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POSTER ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

Platelet Response in Pacritinib-Treated Patients with Cytopenic Myelofibrosis: A Retrospective Analysis of PERSIST-2 and PAC203 Studies

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Background: Myelofibrosis (MF) is a myeloid malignancy characterized by clonal hematopoisis, bone marrow fibrosis (BMF) and ineffective extramedullary hematopoiesis, resulting in progressive cytopenias. Thrombocytopenia is both prognostic of poor outcomes and predictive of treatment intolerance with the JAK1/2 inhibitor ruxolitinib, which exacerbates cytopenias. Pacritinib is a JAK1-sparing inhibitor of JAK2/IRAK1/ACVR1 that can be administered at full dose to patients regardless of baseline platelet count (PLT). While prior studies have shown that pacritinib is associated with PLT stability in most patients, PLT improvement has not been described outside of a recently published case report (*Yacoub A, et al. JCO Precis Oncol. 2023;7:e2200523*). Here, we report rates of hematologic improvement in PLTs (HI-P) with pacritinib across two clinical trials.
Methods: Patients with baseline PLT $\leq$100x10 ^{9}/L on the pacritinib 200 mg BID arms of the phase 3 PERSIST-2 study (randomized $\geq$12 weeks prior to study termination) or the phase 2 dose-finding PAC203 study were included. HI-P was defined per International Working Group (IWG) criteria (baseline PLT <20x10 ^{9}/L: increase to >20x10 ^{9}/L and by at least 100%; baseline PLT 20-100 x 10 ^{9}/L: absolute increase of $\geq$30x10 ^{9}/L) in the absence of PLT transfusions, sustained over any 8 weeks while on treatment. Efficacy outcomes (reduction in spleen volume, symptom score, and BMF) were compared between HI-P responders vs non-responders (those who did not meet IWG criteria). Rates of PLT improvement were also analyzed on the best available therapy (BAT) arm of the PERSIST-2 study over the treatment period (end of study treatment).
Results: Of 117 patients randomized to pacritinib (75 from PERSIST-2, 42 from PAC203), 16% (n=19) experienced HI-P on study (as defined in methods). Additionally, 14 of the 19 HI-P patients had sustained platelet improvement over $\geq$12 weeks). By contrast, only 5% (4/77) of patients on BAT achieved HI-P response prior to end of study treatment.
HI-P responders on pacritinib compared to non-responders, had numerically higher median baseline PLT count (63 vs 45x10 ^{9}/L) and hemoglobin (Hb; 10.3 vs 8.8 g/dL). A similar percentage had prior (<30 days) JAK2 inhibitor exposure (68.4% vs 66.3%) and JAK2V617F mutation (78.9 vs 74.5%); median JAK2 allele burden was low in both responders and non-responders (26.7% vs 36.9%). Among HI-P responders with prior ruxolitinib exposure, most (85%, 11/13) had recent exposure within the prior 30 days, with median dose of 10 mg BID.
PLT improvement was noted within the first 12 weeks in most HI-P responders, whereas PLT count remained stable, on average, among non-responders (**Figure 1a**). To evaluate if recent ruxolitinib exposure and washout of drug was responsible for HI-P, we analyzed the subset of patients with ruxolitinib exposure in previous 30 days (11/19). The mean platelet count increased from 56 to 141x10 ^{9}/L at week 12. In the remaining 8/19 patients without recent ruxolitinib exposure (n=6 were treatment naïve), platelets increased from 59 to 102 x 10 ^{9}/L at week 12.

While there was no difference in the magnitude of spleen volume or symptom score reduction in HI-P responders vs non-responders, a correlation with change in BMF was noted. Among the 36 patients with available bone marrow data from baseline and week 24, HI-P responders were numerically more likely to have BMF reduction (67%, n=4/6) compared to non-responders (23%, n=7/30, *P*=0.057, **Figure 1b**).

There was no difference in the rate of hemorrhagic events (by standardized MedDRA queries) in PLT responders vs non-responders (47% vs 46%), though grade ≥3 bleeding was observed at lower frequency in responders compared to non-responders (10.5% vs 16%). Other commonly reported adverse events with pacritinib occurred at similar frequency between responders and non-responders.

Discussion: PLT improvement meeting IWG criteria occurs in a subset of MF patients treated with pacritinib and does not seem to be explained by changes in spleen volume. Further studies are warranted to assess the correlation between hematologic improvement and BMF reduction with pacritinib. It is possible that pacritinib's unique mechanism of action as an IRAK1 inhibitor could result in modulation of the bone marrow microenvironment and thrombopoiesis.

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Disclosures Vachhani: *Abbvie, Amgen, Blueprint Medicines, Cogent Biosciences, Incyte, CTI BioPharma Corp, Daiichi Sankyo, GlaxoSmith Kline, Karyopharm, Novartis, Pfizer, Genentech, Inc., Servier, Stemline, MorphoSys, LAVA therapeutics:* Honoraria; *Incyte, CTI BioPharma Corp, Blueprint Medicines:* Speakers Bureau. **Yacoub:** *Novartis:* Consultancy; *CTI Pharma:* Consultancy; *Incyte:* Consultancy; *Pfizer:* Consultancy; *Acceleron Pharma:* Consultancy; *Pharmaessentia:* Consultancy. **Traer:** *Rigel:* Membership on an entity's Board of Directors or advisory committees; *Astellas:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Servier:* Membership on an entity's Board of Directors or advisory committees; *Daiichi-Sankyo:* Membership on an entity's Board of Directors or advisory committees; *Schrodinger:* Research Funding; *Astra-Zeneca:* Research Funding; *Incyte:* Research Funding; *Prelude Therapeutics:* Research Funding; *Abbvie:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Benajiba:** *Gilead:* Research Funding; *Pfizer:* Research Funding. **Passamonti:** *AbbVie, Janssen:* Honoraria. **Kishtagari:** *Servier Pharmaceuticals:* Consultancy; *Geron Corporation:* Honoraria; *CTI BioPharma Corp., a Sobi company:* Consultancy, Honoraria, Speakers Bureau. **Akhtari:** *Sanofi:* Speakers Bureau; *SrcuraBio:* Speakers Bureau; *Janssen:* Speakers Bureau; *PharmaEssentia:* Speakers Bureau; *Takeda:* Speakers Bureau; *Jazz Pharmaceuticals:* Speakers Bureau; *CTI BioPharma Corp., a Sobi company:* Speakers Bureau; *Incyte:* Speakers Bureau; *AbbVie:* Honoraria; *Amgen:* Research Funding; *Ispen:* Speakers Bureau; *Rigel:* Speakers Bureau. **McCloskey:** *AbbVie:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Amgen:* Speakers Bureau; *BMS:* Speakers Bureau; *Incyte:* Speakers Bureau; *Jazz Pharmaceuticals:* Speakers Bureau; *Stemline:* Speakers Bureau; *Takeda:* Speakers Bureau; *CTI BioPharma Corp., a Sobi company:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Novartis:* Consultancy, Membership on an entity's Board of Directors or advisory committees. **Buckley:** *CTI BioPharma Corp., a Sobi company:* Current Employment, Other: Company provided vested and unvested equity awards to author as a company employee as part of overall compensation package, and all such equity grants were subject to accelerated vesting and pay out following Company's sale to new ownership. **Suthar:** *CTI BioPharma Corp., a Sobi company:* Current Employment, Other: Company provided vested and unvested equity awards to author as a company employee as part of overall compensation package, and all such equity grants were subject to accelerated vesting and pay out following Company's sale to new ownership. **Roman-Torres:** *CTI BioPharma Corp., a Sobi company:* Consultancy, Other: Company provided vested and unvested equity awards to author as a company employee as part of overall compensation package, and all such equity grants were subject to accelerated vesting and pay out following Company's sale to new ownership. **Mascarenhas:** *Bristol Myers Squibb, Celgene, CTI BioPharma, Geron, Incyte Corporation, Janssen, Kartos Therapeutics, Merck, Novartis, PharmaEssentia, Roche; Participated in consulting or advisory committees - AbbVie, Bristol Myers Squibb, Celgene, Constellation Pharmac:* Research Funding; *Incyte, Novartis, Roche, Geron, GSK, Celgene/BMS, Kartos, AbbVie, Karyopharm, PharmaEssentia, Galecto, Imago, Sierra Oncology, Pfizer, MorphoSys, CTI Bio:* Consultancy; *Bristol Myers Squibb, Celgene, Constellation Pharmaceuticals/MorphoSys, CTI BioPharma, Galecto, Geron, GSK, Incyte Corporation, Karyopharm Therapeutics, Novartis, PharmaEssentia, Prelude Therapeutics, Pfizer, Merck, Roche, AbbVie, Kartos:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *AbbVie, Bristol Myers Squibb, Celgene, CTI BioPharma, Geron, Incyte Corporation, Novartis, Janssen, Kartos Therapeutics, Merck, PharmaEssentia, Roche:* Research Funding; *AbbVie, CTI BioPharma Corp, a Sobi company, Geron, GlaxoSmithKline, Imago, Incyte, Kartos, Kayropharm, MorphoSys, Novartis, Pfizer, PharmaEssentia, Sierra:* Consultancy; *GSK:* Honoraria.

OffLabel Disclosure: Pacritinib is a kinase inhibitor indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50x10 ^{9}/L. This indication is approved under accelerated approval based on spleen volume reduction. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

Figure 1A. Mean change in platelet count from baseline over time on pacritinib 200 mg BID among HI-P responders vs non-responders
PERSIST-2 & PAC203, pacritinib 200 mg BID

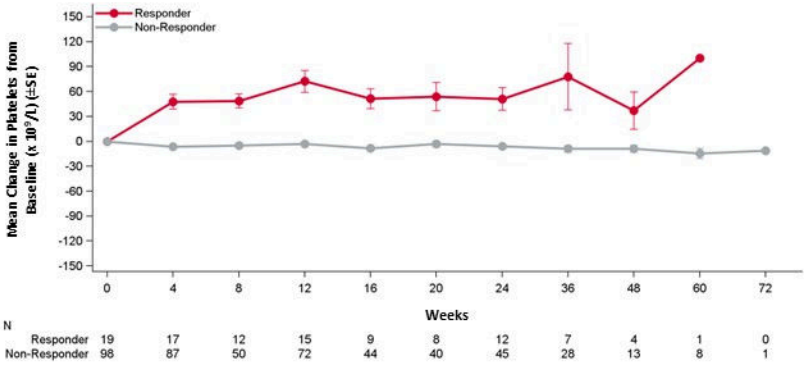
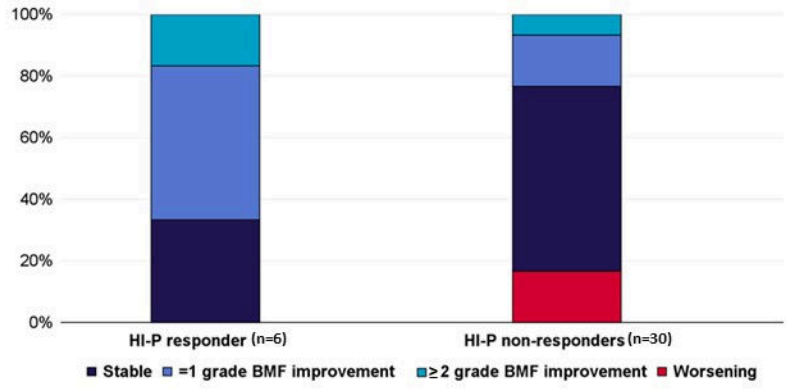


Figure 1B. Bone marrow fibrosis reduction in platelet responders vs non-responders
PERSIST-2 & PAC203, pacritinib 200 mg BID



Abbreviations: BID, twice daily; BL, baseline; BMF, bone marrow fibrosis; HI-P, hematologic improvement in platelets; PLT, platelet; SE, standard errors.

Figure 1

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