EP1075

Add-on Parsaclisib (a PI3K-delta Inhibitor) in Patients With Myelofibrosis and Suboptimal Response to Ruxolitinib: Interim Analysis From a Phase 2 Study

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Background

- Ruxolitinib, a potent and selective Janus kinase (JAK)1/2 inhibitor, improves symptoms, reduces spleen size, and prolongs survival in patients with intermediate- or high-risk myelofibrosis (MF)[1–3]
  - However, some patients may experience suboptimal or declining responses despite continued JAK inhibition
- Activation of the phosphatidylinositol 3-kinase (PI3K) pathway has been reported in patients with MF,[4,5] suggesting a potential benefit of PI3K inhibition
- Parsaclisib is a potent, highly selective, next-generation PI3Kδ inhibitor that exhibits favorable pharmacokinetics for once-daily dosing

Objective

- This phase 2 study (NCT02718300) evaluated optimal dosing, efficacy, and safety of add-on parsaclisib in patients with MF and suboptimal response to stable ruxolitinib treatment

Methods

Key Inclusion Criteria

- Patients ≥18 years of age with primary or secondary (post–polycythemia vera or post–essential thrombocythemia) MF
- Eastern Cooperative Oncology Group performance status ≤2
- Suboptimal response to ruxolitinib monotherapy
  - Received 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)
- Platelet count ≥50 × 10^9/L in the 4 weeks before screening

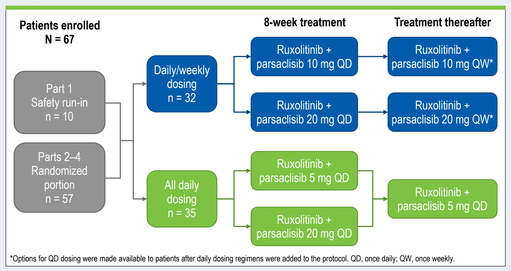
Study Design and Treatment

- 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 (QW) 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)**

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 total symptom score (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



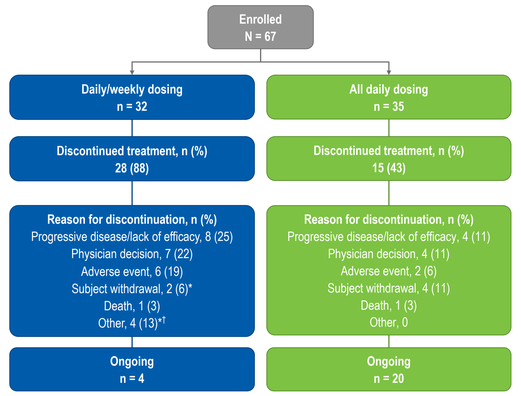
*Options for QD dosing were made available to patients after daily dosing regimens were added to the protocol. QD, once daily; QW, once weekly.

Results

Patients

- As of data cutoff (August 27, 2020), 32 patients had received parsaclisib daily/weekly and 35 patients had received parsaclisib all daily
- Patient disposition is shown in **Figure 2**
- Median (range) duration of treatment was 30.4 (0.6–147.6) weeks
  - Daily/weekly dosing: 48.9 (7.3–147.6) weeks
  - All daily dosing: 24.40 (0.6–91.6) weeks
- Median average daily dose was 5.0 mg/day for parsaclisib and 30.0 mg/day for ruxolitinib
- Baseline characteristics are shown in **Table 1**

Figure 2. Patient Disposition



*One patient in "Subject withdrawal" and 2 patients in "Other" were noted as proceeding to transplant at the end of their treatment. †Patients in the "Other" category discontinued due to proceeding to transplant (n = 2), symptom progression (n = 1), and lack of efficacy (n = 1).

Table 1. Baseline Characteristics

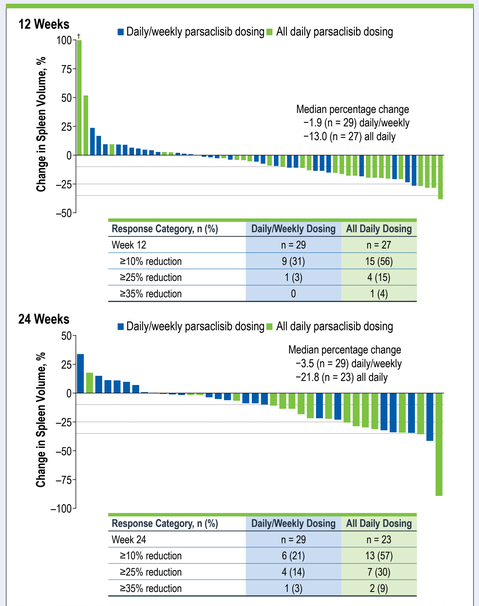
Characteristic	Daily/Weekly Dosing (n = 32)	All Daily Dosing (n = 35)	Total (N = 67)
Age, median (range), years	67 (41–89)	69 (54–84)	68 (41–89)
Male, n (%)	15 (47)	17 (49)	32 (48)
Time since initial diagnosis, median (range), months	30.5 (6.7–268.9)	37.3 (4.9–251.5)	32.2 (4.9–268.9)
Ruxolitinib use, median (range)			
Daily dose, mg	27.8 (2.1–50.0)	30.0 (8.7–44.8)	30.0 (2.1–50.0)
Duration, months	18.3 (6.1–94.0)	16.7 (5.1–78.2)	18.0 (5.1–94.0)
Patients with palpable spleen, n (%)	31 (97)	35 (100)	66 (99)
Median length (range), cm	14 (8–30)	11 (5–30)	13 (5–30)
Spleen volume, median (range), cm^3	2414.5 (327.1–5323.7)*	1885.3 (434.2–3904.1)*	1986.3 (327.1–5323.7)
MFSAF-TSS, median (range)	10.8 (0–47.0)†	16.3 (0.6–38.4)†	13.6 (0–47.0)
Hemoglobin, median (range), g/L	102.0 (70.0–159.0)	96.0 (57.0–155.0)	99.0 (57.0–159.0)
MF subtype, n (%)			
PMF / PPV-MF / PET-MF	17 (53) / 12 (38) / 3 (9)	18 (51) / 11 (31) / 6 (17)	35 (52) / 23 (34) / 9 (13)

*n = 29 patients each for daily/weekly and all daily dosing. †n = 28 patients for daily/weekly dosing; n = 26 patients for all daily dosing. MF, myelofibrosis; MFSAF-TSS, Myelofibrosis Symptom Assessment Form-Total Symptom Score; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post–polycythemia vera.

Efficacy

- Median percentage change in spleen volume from baseline **(Figure 3)**:
  - Week 12: daily/weekly, −1.9% (n = 29); all daily, −13.0% (n = 27)
  - Week 24: daily/weekly, −3.5% (n = 23); all daily, −21.8% (n = 17)
- Compared with the daily/weekly group, a numerically greater percentage of patients in the all daily group achieved ≥10%, ≥25%, and ≥35% spleen volume reduction (SVR) at weeks 12 and 24 **(Figure 3)**
- Mean change in palpable spleen length from baseline to each visit up to week 24 for patients receiving parsaclisib daily/weekly and patients receiving parsaclisib 5 mg all daily is shown in **Figure 4**
- Median percentage change in MFSAF-TSS at week 12 was −14.0% (n = 21) in the daily/weekly group and −37.4% (n = 17) in the all daily group; the percentage of patients achieving ≥50% reduction in MFSAF-TSS was numerically greater in the all daily group than in the daily/weekly group **(Figure 5)**

Figure 3. Percentage Change in Spleen Volume and Response Categories at 12 and 24 Weeks*

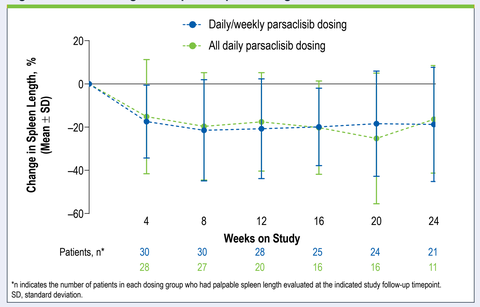


Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	n = 29	n = 27
≥10% reduction	9 (31)	15 (56)
≥25% reduction	1 (3)	4 (15)
≥35% reduction	0	1 (4)

Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 24	n = 29	n = 23
≥10% reduction	6 (21)	13 (57)
≥25% reduction	4 (14)	7 (30)
≥35% reduction	1 (3)	2 (9)

*Evaluable patients were those receiving ≥1 dose of study drug, had spleen volume baseline assessment with a non-zero value, and met ≥1 of the following criteria: 1) had an assessment at the study follow-up week; 2) had discontinued treatment before the study follow-up assessment; or 3) had been on treatment for ≥12 or 24 weeks but no 12- or 24-week assessment, respectively. †Patient had best percentage change from baseline to >100%.

Figure 4. Mean Change in Palpable Spleen Length

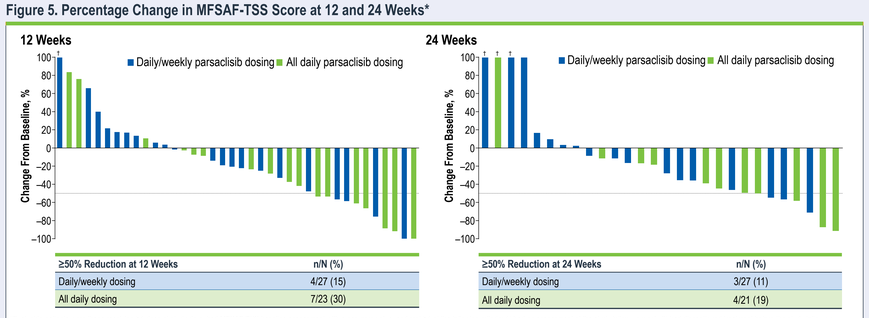


*n indicates the number of patients in each dosing group who had palpable spleen length evaluated at the indicated study follow-up timepoint. SD, standard deviation.

Safety

- Nonhematologic treatment-emergent adverse events (TEAEs) were primarily grade 1/2 **(Table 2)**
- Serious TEAEs occurring in ≥2 patients were urinary tract infection and pyrexia (n = 3 each), and pneumonia and fall (n = 2 each)
- Fatal TEAEs occurred in 6 patients receiving daily/weekly parsaclisib dosing and 1 patient receiving all daily parsaclisib dosing (none were deemed related to treatment)
- In the daily/weekly and all daily groups, 6 of 32 (19%) and 9 of 35 (26%) patients had new-onset grade 3 thrombocytopenia, and 6 of 32 (19%) and 1 of 35 (3%) patients had new-onset grade 4 thrombocytopenia
- Hemoglobin levels remained steady during the study in both groups
- Among transfusion-dependent patients at baseline, the largest reduction (mean [standard deviation]) in number of red blood cell units transfused in any 8-week interval was –1.6 (1.7) for daily/weekly parsaclisib dosing and –1.2 (1.7) for all daily parsaclisib dosing
- No colitis or grade ≥2 diarrhea or rash was observed in patients receiving all daily parsaclisib dosing **(Table 3)**

Figure 5. Percentage Change in MFSAF-TSS Score at 12 and 24 Weeks*



≥50% Reduction at 12 Weeks	n/N (%)
Daily/weekly dosing	4/27 (15)
All daily dosing	7/23 (30)

≥50% Reduction at 24 Weeks	n/N (%)
Daily/weekly dosing	3/27 (11)
All daily dosing	4/21 (19)

*Evaluable patients were those receiving ≥1 dose of study drug, had MFSAF-TSS baseline assessment with a non-zero value, and met ≥1 of the following criteria: 1) had an assessment at the study follow-up week; 2) had discontinued treatment before the study follow-up assessment; or 3) had been on treatment for at least 12 or 24 weeks but no 12- or 24-week assessment, respectively. †Patient had best percentage change from baseline to >100%. Noncompleters assessed as nonresponders. MFSAF-TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score.

Table 2. Nonhematologic TEAEs (≥15% of Patients, Any Grade)

	Daily/Weekly Dosing (n = 32)		All Daily Dosing (n = 35)		Total (N = 67)	
Event, n (%)	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhea	11 (34)	1 (3)	6 (17)	0	17 (25)	1 (2)
Nausea	10 (31)	1 (3)	5 (14)	0	15 (22)	1 (2)
Fall	9 (28)	2 (6)	4 (11)	0	13 (19)	2 (3)
Abdominal pain	8 (25)	1 (3)	5 (14)	0	13 (19)	1 (2)
Cough	7 (22)	0	6 (17)	0	13 (19)	0
Fatigue	9 (28)	1 (3)	3 (9)	1 (3)	12 (18)	2 (3)
Pruritus	6 (19)	1 (3)	4 (11)	0	10 (15)	1 (2)
Dizziness	4 (13)	0	6 (17)	0	10 (15)	0
Dyspnea	5 (16)	0	5 (14)	2 (6)	10 (15)	0

TEAE, treatment-emergent adverse event.

Table 3. TEAEs of Special Interest*

Event, n (%)	Daily/Weekly Dosing (n = 32)	All Daily Dosing (n = 35)	Total (N = 67)
Grade ≥2 diarrhea	4 (12)	0	4 (12)
Grade ≥3 ALT	2 (6)	0	2 (6)
Grade ≥3 AST	2 (6)	0	2 (6)
Grade ≥2 rash	1 (3)	0	1 (3)
Herpes simplex	0	2 (6)	2 (6)
VZV infection	1 (3)	0	1 (3)

*No patients presented with colitis, pneumonitis, dermatitis exfoliative, intestinal perforation, cytomegalovirus infection, or PJP (patients enrolled in the trial received PJP prophylaxis). ALT, alanine aminotransferase; AST, aspartate aminotransferase; PJP, *pneumocystis jirovecii* pneumonia; TEAE, treatment-emergent adverse event; VZV, varicella-zoster virus.

- In the daily/weekly and all daily groups, 18 of 32 and 18 of 35 patients interrupted parsaclisib, and 6 of 32 and 8 of 35 patients interrupted ruxolitinib due to TEAEs, respectively
- TEAEs led to parsaclisib discontinuation in 7 of 32 patients in the daily/weekly group and in 3 of 35 patients in the all daily group, and ruxolitinib discontinuation in 2 of 32 patients in the daily/weekly group and 1 of 35 patients in the all daily group

Conclusions

- **In patients with MF with suboptimal response on stable dose of ruxolitinib, add-on parsaclisib resulted in additional SVR and improvement in symptom burden**
  - **The benefit was observed early and was durable**
- **The addition of parsaclisib to ruxolitinib was generally well tolerated, with limited grade 3/4 adverse events and TEAE-related discontinuations**
  - **TEAEs common to PI3Kδ inhibitors (eg, hepatic, rash, colitis) were infrequent with the addition of parsaclisib**
- **The all daily parsaclisib dosing schedule appeared to be more efficacious and to have a more favorable adverse event profile compared with daily followed by weekly dosing**
- **Results from the current study informed the development of phase 3 studies of parsaclisib as add-on to ruxolitinib (NCT04551053) and parsaclisib plus ruxolitinib in the frontline setting (NCT04551066), which are currently enrolling patients**
  - **Further details of these studies are in abstracts published for this meeting: PB175 and PB176**

Disclosures

Yacoub: Speaker's bureau – *Incyte Corporation*. **Borate:** Membership on an entity's Board of Directors or advisory committees – *Daiichi Sankyo, Genentech, Novartis, Pfizer, Takeda*; Research funding – *Jazz Pharmaceuticals, Novartis, Pfizer, Takeda*; Investigator – *AbbVie-funded clinical trials*. **Rampal:** Consultancy – *AbbVie, Blueprint Medicines, Celgene, CTI Biopharma, Galecto, Incyte Corporation, Jazz Pharmaceuticals, PharmaEssentia, Promedia, Stemline Therapeutics*; Research funding – *Constellation Pharmaceuticals, Incyte Corporation, Stemline Therapeutics*. **Ali:** Consultancy and speakers' bureau – *Incyte Corporation*. **Wang:** Consultancy – *AbbVie, Astellas, Bristol Myers Squibb (Celgene), Genentech, Jazz Pharmaceuticals, MacroGenics, PTC Therapeutics*; Speakers' bureau – *Pfizer, Stemline Therapeutics*. **Gerds:** Advisory board – *AbbVie, Bristol Myers Squibb, Constellation Pharmaceuticals, Novartis, Sierra Oncology*. **Hobbs:** Research support – *Bayer, Constellation Pharmaceuticals, Incyte Corporation, Merck*; Scientific advisory board – *AbbVie, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, Novartis*. **Kremyanskaya:** Research funding – *Astex Pharmaceuticals, Bristol Myers Squibb, Constellation Pharmaceuticals, Incyte Corporation, Protagonist Therapeutics*; Consultancy – *Protagonist Therapeutics*. **Winton:** No disclosures. **O'Connell:** No disclosures. **Goel:** No disclosures. **Oh:** Consultancy/advisory boards – *Blueprint Medicines, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, CTI BioPharma, Disc Medicine, Gilead Sciences, Incyte Corporation, Kartos Therapeutics, Novartis, PharmaEssentia*. **Schiller:** Research funding – *Incyte Corporation*. **Assad, Erickson-Viitanen, Chen, Zhou:** Employment and stock ownership – *Incyte Corporation*. **Daver:** Research funding – *AbbVie, Astellas, Amgen, Bristol Myers Squibb, Daiichi Sankyo, Fate Therapeutics, Genentech, Gilead Sciences, GlycoMimetics, Hanmi Pharmaceutical, ImmunoGen, Novimmune, Pfizer, Servier, Trovagene*; Consulting/advisory role – *AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Genentech, Gilead Sciences, ImmunoGen, Novartis, Pfizer, Servier, Syndax, Trillium Therapeutics*.

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