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SOHO State of the Art Updates and Next Questions: Novel Therapeutic Strategies in Development for Myelofibrosis

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Abstract

Development of myelofibrosis (MF) therapeutics has reached fruition as the transformative impact of JAK2 inhibitors in the MPN landscape is complemented/expanded by a profusion of novel monotherapies and rational combinations in the frontline and second line settings. Agents in advanced clinical development span various mechanisms of action (e.g., epigenetic or apoptotic regulation), may address urgent unmet clinical needs (cytopenias), increase the depth/duration of spleen and symptom responses elicited by ruxolitinib, improve other aspects of the disease besides splenomegaly/constitutional symptoms (e.g., resistance to ruxolitinib, bone marrow fibrosis or disease course), provide personalized strategies, and extend overall survival (OS). Ruxolitinib had a dramatic impact on the quality of life and OS of MF patients. Recently, pacritinib received regulatory approval for severely thrombocytopenic MF patients. Momelotinib is advantageously poised among JAK inhibitors given its differentiated mode of action (suppression of hepcidin expression), leading to significant improvements in anemia and OS; momelotinib will likely receive regulatory approval in 2023. An array of other novel agents combined with ruxolitinib, such as pelabresib, navitoclax, parsaclisib, or as monotherapies (navtemadlin) are evaluated in pivotal phase 3 trials. Imetelstat (telomerase inhibitor) is currently evaluated in the second line setting; OS was set as the primary endpoint, marking an unprecedented goal in MF trials, wherein SVR35 and TSS50 at 24 weeks have been typical endpoints heretofore. Transfusion independence may be considered another clinically meaningful endpoint in MF trials given its correlation with OS. Overall, therapeutics are at the cusp of an exponential expansion and advancements that will likely lead to the golden era in MF treatment.

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Authors' Contributions

H.T.C. reviewed the literature and wrote the article. L.M. reviewed the article for important intellectual content. S.V. conceived and guided the study and critically reviewed the article for important intellectual content. All the authors have read and approved the final article.

Keywords

Myeloproliferative neoplasms (MPNs); momelotinib; pelabresib; luspatercept; imetelstat

Introduction

Among myeloproliferative neoplasms (MPN), myelofibrosis (MF) is the most aggressive and is characterized by clonal myeloproliferation, bone marrow fibrosis, splenomegaly, worsening anemia, systemic symptoms, and increased production of inflammatory cytokines.[1] In addition, MF can transform to the accelerated phase[2] and blast phase MPN[3,4] or post-MPN acute myeloid leukemia, which are diagnosed when blasts in the peripheral blood/bone marrow are in the range 10–19% and ≥20%, respectively.

Clinical development and regulatory approval (in 2011) of ruxolitinib- a selective JAK1/2 inhibitor targeting the overactivated JAK signal and transducer of transcription (JAK/STAT) pathway- revolutionized treatment of intermediate- and high-risk MF and dramatically improved quality-of-life, splenomegaly and constitutional symptoms in MF patients.[5] Ruxolitinib has become the cornerstone treatment for MF, conferring significant prolongation of survival in MF patients[6,7] besides other clinical benefits. The survival benefit of ruxolitinib treatment evidenced from clinical data[5] was complemented by an analysis of real-world data from patients diagnosed with intermediate- to high-risk MF between 2010 and 2017: the 1-year survival rates for post-approval ruxolitinib-exposed vs. post-approval ruxolitinib-unexposed vs. pre-approval of ruxolitinib unexposed patients were 82.3% vs. 72.5% vs. 55.6%, respectively.[7] The tremendous impact of ruxolitinib in prolonging overall survival (OS) of MF patients in the last decade was also demonstrated in another retrospective study of patients stratified in groups by decade (2000–2010 and 2011–2020): the overall survival with ruxolitinib treatment was nine times higher compared to that with other agents during the second decade.[6] Notably, the updated multivariate analysis of the real-world ERNEST (European Registry for Myeloproliferative Neoplasms) study, which evaluated the outcomes of 1,010 patients with MF from 13 centers in 5 European countries, demonstrated the significant benefit of ruxolitinib treatment in extending OS compared to hydroxyurea.[8] While the survival advantage of ruxolitinib has even been recognized by regulatory bodies (Federal Drug Administration) and is listed as a benefit of ruxolitinib on its label in the US, a few investigators still find this issue controversial.[9] The EXPAND study (NCT01317875) showed that ruxolitinib treatment at 10 mg bid elicited meaningful clinical efficacy (reduction of spleen size and symptoms) in patients with MF and baseline platelet counts in the range 50 to $<100 \times 10^9$/L;[10] patients with platelet counts in the former range were included in the EXPAND study because the COMFORT-I and COMFORT-II trials, which compared ruxolitinib efficacy to placebo and best available therapy (BAT), respectively, included patients with platelet counts $\geq 100 \times 10^9$/L.[11,12]

Fedratinib, the second JAK2 inhibitor, received regulatory approval for intermediate-2 and high-risk MF in 2019,[13,14] and is an option primarily in the post-ruxolitinib setting. Post-hoc analysis of the JAKARTA-2 trial demonstrated spleen volume reduction ≥35% (SVR35) 31% and ≥50% improvement in total symptom score (TSS50) 27%.[15] Notwithstanding

the notable benefits of ruxolitinib and fedratinib in treatment of MF, disease-related cytopenias that can be exacerbated by JAK-inhibitor induced myelosuppression[16]- anemia[17] and thrombocytopenia[18]- can develop and are associated with poor prognosis.[19,20,21] Patients who discontinued ruxolitinib (primarily due to disease progression, including cytopenias)[22,23] or acquired ≥3 non-driver mutations[24] had a limited median overall survival (ranging between 11 and 16 months in several studies).[25,26,27,28] In February 2022, the field of MPNs was marked by the accelerated regulatory approval of pacritinib, a relatively non-myelosuppressive JAK2 and interleukin-1 receptor-associated kinase 1 (IRAK1) inhibitor, as a treatment for patients with intermediate- or high-risk MF and severe thrombocytopenia (platelet count below 50×10^9/L).[29,30,31,32] Pacritinib's approval was primarily based on the results of the PERSIST-2 trial (NCT02055781)[33] and the PAC203 dose-finding trial (NCT03165734).[34] Currently, pacritinib is compared to "physician's choice" (low dose ruxolitinib, danazol, steroids, hydroxyurea) in the phase 3 PACIFICA trial (NCT03165734) in patients with advanced MF and severe thrombocytopenia.[35] Despite the development of pacritinib to treat thrombocytopenic patients with MF, significant areas of unmet need still remain, such as anemia, suboptimal response or resistance to ruxolitinib, modification of disease course, prolongation of survival; and have sparked a plethora of endeavors to develop novel medications and treatment strategies for MF.[36,37,38,39,40] Furthermore, in light of the fact that deeper spleen responses with ruxolitinib treatment have been associated with prolonged OS,[41,42,43] combination regimens with ruxolitinib may further improve spleen and symptom responses and prolong OS. A collection of novel agents that act through various mechanisms, have been explored as monotherapies and complimentary or synergistic combinations with ruxolitinib.[36] In this review, we highlight several new concepts for treatment of MF and the corresponding investigational agents that were recently evaluated (Table 1) or are currently being appraised (Table 2) in the frontline and second line settings, focusing on advanced phase 3 clinical trials.

Concept #1:Combination of anemia therapeutic with a JAK1/2 inhibitor

One of the cardinal features of MF that affects OS is anemia[17,21] and red blood cell (RBC) transfusion dependence, which are associated with substantial clinical burden[44] and constitute adverse prognostic factors in MF.[45] In a study that was performed at Mayo Clinic, more than 50% of the patients with primary MF were anemic when they were referred to the institution (at diagnosis, within one year of diagnosis and more than 1 year after diagnosis), and approximately one quarter of the patients required RBC transfusions at initial diagnosis;[46] nearly all MF patients become anemic over the course of the disease.[23] Currently, anemia treatments are not satisfactory, and there is a critical unmet need to improve anemia in MF patients.

Luspatercept is an activin receptor IIB ligand trap enhancing late-stage erythropoiesis that is being studied in MF patients with anemia. This novel class of fusion proteins ameliorates anemia of diverse etiologies by sequestering ligands of the transforming growth factor beta (TGF-β) superfamily that bind to the activin receptor; thus promoting terminal erythroid differentiation and improvement of anemia (via potent inhibition of downstream Smad2/3 signaling).[47] Luspatercept recently received regulatory approval for treatment of anemia in β-thalassemia and myelodysplastic syndromes with ring sideroblasts. The phase 2 trial

evaluated luspatercept in MF patients who were on a stable dose of ruxolitinib for ≥16 weeks prior to enrollment and required RBC transfusions (NCT03194542, cohort 3B); in cohort 3B of the study, 27% of the patients became RBC transfusion-independent over any 12 consecutive weeks during the first 24 weeks (primary endpoint), 36% of the patients achieved RBC transfusion-independence for 12 consecutive weeks or more when assessing the entire treatment period, and 46% of the patients achieved ≥50% reduction of RBC transfusion burden (≥4 units) over 12 weeks (Table 1).[48] Luspatercept is currently evaluated versus placebo in a registrational, randomized phase 3 trial (INDEPENDENCE; NCT04717414; Table 2) in MF patients who are concomitantly receiving ruxolitinib and require RBC transfusions (4–12 transfusions in the 12 weeks immediately prior to randomization).[49]

Concept #2: Agents in combination with a JAK1/2 inhibitor in the frontline setting

1. Bromodomain and Extra-terminal (BET) Inhibitor (Pelabresib).—Preclinical studies in *JAK2*-mutated MPN mouse models demonstrated that BET inhibitor proteins (epigenetic "reader" proteins that bind acetylated lysine residues in histones; acetylation of lysine residues in histones is critical in epigenetic control of gene transcription) in combination with ruxolitinib synergistically suppressed inflammatory cytokine production and megakaryocyte infiltration, and eliminated fibrosis.[50,51] In addition, JQ1 (BETg inhibitor) acted synergistically with ruxolitinib to induce apoptosis of primary MPN-BP patient-derived cells *in vitro,* and prolonged survival of an immunodeficient mouse model transplanted with MPN-BP patient-derived blast progenitor cells.[52]

In the phase 2 MANIFEST trial (NCT02158858), which comprised 3 Arms, pelabresib (selective BET protein inhibitor of BD1 and BD2 bromodomains) was studied in MF patients who were no longer on ruxolitinib and received pelabresib monotherapy (Arm 1); patients with a suboptimal response to ruxolitinib who received pelabresib as an "add-on" to a stable dose of ruxolitinib (Arm 2); and JAK inhibitor naïve patients who received the combination of pelabresib and ruxolitinib from the start (Arm 3). Patients in Arms 1 and 2 of the study were stratified in transfusion-independent and transfusion-dependent cohorts.

In Arm 3 (frontline) of the MANIFEST study, pelabresib in combination with ruxolitinib elicited SVR35 and TSS50 from baseline in 68% (median change −50%) and 56% (median change −59%) of the JAK inhibitor-naïve MF patients, respectively, at week 24 (Table 1); moreover, 24% of the patients had a mean hemoglobin increase of 1.5 g/dL or more compared to baseline over 12 weeks (without RBC transfusions).[53] The spleen and symptom response rates that were recorded in Arm 3 were considerably higher than the historical data reported for ruxolitinib monotherapy in phase 2 and 3 trials; for example, in the COMFORT-1 trial, the SVR35 and TSS50 rates were 42% and 46%, respectively[54]). In the MANIFEST study, more than half of the patients had primary MF and harbored high molecular risk mutations; notably, clinical efficacy was noted regardless of the mutational profiles, which included high molecular risk mutations, such as *ASXL1*.[55] In addition, bone marrow fibrosis decreased by ≥1 grade compared to baseline in 31% of the patients, in Arm 3.[53] Based on the notable findings of pelabresib in combination with ruxolitinib in the frontline setting of the MANIFEST trial (Arm 3), the combination of pelabresib

with ruxolitinib versus placebo and ruxolitinib is currently further evaluated in the global, randomized registrational phase 3 MANIFEST-2 trial (NCT04603495) in JAK inhibitor-naïve patients with intermediate or high-risk MF for control of splenomegaly and symptom burden (Table 2).[56]

2. BcL-xl Inhibitor (Navitoclax).—Navitoclax is an orally bioavailable small molecule that potently inhibits the anti-apoptotic B-cell lymphoma-2/extra-large (Bcl-2/Bcl-xL) family of proteins (primarily Bcl-xL). Preclinical studies demonstrated synergism between ruxolitinib and the non-clinical analog of navitoclax (ABT-737) in inducing a significantly higher apoptotic rate of leukocytes in MF patients.[57] In a multicenter, open-label phase 2 study in JAK inhibitor-naïve and BET inhibitor-naïve patients with MF (REFINE, NCT03222609; Cohort 3), treatment with navitoclax in combination with ruxolitinib resulted in SVR35 and TSS50 in 52% and 31% of the patients at week 24, respectively; and improved anemia and bone marrow fibrosis by ≥1 grade in 55% and 35% of the patients (at any time during treatment), respectively.[58] SVR35 and TSS50 were noted in 76% and 56% of the patients, respectively, compared to baseline at any time during the study.[58] Grade 3 or higher thrombocytopenia was noted in 31% of the patients treated with the combination (platelet counts were $\leq 150 \times 10^9$/L and $>150 \times 10^9$/L at baseline for patients receiving 100 mg and 200 mg daily, respectively). Navitoclax in combination with ruxolitinib is currently being evaluated in the placebo-controlled phase 3 trial TRANSFORM-1 (NCT04472598) in JAK- and BET-inhibitor-naïve patients with intermediate-2 and high-risk MF.[59] The primary endpoint is SVR35 at week 24, and TSS50 at week 24 is included among the secondary endpoints of the trial (Table 2).

3. PI3K Inhibitor (Parsaclisib).—Parsaclisib is a potent, highly selective inhibitor of phosphatidylinositol 3-kinase (PI3K)-delta, an isoform that is important in hematologic malignancies.[60] Preclinical studies showed synergism of PI3K and JAK2 inhibitors,[61,62] thereby supporting the clinical assessment of parsaclisib in combination with ruxolitinib in MF patients.[63] To this effect, parsaclisib is evaluated in combination with ruxolitinib in the placebo-controlled phase 3 trial LIMBER-313 (NCT04551066) in MF patients (with a DIPSS risk category of at least intermediate-1) who are JAK- and PI3K- inhibitor naïve.[64] The primary endpoint is evaluation of SVR at week 24; secondary objectives include evaluation of TSS, OS, and duration of spleen response among others.

Concept #3: "Add-on" agents to a JAK1/2 inhibitor in the second line setting

1. BcL-xl Inhibitor (Navitoclax).—In preclinical models, resistance of *JAK2* V617F-expressing MPN cells to ruxolitinib was overcome by treatment with ABT-737, the non-clinical analog of navitoclax.[65] In the open-label, phase 2 REFINE trial (NCT03222609) that was conducted in patients who progressed or had suboptimal response to ruxolitinib monotherapy, the addition of navitoclax to ruxolitinib resulted in SVR35 and TSS50 in 26.5% and 30% of MF patients, respectively, at week 24 (Cohort 1a); and 41% of the patients achieved SVR35 at any time on the study (Table 1).[66] In the same trial, 33% of the evaluable patients showed improvement in bone marrow fibrosis (1–2 grades), and 64% of the patients demonstrated an anemia response (improvement in Hb of ≥2 g/dL).[66] Notably, 58% of the patients harbored high molecular risk mutations, and 52% had ≥3 mutations.[66]

Post-hoc analysis of molecular biomarkers demonstrated that spleen responses were noted regardless of the number of mutated genes and high molecular risk mutations (*ASXL1*, *SRSF2*, *EZH2*, *U2AF1*, *IDH1*) at baseline.[67] Variant allele frequencies (VAF) of the driver genes *JAK2* and *CALR* were reduced by ≥20% compared to baseline in 23% of the patients; patients with VAF reduction of ≥20% and improvement in bone marrow fibrosis of ≥1 grade exhibited better OS (median not reached) compared to those who did not achieve a reduction in VAF or bone marrow fibrosis (median OS 28.5 months).[67]The combination of navitoclax with ruxolitinib is currently being evaluated vs. BAT in the randomized phase 3 trial TRANSFORM-2 (NCT04468984) in patients with intermediate-2 and high-risk MF who relapsed or are refractory to JAK2 inhibition; the primary endpoint of the trial is SVR35 at week 24.[68]

2. PI3K Inhibitor (Parsaclisib).—Besides the frontline setting, parsaclisib was assessed as an "add-on" agent to ruxolitinib in MF patients with suboptimal response to ruxolitinib[22] in a phase 2 trial (NCT02718300).[69] The final results of the phase 2 trial demonstrated that 28.6% and 7.1% of the patients achieved SVR ≥25% and ≥35%, respectively, at 24 weeks, on a daily dosing schedule of parsaclisib, which were more efficacious compared to daily/weekly dosing in inducing SVR and TSS reduction.[69] The combination of ruxolitinib and parsaclisib (as "add on") compared to ruxolitinib and placebo will be further evaluated in the phase 3 trial LIMBER-304 (NCT04551053) in MF patients who had a suboptimal response to ruxolitinib monotherapy (Table 2).

3. HDM2 Inhibitor (Navtemadlin).—Navtemadlin (formerly KRT-232) is a first-in-class, potent, bioavailable inhibitor of human double minute 2 (HDM2), a key negative regulator of the tumor suppressor p53. HDM2 is overexpressed in MF CD34+ hematopoietic/progenitor cells compared to normal CD34+ cells,[70] and *TP53* mutations are uncommon in chronic phase MF,[71] thus HDM2 inhibition is a rational target in MF. Accordingly, navtemadlin restores p53 function and mediates apoptosis of neoplastic cells. Presently, navtemadlin is evaluated as an "add-on" to ruxolitinib in an open-label, global phase 1b/2 study (NCT04485260) in *TP53* wild-type MF patients with a suboptimal response to ruxolitinib monotherapy after ≥18 weeks of treatment on a stable dose in the 8 weeks prior to study entry (Table 2).[72] In the first part of the trial, the maximum tolerated dose of navtemadlin in combination with ruxolitinib will be determined; in the dose expansion phase, the maximum tolerated dose will be combined with a stable dose of ruxolitinib to evaluate the safety and efficacy of the regimen (phase 2).[72]

4. IDH2 Inhibitor (Enasidenib).—Enasidenib is an IDH2 inhibitor that received regulatory approval for treatment of *IDH2*-mutated patients with relapsed/refractory acute myeloid leukemia (AML) and is currently being evaluated in combination with other regimens for AML.[73] Notably, enasidenib in combination with ruxolitinib demonstrated synergistic activity in double-mutant *IDH2*/*JAK2* V617F MPN and blast phase MPN patient-derived cells.[74] Treatment with enasidenib-based combinations[75] or enasidenib monotherapy[76] elicited significant responses, including complete hematological and molecular remissions, negative measurable residual disease, and prolonged survival, in small groups of *IDH2*-mutated patients with blast phase and accelerated/blast phase MPN. The

combination of enasidenib with ruxolitinib is currently being evaluated in patients with *IDH2*-mutated accelerated/blast phase MPN or chronic-phase MF (4–9% circulating blasts) in a phase 2 trial (NCT04281498; Table 2); preliminary results of the aforementioned trial demonstrated an overall response rate of 50% in the evaluable cohort (2 patients achieved complete remission).[77]

Concept #4: Unique JAK1/2 inhibitor to improve anemia, splenomegaly, and constitutional symptoms in the second line setting

Besides selectively inhibiting JAK1/2 and thereby treating splenomegaly and constitutional symptoms, momelotinib has a differentiated mode of action because it also suppresses expression of hepcidin, the master regulator of iron metabolism; hepcidin suppression occurs by inhibiting the type 1 activin receptor (ACVR1) or activin receptor-like kinase-2 (ALK2), thereby restoring iron homeostasis, stimulating erythropoiesis, and leading to a remarkable suite of anemia benefits in MF patients.[78] In particular, momelotinib inhibits the primary bone morphogenetic protein 6 (BMP6)/ACVR1/SMAD1/5/8 iron-sensing pathway and the inflammation-driven IL-6/STAT3 axis[79]– two pro-erythropoietic pathways controlling expression of the hepatic-secreted hormone hepcidin. Hepcidin is elevated in MF patients as a result of aberrant hyperactivation of the BMP6-stimulated kinase ACVR1/ALK2 (BMP6 receptor) signaling and inflammatory cytokine signaling via IL-6, which is also elevated in MF patients.[78] Preclinical studies in a rat model of anemia of chronic disease demonstrated a dose-dependent decrease in ACVR1-mediated hepcidin expression following momelotinib administration, mediated via selective inhibition of ACVR1/ALK2 and IL-6-induced pSTAT3.[79] In the rat model, inhibition of hepcidin expression resulted in increased release of stored iron from the reticuloendothelial system (via the hepcidin-ferroportin axis), higher circulating iron concentrations, and thereby stimulated erythropoiesis.[79]

In accordance with these preclinical findings and the pro-erythropoietic mechanism of momelotinib, 41 transfusion-dependent MF patients demonstrated declining serum hepcidin levels versus baseline over 24 weeks of treatment with momelotinib in a translational biology phase 2 study.[80] In this study, 41% of the patients achieved transfusion-independence for 12 weeks or more at any time during the study, including 34% of the patients who became transfusion-independent by week 24.[80] Analogous marked and sustained transfusion-independence benefits were noted in a total of 558 MF patients who participated in the two phase 3 SIMPLIFY trials and were treated with momelotinib, besides experiencing improvements in splenomegaly and constitutional symptoms. In the SIMPLIFY-1 trial, 66.5% of the JAK-inhibitor naïve patients participating in the momelotinib arm achieved or maintained transfusion-independence versus 49.3% in the ruxolitinib arm at week 24.[81] Notably, the median duration of transfusion independence was not reached with momelotinib in the SIMPLIFY-1 trial after follow-up of ≥3 years.[82] In the SIMPLIFY-2 trial, 43% of the second-line MF patients achieved or maintained transfusion-independence in the momelotinib arm versus 21% in the control arm (BAT), which primarily involved ruxolitinib (89%), at week 24 (Table 1).[83] Furthermore, according to the findings of a zero-inflated negative binominal model, the odds of momelotinib-treated patients remaining transfusion-independent were 9.69 times higher versus ruxolitinib-treated patients in the SIMPLIFY-1 trial; and a patient on momelotinib had an 83% chance of

not receiving RBC transfusions versus 34% if treated with ruxolitinib.[84,85] Moreover, the hazard ratio for transfusion of an RBC unit for patients treated with momelotinib was about one-half as compared to patients receiving ruxolitinib.[85] Importantly, momelotinib showed robust OS benefits in both frontline and ruxolitinib-treated MF patients who crossed over to momelotinib after 24-weeks in both the SIMPLIFY-1 and SIMPLIFY-2 trials.[82] In particular, in the SIMPLIFY-2 trial, the patients who crossed over to momelotinib after randomization to BAT (ruxolitinib 89%) for 24 weeks had a median OS of 37.5 months, and the patients who were initially randomized to momelotinib had a median OS of 34.3 months;[82] the aforementioned median OSs noted in SIMPLIFY-2 compare favorably with the median OS reported for patients who discontinued ruxolitinib.[25,26,27,28] In the SIMPLIFY-1 trial, the median OS was not reached, and the 5-year survival probability was ~55% in both arms.[82,86] In SIMPLIFY-2, the median OS was ~3 years and the 2-year survival rate was 66% in the momelotinib arm and 61% in the BAT to momelotinib cross-over arm, with extended momelotinib treatment.[86] Notably, analysis of the data from the SIMPLIFY-1 and SIMPLIFY-2 trials demonstrated an association of transfusion independence at baseline with prolonged OS in MF patients (HR = 0.474, P =0.0001 in SIMPLIFY-1; HR = 0.226, P = 0.0005 in SIMPLIFY-2).[86] Univariate and multivariate analyses of the SIMPLIFY-1 trial data showed that achievement of transfusion-independence at 24 weeks in JAK inhibitor-naïve MF patients randomized to momelotinib was strongly associated with prolonged OS (HR = 0.323, P <0.0001; HR = 0.311, P <0.0001, respectively); in SIMPLIFY-1, the 3-year survival rate for patients who achieved transfusion independence was 77.2% vs. 51.6% for transfusion independence non-responders.[86] The aforementioned findings indicate that transfusion independence at week 24 may be a reasonable surrogate endpoint to predict OS in JAK inhibitor-naïve patients treated with momelotinib.[86] This finding may expand the primary endpoints of clinical trials for MF to include transfusion-independence beyond SVR35 and TSS50 at week 24, which have been the usual endpoints for JAK inhibitors heretofore. Interestingly, a recent targeted literature review of 15 publications that reported on anemia and RBC transfusion-related outcomes of MF patients participating in clinical trials demonstrated the highest improvement in RBC transfusion-independence rates with momelotinib compared to the other JAK inhibitors (ruxolitinib, fedratinib, pacritinib).[44]

Notable results showing the superior efficacy of momelotinib in comparison to danazol were recently reported in the pivotal, randomized, double-blind phase 3 trial (MOMENTUM; NCT04173494),[87] in JAK-inhibitor treated (195 and 9 patients were treated with ruxolitinib and fedratinib, respectively), symptomatic (TSS≥10) and anemic (Hb <10 g/dL) patients with intermediate- or high-risk MF (and platelet counts $\geq 25\times10^9$/L).[88] Danazol was selected as the comparator because it is recommended for treatment of anemia in the guidelines of the National Comprehensive Cancer Network and the European Society of Medical Oncology.[78] In the MOMENTUM trial, momelotinib met both the primary (TSS50 response from baseline at week 24) and key secondary endpoints. In particular, the TSS50 response rate was 24.6% for the cohort treated with momelotinib (Table 1) vs. 9.2% for danazol. The respective secondary endpoints, sequentially assessed, for momelotinib and danazol were the following at week 24 (rates): RBC transfusion independence (30.8% vs. 20.0%), SVR ≥25% from baseline (40.0% vs. 6.2%), TSS change from baseline (−9.36 vs. −3.13),

SVR ≥35% from baseline (23.1 vs. 3.1%), and zero units transfused compared to baseline (35.4% vs. 16.9%).[88] Interim analysis of the data collected in the MOMENTUM trial demonstrated that patients who achieved transfusion-independence with momelotinib at 24 weeks had prolonged OS compared to the patients who remained transfusion-dependent (HR = 0.15, P = 0.0364), suggesting that transfusion-independence at week 24 could be a potential surrogate endpoint to predict improved OS in MF patients.[89] Furthermore, data analysis of the broader thrombocytopenic subgroups (baseline platelet counts <150 × 10^9/L, <100 × 10^9/L, and <50 ×10^9/L) at 24 weeks demonstrated the superiority of momelotinib vs. danazol regarding symptom and spleen responses, RBC transfusion independence rate; and favorable OS.[88,90] Collectively, the results of the MOMENTUM trial confirmed that momelotinib is a highly promising treatment for MF patients who are RBC transfusion-dependent and will likely result in regulatory approval of momelotinib in the near future.[39,78,85] Notably, in August 2022, the Federal Drug Administration accepted a new drug application for momelotinib as a treatment for MF patients with anemia.

Concept #5: HDM2 inhibitor in the second line setting

In a phase 2 study, navtemadlin (administered once daily 240 mg, days 1–7/28-day cycle) demonstrated encouraging clinical efficacy (16% and 30% of the patients achieved SVR35 and TSS50, respectively; and CD34+ cells were reduced by 87% in the peripheral blood at week 24)[91] and tolerability in *TP53*-wild type MF patients who had failed ruxolitinib treatment (median prior treatments were 2) and had poor prognosis. In this study, a notable correlation was found between SVR responses and ≥20% VAF decrease in high molecular risk (*ASXL1, EZH2, IDH1/2, SRSF2, U2AF1*) or driver (*JAK2*, *CALR*, *MPL*) mutations (34% of evaluable patients; 29% had VAF below the detection limit), lower peripheral CD34+ cell counts, improved bone marrow fibrosis scores, and reduction in the serum levels of the inflammatory cytokine TNFα.[92] On the basis of the phase 2 study results, navtemadlin (dosing: 240 mg, days 1–7/28-day cycle) is being assessed in comparison to BAT (chemotherapy, hydroxyurea, and supportive care, excluding JAK inhibitors) in a global phase 3 trial (BOREAS, NCT03662126) in MF patients who are refractory or resistant to JAK inhibitors (Table 2).[93] In this trial, the primary endpoint is the proportion of patients who reach SVR35 compared to baseline at week 24; the secondary endpoints are progression-free survival, OS, duration of spleen response; and the proportion of patients who achieve TSS50 and RBC transfusion-independence at 24 weeks.[93]

Concept #6: Telomerase inhibitor to prolong survival in the second line setting

Imetelstat is a first-in-class potent telomerase inhibitor that was evaluated in two doses (4.7 and 9.4 mg/kg, administered intravenously once every three weeks) in patients with intermediate-2 or high-risk MF relapsed/refractory to JAK inhibitors in the phase 2 study IMbark (NCT02426086).[94] Importantly, a notable median OS (one of the secondary endpoints) of 29.9 months was noted with the higher dose of imetelstat (9.4 mg/kg); furthermore, 40.5% of the patients treated with 9.4 mg/kg of imetelstat demonstrated improvement in bone marrow fibrosis by ≥1 grade, the VAFs of the 3 driver mutations (*JAK2* V617F, *CALR, MPL*) decreased by ≥ 25% in 42.1% of evaluable patients compared to baseline, and 32.2% of the patients experienced TSS50 at week 24 (Table 1).[94] In this study, the reduced telomerase activity and lower expression levels of human telomerase

reverse transcriptase (hTERT) correlated with spleen and symptom responses and longer median OS. Also, prolonged OS was noted in patients who had ≥20% decrease in VAF compared to patients without VAF reduction; dose-dependent reductions of mutation burden (≥20%) compared to baseline by imetelstat correlated with higher spleen (12.3% vs. 3%) and symptom (31.3% vs. 24.2%) responses, improvement in bone marrow fibrosis (54.4% vs. 21.5%), and prolongation of OS (31.6 vs. 21.5 months).[95] Importantly, the higher dose of imetelstat conferred a survival benefit that compared favorably with matched historical data for treatment with BAT; in particular, analysis of the data from 59 MF patients treated with 9.4 mg/kg of imetelstat in the IMbark trial and 38 propensity score-matched MF patients treated with BAT (after JAK inhibitor failure) from real world data collected at a major academic center demonstrated the significant survival benefit that imetelstat conferred vs. BAT (30 vs. 12 months, respectively).[96] Notably, higher-risk "triple-negative" MF patients (who are known to have a poor prognosis[97,98,99] exhibited superior OS and clinical outcomes compared to the non "triple-negative" cohort.[100] On the basis of the promising results noted in the IMbark trial, the international, registrational phase 3 trial (IMpactMF; NCT04576156) is underway to assess the OS (primary endpoint) advantage− an unprecedented endpoint in MF clinical trials− that imetelstat (at 9.4 mg/kg as an intravenous infusion every 21 days) compared to BAT (excluding JAK inhibitors) may confer to intermediate-2 or high-risk MF patients who are refractory to JAK-inhibitors (Table 2).[101] Spleen and symptom responses at week 24, progression-free survival and reduction of bone marrow fibrosis are included in the secondary objectives; molecular responses and other biomarkers are included in the exploratory objectives of the trial.[101]

Future Outlook

Despite the transformative impact of JAK inhibitors in the MPN landscape and their pivotal role in MF treatment,[102] there are limitations in their activity. The recent regulatory approval of pacritinib for MF patients with severe thrombocytopenia and the plausible approval of momelotinib for MF patients with anemia[78,103] in the near future are welcome developments in the therapeutic landscape of MF. Several promising novel agents with various mechanisms of action beyond the JAK-STAT pathway, administered as monotherapies or in combination with ruxolitinib, have been in advanced clinical development, in the frontline and second line settings;[36,104] these strategies are poised to expand the arsenal of MF therapeutics with novel disease-modifying agents that complement or expand the clinical benefits of ruxolitinib. For example, novel agents in clinical development are aimed to increase the depth and duration of spleen and symptom responses via ruxolitinib-based synergistic combinations; improve other aspects of the disease besides splenomegaly and constitutional symptom burden (for example, decrease driver mutation burden); address unmet therapeutic needs of MF patients (for example, anemia, resistance to ruxolitinib); prolong survival beyond ruxolitinib; modify the proclivity of the disease; and thwart leukemic transformation.[2,3,4] In clinical trials assessing promising investigational agents and strategies for treatment of MF, new endpoints beyond the usual ones (SVR35 and TSS50 at week 24), such as achievement of RBC transfusion independence and OS, may be considered.[105,106] Notably, deeper spleen responses (for example, with ruxolitinib treatment[41,42,43]) and achievement of RBC transfusion independence (for example, with momelotinib treatment[86,89]) have been correlated with increased OS.

An array of novel agents, such as BET inhibitors (pelabresib), BcL-xl inhibitors (navitoclax) and PI3K inhibitors (parsaclisib) in the frontline and the second-line settings are promising agents that may be paired with a JAK inhibitor to benefit certain cohorts of patients. The extent of cytopenias, driver/non-driver mutations and allele burden influence the phenotype and could potentially guide the choice of JAK inhibitors for first and second-line treatment.[30,107] or targeted treatments (for example, IDH2 inhibitors for treatment of *IDH2*-mutated patients with advanced myelofibrosis.[75,76,77] Novel immunotherapies, such as neoepitope-directed vaccines and monoclonal antibodies directed against mutant-driven MPNs (*CALR* exon 9 frameshift and *JAK2*V617F mutations) are explored in preclinical studies and in clinical trials in patients with MPNs (for example, trials NCT03566446, NCT05444530); both *CALR* exon 9 and *JAK2*V617 driver mutations, which lead to constitutive activation of the JAK/STAT pathway and malignant cell proliferation, have been reported to be immunogenic and are promising targets for immunotherapy (for example, mCALR vaccine treatments) in MPN patients harboring these mutations.[108,109,110 111,112,113,114] Furthermore, monotherapy with imetelstat or navtemadlin may be particularly suited for treatment of high-risk MF patients in the second line setting who do not require RBC transfusions.[39] The aforementioned treatment options could result in personalized treatment of MF patients that will take into consideration the hematological and molecular profiles and result in optimum responses and prolonged survival in the near future. Following JAK inhibitors as the sole medications for MF treatment heretofore, clinical development of many promising agents[36] is a welcome advancement in the field.

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Table 1.

Selected Completed Clinical Trials on Agents in Clinical Development for MF.

Investigational Agent	Mechanism of Action	Clinical Trial Identifier and Setting	Enrolled Patients	Phase	SVR35 response	TSS50 response	Anemia response	VAF reduction	BMF reduction
Concept #1:Combination of anemia therapeutic with a JAK1/2 inhibitor									
Luspatercept[48] (on a stable dose of ruxolitinib)	Activin receptor IIB ligand trap	ACE-536-MF-001 (NCT03194542)	MF patients who were on a stable dose of ruxolitinib for ≥16 weeks prior to enrollment and required RBC transfusions (Cohort 3B)	2	NR	NR	27% became RBC TI over any12 consecutive wks during the first 24 wks; 36% became RBC TI for ≥12 wks over the entire treatment period; 46% had ≥50% reduction in RBC transfusions (>4 units) over 12 wks	NR	NR
Concept #2: Agents in combination with a JAK1/2 inhibitor in the frontline setting									
Pelabresib[53]**(+ Ruxolitinib)**	BET inhibitor	MANIFEST (NCT02158858) First-line	MF patients who were JAK inhibitornaive (Arm 3)	2	68%¥	56%	24% had a mean Hb increase ≥1.5 g/dL over 12 wks	NR	28% of the patient s had ≥ 1 grade reducti on
Navitoclax[58]**(+ Ruxolitinib)**	Bcl-2/Bcl-xL inhibitor	REFINE (NCT03222609) (Cohort 3) First-line	MF patients who were JAK inhibitornaive and BET inhibitornaive	2	52%¥ 76% at any time post-baseline	31% 56% at anytime post-baseline	Of those with Hb<10 g/dL or TD; increase of Hb >2 g/dL or TI: 55%	NR	35% of the patients had a 1 grade reduction at any time post-baseline
Concept #3:"Add-on" agents to a JAK1/2 inhibitor in the second line setting									
Navitoclax[66]**(+Ruxolitinib)**	Bcl-2/Bcl-xL inhibitor	REFINE (NCT03222609) "Add-on" to ruxolitinib (Cohort 1a)	MF patients with suboptimal response to ruxolitinib	2	26.5%¥	30%	Of those with Hb<10 g/dL or TD; increas e of Hb ≥2 g/dL or TI: 64%	46% of the patients had >10% reducti on in VAF of driver mutatio ns	21% and 33% of the patients had ≥ 1 grade reducti on at 24 wks and at any time, respectively
Parsaclisib[69]**(+ Ruxolitinib)**	PI3Kδ inhibitor	NCT02718300 "Add-on" to ruxolitinib	MF patients with suboptimal response to ruxolitinib	3	7.1%	15.6%	NR	NR	NR
Concept #4: JAK1/2 inhibitor to treat anemia, splenomegaly, and constitutional symptoms in the second line setting									

Investigational Agent	Mechanism of Action	Clinical Trial Identifier and Setting	Enrolled Patients	Phase	SVR35 response	TSS50 response	Anemia response	VAF reduction	BMF reduction
Momelotinib [83]	ACVR 1 and JAK1/2 inhibitor	SIMPLIFY-2 (NCT02101268) Second-line	Anemic patients with MF previously treated with ruxolitinib	3	7%¥	26%	RBC TI: 43% at wk 24; Rate of zero transfusions over entire treatment phase: 40%	NR	NR
Momelotinib[87,88,89]	ACVR 1 and JAK1/2 inhibitor	MOMENTUM (NCT04173494) Second-line	Symptomatic (TSS ≥ 10), anemic (Hb <10 g/dL) MF patients who were previously treated with an approved JAK inhibitor	3	23.1%	24.6%¥	RBC TI: 31% at wk 24; zero RBC transfusion rate: 35%	NR	NR
Concept #5: HDM2 inhibitor in the second line setting									
Navtemadlin[91,92,93]	HDM2 inhibitor	BOREAS (NCT03662126) Second-line Phase 2: 240 mg, days 1–7/28-day cycle	Wild type *TP53* MF patients who relapsed or are refractory/ resistant to JAK inhibitors	2/3	Ph. 2: 16%¥	Ph.2:30%	NR	34% of the patients had ≥20% VAF decrease in HMR or driver mutations; 29% had VAF<d etection limit	27% had ≥ 1 grade reduction, and 51% had stable BMF scores
Concept #6: Telomerase inhibitor to prolong survival in the second line setting									
Imetelstat [94]	Telomerase inhibitor	IMbark (NCT02426086) 9.4 mg/kg once every 3 wks	Patients with intermediate −2 or high-risk MF that relapsed or were refractory to JaK inhibitors	2	10.2%†,§	32.2%†	25% TI for ≥12 wks	42.1% of the patients had ≥25% reduction in VAF of driver mutations	40.5% of the patients

Abbreviations: ACVR1 = activin A receptor type 1; Bcl-2/Bcl-xL = B-cell lymphoma-2/extra-large; BET = bromodomain and extra-terminal; BMF = bone marrow fibrosis; HDM2 = human double minute 2; Hb = hemoglobin; HMR = high molecular risk; JAK = Janus kinase; MF = myelofibrosis; NR = not reported; PI3Kδ = phosphatidylinositol 3-kinase-delta; RBC = red blood cell; SVR35 = spleen volume reduction ≥35% from baseline to week 24; TD = transfusion-dependent; TI = transfusion-independent; TSS50: ≥50% improvement in total symptom score from baseline to week 24; VAF = variant allele frequency; wk = week.

¥Primary endpoint.

†Coprimary endpoints.

§Median OS (one of the secondary endpoints) was 29.9 months for the subgroup treated with 9.4 mg/kg of imetelstat.

Table 2.

Selected Ongoing Clinical Trials on Agents in Clinical Development for MF.

Investigational Agent	Mechanism of Action	Clinical Trial Identifier and Setting	Enrolled Patients	Phase	Primary Endpoint	Secondary Endpoint(s)
Concept #1 :Combination of anemia therapeutic with a JAK1/2 inhibitor						
Luspatercept[49] (on a stable dose of ruxolitinib)	Activin receptor IIB ligand trap	INDEPENDENCE (NCT04717414)	Anemic MF patients on a stable dose of ruxolitinib, requiring 4–12 RBC transfusions in the 12 weeks before randomization	3	% RBC TI for any 12 consecutive wks during the first 24 wks	% RBC TI for any consecutive 16 wks, ≥50% reduction of transfusion burden by ≥4 units for any 12 consecutive wks and duration of reduction
Concept #2: Agents in combination with a JAK1/2 inhibitor in the frontline setting						
Pelabresib[56]**(+ Ruxolitinib)**	BET inhibitor	MANIFEST-2 (NCT04603495) Frontline	MF patients who are JAK inhibitornaive	3	SVR35 response	TSS50 response BMF reduction SVR35 duration TSS50 duration PFS, OS, TD to TI at 24 wks
Navitoclax[59]**(+ Ruxolitinib)**	Bcl-2/Bcl-xL inhibitor	TRANSFORM-1 (NCT04472598) Frontline	MF patients who are JAK in hibitor-naïve a nd BET inhibitor-naïve	3	SVR35 response	TSS50, SVR35 duration, anemia response, BMF reduction, OS, LFS
Parsaclisib[64]**(+ Ruxolitinib)**	PI3Kδ inhibitor	LIMBER-313 (NCT0455106 Frontline	Patients with MF who are JAK inhibitor-naïve	3	SVR35 response	Time to first TSS50, OS, SVR35 duration
Concept #3-"Add- on" agents to a JAK1/2 inhibitor in the second line setting						
Navitoclax[68]**(+ Ruxolitinib)**	Bcl-2/Bcl-xL inhibitor	TRANSFORM-2 (NCT04468984) "Add-on" to ruxolitinib	MF patients who are refractory/resistant to JAK2 inhibitors	3	SVR35 response	TSS50, SVR35 duration, anemia response, OS, LFS, BMF reduction
Parsaclisib (+ Ruxolitinib)	PI3Kδ inhibitor	LIMBER-304 (NCT04551053) "Add-on" to ruxolitinib	Patients with MF who had suboptimal response to ruxolitinib	3	SVR35 response	TSS50, TSS change, time to TSS50, OS
Navtemadlin[72]**(+ Ruxolitinib)**	HDM2 inhibitor	NCT04485260 "Add-on" to ruxolitinib	*TP53*-wild type MF patients who had a suboptimal response to ruxolitinib after ≥18 wks, at a stable dose for ≥8 wks	1b/2	RP2D of navtemadlin in combination with ruxolitinib	SVR35 response, TSS at any time point, SVR35 duration, TI rate, OS, PFS,LFS
Enasidenib (+ Ruxolitinib) [77]	IDH2 inhibitor	NCT04281498	*IDH2*-mutated, persistent or progressive MF with 4–9% blasts or *IDH2*-mutated AP/BP-MPN	2	Proportion of responders within 6 cycles of combined therapy	Proportion of participants with blast response or any response in 6 months
Concept #4: JAK1/2 inhibitor to treat anemia, splenomegaly, and constitutional symptoms in the second line setting						
Momelotinib[87,88,89]	ACVR 1 and JAK1/2 inhibitor	MOMENTUM (NCT04173494) Second-line	Symotonatic (TSS ≥ 10), aremic (Hb <10 g/dL) MF patients who were previously treated with an approved JAK inhibitor	3	TSS50 response	Rate of RBC TI patients for ≥12 wks prior to the end of wk 24, SVR35, mean TSS change, zero

Investigational Agent	Mechanism of Action	Clinical Trial Identifier and Setting	Enrolled Patients	Phase	Primary Endpoint	Secondary Endpoint(s)
						RBC transfusion rate
Concept #5: HDM2 inhibitor in the second line setting						
Navtemadlin[91,93]	HDM2 inhibitor	BOREAS (NCT03662126) Second-line Phase 3: 240 mg, days 1-7/28-day cycle	Wild type *TP53* MF patients who relapsed or are refractory/resistant to JAK inhibitors	2/3	SVR35 response	TSS50, PFS, OS, best overall SVR35, SVR35 duration
Concept #6: Telomerase inhibitor to prolong survival in the second line setting						
Imetelstat [101]	Telomerase inhibitor	IMpactMF (NCT04576156) Second-line	Patients with intermediate-2 or high-risk MF who failed JAK inhibitor therapy	3	OS	TSS50, PFS, SVR35, BMF reduction

Abbreviations: ACVR1 = activin A receptor type 1; AP = accelerated phase; Bcl-2/Bcl-xL = B-cell lymphoma-2/extra-large; BET = bromodomain and extra-terminal; BMF = bone marrow fibrosis; BP = blast phase; HDM2 = human double minute 2; Hb = hemoglobin; JAK = Janus kinase; LFS = leukemia-free survival; MF = myelofibrosis; OS = overall survival; PFS = progression-free survival; PI3Kδ = phosphatidylinositol 3-kinase-delta; RBC = red blood cell; RP2D = recommended phase 2 dose; SVR35 = spleen volume reduction ≥35% from baseline to week 24; TI = transfusion-independent; TSS50: ≥50% improvement in total symptom score from baseline to week 24; wk = week.