

# Evaluating the Safety, Efficacy, and Therapeutic Potential of Momelotinib in the Treatment of Intermediate/High-Risk Myelofibrosis: Evidence to Date

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**Abstract:** Myelofibrosis is a heterogeneous disorder with regard to both molecular pathogenesis and clinical phenotype, ranging from an initial fairly indolent condition in some through to an aggressive and debilitating scenario with profound constitutional symptoms, cytopenia frequently requiring transfusional support, and massive splenomegaly. Many advances have been made within the therapeutic arena, and an increasing array of novel agents are now available for disease management. Within this review, we focus on the current and predicted role of the JAK inhibitor momelotinib (Sierra Oncology) in myelofibrosis, with an emphasis on clinical trial evaluation, drug efficacy and safety, and discuss the suggested place in the therapeutic paradigm of myelofibrosis in 2020 and beyond.

**Keywords:** myelofibrosis, JAK inhibitors, momelotinib

## Introduction

Myelofibrosis (MF) is a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) with an estimated combined annual incidence of 0.5 per 100,000 population.<sup>1</sup> Clinicopathological features can be heterogeneous, ranging from the presence of constitutional symptoms (e.g. night sweats, weight loss and loss of appetite), variable degrees of splenomegaly and cytopenia, with significant anemia being a well-documented adverse prognostic feature, and an inherent risk of development of acute leukemia over the disease course.<sup>2-4</sup> Many advances in understanding disease pathogenesis followed the description of the somatic *JAK2*<sup>V617F</sup> mutation in MPN by four groups in 2005 and the subsequent delineation of the role of *CALR* mutations in MF and other MPNs in 2012.<sup>5-9</sup> Multiple therapeutic agent targeting, either directly or indirectly, disease-associated deregulated JAK-STAT signaling have entered the clinical arena.<sup>2</sup> At the time of writing, two JAK inhibitors — ruxolitinib (Rux; Incyte Pharmaceuticals, Wilmington, DE) and fedratinib (Inrebic; Celgene) — have US Food and Drug Administration (FDA) approval for use in MF (either first or second line), whereas in the UK Rux remains the only licensed agent to date.<sup>10</sup> Over the last decade, following the two large pivotal phase III trials COMFORT-1 and -2, Rux has certainly revolutionized the treatment of MF for many patients globally, yet there remains a growing need for effective treatments for patients who are intolerant to this agent or display resistant/refractory disease.<sup>11-13</sup> In particular, one of the biggest

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challenges in managing patients with MF is adequately addressing the significant burden associated with anemia.<sup>3</sup> Evidence suggests that anemia may be present in 40% of patients at the time of diagnosis and that up to one in four may be red cell transfusion-dependent, highlighting a significant unmet need.<sup>14</sup> In this article, we provide a comprehensive review of currently available preclinical and clinical trial data on momelotinib (Mmb; Sierra Oncology) in MF, with emphasis on drug efficacy and safety and suggested place in the therapeutic paradigm.

## Clinical Features of Myelofibrosis and Prognostic Scores for Therapeutic Stratification

As stated, MF is a heterogeneous disease and can present either de novo, termed primary MF, or following antecedent essential thrombocythemia (ET) or polycythemia vera (PV), termed post-ET MF (PET-MF) and post-PV MF (PPV-MF), respectively. The clinical phenotype can vary markedly, with some patients displaying no symptoms through to those with debilitating constitutional symptoms, problematic splenomegaly, cytopenia and risks of both thrombosis and hemorrhage. Therapeutic decisions are frequently made upon considering both clinical features and assigned prognostic group. Commonly used prognostic scores within the clinical setting include the International Prognostic Scoring System (IPSS) for PMF, applied at the time of diagnosis and based upon five factors influencing survival: age >65 years, presence of anemia with hemoglobin <100 g/L, white blood-cell count >25×10<sup>9</sup>/L, presence of constitutional symptoms, and peripheral blood blasts ≥1%.<sup>15</sup> This permits delineation of four distinct groups: low risk (0 risk factors, median survival 135 months), intermediate risk 1 (one risk factor, median survival 95 months), intermediate risk 2 (two risk factors, median survival 48 months), and high risk (three or more risk factors, median survival of 27 months). Subsequent refinements have occurred with the Dynamic IPSS (DIPSS; allows prognostication at any time in the disease course of PMF and gives more adverse prognostic weighting to the presence of anemia) and DIPSS-plus prognostic scoring, which includes three additional adverse prognostic factors: presence of thrombocytopenia (platelets <100×10<sup>9</sup>/L), red cell-transfusion dependence and adverse karyotype.<sup>16,17</sup> Forward-thinking scores have also been developed based on the presence of conventional risk factors and extended molecular screening and/or karyotypic abnormalities, such as the mutation-enhanced IPSS (MIPSS70) version 2.0 and the genetically inspired prognostic

score (GIPSS).<sup>18,19</sup> With regard to PET-MF and PPV-MF, the myelofibrosis secondary to PV and ET-prognostic model (MYSEC-PM) permits classification into four groups with markedly different survival estimates.<sup>20</sup> Summaries of these scores are highlighted in Table 1. Lastly, individualized scores have also been developed based upon clinical factors and comprehensive genomic characterization that can more accurately predict personalized outcomes.<sup>21</sup>

## Anemia in Myelofibrosis: Extent of the Problem

Evidence suggests that approximately 40% of MF patients are anemic at diagnosis and almost 25% red cell transfusion-dependent.<sup>14</sup> As the disease progresses, anemia can become more prominent, either through a direct consequence of the progression or indeed the therapies used. The etiology of the anemia is frequently multifactorial, resulting from impaired erythropoiesis because of a hostile and fibrotic marrow microenvironment, increased red blood cell (RBC) turnover, and sequestration due to splenomegaly and a proinflammatory milieu that disrupts normal erythropoiesis.<sup>3</sup> Moreover, in MF there is upregulated expression of hepcidin, which abrogates normal iron metabolism and utilization.<sup>22</sup> Recent studies have additionally suggested an association between the presence of *U2AF*-spliceosome mutations and MF-related anemia.<sup>4</sup> Management strategies for anemia are varied and dependent on disease stage, degree of anemia, patient age, performance status, baseline endogenous erythropoietin levels, and available therapies. Frequently, those with significant anemia require RBC transfusions on a regular basis, with the inherent risk of alloimmunization, transfusion-related complications, and iron overload. Transfusion dependence has been shown to be an independent adverse prognostic factor, as already discussed.<sup>17</sup> Erythropoiesis-stimulating agents have a role in some patients, and appear more effective in those with MF-associated anemia who are RBC transfusion-independent and have low serum erythropoietin (<125 U/L) levels, albeit responses are often heterogeneous and unpredictable.<sup>3,23,24</sup>

Erythropoiesis-stimulating agents have also been combined with Rux, both in the COMFORT-2 trial and in a non-trial setting.<sup>25</sup> Immunomodulatory agents, such as lenalidomide and thalidomide, have been tried with limited success, additionally compromised by toxicities or myelosuppression, and low-dose pomalidomide, albeit initially of great interest in this area, failed to show significant benefit over placebo in a large phase III study in MF with RBC-transfusion

**Table I** Summary of prognostic scores for therapeutic stratification in MF

Assigned number of points for individual risk factors, according to each risk score								
Risk factors	IPSS <sup>15</sup>	DIPSS <sup>16</sup>	DIPSS-Plus <sup>17</sup>	MIPSS70 <sup>18</sup>				
Age >65 years	1	1	1	1.5§				
Hemoglobin <100 g/L	1	2	1	0.5				
Leukocyte count >25×10 <sup>9</sup> /L	1	1	1	NA				
Circulating blasts ≥1%	1	1	1	NA				
Presence of constitutional symptoms*	1	1	1	0.5				
Unfavourable cytogenetics <sup>#</sup>	NA	NA	1	NA				
Red cell–transfusion need	NA	NA	1	NA				
Platelet count <100×10 <sup>9</sup> /L	NA	NA	1	NA				
Platelet count <200×10 <sup>9</sup> /L	NA	NA	NA	1				
Triple negativity	NA	NA	NA	1.5				
<i>JAK2/MPL</i> mutation	NA	NA	NA	0.5				
<i>ASXL1</i> mutation	NA	NA	NA	0.5				
<i>SRSF2</i> mutation	NA	NA	NA	0.5				
Risk categorization and median survival								
Risk	IPSS	Median survival	DIPSS	Median survival	DIPSS-plus	Median survival	MIPSS	Median survival
Low	0	11.3	0	NR	0	15.4	0–0.5	26.4
Int-1	1	7.9	1–2	14.2	1	6.5	1–1.5	9.7
Int-2	2	4	3–4	4	2–3	2.9	2–3.5	6.4
High	≥3	2.3	5–6	1.5	≥4	1.3	≥4	1.9

**Notes:** \*Fever, night sweats, weight loss >10% from baseline; <sup>#</sup>+8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), 11q23 rearrangement; §age >60 years for MIPSS.

**Abbreviations:** Int-1, intermediate-1; Int-2, intermediate-2; NR, not reached.

dependence.<sup>26–28</sup> Danazol is an androgenic steroid effective in approximately 30% of MF patients with anemia. Response rates, however, are slow (median time to response is on average 5 months), less common in the presence of RBC dependency, and appropriate monitoring for potential toxicity is mandated.<sup>29</sup> Novel agents in clinical trials, such as the oral BET inhibitor CPI-0610 (Constellation Pharmaceuticals), alone or in combination with Rux, has demonstrated hemoglobin responses alongside spleen/symptom responses, and the erythroid maturation agent luspatercept (Celgene) has demonstrated clinically significant anemia responses in a proportion of MF patients in an ongoing phase II study. Final results from these trials are awaited with interest.<sup>30–32</sup> As will be discussed, Mmb has a specific role in the field of MF management in that it can address the three main hallmarks of the disease: splenomegaly, symptom burden, and potentially MF-associated anemia.

## Pre- and Early Clinical Characterization of Momelotinib

Mmb, previously known as CYT387 (*N*-(cyanomethyl)-4-[2-[[4-(4-morpholinyl)phenyl]amino]-4-pyrimidinyl]-

benzamide), is an aminopyrimidine-derivative ATP-competitive small-molecule inhibitor of JAK1 and JAK2, with IC<sub>50</sub> values of 11 and 18 nM, respectively. The IC<sub>50</sub> for JAK3 is approximately nine times that. Early preclinical characterization more than a decade ago showed that Mmb inhibited in vitro growth of Ba/F3-*JAK2*<sup>V617F</sup>, human erythroleukemia (HEL) cells and Ba/F3-*MPL*<sup>W515L</sup> cells and induced dose-dependent decreases in both STAT3 and STAT5 phosphorylation.<sup>33</sup> Moreover, Mmb effectively inhibited growth of erythroid colonies containing the *JAK2*<sup>V617F</sup> mutation in vitro derived from patients with PV. Tyner et al demonstrated efficacy in a murine model of MPN (irradiated BALB/c mice were transplanted with marrow transduced with a *JAK2*<sup>V617F</sup> retrovirus) showing normalization of white blood-cell counts, reductions in splenomegaly, and extramedullary hematopoiesis coupled with modulation of proinflammatory cytokines.<sup>34</sup> Focusing on erythroid responses, Asshoff et al investigated the erythroid-specific effects of Mmb in a group A streptococcal peptidoglycan-polysaccharide fragment-induced rat model of chronic anemia and found both an increase in RBC numbers and normalization of hemoglobin values.<sup>35</sup> Mmb mediates these effects through

inhibition of the BMPR kinase ACVR1, a member of the TGF $\beta$  superfamily of receptors, with resultant decreased hepcidin production from the liver and increased iron availability, and hence stimulates erythropoiesis. Two phase I open-label adaptive studies investigated the pharmacokinetics of a single dose of Mmb 200 mg administered orally in those with impaired hepatic or renal function compared to matched healthy controls.<sup>36</sup> There was no clinically significant difference in plasma exposure of Mmb and its main active metabolite between healthy controls and those with either moderate hepatic impairment or moderate/severe renal impairment. However, for severe hepatic impairment, Mmb plasma exposure was increased compared to healthy control subjects, and consideration of dose/avoidance would be necessitated.

## Clinical Trial Data of Momelotinib in Myelofibrosis: What Do We Know and Where Are We Going?

The first trial investigating the utility of Mmb in MF was an open label nonrandomized phase I/II study performed in two parts: part 1 was a dose-escalation study (n=60 patients) to confirm the therapeutic dose, pharmacokinetic behavior and efficacy of Mmb with a second phase enrolling a further 106 patients across multiple centers in the dose confirmation phase of the trial.<sup>37</sup> All patients had intermediate 2 or high-risk MF, with some intermediate-1-risk patients included with symptomatic splenomegaly or those who had failed other available therapies. A total of 52 (87%) patients completed phase I of the trial, receiving at least nine cycles of Mmb. The median age was 65 (range 34–85) years and median hemoglobin level 94 (range 71–144) g/L. In the initial report, only six patients had discontinued the trial due to adverse events (AEs) within this period, with only one felt to be related to the trial medication and two patients for lack of response. Five patients died during the trial, none of the causes being related to the trial medication. Within the early stages of the dose escalation, it was found that both the 150 mg (n=18) and 300 mg (n=21) doses were “biologically effective” and hence brought forward for the remaining patients enrolled to the study. A total of 52 patients were assessable for spleen response: 25 patients (48%) achieved a spleen response as per International Working Group–Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria, with no differences between the two dose groups (300 mg versus 150 mg daily). There

were demonstrable improvements in anemia in those evaluable (n=41), with many transfusion-dependent patients becoming transfusion-independent on IWG-MRT criteria. Median duration of transfusion independence at data cutoff was 9.6 months, with ongoing responses. Of note, there was no significant difference in transfusion responses between the 150 mg and 300 mg doses. Dose-linear  $C_{max}$  and area under the curve were observed for both the 150- and 300 mg/day doses. Dizziness (mostly grade 1) was seen in approximately a quarter of patients within the first hour of initiating Mmb, on some occasions associated with postural hypotension, but symptoms commonly resolved spontaneously within a few hours. Subsequent management strategies included “holding” antihypertensive therapies the day prior to commencing dosing and encouraging good oral hydration. No correlation existed between this symptom and dose administered. Gastrointestinal AEs were mild, frequently ranging from grade 1–2, and often self-limiting (incidence of nausea 18%, diarrhea 13%), requiring no dose reductions. In terms of hematologic AEs, thrombocytopenia was the most commonly reported, with 32% grade 3/4, particularly for those with platelet count  $<100 \times 10^9/L$ , while treatment-related anemia and neutropenia were not common, affecting two and three patients, respectively, at grade 3/4 severity. Non hematologic grade 3 or 4 AEs included increased aspartate aminotransferase (3%) and alanine aminotransferase (3%) levels, headache (3%), and hyperlipasemia (5%). Of particular note, 16 patients (27%) reported neurological symptoms, with 13 having new-onset peripheral neuropathy and three worsening of pre-existing neuropathy. Median time to development of reportable peripheral neuropathy was 141 days. Interestingly, half the affected patients had complete resolution of neuropathy despite continuing Mmb therapy, although 38% with neuropathy required dose reduction or treatment discontinuation. Subsequent updated analyses looked at patients both in the core study and enrolled in the extension phase with a data cutoff in February 2015.<sup>38</sup> Overall, 124 (75%) patients completed the core study and 120 enrolled in the extension study. Median age was 67 years and approximately two-thirds had PMF. During the course of the core/extension phase, of 111 anemia response-evaluable patients, 75% of transfusion-dependent patients achieved transfusion independence and 28.2% with hemoglobin  $<100$  g/L achieved a hemoglobin response, indicating the beneficial response for those with MF-associated anemia.

Tefferi et al subsequently reported long term (7-year) follow-up of 100 patients (64 with primary MF, 22 PPV-MF, and 14 PET-MF; median age 66 years) who had been treated with Mmb during 2009–2010 in the aforementioned phase I/II study.<sup>39</sup> Distribution of the cohort across DIPSS-plus risk stratification was 63% high risk, 36% intermediate 2, and 1% intermediate 1 risk. As of July 2017, treatment had been discontinued in 91% of patients after a median treatment duration of 1.4 (range 0.02–6.2) years. Clinical improvements occurred in 57% of those treated, with 44% gaining an anemia response and a similar proportion a spleen response, which were more likely to occur in the absence of *ASXL1* mutations and with circulating blasts <2%. Most frequent reasons for Mmb discontinuation were suboptimal response and progressive disease. Seven patients discontinued due to peripheral neuropathy, and overall grade 1/2 peripheral neuropathy was reported in 47% of the cohort. Of note, a comparative analysis of the Mmb-treated cohort with a similar risk-matched MF cohort did not reveal significant differences in overall survival. A summary of clinical trial outcomes and safety issues is given in [Tables 2 and 3](#).

## SIMPLIFY-1

SIMPLIFY-1 (S1) was a randomized double-blind phase III trial that compared Mmb to Rux in JAK inhibitor-naïve patients with intermediate 2, high-risk, or symptomatic intermediate-risk 1 disease.<sup>40</sup> There was 1:1 allocation to either treatment arm, with 214 patients receiving Mmb 200 mg once daily and 216 receiving Rux 20 mg twice a day (dosing could be modified according to license). Patients in the Rux cohort had the opportunity to switch to open-label Mmb therapy at 24 weeks. The primary end point was spleen-volume reduction (SVR)  $\geq 35\%$  from baseline at 24 weeks, and four secondary end points were analyzed: total symptom score (TSS) response rate, RBC transfusion-independence rate (proportion of patients transfusion-independent at week 24), RBC transfusion-dependence rate, and rate of RBC transfusion (average RBC units per subject-month during treatment). Treatment discontinuations were 18.6% (Mmb) and 7.4% (Rux). At week 24, 184 Mmb and 204 Rux patients had spleen volume assessment: 26.5% of the Mmb group and 29% of the Rux group (noninferior;  $p=0.011$ ) achieved this end point, and thus with regard to SVR Mmb was noninferior to Rux. In contrast, with regard to TSS response at week 24, fewer patients in the Mmb arm (28.4%) than the Rux arm (44.2%) achieved a reduction in TSS of  $\geq 50\%$  from baseline. Initial analyses demonstrated

the potential benefit of Mmb for anemia: at week 24, 66.5% of patients in the Mmb cohort were transfusion-independent compared to 49.3% of those in the Rux cohort (nominal  $P<0.001$ ), and the median rate of RBC transfusion was 0 units/month in the Mmb group compared with 0.4 units/month in the Rux group (nominal  $P<0.001$ ). Although Mmb did not meet the TSS end point with regard to Rux non-inferiority, the proportion of patients who achieved the collective end points of SVR  $\geq 35\%$ , TSS  $\geq 50\%$ , and transfusion independence was slightly higher in the Mmb (10.2%) than the Rux (7.8%) group.

Updated analyses presented at the American Society of Hematology meeting in 2019 investigated further novel anemia endpoints, recognising the clinical importance of hemoglobin responses and transfusion independence within this cohort of MF patients. For Mmb and Rux, the proportion of patients receiving  $\leq 4$  RBC units was 83% and 62% ( $p<0.0001$ ), respectively, and analyses revealed that Mmb increased the odds of having zero units transfused by a factor of 9.3 versus Rux ( $P<0.0001$ ).<sup>41</sup> Relative transfusion events between groups were analysed by Kaplan–Meier estimates of time to first, third, and fifth RBC units. An immediate and sustained Mmb effect compared to Rux was identified with regard to time to first transfusion (log-rank  $P<0.0001$ ). First-dose effects were reported in both groups, with 14 patients (6.5%) in the Mmb group and two (0.9%) in the Rux group experiencing these. Symptoms included hypotension, dizziness, flushing, nausea, or headache, either in isolation or combination. All episodes were grade 1 or 2, excluding one grade 3 event reported in a patient receiving Mmb that required dose reduction. Only 25% of patients receiving Mmb had AEs of grade  $\geq 3$  compared to 43.5% of those receiving Rux, albeit 13.1% of the Mmb cohort had AEs requiring drug discontinuation compared to 5.6% in the Rux cohort. There was no statistical significance detected between the cohort arms with regard to leukemic transformation or death. Peripheral neuropathy was reported in both groups, with 28 events in the Mmb arm and eleven in the Rux arm, all graded as grade 1 or 2, with the exception of one grade 3 sensory neuropathy reported in a patient receiving Rux. There was no indicated need for discontinuation as a result of peripheral neuropathy in any cases at the time of study report.

## SIMPLIFY-2

SIMPLIFY-2 was a multinational phase III open-label trial comparing Mmb with best alternative therapy (BAT) in MF

**Table 2** Summary of clinical trials using momelotinib in management of MF

Phase	Trial	Patients enrolled (n)	Description and objectives	Outcome measures	Outcomes	Ref
I/II	NCT00935987	166	Open-label, dose-escalation study evaluating the safety and efficacy of CYT387, a JAK1 and JAK2 inhibitor	<p><b>Primary</b></p> <ol style="list-style-type: none"> <li>Safety and tolerability (dose-limiting toxicities) and maximum tolerated dose up until 30 days after the last dose of CYT387</li> <li>Objective response rate measured as complete response, partial response, or clinical improvement</li> <li>Pharmacokinetics of CYT387 (baseline to end of cycle 1)</li> </ol> <p><b>Secondary</b></p> <ol style="list-style-type: none"> <li>Effect of CYT387 on:                             <ol style="list-style-type: none"> <li>Bone marrow or peripheral blood cytogenetics (assessed at the end of every third cycle)</li> <li>Peripheral blood-granulocyte JAK2<sup>v617F</sup> - allele burden (assessed at the end of each cycle of therapy)</li> <li>Peripheral blood endogenous myeloid-colony formation (from baseline to study completion)</li> <li>Plasma levels of inflammatory fibrogenic and angiogenic cytokines (baseline to study completion)</li> </ol> </li> <li>Pharmacodynamic correlates of CYT387 activity in patients with PMF or PET/PPV MF</li> </ol>	<p><b>Primary</b></p> <ul style="list-style-type: none"> <li>Dose-linear C<sub>max</sub> and exposure observed between the 150 and 300 mg/day doses, with mean elimination t<sub>1/2</sub> 3.9–6.1 hours</li> <li>None of the patients had peripheral blood that qualified as complete response, so bone-marrow biopsies were not performed</li> </ul> <p><b>Secondary</b></p> <ul style="list-style-type: none"> <li>Change in IL1RA and -Iβ associated with transfusion-independent response</li> <li>Spleen response was significantly associated with IL1RA, IL1β, IL2, bFGF, TNFα, MIP1β</li> <li>Treatment-associated decrease in cytokine levels associated with anemia ± spleen response</li> <li>Dominant cluster of overexpressed genes identified in anemia responders vs nonresponders</li> </ul>	37
I/II	NCT00935987 7-year follow-up	100	Seven-year follow up of phase I/II study of patients with MF being treated with CYT387	<p><b>Primary</b></p> <p>Effect of Mmb on overall and leukemia-free survival</p> <p><b>Secondary</b></p> <p>Impact of driver and other mutations on response rates, leukemia-free survival and relapse-free survival</p>	<p><b>Primary</b></p> <p>73% of deaths occurred at a median of 2.5 years and 15% leukemic transformations occurred at median of 3.6 years</p> <p>At publication of results, 27% of patients were alive with median of 6.6 years from entering the study.</p> <p><b>Secondary</b></p> <p>Median treatment time with Mmb 1.4 years: clinical improvement in 57% of patients, with 43% achieving anemia response and 43% receiving spleen response</p> <p>Clinical improvement (CI) more likely to occur in ASXL1-unmutated patients and those with circulating blast count &lt;2%</p> <ul style="list-style-type: none"> <li>CI not influenced by mutational status, DIPSS-plus risk, SRSF2 mutations, abnormal or unfavorable karyotype, prior JAK2-inhibitor therapy, leukocyte count, platelet count, or spleen size</li> </ul>	39

III	SIMPLIFY-1 NCT01969838	432	An international randomized, double-blind, double-dummy, controlled study of Mmb versus Rux in subjects who were JAK kinase inhibitor-naïve with MF 215 patients received Mmb 217 patients received RUX	<p><b>Primary</b> Splenic response rate at 24 weeks: proportion of participants achieving ≥35% splenic volume reduction at week 24 on MRI or CT scan</p> <p><b>Secondary</b> 1. Response in TSS: proportion of patients achieving ≥50% reduction in TSS at week 24 2. Rate of RBC transfusion/Average number of RBC units transfused per participant per month throughout 24-week period 3. RBC-transfusion independent/Proportion of patients transfusion-independent at week 24 (absence of RBC transfusions and no hemoglobin levels &lt;8 g/dL in prior 12 weeks) 4. RBC transfusion-dependence rate/Proportion of patients transfusion-dependent at week 24 (defined as at least four units RBC transfusions, or hemoglobin &lt;8g/dL in prior 8 weeks) In addition to above, SIMPLIFY-2 also assessed total spleen response as a fifth secondary outcome</p>	<p><b>Primary</b> Mmb noninferior to Rux and spleen-response rate had 34% reduction from baseline</p> <p><b>Secondary</b> 1. Only 28.4% of patients taking Mmb reported a reduction in TSS score ≥50% from baseline compared to 42.2% of patients in Rux arm, so Mmb was inferior to Rux in symptom response 2. Median rate of RBC transfusions at week 24 was 0 units/month in the Mmb group compared to 0.4 units/month in the Rux group 3. 66.5% taking Mmb were transfusion-independent by week 24 compared to 29.3% taking Rux 4. 30.2% of patients taking Mmb were transfusion-dependent by week 24 compared to 40.1% of patients taking Rux</p>	40
III	SIMPLIFY-2 NCT02101268	156	International open-label randomized controlled trial comparing the efficacy of Mmb versus best-available therapy in anemic and thrombocytopenic patients with PMF or post-PV/ET MF treated with RUX 104 patients received Mmb 52 received BAT (ruxolitinib 89%)	<p><b>Primary</b> Mmb noninferior to Rux for reduction in spleen size by at least 35% from baseline via CT or MRI assessment</p> <p><b>Secondary</b> 1. 27 (26%) patients receiving Mmb had a total reduction in TSS ≥50% from baseline, compared to 3 (6%) on BAT (p=0.0006). 2. Median rate of RBC transfusion was 0.5 units per month for Mmb group compared to 1.2 units in BAT group (P=0.39) 3. 42 (40%) Mmb patients did not need transfusion during the 24 weeks compared with 14 (27%) patients receiving BAT 4. 33 (64%) patients receiving Mmb were transfusion-dependent by week 24 compared with 52 (50%) receiving BAT (P=0.1)</p>	<p><b>Primary</b> Mmb noninferior to Rux for reduction in spleen size by at least 35% from baseline via CT or MRI assessment</p> <p><b>Secondary</b> 1. 27 (26%) patients receiving Mmb had a total reduction in TSS ≥50% from baseline, compared to 3 (6%) on BAT (p=0.0006). 2. Median rate of RBC transfusion was 0.5 units per month for Mmb group compared to 1.2 units in BAT group (P=0.39) 3. 42 (40%) Mmb patients did not need transfusion during the 24 weeks compared with 14 (27%) patients receiving BAT 4. 33 (64%) patients receiving Mmb were transfusion-dependent by week 24 compared with 52 (50%) receiving BAT (P=0.1)</p>	41

(Continued)

Table 2 (Continued).

Phase	Trial	Patients enrolled (n)	Description and objectives	Outcome measures	Outcomes	Ref
III	MOMENTUM NCT04173494	180	A randomized, double-blind trial comparing Mmb to Danazol in symptomatic, anemic patients who had previously JAK inhibitor-treated PMF, P-PV/ET MF	<p><b>Primary</b> Proportion of patients achieving <math>\geq 50\%</math> reduction in TSS over the 28 days immediately prior to the end of week 24 compared to baseline</p> <p><b>Secondary</b> I. Transfusion independence Proportion of patients transfusion-independent at week 24 (defined as not needing RBC transfusion for <math>\geq 12</math> weeks prior to the end of week 24 and Hb <math>\geq 8</math> g/dL I. Splenic response rate Proportion of patients with splenic reduction <math>\geq 25\%</math> from baseline at week 24</p>	Study ongoing	NA

Abbreviations: JAK, janus kinase; Mmb, momelotinib; Rux, ruxolitinib; RBC, red blood cell; PMF, primary MF; PV, polycythemia vera; ET, essential thrombocythemia; TSS, total symptom score; BAT, best alternative therapy; MRI, magnetic resonance imaging.

patients who had previously received at least 28 days of Rux therapy and had either required red blood-cell transfusions while receiving Rux (defined as  $\geq 4$  units of RBCs or hemoglobin  $< 8$  g/dL in the 8 weeks prior to randomization) or a dose reduction to  $< 20$  mg twice daily with at least one of grade 3 anemia, thrombocytopenia, hemorrhage at least grade 3, an absence of grade 2 or greater peripheral neuropathy, and a spleen that was at least 5 cm palpable below the costal margin.<sup>42</sup> Those with previous splenectomy, had undergone splenic irradiation, or who had a concomitant uncontrolled concurrent illness were ineligible. Stratification prior to randomization included evaluation of transfusion requirements and degree of symptom burden assessed by the TSS. A 2:1 randomization (Mmb:BAT) was applied to 24 weeks therapy of either 200 mg once daily Mmb or BAT (which could include multiple agents including RUX), and after this period all patients were able to receive extended access to Mmb.

Of note, in the original protocol there was no designated washout period from the previous therapy. The primary end point was SVR  $\geq 35\%$  from baseline at 24 weeks. A total of 156 patients were recruited (Mmb 104 and BAT 52), and in the BAT arm 46 patients (89%) received Rux, with 14 of these receiving Rux in combination with another therapy (e.g. hydroxycarbamide), this being many more individuals on Rux in the BAT that had been anticipated. A total of 73 patients in the Mmb cohort and 40 in the BAT cohort completed the 24-week therapy phase. Median Mmb exposure was 23.9 weeks. At the 24-week analysis, Mmb was not shown to be superior to BAT for achieving SVR  $\geq 35\%$  from baseline: only seven (Mmb) and three (BAT) patients achieved this end point. Of note, all responders in the BAT group were receiving Rux. Most common grade 3/4 AEs were anemia and thrombocytopenia. Other AEs in the Mmb cohort included peripheral neuropathy, occurring in 11%, with one patient having grade 3 peripheral neuropathy. For reductions in TSS, 26% of patients in the Mmb cohort had  $> 50\%$  reduction in TSS compared to only 6% in the BAT cohort. In each group,  $> 50\%$  of patients were transfusion-dependent, and importantly, at week 24 more patients in the Mmb arm were transfusion-independent than the BAT arm (43% versus 21%,  $P=0.0012$ ). Therefore, in conclusion, although the primary end points were not reached, Mmb displayed efficacy in amelioration of symptoms, improved anemia responses, and less red blood-cell transfusion need. Longer-term efficacy data are currently being analyzed.



**Table 3** Summary of momelotinib safety from clinical trials

Trials		7-year follow-up NCT00935987	SIMPLIFY-1 NCT01969838	SIMPLIFY-2 NCT02101268
≥ Grade 3 hematologic adverse event	NCT00935987	<ul style="list-style-type: none"> <li>Thrombocytopenia (24%)</li> <li>Neutropenia (9%)</li> <li>Anemia (5%)</li> <li>Hyperlipasemia (7%)</li> <li>Increased ALT (4%)</li> <li>Increased AST (2%)</li> <li>Headache (2%)</li> <li>Increased ALP (2%)</li> </ul>	<p>Mmb vs Rux</p> <ul style="list-style-type: none"> <li>Thrombocytopenia (7% vs 4.6%)</li> <li>Anemia (5.6% vs 23.1%)</li> <li>Neutropenia (2.8% vs 4.6%)</li> <li>Hypertension (2.8% vs 4.2%)</li> </ul>	<p>Mmb vs BAT</p> <ul style="list-style-type: none"> <li>Thrombocytopenia Seven (7%) vs three (6%)</li> <li>Anemia 14 (14%) vs seven (14%)</li> </ul> <p>Mmb vs BAT</p> <ul style="list-style-type: none"> <li>Abdominal pain One (1%) vs 3 (6%)</li> </ul>
≥ Grade 3 nonhematologic adverse event	NCT00935987	<ul style="list-style-type: none"> <li>Hyperlipasemia (5%)</li> <li>Increased ALT (3%)</li> <li>Increased AST (3%)</li> <li>Headache (3%)</li> </ul>	<p>Mmb vs Rux</p> <p>4.6% of patients had at least grade 3 diarrhea</p> <p>Treatment-emergent adverse events occurring in &gt;10% included nausea (34%), abdominal pain (22%)</p>	<p>Mmb vs BAT</p> <ul style="list-style-type: none"> <li>Diarrhea 32 (31%) grade 1/2, two (2%) grade 3 vs 7 (14%) grade 1/2, one (2%) grade 3</li> <li>Nausea 18 (17%) grade 1/2, two (2%) grade 3 vs four (8%) grade 1/2, one (2%) grade 3</li> <li>Abdominal pain 15 (14%) grade 1/2 and one (1%) grade 3 vs five (10%) grade 1/2 and three (6%) grade 3</li> <li>Constipation 12 (12%) vs two (5%), both grade 1/2</li> </ul>
Gastrointestinal side effects	NCT00935987	<p>All grade 1 or 2:</p> <p>Nausea (23%)</p> <p>Diarrhea (20%)</p> <p>Increased amylase (17%)</p>	<p>Mmb arm: PN noted in 22 patients (10.3%) with 28 adverse events compared to ten patients (4.6%) with eleven adverse events in Rux arm. Two patients receiving Mmb reported PN at baseline compared to one patient receiving Rux.</p> <p>All adverse events were grade 1–2, except for one episode of peripheral sensory neuropathy in Rux arm. PN did not lead to discontinuation of treatment.</p> <p>PN was most commonly reported as peripheral sensory neuropathy, with peripheral motor neuropathy occurring only with Mmb.</p>	<p>15 events of peripheral neuropathy reported in eleven (11%) of patients, all grade 1 or 2, except one case of grade 3 in patients receiving Mmb, two of whom had PN at baseline, compared to 0 patients in BAT group. Three (3%) patients discontinued Mmb due to PN (one resolved case of sensory neuropathy, one ongoing case of peripheral sensorimotor neuropathy, and one case of polyneuropathy).</p>
Peripheral neuropathy (PN)	NCT00935987	<p>Seven patients (15%) 47% had grade 1 or 2 peripheral neuropathy</p>	<p>26% Mmb arm compared to 56% Rux arm needed dose reductions or interruptions (most commonly for adverse events — 17.3% and 25.6%, respectively).</p>	<p>60 (58%) patients receiving Mmb required dose reduction. Discontinuation of BAT was inconsistently reported, due to changes in therapy or intentional no therapy options available for this group.</p>
Dose reductions	NCT00935987	<p>Not discussed in study</p>	<p>16 patients (33%) needed dose reduction, occurring more frequently in patients receiving 300mg than those receiving 150mg. Five patients needed dose reductions due to peripheral neuropathy. There was no clear pattern identified during analysis of adverse events for the remainder.</p>	

(Continued)

**Table 3 (Continued).**

Trials		SIMPLIFY-1 NCT01969838		SIMPLIFY-2 NCT02101268	
	NCT00935987	7-year follow-up NCT00935987			
Dose-limiting toxicities	Grade 3 headache (n=1) Grade 3 hyperlipasemia (n=1) Both reversible on drug discontinuation	Grade 3 headache Grade 3 hyperlipasemia	Reported for 17.8% in Mmb arm and 36.6% in Rux arm	17 (16%) patients receiving Mmb needed dose reduction. Nine (17%) PN patients receiving BAT needed dose reduction due to adverse events.	
Acute leukemic transformation	Not discussed in study	On study: three leukemic transformations During 7-year follow-up, 15 patients had leukemic transformations occurring at median of 3.6 years	Mmb: one patient (grade 4) Rux: two patients (grades 3 and 5)	Mmb: two patients grade 5, one patient grade 4 BAT: one patient grade 1	
Death	Total five deaths, none related to CYT387	On-study deaths: 15 patients During 7-year follow-up: 73 deaths occurring at median of 2.5 years From time of study is 3.2 years, with 5-year survival of 30%	At reported follow-up: Mmb: seven deaths (3.3%) Rux: seven deaths (3.2%)	At reported follow-up: Mmb group: six patients (6%) had died, with two possibly related to Mmb therapy Rux arm: four patients (7%) had died, not related to treatment	
Reference	37	39	40	42	

**Abbreviations:** JAK, janus kinase; Mmb, momelotinib; RBC, red blood cell; BAT, best alternative therapy; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PN, peripheral neuropathy.

## Ongoing Studies: MOMENTUM

MOMENTUM is a multinational phase III trial aiming to confirm the efficacy of Mmb in comparison to danazol in addressing splenomegaly, symptoms, and MF-associated anemia in MF patients who have previously been treated with JAK inhibitors. Patients will be randomized 2:1 between Mmb and danazol, and after 24 weeks of therapy, patients enrolled on the danazol arm will be permitted to cross over to Mmb. The primary end point is TSS reduction at week 24, and secondary end points include 24-week splenic response rates, patient-reported measures of fatigue and physical function, transfusion-independence rates and other anemia end points, such as transfusion-dependence responses, cumulative transfusion burden, and duration of TSS responses at week 48. Planned recruitment is 180 patients globally, with top line data expected in late 2021, and results are eagerly awaited.

## Conclusion

Mmb is a potent JAK1, JAK2, and ACVR1 inhibitor, an attribute that potentially places it in a novel position with competing JAK-inhibitor compounds. Clinical trials to date have suggested that Mmb can not only address MF-associated splenomegaly and symptoms but also has a clear and consistent signature of anemia responses via profound inhibition of the hepcidin–ACVR1 axis. However, despite these findings, the two large phase III trials SIMPLIFY-1 and SIMPLIFY-2 just failed to meet their primary clinical end points, and hence the drug remains unlicensed at present. The FDA, however, granted fast-track designation to Mmb in June 2019, recognizing the potential benefits of this agent. It is important to note that in SIMPLIFY-1, Mmb was associated with clinically significant anemia and transfusion-independence responses and higher response rates for the collective end point of SVR, TSS reduction, and anemia response than Rux. Moreover, the end points may have been somewhat limited by the 24-week duration, and hence extended exposure may demonstrate differential efficacy. Hemoglobin responses were additionally evident in those initially treated with Rux who subsequently switched to Mmb. With regard to overall tolerability, side-effect profile and safety of Mmb, clinical trial data suggest clinicians and patients alike need to be aware of the risk of first-dose hypotension, with some patients additionally noting headache, dizziness, or flushing following dosing. Low-grade gastrointestinal side effects, such as nausea and diarrhea, may be apparent. Mmb-related transaminitis may occur,

and serum amylase and lipase levels can rise in the absence of clinical pancreatitis. Clinicians should additionally be aware of the potential risk of low-grade peripheral neuropathy — frequently grade 1 — which is predominantly sensory in nature.

It appears to date that unlike Rux for some patients, Mmb-dose intensification and exposure is not as limited by myelo-suppression, potentially allowing sustained dose intensification for a longer period across the MF continuum, but this requires confirmation and is currently undergoing evaluation. There remains an unmet need for patients who fail initially to respond to Mmb, those who have an initial response but subsequently become intolerant or resistant, and those who have to stop the drug due to AEs. Mitigating these issues will only evolve as clinical experience grows. For many patients with MF-associated anemia for whom current treatment options may be limited, a role for Mmb is clear. Dependent on results from the MOMENTUM study, potential may arise in future to use Mmb not only as a sole agent but also in combination with other agents, such as antifibrotics, checkpoint inhibitors and BET inhibitors, to name but a few potential strategies.

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