

Safety and Efficacy of Bromodomain and Extra-Terminal Inhibitor INCB057643 in Patients With Relapsed or Refractory Myelofibrosis and Other Advanced Myeloid Neoplasms: A Phase 1 Study

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Background

- 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 inhibitor³
- In a previous phase 1/2 basket study, INCB057643 demonstrated favorable tolerability and encouraging clinical activity as monotherapy or in combination with the JAK1/JAK2 inhibitor ruxolitinib in patients with advanced myelofibrosis³

Objective: To evaluate safety and tolerability of INCB057643

- As monotherapy in patients with r/r MF, ET, MDS, or MDS/MPN overlap syndromes
- In combination with ruxolitinib in patients with advanced chronic or accelerated phase MF and suboptimal response to ruxolitinib or patients with JAK inhibitor treatment-naïve MF

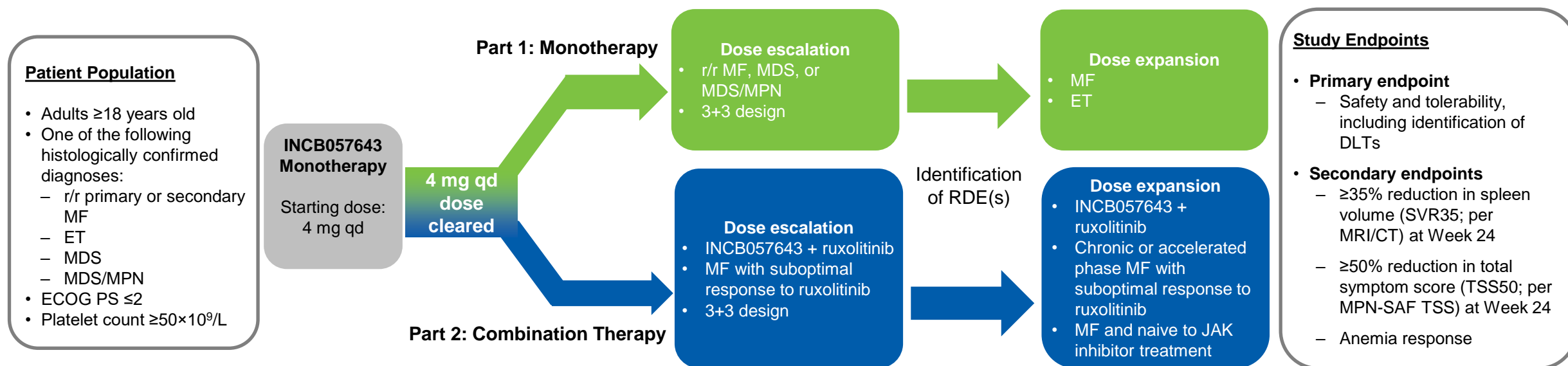
BET, bromodomain and extra-terminal; ET, essential thrombocythemia; JAK, Janus kinase; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; r/r, relapsed/refractory.

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, Phase 1, Dose-Escalation and -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



- Anemia response
 - If transfusion-independent at baseline: ≥1.5 g/dL hemoglobin increase from baseline for ≥12 weeks
 - If transfusion-dependent at baseline: achieving transfusion independence for ≥12 weeks

DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; RDE, recommended dose for expansion; SAF TSS, Symptom Assessment Form total symptom score; SVR35, ≥35% reduction from baseline in spleen volume; TSS50, ≥50% reduction from baseline in MPN-SAF TSS.

Patient Demographics and Baseline Characteristics

Parameter	Part 1 (INCB057643 Monotherapy)				Part 2 (INCB057643 + RUX)
	Dose Escalation (n=18)		Dose Expansion (n=20)		Dose Escalation (n=23)
	MF (n=13)	MDS and MDS/MPN* (n=5)	MF (n=12)	ET (n=8)	MF
Age, median (range), y	71.0 (50.0–79.0)		66.5 (47.0–79.0)		70.0 (50.0–77.0)
Male, n (%)	11 (61.1)		11 (55.0)		14 (60.9)
White, n (%)	14 (77.8)		12 (60.0)		19 (82.6)
Time since initial diagnosis, median (range), y	4.7 (1.8–13.4)	2.0 (0.8–8.2)	5.6 (1.2–17.5)	3.8 (1.2–16.2)	4.1 (0.02–12.9)
RBC transfusion dependent, %	15.4	20.0	16.7	0	8.7
PMF/PPV-MF/PET-MF, %	38.5 / 30.8 / 30.8	NA	50.0 / 33.3 / 16.7	NA	56.5 / 26.1 / 17.4
IWG risk level high/int-2, %	15.4 / 84.6	NA	33.3 / 66.7	NA	8.7 / 78.3
JAK2-positive, %	61.5	NA	50.0	NA	73.9
CALR exon 9 mutation-positive, %	NA	NA	NA	12.5	NA
Spleen volume, median (range), cm ³	2028 (618–4766)	NA	2741.5 (625–4047)	NA	1940 (634–4381)
Spleen length, median (range), cm	11.0 (3–24)	NA	13.0 (5–25)	NA	12.0 (6–25)
TSS, mean (range)	35.5 (22.0–47.0)	NA	36.2 (0–77)	NA	20.3 (0–57.0)

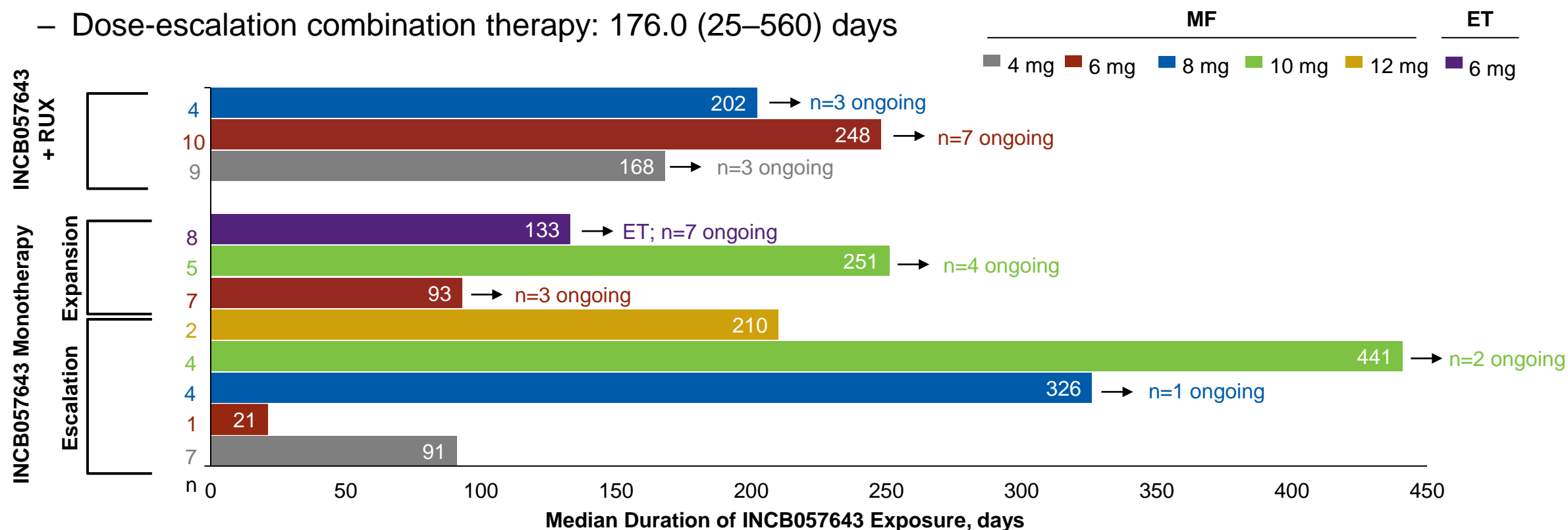
CMML, chronic myelomonocytic leukemia; int, intermediate; IWG, International Working Group; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; RBC, red blood cell; RS-T, ring sideroblasts and thrombocytosis.

* MDS, n=2; CMML, n=1; MDS/MPN-RS-T; n=1; unclassified overlap syndrome, n=1.

Treatment Duration

Data Cutoff: September 9, 2024

- Median (range) duration of INCB057643 exposure
 - Dose-escalation monotherapy: 195.5 (15–812) days
 - Dose-expansion monotherapy: 154.5 (14–341) days
 - Dose-escalation combination therapy: 176.0 (25–560) days



Safety

- There were 2 DLTs with monotherapy:
 - Hyperbilirubinemia
 - Patient with MF, 12-mg cohort
 - Thrombocytopenia
 - Patient with MDS/MPN, 12-mg cohort
- There was 1 DLT with combination therapy:
 - Thrombocytopenia
 - Patient with MF, 6-mg cohort
- There were 3 cases of AML transformation
 - 1 MDS/MPN (4 mg mono), 1 MDS (10 mg mono)
 - 1 MF (4 mg combo with ruxolitinib 20 mg bid)

TEAE, treatment-emergent adverse event.

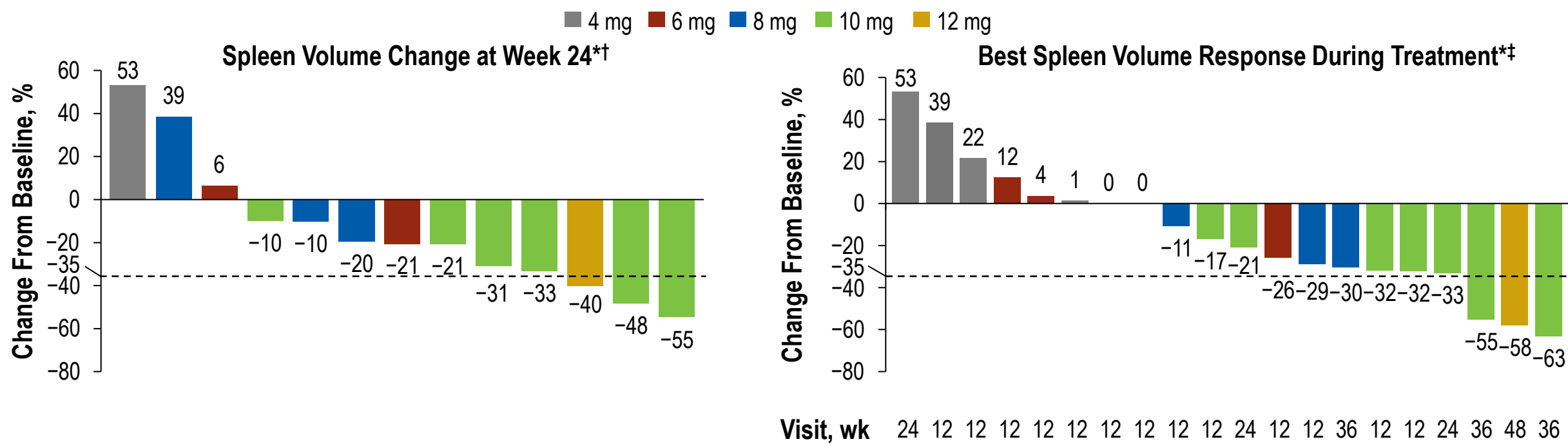
* Grade ≥3 TEAEs occurring in >3 patients: anemia (n=12), thrombocytopenia^{||} (n=16). † TEAEs leading to discontinuation of INCB057643: thrombocytopenia^{||} (n=5), acute myeloid leukemia (n=1), anemia (n=1), bacteremia (n=1), ejection fraction decreased (n=1), skin lesion (n=1). ‡ Fatal TEAEs: AML (acute myeloid leukemia; n=2), cardiac arrest (n=1). § Treatment-related serious TEAEs: hematoma (n=1), herpes zoster (n=1), pneumonia (n=1). ¶ TEAEs occurring in ≥10% of patients in the total population. || Includes thrombocytopenia and platelet count decreased.

Parameter, n (%)	Part 1 (INCB057643 Monotherapy)		Part 2 (INCB057643 + RUX)	Total (N=61)
	Dose Escalation (n=18)	Dose Expansion (n=20)	Dose Escalation (n=23)	
Any TEAE	18 (100)	18 (90.0)	22 (95.7)	58 (95.1)
Grade ≥3 TEAE*	16 (88.9)	8 (40.0)	11 (47.8)	35 (57.4)
TEAE leading to discontinuation†	5 (27.8)	2 (10.0)	2 (8.7)	9 (14.8)
Serious TEAE	8 (44.4)	6 (30.0)	5 (21.7)	19 (31.1)
Fatal TEAE‡	1 (5.6)	0	2 (8.7)	3 (4.9)
Treatment-related TEAE	17 (94.4)	15 (75.0)	16 (69.6)	48 (78.7)
Treatment-related serious TEAE§	1 (5.6)	1 (5.0)	1 (4.3)	3 (4.9)
Treatment-related fatal TEAE	0	0	0	0
Most common TEAEs,¶ n (%)				
Thrombocytopenia	11 (61.1)	5 (25.0)	12 (52.2)	28 (45.9)
Anemia	7 (38.9)	2 (10.0)	6 (26.1)	15 (24.6)
Nausea	9 (50.0)	2 (10.0)	2 (8.7)	13 (21.3)
Blood bilirubin increased	7 (38.9)	2 (10.0)	2 (8.7)	11 (18.0)
Dysgeusia	5 (27.8)	4 (20.0)	2 (8.7)	11 (18.0)
Pruritus	6 (33.3)	0	2 (8.7)	8 (13.1)

Efficacy – Monotherapy

Spleen Volume Response in Individual Patients With MF (n=25)

- Week 24 SVR35 achieved by 3/7 patients receiving INCB057643 ≥ 10 mg and 3/20 all evaluable patients
- Of 23 evaluable patients, BOR SVR35 achieved by 3 patients; SVR25 achieved by 9 patients



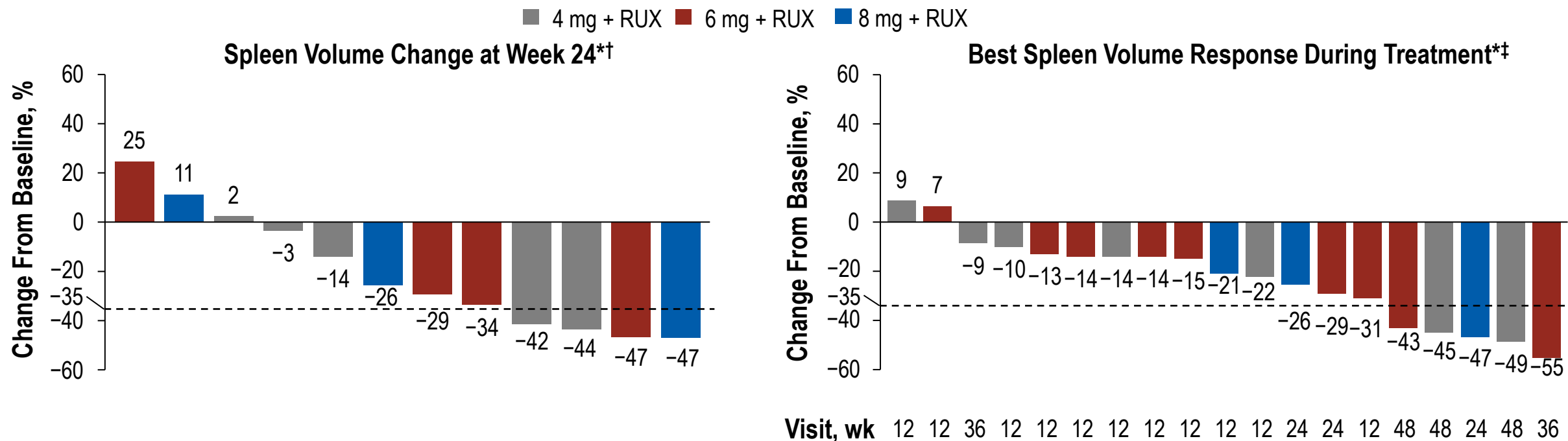
BOR, best overall response.

* Dotted line represents response criteria threshold. † 7 evaluable patients (4 mg, n=4; 6 mg, n=3) discontinued treatment before Week 24; 5 patients were ongoing (6 mg, n=3; 10 mg, n=2) and not evaluable because they were not followed up long enough and had no Week 24 assessment. ‡ 3 evaluable patients (6 mg n=2; 10 mg n=1) discontinued treatment before first postbaseline (Week 12) spleen volume assessment or missed the assessment; 2 patients (6 mg) were not evaluable because they were not followed up long enough to reach the first postbaseline spleen volume assessment.

Efficacy – Combination Therapy (“Add-on”)

Spleen Volume Response in Individual Patients With MF With Suboptimal RUX Response (n=23)

- Week 24 SVR35 achieved by 4/17 evaluable patients
- BOR SVR35 achieved by 5/20 evaluable patients; BOR SVR25 achieved by 8 patients

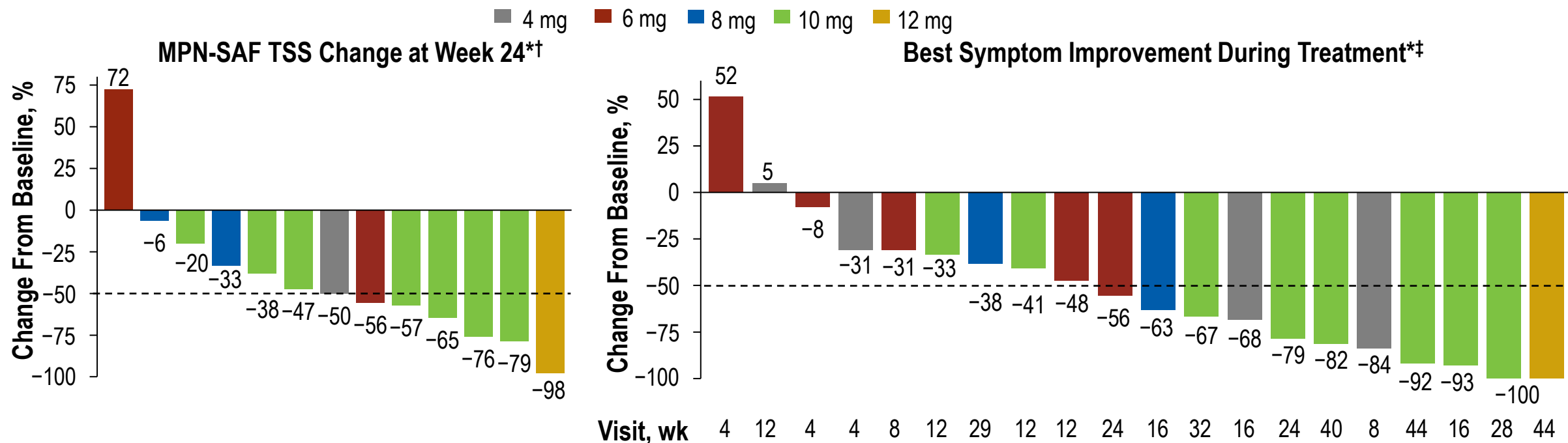


* Dotted line represents response criteria threshold. † 4 evaluable patients (4 mg + RUX, n=3; 6 mg + RUX, n=1) discontinued treatment before Week 24; 1 evaluable patient (6 mg + RUX) was missing Week 24 data; 6 patients were ongoing (4 mg + RUX, n=1; 6 mg + RUX, n=4; 8 mg + RUX, n=1) and not evaluable because they were not followed up long enough and had no Week 24 assessment. ‡ 1 evaluable patient (4 mg) was missing Week 12 data; 3 patients (4 mg, 6 mg, and 8 mg, n=1 each) were not evaluable because they were not followed up long enough to reach the first postbaseline spleen volume assessment.

Efficacy – Monotherapy

Symptom Response in Individual Patients With MF (n=25)

- Week 24 TSS50 achieved by 5/8 evaluable patients receiving INCB057643 ≥ 10 mg; 7/19 all evaluable patients
- BOR TSS50 achieved by 11/20 evaluable patients

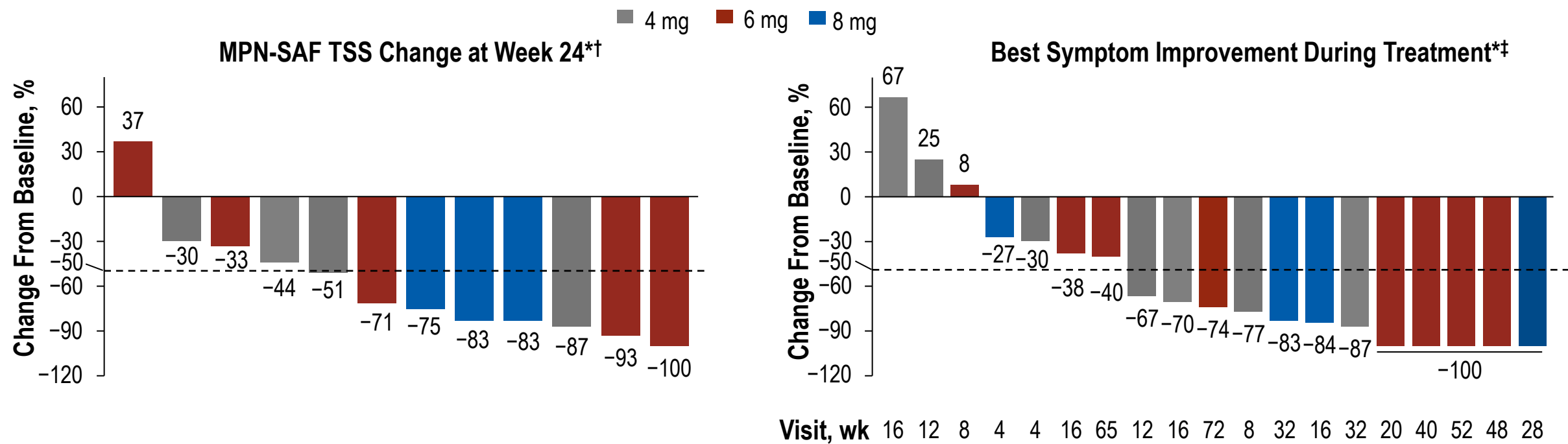


* Dotted line represents response criteria threshold. [†] 6 evaluable patients (4 mg, n=3; 6 mg, n=3) discontinued treatment before Week 24; 6 patients were not evaluable: 1 (4 mg) was missing baseline data, 4 were ongoing (6 mg, n=3; 10 mg, n=1) but not followed up long enough and had no Week 24 assessment, 1 of which (6 mg) and 1 additional (8 mg) had baseline TSS <5. [‡] 5 patients not evaluable: 2 were ongoing but not followed long enough (6 mg), 2 had baseline TSS <5 (6 mg and 8 mg, n=1 each), and 1 did not have baseline data (4 mg).

Efficacy – Combination Therapy (“Add-on”)

Symptom Response in Individual Patients With MF With Suboptimal RUX Response (n=23)

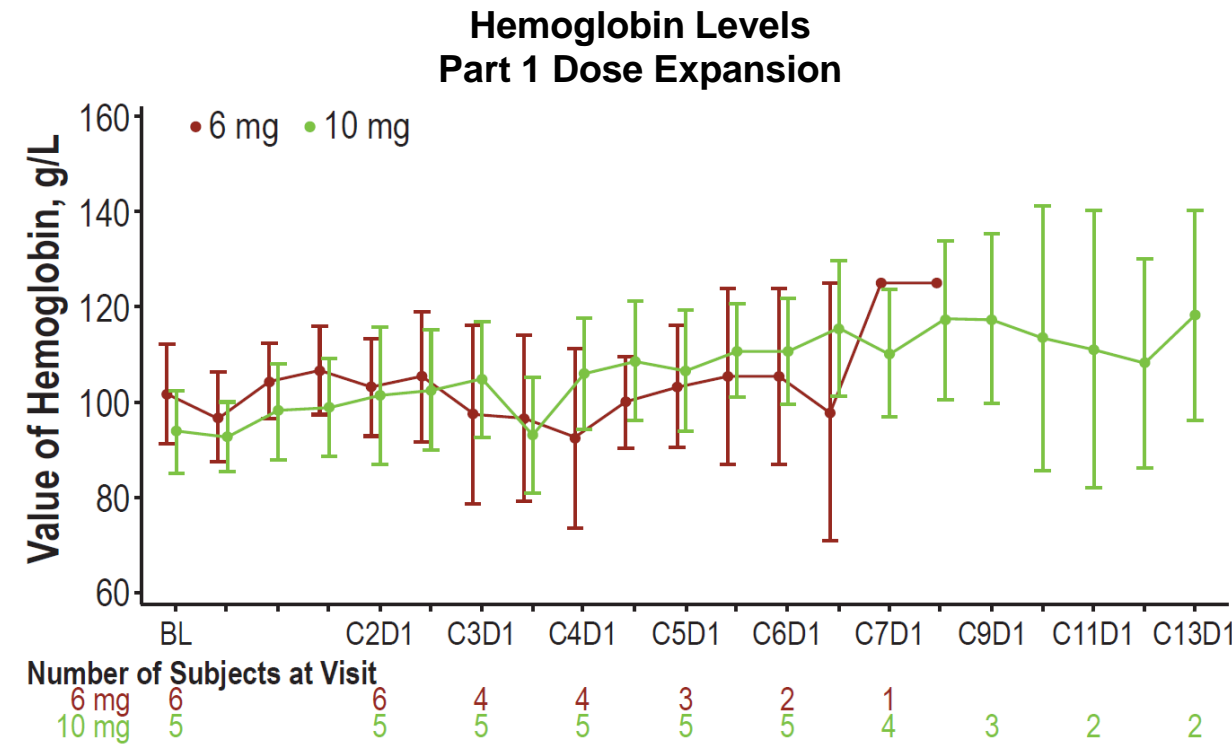
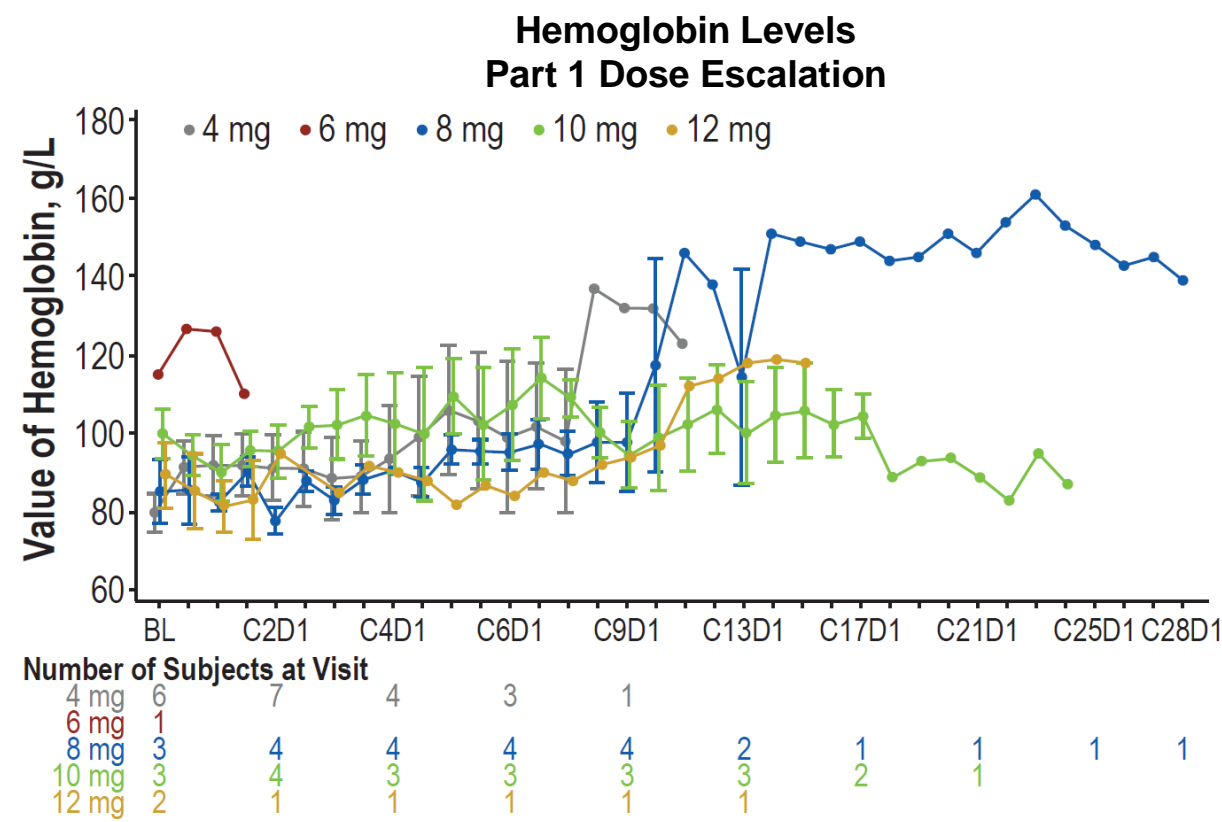
- At Week 24, TSS50 was achieved by 8/16 evaluable patients
- BOR TSS50 achieved by 12/19 evaluable patients



* Dotted line represents response criteria threshold. [†] 4 evaluable patients (4 mg + RUX, n=3; 6 mg + RUX, n=1) discontinued treatment before Week 24; 7 patients were not evaluable, 6 were ongoing but not followed up long enough (4 mg + RUX, n=1; 6 mg + RUX, n=4; 8 mg + RUX, n=1), 2 had baseline TSS <5 (4 mg + RUX and 6 mg + RUX, n=1 each). [‡] 4 patients were not evaluable, 2 were ongoing but did not have postbaseline data (4 mg + RUX and 6 mg + RUX, n=1 each), 2 had baseline TSS <5 (4 mg + RUX and 6 mg + RUX, n=1 each).

Hemoglobin Levels – Monotherapy

- 6/22 (27%) evaluable patients achieved anemia response,* including 4/18 baseline transfusion-independent and 2/4 baseline transfusion-dependent patients



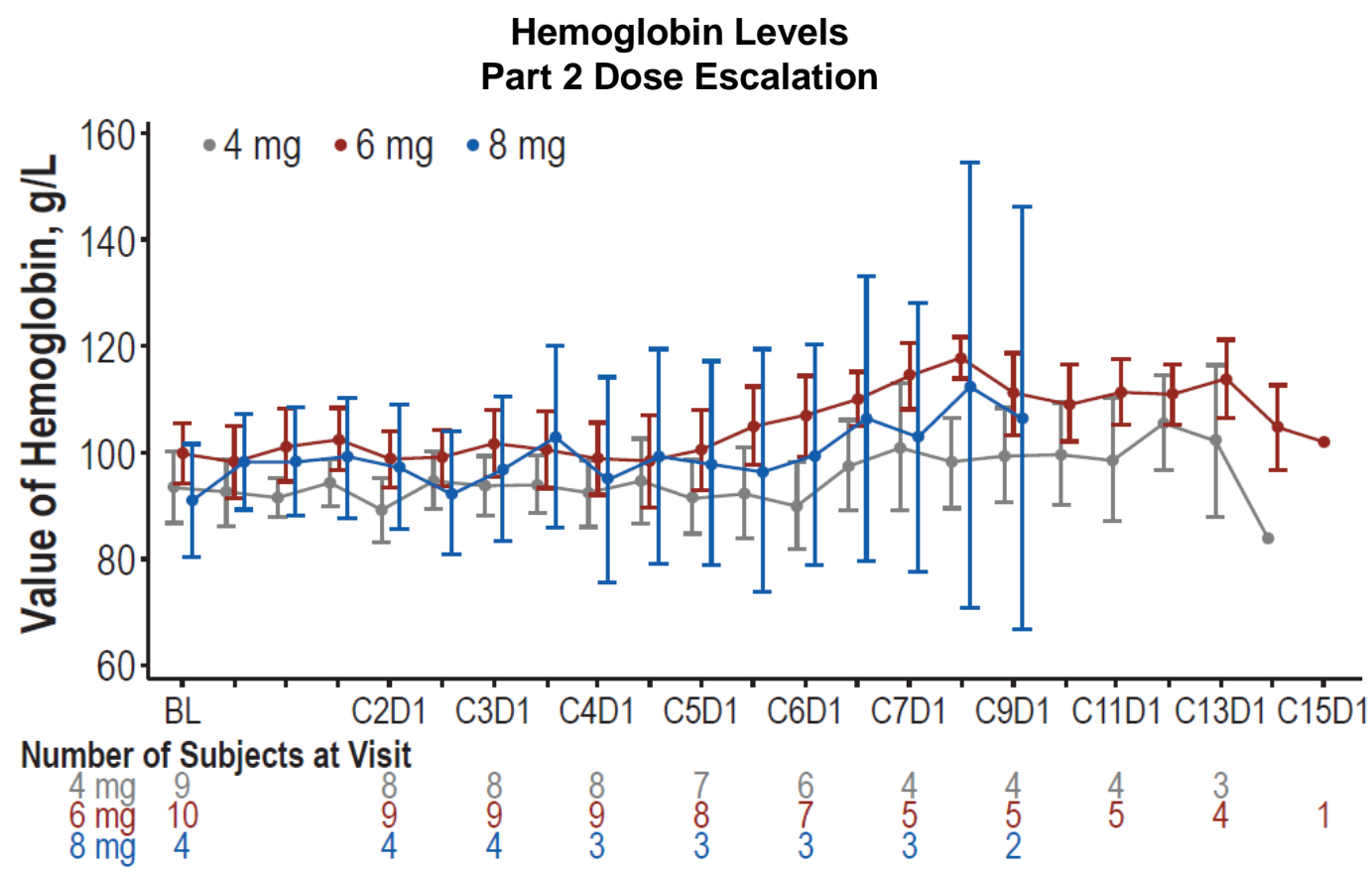
BL, baseline; C, cycle; D, day.

* An anemia response was defined as >1.5 g/dL hemoglobin increase from baseline for transfusion-independent patients at baseline, and achieving transfusion independence for transfusion-dependent patients.

Hemoglobin Levels – Combination Therapy (“Add-on”)

Patients With MF With Suboptimal RUX Response

- 4/20 (20%) evaluable patients achieved anemia response*



* An anemia response was defined as >1.5 g/dL hemoglobin increase from baseline for transfusion-independent patients at baseline, and achieving transfusion independence for transfusion-dependent patients.

Conclusions

- Treatment with INCB057643 monotherapy or in combination with ruxolitinib was generally well tolerated
 - 2 DLTs occurred with INCB057643 monotherapy (12 mg: thrombocytopenia, hyperbilirubinemia)
 - 1 DLT occurred with INCB057643 6-mg combination therapy (thrombocytopenia)
 - There were few treatment-related serious TEAEs and no treatment-related fatal events
 - The most common TEAEs were thrombocytopenia, anemia, nausea, blood bilirubin increased, and dysgeusia
- Improvements in anemia, spleen size, and symptom burden were observed in patients receiving INCB057643 monotherapy and in combination with ruxolitinib
- Dose expansion is ongoing for 6-mg and 10-mg INCB057643 monotherapy
 - 12 patients with MF and 8 with ET have been enrolled in the part 1 expansion phase
- Dose expansion is ongoing for the 4-mg and 8-mg combination (“add-on”) therapy groups
- Enrollment is ongoing for the JAK inhibitor–naïve combination therapy group

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