ANALYSIS OF ADVERSE EVENTS FOLLOWING RUSFERTIDE DOSING IN REVIVE: A PHASE 2 STUDY IN PATIENTS WITH POLYCYTHEMIA VERA

Naveen Pemmaraju, MD[1], Srdan Verstovsek, MD PhD[1] , Marina Kremyanskaya, MD, PhD[2], Frank Valone, MD[3], Nishit B Modi, PhD[3], Sarita Khanna, PhD[3], Paula O'Connor, MD, Suneel K Gupta, PhD[3], Ronald Hoffman, MD[2]

[1]M.D. Anderson Cancer Center, Houston, TX , [2]Division of Hematology Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Protagonist Therapeutics, Newark, CA

Introduction

- Rusfertide (PTG-300) is a potent mimetic of hepcidin that binds to ferroportin causing it to be internalized and degraded, thereby decreasing iron availability to the bone marrow and reducing aberrant erythrocytosis.
- In the phase 2 REVIVE study (PTG-300-004; NCT04057040) of patients with polycythemia vera (PV), rusfertide treatment resulted in sustained control of hematocrit (HCT) at <45% and eliminated requirement for therapeutic phlebotomy (TP) in 84% of patients.
- Rusfertide was well tolerated, with no grade 4 or 5 treatment-emergent adverse events (TEAEs) [Hoffman, ASH 2021].
- We present an analysis of the rusfertide TEAE profile in subgroups of interest.

Methods

- Patients with TP-dependent (i.e. ≥3 TPs within 6-month period) PV were eligible for REVIVE, which comprised 3 parts
  - A 28-week open-label, dose-finding
  - A 12-week double-blind randomized withdrawal
  - A long-term (3-year) extension
- In the dose-finding phase, subcutaneous rusfertide doses (10-120 mg) were administered with TP or with TP plus prior stable cytoreductive agents, with individualized dose titration for rusfertide to maintain HCT <45%.
- This analysis focuses on the 70 patients enrolled in the study with ≥8 weeks of exposure to study treatment. Incidence of treatment emergent adverse events with an incidence of ≥15% were examined in various subgroups:
  - Phlebotomy alone (TP) vs Phlebotomy+Cytoreductive Therapy (CRT)
  - Rusfertide dose (≤20 mg, 21 to ≤40 mg, >40 mg)
  - High-Risk vs Low-Risk
  - Gender (Male, Female)
  - Weight (≤85 kg vs >85 kg)
  - Duration since diagnosis (≤2.5 y vs >2.5 y)

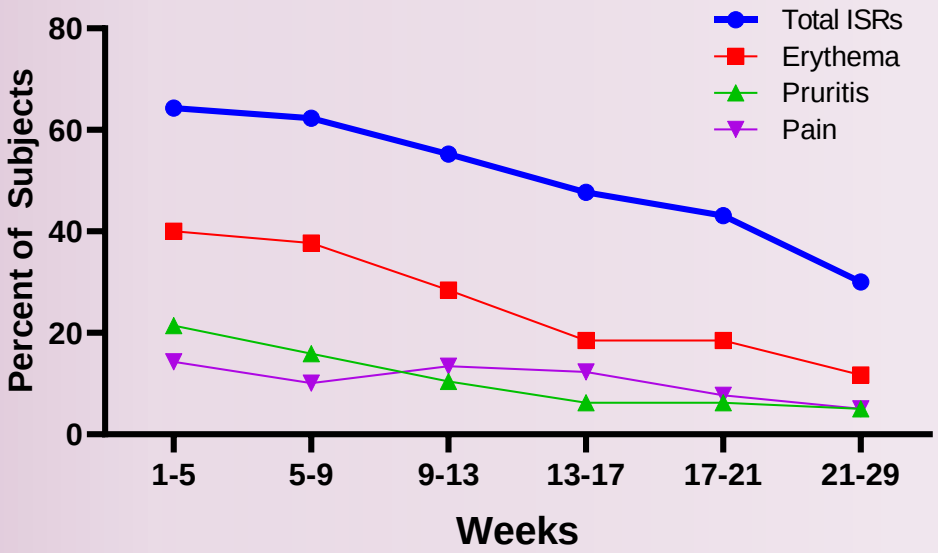
Results

- The majority of TEAEs (84%) were ≤Grade 2. There were no Grade 4 or 5 TEAEs. Grade 3 TEAEs were noted in 16% of patients, with all Grade 3 TEAEs, except syncope, noted in single subjects. Syncope was noted in 2 subjects (1 male and 1 female; 3%).
- No dose relationship noted for TEAEs, including injection site reactions (ISRs), apart for general expected dose-related pharmacologic effects

	All Subjects (N=70)	≤20 mg (N=13)	21 to≤40 mg (N=36)	>40 mg (N=21)
TEAEs	69 (98.6)	12 (92.3)	36 (100)	21 (100)
Pruritus	19 (27.1)	3 (23.1)	10 (27.8)	6 (28.6)
Arthralgia	16 (22.9)	1 (7.7)	9 (25.0)	6 (28.6)
Nausea	15 (21.4)	2 (15.4)	7 (19.4)	6 (28.6)
Anemia	13 (18.6)	2 (15.4)	6 (16.7)	5 (23.8)

Results

Injection site reactions decrease with time



Results

- Overall incidence of TEAEs was similar in all subgroups. Differences noted in individual TEAEs between subgroups:

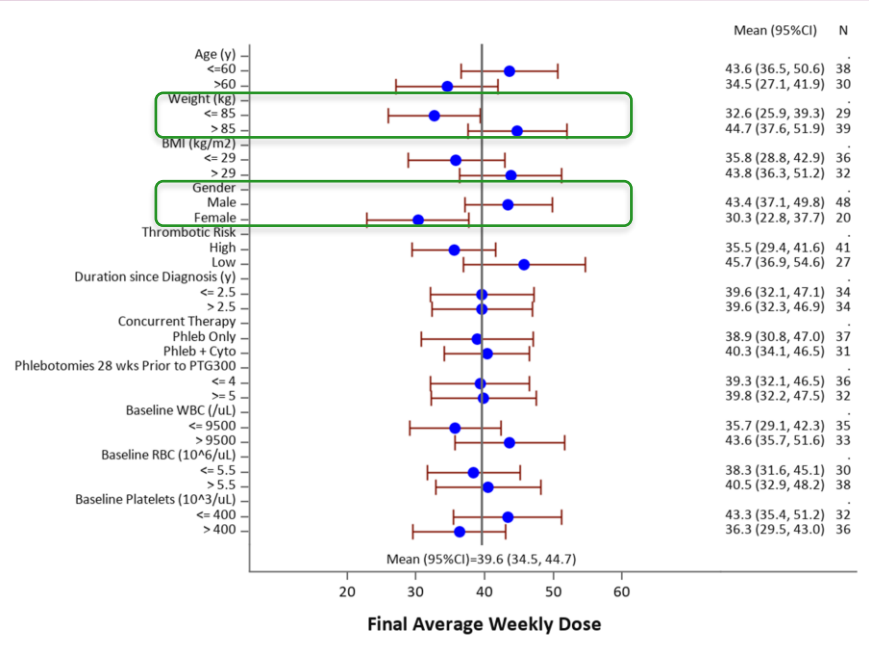
A. Treatment	TP Alone (N=37)	TP + CRT (N=33)
TEAEs	36 (97.3)	33 (100)
Injection site reaction	34 (91.9)	27 (81.8)
Injection site pruritus	17 (45.9)	9 (27.3)
Fatigue	14 (37.8)	7 (21.1)
Pruritus	8 (21.6)	11 (33.3)

B. Risk	High (N=43)	Low (N=27)
TEAEs	43 (100)	26 (96.3)
Injection site erythema	25 (58.1)	20 (74.1)
Injection site pain	15 (34.9)	14 (51.9)
Injection site pruritus	14 (32.6)	12 (44.4)
Injection site swelling	5 (11.6)	10 (37.0)
Anemia	10 (23.3)	3 (11.1)

E. Gender	Male (N=49)	Female (N=21)
TEAEs	48 (98.0)	21 (100)
Injection site reaction	40 (81.6)	21 (100)
Injection site erythema	29 (59.2)	16 (76.2)
Injection site pruritus	14 (28.6)	12 (57.1)
Fatigue	11 (22.4)	10 (47.6)
Pruritus	10 (20.4)	9 (42.9)
Headache	7 (14.3)	9 (42.9)
Dizziness	7 (14.3)	8 (38.1)
Nausea	8 (16.3)	7 (33.3)
Anemia	7 (14.3)	6 (28.6)

Results

- Average weekly rusfertide dose was comparable in all subgroups except those weighing ≤85 kg and female, who had average weekly doses lower than the mean.



Summary

- Majority of TEAEs (84%) were ≤Grade 2. There were no Grade 4 or 5 TEAEs. 16% patients experienced Grade 3 TEAEs.
- No meaningful dose relationship was noted for any of the common TEAEs, including Injection Site Reactions (ISRs)
- Most TEAEs were comparable in patients receiving rusfertide with TP alone and those receiving rusfertide with TP+CRT.
- Frequency of injection site reactions decreased with time.
- Average weekly rusfertide dose was generally comparable in all subgroups except those weighing ≤85 kg/female gender
- Secondary malignancies were identified in 6 patients. Five of these 6 patients had NMSCs. All patients had either prior history of cancer or a pre-existing lesion, and all except one, had prior or concurrent CRT with hydroxyurea or ruxolitinib, each of which are known to be associated with increased risk of NMSC (Verner 2014, Lin 2022).