MPN-075

Efficacy and Safety of Add-on Parsaclisib to Ruxolitinib Therapy in Myelofibrosis Patients With Low Versus Higher Baseline Platelet Counts: A Subgroup Analysis of Data From a Phase 2 Study

Presented at the

10th Annual Meeting of the Society of Hematologic Oncology

Houston, TX, USA • September 28-October 1, 2022

Abdulraheem Yacoub,[1] Uma Borate,[2] Raajit Rampal,[3] Haris Ali,[4] Eunice Wang,[5] Aaron Gerds,[6] Gabriela Hobbs,[7] Marina Kremyanskaya,[8] Elliott Winton,[9] Casey O'Connell,[10] Swati Goel,[11] Stephen Oh,[12] Gary Schiller,[13] Albert Assad,[14] Sue Erickson-Viitanen,[14] Feng Zhou,[14] Naval Daver[15]

[1]University of Kansas Cancer Center, Westwood, KS, USA; [2]Oregon Health & Science University, Portland, OR, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]City of Hope National Medical Center, Duarte, CA, USA; [5]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [6]Cleveland Clinic, Cleveland, OH, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [9]Emory University School of Medicine, Atlanta, GA, USA; [10]University of Southern California, Los Angeles, CA, USA; [11]Montefiore Medical Center, Bronx, NY, USA; [12]Washington University School of Medicine, St. Louis, MO, USA; [13]David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA; [14]Incyte Corporation, Wilmington, DE, USA; [15]University of Texas MD Anderson Cancer Center, Houston, TX, USA

Background

- Despite the demonstrated efficacy of ruxolitinib (potent and selective Janus kinase [JAK] 1 and JAK2 inhibitor) in patients with myelofibrosis (MF),[1-3] suboptimal responses or loss of response to ruxolitinib may occur
  - There is some evidence to suggest persistent activation of the phosphatidylinositol 3-kinase (PI3K) pathway with chronic ruxolitinib therapy[4,5]
- Parsaclisib (INCB050465) is a potent and highly selective next-generation PI3Kδ inhibitor[6]
- Preliminary efficacy of parsaclisib was demonstrated in a phase 2 trial (INCB 50465-201, NCT02718300) of parsaclisib added to stable doses of ruxolitinib for patients with MF who experienced a suboptimal response to ruxolitinib[7]
- JAK inhibitors, including ruxolitinib, are associated with thrombocytopenia[1-3]; therefore, patients with low platelet counts are traditionally more difficult to treat
- Here, we present subgroup analysis results based on baseline platelet count (PC) from the ongoing phase 2 study evaluating the addition of parsaclisib in patients with MF treated with ruxolitinib

Objective

- To evaluate the impact of baseline PC on resulting responses to spleen volume and total symptom score (TSS) at weeks 12 and 24, and safety, in the INCB 50465-201 phase 2 study
  - Patients were grouped as low PC (50 to <100×10^9/L) versus higher PC (≥100×10^9/L) based on baseline counts

Methods

Key Inclusion Criteria

- Patients ≥18 years of age with primary or secondary MF (primary MF, post–polycythemia vera MF, or post-essential thrombocythemia MF)
- Suboptimal response to ruxolitinib monotherapy
  - Treated with ruxolitinib (5-25 mg twice daily) for ≥6 months with stable dose for ≥8 weeks immediately prior to enrollment
  - ***AND***
  - Palpable spleen >10 cm below left subcostal margin on physical examination at screening
  - ***OR***
  - Palpable spleen 5-10 cm below left subcostal margin on physical examination ***AND*** active symptoms of MF at the screening visit defined as 1 symptom score ≥5 or 2 symptom scores ≥3 each, using the Screening Symptom Form (10-point scale for each of the 7 symptoms, which include night sweats, pruritus, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain, and inactivity)
- PC ≥50×10^9/L in the 4 weeks before screening

Study Design and Treatment

- Patients on a stable ruxolitinib dose received add-on parsaclisib 10 mg or 20 mg once daily (QD) for 8 weeks and the same dose once weekly thereafter (daily/weekly group) or parsaclisib 5 mg or 20 mg QD for 8 weeks and 5 mg QD thereafter (all daily group) (**Figure 1**)

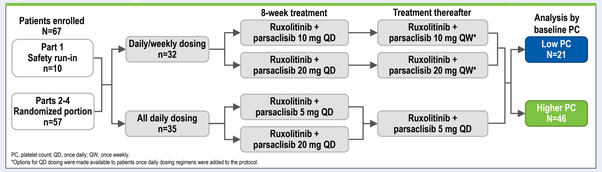
Subgroup Analysis

- Patients were grouped based on baseline PC: low PC versus higher PC

Study Endpoints

- Primary endpoint
  - Change in spleen volume from baseline to week 12 by imaging (magnetic resonance imaging or computed tomography scan)
- Secondary and exploratory endpoints
  - Change in spleen volume from baseline to week 24
  - Change in spleen length from baseline to each study visit
  - Change in TSS (MF Symptom Assessment Form [v3.0] total symptom score [MFSAF-TSS]) from baseline to weeks 12 and 24
  - Safety

Figure 1. Parsaclisib Dosing Schedules in Combination With Stable-Dose Ruxolitinib and Baseline PC Subgroups



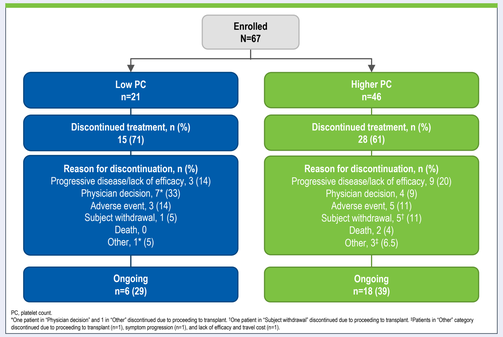
PC, platelet count; QD, once daily; QW, once weekly.
*Options for QD dosing were made available to patients once daily dosing regimens were added to the protocol.

Results

Patients

- As of data cutoff (August 27, 2020), 32 patients had received parsaclisib daily/weekly dosing and 35 patients had received parsaclisib all daily dosing
  - Median (range) duration of treatment was 30.4 (0.6-147.6) weeks
  - Median average daily dose was 5.0 mg/day for parsaclisib and 30.0 mg/day for ruxolitinib
- Based on baseline PC, 21 patients were categorized as low PC and 46 patients as higher PC
- Patient disposition and baseline characteristics based on baseline PC are shown in **Figure 2** and **Table 1**, respectively

Figure 2. Patient Disposition



PC, platelet count.
*One patient in "Physician decision" and 1 in "Other" discontinued due to proceeding to transplant. †One patient in "Subject withdrawal" discontinued due to proceeding to transplant. ‡Patients in "Other" category discontinued due to proceeding to transplant (n=1), symptom progression (n=1), and lack of efficacy and travel cost (n=1).

Table 1. Baseline Characteristics

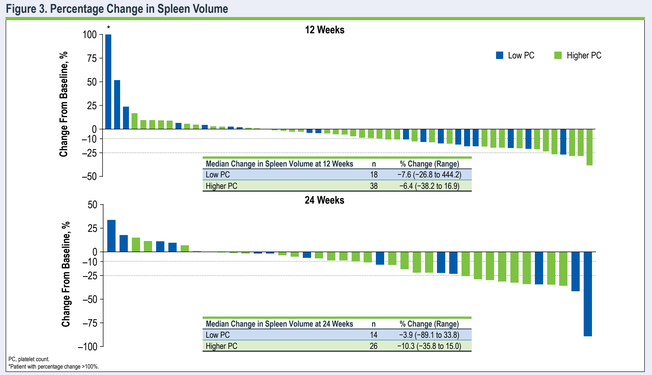
Characteristic	Low PC (50-<100×10^9/L) (n=21)	Higher PC (≥100×10^9/L) (n=46)	Total (N=67)
Age, median (range), y	68 (59-84)	68 (41-89)	68 (41-89)
Male, n (%)	12 (57)	20 (44)	32 (48)
Time since initial diagnosis, median (range), mo	52.6 (10.1-268.9)	30.5 (4.9-212.6)	32.2 (4.9-268.9)
Ruxolitinib use, median (range)			
Daily dose, mg	28.1 (2.1-46.3)	31.0 (13.8-50.0)	30.0 (2.1-50.0)
Duration, mo	34.7 (8.7-93.9)	14.9 (5.1-78.2)	18.0 (5.1-93.9)
Patients with palpable spleen, n (%)	20 (95)	46 (100)	66 (99)
Median length (range), cm	13.5 (5-30)	13 (5-30)	13 (5-30)
Spleen volume, median (range), cm^3	2119 (574-5324)	1934 (327-4793)	1986 (327-5324)
MFSAF-TSS, median (range)	21.4 (0.6-47.0)	10.0 (0-43.0)	13.6 (0-47.0)
Hemoglobin, median (range), g/L	107 (63-155)	95 (57-159)	99 (57-159)
MF subtype, n (%)			
PMF / PPV-MF / PET-MF	10 (48) / 9 (43) / 2 (9)	25 (54) / 14 (30) / 7 (15)	35 (52) / 23 (34) / 9 (13)

MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; PC, platelet count; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post–polycythemia vera; TSS, total symptom score.

Efficacy

- Percentage change in spleen volume from baseline is shown in **Figure 3**
- At week 12, slightly more patients with low PC achieved ≥10% spleen volume reduction compared with patients with higher PC, whereas, at week 24, responses were similar between the 2 groups (**Table 2**)
  - Of patients with ≥10% spleen volume reduction at week 24, 4 of 6 with low PC and 9 of 13 with higher PC were receiving all daily dose regimens
- Mean change in palpable spleen length from baseline to each visit up to week 24 for patients with baseline low PC and higher PC is shown in **Figure 4**
- Percentage change in MFSAF-TSS from baseline is shown in **Figure 5**
  - Median percentage change in MFSAF-TSS was similar between patients with low PC and higher PC

Figure 3. Percentage Change in Spleen Volume



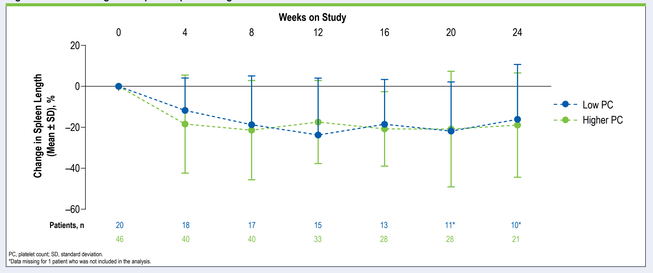
PC, platelet count.
*Patient with percentage change >100%.

Table 2. Spleen Volume Response Categories

Response Category, n (%)	Low PC	Higher PC
Week 12	**n=18**	**n=38**
≥10% reduction	9 (50)	15 (39)
≥25% reduction	1 (6)	4 (11)
≥35% reduction	0	1 (3)
Week 24	**n=17**	**n=35**
≥10% reduction	6 (35)	13 (37)
≥25% reduction	3 (18)	8 (23)
≥35% reduction	2 (12)	1 (3)

PC, platelet count.

Figure 4. Mean Change in Palpable Spleen Length

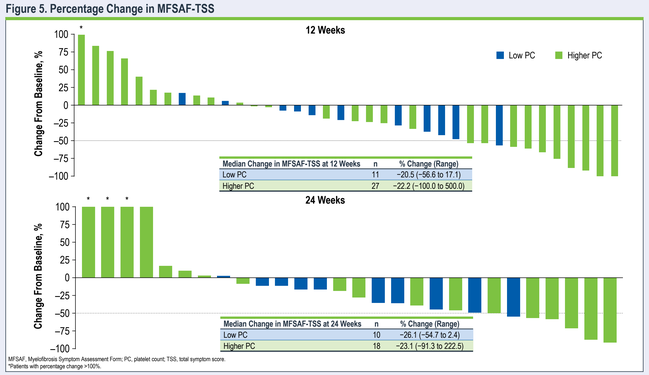


PC, platelet count; SD, standard deviation.
*Data missing for 1 patient who was not included in the analysis.

Disclosures

Yacoub: Speakers' bureau – *Incyte Corporation*. **Borate:** Membership on an entity's Board of Directors or advisory committees – *AbbVie/Genentech, Daiichi Sankyo, Genentech, Novartis, Pfizer, Takeda*. **Rampal:** Consultancy – *AbbVie, Blueprint Medicines, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, CTI BioPharma, Galecto, Inc., Incyte Corporation, Jazz Pharmaceuticals, Kartos Therapeutics, PharmaEssentia Corporation, Promedior, Stemline Therapeutics*; Research funding – *Constellation Pharmaceuticals, Incyte Corporation, Stemline Therapeutics*. **Ali:** Speakers' bureau – *Incyte Corporation*. **Wang:** Consultancy/advisory boards – *AbbVie, Astellas Pharma, Daiichi Sankyo, Dava Oncology (Arog), Genentech, Gilead Sciences, Jazz Pharmaceuticals, Kite Pharma, Kura Oncology, MacroGenics, Pfizer, PTC Therapeutics, Stemline Therapeutics*; Independent data review committees – *AbbVie, Genentech, Rafael Pharmaceuticals*; Speakers' bureau– *Pfizer, Stemline Therapeutics*. **Gerds:** Advisory board – *AbbVie, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, PharmaEssentia, Sierra Oncology*. **Hobbs:** Research support – *Bayer, Constellation Pharmaceuticals, Incyte Corporation, Merck*; Scientific advisory boards – *AbbVie, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, Novartis*. **O'Connell:** Research funding – *Astex Pharmaceuticals, Genentech*; Advisory board – *Astex Pharmaceuticals, Bristol Myers Squibb, Pfizer, Shionogi*. **Oh:** Consultancy/advisory boards – *AbbVie, Blueprint Medicines, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, CTI BioPharma, Disc Medicine, Geron, Incyte Corporation, Kartos Therapeutics, Novartis, PharmaEssentia, Sierra Oncology*. **Schiller:** Research funding and speaker fees – *Incyte Corporation*, Novartis. **Daver:** Advisory board/consultancy – *AbbVie, Agios, Astellas Pharma, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Dava Oncology (Arog), Genentech, Gilead Sciences, Kite Pharma, Novartis, Pfizer, Servier, Shattuck Labs, SOBI, STAR Therapeutics, Syndax Pharmaceuticals, Trillium Therapeutics, Trovagene*; Research funding – *AbbVie, Amgen, Astellas Pharma, Bristol Myers Squibb, Daiichi Sankyo, Fate Therapeutics, Genentech, Gilead Sciences, GlycoMimetics, Hanmi Pharmaceutical, ImmunoGen, Karyopharm Therapeutics, Newave Pharmaceuticals, Novimmune, Pfizer, Servier, Trovagene, Trillium Therapeutics*. **Assad, Erickson-Viitanen, Zhou:** Employment and stock ownership – *Incyte Corporation*. **Kremyanskaya, Winton, Goel:** Nothing to disclose.

Figure 5. Percentage Change in MFSAF-TSS



MFSAF, Myelofibrosis Symptom Assessment Form; PC, platelet count; TSS, total symptom score.
*Patients with percentage change >100%.

Safety

- Nonhematologic treatment-emergent adverse events were primarily grade 1/2; most common (≥20%) treatment-emergent adverse events are summarized in **Table 3**
  - Dyspnea (33%), falls (33%), peripheral edema (29%), and nasal congestion (24%) were most common for patients with low PC
  - Diarrhea (28%), nausea (24%), and abdominal pain (24%) were most common for patients with higher PC
- Interruption of parsaclisib due to thrombocytopenia was observed in 9 of 21 patients (43%) with low PC and 3 of 46 patients (7%) with higher PC
  - One patient with low PC had thrombocytopenia leading to ruxolitinib interruption
  - Dose interruptions were temporary; patients were able to restart treatment

Table 3. Most Common Nonhematologic TEAEs (Any-Grade TEAEs in ≥20% of Patients in Either Low PC or Higher PC)

	Low PC (n=21)		Higher PC (n=46)		Total (N=67)	
Event, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Diarrhea	4 (19)	0	13 (28)	1 (2)	17 (25)	1 (1.5)
Nausea	4 (19)	1 (5)	11 (24)	0	15 (22)	1 (1.5)
Fall	7 (33)	2 (10)	6 (13)	0	13 (19)	2 (3)
Abdominal pain	2 (10)	0	11 (24)	1 (2)	13 (19)	1 (1.5)
Cough	4 (19)	0	9 (20)	0	13 (19)	0
Fatigue	3 (14)	1 (5)	9 (20)	1 (2)	12 (18)	2 (3)
Dyspnea	7 (33)	2 (10)	3 (7)	0	10 (15)	2 (3)
Peripheral edema	6 (29)	1 (5)	1 (2)	0	7 (10)	1 (1.5)
Nasal congestion	5 (24)	0	2 (4)	0	7 (10)	0

PC, platelet count; TEAE, treatment-emergent adverse event.

Conclusions

- **Add-on parsaclisib demonstrated promising preliminary efficacy in patients with MF experiencing suboptimal response to ruxolitinib monotherapy[7]**
- **In this subgroup analysis by baseline PC, responses for spleen volume and MFSAF-TSS reduction were similar in both groups, indicating that patients with low PC can also benefit from this treatment combination**
- **The adverse event profile of the combination in patients with low PC and higher PC indicates that patients can tolerate the combination irrespective of baseline PC**
- **Phase 3 studies of parsaclisib as add-on to ruxolitinib (NCT04551053) and parsaclisib plus ruxolitinib in the frontline setting (NCT04551066) are underway to further assess the combination of JAK and PI3K inhibitors; patients with low platelets are included in both studies**

Acknowledgments

The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study. This study was sponsored by Incyte Corporation (Wilmington, DE). Medical writing assistance was provided by Rachel Shparberg, PhD, of Envision Pharma Group (Philadelphia, PA), and funded by Incyte Corporation.

References

1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807.
2. Harrison C, et al. *N Engl J Med*. 2012;366:787-798.
3. Cervantes F, et al. *Blood*. 2013;122:4047-4053.
4. Grimwade L, et al. *Br J Haematol*. 2009;147:495-506.
5. Oku S, et al. *Br J Haematol*. 2010;150:334-344.
6. Shin N, et al. *J Pharmacol Exp Ther*. 2020;374:211-222.
7. Yacoub A, et al. *HemaSphere*. 2021;5(Suppl 2):e566. Abstract EP1075.

Scan code to download additional information on the ongoing phase 3 studies

Scan code to download a copy of the poster