Neoplasie Mieloproliferative Croniche

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Alessandro M. Vannucchi – Disclosures

-Novartis: *Advisory Board, Speaker, Research support*

-Shire: *Speaker*

Topics

- **Ruxolitinib nella PV:** RESPONSE-2 e dintorni
- **Gravidanza nella PV**
- **Efficacia/sicurezza di ruxolitinib** - "long-term" e "expanded access " **– nella MF**

ET ?????

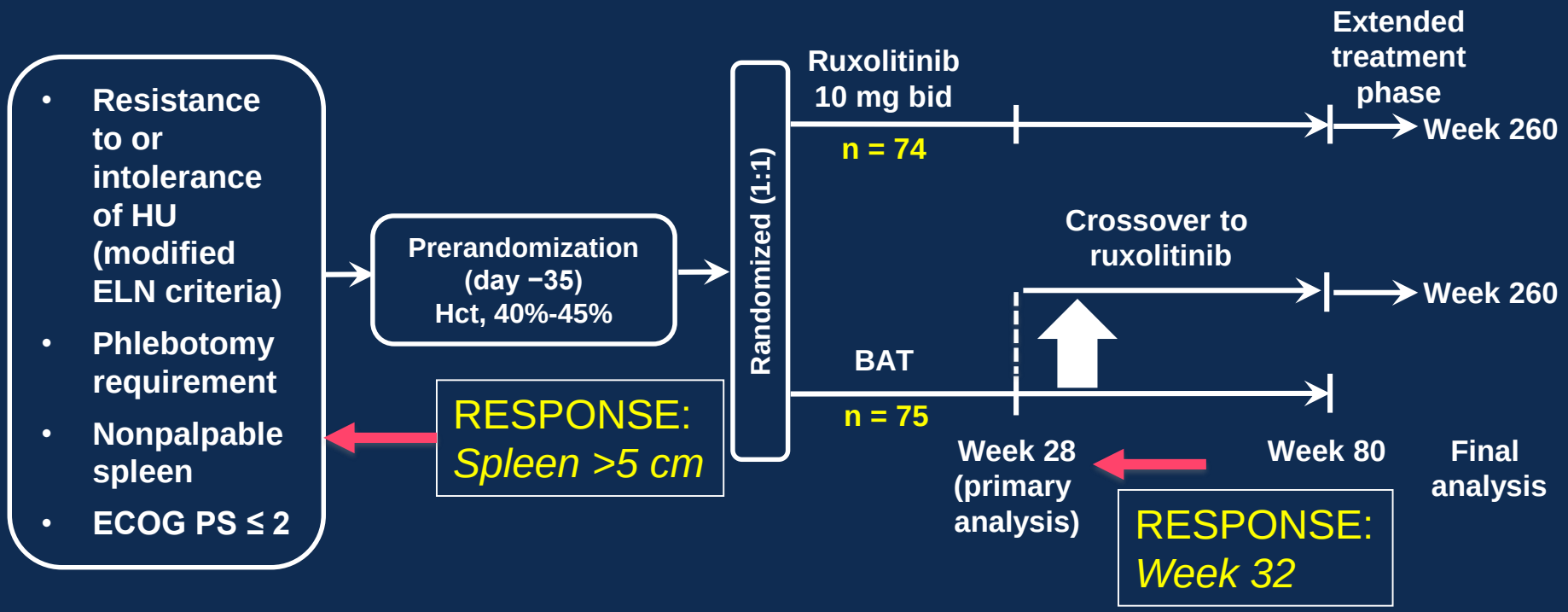
MPN	**Controversies in the diagnostic and the therapy of MPNs**	**Tiziano Barbui (IT)**	**Claire Harrison (UK)**
	Topic / Title	Do we really need new diagnostic criteria for MPN? YES	Do we really need new diagnostic criteria for MPN? NO

Topics

- **Ruxolitinib nella PV: RESPONSE-2 e dintorni**

- Ruxolitinib Proves Superior to Best Available Therapy in Patients With Polycythemia Vera Resistant to or Intolerant of Hydroxyurea Without Splenomegaly: Results From RESPONSE-2. *F. Passamonti et al*.
- Ruxolitinib Reduces *JAK2*V617F Allele Burden in Patients With Polycythemia Vera Enrolled in the RESPONSE Study- *AM Vannucchi et al*.

RESPONSE-2 Study Design



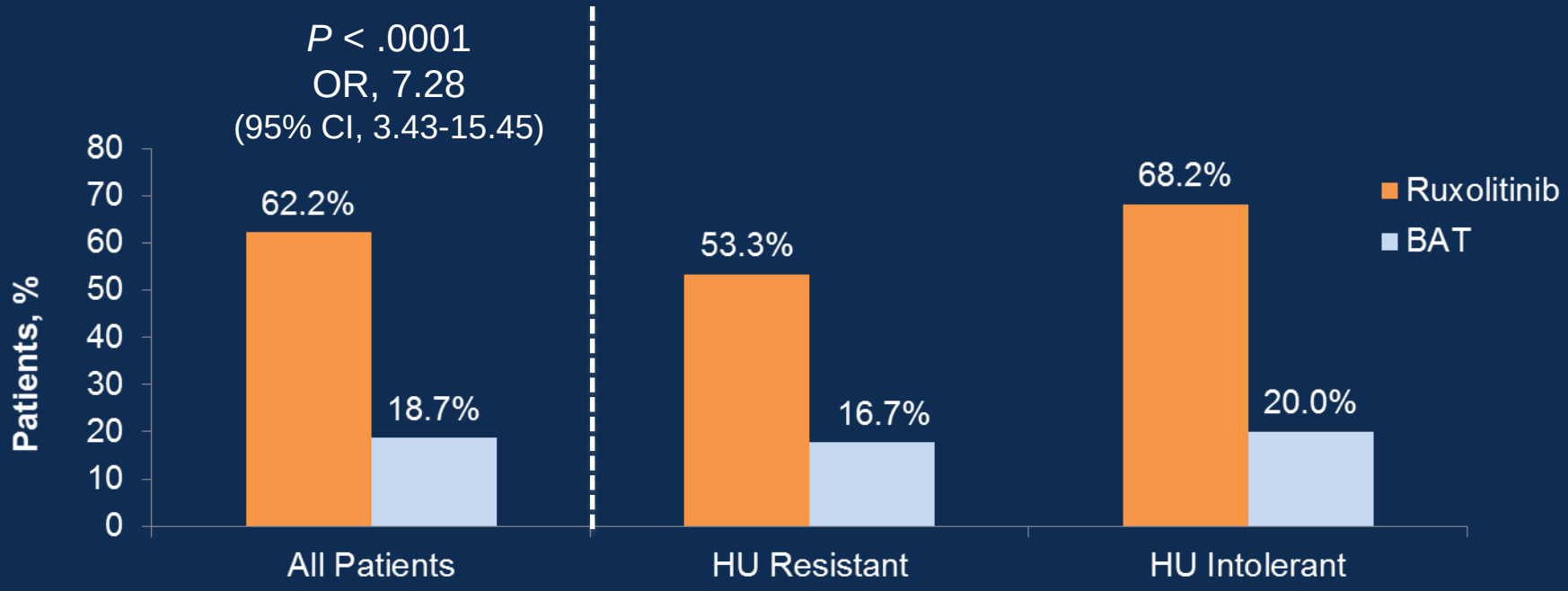
- Ruxolitinib-randomized patients had their doses individually titrated for efficacy and safety (to a maximum of 25 mg bid)
- Investigator-selected BAT as monotherapy included HU (at a tolerated dose if the patient were likely to receive benefit), interferon (IFN)/peg-IFN, anagrelide, pipobroman, immunomodulatory drugs, or observation
- All patients received low-dose aspirin unless medically contraindicated

bid, twice daily; ECOG, Eastern Cooperative Oncology Group; ELN, European LeukemiaNet; PS, performance status.

Efficacy Measures and Endpoints

- The **primary objective** of the study is to compare the efficacy of ruxolitinib with that of BAT as assessed by the proportion of patients achieving Hct control (+ SVR ≥35% by MRI in RESPONSE) at week 28 (week 32 in RESPONSE)
  - Hct control: absence of phlebotomy eligibility from weeks 8 to 28 **(32),** with only 1 post-randomization phlebotomy allowed prior to week 8
- Key **secondary endpoint** (alpha controlled): to compare complete hematologic remission (CHR) at week 28 **(32),**
- **Other secondary endpoints** included changes in patient-reported outcomes (PROs) from baseline to each visit where measured
  - Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)
    - Patients with a baseline score ≥ 20 to be evaluated (reduction of ≥ 10 points from baseline at week 16 and maintained to week 28)
  - Pruritus Symptom Impact Scale (PSIS)
  - Patient Global Impression of Change (PGIC)
  - EuroQol 5 Dimensions 5 Levels (EQ-5D-5L) score
  - Work Productivity and Activity Impairment: Polycythemia Vera (WPAI:PV) V2.0

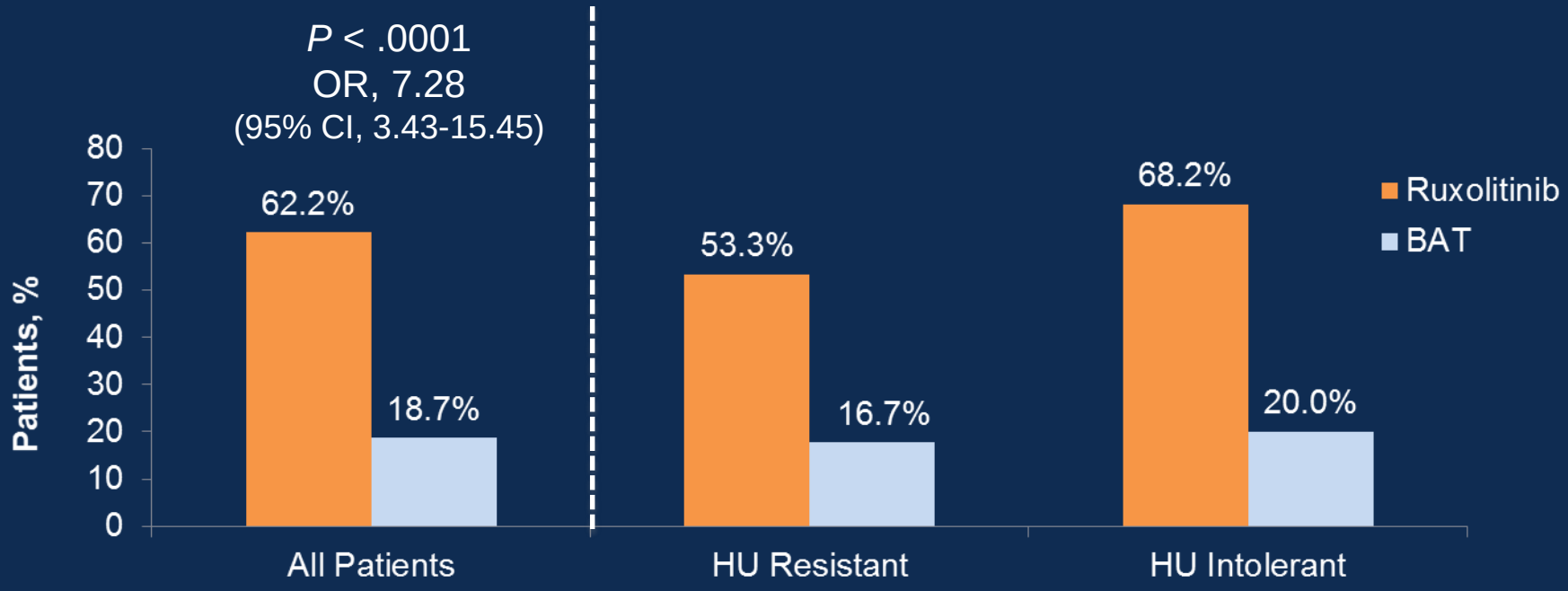
Primary Response: Hct Control at Week 28



- At randomization, BAT monotherapy included HU (49.3% of patients), IFN/peg-IFN (13.3%), pipobroman (6.7%), lenalidomide (1.3%), no medication (28.0%), and other (1.3%)

OR, odds ratio.

Primary Response: Hct Control at Week 28

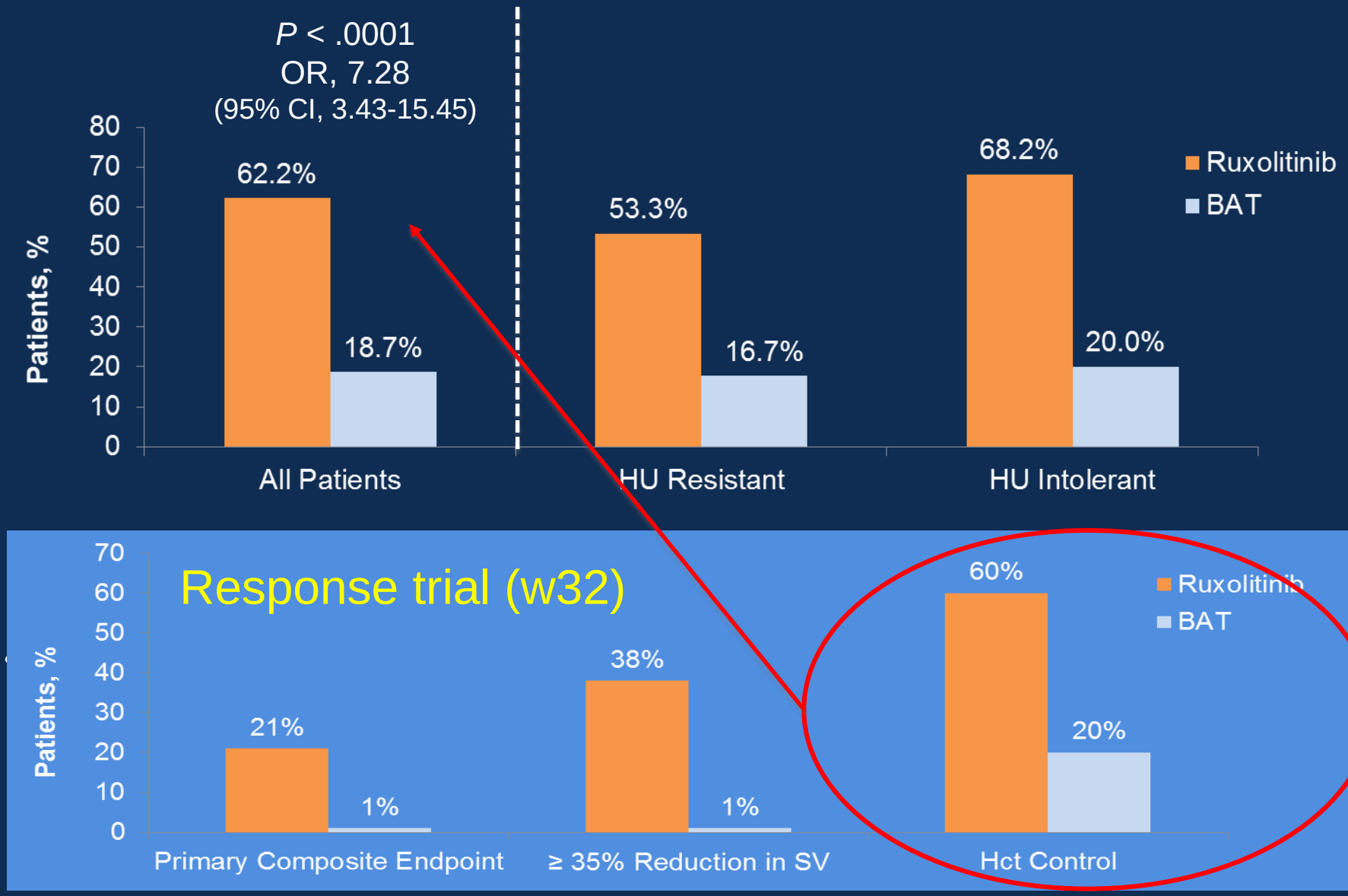


- At randomization, BAT monotherapy included HU (49.3% of patients), IFN/peg-IFN (13.3%), pipobroman (6.7%), lenalidomide (1.3%), no medication (28.0%), and other (1.3%)

- **RESPONSE:** BAT included HU (59%), IFN/pegylated IFN (12%), anagrelide (7%), pipobroman (2%), IMIDs (5%), and observation (15%)

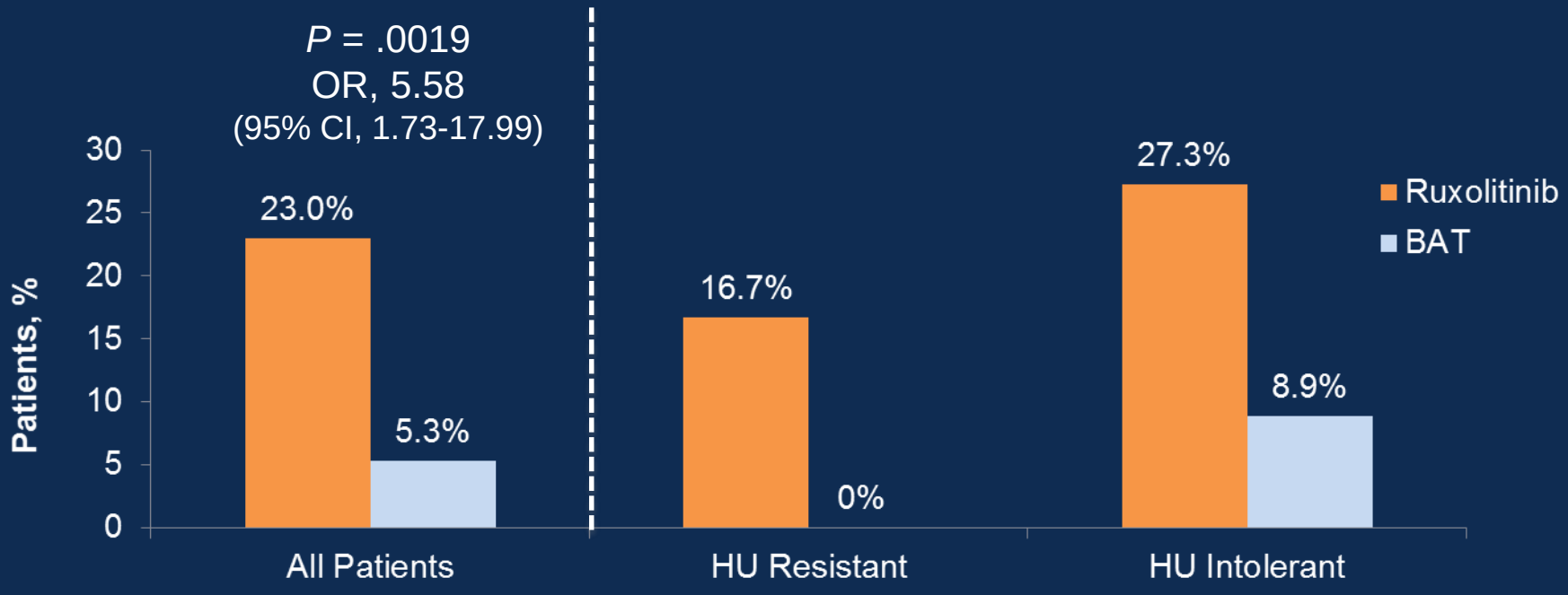
OR, odds ratio.

Primary Response: Hct Control at Week 28



Complete Hematologic Remission at Week 28

CHR defined as Hct control without phlebotomy, PLT count ≤ 400 × 10^9/L, and WBC count ≤ 10 × 10^9/L.



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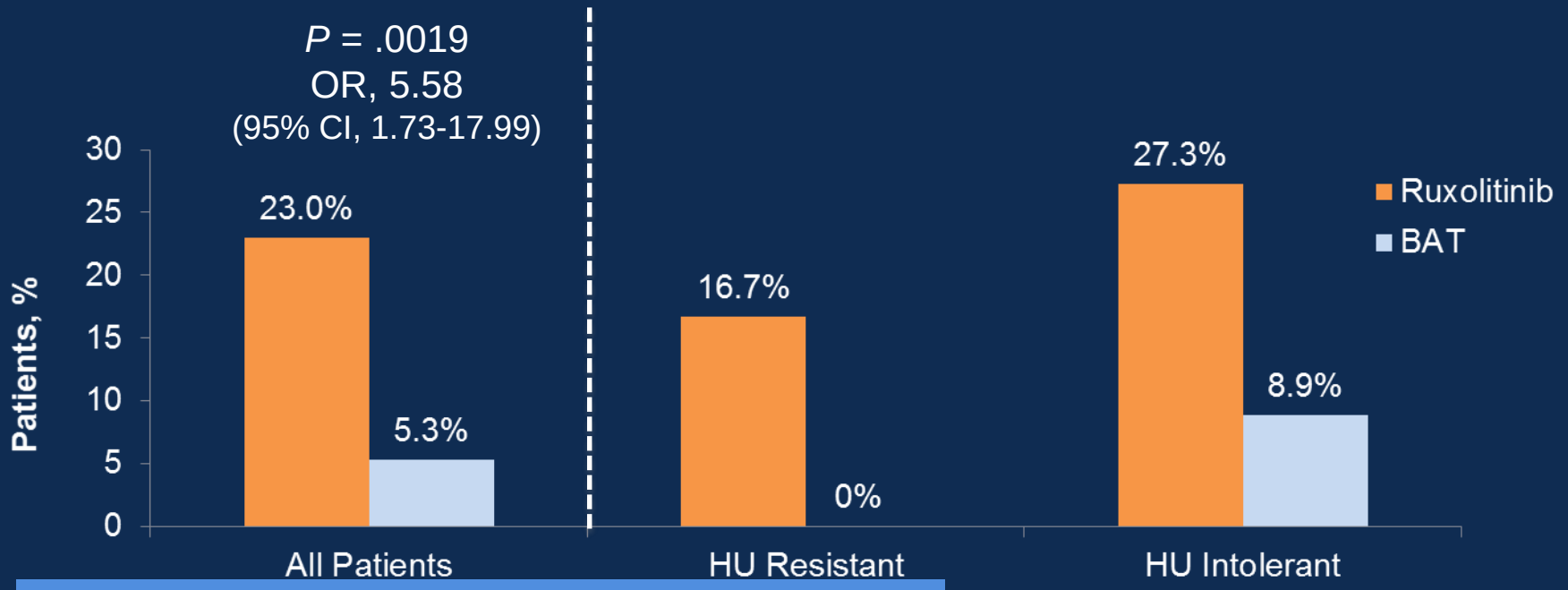
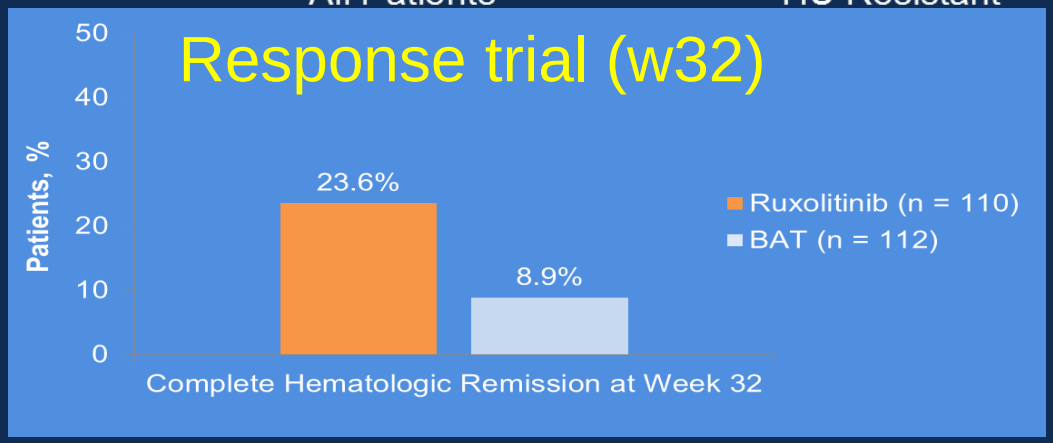
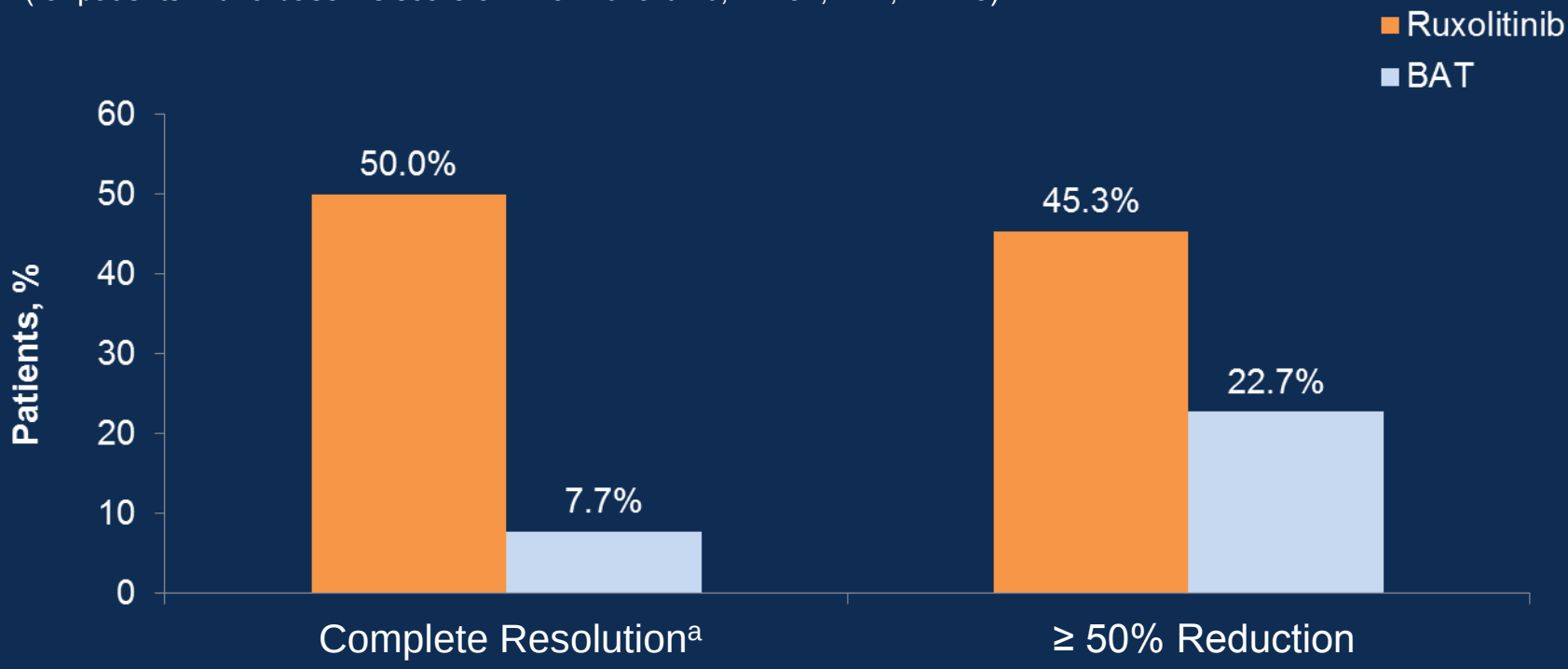




Improvements in Symptoms at Week 28

[a] MPN-SAF TSS score reduction of ≥ 10 points from baseline at week 16 and maintained until week 28 (for patients with a baseline score of ≥ 20. Ruxolitinib, n = 34; BAT, n = 26).



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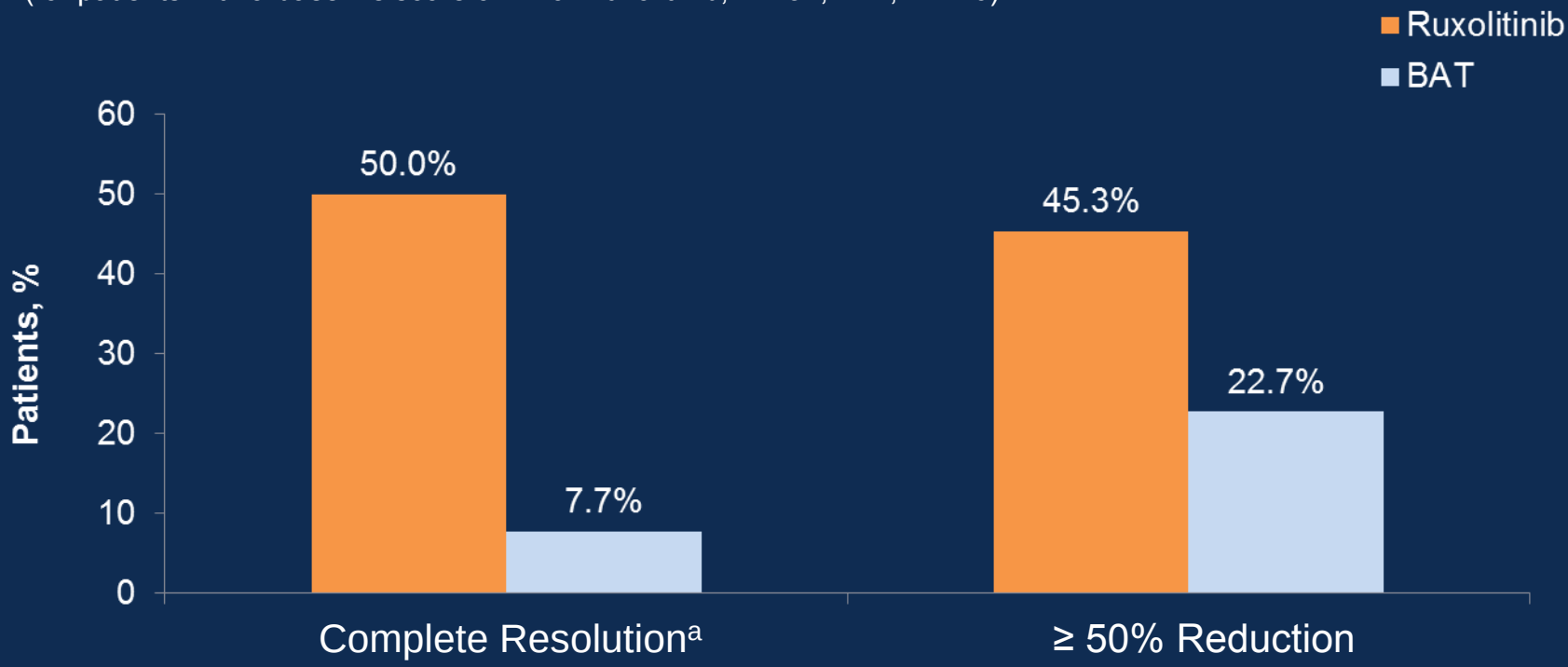
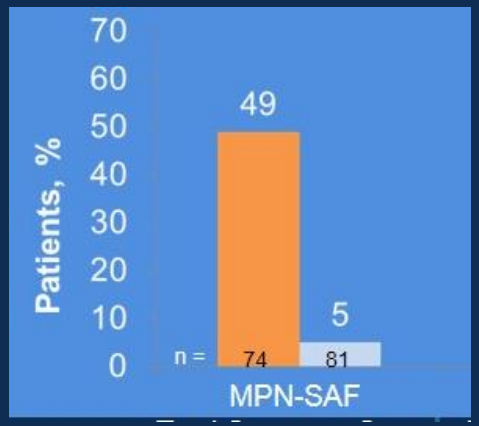


Response trial (w32)



Thromboembolic Events Up to Week 28

Patients, n	Ruxolitinib (n = 74)		BAT (n = 75)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
All thromboembolic events	1	0	2	1
Phlebitis	1	0	0	0
Superficial thrombophlebitis	0	0	1	0
Recurrent syncope due to cerebral microangiopathy	0	0	0	1
Necrosis of the right foot toe	0	0	1	0

- There was 1 thromboembolic event in the ruxolitinib arm and 3 in the BAT arm
- At baseline, 70.3% and 78.7% of patients in the ruxolitinib and BAT arms, respectively, had high-risk PV

Additional Safety Events

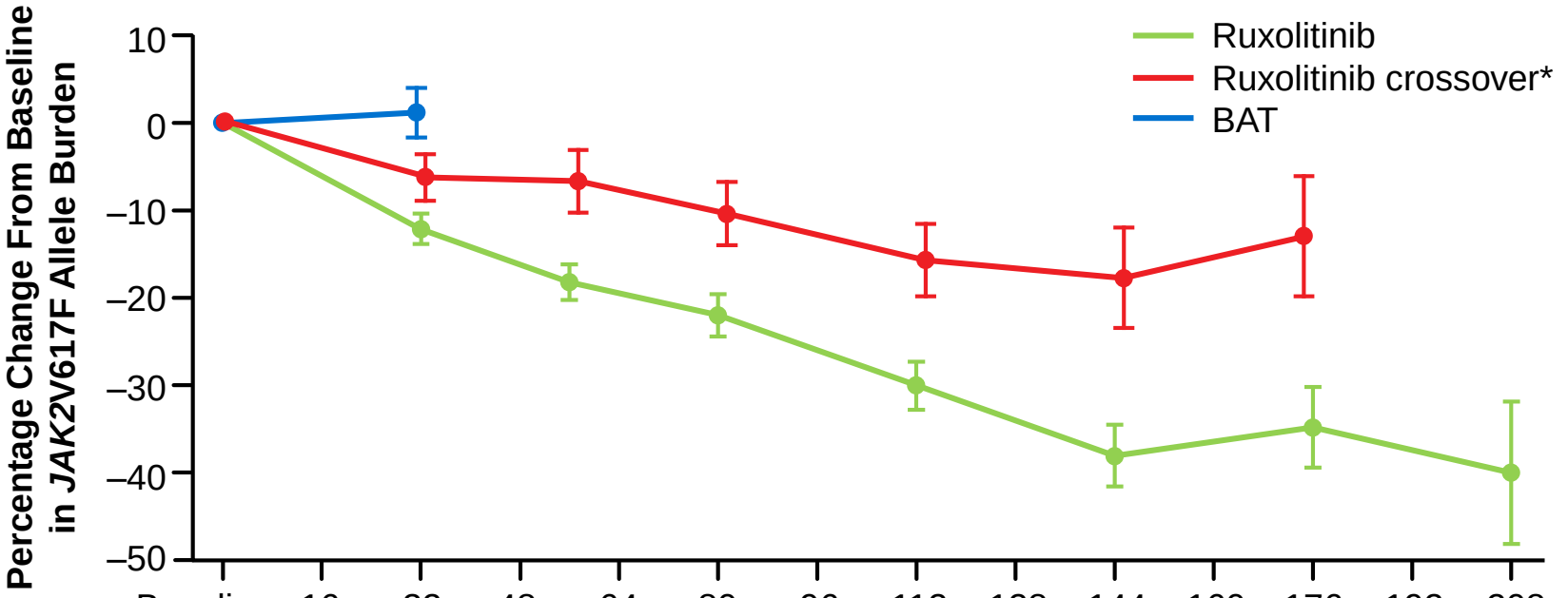
Patients, n (%)	Ruxolitinib (n = 74)	BAT (n = 75)
Infections		
All infections	23 (31.1)	18 (24.0)
Grade 3 or 4	3 (4.1)	1 (1.3)
Herpes zoster Grade 3 or 4	1 (1.4)	0
Nonmelanoma skin cancers		
All NMSCs	1 (1.4)[a]	1 (1.3)[b]

RESPONSE

Patients, n (%)	Ruxolitinib (n = 110)	BAT (n = 111)
Infections		
All infections	46 (41.8)	41 (36.9)
Grade 3 or 4	4 (3.6)	3 (2.7)
Herpes zoster Grade 3 or 4	7 (6.4) 0	0 0
Non-melanoma skin cancers[b]		
All NMSC	4 (3.6)	2 (1.8)
Grade 3 or 4	3 (1.8)	1 (0.9)

Change From Baseline in *JAK2*V617F Allele Burden With Long-Term Treatment

- Patients randomized to ruxolitinib had consistent allele burden reductions from Baseline to Week 208
- Patients who crossed over to ruxolitinib had markedly reduced allele burden over time



Patients, n†								
Ruxolitinib	102	92	89	84	83	74	48	20
Ruxolitinib crossover	94	89	72	79	71	41	21	
BAT	85	80						

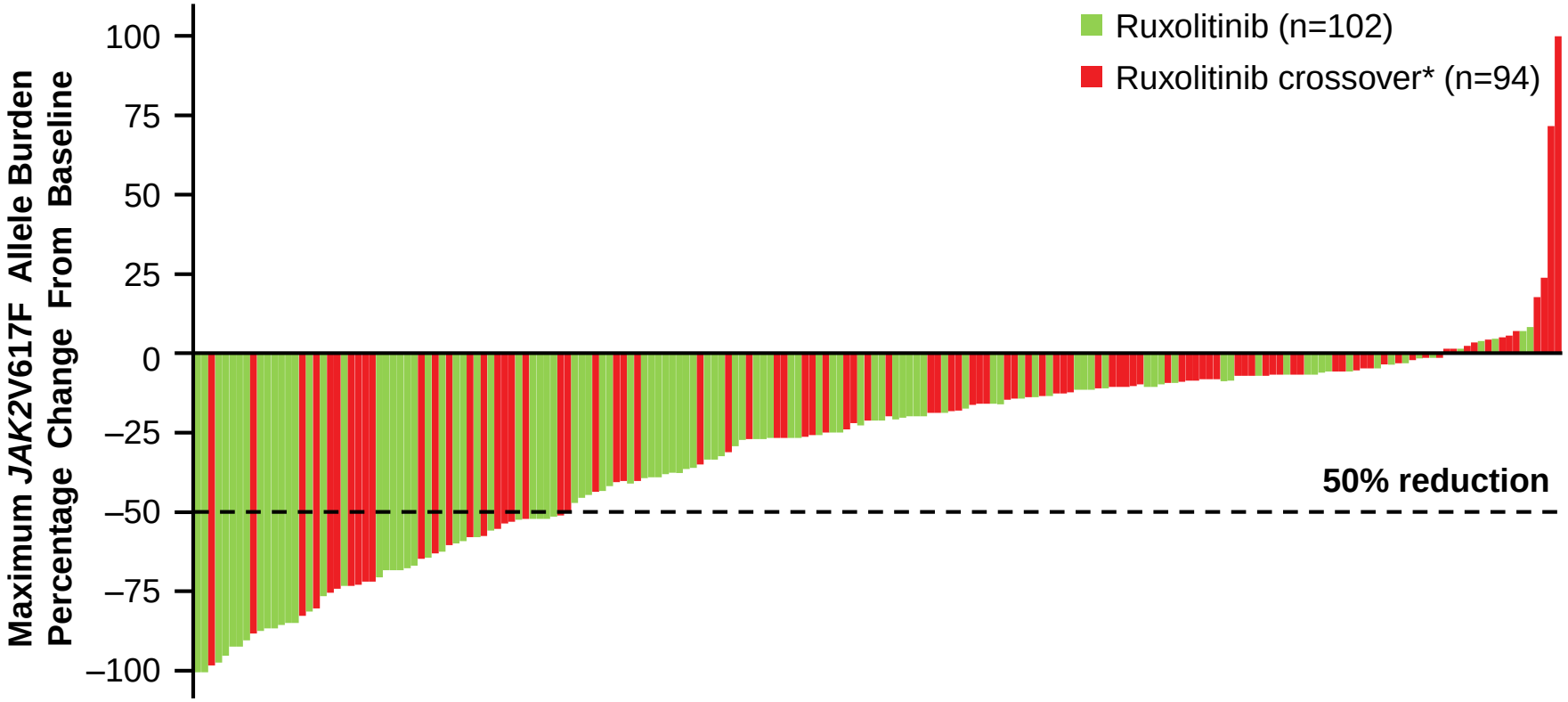
BAT, best available therapy

* Baseline in the ruxolitinib crossover arm was the final assessment before crossing over from BAT to ruxolitinib

† If there were <5 data points at a visit within a treatment group, data were excluded from the figure

Maximum Percentage Change From Baseline in *JAK2*V617F Allele Burden

- The average maximal percentage reductions in allele burden (median time to maximal reduction) in ruxolitinib randomized and ruxolitinib crossover arms were –35.9% (25.9 mo) and –21.2% (18.2 mo), respectively



BAT, best available therapy
* Baseline in the ruxolitinib crossover arm was the final assessment before crossing over from BAT to ruxolitinib

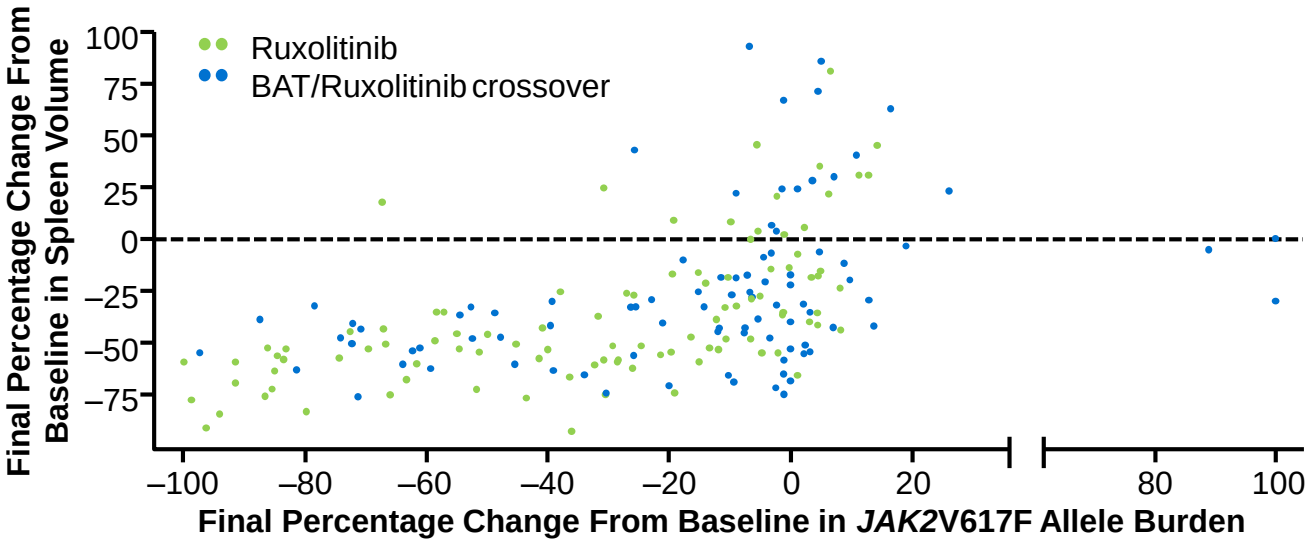
*JAK2*V617F Allele Burden Relation to Clinical Correlates

- No correlation was observed between allele burden changes and changes in hematocrit, white blood cell count, or platelet levels

Final Percentage Change From Baseline in *JAK2*V617F Allele Burden and Spleen Volume*

*JAK2*V617F Allele Burden	Ruxolitinib ≥20% (n=52)	Ruxolitinib <20% (n=47)	Ruxolitinib Crossover ≥20% (n=32)	Ruxolitinib Crossover <20% (n=60)
Spleen Volume, n (%)				
≥35%	45 (86.5)	18 (38.3)	25 (78.1)	20 (33.3)
<35%	7 (13.5)	29 (61.7)	7 (21.9)	40 (66.7)

- Spleen volume reductions tended to be larger for patients who had a *JAK2*V617F allele burden reduction of ≥20% from Baseline compared with patients who had a reduction of <20%



* Only patients with Baseline and post-Baseline values for both spleen volume and allele burden were included
BAT, best available therapy

Topics

- Gravidanza nella PV

  - Outcome of 121 pregnancies in 49 patients with polycythemia vera (PV). M. Griesshammer et al.

Outcome of 121 pregnancies in 49 patients with polycythemia vera

- European Leukemia Net project starting 2006
- 121 PV pregnancies in 49 women with PV in hematological centers in France, Italy, Serbia, Romania, Switzerland and Germany
- Retrospective and prospective REGISTER of pregnancies in MPN

- **Group A:** pregnancies before diagnosis of PV (n=38)
- **Group B:** represents all pregnancies after diagnosis PV (n=83)

Outcome of 121 pregnancies in 49 patients with PV
- Live birth rate vs. miscarriages -

- **113 pregnancies** -> 75 live births (66,4%)
  -> 38 miscarriages (33,6%)

- **6 twin pregnancies** -> 5 live births (83%)
  -> 1 stillbirth in week 22 (17%)

- **Group A (n=38)** -> 17 live births (44,7%*)
  -> 21 miscarriages (55,3%)

***Chi-square p< 0.001**

- **Group B (n=75)** -> 58 live births (77,3%*)
  -> 17 miscarriages (22,4%)

Group A: pregnancies before diagnosis of PV (n=38)
Group B: represents all pregnancies after diagnosis PV (n=75 evaluable)

Outcome of 121 pregnancies in 49 patients with PV

- Fetal outcome -

	Overall (n=113)	Group A (n=38)	Group B (n=75)
Full term normal delivery (FTND)	50,4 %	26,3 %	62,6 %
Spontaneous abortion (SA)	22 %	26,3 %	20 %
Stillbirth (SB)	8,8 %	18,4 %	4 %
Late fetal loss (LFL)	3,5 %	10,5 %	0 %
Preterm delivery (PTD)	12,9 %	18,4 %	9,3 %
Growth retardation	9,7 %	13,1 %	8 %

SA: miscarriage before 20th week
SB: miscarriage from 20th to 28 week
LFL: 28 completed weeks of gesation and later

Group A: pregnancies before diagnosis of PV (n=38)
Group B: represents all pregnancies after diagnosis PV (n=75 evaluable)

Outcome of 121 pregnancies in 49 patients with PV

- Maternal complications -

	Group A (n=38)	Group B (n=75)
Thrombosis*	1 (2,6%)	2 (2,7%)
Bleeding	1 (2,6%)	11 (14,6%)
Major bleeding	-	4 (5,3%)
Minor bleeding	1 (2,6%)	7 (9,3%)
Pre-eclampsia	3 (7,9%)	-
Hypertension	0	2 (2,7%)
Placental insufficiency	1 (2,6%)	-
Ectopic pregnancy	-	1 (1,3%)

- *Group A : n= 1, one post partum pulmonary embolism with cardiogenic shock
- *Group B: n = 2, one post partum Budd Chiari and another 3. trimester Budd Chiari

Group A: pregnancies before diagnosis of PV (n=38)
Group B: represents all pregnancies after diagnosis PV (n=75 evaluable)

Outcome of 121 pregnancies in 49 patients with PV - Conclusions -

- Success rate was significantly better (49% versus 77%) for patients in whom the diagnosis of PV was known and appropriate management was performed
- Thrombosis rate ~ 2,6 %
- Bleeding rate ~ 15 % with a major bleeding ~ 5 %
- Aspirin + LMWH ↑ live birth rate, PEG INF is a good option in high risk PV pregnancy

Topics

- Efficacia/sicurezza di ruxolitinib - "long-term" e "expanded access " – nella MF

- Long-Term Outcomes of Ruxolitinib Therapy in Patients With Myelofibrosis: 5-Year Final Efficacy and Safety Analysis From COMFORT-I. *Verstovsek et al.*
- SAFETY AND EFFICACY OF RUXOLITINIB IN PATIENTS WITH DIPSS INTERMEDIATE-1–RISK MYELOFIBROSIS (MF) FROM JUMP: AN OPEN-LABEL, MULTICENTER, SINGLE-ARM, EXPANDED-ACCESS STUDY. *Passamonti F et al*. (poster)

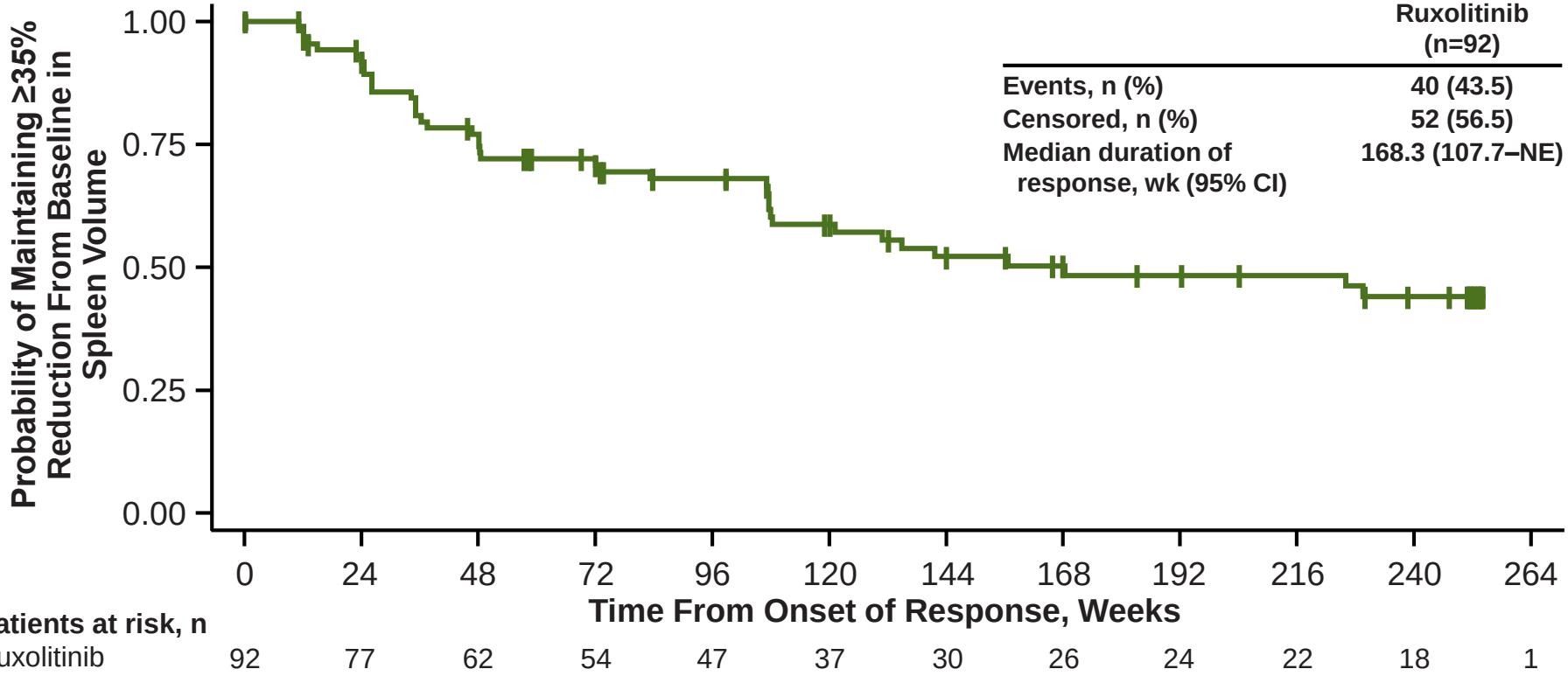
Patient Disposition and Treatment Exposure

	Ruxolitinib Randomized (n=155)	Placebo Randomized (n=151*)	Ruxolitinib Crossover (n=111)
Overall Exposure, median (range), weeks	149 (4-296)	37 (4-65)	111 (1-256)
Patient Disposition, n (%)			
Patients on treatment at data cutoff	43 (27.7)	0	28 (25.2)
Discontinued before the 5-year data cutoff	112 (72.3)	40 (26.5)	83 (74.8)
Adverse event	47 (30.3)	16 (10.6)	33 (29.7)
Disease progression	23 (14.8)	13 (8.6)	22 (19.8)
Patient consent withdrawn	14 (9.0)	7 (4.6)	14 (12.6)
Noncompliance or protocol deviation	3 (1.9)	0	2 (1.8)
Other†	25 (16.1)	4 (2.6)	12 (10.8)

*3 additional patients were randomized to placebo but were not evaluable for safety and were excluded from the percentage of patients who discontinued
†Including, but not limited to, receiving a different therapy, transitioning to commercial ruxolitinib, and loss of response

Duration of ≥35% Reduction From Baseline in Spleen Volume

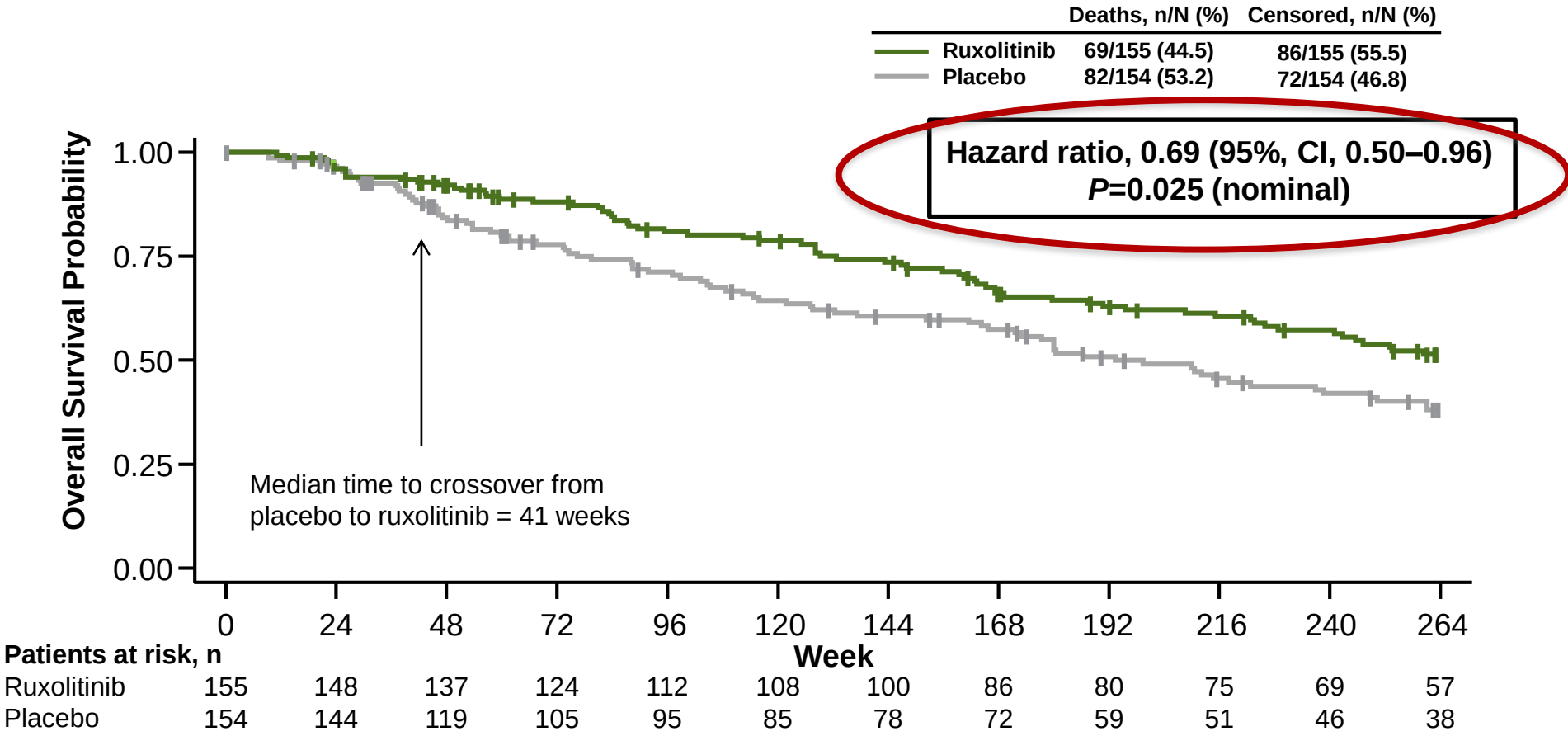
- 59% (92/155) of patients originally randomized to ruxolitinib had a ≥35% spleen volume response at any time on study*
- The median duration of response was 168.3 weeks



*The median time to loss of spleen response was defined as the interval from the first spleen response to the first spleen volume that was a <35% reduction from Baseline and a >25% increase from the nadir

Overall Survival: 5-Year Analysis (ITT)

- Median OS was not reached for patients randomized to ruxolitinib (median follow-up 268 weeks) and was 200 weeks for patients in the placebo arm (median follow-up 269 weeks)



OS, overall survival

Hematologic Abnormalities Based on Laboratory Values

	Ruxolitinib Randomized (n=155)		Placebo (n=151)		Ruxolitinib Crossover (n=111)	
Patient-years of study drug exposure	460.4		98.9		254.9	
Hematologic abnormality,* %	All Grades	Grades 3 or 4	All Grades	Grades 3 or 4	All Grades	Grades 3 or 4
Anemia	98.7	54.2	88.1	20.5	95.5	54.1
Thrombocytopenia	83.9	22.6	33.1	2.6	90.1	28.8
Neutropenia	26.5	14.2	4.6	3.3	18.9	5.4

*The data shown are for events of the worst grade during the study, regardless of whether this grade was a change from the Baseline grade

- Percentages consistent with those observed at the primary analysis

Most Common Treatment-Emergent AEs Leading to Death

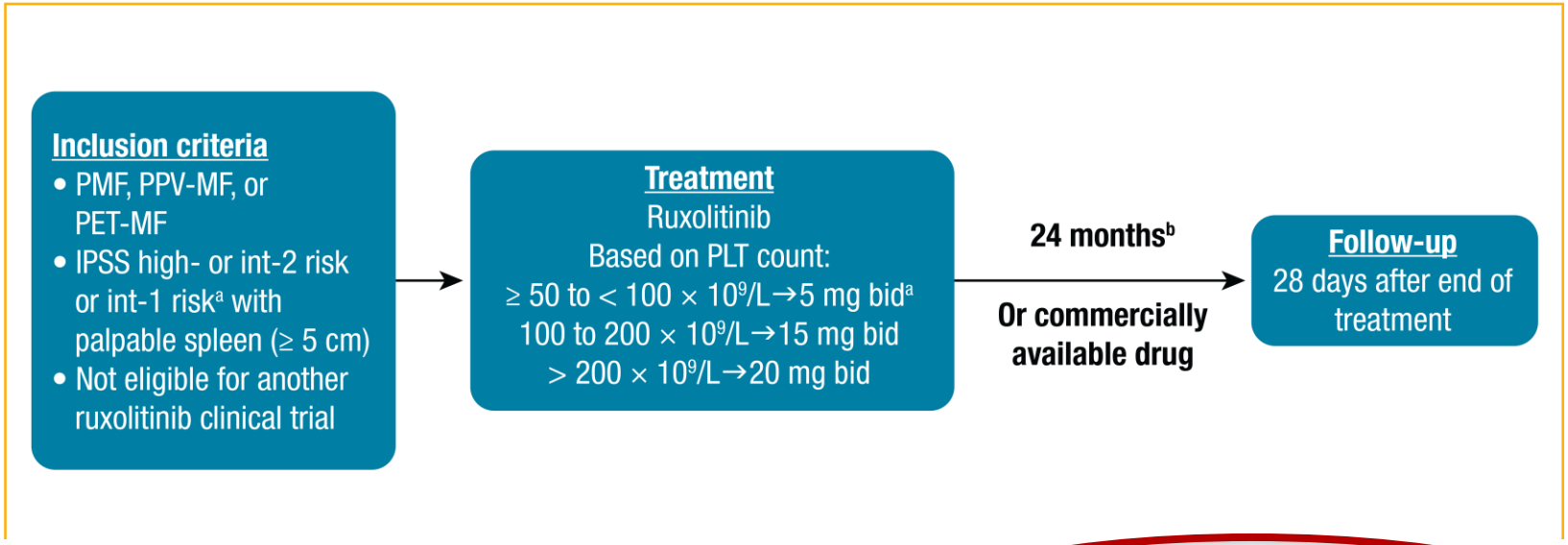
	Ruxolitinib Randomized (n=155)	Placebo (n=151)	Ruxolitinib Crossover (n=111)
Patient-years of study drug exposure	460.4	98.9	254.9
Adverse event,* n (%)			
Sepsis/septic shock	6 (3.9)	1 (0.7)	4 (3.6)
Disease progression	3 (1.9)	3 (2.0)	4 (3.6)
Pneumonia/pneumonia aspiration	3 (1.9)	1 (0.7)	3 (2.7)
AML	2 (1.3)	0	3 (2.7)
Renal failure/acute renal failure	2 (1.3)	0	1 (0.9)
Cardiac failure/congestive cardiac failure	0	0	3 (2.7)
MF	0	1 (0.7)	2 (1.8)

*Adverse events leading to death in ≥2 patients treated with ruxolitinib

AML, acute myeloid leukemia; MF, myelofibrosis

DIPSS Intermediate-1 Patients in JUMP Study

Figure 1. Study Design



- This analysis includes results for 700 patients DIPSS Int-1 with ≥ 1 year of follow-up from baseline to data cutoff (median follow-up, 65 weeks)

Safety

The most common hematologic AEs were

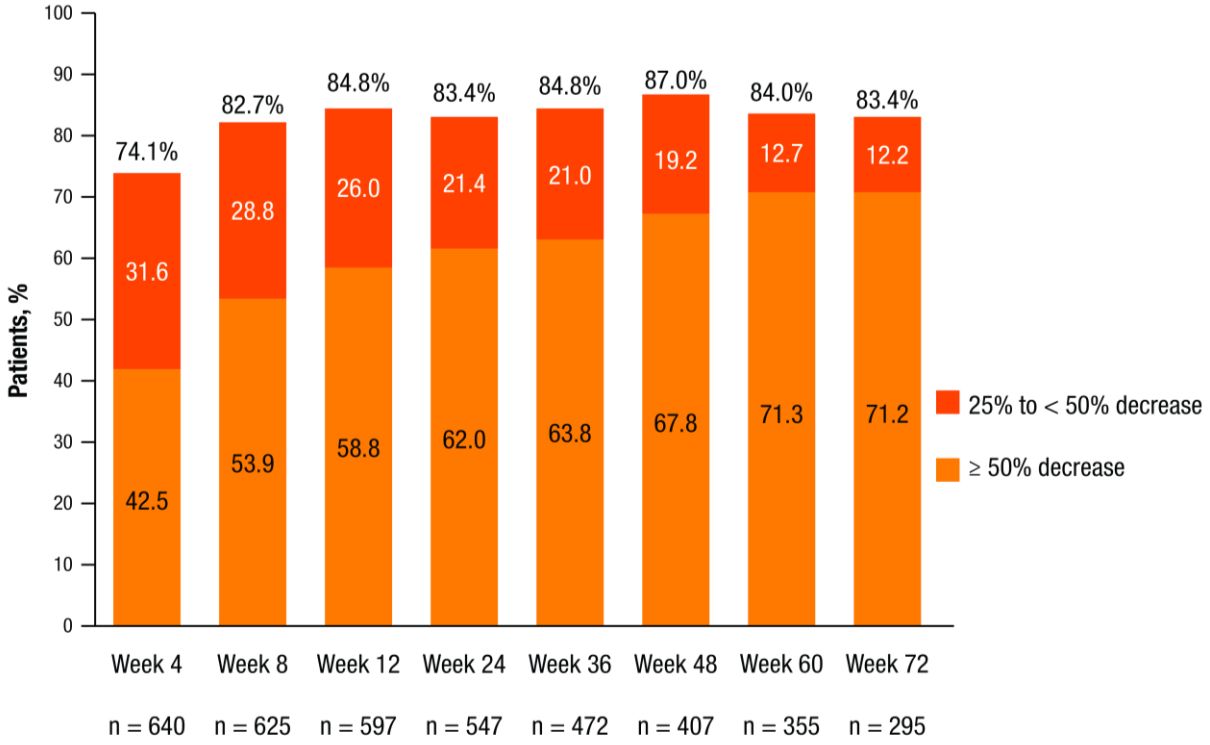
- anemia (55.1%; grade 3/4, 22.0%),
- thrombocytopenia (39.7%; grade 3/4, 10.3%),
- leukopenia (5.4%; grade 3/4, 2.4%)

The most common nonhematologic AEs (in ≥ 5% of patients) were primarily grade 1/2 infections (≥ 5%) including

- urinary tract infection (6.4%),
- herpes zoster (6.0%)
- nasopharyngitis (5.4%)
- 1 report of hepatitis B reactivation (grade 3/4)

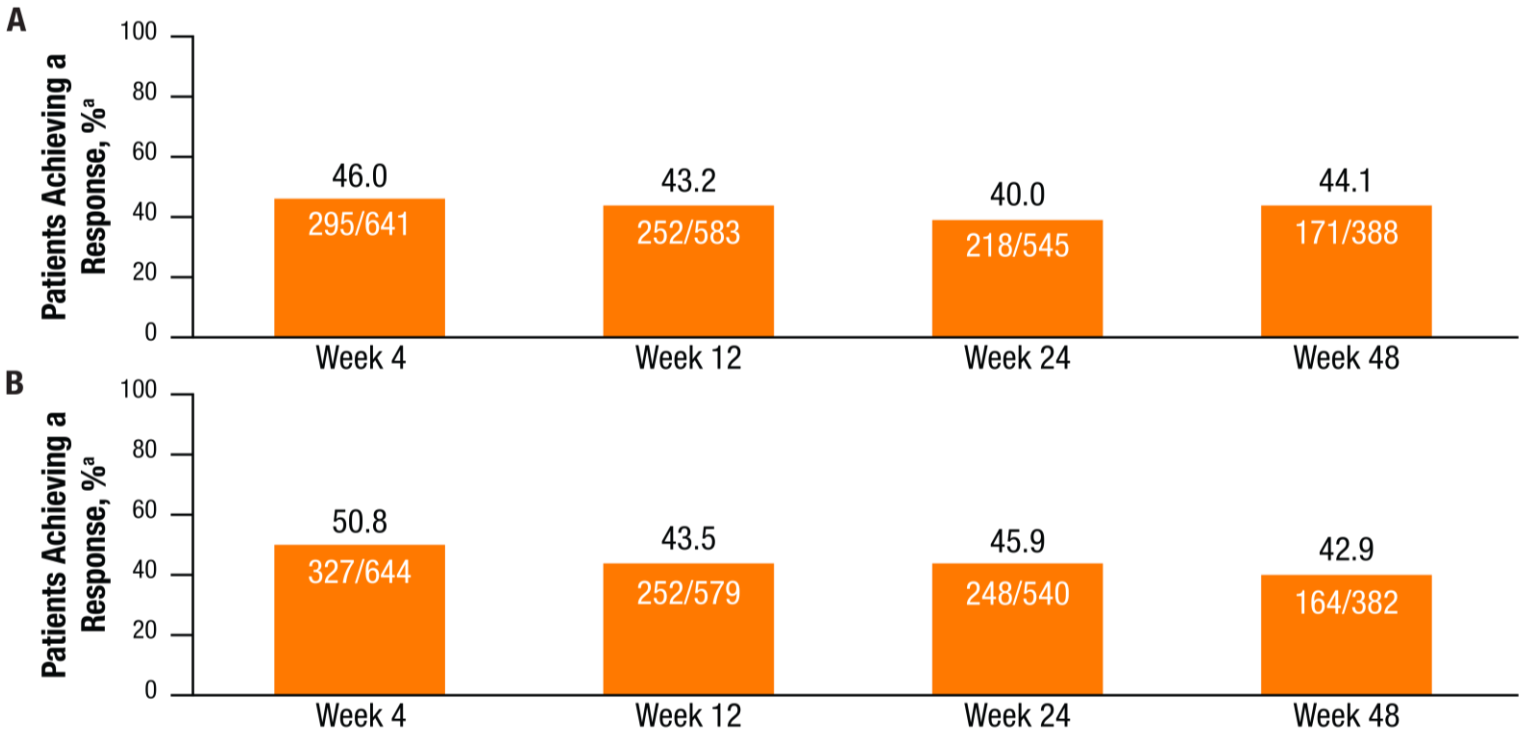
- **Serious AEs** were reported for 26.6% of patients
  - pneumonia (3.7%)
  - anemia (2.2%)
  - cardiac failure (1.6%)
  - sepsis (1.1%)

Efficacy: Spleen Volume Reduction



- 78.5% of the patients experienced a ≥ 50% reduction in spleen length from baseline at any time by week 72;
  - 29.4% of patients (192/652) had a spleen that became nonpalpable
- The median time to first ≥ 50% reduction in spleen length was 4.7 weeks (range, 0.1-75.0 weeks)
- The Kaplan-Meier estimated probability of maintaining a ≥ 50% reduction from baseline in palpable spleen length for 48 weeks was 0.92 (95% CI, 0.89-0.94)

Proportion of Patients Achieving a Response (A) in the FACT-Lym TS and (B) on the FACIT-Fatigue Scale



Response was defined as the upper limit of the minimally important difference (FACT-Lym TS, 11.2 points[7]; FACIT-Fatigue scale, 3 points[8]).

Neoplasie Mieloproliferative Croniche