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Managing Myelofibrosis: Matching Advances in Treatments With Clinical Unmet Needs

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ABSTRACT

Myelofibrosis (MF) is characterized by anemia, constitutional symptoms, hepatosplenomegaly and bone marrow fibrosis, and is associated with poor survival. The janus kinase inhibitor (JAKi) ruxolitinib has been the mainstay of treatment for over a decade. Despite demonstrated symptomatic and quality of life improvement, unmet clinical needs persist. A literature review identified promising novel targeted treatment options in MF using pre-set selection criteria (available Phase 2 or 3 data, minimum enrollment of 50 patients, trial end date within the last 5 years). Available data for novel and approved therapies were extracted, tabulated, and analyzed for clinical relevancy. From an initial shortlist of 48, 16 retained molecules were selected for inclusion. Other JAKi (pacritinib, momelotinib, jaktinib) address treatment-related cytopenia, expanding the therapeutic utility of this class of agents to patients with baseline anemia or thrombocytopenia. Novel candidates exploit multiple molecular pathways, and offer the potential to improve the management of MF-associated cytopenia (imetelstat, pelabresib, navitoclax, selinexor, luspatercept, sotatercept, elritercept, LCL161, bomedemstat) and recover bone marrow fibrosis (imetelstat, pelabresib, navitoclax and bomedemstat). It remains to be seen if these newer agents can induce any remission in MF and enable patients to come off therapy, but the future is beginning to look much brighter.

1 | Introduction

Myelofibrosis (MF) is myeloproliferative neoplasia, which develops *de novo* as primary myelofibrosis (PMF), or secondary to essential thrombocythemia (ET) or polycythemia vera (PV). Although uncommon, it is associated with poor overall survival [1]. Biologically MF is characterized by expansion of malignant hematopoietic stem and progenitor cells, and its pathogenesis has been related to aberrant cytokine production caused by the upregulation of the janus kinase-signal transducer of activation (JAK-STAT) signaling pathways [2]. The majority of patients have a somatic mutation in one of three JAK-STAT pathway genes. Clinical presentation is highly heterogenous and includes severe anemia, constitutional symptoms, hepatosplenomegaly, cachexia, bone marrow fibrosis (BMF) and a propensity toward evolution to acute myeloid leukemia [3]. Inferior survival is associated older age, anemia, leukocytosis, thrombocytopenia, presence of constitutional symptoms, and transfusion dependence (TD) [4]. Prognosis is further influenced by cytogenic features including karyotype abnormalities and the presence of high molecular risk mutations (e.g., *ASXL1, SRSF2*, *U2AF*1-Q157*, EZH2, and IDH1/2*) [3].

Management is typically risk-adapted, being guided by disease risk scores, category (high, low), symptoms and medical fitness [3]. While allogeneic hematopoietic stem cell transplantation is potentially curative, its risk-benefit ratio is such that it is reserved for carefully selected patients [5]. The introduction of the first JAK inhibitor (JAKi), ruxolitinib, transformed patient management and after more than 10 years in clinical use has become established as the standard of care [6]. More recently three other JAKi, momelotinib, pacritinib and fedratinib, have gained regulatory approval. Despite demonstrated symptomatic and quality of life improvement, unmet clinical needs persist. A diverse range of novel targeted treatment candidates aim to address these clinical gaps. This review of the available data provides clinical insights into their potential role in MF.

2 | Methods

A series of systematic searches of the PubMed database was undertaken using predefined clinical queries filters, key words and publication date (01-Jan-2013 to 31-Dec-2024). The ClinicalTrials.gov database was searched using "myelofibrosis" as the indication and filtering for trials that had commenced on or after 01-Jan-2013. The abstracts of major international hematology conferences up to and including December 2024 were reviewed. These search outputs were cross tabulated to generate a list of identified novel molecules. Molecule selection criteria (minimum development with positive Phase 2 data, minimum enrollment of 50 patients, and trial end date within the last 5 years) were then applied to create a shortlist of therapies most likely to progress toward regulatory approval. Available published data for these molecules were then extracted and tabulated for review by development phase (Approved, Phase 3 or Phase 2) and treatment strategy (JAKi, other targeted therapy, JAKi/ruxolitinib combination therapy).

3 | Results

The search strategy identified 48 molecules, 32 of which did not meet the selection criteria (Table S1). The 16 retained molecules comprised four approved JAKi, seven therapies in Phase 3 ($N = 7$) and five in Phase 2 development. Each of these therapies targets a different aspect of MF pathophysiology (Figure 1).

3.1 | Approved Therapies

JAKi are central to the management of MF. Data from pivotal trials supporting the regulatory approval of ruxolitinib (2011) [7, 8], fedratinib (2019) [9, 10], pacritinib (2022) [11, 12], and momelotinib (2023) (13-16) in MF, summarized in Table 1, have recently been reviewed [17]. Established limitations to the use of ruxolitinib include treatment-related anemia, with associated requirements for dose reductions, dose interruptions and management with adjunctive therapies, and clinical resistance [18]. Fedratinib offers the convenience of once-daily dosing, but treatment-related anemia remains a limitation. Momelotinib and pacritinib enable JAKi use in the setting of cytopenias. Momelotinib offers the benefit of JAKi therapy alongside favorable anemia-related end points, including a reduction in transfusion dependence rates [15, 16, 19]. The ongoing Phase 3 PACIFICA trial (NCT03165734) aims to confirm the efficacy and safety of pacritinib in patients with no or only limited (< 90 days) prior exposure to JAKi [20].

3.2 | Targeted Therapies in Phase 3 Development

New therapies in Phase 3 development (Table 2) include a JAKi (jaktinib), two non-JAK targeted monotherapies (navtemadlin, imetelstat) and five novel therapies (navtemadlin, pelabresib, navitoclax, selinexor, luspatercept) in combination with ruxolitinib. Many of these Phase 3 trials are ongoing with no available data, relevant data from the Phase 2 trials programs are presented (Table 3).

Jaktinib is a pan-JAK and ACRV1 inhibitor and a deuterated isotope of momelotinib [35]. It further extends the role of combining JAK and ACVR1 to improve JAK inhibitor treatment options in patients with baseline cytopenias. A Phase 3 trial of jaktinib versus hydroxyurea in ruxolitinib naïve patients has completed, but not yet reported. A pre-specified interim analysis showed good clinical response with less cytopenia compared with the control arm (Table 2) [21]. Incidence rates for the most common hematologic treatment-emergent adverse events were lower in the jaktinib arm—anemia (25.5% vs. 43.5%), thrombocytopenia (17.0% vs. 39.1%), leukopenia (2.1% vs. 21.7%), neutropenia (2.1% vs. 21.7%) and decreased lymphocyte count (2.1% vs. 13.0%). A Phase 2 trial demonstrated efficacy in spleen, symptom and hematologic responses in JAKi naïve patients (Table 3) [27]. Similar results were reported in two smaller Phase 2 trials assessing jaktinib 100 mg twice-daily monotherapy. The spleen, symptom and hematologic responses were 43.2%, 61.8% and 41.9% in 51 ruxolitinib intolerant patients (NCT04851535) [36] and 32.4%, 46.4% and 50% in 34 ruxolitinib refractory/relapsed MF patients (NCT04217993) [37, 38].

Navtemadlin (KRT-232) is a potent, selective, orally available mouse double minute 2 (MDM2) inhibitor. MDM2 is a negative regulator of the tumor suppressor protein p53 and is overexpressed in circulating $CD34^+$ hematopoietic stem/progenitor cells in patients with MF [39]. The p53 pathways regulate pro-survival and pro-death cell signals; navtemadlin induces apoptosis in *TP53* wild-type ($TP53^{WT}$) $CD34^+$ myeloblasts by overcoming dysregulated MDM2 [39]. Single agent navtemadlin is being evaluated in patients who have relapsed or are refractory to ruxolitinib, but excluding those who are ruxolitinib intolerant (NCT03662126, BOREAS). Phase 2 data demonstrated survival improvements with an associated reduction in disease biomarkers ($CD34^+$ cell counts) [40]. Interim analysis of 183 patients in the Phase 3 study showed improved clinical outcomes versus BAT at week 24 (Table 2) [22]. Analysis supports a significant ($P < 0.001$) correlation between improved biomarkers (reduced $CD34^+$ cell counts, driver mutation burden, inflammatory cytokines and improved BMF) and the magnitude of SVR response, supporting a disease modifying effect [41]. The most common treatment-emergent adverse events were gastrointestinal or cytopenic (thrombocytopenia 37% vs21%, anemia 29% vs. 25%, neutropenia 24% vs. 12%) [22].

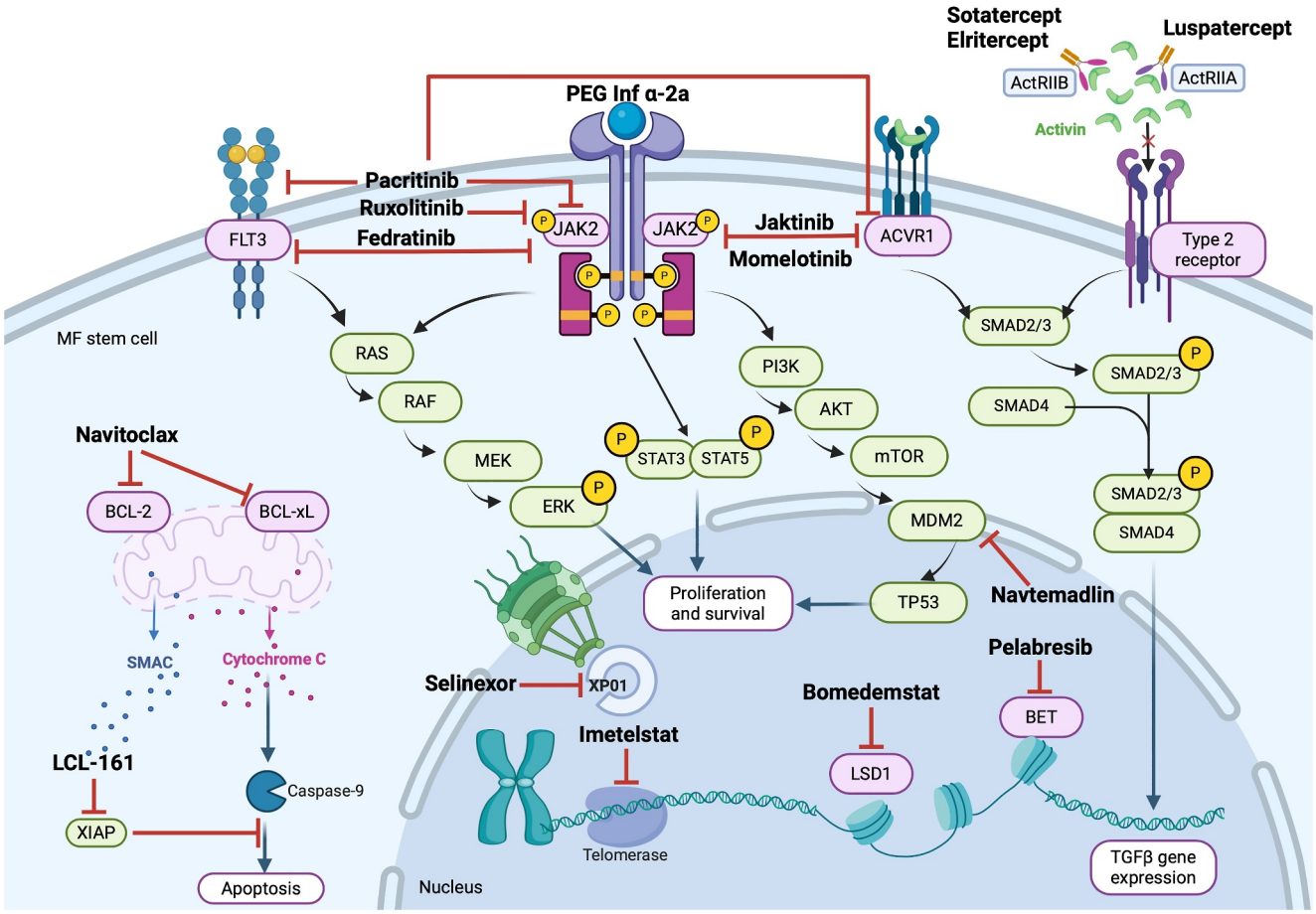

FIGURE 1 | Approved (ruxolitinib, fedratinib, momelotinib and pacritinib) and novel therapies target multiple pathways in MF pathophysiology. ActRIIA, activin receptor type IIA; ActRIIB, activin receptor type IIB; ACVR1, Activin A receptor type I BCL-2/xL, B-cell lymphoma 2/xL; BET, bromodomain and extraterminal; FLT3, Fms-like tyrosine kinase 3; JAK, Janus Kinase; LSD1, lysine-specific demethylase 1; MDM2, mouse double minute 2; TGF-β, transforming growth factor-β; XPO1, exportin 1.

Navtemadlin is also being explored as a candidate for add-on therapy to ruxolitinib in patients with sub-optimal responses to initial ruxolitinib therapy. Phase 1b/2 data (NCT04485260) support clinically relevant improvements and acceptable safety (Grade 3/4 anemia 13%, thrombocytopenia 21%) in patients on stable ruxolitinib doses [42]. A Phase 3 trial in this setting now open for recruitment (Table 2).

Imetelstat, a first-in-class telomerase inhibitor, reduces human telomerase reverse transcriptase (hTERT) and STAT3 mRNA expression and downregulates JAK2 phosphorylation and downstream JAK-STAT signaling [43]. In a Phase 2 study (NCT02426086, MYF2001/IMbark), in patients who had relapsed or were refractory to ruxolitinib, spleen and symptom response rates favored the 9.4 mg/kg dose (Table 3) [30]. The higher dose showed prolonged survival (median overall survival [OS] 29.9 months), a fair hematologic response (25%) and an improvement in BMF in 40.5% of patients. Grade 3 or 4 reversible cytopenias were the most common treatment-emergent adverse events in both dose arms. Further analysis showed that median OS on imetelstat 9.4 mg/kg was more favorable than that of a real-world cohort of patients closely matched to the Phase 2 study inclusion criteria and who had discontinued ruxolitinib and were subsequently treated with best available therapy (30 vs. 12 months, respectively) [44]. To date, the Phase 3 trial (MYF3001, ImpactMF, NCT04576156) has recruited 212 patients recruiting patients who have relapsed or are refractory to ruxolitinib, interim analysis is anticipated in 2026 [45].

Pelabresib is a bromodomain and extraterminal domain (BET) inhibitor. BET proteins are involved in gene transcription, and it has been hypothesized that they could modify megakaryocyte differentiation and proliferation in MF [31]. Arm 3 of the Phase 2 MANIFEST trial demonstrated that, in combination with ruxolitinib, pelabresib achieved meaningful spleen, symptom, and hematologic responses (Table 3), while also improving BMF (28% with ≥ 1 grade improvement) and reducing mutation burden (29.5% with > 25% reduction in JAK2V617F-mutant allele fraction). Interim data from the ongoing Phase 3 MANIFEST-2 trial (NCT04603495) evaluating combination pelabresib/ruxolitinib versus single agent ruxolitinib in JAKi naïve patients with intermediate-1 and higher risk MF demonstrate positive clinical outcomes (Table 3) and good tolerability, supporting the benefits of a potential paradigm shift toward combination therapy [24, 25]. In sub-group analyses, SVR35 was consistent across all DIPSS risk groups, further data will be needed to determine the clinical benefits of commencing treatment at an early stage of the disease in patients with intermediate-1 risk.

TABLE 1 | FDA-approved therapies for MF: Overview of 24-week treatment response data from pivotal trials.

Therapy primary target	*N*	Arm	Spleen response (SVR35)	Symptom response (TSS50)	Hematologic response (TI)	Trial
Ruxolitinib JAK1, JAK2	309	Ruxolitinib Placebo	41.9% 0.7%	45.9% 5.3%	—	COMFORT-1 [7]
	219	Ruxolitinib BAT	31.9% 0%	—	—	COMFORT-2 [8]
Fedratinib JAK2, FLT3, BRD4	289	Fedratinib Placebo	47% 1%[a]	40% 9%[a]	—	JAKARTA [9]
	97	Fedratinib	31%	27%	—	JAKARTA[b]2 [10]
Pacritinib JAK2, FLT3, ACVR1, IRAK1, CSF1R	327	Pacritinib BAT (excl ruxolitinib)	19% 5%	19% 10%	25% 0%	PERSIST-1 [11]
	311	Pacritinib 400 mg, QD Pacritinib 200 mg, BID BAT	14.7% 21.6% 2.8%	17.3% 32.4% 13.9%	13%[c] 25%[c] 12%[c]	PERSIST-2 [12]
Momelotinib JAK1, JAK2, ACVR1	432	Momelotinib Ruxolitinib	26.5% 29%	28.4% 42.2%	66.5% 49.3%	SIMPLIFY-1 [13]
	156	Momelotinib BAT	7% 6%	26% 6%	43% 21%	SIMPLIFY 2 [14, 15],
	195	Momelotinib Danazol	22.3% 3.1%	24.6% 9.2%	30% 20%	MOMENTUM [16]

Note: Hematologic response (TI), proportion of patients achieving transfusion independence at week 24; spleen response (SVR35), proportion of patients with a spleen volume reduction of at least 35% from baseline to week 24; symptom response (TSS50), proportion of patients with an improvement in total symptom score of at least 50% from baseline to week 24.
Abbreviations: ACVR1, activin A receptor type 1; ADR, adverse drug reaction; BAT, best available therapy; BID, twice-daily; BRD4, bromodomain-containing protein 4; CSF1R, colony stimulating factor 1 receptor; FLT3, fms-like tyrosine kinase 3; IRAK1, interleukin-1 receptor-associated kinase; JAK, janus kinase; QD, once-daily.
[a]Updated analysis (basis for regulatory approval).
[b]Phase 2 study, data presented from intention-to-treat analysis principles without last observation carried forward.
[c]Clinical improvement in hemoglobin.

Navitoclax is a novel anti-apoptotic B cell leukemia 2 (Bcl-2) inhibitor, that neutralizes prosurvival proteins required for cancer cell survival [46]. In Phase 2 (REFINE) combination navitoclax/ruxolitinib reported positive spleen, symptom and hematologic responses (Table 3) as well as a > 5% reduction in driver mutation allelic burden in 42% of patients, and reduction BMF by at least 1 grade in 25% of patients [32]. The recently completed Phase 3 trial (NCT04472598, TRANSFORM-1) demonstrated improved clinical response in the combination arm versus ruxolitinib alone in JAKi naïve patients (Table 2). The most common adverse events were thrombocytopenia, anemia, diarrhea, and neutropenia. Additional evaluation is ongoing [26]. A second Phase 3 trial (NCT04468984, TRANSFORM-2) in patients relapsed, refractory or resistant to single-agent JAKi is recruiting [46].

Selinexor, a selective inhibitor of nuclear export (XPO1) inhibitor, induces tumor suppressor proteins and selectively induces apoptosis. Favorable efficacy and tolerability data from Phase 1 development support the combination of 60 mg selinexor once-weekly with twice-daily ruxolitinib in JAKi naïve patients [47, 48]. This combination has now entered Phase 3 (XPORT-MF-034, NCT04562389) in JAKi naïve patients with intermediate-1 or higher risk MF [49]. Preliminary data from the Phase 1 ESSENTIAL trial supports single agent activity with once weekly selinexor dosing (SVR35@W24: 22% [2/9]), with preliminary hematologic response with one of two patients who were red blood cell transfusion dependent at baseline becoming transfusion independent at 36 weeks [50]. Two Phase 2 (XPORT-MF-044 and XPORT-MF-035) studies have now commenced evaluating selinexor monotherapy in the JAKi naive and relapsed/refractory settings (Table 4) [56].

Luspatercept is an activin receptor (ActR) ligand trap, which binds to select TGF-β superfamily ligands to reduce aberrant SMAD2/3 signaling and enhance late-stage erythropoiesis. Promising Phase 2 data (Table 3) demonstrate a greater than 50% reduction in transfusion burden with a combination of luspatercept and stable dose ruxolitinib in patients with MF-associated anemia [59, 60]. The Phase 3 INDEPENDECE trial (NCT04717414) is evaluating its efficacy and safety in patients with MF and anemia on concomitant JAKi who require blood transfusions [61].

3.3 | Targeted Therapies in Phase 2 Development

New therapies currently in Phase 2 development for which data are available (Table 4) include LCL161, sotatercept, bomedemstat, and elritercept [KER050] monotherapy and two ruxolitinib-

TABLE 2 | Novel targeted therapies currently in Phase 3 development.

Molecule	Target	Study population	Accrual	Comparator	Primary endpoint	Available data	Status	Trial/reference
Monotherapy								
Jaktinib	JAK 1/2/3 & AVCR1	JAKi naive	105	Hydroxyurea	SVR35 at Week 24	Interim analysis [21] SVR35: 72.3% vs 17.4% TSS50: 63.8% vs 43.5% Hb ⇑: 39.3% vs 15.4%	Phase 3, completed	NCT04617028
Navtemadlin	MDM2 inhibitor	ruxolitinib refractory/relapsed	385	BAT	SVR35 at week 24	Interim analysis [22] SVR35: 15% vs 5% TSS50: 24% vs 12%	Phase 3, RCT Active Completion Dec 2025	NCT03662126 BOREAS (PART B)
Imetelstat	Telomerase inhibitor	ruxolitinib refractory/relapsed	320	BAT	Overall survival	DATA NOT YET PRESENTED	Phase 3, RCT Active Completion April 2026	NCT04576156 MYF3001/ IMpactMF [23]
Combination therapy								
Navtemadlin + ruxolitinib	MDM2 inhibitor	JAKi naïve[a]	600	Placebo + ruxolitinib	SVR35 at week 24	DATA NOT YET PRESENTED	Phase 3, RCT Active Completion Dec 2026	NCT06479135 POIESIS
Pelabresib + ruxolitinib	BET inhibitor	JAKi naive	430	Placebo + ruxolitinib	SVR35 at week 24	Interim analysis [24, 25] SVR35: 66% vs 35% TSS50: 52% vs 46%	Phase 3, RCT Active Completion August 2027	NCT04603495 MANNIFEST-2
Navitoclax + ruxolitinib	BCL-2 inhibitor	JAKi naive	252	Placebo + ruxolitinib	SVR35 at week 24	Interim analysis [26] SVR35: 63.2% vs 31.5%	Phase 3, RCT Active Completion October 2023	NCT04472598 TRANSFORM-1 Preliminary data (abstract)
		ruxolitinib refractory/relapsed	295	BAT	SVR35 at week 24	DATA NOT YET PRESENTED	Phase 3, RCT Active Completion Jan 2031	NCT04468984 TRANSFORM-2

(Continues)

TABLE 2 | (Continued)

Molecule	Target	Study population	Accrual	Comparator	Primary endpoint	Available data	Status	Trial/reference
Selinexor + ruxolitinib	SINE compound	JAKi naive	330	Placebo + ruxolitinib	SVR35 at week 24	DATA NOT YET PRESENTED	Phase 3, RCT Active Completion March 2028	NCT04562389 XPORT-MF-034/ SENTRY
Luspatercept + any JAKi	ACVR IIB	Anemic or RBC TD	309	Placebo + any JAKi	Anemia response rate	DATA NOT YET PRESENTED	Phase 3, RCT Active Completion August 2025	NCT04717414 INDEPENDENCE

Note: Spleen response (SVR35): proportion of patients with a spleen volume reduction of at least 35% from baseline to week 24. Symptom response (TSS50), proportion of patients with an improvement in total symptom score of at least 50% from baseline to week 24. Hematological response (Hb ⇑): Proportion with baseline hemoglobin ≤ 10 g/dlL who achieved hemoglobin elevation of ≥ 2 g/dL.

Abbreviations: ACVR1, activin A receptor type 1; ACVR II B, activin A receptor type 2B; Bcl-2, B cell leukemia 2; BAT, best available therapy; BET, bromodomain and extraterminal domain; JAK, janus kinase; MDM2, mouse double minute 2; SINE, selective inhibitor of nuclear export.

[a]Participants with a suboptimal response during a ruxolitinib run-in period will be randomized.

combination therapies (elritercept, PEG-interferon alpha-2a). Three of these novel agents have reported promising anemia responses. Weekly administration of the **LCL161** (a second mitochondrial activator of caspases [SMAC] mimetic) in an older, ruxolitinib-resistant population with intermediate-1, 2 or high-risk MF reported prolonged survival (median OS 34 months) and an anemia response in 6 (12%) of patients [51]. **Sotatercept** is an ActR type IIA ligand trap, developed as a first-in-class targeted treatment to address MF-associated anemia. An early, open-label Phase 2 trial (ACE-011) in anemic patients reported a response rate of 30% when used alone ($N = 34$) and 32% when used in conjunction with a stable dose of ruxolitinib ($N = 21$) [62]. Results from the ongoing Phase 2 RESTORE trial with **elritercept**, another ActR type IIA ligand trap specifically designed to inhibit select TGF-ß superfamily ligands, demonstrate improved hemoglobin, reduced transfusion burden and stable platelets, highlighting the potential to address ineffective hematopoiesis and mitigate ruxolitinib-mediated cytopenia [63]. Amongst patients requiring 3 or more RBC units every 12 weeks at baseline, 73% had a ≥ 50% reduction and 45% achieved TI when dosed with elritercept (≥ 3 mg/kg) in combination with ruxolitinib [63]. Lysine-specific demethylase-1 (LSD-1) is a key regulator of hematopoietic differentiation and **bomedemstat**, an LSD-1 inhibitor, has shown promise as a second-line option in patients with intermediate-1, 2 or high-risk MF without thrombocytopenia [54, 55]. Preliminary results from the ongoing Phase 2 trial (NCT03136185) evaluating **bomedemstat** add on therapy to ruxolitinib in patients with sub-optimal response to ruxolitinib (cohort A) or treatment-naïve (cohort B) demonstrate spleen (SVR35@W24, Cohort A: 7.4%; Cohort B: 38.5%) and symptom response rates (TSS50@W24, Cohort A: 25.9%; Cohort B: 30.7%), alongside Hb stabilization (stable or improved Hb: Cohort A: 51.9%; Cohort B: 46.3%) [64]. **Interferon alpha 2a** can reduce mutant allele burden and fibrosis in MF, but is poorly tolerated. In the COMBI study, patients who were previously intolerant or refractory to PEG interferon alpha 2a were treated with the combination regimen, resulting in improvements in reduced bone marrow cellularity and fibrosis, mutation burden and a reduction in symptoms with acceptable toxicity [57].

4 | Discussion

The centrality of the JAK-STAT pathway in MF development underpinned the initial development of JAKi as a therapeutic option. While ruxolitinib remains the established first-line therapy in MF providing spleen and symptom improvement, the development of novel agents acting outside of the JAK-STAT pathway offers the potential to widen the scope of treatment and address current unmet clinical needs – anemia, disease burden, and disease modification.

Cytopenias are prevalent in MF and, because JAK-STAT signaling through erythropoietin and thrombopoietin receptors regulates red blood cell and platelet production, they are further compounded by JAKi use [65]. Treatment-emergent anemia and thrombocytopenia constrains ruxolitinib and fedratinib use in patients with disease-related cytopenias. ACVR1 inhibition, with a subsequent downstream reduction in hepcidin production and improvement in erythropoiesis, represents a viable target to

TABLE 3 | Novel targeted therapies that have progressed to Phase 3: Overview of treatment response data from Phase 2 trials.

Therapy	Target	Study population	*N*	Spleen response (SVR35)	Symptom response (TSS50)	Hematologic response	BMF reduction (≥ 1 grade)	Trial
Monotherapy								
Jaktinib	JAK 1/2/ 3 & AVCR1	JAKi naive	118	100 mg BID 54.8% 200 mg QD: 31.3%	69.6% 57.5%	43.3%[b] 27.6%[b]		NCT03886415 [27]
Navtemadlin	MDM2 inhibitor	ruxolitinib refractory/ relapsed	82	16%	30%	—		NCT03662126 BOREAS [PART A] [28, 29]
Imetelstat	Telomerase inhibitor	ruxolitinib refractory/ relapsed	107	4.7 mg/ kg: 0% 9.4 mg/ kg: 10.2%	6.3% 32.2%	4.2%[c] 6.8%[c]	20.0% 40.5%	NCT02426086 MYF2001/ IMbark [30]
Combination therapy								
Pelabresib + ruxolitinib	BET inhibitor	JAKi naive	84	68%	56%	36%[d]	28%	NCT02158858 MANIFEST [31]
Navitoclax + ruxolitinib	BCL-2 inhibitor	ruxolitinib refractory/ relapsed	125	23%	24%	23%[d]	39%	NCT03222609 REFINE Cohort 1 [32]
		JAKi naïve		52%	31%	55%[d]	30%	NCT03222609 REFINE Cohort 2, *N* = 32 [33]
Luspatercept + any JAKi	ACVR II B	MF with anemia	95	—	15.8%[a]	50%[e]		NCT03194542 ACE-536-MF-001(48) [34],

Note: Spleen response (SVR35), proportion of patients with a spleen volume reduction of at least 35% from baseline to week 24. Symptom response (TSS50), proportion of patients with an improvement in total symptom score of at least 50% from baseline to week 24.
Abbreviations: ACVR1, activin A receptor type 1; ACVR II B, activin A receptor type 2B; ADR, adverse drug reaction; Bcl-2, B cell leukemia 2; BET, bromodomain and extraterminal domain; BID, twice-daily; BMF, bone marrow fibrosis; JAK, janus kinase; MDM2, mouse double minute 2; SINE, Selective inhibitor of nuclear export; Q3W, once every 3 weeks; QD, once-daily; QW, once-weekly.
[a]TSS50 was achieved by 15.8% pts in cohort 3B, 9.5% in cohort 2, 9.1% in cohort 1%, and 21.4% in cohort 3A. Hematologic response.
[b]Proportion with baseline hemoglobin ≤ 10 g/dL who achieved hemoglobin elevation of ≥ 2 g/dL.
[c]Proportion with mean hemoglobin increase of ≥ 1.5 g/dL from baseline over any 12-week period without red blood cell transfusions.
[d]Proportion with total anemia response per modified International Working Group criteria (transfusion independence (TI) in pts with BL Hb < 10 g/dL with Hb increase ≥ 2 g/dL + TI in those who were transfusion-dependent at baseline).
[e]Proportion with reduced transfusion burden by ≥ 50% during the primary treatment period.

address anemia management in MF [66]. JAKi that also target ACVR1 (pacritinib, momelotinib and jaktinib) open up the benefits of JAK pathway inhibition in a cohort of patients who have previously been contraindicated to this class of agents. Alternatively, building on the established position of ruxolitinib as the main backbone, combination strategies with novel agents (luspatercept, sotatercept and elritercept) that utilize the ActRIIA/B pathway to stimulate erythropoiesis and have shown promise in reducing the transfusion burden in patients with anemia at baseline. Other novel therapies (pelasbresib, navitoclax) have shown favorable hematologic outcomes in early phase trials investigating their potential in ruxolitinib combination strategies in JAKi naïve patients with intermediate-2 and high-risk disease, creating the potential of a new treatment paradigm as well as addressing anemia. Despite the limitations of an IV infusion, imetelstat offers a non-JAK inhibitor option with the potential for reduced transfusion dependence and an improved overall survival benefit in patients who have previously failed first-line JAKi.

In clinical practice at least 40% of patients relapse or become refractory to ruxolitinib within a few years of starting therapy [67, 68], requiring consideration of alternate management approaches (such as a second-line JAKi or clinical trial). Fedratinib serves a similar patient population to ruxolitinib, presenting a possible alternative in patients who are refractory or intolerant to ruxolitinib. Clinical decision making is hampered by the lack of a formalized definition of failure or sub-optimal ruxolitinib response. The RR6 prognostic model provides a validated metric accounting for dose, spleen response, and transfusion requirements aimed at the early identification of patients who

TABLE 4 | Trial status of targeted therapies for MF that are currently in Phase 2 development.

Combination	Target	Inclusion criteria[a]	Accrual	Primary endpoint	Status	Trial/Reference
Monotherapy						
LCL161	SMAC mimetic	Intermediate-1 with symptoms Intermediate-2 High-risk	50	Overall response rate	Phase 2, OL, completed May 2022	NCT02098161 [51]
Sotatercept	ActRIIA	Anemic or RBC TD	56	Anemia response rate	Phase 2, OL, completed May 2022	NCT01712308 ACE-011 [52]
Elritercept (KER050)	ActRIIA	Anemic or RBC TD	110	Safety Anemia response rate	Phase 2, OL, Active, Completion Apr 2025	NCT05037760 RESTORE [53]
Bomedemstat	LSD1 inhibitor	Intermediate-2 High-risk	90	Spleen response (SVR35)	Phase 2, OL completed Mar 2022	NCT03136185 IMG-7289-CTP-102 [54, 55]
Selinexor	SINE compound	Intermediate-1 with symptoms Intermediate-2 High-risk	118	Spleen response (SVR35)	Phase 2, OL, Completion 2028[b]	NCT05980806 XPORT-MF-044/ SENTRY-2 [56]
Selinexor	SINE compound	ruxolitinib refractory/ relapsed	112	Spleen response (SVR35)	Phase 2, randomized OL; Completion 2025 Comparator: BAT	NCT04562870 XPORT-MF-035
Combination therapy						
Elritercept (KER050) + ruxolitinib	ActRIIA	Anemic or RBC TD	110	Safety Anemia response rate	Phase 2, OL, Active, Completion Apr 2025	NCT05037760 RESTORE [53]
PEG INF alpha 2a + ruxolitinib	Interferon-alpha	ruxolitinib refractory/ intolerant	50	Response rate[c]	Phase 2, OL, completed	NCT02742324 RUXOPeg [57, 58]

[a]Dynamic International Prognostic Scoring System (DIPSS) prognosis grading criteria.
[b]Monotherapy trial, study design includes optional add-on JAKi therapy based on SVR at week12 and 24.
[c]2013 European Leukemia Net and International Working Group-Myeloproliferative Neoplasms Research and Treatment response criteriaActRIIA, activin receptor type 2A; ActRII B, activin receptor type 2B; BAT, best available therapy; LDS1, Lysine-specific demethylase-1; OL, open label; RBC TD, red blood cell transfusion dependent; SINE, Selective inhibitor of nuclear export; SMAC, second mitochondrial activator of caspases, SVR35, proportion of patients with a spleen volume reduction of at least 35% from baseline to week 24.

might benefit from a therapy switch [69]. A recent US-based consensus provides practical considerations for differentiating between primary refractory status, loss of response, intolerance of adverse events and disease progression, with an overall agreement that no symptom improvement or reduction in spleen size, combined with progressive disease or intolerance after 3 or more months on the highest dose therapy would constitute ruxolitinib failure [70].

Higher fibrosis grades have been linked to worse prognosis, highlighting the clinical significance of BMF in MF [71]. A definitive association between disease modification and a reduction in BMF has not been characterized [72]. Emerging data from four novel therapies (imetelstat, pelasbresib, navitoclax and bomedemstat) report improvements in BMF. However, the clinical impact of these early findings has not been determined. Interpretation of BMF improvement as a surrogate for disease response is fraught with challenges, particularly when long-term survival data are not yet available. Subgroup analysis of patients in the high dose of the imetelstat Phase 2 trial showed a correlation, with significantly longer OS in patients who had a BMF improvement versus those without (HR 0.54; 95% CI, 0.23–1.29) [30]. Conversely, analysis of BMF data from the Phase 3 SIMPLIFY-I trial reported an improvement in BMF by at least 1 grade in around 20% of JAKi-naïve patients treated with ruxolitinib or momelotinib, but this was not associated with an overall survival advantage [73]. Advances in mutation profiling data have progressed the understanding of MF. While JAKi have been demonstrated to reduce JAK2 mutation burden, clonal evolution during treatment supports the need for novel therapies [74]. Preliminary findings with novel therapies in combination, with JAKi demonstrate promising results on mutation burden, but more data are needed to determine the extent to which these novel therapies can reduce MF clones and improve clinical outcomes in MF [75].

The goal in MF management is to prolong survival with good quality of life to the extent that patients are able to come off therapy. While we have not yet reached that point, the future looks much brighter. The nature and severity of underlying clinical disease-related factors directs the choice of disease modifying and supportive symptom-driven therapy in patients with MF. Current therapeutic options in symptomatic MF include a continued role for JAKi as the mainstay of therapy; with ruxolitinib or fedratinib in patients with platelet counts above 50×10^9/L, pacritinib in those with platelet counts below 50×10^9/L and momelotinib in patients who are transfusion dependent at baseline. Ruxolitinib has been shown to improve quality of life and also prolong survival [6], but has not been able to induce remission in MF. The pipeline of novel targeted therapies widens the therapeutic landscape. These novel targeted agents exploit multiple molecular pathways and offer the potential to improve the management of MF-associated cytopenia, recover BMF and, potentially modify disease activity. It remains to be seen if these newer agents, whether alone or in combination, can induce any remission in MF. Only time will tell if these agents will be best placed to replace JAKi as first-line therapy or positioned as strategic partners in rational combination regimens.

Author Contributions

Chan Tze Wei: conceptualization (equal), investigation(equal), writing–original draft (equal), writing–review and editing (equal). **Hein Than:** conceptualization(equal), investigation (equal), writing–original draft (equal), writing–review and editing (equal). **Feng-Ju Huang:** conceptualization (lead), investigation (equal), funding (lead),writing–original draft (equal), writing–review and editing (equal). **Gauri Billa:** conceptualization (equal), writing–original draft (equal), writing–review andediting (equal). **Lai Heng Lee:** conceptualization (lead), investigation (equal), writing–original draft (equal), writing–review and editing (equal).

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Ethics Statement

Ethical approval was not sought, no new datasets were generated or analyzed during the current study.

Consent

The authors have nothing to report.

Conflicts of Interest

Hein Than, Lai Heng Lee and Chan Tze Wei have no conflicts of interest to declare. Feng-Ju Huang and Gauri Billa are employees of Novartis (Singapore) Pte Ltd.

Data Availability Statement

Data sharing not applicable to this article as no new datasets were generated or analyzed during the current study.

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Transparency Declaration

All authors have read and agreed to the published version of the manuscript. The authors affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.