Achieving Balance Between Efficacy and Toxicity in the Management of Polycythemia Vera (PV)

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Topics for Consideration

- Strengths and weaknesses of approved and investigational agents
- Quality of life as a therapeutic target in PV
- Can we control disease without sacrificing quality of life?

Who to Treat?

Avoid	Cause
Thrombosis	Myelosuppression
Hemorrhage	MDS/AML
Anxiety	Anxiety
?Impaired QoL	Side effects

QoL, quality of life; MDS, myelodysplastic syndrome; AML, acute myeloid leukemia

Hydroxyurea (HU) vs Interferon (IFN)

- Comparative trials not yet completed

.....Please help us to complete them!

Hydroxyurea = hydroxycarbamide

National Institutes of Health, Available at: http://clinicaltrials.gov/ct2/results?term=NCT01387763. Accessed: October 7, 2014.

Properties of HU, vs IFN-α

	HU	IFN-α
Drug class	Antimetabolite	Biologic response
Mechanism	Impairs DNA repair	Myelosuppressive / Immune modification
Onset	3-5 days	3-26 weeks
Side effects in >10%	Neutropenia, anemia, mouth ulcers, pigmentation	Flu-like symptoms, alopecia, weight loss
SE in <10%	Leg ulcers, gastrointestinal toxicity, ? mutagenic	Confusion, arthritis, autoimmune toxicity, depression, ? Safe in pregnancy

HU, hydroxyurea; SE, serious events

Is Hydroxyurea Leukemogenic?

Current data suggests:

• Intrinsic risk	? <1%
• Busulfan	5%-10%
• P^{32}	10%-15%
• Hydroxyurea	?? <1%-5% (17p)
• Hydroxyurea + busulfan	14%-33%
• Interferon-α	very low

Sterkers Y, et al. *Blood.* 1998;91(2):616-622. Finazzi G, et al. *Blood.* 2005;105(7):2664-2670.

Long-Term Follow-Up of FPSG Study

- Trial conducted: 1980-1996, 292 PV patients, <65 years
- 1997: No difference in overall survival, thrombosis risk or AML / MDS / MF evolution
- Updated 2011 median follow-up: 16.3 years, 94 HU only, 130 pipobroman only
- 95 deaths: 51 AML / MDS, 19 vascular, 11 cancer

Results	HU	*P* value	Pipobroman
Median survival	20.3 years	.008	15.4 years
Cumulative incidence AML / MDS at 10, 15, and 20 years			
Intention-to-treat (ITT)	6.6; 16.5; 24%	.004	13; 34; 52%
Treatment received	7; 14; 22%	.008	12; 37; 56%
Cumulative incidence MF at 10,15, and 20 years			
ITT	12.6; 19; 27%	NS	7.8; 16; 27%
Treatment received	15; 24; 32%	.02	5; 10; 21%

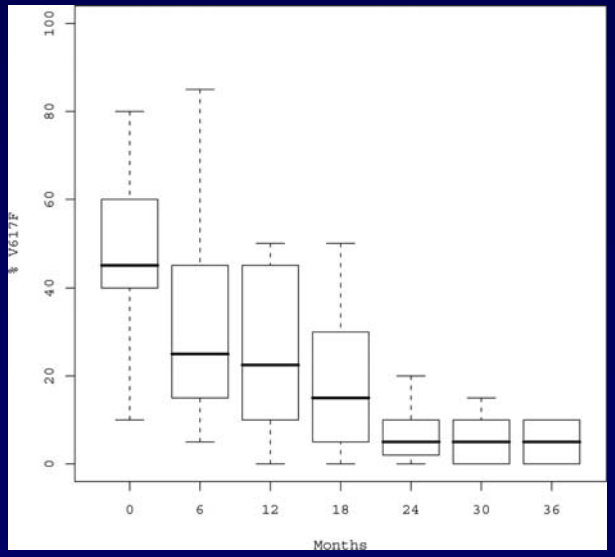
Powerful data from Swedish cancer registry: No increased risk

FPSG, French Polycythemia Study Group; MF, myelofibrosis

Kiladjian JJ, et al. *J Clin Oncol.* 2011;29(29): 3907-3913; Björkholm M, et al. *J Clin Oncol.* 2011;29(17): 2410-2415.

Pegylated Interferon-α-2a in PV

- 40 PV patients (median age 49 years, untreated or <2 years)
- Complete hematological response (CHR) at 12 months: 94.6%
- **Adverse events (AE) in 89% (grade 1, 2) decrease over time**
- **Discontinuation due to toxicity: 24%**
- **29% of patients stopping pegylated interferon maintained CHR**



***JAK2* (V617F) allele burden response**

- **Complete response (CR): 7/29 (24%)**
- **Partial response (PR): 14/29 (48%)**
- **Targets *JAK2* (V617F) clones without affecting TET2 mutant cells**

Kiladjian JJ, et al. *Blood*. 2008;112(8):3065-3072. Turlure P, et al. *Blood* 2011;118(21): Abstract 280.

HDAC Data

HDAC, histone deacetylases

Givinostat in PV and ET

29 patients with PV / ET / MF *JAK2* (V617F) positive

- **Reason for treatment discontinuation:**
  Disease progression (n = 6), thrombocytopenia (n = 1), psychiatric symptoms (n = 1)

- **13 PV / ET: 1 CR, 6 PR, 4 NR, 2 off study**
- **Trend to reduction of *JAK2* (V617F) mutant alleles**

ET, essential thrombocytosis

Rambaldi A, et al. *Br J Haematol.* 2010;150(4):446-455.

Vorinostat in PV and ET

63 patients: 21 ET, 42 PV

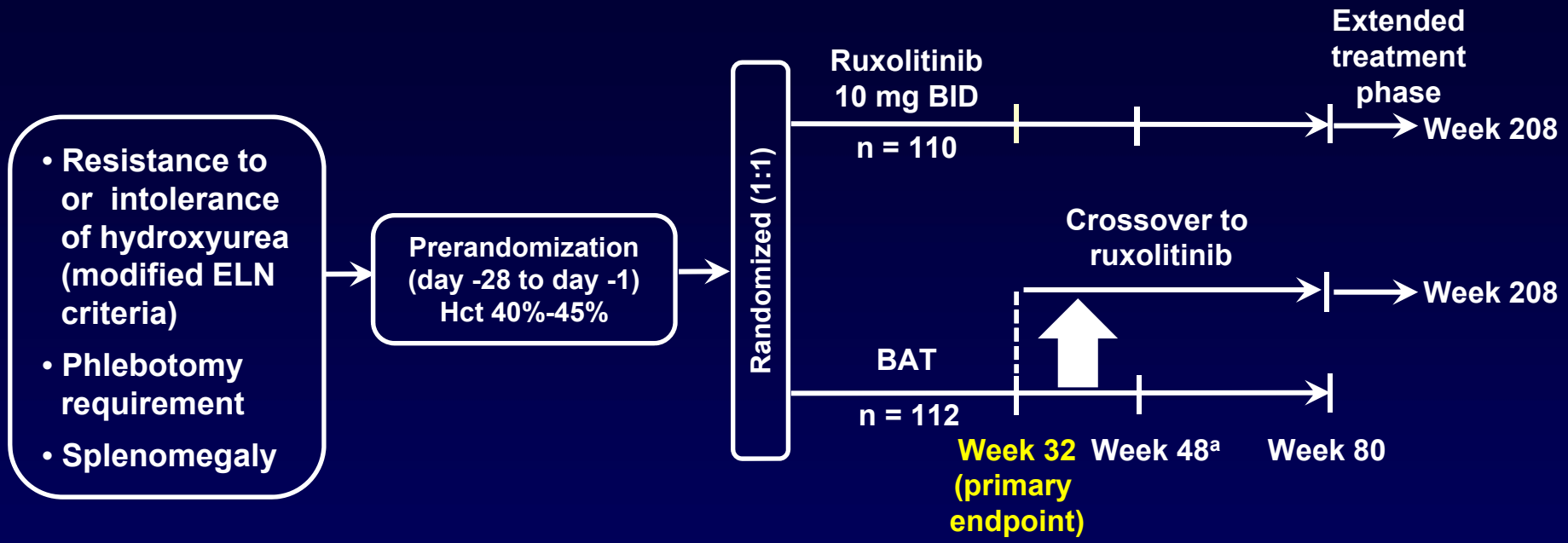
- 81% responded: PR (N = 20), CR (N = 5), by ELN criteria
- Splenomegaly decrease from 48% to 24% of patients
- Significant reduction of *JAK2* allele burden

- AE: Fatigue, GI, hair loss (70%), renal toxicity (17%)
- 40 patients (63 %) discontinued due to the following reasons:
  - Adverse events (65%)
  - Unknown (17.5%)
  - Withdrawal of consent (7.5%)
  - No response (2.5%)
  - Progression to acute leukemia (7.5%)

Andersen CL, et al. *Blood* 2012;120(21): Abstract 803.

JAK Inhibitor
Ruxolitinib

RESPONSE Study Design



- Ruxolitinib-randomized patients were individually titrated for efficacy and safety (to a maximum of 25 mg BID)
- 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

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

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Nonhematologic Adverse Events Up to Week 32 (Regardless of Causality)

	Ruxolitinib (n = 110)		Best available therapy (BAT) (n = 111)	
Patients, %	All grades	Grade 3/4	All grades	Grade 3/4
Headache	16.4	0.9	18.9	0.9
Diarrhea	14.5	0	7.2	0.9
Fatigue	14.5	0	15.3	2.7
Pruritus	13.6	0.9	22.5	3.6
Dizziness	11.8	0	9.9	0
Muscle spasms	11.8	0.9	4.5	0
Dyspnea	10.0	2.7	1.8	0
Abdominal pain	9.1	0.9	11.7	0
Asthenia	7.3	1.8	10.8	0

- **When adjusted for exposure (per 100 patient/years), the rates of AEs and grade 3/4 AEs of the entire course of treatment were lower in patients randomized to ruxolitinib compared with BAT (64.7 vs 145.6 and 28.8 vs 44.0)**
- **The exposure-adjusted rates of SAEs per 100 patient-years were comparable in both arms (15.3 vs 13.7)**

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Other Adverse Events of Interest Up to Week 32

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	7 (6.4)	0
Grade 3 or 4	0	0
Progression to MF and AML		
MF	2 (1.8)	1 (0.9)
AML	1 (0.9)	0
Nonmelanoma skin cancers (NMSC)		
All NMSC	4 (3.6)	2 (1.8)
Grade 3 or 4	3 (1.8)	1 (0.9)

Verstovsek S, et al. *J Clin Oncol.* 2014;32(5s): Abstract 7026.

NMSC in RESPONSE: The Facts…

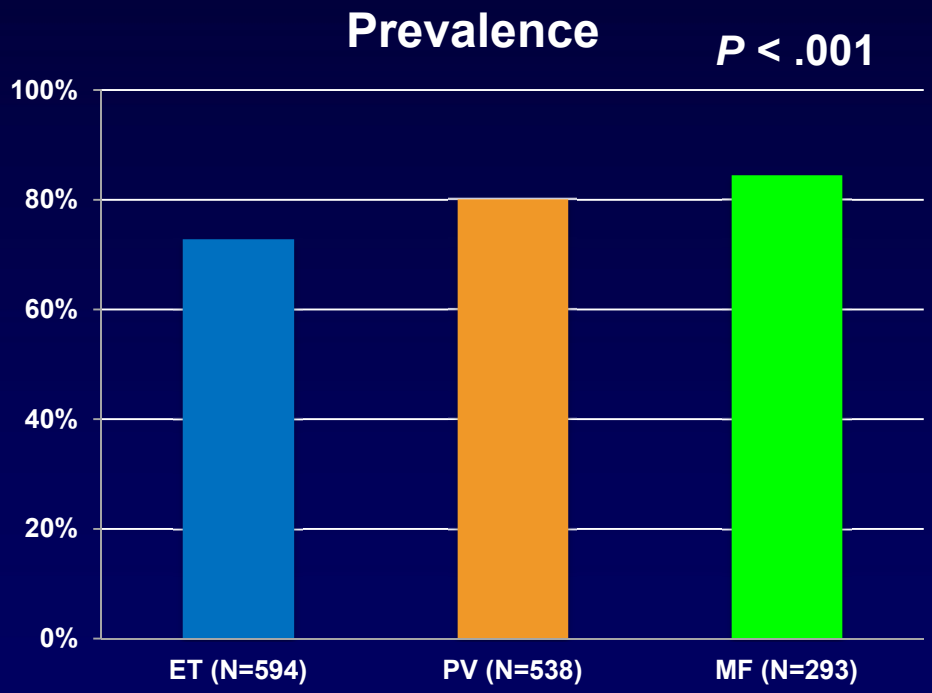
- Higher rates reported in the ruxolitinib arm (4.7 vs 2.7 patients / 100-PY); no patients discontinued treatment for NMSC
- Higher proportion of patients in the ruxolitinib arm had a prior history of NMSC / precancerous skin condition vs BAT arm (10.9% vs 6.3%)
- Patients randomized to ruxolitinib had a longer prior exposure to HU (162.9 vs 145.6 weeks)

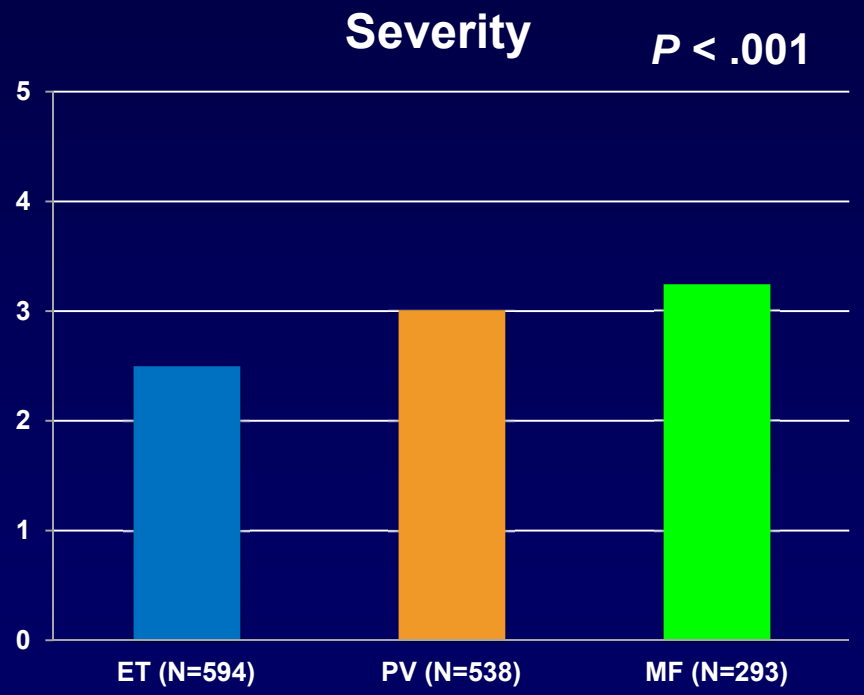
Verstovsek S, et al. *J Clin Oncol.* 2014;32(5s): Abstract 7026.

Quality of Life as a Therapeutic Target

What Do We Know?

Decreased QoL in 1433 MPN Patients





Emanuel RM, et. al. *J Clin Oncol.* 2012;30(33):4098-4103.

Quality of Life in PV

- **Symptoms and complications have been associated with declines in physical, functional, and overall health status using a variety of QoL assessment tools[1,2,3]**
  - **MPN-SAF, EORTC QLQ-C30, BFI, FACT-An, Godin LAS**

MPN-SAF[a]		EORTC QLQ-C30 Scores (mean ± SD)[b]		
Symptom	Mean Score (95% CI)		PV (n = 145)	General Population (N = 7,802)
Fatigue (BFI score)	3.0 (2.6–3.4)	***Functional scales***		
Early satiety	2.3 (1.9–2.8)	Physical functioning	83.3 ± 17.7	89.8 ± 16.2
Abdominal pain	1.2 (0.8–1.5)	Role functioning	85.2 ± 22.7	84.7 ± 25.4
Abdominal discomfort	1.6 (1.2–2.0)	Emotional functioning	78.2 ± 20.8	76.3 ± 22.8
Inactivity	1.9 (1.5–2.4)	Cognitive functioning	83.0 ± 18.8	86.1 ± 20.0
Headache	1.4 (1.1–1.8)	Social functioning	88.3 ± 20.1	87.5 ± 22.9
Concentration problems	2.3 (1.8–2.7)	***Symptom Scales***		
Dizziness	1.8 (1.4–2.2)	Fatigue	29.3 ± 21.9	24.1 ± 24.0
Numbness	2.6 (2.1–3.0)	Nausea/vomiting	3.3 ± 8.2	3.7 ± 11.7
Insomnia	3.0 (2.5–3.5)	Pain	14.6 ± 20.4	20.9 ± 27.6
Sad mood	2.2 (1.7–2.6)	Dyspnea	19.6 ± 24.2	11.8 ± 22.8
Sexuality problems	2.8 (2.2–3.4)	Insomnia	26.6 ± 28.0	21.8 ± 29.7
Cough	1.3 (1.0–1.6)	Appetite loss	10.3 ± 21.7	6.7 ± 18.3
Night sweats	2.3 (1.8–2.7)	Constipation	13.4 ± 24.5	6.7 ± 18.4
Itching	2.8 (2.3–3.3)	Diarrhea	6.3 ± 16.3	7.0 ± 18.0
Bone pain	2.1 (1.6–2.6)	Financial difficulties	6.4 ± 15.9	9.5 ±23.3
Fever	0.3 (0.1–0.4)	***Global health status/QoL***		
Weight loss	1.1 (0.7–1.5)	Global health status/QoL	65.7 ± 24.8	71.2 ± 22.4
Quality of life	3.1 (2.7–3.4)			

MPN-SAF, myeloproliferative neoplasm symptom assessment form

1. Scherber R, et al. *Blood*. 2011;118(2):401-408. 2. Emanuel RM, et al. *J Clin Oncol*. 2012;30(33):4098-4103.
3. Mesa RA, et al. *Cancer.* 2007;109(1):68-76. 4. Siegel FP, et al. *Am J Hematol*. 2013;88(8):665-669.

How Do We Measure It?

MPN-SAF Total Symptom Score (TSS) or MPN 10

- **MPN-SAF TSS is a key tool in measuring response to treatment in PV[1]**
- **MPN-SAF TSS allows a quantitative assessment of**
  - **Symptom burden**
  - **Disease progression**
  - **Treatment response**
- **In clinical practice, the MPN-SAF TSS enhances communication between physicians and patients**
  - **Allows physicians to note changes and better manage the disease**

Rate the following symptoms on a scale of 1 to 10 (0 if absent), with 1 being most favorable and 10 being the worst imaginable.

0	1	2	3	4	5	6	7	8	9	10
	(Most favorable)						(Worst imaginable)			

- **Your WORST level of fatigue during past 24 hours**
- **Filling up quickly when you eat (early satiety)**
- **Abdominal discomfort**
- **Inactivity**
- **Problems with concentration**
- **Numbness/tingling (in hands and feet)**
- **Night sweats**
- **Itching (pruritus)**
- **Bone pain (diffuse, not joint pain or arthritis)**
- **Fever (>100° F)**
- **Unintentional weight loss in last 6 months**

1. Barosi G, et al. *Blood.* 2013;121(23):4778-4781. 2. Emanuel RM, et al. *J Clin Oncol.* 2012;30(33):4098-4103.

Can We Achieve Therapeutic Control Without Sacrificing Quality of Life?

To answer the question you must first understand it…
Therapeutic control…what does that mean?

2013 ELN Response Criteria for PV

Complete remission

A	Durable[a] resolution of disease-related signs, including palpable splenomegaly, large symptom improvement[b] *and*
B	Durable[a] peripheral blood count remission, defined as Hct <45% without phlebotomies, platelet (PLT) count ≤400 × 10^9/L, WBC count <10 × 10^9/L, *and*
C	Without progressive disease, and absence of any hemorrhagic or thrombotic event, *and*
D	Bone marrow histological remission defined as the presence of age-adjusted normocellularity and disappearance of trilinear hyperplasia, and absence of grade >1 reticulin fibrosis

Partial remission

A, B, C, without bone marrow histological remission

No response	**Any response that does not satisfy partial remission**
Progressive disease	**Transformation into post-PV MF, MDS, or acute leukemia**

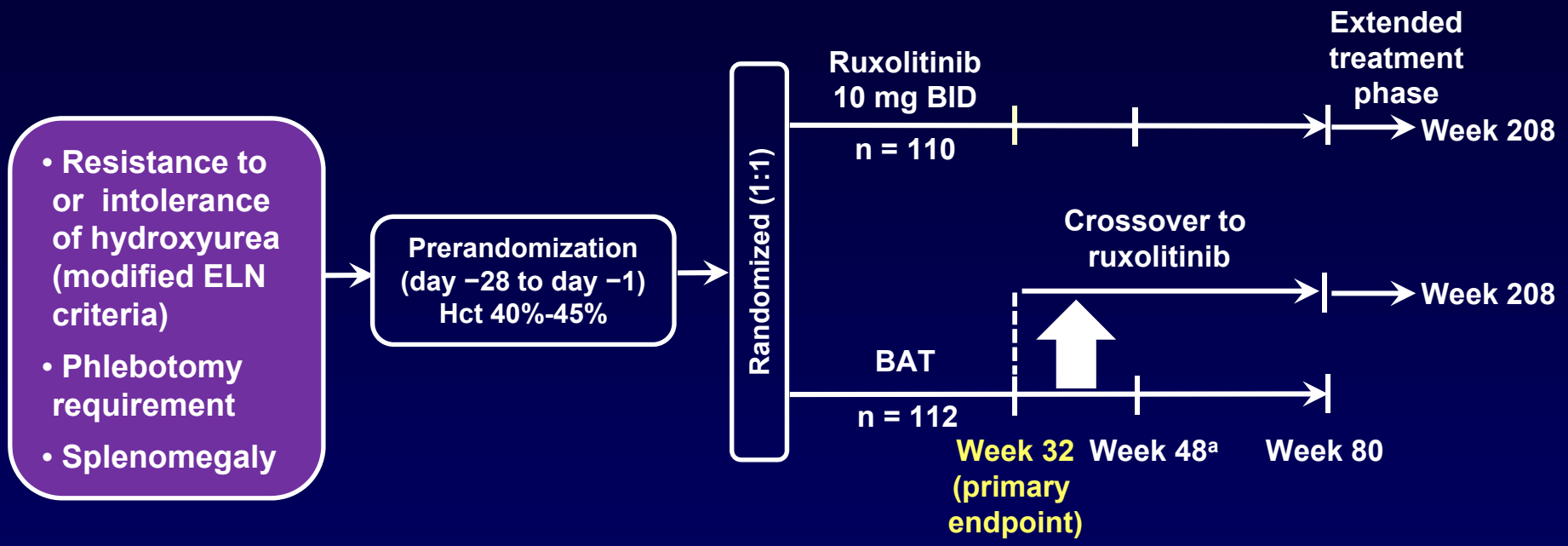
[a]≥12 [illegible], [b]≥10-point decrease in MPN-SAF TSS

Barosi G, et al. *Blood.* 2013;121(23):4778-4781.

What Is Known for Standard Therapies?

- ??? ongoing studies hope to provide answers
- MEASURES a QoL study is ongoing

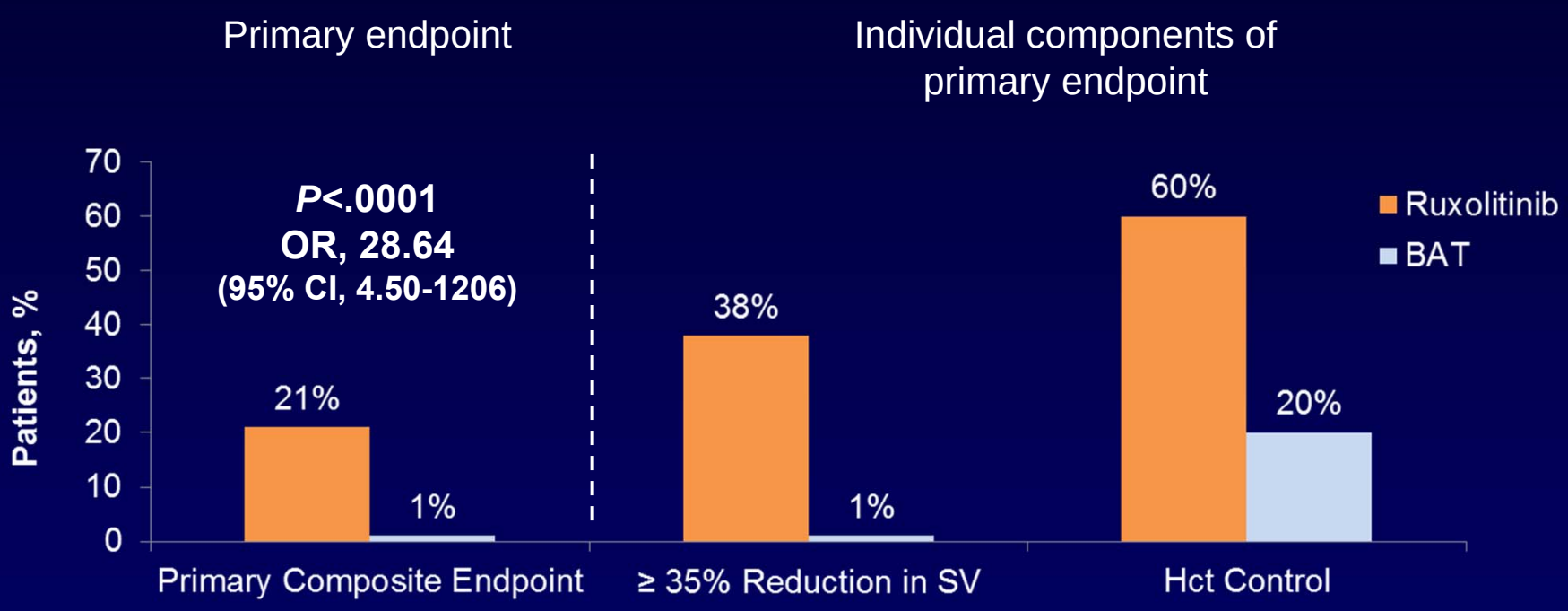
RESPONSE Study Design



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

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

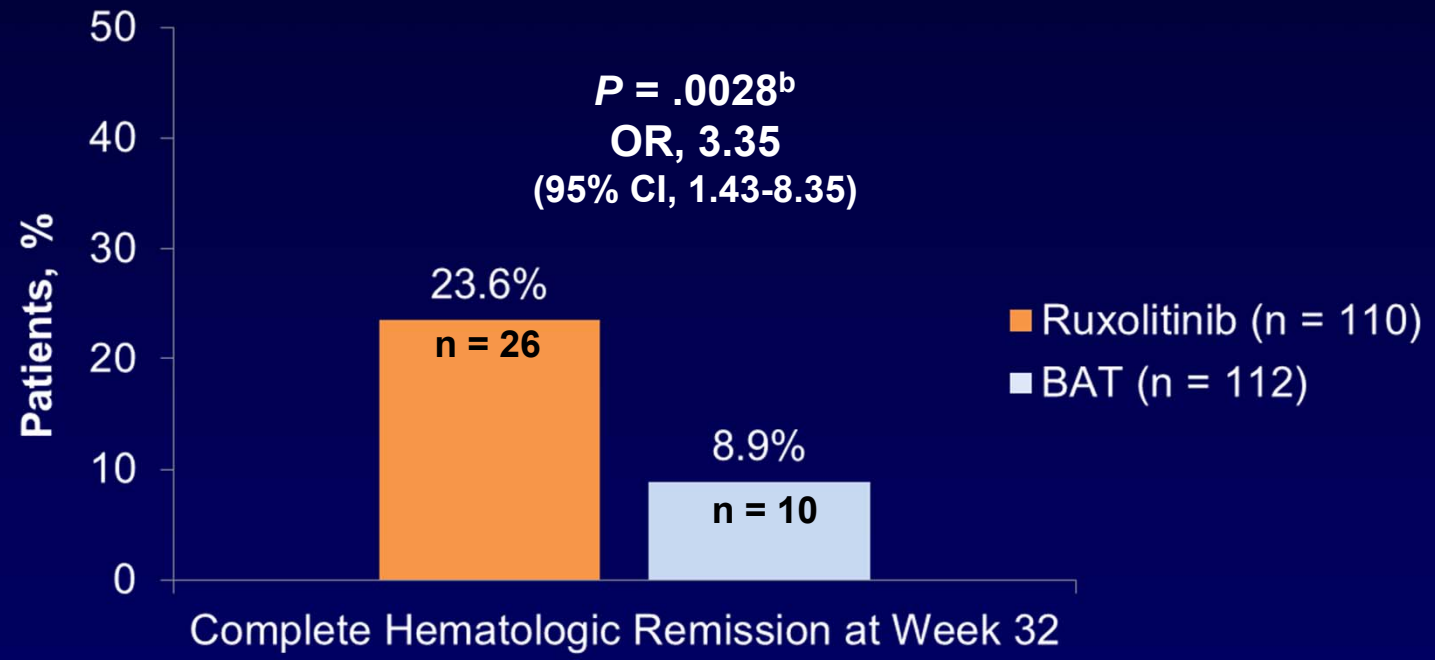
Primary Response at Week 32



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

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Complete Hematologic Remission at Week 32



- **88.5% of patients who achieved CHR had a durable response at week 48**

CHR is defined as Hct control, platelet count ≤400 × 10^9/L, and WBC count ≤10 × 10^9/L.

[b]*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.

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Thromboembolic Events (All Grades) Up to Week 32

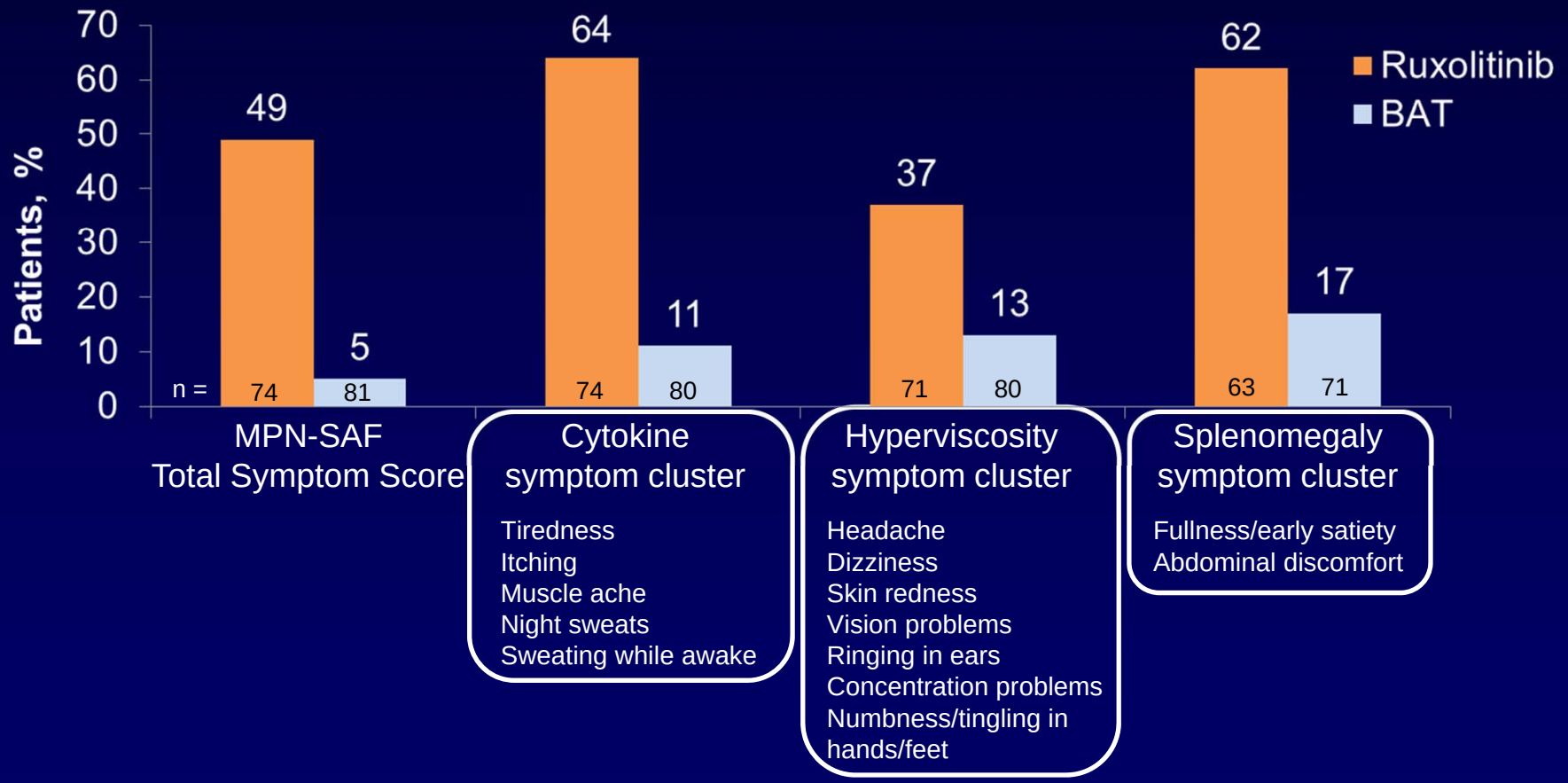
Patients, n (%)	Ruxolitinib (n = 110)		BAT (n = 111)	
	All grade	Grade 3/4	All grade	Grade 3/4
All thromboembolic events	1 (0.9)	1 (0.9)	6 (5.4)[a]	2 (1.8)[a]
Portal vein thrombosis	1 (0.9)	1 (0.9)	0	0
Myocardial infarction	0	0	1 (0.9)	1 (0.9)
Deep vein thrombosis	0	0	2 (1.8)	1 (0.9)
Pulmonary embolism	0	0	1 (0.9)	1 (0.9)
Splenic infarction	0	0	1 (0.9)	0
Thrombophlebitis	0	0	1 (0.9)	0
Thrombosis	0	0	1 (0.9)	0

[a]1 patient in the BAT group had both myocardial infarction and pulmonary embolism

- **A higher proportion of patients in the ruxolitinib arm had a history of prior thromboembolic events at baseline compared with BAT (35.5% vs 29.5%)**
- **After week 32, there was 1 additional event in the ruxolitinib group over the course of randomized treatment (median exposure 81 weeks)**

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

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



[a]In patients with scores at both baseline and week 32

Vannucchi A, et al. *Haematologica.* 2014;99(Suppl): Abstract LB2436.

Nonhematologic AEs Up to Week 32 (Regardless of Causality)

	Ruxolitinib (n = 110)		BAT (n = 111)	
Patients, %	All grades	Grade 3/4	All grades	Grade 3/4
Headache	16.4	0.9	18.9	0.9
Diarrhea	14.5	0	7.2	0.9
Fatigue	14.5	0	15.3	2.7
Pruritus	13.6	0.9	22.5	3.6
Dizziness	11.8	0	9.9	0
Muscle spasms	11.8	0.9	4.5	0
Dyspnea	10.0	2.7	1.8	0
Abdominal pain	9.1	0.9	11.7	0
Asthenia	7.3	1.8	10.8	0

Events occurring in at least 10% of patients in either treatment group

- **When adjusted for exposure (per 100 patient-years), the rates of AEs and grade 3/4 AEs of the entire course of treatment were lower in patients randomized to ruxolitinib compared with BAT (64.7% vs 145.6% and 28.8% vs 44.0%)**
- **The exposure-adjusted rates of SAEs per 100 patient-years were comparable in both arms (15.3% and 13.7%)**

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Can We Achieve Therapeutic Control Without Sacrificing Quality of Life?

ONLY comparative and detailed evidence comes from the RESPONSE trial……HERE

- **MPN TSS used, with success defined as 50% reduction rather than ELN criteria (10 point reduction)**
- **Assessed "difficult" (ie, failing) patients and compared a new therapy with a collection of different therapies**
- **Not "perfect" data to answer this question BUT suggests this is possible**

Summary

- Each patient with PV provides a unique constellation of disease risks and targets
- “Omni-comprehensive management” or a continuous personalized approach is required in the management of this complex disease
- The cause of symptoms and impaired QoL is uncertain and the ability of standard therapies to impact this has not been formally assessed
- So far the RESPONSE study suggests ruxolitinib is superior to standard therapy but further data is needed