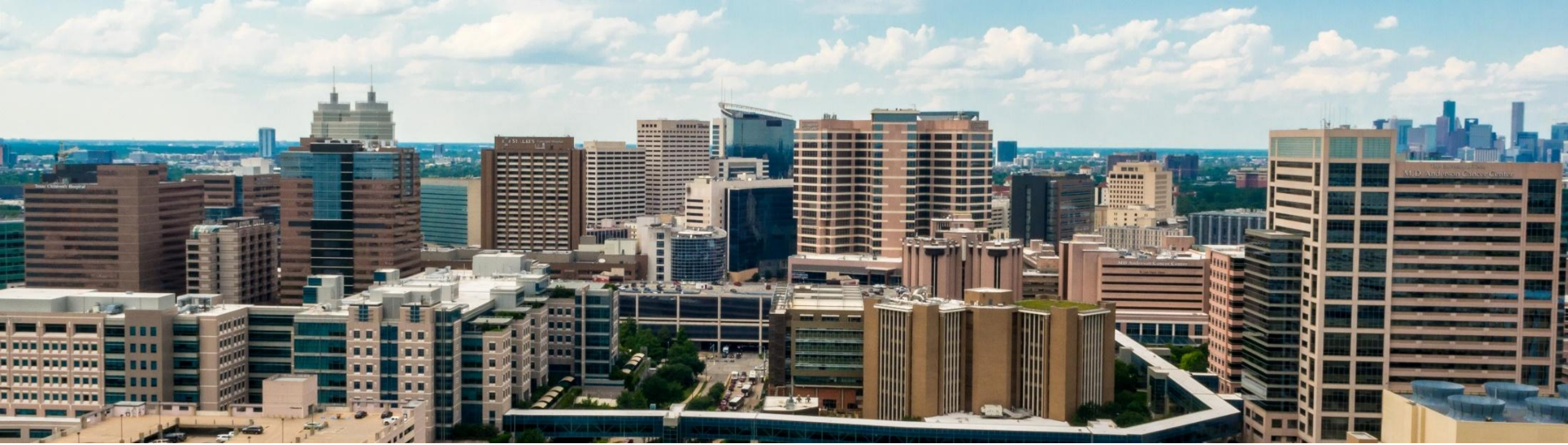


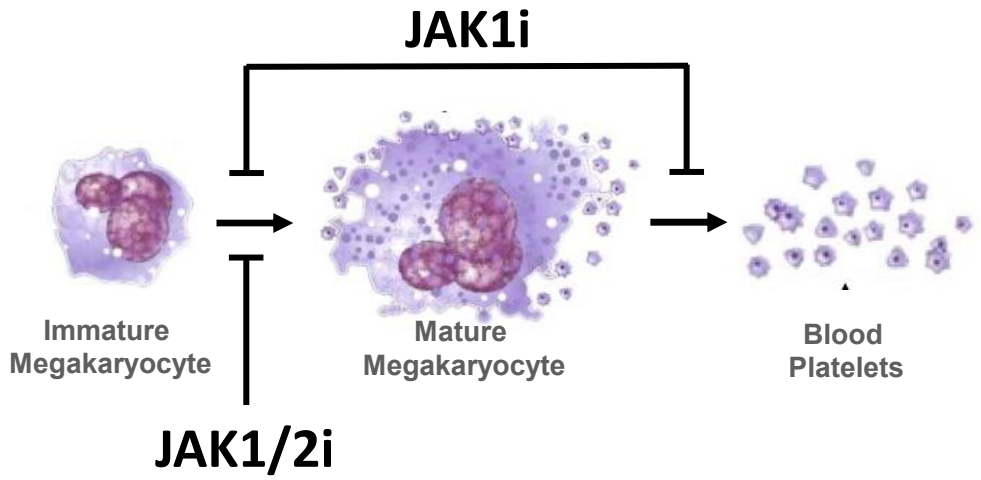
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

Pacritinib for the Management of Myelofibrosis

Prithviraj Bose, M.D.
Professor, Department of Leukemia
Co-Leader, Section of Myeloproliferative Neoplasms

September 12, 2024

Pacritinib (PAC) A selective inhibitor of JAK2 and IRAK1



- JAK1/2 inhibitors impair megakaryopoiesis while preserving thrombopoiesis, whereas JAK1 inhibition impairs both megakaryopoiesis and platelet release *in vitro* and can exacerbate thrombocytopenia in MF.*
- Minimal JAK1 inhibition uniquely positions Pacritinib for use in thrombocytopenic MF patients.

*Jadwiga J, et. al. Blood (2018) 132 (Supplement 1): 2559.; Mascarenhas JO, et. al. Haematologica 2017; 102(2):327.

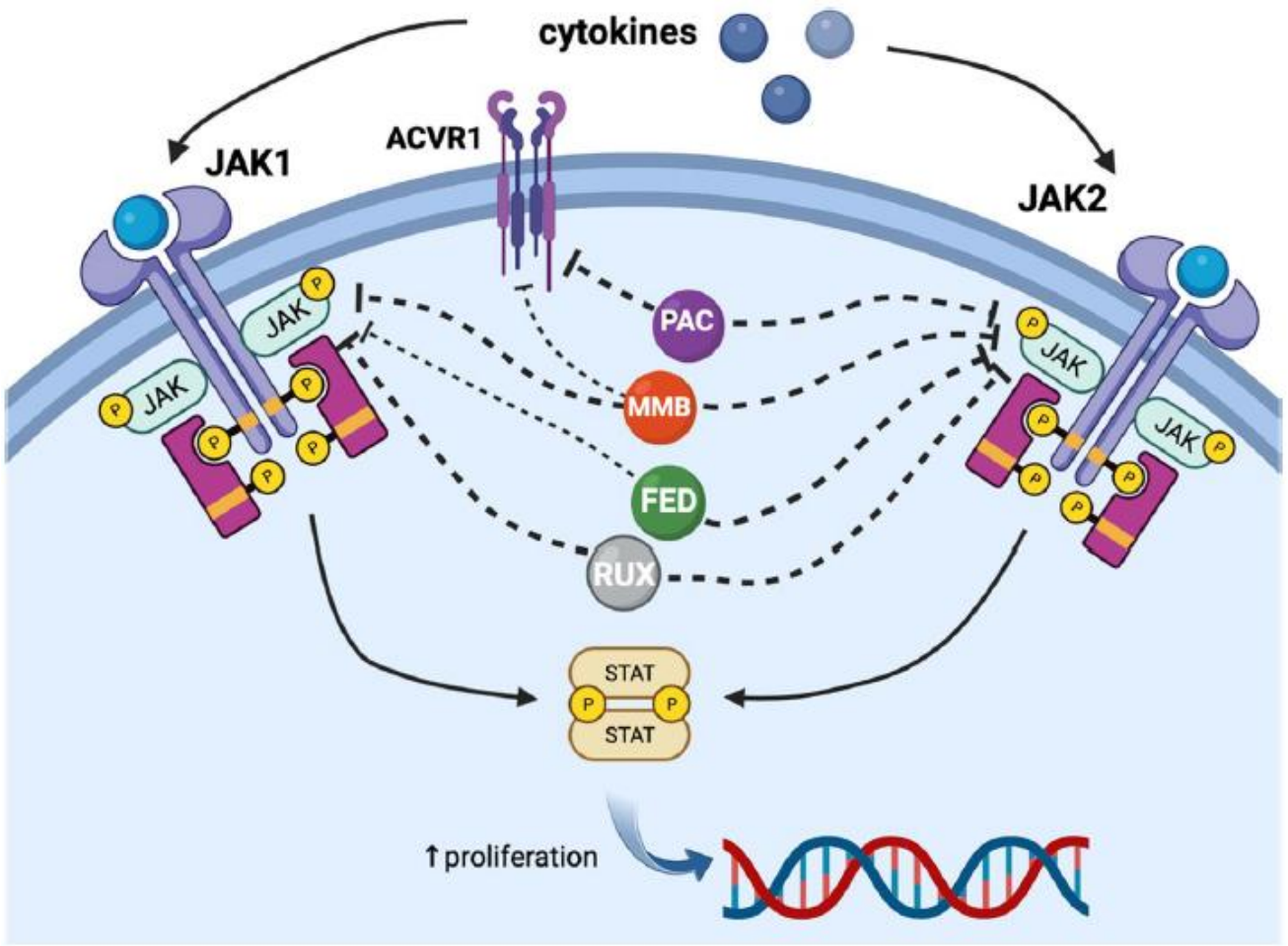
Kinase[1]	IC_{50} (nM)
JAK1	>1000
$JAK2^{wt}$	6.0
$JAK2^{V617F}$	9.4
JAK3	18.3
TYK2	27.0
FLT3-ITD	13.4
$FLT3^{D835Y}$	4.7
CSF1R	39.5
IRAK1	13.6

IC_{50}, half-maximal inhibitory concentration; **JAK**, Janus kinase; **TYK**, tyrosine kinase; **FLT**, FMS-like tyrosine kinase; **ITD**, internal tandem duplication; **CSF1R**, colony stimulating factor 1 receptor; **IRAK**, interleukin-1 receptor-associated kinase

PACIFICA | cti BIOPHARMA

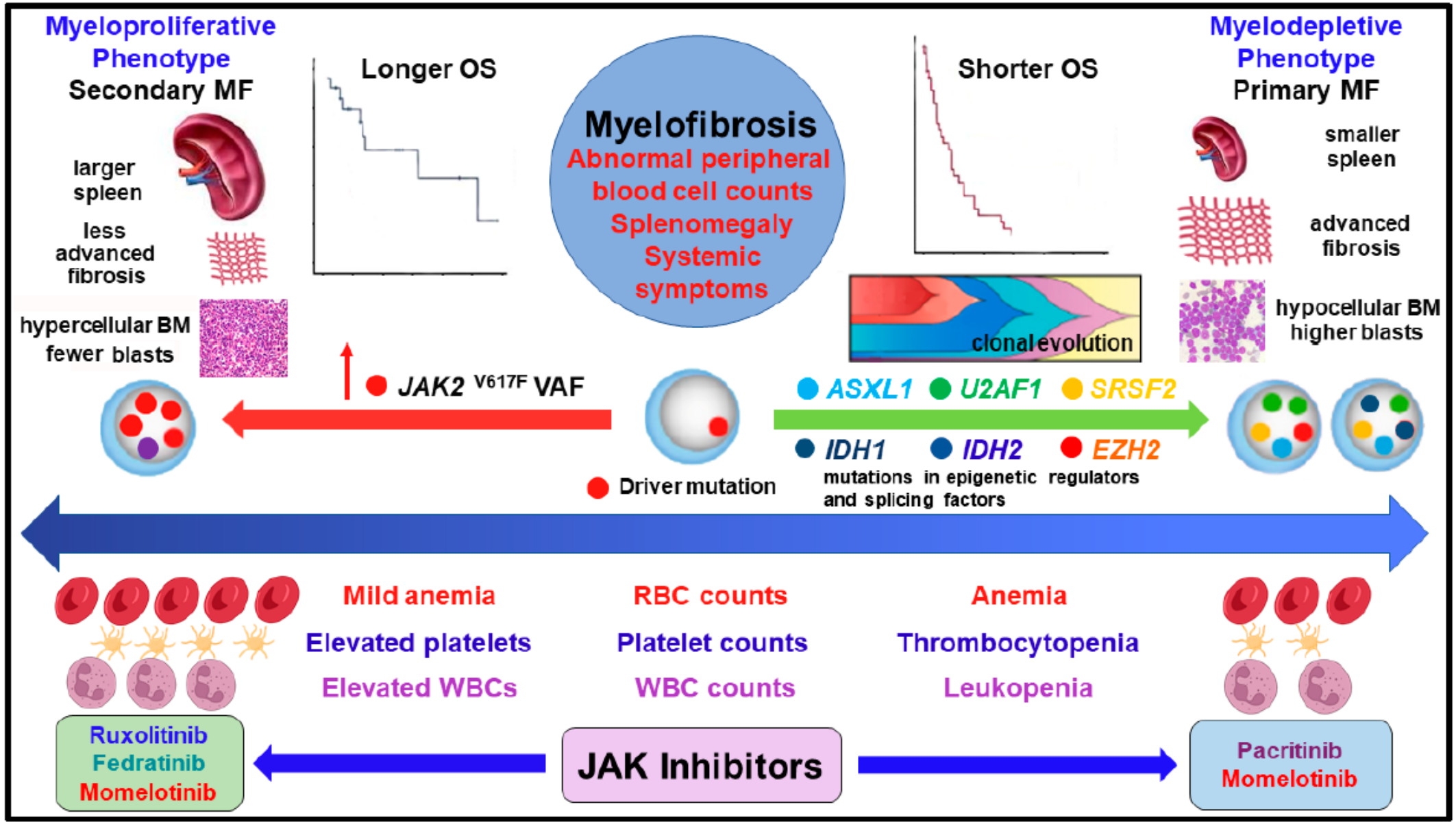
Singer et al. ASH, 2014, Abstract 1874.

Therapeutic Targets of JAK Inhibitors



PAC: pacritinib; MMB: momelotinib;
FED: fedratinib; RUX: ruxolitinib

Duminuco A, et al. *Curr Hematol Malig Rep.* 2023;18:176-189.



Chifotides HT, Verstovsek S, Bose P. *Cancers.* 2023;15:3331.

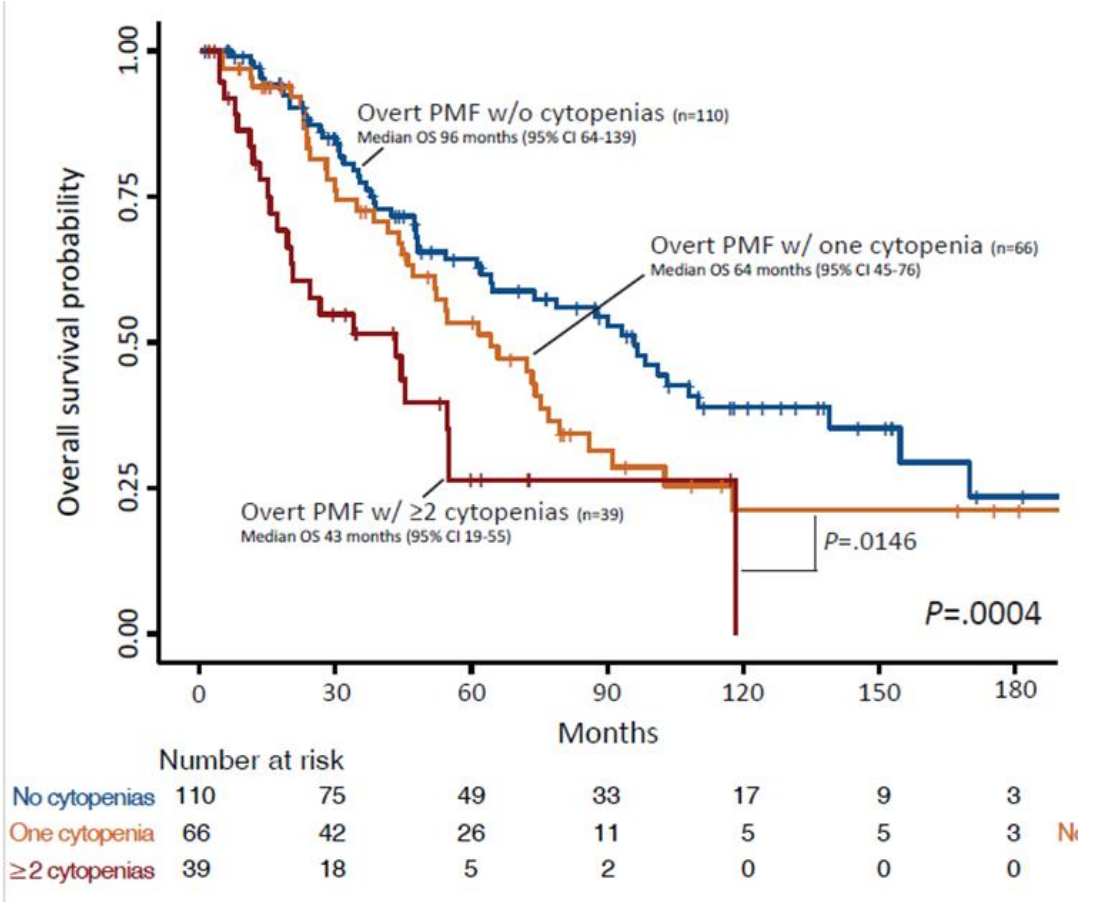
Cytopenic MF as More Aggressive

Cytopenic MF defined as **any one** of the following:

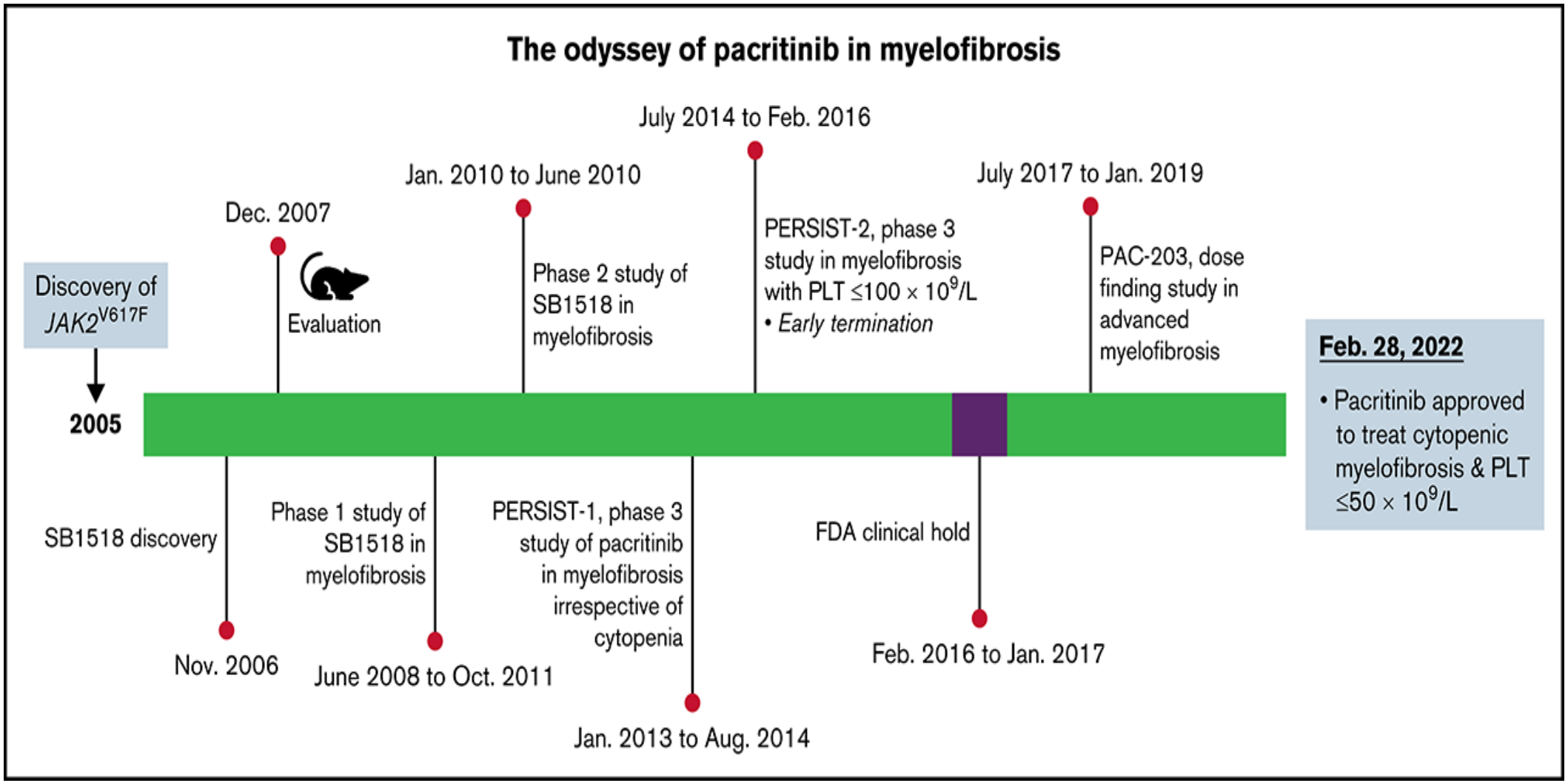
- Leukocytes <4 x 10^9/L
- Hemoglobin <11 g/dL (males) and <10 g/dL (females)
- Platelets <100 x 10^9/L

In overt PMF the impact on OS seemed to be affected mainly by the cytopenia severity, with anemia and thrombocytopenia having the greatest impact

Median survival ~ 14 months post ruxolitinib discontinuation<100K platelets



Coltro G, et al. *Blood Cancer J.* 2022;12:116.
Supplement to Coltro G, et al. *Blood Cancer J.* 2022;12:116.



Sangeetha Venugopal,John Mascarenhas, The odyssey of pacritinib in myelofibrosis, Blood Adv, 2022,

Pacritinib in MF: PERSIST Phase 3 Trials

PERSIST-1[a]

- Primary/secondary MF
- No exclusion for baseline plt
- No prior JAK2 inhibitors allowed

R 2:1

N = 327

Pacritinib
400 mg once daily

BAT
(excluding RUX)

- Primary endpoint (week 24): ≥35% SVR
- Secondary endpoint: ≥50% reduction in TSS

PERSIST-2[b]

- Primary/secondary MF
- Plt ≤100,000/mcL
- Prior JAK2 inhibitors allowed

R 1:1:1

N = 311

Pacritinib
400 mg once daily

Pacritinib
200 mg twice daily

BAT
(including RUX)

Coprimary endpoints (week 24): ≥35% SVR and ≥50% reduction in TSS

a. Mesa RA, et al. Lancet Haematol. 2017;4:e225-e236; b. Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659

PERSIST-1 Study

- PMF, PPV-MF, or PET-MF
- ≥ 18 y old
- Int-1, -2, or high risk (DIPSS)
- PB < 10%
- Palpable spleen ≥ 5 cm
- ANC > 500
- TSS ≥ 13
- ECOG PS ≤ 3
- No prior HCT or JAKi

N = 327

Stratified by DIPSS, PLT, geographic region

R
2:1

PAC 400 mg orally once daily
n = 220

BAT;
HU (57%) and no Rx (25%)
Excluded JAKi
n = 107

- Primary endpoint: Number of patients in whom SVR was ≥ 35% from BL to week 24 as measured by MRI (or CT scan in applicable patients)
- Key secondary endpoint: Proportion of patients with ≥ 50% reduction in TSS at week 24
- Proportion of patients with BL or severe thrombocytopenia in whom SVR was achieved

HU, hydroxyurea; Rx, prescribed medication.

Mesa R, et al. Lancet Haematol. 2017;4;e225-e236

PERSIST-1: Patient and Disease Characteristics

Parameter	PAC (n = 220)	BAT (n = 107)
Age, median (range), y	67 (60 to 73)	65 (59 to 72)
Male/Female, %	57/43	56/44
Disease subtype, %		
PMF	65	55
PPV-MF	22	31
PET-MF	12	14
Int-1 risk, %	56	46
Int-2 risk, %	29	40
High risk, %	15	14
PLT count < 50,000	16	15
PLT count 50 to < 100,000	17	17
PLT count ≥ 100,000	67	68
Median spleen volume, cm^3	2005.6	2152.7
Jak2 v6717f positive (%)	70	86

Mesa R, et al. Lancet Haematol. 2017;4;e225-e236

PERSIST-1: Endpoints

≥ 35% SVR at Week 24

	ITT, n/N (%)			Evaluable, n/N (%)		
	PAC	BAT	*P* value	PAC	BAT	*P* value
Overall	42/220 (19)	5/107 (5)	.0003	42/168 (25)	5/85 (6)	.0001
PLT count						
< 100,000/μL	12/72 (17)	0/34	.0086	12/51 (24)	0/24	.0072
< 50,000/μL	8/35 (23)	0/16	.045	8/24 (33)	0/11	.037

≥ 50% Reduction in TSS

	Week 24			Week 48		
	PAC	BAT	*P* value	PAC	BAT	*P* value
Overall	19/100 (19)	5/48 (10)	.24	15/100	0/48	.0027
PLT count						
< 100,000/μL	7/28 (25)	1/13 (8)	.40	3/28 (11)	0/13	.54
< 50,000/μL	3/11 (27)	0/5	.51	2/11 (18)	0/5	> .99

Mesa R, et al. Lancet Haematol. 2017;4;e225-e236

PERSIST-I: Safety

Adverse Reactions	PAC (n = 220)		BAT (n = 106)	
	All Grades, %	Grade 3/4, %	All Grades, %	Grade 3/4, %
Diarrhea	55	5	10	0
Nausea	27	1	7	0
Anemia	24	17	20	15
Thrombocytopenia	17	11	14	11
Vomiting	16	1	6	0
Fatigue	10	2	9	1
Abdominal pain	10	1	9	0
Peripheral edema	8	<1	12	1

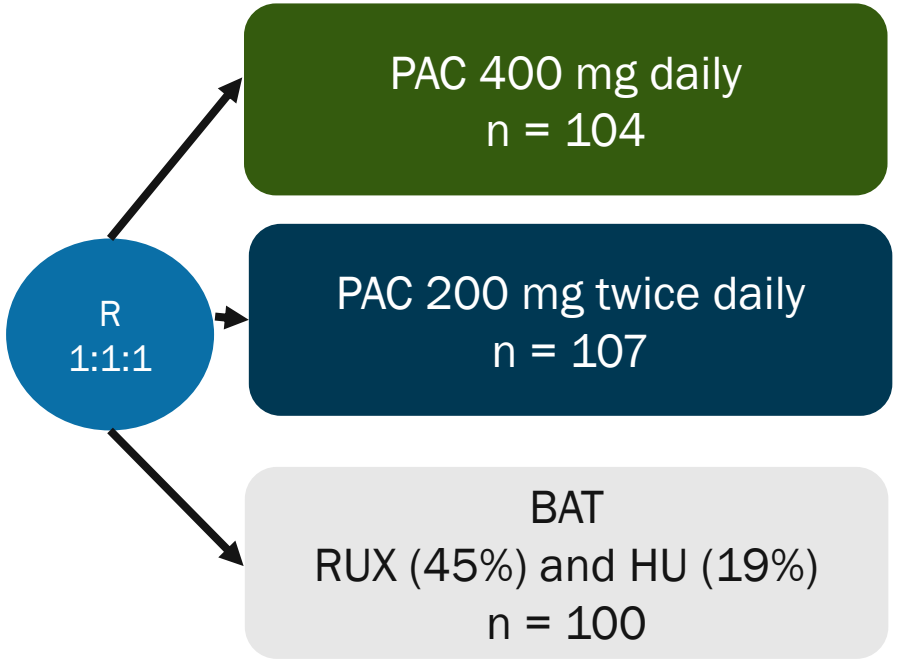
Mesa R, et al. Lancet Haematol. 2017;4;e225-e236

PERSIST-2 Study

Phase 3, randomized, international, multicenter study

- PMF, PPV-MF, or PET-MF
- Int-1, -2, or high risk (DIPSS)
- Palpable spleen > 5 cm
- PB < 10%
- ANC > 500
- PLT count ≤ 100,000
- ECOG PS ≤ 3
- TSS ≥ 13
- Prior Rx with JAKi allowed

N = 311

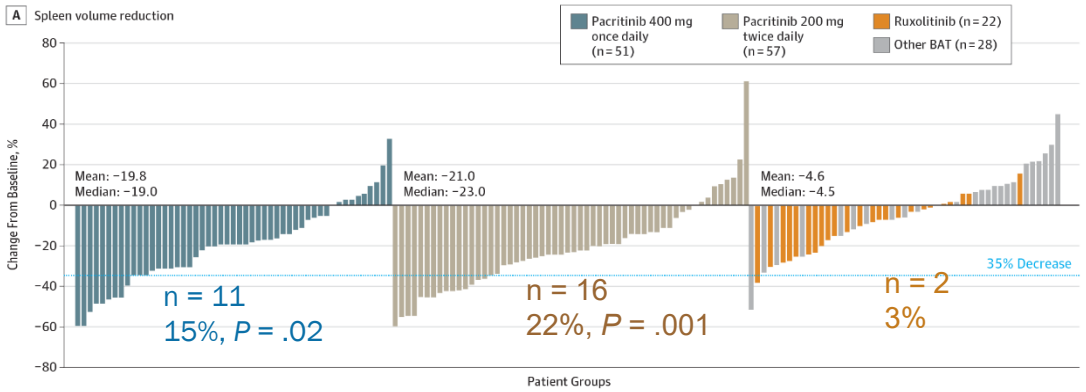


- Primary endpoint: ≥ 35% SVR from BL to week 24 as measured by MRI (or CT scan in applicable patients) and ≥ 50% reduction in TSS from BL to week 24 (MFSAF 2.0) powered to compare PAC as pooled group
- Key secondary endpoint: Compare efficacy of PAC 400 daily vs 200 twice daily vs BAT

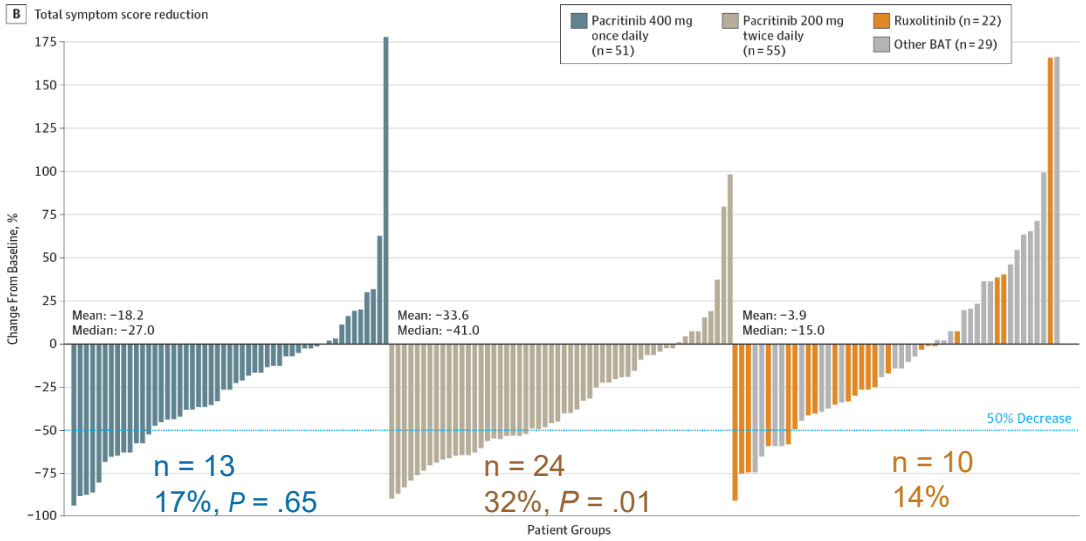
Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

PERSIST-2: Endpoints

N = 27
18%, *P* = .001

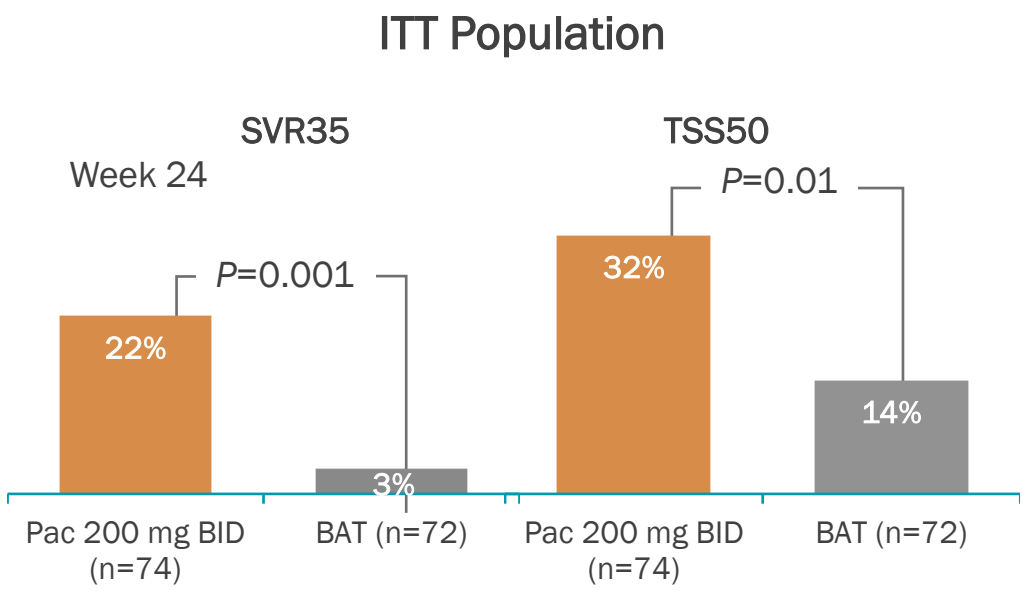


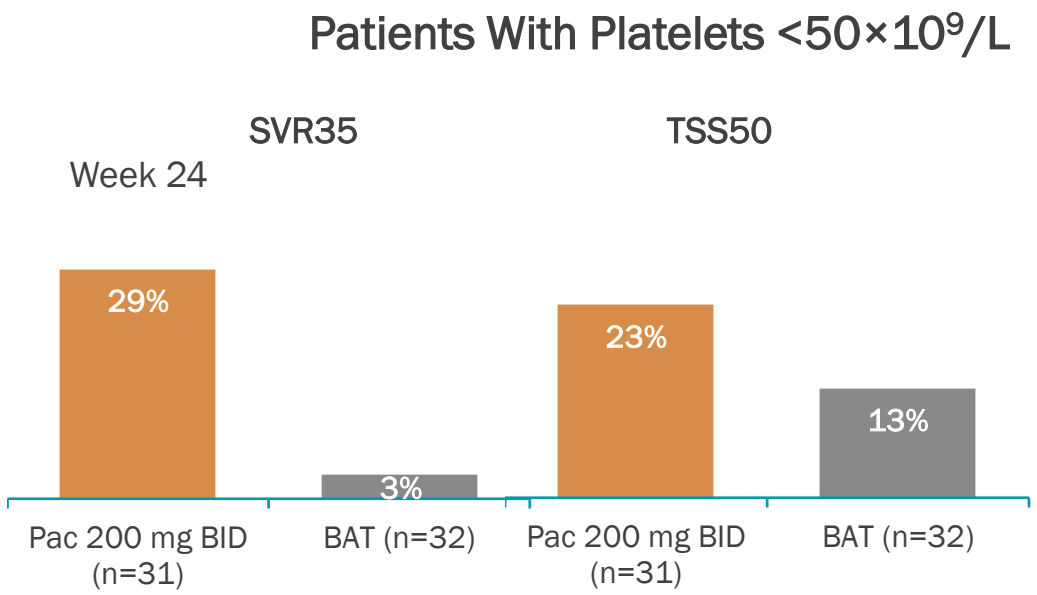
N = 37
25%, *P* = .08



Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

PERSIST-2: Spleen/Symptom Response





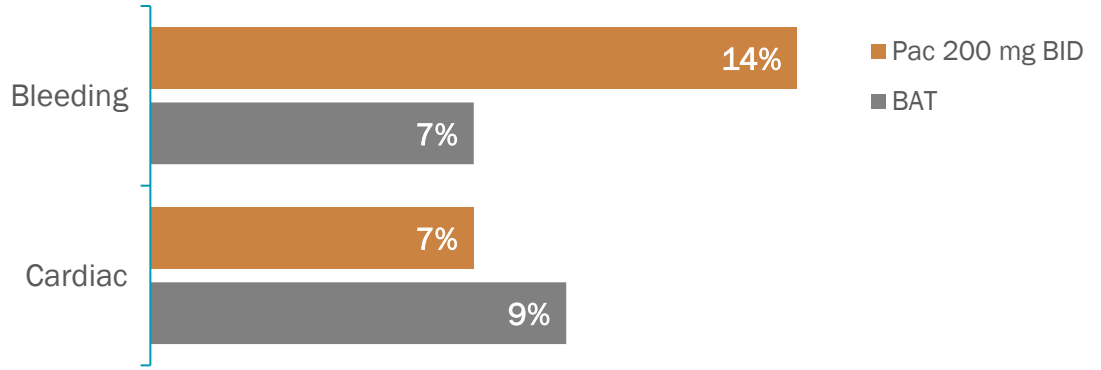
Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659.

PERSIST-2: Adverse Event Profile[1]

Adverse Reactions	Pac 200 mg BID (n=106)	BAT (n=98)
Any grade AEs in ≥15% of patients in either arm, %		
Diarrhea	48	15
Thrombocytopenia	34	23
Nausea	32	11
Anemia	24	15
Peripheral edema	20	15
Vomiting	19	5
Fatigue	17	16
Grade ≥3 AEs in ≥5% of patients in either arm, %		
Thrombocytopenia	32	18
Anemia	22	14
Neutropenia	7	5
Pneumonia	7	3
Serious AEs in ≥3% of patients in either arm, %		
Anemia	8	3
Thrombocytopenia	6	2
Pneumonia	6	4
Congestive heart failure	4	2

- Diarrhea with pacritinib most often occurred during weeks 1-8, was manageable, and resolved within 1-2 weeks
- Neurological AEs and opportunistic infections rarely reported with pacritinib

Grade ≥3 Events (Pooled[a])

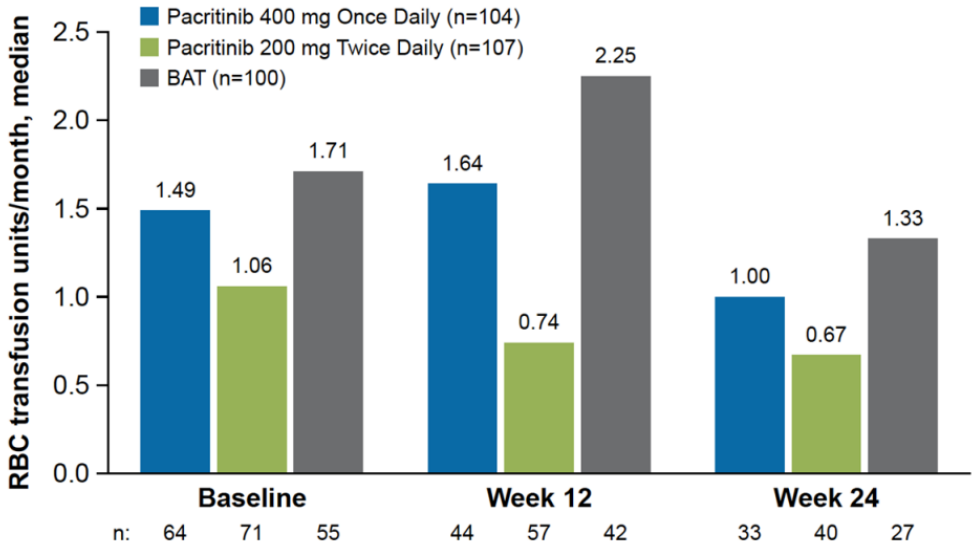


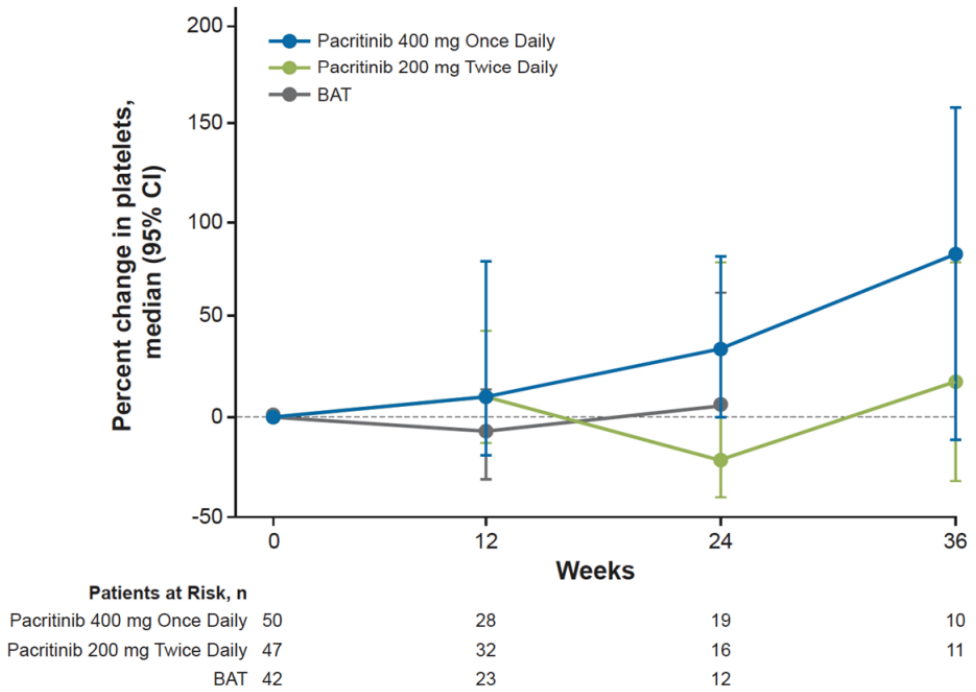
- Full clinical hold had been placed on pacritinib by the FDA due to concerns over bleeding and cardiovascular events and deaths on PERSIST-1 and -2; this hold was subsequently lifted and pacritinib is now approved for use in patients with platelets <50×10^9/L[2,3]

[a] Pooled, per standardized MedDRA queries.

1. Mascarenhas J, et al. *JAMA Oncol*. 2018;4(5):652-659. 2. CTI BioPharma Announces Removal Of Full Clinical Hold On Pacritinib. Updated January 5, 2017. Accessed August 1, 2022. https://investors.ctibiopharma.com/news-releases/news-release-details/cti-biopharma-announces-removal-full-clinical-hold-pacritinib/ 3. CTI BioPharma Announces FDA Accelerated Approval of VONJO™ (pacritinib) for the Treatment of Adult Patients with Myelofibrosis and Thrombocytopenia. Updated February 28, 2022. Accessed August 1, 2022. https://investors.ctibiopharma.com/news-releases/news-release-details/cti-biopharma-announces-fda-accelerated-approval-vonjotm/

PERSIST-2: RBC Transfusions Over Time And Platelets



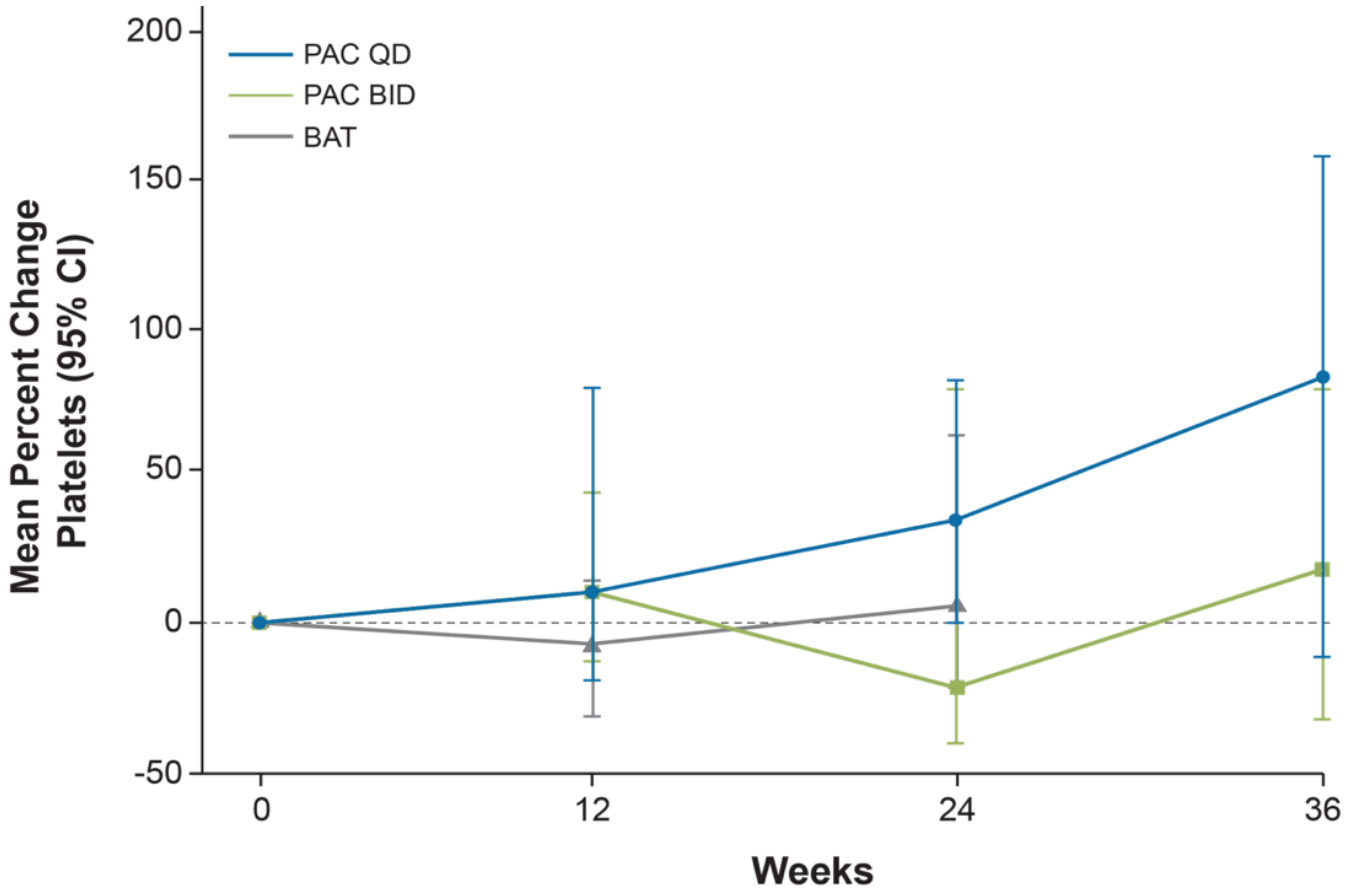


Among patients not RBC transfusion-independent at baseline	
Proportion of patients w/ reduced RBC transfusion burden at week 24	• Pacritinib BID: 22% (8/26) • BAT: 9% (8/36)

Mascarenhas J, et al. *JAMA Oncol*. 2018;4:652-659.

PERSIST-2 % Change in PLT Count: BL PLT Count < 50,000/µL*

*Based on central laboratory values.

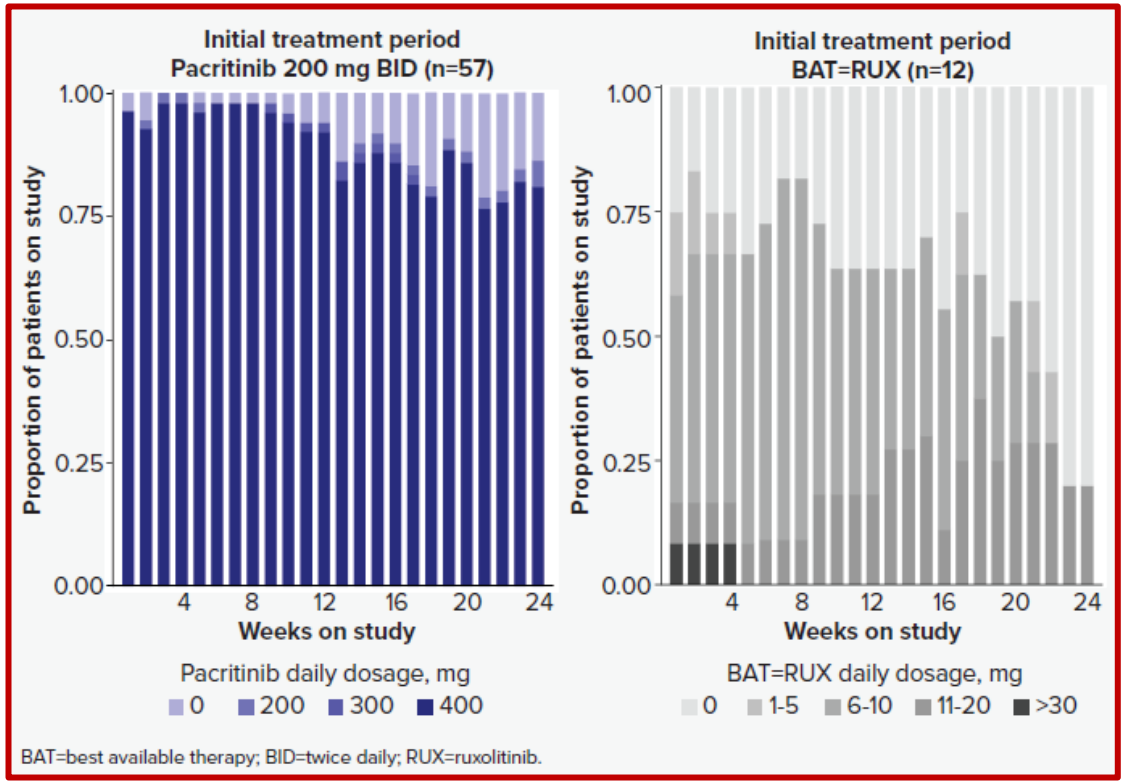


Paitents at Risk				
PAC QD	50	28	19	10
PAC BID	47	32	16	11
BAT	42	23	12	

Mascarenhas J, et al. JAMA Oncol. 2018;4:652-659.

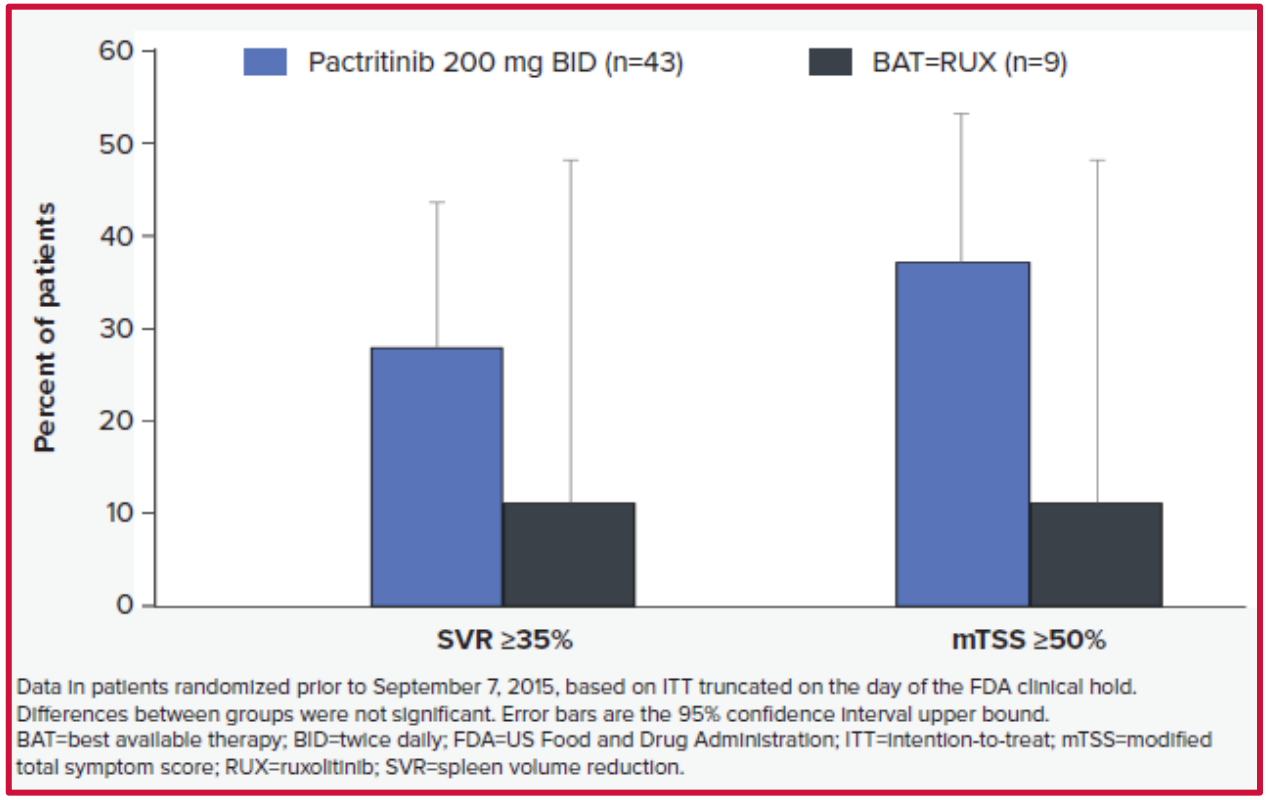
PERSIST-2: PAC vs. RUX in RUX-naïve pts

- The majority of patients treated with pacritinib were able to maintain full doses over time at weeks 12 and 24
  - (median dose = 400 mg/day)
- By contrast, patients on ruxolitinib received:
  - a median starting dose of 10 mg (interquartile range [IQR] 10-10 mg) daily at baseline
  - 10 mg (IQR, 0-10 mg) daily at week 12
  - 10 mg (IQR, 0-20 mg) daily at week 24



PERSIST-2: PAC vs. RUX in RUX-naïve pts

- Patients treated with pacritinib had numerically higher rates of SVR (28% vs 11%) and mTSS response (37% vs 11%) compared with patients treated with ruxolitinib.



Data in patients randomized prior to September 7, 2015, based on ITT truncated on the day of the FDA clinical hold. Differences between groups were not significant. Error bars are the 95% confidence interval upper bound.
BAT=best available therapy; BID=twice daily; FDA=US Food and Drug Administration; ITT=intention-to-treat; mTSS=modified total symptom score; RUX=ruxolitinib; SVR=spleen volume reduction.

Pacritinib Is a Potent ACVR1 Inhibitor

- **Pacritinib is ~4x more potent** than momelotinib against ACVR1

	+ Control LDN 193189[a]	PAC C_{max} 213 nM	MMB C_{max} 168 nM	FED C_{max} 275 nM	RUX C_{max} 47 nM
Replicate 1 ACVR1 IC_{50} (nM)	**20.4**	**22.6**	**70.2**	**312.0**	**>1000**
Replicate 2 ACVR1 IC_{50} (nM)	**32.4**	**10.8**	**34.9**	**235.0**	**>1000**
Mean ACVR1 IC_{50} (nM)	**26.4**	**16.7**	**52.6**	**273.5**	**>1000**
Potency[b] (C_{max}:IC_{50})	**N/A**	**12.7**	**3.2**	**1.0**	**<0.01**

Legend

Higher potency

Lower potency

[a]LDN 193189 is an ACVR1 inhibitor.

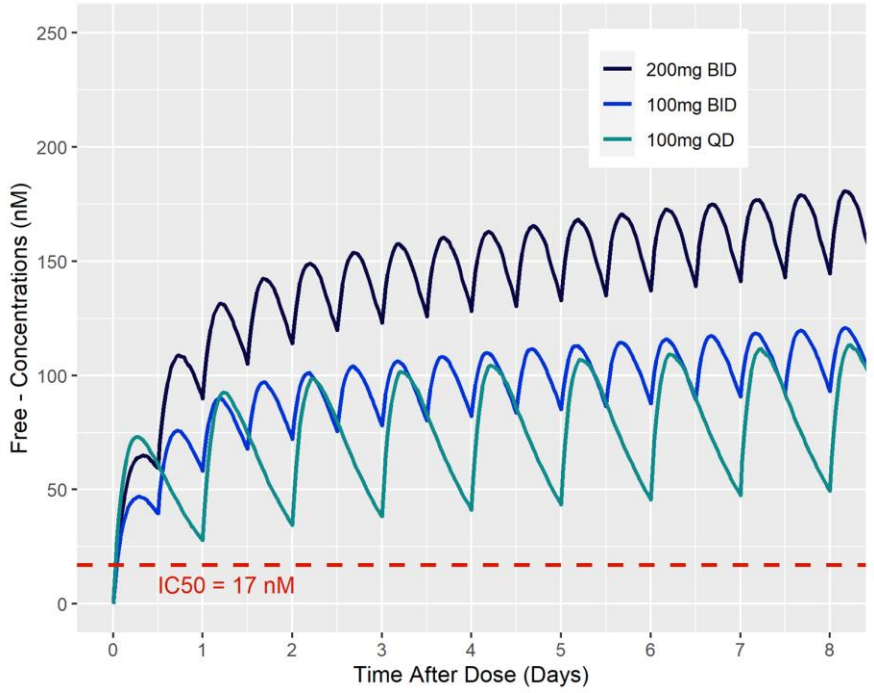
[b]C_{max} is the maximum unbound plasma concentration at the clinical recommended dose in humans.

ACVR1= Activin A receptor type 1; FED=fedratinib; IC_{50}=half maximal inhibitory concentration; MOM=momelotinib; PAC=pacritinib; RUX=ruxolitinib.

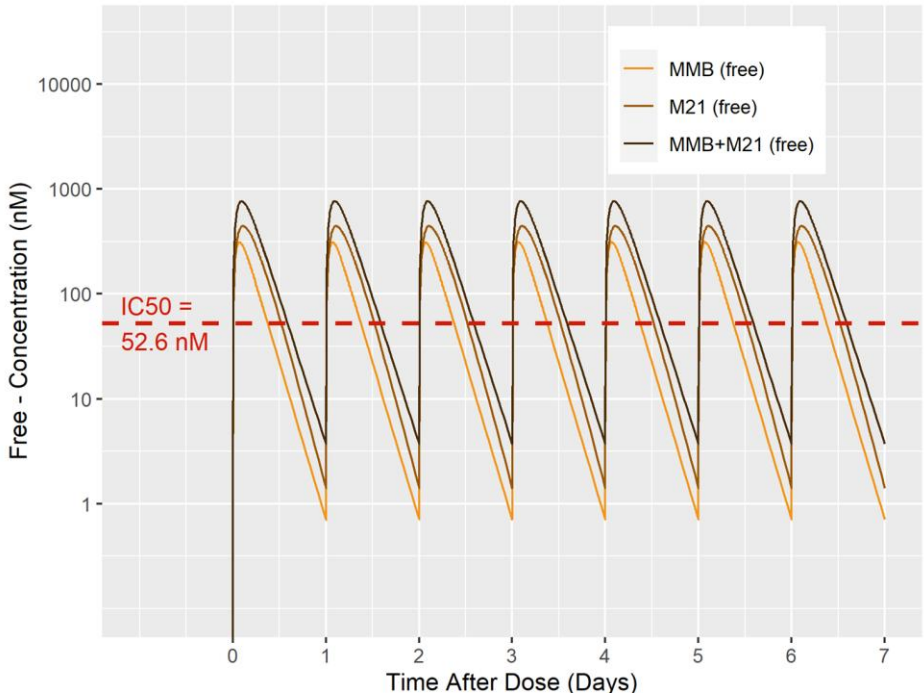
Pacritinib Is a Potent ACVR1 Inhibitor

- Pacritinib concentration exceeds ACVR1 IC_{50} **100% of the time at all dose levels**
- Momelotinib concentration exceeds ACVR1 IC_{50} **55% of the time only** (accounting for both momelotinib and its metabolite [M21])

Pacritinib Concentration-Time Curve



Momelotinib Concentration-Time Curve



ACVR1= Activin A receptor type 1; BID=twice daily; IC_{50}=half maximal inhibitory concentration; MMB=momelotinib; QD=once daily.

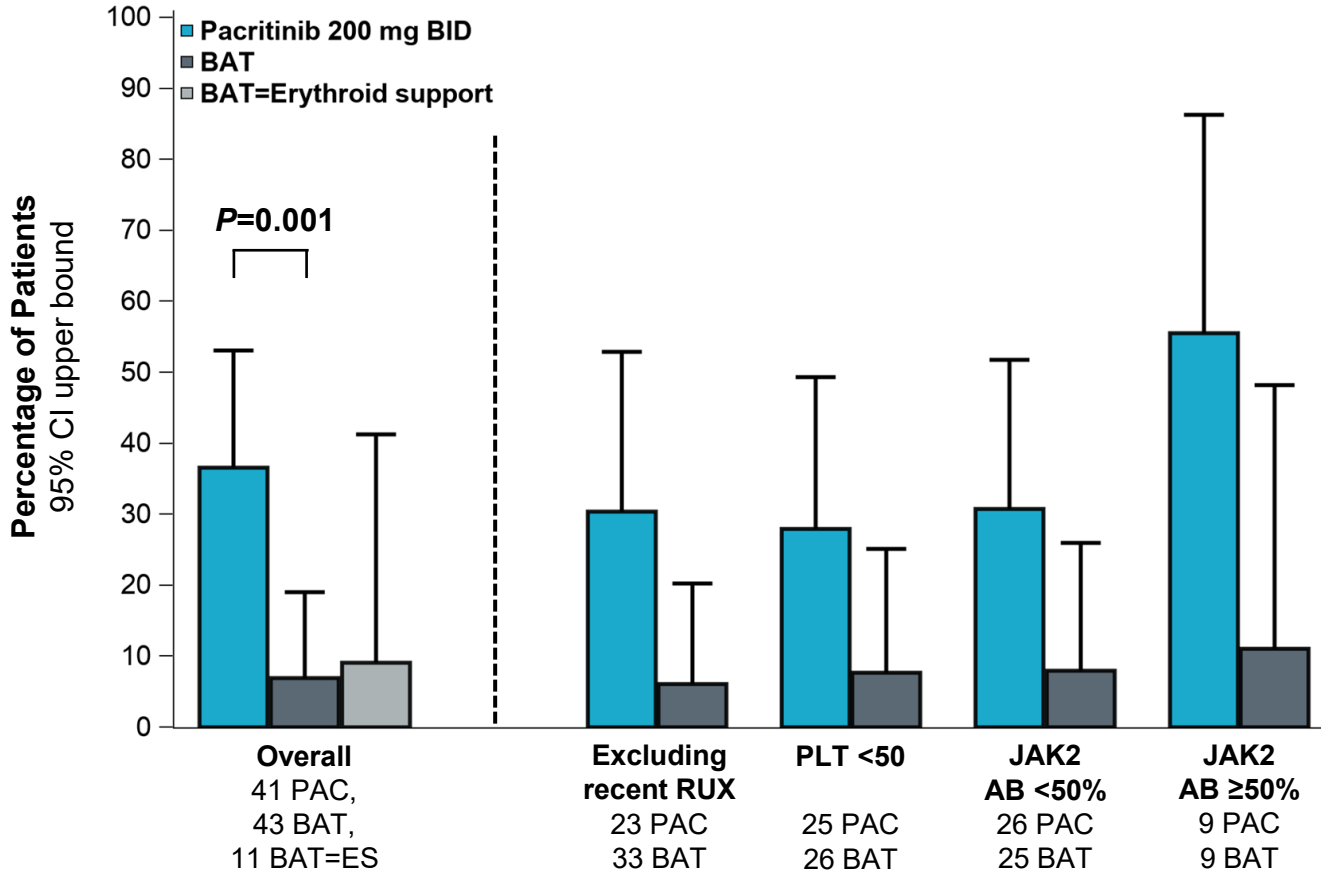
More Pacritinib Patients Achieved TI (Gale)

TI Conversion Rate

Pacritinib N=41	BAT N=43	*P*-value
37%	7%	0.001

- TI conversion better on pacritinib than BAT, including patients receiving erythroid support agents as BAT
  - Erythroid support agents were prohibited on the pacritinib arm

Rate of TI (Gale criteria) through Week 24



AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX=no ruxolitinib in prior 30 days; TI=transfusion independence.

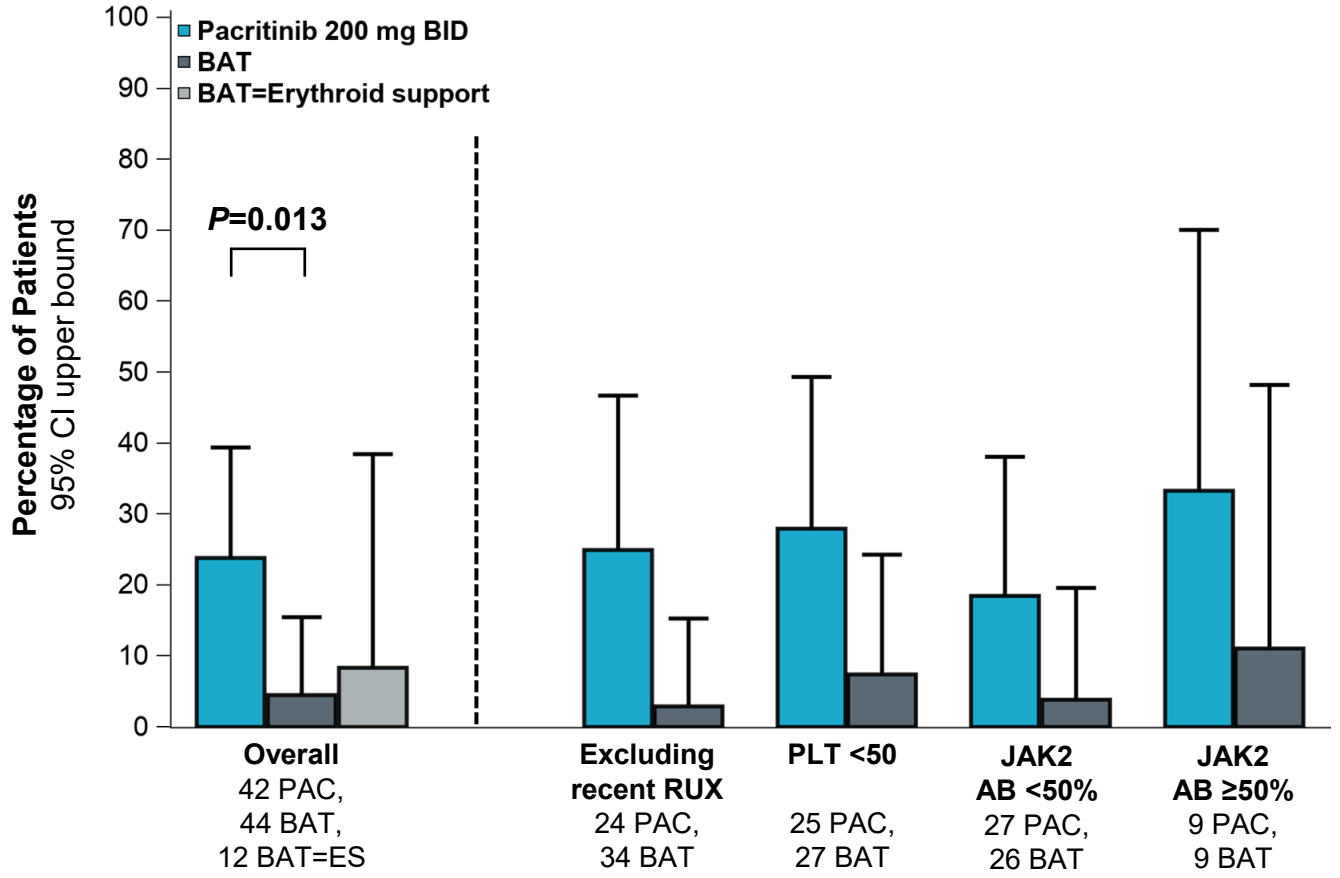
More Pacritinib Patients Achieved TI (SIMPLIFY)

TI Conversion Rate

Pacritinib N=42	BAT N=44	*P*-value
24%	5%	0.013

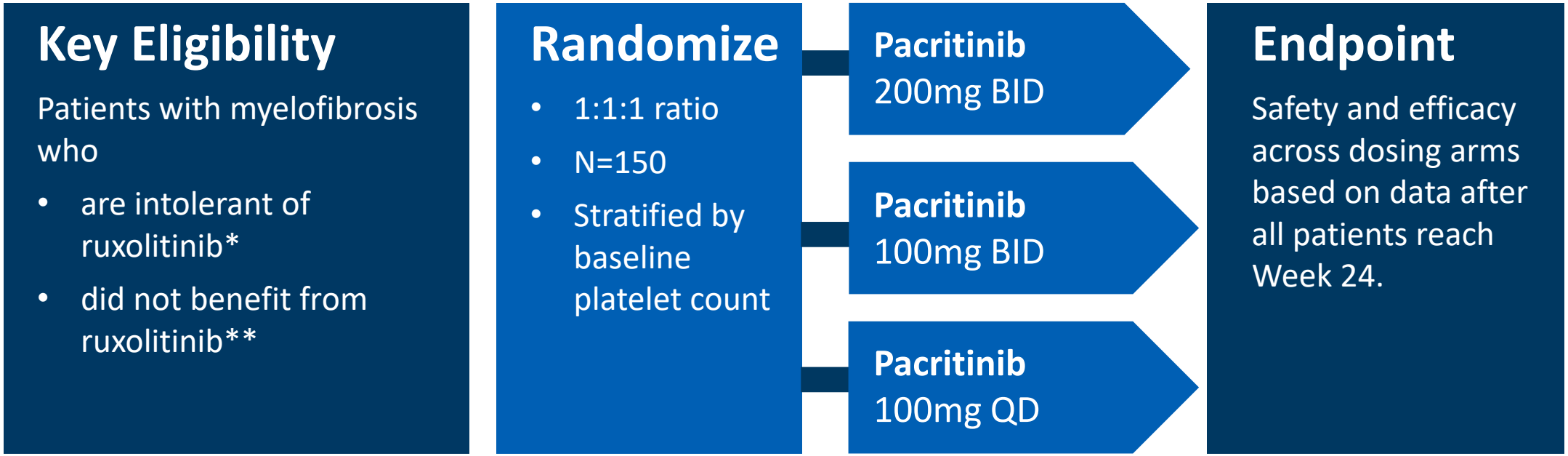
- Similar results based on SIMPLIFY criteria for TI

Rate of TI (SIMPLIFY criteria) through Week 24



AB=allele burden; BAT=best available therapy; ES=erythroid support; JAK=Janus associated kinase; PAC=pacritinib; PLT=platelets; recent RUX=no ruxolitinib in prior 30 days; TI=transfusion independence.

PAC203 Schema



* **Intolerance**: ruxolitinib for ≥28 days complicated by development of red cell transfusion requirement or grade ≥ 3 anemia, thrombocytopenia, or hemorrhage while on <20mg BID

** **Failure to benefit**: ruxolitinib for ≥3 months with <10% spleen volume reduction or <30% decrease in spleen length, or regrowth to these parameters

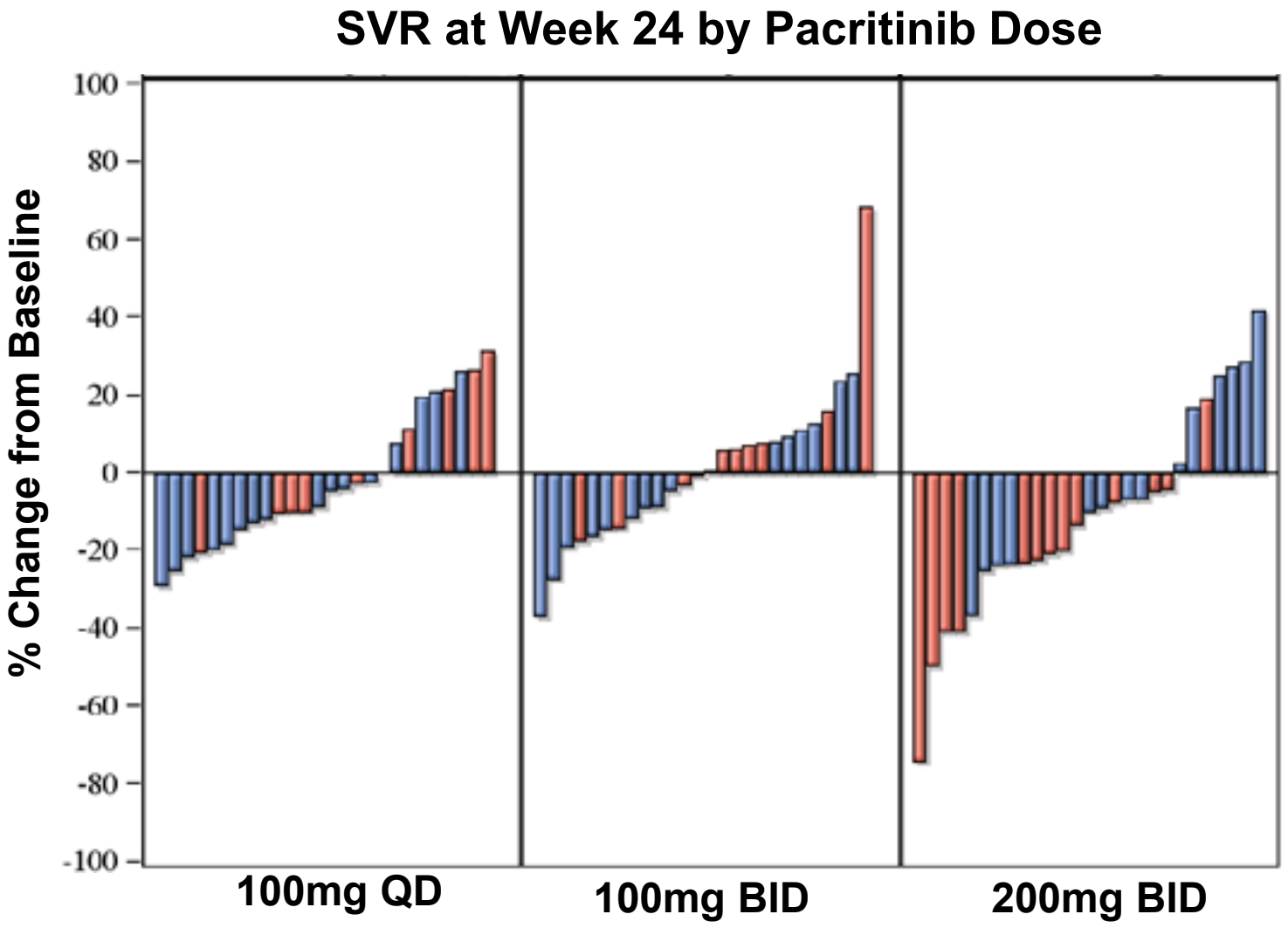
PAC203 Patient Characteristics

Characteristic	All Doses (N=161)
Age (years [median, IQR])	**69 (64-73)**
Platelets (/μL [median, IQR])	**55,000 (36,000-102,000)**
Hemoglobin <10g/dL (%)	**71%**
Peripheral Blasts ≥1% (%)	**58%**
Ruxolitinib duration (years [median, IQR])	**1.7 (0.6-3.3)**
Ruxolitinib exposure Treatment failure Intolerance Both	 **76%** **73%** **50%**
Molecular risk (N=110) High Molecular Risk[1,2] TP53 mutation	 **41%** **7.3%**
Mutations per patient[2] (mean, IQR)	**2.5 [1.25-3.75]**

IQR, inter-quartile range

[1] Tefferi et al. MIPSS70+ Version 2.0: Mutation and Karytype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. J Clin Oncol. 2018;36(17):1769-70.
[2] O'Sullivan et al. Molecular Analysis in the Pacritinib Dose-Finding PAC203 Study in Patients with Myelofibrosis Refractory or Intolerant to Ruxolitinib. ASH 2019 abstract #4214.

Spleen Volume Response (SVR) at Week 24



Dose Group	Patients with ≥35% SVR
100mg QD	0/52 (0%)
100mg BID	1/55 (1.8%)
200mg BID PLT <50,000/μL	5/54 (9.3%) 4/24 (17%)

Baseline platelet level

- <50,000/μL
- ≥50,000/μL

Symptom Improvement at Week 24

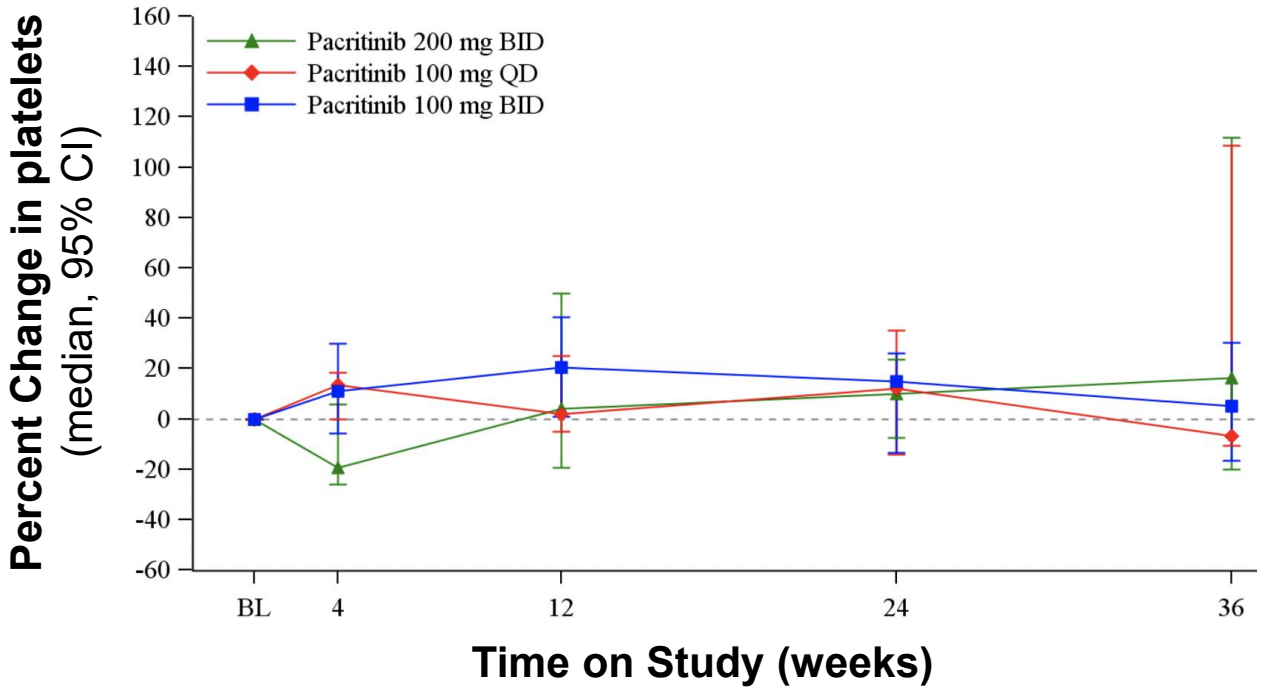
Patients with improvement Total Symptom Score (TSS) at Week 24

Dose Group	≥50% TSS reduction	Median TSS reduction (IQR)
100mg QD	4/52 (7.7%)	-3% (-30% to 29%)
100mg BID	4/55 (7.3%)	-16% (-44% to 1%)
200mg BID	4/54 (7.4%)	-27% (-39% to 1%)

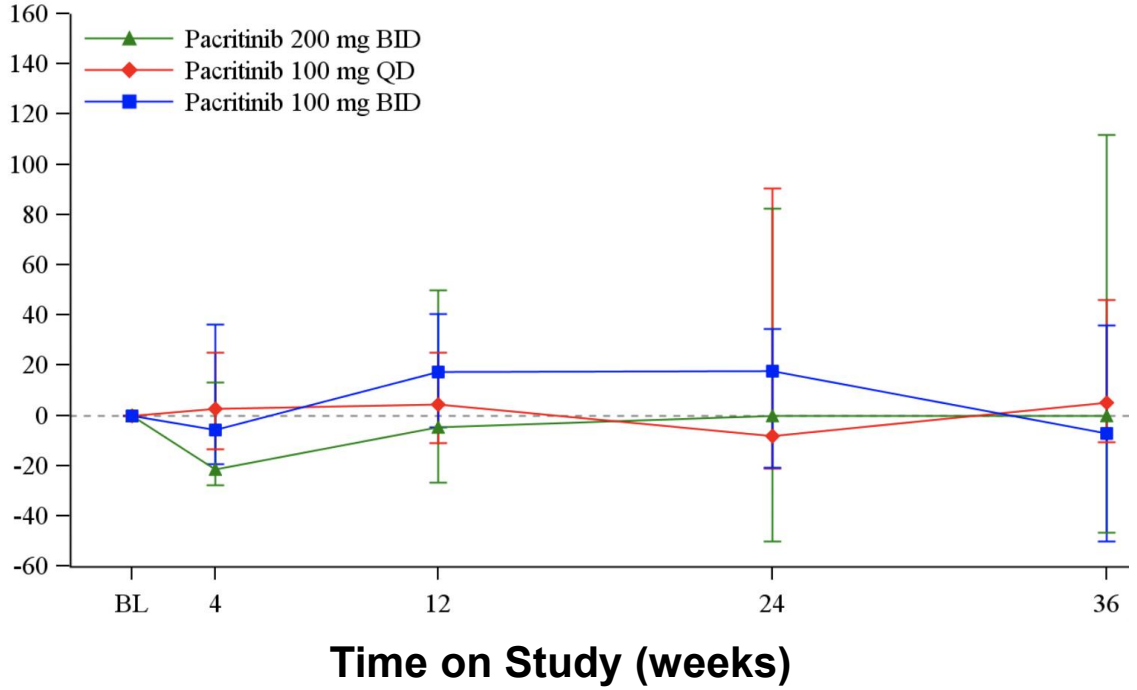
IQR, inter-quartile range

Platelet Count Stability on Study

Overall population



Baseline platelet count <50,000/μL



Dose Arm	Number of subjects									
100mg QD	53	49	38	26	14		24	24	20	13	9
100mg BID	52	44	37	22	11		23	23	16	8	4
200mg BID	55	49	42	24	16		24	23	19	9	6

Treatment-Emergent Adverse Events (>12%)

TEAE Term*	100mg QD N=52	100mg BID N=55	200mg BID N=54
Diarrhea	10 (**19.2%**)	12 (**21.8%**)	16 (**29.6%**)
Thrombocytopenia**	11 (**21.2%**)	12 (**21.8%**)	22 (**40.7%**)
Nausea	12 (**23.1%**)	11 (**20.0%**)	15 (**27.8%**)
Fatigue	9 (**17.3%**)	13 (**23.6%**)	13 (**24.1%**)
Abdominal pain	9 (**17.3%**)	6 (**10.9%**)	13 (**24.1%**)
Pyrexia	8 (**15.4%**)	9 (**16.4%**)	7 (**13.0%**)
Anemia	5 (**9.6%**)	6 (**10.9%**)	13 (**24.1%**)
Peripheral edema	7 (**13.5%**)	5 (**9.1%**)	9 (**16.7%**)
Decreased appetite	6 (**11.5%**)	4 (**7.3%**)	10 (**18.5%**)

* All events reported regardless of relatedness
** Includes terms '*thrombocytopenia*' and *'platelet count decrease*'

Comparison of TEAEs on PAC203 and PERSIST

Hemorrhagic Event Grade	PAC203 200mg BID N=54	PERSIST-2 200mg BID N=106	PERSIST-2 BAT N=98
Grade 3	5.6%	14.2%	7.1%
Grade 4	0	0	1.0%
Grade 5	1.9%	1.9%	0

Cardiac Event Grade	PAC203 200mg BID N=54	PERSIST-2 200mg BID N=106	PERSIST-2 BAT N=98
Grade 3	3.7%	4.7%	5.1%
Grade 4	0	1.9%	2.0%
Grade 5	0	0	4.1%

BAT, Best Available Therapy (included 19% of patients receiving "**watch and wait**" only)

Events determined by Standard MedDRA Query (SMQ).