Supplementary Information for

Ruxolitinib *versus* Best Available Therapy for PV intolerant or resistant to Hydroxycarbamide in a Randomized trial

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Trial design

MAJIC is a parallel, open-label, randomized controlled trial of ruxolitinib *vs* BAT (Trial schema, Fig S1; inclusion and exclusion criteria Table S1). The trial was registered at www.isrctn.com (registration number ISRCTN61925716), reviewed by an independent research ethics committee and conduced at 38 sites across the UK between August 2012 and August 2016. All patients entering the trial gave written informed consent in accordance with the Declaration of Helsinki. Patients aged ≥18 with high-risk ET or PV, who met modified criteria for intolerance or resistance to HC, were recruited (Table S1). High-risk PV was defined by age > 60 years; previous thrombosis, erythromelalgia or migraine; diabetes or hypertension; significant splenomegaly or platelets $>1000\times10^9$/L (Table S1). Patients were stratified by gender and randomized by computer on a 1:1 ratio to receive either ruxolitinib (starting dose 10mg twice daily (bd) or 5mg bd, if baseline platelets were $100\text{-}200\times10^9$/L) or BAT for a minimum of 1 year.

Clinical outcome measures

The primary outcome measure was achievement of Complete Response (CR) rates as defined by European Leukemia Net (ELN) criteria[1] within 1 year of treatment. CR in PV patients was defined by achieving all of the following criteria: haematocrit <45% without venesection for 3 months; platelet count $\leq400\times10^9$/L; normal spleen size on imaging; white blood cell count $\leq10\times10^9$/L. Secondary outcomes included Partial Response (PR) rates per ELN criteria within 1 year of treatment, duration of response (both CR and PR) and overall response (CR+PR), toxicity profile of ruxolitinib based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4, dose intensity, histological response, molecular response; hemorrhagic and thromboembolic event rate, disease transformations, QoL and disease symptom burden, overall and progression free survival. In addition to the pre-

specified outcomes, the composite outcome of event-free survival was also added. These outcomes assessed time until the first of the following events, major thromboembolic or major hemorrhagic event, progression or death. Similarly to EFS, duration of complete response was also analyzed. Duration of response and duration of complete response was defined as the time of response to the first loss of response lasting six months or more. The safety population included all patients who received at least one dose of protocol treatment. All hemorrhagic and thrombotic events were collected and centrally reviewed. QoL and symptom assessment questionnaires included the 10-item Myeloproliferative Neoplasm Symptom Assessment Form (MPN-10) Total Symptom Score (TSS), EQ-5D and M.D. Anderson Symptom Inventory (MDASI) and were completed by patients at baseline (prior to treatment, 7 consecutive days for the MPN-10 and once for the other questionnaires), 2 months and 4 months post randomization and continued 4 monthly whilst on trial (once per time point per questionnaire). Overall symptom response was defined as at least a 50% reduction in TSS from baseline (average of the 7 baseline days with at least 4 of 7 days scored) at any post-baseline time point up to Month 60.

Sample size justification

Sample size calculations were based upon rates obtained from preliminary data with ruxolitinib in PV patients using a one-sided normal test without continuity correction and unpooled variance. The CR rate for the control group was estimated to be 35%. A clinically significant improvement was considered to be 15%. Thus, assuming CR rates in the control and treatment group were 35% and 50% respectively, 90 patients were required in each arm to detect the clinically significant differences with 78% statistical power at 10% level of significance. Allowing for a 5% drop out rate, the total number required was 190 patients.

Statistical analysis of clinical data

A $P<.10$ was considered statistically significant for the primary outcome. Descriptive statistics were presented by treatment group and overall, with categorical variables tabulated with the number and percentage of patients, and continuous measures summarized using means (and standard deviations (SD)) or medians (and ranges), as appropriate. Multilevel models with time transformed using restricted cubic splines were used to analyze longitudinal data such as blood counts and the ruxolitinib dose. Time-to-event outcomes were predominantly analyzed using the method of Kaplan and Meier, with differences in survival analyses determined using the Cox model, adjusting for the stratification factor (gender), and treatment (when not the primary variable of interest). Supporting analysis, censoring BAT patients at the time that they started ruxolitinib was also conducted. Investigation into the impact of venesection on thrombosis was analysed using a Fine and Gray model to account for the competing risk of death. To determine the effect of the primary outcome on event-free survival, attainment of CR was treated as a time varying covariate. Apart from the primary outcome, additional hypotheses tests were exploratory, unpowered, two-sided and considered $P<.05$ statistically significant. A test of the difference in proportions was applied. We then fitted multivariable logistic regression models to see the effect of the stratification factors and clinically relevant baseline measures on the primary outcome. Subgroup analysis were performed using the interaction method, also adjusting for gender, and were presented graphically using a Forest plot (Figure S6). Heterogeneity was assessed with a likelihood ratio test for each subgroup. All summaries and statistical analyses for efficacy were primarily carried out on a modified intention to treat (mITT) basis, including patients analyzed according to their randomized treatment allocation, who started treatment within one year of randomization and for whom at least one response was available. Summary statistics for safety variables were based on the safety population, which included patients according to the treatment they actually received and who received

one or more doses of treatmentAll above statistics analyses were performed using Stata v16.0 and v17.0, SAS v9.4 and R.

Statistical analysis of quality of life assessment

Quality of life (QoL) was assessed over 0-60 months using the Myeloproliferative Neoplasms Symptom Assessment Form (MPN-SAF). MPN-SAF Total Symptom Score (TSS) was computed as the average of all completed items multiplied by 10 (scale 0-100, higher score represents higher symptom burden). Estimates of change from baseline and between arm differences in change by timepoint were made using a linear mixed model with compound symmetry covariance structure, which included covariates for categorical time point, treatment arm, and the interaction between time point and treatment arm. The difference between arms in proportion of patients with best post-baseline TSS response of 50% or greater was tested using a Chi-square test. QoL analyses were performed using SAS version 9.4.

Treatment and clinical assessment

Ruxolitinib treatment was initiated at an appropriate dose based on baseline platelet count. BAT was assigned according to physician's choice but had to be an active agent. Patients were permitted to change or combine BAT therapies with the aim of achieving a CR. No crossover of BAT patients to ruxolitinib was permitted. Low-dose aspirin (75mg od) was also advised for all patients unless contraindicated. Protocol specified dose reductions for ruxolitinib were in place for hematological, renal and hepatic toxicities and patients were allowed to re-escalate following a dose reduction if the toxicity had resolved. The lowest permitted dose of ruxolitinib was 5mg once daily. Patients were also permitted to increase the dose of ruxolitinib, up to 25mg twice daily, but not combine therapies. Patients were assessed for hematological response every 2 weeks for 3 months and then every 6 weeks during the first year of treatment

in order to determine the primary outcome of CR during year 1 (cut-off week 54). Ultrasound was performed at baseline and repeated at suspected CR for patients who had splenomegaly at baseline, reports were centrally reviewed. An analysis of histological response according to ELN Criteria (REF) was also performed on bone marrow trephine samples from baseline and 1 year. Patients continued to receive ruxolitinib beyond 1 year provided a CR or PR was maintained and all patients were assessed every 4 months for a total of 5 years. Those discontinuing ruxolitinib moved to the BAT arm for continued follow-up. Patients who underwent transformation to myelofibrosis (PPV-MF), myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) discontinued the trial but were followed up for survival.

Serial *JAK2*V617F qPCR testing and defining *JAK2*V617F molecular responders.

Annual and serial quantitative PCR for allele specific *JAK2*V617F was analysed in sequential DNA samples from patients regardless of therapy, provided patients had a minimum of a baseline sample at trial entry together with at least one sample available at either 12 or 24 months. Sequential samples were either all whole blood or all granulocyte DNA, and different sources of DNA were not utilized for serial measurements within individual patients. DNA samples were diluted to the same concentration and run within the same assay on the same day to ensure no inter-run differences and batch effects. The same set of DNA standards were used in all experiments to control for changes across assay runs as published previously[2]. The sensitivity of the assay is consistently <0.05%. Multiple serial samples were available from 70 and 57 patients in Ruxolitinib and BAT arms respectively, including the baseline and 12m/24m time-points. Of these, 58/70 and 42/57 had follow up DNA samples at or beyond 24m respectively. The change in *JAK2*V617F variant allele frequency (VAF, %) between baseline and subsequent time points was calculated either as proportionate change (%) from baseline VAF, or as a raw difference in VAF from baseline. We defined a patient who showed a 50%

proportionate *JAK2*V617F VAF reduction as a '*JAK2*V617F molecular responder'. In order to ascertain the optimal % reduction in VAF, we assessed VAF reduction and event free survival by ROC curve analysis (Figure S3d) which did not illustrate that any particular VAF reduction was superior at defining people likely to have reduced events. However, through longitudinal sampling we observed that those achieving >50% VAF reduction generally had durable responses subsequently. "Molecular responders", when defined as >50% reduction in allele burden at last time-point, had a median reduction of 33% at 12m and 85% at last time point, but non-responders had a median reduction of 3.1% and 2.4% respectively. Comparison by response at last time point using the Mann-Whitney test gave p-value for this difference in reduction of allele burden of $p<0.001$. This shows "responders" as defined generally had a durable response with trend towards response initiated and maintained and VAF further reduced at more than one time point after initiation of treatment. Associations between *JAK2*V617F molecular responders and the occurrence of a major event were measured using chi-squared tests.

Targeted gene sequencing and outcome analysis

The full coding region of 35 genes below, as well as genome wide single nucleotide polymorphisms, were captured using Agilent SureSelect RNA bait capture and underwent 150bp paired end sequencing on Illumina Novaseq, in order to identify somatic mutations and copy number aberrations in baseline peripheral blood derived granulocyte DNA samples. A total of 175 patients were sequenced. Following read alignment, nonsynonymous exonic single nucleotide substitution variants (SNV) in targeted genes were identified using CaVEMan[3]. For insertions and deletions, the Pindel algorithm[4] was used. Preprocessed single nucleotide variants were further annotated using ANOVAR[5], RefGene[6], exac3db[7], 1000 Genomes db[8], dbSNP[9], and COSMIC v.92[10] databases for variants annotation. Final variants met the

following criteria (1) Exac db values < 0.001, (2) mutant reads => 2 (unless *JAK2*V617F in which case a single mutant read was accepted), (3) presence of the variant as a confirmed somatic mutation in a haematological tissue in COSMIC v.92, (4) presence of the variant on both forward and reverse sequencing reads. Following identification of variants, the package cgpVAF (https://github.com/cancerit/vafCorrect) was used to detect additional samples with these variants with VAFs below initial pipeline thresholds. Identification of copy number changes was performed as described in[11]. Briefly, VAF values for set of SNPs from 1000 Genome project were used to generate allele frequency and coverage plots, to classify chromosomal changes into gains, losses, or copy-neutral loss-of-heterozygosity (CN-LOH).

Genes included in targeted gene sequencing:

ASXL1	EZH2	KIT	PHF6	SRSF2
BCOR	GATA2	KRAS	PPM1D	SH2B3
CALR	GNAS	MLL3	PTPN11	STAG2
CBL	GNB1	MPL	RB1	TET2
CSF3R	IDH1	NF1	RUNX1	TP53
CUX1	IDH2	NFE2	SETBP1	U2AF1
DNMT3A	JAK2	NRAS	SF3B1	ZRSR2

Of 175 patients sequenced at baseline for extended molecular profiling, 5 patients were excluded from outcome analysis due to the absence of time-to-event data post baseline, and 3 patients were excluded due to the absence of any identifiable somatic mutations or copy number changes, including in *JAK2.* 113 patients had molecular response data for *JAK2*VAF at 12 months (63 in Ruxolitinib and 50 in BAT arms). Median age in patients with and without additional drivers was compared using a Mann-Whitney test.

Table S1: Inclusion criteria, definition of high-risk PV and modified criteria for hydroxycarbamide resistance or intolerance

MAJIC PV Inclusion criteria (ALL of)		
Patient aged ≥ 18 years old		
Confirmed diagnosis of PV		
Meeting criteria for High risk disease (any ONE of the following):		
	Age ≥ 60 years old	
	Previous documented thrombosis felt to be secondary to PV at or within 10 years of diagnosis	
	Significant splenomegaly (>5cm below costal margin) or symptomatic (splenic infarcts or needing analgesia)	
	Platelets > 1000 x 10^9/L	
	Diabetes or hypertension requiring pharmacological therapy for > 6 months	
Meeting criteria for hydroxycarbamide (HC) resistance or intolerance (any ONE of the following) at ANY time point:		
	Platelets > 600 x 10^9/L after at least 2g/day or maximum tolerated dose (MTD) of HC	
	Platelets >400 x 10^9/L and WBC <2.5 x 10^9/L at any dose of HC for a period of at least 8 weeks	
	Platelets >400 x 10^9/L and Hb <110g/L at any dose of HC for a period of at least 8 weeks	
	Platelet count persistently <100 x 10^9/L at any dose of HC for a period of at least 8 weeks	
	Progressive splenomegaly or hepatomegaly (i.e. enlargement by more than 5cm or appearance of new splenomegaly or hepatomegaly on HC treatment	
	Not achieving the desired reduction of hematocrit or packed cell volume with the addition of HC in patients who do not tolerate frequent venesections after 8 weeks of at least 2g/day or MTD of HC	
	Not achieving the desired stable reduction of WBC, when leucocytes are a target of therapy after 8 weeks of at least 2g/day or MTD of HC	
	Thrombosis or hemorrhage (including transient ischaemic attack) while on therapy	
	Presence of leg ulcers or other unacceptable HC-related non-hematological toxicities such as unacceptable mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of HC; or cycling platelet counts on therapy	
	Disease related symptoms not controlled by HC	

PV polycythemia vera, HC hydroxycarbamide, MTD maximum tolerated dose, WBC white blood cell count, Hb hemoglobin

Table S2: Individual patients who received ruxolitinib as part of BAT arm (n=10)

Starting dose of Ruxolitinib	Time since randomisation
15 mg daily	887 days
	848 days
	538 days
	1452 days
5 mg twice a day	1044 days
	1071 days
10 mg twice a day	542 days
15 mg twice a day	334 days
	192 days
20 mg twice a day	884 days

BAT best available therapy

Table S3: Best available therapies given during the course of MAJIC PV

Total number of different BATs given throughout the trial	
N	87
Median	1
Numbers of patients who received 1,2,3 or 4 BAT agents. (n, %)	
1	46 (53)
2	31 (36)
3	9 (10)
4	1 (1)
Total	87
BAT Drugs given (regardless of timing / order) (n, %)	
32P	1 (1)
Anagrelide	3 (3)
Busulfan	1 (1)
Hydroxycarbomide	28 (32)
Interferon	13 (15)
32P, Hydroxycarbomide	1 (1)
Anagrelide, Hydroxycarbomide	9 (10)
Anagrelide, Interferon	3 (3)
Anagrelide, Ruxolitinib	1 (1)
Busulfan, Interferon	2 (2)
Busulfan, Ruxolitinib	1 (1)
Hydroxycarbomide, Interferon	10 (11)
Hydroxycarbomide, Ruxolitinib	1 (1)
Interferon, Pipobroman	1 (1)
Interferon, Ruxolitinib	2 (2)
32P, Anagrelide, Interferon	1 (1)
Anagrelide, Hydroxycarbomide, Interferon	3 (3)
Anagrelide, Interferon, Ruxolitinib	1 (1)
Busulfan, Hydroxycarbomide, Interferon	1 (1)
Hydroxycarbomide, Interferon, Ruxolitinib	3 (3)
Anagrelide, Hydroxycarbomide, Interferon, Ruxolitinib	1 (1)
Total	87

BAT best available therapy

Table S4: Reasons for treatment discontinuation

Reason for treatment discontinuation (n, %)	BAT (n = 23)	Ruxolitinib (n = 30)	Overall (n = 53)
Death	1 (4)	3 (10)	4 (8)
Other	5 (22)	10 (33)	15 (28)
Toxicity	2 (9)	4 (13)	6 (11)
Toxicity, Other	1 (4)	1 (3)	2 (4)
Transformation	9 (39)	7 (23)	16 (30)
Withdrawn patient consent	3 (13)	2 (7)	5 (9)
Withdrawn patient consent, Other	1 (4)	1 (3)	2 (4)
Withdrawn patient consent, Toxicity	1 (4)	2 (7)	3 (6)

BAT best available therapy

Table S5: Best response with 12 months

Response	Best Available Therapy	Ruxolitinib	Overall
Complete response	23 (26%)	40 (43%)	63 (35%)
Partial response	58 (67%)	50 (54%)	108 (60%)
No response	6 (7%)	3 (3%)	9 (5%)

Table S6A: Results for the primary outcome including the gender stratification factor

		Odds ratio	90% CI	
Treatment	Ruxolitinib	2.12	(1.25, 3.60)	p=0.02
Sex	Female	1.24	(0.73, 2.10)	p=0.51

Table S6B: Results of the multivariable analysis for the primary outcome

		Odds ratio	90% CI	
Treatment	Ruxolitinib	2.03	(1.09, 3.78)	p=0.06
Age, per year		1.01	(0.98, 1.04)	p=0.51
Haemoglobin, per g/dl		1.02	(1.00, 1.04)	p=0.21
Number of previous therapies, per therapy		0.77	(0.53, 1.13)	p=0.26
Sex	Female	0.97	(0.52, 1.84)	p=0.95
Previous thrombosis	Yes	0.63	(0.33, 1.22)	p=0.25
Resistance or intolerance to hydroxycarbomide	Intolerant (only)	0.94	(0.46, 1.92)	p=0.88
	Intolerant and resistant	0.70	(0.31, 1.58)	p=0.47
Splenomegaly at baseline	Splenomegaly	0.13	(0.07, 0.24)	p<0.01
	Splenectomy	1.26	(0.09, 17.43)	p=0.89

Table S7A Venesections by treatment arm

	Number of venesections during the trial		Number of venesections during treatment		Average treatment length
	Total	Median (range) per patient	Total	Median (range) per patient	Median (range)
Best Available Therapy	307	1 (0, 25)	298	1 (0, 25)	42 months (1, 73)
Ruxolitinib	83	0 (0, 13)	77	0 (0, 13)	52 months (1,73)

Table S7B: Venesections by treatment arm

Treatment Arm		BAT	Ruxolitinib	Overall
Total number of venesections across treatment arm		307	84	391
Number of patients who received at least one venesection		45	27	72
Number of venesections per patient:	1	5	10	15
	2	6	6	12
	3	4	4	8
	4	4	1	5
	5	1	1	2
	6	5	2	7
	8	7	2	9
	9	2	0	2
	10	2	0	2
	11	4	0	4
	12	1	0	1
	13	1	1	2
	15	1	0	1
	24	1	0	1
	25	1	0	1

BAT best available therapy

Table S8A: Deaths on trial

Cause of death (n, %)	BAT (n = 17)	Ruxolitinib (n = 15)	Overall (n = 32)
Disease related	1 (6)	2 (13)	3 (9)
Disease and trial treatment related	1 (6)	0 (0)	1 (3)
Thrombosis or hemorrhage	4 (24)	1 (7)	5 (16)
Other cancer	3 (18)	4 (27)	7 (22)
Other Non-cancer	6 (35)	5 (33)	11 (34)
Not Known	1 (6)	2 (13)	3 (9)
Disease related, Other cancer	1 (6)	0 (0)	1 (3)
Trial treatment related, Other cancer	0 (0)	1 (7)	1 (3)

BAT best available therapy

Table S8B: Deaths attributable to other cancers

Treatment arm	Time on study	Treatment length	Primary cause of death	Type of other cancer
Best Available Therapy	18 months	18 months	Other cancer	Brain tumour
	22 months	22 months	Other cancer	Pancreatic
	36 months	36 months	Disease related and other cancer	Breast
	42 months	42 months	Other cancer	Unknown
Ruxolitinib	17 months	17 months	Other cancer	Ovarian
	27 months	26 months	Trial treatment related and other cancer	Squamous cell carcinoma
	29 months	27 months	Other cancer	Lung
	30 months	6 months	Other cancer	Acute Myeloid Leukaemia
	52 months	52 months	Other cancer	Unknown

Table S9: Thrombotic and hemorrhagic events during the study

Event	Toxicity	CTCAE Grade (Events (Patients))										
		Minor					Major					
		1	2	3	4	Any	1	2	3	4	5	Any
Hemorrhage	Gastric hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	1 (1)	0 (0)	0 (0)	3 (3)
	Intracranial hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)	3 (3)
	Hematoma	3 (1)	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Epistaxis	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Acute (L) subdural hematoma	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
	Colitis with hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
	Gastrointestinal bleed	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Intra-abdominal hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
	Laryngeal hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
	Retroperitoneal hemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Upper gastrointestinal haemorrhage	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
	Oral hemorrhage	2 (1)	1 (1)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Rectal hemorrhage	3 (1)	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Hematuria	2 (1)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Anal hemorrhage	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Hemorrhoids	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Menorrhagia	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Purpura	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Right eye subconjunctival haemorrhage	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Vitreous hemorrhage	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Thrombosis	Thromboembolic event	0 (0)	0 (0)	1 (1)	1 (1)	2 (2)	0 (0)	5 (1)	4 (1)	1 (1)	2 (1)	12 (11)
	Transient ischemic attacks	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	2 (1)	0 (0)	0 (0)	0 (0)	5 (5)
	Stroke	0 (0)	1 (1)	1 (1)	0 (0)	2 (2)	1 (1)	0 (0)	3 (1)	0 (0)	0 (0)	4 (3)
	Peripheral ischemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	0 (0)	2 (1)
	Chest pain - cardiac	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Acute coronary syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Cardiac arrest	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
	Gangrene on 3rd and 4th toes of R foot	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)

	Ischemia cerebrovascular	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
	Uncomplicated PE	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Lower limb ischaemia	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)

PE pulmonary embolism

Table S10: Estimated differences (Ruxolitinib minus BAT, negative difference indicates larger improvement from baseline in Rux arm) in mean change from baseline, MPN-10

MPN-10 Measure	Month	Mean Difference (95% CI) Rux – BAT	p-value
Total Symptom Score	2	-9.6 (-14.1, -5.2)	<0.001
	4	-11.3 (-15.7, -6.9)	<0.001
	8	-10.2 (-14.8, -5.7)	<0.001
	12	-9.8 (-14.5, -5.0)	<0.001
	16	-6.5 (-11.4, -1.7)	0.008
	20	-8.8 (-13.5, -4.1)	<0.001
	24	-9.3 (-14.0, -4.5)	<0.001
	28	-5.6 (-10.7, -0.6)	0.03
	32	-9.3 (-14.3, -4.3)	<0.001
	36	-3.2 (-8.2, 1.8)	0.21
	40	-3.0 (-8.0, 2.0)	0.24
	44	-5.9 (-11.1, -0.7)	0.03
	48	-6.0 (-11.6, -0.3)	0.04
	52	-2.8 (-8.6, 3.0)	0.35
	56	-2.1 (-8.5, 4.2)	0.51
	60	-3.1 (-9.6, 3.4)	0.35
Fatigue	2	-1.4 (-2.4, -0.3)	0.009
	4	-1.1 (-2.1, -0.1)	0.03
	8	-0.8 (-1.8, 0.2)	0.12
	12	-1.6 (-2.7, -0.6)	0.002
	16	-0.8 (-1.9, 0.3)	0.13
	20	-0.6 (-1.7, 0.4)	0.22
	24	-1.0 (-2.1, 0.0)	0.06
	28	-0.1 (-1.2, 1.1)	0.92
	32	-1.1 (-2.2, -0.0)	0.047
	36	0.1 (-1.0, 1.2)	0.88
	40	-0.1 (-1.2, 1.0)	0.87
	44	-1.9 (-3.1, -0.8)	<0.001
	48	-1.2 (-2.4, 0.1)	0.08
	52	-0.3 (-1.6, 0.9)	0.61
	56	-0.2 (-1.6, 1.2)	0.79
	60	-0.8 (-2.3, 0.6)	0.27
Early satiety	2	-1.2 (-2.1, -0.2)	0.02
	4	-1.1 (-2.1, -0.1)	0.03
	8	-1.6 (-2.6, -0.6)	0.002
	12	-1.3 (-2.3, -0.2)	0.02
	16	-1.4 (-2.5, -0.3)	0.01
	20	-1.4 (-2.4, -0.4)	0.008
	24	-1.7 (-2.8, -0.7)	0.001
	28	-0.9 (-2.0, 0.2)	0.12
	32	-1.1 (-2.2, 0.0)	0.06

	36	-1.1 (-2.2, -0.0)	0.046
	40	-0.8 (-1.9, 0.3)	0.16
	44	-0.2 (-1.4, 0.9)	0.71
	48	-2.0 (-3.2, -0.7)	0.002
	52	-0.5 (-1.8, 0.7)	0.41
	56	0.1 (-1.2, 1.5)	0.83
	60	-0.8 (-2.3, 0.6)	0.26
Abdominal discomfort	2	-0.3 (-1.2, 0.6)	0.53
	4	-0.3 (-1.2, 0.6)	0.48
	8	-1.4 (-2.3, -0.5)	0.003
	12	-0.3 (-1.2, 0.7)	0.6
	16	0.1 (-0.9, 1.1)	0.83
	20	-0.1 (-1.1, 0.8)	0.79
	24	-0.6 (-1.6, 0.4)	0.22
	28	-0.6 (-1.6, 0.4)	0.26
	32	-0.3 (-1.3, 0.8)	0.61
	36	0.2 (-0.8, 1.2)	0.69
	40	0.1 (-0.9, 1.1)	0.87
	44	-0.7 (-1.7, 0.4)	0.21
	48	-0.9 (-2.0, 0.3)	0.13
	52	-0.2 (-1.4, 1.0)	0.71
	56	-0.0 (-1.3, 1.2)	0.95
	60	0.2 (-1.1, 1.6)	0.73
Inactivity	2	-0.8 (-1.8, 0.2)	0.13
	4	-0.9 (-1.9, 0.0)	0.06
	8	-1.0 (-2.0, 0.0)	0.06
	12	-0.9 (-1.9, 0.2)	0.11
	16	-0.5 (-1.6, 0.6)	0.36
	20	-0.3 (-1.4, 0.7)	0.54
	24	-0.7 (-1.8, 0.3)	0.19
	28	-0.3 (-1.4, 0.9)	0.65
	32	-1.2 (-2.3, -0.1)	0.03
	36	0.7 (-0.4, 1.8)	0.24
	40	-0.0 (-1.1, 1.1)	0.97
	44	-0.3 (-1.4, 0.9)	0.63
	48	-0.1 (-1.4, 1.2)	0.88
	52	-0.9 (-2.2, 0.3)	0.15
	56	0.6 (-0.8, 2.0)	0.44
	60	0.3 (-1.1, 1.8)	0.66
Concentration problems	2	-0.8 (-1.7, 0.0)	0.06
	4	-1.1 (-2.0, -0.2)	0.01
	8	-0.8 (-1.7, 0.1)	0.08
	12	-0.8 (-1.8, 0.1)	0.08
	16	-0.3 (-1.2, 0.6)	0.53
	20	-0.3 (-1.2, 0.6)	0.51
	24	-0.8 (-1.7, 0.1)	0.09

	28	-0.4 (-1.4, 0.6)	0.43
	32	-0.2 (-1.1, 0.8)	0.73
	36	0.3 (-0.6, 1.3)	0.49
	40	0.1 (-0.8, 1.1)	0.78
	44	-0.1 (-1.2, 0.9)	0.78
	48	-0.2 (-1.3, 0.9)	0.77
	52	0.3 (-0.8, 1.4)	0.61
	56	0.1 (-1.2, 1.3)	0.93
	60	-0.3 (-1.5, 1.0)	0.68
Night sweats	2	-1.1 (-2.0, -0.2)	0.02
	4	-1.2 (-2.1, -0.3)	0.008
	8	-1.0 (-1.9, -0.1)	0.04
	12	-1.8 (-2.8, -0.9)	<0.001
	16	-1.1 (-2.1, -0.2)	0.02
	20	-1.1 (-2.1, -0.2)	0.02
	24	-1.0 (-2.0, -0.0)	0.04
	28	-0.7 (-1.8, 0.3)	0.16
	32	-1.2 (-2.3, -0.2)	0.02
	36	-1.1 (-2.1, -0.1)	0.03
	40	-0.5 (-1.5, 0.5)	0.32
	44	-0.9 (-2.0, 0.1)	0.09
	48	-0.1 (-1.3, 1.0)	0.85
	52	-0.4 (-1.6, 0.8)	0.53
	56	0.2 (-1.1, 1.5)	0.79
	60	-0.8 (-2.1, 0.5)	0.22
Itching	2	-2.2 (-3.2, -1.2)	<0.001
	4	-2.2 (-3.2, -1.3)	<0.001
	8	-1.4 (-2.4, -0.4)	0.005
	12	-1.7 (-2.8, -0.7)	<0.001
	16	-1.2 (-2.3, -0.2)	0.02
	20	-1.5 (-2.5, -0.5)	0.004
	24	-1.5 (-2.5, -0.5)	0.004
	28	-1.1 (-2.2, -0.0)	0.04
	32	-1.9 (-3.0, -0.8)	<0.001
	36	-1.1 (-2.2, -0.0)	0.04
	40	-0.6 (-1.7, 0.4)	0.24
	44	-1.2 (-2.4, -0.1)	0.03
	48	-0.4 (-1.7, 0.8)	0.47
	52	-0.1 (-1.4, 1.1)	0.83
	56	-0.7 (-2.0, 0.7)	0.35
	60	-0.7 (-2.1, 0.7)	0.31
Bone pain	2	-0.9 (-1.8, -0.0)	0.048
	4	-1.3 (-2.2, -0.5)	0.003
	8	-1.2 (-2.1, -0.3)	0.008
	12	-1.0 (-2.0, -0.1)	0.04
	16	-0.7 (-1.7, 0.3)	0.16

	20	-1.8 (-2.7, -0.8)	<0.001
	24	-1.2 (-2.1, -0.2)	0.02
	28	-0.9 (-1.9, 0.1)	0.09
	32	-0.8 (-1.8, 0.2)	0.11
	36	-0.2 (-1.2, 0.8)	0.65
	40	-0.6 (-1.6, 0.4)	0.21
	44	-0.6 (-1.6, 0.5)	0.29
	48	-1.0 (-2.1, 0.2)	0.09
	52	-0.4 (-1.5, 0.8)	0.52
	56	-0.8 (-2.1, 0.5)	0.22
	60	-1.1 (-2.4, 0.2)	0.08
Fever	2	-0.0 (-0.5, 0.5)	0.88
	4	-0.0 (-0.5, 0.5)	0.97
	8	0.1 (-0.4, 0.6)	0.75
	12	0.1 (-0.4, 0.7)	0.64
	16	-0.2 (-0.7, 0.4)	0.52
	20	-0.2 (-0.8, 0.3)	0.37
	24	-0.2 (-0.7, 0.3)	0.49
	28	0.0 (-0.6, 0.6)	0.99
	32	-0.5 (-1.0, 0.1)	0.1
	36	0.1 (-0.5, 0.7)	0.77
	40	0.1 (-0.4, 0.7)	0.62
	44	0.5 (-0.1, 1.0)	0.13
	48	0.5 (-0.1, 1.1)	0.12
	52	0.0 (-0.6, 0.7)	0.93
	56	-0.3 (-1.0, 0.4)	0.43
	60	0.4 (-0.3, 1.1)	0.28
Weight loss	2	-1.4 (-2.3, -0.5)	0.002
	4	-2.2 (-3.1, -1.4)	<0.001
	8	-2.0 (-2.9, -1.1)	<0.001
	12	-1.6 (-2.5, -0.6)	0.001
	16	-1.2 (-2.2, -0.2)	0.01
	20	-1.9 (-2.8, -0.9)	<0.001
	24	-1.2 (-2.2, -0.3)	0.01
	28	-1.6 (-2.6, -0.6)	0.001
	32	-2.0 (-3.0, -1.0)	<0.001
	36	-1.7 (-2.7, -0.7)	<0.001
	40	-0.9 (-1.9, 0.1)	0.07
	44	-1.2 (-2.3, -0.2)	0.02
	48	-1.7 (-2.9, -0.6)	0.002
	52	-1.3 (-2.5, -0.2)	0.02
	56	-1.6 (-2.9, -0.3)	0.01
	60	-0.1 (-1.4, 1.2)	0.93

Rux Ruxolitinib, BAT Best available therapy

Table S11A Adverse events; presented as Categories and Toxicities for categories experienced by at least 10% of patients

	BAT			Ruxolitinib		BAT+Ruxolitinib
Toxicity (Events (Patients))	**Grade 3**	**Grade 4**	**Grade 5**	**Grade 3**	**Grade 4**	**All grades**
Blood and lymphatic system disorders	**4 (3)**	**0 (0)**	**0 (0)**	**16 (11)**	**0 (0)**	**20 (14)**
Anemia	2 (1)	0 (0)	0 (0)	12 (7)	0 (0)	14 (8)
Leukocytosis	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	4 (4)
Other	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	2 (2)
Cardiac disorders	**2 (2)**	**4 (1)**	**0 (0)**	**3 (3)**	**0 (0)**	**9 (6)**
Ear and labyrinth disorders	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1)**	**0 (0)**	**1 (1)**
Endocrine disorders	**0 (0)**	**0 (0)**	**0 (0)**	**1 (1)**	**0 (0)**	**1 (1)**
Eye disorders	**3 (3)**	**0 (0)**	**0 (0)**	**2 (1)**	**0 (0)**	**5 (4)**
Gastrointestinal disorders	**9 (6)**	**3 (3)**	**0 (0)**	**12 (9)**	**0 (0)**	**25 (18)**
Abdominal pain	3 (2)	0 (0)	0 (0)	1 (1)	0 (0)	4 (3)
Ascites	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Colonic obstruction	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Dental caries	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Diarrhea	2 (2)	2 (2)	0 (0)	2 (2)	0 (0)	6 (5)
Dry mouth	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Nausea	1 (1)	0 (0)	0 (0)	2 (2)	0 (0)	3 (3)
Other	1 (1)	1 (1)	0 (0)	3 (3)	0 (0)	5 (5)
Retroperitoneal hemorrhage	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Vomiting	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	2 (2)
General disorders and administration site conditions	**6 (5)**	**0 (0)**	**0 (0)**	**6 (6)**	**0 (0)**	**12 (11)**
Hepatobiliary disorders	**5 (5)**	**0 (0)**	**0 (0)**	**0 (0)**	**0 (0)**	**5 (5)**
Infections and infestations*	**4 (4)**	**7 (4)**	**0 (0)**	**18 (14)**	**2 (2)**	**33 (25)**
Injury, poisoning and procedural complications	**4 (4)**	**0 (0)**	**0 (0)**	**9 (6)**	**1 (1)**	**15 (11)**
Investigations	**2 (2)**	**0 (0)**	**0 (0)**	**11 (9)**	**1 (1)**	**14 (12)**
Alanine aminotransferase increased	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	2 (2)
Alkaline phosphatase increased	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Blood bilirubin increased	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Lymphocyte count decreased	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
Neutrophil count decreased	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	2 (2)
Other	0 (0)	0 (0)	0 (0)	4 (4)	0 (0)	4 (4)
Platelet count decreased	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
Weight loss	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)
White blood cell decreased	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Metabolism and nutrition disorders	**6 (4)**	**1 (1)**	**0 (0)**	**8 (6)**	**1 (1)**	**16 (11)**
Musculoskeletal and connective tissue disorders	**2 (2)**	**0 (0)**	**0 (0)**	**10 (6)**	**0 (0)**	**12 (8)**
Neoplasms benign, malignant and unspecified (incl cysts and polyps)*	**3 (3)**	**1 (1)**	**0 (0)**	**7 (6)**	**1 (1)**	**12 (11)**
Nervous system disorders	**8 (7)**	**1 (1)**	**1 (1)**	**9 (7)**	**0 (0)**	**20 (17)**
Depressed level of consciousness	0 (0)	0 (0)	0 (0)	2 (1)	0 (0)	2 (1)
Dizziness	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Headache	1 (1)	0 (0)	0 (0)	2 (2)	0 (0)	3 (3)
Intracranial haemorrhage	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	2 (2)
Other	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)
Paresthesia	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Stroke	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	3 (2)
Syncope	3 (3)	0 (0)	0 (0)	2 (1)	0 (0)	5 (4)
Vasovagal reaction	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Psychiatric disorders	**1 (1)**	**0 (0)**	**0 (0)**	**1 (1)**	**2 (2)**	**4 (4)**
Renal and urinary disorders	**2 (2)**	**1 (1)**	**0 (0)**	**0 (0)**	**0 (0)**	**3 (3)**

Respiratory, thoracic and mediastinal disorders	**4 (4)**	**2 (2)**	**0 (0)**	**8 (5)**	**1 (1)**	**15 (11)**
Skin and subcutaneous tissue disorders	**1 (1)**	**0 (0)**	**0 (0)**	**13 (10)**	**0 (0)**	**16 (13)**
Other	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)	4 (4)
Pruritus	0 (0)	0 (0)	0 (0)	5 (3)	0 (0)	6 (4)
Skin ulceration	1 (1)	0 (0)	0 (0)	5 (4)	0 (0)	6 (5)
Surgical and medical procedures	2 (2)	0 (0)	0 (0)	2 (2)	0 (0)	4 (4)
Vascular disorders	7 (6)	1 (1)	2 (2)	14 (8)	0 (0)	24 (16)

* Malignancies and infections were deemed adverse events of special interest and have been presented separately.

No Grade 5 events occurred in the Ruxolitinib arm
BAT Best available therapy

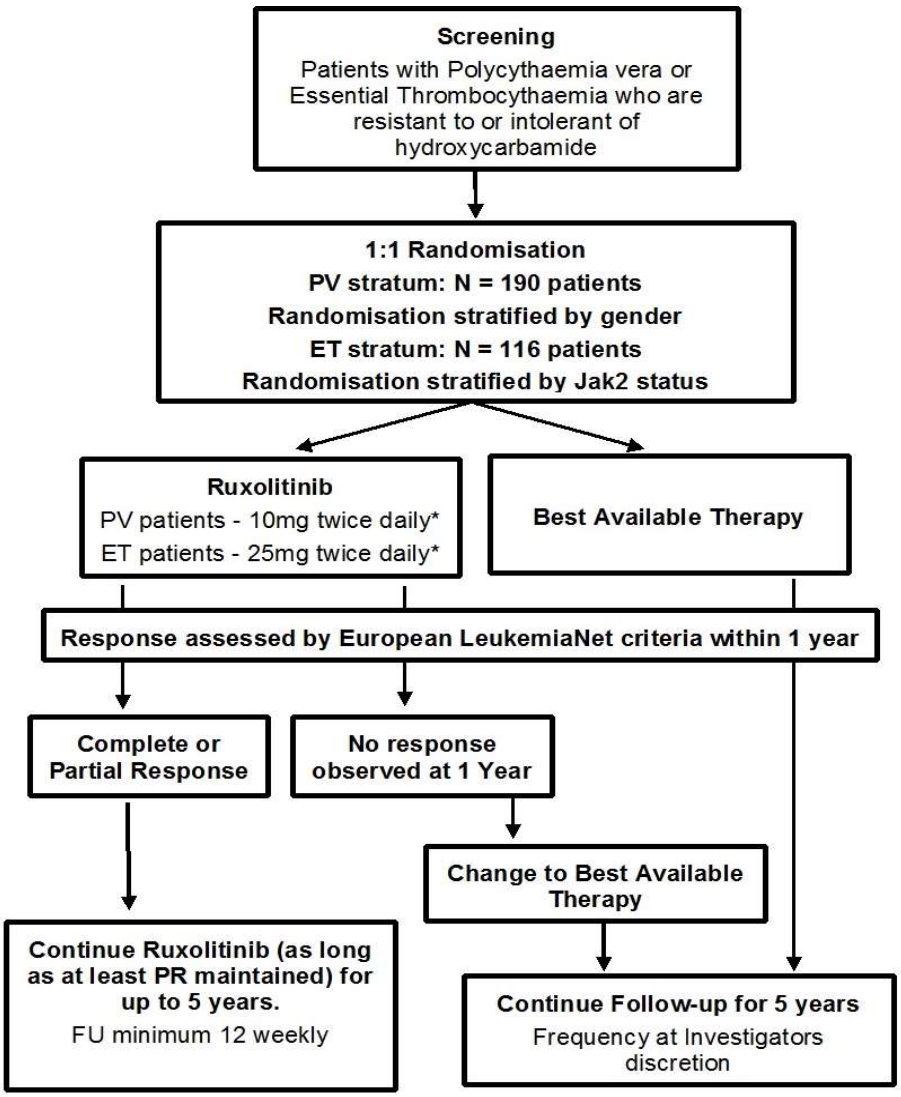
Table S11B: Specific details of infection and malignant neoplasm adverse events

Toxicity (Events (Patients))		BAT				Ruxolitinib				
		Grade 1/2	Grade 3	Grade 4	Any grade	Grade 1/2	Grade 3	Grade 4	Grade 5	Any grade
Infections	Respiratory	42 (25)	4 (4)	0 (0)	46 (28)	44 (28)	10 (7)	1 (1)	0 (0)	55 (33)
	Cutaneous	19 (15)	0 (0)	1 (1)	20 (16)	27 (21)	4 (4)	0 (0)	0 (0)	31 (22)
	Genitourinary	10 (9)	0 (0)	0 (0)	11 (10)	17 (11)	1 (1)	0 (0)	0 (0)	19 (12)
	Gastrointestinal	12 (9)	0 (0)	0 (0)	12 (9)	7 (7)	5 (3)	0 (0)	0 (0)	12 (10)
	Herpes Zoster	3 (3)	0 (0)	0 (0)	3 (3)	8 (8)	1 (1)	0 (0)	0 (0)	9 (9)
	Sepsis	0 (0)	1 (1)	6 (4)	7 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Musculoskeletal	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	3 (1)
	Conjunctivitis	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)
	Lymph gland infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	2 (2)
	Ear and labyrinthine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Endocarditis infective	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Neurological	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
	Non specified viral	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Malignant neoplasms	Transformation - Myelofibrosis	6 (6)	4 (4)	0 (0)	10 (10)	1 (1)	4 (4)	0 (0)	0 (0)	5 (5)
	Transformation - AML	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (4)	0 (0)	0 (0)	4 (4)
	Transformation - MDS	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Skin - Squamous cell carcinoma	0 (0)	0 (0)	0 (0)	0 (0)	9 (5)	2 (2)	0 (0)	0 (0)	11 (6)
	Skin - Basal cell carcinoma	1 (1)	0 (0)	0 (0)	1 (1)	3 (3)	0 (0)	0 (0)	0 (0)	3 (3)
	Skin - Melanoma	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Skin - type not specified	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Breast cancer	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	2 (2)
	Malignant neoplasm	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Neurological	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Ovarian cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
	Prostate cancer	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Toxicity (Events (Patients))		BAT				Ruxolitinib				
		Grade 1/2	Grade 3	Grade 4	Any grade	Grade 1/2	Grade 3	Grade 4	Grade 5	Any grade
Infections	**Infections**									
	Respiratory	42 (25)	4 (4)	0 (0)	46 (28)	44 (28)	10 (7)	1 (1)	0 (0)	55 (33)
	Cutaneous	19 (15)	0 (0)	1 (1)	20 (16)	27 (21)	4 (4)	0 (0)	0 (0)	31 (22)
	Genitourinary	10 (9)	0 (0)	0 (0)	11 (10)	17 (11)	1 (1)	0 (0)	0 (0)	19 (12)
	Gastrointestinal	12 (9)	0 (0)	0 (0)	12 (9)	7 (7)	5 (3)	0 (0)	0 (0)	12 (10)
	Herpes Zoster	3 (3)	0 (0)	0 (0)	3 (3)	8 (8)	1 (1)	0 (0)	0 (0)	9 (9)
	Sepsis	0 (0)	1 (1)	6 (4)	7 (5)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Musculoskeletal	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)	0 (0)	0 (0)	0 (0)	3 (1)
	Conjunctivitis	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)	2 (2)
	Lymph gland infection	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	2 (2)
	Ear and labyrinthine	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Endocarditis infective	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Neurological	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
	Non specified viral	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)
Malignant neoplasms	Malignant neoplasms									
	Transformation - Myelofibrosis	6 (6)	4 (4)	0 (0)	10 (10)	1 (1)	4 (4)	0 (0)	0 (0)	5 (5)
	Transformation - AML	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (4)	0 (0)	0 (0)	4 (4)
	Transformation - MDS	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Skin - Squamous cell carcinoma	0 (0)	0 (0)	0 (0)	0 (0)	9 (5)	2 (2)	0 (0)	0 (0)	11 (6)
	Skin - Basal cell carcinoma	1 (1)	0 (0)	0 (0)	1 (1)	3 (3)	0 (0)	0 (0)	0 (0)	3 (3)
	Skin - Melanoma	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Skin - type not specified	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Breast cancer	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	2 (2)
	Malignant neoplasm	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
	Neurological	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Ovarian cancer	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1)	1 (1)
	Prostate cancer	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

BAT Best available therapy, AML acute myeloid leukemia, MDS myelodysplastic syndrome

Figure S1: Trial schema



*Patients with platelet count between 100 and 200 x 10^9/L will be started on a reduced dose

Figure S2: Mean total daily ruxolitinib dose over time

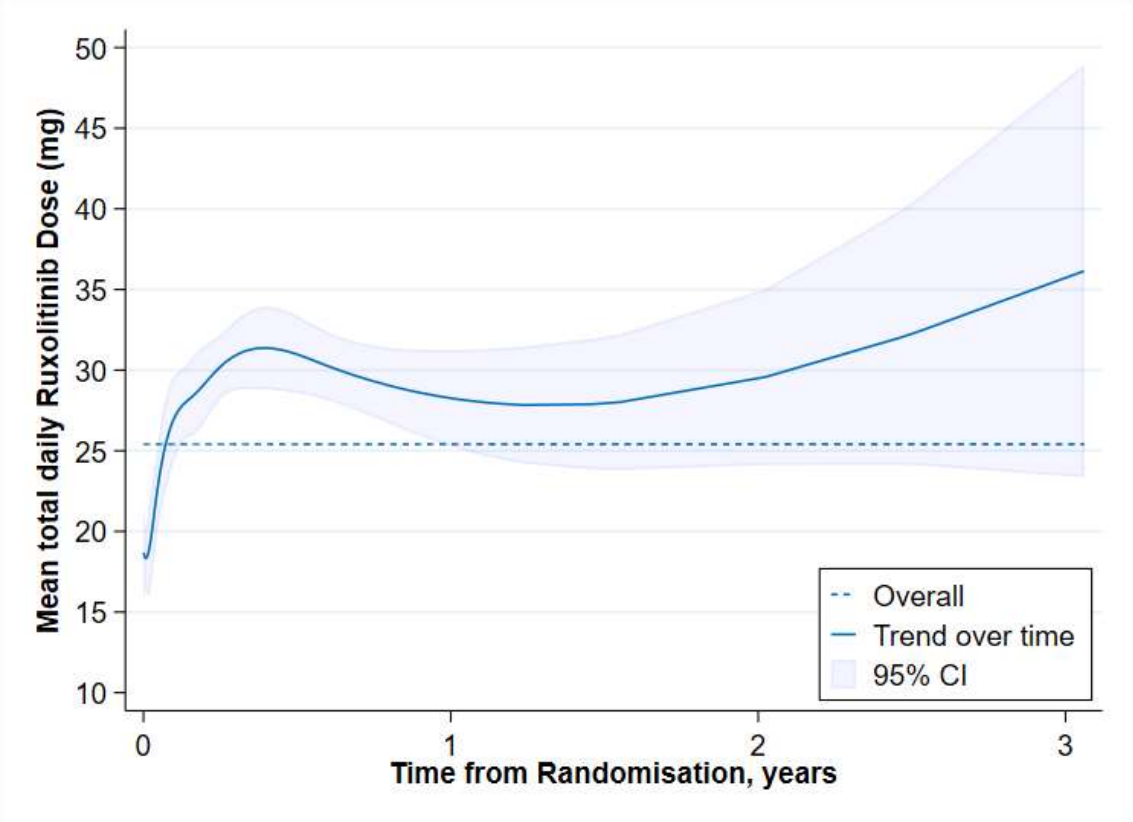
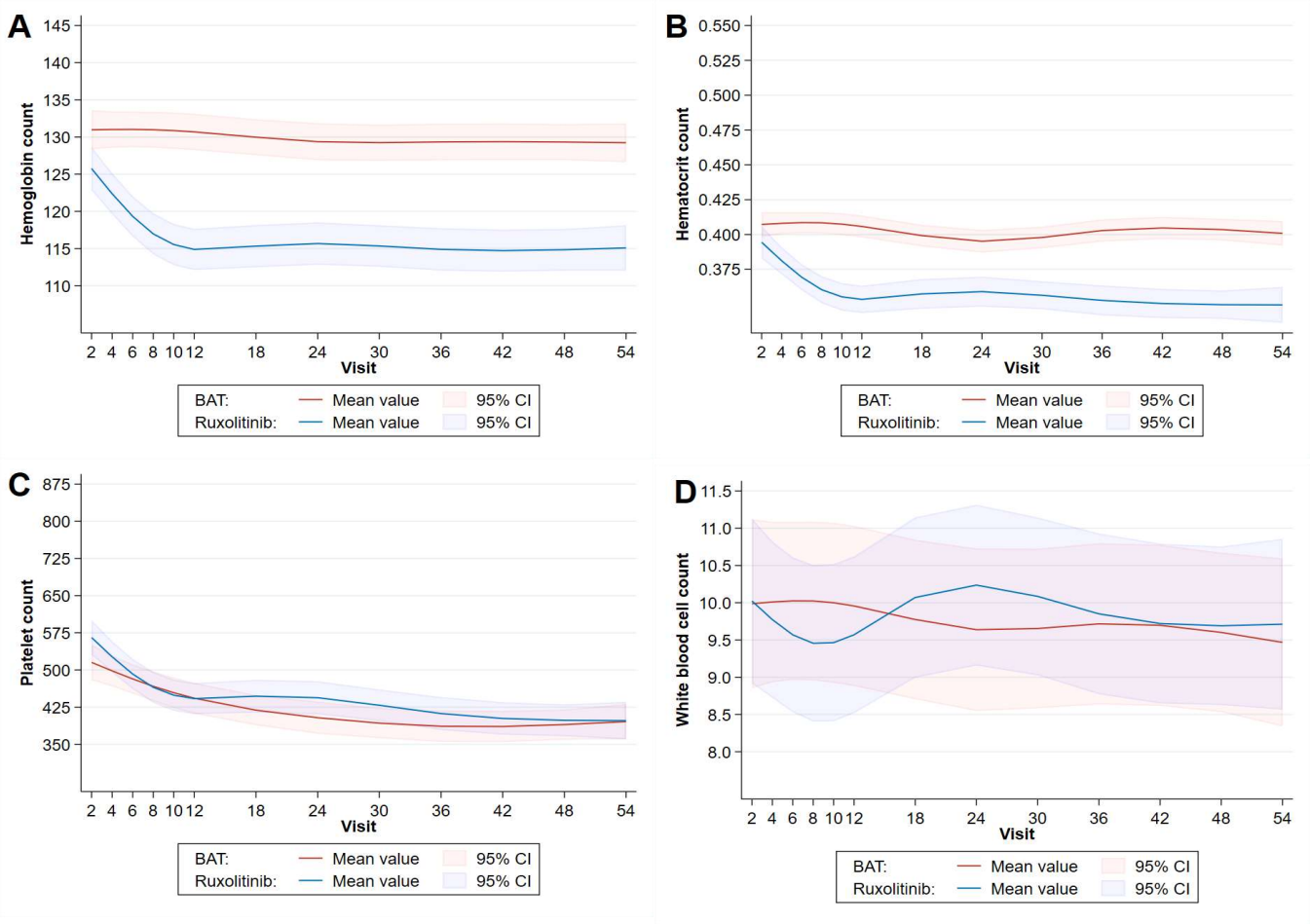
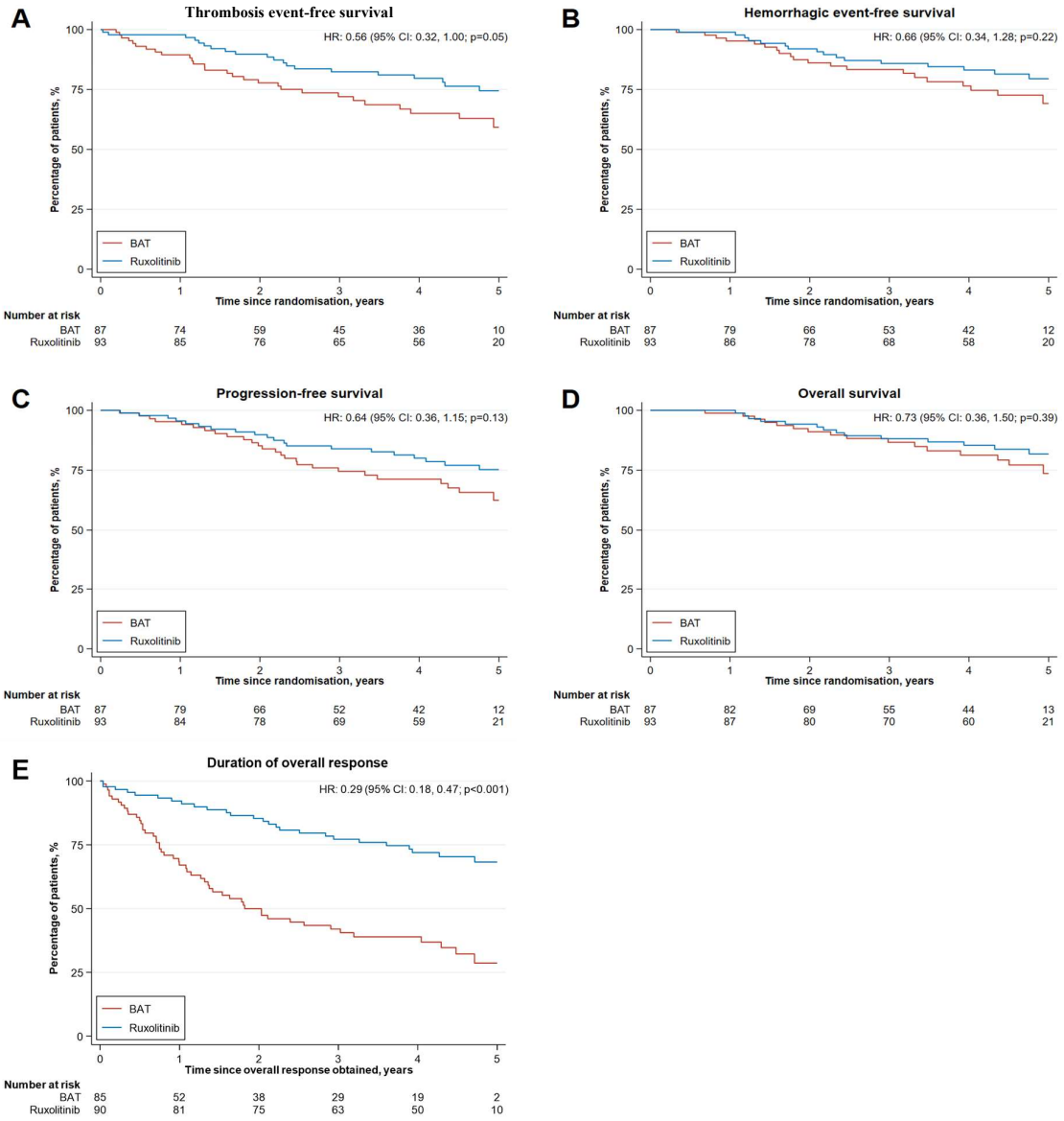


Figure S3: Hematological parameters by treatment arm



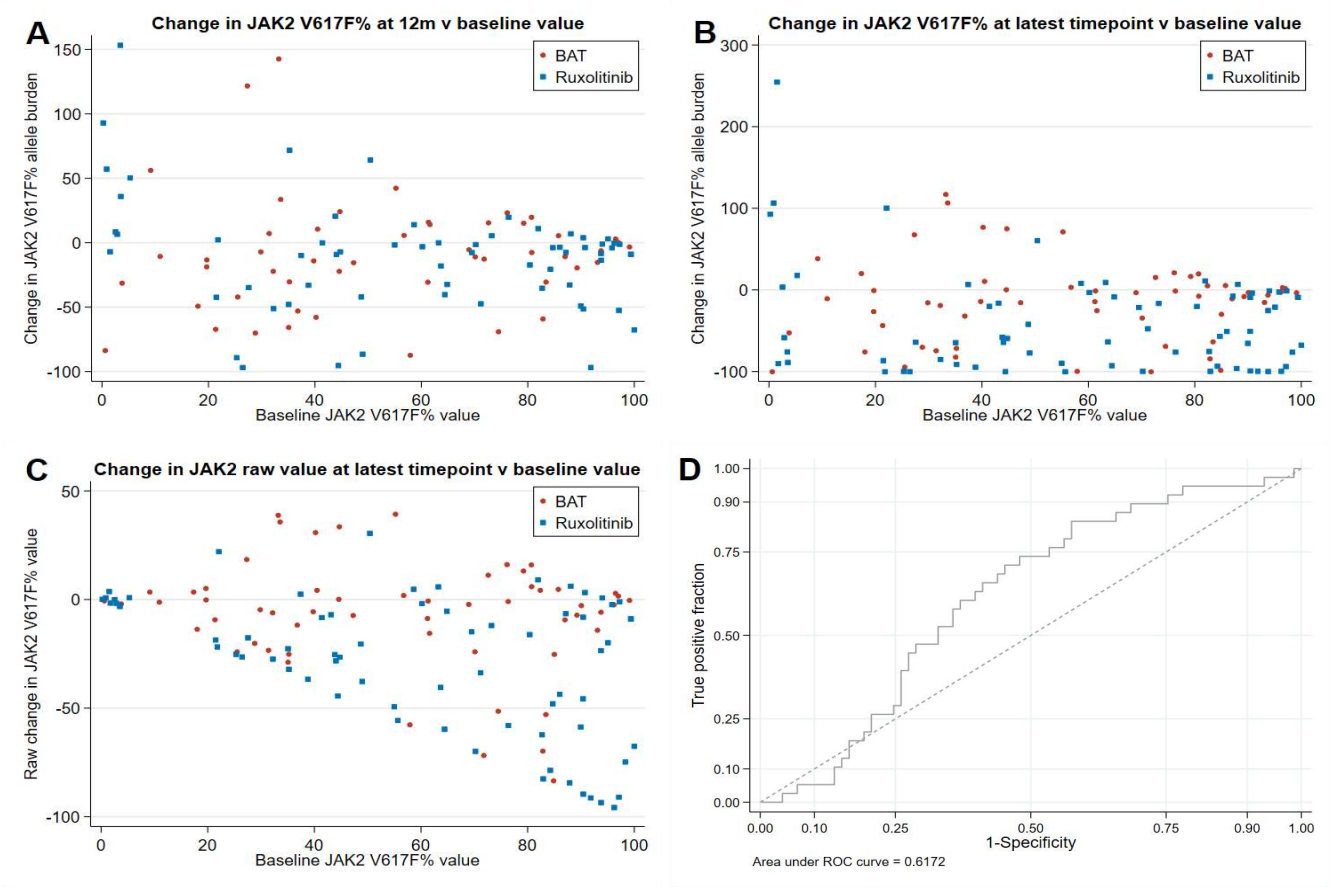
Hematological parameters over the course of the study, ruxolitinib (RUX) in blue, Best Available Therapy (BAT) in red.
A) Hemoglobin, B) Hematocrit, C) Platelets, D) White blood cells (WBC).

Figure S4: Clinical endpoints by treatment arm



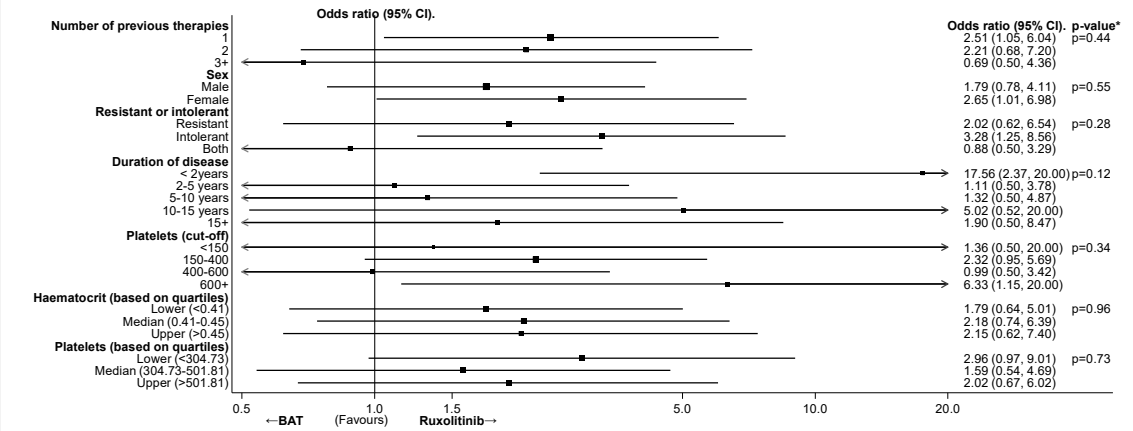
Kaplan-Meier plots of outcome by treatment arm, p value obtained from a Cox model adjusting for sex. ruxolitinib in blue, Best Available Therapy (BAT) in red, A) Major thrombosis, B) Major hemorrhage, C) Progression-free survival, D) Overall-Survival, E) Duration of overall response.

Figure S5 Molecular responses for patients in MAJIC-PV



Scatter plots of JAK2V617F% at baseline vs A) % change at 12m, and B) % change at the last time point available, and C) raw difference between baseline and the last time point. Ruxolitinib treated patients are in blue, Best Available Therapy (BAT) patients in red. D) ROC curve analysis of percentage change in *JAK2*V617F allele burden

Figure S6 Forest plot for subgroup analysis of the primary outcome in MAJIC-PV



Forest plot of gender-adjusted odds ratios from the subgroup analysis for obtaining a complete response within 12 months. P-values presented describe the heterogeneity of the subgroup, as obtained using likelihood ratio tests.

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