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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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Justin Watts, MD,[1,*] Anthony M. Hunter, MD,[2] Alessandra Iurlo, MD, PhD,[3] Blanca Xicoy, MD,[4] Francesca Palandri, MD, PhD,[5] Brandi Reeves, MD,[6] Alessandro M. Vannucchi, MD,[7] Prithviraj Bose, MD,[8] Rosa Ayala Diaz, MD,[9] Anna B. Halpern, MD,[10] Xuejun Chen, PhD,[11] Francis Seguy, MSc,[12] Feng Zhou, PhD,[11] Fred Zheng, MD,[11] Pankit Vachhani, MD[13]

[1]Sylvester Cancer Center, University of Miami, Miami, FL, USA; [2]Emory University School of Medicine, Atlanta, GA, USA; [3]Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [4]Hospital Germans Trias i Pujol, Institut Català d'Oncologia, Josep Carreras Leukemia Research Institute, Universitat Autònoma de Barcelona, Badalona, Spain; [5]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seràgnoli," Bologna, Italy; [6]University of North Carolina School of Medicine, Chapel Hill, NC, USA; [7]AOU Careggi, University of Florence, Florence, Italy; [8]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [9]Hospital Universitario 12 de Octubre, Madrid, Spain; [10]Fred Hutchinson Cancer Center, University of Washington, Seattle, WA, USA; [11]Incyte Corporation, Wilmington, DE, USA; [12]Incyte Biosciences International Sàrl, Morges, Switzerland; [13]O'Neal Comprehensive Cancer Center at UAB, Birmingham, AL, USA

*Presenting author
jxw401@miami.edu

Introduction

- Bromodomain and extra-terminal (BET) proteins are epigenetic readers that regulate expression of critical oncoproteins such as B-cell lymphoma-2, nuclear factor kappa B (NF-κB), and c-Myc, which are involved in the pathophysiology of myelofibrosis (MF) and other hematologic malignancies[1,2]
- INCB057643 is a small-molecule, oral BET inhibitor; results from a previous phase 1/2 clinical trial as monotherapy or in combination with the JAK1/JAK2 inhibitor ruxolitinib indicated favorable tolerability and encouraging clinical activity[3]

Objectives

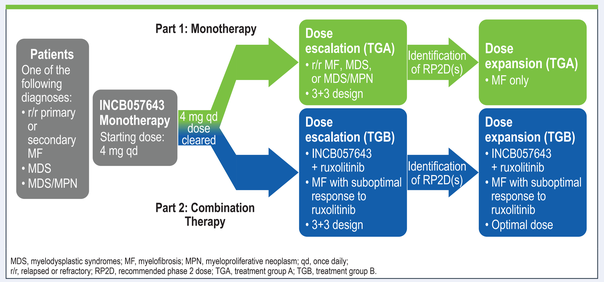
- To evaluate the safety and tolerability of INCB057643:
  - As monotherapy in patients with relapsed/refractory MF, myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndromes
  - In combination with ruxolitinib in patients with advanced MF and suboptimal response to ruxolitinib

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 patients aged ≥18 years (**Figure 1**)
  - Part 1 evaluated INCB057643 monotherapy in patients with histologically confirmed MF, MDS, or MDS/MPN
  - Part 2 evaluated INCB057643 in combination with ruxolitinib in patients with MF and suboptimal response to ruxolitinib
  - Key exclusion criteria included Eastern Cooperative Oncology Group performance status >2, prior BET inhibitor treatment within 5 half-lives, platelet count <50×10^9/L for monotherapy or <75×10^9/L for combination therapy, absolute neutrophil count <0.75×10^9/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
  - All doses were administered continuously in 28-day cycles

Figure 1. Study Design



MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; qd, once daily; r/r, relapsed or refractory; RP2D, recommended phase 2 dose; TGA, treatment group A; TGB, treatment group B.

Study Endpoints

- The primary endpoint is safety and tolerability, including identification of dose-limiting toxicities (DLTs)
- Secondary endpoints in patients with MF
  - Spleen volume response (≥35% reduction from baseline at Week 24 per magnetic resonance imaging/computed tomography scan)
  - Spleen length response (≥50% reduction from baseline at any visit as measured by palpation)
  - Symptom response (≥50% reduction from baseline at Week 24 in MPN-Symptom Assessment Form Total Symptom Score)
- Additional secondary endpoints including overall response rate (patients with MDS or MDS/MPN), anemia response, achievement of red blood cell transfusion independence (if dependent at baseline), and hemoglobin improvement ≥1.5 g/dL from baseline (if transfusion-independent at baseline) will be reported at a later date

Statistical Analyses

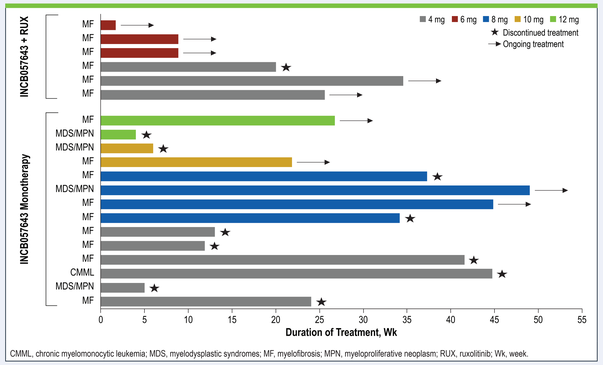
- The full analysis set included all patients who received ≥1 dose of INCB057643 and was used for patient demographics, safety, and efficacy analyses

Results

Enrollment and Treatment Status

- The study has enrolled 20 patients, 16 of whom were evaluable for this analysis (**Figure 2**)

Figure 2. Treatment Duration



CMML, chronic myelomonocytic leukemia; MDS, myelodysplastic syndromes; MF, myelofibrosis; MPN, myeloproliferative neoplasm; RUX, ruxolitinib; Wk, week.

Patients

- At the time of this analysis, 13 patients were treated in Part 1 (4 mg, n=6; 8 mg, n=4; 10 mg, n=1; 12 mg, n=2), and 3 received 4 mg + ruxolitinib in Part 2 (**Table 1**)
  - Overall, 12 patients had MF, and 4 had MDS/MPN
- 11 patients discontinued treatment, 5 due to disease progression or lack of efficacy (all in monotherapy group); 6 due to adverse events (AEs; 5 in monotherapy group, 1 in combination group), the main AE leading to discontinuation is thrombocytopenia (n=5)

Table 1. Patient Demographics and Baseline Characteristics

	INCB057643 Monotherapy					INCB057643 + RUX
Parameter	4 mg (n=6)	8 mg (n=4)	10 mg (n=1)	12 mg (n=2)	Total (n=13)	4 mg + RUX (n=3)
Median (range) age, y	67.5 (59–77)	68.5 (65–79)	74.0 (74–74)	61.5 (50–73)	69.0 (50–69)	72.0 (70–74)
Male, n (%)	4 (67)	3 (75)	0	1 (50)	8 (62)	1 (33)
White	6 (100)	3 (75)	1 (100)	1 (50)	11 (85)	3 (100)
ECOG PS, n (%)						
0	1 (17)	0	0	1 (50)	2 (15)	2 (67)
1	5 (83)	4 (100)	1 (100)	1 (50)	11 (85)	1 (33)
Malignancy type, n (%)						
MF	4 (67)	3 (75)	1 (100)	1 (50)	9 (69)	3 (100)
DIPSS Int-2	4/4 (100)	3/3 (100)	1/1 (100)	1/1 (100)	9/9 (100)	3/3 (100)
Primary MF	2/4 (50)	1/3 (33)	0	0	3/9 (33)	0
Post–PV-MF	2/4 (50)	0	0	0	2/9 (22)	1/3 (33)
Post–ET-MF	0	2/3 (67)	1/1 (100)	1/1 (100)	4/9 (44)	2/3 (67)
Unclassifiable MDS/MPN overlap syndrome	1 (17)	0	0	0	1 (8)	0
CMML	1 (17)	0	0	1 (50)	2 (15)	0
MDS/MPN missing	0	1 (25.0)	0	0	1 (8)	0
RBC transfusion dependent						
Yes	2 (33)	0	0	1 (50)	3 (23)	1 (33)
No	2 (33)	0	1 (100)	1 (50)	4 (31)	1 (33)
Missing	2 (33)	4 (100)	0	0	6 (46)	1 (33)
Prior treatment						
Radiotherapy	1 (17)	1 (25)	0	0	2 (15)	0
Stem cell transplant	0	0	0	0	0	0
Median (range) spleen volume, mL*	2075 (1857–2292)	2104 (2028–2180)	1592 (1592–1592)	1418 (1418–1418)	1943 (1418–2292)	1112 (807–3394)
Median (range) MPN–SAF TSS†	31 (13–44)	NE	33 (33–33)	50 (50–50)	33 (13–50)	27 (6–39)

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; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score; NE, not evaluable; post-ET-MF, post-essential thrombocythemia myelofibrosis; post-PV-MF, post-polycythemia vera myelofibrosis; RBC, red blood cell; RUX, ruxolitinib.
* Among evaluable patients with MF: 4-mg cohort, n=2; 8-mg cohort, n=2; 10-mg cohort, n=1; 12-mg cohort, n=1; 4-mg + RUX cohort, n=3.
† Among patients with baseline MPN-SAF assessment: 4-mg cohort, n=3; 10-mg cohort, n=1; 12-mg cohort, n=1; 4-mg + RUX cohort, n=3.

Safety

- Median (range) duration of INCB057643 exposure in the safety analysis was 91 (15–314) days in Part 1 monotherapy and 77 (58–140) days in Part 2 combination therapy (data cutoff date, January 18, 2023)
- Thrombocytopenia was the most common treatment-emergent adverse event (TEAE; n=9; **Table 2**) and the only TEAE leading to discontinuation (n=3)
- Grade ≥3 TEAEs occurring in >1 patient were thrombocytopenia (n=4), anemia (n=3), and hypokalemia (n=2)
- There were 8 serious AEs across 4 patients, with only COVID-19 occurring in >1 patient (n=2); all but 1 (pneumonia) were considered unrelated to study treatment
- There were 2 DLTs (thrombocytopenia [MDS/MPN patient] and hyperbilirubinemia [MF patient]; both 12-mg cohort) and 2 deaths (both 4-mg cohort due to progressive disease [MF, n=1; MDS/MPN, n=1])

Table 2. Summary of TEAEs Occurring in >1 Patient in the Total Population

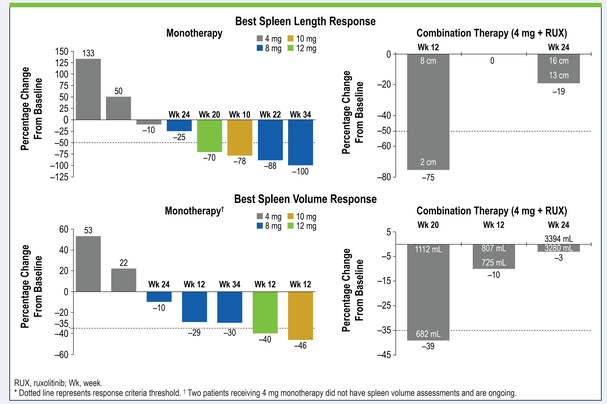
TEAE, n (%)	4 mg (n=6)	8 mg (n=4)	10 mg (n=1)	12 mg (n=2)	4 mg + RUX (n=3)	Total (N=16)
Thrombocytopenia	3 (50)	2 (50)	1 (100)	1 (50)	2 (67)	9 (56)
Dysgeusia	0	1 (25)	1 (100)	2 (100)	1 (33)	5 (31)
Nausea	1 (17)	2 (50)	0	1 (50)	0	4 (25)
Anemia	2 (33)	1 (25)	0	0	0	3 (19)
Blood bilirubin increased	1 (17)	2 (50)	0	0	0	3 (19)
Ejection fraction decreased	0	1 (25)	0	0	2 (67)	3 (19)
COVID-19	0	2 (50)	0	0	1 (33)	3 (19)
Abdominal pain	1 (17)	0	0	1 (50)	0	2 (13)
AST increased	0	1 (25)	0	1 (50)	0	2 (13)
Blood creatinine increased	1 (17)	1 (25)	0	0	0	2 (13)
Hyperbilirubinemia	0	1 (25)	0	1 (50)	0	2 (13)
Hyperuricemia	2 (33)	0	0	0	0	2 (13)
Hypokalemia	2 (33)	0	0	0	0	2 (13)
Pruritus	0	1 (25)	0	1 (50)	0	2 (13)
Rash	0	2 (50)	0	0	0	2 (13)
Diarrhea	0	0	0	0	2 (67)	2 (13)
Decreased appetite	1 (17)	0	0	0	1 (33)	2 (13)

AST, aspartate aminotransferase; RUX, ruxolitinib; TEAE, treatment-emergent adverse event.

Efficacy

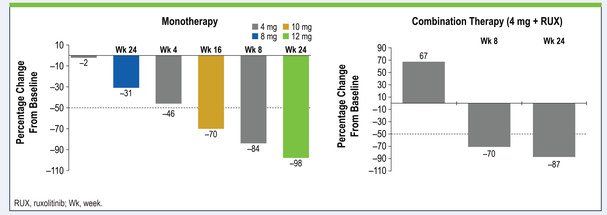
- Median (range) duration of INCB057643 exposure in the efficacy analysis was 150 (15–314) days in Part 1 monotherapy and 142 (127–205) days in Part 2 combination therapy (data cutoff date, March 24, 2023)
- Both evaluable patients with MF receiving INCB057643 ≥10 mg as monotherapy achieved spleen length and volume responses, with initial responses apparent at Weeks 10–12 (**Figure 3**)
  - Improvements in spleen volume were observed in all 3 patients receiving combination therapy, with 1 achieving an initial preliminary spleen volume response at Week 20
- Half of patients receiving INCB057643 monotherapy (1 patient receiving 4 mg and both receiving ≥10 mg) and 2 of 3 receiving INCB057643 4 mg combination therapy achieved symptom response (**Figure 4**)
- One patient receiving INCB057643 4 mg monotherapy also achieved an anemia response and became transfusion independent

Figure 3. Best Spleen Response in Evaluable Patients



RUX, ruxolitinib; Wk, week.
* Dotted line represents response criteria threshold. † Two patients receiving 4 mg monotherapy did not have spleen volume assessments and are ongoing.

Figure 4. Symptom Response in Evaluable Patients



RUX, ruxolitinib; Wk, week.

Conclusions

- **Treatment with INCB057643 monotherapy (4 and 8 mg qd) and in combination (4 mg qd) with ruxolitinib was generally well tolerated in this patient population**
  - **The 12-mg qd monotherapy dose was not tolerated and caused 2 DLTs**
  - **There were no treatment-related fatal events**
  - **The most common TEAEs were thrombocytopenia, dysgeusia, and nausea**
- **Improvements in spleen size and symptom burden were observed in patients receiving INCB057643 ≥8 mg monotherapy or INCB057643 4 mg combination therapy**
- **Dose finding in Part 1 is ongoing with 10 mg qd, after which a recommended phase 2 dose will be declared**
  - **Combination dose escalation is also ongoing**

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