Efficacy and Safety of Add-on Parsaclisib to Ruxolitinib Therapy in Myelofibrosis Patients With Suboptimal Response to Ruxolitinib: Final Results From a Phase 2 Study

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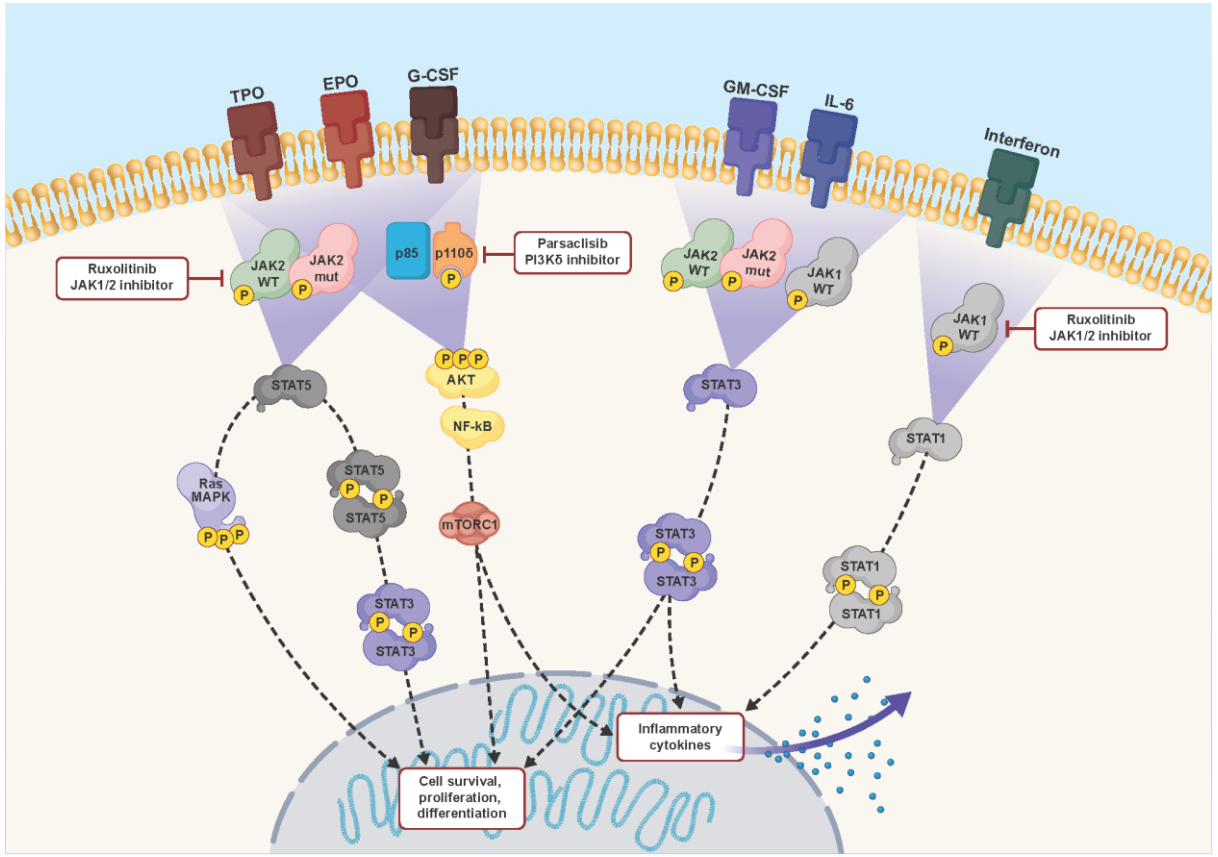
JAK1/2 and PI3K Pathways in Myelofibrosis



Adapted from "Pathogenesis of Myeloproliferative Neoplasms: Role and Mechanisms of Chronic Inflammation" by Hermouet S, et al. Mediators Inflamm. 2015;2015:145293 is licensed under CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/) and Targeting the PI3K pathway in myeloproliferative neoplasms, Gerds AT et al., Expert Rev Anticancer Ther, 2022, Published by Informa UK Limited, trading as Taylor & Francis Group. Reprinted by permission of the Informa UK Limited trading as Taylor & Francis Ltd, http://www.tandfonline.com

- Ruxolitinib, a potent JAK1/2 inhibitor, reduces spleen volume, improves symptoms, and prolongs survival in patients with intermediate- or high-risk MF[1-3]
- Suboptimal responses may occur in a subset of patients, possibly due to continued signaling via the PI3K pathway[4-6] while receiving treatment with JAK inhibitors
- Parsaclisib, a potent and highly selective next-generation PI3Kδ inhibitor, exhibits favorable pharmacokinetics for once-daily dosing[7]
- Combined inhibition of JAK1/2 and PI3K signaling pathways may improve outcomes in MF[6]

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

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.** Gerds AT, et al. *Expert Rev Anticancer Ther.* 2022;22:835-843. **7.** Shin N, et al. *J Pharmacol Exp Ther.* 2020;374:211-222.

Patient Eligibility and Study Endpoints

Key Inclusion Criteria

- ≥18 years of age
- Primary or secondary MF (PMF, PPV-MF, or PET-MF)
- Received ruxolitinib (5-25 mg BID) for ≥6 months with stable dose for ≥8 weeks prior to enrollment
- Suboptimal response to ruxolitinib monotherapy
  - Palpable spleen >10 cm below LSM on physical examination at screening
    OR
  - Palpable spleen 5-10 cm below LSM on physical examination **AND** active symptoms of MF at the screening defined as 1 symptom score ≥5 or 2 symptom scores ≥3 each, using the Screening Symptom Form*
- Platelet count ≥50×10^9/L in the 4 weeks before screening
- Study had no exclusion criteria for anemia or transfusion dependence

Primary Endpoint

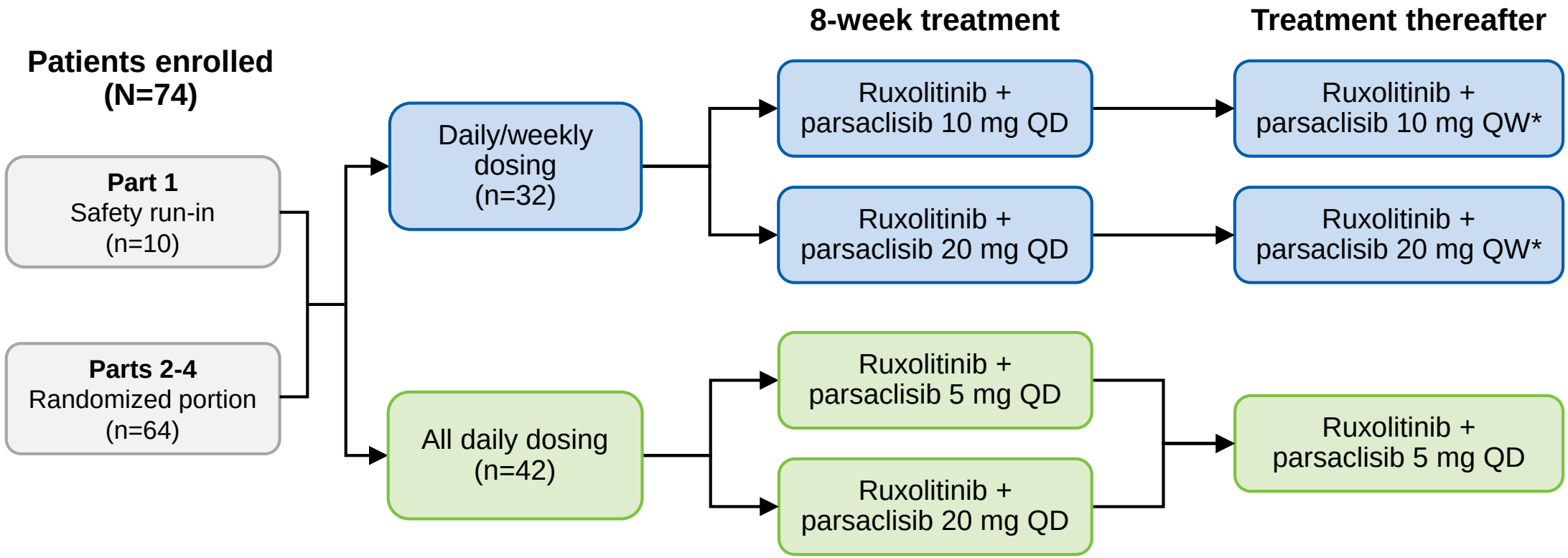
- Change in spleen volume from baseline to week 12 (by MRI or CT scan)

Secondary and Exploratory Endpoints

- Change in spleen volume to week 24
- Change in spleen length
- Change in total symptom score (MFSAF v3.0, MPN-SAF)
- Safety

*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.
BID, twice daily; CT, computed tomography; LSM, left subcostal margin; MFSAF, Myelofibrosis Symptom Assessment Form; MPN-SAF, Myeloproliferative Neoplasms Symptom Assessment Form; MRI, magnetic resonance imaging; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis.

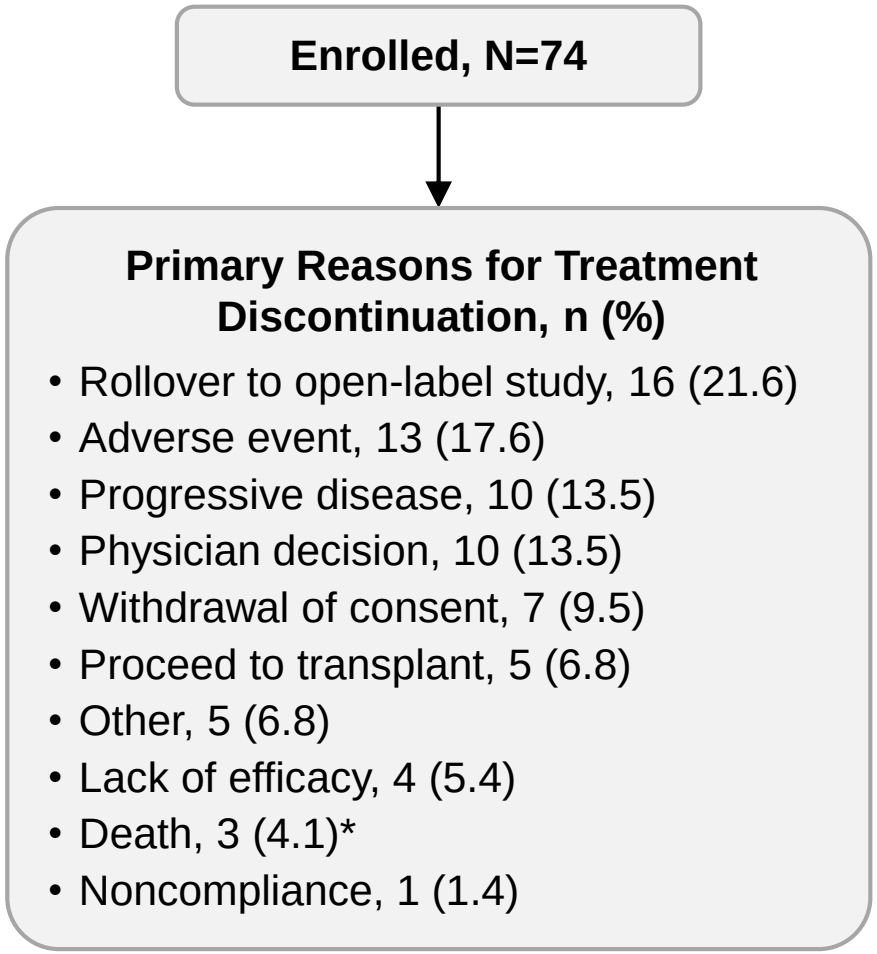
Parsaclisib Dosing Schedules in Combination With Stable-Dose Ruxolitinib (50465-201; NCT02718300)



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

Patient Disposition

- 16 patients (21.6%) continued therapy in an open-label study
- 13 patients (17.6%) discontinued due to adverse events
- 5 patients (6.8%) discontinued due to proceeding to transplant



*Deaths occurring during study treatment were due to pneumonia (2 patients) and intracranial hemorrhage; none attributed to study treatment by the investigator.

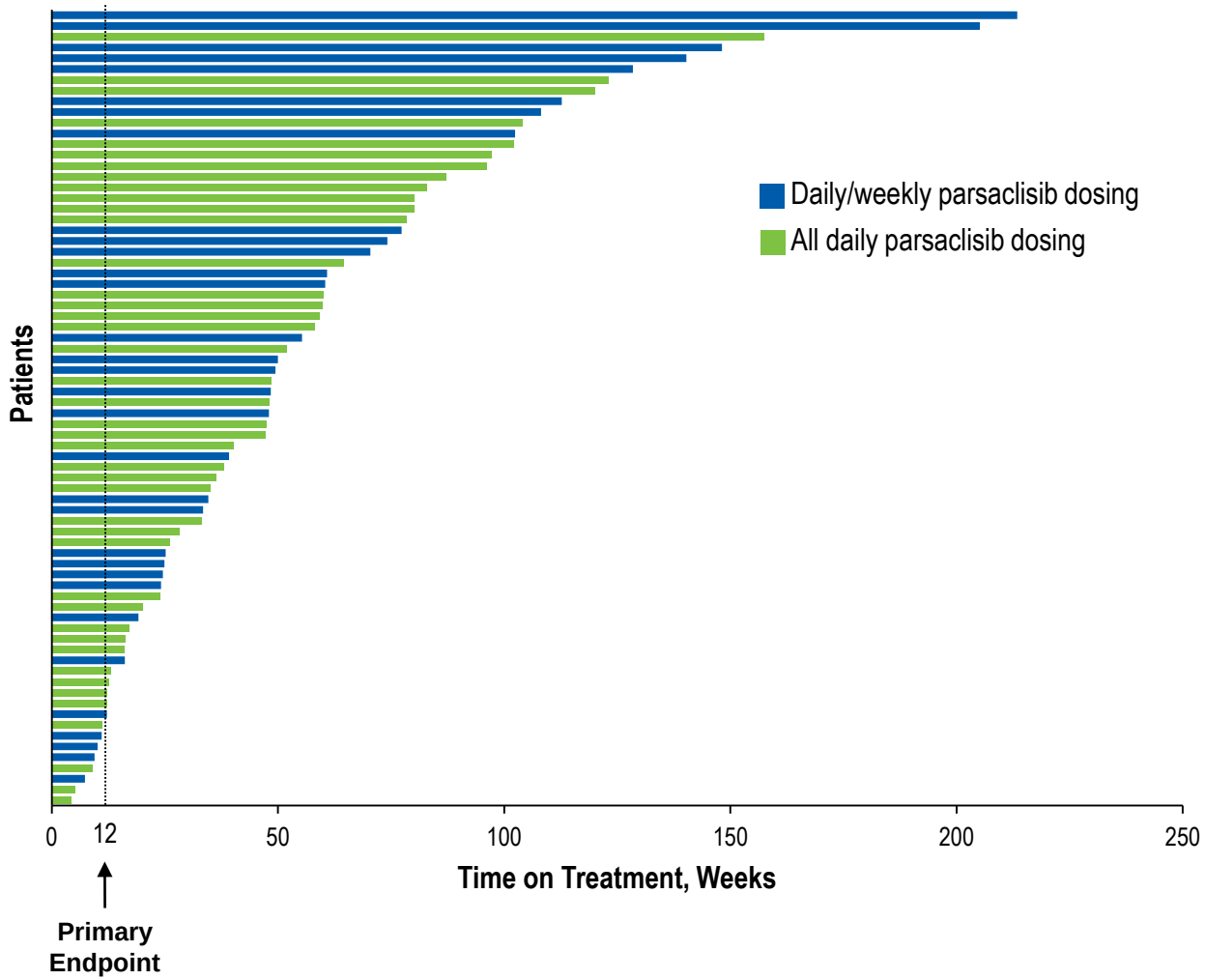
Baseline Characteristics

Characteristic	Daily/Weekly Group (n=32)	All Daily Group (n=42)	Total (N=74)
Age, median (range), y	67 (41-89)	69 (51-84)	68 (41-89)
Male, n (%)	15 (47)	20 (48)	35 (47)
Time since initial diagnosis, median (range), mo	30.5 (6.7-268.9)	37.5 (4.9-251.5)	33.0 (4.9-268.9)
Ruxolitinib use, median (range) Daily dose, mg Duration, mo	 28.9 (13.8-50.0) 18.1 (3.7-93.9)	 29.3 (8.7-44.8) 16.4 (5.1-105.5)	 29.3 (8.7-50.0) 17.2 (3.7-105.5)
Patients with palpable spleen, n (%) Median length (range), cm	31 (97) 14 (8-30)	42 (100) 11 (5-30)	73 (99) 13 (5-30)
Spleen volume, median (range), cm^3	2415 (327-5324)	1878 (434-3904)	1973 (327-5324)
MFSAF-TSS, median (range)	10.8 (0-47.0)	16.3 (0.6-38.4)	13.6 (0-47.0)
MPN-SAF-TSS, median (range)	25.5 (0-83.0)	30.0 (3.0-65.0)	29.0 (0-83.0)
Hemoglobin, median (range), g/L	102.0 (70-159)	97.5 (57-155)	99.5 (57-159)
DIPSS risk level at baseline, n (%) High / Intermediate-2 / Intermediate-1 / Low	 5 (16) / 10 (31) / 13 (41) / 4 (12.5)	 10 (24) / 19 (45) / 12 (29) / 1 (2)	 15 (20) / 29 (39) / 25 (34) / 5 (7)
MF subtype, n (%) PMF / PPV-MF / PET-MF	 17 (53) / 12 (38) / 3 (9)	 23 (55) / 12 (29) / 7 (17)	 40 (54) / 24 (32) / 10 (14)

DIPSS, Dynamic International Prognostic Scoring System; TSS, total symptom score.

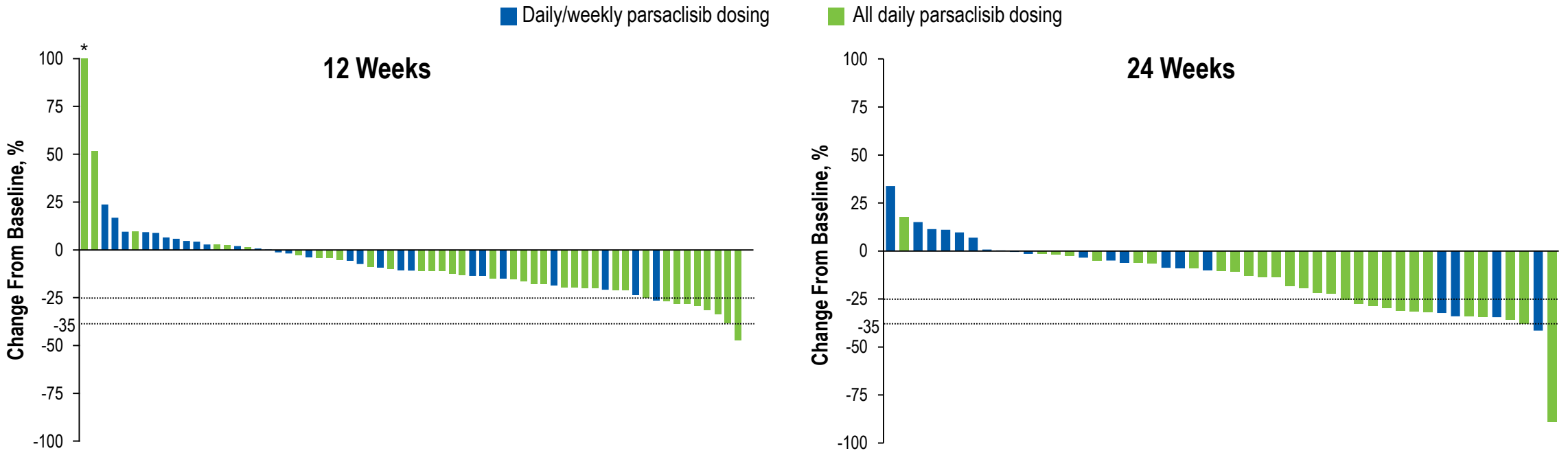
Results

Duration of Treatment



- Median (range) treatment duration was 48.1 (4.3-213.4) weeks
  - Daily/weekly: 48.9 (7.3-213.4) weeks
  - All daily: 47.4 (4.3-157.4) weeks
- Median daily dose:
  - 5.0 mg/d for parsaclisib
  - 29.8 mg/d for ruxolitinib
- 66 patients (89.2%) received treatment for ≥12 weeks
- 31 patients (41.9%) received study treatment for ≥1 year, and 10 patients (13.5%) for ≥2 years
- After the study was ended, 16 patients (21.6%) continued to an open-label study of parsaclisib

Percentage Change in Spleen Volume and Response Categories at 12 and 24 Weeks

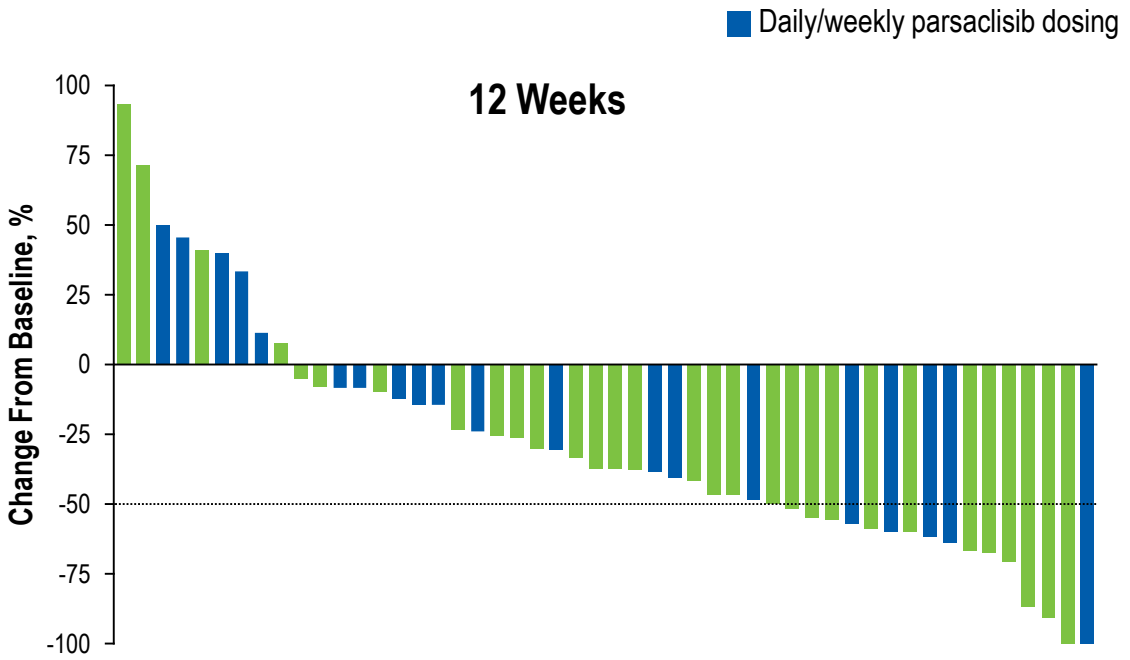


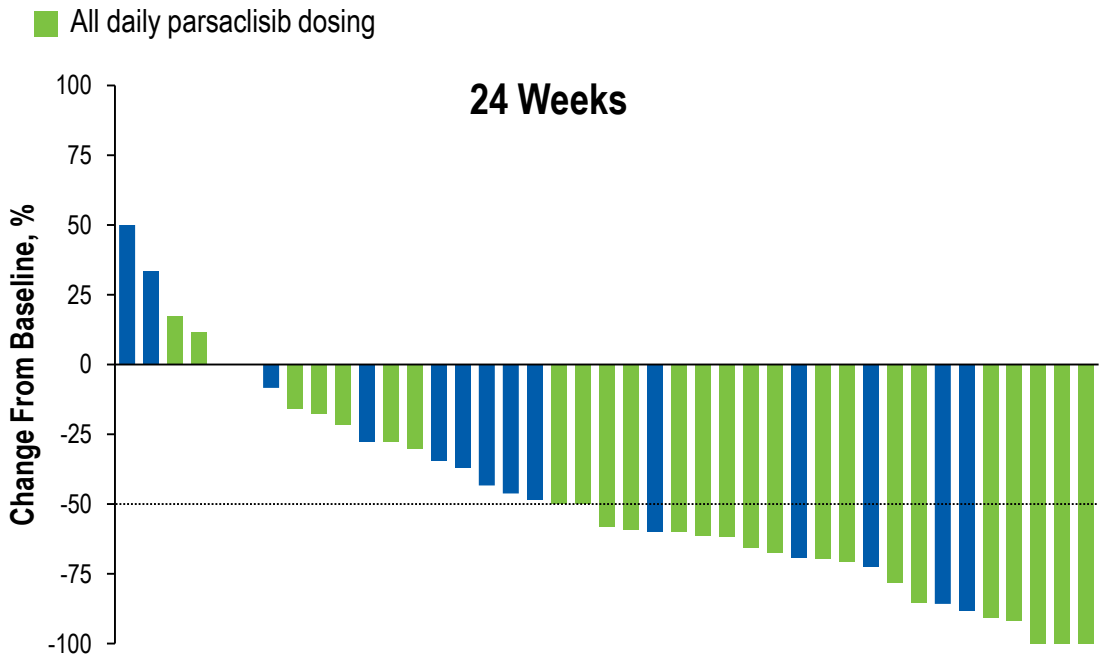
Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	n=32	n=42
≥10% reduction	9 (28.1)	25 (59.5)
≥25% reduction	1 (3.1)	9 (21.4)
≥35% reduction	0	2 (4.8)

Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 24	n=32	n=42
≥10% reduction	4 (12.5)	21 (50.0)
≥25% reduction	4 (12.5)	12 (28.6)
≥35% reduction	1 (3.1)	3 (7.1)

*Patient had best percentage change from baseline to >100%.

Change in MPN-SAF Symptom Score and Response Categories at 12 and 24 Weeks

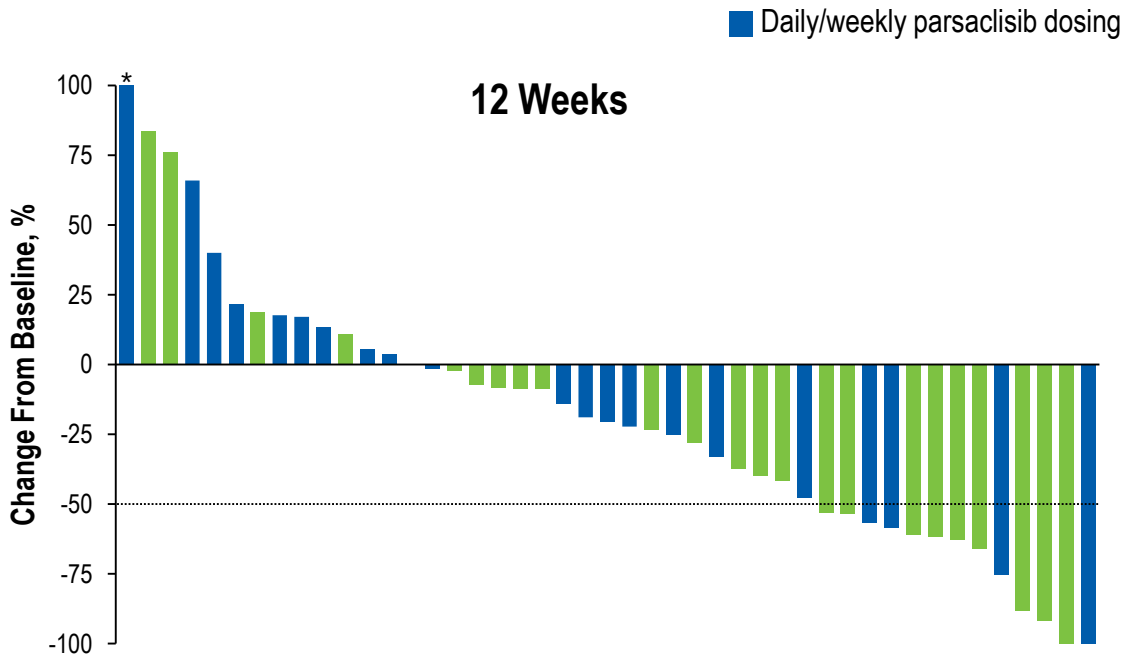


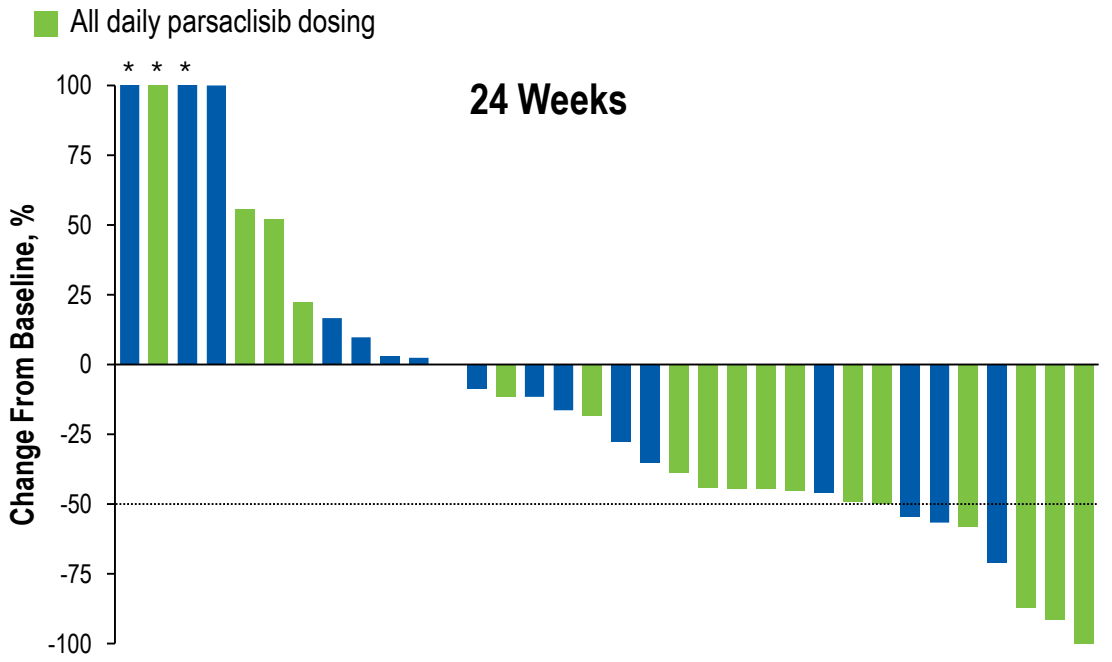


Median Change in MPN-TSS at 12 Weeks	n	% Change (Range)
Daily/weekly dosing	20	-19.2 (-100.0 to 50.0)
All daily dosing	30	-39.8 (-100.0 to 93.3)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**
Daily/weekly dosing	27	5/27 (18.5)
All daily dosing	37	12/37 (32.4)

Median Change in MPN-TSS at 24 Weeks	n	% Change (Range)
Daily/weekly dosing	15	-43.3 (-88.2 to 50.0)
All daily dosing	26	-60.8 (-100.0 to 17.5)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**
Daily/weekly dosing	27	5/27 (18.5)
All daily dosing	37	18/37 (48.6)

Change in MFSAF Symptom Daily Diary Score and Response Categories at 12 and 24 Weeks



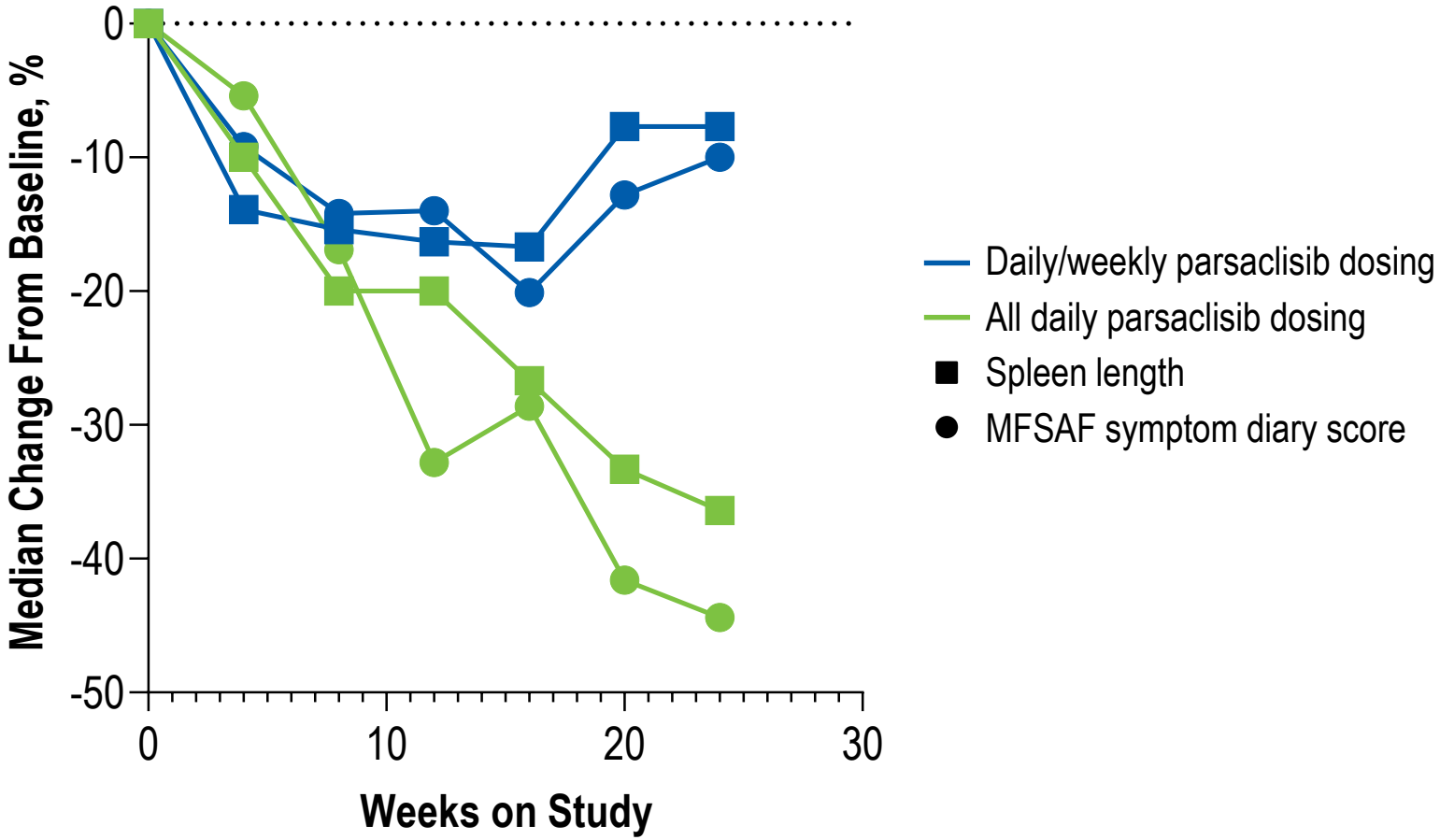


Median Change in MFSAF-TSS at 12 Weeks	n	% Change (Range)
Daily/weekly dosing	21	-14.0 (-100.0 to 500.0)
All daily dosing	24	-32.8 (-100.0 to 83.7)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**
Daily/weekly dosing	28	4/28 (14.3)
All daily dosing	32	9/32 (28.1)

Median Change in MFSAF-TSS at 24 Weeks	n	% Change (Range)
Daily/weekly dosing	16	-10.0 (-71.0 to 222.5)
All daily dosing	18	-44.4 (-100.0 to 152.4)
Proportion Reaching 50% Decrease in TSS		**n/N (%)**
Daily/weekly dosing	28	3/28 (10.7)
All daily dosing	32	5/32 (15.6)

*Patients had best percentage change from baseline to >100%.

Change in Spleen Length and Symptom Score by Dosing Group



Most Common Nonhematologic, Serious, and Fatal TEAEs Among All Treated Patients

Nonhematologic TEAEs (≥15% of Patients Overall)

Event, n (%)	Daily/Weekly Dosing (n=32)		All Daily Dosing (n=42)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	10 (31.3)	1 (3.1)	7 (16.7)	0
Diarrhea	9 (28.1)	1 (3.1)	7 (16.7)	0
Abdominal pain	7 (21.9)	1 (3.1)	7 (16.7)	0
Fatigue	9 (28.1)	1 (3.1)	5 (11.9)	1 (2.4)
Cough	7 (21.9)	0	6 (14.3)	0
Dyspnea	5 (15.6)	0	8 (19.0)	2 (4.8)
Dizziness	4 (12.5)	0	8 (19.0)	0
Fall	6 (18.8)	2 (6.3)	6 (14.3)	0

- Serious TEAEs occurring in ≥2 patients overall:
  - Pneumonia (n=6; 3 daily/weekly, 3 all daily)
  - Fall (n=3; 2 daily/weekly, 1 all daily)
  - Pyrexia (n=2; 1 daily/weekly, 1 all daily)
- Fatal TEAEs were reported in 6 patients (none assessed as drug-related by the investigator)*
  - Pneumonia (n=3; 2 daily/weekly, 1 all daily)
  - Blood bilirubin increased (n=1; daily/weekly)
  - Metastatic breast cancer (n=1; daily/weekly)
  - Intracranial hemorrhage (n=1; all daily)

*All 3 patients with fatal pneumonia were males, over 70 years; 1 had the event in 2018, 1 in 2019, and the other in 2020 (none suspected to be COVID or PJP related). The patient with intracranial hemorrhage had day 1 platelet count of 106 g/L; 3 days prior to the event, the platelet count was 112 g/L.

PJP, *Pneumocystis jirovecii* pneumonia; TEAE, treatment-emergent adverse event.

TEAEs of Special Interest

Event, n (%)	Daily/Weekly Dosing (n=32)	All Daily Dosing (n=42)
Grade ≥2 diarrhea	4 (12.5)	0
Grade ≥3 ALT increase	2 (6.3)	0
Grade ≥3 AST increase	2 (6.3)	0
Grade ≥2 rash	1 (3.1)	0
Herpes simplex*	1 (3.1)	2 (4.8)
VZV infection	1 (3.1)	2 (4.8)
Colitis	0	0
Pneumonitis	0	0

- No reports of dermatitis exfoliative, intestinal perforation, cytomegalovirus infection, or PJP†

*Includes herpes simplex, oral herpes, and genital herpes. †Patients enrolled received PJP prophylaxis.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; VZV, *varicella zoster* virus.

Hematologic TEAEs (Laboratory Assessment): New-Onset Thrombocytopenia by Dosing Group

Daily/Weekly Dosing (n=32)

Baseline		Worst Abnormal Value on Study				
Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0	13 (40.6)	6 (46.2)	3 (23.1)	2 (15.4)	1 (7.7)	1 (7.7)
Grade 1	11 (34.4)	0	3 (27.3)	5 (45.5)	2 (18.2)	1 (9.1)
Grade 2	7 (21.9)	0	0	1 (14.3)	3 (42.9)	3 (42.9)
Grade 3	1 (3.1)	0	0	0	0	1 (100)
Grade 4	0	0	0	0	0	0
Total	32	6	6	8	6	6

- 6/32 patients (18.8%) each had grade 3 and grade 4 new-onset thrombocytopenia in daily/weekly dosing group
- 3/6 patients with new-onset grade 3 entered the study at grade 2, and 4/6 with new-onset grade 4 entered the study at grade 2 or 3

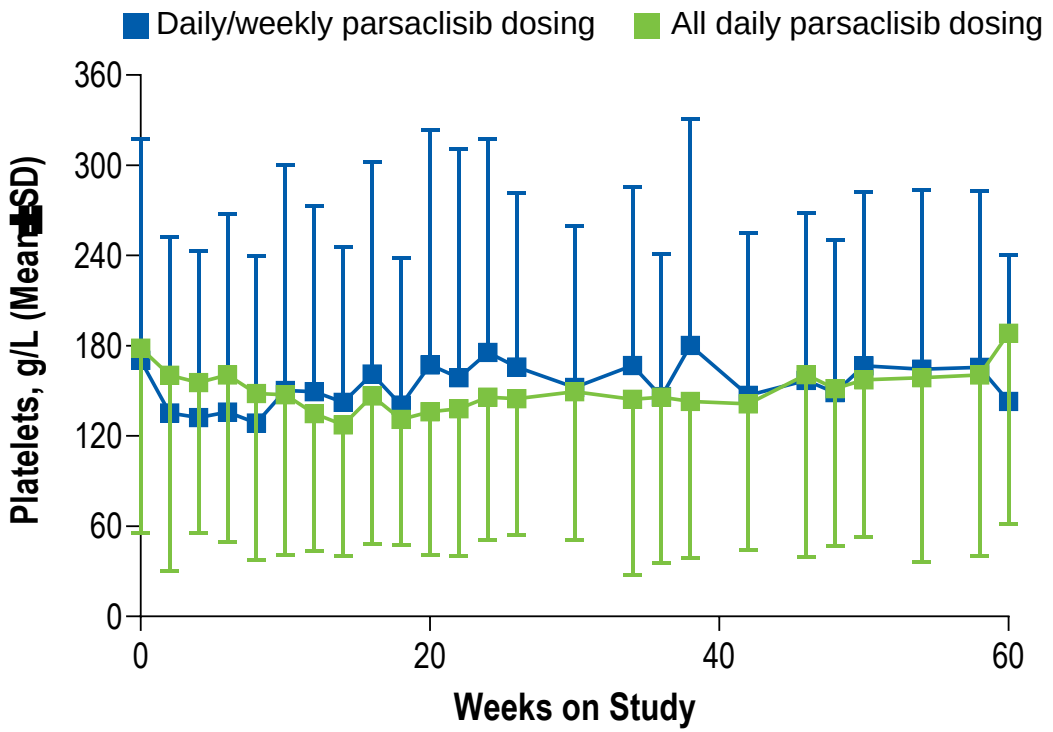
All Daily Dosing (n=42)

Baseline		Worst Abnormal Value on Study				
Grade	n (%)	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Grade 0	19 (45.2)	9 (47.4)	7 (36.8)	2 (10.5)	0	1 (5.3)
Grade 1	15 (35.7)	0	3 (20.0)	7 (46.7)	4 (26.7)	1 (6.7)
Grade 2	8 (19.0)	0	0	0	7 (87.5)	1 (12.5)
Grade 3	0	0	0	0	0	0
Grade 4	0	0	0	0	0	0
Total	42	9	10	9	11	3

- 11/42 patients (26.2%) had grade 3 and 3/42 (7.1%) had grade 4 new-onset thrombocytopenia in all daily dosing group
- 7/11 patients with new-onset grade 3 entered the study at grade 2, and 1/3 with new-onset grade 4 entered the study at grade 2

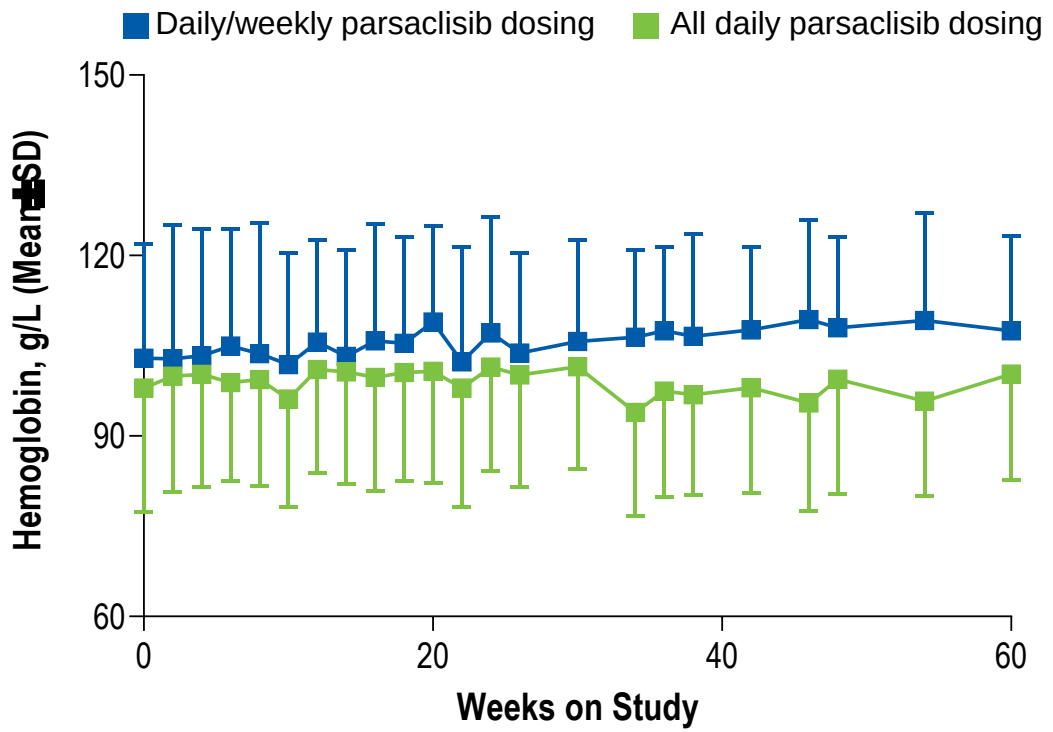
Hematologic TEAEs (Laboratory Assessment): Platelet and Hemoglobin Levels by Dosing Group

Platelet Levels



- Platelet levels remained steady over time
  - Study had no exclusion for transfusion dependence

Hemoglobin Levels



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

SD, standard deviation.

TEAEs Leading to Treatment Discontinuation

Event, n (%)	Daily/Weekly Dosing (n=32)	All Daily Dosing (n=42)
Patients with any TEAE leading to parsaclisib discontinuation	**5 (15.6)**	**4 (9.5)**
Thrombocytopenia	0	2 (4.8)
Blood creatinine increased	0	1 (2.4)
Hyperuricemia	0	1 (2.4)
Leukocytosis	0	1 (2.4)
Metastatic squamous cell carcinoma	0	1 (2.4)
Abdominal pain	1 (3.1)	0
Cholangitis	1 (3.1)	0
Disseminated tuberculosis	1 (3.1)	0
Fatigue	1 (3.1)	0
Liver function text increased	1 (3.1)	0
Metastatic breast cancer	1 (3.1)	0
Organizing pneumonia	1 (3.1)	0
Pathological fracture	1 (3.1)	0
Platelet count decreased	1 (3.1)	0
Patients with any TEAE leading to ruxolitinib discontinuation	**2 (6.3)**	**2 (4.8)**

Conclusions

- In patients with MF with suboptimal response on stable and optimized dose of ruxolitinib, add-on parsaclisib resulted in additional spleen volume reduction and improvement in symptom burden
- Addition of parsaclisib to ruxolitinib was generally well-tolerated, with limited grade 3 or 4 adverse events and TEAE-related discontinuations
  - TEAEs common to PI3K inhibitors in lymphoma (eg, hepatic, rash, colitis) were infrequent or absent 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
- Phase 3 studies of parsaclisib as add-on to ruxolitinib (LIMBER 304, NCT04551053) and parsaclisib plus ruxolitinib in the frontline setting (LIMBER 313, NCT04551066) are underway to further assess the combination of JAK and PI3K inhibitors; patients with low platelets are included in both studies

Acknowledgments

Principal Investigator	Affiliation	Country
Aaron Gerds	The Cleveland Clinic Foundation	USA
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Gary Schiller	UCLA School of Medicine	USA
Haris Ali	City of Hope National Medical Center	USA
Houston Holmes	Baylor Charles A. Sammons Cancer Center – Clinical Trials Office	USA
James McCloskey	Hackensack University Medical Center PARTNER	USA
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Swati Goel	Montefiore Medical Center PRIME	USA
Uma Borate / Ronan Swords	Oregon Health & Science University	USA

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Scan code for information on ongoing phase 3 studies

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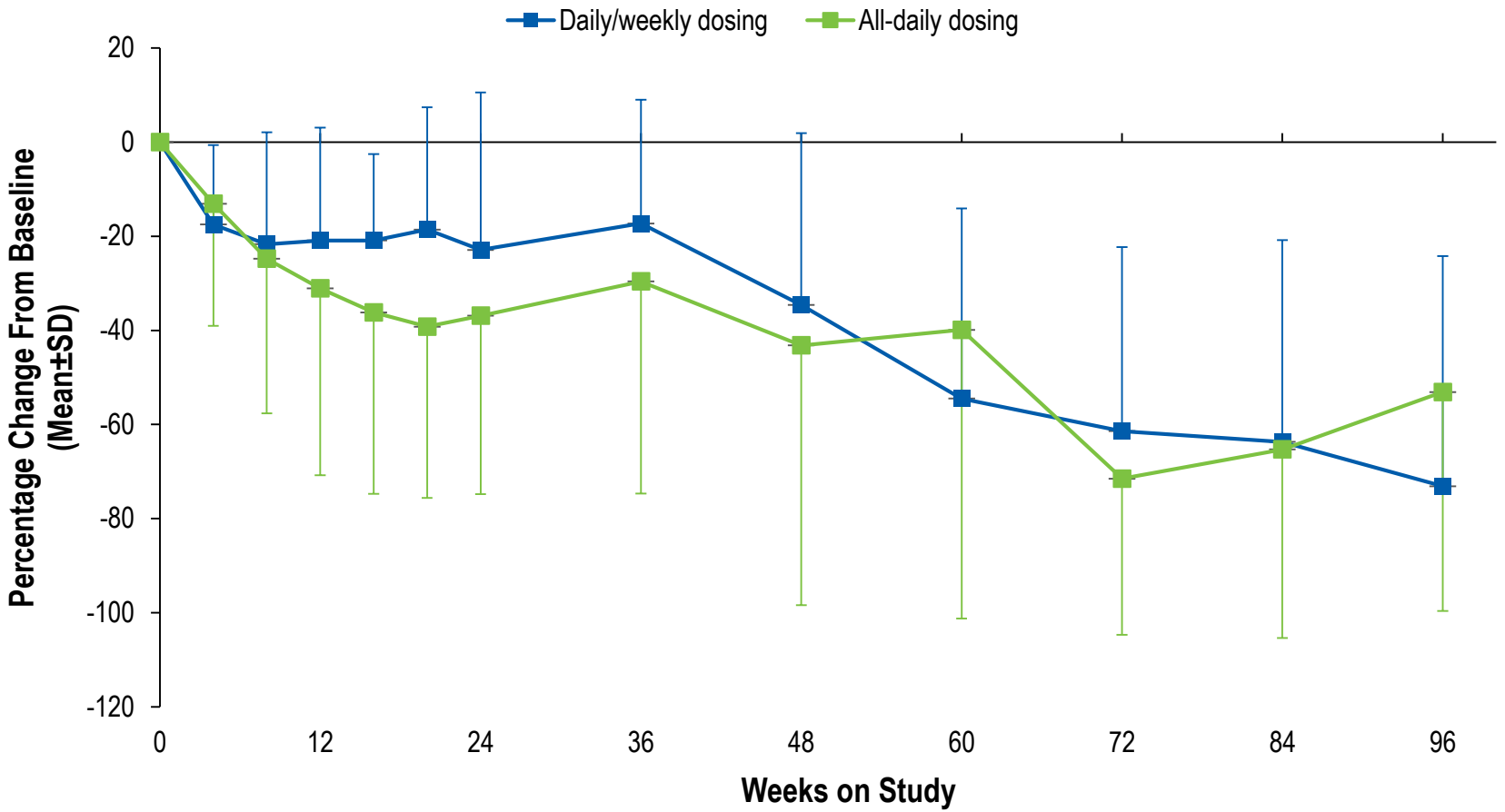
Back-up Slides

Change in Palpable Spleen Length Over Time



Daily/weekly, n*	31	26	18	14	11	9	8	5	4
All-daily, n*	42	34	25	19	14	12	11	8	5

*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.

Hematologic TEAEs (Laboratory Assessment): New-Onset Neutropenia

Dosing Group	Grade 3, n (%)	Grade 4, n (%)
Daily/weekly, n=32	2 (6.3)	1 (3.1)
All daily, n=42	2 (4.8)	2 (4.8)

TEAE, treatment-emergent adverse event.

Transfusion Frequency in Patients Dependent on Blood Transfusions at Baseline

Parameter	Daily/Weekly Dosing (n=32)	All Daily Dosing (n=42)	Total (N=74)
RBC transfusions before day 1, n (%)	5 (15.6)	7 (16.7)	12 (16.2)
Decrease in transfusions, n/N (%)	3/5 (60.0)	4/7 (57.1)	7/12 (58.3)

RBC, red blood cell.