THE LANCET
Haematology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Mesa RA, Vannucchi AM, Mead A, et al. Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial. *Lancet Haematol* 2017; published online March 20. http://dx.doi.org/10.1016/S2352-3026(17)30027-3.

Supplementary Appendix

Investigator List

Study Site	Principal Investigator	Patients Randomized, n
First Republican Clinical Hospital of Ministry of Health of the Udmusrt Republic	Alexander Suvorov	14
Kaposi Mor Okato Korhaz	Miklos Egyed	14
SZTE II. Sz Belgyogyoszati Klinika es Kardiologiai Kozpont	Zita Borbenyi	14
Bekes Megyei Pandy Kalman Korhaz	Janos Jakucs	13
Haematology and Oncology Clinics of Australia	Andrew Perkins	12
Royal Hobart Hospital	Ritam Prasad	10
Semmelweis Egyetem AOK	Judit Demeter	10
Faculty Hospital Brno-Bohunice	Jiri Mayer	10
Andrew Love Cancer Centre	Philip Campbell	9
Canterbury District Health Board	Peter Ganly	8
CHU Caremeau Nimes	Eric Jourdan	7
CHU Purpan	Chrisitan Recher	7
Debreceni Egyetem Orvos-es Egesz Segtudomanyi Centrum Belgyogyasazati Intezet	Arpad Illes	7
Van Megyei Markusovszky Korhoz Nonprofit Zrt	Janos Laszlo Ivanyi	7
North Shore Hospital	Anna Elinder-Camburn	7
Republican Hospital n.a. V.A. Baranov	Aleksandr Myasnikov	7
University Hospital Maastricht	Harry Schouten	6
Erasmus MC	Peter te Boekhorst	6
University Medical Center Utrecht	Reinier Raymakers	6
Haematology Research Center	Elena Lukina	6
CHU Amiens Picardie	Jean Pierre Marolleau	6
Russian Research Institute of Haematology & Transfusiology	Kudrat Mugutdinovich Abdulkadyrov	6
Gosford Hospital	Campbell Tiley	6
Box Hill Hospital	Paul Coughlin	5
Hospital St. Louis	Jean-Jacques Kiladjian	5
Military Medical Academy n.a. S Kirov	Vadim Vitalievich Tyrenko	5
Volgograd Regional Clinical Oncology Dispensary #1	Kamil Kaplanov	5
Ospedale “Infermi”, Rimini	Patrizia Tosi	5
The Christie NHS Foundation Trust	Tim Somervaille	5
Cardiff University/Hospital of Wales	Steven Knapper	5
Guys and St Thomas – NHS Foundation Trust	Claire Harrison	5
Faculty Hospital Olomouc	Karel Indrak	5
Dunedin Hospital	Shingirai Chiruka	4
Saint-Petersburg State Medical University n.a. academician I.P. Pavlov	Boris Afanasyev	4
Samara Regional Clinical Hospital n.a. M.I.Kalinin	Victor Rossiev	4
Hammersmith Hosp – ICH NHS Trust	Dragana Milojokovic	4
Coffs Harbour Health Campus	Martin Browne	4
Dipartimento di Oncoematologia	Fabio Ciceri	4
University Hospital Pilsen	Pavel Jindra	3
Istituto di Ematologia L. & A. Seragnoli	Giovanni Martinelli	3
San Gerardo Hospital	Carlo-Gambacorti-Passerini	3
VU University Medical Center	Sonja Zweegman	3
Hematology-Oncology Associates of Northern Jersey	Charles Farber	3
ZNA – Stuivenberg	Pierre G G B J Zachee	3
Hospital Claude Huriez	Nathalie Cambier	3
Hopital Haut-Leveque	Axelle Lascaux	3
Jasz-Nagykun-Szolnok	Gyorgy Ujj	3
Oxford University Hospitals NHS Trust	Adam Mead	3
University of Florence, Hospital Careggi	Alessandro Vannucchi	3
CHU de Strasbourg	Shanti Natarajan-Ame	2
ZNA – Middelheim	Dr. De Bock	2
Centre Hospitalier de Jolimont-Lobbes	Nicole Straetmans	2
Upstate Oncology Associates	Fahd Quddus	2
Bàcs-Kiskun Megyei Kórház Szegedi Tudományegyetem	Mihaly Gurzo	2
Azienda Ospedaliera di Padova	Maria Randi	2
Addenbrookes Hospital	Anthony Green	2
Klinik I fur Innere Medizin, Universitat Koln	Christof Scheid	2
Municipal Health Care Institution Sochi Oncology Dispensary No2	Dmitriy Petrovich Udovitsa	2

AZ Sint Jan Brugge-Oostende AV	Jan van Droogenbroeck	1
Cliniques Universitaires Saint-Luc	Laurent Knoops	1
CHU de Caen	Khaled Benabed	1
Centre Hospitalier Lyon Sud	Fiorenza Barraco	1
S.C. Ematologia, A.O. Arcispedale Santa Maria Nuova-IRCCS	Alessia Tieghi	1
Birmingham Heartlands Hospital	Jo Ewing	1
Gemeinschaftspraxis Hämatologie/Onkologie	Thomas Illmer	1
University Hospital Leipzig	Dietget Niederwieser	1
Waikato Hospital	Shadul Islam	1
Mayo Clinic Arizona	Ruben A Mesa	0
Central Clinical Hospitital #2 n.a. Semashko	Andrey Gubkin	0
University of Munster	Tim Sauer	0
Universitatsklinikum Essen	Juergen Novotny	0
University of Nebraska	Krishna Gundabolu	0
Städtisches Klinikum München GmbH	Meinolf Karthaus	0
Universitatsklinikum Mainz	Thomas Kindler	0
Campus Virchow, Charite, Humboldt University, Berlin	Phillipp Le Coutre	0
The Royal Bournemouth Hospital	Joseph Chacko	0
Uniklinik Freiburg	Nikolas von Bubnoff	0
Institute of Haematoogy and Blood Transfusion	Jiri Schwarz	0
Centre Hospitalo Universitaire de Grenoble	Jean-Yves Cahn	0
Centre Hospitalier de Lens	Brigitte Dupriez	0
Hopital St Antoine	Nicole Casadevall	0

Supplementary Table 1. Six Common Symptoms Across MPN-SAF TSS Versions.

TSS (Original Version)	TSS 2·0
Fatigue (weariness, tiredness)	Tiredness
Filling up quickly when you eat (early satiety)	Filling up quickly when you eat (early satiety)
Abdominal discomfort	Abdominal discomfort
Inactivity*	Inactivity*
Problems with concentration – compared to prior to my MPD	NA
Night sweats	Night sweats
Itching (pruritus)	Itching (pruritus)
Bone pain (diffuse not joint pain or arthritis)	Bone pain (diffuse not joint pain or arthritis)
Fever (>100° F)	NA
Unintentional weight loss last 6 months	NA
NA	Pain under ribs on the left side

*Inactivity is not counted in TSS.

MPD, myeloproliferative disorder; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; NA, not applicable; TSS, total symptom score.

Supplementary Table 2. Distribution of Risk Factors at Baseline by Randomized Treatment and Baseline White Blood Cell (WBC) Risk Group.

Other Risk Factors at Baseline, n (%)	WBC>25,000/µL		WBC≤25,000/µL	
	Pacritinib (n=43)	BAT (n=26)	Pacritinib (n=177)	BAT (n=80)
Peripheral blood blasts ≥1%	29 (67·4)	11 (42·3)	83 (46·9)	36 (45·0)
Platelet count <100,000/µL	18 (41·9)	6 (23·1)	54 (30·5)	27 (33·8)
Hemoglobin <10 g/dL	19 (44·2)	7 (26·9)	65 (36·7)	40 (50·0)
MF Fibrosis Grade >1	40 (93·0)	19 (73·1)	140 (79·1)	64 (80·0)
Age >65 years	30 (69·8)	12 (46·2)	96 (54·2)	37 (46·3)
Number of risk factors, n (%)				
6	8 (18·6)	0	0	0
5	8 (18·6)	5 (19·2)	9 (5·1)	3 (3·8)
4	14 (32·6)	5 (19·2)	32 (18·1)	18 (22·5)
3	9 (20·9)	5 (19·2)	38 (21·5)	15 (18·8)
2	4 (9·3)	7 (26·9)	49 (27·7)	25 (31·3)
1	0	1 (3·8)	24 (13·6)	11 (13·8)
0	0	0	9 (5·1)	4 (5·0)
Missing	0	3 (12)	16 (9·0)	4 (5·0)

.BAT, best available therapy.

Supplementary Table 3. Most Common Treatments in the BAT Arm.

WHO Drug Term, n (%)	BAT (n=106)		BAT (n=106)
Watchful waiting (no active treatment)	27 (25·5)		
Hydroxyurea	60 (56·6)	Anagrelide	1 (0·9)
Prednisone	7 (6·6)	Azacitidine	1 (0·9)
Interferon alfa	7 (6·6)	Epoetin alfa	1 (0·9)
Thalidomide	6 (5·7)	Epoetin theta	1 (0·9)
Danazol	4 (3·8)	Everolimus	1 (0·9)
Prednisolone	4 (3·8)	Lenalidomide	1 (0·9)
Busulfan	2 (1·9)	Mercaptopurine	1 (0·9)
Cytarabine	2 (1·9)	Methotrexate	1 (0·9)
Peginterferon alfa-2a	2 (1·9)	Vincristine	1 (0·9)

BAT, best available therapy.

Supplementary Table 4. Demographic and Disease Characteristics With Apparent Imbalances Across BAT Therapies

Characteristic, n (%)	Watch and Wait Only (n=27)	Hydroxyurea Only (n=40)	Other (n=40)
Age ≥65 years	11 (40·7)	17 (42·5)	27 (67·5)
Male sex	15 (55·6)	20 (50·0)	25 (62·5)
ECOG PS 2-3	4 (14·8)	1 (2·5)	6 (15·0)
Hypocellular (<20%) bone marrow	5 (18·5)	5 (12·5)	7 (17·5)
JAK2^{V617F}-positive	23 (85·2)	38 (95·0)	31 (77·5)
Platelet count			
<50,000/μL	6 (22·2)	4 (10·0)	6 (15·0)
≥50,000 to <100,000/μL	8 (29·6)	2 (5·0)	8 (20·0)
Primary myelofibrosis	19 (70·4)	16 (40·0)	24 (60·0)
Anemia	21 (77·8)	19 (47·5)	30 (75·0)
Current DIPSS intermediate-2 or high	16 (59·3)	17 (42·5)	25 (62·5)
RBC-TD (Gale criteria)	6 (22·2)	3 (7·5)	6 (15·0)

BAT, best available therapy; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; RBC-TD, red blood cell transfusion-dependent.

Supplementary Table 5. Spleen Volume Reduction (SVR) at Week 24 by Treatment and Baseline *JAK2* Status

Treatment	Baseline *JAK2* Status	Percent SVR at Week 24				
		n	Mean (SD)	Median (IQR)	Min	Max
Pacritinib	JAK2^{WT}	58	-24.3 (19·80)	-24·5 (-34·0, -13·0)	-76·0	38·0
	JAK2^{V617F}	109	-23·4 (16·92)	-23·0 (-35·0, -14·0)	-67·0	39·0
BAT	JAK2^{WT}	42	-5·9 (18·73)	-5·0 (-15·0, 7·0)	-51·0	47·0
	JAK2^{V617F}	42	5·4 (15·13)	3·0 (-5·0, 17·0)	-27·0	41.0

BAT, best available therapy; WT, wild type.

Supplementary Table 6. Reductions in Allele Burden

Treatment	n	Mean	Std Dev	Median	Q1	Q3	Min	Max
Pacritinib	154	-34·4	39·87	-31·6	-57·5	-7·5	-100·0	101·3
BAT	89	-11·1	42·12	-10·4	-28·0	0·4	-100·0	200·0

BAT, best available therapy; Std Dev; standard deviation; Q, quartile.

Supplementary Table 7. Proportion of Patients Achieving ≥50% Reduction in TSS at Week 24 by TSS Version.

Patients Achieving ≥50% TSS Reduction, n/N (%) [95% CI]	TSS (Original Version)			TSS 2.0		
	Pacritinib	BAT	P value	Pacritinib	BAT	P value
All Patients	36/120 (30·0) [22·0-39·0]	3/59 (5·1) [1·1-14·1]	<0.0001	19/100 (19·0) [11·8-28·1]	5/48 (10·4) [3·5-22·7]	0.24
Platelets <100,000/μL	11/44 (25·0) [13·2-40·3]	2/21 (9·5) [1·2-30·4]	0.19	6/28 (21·4) [8·3-41·0]	1/13 (7·7) [0·2-36·0]	0.40
Platelets <50,000/μL	4/24 (16·7) [4·7-37·4]	1/11 (9·1) [0·2-41·3]	1.0	2/11 (18·2) [2·3-51·8]	0/5 (0.0) [0·0-52·2]	1.0
Platelets ≥100,000/μL	25/76 (32·9) [22·5-44·6]	1/38 (2·6) [0·1-13·8]	0.0001	13/72 (18·1) [1·00-28·9]	4/35 (11·4) [3·2-26·7]	0.57

BAT, best available therapy; TSS, total symptom score.

Supplementary Table 8. Summary of Patient Global Impression of Change by TSS Version in Evaluable Patients at Week 24.

Patient Global Impression of Change, n (%)	TSS (Original Version)		TSS 2·0	
	Pacritinib (n=76)	BAT (n=33)	Pacritinib (n=68)	BAT (n=35)
Very much improved	9 (11·8)	0	9 (13·2)	0
Much improved	32 (42·1)	4 (12·1)	22 (32·4)	2 (5·7)
Minimally improved	19 (25·0)	5 (15·2)	25 (36·8)	3 (8·6)
No change	10 (13·2)	16 (48·5)	7 (10·3)	24 (68·6)
Minimally worse	5 (6·6)	5 (15·2)	5 (7·4)	6 (17·1)
Much worse	1 (1·3)	3 (9·1)	0	0
Very much worse	0	0	0	0

BAT, best available therapy, TSS, total symptom score.

Supplementary Table 9. Mean Change From Baseline in Individual Symptom Scores.

Percentage change, mean* (IQR) [range]	Week 24			Week 48		
	Pacritinib (n=146)	BAT (n=73)	BAT Crossover† (n=56)	PAC (n=99)	BAT (n=6)	BAT Crossover† (n=22)
Worst fatigue/tiredness	-21 (-50,-3) [-100, 279]	+48 (-26, 32) [-100, 2850]	+5 (-17, 8) [-66, 233]	-25 (-61, -2) [-100, 144]	+5 (-33, 53) [-100, 112]	-15 (-29, 4) [-94, 31]
Early satiety	-35 (-73, -3) [-100, 148]	+4 (-27, 22) [-100, 313]	-16 (-46, 7) [-100, 76]	-42 (-99, -11) [-100, 200]	+86 (-21, 192) [-42, 312]	-35 (-74, -6) [-100, 55]
Abdominal discomfort	-26 (-83, -4) [-100, 600]	+82 (-32, 27) [-100, 3436]	+10 (-45, 6) [-98, 736]	-30 (-84, -26) [-100, 600]	+48 (-88, 62) [-98, 338]	-8 (-41, 2) [-97, 136]
Night sweats	-53 (-100, -35) [-100, 600]	+101 (-34, 47) [-100, 2025]	-25 (-82, 0) [-100, 185]	-55 (-100, -36) [-100, 133]	+96 (-71, 102) [-100, 536]	-27 (-66, 20) [-100, 100]
Pruritus	-33 (-89, 7) [-100, 470]	+39 (-49, 28) [-100, 1250]	+16 (-80, 12) [-100, 1369]	-52 (-100, -39) [-100, 250]	+198 (56, 315) [56, 315]	-18 (-84, 0) [-100, 104]
Bone pain	-24 (-97, 4) [-100, 509]	+4 (-36, 39) [-100, 242]	-14 (-28, 2) [-100, 70]	-14 (-100, -1) [-100, 653]	-65 (-97, -35) [-100, -4]	0 (-23, 46) [-100, 68]

*Green indicates improvement from baseline; red indicates worsening from baseline.
†From time of crossover.
BAT, best available therapy.

Supplementary Table 10. Correlation of Overall Survival with Spleen Volume Reduction at Week 24

	Pacritinib (n=220)		BAT (n=107)	
	n	HR (95% CI)	n	HR (95% CI)
SVR, %				
≥35	42	0·234 (0·113-0·485)	5	0·000 (0·000-NR)
20 to <35	60	0·246 (0·133-0·454)	6	1·851 (0·551-6·216)
≥10 to <20%	38	0·387 (0·207-0·726)	15	0·922 (0·317-2·676)
<10%	80	Reference	81	Reference

BAT, best available therapy; SVR, spleen volume reduction.

Supplementary Table 11. Deaths on Study.

Cause of Death	Events, n
Pacritinib arm	**76**
≤24 weeks	**11**
>24 weeks	**65**
Disease progression	28
Adverse event	28
Disease progression	6
Pneumonia	3
Cardiac failure acute	2
Acute myeloid leukemia	2
Pneumonia aspiration	1
Renal failure, acute	1
Multiorgan failure	1
Hemorrhage	1
Traumatic intracranial hemorrhage	1
Shock	1
Hypoxia	1
Cardiopulmonary arrest	1
Cardiac arrest	1
Sudden death	1
Head injury	1
Sepsis	1
Myocardial infarction	1
Hepatic failure	1
Cardiac failure congestive	1
Other	20
BAT arm	**29**
≤24 weeks	**7**
>24 weeks	**22**
Disease progression	8
Adverse event (during initial study phase)	3
Disease progression	1
Cardiac failure	1
Sepsis	1
Adverse event (after crossover)	11
Sudden death	2
Pneumonia	2
Status epilepticus	1
Disseminated intravascular coagulation	1
Splenic rupture	1
Disease progression	1
Hemorrhage intracranial	1
Acute leukemia	1
Metastatic squamous cell carcinoma	1
Other	7

Supplementary Table 12. Multivariate Cox Model of OS

Covariates in the final model	HR (95% CI)
Baseline platelet count (per 100 unit of 10^9/L)	0·785 (0·685-0·899)
Baseline hemoglobin (per 10 unit g/L)	0·827 (0·752-0·910)
Baseline WBC (per 10 unit of 10^9/L)	1·229 (1·132 -1·334)
Age (per 10 years)	1·463 (1·161-1·843)

All variables assessed: DIPSS risk, platelet count, hemoglobin, white blood cells (WBCs), RBC-transfusion dependency, primary vs secondary myelofibrosis, JAK2 mutation status, time from diagnosis, myelofibrosis fibrosis grade, ECOG PS, age.

Supplementary Table 13. Hematologic Toxicities at Baseline and Worst Grade, Through Week 24 or Initial Treatment Discontinuation

	Pacritinib (n=220)					BAT (n=106)				
	Baseline grade					Baseline grade				
	0	**1**	**2**	**3**	**4**	**0**	**1**	**2**	**3**	**4**
Hemoglobin, n (%)*	**n=62**	**n=74**	**n=71**	**n=13**	**n=0**	**n=33**	**n=26**	**n=30**	**n=16**	**n=0**
Grade 0	36 (58·1)	6 (8·1)	1 (1·4)	1 (7·7)	0	19 (57·6)	2 (7·7)	1 (3·3)	1 (6·3)	0
Grade 1	13 (21·0)	27 (36·5)	13 (18·3)	2 (15·4)	0	4 (12·1)	11 (42·3)	4 (13·3)	1 (6·3)	0
Grade 2	0	22 (29·7)	27 (38·0)	1 (7·7)	0	1 (3·0)	1 (3·8)	7 (23·3)	2 (12·5)	0
Grade 3	0	1 (1·4)	9 (12·7)	2 (15·4)	0	0	1 (3·8)	2 (6·7)	6 (37·5)	0
Grade 4	0	0	0	0	0	0	0	0	0	0
Grade 5	0	0	0	0	0	0	0	0	0	0
Platelet count, n (%)*	**n=119**	**n=39**	**n=16**	**n=21**	**n=13**	**n=59**	**n=19**	**n=5**	**n=6**	**n=10**
Grade 0	69 (58·0)	7 (17·9)	1 (6·3)	0	0	27 (45·8)	2 (10·5)	0	0	0
Grade 1	15 (12·6)	10 (25·6)	1 (6·3)	2 (9·5)	0	2 (3·4)	6 (31·6)	0	0	0
Grade 2	2 (1·7)	6 (15·4)	0	2 (9·5)	0	1 (1·7)	2 (10·5)	0	0	1 (10·0)
Grade 3	1 (0·8)	3 (7·7)	4 (25·0)	7 (33·3)	2 (15·4)	0	2 (10·5)	3 (60·0)	1 (16·7)	1 (10·0)
Grade 4	1 (0.8)	0	0	2 (9·5)	4 (30.8)	0	0	0	0	5 (50·0)
Grade 5	0	0	0	0	0	0	0	0	0	0

*Green indicates ≥1 grade improvement from baseline; red indicates a ≥1 grade worsening from baseline.
BAT, best available therapy.

Supplementary Table 14. Most Common Adverse Events and Hematologic Toxicities With Pacritinib at Any Time on Study

All grade in >10% or grade 3 in >2% of Patients, n (%)	Pacritinib (n=220)				
	Grade 1/2	Grade 3	Grade 4	Grade 5	All
Diarrhea	127 (57·7)	16 (7·3)	0	0	143 (65·0)
Nausea	67 (30·5)	3 (1·4)	0	0	70 (31·8)
Anemia	10 (4·5)	48 (21·8)	9 (4·1)	0	67 (30·5)
Thrombocytopenia	14 (6·4)	16 (7·3)	21 (9·5)	0	51 (23·2)
Vomiting	41 (18·6)	6 (2·7)	0	0	47 (21·4)
Fatigue	28 (12·7)	5 (2·3)	0	0	33 (15·0)
Abdominal pain	24 (10·5)	6 (2·7)	0	0	30 (13·6)
Peripheral edema	24 (10·9)	1 (0·5)	0	0	25 (11·4)
Pneumonia	8 (3·6)	12 (5·5)	2 (0·9)	3 (1·4)	25 (11·4)
Pyrexia	14 (6·4)	5 (2·3)	0	0	19 (8·6)
Hypertension	5 (2·3)	6 (2·7)	0	0	11 (5·0)
Leukopenia	2 (0·9)	5 (2·3)	2 (0·9)	0	9 (4·1)
Cardiac failure	3 (1·4)	6 (2·7)	0	0	9 (4·1)
Febrile neutropenia	0	5 (2·3)	0	0	5 (2·3)
Hematologic Toxicity Worst Grade, n (%)*	**Baseline grade**				
	0	**1**	**2**	**3**	**4**
Hemoglobin	**n=62**	**n=74**	**n=71**	**n=13**	**n=0**
Grade 0	33 (53·2)	1 (1·4)	0	0	0
Grade 1	21 (33·9)	22 (29·7)	3 (4·2)	0	0
Grade 2	8 (12·9)	36 (48·6)	26 (36·6)	1 (7·7)	0
Grade 3	0	15 (20·3)	40 (56·3)	12 (92·3)	0
Grade 4	0	0	0	0	0
Grade 5	0	0	0	0	0
Platelet count	**n=119**	**n=39**	**n=16**	**n=21**	**n=13**
Grade 0	69 (58·0)	4 (10·3)	0	0	0
Grade 1	34 (28·6)	10 (25·6)	0	0	0
Grade 2	9 (7·6)	14 (35·9)	6 (37·5)	1 (4·8)	0
Grade 3	3 (2·5)	10 (25·6)	7 (43·8)	8 (38·1)	0
Grade 4	2 (1.7)	1 (2·6)	3 (18·8)	12 (57·1)	12 (92.3)
Grade 5	0	0	0	0	0

*Green indicates ≥1 grade improvement from baseline; red indicates a ≥1 grade worsening from baseline.
AE, adverse event; BAT, best available therapy.
Additional grade 4 or 5 adverse events with pacritinib: neutropenia (6 gr 4), bone marrow failure (1 gr 4), thrombocytosis (1 gr 4), cardiac failure congestive (1 gr 4, 1 gr 5), pericardial effusion (1 gr 4), gastric varices hemorrhage (1 gr 4), gastrointestinal hemorrhage (1 gr 4), esophageal hemorrhage (1 gr 4), disease progression (2 gr 4, 5 gr 5), portal hypertension (1 gr 4), anaphylactoid reaction (1 gr 4), lobar pneumonia (1 gr 4), sepsis (2 gr 4, 1 gr 5), septic shock (1 gr 4), delayed hemolytic transfusion reaction (1 gr 4), subdural hematoma (1 gr 4), platelet count decreased (4 gr 4), neutrophil count decreased (1 gr 4), blood glucose decreased (1 gr 4), hyperuricemia (3 gr 4), hypercalcemia (1 gr 4), hyperkalemia (1 gr 4), hypomagnesemia (1 gr 4), syncope (1 gr 4), cerebral hemorrhage (1 gr 4), coma (1 gr 4), diabetic neuropathy (1 gr 4), renal failure acute (1 gr 4, 1 gr 5), acute respiratory distress syndrome (1 gr 4), pharyngeal hemorrhage (1 gr 4), hypertensive crisis (2 gr 4), shock hemorrhagic (1 gr 4).

Supplementary Table 15. Most Common Serious Adverse Events, Through Week 24 or Initial Treatment Discontinuation

Serious adverse events in >1 patient in either arm, n (%)	Pacritinib (n=220)	BAT (n=106)
Anemia	10 (4·5)	5 (4·7)
Cardiac failure	5 (2·3)	1 (0·9)
Pyrexia	4 (1·8)	1 (0·9)
Pneumonia	4 (1·8)	1 (0·5)
Atrial fibrillation	3 (1·4)	0
Cardiac failure congestive	3 (1·4)	0
Diarrhea	3 (1·4)	0
Lobar pneumonia	2 (0·9)	0
Basal cell carcinoma	2 (0·9)	0
Squamous cell carcinoma of skin	2 (0·9)	0
Renal failure acute	2 (0·9)	0
Pleural effusion	2 (0·9)	1 (0·9)
Epistaxis	2 (0·9)	0
Sepsis	1 (0·5)	2 (1·9)
Dyspnea	1 (0·5)	2 (1·9)

BAT, best available therapy.

Supplementary Table 16. Incidence of Diarrhea Over Time (All Grades)

Time Interval	Pacritinib (n=220), n/n at risk (%)	BAT Initial Treatment (n=106), n/n at risk (%)	BAT Crossover (n=90), n/n at risk (%)[a]
Week 1 – Week 8	113/220 (51·4)	6/106 (5·7)	42/90 (46·7)
Week 8 – Week 16	26/210 (12·4)	4/103 (3·9)	13/83 (15·7)
Week 16 – Week 24	17/195 (8·7)	5/100 (5·0)	7/75 (9·3)
Week 24 – Week 32	11/177 (6·2)	1/89 (1·1)	1/72 (1·4)
Week 32 – Week 40	12/157 (7·6)	1/33 (3·0)	3/65 (4·6)
Week 40 – Week 48	4/140 (2·9)	1/13 (7·7)	2/61 (3·3)
Week 48 – Week 56	5/131 (3·8)	1/7 (14·3)	1/55 (1·8)
Week 56 – Week 64	4/121 (3·3)	1/6 (16·7)	3/48 (6·3)
Week 64 – Week 72	8/114 (7·0)	1/6 (16·7)	0/38
Week 72 – Week 80	7/109 (6·4)	0/5	1/32 (3·1)
Week 80 – Week 88	4/103 (3·9)	0/5	0/19
Week 88 – Week 96	2/93 (2·2)	0/5	0/13
Week 96 – Week 104	3/73 (4·1)	1/4 (25·0)	0/7
Week 104 – Week 112	1/60 (1·7)	0/3	1/5 (20·0)
Week 112 – Week 120	1/49 (2·0)	1/3 (33·3)	0/2
Week 120 – Week 128	1/41 (2·4)	0/3	0/1
Week 128 – Week 136	1/24 (4·2)	0/1	0
Week 136 – Week 144	0/13	0/1	0
Week 144 – Week 152	0/6	0	0
Week 152 – Week 160	0/1	0	0
Week 160 – Week 168	0	0	0

[a] From the time of crossover.
BAT, best available therapy.

Supplementary Table 17. Adverse Events Through Week 24 or Initial Treatment Discontinuation in Patients With Baseline Platelet Count <50,000/μL vs Overall

Pacritinib-treated patients, n (%)	<50,000/μL (n=35)	Overall (n=220)
All grade AEs	33 (94·3)	192 (87·3)
Grade 3/4 AEs	24 (68·6)	107 (48·6)
Serious AEs	14 (40·0)	65 (29·5)
AEs leading to drug interruption	13 (37·1)	48 (21·8)
AEs leading to dose reduction	4 (11·4)	22 (10·0)
AEs leading to discontinuation	5 (14·3)	22 (10·0)
AEs leading to death	3 (8.6)	8 (3·6)
BAT-treated patients, n (%)	<50,000/μL (n=15)	Overall (n=106)
All grade AEs	11 (73·3)	79 (74·5)
Grade 3/4 AEs	6 (40·0)	42 (39·6)
Serious AEs	3 (20·0)	23 (21·7)
AEs leading to drug interruption	0	5 (4·7)
AEs leading to dose reduction	0	9 (8·5)
AEs leading to discontinuation	0	3 (2·8)
AEs leading to death	1 (6·7)	3 (2·8)

Note: additional data for additional platelet subgroups (as shown below in Supplementary Table 18) are not available here as week 24 was not the primary analysis point for safety.
AE, adverse event.

Supplementary Table 18. Adverse Events at Any Time on Study in Pacritinib-Treated Patients by Baseline Platelet Count Subgroups and Overall

Pacritinib-treated patients, n (%)	Platelets <50,000/μL (n=35)	Platelets <100,000/μL (n=72)	Platelets ≥100,000/μL (n=148)	Overall (n=220)
All grade AEs	34 (97·1)	69 (95·8)	138 (93·8)	207 (94·1)
Grade 3/4 AEs	29 (82·9)	61 (84·7)	96 (64·9)	157 (71·4)
Serious AEs	20 (57·1)	43 (59·7)	77 (52·0)	120 (54·5)
AEs lading to drug interruption	17 (48·6)	31 (43·1)	47 (31·8)	78 (35·5)
AEs leading to dose reduction	6 (17·1)	12 (16·7)	21 (14·2)	33 (15·0)
AEs leading to discontinuation	14 (40·0)	25 (34·7)	25 (16·9)	50 (22·7)
AEs leading to death	9 (25·7)	14 (19·4)	13 (8·8)	27 (12·3)

AE, adverse events.

Supplementary Table 19. Bleeding Events By SMQ Through Week 24

Bleeding events, n (%)	Pacritinib (n=220)		BAT (n=106)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Epistaxis	10 (4·5)	2 (0·9)	9 (8·5)	1 (0·9)
Contusion	7 (3·2)	0	5 (4·7)	0
Hematoma	7 (3·2)	1 (0·5)	4 (3·8)	0
Hematuria	3 (1·4)	1 (0·5)	0	0
Purpura	3 (1·4)	0	0	0
Gingival bleeding	3 (1·4)	0	2 (1·9)	0
Conjunctival hemorrhage	2 (0·9)	0	0	0
Post procedural hemorrhage	2 (0·9)	1 (0·5)	0	0
Spontaneous hematoma	1 (0·5)	1 (0·5)	0	0
Hemoglobin decreased	1 (0·5)	1 (0·5)	0	0
Cerebral hemorrhage	1 (0·5)	1 (0·5)	0	0
Vitreous hemorrhage	1 (0·5)	0	1 (0·9)	0
Eye hemorrhage	1 (0·5)	0	1 (0·9)	0
Hemorrhoidal hemorrhage	1 (0·5)	0	0	0
Vessel puncture site bruise	1 (0·5)	0	0	0
Ear hemorrhage	1 (0·5)	0	0	0
Traumatic hematoma	1 (0·5)	0	1 (0·9)	0
Subdural hematoma	1 (0·5)	0	0	0
Traumatic intracranial hemorrhage	1 (0·5)	0	0	0
International normalized ratio increased	1 (0·5)	0	0	0
Petechia	1 (0·5)	0	1 (0·9)	0
Skin hemorrhage	1 (0·5)	0	0	0
Bleeding varicose vein	1 (0·5)	0	0	0
Melena	0	0	1 (0·9)	0
Rectal hemorrhage	0	0	1 (0·9)	0
Anal hemorrhage	0	0	1 (0·9)	1 (0·9)
Periorbital hematoma	0	0	1 (0·9)	0
Subarachnoid hemorrhage	0	0	1 (0·9)	0
Hemarthrosis	0	0	1 (0·9)	0
Hemothorax	0	0	1 (0·9)	1 (0·9)
Hemorrhage subcutaneous	0	0	1 (0·9)	0

BAT, best available therapy.

Supplementary Table 20. Incidence of Bleeding Events By SMQ Over Time (Grade 3/4)

Time Interval	Pacritinib (n=220), n/n at risk (%)	BAT Initial Treatment (n=106), n/n at risk (%)	BAT Crossover (n=90), n/n at risk (%)[a]
Week 1 – Week 8	2/220 (0·9)	1/106 (0·9)	3/90 (3·3)
Week 8 – Week 16	3/210 (1·4)	1/103 (1·0)	2/83 (2·4)
Week 16 – Week 24	3/195 (1·5)	0/100	0/75
Week 24 – Week 32	2/177 (1·1)	0/89	0/72
Week 32 – Week 40	2/157 (1·3)	1/33 (3·0)	2/65 (3·1)
Week 40 – Week 48	1/140 (0·7)	0/13	1/61 (1·6)
Week 48 – Week 56	2/131 (1·5)	0/7	0/55
Week 56 – Week 64	0/121	0/6	0/48
Week 64 – Week 72	1/114 (0·9)	0/6	0/38
Week 72 – Week 80	1/109 (0·9)	0/5	1/32 (3·1)
Week 80 – Week 88	0/103	0/5	0/19
Week 88 – Week 96	1/93 (1·1)	0/5	0/13
Week 96 – Week 104	0/73	0/4	0/7
Week 104 – Week 112	0/60	0/3	0/5
Week 112 – Week 120	0/49	0/3	0/2
Week 120 – Week 128	0/41	0/3	0/1
Week 128 – Week 136	0/24	0/1	0
Week 136 – Week 144	0/13	0/1	0
Week 144 – Week 152	0/6	0	0
Week 152 – Week 160	0/1	0	0
Week 160 – Week 168	0	0	0

[a] From the time of crossover.
BAT, best available therapy.

Supplementary Table 21. Bleeding Events By SMQ With Pacritinib at Any Time on Study

Bleeding events, n (%)	Pacritinib (n=220)	
	All Grade	Grade 3/4
Epistaxis	19 (8·6)	4 (1·8)
Contusion	11 (5·0)	0
Hematoma	9 (4·1)	2 (0·9)
Hematuria	6 (2·7)	1 (0·5)
Gingival bleeding	5 (2·3)	0
Post procedural hemorrhage	4 (1·8)	2 (0·9)
Petechia	3 (1·4)	0
Purpura	3 (1·4)	0
Gastrointestinal hemorrhage	2 (0·9)	1 (0·5)
Subdural hematoma	2 (0·9)	1 (0·5)
Hemarthrosis	2 (0·5)	1 (0·5)
Hemoglobin decreased	2 (0·9)	1 (0·5)
Conjunctival hemorrhage	2 (0·9)	0
International normalized ratio increased	2 (0·9)	0
Spontaneous hematoma	1 (0·5)	1 (0·5)
Melena	1 (0·5)	1 (0·5)
Abdominal wall hematoma	1 (0·5)	1 (0·5)
Esophageal hemorrhage	1 (0·5)	1 (0·5)
Cerebral hemorrhage	1 (0·5)	1 (0·5)
Pharyngeal hemorrhage	1 (0·5)	1 (0·5)
Shock hemorrhagic	1 (0·5)	1 (0·5)
Ear hemorrhage	1 (0·5)	0
Vitreous hemorrhage	1 (0·5)	0
Eye hemorrhage	1 (0·5)	0
Eyelid bleeding	1 (0·5)	0
Gastric varices hemorrhage	1 (0·5)	0
Hemorrhoidal hemorrhage	1 (0·5)	0
Mouth hemorrhage	1 (0·5)	0
Vessel puncture site bruise	1 (0·5)	0
Traumatic hematoma	1 (0·5)	0
Pulmonary contusion	1 (0·5)	0
Traumatic intracranial hemorrhage	1 (0·5)	0
Hemorrhage intracranial	1 (0·5)	0
Hemoptysis	1 (0·5)	0
Ecchymosis	1 (0·5)	0
Nail bed bleeding	1 (0·5)	0
Skin hemorrhage	1 (0·5)	0
Bleeding varicose vein	1 (0·5)	0
Hemorrhage	1 (0·5)	0

Supplementary Table 22. Cardiac Events By SMQ Through Week 24

Cardiac events, n (%)	Pacritinib (n=220)		BAT (n=106)	
	All Grade	Grade 3/4	All Grade	Grade 3/4
Edema peripheral	18 (8·2)	1 (0·5)	13 (12·3)	1 (0·9)
Electrocardiogram QT prolonged	12 (5·5)	3 (1·4)	1 (0·9)	0
Cardiac failure	6 (2·7)	5 (2·3)	2 (1·9)	2 (1·9)
Atrial fibrillation	4 (1·8)	3 (1·4)	1 (0·9)	0
Cardiac failure congestive	3 (1·4)	3 (1·4)	0	0
Pulmonary edema	2 (0·9)	1 (0·9)	0	0
Syncope	1 (0·5)	1 (0·5)	2 (1·9)	2 (1·9)
Angina pectoris	1 (0·5)	1 (0·5)	1 (0·9)	0
Cardiac fibrillation	1 (0·5)	1 (0·5)	0	0
Sinus tachycardia	1 (0·5)	1 (0·5)	0	0
Portal vein thrombosis	1 (0·5)	1 (0·5)	0	0
Cerebrovascular accident	1 (0·5)	1 (0·5)	0	0
Arrhythmia	1 (0·5)	0	0	0
Atrial flutter	1 (0·5)	0	0	0
Cardio-respiratory arrest	1 (0·5)	0	0	0
Left ventricular dysfunction	1 (0·5)	0	0	0
Palpitations	1 (0·5)	0	0	0
Heart rate increased	1 (0·5)	0	0	0
Coronary artery disease	0	0	1 (0·9)	1 (0·9)
Splenic infarction	0	0	1 (0·9)	1 (0·9)
Angina unstable	0	0	1 (0·9)	1 (0·9)
Pulmonary embolism	0	0	1 (0·9)	1 (0·9)
Sick sinus syndrome	0	0	1 (0·9)	0
Bundle branch block left	0	0	1 (0·9)	0
Tachycardia	0	0	1 (0·9)	0
Transient ischemic attack	0	0	1 (0·9)	0
Arterial thrombosis	0	0	1 (0·9)	0

BAT, best available therapy.

Supplementary Table 23. Incidence of Cardiac Events By SMQ Over Time (Grade 3/4)

Time Interval	Pacritinib (n=220), n/n at risk (%)	BAT Initial Treatment (n=106), n/n at risk (%)	BAT Crossover (n=90), n/n at risk (%)
Week 1 – Week 8	8/220 (3·6)	2/106 (1·9)	1/90 (1·1)
Week 8 – Week 16	7/210 (3·3)	4/103 (3·9)	0/83
Week 16 – Week 24	6/195 (3·1)	0/100	3/75 (4·0)
Week 24 – Week 32	1/177 (0·6)	0/89	1/72 (1·4)
Week 32 – Week 40	2/157 (1·3)	0/33	0/65
Week 40 – Week 48	1/140 (0·7)	0/13	2/61 (3·3)
Week 48 – Week 56	2/131 (1·5)	0/7	1/55 (1·8)
Week 56 – Week 64	0/121	0/6	0/48
Week 64 – Week 72	0/114	0/6	1/38 (2·6)
Week 72 – Week 80	0/109	0/5	0/32
Week 80 – Week 88	1/103 (1·0)	0/5	0/19
Week 88 – Week 96	1/93 (1·1)	0/5	0/13
Week 96 – Week 104	1/73 (1·4)	0/4	0/7
Week 104 – Week 112	0/60	0/3	0/5
Week 112 – Week 120	0/49	0/3	0/2
Week 120 – Week 128	1/41 (2·4)	0/3	0/1
Week 128 – Week 136	0/24	0/1	0
Week 136 – Week 144	0/13	0/1	0
Week 144 – Week 152	0/6	0	0
Week 152 – Week 160	0/1	0	0
Week 160 – Week 168	0	0	0

[a] From the time of crossover; BAT, best available therapy.

Supplementary Table 24. Cardiac Events By SMQ With Pacritinib at Any Time on Study

Cardiac events, n (%)	Pacritinib (n=220)	
	All Grade	Grade 3/4
Edema peripheral	25 (11·4)	1 (0·5)
Electrocardiogram QT prolonged	12 (5·5)	3 (1·4)
Cardiac failure	9 (4·1)	6 (2·7)
Atrial fibrillation	8 (3·6)	4 (1·8)
Cardiac failure congestive	4 (1·8)	4 (1·8)
Pulmonary edema	3 (1·4)	2 (0·9)
Syncope	2 (0·9)	2 (0·9)
Cardiac failure acute	2 (0·9)	0
Angina pectoris	1 (0.5)	1 (0·5)
Acute myocardial infarction	1 (0·5)	1 (0·5)
Cardiac fibrillation	1 (0·5)	1 (0·5)
Right ventricular failure	1 (0·5)	1 (0·5)
Sinus tachycardia	1 (0·5)	1 (0·5)
Portal vein thrombosis	1 (0·5)	1 (0·5)
Ejection fraction decreased	1 (0·5)	1 (0·5)
Cerebrovascular accident	1 (0·5)	1 (0·5)
Deep vein thrombosis	1 (0·5)	1 (0·5)
Supraventricular tachycardia	1 (0·5)	0
Tachycardia	1 (0·5)	0
Arrhythmia	1 (0·5)	0
Atrial flutter	1 (0·5)	0
Cardiac arrest	1 (0·5)	0
Cardio-respiratory arrest	1 (0·5)	0
Left ventricular dysfunction	1 (0·5)	0
Myocardial infarction	1 (0·5)	0
Myocardial ischemia	1 (0·5)	0
Palpitations	1 (0·5)	0
Sudden death	1 (0·5)	0
Heart rate increased	1 (0·5)	0

BAT, best available therapy.

Supplementary Table 25. Changes in Leukocyte and Neutrophil Counts From Baseline to Week 24.

Parameter	Pacritinib (n=220)		BAT (n=106)	
	Baseline	Week 24	Baseline	Week 24
Median leukocytes, × 10^9/L (range)	n=220 9·9 (1·2-169·6)	n=160 8·1 (1·1-249·3)	n=105 11·7 (1·9-85·0)	n=64 10·1 (2·0-44·4)
Median neutrophils, × 10^9/L (range)	n=201 7·2 (0·2-84·8)	n=129 5·6 (0·2-65·9)	n=99 8·3 (1·3-52·7)	n=54 6.1 (1·2-39·2)

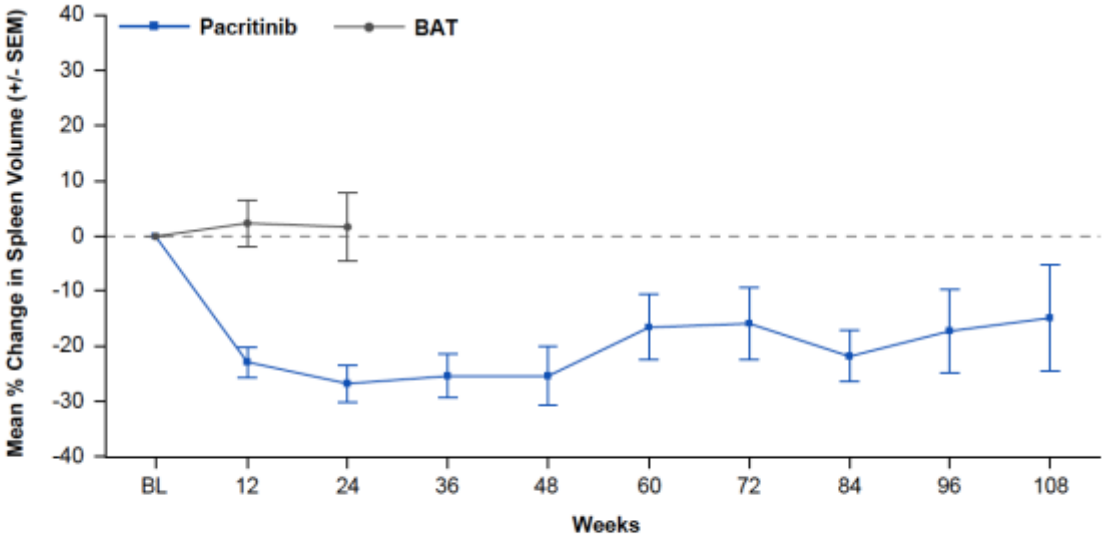
BAT, best available therapy.

Supplementary Table 26. Discontinuations Due to Adverse Events Through Week 24.

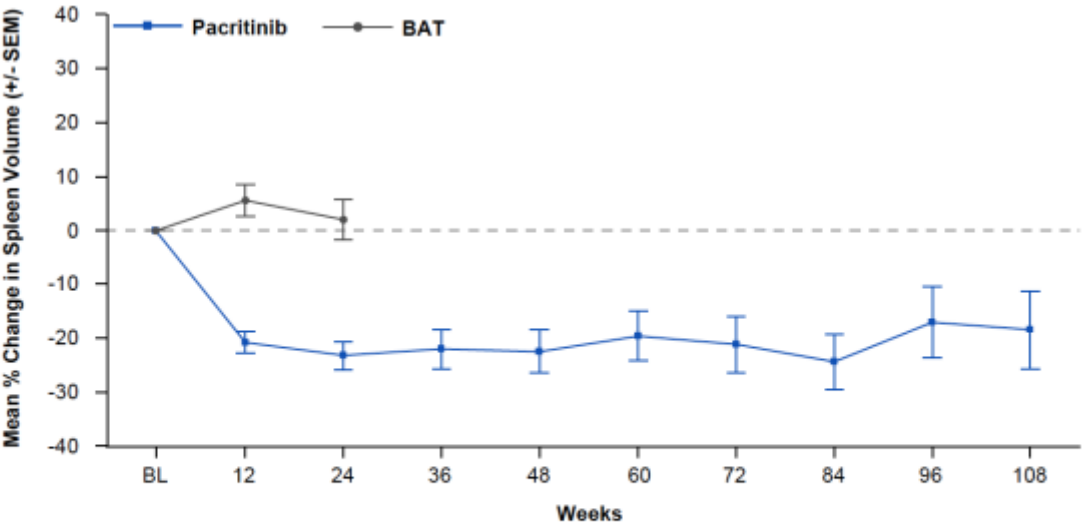
Adverse Event, n (%)	Pacritinib (n=220)	BAT (n=106)
Patients with ≥1 AE leading to study drug discontinuation	22 (10·0)	3 (2·8)
Diarrhea	3 (1·4)	0
Thrombocytopenia	2 (0·9)	0
Anemia	1 (0·5)	0
Abdominal pain	1 (0·5)	0
Diverticular perforation	1 (0·5)	0
Splenomegaly	1 (0·5)	0
Thrombocytosis	1 (0·5)	0
Platelet count decreased	1 (0·5)	0
Cardiac failure	1 (0·5)	0
Cardiac failure, congestive	1 (0·5)	0
Portal vein thrombosis	1 (0·5)	0
Peritonitis	1 (0·5)	0
Pneumonia	1 (0·5)	0
Traumatic intracranial hemorrhage	1 (0·5)	0
Hyponatremia	1 (0·5)	0
Bone pain	1 (0·5)	0
Non-small cell lung cancer	1 (0·5)	0
Cerebral hemorrhage	1 (0·5)	0
Cerebrovascular accident	1 (0·5)	0
Coma	1 (0·5)	0
Parkinson's disease	1 (0·5)	0
Azotemia	1 (0·5)	0
Hematuria	1 (0·5)	0
Ocular rosacea	0	1 (0·9)
Septic shock	0	1 (0·9)
Parasthesia	0	1 (0·9)
Renal failure	0	1 (0·9)
Acute respiratory distress syndrome	0	1 (0·9)

AE, adverse event; BAT, best available therapy.

Supplementary Figure 1. Mean percentage change in spleen volume over time for evaluable patients.
(A) patients with baseline platelet count <50,000/μL, (B) patients with baseline platelet count <100,000/μL

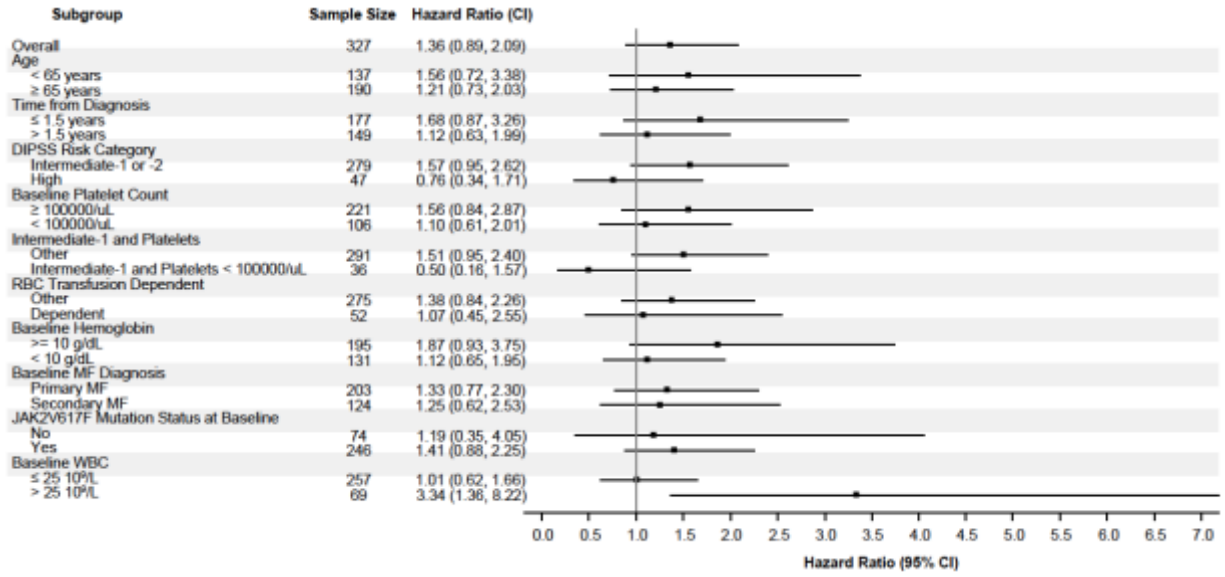


Number of Patients										
Pacritinib	35	29	24	18	13	14	12	12	10	7
BAT	16	13	11							

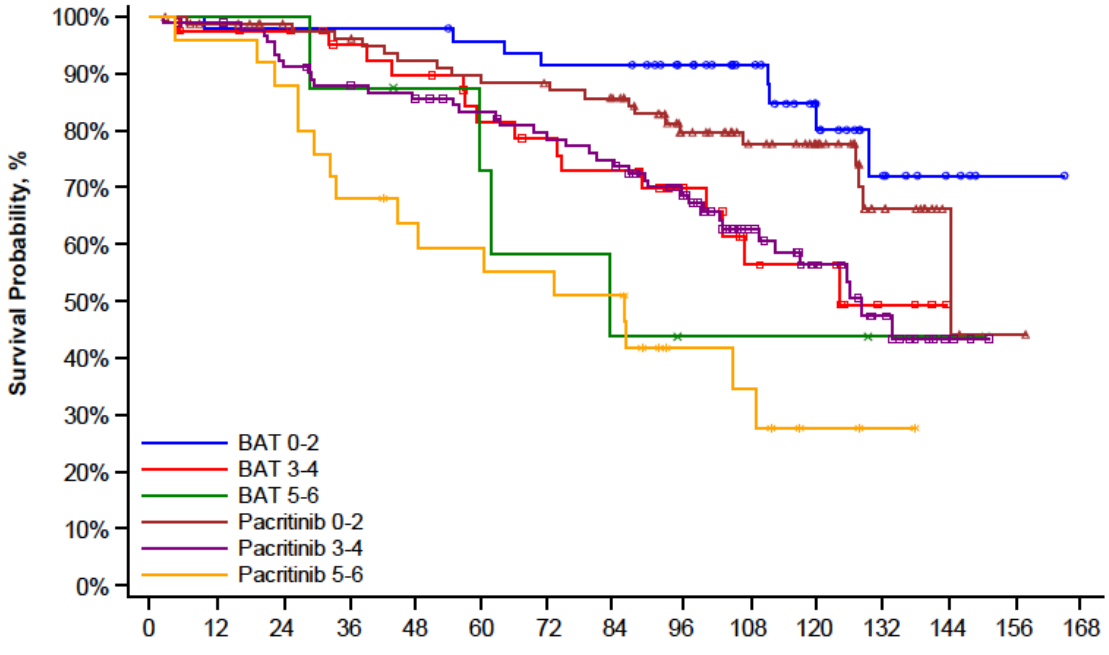


Number of Patients										
Pacritinib	72	63	51	37	32	31	24	21	17	13
BAT	34	29	24							

Supplementary Figure 2. Forest Plot of Hazard Ratio for OS Estimates by Subgroup.



Supplementary Figure 3. OS by Number of Risk Factors in Patients Randomized to Pacritinib (PAC) or BAT.

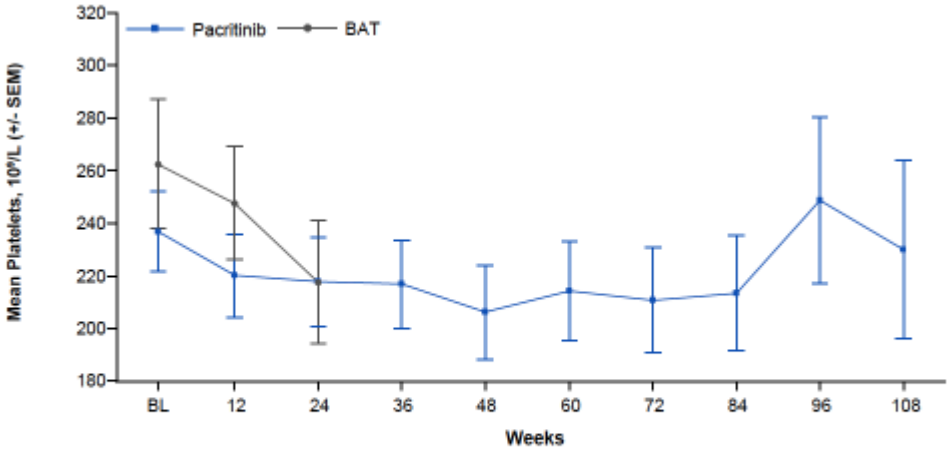


Patients at Risk

BAT	0-2	48	47	47	47	47	45	43	43	37	29	19	9	4	1	0
BAT	3-4	43	41	40	36	34	29	27	25	19	11	9	3	0	0	0
BAT	5-6	8	8	8	7	6	5	4	3	2	2	2	1	1	0	0
Pacritinib	0-2	86	82	78	75	71	68	67	63	47	36	30	12	3	1	0
Pacritinib	3-4	93	91	84	79	75	71	66	62	51	34	22	13	4	0	0
Pacritinib	5-6	25	24	22	17	15	14	13	12	6	5	2	1	0	0	0

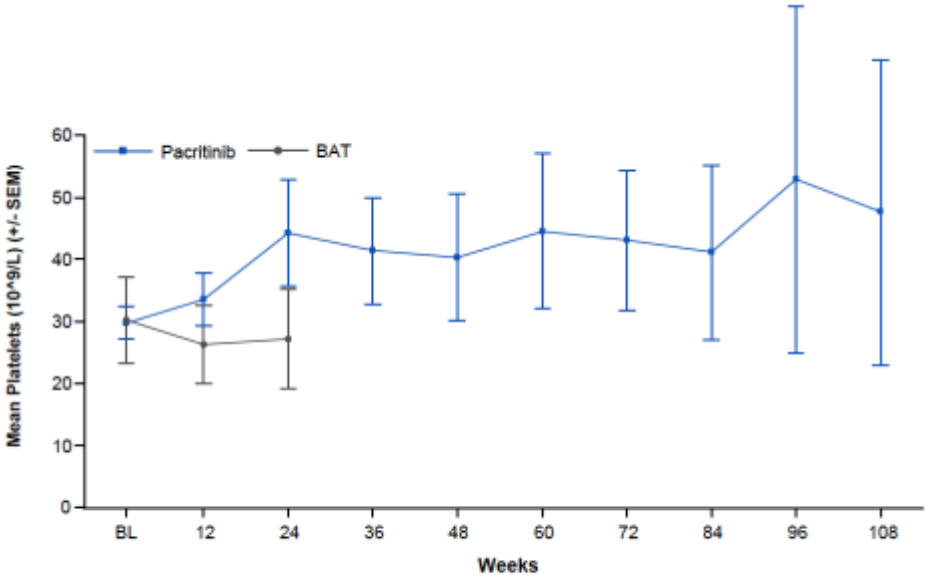
Supplementary Figure 4. Changes in Platelet Counts and Hemoglobin Levels During Treatment. Mean platelet counts over time (±SEM) from baseline in (A) all patients and (B) patients with baseline platelets <50,000/µL. (C) Mean percentage change in platelets (±SEM) in patients with baseline platelets <50,000/µL. (D) Mean hemoglobin levels (±SEM) from baseline in pacritinib- and BAT-treated patients. (E) Mean hemoglobin levels (±SEM) in patients with baseline hemoglobin <10 g/dL, including patients who received red blood cell transfusions.

A



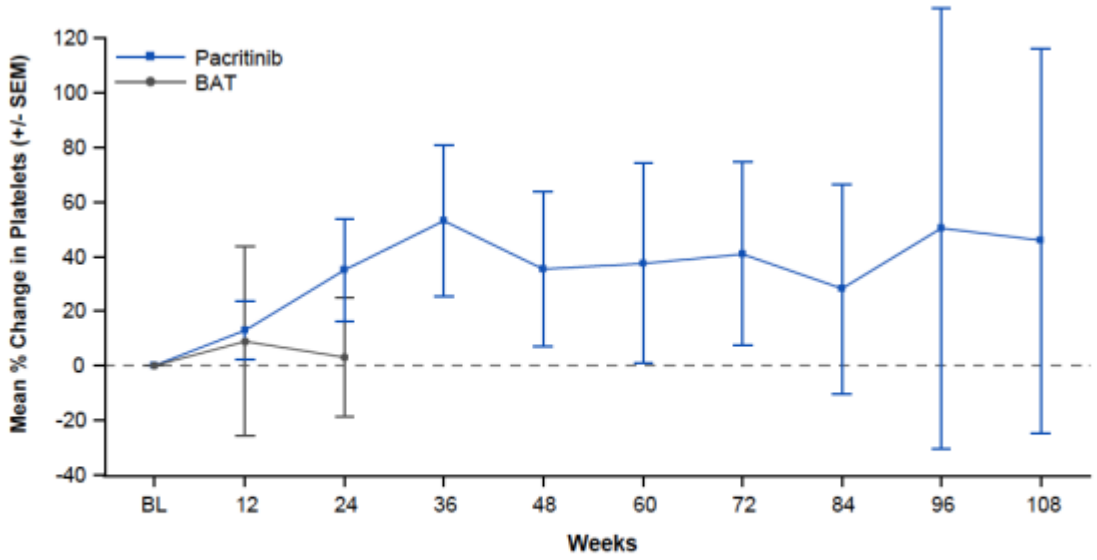
Number of Subjects										
Pacritinib	213	172	144	126	110	103	91	78	52	42
BAT	102	87	57							

B



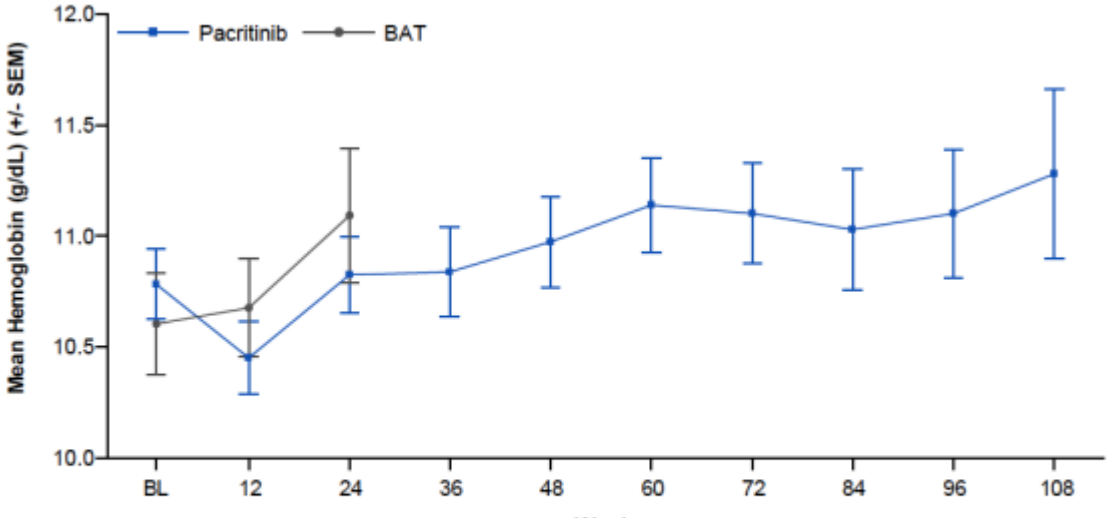
Number of Subjects										
Pacritinib	33	27	20	14	14	12	13	11	6	5
BAT	14	11	8							

C



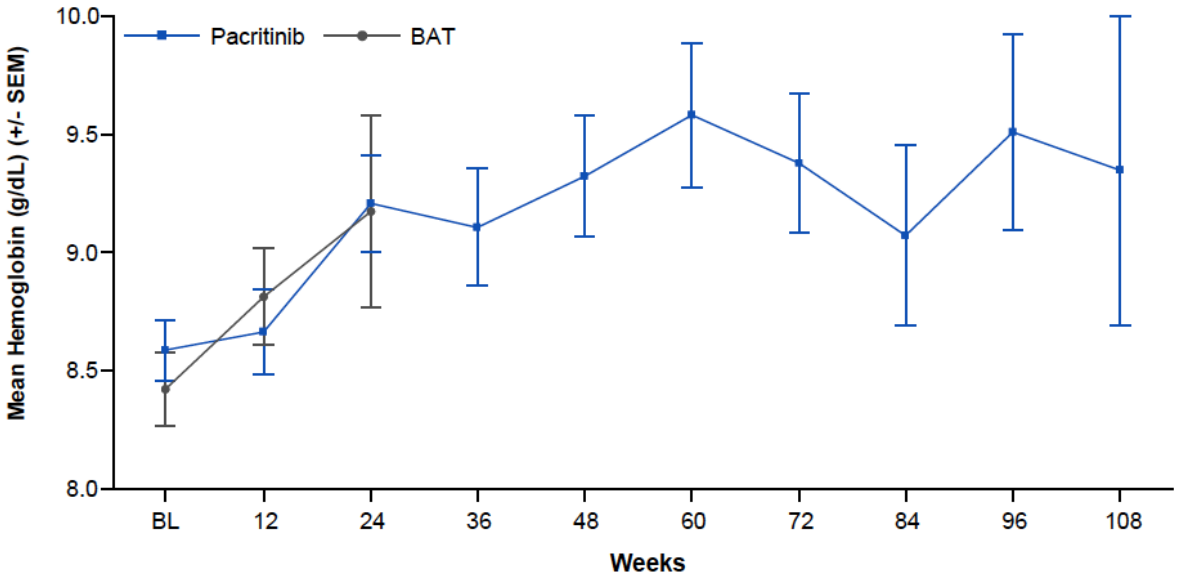
Number of Subjects										
Pacritinib	33	25	19	13	13	10	11	10	5	4
BAT	14	10	7							

D



Number of Subjects										
Pacritinib	220	188	161	135	123	113	101	86	61	48
BAT	105	97	64							

E



Number of Subjects										
Pacritinib	84	71	56	44	41	33	28	23	15	13
BAT	46	40	24							