Review Article

Novel Therapies in Myeloproliferative Neoplasms: Beyond JAK Inhibitor Monotherapy

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ABSTRACT

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders that consist classically of polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). Janus kinase (JAK) inhibitors have become the standard of therapy in treating patients with intermediate- to higher-risk MF. However, JAK inhibitor (JAKi) treatment can be associated with development of resistance, suboptimal response, relapse, or treatment-related adverse effects. With no approved therapies beyond the JAKi class, the estimated median survival, post JAKi failure, is approximately two years or less; therefore, novel therapies are urgently needed in the MF field. In this review, we discuss ruxolitinib use in MPNs as well as causes of ruxolitinib failure or discontinuation. In addition, we review novel therapies being investigated alone or in combination with JAKi administration. We summarize concepts and mechanisms behind emerging novel therapies being studied for MPNs. This review of emerging novel therapies outlines several novel mechanisms of agents, including via promotion of apoptosis, alteration of the microenvironment, activation or inactivation of various pathways, targeting fibrosis, and telomerase inhibition.

Keywords: myeloproliferative neoplasms, MPN, myelofibrosis, JAK inhibitor, ruxolitinib, novel therapy

INTRODUCTION

Myeloproliferative neoplasms (MPNs) are clonal hematopoietic disorders that include polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis (MF). The prognosis of patients with MPNs varies, with survival duration from months to decades. Many patients with PV and ET have good long-term prognoses, with 15-year survival of 65% for PV and 73% for ET.[1] Patients with primary myelofibrosis (PMF) have median survival ranging from 2.5–12.3 years, based on the associated existing molecular mutations with prognostic value.[2,3] On the other hand, studies consistently indicate poor prognosis in patients with leukemic transformation with median overall survival ranging from 2.6–6.2 months.[4,5] The most commonly acquired somatic mutation in MF is Janus kinase 2 (*JAK2*) V617F.[6,7] The next most commonly found mutations include alterations in *CALR* and *MPL*, with those negative for any of the three most common driver mutations termed *triple negative*.[8] Despite improvements in survival over the years, patients still encounter refractory disease, loss of response over time, or adverse events leading to contraindication to the use of JAK inhibitors (JAKis). Unfortunately, there are no approved therapies at this time beyond JAKis for patients with MF. Patients who do not achieve response to JAKis and subsequently develop clonal evolution have overall poor outcomes, with a median survival of approximately 2 years or less.[9,10]

The only potential curative therapy for MF remains allogeneic stem cell transplant (ASCT), which has shown significantly prolonged survival in selected patients.[4,5] However, transplant-related mortality remains high (18–

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35%), and only about 1/3 of the patients receiving ASCT reach long-term relapse-free survival.[11] Relapse risk is estimated to be up to 22% at 3 years and 28% at 5 years.[12,13] In this review, we will summarize current evidence on the new treatment options for MPNs beyond use of JAKis.

JAK INHIBITORS (JAKis)

JAKi Approval for MPNs

Verstovsek et al.[14] initially demonstrated that patients with MF showed a rapid objective response to the novel agent ruxolitinib, including a significant and clinically meaningful reduction in splenomegaly; patients had significantly improved quality of life, and in longer-term follow-up, improved overall survival. Grade 3 or 4 adverse events occurred in less than 10% of patients; the most common such event was reversible myelosuppression.[15] In the subsequent randomized phase III trials with intermediate or high-risk MF patients (COMFORT I and COMFORT II), patients treated with ruxolitinib demonstrated a greater reduction in spleen volume and disease-related symptom burden than with placebo or best available therapy.[14,16,17] Likewise, a randomized study using ruxolitinib in 222 patients with PV who had an inadequate response to or severe adverse effects from hydroxyurea showed significant efficacy of ruxolitinib in hematocrit control and spleen volume reduction when compared to best available therapy.[16,18] Ruxolitinib became the first drug to be US Food and Drug Administration (FDA) approved for treatment for intermediate- or high-risk MF (PMF and secondary MF) and PV with inadequate response to or intolerant of hydroxyurea.[16]

Fedratinib, a highly selective JAK2 inhibitor, is the second-in-class JAKi that the FDA recently approved for adults with intermediate- or high-risk MF. In a double-blinded, randomized, and placebo-controlled trial enrolling 289 patients with MF (JAKARTA, NCT01437787)[19], 37% of patients achieved the primary outcome of 35% or greater reduction in spleen volume. The median duration of splenic response was 18.2 months, with 40% of patients also experiencing 50% or greater reduction in MF-related symptoms. Currently, the recommended dose of fedratinib is 400 mg orally once daily. Importantly, fedratinib use comes with a "black box" warning for encephalopathy, including Wernicke encephalopathy. Monitoring thiamine level before and during treatment while replacing thiamine as indicated is also recommended.[20,21]

Other JAKis, including momelotinib and pacritinib, are currently being actively investigated in later-stage clinical trials. Each of these JAKis carries unique activity. Momelotinib directly inhibits hepcidin production, which results in increase in iron availability and subsequent improvement in erythropoiesis and benefit in anemia. The clinical efficacy of momelotinib in patients with MF is currently undergoing phase III trial investigation in a study of momelotinib versus danazol for patients with MF, anemia, a defined MPN symptom burden, and splenomegaly (MOMENTUM, NCT04173494).[22] Pacritinib specifically targets both JAK2 and IRAK1, which are thought to be a key driver of MF. Additionally, this drug does not inhibit JAK1, which has been associated with immune dysfunction and worsening cytopenias. An ongoing phase III trial of pacritinib in patients with MF will follow spleen volume reduction as a primary outcome and overall survival as a secondary outcome, focusing specifically on patients with MF and thrombocytopenia (PACIFICA, NCT03165734). [23]

Ruxolitinib Failure

Remarkably, there are still no uniform criteria for the definition of ruxolitinib "treatment failure." According to a retrospective data analysis with Intercontinental Medical Statistics database, the clinical practice discontinuation rate was 60.9 and 73% at 3 and 6 months, respectively. A large retrospective database analysis also showed discontinuation rates of 41.1 and 48.4% at 3 and 6 months follow-up, respectively.[24] A centralized database supported by 20 European hematology centers also reported a high discontinuation rate of 51.1% (268 of 524 patients) with a median drug exposure of 17.5 months.[10] These studies agree with the most recent retrospective study by Pemmaraju and colleagues[25] in 2020, which showed treatment interruption in 50% of the patients.

Ruxolitinib failure arises from various causes, including primary resistance, suboptimal response, secondary resistance, progression to post-MPN acute myeloid leukemia (AML), and treatment-related toxicities. Kuykendall and colleagues[26] highlight observed reasons for discontinuation, including cytopenias (24 of 64 patients; 38%) with anemia most implicated (21 patients; 33%), non–hematology-related treatment intolerance (6 patients), AML (8 patients), disease progression in symptoms or spleen size (7 patients), suboptimal response (9 patients), and allogeneic hematopoietic stem cell transplant (10 patients). Herein, we explore each cause of treatment failure and present several working definitions. Of note, these definitions are not uniformly agreed upon; however, we believe that exploring the causes of treatment failure will help us to better understand development areas for therapeutic interventions beyond JAKi therapy.

Primary resistance—refractoriness

IWG (International Working Group-Myeloproliferative Neoplasms Research and Treatment) and ELN (European LeukemiaNet) provide practical guidelines on how to assess clinical response to JAKi, such as meaningful improvement in symptoms, spleen size, and transfusion needs, as well as criteria for cytogenetic and molecular remissions.[27] Primary resistance or refractoriness would mean a failure to achieve any clinical benefit.

Suboptimal response

Although definitions may vary from study to study, a general understanding of suboptimal response occurs

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when patients do not achieve minimum clinical improvement within approximately 12 weeks or have mixed response with dose reduction or treatment interruptions due to adverse events.[27] While suboptimal response encompasses primary resistance, this group also captures patients with mixed responses and those with clinical responses that do not meet IWG or ELN criteria. Additionally, a study to understand ruxolitinib failure, such as the PAC203 study, describes "failure to benefit" as ruxolitinib use for at least 3 months with less than 10% spleen volume reduction, less than 30% decrease in spleen length, or regrowth to these parameters.[28]

Secondary resistance—relapse

Disease relapse is a loss of previously confirmed clinical response, which can occur for spleen, symptom, or anemia response or improvement. For example, the COMFORT trial II with ruxolitinib treatment aimed to define this as the loss of splenic response as an increase in spleen volume greater than 25% above the on-study nadir.[29]

Leukemic transformation

Leukemic transformation is defined as progression from the MPN state to AML. Leukemia transformation is often referred to as "blast phase," and the development of more than 10% blasts would also be a concern for disease progression to "accelerated phase." Disease progression to post-MPN AML was seen in two patients in the COMFORT I study and five patients in the COMFORT II study.[17,29] Further, five of 40 patients (13%) had progression to AML in a single institution analysis.[30] However, patients require continued monitoring in both short- and longer-term settings to assess over time for leukemic transformation.

Treatment-related toxicities

Treatment-related adverse events include anemia, thrombocytopenia, leukopenia, infections, bleeding, and thromboembolic events, with the highest rates occurring within the first 6 months of the treatment. PAC203 study further defines intolerance as ruxolitinib for 28 days or longer, complicated by development of red cell transfusion requirement or at least grade 3 anemia or thrombocytopenia, and/or hemorrhage while taking less than 20 mg twice a day [28] Although most experienced grade 1 to 2 adverse effects, often reversible, the COMFORT II study identified discontinuation of treatment in two patients due to anemia and in seven patients due to thrombocytopenia.[29]

On the other hand, Palandri and colleagues[10] reported ruxolitinib-related adverse events of 27.5% and unrelated adverse events of 9.2%. Related events included anemia, thrombocytopenia, infection, and neurologic side effects. Unrelated events included second solid neoplasm, thrombosis, heart failure, and pleural effusion. Three top clinical reasons for ruxolitinib discontinuation in patients with MF were suboptimal response in spleen size (34.8%), anemia and thrombocytopenia (17.4%), and infectious events (9.2%). Although their study found no significant difference in overall survival between the patients who discontinued ruxolitinib due to suboptimal response versus drug-related toxicity (median survival of 30 vs 13.2 months), they emphasize that this finding still may be clinically relevant. Patients who discontinued ruxolitinib due to toxicity will certainly be most vulnerable with limited therapeutic possibilities after ruxolitinib.[10]

NOVEL THERAPIES, MOVING BEYOND JAK2 INHIBITORS

There is no standard therapeutic approach for patients with intermediate- or high-risk MF who experienced treatment failure, lost response, or developed intolerance to JAKis. Treatments considered for post-JAKi patients unable to qualify for transplant would aim to treat each patient's specific problem such as anemia, splenomegaly, or symptoms. Moreover, ASCT remains the only potentially curative therapy for the subset of selected, fit patients with MF. Here, we review novel therapies currently undergoing investigation in active clinical trials and their proposed mechanisms. Studies of combination therapies with JAKi plus novel therapies (often referred to as "add-on" or "add-back" studies) and novel agent monotherapies are listed in Tables 1 and 2, respectively.

Combinations With JAKis

JAKis, in combination with various drugs, may lead to clinical benefit in patients with MPNs. Current studies aim to identify optimal drug combinations with JAKi. These studies will be especially valuable in patients who cannot tolerate or become resistant to current JAKi monotherapy. Current drug combination trials with JAKi include azacitadine, HSP90 inhibitor (PU-H71), BCL-xL inhibitor (navitoclax), thalidomide, HDACi (pracinostat), and more (Table 1).[31,32] These combination strategies aim to deepen spleen volume reduction and improve anemia while prolonging remission duration and overall survival.

Promotion of Apoptosis

Heaton et al.[33] reported that the level of tumor necrosis factor-alpha (TNF-α) is increased in MF, promoting the clonal dominance of malignant cells. This study found reduced expression of X-linked inhibitor of apoptosis (XIAP) and mitogen-activated protein kinase 8 (MAPK8) in both JAK2V617F-positive murine cells with MPN and human MF cells. Conversely, MF cells had increased cellular inhibitor of apoptosis protein (cIAP) expression in comparison to normal cells. XIAP expression induces apoptosis and regulates cIAPs, which has a role in nuclear factor kappa B (NF-kB) activation involved in TNF-dependent signaling. Overall, this study suggests that MF tumor cells promote their survival by upregulating TNF-α–dependent pathway via decreasing

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Table 1. Selection of current clinical trials of combination therapies with JAK inhibitors

Combination Study	NCT No.	Malignancy	Phase	No. of Patients Enrolled	Outcome Measures
Ruxolitinib + 9-ING-41 vs 9-ING-41	NCT04218071[112]	MF	II	58	RR
Ruxolitinib + ABBV-744 vs ABBV-744	NCT04454658[113]	MF	I	130	Adverse events, spleen volume reduction, pharmacokinetic profile
Ruxolitinib + APG-1252 vs APG-1252	NCT04354727[114]	MF	I/II	60	DLT, spleen volume reduction
Ruxolitinib + Azacitidine[31]	NCT01787487[96]	MPN, PMF, SMF	II	125	CR, PR, clinical improvement, incidence of adverse events
Ruxolitinib + CPI-0610 vs CPI-0610	NCT02158858[92]	MPN, MDS, AML, MF	I/II	271	Spleen response, RBC transfusion independence rate
Ruxolitinib + Daunorubicin	NCT03878199[115]	Secondary AML, MPN	I/II	47	DLT, CCR, CR, Cri, OS, EFS, RFS, remission duration
Ruxolitinib + Decitabine[32]	NCT02257138[116]	AML, MPN, PMF, SMF	I/II	34	MTD, overall response
Ruxolitinib + Decitabine[32]	NCT02257138[116]	post AML-MPN	I/II	34	MTD, CR
Ruxolitinib + Enasidenib	NCT04281498[117]	Accelerated/blast-phase MPN, MF	II	32	RR
Ruxolitinib + Itacitinib	NCT03144687[118]	MPN	II	23	Safety and tolerability, spleen volume reduction
Mivebresib +/− Ruxolitinib or Navitoclax	NCT04480086[119]	MF	I	130	Adverse events, change in spleen volume, ORR, pharmacokinetic profile
Ruxolitinib + Navitoclax	NCT04472598[47]	MF	III	230	Spleen volume reduction, reduction in TSS*, OS, ORR, leukemia-free survival
Ruxolitinib + Navitoclax	NCT04468984[120]	MF	III	330	Spleen volume reduction, reduction in TSS*, OS, ORR, leukemia-free survival
Ruxolitinib + Navitoclax vs Navitoclax	NCT03222609[46]	MF	II	164	Spleen volume reduction, change in TSS*, ORR
Ruxolitinib + Parsaclisib	NCT02718300[121]	MPN	II	90	DLT, change in spleen volume, adverse events
Ruxolitinib + Pevonedistat	NCT03386214[122]	MF	II	18	Safety and tolerability, spleen volume reduction
Ruxolitinib + PU-H71	NCT03373877[58]	PMF, SMF	I	30	Adverse events, MTD, RP2D, pharmacokinetic profile
Ruxolitinib + TGR-1202	NCT02493530[127]	PV, MF	I	60	Safety, overall response
Ruxolitinib + Thalidomide	NCT03069326[123]	MF	II	30	ORR
Ruxolitinib or Fedratinib + Decitabine	NCT04282187[124]	AML, MPN, PMF, SMF	II	25	Remission rate, OS, RFS, mutational data, response rate, OS
Fedratinib + Luspatercept	NCT03755518[125]	PMF, post-PV MF	III	110	Spleen volume reduction, adverse events, SRR, anemia response

AML: acute myeloid leukemia; CCR: composite complete remission; CML: chronic myeloid leukemia; CR: complete remission; Cri: complete remission with incomplete marrow recovery; CRR: complete response rate; DLT: dose-limiting toxicity; EFS: event-free survival; JAK: Janus kinase; MDS: myelodysplastic syndrome; MF: myelofibrosis; MPN: myeloproliferative neoplasm; MTD: maximum tolerated dose; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; PMF: primary myelofibrosis; PR: partial remission; PV: polycythemia vera; RBC: red blood cell; RFS: relapse-free survival; RP2D: recommended phase 2 dose; RR: response rate; SMF: secondary myelofibrosis; SRR: symptom response rate; TFR: treatment-free events; TSS: total score system.
*Based on the Myelofibrosis Symptom Assessment Form.

XIAP and MAPK8 with a subsequent increase in cIAPs.[33,34] Targeting this pathway by inhibiting XIAP with AEG35156 (XIAP inhibitor) combined with idarubicin and cytarabine in relapsed/refractory AML cells resulted in all phase II patients achieving response with apoptosis induction.[35]

SMAC (second mitochondrial activator of caspase) mimetics

Du and colleagues[36] discovered a new protein called second mitochondrial activator of caspase (SMAC) that promotes apoptosis by binding to cIAPs. A SMAC mimetic is designed to bind to cIAP and overcome cIAP-mediated apoptosis-resistant cells, preferentially inhibiting TNF-induced activation. This results in caspase activation and subsequent apoptosis.[37] Overexpression of SMAC also increases sensitivity to apoptotic stimuli, making this target very important in resistant patients.[36] A phase Ib study with birinapant (intravenous SMAC mimetic) combined with 5-azacitadine in patients with MDS, including those with refractory disease or with relapse to 5-azacitadine, confirmed clinical efficacy with an acceptable safety profile.[38] Another SMAC mimetic, oral agent LCL161, showed activity against MPN cells in vitro and in vivo and induced a reduction in splenomegaly in a murine model

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Table 2. Selection of current clinical trials of novel therapies beyond JAK inhibitors

Intervention	NCT No.	Malignancy	Phase	No. of Patients Enrolled	Research Question
AVID200	NCT03895112[78]	PMF, SMF	I	24	MTD, CR, PR, cryptogenic remission, molecular remission, clinical response, bone marrow fibrosis
IMG-7289	NCT03136185[102]	PMF, SMF	II	50	Emergent adverse events, safety and tolerability, drug concentration, spleen volume reduction
IMG-7289	NCT04262141[101]	ET, PV	II	24	Hematologic response rates, toxicity, TSS§, mutational allele burden, spleen volume reduction, fibrosis score
KRT-232	NCT03669965[66]	PV	II	20	Spleen volume reduction, phlebotomy independence
KRT-232	NCT03662126[65]	PMF, SMF	II	203	Spleen volume reduction, TSS*§, transfusion independence
LCL161[40]	NCT02098161[126]	PV, PMF, SMF	II	50	ORR, grade 3–4 toxicity, duration of response, time to response
Luspatercept[75]	NCT04064060[77]	MDS, MPN associated MF, beta-thalassemia	III	665	Safety
Luspatercept	NCT03194542[76]	PMF, anemia	II	103	Anemia response
Navitoclax[45]	NCT04041050[44]	MPN	II	12	DLT, pharmacokinetic profile
PU-H71	NCT03935555[57]	PMF, SMF	I	24	Safety and tolerability, pharmacokinetics, treatment response
PU-H71	NCT01393509[56]	MPN, lymphoma, metastatic solid tumor	I	47	Safety and tolerability, pharmacokinetics
Sotatercept	NCT01712308[73]	MDS, MPN, MF, anemia	II	60	Incidence of toxicities, anemia response
Tagraxofusp	NCT02268253[53]	MF, CMML	II	130	Rate response, rate and severity of treatment emergent adverse events

AML: acute myeloid leukemia; CMML: chronic myelomonocytic leukemia; CR: complete remission; DLT: dose-limiting toxicity; ET: essential thrombocythemia; JAK: Janus kinase; MDS: myelodysplastic syndrome; MF: myelofibrosis; MLFS: morphologic leukemia-free state; MPN: myeloproliferative neoplasm; MTD: maximum tolerated dose; ORR: overall response rate; PMF: primary myelofibrosis; PR: partial remission; PV: polycythemia vera; RP2D: recommended phase 2 dose; SMF: secondary myelofibrosis; TSS: total score system.
*Based on the Myelofibrosis Symptom Assessment Form.
§Based on the Myeloproliferative Neoplasm Symptom Assessment Form.

of JAK2V617F-driven MPN.[39] A phase II clinical trial study in patients with PMF, post-PV MF, and post-ET MF further demonstrated an objective response in 38% (6/16) of the patients. The median time to response was about 1.4 months (range, 0.9–9.1 months) with treatment duration of 31.5 months (range, 3.6–55.2+ months). Median overall survival has not yet been reached. The most common adverse event leading to dose reduction or study discontinuation was grade 2 fatigue. Overall data demonstrated LCL161's successful inhibition of tumor activity via antagonizing XIAP and inhibiting cIAPs in high TNF-α–expressing models.[40]

Inhibition of Bcl-xL

The Bcl-2 family is a key regulator of apoptosis, promoting the antiapoptotic survival of the cell lines. Its members, such as Bcl-xL, are linked to resistant tumor cells particularly in MF model systems. In previous studies, Bcl-xL inhibitor showed enhancement of apoptotic signals and synergistic cytotoxicity with combined chemotherapy.[41–43] Navitoclax (Bcl-xL inhibitor) is currently in active clinical investigation in the setting of its hypothesized activity in MF (NCT04041050).[44] A phase II single-arm, multi-center, open-label study using a combination of navitoclax and ruxolitinib demonstrated clinical significance in MF patients: spleen volume reduction of 35% or greater from baseline in 29% (7 of 24) of patients, median total symptom score with 20% improvement from baseline, reduction in driver mutation allelic burden of more than 5% in 42% (10) of patients, and bone marrow fibrosis improvement of at least 1 grade in six patients (NCT03222609).[45,46] This novel approach is being planned for an upcoming phase III trial (TRANSFORM-1, NCT04472598)[47] that will feature the combination of ruxolitinib with navitoclax versus ruxolitinib plus placebo in the upfront setting for patients with MF.

Targeting of Hematopoietic Stem Cell/Microenvironment

CD123 (interleukin-3 receptor alpha subunit) is highly expressed in a variety of hematologic malignancies. Notably, CD123 is expressed in subsets of MPNs, marking a potential therapeutic target.[48,49] Tagraxofusp (SL-401) is a drug that consists of a chimeric junction between a truncated diphtheria toxin and IL-3 (interleukin-3). The toxin is fused to IL-3 and successfully targets CD123. Once bound to the receptor, the drug is internalized by endocytosis and ultimately leads to cell death.[50] Due to its potent activity against CD123-

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expressing malignant cells, tagraxofusp was recently approved by the FDA for blastic plasmacytoid dendritic cell neoplasm (BPDCN), a historically aggressive hematologic malignancy that is known to overexpress CD123 in 100% of cases.[51] In a study with MF, 45% (9 of 20) of patients treated with tagraxofusp demonstrated symptom reduction, and all patients (6 of 6) had a reduction in spleen size.[52] A phase I/II clinical trial with tagraxofusp in patients with intermediate- or high-risk and relapsed/refractory MF is currently ongoing (NCT02268253).[53] The most notable toxicity of tagraxofusp is capillary leak syndrome, which is part of the "black box" package label warning for BPDCN approval. This toxicity is actively being monitored in the ongoing phase II MF clinical trial with tagraxofusp.

Another early program in clinical development in the MF field is that of heat shock protein inhibition. Heat shock protein-90 (HSP90) is a chaperone protein that aids in the stability of oncogenes (ie, JAK2) against environmental stress, an essential function for oncogenic transformation.[54,55] A growing interest in HSP90 inhibitors as anticancer therapy is driving current active research. Investigation in PU-H71 (HSP90 inhibitor) as a monotherapy or combined with ruxolitinib for safety and tolerability and pharmacokinetic profile in patients with MPN is ongoing (NCT01393509, NCT03935555, NCT03373877).[56,57,58]

Activation of the TP53 Pathway

The TP53 tumor suppressor protein plays an essential role in cellular stability against environmental stressors such as DNA damage and hypoxia. Activation of this protein leads to cell arrest or apoptotic cell death, whereas the loss of this protein promotes oncogenic proliferation and tumorigenesis. Regulation of TP53 is mediated by a TP53-interacting protein called murine double minute clone 2 (MDM2). In normal cells under nonstressed conditions, MDM2 increases ubiquitination and proteasome-dependent degradation of TP53. Conversely, overexpression of MDM2 suppresses the tumor suppressor gene *TP53*, resulting in oncogenicity.[59,60] The working hypothesis has been that various types of cancer have a higher expression of MDM2.[61] MDM2 quickly emerged as a drug target to inhibit the activity of TP53.

Idasanutlin is the first long-acting MDM2 antagonist that has been widely investigated in this field. In phase I/Ib study observing idasanutlin use in AML patients, durable response (relapse-free for over 60 days) was observed in selected patients.[62] Notably, idasanutlin has been investigated in treatment of patients with PV (NCT03287245).[63] The primary outcome of this study is the percentage of patients achieving hematocrit control without supportive phlebotomy.

Additionally, KRT232 is another MDM2-targeting agent currently under investigation. A multi-center phase I/II study with KRT232 combined with low-dose cytarabine or decitabine is planned for patients with AML secondary to MPN (NCT04113616).[64] This study is measuring dose-limiting toxicity (DLT), complete remission (CR), and partial remission (PR) rate, and morphologic leukemia-free state (MLFS) rate. Monotherapy of KRT232 in PMF, post-PV MF, and post-ET MF patients is also under investigation as a phase II study (NCT03662126).[65] Primary outcomes of this study are spleen volume reduction, symptom reduction, and blood transfusion independence. Finally, monotherapy of KRT232 versus ruxolitinib in PV patients is under study, measuring outcomes of spleen volume reduction and duration of response (NCT03669965).[66] Of importance, one must consider, in development of novel agents beyond JAKis, the patient-centered experience, including recognizing and mitigating gastrointestinal toxicities common to this class of therapies, when designing MDM2 inhibitor programs.

Inactivation of TGF-β (Transforming Growth Factor-Beta) Pathway

Members of the TGF-β superfamily, which includes growth differentiation factor 11 (GDF11) and activin, are secreted by bone marrow stromal cells and share a role in proliferation and differentiation of the erythroid precursor cells. Sotatercept (ACE011) is a recombinant fusion protein of the extracellular domain of activin receptor type II (ActRII). It binds to activin and GDF11 to inhibit activation of subsequent pathway.[67] Inactivation of GDF11 relieves suppression of terminal erythropoiesis and corrects the abnormal ratio of immature erythroblasts by inducing apoptosis of immature cells.[68,69] Sotatercept improved erythrocytosis in preclinical models of beta-thalassemia, Diamond-Blackfan anemia, and hepcidin transgenic mice.[68,70–72] As anemia is a common complication of PMF, post-PV MF, post-ET MF, and ruxolitinib therapy, sotatercept's success in improving anemia would greatly aid in mitigating the disease and treatment complication; sotatercept use may also potentially prolong ruxolitinib therapy. A current phase II clinical trial with sotatercept to treat patients with MDS, MPN, and chronic myelomonocytic leukemia (CMML) is ongoing (NCT01712308, NCT01736683).[73,74]

Additionally, luspatercept is an investigational erythroid maturation agent that neutralizes select TGF-β superfamily ligands to inhibit SMAD protein pathway signaling. In a phase II study with lower-risk MDS patients, luspatercept at high-dose concentration (0.75–1.75 mg/kg) yielded hematologic improvement with a reduction in the number of red blood cell transfusions (52%; 14 of 27 patients).[75] Luspatercept also demonstrated clinical efficacy in enhancing late-stage erythropoiesis in MDS models.[67] Current ongoing trials include luspatercept in patients with PMF and anemia to assess anemia response (NCT03194542)[76] and in patients with MDS, MPN-associated MF, and beta-thalassemia to assess the safety of the drug (NCT04064060).[77]

Furthermore, AVID200 is an engineered drug that selectively targets TGF-β1 and TGF-β3. A current phase I

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study is based on the hypothesis that inhibiting the TGF-β signaling pathway will decrease fibrogenic stimuli, which leads to MF (NCT03895112).[78]

Targeting Fibrosis

In terms of the advanced abnormal bone marrow fibrosis state in MF, there is no current standard therapy that specifically aims to reverse marrow fibrosis.[79] Owing to the hypothesis that reduction in marrow fibrosis will restore hematopoiesis and improve cytopenias, more studies aim to identify the fibrosis-driving cells and inhibit their activity. Although progressive bone marrow fibrosis in MF was initially thought to be secondary to mesenchymal stromal cells, tissue fibrosis in other diseases has been linked to fibrocytes. For instance, serum amyloid P (SAP; pentraxin-2), known as fibrocyte inhibitor, has previously shown success in inhibiting progressive fibrotic disease of the kidney.[80] Importantly, it has been demonstrated that patients with MF have low pentraxin-2 (PTX-2) levels, allowing the hypothesis that an increase in its level may lead to inhibition of progressive fibrosis in the bone marrow. Based on this rationale, PTX-2 was tested for its efficacy in MF. In xenograft mice models, PTX-2 significantly prolonged survival and slowed bone marrow fibrosis.[81]

PRM151 is a recombinant human PTX-2. It acts as an endogenous regulator of tissue repair by binding to the damaged tissue to prevent and reverse fibrosis. A current phase II trial with PRM151 is targeting patients with PMF, PV, and post-ET MF (NCT01981850).[82] The primary outcome measure of this study is the bone marrow response rate, defined as the percentage of subjects with a reduction in bone marrow fibrosis by at least 1 grade according to World Health Organization criteria.

Aurora Kinase Inhibition

Several studies suggest that an increased number of megakaryocytes contributes to bone marrow fibrosis.[83–85] In consideration of these data, the aurora kinase alpha inhibitor (alisertib) has emerged a novel therapeutic target in MF. It successfully induced apoptosis of malignant megakaryocytes and reduced subsequent antifibrotic and antitumor activity in MPN cells.[85] A phase I trial successfully demonstrated the efficacy of aurora kinase alpha inhibition, normalizing megakaryocytes, and reducing bone marrow fibrosis in five of seven patients with MF. Its use also reduced splenomegaly and symptom burden in 29% and 32% of patients, respectively.[86]

Epigenetic-Directed Therapies

Inhibition of BET (bromodomain and extraterminal) family of proteins

BET family of proteins has been recently put forward as a potential therapeutic target in the MPN field. Bromodomain proteins are chromatin readers that recruit chromatin-regulating enzymes to attempt to modify histone to stimulate gene expression.[87] Their proposed role includes transcribing pro-oncogenes such as c-*MYC*, *BCL2*, and *CDK6*.[88] Successful inhibition of BET-induced apoptosis in murine and human AML cells led to subsequent clinical trials.[89,90] The efficacy of BET-induced apoptosis inhibitors has been demonstrated in vitro in patients who developed post-MPN AML cells. Combination treatment with an HSP90 inhibitor also synergistically worked against previously ruxolitinib-failed malignant cells.[91] A phase I/II study of BET inhibitor (oral drug, CPI-0610) combined with ruxolitinib or alone in patients with MDS, MF, MPN, and AML is currently underway (NCT02158858).[92] The study measures efficacy through spleen volume reduction and red blood cell transfusion independence rate. Preliminary data show clinical efficacy and a generally well-tolerated safety profile in patients with MF and inadequate response or disease refractory to ruxolitinib.[93] This promising program is being planned for upcoming phase III investigation as frontline combination versus JAKi plus placebo. Phase III, randomized study comparing CPI-610 and ruxolitinib with placebo and ruxolitinib in patients with MF has been initiated (MANIFEST-2, NCT04603495).[94] This study will measure splenic and symptom response.

DNA hypomethylation

DNA methylation can silence genes involved in tumor suppression and DNA repair. Hypomethylating agents such as azacitidine and decitabine reverse dysregulated DNA methylation. This treatment mechanism likely most benefits patients with aberrant hypermethylation. Masarova and colleagues,[95] in a 2018 phase II study of ruxolitinib combined with azacitidine (RUX + AZA), demonstrated a favorable response in historical comparison with ruxolitinib monotherapy (NCT01787487).[96] Among 46 patients enrolled after a median follow-up of 28 months (range, 4–50+ months), the median time to response was 1.8 months (range, 0.7–19 months), and median overall survival was 28 months (range, 4–39+ months). RUX + AZA had an overall response rate of 72%, including greater than 50% spleen volume reduction in 79% of the patients. Treatment-related toxicities that halted the therapy occurred in four patients (9%) due to significant cytopenias. Of note, spleen volume reduction in this study was measured as spleen length reduction by palpation during physical examination.[95]

Inhibition of Lysine-Specific Demethylase 1A (LSD1)

LSD1 is a histone demethylase that removes methyl groups specifically at histone 3 and lysine 4, leading to active transcription. This action ultimately leads to cell proliferation.[97] LSD1 has been linked to the progression of several cancers, including breast and prostate cancer.[98,99] In recent years, LSD1 overexpression has also been found in hematologic malignancies, including MPNs and CMML.[100] IMG-7289 is an irreversible LSD1 inhibitor studied in phase II clinical trial for MPNs

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(NCT04262141, NCT03136185).[101,102]Preliminary data at 12 weeks with this inhibitor in MF patients showed a reduction in spleen volume in 50% (7 of 14) of patients, reduction in symptoms in 79% (11 of 14) of patients, and improved bone marrow fibrosis in two patients.[103] Subsequent phase IIb study is to follow, aiming more aggressive dosing while preserving safety and enhancing efficacy.

Telomerase Inhibition

Telomeres represent specialized tandem repeats of DNA sequence at the end of a eukaryotic chromosome that function in protection and replication.[104] Normal somatic cells undergo a finite number of cell divisions and enter senescence due to telomere shortening; these cells are absent in telomerase expression.[105] Telomerase is a ribonuclear protein complex that synthesizes telomeric DNA onto the chromosome to further protect the DNA and, thereby, enable continued replication.[104] Ex vivo studies in human tissues have identified telomerase expression in about 90% of all malignant tumors. Unlike normal somatic cells, cancer cells escape senescence by acquiring telomerase expression that can aid in maintaining and lengthening telomeres, creating telomere stability and cells' continued division.[104–106] Imetelstat is a competitive inhibitor of telomerase. An in vitro study by Wang and colleagues[107] demonstrated that its use resulted in selective induction of apoptosis in MF stem cells. Imetelstat induced hematologic responses in all patients with ET (18 of 18 patients) and complete hematologic response in 16 patients (89%) with a median follow-up of 17 months (range, 7–32+ months).[108] A pilot study of imetelstat in patients with MF also demonstrated complete remission, although caution was advised against clinically significant myelosuppression.[109] Additionally, a phase II study evaluated its efficacy in patients with intermediate-2 or higher-risk MF and previously treated with a JAKi (NCT02426086).[110] Its preliminary results show dose-dependent median overall survival of 19.9 months at 4.7-mg/kg dose and 29.9+ months at 9.4-mg/kg dose. This finding is comparable to the reported median survival of 13–14 months in MF patients after ruxolitinib failure or discontinuation.[9,10,26] A phase III trial of imetelstat in patients with refractory MF is ongoing with a notably novel primary endpoint of median overall survival.[111]

CONCLUSIONS

Ruxolitinib is now FDA approved for three separate indications: intermediate/high-risk MF, PV that is intolerant/resistant to hydroxyurea, and steroid-refractory acute graft-versus-host disease for patients aged 12 and older. Despite advancements in treating MPNs with ruxolitinib, multiple reports indicate a high discontinuation rate of ruxolitinib due to resistance, relapse, and treatment-related toxicities. With no approved therapy beyond JAKis, many patients with MF and ruxolitinib failure face a poor prognosis. Fedratinib, recently approved with a broad indication in MF, is the second JAKi now widely available, an agent which may provide an alternative to ruxolitinib or used in the postruxolitinib setting. Studies supporting the use of this drug encourage the routine practice of monitoring for encephalopathy and thiamine deficiency.

With a growing understanding of the pathobiology of MPNs, the field is now seeing an active development of many novel classes of drug targets. We expect current investigations of drugs combined with JAKi treatment ("add-back, or "add-on") and investigation of novel targeted therapies alone without JAKi treatment to be an emerging area of active clinical development in the coming years. For clinicians, providing details of each therapeutic option and understanding the patient's goals will be essential for finding an individualized, optimal therapy. Attention must be paid to short- and longer-term novel toxicities in the development of each class of novel therapies, particularly those that may overlap with administration of JAKis.

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