

Ruxolitinib: The First FDA Approved Therapy for the Treatment of Myelofibrosis

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Abstract

The BCR-ABL1–negative myeloproliferative neoplasms (e.g., essential thrombocythemia, polycythemia vera, and primary myelofibrosis) are a group of heterogeneous hematologic malignancies that involve a clonal proliferation of hematopoietic stem cells. Thrombosis, bleeding, and transformation to acute leukemia reduce the overall survival of patients with myelofibrosis, a disease typified by progressive splenomegaly and disease-related symptoms such as fatigue, pruritus, and bony pains. Hematopoietic stem cell transplant offers the only potential for cure in a minority of eligible patients, leaving a serious unmet need for improved therapies. Recent advances in our understanding of the pathogenetic mechanisms underlying these diseases have led to an explosion of clinical trials evaluating novel therapies. The discovery of an activating mutation in the Janus-activated kinase 2 (JAK2) gene provided a therapeutic target to downregulate this activated signaling pathway, which influences the phenotype of these diseases. Ruxolitinib (Jakafi; Incyte) is a small-molecule inhibitor of JAK1/2 that has proved to be effective at reducing splenomegaly and ameliorating symptoms in myeloproliferative neoplasms. Based on the results of 2 pivotal randomized phase III clinical trials, ruxolitinib has become the first therapeutic to be approved by the U.S. Food and Drug Administration for treatment of patients with myelofibrosis. Ruxolitinib offers a well-tolerated oral therapeutic option for patients with myelofibrosis with symptomatic splenomegaly and debilitating disease-related symptoms, but it does not seem to be effective at eliminating the underlying hematological malignancy. *Clin Cancer Res*; 18(11); 3008–14. ©2012 AACR.

Introduction

The myeloproliferative neoplasms (MPN) are a group of clonal hematological malignancies that originate at the level of pluripotent hematopoietic stem cells (HSC) and include chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). PV and ET can both progress to myelofibrosis (termed post-ET/PV MF), which is clinically indistinguishable from PMF. Collectively, PMF and post- ET/PV MF are referred to simply as MF. CML is distinguished from the other MPNs by the requisite presence of the *BCR-ABL1* proto-oncogene, which is believed to be the disease-initiating event. BCR-ABL1 is a tyrosine kinase with constitutive activity that deregulates cell differentiation, division, and adhesion. Imatinib (Gleevec; Novartis) was the first tyrosine kinase inhibitor

to be developed for the treatment of CML, and revolutionized the treatment of this MPN.

The BCR-ABL1–negative MPNs are not characterized by a uniform recurrent cytogenetic or molecular abnormality, and thus it is difficult to identify targets for drug therapies. More than 12 mutations, as well as multiple epigenetic alterations, have been identified in MPNs. They occur with varying frequencies, and coexpression patterns reveal a complicated pathobiology that makes it unlikely that an agent targeting a single pathway will be successful in eliminating the malignant HSCs that are responsible for MF. Additional mutations in MF cells involving genes that encode a growing list of proteins (e.g., MPL, EZH2, ASXL1, IDH1/2, TET2, CBL, IKZF1, and p53) with varying frequency have been identified. The acquisition of some of these mutations may be associated with disease progression and/or transformation to leukemia (1).

Of the BCR-ABL1–negative MPNs, MF holds the worst prognosis and is characterized by a chronic yet progressive course, with a median age at diagnosis of 65 years. The malignancy occurs at the level of the HSCs, and the marrow fibrosis is believed to be largely a reactive process resulting from the effects of a number of cytokines elaborated by the cellular progeny of the malignant clone. The elaboration of fibrogenic cytokines such as platelet-derived growth factor

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doi: 10.1158/1078-0432.CCR-11-3145

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(PDGF), TGF- β , and basic fibroblast growth factor (bFGF) have been implicated in the pathobiology of marrow fibrosis in PMF, and may be due in part to pathologic interactions between neutrophils and megakaryocytes belonging to the malignant clonal (2, 3). Cytogenetic studies of fibroblasts from patients with PMF support the hypothesis that reactive fibrosis occurs in response to the underlying malignant process (4, 5). Clinical features include the presence of constitutional signs, progressive hepatosplenomegaly, gout, and cachexia, and laboratory findings include anemia, thrombocytopenia, leukopenia or leukocytosis, and a hypercellular bone marrow with dysplastic megakaryocytic hyperplasia and the eventual accumulation of marrow reticulin/collagen fibrosis. The systemic symptoms include fever, weight loss, pruritus, night sweats, and bone pain compromise the quality of life of patients with MF and have been attributed to the elaboration of a number of cytokines, chemokines, and proteases. Complications related to thrombosis, bleeding, and transformation to acute leukemia (10–20% during the first decade from diagnosis) contribute to an abbreviated lifespan in patients with MF. MF is associated with a median overall survival of 69 months, with a broad range depending on the degree of advancement of the disease (6). The International Prognostic Scoring System created by the International Working Group for Myelofibrosis Research and Treatment was developed to define the prognosis of patients with MF, with the hope of determining which therapeutic options are appropriate for individual patients (6). This prognostic scoring system is based on 5 independent clinical factors (age > 60, hemoglobin < 10 g/dL, peripheral blood blast count \geq 1%, presence of constitutional symptoms, and leukocyte count \geq $25 \times 10^9/L$), all of which have been determined to be predictive of a poor prognosis following multivariate analysis. Four distinct risk groups can be identified based on the presence of 0 (low risk), 1 (intermediate risk-1), 2 (intermediate risk-2), or \geq 3 (high risk) of these variables, with median survivals of 135, 95, 48, and 27 months, respectively ($P < 0.001$). Patients with low/intermediate-1 risk status are typically followed with a watch-and-wait approach, whereas patients with intermediate-2/high-risk status are treated with traditional agents or considered for entry into clinical trials or, if appropriate, HSC transplantation.

Current therapies that are used in the treatment of MF include immunomodulatory agents (IMiD; e.g., thalidomide and lenalidomide), erythropoietin-stimulating agents (e.g., erythropoietin and darbepoetin), androgens (e.g., danazol), chemotherapeutics (e.g., hydroxyurea, busulfan, melphalan, and 2-chlorodeoxyadenosine), and biologics (e.g., interferon- α). Additionally, radiation to sites of extramedullary hematopoiesis can sometimes offer palliation of symptoms, and splenectomy remains an option for patients with symptomatic splenomegaly or severe cytopenia that is either refractory or prevents medical management. None of these therapeutic options have been proved to modify MF or to definitively alter the natural course and history of this disease. Experimental therapeutic

options include pomalidomide (an IMiD), Janus-activated kinase 2 (JAK2) inhibitors, histone deacetylase inhibitors (HDACi), and heat shock protein 90 inhibitors (HSP90i). Stem cell transplantation remains the only therapeutic option that offers the potential for cure in MF patients, preferably younger patients with a good performance status and an available 10/10 human leukocyte antigens (HLA)-matched sibling donor.

In 2005, 4 independent laboratory groups reported the finding of an activating point mutation in the *JAK2* gene that can be observed in approximately 96%, 50%, and 50% of patients with PV, ET, and PMF, respectively (7–10). JAK2 is a member of a family of cytoplasmic tyrosine kinases that include JAK1, JAK3, and Tyk2, and function to transmit intracellular signals from cognate growth factor receptors to transcription complexes mediating the expression of genes that are responsible for diverse cellular functions such as differentiation, proliferation, and avoidance of apoptosis (11). JAK1 is known to mediate the effects of proinflammatory cytokines such as interleukin 2 (IL-2), IL-6, and TNF- α , thereby allowing a JAK1 inhibitor to reduce the effects of these cytokines in a variety of chronic inflammatory states, such as psoriasis, atopic dermatitis, and rheumatoid arthritis. JAK1/2 inhibitors may be considered pleiotropic in some respects. They are capable of reducing the signaling of pathogenic cytokines such as IL-6 and IL-23, and as a result can inhibit the production of an array of additional proinflammatory cytokines, chemokines, and adhesion molecules by other cell types, leading to interruption of the so-called cytokine cascade.

A number of tyrosine kinase inhibitors with varying anti-JAK2 potency and specificity, as well as different toxicity profiles, have been or are currently being evaluated in clinical trials. These include lestaurtinib (Cephalon), AZD1480 (AstraZeneca), BMS911543 (Bristol-Myers Squibb), CYT387 (YM Bioscience), and SAR302503 [Sanofi-Aventis (12)]. All of these agents were initially evaluated in patients with advanced MF because of the limited survival experienced by such patients, which was believed to justify their entry into clinical trials involving experimental therapeutics. Initially called INCB18424, ruxolitinib (Jakafi; Incyte), a potent JAK1/2 inhibitor, was the first drug of this class to enter clinical trials, and it is currently being evaluated in the setting of ET, PV, MF, and acute leukemia. On November 16, 2011, ruxolitinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of intermediate/high-risk MF based on the combined results of the Controlled Myelofibrosis Study with Oral JAK2 Inhibitor Treatment (COMFORT)-I and COMFORT-II trials.

Mechanism of Action

JAKs are associated with the intracellular domain of growth factor receptors [e.g., erythropoietin receptor, thrombopoietin receptor (MPL), and granulocyte-colony stimulating factor], and conformational changes within the receptor induced by ligand binding bring JAKs in close

physical approximation (13). This causes autophosphorylation of JAKs and induces a conformational change in the JAK protein and tyrosine phosphorylation of specific residues on the receptor that act as binding sites for STATs. The recruitment of STATs to the receptor then allow for activation by JAK-mediated phosphorylation and ultimately the dimerization and translocation of STATs to the nucleus, where they bind specific enhancer regions that promote the transcription of genes that mediate cell growth, differentiation, and apoptosis.

JAK2V617F, which occurs in exon 14 of *JAK2* located on chromosome 9p24, is the most commonly observed mutation in MPNs involving a G-to-A point mutation, resulting in substitution of valine for phenylalanine at amino acid position 617 (V617F) in the pseudokinase domain (JH2). This mutation turns off the autoinhibitory function of the pseudokinase domain, causing constitutive activation of the catalytic component (JH2) of the *JAK2* protein (14). Thus, dysregulated activity of *JAK2* appears to be the logical target for therapeutic intervention. In addition, because the hypercatabolic state and severe constitutional symptoms that often accompany disease progression in MF appear to be driven by the elevated proinflammatory cytokine state, inhibition of *JAK1* signaling was also thought to be of potential value. Furthermore, even in patients with MF lacking *JAK2V617F*, activation of the *JAK/STAT* pathways has been documented.

Ruxolitinib [(R)-3-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)-3-cyclopentylpropanenitrile phosphate] is a potent *JAK1* and *JAK2* inhibitor with an IC_{50} of 3.3 and 2.8 nM, respectively. Ruxolitinib exerts its anti-*JAK* activity by competitive inhibition of the ATP-binding catalytic site of the kinase domain. Inhibition of the *JAK-STAT* pathway results in decreased *STAT-3/5*, *Akt*, and *ERK* phosphorylation, as shown in correlative biomarker studies within clinical trials (15). Ruxolitinib is not specific for the mutated form of *JAK2*, and inhibits both the wild type and *JAK2V617F*.

Pharmacokinetics/Pharmacodynamics

The pharmacokinetics of ruxolitinib was evaluated in healthy volunteers in 2 double-blind, randomized, placebo-controlled studies (16). The drug showed good oral bioavailability independently of fasted or fed state, dose-proportional systemic exposure with a small volume of distribution, and an ~3-hour plasma half-life. Oral doses of 25 mg twice a day and 100 mg once a day were established as the maximum tolerated dose in healthy volunteers. Studies of metabolism and excretion in healthy volunteers showed that ruxolitinib was well absorbed at >95% and there was no accumulation of the parent compound or metabolites after single or multiple dosing (17).

For pharmacodynamic evaluations, investigators have relied on measuring the levels of downstream targets of *JAK* signaling and assessing the change in inflammatory markers in response to therapy. In the initial phase I/II

reported by Verstovsek and colleagues (15), maximal mean inhibition of *p-STAT-3* expression ranged from ~40% at the lowest dose tested to >90% inhibition at the highest dose tested, and returned to baseline levels by 24 hours. A dose- and time-dependent reduction of phosphorylated *STAT-3* was observed with ruxolitinib treatment and was reported in patients with *JAK2V617F* and wild-type *JAK2*. Elevated baseline levels of *IL-6*, *IL-1ra*, *IL-8*, *MIP-1 β* , *TNF- α* , and *CRP* were all dramatically reduced with ruxolitinib treatment in MF patients.

Preclinical Studies

Transfection of Ba/F3 cells with retrovirus containing *JAK2V617F* vectors showed constitutive activation of *STAT-5* and cytokine-independent growth of erythroid colony-forming units, and erythropoietin hypersensitivity that was not reproducible in vectors containing *JAK2* wild type (18).

Murine transplant models with grafts genetically modified to express *JAK2V617F* recapitulate the PV phenotype with leukocytosis and erythrocytosis, culminating in progressive splenomegaly and bone marrow fibrosis leading to premature death (18–20). Investigators have generated *JAK2V617F* transgenic mouse models expressing human *JAK2* to elucidate how levels of gene expression may affect disease phenotype and possibly account for the finding of mutated *JAK2* in patients with ET, PV, and PMF. When the ratio of mutant to wild-type *JAK2* is low, an ET phenotype is appreciated with isolated thrombocytosis in mice, whereas ratios that are equal in expression produce mice with a PV phenotype characterized by neutrophilia, erythrocytosis, and thrombocytosis. Marrow fibrosis occurs with varying frequency in such mice and is thought to be likely related to the elevated megakaryocyte mass observed in the bone marrow (21).

Exposure of *JAK2V617F*-positive Ba/F3 cells to ruxolitinib was shown to result in reduced cellular proliferation and induction of apoptosis that was accompanied by inhibition of *JAK2V617F*, *STAT5*, and *ERK1/2* phosphorylation (22). In a mouse model of *JAK2V617F*-positive MPN, the administration of oral ruxolitinib markedly reduced splenomegaly and circulating levels of proinflammatory cytokines, and preferentially eliminated neoplastic cells bearing mutated *JAK2*, resulting in significantly prolonged survival without significant myelosuppression (22). In primary cell cultures, ruxolitinib suppressed erythroid colony formation from *JAK2V617F*-positive PV patients with $IC_{50} = 67$ nM versus healthy controls with $IC_{50} > 400$ nM.

However, in another murine model of MPN (MPLW/515L-induced thrombocytosis and myelofibrosis), treatment with a small-molecule selective *JAK2* inhibitor (INCB16562) normalized the leukocyte and platelet counts, and reduced splenomegaly and marrow fibrosis, but did not result in a decrease in the size of the malignant clone in the bone marrow of treated mice (23). These findings provide a hint that *JAK2* inhibitor therapy alone may not be curative.

Clinical Studies

Initial phase I/II study

A phase I/II study of ruxolitinib was conducted by Verstovsek and colleagues (15) in JAK2V617F-positive and -negative MF patients at ascending doses starting at oral doses with a twice-daily schedule of 10 mg, 15 mg, 20 mg, 25 mg, and 50 mg, and once-daily dosing at 25 mg, 50 mg, 100 mg, and 200 mg. Ruxolitinib at 25 mg twice a day or 100 mg once a day was established as the maximum tolerated dose based on the dose-limiting toxicity of reversible thrombocytopenia.

At 15 mg twice a day, ruxolitinib treatment was associated with sustained reductions of splenomegaly, resolution of constitutional symptoms, improvement in exercise tolerance and performance status, and meaningful weight gain. Durable improvements in symptoms and splenomegaly were seen in both JAK2-mutated and wild-type patients, and 52% of treated patients had a rapid objective response in splenomegaly of >50% reduction for ≥ 12 months. The dramatic responses seen in splenomegaly were not accompanied by tumor lysis syndrome or compromised hematopoiesis. Marked depression in the heightened expression of proinflammatory cytokines (IL-6, IL-1ra, MIP-1 β , TNF- α , and CRP) were seen with ruxolitinib treatment and correlated with improvement in night sweats, fevers, fatigue, weight loss, and pruritus. After 12 cycles of therapy, there was a mean maximal suppression of JAK2V617F allele burden by a modest 13% with ruxolitinib treatment.

Although the follow-up was limited to 2 years and the study did not include a comparator arm, there was a trend to improvement in survival and a suggestion of a reduction in rate of transformation to acute leukemia in comparison with historical controls (24). In multivariate analysis, treatment with ruxolitinib was found to be a significant independent variable for improved survival. It is important to consider that this comparison is colored by the use of a historical control group that had more high-risk patients, lower hemoglobins at baseline, and an older median age. Also, patients with platelet counts $< 100 \times 10^9/L$ were not allowed to enter any of these trials. This is of great practical importance because thrombocytopenia is frequently predictive of a poor prognosis and thus would limit the amount of drug that could be administered and influence the tolerability of the drug.

The other potential limitation of ruxolitinib is the possible rapid return of splenomegaly following discontinuation of the drug and the occasional occurrence of life threatening syndromes attributed to the rapid re-elevation of inflammatory cytokines. This "ruxolitinib withdrawal syndrome" has been described in 5 of the 47 MF patients treated at Mayo Clinic that had rapid discontinuation and the authors advise tapering the drug when possible (25).

COMFORT-I. COMFORT-I was a randomized (1:1), double-blind, phase III study sponsored by Incyte that

compared ruxolitinib with placebo in patients with intermediate-2 or high-risk MF and a baseline platelet count of at least $100 \times 10^9/L$ (26). Oral ruxolitinib was dosed at 15 mg twice a day for patients with platelet counts between 100 and $200 \times 10^9/L$, and 20 mg twice a day for patients with counts $> 200 \times 10^9/L$. A total of 309 patients were randomized (ruxolitinib: $N = 155$; placebo: $N = 154$; median age: 68 years). The primary endpoint of this study was a reduction in spleen volume of at least 35% by MRI or computed tomography. The 35% reduction in spleen volume was chosen based on previous studies that established a correlation of 35% reduction in volume by imaging to $\sim 50\%$ reduction by manual palpation on physical exam. Secondary endpoints included assessment of duration of spleen reduction and improvement in disease-related symptoms according to the Myelofibrosis Symptom Assessment Form (27). Patients were allowed to cross over from placebo if they had a $>25\%$ increase in spleen volume by imaging from baseline, and all patients were unblinded and could cross over when every patient had completed week 24 or discontinued the treatment and 50% of remaining patients had completed week 36.

Grade 3/4 anemia was the most frequent hematologic adverse event and was observed in 45% and 19.2% of patients in the ruxolitinib and placebo arms, respectively. Grade 3/4 thrombocytopenia was observed in 12.9% and 1.3% of patients in the ruxolitinib and placebo arms, respectively. Grade 3/4 neutropenia was observed in 7.1% and 2% of patients in the ruxolitinib and placebo arms, respectively. The most common non-hematologic adverse event seen with any grade in the ruxolitinib-treated group was diarrhea (23.2%, compared with 21.2% in the placebo group). All in all, this was a well-tolerated drug.

At 24 weeks, 41.9% of patients treated with ruxolitinib experienced a $\geq 35\%$ reduction in spleen volume, compared with 0.7% of patients who received the placebo ($P < 0.0001$). Regardless of their JAK2 mutational status, 45.9% of the ruxolitinib-treated patients experienced a $\geq 50\%$ improvement in constitutional symptoms, as compared with 0.7% in the placebo group.

An analysis of survival on extended ruxolitinib therapy with a mean follow-up of 52 weeks showed a statistically significant reduction in death with a hazard ratio of 0.499 (0.254, 0.98) and a probability of survival compared with placebo of 0.98 versus 0.90 and 0.84 versus 0.77 in patients with a baseline hemoglobin > 10 g/dL and < 10 g/dL, respectively (28). In a further subset analysis, patient age of ≤ 65 years appeared to have a survival benefit over >65 years of age with a hazard ratio of 0.22 (0.06, 0.84) with ruxolitinib therapy.

The drug therapy was uniformly ineffective at reversing histopathological abnormalities in the peripheral blood or marrow, eliminating marker cytogenetic abnormalities, or reducing the JAK2V617F allele burden

to a degree associated with tyrosine kinase inhibitor therapy of BCR/ABL1 for chronic myeloid leukemia.

COMFORT-II. COMFORT-II was a randomized (2:1), Novartis-sponsored, open-label, phase III clinical trial that was conducted in nine European countries and compared ruxolitinib with the best available therapy [BAT (29)]. Hydroxyurea (46.6%), steroids (16.4%), and supportive therapy (32.9%) comprised the BAT arm. A total of 219 patients with intermediate-2 or high-risk MF were randomized (ruxolitinib: $N = 146$; BAT: $N = 73$; median age: 66 years).

The primary endpoint was met at 48 weeks, when 28.5% of patients treated with ruxolitinib achieved a $\geq 35\%$ reduction in spleen volume, compared with 0% of patients in the BAT arm ($P < 0.0001$). The secondary endpoint of spleen reduction at 24 weeks was 31.9% and 0% in the ruxolitinib and BAT arms, respectively.

As was seen in the COMFORT-I study, hematologic toxicity of all grades was frequent with ruxolitinib (44.5% thrombocytopenia and 40.4% anemia), and was grade 3/4 thrombocytopenia (7.5% vs. 4.1%) and anemia (11% vs. 4.1%) in the ruxolitinib and BAT arms, respectively. The most frequent nonhematologic adverse event was diarrhea of all grades, which was seen in 23% of ruxolitinib-treated patients, and grade 3/4 was observed in 1%.

There was no statistically significant difference between the 2 treatment arms in terms of progression-free survival, leukemia-free survival, and overall survival.

Phase II study in acute myeloid leukemia

Ruxolitinib was also explored in the setting of *de novo* acute myeloid leukemia (AML) and MPN in blast phase (MPN-BP) in an exploratory phase II study from MD Anderson (30). Thirty-eight patients with relapsed/refractory AML, 7 of whom had JAK2V617F-positive MPN-BP, received oral ruxolitinib at 25 mg twice a day with permitted dose escalation to 50 mg twice a day. At a median of 2 cycles (4 weeks) of therapy (range of 1–18 cycles), 2 of the patients with MPN-BP showed improvement in splenomegaly symptoms and obtained complete morphologic response in the marrow. Grade 3 transaminitis, neutropenia, thrombocytopenia, and an episode of fatal intracranial hemorrhage were noted. The results collectively appear to show a modest effect of ruxolitinib in MPN-related acute leukemia when compared with *de novo* AML. The mature results of this study have not yet been published.

Current and future studies

Currently ongoing studies in patients with MF include ruxolitinib in a sustained release formulation, alternate dosing schedules, and evaluation of drug tolerability in patients with baseline platelet counts between 50 and $99 \times 10^9/L$. The RESPONSE trial is a phase III study of ruxolitinib in the treatment of advanced PV with a composite primary endpoint of phlebotomy independence and spleen volume reduction at 32 weeks. Future

directions in clinical trial design include the use of ruxolitinib in combination with IMiDs, erythropoiesis-stimulating agents, androgens (e.g., danazol), chromatin-modifying agents (e.g., HDACi and DNA methyltransferase inhibitors), and JAK2 inhibition prior to HSCT in patients with MF.

Non-MPN studies

Ruxolitinib is also being evaluated outside of MPNs, and studies are ongoing or have been completed in relapsed/refractory solid tumors, androgen-independent metastatic prostate cancer, pancreatic cancer, and multiple myeloma and lymphoma. Studies in nonmalignant conditions such as psoriasis and rheumatoid arthritis have a scientific rationale and appear promising.

Conclusions

Just 6 years after the discovery of the JAK2 mutation, with an evolving understanding of the pathobiology of MPNs, investigators are aggressively evaluating a new class of tyrosine kinase inhibitors that abrogate the overactivity of the JAK-STAT pathway in clinical trials. These agents have shown the ability to downregulate proinflammatory cytokines and downstream mediators of JAK signaling, which provides biomarker evidence for their mechanism of action in improving debilitating constitutional and hypercatabolic symptoms and reducing splenomegaly in patients with MPNs (see Fig. 1). Ruxolitinib leads this class of agents and is currently the only FDA-approved drug for the treatment of intermediate- and high-risk MF. The addition of ruxolitinib to the hematologist's armamentarium will surely alter the treatment approach for many patients with MF and influence the accrual of patients to current and future clinical trials. Anti-JAK therapy and ruxolitinib in particular represent important advances in the treatment of MF and should be considered in patients who are symptomatic without limiting cytopenias. Currently, we do not have sufficient evidence to indicate that ruxolitinib has the ability to correct pathologic features in the bone marrow, induce cytogenetic/molecular remissions, modify the natural history and progression of disease, or significantly alter survival in MF. However, the palliative effects of ruxolitinib are an important accomplishment and are being enjoyed by patients and physicians. Future studies will definitively establish the role of this drug in patients with PV, ET, and AML, either alone or in combination with other novel agents.

Disclosure of Potential Conflicts of Interest

John Mascarenhas is a consultant to and serves on the advisory board of Incyte. No other potential conflicts of interest were disclosed.

Grant Support

National Institutes of Health (P01 CA108671 to R. Hoffman).

Received February 17, 2012; revised March 15, 2012; accepted March 18, 2012; published OnlineFirst April 2, 2012.

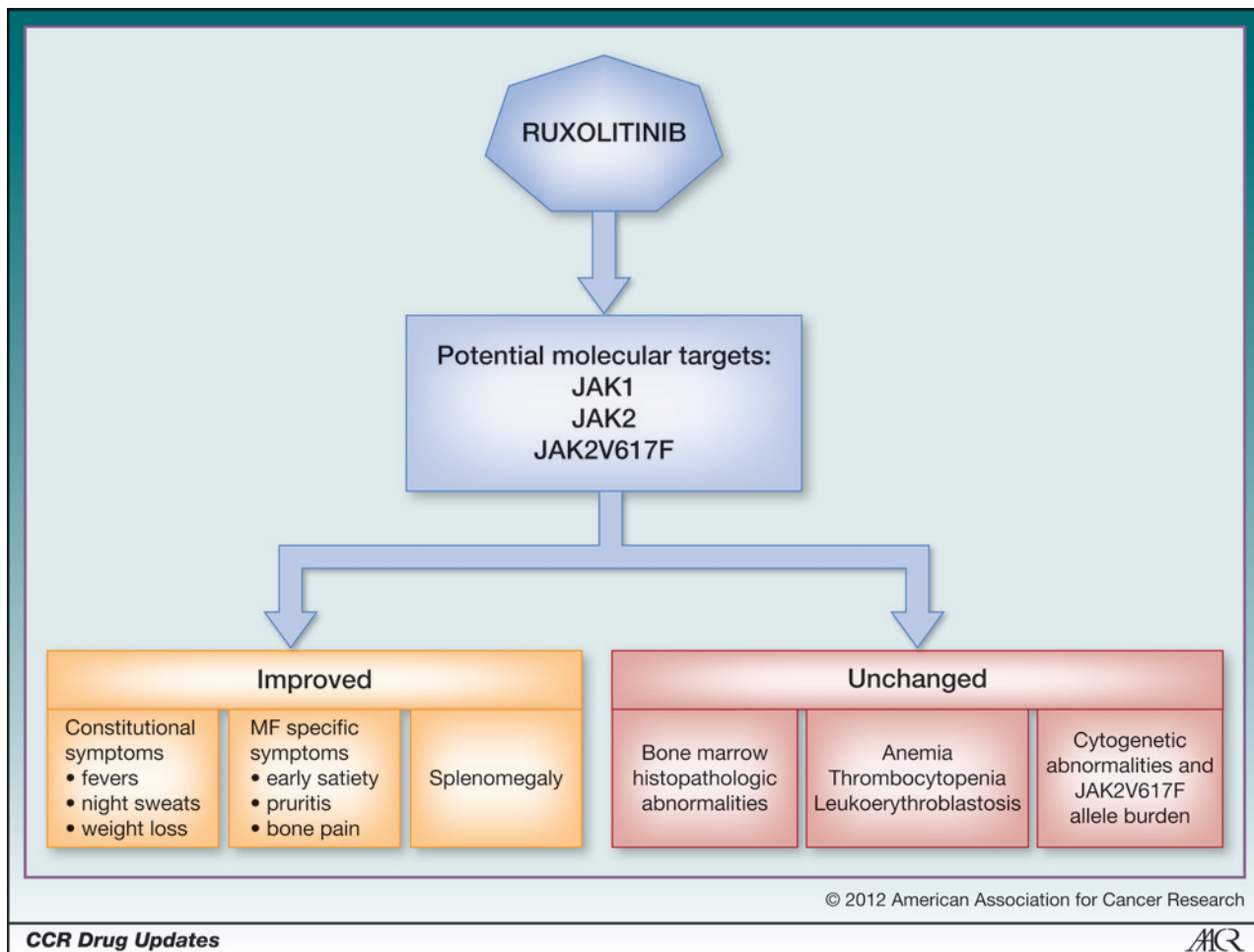


Figure 1. The constitutive activity of the JAK-STAT signaling pathway, present within the hematopoietic stem cells of patients with myelofibrosis, is irrespective of JAK2 mutational status and was thought to underlie the many pathologic, hematologic, and clinical features of this disease. Interruption of this pathway with ruxolitinib, a potent JAK1/2 small molecular tyrosine kinase inhibitor, abrogates JAK1 and JAK2 signaling, resulting in downregulation of STAT3/5 phosphorylation as well as other downstream mediators of transcription. The well documented improvements in splenomegaly, constitutional symptoms, and other MF-related symptoms in the COMFORT-1 and -2 studies with ruxolitinib treatment appear to be mediated by its anti-JAK activity. However, meaningful changes in bone marrow histopathology or marrow fibrosis, improvement in anemia and thrombocytopenia, and elimination of cytogenetic or molecular abnormalities or substantial reduction in JAK2V617F allele burden have not been seen.

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