Thrombocytopenic myelofibrosis patients previously treated with a JAK inhibitor in a phase 3 randomized study of momelotinib versus danazol [MOMENTUM]

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BACKGROUND

- MF is a myeloproliferative neoplasm characterized by dysregulated JAK-STAT signaling that typically manifests as bone marrow fibrosis, anemia, splenomegaly, and debilitating symptoms (ie, fatigue, cachexia, fever, night sweats)[1]
- Approved JAK inhibitors provide spleen and symptom improvements but fail to address—and may induce or worsen—anemia and thrombocytopenia[2]
- MF-associated or treatment-exacerbated cytopenias may necessitate attenuated JAK inhibitor dosing or discontinuation, which limit treatment efficacy and are associated with poor survival[3,4]
- Momelotinib (MMB) is the first JAK1 and JAK2 inhibitor to also inhibit ACVR1, a key regulator of iron homeostasis, which reduces hepcidin and induces erythropoiesis[5,6]
- MMB has demonstrated symptom, spleen, and anemia benefits in MF, including in patients with thrombocytopenia[7,8]
- MOMENTUM is a pivotal phase 3, international, randomized, double-blind study of MMB vs danazol (DAN) in symptomatic, anemic MF patients previously treated with a JAK inhibitor

OBJECTIVE

- To evaluate MOMENTUM patients with baseline platelet counts ≤150, <100, and <50 x 10^9/L

METHODS

Eligibility

- Age ≥18 years; diagnosis of primary or post-ET/PV MF; DIPSS high risk, Int-2, or Int-1; MFSAF TSS ≥10; Hgb <10 g/dL; prior JAK inhibitor for ≥90 days, or ≥28 days if RBC transfusions ≥4 units in 8 weeks or grade 3/4 thrombocytopenia, anemia, or hematoma; palpable spleen ≥5 cm; platelets ≥25 x 10^9/L

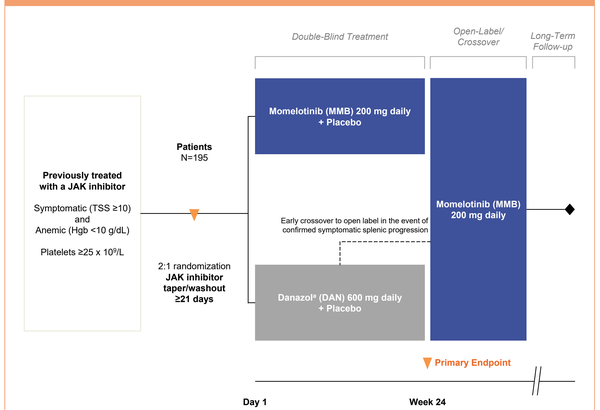
Study Design and Randomization

- JAK inhibitor taper and washout was ≥21 days. Patients were randomized 2:1 to MMB 200 mg QD plus DAN placebo or DAN 600 mg QD plus MMB placebo for 24 weeks, stratified by MFSAF TSS (<22 vs ≥22), palpable spleen length (<12 cm vs ≥12 cm), and transfused units in the 8 weeks before randomization (0 vs 1-4 vs ≥5 units)

Endpoints

- Primary: TSS response rate (≥50% reduction from baseline) at week 24
- Key secondary (select): RBC transfusion independence rate at week 24; splenic response rate (≥35% reduction in volume from baseline) at week 24

MOMENTUM Study Design



ClinicalTrials.gov: **NCT04173494**.

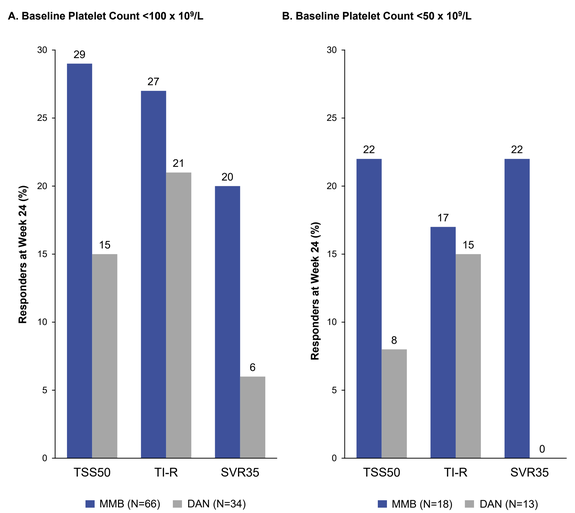
[a] Danazol was selected as an appropriate comparator given its use to ameliorate anemia in MF patients, as recommended by guidelines.

RESULTS

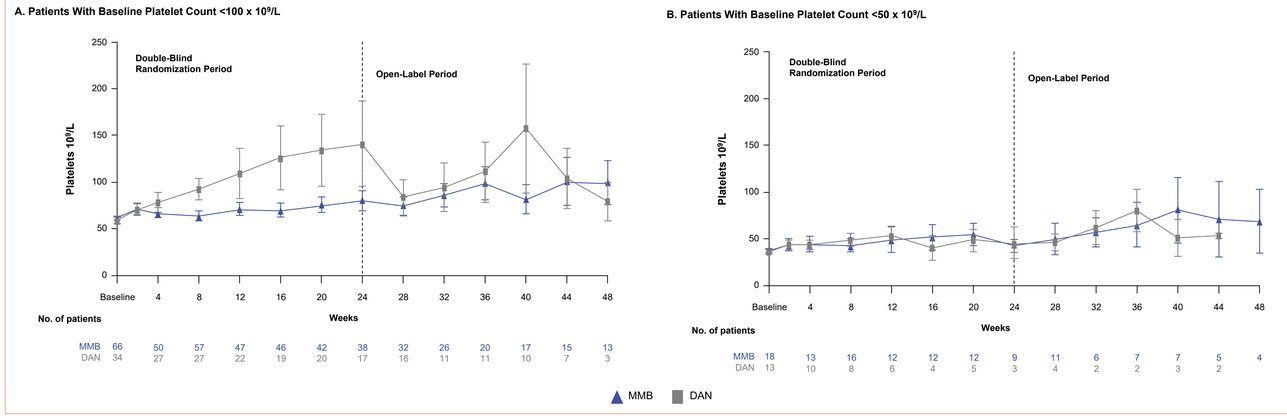
Baseline Patient Characteristics

	Baseline Platelet Count <100 x 10^9/L		Baseline Platelet Count <50 x 10^9/L	
	MMB (n=66)	DAN (n=34)	MMB (n=18)	DAN (n=13)
Mean age, years (SD)	70.0 (7.6)	70.6 (6.9)	72.6 (4.0)	70.2 (6.9)
Male, n (%)	40 (60.6)	23 (67.6)	11 (61.1)	7 (53.8)
White, n (%)	53 (80.3)	25 (73.5)	15 (83.3)	7 (53.8)
ECOG PS, n (%)				
1	37 (56.1)	18 (52.9)	12 (66.7)	5 (38.5)
2	20 (30.3)	9 (26.5)	4 (22.2)	5 (38.5)
MF subtype, n (%)				
Primary	40 (60.6)	24 (70.6)	12 (66.7)	10 (76.9)
Post-PV	19 (28.8)	6 (17.6)	5 (27.8)	1 (7.7)
Post-ET	7 (10.6)	4 (11.8)	1 (5.6)	2 (15.4)
Mean TSS (SD)	27.7 (13.9)	24.9 (13.4)	29.4 (14.1)	27.2 (17.3)
DIPSS risk category, n (%)				
Int-2	39 (59.1)	21 (61.8)	8 (44.4)	6 (46.2)
High	24 (36.4)	11 (32.4)	9 (50.0)	5 (38.5)
Mean Hgb, g/dL (SD)	8.1 (1.1)	7.8 (0.9)	7.7 (1.1)	8.0 (0.6)
Hgb <8 g/dL, n (%)	34 (51.5)	17 (50.0)	12 (66.7)	6 (46.2)
Mean prior JAK inhibitor duration, weeks (SD)	145.6 (127.5)	137.8 (119.4)	150.7 (144.6)	110.6 (87.8)

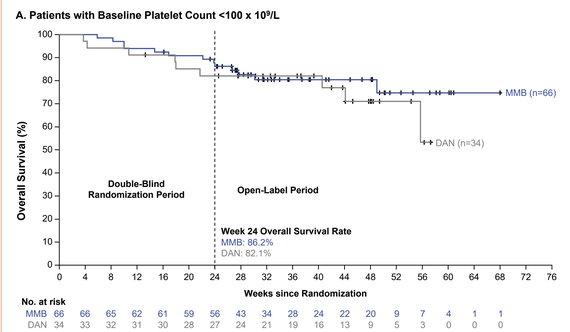
Efficacy at Week 24 by Baseline Platelet Count



Mean Platelet Counts Over Time by Baseline Platelet Count



Overall Survival by Baseline Platelet Count



TEAEs During the 24-Week Randomization Period by Baseline Platelet Count

	Baseline Platelet Count <100 x 10^9/L		Baseline Platelet Count <50 x 10^9/L	
	MMB (n=66)	DAN (n=34)	MMB (n=18)	DAN (n=13)
Any grade TEAEs, n (%)	61 (92.4)	32 (94.1)	18 (100)	13 (100)
Grade ≥3 TEAEs, n (%)	40 (60.6)	21 (61.8)	10 (55.6)	9 (69.2)
Serious TEAEs, n (%)	28 (42.4)	11 (32.4)	8 (44.4)	6 (46.2)
TEAEs leading to treatment discontinuation, n (%)	12 (18.2)	5 (14.7)	2 (11.1)	3 (23.1)
TEAEs leading to treatment interruption and/or dose reduction, n (%)	26 (39.4)	9 (26.5)	8 (44.4)	2 (15.4)
Most common any grade TEAEs (occurring in ≥20% in either treatment arm), n (%)				
Thrombocytopenia[a]	23 (34.8)	9 (26.5)	8 (44.4)	2 (15.4)
Diarrhea	16 (24.2)	4 (11.8)	6 (33.3)	1 (7.7)
Anemia	10 (15.2)	5 (14.7)	5 (27.8)	3 (23.1)
Nausea	10 (15.2)	3 (8.8)	5 (27.8)	2 (15.4)
Abdominal pain upper	2 (3.0)	4 (11.8)	1 (5.6)	3 (23.1)
Hypertension	0 (0)	4 (11.8)	0 (0)	3 (23.1)
Weight decreased	8 (12.1)	3 (8.8)	4 (22.2)	2 (15.4)
Asthenia	10 (15.2)	2 (5.9)	4 (22.2)	0 (0)
Pyrexia	7 (10.6)	1 (2.9)	4 (22.2)	1 (7.7)
ALT increase	5 (7.6)	1 (2.9)	4 (22.2)	0 (0)
Contusion	4 (6.1)	0 (0)	4 (22.2)	0 (0)
Most common grade ≥3 TEAEs (occurring in ≥10% in either treatment arm), n (%)				
Thrombocytopenia[a]	22 (33.3)	7 (20.6)	8 (44.4)	2 (15.4)
Anemia	6 (9.1)	4 (11.8)	4 (22.2)	3 (23.1)
Dyspnea	2 (3.0)	1 (2.9)	2 (11.1)	0 (0)
Frequency of grade ≥3 hemorrhage[b], n (%)	4 (6.1)	0 (0)	1 (5.6)	0 (0)

[a] Thrombocytopenia includes preferred terms "Thrombocytopenia" or "Platelet count decreased"; [b] Hemorrhage includes narrow Standardized MedDRA Queries set of preferred terms.

- The broader thrombocytopenic subgroup with baseline platelet count ≤150 x 10^9/L encompassed 15 more MMB patients and 9 more DAN patients than the <100 x 10^9/L subgroup and demonstrated similar efficacy and safety, as described in the published abstract, with week 24 overall survival rates of 88.8% with MMB and 78.8% with DAN

CONCLUSIONS

- In thrombocytopenic, symptomatic, and anemic patients with MF, including those with platelet counts as low as 25×10^9/L, momelotinib was administered safely and demonstrated improvements in symptom responses, transfusion independence rates, and spleen responses as compared with danazol
- Consistent with the overall intent-to-treat MOMENTUM population, platelet counts remained stable over time, and a trend toward improved overall survival versus danazol was maintained, in thrombocytopenic MF patients treated with momelotinib
- Momelotinib, which is the first and only JAK1 and JAK2 inhibitor that decreases hepcidin through ACVR1 inhibition, may address a critical unmet need particularly in symptomatic MF patients with anemia and thrombocytopenia

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Abbreviations

ACVR1, activin A receptor type 1; ALT, alanine aminotransferase; DAN, danazol; DIPSS, Dynamic International Prognostic Scoring System; ECOG PS, Eastern Cooperative Oncology Group performance status; ET, essential thrombocythemia; Hgb, hemoglobin; Int, intermediate; JAK, Janus kinase; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MMB, momelotinib; PV, polycythemia vera; QD, once daily; RBC, red blood cell; SVR35, ≥35% spleen volume reduction from baseline; STAT, signal transducer and activator of transcription; TEAE, treatment-emergent adverse event; TI-R, transfusion independence response; TSS, Total Symptom Score; TSS50, ≥50% reduction in Total Symptom Score from baseline.

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