New **D**rugs in **H**ematology
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Ruxolitinib in Polycythemia Vera

Alessandro M. Vannucchi
CRIMM- Center of Research and Innovation for MPN
Azienda Ospedaliera Universitaria Careggi
University of Florence, Italy

UNIVERSITÀ DEGLI STUDI FIRENZE
aouc Azienda Ospedaliero Universitaria Careggi
AIRC Programma Clinical Molecular Oncology AGIMM

Disclosures

- Novartis (speaker, research grants)
- Shire (speaker)

ELN European LeukemiaNet

Current Recommendations for PV Therapy

FIRST LINE	SECOND LINE
ALL: Manage CV risk factors	• Interferon-α, if HU resistant/intolerant
ALL: Low-dose aspirin to all	• Hydroxyurea, if IFN-α resistant/intolerant
• **Low risk:** Phlebotomies only	• [Pipobroman], busulfan, [^{32}P]
• **High risk[&]:** Hydroxyurea*/ Interferon-α ± Phlebotomies	
• Elderly: Busulfan	

* use with caution in young pts (<40 yr)

[§]**Additional reasons** to use cytoreduction: Poor control with, or intolerance to, phlebotomy; Progressive leuko/thrombocytosis; Disabling symptoms; Progressive splenomegaly

Barbui T, et al. *JCO* 2011; 29:761-70.

Resistance or Intolerance to Hydroxyurea

ELN European LeukemiaNet

RESISTANCE	INTOLERANCE	Hydroxyurea (HU)
• Need of phlebotomy to maintain Hct <45%		After 3 months of ≥2 g/day HU
• PLT >400x10^9/L *and* • WBC >10x10^9/L		
• Spleen reduction by <50% *or* • No complete relief of spleen-related symptoms		
	• ANC <10^9/L *or* • PLT <100x10^9/L *or* • Hb <100g/L	At the lowest dose required for complete or partial hematologic response
	• Leg ulcers *or* • Other unacceptable HU-related toxicities*	At any dose of HU

Plt, platelets;
WBC, white blood count;
ANC, absolute neutrophil count

*Mucocutaneous, gastrointestinal, pneumonitis, fever

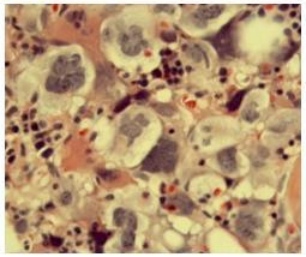
- **More than one-quarter of patients receiving HU for PV suffer from side effects**

Barosi G, et al. Br J Haematol. 2010;148(6):961-963.

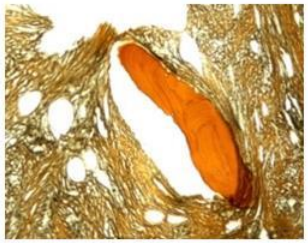
Abnormal JAK1 and JAK2 Signaling Lead to Clinical Manifestations of MPN

JAK2 JAK1

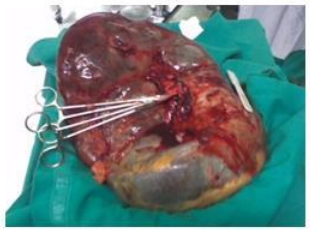
Myeloproliferation

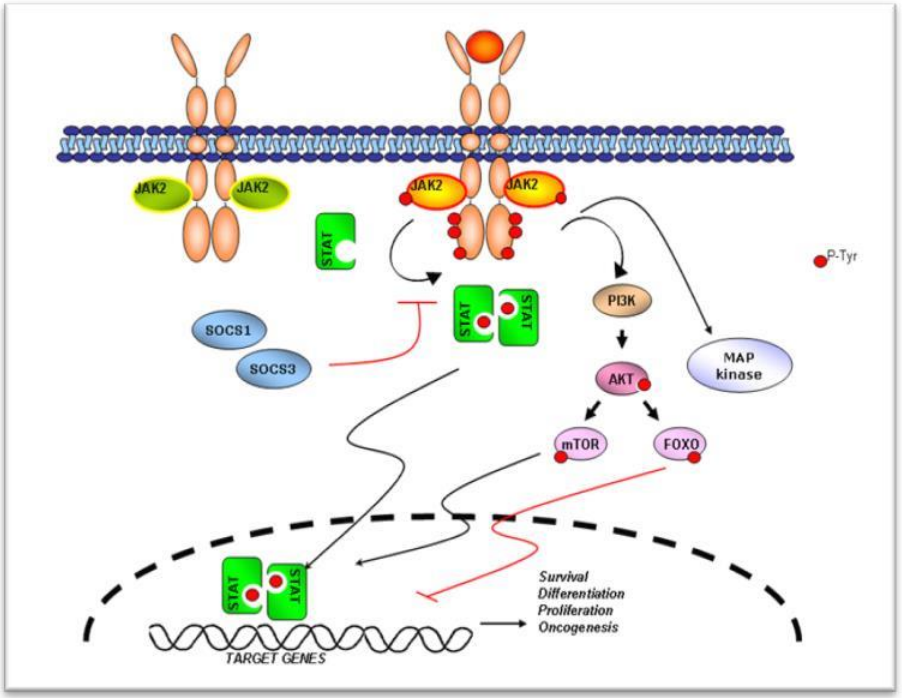


Fibrosis

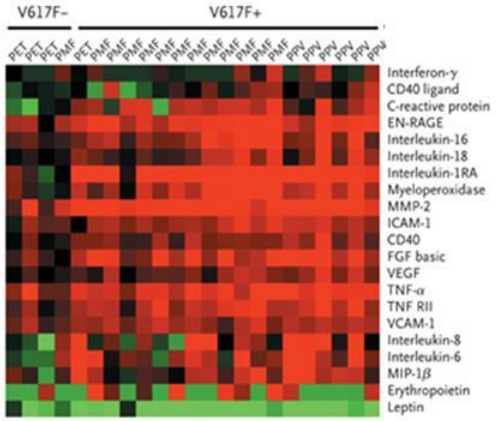


Extramedullary hematopoiesis





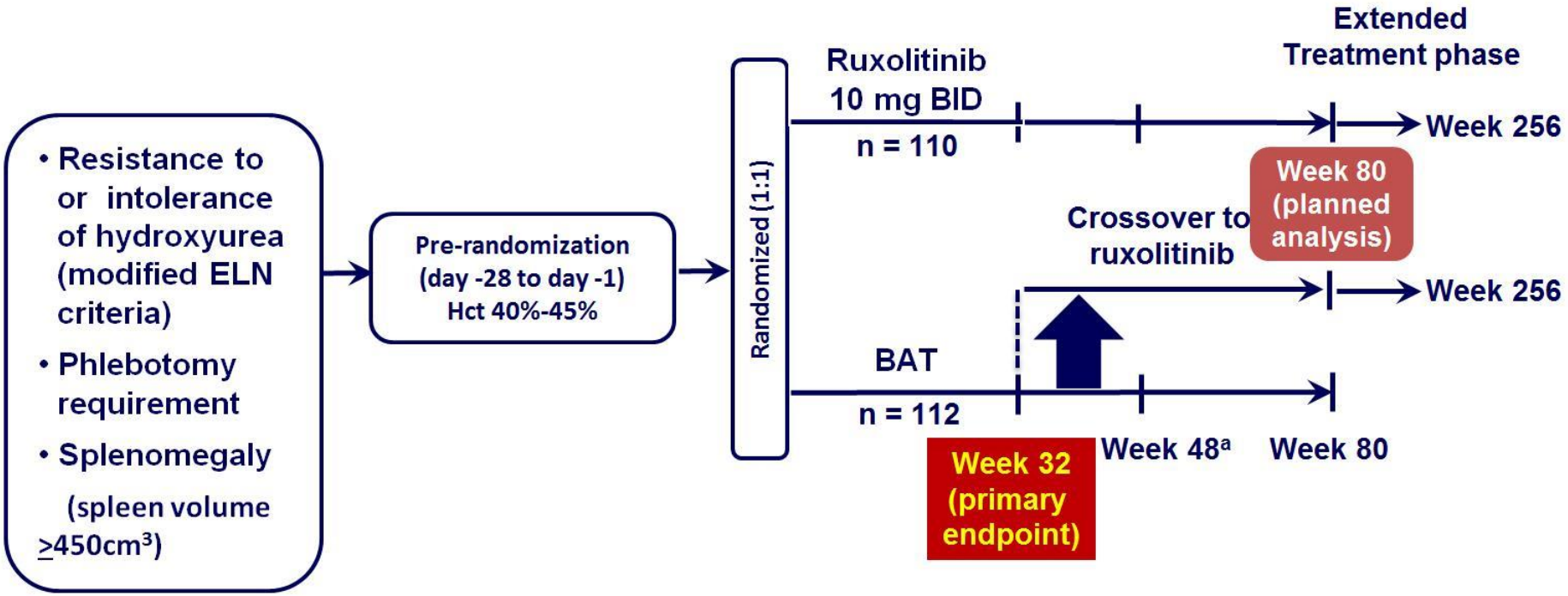
↑ Inflammatory cytokines



Constitutional symptoms

Verstovsek S, et al. *N Engl J Med*. 2010; 363:1117-27

The RESPONSE Trial



- Investigator-selected best available therapy (BAT) as monotherapy (hydroxyurea, IFN/peg-IFN, anagrelide, pipobroman, IMIDs, or observation); BAT could be changed in case of lack of response or BAT-related toxicity requiring drug discontinuation
- Patients randomized to BAT were permitted to cross over to ruxolitinib at Week 32 if they did not meet the primary endpoint or after Week 32 in case of phlebotomy eligibility or splenomegaly progression

[a]The primary analysis occurred after all patients completed week 48.

Vannucchi AM, et al. NEJM, 2015; 372:426-35

Baseline Characteristics

Parameter	Ruxolitinib (n = 110)	BAT (n = 112)
Age, median (range), years	62 (34-90)	60 (33-84)
Male, %	60	71
Time since diagnosis, median (range), years	**8.2 (0.5-35)**	**9.3 (0.5-22)**
Duration of prior HU therapy, median (range), years	3.1 (0.001-20.9)	2.8 (0.001-20.9)
HU resistance/intolerance, %	46 / 54	45.5 / 54.5
JAK2 V617F mutation positive, %	94.5	95.5
History of prior thromboembolic event, %	**35.5**	**29.5**
Hct, mean (SD), %[a]	44 (2)	44 (2)
WBC × 10^9/L, mean (SD)	18 (10)	19 (12)
Platelet count × 10^9/L, mean (SD)	485 (323)	499 (319)
≥ 3 phlebotomies in prior 24 weeks, %	**31**	**42**
Palpable spleen length, median (range), cm	7 (0-24)	7 (0-25)
Spleen volume, median (range), cm^3	1195 (396-4,631)	1322 (254-5,147)

Vannucchi AM et al, 2015; 372:426-35

Patient Disposition at the Planned 80-Week Analysis

- Due to lack of efficacy, most patients in the BAT arm crossed over to receive ruxolitinib at or soon after the Week 32 visit

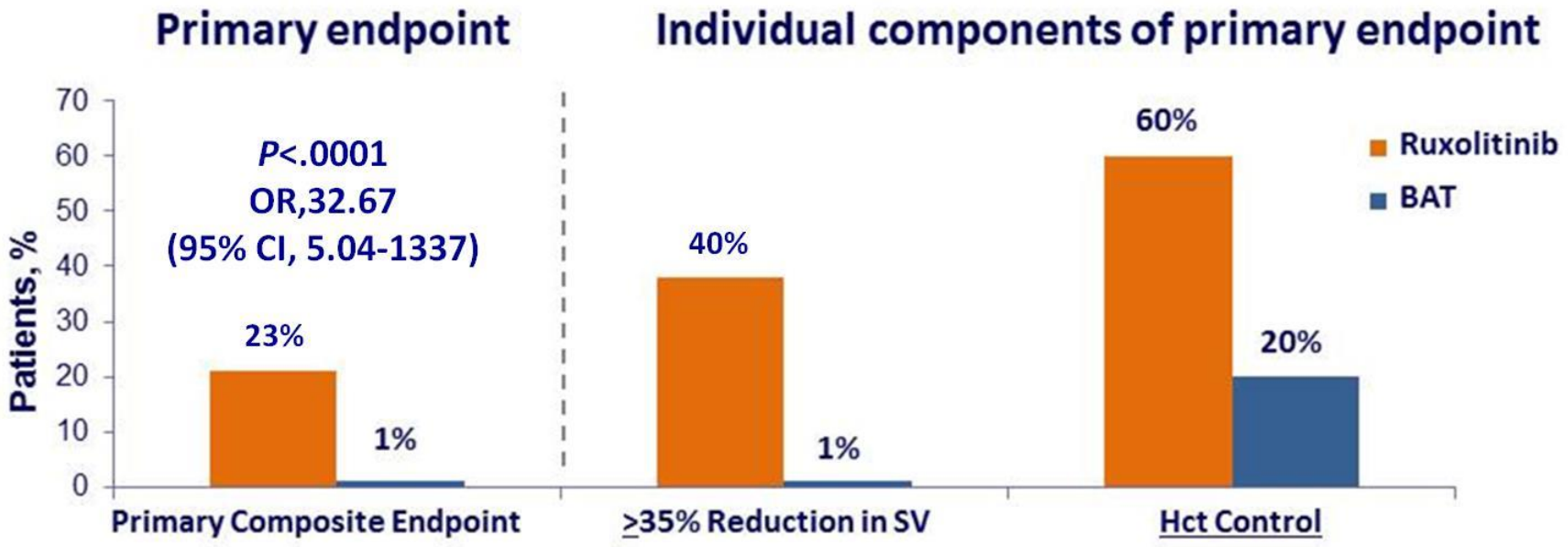
	Ruxolitinib (n=110)	BAT* (n=112)	Ruxolitinib Crossover (n=98)
Ongoing treatment, n (%)	91 (82.7)	0	81 (82.7)
Reason for discontinuation of treatment, n (%)			
Disease progression	6 (5.5)	1 (0.9)	5 (5.1)
Patient decision	6 (5.5)	5 (4.5)	2 (2.0)
Adverse event	5 (4.5)	2 (1.8)	9† (9.2)
Physician decision	2 (1.8)	2 (1.8)	0
Lost to follow-up	0	0	1 (1.0)
Lack of efficacy	0	100 (89.3)	0
Completed	0	1 (0.9)	0
Median treatment exposure, wk	111	34	76

*Initial BAT included HU (n=66), IFN/pegylated IFN (n=13), anagrelide (n=8), IMIDs (n=5), pipobroman (n=2), and observation (n=17)
†Includes 2 deaths (1 due to central nervous system hemorrhage; 1 due to multi-organ failure and hypovolemic shock) reported after crossover to ruxolitinib; neither was considered to be related to study drug

Verstovsek S et al. , Haematologica 2016, online

RESPONSE: Primary Endpoint of the Study

- **Primary endpoint (composite):** Percentage of patients who achieved both Hct control (Hct <45% and no phlebotomy) and spleen response (reduction of SV to ≤35% from baseline assessed by MRI) at week 32.

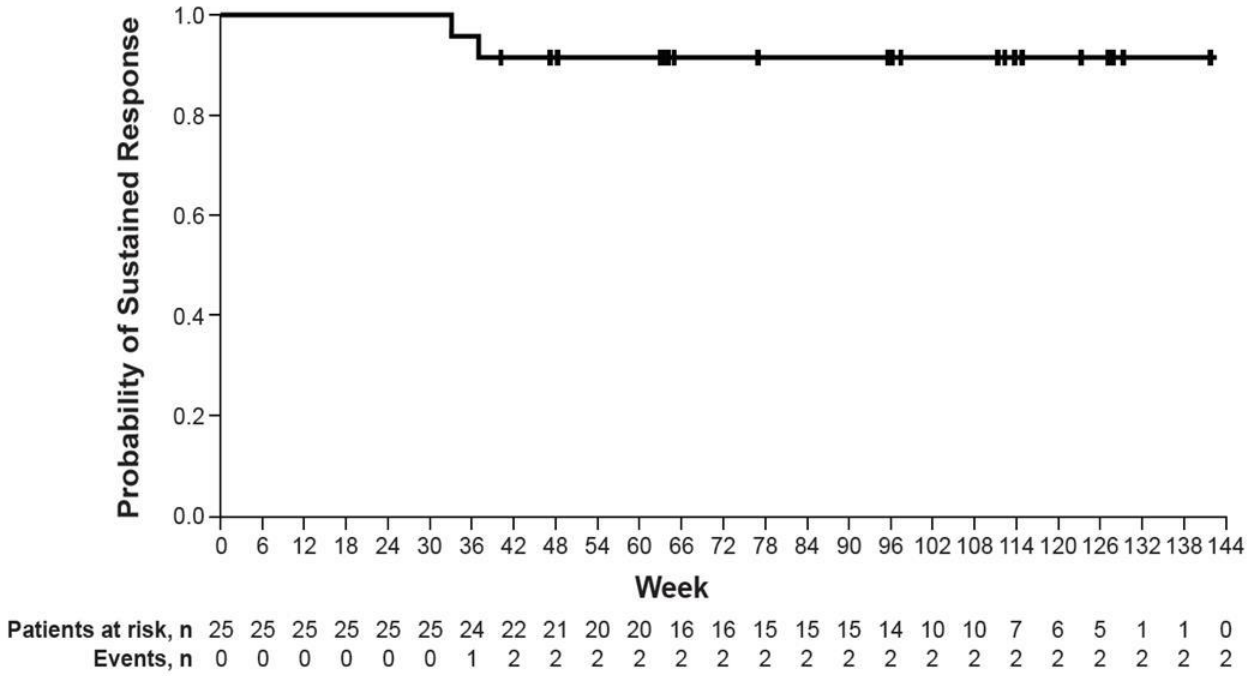


- 77% of patients randomized to ruxolitinib met at least 1 component of the primary endpoint

SV, spleen volume

Vannucchi AM, et al. NEJM, 2015; 372:426-35.

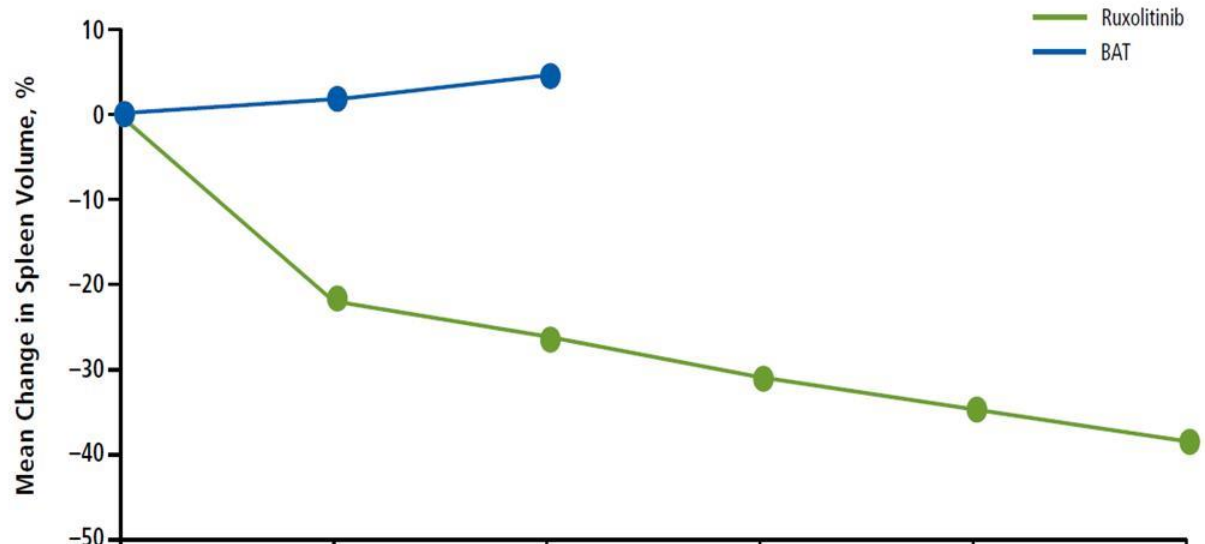
Durability of Primary Response With Ruxolitinib



- 20/25 (80%) ruxolitinib-treated patients had a durable primary response defined as maintenance for 48 weeks after initial response
  - 3 of the 5 without durable response were classified as nonresponders because of missing assessments
- **The probability of maintaining the primary response in the ruxolitinib arm for at least 80 weeks from time of response was 92%**

Verstovsek S et al. , Haematologica 2016, online

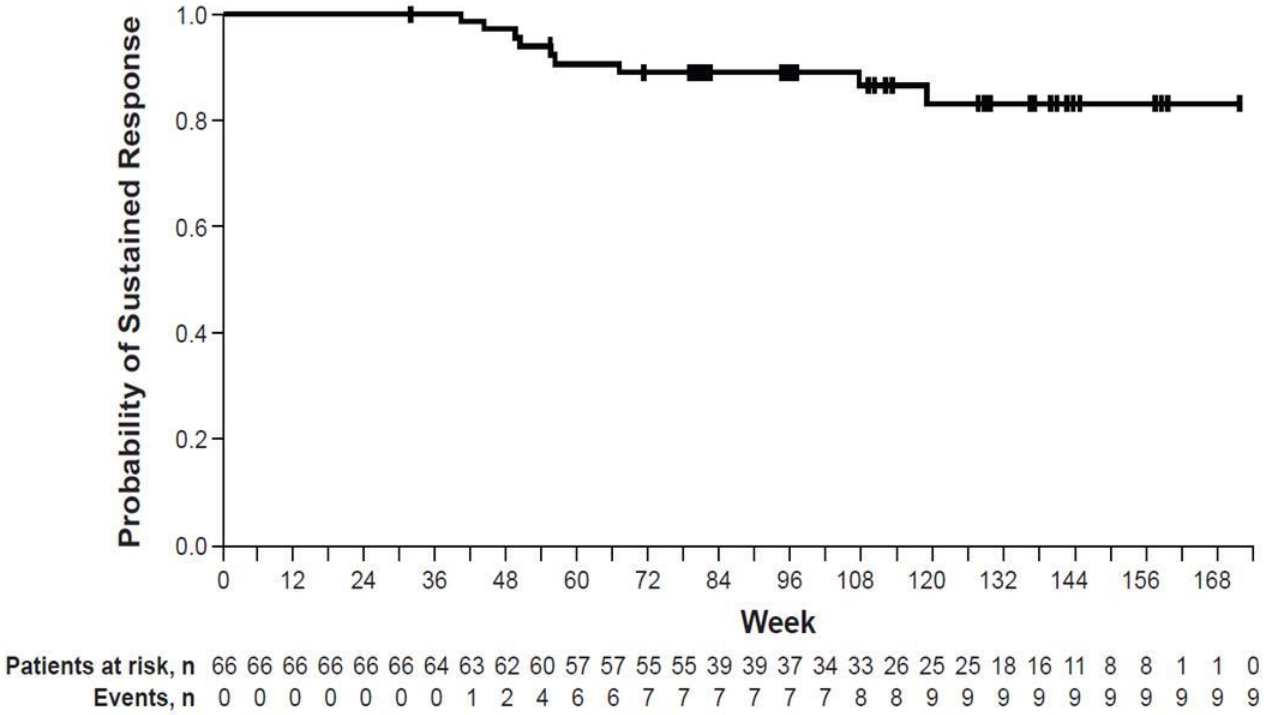
Primary Response Components: Spleen Volume Changes



- Spleen volume decreased over time with ruxolitinib treatment
- Of the 40% of patients in the ruxolitinib arm who achieved a ≥35% reduction in spleen volume, **none lost their response at the time of the Week 80 data cutoff**

Verstovsek S et al. , Haematologica 2016, online

Primary Response Components: Durability of Hematocrit Control



- **The probability of maintaining Hct control in the ruxolitinib arm for at least 80 weeks from time of response was 89%**

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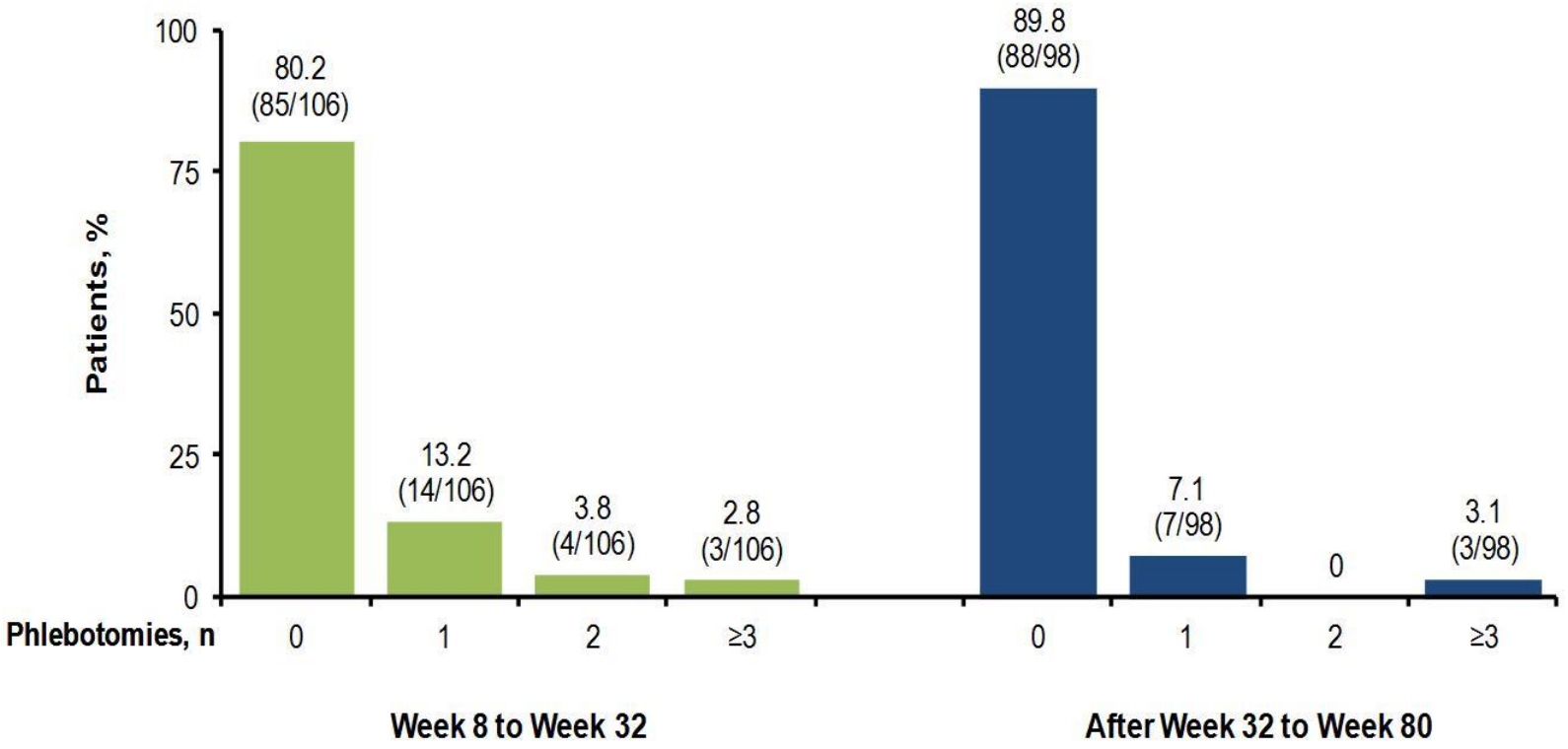
Phlebotomy Procedures in the Ruxolitinib Arm



- Of the 98 patients who did not discontinue ruxolitinib at Week 32, 88 **(89.8%) had no phlebotomy between Weeks 32 and 80**

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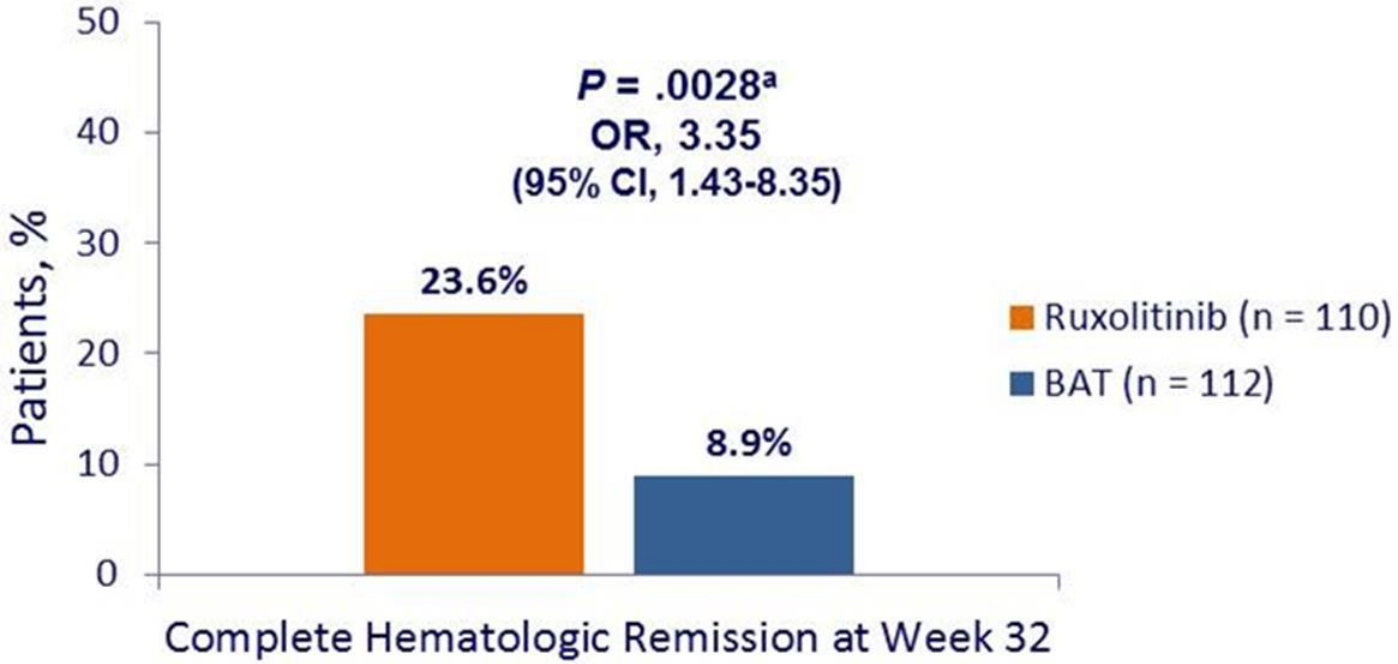
Complete Hematological Remission

- **CHR is defined as Hct control, PLT count ≤400 × 10^9/L, and WBC count ≤10 × 10^9/L**



[a]*P* value, odds ratio and 95% CI were calculated using stratified exact Cochran-Mantel-Haenszel test by adjusting for the WBC/PLT status (abnormal vs normal) at baseline. WBC/PLT status was defined as abnormal if WBC count was >15 × 10^9/L, and/or PLT count >600 × 10^9/L.

Plt, platelets; WBC, white blood count; ANC, absolute neutrophil count

Vannucchi AM, et al. NEJM, 2015; 372:426-35.

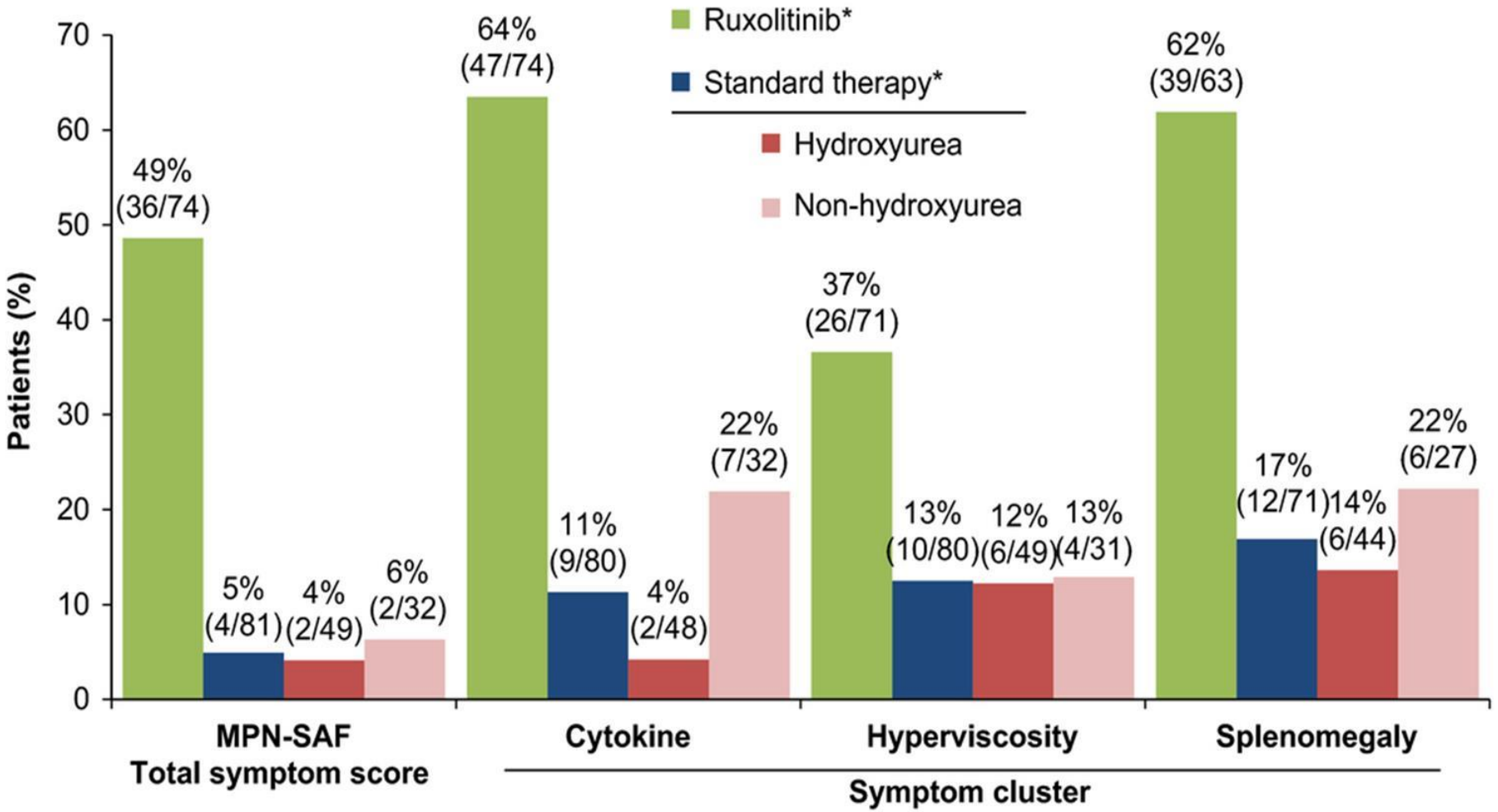
Sustained Control of Blood Cell Counts in Patients Receiving Ruxolitinib

Changes in WBC Counts and Platelet Counts in Ruxolitinib Arm	N	Week 32 % Patients	Week 80 % Patients
WBC ≤10 x 10^9/L in patients with baseline WBC >10 x 10^9/L	87	31.0	47.1
WBC ≤10 x 10^9/L in patients with baseline WBC >15 x 10^9/L	64	26.6	42.2
Platelets ≤400 x 10^9/L in patients with baseline platelet count >400 x 10^9/L	54	44.4	59.3

- **The probability of maintaining CHR for ≥80 weeks from time of response was 69%**
- Percentage of patients with normalized WBC and platelet counts improved over time with ruxolitinib treatment

Verstovsek S et al. , Haematologica 2016, online

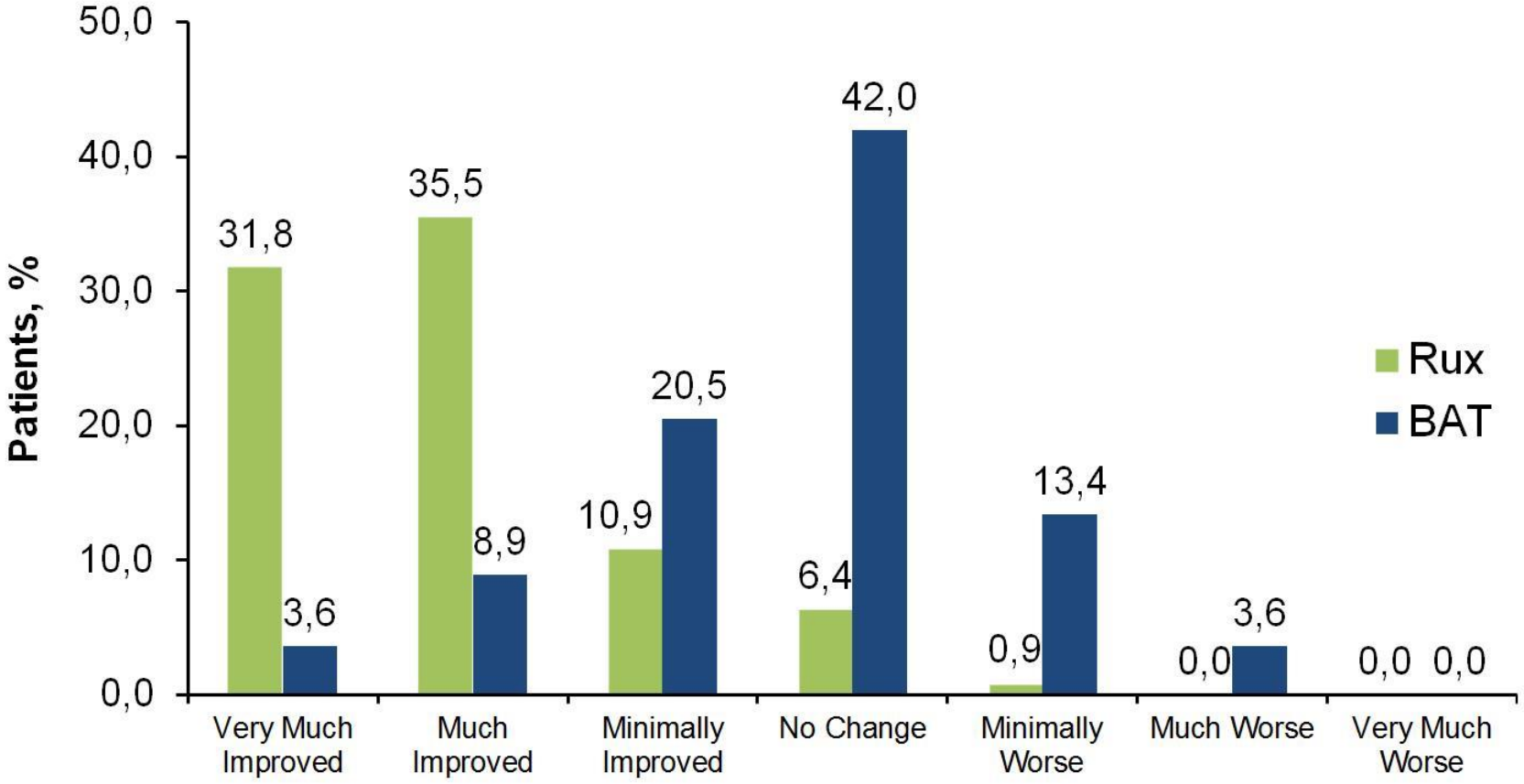
Changes in Disease-Related Symptoms in patients Receiving Ruxolitinib or BAT



Vannucchi AM et al, NEJM 2015; 372:426-35. Mesa R et al, EJH 2016, online

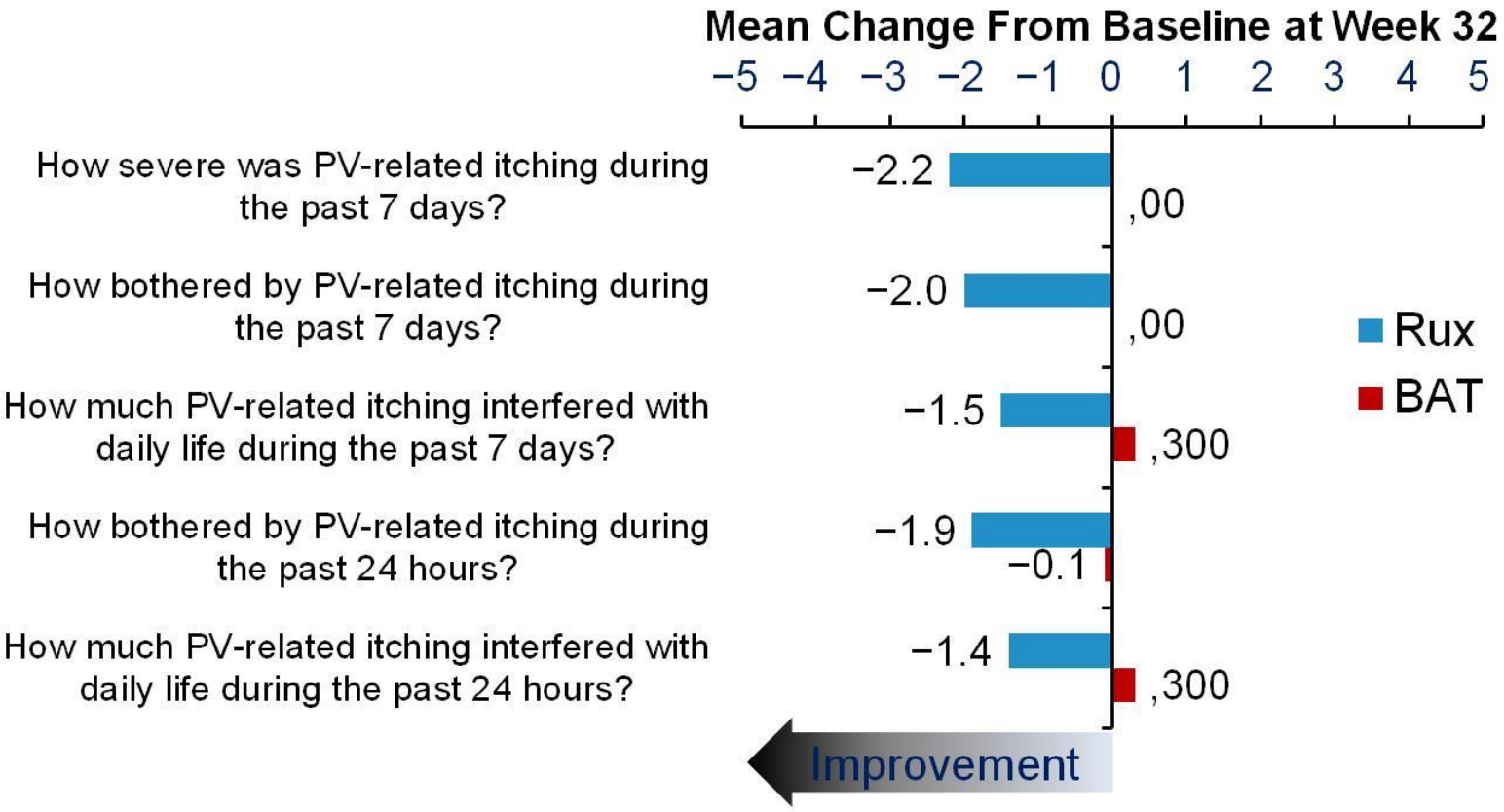
Patient Global Impression of Change at Week 32

- A greater proportion of patients receiving Rux compared with BAT reported their symptoms as “very much improved” or “much improved”



Vannucchi AM, et al. NEJM, 2015; 372:426-35

Impact of Ruxolitinib on Pruritus by the PSIS* Scale at Week 32

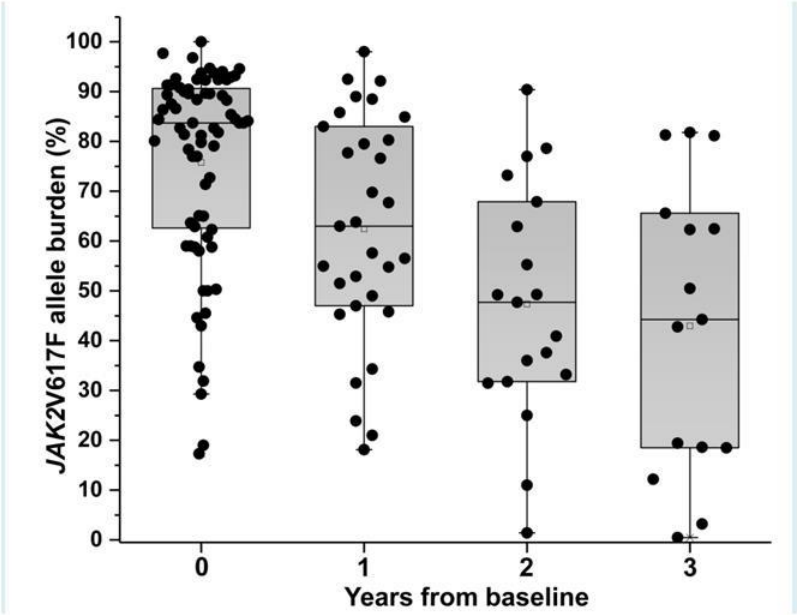


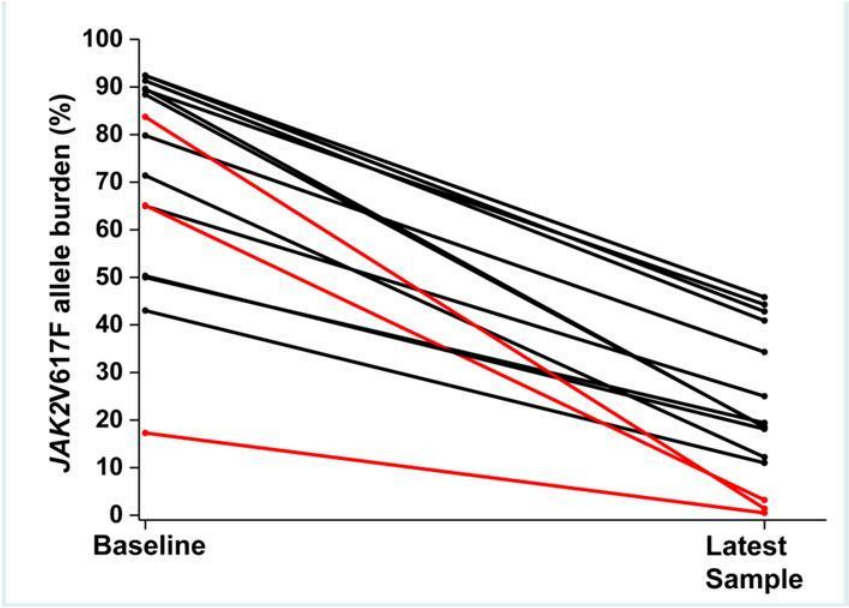
- Pruritus severity and its interference on daily life improved with ruxolitinib and was unchanged/worsened with BAT

***Patients responded to each question on a scale of 0 (not at all) to 10 (worst imaginable)**

Vannucchi AM, et al. *N Engl J Med.* 2015;372:426-435.

Effect of Long-Term Ruxolitinib on *JAK2*V617F Allele Burden





*JAK2*V617F allele burden reductions in patients randomized to Ruxolitinib at baseline after 1, 2 and 3 years of treatment

- 15 (20.3%) patients had >50% of *JAK2*V617F allele burden reduction
- 3 patients (red lines) attained an allele burden below 5%

Guglielmelli P et al, ASH 2015, Abs 4087

Nonhematologic Adverse Events Regardless of Causality

	80-Week Analysis			
Exposure, Patient-Years	Ruxolitinib (n=110) 227.7		BAT (n=111*) 73.6	
Rate per 100 Patient-Years of Exposure	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Headache	10.5	0.9	28.5	1.4
Diarrhea	9.7	0	12.2	1.4
Pruritus	9.7	0.4	32.6	5.4
Fatigue	8.3	0.4	23.1	4.1
Muscle spasms	7.9	0.4	9.5	0
Dizziness	7.5	0	14.9	0
Increased weight	7.5	0.4	1.4	0
Dyspnea	7.0	1.3	2.7	0
Abdominal pain	6.6	0.9	17.7	0
Arthralgia	6.1	0	10.9	1.4

*1 patient was randomized to BAT but did not receive study treatment
†Occurring at a rate >6 per 100 patient-years of exposure (all grades) in the ruxolitinib arm at the week 80 analysis

Verstovsek S et al. , Haematologica 2016, online

New or Worsening Hematologic Laboratory Abnormalities

	80-Week Analysis			
Exposure, Patient-Years	Ruxolitinib (n=110) 227.7		BAT (n=111*) 73.6	
Rate per 100 Patient-Years of Exposure	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Decreased hemoglobin	27.2	0.9	47.6	0
Decreased lymphocytes	27.2	9.7	78.8	27.2
Decreased platelets	14.9	2.6	29.9	5.4
Decreased leukocytes	6.6	0.9	19.0	2.7
Decreased neutrophils	2.2	0.4	12.2	1.4

*1 patient was randomized to BAT but did not receive study treatment

Verstovsek S et al. , Haematologica 2016, online

Adverse Events of Interest

Exposure, Patient-Years	Ruxolitinib (n=110) 227.7 n (exp adjusted rate)	BAT (n=111*) 73.6 n (exp adjusted rate)
All infections	67 (29.4)	43 (58.4)
Grade 3 or 4	9 (4.0)	3 (4.1)
Herpes zoster infection	12 (5.3)	0
Grade 3 or 4	2 (0.9)	0
Nonmelanoma skin cancer†	10 (4.4)	2 (2.7)
Patients with a history of NMSC	6 (24.2)	1 (22.3)
Patients without a history of NMSC	4 (2.0)	1 (1.4)
Disease progression‡		
Myelofibrosis	3 (1.3)	1 (1.4)
AML	1 (0.4)	0

*1 patient was randomized to BAT but did not receive study treatment

†There were 3 additional events of NMSC after crossover, 1 in a patient with a history of skin cancer or precancer
Patients with history of NMSC: n=12, 24.8 pt-yrs exposure in ruxolitinib arm; n=7, 4.5 pt-yrs exposure in BAT arm
Patients without a history of NMSC: n=98, 202.9 pt-yrs exposure in ruxolitinib arm, n=104, 69.1 pt-yrs exposure in BAT arm

‡ There was 1 additional report of myelofibrosis in the ruxolitinib arm, but this was not confirmed with bone marrow biopsy; there were 3 cases of myelofibrosis in the BAT arm after crossover to ruxolitinib; 1 of these patients developed AML

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Other Adverse Events of Interest

Exposure, Patient-Years	Ruxolitinib (n=110) 227.7 n (exp adjusted rate)	BAT (n=111*) 73.6 n (exp adjusted rate)
All infections	67 (29.4)	43 (58.4)
Grade 3 or 4	9 (4.0)	3 (4.1)
Herpes zoster infection	12 (5.3)	0
Grade 3 or 4	2 (0.9)	0
Nonmelanoma skin cancer†	10 (4.4)	2 (2.7)
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Myelofibrosis	3 (1.3)	1 (1.4)
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Verstovsek S et al. , Haematologica 2016, online

Thromboembolic Adverse Events

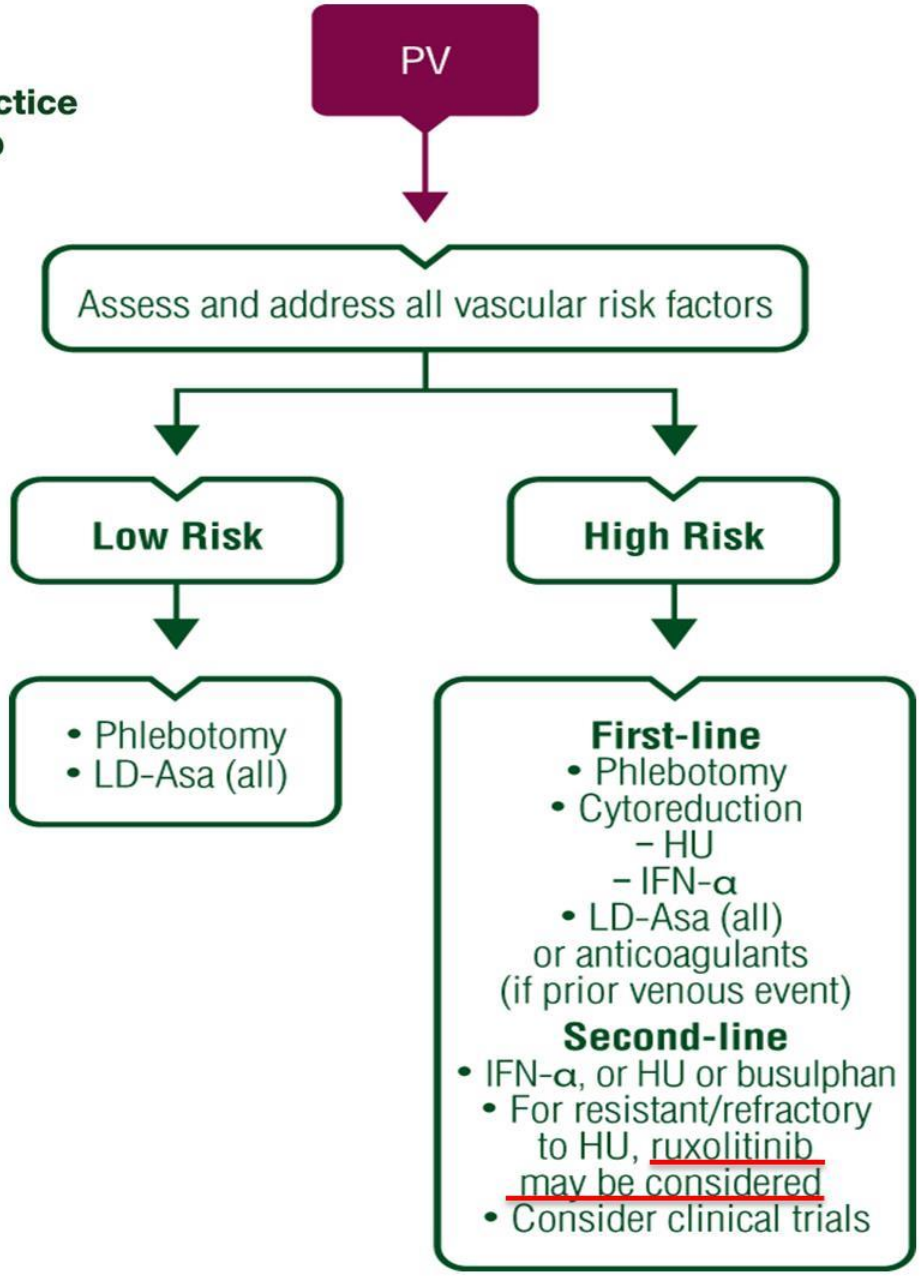
- At the Week 80 analysis, the rates of thromboembolic events per 100 patient-years of exposure were 1.8 in the ruxolitinib arm vs 8.2 in the BAT arm

Exposure, Patient-Years	Ruxolitinib (n=110) 227.7 n (exp adjusted rate)		BAT (n=111*) 73.6 n (exp adjusted rate)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
All thromboembolic events	4 (1.8)	2 (0.9)	6 (8.2)†	2 (2.7)
Portal vein thrombosis	1 (0.4)	1 (0.4)	0	0
Cerebral infarction	1 (0.4)	1 (0.4)	0	0
Ischemic stroke	1 (0.4)	0	0	0
Retinal vascular thrombosis	1 (0.4)	0	0	0
Myocardial infarction	0	0	1 (1.4)	1 (1.4)
Deep vein thrombosis	0	0	2 (2.7)	1 (1.4)
Pulmonary embolism	0	0	1 (1.4)	1 (1.4)
Splenic infarction	0	0	1 (1.4)	0
Thrombophlebitis	0	0	1 (1.4)	0
Thrombosis	0	0	1 (1.4)	0

*1 patient was randomized to BAT but did not receive study treatment
†1 patient in the BAT arm had both pulmonary embolism and deep vein thrombosis

Verstovsek S et al. , Haematologica 2016, online

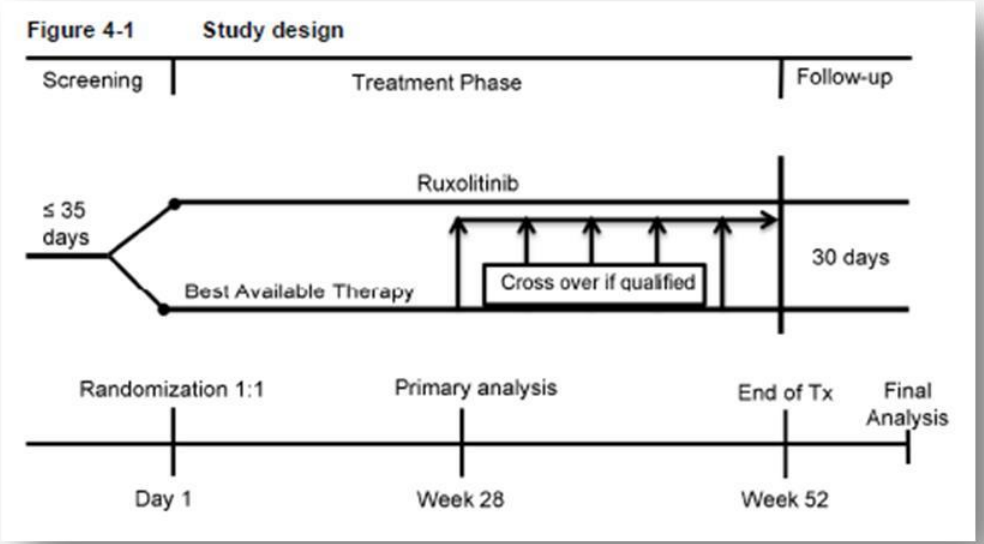
Philadelphia chromosome-negative chronic myeloproliferative neoplasms: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up



Vannucchi AM et al, Ann Oncol 2015; Online Aug 2015

RESPONSE-2: Study Design

- Intollerance or resistance to HU (ELN modified criteria)
- In need of phlebotomy
- NO splenomegaly



Primary Endpoint

- Proportion of patients achieving hematocrit control at week 12 and maintaining it up to week 24 in the absence of phlebotomy eligibility

Seconday Endpoints

- Proportion of patients achieving complete hematologic remission at week 12 and maintaining it up to week 24
- Proportion of patients achieving control of disease-associated symptoms at week 12 and maintaining it up to week 24