

Health-Related Quality of Life and Symptoms in Myelofibrosis Patients Treated With Ruxolitinib Versus Best Available Therapy

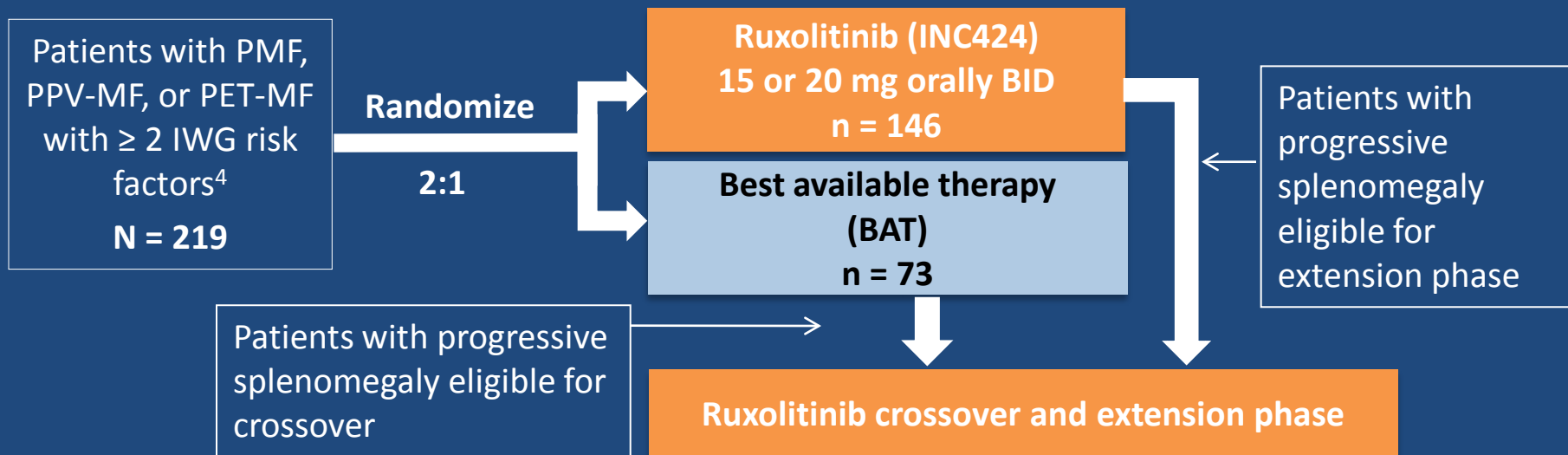
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Symptoms in MF

- This complex of MF-associated symptoms can substantially compromise the quality of life (QoL) of patients with MF and can contribute to shortened survival
 - Anemia
 - Fatigue
 - Cachexia
 - Pruritus
 - Night sweats
 - Fever
 - Spleen-associated symptoms:
 - Early satiety
 - Pain
 - Limitations of movement
 - Dyspnea

COMFORT-II Study Design

- Ruxolitinib is a potent and selective oral JAK1/2 inhibitor that has demonstrated rapid and durable reductions in splenomegaly, improved disease-related symptoms and QoL, and prolonged overall survival for patients with MF¹⁻³
- COMFORT-II is a randomized, open-label, multicenter phase 3 trial



- Patients were stratified based on baseline IWG prognostic risk group⁴

1. Verstovsek S, et al. Oral presentation at 2011 ASCO Annual Meeting; June 3-7, 2011. Abstract 6500.

2. Harrison C, et al. Oral presentation at 16th Congress of EHA; June 9-12, 2011. Abstract 1020.

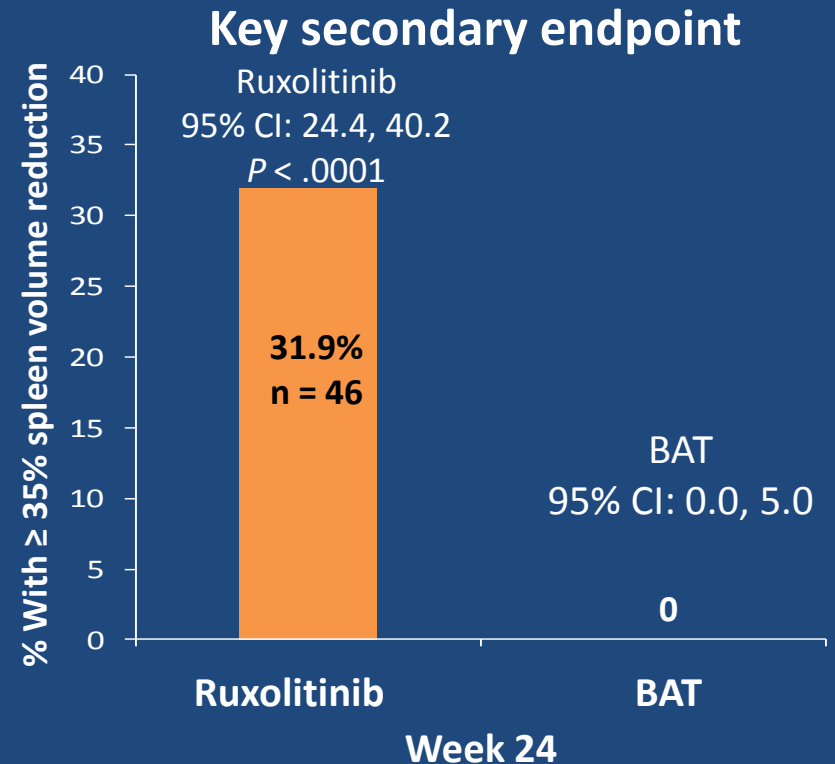
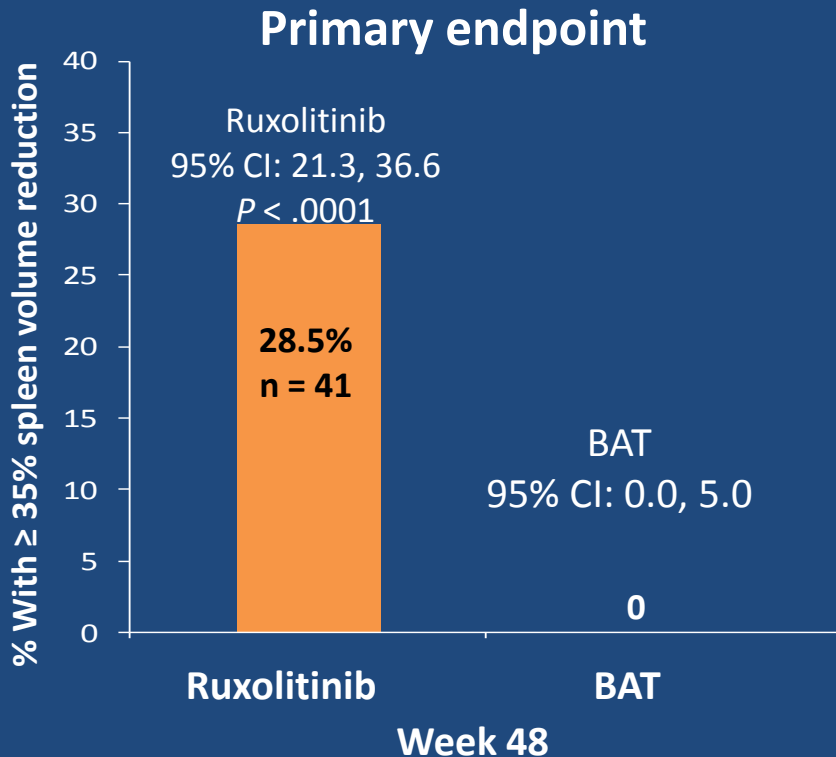
3. Verstovsek S, et al. Oral presentation at 53rd ASH Annual Meeting; Dec 10-14, 2011. Abstract 278.

4. Cervantes F, et al. *Blood*. 2009;113(13):2895-2901.

COMFORT-II Endpoints

Primary and key secondary endpoints

- Proportion of patients achieving $\geq 35\%$ reduction in spleen volume from baseline at weeks 48 and 24 as measured by MRI/CT^a



- Median time to response, 12.3 weeks
- Of the 69 patients who achieved $\geq 35\%$ reduction in spleen volume at any time during the study, 44 (64%) did so at the first assessment

^a CT for patients unable to undergo MRI.

Demographics and Baseline Patient Characteristics (ITT)

	Ruxolitinib (n = 146)	BAT (n = 73)
Age, median, y	67	66
≤ 65 years, n (%)	69 (47)	36 (49)
Male, n (%)	83 (57)	42 (58)
Myelofibrosis type, n (%)		
PMF	77 (53)	39 (53)
PPV-MF	48 (33)	20 (27)
PET-MF	21 (14)	14 (19)
Platelet count > 200 x 10 ⁹ /L, n (%) ^a	88 (61)	47 (65)
High/intermediate-2 IWG risk	49%/51%	49%/51%
<i>JAK2V617F</i> positive, n (%)	110 (75)	49 (67)
Palpable spleen size below costal margin, margin, cm	14	15
Spleen volume, ^b median, cm ³	2408	2318
Prior hydroxyurea therapy, n (%)	110 (75)	50 (68)

^a Ruxolitinib, n = 144; BAT, n = 72.

^b Normal spleen volume is 150 to 200 cm³.

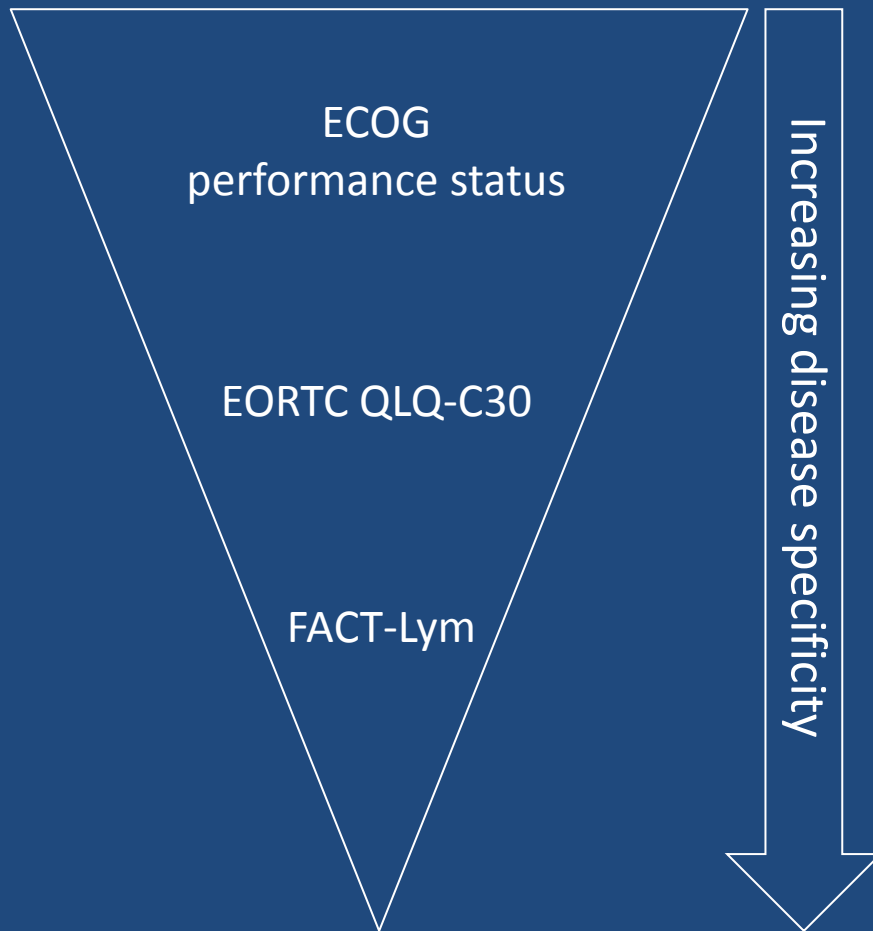
ITT, intention-to-treat.

Patient Disposition

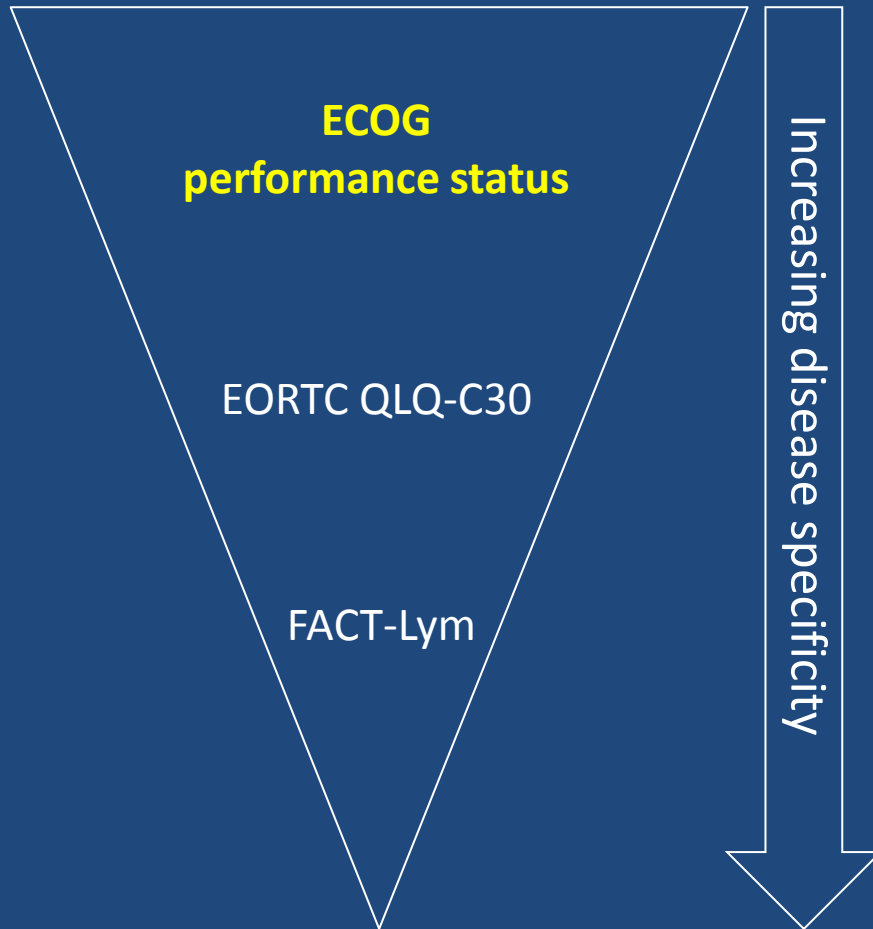
Patients	Ruxolitinib (n = 146)	BAT (n = 73)
Still on randomized treatment by week 48	64% (94/146) ^a	48% (35/73)
^a An additional 29 patients (20%) continued ruxolitinib therapy in the extension phase of COMFORT-II		
EORTC QLQ-C30 questionnaire		
Patients with baseline and at least 1 postbaseline assessment (up to 48 weeks)	89% (130/146)	79% (58/73)
Completed week 48 assessment	83% (78/94)	86% (30/35)
FACT-Lym questionnaire		
Patients with baseline and at least 1 postbaseline assessment (up to 48 weeks)	93% (135/146)	82% (60/73)
Completed week 48 assessment	82% (77/94)	86% (30/35)

Health-Related QoL Assessments

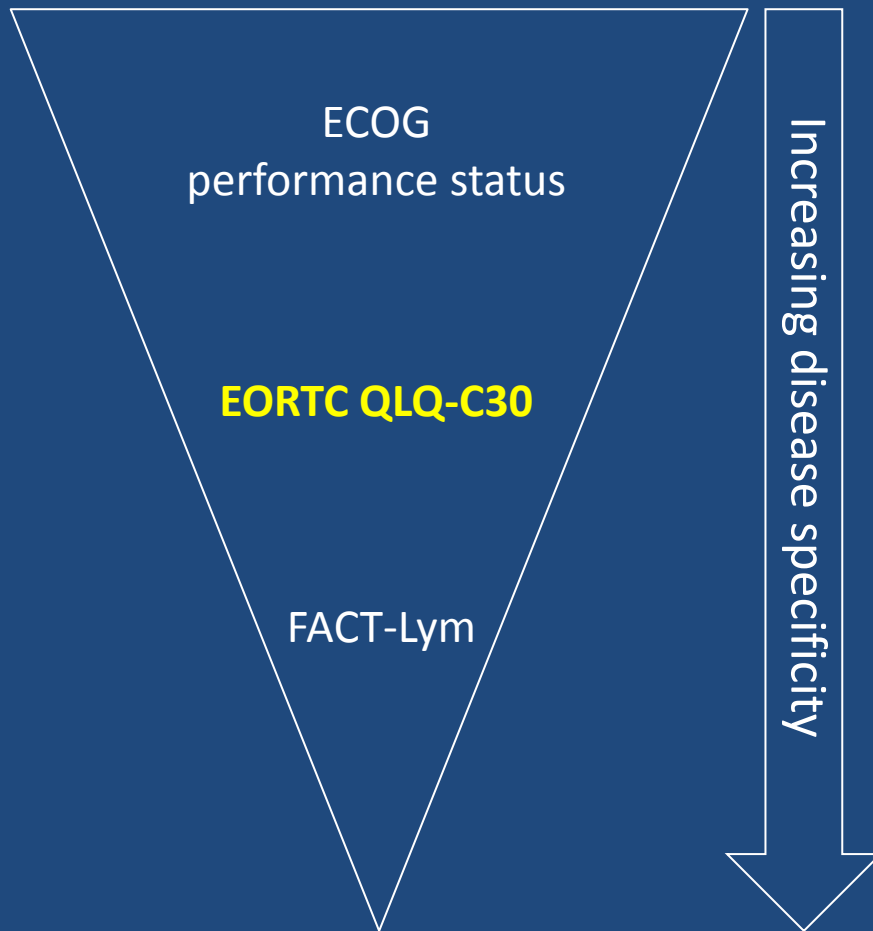
Validated instruments used at weeks 8, 16, 24, and 48, and not after disease progression or crossover



Health-Related QoL Assessments



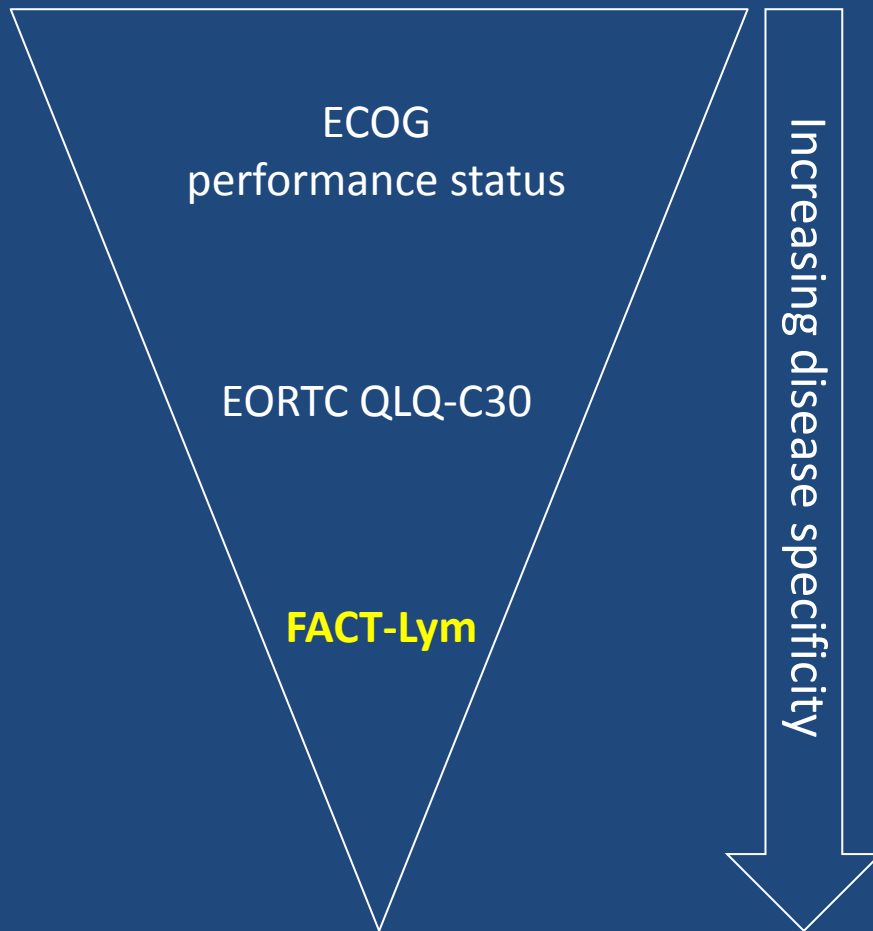
Health-Related QoL Assessments: EORTC QLQ-C30



- The EORTC QLQ-C30 consists of
 - Global health status/QoL scale
 - 5 functional scales:
 - Physical, role, emotional, cognitive, and social
 - 9 symptom scales:
 - fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial impact

Health-Related QoL Assessments: FACT-Lym

Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)

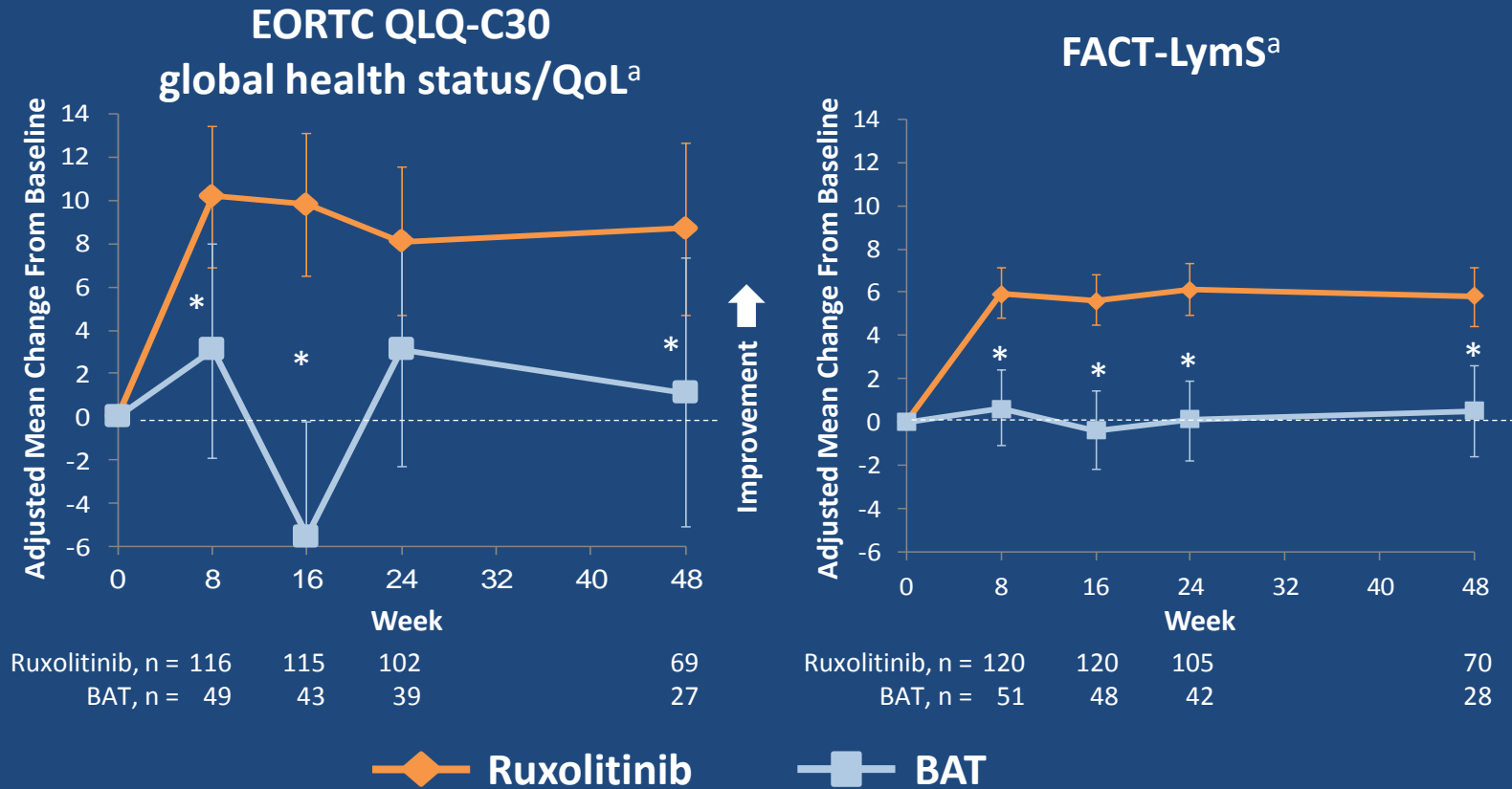


- FACT-Lym Total consists of
 - FACT-G: a generic questionnaire of 27 items divided into 4 domains
 - Physical well-being
 - Social/family well-being
 - Emotional well-being
 - Functional well-being
 - Lymphoma subscale (LymS): a cancer-specific questionnaire of 15 items used to evaluate response to treatment
- FACT-Lym Trial Outcome Index (TOI)
TOI = Physical + Functional well-being + LymS

Methods

- Mixed-model analyses were used to evaluate treatment differences as a continuous variable
- Advantages of mixed-effect models include:
 - All data in one analysis
 - Use of all reported scores without loss of information
 - Allowance for treatment differences to vary by time
 - Adjusted for confounders including age, sex, baseline score, and prognostic risk category
- In the responder analysis, for each outcome score, responders were defined based on a minimally important difference (MID) defined as a change in score of at least the upper bound of previously published ranges

Change From Baseline in EORTC QLQ-C30 Global Health Status/QoL and FACT-LymS



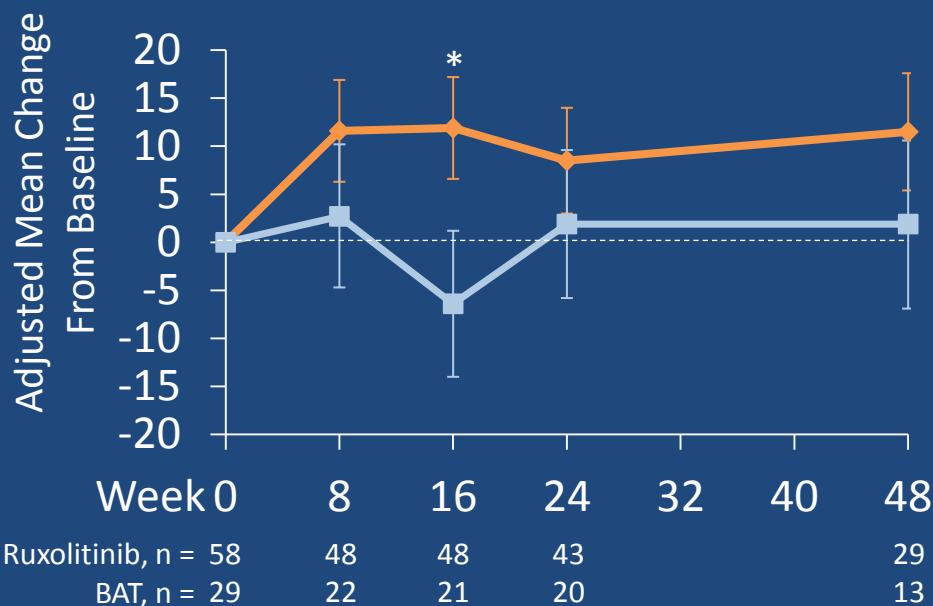
Compared with the BAT arm, Global Health Status/QoL and the FACT-LymS were significantly improved in the ruxolitinib arm at weeks 8, 16, and 48

^a Adjusted for age, sex, baseline score, and prognostic risk category.

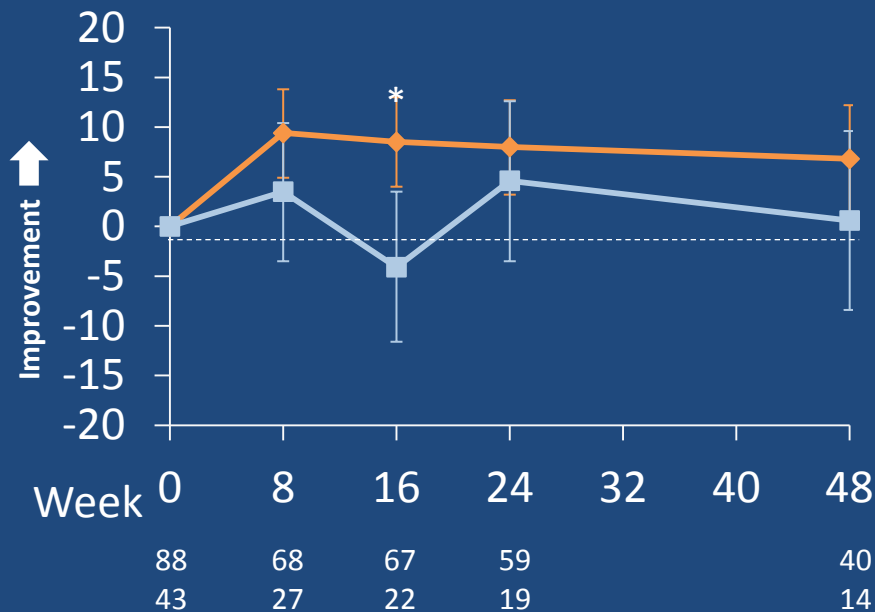
* $P < .05$ for treatment difference (from the mixed model).

Change From Baseline in EORTC QLQ-C30 Global Health Status/QoL by Risk Group

Intermediate risk-2^a



High risk^a



◆ Ruxolitinib ■ BAT

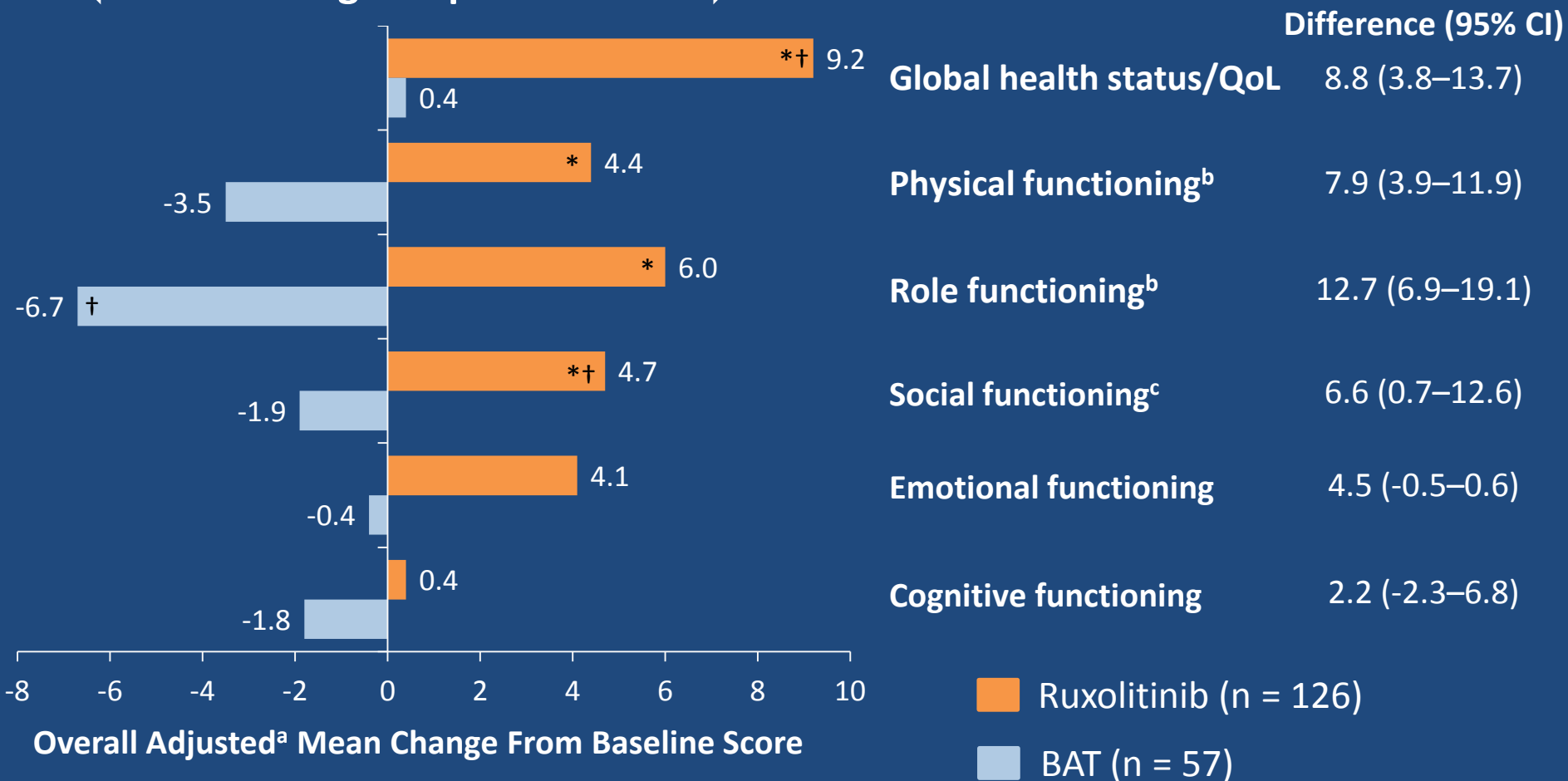
The treatment effect between the high-risk and intermediate risk-2 prognostic groups was not significantly different

^a Adjusted for age, sex, baseline score, and prognostic risk category.

* $P < .05$ for treatment difference (from the mixed model).

EORTC QLQ-C30 QoL and Functional Scales (overall across time)

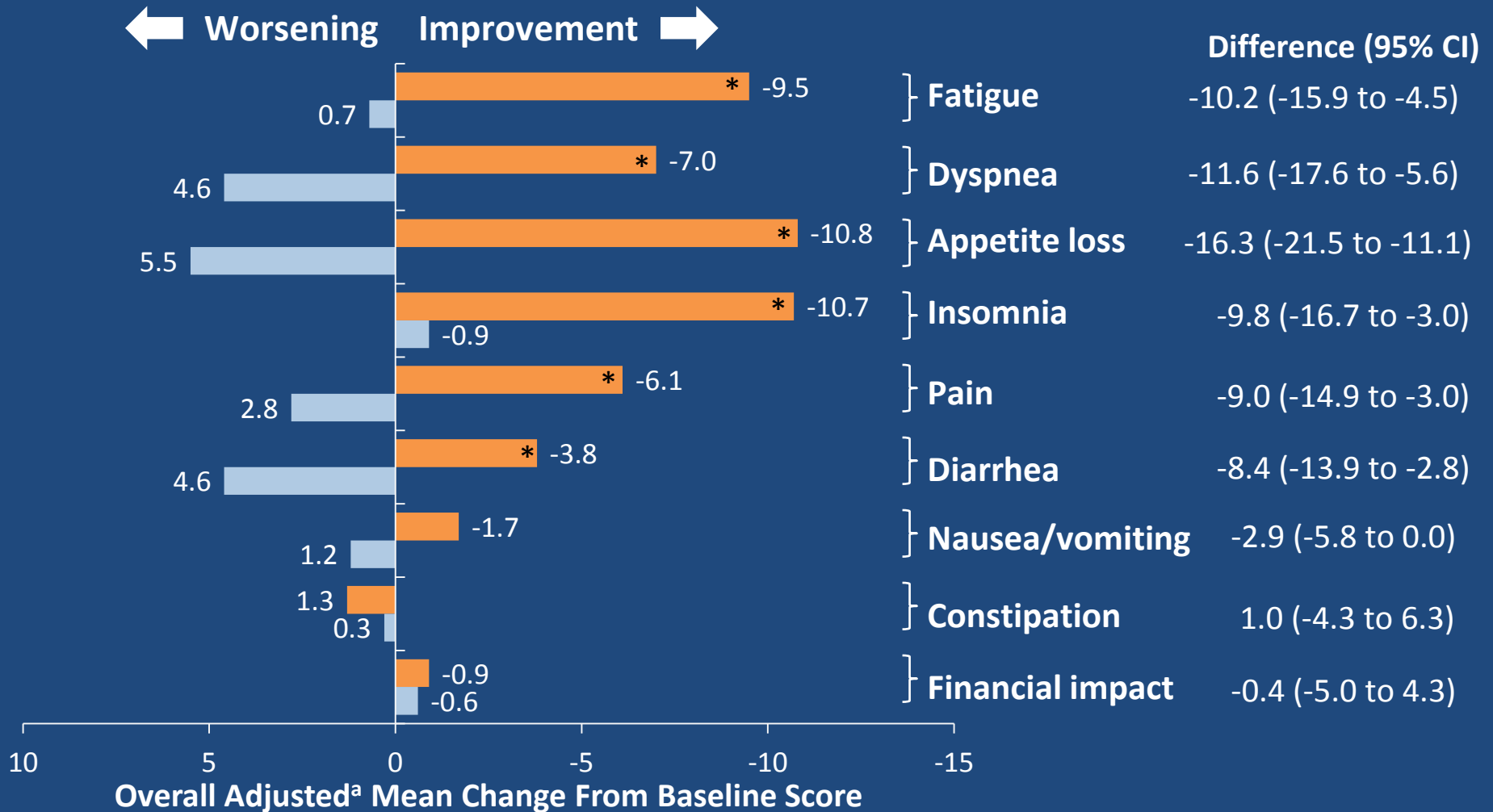
← Worsening Improvement →



^a Adjusted for age, sex, baseline score, and prognostic risk category; ^b Ruxolitinib, n = 130; ^c Ruxolitinib, n = 125;

* $P < .05$ for treatment difference (from the mixed model); † Clinically significant difference.

EORTC QLQ-C30 Symptom Scales (overall across time)



^a Adjusted for age, sex, baseline score, and prognostic risk category.

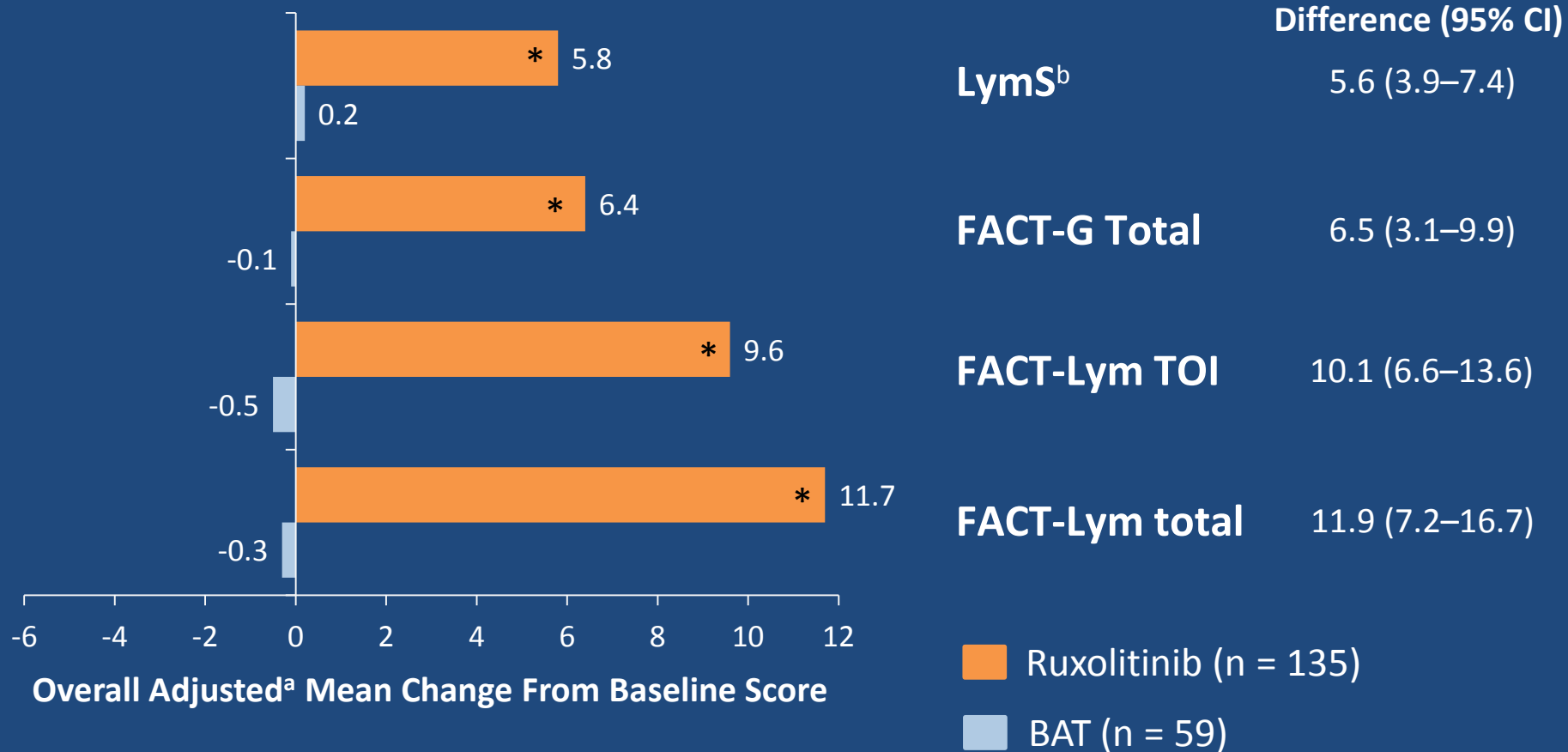
* $P \leq .01$, for treatment difference (from the mixed model).

[†] Ruxolitinib sample size = 125 to 130 patients.

[‡] BAT sample size = 56 to 57 patients.

FACT-Lymphoma Scores (overall across time)

← Worsening Improvement →



^a Adjusted for age, sex, baseline score, and prognostic risk category.

^b Ruxolitinib, n = 133.

* $P < .001$ for treatment difference (from the mixed model).

Responder Analysis

Clinically significant or minimally important difference (MID) is defined as a change in score of at least the upper bound of previously published ranges

QoL Outcome	Possible score	Analysis MID (published ranges)
EORTC QLQ-C30 Global Health Status/QoL ^{1,2}	0-100	17 (6-17)
FACT-G total ³	0-108	7 (3-7)
FACT-Lym subscale ⁴	0-60	5.4 (2.9-5.4)
FACT-Lym TOI ⁴	0-116	11 (5.5-11)
FACT-Lym total ⁴	0-168	11.2 (6.5-11.2)

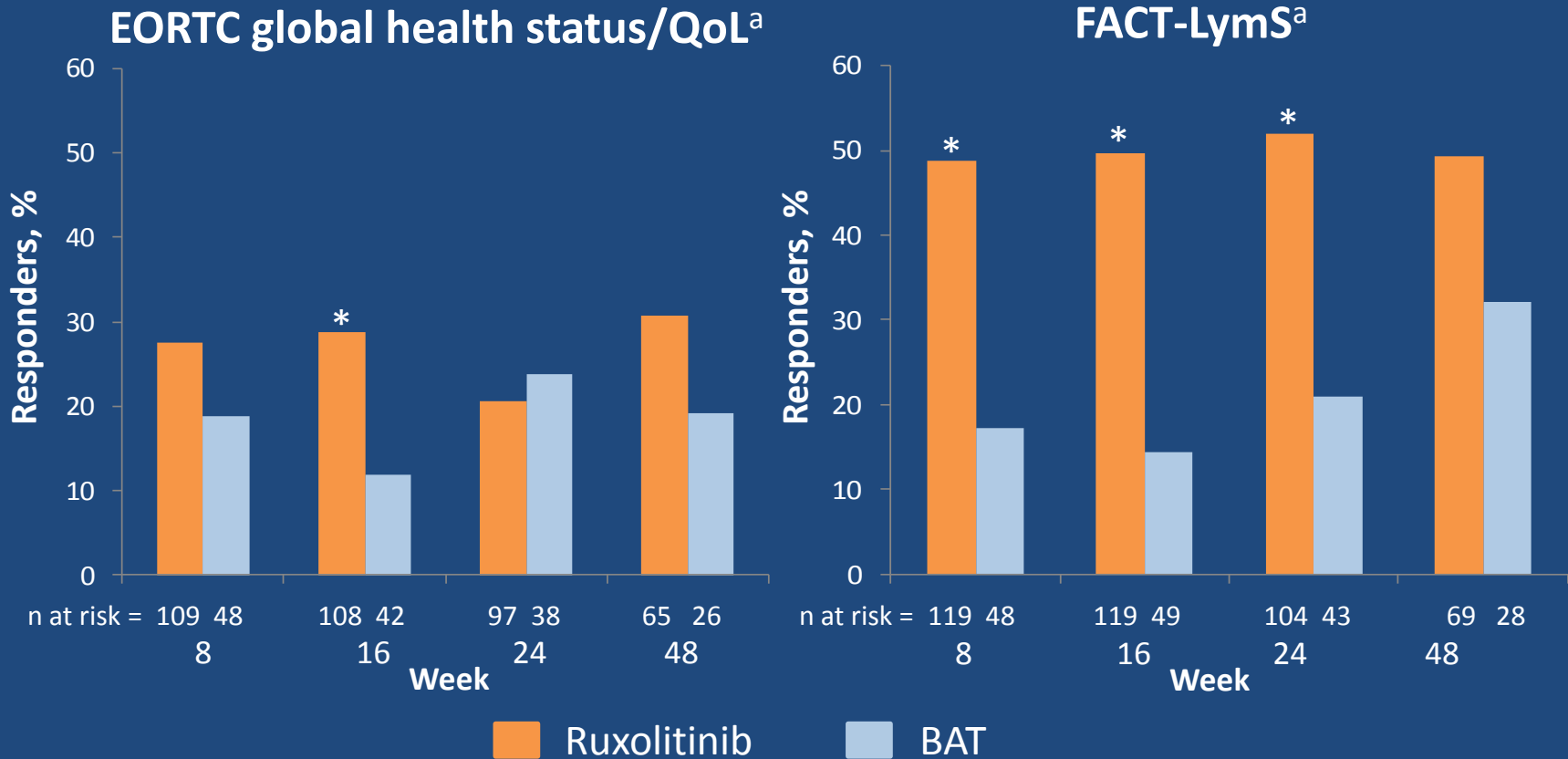
1. Kvam AK, et al. *Eur J Haematol*. 2010;84(4):345-353.

2. Osoba D, et al. *J Clin Oncol*. 1998;16(1):139-144.

3. Webster K, et al. *Health Qual Life Outcomes*. 2003;1:79.

4. Carter GC, et al. Presented at the 50th ASH Annual Meeting and exposition; Dec 7, 2008.

Percentage of Responders



Similar results were observed on the FACT-G total, FACT-Lym total, and FACT-Lym TOI subscales

^a For patients with change from baseline scores at each visit. Patients with a best possible score at baseline were excluded from analysis.

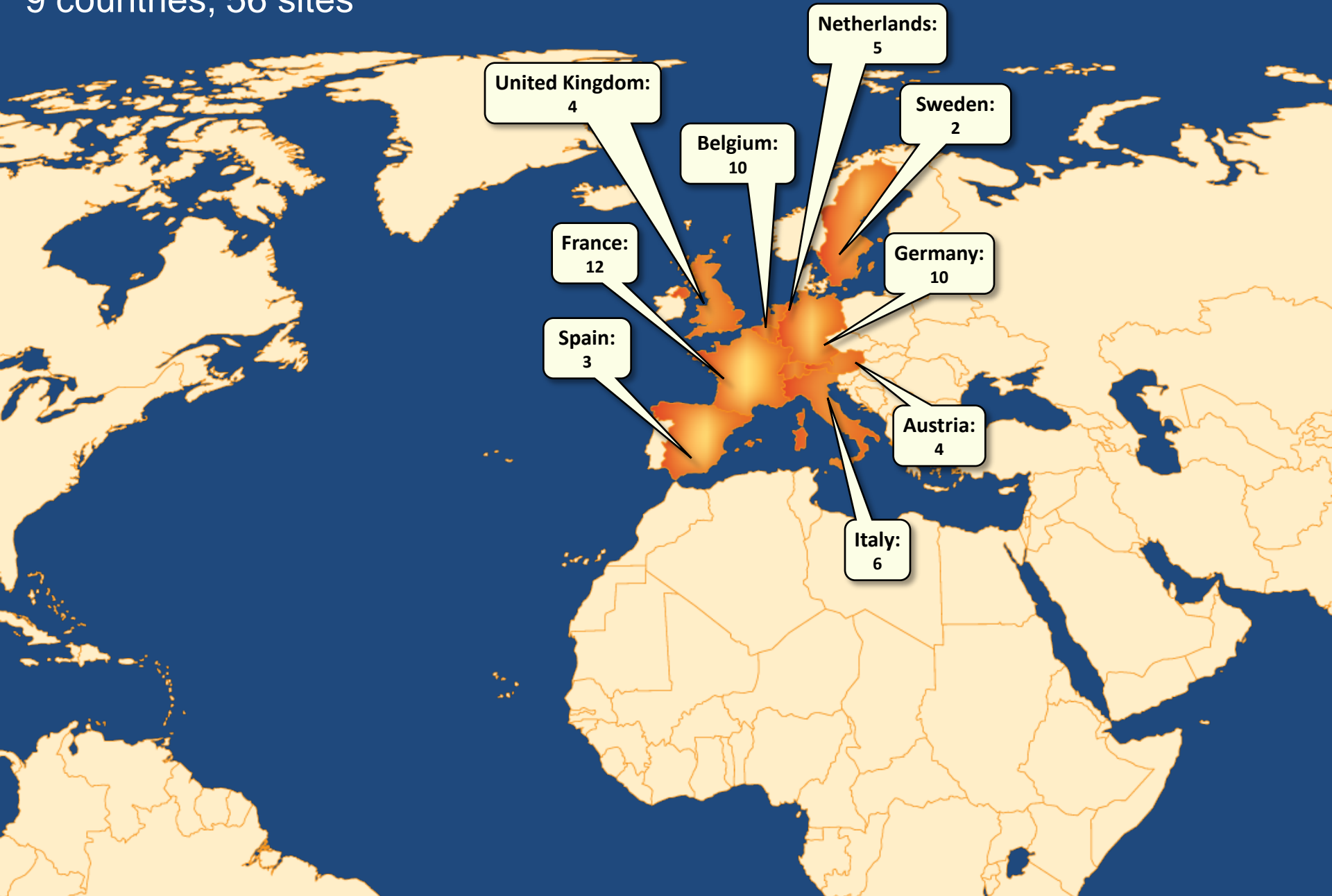
* $P < .05$ (Fisher's exact test).

Conclusions

- First presentation of a rigorous statistical analyses of QoL data from the COMFORT-II study across the 48 week duration of the study
- Both mixed-model and responder analyses show statistically significant benefit for ruxolitinib compared with conventional therapies (BAT) in both EORTC QLQ-C30 and FACT-Lym instruments
- QoL scores for BAT patients often worsened
- This demonstrates a clinically important, novel therapeutic benefit of ruxolitinib therapy

COMFORT-II

9 countries, 56 sites



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