JAK2 inhibitors update: ruxolitinib and SB1518

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Update on Efficacy and Safety of JAK1 & JAK2 Inhibitor Ruxolitinib (INCB018424) in Myelofibrosis

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Phase I/II Study Of Ruxolitinib In Myelofibrosis

- **Phase 1:**
  - Established 25 mg twice a day (BID) orally as maximum tolerated dose (MTD)
    - Thrombocytopenia was dose limiting toxicity (DLT)
- **Phase 2:**
  - Expansion of 10, 15, and 25 mg BID cohorts
  - Development of individualized dose optimization approach based on safety and efficacy
- Median time on study in June 2010: 19.4 months
- 115/157 patients remain on study (73%)

Optimized Dose Regimen

- Optimized dose regimen:
  - start at 15 mg BID (or at 10 mg BID if platelet count < 200,000/µL)
  - increase to 20 mg BID after 1 month if response inadequate and no toxicity
  - Second increase, to 25 mg BID allowed if still inadequate response and no toxicity after 2 months of therapy
  - Decrease the dose if platelets fall below 100,000/µL

Current Distribution of Dose Regimens
(All Subjects Currently on Study)

<10 BID	10 BID	15 BID to 20 BID	25 BID	QD
9.5 %	27.0 %	27.8 %	20.0 %	15.7 %

Patient Demographics

N	157
Median age	65.0
Male/female (%)	63/37
V617F positive (%)	81.6%
Disease subtype (%) PMF Post-PV-MF Post-ET-MF	 52.5 32.5 15.3
Risk category (%) High Intermediate-2 Not known	 64 28 7.6
Transfusion dependent (%)	35.7
Median platelet count ($\times 10^{-9}$/L)	257
Median hemoglobin (g/L)	107
Median WBC ($\times 10^{-9}$/L)	17.3
Neutrophils ($\times 10^{-9}$/L)	12.2

Safety Update Based on 19 Month Follow up: Non-hematologic Toxicity

Related Adverse Events* (%) N=157	Frequency All Grades (%)	Frequency Grade 3† (%)
Diarrhea	6.4	0
Weight Increased	6.4	0.6
Fatigue	5.1	1.9
Headache	3.8	0
Peripheral edema	2.5	0
Pain in extremities	2.5	0
Epistaxis	2.5	0
Muscle Spasms	2.5	0

* Assessed as at least possibly related in at least 2% of the study population with CTCAE (common terminology criteria for adverse events) used.

† No grade 4 toxicity recorded.

Safety Update Based on 19 month Follow up: Hematologic Toxicity

Related and Unrelated Events	10 mg BID	**15 mg BID**	25 mg BID	50 mg BID
N (%)	30	**35**	47	5
Grade 3 Thrombocytopenia	6 (20%)	**1 (3%)**	12 (26%)	3 (60%)
Grade 4 Thrombocytopenia	0	**0**	5 (11%)	1 (20%)
Transfusion Independent at Baseline	19	24	29	2
New Onset Anemia*	6 (31%)	**4 (17%)**	8 (28%)	NA

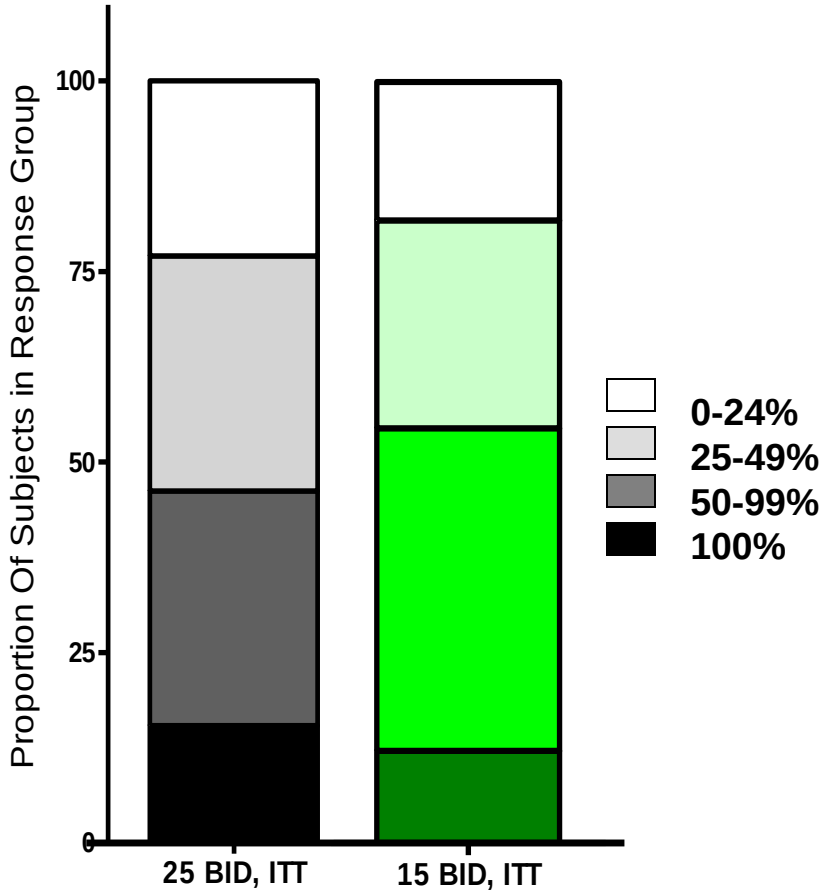
Transfusion independent. New-onset anemia was defined as hemoglobin decline of > 20 g/L, to the grade 3 or grade 4 level, in previously transfusion-independent subjects.

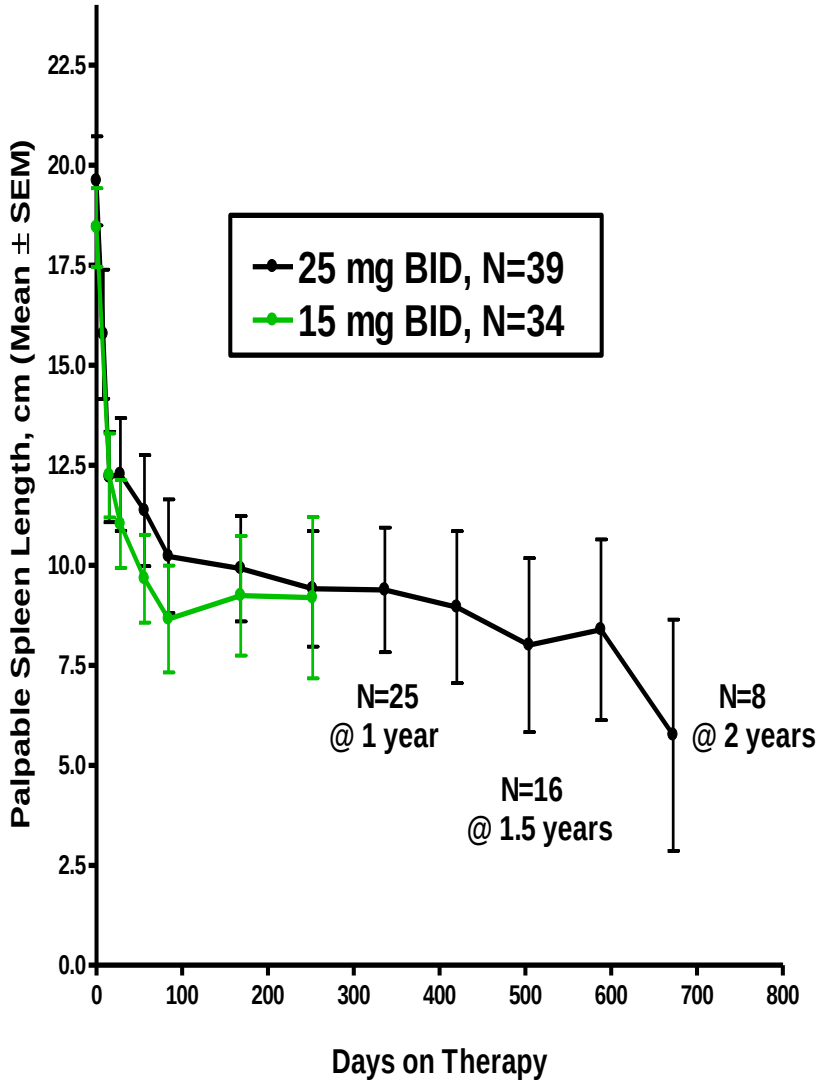
- **Optimized dosing with 15 mg BID starting dose markedly decreases hematologic AEs**

Rapid and Durable Impact on Spleen Size

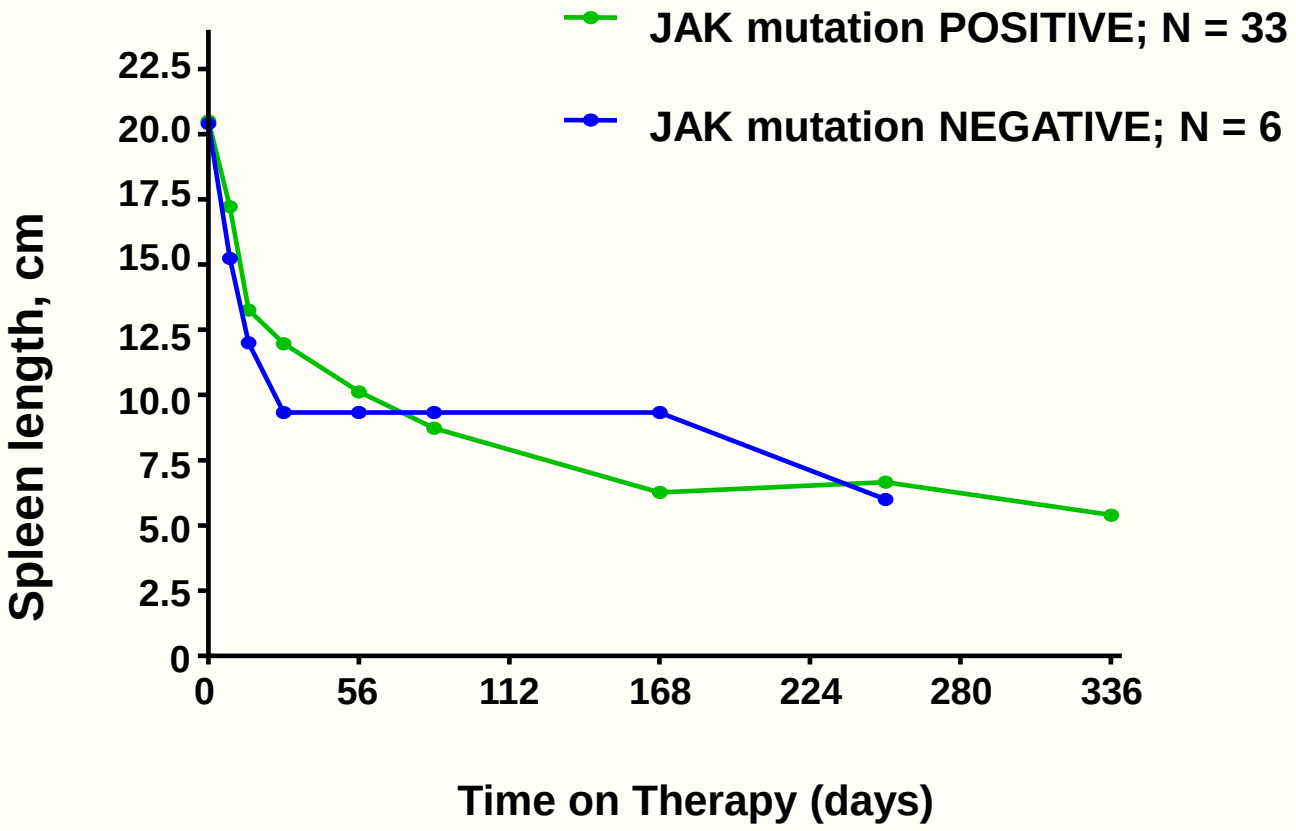
Response analysis based on % spleen reduction

(last on-therapy value)



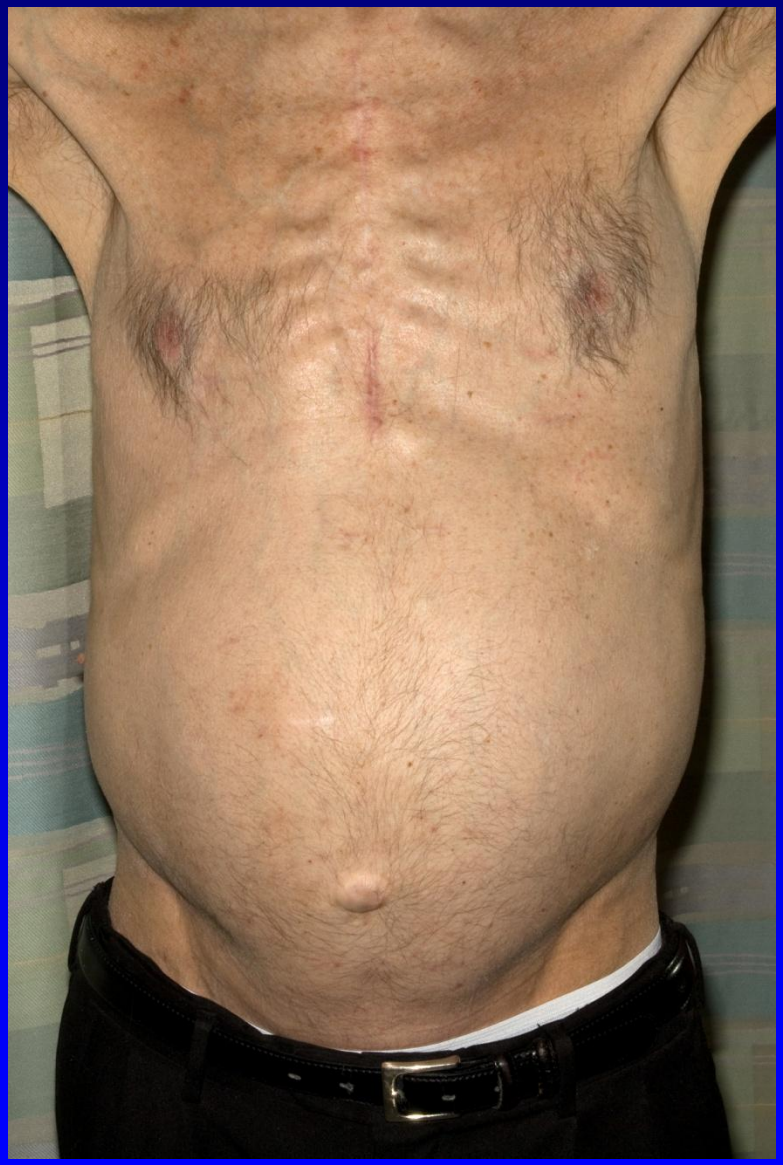


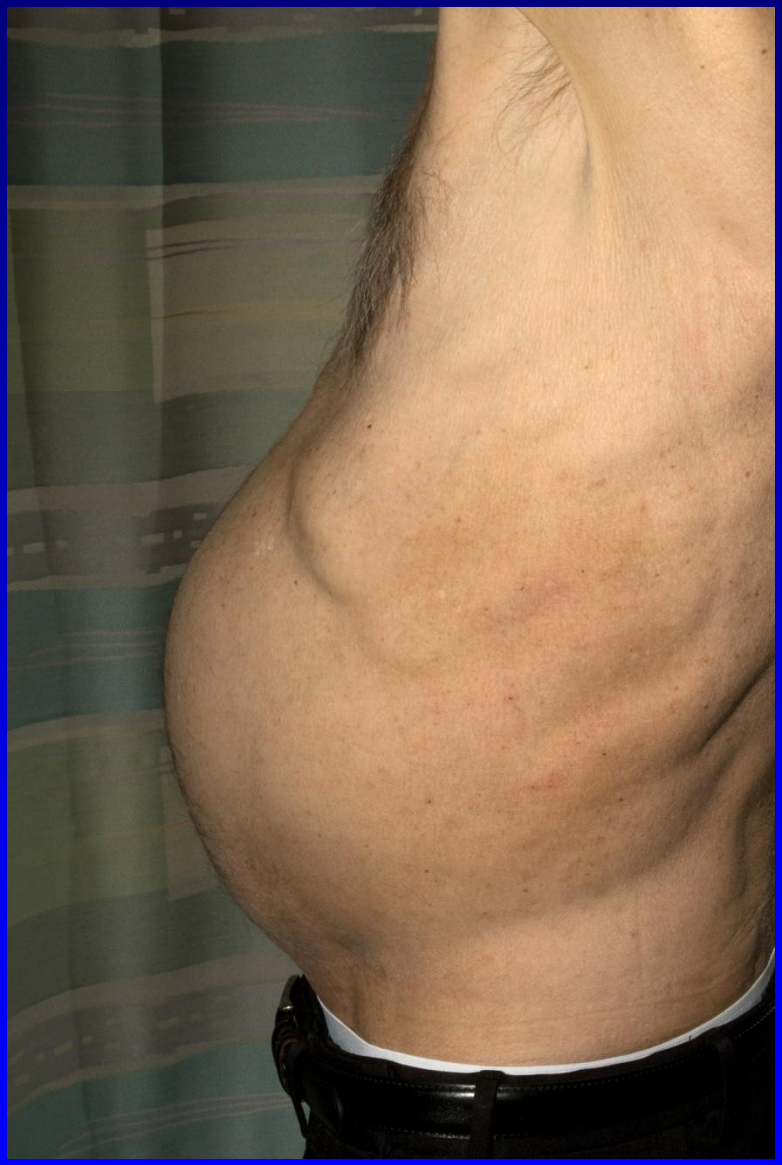
Ruxolitinib Improves Splenomegaly in Patients With and Without JAK2 Mutation



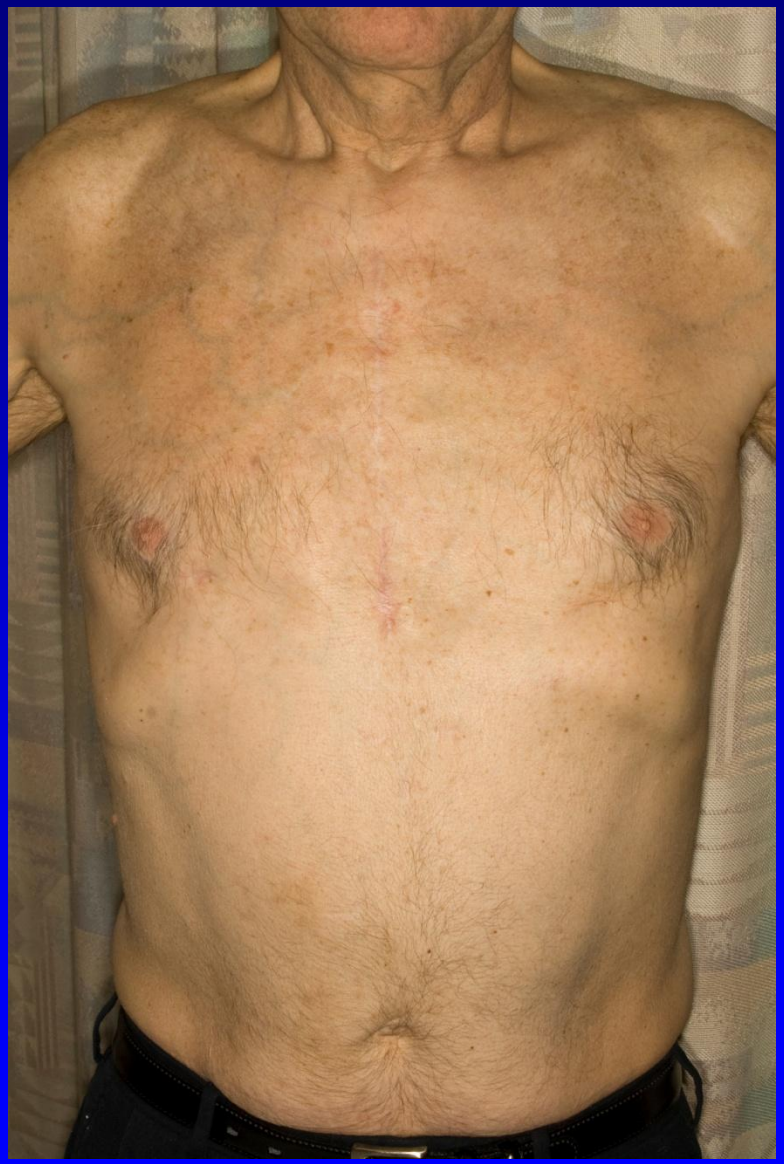
Note: 25mg BID cohort; data are censored after a dose change.

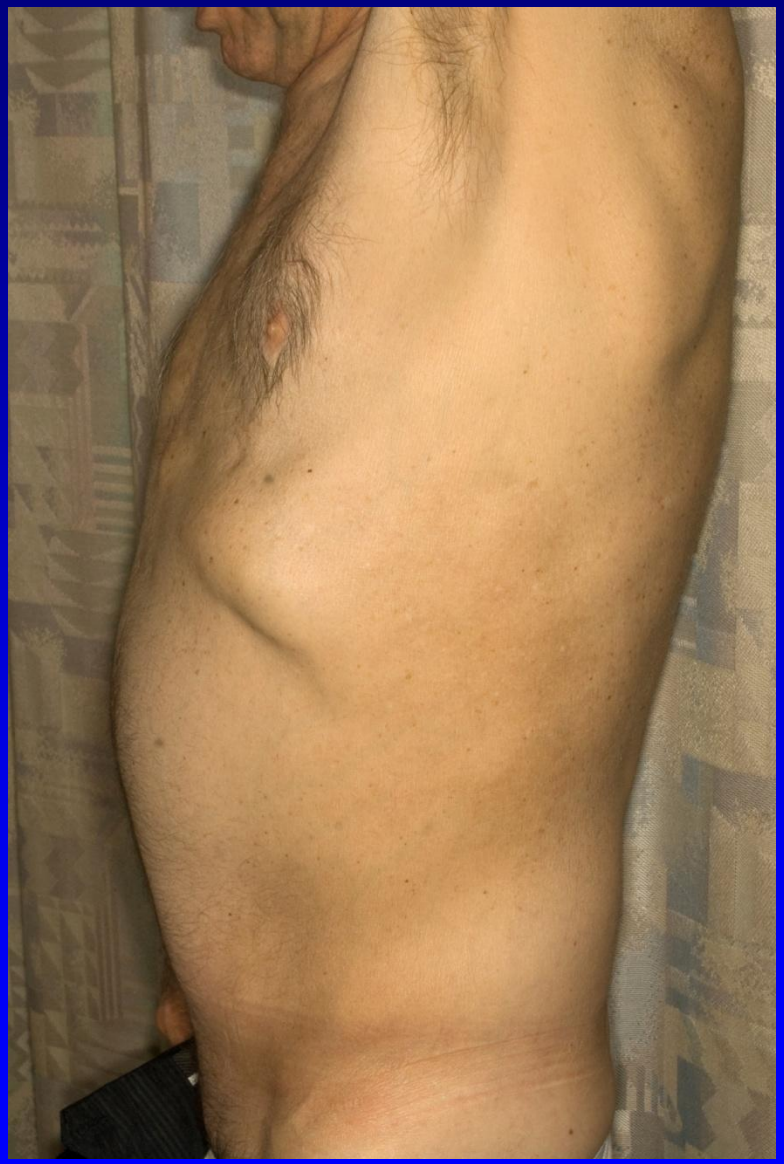
Splenomegaly in MF Patient Pre-Therapy





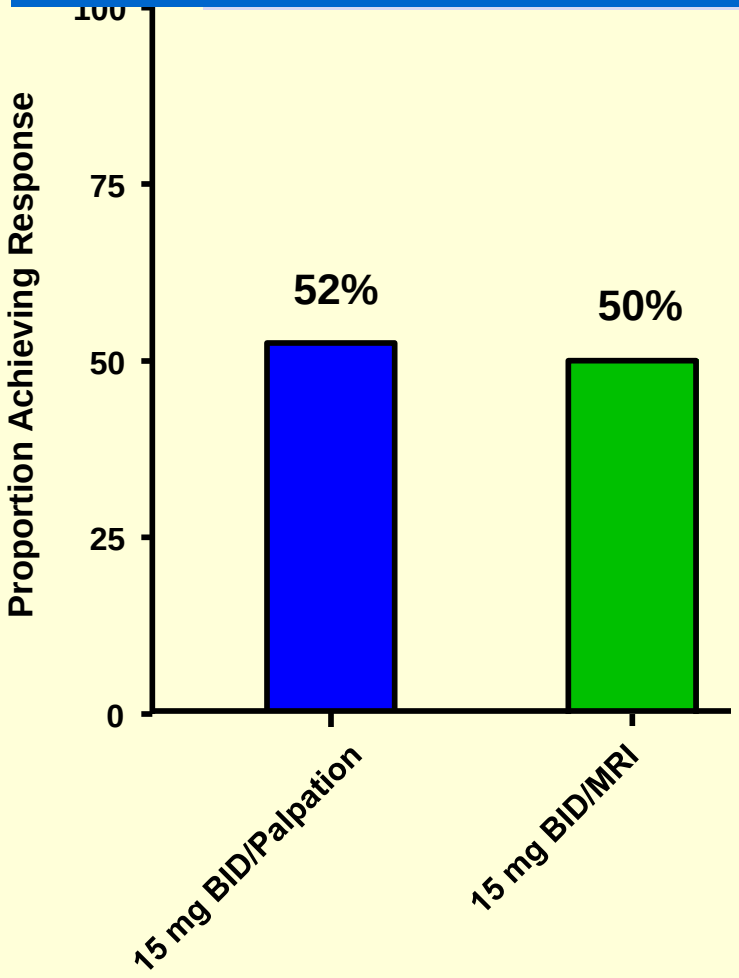
Splenomegaly after 2 Months of Therapy

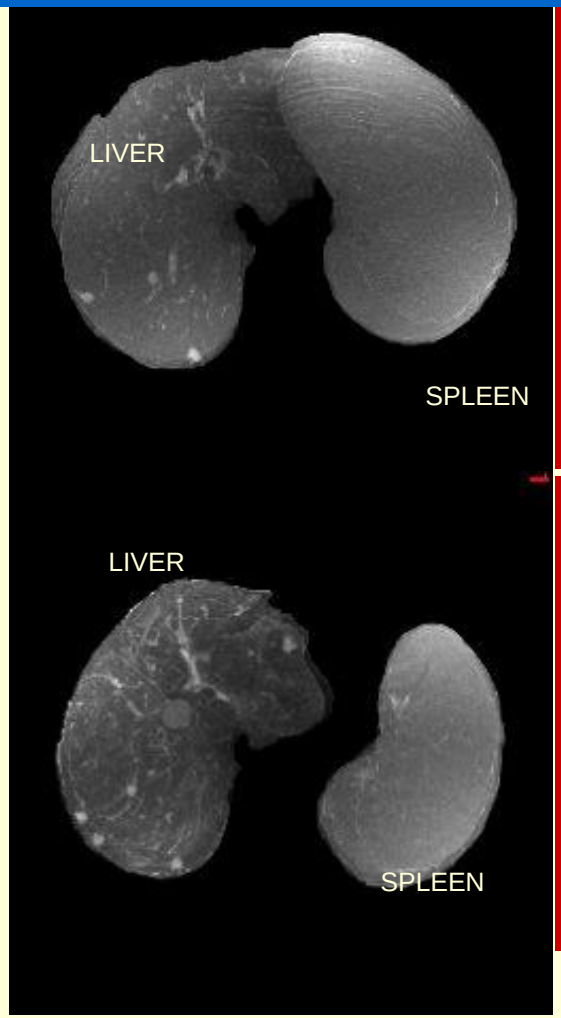




Spleen Volume Decrease by MRI Parallels Spleen Size Reduction by Palpation

50% size reduction by palpation (response by IWG Criteria) corresponds to 35% volume reduction by MRI



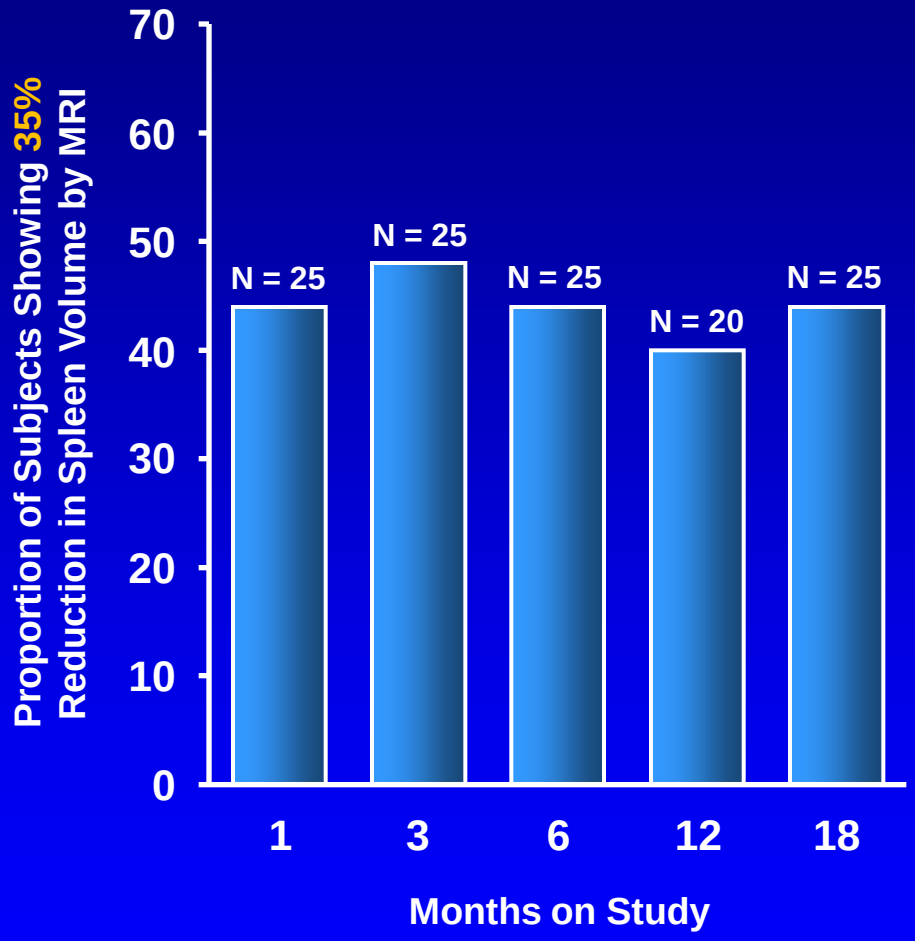


BEFORE THERAPY

AFTER 6 MONTHS

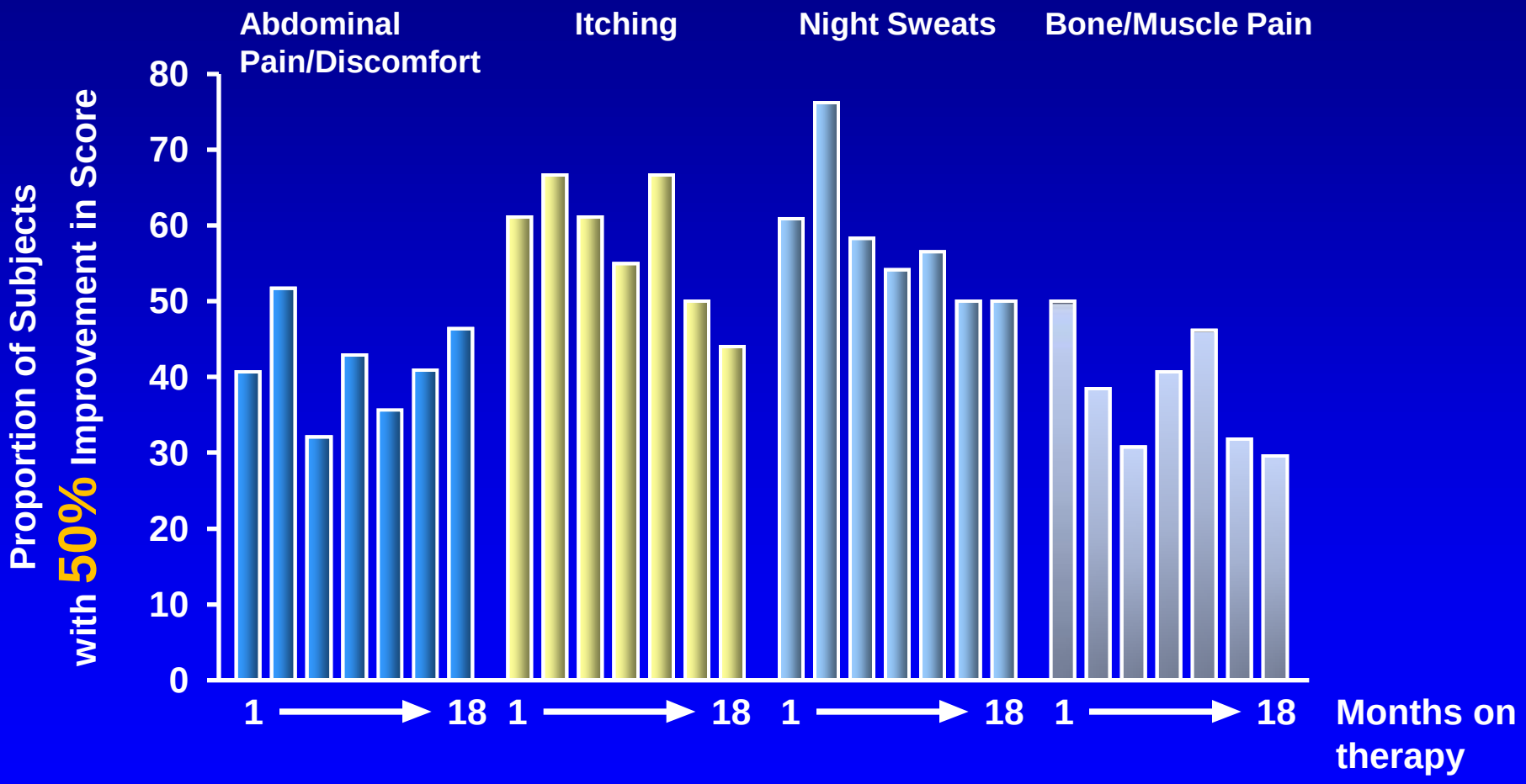
53% decrease In spleen volume, 32% decrease in liver volume

Spleen Size Reduction During 18 Month Follow-up: Reduction in Spleen Volume by MRI (ITT analysis)



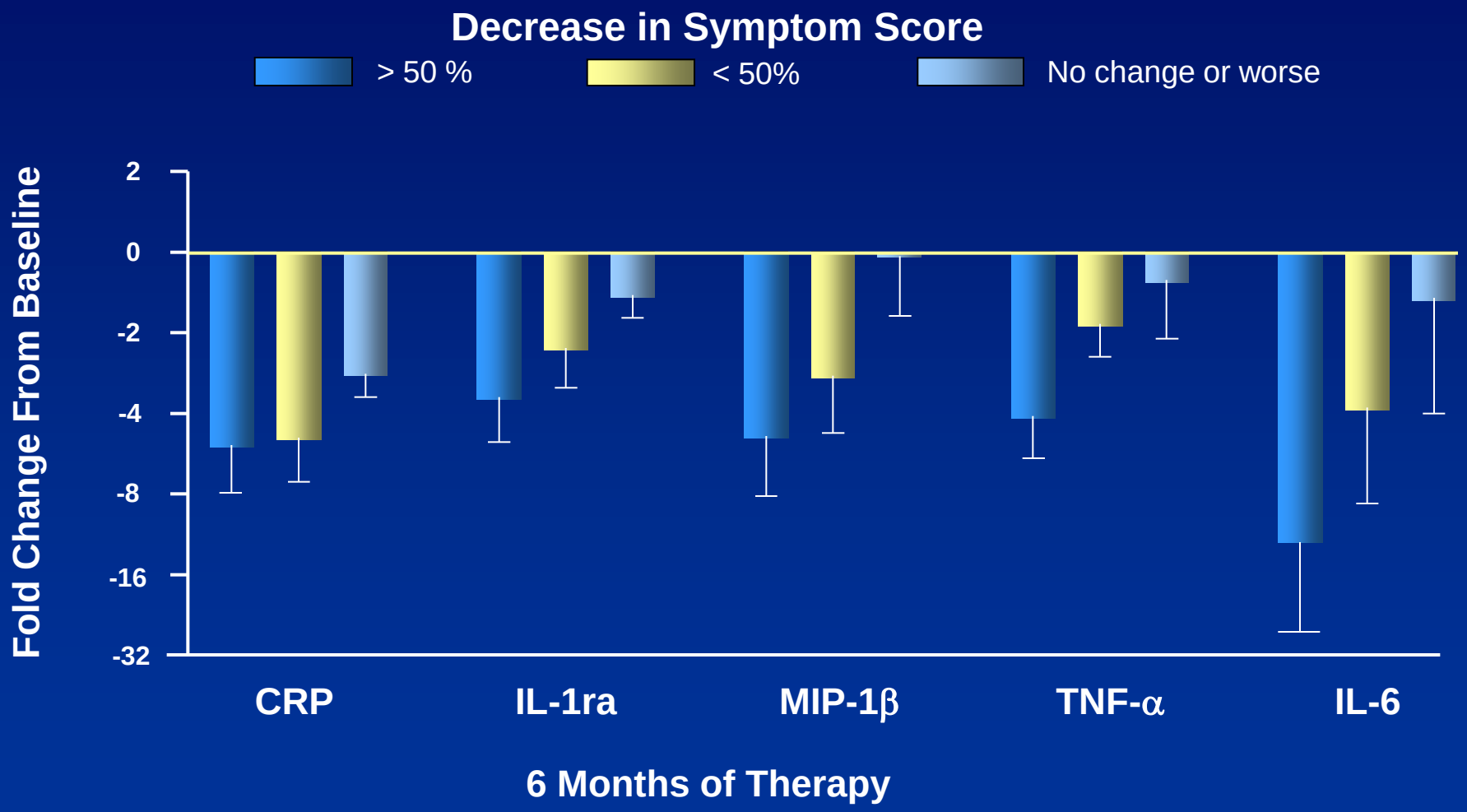
- **Subjects initiated dosing at 15 mg BID with individual optimization**
- **Subjects with a missing observation, but subsequent data were censored for the missing data timepoint**

Rapid and Durable Improvement in Symptoms: Optimized Dosing Regimen (15 mg BID dose)



Data collected using Myelofibrosis Symptom Assessment Form (Mesa et al)

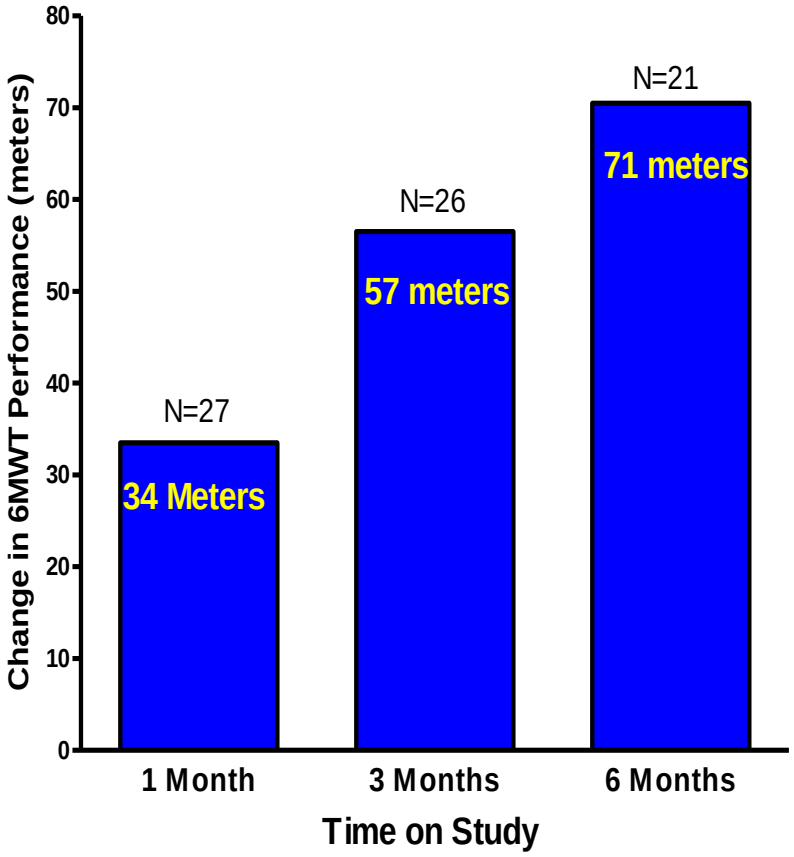
Improvement in Symptoms Associated With Durable Suppression of Inflammatory Cytokines in Plasma

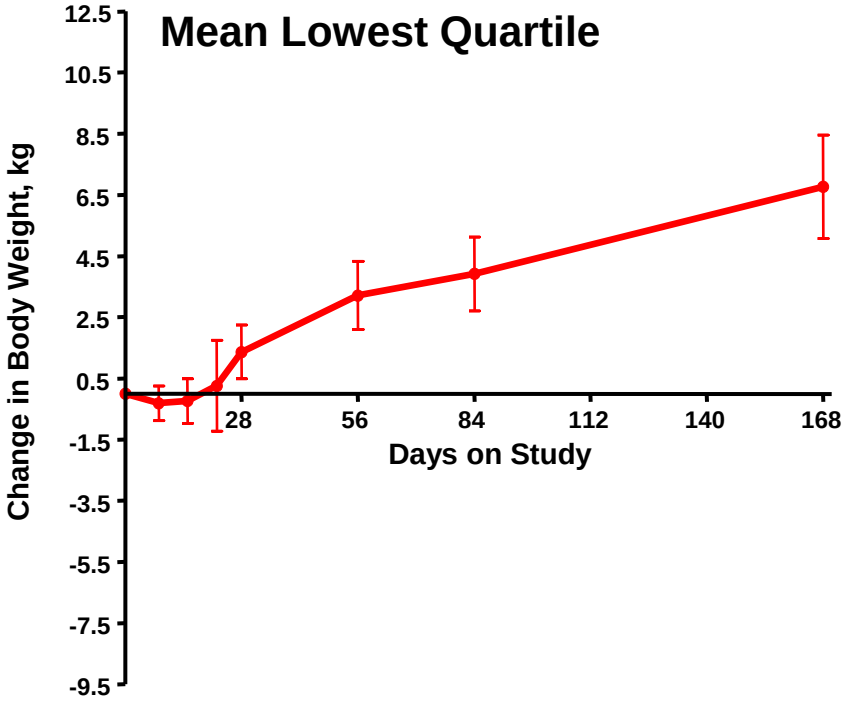


Verstovsek S, et al. NEJM 363:1182.

Improved Exercise Capacity and Body Weight

- 6-minute walk test (6MWT) is well established measure of exercise capacity
- MF patients walk 60-90 meters less than age-matched healthy volunteers





Impact on Blood and Bone Marrow

- High white blood cells and high platelets decrease to normal levels
- 10-15 % of patients achieved long lasting transfusion independence
- Percent blast in blood stays stable
- Bone marrow fibrosis does not change, stays stable
- JAK2V617F allele burden may decrease

Phase III Registration Trials

COMFORT
Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment

COMFORT I

Patients with MF (N = 309)

Randomized 1:1

- **INC424 (oral) 15 mg BID or 20 mg BID**
- **Placebo (oral) BID**

USA, Canada, Australia

COMFORT I Primary Endpoint

- Number of subjects achieving ≥ 35% reduction in spleen volume from baseline to week 24*

COMFORT II

Patients with MF (N = 219)

Randomized 2:1

- **INC424 (oral) 15 mg BID or 20 mg BID**
- **Best available therapy**

EUROPE: Austria, Belgium, France, Germany, Italy, Netherlands, Spain, Sweden, UK

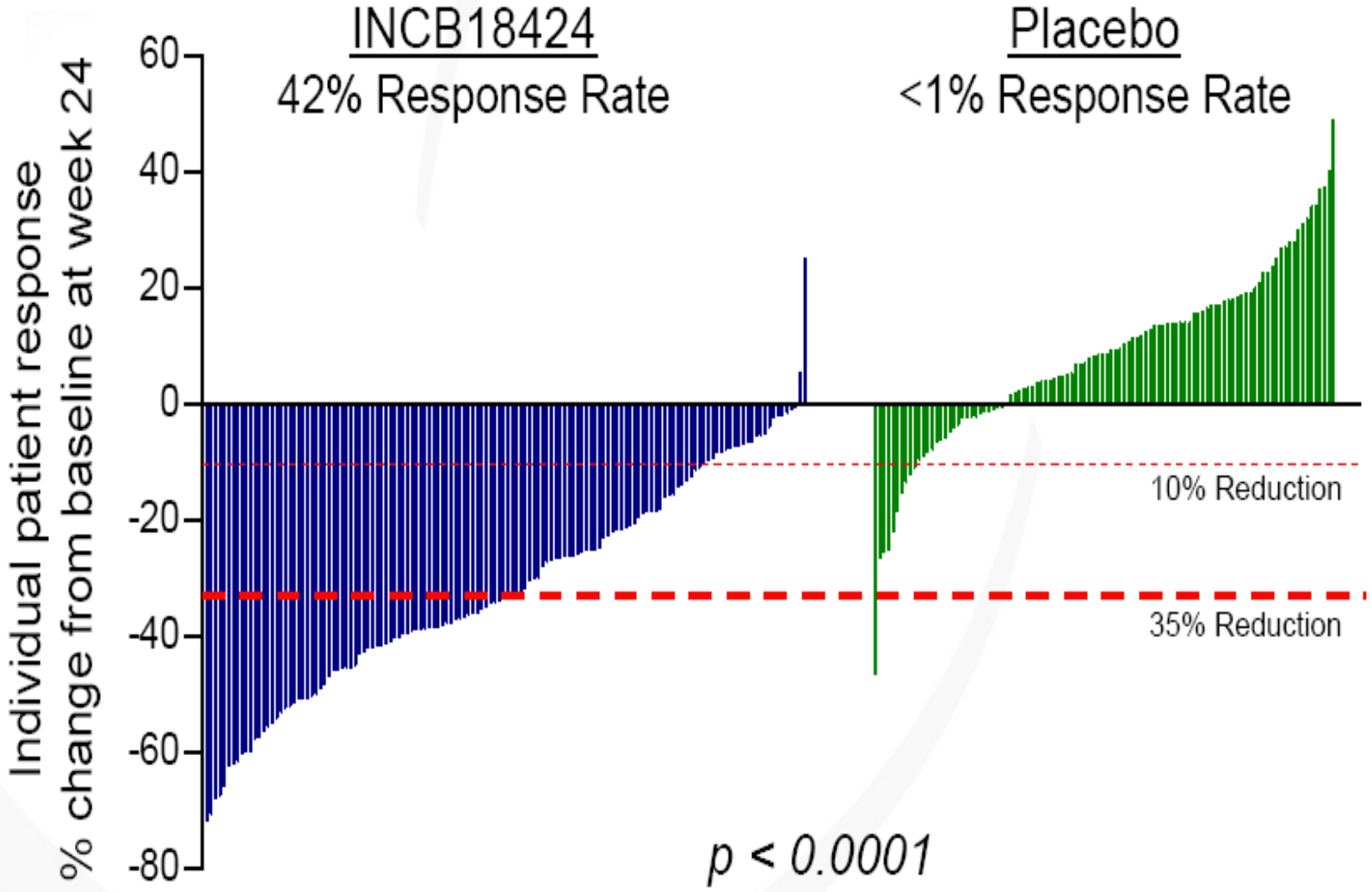
COMFORT II Primary Endpoint

- Number of subjects achieving ≥ 35% reduction in spleen volume from baseline to week 48*

Both trials ongoing but completed enrollment

* As measured by MRI (or CT scan in applicable subjects).

Response defined as ≥ 35% reduction from baseline at week 24



Phase I/2 Study of SB1518, A Novel JAK2/FLT3 Inhibitor, in the Treatment of Primary Myelofibrosis

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[4]S*BIO PTE LTD, Singapore, Singapore

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- **Phase 1:**
  - **100 to 600 mg/day**
- **DLT**
  - **Gi disturbance – nausea and diarrhea**
  - **NO myelosupression**

- **Phase 2 (N = 31): 400 mg/day**

Parameter	(N = 31)
Median Age (Range)	67 (47-83)
Male	22 (71%)
Median time (months) since last MF treatment	2
ECOG Performance Status	0 = 6 (19%) 1 = 17 (55%) 2 = 8 (26%)
Type of Myelofibrosis	
Primary MF	18
PPV/PET MF	11/2
JAK2 mutation: Yes/No	24/7

Demographic and Baseline Characteristics

Parameter	(N = 31)
Previously treated for MF	27 (87%)
Baseline Hematology	
Grade 3 or 4 anemia	4 (13%)
Grade 3 or 4 neutropenia	2 (6%)
Grade 1,2 / 3,4 thrombocytopenia	13 (42%) / 4 (13%)
Spleen size (cm) by PE: Median (range)	19 (8-29)
Spleen volume (mm^3) by MRI: Median (range)	2338 (1216-9084)

Patient Disposition

Characteristic	(N=31)
Discontinued drug	11
Adverse Event	1
Death	1
Disease Progression	1
Lack of Response	7
Withdrew Consent	1

11/31 (35%) patients have discontinued SB1518

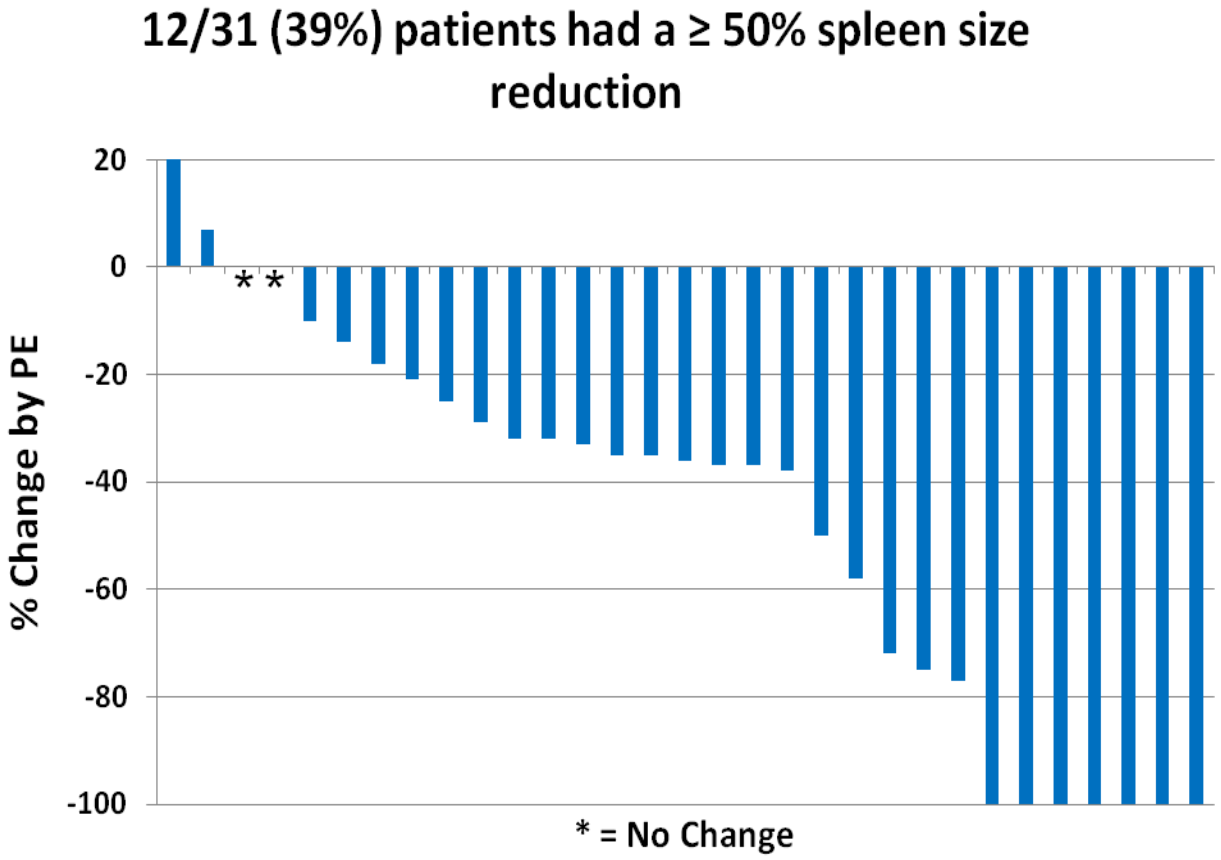
Median time on study: 168 days (36 – 189), final median not reached

Related Treatment Emergent Adverse Events (Non-hematological, ≥ 2 Patients)

Adverse Event (31 Patients)	%			
	1	2	3	4
Diarrhea	48	29	10	0
Nausea	26	13	6	0
Vomiting	23	3	3	0
Fatigue	3	6	0	0
Pain in extremity	0	6	0	0
Pruritus	6	0	3	0

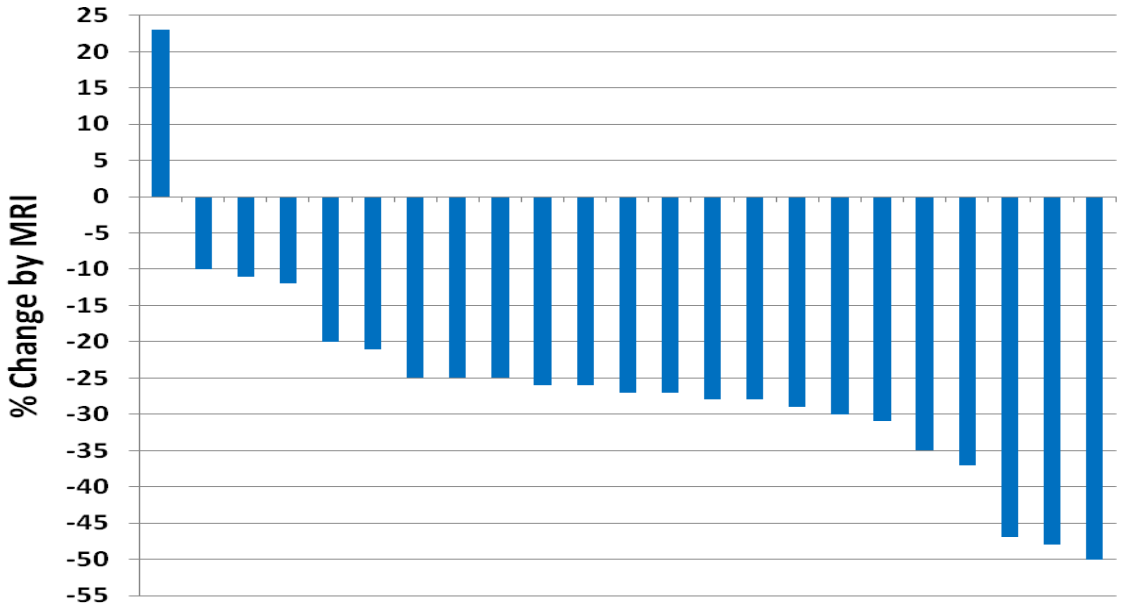
- No significant myelosupression was observed
- SB1518 was equally well tolerated by patients with normal platelet counts and those with thrombocytopenia

SB1518 Significantly Reduces Splenomegaly in MF Patients as Measured by Physical Exam



SB1518 Significantly Reduces Splenomegaly in MF Patients as Measured by MRI

5/30 (17%) had ≥ 35% reduction



- **Correlation between PE and MRI measurements observed**
  - **50% reduction by PE ≈ 25% reduction in spleen volume by MRI**
  - **80% reduction by PE ≈ 35% reduction in spleen volume by MRI**

MF-SAF: Improvement in MF-related Symptoms

(Patients with baseline score ≥ 3)

Symptom	N	C1D1 (baseline)	C7D1	Mean change from baseline	% reduction from baseline
		Mean	Mean		
Abdominal pain	10	5.5	2.0	-3.5	64
Bone pain	9	6.0	3.3	-2.7	45
Early satiety	16	5.5	3.3	-2.2	40
Inactivity	17	4.8	2.7	-2.1	44
Night Sweats	9	5.2	2.9	-2.3	46
Pruritus	6	6.2	2.2	-4	65

- 40-65 % improvement in most symptoms was observed at Month 6 relative to baseline (not ITT analysis)

Benefits at 400 mg/day

- Improvements in splenomegaly and symptoms
- Decrease of high WBC and platelets
- Decrease in JAK2 allele burden
- No decrease in inflammatory cytokines
- No weight gain

- Treatment of patients with significantly impaired hematopoiesis with full-dose, daily SB1518 is possible without exacerbating hematocytopenias
- PLAN: Phase 3 study in MF patients with symptomatic splenomegaly and thrombocytopenia

Not ready for efficacy comparison of different JAK2 inhibitors

- Different:
  - stage of development (phase 1, 2, or 3)
  - # of patients treated
  - duration of time on therapy
  - dose used, optimal vs. maximum tolerated

- Different/imprecise ways to measure benefit:
  - spleen reduction by physical exam vs. volumetric MRI
  - MF specific questionnaire for symptoms vs. others
  - definition of what is transfusion dependence and independence is changing

	Ruxolitinib study	SB1518 study
50% spleen reduction by palpation is equal to…	**35% volume decrease by MRI**	**25% volume decrease by MRI**

Clinical Trials in MPN at MD Anderson

Agent (Company)	Diseases and studies	Type of therapy
Imetelstat (Geron)	ET: phase II	Telomerase inhibitor
LY2784544 (Lilly)	ET/PV/MF: phase I/II	JAK2 inhibitor
AZD1480 (AstraZeneca)	MF: phase I/II	JAK1 and JAK2 inhibitor
Ruxolitinib (Incyte)	MF low platelets: phase I/II MF: phase II (slow release) PV: phase III	JAK1 and JAK2 inhibitor
NS-018 (NS Pharma)	MF: phase I/II	JAK2 inhibitor
BMS911543 (BMS)	MF: phase I/II	JAK2 inhibitor
AB0024 (Gilead)	MF: phase II	LOXL2 antibody
SB939 (S*Bio)	MF: phase II	HDAC inhibitor
Pomalidomide +/- pred	MF: phase II and III	IMID

THANK YOU

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