Results from HARMONY: an open-label, multicenter, 2-arm, phase 1b, dose-finding study assessing the safety and efficacy of the oral combination of ruxolitinib and buparlisib in patients with myelofibrosis

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doi:10.3324/haematol.2018.209965

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.

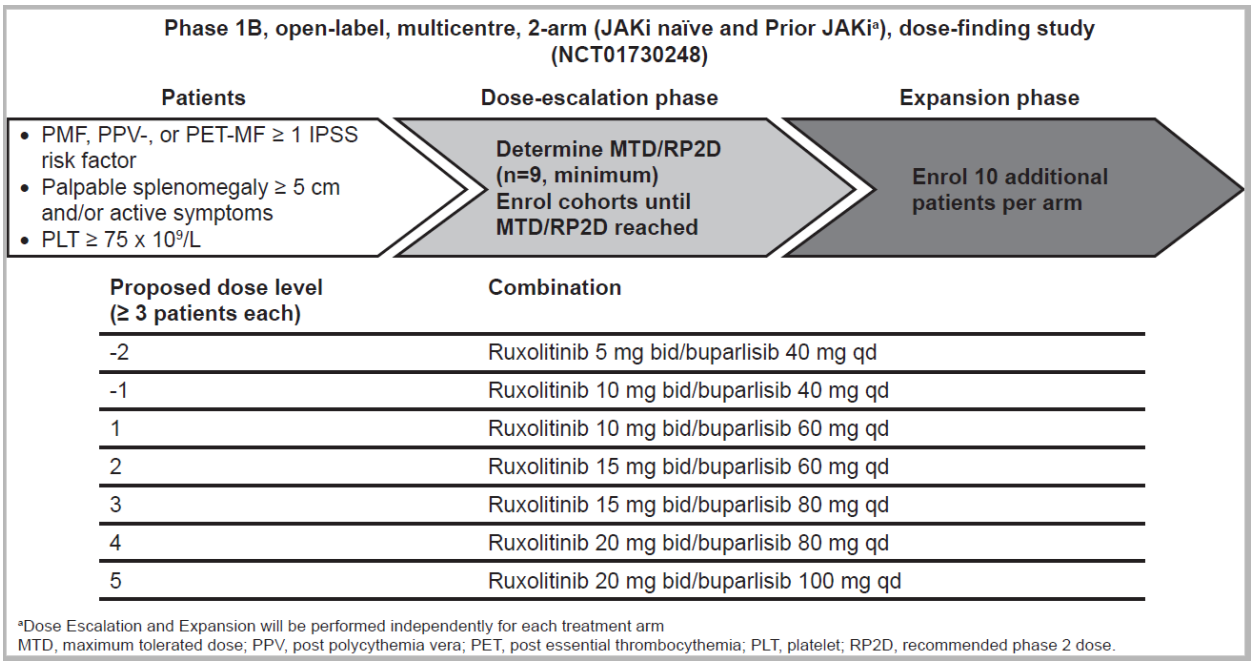
Other secondary objectives

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.

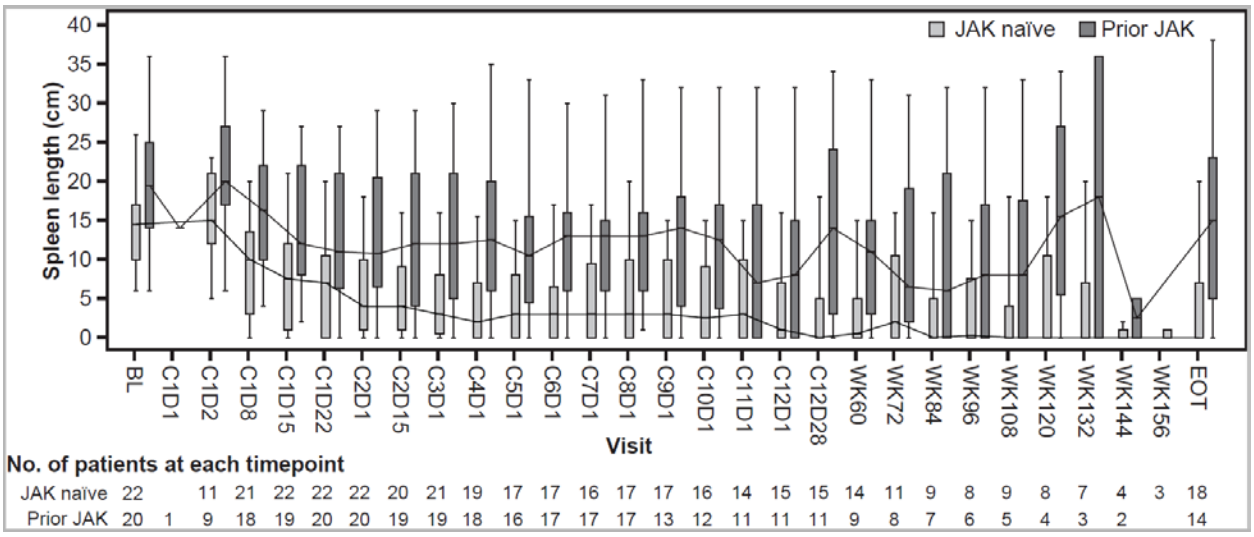
Supplementary Figure 1. Study design and dose levels



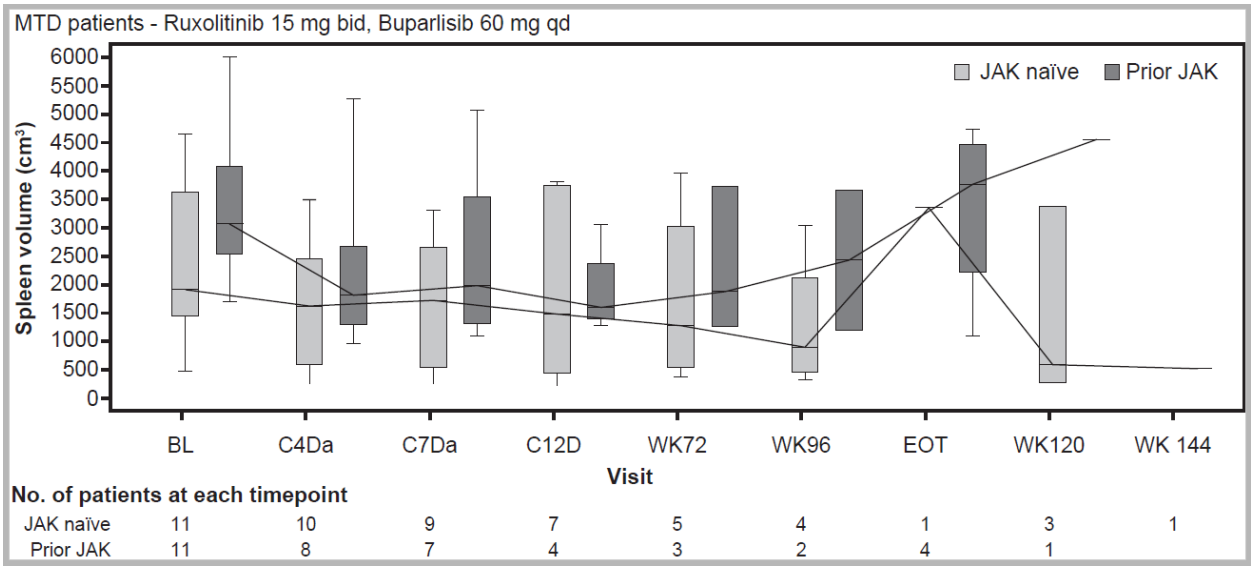
Proposed dose level (≥ 3 patients each)	Combination
-2	Ruxolitinib 5 mg bid/buparlisib 40 mg qd
-1	Ruxolitinib 10 mg bid/buparlisib 40 mg qd
1	Ruxolitinib 10 mg bid/buparlisib 60 mg qd
2	Ruxolitinib 15 mg bid/buparlisib 60 mg qd
3	Ruxolitinib 15 mg bid/buparlisib 80 mg qd
4	Ruxolitinib 20 mg bid/buparlisib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

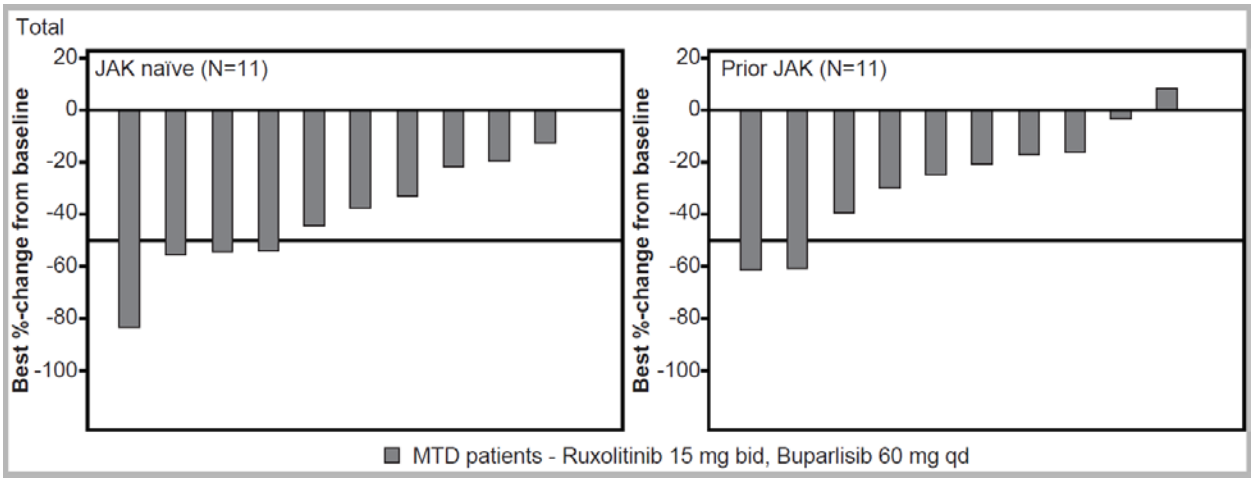
Supplementary Figure 2. (A) Box plot for spleen length in MTD patients (Ruxolitinib 15 mg bid, Buparlisib 60 mg qd)



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.