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

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Introduction

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

Objective

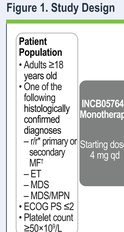
- To evaluate the safety and tolerability of INCB057643
  - As monotherapy in patients with relapsed/refractory MF, essential thrombocythemia (ET), myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndromes
  - In combination with ruxolitinib in patients with advanced chronic or accelerated-phase MF who have suboptimal response to ruxolitinib, or JAK inhibitor treatment–naive MF

Methods

Study Design and Patients

- This ongoing phase 1, open-label, 3+3 dose-escalation/expansion study (NCT04279847) is evaluating the safety and tolerability of INCB057643 in adult patients (**Figure 1**)
  - Key exclusion criteria included Eastern Cooperative Oncology Group performance status >2, prior BET inhibitor treatment within 5 half-lives, platelet count <50×10⁹/L for monotherapy or <75×10⁹/L for combination therapy, absolute neutrophil count <0.75×10⁹/L, and allogeneic transplant ≤6 months before enrollment
- The initial INCB057643 dose was 4 mg once daily (qd) with dose escalation up to 12 mg qd for monotherapy; the highest INCB057643 dose used in combination therapy will not exceed the maximum tolerated dose selected from the monotherapy portion of the study
  - All doses were administered continuously in 28-day cycles

Figure 1. Study Design



CT, computed tomography; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; JAK, Janus kinase; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; MRI, magnetic resonance imaging; qd, once daily; RDE, recommended doses for expansion; r/i, relapsed/refractory; SVR35, ≥35% reduction from baseline in spleen volume per MRI/CT; TSS50, ≥50% reduction from baseline in MPN-SAF TSS.
* 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 JAK inhibitor, such as ruxolitinib.
‡ Patients who have been receiving a stable dose of ruxolitinib 5–25 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.
§ Hemoglobin increase of ≥1.5 g/dL from baseline lasting ≥12 weeks during the treatment period if transfusion dependent at baseline or achieving transfusion independence for ≥12 weeks if transfusion-dependent at baseline. "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.

Statistical Analyses

- The full analysis set included all patients who received ≥1 dose of INCB057643 and was used for patient demographics, safety, and efficacy analyses

Results

Patient Characteristics

- As of the March 29, 2024, data cutoff, 18 patients were treated in part 1 dose escalation, 10 in part 1 dose expansion, and 16 in part 2 dose escalation (**Tables 1** and **2**)

Table 1. Patient Demographics

Parameter	Part 1 (INCB057643 Monotherapy)		Part 2 (INCB057643 + RUX)
	Dose Escalation (n=18)	Dose Expansion (n=10)	Dose Escalation (n=16)
Age, median (range), y	71 (50–79)	68 (50–79)	71 (50–76)
Male, n (%)	11 (61.1)	7 (70.0)	10 (62.5)
Race, n (%)			
White	14 (77.8)	5 (50.0)	14 (87.5)
Black	0	2 (20.0)	0
Asian	1 (5.6)	3 (30.0)	2 (12.5)
Other	3 (16.7)	0	0
ECOG PS, n (%)			
0	2 (11.1)	4 (40.0)	8 (50.0)
1	16 (88.9)	6 (60.0)	7 (43.8)
2	0	0	1 (6.3)

ECOG PS, Eastern Cooperative Oncology Group performance status; RUX, ruxolitinib.

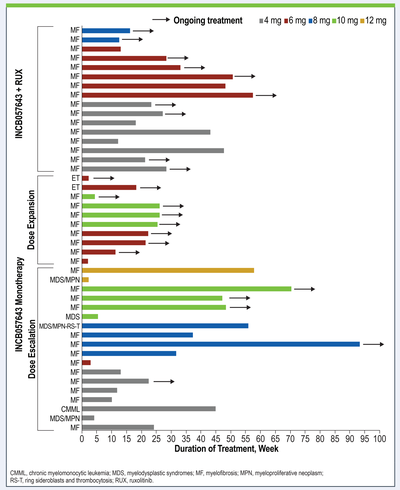
Table 2. Baseline Disease Characteristics

Parameter	Part 1 (INCB057643 Monotherapy)				Part 2 (INCB057643 + RUX)
	MF		MDS and MDS/MPN	ET	MF
	Dose Escalation (n=13)	Dose Expansion (n=8)	Dose Escalation (n=5)	Dose Expansion (n=2)	Dose Escalation (n=16)
Time since initial diagnosis, median (range), y	4.7 (1.8–13.4)	5.6 (1.9–15.1)	0.06 (0.04 –0.1)	10.3 (4.3–16.2)	3.9 (0.4–12.9)
RBC transfusion dependent, n (%)					
Yes	2 (15.4)	2 (25.0)	1 (20.0)	0	2 (12.5)
No	11 (84.6)	6 (75.0)	4 (80.0)	2 (100)	14 (87.5)
MF type, n (%)					
Primary MF	5 (38.5)	4 (50.0)	—	—	8 (50.0)
Post-PV	4 (30.8)	3 (37.5)	—	—	4 (25.0)
Post-ET	4 (30.8)	1 (12.5)	—	—	4 (25.0)
MDS/MPN type, n (%)					
MDS	—	—	2 (40.0)	—	—
CMML	—	—	1 (20.0)	—	—
Unclassified MDS/MPN overlap syndrome	—	—	1 (20.0)	—	—
MDS/MPN-RS-T	—	—	1 (20.0)	—	—
IWG risk level, n (%)					
High	2 (15.4)	4 (50.0)	—	—	1 (6.3)
Int-2	11 (84.6)	4 (50.0)	—	—	15 (93.8)
JAK2-positive, n (%)	8 (61.5)	5 (62.5)	—	—	12 (75.0)
CALR exon 9 mutation-positive, n (%)	—	—	—	1 (50.0)	—
Spleen volume, median (range), cm³	2028.0 (618–4766)	—	—	367.0 (205–529)	1794.5 (638–4381)
Spleen length, median (range), cm	12 (3–24)	12 (5–25)	—	—	12 (6–25)
TSS, mean (SD)	35.5 (21.0)	—	—	0.5 (0.7)	20.1 (12.6)

CMML, chronic myelomonocytic leukemia; ET, essential thrombocythemia; Int, intermediate; IWG, International Working Group; JAK, Janus kinase; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythemia vera; RBC, red blood cell; RS-T, ring sideroblasts and thrombocytosis; RUX, ruxolitinib; TSS, total symptom score.

- Median (range) duration of INCB057643 exposure was 195.5 (15–654) days in the monotherapy dose-escalation cohort, 139.0 (14–183) days in the monotherapy dose-expansion cohort, and 194.0 (85–402) days in the combination therapy dose-escalation cohort (**Figure 2**)

Figure 2. Treatment Duration



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

Safety

- Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 61.4% and serious TEAEs in 25.0% of patients (**Table 3**)

Table 3. Safety Summary

Parameter, n (%)	Part 1 (INCB057643 Monotherapy)		Part 2 (INCB057643 + RUX)	Total (N=44)
	Dose Escalation (n=18)	Dose Expansion (n=10)	Dose Escalation (n=16)	
Any TEAE	18 (100)	9 (90.0)	16 (100.0)	43 (97.7)
Grade ≥3 TEAE*	15 (83.3)	3 (30.0)	9 (56.3)	27 (61.4)
TEAE leading to discontinuation†	4 (22.2)	1 (10.0)	1 (6.3)	6 (13.6)
Serious TEAE	6 (33.3)	1 (10.0)	4 (25.0)	11 (25.0)
Fatal TEAE‡	1 (5.6)	0	0	1 (2.3)
Treatment-related TEAE	17 (94.4)	9 (90.0)	13 (81.3)	39 (88.6)
Treatment-related serious TEAE§	1 (5.6)	0	1 (6.3)	2 (4.5)
Treatment-related fatal TEAE	0	0	0	0
Most common TEAEs¶				
Thrombocytopenia‖	11 (61.1)	4 (40.0)	11 (68.8)	26 (59.1)
Nausea	9 (50.0)	2 (20.0)	2 (12.5)	13 (29.5)
Anemia	6 (33.3)	1 (10.0)	5 (31.3)	12 (27.3)
Dysgeusia	5 (27.8)	3 (30.0)	2 (12.5)	10 (22.7)
Blood bilirubin increased	7 (38.9)	0	2 (12.5)	9 (20.5)

RUX, ruxolitinib; TEAE, treatment-emergent adverse event.
* Grade ≥3 TEAEs occurring in >2 patients: thrombocytopenia or platelet count decreased (n=16), anemia (n=9).
† TEAEs leading to discontinuation of INCB057643: thrombocytopenia or platelet count decreased (n=5), anemia (n=1), and bacteremia (n=1).
‡ Fatal TEAE: transformation to acute myeloid leukemia (n=1).
§ Treatment-related serious TEAEs: pneumonia (n=1), hematoma of right groin (n=1).
¶ TEAEs occurring in ≥20% of patients in the total population.
‖ Includes thrombocytopenia and platelet count decreased.

- 6 patients discontinued treatment due to TEAEs (n=5 with monotherapy)
- Thrombocytopenia was the most common TEAE (n=26) and most common leading to discontinuation (n=5)
- There were 2 dose-limiting toxicities (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 + ruxolitinib [RUX] cohort)

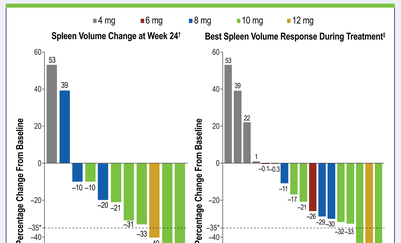
Efficacy

- At Week 24, ≥35% reduction from baseline in spleen volume (SVR35) was achieved by 3/7 evaluable monotherapy patients receiving INCB057643 ≥10 mg (**Figure 3**)
  - 8/19 evaluable patients treated at any dose achieved best response of ≥25% reduction in spleen volume during the treatment period
- At Week 24, SVR35 was achieved by 3/12 evaluable patients receiving combination therapy (**Figure 4**)
  - Improvements in spleen volume were observed in 13/16 evaluable patients, with 5 achieving best response of ≥25% reduction in spleen volume during the treatment period
- At Week 24, ≥50% reduction from baseline in MPN-SAF TSS (TSS50) was achieved by 5/14 evaluable monotherapy patients and by 5/7 evaluable patients receiving INCB057643 ≥10 mg (**Figure 5**)
  - 12/19 evaluable patients treated at any dose achieved best response of TSS50 during the treatment period
- At Week 24, TSS50 was achieved by 6/11 evaluable patients receiving combination therapy (**Figure 6**)
  - 10/15 evaluable patients treated at any dose achieved best response of TSS50 during the treatment period

Hemoglobin Levels

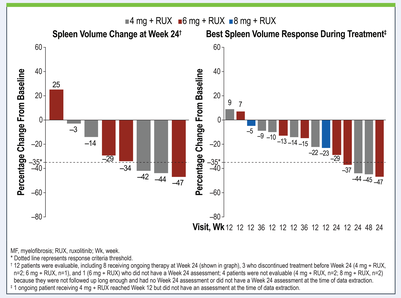
- Among the 19 evaluable patients in part 1 who were not transfusion-dependent at baseline, 3 had >1.5 g/dL increases from baseline in hemoglobin for ≥12 weeks on treatment (all 3 had MF; **Figure 7**)
- Among the 14 patients in part 2 who were not transfusion-dependent at baseline, 3 (4 mg + RUX, n=1; 6 mg + RUX, n=2) had >1.5 g/dL hemoglobin increases from baseline (**Figure 7**)
- Among 6 evaluable patients who were transfusion-dependent at baseline (part 1, n=4; part 2, n=2), 2 achieved transfusion independence (both in part 1)

Figure 3. Spleen Volume Response in Individual Patients With MF Receiving INCB057643 Monotherapy (n=21)



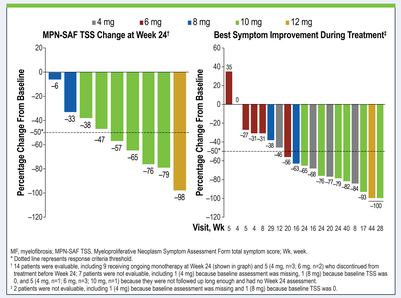
MF, myelofibrosis; Wk, week.
* Dotted line represents response criteria threshold.
† 19 patients were evaluable, including 2 (6 mg) who discontinued from treatment before first post-baseline (Week 12) spleen volume assessment; 2 were not evaluable (6 mg, n=1; 10 mg, n=1) because they were not followed up long enough and had no Week 12 assessment.

Figure 4. Spleen Volume Response in Individual Patients With MF Receiving INCB057643 Combination Therapy (n=16)



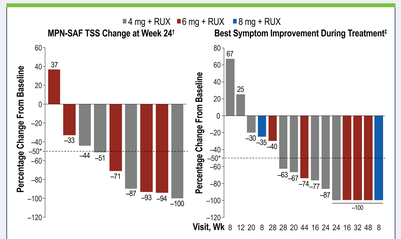
MF, myelofibrosis; RUX, ruxolitinib; Wk, week.
* Dotted line represents response criteria threshold.
† 12 patients were evaluable, including 8 receiving ongoing therapy at Week 24 (shown in graph), 3 who discontinued treatment before Week 24 (4 mg + RUX, n=2; 6 mg + RUX, n=1), and 1 (8 mg + RUX) who did not have a Week 24 assessment; 4 patients were not evaluable (4 mg + RUX, n=2; 8 mg + RUX, n=2) 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 ongoing patient receiving 4 mg + RUX reached Week 12 but did not have an assessment at the time of data extraction.

Figure 5. Symptom Response in Individual Patients With MF Receiving INCB057643 Monotherapy (n=21)



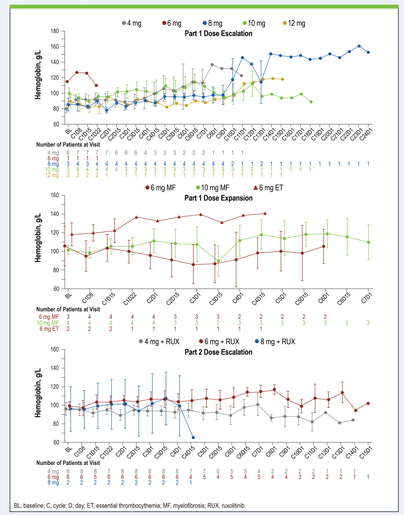
MF, myelofibrosis; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; Wk, week.
* Dotted line represents response criteria threshold.
† 14 patients were evaluable, including 9 receiving ongoing monotherapy at Week 24 (shown in graph) and 5 (4 mg, n=3; 6 mg, n=2) who discontinued from treatment before Week 24; 7 patients were not evaluable, including 1 (4 mg) because baseline assessment was missing, 1 (8 mg) because baseline TSS was 0, and 5 (4 mg, n=1; 6 mg, n=3; 10 mg, n=1) because they were not followed up long enough and had no Week 24 assessment.
‡ 2 patients were not evaluable, including 1 (4 mg) because baseline assessment was missing and 1 (8 mg) because baseline TSS was 0.

Figure 6. Symptom Response in Individual Patients With MF Receiving INCB057643 Combination Therapy (n=16)



MF, myelofibrosis; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; RUX, ruxolitinib; Wk, week.
* Dotted line represents response criteria threshold.
† 11 patients were evaluable, including 9 receiving ongoing therapy at Week 24 (shown in graph) and 2 (4 mg + RUX) who discontinued from treatment before Week 24; 5 patients were not evaluable, including 4 receiving ongoing combination therapy (4 mg + RUX, n=2; 8 mg + RUX, n=2) because they were not followed up long enough and had no Week 24 assessment, and 1 (6 mg + RUX) who did not have a baseline assessment.
‡ 11 patient (6 mg + RUX) who did not have a baseline assessment was not evaluable.

Figure 7. Hemoglobin Levels



BL, baseline; C, cycle; D, day; ET, essential thrombocythemia; MF, myelofibrosis; RUX, ruxolitinib.

Conclusions

- Treatment with INCB057643 monotherapy or in combination with ruxolitinib was generally well tolerated
  - 2 DLTs occurred with INCB057643 monotherapy (12 mg, thrombocytopenia, hyperbilirubinemia) and 1 DLT with INCB057643 6 mg combination therapy (thrombocytopenia)
  - There were 2 treatment-related serious TEAEs and no treatment-related fatal events
  - The most common TEAEs were thrombocytopenia, nausea, and anemia
- Improvements in spleen size and symptom burden were observed in patients receiving INCB057643 ≥6 mg monotherapy and INCB057643 ≥4 mg combination therapy
- Dose expansion is ongoing for 6 mg and 10 mg INCB057643 monotherapy
  - 8 patients with MF and 2 with ET have been enrolled in the part 1 expansion phase
- Dose escalation is ongoing in the combination therapy group

Disclosures

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