




REVIEW

JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders [version 1; referees: 2 approved]

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Abstract

JAK inhibitors have been developed following the discovery of the *JAK2V617F* in 2005 as the driver mutation of the majority of non-*BCR-ABL1* myeloproliferative neoplasms (MPNs). Subsequently, the search for JAK2 inhibitors continued with the discovery that the other driver mutations (*CALR* and *MPL*) also exhibited persistent JAK2 activation. Several type I ATP-competitive JAK inhibitors with different specificities were assessed in clinical trials and exhibited minimal hematologic toxicity. Interestingly, these JAK inhibitors display potent anti-inflammatory activity. Thus, JAK inhibitors targeting preferentially JAK1 and JAK3 have been developed to treat inflammation, autoimmune diseases, and graft-versus-host disease. Ten years after the beginning of clinical trials, only two drugs have been approved by the US Food and Drug Administration: one JAK2/JAK1 inhibitor (ruxolitinib) in intermediate-2 and high-risk myelofibrosis and hydroxyurea-resistant or -intolerant polycythemia vera and one JAK1/JAK3 inhibitor (tofacitinib) in methotrexate-resistant rheumatoid arthritis. The non-approved compounds exhibited many off-target effects leading to neurological and gastrointestinal toxicities, as seen in clinical trials for MPNs. Ruxolitinib is a well-tolerated drug with mostly anti-inflammatory properties. Despite a weak effect on the cause of the disease itself in MPNs, it improves the clinical state of patients and increases survival in myelofibrosis. This limited effect is related to the fact that ruxolitinib, like the other type I JAK2 inhibitors, inhibits equally mutated and wild-type JAK2 (JAK2WT) and also the JAK2 oncogenic activation. Thus, other approaches need to be developed and could be based on either (1) the development of new inhibitors specifically targeting *JAK2V617F* or (2) the combination of the actual JAK2 inhibitors with other therapies, in particular with molecules targeting pathways downstream of JAK2 activation or the stability of JAK2 molecule. In contrast, the strong anti-inflammatory effects of the JAK inhibitors appear as a very promising therapeutic approach for many inflammatory and auto-immune diseases.

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Introduction

Janus kinases (JAKs) play a central role in the regulation of hematopoiesis as being mandatory for signaling by receptors for hematopoietic/immunological cytokines¹. They control survival, proliferation, and differentiation of hematopoietic cells as well as the function of mature cells by binding to hematopoietic type I and type II cytokine receptors, which are devoid of catalytic activity (Figure 1). JAKs pre-associated to these receptors to form a functional signaling complex¹. Cytokine binding induces or re-orient receptor dimerization, such that JAK kinase domains face each other in a productive conformation for transactivation and phosphorylation of the cytokine receptor cytoplasmic tails¹. The latter and JAKs themselves become scaffolds for signaling molecules, particularly for the members of the signal transducer and activator of transcription (STAT) family, which in turn are phosphorylated and homo/hetero-dimerize before translocating to the nucleus. JAK activation also initiates activation of mitogen-activated protein kinase (MAPK), phosphatidylinositol-3'-kinase (PI3K), and AKT/mammalian target of rapamycin (mTOR) (Figure 2)².

The JAK/STAT pathway is frequently dysregulated in malignant diseases and in disorders with an abnormal immunological response³.

The discovery that classic *BCR-ABL1*-negative myeloproliferative neoplasms (MPNs) are constantly associated with abnormal JAK2 activation due to different mutations, has paved the way for the development of JAK inhibitors in the therapy of these disorders as well as of other diseases with either genetic alterations in the JAK pathway or JAK-induced activation by autocrine and paracrine cytokine loops^{4,5}. Here, we focus on the role of JAKs as potential therapeutic targets, the development of JAK inhibitors and their limitations, and potential new strategies targeting the JAKs.

Janus kinases

The human genome codes for four JAKs: JAK1, JAK2, JAK3, and TYK2¹. Like the god Janus, who has two faces and opens doors, JAKs possess two kinase domains—one catalytically active domain at the C-terminus and an upstream pseudokinase domain that binds ATP—but does not phosphorylate substrates (except weakly itself). At the N-terminus, JAKs possess a FERM (band four-point-one, ezrin, radixin, moesin)-like domain and an Src homology 2 (SH2)-like domain (Figure 3A). The non-covalent attachment of JAKs to cytokine receptor tails is specific and depends on the FERM domain and on the juxtamembrane receptor sequence containing a proline-rich Box 1 and a motif denoted Box 2 with both hydrophobic and negatively charged residues as well as the

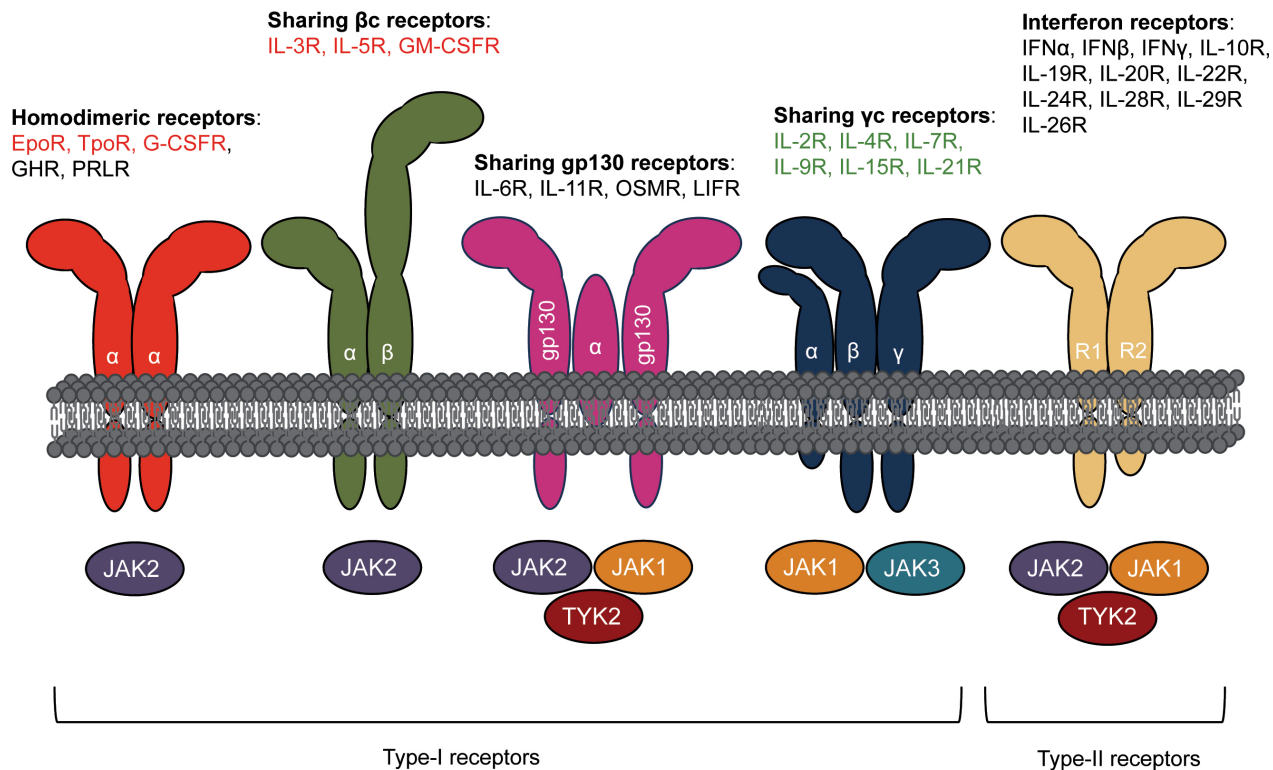


Figure 1. Janus kinases (JAKs) and the cytokine receptor superfamily. Schematic representation of type I and type II cytokine receptor subfamilies based on the extracellular domain sequence homologies. The different JAKs (JAK1, JAK2, JAK3, and TYK2) are employed by each class of receptors, as indicated. Type I receptors can form homodimers (α/α), heterodimers (α/β), or oligomers (gp130/ α /gp130); ($\alpha/\beta/\gamma$), although the α chain is mainly responsible for cytokine binding. Cytokine receptor complexes composed of two or more different chains activate at least two different JAKs, while single-chain receptors such as homodimeric receptors activate JAK2 only (although TpoR/MPL and G-CSFR/CSF3R can also use TYK2 and JAK1, respectively). The myelopoiesis-related cytokine receptors are denoted in red, and the lymphopoiesis-related cytokines receptors are denoted in green.

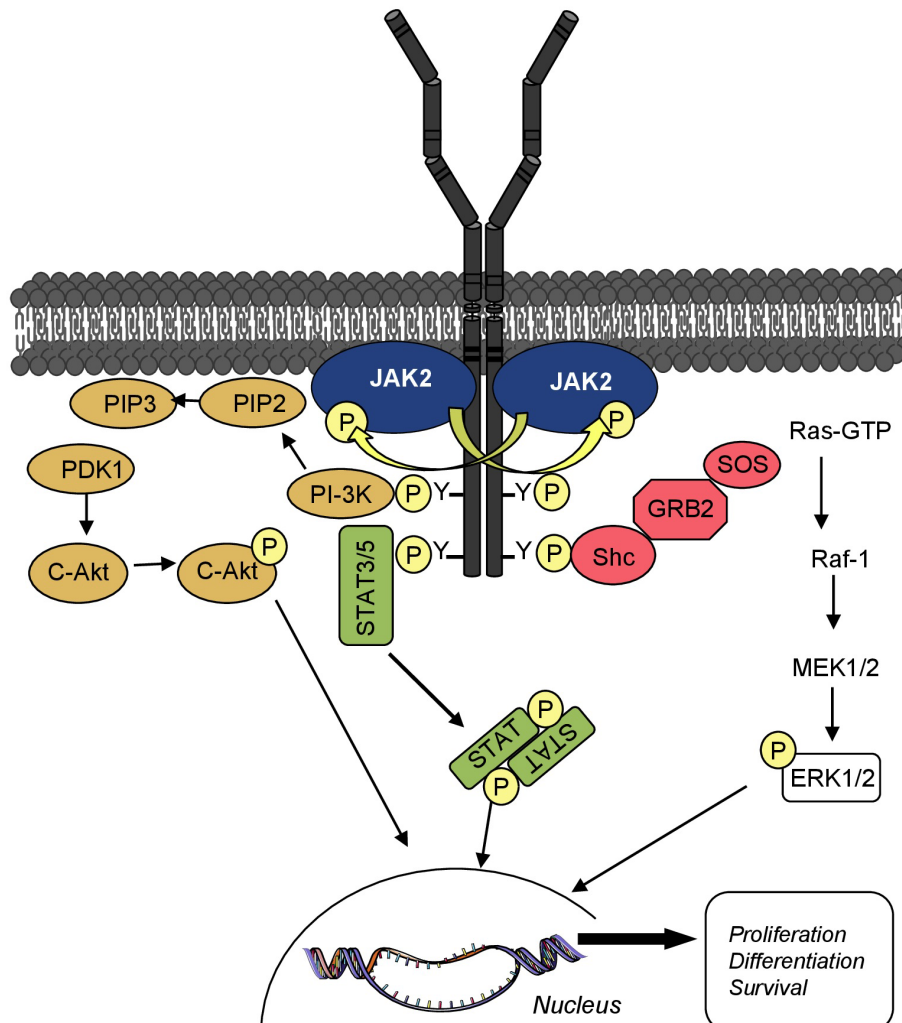


Figure 2. Principal signaling pathways activated by homodimeric cytokine receptors. Cytokine binding to the extracellular domain of receptors induces conformation changes that enable cross-phosphorylation of the appended Janus kinases (JAKs), which then can activate each other. As a result, JAK molecules phosphorylate tyrosine residues on the intracellular part of the receptor, which then can serve as docking sites for SH2 domain containing signaling molecules such as signal transducer and activator of transcription (STAT) but also proteins from the phosphatidylinositol-3'-kinase (PI3K) and mitogen-activated protein kinase (MAPK) pathways.

sequences stretching from Box 1 to Box 2^{6,7}. JAK2 associates with the three homodimeric receptors: erythropoietin receptor (EPOR), thrombopoietin receptor (MPL/TPOR), and the granulocyte colony-stimulating factor receptor (G-CSFR/CSF3R). JAK1, JAK2, and TYK2 can also associate with heterodimeric or trimeric receptors, and JAK3 only with receptors containing the γ -chain with solely JAK1 as partner (Figure 1)¹. The precise structure of receptor/JAK complexes remains unknown. Recently, the structures of the kinase and pseudokinase domains of JAK1, JAK2, and TYK2 were obtained and represent a major asset for the identification of novel (allosteric) inhibitors (see below)⁸⁻¹⁰. Interestingly, JAKs also play a role of chaperones for traffic and stability at the cell surface of several cytokine receptors¹¹.

Disease associated with abnormal JAK activation

Autonomous activation of the JAK/STAT pathway is central in several pathologies. Genetic alterations targeting this signaling pathway are associated mainly with hematologic malignancies. Pathological JAK activation also occurs in diseases linked to abnormal cytokine stimulation.

Hematologic malignancies

In many myeloid and lymphoid malignancies, driver mutations leading to constitutive JAK activation can be found. The paradigm is represented by *BCR-ABL1*-negative MPNs as they are all related to mutations activating JAK2, which in more than 50% of the cases both initiate and drive the disease phenotype. Thus, the

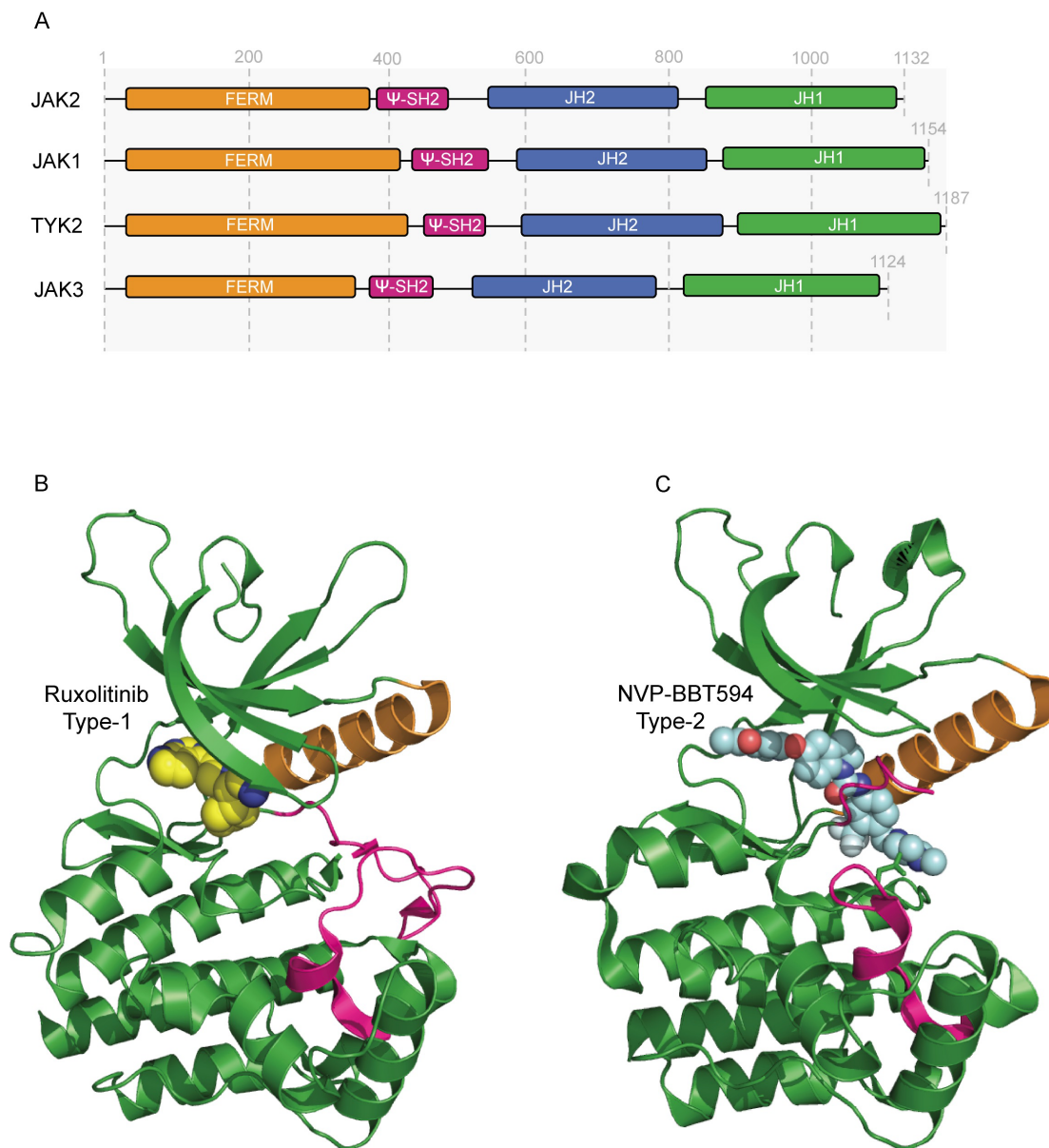


Figure 3. The kinase domain of Janus kinase 2 (JAK2) has been commonly targeted by the current inhibitors. (A) Secondary structure of JAK molecules. They are composed (from the N- to C-terminal end) of a FERM domain (band 4.1, erzin, radixin, moeisin domain), a pseudo-SH2 domain (ψ -SH2), a pseudokinase domain (JH2), and a kinase domain (JH1). While the major function of the N-terminus region is to specifically bind to cytokine receptor intracellular tail, the carboxyl-terminal region contains the catalytically active kinase domain, JH1, and the regulatory domain, JH2, of which the exact function is still matter of debate. **(B)** Three-dimensional representation of JAK2 kinase domain in its active conformation (PDB: 3KRR¹²) bound to type 1 inhibitor, ruxolitinib (show in yellow spheres). The binding of ruxolitinib has been modelled on the basis of the co-crystal of ruxolitinib-bound Scr (PDB: 4U5J¹³). The activation loop, colored in pink, adopts an 'open' (active) conformation stabilized by phosphorylation of tyrosine residues 1007 and 1008. The α C is colored in orange. **(C)** Three-dimensional representation of JAK2 kinase domain in its inactive conformation bound to a type 2 inhibitor, NVP-BBT594 (PDB: 3UGC¹⁴). The activation loop, colored in pink, adopts a 'closed' (inactive) conformation. The compound is shown in cyan spheres, and the α C in orange. **(D)** Illustration of the structures of the main compounds discussed in this review.

development of JAK2 inhibitors is particularly critical for MPNs.

Classic BCR-ABL1-negative MPNs. The classic *BCR-ABL1*-negative MPNs (hereafter, MPNs) include three different

disorders—essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF)—and are caused by constitutive activation of the cytokine receptor/JAK2 pathway due to acquired somatic mutations in three major genes¹⁵. *JAK2V617F* is the most prevalent mutation in MPNs associated

with the three disorders (65–70%) and is present in 95% of PVs. Mutations in the exon 12 of *JAK2* are found in around 2% of PV, which are negative for the *JAK2V617F* mutation (reviewed in 15). Interestingly, these two *JAK2*-activating mutations are not located in the kinase domain of the protein but involve amino acid changes in the pseudokinase (JH2) domain (*JAK2V617F*) and the SH2-JH2 linker domain (*JAK2 exon 12*) (Figure 3A and see below). Mutations in the thrombopoietin receptor (*MPL*) gene are much rarer than *JAK2* mutations and are present in 3% of MPNs (4–5% of ET and myelofibrosis [MF]). The recurrent mutations are located in the exon 10. The most frequent are substitutions of the W515 residue to many other amino acids, mostly L or K but also R or A (reviewed in 15). In MPNs, the *MPLS505N* mutation is also found but less frequently than in hereditary thrombocytosis. Rarer mutations of *MPL* have been described in both the extracellular and intracellular domains. The third gene found frequently mutated in MPNs is calreticulin (*CALR*), which is affected by mutations leading to a +1 frameshift in the exon 9^{16,17}. As for *MPL*, *CALR* mutations are associated with ET and MF but with a higher frequency (25%). *CALR* is not a molecule directly involved in activation of *JAK2*, but the new C-terminus common to all mutants allows the *CALR* mutants to tightly bind and activate *MPL* and *JAK2*^{18–21}.

All of these activating mutations mimic the effects of hematopoietic cytokines by inducing constitutive signaling via the STAT, PI3K, and ERK/MAPK pathways. To achieve this, *JAK2V617F* must be bound to cytokine receptors, more particularly homodimeric receptors (EPOR, CSF3R/G-CSFR, and MPL/TPOR), which allow its dimerization and activation²². *CALR* mutants specifically activate *MPL* and (to a lesser extent) G-CSFR, and *MPL* mutations result in an active conformation of the receptor¹⁸. Loss-of-function mutations in *SH2B3*, a negative regulator of *JAK2*, have been described as drivers in MPNs and idiopathic erythrocytosis^{23,24}, but there is evidence that in the majority of the cases it is either a secondary mutation or a germline mutation predisposing to MPNs²⁵.

In 20–30% of patients with MPNs, mutations besides driver *JAK2*-activating mutations have been identified in genes involved in splicing (*SRSF2* and *U2AF1*) and epigenetic regulation (*TET2*, *DNMT3A*, *ASXL1*, *EZH2*, and *IDH1/IDH2*) and in tumor suppressor genes (*TP53*)^{15,26,27}. They could predate or follow the driver mutations^{28–30}. Mutations, such as in *TET2*, *DNMT3A*, or *EZH2*, favor clonal dominance and disease initiation^{28,31}. Of note, these associated mutations promote progression to MF or leukemic transformation (*ASXL1*, *IDH1/2*, *EZH2*, and *TP53*)^{32,33}. Almost always, one such mutation is present in PMF, and the number of such mutations correlates with the severity of the disease^{32,33} and might modulate the response to *JAK2* inhibition.

Other myeloid malignancies

MPN associated with *JAK2* fusion proteins

Four fusion proteins—ETV6 (TEL)-*JAK2* (t(9;12) (p24;p13), PCM1-*JAK2* (t(8;9) (p22;p24), BCR-*JAK2* (t(9;22) (p24;q11.2), and RPN1-*JAK2* (t(3;9) (q21;p24)—have been described in some MPNs—PMF, chronic eosinophilic leukemia (CEL), atypical chronic myeloid leukemia (aCML), and unclassified MPNs—or

in mixed MPN/myelodysplastic syndrome (MPN/MDS)^{34–37}. The translocation partner of *JAK2* sets the expression level and induces dimerization of *JAK2* kinase domains.

Chronic neutrophilic leukemia, an MPN associated with G-CSFR (*CSF3R*) mutations

Acquired activating *CSF3R* mutations have been found in the great majority of chronic neutrophilic leukemias (CNLs). Most CNLs carry a T618I mutation (T595I if the first counted residue is after the peptide signal sequence)³⁸. The T615N (T592N) mutation has also been described but more rarely. *CSF3R* mutations have also initially been described in aCML but are much less frequent than in CNL.

JAK2V617F and (to a lower extent) *MPL* and *CALR* mutations are extremely prevalent in refractory anemia with ring sideroblasts and thrombocytosis and are associated with *SF3B1* mutations³⁹.

Mutations in *JAK2* or cytokine receptors are rare in the other myeloid malignancies. They can be found in chronic myelomonocytic leukemia (CMML) but always associated with other mutations.

In acute myeloid leukemia (AML), mutations in *JAKs* are rare and, when present, mostly involve *JAK1*. *CSF3R* mutations have also been described but as late events. The only AML associated frequently with *JAK* mutations is Down syndrome acute megakaryoblastic leukemia (AMKL), where *JAK1*, *JAK2*, and also *JAK3* mutations are found in around 20% of cases^{40,41}.

Lymphoid malignancies. *JAK2* activation may play a more significant role in the pathogenesis of B and T neoplasms than previously thought, although they might be only secondary events. *JAK/STAT* activation occurs via either mutations/translocations or cytokine paracrine/autocrine loops.

Acute lymphoblastic leukemia

In B-cell acute lymphoblastic leukemia (B-ALL), a new subtype has emerged called *BCR-ABL1*-like subtype (15% of pediatric ALL and 50% of ALL with Down syndrome), as it exhibits a transcriptional profile similar to that of *BCR-ABL1*-positive ALL with poor prognosis⁴². Half of them have *JAK1* and *JAK2* mutations and rearrangement of *CRLF2*, a gene encoding a cytokine receptor^{43,44}. The most frequent *JAK2* mutations target the R683 (R683G/S), a residue present in the DIREED motif located in the hinge between the N- and C-lobes of the pseudokinase domain of *JAK2*^{44,45}. Fusion with partners ETV6, BCR, PAX, and SSBP2 results in the activation of *JAK2* kinase domain. Mutations in *JAK1* are relatively rare in B-ALL in comparison with T-cell ALL (T-ALL)⁴⁶ and are located in the FERM domain and the pseudokinase domain. For instance, *JAK1V658F* is the equivalent of *JAK2V617F*⁴⁷. In most cases, *JAK2* mutations are associated with an aberrant expression of *CRLF2*, a cytokine receptor chain which associates with *IL-7RA* to bind the thymic stromal lymphopoietin (TSLP)⁴⁸. The F232C-activating mutation in *CRLF2* induces homodimerization of *CRLF2* and is detected in 10% of cases overexpressing *CRLF2*⁴⁹. Activating mutations in the *IL-7RA* have been described either as point mutation

(S185C) or as an insertion-deletion in the transmembrane domain inducing homodimerization of the IL-7RA⁵⁰. Truncating rearrangements of the *EPOR* have also been identified⁵¹.

In T-ALL, mutations in *JAK1*, *JAK2*, *JAK3*, and the *IL-7R* are found in around 15% of cases, more particularly in early T-cell progenitor (ETP)-ALL⁵². Targeting JAKs in these two types of ALL appears to be a valuable approach.

Hodgkin lymphoma and primary mediastinal B-cell lymphoma

Hodgkin lymphoma and primary mediastinal B-cell lymphoma (PMBL) have some common mechanisms of lymphomagenesis, being driven by alterations in the nuclear factor-kappa B (NFκB) and JAK/STAT pathways^{53,54}. In rare cases (3%), a JAK2 fusion protein (SEC31A-JAK2) is present⁵⁵.

Other lymphoma

In T-cell pro-lymphocytic leukemia, mutations in *JAK1* (8%) and *JAK3* (30%) (more particularly M511I) have been described⁵⁶. *JAK3* mutations (particularly A572V and A573V) are frequent (35%) in natural killer/T-cell lymphomas⁵⁷. Mutations or silencing of negative regulators of JAKs (*PTPN2* and *SOC3*) is also frequent in diffuse large B-cell lymphoma, follicular lymphoma, and peripheral T-cell lymphoma.

An autocrine/paracrine cytokine loop induced by IL-6, IL-10, and IL-13 activates JAKs. This occurs in several types of lymphoma as well as in chronic lymphocytic leukemia and Waldenström macroglobulinemia⁵⁸.

Disorders other than hematologic malignancies

Inherited disorders of the hematopoietic system. The majority of inherited thrombocytosis are related to spontaneous activation of the MPL/JAK2 pathways due to *MPL* or *JAK2* mutations^{59,60}. The other mechanism is related to an excess of plasma thrombopoietin (TPO) due either to an excessive synthesis or to a defect in its clearance as a consequence of *MPL* mutations affecting receptor trafficking. This excess of TPO induces JAK2 activation^{59,60}.

Inherited erythrocytosis are related to excess erythropoietin (EPO) synthesis or to gain-of-function mutations in *EPOR* that activate JAK2⁶⁰. Hereditary neutrophilia carry activating mutations of *CSF3R* that activate JAK2⁶¹.

Inflammatory and autoimmune diseases. A large spectrum of diseases of the immune system involves an activation of JAKs through autocrine or paracrine cytokine loops⁶². In inflammatory pathologies, such as rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease, and alopecia areata, the most important JAK to be targeted is JAK1⁶². In autoimmune disease, JAK1 is also the main JAK to be targeted as both the IL-6 and the type I interferon (IFN) pathways are involved. Blocking JAK1/2 in graft-versus-host disease (GVHD) is useful as type II IFN and IL-6 are pathogenic⁶³. Lastly, JAK inhibition can be useful to curb oncogenic inflammatory responses in a wide range of solid tumors.

JAK inhibitors

Several types of inhibitors exist according to their mechanism/region targeted in JAKs⁶⁴.

Type I inhibitors

Type I inhibitors target the ATP-binding site of the JAKs under the active conformation of the kinase domain (Figure 3B)⁶⁴. All clinically tested inhibitors are type I. They differ in their specificity for each JAK. Many inhibitors target JAK2, JAK1, and eventually TYK2 (ruxolitinib, momelotinib, AZD1480, and baricitinib) or JAK3 and JAK1 (tofacitinib). Some are pan-JAK inhibitors (gandotinib, XL019, NVP-BSK805, peficitinib, and pyridone 6). Less frequently, they target only JAK2 (NS-018, pacritinib, CEP-33779, NVP-BVB808, TG101209, fedratinib, and AZD960), JAK1 (filgotinib and itacitinib), or JAK3 (decernotinib, janex1, and JAK3-IN-1). However, they also target other kinases, in particular FLT3 (pacritinib, NVP-BVB808, TG101209, and fedratinib), Src (NS018), or Aurora A (AZD1480) (Table 1 and Figure 3B).

The differences in specificities for JAK are the basis for the different trials: JAK2 specificity for MPNs and certain malignant disorders^{65,66} and JAK1 and JAK3 for inflammation and auto-immune diseases⁶⁷. The clinical toxicity can be related to the precise JAK protein that is inhibited—hematological toxicity, eventually immune suppression for JAK2⁶⁶,—immune suppression and long-term effects on hematopoietic stem cells (HSCs) for JAK1 and JAK3⁶⁸. It can be also due to an off-target inhibition. It has been suggested that the gastrointestinal toxicity was related to FLT3 inhibition⁶⁹ and the Wernicke encephalitis observed in rare patients treated with fedratinib to inhibition of thiamine uptake⁷⁰.

Currently, only three JAK inhibitors are US Food and Drug Administration (FDA) or European Medicines Agency (EMA)-approved for treatment: ruxolitinib for the treatment of MF and hydroxyurea (HU)-resistant or -intolerant PVs⁶⁵, tofacitinib and Baricitinib for the treatment of methotrexate-resistant RA⁷¹.

The major limitation of type I inhibitors that bind to active state kinases is that while they block catalysis they allow increased phosphorylation of the activation loop on Y1007, which upon overexpression of JAK2 or other JAKs can create heteromeric JAK complexes that re-set signaling⁷². This might explain why resistance to JAK2 inhibition is not related to mutations but to functional inhibition⁷³.

Type II inhibitors

The type II inhibitors bind to the ATP-binding pocket of kinase domains in inactive conformation, and the F of the DFG pocket is in an out conformation (Figure 3C)^{64,74}. Inhibition is more efficient and is not reversed by drug detachment¹⁴. The best example is imatinib and the second generation of BCR-ABL inhibitors⁷⁴. Two type II JAK2 inhibitors (NVP-BBT594 and NVP-CHZ868) have been developed. NVP-CHZ868 has been used in preclinical models and was very effective^{75,76}. Both inhibitors were not amenable for drug development. Owing to their powerful activity, the type II JAK2 inhibitors present the

Table 1. JAK inhibitors, their targets, and their applications to pathologies.

Inhibitors	Selectivity	Off-target	Diseases	Clinical phases
Type I				
Ruxolitinib	JAK2>JAK1>JAK3		MF and hydroxyurea resistant or intolerant PV Refractory leukemia (post-MPN leukemia) Pancreatic cancers Corticosteroid refractory-GVHD Psoriasis Alopecia Vitiligo	FDA-approved ⁷⁷⁻⁷⁹ Phase 2 ⁸⁰ Phase 2 in combination with capecitabine (after gemcitabine failure) ⁸¹ In evaluation ⁸² Phase 2 ⁸³ Open-label clinical trial ⁸⁴ Case report ⁸⁵
Momelotinib (CYT-387)	JAK2>JAK1>JAK3	ALK-2 TBK1 IKKε	PMF Post PV/ET MF PV/ET	Phase 3 - SIMPLIFY-1/2 (Stopped) ⁸⁶ Phase 2 (terminated) ⁸⁷
AZD1480	JAK2>JAK1	Aurora A FGFR1 FLT4	PMF Post PV/ET MF B-ALL Solid tumors	Phase 1 (completed) ⁸⁸ In evaluation (preclinic) ⁸⁹ Phase 1 (terminated) ⁹⁰
Baricitinib (INCB-028050)	JAK2>JAK1		Rheumatoid arthritis Psoriasis	Phase 3 (FDA approval in process, EMA-approved) ⁹¹ Phase 2 ⁹²
Tofacitinib	JAK1>JAK3		Methotrexate-resistant rheumatoid arthritis Crohn's Psoriasis Alopecia areata Dermatomyositis, vitiligo	FDA-approved ⁹³ Phase 2 ⁹⁴ Phase 3 ⁹⁵ Phase 2 ⁹⁶ Case report ⁹⁶
Gandotinib (LY2784544)	Pan-JAK JAK2V617F>JAK2		JAK2V617F-positive MF, ET and PV patients	Phase 1 ⁹⁷ Phase 2 (in progress)
XL019	Pan-JAK		PV, MF	Phase 1 (terminated) ⁹⁸
NVP-BSK805	JAK2		JAK2V617F	Cellular models ⁹⁹
NS-018	JAK2V617F>JAK2	Src	PMF, post PV/ET MF patients JAK2V617F selective	Phase 2 ¹² In vitro ¹⁰⁰
Pacritinib (SB11518)	JAK2	FLT3	MF	Phase 3 PERSIST-1 ¹⁰¹ , PERSIST-2 ¹⁰² PAC203 study evaluating the effect of lower doses
CEP-33779	JAK2		Rheumatoid arthritis, colorectal cancer, lupus nephritis	Preclinical mouse models ¹⁰³
NVP-BVB808	JAK2	FLT3	MPN	Cell lines ¹⁰⁴
TG101209	JAK2	FLT3	MPN, systemic sclerosis	Cellular models ¹⁰⁵

Inhibitors	Selectivity	Off-target	Diseases	Clinical phases
Fedratinib (TG101348)	JAK2	FLT3 BRD4	MF	Phase 3 JAKARTA ¹⁰⁶ FDA removed the clinical hold in August 2017
AZ960	JAK2		ATL, other leukemia	Cell lines
Filgotinib (GLPG0634)	JAK1>JAK2		Rheumatoid arthritis Bowel and Crohn's diseases Lupus and psoriasis	Phase 3 ¹⁰⁷ Phase 2 ¹⁰⁸ Phase 2 ¹⁰⁹
Itacitinib (INCB-039110)	JAK1		MF Psoriasis Non-small cell lung cancer GVHD B-cell lymphoma BRAF-mutant melanoma and other solid tumors	Phase 2 (alone or in combination with low-dose of ruxolitinib) ¹¹⁰ Phase 2 ¹¹¹ Phase 2 (combination with EGFR inhibitor, osimertinib) (in progress) Phase 3 (combination with corticosteroids) (in progress) Phase 1/2 (combination with BTK inhibitor, ibrutinib) (in progress) Phase 1 (in combination with MAPK inhibitors, dabrafenib or trametinib) (in progress)
INCB52793	JAK1		Advanced malignancies	Phase 1 (in progress)
PF-04965842	JAK1		Moderate to severe psoriasis	Phase 2 ¹¹²
Upadacitinib (ABT-494)	JAK1		Rheumatoid arthritis	Phase 2 ¹¹³ Phase 3 (in progress)
Decernotinib (VX-509)	JAK3		Rheumatoid arthritis	Phase 2/3 ¹¹⁴
WHI-P131/ JANEX-1	JAK3		GVHD	Preclinical mouse model ¹¹⁵
JAK3-IN-1	JAK3		N/A	N/A
Peficitinib (ASP015K)	JAK3		Psoriasis Rheumatoid arthritis	Phase 2 ¹¹⁶ Phase 2 ¹¹⁷
Type II				
NVP-BBT594	JAK2	BCR-ABL KDR FLT3 RET		Cellular models ¹⁴
NVP-CHZ868	JAK2	KIT, PDGFR VEGFR	MPN B-ALL	Preclinical mouse models ⁷⁵
Allosteric inhibitors				
LS104	JAK2	BCR-ABL	MPN	JAK2V617F cell lines ¹¹⁸
ON044580	JAK2	BCR-ABL	MPN	BCR-ABL cell lines ¹¹⁹

ATL, adult T-cell leukemia; B-ALL, B-cell acute lymphoblastic leukemia; BTK, Bruton's tyrosine kinase; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; ET, essential thrombocythemia; FDA, US Food and Drug Administration; GVHD, graft-versus-host disease; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; MF, myelofibrosis; MPN, myeloproliferative neoplasm; N/A, not applicable; PMF, primary myelofibrosis; PV, polycythemia vera.

risk of inducing profound cytopenia, limiting its future use in PV or ET.

Allosteric inhibitors

Allosteric inhibitors are molecules that do not bind to the active kinase site but to another site⁶⁴. Theoretically, they would be more specific than an ATP-pocket inhibitor given the high homology of ATP-binding sites. Allosteric inhibition could be interesting to specifically target only the mutated JAKs (*JAK2V617F*: 60–70% of MPNs and *JAK2* exon 12: 1%) as *JAK2WT* is indispensable for normal hematopoiesis. An efficient *JAK2WT* inhibition will always lead to a cytopenia.

Within allosteric inhibitors, type III bind to a site close to the ATP-binding site while type IV bind to an allosteric site distant from the ATP-binding site. This means that in the case of *JAK2V617F* it might be important to target the pseudokinase domain (type IV inhibitors, see last section). To our knowledge, there is currently no allosteric inhibitor of *JAK2V617F* in development.

Other types of inhibitors

For kinases other than JAKs, additional types of inhibitors have been developed⁶⁴:

Type V. Such inhibitors reversibly bind to two sites of the kinase domain.

Covalent. They irreversibly bind on a nucleophilic residue (usually a cysteine) located in the ATP-binding site.

JAK inhibitor therapies

BCR-ABL –negative MPNs

Triggered by the discovery of *JAK2V617F*, *JAK2* inhibitors have been developed, but none of them is specific to the mutant protein and most of them also target other kinases such as *JAK1* and *FLT3*. One advantage is that their use can be extended to the *JAK2V617F*-negative MPNs or other pathologies associated with *JAK2* activation that include inflammatory diseases and certain other cancers. Theoretically, it is not conceivable to completely inhibit *JAK2* in the long term, because this will lead to a profound cytopenia and eventually aplastic anemia. Thus, these inhibitors can be used because they only partially inhibit *JAK2* *in vivo* for different reasons (pharmacokinetics and resistance). This explains why such inhibitors give similar clinical results in MF's improving quality of life, decreasing the splenomegaly, and improving survival. The evolution of the disease is not changed, nor apparently is the rate of MPN transformation. The differences between inhibitors concern the side effects that may essentially be related to distinct off-targets (Table 1).

Ruxolitinib. Ruxolitinib (Figure 3B and D) was the first *JAK2* inhibitor approved for therapy of MF (high and intermediate risks). It is now the only *JAK* inhibitor for which a long-term follow-up has been reached. In intermediate-2 and high-risk MF, a very significant effect is found in more than 50% of the patients with a reduced spleen size (clinical trials COMFORT-1 and COMFORT-2) at any point in the trial and even a more marked

effect on the general symptoms, in particular the pruritus^{77–79}. These results have been extended to low- and intermediate-1 risk MF¹²⁰. In HU-refractory PVs, ruxolitinib allows the control of hematocrit in more than 60% of patients and induces a spleen volume reduction in 38% of cases at 32 weeks. In addition, a molecular decrease of *JAK2V617F* allele burden reaching a mean of 40% at 208 weeks was observed^{78,121}. In HU-resistant or -intolerant ET, there are divergent results. In one study, ruxolitinib offered no advantage compared with other therapies in the control of the thrombocytosis and disease complications but did alleviate general symptoms and pruritus¹²². In the other¹²³, which was an open-label phase 2 trial, ruxolitinib induced a meaningful reduction in platelet levels and attenuated ET-related symptoms. These preliminary results seemed superior to historically observed results, but this study was done in the absence of a comparison with another treatment.

Overall, ruxolitinib is a well-tolerated oral treatment with approximately 25–33% of adverse effects. The main toxicities are hematological, moderate anemia that may correct with time, and thrombocytopenia, which can be very severe in high-risk MF. Weight gain is also observed with possible abnormalities in lipid metabolism. Middle-term toxicity is an immune suppression that may be responsible for reactivation of viral infections, particularly herpes zoster and HIV1 and bacterial infections such as pneumonia, tuberculosis reactivation and urinary tract infections^{124,125}. Long-term monitoring will be important because ruxolitinib decreases natural killer cell functions with a potential risk of solid tumor and lymphoma development^{126,127}. This is particularly important if indications are extended to low-risk MF, PV, and ET. Analysis of patients treated for several years with ruxolitinib indicates an increase in survival in MF, but progression to leukemia is not significantly different¹²⁸. It is possible that most pro-survival effects derive from its palliative anti-inflammatory effects⁶⁵.

Other *JAK2* inhibitors. Momelotinib (CYT38) (Figure 3D) is a *JAK1/JAK2* inhibitor that has shown activity resembling ruxolitinib with respect to spleen size reduction and constitutional symptom alleviation^{129–131}. Importantly, momelotinib was shown to ameliorate anemia, which is a major concern in MF. The mechanism appears to be the reduction of hepcidin production through a direct inhibition of the activin receptor-like kinase-2 (ALK-2)¹³². Thus, momelotinib was thought to be an alternative to ruxolitinib for patients with anemia. These promising results led to the opening of a phase III trial for the SIMPLIFY-1 and -2 studies in MF. However, the results of the two clinical trials did not show a major advantage of momelotinib on ruxolitinib, although momelotinib was associated with a decrease in transfusion requirement⁸⁶. Momelotinib development has been stopped.

NS-018 (Figure 3D) is a *JAK2/Src* inhibitor that has been assessed in patients with *JAK2V617F*-positive MF, ET, and PV. NS-018 shows an apparent increased potency for the *JAK2V617F* mutant in mouse models, possibly leading to less immunosuppressive effects¹⁰⁰. It was tested in MF with symptom improvement but minor impact on the numbers of *JAK2V617F* cells¹³³. Gandotinib (LY2784544) (Figure 3D) is a potent *JAK2* inhibitor, which

also exhibits a certain selectivity toward JAK2V617F. It was evaluated for safety and tolerability in ET, PV, and MF⁹⁷.

Pacritinib (SB1518) (Figure 3D) is a JAK2/FLT3 inhibitor. Promising results were obtained in phase 1–2 clinical trials. It showed good activity in patients with less immunosuppressive effects¹³⁴. Pacritinib could be administered to patients with low platelet levels, as it does not induce thrombocytopenia. The reasons behind this feature are unclear; they could be linked to reduced specificity for MPL/JAK2 complexes. Subsequently, two phase 3 clinical trials (PERSIST 1 and 2) were started with different doses of pacritinib. In 2016, the FDA put a complete clinical hold on the trials because of an excess of intracranial hemorrhage and cardiac failure in treated patients¹³⁵. This hold was lifted in 2017¹³⁶. As a consequence, CTI BioPharma has just launched the PAC203 study evaluating the effect of pacritinib at different doses.

Fedratinib (TG101348) (Figure 3D) was assessed during the JAKARTA trials with interesting clinical results, including fibrosis reduction^{137–139}, but rare patients developed Wernicke encephalopathy, which led to its stop¹³⁹. It was assumed that it was related to an inhibition of thiamine uptake, although fedratinib does not lead to inhibition of thiamine uptake in rats^{70,140}. FDA removed the clinical hold in august 2017 and clinical trials are being planned in 2018.

JAK1 inhibition has also been proposed in MPNs, as an anti-inflammatory strategy, and an alternative to JAK2 inhibitors to avoid anemia and thrombocytopenia^{65,66}. A preliminary study has produced mixed results with a modest reduction in spleen size¹¹⁰. Recently, it has been demonstrated that JAK1 plays essential and non-redundant roles at the level of HSC and therefore long-term JAK1 inhibition might have negative effects on HSCs⁶⁸.

Other malignant disorders

Ruxolitinib was also used in refractory leukemia, including post-MPN leukemia, and 3 out of 18 patients achieved complete remission⁸⁰. Ruxolitinib was unexpectedly used in combination with chemotherapeutic agents in solid cancers (pancreatic and lung cancer) and there was some benefit¹⁴¹. This was based on JAK1 involvement in the signaling of several cytokine receptors, inflammation, and possibly progression of the malignant clone^{81,142}.

Ruxolitinib has been used both in myeloid malignancies with JAK2 fusion proteins and in CNL with a very good initial response but was inefficient to cure the diseases^{143–146}.

Itacitinib (INCB39110), which is also a selective JAK1 inhibitor, is being tested in non-small cell lung cancer in combination with an epidermal growth factor receptor inhibitor. Another JAK1 inhibitor, INCB52793, is also in development in advanced malignancies.

Inflammatory and autoimmune diseases

JAK1 inhibitors have been used in inflammatory/immune diseases^{67,147}. Tofacitinib was authorized by the FDA in RA¹⁴⁸ but is currently being tested in Crohn's disease, psoriasis, and other

diseases^{149,150}. It decreases inflammation particularly by lowering T-cell and macrophage infiltrates. Filgotinib is currently in phase 3 clinical trials in RA and Crohn's disease and in phase 2 clinical trials in lupus and psoriasis. Itacitinib (INCB39110) is being tested in phase 2 trials in psoriasis and in MF with meaningful improvements.

Ruxolitinib, also a good inhibitor of JAK1, was shown to reduce GVHD in mice and in patients with corticosteroid-refractory GVHD^{82,151}. Indeed, in GVHD, severe complications are due to high levels of proinflammatory cytokines that are inhibited by ruxolitinib. Itacitinib will be assessed as monotherapy in GVHD.

A JAK1 inhibitor, PF-04965842, is also in clinical trials in atopic dermatitis and severe psoriasis¹¹². Both topical tofacitinib and ruxolitinib are tested for alopecia and vitiligo.

Baricitinib (Olumiant), a JAK1/2 inhibitor (half maximal inhibitory concentration [IC_{50}] values of 5.9 and 5.7 nM, respectively), has been initially identified by Incyte and subsequently developed by Eli Lilly and Company for RA. It also inhibits TYK2 (IC_{50} of around 53 nM). A phase 3 clinical trial was conducted, and the molecule was approved by the EMA but not yet by the FDA^{148,152}. It may be of interest in MPN treatment given its similarities with ruxolitinib but with a longer half-life (12.5 hours). Upadacitinib (ABT-494, AbbVie) is a highly selective JAK1 inhibitor that will enter phase 3 trials for RA, psoriasis, and ulcerative colitis.

Two JAK3 inhibitors were evaluated. ASP015K, also designated JNJ-54781532, displays a moderate selectivity on JAK3 over JAK1 and JAK2. It was shown to induce efficacy and safety in psoriasis¹¹⁶. It has demonstrated efficacy in preclinical models of RA and dermatitis. Decernolitinib is also a potent and selective inhibitor of JAK3 developed as a second-generation inhibitor in autoimmune diseases, particularly in RA. However, at high doses, it leads to anemia, indicating that its selectivity *in vivo* could be different¹⁵³. In MPNs, these types of inhibitors could also be useful to decrease inflammation, especially in MF.

The major drawback of these JAK1 and JAK3 inhibitors affecting the inflammatory response is that they can induce autoimmune diseases (thyroiditis or myocarditis) or can prime the development of many infections in patients with MPN. Furthermore, it appears that for the IL-2/IL-4/IL-7/IL-9/IL-15/IL-21 complexes, JAK1 is the initiating kinase for signaling, and a JAK3 that is inhibited can still fulfill its scaffolding role in the complex, its inhibition not giving results comparable to the absence of JAK3 by autosomal mutation¹⁵⁴.

Perspectives in JAK inhibition

The goal of JAK2 inhibition in MPNs has switched from a curative therapy to a symptomatic and anti-inflammatory therapy with certain clinical benefits⁶⁵. However, this aim is far from what is expected for a targeted therapy⁶⁹. Although several *in vitro* studies identified potential kinase domain mutations that would give resistance to JAK2 inhibitors^{155,156}, no such mutations were identified in patients⁷², further arguing that the current inhibitors are weak. Thus, there is a need for new inhibitors or combination of therapies.

New inhibitors

First, a new generation of JAK2-specific compounds, including allosteric inhibitors targeting unique sequences in JAK2, should come to light. Such inhibitors would provide more specificity toward JAK2 or JAK2V617F, thereby ameliorating normal JAK2 inhibition-based immune suppression. Two inhibitors have been developed (LS104 and ON044580) that inhibit kinase activities in a non-ATP-competitive manner^{118,119}. LS104 preferentially inhibits JAK2V617F kinase and can synergize with ATP-competitive inhibitors¹¹⁸, whereas ON044580 inhibits BCR-ABL and its T315I mutant¹¹⁹. The precise targeted residues remain unknown.

Identification of allosteric sites in enzymes has been accomplished for several years and is the basis for the development of a new class of pharmaceuticals. One example is the development

of the BCR-ABL allosteric inhibitor GNF-2 that can overcome the effect of resistant mutations and also exhibits an increased potency when used in combination with classic ATP-competitive inhibitors¹⁵⁷. Another example is the development of MEK allosteric inhibitors. It was shown that analogues of PD184352 could specifically bind to a unique region adjacent to the ATP pocket created by the displacement of the helix α C of the kinase in the active conformation¹⁵⁸.

As the main conformational difference between JAK2V617F and JAK2WT is around the helix α C of the pseudokinase JH2 domain¹⁵⁹, a rational design of similar molecules targeting this region could be efficient (Figure 4). Recent structural and mechanistic data on JH2 V617F might help in designing such small molecules. Moreover, targeting JH2 might become feasible as shown by the recent publication of co-crystals of JH2

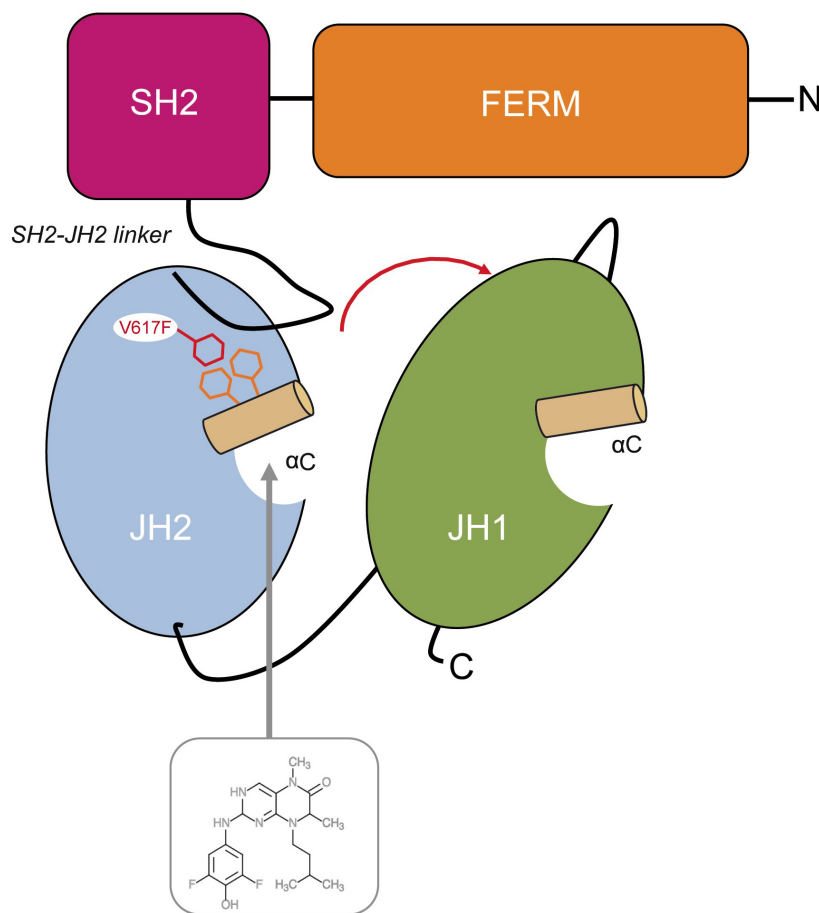


Figure 4. Graphic representation of the V617F-activation mechanism in Janus kinase2 (JAK2). The V617F activation has been suggested to derive from a combination of several molecular events triggered from a region surrounding the JH2 α C but also involving the SH2-JH2 linker. Phenylalanine 617 interacts with F594 and F595 from the JH2 α C and F537 from the SH2-JH2 linker, as supported by structural data^{9,159}, then induces putative conformational changes that are transmitted to the adjacent catalytic kinase domain where activation is initiated. Targeting the ATP-binding pocket of JH2 that is spatially close the α C represents an appealing approach for specific targeting of the mutant JAK2V617F. Small molecules, such as BI-D1870 (as represented here¹⁶⁰), have been co-crystallized as bound to the JH2 ATP-binding site. The use of amendable compounds targeting the JH2 pocket has recently become a tantalizing concept and will represent the future challenge for drug design.

with several compounds. Future therapeutics should target small conformational changes that are specific for a particular mutant protein or its constitutive activity.

The activating mutation, *JAK2V617F*, is located in the pseudokinase domain of JAK2 and allosterically regulates the activity of JAK2 kinase domain. Another strategy would be to interrupt these specific intramolecular changes induced by V617F on the kinase domain of JAK2. The aromatic phenylalanine at position 617 interacts with the α C helix phenylalanines 594 and 595¹⁶¹ and with phenylalanine 537 from the SH2-JH2 linker⁹ to produce an autonomous activation to the adjacent catalytically active domain, JH1 (Figure 4). Both of these aberrant hydrophobic contacts induce critical conformational changes that can be visualized on the JH2 V617F crystal structures^{9,159}. Any small molecules that would interfere with these specific atomic configurations exclusively present in the conformation of *JAK2V617F* would most likely generate mutant-specific inhibitors. Evidence was provided that V617F activates JAK2 through a community of residues across JAK2 (from JH2 to JH1 through the SH2-JH2 linker) and that reversing the charge of the negative residue, E596, located on the solvent-exposed face of the JH2 α C helix, can efficiently uncouple *JAK2V617F* activation from cytokine-induced activation, thereby restoring auto-inhibition of JAK2.

Finally, methotrexate, a well-known drug used in autoimmune disease was shown to also inhibit the JAK/STAT pathway and in theory could be tested for selective effects on the MPN clones¹⁶². An advantage of this treatment is its low cost, while its side effects are well known.

Combination of therapies

The goal of certain combinations is to improve the anemia of MF, which can be worsened by ruxolitinib⁶⁵. Trials have been performed in combination with androgen without benefit. Trials are ongoing with pomalidomide or thalidomide and also with sotatercept, an activin receptor IIa ligand trap¹⁶³. Treatment with erythropoiesis-stimulating agents is also conceivable, although they are theoretically antagonistic with JAK2 inhibitors¹⁶⁴.

Downstream JAK2 are activations of STATs, PI3K-AKT/mTOR, and RAS-MAPK ERK1/2 (Figure 2)¹⁶⁵. Specific inhibitors of STAT5 and STAT3 are now being tested in preclinical studies¹⁶⁶. A combination of JAK2 and STAT5 inhibitors might be effective in MPNs. In preclinical models, JAK2 and pan type I PI3K and mTOR inhibitors synergize to block *JAK2V617F*-induced proliferation^{167,168} but less on mutant CALR-induced proliferation¹⁸. Other molecules involved in the inhibition of the PI3K, AKT, or mTOR pathway were tested in preclinical models or clinical trials.

The HSP90 chaperone is involved in JAK2 stability and is controlled via its acetylation status¹⁶⁹. HSP90 inhibitors or histone deacetylase inhibitors were tested¹⁶⁹. Notably, panobinostat and pracinostat were studied in combination with ruxolitinib in

a phase 2 trial with a better spleen response in MF¹⁷⁰. Furthermore, a preliminary trial using an HSP90 inhibitor showed some clinical benefit¹⁷¹. Combinations of ruxolitinib with CDK4/6 inhibitors, PIM1 kinase inhibitors, BH3 mimetics, or MDM2 inhibitors appear logical because they target molecules, which are downstream of JAK2 signaling, thus curbing any residual activation due to incomplete JAK2 inhibition due to short half-life of inhibitor and type I inhibition mechanism that allows rapid reactivation. Intriguingly, it has been reported that an association of ruxolitinib with pegylated interferon alpha was synergistic in a preliminary clinical trial, and a new larger clinical trial is ongoing¹⁷². Normally, a JAK1 inhibitor should decrease interferon alpha signaling and should limit the effects of pegylated interferon; thus, the synergy might reflect how inefficiently ruxolitinib can actually inhibit JAKs *in vivo*. The main risk of all these different associations is to induce important cytopenia.

In MF, it has also been suggested to combine ruxolitinib with MEK inhibitors and PRM-151, a molecule that inhibits differentiation of fibrocytes¹⁷³, which are implicated in fibrosis development¹⁷⁴. Both drugs exhibit an effect on bone marrow fibrosis in preclinical studies or in clinical trials¹⁷⁵. An inhibitor of hedgehog signaling pathway (LDE225) was also tested in phase I in ET/PV and MF with disappointing results¹⁷⁶. However, recent evidence points to targeting Gli1 in association with ruxolitinib because Gli1⁺ mesenchymal cells may play a central role in fibrosis development¹⁷⁷.

JAK2V617F can increase the protein methylation demonstrated by activation of PRMT5 arginine methyltransferase¹⁷⁸. It also prevents the binding of heterochromatin factor HP1 to chromatin¹⁷⁹. It is possible that some key genes could be hypermethylated as in many cancers. Therefore, it was postulated that demethylating agents such azacytidine and decitabine may have some impact. However, administered alone, they showed minor responses in two clinical trials^{180,181}. They were thus combined with ruxolitinib in a few patients with MF and the clinical response was good.

Conclusions

After the discovery of *JAK2V617F* and the demonstration that *BCR-ABL*-negative MPNs are driven by abnormal JAK2 activation, there were curative expectations for JAK inhibitors. Despite nearly 10 years of development in MPNs, only one JAK2 inhibitor (ruxolitinib) has been clinically approved. Most other inhibitors had their development stopped because of neurotoxicity or the absence of superiority compared with ruxolitinib. Only pacritinib (Figure 3B) is still in phase 3 clinical testing and fedratinib is being reevaluated. Although ruxolitinib offers clear benefits for patients, its effects are quite limited on the disease itself in MF. On one hand, this may be explained by the additional mutations detected by MF clones, which act independently from JAK2 and which place MF at the boundary between MPN and MDS. On the other hand, ruxolitinib has a short half-life and acts as a type I inhibitor, which means that each time inhibitor is consumed, re-activation of JAK2 will occur.

Thus, it seems important in PV and ET, which are JAK2-dependent MPNs, to obtain specific inhibitors of JAK2V617F or even to preferentially target the constitutive active JAK2 over cytokine-activated JAK2 in the cases of mutated *MPL* and *CALR* ET and MF. It is expected that such inhibitors will be less toxic and will really target the clonal disease. In MF, the low-hanging fruit of combination therapies could be a valuable approach that holds a risk for significant toxicities.

An important finding of the clinical trials in MPNs was the discovery that JAK inhibition is a valuable approach for treatment of inflammatory diseases. Thus, it can be expected that one of the main applications of JAK inhibitors will be for inflammatory diseases, autoimmune diseases, and possibly other diseases, which may include an inflammatory response, including neurodegenerative disorders or cancers where inflammation contributes to oncogenesis.

Competing interests

The author(s) declared that they have no competing interests.

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References



- Ihle JN: **The Janus protein tyrosine kinases in hematopoietic cytokine signaling.** *Semin Immunol.* 1995; 7(4): 247–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Constantinescu SN, Ghaffari S, Lodish HF: **The Erythropoietin Receptor: Structure, Activation and Intracellular Signal Transduction.** *Trends Endocrinol Metab.* 1999; 10(1): 18–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Vainchenker W, Constantinescu SN: **JAK/STAT signaling in hematological malignancies.** *Oncogene.* 2013; 32(21): 2601–13.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Rampal R, Al-Shahrour F, Abdel-Wahab O, et al.: **Integrated genomic analysis illustrates the central role of JAK-STAT pathway activation in myeloproliferative neoplasm pathogenesis.** *Blood.* 2014; 123(22): e123–33.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Vainchenker W, Constantinescu SN, Plo I: **Recent advances in understanding myelofibrosis and essential thrombocythemia [version 1; referees: 2 approved].** *F1000Res.* 2016; 5: pii: F1000 Faculty Rev-700.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Huang LJ, Constantinescu SN, Lodish HF: **The N-terminal domain of Janus kinase 2 is required for Golgi processing and cell surface expression of erythropoietin receptor.** *Mol Cell.* 2001; 8(6): 1327–38.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Ferrao R, Lupardus PJ: **The Janus Kinase (JAK) FERM and SH2 Domains: Bringing Specificity to JAK-Receptor Interactions.** *Front Endocrinol (Lausanne).* 2017; 8: 71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Leroy E, Dusa A, Colau D, et al.: **Uncoupling JAK2 V617F activation from cytokine-induced signalling by modulation of JH2 α C helix.** *Biochem J.* 2016; 473(11): 1579–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Toms AV, Deshpande A, McNally R, et al.: **Structure of a pseudokinase-domain switch that controls oncogenic activation of Jak kinases.** *Nat Struct Mol Biol.* 2013; 20(10): 1221–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Silvennoinen O, Ungureanu D, Niranjani Y, et al.: **New insights into the structure and function of the pseudokinase domain in JAK2.** *Biochem Soc Trans.* 2013; 41(4): 1002–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Royer Y, Staerk J, Costuleanu M, et al.: **Janus kinases affect thrombopoietin receptor cell surface localization and stability.** *J Biol Chem.* 2005; 280(29): 27251–61.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Verstovsek S, Talpaz M, Ritchie EK, et al.: **Phase 1/2 Study of NS-018, an Oral JAK2 Inhibitor, in Patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera Myelofibrosis (postPV MF), or Post-Essential Thrombocythemia Myelofibrosis (postET MF).** *Blood, 58th Annual Meeting and Exposition of the American Society of Hematology, San Diego, CA.* 2016; 128(22): 1936.
[Reference Source](#)
- Duan Y, Chen L, Chen Y, et al.: **c-Src binds to the cancer drug Ruxolitinib with an active conformation.** *PLoS One.* 2014; 9(9): e106225.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Andraos R, Qian Z, Bonenfant D, et al.: **Modulation of activation-loop phosphorylation by JAK inhibitors is binding mode dependent.** *Cancer Discov.* 2012; 2(6): 512–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Vainchenker W, Kralovics R: **Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms.** *Blood.* 2017; 129(6): 667–79.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Klampfl T, Gisslinger H, Harutyunyan AS, et al.: **Somatic mutations of calreticulin in myeloproliferative neoplasms.** *N Engl J Med.* 2013; 369(25): 2379–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Nangalia J, Massie CE, Baxter EJ, et al.: **Somatic CALR mutations in myeloproliferative neoplasms with nonmutated JAK2.** *N Engl J Med.* 2013; 369(25): 2391–405.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
- Chachoua I, Pecquet C, El-Khoury M, et al.: **Thrombopoietin receptor activation by myeloproliferative neoplasm associated calreticulin mutants.** *Blood.* 2016; 127(10): 1325–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Marty C, Pecquet C, Nivarthi H, et al.: **Calreticulin mutants in mice induce an MPL-dependent thrombocytosis with frequent progression to myelofibrosis.** *Blood.* 2016; 127(10): 1317–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Elf S, Abdelfattah NS, Chen E, et al.: **Mutant Calreticulin Requires Both Its Mutant C-terminus and the Thrombopoietin Receptor for Oncogenic Transformation.** *Cancer Discov.* 2016; 6(4): 368–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Araki M, Yang Y, Masubuchi N, et al.: **Activation of the thrombopoietin receptor by mutant calreticulin in CALR-mutant myeloproliferative neoplasms.** *Blood.* 2016; 127(10): 1307–16.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
- Lu X, Huang LJ, Lodish HF: **Dimerization by a cytokine receptor is necessary for constitutive activation of JAK2V617F.** *J Biol Chem.* 2008; 283(9): 5258–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Oh ST, Simonds EF, Jones C, et al.: **Novel mutations in the inhibitory adaptor protein LNK drive JAK-STAT signaling in patients with myeloproliferative neoplasms.** *Blood.* 2010; 116(6): 988–92.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Lasho TL, Pardanani A, Tefferi A: **LNK mutations in JAK2 mutation-negative**

- erythrocytosis. *N Engl J Med*. 2010; **363**(12): 1189–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. **F** Rumi E, Harutyunyan AS, Pietra D, *et al.*: **LNK mutations in familial myeloproliferative neoplasms**. *Blood*. 2016; **128**(1): 144–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 26. Nangalia J, Griffin J, Green AR: **Pathogenesis of Myeloproliferative Disorders**. *Annu Rev Pathol*. 2016; **11**: 101–26.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Viny AD, Levine RL: **Genetics of myeloproliferative neoplasms**. *Cancer J*. 2014; **20**(1): 61–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 28. **F** Delhommeau F, Dupont S, Della Valle V, *et al.*: **Mutation in TET2 in myeloid cancers**. *N Engl J Med*. 2009; **360**(22): 2289–301.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 29. Saint-Martin C, Leroy G, Delhommeau F, *et al.*: **Analysis of the ten-eleven translocation 2 (TET2) gene in familial myeloproliferative neoplasms**. *Blood*. 2009; **114**(8): 1628–32.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. **F** Ortmann CA, Kent DG, Nangalia J, *et al.*: **Effect of mutation order on myeloproliferative neoplasms**. *N Engl J Med*. 2015; **372**(7): 601–12.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 31. **F** Shimizu T, Kubovcakova L, Nienhold R, *et al.*: **Loss of Ezh2 synergizes with JAK2-V617F in initiating myeloproliferative neoplasms and promoting myelofibrosis**. *J Exp Med*. 2016; **213**(8): 1479–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 32. Guglielmelli P, Lasho TL, Rotunno G, *et al.*: **The number of prognostically detrimental mutations and prognosis in primary myelofibrosis: an international study of 797 patients**. *Leukemia*. 2014; **28**(9): 1804–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. Tefferi A, Vannucchi AM: **Genetic Risk Assessment in Myeloproliferative Neoplasms**. *Mayo Clin Proc*. 2017; **92**(8): 1283–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 34. Griesinger F, Hennig H, Hillmer F, *et al.*: **A BCR-JAK2 fusion gene as the result of a t(9;22)(p24;q11.2) translocation in a patient with a clinically typical chronic myeloid leukemia**. *Genes Chromosomes Cancer*. 2005; **44**(3): 329–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
 35. Mark HF, Sotomayor EA, Nelson M, *et al.*: **Chronic idiopathic myelofibrosis (CIMF) resulting from a unique 3;9 translocation disrupting the janus kinase 2 (JAK2) gene**. *Exp Mol Pathol*. 2006; **81**(3): 217–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
 36. Peeters P, Raynaud SD, Cools J, *et al.*: **Fusion of TEL the ETS-variant gene 6 (ETV6), to the receptor-associated kinase JAK2 as a result of t(9;12) in a lymphoid and t(9;15;12) in a myeloid leukemia**. *Blood*. 1997; **90**(7): 2535–40.
[PubMed Abstract](#)
 37. Reiter A, Walz C, Watmore A, *et al.*: **The t(8;9)(p22;p24) is a recurrent abnormality in chronic and acute leukemia that fuses PCM1 to JAK2**. *Cancer Res*. 2005; **65**(7): 2662–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
 38. Maxson JE, Gotlib J, Pollyea DA, *et al.*: **Oncogenic CSF3R mutations in chronic neutrophilic leukemia and atypical CML**. *N Engl J Med*. 2013; **368**(19): 1781–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 39. Patnaik MM, Tefferi A: **Refractory anemia with ring sideroblasts (RARS) and RARS with thrombocytosis (RARS-T): 2017 update on diagnosis, risk-stratification, and management**. *Am J Hematol*. 2017; **92**(3): 297–310.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 40. Yoshida K, Toki T, Okuno Y, *et al.*: **The landscape of somatic mutations in Down syndrome-related myeloid disorders**. *Nat Genet*. 2013; **45**(11): 1293–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 41. Malinge S, Ragu C, Della-Valle V, *et al.*: **Activating mutations in human acute megakaryoblastic leukemia**. *Blood*. 2008; **112**(10): 4220–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 42. Mullighan CG: **The molecular genetic makeup of acute lymphoblastic leukemia**. *Hematology Am Soc Hematol Educ Program*. 2012; **2012**: 389–96.
[PubMed Abstract](#)
 43. Mullighan CG, Collins-Underwood JR, Phillips LA, *et al.*: **Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia**. *Nat Genet*. 2009; **41**(11): 1243–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 44. **F** Mullighan CG, Zhang J, Harvey RC, *et al.*: **JAK mutations in high-risk childhood acute lymphoblastic leukemia**. *Proc Natl Acad Sci U S A*. 2009; **106**(23): 9414–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 45. Malinge S, Ben-Abdelali R, Settegrana C, *et al.*: **Novel activating JAK2 mutation in a patient with Down syndrome and B-cell precursor acute lymphoblastic leukemia**. *Blood*. 2007; **109**(5): 2202–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
 46. Flex E, Petrangeli V, Stella L, *et al.*: **Somatically acquired JAK1 mutations in adult acute lymphoblastic leukemia**. *J Exp Med*. 2008; **205**(4): 751–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 47. Hornakova T, Staerk J, Royer Y, *et al.*: **Acute lymphoblastic leukemia-associated JAK1 mutants activate the Janus kinase/STAT pathway via interleukin-9 receptor alpha homodimers**. *J Biol Chem*. 2009; **284**(11): 6773–81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 48. Tasian SK, Loh ML: **Understanding the biology of CRLF2-overexpressing acute lymphoblastic leukemia**. *Crit Rev Oncog*. 2011; **16**(1–2): 13–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 49. Hertzberg L, Vendramini E, Ganmore I, *et al.*: **Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group**. *Blood*. 2010; **115**(5): 1006–17.
[PubMed Abstract](#) | [Publisher Full Text](#)
 50. **F** Shochat C, Tal N, Bandapalli OR, *et al.*: **Gain-of-function mutations in interleukin-7 receptor- α (IL7R) in childhood acute lymphoblastic leukemias**. *J Exp Med*. 2011; **208**(5): 901–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 51. Iacobucci I, Li Y, Roberts KG, *et al.*: **Truncating Erythropoietin Receptor Rearrangements in Acute Lymphoblastic Leukemia**. *Cancer Cell*. 2016; **29**(2): 186–200.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 52. Neumann M, Greif PA, Baldus CD: **Mutational landscape of adult ETP-ALL**. *Oncotarget*. 2013; **4**(7): 954–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 53. Rui L, Emre NC, Kruhlik MJ, *et al.*: **Cooperative epigenetic modulation by cancer amplicon genes**. *Cancer Cell*. 2010; **18**(6): 590–605.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 54. Gunawardana J, Chan FC, Telenius A, *et al.*: **Recurrent somatic mutations of PTPN1 in primary mediastinal B cell lymphoma and Hodgkin lymphoma**. *Nat Genet*. 2014; **46**(4): 329–35.
[PubMed Abstract](#) | [Publisher Full Text](#)
 55. Van Roosbroeck K, Cox L, Tousseyn T, *et al.*: **JAK2 rearrangements, including the novel SEC31A-JAK2 fusion, are recurrent in classical Hodgkin lymphoma**. *Blood*. 2011; **117**(15): 4056–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
 56. Bellanger D, Jacquemin V, Chopin M, *et al.*: **Recurrent JAK1 and JAK3 somatic mutations in T-cell prolymphocytic leukemia**. *Leukemia*. 2014; **28**(2): 417–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 57. Lee S, Park HY, Kang SY, *et al.*: **Genetic alterations of JAK/STAT cascade and histone modification in extranodal NK/T-cell lymphoma nasal type**. *Oncotarget*. 2015; **6**(19): 17764–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 58. **F** Ngo VN, Young RM, Schmitz R, *et al.*: **Oncogenically active MYD88 mutations in human lymphoma**. *Nature*. 2011; **470**(7332): 115–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
 59. Plo I, Bellanné-Chantelot C, Mosca M, *et al.*: **Genetic Alterations of the Thrombopoietin/MPL/JAK2 Axis Impacting Megakaryopoiesis**. *Front Endocrinol (Lausanne)*. 2017; **8**: 234.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 60. Hong WJ, Gotlib J: **Hereditary erythrocytosis, thrombocytosis and neutrophilia**. *Best Pract Res Clin Haematol*. 2014; **27**(2): 95–106.
[PubMed Abstract](#) | [Publisher Full Text](#)
 61. Plo I, Zhang Y, Le Couédic JP, *et al.*: **An activating mutation in the CSF3R gene induces a hereditary chronic neutrophilia**. *J Exp Med*. 2009; **206**(8): 1701–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 62. **F** Clark JD, Flanagan ME, Telliez JB: **Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases**. *J Med Chem*. 2014; **57**(12): 5023–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 63. Choi J, Ziga ED, Ritchey J, *et al.*: **IFN γ R signaling mediates alloreactive T-cell trafficking and GVHD**. *Blood*. 2012; **120**(19): 4093–103.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 64. Leroy E, Constantinescu SN: **Rethinking JAK2 inhibition: towards novel strategies of more specific and versatile janus kinase inhibition**. *Leukemia*. 2017; **31**(5): 1023–38.
[PubMed Abstract](#) | [Publisher Full Text](#)
 65. Bose P, Verstovsek S: **JAK2 inhibitors for myeloproliferative neoplasms: what is next?** *Blood*. 2017; **130**(2): 115–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 66. Tefferi A: **Challenges facing JAK inhibitor therapy for myeloproliferative neoplasms**. *N Engl J Med*. 2012; **366**(9): 844–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
 67. Schwartz DM, Bonelli M, Gadina M, *et al.*: **Type I/II cytokines, JAKs, and new strategies for treating autoimmune diseases**. *Nat Rev Rheumatol*. 2016; **12**(1): 25–36.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 68. **F** Kleppe M, Spitzer MH, Li S, *et al.*: **Jak1 Integrates Cytokine Sensing to Regulate Hematopoietic Stem Cell Function and Stress Hematopoiesis**. *Cell Stem Cell*. 2017; **21**(4): 489–501.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
 69. Tefferi A: **JAK inhibitors for myeloproliferative neoplasms: clarifying facts from myths**. *Blood*. 2012; **119**(12): 2721–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
 70. Zhang Q, Zhang Y, Diamond S, *et al.*: **The Janus kinase 2 inhibitor fedratinib**

- inhibits thiamine uptake: a putative mechanism for the onset of Wernicke's encephalopathy. *Drug Metab Dispos.* 2014; 42(10): 1656–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
71. Fleischmann R: **Tofacitinib in the treatment of active rheumatoid arthritis in adults.** *Immunotherapy.* 2018; 10(1): 39–56.
[PubMed Abstract](#) | [Publisher Full Text](#)
72. Koppikar P, Bhagwat N, Kilpivaara O, et al.: **Heterodimeric JAK-STAT activation as a mechanism of persistence to JAK2 inhibitor therapy.** *Nature.* 2012; 489(7414): 155–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
73. Meyer SC, Levine RL: **Molecular pathways: molecular basis for sensitivity and resistance to JAK kinase inhibitors.** *Clin Cancer Res.* 2014; 20(8): 2051–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
74. Blanc J, Geney R, Menet C: **Type II kinase inhibitors: an opportunity in cancer for rational design.** *Anticancer Agents Med Chem.* 2013; 13(5): 731–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. **F** Meyer SC, Keller MD, Chiu S, et al.: **CHZ868, a Type II JAK2 Inhibitor, Reverses Type I JAK Inhibitor Persistence and Demonstrates Efficacy in Myeloproliferative Neoplasms.** *Cancer Cell.* 2015; 28(1): 15–28.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
76. **F** Wu SC, Li LS, Kopp N, et al.: **Activity of the Type II JAK2 Inhibitor CHZ868 in B Cell Acute Lymphoblastic Leukemia.** *Cancer Cell.* 2015; 28(1): 29–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
77. Harrison C, Kiladjian JJ, Al-Ali HK, et al.: **JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis.** *N Engl J Med.* 2012; 366(9): 787–98.
[PubMed Abstract](#) | [Publisher Full Text](#)
78. **F** Vannucchi AM, Kiladjian JJ, Griesshammer M, et al.: **Ruxolitinib versus standard therapy for the treatment of polycythemia vera.** *N Engl J Med.* 2015; 372(5): 426–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
79. Verstovsek S, Mesa RA, Gotlib J, et al.: **A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis.** *N Engl J Med.* 2012; 366(9): 799–807.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. Eghtedar A, Verstovsek S, Estrov Z, et al.: **Phase 2 study of the JAK kinase inhibitor ruxolitinib in patients with refractory leukemias, including postmyeloproliferative neoplasm acute myeloid leukemia.** *Blood.* 2012; 119(20): 4614–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
81. **F** Hurwitz HI, Uppal N, Wagner SA, et al.: **Randomized, Double-Blind, Phase II Study of Ruxolitinib or Placebo in Combination With Capecitabine in Patients With Metastatic Pancreatic Cancer for Whom Therapy With Gemcitabine Has Failed.** *J Clin Oncol.* 2015; 33(34): 4039–47.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
82. **F** Zeiser R, Burchert A, Lengerke C, et al.: **Ruxolitinib in corticosteroid-refractory graft-versus-host disease after allogeneic stem cell transplantation: a multicenter survey.** *Leukemia.* 2015; 29(10): 2062–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
83. Punwani N, Scherle P, Flores R, et al.: **Preliminary clinical activity of a topical JAK1/2 inhibitor in the treatment of psoriasis.** *J Am Acad Dermatol.* 2012; 67(4): 658–64.
[PubMed Abstract](#) | [Publisher Full Text](#)
84. Mackay-Wiggan J, Jabbari A, Nguyen N, et al.: **Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata.** *JCI Insight.* 2016; 1(15): e89790.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. **F** Harris JE, Rashighi M, Nguyen N, et al.: **Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA).** *J Am Acad Dermatol.* 2016; 74(2): 370–1.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
86. Mesa RA, Kiladjian JJ, Catalano JV, et al.: **SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor-Naïve Patients With Myelofibrosis.** *J Clin Oncol.* 2017; 35(34): 3844–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
87. Verstovsek S, Courby S, Griesshammer M, et al.: **A phase 2 study of momelotinib, a potent JAK1 and JAK2 inhibitor, in patients with polycythemia vera or essential thrombocythemia.** *Leuk Res.* 2017; 60: 11–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
88. Verstovsek S, Hoffman R, Mascarenhas J, et al.: **A phase I, open-label, multicenter study of the JAK2 inhibitor AZD1480 in patients with myelofibrosis.** *Leuk Res.* 2015; 39(2): 157–63.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. Suryani S, Bracken LS, Harvey RC, et al.: **Evaluation of the *in vitro* and *in vivo* efficacy of the JAK inhibitor AZD1480 against JAK-mutated acute lymphoblastic leukemia.** *Mol Cancer Ther.* 2015; 14(2): 364–74.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
90. Plimack ER, Lorusso PM, McCoon P, et al.: **AZD1480: a phase I study of a novel JAK2 inhibitor in solid tumors.** *Oncologist.* 2013; 18(7): 819–20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
91. Keystone EC, Taylor PC, Tanaka Y, et al.: **Patient-reported outcomes from a phase 3 study of baricitinib versus placebo or adalimumab in rheumatoid arthritis: secondary analyses from the RA-BEAM study.** *Ann Rheum Dis.* 2017; 76(11): 1853–61.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
92. Papp KA, Menter MA, Raman M, et al.: **A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis.** *Br J Dermatol.* 2016; 174(6): 1266–76.
[PubMed Abstract](#) | [Publisher Full Text](#)
93. **NICE issues positive recommendation for XELJANZ® (tofacitinib citrate) as a new treatment option for adults with severe rheumatoid arthritis.** *Rheumatology (Oxford).* 2017; 56(12): e49.
[PubMed Abstract](#) | [Publisher Full Text](#)
94. Panés J, Sandborn WJ, Schreiber S, et al.: **Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials.** *Gut.* 2017; 66(6): 1049–59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
95. Feldman SR, Taçi D, Gooderham M, et al.: **Tofacitinib improves pruritus and health-related quality of life up to 52 weeks: Results from 2 randomized phase III trials in patients with moderate to severe plaque psoriasis.** *J Am Acad Dermatol.* 2016; 75(6): 1162–1170.e3.
[PubMed Abstract](#) | [Publisher Full Text](#)
96. Vu M, Heyes C, Robertson SJ, et al.: **Oral tofacitinib: a promising treatment in atopic dermatitis, alopecia areata and vitiligo.** *Clin Exp Dermatol.* 2017; 42(8): 942–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
97. **F** Verstovsek S, Mesa RA, Salama ME, et al.: **A phase 1 study of the Janus kinase 2 (JAK2)^{SH2} inhibitor, gandotinib (LY2784544), in patients with primary myelofibrosis, polycythemia vera, and essential thrombocythemia.** *Leuk Res.* 2017; 61: 89–95.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
98. Verstovsek S, Tam CS, Wadleigh M, et al.: **Phase I evaluation of XL019, an oral, potent, and selective JAK2 inhibitor.** *Leuk Res.* 2014; 38(3): 316–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
99. Baffert F, Régnier CH, De Pover A, et al.: **Potent and selective inhibition of polycythemia by the quinoxaline JAK2 inhibitor NVP-BSK805.** *Mol Cancer Ther.* 2010; 9(7): 1945–55.
[PubMed Abstract](#) | [Publisher Full Text](#)
100. Nakaya Y, Shide K, Niwa T, et al.: **Efficacy of NS-018, a potent and selective JAK2/Src inhibitor, in primary cells and mouse models of myeloproliferative neoplasms.** *Blood Cancer J.* 2011; 1(7): e29.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
101. Mesa RA, Vannucchi AM, Mead A, et al.: **Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial.** *Lancet Haematol.* 2017; 4(5): e225–e236.
[PubMed Abstract](#) | [Publisher Full Text](#)
102. Mascarenhas J, Hoffman R, Talpaz M, et al.: **Results of the Persist-2 Phase 3 Study of Pacritinib (PAC) versus Best Available Therapy (BAT), Including Ruxolitinib (RUX), in Patients with Myelofibrosis and Platelet Counts <100,000/μL.** *Blood, 58th American Society of Hematology (ASH) Annual Meeting, 3–6 Dec 2016, San Diego.* 2016.
[Reference Source](#)
103. Stump KL, Lu LD, Dobrzanski P, et al.: **A highly selective, orally active inhibitor of Janus kinase 2, CEP-33779, ablates disease in two mouse models of rheumatoid arthritis.** *Arthritis Res Ther.* 2011; 13(2): R68.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
104. Ringel F, Kaeda J, Schwarz M, et al.: **Effects of Jak2 type 1 inhibitors NVP-BSK805 and NVP-BVB808 on Jak2 mutation-positive and Bcr-Abl-positive cell lines.** *Acta Haematol.* 2014; 132(1): 75–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
105. Pardanani A, Hood J, Lasho T, et al.: **TG101209, a small molecule JAK2-selective kinase inhibitor potently inhibits myeloproliferative disorder-associated JAK2V617F and MPLW515L/K mutations.** *Leukemia.* 2007; 21(8): 1658–68.
[PubMed Abstract](#) | [Publisher Full Text](#)
106. Pardanani A, Tefferi A, Jamieson C, et al.: **A phase 2 randomized dose-ranging study of the JAK2-selective inhibitor fedratinib (SAR302503) in patients with myelofibrosis.** *Blood Cancer J.* 2015; 5(8): e335.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
107. Vanhoutte F, Mazur M, Voloshyn O, et al.: **Efficacy, Safety, Pharmacokinetics, and Pharmacodynamics of Filgotinib, a Selective JAK-1 Inhibitor, After Short-Term Treatment of Rheumatoid Arthritis: Results of Two Randomized Phase IIa Trials.** *Arthritis Rheumatol.* 2017; 69(10): 1949–59.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
108. Vermeire S, Schreiber S, Petryka R, et al.: **Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study): results from a phase 2, double-blind, randomised, placebo-controlled trial.** *Lancet.* 2017; 389(10066): 266–75.
[PubMed Abstract](#) | [Publisher Full Text](#)
109. **F** Baker KF, Isaacs JD: **Novel therapies for immune-mediated inflammatory diseases: What can we learn from their use in rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, psoriasis, Crohn's disease and ulcerative colitis?** *Ann Rheum Dis.* 2017; pii: annrheumdis-2017-211555.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
110. **F** Mascarenhas JO, Talpaz M, Gupta V, et al.: **Primary analysis of a phase**

- II open-label trial of INCB039110, a selective JAK1 inhibitor, in patients with myelofibrosis.** *Haematologica*. 2017; **102**(2): 327–35.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
111. Bissonnette R, Luchi M, Fidelus-Gort R, *et al.*: **A randomized, double-blind, placebo-controlled, dose-escalation study of the safety and efficacy of INCB039110, an oral janus kinase 1 inhibitor, in patients with stable, chronic plaque psoriasis.** *J Dermatolog Treat*. 2016; **27**(4): 332–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
112. Schmieder GJ, Draelos ZD, Pariser DM, *et al.*: **Efficacy and safety of the Janus Kinase 1 inhibitor PF-04965842 in patients with moderate to severe psoriasis: phase 2, randomized, double-blind, placebo-controlled study.** *Br J Dermatol*. 2017.
[PubMed Abstract](#) | [Publisher Full Text](#)
113. Klünder B, Mohamed MF, Othman AA: **Population Pharmacokinetics of Upadacitinib in Healthy Subjects and Subjects with Rheumatoid Arthritis: Analyses of Phase I and II Clinical Trials.** *Clin Pharmacokinet*. 2017; 1–12.
[PubMed Abstract](#) | [Publisher Full Text](#)
114. Fleischmann RM, Damjanov NS, Kivitz AJ, *et al.*: **A randomized, double-blind, placebo-controlled, twelve-week, dose-ranging study of decernotinib, an oral selective JAK-3 inhibitor, as monotherapy in patients with active rheumatoid arthritis.** *Arthritis Rheumatol*. 2015; **67**(2): 334–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
115. Uckun FM, Roers BA, Waurzyniak B, *et al.*: **Janus kinase 3 inhibitor WHI-P131/JANEX-1 prevents graft-versus-host disease but spares the graft-versus-leukemia function of the bone marrow allografts in a murine bone marrow transplantation model.** *Blood*. 2002; **99**(11): 4192–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
116. **F** Papp K, Pariser D, Catlin M, *et al.*: **A phase 2a randomized, double-blind, placebo-controlled, sequential dose-escalation study to evaluate the efficacy and safety of ASP015K, a novel Janus kinase inhibitor, in patients with moderate-to-severe psoriasis.** *Br J Dermatol*. 2015; **173**(3): 767–76.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
117. Takeuchi T, Tanaka Y, Iwasaki M, *et al.*: **Efficacy and safety of the oral Janus kinase inhibitor peficitinib (ASP015K) monotherapy in patients with moderate to severe rheumatoid arthritis in Japan: a 12-week, randomised, double-blind, placebo-controlled phase IIb study.** *Ann Rheum Dis*. 2016; **75**(6): 1057–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
118. Lipka DB, Hoffmann LS, Heidel F, *et al.*: **LS104, a non-ATP-competitive small-molecule inhibitor of JAK2, is potently inducing apoptosis in JAK2V617F-positive cells.** *Mol Cancer Ther*. 2008; **7**(5): 1176–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
119. Jatiani SS, Cosenza SC, Reddy MV, *et al.*: **A Non-ATP-Competitive Dual Inhibitor of JAK2 and BCR-ABL Kinases: Elucidation of a Novel Therapeutic Spectrum Based on Substrate Competitive Inhibition.** *Genes Cancer*. 2010; **1**(4): 331–45.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
120. Al-Ali HK, Griesshammer M, Le Coutre P, *et al.*: **Safety and efficacy of ruxolitinib in an open-label, multicenter, single-arm phase 3b expanded-access study in patients with myelofibrosis: a snapshot of 1144 patients in the JUMP trial.** *Haematologica*. 2016; **101**(9): 1065–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
121. **F** Passamonti F, Griesshammer M, Palandri F, *et al.*: **Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study.** *Lancet Oncol*. 2017; **18**(1): 88–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
122. **F** Harrison CN, Mead AJ, Panchal A, *et al.*: **Ruxolitinib vs best available therapy for ET intolerant or resistant to hydroxycarbamide.** *Blood*. 2017; **130**(17): 1889–97.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
123. **F** Verstovsek S, Passamonti F, Rambaldi A, *et al.*: **Ruxolitinib for essential thrombocythemia refractory to or intolerant of hydroxyurea: long-term phase 2 study results.** *Blood*. 2017; **130**(15): 1768–71.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
124. Curto-Garcia N, Harrison CN: **An updated review of the JAK1/2 inhibitor (ruxolitinib) in the Philadelphia-negative myeloproliferative neoplasms.** *Future Oncol*. 2017; **14**(2): 137–150.
[PubMed Abstract](#) | [Publisher Full Text](#)
125. Saeed I, McLornan D, Harrison CN: **Managing side effects of JAK inhibitors for myelofibrosis in clinical practice.** *Expert Rev Hematol*. 2017; **10**(7): 617–25.
[PubMed Abstract](#) | [Publisher Full Text](#)
126. **F** Schönberg K, Rudolph J, Vonnahme M, *et al.*: **JAK Inhibition Impairs NK Cell Function in Myeloproliferative Neoplasms.** *Cancer Res*. 2015; **75**(11): 2187–99.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
127. **F** Curran SA, Shyer JA, St Angelo ET, *et al.*: **Human Dendritic Cells Mitigate NK-Cell Dysfunction Mediated by Nonselective JAK1/2 Blockade.** *Cancer Immunol Res*. 2017; **5**(1): 52–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
128. **F** Verstovsek S, Gotlib J, Mesa RA, *et al.*: **Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses.** *J Hematol Oncol*. 2017; **10**(1): 156.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
129. Pardanani A, Abdelrahman RA, Finke C, *et al.*: **Genetic determinants of response and survival in momelotinib-treated patients with myelofibrosis.** *Leukemia*. 2015; **29**(3): 741–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
130. Gupta V, Mesa RA, Deininger MW, *et al.*: **A phase 1/2, open-label study evaluating twice-daily administration of momelotinib in myelofibrosis.** *Haematologica*. 2017; **102**(1): 94–102.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
131. Pardanani A, Gotlib JR, Gupta V, *et al.*: **Update On The Long-Term Efficacy and Safety Of Momelotinib, a JAK1 and JAK2 Inhibitor, For The Treatment Of Myelofibrosis.** *Blood*. 2013; **122**(21): 108.
[Reference Source](#)
132. **F** Asshoff M, Petzer V, Warr MR, *et al.*: **Momelotinib inhibits ACVR1/ALK2, decreases hepcidin production, and ameliorates anemia of chronic diseases in rodents.** *Blood*. 2017; **129**(13): 1823–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
133. **F** Verstovsek S, Talpaz M, Ritchie E, *et al.*: **A phase I, open-label, dose-escalation, multicenter study of the JAK2 inhibitor NS-018 in patients with myelofibrosis.** *Leukemia*. 2017; **31**(2): 393–402.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
134. **F** Verstovsek S, Odenike O, Singer JW, *et al.*: **Phase 1/2 study of pacritinib, a next generation JAK2/FLT3 inhibitor, in myelofibrosis or other myeloid malignancies.** *J Hematol Oncol*. 2016; **9**(1): 137.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
135. BioPharma C: **CTI BioPharma Provides Update On Clinical Hold Of Investigational Agent Pacritinib And New Drug Application In U.S.** 2016.
[Reference Source](#)
136. PR Newswire CB: **CTI BioPharma Announces Removal Of Full Clinical Hold On Pacritinib.** 2017.
[Reference Source](#)
137. **F** Harrison CN, Schaap N, Vannucchi AM, *et al.*: **Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study.** *Lancet Haematol*. 2017; **4**(7): e317–e324.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
138. **F** Jamieson C, Hasserjian R, Gotlib J, *et al.*: **Effect of treatment with a JAK2-selective inhibitor, fedratinib, on bone marrow fibrosis in patients with myelofibrosis.** *J Transl Med*. 2015; **13**: 294.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
139. Pardanani A, Harrison C, Cortes JE, *et al.*: **Safety and Efficacy of Fedratinib in Patients With Primary or Secondary Myelofibrosis: A Randomized Clinical Trial.** *JAMA Oncol*. 2015; **1**(5): 643–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
140. **F** Hazell AS, Afadali S, Cheresh DA, *et al.*: **Treatment of rats with the JAK-2 inhibitor fedratinib does not lead to experimental Wernicke's encephalopathy.** *Neurosci Lett*. 2017; **642**: 163–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
141. Buchert M, Burns CJ, Ernst M: **Targeting JAK kinase in solid tumors: emerging opportunities and challenges.** *Oncogene*. 2016; **35**(8): 939–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
142. **F** Yu HA, Perez L, Chang Q, *et al.*: **A Phase 1/2 Trial of Ruxolitinib and Erlotinib in Patients with EGFR-Mutant Lung Adenocarcinomas with Acquired Resistance to Erlotinib.** *J Thorac Oncol*. 2017; **12**(1): 102–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
143. Dao KT, Solti MB, Maxson JE, *et al.*: **Significant clinical response to JAK1/2 inhibition in a patient with CSF3R-T618L-positive atypical chronic myeloid leukemia.** *Leuk Res Rep*. 2014; **3**(2): 67–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
144. Lierman E, Selleslag D, Smits S, *et al.*: **Ruxolitinib inhibits transforming JAK2 fusion proteins in vitro and induces complete cytogenetic remission in t(8;9)(p22;p24)/PCM1-JAK2-positive chronic eosinophilic leukemia.** *Blood*. 2012; **120**(7): 1529–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
145. Rumi E, Milosevic JD, Selleslag D, *et al.*: **Efficacy of ruxolitinib in myeloid neoplasms with PCM1-JAK2 fusion gene.** *Ann Hematol*. 2015; **94**(11): 1927–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
146. Schwaab J, Knut M, Haferlach C, *et al.*: **Limited duration of complete remission on ruxolitinib in myeloid neoplasms with PCM1-JAK2 and BCR-JAK2 fusion genes.** *Ann Hematol*. 2015; **94**(2): 233–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
147. Welsch K, Holstein J, Laurence A, *et al.*: **Targeting JAK/STAT signalling in inflammatory skin diseases with small molecule inhibitors.** *Eur J Immunol*. 2017; **47**(7): 1096–107.
[PubMed Abstract](#) | [Publisher Full Text](#)
148. **F** Winthrop KL: **The emerging safety profile of JAK inhibitors in rheumatic disease.** *Nat Rev Rheumatol*. 2017; **13**(4): 234–43.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
149. Archer TP, Moran GW, Ghosh S: **Tofacitinib in ulcerative colitis.** *Immunotherapy*. 2016; **8**(5): 495–502.
[PubMed Abstract](#) | [Publisher Full Text](#)
150. Costa L, Del Puente A, Peluso R, *et al.*: **Small molecule therapy for managing moderate to severe psoriatic arthritis.** *Expert Opin Pharmacother*. 2017; **18**(15):

- 1557–67.
[PubMed Abstract](#) | [Publisher Full Text](#)
151. Spoerl S, Mathew NR, Bscheider M, *et al.*: **Activity of therapeutic JAK 1/2 blockade in graft-versus-host disease.** *Blood.* 2014; **123**(24): 3832–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
152. **F** Richez C, Truchetet M, Kostine M, *et al.*: **Efficacy of baricitinib in the treatment of rheumatoid arthritis.** *Expert Opin Pharmacother.* 2017; **18**(13): 1399–407.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
153. **F** Genovese MC, Yang F, Østergaard M, *et al.*: **Efficacy of VX-509 (decernotinib) in combination with a disease-modifying antirheumatic drug in patients with rheumatoid arthritis: clinical and MRI findings.** *Ann Rheum Dis.* 2016; **75**(11): 1979–83.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
154. Haan C, Rolvering C, Raulf F, *et al.*: **Jak1 has a dominant role over Jak3 in signal transduction through γ c-containing cytokine receptors.** *Chem Biol.* 2011; **18**(3): 314–23.
[PubMed Abstract](#) | [Publisher Full Text](#)
155. Deshpande A, Reddy MM, Schade GO, *et al.*: **Kinase domain mutations confer resistance to novel inhibitors targeting JAK2V617F in myeloproliferative neoplasms.** *Leukemia.* 2012; **26**(4): 708–15.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
156. Hornakova T, Springuel L, Devreux J, *et al.*: **Oncogenic JAK1 and JAK2-activating mutations resistant to ATP-competitive inhibitors.** *Haematologica.* 2011; **96**(6): 845–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
157. Zhang J, Adrián FJ, Jahnke W, *et al.*: **Targeting Bcr-Abl by combining allosteric with ATP-binding-site inhibitors.** *Nature.* 2010; **463**(7280): 501–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
158. **F** Ohren JF, Chen H, Pavlovsky A, *et al.*: **Structures of human MAP kinase kinase 1 (MEK1) and MEK2 describe novel noncompetitive kinase inhibition.** *Nat Struct Mol Biol.* 2004; **11**(12): 1192–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
159. **F** Bandaranayake RM, Ungureanu D, Shan Y, *et al.*: **Crystal structures of the JAK2 pseudokinase domain and the pathogenic mutant V617F.** *Nat Struct Mol Biol.* 2012; **19**(8): 754–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
160. Puleo DE, Kucera K, Hammarén HM, *et al.*: **Identification and Characterization of JAK2 Pseudokinase Domain Small Molecule Binders.** *ACS Med Chem Lett.* 2017; **8**(6): 618–21.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
161. Dusa A, Staerk J, Elliott J, *et al.*: **Substitution of pseudokinase domain residue Val-617 by large non-polar amino acids causes activation of JAK2.** *J Biol Chem.* 2008; **283**(19): 12941–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
162. **F** Thomas S, Fisher KH, Snowden JA, *et al.*: **Methotrexate Is a JAK/STAT Pathway Inhibitor.** *PLoS One.* 2015; **10**(7): e0130078.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
163. **F** Dussiot M, Maciel TT, Fricot A, *et al.*: **An activin receptor IIA ligand trap corrects ineffective erythropoiesis in β -thalassemia.** *Nat Med.* 2014; **20**(4): 398–407.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
164. **F** McMullin MF, Harrison CN, Niederwieser D, *et al.*: **The use of erythropoiesis-stimulating agents with ruxolitinib in patients with myelofibrosis in COMFORT-II: an open-label, phase 3 study assessing efficacy and safety of ruxolitinib versus best available therapy in the treatment of myelofibrosis.** *Exp Hematol Oncol.* 2015; **4**: 26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
165. Ihle JN, Witthuhn BA, Quelle FW, *et al.*: **Signaling through the hematopoietic cytokine receptors.** *Annu Rev Immunol.* 1995; **13**: 369–98.
[PubMed Abstract](#) | [Publisher Full Text](#)
166. Lai P, Rosa DA, Magdy Ali A, *et al.*: **A STAT inhibitor patent review: progress since 2011.** *Expert Opin Ther Pat.* 2015; **25**(12): 1397–421.
[PubMed Abstract](#) | [Publisher Full Text](#)
167. **F** Bartalucci N, Tozzi L, Bogani C, *et al.*: **Co-targeting the PI3K/mTOR and JAK2 signalling pathways produces synergistic activity against myeloproliferative neoplasms.** *J Cell Mol Med.* 2013; **17**(11): 1385–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
168. Choong ML, Pecquet C, Pendharkar V, *et al.*: **Combination treatment for myeloproliferative neoplasms using JAK and pan-class I PI3K inhibitors.** *J Cell Mol Med.* 2013; **17**(11): 1397–409.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
169. Marubayashi S, Koppikar P, Taldone T, *et al.*: **HSP90 is a therapeutic target in JAK2-dependent myeloproliferative neoplasms in mice and humans.** *J Clin Invest.* 2010; **120**(10): 3578–93.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
170. **F** Mascarenhas J, Sandy L, Lu M, *et al.*: **A phase II study of panobinostat in patients with primary myelofibrosis (PMF) and post-polycythemia vera/essential thrombocythemia myelofibrosis (post-PV/ET MF).** *Leuk Res.* 2017; **53**: 13–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
171. **F** Hobbs GS, Hanasoge Somasundara AV, Kleppe M, *et al.*: **Hsp90 inhibition disrupts JAK-STAT signaling and leads to reductions in splenomegaly in patients with myeloproliferative neoplasms.** *Haematologica.* 2018; **103**(1): e5–e9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
172. **F** Bjørn ME, Hasselbalch HC: **Minimal residual disease or cure in MPNs? Rationales and perspectives on combination therapy with interferon-alpha2 and ruxolitinib.** *Expert Rev Hematol.* 2017; **10**(5): 393–404.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
173. Duffield JS, Lupher ML Jr: **PRM-151 (recombinant human serum amyloid P/pentraxin 2) for the treatment of fibrosis.** *Drug News Perspect.* 2010; **23**(5): 305–15.
[PubMed Abstract](#) | [Publisher Full Text](#)
174. Verstovsek S, Manshouri T, Pilling D, *et al.*: **Role of neoplastic monocyte-derived fibrocytes in primary myelofibrosis.** *J Exp Med.* 2016; **213**(9): 1723–40.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
175. Stein BL, Swords R, Hochhaus A, *et al.*: **Novel myelofibrosis treatment strategies: potential partners for combination therapies.** *Leukemia.* 2014; **28**(11): 2139–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
176. Sasaki K, Gottlib JR, Mesa RA, *et al.*: **Phase II evaluation of IPI-926, an oral Hedgehog inhibitor, in patients with myelofibrosis.** *Leuk Lymphoma.* 2015; **56**(7): 2092–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
177. **F** Schneider RK, Mullally A, Dugourd A, *et al.*: **Gli1+ Mesenchymal Stromal Cells Are a Key Driver of Bone Marrow Fibrosis and an Important Cellular Therapeutic Target.** *Cell Stem Cell.* 2017; **20**(6): 785–800.e8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
178. Liu F, Zhao X, Perna F, *et al.*: **JAK2V617F-mediated phosphorylation of PRMT5 downregulates its methyltransferase activity and promotes myeloproliferation.** *Cancer Cell.* 2011; **19**(2): 283–94.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
179. **F** Dawson MA, Bannister AJ, Göttgens B, *et al.*: **JAK2 phosphorylates histone H3Y41 and excludes HP1alpha from chromatin.** *Nature.* 2009; **461**(7265): 819–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
180. **F** Badar T, Kantarjian HM, Ravandi F, *et al.*: **Therapeutic benefit of decitabine, a hypomethylating agent, in patients with high-risk primary myelofibrosis and myeloproliferative neoplasm in accelerated or blastic/acute myeloid leukemia phase.** *Leuk Res.* 2015; **39**(9): 950–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
181. **F** Quintás-Cardama A, Tong W, Kantarjian H, *et al.*: **A phase II study of 5-azacitidine for patients with primary and post-essential thrombocythemia/polycythemia vera myelofibrosis.** *Leukemia.* 2008; **22**(5): 965–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

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