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Real world outcomes of momelotinib in myelofibrosis patients with anemia: results from the MOMGEMFIN study

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Standard treatment for symptomatic myelofibrosis (MF) patients includes JAK inhibitors (JAKi) like ruxolitinib and fedratinib [1–4], but their effectiveness is often limited by transient responses and the development of cytopenias [5]. Recently, momelotinib received FDA and EMA approval for treating splenomegaly and disease-related symptoms in adult patients with MF and anemia. In addition to JAK1/JAK2 inhibition, momelotinib targets the activin A receptor type 1 (ACVR1), which regulates iron metabolism through hepcidin, contributing to its unique therapeutic profile [6]. The efficacy of momelotinib in improving symptoms, reducing spleen size, increasing hemoglobin (Hb) levels, and reducing transfusion dependency in both JAKi naïve and JAKi exposed MF patients has been demonstrated in several clinical trials [7–11].

Given its recent approval, real-world data on momelotinib use is still limited. To gather evidence on its efficacy and safety in routine practice, the Spanish Group of Philadelphia-negative Myeloproliferative Neoplasms (GEMFIN) initiated the MOMGEMFIN study, analyzing MF patients treated with momelotinib through a managed access program.

This study was a multicenter, retrospective analysis of adult patients treated with momelotinib (JAK-naïve or JAK-exposed) from March 2023 to July 2024. Eligible participants had primary or secondary MF with anemia and disease-related symptoms or symptomatic splenomegaly. Anemia was defined as Hb values less than 11 g/dL for men and less than 10 g/dL for women. Anemia response was based on the 2024 IWG-ELN criteria [12]. Transfusion dependency was classified as requiring at least one red blood cell (RBC) unit per month or three or more units over 12 weeks. Spleen evaluation followed the 2013 ELN (IWG-MRT) criteria [13]. Adverse events (AEs) were graded per CTCAE version 5.0.

A total of 154 patients from 74 centers were included, with a median age of 73 years at momelotinib initiation (range 42–87). Baseline characteristics are summarized in Table 1. Of these, 118 patients (76.6%) had prior exposure to a JAKi, most commonly ruxolitinib (117 patients, 99%), followed by fedratinib (4 patients) and pacritinib (1 patient). The ruxolitinib dose before discontinuation was ≤15 mg/12 h in 71% of patients, primarily due to cytopenias. The median duration of prior JAKi treatment was 16.8 months (range 0.4–128). Among these patients, 58.8% transitioned to momelotinib immediately or within 7 days of JAKi discontinuation, while the remaining 41.2% initiated treatment after a median interval of 2.75 months (range 0.3–41). The remaining 36 patients (23.4%) received momelotinib as their first JAKi.

A total of 77% of patients had prior exposure to erythropoietin-stimulating agents (ESAs), and 11% had received danazol. At the time of momelotinib initiation, 16.2% of patients (25/154) had platelet counts $<50 \times 10^9$/L. The starting momelotinib dose was 200 mg daily, except for 4 (2.6%) patients who started with 150 mg. Median follow up of the cohort was 5.05 months (range 1–14 months).

A total of 122 patients who met the 2024 IWG-ELN criteria for anemia [12] were assessed for anemia response. The median Hb level in this cohort was 8.0 g/dL (range 4.7–10.8 g/dL). Among these patients, 73.8% met the criteria for transfusion dependency.

In the Transfusion Dependent Anemia (TDA) group, the median Hb level prior to initiating momelotinib was 7.7 g/dL (range 4.7–9.8), and the median RBC transfusion frequency was 4 units per month [range 1–8] (Table 2 and Fig. 1). At 3 months of follow-up, 26.9% of patients achieved a major response, while 31.3% achieved a minor response. The median Hb increased from 7.7 to 8.7 g/dL. At 6 months, the proportions of patients with major and minor responses slightly increased to 30.6% and 36.1%, respectively. The median RBC transfusion frequency in the TDA cohort decreased from 4 to 1 unit at both 3 and 6 months. In the subanalysis by prior JAKi exposure, the overall response rates (ORR; major + minor) were 60% in JAKi-exposed patients (with 10.9% of patients unavailable) compared to 50% in JAKi-naïve patients at 3 months, and 67.8% (10.7% unavailable) vs. 62.5% at 6 months, respectively. Among TDA patients, 48.4% achieved transfusion independence at 3 months and 45.7% at 6 months.

In the Non-TDA group, the median Hb level prior to momelotinib initiation was 8.9 g/dL (range 7.2–10.8). At 3 months, 47.8% of patients achieved a major response, while 8.7% achieved a minor response. At 6 months, the proportions of patients with major and minor responses were 36.4% and 27.3%, respectively. The median Hb increased from 8.9 to 10.2 g/dL at 3 months and remained 10.1 g/dL at 6 months. In the subanalysis by prior JAKi exposure, the ORR at 3 months were 70.6% in JAKi-exposed patients compared to 16.6% in JAKi-naïve patients, and 85.7% vs. 25% at 6 months, respectively. The previous toxicity associated with prior JAK inhibitors in the exposed group may help explain these results.

Out of 122 patients, 72 (59%) received momelotinib in combination with other anemia-directed therapies—71 with ESA and 2 with danazol (one received both ESA plus danazol). Notably, 89% of these patients had been on ESA or danazol for varying durations before starting momelotinib, typically alongside prior JAKi treatment. Additionally, 45 patients were treated with momelotinib alone, while data on concomitant treatment was missing for 5 patients. At the 3-month follow-up, the overall response rate (major + minor) was 71.5% in the combination treatment group and 50% in the monotherapy group ($p = 0.04$) (Table S1). However, this difference was not sustained at 6 months (68% vs. 70.6%). While these data suggest that combination therapy may lead to earlier responses, further controlled studies are needed to confirm this finding.

A total of 45 patients with splenomegaly > 5 cm at baseline were assessed for spleen response (Table S2); their median spleen

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Table 1. Patient Baseline Characteristics, previous lines and baseline data prior momelotinib start.

Baseline characteristics		**$n = 154$**
Age at MMB start, years	Median, IQR	73 (10.7)
Sex, (%)	Male	95 (61.7)
	Female	58 (37.7)
Myelofibrosis subtype, (%)		
Primary		92 (60)
After essential thrombocythemia		44 (29)
After polycythemia vera		16 (10)
Unknown		2 (1)
Driver mutation, (%)		
JAK2		97 (63)
CALR		35 (22.7)
	Type 1	25 (71.4)
	Type 2	7 (20.0)
	NA	3 (8.6)
MPL		9 (5.8)
Triple negative		10 (6.5)
Not available		3 (2)
Previous lines		
JAKi naïve, (%)	36 (23.4)	
JAKi exposed, (%)	118 (76.6)	
Number of previous lines	Median, IQR	1 (1)
Prior treatments, (%)		
	Previous JAKi	118 (76.6)
	Ruxolitinib	117 (76.9)
	Hydroxyurea	27 (17.5)
	Corticosteroids	11 (7.1)
	Clinical trial	8 (5.2)
	Thalidomide/ lenalidomide	5 (3.2)
	Fedratinib	4 (2.6)
	Anagrelide	4 (2.6)
	Interferon	3 (1.9)
Baseline data prior to MMB start	**$n = 154$**	
DIPSS-plus risk category, (%)		
Low	0	
Intermediate-1	6 (3.9)	
Intermediate-2	67 (43.5)	
High	66 (42.9)	
Unknown	15 (9.7)	
Cytogenetics*, (%)	Available in $n = 94$ (61)	
Unfavorable	11/94 (11.7)	
Very high-risk	5/94 (5.3)	
Additional mutations by NGS, (%)	Available in $n = 108$ (70)	
ASXL1	37 (34.3)	
SRSF2	9 (8.3)	
EZH2	9 (8.3)	
IDH1/2	4 (3.7)	
U2AF1	12 (11.1)	
No additional mutations	46 (42.6)	

Table 1. continued

Baseline data prior to MMB start	**$n = 154$**
Hemoglobin (g/dL)	
Median, (IQR) [range]	8 (1.6) [4,5,7–13]
Platelet count ($\times 10^9$cells per L)	
Median, (IQR) [range]	160 (217) [3-1812]
Leukocyte count ($\times 10^9$cells per L)	
Median, (IQR) [range]	6.3 (9.55) [0.5-101]
Peripheral blasts, %	
Median, (IQR) [range]	1 (2) [0-13]
Transfusion dependent, *n* (%)	108 (70.1)
RBC units/month in TD, Median, (IQR) [range]	4 (3) [1–8]

IQR Interquartile Range, *JAK2* Janus Kinase 2, *CALR* Calreticulin, *NA* Not Available, *JAKi* Inhibitor of JAK, *SD* Standard Deviation, *MMB* Momelotinib, *NGS* Next Generation Sequencing, *RBC* Red Blood Cells, *TD* Transfusion Dependent.

*Unfavorable cytogenetics is defined as any abnormalities that do not include single abnormalities of 20q-, 13q-, +9, chromosome 1 translocations/duplications, or sex chromosome anomalies (e.g., -Y). Very high-risk karyotypes include -7, i(17q), inv(3)/3q21, and 12p-/12p11.2, or 11q-/11q23 abnormalities.

size was 10 cm (range 5–25). Among them, 28 patients (62.2%) showed spleen size reduction, with a median decrease of 5 cm (range 2–15 cm). According to the 2013 ELN (IWG-MRT) criteria, 24.4% qualified for spleen response, achieving a median reduction of 10 cm (range 6–15 cm). Subgroup analysis indicated similar response rates for JAKi-exposed (61.8%) and JAKi-naïve (63.6%) patients, although the median spleen size reduction was greater in the JAKi-naïve group (median 12 cm) compared to the JAKi-exposed group (median 8 cm).

For symptom response analysis (Table S3 and Fig. S1), 94% of the 134 patients had disease-related symptoms at baseline. Among these, 92% demonstrated sustained improvement, with notable reductions in asthenia (76%), anorexia (65%), weight loss (51%), abdominal discomfort (47%), and pruritus (75%).

Regarding safety (Fig. S2), thrombocytopenia was the most common hematological AE (10.3% of patients, 6.2% grade 3–4). Other hematological AEs included anemia (4.8%) and neutropenia (1.4%). Although thrombocytopenia was the most common hematological adverse event, median platelet counts remained stable at 3, 6, and 9 months, with no significant reduction compared to baseline, even in patients with platelet counts $<100 \times 10^9$/L and $<50 \times 10^9$/L. Most frequent extra-hematological AEs were diarrhea (11.7%), infections (9%), and hepatotoxicity (5.6%). A total of 26 patients (17%) required dose reductions, and 10 patients needed temporary treatment discontinuation due to AEs. Six patients discontinued treatment permanently due to toxicity, including infections, diarrhea, nephritis, renal failure, and hypotension. At the last follow-up, 79% of patients continued treatment. Discontinuations were due to stem cell transplantation (3 patients), lack of efficacy (5 pts), progression (2), transformation to acute myeloid leukemia (5 pts), toxicity (6), and death (11).

This study presents the largest real-world cohort of MF patients treated with momelotinib and is the first to apply the recently proposed 2024 criteria for anemia response. The results are consistent with or exceed those from clinical trials regarding anemia and spleen responses. In the MOMENTUM trial [9], 27% of patients achieved transfusion independence at week 24, while our study reported a substantially higher rate of 45.7%. Similarly, the SIMPLIFY-2 trial [8] documented an increase in transfusion independence from 31% at baseline to 43% at week 24; in our

Table 2. Anemia response in transfusion-dependent and non-transfusion-dependent patients, subdivided by prior exposure to JAKi.

n* = 122	**TDA (all)** ***n* = 90**	**JAKi exposed TDA** ***n* = 71**	**JAKi naïve TDA** ***n* = 19**	**Non-TDA** ***n* = 32**	**JAKi exposed non-TDA** ***n* = 24**	**JAKi naïve non-TDA** ***n* = 8**
Median Hb (IQR), [range]	7.7 (1.375) [4.7-9.8]	7.6 (1.5) [4.7-9.8]	8 (0.8) [5.8-9.4]	8.9 (1.175) [7.2-10.8]	8.9 (1.45) [7.2-10.8]	8.8 (0.65) [8-10.4]
Median RBC/month (IQR), [range]	4 (3) [1–8]	3 (3) [1–8]	4 (2.75) [1–8]	N/A	N/A	N/A
Last follow up (*n* = 124)	*n* = 90	*n* = 71	*n* = 19	*n* = 32	*n* = 24	*n* = 8
Median Hb (IQR), [range]	8.55 (1.775) [5-12.6]	8.6 (1.9) [5-12.6]	8.5 (1.2) [7-11.5]	10.2 (2.325) [6.5-17.2]	10.85 (2.325) [7.9-17.2]	9.1 (1.7) [6.5-10.2]
Median RBC/month (IQR), [range]	1 (3) [0-16]	0.75 (2.375) [0-16]	2 (2.5) [0-6]	N/A	N/A	N/A
Major response	23 (25.6)	21 (29.6)	2 (10.5)	14 (43.8)	14 (58.3)	0 (0)
Minor response	32 (35.6)	25 (35.2)	7 (36.8)	3 (9.4)	2 (8.3)	1 (12.5)
No minor or major response	29 (32.2)	20 (28.2)	9 (47.4)	15 (46.9)	8 (33.3)	7 (87.5)
ND	6 (6.7)	5 (7.0)	1 (5.3)	0 (0)	0 (0)	0 (0)
3 months follow-up (*n* = 90)	*n* = 67	*n* = 55	*n* = 12	*n* = 23	*n* = 17	*n* = 6
Median Hb (IQR), [range]	8.7 (1.55) [6.3-13]	8.6 (1.65) [6.3–13]	9.1 (1.175) [6.8–10.2]	10.2 (2.1) [8.1–17.2]	10.5 (1.5) [8.1–17.2]	9.05 (0.95) [8.3–10.6]
Median RBC/month (IQR), [range]	1 (3) [0-8]	0.5 (2.75) [0–8]	2 (2.775) [0–5]	N/A	N/A	N/A
Major response	18 (26.9)	16 (29.1)	2 (16.7)	11 (47.8)	10 (58.8)	1 (16.7)
Minor response	21 (31.3)	17 (30.9)	4 (33.3)	2 (8.7)	2 (11.8)	0 (0)
No minor or major response	21 (31.3)	16 (29.1)	5 (41.7)	10 (43.5)	5 (29.4)	5 (83.3)
ND	7 (10.4)	6 (10.9)	1 (8.3)	0 (0)	0 (0)	0 (0)
6 months follow-up (*n* = 47)	*n* = 36	*n* = 28	n = 8	*n* = 11	*n* = 7	*n* = 4
Median Hb (IQR), [range]	8.75 (2.05) [6–12.1]	8.6 (2.125) [6–12.1]	8.95 (1.275) [7–10.2]	10.1 (2.4) [7.7–12.5]	11 (2.25) [9-12.5]	9.25 (0.975) [7.7-–10.1]
Median RBC/month (IQR), [range]	1 (3) [0-16]	0.75 (2.75) [0-16]	1.65 (3.125) [0-6]	N/A	N/A	N/A
Major response	11 (30.6)	9 (32.1)	2 (25)	4 (36.4)	4 (57.1)	0 (0)
Minor response	13 (36.1)	10 (35.7)	3 (37.5)	3 (27.3)	2 (28.6)	1 (25)
No minor or major response	9 (25)	6 (21.4)	3 (37.5)	4 (36.4)	1 (14.2)	3 (75)
ND	3 (8.3)	3 (10.7)	0 (0)	0 (0)	0 (0)	0 (0)

*The analysis included patients with anemia per the 2024 IWG-ELN criteria who had at least one month of follow-up for response evaluation. n: Number of patients, m: months, *TDA* Transfusion-Dependent Anemia, *JAKi* Janus Kinase Inhibitor, Hb: Hemoglobin, *IQR* Interquartile Range, *RBC* Red Blood Cells, *N/A* Not Applicable, *ND* No Data.

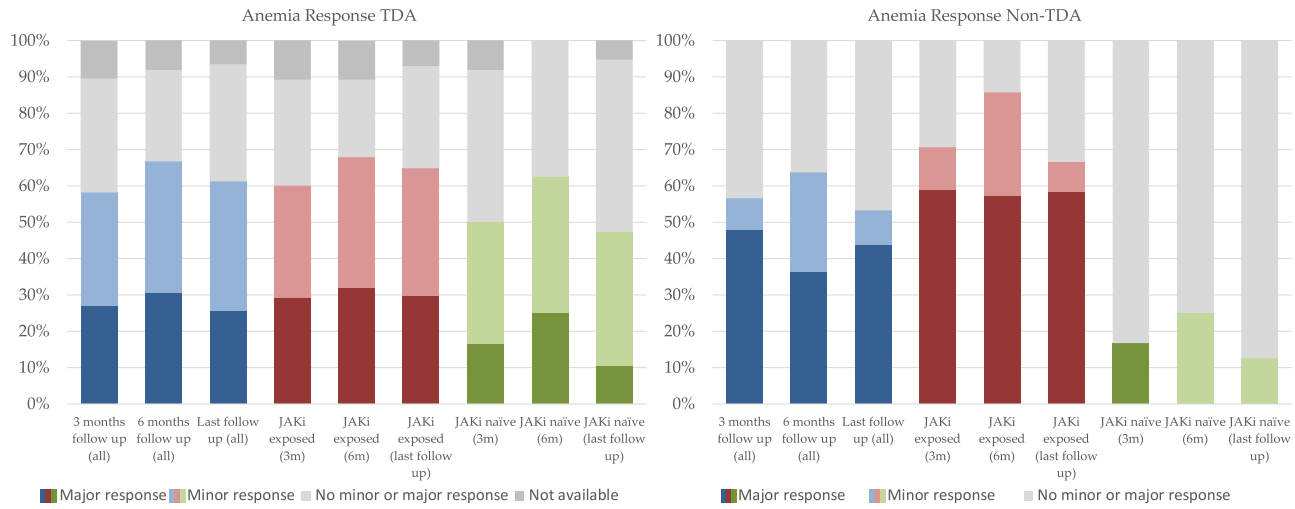

Fig. 1 Anemia Response in transfusion-dependent and non-transfusion-dependent patients, subdivided by prior exposure to JAKi (graphic version). Patients with prior JAK inhibitor exposure are shown in red, naive patients are depicted in green. *The analysis included patients with anemia per the 2024 IWG-ELN criteria who had at least one month of follow-up for response evaluation. m: months, TDA: Transfusion-Dependent Anemia, JAKi: Janus Kinase Inhibitor.

cohort, these rates rose from 26.2% to 54.3%. Our results are also better than those recently reported in a series of 60 MF patients receiving momelotinib in routine clinical practice in Germany [14]. The differences in criteria used to evaluate transfusion independence and response across studies and the high rate of concurrent ESAs in our study, may contribute to the observed discrepancies in outcomes.

Spleen response according to the 2013 ELN (IWG-MRT) criteria [13] in our study, is consistent with MOMENTUM findings and significantly better than the 9% response rate in SIMPLIFY-2. Furthermore, our data indicate that the majority of symptomatic patients experienced a reduction in disease-related symptoms during treatment with momelotinib, with responses being sustained over time. Unlike clinical trials, these data were based on routine clinical evaluation, reflecting real-world practice but limiting comparison to standardized assessments.

The safety profile observed in our study was consistent with that reported in clinical trials, with diarrhea and infections as the most common non-hematological AEs. Peripheral neuropathy occurred in 4.8% of patients (primarily grade 1–2), comparable to the 4% reported in the MOMENTUM trial [9], but significantly lower than the 13% and 11% rates observed in the SIMPLIFY-1 [7] and SIMPLIFY-2 [8], studies, respectively. Renal insufficiency was low, at 1.4% across all grades. The incidence of thrombocytopenia ≥ grade 3 was 6.2%, aligning with the SIMPLIFY studies (7%), and significantly lower than the 28% reported in the MOMENTUM trial [9]. Importantly, most patients with thrombocytopenia, maintained stable platelet counts during treatment. The discontinuation rate was low (4%), in contrast to 14% in SIMPLIFY-2 and 12% in MOMENTUM, potentially due to the shorter follow-up period of our cohort.

This study is limited by its retrospective design and short follow-up duration, which restricts our ability to assess the long-term sustainability of treatment responses. Nonetheless, our findings offer valuable real-world evidence regarding the efficacy and safety of momelotinib, complementing existing clinical trial data. Our results support that momelotinib is an effective and well-tolerated treatment for MF patients in routine clinical practice, demonstrating efficacy in both JAK-naïve and previously JAK-treated patients with cytopenias.

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DATA AVAILABILITY

The data presented in this study are available upon request from the corresponding author.

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AUTHOR CONTRIBUTIONS

VGG, LPL, ASD, and JCHB designed the study, performed the statistical analysis, analyzed and interpreted the results and wrote the paper. RGD, AAL, MAS, EM, MLF, IPG, GA, SGP, RPL, DMTC, AA, CAL, PLA, MV, JAVG, DDML, AFR, AMS, AHM, MTGC, RS, GCT, NLHR, BX, MPE, RMS, LNMB, FFM, NAS, CGR, PV, LLE, SM, ILK, ECL, AG, SMCR, FMDL, MJOMF, MLMM, TA, ECP, LALG, AMH, AT, EHP, MIMV, ICV, MJF, CA, MS, AGM, BNE, MAD, MPS, THS, MAMJ, JDV, WTJ, JAG, HATM, TCR, AAB, FP, MJLF, PBV, RP, FH, ECG, RJB, MGK, SGDV, MTTMR, MMC, BCR, MFS, SGP, RLP, ALV collected the data and approved the final version.

COMPETING INTERESTS

LPL: Novartis, Incyte and GSK; travel grants. GSK and Novartis speaker honoraria. AAL: honoraria fees for participating in advisory board from AOP and for lectures from Novartis and GSK. RJB: Novartis, GSK; speaker honoraria. VGG: Novartis; BMS; Incyte; Pfizer and GSK; travel grants, research funding, advisory board. ASD: Novartis; BMS; Incyte and Pfizer; travel grants. Novartis; research funding, advisory board. JCHB: advisory honoraria from Incyte, GSK, Novartis, Pfizer, BMS, and AOP Health; travel support from Incyte and Pfizer; speaker fees from GSK, Novartis, Pfizer, and Incyte.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study received approval from the Ramón y Cajal Hospital Ethics Committee (code number 176/24) and the GEMFIN Scientific Committee, and adhered to ethical standards for medical research involving human subjects. The study was conducted in accordance with the Declaration of Helsinki and other relevant guidelines and regulations. Written informed consent was obtained from all participants.

ADDITIONAL INFORMATION

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