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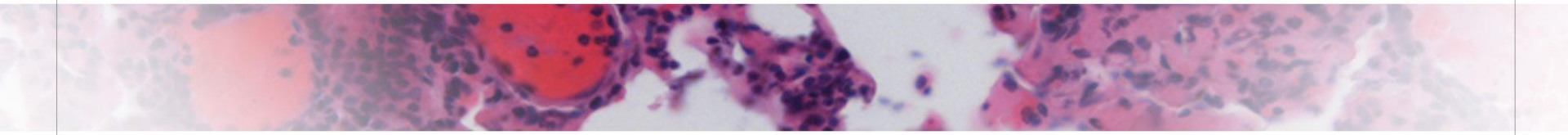
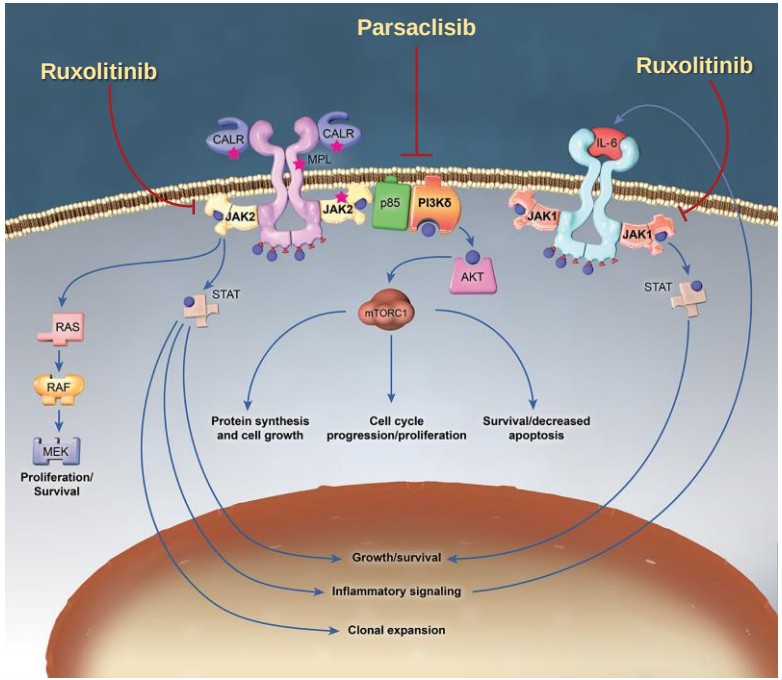


A Phase 2 Study of the Safety and Efficacy of INCB050465, a Selective PI3Kδ Inhibitor, in Combination With Ruxolitinib in Patients With Myelofibrosis

Naval Daver,[1] Marina Kremyanskaya,[2] Casey O'Connell,[3] Kim-Hien Dao,[4] Stephen T. Oh,[5] Aaron T. Gerds,[6] Srdan Verstovsek,[1] Sue Erickson-Viitanen,[7] Feng Zhou,[7] Albert Assad,[7] and Abdulraheem Yacoub[8]

[1]University of Texas MD Anderson Cancer Center, Houston, TX; [2]Mount Sinai Health System, New York, NY; [3]University of Southern California, Los Angeles, CA; [4]Oregon Health & Science University, Knight Cancer Institute, Portland, OR; [5]Washington University School of Medicine, Saint Louis, MO; [6]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [7]Incyte Corporation, Wilmington, DE; [8]University of Kansas Medical Center, Kansas City, KS

Background/Rationale



- Ruxolitinib, a JAK1/2 inhibitor, improved symptoms, reduced spleen size, and improved survival in intermediate- or high-risk MF[1–3]
  - However, some patients have suboptimal responses or declining activity over time
- Activation of the PI3K pathway has been reported in patients with MF[4,5]
- Addition of a PI3K inhibitor is a potential strategy in patients with suboptimal or declining response to ruxolitinib

1. Verstovsek S, et al. *N Engl J Med*. 2012;366:799–807; **2.** Harrison C, et al. *N Engl J Med*. 2012;366:787–98; **3.** Cervantes F, et al. *Blood*. 2013;122:4047–53; **4.** Grimwade L, et al. *Br J Haematol*. 2009;147:495–506; **5.** Oku S, et al. *Br J Haematol.* 2010;150:334–44.
JAK, Janus kinase; MF, myelofibrosis; PI3K, phosphatidylinositol 3-kinase.

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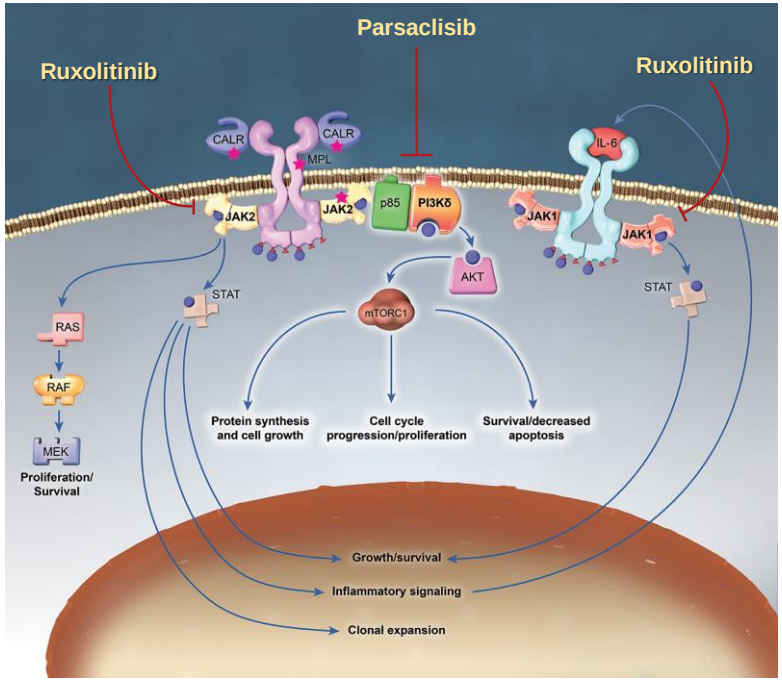

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Background/Rationale

Parsaclisib (INCB050465)

- Potent, highly selective, next-generation PI3Kδ inhibitor
- Designed to avoid hepatotoxicity
- Exhibits favorable PK for once-daily dosing

Comparative Potency and Isoform Selectivity*

	Parsaclisib[1]	Idelalisib[2]	Copanlisib[3]	Umbralisib[4]
PI3Kδ IC_{50}, nM	**1**	**2.5**	**0.7**	**22**
Fold selectivity				
PI3Kα	>20,000	>300	1	>1000
PI3Kβ	>20,000	>200	5	>50
PI3Kγ	19,000	>35	10	>48

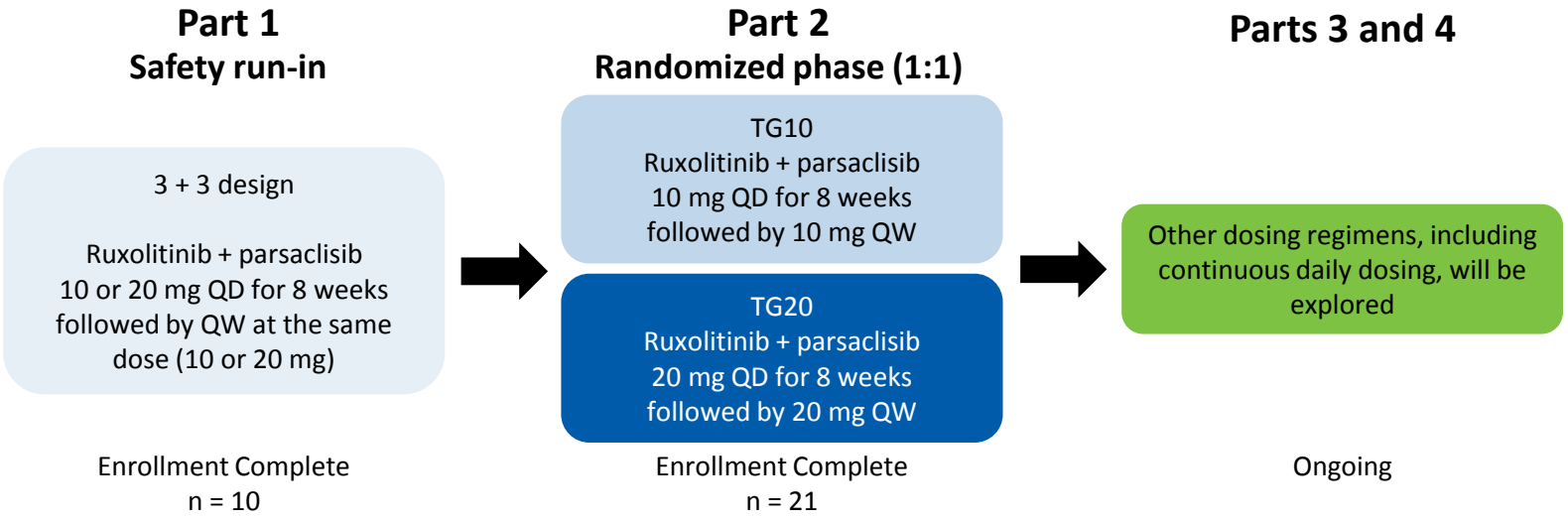
*Biochemical assay.

1. Shin N, et al. AACR Annual Meeting; April 18–22, 2015; Philadelphia, PA, USA. Abstract 2671; **2.** Lanutti BJ, et al. *Blood*. 2011;117:591–4; **3.** Liu N, et al. *Mol Cancer Ther*. 2013;12:2319–30; **4.** Burris HA, et al. ASCO Annual Meeting; June 3–7, 2016; Chicago, IL, USA. Poster 7512.

IC_{50}, 50% inhibitory concentration; PI3K, phosphatidylinositol 3-kinase; PK, pharmacokinetics.

Study Design

- Phase 2 study of PI3Kδ inhibitor, parsaclisib, and the JAK 1/2 inhibitor, ruxolitinib
- Patients with primary or secondary MF who have suboptimal response with ruxolitinib monotherapy (NCT02718300)



JAK, Janus kinase; MF, myelofibrosis; PI3K, phosphatidylinositol 3-kinase; QD, once daily; QW, once weekly; TG, treatment group.

Suboptimal Response to Ruxolitinib

- Treated with ruxolitinib for ≥6 months with stable dose for ≥8 weeks immediately prior to enrollment
- 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.

Study Population

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

BID, twice daily; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis.

Endpoints

Primary Endpoints

- Part 1: Identify tolerable dose of parsaclisib
- Part 2: Spleen volume assessment at week 12

Secondary Endpoints

- Safety and tolerability
- Symptoms as measured by MPN-SAF
- ORR using IWG-MRT
- PGIC score

Data cutoff date: August 29, 2018

IWG-MRT, International Working Group – Myeloproliferative Neoplasms Research and Treatment; MF-SAF, Myelofibrosis Symptom Assessment Form; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; ORR, objective response rate; PGIC, Patient Global Impression of Change.

Baseline Characteristics

Characteristic	N = 31
Age, median (range), years	68 (41–89)
Male, n (%)	15 (48)
Time since initial diagnosis, median (range), months	32 (7–278)
Duration of prior ruxolitinib use, median (range), months	15 (6–95)
Patients with palpable spleen, n (%) Median length (range), cm	31 (100) 14 (8–30)
Spleen volume, median (range), cm^3	2436 (327–5324)
TSS score by MPN-SAF, median (range)	27 (0–83)
JAK2 V617F positive, n/N* (%)	24/28* (77)
Hemoglobin, median (range), g/L	103 (70–159)
MF subtype, n (%) PMF / PPV-MF / PET-MF	15 (48) / 12 (39) / 4 (13)
DIPSS risk category, n (%) High risk / Intermediate-2 / Intermediate-1 / Low risk	6 (19) / 13 (42) / 10 (32) / 2 (7)

* *JAK2* mutation status was assessed in 28 of the 31 patients enrolled in Parts 1 and 2 of the study.

Study Drug Dosing

Ruxolitinib Starting Dose

Dose	5 mg BID	10 mg BID	15 mg BID	20 mg BID	25 mg BID	Total
Patients, n	1	9	4	11	6	31

Parsaclisib Starting Dose

Dose	10 mg QD followed by 10 mg QW	20 mg QD followed by 20 mg QW	Total
Patients, n	14	17	31

- No patient increased ruxolitinib dose
- 3 patients had interruptions and resumed at initial dose
- 1 patient had a dose reduction

- No patient increased parsaclisib dose
- 10 patients had brief dose interruptions and resumed at initial dose
- 2 patients had dose reductions

Median (range) duration of treatment: 196 (51–462) days

17 patients (55%) have been on study treatment for >6 months

BID, twice daily; QD, once daily; QW, once weekly.

Safety: AEs and SAEs Irrespective of Attribution

Nonhematologic AEs Occurring in >10% of Patients

Total (N = 31)	Any Grade, n (%)	Grade ≥3, n (%)
Nausea	8 (26)	1 (3)
Cough	7 (23)	0
Rash	6 (19)	0
Epistaxis	6 (19)	0
Fatigue	6 (19)	1 (3)
Abdominal pain	5 (16)	0
Contusion	5 (16)	0
Diarrhea	5 (16)	1 (3)
Fall	5 (16)	2 (6)
Headache	5 (16)	0
Vomiting	5 (16)	1 (3)
Blood creatinine increased	4 (13)	1 (3)
Dizziness	4 (13)	0
Pyrexia	4 (13)	1 (3)
Stomatitis	4 (13)	0

AE, adverse event; SAE, serious adverse event.

7 patients experienced a total of 10 SAEs

- Fall (2 events)
- Disseminated tuberculosis
- Blood bilirubin increased
- Hematoma
- Influenza
- Lung infection
- Nausea
- Pyrexia
- Urinary tract infection

2 patients had fatal AEs (not treatment-related)

- Blood bilirubin increased (developed AML)
- Lung infection

2 patients discontinued because of AEs (both treatment-related)

- Thrombocytopenia
- Fatigue

Safety: AEs of Special Interest Irrespective of Attribution

Liver Enzymes

Patient	Liver Enzyme Elevated	Grade	Day of Onset	Resolved on Study	Duration, days
A	ALT/AST	3	143	No	15 (Measurable blasts at screening, rising to 20% by week 20; died of PD [AML])
B	ALT (2 events*)	2	52 / 56	Yes	3 / 2 (ALT elevations coincided with AE of disseminated TB beginning on day 18)

Rash

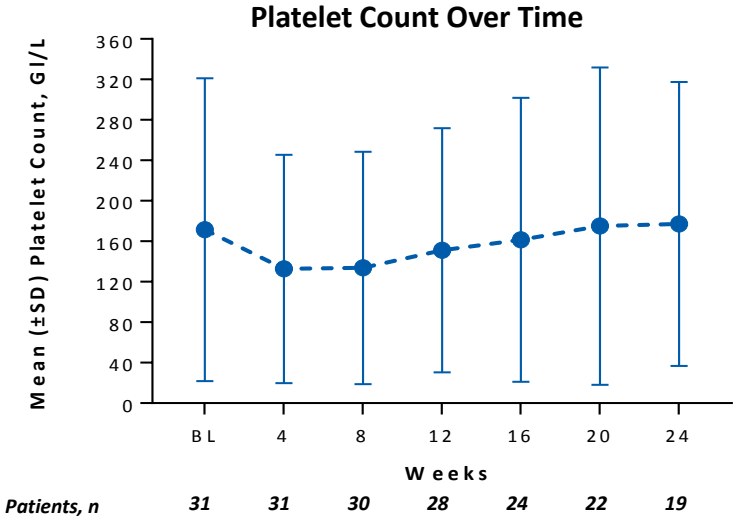
Patient	Rash	Grade	Day of Onset	Resolved on Study	Duration, days
A	Facial	2	261	Yes	90
B	Nostril	1	30	Yes	42
C	Fungal	1	86	Yes	28
D	Knee	1	67	Yes	5
E	Forehead*	1	24	Yes	1
F	Papulopustular	1	37 (drug interrupted on day 30 for low platelets)	NA	Patient discontinued per physician's decision

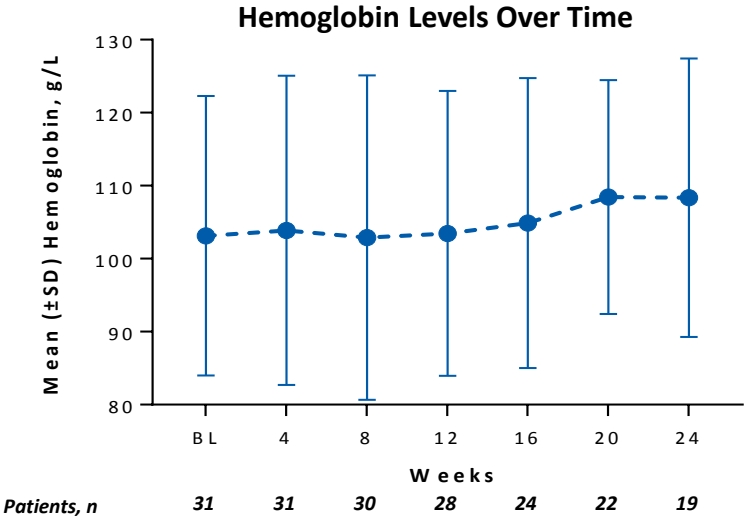
Colitis – Not reported

* Assessed as treatment-related.

AE, adverse event; ALT, alanine aminotransferase; AML, acute myeloid leukemia; AST, aspartate aminotransferase; NA, not available; PD, progressive disease; TB, tuberculosis.

Safety: Hematology





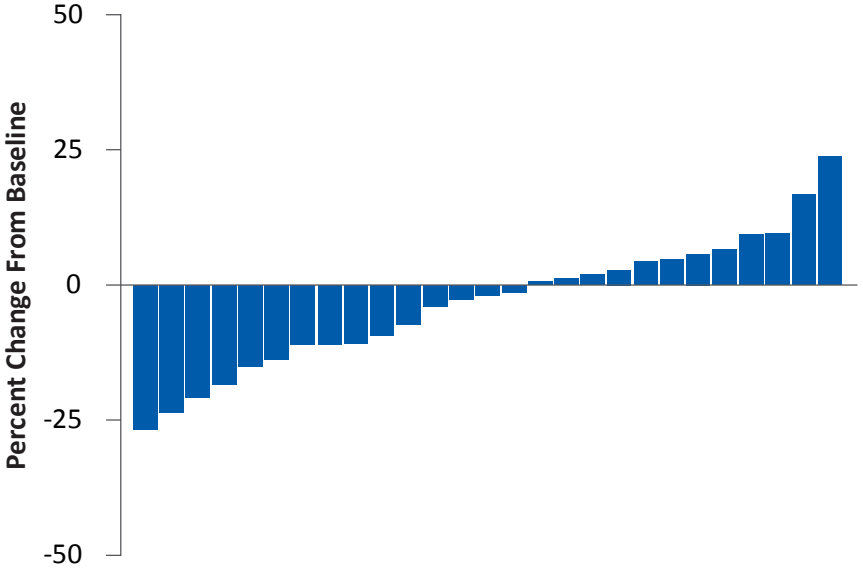
Most Common New or Worsening Hematologic AEs

Total (N = 31)	Grade 3, n (%)	Grade 4, n (%)
Thrombocytopenia	4 (13)	6 (19)
Neutropenia	1 (3)*	1 (3)*

* Both patients had grade 2 neutropenia at baseline.

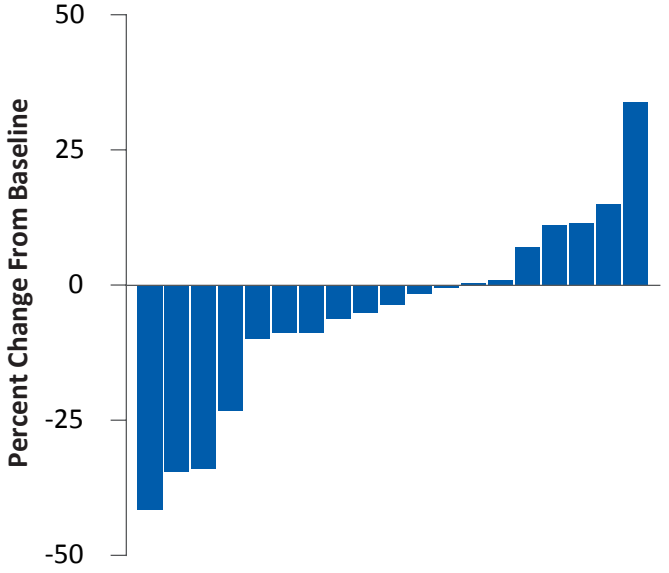
AE, adverse event; BL, baseline.

Efficacy: Spleen Volume Reduction at Weeks 12 and 24 (MRI or CT)



Week 12 (n = 27)*

- Patients with reduced spleen volume: 56% (15/27)
- Median (range) reduction: –10.9% (–26.6% to –1.29%)



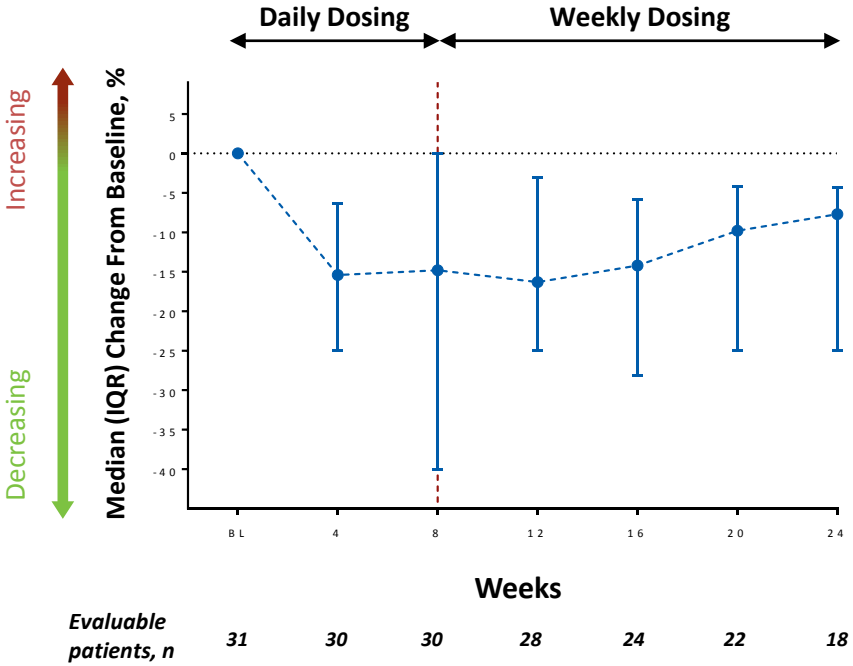
Week 24 (n = 19)†

- Patients with reduced spleen volume: 63% (12/19)
- Median (range) reduction: –8.8% (–41.5% to –0.55%)

* 4 patients not shown; all did not have spleen volume measurements due to treatment discontinuation.

† 12 patients are not shown; 4 patients did not have spleen volume measurements due to treatment discontinuation, 8 patients had not reached the response assessment at the time of the data cutoff date.

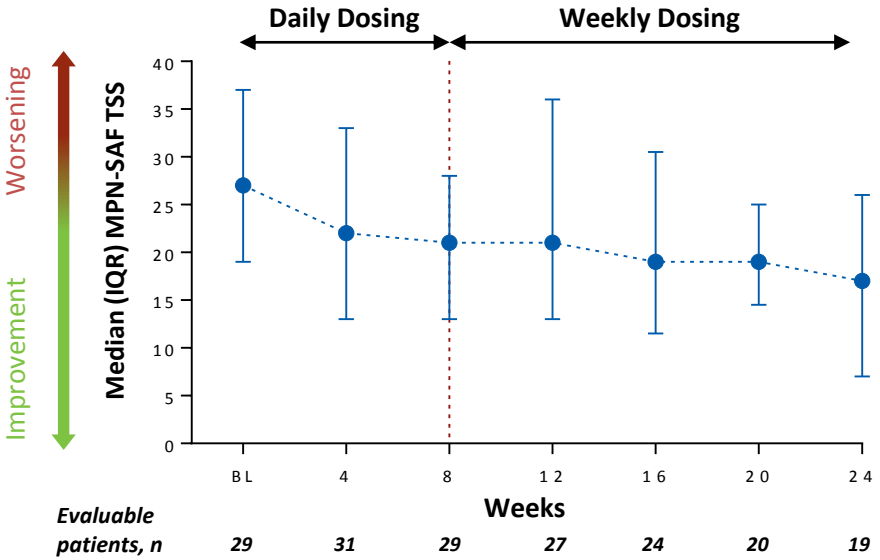
Efficacy: Change in Palpable Spleen Length

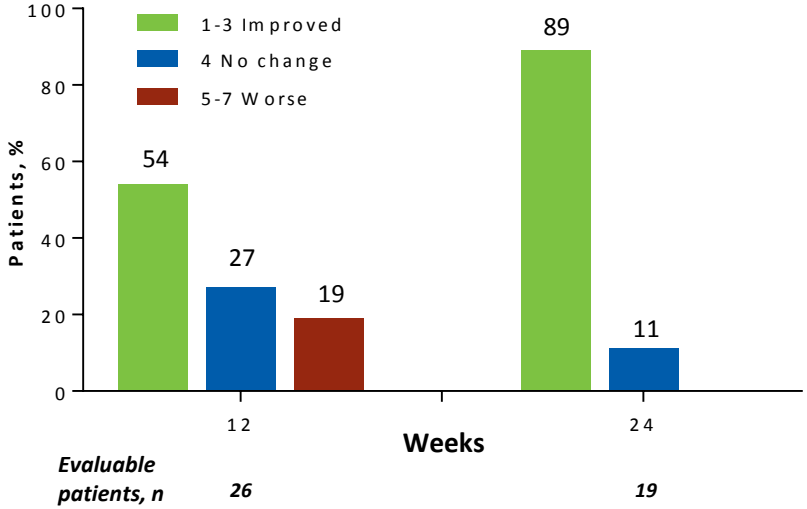


- Substantial reduction observed as early as week 4 (first assessment)
- Spleen length appears to rebound after switch from daily to weekly dosing at week 8
- Demonstrates dose response

BL, baseline; IQR, interquartile range (Q1, Q3).

Efficacy: Symptoms by MPN-SAF and Overall Well-being as Assessed by PGIC

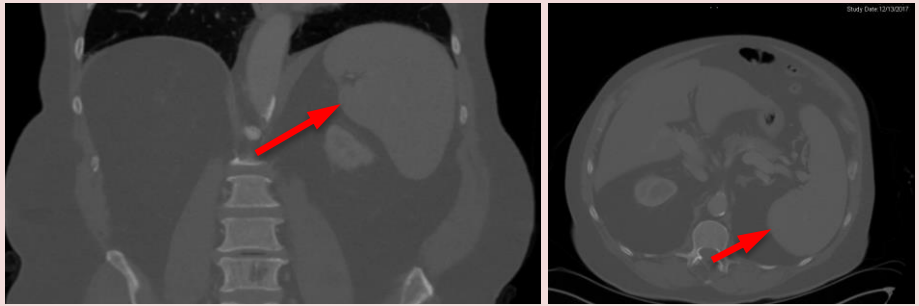




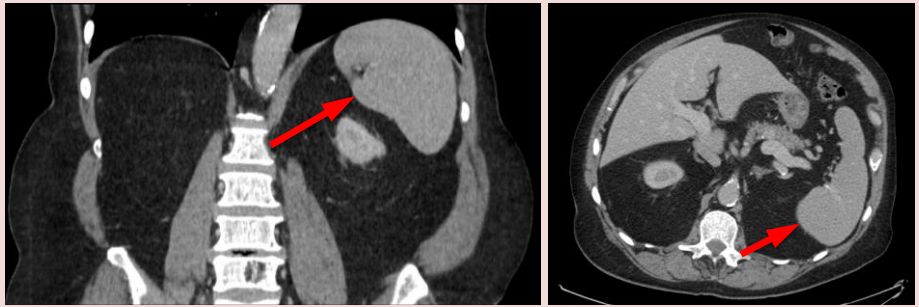
- Median (range) percent change in TSS by MPN-SAF:
  - Week 12, –14.4% (–100.0% to +50.0%)
  - Week 24, –35.9% (–88.2% to +33.3%)

PGIC uses a 7-point rating scale with 1 = “very much improved” and 7 = “very much worse.”
BL, baseline; IQR, interquartile range (Q1, Q3); MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PGIC, Patient Global Impression of Change; TSS, Total Symptom Score.

Patient A: Before and After 48 Weeks of Therapy



Study Baseline



Week 48

Baseline Characteristics

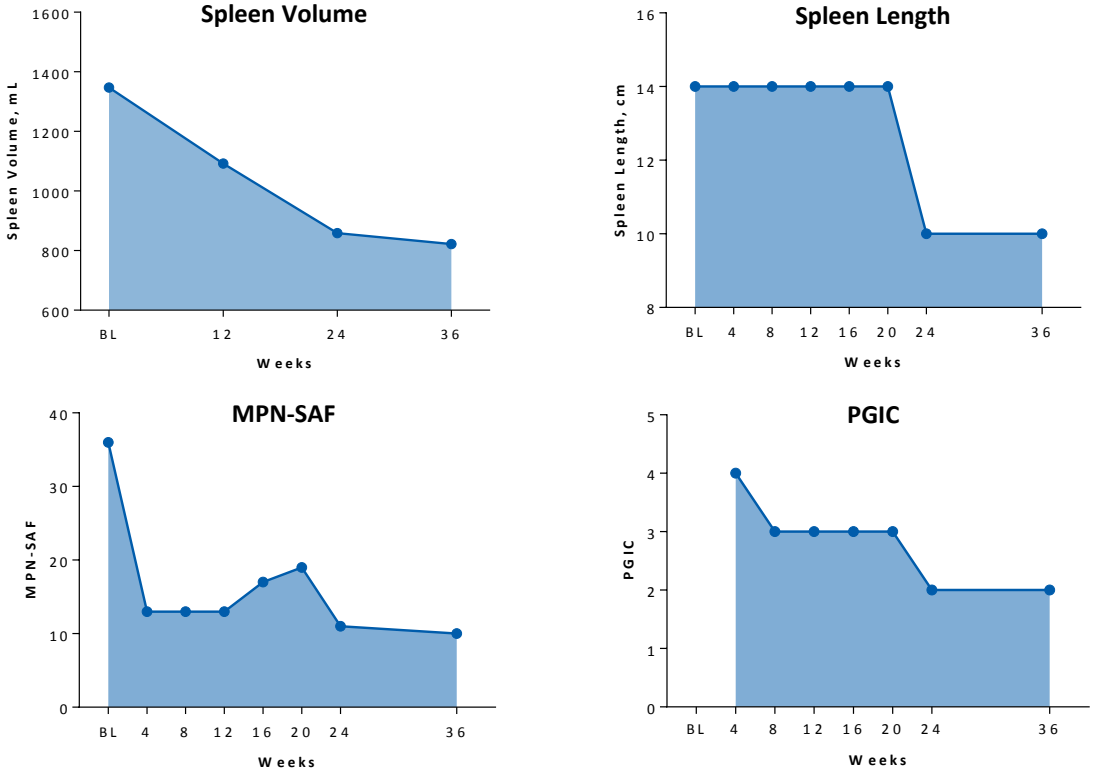
- 72-year-old man with medical history of AF, TIA, and HTN; on anti-coagulant therapy
- PV since 2005; PPV-MF in 2012; DIPSS: Intermediate-2
- Ruxolitinib therapy: 10 mg BID since May 2013, increased to 20 mg BID since May 2015 (31 months at 20 BID)
- Spleen volume: 1347 mL
- Major symptoms: fatigue, night sweats, itching, early satiety, inactivity, and difficulty concentrating

Parsaclisib + Ruxolitinib Treatment

- Began parsaclisib 20 mg QD + ruxolitinib 20 mg BID (December 20, 2017)
- Treatment with parsaclisib ongoing for ~8 months at data cutoff date
- Spleen volume: 584 mL (57% reduction) at week 48 (past data cutoff date)

AF, atrial fibrillation; BID, twice daily; DIPSS, Dynamic International Prognostic Scoring System; HTN, hypertension; IPSS, International Prognostic Scoring System; PV, polycythemia vera; PPV-MF, post-polycythemia vera myelofibrosis; QD, once daily; TIA, transient ischemic attack.

Patient A: Efficacy Parameters Over Time



BL, baseline; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; PGIC, Patient Global Impression of Change.

Conclusions and Path Forward

- Add-on therapy with parsaclisib appears to provide additional clinical benefit in patients with MF who have suboptimal responses to ruxolitinib monotherapy
  - Reduction in spleen volume in 56% of patients at week 12 and 63% of patients at week 24
  - Symptoms improved as early as 4 weeks; median symptom improvement at 24 weeks was 36%
- The combination appears to be well tolerated
  - No DLTs in Part 1 and an expected grade 3/4 AE profile
  - 17 patients on therapy >6 months, only 2 (7%) discontinuations due to AEs
  - AEs (eg, hepatic, rash, colitis) common to PI3Kδ inhibitors were infrequent
- To mitigate loss of response on switching to weekly dosing, continuous daily dosing regimens are being explored in Parts 3 and 4 of the study

Acknowledgments

- The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study
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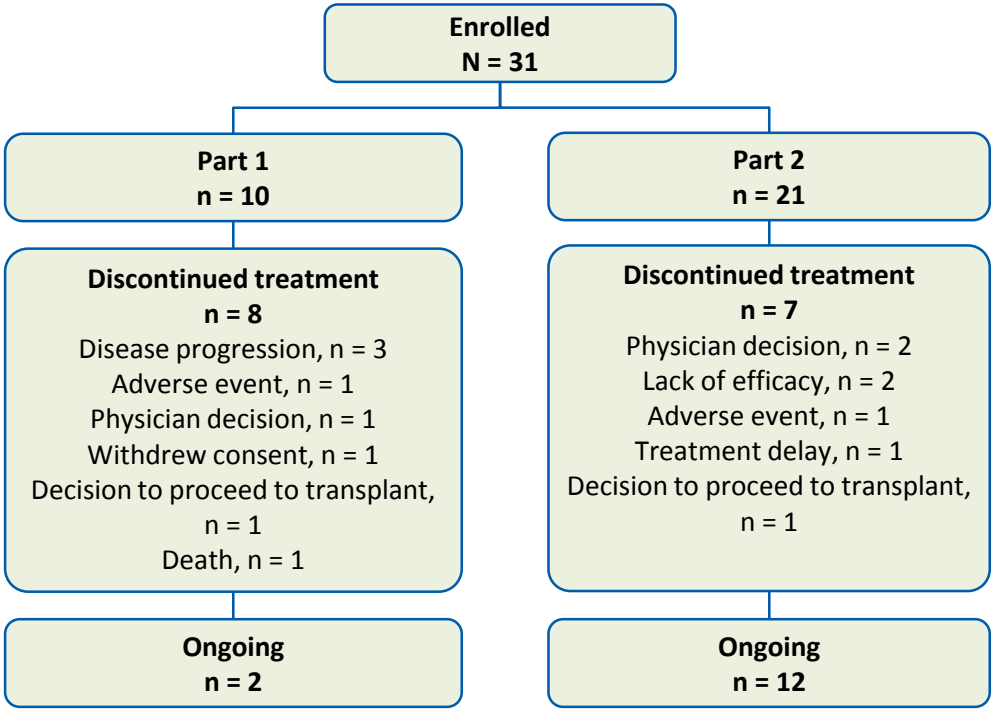
- Medical writing assistance was provided by Sneha DSilva, MD, of Evidence Scientific Solutions (Philadelphia, PA), funded by Incyte

BACKUP SLIDES

Patient Disposition



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