P699

PACRITINIB VS BEST AVAILABLE THERAPY, INCLUDING RUXOLITINIB, IN PATIENTS WITH MYELOFIBROSIS AND BASELINE THROMBOCYTOPENIA: FOCUS ON ANEMIA IN THE PHASE 3 PERSIST-2 TRIAL

Moshe Talpaz[1], John Mascarenhas[2], Ronald Hoffman[2], Aaron T. Gerds[3], Brady Stein[4], Vikas Gupta[5], Anita Szoke[6], Mark Drummond[7], Alexander Pristupa[8], Tanya Granston[9], Robert Daly[9], Suliman Al-Fayoumi[9], Jennifer A. Callahan[9], Jack W. Singer[9], Jason Gotlib[10], Catriona Jamieson[11], Claire Harrison[12], Ruben Mesa[13], Srdan Verstovsek[14]

[1]University of Michigan, Comprehensive Cancer Center, Ann Arbor, MI, USA; [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [3]Cleveland Clinic, Cleveland, OH, USA; [4]Northwestern University, Feinberg School of Medicine, Chicago, IL, USA; [5]Princess Margaret Cancer Center, University of Toronto, Ontario, Canada; [6]Albert Szent-Györgyi Clinical Center, University of Szeged, Szeged, Hungary; [7]Beatson West of Scotland Cancer Centre, Glasgow, UK; [8]Ryazan's Clinical Hospital, Ryazan, Russia; [9]CTI BioPharma Corp., Seattle, WA, USA; [10]Stanford Cancer Institute, Stanford, CA, USA; [11]University of California-San Diego, La Jolla, CA, USA; [12]Guy's and St Thomas' NHS Foundation Trust, London UK; [13]Mayo Clinic, Scottsdale, AZ, USA; [14]MD Anderson Cancer Center, Houston, TX, USA.

INTRODUCTION

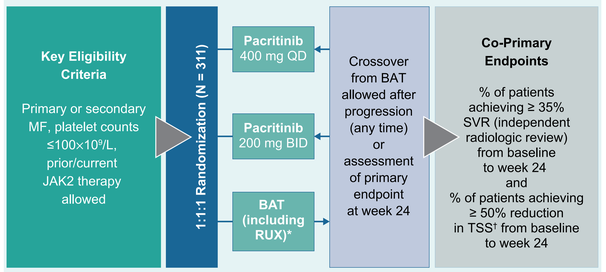
- Myelofibrosis (MF) is a life-threatening hematologic malignancy characterized by splenomegaly, debilitating constitutional symptoms, and progressive cytopenias[1-3]
  - Thrombocytopenia is an adverse prognostic variable that increases in prevalence with disease progression and is associated with high symptom burden and shorter survival[3-5]
- Approved JAK1/2 inhibitor ruxolitinib reduces splenomegaly and symptoms in patients with MF, but is associated with dose-limiting thrombocytopenia and exacerbation of anemia[6,7]
- Patients with MF frequently develop red blood cell (RBC) transfusion requirements with disease progression[8]
  - Ruxolitinib (RUX) may increase the need for RBC transfusions[6,7]
- Pacritinib (PAC), a JAK2/FLT3 inhibitor without activity against JAK1[9] is clinically active in patients with MF and produces minimal myelosuppression[10]
- In the phase 3 PERSIST-2 trial of PAC vs best available therapy (BAT; including RUX) in patients with MF and baseline thrombocytopenia, PAC 200 mg twice daily (BID) was significantly more effective in terms of spleen volume reduction (SVR) and reduction in total symptom score (TSS) and appeared to have a better benefit/risk profile vs PAC 400 mg once daily (QD) or BAT[11]

OBJECTIVE

- Examine the impact of baseline anemia or transfusion-dependence on efficacy outcome measures, as well as the effects of therapy on anemia in patients from the phase 3 PERSIST-2 study

METHODS

Figure 1. Study Schema



*BAT includes any physician-selected treatment for MF, as well as symptom-directed treatment, or no treatment, and may include any treatment received before study entry.
†TSS, total symptom score (MPN-SAF TSS 2.0) with daily patient reporting of disease-related symptoms by e-diary.
RUX, ruxolitinib.

- Stratification at randomization: geographic region, risk category, and rebound platelet count
- Efficacy analyses used the intent-to-treat (ITT)-efficacy population, which included all patients with a randomization date allowing them to contribute data for a week-24 endpoint
- Anemia at baseline was defined as hemoglobin <10 g/dL
- Clinical improvement in hemoglobin was defined based on International Working Group (IWG) criteria: increase of ≥2.0 g/dL or RBC transfusion independence for ≥8 weeks prior
- RBC transfusion endpoints were defined according to Gale criteria[12]:
  - RBC transfusion-independence (TI): no RBC transfusions for 3 months
    - Not RBC-TI at baseline indicates patients with transfusion burden who did or did not meet the definition of RBC-transfusion-dependence (TD)
  - Reduced TD: ≥50% decrease in average number of RBC transfusions per month for 3 months
  - RBC-TD: average of ≥2 RBC units/month for the preceding 3 months

RESULTS

- At baseline, 59% of patients in the ITT-efficacy population had anemia (**Table 1**)
  - Patients with anemia at baseline were more likely to have primary MF (71% vs 57%), high DIPSS score (41% vs 14%), and baseline platelet count <50,000/μL (51% vs 38%)
- BAT patients received a variety of agents; the most commonly used were ruxolitinib (45%), hydoxyurea (19%), and prednisone/prednisolone (13%)
  - 19% of BAT patients had watchful-waiting only

Table 1. Key Baseline Characteristics (ITT-Efficacy Population)

	PAC QD		PAC BID		BAT	
	Anemic (n=45)	Nonanemic (n=30)	Anemic (n=44)	Nonanemic (n=30)	Anemic (n=41)	Nonanemic (n=31)
Median age, years (range)	69 (56-85)	67 (39-84)	67 (50-85)	68 (39-77)	68 (50-83)	69 (32-82)
≥65 years, n (%)	35 (78)	18 (60)	26 (59)	20 (67)	29 (71)	22 (71)
Male, n (%)	28 (62)	10 (33)	27 (61)	21 (70)	25 (61)	14 (45)
ECOG PS, n (%)						
0-1	33 (73)	24 (80)	39 (89)	26 (87)	31 (76)	23 (74)
2-3	11 (24)	6 (20)	4 (9)	4 (13)	10 (24)	5 (16)
MF diagnosis, n (%)						
Primary	31 (69)	15 (50)	35 (80)	20 (67)	26 (63)	17 (55)
PPV	6 (13)	10 (33)	6 (14)	8 (27)	4 (10)	12 (39)
PET	8 (18)	5 (17)	3 (7)	2 (7)	11 (27)	2 (6)
DIPSS risk category, n (%)						
Intermediate-1	1 (2)	12 (40)	1 (2)	13 (43)	1 (2)	12 (39)
Intermediate-2	25 (56)	15 (50)	27 (61)	11 (37)	22 (54)	15 (48)
High	19 (42)	3 (10)	16 (36)	6 (20)	18 (44)	4 (13)
JAK2^{V617F} positive, n (%)	34 (76)	26 (87)	34 (77)	25 (83)	25 (61)	26 (84)
Median spleen length*, cm	12 (5-31)	14 (3-33)	15 (5-32)	15 (5-28)	11 (2-34)	14 (5-25)
Platelet count <50×10⁹/L, n (%)	24 (53)	14 (47)	21 (48)	10 (33)	21 (51)	11 (35)
Peripheral blasts category, n (%)						
0-<5%	38 (84)	24 (80)	35 (80)	26 (87)	35 (85)	25 (81)
≥5%	4 (9)	5 (17)	4 (9)	3 (10)	4 (10)	3 (10)
Missing	3 (7)	1 (3)	5 (11)	1 (3)	2 (5)	3 (10)
WBC count >25×10⁹/L, n (%)	7 (16)	8 (27)	8 (18)	9 (30)	4 (10)	10 (32)
Received prior RUX, n (%)	19 (42)	12 (40)	21 (48)	10 (33)	19 (46)	14 (45)

DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; PET, post-essential thrombocythemia; PPV, post-polycythemia vera; WBC, white blood cell.
*By physical examination.

- For those with baseline anemia (regardless of RBC transfusion-dependence):
  - No clinically meaningful decreases in mean hemoglobin levels through week 24 (central laboratory assessment; **Figure 2**)
  - The rate of clinical improvement in hemoglobin at week 24 was higher with PAC BID compared with PAC QD or BAT (**Figure 3**)
- For the 49% of patients not RBC-transfusion independent at baseline, reduction in RBC transfusion-dependency at week 24 was achieved at higher rates with PAC QD and PAC BID vs BAT (**Figure 3**)
  - 2 PAC (1 QD, 1 BID) and 0 BAT patients achieved RBC-TI (Gale criteria) by week 24
- For patients who received ≥1 RBC unit on study, transfusion requirements at weeks 12 and 24 were lower with PAC BID vs PAC QD or BAT (**Figure 4**)

Figure 2. Mean Hemoglobin Levels Through Week 24 in (A) All Patients and (B) Patients With Baseline Anemia (Safety Population, Central Laboratory Assessment)

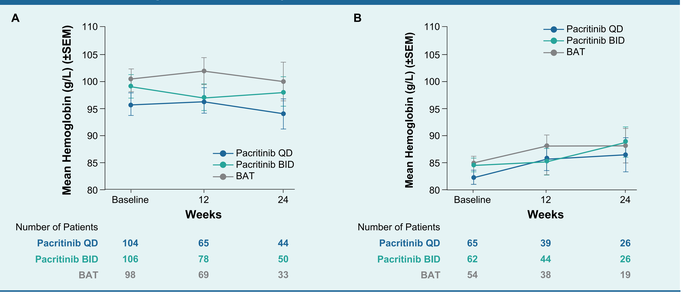
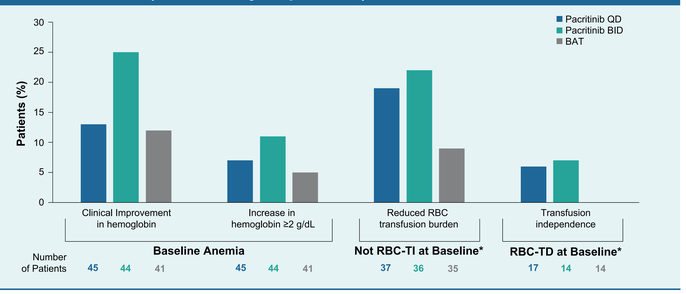
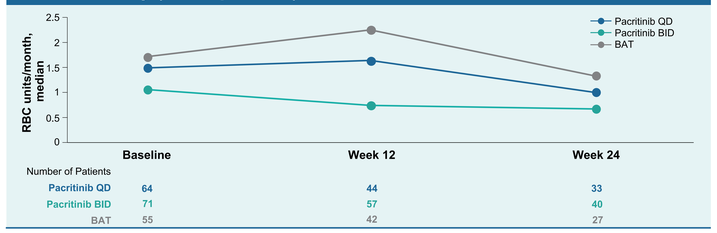


Figure 3. Improvement in Hemoglobin (A) and Transfusion Burden (B) at Week 24 (ITT-Efficacy Population)



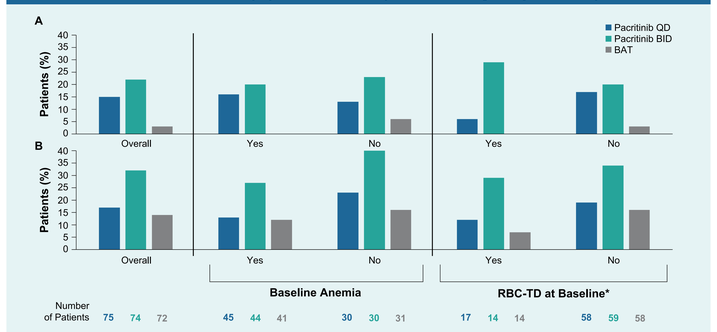
*Gale criteria.

Figure 4. RBC Transfusions Over Time in All Patients With ≥1 RBC Unit on Study (ITT Population)



- In PAC patients, SVR ≥35% and TSS reduction ≥50% at week 24 were observed regardless of baseline anemia or RBC-TD (**Figure 5**)
  - Highest rates were observed with PAC BID
- PAC patients achieved SVR ≥35% regardless of patient baseline subgroup, including cytopenias, sex, age, JAK2^{V617F} mutation status, and prior treatment with JAK2 inhibitors

Figure 5. Spleen Volume Reduction ≥35% (A) and Total Symptom Score Reduction ≥50% (B) at Week 24 (ITT-Efficacy Population)



*Gale criteria.

- At baseline, 16% of patients (safety population) had grade 3 anemia (no grade >3; **Table 2**)

Table 2. Summary of Anemia Adverse Events (Safety Population)

Anemia event*, n (%)	PAC QD (n=104)	PAC BID (n=106)	BAT (n=98)†
Grade 3 anemia at baseline	19 (18)	16 (15)	14 (14)
Any grade anemia TEAE	29 (28)	26 (25)	15 (15)
Treatment-related anemia	15 (14)	15 (14)	7 (7)
Grade 3/4 anemia TEAE	28 (27)	24 (23)	14 (14)
Serious TEAE of anemia	5 (5)	8 (8)	3 (3)
Dose reduction due to anemia	4 (4)	1 (1)	0
Dose interruption due to anemia	4 (4)	5 (5)	1 (1)
Discontinuation due to anemia	2 (2)	3 (3)	0

TEAE, treatment-emergent adverse event.
*Preferred terms of anemia and hemoglobin decreased. †Including 19 patients who had watchful waiting only.

- Incidence of treatment-emergent anemia was highest during the first 16 weeks of PAC (20% and 9% weeks 1-8, 9% and 13% weeks 8-16 for QD and BID, respectively) and first 8 weeks of BAT (10%)

Table 3. Treatment-Emergent Adverse Events (Safety Population)

	PAC QD		PAC BID		BAT	
	Anemic (n=65)	Nonanemic (n=39)	Anemic (n=62)	Nonanemic (n=44)	Anemic (n=54)	Nonanemic (n=44)
Any grade TEAEs in ≥20% in PAC QD, PAC BID, or BAT arm, n (%)						
Any TEAE	65 (100)	39 (100)	58 (94)	42 (95)	49 (91)	38 (86)
Diarrhea	39 (60)	31 (79)	26 (42)	25 (57)	7 (13)	8 (18)
Nausea	21 (32)	18 (46)	20 (32)	14 (32)	6 (11)	5 (11)
Thrombocytopenia*	26 (40)	9 (23)	24 (39)	14 (32)	15 (28)	9 (20)
Anemia†	18 (28)	11 (28)	19 (31)	7 (16)	11 (20)	4 (9)
Vomiting	12 (18)	10 (26)	11 (18)	9 (20)	2 (4)	3 (7)
Peripheral edema	7 (11)	7 (18)	16 (26)	5 (11)	9 (17)	6 (14)
Grade 3/4 TEAEs in ≥10% in PAC QD, PAC BID, or BAT arm, n (%)						
Any grade 3/4 events	52 (80)	27 (69)	44 (71)	30 (68)	32 (59)	16 (36)
Thrombocytopenia*	26 (40)	7 (18)	22 (35)	13 (30)	13 (24)	6 (14)
Anemia†	17 (26)	11 (28)	17 (27)	7 (16)	11 (20)	3 (7)
Serious TEAEs in ≥5% in PAC QD, PAC BID, or BAT arm, n (%)						
Any serious event	34 (52)	14 (36)	28 (45)	22 (50)	17 (31)	13 (30)
Anemia†	5 (8)	0	8 (13)	0	3 (6)	0
Thrombocytopenia*	2 (3)	0	5 (8)	1 (2)	1 (2)	1 (2)
Pneumonia	4 (6)	1 (3)	5 (8)	1 (2)	2 (4)	2 (5)
Renal failure, acute	2 (3)	3 (8)	1 (2)	1 (2)	0	2 (5)

*Preferred terms of thrombocytopenia and platelet count decreased. †Preferred terms of anemia and hemoglobin decreased.

- Incidence of grade 3/4 treatment-emergent anemia was similar in PAC QD patients with/without baseline anemia and lower in patients without baseline anemia in PAC BID and BAT patients (**Table 3**)
- All instances of treatment-emergent serious anemia occurred in patients with baseline anemia and dose modifications, or discontinuations due to anemia were uncommon in PAC-treated patients (**Table 2**)
- In exposure-response analyses with PAC, no relationship was evident for grade ≥2 treatment-emergent anemia
- Rates of any treatment-emergent grade 3/4 and serious AEs were higher in patients with baseline anemia on the PAC QD and BAT arms, but not on the PAC BID arm (**Table 3**)

CONCLUSIONS

- In the phase 3 PERSIST-2 study of PAC vs BAT in patients with MF and baseline thrombocytopenia, PAC treatment demonstrated SVR and symptom control, regardless of baseline anemia or transfusion burden
  - Highest rates were observed with PAC BID overall and across patient subgroups
- PAC treatment led to clinical improvement in hemoglobin and reduced RBC transfusion needs vs BAT
  - Effects observed have been limited by study truncation due to FDA clinical hold (hold later removed after review of complete phase 3 data)
- Serious anemia and dose modifications due to anemia were uncommon
- Rates of any treatment-emergent grade 3/4 AEs were markedly higher in patients with baseline anemia on the PAC QD and BAT arms, but not the PAC BID arm
- PAC 200 mg BID provides a treatment option for patients with MF and baseline cytopenias (anemia and/or thrombocytopenia), for whom available options are limited

REFERENCES

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. Verstovsek S, et al. *N Engl J Med.* 2012;366:799-807.
7. Harrison C, et al. *N Engl J Med.* 2012;366:787-798.
8. Keohane C, et al. *Biologics.* 2013;7:189-198.
9. Singer JW, et al. *J Exp Pharmacol.* 2016;8:11-9.
10. Komrokji RS, et al. *Blood.* 2015;125:2649-55.
11. Mascarenhas J, et al. *Blood.* 2016;128:LBA-5.
12. Gale RP, et al. *Leukemia Res.* 2011;35:8-11.

ACKNOWLEDGEMENTS

- We would like to thank all the personnel who contributed to this study
- Editorial assistance funded by CTI BioPharma Corp. was provided by Nexus Global Group Science, LLC (Stacey Rose, PhD)

Copies of this poster obtained through Quick Response Code are for personal use only and may not be reproduced without permission from the author of this poster and the European Hematology Association

Poster presented at the European Hematology Association (EHA) Annual Congress, June 22–25, 2017, Madrid, Spain.