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Management of myelofibrosis after ruxolitinib failure

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Abstract

Over the last decade, the Janus kinase1/2 (JAK1/2) inhibitor ruxolitinib has emerged as a cornerstone of myelofibrosis (MF) management. Ruxolitinib improves splenomegaly and symptoms regardless of driver mutation status, and confers a survival advantage in patients with intermediate-2/high risk MF. However, cytopenias remain problematic, and evidence for a robust anti-clonal effect is lacking. Furthermore, the median duration of spleen response to ruxolitinib in clinical trials is approximately 3 years, and ruxolitinib does not appear to affect the risk of leukemic transformation. There is no therapy approved specifically for patients whose disease “progresses” on ruxolitinib, defining which remains challenging. The recent regulatory approval of the JAK2 inhibitor fedratinib partially fulfills this unmet need, but much remains to be done. Other JAK inhibitors and a plethora of novel agents are being studied in the ruxolitinib “failure” setting, as well as “add-on” therapies to ruxolitinib in patients having a “sub-optimal” response.

Keywords

myelofibrosis; ruxolitinib failure; sub-optimal; add-on; fedratinib; momelotinib; clinical trials; rational combinations

Introduction

Since its approval in 2011 based on the pivotal COMFORT trials,[1, 2] the Janus kinase (JAK) 1/2 inhibitor ruxolitinib (Jakafi®, Incyte Corporation, Wilmington, DE) has become a central component of the therapeutic arsenal for patients with myelofibrosis (MF). Although the COMFORT trials studied intermediate-2 and high risk patients with baseline platelet counts $100 \times 10^9/L$, a substantial body of evidence exists to support the use of the drug in patients with intermediate-1 risk disease (in whom it is generally more effective and less toxic)[3–5] and lower ($50\text{--}99 \times 10^9/L$) platelet counts,[6, 7] and guidelines from the US National Comprehensive Cancer Network (NCCN) also endorse its use in symptomatic, low risk patients.[8] No predictive factors for benefit from ruxolitinib, or lack thereof, emerged from the COMFORT trials,[9] although other analyses have suggested greater efficacy in patients with a mutant *JAK2* allele burden of $>50\%$ [10] and lower odds of spleen response and inferior survival in those with 3 mutations in non-driver, myeloid genes.[11] Five-year follow-up of the COMFORT trials has established the long-term safety and tolerability

of ruxolitinib, and demonstrated a survival benefit for it, despite early and very frequent crossover.[12, 13]

However, the primary benefits of ruxolitinib remain its effects on splenomegaly and the symptom burden characteristic of patients with MF, believed to result not only from the drug's potent anti-inflammatory actions, but also its ability to suppress a broad range of cytokines.[14] Ruxolitinib does not appear to have substantial impacts on the driver mutation allele burden or on the grade of bone marrow fibrosis in most patients.[12, 13] Indeed, most experts do not recommend using ruxolitinib solely for its survival benefit, i.e., in patients without symptoms or splenomegaly.[15] Anemia is not improved and, may be worsened, especially early on, by ruxolitinib, and represents the leading cause of ruxolitinib discontinuation in clinical practice.[16] NCCN guidelines recommend anemia-directed therapy, rather than ruxolitinib, in patients in whom anemia is the only or main disease manifestation.[17] In anemic patients needing ruxolitinib, alternative dosing strategies[18, 19] and combinations of ruxolitinib with conventional[20] and emerging[21] agents for anemia may be employed to mitigate the problem. There are no guidelines available for dosing of ruxolitinib in patients with platelets $<50 \times 10^9/L$ and, although clinicians are increasingly comfortable using low doses of ruxolitinib (e.g., 5 mg once or twice daily) in these situations, the dose proportionality of the spleen response to ruxolitinib[22, 23] makes this a sub-optimal approach.

Ruxolitinib “failure”

Importantly, clinical resistance to ruxolitinib eventually develops. The median duration of spleen response in the COMFORT trials was ≈ 3 years,[12, 13] and has been reported to be shorter in some real-world analyses,[24] though not in others.[25] Kinase mutations impairing drug binding have not been found to be a major driver of resistance; instead, “JAK2 inhibitor persistence”, in which JAK-signal transducer and activator of transcription (STAT) signaling continues despite the presence of the inhibitor owing to heterodimerization of JAK2 with other members of the JAK family and transactivation of JAK2,[26] may underlie some of these cases. Although “disease progression” per the International Working Group for MPN Research and Treatment (IWG-MRT) criteria[27] is defined only by worsening of or the appearance of new splenomegaly and increasing circulating and bone marrow blast counts, patients may progress in a variety of other ways as well, e.g., worsening symptoms, anemia, thrombocytopenia, leukocytosis or leukopenia. Ruxolitinib rechallenge after withdrawal has been reported to be effective in some patients whose disease is progressing on ruxolitinib.[28] We and others have reported on the poor survival of patients after ruxolitinib discontinuation, particularly in the presence of clonal evolution and/or declining platelet counts while on ruxolitinib.[16, 25, 29] There is no uniform definition of ruxolitinib “failure”, and clinical trials evaluating new agents post-ruxolitinib have used varying eligibility criteria, sometimes leaving this crucial determination entirely up to physician discretion. This has complicated the interpretation of clinical trial results, although a consensus definition may be emerging (for use in clinical trials, see Table 1). Also not clear are: what endpoints are optimal for clinical trials in the ruxolitinib failure setting and whether using the conventional endpoints of 35% spleen volume reduction (SVR) and 50% reduction in total symptom score (TSS) are reasonable benchmarks of

efficacy to use for investigational agents in the post-ruxolitinib setting. Finally, the outcome of patients with leukemic transformation (LT) of myelofibrosis or other MPNs, which ruxolitinib does not prevent, remains dismal,[30] with remission induction followed by successful allogeneic hematopoietic cell transplantation (allo-HCT) offering the only chance of long-term remission.[31]

Other JAK inhibitors

Fedratinib—The JAK2/fms-like tyrosine kinase 3 (FLT3) inhibitor fedratinib (Inrebic®, Celgene Corporation, Summit, NJ, now a Bristol Myers Squibb company), at doses of 400 and 500 mg daily, beat placebo in the phase 3 JAKARTA trial[32] in 289 patients with intermediate-2/high risk MF and baseline platelet counts $50 \times 10^9/L$ (35% SVR rate at 24 weeks (confirmed by repeat imaging 4 weeks later), 36% for fedratinib, 400 mg/d versus 1% for placebo; 50% TSS reduction rate at 24 weeks, 36% for fedratinib, 400 mg/d versus 7% for placebo). In August, 2019, fedratinib was approved by the US Food and Drug Administration (FDA) for the treatment of adults with intermediate-2 or high risk MF. The development of fedratinib was significantly hampered by the occurrence of several cases of what appeared to be Wernicke's encephalopathy (WE). The 8 putative cases (across all fedratinib clinical trials) were later re-analyzed: one was felt to be a confirmed case, while in 2 cases, clinical and/or imaging findings suggested WE, but there were additional confounding abnormalities.[33] The remaining 5 cases were either unlikely to be WE, or not WE. Studies have arrived at different conclusions on whether fedratinib inhibits neuronal thiamine uptake.[34–36] Regardless, concern regarding WE led to a full clinical hold being imposed on the fedratinib development program, and the clinical development of fedratinib being halted, before the drug was resurrected in 2017. The US prescribing information for fedratinib contains a black box warning regarding “encephalopathy including Wernicke's”, with a recommendation to check thiamine levels in all patients prior to fedratinib initiation and replete if deficient before beginning fedratinib.

JAKARTA-2 was a single-arm, open-label, non-randomized trial of fedratinib, 400 mg daily, in 97 patients with MF who had been exposed to ruxolitinib for a minimum of 2 weeks (median duration of prior ruxolitinib exposure was 10.7 months) and felt to be resistant ($\approx 2/3$) or intolerant ($\approx 1/3$) by their treating physician.[37] The rather loose eligibility criteria with regards to ruxolitinib “failure” likely reflects the timing of the design of JAKARTA-2, in the relatively early days of ruxolitinib availability. A 14 day washout from ruxolitinib was required. JAKARTA-2 was terminated prematurely because of the aforementioned clinical hold, with the result that a number of patients could not receive 6 cycles of fedratinib. In the original, per-protocol analysis, 46 of 83 evaluable patients (55%) were reported to have achieved 35% SVR at week 24, but week 12 spleen volume measurements were imputed for missing week 24 values (“last observation carried forward (LOCF)” method).[37] By a subsequent intention-to-treat (ITT) analysis ($n = 97$) without LOCF imputation, the rates of 35% SVR and 50% TSS reduction at 24 weeks, respectively, were 31% and 27%.[38] A “ruxolitinib failure” cohort ($n = 79$, 65 relapsed/refractory and 14 intolerant) was also defined in this re-analysis using the “stringent” criteria set forth in Table 1 (panel A). The median duration of prior ruxolitinib treatment in these patients was 11.5 months. In this subgroup of patients, also, the rate of 35% SVR at week 24 was 30% and

that of 50% TSS reduction was 27%. These stringent criteria also define eligibility for the ongoing FREEDOM (NCT03755518, single arm, open-label, phase 3b) and FREEDOM-2 (NCT03952039, phase 3, randomized against best available therapy, BAT) trials of fedratinib in MF patients previously treated with ruxolitinib. The commercial availability of fedratinib in the US is likely to impede accrual to the FREEDOM study. Successful completion of the FREEDOM studies will be important, considering that owing to the clinical hold, which compelled all patients on ongoing trials of fedratinib to come off, long-term safety and efficacy data for fedratinib in MF are not available from the JAKARTA trials. Of note, across JAKARTA and JAKARTA-2 (ITT population as well as stringent criteria cohort), analyses of spleen and symptom responses to fedratinib by baseline platelet count ($50\text{--}99 \times 10^9/\text{L}$ versus $100 \times 10^9/\text{L}$) showed similar rates of 35% SVR and 50% TSS improvement.[39]

Momelotinib—Like ruxolitinib, momelotinib (Sierra Oncology, Vancouver, BC) is a JAK1/2 inhibitor that has the added benefit of possibly improving anemia in patients with MF, putatively via suppression of hepatic hepcidin production through inhibition of the type 1 activin receptor (ACVR1).[40] Some clinical validation of this concept was provided by a phase 2, open-label study of 41 transfusion-dependent (TD) patients with MF who received 200 mg of momelotinib once daily.[41] Median blood hepcidin levels decreased 6 hours after momelotinib dosing at every study visit. Among the 14 patients (34.1%) who achieved transfusion independence (TI), serum iron, transferrin, hemoglobin, reticulocytes and hematocrit increased at week 2. Thereafter, serum iron declined while hemoglobin, hematocrit and platelets increased through week 24. Baseline factors associated with a TI response were hemoglobin ≥ 8 g/dL, lower morning hepcidin levels, younger age and lower DIPSS score. Momelotinib was compared head to head against ruxolitinib in 432 JAK inhibitor-naïve patients with intermediate-2/high or symptomatic intermediate-1 risk MF and baseline platelets $\leq 50 \times 10^9/\text{L}$ in the SIMPLIFY-1 trial, and found to be non-inferior for 35% SVR at 24 weeks (26.5% for momelotinib versus 29% for ruxolitinib, $p = 0.011$) but not for 50% TSS reduction (28.4% for momelotinib versus 42.2% for ruxolitinib, $p = 0.98$).[42] The rate of TI at week 24 was higher in the momelotinib group (66.5%) than in the ruxolitinib group (49.3%, nominal $p < 0.001$); conversely, fewer patients in the momelotinib arm were TD at week 24 (30.2%) than in the ruxolitinib arm (40.1%, nominal $p = 0.019$). The median rate of RBC transfusion through week 24 was zero units/month in the momelotinib group compared to 0.4 units/month in the ruxolitinib group (nominal $p < 0.001$). However, formal statistical significance could not be claimed for any of these α -controlled, anemia-related endpoints because of the hierarchical design, non-inferiority of momelotinib to ruxolitinib for TSS reduction at 24 weeks having not been met.

Momelotinib was also compared 2:1 to BAT in 156 patients previously treated with ruxolitinib in the SIMPLIFY-2 study.[43] Patients had to have had prior ruxolitinib for ≥ 28 days and have either required RBC transfusions while on ruxolitinib or ruxolitinib dose reduction to <20 mg twice daily with grade ≥ 3 thrombocytopenia, anemia or bleeding. The BAT arm could include ruxolitinib, and ruxolitinib happened to be the BAT in 89% of patients. This study did not meet its primary endpoint of 35% SVR at 24 weeks (6.7% for momelotinib and 5.8% for BAT, $p = 0.9$). There was no washout from prior ruxolitinib. Although, again, formal statistical significance could not be claimed because of the primary

endpoint not having been met (hierarchical design), momelotinib appeared superior for 50% TSS reduction at 24 weeks (26.2% versus 5.9% with BAT, nominal $p = 0.0006$). At week 24, 43% of momelotinib patients had achieved TI, as compared to 21% of BAT patients (nominal $p = 0.0012$). Conversely, fewer patients receiving momelotinib were TD at week 24 (50%) than those receiving BAT (64%, nominal $p = 0.1$). The median rate of RBC transfusion through week 24 was 0.5 units/month in the momelotinib arm compared with 1.2 units/month in the BAT arm (nominal $p = 0.39$). Momelotinib will now be compared 2:1 to danazol in the MOMENTUM trial ([NCT04173494](#)) in 180 symptomatic (TSS ≥ 10) and anemic (hemoglobin <10 g/dL), JAK inhibitor-exposed patients with MF. The primary endpoint of this study is the rate of 50% TSS reduction at week 24. The rates of RBC TI and 35% SVR at week 24, as well as the durability of TSS reduction and other measures of anemia benefit constitute secondary endpoints. A minimum platelet count of $25 \times 10^9/L$ is required for eligibility.

Pacritinib—Pacritinib (CTI BioPharma Corporation, Seattle, WA) is an oral inhibitor of JAK2, FLT3 and IRAK1 that beat BAT (excluding ruxolitinib) in terms of 35% SVR (primary endpoint) at 24 weeks (19% versus 5%, $p = 0.0003$) in 327 JAK inhibitor-naïve patients with MF in the phase 3 PERSIST-1 trial.[44] Pacritinib being relatively non-myelosuppressive, there was no minimum platelet count stipulated for study entry. Among 106 patients with baseline thrombocytopenia (platelets $<100 \times 10^9/L$), the rates of 35% SVR were 17% and zero, respectively, for pacritinib and BAT. Among 51 patients with severe thrombocytopenia (platelets $<50 \times 10^9/L$), pacritinib produced a 23% rate (8 of 35 patients) of 35% SVR; none of 16 patients in the BAT arm responded. With regards to 50% TSS improvement, the difference between the pacritinib and BAT groups was not statistically significant (in the ITT population) at week 24, but was at week 48.

Two doses of pacritinib (200 mg bid and 400 mg once daily) were compared against BAT (which could include ruxolitinib and was ruxolitinib in 45% of the patients) in 311 thrombocytopenic patients (baseline platelets $<100 \times 10^9/L$) with MF in the PERSIST-2 trial.[45] Prior ruxolitinib was allowed, and 48% of patients had received prior ruxolitinib. Enrollment to this trial was affected by the placement of a full clinical hold by the FDA on the pacritinib development program based on concern regarding excess mortality from bleeding and cardiac arrhythmias, etc., in patients receiving pacritinib.[46] The ITT efficacy population ultimately included 75 patients who received pacritinib 400 mg once daily, 74 who received pacritinib 200 mg twice daily and 72 who received BAT. PERSIST-2 used 35% SVR and 50% TSS reduction at 24 weeks as co-primary endpoints. Pacritinib (arms combined) was statistically significantly superior to BAT for 35% SVR (18% versus 3%, $p = 0.001$) but not for 50% TSS reduction (25% versus 14%, $p = 0.08$) at week 24. The 200 mg twice daily arm was superior to BAT for both co-primary endpoints. This arm also saw the greatest clinical improvement (CI) in hemoglobin and reduction in RBC transfusion requirements.

Pacritinib was subsequently (after the full clinical hold was lifted by the FDA)[47] studied in a phase 2 dose-finding study (PAC203), in which 161 patients with MF who had failed ruxolitinib (as defined in Table 1, panel A) were randomized 1:1:1 to pacritinib doses of 100 mg daily, 100 mg twice daily and 200 mg twice daily.[48] PAC203 was originally intended

to recruit only thrombocytopenic patients, but the platelet count requirement for eligibility was later removed. The median platelet count at study entry was $55 \times 10^9/L$ and the median duration of prior ruxolitinib was 1.7 years. Efficacy was modest overall, and was highest in the 200 mg bid dose group, with 9.3% of patients achieving 35% SVR at week 24. The corresponding rate of 50% TSS reduction was 7.4%. Interestingly, 4 of 24 patients (17%) in the 200 mg bid dose arm with baseline platelets $<50 \times 10^9/L$ achieved 35% SVR at 24 weeks. Pacritinib at this dose will now be studied in a phase 3 randomized controlled trial (RCT), PACIFICA ([NCT03165734](#)), in severely thrombocytopenic (i.e., platelets $<50 \times 10^9/L$) patients with MF who have received no more than 90 days of prior ruxolitinib. Ruxolitinib, 5 mg once or twice daily, will be permitted as a “physician’s choice” therapy in the comparator arm. Thus, the current development plan for pacritinib appears to be moving away from the ruxolitinib failure setting towards the JAK inhibitor-naïve setting, attempting to position this drug in an area without any approved therapies (i.e., MF patients with platelet counts $<50 \times 10^9/L$).

Ruxolitinib-based combinations for “sub-optimal” responders to ruxolitinib (Table 2)

There is much interest currently in developing rational combinations that build on ruxolitinib by adding a targeted agent to it for synergy, the so-called “add-on” approach, in patients having a sub-optimal or insufficient response to ruxolitinib monotherapy. The latter has been variously defined and, in some trials, left up to investigator discretion. Early results from some of these trials have been presented at recent meetings and are summarized below. Other synergistic strategies, such as those combining ruxolitinib with heat shock protein 90 (HSP90) inhibitors, inhibitors of protein neddylation, poly (ADP-ribose) polymerase inhibitors, PIM kinase inhibitors and mitogen activated protein kinase (MAPK) inhibitors are either in early stages of clinical testing (e.g., [NCT03935555](#), [NCT03386214](#), [NCT02587598](#)) or soon to enter the clinic.[49–54] An “add-on” trial of the murine double minute 2 (MDM2) inhibitor KRT-232 is also being initiated.

Phosphatidylinositol-3-kinase delta inhibitors: piasclisib and umbralisib—

JAK2 signals downstream to the phosphatidylinositol-3-kinase (PI3K)-Akt-mammalian target of rapamycin (mTOR) pathways and preclinical studies have demonstrated synergism between JAK2 inhibitors and agents that interrupt PI3K-Akt-mTOR signaling.[55, 56] Piasclisib (Incyte Corporation, Wilmington, DE) and umbralisib (TG Therapeutics, New York, NY) are two oral inhibitors of the delta isoform of PI3K that have been studied in add-on fashion to ruxolitinib in patients having a sub-optimal response to ruxolitinib. For enrollment on to the piasclisib trial (n = 31), MF patients on ruxolitinib for 6 months (and a stable dose for 8 weeks before enrollment) had to have either splenomegaly palpable 10 cm below the left costal margin (LCM) or 5–10 cm with active symptoms (1 symptom score 5 or 2 symptom scores 3 each). [57] The median SVR was 10.9% at week 12 (27 evaluable) and 8.8% at week 24 (19 evaluable), while the median TSS reductions at these time points were 14.4% and 35.9%, respectively. Tolerability was good; in particular, immune-related adverse events were infrequent. Colitis was not seen. This trial ([NCT02718300](#)) is ongoing and updated results are expected this year (personal communication, Naval Daver, MD). The umbralisib trial ([NCT02718300](#), n = 23) also required a stable dose of ruxolitinib for 8 weeks, but the definition of lost, sub-optimal or

no response to ruxolitinib, all of which were acceptable for enrollment, was left up to the judgement of the treating physician.[58] Two patients achieved complete response (CR) and 11 CI per IWG-MRT criteria. The median SVR was 13% and the median TSS reduction was 35%. Five patients had >2 g/dL increases in hemoglobin levels. The combination was well-tolerated, with mild and transient episodes of transaminitis, 1 event of colitis and no pneumonitis reported.

Bromodomain and extra-terminal (BET) protein inhibitors: CPI-0610—

Bromodomain and extra-terminal (BET) proteins are epigenetic readers that are critical to the transcription of a number of oncoproteins of importance in MPN, in particular nuclear factor kappa B (NF- κ B) and c-Myc.[59] Synergism between ruxolitinib and the laboratory BET inhibitor JQ1 has been demonstrated both *in vitro* (MPN cell lines and primary MPN cells) and *in vivo* (*JAK2*^{V617F}- and *MPL*^{W515L}-mutant mice).[60] CPI-0610 (Constellation Pharmaceuticals, Cambridge, MA) is a potent, orally bioavailable inhibitor of BET proteins that is being studied in different clinical scenarios (as a single agent after ruxolitinib, as an “add-on” therapy to ruxolitinib and in combination with ruxolitinib in JAK inhibitor naïve patients with MF) in the ongoing MANIFEST trial (NCT02158858). To receive CPI-0610 in add-on fashion, patients must have been on ruxolitinib for 6 months with a stable dose for 8 weeks. For both the CPI-0610 monotherapy and add-on arms, baseline platelets of $75 \times 10^9/L$, measurable symptoms and either RBC TD or splenomegaly are required. Results on 90 patients (36 receiving CPI-0610 alone and 54, CPI-0610 added on to ruxolitinib) were recently presented.[61] Somewhat strikingly, the drug appeared most active in RBC transfusion dependent patients on ruxolitinib. In this cohort, 3 of 12 (25%) patients achieved 35% SVR, 7 of 13 (54%) experienced a 50% TSS reduction and 6 of 14 (43%) of patients with RBC TD achieved TI at week 24. In contrast, none of 13 evaluable non-transfusion dependent patients on the add-on arm achieved 35% SVR at week 24. Ten of 23 (43.5%) evaluable patients receiving CPI-0610 added on to ruxolitinib achieved 1 grade improvement in bone marrow fibrosis. The results with CPI-0610 monotherapy in the post-ruxolitinib setting are discussed below. Based on early encouraging data from the frontline cohort of the MANIFEST study (35% SVR in 12 of 15 evaluable patients (80%) at 12 weeks), a phase 3 RCT comparing the combination of ruxolitinib and CPI-0610 to ruxolitinib alone in patients with MF who have not previously received a JAK inhibitor is under development.

BH3-mimetics: Navitoclax—Navitoclax (formerly ABT-263, Abbvie, North Chicago, IL) is an orally bioavailable BH3-mimetic compound that antagonizes the anti-apoptotic functions of both BCL-2 and B-cell lymphoma extra long (BCL-xL).[62] ABT-737, the non-clinical counterpart of navitoclax used widely as a laboratory tool compound, was shown to synergize with ruxolitinib against *JAK2*^{V617F}-driven MPN cells.[63] These findings led to an “add-on” trial of navitoclax in 34 patients with MF on ruxolitinib for 12 weeks (median 21 months) with a stable dose of 10 mg bid for at least 8 weeks, the first results from which were recently presented.[64] As thrombocytopenia is an expected, on-target effect of navitoclax stemming from its inhibition of BCL-xL,[65] the study only enrolled patients with baseline platelets $100 \times 10^9/L$, and the dose of navitoclax was stepped up weekly from 50 to a maximum of 300 mg daily (achieved by 68% of patients). Thirty percent of

patients (9 of 30 evaluable) achieved 35% SVR at week 24 and 35% (6 of 17 evaluable) experienced 50% TSS improvement at week 24. Eight of 32 (25%) evaluable patients had a 1 grade reduction in bone marrow fibrosis. The baseline mean platelet count was $232 \times 10^9/L$ and the nadir (week 8) mean platelet count was $95 \times 10^9/L$; in general, platelet counts stabilized after 6–8 weeks. This trial ([NCT03222609](#)) will be expanded to evaluate the combination in a larger number of patients. A clinical trial evaluating the combination of ruxolitinib and navitoclax in the JAK inhibitor-naïve setting has also been announced.

Beyond JAK inhibition: novel single agent approaches in patients whose disease progresses on or who do not tolerate ruxolitinib (Table 3)

A number of investigational agents representing diverse drug classes are being studied as monotherapy in patients who have failed or are not candidates for ruxolitinib. Although promising in preclinical studies, targeting hedgehog signaling with smoothened inhibitors has not proven successful clinically.[66, 67] As alluded to above, 36 patients in the ongoing MANIFEST trial received the BET inhibitor CPI-0610 alone in the post-ruxolitinib setting. Of 9 patients evaluable for spleen response at week 24, none achieved 35% SVR, but 3 of 6 (50%) evaluable patients achieved 50% TSS reduction at this time point.[61] No patient with baseline RBC TD achieved TI. Results in the public domain from clinical trials of several novel agents conducted in ruxolitinib-resistant/intolerant/ineligible patients are discussed briefly below. Yet other drugs being studied in similar settings include the selective inhibitor of nuclear export (SINE) selinexor ([NCT03627403](#)),[68] the transforming growth factor beta (TGF β) ligand trap AVID200 ([NCT03895112](#)),[69] the PIM kinase inhibitor TP-3654 ([NCT04176198](#))[53] and the MDM2 inhibitor KRT-232 ([NCT03662126](#)).

Telomerase inhibition: Imetelstat—The telomerase inhibitor imetelstat (Geron Corporation, Menlo Park, CA) generated considerable excitement when 7 complete and partial responses were reported in a pilot study in 33 patients with MF, 48% of whom had received prior JAK inhibitor therapy; however, responses did not correlate with baseline telomere length.[70] Responses were restricted to *JAK2*-mutated patients, and no patient with an *ASXL1* mutation responded. The CR rate was significantly higher among patients with mutations in the RNA splicing genes *SF3B1* or *U2AF1*. Imetelstat has also been reported to selectively deplete MF stem and progenitor cells.[71] Imetelstat was subsequently studied in the multi-center IMBARK™ trial in 107 patients with intermediate-2/high risk MF that had relapsed after or was refractory to a JAK inhibitor (see Table 1, panel B for definition).[72] The lower dose (4.7 mg/kg) arm was closed due to insufficient efficacy, and the rate of 35% SVR at 24 weeks was a modest 10% in the higher dose (9.4 mg/kg) arm, while 32% of patients in the latter arm achieved 50% TSS reduction at week 24. However, median survival was 29.9 months in the 9.4 mg/kg dosing arm and 19.9 months in the 4.7 mg/kg dosing arm, in marked contrast to the 13–14 months reported by several groups in patients who discontinue ruxolitinib.[16, 25, 29] These data were compared to the outcomes of matched historical controls at the Moffitt Cancer Center, and the survival advantage associated with imetelstat (9.4 mg/kg) treatment was validated. [73] Imetelstat is administered intravenously every 3 weeks. Results with longer follow-up of the IMBARK™ trial participants are expected this year (personal communication, John Mascarenhas, MD).

Aurora kinase A inhibition: Alisertib—Evidence that down-regulation of the transcription factor GATA1 was associated with impaired maturation of and a pro-proliferative effect on megakaryocytes in PMF.[74] and that treatment with alisertib (formerly MLN8237, Takeda Pharmaceuticals, Osaka, Japan), an aurora kinase A (AURKA) inhibitor, promoted differentiation of PMF megakaryocytes and ameliorated bone marrow fibrosis *in vivo* in mouse models of PMF[75] led to a phase 1 clinical trial of this agent in 24 patients with MF who were refractory to, intolerant of or unlikely to benefit from ruxolitinib. [76] Responses were adjudicated by IWG-MRT criteria; 4 of 14 evaluable patients (29%) achieved a spleen response by palpation, 7 of 22 evaluable patients (32%) experienced a symptom response and 2 of 19 evaluable patients (11%) exhibited an anemia response (both RBC TI), while 5 of 7 patients (71%) with serial bone marrow biopsies had a 1 grade reduction in fibrosis. Further clinical development of alisertib in MF is planned (personal communication, John D. Crispino, Ph.D., MBA).

Targeting bone marrow fibrosis: PRM-151—Preclinical studies show that fibrocytes, the fibrosis-driving cells in the PMF bone marrow, are clonal (neoplastic) and derived from monocytes.[77] PRM-151 (Promedior, Inc., Lexington, MA) is a recombinant form of human pentraxin-2 (serum amyloid protein, SAP) that inhibits fibrocyte differentiation and promising results have been obtained in patients with idiopathic pulmonary fibrosis.[78] In the first stage of a clinical trial of PRM-151 in patients with MF who were either on ruxolitinib or not candidates for it, 18 of 27 patients derived long-term benefit, staying on the study for a median of 30.9 months.[79] Bone marrow reticulin and collagen grade improvements were observed in 50% and 44% of these patients, respectively, and reductions in palpable splenomegaly and in TSS were seen both in patients receiving PRM-151 alone (n = 9) and in those receiving it in combination with ruxolitinib (n = 9). Mean hemoglobin levels and platelet counts were stable or improving at 48 cycles in these 18 patients. The second stage of this trial explored PRM-151 alone at 3 different doses, each administered intravenously every 4 weeks, in 97 patients with MF who were ineligible for, intolerant of, or inadequate responders to ruxolitinib.[80] Overall, 27.8% of patients experienced a decrease in bone marrow fibrosis grade at any time, but the rates were not significantly different between the 0.3 mg/kg, 3 mg/kg and 10 mg/kg dose levels. Fifty one patients (53%) completed study therapy (9 cycles), 48 of whom continued in an open-label extension phase. Five of 31 patients (16%) with RBC TD at baseline achieved TI, as did six of 13 patients (46%) with platelet transfusion dependence at baseline. Thirty four percent of patients had a 50% reduction in TSS, and 41% of patients achieved some degree of SVR at any time point. There are plans to take this agent forward into a phase 3 clinical trial in patients with MF. Improvement in bone marrow fibrosis by 1 grade has been reported with a number of novel agents, including several discussed in this article. At the present time, the clinical significance of this remains unclear, unless accompanied by improvements in disease-related cytopenias.

Targeting CD123: Tagraxofusp—Tagraxofusp (formerly SL-401, Stemline Therapeutics, New York, NY) is a CD123-directed, diphtheria toxin-containing fusion protein approved for the treatment of blastic plasmacytoid dendritic cell neoplasm.[81] Twenty nine patients with MF, 20 of whom (77%) had received prior JAK inhibitor therapy,

received tagraxofusp, intravenously on 3 consecutive days per cycle, in a phase 1/2 trial (NCT02268253).[82] Three of 20 evaluable patients had CI in symptoms per IWG-MRT criteria, and 8 of 15 patients (53%) with baseline palpable splenomegaly ≥ 5 cm below the LCM had some reduction in spleen size as their best response. One case of grade 3 capillary leak syndrome occurred. This study is ongoing, but the development path forward for tagraxofusp in MF remains unclear at present. Results with this agent may be more encouraging in patients with chronic myelomonocytic leukemia (CMML).[83]

Lysine-specific demethylase 1 (LSD1) inhibition: Bomedemstat—Lysine-specific demethylase-1 (LSD1) has recently emerged as a novel epigenetic target in the MPN.[84] LSD1 is essential for differentiation of megakaryocyte-erythroid progenitors (MEPs) to mature megakaryocytes, is required for normal megakaryocyte function, and is overexpressed in the MPN.[85, 86] Bomedemstat (formerly IMG-7289, Imago BioSciences, South San Francisco, CA) is an orally administered inhibitor of LSD1 that was studied in an ongoing phase 1/2 trial (NCT03136185) in 31 patients with MF and baseline platelets $100 \times 10^9/L$; the dose of bomedemstat was uptitrated intra-patient to achieve a target platelet count ($50\text{--}75 \times 10^9/L$ in the phase 2b portion).[87] At 24 weeks, 1 of 8 evaluable patients (12.5%) achieved $\geq 35\%$ SVR, and 4 of 9 evaluable patients (44.4%) had a $\geq 50\%$ reduction in TSS. One of 9 patients with RBC TD at baseline achieved TI, while 2 of 13 evaluable patients (15%) experienced improvements in bone marrow fibrosis of ≥ 1 grade by 12 weeks or end of treatment. There are plans to study this agent in essential thrombocythemia (ET) as well.

Antagonism of inhibitor of apoptosis (IAP) proteins: LCL-161—The MF bone marrow milieu is rich in tumor necrosis factor alpha (TNF α), and JAK2^{V617F} confers TNF α resistance, promoting clonal selection.[88] Cellular inhibitor of apoptosis (cIAP) proteins are overexpressed in MF CD34⁺ cells as compared to normal bone marrow CD34⁺ cells, likely explaining higher TNF α -induced NF- κ B activity in the former.[89] These observations formed the basis for a phase 2 clinical trial of the oral IAP antagonist (second mitochondrial activator of caspases (Smac) mimetic), LCL-161 (Novartis, Basel, Switzerland), in 50 patients with intermediate or high risk MF who were not candidates for, intolerant of or resistant to JAK inhibitor therapy.[90] Like in the tagraxofusp trial discussed above, there was no minimum platelet count stipulated for study entry. An overall response rate (ORR) of 30% was reported in the final analysis of this recently completed study, the majority of responses being CI in symptoms or anemia. Up-regulation of X-linked inhibitor of apoptosis (XIAP) was identified as a possible mechanism of resistance.

Conclusions

Ruxolitinib “failure” in patients with MF presents a significant management challenge, and there is tremendous enthusiasm at present for development of new drugs in this setting. The regulatory approval of fedratinib has provided an important new option for these patients, and momelotinib, if approved, could prove to be another important addition to the JAK inhibitor armamentarium, especially for anemic patients. Advancements in our understanding of the biology of MF have opened up many new avenues for clinical investigation beyond JAK inhibition, as reviewed in this article. The results with some of these, such as imetelstat and the ruxolitinib-CPI-0610 combination, are particularly

intriguing, and need to be validated in larger numbers of patients. It is likely that a number of fedratinib-based rational combinations will also emerge in the coming years. Overall, it is an exciting time for drug development in MF. Hopefully, the rapid pace of basic science discoveries and promising early signals of efficacy we are witnessing in clinical trials will translate soon into new and effective therapies for our patients.

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Table 1.

Criteria for ruxolitinib (RUX) failure used in recently reported clinical trials.

A. Criteria used for the re-analysis of JAKARTA-2[38] and in PAC203.[48]	
Relapsed	RUX for 3 mos with regrowth (defined as < 10% SVR or < 30% decrease in spleen size by palpation from baseline following an initial response)
Refractory	RUX for 3 mos with < 10% SVR or < 30% decrease in spleen size by palpation from baseline
Intolerant	RUX for 28 days complicated by development of RBC transfusion requirement (≥ 2 units/mo for 2 mos); or grade ≥ 3 thrombocytopenia, anemia, hematoma/hemorrhage while on RUX

B. JAK inhibitor failure as defined in the IMBARK™ trial of imetelstat.[72]
<p>➤ Worsening of splenomegaly-related abdominal pain at any time after the start of JAK inhibitor therapy <u>and</u> EITHER:</p> <ul style="list-style-type: none"> ❖ No reduction in spleen volume or size after 12 weeks of JAKi therapy, <u>OR</u> ❖ Worsening splenomegaly at any time after the start of JAKi therapy documented by: <ul style="list-style-type: none"> • Increase in spleen volume from nadir by 25% measured by MRI or CT, <u>or</u> • Increase in spleen size by palpation

Abbreviations: RUX, ruxolitinib; SVR, spleen volume reduction; mo, month; JAKi, Janus kinase inhibitor; MRI, magnetic resonance imaging; CT, computed tomography.

Table 2.

“Add-on” approaches to ruxolitinib being studied in ongoing clinical trials with results available in the public domain.

Agent (class)	Phase (NCT #)	Main eligibility criteria	Major efficacy results	Highlights of safety profile	Other noteworthy observations
Parsaclisib (PI3Kδi)	2 (NCT02718300)	RUX x 6 m with stable dose x 8 wks. Spleen >10 cm or 5–10 cm with active symptoms. Plts $50 \times 10^9/L$.	31 pts; 19 evaluable for SVR & TSS at wk 24: 12 (63%) with some SVR (median 8.8% reduction); median TSS reduction 35.9%	Colitis was not seen. Rashes and elevation of liver enzymes occurred.	Change from daily to weekly dosing after 8 weeks may have reduced efficacy.
Umbralisib (PI3Kδi)	1 (NCT02493530)	Stable dose of RUX x 8 wks with lost, suboptimal or no response per physician discretion.	23 pts; per IWG-MRT response criteria, 2 CR, 11 CI, 8 SD. Median SVR 13% (evaluable 17), median TSS reduction 35% (evaluable 22).	DLTs were asymptomatic gr 3 amylase/lipase elevations. Gr 3 colitis, pneumonia and dyspnea occurred in 1 pt each. No gr 2 AST/ALT elevation.	2 patients with post-PV/ET MF achieved CR.
CPI-0610 (BETi)	2 (NCT02158858)	RUX x 6 m with stable dose x 8 wks. Spleen volume 450 ml or TD. Plts $75 \times 10^9/L$. 2 cohorts: TD and non-TD.	54 pts; 3 of 12 evaluable (25%) in TD cohort had 35% SVR at wk 24; 7 of 13 evaluable (54%) had 50% TSS reduction at wk 24; 6 of 14 became TI.	Well-tolerated; most common AEs were GI, anemia and thrombocytopenia. Most common gr 3 AEs: anemia and thrombocytopenia.	10 of 23 (43.5%) had improvement in BMF; 4 of 23 (17.4%) had BMF improvement and 1.5 g/dL rise in Hgb; 4 of 11 (36.4%) had BMF improvement and TD→TI conversion.
Navitoclax (BCL-2/BCL-xL antagonist)	2 (NCT03222609)	RUX x 12 wks with stable dose of 10 mg bid x 8 wks. 5 cm palpable spleen. Plts $100 \times 10^9/L$.	34 pts; 9 of 30 evaluable (30%) achieved 35% SVR at wk 24. 6 of 17 evaluable (35%) had 50% TSS reduction.	Mean plt count at baseline, $232 \times 10^9/L$; nadir mean plt count at wk 8, $95 \times 10^9/L$.	Platelet counts were monitored weekly prior to navitoclax dose adjustment. 68% reached max dose (300 mg/d). 8 of 32 pts (25%) had 1 gr BMF reduction.

Abbreviations: i, inhibitor; plt, platelet; wk, week; m, month; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score; DLT, dose-limiting toxicity; IWG-MRT, International Working Group for Myeloproliferative Neoplasm Research and Treatment; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CR, complete response; CI, clinical improvement; SD, stable disease; GI, gastrointestinal; bid, twice daily; BMF, bone marrow fibrosis; TD, transfusion dependent; TI, transfusion independent; PV, polycythemia vera; ET, essential thrombocythemia; MF, myelofibrosis; PI3K, phosphatidylinositol-3-kinase; BET, bromodomain and extra-terminal; BCL-2, B-cell lymphoma-2; BCL-xL, B-cell lymphoma extra long; gr, grade; AE, adverse event.

Table 3.

Novel agents under study as monotherapy after ruxolitinib or in patients not candidates for ruxolitinib.

Agent (class)	Phase (NCT #)	Main eligibility criteria	Major efficacy results	Highlights of safety profile	Other noteworthy observations
Imetelstat (telomerase inhibitor)	2 (NCT02426086)	See Table 1, panel B. Int-2/ high risk MF relapsed/ refractory to JAKi with active symptoms of MF and spleen 5 cm or 450 ml on MRI. 2 dose arms: 4.7 and 9.4 mg/kg IV q3wks. Plts $75 \times 10^9/L$.	59 pts in 9.4 and 48 pts in 4.7 mg/kg dose arms (closed early). 10% had 35% SVR and 32% had 50% TSS reduction at wk 24 (9.4 mg/kg arm).	Grade 3 cytopenias frequent in 9.4 mg/kg arm (30–40% range).	Median OS 29.9 m in 9.4 mg/kg and 19.9 m in 4.7 mg/kg dose arms. 18% overall had improvement in BMF.
Alisertib (AURKA inhibitor)	1 (NCT02530619)	Int/high risk MF intolerant or refractory to RUX, or unlikely to benefit from RUX. Plts $50 \times 10^9/L$. Administered PO twice daily.	24 pts; spleen response by palpation in 29% (14 evaluable), anemia response in 11% (19 evaluable) and 50% TSS reduction in 32% (22 evaluable)	Most gr 3/4 drug-related AEs hematologic (20–40%)	No consistent effect on inflammatory cytokines. Normalization of megakaryocyte morphology and BMF reduction observed in 5 of 7 pts with sequential marrows.
PRM-151 (recombinant pentraxin-2)	2 (NCT01981850)	Int/high risk MF with gr 2/3 BMF and anemia and/or thrombocytopenia, RUX-exposed or not eligible for RUX. 3 dose arms: 0.3, 3 and 10 mg/kg IV q4wks x 9 cycles.	97 pts; 27.8% had BMF gr decrease at any time. 5 of 31 TD pts (16%) became TI. 6 of 13 plt TD pts (46%) became plt TI. 41% (76 evaluable) had some SVR; 34% (94 evaluable) had 50% TSS reduction.	Very well-tolerated; no major safety concerns. IRR and anaphylactic reaction in 1 pt each (both SAEs).	No clear relationship between dose and efficacy. Pts in 10 mg/kg dose cohort had more advanced disease and a trend towards OS benefit.
Bomedemstat (LSD1 inhibitor)	1/2 (NCT03136185)	Int-2/high risk MF refractory or resistant to, intolerant of, or ineligible for RUX. Plts $100 \times 10^9/L$. Administered PO once daily.	1 of 8 pts (12.5%) had 35% SVR by wk 24. 4 of 9 pts (44%) had 50% TSS reduction by wk 24. 1 TD $\rightarrow$ TI conversion.	No DLTs. Most common all grade drug-related AEs anemia, nausea and dysgeusia (gr 3/4, anemia and neutropenia).	Intra-pt dose titration (bi-weekly) to target plts $50\text{--}75 \times 10^9/L$. 1 gr BMF improvement in 15%. FDA fast-track designation, August 2019.
Tagraxofusp (CD123-targeting fusion protein)	2 (NCT02268253)	Int/high risk MF relapsed after, refractory or intolerant to, or ineligible for JAKi. Plts $<50 \times 10^9/L$ allowed. Administered IV on d1–3 of a 21d cycle.	29 pts; 3 pts had CI-symptoms per IWG-MRT. 8 of 15 evaluable pts (53%) had some spleen length reduction.	Overall well-tolerated; 1 case of CLS (gr 3).	Possible efficacy signal in pts with monocytosis.
LCL-161 (Smac-mimetic/IAP antagonist)	2 (NCT02098161)	Int/high risk MF relapsed after, refractory or intolerant to, or ineligible for JAKi. Plts $<50 \times 10^9/L$ allowed. Administered PO weekly.	50 pts; ORR 30%: CI-symptoms in 11, CI-anemia in 6, CI-spleen in 1. 1 CCyR.	Drug-related gr 3/4 AEs: syncope, N/V, anemia, thrombocytopenia. Gr 1/2 N/V, fatigue and dizziness/vertigo very common.	Reduction in cIAP1 correlated with response; increase in XIAP with loss of response.
CPI-0610 (BET inhibitor)	2 (NCT02158858)	Int-2/high risk MF refractory or resistant to, intolerant of, or ineligible for RUX. Plts $75 \times 10^9/L$. Spleen volume 450 ml or TD. Administered PO once daily. 2 cohorts: TD and non-TD.	36 pts; at 24 wks, no pt achieved 35% SVR; 3 of 5 pts (60%) in non-TD cohort achieved 50% TSS reduction. No TD $\rightarrow$ TI conversion. 6 of 11 pts (55%) had 1.5 g/dL rise in Hgb.	Well-tolerated; most common AEs were GI, anemia and thrombocytopenia. Most common gr 3 AEs: anemia and thrombocytopenia.	2 of 9 pts (22.2%) had BMF improvement and 1.5 g/dL rise in Hgb. FDA fast track designation, Nov 2018.

Abbreviations: d, day; plt, platelet; wk, week; m, month; RUX, ruxolitinib; SVR, spleen volume reduction; TSS, total symptom score; DLT, dose-limiting toxicity; IWG-MRT, International Working Group for Myeloproliferative Neoplasm Research and Treatment; CR, complete response; CI, clinical improvement; SD, stable disease; N/V, nausea/vomiting; GI, gastrointestinal; BMF, bone marrow fibrosis; TD, transfusion dependent; TI, transfusion independent; MF, myelofibrosis; BET, bromodomain and extra-terminal; gr, grade; IV, intravenous, PO, oral; OS, overall survival; FDA, Food and Drug Administration; Hgb, hemoglobin; CLS, capillary leak syndrome; JAKi, Janus kinase inhibitor; AE, adverse event; SAE, serious adverse event; IAP, inhibitor of apoptosis; cIAP, cellular IAP; XIAP, X-linked IAP.

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