Ruxolitinib as an emerging treatment in myelofibrosis

Robyn M Emanuel1
Holly L Geyer1
Ruben A Mesa2

1Department of Internal Medicine, 2Department of Hematology and Oncology, Mayo Clinic, Scottsdale, AZ, USA

Abstract: Essential thrombocythemia, polycythemia vera, and myelofibrosis belong to the class of Bcr-Abl negative hematologic neoplasms, which arise in part from varying Janus kinase-2 (JAK2) cellular deregulation. With the development of novel tyrosine kinase inhibitors capable of successfully inhibiting JAK in vivo, an influx of JAK2 inhibitors has come under clinical investigation. Ruxolitinib (Jakafi®; Incyte Corporation, Wilmington, DE, USA) was the first of these compounds to gain US Food and Drug Administration approval in late 2011 for the treatment of intermediate- and high-risk myelofibrosis. Two Phase III clinical trials – Controlled Myelofibrosis Study with Oral JAK Inhibitor Treatment-I and -II (COMFORT-I and -II) – played key roles in the US Food and Drug Administration approval of ruxolitinib with successful demonstration of spleen reduction and symptom palliation. Well tolerated in most patients, common side effects include cytopenias and gastrointestinal toxicities. The majority of preliminary data appears to suggest that if administered in a dose-titrated fashion, ruxolitinib can be used safely in a clinical practice setting. Additionally, patients most likely to benefit from ruxolitinib treatment are those with moderate to severe constitutional symptoms or splenomegaly. Future studies are ongoing in applying ruxolitinib to other hematologic and solid tumor malignancies. More clinical experience is recommended before the utility of this medication in a routine clinical practice setting can be fully determined.

Keywords: myeloproliferative neoplasms, myelofibrosis, ruxolitinib, JAK2 inhibitors, INCB018424

Introduction
First designated as a disease class in 1951 by Sir William Dameshek, the classical Bcr-Abl negative myeloproliferative neoplasms (MPNs) include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). MF can arise as a primary event (primary MF [PMF]), or can arise from antecedent PV (post-PV MF) or ET (post-ET MF). Arising individually from genetic and epigenetic changes to the DNA structures of the hematopoietic cell, each MPN subtype is associated with a variable presentation, disease course, and prognosis. The nuances to each disease subtype’s diagnosis, prognosis, and optimal treatment have only recently been brought to light with the discovery of the Janus kinase-2 (JAK2) mutation, JAK2V617F, in 2004 and the subsequent publication of this finding in 2005. This revolutionary discovery became the first clue to the specific disease mechanism and concomitantly aided in the development of effective molecular targets. In this new age of gene-targeted therapies, JAK2 inhibitors have displayed particular effectiveness in decreasing splenomegaly and resolving constitutional symptoms with minimal...
myelosuppression and drug-related toxicities. Moreover, recent data suggests that certain JAK2 inhibitors may even offer a therapeutic survival advantage. Ruxolitinib (Jakafi®; Incyte Corporation, Wilmington, DE, USA) was the first of these unique therapies to receive US Food and Drug Administration approval in November 2011. This review will discuss the disease pathophysiology, molecular genetics, benefits, toxicities, and ongoing applications of this innovative therapy.

Mutation of JAK2V617F is present within 55% of ET patients, 96% of PV, and 65% of PMF patients. These MPNs have been found to occur at an incidence of approximately six per 100,000 individuals and are commonly diagnosed beyond the fifth decade of life. MPN life expectancy varies by subtype. Studies of over 2000 patients with PV and ET indicate that ET has a life expectancy similar to age-matched controls. PV patients have an expectancy of approximately 19 years. For patients with PV or ET, progression into post-ET or post-PV MF and later transformation to acute leukemia occurred at a rate of approximately 0.7% and 2.5% over a period of 10 years, respectively. MF carries the worst prognosis among the Bcr-Abl negative MPNs, with a life expectancy of only 4–7 years and a mean age at diagnosis of 65 years. For patients with MF, primary or secondary transformation into acute myeloid leukemia is common, occurring at a rate of approximately 9% over a period of 5 years for patients with PMF.

### MPN prognostic scoring

Due to challenges with estimating prognosis in PMF, three main prognostic scoring systems are available (Table 1). PMF prognosis can be scored at the time of diagnosis using the International Working Group Prognostic Scoring System (IPSS). IPSS scoring utilizes the factors of age (≥65 years), blasts present in peripheral blood (≥1%), hemoglobin (<10 g/dL), leukocyte count (>25 × 10⁹/L), and the presence of constitutional symptoms (including weight loss > 10%, night sweats, or fevers). The Dynamic International Prognostic Scoring System can be used at any time to estimate prognosis at any time in the disease. Although the same five items are utilized as the IPSS score, this revised scoring system assigns anemia with two points due to an increased hazard ratio observed with anemia. Patients in this scoring system are separated into low-, intermediate-1-, intermediate-2-, and high-risk categories with survival estimates of 135, 95, 48, and 27 months (P < 0.001), respectively. A final scoring system, called Dynamic International Prognostic Scoring System Plus, incorporates mutational status, platelets, and transfusion requirements to further assess the likelihood of leukemia-free survival.

<table>
<thead>
<tr>
<th>Timeframe/assessment</th>
<th>IPSS9</th>
<th>DIPSS10</th>
<th>DIPSS plus11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis/survival</td>
<td></td>
<td>Any time point after diagnosis/survival</td>
<td>Any time point after diagnosis/survival leukemia-free survival</td>
</tr>
<tr>
<td>Age</td>
<td>≥65 years (2 points)</td>
<td>≥65 years (1 point)</td>
<td>–</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>&gt;25 × 10⁹/L (1 point)</td>
<td>&gt;25 × 10⁹/L (1 point)</td>
<td>–</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>&lt;10 (1 point)</td>
<td>&lt;10 (2 points)</td>
<td>–</td>
</tr>
<tr>
<td>Constitutional symptoms*</td>
<td>Present (1 point) versus absent</td>
<td>Present (1 point)</td>
<td>–</td>
</tr>
<tr>
<td>Blasts</td>
<td>≥1% (1 point)</td>
<td>≥1% (1 point)</td>
<td>–</td>
</tr>
<tr>
<td>DIPSS score</td>
<td>Low: 0 points</td>
<td>1 point</td>
<td>2 points</td>
</tr>
<tr>
<td></td>
<td>Intermediate-1: 1 point</td>
<td>2 points</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intermediate-2: 3 points</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High: Yes (1 point)</td>
<td>Yes (1 point)</td>
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</tr>
<tr>
<td>Mutational status</td>
<td>Yes (1 point)</td>
<td>Yes (1 point)</td>
<td></td>
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<tr>
<td>Platelets</td>
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<td>Yes (1 point)</td>
<td></td>
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<tr>
<td>Transfusion dependent</td>
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<td>Risk group cutoffs (points)</td>
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<tr>
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<td>Intermediate-1: 1</td>
<td>1–2</td>
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<tr>
<td></td>
<td>Intermediate-2: 2</td>
<td>3–4</td>
<td>2–3</td>
</tr>
<tr>
<td></td>
<td>High: ≥3</td>
<td>5–6</td>
<td>4–6</td>
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</tbody>
</table>

*Constitutional symptoms being scored positively if patient had weight loss > 10% in previous 6 months, night sweats, or fevers.

**Abbreviation:** DIPSS, Dynamic International Prognostic Scoring System.
MPN therapies
Preceding the discovery of JAK2 inhibitors, MPN treatment was limited to targeting disease symptoms and included cytoreductive therapy (hydroxyurea, anagrelide, and phlebotomies), immunomodulatory therapy (thalidomide and lenalidomide), antiplatelet agents (aspirin), androgens (danazol), and steroids. For individuals with medication-refractory splenomegaly and severe anemia, thrombocytopenia, and constitutional symptoms, splenectomy was considered a final option due to its significant surgical morbidity (31%) and mortality (9%). Stem cell transplantation remains the only potentially curative therapy but is available to a limited population of MPN patients with aggressive disease.

Cellular mutations in MF
The JAK2V617F mutation is a gain-of-function tyrosine kinase mutation which promotes hematopoietic cell growth and signaling. It is mutated in the majority of MF patients and subsequently represents an attractive target for therapies. The mutation ultimately results in constitutive activation of the kinase domain of JAK1/2 resulting in downstream signal transducer and activator of transcription (STAT) signaling and gene expression that enhances angiogenesis (vascular endothelial growth factor), resists apoptosis (BCL2L1, BIRC5, MCL1), and stimulates cellular growth and regeneration (CCND1). The JAK2 pathway has been shown to be critical in the maturation pathways of both erythropoiesis and thrombopoiesis. Uniquely, low JAK2 allele burden is associated with poor survival in MF patients, suggesting that the JAK2V617F mutation is not disease initiating but instead represents the complex genotypic aberrancies inherent to the condition. Discovery of the JAK2 mutation, JAK2V617F, propelled forward an influx of small-molecule inhibitors specifically targeting the kinase activity. Additional mutations found in MF patients include MPL, EXH2, ASXL1, IDH1/2, TET2, CBL, IKZF1, and p53.

Pharmacokinetics and pharmacodynamics
3-(4-[[7H-pyrrolo[2,3-d]pyrimidin-4-yl]-1H-pyrazol-1-yl]-3-cyclopentylpropanenitrile, later named INCBO18424 or ruxolitinib, is a potent orally administered JAK1, JAK2, and JAK3 inhibitor with additional efficacy against the JAK2V617F mutation. Results of the metabolism and excretion of ruxolitinib were published by Shi et al. Radiolabeled orally administered doses of the drug displayed rapid uptake, metabolism, and 95% absorption. Time to reach the maximal systemic concentrations was <1 hour. The majority of radioactivity was recovered in the form of the parent compound, indicating that the metabolism of ruxolitinib at therapeutic levels of treatment is minimal. The most prevalent metabolite of the compound was 2-hydroxycyclopentyl INCBO18424, present in a 16.5% abundance compared to the unmetabolized compound during day one. Approximately three-quarters of the drug was renally excreted, whereas the rest was removed via fecal elimination.

In 2011, a second study evaluating ruxolitinib metabolism was published by Shi et al, which evaluated the pharmacodynamics and pharmacokinetics among two healthy volunteers. Doses of 5–200 mg/day were evaluated in both once and twice daily administrations. Maximum tolerated doses were determined to be 25 mg twice daily or 100 mg once daily. Oral availability was excellent despite varying food administration. Plasma half-life was found to be approximately 180 minutes, with elimination of the drug being mainly by liver metabolism with minimal kidney filtration. Additionally, molecular testing was able to indicate higher levels of dephosphorylated STAT3 which correlated with higher levels of ruxolitinib concentration in the blood.

Ruxolitinib is metabolized via the cytochrome P450 3A4 (CYP3A4) pathway, thereby lending itself to many potential drug interactions. In a study conducted by Shi et al, ruxolitinib plasma concentrations were found to increase by 91% and 27% when exposed to ketoconazole (strong CYP3A4 inhibitor) and erythromycin (weak CYP3A4 inhibitor), respectively. Additionally, pretreatment with a CYP3A4 inducer – rifampin – decreased plasma concentrations by 71% but only decreased overall pharmacodynamics activity by 10% due to the prevalence of active metabolites. Subsequently, it is recommended that ruxolitinib doses be reduced by half in the setting of strong CYP3A4 inhibitors, with no dose adjustments needed for weak CYP3A4 inhibitors or inducers.

Initial landmark studies
In November 2010, a landmark Phase I/II joint study by The University of Texas MD Anderson Cancer Center (Houston, TX, USA) and Mayo Clinic (Scottsdale, AZ, USA) demonstrated ruxolitinib’s safety and effectiveness among a trial of 153 MF patients. Patients were started on 25 mg twice daily or 25 mg once daily with dose titration ≤ 50 mg twice
daily or 200 mg once daily. Thrombocytopenia was determined to be the dose-limiting side effect with the maximum tolerated administration being 25 mg twice daily or 100 mg once daily. The majority of participants achieved the primary endpoint of the study, which was ≥25% reduction in spleen length. The effects on spleen size were durable after a mean follow-up of 2 years.25

**Phase III clinical trials**

**Controlled MF Study with Oral JAK Inhibitor Treatment-I (COMFORT-I)**

COMFORT-I represents the first Phase III trial of ruxolitinib funded by Incyte Corporation (N = 309; Table 2). Conducted among IPSS score intermediate-2- or high-risk MF patients including PMF, post-ET MF, and post-PV MF, the COMFORT-I trial randomized patients in a 1:1 ratio to receive ruxolitinib (n = 155) or placebo (n = 154), with a primary endpoint of >35% reduction in spleen volume as assessed by magnetic resonance imaging at 24 weeks.26 Secondary endpoints included reduction in symptoms, sustainable drug response, and all-cause mortality. Ruxolitinib-treated patients were administered starting doses of 15 mg twice daily or 20 mg twice daily depending on platelet count. The dose was titrated based on side effects or lack of response. Results of the study indicated that ruxolitinib was successful in reducing spleen size in 41.9% of patients as compared with 0.7% in the placebo group at the end of 24 weeks (P < 0.001). This effect was durable, with 67% of patients sustaining a spleen response for ≥48 weeks. Symptom burden, as assessed by the MPN Symptom Assessment Form Total Symptom Score indicated that 45.3% of patients had a reduction in total score. Reductions in JAK2 allele burden were seen in 10.9% and 21.5% of the ruxolitinib-treated patients at weeks 24 and 48, respectively.

Overall rates of adverse events were similar between both ruxolitinib- and placebo-treated groups (11% of patients receiving ruxolitinib versus 10.6% of patients receiving placebo). For ruxolitinib-treated patients, grade I/II events included bruising, dizziness, and headaches. Grade III/IV effects included anemia and thrombocytopenia. These hematologic adverse events were noted to occur at a greater frequency in the ruxolitinib-treated group than among placebo-treated patients (thrombocytopenia: 12.9% ruxolitinib versus 1.3% placebo; anemia: 45.2% ruxolitinib versus 19.2% placebo). Overall, study authors noted a significant survival advantage among patients who received ruxolitinib during a 4-month post study follow-up (13 deaths ruxolitinib versus 24 deaths placebo; P = 0.04).

**COMFORT-II**

COMFORT-II was an open-label investigation sponsored by Novartis AG (Basel, Switzerland) comparing ruxolitinib to best available therapy in patients with IPSS intermediate-2- or high-risk PMF, post-PV MF, and post-ET MF (N = 219).27 Patients were randomized in a 1:2 ratio to either receive best available therapy as determined by the investigators (n = 73) or to receive 15–20 mg twice per day ruxolitinib (n = 146). Similar to COMFORT-I, the primary endpoint was reduction in spleen volume (>35% reduction in volume based on magnetic resonance imaging or computed tomography) assessed at 48 weeks post baseline. In addition to including overall survival similar to COMFORT-I, secondary endpoints were expanded to include leukemia-free and progression-free survival and change in bone marrow morphology. Patients were intended to undergo 48 weeks of treatment, but 25% of best available therapy-treated patients

### Table 2 Comparison of Phase III Controlled Myelofibrosis Study with Oral Janus Kinase Inhibitor Treatment (COMFORT) studies

<table>
<thead>
<tr>
<th>Study design</th>
<th>COMFORT-I26</th>
<th>COMFORT-II27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomization</td>
<td>1:1 (155 ruxolitinib: 154 placebo)</td>
<td>2:1 (146 ruxolitinib: 73 best available therapy)</td>
</tr>
<tr>
<td>Ruxolitinib dose</td>
<td>15–20 mg bid</td>
<td>15–20 mg bid</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td>&gt;35% reduction in spleen based on MRI at 24 weeks</td>
<td>&gt;35% reduction in spleen volume (based on MRI or CT) at 48 weeks</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td>• Duration of spleen reduction &gt; 35%</td>
<td>• Overall survival including</td>
</tr>
<tr>
<td></td>
<td>• Proportion of subjects with &gt;50% reduction in MPN-SAF TSS at week 24</td>
<td>– Progression-free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>– Leukemia-free survival</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• &gt;35% reduction in spleen volume at week 24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Duration of spleen reduction &gt; 35%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Change in bone marrow histomorphology</td>
</tr>
</tbody>
</table>

**Abbreviations:** CT, computed tomography; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; MRI, magnetic resonance imaging.
switched to ruxolitinib due to disease progression during this time. In patients treated with best available therapy, 67% received at least one medication – the most frequent being hydroxyurea (47%) and steroids (16%). Symptoms and quality of life were assessed via the European Organization for Research and Treatment of Cancer quality of life questionnaire core model (QLQ-C30) and the Functional Assessment of Cancer Therapy – Lymphoma scales.

Using intention-to-treat analysis, 28.1% of patients reached the primary endpoint goal of a spleen volume reduction ≥35% (compared to 0% of best available therapy patients; \( P < 0.001 \)). Median time to spleen response was 12.3 weeks. At week 48, 30% of ruxolitinib-treated patients had experienced progression versus 26% of patients receiving best available therapy. Six patients treated with ruxolitinib progressed to leukemia or died compared to four patients receiving best available therapy. Analysis of symptoms revealed that ruxolitinib treatment resulted in marked reductions in symptom burden as assessed by both the Functional Assessment of Cancer Therapy – Lymphoma and QLQC30 scales, whereas best available therapy worsened or did not alter symptom burden. Ruxolitinib also appeared to be safe, with the greatest nonhematologic adverse events being diarrhea (23%) and abdominal pain (3%). Similar to COMFORT-I, the most serious adverse hematologic events were anemia and thrombocytopenia, which rarely required ruxolitinib discontinuation and were managed by dose titration or transfusions. At the conclusion of the randomization period, 53% of patients receiving ruxolitinib electively chose to continue ruxolitinib due to its clinical benefit.

**Symptom burden relief**

It is estimated that ruxolitinib may be useful in reducing symptom burden among 30% of MF patients. \(^{30} \) In Phase III clinical trials, symptom palliation experienced during ruxolitinib therapy was found to be profound and durable. \(^{31} \) In-depth analysis of COMFORT-I data by Verstovsek et al found that the MPN Symptom Assessment Form Total Symptom Score, a ten-item measure assessing the most representative and pertinent of symptoms among MPN patients, indicated consistent improvement in symptom burden regardless of JAK2 mutational status, age (>65 years or <65 years), palpable spleen length, baseline hemoglobin (>10 g/dL or <10 g/dL), or IPSS prognostic group status. \(^{32} \) Importantly, 46% of these patients experienced a ≥50% improvement in symptoms, \(^{33} \) compared with only 5.3% of individuals in the placebo group (\( P < 0.001 \)). Similar findings were found by Harrison et al in an updated analysis of quality of life outcomes from COMFORT-II. \(^{34} \) In this study, patients receiving ruxolitinib had persistently improved symptom status assessed by the QLC-C30 and global health status/health-related quality of life as compared to patients receiving best available alternative therapy at weeks eight and 48. It has been hypothesized that the majority of these effects stem mainly from its anticytokine effects (eg, suppression of interleukin-6 and tumor necrosis factor-\( \alpha \)) and, to a lesser extent, nonspecific immunosuppression. \(^{35} \)

**Spleen size reduction**

Splenomegaly stemming from extramedullary hematopoiesis among MF patients is associated with symptoms of early satiety, abdominal discomfort, and pain. \(^{36} \) Palliation of massive splenomegaly, traditionally only achievable by means of hydroxyurea, alkylating agents, immunomodulatory drugs, chemotherapy, or splenectomy, may be beneficial for alleviating symptoms. However, no clear improvement exists in overall survival, disease progression, or anemia. \(^{37} \)

In 2008, Verstovsek et al published results that indicated that administration of ruxolitinib resulted in a rapid decrease in spleen size in >93% of MF patients with a mean prestudy spleen size of >20 cm (including post-ET, post-PV, and PMF patients). \(^{38} \) The decrease in spleen size appeared to be dose dependent, with a reduction of spleen size of ≥50% in 35% of patients dosed with 10 mg twice daily or 50 mg once daily compared to 59% of patients dosed with 25 mg twice daily. One year later, updated data released by Verstovsek et al (\( N = 309 \)) demonstrated that sustainable reductions in spleen volumes were achieved among patients achieving ruxolitinib compared to placebo even after controlling for PMF versus secondary MF, age, risk stratification, presence of JAK2\( ^{V617F} \) mutational status, anemia status, symptom burden, or spleen size. \(^{32} \)

**Side effects**

Given the critical role of JAK–STAT signaling on erythroid and thrombopoietic production, inhibition of JAK2 secondarily lends itself to key side effects of anemia and thrombocytopenia. This effect was well observed in both COMFORT-I and -II with dose-limiting toxicities being thrombocytopenia. Notably, cytopenias appear to be reversible and dose dependent. \(^{35} \) Overall, it appeared that patients started on lower starting doses of ruxolitinib required fewer transfusions (41% among patients receiving 15 mg twice daily compared to 58% among patients receiving 20 mg
twice daily). Upon drug discontinuation, a gradual return of reflexive symptoms may occur. Generally, these concerning side effects have been successfully managed with dose reduction and tapering.

**Future directions**

Applications for ruxolitinib have not been limited to MF. JAK2 mutation and abnormal cytokine expression also play an important role in the pathogenesis of ET, PV, solid tumor malignancies, and immunologic diseases including psoriasis. In patients with hydroxyurea-intolerant or refractory PV and ET, preliminary studies have demonstrated efficacy in improving erythrocytosis, leukocytosis, thrombocytosis, splenomegaly, and phlebotomy independence with ruxolitinib. Additionally, Phase II studies of ruxolitinib in refractory MPNs including post-MPN acute myeloid leukemia, have demonstrated promising results in clinical trials. 

**Conclusion**

The discovery of the JAK mutation influential in the development of MPNs provided scientists with a new therapeutic platform from which to develop targeted treatment strategies. Ruxolitinib represents the first of these compounds and is currently US Food and Drug Administration approved for the treatment of intermediate- and high-risk MF. The pluripotent effects of this therapy stem from its anticytokine effects that result in symptom palliation and reduction of spleen size.

**Alternative novel MPN therapies**

Many alternative novel compounds are currently in varying stages of investigation for the treatment of MPNs. At least seven JAK inhibitors are currently under investigation, with many of these compounds displaying varying degrees of inhibition to other members of the JAK family, including JAK1, JAK2, JAK3, and tyrosine kinase-2 (Table 3). Along with differences in drug pharmacokinetics and specificity, JAK inhibitor compounds have shown much variation in hematologic toxicity profiles. Currently, no specific compound is under investigation that specifically targets the JAK2V617F mutation. Pomalidomide is an immunomodulating agent currently in Phase III trials that has been shown to improve anemia with minimal myelosuppression and anemia. Everolimus (RAD001), a potent mammalian target of rapamycin inhibitor, has been successful in preventing in vitro proliferation of JAK2V617F mutated cells and resolving systemic symptoms and pruritus in a cohort of 39 MF patients. Histone deacetylase inhibitors also represent a growing epigenetic target, with many novel histone deacetylase inhibitors demonstrating the ability to decrease JAK signaling. Clinical trials of these compounds, including givinostat and panobinostat, are currently ongoing. Additionally, alternative epigenetic agents including the hypomethylating agents azacitidine and decitabine – which function by blocking DNA methyltransferase – have demonstrated promising results in clinical trials.

**Table 3** Novel Janus kinase-2 inhibitor compounds currently under investigation

<table>
<thead>
<tr>
<th>JAK2 inhibitor</th>
<th>Alternative molecular targets</th>
<th>Phase of investigation</th>
<th>Essential thrombocytopenia</th>
</tr>
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<tbody>
<tr>
<td>Ruxolitinib (INCB018424)</td>
<td>JAK1, JAK2, JAK3, JAK2V617F, STAT3</td>
<td>III/FDA approved</td>
<td>II</td>
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<tr>
<td>SAR302503 (TG101348)</td>
<td>FLT3, Ret</td>
<td>III</td>
<td>I</td>
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<td>CYT387</td>
<td>JNK1, CDK2</td>
<td>I/I</td>
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<td>FLT3, TrkA</td>
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**Abbreviation:** FDA, US Food and Drug Administration.
medication in a routine clinical practice setting can be fully determined.

Disclosure

The authors report no conflicts of interest in this work.

References


