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MD Anderson Cancer Center
Making Cancer History®

JAK2 Inhibitors: where do we stand?

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

Main Clinical Problems in MF

Clinical need	
Anemia (Hb <10 g/dL)	36%
Leukocytosis (>25x10^9/L)	10%
Thrombocytopenia (<100x10^9/L)	16%
Splenomegaly	83%
Hepatomegaly	65%
Extramedullary hematopoiesis	1-3%
Thrombosis	7.2 %
Constitutional symptoms	27%
Leukemia transformation	13%

Traditional Therapeutic Options for MF

Medicines for Anemia

- *Prednisone*
- *Androgens*
- *EPO*
- *Thalidomide*

+/- prednisone

Medicines for Spleen

- *Hydroxyurea*
- *Busulfan*
- *2-CDA*

- *Splenectomy*
- *Splenic Radiation*

Medicines for Anemia & Spleen

- *Lenalidomide*

+/- prednisone

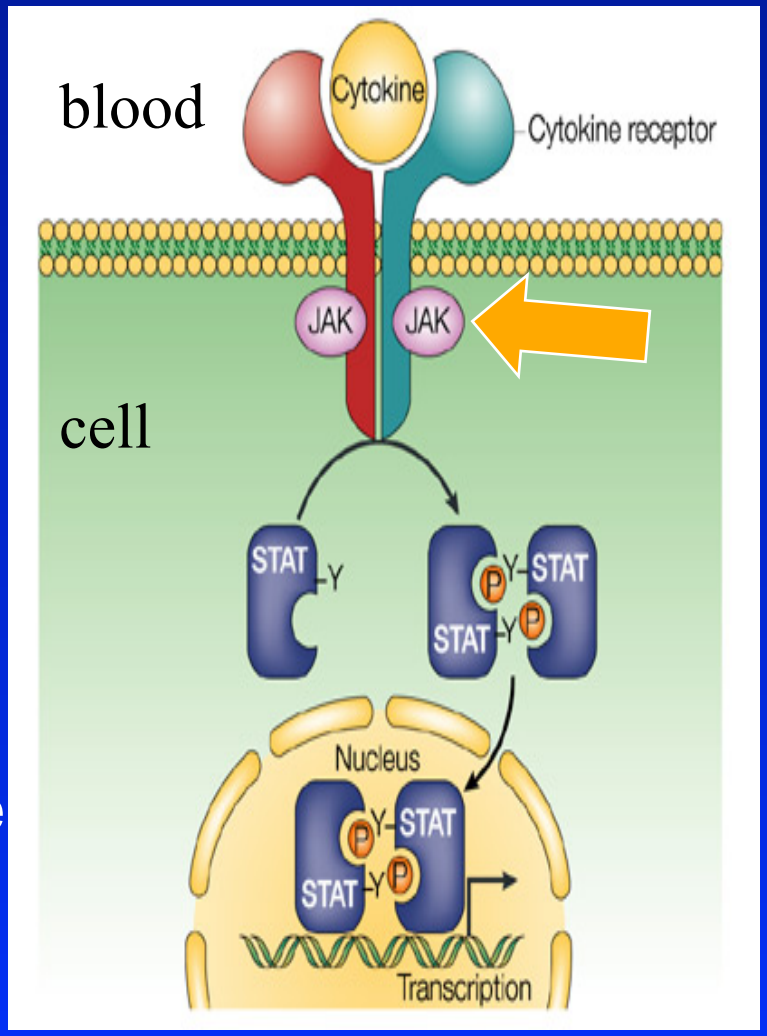
Medicines for Symptoms

- *Prednisone*

"BAT"

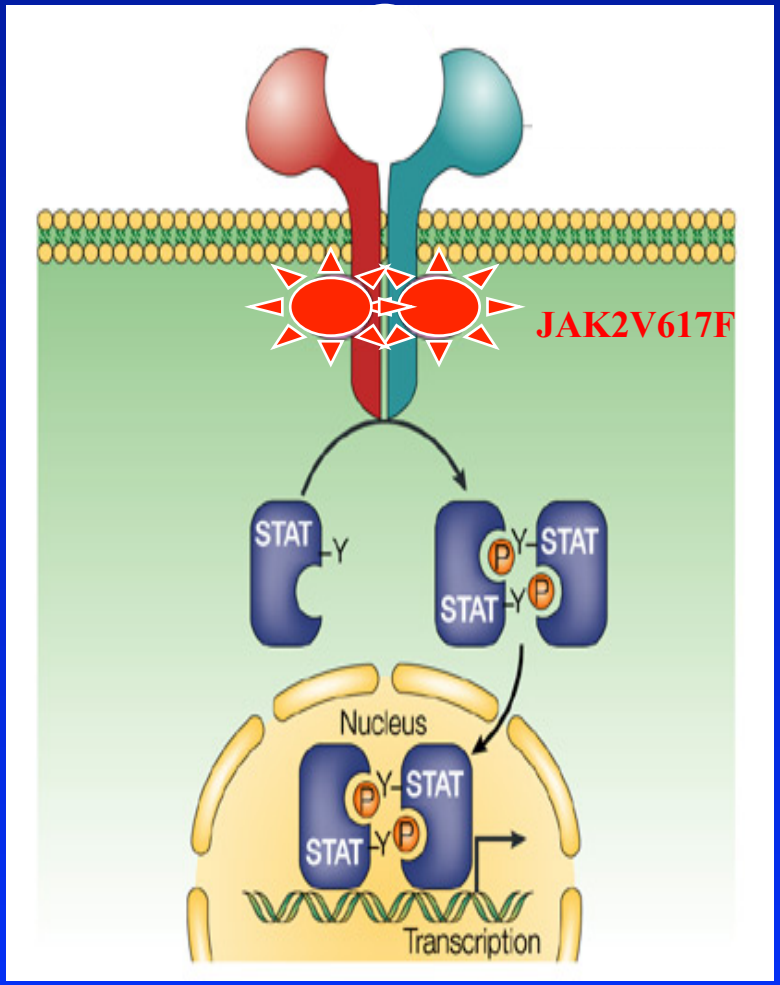
JAK-STAT Signaling

- 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)



JAK2V617F in MPN: 2005

- Acquired mutation in a gene
- Results in constitutively active JAK2 tyrosine kinase (always active enzyme)
- Causes disease in mice (PV → MF)
- Present in ~50% of ET and MF patients, ~97% PV



JAK2V617F in MPN: 2013

- Other mutations identified (about 20 so far); clonal hyerarchy → "multiclonal" state
- JAK2 mutation is not a cause for the disease presence in humans; just contributor to the disease existence
- JAK-STAT pathway dysregulation, regardless of JAK2 mutational status, is a key pathologic feature of MPNs

JAK2 Inhibitors

- Not selective for mutated JAK2V617F enzyme
- 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

JAK inhibitor (Company)	Diseases and studies
CEP701 (Cephalon)	MF: phase II finished and I/II (new formulation) ongoing ET/PV: phase II completed
AZD1480 (AstraZeneca)	MF: phase I finished, development stopped
XL019 (Exelixis)	MF: phase I finished, development stopped
NS-018 (NS Pharma)	MF: phase I ongoing
BMS-911543 (BMS)	MF: phase I ongoing
LY2784544 (Lilly)	ET/PV/MF: phase I finished, phase II ongoing
SB1518 (CTI/S*Bio)	MF: phase I/IIx2 completed, phase III ongoing
CYT387 (YM/Cytopia)	MF: phase I/II QD completed; phase I/II BID completed
SAR302503/TG101348 (Sanofi/Targegen)	MF: phase I/II completed; phase II completed, phase III completed ET/PV: phase II ongoing
INCB018424/Ruxolitinib (Incyte/Novartis)	MF: phase I/II and III completed and approved; phase II (for pts with low platelets) ongoing ET/PV: phase II completed; PV: phase III ongoing

Evaluation of JAK2 Inhibitors in MF

Efficacy:

- Splenomegaly
- Quality of life/Performance status
- Anemia

Toxicity:

- Blood cell suppression, other ?

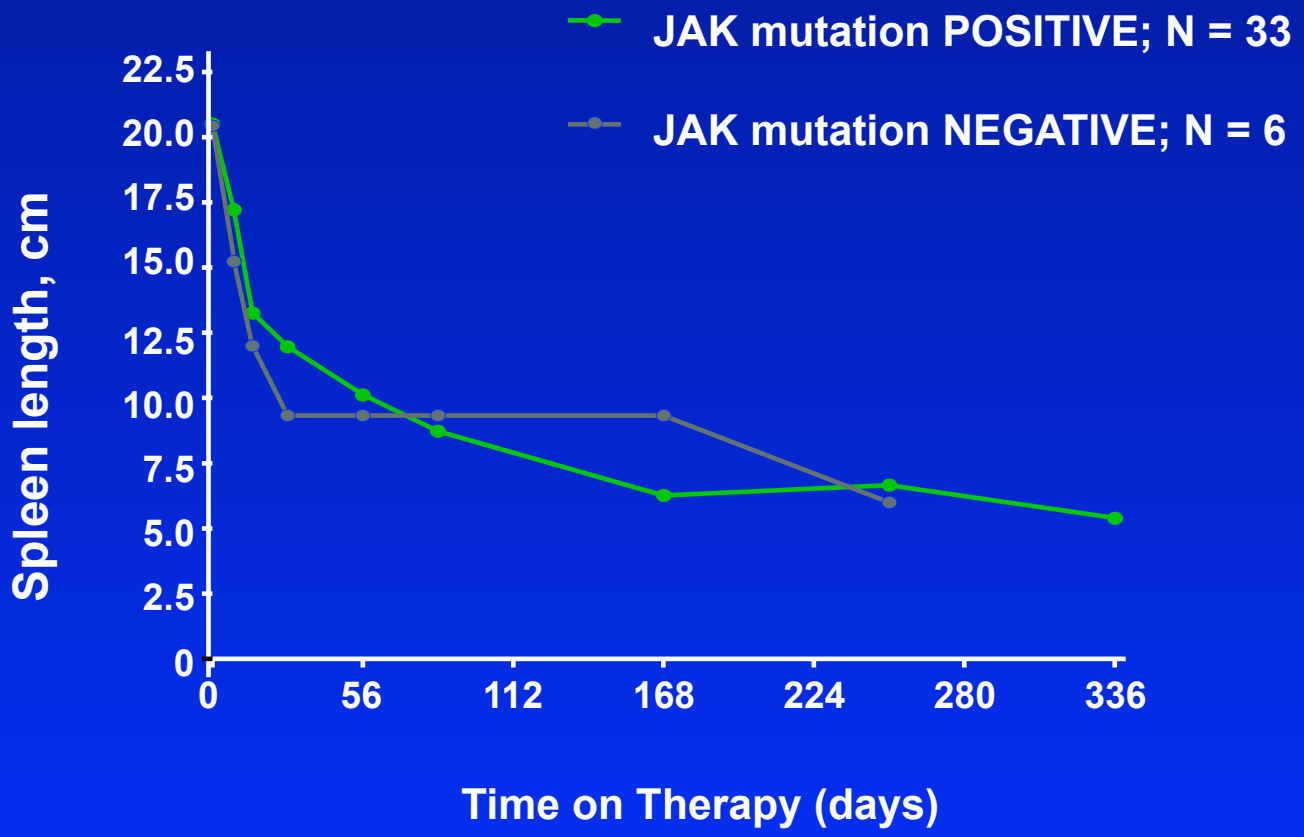
Benefits of JAK Inhibitor Therapy in MF

Splenomegaly

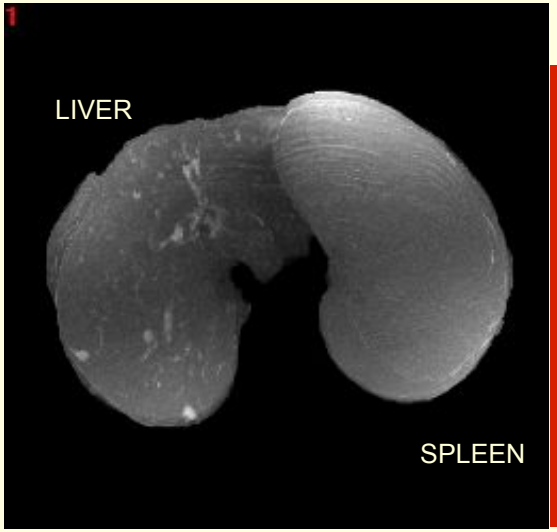
Splenomegaly in MF Patient Pre-Therapy

Splenomegaly after 2 Months of Therapy

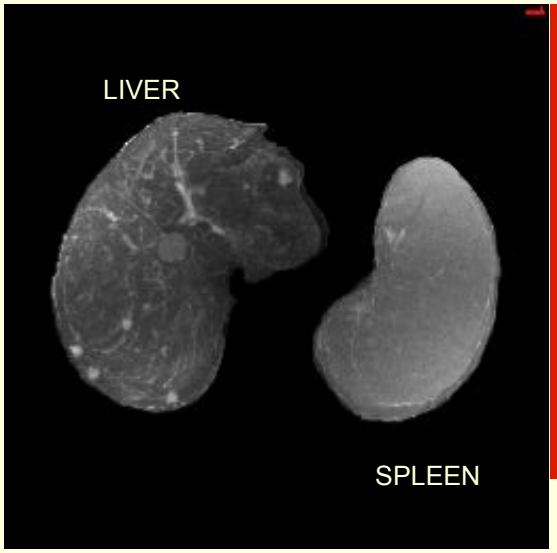
Rapid and Durable Impact on Spleen Size in Patients With and Without JAK2V617F Mutation



Spleen Volume Decrease by MRI



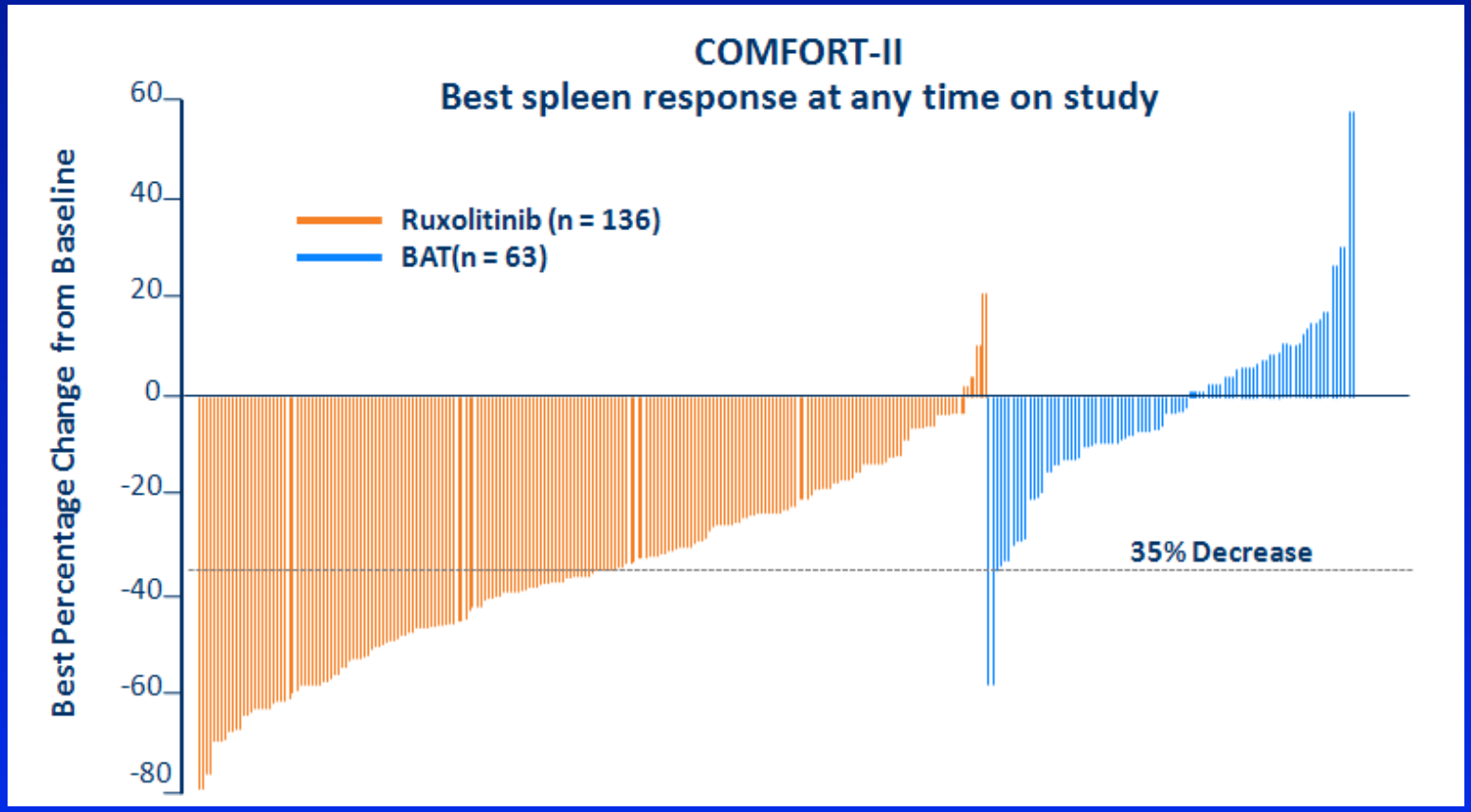
BEFORE THERAPY



AFTER 6 MONTHS

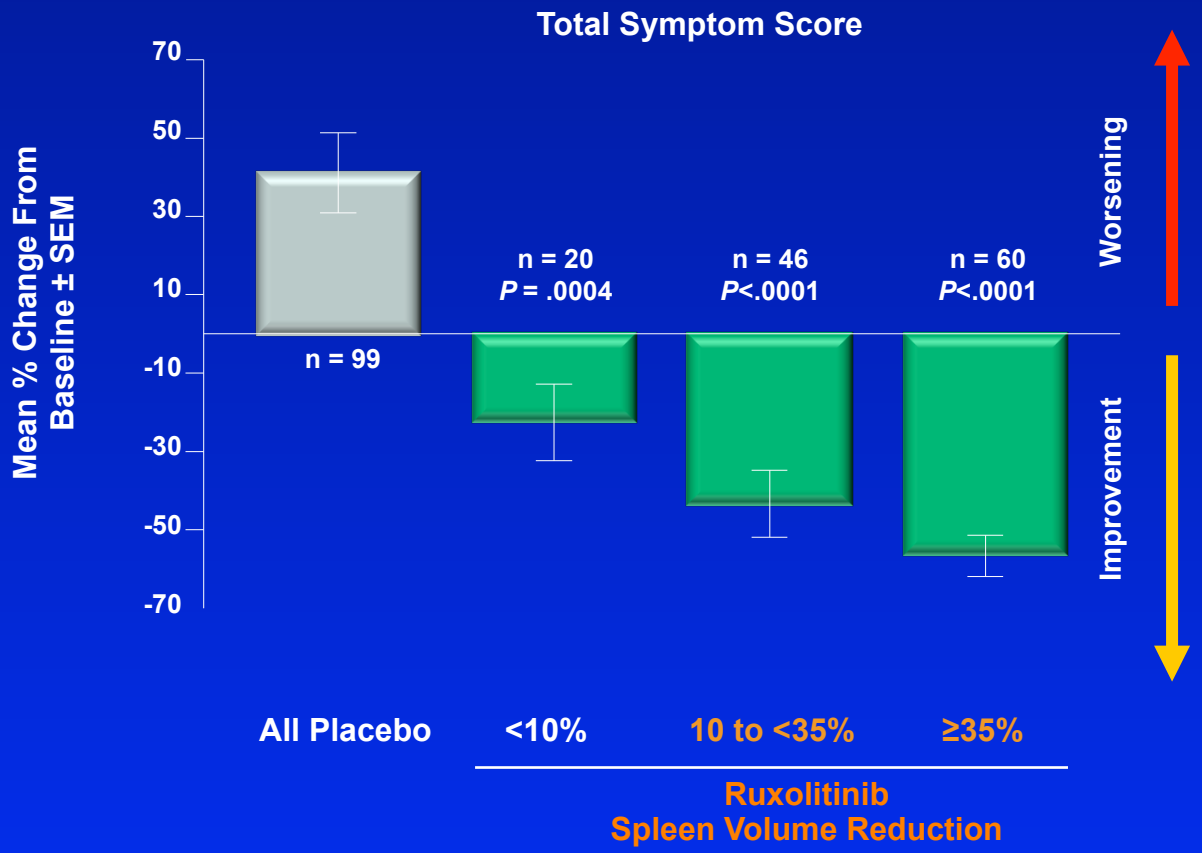
53% decrease In spleen volume, 32% decrease in liver volume

Spleen Volume Response: Ruxolitinib vs. BAT



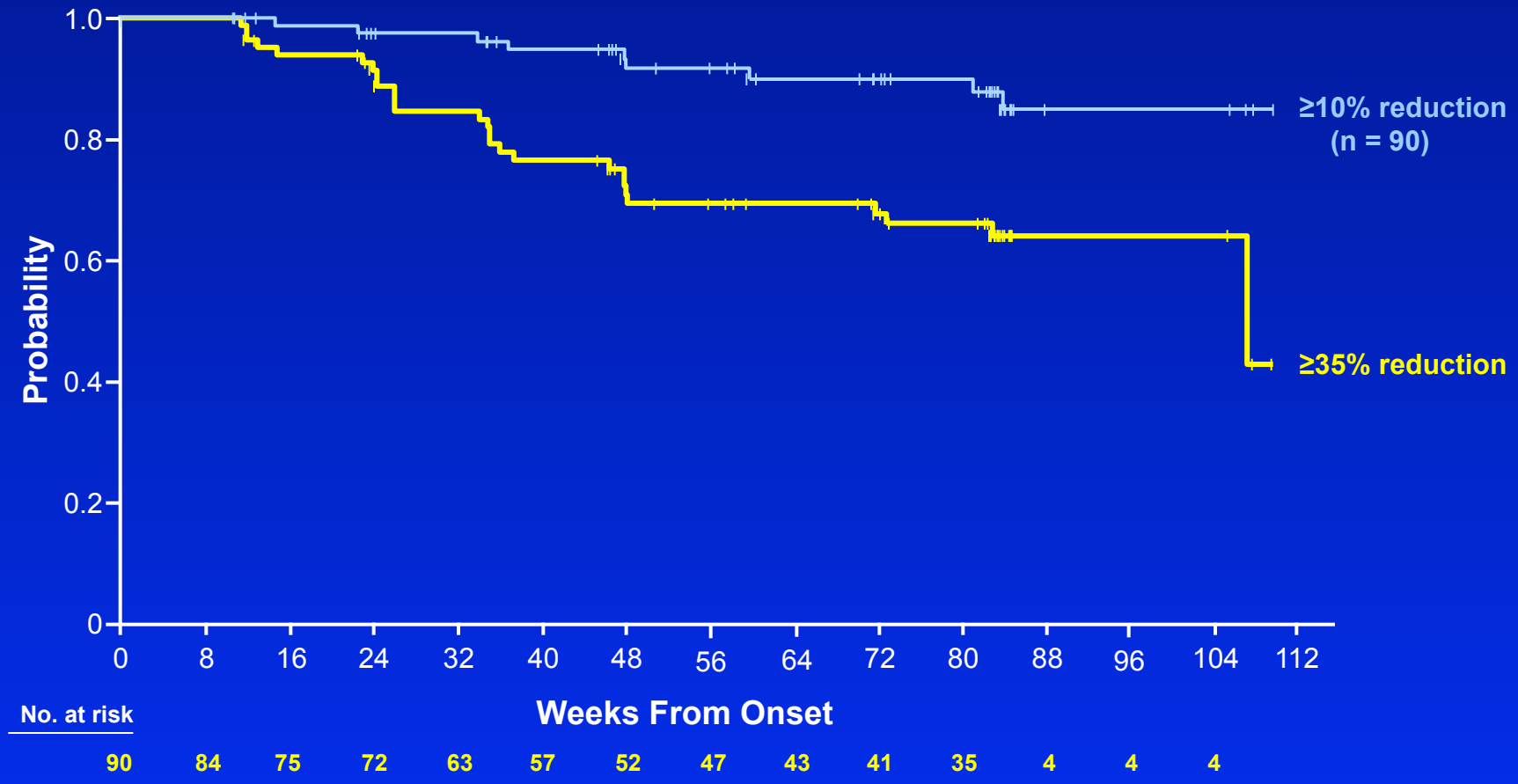
	Ruxolitinib	BAT
↓ Spleen volume	132 (97%)	35 (56%)
↑ Spleen volume	4 (3%)	28 (44%)

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



P value vs all placebo.

Durability of Spleen Volume Reduction



- 90/155 (58%) had a 35% reduction at any time point during the study
- 64% maintained a ≥35% reduction for at least 2 years

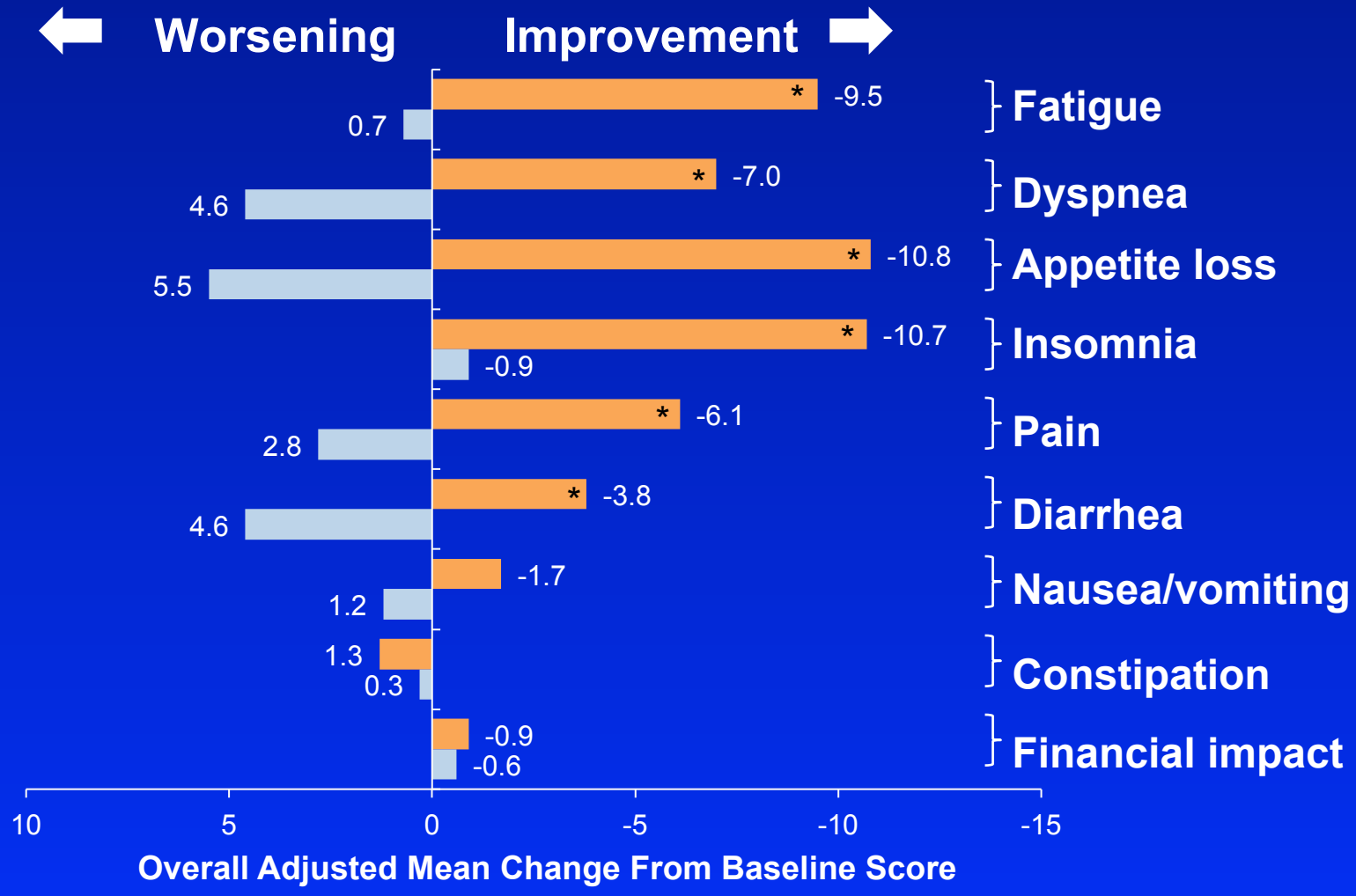
Benefits of JAK Inhibitor Therapy in MF

Quality of life/
Performance status

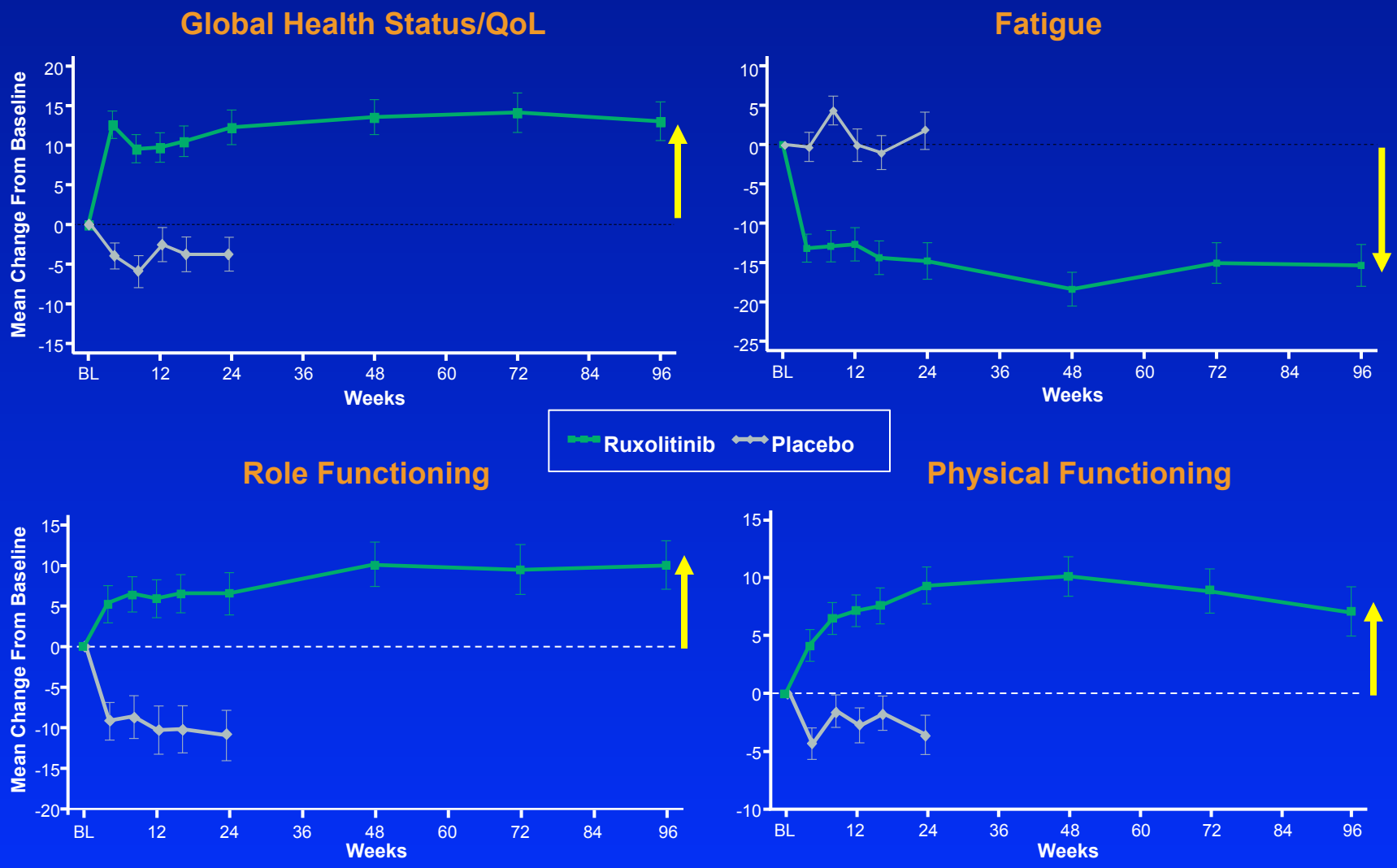
4/2008

11/2012

Improvement in Symptoms



Duration of Symptom Improvement

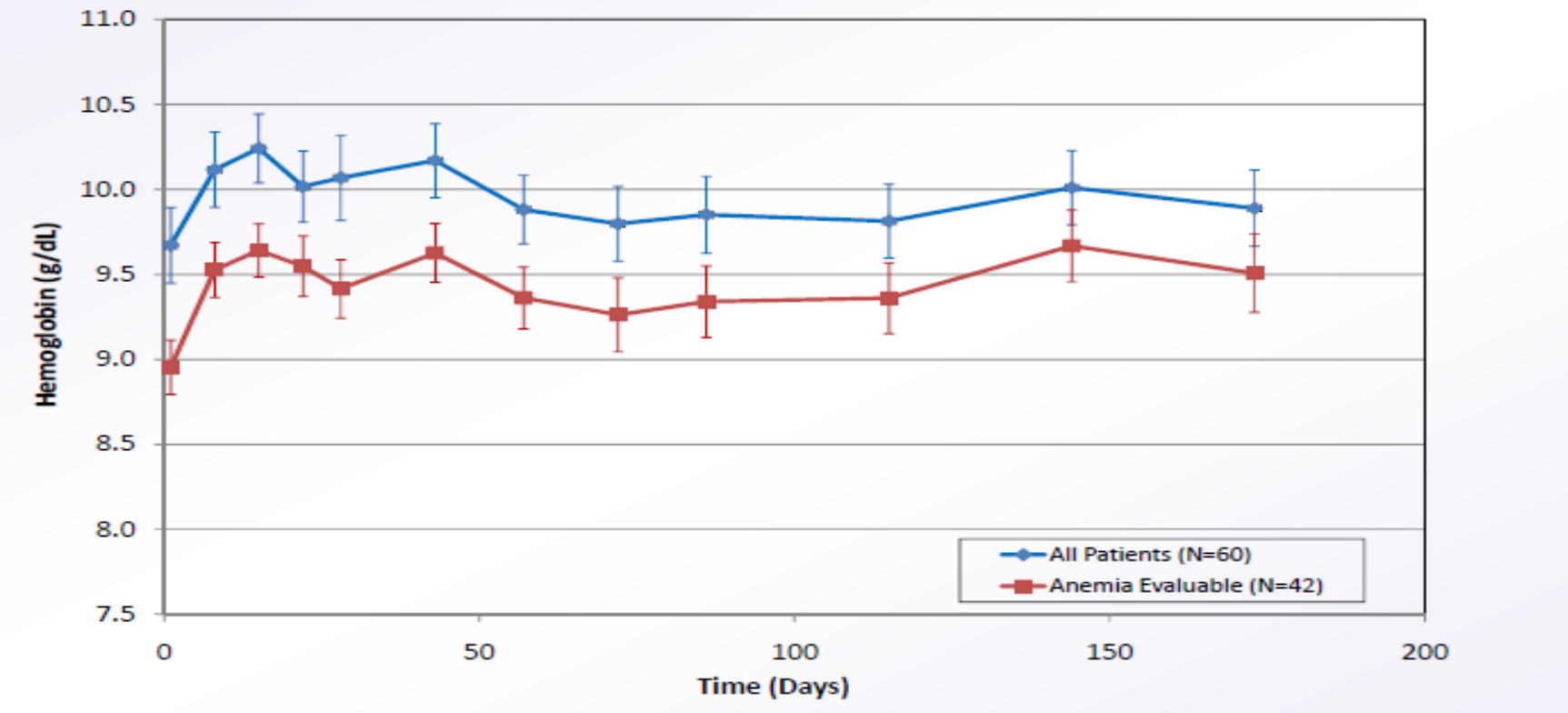


Arrows indicate improvement.

Evaluation of JAK2 Inhibitors in MF

Anemia

Hemoglobin levels on JAK inhibitor therapy



- In general no significant improvement

Impact on Blood and Bone Marrow

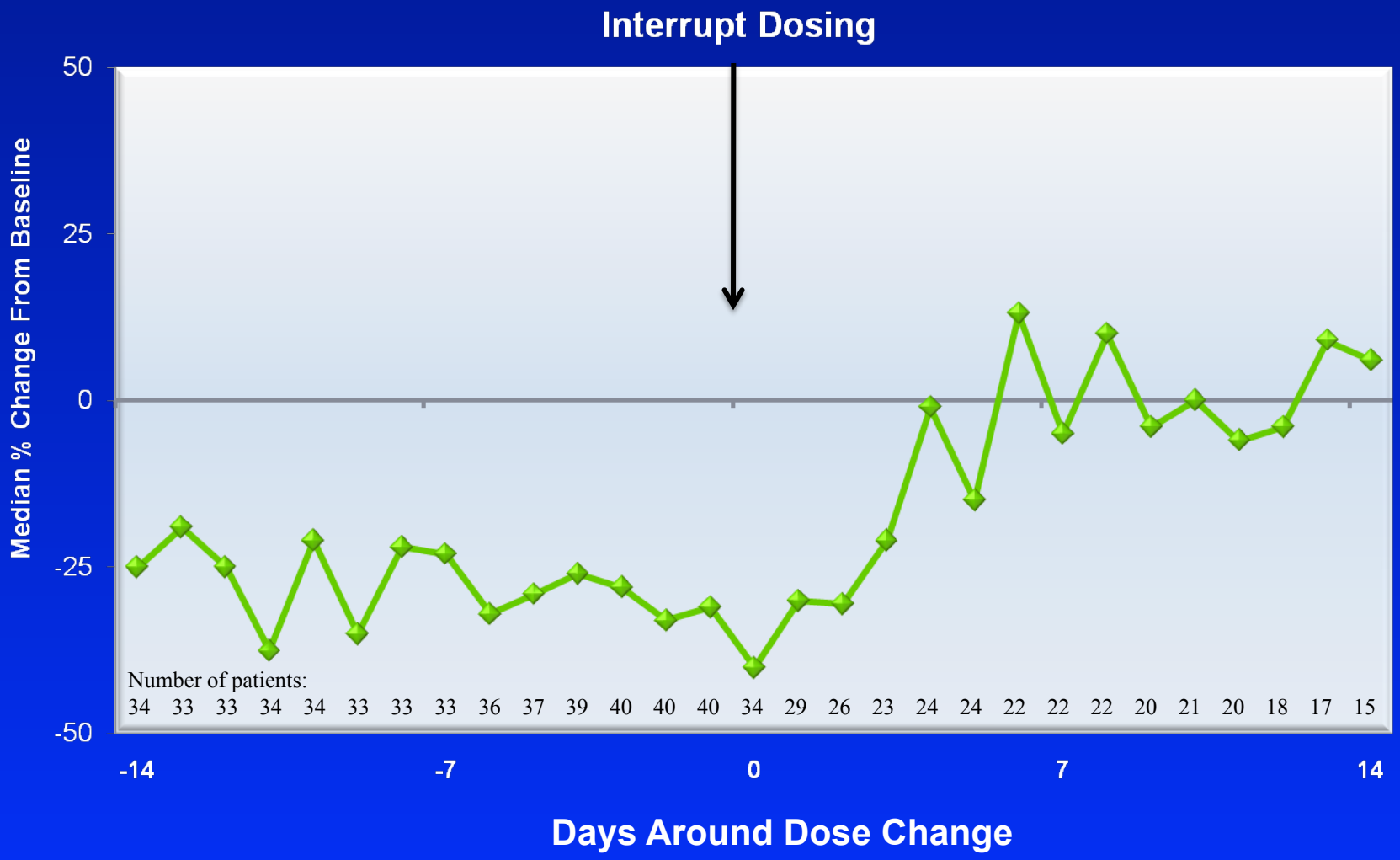
In general:

- High white blood cells and high platelets decrease to normal levels
- Red blood cell count does not significantly improve
- Bone marrow fibrosis does not change, stays stable

JAK2 Inhibitor Side Effects from Phase II Studies

	GI	Anemia	Platelets	Neuropathy
Ruxolitinib		X	X	
SAR302503	X	X	X	
SB1518	X			
CYT387			X	X

What happens if the therapy with JAK2 inhibitor is interrupted?



- Return of the symptoms within 7 days

Serious Adverse Events After Therapy Interruption

Adverse Event	Ruxolitinib (n = 155)	Placebo (n = 151)
Total with interruption, n	49	54
Total SAEs, n (%)	**3 (6.1)**	**3 (5.6)**

- no report of “withdrawal syndrome”

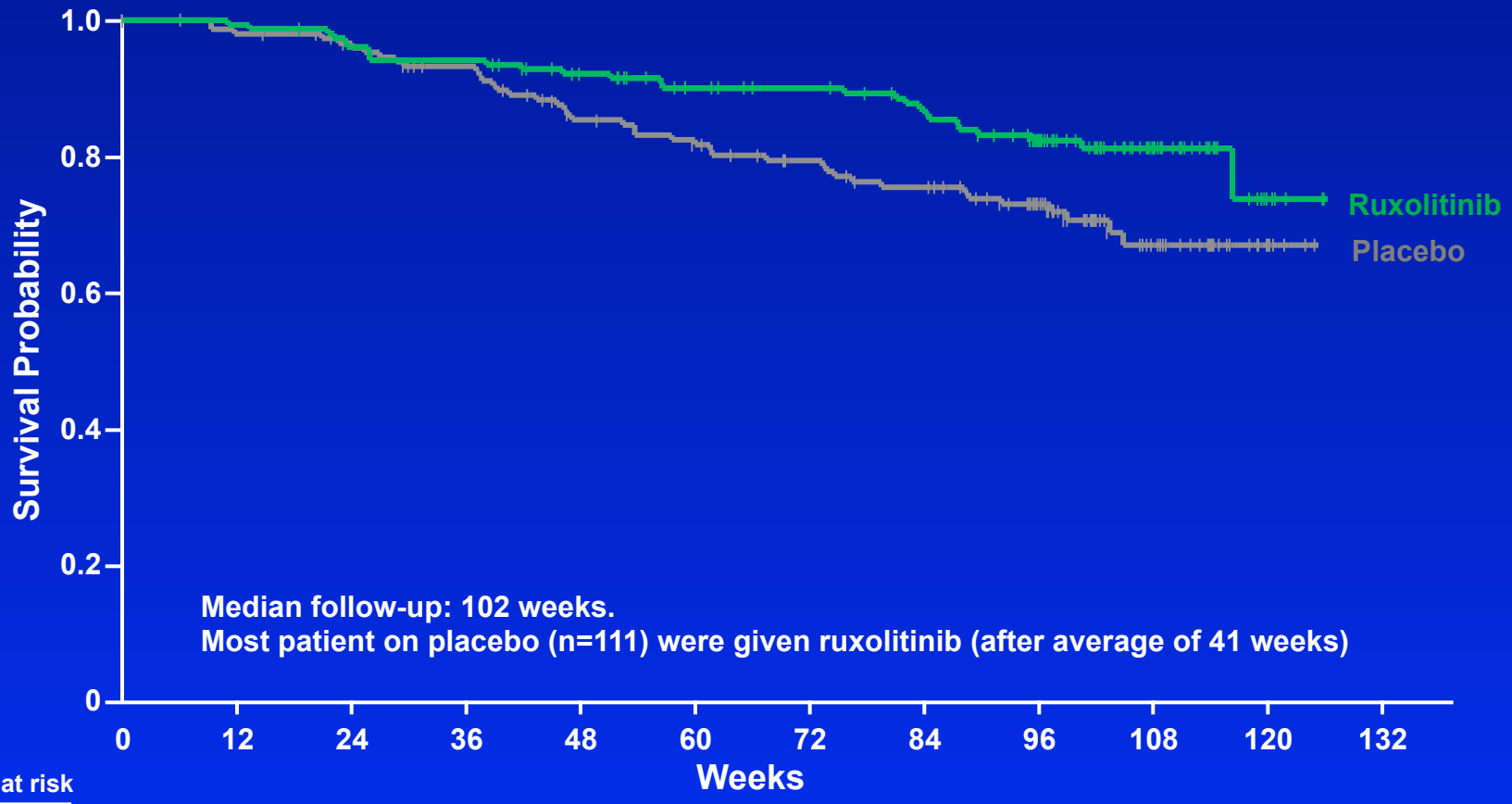
•Percent of patients that discontinued ruxolitinib due to side effects was 11%

•Percent of patient that discontinued placebo due to side effects was 11%

JAK2 Inhibitors in MF

Can JAK2 inhibitors prolong life of patients with MF?

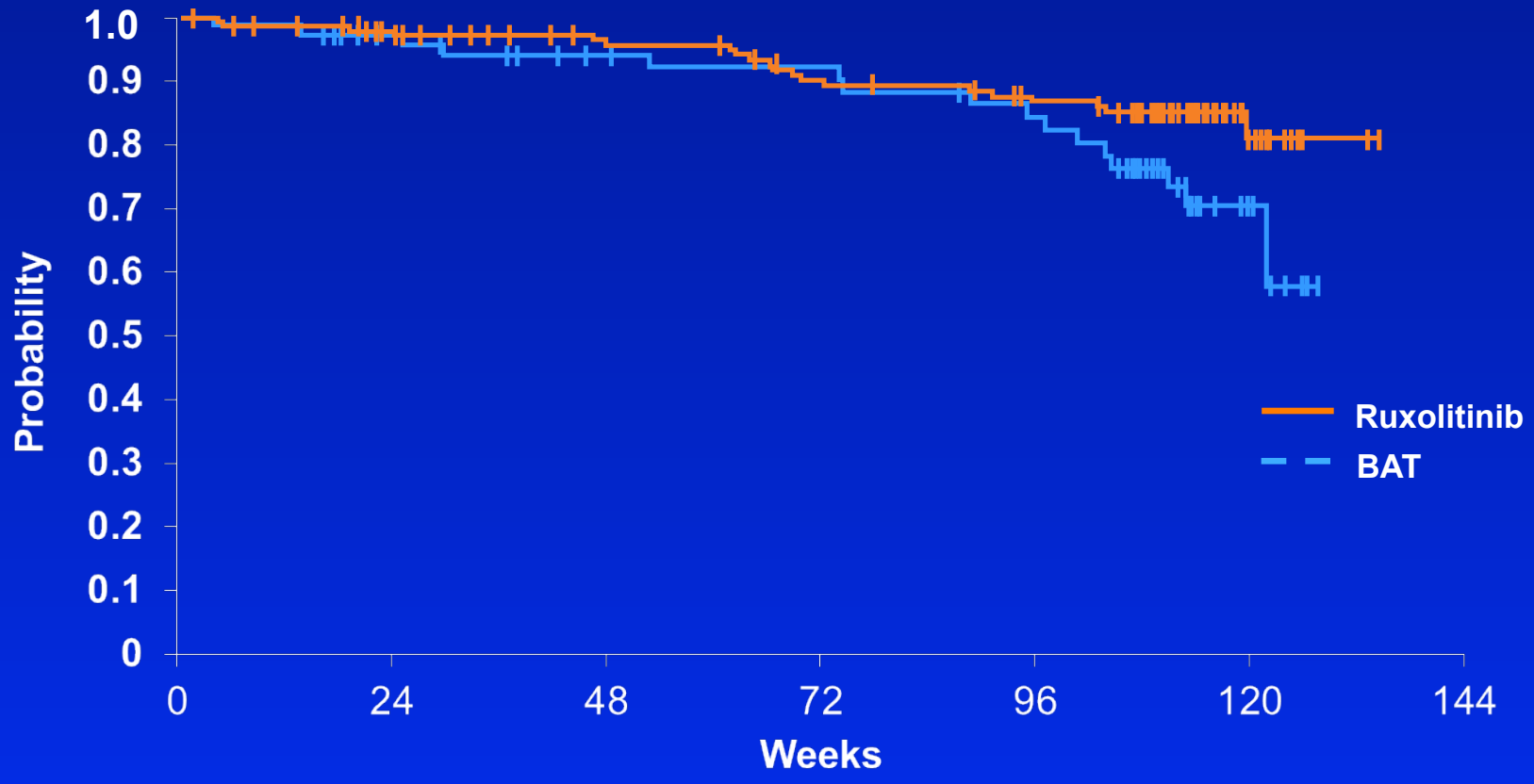
Overall Survival: ruxolitinib vs. placebo



No. at risk											
Ruxolitinib	155	154	148	145	136	125	121	113	96	44	6
Placebo	154	148	142	133	117	111	102	95	74	32	7

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

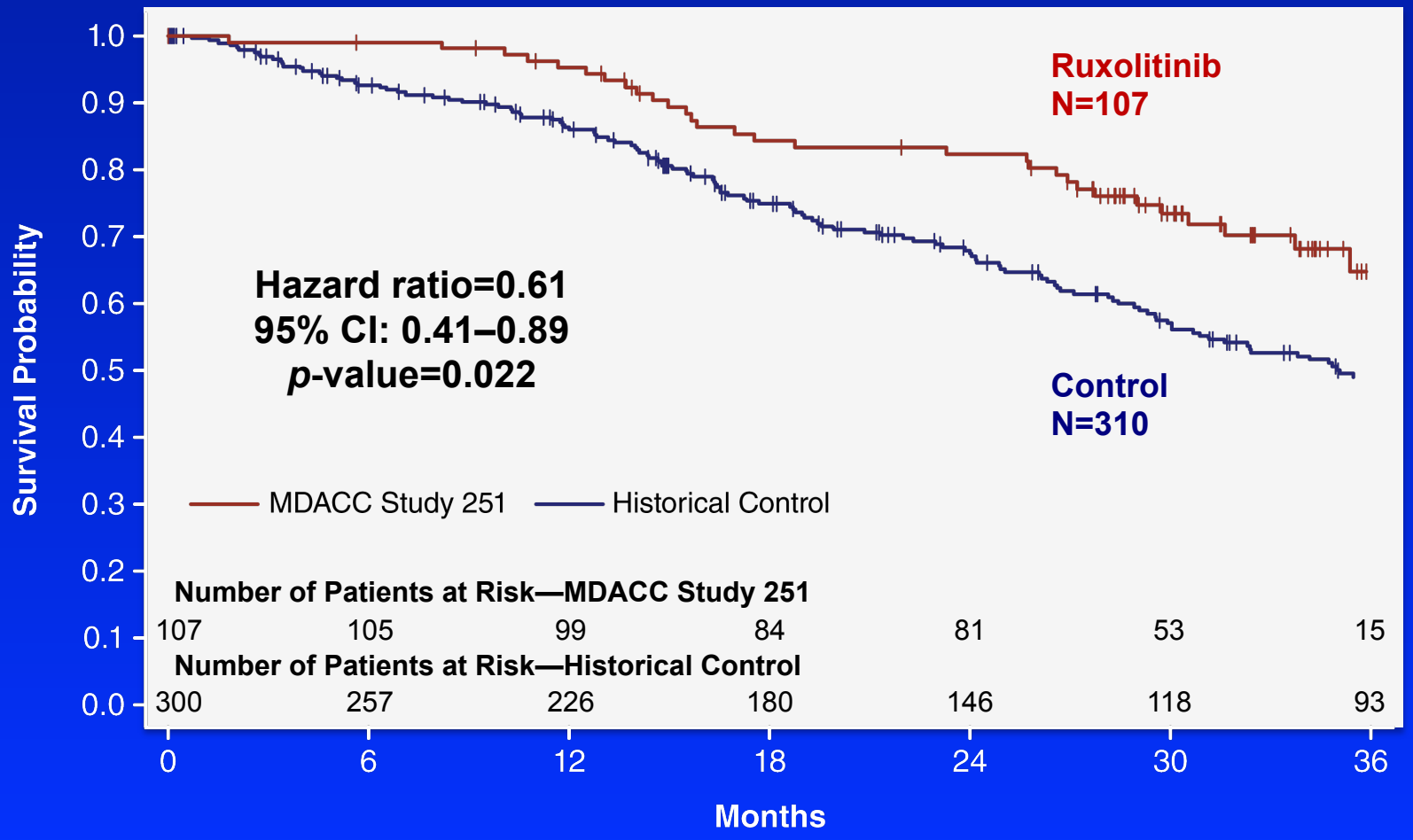
Overall Survival: ruxolitinib vs. BAT



	Ruxolitinib	BAT
No. of Patients	146	73
Events	20 (13.7%)	16 (21.9%)

Suggests a relative reduction in the risk of death with ruxolitinib compared with BAT (HR = 0.51; 95% CI, 0.26-0.99), *P* = .041

Overall Survival: Ruxolitinib vs. matched historical control



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:
  - spleen size reduction and significant improvement in quality of life and performance status = better control of MF
  - possible prolongation of life in patients with advanced disease

WHAT IS NEXT:
combination trials with JAK2 inhibitors

- To increase benefits seen with JAK2 inhibitors (splenomegaly, symptoms) as well as to bring additional benefits (anemia, BM fibrosis, clone elimination)
- To reduce unwanted side effects (anemia, thrombocytopenia) but maintain clinical benefits
- To improve stem cell transplant result

Ongoing/Planned Ruxolitinib-based Combinations

- plus Panobinostat (USA: Mt Sinai Hospital NYC)
- plus Lenalidomide (USA: MD Anderson)
- plus hedgehog inhibitor (USA: MD Anderson, others)
- plus peg-Interferon-alpha2a (France)
- plus Everolimus (Italy)
- plus Pomalidomide (Germany)
- plus erythropoietin (Germany)
- plus Azacytidine (USA: MD Anderson)
- plus Decitabine in MPN-related AML (USA: Mt Sinai Hospital NYC)

JAK2 Inhibitors as Part of the Transplant Procedure

Clinical study: Feasibility of administering **Ruxolitinib** with reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (**RIC-ASCT**) in MF patients

(*Canada, USA, Italy, Germany, UK, Israel*)

THANK YOU

sverstov@mdanderson.org