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by Simon T. Durrant, Arnon Nagler, Paola Guglielmelli, David Lavie, Philipp le Coutre, Heinz Gisslinger, Charles Chuah, Margherita Maffioli, Savita Bharathy, Tuochuan Dong, Monika Wroclawska, and Joaquin Martinez-Lopez

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Myelofibrosis (MF) is a myeloproliferative neoplasm characterized by bone marrow fibrosis, cytopenias, splenomegaly, and elevated proinflammatory cytokine levels. The Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway is the central pathway implicated in the pathogenesis of MF.[1,2] One of the other pathways dysregulated in MF includes the phosphatidylinositol-3-kinase (PI3K)/Akt pathway.[3] Ruxolitinib, a first-in-class JAK1/2 inhibitor (JAKi), is approved in the US and EU for treatment of MF and polycythemia vera after an inadequate response or intolerance to hydroxyurea. Buparlisib, an oral pan-PI3K inhibitor, showed favorable tolerability/efficacy profile in patients with solid tumors.[4]

Targeting multiple signaling pathways might have a synergistic therapeutic effect on the underlying pathogenesis of MF.[5] For patients who do not respond to JAKi or those who lose their response, a rational combination of other targeted agents is a promising strategy.[6,7] Preclinical data suggest that inhibition of the PI3K/mTOR pathway has beneficial effects in MF.[8-10] HARMONY, a phase 1b, 2-arm, open-label, multicenter, dose-finding study, investigated the safety and efficacy of the oral combination of ruxolitinib and buparlisib in adult patients with intermediate/high-risk primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF (*Online Supplementary Figure 1*). The maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) was established at 15 mg twice daily (bid) for ruxolitinib and 60 mg once daily (qd) for buparlisib. The dose-limiting toxicity (DLT) and adverse event (AE) profile of the combination was similar to the safety profile of the individual drugs and resulted in an overall moderate clinical benefit compared with ruxolitinib monotherapy.

Patients without prior JAKi treatment (JAKi naïve) and with prior JAKi treatment including ruxolitinib (prior JAKi) were enrolled simultaneously into the 2 arms of the study.

The study consisted of 2 periods, namely the treatment period (cycle 1 day 1 to cycle 7 day 1 [C7D1]) and treatment extension period (C7D1 to cycle 12 day 28 [C12D28]). The treatment period comprised 6 cycles of 28 days per cycle. At the end of the treatment period, on C7D1, patients benefiting from the treatment as per the investigator's discretion with no evidence of disease progression could enter the treatment extension period. Patients not meeting this criteria were discontinued from the study at the end of the treatment period. A follow-up visit was scheduled 30 days after the end-of-treatment visit (C7D1, C12D28, or premature discontinuation).

The study comprised dose-escalation and expansion phases. In the dose-escalation phase, successive cohorts of minimum 3 patients received increasing doses of ruxolitinib (5 mg bid to 40 mg bid) and

buparlisib (40 mg qd to 100 mg qd) until the MTD/RP2D was reached. An additional 6 patients were enrolled to determine a dose level as the MTD/RP2D.

The primary objective was to establish the MTD/RP2D of the combination of ruxolitinib and buparlisib in each arm as assessed by the incidence rate of DLTs. The key secondary objective was to evaluate safety. Further details of the eligibility criteria, methods, other secondary objectives, and the statistical analysis used for this study are provided in the *Online Supplementary Material*.

Sixty-three patients (46% with primary MF, 31.7% with post-polycythemia vera MF, and 22.2% with post-essential thrombocythemia MF) were enrolled in the study (JAKi naïve, n=33; prior JAKi, n=30). The baseline characteristics and patient disposition are summarized in Table 1. At baseline, prior JAKi patients had lower hemoglobin and platelet counts and a higher white blood cell count compared with JAKi-naïve patients. AEs (33.3%) were the primary reason for end of treatment. In the dose-escalation phase, dose levels included for the ruxolitinib bid/buparlisib qd combination were 10 mg/60 mg (dose level 1, n=15), 15 mg/60 mg (dose level 2, n=42), 15 mg/80 mg (dose level 3, n=3), and 20 mg/80 mg (dose level 4, n=3). The median duration of exposure to ruxolitinib at MTD was 79.5 weeks (12–167.6 weeks) and 54.6 weeks (8–151.3 weeks) in the JAKi-naïve and prior JAKi arms, respectively, and to buparlisib was 79.4 weeks (2.4–167.4 weeks) and 54.5 weeks (7.1–151.1 weeks), respectively. The analysis set per dose level is presented in *Online Supplementary Table 1*.

In the overall population, 5 patients (JAKi naïve, n=3; prior JAKi, n=2) experienced DLTs during the first 28 days; thrombocytopenia (JAKi naïve, n=2; prior JAKi, n=1), anxiety (JAKi naïve, n=1; prior JAKi, n=0), and depression (JAKi naïve, n=0; prior JAKi, n=1). MTD/RP2D was established at ruxolitinib 15 mg bid/buparlisib 60 mg qd (dose level 2) for both arms.[11] The MTD/RP2D remained the same as confirmed by the results of the expansion cohort, based on the 56 patients in the dose-determining set (Table 2).

All patients included in the safety set (n=63) experienced ≥1 AE (*Online Supplementary Table 2*). In the MTD population, anxiety, depression, dizziness, dyspnea, and stomatitis were the most common nonhematologic AEs. The most frequent all-grade hematologic AEs included thrombocytopenia (JAKi naïve, 63.6%; prior JAKi, 55.0%) and anemia (JAKi naïve, 50.0%; prior JAKi, 55.0%). Grade 3/4 thrombocytopenia was higher with prior JAKi (35.0%) compared with JAKi naïve (22.7%). Pneumonia (JAKi naïve, 9.1%; prior JAKi, 15%) and pyrexia (JAKi naïve, 4.5%; prior JAKi, 10%) were the most common serious AEs in both arms. Progression to acute myeloid leukemia was also reported (JAKi naïve, 4.5%; prior JAKi, 10%).

Primary AEs leading to study drug discontinuation in the MTD population included thrombocytopenia (n=3), anxiety (n=2), and depression (n=2) in the JAKi-naïve arm and progression to acute myeloid leukemia (n=2) in the prior JAKi arm. Dose reduction/interruptions in the JAKi-naïve arm and prior JAKi arm were due to thrombocytopenia (n=10; n=8, respectively) and anemia (n=2 in both arms).

The frequency of infections, thrombocytopenia, and psychiatric disorders were similar or slightly higher in the prior JAKi arm compared with the JAKi-naïve arm (Table 3). Seven on-treatment deaths occurred, which were not related to the study treatment (*Online Supplementary Table 3*).

At C7D1 and C12D28, proportion of MTD patients achieving ≥50% of reduction in spleen length was 12 of 16 (75.0%) and 13 of 15 (86.7%), respectively, in the JAKi-naïve arm and 6 of 17 (35.3%) and 4 of 11 (36.4%), respectively, in the prior JAKi arm. At C7D1, proportion of MTD patients in the expansion phase achieving ≥35% of reduction in spleen volume was 5 of 9 (55.6%) in the JAKi-naïve arm and 3 of 7 (42.9%) in the prior JAKi arm (*Online Supplementary Figure 2A* and *Online Supplementary Figure 2B*). Best response in spleen volume reduction in MTD patients is presented in *Online Supplementary Figure 2C*.

There was remarkable improvement in global health status/quality of life, which was more prominent in the JAKi-naïve arm than the prior JAKi arm at both C7D1 and C12D28. Improvement in the 7-day Myelofibrosis Symptom Assessment Form (MFSAF) from baseline to week 24 in both the arms is shown in *Online Supplementary Table 4*. A modest effect was observed on allele burden in both the arms. Among MTD patients, improvement in bone marrow fibrosis (n=1 in each arm), stabilization (JAKi naïve, n=2; prior JAKi, n=4), and worsening by the end of treatment (JAKi naïve, n=1) were observed. Data for overall population are presented in *Online Supplementary Table 5*. Buparlisib did not impact the pharmacokinetics of ruxolitinib (*Online Supplementary Table 6*).

To the best of our knowledge, HARMONY is the first study presenting safety and efficacy data on ruxolitinib and buparlisib combination in patients with MF. MTD for the combination was determined to be 15 mg bid for ruxolitinib and 60 mg qd for buparlisib in both JAKi-naïve and prior JAKi arms.[11] Individual MTDs were 25 mg bid for ruxolitinib and 100 mg qd for buparlisib.[12,13] In our study, MTD for the combination constituted lower doses for both the drugs when compared with the single agents. Additionally, no unexpected DLTs were observed with the combination. Thrombocytopenia, anxiety, and depression were the DLTs observed with the combination in our study, which are consistent with the known profile of these 2 drugs.[12,13] The combination was well tolerated with a manageable safety profile and provided clinically relevant efficacy. No new safety signals were observed.

Approximately, 40% of the patients had a spleen volume reduction of ≥35% with the combination in the expansion phase. With ruxolitinib alone, 41.9% of patients at week 24 in COMFORT-I and 28% of patients at week 48 in COMFORT-II achieved spleen volume reduction of ≥35%.[14,15] In our study, the anticipated synergistic effect of the combination was not observed on spleen response. The combination demonstrated a modest effect in *JAK* allele burden in both the arms, and only a few patients had improvement or stabilization in bone marrow fibrosis. However, 2 factors have to be taken into account before interpreting this data; the small sample size and short duration of the study.

Based on the modest, overall benefit-risk profile and efficacy, the ruxolitinib and buparlisib combination will not be progressed at this time.

References:

1. Keohane C, Radia DH, Harrison CN. Treatment and management of myelofibrosis in the era of JAK inhibitors. Biologics. 2013;7:189-198.
2. Rampal R, Al-Shahrour F, Abdel-Wahab O, et al. Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in myeloproliferative neoplasm pathogenesis. Blood. 2014;123(22):e123-133.
3. Bartalucci N, Guglielmelli P, Vannucchi AM. Rationale for targeting the PI3K/Akt/mTOR pathway in myeloproliferative neoplasms. Clin Lymphoma Myeloma Leuk. 2013;13 Suppl 2:S307-S309.
4. Ragon BK, Kantarjian H, Jabbour E. Buparlisib, a PI3K inhibitor, demonstrates acceptable tolerability and preliminary activity in a phase I trial of patients with advanced leukemias. Am J Hematol. 2017;92(1):7-11.
5. Bogani C, Bartalucci N, Martinelli S, et al; Associazione Italiana per la Ricerca sul Cancro AGIMM Gruppo Italiano Malattie Mieloproliferative. mTOR inhibitors alone and in combination with JAK2 inhibitors effectively inhibit cells of myeloproliferative neoplasms. PLoS One. 2013;8(1):e54826.
6. Bose P, Verstovsek S. Myelofibrosis: an update on drug therapy in 2016. Expert Opin Pharmacother. 2016;17(18):2375-2389.
7. Harrison CN, Kiladjian J, Passamonti F, et al. A phase 1b dose-finding study of ruxolitinib plus panobinostat in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis [abstract 0364]. Haematologica. 2012;97 Suppl 1:146.
8. Bartalucci N, Calabresi L, Balliu M, et al. Inhibitors of the PI3K/mTOR pathway prevent STAT5 phosphorylation in *JAK2V617F* mutated cells through PP2A/CIP2A axis. Oncotarget. 2017;8(57):96710-96724.
9. Bartalucci N, Tozzi L, Bogani C, et al. Co-targeting the PI3K/mTOR and JAK2 signalling pathways produces synergistic activity against myeloproliferative neoplasms. J Cell Mol Med. 2013;17(11):1385-1396.
10. Choong ML, Pecquet C, Pendharkar V, et al. Combination treatment for myeloproliferative neoplasms using JAK and pan-class I PI3K inhibitors. J Cell Mol Med. 2013;17(11):1397-1409.
11. Durrant S, Nagler A, Vannucchi AM, et al. An open-label, multicenter, 2-arm, dose-finding, phase 1b study of the combination of ruxolitinib and buparlisib (BKM120) in patients with myelofibrosis: results from HARMONY study. Blood. 2015;126:827.
12. Bendell JC, Rodon J, Burris HA, et al. Phase I, dose-escalation study of BKM120, an oral pan-Class I PI3K inhibitor, in patients with advanced solid tumors. J Clin Oncol. 2012;30(3):282-290.
13. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. N Engl J Med. 2010;363(12):1117-1127.
14. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012;366(9):787-798.
15. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012;366(9):799-807.

Table 1. Baseline patient characteristics and patient disposition (full analysis set)

Demographic Variable	MTD		Overall		
	JAKi naïve N=22 n (%)	Prior JAKi N=20 n (%)	JAKi naïve N=33 n (%)	Prior JAKi N=30 n (%)	Total N=63 n (%)
Age, median (range), years	63.0 (37, 83)	63.5 (50, 79)	64.0 (37, 83)	62.0 (50, 79)	63.0 (37,83)
≥65 years	9 (40.9)	10 (50.0)	14 (42.4)	13 (43.3)	27 (42.9)
Male	15 (68.2)	15 (75.0)	20 (60.6)	20 (66.7)	40 (63.5)
MF subtype					
PMF	9 (40.9)	12 (60.0)	12 (36.4)	17 (56.7)	29 (46.0)
PPV MF	9 (40.9)	5 (25.0)	12 (36.4)	8 (26.7)	20 (31.7)
PET MF	4 (18.2)	3 (15.0)	9 (27.3)	5 (16.7)	14 (22.2)
IPSS at study entry					
Intermediate 1	6 (27.3)	1 (5.0)	9 (27.3)	3 (10.0)	12 (19.0)
Intermediate 2	6 (27.3)	6 (30.0)	7 (21.2)	8 (26.7)	15 (23.8)
High risk	10 (45.5)	13 (65.0)	17 (51.5)	19 (63.3)	36 (57.1)
Outcome of previous treatment with JAKi					
Nonresponder	0	5 (25.0)	0	8 (26.7)	8 (12.7)
Suboptimal responder (<25%)	0	2 (10.0)	0	3 (10.0)	3 (4.8)
Suboptimal responder (25%–49%)	0	3 (15.0)	0	4 (13.3)	4 (6.3)
Prior spleen responder with subsequent progression	0	10 (50.0)	0	15 (50.0)	15 (23.8)
NA	22 (100.0)	0	33 (100.0)	0	33 (52.4)
Median time since diagnosis, months	6.57 (0.46, 209.71)	43.55 (9.63, 304.79)	7.852 (0.46, 209.71)	54.85 (9.63, 304.79)	31.70 (0.46, 304.79)
JAK2 V617F-positive	15 (68.2)	13 (65.0)	24 (72.7)	20 (66.7)	44 (69.8)
JAK2 V617F-positive allele burden, median (range)	73.49 (2.5, 95)	47.81 (2.5, 95)	65.24 (2.5, 95)	47.81 (2.5, 95)	52.02 (2.5, 95)
Hemoglobin, g/L, median (range)	113.5 (85, 141)	94 (71, 156)	110 (81, 144)	96.5 (71, 157)	106 (71, 157)
Platelet count, $\times 10^9$/L, median (range)	237 (113, 627)	169 (81, 939)	231 (83, 627)	159 (80, 939)	209 (80, 939)

WBC, $\times 10^9$/L, median (range)	16.5 (2.6, 90)	21.9 (3.1, 86)	17 (2.6, 199.5)	14.6 (3.1, 86)	15.9 (2.6, 199.5)
Blast percentage, median (range)	2 (0, 9)	2 (0, 6)	1 (0, 9)	2 (0, 6)	2 (0, 9)
Reason for disposition					
End of treatment	22 (100.0%)	20 (100.0%)	33 (100.0%)	30 (100.0%)	63 (100.0%)
Primary reasons for end of treatment					
Adverse event(s)	10 (45.5%)	6 (30.0%)	12 (36.4%)	9 (30.0%)	21 (33.3%)
Subject withdrew consent	2 (9.1%)	0	3 (9.1%)	1 (3.3%)	4 (6.3%)
Administrative problems	4 (18.2%)	3 (15.0%)	6 (18.2%)	4 (13.3%)	10 (15.9%)
Death	1 (4.5%)	1 (5.0%)	2 (6.1%)	1 (3.3%)	3 (4.8%)
Disease progression	2 (9.1%)	6 (30.0%)	3 (9.1%)	8 (26.7%)	11 (17.5%)
Treatment duration completed	2 (9.1%)	2 (10.0%)	4 (12.1%)	5 (16.7%)	9 (14.3%)
Lack of efficacy	1 (4.5%)	2 (10.0%)	3 (9.1%)	2 (6.7%)	5 (7.9%)
Primary reasons for study evaluation completion					
Adverse event(s)	5 (22.7%)	4 (20.0%)	7 (21.2%)	5 (16.7%)	12 (19.0%)
Subject withdrew consent	2 (9.1%)	0	2 (6.1%)	1 (3.3%)	3 (4.8%)
Administrative problems	4 (18.2%)	1 (5.0%)	5 (15.2%)	1 (3.3%)	6 (9.5%)
Death	2 (9.1%)	4 (20.0%)	3 (9.1%)	4 (13.3%)	7 (11.1%)
Disease progression	2 (9.1%)	2 (10.0%)	3 (9.1%)	3 (10.0%)	6 (9.5%)
Follow-up phase completed as per protocol	7 (31.8%)	8 (40.0%)	11 (33.3%)	15 (50.0%)	26 (41.3%)
Lack of efficacy	0	1 (5.0%)	2 (6.1%)	1 (3.3%)	3 (4.8%)

IPSS, International Prognostic Scoring System; JAKi=janus kinase inhibitor; MF=myelofibrosis; MTD=maximum tolerated dose; PET MF=post-essential thrombocythemia myelofibrosis; PMF=primary myelofibrosis; PPV MF=post-polycythemia vera myelofibrosis; WBC=white blood count.

Table 2. Dose-limiting toxicities occurring during cycle 1 (dose-determining set)

	Thrombocytopenia n (%)	Anxiety n (%)	Depression n (%)
JAKi naïve			
Dose level 1 (N=8)	1 (12.5)	0 (0.0)	0 (0.0)
Dose level 2* (N=19)	1 (5.3)	1 (5.3)	0 (0.0)
Total (N=27)	2 (7.4)	1 (3.7)	0 (0.0)
JAKi prior			
Dose level 1 (N=4)	0 (0.0)	0 (0.0)	0 (0.0)
Dose level 2* (N=19)	0 (0.0)	0 (0.0)	0 (0.0)
Dose level 3 (N=3)	0 (0.0)	0 (0.0)	0 (0.0)
Dose level 4 (N=3)	1 (33.3)	0 (0.0)	1 (33.3)
Total (N=29)	1 (3.4)	0 (0.0)	1 (3.4)

*MTD. Dose level 1, ruxolitinib 10 mg bid/buparlisib 60 mg qd; dose level 2, ruxolitinib 15 mg bid/buparlisib 60 mg qd; dose level 3, ruxolitinib 15 mg bid/buparlisib 80 mg qd; dose level 4, ruxolitinib 20 mg bid/buparlisib 80 mg qd. bid=twice weekly; JAKi=Janus kinase inhibitor; MTD=maximum tolerated dose; qd=once daily.

Table 3. Adverse events of special interest (≥30% in either arm) for ruxolitinib and buparlisib, regardless of study drug relationship by arm (safety set)

Specific safety events	All JAKi-naïve patients N=33 n (%)	All prior JAKi patients N=30 n (%)
Any specific safety event categories for ruxolitinib		
Total	32 (97.0)	29 (96.7)
Infections excluding tuberculosis	23 (69.7)	21 (70.0)
Thrombocytopenia	19 (57.6)	21 (70.0)
Anemia	16 (48.5)	14 (46.7)
Hemorrhage	15 (45.5)	14 (46.7)
Any specific safety event categories for buparlisib		
Total	33 (100)	30 (100)
Thrombocytopenia, anemia, lymphopenia, neutropenia	24 (72.7)	24 (80.0)
Nausea, vomiting diarrhea	20 (60.6)	22 (73.3)
Respiratory tract infections	15 (45.5)	17 (56.7)
Psychiatric disorders	15 (45.5)	16 (53.3)
Asthenia, fatigue	8 (24.2)	18 (60.0)
Lipase increase	11 (33.3)	15 (50.0)
Hyperglycemia	12 (36.4)	12 (40.0)
Cardiovascular events	5 (15.2)	9 (30.0)

JAKi=janus kinase inhibitor.

HARMONY Letter to the Editor Supplemental Material

Eligibility criteria

Patients were eligible to enroll in the study if they met all the following criteria at screening: intermediate or high-risk prognostic criteria, palpable splenomegaly ≥ 5 cm below the costal margin, active symptoms of MF as demonstrated by MF Screening Symptom Form, platelet counts ≥ 75 x 10^9/L not reached with the aid of transfusions and an Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2. Patients were excluded if they had received previous treatment with PI3K inhibitors, AKT inhibitors, and JAKi (including ruxolitinib) that resulted in clinically significant toxicities at the discretion of the investigator. Patients who have had splenic irradiation within 12 months prior to screening, patients with specific mood disorders, active infection, inadequate liver or renal function, history of bleeding diathesis, and patients who were ready for a stem cell transplantation at the time of the screening were excluded.

Methods

As per protocol, disease progression was defined as a spleen length increase of >40% from the baseline as assessed by palpation. The end of study had occurred after all patients in the study had completed their last assessment as per protocol. The dose escalation was guided by a Bayesian logistic regression model with overdose control, dependent on dose-limiting toxicities (DLTs) in cycle 1 and other safety findings. A DLT was defined as an adverse event (AE) or abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurs within the first 28 days.

The MTD/RP2D was defined as the dose level most closely associated with a posterior DLT probability of between 16% and 35% that does not also have a greater than 25% of probability of excessive toxicity (determined independently for both the arms). Once the MTD level was reached, patients entered in the expansion phase. In the expansion phase, an additional 10 patients in each arm, in addition to those treated at the MTD and/or RP2D during dose escalation, were treated at the respective MTD and/or RP2D for their respective arm. In total, approximately 62 patients were planned to be enrolled in dose determining set. Unless specified

otherwise, safety and efficacy data presented were by dose level, by arm, and for overall and/or MTD population.

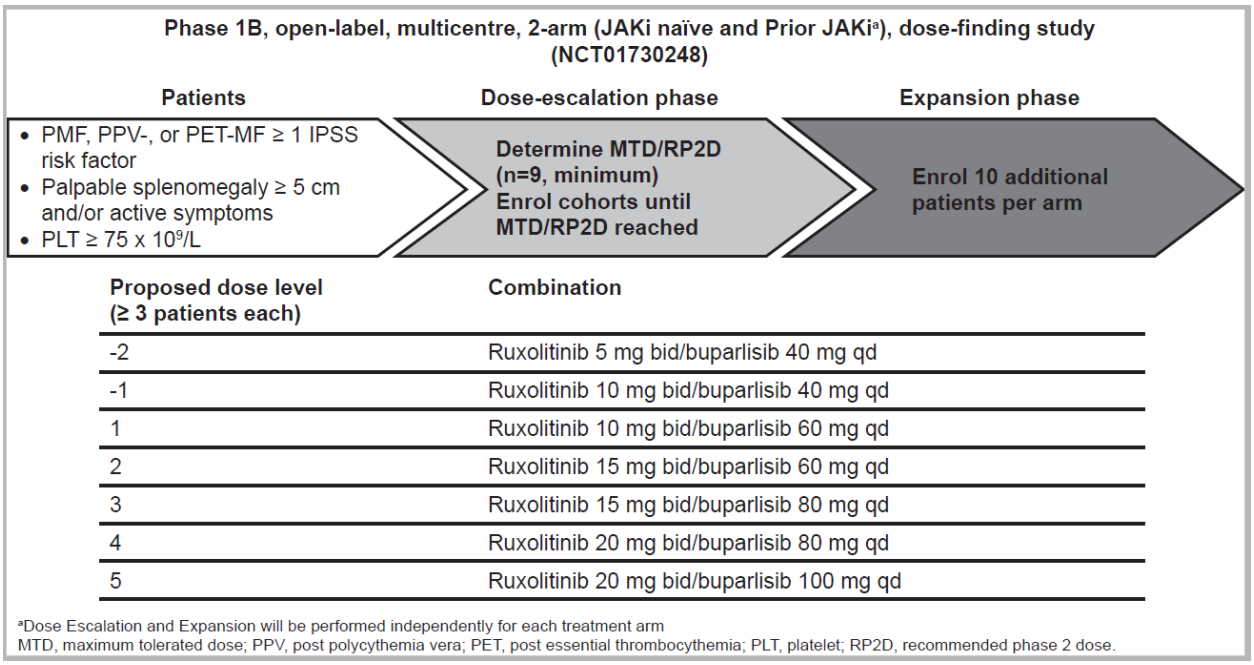
Other secondary objectives

The other secondary objective was to characterize the pharmacokinetics of ruxolitinib alone and in combination with buparlisib, as well as the pharmacokinetics of buparlisib at varying doses when given in combination in patients with MF. The exploratory objectives included estimates of efficacy (spleen length assessed by palpations and volumetric spleen size by magnetic resonance imaging [MRI]/computed tomography [CT]), changes in symptoms of MF, patient-reported outcomes, changes in transfusion dependence, potential predictive biomarkers of response to the combination, changes in markers of disease burden and symptoms, and pharmacokinetic-pharmacodynamics (PK-PD) relationship of this combination.

Statistical analysis

No formal statistical power calculations were performed to determine the sample size of this study. The full analysis set included all patients who received at least one dose of ruxolitinib or buparlisib. The safety set included all patients who received at least one dose of ruxolitinib or buparlisib, and had at least one valid post-baseline safety assessment. The dose-determining set consisted of all patients from the safety set who either met a minimum exposure criterion (received ≥80% of twice daily doses of ruxolitinib and ≥80% of planned daily doses of buparlisib) and had sufficient safety evaluations during cycle 1 or experienced a DLT during cycle 1. The pharmacokinetic (PK) analysis set consisted of all patients who had at least one blood sample providing evaluable PK data. The study was not adequately powered to assess the specific biomarker-related hypotheses; thus, statistical analyses of these data should be considered to be exploratory in nature.

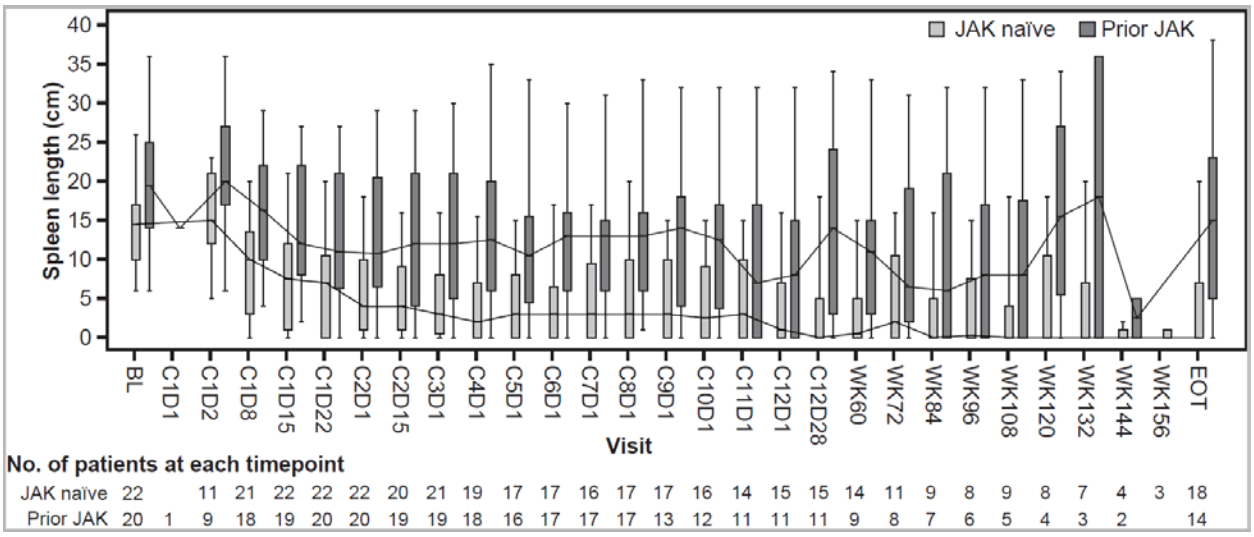
Supplementary Figure 1. Study design and dose levels



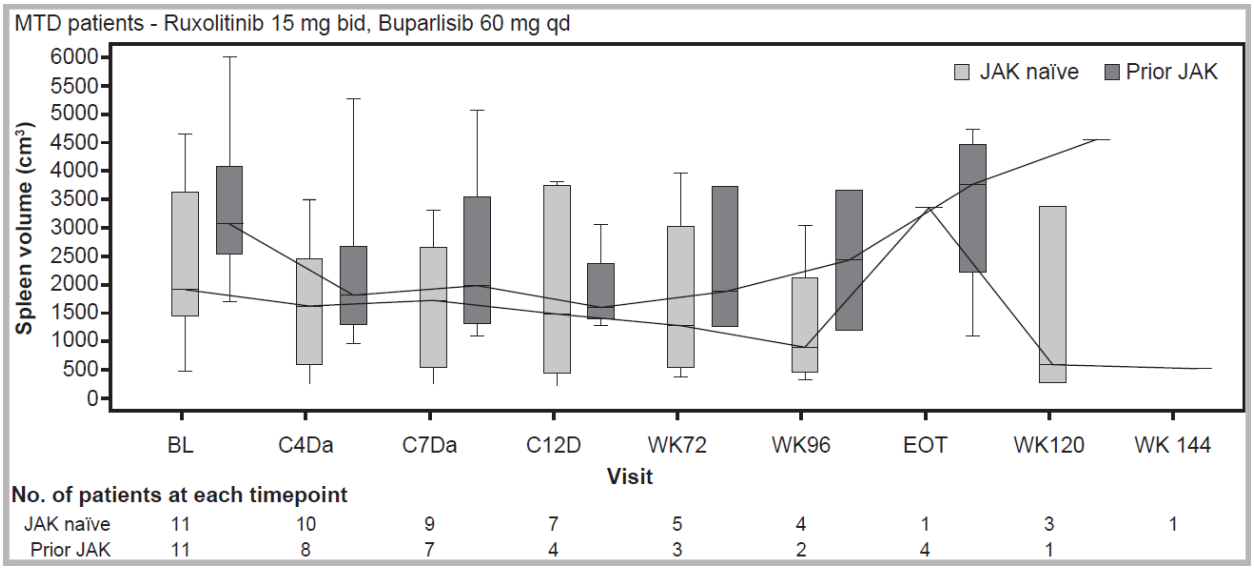
Proposed dose level (≥ 3 patients each)	Combination
-2	Ruxolitinib 5 mg bid/buparlisib 40 mg qd
-1	Ruxolitinib 10 mg bid/buparlisib 40 mg qd
1	Ruxolitinib 10 mg bid/buparlisib 60 mg qd
2	Ruxolitinib 15 mg bid/buparlisib 60 mg qd
3	Ruxolitinib 15 mg bid/buparlisib 80 mg qd
4	Ruxolitinib 20 mg bid/buparlisib 80 mg qd
5	Ruxolitinib 20 mg bid/buparlisib 100 mg qd

[a]Dose Escalation and Expansion will be performed independently for each treatment arm
MTD, maximum tolerated dose; PPV, post polycythemia vera; PET, post essential thrombocythemia; PLT, platelet; RP2D, recommended phase 2 dose.

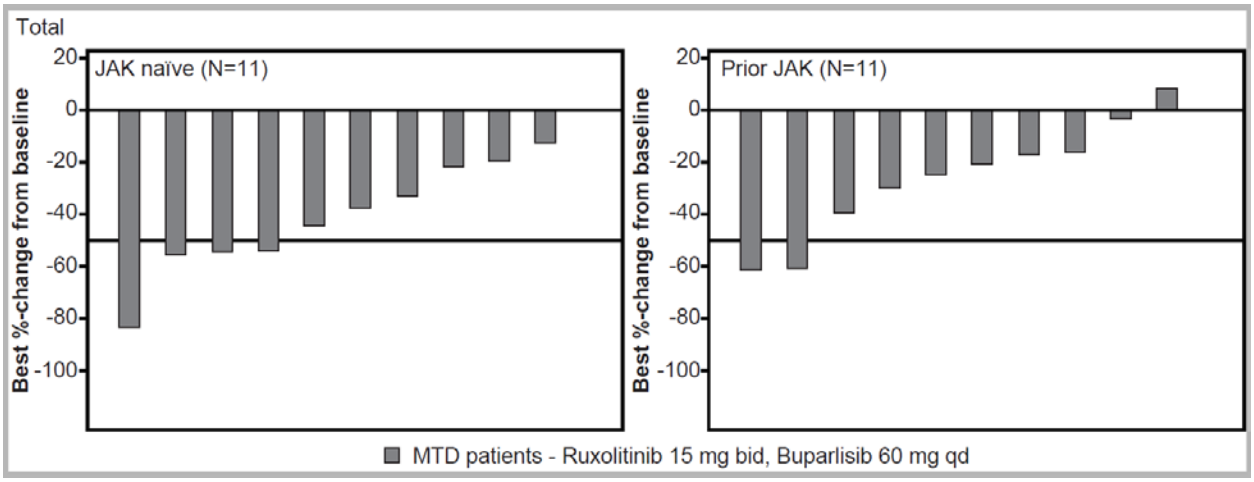
Supplementary Figure 2. (A) Box plot for spleen length in MTD patients (Ruxolitinib 15 mg bid, Buparlisib 60 mg qd)



Supplementary Figure 2. (B) Box plot for spleen volume in MTD patients (Ruxolitinib 15 mg bid, Buparlisib 60 mg qd)



Supplementary Figure 2. (C) Best response in spleen volume (cm^3) by arm (Expansion patients in Full analysis set)



	JAK naïve	Prior JAK
Decrease in best percentage change from baseline	90.9% (10)	81.8% (9)
Increase in best percentage change from baseline	0.0% (0)	9.1% (1)
No change from baseline	0.0% (0)	0.0% (0)
Missing post-baseline assessments	9.1% (1)	9.1% (1)
N is the number of patients in Full Analysis Set. Percentages above use N as denominator.		

Supplementary Table 1. Analysis set

	Dose level 1 N=15 n (%)	Dose level 2* N=42 n (%)	Dose level 3 N=3 n (%)	Dose level 4 N=3 n (%)	All patients N=63 n (%)
Full analysis set	15 (100)	42 (100)	3 (100)	3 (100)	63 (100)
JAKi naïve	11 (73·3)	22 (52·4)			33 (52·4)
Prior JAKi	4 (26·7)	20 (47·6)	3 (100)	3 (100)	30 (47·6)
Safety set	15 (100)	42 (100)	3 (100)	3 (100)	63 (100)
JAKi naïve	11 (73·3)	22 (52·4)			33 (52·4)
Prior JAKi	4 (26·7)	20 (47·6)	3 (100)	3 (100)	30 (47·6)
Dose-determining set	12 (80.0)	38 (90·5)	3 (100)	3 (100)	56 (88·9)
JAKi naïve	8 (53·3)	19 (45·2)			27 (42·9)
Prior JAKi	4 (26·7)	19 (45·2)	3 (100)	3 (100)	29 (46·0)
Pharmacokinetic analysis set	15 (100)	42 (100)	3 (100)	3 (100)	63 (100)
JAKi naïve	11 (73·3)	22 (52·4)			33 (52·4)
Prior JAKi	4 (26·7)	20 (47·6)	3 (100)	3 (100)	30 (47·6)

*Maximum tolerated dose (MTD). Dose level 1, ruxolitinib 10 mg bid/buparlisib 60 mg qd; dose level 2, ruxolitinib 15 mg bid/buparlisib 60 mg qd; dose level 3, ruxolitinib 15 mg bid/buparlisib 80 mg qd; dose level 4, ruxolitinib 20 mg bid/buparlisib 80 mg qd. JAKi=Janus kinase inhibitor.

Supplementary Table 2. Adverse events (≥10% cut off for all grades at MTD in the respective arm), regardless of study drug relationship per dose level and arm (safety set)

(A) JAKi naïve

	Dose level 1 N=11 n (%)		Dose level 2* N=22 n (%)	
	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)
Total	11 (100)	9 (81.8)	22 (100)	16 (72.7)
Thrombocytopenia	3 (27.3)	2 (18.2)	14 (63.6)	5 (22.7)
Anemia	5 (45·5)	5 (45·5)	11 (50.0)	5 (22.7)
Anxiety	2 (18.2)	1 (9.1)	6 (27.3)	3 (13.6)
Diarrhea	0 (0.0)	0 (0.0)	5 (22.7)	0 (0.0)
Dizziness	1 (9.1)	0 (0.0)	5 (22.7)	0 (0.0)
Asthenia	0 (0.0)	0 (0.0)	4 (18.2)	1 (4.5)
Decreased appetite	0 (0.0)	0 (0.0)	4 (18.2)	0 (0.0)
Depression	0 (0.0)	0 (0.0)	4 (18.2)	1 (4.5)
Dyspnea	1 (9.1)	1 (9.1)	4 (18.2)	1 (4.5)
Hematoma	1 (9.1)	0 (0.0)	4 (18.2)	0 (0.0)
Abdominal pain	1 (9.1)	0 (0.0)	3 (13.6)	0 (0.0)
Upper Abdominal pain	1 (9.1)	0 (0.0)	3 (13.6)	0 (0.0)
Epistaxis	2 (18.2)	0 (0.0)	3 (13.6)	1 (4.5)
Fatigue	1 (9.1)	0 (0.0)	3 (13.6)	0 (0.0)
Nausea	1 (9.1)	0 (0.0)	3 (13.6)	0 (0.0)
Night sweats	0 (0.0)	0 (0.0)	3 (13.6)	0 (0.0)
Decreased platelet count	0 (0.0)	0 (0.0)	3 (13.6)	1 (4.5)
Pneumonia	1 (9.1)	0 (0.0)	3 (13.6)	2 (9.1)
Pruritus	1 (9.1)	0 (0.0)	3 (13.6)	0 (0.0)
Stomatitis	1 (9.1)	0 (0.0)	3 (13.6)	1 (4.5)
Urinary tract infection	3 (27.3)	0 (0.0)	3 (13.6)	0 (0.0)

(B) Prior JAKi

	Dose level 1 N=4 n (%)		Dose level 2* N=20 n (%)		Dose level 3 N=3 n (%)		Dose level 4 N=3 n (%)	
	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)	All grades n (%)	Grade 3 or 4 n (%)
Total	4 (100)	3 (75·0)	20 (100)	16 (80.0)	3 (100)	3 (100)	3 (100)	3 (100)
Anemia	1 (25.0)	0 (0.0)	11 (55·0)	8 (40.0)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)
Thrombocytopenia	4 (100)	3 (75·0)	11 (55·0)	7 (35·0)	3 (100)	1 (33.3)	1 (33.3)	1 (33.3)
Pyrexia	0 (0.0)	0 (0.0)	10 (50.0)	2 (10.0)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)
Abdominal pain	0 (0.0)	0 (0.0)	8 (40.0)	1 (5·0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Diarrhea	2 (50.0)	0 (0.0)	8 (40.0)	1 (5·0)	2 (66.7)	0 (0.0)	1 (33.3)	1 (33.3)
Cough	0 (0.0)	0 (0.0)	8 (40.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Peripheral edema	0 (0.0)	0 (0.0)	7 (35·0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Dyspnea	1 (25.0)	0 (0.0)	6 (30.0)	1 (5·0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Fatigue	1 (25.0)	0 (0.0)	6 (30.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Asthenia	3 (75·0)	0 (0.0)	5 (25.0)	2 (10.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Upper respiratory tract infection	1 (25.0)	0 (0.0)	5 (25.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Decreased appetite	1 (25.0)	0 (0.0)	4 (20.0)	1 (5·0)	2 (66.7)	1 (33.3)	2 (66.7)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	4 (20.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Epistaxis	1 (25.0)	0 (0.0)	4 (20.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Pneumonia	0 (0.0)	0 (0.0)	3 (15.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Back pain	0 (0.0)	0 (0.0)	3 (15.0)	1 (5·0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Blood creatinine increased	0 (0.0)	0 (0.0)	3 (15.0)	1 (5·0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperglycemia	0 (0.0)	0 (0.0)	3 (15.0)	1 (5·0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)
Hyperuricemia	1 (25.0)	0 (0.0)	3 (15.0)	1 (5·0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pruritus	1 (25.0)	0 (0.0)	3 (15.0)	1 (5·0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Dizziness	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Oropharyngeal pain	1 (25.0)	0 (0.0)	3 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Respiratory tract infection	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Vomiting	0 (0.0)	0 (0.0)	3 (15.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	0 (0.0)
Acute myeloid leukaemia	0 (0.0)	0 (0.0)	2 (10.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	2 (10.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	2 (10.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Generalised oedema	0 (0.0)	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hyperkalaemia	0 (0.0)	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Hypocalcaemia	1 (25.0)	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	1 (25.0)	0 (0.0)	2 (10.0)	1 (5.0)	1 (33.3)	0 (0.0)	2 (66.7)	0 (0.0)
Renal impairment	0 (0.0)	0 (0.0)	2 (10.0)	1 (5.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	1 (25.0)	0 (0.0)	2 (10.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Aspartate aminotransferase increased	1 (25.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Blood glucose increased	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Bone pain	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Dehydration	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Depressed mood	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	2 (66.7)	1 (33.3)	0 (0.0)	0 (0.0)
Early satiety	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Fluid overload	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hematoma	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Hepatomegaly	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	1 (33.3)	0 (0.0)		0 (0.0)
Insomnia	1 (25.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	2(66.7)	0 (0.0)
Lethargy	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Localized edema	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Muscle spasm	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)
Night sweats	3 (75.0)	0 (0.0)	2 (10.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)
Petechiae	1 (25.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pharyngitis	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rash	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Viral upper respiratory tract infection	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)

Weight decreased	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Weight increased	0 (0.0)	0 (0.0)	2 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*MTD. Dose level 1, ruxolitinib 10 mg bid/buparlisib 60 mg qd; dose level 2, ruxolitinib 15 mg bid/buparlisib 60 mg qd; dose level 3, ruxolitinib 15 mg bid/buparlisib 80 mg qd; dose level 4, ruxolitinib 20 mg bid/buparlisib 80 mg qd. JAKi=Janus kinase inhibitor; MTD=maximum tolerated dose; NR=not reported.

Supplementary Table 3. On-treatment deaths (safety set)

	JAKi-naïve		Prior JAKi[a] dose level 2* N=20 n (%)	All patients N=63 n (%)
	Dose level 1 N=11 n (%)	Dose level 2* N=22 n (%)		
Total	1 (9.1)	2 (9.1)	4 (20.0)	7 (11·1)
Acute myeloid leukemia	0 (0.0)	0 (0.0)	1 (5.0)	1 (1·6)
Myeloid leukemia	0 (0.0)	0 (0.0)	1 (5.0)	1 (1·6)
Leukemia	0 (0.0)	1 (4.5)	0 (0.0)	1 (1·6)
Intracranial hemorrhage	0 (0.0)	0 (0.0)	1 (5·0)	1 (1·6)
Congestive cardiac failure	0 (0.0)	1 (4.5)	0 (0.0)	1 (1·6)
Duodenal ulcer hemorrhage	1 (9.1)	0 (0.0)	0 (0.0)	1 (1·6)
Multiple organ dysfunction syndrome	0 (0.0)	0 (0.0)	1 (5·0)	1 (1·6)

[a]No deaths were reported in prior JAKi dose level 1, 3, 4 cohorts. *MTD. Dose level 1, ruxolitinib 10 mg bid/buparlisib 60 mg qd; dose level 2, ruxolitinib 15 mg bid/buparlisib 60 mg qd; dose level 3, ruxolitinib 15 mg bid/buparlisib 80 mg qd; dose level 4, ruxolitinib 20 mg bid/buparlisib 80 mg qd. JAKi=Janus kinase inhibitor; MTD=maximum tolerated dose.

Supplementary Table 4. Proportion of patients achieving at least 50% reduction from baseline in total symptom scores of seven day MFSAF (Full analysis set)

	MTD in JAKi-naïve arm (N=22)	MTD in prior JAK arm (N=20)
n at Week 24	17	17
Number of patients achieving ≥50% reduction in TSS at Week 24, n (%)	12 (70.6)	12 (70.6)
95% CI of the response rate	(44.0, 89.7)	(44.0, 89.7)

N only included patients that had a valid baseline assessment. N at Week 24 include patients that had Daily Total Scores at Week 24.

Supplementary Table 5. Shift table for bone marrow fibrosis grade by arm in the overall population (Full analysis set)

Time	Post-baseline fibrosis grading	JAK naïve N=33 Baseline fibrosis grade, n (%)					Prior JAKi N=30 Baseline fibrosis grade, n (%)				
		0	1	2	3	Missing	0	1	2	3	Missing
Cycle 7 day 1	0	0 (0.0)	2 (6·1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3·3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	2 (6·1)	0 (0.0)	0 (0.0)	1 (3·3)	0 (0.0)	0 (0.0)	0 (0.0)
	2	1 (3·0)	0 (0.0)	6 (18.2)	1 (3·0)	0 (0.0)	0 (0.0)	1 (3·3)	1 (3·3)	2 (6·7)	0 (0.0)
	3	0 (0.0)	1 (3·0)	1 (3·0)	5 (15·2)	1 (3·0)	0 (0.0)	0 (0.0)	0 (0.0)	10 (33.3)	0 (0.0)
	Missing	1 (3·0)	1 (3·0)	5 (15·2)	4 (12·1)	2 (6·1)	0 (0.0)	2 (6·7)	4 (13·3)	6 (20.0)	2 (6·7)
Week 96	0	0 (0.0)	0 (0.0)	0 (0.0)	1 (3·0)	0 (0.0)	0 (0.0)	1 (3·3)	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	1 (3·0)	0 (0.0)	0 (0.0)	1 (3·0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	1 (3·0)	0 (0.0)	2 (6·1)	0 (0.0)	0 (0.0)	1 (3·3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3·3)
	3	0 (0.0)	0 (0.0)	1 (3·0)	2 (6·1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (16·7)	0 (0.0)
	Missing	1 (3·0)	3 (9.1)	9 (27.3)	9 (27.3)	2 (6·1)	0 (0.0)	3 (10.0)	5 (16·7)	13 (43·3)	1 (3·3)
EOT	0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	1	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	2	0 (0.0)	1 (3·0)	0 (0.0)	2 (6·1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (3·3)	0 (0.0)
	3	0 (0.0)	0 (0.0)	1 (3·0)	2 (6·1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (16·7)	0 (0.0)
	Missing	2 (6·1)	3 (9.1)	11 (33.3)	8 (24·2)	3 (9.1)	1 (3·3)	4 (13·3)	5 (16·7)	12 (40.0)	2 (6·7)

In the above figure, the green color indicates improvement; the orange color indicates stabilization, and the red color indicates worsening of bone marrow fibrosis. EOT=end of treatment; JAKi=Janus kinase inhibitor.

Supplementary Table 6. Summary of (A) ruxolitinib and (B) buparlisib pharmacokinetics

A) Ruxolitinib pharmacokinetics

PK parameter		Dose level 1 N=15	Dose level 2* N=42	Dose level 3 N=3	Dose level 4 N=3
AUC_{last} (h*ng/mL)	N	12	24	3	2
	Mean (SD)	435 (165)	564 (195)	550 (112)	1040 (55.3)
	Median (range)	399 (218, 797)	510 (264, 950)	507 (466, 677)	1040 (1000, 1080)
C_{max} (ng/mL)	N	12	24	3	2
	Mean (SD)	136 (37.1)	189 (51.2)	231 (49.7)	383 (158)
	Median (range)	139 (77.3, 189)	178 (97.2, 293)	205 (199, 288)	383 (271, 494)
T_{max} (h)	N	12	24	3	2
	Median (range)	1.00 (0, 1.50)	1.00 (0.417, 2.05)	0.500 (0.500, 0.517)	1.50 (1.50, 1.50)

B) Buparlisib pharmacokinetics

PK parameter		Dose level 1 N=15	Dose level 2* N=42	Dose level 3 N=3	Dose level 4 N=3
AUC_{last} (h*ng/mL)	N	12	19	3	3
	Mean (SD)	3630 (1270)	3100 (1420)	5660 (1440)	4630 (738)
	Median (range)	3530 (2190, 6600)	3010 (563, 5670)	4900 (4760, 7320)	4650 (3890, 5360)
C_{max} (ng/mL)	N	12	19	3	3
	Mean (SD)	444 (160)	414 (208)	564 (185)	579 (319)
	Median (range)	416 (241, 724)	360 (113, 870)	485 (432, 776)	488 (315, 934)
T_{max} (h)	N	12	19	3	3
	Median (range)	1.73 (0.50, 2.05)	1.00 (0.50, 24.0)	1.50 (1.00, 1.98)	2.00 (1.00, 4.15)

Maximum tolerated dose (MTD). Dose level 1, ruxolitinib 10 mg bid/buparlisib 60 mg qd; dose level 2, ruxolitinib 15 mg bid/buparlisib 60 mg qd; dose level 3, ruxolitinib 15 mg bid/buparlisib 80 mg qd; dose level 4, ruxolitinib 20 mg bid/buparlisib 80 mg qd.