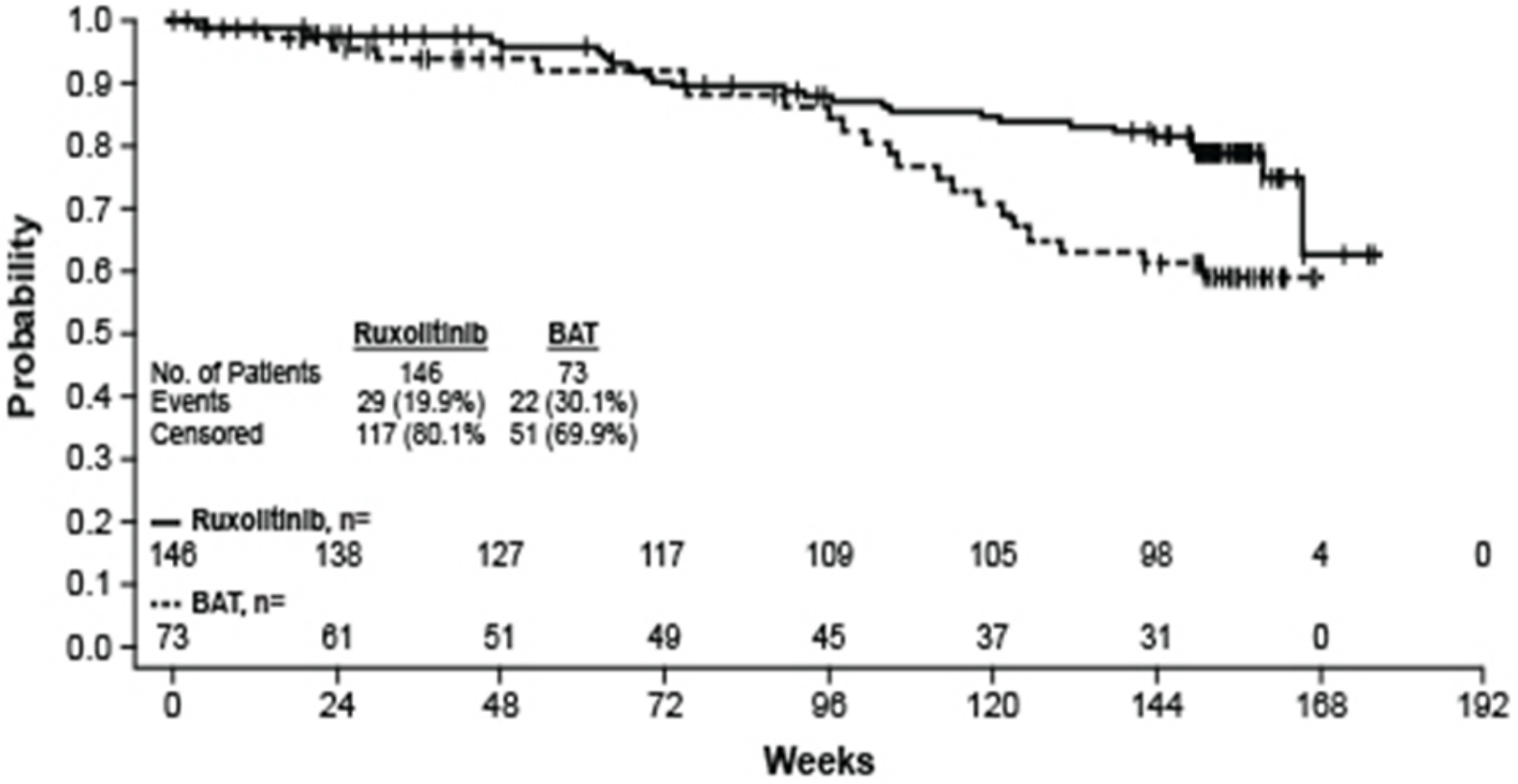
Overall Survival: ruxolitinib vs. placebo (int-2/high risk MF)



No. of deaths: Ruxolitinib = 27; Placebo = 41; HR = 0.58 (95% CI: 0.36, 0.95); *P* = .028

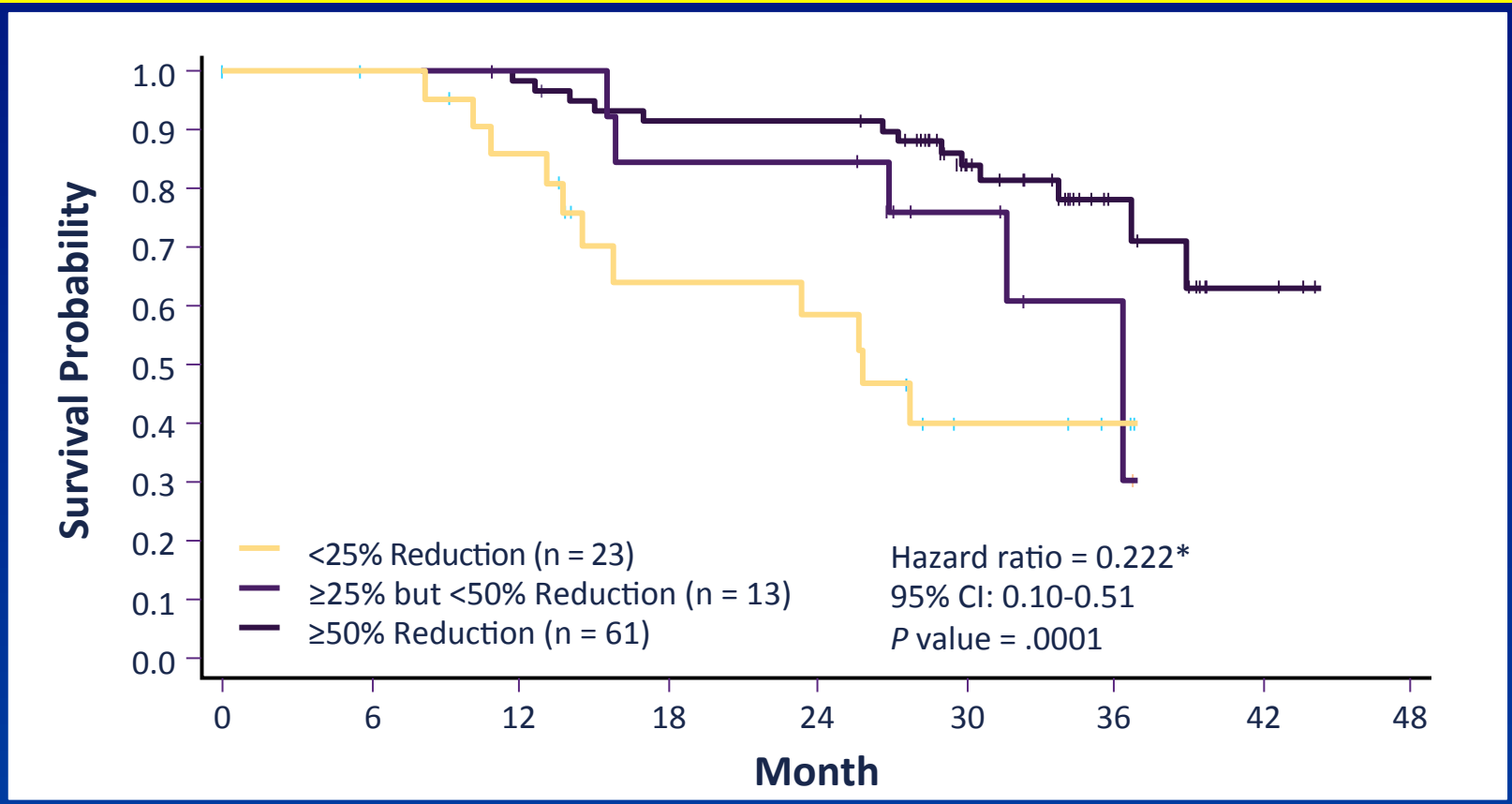
Overall Survival: ruxolitinib vs. BAT (int-2/high risk MF)

Figure 2. Kaplan-Meier Analysis of Overall Survival



52% reduction in risk of death in the ruxolitinib arm compared to BAT arm (HR = 0.48; 95% CI, 0.28-0.85; log-rank P = .009)

Reduction in spleen size was predictive for improved overall survival



Stratification by degree of reduction in spleen length at first confirmed spleen response predicted a significant difference in rate of overall survival within MD Anderson Cancer Center study cohort

*Comparison of <25% reduction vs ≥50% reduction.

Verstovsek S. et al. *Blood.* 2012

JAK2 Inhibitors for Myelofibrosis

- Not selective for JAK2V617F (patients with and without JAK2 mutation benefit)

- Safety: lowering of blood count (not a cause for stopping therapy), others
- Efficacy:
  - Excellent therapy for disease-related symptomatic splenomegaly **or** general constitutional symptoms
  - Possible prolongation of life in patients with advanced disease