Hepcidin Suppression by Momelotinib Is Associated With Increased Iron Availability and Erythropoiesis in Transfusion-Dependent Myelofibrosis Patients

Stephen T. Oh[1], Moshe Talpaz[2], Aaron T. Gerds[3], Vikas Gupta[4], Srdan Verstovsek[5], Ruben Mesa[6], Carole Miller[7], Candido Rivera[8], Angela Fleischman[9], Swati Goel[10], Mark Heaney[11], Casey O'Connell[12], Murat Arcasoy[13], Yafeng Zhang[14], Jun Kawashima[14], Tomas Ganz[15], Carrie Baker Brachmann[14]

[1]Washington University School of Medicine, St Louis, MO; [2]University of Michigan, Ann Arbor, MI; [3]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; [4]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [5]The University of Texas MD Anderson Cancer Center, Houston, TX; [6]Mays Cancer Center at University of Texas Health San Antonio MD Anderson Cancer Center, San Antonio, TX; [7]St. Agnes Hospital, Baltimore, MD; [8]Mayo Clinic, Jacksonville, FL; [9]University of California Irvine Medical Center, Irvine, CA; [10]Albert Einstein College of Medicine Montefiore Medical Center, Bronx, NY; [11]Columbia University Medical Center/NewYork-Presbyterian, New York, NY; [12]University of Southern California, Keck School of Medicine, Los Angeles, CA; [13]Duke University School of Medicine, Durham, NC;[14]Gilead Sciences, Inc., Foster City, CA; [15]David Geffen School of Medicine, Los Angeles, CA

INTRODUCTION

- Patients develop anemia as a result of myelofibrosis (MF) development, progression, and/or its treatment, including with ruxolitinib and other experimental Janus kinase (JAK) inhibitors[1,2]
- Momelotinib (MMB) is a JAK1/2 and Activin A receptor type I (ACVR1) inhibitor with demonstrated clinical activity for the splenomegaly and symptomatology common in MF[3,4]
- MMB also improved anemia endpoints and transfusion independence in prior clinical trials[3,4]
- JAK1/2 and ACVR1 respond to inflammation and iron stores to control iron availability through hepcidin, the key regulator of iron entry into circulation[5]
- Like other inflammatory diseases, MF is characterized by high hepcidin. MMB inhibited ACVR1 to modulate hepcidin, increase hemoglobin and ameliorate anemia in a rodent model[6]
- In this translational biology study, we determined the impact of MMB on plasma hepcidin, markers of iron storage and availability, erythropoiesis, and inflammation to explore mechanisms of the favorable effects of MMB on MF-associated anemia and transfusion independence

OBJECTIVES

- Primary objective: determine the transfusion independence response rate for transfusion-dependent (TD) subjects with MF treated with MMB
- Secondary objectives:
  - Evaluate baseline levels and changes in markers of iron metabolism
  - Assess inhibition of JAK1/2
  - Evaluate MMB pharmacokinetics in TD subjects with MF

METHODS

Key Inclusion Criteria

- Age ≥18 years old with diagnosis of primary MF (PMF), post-polycythemia vera MF (post-PV MF), or post-essential thrombocythemia MF (post-ET MF) and requiring MF therapy (in the opinion of the investigator)
- High risk or intermediate-2 risk defined by the dynamic international prognostic scoring system (DIPSS), or intermediate-1 risk defined by DIPSS and associated with symptomatic splenomegaly and/or hepatomegaly
- TD at baseline, defined as ≥4 U red blood cell (RBC) transfusion in the 8 weeks prior to the first dose of MMB
- Acceptable organ function as determined by laboratory values; platelet count ≥50x10^9/L

Key Exclusion Criteria

- Prior splenectomy or splenic irradiation within 3 months prior to the first dose of MMB
- Prior treatment with MMB, a JAK inhibitor within 21 days of the planned first dose of MMB, or use of strong cytochrome P450 enzyme (CYP) 3A4 inducer within 2 weeks prior to the first dose of MMB
- Documented myocardial infarction or unstable/uncontrolled cardiac disease
- Presence of peripheral neuropathy ≥Grade 2
- HIV positive; chronic active or acute viral hepatitis A, B, or C infection (testing required for hepatitis B and C); or hepatitis B or C carrier

Study Design

- This was an exploratory single-arm, open-label study (NCT02515630) of MMB in subjects with PMF, post-PV MF, or post-ET MF who were TD
- Subjects received MMB (first dose at enrollment visit) for 24 weeks (±7 days) on study
- Progressive splenomegaly or symptomatology were not required for study inclusion

Measurements

- Hepcidin: because of diurnal variation in hepcidin levels, samples were drawn in the morning (normal trough) prior to receiving MMB, and in the afternoon/6 hours post-MMB dosing at the following times: Baseline visit (no MMB), enrollment, Weeks 2, 4, 8, 12, 16, 20, and 24
- hsCRP: measured at Baseline and Weeks 2, 12, and 24 using the high-sensitivity C-reactive protein (hsCRP) test
- Liver iron content: measured by MRI at Baseline and Week 24

Outcomes

- Primary endpoint: transfusion independence response (TI-R) rate by Week 24, defined as becoming transfusion independent for ≥12 weeks at any time on study
- Secondary endpoints
  - Response rate for transfusion independence ≥8 weeks, defined as no RBC transfusions for at least 8 weeks at any time on study
  - Baseline and change in hepcidin, anemia-related biomarkers, liver iron content and CRP
  - Splenic response rate (SRR) at Week 24, defined as the proportion of subjects who achieved a ≥35% reduction in spleen volume at Week 24 from Baseline as measured by MRI
  - Response rate in total symptom score (TSS) at Week 24, defined as the proportion of subjects who achieved a ≥50% reduction from Baseline to Week 24 in TSS based on the modified Myeloproliferative Neoplasm Symptom Assessment Form

RESULTS

- 41 patients (mean age 70 years, 63% male, 88% white) received MMB. A high rate of advanced (Grade 3) bone marrow fibrosis (73%) was observed in this TD population (**Table 1**)

Table 1. Baseline patient characteristics

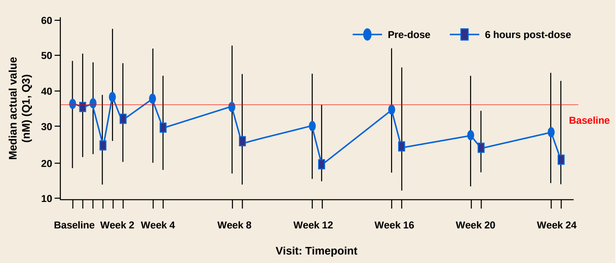
Baseline Characteristic	Overall N=41
Age, mean (SD) years	70 (9.0)
≥65 years old, n (%)	30 (73.2)
Males, n (%)	26 (63.4)
White race, n (%)	36 (87.8)
Type of MF, n (%)	
PMF	32 (78.0)
Post-PV/ET MF	9 (22.0)
Time since MF diagnosis, mean (SD) years	3.3 (2.78)
RBC units transfused ≤8 weeks prior to enrollment, mean (SD)	6 (2.3)
Bone marrow fibrosis grade, n (%)	
0 or 1	2 (4.9)
2	6 (14.6)
3	30 (73.2)
DIPSS risk level, n (%)	
Intermediate-1/2	27 (65.9)
High	14 (34.1)
JAK2 V617F mutation-positive, n (%)	28 (68.3)
Spleen volume, mean (SD) cm^3	2057.1 (1299.8)
TSS, mean (SD)	20.73 (14.65)
Hemoglobin, mean (SD) g/dL	8.3 (0.96)
< 8 g/dL (%)	29.3
≥ 8 g/dL (%)	70.7
Platelets, mean (SD) x10^3/uL	181 (129.9)

- By Week 24, 14 (34.1%, 90% CI: 22.0–48.1%) patients had a TI-R and 39.0% had no RBC transfusion for ≥8 weeks at any time (90% CI: 26.2–53.1%)

Transfusion Independence Response (TI-R)	
≥12 week period	≥8 week period
34.1%	**39.0%**

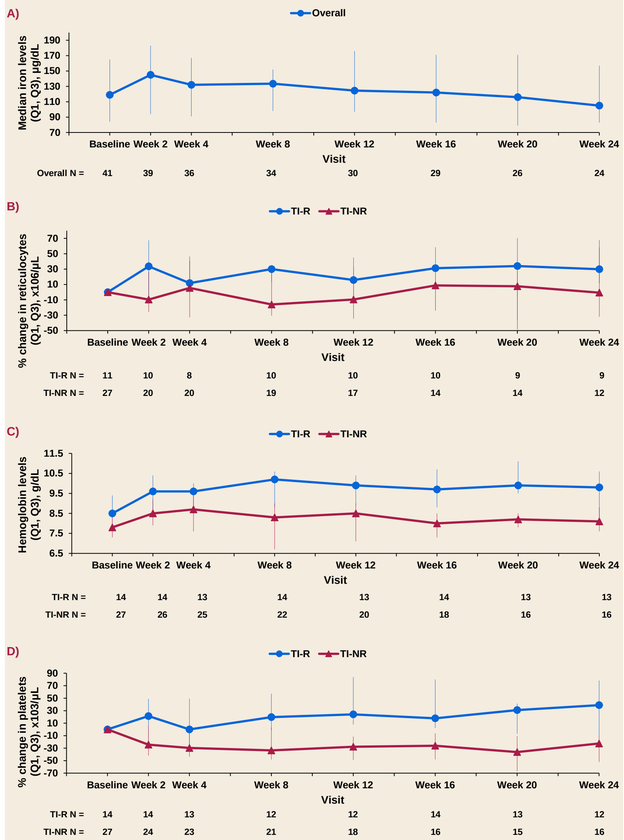
- In those patients with Week 24 data, the TSS and SRR were 28.6% and 19.2%, respectively
  - TSS and spleen volume assessments were not available for 17 (44.5%) and 15 (36.6%) patients, respectively
- At every study visit, median plasma hepcidin decreased 6 hours after dosing with MMB, and at the end of the 24-week dosing period median hepcidin levels were lower than at Baseline indicating an overall trend to decreased hepcidin over time (**Figure 1**)

Figure 1. Plasma hepcidin levels over the 24 week MMB treatment period



- Serum iron peaked at Week 2 **(Figure 2A)** and thereafter declined, consistent with the restoration of iron homeostasis and improved erythropoiesis
- Reticulocytes and hemoglobin increased **(Figures 2B and C)** through Week 24 in TI-R patients (as did transferrin and hematocrit [data not shown])
- In contrast to the known thrombocytopenic effect of RUX and other JAK inhibitors, platelet count also increased during the MMB treatment period in TI-R patients **(Figure 2D)**. Across all patients, CRP also decreased a median 54.8% from Baseline, indicating overall reduced inflammation (data not shown)

Figure 2. Level of A) iron, B) reticulocytes, C) hemoglobin, and D) platelets by TI-R and TI-NR subgroups



TI-R, transfusion independence responders; TI-NR, transfusion independence non-responders

- TI-non-responders (TI-NR) may also have had an anemia benefit where 77.8% (n=21/27) of patients achieved a ≥50% decrease in transfusion burden (units of RBC; minimum of 2 unit decrease) for at least one 8 week period during the 24-week dosing period

Decreased Transfusion Burden (≥50%) in TI-NR Patients
At least one 8 week period
77.8%

- In this exploratory study, TI-R was associated with lower baseline hepcidin, liver iron concentration, serum iron, reduced inflammation (CRP and ferritin), and higher hematocrit, erythrocytes, reticulocytes, platelets, and hemoglobin compared to TI-NR (**Table 3**)

Table 3. Baseline differences between TI-R and TI-NR subgroups

Anemia Biomarker	Mean Difference (90% CI)
Hepcidin (nM), Pre-dose	-21.5 (-33.7, -9.3)
Hepcidin (nM), 6.0 hours post-dose	-19.3 (-30.6, -8)
C reactive protein (mg/dL)	-1.1 (-2.3, 0)
Erythrocytes (x10^6/mL)	0.2 (0, 0.5)
Ferritin (ng/mL)	N/A
Hematocrit (%)	2.7 (0.7, 4.7)
Hemoglobin (g/dL)	0.6 (0, 1.2)
Iron (mg/dL)	-34.5 (-68.5, -0.4)
Liver iron concentration (mg/g)	-4 (-7.9, -0.2)
Reticulocytes (x10^6/mL)	0.023 (0.001, 0.044)
Platelets (x10^3/uL)	78 (8.1, 147.9)
Soluble transferrin receptor (mg/L)	2.4 (1.3, 3.6)
Total iron binding capacity (mg/dL)	-17.4 (-59.5, 24.7)
Transferrin saturation (%)	-10.8 (-20.9, -0.7)
Unsaturated iron binding capacity (mg/dL)	14.9 (-23.8, 53.6)

- In multivariable analysis, TI-R was strongly associated with baseline hemoglobin ≥8 g/dL and lower morning hepcidin (**Table 4**)

Table 4. Multivariate* analysis for associations with TI-R at Week 24

Variable	Comparison	Odds ratio (90% CI)	P-value
Baseline hemoglobin	≥8 g/dL vs <8 g/dL	27.96 (2.04, 383.32)	0.036
Pre-dose morning hepcidin	≥median vs <median	0.02 (<0.01, 0.25)	0.013
DIPSS Assessment	High vs intermediate-1/2 risk	0.07 (<0.01, 0.82)	0.075
Age	≥65 years vs <65 years	0.09 (<0.01, 0.80)	0.070

*Variables include age, gender, race, DIPPS assessment, type of MF, JAK2 V617F mutation status, baseline TSS and spleen volume, and baseline levels of hemoglobin, morning hepcidin, liver iron concentration and TSAT.

SAFETY

- Adverse events (AEs, **Table 5**) were consistent with previous studies of MMB in MF

Table 5. Summary of treatment-emergent AEs and deaths

	N=41
AE category, n (%)	
Any AE all; [Related to MMB]	39 (95.1); [22 (53.7)]
Grade 3 or 4 all; [Related to MMB]	20 (48.8); [9 (22.0)]
Serious AE all; [Related to MMB]	14 (34.1); [2 (4.9)]
AE leading to dose modification/interruption	10 (24.4)
AE leading to study drug discontinuation	6 (14.6)
Death from any cause, n (%)	3 (7.3)
AE occurring in ≥15% of patients, n (%); any causality	
Cough	12 (29.3)
Diarrhea	10 (24.4)
Nausea	9 (22.0)
Fatigue	8 (19.5)
Dizziness	7 (17.1)
Pruritus	7 (17.1)
Thrombocytopenia	7 (17.1)
Vomiting	7 (17.1)
Grade ≥3 AEs occurring in ≥5% of patients, n (%); [Related to MMB]	
Anemia	5 (12.2); [0 (0.0)]
Neutropenia	5 (12.2); [4 (9.8)]
Thrombocytopenia	3 (7.3); [3 (7.3)]

CONCLUSIONS

- MMB treatment elicited a significant rate of transfusion independence in this advanced, TD population (34.1% for ≥12 weeks and 39.0% for ≥8 weeks)
- These findings were consistent with the optimized and differentiated activity of MMB against JAK1, JAK2, *and* ACVR1 leading to decreased plasma hepcidin, improved iron homeostasis and increased erythropoiesis
- In this exploratory study, TI-R was associated with reduced inflammation, lower hepcidin, and improved erythropoiesis and bone marrow function at Baseline
- Anemia benefit may also have been observed in TI-non-responders where decreased transfusion requirements were evident in most patients versus Baseline
- Rates of TI-R were similar to those for TD MF patients in other MMB trials
- Safety was consistent with previous studies of MMB in MF
- Overall, the study suggests that modulation of hepcidin by MMB is sufficient to boost erythropoiesis, particularly in MF patients with lower baseline inflammation and greater erythropoietic potential. MMB's net anemia benefit differentiates it from other JAK inhibitors

REFERENCES

1. Tefferi A. *Am J Hematol.* 2018. doi: 10.1002/ajh.25230. [Epub ahead of print]. 2. Curto-Garcia N, et al. *Future Oncol.* 2018;14(2):137-150. 3. Mesa RA, et al. *J Clin Oncol.* 2017;35(34):3844-3850. 4. Pardanani A, et al. *Leukemia.* 2018;32(4):1035-1038. 5. Ganz T, Nemeth E. Biochim Biophys Act. 2012, 1823(9):1434-43. 6. Asshof M, et al. *Blood.* 2017;129(13):1823-1830.

ACKNOWLEDGMENTS

We extend our thanks to the patients and their families.

DISCLOSURES

Conflicts of interest: MT, ATG, VG, CR, AF, SG, and COC: No relationships to disclose; SV, YZ, JK, and CBB: Gilead; STO: Incyte, Gilead, CTI BioPharma, Janssen, Takeda; RM: Novartis, Incyte, Celgene, Genentech; CM: Gilead, Incyte, Novartis; MH: Roche, Incyte, Blueprint, Novartis, Deciphera; MA: Gilead Sciences, Incyte, CTI BioPharma, Samus Therapeutics; TG: Intrinsic LifeScience, Silarus Pharma, Keryx Pharma, Akebia, Vifor, Gilead, Ablynx, La Jolla Pharma.

SPONSORSHIP

This study was funded by Gilead Sciences, Inc (NASDAQ: GILD). Sierra Oncology Inc. (NASDAQ: SRRA) acquired MMB in August 2018 and is now the compound sponsor.

Abstract #4282: Presented at ASH 60th Annual Meeting & Exposition: December 1-4, 2018, San Diego, CA