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Presented at the
64th American Society of Hematology (ASH) Annual Meeting and Exposition
New Orleans, LA • December 10–13, 2022

INCB057643 Monotherapy in Patients With Relapsed or Refractory Myelofibrosis: A Phase 1 Study

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Introduction

- Bromodomain and extra-terminal (BET) proteins are a class of epigenetic readers that regulate expression of proteins[1,2]
  - These include factors implicated in oncogenesis of hematologic malignancies including myelofibrosis (MF), such as B-cell lymphoma-2, c-Myc, and nuclear factor kappa B (NF-κB)
- INCB057643 is an oral, small-molecule inhibitor of BET that was evaluated in a phase 1/2 study[3,4]
  - INCB057643 was generally well tolerated, with a favorable pharmacokinetic (PK) profile when administered as monotherapy or in combination with the Janus kinase inhibitor ruxolitinib in patients with advanced malignancies
  - Encouraging clinical activity was observed in 2 of 3 patients with MF

Objectives

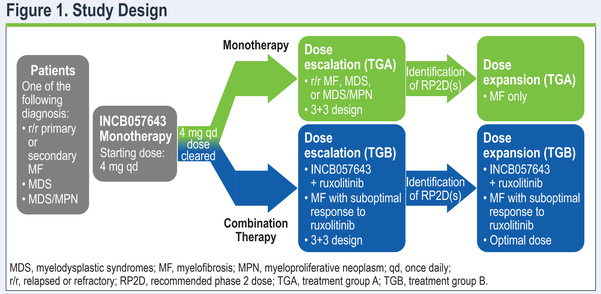
- To evaluate the safety and tolerability of INCB057643
  - As monotherapy in patients with relapsed/refractory MF, myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndromes
  - In combination with ruxolitinib in patients with advanced MF and suboptimal response to ruxolitinib

Methods

Study Design and Patients

- This ongoing phase 1, open-label study (NCT04279847) includes a 3+3 design dose-escalation phase (part 1) followed by a dose-expansion phase (part 2)
- Part 1, reported here, enrolled adult patients with histologically confirmed MF, MDS, or MDS/MPN (**Figure 1**)
  - Exclusion criteria included Eastern Cooperative Oncology Group performance status >2, prior BET inhibitor treatment within 5 half-lives, platelet count <50×10^9/L, 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
- INCB057643 doses that are deemed safe and tolerable in part 1 will be further evaluated in part 2 as monotherapy or in combination with ruxolitinib in patients with MF

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)
- Spleen volume and length in patients with MF were evaluated as secondary endpoints
- Additional secondary endpoints including overall response rate, symptom response, anemia response, and red blood cell transfusion requirement will be reported at a later date
- PK was evaluated as an exploratory endpoint

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
- The PK-evaluable population included all patients who received ≥1 dose of INCB057643 and provided ≥1 postdose plasma sample
- PK data were analyzed using noncompartmental analysis

Results

Patients

- A total of 10 patients have been evaluated in part 1 (4-mg cohort, n=6; 8-mg cohort, n=4; **Table 1**)

Table 1. Patient Demographics and Baseline Characteristics

Parameter	INCB057643 Treatment Group 4 mg (n=6)	8 mg (n=4)	Total (N=10)
Median (range) age, y	67.5 (59–77)	68.5 (65–79)	68.0 (59–79)
Male, n (%)	4 (66.7)	3 (75.0)	7 (70.0)
White	6 (100.0)	3 (75.0)	9 (90.0)
ECOG PS, n (%)			
0	1 (16.7)	0	1 (10.0)
1	5 (83.3)	4 (100.0)	9 (90.0)
Malignancy type, n (%)			
Primary MF	2 (33.3)	1 (25.0)	3 (30.0)
DIPSS Int-2	2 (33.3)	1 (25.0)	3 (30.0)
Post–PV-MF	2 (33.3)	0	2 (20.0)
DIPSS Int-2	2 (33.3)	0	2 (20.0)
Post–ET-MF	0	2 (50.0)	2 (20.0)
DIPSS Int-1	0	1 (25.0)	1 (10.0)
DIPSS Int-2	0	1 (25.0)	1 10.0)
Unclassifiable MDS/MPN overlap syndrome	1 (16.7)	1 (25.0)	2 (20.0)
CMML	1 (16.7)	0	1 (10.0)
RBC transfusion dependent	2 (33.3)	0	2 (20.0)
Prior treatment			
Ruxolitinib	4 (66.7)	3 (75.0)	7 (70.0)
Radiotherapy	1 (16.7)	1 (25.0)	2 (20.0)
Stem cell transplant	0	0	0
Mean (SD) spleen length below left costal margin, cm*	7.0 (3.6)	15.7 (0.6)	11.3 (5.3)

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; RBC, red blood cell.
* Among evaluable patients with MF: 4-mg cohort, n=3; 8-mg cohort, n=4.

- 5 patients remain on treatment (4-mg cohort, n=1; 8-mg cohort, n=4); treatment discontinuation in the 4-mg cohort was due to progressive disease (n=3), treatment-emergent adverse events (TEAEs; thrombocytopenia, n=1), and physician decision (n=1)
  - Duration of INCB057643 exposure ranged from 29–268 days in the 4-mg cohort and 73–102 days in the 8-mg cohort

Safety

- All 10 patients experienced TEAEs (**Table 2**), with 9 patients experiencing TEAEs considered related to study treatment

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

Most common TEAEs, n (%)	INCB057643 Treatment Group 4 mg (n=6) Any	Grade ≥3	8 mg (n=4) Any	Grade ≥3	Total (N=10) Any	Grade ≥3
Thrombocytopenia*	3 (50.0)	1 (16.7)	1 (25.0)	1 (25.0)	4 (40.0)	2 (20.0)
Nausea	1 (16.7)	0	2 (50.0)	0	3 (30.0)	0
Anemia	2 (33.3)	2 (33.3)	0	0	2 (20.0)	2 (20.0)
Hyperuricemia	2 (33.3)	0	0	0	2 (20.0)	0
Hypokalemia	2 (33.3)	2 (33.3)	0	0	2 (20.0)	2 (20.0)

* Two of the 4 patients had moderate thrombocytopenia at baseline.

- Grade ≥3 TEAEs were experienced by 7 patients (4-mg cohort, n=5; 8-mg cohort, n=2)
- Grade ≥3 TEAEs experienced by 2 patients are reported in **Table 2**; those occurring in 1 patient included chronic obstructive pulmonary disease (COPD), leukocytosis, pancytopenia, and transformation to acute myeloid leukemia in the 4-mg cohort and neutrophil count decrease and pneumonia in the 8-mg cohort
- There were 6 serious TEAEs across 4 patients (4-mg cohort: COPD [n=1], pancytopenia and acute myeloid leukemia transformation [n=1]; 8-mg cohort: COVID-19 and pneumonia [n=1], COVID-19 [n=1])
  - One serious TEAE (pneumonia, 8-mg cohort) was considered related to treatment
- No DLTs or fatal TEAEs were observed

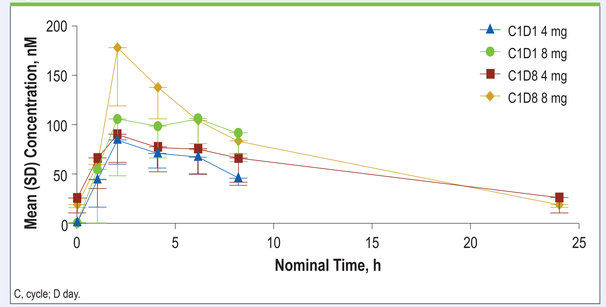
Pharmacokinetics

- The mean steady-state maximum plasma concentration and area under the concentration-time curve for INCB057643 4 mg qd were 92.4 nM and 1260 h·nM, respectively, and with 8 mg qd were 178 nM and 1580 h·nM (**Figure 2**)
  - The limited number of participants in the 8-mg cohort precluded any meaningful comparison between the 2 dose groups

Efficacy

- Reductions in spleen volume and length from baseline were observed (**Table 3**)
- Median (range) best percentage change from baseline in LDH levels was −27.7% (−60.6% to −1.5%) in the 4-mg cohort and −44.4% (−83.0% to −12.4%) in the 8-mg cohort (**Figure 3**)

Figure 2. INCB057643 Plasma Concentration



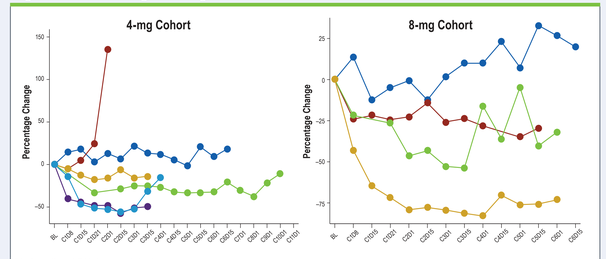
C, cycle; D day.

Table 3. Best Percentage Change From Baseline in Spleen Volume and Length

Patient	Disease	Dose cohort	Spleen volume change,* %	Spleen length change,* %
1	PMF	4 mg	+53.3	+50.0
2	PMF	4 mg	NA	+133.3
3	Post–PV-MF	4 mg	+21.6	−10.0
4	PMF	8 mg	−29.0	−100
5	Post–ET-MF	8 mg	−5.5	0
6	Post–ET-MF	8 mg	NA	−25.0

ET, essential thrombocythemia; MF, myelofibrosis; NA, not available; PMF, primary myelofibrosis; PV, polycythemia vera.
* Negative value indicates reduction in spleen size.

Figure 3. Percentage Change From Baseline in LDH Levels in Individual Patients



BL, baseline; LDH, lactate dehydrogenase.

Conclusions

- **INCB057643 monotherapy administered at doses of 4 and 8 mg qd was generally well tolerated in patients with relapsed or refractory MF, MDS, and MDS/MPN in dose-escalation cohorts, with no DLTs or fatal TEAEs**
- **The most common TEAEs were thrombocytopenia, nausea, anemia, hyperuricemia, and hypokalemia**
- **The study is currently enrolling the cohort of INCB057643 12 mg as monotherapy in patients with MF, MDS, or MDS/MPN**
- **The study is also enrolling a cohort of INCB057643 4 mg in combination with ruxolitinib in patients with MF and suboptimal response to ruxolitinib**

Acknowledgments

Writing assistance was provided by Cory Pfeiffenberger, PhD, an employee of ICON (Blue Bell, PA), and was funded by Incyte Corporation (Wilmington, DE).

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