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Developmental Therapeutics in Myeloproliferative Neoplasms

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Abstract

The unprecedented success of the Janus kinase (JAK) 1/2 inhibitor ruxolitinib in myelofibrosis provided much-needed impetus for clinical drug development for the Philadelphia chromosome negative myeloproliferative neoplasms (MPN). The survival benefit conferred by this agent, along with its marked efficacy with regard to spleen volume and symptom reduction, have made ruxolitinib the cornerstone of drug therapy in myelofibrosis. However, there remain significant unmet needs in the treatment of patients with MF, and many novel classes of agents continue to be investigated in efforts to build upon the progress made with ruxolitinib. These include inhibitors of histone deacetylases (HDACs) and DNA methyltransferases, phosphatidylinositol-3-kinase isoforms, heat shock protein 90, cyclin-dependent kinases 4/6, and Hedgehog signaling, among others. In parallel, other JAK inhibitors with potential for less myelosuppression or even improvement of anemia, greater selectivity for JAK1 or JAK2, and the ability to overcome JAK inhibitor “persistence” are in various stages of development. First-in-class agents such as the activin receptor IIA ligand trap sotatercept (for anemia of myelofibrosis), the telomerase inhibitor imetelstat, and the anti-fibrotic agent PRM-151 (recombinant human pentraxin-2) are also in clinical trials. In polycythemia vera, a novel interferon administered every 2 weeks is being developed for frontline therapy in high-risk individuals, and inhibitors of human double minute 2 (HDM2) have shown promise in preclinical studies, as have HDAC inhibitors, e.g., givinostat (both in the laboratory and in the clinic). Ruxolitinib is approved for second-line therapy of polycythemia vera, and is being developed for essential thrombocythemia.

Keywords

MPN; JAK inhibitors; HDAC inhibitors; hypomethylating agents; MDM2 inhibitors; KIT inhibitors; CDK inhibitors; PRM-151; imetelstat; sotatercept

Introduction

The marked improvement in symptoms and reduction in splenomegaly among patients with intermediate-2 or high risk myelofibrosis (MF) receiving ruxolitinib observed in the pivotal COMFORT I and II trials when compared to placebo and best available therapy (BAT),

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respectively, led to the approval of this agent by the Food and Drug Administration in 2011 for the treatment of patients with intermediate or high risk MF.^{1,2} Additionally, an overall survival (OS) benefit of ruxolitinib treatment was observed in COMFORT I after a median follow-up of 12 months;¹ in COMFORT II, this took a median of 3 years to emerge.³ In both trials, extensive crossover occurred after the primary endpoint had been assessed; despite this, the survival advantage for patients originally randomized to ruxolitinib persisted after a median of 5 years of follow-up (median survival not reached versus 4.1 years for BAT in COMFORT II).⁴ The prolongation of survival with ruxolitinib in higher risk patients with MF has also been seen in multiple retrospective comparisons,^{5,6} as well as in a pooled analysis of the COMFORT trials.⁷ Ruxolitinib's efficacy appears unaffected by mutational status,⁸ although the number of mutations does seem to matter (lower rates of spleen response, shorter time to treatment discontinuation and shorter OS in patients with 3 myeloid malignancy-associated mutations).⁹ Spleen responses to ruxolitinib are dose-dependent and correlate with survival.^{5,10} While the COMFORT trials specifically studied intermediate-2 and high risk patients, substantial data exist to support the efficacy of ruxolitinib in intermediate-1 risk patients as well.^{11,12} The benefits of ruxolitinib observed in clinical trials have been recapitulated in "real life" settings, including those of early initiation of treatment.¹⁰ Accordingly, ruxolitinib is now being studied in "high molecular risk" patients without significant symptoms or splenomegaly in the placebo-controlled ReTHINK trial in Europe.¹³ For the above reasons, ruxolitinib has evolved to become the standard of care for most patients with MF.¹⁴

Despite these positives, ruxolitinib has several shortcomings. On-target anemia and thrombocytopenia stemming from JAK2 inhibition are common, and the drug is difficult to use in MF patients with severe thrombocytopenia (platelets <50,000/ μ L), who have a poor prognosis.¹⁵ Furthermore, regression of bone marrow (BM) fibrosis is infrequent, and complete molecular remissions are rare.^{4,16,17} As such, efforts are ongoing to develop other JAK inhibitors that are less myelosuppressive, drugs that may offset ruxolitinib-induced anemia, enabling dose optimization, find synergistic ruxolitinib-based combinations to achieve a greater disease-modifying effect in MF, and identify new therapeutic targets and novel drug classes.

Reduction of thrombotic risk is the major goal of therapy in patients with polycythemia vera (PV) and essential thrombocythemia (ET), and hydroxyurea (HU) is usually the first-line agent of choice for patients who require cytoreduction.¹⁸ In addition, most patients should receive aspirin. In PV, achievement of hematocrit < 45% is an important goal,¹⁹ and ruxolitinib is approved as second-line therapy for patients who are resistant or intolerant to HU²⁰ based on the findings of the RESPONSE trial.²¹ Anagrelide is typically chosen as second-line therapy in ET.¹⁸ Interferon preparations, while clearly active in PV and ET with the added ability to induce clonal remissions,^{22–24} are not approved yet for these indications. Because of their lack of leukemogenicity, interferons are often preferred for younger, high-risk patients with PV or ET.¹⁸

Developmental Therapeutics in PV and ET

Interferons

As alluded to above, interferons are highly active in PV and ET. Results after a median of 7 years (82.5 months) of follow-up of a phase II study of pegylated interferon alfa-2a conducted at the MD Anderson Cancer Center were recently presented.²⁵ Patients (43 PV, 40 ET) could be newly diagnosed or previously treated. The overall median exposure to therapy was 87 months. At the time of writing, 32 (39%) patients were still on study (9 (28%) receiving 90 mcg weekly, 15 (47%) 45 mcg weekly and 8 (25%) with treatment on hold due to toxicity or financial constraints). *JAK2* status or allele burden had no impact on achievement of response (clinical or molecular), time to response or duration of therapy. Median durations of hematologic and molecular responses were 66 and 53 months, respectively; complete molecular responses (CMRs) were the most durable. 35% of patients discontinued due to toxicity, and new, late (> 2 years from therapy initiation) treatment-emergent grade 3/4 toxicity was seen in 17%. Even among patients in complete hematologic remission (CHR), vascular adverse events (AEs) and disease transformation occurred in 5 patients each.²⁵

The Myeloproliferative Disorders Research Consortium (MPD-RC) recently reported the results from an interim analysis (n = 75) of a global phase III trial of frontline pegylated interferon alfa-2a compared with HU in high-risk patients with PV or ET.²⁶ The overall response rate (ORR) was not significantly different between the two arms: 69% for HU and 53% for pegylated interferon alfa-2a (p = 0.6). The percentages of patients achieving CHR (the primary endpoint) in the two arms were similar even when the analysis was broken down by diagnosis, and also when patients who never initiated treatment were excluded. The rate of phlebotomy use among the 38 patients with PV significantly favored pegylated interferon alfa-2a, which was also clearly associated with higher rates of grade 3 toxicity.²⁶

Ropeginterferon alfa-2b is a next-generation, mono-pegylated interferon alfa-2b isoform with a longer elimination half-life, permitting administration every two weeks.²⁷ In a phase I/II study in 51 patients with PV, there were no dose-limiting toxicities (DLTs), and the ORR was 90% (CHR in 47% and partial hematologic remission (PHR) in 43%). The best molecular response was CMR in 21% and partial in 47%. Responses did not correlate with dose.²⁷ Based upon these findings, the PROUD-PV trial, a phase III randomized controlled trial (RCT) comparing this agent to HU in 257 patients with PV, was conducted.²⁸ Patients could be naïve to cytoreduction or have previously received HU (cumulative exposure > 3 years), but if the latter, must not have been intolerant of HU or complete responders to it. This was a non-inferiority trial with CHR as the primary endpoint. At 12 months, the rate of CHR in the ropeginterferon alfa group was 43.1% and in the HU group, it was 45.6%, demonstrating non-inferiority (p = 0.0028). When considering CHR with normalization of spleen length, the rates were 21.3% and 27.6%, respectively, but the median spleen length at baseline was near-normal and the observed change not clinically relevant. Cytopenias were significantly more frequent with HU, as was nausea, while increased gamma glutamyl transferase was seen significantly more frequently in the ropeginterferon alfa arm. While not

statistically significant, autoimmune, endocrine, psychiatric and cardiovascular disorders were more common among patients receiving ropeginterferon alfa.²⁸

Ruxolitinib

As noted above, ruxolitinib was approved in 2014 for HU-resistant/intolerant patients with PV, based on the results of the RESPONSE trial.²¹ In this RCT, ruxolitinib proved statistically significantly superior to BAT in terms of the primary endpoint, which was a composite of hematocrit control through week 32 and a ≥35% spleen volume reduction (SVR), as well as each individual component of the primary endpoint, CHR rates and the rate of ≥50% reduction in the myeloproliferative neoplasm-symptom assessment form (MPN-SAF) total symptom score (TSS) at week 32.²¹ Of note, the majority of patients in the BAT arm received HU despite having previously shown evidence of resistance or intolerance to this agent, reflecting the lack of effective options for this population. The benefits of ruxolitinib were sustained after a minimum of 80 weeks of follow-up.²⁹ Most BAT patients crossed over to ruxolitinib at or soon after week 32. Among these patients, 79.2% did not require phlebotomy, and 18.8% achieved a ≥35% SVR after 32 weeks of treatment. Importantly, the rate of thromboembolic events was 1.8 per 100 patient-years among patients originally randomized to ruxolitinib versus 8.2 per 100 patient-years among patients originally randomized to BAT.²⁹ The mean percent change from baseline *JAK2* V617F allele burden among the 104 patients randomized to ruxolitinib was -40% at week 208.³⁰

Because the pivotal RESPONSE trial required the presence of splenomegaly, a finding present in less than half of PV patients at diagnosis,³¹ the very similarly designed phase IIIB RESPONSE-2 RCT was subsequently conducted to assess the efficacy of ruxolitinib versus BAT in HU-resistant/intolerant patients without palpable splenomegaly.³² The primary endpoint, the proportion of patients achieving hematocrit control at week 28, was achieved in 46 of 74 (62%) patients receiving ruxolitinib, and 14 of 75 (19%) patients receiving BAT which, again, was HU in 37 of 75 (49%) patients at randomization.³²

Ruxolitinib was also investigated for its symptom benefit in another phase IIIB RCT, RELIEF, in patients with PV well-controlled on HU in terms of hematological parameters but with persistent PV-related symptoms.³³ Patients were randomized 1:1 to switch to ruxolitinib (n = 54) or stay on HU (n = 56), with crossover to ruxolitinib permitted after week 16. This trial missed its primary endpoint, a ≥50% improvement from baseline in the MPN-SAF TSS cytokine symptom cluster (the sum of tiredness, itching, muscle aches, night sweats, and sweats while awake) at week 16, although this was achieved by more patients in the ruxolitinib than in the HU continuation group (43.4% versus 29.6%, p = 0.139).³³

NCT02962388 is an upcoming phase II/III trial in France which will compare ruxolitinib to BAT (either anagrelide or interferon-alfa) in high-risk patients with ET who meet the European LeukemiaNet criteria for resistance or intolerance to HU.³⁴ A similar trial is planned in the US using anagrelide as the active comparator. Ruxo-BEAT (NCT02577926) is an ongoing phase III trial in Germany comparing ruxolitinib to BAT in patients with high-risk PV or ET. ET patients may be treatment-naïve or previously treated. PV patients cannot have received cytoreductive therapy for more than 6 weeks.

Histone deacetylase (HDAC) inhibitors

HDAC inhibitors are pleiotropic agents that have multiple potential mechanisms of action in MPN cells, prominent among them being down-regulation of JAK2 via inhibition of the chaperone protein function of heat shock protein 90 (HSP90).³⁵ Givinostat and vorinostat are clearly active in patients with PV and ET, producing both spleen and hematologic responses in a substantial proportion of patients, apparently without regard to the mutational status of *JAK2*.^{36–38} In these trials, reduction of the allele burden of mutated *JAK2* was modest, and the drugs were particularly effective for pruritus. Fatigue and gastrointestinal AEs were significant concerns.^{36–38} Nevertheless, givinostat continues to be developed for PV, with a 100% ORR among evaluable patients with active/uncontrolled disease noted after 3 cycles in an ongoing phase IB/II trial.³⁹ “Active/uncontrolled” was defined in this study as hematocrit > 45% (or < 45% because of phlebotomy), platelets > 400 x 10⁹/L and leukocytes > 10 x 10⁹/L.³⁹

Human double minute 2 (HDM2) inhibitors

HDM2 is an important negative regulator of p53 (promotes degradation of p53) and small-molecule inhibitors of HDM2 can trigger apoptosis in cells with intact p53 function by activating p53. Because interferon alfa targets *JAK2*^{V617F+} progenitors in PV through activation of mitogen activated protein kinase (MAPK) and signal transducer and activator of transcription 1 (STAT1), thereby increasing p53 transcription,⁴⁰ the combination of interferon alfa with HDM2 inhibitors, which prevent the degradation of p53, provides an opportunity to induce p53-dependent apoptosis through disparate mechanisms. Indeed, combination treatment with subtherapeutic doses of pegylated interferon alfa-2a and the HDM2 antagonist Nutlin-3 triggered increased apoptosis in PV CD34⁺ cells and inhibited proliferation of these cells to a greater extent than normal CD34⁺ cells.⁴¹ The combination also reduced the proportion of *JAK2*^{V617F+} progenitors in 6 PV patients studied.⁴¹ Very similar observations were made upon substituting the orally available HDM2 inhibitor RG7112 in place of Nutlin-3. Low doses of RG7112, with and without pegylated interferon alfa-2a, significantly decreased MPN colony formation and preferentially eliminated *JAK2*^{V617F+} progenitors.⁴² Combination treatment of PV and primary myelofibrosis (PMF) CD34⁺ cells, followed by transplantation into immunodeficient mice, decreased the extent of donor-derived chimerism as well as the *JAK2*^{V617F} allele burden, suggesting that such combinatorial approaches may deplete MPN hematopoietic stem cells (HSCs).⁴² The clinical candidate HDM2 inhibitor idasanutlin is currently being studied in a phase I trial in patients with PV or ET (NCT02407080), with a provision for adding pegylated interferon alfa-2a in subjects not achieving at least a partial remission (PR) after 3 cycles. Of note, HDM2 inhibitors can cause significant thrombocytopenia by promoting p53-mediated apoptosis of megakaryocyte progenitors.⁴³

BCL-2 homology domain 3 (BH3)-mimetics

BH3-mimetic drugs such as navitoclax and venetoclax bind to the BH3-binding groove of anti-apoptotic proteins of the BCL-2 family, e.g., Bim, thereby displacing pro-apoptotic “BH3-only” proteins, which then trigger apoptosis through the mitochondrial pathway by activating the apoptosis effectors Bax and Bak.⁴⁴ Despite promising activity in a number of

different tumor types,^{45–48} the development of navitoclax was halted because of dose-limiting thrombocytopenia, an on-target effect resulting from inhibition of BCL-xL.⁴⁹ Similar to the preclinical data with the combination of HDM2 inhibitors and pegylated interferon alfa discussed above, the combination of interferon alfa and the BCL-2/-xL antagonist ABT-737 has also been shown to specifically target *JAK2*^{V617F} hematopoietic progenitor cells (HPCs) in PV.⁵⁰ Synergism between JAK2 inhibitors and ABT-737 has also been demonstrated in *JAK2*^{V617F}-driven MPN cells as a means of overcoming ruxolitinib resistance. It is possible that agents such as idasanutlin and navitoclax will find a place in therapy of MPN such as PV and ET where thrombocytopenia is less likely to be a problem in the clinical setting.

Developmental Therapeutics in MF

New agents for anemia

Anemia, present in ~30% of patients with MF at diagnosis and developing in essentially all patients at some point in their disease course, is difficult to treat.⁵¹ No agent is specifically approved for this indication, and anemia is worsened, particularly early in therapy, by ruxolitinib, although anemia related to ruxolitinib does not carry the same adverse prognosis as disease-related anemia.⁵² Response rates in real world settings to currently available agents such as danazol, erythroid stimulating agents (ESAs) and immunomodulatory drugs such as thalidomide or lenalidomide are in the 20–30% range. Furthermore, lenalidomide is difficult to combine with ruxolitinib because of additive myelosuppressive effects.⁵³ Pomalidomide appeared highly promising in a single-arm phase II trial,⁵⁴ but a subsequent phase III comparison with placebo in transfusion-dependent (TD) patients with MF yielded the exact same rate of transfusion independence (TI) in both arms (16%).⁵⁵

Sotatercept is a first-in-class fusion protein consisting of the extracellular domain of activin receptor type IIA conjugated to the Fc fragment of human IgG1 that “traps” ligands of the transforming growth factor beta (TGF- β) superfamily such as growth and differentiation factor 11 (GDF11) secreted by BM stromal cells and, in doing so, relieves their blockade of terminal erythropoiesis.^{56,57} In preclinical models of beta-thalassemia, sotatercept corrects ineffective erythropoiesis and improves anemia.⁵⁸ RAP-011, a “murinized” ortholog of sotatercept, has similar effects in hepcidin transgenic mice⁵⁹ and in a zebrafish model of Diamond-Blackfan anemia.⁶⁰ Sotatercept displayed promising evidence of clinical activity (40% rate of hematologic improvement in the erythroid lineage, HI-E) in a cohort (n = 53) of mostly high transfusion burden, ESA-refractory patients with lower risk myelodysplastic syndrome (MDS) or chronic myelomonocytic leukemia (CMML) and was well-tolerated.⁶¹ Early results from an ongoing phase II study of sotatercept in patients with MF and anemia were recently presented.⁶² Responses, including TI as defined by the International Working Group for MF Research and Treatment (IWG-MRT),⁶³ were noted in 5 of 14 (36%) evaluable patients. A separate cohort investigating the addition of sotatercept in anemic patients on a stable dose of ruxolitinib has now been added to this trial (NCT01712308).⁶²

Newer JAK inhibitors

Although a number of JAK inhibitors have been investigated in clinical trials over the years, only a few remain in clinical development and ruxolitinib is the only one approved for MPN, most of the others having been discontinued due to toxicity.

Pacritinib—Pacritinib is a JAK2-selective inhibitor (does not inhibit JAK1) that also inhibits fms-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF1R) and interleukin-1 receptor-associated kinase 1 (IRAK1) at nanomolar concentrations.⁶⁴ In a phase II study in MF patients (n = 35, 26 evaluable) that allowed any degree of cytopenia, it produced a 31% rate of SVR (35%, by magnetic resonance imaging (MRI)) and a 50% reduction in palpable spleen length in 42% of subjects from baseline up to week 24; median MF symptom improvement was 50% for all symptoms except fatigue.⁶⁵ Symptom responses were durable, and a 50% reduction in TSS from baseline was observed in 15 of 31 patients (48.4%) up to week 24; this increased to 18 of 31 patients (58.1%) up to the last visit on treatment, with the three additional responses occurring at week 36. Grade 1/2 gastrointestinal toxicities, anemia and thrombocytopenia were the most common AEs. Nine patients (26%) discontinued due to AEs. This trial was prematurely terminated by the sponsor for commercial reasons, which affected 8 patients (23%) still on therapy.⁶⁵ The overall results with pacritinib were similar in another phase I/II trial, in which 31 patients with MF and any degree of cytopenias received pacritinib, 400 mg daily, in the phase II portion.⁶⁶ The primary endpoint of 35% SVR by MRI was reached in 4 of 17 evaluable patients (23.5%) at week 24, although a much higher proportion (47.4%) of evaluable patients achieved 50% spleen length reduction by palpation. Seven of 18 evaluable patients (38.9%) achieved a 50% decrease in symptom score at week 24.⁶⁶

Based on these encouraging results, pacritinib was evaluated in two phase III trials, PERSIST-1 and PERSIST-2. PERSIST-1 compared pacritinib (400 mg daily) to BAT 2:1 in 327 JAK inhibitor-naïve patients with intermediate or high risk MF, absolute neutrophil count (ANC) $> 0.5 \times 10^9/L$, palpable splenomegaly ≥ 5 cm and a MPN-SAF TSS ≥ 13 .⁶⁷ BAT could not include ruxolitinib. 32% and 15% of patients, respectively, had platelet counts $< 100 \times 10^9/L$ and $< 50 \times 10^9/L$. The 35% SVR (primary endpoint) rates in the intention-to-treat (ITT) analysis were 19.1% for pacritinib and 4.7% for BAT at week 24 (p = 0.0003). By ITT analysis, 24.5% of pacritinib-treated patients versus 6.5% of BAT-treated patients achieved 50% improvement in the TSS (p < 0.0001). The superior efficacy of pacritinib over BAT was preserved among the patients with baseline platelets $< 100 \times 10^9/L$ and $< 50 \times 10^9/L$. Among erythrocyte-TD patients, 25.7% of patients in the pacritinib arm achieved TI, as opposed to no patients in the BAT arm (p = 0.043).⁶⁷ At week 60, 24% of evaluable pacritinib-treated patients achieved SVR 35%.⁶⁸ Crossover from BAT to pacritinib was permitted after week 24 or earlier in the event of disease progression. 90 of 107 (84%) patients crossed over from BAT to pacritinib; 19% of evaluable crossover patients achieved 35% SVR at week 36 after crossover. Treatment-emergent diarrhea with pacritinib was most common during the first 8 weeks of treatment (all grades, 51%; grade 3/4, 2.7%). Cytopenias were more common with pacritinib versus BAT, while peripheral neuropathy (PN) occurred more frequently in BAT-treated patients.⁶⁸

In contrast to PERSIST-1, PERSIST-2 was conducted exclusively in patients with platelets $100 \times 10^9/L$, a recognized adverse prognostic feature in MF,⁶⁹ and both prior JAK inhibitor use and use of ruxolitinib in the BAT arm were allowed.⁷⁰ Patients were randomized 1:1:1 to pacritinib 200 mg twice daily, 400 mg once daily or BAT. The percentages of patients achieving 35% SVR by imaging and 50% reduction in TSS, both from baseline to week 24, were co-primary endpoints. Thirty-two (44%) BAT patients in the ITT efficacy population received ruxolitinib at some point during the study. Pacritinib (pooled data) was significantly more effective at inducing a 35% SVR than BAT (18% versus 3%, $p = 0.001$), and 25% of pacritinib patients achieved a 50% reduction in their TSS, as compared to 14% of BAT patients ($p = 0.079$). Considering the two pacritinib dose cohorts individually, pacritinib 200 mg twice daily was significantly better than BAT on both counts (SVR and TSS), while pacritinib 400 mg once daily beat BAT in terms of SVR but not in terms of TSS improvement. Erythrocyte-TD improved by week 24 in more patients on pacritinib than on BAT. Treatment-emergent AEs for pacritinib were as expected (gastrointestinal and hematologic) and generally less frequent for twice daily as compared to once a day administration. The former also achieved higher steady-state plasma levels but lower peak concentrations.⁷⁰

On February 8th, 2016, the Food and Drug Administration (FDA) placed a full clinical hold on pacritinib based on excess mortality and cardiac and hemorrhagic events in PERSIST-1, which was only lifted on January 4th, 2017.⁷¹ This impacted the PERSIST-2 study and all other ongoing studies of pacritinib, such that although 311 patients underwent randomization, only 221 (74 and 75 in the pacritinib twice and once daily groups, respectively, and 72 in the BAT group) could be included in the ITT efficacy population (i.e., had completed 24 weeks and undergone evaluation for the co-primary endpoints). At the request of the FDA, CTI BioPharma will conduct a dose exploration study of pacritinib (100 mg once daily, 100 mg twice daily and 200 mg twice daily) in approximately 105 patients with PMF who have failed prior ruxolitinib.

Momelotinib—Momelotinib is a JAK1/2 inhibitor that appears to have the unique property of improving anemia in patients with MF.⁷² A phase I/II study of momelotinib was performed in 166 patients with intermediate-2 or high risk MF or, if intermediate-1 risk, with symptomatic splenomegaly or hepatomegaly and/or unresponsive to available therapy.⁷³ In the dose expansion phase of this study, subjects received either 150 mg or 300 mg once daily, or 150 mg twice daily for nine months. The spleen response rate was 39% (57 of 148 evaluable patients) and the anemia response rate (composite of TI rate among erythrocyte-TD patients and rate of hemoglobin improvement in transfusion-independent, anemic patients) was 53% (59 of 111 patients). The median duration of spleen response was 324 days, and the median durations of 12-week TI and anemia response (in transfusion-independent patients) had not been reached at the time of presentation. Of note, spleen responses in this study were determined by palpation, and baseline transfusion dependence was loosely defined. Grade 3/4 thrombocytopenia and neutropenia related to momelotinib occurred in 29% and 5%, respectively, and grade 1/2 PN was reported by 38% of patients.⁷³

Data on 100 patients from the above study enrolled at the Mayo Clinic (Rochester, MN) were published separately⁷⁴ and this sponsor-independent analysis was recently updated

(median follow-up 3.2 years).⁷⁵ Of these 100 patients, 63%, 36% and 1% had high, intermediate-2 and intermediate-1 risk disease, respectively; 49% were erythrocyte-TD, 50% had an abnormal karyotype, and 21% had previously received another JAK inhibitor. After a median treatment duration of 1.7 years, momelotinib-related grade 3/4 AEs included thrombocytopenia (34%), neutropenia (9%), anemia (5%), elevated lipase (7%), liver enzyme abnormalities (2–4%) and headaches (2%). Grade 1/2 PN occurred in 47% of patients. Momelotinib treatment-emergent PN tends not to be reversible.⁷⁶ Clinical improvement (CI)⁶³ was noted in 57%, anemia responses in 44% and spleen responses in 43% of patients. 51% of erythrocyte-TD patients achieved TI. MF-related symptoms improved markedly in most subjects.⁷⁵

Twice-daily administration of momelotinib was evaluated in a separate phase I/II study in 61 patients with intermediate or high risk MF.⁷⁷ The dose chosen for expansion in the phase II portion was 200 mg twice daily. Diarrhea (45.9%), PN (44.3%), thrombocytopenia (39.3%) and dizziness (36.1%) were the most common AEs. Using the 2006 IWG-MRT criteria for response assessment,⁷⁸ the spleen response rate (by palpation) was 72% and anemia response rate 45% (among evaluable subjects). One patient achieved a PR, and 56.7% had CI. By MRI, the spleen response rate was 54% among subjects with palpable splenomegaly at baseline. 15 of 29 (51.7%) erythrocyte-TD subjects achieved 8-week TI, but on applying the newer, more stringent criteria for transfusion dependence and independence,⁶³ 4 of 19 (21.1%) of subjects achieved (12-week) TI. MF symptoms improved in most subjects, and the median reduction in the JAK2 V617F allele burden was 21.1% at 24 weeks.⁷⁷

Momelotinib has been compared head-to-head with ruxolitinib in a phase III RCT in patients (n = 432) with JAK inhibitor-naïve MF (SIMPLIFY-1) and with BAT (2:1) in a phase III RCT in patients (n = 156) previously treated with, but not refractory to, ruxolitinib (SIMPLIFY-2). The primary endpoint in both studies was the proportion of patients achieving a 35% SVR (by imaging) at week 24. Secondary endpoints included the proportion of patients achieving a 50% reduction in their MPN-SAF TSS, and the proportion achieving TI at week 24. At the present time, publicly available information on the results of these trials is limited to a press release from the company.⁷⁹ SIMPLIFY-1 was a non-inferiority study and while non-inferiority of momelotinib to ruxolitinib was achieved in terms of 35% SVR at week 24 (momelotinib: 26.5%; ruxolitinib: 29%), it was not achieved in terms of symptomatic benefit. Expectedly, momelotinib performed better than ruxolitinib with respect to anemia-related endpoints, but formal statistical testing was not undertaken for these. In SIMPLIFY-2, the vast majority (88%) of BAT-treated patients continued to receive ruxolitinib. The trial did not meet its primary endpoint of superiority of momelotinib in terms of 35% SVR at week 24. Momelotinib outperformed BAT in terms of TSS improvement and achievement of TI, but formal statistical testing was not undertaken.

How momelotinib might improve anemia despite inhibiting JAK1/2 is not well understood, and one putative mechanism is inhibition of ALK2-mediated hepcidin expression in the liver, which in turn results in increased release of storage iron and promotion of erythropoiesis.⁸⁰ NCT02515630 is a phase II study investigating momelotinib in

erythrocyte-TD patients with MF that examines changes in pharmacodynamic biomarkers and markers of anemia in addition to clinical endpoints.

NS-018—NS-018 is a JAK2-selective inhibitor with an IC₅₀ of < 1 nM and 30–50-fold greater selectivity for JAK2 than for other JAK family kinases (JAK1, JAK3, TYK2) that also inhibits Src-family kinases.⁸¹ NS-018 potently kills cell lines expressing constitutively activated JAK2, suppresses endogenous erythroid colony formation by primary cells from PV patients and reduces leukocytosis and splenomegaly, improves BM fibrosis and prolongs survival in a mouse model of *JAK2*^{V617F}-driven MF without causing peripheral anemia or thrombocytopenia.^{81,82} Forty-eight patients with MF, 23 (48%) of whom had previously been treated with a JAK inhibitor, received NS-018 in a phase I trial.⁸³ The most frequent drug-related AEs were thrombocytopenia (27%), anemia (15%), dizziness (23%) and nausea (19%). The recommended phase II dose (RP2D) was 300 mg daily. 56% of patients (47% of those who had previously received a JAK inhibitor) achieved a 50% reduction in palpable spleen size and improvements in MF-related symptoms were noted. Eleven of 30 (37%) evaluable patients had improvement in BM fibrosis from baseline after three cycles, although the mutant *JAK2* allele burden did not change significantly.⁸³

INCB039110—It has been suggested that specific targeting of JAK1 might abrogate the cytokine excess associated with MF and consequently improve constitutional symptoms while minimizing the risk of myelosuppression mediated by JAK2 inhibition.⁸⁴ A phase II study evaluated three dose levels of INCB039110, a potent and selective JAK1 inhibitor, in patients with intermediate or high risk MF and platelets $\geq 50 \times 10^9/L$.⁸⁵ The primary outcome was a 50% reduction in the TSS at 12 weeks, which was achieved by 35.7% and 32.3% of patients in the 200 mg twice daily and 600 mg once daily cohorts, respectively. At 24 weeks, these rates were 28.6% at the 200 mg twice daily dose and 35.5% at the 600 mg once daily dose. The median SVRs at week 12 were 14.2% and 17.4%, respectively, in the 200 mg twice daily and 600 mg once daily cohorts. Twenty-one of 39 (53.8%) erythrocyte-TD patients achieved a 50% reduction in the number of red blood cell (RBC) units transfused up to 24 weeks on study. Myelosuppression was limited, and most non-hematologic AEs were grades 1/2.⁸⁵

CHZ868—JAK2 inhibitor “persistence” is a phenomenon in which JAK-signal transducer and activator of transcription (STAT) signaling can be reactivated via heterodimerization between activated JAK2 and JAK1 or TYK2 despite continued therapy with a JAK2 inhibitor.⁸⁶ In fact, JAK2 inhibitor withdrawal is associated with resensitization to JAK2 inhibitors in this setting. However, this phenomenon of persistence appears restricted to type I JAK2 inhibitors, which bind the kinase in its active conformation.⁸⁷ CHZ868 is a type II JAK inhibitor which binds to and stabilizes the inactive conformation of the kinase.⁸⁸ In preclinical studies, this agent was effective against *JAK2*- and *MPL*-mutant cell lines, including those exhibiting type I JAK inhibitor persistence. CHZ868 was also active *in vivo*, inducing greater reductions in the allele burden of mutant *JAK2* in murine models than typically seen with type I JAK inhibitors.⁸⁸

Imetelstat

The telomerase inhibitor imetelstat generated substantial interest when a pilot study in 33 patients with intermediate-2 or high risk MF, 48% of whom had received prior JAK inhibitor therapy, reported complete remission (CR) or PR in 7 patients (21%) that lasted between 7 and 20+ months (median for PRs, 10 and for CRs, 18 months).⁸⁹ Furthermore, BM fibrosis was reversed in all four patients who achieved CR, and three of these patients had a molecular response. Responses did not, however, correlate with baseline telomere length. At the dose and schedule used in this study (9.4 mg/kg intravenously every 1–3 weeks), imetelstat was quite toxic, with high rates of myelosuppression (grade 3 anemia in 30% and grade 4 neutropenia and thrombocytopenia in 12% and 18% of patients, respectively). Grade 1/2 increases in bilirubin (12%), alkaline phosphatase (21%) and aspartate aminotransferase (27%) were frequent as well.⁸⁹

Based on these data, the IMbarkTM trial (NCT02426086) was designed as a phase II study evaluating 4.7 or 9.4 mg/kg of imetelstat administered intravenously every 3 weeks in approximately 200 patients with intermediate-2/high risk MF failing prior JAK inhibitor therapy. After a planned internal interim review at the 12-week time point, the sponsor decided to close the 4.7 mg/kg dosing arm due to insufficient activity.⁹⁰ For the 9.4 mg/kg dosing arm, it was decided to suspend new patient enrollment while continuing to treat existing patients, with plans for a second internal data review at 24 weeks, at which point further decisions regarding continued development of this agent for MF will be taken.⁹⁰

PRM-151

PRM-151 is recombinant pentraxin 2 (serum amyloid P), a highly phylogenetically conserved, circulating plasma protein and soluble pattern recognition receptor of the innate immune system that may localize to sites of injury to aid in removal of damaged tissue.⁹¹ It is currently in clinical development for the treatment of various fibrotic diseases. In an open-label, adaptive trial, PRM-151 was administered at a dose of 10 mg/kg intravenously weekly or every 4 weeks, with or without ruxolitinib, for 24 weeks to patients with intermediate or high risk MF and grade 2 BM fibrosis.⁹² At study entry, patients could either be on no therapy or on a stable (for 12 weeks) dose of ruxolitinib. There was no restriction with regard to platelet count and splenomegaly was not required. 22% of patients were JAK inhibitor-naïve and 52% had received prior JAK inhibitor therapy, not including patients on ruxolitinib at the time of enrollment. The ORR was 35% (9 of 26), with at least one response in each arm. Four patients had CI in symptoms and six had BM fibrosis responses (one patient had both). PRM-151 was very well tolerated.⁹² Patients deriving clinical benefit were permitted to continue PRM-151 beyond week 24, and results on 13 patients who had completed 72 weeks on therapy were presented.⁹³ 31% were JAK inhibitor-naïve and 69% had either received a JAK inhibitor in the past or were on ruxolitinib at study entry. 54% of patients had a morphologic response in their BM, and 85% had a response by computer-assisted image analysis. Three of five patients who were receiving RBC transfusions at baseline achieved TI, as did all four who were receiving platelet transfusions at baseline. Two of nine patients with palpable splenomegaly at baseline achieved a 50% reduction lasting > 12 weeks. The TSS improved from baseline by 50% and 100% between 24 and 72 weeks in 69% and 38% of patients, respectively.⁹³

LCL-161

Preclinical studies reveal a central role for tumor necrosis factor alpha (TNF- α) in promoting clonal dominance of *JAK2*^{V617F}-expressing cells in MPN.⁹⁴ *JAK2*^{V617F} appears to confer TNF- α resistance to a pre-neoplastic TNF- α -sensitive cell, while creating a TNF- α -rich environment at the same time.⁹⁴ Second mitochondrial activator of caspases (Smac)-mimetics are novel apoptosis-inducing agents that stimulate the ubiquitinylation and proteasomal degradation of cellular inhibitors of apoptosis (IAPs),⁹⁵ proteins that play an important role in tumor cell resistance to cytotoxicity mediated by TNF superfamily cytokines.⁹⁶ These agents have been shown to sensitize cancer cells to TNF family-induced apoptosis.⁹⁶ Results from a phase II trial of the Smac-mimetic LCL-161 in 21 patients with intermediate or high risk MF who were intolerant of, ineligible for or relapsed/refractory to JAK inhibitors were recently presented.⁹⁷ There were no eligibility cutoffs for spleen size or blood counts. Most patients (81%) had received ≥ 2 prior therapies, and two-thirds had received a JAK inhibitor in the past. Six of sixteen evaluable patients (38%) had nine objective responses, all of which were CIs except one, which was a cytogenetic remission. Fatigue was the most prominent AE.⁹⁷

Rational ruxolitinib-based combinations

Given that ruxolitinib is the first and only drug to improve the survival of patients with MF, numerous efforts have been made to develop rational, mostly laboratory-based, combinations involving ruxolitinib and other novel agents in hopes of translating preclinical findings of synergism to the clinic.

Combinations with HSP90 and HDAC inhibitors—As JAK2 is a client of the chaperone protein HSP90, pharmacologic inhibition of HSP90 should lead to mis-folding and degradation of JAK2 protein. This was demonstrated in MPN cell lines, primary MPN patient samples and mouse models of PV and ET with the HSP90 inhibitor PU-H71 without degradation of JAK2 in normal tissues or substantial toxicity.⁹⁸ Degradation of JAK2 via HSP90 inhibition has also been shown to be a way of circumventing JAK2 inhibitor persistence.⁸⁶ Synergism between the HSP90 inhibitor AUY922 and the JAK2 inhibitor TG101209 has been demonstrated in human CD34⁺ MPN cells, which exhibited significantly greater apoptosis than did normal HPCs.⁹⁹ Combination therapy with PU-H71 and ruxolitinib has been shown to more potently inhibit JAK2 downstream signaling than ruxolitinib alone, which translated to greater improvements in blood counts, spleen weights and BM fibrosis *in vivo*.¹⁰⁰ While a trial of AUY922 in patients with MPN was terminated prematurely due to toxicity,¹⁰¹ PU-H71, currently in a phase I trial (NCT01393509) for patients with advanced solid tumors, lymphoma or MPN, may be better tolerated (personal communication, Raajit K. Rampal, Memorial Sloan Kettering Cancer Center, New York, NY).

While HDAC inhibitors have multiple potential mechanisms of action in MPN,³⁵ a major one is believed to be the down-regulation of JAK2 via HSP90 inhibition (through acetylation) by drugs that inhibit HDAC6.¹⁰² This has been demonstrated in preclinical studies showing synergism between panobinostat and TG101209 in primary CD34⁺ MPN cells, in which panobinostat disrupted the chaperone association of JAK2^{V617F} with HSP90,

resulting in proteasomal degradation of JAK2^{V617F}.¹⁰³ Both panobinostat^{104,105} and pracinostat¹⁰⁶ have been studied as single agents in MF. Although panobinostat was better tolerated at a dose of 25 mg three times a week than 40 mg three times a week, discontinuation was still frequent because of perceived therapy ineffectiveness.^{104,105} Compounding the issue of chronic toxicities such as fatigue, diarrhea and thrombocytopenia is the fact that the disease-modifying effects of HDAC inhibitors in MF take long to emerge.^{105,107} Both panobinostat and pracinostat are being studied in combination with ruxolitinib in patients with MF (NCT01433445, NCT01693601, NCT02267278). The RP2Ds of panobinostat and ruxolitinib in combination were found to be 25 mg three times a week every other week for panobinostat and 15 mg twice daily of ruxolitinib.¹⁰⁸ Spleen responses (35% SVR) to the combination (57% and 39% at 24 and 48 weeks, respectively) were higher than seen with ruxolitinib alone in the COMFORT trials, without overt increases in toxicity.¹⁰⁸

Combinations with hypomethylating agents—Abnormalities of methylation are common in MPN,¹⁰⁹ and JAK2 has a number of non-canonical actions that profoundly affect epigenetic processes. For example, JAK2 phosphorylates histone H3 (HH3) at residue Y41, thereby preventing the binding of heterochromatin protein 1 alpha (HP1α) to this region of HH3.¹¹⁰ Furthermore, JAK2 phosphorylates the arginine methyltransferase PRMT5, impairing its ability to methylate its histone substrates and driving myeloproliferation.¹¹¹ Results on 41 patients (23 previously treated) with MF who received ruxolitinib and azacitidine (begun 3 months after initiation of ruxolitinib at a dose of 25 mg/m²/day on days 1–5 in 28-day cycles, with gradual increases permitted up to 75 mg/m²/day) on a phase II clinical trial (NCT01787487) were recently presented.¹¹² The ORR was 69%, and the median time to any response was 1 month. 14 of 29 patients (48%) with baseline palpable splenomegaly ≥ 5 cm achieved a 50% reduction in palpable spleen length at 24 weeks, and 23 of 29 (79%) achieved this at any time on the study.¹¹² The combination of ruxolitinib and decitabine appears promising in patients with accelerated or blast phase MPN (post-MPN acute myeloid leukemia) in small studies.^{113,114}

Combinations with phosphatidylinositol-3-kinase (PI3K) pathway inhibitors—The JAK-STAT pathway signals downstream to the PI3K-Akt-mammalian target of rapamycin (mTOR) pathway,¹¹⁵ providing a rationale to test combined inhibition of JAK-STAT and PI3K-Akt-mTOR signaling. As a single agent, the mTOR inhibitor everolimus produced an ORR of 23% (by the 2006 IWG-MRT criteria)⁷⁸ in 30 patients with intermediate or high risk MF, although 69% and 80%, respectively, experienced complete resolution of systemic symptoms and pruritus, whereas 50% spleen reduction occurred in only 20% of subjects and 15–25% had responses in leukocytosis, anemia and thrombocytosis.¹¹⁶ Synergism between the Akt inhibitor MK-2206 and ruxolitinib, as well as between the dual PI3K/mTOR inhibitor BEZ235 and other JAK2 inhibitors in JAK2^{V617F} cell lines and primary CD34⁺ MPN (MF) cells has been demonstrated.^{117,118} The maximum tolerated doses (MTDs) for the combination of ruxolitinib and the PI3K inhibitor buparlisib were established as 15 mg twice daily of ruxolitinib and 60 mg daily of buparlisib in a phase IB study in patients with intermediate/high risk MF and palpable splenomegaly ≥ 5 cm.¹¹⁹ In the expansion phase at week 24, five of eleven (45%) JAK inhibitor-naïve patients and

two of eleven (18%) patients previously treated with JAK inhibitors achieved a 35% SVR from baseline.¹¹⁹

While buparlisib is a pan-PI3K inhibitor, ruxolitinib is also being studied in combination with inhibitors of the delta isoform of PI3K (NCT02493530, NCT02718300). Preliminary results from a phase I trial of ruxolitinib and the next-generation PI3K delta inhibitor TGR-1202 were recently presented.¹²⁰ TGR-1202 was added to ruxolitinib in eleven patients with suboptimal responses to ruxolitinib and a stable dose for at least eight weeks. One of nine evaluable patients achieved a CR, seven had improvements in hematologic parameters and eight had decreases in MF symptoms (median reduction in TSS, 33%). MTDs were not established. Grade 3 asymptomatic amylase and lipase elevations were identified as DLTs in two patients.¹²⁰

Combinations with inhibitors of Hedgehog (HH) signaling—Excess HH ligand secretion and loss of PTCH2 drive canonical and non-canonical HH signaling in MPN, and PTCH2 double knockout mice develop a MPN phenotype.¹²¹ Combination treatment with ruxolitinib and the HH (smoothened) inhibitor sonidegib led to significant reductions in leukocyte and platelet counts, reduced the mutant *JAK2* allele burden in the bone marrow and significantly reduced BM fibrosis in a murine model of ET/MF.¹²² These findings formed the basis of a phase IB/II study (NCT01787552) of this drug combination in intermediate/high risk patients (n = 27) with MF and palpable splenomegaly who had not previously received a JAK or HH inhibitor.¹²³ The RP2Ds were determined to be 20 mg twice daily of ruxolitinib and 400 mg once daily of sonidegib. At 24 weeks, twelve patients (44.4%) achieved a 35% SVR by imaging.¹²³ The currently licensed (for advanced basal cell carcinoma) HH (smoothened) inhibitor vismodegib is also being studied in combination with ruxolitinib in JAK/HH inhibitor-naïve patients with intermediate/high risk MF and palpable splenomegaly ≥ 5 cm in a placebo-controlled trial (NCT02593760).

Combinations with cyclin-dependent kinase (CDK) inhibitors—The CDKs are serine/threonine kinases that, together with the cyclins, serve as the engines of the cell cycle. In recent years, CDKs 4/6 have emerged as important targets for cancer therapy, and mechanistically, their combination with JAK inhibitors has been proposed as a potentially synergistic one.¹²⁴ *JAK2*^{V617F} promotes myeloproliferation by translationally up-regulating CDC25A, a phosphatase that serves as a key regulator of the G1/S cell cycle checkpoint¹²⁵ and down-regulating p27, an endogenous CDK inhibitor.¹²⁶ The combination of ruxolitinib and the CDK4/6 inhibitor ribociclib was recently shown to be synergistic in a *JAK2*^{V617F} xenograft model.¹²⁷ The triple combination of ruxolitinib, ribociclib and PIM447, a PIM kinase inhibitor (PIM kinases activate D-type cyclins) was found to be even more effective *in vivo*, findings that were confirmed (with no additive toxicity) in a *MPL*^{W515L} mouse model that most closely recapitulates human ET/MF.¹²⁷ Based upon these findings, a phase I trial of these three agents in combination is underway in patients with *JAK2*^{V617F} MF with splenomegaly ≥ 5 cm by MRI and adequate bone marrow function (NCT02370706).

Conclusion

Although ruxolitinib remains the only approved therapy for MF today, efforts are ongoing on multiple fronts to identify rational combination partners for ruxolitinib based on translational studies so as to further modify the natural history of this difficult disease. In parallel, the search continues for agents that might effectively combat the anemia of MF, thereby allowing dose optimization of ruxolitinib. While none of these agents is close to regulatory approval, several are promising, as outlined in this article. However, the experience with a number of different JAK inhibitors, many of which were discontinued due to toxicity concerns, tells a cautionary tale, particularly in light of recent information on pacritinib and momelotinib. Drug development in PV and ET poses different challenges, given the prolonged survival associated with these conditions. In the near future, one hopes that ropeginterferon alfa-2b and ruxolitinib will be important new additions to the therapeutic armamentarium for PV and ET, respectively.

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