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

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Abstract

The BCR-ABL1-negative myeloproliferative neoplasms (essential thrombocythemia, polycythemia vera, and primary myelofibrosis) are a group of heterogeneous hematologic malignancies involving 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 the understanding of the pathogenetic mechanisms underlying these diseases has led to an explosion of clinical trials evaluating novel therapies. The discovery of an activating mutation in the Janus associated kinase 2 (JAK2) gene provided a therapeutic target to down-regulate this activated signaling pathway influencing the phenotype of these diseases. Ruxolitinib (Jakafi, Incyte) is a small molecule inhibitor of JAK1/2 that has proven to be effective in reducing splenomegaly and ameliorating symptoms in myeloproliferative neoplasms. Based on the results of two pivotal randomized phase III clinical trials, Ruxolitinib has become the first FDA approved therapeutic for the treatment of patients with myelofibrosis. Ruxolitinib offers a well-tolerated oral therapeutic option for MF patients with symptomatic splenomegaly and debilitating disease related symptoms, but does not appear effective in eliminating the underlying hematological malignancy.
Introduction

The myeloproliferative neoplasms (MPNs) are a group of clonal hematological malignancies that include chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocytemia (ET), and primary myelofibrosis (PMF) which originate at the level of the pluripotent hematopoietic stem cell. PV and ET can both progress to myelofibrosis, termed Post-ET/PV MF which are clinically indistinguishable from PMF. Collectively, PMF and Post-ET/PV MF are referred to as simply MF. CML is distinguished from the other MPNs by the requisite presence of the \textit{BCR-ABL1} proto-oncogene, which is believed to be the disease-initiating event. BCR-ABL1 is a tyrosine kinase with constitutive activity deregulating cell differentiation, division, and adhesion. Imatinib (Gleevec, Novartis) was the first tyrosine kinase inhibitor 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, the identification of targets for drug therapies has been difficult. Over a dozen mutations as well as multiple epigenetic alterations have been identified in MPNs occurring with varying frequencies and co-expression patterns revealing a complicated pathobiology that makes it unlikely that an agent targeting a single pathway will be successful in eliminating the malignant hematopoietic stem cells (HSCs) responsible for MF. Acquisition of additional mutations in MF cells involving genes encoding a growing list of proteins including MPL, EZH2, ASXL1, IDH1/2, TET2, CBL, IKZF1 and p53 have been identified at varied
frequency. 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 HSC, while the marrow fibrosis is believed to be largely a reactive process occurring due to 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 (PDGF), transforming growth factor beta (TGF-β) and basic fibroblast growth factor (bFGF) have been implicated in the pathobiology of marrow fibrosis in PMF and may be in part a consequence of pathologic interactions between neutrophils and megakaryocytes belonging to the malignant clonal (2, 3). Cytogenetic studies of fibroblasts from PMF patients 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 MF patients and has 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 upon the degree of advancement of the disease. (6). The International Prognostic Scoring System (IPSS) created by the International Working Group for Myelofibrosis Research
and Treatment (IWG-MRT) 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 <10g/dL, peripheral blood blast count ≥1%, presence of constitutional symptoms, and leukocyte count ≥ 25 x10^9/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 ≥ to 3 (high risk) of these variables, with median survivals of 135, 95, 48, and 27 months, respectively (P < .001). Patients with low/intermediate-1 risk status are typically followed with a watch and wait approach while patients with intermediate-2/high risk status are treated with traditional agents or considered for entry onto clinical trials or if appropriate, hematopoietic stem cell transplantation.

Current therapies that are used in the treatment of MF include immunomodulatory agents (IMiDs: thalidomide, lenalidomide), erythropoietin stimulating agents (erythropoietin, darbepoetin), androgens (danazol), chemotherapeutics (hydroxyurea, busulfan, melphalan, 2-Chlorodeoxyadenosine) and biologics (interferon-alfa). Additionally, radiation to sites of extramedullary hematopoiesis (EMH) can sometimes offer palliation of symptoms, while splenectomy remains an option for patients with symptomatic splenomegaly or severe cytopenias that is either refractory or prevents medical management. None of these therapeutic options have proven to be disease modifying and do not definitively alter the natural course and history of MF. Experimental therapeutic options include pomalidomide (IMiD), JAK2 inhibitors, histone deacetylase inhibitors (HDACi), or heat shock protein 90 inhibitors (HSP90i). Stem cell transplantation remains the only therapeutic option that offers the potential for cure in MF.
patients that are preferably younger in age with a good performance status and an available 10/10 HLA-matched sibling donor.

In 2005, four independent laboratory groups reported the finding of an activating point mutation in the Janus-associated kinase 2 (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 responsible for diverse cellular functions such as differentiation, proliferation and avoidance of apoptosis (11). JAK1 is known to mediate the effects of pro-inflammatory cytokines such as IL-2, IL-6, 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. JAK 1/2 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, inhibiting the production of an array of additional pro-inflammatory cytokines, chemokines, and adhesion molecules by other cell types leading to the interruption of a so-called cytokine cascade.

A number of tyrosine kinase inhibitors with varying anti-JAK2 potency and specificity as well as differing toxicity profiles have been or are currently being evaluated in clinical trials [Lestautinib (Cephalon), AZD1480 (AstraZeneca), BMS911543 (Bristol-Myers Squibb), CYT387 (YM Bioscience), SAR302503 (Sanofi-Aventis)] (12). All of these agents were initially evaluated in patients with advanced MF due to the limited survival experienced by such patients which was felt to justify their entry onto 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 is currently being evaluated in the setting of ET, PV, MF and acute leukemia. On November 16 2011, rRuxolitinib was approved by the U.S. Food and Drug Administration (FDA) for the treatment of intermediate/high-risk MF based upon the combined results of the COMFORT-I and COMFORT-II Trials.

**Mechanism of action**

JAKs are associated with the intracellular domain of growth factor receptors (erythropoietin receptor, EPOR; thrombopoietin receptor, MPL; granulocyte-colony stimulating factor (G-CSF) and conformational changes within the receptor induced by ligand binding bring associated JAKs in close approximation (13). This causes autophosphorylation of JAKs inducing a conformational change in the JAK protein and tyrosine phosphorylation of specific residues on the receptor that act as binding sites for signal transducers and activators of transcription (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 promoting transcription of genes that mediate cell growth, differentiation and apoptosis.

JAK2V617F, occurring 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 auto-inhibitory 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, since the hypercatabolic state and severe constitutional symptoms that often accompany disease progression in MF appear to be driven by the elevated pro-inflammatory 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 IC₅₀ of 3.3 and 2.8nm, 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 and this has been documented in correlative biomarker studies within clinical trials (15). Ruxolitinib is not specific for the mutated form of JAK2 and inhibits both wild type and JAK2V617F.

Pharmacokinetics/Pharmacodynamics

The pharmacokinetics (PKs) of Ruxolitinib was evaluated in healthy volunteers in 2 double-blind, randomized, placebo controlled studies (16). The drug demonstrated good oral bioavailability independent of fasted or fed state and dose-proportional systemic exposure with a small volume of distribution, and an approximate 3-hour plasma half-life. Oral doses of 25mg...
BID and 100mg QD were established as the maximally tolerated dose (MTD) in healthy volunteers. Studies of metabolism and excretion in healthy volunteers proved ruxolitinib to be well absorbed at >95% and without accumulation of parent compound or metabolites after single or multiple dosing (17).

Pharmacodynamic evaluation has relied on measuring the levels of down-stream targets of JAK signaling and assessing the change in inflammatory markers in response to therapy. In the initial phase I/II reported by Verstovsek, maximal mean inhibition of p-STAT-3 expression ranged from approximately 40% at the lowest dose tested to greater than 90% inhibition at the highest dose tested and returned to baseline levels by 24 hours (15). Dose and time dependent reduction of phosphorylated STAT-3 was observed with ruxolitinib treatment and was reported in patients with JAK2V617 and wild type JAK2. Elevated baseline levels of IL-6, IL-1ra, IL-8, MIP-1β, TNF-α, and CRP were all dramatically reduced with ruxolitinib treatment in MF patients.

Pre-clinical studies

Transfection of Ba/F3 cells with retroviral containing JAK2V617F vectors demonstrated constitutive activation of STAT-5 and cytokine-independent growth of erythroid colony-forming units (CFU-E) 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 causing premature death (18-20). JAK2V617F transgenic mouse models expressing human JAK2 have been generated in order to understand
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 the mouse, while ratios that are equal in expression produce mice that have a PV phenotype characterized by neutrophilia, erythrocytosis and thrombocytosis. Marrow fibrosis occurs in varying frequency in these 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, results in reduced cellular proliferation and induction of apoptosis that is accompanied by inhibition of JAK2V617F, STAT5 and ERK 1/2 phosphorylation (22). In a mouse model of JAK2V617F-positive MPN, the administration of oral ruxolitinib markedly reduced splenomegaly and circulating levels of pro-inflammatory 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 in IC$_{50}$ = 67nM versus healthy controls with an IC$_{50}$ > 400nM.

However, in another murine model of MPN (MPLW/515L-induced thrombocytosis and myelofibrosis), treatment with a small molecule selective JAK2 inhibitor (INCB16562) did normalize the leukocyte and platelet counts, reduce 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 might not be curative.

**Clinical studies**
Initial Phase I/II Study

A phase I/II study of ruxolitinib was conducted by Verstovsek et al. in JAK2V617F-positive and –negative MF patients at ascending doses starting at oral doses with a BID schedule of 10mg, and included 15mg, 20mg, 25mg and 50mg and QD dosing at 25mg, 50mg, 100mg, and 200mg (15). Ruxolitinib at 25mg BID or 100mg QD was established as the maximally tolerated dose (MTD) based on the dose limiting toxicity (DLT) of reversible thrombocytopenia. At 15mg BID, ruxolitinib treatment was associated with sustained reductions of splenomegaly, resolution of constitutional symptoms, improvement in exercise tolerance and performance status as well as 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. Dramatic responses seen in splenomegaly were not accompanied by tumor lysis syndrome or compromised hematopoiesis. Marked depression in the heightened expression of pro-inflammatory cytokines (IL-6, IL-1ra, MIP-1β, TNF-α, 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 there was no comparator arm, there was a trend to improvement in survival and a suggestion of a reduction in rate of transformation to acute leukemia when compared to 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 containing more high risk patients, lower hemoglobinics at baseline and an older median age.
Also patients with platelet counts less than 100 x 10^9/L were not allowed entry onto any of these trials; this is of great practical importance since thrombocytopenia is frequently predictive of a poor prognosis and would limit the amount of drug that can be administered and influence the tolerability of the drug.

**COntrolled MyeloFibrosis Study with ORal JAK2 inhibitor Treatment (COMFORT-1)**

This was a randomized (1:1), double-blinded phase III study sponsored by Incyte comparing Ruxolitinib to placebo in patients with intermediate-2 or high risk MF and a baseline platelet count of at least 100 x 10^9/L (25). Oral ruxolitinib was dosed at 15mg BID for patients with platelet counts between 100-200 x 10^9/L and 20mg BID for patients with >200 x 10^9/L. A total of 309 patients were randomized (ruxolitinib 155, placebo 154), with a median age of 68 years. The primary endpoint of this study was a reduction in spleen volume of at least 35% by either MRI/CT. The 35% reduction in spleen volume was chosen based on previous studies that established a correlation of 35% reduction in volume by imaging to approximately 50% reduction by manual palpation on physical exam. Secondary endpoints included assessment of duration of spleen reduction and improvement in disease related symptoms as assessed by the MFSAF (myelofibrosis symptom assessment form) (26). Patients were allowed to crossover from placebo if they had a greater than 25% increase in spleen volume by imaging from baseline and all patients were un-blinded and could crossover 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 AE observed in 45% vs 19.2%, in the ruxolitinib vs placebo arm, respectively. Grade 3/4 thrombocytopenia was observed in 12.9% vs
1.3% in patients treated with ruxolitinib vs placebo, respectively. Neutropenia that was grade 3/4 was observed in 7.1% vs 2% in the ruxolitinib vs placebo arm, respectively. The most common non-hematologic adverse event seen of any grade in the ruxolitinib treated group was diarrhea 23.2% (compared to 21.2% in placebo group). All in all, this was a well tolerated drug.

At 24 weeks, 41.9% of patients treated with ruxolitinib experienced a 35% or greater reduction in spleen volume compared to 0.7% of patients receiving placebo ($P < 0.0001$). 45.9% of ruxolitinib treated patients regardless of their JAK2 mutational status experienced a ≥50% improvement in constitutional symptoms as compared to 0.7% in the placebo group.

Survival analysis 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 to placebo of 0.98 vs 0.90 and 0.84 vs 0.77 in patients with a baseline hemoglobin >10g/dL and <10g/dL, respectively (27). In further subset analysis, patient age ≤ 65 years appeared to have a survival benefit over > 65 years of age with a HR 0.22 (0.06,0.84) with ruxolitinib therapy.

The drug therapy was uniformly ineffective in 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. The other limitation of the agent that has been the rapid return of splenomegaly following discontinuation of the drug and the occasional occurrence of life threatening syndromes attributed to the rapid elevation of 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 in addition to upfront discussion with the patient regarding this potential drug associated serious adverse event (28).

**CONTROLLED MYELOFIBROSIS STUDY WITH ORAL JAK2 INHIBITOR TREATMENT COMFORT-2**

This was a randomized (2:1), Novartis sponsored, open-label phase III clinical trial conducted in nine European countries comparing ruxolitinib to best available therapy (BAT) (29). Hydroxyurea (46.6%), steroids (16.4%) and supportive therapy (32.9%) comprised the BAT arm. At a median age of 66 years, 219 patients with intermediate-2 or high risk MF were randomized (146 ruxolitinib, 73 BAT).

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

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

Progression-free survival, leukemia-free survival and overall survival were not statistically significant between the two treatment arms.
Phase II in Acute Myeloid Leukemia

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

Current and future studies

Current ongoing studies in MF patients include ruxolitinib in a sustained release formulation, alternate dosing schedules and the evaluation of drug tolerability in patients with baseline platelet counts between 50 - 99 x 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 ruxolitinib in combination with IMiDs, ESAs (danazol) and chromatin modifying agents (CMA) such as HDACi and DNA methyltransferase inhibitors (DNMTi) as well as the use of JAK2 inhibition prior to HSCT in MF patients.

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

Conclusions

In just 6 years after the discovery of the JAK2 mutation with an evolving understanding of the pathobiology of MPNs, a new class of tyrosine kinase inhibitors that abrogate the over-activity of the JAK-STAT pathway are being aggressively evaluated in clinical trials. These agents have shown the ability to down regulate pro-inflammatory cytokines and downstream mediators of JAK signaling which provide biomarker evidence for their mechanism of action in improving the debilitating constitutional and hypercatabolic symptoms and reducing splenomegaly in patients with MPNs (see figure 1). Ruxolitinib leads this class of agents and is now 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 prove to alter the treatment approach of many MF patients in the community and influence the accrual of patients to current and future clinical trials. Anti-JAK therapy and ruxolitinib in particular, is an important advance in the treatment of MF and should be considered in patients that are symptomatic without limiting cytopenias. Currently, there is not sufficient evidence to indicate that ruxolitinib possesses 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.
References


RUXOLITINIB

Potential molecular targets:
JAK1
JAK2
JAK2V617F

Improved
Constitutional symptoms
- fevers
- night sweats
- weight loss

MF specific symptoms
- early satiety
- pruritis
- bone pain

Splenomegaly

Unchanged
Bone marrow histopathologic abnormalities
Anemia
Thrombocytopenia
Leukoerythroblastosis
Cytogenetic abnormalities and JAK2V617F allele burden
Clinical Cancer Research

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