RUSFERTIDE IMPROVES MARKERS OF IRON DEFICIENCY IN PATIENTS WITH POLYCYTHEMIA VERA

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INTRODUCTION

- Polycythemia vera (PV) is a chronic myeloproliferative neoplasm characterized by erythrocytosis defined by an acquired increase in hemoglobin (Hb)/hematocrit (HCT)
- Disease complications are associated with increased blood viscosity, thrombotic events and iron deficiency[1]
- Most patients with PV are iron deficient and therapeutic phlebotomy may exacerbate iron deficiency[2]

STUDY DESIGN

- PTG-300-08 (clinicaltrials.gov NCT04767802, PACIFIC study) was an open-label, 52-week, phase 2 study that investigated the efficacy and safety of rusfertide in 20 patients enrolled in Malaysia and Republic of Korea with poor hematocrit (HCT) control as noted by HCT >48%
- Treatment was initiated with 40 mg subcutaneous (SC) rusfertide twice a week
- Once HCT was <45%, the dose was changed to 40 mg once a week with subsequent dose adjustments made to maintain HCT <45%

AIM

- To assess the effects of rusfertide on erythrocyte morphology and biomarkers reflective of iron biology

RESULTS

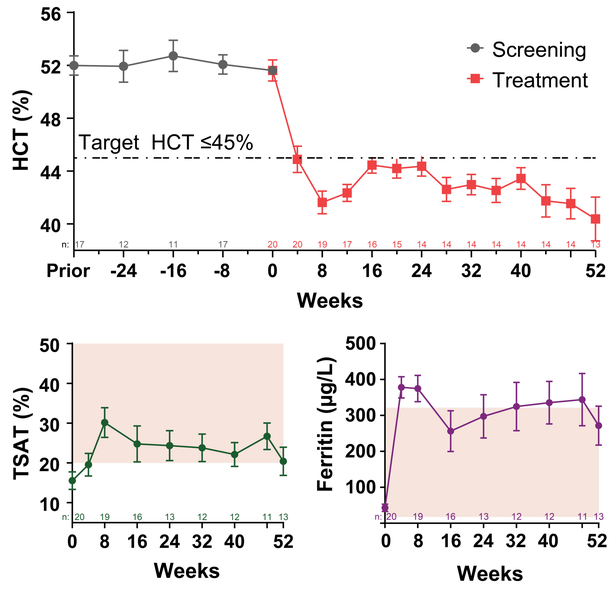
- Demographics and baseline characteristics are depicted in **Table 1**
- Rusfertide rapidly and robustly reduced mean HCT and sustained mean HCT <45% for the duration of treatment and transferrin saturation (TSAT), ferritin, and MCV increased (**Figure 1**)
- Among patients with evidence of baseline iron deficiency (ferritin ≤20 µg/L), rusfertide normalized iron levels while iron levels remained stable in patients with normal iron levels at baseline (**Figure 2a**)
- Patients with iron deficiency had low MCV (<80 fL) at baseline which increased following initiation of rusfertide treatment. In patients with normal iron levels, MCV remained stable in the normal range (**Figure 2b**).
- Median EPO concentration was below the limit of detection and remained so following treatment. Erythroferrone concentration decreased modestly with rusfertide dosing consistent with reduced erythropoietic drive (**Table 2**).

Table 1. Demographics and Baseline Characteristics

Category	n (%)
Age (years)	
≤60	13 (65.0)
>60	7 (35.0)
Sex	
Male	15 (75.0)
Female	5 (25.0)
PV Duration (years)	
≤1	3 (15.0)
>1 - ≤5	11 (55.0)
>5	6 (30.0)
Positive for JAK2 V617F mutation[a]	20 (100.0%)
Risk Category	
High Risk: Age[b]	8 (40.0)
Low Risk	12 (60.0)
Cytoreductive Therapy at Treatment Initiation	
Concurrent Exposure: No	3 (15.0)
Concurrent Exposure: Hydroxyurea[c]	17 (85.0)

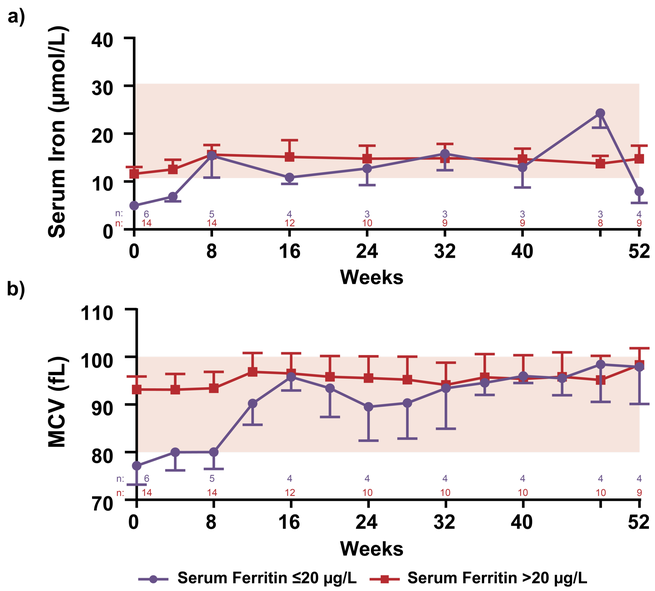
[a]All 20 patients were JAK2 positive (the average JAK2 V617F allele burden was 66.1 ± 20.8%).
[b]No patients had a prior history of thromboembolic events.
[c]Average daily hydroxyurea dose was 811 mg for the 17 patients who received hydroxyurea in PACIFIC.

Figure 1. Treatment Initiation with Rusfertide Sustains HCT <45% and Increases Mean Ferritin and TSAT, Mean (Standard Error of the Mean)



Shaded regions represent normal ranges.

Figure 2. Treatment Initiation with Rusfertide Normalizes Serum Iron (a) and MCV (b) in Iron Deficient Patients, Mean (Standard Error of the Mean)



Shaded regions represent normal ranges.

Table 2. Summary of Erythropoietin, Erythroferrone and STfR Following Rusfertide Treatment, Median (Interquartile Range)

	Baseline	4 Weeks	16 Weeks	32 Weeks
Erythropoietin (mIU/mL)	<2.5 (<2.5, <2.5)	<2.5 (<2.5, 3.9)	<2.5 (<2.5, <2.5)[a]	<2.5 (<2.5, <2.5)[c]
Erythroferrone (ng/mL)	3.4 (1.6, 6.1)	1.9 (0.9, 4.9)	2.6 (1.0, 5.1)[a]	2.6 (1.0, 6.5)[b]
sTfR (µg/mL)	2.7 (2.1, 5.0)	2.8 (1.5, 3.8)	2.9 (1.8, 4.2)[a]	2.4 (1.9, 4.1)[b]

[a] N=16, [b] N=14, [c] N=15. sTfR, soluble transferrin receptor.

METHODS

- HCT, mean corpuscular volume (MCV), erythroferrone (ERFE), erythropoietin (EPO), and soluble transferrin receptor (sTfR) were measured at Week 0 (baseline) and Weeks 4, 16, and 32 following initiation of rusfertide treatment
- To examine the effects of iron deficiency on iron parameters patients were stratified by baseline ferritin levels (those with ferritin ≤20 µg/L) compared to patients with ferritin >20 µg/L

CONCLUSIONS

- Treatment with rusfertide resulted in rapid, robust, and sustained reduction in HCT levels in PV patients with elevated HCT levels at baseline
- Increases in ferritin and normalization of serum iron and MCV following rusfertide in patients who were iron deficient at baseline were seen
- Improvements in iron deficiency following rusfertide are suggestive of clinical benefits and merit further investigation

REFERENCES

1. Marchioli R, Finazzi G, Specchia G et al. Cardiovascular events and intensity of treatment in polycythemia vera. *N Engl J Med*. 2013;368:22-33.
2. Ginzburg YZ, Feola M, Zimran E et al. Dysregulated iron metabolism in polycythemia vera: etiology and consequences. *Leukemia*. 2018;32:2105-2116.

DISCLOSURES

YG: Consultancy and research funding from Protagonist Therapeutics, Inc. **LC:** Research funding from Protagonist Therapeutics, Inc. **NM, SG, AM, NBM:** Employees of Protagonist and have an equity interest in the company.

ACKNOWLEDGEMENTS

The study was sponsored by Protagonist Therapeutics, Inc. (Newark, CA, USA). The authors thank Phil Dinh, Ph.D. (Protagonist Therapeutics, Inc.) for statistical support. Editorial assistance was provided by Elizabeth Claus, PharmD, and Scott Bergfeld, PhD, of MedVal Scientific Information Services, LLC (Princeton, NJ, USA), and was funded by Protagonist Therapeutics, Inc.

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