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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Kiladjian J-J, Zachee P, Hino M, et al. Long-term efficacy and safety of ruxolitinib versus best available therapy in polycythaemia vera (RESPONSE): 5-year follow up of a phase 3 study. *Lancet Haematol* 2020; published online Jan 23. https://doi.org/10.1016/S2352-3026(19)30207-8.

Supplementary Table 1. Summary of reasons of screen failures

Reasons for exclusion	N=120
Patients meeting the following exclusion criteria	
Active malignancy over the previous 5 years with exception as described in the study protocol and with no evidence for recurrence in the past 3 years	5 (4.2%)
Alcohol or drug addiction that would interfere with the ability to comply with the study requirements	1 (0.8%)
Clinically significant bacterial, fungal, parasitic or viral infection which requires therapy or known active hepatitis A, B or C at screening or known HIV positivity	1 (0.8%)
Clinically significant cardiac disease (NYHA class III or IV)	1 (0.8%)
Subject of childbearing potential who are unwilling to take appropriate precautions as described in study protocol	2 (1.7%)
Physician decision	1 (0.8%)
Subject decision	3 (2.5%)
Uncontrolled intercurrent illness or any concurrent condition that would jeopardize the safety of the subject or compliance with the protocol	7 (5.8%)
Patients not meeting the following inclusion criteria	
ANC $\geq$1.5 X 10^9/L and PLT $\geq$100 X 10^9/L at screening	3 (2.5%)
At least one of the following at screening: A. WBC >15 X 10^9/L. B. PLT >600 X 10^9/L	14 (11.7%)
Subject with/without a palpable spleen defined with volume $\geq$450 cm^3	30 (25.0%)
Two or more phlebotomies within 24 weeks of screening with at least one within 12 weeks	29 (24.2%)
Palpable spleen $\geq$5 cm	4 (3.3%)
PEG-IFN-Alpha-2A within 5 weeks of screening or having a prior history of 32P therapy	1 (0.8%)
Peripheral blood blast count of 0% at screening	10 (8.3%)
PV diagnosis for at least 6 months prior to screening	4 (3.3%)
Resistance or intolerance to hydroxyurea	11 (9.2%)
Stable regimen for at least 2 weeks prior to screening and no less than 4 weeks prior to randomization	2 (1.7%)

A patient may have several reasons for screening failure;

ANC, absolute neutrophil count; HIV, human immunodeficiency virus; PLT, platelet; PV, polycythemia vera; WBC, white blood corpuscle

Supplementary Table 2. Baseline Patient Characteristics

n (%)	Ruxolitinib n = 110	BAT n = 112
Median age (range) — years	62.0 (34-90)	60.0 (33-84)
Men — %	60.0	71.4
Median time since PV diagnosis (range) — years	8.2 (0.5-36)	9.3 (0.5-23)
Median duration of prior HU therapy (range) — years	3.1 (<0.1–20.9)	2.8 (<0.1–20.9)
ECOG performance status — %		
0	69.1	68.8
1	28.2	30.4
2	2.7	0.9
Resistance/intolerance to HU — %		
Intolerance	53.6	54.5
Resistance	46.4	45.5
Prior thromboembolic event — %	35.5	29.5
JAK2 V617F mutation positive — %	94.5	95.5
Mean allele burden (SD) — %	76.2 (17.8)	75.0 (22.6)
Median spleen length below costal margin (range) — cm	7.00 (0.0-24.0)	7.00 (0.0-25.0)
Spleen length < 10 cm — %	64.5	59.8
Median spleen volume (range) — cm^3	1195 (396-4631)	1322 (254-5147)
Mean hematocrit (SD) — %[a]	43.6 (2.2)	43.9 (2.2)
Hematocrit category – %		
40%-45%	71.8	74.1
> 45%	25.5	22.3
Mean WBC count (SD), $\times 10^9$/L	17.6 (9.6)	19.0 (12.2)
Mean platelet count (SD), $\times 10^9$/L	484.5 (323.3)	499.4 (318.6)
Median number phlebotomies in the 24 weeks prior to screening (range)	2.0 (1.0-8.0)	2.0 (0-16.0)

[a] Following HCT control period before randomization. Patients who achieved an HCT between 40% and 45% within 14 days before their day 1 visit could proceed to randomization; however, HCT at baseline may have been higher or lower.

ECOG, Eastern Cooperative Oncology Group; HCT, hematocrit; HU, hydroxyurea; PV, polycythemia vera; SD, standard deviation; WBC, white blood cells.

Supplementary Table 3. Patient disposition at completion of the RESPONSE study (5-year final analysis)

	Ruxolitinib (n = 110)	BAT[a] (n = 112)	Ruxolitinib after crossover from BAT (n = 98)
Reasons for discontinuation of treatment, n (%)			
Completed treatment period	72 (65·5)	1 (0·9)	64 (65·3)
Adverse event	16 (14·5)	2 (1·8)	16 (16·3)
Disease progression	12 (10·9)	1 (0·9)	9 (9·2)
Patient decision	6 (5·5)	5 (4·5)	6 (6·1)
Lack of efficacy	0	100 (89·3)	0
Others (protocol deviation and/or lost to follow-up and/or physician decision)	3 (2·7)	2 (1·8)	3 (3·1)
Death[b]	1 (0·9)	0	0
Median (Interquartile range) treatment exposure, weeks	255 (158 – 256)	34 (32 – 36)	220 (135 – 223)

[a] One patient was randomised to BAT but did not receive study treatment. Initial BAT included hydroxyurea (n = 66), IFN/pegylated IFN (n = 13), anagrelide (n = 8), IMIDs (n = 5), pipobroman (n = 2), and observation (n = 17).
For patients who were randomised to BAT and then crossed over to ruxolitinib, the reasons for end of BAT are reported in the "BAT" column.
[b] One patient in the ruxolitinib arm, determined by the investigator to have discontinued the study treatment due to AEs, died afterwards.
Abbreviations: AE, adverse event; BAT, best available therapy; IFN, interferon; IMID, immunomodulator.

Supplementary Table 4. Principle causes of deaths in the ruxolitinib and BAT arms

Ruxolitinib (N = 10)	**BAT (N = 9)**
Pneumonia (n = 1)	Cecal neoplasia with local ganglionic metastasis (n = 1)
Worsening of colon carcinoma (n=1)	Acute myeloid leukemia (n = 1)
Unknown (n = 1)	Hepatorenal syndrome (n = 1)
Multiple comorbidities (n = 1)	Disease progression (n = 1)
Gastric adenocarcinoma (n = 1)	Pulmonary carcinoma (n = 1)
Sternal tumor invasion (n = 1)	Shock (n = 1)
Recurrence of breast cancer (n = 1)	Adverse events (n = 1)
Heart failure and atrial fibrillation (n = 1)	Study indication (n = 1)
Acute myeloid leukemia (n = 1)	CNS hemorrhage (n = 1)
Multifocal metastatic lesion (n = 1)	

Abbreviations: BAT, best available therapy; CNS, central nervous system.

Supplementary Table 5. Exposure-adjusted rates (per 100 patient-year) of second malignancy events

Event	Ruxolitinib rate per 100 patient-year of exposure N = 110 Exposure = 428·4 patient-year	BAT rate per 100 patient-year of exposure N = 111 Exposure = 73·6 patient-year	Crossover rate per 100 patient-year of exposure N = 98 Exposure = 329·9 patient-year
Number of patients (rate[a])	**All grades**	**All grades**	**All grades**
All second malignancies[a,b]	**30 (7·0)**	**3 (4·1)**	**15 (4·5)**
Non-melanoma skin cancer	22 (5·1)	2 (2·7)	9 (2·7)
Squamous cell carcinoma[c]	6 (1·4)	0 (0·0)	4 (1·2)
Malignant melanoma	1 (0·2)	1 (1·4)	0 (0·0)
Prostate cancer	1 (0·2)	0 (0·0)	2 (0·6)
Breast cancer	2 (0·4)	0 (0·0)	0 (0·0)
Lymphoma	0 (0·0)	0 (0·0)	0 (0·0)
Disease progression[d]			
Acute myeloid leukemia	1 (0·2)	0 (0·0)	2 (0·6)
Myelofibrosis	9 (2·1)	1 (1·4)	6 (1·8)

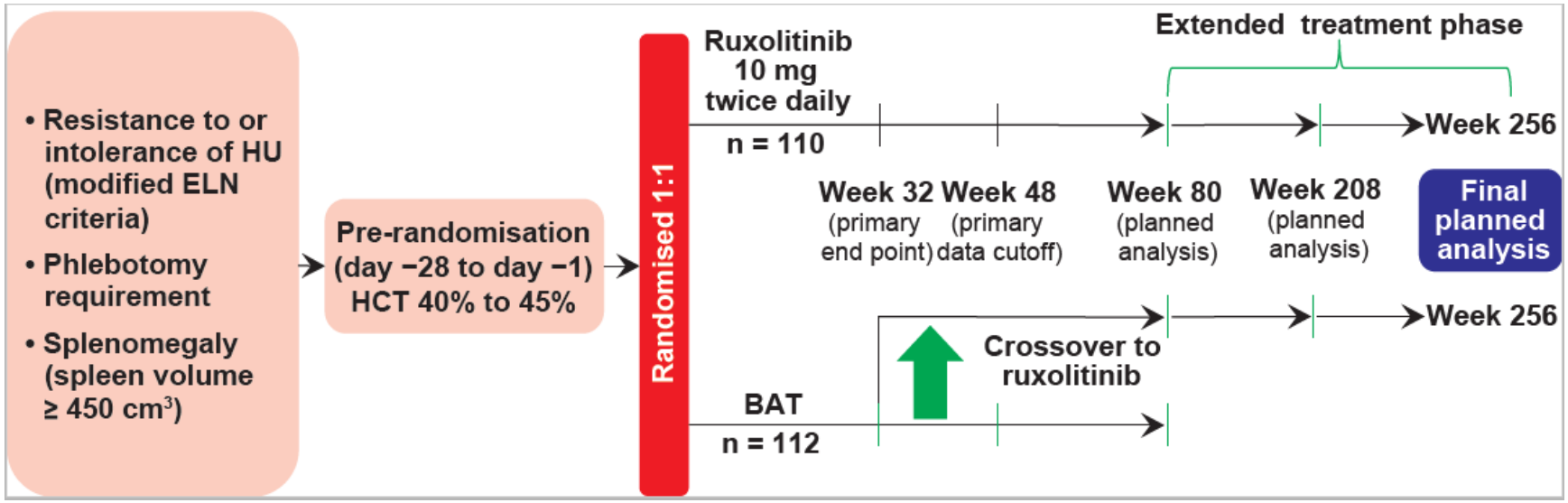
[a] Adjusted rates were calculated as the number of events per 100 patient-years of exposure.
[b] Events occurring in ≥ 0·5% of patients in any group.
[c] All events were squamous cell carcinoma of the skin, including the region of parotid gland. No case of metastatic disease was reported.
[d] Events occurring in ≥ 1 patient(s) in any group.
Abbreviation: BAT, best available therapy.

Supplementary Table 6. Exposure-adjusted rates (per 100 patient-year) of non-melanoma skin cancer events by prior history of malignancy status

Non-melanoma skin cancer events[a,b]	Ruxolitinib rate per 100 patient-year of exposure N = 110 Exposure = 428·4 patient-year		BAT rate per 100 patient-year of exposure N = 111 Exposure = 73·6 patient-year		Crossover rate per 100 patient-year of exposure N = 98 Exposure = 329·9 patient-year	
Prior history of non-melanoma skin cancer	**No (n = 97)**	**Yes (n = 13)**	**No (n = 105)**	**Yes (n = 6)**	**No (n = 92)**	**Yes (n = 6)**
Patient-year of exposure	**385·3**	**43·0**	**70·1**	**3·5**	**307·5**	**22·4**
Total events	**14 (3·6)**	**8 (18·6)**	**1 (1·4)**	**1 (28·5)**	**6 (2·0)**	**3 (13·4)**
Basal cell carcinoma	10 (2·6)	7 (16·3)	1 (1·4)	0 (0·0)	4 (1·3)	1 (4·5)
Squamous cell carcinoma of skin	5 (1·3)	4 (9·3)	0 (0·0)	0 (0·0)	3 (1·0)	1 (4·5)
Squamous cell carcinoma[b]	3 (0·8)	3 (7·0)	0 (0·0)	0 (0·0)	2 (0·7)	2 (8·9)
Bowen's disease	1 (0·3)	1 (2·3)	0 (0·0)	1 (28·5)	0 (0·0)	0 (0·0)
Carcinoma in situ of skin	0 (0·0)	2 (4·6)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Metastatic squamous cell carcinoma	0 (0·0)	2 (4·6)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)
Keratoacanthoma	1 (0·3)	0 (0)	0 (0·0)	0 (0·0)	0 (0·0)	0 (0·0)

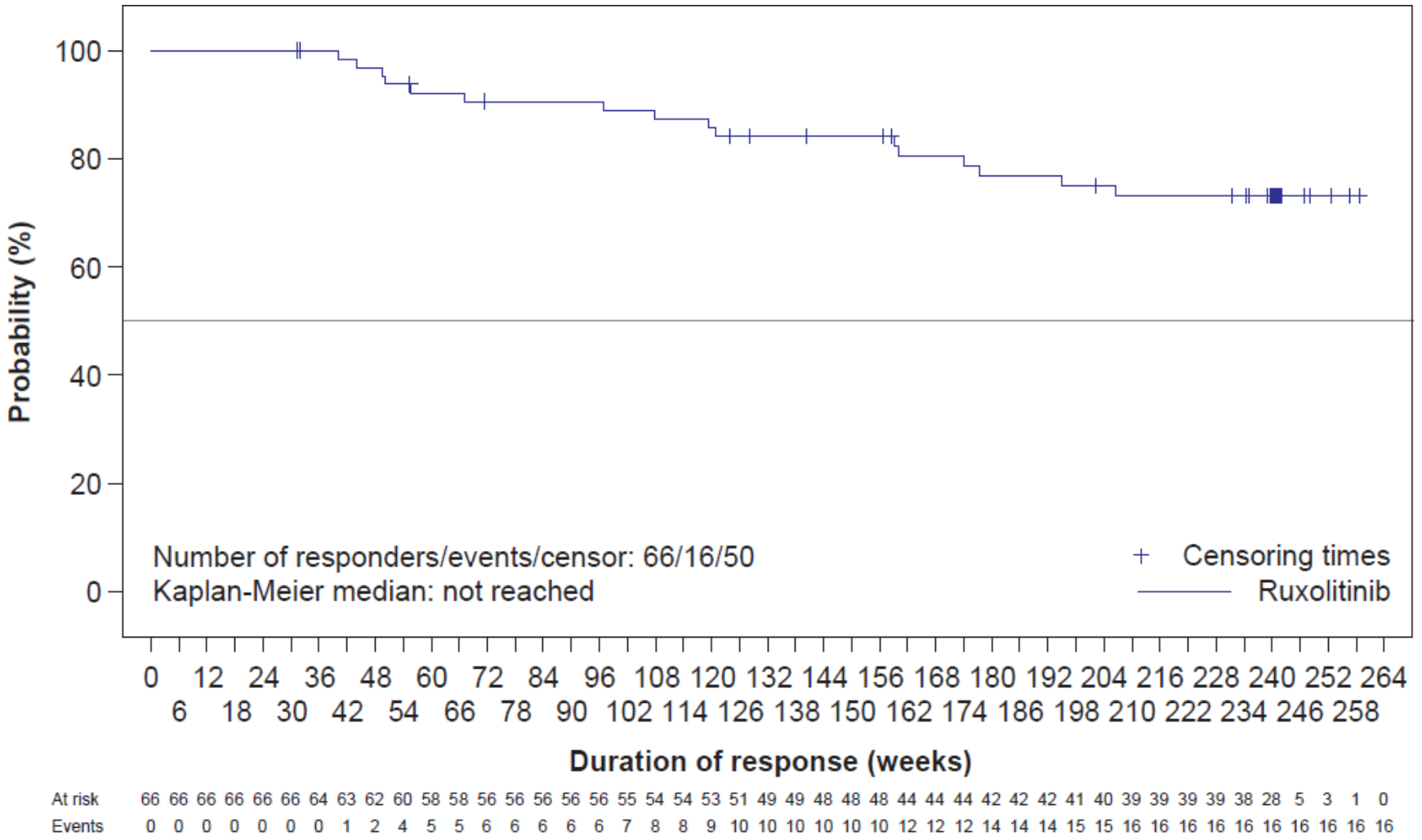
[a] Adjusted rates were calculated as the number of events per 100 patient-years of exposure.
[b] All events were squamous cell carcinoma of the skin, including the region of parotid gland. No case of metastatic disease was reported.
Abbreviation: BAT, best available therapy.

Supplementary Figure 1. RESPONSE study design

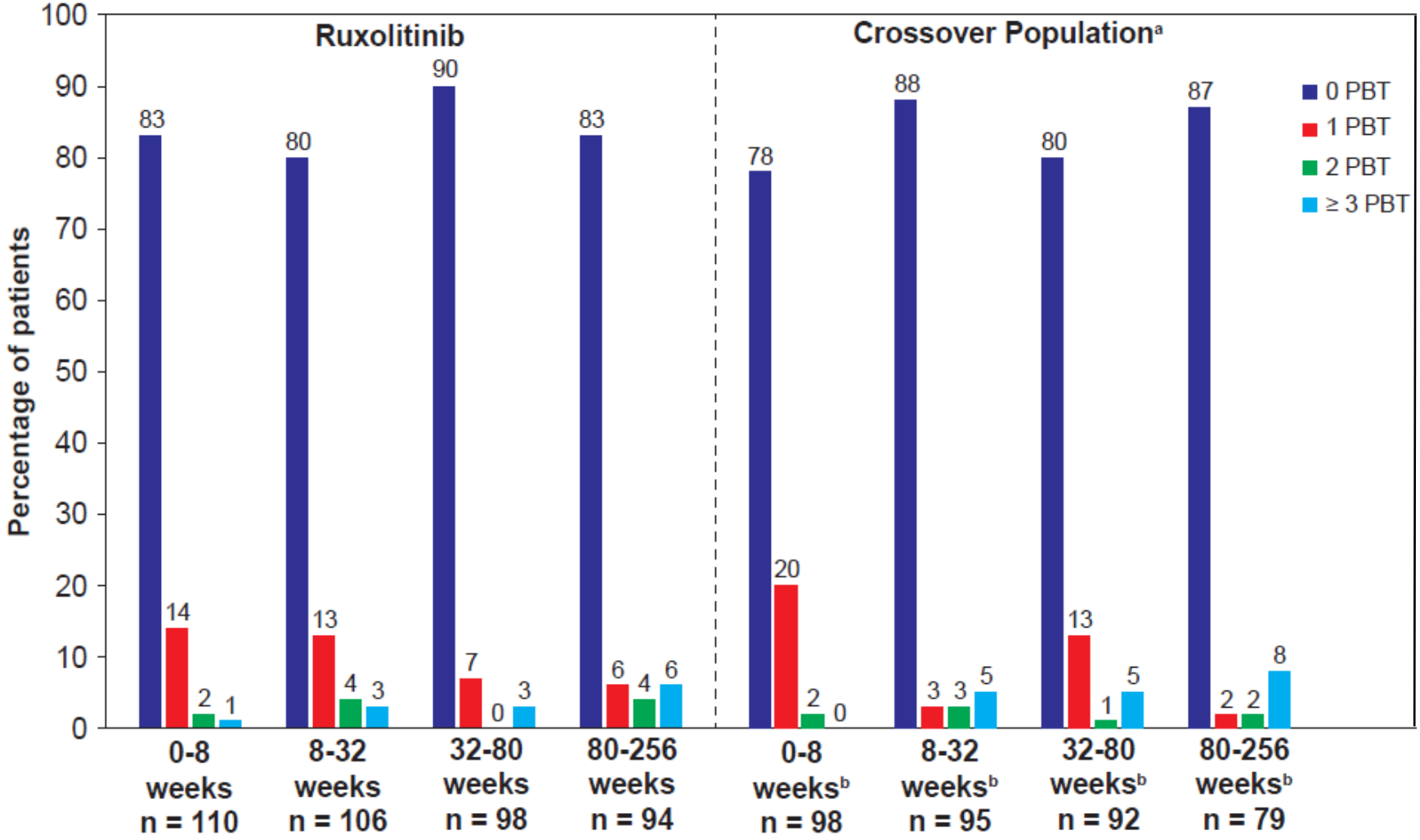


Abbreviations: BAT, best available therapy; ELN, European LeukemiaNet; HCT, haematocrit; HU, hydroxyurea.

Supplementary Figure 2. Durability of hematocrit control with ruxolitinib



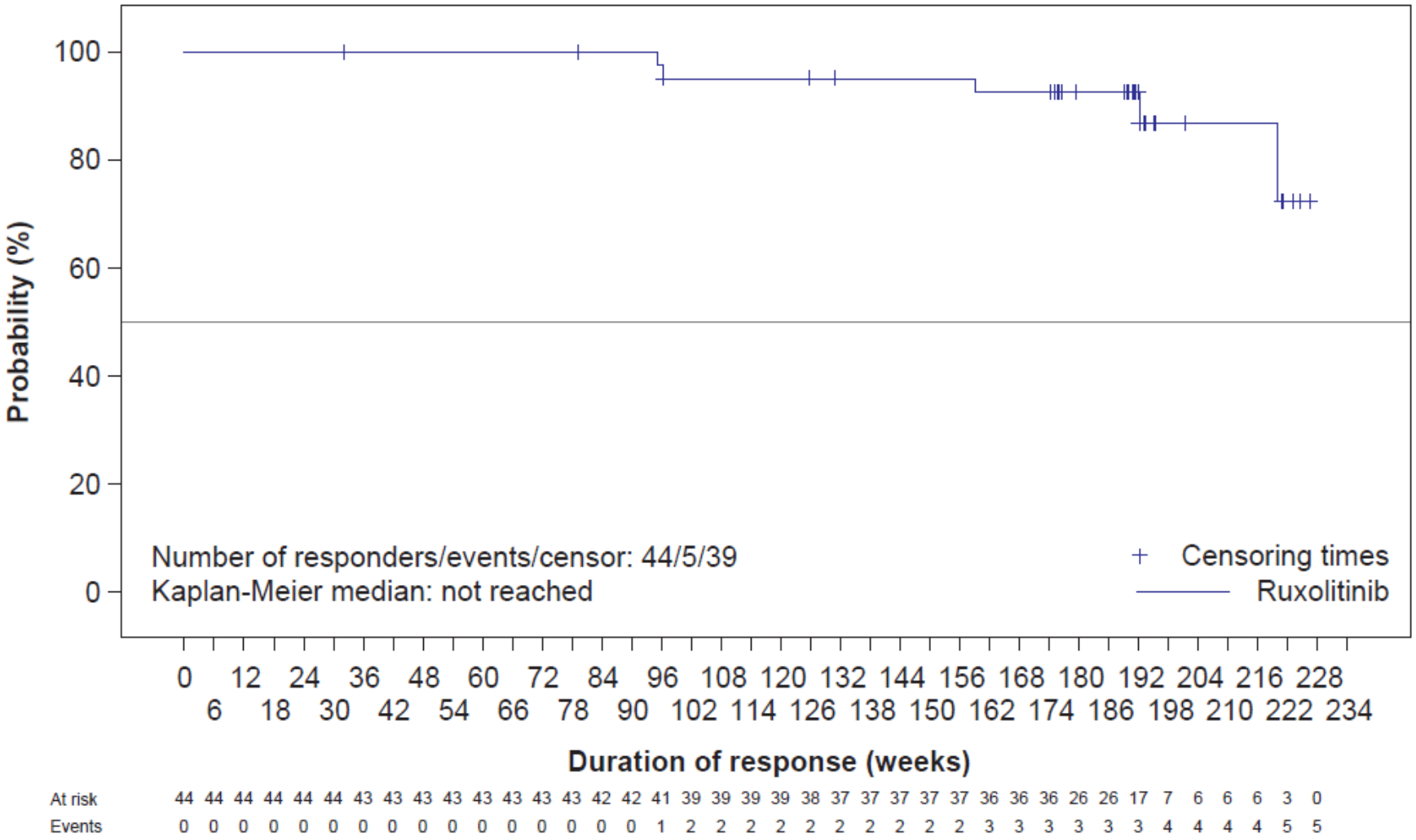
Supplementary Figure 3: Number of phlebotomy procedures over time in ruxolitinib-treated patients



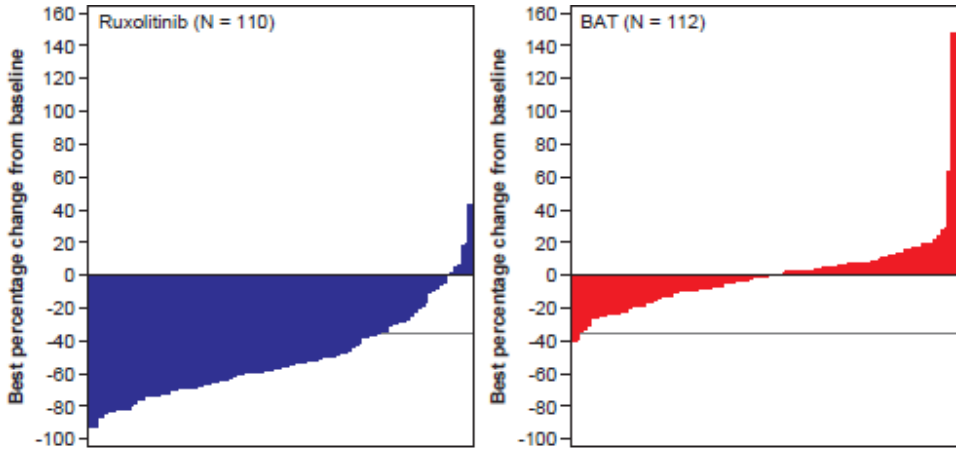
[a]All patients who crossed over from BAT. [b]From the time of crossover.

BAT, best available therapy; PBT, phlebotomy.

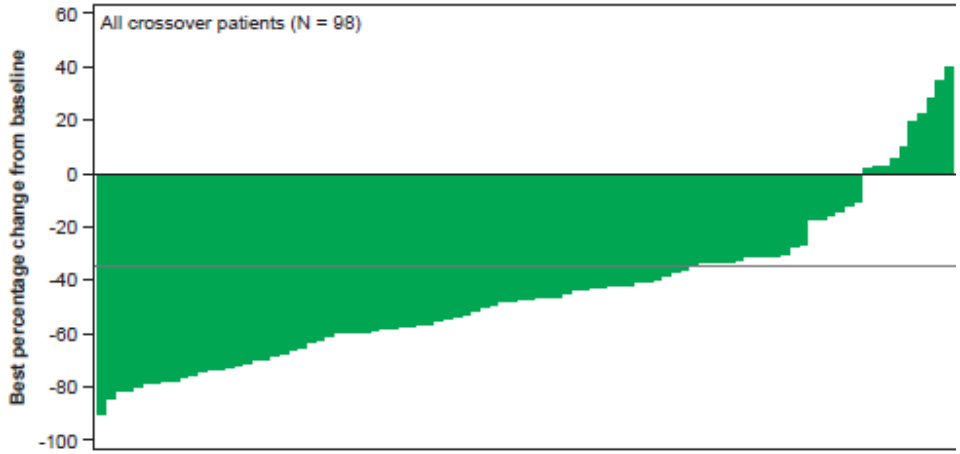
Supplementary Figure 4. Durability of spleen response with ruxolitinib



Supplementary Figure 5. Best percentage change from baseline in spleen volume



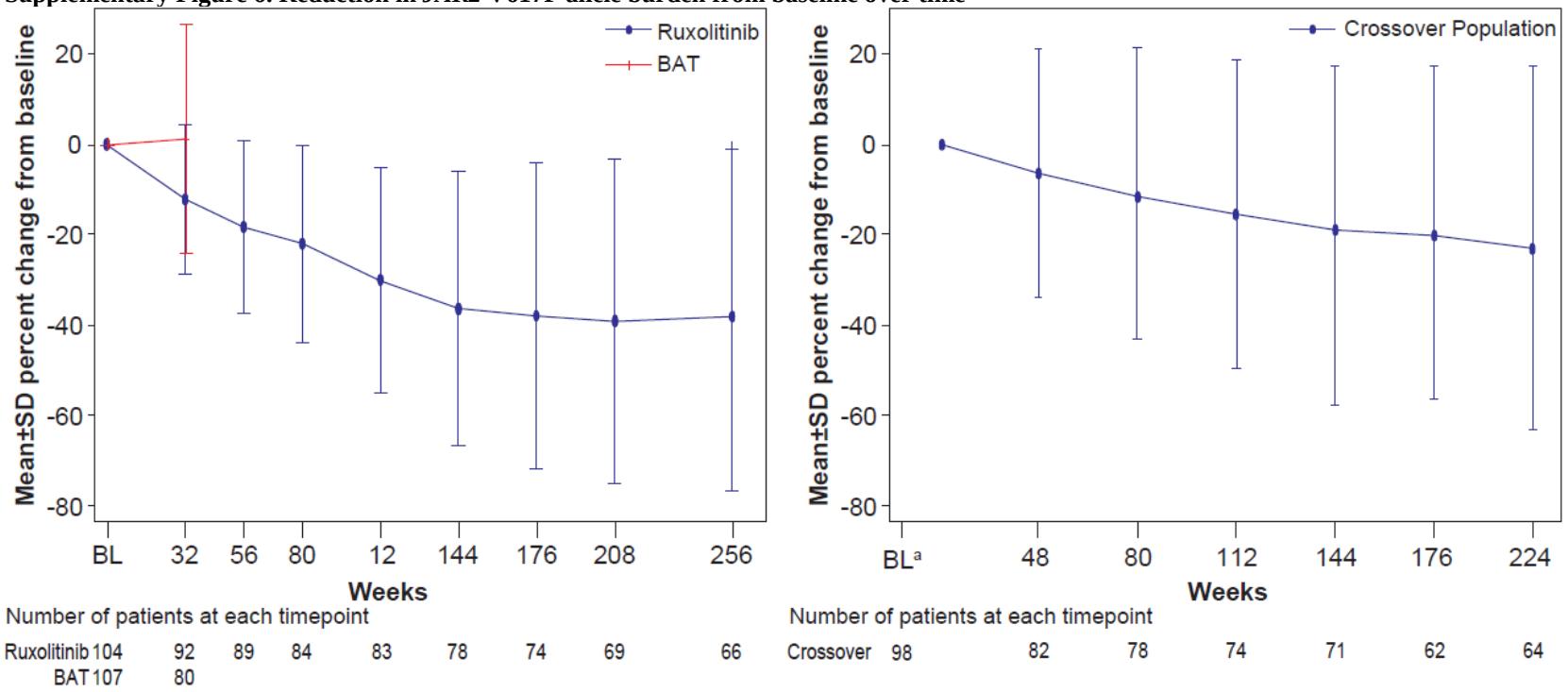
Treatment:	Ruxolitinib	BAT
Decrease in percentage change from baseline	89·1% (98)	49·1% (55)
Increase in percentage change from baseline	5·5% (6)	43·8% (49)
No change from baseline	0·0% (0)	0·0% (0)
Missing baseline or post baseline	5·5% (6)	7·1% (8)



Decrease in percentage change from baseline	85·7% (84)
Increase in percentage change from baseline	10·2% (10)
No change from baseline	0·0% (0)
Missing baseline or post baseline	4·1% (4)
Achieving ≥35% reduction from baseline	66·3% (65)

Abbreviations: BAT, best available therapy.

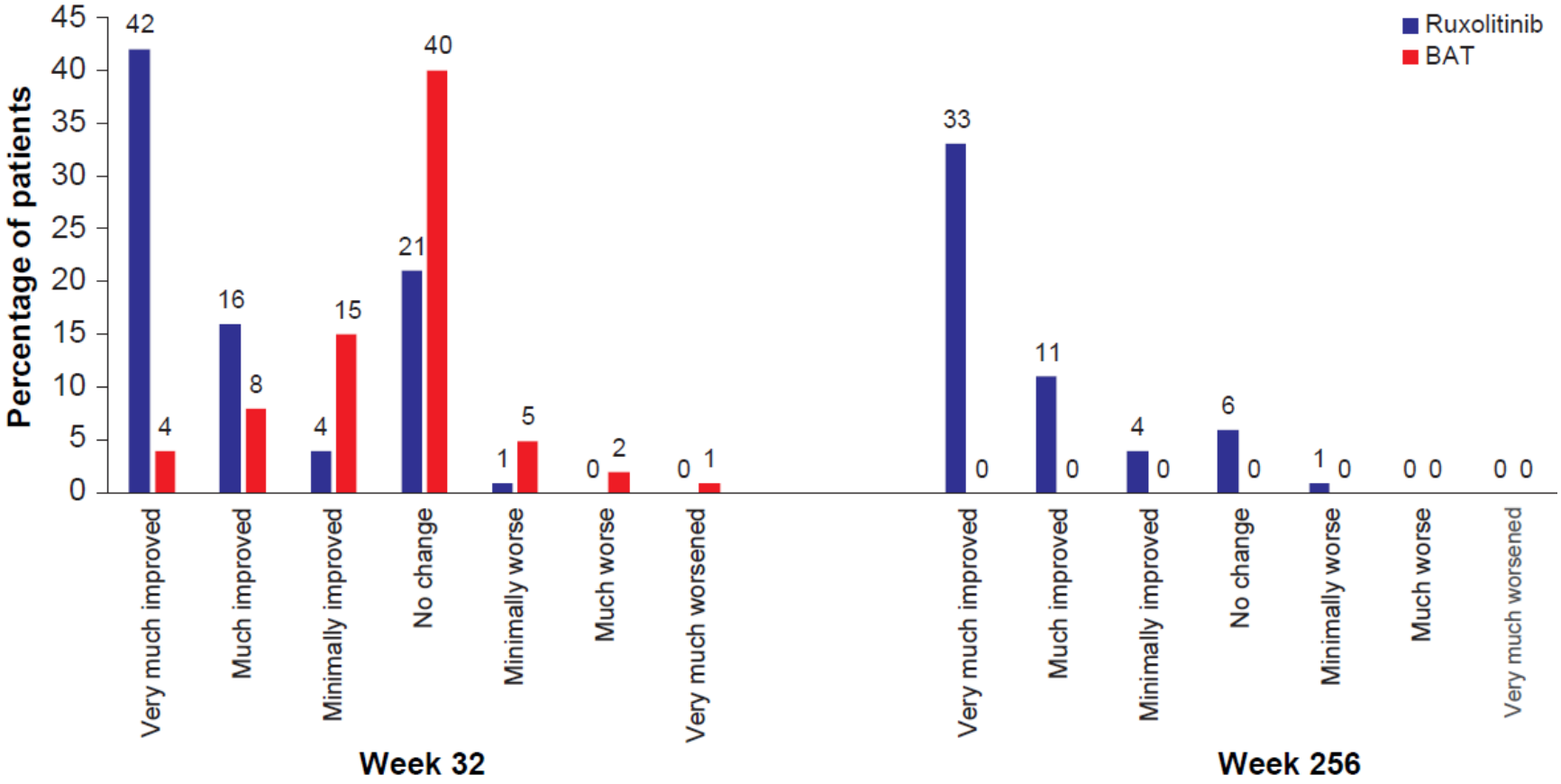
Supplementary Figure 6. Reduction in *JAK2* V617F allele burden from baseline over time



[a]Defined as the last assessment prior to first dose of ruxolitinib crossover treatment

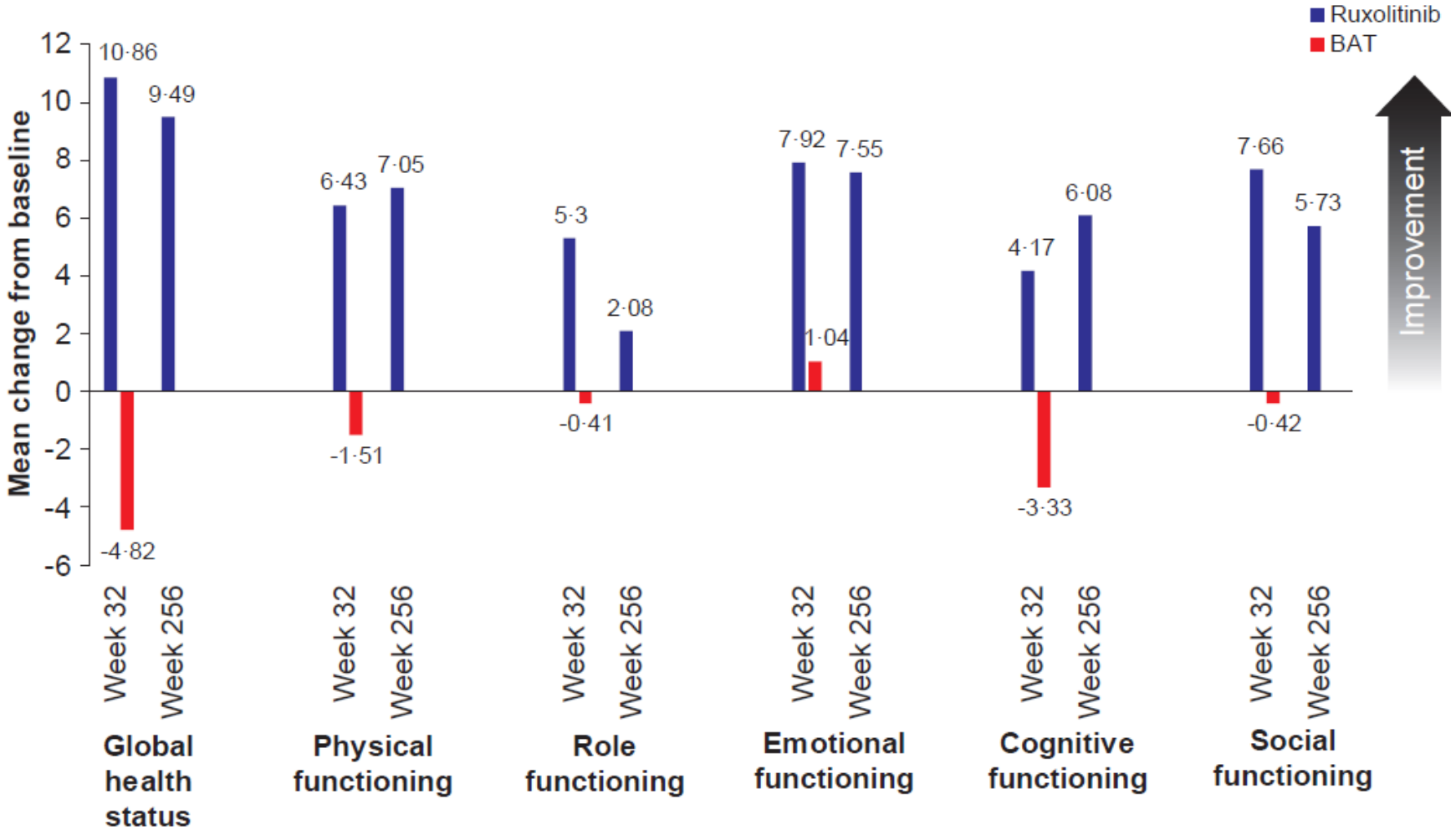
BAT, best available therapy; BL, baseline; SD, standard deviation.

Supplementary Figure 7. Pruritus Symptom Impact Scale over time in patients originally randomized to ruxolitinib



Abbreviations: BAT, best available therapy.

Supplementary Figure 8. EORTC QLQ-C30 global health status–quality of life scale in patients originally randomized to ruxolitinib



Abbreviations: BAT, Best available therapy; EORTC QLQ-C30, the European Organization for the Research and Treatment of Cancer core quality of life questionnaire.

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