Drug Development Pipeline for Myeloproliferative Neoplasms: Potential Future Impact on Guidelines and Management

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Abstract

The unprecedented success of ruxolitinib in myelofibrosis (MF) has paved the way for the development of other Janus kinase (JAK) inhibitors and other agents representing diverse drug classes and mechanisms of action in myeloproliferative neoplasms (MPNs). In particular, the symptomatic benefits afforded by ruxolitinib have led to the recognition of “clinical improvement” in symptoms and the spleen in international consensus response criteria for MF. Ruxolitinib is also approved for the second-line treatment of polycythemia vera and is being developed for essential thrombocythemia. Appreciation of the universal role of activated JAK/signal transducer and activator of transcription (STAT) signaling in MPNs and improved understanding of the canonical and noncanonical actions of JAK2 have yielded a number of drug targets beyond JAK2 in MPNs, which form the basis for a number of ruxolitinib-based rational combinations that are being explored in MF. Other JAK inhibitors with the potential for significantly less myelosuppression or even improvement of anemia continue to be tested. Finally, agents with very distinct mechanisms of action, such as novel interferon formulations, antifibrotic agents, and telomerase inhibitors, are being pursued in polycythemia vera and MF, respectively. This article reviews the current landscape of clinical drug development in MPNs, focusing on the most promising agents and combinations.

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Background

2016 marks the inception of formal management guidelines from NCCN on the Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs). Guidelines recently released by ESMO¹ distinguished between the major goals of therapy in essential thrombocythemia (ET) and polycythemia vera (PV)—the prevention of thrombosis and bleeding—from those in myelofibrosis (MF), in which prolongation of survival and management of anemia, constitutional symptoms, and splenomegaly are most important. Underlying these disparate goals of therapy is the fundamentally different natural history of these MPNs: survival in MF is short (median, 6.5 years in 1996–2007 in one international study),² whereas ET and PV are each characterized by an indolent clinical course and prolonged survival, al-

though shorter than that of the age- and sex-matched US population.^{3,4}

MPNs are characterized by universal activation of Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling,^{5,6} in most cases due to gain-of-function mutations in JAK2,^{7–11} MPL,^{12,13} or CALR.^{14,15} The first-in-class JAK1/2 inhibitor, ruxolitinib, approved for the treatment of intermediate- or high-risk MF^{16,17} and hydroxyurea-resistant/intolerant PV (see Table 1 for definition of resistance and intolerance to hydroxyurea),¹⁸ represents the first example of disease-modifying pharmacologic therapy in MPNs, and the inaugural NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) contain special guidance on the use of ruxolitinib (in this issue; to view the most recent version, visit NCCN.org). Long-term follow-up of the pivotal COMFORT trials has demon-

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Table 1. Definition of Resistance/Intolerance to Hydroxyurea in Polycythemia Vera

1. Need for phlebotomy to keep hematocrit <45% after 3 months of ≥2 g/d of hydroxyurea, OR
2. Uncontrolled myeloproliferation (ie, platelets >400 x 10 ⁹ /L AND leukocytes >10 x 10 ⁹ /L after 3 months of ≥2 g/d of hydroxyurea), OR
3. Failure to reduce massive ^a splenomegaly by ≥50% as measured by palpation, OR failure to completely relieve symptoms related to splenomegaly after 3 months of ≥2 g/d of hydroxyurea, OR
4. Absolute neutrophil count <1.0 x 10 ⁹ /L OR platelet count <100 x 10 ⁹ /L OR hemoglobin <100 g/L at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response, ^b OR
5. Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, gastrointestinal symptoms, pneumonitis, or fever at any dose of hydroxyurea

^aOrgan extending by >10 cm from the costal margin.
^bComplete response defined as hematocrit <45% without phlebotomy, platelets ≤400 x 10⁹/L, leukocytes ≤10 x 10⁹/L, and no disease-related symptoms. Partial response defined as hematocrit <45% without phlebotomy or response in ≥3 of the other criteria.¹⁰⁵ Modified from Barosi G, Birgegard G, Finazzi G, et al. A unified definition of clinical resistance and intolerance to hydroxycarbamide in polycythemia vera and primary myelofibrosis: results of a European LeukemiaNet (ELN) consensus process. *Br J Haematol* 2010;148:962.

strated that ruxolitinib improves overall survival in patients with intermediate-2– or high-risk MF when compared with placebo and best available therapy (BAT), respectively, despite extensive crossover,^{19,20} as well as reduces the mutated JAK2 allelic burden and improves bone marrow (BM) fibrosis in a minority of patients.²⁰ The salutary benefits of this agent on constitutional symptoms of MF²¹ led to the recognition of clinical improvement in symptoms as a response criterion by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT),²² resulting in the incorporation of the MPN Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)²³ as a tool for formal assessment of symptom response in MPNs. Ruxolitinib is effective without regard for the mutational status of JAK2.^{16,17,24} These successes have led to a wave of clinical trials of ruxolitinib-based rational combinations with other novel targeted agents, as well as antianemia medications, in MF.²⁵ Simultaneously, development of other JAK inhibitors and new classes of agents with therapeutic promise in MF has continued. However, allogeneic hematopoietic stem cell transplantation (HSCT), recommended in pa-

tients younger than 70 years with intermediate-2– or high-risk disease, as well as in those younger than 65 years with intermediate-1–risk disease but with known poor-risk features (eg, red cell transfusion dependence, >2% circulating blasts, or adverse cytogenetics) remains the only potential cure for MF.²⁶ Although widely used, especially for spleen shrinkage, the optimal duration of JAK inhibitor therapy before HSCT remains unknown. There is also interest in the use of these drugs post-HSCT, particularly in light of recent findings supporting a role for JAK1/2 inhibitors in treating graft-versus-host disease.^{27,28}

Drug Development in PV and ET

The indolent natural course of PV and ET, leading to prolonged overall survival,^{3,4} has meant that drug therapy in these conditions has mostly been limited to the use of aspirin²⁹ and hydroxyurea or anagrelide (in ET) in high-risk patients requiring cytoreduction for prevention of thrombotic complications.^{30–32} Hematocrit control (to <45%)³³ in low-risk patients with PV is usually achieved with phlebotomy alone. However, patients with PV and ET, especially the former, can have a substantial symptom burden.^{23,34–36} In the RESPONSE trial, which led to the recent approval of ruxolitinib for the treatment of hydroxyurea-resistant/intolerant PV, 49% of patients in the ruxolitinib group achieved a 50% or more reduction in their total symptom score (TSS) at 32 weeks compared with 5% in the standard therapy group.¹⁸ Hematocrit control was achieved by 60% versus 20%, respectively, and a 35% or more spleen volume reduction (SVR) by 38% and 1%, respectively.¹⁸ Additionally, 24% in the ruxolitinib arm achieved complete hematologic remission (CHR) compared with 9% in the standard therapy arm¹⁸; these benefits were maintained in most patients after a minimum of 80 weeks of follow-up.³⁷ No patient lost their spleen response between weeks 32 and 80, and 90% of patients still receiving ruxolitinib at week 32 had no phlebotomies performed during this period. RESPONSE was not designed to evaluate rates of thrombosis, but at week 32, before crossover to ruxolitinib, there were 6 thromboembolic events in the standard therapy arm and only 1 in the ruxolitinib arm.¹⁸ At the 80-week analysis, the rates of all-grade and grade 3/4 thromboembolic events per 100 patient-years of exposure were 1.8 and 0.9, respectively, among patients originally randomized to ruxolitinib,

versus 4.1 and 2.7 in those receiving ruxolitinib after crossover, and 8.2 and 2.7 in those receiving BAT.³⁷ Because ruxolitinib is immunosuppressive, infections are a concern with this agent. Grade 1/2 herpes zoster infections occurred in 7 patients in the ruxolitinib group (6.4%) compared with none in the standard therapy group through week 32.¹⁸ With longer follow-up (minimum 80 weeks), rates remained higher with ruxolitinib: 5.3 and 5.4 per 100 patient-years of exposure among patients originally randomized to and those who crossed over to ruxolitinib, respectively, versus none among patients receiving standard therapy.³⁷ Overall, the rate of infections (any grade) was 41.8% in the ruxolitinib group and 36.9% in the standard-therapy group; the rate of grade 3/4 infection was 3.6% and 2.7%, respectively, in the primary analysis.¹⁸ Per 100 patient-years of exposure, the rates of all-grade and grade 3/4 infections were 29.4, 27.8, and 58.4, and 4.0, 5.4, and 4.1 for patients originally randomized to ruxolitinib (n=110), those crossed over to ruxolitinib (n=98), and those originally assigned to BAT (n=111), respectively.³⁷ Evaluation of ruxolitinib in patients with ET is ongoing (ClinicalTrials.gov identifiers: NCT00726232, NCT02577926).

Although not specifically approved for MPN therapy, high response rates, including molecular responses, have been reported with the use of pegylated interferon- α -2a in both PV and ET.^{38,39} One study in 40 patients with PV reported a CHR rate of 94.6% and a decrease in the percentage of mutated *JAK2* in 89.6% of patients, with improvement over time in the depth of molecular responses.³⁸ A total of 7 patients achieved a complete molecular remission (CMR), which persisted after treatment discontinuation in 5 patients.³⁸ In another study, CHR rates of 70% and 76% were reported among patients with PV and ET, respectively, with molecular response rates of 38% in ET and 54% in PV (CMR in 6% and 14%, respectively).³⁹ After a median follow-up of 82.5 months, 32 of 83 enrolled patients (39%) remained on this study, but therapy was on hold for 8 of these patients.⁴⁰ The median durations of hematologic and molecular responses were 66 and 53 months, respectively.⁴⁰ *JAK2* status or allele burden had no impact on achievement of response (clinical or molecular), time to response, or duration of therapy, but patients achieving CMR had the longest response duration.⁴⁰ Pegylated interferon- α -2a also significantly decreased the allelic burden of mutant *CALR* from a median of 41% at baseline to 26% after treatment in

a study of 31 patients with *CALR*-mutated ET, with 2 patients achieving CMR.⁴¹

Recently, a next-generation, mono-PEGylated interferon- α -2b isoform with a long elimination half-life enabling administration every 2 weeks, ropeginterferon α -2b, has been developed for PV.⁴² In a phase I/II trial in 51 patients, there were no dose-limiting toxicities and the overall response rate was 90%, including CHR in 47%.⁴² A CMR was obtained in 21% of patients and a partial molecular response in 47%.⁴² A steady decrease in the allelic burden of *JAK2* V617F was also noted with ruxolitinib therapy in the RESPONSE trial in patients with hydroxyurea-resistant/intolerant PV; the mean percentage decrease from baseline was 40% by week 208 (12.2% at week 32; 22% at week 80).^{37,43} Although decreases in *JAK2* V617F allelic burden are often considered to represent evidence of disease-modifying activity, it is important to remember that although it is the most common mutation in MPN, *JAK2* V617F is not the disease-initiating mutation⁴⁴ and can be a late genetic event.⁴⁵ For example, *TET2* mutations can precede *JAK2* mutations, and the order of mutation acquisition can affect disease phenotype, thrombosis risk, and in vitro sensitivity of *JAK2*-mutant progenitors to ruxolitinib, as well as the proliferative response to *JAK2* V617F.⁴⁶ Importantly, notwithstanding its effects on *JAK2* V617F-positive clones, pegylated interferon- α -2a appears not to affect *TET2*-mutant cells.⁴⁷ In the study of *CALR*-mutated ET mentioned earlier, molecular responses to pegylated interferon- α were poorer (minor to no molecular responses) in patients who also had *TET2*, *ASXL1*, *IDH2*, and/or *TP53* mutations.⁴¹ All patients who achieved a CMR or partial molecular response to pegylated interferon- α had no additional mutations besides *CALR*.⁴¹ Achievement of a complete molecular response (in terms of *JAK2* V617F but not *TET2*) to ruxolitinib, though infrequent, has been reported in patients with PV and ET (3 of 22 patients in one study at the 5-year time point).⁴⁸

The telomerase inhibitor, imetelstat, was evaluated in a small phase II study in 18 patients with previously treated ET, with a primary end point of best hematologic response.⁴⁹ All patients responded at some point in time, and 16 (89%) had a CHR as their best response. Molecular responses occurred in 7 of 8 patients with *JAK2* V617F-positive mutations; *CALR* and *MPL* mutant allele burdens also decreased by 15% to 66%. Myelosuppression and hepatotoxicity were the major adverse events.⁴⁹ Imetelstat is

administered intravenously, and was initially administered once weekly in this study (maintenance dosing at a reduced frequency began after achievement of a CHR or partial hematologic response), a route and schedule that may be hard to justify when treating an indolent disease with a long natural history (median survival, 19.8 years even at a large, tertiary care referral center).³ Histone deacetylase inhibitors (HDACIs) are efficacious preclinically in MPN, both in vitro and in vivo,^{50,51} and are clearly active in patients with PV and ET, but the chronic low-grade toxicities of these agents (eg, fatigue, diarrhea, nausea, myelosuppression) make them difficult to tolerate long-term.^{52–54}

Drug Development Pipeline in MF

The need for disease-modifying therapies is significantly greater in MF than in PV or ET, owing to the substantially more aggressive disease biology in MF. Although current pharmacologic therapy of primary MF centers on ruxolitinib,⁵⁵ efforts are ongoing to develop novel ruxolitinib-based combinations, new JAK2 inhibitors, and other classes of drugs, such as antifibrotic agents and telomerase inhibitors. Given the survival benefit of ruxolitinib in patients with advanced MF,^{16,19,56} it is now being studied in patients with earlier stages of MF and one or more prognostically detrimental mutations (*ASXL1*, *EZH2*, *SRSF2*, *IDH1*, *IDH2*)⁵⁷ in the ReTHINK trial (ClinicalTrials.gov identifier: NCT02598297).

Ruxolitinib-Based Combination Strategies

Combinations With Antianemia Medications: Anemia is both a hallmark of MF and an on-target effect of ruxolitinib, because erythropoiesis is critically dependent on JAK-STAT signaling.⁵⁸ In fact, dose-limiting anemia and thrombocytopenia have been suggested as one potential explanation for the rather modest effect of ruxolitinib on *JAK2* V617F allele burden reduction in MF.⁵⁹ Medications generally used to alleviate the anemia of MF include danazol, erythropoiesis-stimulating agents (ESAs), immunomodulatory drugs (IMiDs; eg, thalidomide, lenalidomide, pomalidomide), and steroids.⁵⁵ Anemia response rates to IMiDs are in the 20% to 30% range, whereas response rates to ESAs and androgens vary from 20% to 60%.⁵⁵ Naturally, there is considerable interest in combining these agents with ruxolitinib,

monotherapy with which causes an initial decline in the hemoglobin level, followed by the establishment of a new lower baseline.^{16,17} However, the simultaneous administration of ruxolitinib and lenalidomide is difficult because of excessive myelosuppression.⁶⁰

POMINC is a trial of ruxolitinib and pomalidomide in MF that is ongoing in Germany (ClinicalTrials.gov identifier: NCT01644110), and one of ruxolitinib and thalidomide is planned in the United States. Although in theory, JAK2 inhibition would be expected to antagonize the effects of ESAs,⁵⁸ in practice some improvement of anemia may be seen with the addition of ESAs to ruxolitinib. A trial of ruxolitinib plus danazol (n=14) was halted secondary to lack of anemia response⁶¹; 3 patients (21.4%) had clinical improvement in spleen size according to IWG-MRT criteria.²² These trials are listed in Table 2.

Finally, a new class of agents termed *activin receptor IIA ligand traps* have been shown to correct ineffective erythropoiesis and improve anemia in mouse models of α -thalassemia through inactivation of GDF11, a cytokine that blocks terminal erythroid maturation.⁶² These drugs have shown considerable efficacy in myelodysplastic syndrome (MDS) with ringed sideroblasts,⁶³ and evaluation in MF is ongoing, with plans for combination with ruxolitinib (ClinicalTrials.gov identifier: NCT01712308).

Mechanism-Based Combinations With Other Targeted Agents: A number of different classes of targeted agents continue to be explored in combination with ruxolitinib in MF.²⁵ These include epigenetic therapies such as DNA methyltransferase inhibitors (DNMTI) and HDACIs, phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR inhibitors, and hedgehog inhibitors. Table 2 lists ongoing trials of ruxolitinib-based combinations in MF.

Epigenetic abnormalities are frequent in MF, and JAK2 influences nuclear gene transcription in a variety of ways, such that a number of mechanisms⁶⁴ underlie the synergism observed between JAK2 inhibitors and epigenetic modifiers in MF. For HDACIs, an important concept is the downregulation, through acetylation, by HDAC6 inhibitors of the chaperone protein, heat shock protein 90, of which JAK2 is a client.⁶⁵ This is a major mechanism through which HDACIs promote the degradation of JAK2 V617F and potentiate the effects of JAK2 inhibitors in MPN cells.⁶⁶ HDACI monotherapy is definitely active in MF in terms of symptom and spleen responses

Table 2. Clinical Trials (Nontransplant) of Ruxolitinib-Based Combinations in MF

Clinicaltrials.gov Identifier	Partner Drug	Major Inclusion Criteria	Phase	Comments
NCT02718300	INCB050465 (PI3K delta inhibitor)	PMF or post-PV/ET MF; spleen >10 cm below LCM or 5–10 cm with MF symptoms	II	
NCT01433445	Panobinostat (HDAC inhibitor)	PMF or post-PV/ET MF; spleen ≥5 cm below LCM, platelets >100 × 10 ⁹ /L, <10% blasts	I/II	RP2D, 15 mg bid of rux and 25 mg 3 times a week of panobinostat ⁷⁰
NCT01693601	Panobinostat (HDAC inhibitor)	PMF or post-PV/ET MF in CP or AP; intermediate-2– or high-risk; platelets ≥75 × 10 ⁹ /L, ANC ≥0.75 × 10 ⁹ /L	I/II	
NCT01732445	Danazol	PMF or post-PV/ET MF, intermediate- or high-risk; Hgb <10 g/dL or TD; platelets ≥50 × 10 ⁹ /L, ANC ≥1 × 10 ⁹ /L	II (pilot)	Closed early ⁶¹
NCT02370706	PIM447 (PIM kinase inhibitor) and/or LEE011 (CDK4/6 inhibitor)	PMF or post-PV/ET MF, JAK2 V617F–positive; splenomegaly ≥5 cm by MRI; platelets ≥100 × 10 ⁹ /L, ANC ≥1.5 × 10 ⁹ /L; Hgb ≥9 g/dL	I	Dose escalation and expansion parts have different inclusion criteria: only patients with insufficient spleen response to ≥6 mo of rux allowed in escalation phase
NCT01787487	Azacitidine (HMA)	PMF or post-PV/ET MF, intermediate- or high-risk if newly diagnosed; platelets ≥50 × 10 ⁹ /L, ANC ≥1 × 10 ⁹ /L	II	Completed accrual to MF arm ⁷⁴ ; currently accruing patients with MDS/MPN
NCT02493530	TGR-1202 (PI3K delta inhibitor)	PMF or post-PV/ET MF, intermediate- or high-risk, with grade ≥1 marrow fibrosis; patients with PV meeting rux indications	I	Escalation stage 1 enrolls only patients with insufficient response to ≥8 wk of rux; stage 2 is for JAK inhibitor-naïve patients; PI3K or mTOR inhibitors not allowed in prior 6 mo
NCT02436135	Idelalisib (PI3K delta inhibitor)	PMF or post-PV/ET MF, intermediate- or high-risk, with disease relapse or progression on rux	I	Patients must have been on a stable dose of rux for ≥4 wk
NCT02267278	Pracinostat (HDAC inhibitor)	PMF or post-PV/ET MF, intermediate- or high-risk if newly diagnosed, spleen ≥5 cm below LCM; platelets ≥50 × 10 ⁹ /L, ANC ≥1 × 10 ⁹ /L	II	Prior rux allowed only if duration <3 mo; no prior HDAC inhibitor allowed
NCT01375140	Lenalidomide (IMiD)	PMF or post-PV/ET MF, intermediate- or high-risk if newly diagnosed; platelets ≥100 × 10 ⁹ /L, ANC ≥1 × 10 ⁹ /L	II	Simultaneous administration of rux and lenalidomide is difficult due to excessive myelosuppression ⁶⁰
NCT01644110	Pomalidomide (IMiD)	PMF or post-PV/ET MF, splenomegaly >11 cm (total diameter) and/or leukoerythroblastosis; Hgb <10 g/dL or TD; platelets ≥100 × 10 ⁹ /L, ANC ≥0.5 × 10 ⁹ /L	I/II	Although promising in a phase II study as a treatment for anemia of MF, ¹⁰⁶ pomalidomide was not superior to placebo in a phase III study in MF ¹⁰⁷
NCT02593760	Vismodegib (Hedgehog inhibitor)	PMF or post-PV/ET MF, intermediate- or high-risk; spleen >5 cm below LCM; ANC >1 × 10 ⁹ /L, platelets ≥100 × 10 ⁹ /L, <10% peripheral blasts	I/II	Placebo-controlled trial; prior JAK or hedgehog inhibitor not allowed
NCT02742324	Pegylated interferon-α-2a	PMF or post-PV/ET MF, intermediate- or high-risk, with need for active therapy; ANC ≥ 1.5 × 10 ⁹ /L, platelets ≥150 × 10 ⁹ /L, ≤10% peripheral blasts	I/II	Interferon-α alone has been disappointing in MF; ^{108,109} although it may retard the progression of early PMF ¹¹⁰ ; prior interferon-α or JAK2 inhibitor not allowed
NCT01787552	Sonidegib (Hedgehog inhibitor)	PMF or post-PV/ET MF, symptomatic, spleen ≥5 cm below LCM, intermediate- or high-risk; platelets ≥75 × 10 ⁹ /L	I/II	RP2D, 20 mg bid of rux and 400 mg/d of sonidegib ⁸³ ; prior JAK or smoothened inhibitors not allowed
NCT02076191	Decitabine (HMA)	MPN in AP or post-MPN AML	I/II	
NCT02257138	Decitabine (HMA)	Phase I portion: R/R AML Phase II portion: post-MPN AML or MDS/MPN with >20% blasts	I/II	

Abbreviations: AML, acute myeloid leukemia; ANC, absolute neutrophil count; AP, accelerated phase; CDK, cyclin-dependent kinase; CP, chronic phase; ET, essential thrombocythemia; HDAC, histone deacetylase; Hgb, hemoglobin; HMA, hypomethylating agent; IMiD, immunomodulatory drug; JAK, Janus kinase; LCM, left costal margin; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PI3K, phosphatidylinositol-3-kinase; PMF, primary myelofibrosis; PV, polycythemia vera; RP2D, recommended phase II dose; R/R, relapsed/refractory; rux, ruxolitinib; TD, transfusion-dependent.

and even improvement of anemia, but long-term therapy is required for disease-modifying effects (eg, regression of BM fibrosis) to emerge, and the tolerability of chronic therapy with these agents is an important concern.^{67–69} In a phase Ib trial⁷⁰ of ruxolitinib and the pan-HDACI panobinostat in patients with intermediate- or high-risk⁷¹ MF and palpable splenomegaly of 5 cm or greater, 15 mg twice daily of ruxolitinib and 25 mg 3 times a week of panobinostat was found to be reasonably well-tolerated, and reductions in spleen volume and the allelic burden of mutant *JAK2* by 35% or greater and 20% or greater, respectively, were achieved in a greater proportion of patients at earlier time points than has been reported with ruxolitinib alone.⁵⁶

Although aberrant promoter hypermethylation is characteristic of PV and ET, primary MF is characterized by both aberrant hypermethylation and hypomethylation.⁷² The DNMTI azacitidine has limited clinical activity on its own in patients with MF,⁷³ but has been combined with ruxolitinib in a phase II trial in these patients.⁷⁴ Azacitidine was introduced at a dose of 25 mg/m²/d for 5 days in 28-day cycles after 3 months of ruxolitinib alone, with provision for gradual dose increase to 75 mg/m²/d as tolerated. The response rate²² among 28 evaluable patients was 82%, with a median time to response of 1 month; 11 of 13 serially evaluable responders experienced a reduction in their *JAK2* V617F allelic burden (2 experienced >50% reduction) and 6 of 22 (27%) had improvement in BM fibrosis grade. Most patients required dose interruptions and/or adjustments.⁷⁴ In a study of 54 patients with post-MPN MDS or acute myeloid leukemia, azacitidine produced an overall response rate of 52% with a median response duration of 9 months and median overall survival of 11 months.⁷⁵ Decitabine also appears active in patients with high-risk primary MF and MPN in accelerated or blastic phase,⁷⁶ and clinical trials of ruxolitinib in combination with decitabine in the latter populations are ongoing (ClinicalTrials.gov identifiers: NCT02076191, NCT02257138).

Activation of the PI3K/Akt/mTOR pathway is an important downstream consequence of JAK-STAT signaling in MPN,⁷⁷ and the dual PI3K/mTOR inhibitor, BEZ235, synergistically enhances the activity of *JAK2* inhibitors against cultured and primary CD34-positive MPN cells, with relative sparing of normal CD34-positive hematopoietic progenitor cells.⁷⁸ Rux-

olitinib was combined with the pan-PI3K inhibitor buparlisib in a 2-arm, phase Ib study in intermediate- or high-risk patients with MF who could either be *JAK* inhibitor-naïve (arm A, n=22) or previously treated with *JAK* inhibitors (arm B, n=20).⁷⁹ The maximum tolerated dose for the combination was determined to be 15 mg twice daily of ruxolitinib, along with 60 mg daily of buparlisib. A total of 55% and 20% of patients in arms A and B, respectively, achieved a 50% or greater reduction in palpable spleen length (considered approximately equivalent to ≥35% SVR) at week 24, but these percentages decreased to 45% and 18%, respectively, when only patients in the expansion phase receiving uniform drug doses were considered. After 24 weeks of treatment at the maximum tolerated dose, only 4 patients (3 in arm A; 1 in arm B) exhibited an improvement in BM fibrosis, whereas 2 in arm A had worsening BM fibrosis.⁷⁹ Although the IWG-MRT response rate²² to everolimus (mTOR inhibitor) monotherapy in intermediate- or high-risk MF was only 23%, most patients experienced complete resolution of systemic symptoms.⁸⁰

Excess hedgehog ligand secretion and loss of PTCH2, which drives canonical and noncanonical hedgehog signaling, have been described in MPN.⁸¹ The smoothened inhibitor, sonidegib, has been shown to improve leukocytosis and thrombocytosis, reduce the allelic burden of mutant *JAK2*, and significantly reduce BM fibrosis in a murine model of ET/MF.⁸² In a phase Ib/II study, the recommended phase II doses for combination ruxolitinib and sonidegib were found to be 20 mg twice daily and 400 mg daily, respectively.⁸³ A total of 27 *JAK* inhibitor-naïve patients with intermediate- or high-risk MF and palpable splenomegaly were treated at these doses for a median of 28.6 weeks. Seventeen patients (63%) experienced adverse events requiring dose adjustment or interruption. At the end of week 24, 12 patients (44.4%) had a 35% or greater reduction in spleen volume (although 15 [55.6%] achieved ≥50% reduction in palpable spleen length), the mean reduction in *JAK2* V617F allelic burden was 9%, and 2 patients had an improvement in BM fibrosis, whereas 3 had worsening.⁸³

Newer *JAK2* Inhibitors

A number of investigational *JAK2* inhibitors have been discontinued, mostly owing to toxicity concerns, and ruxolitinib remains the only one currently approved for oncologic indications.⁸⁴ Among the

Drug Development in Myeloproliferative Neoplasms

other compounds, only momelotinib, pacritinib, and NS-018 remain in clinical trials.⁸⁴ Table 3 lists ongoing trials of these agents in MF.

Momelotinib is a JAK1/2 inhibitor that may produce significant anemia responses, in addition to spleen and symptom responses, among patients with MF.⁸⁵ Some data suggest that momelotinib inhibits ALK2-mediated expression of hepcidin in the liver,

which results in increased release of iron from sequestered cellular stores and enhanced erythropoiesis.⁸⁶ In separate phase I/II studies (n=166⁸⁷ and n=61,⁸⁸ respectively) in patients with intermediate-2- or high-risk⁷¹ MF, or intermediate-1-risk⁷¹ MF with symptomatic organomegaly or unresponsiveness to available therapy, momelotinib produced spleen responses (by physical examination) in 39% and 72%, and anemia

Table 3. Ongoing Clinical Trials (Nontransplant) of JAK Inhibitors Other Than Ruxolitinib in MF

Clinicaltrials.gov Identifier	Drug	Phase	Major Inclusion Criteria	Comments
NCT02515630	Momelotinib	II	PMF or post-PV/ET MF requiring therapy, intermediate-2- or high-risk, or intermediate-1-risk with symptomatic organomegaly, TD, platelets $\geq 50 \times 10^9/L$	21-day washout from prior JAK inhibitor; grade ≥ 2 PN not allowed
NCT02101268	Momelotinib	III	PMF or post-PV/ET MF, spleen palpable ≥ 5 cm below LCM, intermediate-2- or high-risk, or intermediate-1-risk with symptomatic organomegaly, $<10\%$ peripheral blasts, ANC $>0.75 \times 10^9/L$, current or prior rux required	Comparator: BAT; grade ≥ 2 PN not allowed; designed for rux failures and rux-intolerant patients
NCT02124746	Momelotinib	II	Long-term extension study for patients with PMF, post-PV/ET MF, PV or ET who have tolerated momelotinib and achieved stable disease or better on a previous trial	Patients receive momelotinib for up to 4 y
NCT01969838 (SIMPLIFY-1)	Momelotinib vs rux	III	PMF or post-PV/ET MF requiring therapy, intermediate-2- or high-risk, or intermediate-1-risk with symptomatic organomegaly, anemia (Hgb <10 g/dL), and/or unresponsive to available therapy; platelets $\geq 50 \times 10^9/L$, ANC $\geq 0.75 \times 10^9/L$, $<10\%$ peripheral blasts	Frontline, head-to-head study; patients must be JAK inhibitor-naïve; grade ≥ 2 PN not allowed
NCT02055781 (PERSIST-2)	Pacritinib (400 mg daily or 200 mg bid)	III	Intermediate- or high-risk MF with platelets $\leq 100 \times 10^9/L$, spleen palpable ≥ 5 cm below LCM, MPN-SAF TSS ≥ 13	Comparator: BAT; cannot have had >2 prior JAK2 inhibitors
NCT01773187 (PERSIST-1) ⁹⁴	Pacritinib (400 mg daily)	III	Intermediate- or high-risk MF, spleen palpable ≥ 5 cm below LCM, MPN-SAF TSS ≥ 13	Comparator: BAT; prior JAK2 inhibitor not allowed
NCT02564536	Pacritinib (200 mg bid) plus decitabine	0 (pilot)	Intermediate- or high-risk PMF or post-PV/ET MF who are unresponsive to or unable to receive current therapy, or patients with MDS/MPN; ANC $\geq 0.5 \times 10^9/L$, $<20\%$ BM blasts	Decitabine administered subcutaneously on days 1, 5, 8, 12, 15, 19, 22, and 26 of a 28-d cycle
NCT01423851	NS-018	I/II	PMF or post-PV/ET MF requiring therapy; prior JAK2 inhibitor therapy required, R/R or intolerant; ANC $>1 \times 10^9/L$, platelets $>25 \times 10^9/L$	Preliminary results available ⁹⁵

Abbreviations: ANC, absolute neutrophil count; BAT, best available therapy; BM, bone marrow; ET, essential thrombocythemia; Hgb, hemoglobin; JAK, Janus kinase; LCM, left costal margin; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; MPN-SAF TSS, MPN Symptom Assessment Form Total Symptom Score; PMF, primary myelofibrosis; PN, peripheral neuropathy; PV, polycythemia vera; R/R, relapsed/refractory; rux, ruxolitinib; TD, transfusion-dependent.

responses in 53% and 16.7%, respectively.^{87,88} In both studies, spleen response was a composite of 50% or greater reduction in palpable spleen length for those with baseline splenomegaly 10 cm or greater, and resolution of palpable splenomegaly for those with baseline splenomegaly between 5 and 10 cm, and had to last at least 8 weeks. Similarly, anemia response was a composite of the achievement of transfusion independence for 12 weeks or greater in those who were transfusion-dependent at baseline, and a sustained increase in hemoglobin level of 2 g/dL or greater in those who were not transfusion-dependent at baseline, but had a baseline hemoglobin level of less than 10 g/dL. In the second study, the spleen response rate at 24 weeks by imaging was 45.8%.⁸⁸ Most patients had a 50% or greater improvement in pruritus, cough, bone pain, fever, and night sweats at 3 months in the first study,⁸⁷ and the MPN-SAF TSS²³ decreased by 50% or greater at 6 months in approximately one-third of patients in the second study.⁸⁸ Peripheral neuropathy (PN) is an important side effect of momelotinib.⁸⁹ In the Mayo Clinic experience, momelotinib treatment-emergent PN occurred in 44 of 100 patients (44%) with MF; median time to onset was 32 weeks and duration was 11 months.⁸⁹ Improvement after dose reduction or discontinuation of momelotinib was documented in only 2 patients. Treatment-emergent PN did not correlate with initial or maximal momelotinib dose, or with prior thalidomide exposure.⁸⁹ In the second study that used twice daily dosing of momelotinib, PN also occurred in 44% of subjects (27 of 61) and was mainly sensory in nature⁸⁸; all but 2 were grade 1/2 events. Median time to onset was again 227 days (32 weeks), and overall, 5 subjects discontinued from the study because of PN.⁸⁸ Multiple doses of momelotinib (150, 200, and 250 mg twice daily, 300 mg once daily) have been tested in these studies,^{87,88} and the 300-mg daily dose is the one currently being evaluated in phase III studies (Table 3).

The JAK2/FMS-like receptor tyrosine kinase 3 (FLT3) inhibitor pacritinib also potently inhibits colony-stimulating factor 1 receptor, and interleukin-1 receptor-associated kinase 1 and does not inhibit JAK1; these actions may explain its lack of myelosuppression.⁹⁰ Pacritinib was evaluated in a phase II study in 35 patients with MF who were either newly diagnosed with an intermediate- or high-risk Lille score⁹¹ and not candidates for stan-

dard therapy or had splenomegaly that was poorly controlled with standard therapy.⁹² Patients with any degree of cytopenia were eligible. A total of 42% of evaluable patients experienced a 50% or greater reduction in spleen size from baseline up to week 24 by physical examination (31% of evaluable patients had $\geq 35\%$ SVR on imaging) and 48.4% of patients had a 50% or greater reduction in TSS (using the Myelofibrosis Symptom Assessment Form [MFSAF])⁹³ from baseline up to week 24. Grade 1 or 2 diarrhea (69%) and nausea (49%) were the most common adverse events.⁹² Pacritinib was then compared with BAT (excluding ruxolitinib) in the phase III PERSIST-1 trial in patients with MF.⁹⁴ SVR rates at week 24 were 19.1% for pacritinib versus 4.7% for BAT in the intention-to-treat (ITT) analysis, and 25% versus 5.9%, respectively, among evaluable patients. A total of 24.5% versus 6.5% (ITT) and 40.9% versus 9.9% (evaluable population) of patients, respectively, had a 50% or greater reduction in their MPN-SAF TSS.²³ A total of 25.7% of pacritinib patients became transfusion-independent versus 0% of patients randomized to BAT. Most adverse events in the pacritinib arm were grade 1/2 diarrhea, nausea, or vomiting.⁹⁴ However, the FDA placed a “full clinical hold” on pacritinib after reports of deaths due to intracranial hemorrhage, cardiac failure, and cardiac arrest in the phase III PERSIST-2 trial (Table 3).

NS-018 is a JAK2-selective inhibitor currently undergoing phase II testing in patients with intermediate- or high-risk MF (ClinicalTrials.gov identifier: NCT01423851; Table 3). The recommended phase II dose based on data from the phase I portion of this trial is 300 mg/d.⁹⁵ A total of 23 of the 48 patients enrolled on the phase I portion had received prior JAK2 inhibitor therapy. A 50% or greater reduction in palpable spleen size was achieved in 56% of patients, including 47% of patients with prior JAK inhibitor treatment.⁹⁵ After 3 cycles of treatment, reductions in MFSAF scores⁹³ were observed for all symptoms, and 11 of 30 (37%) evaluable patients had a reduction in BM fibrosis by 1 grade or more, although the JAK2 V617F allelic burden was largely unchanged.⁹⁵ There was a hint from this study that NS-018 may elicit an early improvement in BM fibrosis in some patients, and that this might correlate with improvements in anemia and thrombocytopenia, as well as with spleen responses; however, the numbers were small, precluding firm conclusions. The cytokine

regulation profile for NS-018 appears to be slightly different from that of ruxolitinib.⁹⁵

Antifibrotic Agents

PRM-151 is an intravenously administered recombinant form of human pentraxin-2 (serum amyloid P, a highly conserved, naturally circulating plasma protein and soluble pattern recognition receptor of the innate immune system that may localize specifically to sites of injury and function to aid in the removal of damaged tissue)⁹⁶ that was studied on weekly and every-4-week schedules, either alone or in conjunction with ruxolitinib, in 27 patients with intermediate- or high-risk⁹⁷ MF and grade 2 or greater BM fibrosis.⁹⁸ More than half had received a prior JAK inhibitor. In the first stage of the trial (24 weeks of therapy), 9 of 26 (35%) evaluable patients experienced response, 4 had symptoms of clinical improvement, and 6 had BM fibrosis responses.²² PRM-151 was well-tolerated in all 4 arms.⁹⁸ A total of 18 patients continued onto an extension phase (stage 2), and data on 13 who had completed at least 72 weeks of treatment were presented last year.⁹⁹ Symptom and spleen responses continued to improve over time, as did anemia and thrombocytopenia, with most transfusion-dependent patients becoming transfusion-independent. A total of 54% had a BM morphologic response, and 85% showed a response via computer-assisted image analysis; 69% and 38% of patients experienced a 50% or greater and 100% reductions from baseline, respectively, in their TSS²³ between 24 and 72 weeks.⁹⁹ In 5 patients with baseline hemoglobin level less than 10 g/dL, the median hemoglobin level increased from 8.6 g/dL at baseline to 10.7 g/dL at week 72. Three of these patients who were receiving transfusions at baseline achieved transfusion independence, with durations of 32 to 60 weeks.⁹⁹ Similarly, of 9 patients with baseline platelet counts of less than $100 \times 10^9/L$, the median platelet count increased from $38 \times 10^9/L$ at baseline to $52 \times 10^9/L$. Four of these patients were receiving platelet transfusions at baseline, and all became transfusion-independent.⁹⁹ No serious adverse events related to PRM-151 occurred.⁹⁹

Imetelstat

Imetelstat is an intravenously administered lipid-conjugated oligonucleotide telomerase inhibitor that was studied in 33 patients with intermediate-2- or high-risk¹⁰⁰ MF, 48% of whom had received prior

JAK inhibitor therapy¹⁰¹; 7 patients (21%) achieved a complete or partial response.²² BM fibrosis was reversed in all 4 patients with a complete response, 3 of whom also experienced a molecular response. Responses did not correlate with baseline telomere length. Responses were restricted to patients with mutated JAK2, and were not seen in the presence of ASXL1 mutations.¹⁰¹ Furthermore, responses appeared to correlate with the presence of mutations in the RNA splicing genes, *SF3B1* or *U2AF1*. Grade 3/4 myelosuppression and grade 1/2 hepatotoxicity were frequent. However, none of the abnormalities in liver-enzyme levels were linked to clinically overt liver damage and most were reversible.¹⁰¹ Imetelstat, 9.4 or 4.7 mg/kg every 3 weeks, is currently being evaluated in patients with intermediate-2- and high-risk MF that failed to respond to therapy with a JAK inhibitor in a phase II study (ClinicalTrials.gov identifier: NCT02426086). In a recent press release, Geron Corporation (Menlo Park, CA) announced that the 4.7-mg/kg dose will not be evaluated further due to insufficient activity.¹⁰²

Conclusions

This review summarizes the drugs currently in clinical development for MPNs, with a focus on those most likely to influence MPN management guidelines over the next several years, as has occurred with ruxolitinib. It is possible that ruxolitinib will be used in lower-risk patients with MF, particularly those with adverse genomic features, based on findings from the ReTHINK study. Ruxolitinib-based combinations, particularly with DNMTI and HDACIs, as well as with antianemia medications, are likely to gain widespread acceptance. Regulatory approval of one or more JAK inhibitors beyond ruxolitinib is anticipated, although the discontinuation of many of these agents tells a cautionary tale. The experience with PRM-151 and imetelstat is limited, but these drugs are attractive by virtue of their ability to improve or reverse BM fibrosis.

Despite the success of ruxolitinib, there remain many unmet needs in terms of drug development for patients with MF. First and foremost, the survival of these patients remains short, and the modest gains in survival achieved with ruxolitinib may be more attributable to improvement in appetite, weight gain, correction of hypocholesterolemia, and reversal of

cachexia than to actual targeting of the neoplastic clone.¹⁰³ Other areas where novel therapeutics are needed include anemia of MF, whether from the disease or worsened by ruxolitinib. The infectious risks of long-term JAK inhibitor therapy remain an important concern. Ruxolitinib's approval is a welcome advancement in the treatment of PV, as is the advent of ropeginterferon- α . Approval of these or other agents is awaited by patients with ET who have troublesome symptoms. Finally, no current therapy reliably prevents progression of PV or ET to MF or acute myeloid leukemia.

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Drug Development in Myeloproliferative Neoplasms

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