Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med 2010;363:1117-27.

SUPPLEMENTARY APPENDIX

Treatment Plan

Four weeks was considered 1 cycle of therapy. Baseline evaluations included a complete physical examination, complete blood count, comprehensive biochemistry panel, electrocardiogram, urinalysis, CD34+ blood cell count, bone marrow biopsy and aspirate with cytogenetic analysis, and molecular test for *JAK2* V617F mutation (including a determination of a percentage of *JAK2* V617F DNA in total *JAK2* DNA [i.e., *JAK2* V617F allele burden] using the previously published method[1]). Patients were seen after each cycle for the first 3 cycles (patients in the phase I part were seen weekly during the first cycle), then every 3 cycles. If grade 3/4 toxicity occurred, a weekly telephone assessment with a review of blood tests was done. A complete blood count, comprehensive biochemistry panel, and urinalysis were obtained every 1 to 2 weeks for the first 3 cycles, then every 2 to 4 weeks thereafter. Electrocardiogram, CD34+ blood cell count and *JAK2* mutational analysis in peripheral blood were obtained after each cycle for 3 cycles, then every 3 cycles. Bone marrow biopsy with staining for fibrosis, cytogenetic analysis (if abnormal before therapy), and *JAK2* mutational analysis (if present before therapy) were performed every 3 to 6 cycles.

Dose modifications were allowed in case of toxicity or lack of response. Patients who developed grade 3/4 hematologic toxicity had to interrupt therapy until counts recovered, and therapy was restarted at a lower dose. Use of granulocyte growth factors was allowed in cases of drug-induced neutropenia while the drug was on hold. Erythropoietin and glucocorticoids (equivalent to prednisone >10 mg/d) were not allowed during the study. Patients who developed grade 3/4 nonhematologic toxicity could interrupt therapy until adverse events resolved, and then therapy was restarted, frequently at a lower dose. If toxicity did not resolve within 2 cycles, therapy was discontinued. Dose escalation was allowed for patients who started therapy at lower than the maximum tolerated dose, who did not respond after the initial 1 to 3 cycles of therapy, and had no drug-related grade 3/4 toxicities. Toxicities were evaluated using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Patients may continue on therapy indefinitely, provided they have no evidence of disease progression and are receiving clinical benefit as judged by the treating physician.

Risk Categories and Response Evaluation

A new risk stratification system identified 5 adverse risk factors including age greater than 65 years, presence of constitutional symptoms, hemoglobin level less than 10 g/dL, leukocyte count greater than 25 x 10(9)/L, and circulating blast cells 1% or greater as predictors of shortened survival.[2] Based on the presence of 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2) or greater than or equal to 3 (high risk) of these variables, 4 risk groups with no overlapping in their survival curves were delineated with respective median survivals of 135, 95, 48, and 27 months (P< .001)[2] (**Supplementary Table 1A**). International Working Group for Myelofibrosis Research and Treatment response criteria were used to evaluate objective responses in this study[3] (**Supplementary Table 1B**). Objective response assessments were performed after every cycle for the first 3 cycles, then every 3 cycles.

The baseline characteristics of patients in the different dose groups are summarized in **Table 2,** and a summary of the dose groups and assessments conducted (via protocol amendments) for various groups is shown in **Supplementary Figure 1**. Changes in spleen and liver volume were assessed by magnetic resonance imaging in a subset of patients (**Supplementary Figure 2).** This objective parameter was implemented for approximately the last 20% of subjects enrolled in the study, and included 23 patients who initiated therapy at 15 mg BID**.** Symptomatic response to treatment and overall quality of life were assessed using a modified version of the Myelofibrosis Symptom Assessment Form (MFSAF)[4] (**Supplementary Table 3**). Implementation of the MFSAF assessment occurred at the midpoint of the study; data are available for all patients initiating therapy at 15 mg twice-daily and for 15 patients starting at 10 mg twice-daily, 13 at 25 mg twice-daily, 19 at 50 mg once-daily, and 3 each at 100 mg once-daily and 200 mg once-daily. Subjects who did not have a given symptom score at baseline or for whom the baseline symptom score was zero were excluded from analyses of percent improvement for that score or combined score. Functional improvement was assessed using the 6-minute walk test (6MWT), a self-paced, submaximal exercise capacity assessment conducted under strict guidelines.[5] The 6MWT was only conducted in patients who initiated therapy under the individual dose-optimization paradigm (15 or 10 mg twice-daily). Responses/improvements were tabulated using summary statistics. Post hoc subgroup analyses were conducted on subjects with and without the JAK2V617F mutation and on pools of subjects based on their MF subtype. Response rates were compared using exact confidence intervals.

Laboratory Correlates

Pharmacodynamic studies were performed to assess the consequences of JAK1 and 2 inhibition (**Supplementary Figure 3**). Whole blood collected at baseline and at different times after treatment was used for the evaluation of phosphorylated STATs 3 and 5, using anti-pSTAT3 and pSTAT5 antibodies and western blotting and/or enzyme-linked immunosorbent assay. Changes from baseline were estimated with 95% confidence intervals. Plasma, separated from whole blood received after overnight shipment from controls and patients, was used for the measurement of cytokines and growth factors using multiplexed immunoassays and Rules-Based Medicine, Inc. (Austin, TX) Human MAP panel. Microsoft Excel (Redmond, WA) was used to calculate fold-changes, with the log2-transformed data being further analyzed by 2-dimensional hierarchical clustering using Cluster 3.0.[6,7] The resulting clusters were visualized and further analyzed in Java Treeview.[8] Changes in *JAK2* V617F allele burden in whole blood during therapy were measured according to the previously published method.[9]

Pharmacokinetic and Pharmacodynamic Properties

INCB018424 was absorbed rapidly, with peak plasma concentration occurring 1 to 3 hours after dosing. Thereafter, the plasma concentrations declined rapidly in a biphasic manner, with a terminal half-life of 2 to 3 hours. Drug exposures increased in a linear fashion and did not show plateau at doses up to 200mg once-daily. Phosphorylated STAT (pSTAT), a marker of activated JAK-STAT pathway that is typically absent in healthy volunteers, was evident in patients' blood samples at baseline regardless of the *JAK2* V617F mutation status (**Supplementary Figure 3A**). A dose-dependent reduction in pSTAT3, measured 2 hours after treatment administration, was observed, reaching 70% inhibition at the 25-mg dose (**Supplementary Figure 3B**). In a representative set of patients (25mg twice-daily group; n=24, *JAK2* V617F-positive (N=20), *JAK2* V617F-negative (N=4)) after 4 weeks of therapy, mean pSTAT3 levels were reduced to background levels similar to those detected in normal volunteers (**Supplementary Figure 3C**).

Performance Status Improvement and Survival Analysis

After the first cycle of treatment, the percentage of patients with Eastern Cooperative Oncology Group performance level 0, compared with baseline, increased across all treatment groups (16% at baseline versus 48% after 1 month of therapy), whereas those with ECOG 1 and 2 decreased (73% versus 50%, and 11% versus 2%, at baseline versus 1 month of therapy,

respectively). These improvements were generally maintained during follow-up. Kaplan-Meier methodology was used to generate survival curves (**Supplementary Figure 5**).

References

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Supplementary Table 1A: Risk Factors and risk groups in primary myelofibrosis according to prognostic scoring system of primary myelofibrosis

Risk Factors	**Association with Survival (Statistical significance)**	
Age >65 years	P<0.001	
Constitutional Symptoms	P<0.001	
Hb < 10g/dL	P<0.001	
WBC count >25 x 10^9/L	P<0.001	
Blood Blasts >1%	P<0.001	
Risk Group	**No. of Factors**	**Median Survival (mo; 95% Conf. Int)**
Low	0	135 (117 – 181)
Intermediate -1	1	95 (79-114)
Intermediate – 2	2	48 (43 – 59)
High	>3	27 (23 – 31)

Supplementary Table 1B: International Working Group for Myelofibrosis Research and Treatment Response Criteria

Complete remission (CR):

- Complete resolution of disease-related symptoms and signs including palpable hepatosplenomegaly.
- Peripheral blood count remission defined as hemoglobin level at least >11 g/dL, platelet count at least $100x10^9$/L, and absolute neutrophil count at least $1.0x10^9$/L. In addition, all 3 blood counts should be no higher than the upper normal limit.
- Normal leukocyte differential including disappearance of nucleated red blood cells and immature myeloid cells in the peripheral smear, in the absence of splenectomy.*
- Bone marrow histologic remission defined as the presence of age-adjusted normocellularity, no more than 5% myeloblasts, and an osteomyelofibrosis grade no higher than 1.**

Partial remission (PR): Requires all of the above criteria for CR except the requirement for bone marrow histologic remission. However, a repeat bone marrow biopsy is required in the assessment of PR and may or may not show favorable changes that do not however fulfill criteria for CR.

Clinical improvement (CI): Requires one of the following in the absence of both disease progression (as outlined below) and CR/PR assignment (CI response is validated only if it lasts for no fewer than 8 weeks).

- A minimum 2 g/dL increase in hemoglobin level or becoming transfusion independent (applicable only for patients with baseline hemoglobin level of less than 10 g/dL).§
- Either a minimum 50% reduction in palpable splenomegaly of a spleen that is at least 10 cm at baseline or a spleen that is palpable at more than 5 cm at baseline becomes not palpable.§§
- A minimum 100% increase in platelet count and an absolute platelet count of at least 50,000 x 10^9/L (applicable only for patients with baseline platelet count below $50x10^9$/L).
- A minimum 100% increase in ANC and an ANC of at least $0.5x10^9$/L (applicable only for patients with baseline absolute neutrophil count below $1x10^9$/L).

Progressive disease: Requires one of the following:¶

- Progressive splenomegaly that is defined by the appearance of a previously absent splenomegaly that is palpable at greater than 5 cm below the left costal margin or a minimum 100% increase in palpable distance for baseline splenomegaly of 5-10 cm or a minimum 50% increase in palpable distance for baseline splenomegaly of greater than 10 cm.
- Leukemic transformation confirmed by a bone marrow blast count of at least 20%.
- An increase in peripheral blood blast percentage of at least 20% that lasts for at least 8 weeks.

Stable disease: None of the above.

Relapse: Loss of CR, PR, and CI. In other words, a patient with CR or PR is considered to have undergone relapse when he or she no longer fulfils the criteria for even CI. However, changes from either CR to PR or CR/PR to CI should be documented and reported.

*Because of subjectivity in peripheral blood smear interpretation, CR does not require absence of morphological abnormalities of red cells, platelets, and neutrophils.

** In patients with CR, a complete cytogenetic response is defined as failure to detect a cytogenetic abnormality in cases with a pre-existing abnormality. A partial cytogenetic response is defined as 50% or greater reduction in abnormal metaphases. In both cases, at least 20 bone marrow- or peripheral blood-derived metaphases should be analyzed. A major molecular response is defined as the absence of a specific disease-associated mutation in peripheral blood granulocytes of previously positive cases. In the absence of a cytogenetic/molecular marker, monitoring for treatment-induced inhibition of endogenous myeloid colony formation is encouraged. Finally, baseline and post-treatment bone marrow slides are to be stained at the same time and interpreted at one sitting by a central review process.

§Transfusion dependency is defined by a history of at least 2 units of red blood cell transfusions in the last month for a hemoglobin level of less than 8.5 g/dL that was not associated with clinically overt bleeding. Similarly, during protocol therapy, transfusions for a hemoglobin of 8.5 g/dL or more is discouraged unless it is clinically indicated.

§§In splenectomized patients, palpable hepatomegaly is substituted with the same measurements.

¶It is acknowledged that worsening cytopenia might represent progressive disease but its inclusion as a formal criterion was avoided because of the difficulty distinguishing disease-associated from drug-induced myelosuppression. However, a decrease in hemoglobin of ≥ 2 g/dL, a 100% increase in transfusion requirement, and new development of transfusion dependency, each lasting for more than 3 months after the discontinuation of protocol therapy can be considered disease progression.

Supplementary Table 2: Baseline Characteristics of Patients in Different Dose Groups

Parameter	10 mg BID	15 mg BID	25 mg BID	50 mg BID	25 mg QD	50 mg QD	100 mg QD	200 mg QD
n	29	35	47	5	6	22	6	3
Median age, y	61.0	65.0	67.0	62.0	60.5	65.5	71.0	75.0
Men/women, %	59/41	66/34	66/34	60/40	83/17	46/54	83/17	67/33
Risk category,* %								
Intermediate-2	34.5	17.1	23.4	20.0	33.3	40.9	33.3	33.3
High	62.0	74.3	68.0	80.0	50.0	54.5	50.0	66.7
Not determined	0.5	8.6	8.6	0	16.7	4.6	16.7	0
Tumor type, %								
PMF	41.4	54.3	50.0	60.0	80.0	63.6	83.3	0
PPV-MF	41.4	28.6	32.6	40.0	20.0	18.2	16.7	100.0
PET-MF	17.2	17.1	17.4	0	0	18.2	0	0
Peripheral blast count ≥1, %	100	90	100	100	100	100	100	100
JAK2V617F-positive, %	95.5	81.0	86.2	60.0	50.0	61.1	75.0	100.0
History of prior transfusions, %	34.5	31.4	36.2	60.0	33.3	31.8	33.3	0
Median hemoglobin, g/L	97	109	105	92	106	102	108	119
(range)	(81–130)	(74–145)	(75–169)	(74–134)	(91–153)	(72–144)	(88–121)	(112–130)
Median (range) platelet count, $x10^9$/L	208 (113–761)	351 (208–683)	263 (116–1195)	319 (102–611)	155 (130–978)	225 (101–1048)	258 (131–557)	245 (219–442)
Median (range) ANC, $x10^9$/L	9.3 (1.1–135)	13.2 (1.9–59)	13.3 (1.8–76)	8.8 (1.9–17)	8.9 (2.0–17)	13.8 (1.9–77)	15.2 (3.0–38)	16.9 (4.2–25)
Median (range) WBC, $x10^9$/L	13.7 (2.0–202)	16.7 (2.5–88)	23.4 (3.7–136)	11.9 (3.4–38)	14.6 (3.5–82)	18.7 (3.7–159)	21.6 (8.5–41)	26.8 (5.3–33)
Splenomegaly, %	93	97	83	80	100	100	100	100
Splenectomy, #	0	3	2	0	0	0	0	0
Median (range) palpable spleen length, cm, in splenomegaly	19 (3–35)	17.5 (10–29)	20 (3–32)	19 (5–22)	20 (2.5–30)	20 (2–36)	22 (11–29)	15 (10–22)

QD = once daily
BID = twice daily
ANC=absolute neutrophil count; MF=myelofibrosis; PET=post–essential thrombocythemia; PMF=primary myelofibrosis; PPV=post–polycythemia vera; WBC=white blood cell count.
*Risk category as defined by Cervantes et al.[1]

Supplementary Table 3: Modified Myelofibrosis Symptom Assessment Form

Patient ID ⊥⊥⊥⊥⊥⊥⊥⊥
Visit Day **Cycle 1 Day 1**

Modified Myelofibrosis Symptom Assessment Form (MFSAF)

The form is to be completed **by the patient** according to standard instructions on clinic visit days per Schedule of Observations *(refer to publication Tefferi et al).*
Patient's assessments must be done independent of the Investigator assessments.

Pease fill in your initials: ⊥⊥⊥⊥
Your date of birth (Day-Month-Year): ⊥⊥-⊥⊥⊥-⊥⊥⊥⊥
Today's date: (Day-Month-Year): ⊥⊥-⊥⊥⊥-⊥⊥⊥⊥

Symptom	1 to 10 (0 if absent) ranking* 1 is most favorable and 10 least favorable
General fatigue	
Night Sweats	
Itching	
Muscle or bone Pain	
Fever or uncomfortable feeling of warmth	
Cough	
Ability to move and walk around including exercise	
Swelling of extremities (arms and legs)	
Ability to bend down including to tie shoes	
Abdominal discomfort/bloating/pain	
Altered bowel movement and/or difficult or painful urination	
Appetite (include weight gained or lost)	
Difficulty sleeping	
Body image and hindrance to perform daily activities	
Patient's perception on overall quality of life	

*As reported by patient
**National Cancer Institute Common Terminology Criteria for Adverse Events
Use NA when "Not applicable" and UNK when "Unknown"

Supplimentary Table 4: Serious Adverse Events

Serious Adverse Events	All Causality Number of Patients (%)	At Least Possibly Related Number of Patients (%)
All SAEs	59 (39)	12 (7.8)
Common SAEs (>1 Patient)		
Pneumonia	10 (6.5)	1 (0.7)
Fever	6 (3.9)	2 (1.3)
Anemia	4 (2.6)	3 (2.0)
Acute Myeloid Leukemia	3 (2.0)	0
Asthenia	3 (2.0)	3 (2.0)
GI hemorrhage	3 (2.0)	0
Worsening splenomegaly	3 (2.0)	0
Systemic Inflammatory Response Syndrome (SIRS) †	2 (1.3)	2 (1.3)
Anxiety	2 (1.3)	2 (1.3)
Constitutional Symptoms	2 (1.3)	2 (1.3)
Insomnia	2 (1.3)	2 (1.3)
Multi Organ Failure	2 (1.3)	0
Disease Progression	2 (1.3)	0
Bronchitis	2 (1.3)	0
Cellulitis	2 (1.3)	0
Diarrhea	2 (1.3)	0
Sepsis	2 (1.3)	0

SAEs=serious adverse events; SIRS=Systemic Inflammatory Response Syndrome.

†SIRS occurred after abrupt cessation of INCB018424 therapy in patients with previous history of underlying cardiopulmonary disease.

SAEs occurring in a single patient and considered at least possibly related:
Bone marrow suppression, febrile neutropenia, syncope, progression to CMMoL, B-cell lymphoma, pharyngotonsillitis, pharyngitis, myalgia, sinusitis, cerebral hemorrhage.

SAEs occurring in a single patient and considered unrelated:
Benign prostatic hyperplasia, upper respiratory/pulmonary, mood altered, depression, altered mental status, appendicitis, extramedullary hematopoiesis, bilateral scrotal hydroceles, myocardial infarction, atrial tachycardia, pericarditis, worsening hairy cell leukemia, AV block, cardiac arrest, carotid artery stenosis, congestive heart failure, chest pain, myocardial ischemia, renal pain, pain in extremities, edema, prostate hemorrhage, urinary tract infection, cholestasis, diverticulitis, vomiting, abdominal pain, C. difficile colitis, pseudomembranous colitis, obstructive stenosis of airway, orthopnoea, gouty arthritis, hyperkalemia, herpes zoster, post herpetic neuralgia, arthralgia, angioedema, odynophagia, dyspnea, ruptured ovarian cyst, total mastectomy, breast cancer, patella fracture, spinal compression fracture, splenic rupture, epistaxis, non cardiac chest pain, increased demand for hemoglobin.

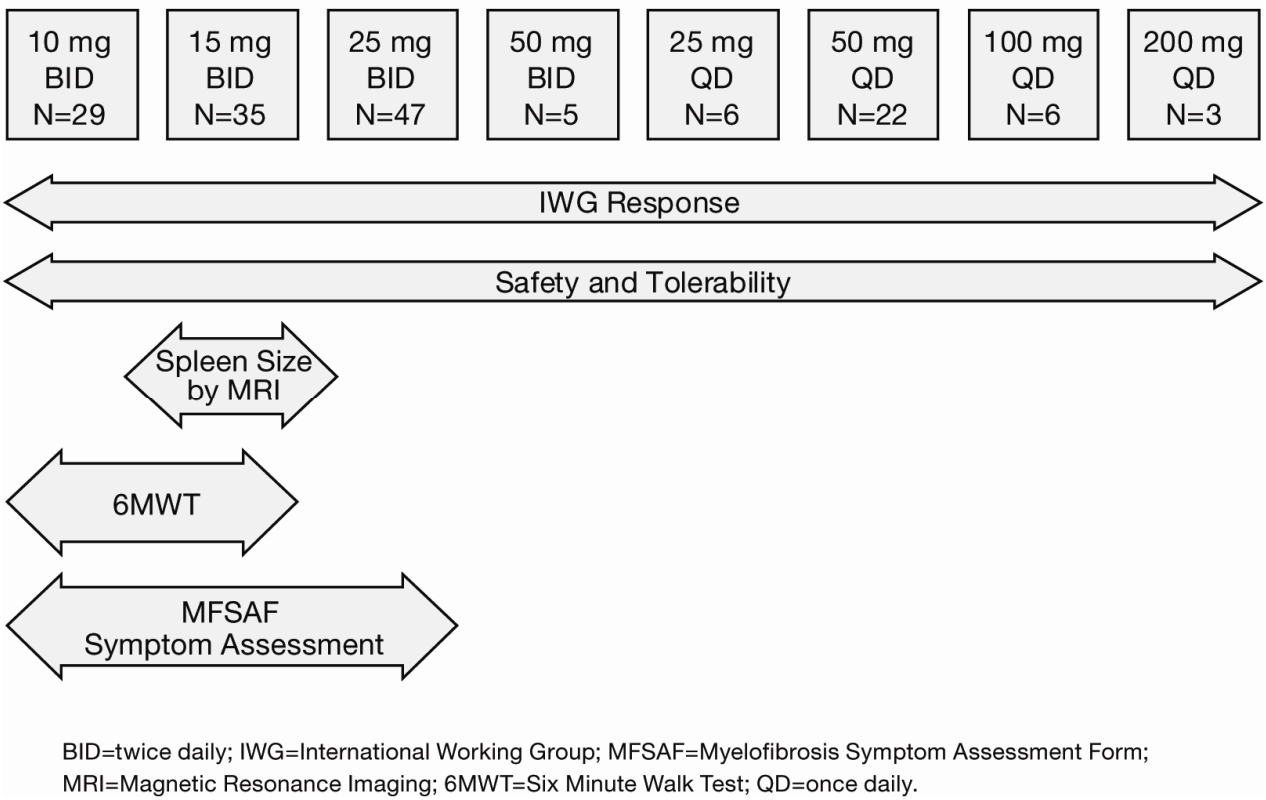
Supplementary Table 5: Patients Discontinuing Study Participation Owing to Death, Disease Progression, Unacceptable Toxicity, or Intercurrent Illness

Patient	Age/Sex	Starting Dose	Days on Drug	Details of Discontinuation	Relationship to Study Drug
1	69/Male	25 mg BID	374	Intracerebral hemorrhage without thrombocytopenia; death	Possibly related
2	71/Male	25 mg BID	147	Progression to CMMoL; evidence of CMMoL at screening	Possibly related
3	56/Female	50 mg BID	278	Thrombocytopenia (grade 3)	Possibly related
4	74/Male	50 mg BID	57	Thrombocytopenia (grade 3)	Possibly related
5	73/Male	25 mg BID	180	Multiorgan failure; death	Unrelated
6	79/Female	50 mg QD	390	Multiorgan failure; death	Unrelated
7	66/Male	25 mg QD	178	Disease progression; death	Unrelated
8	67/Male	10 mg BID	61	Cardiac arrest and death	Unrelated
9	64/Female	50 mg QD	175	Increase in peripheral blasts, diagnosis of AML	Unrelated
10	76/Male	25 mg BID	480	Development of AML	Unrelated
11	62/Female	15 mg BID	88	Disease progression	Unrelated
12	80/Female	50 mg QD	60	Intercurrent illness	Unrelated
13	64/Female	10 mg BID	236	Intercurrent illness	Unrelated
14	70/Male	25 mg BID	128	Intercurrent illness	Unrelated

QD = once daily
BID = twice daily

AML=acute myeloid leukemia; CMMoL=chronic myelomonocytic leukemia.

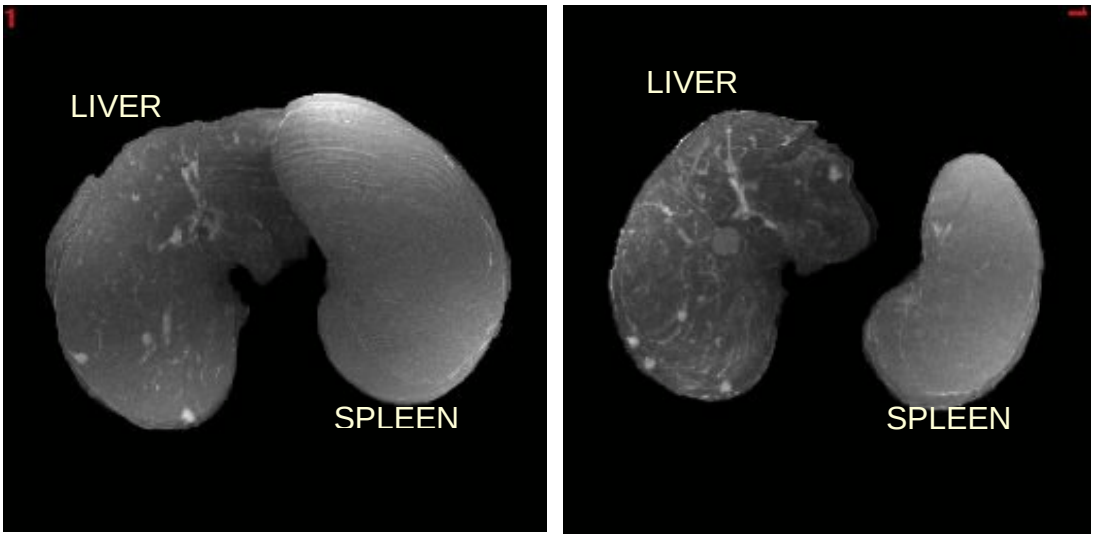
Supplementary Figure 1: Various Analyses of Study Groups



BID=twice daily; IWG=International Working Group; MFSAF=Myelofibrosis Symptom Assessment Form; MRI=Magnetic Resonance Imaging; 6MWT=Six Minute Walk Test; QD=once daily.

Supplementary Figure 2: MRI Analysis of Spleen Volume

A



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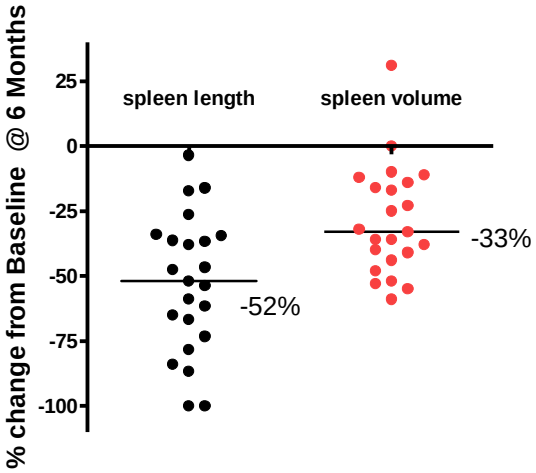
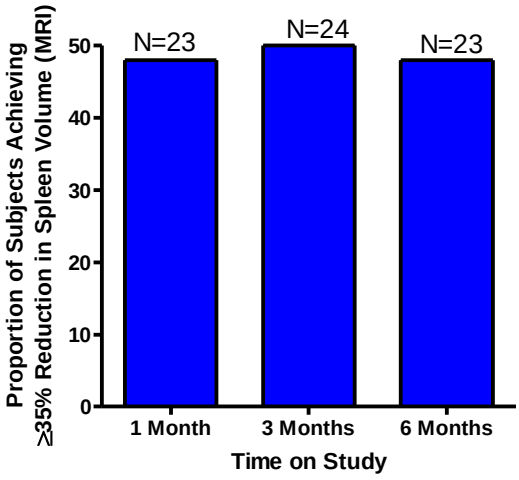


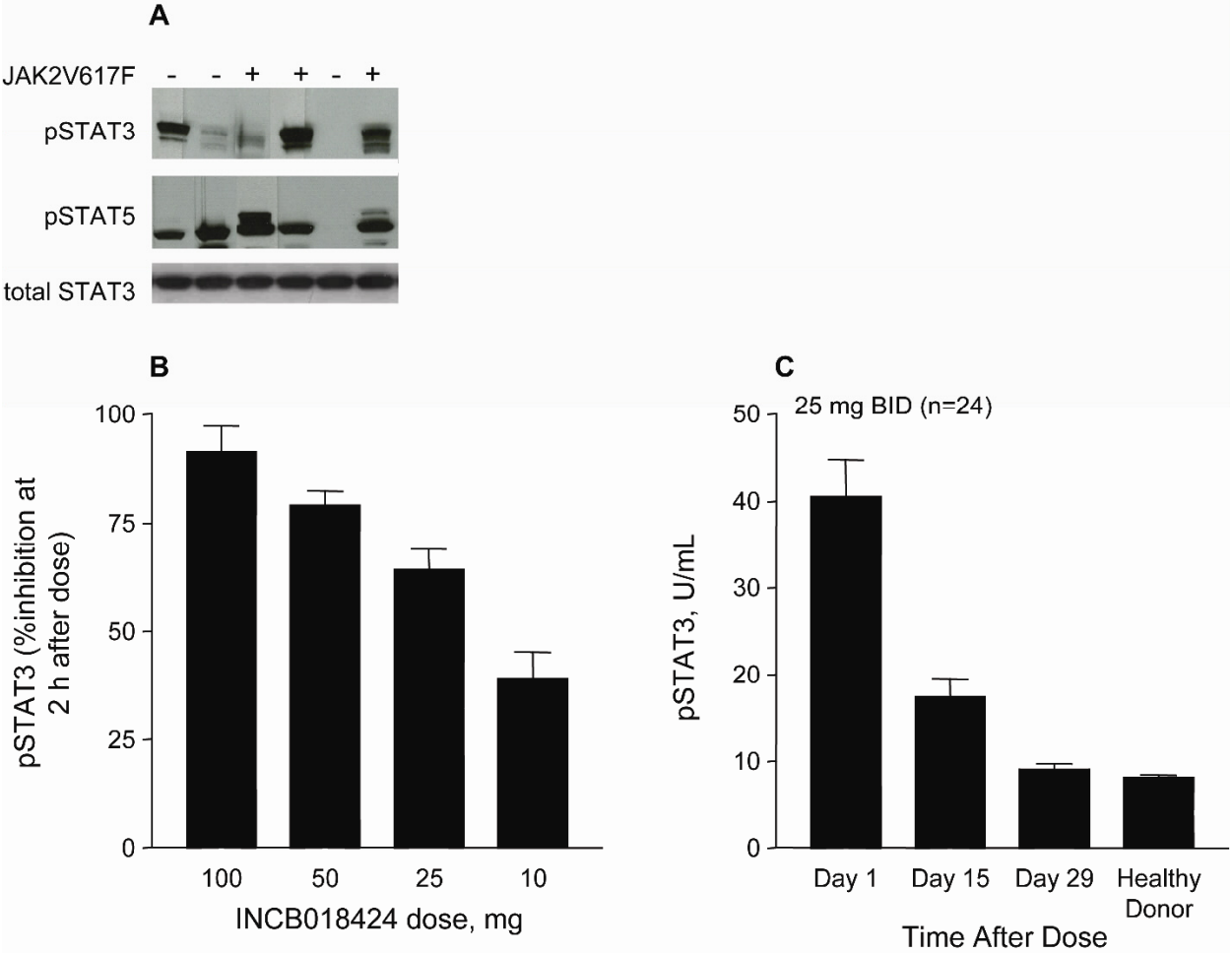
C



MRI Analysis of Spleen Volume Following INCB018424 Treatment.

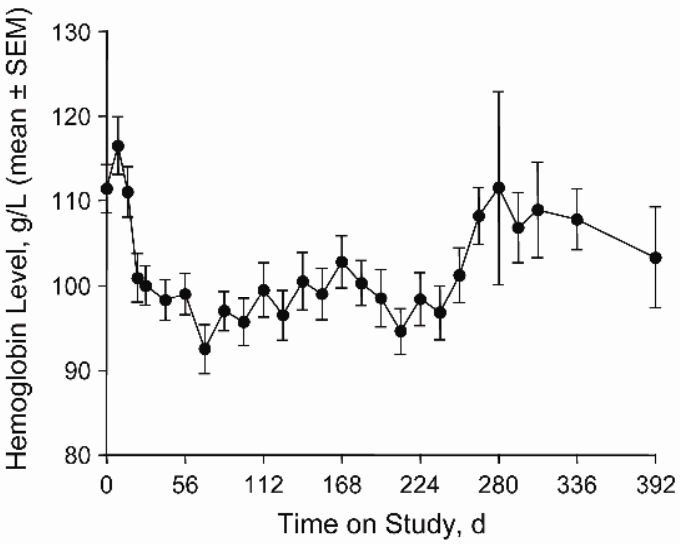
Abdominal MRI was conducted using 5-mm splice thickness, and the volume was calculated using least squares method. A 3-dimensional reconstruction of spleen and liver images are shown in panel A. A comparison of spleen volume and palpable spleen length changes after 6 months of INCB018424 treatment (15 mg BID starting dose) are shown in Panel B. About half of the patients achieved >35% reduction in spleen volume following 1 month of treatment and the reduction was maintained over a 6-month period (Panel C).

Supplementary Figure 3: Pharmacodynamic Properties of INCB018424



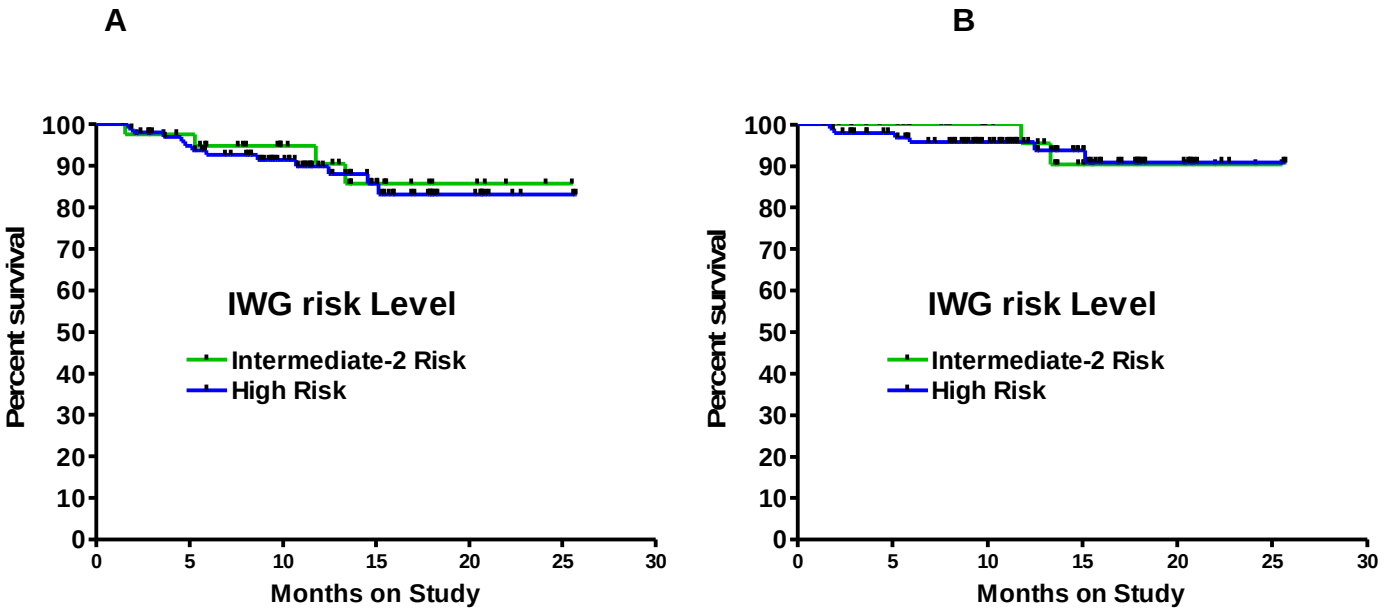
Effect INCB018424 Treatment on STAT Activation. Phosphorylated STAT3 and STAT5 were measured in whole blood collected from patients at different time points. Representative data shown indicate that constitutively active STAT as evidenced by pSTAT3 and/or pSTAT5 were present at baseline in both JAKV617F-positive and -negative patients (Panel A).Treatment with INCB018424 decreases pSTAT3 in a dose-dependent manner (Panel B). Following 28 days of treatment at 25 mg BID, mean baseline pSTAT3 levels in MF patients (*JAK2* V617F-positive (N=20), *JAK2* V617F-negative (N=4)) were reduced to levels seen in normal volunteers (Panel C).

Supplementary Figure 4: Long-term Effect of INCB018424 on Mean Hemoglobin Levels.



BID=twice daily.
Mean hemoglobin levels for patients initiating therapy at 15 mg BID or 25 mg BID.
Mean ± SEM hemoglobin levels for the combined 15-mg BID and 25-mg BID dose groups are shown.

Supplementary Figure 5: Overall Survival Analysis



Overall Survival Analysis. Patients were retrospectively assigned to high-risk or intermediate-2–risk groups[1] based on their characteristics at study entry. The relative survival was estimated using the Kaplan-Meier method considering all deaths, including those that occurred after the patient discontinued from the study (Panel A), or considering only deaths that occurred on study or within 30 days of drug discontinuation (protocol-defined follow-up period; Panel B). IWG=International Working Group.