ELSEVIER

Blood 142 (2023) 750–752

The 65th ASH Annual Meeting Abstracts

ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

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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Introduction: Bromodomain and extra-terminal (BET) proteins are epigenetic readers that regulate expression of critical oncoproteins involved in the pathophysiology of myelofibrosis (MF) and other hematologic malignancies including B-lymphoma-2, nuclear factor kappa, and c-Myc. In a previous phase 1/2 clinical trial, the small-molecule oral BET inhibitor INCB057643, evaluated as monotherapy and in combination with ruxolitinib, was associated with favorable tolerability and encouraging clinical activity in patients with advanced malignancies.
Methods: This ongoing phase 1, 3+3 dose-escalation/expansion study (NCT04279847) is evaluating the safety and tolerability of INCB057643 (4 mg once daily [qd] with escalation up to 12 mg qd) in patients aged ≥18 years as (1) monotherapy (part 1) in relapsed or refractory (R/R) MF, myelodysplastic syndromes (MDS), or MDS/myeloproliferative neoplasm (MPN) overlap syndromes (MDS/MPN) or (2) added to ruxolitinib (part 2) in patients with MF and suboptimal response to ruxolitinib. The primary endpoints are safety and tolerability, including identification of dose-limiting toxicities (DLTs). Secondary endpoints in patients with MF include spleen volume response (≥35% reduction from baseline at Week 24 per magnetic resonance imaging/computed tomography scan) and symptom response (≥50% reduction from baseline at Week 24 in MPN-Symptom Assessment Form Total Symptom Score [MPN-SAF TSS]).
Results: As of data cutoff on June 1, 2023, 14 patients were treated in part 1 (4 mg, n=6; 8 mg, n=4; 10 mg, n=2; 12 mg, n=2), and 6 were treated in part 2 (4 mg, n=3, 6 mg, n=3). In part 1, patients had a median (range) age of 69.5 (50.0-79.0) years and a median (range) study treatment duration of 177 (9-375) days; 8 were men. In part 2, patients had a median (range) age of 71 (64-76) years; median (range) study treatment duration of 92.5 (46-274) days; 3 were men. 16 patients had MF; 4 had MDS/MPN, including 1 with chronic myelomonocytic leukemia. A total of 10 patients discontinued treatment, 4 for lack of efficacy or disease progression and 4 due to adverse events (AEs; 3 in the monotherapy group, 1 in the combination group).

Thrombocytopenia (n=3) and anemia/thrombocytopenia (n=1) were the only treatment-emergent AEs (TEAEs) leading to discontinuation, and thrombocytopenia was the most common TEAE (n=11). Grade ≥3 TEAEs occurring in ≥1 patient were thrombocytopenia (n=5), anemia (n=4), and hypokalemia (n=2). 12 serious AEs occurred across 5 patients (only COVID-19 occurred in >1 patient [n=2]); all but one serious AE (pneumonia) was considered unrelated to study treatment. There were 2 DLTs: thrombocytopenia in 1 patient with MDS/MPN in the 12 mg cohort and hyperbilirubinemia in 1 patient with MF in the 12 mg cohort. 2 deaths occurred on study, both in the 4 mg monotherapy cohort due to disease progression (MF, n=1; MDS/MPN, n=1).

Overall, 5 patients on monotherapy and 2 on combination therapy demonstrated a reduction in spleen volume at Week 12 (≥35% reduction in 2 patients and 1 patient, respectively); at Week 24, 3 patients on monotherapy and 2 on combination therapy had a reduction in spleen volume (≥35%: 1 patient and 1 patient, respectively; Figure 1). Percentage change from baseline in MPN-SAF TSS in individual patients is reported in Figure 2; at Week 12, ≥50% improvement from baseline occurred in 3 patients on monotherapy and 1 on combination therapy (≥50% improvement at Week 24: 2 patients and 1 patient).

Conclusions: INCB057643 monotherapy (4 and 8 mg qd) and combined (4 and 6 mg qd) with ruxolitinib was generally well tolerated, whereas the 12 mg qd monotherapy dose caused 2 DLTs. There were no treatment-related fatal events. Improvements in spleen size and symptom burden were observed in patients receiving ≥8 mg in the monotherapy group and 4 mg in the combination therapy group. Dose finding (part 1) is ongoing with 10 mg qd, after which the recommended dose(s) for expansion will be declared. Dose escalation is also ongoing in the combination therapy group.

Disclosures Watts: *Servier:* Consultancy; *Daiichi Sankyo:* Consultancy; *Reven Pharma:* Consultancy; *Rafael Pharma:* Consultancy; *Aptose:* Consultancy; *Takeda:* Consultancy, Research Funding; *Immune Systems Key:* Research Funding; *Rigel:* Consultancy; *BMS:* Consultancy. **Vannucchi:** *Novartis:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Incyte:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *AOP:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Blueprint:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *GSK:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Imago BioSciences, Inc., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA:* Research Funding; *AbbVie:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *BMS:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau. **Hunter:** *Sierra Oncology:* Membership on an entity's Board of Directors or advisory committees. **McMahon:** *GSK, PharmaEssentia:* Consultancy. **Tantravahi:** *Partnership for Health Analytic Research LLC:* Consultancy, Honoraria; *Incyte:* Consultancy, Honoraria; *MorphoSys:* Consultancy, Honoraria; *CTI BioPharma:* Consultancy, Honoraria; *Novartis:* Consultancy, Honoraria; *Karyopharm Therapeutics Inc:* Consultancy, Honoraria, Research Funding; *AbbVie:* Consultancy, Honoraria. **Iurlo:** *Novartis, Pfizer, Incyte, BMS, GSK, AOP Health:* Honoraria. **Palandri:** *Novartis, BMS, Celgene, GSK, Amgen, AbbVie, Karyopharm, AOP, Sierra Oncology, Janssen:* Consultancy, Honoraria. **Searle:** *Sanofi:* Membership on an entity's Board of Directors or advisory committees; *Abbvie:* Honoraria; *Janssen:* Honoraria; *Shattuck:* Membership on an entity's Board of Directors or advisory committees. **Reeves:** *PharmaEssentia, Incyte, BMS:* Honoraria. **Bose:** *Kartos, Telios, Ionis, Disc, Janssen, Geron:* Research Funding; *Incyte, BMS, CTI, Morphosys, Blueprint, Cogent, Sumitomo:* Honoraria, Research Funding; *GSK, Novartis, Karyopharm, AbbVie, Pharma Essentia, Jubilant, Morphic:* Honoraria. **Ayala:** *Novartis:* Consultancy, Speakers Bureau; *Incyte:* Consultancy; *Astellas, BMS:* Speakers Bureau. **Halpern:** *Abbie, Notable Labs, Agios:* Consultancy; *Imago Bioscience, Bayer, Gilead, Jazz, Incyte, Karyopharm Therapeutics, Disc Medicine:* Research Funding. **Chen:** *Incyte:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Burke:** *Incyte:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Zhou:** *Incyte:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Zheng:** *Incyte:* Current Employment, Current equity holder in private company, Current holder of *stock options* in a privately-held company. **Vachhani:** *Incyte, CTI BioPharma Corp, Blueprint Medicines:* Speakers Bureau; *Abbvie, Amgen, Blueprint Medicines, Cogent Biosciences, Incyte, CTI BioPharma Corp, Daiichi Sankyo, GlaxoSmith Kline, Karyopharm, Novartis, Pfizer, Genentech, Inc., Servier, Stemline, MorphoSys, LAVA therapeutics:* Honoraria.

OffLabel Disclosure: INCB057643 is a small-molecule oral BET inhibitor being evaluated in myelofibrosis and other hematologic malignancies

Figure 1: Percentage Change From Baseline in Spleen Volume at Weeks 12 and 24

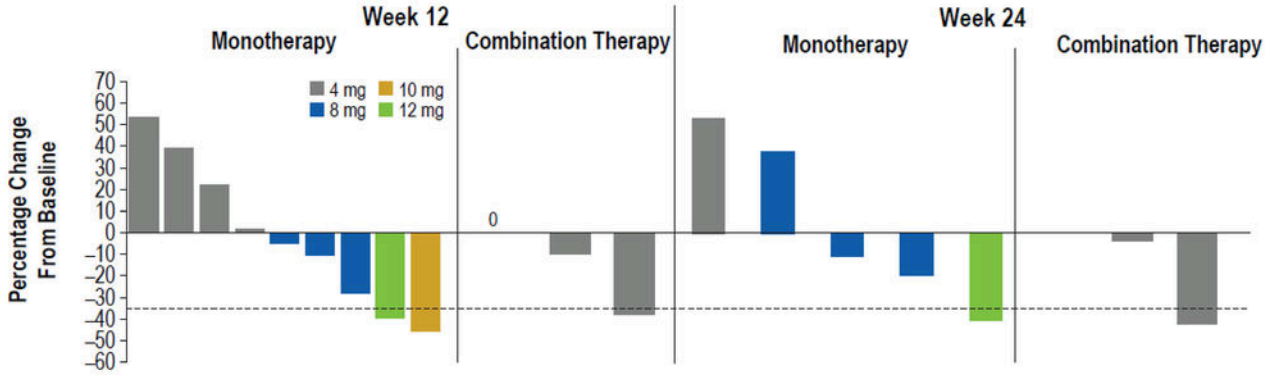
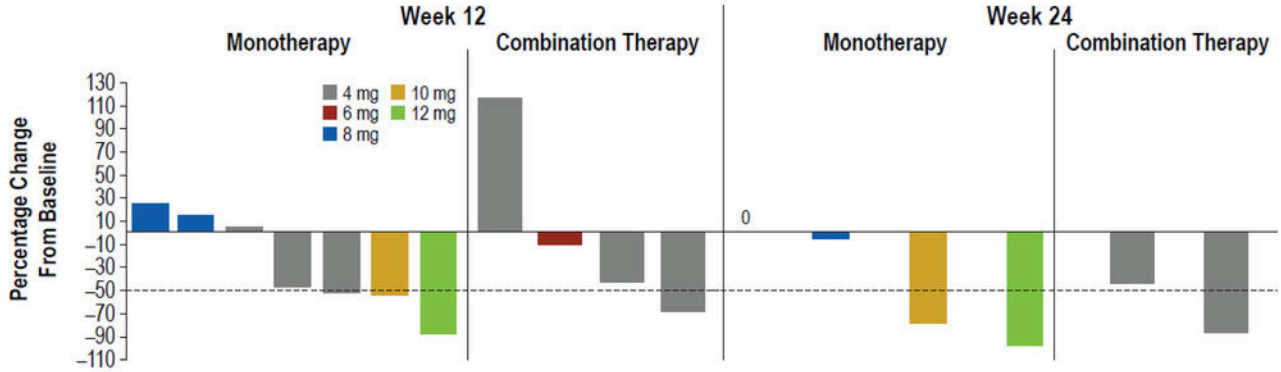


Figure 2: Percentage Change From Baseline in MPN-SAF TSS at Weeks 12 and 24



One patient in the 6 mg combination therapy cohort had assessment of percentage change from baseline in MPN-SAF TSS at Week 12 but did not have assessment of percentage change from baseline in spleen volume.
MPN-SAF TSS, Myeloproliferative Neoplasm–Symptom Assessment Form Total Symptom Score.

Figure 1

https://doi.org/10.1182/blood-2023-179428