Bromodomain and Extra-Terminal Inhibitor INCB057643 (LIMBER-103) in Patients With Relapsed or Refractory Myelofibrosis and Other Advanced Myeloid Neoplasms: A Phase 1 Study

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Background

- Bromodomain and extra-terminal (BET) proteins are epigenetic readers that regulate expression of critical oncoproteins involved in the pathophysiology of hematologic malignancies, including MF[1,2]
- INCB057643 is an oral, small-molecule, BET inhibitor[3]
- In a phase 1/2 study, INCB057643 demonstrated favorable tolerability and encouraging clinical activity as monotherapy or in combination with the JAK1/JAK2 inhibitor ruxolitinib in patients with advanced malignancies[3]

Objective: To evaluate the safety and tolerability of INCB057643

- As monotherapy in patients with relapsed/refractory (r/r) MF, MDS, or MDS/MPN overlap syndromes
- In combination with ruxolitinib in patients with advanced MF and suboptimal response to ruxolitinib

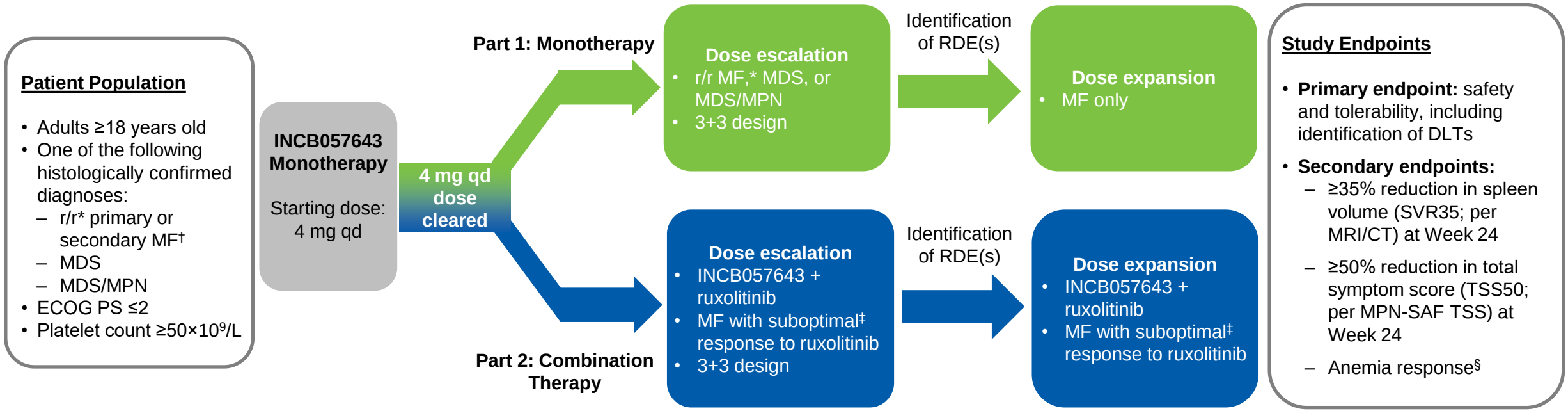
JAK, Janus kinase; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm.

1. Bose P, et al. *Cancers (Basel)*. 2020;12(10);2891. **2.** Hajmirza A, et al. *Biomedicines*. 2018;6(1);16. **3.** Falchook G, et al. *Clin Cancer Res*. 2020;26(6):1247-1257.

Study Design

Ongoing open-label, multicenter, phase 1 dose-escalation and dose-expansion study (NCT04279847)

- The initial INCB057643 dose was 4 mg qd with dose escalation up to 12 mg qd
  - All doses were administered continuously in 28-day cycles



CT, computed tomography; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; MRI, magnetic resonance imaging; qd, once daily; RDE, recommended doses for expansion; r/r, relapsed/refractory; SAF TSS, Symptom Assessment Form Total Symptom Score.
* Patients who have received ≥1 line of prior therapy and experienced a recurrence of their disease or failed to respond to the last treatment, and for whom no additional known therapy is available to offer clinical benefits. † Patients with MF must have received ≥1 Janus kinase inhibitor, such as ruxolitinib. ‡ Patients who have been receiving a stable dose of ruxolitinib 5 to 25 mg twice daily for ≥8 weeks before the first dose of study treatment but are not experiencing an optimal response to ruxolitinib monotherapy; 1 dose reduction due to toxicities within 8 weeks before Study Day 1 was permitted. § Defined as a hemoglobin increase of ≥1.5 g/dL from baseline lasting ≥12 weeks during the treatment period if transfusion-independent at baseline OR achieving transfusion independence for ≥12 weeks during the treatment period if transfusion-dependent at baseline.

Patient Demographics and Baseline Characteristics

Parameter	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)
Age, median (range), y	70.0 (50–79)	70.0 (50–76)
Male, n (%)	11 (61.1)	6 (54.5)
White, n (%)	14 (77.8)	10 (90.9)
Malignancy type, n (%)		
MF	13 (72.2)	11 (100.0)
DIPSS Int-2	12/13 (92.3)	10 (90.9)
DIPSS high risk	1/13 (7.7)	0
MF risk missing	0	1 (9.1)
Primary MF	4/13 (30.8)	5 (45.5)
Post–PV-MF	5/13 (38.5)	2 (18.2)
Post–ET-MF	4/13 (30.8)	4 (36.4)
CMML	2 (11.1)	0
MDS	1 (5.6)	0
MDS/MPN-RS-T	1 (5.6)	0
Unclassifiable MDS/MPN overlap syndrome	1 (5.6)	0

Parameter	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)
ECOG PS, n (%)		
0	2 (11.1)	6 (54.5)
1	16 (88.9)	4 (36.4)
2	0	1 (9.1)
JAK2-positive [among MF pts], n (%)	9/13 (69.2)	8/11 (72.7)
RBC transfusion dependent, n (%)		
Yes	2 (11.1)	0
No	16 (88.9)	11 (100.0)
Prior treatment, n (%)		
Systemic therapy	17 (94.4)	11 (100.0)
Radiotherapy	2 (11.1)	0
Stem cell transplant	0	0
Spleen volume [among MF pts],* median (range), mL	2028.0 (618–4766)	1747.0 (702–4381)
MPN-SAF TSS [among MF pts],† median (range)	32.0 (0–78)	23.0 (2–43)

CMML, chronic myelomonocytic leukemia; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; Int, intermediate; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; post–ET-MF, post–essential thrombocythemia myelofibrosis; post–PV-MF, post–polycythemia vera myelofibrosis; pts, patients; RBC, red blood cell; RS-T, ring sideroblasts and thrombocytosis; RUX, ruxolitinib; SAF TSS, Symptom Assessment Form total symptom score.

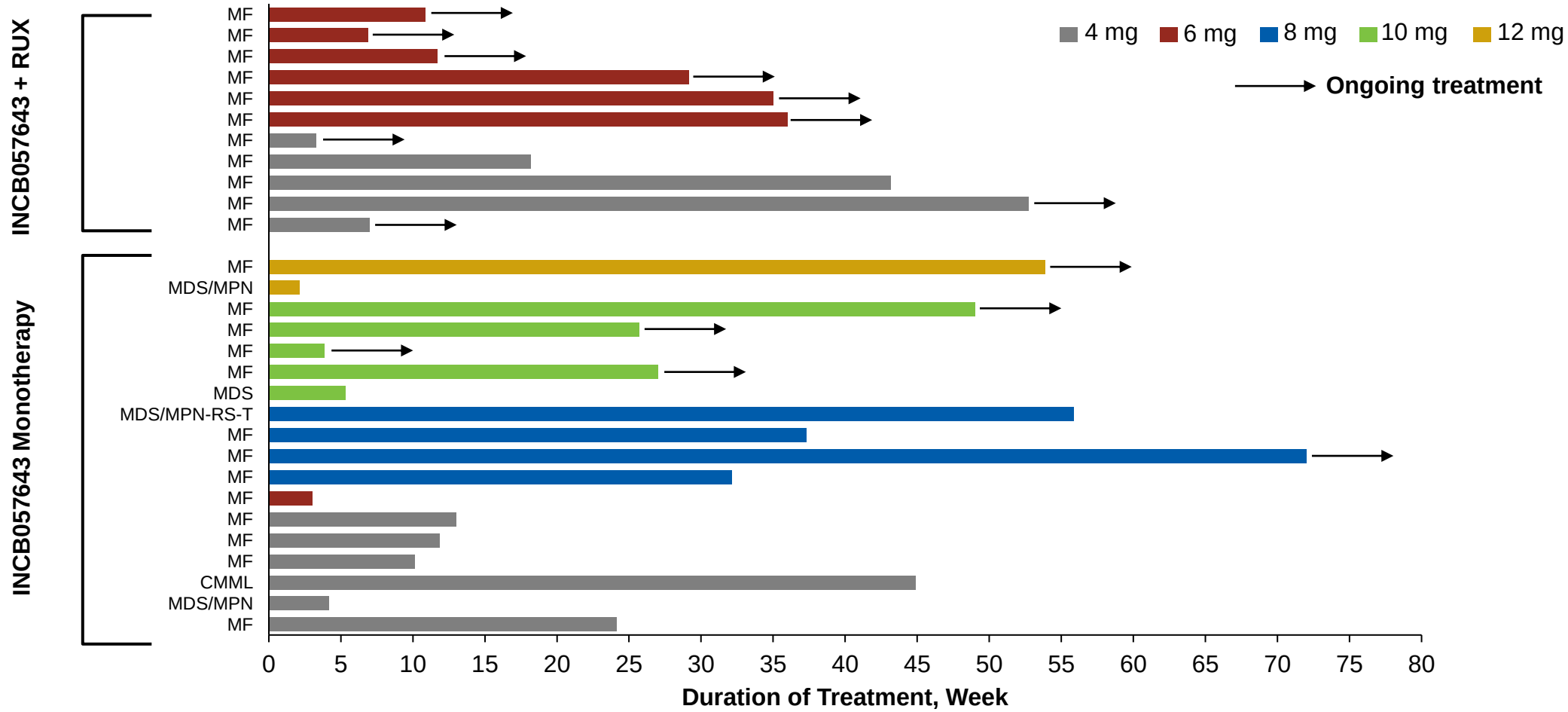
* Among evaluable patients with MF: 4-mg cohort, n=4; 6-mg cohort, n=1; 8-mg cohort, n=3; 10-mg cohort, n=4; 12-mg cohort, n=1; 4-mg + RUX cohort, n=5; 6-mg + RUX cohort, n=6.

† Among patients with baseline MPN-SAF assessment: 4-mg cohort, n=3; 6-mg cohort, n=1; 8-mg cohort, n=3; 10-mg cohort, n=4; 12-mg cohort, n=1; 4-mg + RUX cohort, n=5; 6-mg + RUX cohort, n=5.

Treatment Duration

Data Cutoff, November 6, 2023

- Median (range) duration of INCB057643 exposure was 174.5 (15–504) days in the monotherapy group (MF patients only, 169.0 [21–504] days) and 127.0 (23–369) days in the combination therapy group



CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; RS-T, ring sideroblasts and thrombocytosis; RUX, ruxolitinib.

Safety

- Grade ≥3 TEAEs occurred in 65.5% and serious TEAEs in 20.7% of patients
- There were 2 DLTs with monotherapy and 1 DLT with combination therapy
  - Hyperbilirubinemia (MF patient, 12-mg cohort)
  - Thrombocytopenia (MDS/MPN patient, 12-mg cohort; MF patient, 6 mg + RUX cohort)

	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)	Total (N=29)
Any TEAE	18 (100.0)	11 (100.0)	29 (100.0)
Grade 3 TEAE*	13 (72.2)	6 (54.5)	19 (65.5)
TEAE leading to discontinuation†	4 (22.2)	1 (9.1)	5 (17.2)
Serious TEAE	5 (27.8)	1 (9.1)	6 (20.7)
Fatal TEAE‡	1 (5.6)	0	1 (3.4)
Treatment-related TEAE	17 (94.4)	7 (63.6)	24 (82.8)
Treatment-related serious TEAE§	1 (5.6)	0	1 (3.4)
Treatment-related fatal TEAE	0	0	0

	INCB057643 Monotherapy (n=18)	INCB057643 + RUX (n=11)	Total (N=29)
Most common TEAEs, n (%)¶			
Thrombocytopenia	8 (44.4)	7 (63.6)	15 (51.7)
Nausea	8 (44.4)	0	8 (27.6)
Anemia	6 (33.3)	2 (18.2)	8 (27.6)
Blood bilirubin increased	6 (33.3)	2 (18.2)	8 (27.6)
Hyperuricemia	6 (33.3)	0	6 (20.7)
Dysgeusia	5 (27.8)	1 (9.1)	6 (20.7)
Blood creatinine increased	3 (16.7)	3 (27.3)	6 (20.7)

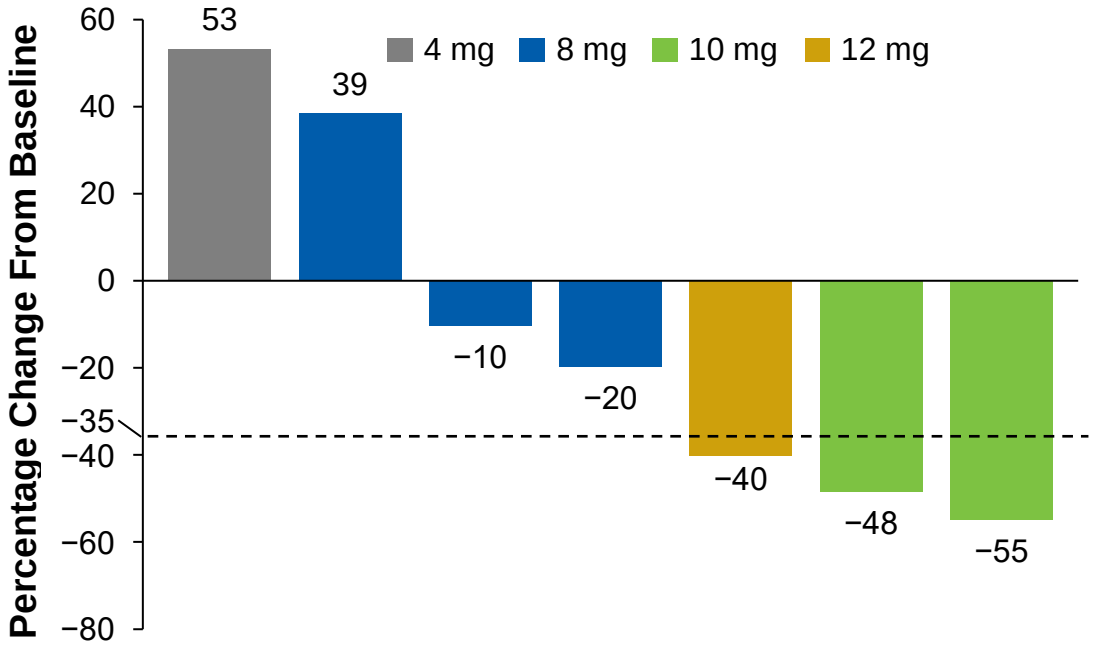
DLT, dose-limiting toxicity; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; RUX, ruxolitinib; TEAE, treatment-emergent adverse event.
* Grade ≥3 TEAEs occurring in ≥2 patients: anemia (n=6), thrombocytopenia (n=8), hypokalemia (n=2), platelet count decreased (n=2). † TEAEs leading to discontinuation of INCB057643: thrombocytopenia (n=4), anemia (n=1), and bacteremia (n=1).
‡ Fatal TEAE: transformation to acute myeloid leukemia (n=1). § Treatment-related serious TEAE: pneumonia (n=1). ¶TEAEs occurring in ≥20% of patients in the total population.

Efficacy – Monotherapy

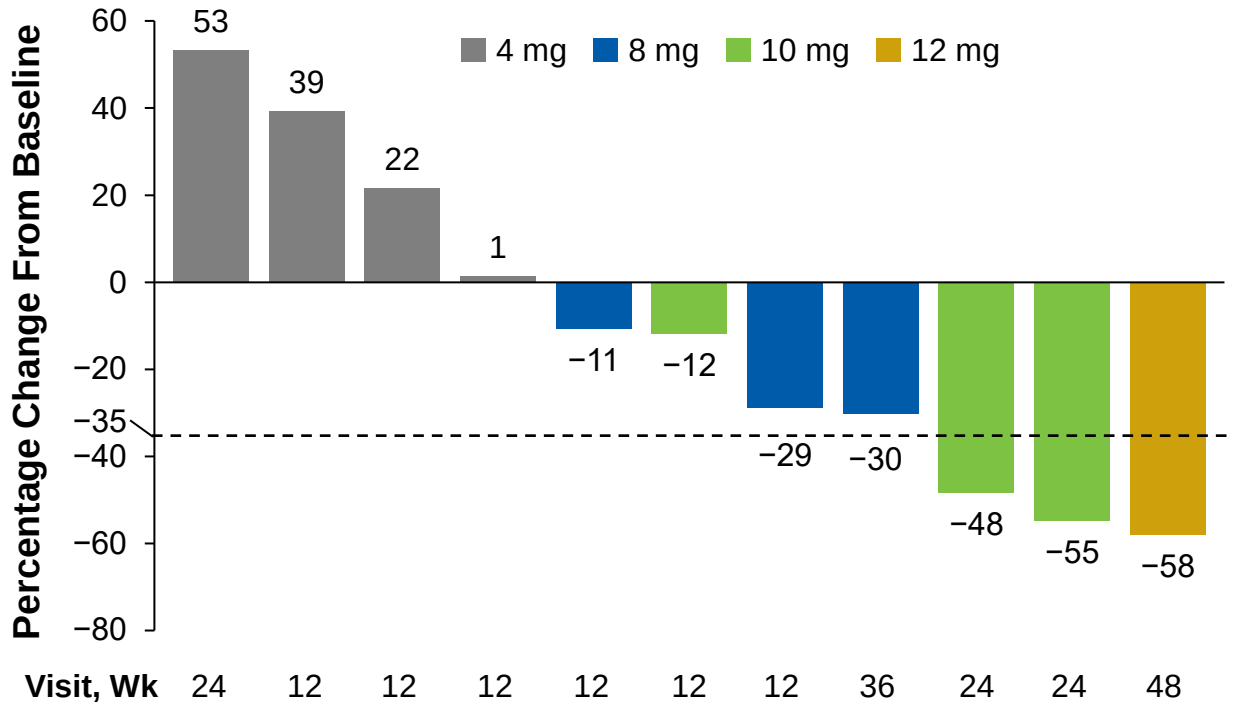
Spleen Volume Response in Individual Patients With MF (n=13)

- At Week 24, SVR35 was achieved by 3/3 evaluable patients receiving INCB057643 ≥10 mg
- 5/12 evaluable patients treated at any dose achieved best response of ≥25% reduction in spleen volume during the treatment period

Spleen Volume Change at Week 24†



Best Spleen Volume Response During Treatment‡



MF, myelofibrosis; SVR35, 35% reduction from baseline in spleen volume; Wk, week.

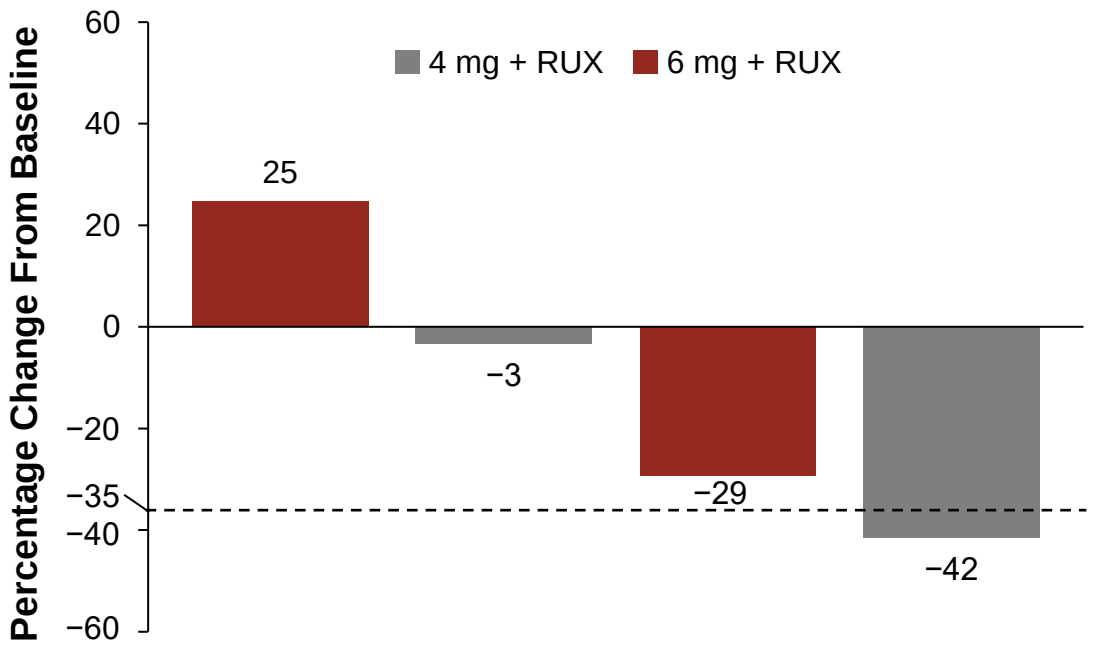
* Dotted line represents response criteria threshold. † 4 evaluable patients receiving monotherapy (4-mg, n=3 and 6-mg, n=1) discontinued from treatment before Week 24; 2 patients receiving ongoing 10-mg monotherapy were not evaluable because they were not followed up long enough and had no Week 24 assessment. ‡ 1 evaluable patient receiving 6-mg monotherapy discontinued from treatment before first post-baseline (Week 12) spleen volume assessment; 1 patient receiving ongoing 10-mg monotherapy was not evaluable because they were not followed up long enough and had no Week 12 spleen volume assessment.

Efficacy – Combination Therapy

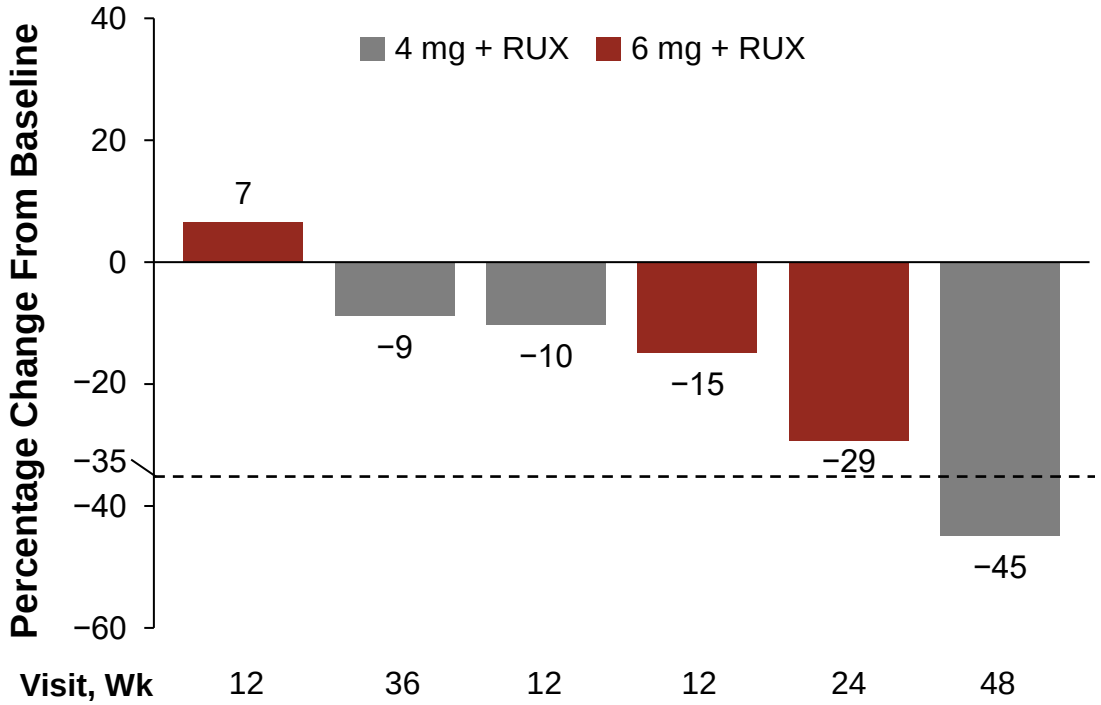
Spleen Volume Response in Individual Patients With MF (n=11)

- At Week 24, SVR35 was achieved by 1/5 evaluable patients
- Improvements in spleen volume were observed in 5/7 evaluable patients, with 2 achieving best response of ≥25% reduction in spleen volume during treatment period

Spleen Volume Change at Week 24†



Best Spleen Volume Response During Treatment‡



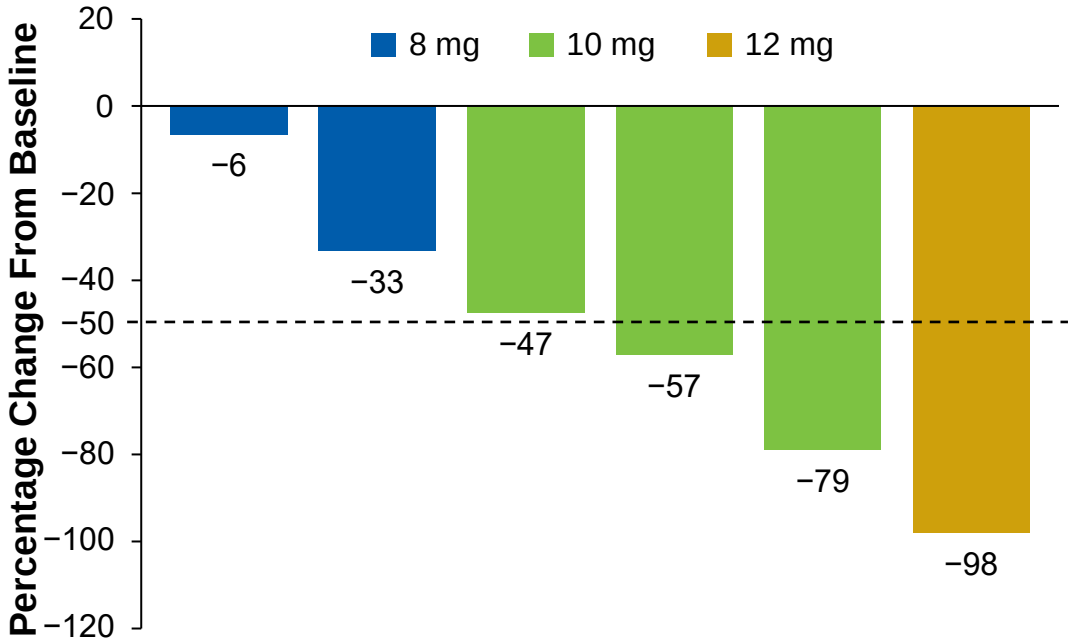
MF, myelofibrosis; RUX, ruxolitinib; SVR35, 35% reduction from baseline in spleen volume; Wk, week.
* Dotted line represents response criteria threshold. † 1 evaluable patient receiving 4-mg + RUX discontinued from treatment before Week 24; 2 patients receiving ongoing 4-mg + RUX and 4 patients receiving ongoing 6-mg + RUX were not evaluable because they were not followed up long enough and had no Week 24 assessment or did not have a Week 24 assessment at the time of data extraction. ‡ 1 evaluable patient receiving 4-mg + RUX discontinued from treatment before first post-baseline (Week 12) spleen volume assessment; 1 patient receiving ongoing 4-mg + RUX and 3 receiving ongoing 6-mg + RUX were not evaluable because they were not followed up long enough and had no Week 12 spleen volume assessment.

Efficacy – Monotherapy

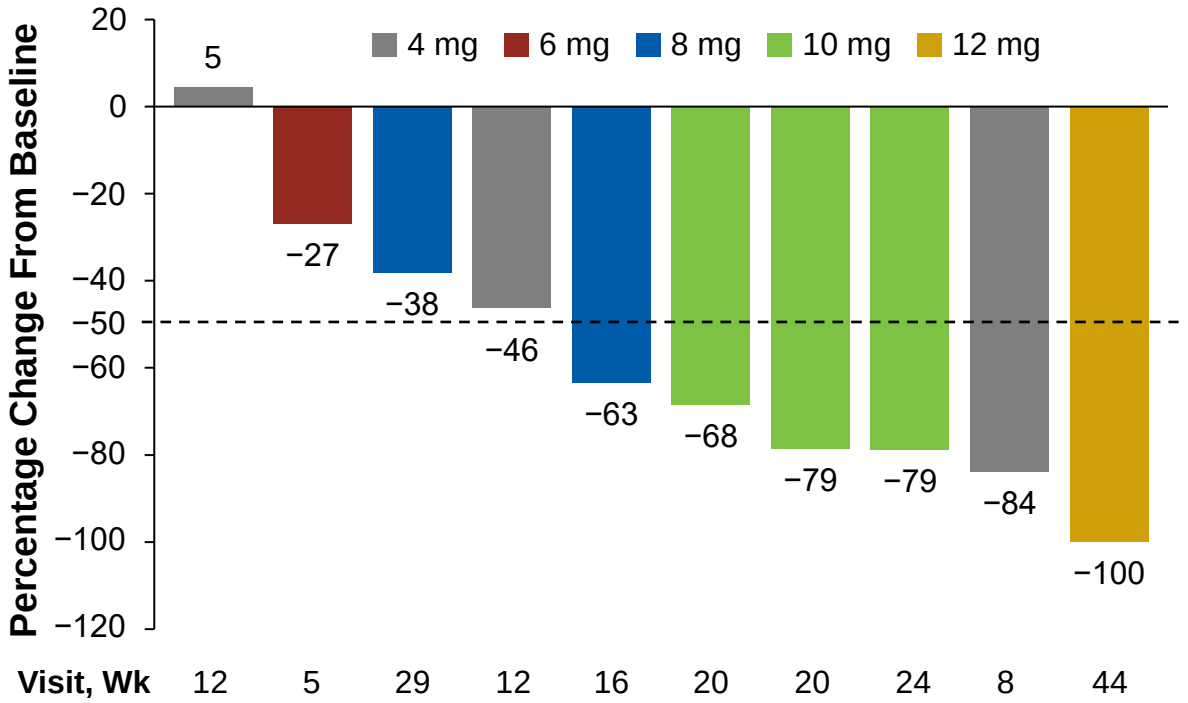
Symptom Response in Individual Patients With MF (n=13)

- At Week 24, TSS50 was achieved by 3/10 evaluable patients, and by 3/4 evaluable patients receiving INCB057643 ≥10 mg
- 6/10 evaluable patients treated at any dose achieved best response of TSS50 during the treatment period

MPN-SAF TSS Change at Week 24†



Best Symptom Improvement During Treatment‡



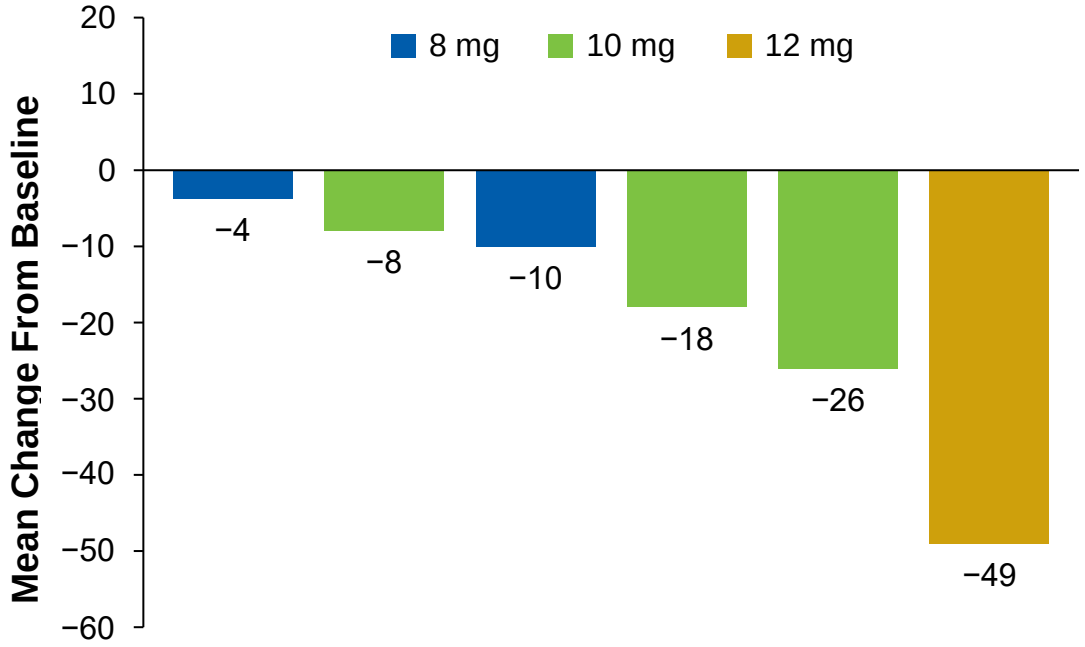
MF, myelofibrosis; MPN-SAF TSS, myeloproliferative neoplasm-Symptom Assessment Form Total Symptom Score; TSS50, ≥50% reduction from baseline in MPN-SAF TSS; Wk, week.
* Dotted line represents response criteria threshold. † 4 evaluable patients receiving monotherapy (4-mg, n=3 and 6-mg, n=1) discontinued from treatment before Week 24; 3 patients receiving monotherapy were not evaluable because baseline assessment was missing (4-mg, n=1 and 8-mg, n=1) or they were ongoing but not followed up long enough and had no Week 24 assessment (10-mg, n=1). ‡ 3 patients receiving monotherapy were not evaluable, 2 patients (4-mg, n=1 and 8-mg, n=1) did not have baseline assessment and 1 receiving 10-mg monotherapy did not have post-baseline MPN-SAF TSS assessment.

Efficacy – Monotherapy

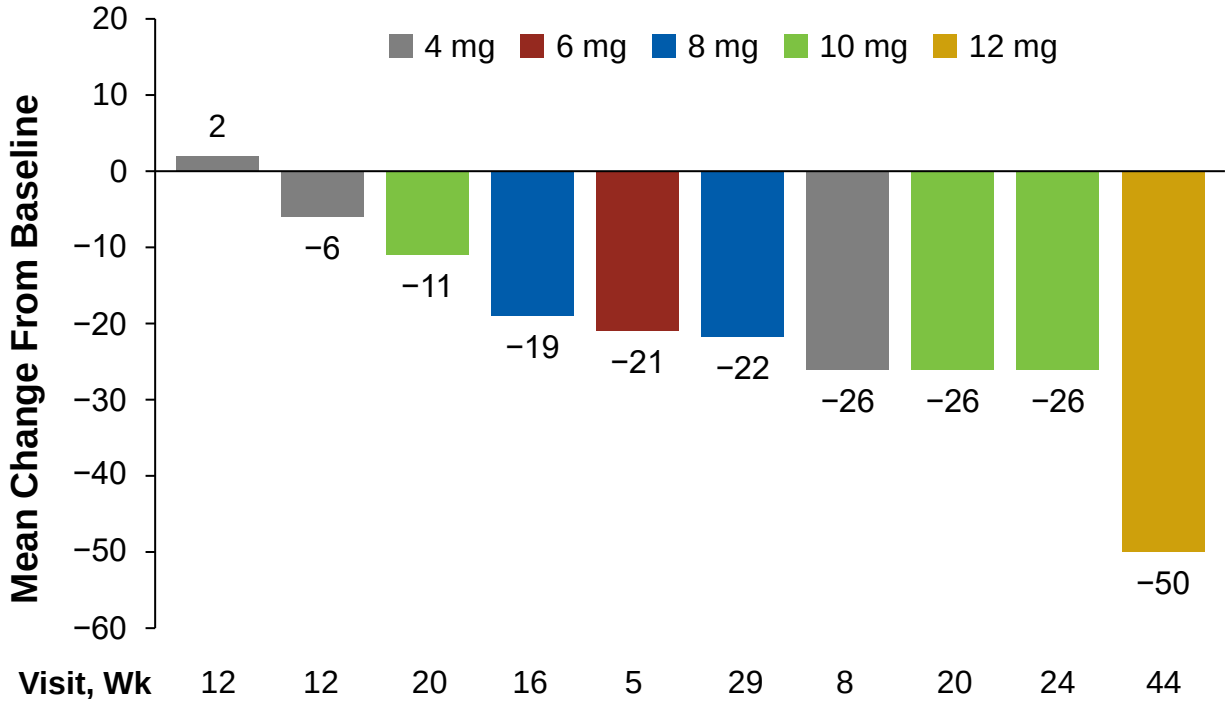
Mean MPN-SAF TSS Change in Individual Patients With MF (n=13)

- At Week 24, improvements in mean MPN-SAF TSS occurred in 6/10 evaluable monotherapy patients
- Decrease in mean MPN-SAF TSS from baseline was seen in 9/10 evaluable patients treated at any dose during the treatment period

Mean MPN-SAF TSS Change at Week 24†



Best Symptom Improvement During Treatment‡



MF, myelofibrosis; MPN-SAF TSS, myeloproliferative neoplasm-Symptom Assessment Form Total Symptom Score; Wk, week.

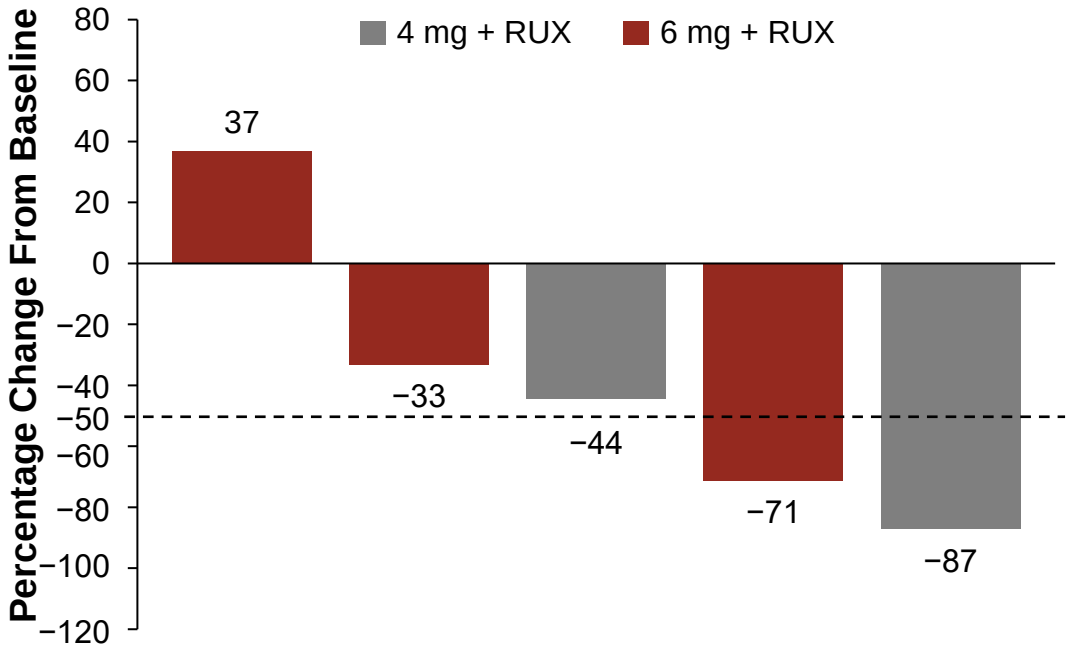
† 4 evaluable patients receiving monotherapy (4-mg, n=3 and 6-mg, n=1) discontinued from treatment before Week 24; 3 patients receiving monotherapy were not evaluable because baseline assessment was missing (4-mg, n=1 and 8-mg, n=1) or they were ongoing but not followed up long enough and had no Week 24 assessment (10-mg, n=1). ‡ 3 patients receiving monotherapy were not evaluable, 2 patients (4-mg, n=1 and 8-mg, n=1) did not have baseline assessment and 1 receiving 10-mg monotherapy did not have post-baseline MPN-SAF TSS assessment.

Efficacy – Combination Therapy

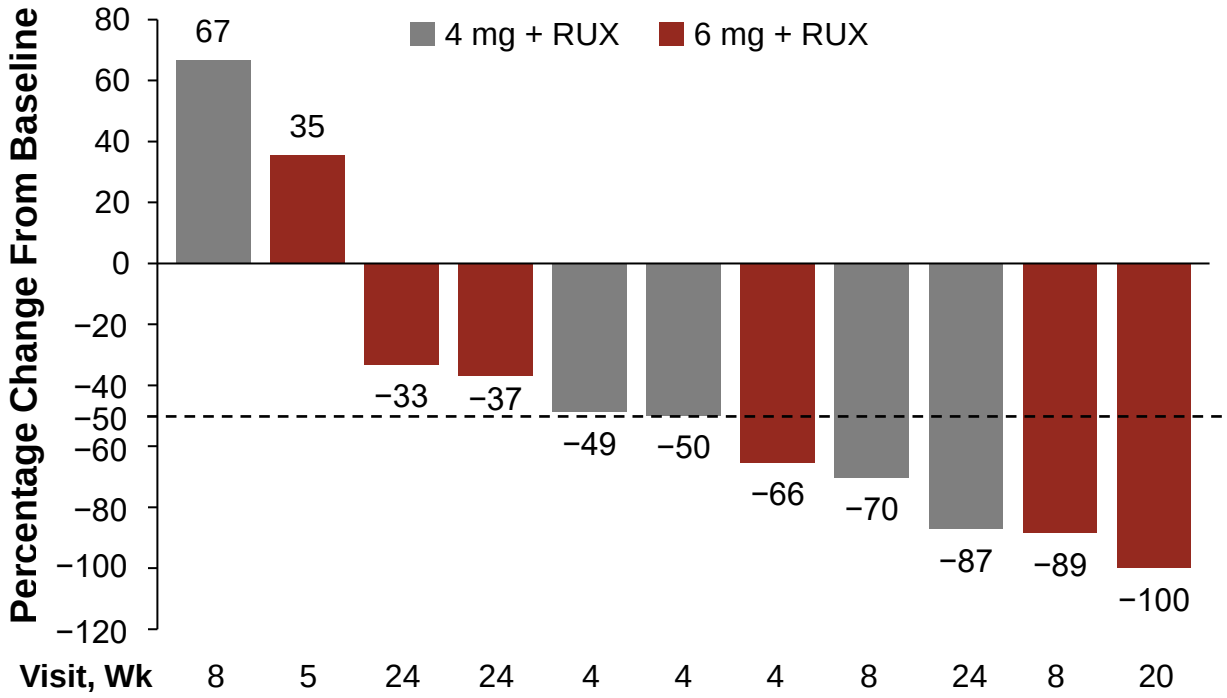
Symptom Response in Individual Patients With MF (n=11)

- At Week 24, TSS50 was achieved by 2/6 evaluable patients (1 in each cohort)
- 6/11 evaluable patients treated at any dose achieved best response of TSS50 during the treatment period

MPN-SAF TSS Change at Week 24†



Best Symptom Improvement During Treatment



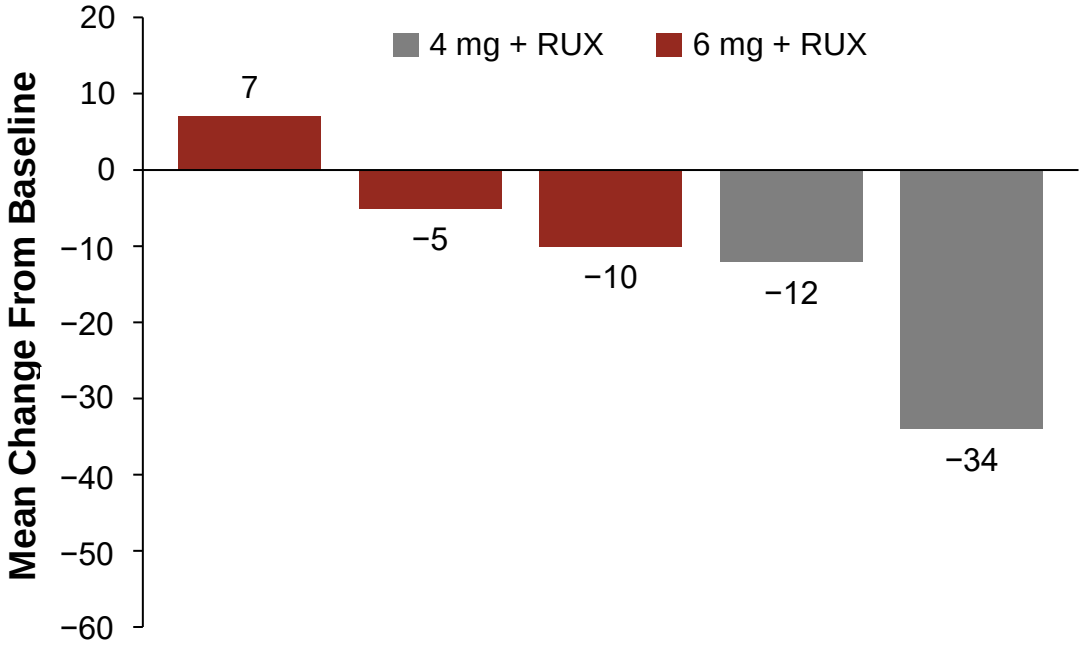
MF, myelofibrosis; MPN-SAF TSS, myeloproliferative neoplasm-Symptom Assessment Form Total Symptom Score; RUX, ruxolitinib; TSS50, ≥50% reduction from baseline in MPN-SAF TSS; Wk, week.
* Dotted line represents response criteria threshold. † 1 evaluable patient receiving 4-mg + RUX discontinued from treatment before Week 24; 5 patients ongoing combination therapy were not evaluable because they were not followed up long enough and had no Week 24 assessment (4-mg + RUX, n=2 and 6-mg + RUX, n=3).

Efficacy – Combination Therapy

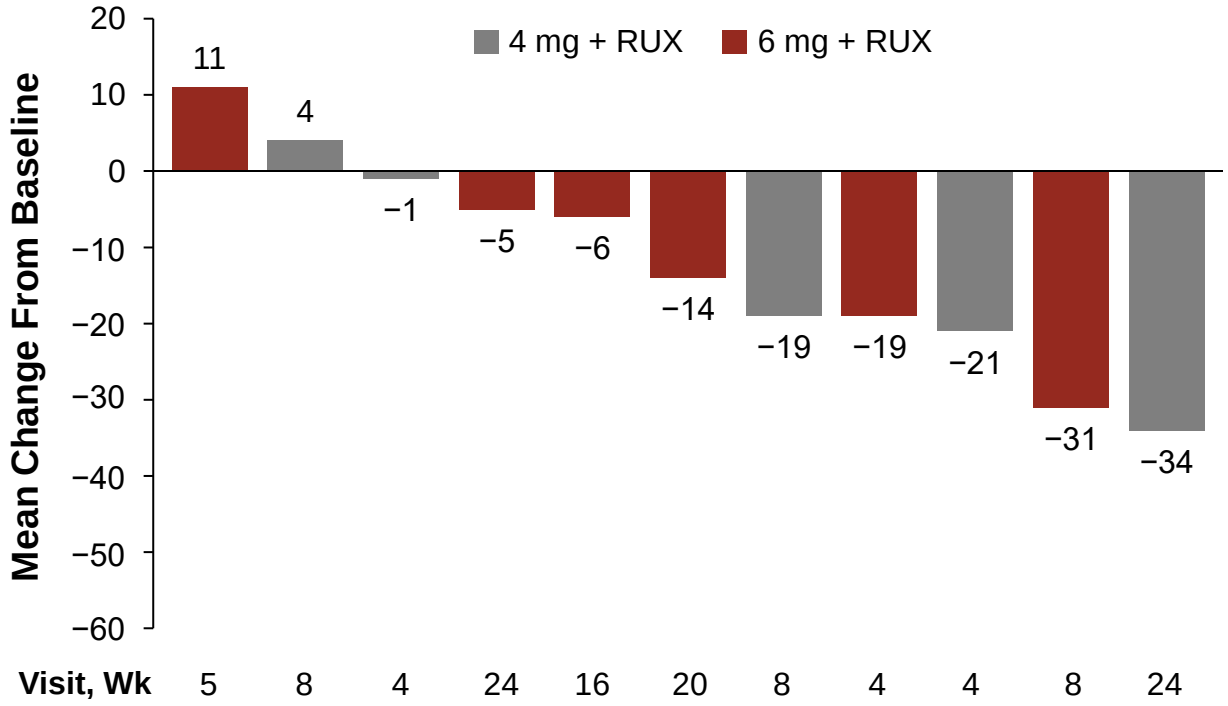
Mean MPN-SAF TSS Change in Individual Patients With MF (n=11)

- At Week 24, improvements in mean MPN-SAF occurred in 4/6 evaluable combination therapy patients
- Decrease in mean MPN-SAF TSS from baseline was seen in 9/11 patients receiving INCB057643 + RUX combination therapy during the treatment period

Mean MPN-SAF TSS Change at Week 24†



Best Symptom Improvement During Treatment

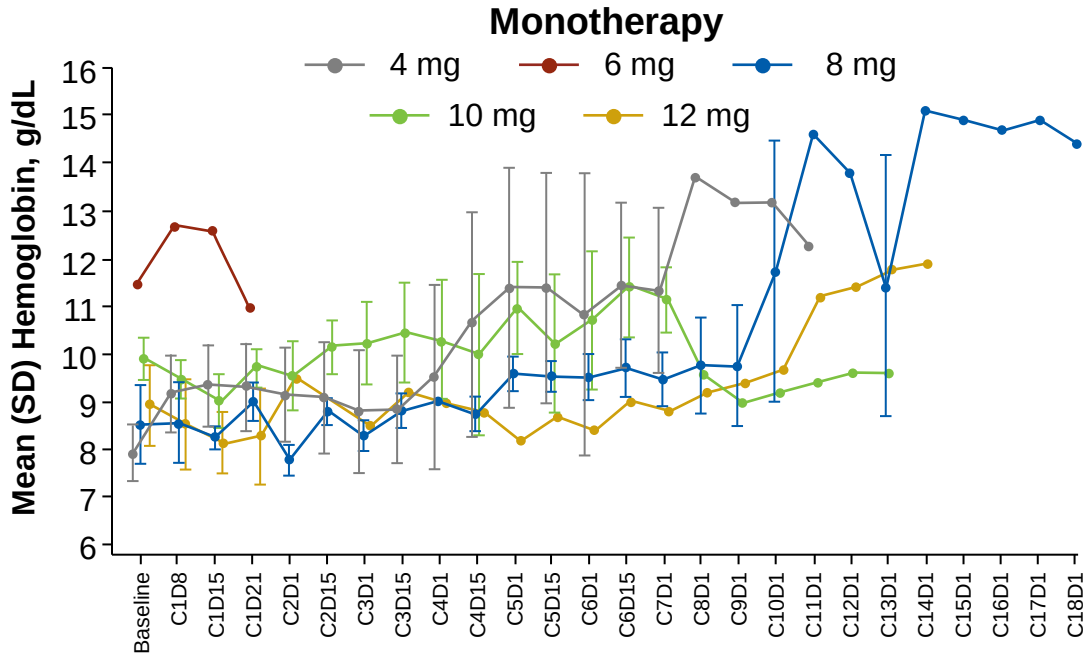


MF, myelofibrosis; MPN-SAF TSS, myeloproliferative neoplasm-Symptom Assessment Form Total Symptom Score; RUX, ruxolitinib; Wk, week.

† 1 evaluable patient receiving 4-mg + RUX discontinued from treatment before Week 24; 5 patients ongoing combination therapy were not evaluable because they were not followed up long enough and had no Week 24 assessment (4-mg + RUX, n=2 and 6-mg + RUX, n=3).

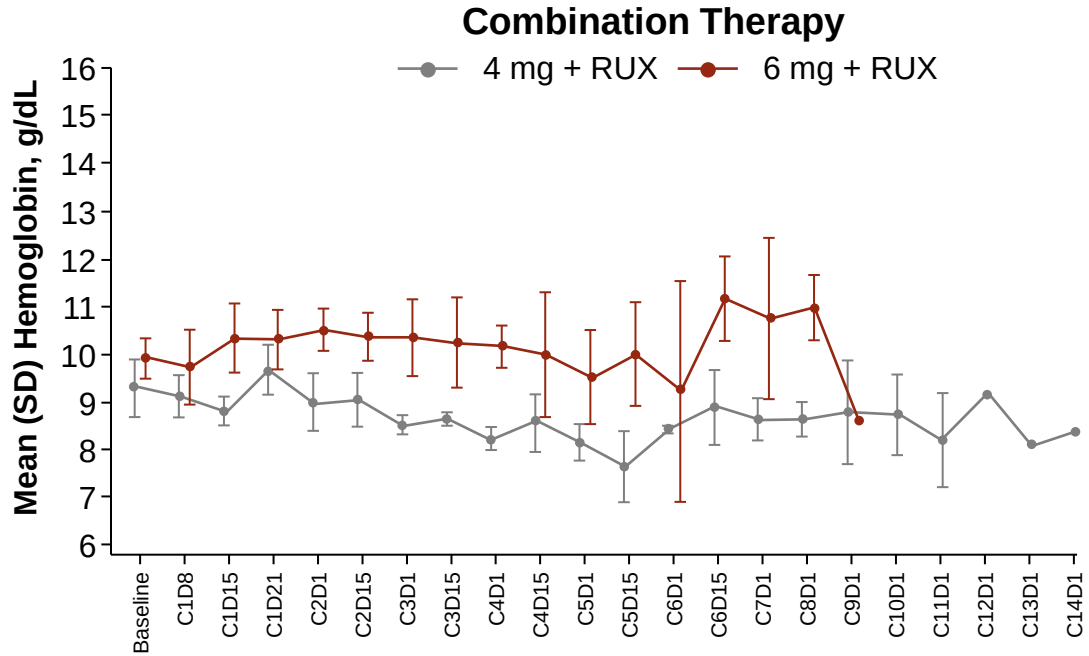
Hemoglobin Levels

- One patient who was transfusion-independent at baseline had >1.5 g/dL increase from baseline in hemoglobin for ≥12 weeks on treatment (12-mg monotherapy)
- One patient who was transfusion dependent at baseline became transfusion independent for >1 year on treatment (8-mg monotherapy)



Evaluable patients, n

4 mg qd	5	6	6	6	6	5	5	5	3	2	2	2	2	2	2	1	1	1	1						
6 mg qd	1	1	1	1																					
8 mg qd	3	4	3	4	4	4	4	4	4	4	4	4	4	4	4	4	4	2	1	1	2	1	1	1	1	1
10 mg qd	4	5	5	5	4	4	3	3	3	3	3	3	3	3	3	1	1	1	1	1	1					
12 mg qd	2	2	2	2	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1				



Evaluable patients, n

4 mg qd	5	5	5	4	5	4	3	3	3	3	3	2	2	2	2	2	2	2	2	1	1	1			
6 mg qd	6	6	5	6	6	6	5	5	3	3	3	3	2	2	2	2	2	1							

C, cycle; D, day; qd, once daily; RUX, ruxolitinib.
"Transfusion dependent at baseline" was defined as patients requiring ≥4 units of packed red blood cells in the 56 days before enrollment, with ≥1 transfusion occurring during the 28 days before enrollment. Patients not meeting criteria for transfusion dependent at baseline were considered transfusion independent.

Conclusions

- Treatment with INCB057643 monotherapy or in combination with ruxolitinib was well tolerated
  - 2 DLTs occurred with INCB057643 12-mg monotherapy (thrombocytopenia, hyperbilirubinemia) and 1 DLT with INCB057643 6-mg combination therapy (thrombocytopenia)
  - There were no treatment-related fatal events and 1 treatment-related serious TEAE
  - The most common TEAEs were thrombocytopenia, nausea, anemia, and blood bilirubin increased
- Improvements in spleen size and symptom burden were observed in patients receiving INCB057643 ≥8-mg monotherapy and INCB057643 4- and 6-mg combination therapy
- 6 mg and 10 mg INCB057643 were identified as monotherapy doses for expansion; patients will be allocated to either starting dose based on platelet counts, and intra-patient dose titration is allowed
  - 3 MF patients (6-mg cohort, n=1; 10-mg cohort, n=2) have been enrolled in the expansion phase
- Dose escalation is ongoing in the combination therapy group; currently enrolling in the 8-mg cohort
- New cohorts for ET in the monotherapy group and JAK inhibitor-naive MF in the combination group

DLT, dose-limiting toxicity; ET, essential thrombocythemia; JAK, Janus kinase; MF; myelofibrosis; TEAE, treatment-emergent adverse event.

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