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Emerging drugs for myelofibrosis

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Abstract

Introduction—Myelofibrosis (MF), a Philadelphia chromosome-negative myeloproliferative neoplasm, is a life-threatening heterogeneous disorder characterized by dysregulation of the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling network. The clinical hallmarks of MF are progressive splenomegaly, anemia and debilitating symptoms attributable to ineffective hematopoiesis and excessive production of proinflammatory cytokines.

Areas covered—This review describes the pathogenesis, clinical features and current treatment of MF, clinical data for ruxolitinib, a potent oral JAK1/JAK2 inhibitor and the only therapy approved for the treatment of MF, and agents in development for the treatment of MF. Information was derived from relevant MF articles identified in the published literature and abstracts of recent congresses.

Expert opinion—Ruxolitinib reduces spleen size and alleviates MF-related symptoms, thereby improving quality of life. Ruxolitinib may increase the risk of anemia and thrombocytopenia and does not appear to reverse bone marrow fibrosis. Studies are exploring ruxolitinib dosing strategies for patients with low platelet counts and combination therapies. Several other JAK inhibitors and other agents (i.e., immunomodulators, antifibrotic agents, anti-anemia agents, mammalian target of rapamycin [mTOR] inhibitors, epigenetic modifiers, pegylated interferon- α 2a) to treat various aspects of MF (i.e., to improve blood counts or forestall marrow fibrosis) are in early clinical development.

Keywords

everolimus (RAD001); fresolimumab (GC1008); GS-6624 (formerly AB0024); JAK 2 inhibitor; momelotinib (CYT387); myelofibrosis; myeloproliferative neoplasm; pacritinib (SB1518); panobinostat (LBH589); peg-interferon; pomalidomide (CC-4047); ruxolitinib; SAR302503 (formerly TG101348)

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1. Background

Myelofibrosis (MF) is a rare chronic disease characterized by progressive bone marrow fibrosis and inefficient hematopoiesis [1] that primarily affects older individuals. MF is a Philadelphia chromosome-negative myeloproliferative neoplasm (Ph-negative MPN), a classification that also includes polycythemia vera (PV) and essential thrombocythemia (ET) [2]. The US incidence rates (2001 – 2003) for primary MF (PMF), PV and ET were 0.22, 0.95 and 0.51 per 100,000 persons per year, respectively [1]. Patients with PV and ET have a 10-year risk as high as 10 and 1%, respectively, for developing secondary MF, that is, post-PV and post-ET MF [3].

1.1 Pathogenesis

Ph-negative MPNs have distinct histopathologic, morphologic and cytogenetic features, depending on which hematopoietic cell lineages are primarily affected [4]; however, the clinical and pathophysiological characteristics of MF are similar across underlying MPNs [5]. Although the precise disease-initiating event for each MPN remains unknown, Ph-negative MPNs are believed to be monoclonal or oligoclonal malignancies that differ in the type of blood cells primarily affected by malignant growth [6]. They share a common pathogenesis, characterized by somatic mutations causing dysregulation of Janus kinase 2 (JAK2)/signal transducer and activator of transcription (STAT) signaling in hematopoietic stem cells or early progenitor cells [7], which leads to overexpression of cytokines controlling blood cell production. The signs and symptoms of MF are believed to be mostly a reaction to excessive fibrogenic cytokine production and overproduction of proinflammatory cytokines [8,9]. The mutations that have been identified in MPNs are generally not disease-specific and are not necessarily mutually exclusive [6]. By far the most common mutation is the JAK2^{V617F} gain-of-function mutation, which results in constitutive activation of JAK2 and is present in > 95% of patients with PV and ~ 60% of patients with PMF or ET [7]. Dysregulation of JAK2 signaling may occur as a result of JAK2 exon 12 mutations or indirectly through mutations in regulators of the JAK/STAT pathway, including epigenetic modifiers that affect gene activity by controlling DNA methylation or histone modification [7].

1.2 Clinical presentation and prognosis

Clinical presentation, natural history and symptom severity of MF vary widely from patient to patient. Early stages may be asymptomatic and mainly characterized by overproduction of platelets (thrombocytosis) and/or white blood cells (leukocytosis) [10]. In contrast, the clinical hallmarks of more advanced MF are massive enlargement of the spleen (splenomegaly) due to extramedullary hematopoiesis and splenic sequestration of immature blood cells, severe anemia due to insufficient hematopoiesis and debilitating symptoms caused by high circulating levels of inflammatory cytokines [11]. Common symptoms include fatigue, night sweats, itching (pruritus), feeling full (early satiety), abdominal and bone pain and severe weight loss (cachexia) [11]. Further complications of disease progression may include hepatomegaly (particularly in post-splenectomy patients), portal hypertension, splenic infarcts and thrombosis [12]. Patients with advanced MF also have an increased risk of developing MPN blast phase (MPN-BP) (characterized by > 20% of

immature blood cells) [13], also known as post-PMF blast phase or post-PV/ET MF blast phase [14].

Patients with MF have a substantially reduced life expectancy, with a median survival time of only 6 years for those diagnosed with PMF [15]. Although secondary acute myelogenous leukemia (sAML) is the single most common cause of death, the majority of patients die from MF-related complications [15]. A number of prognostic scoring systems have been developed that predict survival based on age, symptom severity and hematologic and cytogenetic findings [15–17]. Patients with PMF classified as low, intermediate-1, intermediate-2 or high risk (based on International Prognostic Scoring System) have estimated median survival times of 135, 95, 48 and 27 months, respectively [15]. Patients with MPN-BP have an estimated median survival time of < 3 months [18].

2. Medical need and existing treatments

MF is a life-threatening disease and its dominant clinical manifestations, splenomegaly, MF-related symptoms and anemia, are associated with substantial impairment of physical and emotional functioning and decreased quality of life [19,20]. Before the recent market approval of ruxolitinib (discussed in detail in Sections 3 and 6), available therapies were limited to agents that are not approved for the treatment of MF and are essentially palliative in nature, including androgens, corticosteroids, erythropoiesis-stimulating agents, danazol, cladribine, hydroxyurea, pegylated interferon (peg-IFN)- α 2a and the immunomodulatory agents thalidomide and lenalidomide. These agents have not been evaluated in prospective randomized controlled Phase III studies in patients with MF and have not been shown to prolong life or alter the natural history of the disease [21,22].

2.1 Allogeneic stem cell transplantation

Currently, allogeneic stem cell transplantation (ASCT) is the only known potentially curative treatment available for patients with MF [23]. However, the use of ASCT with curative intent is associated with high risk of relapse, postoperative morbidity (including chronic graft versus host disease) and mortality [24–26]. Results of a large retrospective analysis of data from 289 patients with MF revealed that the 1-year rate of ASCT-related mortality was 27% overall and 43% when recipient and donor were unrelated [25]. There is also no conclusive evidence that ASCT is associated with prolonged survival [27]. Consequently, ASCT is rarely performed, for example, in less than 2% of patients with MF in one study [17], and should be reserved primarily for younger patients with intermediate-2 or high-risk MF and those in MPN blast phase (after achieving a response to intensive chemotherapy) [18,22]. However, the number of ASCTs performed in the United States is gradually increasing as shown by data from the Center of International Blood and Marrow Transplant Research (CIBMTR) [28]. This may be attributed in part to the increasing use of reduced-intensity conditioning (RIC) regimens, which have the potential to allow ASCT to be considered in older adults with MF and higher-risk disease [29,30]. In addition, the use of JAK2 inhibitors may improve the functional status of patients with MF, which in turn may increase the number of patients eligible for ASCT.

2.2 Treatment of splenomegaly and MF-associated symptoms

Splenomegaly may be associated with severe symptoms, including pain; in patients unresponsive to pharmacotherapy, splenectomy remains the only option with any promise of symptom relief. However, splenectomy is associated with substantial risk of perioperative complications, including hepatomegaly and death [31,32]. Before the advent of ruxolitinib, the cytoreductive agent hydroxyurea was the therapy of choice for the treatment of leukocytosis, thrombocytosis and splenomegaly [21]. Although data from a single-site study in 40 patients, 26 of whom had palpable spleen size < 10 cm, indicated that treatment with hydroxyurea achieved a 40% response with regard to splenomegaly and that the median duration of response was 13.2 months (range 3 – 126.2 months) [33], in other studies, the efficacy of hydroxyurea in reducing spleen size was modest and nondurable, particularly in patients without the JAK2^{V617F} mutation and in those with marked splenomegaly (palpable spleen size > 10 cm) [22,34]. Adverse effects of hydroxyurea include myelosuppression, xeroderma and mucocutaneous ulcers [22,33]. Other conventional therapies used for the treatment of splenomegaly include busulphan or melphalan for patients intolerant of or refractory to hydroxyurea and intravenous cladribine for patients with marked splenomegaly refractory to other treatments [21]. All of these agents are highly myelosuppressive and may cause severe cytopenias [21]. Results of a Phase III study comparing the effects of ruxolitinib and best available therapy in patients with intermediate-2 or high-risk MF further showed that best available therapy, including hydroxyurea in 47% of patients, provided marginal or no clinical benefit in terms of reductions in spleen volume or quantifiable improvements in quality of life [35].

2.3 Treatment of anemia

Approximately half of all patients with PMF are anemic, complain of extreme fatigue [19] and may require frequent blood transfusions. Both thalidomide and lenalidomide, with or without concomitant prednisone, have shown activity in alleviating MF-associated anemia, splenomegaly and thrombocytopenia in various Phase II studies [36–39]. However, thalidomide provided no significant clinical benefit in a placebo-controlled study [40], elicits only transient treatment responses [41] and is poorly tolerated at higher doses due to neurologic adverse effects [36,41]. Although lenalidomide plus prednisone is better tolerated and may have longer lasting treatment effects [41], results of a recent Phase II study of this combination in 48 patients with MF and anemia showed only modest response rates (23% based on criteria by the International Working Group for Myelofibrosis Research and Treatment [IWG-MRT]) and severe hematologic toxicity (grade 3) in 88% of patients [38].

3. Market review

In November 2011, ruxolitinib, an oral JAK1/JAK2 inhibitor, was the first pharmacotherapy approved by the US Food and Drug Administration for the treatment of patients with intermediate- or high-risk MF, including PMF, post-PV MF and post-ET MF [42]. Ruxolitinib was developed and is marketed as Jakafi® in the United States by Incyte Corp. (Wilmington, DE, USA). The licensee for marketing outside the United States, Novartis AG (Basel, Switzerland), obtained Canadian market approval for ruxolitinib (Jakavi®) in July 2012 [43] as well as European market approval (under the same trade name, Jakavi®) in

August 2012 [44]. In two Phase III clinical studies in patients with MF, ruxolitinib provided significant and durable reductions in spleen volume, MF-related symptoms and quality of life compared with placebo or best available therapy [35,45].

4. Current research goals

Post-launch evaluation of ruxolitinib is underway to assess the benefits and risks associated with long-term therapy and to evaluate the efficacy and safety of dosing strategies in patients with low platelet counts. Most clinical development efforts in MF are focused on JAK2 inhibitors with varying degrees of potency and selectivity and with potentially different adverse event profiles; however, effective treatment of anemia and fibrosis remains an important clinical need, as anemia is associated with decreased survival, and fibrosis contributes to ineffective hematopoiesis and bone marrow failure. Pomalidomide (CC-4047, Celgene Corp., Summit, NJ, USA), a potent third-generation immunomodulator, is currently in Phase III development for the treatment of MF-related transfusion dependence, and a number of antifibrotic agents are in early clinical development for the treatment of MF (Table 1). In addition, combination therapies of ruxolitinib with anti-anemia (lenalidomide, pomalidomide) and antifibrotic (GS6624; formerly AB0024; Gilead, Foster City, CA, USA) agents are being evaluated in clinical pilot studies (Table 2). Furthermore, clinical development of a number of agents that affect aberrant myeloproliferation and cytokine production through mechanisms other than direct JAK inhibition is underway. These agents include everolimus, an inhibitor of mammalian target of rapamycin (mTOR) and epigenetic modifiers such as inhibitors of histone deacetylation (givinostat [ITF2357; Italfarmaco, Milan, Italy], panobinostat [LBH589; Novartis AG, Basel, Switzerland]) and DNA hypermethylation (decitabine; Table 1).

5. Scientific rationale for the use of ruxolitinib

Irrespective of the precise pathogenesis of the underlying MPN, MF is characterized by dysregulated JAK/STAT signaling (Figure 1). JAKs belong to a family of cytoplasmic tyrosine kinases, including JAK1, JAK2, JAK3 and Tyk2, which are activated through association with ligand-activated cytokine receptors lacking intrinsic tyrosine kinase activity [46]. JAK/STAT signaling is mediated by subsequent recruitment of STATs to the activated receptor complex. During normal hematopoiesis, JAK2 activation requires binding of hematopoietic growth factors such as erythropoietin (EPO) and thrombopoietin (Tpo) to their cognate receptors (EPO-R and Tpo-R, respectively) to initiate receptor complex formation [46]. In contrast, dysregulated and excessive JAK2 activity independent of receptor stimulation is an important pathogenic mechanism of aberrant hematopoiesis in Ph-negative MPNs [7]. Thus, JAK2 is the logical primary drug target for MF, explaining the large number of JAK2 inhibitors currently in development. However, specific MF disease characteristics further suggest that patients with MF may benefit from drugs that target not only JAK2 but also JAK1. JAK1 is involved in mediating inflammatory responses, and patients with MF have been shown to have significantly increased levels of proinflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor (TNF)- α [47,48]. This 'proinflammatory' state is believed to be a major reason for the debilitating symptoms associated with MF.

Ruxolitinib is a potent inhibitor of JAK1 ($IC_{50} = 3.3$ nmol/L) and JAK2 ($IC_{50} = 2.5$ nmol/L), with sixfold and 130-fold selectivity against Tyk1 and JAK3, respectively, in *in vitro* kinase assays [49]. Ruxolitinib has been shown to inhibit the growth of and induce apoptosis in cells engineered to express JAK2^{V617F} and to inhibit proliferation of mutant erythroid progenitor cells obtained from patients with PV. Results from a mouse model of JAK2^{V617F}-driven malignancy further demonstrated that ruxolitinib significantly reduced spleen weight and lowered circulating levels of IL-6 and TNF- α [49]. Moreover, by the 22nd day of induced malignancy, > 90% of mice that received vehicle had died, whereas > 90% of those treated with ruxolitinib had survived. Overall, these findings suggested that ruxolitinib might be an effective therapy for patients with MF, providing a strong rationale for clinical development of this JAK1/JAK2 inhibitor.

6. Competitive environment

This section summarizes the available clinical data for ruxolitinib and agents in clinical development, including important design characteristics of planned and ongoing registered clinical trials.

6.1 Ruxolitinib

The efficacy and safety of ruxolitinib in patients with MF have been evaluated in one Phase I/II study [9] and two Phase III studies, the Controlled Myelofibrosis Study with Oral JAK1/JAK2 Inhibitor Treatment (COMFORT)-I [45] and COMFORT-II (Table 3) [35].

6.1.1 Efficacy—In the open-labeled Phase I/II study (INCB18424-251; NCT00509899), which was carried out at two sites (the MD Anderson Cancer Center [MDACC] and the Mayo Clinic-Rochester) in 153 patients with MF (65.4% high-risk, 27.5% intermediate-2 risk), 52 and 49% of those with splenomegaly receiving 15 and 25 mg b.i.d., respectively, achieved a 50% reduction in palpable spleen size (IWG-MRT criterion for response) after 12 weeks of treatment [9]. In the two dose groups, 73 and 78%, respectively, of those who had this response maintained it after 12 months of therapy. In the majority of patients, ruxolitinib at doses of 10 to 25 mg b.i.d. was associated with a rapid and durable 50% reduction in combined symptom score as assessed by the Myelofibrosis Symptom Assessment Form (MFSAF) [9].

COMFORT-I (INCB18424-351; NCT00952289) was a randomized double-blind study of ruxolitinib ($n = 155$) versus placebo ($n = 154$) in patients with high-risk or intermediate-2 risk PMF, post-ET MF or post-PV MF [45]. Ruxolitinib starting doses were 15 and 20 mg b.i.d. depending on baseline (BL) platelet count ($100 - 200 \times 10^9/L$ and $> 200 \times 10^9/L$, respectively). The primary endpoint, a 35% reduction in spleen volume (assessed by magnetic resonance imaging) at week 24, was reached by 41.9% of patients treated with ruxolitinib compared with 0.7% in the placebo group ($p < 0.001$, Figure 2). In addition, 45.9% of patients treated with ruxolitinib compared with 5.3% receiving placebo achieved a 50% reduction in total symptom score (TSS) as measured by the modified MFSAF version 2.0 ($p < 0.001$) [45]. The majority of patients receiving ruxolitinib experienced some reduction in spleen volume or improvement in symptoms. Notably, ruxolitinib therapy resulted in median weight gain (compared with median weight loss in the placebo group)

and significant alleviation of fatigue (compared with worsening in the placebo group, $p < 0.0001$) as determined by the Patient-Reported Outcomes Measurements Information System (PROMIS) Fatigue score. The significant reduction in symptom burden was accompanied by substantial reductions in plasma levels of the proinflammatory cytokines IL-6 and TNF- α . At week 24, patients treated with ruxolitinib also achieved significant improvement in quality of life (vs placebo, $p < 0.0001$), as determined by the European Organization for Research and Treatment of Cancer Quality of Life 30 Questionnaire (EORTC QLQ-C30), including scores for physical, role, emotional and social functioning (vs placebo, $p < 0.001$). According to Patient Global Impression of Change scores, 34.5 and 32.4% of patients treated with ruxolitinib rated their condition as much and very much improved, respectively, whereas most patients in the placebo group rated their condition as unchanged or worse [45].

COMFORT-II (CINC424A2352; NCT00934544) was a randomized study comparing ruxolitinib and best available therapy in 219 patients with MF [35]. COMFORT-II had inclusion criteria similar to those in COMFORT-I and used the same ruxolitinib dosing criteria, but the randomization ratio was 2:1 in favor of ruxolitinib and the primary endpoint was 35% reduction in spleen volume at 48 weeks. The primary endpoint was reached by 28% of patients in the ruxolitinib group compared with no patient in the best available therapy group ($p < 0.001$). The ruxolitinib treatment effect was durable, as 80% of treated patients still responded at a median follow-up of 12 months. At week 48, ruxolitinib also was associated with improvements in global health status/quality of life and role functioning and with marked reductions in MF-related symptoms (based on EORTC QLQ-C30 core model and symptom scores). In contrast, best available therapy was associated with decline in role functioning and with symptom worsening [35].

6.1.2 Safety and tolerability—In both Phase III studies, the most common adverse events were anemia and thrombocytopenia [35,45]. In COMFORT-I, 45.2% of patients in the ruxolitinib group compared with 19.2% in the placebo group experienced grade 3 or grade 4 anemia, and 12.9% in the ruxolitinib group compared with 1.3% in the placebo group experienced grade 3 or grade 4 thrombocytopenia [45]. However, thrombocytopenia and anemia were manageable with dose modifications, treatment interruptions and blood transfusions, illustrated by the fact that for each type of event only one patient in each treatment group discontinued COMFORT-I study participation [45]. In COMFORT-II, 42% of patients in the ruxolitinib group experienced grade 3 or grade 4 anemia and 8% experienced grade 3 or grade 4 thrombocytopenia. Thrombocytopenia prompted dose modifications in 41% of patients in the ruxolitinib group and one patient discontinued ruxolitinib because of thrombocytopenia [35].

In the Phase I/II study, the dose-limiting toxicity was reversible thrombocytopenia. In addition, it was reported that upon treatment discontinuation, 5 of the 51 patients treated at the Mayo Clinic-Rochester site of the Phase I/II study experienced acute relapse of their symptoms that required hospitalization. Complications included respiratory distress, anemia requiring transfusion, splenomegaly, septic shock-like syndrome, pleural effusion, pericardial effusion and disseminated intravascular coagulation-like syndrome [50]. Such complications were not reported after discontinuation of ruxolitinib in patients treated at the

MDACC site of the Phase I/II study [9], and furthermore no specific pattern of adverse events has been reported in patients who discontinued ruxolitinib treatment in either COMFORT-I or COMFORT-II [35,45]. The US prescribing information for ruxolitinib suggests consideration of gradual tapering of the dose when discontinuing treatment for reasons other than thrombocytopenia [42].

6.1.3 Survival—In the Phase I/II study, conflicting results regarding survival were obtained at the two study sites. At the MDACC site, the survival rate of 107 patients after a median follow-up of 32 months was 69%; compared with historical controls, patients treated with ruxolitinib had significantly greater overall survival (hazard ratio [HR] = 0.58; 95% confidence interval [CI]: 0.39 – 0.85) [51]. In contrast, at the Mayo Clinic-Rochester site, the survival rate of the 51 patients did not differ significantly from that of historical controls ($p = 0.43$) [52].

The effect of ruxolitinib treatment on survival was also evaluated in both of the randomized Phase III trials. In COMFORT-I, ruxolitinib was associated with a significant reduction in mortality rate compared with placebo in an analysis conducted at a median follow-up of 51 weeks (HR = 0.50; 95% CI: 0.25 – 0.98; $p = 0.04$) [45], whereas no survival benefit of ruxolitinib versus best available therapy was apparent in the COMFORT-II study at a median follow-up of 61 weeks (HR = 1.01; 95% CI: 0.32 – 3.24) [35]. More recently, overall survival was evaluated in each of the COMFORT trials after a median 2-year follow-up. In these updated long-term analyses, ruxolitinib was associated with a significant survival advantage compared with both placebo (HR = 0.58; 95% CI: 0.36 – 0.95) [53] and best available therapy (HR = 0.52; 95% CI: 0.27 – 1.00) [54].

6.1.4 Ongoing clinical trials—An ongoing 24-week Phase II study sponsored by Incyte (INCB18424-258; ‘258’; NCT01348490) is evaluating the efficacy and safety of ruxolitinib in intermediate- and high-risk patients with platelet counts of $50 - 100 \times 10^9/L$, using individualized dose optimization after a starting dose of 5 mg b.i.d. Preliminary results ($n = 41$) suggest that the majority of patients at the time of analysis were able to optimize dosing to 10 mg b.i.d. with consequent reduction in spleen length and symptom improvement while maintaining stable mean hemoglobin over time [55]. Other Incyte-sponsored Phase II studies in patients with MF are evaluating the efficacy and safety of a once-daily sustained-release formulation (INCB18424-260; NCT01340651) and an alternative dosing approach to decrease the risk of treatment-associated anemia (INCB18424-261; NCT01445769). A Phase IV UK-based study (Table 3) sponsored by Novartis is assessing the effects of ruxolitinib on a variety of outcome measures, including 50% reduction in palpable spleen length and TSS, best overall response as determined by the investigator, quality of life, frequency and duration of hospitalization, frequency of emergency and additional outpatient office visits, transfusion dependency, splenectomy and splenic irradiation, use of concomitant medications for MPN-related symptoms and overall safety (CINC424AGB02; UK MACS2030; NCT01558739). In addition, a number of studies of combination therapies with ruxolitinib are ongoing (discussed below in Section 7).

6.2 JAK2 inhibitors in clinical development

SAR302503 (formerly TG101348; Sanofi, Paris, France) is the only JAK2 inhibitor in an ongoing Phase III study (Table 3). However, Phase III study initiation by the end of 2012 has been announced for both momelotinib (CYT387; YM Biosciences, Mississauga, Ontario, Canada) [56] and pacritinib (SB1518; S*Bio, Singapore, Singapore) [57]. In addition, a number of JAK2 inhibitors are in Phase I/II study, including AZD1480 (AstraZeneca, London, UK); BMS-911543 (Bristol-Myers Squibb, New York, NY, USA); NS-018 (Nippon Shinyaku, Kyoto, Japan) and LY2784544 (Eli Lilly, Indianapolis, IN, USA), a selective JAK2^{V617F} inhibitor (Table 1). Since no clinical data have been published to date for AZD1480, BMS-911543 or NS-018, these agents will not be discussed further. Moreover, development of lestaurtinib (CEP-701; Cephalon/Teva, Petach Tikva, Israel) has been put on hold after lestaurtinib showed modest efficacy and was associated with high rates of gastrointestinal adverse events in Phase II study [58].

6.2.1 SAR302503 (formerly TG101348)—SAR302503 is a highly selective JAK2 inhibitor with similar *in vitro* potency for JAK2 ($IC_{50} = 3 \text{ nmol/L}$) as ruxolitinib. However, SAR302503 is 35 times more selective for JAK2 than for JAK1 and has no appreciable inhibitory activity against other members of the JAK family [59]. In preclinical models, SAR302503 inhibited JAK2^{V617F}-driven engraftment of human PV erythroid progenitor cells [60] and reduced hematocrit, leukocyte count and extramedullary hematopoiesis in mice with JAK2^{V617F}-induced PV [59]. In a 24-week Phase I study in 59 patients with high- or intermediate-risk MF, SAR302503 therapy at doses up to the maximum tolerated dose of 680 mg/day was associated with a 50% reduction in palpable spleen size for 8 weeks in 39% of the patients [61]. In addition, SAR302503 therapy was associated with rapid and durable symptom improvement and normalization of blood counts in most patients with leukocytosis or thrombocytosis at BL. It also achieved a significant reduction of JAK2^{V617F} allele burden ($n = 51$, $p = 0.04$), although the clinical significance of this effect is unknown, as the number of patients was too small to correlate clinical responses with reduction of mutant alleles. The dose-limiting toxicity was grade 3 or grade 4 hyperamylasemia. The most common nonhematologic events were dose-dependent grade 1 gastrointestinal events. Grade 3 or grade 4 anemia occurred in 35% of patients, whereas grade 3 or grade 4 thrombocytopenia occurred in 24% of patients.

The double-blind placebo-controlled JAKARTA study (EFC12153; NCT01437787) sponsored by Sanofi is a Phase III study of SAR302503 in patients with intermediate-2 or high-risk MF with splenomegaly and a minimum platelet count of $50 \times 10^9/\text{L}$ [62]. Using six 28-day treatment cycles, this three-arm study with an enrollment target of 75 patients per arm is evaluating the efficacy and safety of oral doses of 400 and 500 mg q.d. compared with placebo [62]. In addition, an ongoing Phase II study is evaluating the efficacy of SAR302503 in MF patients who previously received ruxolitinib (NCT01523171).

6.2.2 Momelotinib (CYT387)—Momelotinib is a JAK1/JAK2 inhibitor with *in vitro* IC_{50} values of 11 and 18 nmol/L, respectively [63]. Momelotinib has been shown to suppress growth and induce apoptosis in JAK2-dependent hematopoietic cell lines and to elicit responses in an MPN mouse model that included normalization of blood cell counts and

spleen size and restoration of physiologic levels of inflammatory cytokines [64]. Preliminary findings from an ongoing multicenter Phase I/II study and its long-term extension companion substudy (CCL09101 & CCL09101E; NCT01236638), as well as an additional open-label safety study (YM387-II-02; NCT01423058) in patients with MF suggest that CYT387 therapy may improve spleen size and symptoms and possibly transfusion dependence [65,66]. Data presented to date suggest that of 42 patients evaluable for ‘anemia response’ according to IWG-MRT criteria [67], 50% achieved transfusion independence with a median duration of 20 weeks (range 12–54 weeks) [65]. Of note, these data emanate from a single-arm study with no controls, and the results need to be interpreted cautiously, considering the multiple caveats with the definition of transfusion dependency in similar trials [68]. Enrollment for a pivotal Phase III trial is expected to start sometime between the fourth quarter of 2012 and first half of 2013 [56].

6.2.3 Pacritinib (SB1518)—Pacritinib is an oral JAK2 inhibitor with similar *in vitro* potency against JAK2 ($IC_{50} = 23$ nmol/L) and FLT-3 (22 nmol/L) and potent antiproliferative activity against both myeloid and lymphoid cell lines [69]. A Phase II study of pacritinib 400 mg/day in 33 patients with MF and splenomegaly ≥ 5 cm below the left costal margin found that after 6 months of treatment, 17 of 30 patients (57%) assessed by MRI achieved a spleen volume reduction of $\geq 25\%$, and an overall reduction of MF-related symptom intensity of 40–65% was reported. Common adverse events (diarrhea, nausea, vomiting and fatigue) were reported as ‘manageable’ and no grade 3 or grade 4 neutropenia or thrombocytopenia was reported [70]. In a recent 24-week Phase II study of pacritinib 400 mg/day in 34 patients with MF and palpable splenomegaly (44% of whom had platelet counts below $100 \times 10^9/L$), 32% of all patients achieved a $\geq 35\%$ reduction in spleen volume and 18% achieved complete resolution of splenomegaly [71]. In addition, clinically significant improvement of MF-associated symptoms was noted. The most common treatment-related adverse events were generally low grade gastrointestinal disturbances [71]. Initiation of a Phase III study in MF patients with low platelet counts is planned for the fourth quarter of 2012 [57].

6.2.4 LY2784544—LY2784544 is an oral JAK2 inhibitor with 41-fold *in vitro* selectivity for JAK2^{V617F} ($IC_{50} = 55$ nmol/L) over wild-type JAK2 (2.26 μ mol/L) [72]. LY2784544 has been shown to inhibit JAK2^{V617F}-driven cell proliferation and induce apoptosis and to selectively reduce JAK2^{V617F} allele burden in a murine MPN model without affecting erythroid progenitor cells [72]. In a Phase I study including 17 patients with MF and one patient each with PV and ET, 76% of all patients achieved a $\geq 35\%$ reduction in palpable spleen length and 59% reported a $\geq 50\%$ improvement in key MPN-related symptoms. However, a reduction in mutant allele burden was not observed. In four patients LY2784544 therapy was associated with serious drug-related adverse events indicative of tumor lysis syndrome (TLS), including grade 4 hyperuricemia in two patients, grade 2 creatinine increase in four patients and grade 1 hyperkalemia in one patient [73]. Currently, a Phase II study (LY 13861; NCT01594723) is evaluating the effects of different doses of LY2784544 on objective response in patients with MF, PV or ET, while a Phase I dose-finding study in patients with MF is testing alternative dosing strategies (NCT01520220).

6.3 Other agents

6.3.1 Everolimus (RAD001)—Everolimus is a specific inhibitor of mTOR approved for a variety of cancers, including renal cell carcinoma, tuberous sclerosis and pancreatic neuroendocrine tumors, and under investigation for lymphoma. Recently, dysregulated mTOR signaling has been implicated in JAK2^{V617F}-driven pathogenesis in MPNs, and everolimus has been shown to inhibit growth of JAK2^{V617F}-mutant cell lines and hematopoietic progenitor cells from MPN patients [74]. Results of a Phase II study (EudraCT 2008-000522-39) in 30 patients with MF showed that everolimus 10 mg/day provided rapid and sustained > 30% reduction in spleen length in 44% of patients and complete resolution of systemic symptoms in 69% of patients. Complete response rates (according to European Network for Myelofibrosis [EUMNET] criteria) for leukocytosis, anemia and thrombocytosis were 15, 25 and 25%, respectively. The clinical responses were not accompanied by reductions in JAK2^{V617F} allele burden or cytokine levels [75].

6.3.2 Pomalidomide (CC-4047)—The efficacy of pomalidomide with or without prednisone in patients with MF has been evaluated in 94 participants of two consecutive Phase II studies conducted at the Mayo Clinic [76–79]. Pomalidomide had no clinically significant effect on splenomegaly. The overall rate of anemia response according to IWG-MRT criteria was 27%, with higher rates observed among patients with spleen size < 10 cm (46%) and those with < 5% circulating blast cells (32%) [79]. Pomalidomide was associated with a 2-year discontinuation rate of 89%. Although long-term data showed that pomalidomide therapy caused grade 1 sensory neuropathy in four of 30 patients treated for more than 1 year, this condition was triggered in all cases by high doses of pomalidomide (2 mg/day) [79], which generally were less effective than low-dose pomalidomide (0.5 mg/day) [76,77]. Currently, a double-blind placebo-controlled Phase III study (RESUME; NCT01178281) is evaluating the safety and efficacy of pomalidomide 0.5 mg q.d. in patients with MF who are red blood cell (RBC) transfusion-dependent. The primary endpoint is the percentage of patients who achieve transfusion independence within 6 months.

6.3.3 Epigenetic modifiers—Among epigenetic modifiers recently evaluated in pilot clinical studies, the deacetylase inhibitors panobinostat and givinostat and the DNA methyltransferase inhibitor decitabine have shown activity in patients with MF. Findings from Phase I and Phase II studies [80,81] in patients with MF showed that treatment with panobinostat was associated with reduction of JAK2^{V617F} allele burden, symptom improvement and 30% median reduction of palpable spleen size. In addition, improvement of anemia, resolution of splenomegaly and leukoerythroblastosis and decrease of bone marrow fibrosis was observed in individual patients [80]. Panobinostat was generally well tolerated, with reversible thrombocytopenia as the dose-limiting toxicity [80]. Givinostat was evaluated in a Phase II study including 13 patients with PV or ET and 16 patients with MF [82]. Although givinostat elicited seven complete or partial responses in PV/ET patients, only two patients with MF had clinical improvement and five maintained stable disease (SD) based on IWG-MRT criteria [82]. In a single-stage Phase II study, low-dose decitabine was given subcutaneously to 10 MF patients with myeloid metaplasia and anemia or splenomegaly [83]. Of seven evaluable patients, three responded and four had SD. Responses included one complete response (normalization of blood counts and achievement

of transfusion independence), one partial response (improvement in hematocrit) and one hematologic improvement in blast phase [83].

6.3.4 Antifibrotic agents—Two monoclonal antibodies, fresolimumab (GC-1008; Genzyme/Sanofi, Paris, France) and GS-6624 (formerly AB0024), are in early phase clinical development for the treatment of MF-associated bone marrow fibrosis (Table 1). Fresolimumab is a human monoclonal antibody that inhibits transforming growth factor (TGF)- β , which has been implicated as a key factor in the pathogenesis of MF-associated bone marrow fibrosis [8]. A Phase I study sponsored by the Mount Sinai School of Medicine (NCT01291784) is evaluating the safety of fresolimumab as well as effects on bone marrow fibrosis, disease markers and MPN-associated symptoms in MF patients. GS-6624 is a monoclonal antibody against lysyl oxidase-like protein 2 (LOXL2), an enzyme involved in extracellular matrix remodeling during angiogenesis and fibrosis [84]. A multicenter Phase II study (NCT01369498) is currently evaluating the effects of low- and high-dose GS-6624 alone and in combination with ruxolitinib on bone marrow fibrosis (primary endpoint), hematologic parameters, safety, symptoms, cytokine levels and formation of anti-GS-6624 antibodies in patients with MF.

6.3.5 Pegylated interferon- α 2a—Various forms of interferon- α , including pegylated interferon- α 2a (peg-IFN- α 2a), have been shown in Phase II studies to provide high rates of hematologic and molecular response in patients with PV or ET [85–88]. In addition, a small retrospective study by the GEM/FIM French Intergroup in 18 patients with MF found that peg-IFN- α 2a therapy was associated with high rates of complete resolution of leucocytosis and thrombocytosis [89]. Moreover, two of three patients with transfusion dependence became ‘transfusion independent’, and four of five additional patients with anemia achieved normalization of hemoglobin levels [89]. A recent retrospective study of peg-IFN- α 2a in an international cohort of 118 patients with advance Ph-negative MPNs included 17 patients with MF [90]. Of those, no patient achieved a complete response according to IWG-MRT criteria, but 30% achieved a partial response or clinical improvement and 41% maintained SD according to the same criteria. Treatment was well tolerated, with no case of hematologic adverse events grade ≥ 3 [88]. A multicenter Danish Phase III study (DALIAH; NCT01387763) is comparing the effects of low-dose peg-IFN- α 2a and hydroxyurea on molecular response (primary endpoint), toxicity and quality of life in patients with PV, ET or PMF.

7. Combination therapy with ruxolitinib

As described above, ruxolitinib, while substantially reducing spleen size and symptom burden, does not treat or reverse all aspects of MF. Combination therapies of other agents with ruxolitinib may produce effective and well-tolerated synergies. Two pilot studies (Table 2) in the United States and Germany are evaluating the effects of ruxolitinib combined with lenalidomide and pomalidomide, respectively, on response rates in patients with MF. A Phase II study is evaluating the effects of the recombinant antibody GS-6624 on bone marrow fibrosis in the presence and absence of ruxolitinib therapy. A European Phase Ib study is evaluating the effect of ruxolitinib plus panobinostat on palpable spleen length

reduction (Table 2). Several additional combination studies are currently in the planning phase both in the United States and internationally.

8. Potential development issues

Myelosuppression leading to anemia and/or thrombocytopenia are challenges for many agents in development in MF, including JAK2 inhibitors. In the case of ruxolitinib, regular monitoring of blood counts, RBC transfusions for anemia and early dose titration to a stable, efficacious and well-tolerated long-term dose through dose reductions and/or treatment interruptions with carefully controlled reintroduction of treatment appear to be sufficient for successful management of the vast majority of cases of drug-induced new (or worsening) anemia and thrombocytopenia [9,35,45]. The efficacy and adverse event profile of JAK inhibitors and other agents may be associated with potency of myelosuppression, selectivity profile and pharmacodynamics. In this respect it is noteworthy that lestaurtinib, an FLT3 and JAK2 inhibitor, showed only modest efficacy (clinical improvement in 5 of 22 MF patients) but a high degree of gastrointestinal toxicity (9% grade 3 diarrhea) in a recent Phase II trial [58]. In addition, the JAK2^{V617F}-specific inhibitor LY2784544 so far is the only JAK inhibitor that has been associated with a risk of TLS [73].

9. Conclusion

The shortcomings of palliative therapies led to investigations of more specific and active treatments for MF, which resulted in the recent approval of ruxolitinib and investigation of other agents currently in clinical development. The availability of ruxolitinib as the first approved agent for the treatment of intermediate- or high-risk MF based on two landmark Phase III trials marks a key step in understanding this disease and developing further treatment options to address the remaining medical needs for patients with MF. Ruxolitinib provides significant relief for patients with splenomegaly and debilitating MF-related symptoms, which is clinically meaningful. Further, ruxolitinib is associated with a life-prolonging effect, but it has not currently demonstrated effects on anemia. Whether long-term ruxolitinib halts (or even perhaps reverses) bone marrow fibrosis is currently unknown and remains a focus of investigation. The above limitations of treatment are currently being addressed through early development studies combining ruxolitinib with immunomodulators or the anti-TGF- β antibody GS-6624 and (for anemia) by a placebo-controlled Phase III study of pomalidomide. Of JAK2 inhibitors in clinical development, momelotinib (CYT387) has been reported to promote transfusion independence; however, these findings need to be confirmed using more stringent clinically relevant response criteria and in the setting of a controlled clinical trial. The design of a Phase II trial for SAR302503 suggests that the indication sought for this drug may include use in patients who have failed to respond to ruxolitinib. Although there is a lack of published experience with ruxolitinib or other JAK inhibitors in patients with low platelet counts ($< 100 \times 10^9/L$), clinical studies are in progress to address questions of dosing, efficacy and safety in this population.

10. Expert opinion

The Phase III studies of ruxolitinib, which led to the first market approval of any medical therapy for MF, present a significant and unprecedented milestone in the clinical research aimed at addressing the unmet clinical needs of patients with this heterogeneous disorder. Findings from these studies both validated the approach of targeting dysregulated JAK/STAT signaling as the key pathogenic mechanism in MF and revealed some important limitations of this approach. Splenomegaly can now be treated effectively with ruxolitinib. In addition, ruxolitinib provides effective and clinically meaningful relief of MF-related symptoms, many of which develop as a result of the proinflammatory state characteristic of MF, independent of splenomegaly. Consequently, patients treated with ruxolitinib achieve significant and durable improvement in their quality of life as well as increased survival. The COMFORT-II results illustrated the notable lack of efficacy of what has been considered for decades as ‘best available therapy’, which did not alleviate splenomegaly or symptoms or provide any meaningful or sustained improvements in quality of life. Although ruxolitinib may induce or exacerbate cytopenias, these adverse effects are generally manageable by dose reductions or treatment interruptions or by RBC transfusions in patients with anemia. Careful monitoring of blood cell counts during ruxolitinib therapy is highly recommended, particularly during early dose adjustments, that is, before a long-term stable well-tolerated dose has been established.

New areas of research include addressing the medical need for transfusion independence in patients with anemia and effects on bone marrow fibrosis. The most promising strategy to overcome these limitations may be a combination therapy of ruxolitinib with agents that have anti-anemic and antifibrotic activity. Historically, the use of immunomodulatory agents (thalidomide, lenalidomide) for the treatment of MF-related anemia has been hampered by the significant toxicity of these agents. Results of an ongoing Phase III study will show whether pomalidomide, a third-generation immunomodulator with increased potency, might be able to provide effective and durable anemia responses, together with a better adverse events profile. Notwithstanding these caveats, appropriately dosed lenalidomide (with prednisone) or pomalidomide in combination with ruxolitinib may have the potential to benefit patients who have anemia in addition to splenomegaly and MF-associated symptoms. Also, monoclonal antibodies with antifibrotic activity as part of combination therapies may prove useful for the treatment of MF; however, currently available clinical data are too limited to allow any firm conclusions regarding the efficacy of these agents. Similarly, it is too early to clearly delineate the future role of many other agents currently in development in the treatment of MF, including peg-IFN- α , the mTOR inhibitor everolimus and epigenetic modifiers. Preliminary data suggest that most of these agents may be only moderately effective in patients with MF; however, given the marked clinicolaboratory heterogeneity of MF, some may have a role in the context of individualized combination therapies for specific patients.

An important finding of the ruxolitinib Phase III studies is that the observed benefits of ruxolitinib did not require the presence of JAK2^{V617F}-positive clones; the majority of patients in both trials achieved some improvement in spleen size and symptoms. This diversifies the patient population that can potentially benefit from ruxolitinib. On the other

hand, the moderate effect of ruxolitinib and other JAK2 inhibitors on JAK2^{V617F} allele burden in the subset of patients with this mutation suggests that cure through clonal elimination remains an elusive goal. In this context, it is noteworthy that even LY2784544, a reportedly JAK2^{V617F}-specific JAK2 inhibitor, produced no major reduction in allele burden in a Phase I study, despite effects on spleen size and symptom burden. A number of JAK2 inhibitors with efficacy in spleen size and symptom reduction but with different in vitro kinase selectivity and possibly different adverse events profiles than ruxolitinib are being evaluated (SAR302503) or are about to be evaluated (mometotinib, pacritinib) in future Phase III studies. The results of these studies may reveal whether these agents provide similar or additional benefits compared with ruxolitinib.

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Figure 1. JAK/STAT dysregulation in MF
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Figure 2. Efficacy of ruxolitinib in reversing splenomegaly

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Table 1

Competitive environment.

Compound	Company	Chemical name	Indication	Development stage	Mechanism of action
Ruxolitinib	Incyte	R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate	Intermediate/high-risk MF	Approved	JAK1/JAK2 inhibitor
SAR302503 (TG101348)	Sanofi	(N-tert-butyl-3-(5-methyl-2-(4-(2-(pyrrolidin-1-yl)ethoxy)phenylamino) pyrimidin-4-ylamino) benzenesulfonamide)	Intermediate/high-risk MF MF previously treated with ruxolitinib	III	JAK2/FLT3 inhibitor
Momelotinib (CYT387)	YM BioSciences	N-(cyanomethyl)-4-[2-[[4-(4-morpholinyl)phenyl]amino]-4-pyrimidinyl]-benzamide	Idiopathic MF	III	JAK1/JAK2 Inhibitor
Pacritinib (SBI1518)	Cell Therapeutics, Inc. (CTI)	11-(2-pyrrolidin-1-yl)-ethoxy)-14,19-dioxo-5,7,26-triaza-tetracyclo[19.3.1.1(2.6).1(8,12)] heptacos-1(25),2(26),3,5,8,10,12 (27),16,21,23-decaene	MF and low platelet counts	III	JAK2/FLT3 inhibitor
LY2784544	Eli Lilly	3-(4-chloro-2-fluorobenzyl)-2-methyl-N-(3-methyl-1H-pyrazol-5-yl)-8-(morpholinomethyl)imidazol[1,2-b]pyridazin-6-amine	JAK2 ^γ V617E-positive MPNs	II	JAK2 ^γ V617E inhibitor
AZD1480	AstraZeneca	(S)-5-chloro-N2-(1-(5-fluoropyrimidin-2-yl) ethyl)-N4-(5-methyl-1H-pyrazol-3-yl)pyrimidine-2,4-diamine	Idiopathic MF	II	JAK2 inhibitor
BMS-911543	Bristol-Myers Squibb	N,N-dicyclopropyl-4-(((1,5-dimethyl-1 H-pyrazol-3-yl)amino)-6-ethyl-1 -methyl-1,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridine-7-carboxamide	MF	I/II	JAK2 inhibitor
NS-018	NS Pharma	Not available	Idiopathic MF	I/II	JAK2 inhibitor
Everolimus	Novartis	42-O-(2-hydroxyethyl)-rapamycin	Idiopathic MF	II	mTOR inhibitor
Panobinostat	Novartis	(2E)-N-hydroxy-3-[[4-((12-(2-methyl-1H-indol-3-yl)ethyl)amino) methyl]phenyl]prop-2-enamide	Idiopathic MF	II	Pan-deacetylase inhibitor
Givinostat	Italfarmaco	(6-(diethylamino)methyl)naphthalen-2-yl) methyl (4-(4-hydroxycarbonyl)phenyl) carbamate	Idiopathic MF, MPNs	IIa	Histone deacetylase inhibitor
Pomalidomide	Celgene	4-amino-2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione	MF and RBC transfusion dependence	III	Immunomodulator
Decitabine	Eisai	2'-deoxy-5-azacytidine	MF with myeloid metaplasia	II	DNA methyltransferase inhibitor
Zoledronic acid	Novartis	[1 -hydroxy-2-(1 H-imidazol-1 -yl)ethylidene]bisphosphonic acid	MF with myeloid metaplasia	II	Osteoclast inhibitor
GS-6624 (AB0024)	Gilead Sciences	Humanized monoclonal antibody	Bone marrow fibrosis	II	Anti-LOXL2 monoclonal antibody
Fresolimumab (GC-1008)	(Genzyme/Sanofi) -(originator: AstraZeneca)	Human monoclonal antibody	Bone marrow fibrosis	I	Anti-TGF-β monoclonal antibody
Peg-IFN-α2a	Roche	peg-IFN-α2a	Chronic MPNs	II	Immunomodulator

FLT3: Fms-like tyrosine kinase-3; JAK: Janus kinase 2; LOXL2: Lysyl oxidase-like protein 2; MF: Myelofibrosis; mTOR: Mammalian target of rapamycin; MPN: Myeloproliferative neoplasm; peg-IFN: Pegylated interferon; RBC: Red blood cell; TGF: Transforming growth factor.

Table 2

Ongoing trials of combination therapy with ruxolitinib.

Clinical trial	Phase	Sponsor/collaborator	Region	Subjects	Treatments	Primary outcome
NCT01375140	II	MDACC/Incyte	US	n = 62; PMF, post-PV, post-ET MF	Ruxolitinib 15 mg b.i.d. + lenalidomide 5 mg/day days 1–21, followed by 7 days no therapy ± prednisone	Objective response rate (over 3 cycles) as defined by IWG-MRT
NCT01369498	II	Gilead Sciences	US	n = 54; PMF, post-PV, post-ET MF	GS-6624 200 mg, 700 mg with or without ruxolitinib	Reduction in bone marrow fibrosis
NCT01644110	Ib/II	University of Ulm/Novartis	Germany	n = 72; Primary and secondary MF	Ruxolitinib 10 mg b.i.d. (starting dose) + pomalidomide 0.5 mg q.d.	Best response rate within 12 treatment cycles according to the IWG-MRT criteria and RBC transfusion independence
NCT01433445	Ib	Novartis	Europe	n = 45; PMF, post-PV, post-ET MF	Panobinostat + ruxolitinib	Percentage of patients with 50% reduction in palpable spleen length from BL to week 12 and maintained until week 24

b.i.d.: Twice daily; BL: Baseline; ET: Essential thrombocythemia; IWG-MRT: International Working Group/Myelofibrosis Research and Treatment; MDACC: MD Anderson Cancer Center; MF: Myelofibrosis; PMF: Primary myelofibrosis; PV: Polycythemia vera; q.d.: Once daily; RBC: Red blood cell

Table 3

Registered completed and ongoing Phase III and Phase IV studies in MF.

Clinical Trial	Phase	Sponsor	Region	Subjects	Treatment	Primary outcome
NCT00952289 COMFORT-1 (complete; reported)	III	Incyte	US	n = 309; intermediate-2 or high-risk MF; platelet count $100 \times 10^9/L$	Ruxolitinib 1.5 – 20 mg b.i.d. vs placebo	Proportion of patients with 35% reduction in spleen volume from BL to week 24
NCT00934544 COMFORT-II (complete; reported)	III	Novartis	Europe	n = 219; intermediate-2 or high-risk MF; platelet count $100 \times 10^9/L$	Ruxolitinib 1.5 – 20 mg b.i.d. vs best available therapy	Proportion of patients with 35% reduction in spleen volume from BL at week 48
NCT01437787 JAK ARTA (complete; not yet reported)	III	Sanofi	Global	n = 225; intermediate-2 or high-risk MF; platelet count $50 \times 10^9/L$	SAR302503 400 or 500 mg q.d. vs placebo	Proportion of patients with 35% reduction in spleen volume at the end of cycle 6 (28 days per cycle), and confirmed 4 weeks thereafter
NCT01178281 RESUME (complete; not yet reported)	III	Celgene	Global	n = 210; MF with transfusion dependence	Pomalidomide 0.5 mg q.d. vs placebo	Proportion of patients achieving RBC transfusion independence in 6 months
NCT01558739 UK-MACS2030 (accruing)	IV	Novartis	UK	n = 33; intermediate- or high-risk MF	Ruxolitinib 1.5 – 20 mg b.i.d.	50% reduction in palpable spleen length and/or 50% improvement in TSS at 48 weeks

b.i.d.: Twice daily; BL: Baseline; MF: Myelofibrosis; q.d.: Once daily; RBC: Red blood cell