RESULTS OF THE PERSIST-2 PHASE 3 STUDY OF PACRITINIB (PAC) VERSUS BEST AVAILABLE THERAPY (BAT), INCLUDING RUXOLITINIB (RUX), IN PATIENTS WITH MYELOFIBROSIS (MF) AND PLATELET COUNTS ≤100,000/μL

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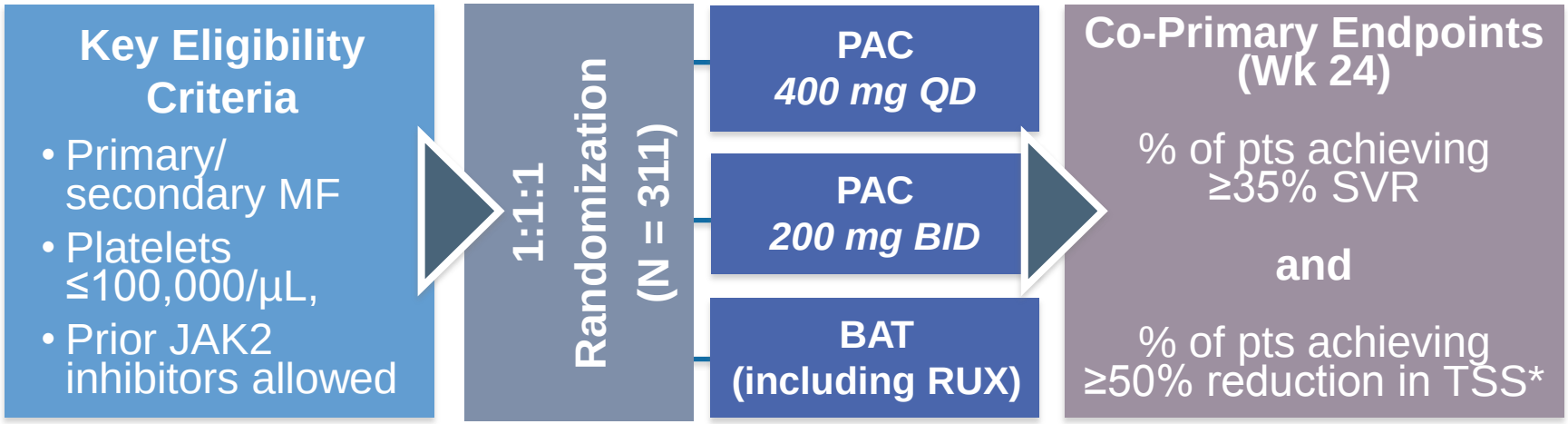
Background

- MF is a life-threatening hematologic malignancy characterized by splenomegaly and debilitating constitutional symptoms[1-3]
  - ~1/4 of MF pts present with thrombocytopenia;[4] platelets <50,000/µL associated with reduced QoL,[1] more severe symptom burden, and shorter overall survival[5]
- Approved JAK1/2 inhibitor RUX reduces splenomegaly and symptoms, but is associated with dose-limiting cytopenias and not indicated for pts with platelets <50,000/µL[6,7]
- PAC: oral kinase inhibitor with specificity for JAK2, FLT3, IRAK1, & CSF1R[8]
- PERSIST-1 trial: sustained spleen volume reduction (SVR) and symptom control with PAC vs BAT (excluding JAK2 inhibitors) in pts with MF regardless of baseline platelet count[9]
- PAC placed on full clinical hold by the US FDA (2/8/2016) due to concerns over interim survival results, bleeding, and cardiovascular events

1. Tefferi A, et al. *Blood*. 2013;122:1395-1398. 2. Mesa et al. Cancer. 2007;109:68-76. 3. Geyer HL, et al. *Blood*. 2014;124:3529-3537. 4. Tefferi A, et al. *Mayo Clinic Proc*. 2012;87:25-33. 5. Alhuraiji A, et al. *J Clin Oncol*. 2016;34(suppl):abstract 7068. 6. Harrison C, et al. *N Engl J Med*. 2012;366:787-798. 7. Verstovsek S, et al. *N Engl J Med*. 2012;366:799-807. 8. Hart S, et al. *Leukemia*. 2011;25:1751-1759. 9. Mesa RA, et al. ASCO 2015. Abstract LBA7006.

PERSIST-2 Phase 3 Study Design



*TSS, total symptom score by MPN-SAF 2.0

- In PK simulations, PAC 200 mg BID was predicted to have higher C_{min} and lower C_{max} than PAC 400 QD
- Crossover from BAT allowed after progression (any time) or at Wk 24
- **Study Objectives:**
  - Primary: efficacy of pooled QD and BID PAC vs BAT
  - Secondary: efficacy of QD PAC or BID PAC separately vs BAT

PK, pharmacokinetics; PPV, post-polycythemia; PET, post-essential thrombocythemia.

Patient Demographics (ITT Efficacy Population*)

Characteristic	PAC QD n=75	PAC BID n=74	BAT n=72
Median age, yrs (range)	69 (39-85)	67 (39-85)	69 (32-83)
≥65 yrs, n (%)	53 (71)	46 (62)	51 (71)
Male, n (%)	38 (51)	48 (65)	39 (54)
ECOG PS, n (%)			
0-1	57 (76)	65 (88)	54 (75)
2-3	17 (23)	8 (11)	15 (21)
MF diagnosis, n (%)			
Primary	46 (61)	55 (74)	43 (60)
PPV	16 (21)	14 (19)	16 (22)
PET	13 (17)	5 (7)	13 (18)
DIPSS risk category, n (%)			
Int-1	13 (17)	14 (19)	13 (18)
Int-2	40 (53)	38 (51)	37 (51)
High	22 (29)	22 (30)	22 (31)
JAK2^{V617F} positive, n (%)	60 (80)	59 (80)	51 (71)

*Included all pts with randomization date that allowed them to contribute data for a wk 24 endpoint (pts randomized prior to September 7, 2015; ≥ 22 wks prior to clinical hold)

Patient Demographics (Cont'd) (ITT Efficacy Population)

Characteristic	PAC QD n=75	PAC BID n=74	BAT n=72
Median spleen length by physical exam, cm (range)	13 (3-33)	15 (5-32)	13 (2-34)
Platelet count <50,000/μL, n (%)	38 (51)	31 (42)	32 (44)
Hemoglobin <10 g/dL, n (%)	45 (60)	44 (59)	41 (57)
Peripheral blasts category, n (%)			
0-<1%	41 (55)	38 (51)	36 (50)
≥1%	30 (40)	30 (41)	31 (43)
0-<5%	62 (83)	61 (82)	60 (83)
≥5%	9 (12)	7 (9)	7 (10)
Missing	4 (5)	6 (8)	5 (7)
White blood cell category, n (%)			
>25 x 10^9/L	15 (20.0)	17 (23)	14 (19)
≤25 x 10^9/L	60 (80.0)	57 (77)	58 (81)
Received prior RUX, n (%)	31 (41.3)	31 (42)	33 (46)

Patient Disposition

Characteristic	PAC QD	PAC BID	BAT
Patients randomized, n	104	107	100
Safety population	104	106	98
ITT efficacy population	75	74	72
Discontinued treatment, n (%)	104 (100)	106 (99)	98 (98)
Deaths	5 (5)	2 (2)	5 (5)
Adverse events	15 (14)	10 (9)	4 (4)
Progressive disease	5 (5)	7 (7)	11 (11)
Physician decision (most due to crossover)	5 (5)	3 (3)	41 (41)
Withdrawal by pt	9 (9)	5 (5)	4 (4)
Other (most due to clinical hold)	65 (63)	79 (74)	33 (33)

- 50/100 BAT pts crossed over to PAC, 86% at or after Wk 24

Study Treatment

Exposure	PAC QD (N=104)	PAC BID (N=106)	BAT (N=98)
Median exposure, wks (range)	23 (1-82)	25 (1-84)	21 (1-56)
Dose modifications due to AEs, n (%)			
Dose interruptions	39 (38)	29 (27)	10 (10)
Dose reductions	21 (20)	13 (12)	7 (7)
Discontinuations	20 (19)	16 (15)	12 (12)

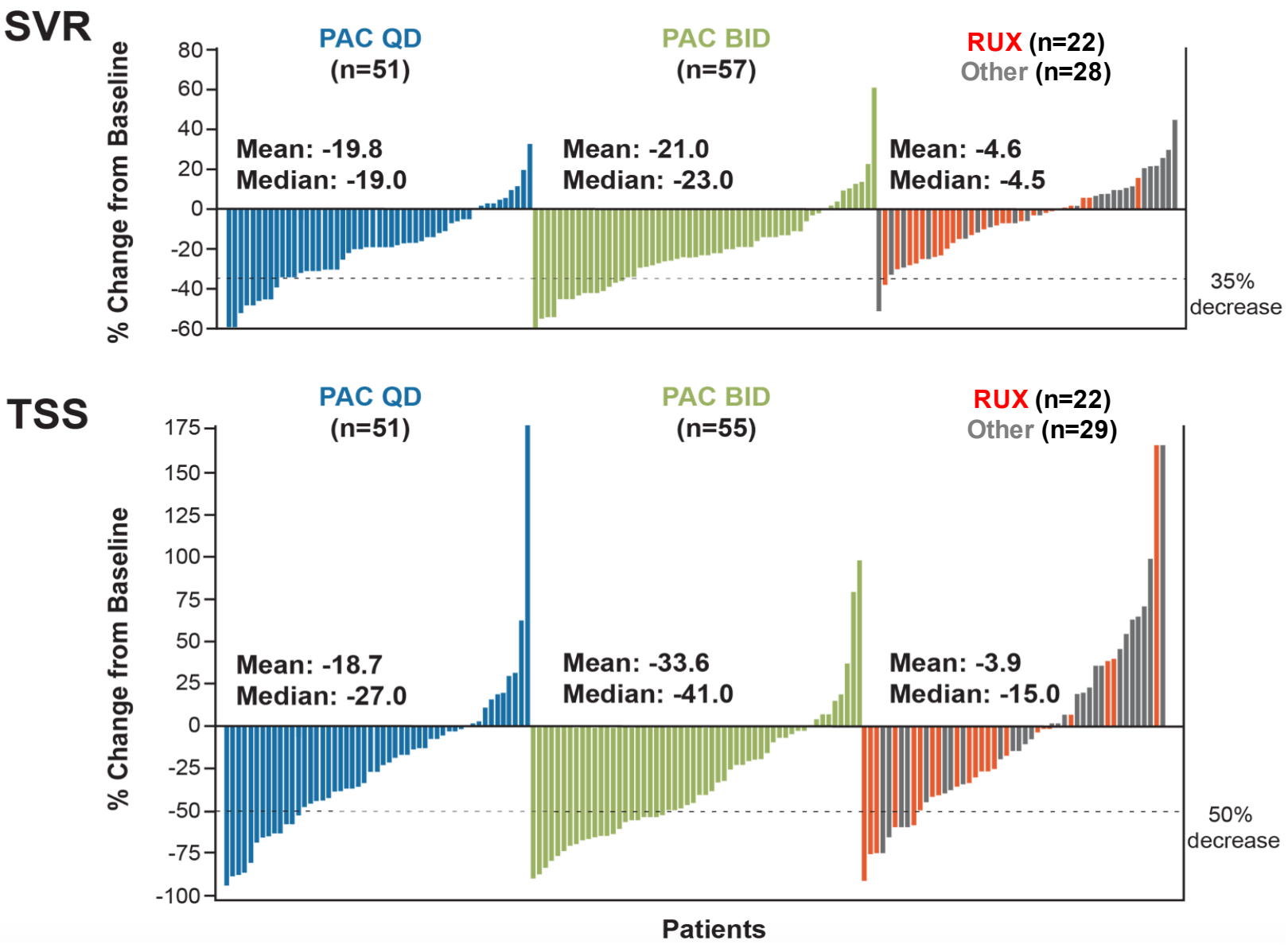
- The most common BATs were RUX (45%) and hydroxyurea (19%)
- 19% of BAT patients had “watch and wait” only

Efficacy Summary

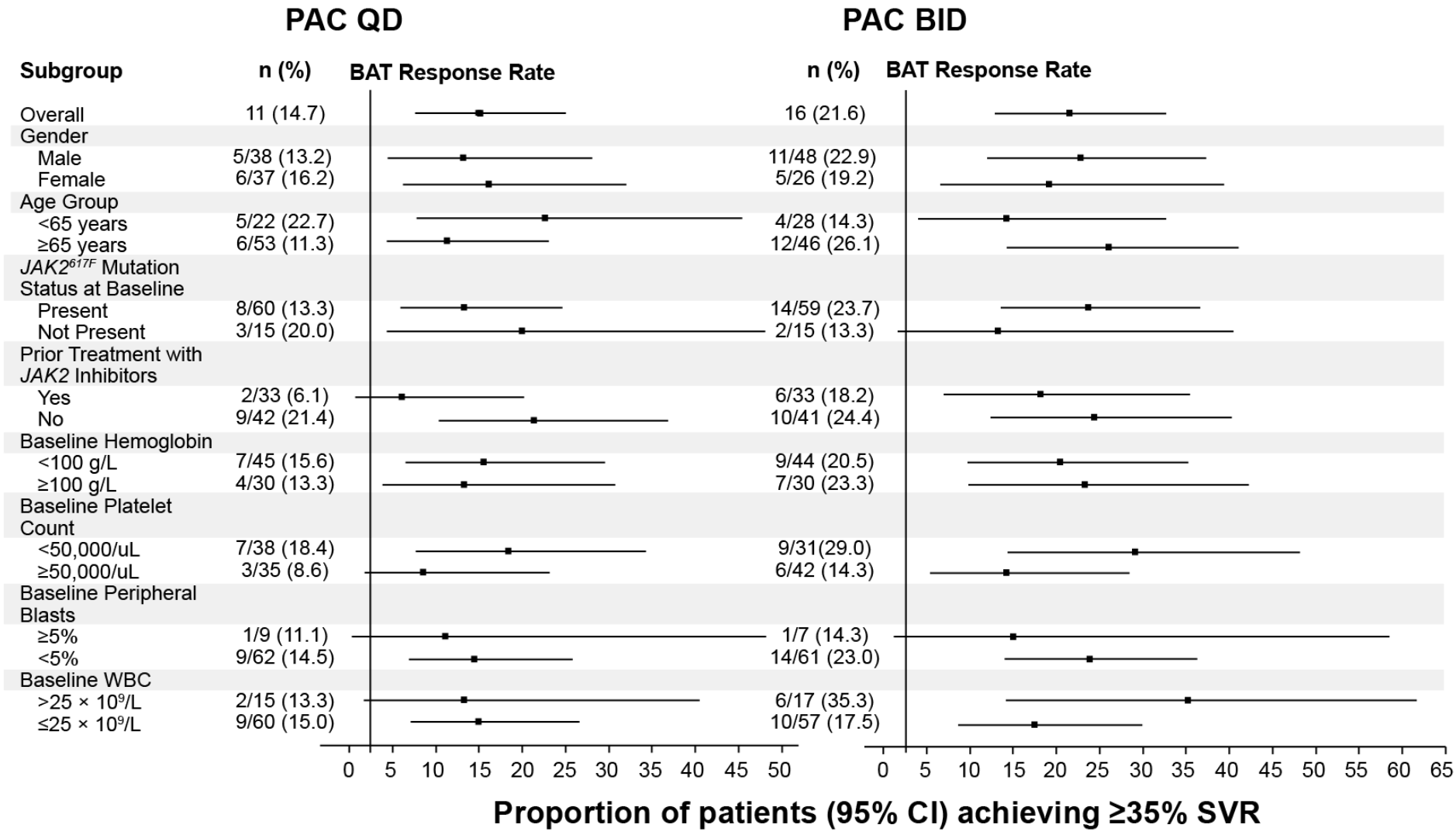
Endpoint	Statistics	PAC QD+BID (n=149)	PAC QD (n=75)	PAC BID (n=74)	BAT (n=72)
Patients with ≥35% SVR from BL to Wk 24	n (%)	27 (18.1)	11 (14.7)	16 (21.6)	2 (2.8)
	95% CI*	12.3-25.3	7.6-24.7	12.9-32.7	0.3-9.7
	P value vs BAT	**0.001**	**0.017**	**0.001**	-
Patients with ≥50% reduction in TSS from BL to Wk 24	n (%)	37 (24.8)	13 (17.3)	24 (32.4)	10 (13.9)
	95% CI*	18.1-32.6	9.6-27.8	22.0-44.3	6.9-24.1
	P value vs BAT	0.079	0.652	**0.011**	-

*Clopper-Pearson method.

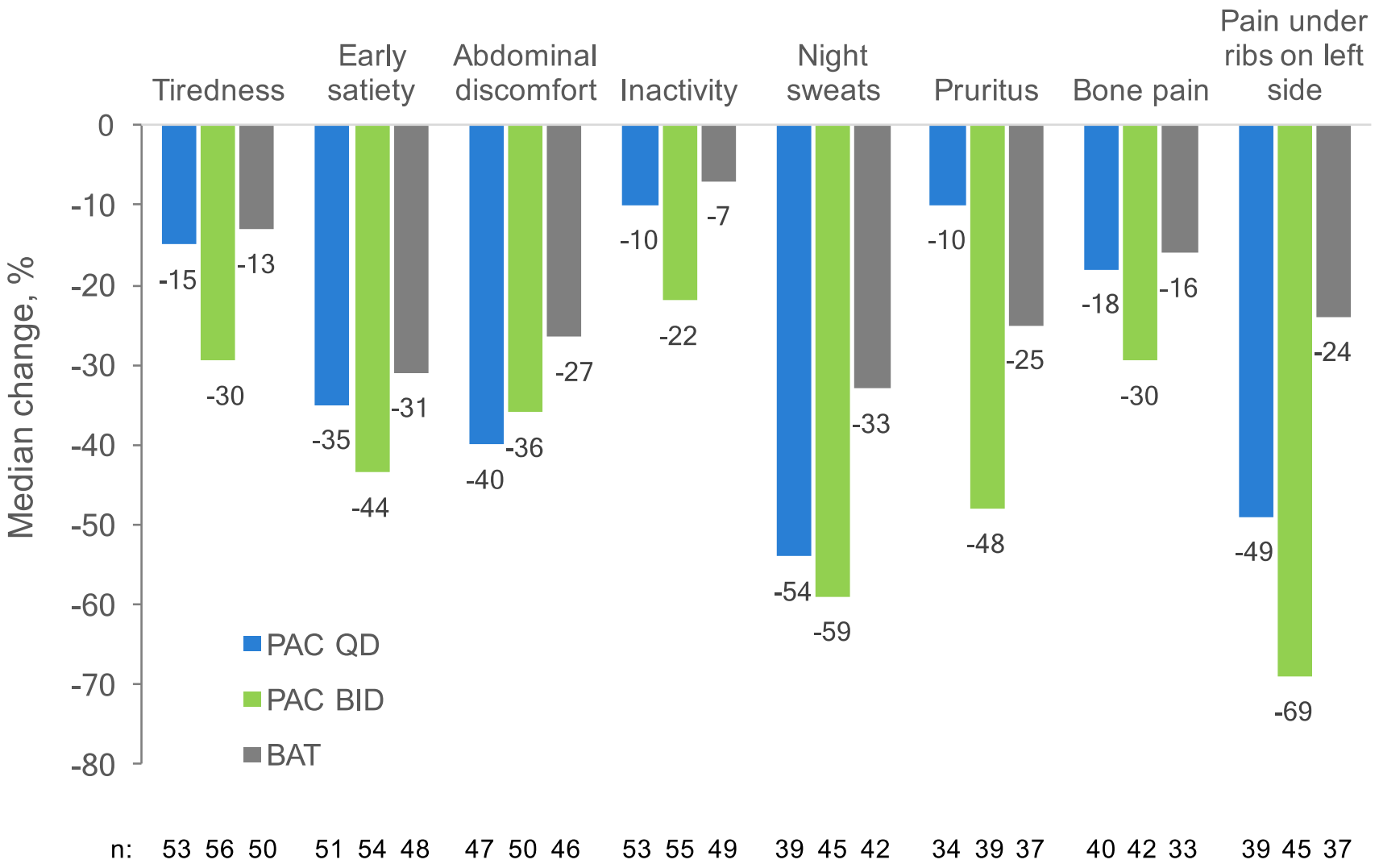
Efficacy: Analysis by Arm



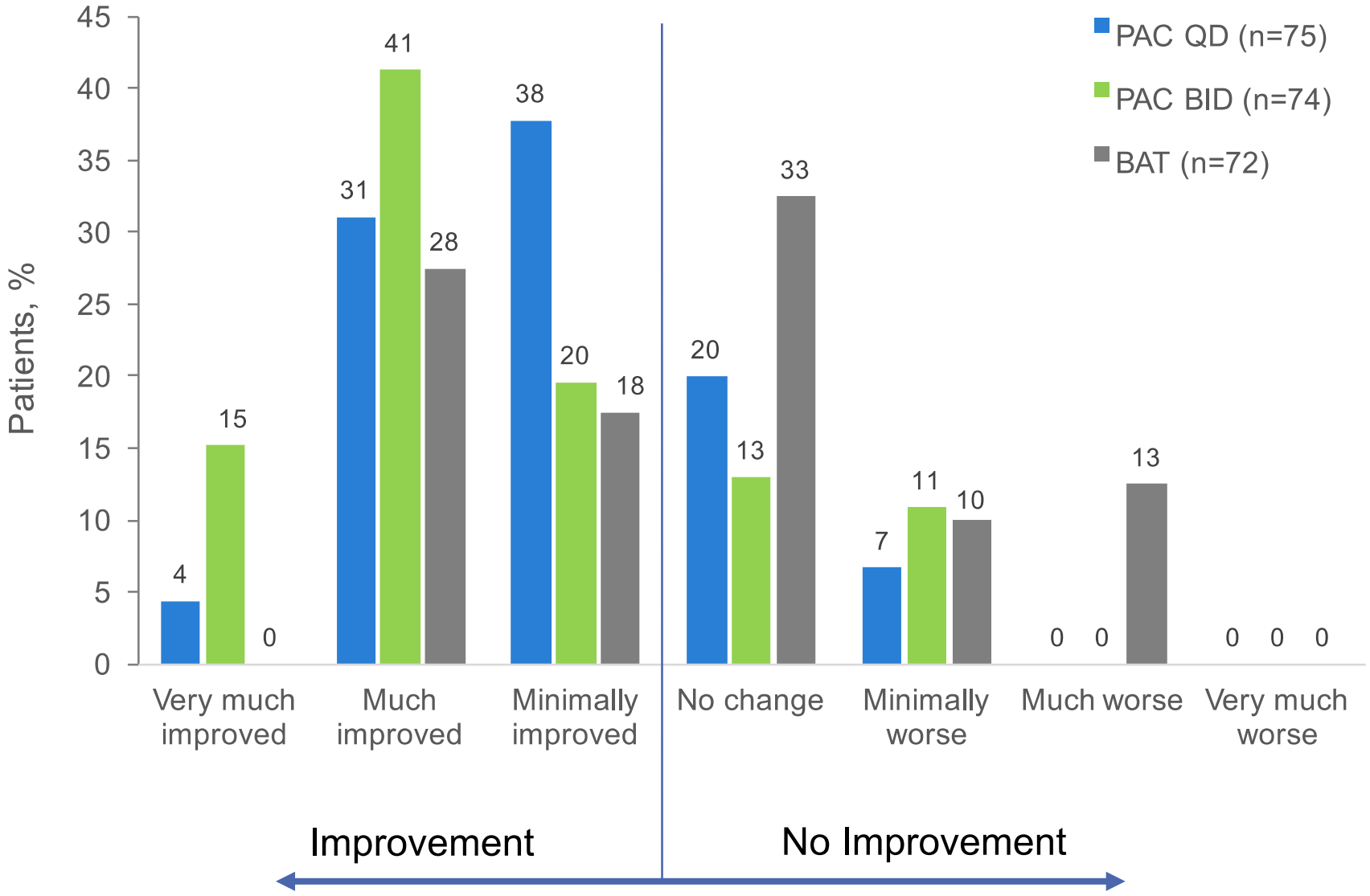
Forest Plots for SVR



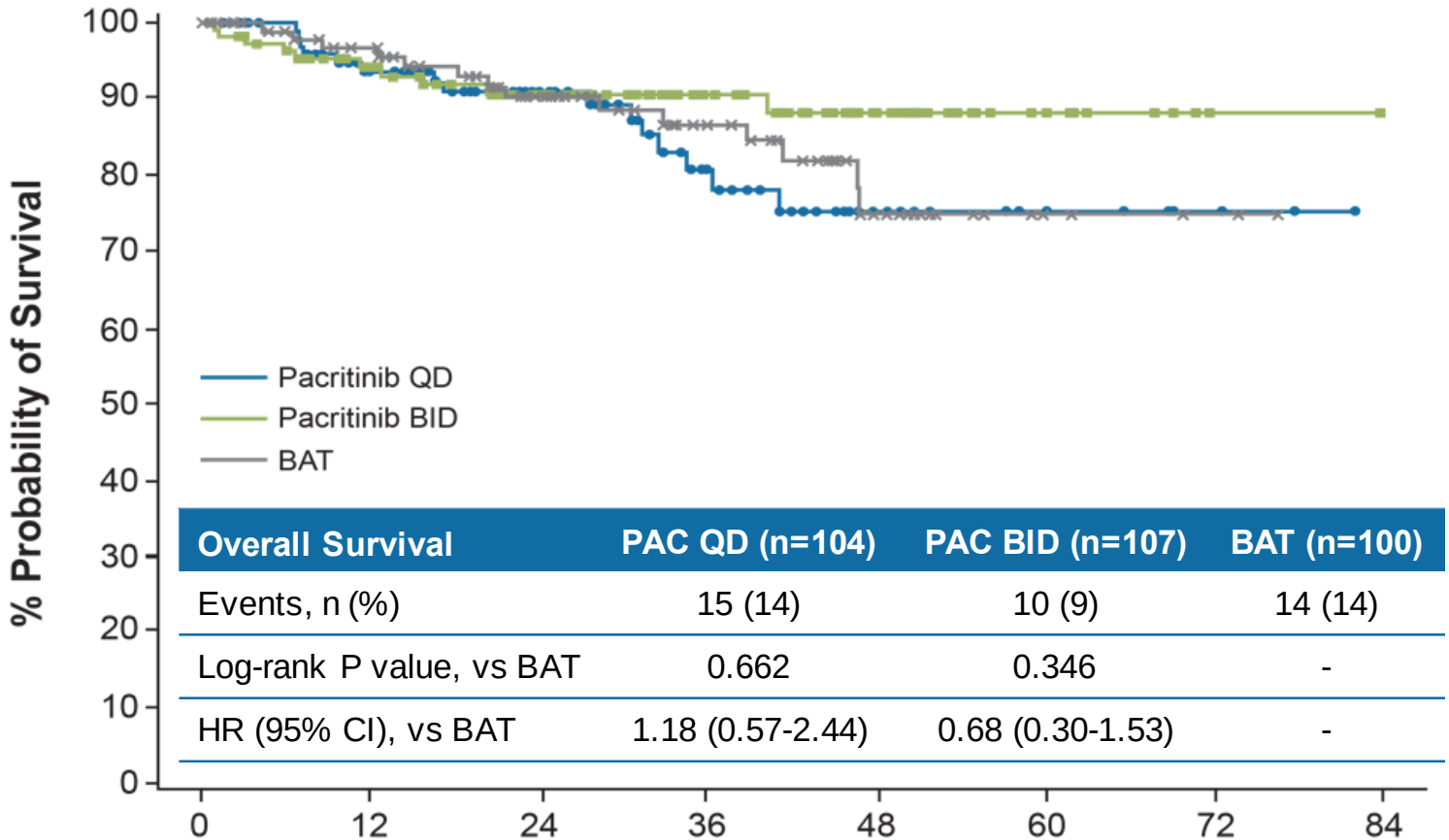
Changes in Individual Symptom Scores per MPN-SAF TSS 2.0



Global Impression of Change



Overall Survival (Censored at Date of Clinical Hold)

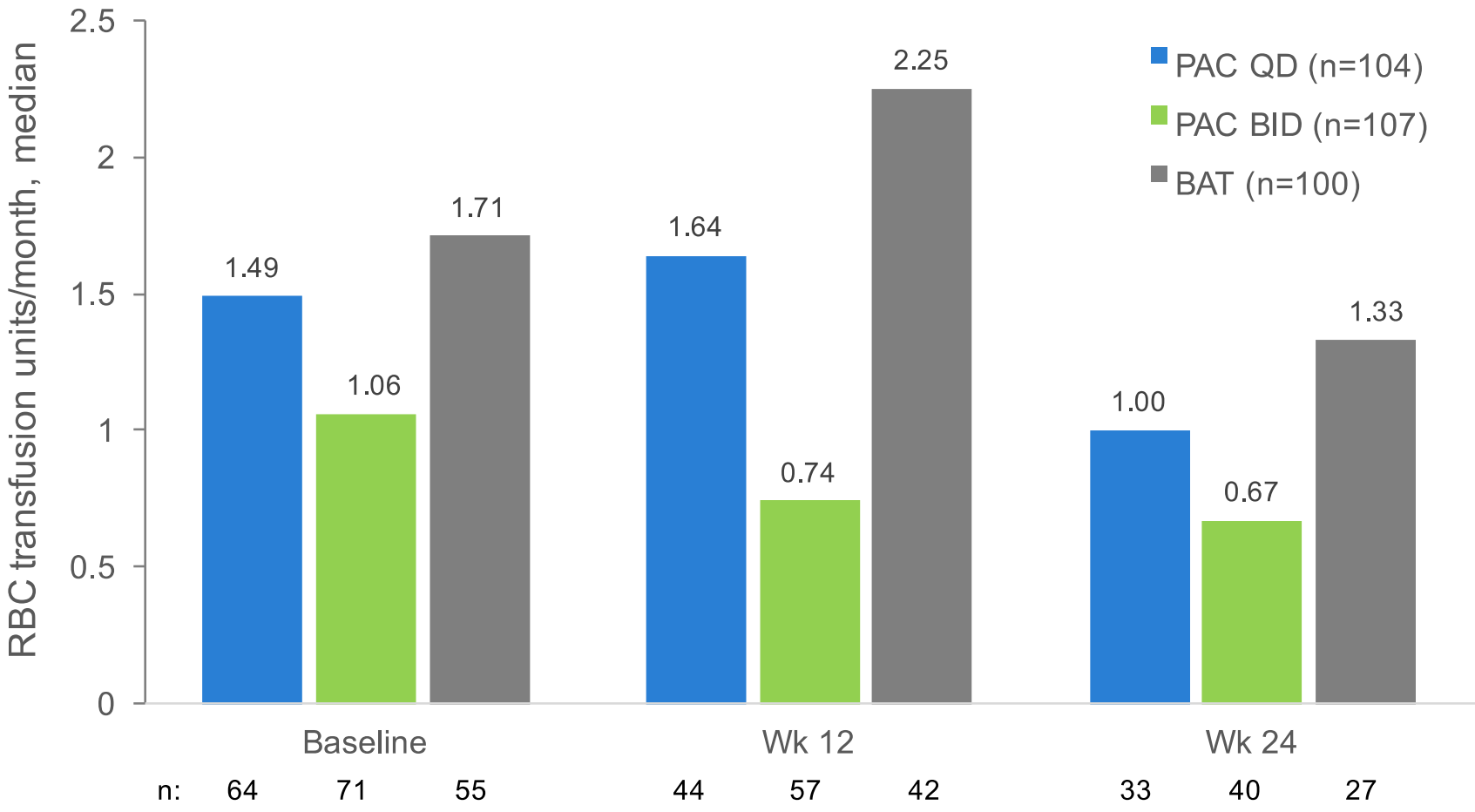


Overall Survival	PAC QD (n=104)	PAC BID (n=107)	BAT (n=100)
Events, n (%)	15 (14)	10 (9)	14 (14)
Log-rank P value, vs BAT	0.662	0.346	-
HR (95% CI), vs BAT	1.18 (0.57-2.44)	0.68 (0.30-1.53)	-

Paitents at Risk

Pacritinib QD	104	80	55	31	13	7	3	0
Pacritinib BID	107	85	62	41	22	9	1	0
BAT	100	83	60	41	18	4	2	0

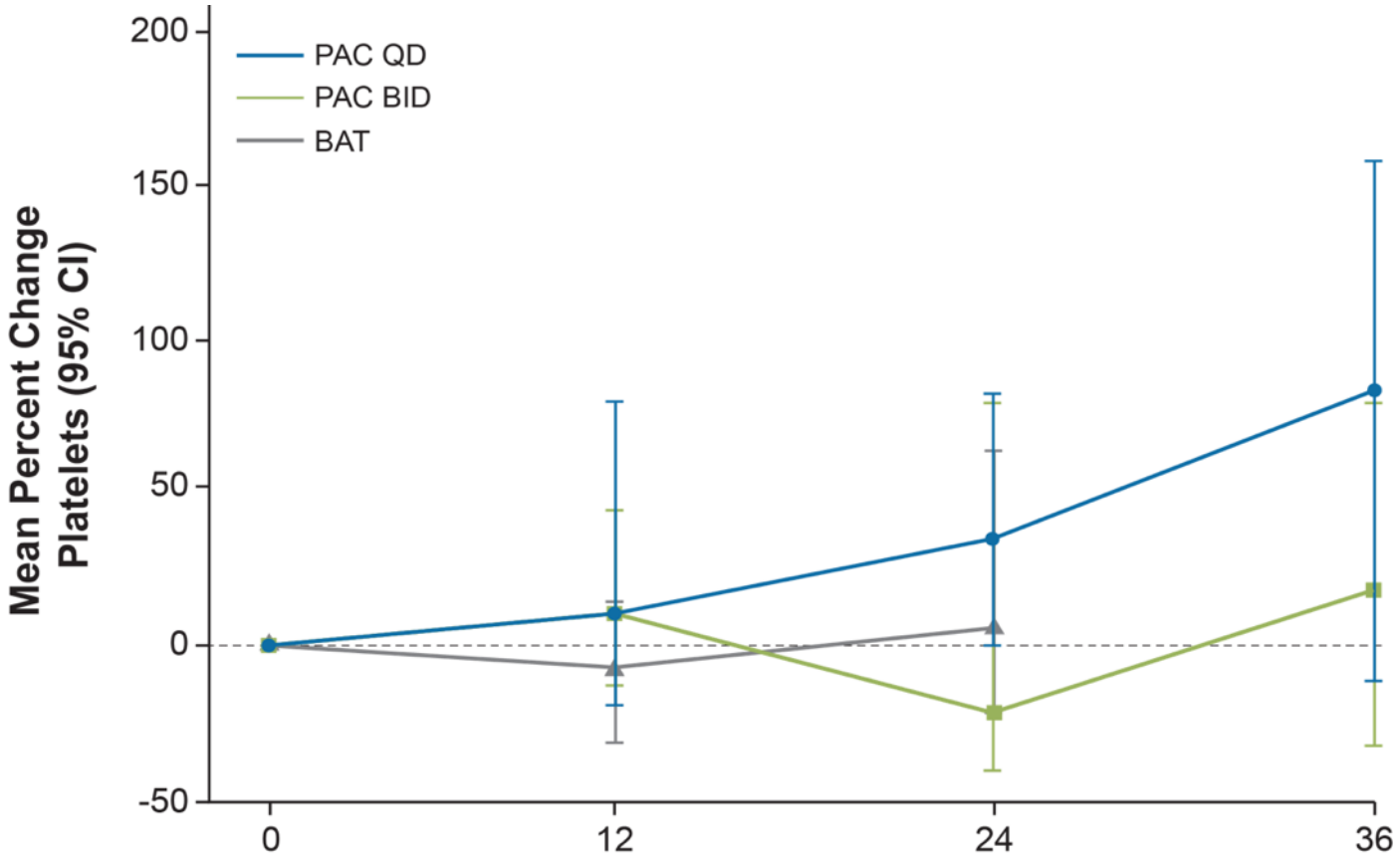
RBC Transfusions



- Patients treated with PAC had lower RBC transfusion requirements than those treated with BAT at Week 12 and Week 24

RBC, red blood cell.

Percent Change in Platelet Count - Baseline Platelets <50,000/µL*



Paitents at Risk				
PAC QD	50	28	19	10
PAC BID	47	32	16	11
BAT	42	23	12	

*Based on central laboratory values.

Most Common TEAEs (≥10%)

Characteristic	PAC QD n=104	PAC BID n=106	BAT n=98
Pts with ≥1 TEAE	104 (100)	100 (94)	87 (89)
Diarrhea	70 (67)	51 (48)	15 (15)
Nausea	39 (38)	34 (32)	11 (11)
Thrombocytopenia	34 (33)	36 (34)	23 (23)
Anemia	29 (28)	25 (24)	15 (15)
Vomiting	22 (21)	20 (19)	5 (5)
Fatigue	18 (17)	18 (17)	16 (16)
Peripheral edema	14 (13)	21 (20)	15 (15)
Dizziness	15 (14)	16 (15)	5 (5)
Abdominal pain	20 (19)	10 (9)	19 (19)
Pyrexia	11 (11)	16 (15)	3 (3)
Decreased appetite	13 (13)	13 (12)	11 (11)
Epistaxis	11 (11)	13 (12)	13 (13)
Constipation	15 (14)	8 (8)	6 (6)
Insomnia	12 (12)	10 (9)	4 (4)
Pruritus	10 (10)	11 (10)	6 (6)
Cough	11 (11)	9 (8)	10 (10)
Dyspnea	9 (9)	11 (10)	9 (9)
Upper respiratory tract infection	8 (8)	11 (10)	6 (6)

Serious TEAEs

	PAC QD n=104	PAC BID n=106	BAT n=98
Any SAE, n (%)	48 (46)	50 (47)	30 (31)
Most common SAEs (≥5 in any arm), n (%)			
Anemia	5 (5)	8 (8)	3 (3)
Thrombocytopenia	2 (2)	6 (6)	2 (2)
Pneumonia	5 (5)	6 (6)	4 (4)
Renal failure, acute	5 (5)	2 (2)	2 (2)
SAEs of interest, n (%)			
CHF	1 (1)	4 (4)	2 (2)
Atrial fibrillation	3 (3)	0	3 (3)
Cardiac arrest	2 (2)	0	0
Epistaxis	2 (2)	2 (2)	1 (1)
Subdural hematoma	2 (2)	0	0

Summary of Deaths

	PAC QD n=104	PAC BID n=107	BAT* n=100
ITT, censored at the time of full clinical hold			
Deaths	15 (14)	10 (9)	14 (14)
Due to AEs	8 (8)	4 (4)	6 (6)
Cardiac AEs	2 (2)	0	2 (2)
Bleeding AEs	0	3 (3)	1 (1)
Due to PD	5 (5)	5 (5)	7 (7)
Other	2 (2)	1 (1)	1 (1)
After the full clinical hold			
Deaths	7 (7)	10 (9)	6 (6)
Due to AEs	3 (3)	1 (1)	1 (1)
Cardiac AEs	1 (1)	0	2 (2)
Bleeding AEs	1 (1)	0	0
Due to PD	2 (2)	5 (5)	2 (2)
Other	2 (2)	4 (4)	3 (3)

*7 of 20 pts who died did so after crossover to PAC; 5 due to AEs (3 cardiac, 1 bleeding, 1 other)

Conclusions

Despite study truncation due to the clinical hold:

- PAC (QD+BID) was significantly more effective than BAT (including RUX) for SVR (p=0.001) and trended toward improved TSS (p=0.079)
- PAC BID appeared more effective than PAC QD versus BAT for SVR and TSS
- SVR and TSS responses to PAC BID were consistent across demographic and disease risk characteristics
- PAC BID appeared to have a better benefit/risk profile than BAT, which included RUX

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