RELATIONSHIP BETWEEN PATIENT-REPORTED OUTCOMES (PROS) AND HEALTH-RELATED QUALITY OF LIFE (HRQOL) AND EFFICACY IN PATIENTS WITH MYELOFIBROSIS IN THE PHASE III PERSIST-1 TRIAL OF PACRITINIB VS. BEST AVAILABLE THERAPY (BAT)

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INTRODUCTION

- Myelofibrosis (MF) is a rare hematologic malignancy characterized by splenomegaly and debilitating constitutional symptoms that may have a substantial negative impact on 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]
- The Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) is a PRO tool designed to measure MF-related symptom burden[4]
  - MPN-SAF was modified for use in the PERSIST-1 (MPN-SAF total symptom score [TSS] and TSS 2.0) and PERSIST-2 (TSS 2.0) phase III trials of pacritinib[5]
- Pacritinib-treated patients in the PERSIST-1 trial had significant reductions in TSS overall and in individual symptoms vs. BAT when examining the 6 common symptoms in both TSS versions **(Table 1)**[6]
  - In addition, the proportion of patients achieving spleen volume reduction (SVR) ≥35% was significantly greater with pacritinib vs. BAT (19.1% vs. 4.7%, p=0.0003)[5]
- PERSIST-1 is a global, multicenter, phase III trial comparing the safety and efficacy of pacritinib vs. BAT excluding ruxolitinib, in patients with intermediate-to-high-risk PMF, post-polycythemia vera MF, or post-essential thrombocythemia MF, regardless of baseline platelet count or hemoglobin levels **(Figure 1)**
- This analysis examines relationships between TSS improvement and changes in splenomegaly and HRQoL outcomes in the PERSIST-1 overall patient population and in patients with baseline thrombocytopenia

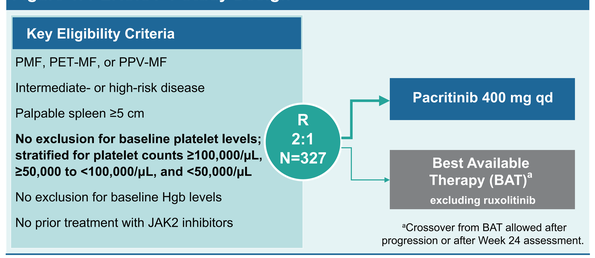
Table 1. The 6 Common Symptoms for TSS Analysis

TSS (Original Version)[4]	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[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; NA, not applicable.

METHODS

Figure 1. PERSIST-1 Study Design



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

- 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
- Trial conducted in United States, Europe, Russia, and Oceania

Table 2. PRO Tools

Tool	Description	Administration
MPN-SAF	Designed to quantify and evaluate patient burden • Due to differences in questions and recall periods between the MPN-SAF TSS 2.0 and the original MPN-SAF TSS (used prior to protocol amendment 3), patients administered the MPN-SAF TSS questionnaires at study entry were analyzed separately and in combination with TSS 2.0 as supportive analyses • To fully evaluate symptom reduction for all patients, a combined analysis (TSS + TSS 2.0) using the 6 symptoms common to both versions was performed • 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[7]	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

EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQol-5 dimensions, 5 levels.

- In logistic regressions, the odds of TSS reduction ≥50% at Week 24 were evaluated as a function of Week 24 SVR ≥35%, spleen length reduction (SLR) ≥50%, PGIC, improvement in each EORTC scale, and improvement in EQ-5D-5L overall health state (OHS) and in each dimension individually, adjusting for treatment (pacritinib vs. BAT)
- Correlations were examined in all patients (overall patient population) and by baseline platelet counts (<50,000/µL, <100,000/µL, and ≥100,000/µL)

RESULTS

Baseline Characteristics

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

Table 3. Baseline Characteristics

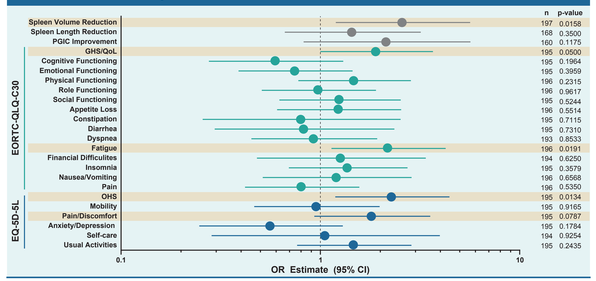
Characteristic	PAC (n=220)		BAT (n=107)	
Median age, years (range)	67	(23-87)	65	(37-84)
≥65 years, n (%)	135	(61.4)	55	(51.4)
Male, n (%)	125	(56.8)	60	(56.1)
ECOG PS, n (%)				
0-1	192	(87.3)	96	(89.7)
2-3	28	(12.7)	11	(10.3)
MF diagnosis, n (%)				
Primary MF	144	(65.5)	59	(55.1)
Post-polycythemia vera MF	48	(21.8)	33	(30.8)
Post-essential thrombocythemia MF	27	(12.3)	15	(14.0)
Missing	1	(0.5)	0	0
DIPSS score, n (%)				
Int-1	124	(56.4)	49	(45.8)
Int-2	63	(28.6)	43	(40.2)
High	32	(14.5)	14	(13.1)
Median spleen length by physical examination, cm (range)[a]	12	(4-33)	12	(4-30)
Median spleen volume by MRI/CT, cm^3 (range)[b]	2005.6	(472.1-7947.9)	2152.7	(436.1-5403.6)
JAK2V617F positive, n (%)	154	(70.0)	92	(86.0)
BM biopsy completed, n (%)	219	(99.5)	107	(100)
Reticulin and collagen fibrosis staging				
MF 0-1	32	(14.6)	18	(16.8)
MF 2-3	180	(82.2)	83	(77.6)
Missing	7	(3.2)	6	(5.6)
Peripheral blasts, n (%)				
<1%	78	(35.5)	44	(41.1)
≥1%	94	(42.7)	38	(35.5)
<5%	159	(72.3)	74	(69.2)
≥5%	13	(5.9)	8	(7.5)
Missing	48	(21.8)	25	(23.4)
White blood cell count, n (%)				
≤25 × 10^9/L	177	(80.5)	80	(74.8)
>25 × 10^9/L	43	(19.5)	26	(24.3)
Hemoglobin, %				
<10 g/dL	84	(38.2)	47	(43.9)
≥10 g/dL	136	(61.8)	59	(55.1)
Platelet count group, n (%)				
<50,000/µL	35	(15.9)	16	(15.0)
≥50,000 to <100,000/µL	37	(16.8)	18	(16.8)
≥100,000/µL	148	(67.3)	73	(68.2)

[a]n=219 for PAC, n=106 for BAT; [b]n=218 for PAC, n=107 for BAT.
BAT, best available therapy; BM, bone marrow; CT, computed tomography; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; Int, intermediate; JAK, Janus kinase; MF, myelofibrosis; MRI, magnetic resonance imaging; PAC, pacritinib; TSS, total symptom score.

Correlations With TSS Response: Overall Patient Population

- A significantly greater proportion of pacritinib-treated patients achieved ≥50% reduction in TSS compared with BAT-treated patients (24.5% vs. 6.5%, p<0.0001)[6]
  - Similarly, a greater proportion of pacritinib-treated patients with baseline thrombocytopenia achieved ≥50% reduction in TSS vs. BAT-treated patients, but these results did not reach statistical significance
- In the total patient population, there was a significant association between TSS response and spleen volume response (odds ratio [OR]=2.600, 95% CI: 1.196-5.651, p=0.0158) **(Figure 2)**
- There was also a significant association between TSS response and improvements in OHS as measured by EQ-5D-5L (OR=2.298, 95% CI: 1.188-4.445, p=0.0134)
- TSS response was marginally associated with improvements in EORTC-QLQ-C30 global health status (GHS)/QoL scale (OR=1.917, 95% CI: 1.000-3.676, p=0.0500)
- Although not statistically significant, there was a trend toward improvement in OHS as measured by PGIC (OR=2.159, 95% CI: 0.824-5.661, p=0.1175)

Figure 2. Treatment-Adjusted Correlations With TSS Response: Overall Patient Population

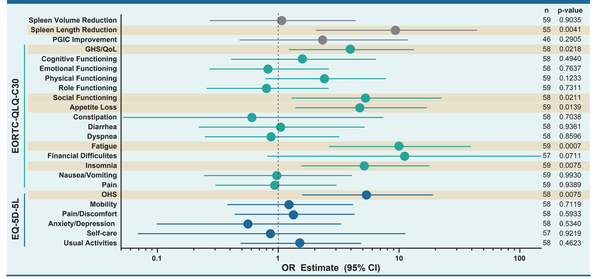


EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQol-5 dimensions, 5 levels; GHS, global health status; OHS, overall health state; OR, odds ratio; PGIC, Patient Global Impression of Change; QoL, quality of life.

Correlations With TSS Response: Patients With Platelets <100,000/µL

- TSS response was significantly associated with reductions in splenomegaly (SLR ≥50%, OR=9.526, 95% CI: 2.044-44.403, p=0.0041) **(Figure 3)**
- Improvements in TSS were also significantly associated with improvements in the EORTC-QLQ-C30 GHS/QoL domain (OR=4.031, 95% CI: 1.225-13.265, p=0.0218), as well as the EQ-5D-5L OHS (OR=5.487, 95% CI: 1.575-19.119, p=0.0075)
- Significant associations were also observed between TSS response and improvements in fatigue, social functioning, appetite loss, and insomnia, as measured by the EORTC-QLQ-C30

Figure 3. Treatment-Adjusted Correlations With TSS Response: Patients With Platelets <100,000/µL

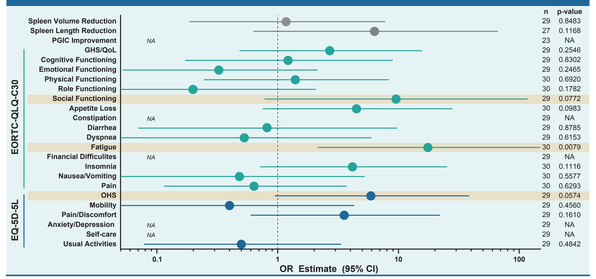


EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQol-5 dimensions, 5 levels; GHS, global health status; OHS, overall health state; OR, odds ratio; PGIC, Patient Global Impression of Change; QoL, quality of life.

Correlations With TSS Response: Patients With Platelets <50,000/µL

- TSS response was significantly associated with improvements in fatigue as measured by the EORTC-QLQ-C30 **(Figure 4)**
- Improvement in EQ-5D-5L OHS was marginally associated with TSS response in patients with platelets <50,000/µL

Figure 4. Treatment-Adjusted Correlations With TSS Response: Patients With Platelets <50,000/µL



EORTC-QLQ-C30, European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D-5L, EuroQol-5 dimensions, 5 levels; GHS, global health status; NA, not applicable; OHS, overall health state; OR, odds ratio; PGIC, Patient Global Impression of Change; QoL, quality of life.

Treatment-Adjusted Correlations With TSS Reduction: Patients Without Thrombocytopenia (Platelets ≥100,000/µL)

- In patients without thrombocytopenia, significant associations were observed between TSS response and spleen volume response (OR=3.994, 95% CI:1.533-10.409, p=0.0046)
- Although not statistically significant, there were trends toward improvements in cognitive function (EORTC-QLQ-C30) and pain/discomfort (EQ-5D-5L), as well as reductions in TSS

CONCLUSIONS

- Treatment with pacritinib has been associated with significant reductions in spleen volume compared with BAT, as well as improvements in TSS
- In the overall patient population, TSS response was associated with improvements in spleen volume response and perceived OHS
  - This trend was also observed in patients with low baseline platelet counts (<50,000/µL and <100,000/µL)
- In all patient populations analyzed, TSS response was significantly associated with improvements in fatigue, a major contributor to poor HRQoL in patients with MF
  - Significant improvements in social functioning, appetite loss, and insomnia were also observed in patients with baseline thrombocytopenia
- These data reinforce the clinical relevance of patient-reported symptoms, as measured with the validated TSS, as an endpoint in MF trials

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