MPN-120

A Real-World Evaluation of Risk Factors for Disease Progression in Patients With Polycythemia Vera (PV): An Analysis From the Prospective Observational Study of Patients With Polycythemia Vera in US Clinical Practices (REVEAL)

Presented at the
12th Annual Meeting of the Society of Hematologic Oncology (SOHO 2024)
Houston, TX, USA · September 4-7, 2024

Michael R. Grunwald,[1] Jeffrey I. Zwicker,[2,3] Aaron T. Gerds,[4] John M. Burke,[5] Zhenyi Xue,[6] Erin L. Crowgey,[6] Justine Carl,[6] Patricia Feldman,[6] Evan M. Braunstein,[6] Stephen T. Oh[7]

[1]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Department of Medicine, Weill Cornell Medical College, New York, NY, USA; [4]Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA; [5]Rocky Mountain Cancer Centers, Aurora, CO, USA; [6]Incyte Corporation, Wilmington, DE, USA; [7]Washington University School of Medicine, St. Louis, MO, USA

Introduction

- Polycythemia vera (PV) is a myeloproliferative neoplasm complicated by symptom burden, splenomegaly, vascular events, and disease progression to myelofibrosis (MF)[1]
- Progression to MF represents a major cause of morbidity and mortality for patients with PV[2]
- Current PV risk models include advanced age and history of thrombotic events (TEs)[1]; however, the risk factors influencing progression of PV to MF remain unclear
- The large, real-world, multicenter, prospective, observational study of patients with PV in US clinical practices (REVEAL; NCT02252159) collected demographics, treatment, disease burden, and patient-reported outcomes data from 2510 patients across 227 community or academic centers between 2014 and 2019[3]

Objective

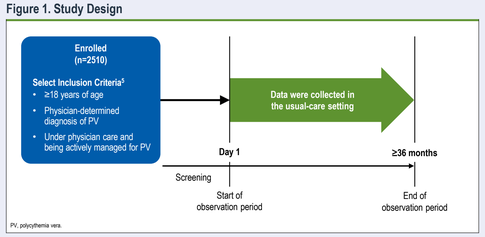
- To identify risk factors associated with PV progression to MF based on an analysis of data from REVEAL

Methods

Study Design

- REVEAL is a prospective, observational, noninterventional, nonrandomized, open-label study of patients with PV conducted in community and academic study sites throughout the United States **(Figure 1)**[4,5]
- Criteria for enrollment in REVEAL included a physician-reported PV diagnosis; key criteria for inclusion in this analysis are shown in **Figure 1**

Figure 1. Study Design



PV, polycythemia vera.

- Disease progression on study was defined by meeting any of the criteria outlined in **Table 1**

Table 1. Criteria for Disease Progression on Study*

Criterion 1	Death owing to MF/MDS/AML
Criterion 2	New/worsening splenomegaly and ≥2 of: WBC count >11×10⁹/L, Hb <10 g/dL, and platelet count <100×10⁹/L
Criterion 3	Bone marrow biopsy and fibrosis grade ≥2 or pathologic diagnosis of MF
Criterion 4	Circulating blasts >1% and new/worsening splenomegaly

Progression criteria defined for use in this analysis have not been validated across other studies.
‡Laboratory values were required from ≥1 time point.
AML, acute myeloid leukemia; Hb, hemoglobin; MDS, myelodysplastic syndrome; MF, myelofibrosis; WBC, white blood cell.

Statistics

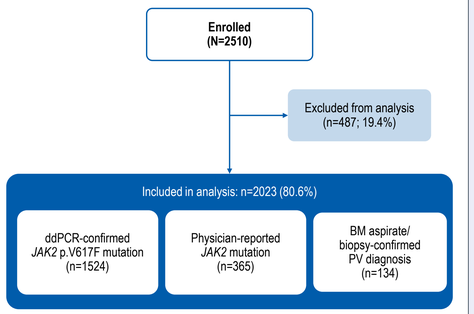
- Descriptive statistics were used to summarize demographics, disease characteristics, and treatment patterns
- Univariate and multivariate logistic regression analyses were performed to assess risk factors of PV progression

Results

Patient Disposition

- Of the 2510 patients enrolled in REVEAL, PV diagnosis was confirmed for 2023 patients **(Figure 2)**
- Among the 2023 patients with confirmed PV diagnosis:
  - 1524 of 1871 patients with available biospecimens were positive for *Janus kinase 2* (*JAK2*) p.V617F using droplet digital polymerase chain reaction
  - 365 without available biospecimens had a physician-reported *JAK2* mutation
  - 134 without available biospecimens had a PV diagnosis confirmed by bone marrow aspirate/biopsy
- 487 patients (19.4%) did not meet any diagnostic criteria and were excluded from the analysis
- Median (range) follow-up for patients with and without progression was 3.4 (0-4.9) and 3.7 (0-5.0) years, respectively

Figure 2. Patient Disposition



BM, bone marrow; ddPCR, droplet digital polymerase chain reaction; JAK, Janus kinase; PV, polycythemia vera.

Disease Progression

- Among the 2023 patients with confirmed PV diagnosis:
  - 135 (6.7%) met the criteria for PV to MF progression during the study
  - 30 patients (1.5%) met ≥2 progression criteria
  - Criterion 3 (bone marrow fibrosis) was the most common progression criterion met (3.4%; **Table 2**)

Table 2. Progression Criteria Met During Study

Progression Criteria	n (%)
Criterion 1: Death owing to MF/MDS/AML	22 (1.1)
Criterion 2: New/worsening splenomegaly and ≥2 of: WBC count >11×10⁹/L, Hb <10 g/dL, and platelet count <100×10⁹/L	45 (2.2)
Criterion 3: Bone marrow biopsy with fibrosis grade ≥2 or pathologic diagnosis of MF	69 (3.4)
Criterion 4: Circulating blasts >1% and new/worsening splenomegaly	37 (1.8)

AML, acute myeloid leukemia; Hb, hemoglobin; MDS, myelodysplastic syndrome; MF, myelofibrosis; WBC, white blood cell.

Clinical Characteristics

Table 3. Enrollment Demographics and Clinical Characteristics in Patients With vs Without Disease Progression

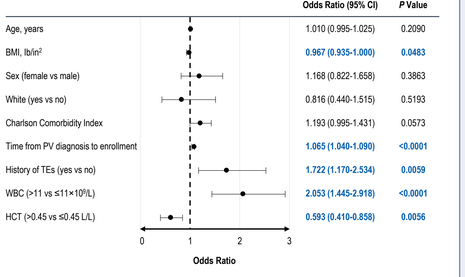
Characteristic	PV Progression (n=135)	No PV Progression (n=1888)	*P* Value	Total (n=2023)
Age at enrollment, years, median (range)	69.0 (32-92)	68.0 (22-95)	0.2089	68.0 (22-95)
≥60 years, n (%)	106 (78.5)	1397 (74.0)	0.2451	1503 (74.3)
Male, n (%)	74 (54.8)	962 (51.0)	0.3859	1036 (51.2)
Race, n (%)			0.5188	
White	114 (84.4)	1688 (89.4)		1802 (89.1)
Non-White	12 (8.9)	145 (7.7)		157 (7.8)
No information	9 (6.7)	55 (2.9)		64 (3.2)
Time from PV diagnosis to enrollment, years, median (range)	**7.2 (0-34.1)**	**3.7 (0-38.5)**	**<0.0001**	3.8 (0-38.5)
<5 years, n (%)	**52 (38.5)**	**1141 (60.4)**	**<0.0001**	1193 (59.0)
≥5 years, n (%)	**83 (61.5)**	**742 (39.3)**		825 (40.8)
PV risk at enrollment, n (%)			**0.0446**	
Low risk	**19 (14.1)**	**403 (21.3)**		422 (20.9)
High risk	**116 (85.9)**	**1485 (78.7)**		1601 (79.1)
History of TEs at enrollment, n (%)	**40 (29.6)**	**371 (19.7)**	**0.0054**	411 (20.3)
Clinical practice setting, n (%)			**0.0455**	
Academic	**32 (23.7)**	**320 (16.9)**		352 (17.4)
Community	**103 (76.3)**	**1568 (83.1)**		1671 (82.6)
PV treatment at enrollment, n (%)				
Watchful waiting only	9 (6.7)	103 (5.5)	0.5522	112 (5.5)
Phlebotomy	**24 (17.8)**	**524 (27.8)**	**0.0117**	548 (27.1)
Hydroxyurea	52 (38.5)	587 (31.1)	0.0729	639 (31.6)
Hydroxyurea and phlebotomy in combination	**24 (17.8)**	**515 (27.3)**	**0.0159**	539 (26.6)
Other*	**26 (19.3)**	**159 (8.4)**	**<0.0001**	185 (9.1)

Significant values (*P*<0.05) are shown in **bold** font.
*"Other" includes treatments such as ruxolitinib, recombinant interferon-alfa, pegylated recombinant interferon-alfa, busulfan, and anagrelide.
PV, polycythemia vera; TE, thrombotic event.

Associations Between Patient Characteristics and PV Progression

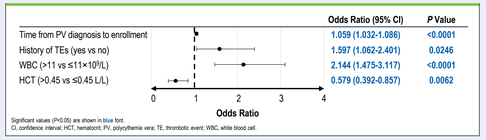
- In univariate analysis of patients with vs without progression, significant covariates were time from PV diagnosis to enrollment, history of TEs, hematocrit (HCT) ≤0.45 L/L, and white blood cell (WBC) count >11×10⁹/L at enrollment (*P*<0.006; **Figure 3**)
- Each covariate remained significant in multivariate analyses with stepwise model selection **(Figure 4)**

Figure 3. Univariate Logistic Regression on PV Disease Progression



Significant values (*P*<0.05) are shown in blue font.
BMI, body mass index; CI, confidence interval; HCT, hematocrit; PV, polycythemia vera; TE, thrombotic event; WBC, white blood cell.

Figure 4. Multivariate Logistic Regression on PV Disease Progression With Stepwise Model Selection



Significant values (*P*<0.05) are shown in blue font.
CI, confidence interval; HCT, hematocrit; PV, polycythemia vera; TE, thrombotic event; WBC, white blood cell.

- At enrollment, patients with HCT ≤0.45 L/L vs >0.45 L/L had a significantly longer duration from PV diagnosis, had higher PV risk, and were more likely to be receiving hydroxyurea or other cytoreductive treatment, which potentially confounds the HCT ≤0.45 L/L covariate **(Table 4)**
- These confounders were not observed in patients with WBC >11×10⁹/L vs ≤11×10⁹/L **(Table 5)**

Table 4. Enrollment Demographics and Clinical Characteristics of Patients With HCT ≤0.45 vs >0.45 L/L

Characteristic	HCT ≤0.45 L/L (n=1103)	HCT >0.45 L/L (n=899)	*P* Value
Time from PV diagnosis to enrollment, years, median (range)	**4.4 (0-36.3)**	**2.9 (0-38.5)**	**<0.0001**
≥5 years, n (%)	**492 (44.6)**	**326 (36.3)**	**0.0007**
PV risk at enrollment, n (%)			
Low	**211 (19.1)**	**206 (22.9)**	**0.0381**
High	**892 (80.9)**	**693 (77.1)**	
PV treatment at enrollment, n (%)			
Watchful waiting only	63 (5.7)	44 (4.9)	0.4187
Phlebotomy	**207 (18.8)**	**337 (37.5)**	**<0.0001**
Hydroxyurea and phlebotomy in combination	**241 (21.8)**	**297 (33.0)**	**<0.0001**
Hydroxyurea	**444 (40.3)**	**184 (20.5)**	**<0.0001**
Other*	**148 (13.4)**	**37 (4.1)**	**<0.0001**

Significant values (*P*<0.05) are shown in **bold** font.
*"Other" includes treatments such as ruxolitinib, recombinant interferon-alfa, pegylated recombinant interferon-alfa, busulfan, and anagrelide.
HCT, hematocrit; PV, polycythemia vera.

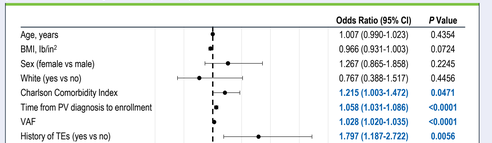
Table 5. Enrollment Demographics and Clinical Characteristics of Patients With WBC >11 vs ≤11×10⁹/L

Characteristic	WBC ≤11×10⁹/L (n=1357)	WBC >11×10⁹/L (n=647)	*P* Value
Time from PV diagnosis to enrollment, years, median (range)	3.7 (0-36.3)	4.2 (0-38.5)	0.2334
≥5 years, n (%)	532 (39.2)	288 (44.5)	0.0698
PV risk at enrollment, n (%)			
Low	278 (20.5)	140 (21.6)	0.5529
High	1079 (79.5)	507 (78.4)	
PV pharmacotherapy at enrollment, n (%)			
Watchful waiting only	**62 (4.6)**	**46 (7.1)**	**0.0185**
Phlebotomy	**301 (22.2)**	**242 (37.4)**	**<0.0001**
Hydroxyurea and phlebotomy in combination	372 (27.4)	166 (25.7)	0.4067
Hydroxyurea	**496 (36.6)**	**134 (20.7)**	**<0.0001**
Other*	126 (9.3)	59 (9.1)	0.9044

Significant values (*P*<0.05) are shown in **bold** font.
*"Other" includes treatments such as ruxolitinib, recombinant interferon-alfa, pegylated recombinant interferon-alfa, busulfan, and anagrelide.
PV, polycythemia vera; WBC, white blood cell.

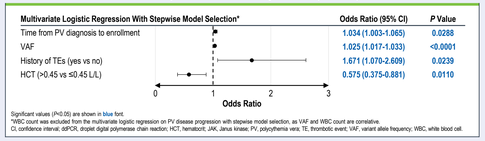
- In a subset analysis of patients with quantitative allele burden data, variant allele frequency (VAF) was a significant covariate (*P*<0.0001; **Figure 5**)
- Mean (standard deviation) *JAK2* p.V617F VAF was higher in patients with vs without PV progression (67.9 [31.4] vs 46.0 [29.2]; *P*<0.0001)
- VAF was retained as a significant covariate in multivariate analyses with stepwise model selection **(Figure 6)**
  - WBC (>11 vs ≤11×10⁹/L) was excluded from the multivariate analysis models because VAF and WBC (>11 vs ≤11×10⁹/L) are confounded variables **(Figure 7)**

Figure 5. Univariate Logistic Regression on PV Disease Progression in Patients With *JAK2* p.V617F Mutation by ddPCR (n=1524)



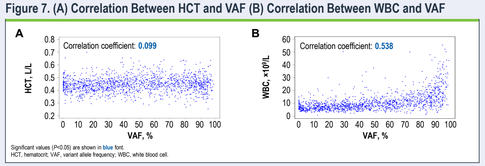
Significant values (*P*<0.05) are shown in blue font.
BMI, body mass index; CI, confidence interval; ddPCR, droplet digital polymerase chain reaction; HCT, hematocrit; JAK, Janus kinase; PV, polycythemia vera; TE, thrombotic event; VAF, variant allele frequency; WBC, white blood cell.

Figure 6. Multivariate Logistic Regression on PV Disease Progression With Stepwise Model Selection in Patients With *JAK2* p.V617F Mutation by ddPCR (n=1524)



Significant values (*P*<0.05) are shown in blue font.
*WBC count was excluded from the multivariate logistic regression on PV disease progression with stepwise model selection, as VAF and WBC count are correlative.
CI, confidence interval; ddPCR, droplet digital polymerase chain reaction; HCT, hematocrit; JAK, Janus kinase; PV, polycythemia vera; TE, thrombotic event; VAF, variant allele frequency; WBC, white blood cell.

Figure 7. (A) Correlation Between HCT and VAF (B) Correlation Between WBC and VAF



Significant values (*P*<0.05) are shown in blue font.
HCT, hematocrit; VAF, variant allele frequency; WBC, white blood cell.

Conclusions

- **REVEAL is the largest prospective observational clinical study of patients with PV to date**
- **This analysis found that 6.7% of patients with PV progressed to MF over the median 3.7 years of follow-up**
- **5 predictors of PV progression were identified: disease duration, TE history, WBC count >11×10⁹/L, HCT ≤0.45 L/L, and VAF**
  - **However, HCT ≤0.45 L/L may be confounded by disease duration and cytoreductive treatment covariates**
- **These results provide additional support for the use of disease duration and elevated WBC and VAF as risk factors for disease progression, and identify history of TEs as a potential novel risk factor**

Disclosures

Grunwald: Consulting fees – *AbbVie, Agios/Servier, Amgen, Astellas Pharma, Blueprint Medicines, Bristol Myers Squibb, Cardinal Health, CTI BioPharma/Sobi, Daiichi Sankyo, Gamida Cell, Genentech, Gilead Sciences, GlaxoSmithKline/Sierra Oncology, Incyte Corporation, Invitae, Jazz Pharmaceuticals, Novartis, Ono Pharmaceutical, Pfizer, Pharmacosmos, Premier, Stemline Therapeutics*; Research support – *Incyte Corporation, Janssen*; Stock ownership – *Medtronic*.

Acknowledgments

The authors wish to thank the patients, investigators, and site personnel who participated in REVEAL. This study was sponsored by Incyte Corporation (Wilmington, DE, USA). Medical writing assistance was provided by Sophie Pickles, PhD, of Envision Pharma Group (Fairfield, CT, USA) and funded by Incyte Corporation.

References

1. Bewersdorf JP, et al. *Blood*. 2023;142:1859-1870. **2.** Baumeister J, et al. *Cells*. 2021;10:3551. **3.** Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk*. 2020;20:219-225. **4.** Grunwald MR, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:788-795.e2. **5.** ClinicalTrials.gov. NCT02252159. https://clinicaltrials.gov/ct2/show/NCT02252159. Accessed December 5, 2023.

To download a copy of this poster, scan code

Originally presented at ASH 2023 and EHA 2024