Pacritinib and its use in the treatment of patients with myelofibrosis who have thrombocytopenia

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The treatment landscape for myelofibrosis (MF) has reached the molecular era by targeting different pathways that are implied in this myeloproliferative neoplasm. A few years ago, the first-in-class JAK1/JAK2 inhibitor ruxolitinib, demonstrated reductions in both constitutional symptoms and splenomegaly, leading to the US FDA approval. The development or worsening of cytopenias in patients receiving ruxolitinib uncovered an unmet need that has been addressed by alternative approaches. Pacritinib, a dual JAK2 and FLT3 inhibitor which also inhibits IRAK1, has demonstrated the ability to favorably impact MF-associated splenomegaly and symptom burden, while having limited myelosuppression with manageable gastrointestinal toxicity. Herein, we provide an overview of pacritinib, from early preclinical studies to the latest and ongoing PAC203 trial, as an emerging therapy for MF.

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Myelofibrosis (MF) is the least common but most aggressive myeloproliferative neoplasm (MPN). Its median age at diagnosis is 67 years old; 70% of the cases are diagnosed after 60 years of age and close to 10% of the cases diagnosed on those younger than 45 years of age [1]. Signs and symptoms are heterogeneous (Table 1) to include splenomegaly due to extramedullary hematopoiesis, an increase in circulating CD34⁺ cells, anemia, variable changes in the platelet and leukocyte counts, and constitutional symptoms due to inflammatory cytokine production [2–4]. MF is a BCR-ABL1-negative MPN and constitutes a clonal disorder, being JAK2, CALR and MPL, the so-called ‘driver’ mutations causing this disease [5–8]. In patients with primary MF (PMF), the mutation in JAK2 exon 14 gene occurs in about 60% of patients and results in a valine (V) to phenylalanine (F) substitution at codon 617, CALR mutation is present in 20–25% cases and MPL mutations have been reported approximately 5% of cases [9–11]. On the other hand, approximately 10% of patients with PMF are triple-negative (nonmutated *JAK2*, *CALR* and *MPL*), have a poor prognosis and demonstrate a high rate of leukemic transformation [12–14].

As with any other condition, evaluation of the disease burden has become of paramount importance, as MF possesses a mixed-bag type of symptoms and assessment of those provides us – in general terms – a more paved road when thinking about treatment [17–19]. According to guidelines, assessment of MPN symptoms using the MPN Symptom Assessment Form (MPN-SAF) is recommended at baseline and also during treatment [20]. Moreover, robust prognostic tools are widely available and very useful in deciding a risk-adapted therapy. Current prognostic models in MF include the International Prognostic Scoring System (IPSS) [21], applicable at the time of diagnosis, the Dynamic IPSS (DIPSS) [22], applicable at any time in the clinical course of the disease and the refined DIPSS-Plus that incorporates karyotype information as independent risk factor is able to predict median survival from 15 years down to 1.3 years depending on the risk stratification [23]. Alternative scoring systems have been proposed taking into consideration the fact that genetic mutations can impact the prognosis; those are the mutation-enhanced IPSS that integrates clinical and genetic risk factors based on individual patient’s mutation profile, and the genetics-based prognostic scoring system that combines patient’s age and genetic risk factors. Validation of the last two score systems is still required before they can be widely adopted [24–26].

Table 1. Common signs and symptoms in patients with myelofibrosis.

Myelofibrosis signs and symptoms	Percentages
Constitutional symptoms	34
Palpable spleen >10 cm	31
Leukocytes >25,000 μ l	16
Hemoglobin <10 g/dl	54
Platelet count <100,000 μ l	26
Thrombotic events	9.5
Data taken from [15,16].	

Sadly, great burden of morbidity in patients with MF is due to progression to acute myeloid leukemia (AML), thrombotic and hemorrhagic complications, infections, transfusion dependency as a result of severe anemia and thrombocytopenia leading to iron-overload syndromes. Mortality, is as well, related to the above difficulties and unfortunately despite a better understanding of the disease, allogeneic stem cell transplantation remains the only curative therapy for only few eligible patients [17,18,27,28].

JAK-STAT pathway

12 years ago, the discovery of JAK2 mutation and dysregulation of JAK-STAT pathway in MF made biologically evident that the development of JAK2 inhibitors could improve the outcomes in patients suffering of this condition. Within this rational, ruxolitinib, a first-in-class inhibitor of JAK1 and JAK2, was developed and tested showing signals of safety and efficacy leading to two large pivotal multisite Phase III randomized trials, COMFORT-1 and COMFORT-2, where ruxolitinib was compared against placebo and against best available therapy (BAT) in patients with intermediate-2 or high-risk MF per IPSS, respectively [29,30]. Both studies demonstrated that ruxolitinib was safe, in most cases well tolerated and able to achieve reductions in splenomegaly and symptom burden with concomitant improvements in quality of life (QOL); however, anemia and thrombocytopenia were described as well as a resultant of dose-limiting myelosuppression. Dose-related cytopenias were mostly observed in the first 8–12 weeks of treatment but were effectively managed with dose reductions, which were still associated with clinically meaningful reductions in spleen volume and symptom improvement at week 24 [31]. Follow-up data from patients in the COMFORT-1 trial demonstrate that the responses induced by ruxolitinib seem to be durable in time, as patients randomized to ruxolitinib had a median spleen response duration of 168.3 weeks and prolonged median overall survival versus placebo despite the crossover to ruxolitinib [32]. Likewise, long-term follow-up of COMFORT-2 showed that among 53.4% of the patients in the ruxolitinib arm who achieved $\geq 35\%$ spleen volume reduction (SVR) at any time, the probability of maintaining response was 0.48 (95% CI: 0.35–0.60) at 5 years (median, 3.2 years). Median overall survival was not reached in the ruxolitinib arm and was 4.1 years in the BAT arm [33]. So, in summary, the clinical benefits obtained from long-term use of ruxolitinib were generally maintained in addition to survival advantage evidence of ruxolitinib over placebo or BAT.

Eligibility criteria for the COMFORT-1 and COMFORT-2 studies that led to the US FDA approval of ruxolitinib on 16 November 2011, included only patients with platelet counts above 100,000/ μ l. Anemia and thrombocytopenia, as above described, were commonly seen 8–12 weeks after drug initiation, after which time blood counts often returned to baseline. Thrombocytopenia could be managed with dose modifications based on the baseline platelet count and even though no specific contraindications have been determined, ruxolitinib is not recommended for use in patients with platelet counts of less than 50,000/ μ l [34,35].

In order to allow additional collection of safety and efficacy data, an open-label, multicenter study of ruxolitinib in patients with MF was started in 2011. The JUMP study, was a Phase IIIB expanded-access trial for patients in countries without access to ruxolitinib outside of a clinical study and included those classified as intermediate-1 risk, a population that was not included in the COMFORT trials. A total of 2233 patients were enrolled at more than 200 study sites in 26 countries, with a final analysis that included results for 1144 patients with intermediate- or high-risk MF who started ruxolitinib ≥ 1 year before the data cutoff date, as well as a separate analysis of 163 patients with intermediate-1 risk MF. The median age of the patients was 68 years (range: 18–89 years) with most patients completing treatment per protocol and median exposure to ruxolitinib of about 11 months. Consistent with the mechanism of action of ruxolitinib, the most common adverse events (AEs) were anemia and thrombocytopenia that led to treatment discontinuation in only a few cases. The majority of patients achieved

Table 2. Kinase profile comparing pacritinib versus ruxolitinib and momelotinib.

Kinase	FDA approved	Not FDA approved	
	Ruxolitinib (IC ₅₀ at 1 μ M)	Pacritinib (IC ₅₀ [nM])	Momelotinib (IC ₅₀ [nM])
JAK1	++	+	++++
JAK2	++	++++	++++
JAK2(V617F)	NR	++++	+
FLT3	NR	++++	+++
FLT3 (ITD)	NR	++++	NR
FLT3 (D835Y)	NR	++++	NR
TYK2	++	+++	NR
JAK3	++	++++	+
TRKC	NR	++++	NR
TNKi	NR	++++	NR
ROSI	NR	++++	++
c-kit	NR	+++	NR
c-src	NR	+++	+
CSF1R (c-fms)	NR	+++	++
HIPK4	NR	++++	++
IRAK1	NR	++++	NR

Ruxolitinib scale: ++, IC₅₀ at 1 μ M.
Pacritinib scale: +++++, <25 nM; +++, 25–<50 nM; +, >100 nM.
Momelotinib scale: +++++, <25 nM; +++, <100 nM; ++, <1 μ M; +, >1 μ M.
NR: Not reported.
Data taken from [39].

$\geq 50\%$ reduction from baseline in palpable spleen length and also there was evidence of rapid clinically significant improvements in symptoms in near half of the patients, as assessed by various quality of life questionnaires. Thus far, the data collected proved ruxolitinib to be an agent capable of providing clinically meaningful reductions in spleen length and symptoms in patients with MF, with safety and efficacy profile consistent with that reported in the COMFORT studies [36].

As referenced above, thrombocytopenia in patients with MF constitutes an unmet need in the era of targeted therapy, where an agent with proven safety, efficacy and advantageous toxicity profile is needed for patients in this situation, who otherwise have no approved treatment option.

Pacritinib as an alternative

Pacritinib is a novel oral tyrosine kinase inhibitor that combines a dual inhibition of JAK2 and FLT3, and also has demonstrated activity inhibiting other inflammatory pathways such as IRAK1 and CSF1R. Pacritinib, former SB1518, is a low molecular weight agent with a unique macrocyclic (4-aryl-2-aminopyrimidine) structure [37] proven to have selective inhibitory activity of multiple members of JAK and FLT3 family. Preclinically, cell cycle arrest in G1 phase leading to apoptosis was noted at different concentrations of pacritinib in myeloid and lymphoid cells driven by JAK2 of FLT3 mutation, with an effect seen as well in both JAK2 (V617F) mutated and JAK2 wild-type expressing cells [38]. Singer *et al.* reported pacritinib IC₅₀ for JAK2WT, JAK2V617F, FLT3 wild-type, FLT3-ITD and IRAK1 as 6, 9.4, 14.8, 13.4 and 13.6 nM, respectively. Also several other pathways were tested, where pacritinib demonstrated an interesting and combined ability to suppress signaling by kinases involved in microenvironmental tumor interactions as well as by kinases thought to be involved in tumor progression [39]. A direct kinase profile comparison was performed with ruxolitinib and momelotinib (Table 2) being the latter an agent no longer in development. Based on kinase profile data, one may think that the lack of suppression of signaling mediated by JAK1 may have a role in the lack of myelosuppression associated with pacritinib, although the mechanism remains to be elucidated [39].

Pharmacokinetic characteristics of pacritinib were described by Verstovsek *et al.* and Younes *et al.* The doses ranged 100–600 mg/day with assessments scheduled on days 1 and 15 demonstrating moderately fast absorption followed by a long terminal phase and mean time to peak concentration between 5 and 9 h on day 1; the mean terminal half-life was 1–4 days and importantly, there was no significant accumulation on day 15 [40,41].

Clinical efficacy & early studies

Translation to early Phase I and II has been led by different investigators (Table 3), looking at safety, dose range and signals of efficacy on different cohort of patients. Three different Phase I studies were performed where pacritinib was assessed at dosages from 100 to 600 mg once-daily (q.d.), followed by two Phase II studies only in patients with MF using pacritinib at a recommended dose of 400 mg q.d. [40–44].

Taking them all together, a total of 191 patients were exposed to pacritinib, those included 122 (64%) patients with MF, 62 (32%) with advanced lymphoid malignancies (Hodgkin and non-Hodgkin lymphomas) and seven (4%) patients with AML. The median age was 65 years and the median time from initial diagnosis was 3.8 years. 44% of patients with myeloid disorders had baseline platelet counts $<100,000/\mu\text{l}$ [45].

Responses in the intent-to-treat population of patients with MF and advanced myeloid malignancies ranged from 10 to 39% in the percentage of patients with $\geq 50\%$ spleen reduction by physical exam [45]. The best response was observed by Deeg *et al.*; in this study, 33 patients were enrolled with a median spleen enlargement by physical exam at baseline of 18 cm below left costal margin. Of the 30 patients who were assessed by MRI, 29 had SV and 17 (57%) had a reduction $\geq 25\%$. Of 31 patients assessed by PE, 12 (39%) had a reduction of $\geq 50\%$ and seven (23%) had a reduction of 100% [44].

Out of the 62 (32%) patients with lymphoid malignancies, 55 (89%) patients had at least one follow-up tumor assessment, where one patient had complete response (CR), five had partial response (PR) and 34 had stable disease (SD) [45].

The most common AEs were gastrointestinal (GI) in nature (all grades/grade 3–4): diarrhea (73/8%), nausea (48/1%), vomiting (30/1%), constipation (24/0%) and abdominal pain (21/4%). Serious AEs were seen in about 42% of myeloid patients and 27% of lymphoid patients. The most frequent serious AEs ($>2\%$) included: pneumonia (4.7%), anemia (3.1%), abdominal pain (2.1%), AML (2.1%), congestive heart failure (2.1%), sepsis (2.1%) and subdural hematoma (2.1%). 22 deaths (11.5%) reported as treatment emergent and 21 patients died of nondrug-related causes [45].

The integrated overview of Phase I and II clinical trials, where safety and efficacy were analyzed, included 129 patients with advanced myeloid malignancies and MF. 65 patients with MF were treated with pacritinib 400 mg q.d. in two Phase II studies. Of these, 28 patients with MF had platelet count $<100,000/\mu\text{l}$. After examining the outcome of this last subset of patients, 37 and 43% of all evaluable patients and patients with $\leq 100,000/\mu\text{l}$ platelets, respectively, had $\geq 35\%$ reduction in spleen volume from baseline.

The above data supported the feasibility and potential of pacritinib for further investigation in larger Phase III trials in patients with MF and anemia–thrombocytopenia, an unmet need for which to date there is no treatment option [45,46].

Transition to Phase III studies

Encouraging findings on early studies led to two larger randomized, controlled, Phase III clinical trials.

PERSIST-1 was designed based on data from Phase II studies to improve spleen size and symptoms in patients with MF. It compared pacritinib against BAT and there was no exclusion criteria based on the degree of thrombocytopenia, so it was really the first study that allowed patients with intermediate–high risk MF to go into a study within that setting.

Investigators observed that pacritinib was as safe and efficacious as suggested in previous studies, there was significant improvement in splenomegaly, particularly in those patients with baseline platelet count less than $100,000/\mu\text{l}$ and less than $50,000/\mu\text{l}$ and also some of the patients became red blood cells transfusion independent [47]. On the second hand, PERSIST-2 evaluated pacritinib at two different dose levels versus BAT allowing patients who have been previously exposed to JAK inhibitors and/or failed either ruxolitinib and/or other JAK inhibitors to enroll into this second Phase III study, so really assessed it in the second-line setting. This time, investigators reported that pacritinib at 200 mg twice-a-day (b.i.d.) dosage was superior to BAT but also that 400 mg q.d. dosage was not as favorable as the twice-a-day dosage compared with BAT [48]. The data are complementary in essence due to the fact that pacritinib demonstrated striking superiority when compared against BAT, not only in intermediate–high risk patients but also in those who have been treated with ruxolitinib, in terms of spleen size reduction, symptoms and safety.

More in detail, PERSIST-1 enrolled a total of 327 patients, 220 were assigned to pacritinib and 107 were assigned to BAT, and as mentioned above did not exclude patients with thrombocytopenia, as no minimum baseline platelet count was required. The primary and secondary end points were SVR $\geq 35\%$ from baseline to week 24 as assessed

Table 3. Summary of Phase I–III studies of pacritinib.

Study	Phase	n	Disease	Dose range	Response	Hematologic toxicities	Nonhematologic toxicities	DLT
Seymour <i>et al.</i>	Phase I	20	MF	160–600 mg q.d.			Diarrhea 89% (G3 11%), nausea/vomiting 39%, abdominal pain 22%, fatigue 22%, rash 17%, dysgeusia 17%	600 mg, diarrhea/nausea G3 in two of four patients
Verstovsek <i>et al.</i>	Phase I	43	MF, AML	100–600 mg q.d.	>35% SSR in 41% of patients with MF	Thrombocytopenia 4% (all G3–G4)	Diarrhea 33% (G3 4%), nausea 13%	600 mg, GI DLT in three of six patients
Younes <i>et al.</i>	Phase I	35	HL and NHL (excluding Burkitt's and CNS lymphoma)	100–600 mg q.d.	55% reduction in target tumor measurement (range: 4–70%)	Neutropenia 12% (G3–G4 6%), anemia 12% (G3–G4 3%), thrombocytopenia 12% (G3–G4 3%)	Diarrhea 32%, (all G1–G2), nausea 29% (all G1–G2)	One DLT each, 600 mg G4 sepsis; 400 mg G4 thrombocytopenia; 300 mg G4 Neutropenia
Komrokji <i>et al.</i>	Phase II	35	MF	400 mg q.d.	>35% SSR in 31% of patients and >50% SSR in 42% of patients	Anemia 34% (G3–G4 25.7%), thrombocytopenia 23% (G3–G4 20%)	Diarrhea 77% (G3–G4 8.6%), nausea 49% (G1–G2), vomiting 31%, fatigue 37%	Permanent dose reduction in nine patients due to increased AST and lipase, hyponatremia, nausea, vomiting, diarrhea
Deeg <i>et al.</i>	Phase II	33	MF	400 mg q.d.	>25% SSR by MRI in 57% of patients, >50% SSR by PE in 39% of patients	No significant anemia or thrombocytopenia. No G3–G4 events	Diarrhea 81% (G3 6%), nausea 41% (all G1–G2), vomiting 22% (all G1–G2), fatigue 9% (all G1–G2)	N/A
Verstovsek <i>et al.</i>	Phase I–II safety overview	191	MF, AML, HL, NHL	100–600 mg q.d in Phase I, 400 mg q.d. in Phase II	N/A	All grades/G3–G4: anemia 52/1%; thrombocytopenia 60/8%	All grades/G3–G4: diarrhea 73/8%; nausea 48/1%; vomiting 30/1%; constipation 24/0%; abdominal pain 21/4%	
Verstovsek <i>et al.</i>	Safety analysis of Phase II trial data	129	MF (65), advanced myeloid malignancies (64)	400 mg q.d.	>35% SVR in 37% of patients, >35% SVR in 43% patients with platelets <100,000/ μ L; Hb improved by one grade in 16 and 18% of patients	One grade worsening in 28 and 30% in Hb and platelet counts	Diarrhea 69% (G1–G2)	
Mesa <i>et al.</i>	Phase III	327	MF	400 mg q.d. vs BAT	At week 24, >35% SVR in 19 vs 5% in BAT group	All grades/G3–G4: anemia 24/17%; thrombocytopenia 16/11%	All grades/G3–G4: diarrhea 55/5%; nausea 27/1%; vomiting 16/1%; fatigue 10/2%; abdominal pain 9/1%	
Mascarenhas <i>et al.</i>	Phase III	311	MF	200 mg b.i.d. vs 400 mg q.d. BAT	PAC b.i.d.: >35% SVR in 22% of patients vs 3% in BAT; PAC q.d.: SVR >35% in 15% of patients vs 3% BAT	Anemia and thrombocytopenia, less frequent in PAC b.i.d. vs PAC q.d. group	Most common AEs were GI (diarrhea, N, V), but less frequent in PAC b.i.d. group vs PAC q.d.; G3–G4 cardiac AE in 7% (PAC b.i.d.), 9% (PAC q.d.), 13% (BAT); G3–G4 bleeding AE in 14% (PAC b.i.d.), 7% (PAC q.d.), 7% (BAT)	

AE: Adverse event; AML: Acute myeloid leukemia; AST: Aspartate aminotransferase; BAT: Best available therapy; b.i.d.: Twice-a-day; DLT: Dose-limiting toxicity; GI: Gastrointestinal; Hb: Hemoglobin; HL: Hodgkin lymphoma; MF: Myelofibrosis; N: Number; N/A: Not available; NHL: Non-Hodgkin lymphoma; PAC: Pacritinib; PE: Physical examination; q.d.: Once-daily; SVR: Spleen volume reduction; V: Vomiting. Data taken from [40–48].

by MRI or CT scan, and the proportion of patients achieving a reduction $\geq 50\%$ in total symptom score (TSS) from baseline to week 24 on MPN-SAF TSS 2.0. Other secondary end points were proportions of patients with baseline platelet count less than 100,000/ μL or $< 50,000/\mu\text{L}$ who achieved SVR $\geq 35\%$ or $\geq 50\%$ reduction or greater in TSS from baseline to week 24. Patients were randomized 2:1 to pacritinib versus BAT. 32% of patients enrolled had platelet count less than 100,000/ μL , while 16% had platelet count less than 50,000/ μL . The median duration of treatment was 16.2 and 5.9 months for pacritinib and BAT, respectively [47].

In the intention to treat (ITT) population, 42 (19%) patients receiving pacritinib achieved $\geq 35\%$ SVR versus five (5%) patients receiving BAT ($p = 0.0003$) and in patients evaluable for response, the rates of SVR were 25% for pacritinib group versus 6% for BAT group ($p = 0.0001$). Patients on the pacritinib arm consistently achieved $\geq 35\%$ reduction in spleen volume regardless of baseline platelet counts. As far as reduction in TSS 2.0 from baseline to week 24, no difference was observed in the ITT population achieving $\geq 50\%$ reduction between patients receiving pacritinib and BAT. On the other hand, in the evaluable population, 19 (36%) of 53 patients receiving pacritinib achieved this end point compared with five (14%) of 36 patients receiving BAT ($p = 0.029$) [47].

In addition, pacritinib compared with BAT resulted in improvement in severe thrombocytopenia and anemia, and achievement of red blood cell transfusion independence (25.7 vs 0%; $p = 0.043$). As far as treatment-related toxicities, GI symptoms were frequent but manageable in the pacritinib arm versus BAT, including mild-to-moderate diarrhea (53 vs 12%) and nausea (27 vs 6%). No grade 4 GI side effects were reported. Hematologic toxicities were found at a similar rate between the two arms, anemia (22 vs 20%) and thrombocytopenia (17 vs 13%). Dose reduction for pacritinib was required in 10% of patients due to diarrhea and anemia. Dose interruption for pacritinib was required in 22% of patients due to diarrhea, thrombocytopenia and anemia [47].

PERSIST-2 enrolled 311 patients who were randomized in 1:1:1 fashion to pacritinib 200 mg b.i.d. (107), pacritinib 400 mg q.d. (104) or BAT (100). The ITT efficacy population included 74, 75 and 72 patients for the pacritinib b.i.d., pacritinib q.d. and BAT arms, respectively. The coprimary end points were the proportion of patients achieving reduction in spleen volume by $\geq 35\%$ and reduction in TSS by $\geq 50\%$ using MPN-SAF TSS 2.0, both from baseline to week 24. It is important to note that the ITT population, a total of 221 patients, were enrolled at least 24 weeks before pacritinib became subject to a full clinical hold issued by the FDA, thus far these patients were the population used to evaluate the study end points [48].

Almost half of the patients in the BAT arm (44%), analyzed with ITT, received ruxolitinib as treatment at some point during the study. 18% of patients in the pooled pacritinib arm (b.i.d. and q.d.) achieved SVR $\geq 35\%$ versus 3% of patients in the BAT arm ($p = 0.001$). Also, 25% of pacritinib patients had $\geq 50\%$ reduction in TSS versus 14% of BAT patients ($p = 0.079$). However, it was noted that in secondary analyses that looked at each pacritinib dosing group, the twice-a-day dosing demonstrated a significant improvement over BAT for both primary end points with 22 versus 3% achieving SVR $\geq 35\%$ ($p = 0.001$) and 32 versus 14% achieving $\geq 50\%$ reduction in TSS ($p = 0.011$). Moreover, patients in pacritinib arms reduced their red blood cell transfusion dependence at week 24 with 19% in the pacritinib q.d. arm, 22% in pacritinib b.i.d. and 9% in BAT. As far as toxicities, the most common treatment-related AEs associated with pacritinib were GI in nature (diarrhea, nausea, vomiting) and hematologic (anemia and thrombocytopenia), and were generally less frequent for twice-a-day versus once-daily administration [48].

Deaths attributed to intracranial hemorrhage, cardiac failure and cardiac arrest were observed on both Phase III clinical trials. On PERSIST-1, deaths due to AEs were observed in 12% of patients in the pacritinib group (4% during the first 24 weeks of treatment) and 13% patients in the BAT group (10% after crossover to pacritinib). On PERSIST-2, nine patients had cardiac failure (2% pacritinib q.d., 4% pacritinib b.i.d., 3% BAT) and one (1% pacritinib q.d.) had intracranial hemorrhage [47,48].

Regulatory affairs

Due to fatality related to intracranial hemorrhage, cardiac failure and cardiac arrest in Phase III trials, the FDA placed a clinical hold on both clinical studies in February 2016, citing excess mortality and other AEs noted in patients treated with pacritinib that were most evident after 87% of patients in BAT arm had crossed over to pacritinib, majority occurring immediately after week 24. During the initial 24 weeks of randomized treatment, the mortality rates were similar between arms. One might deduct that these could be due to high-risk population included on both trials, such as patients with severe thrombocytopenia making them prone to a life-threatening bleeding at baseline. Just a few months after the initial hold, the FDA allowed some patients to re-enter the trial as part of a compassionate use program while a full investigation was taking place. After almost 1 year of further

in-depth analysis that included study of the final reports and datasets from PERSIST-1 and PERSIST-2 by the FDA, it was not clear that the deaths seen on the studies were a side effect of pacritinib and probably those were related to adverse patient selection. With certain modifications to protocols and study-related documents, the clinical hold was lifted in January 2017 and the FDA recommended conducting dose exploration trials for pacritinib in patients with MF with the aim of further refine the most efficacious lower dose [49].

Following the recommendation, a new trial PAC203 was designed to support a pacritinib dosage selection decision. Three dosages will be evaluated, with patients randomized 1:1:1 to pacritinib 100 mg q.d., pacritinib 100 mg b.i.d. or pacritinib 200 mg b.i.d. It targets patients with intermediate-1–high-risk MF who have failed prior ruxolitinib therapy on the basis of intolerance or loss of efficacy, are thrombocytopenic ($<100,000/\mu\text{l}$) and have splenomegaly looking again at the efficacy of the pacritinib, and also aiming to characterize its toxicity and safety by assessing dose–response relationship for efficacy (SVR at 24 weeks) of the above three dose regimens. This study is currently enrolling patients.

In summary, pacritinib is a first-in-class JAK2/FLT3 and IRAK1 inhibitor that has demonstrated to be efficacious in its ability to reduce splenomegaly and improve symptoms in patients with MF. Moreover, its nonmyelosuppressive properties make it an agent that could probably fill the gap when treatment options are required in intermediate- and high-risk patients with MF and low platelet counts of less than $50,000/\mu\text{l}$, for which no other therapeutic approach is approved to date.

Future development

Some other inhibitors of the JAK-STAT pathway that have been tested are fedratinib and momelotinib.

Fedratinib (JAK-2 inhibitor) was evaluated in the JAKARTA trial. This Phase III, randomized, placebo-controlled, three-arm study of 289 patients with MF, assessed fedratinib at a dose of 400 or 500 mg q.d. demonstrated clinically meaningful and statistically significant reductions in splenic volume and MF-associated symptom burden versus placebo, although these benefits were accompanied by toxic events, being encephalopathy of unknown mechanism the most important [50]. In the JAKARTA-2 trial, fedratinib was assessed in patients with MF previously treated with ruxolitinib. Primary end point was spleen response (defined as the proportion of patients with a $\geq 35\%$ SVR). 97 patients were originally enrolled in this study and received at least one dose of fedratinib, and 83 were considered assessable for efficacy evaluation purposes. 46 (55%) patients achieved a spleen response. Common grade 3–4 AEs included anemia (38% of patients) and thrombocytopenia (22% of patients) [51]. Due to concerns of toxicities noted, especially encephalopathy of unknown mechanism as described in the JAKARTA trial, clinical development of fedratinib was subsequently discontinued.

Momelotinib (JAK-1 and JAK-2 inhibitors) showed in early trials to reduce spleen volume, improve disease-associated symptoms and improve red blood cells (RBC) transfusion requirements in patients with MF, which led to two Phase III studies, SIMPLIFY-1 and SIMPLIFY-2. On both studies, the primary end point was $\geq 35\%$ SVR from baseline at week 24 assessed by MRI or CT scan. In SIMPLIFY-1, momelotinib demonstrated to be noninferior to ruxolitinib for spleen response but not for symptom response, also momelotinib treatment was associated with a reduced transfusion requirement. In SIMPLIFY-2, momelotinib was not superior to BAT for spleen response, but significantly better in improving disease-related symptoms and transfusion independence. The most common grade 3 side effects with momelotinib use were anemia and thrombocytopenia, not worse compared with competitors on both trials. The analysis of the discouraging above Phase III data led to cessation of momelotinib development [52,53].

NS-018 (JAK-2 inhibitor) is currently in Phase I–II development. Its use has been explored in patients with intermediate-1–high-risk MF not eligible for hematopoietic stem cell transplant. Here, 48 patients were enrolled for dose escalation and 300 mg q.d. was chosen as the recommended dose for the Phase II portion of the study in terms of tolerability and efficacy. NS-018 demonstrated efficacy among 36 splenic evaluable patients by achieving $\geq 50\%$ reduction in palpable spleen size in 56% of patients and improvements in MF-associated symptoms [54]. The Phase II segment of the study had 29 patients who were exposed to JAK inhibition treatment prior to enrollment. As far as AEs, most of the grade 1/2 were nonhematologic being nausea (14%) present in greater than 10% of the patients, whereas most of grade 3/4 AEs were hematologic, being anemia (21%) and thrombocytopenia (17%) the most common hematologic toxicities [55].

Itacitinib (INCB039110) is a selective JAK1 inhibitor that is currently in Phase II, it has been essentially tested in patients with intermediate–high-risk MF and platelet counts of $\geq 50,000/\mu\text{l}$ looking at efficacy and safety of three dose levels, so far providing evidence of clinically meaningful symptom relief, the modest SVR and limited

myelosuppression [56]. Itacitinib is also being evaluated in parallel in an open-label multicenter Phase II study in combination with low-dose ruxolitinib or itacitinib alone in patients with MF is currently recruiting participants [57].

Conclusion

Pacritinib is a selected agent that combines JAK-2, FLT-3 and IRAK1 inhibition and has demonstrated efficacy in patients with intermediate-2 and high-risk MF not eligible for allogeneic stem cell transplantation. It has the ability to reduce splenomegaly and improve symptoms even among patients with marked thrombocytopenia ($<100,000/\mu\text{l}$ or $<50,000/\mu\text{l}$ platelets), and its toxicities were in general terms manageable. In-depth analysis of Phase III trials regarding mortality indicated that this was likely secondary to an adverse patient selection with a high burden of disease and marked thrombocytopenia, which led to a lift of the previous hold imposed by the FDA. Based on available data, pacritinib could remain as a potential option for patients with marked thrombocytopenia, anemia or second line after ruxolitinib therapy.

Executive summary

Prognostic tools are available when deciding treatment of myelofibrosis

- Assessment of myeloproliferative neoplasm symptoms is recommended at baseline and during treatment.
- Available scoring systems such as the International Prognostic Scoring System or Dynamic International Prognostic Scoring System are very useful in deciding risk-adapted therapy.

Patients with intermediate-2 or high-risk myelofibrosis benefit from ruxolitinib

- COMFORT-1 and COMFORT-2 trials proved ruxolitinib to be safe, in general well tolerated and able to achieve reductions in splenomegaly and symptom burden.
- Clinical benefits of long-term ruxolitinib use appear to be sustained, also there is evidence of survival advantage benefit.
- The JUMP trial corroborated at a major scale, the benefits offered by ruxolitinib.

Thrombocytopenia remains at large an unmet need

- Development or worsening of baseline cytopenias was described with ruxolitinib use.
- Ruxolitinib remains the only US FDA-approved medication for intermediate-2 or high-risk myelofibrosis (MF), however, it is not indicated for patients with platelet count of less than $100,000/\mu\text{l}$.

Pacritinib offers an alternative for patients with MF & thrombocytopenia

- Pacritinib is a novel tyrosine kinase inhibitor that combines JAK2 and FLT3 inhibition, and also inhibits other inflammatory pathways such as IRAK-1 and CSF1R.
- Data provided by Phase I and II studies led to two larger randomized, controlled Phase III studies (PERSIST-1 and PERSIST-2) that were conducted on patients with intermediate-high-risk MF and underlying thrombocytopenia.
- Pacritinib demonstrated clinical efficacy by positively impacting MF-related splenomegaly and symptom burden.
- The clinical hold placed from February 2016 until January 2017 was largely due to fatality related to intracranial hemorrhage, cardiac failure and cardiac arrest. In-depth data analysis suggested that the excess mortality could have been related to adverse patient selection, and further recommendations by the FDA warranted dose exploration trials with the aim of identifying the lowest most efficacious dose.

Conclusion

- In the current era, prognostic tools are useful when deciding risk-adapted therapy.
- Ruxolitinib is still the only FDA-approved agent for patients with intermediate-2-high-risk MF.
- Pacritinib is a reasonable option for patients with MF and thrombocytopenia.

Company review

In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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