Blood and Lymphatic Cancer: Targets and Therapy

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REVIEW

The Ongoing Challenges of Managing Cytopenic Myelofibrosis in 2025: The Emergence of Non-JAK Inhibitor Therapies

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Abstract: Primary myelofibrosis (PMF) is a myeloproliferative neoplasm that is felt to arise from somatic mutations with hematopoietic stem and progenitor cells (HSPC's), leading to the development of atypical megakaryocytic hyperplasia. Associated dysregulated cytokine signaling and the trafficking of fibroblasts to the marrow compartment then leads to the deposition of collagen in the marrow compartment. On a molecular level, several well-established driver mutations in *JAK2, CALR* or *MPL* activate signaling through JAK/STAT, producing the proliferative phenotype of myelofibrosis. JAK inhibition, accordingly, has been and remains a mainstay in MF-directed therapy. In patients whose disease becomes refractory to Jak inhibitors or in those who experience intolerable adverse effects, however, options from different therapeutic classes are available. Despite this broad availability that includes erythropoiesis-stimulating agents, androgens and TGF-β inhibitors, one of the major challenges in management remains the implementation and successful long-term use of agents to treat cytopenic myelofibrosis. Research into alternative drivers has now led not only to the identification of alternative signaling mechanisms in MF but also to the development and now approval of new therapies outside of Jak inhibitors.

Keywords: myelofibrosis, cytopenic, splenomegaly

Introduction

Primary myelofibrosis (PMF) is a myeloproliferative neoplasm (MPN) that is characterized morphologically by atypical megakaryocytic hyperplasia and reticulin fibrosis.[1] Driver mutations involving *JAK2, CALR* or *MPL* activate JAK/STAT signaling and give rise to the proliferative phenotype and are often accompanied by additional mutations involving splicing, DNA-methylation, or proliferation.[2] As a result, patients experience dysregulated cytokine signaling, recruitment of fibroblasts to the marrow compartment and subsequent collagen deposition, creating an inhospitable environment for normal hematopoiesis.[3] Clinically, PMF manifests with anemia, extramedullary hematopoiesis (ie splenomegaly and hepatomegaly) and constitutional symptoms such as fever, chills, night sweats, and weight loss. The current treatment paradigm in MF focuses on inhibition of JAK/STAT signaling, which leads to improvement in splenomegaly and disease-related symptoms, though this approach often exacerbates anemia and thrombocytopenia. For patients either unfit for or intolerant to JAK inhibitors, the therapeutic arsenal is generally limited to agents that have been proven in clinical trials or pre-clinical studies only to improve hematologic parameters and/or improve symptoms. Expanded research into non-classical drivers, however, has resulted in the global investigation of alternative signaling mechanisms in this complex disease, which are poised to transform the landscape of therapies available to patients.

Molecular Heterogeneity in Primary Myelofibrosis

Despite features that are common amongst all patients, PMF is a clinically and pathologically heterogeneous disease. Much of this can be attributed to the molecular diversity that has been well described.[4]

Received: 25 June 2025
Accepted: 30 August 2025
Published: 24 September 2025

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Phenotype-driving mutations in *JAK2, CALR* and *MPL* are seen in approximately 85–90% of patients.[5] Beyond this, patients also frequently harbor additional mutations in genes that regulate splicing, epigenetic modulation, and signaling. These can include mutations in *ASXL1*, *TET2*, *SRSF2*, U2AF1, and within the RAS-pathway.[6–9] These additional mutations are enriched in patients with "triple-negative" PMF who lack a classical driver mutation but retain the clinical and histologic features of the disease. Within this smaller subset, the clonal architecture is felt to be even more expansive and includes mutations in regulators of cellular metabolism, including in isocitrate dehydrogenase (*IDH*), in tumor suppressor genes such as *TP53* and again in genes within the Ras/MAP Kinase signaling pathway (outlined in Figure 1).[10–13]

Dysregulated pro-inflammatory cytokine signaling outside of the JAK/STAT pathway has been demonstrated in multiple pre-clinical models to promote inflammation in the marrow microenvironment, leading to marrow fibrosis through a variety of mechanisms. One key mechanism is the remodeling in mesenchymal stem cells (MSC's) with increased recruitment to the bone marrow compartment, leading to fibroblast formation and subsequent collagen deposition.[15–17] Specific cytokine pathways implicated in PMF development and progression include those that signal through CXCL8/CXCR2, interleukin 1β (IL-1β) and NF-κB.[18–20]

Phenotypic Classification of Primary Myelofibrosis

The complex molecular nature of MF leads to highly variable clinical manifestations in patients and a wide phenotypic spectrum of the disease. When it comes to the general approach to clinical decision-making, however, patients generally fall into one of two categories, the first of which is proliferative MF and the second being cytopenic MF.[21,22] Patients with proliferative MF more commonly have elevated or normal leukocytes with mild, non-transfusion-dependent anemia and preserved platelet counts. Alternatively, patients with cytopenic disease exhibit or more cytopenia which can limit

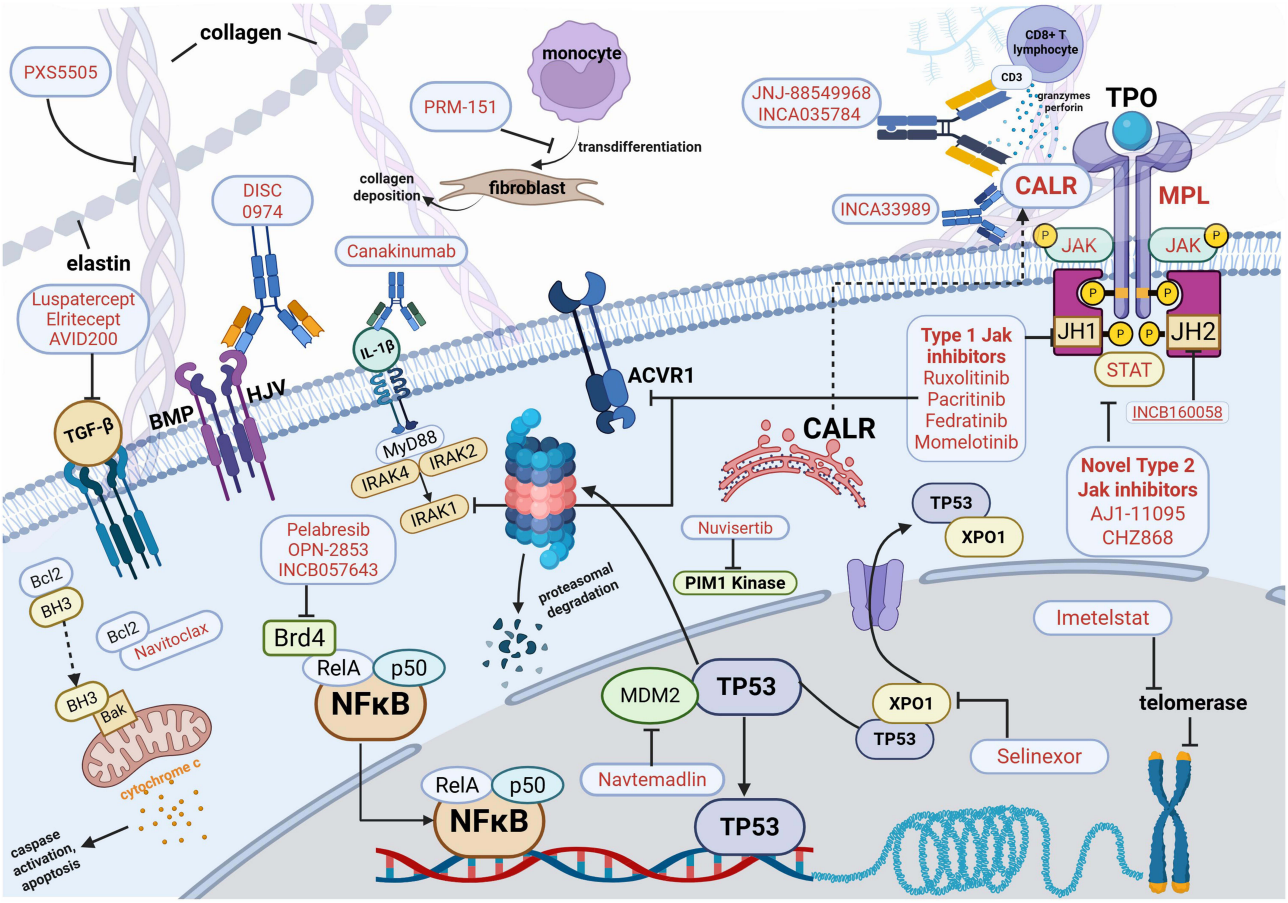

Figure 1 Rendering of various intra- and extracellular targets and processes in myelofibrosis, specifically pertaining to the mechanisms of established and novel agents.[14]

their ability to receive and benefit from standard therapies. The degree of cytopenias, specifically anemia and thrombocytopenia, has been correlated in multiple retrospective analyses with shortened overall survival (OS).[23,24] Severe thrombocytopenia to $<50\times10^9$/L also corresponds with an increased risk for transformation for acute myeloid leukemia (eg blast phase disease).[25] One of the key challenges in approaching this classification is its intrinsic rigidity and that the myelofibrosis phenotype, in clinical practice, is more fluid. Patients with pre-fibrotic disease, for instance, may have a different clinical course than patients whose MF evolved from pre-existing essential thrombocythemia or polycythemia vera. There are even patients whose disease, at presentation, is evolving to AML. The identification of the precise subtype in MF, therefore, can be difficult in what is a perpetually evolving disease state. For the sake of simplicity, the following sections will describe the most updated management strategies in both proliferative and cytopenic myelofibrosis.

Historical Management of Proliferative Myelofibrosis

Jak Inhibitors

Ruxolitinib is a non-selective JAK1/2 inhibitor which competes at the ATP-binding sites of their kinase domains.[26] The efficacy of ruxolitinib was evaluated in COMFORT-I, a randomized Phase III trial evaluating the efficacy of the Jak inhibitor administered twice daily as compared to placebo in 155 and 154 patients, respectively, with a primary endpoint at 24 weeks of splenic volume reduction of ≥35% (SVR35).[27] The proportion of patients meeting this primary endpoint was 41.9% in the ruxolitinib arm compared to only 0.7% in those receiving placebo ($p<0.001$). Total symptom score reduction in of ≥50% (TSS50, secondary endpoint) was achieved in 45.9% of patients receiving ruxolitinib as compared to 5.3% with placebo ($p<0.001$). COMFORT-II had a similar design and endpoints but instead compared ruxolitinib to best available therapy (BAT).[28] At 48 weeks, 28% of patients receiving ruxotlinib achieved SVR35 compared to 0% of the BAT arm ($p<0.001$). The results of these trials would ultimately lead to an FDA approval of ruxolitinib and its widespread institution as an initial pharmacologic agent in patients with PMF.[26] Despite this, both COMFORT I and II only enrolled with baseline platelet values of $>100\times10^9$/L, making its historical (and ongoing) utilization in clinical care challenging in patients with cytopenic disease.

Fedratinib is a more selective inhibitor of JAK2 (with weaker JAK1 inhibition) and acts at both the kinase domain peptide-substrate and ATP binding sites; it also exerts an inhibitory effect on fms-like tyrosine kinase 3 (FLT3).[29] In the Phase III JAKARTA study, fedratinib was compared to placebo in the frontline setting in 289 total patients with various MF subtypes, including intermediate-2 and high-risk PMF in addition to post-essential thrombocythemia and post-polycythemia vera disease; as in the COMFORT studies, SVR35 and TSS50 were utilized as endpoints.[30] At week 24, SVR35 was reached in 36% and 40% of patients receiving fedratinib 400 and 500 mg, respectively, compared to 1% of patients on placebo ($p<0.001$). TSS50 were approximately 35% with fedratinib and 7% with placebo ($p<0.001$). The JAKARTA2 study evaluated fedratinib in a single-arm Phase 2 study that enrolled patients who were either intolerant or resistant to ruxolitinib.[31] Of 97 patients enrolled, 55% achieved SVR35, which was sustained (albeit to a lesser degree with SVR35 of 30%) on a subsequent analysis of patients who met stringent criteria for failure of ruxolitinib.[32] Despite fedratinib meeting is endpoints in JAKARTA 2, cytopenias were a common adverse event, with anemia being reported in 38% of patients and thrombocytopenia in 22%. Investigators in both JAKARTA trials limited enrollment to patients with baseline platelet values of $>50\times10^9$/L; this and other reported adverse effects from these studies, most notably gastrointestinal toxicities and rare Wernicke's encephalopathy, have limited the widespread adoption of fedratinib into clinical practice for patients with cytopenic MF.[30,31]

Management of Cytopenic Myelofibrosis

Cytopenic MF reflects an increasingly recognized phenotype of MF that presents unique challenges. Anemia is present in nearly half of patients with MF at diagnosis while significant thrombocytopenia is less common at presentation, present in approximately 26% of patients.[33] Patients with transfusion-dependent anemia or severe thrombocytopenia (platelets $<50\times10^9$/L) at diagnosis or during the course of therapy represent a challenge for hematologists since many JAK inhibitors can worsen cytopenias.[21] Two recently approved JAK inhibitors offer optimism for patients with cytopenic MF

due in part to inhibition of non-JAK2 targets. Additionally, a variety of other agents across multiple drug classes have demonstrated utility of this patient population.

JAK Inhibitors for Cytopenic MF

In addition to inhibition of JAK2, pacritinib has demonstrated potent inhibitory activity against interleukin-1 receptor-associated kinase 1 (IRAK1) and activin A receptor type 1 (ACVR1). Pacritinib has demonstrated efficacy in terms of symptom improvement and spleen volume reduction in multiple Phase 3 clinical trials.[34] In PERSIST-1, investigators randomized patients 2:1 to receive either pacritinib 400 mg daily or best available therapy (BAT not including other Jak inhibitors) with a primary endpoint of SVR35 at 24 weeks; patients with red cell transfusion dependence and thrombocytopenia to $<50\times10^9$/L were not excluded.[35] The primary endpoint was met in 42 pacritinib-treated patients (19%) compared to 5 (5%) of patients receiving BAT (p=0.0003). Frequency of adverse effects was comparable between the two groups. PERSIST-2 leveraged the lack of existing treatment options for patients with thrombocytopenia and enrolled 311 patients with platelet counts of $\leq100\times10^9$/L. Patients were randomized 1:1:1 to pacritinib 400 mg daily, 200 mg BID and BAT.[36] At week 24, the patients receiving two separate doses of pacritinib treated were pooled and demonstrated superior spleen volume reduction compared to BAT; however, although symptom improvement did not reach statistical significance (p = 0.08). Notably, patients treated with pacritinib 200 mg BID had superior outcomes over BAT, suggesting this was the optimal dosing strategy. The phase 2 PAC203 trial further reaffirmed this dosing decision. Pacritinib received accelerated FDA approval in 2022 for patients with platelet counts $<50\times10^9$/L. The ongoing, confirmatory PACIFICA study randomizes patients with platelets of $<50\times10^9$/L with limited prior exposure to Jak inhibitors 2:1 to either pacritinib or physicians-choice therapy.[37] Recently, pacritinib was found to be a potent inhibitor of ACVR1; a target shown to be of relevance in MF-associated anemia. Post-hoc analysis of the PERSIST studies have demonstrated favorable anemia outcomes in pacritinib-treated patients supporting its use in this patient population.

Momelotinib is a JAK1/JAK2 inhibitory action against ACVR1.[38] In the SIMPLIFY-1 study, momelotinib was compared to ruxolitinib in a phase 3, non-inferiority study enrolling treatment-naïve patients with MF. The primary endpoint was SVR35 at 24 weeks of therapy with a secondary endpoint of TSS50.[39] Statistically, momelotinib was shown to be non-inferior to ruxolitinib in terms of spleen volume responses (p=0.011); however, non-inferiority was not achieved with regard to symptom reduction (p=0.98). The Phase 3 SIMPLIFY-2 study compared momelotinib to BAT in patients previously treated with ruxolitinib. Spleen volume responses were similar in momelotinib- vs BAT-treated patients likely owing to the fact that 89% of BAT patients were treated with ruxolitinib and there was no washout required from prior ruxolitinib. Notably, momelotinib-treated patients had significant symptom improvement compared to ruxolitinib in this second-line setting.[40] The experience from SIMPLIFY-1 and SIMPLIFY-2 showed that momelotinib had activity in terms of spleen volume reduction and symptom improvement and, importantly, was associated with favorable impact on anemia compared to ruxolitinib. This led to the phase 3 MOMENTUM study which enrolled anemic MF patients with splenomegaly and disease-related symptoms who had previously received ruxolitinib. About 195 patients were randomized 2:1 to receive either momelotinib or danazol. Patients with pre-existing thrombocytopenia were permitted provided that platelet values were $\geq25\times10^9$/L.[41–44] At 24 weeks, the primary endpoint of TSS50 at 24 weeks was met in 32/130 (25%) of patients receiving momelotinib compared to 6/65 (9%) receiving danazol, corresponding with a difference in proportion of 16% (p=0.0095). Momelotinib-treated patients also demonstrated superior spleen volume responses and higher rates of transfusion independence after 24 weeks compared to danazol. Momelotinib was approved by the FDA in September 2023 for patients with MF and anemia.[45]

Androgens

While not widely utilized as frontline therapy nor in patients with thrombocytopenia-predominant disease, androgens can improve anemia in patients with MF. Various mechanisms underlying the impact of androgens on hematologic neoplasms have been proposed in pre-clinical studies, including stimulation of erythropoiesis, immunomodulation and even elongation of telomeres.[46] Danazol was specifically evaluated in a small cohort of 50 patients with anemia from myelofibrosis, 30% of whom experienced a response in anemia, defined by ≥12 weeks of sustained increase in hemoglobin of >2 g/dL or cessation in transfusion dependence.[47] Interestingly, the aforementioned MOMENTUM

study further demonstrated the activity of danazol in MF where, as the comparator to momelotinib, danazol showed the ability to improve transfusion independence rates, increase platelet counts, and lead to symptom responses in a subset of patients with MF. Danazol has also been studied in combination with ruxolitinib wherein clinical responses were rare but the combination was safe to administer.[48]

Erythropoiesis-Stimulating Agents

The impact of erythropoiesis-stimulating agents (ESA's, including epoetin alfa and darbepoetin) on anemia in MF has been evaluated in multiple retrospective studies with variable outcomes.[49] One report in 59 patients treated with a combination of ESA's with ruxolitinib, over half of whom were transfusion-dependent.[50] At 5 years, the rate of anemia response (AR) was 54% and 63% in patients with endogenous EPO levels of <125 u/L; 78% of patients also experienced a reduction in spleen size. ESAs continue to be utilized in patients with anemia and myelofibrosis, particularly in those with lower endogenous EPO levels and who are not transfusion dependent.

Immunomodulatory Agents

Immunomodulatory (imid) agents are available in select cases of patients with myelofibrosis and have been evaluated in cytopenic populations. Lenalidomide, for instance, was evaluated in pooled data from two phase 2 studies (68 patients in total) evaluating its use in patients with symptomatic MF with myeloid metaplasia (termed MMM). Here, the overall response in anemia was 22% and 50% in thrombocytopenia, the latter of which was defined as ≥50% improvement from baseline.[51] Use of thalidomide was evaluated in a similar pooled analysis of five different phase 2 studies in 62 total patients with MMM.[52] Authors in this study reported that 29% of patients with baseline moderate/severe anemia experienced either a reduction or resolution in transfusion burden and 38% with moderate/severe thrombocytopenia experienced an improvement in platelets. Another retrospective analysis reported on 176 patients with MF at a single institution who had been on therapy with either thalidomide or lenalidomide for ≥4 weeks. In 83 assessable patients treated with lenalidomide, 41 (49%) experienced a clinical benefit (CB, largely in anemia). Findings were similar in patients who had received thalidomide, with 28 (42%) deriving CB.[53] Pomalidomide was evaluated in a Phase 3 study in which patients were randomized 2:1 to study drug or placebo with a primary endpoint at 6 months of red cell transfusion independence.[54,55] While responses in anemia in this study were comparable between study arms, the response in thrombocytopenia was more pronounced in patients receiving pomalidomide. Immunomodulatory agents remain an option in patients with cytopenic myelofibrosis.

TGF-β Inhibitors

Transforming growth factor beta (TGF-β) is a cytokine that is maintained in the extracellular matrix (ECM) and is associated via non-covalent binding with latency-active protein (or LAP) and is directly involved in increasing synthesis of Types I, III and IV collagen.[56] In one Phase 2 study evaluating 79 patients with concurrent MF and anemia, patients were enrolled into one of 4 cohorts, including transfusion-dependence and independence while on and off ruxolitinib, all of whom received luspatercept every 21 days for 168 total days. The primary endpoint of independence from transfusions for at least 12 consecutive weeks during the initial 24-week study period (or RBC-TI) was highest in the patient transfusion-dependent patients on stable doses of ruxolitinib.[57] A phase 3 trial comparing luspatercept to placebo (INDEPENDENCE) is underway.[57,58]

Elritecept has a similar mechanism as a type IIA modified activin receptor ligand trap and was evaluated in the Phase 2 RESTORE study, which enrolled 23 patients to receive the investigational agent alone (Arm A) and 31 to combination therapy with ruxolitinib (B).[59] During the initial 24 weeks, a mean increase in hemoglobin to ≥1.0 g/dL over a consecutive 12 weeks was observed in non-transfusion dependent patients in both arms (3/8 in Arm A, 7/12 in Arm B).

AVID200 is another TGF-β 1/3 ligand trap that was utilized in 21 patients with advanced myelofibrosis through a multicenter investigator-initiated Phase 1b trial.[60] Following 6 cycles of AVID200 monotherapy, while clinical benefit as defined by the International Working Group for MPN Research and Treatment (IWG-MRT) was seldom, 17 (81%) of patients experienced an improvement in platelet count, 3 of whom had a normalization in platelet values. This finding, while only present in a small subset of patients, would be unique to the current class of TGF-β inhibitors as luspatercept

and elritcept have been predominantly studied and utilized for their benefit in anemia-predominant myeliofibrosis but their effect in thrombocytopenic disease has not been consistently demonstrated. Cytokine modulation in PMF will be discussed in greater detail under the Emerging Therapies section.

Emerging Therapies in Myelofibrosis

Therapies and classes of therapies that target non-canonical cellular (and extra-cellular) signaling mechanisms in myelofibrosis represent an expanding area of research in myelofibrosis. The majority of the approaches discussed in the following sections are actively being studied in translational and/or early-phase clinical trial settings. The sections that follow provide an overview of the results of both the published and ongoing research, particularly the impact of individual agents on cytopenic MF where data is available.

Bcl-2 Inhibition

The B-cell leukemia 2 (Bcl2) protein family is a set of anti-apoptotic proteins and mulitple strategies have been developed to modulate their effects, notably through the development of BH3 mimetics, which displace the anti-apoptotic protein and promote apoptosis through mitochondrial outer membrane permeabilization (MOMP). Several studies implementing Bcl2 inhibitors/BH3 mimetics have been and are being conducted, most notably with navitoclax. Investigators in the Phase 2 REFINE study enrolled patients with relapsed/refractory disease to receive navitoclax + ruxolitinib if a suboptimal response to ruxolitinib (at least 10 mg twice per day) either by 12 (Cohort 1a) or 24 weeks (1b).[61] SVR35 at 24 weeks, the primary endpoint, and anemia response (secondary) were both reached in 23% of patients, although thrombocytopenia was a common adverse effect. In the Phase 3 clinical study TRANSFORM-1, investigators enrolled JAK inhibitor-naïve patients with intermediate-2/high risk MF symptomatic disease, including those with splenomegaly, 1:1 to either navitoclax + ruxolitinib or placebo + ruxolitinib.[62] The study met its primary endpoint as approximately 63% of patients in the navitoclax arm achieved SVR35 at 24 weeks as compared to 31.5% in the ruxolitinib alone arm ($p<0.0001$). Unfortunately, a key secondary endpoint of symptom improvement was not met. Thrombocytopenia was common and required frequent dose interruption and reduction. Further investigations into navitoclax are in progress.

BET Inhibition

The bromodomain extra-terminal domain (BET) family consists of 4 proteins, one of which in Brd4 has been demonstrated to co-activate nuclear factor kappa beta (NFκB) by binding to its acetylated RelA subunit, thereby enhancing pro-inflammatory signaling and promoting fibrogenesis.[21,63–65] Pelabresib is an oral BET inhibitor that was evaluated in MANIFEST, a multi-cohort Phase 2 study for patients naïve to Jak inhibition.[66] Here, 84 patients received at least 1 dose of ruxolitinib and pelabresib, 66% of whom had baseline anemia to a hemoglobin of <10 g/dL. At 24 weeks, SVR35 was achieved in 68% of patients, TSS50 in 56% and improved hemoglobin (median of 0.8 g/dL) in 36%; thrombocytopenia was observed in 12% of patients. In the subsequent Phase 3 MANIFEST-2 study, patients were randomized 1:1 to either pelabresib + ruxolitinib or placebo + ruxolitinib; the primary endpoint again of SVR35 at 24 weeks was met in 65.9% and 35.2% of patients, respectively ($p<0.001$).[67] Interestingly, and in keeping with the mechanism of BET inhibition, degree of marrow fibrosis and levels of proinflammatory cytokines were lower with combination therapy, although anemia and thrombocytopenia were also more common, occurring in 52.8% patients.

OPN-2853 is another BET inhibitor being evaluated presently in the Phase 1 PROMise study, where patients with intermediate-2 or high-risk MF receive treatment together with ruxolitinib.[68] While trial therapy is still in progress, preliminary reported data has included reductions in spleen size. The BET inhibitor INCB057643 is also under investigation through an open-label Phase 1 dose-escalation/expansion study in patients with various myeloid neoplasms, including relapsed/refractory myelofibrosis.[69] To date, amongst evaluable patients receiving INCB057643 monotherapy, 13 of 19 treated with any dose of therapy have achieved SVR35 by week 24. The role of BET inhibition in cytopenic myelofibrosis has yet to be ascertained; additional agents from Incyte and Opna Bio are also under active development.

IL-1β Inhibition

Other strategies to modulating cytokine signaling in myelofibrosis are also being investigated, one of which is an IL-1β neutralizing monoclonal antibody in canakinumab, which also signals through IRAK1 and whose efficacy has also been evaluated in myelodysplastic syndrome (MDS).[2,70] A Phase 2 study for patients with either PMF or post-ET/PV disease is ongoing and is enrolling patients to receive subcutaneous canakinumab once every 21 days for 8 total cycles.[71] To be eligible for enrollment, patients are required to have either baseline hemoglobin of <10 g/dL, transfusion dependence, splenomegaly or a total symptom score ≥10.

PIM1 Kinase Inhibition

Nuvisertib (TP-3654), a selective PIM1 kinase inhibitor, is currently being administered as monotherapy in a phase 1/2 study, where investigators are enrolling patients with JAK inhibitor-naïve primary or secondary myelofibrosis.[72,73] For patients who received a stable therapeutic dose for at least 12 weeks, an SVR25 was attained in 31% (5/16) and TSS50 of 50% (8/16). Notably, 32% (7/22) patients with baseline thrombocytopenia to platelet values of $<100\times10^9$/L experienced a sustained improvement in platelet of at least 30×10^9/L for ≥4 weeks. Enrollment in the study is ongoing and will examine the combination of nuvisertib with ruxolitinib as well as momelotinib.

Telomerase Inhibition

Imetelstat is a telomerase inhibitor that, as of 2024, has been approved in patients with low-risk MDS who are either refractory in/ineligible for ESA's or who are transfusion dependent.[74] In the Phase 2 IMbark study, patients with relapsed/refractory disease with prior Jak inhibitor exposure were randomized to one of two doses of intravenous imetelstat (4.7 or 9.4 mg) every 3 weeks with coprimary endpoints of SVR35 and TSS50 at 24 weeks.[75] Results were noteworthy for an SVR35 of 10% at the 9.4 mg/kg dose and 6.3% in for 4.7 mg/kg. Investigators also reported an improvement in marrow fibrosis and driver mutation variant allele frequency reduction in 40.5% and 42.1% of patients, respectively. IMpactMF is an ongoing multi-center Phase 3 study randomizing patients 2:1 to imetelstat or best available therapy (BAT) in patients with intermediate-2 or high-risk disease with prior Jak inhibitor exposure and who are ineligible for either further Jak inhibition or transplant.[76] Imetelstat, based on historical data and depending on the forthcoming results of this study, may represent a variable therapeutic option in patients with cytopenic myelofibrosis, specifically in those with anemia-predominant disease or transfusion dependence.

Fibrosis Inhibition

Anti-fibrotic agents are still considered investigational to an extent in myelofibrosis but have been studied in trial settings, one example of which is PRM-151. A recombinant pentraxin-2 molecule, PRM-151 was first evaluated in pre-clinical settings to alter fibrosis by targeting the process by which monocytes transdifferentiate into fibrocytes.[77] In one 2018 open label extension study, patients received PRM 151 either as monotherapy or in combination with ruxolitinib and did experience improvements in both collective symptoms and splenomegaly. Investigations in the subsequent Phase 2 S828 study randomized patients with intermediate-1, 2 or high-risk PMF or post-ET/PV disease who were intolerant to, ineligible for or had a suboptimal response to prior ruxolitinib were randomized to receive one of 3 doses of PRM-151 at 0.3, 3 and 10 mg/kg.[78] Approximately 16–29% of patients who were either dependent on red cell transfusions or with anemia to <10 g/dL at baseline experienced at least a 50% reduction in RBC transfusion burden. Similarly, 31–40% of those with baseline thrombocytopenia with platelet transfusion dependence experienced had the same degree of improvement. PXS-5505 is another recently developed agent that inhibits pan-lysyl oxidase (LOX), thereby preventing elastin and collagen cross-linking. The dose escalation and cohort expansion phases of the Phase 1/2a PXS5505-MF-101 study and have established a dose of 200 mg for the pan-LOX inhibitor. Patients actively enrolling will now receive twice daily therapy for up to 1 year and are allowed to continue ruxolitinib during the study period. Study results are forthcoming.[79] Anti-fibrotic agents have yet to be adopted into routine clinical practice but, based on limited trial data, could play a role in the management of cytopenic disease.

CALR-Directed Therapies

Another recently developed agent in INCA33989, a monoclonal antibody targeting CD34+ *CALR*-mutated cells (mutCALR), has been demonstrated in pre-clinical models to both prevent megakaryocytic accumulation and reduce renewal capacity of oncogenic mutCALR-positive cells in the bone marrow.[80,81] Early-phase clinical studies are in progress.

Various novel bispecific antibodies in both JNJ-88549968 and INCA035784 have recently been developed as T-cell redirecting agents with dual binding to CD3 and cell surfaces of *CALR*-mutant CD34+ cells in patients with myeloproliferative neoplasms.[82,83] Their use is now being studied actively in clinical trials with the function goal of T-cell activation with subsequent cytotoxicity against mutant hematopoietic stem/progenitor cells.

Novel Jak Inhibitors

CHZ868 is another novel type II Jak inhibitor that also demonstrated activity in a pre-clinical model using *MPL*-mutant cells, which were sensitive to the agent even with pre-existing resistance to type I Jak inhibition.[81] INCB160058 has also recently been developed as a mutant-specific JAK2 inhibitor that specifically targets the JAK2V617F JH2 domain.[84] CHZ868 and INCB160058 have not been adopted into clinical practice and their use again remains investigational.

AJ1-11095 is a non-covalent type II tyrosine kinase inhibitor that prevents TYK2 and JAK1 heterodimerization. A multicenter Phase 1 clinical trial enrolling patients with PMF as well as post-ET and PV MF who have previously been exposed to type I JAK2 inhibition is currently underway.[85] Patients are required to have a baseline platelet count of at least 75×10^9/L with at least intermediate-2 disease by the Dynamic International Prognostic Scoring System (DIPSS).

Other Agents

DISC0974 is a monoclonal antibody directed at hemojuvelin and thereby, as demonstrated in preclinical models, suppressing hepcidin and increasing serum iron.[86] A recent Phase 1b/2 study was conducted and evaluated, in addition to safety and pharmacokinetics, the efficacy of DISC0974 in patients with intermediate-2 or high-risk myelofibrosis and anemia to baseline hemoglobin <10 g/dL.[87] Hemoglobin responses were attained in 69% or non-transfusion dependent patients but only 1 transfusion-dependent patient had a durable hemoglobin response. Follow-up data is anticipated.

MDM2 is an E3 ubiquitin ligase that tags p53 for proteasomal degradation.[88] Navtemadlin, by inhibiting MDM2, effectively restores function of p53 and was recently compared to best available therapy (BAT) in the phase III BOREAS study.[89] Here, adults with Jak-inhibitor resistant intermediate or high-risk and $TP53^{WT}$ myelofibrosis were randomized in a 2:1 fashion to either navtemadlin at 240 mg daily for one week in 28-day cycles or BAT. At 24 weeks in the intention to treat population, 15% of patients receiving navtemadlin had achieved SVR35 as compared to 5% with BAT (p=0.08) while TSS50 was achieved in 24% and 12% (p=0.05), respectively. The Phase III POIESIS study investigating navtemadlin introduction for $TP53^{WT}$ patients with suboptimal ruxolitinib responses is underway.[90]

Exportin 1 (XPO1) is overexpressed in various malignancies and is felt to promote both inflammation and oncogenesis through the exportation and thereby inactivation of tumor suppressing proteins from the nucleus.[91] Selinexor is a selective XP01 inhibitor and is currently being evaluated in the Phase 1/3 SENTRY study evaluating both efficacy and safety in combination with ruxolitinib for patients with myelofibrosis who are naïve to JAK inhibitors. Primary endpoints will be SVR35 and TSS50 at 24 weeks.

Conclusion

Cytopenic myelofibrosis is a challenging disease space in patients who have this phenotype at the onset of PMF, in those who experience marrow suppression from primary therapy or as a manifestation of disease progression. Patients who present with a more classical MF phenotype at diagnosis, specifically with thrombocytosis stemming from atypical megakaryocytic hyperplasia at the level of the marrow, provide hematologists with a wider selection of approved (and more well-studied) agents. Those with cytopenic disease at baseline are more limited in not only available therapies but also in terms of what will be tolerated from the standpoint of not worsening their cytopenias while providing a restoration of functional hematopoiesis. The development of new Jak inhibitors and more novel approaches/targets in myelofibrosis

has led to a multitude of new and now-expanding set of therapies available to symptomatic patients who are unfit for transplant. Ongoing research into MF disease modification is poised to enact a paradigm shift in how hematologists approach management of this pleiomorphic hematologic condition.

Disclosure

Dr Rami Komrokji reports personal fees and/or grants from Abbvie, BMS, DSI, Geron, GSK, Takeda, pharma essentia, Rigel, Novartis, Servier, SOBI, Stem line, and Sumitomo, outside the submitted work. Dr Andrew Kuykendall reports grants, personal fees, and/or non-financial support from GSK, Abbvie, Protagonist, Silence Therapeutics, Blueprint Medicines, MorphoSys/Novartis, Incyte, Geron, Janssen, Sobi, Cogent, Kartos, BMS, and Takeda, outside the submitted work. The authors report no other conflicts of interest in this work.

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