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Sotatercept for anemia of myelofibrosis: a phase II investigator-initiated study

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Author contributions

PB performed data collection, analysis, interpretation and wrote the manuscript. SV designed the study and critically reviewed the manuscript for important intellectual content. XW helped design the study. LM, NP, NGD, EJJ, TMK, ZEV, SMK, MA, NJ, JEC, GB, YA, GGM and HK enrolled patients. LZ and SAP collected data. PB, LZ and SAP directly accessed and verified the underlying data. SDB, MAR, MHD, SAM and AMP helped collect data and conducted the trial on a day-to-day basis. PB supervised the overall conduct of the trial.

Conflicts of interest disclosures

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Patient Consent Statement. All participants provided written informed consent.

To the Editor:

Anemia (hemoglobin <10 g/dL) is common in myelofibrosis (MF), present in about a third of patients at diagnosis and eventually developing in all patients. The Janus kinase 1/2 (JAK1/2) inhibitor ruxolitinib ameliorates splenomegaly and symptoms of MF and prolongs survival;[1] however, on-target anemia from JAK2 inhibition, especially pronounced in the first 12-24 weeks of therapy, is a significant problem. Anemia may be the most common cause of ruxolitinib discontinuation,[2] and frequently results in dose reduction. Spleen responses to ruxolitinib are dose-dependent and correlate with survival.[3,4] Thus, counteracting ruxolitinib-induced anemia remains an important goal. Very recently, the JAK1/2 and activin receptor type 1 (ACVR1) inhibitor, momelotinib, was approved in the US for anemic patients with intermediate/high-risk myelofibrosis, based on the SIMPLIFY-1 and MOMENTUM trials.[5,6]

Therapies currently used specifically for anemia of MF include corticosteroids, danazol, erythroid stimulating agents (ESAs) and immunomodulatory drugs, but responses are infrequent and often short-lived. Sotatercept (formerly ACE-011, Acceleron Pharma, Cambridge, MA, now Merck, Kenilworth, NJ), a novel fusion protein, is a first-in-class, activin receptor type IIA (ActRIIA) “ligand trap” that sequesters MF bone marrow-derived TGF-β superfamily ligands (such as Activin A and growth and differentiation factor 11) that inhibit terminal erythropoiesis via Smad signaling upon ActRIIA binding.[7,8] Sotatercept demonstrated substantial efficacy in anemic patients with β-thalassemia and myelodysplastic syndromes (MDS).[9,10]

This was a phase 2, open-label, single-institution, investigator-initiated trial (clinicaltrials.gov identifier NCT01712308). Adults (≥18) with PMF or post-PV/ET MF were eligible if they were anemic (i.e. Hgb <10 g/dL sustained over ≥84 days preceding study entry without RBC transfusions, or Hgb <10 g/dL with occasional transfusions but

not RBC-TD per IWG-MRT criteria), or RBC-TD per IWG-MRT criteria.[11] Sotatercept was administered subcutaneously every 3 weeks. All monotherapy patients after the first patient, who received 0.3 mg/kg, received 0.75 mg/kg or 1 mg/kg. Upon early demonstration of activity, a combination cohort was added: patients must have been on ruxolitinib for ≥6 months with a stable dose for the preceding ≥8 weeks. The sotatercept dose chosen for this cohort was 0.75 mg/kg, as most responses in the monotherapy cohort at the time had been observed at this dose. MF-directed therapies within 2 weeks of sotatercept initiation were not permitted, except ruxolitinib in the combination cohort. Patients with uncontrolled hypertension were excluded. Additional eligibility criteria are listed in the study protocol, available as a supplement. Sotatercept was held for Hgb values ≥11.5 g/dL (resumed once the Hgb level was <11 g/dL). Concomitant use of erythroid stimulating agents or any other MF-directed therapy (except ruxolitinib in the combination cohort) was not permitted. The study was approved by the MD Anderson Cancer Center Institutional Review Board and was conducted according to the principles of the Declaration of Helsinki. All participants provided written informed consent. The study was supported by Celgene Corporation (now Bristol Myers Squibb) through drug supply and funding. BMS/Celgene had no role in the study design, data collection, analysis, interpretation, or manuscript writing.

The primary endpoint of the study was the anemia response rate, a composite of hemoglobin response in non-TD patients, and achievement of TI in RBC-TD patients. Hemoglobin response was defined as an increase from baseline Hgb level of ≥1.5 g/dL sustained for ≥84 days, without RBC transfusions (Gale criteria).[12] The baseline Hgb in anemic patients was the lowest Hgb level in the 84 days preceding study entry. In patients who were RBC-TD at enrollment, TI was defined as no RBC transfusions in any

“rolling” 84-day interval during the treatment period. Secondary endpoints included duration of and time to response. All patients who received at least one dose of sotatercept were evaluable for safety. Patients had to remain on study for ≥84 days to be efficacy-evaluable.

Supplemental Figure 1 shows the patient disposition. A total of 63 patients were enrolled and 56 were treated. One patient received a dose of 0.3 mg/kg for 6 cycles and is not considered further. Thirty-four patients received sotatercept monotherapy (16 at 0.75 mg/kg/dose and 18 at 1 mg/kg/dose), and 21 received sotatercept (0.75 mg/kg/dose) “added” to a stable dose of ruxolitinib. Baseline characteristics appear in **Table 1.** Five patients in the monotherapy cohort were treatment-naïve. Prior therapies in the remainder are available in **Supplemental Table 1**. In the monotherapy cohort, 17 patients each were “anemic” and RBC-TD at study entry. In the combination cohort, 15 patients were “anemic” and 6, RBC-TD at study entry. All patients are currently off-study. The study was terminated after the commercial supporter ended investigational drug supply in December 2021. Four patients, 2 in each cohort, were receiving sotatercept on the study at that point.

Eight patients out of 27 evaluable (30%) in the monotherapy cohort responded. Five were anemia responses (out of 13 evaluable) and three, TI responses (out of 14 evaluable). Six responses (4 anemia and 2 TI) occurred at the 0.75 mg/kg dose, and two (1 anemia and 1 TI) at the 1 mg/kg dose. Of the 7 unevaluable patients, 3 had Hgb increases of ≥1.5 g/dL from baseline but came off-study due to hypertension deemed related to sotatercept (n = 1), or a decision to proceed to allo-HCT (n = 2). The median number of cycles of sotatercept was 6 (1-73), and median time on-study was 4.4 (0.7 – 75.3) months. The median time to (onset of) response was 19 (1-22) days, and the

median duration of response was 23.3 (3.9 – 74.6) months. Reasons for discontinuation of sotatercept included lack or loss of response (n = 14), MF progression in other aspects, e.g., splenic progression (n = 6), allo-HCT (n = 4), logistical/travel-related (n = 3), patient decision (n = 2), study termination (n = 2), transformation to AML (n = 1), hypertension deemed related to sotatercept (n = 1) and medical complications unrelated to sotatercept (n = 1).

In the combination cohort, there were 6 responses (out of 19 evaluable patients, 32%). All were hemoglobin responses (out of 14 evaluable); there were no TI responses (out of 5 evaluable). The median number of cycles of sotatercept was 8 (2-52), and the median time on-study was 5.5 (1.6 – 57.1) months. The median time to (onset of) response was 14 (6 – 147) days, and the median response duration was 20.9 (3.7 – 56.8) months. Reasons for discontinuation of sotatercept included lack or loss of response (n = 8), allo-HCT (n = 4), MF progression in other aspects (n = 2), logistical/travel-related (n = 2), study termination (n = 2), transition to hospice (n = 1), patient decision (n = 1) and loss of insurance (n = 1).

Several responders in both cohorts required sotatercept doses to be held per protocol for Hgb levels ≥11.5 g/dL, with resumption of dosing when the Hgb level was <11 g/dL. Eight responders, 5 in the monotherapy cohort and 3 in the combination cohort, experienced multiple instances of this phenomenon. However, we were not able to identify a molecular biomarker or clinical factor predictive of these robust and durable responses to sotatercept.

We did not observe any consistent effects of sotatercept on other disease-related parameters, such as spleen size, symptoms, leukocyte or platelet counts, bone marrow fibrosis grade and *JAK2* V617F variant allele frequency. No responder in either cohort

had a detectable *SF3B1* mutation at study entry; however, spliceosome genes were not sequenced as part of our institutional next-generation sequencing panel until April 2017. No responder had bone marrow ring sideroblasts (RS) at study entry.

Sotatercept was well-tolerated. **Table 2** lists the AEs felt to at least possibly be related to sotatercept. No grade 4 or 5 AEs occurred. Seven patients experienced grade 3 hypertension on the study, not in the context of high Hgb levels. Hypertension (all grades) occurred in 20% of patients. Pain in the extremities (muscle, bones, joints) on the days following injection of sotatercept was common, occurring in 40%; however, most of these events were grade 1 or 2 in severity, with only 2 patients reporting grade 3 limb pain. There were no on-study deaths.

In conclusion, our study adds to a growing body of evidence supporting the safety and clinical activity of the activin receptor ligand traps in anemic patients with myeloid malignancies. Although sotatercept is currently being developed for the treatment of pulmonary arterial hypertension,[13] luspatercept, an ActRIIB ligand trap, is approved for the treatment of anemia in patients with lower risk MDS with RS, as well as those with myelodysplastic/myeloproliferative neoplasm with RS and thrombocytosis. In a phase 2 study in 95 patients with MF and anemia, luspatercept led to a 26.3% rate of TI during the primary treatment period (24 weeks) in the cohort of RBC-TD patients receiving a stable dose of ruxolitinib (n = 38), and 50% of the patients in this cohort experienced at least halving of their transfusion burden during this time. These results have led to an ongoing, phase 3, placebo-controlled trial of luspatercept (INDEPENDENCE™) in RBC-TD MF patients on a stable dose of a JAK inhibitor.[14] Early data on elritercept, an investigational, modified ActRIIA ligand trap are promising, with some “trifactor” (hematopoiesis, spleen, and symptoms) responses observed.[15]

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Table 1. Characteristics of the patients at baseline.

Characteristics (N=55)		Sotatercept alone (N=34)	Sotatercept + Rux (N=21)
Median age (range)		67 (47-84) years	71 (48-84) years
Diagnosis	PMF	27	14
	Post-ET/PV MF	7 (5 PET/2 PPV)	7 (1 PET/6 PPV)
Gender	Male	20	14
Median baseline Hgb (range)		7.4 (4.7 – 9.3) g/dL	7.4 (4.6 – 9.1) g/dL
Enrolled as	Anemic only	6	6
	Anemic with occasional RBC transfusions	11	9
	RBC transfusion-dependent	17	6
Driver mutation*	*JAK2*	22 (median VAF 37% (1-95.7))	15 (median VAF 43%(22-93.5))
	CALR	4	4
	MPL	6	2
	Triple Negative	1	0
Karyotype	Abnormal	10	11
DIPSS category	Intermediate-1	1	1
	Intermediate-2	28	20
	High	5	0
Bone marrow fibrosis grade	MF-1	0	1
	MF-2	15	10
	MF-3	19	10
Splenomegaly	Present	19	12
Median ruxolitinib dose (range)	10 mg BID (5-25 mg BID)	N/A	10 mg BID (5-25 mg BID)
Previously treated	Yes	28	21
Median number of prior therapies		2 (1-6)	2 (1-6)
Median follow up (alive patients)	55.4 (16.4-91.4) months	53.1 (16.4 – 91.4) months	57.5 (26.1 – 63) months

*Driver mutation status was not known with certainty in one patient in the monotherapy cohort as *CALR* mutational testing had not been performed. *Abbreviations:* BID: twice daily; DIPSS: Dynamic International Prognostic Scoring System; N/A: not applicable; PET, post-essential thrombocythemia; PMF, primary myelofibrosis; PPV, post-polycythemia vera; RBC: red blood cell; Rux, ruxolitinib; VAF, variant allele fraction.

Table 2. Adverse events* at least possibly related to sotatercept.

Adverse events* at least possibly related to sotatercept	Grade			
	1	2	3	4
Pain (extremities (bone/joint/back)), myalgia	15	5	2	-
Headache	3	1	-	-
Constipation	2	-	-	-
Dizziness	6	-	-	-
Nausea	3	-	-	-
Vomiting	2	-	-	-
Rash	2	-	-	-
Pruritus	1	-	-	-
Hypertension	1	3	-	-
Limb edema	1	-	7	-
Elevated UMACR	3	-	-	-
Creatinine elevation	3	1	-	-
Generalized wellness	2	-	-	-
Dyspnea	2	-	-	-
Palpitations	-	1	-	-
Flushing	1	-	-	-
Proteinurea	1	-	-	-
Acute kidney disease	1	-	-	-
Elevated ALT/AST	4	-	-	-

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; UMACR: urine microalbumin/creatinine ratio.

*The numbers represent the number of occurrences of each adverse event (not necessarily the number of patients experiencing them). Adverse events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0.

Supplementary Material

Sotatercept for anemia of myelofibrosis: a phase II investigator-initiated study

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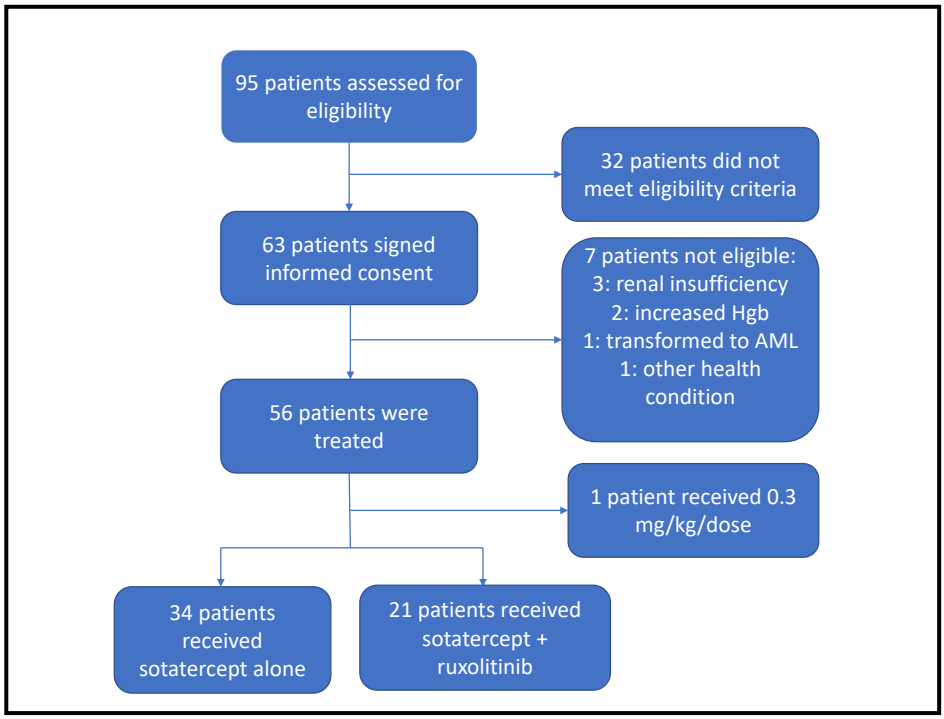

Supplementary Figure 1. Consort diagram of patient disposition on the trial. Data on patients that did not sign informed consent were not collected. Abbreviations: AML: acute myeloid leukemia; Hgb: hemoglobin.

Supplementary Table 1. Prior therapies in the monotherapy cohort (n = 34).

1	None
2	Pomalidomide, momelotinib
3	None
4	Ruxolitinib, danazol
5	ESA, IV iron (previously HU, anagrelide for ET)
6	Investigational JAKi, splenectomy, ESA, investigational anti-fibrotic
7	ESA, investigational Smac-mimetic (previously HU, anagrelide for ET)
8	HU (for ET preceding MF)
9	Danazol/prednisone, pomalidomide/prednisone
10	Thalidomide/prednisone, investigational LOXL2 antibody, pomalidomide/prednisone, investigational JAKi, danazol/deferasirox
11	Pomalidomide/prednisone, momelotinib
12	HU
13	None
14	Ruxolitinib
15	None
16	Danazol
17	ESA
18	Ruxolitinib, thalidomide/prednisone
19	HU
20	Ruxolitinib, splenectomy, thalidomide/prednisone
21	Ruxolitinib, investigational Smac-mimetic
22	ESA
23	ESA
24	HU.
25	Iron, danazol, ESA
26	Pegylated interferon-alfa, iron, ESA
27	Allo SCT, ruxolitinib, investigational PI3K and PLK1 inhibitor
28	ESA
29	HU, danazol, corticosteroids
30	Investigational Smac-mimetic
31	None
32	HU (for ET preceding MF)
33	Danazol
34	Ruxolitinib, lenalidomide

HU, hydroxyurea; ESA, erythroid stimulating agent; LOXL2, lysyl oxidase like-2; Smac, second mitochondrial activator of caspases; JAKi, Janus kinase inhibitor; IV, intravenous; ET, essential thrombocythemia; MF, myelofibrosis; allo SCT, allogeneic stem cell transplant; PI3K, phosphatidylinositol-3-kinase; PLK1, polo-like kinase 1.