Abstract 7067

PACRITINIB (PAC) VS BEST AVAILABLE THERAPY (BAT) IN MYELOFIBROSIS (MF): LONG TERM FOLLOW-UP OF PATIENT REPORTED OUTCOMES (PROS) IN THE PHASE III PERSIST-1 TRIAL

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INTRODUCTION

- Myelofibrosis (MF) is a life-threatening hematologic malignancy characterized by splenomegaly and debilitating constitutional symptoms that can markedly impact both patient HRQoL and overall survival[1-3]
  - Symptoms frequently occurring in patients with MF (≥50%) include fatigue, early satiety, inactivity, concentration problems, abdominal discomfort, night sweats, bone pain, and itching[3]
- Pacritinib (PAC) is an oral kinase inhibitor with specificity for JAK2, FLT3, IRAK1, and CSF1R[4,5]
- The phase 3 PERSIST-1 trial **(Figure 1)** compared pacritinib vs BAT, excluding JAK2 inhibitors, in patients with MF, regardless of baseline (BL) platelet count[7]
  - At Week 24, a significantly greater proportion of PAC vs BAT treated patients achieved ≥35% spleen volume reduction (ITT: 19.1% vs 4.7%, p=0.0003, primary end point) and ≥50% reduction in Total Symptom Score (TSS; ITT: 24.5% vs 6.5%, p<0.0001) by the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF)[7]
- The MPN-SAF is a patient reported outcome (PRO) assessment tool designed to measure MF-related symptom burden[6]
  - MPN-SAF was modified for use in the PERSIST-1 (MPN-SAF total symptom score [TSS] and TSS 2.0) phase 3 trial of pacritinib **(Table 1)**[7]
- On February 8, 2016, the U.S. Food and Drug Administration notified the sponsor that the IND for pacritinib has been placed on full clinical due to concerns over interim survival results, bleeding and cardiovascular events (discussed in Mesa et al. Abstract 7065, ASCO 2016)
- This analysis examines PROs at 48 weeks

METHODS

Figure 1. PERSIST-1 Study Design

Key Eligibility Criteria

- PMF, PET-MF, or PPV-MF
- Intermediate- or high-risk disease
- Palpable spleen ≥5 cm
- **No exclusion for baseline platelet levels; stratified for platelet counts ≥100,000/µL, ≥50,000 to <100,000/µL, and <50,000/µL**
- No exclusion for baseline Hgb levels
- No prior treatment with JAK2 inhibitors

R (2:1) N=327

- Pacritinib 400 mg qd
- Best Available Therapy (BAT)[a] excluding ruxolitinib

[a]Crossover from BAT allowed after progression or after Week 24 assessment.

Hgb, hemoglobin; JAK, Janus kinase; PET-MF, post-essential thrombocythemia myelofibrosis; PMF, primary myelofibrosis; PPV-MF, post-polycythemia vera myelofibrosis; R, randomized.

Table 1. Comparison of Original MPN-SAF and MPN-SAF v2.0

MPN-SAF (Original Version)[a]	MPN-SAF v 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[a]	Inactivity[a]
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

[a]Inactivity is not counted in TSS.
MPD, myeloproliferative disorder; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; NA, not applicable; TSS, total symptom score.

- Stratification at randomization: platelet count category, risk category, and region
- Study endpoints
  - **Primary:** proportion of patients achieving a ≥35% reduction in spleen volume (by MRI/CT) from baseline to Week 24
  - **Secondary:** proportion of patients with ≥50% reduction in TSS from baseline to Week 24 on the MPN-SAF v2.0[a]
- Trial conducted in United States, Europe, Russia, and Oceania

[a]The MPN-SAF v2.0 was agreed upon with FDA as it more accurately reflects the symptom burden of MF and was implemented during the course of the study; the 6 symptoms common between MPN-SAF and MPN-SAF v2.0 were used for the TSS analyses presented here.

Table 2. PRO Tools

Tool	Description	Administration
MPN-SAF	Designed to quantify and evaluate patient burden • Due to differences between questions and recall periods for the MPN-SAF v2.0 and the original MPN-SAF (used prior to protocol amendment 3), patients administered the MPN-SAF questionnaires at study entry were analyzed separately and in combination with MPN-SAF v2.0 as supportive analyses • The analyses were performed separately using the 6 common symptoms as well as in combination of the 2 versions (MPN-SAF + MPN-SAF v2.0) to fully evaluate symptom reduction for all patients • Symptom severity was measured on a scale from 0 (absent) to 10 (worst imaginable) using an electronic diary daily	Daily
Patient Global Impression of Change (PGIC)	Patient perception of overall health status rated using 7 descriptive terms ranging from *very much worse to very much improved*	Reported every 8 weeks through Week 24 and every 12 weeks thereafter
EORTC-QLQ-C30	Individual patient symptom and overall functioning scores calculated based on response to questionnaire	Administered every 8 weeks through Week 24 and every 12 weeks thereafter
EQ-5D-5L[8]	Questionnaire assesses patient health states in terms of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as an overall health score	Administered every 8 weeks through Week 24 and every 12 weeks thereafter

EQ-5D-5L, EuroQol-5 dimensions, 5 levels; EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form; TSS, total symptom score.

RESULTS

Baseline Characteristics

- 62% of patients had primary MF, 88% had a ECOG PS of 0-1, 32% had baseline platelets <100,000/µL, and 16% of patients had baseline platelets <50,000/µL **(Table 3)**

Table 3. Baseline Characteristics

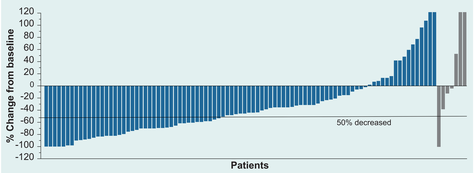
Characteristic	PAC (n=220)		BAT (n=107)	
Median age, years (range)	67	(23-87)	65	(37-84)
≥65 years, n (%)	135	(61)	55	(51)
Male, n (%)	125	(57)	60	(56)
ECOG PS, n (%)				
0-1	192	(87)	96	(90)
2-3	28	(13)	11	(10)
MF diagnosis, n (%)				
Primary MF	144	(65)	59	(55)
Post-polycythemia vera MF	48	(22)	33	(31)
Post-essential thrombocythemia MF	27	(12)	15	(14)
IPSS score, n (%)[a]				
Int-1	30	(14)	18	(17)
Int-2	76	(35)	35	(33)
High	106	(48)	51	(48)
Median spleen length by physical exam, cm (range)[b]	12	(4-33)	12	(4-30)
Median spleen volume by MRI/CT, cm³ (range)[c]	2006	(472-7948)	2153	(436-5404)
JAK2[R617F] positive, n (%)	154	(70)	92	(86)
BM biopsy completed, n (%)				
Reticulin and collagen fibrosis staging	219	(100)	107	(100)
MF 0-1	32	(15)	18	(17)
MF 2-3	**180**	**(82)**	**83**	**(78)**
Missing	7	(3)	6	(6)
Peripheral blasts, n (%)				
<1%	78	(35)	44	(41)
≥1%	94	(43)	38	(36)
<5%	159	(72)	74	(69)
≥5%	13	(6)	8	(7)
Missing	48	(22)	25	(23)
White blood cell count, n (%)				
≤25 ×10⁹/L	177	(80)	80	(75)
>25 ×10⁹/L	43	(20)	26	(24)
Hemoglobin, n (%)				
<10 g/dL	**84**	**(38)**	**47**	**(44)**
≥10 g/dL	136	(62)	59	(55)
Platelet count, n (%)				
<50,000/µL	**35**	**(16)**	**16**	**(15)**
≥50,000 to <100,000/µL	**37**	**(17)**	**18**	**(17)**
≥100,000/µL	148	(67)	73	(68)

[a]Derived from central laboratory data. [b]n=219 for PAC, n=106 for BAT. [c]n=218 for PAC, n=107 for BAT.
BAT, best available therapy; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; MF, myelofibrosis; MRI, magnetic resonance imaging; PAC, pacritinib; PS, performance status.

TSS Reduction From Baseline

- Waterfall plot of reduction in TSS (6 common symptoms) for evaluable patients at Week 48 **(Figure 2)**

Figure 2. Evaluable Patients[a] Achieving TSS Reduction[b] At Week 48

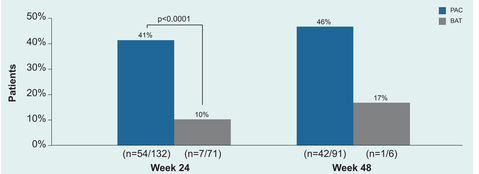


[a]Evaluable patients with baseline and Week 48 TSS values. [b]Using 6 common symptoms between MPN-SAF and MPN-SAF v 2.0
TSS, total symptom score.

TSS Reduction ≥50% Over Time

- The proportion of patients with TSS reduction ≥50% treated with pacritinib improved from Weeks 24 to 48 and was greater than observed with BAT **(Figure 3)**

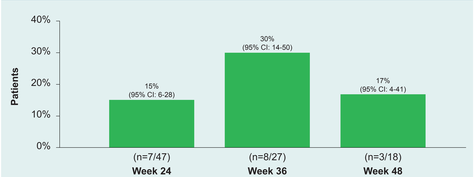
Figure 3. Evaluable Patients[a] Achieving TSS Reduction[b] ≥50% Over Time



[a]Evaluable patients with baseline, Week 24, and Week 48 TSS values. Number of responders in the evaluable population is shown. [b]Using 6 common symptoms between MPN-SAF and MPN-SAF v 2.0.
TSS, total symptom score.

- Among evaluable patients who crossed over from BAT to pacritinib, the percentage of patients that achieved ≥50% reduction in TSS increased from Week 24 to Week 36 post crossover **(Figure 4)**
  - At Week 48 post crossover, 17% of evaluable patients achieved TSS reduction ≥50%, however there were only 18 patients who were evaluable at this time

Figure 4. Evaluable Patients[a] Achieving TSS Reduction[b] ≥50% At Weeks 24, 36, and 48 Post Crossover From BAT to Pacritinib



[a]Evaluable patients with baseline and Week 48 TSS values. Number of responders in the evaluable population is shown. [b]Using 6 common symptoms between MPN-SAF and MPN-SAF v 2.0.
TSS, total symptom score.

- From baseline to Week 24, significant reductions in the 6 common symptoms between MPN-SAF versions were reported with initial pacritinib treatment; for all but bone pain, additional reductions in mean percent change were observed from Week 24 to Week 48 **(Table 4)**
  - A trend toward reductions in individual symptom scores was observed among BAT patients post crossover vs patients who remained on BAT

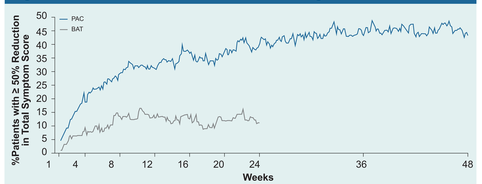
Table 4. Mean% Change from Baseline in Individual Symptom Scores

	Week 24			Week 48		
Initial treatment	PAC (n=146)	BAT (n=73)	BAT Crossover[b] (n=56)	PAC (n=99)	BAT (n=6)	BAT Crossover[b] (n=56)
Worst fatigue/tiredness	–21	+48	+5	–25	+5	–15
Early satiety	–35	+4	–16	–42	+86	–35
Abdominal discomfort	–26	+82	+10	–30	+48	–8
Night sweats	–53	+101	–25	–55	+96	–27
Pruritis	–33	+39	+16	–52	+198	–18
Bone pain	–24	+4	–14	–14	–65	0

[a]p<0.01 for all comparisons by Wilcoxon rank-sum test; [b]From time of crossover.

- Proportions of evaluable patients achieving ≥50% reduction in TSS over time continued to increase among pacritinib-treated patients **(Figure 5)**

Figure 5. TSS Reduction[a] ≥50% Over Time Among Evaluable Patients

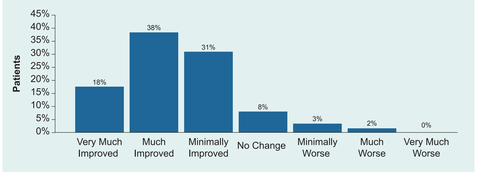


[a]Response rate based on 7-day moving average per MPN-SAF and MPN-SAF v 2.0 (6 questions) over time in evaluable patients.
TSS, total symptom score.

Patient Global Impression of Change

- Approximately 56% of pacritinib-treated evaluable patients reported being "much improved" or "very much improved" at Week 48 by PGIC **(Figure 6)**

Figure 6. PGIC Among Evaluable Pacritinib-Treated Patients (n=120) at Week 48

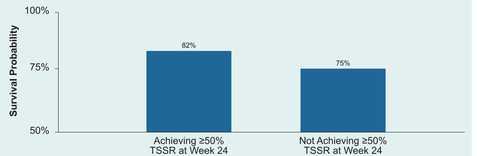


PGIC, Patient Global Impression of Change.

Probability of Survival

- At Week 108, the probability of survival among patients achieving ≥50% reduction in TSS at Week 24 was 82% vs 75% among those not achieving ≥50% reduction in TSS **(Figure 7)**

Figure 7. Survival Probability at Week 108 Among Patients Achieving TSS Reduction[a] ≥50% at Week 24 vs Those Not Achieving TSS Reduction ≥50%



[a]Using 6 common symptoms between MPN-SAF and MPN-SAF v 2.0. TSS, total symptom score; TSSR, total symptom score reduction.

CONCLUSIONS

- Among evaluable patients remaining on initial treatment, pacritinib treatment was associated with significant and durable improvements in TSS
- The proportions of pacritinib-treated patients achieving TSS reductions ≥50% increased with time
- TSS improvements increased from Week 24 to Week 36 from the time of crossover from BAT to pacritinib
- Mean percentage reductions in common symptoms measured in both MPN-SAF versions at Week 48 were greater than those observed at Week 24 among patients treated with pacritinib
- The probability of survival at Week 108 for evaluable patients who achieved ≥50% reduction in TSSR at Week 24 was numerically superior to those patients who did not achieve a ≥50% reduction in TSS

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Disclosures

- **RAM**: research funding from Incyte, CTI BioPharma, Gilead, NS Pharma, Promedior, Genentech, and Pfizer; consultancy for Novartis
- **CNH**: honoraria, research funding, and speakers bureau for Novartis; consultancy, honoraria, and speakers bureau for CTI BioPharma; honoraria from Gilead; honoraria and speakers bureau for Sanofi; speakers bureau for Shire
- **FC**: consultancy and speakers bureau for Novartis, CTI BioPharma, and Baxter; consultancy for Sanofi-Aventis
- **JPD**, **LW**, and **TG**: employment and equity ownership in CTI BioPharma
- **YY**: employment and equity ownership in Baxalta
- **AMV**: advisory committee, research funding, and speakers bureau for Novartis; speakers bureau for Shire; advisory committee for Baxalta
- **AM**: nothing to disclose

Acknowledgments

- We would like to thank all the patients, investigators, and personnel who contributed to this study
- Editorial assistance funded by CTI BioPharma Corp. and Baxalta Incorporated was provided by Janardhan Sampath, PhD of Nexus Global Group Science, LLC

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Poster Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting 2016, Chicago, IL, USA, June 3–7, 2016.