

PACIFICA: A Randomized, Controlled Phase 3 Study of Pacritinib Versus Physician’s Choice in Patients With Primary or Secondary Myelofibrosis and Severe Thrombocytopenia

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BACKGROUND

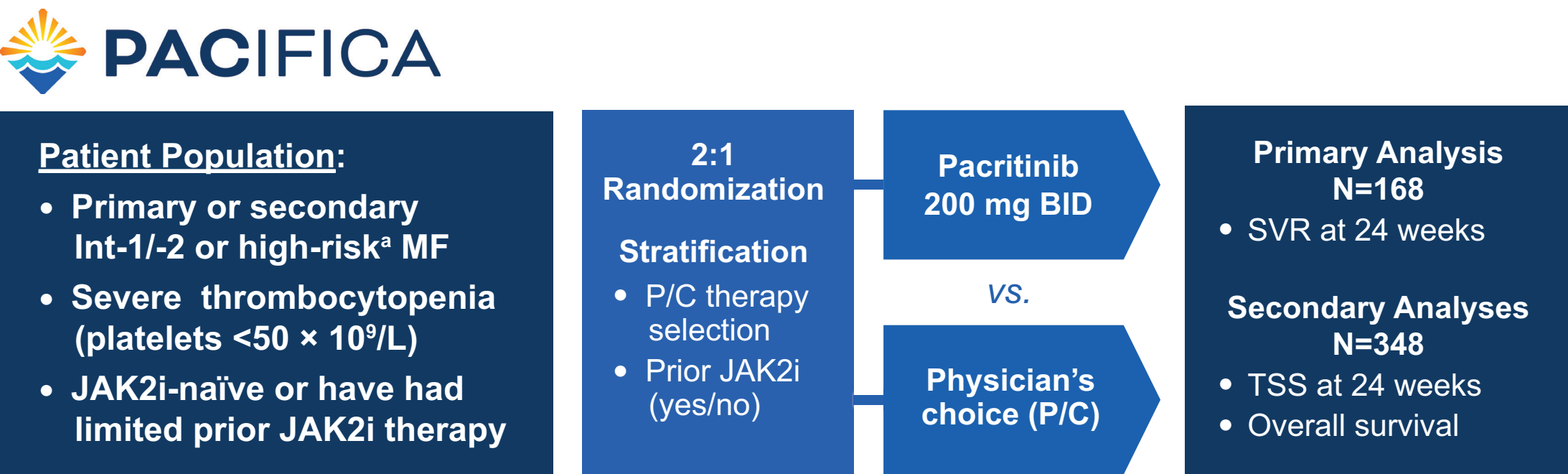
Myelofibrosis With Severe Thrombocytopenia

- Myelofibrosis is a serious and frequently life-threatening clonal myeloproliferative neoplasm (MPN) affecting hematopoietic cells in all lineages resulting in progressive marrow fibrosis and hematopoietic failure.¹
- Patients with cytopenic myelofibrosis and severe thrombocytopenia (platelet counts <50 × 10⁹/L) generally have more advanced disease consisting of severe pancytopenia (often requiring transfusion support), high-grade marrow fibrosis, complex or unfavorable cytogenetics, and shorter overall survival (OS; median 15 months) compared to those with higher platelet counts.²⁻⁴
- Prescribing information for currently approved JAK inhibitors does not provide dosing recommendations for patients with severe thrombocytopenia.^{5,6} For such patients, NCCN and ELN guidelines suggest enrollment in clinical trials due to limited therapeutic options.^{7,8}

Pacritinib Development

- Pacritinib is an oral JAK2/IRAK1 inhibitor with minimal activity against JAK1.⁹
- Pacritinib demonstrated clinical activity in myelofibrosis in two phase 3 studies (PERSIST-1, PERSIST-2) and a phase 2 dose-finding study (PAC203), all of which included patients with severe thrombocytopenia. In the subset of patients with severe thrombocytopenia in each study, clinical activity was consistent with the overall study population.¹⁰⁻¹²
- Based on efficacy and safety data from PERSIST-1, PERSIST-2, and PAC203, as well as dose- and exposure-response analyses conducted on all available data, pacritinib 200 mg BID was selected for the PACIFICA trial.¹⁰⁻¹²
- The phase 3 portion of PAC203, PACIFICA (NCT03165734), is designed to evaluate efficacy and safety of pacritinib 200 mg BID vs. physician’s choice (P/C) therapy in patients with myelofibrosis and severe thrombocytopenia.

STUDY DESIGN



Int, Intermediate; JAK2i, JAK2 inhibitor; SVR, ≥35% spleen volume reduction; TSS, ≥50% reduction in total symptom score.
^aDIPSS (Dynamic International Prognostic Scoring System).

- P/C includes any one of the following: low-dose ruxolitinib (5 mg BID or 5 mg QD starting dose), corticosteroids, hydroxyurea, danazol. Investigators can select an individual P/C agent but cannot combine agents or give them sequentially.
- Patients treated until disease progression, intolerable adverse events, or withdrawal of consent.
- All patients followed for survival until 2.5 years after randomization.

STUDY OBJECTIVES

Primary

- To compare efficacy of pacritinib vs. P/C therapy based on the proportion of patients with ≥35% spleen volume reduction (SVR) at Week 24.

Secondary

- To compare the proportion of patients treated with pacritinib vs. P/C with ≥50% reduction in total symptom score (TSS) at Week 24.
- To compare the OS of patients treated with pacritinib vs. P/C therapy.
- Safety based on the incidence and severity of treatment-emergent adverse events.
- To compare the proportion of patients treated with pacritinib vs. P/C who self-assess as “very much improved” or “much improved” at Week 24 as measured by the Patient Global Impression of Change.

Tertiary

- Time to achievement of SVR of ≥35%
- Best response in SVR by MRI or CT scan
- Proportion of patients achieving ≥25% SVR between baseline and Week 24
- Hematologic improvement (transfusion independence and improvement in hemoglobin and platelet levels)
- Improvement in fatigue as measured by the Patient-Reported Outcomes Measurement Information System v.1.0 – Fatigue – Short Form 7a
- Changes in pharmacodynamic biomarkers
- Changes in genetic mutation and gene expression
- Pharmacokinetic profile of pacritinib

MAJOR ELIGIBILITY CRITERIA

Key Inclusion Criteria

- Adults with primary or secondary myelofibrosis
- Platelet count <50 × 10⁹/L
- DIPSS Intermediate-1, Intermediate-2, or high-risk disease
- Palpable spleen ≥5 cm below left costal margin
- TSS ≥10 (MPN-SAF TSS 2.0) or 1 symptom ≥5 or 2 symptoms ≥3 including only the symptoms of left upper quadrant pain, bone pain, itching, night sweats
- ECOG performance status 0-2
- Left ventricular ejection fraction ≥50%
- Peripheral blasts <10%
- Adequate hepatic and renal function, coagulation parameters, and neutrophil count

References: 1. Vardiman et al. *Blood*. 2009;114:937-951. 2. Hernandez-Boluda et al. *Br J Haematol*. 2018;181:397-400. 3. Masarova et al. *Eur J Haematol*. 2018;100:257-263. 4. Scotch et al. *Leuk Res*. 2017;63:34-40. 5. Jakafi® (ruxolitinib) [prescribing information]. Incyte Corporation; 2020. 6. INREBIC® (fedratinib) [prescribing information]. Celgene Corporation; 2019. 7. NCCN Guidelines. Myeloproliferative Neoplasms. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed April 14, 2021. 8. Barbui et al. *Leukemia*. 2018;32:1057-1069. 9. Singer et al. *J Exp Pharmacol*. 2016;8:11-19. 10. Mesa et al. *Lancet Haematol*. 2017;4:e225-e236. 11. Mascarenhas et al. *JAMA Oncol*. 2018;4:652-659. 12. Gerds et al. *Blood Adv*. 2020;4:5825-5835.

Key Exclusion Criteria

- Prior splenectomy or allogeneic stem cell transplantation
- Any myelofibrosis therapy within 14 days prior to Day 1
- Any prior JAK2 inhibitor treatment for >90 days or prior treatment with ruxolitinib at ≤10 mg total daily dose with a duration of >180 days
- Grade ≥2 bleeding within prior 3 months unless precipitated by an inciting event
- Medications that increase bleeding risk within 14 days prior to Day 1
- Grade ≥2 cardiac conditions within 6 months prior to Day 1 (asymptomatic and stable grade 2 conditions may be considered for inclusion)
- QTc >450 msec or medications that prolong QT interval within 14 days prior to Day 1
- NYHA Class II, III, or IV heart failure
- Active or uncontrolled bowel disorders
- Non-myelofibrosis malignancy within prior 3 years other than curatively treated basal or squamous skin cancer, cervical carcinoma in situ, breast carcinoma in situ, or non-metastatic prostate cancer (prostate cancer under watch-and-wait strategy may be considered for inclusion)

STATISTICAL ANALYSIS

Variable	Plan	
	SVR Primary Endpoint	TSS Secondary Endpoint
Sample Size	168	348
Randomization	2:1 (pacritinib:P/C)	2:1 (pacritinib:P/C)
Power	>80%	80%
alpha	Two-sided 0.05	Two-sided 0.05

- Planned subgroup analyses: age, sex, race, P/C treatment selection, prior JAK2 inhibitor therapy, and geographic region

STUDY STATUS

- Actively enrolling
- 130+ clinical sites worldwide

