Risk-adjusted safety analysis of pacritinib in patients with myelofibrosis

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BACKGROUND

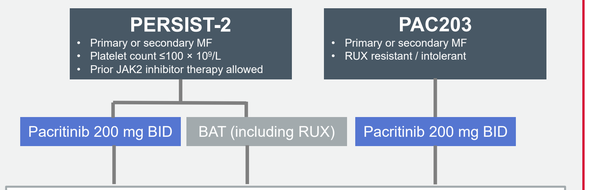
- Pacritinib is a novel JAK2/IRAK1 inhibitor that has shown significant activity in patients with myelofibrosis (MF), including those with platelet counts <50×10^9/L.[1-3]
- Recently, JAK inhibitors have come under increased scrutiny due to specific, emerging toxicities with drugs in this class.[4]
- This safety analysis focuses on these toxicities of interest for patients treated with pacritinib 200 mg twice daily (BID) and best available therapy (BAT), including ruxolitinib (RUX), on the Phase 3 PERSIST-2[2] and Phase 2 PAC203[3] studies.
- Data are presented as risk-adjusted incidences to account for differential time at risk for adverse events (AEs) between arms due to cross-over.

METHODS

Study Design

- The aim of this analysis is to describe the safety profile of pacritinib 200 mg BID, accounting for time on treatment
- Patient inclusion and methodology for calculating risk-adjusted incidence rate is shown in **Figure 1**.
- Risk-adjusted AEs, representing event rate per 100 patient-years, were calculated for overall and fatal AEs, bleeding and cardiac AEs (by Standardized Medical Dictionary for Regulatory Activities Query [SMQ]), major adverse cardiac events (per MACE classification), infections, thromboses, and secondary malignancies.

Figure 1. Study Methodology



Risk-adjusted incidence rate is calculated based on exposure-adjusted incidence per 100 patient-years, as follows:

$$100 \times \frac{N}{T}$$

N ← Number of patients with an event

T ← Total patient-years at risk of the event, calculated as:
- For patients with no event
  - [(date last dose) – (date first dose) + 1] / 365.25
- For patients with an event
  - [(date event) – (date first dose) + 1] / 365.25

BAT=best available therapy; BID=twice per day; JAK=Janus associated kinase; MF=myelofibrosis; RUX=ruxolitinib.

RESULTS

Patient Characteristics

- A total of 160 patients were analyzed as the pooled pacritinib group (n=106 in PERSIST-2; n=54 in PAC203) and 98 pts in the BAT group (44 on RUX). Baseline characteristics are shown in **Table 1**.
- Time on treatment was longer on pacritinib 200 mg BID than BAT
  - PERSIST-2: mean duration of therapy 6.5 months on pacritinib vs 4.9 months on BAT.
  - PAC-203: mean duration of therapy 6.0 months on pacritinib

Table 1. Baseline Patient and Disease Characteristics

Characteristics	PAC203	PERSIST-2			Pooled
	PAC n=54	PAC n=106	BAT n=98	BAT=RUX n=44	PAC n=160
Age (years), median	68.5	67.0	68.0	68.0	68.0
Female gender, n (%)	22 (40.7%)	44 (41.5%)	45 (46%)	15 (34.1%)	66 (41.3%)
ECOG PS ≥2, n (%)	8 (14.8%)	12 (11.3%)	18 (18.4%)	10 (22.7%)	20 (12.5%)
Platelets[a] (x 10^9/L), median	59.0	55.0	57.0	61.0	57.0
Platelets <50 x 10^{9}L, n (%)	**24 (44%)**	**47 (44%)**	**42 (43%)**	**17 (39%)**	**71 (44%)**
Hemoglobin (g/dL), median	8.5	9.7	9.7	9.9	9.2
Receives RBC transfusions, n (%)	34 (63.0%)	49 (46.2%)	47 (48.0%)	19 (43.2%)	83 (51.9%)
Peripheral blasts ≥1%, n (%)	32 (59.3%)	48 (45.3%)	46 (46.9%)	27 (61.4%)	80 (50.0%)
Primary MF, n (%)	37 (68.5%)	82 (77.4%)	60 (61.2%)	22 (50.0%)	119 (74.4%)
DIPSS high risk, n (%)	14 (26%)	29 (27.4%)	26 (26.5%)	12 (27.3%)	46 (28.6%)
Prior JAKi exposure, n (%)	54 (100%)	51 (48%)	52 (53%)	32 (73%)	105 (66%)

[a]Baseline platelet information was not available for all patients in safety population. PERSIST-2 PAC n=105, BAT n=97, BAT=RUX n=43; PAC203 n=53; Pooled n=158.
BAT=best available therapy; DIPSS=Dynamic International Prognostic Scoring System; EGOC=Eastern Cooperative Oncology Group; JAKi=Janus associated kinase inhibitor; MF=myelofibrosis; PAC=pacritinib; PS=performance status; RBC=red blood cell; RUX=ruxolitinib.

Risk-Adjusted Safety Analysis

- The rate of all-grade and grade ≥3 AEs was higher on PAC than BAT
- The rate of fatal AEs was lower on PAC than BAT, including ruxolitinib (**Table 2**).
- The rate of high-grade and fatal events was higher in patients with baseline platelet count <50 x 10^9/L, though the relationship between treatment arms was similar to that observed in the overall population.

Table 2. Risk-Adjusted TEAE Overview

Patients with Events Per 100 Patient-Years at Risk (Number of Patients / Total Patient-Years)	PAC203 PAC	PERSIST-2			Pooled PAC
		PAC	BAT	BAT=RUX	
Any event	**2063** (54/2.6)	**1390** (100/7.2)	**903** (87/9.6)	**1468** (41/2.8)	**1570** (154/9.8)
Any event (PLT <50 x 10^9/L)	**2609** (24/0.9)	**2171** (46/2.1)	**1064** (38/3.6)	**1408** (15/1.1)	**2303** (70/3.0)
Grade ≥3 event	**252** (41/16.3)	**250** (76/30.4)	**167** (48/28.7)	**158** (20/12.7)	**250** (117/46.7)
Grade ≥3 event (PLT <50 x 10^9/L)	**509** (23/4.5)	**371** (39/10.5)	**246** (26/10.6)	**188** (8/4.3)	**413** (62/15.0)
Fatal event	**10** (3/29.6)	**12** (8/65.6)	**22** (9/41.5)	**27** (5/18.4)	**12** (11/95.2)
Fatal event (PLT <50 x 10^9/L)	**20** (3/14.8)	**23** (6/25.8)	**48** (8/16.6)	**81** (5/6.2)	**22** (9/40.6)

BAT=best available treatment; PAC=pacritinib; PLT=platelets; RUX=ruxolitinib; TEAE=treatment-emergent adverse events.

- Cardiac events, including high-grade events, occurred at slightly lower rates on pacritinib compared to BAT. There were no MACE events on pacritinib, whereas there were on BAT (**Table 3**).
- Events of QT prolongation and heart failure were uncommon on all treatment arms; bleeding and thrombosis occurred at similar rates on pacritinib and BAT (**Table 3**).

Table 3. Risk-Adjusted Cardiovascular and Bleeding TEAEs

Patients with Events Per 100 Patient-Years at Risk (Number of Patients / Total Patient-Years)	PAC203 PAC	PERSIST-2			Pooled PAC
		PAC	BAT	BAT=RUX	
Cardiac event[a]	**101** (22/21.7)	**62** (34/55.3)	**81** (27/33.5)	**67** (10/14.8)	**72** (56/77.0)
Cardiac event[a] (PLT <50 x 10^9/L)	**121** (13/10.8)	**77** (16/20.7)	**168** (19/11.3)	**230** (8/3.5)	**92** (29/31.5)
Cardiac event[a] grade ≥3	**7** (2/28.2)	**11** (7/64.5)	**23** (9/39.8)	**11** (2/18.0)	**10** (9/92.7)
Cardiac event[a] grade ≥3 (PLT <50 x 10^9/L)	**15** (2/13.4)	**16** (4/24.7)	**52** (8/15.4)	**35** (2/5.7)	**16** (6/38.1)
MACE[b]	**0** (0/29.6)	**0** (0/65.7)	**5** (2/41.4)	**5** (1/18.5)	**0** (0/95.3)
MACE[b] (PLT <50 x 10^9/L)	**0** (0/14.8)	**0** (0/25.8)	**12** (2/16.4)	**16** (1/6.3)	**0** (0/40.6)
QT prolongation event	**15** (2/27.0)	**3** (2/64.3)	**7** (3/40.6)	**0** (0/18.5)	**7** (6/91.4)
QT prolongation event (PLT <50 x 10^9/L)	**0** (0/14.8)	**0** (0/25.8)	**6** (1/16.8)	**0** (0/6.3)	**0** (0/40.6)
Heart failure / cardiomyopathy[c]	**0** (0/29.6)	**0** (0/65.7)	**2** (1/41.4)	**0** (0/18.5)	**0** (0/95.3)
Heart failure / cardiomyopathy[c] (PLT <50 x 10^9/L)	**0** (0/14.8)	**0** (0/25.8)	**6** (1/16.4)	**0** (0/6.3)	**0** (0/40.6)
Thrombosis[d]	**10** (3/29.4)	**2** (1/65.7)	**2** (1/41.0)	**6** (1/17.8)	**4** (4/95.1)
Thrombosis[d] (PLT <50 x 10^9/L)	**7** (1/14.7)	**0** (0/25)	**6** (1/16.1)	**18** (1/5.5)	**3** (1/40.6)
Bleeding event[a]	**105** (23/21.9)	**98** (45/45.8)	**129** (40/31.1)	**127** (18/14.1)	**100** (68/67.8)
Bleeding event[a] (PLT <50 x 10^9/L)	**239** (18/7.5)	**133** (23/17.3)	**270** (26/9.6)	**229** (10/4.4)	**165** (41/24.8)
Bleeding event[a] grade ≥3	**14** (4/28.9)	**29** (17/59.2)	**17** (7/40.8)	**17** (3/18.1)	**24** (21/88.0)
Bleeding event[a] grade ≥3 (PLT <50 x 10^9/L)	**21** (3/14.1)	**36** (8/22.3)	**31** (5/16.4)	**33** (2/6.1)	**30** (11/36.4)

[a]Cardiac and bleeding events determined by Standardised MedDRA Query (SMQ). [b]MACE includes fatal cardiac events, non-fatal ischemic stroke of any grade, and non-fatal myocardial infarction (MI) of any grade. [c]Includes any event related to heart failure or cardiomyopathy, as determined by medical review. [d]Includes arterial / venous thrombosis, embolic disease, ischemic stroke, and myocardial infarction due to coronary thrombosis (type 1 MI) , as determined by medical review.

Table 4. Risk-Adjusted Malignancy TEAEs

Patients with Events Per 100 Patient-Years at Risk (Number of Patients / Total Patient-Years)	PAC203 PAC	PERSIST-2			Pooled PAC
		PAC	BAT	BAT=RUX	
Malignancy - excluding leukemic transformation[a]	**0** (0/29.6)	**8** (5/63.7)	**7** (3/40.8)	**11** (2/17.8)	**5** (5/93.3)
Malignancy - excluding leukemic transformation[a] (PLT <50 x 10^9/L)	**0** (0/14.8)	**17** (4/24.2)	**6** (1/16.3)	**17** (1/5.8)	**10** (4/39.0)
Non-melanoma skin cancer[b]	**0** (0/29.6)	**5** (3/64.2)	**7** (3/40.8)	**11** (2/17.8)	**3** (3/93.8)
Non-melanoma skin cancer[b] (PLT <50 x 10^9/L)	**0** (0/14.8)	**8** (2/24.7)	**6** (1/16.3)	**17** (1/5.8)	**5** (2/39.5)

[a]Includes all events within the Systems Order Class (SOC) 'Neoplasms benign, malignant, and unspecified', excluding acute leukemia, myelofibrosis, and benign tumors. [b]Includes basal cell and squamous cell carcinoma of the skin, as determined by medical review.

- Malignant neoplasms occurred at similar rates on pacritinib and BAT in PERSIST-2. No malignant neoplasms were noted in patients treated with pacritinib 200 mg BID on PAC203 (**Table 4**).
- Rates of non-melanoma skin cancer were similar on pacritinib and BAT; rates were slightly higher on ruxolitinib.

Table 5. Risk-Adjusted Infection and Encephalopathy TEAEs

Patients with Events Per 100 Patient-Years at Risk (Number of Patients / Total Patient-Years)	PAC203 PAC	PERSIST-2			Pooled PAC
		PAC	BAT	BAT=RUX	
Infection[a]	**103** (23/22.3)	**124** (51/41.2)	**88** (30/34.2)	**80** (12/15.1)	**116** (74/63.6)
Infection[a] (PLT <50 x 10^9/L)	**125** (13/10.4)	**188** (26/13.8)	**119** (15/12.6)	**113** (5/4.4)	**161** (39/24.2)
Viral infection[b]	**7** (2/29.2)	**5** (3/65.1)	**12** (5/41.1)	**11** (2/18.3)	**5** (5/94.3)
Viral infection[b] (PLT <50 x 10^9/L)	**7** (1/14.8)	**8** (2/25.3)	**12** (2/16.5)	**0** (0/6.3)	**8** (3/40.1)
Zoster[c]	**0** (0/29.6)	**0** (0/65.7)	**2** (1/41.5)	**6** (1/18.3)	**0** (0/95.3)
Zoster[c] (PLT <50 x 10^9/L)	**0** (0/14.8)	**0** (0/25.8)	**0** (0/16.8)	**0** (0/6.3)	**0** (0/40.6)
Fungal infection	**10** (3/29.1)	**5** (3.64.1)	**12** (5/40.8)	**6** (1/18.3)	**6** (6/93.1)
Fungal infection (PLT <50 x 10^9/L)	**21** (3/14.3)	**8** (2/24.7)	**19** (3/16.2)	**0** (0/6.3)	**13** (5/39.0)
Encephalopathy	**0** (0/29.6)	**0** (0/65.7)	**0** (0/41.7)	**0** (0/18.5)	**0** (0/95.3)
Encephalopathy (PLT <50 x 10^9/L)	**0** (0/14.8)	**0** (0/25.8)	**0** (0/16.8)	**0** (0/6.3)	**0** (0/40.6)

[a]Includes all events within the Systems Order Class (SOC) 'Infection'. [b]Includes any infection event attributed to a specific virus (e.g., cytomegalovirus reactivation, herpes keratitis), or described as being "viral" (e.g., viral gastroenteritis, viral upper respiratory tract infection), as determined by medical review. [c]Includes any infection event relating to 'zoster' or 'shingles', as determined by medical review. [d]Includes any infection event attributed to a specific fungus, as determined by medical review.

- Infection occurred slightly more frequently on pacritinib than on BAT (**Table 5**).
  - Infection was more common in patients with baseline platelet count <50 x 10^9/L across all treatment arms.
- Fungal and viral infections occurred slightly less frequently on pacritinib, as did herpes zoster reactivation (**Table 5**).

CONCLUSIONS

- **Risk-adjusted analysis demonstrates that the safety profile of pacritinib 200 mg BID is comparable to BAT.**
  - **Rates of bleeding were not elevated on PAC 200 mg BID compared to BAT, including in patients with PLT <50 x 10^9/L.**
  - **Rates of fatal events, thrombosis, MACE, and non-melanoma skin cancer were higher on ruxolitinib than pacritinib.**
- **Pacritinib 200 mg BID may represent a full-dose therapeutic option for patients with MF, including those with thrombocytopenia.**

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