Summary of Malignancies Observed Across 5 Phase 2 Open Label Clinical Trials of the Hepcidin Mimetic Rusfertide

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Objective

- To review all known malignancies in 5 phase 2 open label studies with rusfertide and the prior medical history of these patients

Introduction

- Polycythemia vera (PV) is a chronic myeloproliferative neoplasm (MPN) characterized by erythrocytosis[1]
  - Goals of treatment include resolving disease-related signs and symptoms, controlling blood counts, and reducing risk of thromboembolic events
  - First line recommended treatment for patients with high-risk PV includes hydroxyurea (HU) and interferon
    - Ruxolitinib is US Food and Drug Administration approved for those who have inadequate response or are intolerant to HU
- A higher incidence of secondary malignancies have been suggested in observational studies of patients with MPNs such as PV[2-4]
  - Higher rates of secondary malignancies have also been associated with treatment options for PV including ruxolitinib[5]
- Rusfertide is a hepcidin mimetic that is being investigated in clinical studies[6-11]
- In a 26-week transgenic rasH2 mice study, skin neoplasms (benign papilloma and malignant squamous cell carcinoma) were observed following exposure to rusfertide[12] (**Table 1**)
  - In this nonclinical study, a dose-response was not observed with the occurrence of these neoplasms

Table 1. Mouse Carcinogenicity Study Showed Rusfertide-Related Effects on Skin, Mostly Benign and With No Apparent Dose-Response Relationship

Sex	Rusfertide							
	Male				Female			
Dose Level (mg/kg/dose)	0	6.25	12.5	25	0	6.25	12.5	25
Number of Animals	25	25	25	25	25	25	25	25
Skin/Subcutis								
B-Papilloma, squamous cell	0	2	2	2	0	0	3*	3*
M-Carcinoma, squamous cell	0	1	0	0	0	0	1	0
B-Papilloma, squamous cell or M-Carcinoma, squamous cell	0	3*	2	2	0	0	4*	3*

B, Benign; M, Malignant.
*p<0.05.

Methods

- Patients (N=169) who enrolled in one of 5 phase 2 open label studies with rusfertide were included in the analysis
- The population included:
  - 70 patients with PV in REVIVE (NCT04057040; PTG-300-04)
  - 20 patients with PV in PACIFIC (NCT04767802; PTG-300-08)
  - 63 patients with β-thalassemia (NCT03802201; PTG-300-02)
    - Of the 63 patients with β-thalassemia, 34 enrolled in an extension protocol (NCT04054921; PTG-300-03) and were also included in the analysis
  - 16 patients with hemochromatosis (NCT04202965; PTG-300-06)

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Results

- The cutoff date for this analysis was 15 August 2023
- **Table 2** summarizes all known malignancies in 5 phase 2 open label studies with rusfertide

Table 2. Summary of Patients With ≥1 Malignancies in 5 Phase 2 Studies With Rusfertide

Phase 2 REVIVE Study (NCT04057040)

Proportion of patients with a medical history of cancer: 19/70 (27.1%)
Proportion of patients with a medical history of skin cancer: 10/70 (14.3%)
Proportion of patients with a malignancy on study: 7/70 (10.0%)

Case	Condition	Age	Sex	Race	Malignancy	Day	Medical History	Prior PV treatment
Patients With Prior History of Skin Cancer								
1	PV	72	F	White	SCC in situ	50	Melanoma and multiple SCC	HU ongoing for 5 years prior to event onset
2	PV	64	M	White	BCC	171	Multiple BCC	Ruxolitinib ongoing for 15 months prior to onset of first event
					Malignant melanoma Stage I	171	Multiple BCC	
3	PV	64	M	White	SCC in situ	226	Melanoma and BCC	HU ongoing for ≈5 years prior to onset of events
					AML	253	Radioiodine treatment for thyroid cancer (2015)	
4	PV	70	F	American Indian or Alaska Native	SCC in situ	307	Multiple BCC and SCC	Ruxolitinib for 11 months, stopped ≈1 year before event onset
					BCC	814		
5	PV	68	M	White	BCC	798	BCC	HU ongoing for 6 years prior to event onset
Patients With Preexisting Lesions Prior to Rusfertide Exposure								
6	PV	55	M	White	BCC	234	Preexisting lesion (captured in medical history; diagnosed only after initiation of rusfertide)	None
7	PV	51	M	White	Malignant melanoma Stage I	562	Undiagnosed lesion in the same area present prior to rusfertide exposure; history of atypical moles	None

Phase 2 PACIFIC Study (NCT04767802)

Proportion of patients with a medical history of cancer: 0/20 (0%)
Proportion of patients with a medical history of skin cancer: 0/20 (0%)
Proportion of patients with a malignancy on study: 0/20 (0%)

No cases

Phase 2 β-thalassemia Studies (NCT03802201 or NCT04054921)

Proportion of patients with a medical history of cancer: 0/63 (0%)
Proportion of patients with a medical history of skin cancer: 0/63 (0%)
Proportion of patients with a malignancy on study: 1/63 (1.6%)

Case	Condition	Age	Sex	Race	Malignancy	Day	Medical History	Prior treatment
8	β-thal	54	F	Other	Intrahepatic cholangio-carcinoma	247	History of non-alcoholic fatty acid liver disease/cirrhosis	Transfusion-dependent

Phase 2 Hemochromatosis Study (NCT04202965)

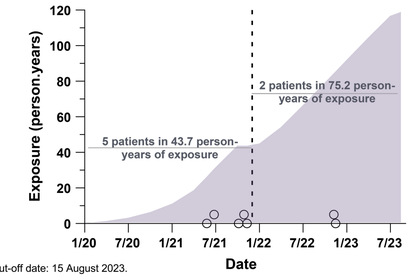
Proportion of patients with a medical history of cancer: 1/16 (6.3%)
Proportion of patients with a medical history of skin cancer: 1/16 (6.3%)
Proportion of patients with a malignancy on study: 1/16 (6.3%)

Case	Condition	Age	Sex	Race	Malignancy	Day	Medical History	Prior treatment
9	Hemochromatosis	71	M	White	Pancreatic adenocarcinoma	12	Lesion identified prior to study entry; melanoma	Phlebotomy

AML, acute myeloid leukemia; BCC, basal cell carcinoma; β-thal, β-thalassemia; HU, hydroxyurea; PV, polycythemia vera; SCC, squamous cell carcinoma.
Day, time from first dose of rusfertide to diagnosis of malignancy on study.

- In total, malignancies were observed in 9/169 patients (5.3%)
- In REVIVE, 7 patients with PV (7/70; 10.0%) reported a malignancy on study following exposure to rusfertide (**Figure 1**)
  - Median time from first dose of rusfertide to diagnosis of malignancy in the REVIVE study was 234 days (range, 50-798 days)
  - Of these 7 patients, 5 had a history of cutaneous malignancy prior to receiving rusfertide; the other 2 patients with no prior medical history of skin cancer had undiagnosed premalignant or preexisting lesions documented in their medical history (**Figure 2**)
  - The most common malignancies were in situ or stage I nonmelanoma skin cancer (NMSC; n=6 patients)
  - Two of the 7 patients were diagnosed with stage I melanoma (1 patient had NMSC and melanoma concurrently)
  - Acute myeloid leukemia (AML) developed in 1 patient with NMSC who also had a prior history of melanoma and thyroid cancer and was treated with radioactive iodine

Figure 1. Exposure vs. Time in the Phase 2 Study REVIVE: Increased Exposure to Rusfertide Did Not Appear to be Associated With Second Malignancies



Data cut-off date: 15 August 2023.

Figure 2. Medical History of PV Patients With Second Malignancies in the Phase 2 REVIVE Study

AML, acute myeloid leukemia; BCC, basal cell carcinoma; Ca, cancer; HU, hydroxyurea; PV, polycythemia vera; RUX, ruxolitinib; SCC, squamous cell carcinoma.
The case numbers in this figure correspond to the case numbers in Table 2. Data cut-off date: 15 August 2023. All patients had either a history of skin cancer or pre-existing lesions prior to receiving rusfertide on study.

- No malignancies were observed in the PACIFIC study
- One patient each developed a malignancy in the β-thalassemia (1 of 63 patients; 1.6%) and hemochromatosis (1 of 16 patients; 6.3%) studies
  - The onset of these events was 247 and 12 days after initiation of rusfertide therapy, respectively
- In REVIVE, 19 of 70 patients (27.1%) reported a malignancy prior to receiving rusfertide, including 10 patients (14.3%) with NMSC and 2 patients (2.9%) with melanoma
  - Other preexisting malignancies occurring in more than one patient included prostate (n=4), breast (n=2), and thyroid (n=2) cancer
  - The development of these other malignancies often preceded the diagnosis of PV

Conclusions

- In this analysis of 5 phase 2 open label studies with concurrent therapies, malignancies were observed in 9/169 patients (5.3%) in the following settings:
  - 7 of 90 patients (7.7%) with PV who enrolled in the REVIVE or PACIFIC studies
  - 1 of 63 patients (1.6%) who enrolled in the β-thalassemia study
  - 1 of 16 patients (6.3%) who enrolled in the hemochromatosis study
- The potential relationship, if any, between rusfertide exposure and development of malignancies is being monitored in patients with PV in the randomized placebo-controlled phase 3 study VERIFY (NCT05210790) that is enrolling patients in Europe, North America, and other regions throughout the world

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