Changes in Quality of Life and Disease-Related Symptoms in Patients With Polycythemia Vera Receiving Ruxolitinib or Best Available Therapy: RESPONSE Trial Results

Abstract #709

Mesa R, Verstovsek S, Kiladjian J-J, Griesshammer M, Masszi T, Durrant S, Passamonti F, Harrison CN, Pane F, Zachee P, He S, Jones MM, Parasuraman S, Li J, Côté I, Habr D, Vannucchi AM

Introduction

- Polycythemia vera (PV) is associated with overactivation of the JAK/STAT pathway and characterized by erythrocytosis and an increased risk of thrombosis[1,2]
- Patients with PV experience a broad range of symptoms that impose a significant burden and may negatively impact quality of life (QoL)[3]
- Primary results from RESPONSE (NCT01243944) indicated that the JAK1/JAK2 inhibitor ruxolitinib (Rux)[4] provided clinically relevant improvements compared with best available therapy (BAT) in maintaining control of hematocrit level without phlebotomy, normalizing blood cell count, reducing spleen volume, and improving symptoms[5,6]
- Rux was recently approved by the FDA for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea
  - Rux is also approved by the FDA for the treatment of intermediate or high-risk myelofibrosis (MF), including primary MF, post-PV MF and post-essential thrombocythemia
- This analysis was conducted to further evaluate the effect of Rux on PV-related symptoms and QoL measures in the RESPONSE trial

1. Tefferi A, et al. *Leukemia*. 2008;22(1):14-22.
2. Tefferi A, et al. *Leukemia*. 2013;27(9):1874-1881.
3. Stein BL, et al. *Ann Hematol*. 2014;93(12):1965-1976.
4. Aittomäki S, et al. *Basic Clin Pharmacol Toxicol*. 2014;114(1):18-23.
5. Verstovsek S, et al. *J Clin Oncol.* 2014;32(Suppl): Abstract 7026.
6. Vannucchi AM, et al. Presented at: European Hematology Association Annual Meeting; June 12-15, 2014; Milan, Italy. Abstract LB-2436.

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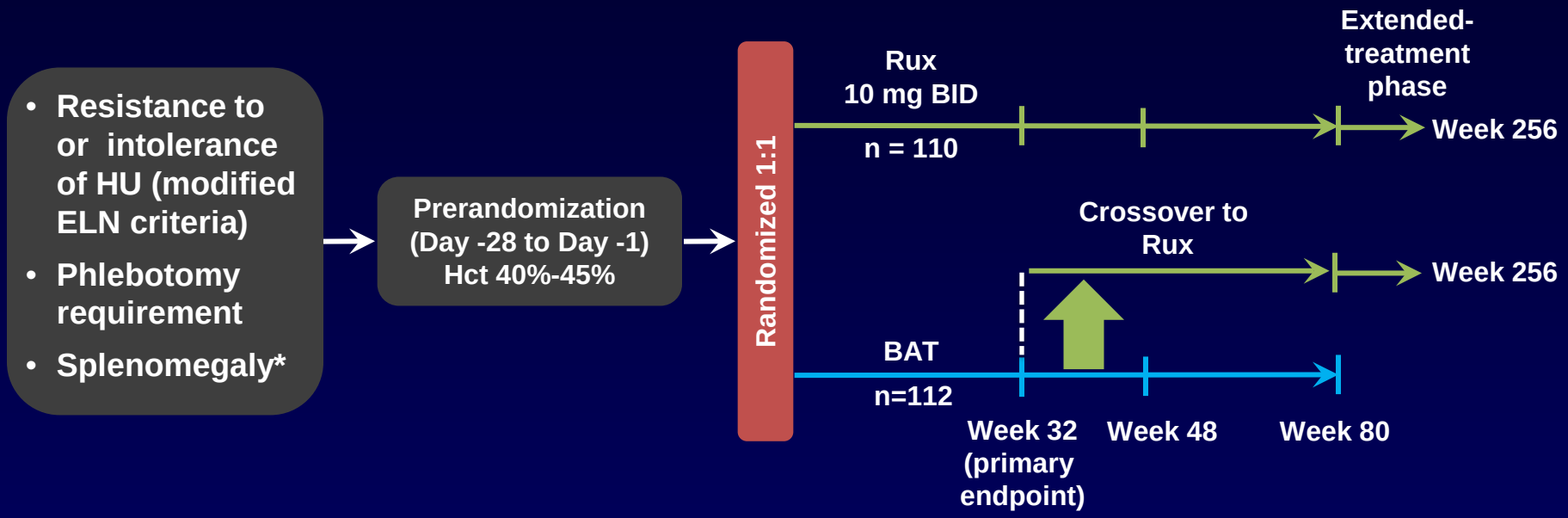
RESPONSE Study Design



- The primary endpoint was a composite of Hct control and ≥35% reduction in spleen volume
  - To achieve Hct control, patients could not be eligible for phlebotomy based on protocol-defined Hct values
  - Phlebotomy eligibility was defined as Hct > 45% and ≥ 3% higher than baseline or a Hct > 48

BID = twice daily; ELN = European LeukemiaNet; Hct = hematocrit; HU = hydroxyurea
*Palpable splenomegaly confirmed by MRI/CT to be ≥450 cm^3 in volume (ie, 2 to 3 times the upper limit of normal); patients with body habitus precluding spleen palpation must have a spleen volume ≥450 cm^3 by MRI/CT

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Baseline Characteristics

Parameter	Rux (n = 110)	BAT (n = 112)
Age, median (range), years	62 (34–90)	60 (33–84)
Male, %	60	71
HU resistance/intolerance, %		
Resistance	46.4	45.5
Intolerance	53.6	54.5
JAK2 V617F mutation positive, %	94.5	95.5
History of prior thromboembolic event, %	35.5	29.5
Hct, mean (SD), %*	43.6 (2.2)	43.9 (2.2)
WBC × 10^9/L, mean (SD)	17.6 (9.6)	19.0 (12.2)
Platelet count × 10^9/L, mean (SD)	485 (323)	499 (319)
≥3 Phlebotomies in prior 24 weeks, %	30.9	42.0
Palpable spleen length, median (range), cm	7 (0–24)	7 (0–25)
Spleen volume, median (range), cm^3	1195 (396–4631)	1322 (254–5147)

*Following Hct control period prior to randomization.

- BAT included HU (n = 66; 59%), IFN/pegylated IFN (n = 13; 12%), anagrelide (n = 8; 7%), IMIDs (n = 5; 4%), pipobroman (n = 2; 2%), and observation (n = 17; 15%)

IFN = interferon; IMID = immunomodulatory drug; PEG = pegylated; WBC = white blood cell

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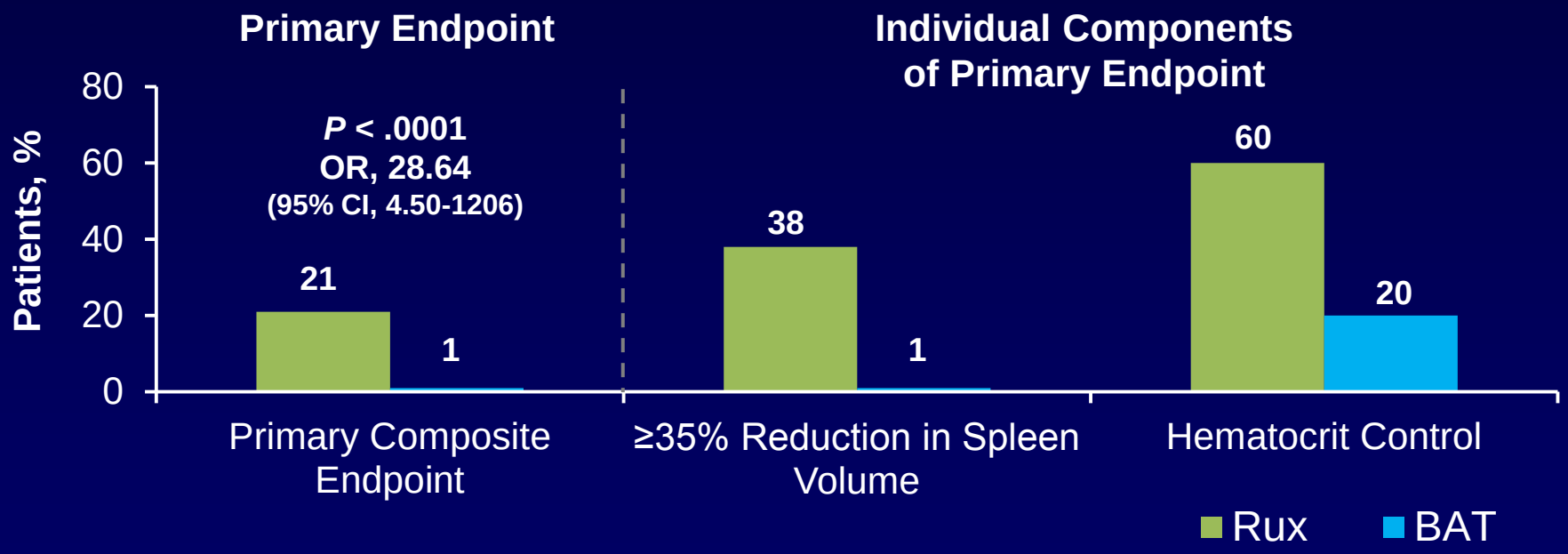
Primary Response at Week 32

- **The primary endpoint was a composite of the percentage of patients who achieved both hematocrit control and ≥35% reduction in spleen volume at Week 32**



- **91% of patients who achieved the primary endpoint had a confirmed response at Week 48**

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How Symptomatic Are PV Patients Based on Eligibility Features in RESPONSE?

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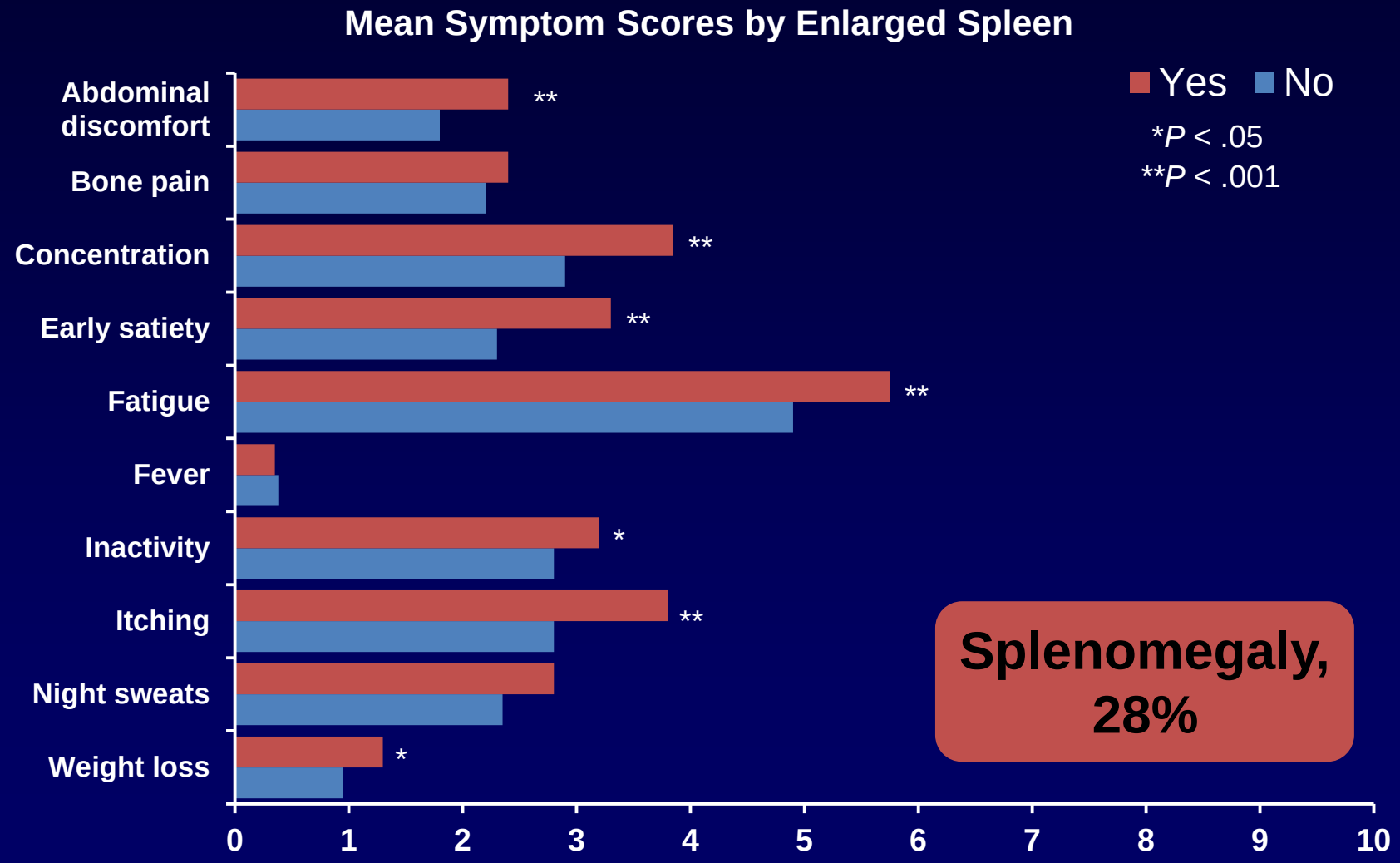
Impact of Palpable Splenomegaly on MPN 10 in 1334 Patients With PV



Splenomegaly, 28%

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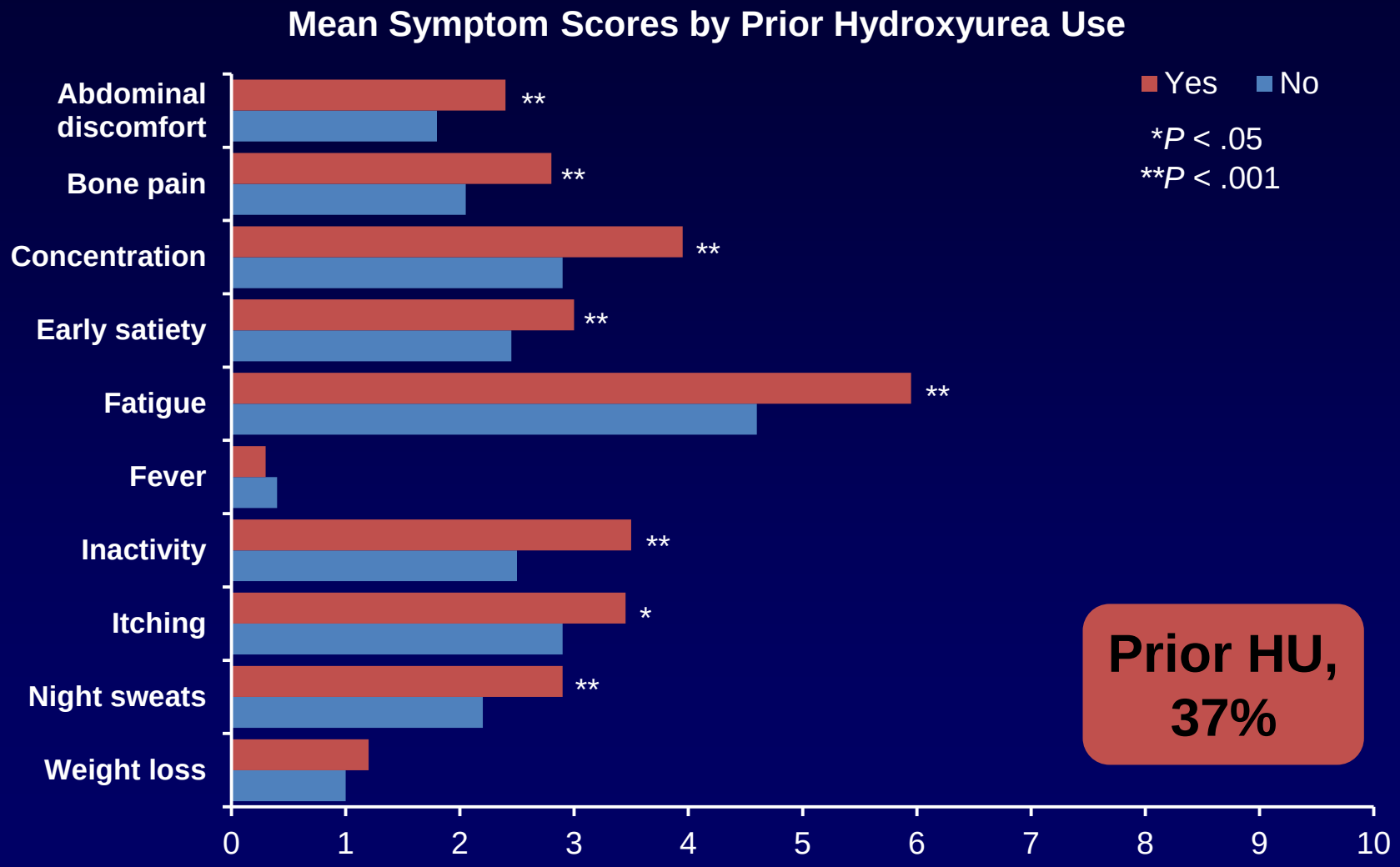
Impact of Prior Hydroxyurea Use on MPN 10 in 1334 Patients With PV



Prior HU, 37%

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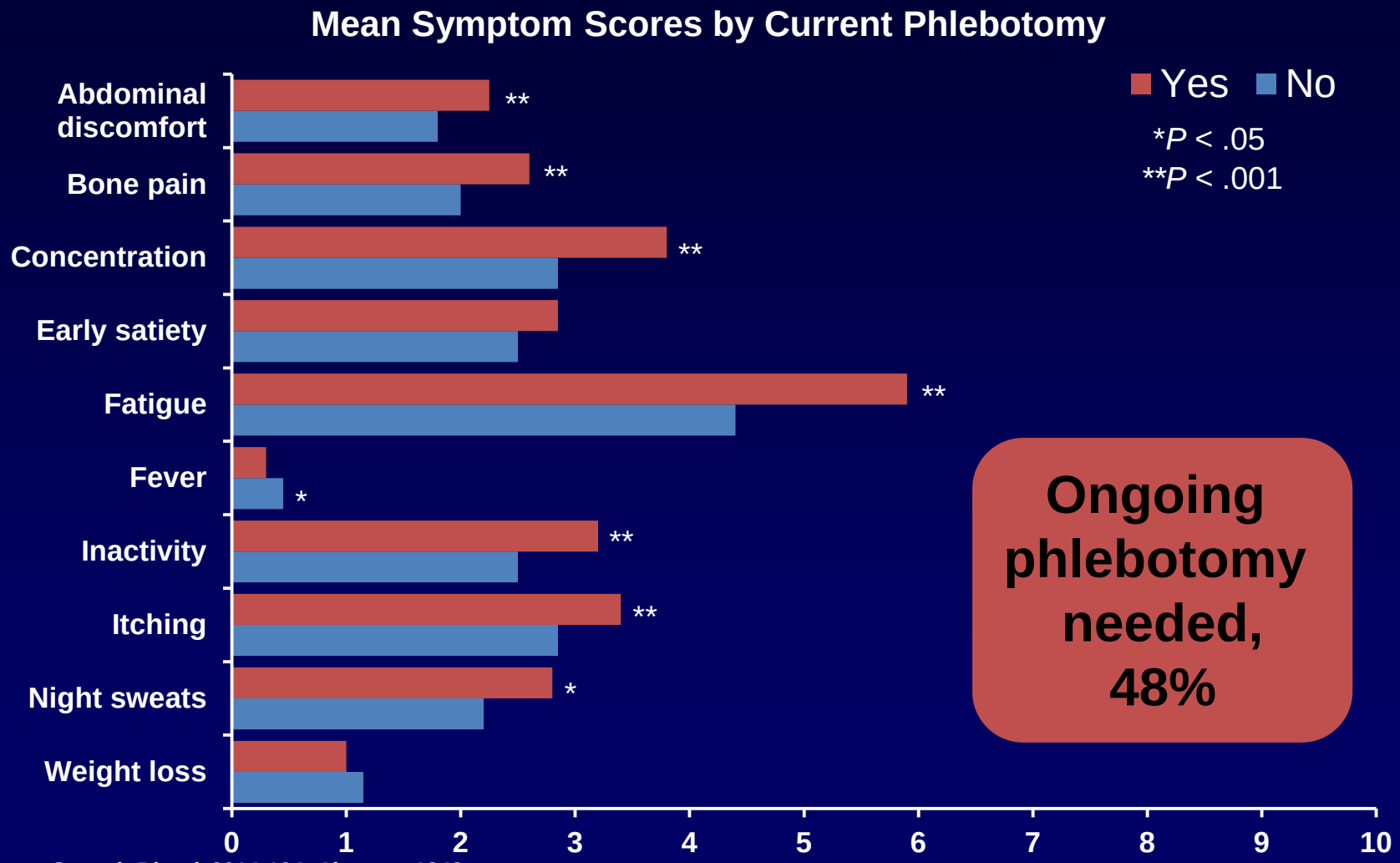
Impact of Ongoing Phlebotomy on MPN 10 in 1334 Patients With PV



Ongoing phlebotomy needed, 48%

Geyer S, et al. *Blood*. 2014;124: Abstract 1848.

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Methods: Patient-Reported Outcome Measures

- European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
  - Patients completed the EORTC QLQ-C30 every 4 weeks until Week 32
  - Scores ranged from 1 to 100 for all questions
    - Higher scores on the Global Health Status/QoL subscale and functional subscales indicated better functioning; higher scores on individual symptom scores indicated worse symptom severity
  - The percentage of patients achieving the minimally important difference (MID) from baseline in the Global Health Status/QoL subscale was summarized
    - MID = 10-point improvement from baseline

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Methods: Patient-Reported Outcome Measures (cont)

- Modified MPN Symptom Assessment Form (MPN-SAF)
  - Total symptom score (TSS; maximum score = 140) was assessed using the 14-item modified MPN-SAF; 3 symptom clusters were defined based on a factor analysis and pathophysiology
    - Symptom clusters: cytokine (sum of scores for tiredness, itching, muscle ache, night sweats, and sweats while awake), hyperviscosity (vision problems, dizziness, concentration problems, headache, numbness/tingling, ringing in ears, and skin redness), and splenomegaly (abdominal discomfort and early satiety)
  - Individual symptoms were ranked on a scale of 0 (absent) to 10 (worst imaginable)
- Pruritus Symptom Impact Scale (PSIS)
  - 5 questions graded on a scale of 0 (not at all) to 10 (worst imaginable)
- Patient Global Impression of Change (PGIC)
  - 7 response options described changes as “very much improved” to “very much worse”

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Mean EORTC QLQ-C30 Scores in PV and Other Hematologic Malignancies and Solid Tumors

EORTC QLQ-C30	PV RESPONSE baseline Rux arm (n = 110)	MF COMFORT-I baseline (N = 309)[1]	MF (N = 96)[2]	CML (N =73)[3]	Breast (N = 2782)[4]	Recurrent/ metastatic cancers (N = 4812)[4]
Global health status/QoL	**59.9**	52.8	59.9	70.2	61.8	56.3
Functional subscales						
Physical functioning	**79.8**	68.4	74.9	78.0	78.4	75.8
Role functioning	**77.8**	63.9	68.8	78.1	70.9	60.7
Emotional functioning	**76.3**	74.4	76.5	78.8	68.6	68.7
Cognitive functioning	**77.6**	80.4	77.0	86.1	81.5	80.5
Social functioning	**81.7**	67.1	74.9	84.3	77.0	70.5
Symptom scales/single items						
Fatigue	**37.9**	52.4	41.0	29.8	33.3	41.8
Pain	**24.7**	29.6	22.6	10.1	28.7	33.7
Dyspnea	**21.2**	36.9	29.8	15.5	18.1	23.4
Insomnia	**26.6**	39.0	33.7	26.9	29.8	33.6
Appetite loss	**12.3**	33.1	15.1	13.7	18.5	28.2

Lower score = worse QoL

Higher score = more severe symptoms

NOTE: Scores are calculated on a 100-point normalized scale with lower scores indicating poorer QoL for functioning subscales and Global Health Status/QoL, and higher scores indicating more severe symptoms on symptom scales
CML=chronic myeloid leukemia; MF=myelofibrosis

1. **Data on file. Incyte Corporation**
2. **Scherber R, et al. *Blood*. 2011;118:401-408.**
3. **Homewood J, et al. *Hematol J*. 2003;4:253-262.**
4. **Scott NW, et al. EORTC QLQ-C30 Reference Values. 2008. Available at: http://groups.eortc.be/qol/sites/default/files/img/newsletter/reference_values_manual2008.pdf. Accessed December 10, 2014.**

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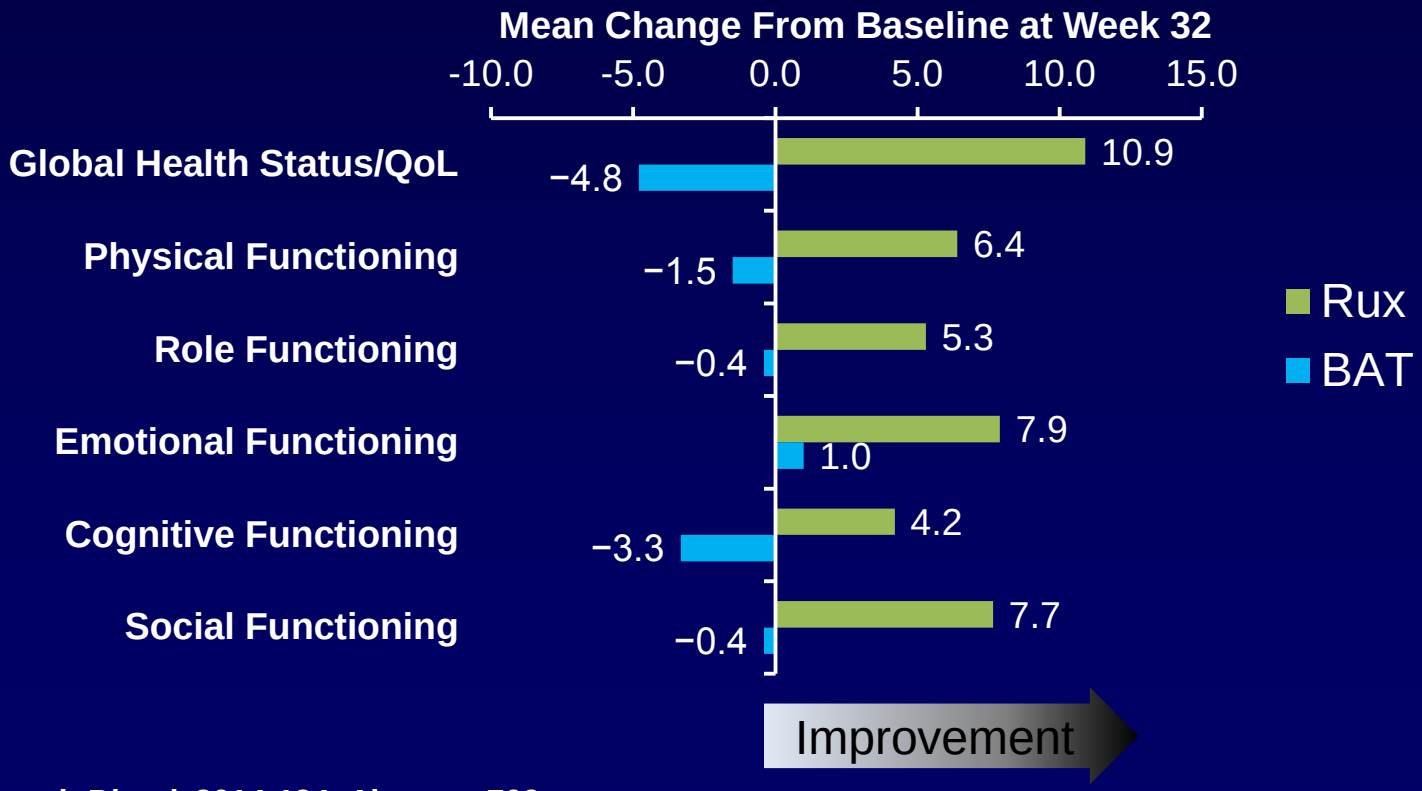
Mean Change From Baseline in EORTC QLQ-C30 Functional Scores at Week 32

- **Treatment with Rux was associated with improvement in mean EORTC QLQ-C30 functional subscale QoL categories, whereas BAT was associated with worsening or little improvement**



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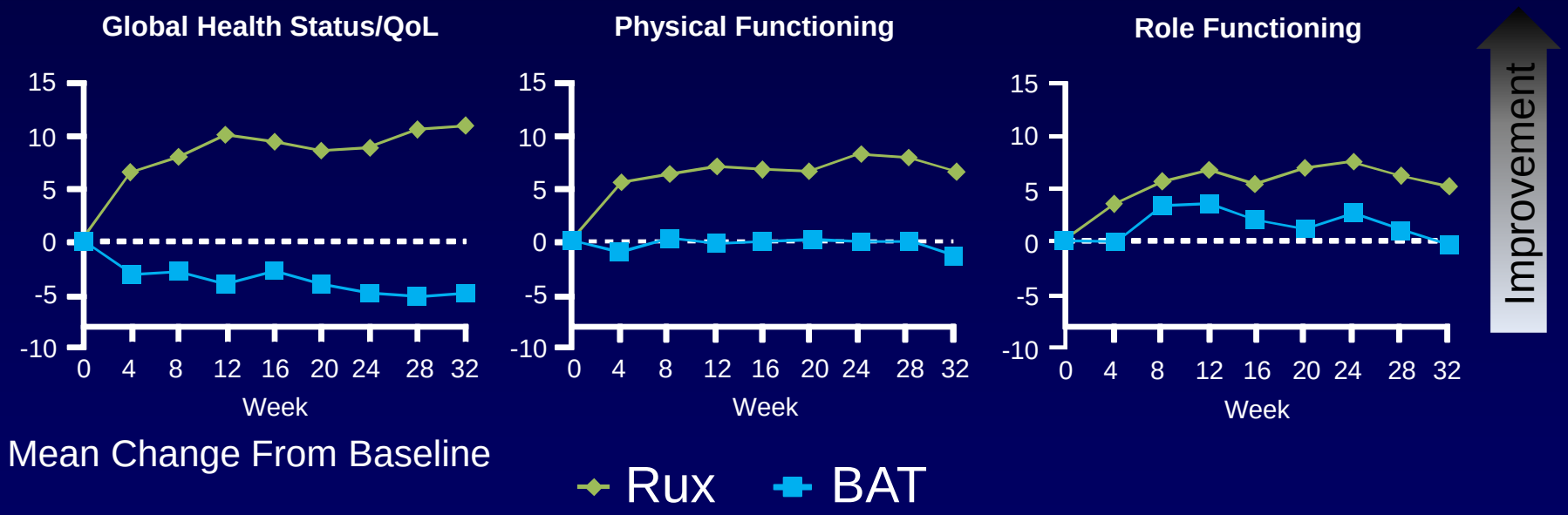
Mean Change From Baseline in EORTC QLQ-C30 Functional Scores Over Time

- **Improvements in functional subscales of the EORTC QLQ-C30 with Rux treatment were rapid and maintained over time**



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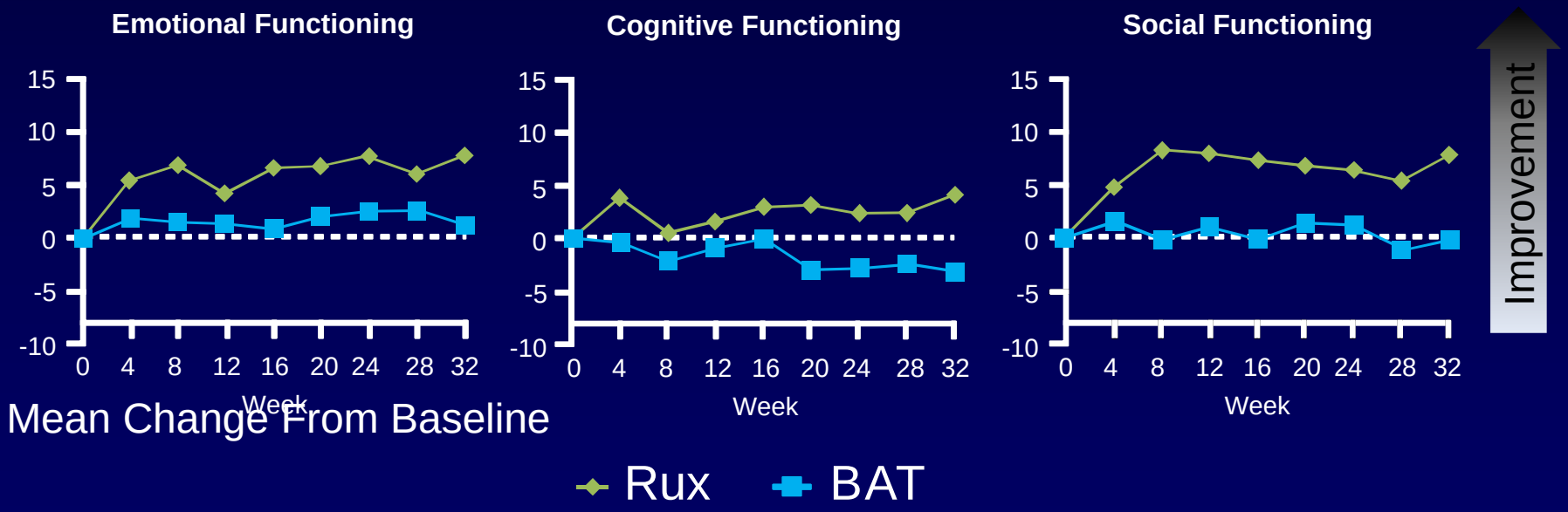
Mean Change From Baseline in EORTC QLQ-C30 Functional Scores Over Time (cont)

- **Improvements in functional subscales of the EORTC QLQ-C30 with Rux treatment were rapid and maintained over time**



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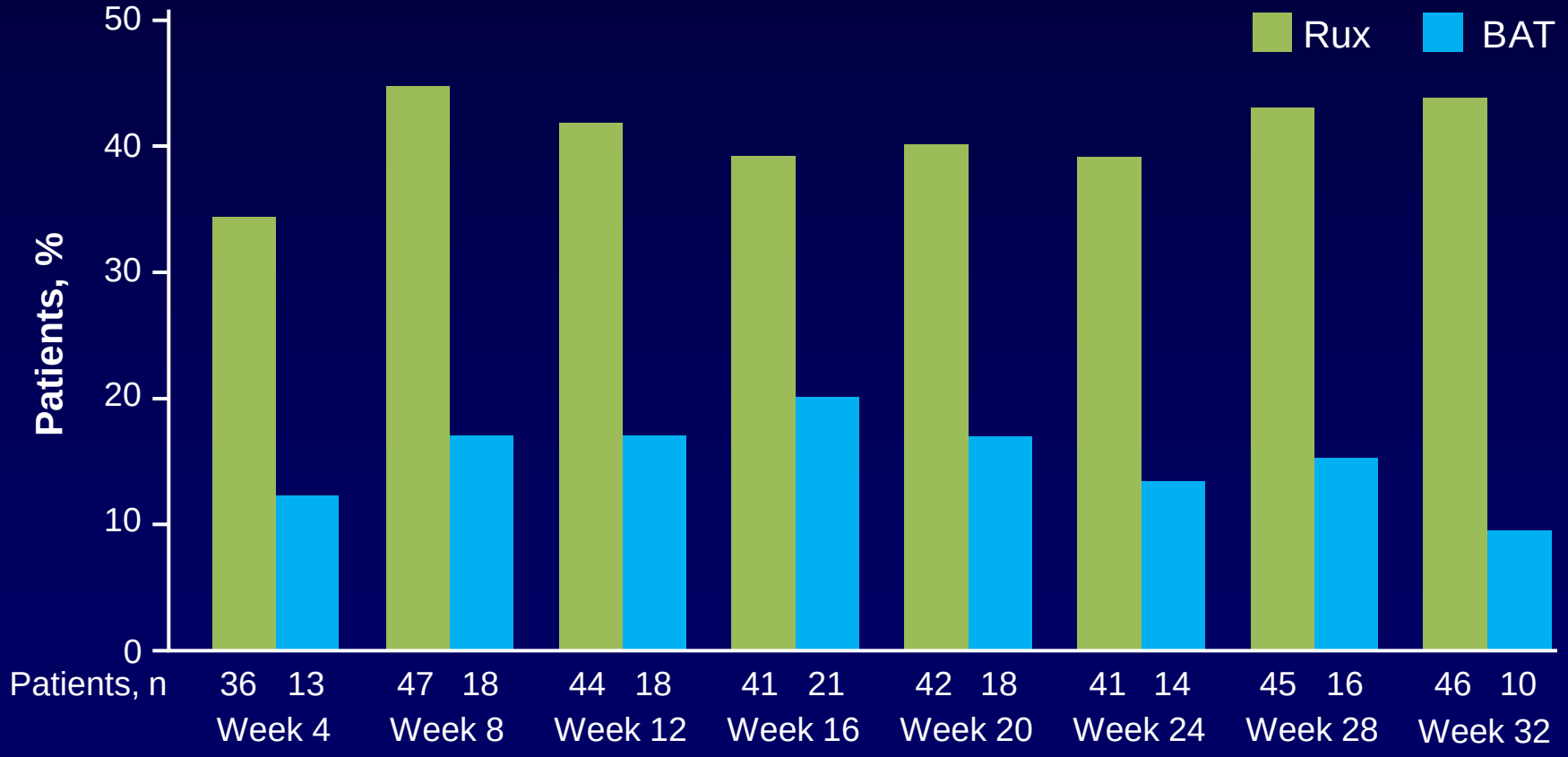
Proportion of Patients Achieving MID* in EORTC QLQ-C30 Global Health Status/QoL Over Time

- **A greater proportion of patients receiving Rux compared with BAT achieved MID at every visit between weeks 4 and 32**



*MID=10-point change

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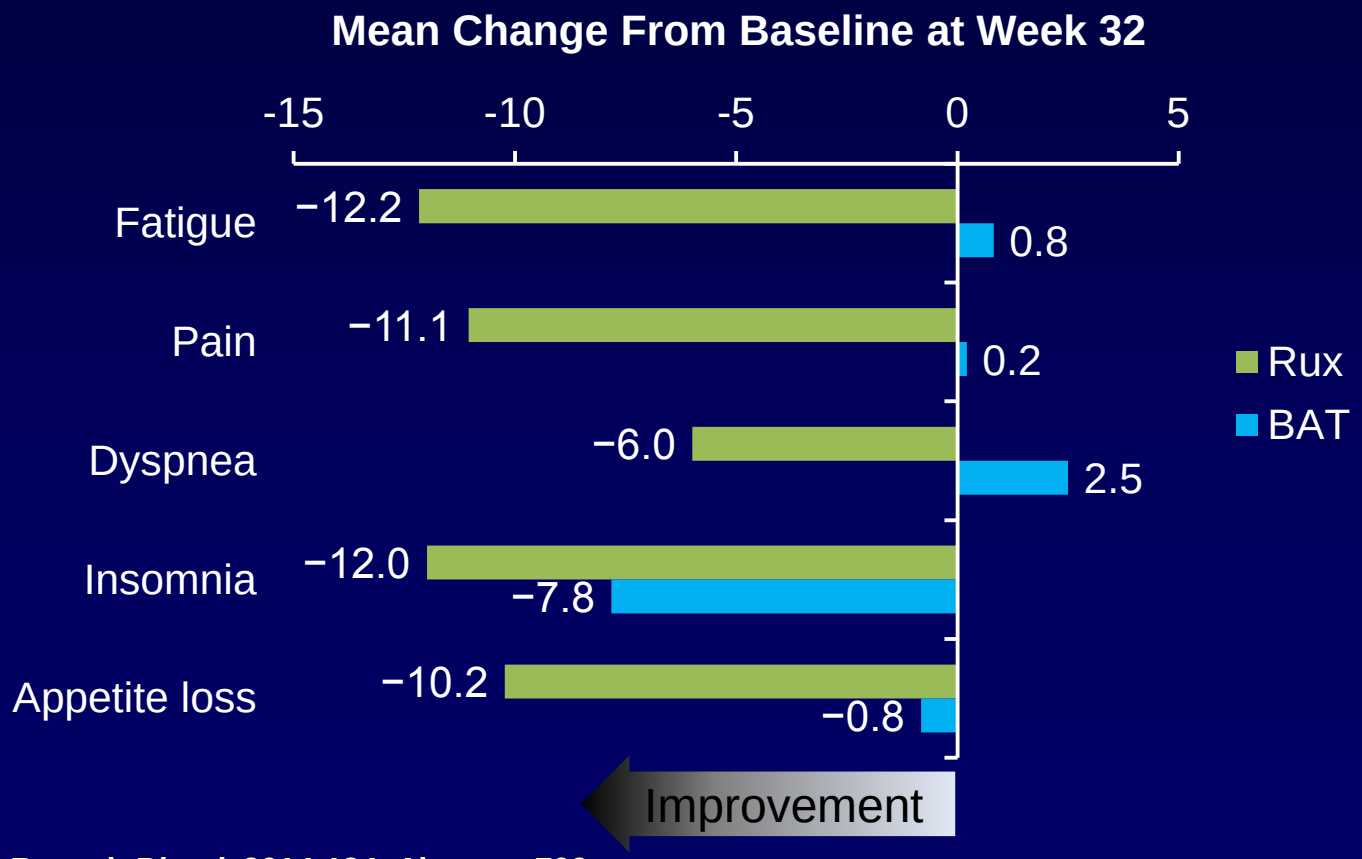
Mean Change From Baseline in EORTC QLQ-C30 Individual Symptom Scores at Week 32

- **Treatment with Rux was associated with improvement in mean EORTC QLQ-C30 symptom subscales, whereas BAT was associated with worsened or comparatively less improvement in symptom scores**



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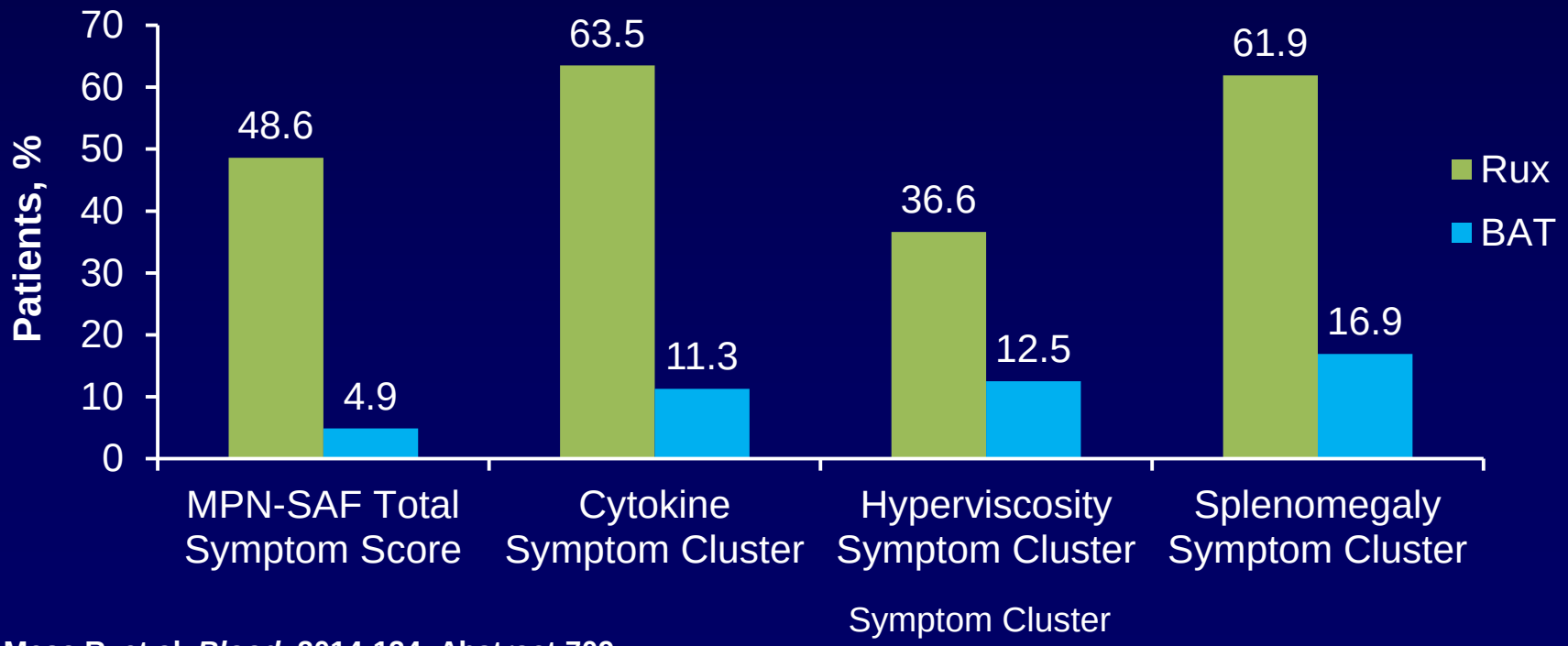
Improvement in MPN-SAF TSS and Symptom Clusters at Week 32

- **A greater proportion of patients treated with Rux compared with BAT experienced a ≥50% improvement in MPN-SAF total symptom score, as well as the cytokine, hyperviscosity, and splenomegaly symptom clusters**

Percentage of Patients With a ≥50% Improvement in MPN-SAF Symptom Scores at Week 32



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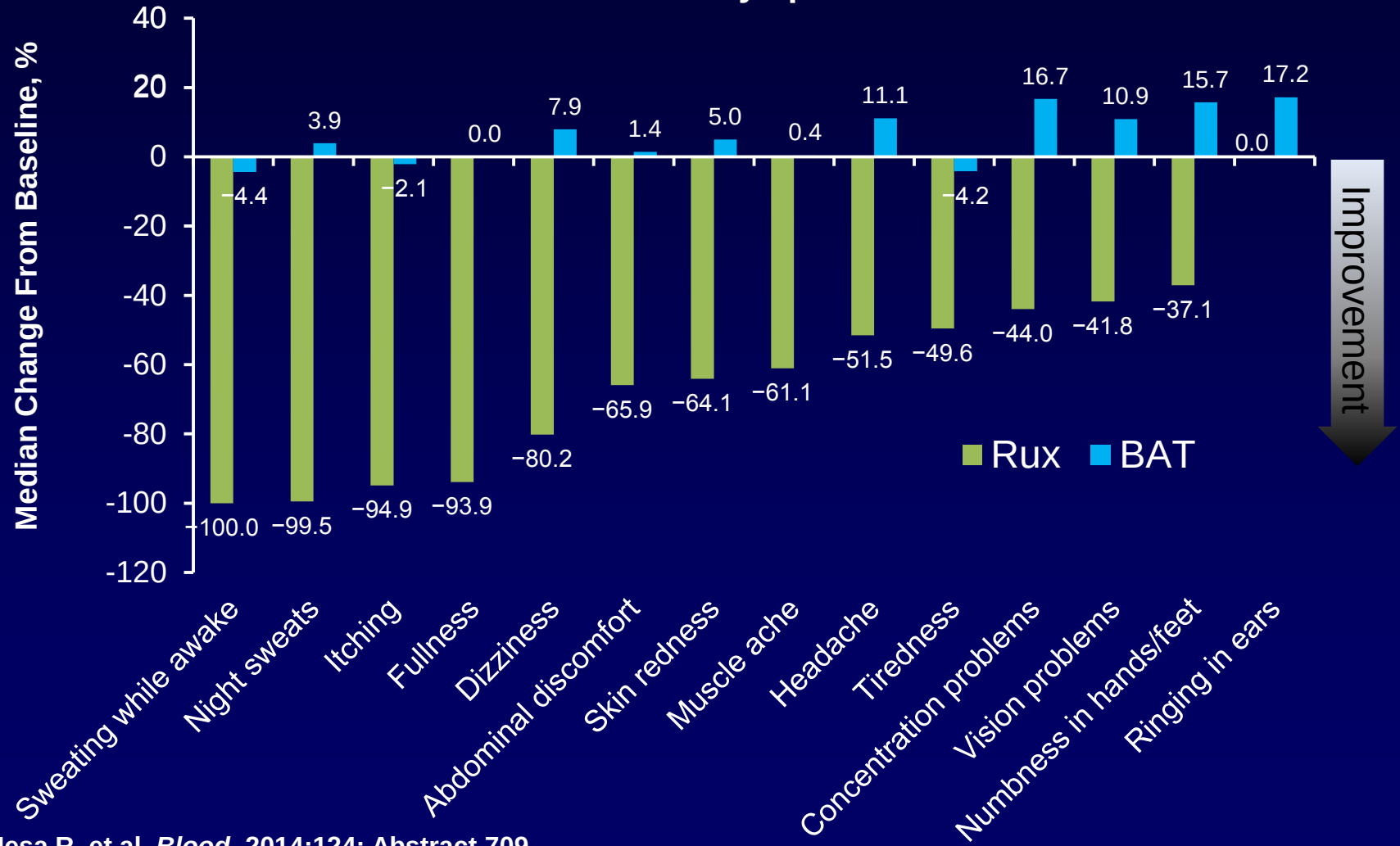
Improvement in Individual Symptoms of the MPN-SAF at Week 32

Median Percentage Changes From Baseline at Week 32 in Individual MPN-SAF Symptom Scores



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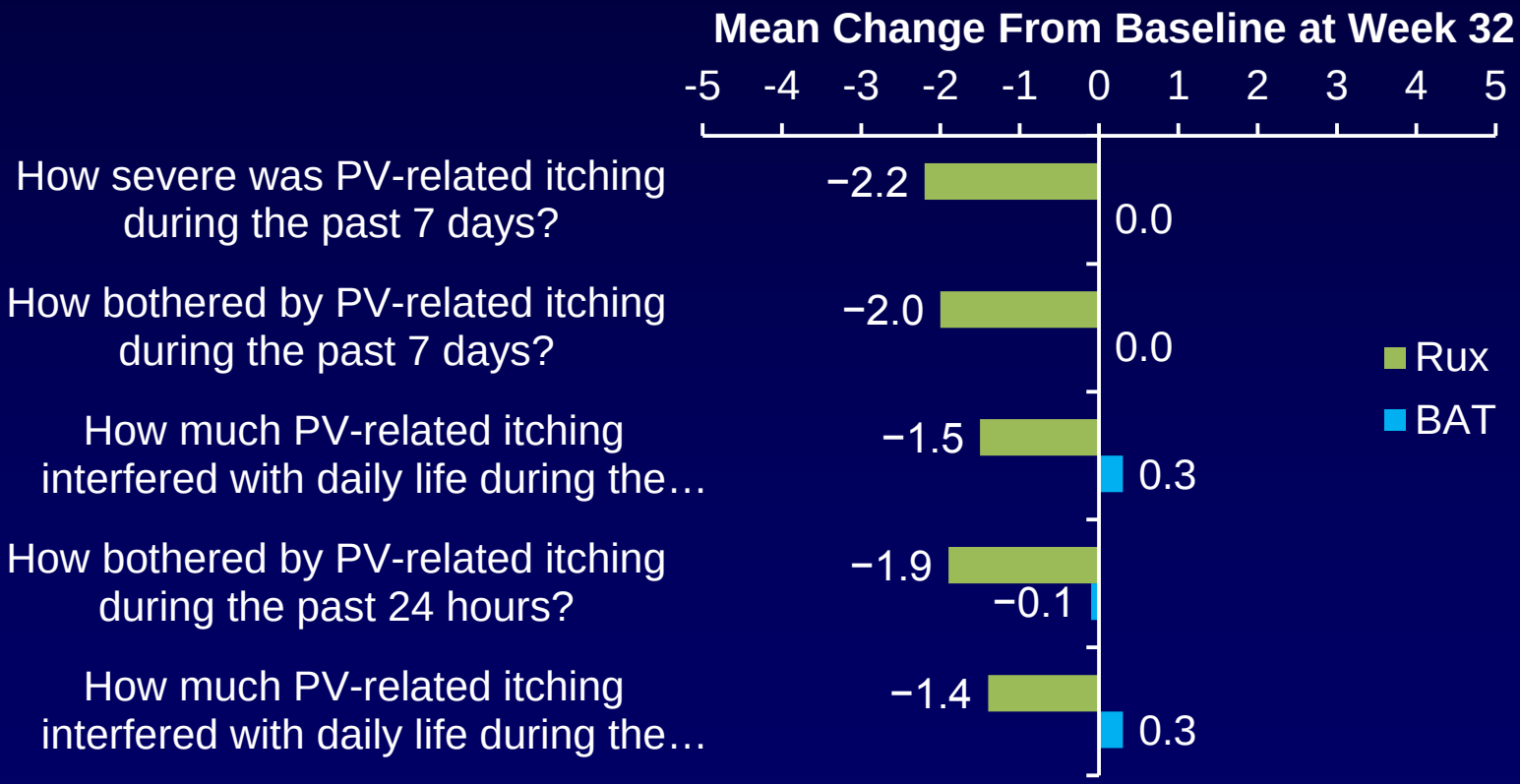
Mean Change From Baseline on the PSIS* at Week 32

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



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

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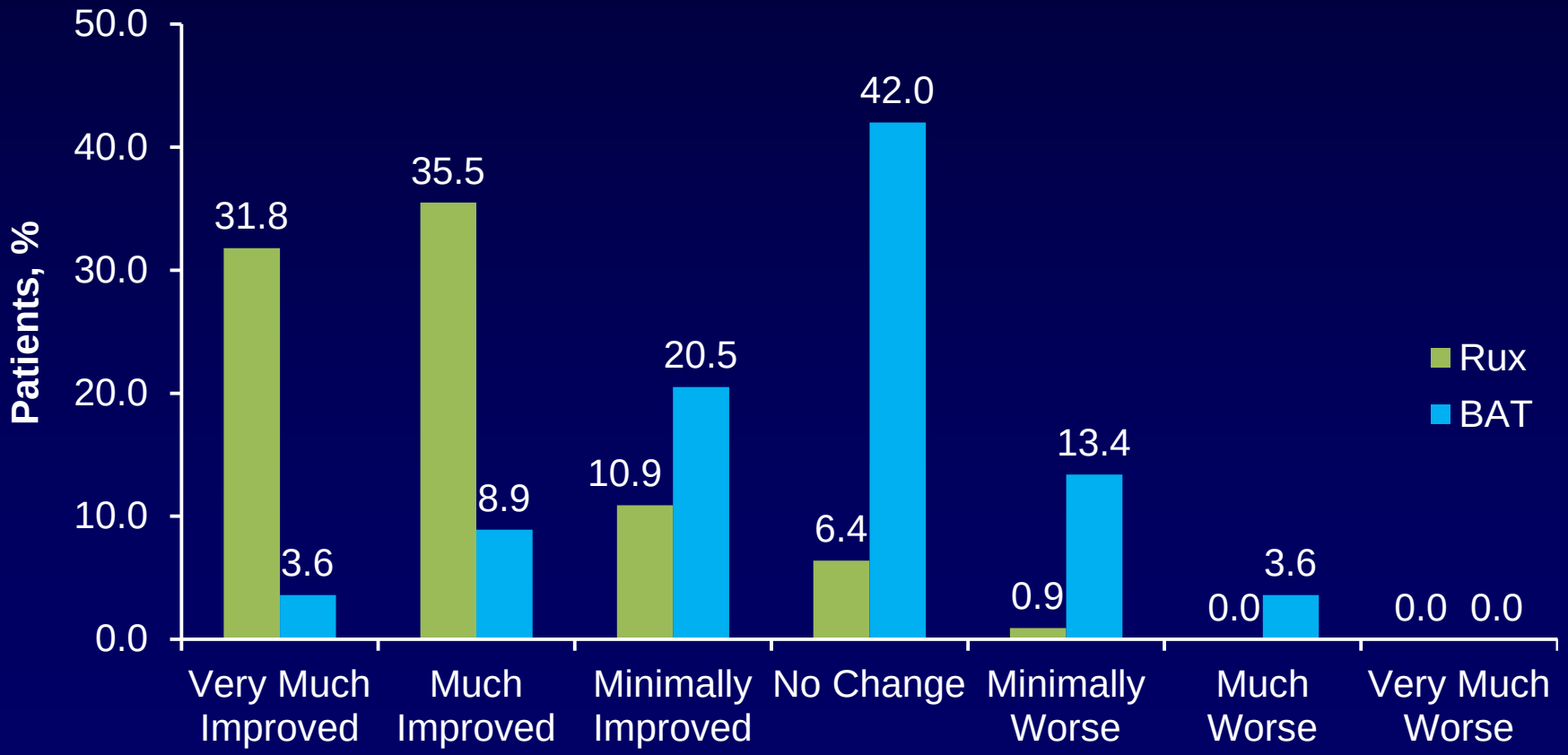
Patient Global Impression of Change at Week 32

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



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Discussion and Conclusions

- **Patients with PV who are resistant to or intolerant of HU per modified ELN criteria experience a broad disease burden that negatively affects QoL**
  - **PV symptoms may be severe, comparable to MF, and are not effectively addressed by standard therapy options**
- **Treatment with Rux was associated with greater and clinically meaningful improvements in PV-related symptom burden and QoL measures that were maintained up to Week 32 compared with BAT**
- **Rux may address an important unmet medical need in patients with PV whose disease is not adequately controlled with available therapies**

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