EUROPEAN HEMATOLOGY ASSOCIATION
EHA25 VIRTUAL

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

Abdulraheem Yacoub,[1] Eunice S. Wang,[2] Raajit K. Rampal,[3] Uma Borate,[4] Marina Kremyanskaya,[5] Haris Ali,[6] Gabriela Hobbs,[7] Casey O'Connell,[8] Albert Assad,[9] Sue Erickson-Viitanen,[9] Feng Zhou,[9] Naval Daver[10]

[1]University of Kansas Medical Center, Kansas City, KS, USA; [2]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]Oregon Health & Science University, Portland, OR, USA; [5]Mount Sinai Hospital, New York, NY, USA; [6]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [7]Massachusets General Hospital, Boston, MA, USA; [8]University of Southern California, Los Angeles, CA, USA; [9]Incyte Corporation, Wilmington, DE, USA; [10]University of Texas MD Anderson Cancer Center, Houston, TX, USA

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SECTION: Novel therapies and pitfalls in MPN

Disclosures

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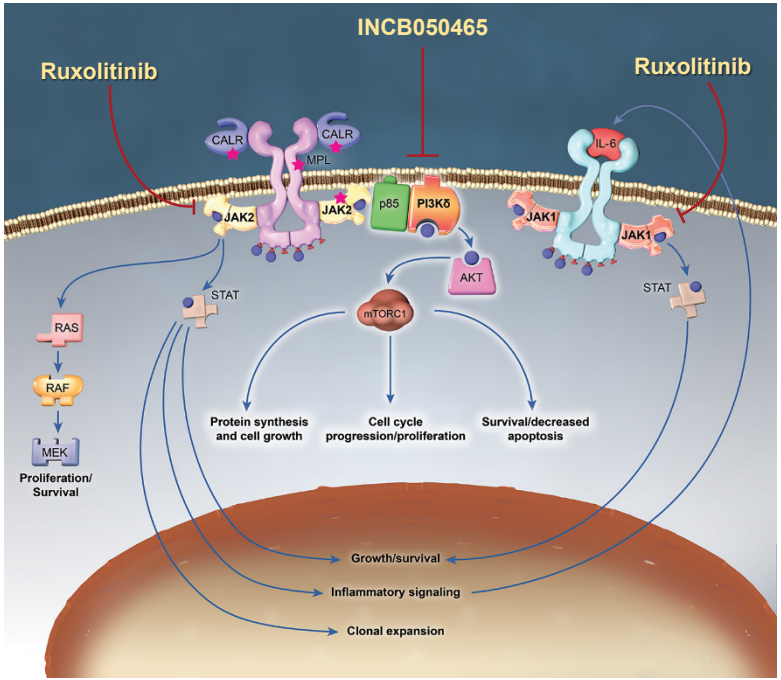
JAK1/2 and PI3K signaling in MF



- Ruxolitinib, a JAK1/2 inhibitor, improves symptoms, reduces spleen size, and prolongs survival in patients with intermediate- or high-risk MF[1–3]
  - However, some patients may experience suboptimal or declining responses despite continued JAK inhibition
- Activation of the 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 PK for once-daily dosing

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.
JAK, Janus kinase; MF, myelofibrosis; PI3K, phosphatidylinositol 3-kinase; PK, pharmacokinetics.

Phase 2 Study of the JAK 1/2 Inhibitor, Ruxolitinib, and Add-on PI3Kδ Inhibitor, Parsaclisib (NCT02718300)

- Enrolled patients with primary or secondary MF who have suboptimal response with ruxolitinib monotherapy
- **Definition of suboptimal response to ruxolitinib:**
  - Treated with ruxolitinib 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*

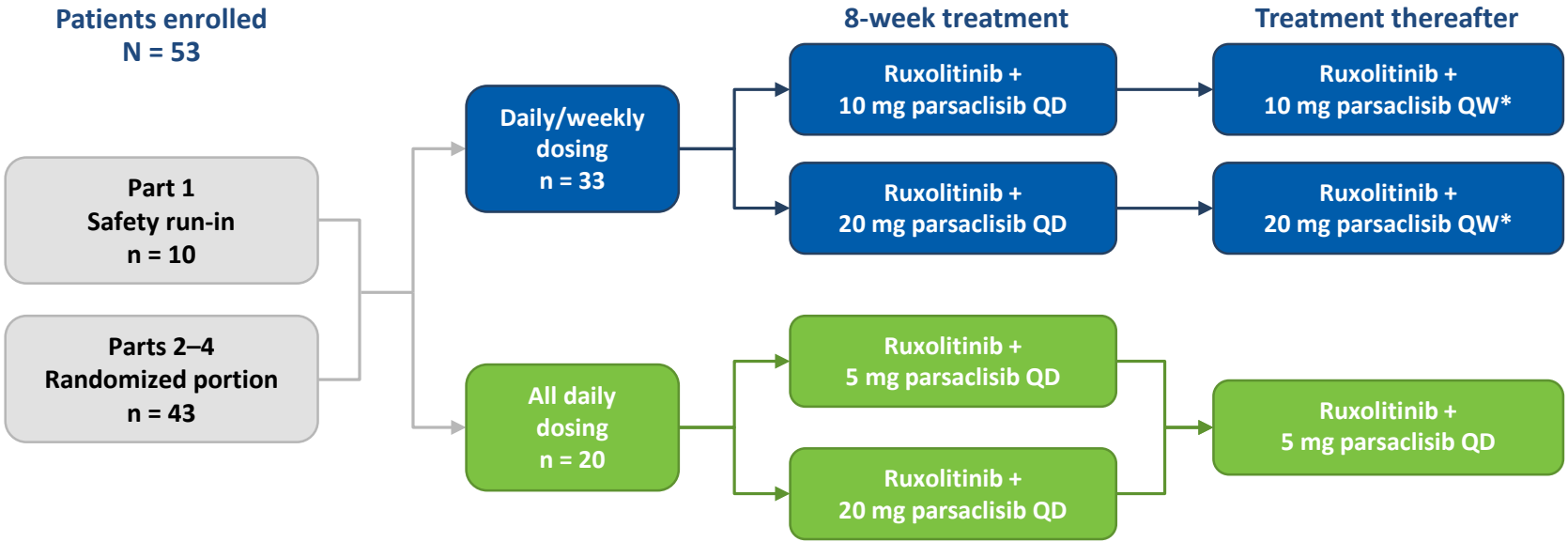
*Screening Symptom Form: 10-point scale for each of the 7 symptoms. Symptoms include: night sweats, pruritus, abdominal discomfort, pain under left ribs, early satiety, bone/muscle pain, and inactivity.
MF, myelofibrosis.

Patients and Study Endpoints

- **Key inclusion criteria**
  - Age ≥18 years
  - Diagnosis of myelofibrosis (PMF, PPV-MF, or PET-MF)
  - Prior treatment with ruxolitinib for ≥6 months, with a stable dose for ≥8 weeks prior to enrollment
    - Acceptable doses of prior ruxolitinib between 5 and 25 mg BID
  - Platelet count ≥50 × 10^9/L in the 4 weeks before screening
- **Primary endpoint**
  - Change in spleen volume from baseline to week 12 by imaging (MRI or CT scan)
- **Secondary endpoints**
  - Change in spleen length
  - Symptoms (MF Symptoms Assessment Form [v3.0] Total Symptom Score [MFSAF-TSS])
  - Safety
- **Data cutoff date:** January 20, 2020

BID, twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis.

Study Design: Parsaclisib Dosing Schedules in Combination With Stable-Dose Ruxolitinib



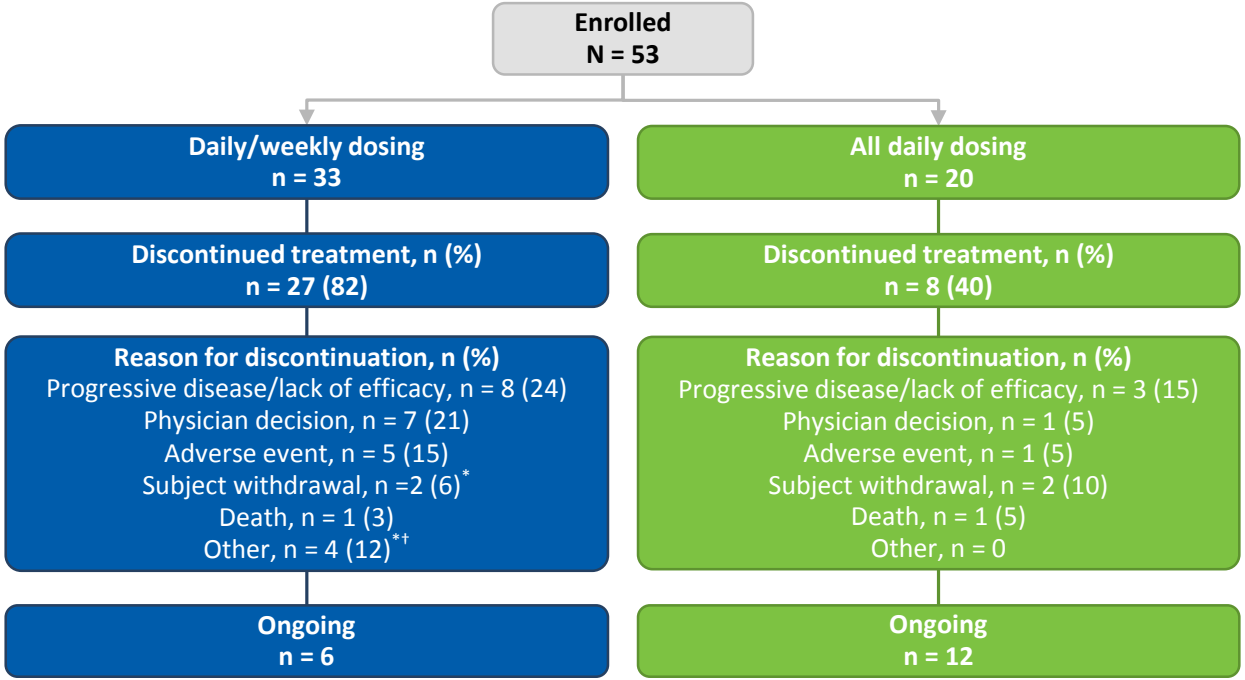
*Options for QD dosing were made available to patients once daily dosing regimens were added to the protocol.
QD, once daily; QW, once weekly.

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)
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)

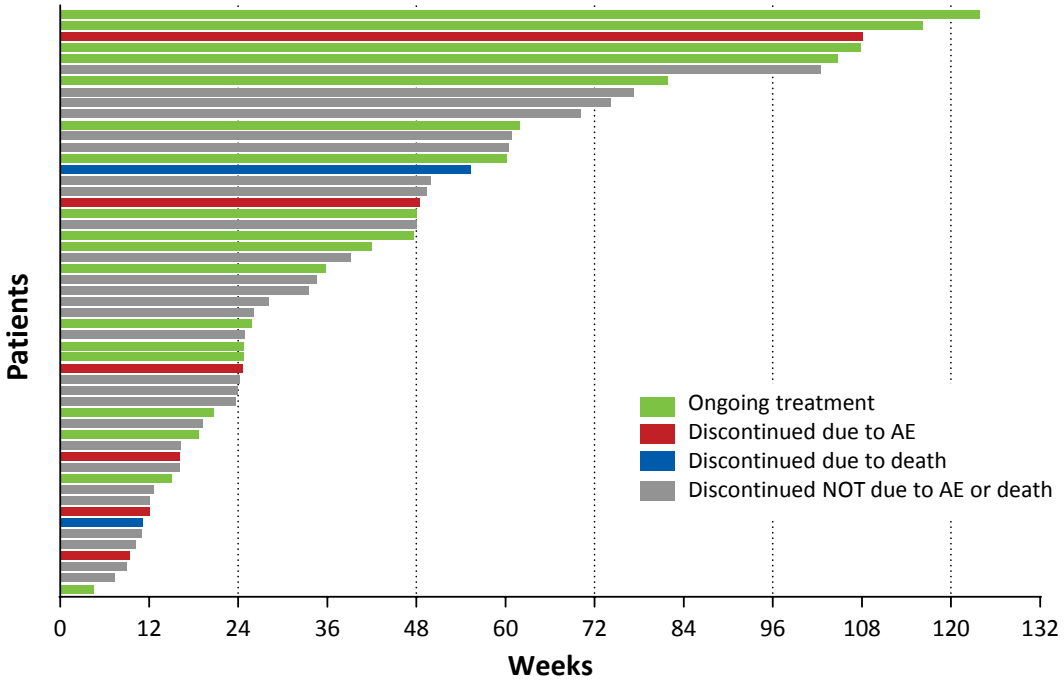
*One patient in the all daily dosing group had received less that 6 months prior treatment with ruxolitinib.
†n = 30 patients for daily/weekly dosing; n = 17 patients for all daily dosing.
‡n = 31 patients for daily/weekly dosing; n = 19 patients for all daily dosing.
MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, total symptom score.

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).

Time on Study Treatment

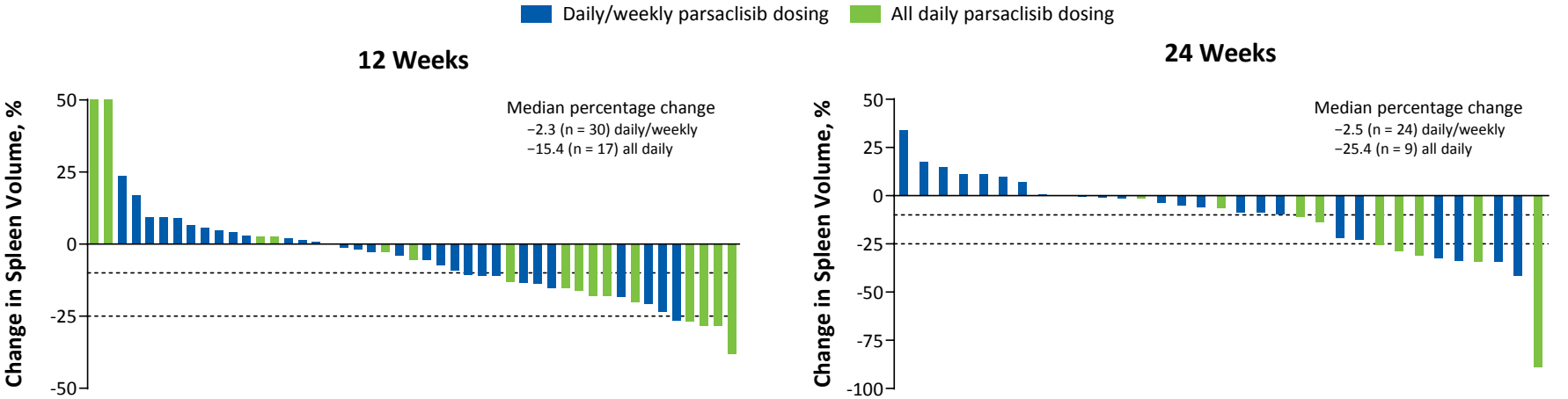


- Median (range) treatment duration: 28 (4.6–123.9) weeks
  - Daily/weekly dosing: 48.4 (7.3–123.8) weeks
  - All daily dosing: 22.4 (4.6–60.1) weeks
- 47/53 patients (89%) had baseline and week 12 spleen volume data

AE, adverse event.

Results

Percentage Change in Spleen Volume and Response Categories

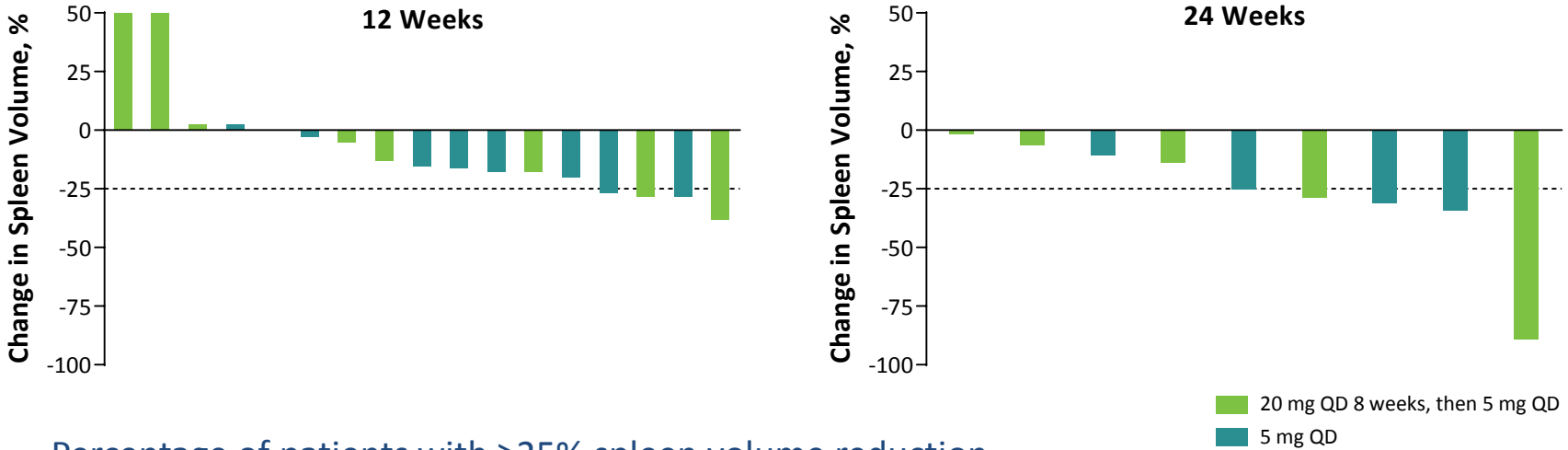


Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	**n = 30**	**n = 17**
≥10% reduction	10 (33)	10 (59)
≥25% reduction	1 (3)	4 (24)
≥35% reduction	0	1 (6)

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 at least 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.

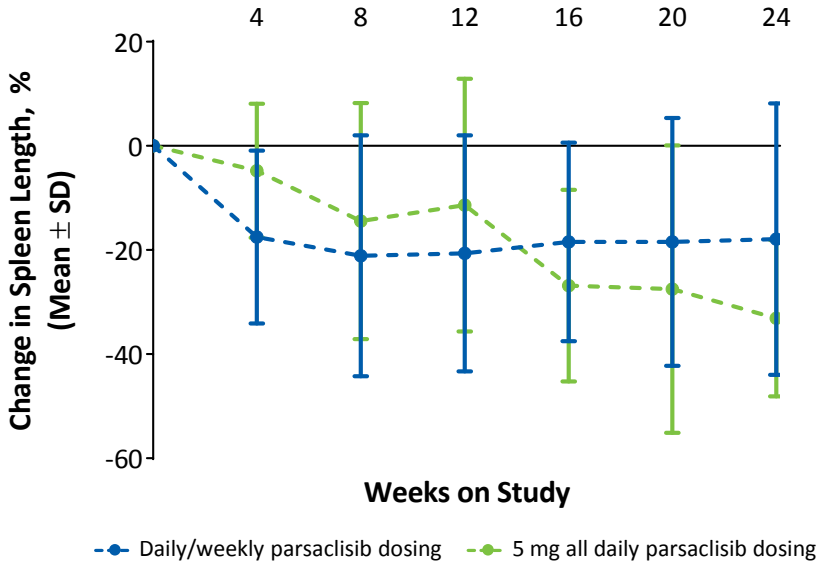
Spleen Volume Response and Responder Analysis Among Patients Receiving All Daily Dosing*



- Percentage of patients with ≥25% spleen volume reduction
  - Week 12: 23% (4/17)
  - Week 24: 36% (5/14)

*Evaluable patients were those receiving ≥1 dose of study drug, had spleen volume baseline assessment with a non-zero value, and met at least 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 were assessed as nonresponders.

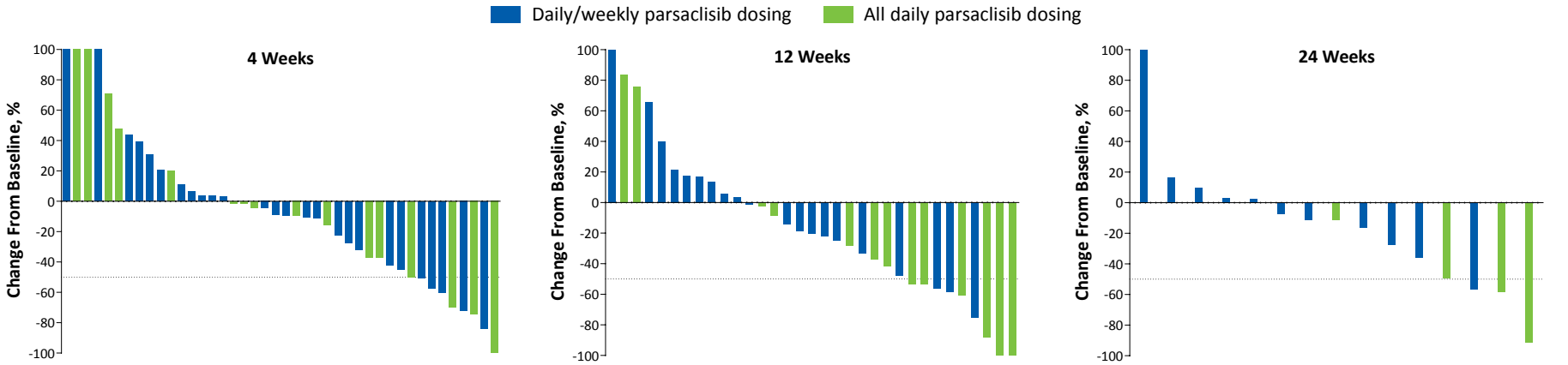
Mean Change in Palpable Spleen Length: Daily/Weekly vs 5 mg All Daily Dosing



Patients, n*	Daily/Weekly Dosing	5 mg All Daily Dosing
4 weeks	31	9
8 weeks	31	8
12 weeks	29	6
16 weeks	26	5
20 weeks	25	5
24 weeks	18	3

*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.

Percentage Change in MFSAF-TSS Score Over Time*



≥50% Reduction at 4 Weeks	n/N (%)
Daily/weekly dosing	5/27 (19)
All daily dosing	3/17 (18)

≥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)

– Median percentage change at week 12 was -14.0 (n = 21) for daily/weekly dosing and -39.6 (n = 12) for all daily dosing

*Evaluable patients were those receiving ≥1 dose of study drug, had MFSAF-TSS baseline assessment with a non-zero value, and met at least 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 4, 12 or 24 weeks but no 4, 12 or 24 week assessment, respectively. Noncompleters assessed as nonresponders.

Most Common Nonhematologic and Serious TEAEs

- Nonhematologic TEAEs (≥15% of patients)

Event, n (%)	Daily/Weekly Dosing (n = 33)		All Daily Dosing (n = 20)	
	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 (12)	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)

- Serious TEAEs occurring in ≥2 patients:
  - Urinary tract infection (n = 3)
  - Pneumonia, pyrexia, and fall (n = 2 each)

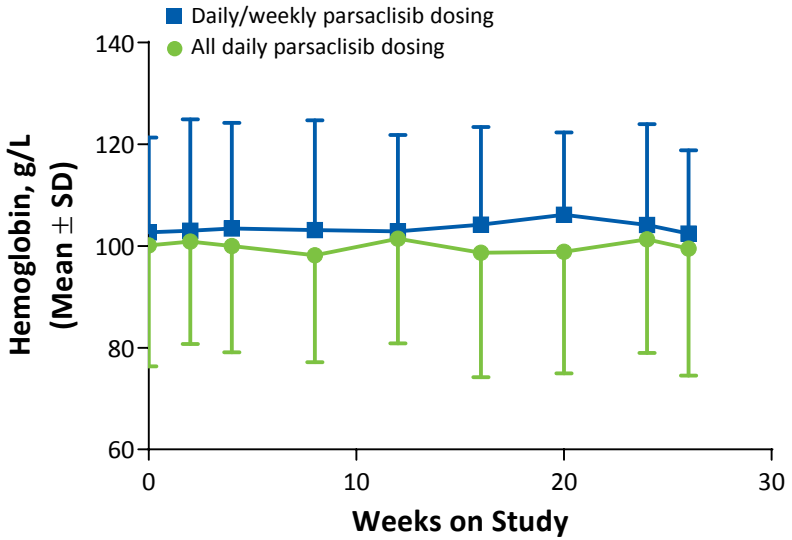
TEAE, treatment-emergent adverse event.

TEAEs of Special Interest

Event, n (%)	Daily/Weekly Dosing (n = 33)	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 virus; LFT, liver function test; PJP, *pneumocystis jiroveci* pneumonia; VZV, varicella-zoster virus.

Hematologic TEAEs (Laboratory Assessment)



- Hemoglobin levels remain steady over time
  - Study had no exclusion for anemia

- New-onset thrombocytopenia

	New-Onset Grade 3, n (%)	New-Onset Grade 4, n (%)
Daily/weekly dosing, n = 33	6 (18)	7 (21)
All daily dosing, n = 20	6 (30)	0

TEAEs With Fatal Outcomes

Event	Assigned Dose Group	Dosing of Parsaclisib Prior to Event	Day of Death	Relevant Medical History/ Ongoing Events	Investigator-Assessed Relation to Parsaclisib or Ruxolitinib
Intracranial hemorrhage	5 mg daily	5 mg daily	78	Hypertension Ongoing grade 1 thrombocytopenia since day 1	Not related
AML blast crisis	20 mg daily/weekly	20 mg weekly	177	3% blasts day 1 20% blasts week 20 40% blasts in hospital prior to death	Not related
AML blast crisis	10 mg daily/weekly	5 mg daily	243	6% blasts day 1 5% blasts week 24 11% blasts week 25 95% blasts in hospital prior to death	Not related
Esophageal ulcer	10 mg daily/weekly	5 mg daily	255	None	Not related
Pneumonia	20 mg daily/weekly	20 mg weekly	387	COPD, emphysema, pleural infection	Not related
Pneumonia	20 mg daily/weekly	20 mg weekly	560	None	Not related
Breast cancer recurrence	20 mg daily/weekly	20 mg weekly	872	Breast cancer (surgically treated)	Not related

AML, acute myeloid leukemia; COPD, chronic obstructive pulmonary disease.

TEAEs Leading to Discontinuation

Event, n (%)	Daily/Weekly dosing (n = 33)	All Daily Dosing (n = 20)
Thrombocytopenia	2 (6)	0
Fatigue	1 (3)	0
Blast crisis	1 (3)	0
Disseminated tuberculosis	1 (3)	0
Pathological fracture	1 (3)	0
Leukocytosis	0	1 (5)

Conclusions

- In patients with MF receiving an optimized and stable dose of ruxolitinib, add-on parsaclisib resulted in additional spleen volume reduction and improvement in symptom burden
  - The benefit was observed early and was durable
- The addition of parsaclisib to ruxolitinib was 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
- 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
- Further studies are warranted

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