CT162

Addition of Parsaclisib (INCB050465), a PI3Kδ Inhibitor, in Patients With Suboptimal Response to Ruxolitinib: a Phase 2 Study in Patients With Myelofibrosis

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Background

- Ruxolitinib, a 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 and efficacy of add-on parsaclisib in patients with MF and suboptimal ruxolitinib response

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; symptoms 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

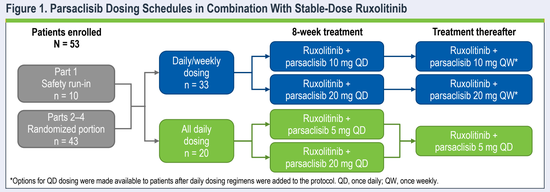
Study Design and Treatment

- Patients on a stable ruxolitinib dose were randomized to receive 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



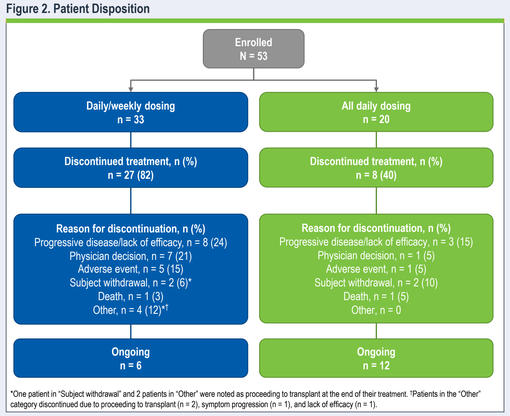
*Options for QD dosing were made available to patients after daily dosing regimens were added to the protocol. QD, once daily; QW, once weekly.

Results

Patients

- At data cutoff (January 20, 2020), 33 patients had received parsaclisib daily/weekly and 20 patients had received parsaclisib all daily
- Patient disposition is shown in **Figure 2**
- Median (range) treatment duration was 28.0 (4.6–123.9) weeks
  - Daily/weekly dosing: 48.4 (7.3–123.8) weeks
  - All daily dosing: 22.4 (4.6–60.1) weeks
- Median average daily dose was 4.9 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

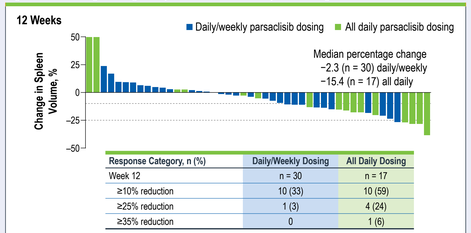
Characteristic	Daily/Weekly Dosing (n = 33)	All Daily Dosing (n = 20)	Total (N = 53)
Age, median (range), years	68 (41–89)	66 (54–84)	66 (41–89)
Male, n (%)	16 (48)	9 (45)	25 (47)
Time since initial diagnosis, median (range), months	31.2 (6.7–268.9)	30.4 (4.9–98.5)	31.2 (4.9–268.9)
Duration of prior ruxolitinib use, median (range), months	18 (6–94)	19 (4.8–56)*	18 (4.8–94)
Patients with palpable spleen, n (%) Median length (range), cm	32 (97) 14 (8–30)	20 (100) 11 (5–21)	52 (98) 13.5 (5–30)
Spleen volume, median (range), cm^3	2333 (327–5324)†	1890 (434–3741)†	1995 (327–5324)
TSS score by MPN-SAF, median (range)	24 (0–69)‡	27 (3–65)‡	25.5 (0–69)
TSS score by MFSAF, median (range)	10.8 (0–47) §	18.7 (0.6–37.4) §	12.9 (0–47)
Hemoglobin, median (range), g/L	101 (70–159)	104 (63–155)	101 (63–159)
MF subtype, n (%) PMF / PPV-MF / PET-MF	17 (52) / 12 (36) / 4 (12)	10 (50) / 8 (40) / 2 (10)	27 (51) / 20 (38) / 6 (11)

*One patient in the all daily dosing group had received <6 months prior treatment with ruxolitinib. †n = 30 patients for daily/weekly dosing; n = 17 patients for all daily dosing. ‡n = 31 patients for daily/weekly dosing; n = 19 patients for all daily dosing. §n = 28 patients for daily/weekly dosing; n = 17 patients for all daily dosing.
MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post–polycythemia vera; TSS, Total Symptom Score.

Efficacy

- Median percentage change in spleen volume from baseline (**Figure 3**):
  - Week 12: daily/weekly, −2.3% (n = 30); all daily, −15.4% (n = 17)
  - Week 24: daily/weekly, −2.5% (n = 24); all daily, −25.4% (n = 9)
- 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 −39.6% (n = 12) 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



Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	n = 30	n = 17
≥10% reduction	10 (33)	10 (59)
≥25% reduction	1 (3)	4 (24)
≥35% reduction	0	1 (6)

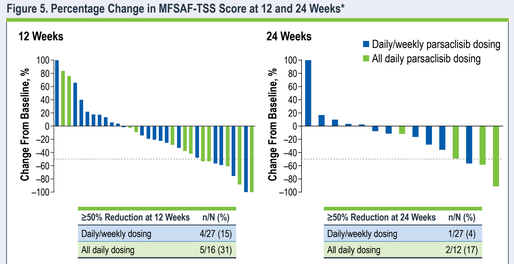
Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 24	n = 30	n = 14
≥10% reduction	6 (20)	7 (50)
≥25% reduction	4 (13)	5 (36)
≥35% reduction	1 (3)	1 (7)

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.

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.

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	5/16 (31)

≥50% Reduction at 24 Weeks	n/N (%)
Daily/weekly dosing	1/27 (4)
All daily dosing	2/12 (17)

*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. Noncompleters assessed as nonresponders. MFSAF-TSS, Myelofibrosis Symptom Assessment Form Total Symptom Score.

Safety

- Nonhematologic treatment-emergent adverse events (TEAEs) were primarily grade 1/2 **(Table 2)**
- Serious TEAEs occurring in ≥2 patients were urinary tract infection (n = 3), pneumonia, pyrexia, 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 was deemed related to treatment)
- In the daily/weekly and all daily groups, 6 of 33 (18%) and 6 of 20 (30%) patients had new-onset grade 3 thrombocytopenia, and 7 of 33 (21%) and 0 of 20 patients had new-onset grade 4 thrombocytopenia
- Hemoglobin levels remained steady during the study in both groups; the study had no exclusion for anemia
- No colitis or grade ≥2 diarrhea or rash were observed in patients receiving all daily parsaclisib dosing **(Table 3)**

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

	Daily/Weekly Dosing (n = 33)		All Daily Dosing (n = 20)	
Event, n (%)	All Grades	Grade ≥3	All Grades	Grade ≥3
Diarrhea	11 (33)	1 (3)	3 (15)	0
Nausea	10 (30)	1 (3)	4 (20)	0
Fatigue	10 (30)	1 (3)	2 (10)	1 (5)
Fall	9 (27)	2 (6)	1 (5)	0
Abdominal pain	8 (24)	0	3 (15)	0
Contusion	8 (24)	0	0	0
Cough	7 (21)	0	5 (25)	0
Back pain	6 (18)	1 (3)	1 (5)	0
Pruritus	6 (18)	0	3 (15)	0
Constipation	5 (15)	0	3 (15)	0
Dyspnea	5 (15)	0	3 (15)	1 (5)

TEAE, treatment-emergent adverse event.

Table 3. TEAEs of Special Interest

Event, n (%)	Daily/Weekly Dosing (n = 33)	All Daily Dosing (n = 20)
Grade ≥2 diarrhea	4 (12)	0
Elevated LFTs	2 (6)	0
Grade ≥2 rash	1 (3)	0
VZV infection	1 (3)	1 (5)
Colitis	0	0
CMV reactivation	0	0
PJP*	0	0
Pneumonitis	0	0

*Patients enrolled in the trial received PJP prophylaxis. CMV, cytomegalovirus; LFT, liver function test; PJP, *pneumocystis jiroveci* pneumonia; TEAE, treatment-emergent adverse event; VZV, varicella-zoster virus.

- In the daily/weekly and all daily groups, 18 of 33 and 10 of 20 patients interrupted parsaclisib, and 4 of 33 and 4 of 20 patients interrupted ruxolitinib due to TEAEs, respectively
- TEAEs led to treatment discontinuation in 6 of 33 patients in the daily/weekly group (thrombocytopenia [n = 2; 6%], fatigue, blast crisis, disseminated tuberculosis, and pathological fracture [each n = 1; 3% each]), and in 1 of 20 patients in the all daily group (leukocytosis [n = 1; 5%])

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**
  - **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**

Disclosures

Yacoub: Speaker's bureau – *Incyte Corporation*. **Wang:** Consultancy – *AbbVie, Astellas, Bristol Myers Squibb (Celgene), Genentech, Jazz Pharmaceuticals, MacroGenics, PTC Therapeutics*; Speakers' bureau – *Pfizer, Stemline Therapeutics*. **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*. **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*. **Kremyanskaya:** Research funding – *Astex Pharmaceuticals, Bristol Myers Squibb, Constellation Pharmaceuticals, Incyte Corporation, Protagonist Therapeutics*; Consultancy – *Protagonist Therapeutics*. **Ali:** Consultancy and speakers' bureau – *Incyte Corporation*. **Hobbs:** Research support – *Bayer, Constellation Pharmaceuticals, Incyte Corporation, Merck*; Scientific advisory board – *AbbVie, Celgene/Bristol Myers Squibb, Constellation Pharmaceuticals, Novartis*. **O'Connell:** No disclosures. **Assad, Erickson-Viitanen, Zhou, Burn:** Employment and stock ownership – *Incyte Corporation*. **Daver:** Research funding: *AbbVie, Astellas, Amgen, Bristol Myers Squibb, Daiichi Sankyo, Fate Therapeutics, Genentech, Gilead, GlycoMimetics, Hanmi Pharmaceutical, ImmunoGen, Novimmune, Pfizer, Servier, Trovagene*; Consulting/advisory role – *AbbVie, Agios, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Genentech, Gilead, ImmunoGen, Novartis, Pfizer, Servier, Syndax, Trillium Therapeutics*.

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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. Grinwade L, et al. *Br J Haematol*. 2009;147:495–506.
5. Oku S, et al. *Br J Haematol*. 2010;150:334–344.

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