A closer look at pacritinib: a JAK2/FLT3 inhibitor for the treatment of myelofibrosis

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Introduction: Myelofibrosis (MF) is a chronic myeloid neoplasm that bears a significant symptom burden, impacts on quality of life and carries a risk of transformation to acute leukemia. Advances in MF therapy by inhibition of Janus kinase type 2 (JAK2) receptor have shown clinical improvements in spleen size and symptom burden, but are often limited by hematological side effects.

Areas covered: Treatment for patients with MF who are not suitable candidates for allogeneic stem cell transplant is limited and, historically, palliative in intent. The approval of ruxolitinib, a JAK2 inhibitor, has enabled clinical improvement in these individuals. In this paper, treatments for MF are briefly reviewed, including historically palliative therapies and the clinical data leading to ruxolitinib approval. This JAK2 therapy is limited by cytopenias, either due to the disease process or a medication side effect. Finally, the preclinical and clinical data of pacritinib use in MF and other hematologic conditions are evaluated.

Expert opinion: Ruxolitinib use in patients with MF who are deemed to be inappropriate transplant candidates can be limited by cytopenias, particularly thrombocytopenia. This demonstrates an unmet therapeutic need in patients with MF. Pacritinib, SB1518, a dual JAK2 and FMS-like tyrosine kinase 3 inhibitor has been suggested to provide clinical benefit to patients with MF without producing adverse hematologic events that restrict ruxolitinib utility. If ongoing phase 3 trials of pacritinib are positive, based on efficacy to improve splenomegaly and constitutional symptoms with a tolerable adverse event profile, pacritinib may provide a much needed oral therapeutic option for patients with MF.

Keywords: hematologic malignancy, Janus kinase type 2 inhibitors, myelofibrosis, myeloproliferative neoplasm, pacritinib, SB1518

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1. Background

1.1 Myelofibrosis: diagnosis and risk
Myeloproliferative neoplasms (MPNs) are a class of bone marrow diseases that result in excessive cell lineage production. Myelofibrosis (MF) is included in the spectrum of Philadelphia chromosome negative MPNs, and it is characterized by dysfunctional and extramedullary hematopoiesis leading to cytopenias and splenomegaly. MF can develop de novo, termed primary MF or following a diagnosis of either PV or ET, termed post-PV-MF and post-ET-MF, respectively. As knowledge regarding MF has grown, identification of risk factors including age > 65, hemoglobin level < 10 g/dl, white blood cell count greater than 25 x 10^9/L, circulating blasts greater than 1%, and presence of constitutional symptoms has allowed for classification as low, intermediate 1 and intermediate 2 and high-risk disease with median
survival between categories of 135, 95, 48 and 27 months, respectively [1]. This International Prognostic Scoring System provides prognostic stratification of patients for healthcare decision making regarding treatment recommendations [1].

1.2 Traditional MPN treatment options
1.2.1 Stem cell transplantation
Historically, treatment options for MF have been limited. The only curative treatment in MF is allogeneic hematological stem cell transplant (HSCT), but it carries significant mortality and morbidity and may not be appropriate for patients with advanced age or multiple comorbidities [2]. It is reserved for patients with intermediate or high-risk disease who are deemed suitable for a trial of transplantation. Reduced intensity conditioning stem cell transplantation (SCT) is currently being evaluated as a viable option for patients with intermediate and high-risk disease unlikely to tolerate the traditional conditioning regimen due to concern for significant mortality and morbidity [3]. The risk versus benefit analysis must be individualized for each patient and particular disease. Prior to 2011, no pharmacotherapy was approved by the FDA to treat MF, with the available therapies focused on palliation of symptoms.

1.2.2 Hyperproliferative symptoms
To address the hyperproliferative symptoms of MPNs, cytoreductive agents are used to address hepatosplenomegaly, leukocytosis, thrombocytosis, erythrocytosis, bone pain and constitutional symptoms.

Hydroxyurea has been shown to improve splenomegaly, anemia, bone pain, constitutional symptoms and pruritus in 40% of patients with MPNs in a small retrospective study of 40 individuals with benefit noted for 13 months [4]. Although 40% noted clinical improvement, 45% of patients experienced hematological toxicities, including worsening anemia or pancytopenia. Hydroxyurea provides modest benefit of hyperproliferative symptoms, with the frequent side effect of anemia often requiring concomitant therapy.

IFN-α use in MF has demonstrated mild benefit but is well tolerated with few significant side effects. Its clinical effect in patients with MF vary from clinical responses of 20% in 1 study of 118 patients [5] and 16 of 18 patients in another study [6], and 1 of 11 patients in another study [7].

Alkylating agents have also been used to treat splenomegaly in MF. Reduction of spleen size in MF by alkylating agents, such as melphalan and busulfan, is countered by the fact that these agents are associated with increased risk of transformation to acute myeloid leukemia (AML) [8].

Surgical intervention for splenomegaly can be considered but due to the risk of mortality and morbidity, candidates require thorough evaluation [9]. Long-term improvement following splenectomy includes improved symptomatic splenomegaly (48%), anemia (50%), portal hypertension (40%) and severe thrombocytopenia (30%). The complication rate of 27% includes bleeding, thrombosis and infection. The

Box 1. Drug summary.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Pacritinib, SB1518</th>
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<tbody>
<tr>
<td>Phase</td>
<td>Two Phase III Studies ongoing</td>
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<tr>
<td>Indication</td>
<td>Refractory myelofibrosis</td>
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<tr>
<td>Mechanism of action</td>
<td>Inhibition of transcription factor activation via inhibition of JAK2 tyrosine kinase</td>
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<tr>
<td>Route of administration</td>
<td>Oral</td>
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<tr>
<td>Pivotal trial(s)</td>
<td>Phase II trials in refractory myelofibrosis</td>
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</table>

Demonstrated clinical benefit regarding splenomegaly and systemic symptoms and infrequent hematological adverse events
Hypoproliferative symptoms

1.2 Background

4 cytopenias seen in 20% of Ruxolitinib. JAK2 targeted therapy

727 (13) [12] Pacritinib

In addition to inhibiting the substitution leads to persistent autophosphorylation and activation of JAK2 and its downstream transcription factors enabling cell proliferation independent of, or hyperresponsive to, cytokine signaling [22]. This mutation has been identified in nearly 95% of cases of PV and nearly half of patients with either ET or PMF [23].

2.2 Ruxolitinib

Ruxolitinib is an oral JAK1 and JAK2 inhibitor [24]. Phase I and II trials, reported in 2010, demonstrated improved constitutional symptoms and exercise tolerance and decreased cytokine (IL-6 and TNF-α) levels, in JAK2V617F-positive and -negative patients, indicating the benefit of this JAK2 inhibitor is irrespective of mutation status [25]. The Phase III trials of ruxolitinib, the COMFORT I and COMFORT II randomized controlled trials, focused on response of splenomegaly, constitutional symptoms and blood product transfusions. The COMFORT I trial of patients from the USA, Canada and Australia compared ruxolitinib with placebo with a primary end point of reduction in spleen size by 35% after 24 weeks of treatment [26]. The ruxolitinib arm of the study demonstrated a RR of 41.9% for spleen size reduction greater than 35, 45% reported symptom improvement > 50%. The most common adverse effects of therapy were hemato logic, with 69% of enrolled patients developing thrombocytopenia of any grade, 96% any grade anemia and 18% any grade neutropenia [26]. The COMFORT II trial of patients with intermediate and high-risk MF in Europe compared ruxolitinib to best available therapy, with best available therapy decided at the discretion of the treating physician [27]. Similar to COMFORT I, the COMFORT II trial results revealed reduction in spleen size in the ruxolitinib group, no such improvement was noted in best available therapy group. Following these trials, ruxolitinib was approved for use in patients with intermediate and high-risk MF with a platelet count > 100,000 per liter [2]. In a comparison of the placebo arm of COMFORT I and the best available therapy arm of COMFORT II, similar trends of increased spleen size and symptom burden concluded that non-JAK inhibitor treatment therapies were no better than placebo in the treatment of MF [28].

3. Pacritinib

3.1 Background data

Pacritinib, SB1518, is a low molecular weight macrocyclic oral selective JAK2 inhibitor as well as an inhibitor of FMS-like tyrosine kinase 3 (FLT3) [17]. Its structure allows formation of two hydrogen bonds to the JAK2 backbone as well as a hydrogen bond to JAK2’s side-chain Ser936, which contributes to its potency for this tyrosine kinase [17]. In addition to inhibiting JAK2V617F, pacritinib also inhibits wild-type JAK2. Pacritinib proves to be an effective inhibitor of JAK2, with a half maximal inhibitory concentration ([IC50]) of 23 nM, and of the mutant JAK2V617F ([IC50] = 19 nM) [29]. Comparatively, it is not a

mortality rate is 6.7% [10]. Similarly, radiotherapy is used in MF to address extramedullary hematopoiesis and splenomegaly. In one study of 23 patients, who received a median course of 277 cGy in 8 fractions, 94% experienced a decreased spleen size whereas 44% experienced cytopenias [11].

1.2.3 Hypoproliferative symptoms

Another segment of MF therapies target the hypoproliferative symptoms of cytopenias that impact quality of life and prognosis. These hypoproliferative symptoms include fatigue attributed to anemia, treatment limiting hemoglobin levels and the frequent need for transfusions.

Efficacy of thalidomide, often in combination with prednisone and occasionally in concert with other immunomodulators (such as cyclophosphamide or etanercept), was investigated in a 50-person study in patients with MF. The study revealed a response rate (RR) of 28% based on the International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) Criteria. Major adverse events were grade 3 – 4 neuropathy in 6%, and grade 3 – 4 cytopenias seen in 20% of patients [12]. Similarly, a Phase II trial in 42 patients with MF treated with lenalidomide and prednisone revealed improved anemia in 10% and splenomegaly in 19% of individuals [13]. Severe adverse effects in patients treated with lenalidomide included grade 3 or 4 hematological effects in 88% of individuals and grade 3 or 4 nonhematological adverse effects in 45%.

Androgen therapy has shown to be beneficial for the treatment of anemia in MF [14]. In patients with inappropriately reduced levels of erythropoietin, administering erythropoietin stimulating agents has also been used with some success in patients with MF associated anemia.

2. JAK2 targeted therapy

2.1 Background

Increased understanding of the pathophysiology of MPNs has provided new opportunity for therapy. Identification of abnormal function within the Janus Kinase and Signal Transducer Activator of Transcription (STAT) pathway, seen in a majority of patients with MPNs, has prompted development of targeted therapeutic agents [15,16]. JAK tyrosine kinase dysfunction has been identified in abnormal immune response, such as asthma and rheumatoid arthritis, as well as defective hematopoiesis in the Philadelphia chromosome negative MPNs [17]. There are four Janus kinases, JAK1, JAK2, JAK3 and TYK2 [18]. The tyrosine kinase JAK2 is instrumental in the differentiation and proliferation of hematopoietic progenitor cell lines by way of leading to phosphorylation and activation of STAT factors that translocate into the nucleus and initiate gene transcription [19]. Numerous JAK2 somatic mutations have been identified in MPN population [20]. The most common mutation of JAK2, the JAK2V617F acquired gain-of-function mutation, results in a substitution of phenylalanine to valine at position 617 [21]. When present
potent inhibitor of the other JAK family kinases, in descending order of effect against TYK2 (IC<sub>50</sub> = 50nM), JAK3 (IC<sub>50</sub> = 520nM), and least potent against JAK1 (IC<sub>50</sub> = 1280nM) [29]. It is likely this discrepancy of JAK protein inhibition that leads to altered safety profile between the JAK inhibitors in various stages of development.

3.2 Preclinical data and pacritinib in hematological conditions

In vitro studies have demonstrated pacritinib results in decreased levels of phosphorylated STAT3, STAT5 and JAK2 in wild-type JAK2 cell lineages [29]. Pacritinib provides antiproliferation activity against cancer cell lines with and without the JAK2 and FLT3 mutations. Pacritinib inhibits cell proliferation in JAK-wild-type and JAK2V617F cells by inducing apoptosis through dose-dependent caspase-3/7 activation and causing cell cycle arrest in G<sub>0</sub> and G<sub>1</sub> phases [29].

When pacritinib was administered to Ba/F3-JAKV617F modified mice that demonstrate JAK2-dependent aggressive MF symptoms of hepatosplenomegaly and hematopoietic risis, at a dose of 150 mg/kg daily for 13 days there was significant normalization of spleen and liver weight without hematological toxicity adverse events in those treated with SB1518 [29].

In addition to potent JAK2 inhibition, pacritinib, also inhibits FLT3. Up to one-third of patients with AML bear a mutation at this tyrosine kinase receptor [30], which serves as a poor prognostic factor associated with autophosphorylation and decreased overall survival [31]. Pacritinib exposure in FLT3-mutated cell lines causes reduced levels of phosphorylated FLT3, STAT3 and STAT5 [32]. Similar to its effect on cell cycle proliferation in JAK2-mutated and wild-type cells, pacritinib induces G<sub>1</sub> cell cycle arrest and caused caspase-dependent apoptosis and cell cycle proliferative inhibition in cell lineages of AML blasts [32].

Studies have shown the possible synergistic effect of combining pacritinib with the oral pan-HDACi inhibitor, Pracinostat, in the treatment of patients with AML [33]. These agents inhibit JAK signaling, phosphorylated STAT and FLT3, and when used together demonstrated synergist decrease in tumor growth and metastasis in a SET2 megakaryocyte AML mouse model carrying JAKV617F mutation and FLT3-ITD AML [33].

Gene amplification of JAK2 is noted in 30% of patients with Hodgkin’s lymphoma [34], and phosphorylated STAT5 levels have been shown to be an independent poor prognostic factor in patients with HL following treatment with adriamycin, bleomycin, vinblastine, dacarbazine chemotherapy regimen [35]. An in vitro study of pacritinib’s effect in the Karpas 1106P cells, a lineage of human mediastinal lymphoma cell line with baseline hyperphosphorylated JAK2 and STAT3, revealed normalization of phosphorylated STAT3 following administration of pacritinib [36].

A Phase I trial of relapsed or refractory lymphoma patients treated with pacritinib noted 55% (17/31) patients demonstrated a reduction in tumor size, and objective response was appreciated in three patients, two with mantle cell lymphoma and one follicular lymphoma patient [37]. There were no complete remissions reported and no identified biomarkers association with activity. Of note, no patients with diffuse large B cell lymphoma responded to pacritinib with a reduction in tumor size. Most common side effects were grade 1 and 2, including diarrhea, constipation, nausea, anorexia and fatigue. The grade 3 and 4 toxicities were less common, including neutropenia (n = 2), fatigue (n = 1) and cerebrovascular accident (n = 1).

A Phase I study of pacritinib in myeloid disease, enrolled 36 patients, 31 with PMF and 5 with AML, treating cohorts at six dose levels with daily doses from 100 to 600 mg [38]. The only dose-limiting toxicity was gastrointestinal and experienced in three of the six patients who received 600 mg daily dosing; this required dose reduction and all three were able to continue with treatment. Decreased splenic size by physical exam of 35% was noted in 7/17 patients with splenomegaly prior to treatment (41%) and by > 50% in 4/17 patients (24%). No drug accumulation was noted despite repeat cycles and decreased levels of pSTAT3 and pSTAT5 were noted 4 – 6 h postingestion in all dosages.

3.3 Clinical studies in MPNs

Pacritinib has been investigated in MF and other hematological malignancies demonstrating clinical benefit and lack of hematological adverse events (see Table 1). Two Phase II studies have been conducted to evaluate the effect of pacritinib in MF. One Phase II study evaluated 33 patients with primary, post-PV-MF and post-ET-MF with splenomegaly deemed poor candidates for standard therapy. Dosing of pacritinib was 400 mg orally per day. Response to therapy was primarily focused on spleen size reduction, which was assessed both by MRI and physical exam. Spleen volume reduction was noted > 25% via MRI in 17 patients and > 50% via physical examination in 12 individuals. Common adverse events included diarrhea, nausea, vomiting and fatigue. There were no grade 3 or 4 adverse hematological events [39].

Another Phase II study of pacritinib in patients with MF, both primary and post-PV-MF and post-ET-MF, primarily focused on spleen size reduction with administration. It enrolled 34 patients, aged 44 – 84, with palpable splenomegaly > 5 cm below the left costal margin. Greater than 40% of patients enrolled (13/34) had thrombocytopenia with platelet level < 100,000/ul. At initial presentation of results, 17 patients had discontinued the study either from adverse events, disease progression or lack of response. There were no dose reductions based on hematopoietic concerns implicating drug effect, though one patient discontinued pacritinib owing to neutropenia and thrombocytopenia attributed to progressive disease. Adverse events were considered mild and tolerable predominantly gastrointestinal in nature. Spleen
size was reduced in 88% of enrollees, with half of those noting > 50% spleen reduction. The clinical improvement of splenomegaly was noted similarly in individuals with and without baseline thrombocytopenia. Cytopenia improvement was mild and infrequent, with two individuals who experienced hemoglobin improvement by IWG-MRT criteria. Constitutional symptom improvement was appreciated after 6 months of treatment [40].

A Phase III trial of pacritinib is currently underway [41]. It is a randomized controlled trial of nonpregnant patients with either intermediate or high-risk primary or secondary MF. Inclusion criteria require diagnosis of intermediate 1 or 2 or high-risk MF, the presence of palpable splenomegaly, a total symptom score of at least 13 on the MPN symptom assessment form, adequate levels of white blood cells, liver function tests and renal function, as well as lack of splenic radiation for 6 months prior to study and no previous therapy with a JAK inhibitor. Enrollees can be platelet or red blood cell transfusion dependent, but must be at least 2 – 4 weeks from their last MF therapy, including erythropoietic or thrombopoietic agent use. Exclusion criteria include previous splenectomy or allogeneic stem cell transplant, ongoing gastrointestinal or cardiovascular condition, uncontrolled illness either infectious or psychiatric, or a life expectancy < 6 months. The treatment arms compare pacritinib 400 mg oral daily with best available therapy, selected by treating physician, which may include hydroxyurea, immunomodulators, erythropoietin stimulating agents, glucocorticoids, interferon, cytarabine, melphalan or other agents. The primary outcome of this clinical trial will be reduction of at least 35% reduction in spleen volume assessed by imaging at 24 weeks. A positive trial would suggest, pacritinib, like ruxolitinib, can be efficacious in patients with intermediate and high-risk MF deemed unacceptable for SCT.

Another Phase III study is currently underway to assess pacritinib efficacy in patients with thrombocytopenia and intermediate or high-risk MF [42]. This study aims to investigate daily and twice a day dosing of pacritinib in nonpregnant patients with either intermediate or high-risk primary or secondary MF.
patients with a platelet count that would preclude treatment with ruxolitinib. The study plans to compare the efficacy of two dosing regimens of pacritinib, 400 mg oral daily versus 200 mg oral twice a day dosing, and best available therapy determined by treating physician, on splenic volume reduction of at least 35% assessed by imaging and improvement of MF symptoms. Inclusion criteria for the study include diagnosis of intermediate 1 or 2 or high-risk MF, thrombocytopenia defined as platelet count < 100,000/µl, palpable splenomegaly, a total symptom score of at least 13 on the MPN symptom assessment form, adequate white blood count, adequate liver and renal function, at least 6 months from previous splenic irradiation and at least 1 – 4 weeks from prior MF therapy. Enrollees can be platelet or red blood cell transfusion dependent. Exclusion criteria includes previous treatment with pacritinib, or two other JAK2 inhibitors, history of splenectomy or allogeneic stem cell transplant, ongoing gastrointestinal or cardiovascular condition, active bleeding requiring hospitalization during screening period for enrollment, a malignancy in the previous 3 years other than skin, cervical, prostate, breast or bladder cancers, uncontrolled illness or life expectancy < 6 months. If positive, this study may solidify efficacy of pacritinib in MF patients with thrombocytopenia that can preclude treatment with the only approved JAK2 inhibitor at this time.

4. Other JAK inhibitors

Following the success of ruxolitinib, additional JAK2 inhibitors have been developed to duplicate clinical benefit in MF (see Table 2). For example, Phase II studies of momelotinib (CYT387) demonstrated improvement in constitutional symptom, spleen size and anemia in patients with intermediate and high-risk MF [43]. Dose limitations were based on severe headache and asymptomatic hyperlipasemia. Significant adverse events (grade 3 or 4) include thrombocytopenia, hyperlipasemia, abnormal liver function test and headache. Unfortunately, ~ 20% of patients developed mild (grade 1) peripheral neuropathy following treatment. Similarly, a Phase II trial in JAK2V617F-positive MF patients treated with the JAK2

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### Table 2. Clinical data for JAK2 inhibitors used in myelofibrosis.

<table>
<thead>
<tr>
<th>Jak2 inhibitor</th>
<th>Stage of development</th>
<th>Response (%)</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Constitutional</td>
<td>Hematologic</td>
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<tr>
<td></td>
<td></td>
<td>symptoms</td>
<td>Splenomegaly</td>
</tr>
<tr>
<td>Ruxolitinib</td>
<td>Approved</td>
<td>Improved* - 45%</td>
<td>29 – 42%</td>
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<td></td>
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<tr>
<td>Pacritinib</td>
<td>Phase II</td>
<td>Improved</td>
<td>32* – 57%</td>
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<tr>
<td></td>
<td>Ongoing Phase III</td>
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<tr>
<td></td>
<td>Trials</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Momelotinib</td>
<td>Phase II</td>
<td>Improved</td>
<td>48%**</td>
</tr>
<tr>
<td>CYT-387</td>
<td>Ongoing Phase III</td>
<td></td>
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<td></td>
<td>Trials</td>
<td></td>
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<tr>
<td>Lastaurtinib</td>
<td>Halted Phase II</td>
<td></td>
<td>18%†</td>
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<tr>
<td>[44] (CEP-701)</td>
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<tr>
<td>Fedratinib</td>
<td>Halted Phase I</td>
<td>&gt; 50%</td>
<td>47%**</td>
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<tr>
<td>[47,45] (SAR302503)</td>
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<tr>
<td>XLD19</td>
<td>Halted Phase I</td>
<td></td>
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<td>[46]</td>
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*Improvement in symptoms reported on European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (QLQ-C30) and Functional Assessment of Cancer Therapy Lymphoma Scales.
† > 50% reduction in total symptom score on the MPN symptom assessment form at 24 weeks of treatment.
‡ > 35% reduction in volume reduction by imaging study.
§ > 25% by imaging.
¶ > 35% by imaging.
** Based on IWG-MRT criteria.
11 = 50% reduction in spleen volume.
IWG-MRT: International Working Group for Myelofibrosis Research and Treatment; QLQ-C30: Cancer Quality of Life Questionnaire.
inhibitor, CEP-701, showed benefit in 6/22 patients (27%) regarding spleen size or transfusion independence [44]. More patients experienced toxicities than clinical improvement, with moderate–severe toxicity seen in myelosuppressive disorders and disruption of the gastrointestinal system with diarrhea, nausea and vomiting [44].

Some JAK2 inhibitors that showed benefit in early studies in MF have since been halted in development due to significant adverse events. The JAK2 inhibitor SAR302503, fedratinib, had been in Phase III trial when the study was closed due to development of Wernicke’s encephalopathy [45]. Similarly, XL019, studies were discontinued when patients developed peripheral neuropathy despite dose reductions [46].

5. Conclusion

MF is a chronic myeloid neoplasm that has a spectrum of disease ranging from asymptomatic, hampered quality of life due to constitutional symptoms and significant cytopenias, to blast transformation. Treatment is limited either by appropriate candidacy for curative intent HSCT or by efficacy in traditional therapies. The class of JAK2 inhibitors provides an option for efficacious treatment for patients with MF, as well as other myeloid conditions. Most JAK2 inhibitors that are either approved or in the development for use in MF convey a risk of myelosuppression that complicates their use. Pacritinib, on the other hand, enjoys a side effect profile of predominantly tolerable gastrointestinal disturbance without worsening cytopenias.

Pacritinib may prove useful in patients with intermediate and high-risk disease who are not candidates for HSCT and have baseline cytopenias. Pacritinib might also prove useful in patients who have been treated with JAK2 inhibitors previously but had therapy dosing limited by myelosuppressive side effects (Box 1). The results of the Phase III trials are anxiously awaited as approval of this JAK2/FLT3 inhibitor may prove beneficial for patients with MF with scarce options for treatment.

6. Expert opinion

MF is a hematological condition with a spectrum of disease symptomatology and a risk of leukemic transformation. Despite the spectrum of symptoms, treatment has been limited either by patient age or comorbidities, therapeutic efficacy or hematological adverse events of pharmacotherapy. The oral JAK2 inhibitors provide options, and hope, in the treatment of MF. However, it is the distinct side effect profile of pacritinib that poises this particular JAK2/FLT3 inhibitor to prove useful in patients with baseline cytopenias that preclude use of ruxolitinib. Also, pacritinib may prove useful in patients with MF who develop cytopenias while on MF therapy, possibly with other JAK2 inhibitors. The results of the Phase III study are anxiously awaited as this may provide a necessary therapeutic option for patients with MF and low blood counts.

Declaration of interest

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Bibliography

Papers of special note have been highlighted as either of interest (●) or of considerable interest (★★) to readers.


Pacritinib
This article describes the COMFORT I, Expert Opinion on Orphan Drugs
This analysis compared the control group efficacy outcomes of the COMFORT I and COMFORT II trials. In COMFORT I trial, the control group was a placebo. In the COMFORT II trial, the control group was best available therapy determined by the treating physician. This study suggested that non-Janus kinase inhibitor therapy is no more effective than placebo in patients with at least intermediate myelofibrosis.


- Built upon information from Phase I study of pacritinib, this study assessed response of pacritinib at a dose of 400 mg daily in a 28 day cycle on spleen size in patients with primary myelofibrosis, or postpolycythemia myelofibrosis or postessential thrombocytosis myelofibrosis with splenic enlargement. Of the 30 patients enrolled assessed by MRI, 29 demonstrated a reduction in spleen size. Myelofibrosis symptom burden improved over 6 months by 40 - 65%. No grade 3 or 4 hematologic side effects were reported.


- A Phase II clinical trial assessing spleen volume reduction in patients with primary, postpolycythemia vera myelofibrosis or postessential thrombocytosis myelofibrosis and splenomegaly. Patients were treated with 400 mg daily dose. There was no exclusion criteria based on hematologic abnormalities, in fact 44% of patients had platelet counts below 100,000/μL. The study revealed efficacy for spleen volume reduction. Primary adverse events were gastrointestinal.

41. Cell Therapeutics. Oral pacritinib versus best available therapy to treat myelofibrosis. In: NLoM. Bethesda, MD: 2013; Clinical Trial Number NCT01773187

42. Cell Therapeutics. Oral pacritinib versus best available therapy to treat myelofibrosis with thrombocytopenia. In: NLoM. Bethesda, MD: 2014; Clinical Trial Identifier Number: NCT02055781


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