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Primary analysis of JUMP, a phase 3b, expanded-access study evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis, including those with low platelet counts

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Summary

Ruxolitinib is a potent Janus kinase (JAK) 1/JAK2 inhibitor approved for the treatment of myelofibrosis (MF). Ruxolitinib was assessed in JUMP, a large (N = 2233), phase 3b, expanded-access study in MF in countries without access to ruxolitinib outside a clinical trial, which included patients with low platelet counts (<100 × 10^9/l) and patients without splenomegaly – populations that have not been extensively studied. The most common adverse events (AEs) were anaemia and thrombocytopenia, but they rarely led to discontinuation (overall, 5·4%; low-platelet cohort, 12·3%). As expected, rates of worsening thrombocytopenia were higher in the low-platelet cohort (all grades, 73·2% vs. 53·5% overall); rates of anaemia were similar (all grades, 52·9% vs. 59·5%). Non-haematologic AEs, including infections, were mainly grade 1/2. Overall, ruxolitinib led to meaningful reductions in spleen length and symptoms, including in patients with low platelet counts, and symptom improvements in patients without splenomegaly. In this trial, the largest study of ruxolitinib in patients with MF to date, the safety profile was consistent with previous reports, with no new safety concerns identified. This study confirms findings from the COMFORT studies and supports the use of ruxolitinib in patients with platelet counts of 50–100 × 10^9/l. (ClinicalTrials.gov identifier NCT01493414).

Keywords: myelofibrosis, ruxolitinib, safety, splenomegaly, symptoms.

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Myelofibrosis (MF) is a chronic myeloproliferative neoplasm that can present as primary disease or evolve from polycythaemia vera (postpolycythaemia vera MF) or essential thrombocythaemia (postessential thrombocythaemia MF) (Tefferi, 2016; Iurlo & Cattaneo, 2017; Rumi & Cazzola, 2017). MF is associated with overactivation of the Janus kinase (JAK) signalling pathway, which can arise as a result of several somatic mutations. *JAK2* V617F is the most common mutation, detected in 50% to 60% of all patients with MF (Tefferi, 2014; Iurlo & Cattaneo, 2017). Bone marrow fibrosis, extramedullary haematopoiesis, anaemia, splenomegaly and constitutional symptoms (weight loss, night sweats, fever) are common clinical manifestations of the disease (Tefferi, 2016; Iurlo & Cattaneo, 2017; Rumi & Cazzola, 2017). The symptom burden is severe, with fatigue being the most frequently reported symptom (Emanuel *et al.*, 2012; Geyer *et al.*, 2014; Mesa *et al.*, 2016; Harrison *et al.*, 2017). Additionally, patients experience shorter survival (Cervantes *et al.*, 2009), with an estimated median overall survival (OS) of 5·7 years (Cervantes *et al.*, 2009). Patients are stratified as low, intermediate-1 (Int-1), intermediate-2 (Int-2), or high risk based on the International Prognostic Scoring System (IPSS), with corresponding median survival of 11, 8, 4 and 2 years respectively (Cervantes *et al.*, 2009; Tefferi, 2016).

Ruxolitinib is a potent JAK1/JAK2 inhibitor and the first JAK inhibitor approved for the treatment of MF. The European Commission approved ruxolitinib for the treatment of disease-related splenomegaly or symptoms in adults with primary MF, postpolycythaemia vera MF, or postessential thrombocythaemia MF, regardless of prognostic risk (Jakavi (ruxolitinib), 2016). In the United States, ruxolitinib is approved for patients with intermediate- or high-risk MF (Jakafi (ruxolitinib), 2017). Approvals were based on the findings from the pivotal phase 3 Controlled Myelofibrosis Study With Oral JAK Inhibitor Treatment (COMFORT) trials, in which ruxolitinib proved superior to placebo (COMFORT-I) (Verstovsek *et al.*, 2012; Verstovsek *et al.*, 2017b) and best available therapy (COMFORT-II) (Harrison *et al.*, 2012; Cervantes *et al.*, 2013; Harrison *et al.*, 2016). In these studies, ruxolitinib demonstrated durable improvements in splenomegaly, MF-related symptoms and quality-of-life measures. Additionally, *post-hoc* analyses of OS in the COMFORT studies demonstrated a survival benefit associated with ruxolitinib treatment compared with conventional therapies (Cervantes *et al.*, 2013; Vannucchi *et al.*, 2015; Harrison *et al.*, 2016; Verstovsek *et al.*, 2017a).

The JAK Inhibitor RUxolitinib in Myelofibrosis Patients (JUMP) study, a phase 3b, expanded-access trial, is the largest and most expansive clinical trial in patients with MF treated with ruxolitinib to date, and patients were enrolled and treated in a setting similar to routine clinical practice (Al-Ali *et al.*, 2016). Here, we present the primary analysis of JUMP, which includes safety and efficacy results for all 2233 patients as well as a subgroup analysis of 138 patients with low platelet counts ($<100 \times 10^9$/l) at baseline treated in this study.

Patients and methods

Study design

JUMP is a global, single-arm, open-label, phase 3b, expanded-access study for patients in countries without access to ruxolitinib outside a clinical study. Patients aged ≥18 years with a diagnosis of primary or secondary MF by World Health Organization and International Working Group for Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria (Barosi *et al.*, 2008; Vardiman *et al.*, 2009) and classified by the treating investigator as high, Int-2, or Int-1 risk using IPSS criteria (Cervantes *et al.*, 2009) were eligible. Int-1-risk patients were required to have palpable splenomegaly ≥5 cm from the costal margin, but patients with Int-2- or high-risk MF could enrol regardless of spleen size. Patients were required to have a baseline platelet count of $\geq 50 \times 10^9$/l, with patients with platelet counts of ≥50 to $<75 \times 10^9$/l and ≥75 to $<100 \times 10^9$/l being incorporated through amendments to the protocol. To allow for comparisons between MF populations, the dynamic IPSS (DIPSS) was also used to calculate risk scores. DIPSS scores were determined using patient characteristics at baseline.

Protocol starting doses of ruxolitinib were based on platelet counts at baseline: 5 mg twice daily (bid; ≥50 to $<100 \times 10^9$/l), 15 mg bid (100–200 $\times 10^9$/l), or 20 mg bid ($>200 \times 10^9$/l). Although not per protocol, some patients started ruxolitinib treatment at other doses, including 10 mg bid. Over the course of treatment, the dose of ruxolitinib was titrated for each patient to a maximum dose of 25 mg bid, depending on safety and efficacy. Dose reductions or interruptions were mandated for safety reasons (e.g., decreasing platelet counts) and were determined using a protocol-specified dosing regimen. Patients were treated for up to 24 months after the last patient's first visit (December 23, 2014) unless discontinuation criteria (i.e., disease progression, unacceptable toxicity, death, discontinuation from the study for any other reason, physician decision, or withdrawal of informed consent) were met or the drug became commercially available. Patients were followed up for 28 days after the end-of-treatment visit (no data were collected for patients beyond the follow-up visit, including for those who transitioned to commercial ruxolitinib). The full details of the study design and patient enrolment criteria have been described previously (Al-Ali *et al.*, 2016).

The study was sponsored and designed by Novartis Pharmaceuticals Corporation (Novartis) in collaboration with an expert steering committee. The study was approved by the institutional review boards of the respective institutions before patient enrolment and was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent. An expert steering committee interpreted the data in collaboration with Novartis and provided recommendations for publication. All authors analysed the data, reviewed and amended the manuscript and take responsibility for the accuracy and completeness of the data. The trial (Protocol CINC424A2401) is registered with ClinicalTrials.gov (NCT01493414).

Endpoints

The primary endpoint was assessment of ruxolitinib safety and tolerability by the frequency, duration and severity of adverse events (AEs). Only descriptive statistics are provided. Additional endpoints included the proportion of patients with a ≥50% reduction in palpable spleen length; patient-reported outcomes [Functional Assessment of Cancer Therapy–Lymphoma total score (FACT-Lym TS) and Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scale]; progression-free survival (defined as time from first study drug administration to date of documented progression based on IWG-MRT response criteria (Barosi *et al.*, 2008) or deaths); survival without transformation to acute myeloid leukaemia (AML-free survival); and OS. Changes in spleen length were assessed in patients with baseline and postbaseline assessments. A 100% decrease from baseline was defined as a non-palpable spleen. Progression-free survival, AML-free survival and OS were estimated using the Kaplan–Meier method. In addition, spleen response was assessed by IWG-MRT criteria (Barosi *et al.*, 2008). To evaluate ruxolitinib in patients with low platelet counts, these endpoints were also assessed in a *post-hoc* analysis of patients with a baseline platelet count of $<100 \times 10^9$/l and compared with patients with a baseline platelet count of $\geq 100 \times 10^9$/l.

Results

Patients

This final report includes results for all 2233 patients treated in JUMP; the last patient's last visit was in January 2017. Patients were treated at 279 clinical sites across 26 countries (Table SI). Patients were from countries in Europe [n = 1831 (82%)], Latin America [n = 190 (8·5%)], North America [n = 53 (2·4%)] and other countries [n = 159 (7·1%)]. Baseline demographic and clinical characteristics are shown in Table I. The median age was 67 years (range, 18–89 years), with a median time since initial diagnosis of 25·8 months (range, <0·1–456·0 months). Overall, 38·3% of patients had haemoglobin levels <100 g/l at baseline; mean spleen length was 13·3 cm. Most patients were Int-1 (37·4%) or Int-2 (33·8%) risk by DIPSS. Overall, 138 patients with baseline platelet counts of $<100 \times 10^9$/l were enrolled (≥50 to $<75 \times 10^9$/l, 20·3%; ≥75 to $<100 \times 10^9$/l, 79·0%). Compared with patients with platelet counts $\geq 100 \times 10^9$/l, patients with low platelet counts had baseline disease characteristics

Table I. Baseline characteristics.

Parameter	All patients (N = 2233)	Platelet count <100 × 10^9/l (n = 138)	Platelet count ≥100 × 10^9/l (n = 2087)
Age, median (range), years	67·0 (18–89)	67·5 (36–86)	67·0 (18·0–89)
≥65 years, *n* (%)	1334 (59·7)	86 (62·3)	1243 (59·6)
Sex, *n* (%)			
Male	1217 (54·5)	76 (55·1)	1135 (54·4)
Female	1016 (45·5)	62 (44·9)	952 (45·6)
Time since initial diagnosis, median (range), months	25·8 (<0·1–456·0)*	36·1 (0·4–312·0)	25·1 (<0·1–456·0)†
MF subtype, *n* (%)			
PMF	1326 (59·4)	99 (71·7)	1226 (58·7)
PPV-MF	532 (23·8)	30 (21·7)	498 (23·9)
PET-MF	374 (16·7)	9 (6·5)	362 (17·3)
Missing	1 (<0·1)	0	1 (<0·1)
DIPSS risk status at study entry, *n* (%)			
Low	60 (2·7)	0	60 (2·9)
Intermediate-1	835 (37·4)	33 (23·9)	802 (38·4)
Intermediate-2	755 (33·8)	60 (43·5)	695 (33·3)
High	194 (8·7)	12 (8·7)	182 (8·7)
Not available	389 (17·4)	33 (23·9)	348 (16·7)
Hemoglobin level, g/l			
Mean (SD)	109·3 (22·90)	100·9 (20·18)	109·8 (22·95)
<100, *n* (%)	856 (38·3)	73 (52·9)	782 (37·5)
≥100, *n* (%)	1370 (61·4)	65 (47·1)	1305 (62·5)
Missing, *n* (%)	7 (0·3)	0	0
Platelet count, × 10^9/l			
Mean (SD)	318·9 (238·61)	81·5 (12·54)	334·6 (238·15)
<50, *n* (%)	1 (<0·1)	1 (0·7)	0
≥50 to <75, *n* (%)	28 (1·3)	28 (20·3)	0
≥75 to <100, *n* (%)	109 (4·9)	109 (79·0)	0
≥100 to <200, *n* (%)	689 (30·9)	0	689 (33·0)
≥200, *n* (%)	1398 (62·6)	0	1398 (67·0)
Missing, *n* (%)	8 (0·4)	0	0
White blood cell count, × 10^9/l			
Mean (SD)	11·7 (11·81)	9·9 (11·55)	11·8 (11·82)
≤25, *n* (%)	1995 (89·3)	125 (90·6)	1870 (89·6)
>25, *n* (%)	208 (9·3)	12 (8·7)	196 (9·4)
Missing, *n* (%)	30 (1·3)	1 (0·7)	21 (1·0)
Peripheral blasts, %			
Mean (SD)	1·1 (2·06)	1·1 (2·10)	1·1 (2·06)
<1%, *n* (%)	1312 (58·8)	77 (55·8)	1235 (59·2)
≥1%, *n* (%)	713 (31·9)	39 (28·3)	674 (32·3)
Missing, *n* (%)	208 (9·3)	22 (15·9)	178 (8·5)
Palpable spleen length below costal margin, mean (SD), cm	13·3 (6·74)‡	14·9 (7·03)$	13·2 (6·71)¶

consistent with more advanced disease, including haemoglobin levels <100 g/l (52·9% vs. 37·5%) and larger mean palpable spleen length (14·9 vs. 13·2 cm) (Table I).

Most patients [n = 1283 (57·5%)] completed treatment per protocol (i.e., treated for up to 24 months after the last patient's first visit or transitioned to commercial drug). Primary reasons for discontinuation included AEs [n = 405 (18·1%)], investigator-determined disease progression [n = 204 (9·1%)], death [n = 101 (4·5%)], physician's decision [n = 93 (4·2%)], withdrawal of consent [n = 79 ([3·5%)], protocol deviation [n = 27 (1·2%)], administrative problems [n = 25 (1·1%)] and loss to follow-up [n = 16 (0·7%)]. Among patients with low platelet counts at baseline, 43·5% (60 of 138) completed treatment per protocol; the primary reasons for treatment discontinuation were AEs [n = 38 (27·5%)], investigator-determined disease

Table I. (*Continued*)

Parameter	All patients (N = 2233)	Platelet count <100 × 10^9/l (n = 138)	Platelet count ≥100 × 10^9/l (n = 2087)
No palpable splenomegaly, *n* (%)	117 (5·2)**	4 (2·9)††	111 (5·3)‡‡
Prior hydroxycarbamide use, *n* (%)	1324 (59·3)	70 (50·7)	1250 (59·9)
Prior transfusions, *n* (%)	578 (25·9)	41 (29·7)	533 (25·5)
FACT-Lym total score, mean (SD)	113·9 (24·0)$$	114·6 (23·1)¶¶	113·8 (24·1)***
FACIT-Fatigue total score, mean (SD)	32·7 (11·9)†††	32·9 (10·9)‡‡‡	32·6 (12·0)$$$

DIPSS, dynamic International Prognostic Scoring System; MF, myelofibrosis; PET-MF, post–essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post–polycythemia vera myelofibrosis; SD, standard deviation.

*n = 2229

†n = 2083

‡n = 2079

$$n$ = 132

¶n = 1941

**Includes 99 patients with nonpalpable spleens and 18 patients who had a prior splenectomy.

††Includes 2 patients with nonpalpable spleens and 2 patients who had a prior splenectomy.

‡‡Includes 96 patients with nonpalpable spleens and 15 patients who had a prior splenectomy.

$$$n$ = 2179

¶¶n = 133

***n = 2046

†††n = 2173

‡‡‡n = 132

$$$$n$ = 2041.

progression [n = 17 (12·3%)], death [n = 8 (5·8%)], physician decision [n = 7 (5·1%)] and withdrawal of consent [n = 3 (2·2%)]. Four patients (2·9%) were lost to follow-up.

The median duration of study follow-up was 13·8 months (range, <0·1–60·6 months). Median exposure to ruxolitinib was 12·4 months (range, <0·1–59·7 months); 1138 patients (51%) had >1 year of exposure, 674 (30%) had >2 years and 289 (13%) had >3 years. Median exposure was lower in the low-platelet cohort [8·3 months (range, 0·5–41·4 months)]. The mean daily dose was 28·7 mg (low-platelet cohort, 13·2 mg); the mean total daily dose over time is shown in Fig 1. Most patients (n = 2165) started ruxolitinib at 5, 15 or 20 mg bid; 68 started treatment at other doses (Fig 1). Most patients [n = 1504 (67·4%)] had dose reductions; 384 (17·2%) had dose increases and 608 (27·2%) had dose interruptions. Among those with a low platelet count at baseline, 58·7% (81 of 138) required dose reductions, 38·4% (53 of 138) had dose increases and 32·6% (45 of 138) had ≥1 dose interruption. Of those in the low-platelet cohort starting at 5 mg bid, 54·5% (61 of 112) had dose reductions and 29·5%

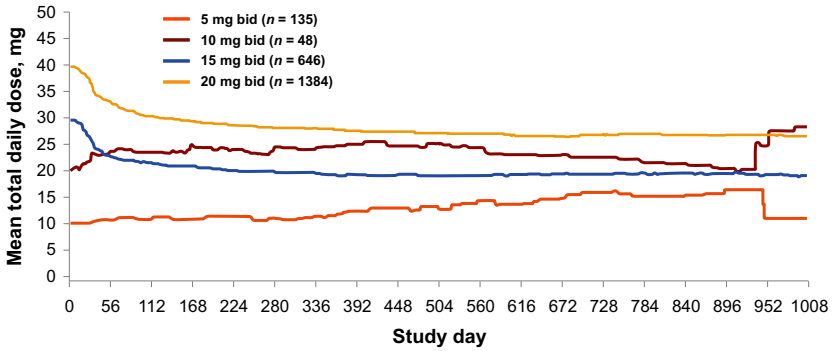

Fig 1. Mean total daily dose. Twenty patients started at doses other than 5, 10, 15, or 20 mg bid: 5 mg qd (n = 1), 10 mg qd (n = 3), 7·5 mg bid (n = 4), 15 mg qd (n = 7) and 20 mg qd (n = 5). (bid, twice daily; qd, once daily.) The median average total daily dose was 36·1 mg for patients starting at 20 mg bid [n = 1384 (62·0%)], 23·1 mg for patients starting at 15 mg bid [n = 646 (28·9%)], 20·5 mg for patients starting at 10 mg bid [n = 48 (6·0%)], 16·2 mg for patients starting at 5 mg bid [n = 135 (2·1%)], and 16·2 mg for those starting at other doses [n = 20 (0·9%)].

(33 of 112) had dose interruptions; 76·9% of patients starting at higher doses (20 of 26) had dose reductions and 46·2% (12 of 26) had dose interruptions.

Safety

The most common haematologic AEs were anaemia [all grades, 59·5% (n = 1328); grade 3/4, 34·8% (n = 776)] and thrombocytopenia [all grades, 53·5% (n = 1194); grade 3/4, 19·3% (n = 432)] (Table II). Similarly, the most common haematologic AEs in the low-platelet cohort were worsening thrombocytopenia [all grades, 73·2% (n = 101); grade 3/4, 54·3% (n = 75)] and anaemia [all grades, 52·9% (n = 73); grade 3/4, 35·5% (n = 49)] (Table II). Few patients discontinued treatment due to these events [anaemia, n = 44 (2·0%); thrombocytopenia, n = 77 (3·4%)], suggesting that these events were manageable in most patients. Median haemoglobin levels decreased from baseline (106 g/l) to a nadir of 95·0 and 94·0 g/l at 8 to 12 weeks respectively, but increased to near-baseline levels after week 12 (Figure S1A). Consistent with this, the number of transfusion-dependent patients at baseline [n = 158 (7·1%)] who received packed red-blood-cell transfusions was highest during the first 12 weeks of treatment but decreased over time (Figure S2). Overall, 19·1% of patients (n = 426) received concomitant erythropoiesis-stimulating agents to manage anaemia.

Median platelet levels decreased from baseline (254 × 10^9/l) during the first four weeks, with a nadir of 153 × 10^9/l and remained stable over time (Figure S1B). In the low-platelet cohort, median platelet counts and haemoglobin levels decreased slightly from baseline (Figure S1C,D). Fourteen patients (10·1%) in the low-platelet cohort discontinued

Table II. Adverse events regardless of study drug relationship (≥5% of patients).

	All patients (N = 2233)		Platelet count <100 × 10^9/l (n = 138)		Platelet count ≥100 × 10^9/l (n = 2087)	
Preferred term*	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)	All grades, n (%)	Grade 3/4, n (%)
Haematologic AEs						
Anaemia	1328 (59·5)	776 (34·8)	73 (52·9)	49 (35·5)	1251 (59·9)	724 (34·7)
Thrombocytopenia	1194 (53·5)	432 (19·3)	101 (73·2)	75 (54·3)	1089 (52·2)	356 (17·1)
Neutropenia	148 (6·6)	103 (4·6)	12 (8·7)	10 (7·3)	136 (6·5)	93 (4·5)
Leukopenia	106 (4·8)	59 (2·6)	7 (5·1)	4 (2·9)	99 (4·7)	55 (2·6)
Non-haematologic AEs						
Pyrexia	358 (16·0)	53 (2·4)	24 (17·4)	5 (3·6)	333 (16·0)	48 (2·3)
Asthenia	343 (15·4)	48 (2·1)	18 (13·0)	2 (1·5)	323 (15·5)	46 (2·2)
Diarrhoea	279 (12·5)	24 (1·1)	14 (10·1)	0	262 (12·6)	24 (1·2)
Fatigue	223 (10·0)	23 (1·0)	7 (5·1)	1 (0·7)	215 (10·3)	22 (1·1)
Headache	193 (8·6)	7 (0·3)	8 (5·8)	0	184 (8·8)	7 (0·3)
Peripheral edema	191 (8·6)	11 (0·5)	9 (6·5)	0	181 (8·7)	11 (0·5)
Cough	190 (8·5)	6 (0·3)	11 (8·0)	0	179 (8·6)	6 (0·3)
Dyspnea	181 (8·1)	45 (2·0)	11 (8·0)	5 (3·6)	170 (8·2)	40 (1·9)
Arthralgia	178 (8·0)	16 (0·7)	11 (8·0)	3 (2·2)	166 (8·0)	13 (0·6)
Abdominal pain	169 (7·6)	29 (1·3)	8 (5·8)	2 (1·5)	161 (7·7)	27 (1·3)
Pneumonia	162 (7·3)	104 (4·7)	13 (9·4)	8 (5·8)	149 (7·1)	96 (4·6)
Pain in extremity	148 (6·6)	11 (0·5)	7 (5·1)	0	141 (6·8)	11 (0·5)
Weight increase	140 (6·3)	12 (0·5)	3 (2·2)	0	137 (6·6)	12 (0·6)
Alanine aminotransferase increased	134 (6·0)	25 (1·1)	4 (2·9)	0	130 (6·2)	25 (1·2)
Nausea	132 (5·9)	3 (0·1)	4 (2·9)	0	128 (6·1)	3 (0·1)
Urinary tract infection	132 (5·9)	27 (1·2)	4 (2·9)	2 (1·5)	128 (6·1)	25 (1·2)
Pruritus	131 (5·9)	4 (0·2)	9 (6·5)	0	121 (5·8)	4 (0·2)
Constipation	122 (5·5)	2 (0·1)	6 (4·4)	0	114 (5·5)	2 (0·1)
Back pain	121 (5·4)	13 (0·6)	7 (5·1)	1 (0·7)	114 (5·5)	12 (0·6)
Dizziness	116 (5·2)	6 (0·3)	1 (0·7)	0	115 (5·5)	6 (0·3)
Herpes zoster	116 (5·2)	11 (0·5)	6 (4·4)	0	110 (5·3)	11 (0·5)
Nasopharyngitis	115 (5·2)	0	4 (2·9)	0	111 (5·3)	0
Epistaxis	113 (5·1)	10 (0·4)	8 (5·8)	0	105 (5·0)	10 (0·5)
Decreased appetite	71 (3·2)	3 (0·1)	8 (5·8)	0	63 (3·0)	3 (0·1)
Upper abdominal pain	108 (4·8)	5 (0·2)	4 (2·9)	0	104 (5·0)	5 (0·2)

AE, adverse event.

*AEs occurring within 28 days of treatment discontinuation are included.

treatment due to thrombocytopenia and three (2·2%) discontinued due to anaemia. Among patients in the low-platelet cohort who discontinued ruxolitinib due to thrombocytopenia, the median platelet count was 32×10^9/l (range, 8–55 $\times 10^9$/l) at the time of discontinuation; five patients discontinued the drug because they reached the per-protocol of $<25 \times 10^9$/l, and nine discontinued for platelet counts of 25 to 47 $\times 10^9$/l without reaching the stopping rule, per treating investigator's decision. Of the 14 patients who discontinued due to thrombocytopenia, two had a grade 1/2 haemorrhage (one conjunctival bleeding and one epistaxis) and one had a grade 3/4 upper gastrointestinal haemorrhage, which occurred after treatment discontinuation. Overall, 10 patients (7·2%) had grade 1/2 haemorrhages (five epistaxis, two conjunctival, one gastric and one vaginal; in addition, one patient had epistaxis and rectal haemorrhage). Six patients had a grade 3/4 haemorrhage, which in all cases was defined by the treating investigator as unrelated to study medication. Grade 3 haemorrhages included one bleeding oesophageal varices, one upper gastrointestinal haemorrhage and one haemorrhage after a molar extraction; platelet counts at the time of these events were 118, 46 and 74 $\times 10^9$/l respectively. Grade 4 haemorrhages included one intercostal left artery haemorrhage, one gastric haemorrhage and one intestinal haemorrhage; platelet counts at the time of these events were 123, 50 and 27 $\times 10^9$/l respectively.

The most common non-haematologic AEs (≥5% of patients) were primarily grade 1/2 (Table II), with pyrexia (16·0%; low-platelet cohort, 17·4%), asthenia (15·4%; low-platelet cohort, 13·0%), diarrhoea (12·5%; low-platelet cohort, 10·1%) and fatigue (10·0%; low-platelet cohort, 5·1%) being the most frequent. Rates of grade 3/4 AEs were low (<2·5%) except for pneumonia (4·7%; low-platelet cohort, 5·8%), which led to study drug discontinuation in 10 patients (0·4%). Rates of infections were low and led to study drug discontinuation in 59 patients (2·6%) in the overall cohort. All-grade infections in ≥5% of patients included pneumonia [n = 162 (7·3%)], urinary tract infection [n = 132 (5·9%)] and nasopharyngitis [n = 115 (5·2%)]. Grade 3/4 infections occurring in >1% of patients included pneumonia [n = 104 (4·7%)], sepsis [n = 33 (1·5%)] and urinary tract infection [n = 27 (1·2%)]. Herpes zoster was reported in 5·2% of patients [n = 116; grade 3/4, 0·5% (n = 11)] and led to treatment discontinuation in one (<0·1%). Tuberculosis was reported in five patients [0·2%; grade 3/4, one patient (0·04%)] and led to treatment discontinuation in three (0·1%). Hepatitis B virus reactivation was reported in one patient (grade 3/4) and led to treatment discontinuation. In the low-platelet cohort, herpes zoster infection was reported in six patients (4·4%); there were no reports of hepatitis B or tuberculosis infection.

Second malignancies were reported in 137 patients (6·1%). Those that occurred in ≥0·1% of patients included non-melanoma skin carcinoma [n = 60 (2·7%)], lung neoplasm [n = 5 (0·2%)], prostate cancer [n = 5 (0·2%)] and lymphoma [n = 4 (0·2%]; the types of lymphomas reported by the investigators were non-Hodgkin lymphoma, n = 2; B-cell lymphoma, n = 1; lymphoma, n = 1). The median time to diagnosis of lymphoma from the time of study initiation was 57·7 weeks (range, 19·9–112·4 weeks). Patients who developed second malignancies other than skin carcinoma discontinued from the study; therefore, treatment for second malignancies, including lymphoma, was not recorded by the investigator. Demographic and baseline clinical characteristics among patients who developed a second malignancy versus those who did not are shown in Table SII. Higher proportions of patients who developed second malignancies were male (61·3% vs. 54·1%), had postpolycythaemia vera MF (34·3% vs. 23·1%), prior hydroxycarbamide exposure (65·0% vs. 58·9%) and elevated neutrophil counts (>25 $\times 10^9$/l; 14·6% vs. 9·0%), and had a shorter median time since initial diagnosis (14·3 vs. 26·5 months).

Serious AEs (occurring in ≥1% of patients) included pneumonia [n = 123 (5·5%)], anaemia [n = 94 (4·2%)], pyrexia [n = 79 (3·5%)], cardiac failure [n = 43 (1·9%)], dyspnoea [n = 36 (1·6%)], sepsis [n = 31 (1·4%)], abdominal pain [n = 28 (1·3%)], respiratory failure [n = 26 (1·2%)], thrombocytopenia [n = 24 (1·1%)] and urinary tract infection [n = 23 (1·0%)].

Efficacy

At week 24, 56·5% of patients (874 of 1546) with splenomegaly achieved a ≥50% reduction from baseline in palpable spleen length; 61·4% (656 of 1068) and 66·5% (423 of 636) achieved a response at weeks 48 and 96 respectively (Fig 2A). Additionally, 25% to <50% reductions from baseline in palpable spleen length were seen in 23·3% of patients (360 of 1546) at week 24, 18·9% (202 of 1068) at week 48 and 14·3% (91 of 636) at week 96. At each assessment, at least two-thirds of patients had a ≥25% reduction from baseline in palpable spleen length. Among evaluable patients in the low-platelet cohort at week 24 (n = 86), 33 (38·4%) achieved reductions from baseline in palpable spleen length of ≥50%; 64·0% (55 of 86) achieved reductions of ≥25% (Fig 2A). Rates were similar at week 48, with 31·9% (15 of 47) and 57·4% (27 of 47) of evaluable patients achieving ≥50% and ≥25% reductions respectively.

Most patients [71·7% (1470 of 2049)] experienced a ≥50% reduction from baseline in spleen length at any time during the study (Fig 2B); 43·8% of patients (57 of 130) in the low-platelet cohort achieved a corresponding response (Fig 2C). Overall, 24·7% of patients (507 of 2049) had resolution of splenomegaly (from a median baseline spleen length of 8 cm). The median time to first ≥50% reduction in spleen length was 5·8 weeks (range, 2·6–236·1 weeks) in the overall cohort and 8·0 weeks (range, 3·3–84·6 weeks) in the low-platelet cohort. The Kaplan–Meier estimated probability of maintaining a ≥50% reduction in palpable spleen length at 48 and 96 weeks was 88% [95% confidence interval (CI),

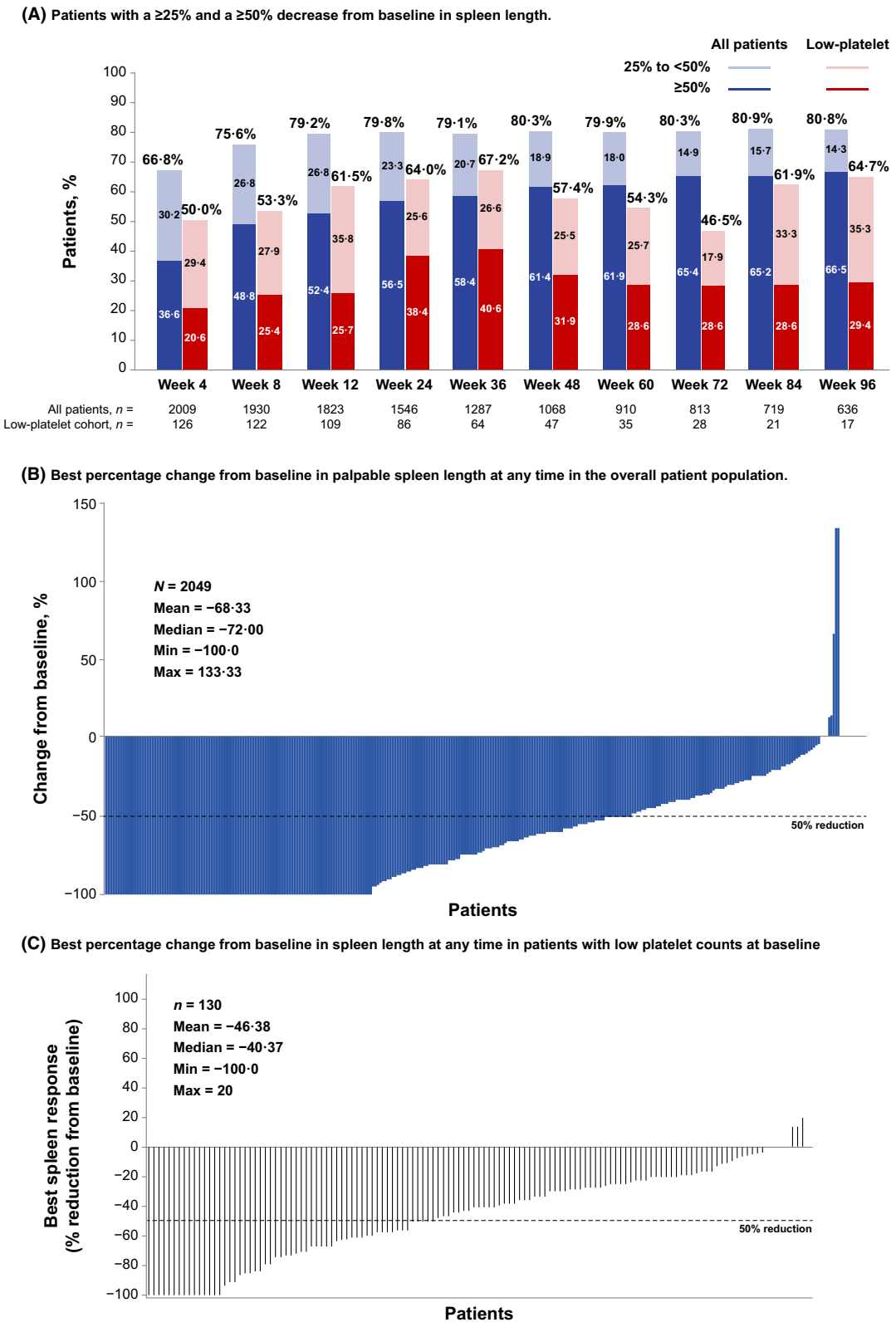

Fig 2. (A) Patients with a ≥25% and a ≥50% decrease from baseline in spleen length. (B) Best percentage change from baseline in palpable spleen length at any time in the overall patient population. (C) Best percentage change from baseline in spleen length at any time in patients with low platelet counts at baseline. Changes in spleen length were assessed in patients with baseline and postbaseline assessments; max, maximum; min, minimum.

86–90%] and 78% (95% CI, 75–81%) respectively in the overall cohort. In the low-platelet cohort, the probability of maintaining a spleen response was 75% (95% CI, 58–86%) at week 48% and 54% (95% CI, 34–71%) at week 96. Overall, 17·5% of patients (low-platelet cohort, 29·8%) had a loss of response (i.e., a return of spleen length to baseline size). Among the 51 evaluable patients with a non-palpable spleen at baseline, most spleens remained non-palpable throughout the study; 94% (29 of 31) were non-palpable at week 24 (two patients had palpable spleens of 1 and 9 cm below the left costal margin respectively), and 4 of 30 evaluable patients (13·3%) had palpable splenomegaly at the end-of-treatment visit.

Spleen response by IWG-MRT criteria (Barosi *et al.*, 2008) at any time during the study was 58% [55% (421 of 765) and 61% (742 of 1224) among patients with a baseline spleen length between 5 and 10 cm and >10 cm respectively]; 189 patients had a baseline spleen length of <5 cm and were not evaluable for response. Stable disease by IWG-MRT criteria (Barosi *et al.*, 2008) was observed in 40% [44% (334 of 765) and 38% (463 of 1224) of patients with a baseline spleen length between 5 and 10 cm and >10 cm respectively]; one patient had progressive disease. The Kaplan–Meier estimated median time to first spleen response by IWG-MRT criteria was 8·86 months (95% CI, 8·43–11·43 months); the estimated median duration of response had not been reached (Figure S3). In the low-platelet cohort, spleen response by IWG-MRT criteria at any time during the study was 78·8% (52 of 66 patients), with a median time to response of 8·1 weeks (range, 3·3–84·6 weeks). The Kaplan–Meier estimated probability of maintaining a spleen response by IWG-MRT criteria was 75% (95% CI, 56–86%) at week 48 and 60% (95% CI, 40–70%) at week 96.

Clinically meaningful improvements in symptoms were seen as early as four weeks after the start of treatment and were maintained over time, as evaluated by the Functional Assessment of Cancer Therapy–Lymphoma (FACT-Lym) total score (TS) (Fig 3A) and Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) scale (Fig 3B). Approximately 55% of patients with a platelet count $\geq 100 \times 10^9$/l achieved a response (i.e., minimally important difference of 6·5 points in improvement from baseline) (Carter *et al.*, 2008) in the FACT-Lym TS at each time point. Approximately 50% of patients achieved a response (i.e., minimally important difference of three points in improvement from baseline) (Cella *et al.*, 2002) on the FACIT-Fatigue scale at each time point. Similar improvements were observed on the FACT-Lym subscale and in the FACT-Lym Trial Outcome Index and FACT-General total scores. Meaningful improvements were also observed in patients with a low platelet count at baseline, with symptom response rates ranging from 30% to 47% over the course of the study.

Improvements in symptoms were also assessed in patients without palpable splenomegaly at baseline ($n = 99$). Mean FACT-Lym TS and FACIT-Fatigue scores at baseline were similar between patients with palpable splenomegaly (FACT-Lym TS, 114·0; FACIT-Fatigue, 32·7) and those without palpable spleens (FACT-Lym TS, 110·7; FACIT-Fatigue, 31·8). Mean scores at baseline were slightly higher in patients with

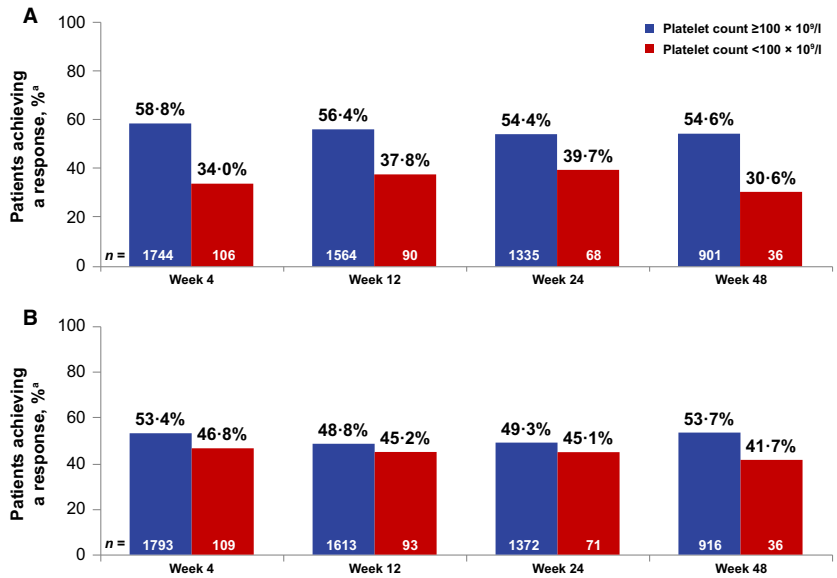

Fig 3. Proportion of patients achieving a response in the (A) FACT-Lym TS and on the (B) FACIT-Fatigue scale. Responses were measured in patients with baseline and postbaseline assessments and defined as the lower limit of the minimally important difference [FACT-Lym TS, 6·5 points (Carter *et al.*, 2008); FACIT-Fatigue scale, 3 points (Cella *et al.*, 2002)]. FACIT, Functional Assessment of Chronic Illness Therapy; FACT-Lym TS, Functional Assessment of Cancer Therapy–Lymphoma total score.

prior splenectomy (n = 18; FACIT-Fatigue, 124·0; FACIT-Fatigue, 36·8). Overall, patients with palpable splenomegaly had improvements in symptoms similar to those seen in patients with no palpable splenomegaly (Fig 4). Approximately 50% to 60% and 40% to 50% of patients achieved a response at each time point in the FACT-Lym TS and on the FACIT-Fatigue scale respectively.

Overall, leukaemia-free and progression-free survival

Overall, 205 deaths (9·2%) were reported on treatment or up to 28 days after the end of treatment. The estimated OS probability was 94% (95% CI, 92–95%) at 48 weeks and 87% (95% CI, 85–89%) at 96 weeks (Fig 5A). Primary causes of death (as determined by the investigator) on study included MF (n = 38), pneumonia (n = 15), septic shock (n = 14), cardiac arrest (n = 13), cardiac failure (n = 12), sepsis (n = 11), respiratory failure (n = 9), multiple organ dysfunction syndrome (n = 9), AML (n = 7), cardiorespiratory arrest (n = 7), pulmonary embolism (n = 6), acute respiratory distress syndrome (n = 4), myocardial infarction (n = 4), cardiogenic shock (n = 4), general physical health deterioration (n = 3), acute kidney injury (n = 3), acute pulmonary oedema, pulmonary oedema, cerebral haemorrhage, bacterial peritonitis, respiratory tract infection, urinary tract infection, cardiac disorder, congestive cardiac failure, disease progression, sudden death, acute leukaemia and leukaemia (each, n = 2), and undetermined cause of death (n = 13). All other causes were reported in one patient each (n = 46). Overall, 18 patients (0·8%) died of second malignancies, including 12 who died of leukaemia [AML (n = 7), acute leukaemia (n = 2), leukaemia (n = 2) and chronic myeloid leukaemia (n = 1)]. Causes of death among patients in the low-platelet cohort included septic shock (n = 3) and multiple organ dysfunction syndrome and progressive myelofibrosis (n = 2 each); all other causes (n = 14) were reported in one patient each. Four patients in the low-platelet cohort developed AML while on study.

The estimated AML-free survival probability at 96 weeks was 85% (95% CI, 83–87%) (Fig 5B). A total of 45 patients developed AML during the study or within 28 days following treatment discontinuation (median follow-up, 60 weeks). The estimated progression-free survival probability [by IWG-MRT criteria (Barosi *et al.*, 2008)] at 96 weeks was 81% (95% CI, 78–83%); median follow-up was 55 weeks (Fig 5C). Overall, patients with higher-risk disease (by DIPSS) had worse survival and a lower probability of progression-free and AML-free survival (Fig 6).

Discussion

The JUMP study is the most extensive study in MF and includes the largest cohort of patients with MF treated with ruxolitinib reported to date. In addition to enrolling patients who matched the eligibility criteria of the COMFORT studies, the JUMP trial enrolled patients with platelet counts of $<100 \times 10^9$/l, patients with Int-2- and high-risk MF without palpable splenomegaly and patients with Int-1-risk MF

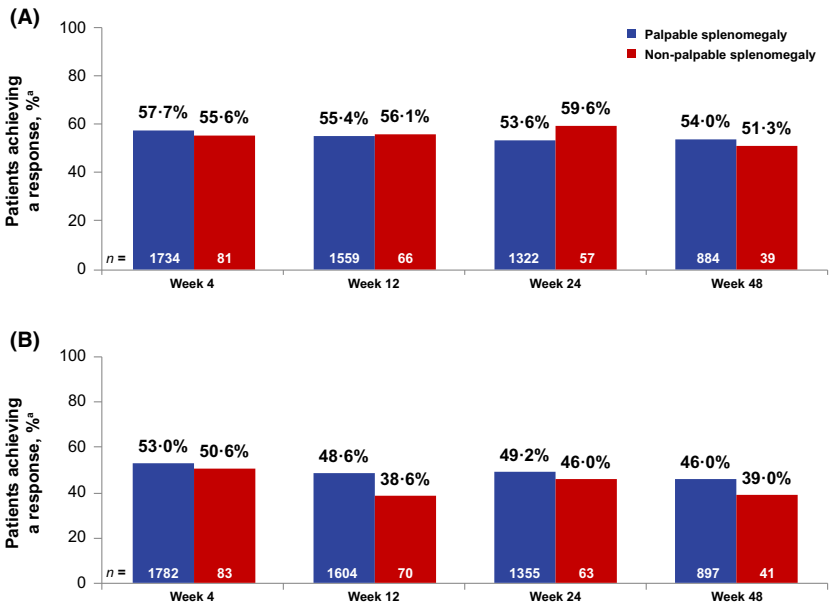

Fig 4. Proportion of patients with or without splenomegaly at baseline achieving a response[a,b] (A) in the FACT-Lym TS and (B) on the FACIT-Fatigue scale. Responses were measured in patients with baseline and postbaseline assessments. FACIT, functional assessment of chronic illness therapy; FACT-Lym TS, functional assessment of cancer therapy–lymphoma total score. [a]Response was defined as the lower limit of the minimally important difference [FACT-Lym TS, 6·5 points (Carter *et al.*, 2008); FACIT-fatigue scale, 3 points (Cella *et al.*, 2002)]. [b]Includes 99 patients with a non-palpable spleen.

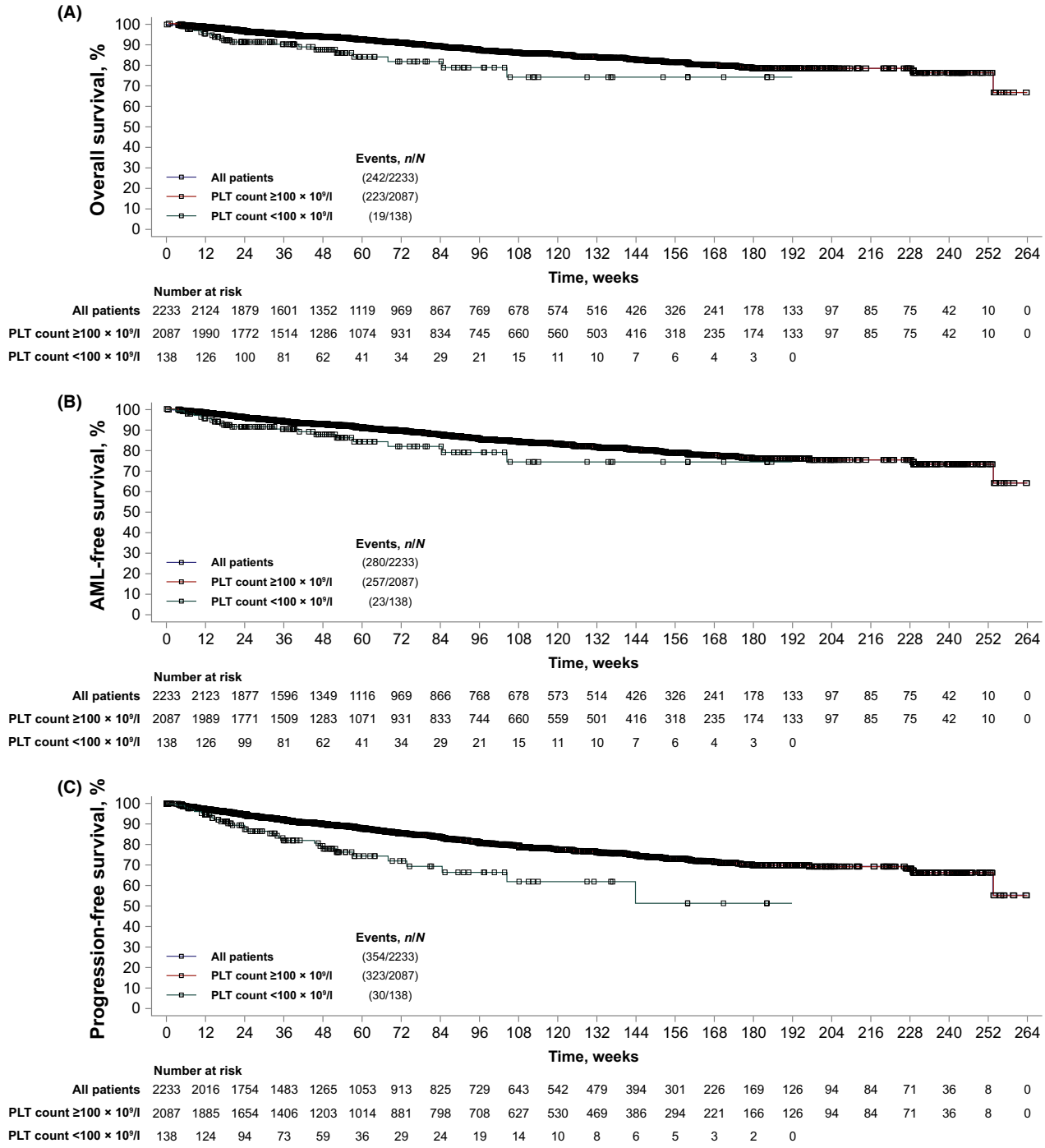

Fig 5. Kaplan–Meier estimate of (A) overall survival, (B) AML-free survival and (C) progression-free survival. AML, acute myeloid leukaemia; PLT, platelet.

(Harrison *et al.*, 2012; Verstovsek *et al.*, 2012; Cervantes *et al.*, 2013; Harrison *et al.*, 2016; Verstovsek *et al.*, 2017b). Overall, the patient baseline and clinical characteristics reported here are comparable to those previously reported for the 1144-patient snapshot, and safety and efficacy findings are consistent across the studies (Al-Ali *et al.*, 2016). Ruxolitinib was well tolerated and had an AE profile consistent with what has been previously reported (Harrison *et al.*, 2012; Verstovsek *et al.*, 2012; Cervantes *et al.*, 2013; Harrison *et al.*, 2016; Verstovsek *et al.*, 2017b), both in the overall and low-platelet cohorts. As expected, given the mechanism of action of ruxolitinib, the most common AEs were anaemia and thrombocytopenia, but they rarely led to discontinuation [44 (2·0%) and 77 (3·4%) patients

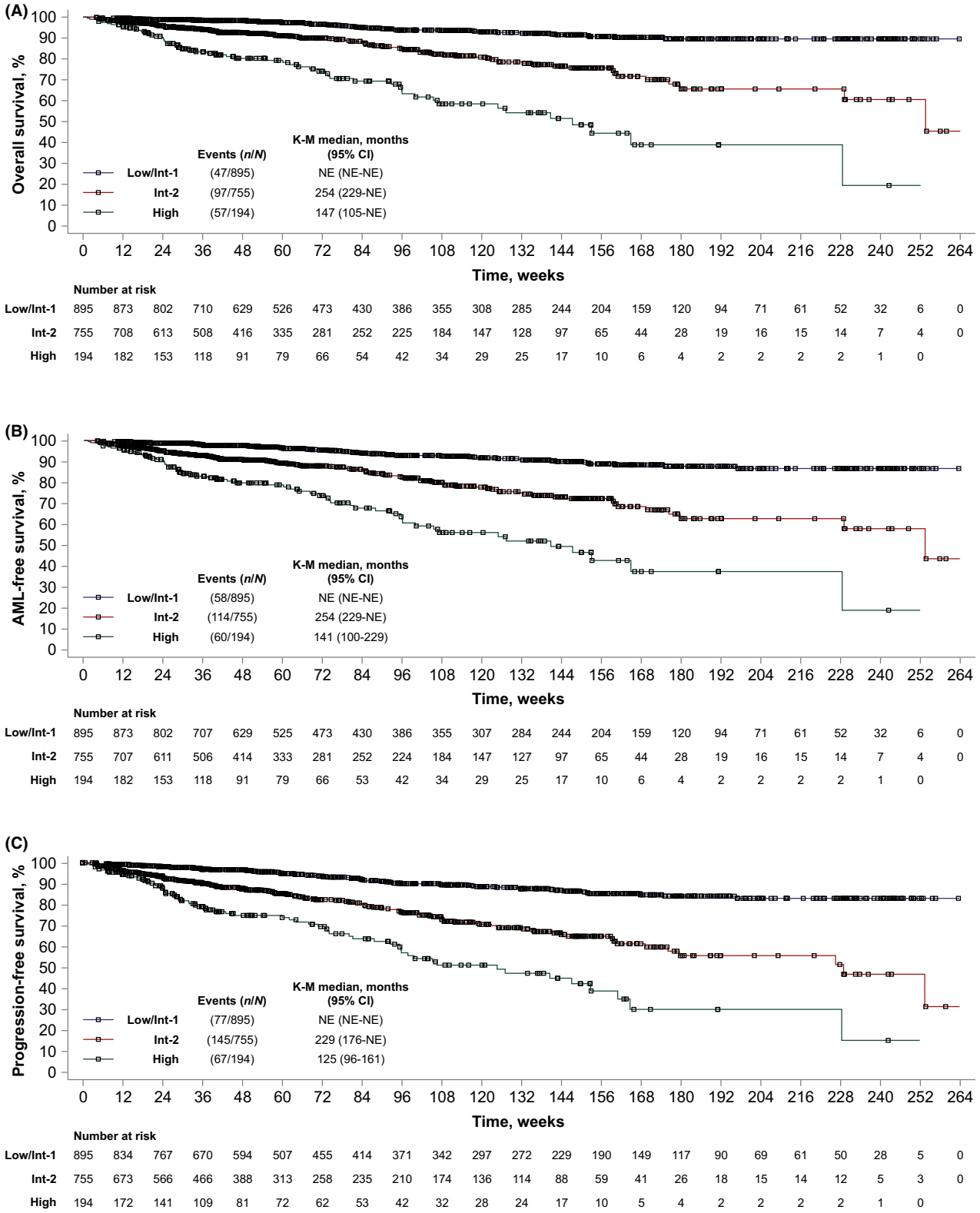

Fig 6. (A) Overall survival, (B) AML-free survival and (C) progression-free survival by risk score. AML, acute myeloid leukaemia; Int, intermediate; K–M, Kaplan–Meier; NE, not evaluable.

discontinued respectively], indicating that these AEs were manageable in most patients. Although the discontinuation rate due to haematologic AEs was higher in patients with low platelet counts (anaemia, 2·2%; thrombocytopenia, 10·1%), no new or unexpected AEs were observed. Rates of worsening thrombocytopenia were higher in patients with a low platelet count than in patients with a platelet count of $\geq 100 \times 10^9$/l (73·2% vs. 52·2%); rates of anaemia were similar (52·9% vs. 59·9%).

Non-haematologic AEs in the JUMP study, including infections, were mainly grade 1/2 and led to few discontinuations. Infections of interest included herpes zoster, tuberculosis and hepatitis B virus reactivation. No new or unexpected infections were observed, and no cases of progressive multifocal leukoencephalopathy were reported. Non-melanoma skin cancer was the most commonly reported second malignancy, potentially a result of patients having received prior hydroxycarbamide treatment. Lymphoma was reported in 0·2% of patients. In addition, a low rate of transformation to AML (2%) was observed. Overall, rates of lymphoma and AML in JUMP were lower than those observed in a population-based Swedish study of patients with myeloproliferative neoplasms [lymphoma, 1·0% (90/9379); AML, 3·0% (278/9379)]; patients had no exposure to ruxolitinib (Landtblom *et al.*, 2018). However, the median duration of follow-up in the JUMP study was short [13·8 months (range, <0·1–60·6 months)], which may have impacted the rate of second malignancies observed.

Most patients in the JUMP study experienced clinically meaningful reductions in spleen size and improvements in disease-related symptoms. Most patients (71·7%) experienced a ≥50% reduction from baseline in spleen length at any time during the study; in 24·7% of patients, the spleen became non-palpable. Responses were durable, with a 78% probability of maintaining a spleen response for 96 weeks. In addition, clinically meaningful improvements in symptoms were seen as early as four weeks after the start of treatment and were maintained over time, as evaluated by the FACT-Lym TS and FACIT-Fatigue scale. Approximately 55% and 50% of patients achieved a response in the FACT-Lym TS and on the FACIT-Fatigue scale respectively. Although differences in study designs and patient populations preclude a direct comparison, these findings are similar to those seen in the phase 3 COMFORT studies, in which patients treated with ruxolitinib experienced substantial reductions in spleen volume and improvements in symptoms (Harrison *et al.*, 2012; Verstovsek *et al.*, 2012; Cervantes *et al.*, 2013; Harrison *et al.*, 2016; Verstovsek *et al.*, 2017b).

Patients in the low-platelet cohort also experienced improvements in spleen length and symptom burden, although rates of spleen and symptom responses were lower than those seen in patients with a platelet count of $\geq 100 \times 10^9$/l. Symptom and spleen response rates might have been higher if the dose had been increased over time for patients with low platelet counts, as was seen in Study 258 (Talpaz *et al.*, 2013). In Study 258, 62% of evaluable patients (23 of 37) were receiving ruxolitinib ≥10 mg bid at the time of the interim analysis, and reductions in spleen size were greater in patients receiving a dose titrated to 10 mg bid than in those receiving a dose of 5 mg bid. These findings are consistent with an analysis of COMFORT-I that showed that patients receiving higher doses achieved greater reductions in spleen volume and symptom burden (Verstovsek *et al.*, 2013). Most patients with a low platelet count in JUMP remained at the 5-mg bid starting dose (dose increases, 38·4%) since dose increases to maximize efficacy were not mandated in the protocol, but depended on physician judgement and patient clinical response. In general, findings from Study 258 and EXPAND (Evaluating Ruxolitinib in Patients with Low Baseline Platelet Counts Diagnosed with Myelofibrosis) (Vannucchi *et al.*, 2019) suggest that higher doses are tolerated in this patient population and may lead to higher spleen response rates. EXPAND will continue to further evaluate the safety and efficacy of ruxolitinib in patients with low platelet counts and help determine whether higher doses of ruxolitinib lead to added clinical benefit in this patient population.

Additionally, patients with higher-risk MF had shorter survival, which is consistent with previous studies (Cervantes *et al.*, 2009; Passamonti *et al.*, 2010). A subanalysis of the JUMP study assessing the association between DIPSS risk status and outcomes found that lower-risk patients achieved better spleen size reductions, had the shortest time to first spleen response and achieved a better overall symptom score (Passamonti *et al.*, 2017). This is in line with an Italian retrospective study, in which higher-risk disease and increased splenomegaly correlated with lower response rates (Palandri *et al.*, 2017). Similarly, an analysis assessing predictors of response in the JUMP study found that more advanced disease (e.g., higher risk scores, anaemia and thrombocytopenia) correlated with lower spleen response rates (Gupta *et al.*, 2017).

In conclusion, ruxolitinib provided clinically meaningful reductions in spleen size and symptoms in patients with MF, including those who had platelet counts of $<100 \times 10^9$/l, and demonstrated a safety and efficacy profile consistent with that observed in the phase 3 COMFORT studies; in this large cohort of patients receiving ruxolitinib, no new safety concerns were identified. Findings from this study not only confirm findings from the COMFORT studies but also provide additional evidence of the efficacy and safety of ruxolitinib in the treatment of patient groups that have not been as extensively studied as those evaluated in the COMFORT studies (e.g., patients with Int-1-risk disease or low platelet counts). However, it is important to interpret our findings with caution given the limitations associated with a single-arm study and the small number of patients in the Int-1-risk and low-platelet cohorts; additionally, because comparisons of patient subgroups were conducted as a *post-hoc* analysis, no statistical testing was performed. Continued analysis of these

patients will be important to determine the long-term efficacy of ruxolitinib. This, together with future analyses of this extensive study, will continue to help shape the management of patients with MF.

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Conflicts of interest

H. K. Al-Ali has received consultancy fees, honoraria and research funding from Novartis and Celgene; honoraria from Alexion; and consultancy fees and honoraria from Gilead. M. Griesshammer has received consultancy fees and honoraria from and has served on speaker's bureaus for Gilead, Baxalta, AOP Orphan, Shire and Novartis and has received honoraria from and has served on speaker's bureaus for Sanofi. L. Foltz has received consultancy fees from Pfizer; research funding from Incyte, Promedior and Gilead; and consultancy fees, honoraria and research funding from Novartis. G. A. Palumbo has served on an entity's board of directors or advisory committees and has served on speaker's bureaus for Novartis and Celgene; has served on speaker's bureaus for Amgen and Teva; and has served on an entity's board of directors or advisory committees for Janssen and Hospira. P. le Coutre has received honoraria from Bristol-Myers Squibb, Novartis, Incyte and Pfizer. A. Zaritskey has received consultancy fees from Janssen and has received consultancy fees from and has served on speaker's bureaus for Novartis. R. Tavares has received consultancy fees from Novartis. V. Gupta has received consultancy fees, honoraria and research funding from Novartis and consultancy fees and research funding from Incyte. P. Raanani has received consultancy fees and grants from and has served on advisory boards for Novartis, Pfizer and Ariad (Medison) and has received consultancy fees from and has served on advisory boards for Bristol-Myers Squibb. T. Sacha has received personal fees from Bristol-Myers Squibb, Novartis, Angelini and Pfizer. C. Bouard, C. Paley and R. Tiwari are employees of Novartis. A. M. Vannucchi has served on speaker's bureaus for Gilead and Shire and has served on an entity's board of directors or advisory committees for, has received research funding from and has served on speaker's bureaus for Novartis. B. Martino, F. Palandri, A. M. Liberati, C. García-Hernández, P. Giraldo, D. Damiani, M. Hänel and F. Mannelli declare no competing interests.

Author contributions

HKA-A, MG, LF, GAP, BM, FP, AML, PC, CG-H, AZ, RT, VG, PR, PG, MH, DD, TS, FM and AMV enrolled patients, performed research and contributed to data collection, analysis and interpretation. RT performed statistical analyses and contributed to data interpretation. CB and CP contributed to data interpretation. The first draft of the manuscript was prepared by HKA-A with the assistance of a medical writer; all authors critically reviewed each version of the manuscript and approved the final version for submission.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Haematologic parameters over time. Haemoglobin levels (A) and platelet counts (B) in the overall cohort. Haemoglobin levels (C) and platelet counts (D) in the low-platelet cohort.

Figure S2. Proportion of patients receiving pRBC transfusions over time by transfusion dependence at baseline (n = 158).

Figure S3. Kaplan–Meier estimate for (A) time to and (B) duration of first spleen response per IWG-MRT criteria.

Table SI. Countries participating in the JUMP study, with corresponding enrolment.

Table SII. Baseline characteristics among patients who developed second malignancies.

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