HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2024 September 19.

Published in final edited form as:

N Engl J Med. 2024 September 19; 391(11): 1015–1027. doi:10.1056/NEJMoa2312749.

Pomalidomide for Epistaxis in Hereditary Hemorrhagic Telangiectasia

Hanny Al-Samkari, M.D.[1], **Raj S. Kasthuri, M.B.B.S.**[2], **Vivek N. Iyer, M.D., M.P.H.**[3], **Allyson M. Pishko, M.D., M.S.C.E.**[4], **Jake E. Decker, M.D.**[5], **Clifford R. Weiss, M.D.**[6], **Kevin J. Whitehead, M.D.**[7], **Miles B. Conrad, M.D., M.P.H.**[8], **Marc S. Zumberg, M.D.**[9], **Jenny Y. Zhou, M.D.**[10], **Joseph Parambil, M.D.**[11], **Derek Marsh, M.S.**[12], **Marianne Clancy, M.P.A.**[13], **Lauren Bradley, M.H.S.**[12], **Lisa Wisniewski, R.N.**[11], **Benjamin A. Carper, M.S.**[12], **Sonia M. Thomas, Dr.P.H.**[12], **Keith R. McCrae, M.D.**[11]

[1]Massachusetts General Hospital, Boston, MA.

[2]University of North Carolina, Chapel Hill, NC.

[3]Mayo Clinic, Rochester, MN.

[4]University of Pennsylvania, Philadelphia, PA.

[5]Medical College of Wisconsin, Milwaukee, WI

[6]Johns Hopkins University, Baltimore, MD.

[7]University of Utah, Salt Lake City, UT.

[8]University of California San Francisco, San Francisco, CA.

[9]University of Florida, Gainesville, FL.

[10]University of California San Diego, San Diego, CA.

[11]Cleveland Clinic, Cleveland, OH

[12]RTI International, Research Triangle Park, NC

[13]CureHHT, Monkton, MD

Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT) is characterized by extensive telangiectasias and arteriovenous malformations. The primary clinical manifestation is epistaxis that results in iron deficiency anemia and reduced health-related quality of life (HRQoL).

Methods: PATH-HHT was a randomized, placebo-controlled trial evaluating safety and efficacy of pomalidomide in HHT. Participants were randomized 2:1 to pomalidomide 4 mg daily or matching placebo for 24 weeks. The primary outcome was the change from baseline in the

Corresponding author: Keith R. McCrae, M.D., Department of Hematology and Oncology, Taussig Cancer Institute; Department of Cardiovascular and Metabolic Sciences, Lerner Research Institute; Department of Vascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, OH 44195, mccraek@ccf.org.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Epistaxis Severity Score, a validated bleeding score in HHT (Table S2.2), from randomization to the end of the treatment. A reduction of 0.71 points or more is considered clinically significant.

Results: PATH-HHT was closed to enrollment in June 2023 after a planned interim analysis met a prespecified threshold for efficacy. One hundred forty-four participants were randomized (95 pomalidomide, 49 placebo). The baseline mean (±SD) Epistaxis Severity Score was 5.0 ± 1.5, consistent with moderate to severe epistaxis. At 24 weeks, the mean difference in Epistaxis Severity Score for pomalidomide compared to placebo treated participants was −0.94 (95% confidence interval, −1.57 to −0.31; p = 0.004). The HHT-specific QoL score, which ranges from 0 to 16 with higher scores indicating more limitations, also decreased more in the pomalidomide group (mean difference, −1.4; 95% confidence interval −2.6 to −0.3;). Adverse events more common in the pomalidomide group included neutropenia, constipation, and rash.

Conclusions: In patients with HHT, pomalidomide resulted in a significant, clinically relevant reduction in epistaxis severity and improved disease specific HRQoL. No unexpected safety signals were identified. (Funded by National Heart Lung and Blood Institute; Clinicaltrials.gov: NCT03910244).

Introduction

Affecting approximately 1 in 3800 persons,[1] hereditary hemorrhagic telangiectasia (HHT) is the second most common inherited bleeding disorder.[2] HHT is an autosomal dominant vasculopathy caused by mutations affecting transforming growth factor-β (TGF-β)/BMP signaling, resulting in fragile mucocutaneous telangiectasias and visceral arteriovenous malformations.[2, 3] Over 95% of patients develop recurrent epistaxis, with frequent psychiatric comorbidity (depression and post-traumatic stress disorder) and reduction in health-related quality of life (HRQoL).[4–7] One-third of patients exhibit gastrointestinal bleeding, and most develop iron deficiency anemia.[8, 9] HHT-associated bleeding usually worsens over the lifespan and results in a requirement for frequent iron infusions and/or red blood cell (RBC) transfusions.[5] Visceral arteriovenous malformations also occur in the lung (~50%), liver (~70%), and brain (~20%)[5] andmay result in embolic stroke, pulmonary hemorrhage, tissue or brain abscesses, high output heart failure, hepatic disease, hemorrhagic stroke, and epilepsy.[2, 3] Despite the morbidity of visceral arteriovenous malformations, patients distinctly identify bleeding as their most important disease manifestation.[10] Patients with HHT may have reduced overall survival relative to the general population.[11]

No treatments for HHT are approved by the U.S. Food and Drug Administration (FDA) or European Medicines Agency. Management of bleeding involves temporizing ablative procedures on telangiectasias in the nose and gastrointestinal tract, off-label use of antifibrinolytic drugs,[5] and potentially more aggressive surgery (e.g., surgical closure of the nares). However, given the systemic angiogenic dysregulation inherent to HHT, repurposing systemic antiangiogenic agents for its treatment has been explored.[12–14] Non-randomized and/or underpowered studies with bevacizumab or thalidomide suggest some effectiveness in treating HHT-associated bleeding.[15–17] Thalidomide, an immunomodulatory imide drug (IMiD), is the only antiangiogenic agent with positive prospective efficacy in

HHT, demonstrated in a 31-patient study.[17] However, thalidomide is associated with serious toxicities, such as thromboembolism and irreversible peripheral neuropathy.[18]

We wished to determine whether pomalidomide, a thalidomide derivative, may have efficacy in treating HHT with a more favorable toxicity profile. IMiDs such as pomalidomide may be disease-modifying in HHT, improving the integrity of fragile telangiectasias and exerting an antiangiogenic effect.[19, 20]

Methods

Patients and Trial Oversight

Adult patients with definite HHT defined by the Curacao criteria[21] with an Epistaxis Severity Score of at least 3 over the three months before screening, and who had anemia at screening and/or received iron infusions or red blood cell (RBC) transfusions in the prior 6 months were eligible (Table S1.1). The Epistaxis Severity Score is a validated HHT-specific bleeding assessment tool with scores between 0 (no epistaxis) and 10 (worst epistaxis) over a period of time (Table S2.2).[22] The protocol was approved by an independent Data and Safety Monitoring Board and the institutional review board at Cleveland Clinic. Trial activities and oversight were conducted in accordance with FDA regulatory requirements. All participants provided written informed consent upon entry.

Trial Design, Randomization, and Treatment

This double-blind randomized trial conducted at 11 U.S. sites compared epistaxis and HRQoL outcomes every 4 weeks during 24 weeks of treatment with pomalidomide or placebo, and at 4 weeks post-treatment. Participants were randomized 2:1: to pomalidomide 4 mg daily or matching placebo using permuted blocks with random sizes of 3 and 6, stratified by site and implemented within the electronic data management system. Participants and study staff were blinded to treatment assignment except for one statistician (BAC) who provided emergency unblinding and interim analyses. Dose reductions to 3 mg or 2 mg were allowed for toxicity. Any clinically indicated interventional treatments were recorded. Oral antifibrinolytic agents taken at a stable dose at study entry could be continued. Participants were managed in accordance with the FDA-mandated risk evaluation and mitigation strategy program for pomalidomide.[23] The protocol and statistical analysis plan are available with this article at NEJM.org. The authors vouch for the data and adherence to the protocol. The manuscript was written without assistance from contract science writers.

Outcomes

The primary outcome was the Epistaxis Severity Score change from baseline at 24 weeks. Epistaxis Severity Score was assessed for the prior 4 weeks at baseline and each 4-week visit. Key secondary outcomes, also assessed at 24 weeks were: 1) HHT-specific HRQoL (HHT-QoL) score,[6] which measures the impact of HHT manifestations on HRQoL in the preceding 4 weeks and ranges from 0 (none) to 16 (worst); 2) daily self-reported epistaxis duration recorded via smartphone diary, averaged over 28 days; 3) number of units of packed red blood cells transfused through 24 weeks; 4) amount of parenteral iron (mg)

infused through 24 weeks; and 5) Neuro-QoL™ Satisfaction with Social Roles and Activities T-score,[24, 25] which is evaluated over the preceding week and is scored relative to a normal population. Other secondary outcomes included changes in levels of hemoglobin, hematocrit, mean corpuscular volume (MCV), mean cellular hemoglobin concentration (MCHC), ferritin, transferrin saturation, individual items of the Epistaxis Severity Score, endoscopic interventions, and PROMIS Depression and Fatigue T-scores.[26, 27] Oral iron preparations, but not dietary iron, were also recorded.

Statistical Analysis

We planned to randomize 159 participants to obtain 90% power to identify a treatment difference in Epistaxis Severity Score change from baseline at 24 weeks of 1.0, assuming a standard deviation of 1.7 and discontinuation rate of 10%.

Efficacy outcomes were analyzed for all randomized and treated participants with post-baseline data (modified intent-to-treat mITT population). A supportive pre-specified per-protocol analysis excluded early discontinuations and participants with treatment compliance less than 80%. Safety outcomes were analyzed for all randomized and treated participants.

Epistaxis Severity Score change at 24 weeks was evaluated for statistical significance at $p<0.0425$ accounting for two planned interim analyses. Five key secondary outcomes were assessed for statistical significance at $p<0.01$ with adjustment for multiple comparisons (Supplemental Methods).. All treatment group comparisons include an estimated difference with 95% confidence interval. Widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. All other p-values are for descriptive purposes.

Changes from baseline outcomes were analyzed with a repeated measures linear model or generalized logistic model which accounts for correlation of measurements over time, with adjustment for baseline value and clinical site.[28] Missed visits after discontinuations are assumed missing at random. Supportive analyses of the primary outcome included evaluation on the per-protocol population and pre-specified subgroups. Sensitivity to the missing at random assumption was assessed with control-based and tipping-point multiple imputation (Supplemental Methods).[29–31] Non-normally distributed outcomes were analyzed with rank analysis of covariance by visit.[32] Analyses were based on a statistical plan prepared by a masked statistician and performed using SAS, version 9.4.[33]

Results

Patients, Treatment Exposure, and Adherence

Between November 5, 2019 and June 27, 2023, 177 patients were screened, and 144 meeting eligibility criteria were randomized (95 pomalidomide, 49 placebo), Figure 1. The study was closed to enrollment after the second planned interim analysis due to meeting pre-specified efficacy criteria. Eleven ongoing participants were terminated after completing at least 12 weeks of treatment. Twenty-seven percent (26/95) of participants in the pomalidomide group

discontinued, including 15 (16%) for adverse events, compared to 10% (5/49) in the placebo group.

Demographic and clinical characteristics were similar between groups (Table 1). Participants included 48% females, 11% race other than white, 3% Hispanic/Latino ethnicity; mean (± standard deviation) age was 58.8 ± 12.2 years. Though extensive demographic data on HHT is not available, our study population appears consistent with previous U.S. studies.[34] (Table S1.2) However, Blacks were underrepresented. The mean Epistaxis Severity Score was 5.0 ± 1.5 (moderate severity) and the mean HHT-QoL score was 6.3 ± 3.1 (Figure S1). At baseline, 99 (69%) had anemia. In the 6 months before screening, 121 (84%) received intravenous iron and 28 (19%) received RBC transfusion.

Efficacy

Primary Outcome—The reduction in the Epistaxis Severity Score at 24 weeks was significantly greater in the pomalidomide compared to the placebo group (−1.84 [95% confidence interval (CI), −2.25 to −1.43] versus −0.90 [95% CI −1.39 to −0.40]; mean difference, −0.94 [95% CI, −1.57 to −0.31], p=0.004) (Table 2, Figure 2A, Table S2.1, Table S2.2). This difference is larger than the minimally important difference of 0.71.[35] Cohen's D (a statistical measure of effect size generated by comparing the means of two groups) was 0.57, indicating a medium effect size. The difference between pomalidomide and placebo became apparent at week 12 (−0.52; 95% CI, −1.04 to −0.01) and was consistent from week 16 (−0.95; 95% CI, −1.56 to −0.34) through the remainder of the study including 4 weeks post-treatment (Week 28) (−1.03; 95% CI, −1.62 to −0.44). Results were consistent across supportive analyses in the per-protocol population (Table-Figure S2.3), in pre-defined and exploratory subgroups including participants with *ENG* or *ACVRL1* mutations, and those with Epistaxis Severity Score baseline scores <6 vs >=6 (Table-Figure S2.4). Efficacy of pomalidomide was also evident in participants with dose reduction at any timepoint (Table-Figure S2.5), and with control-based multiple imputation (Table S2.6) and tipping point sensitivity analyses (Table S2.7).

The incidence of relapse of the Epistaxis Severity Score to the baseline value or greater at the 4-week post-treatment visit was substantially lower in the pomalidomide group (21%) compared with the placebo group (39%) (relative risk, 0.46; 95% CI, 0.15 to 0.77), Table S2.8. Responses to individual items of the Epistaxis Severity Score are shown in Tables and Figures S2.9–S2.11.

Acute visceral bleeds, categorized as serious adverse events, occurred in 6% of participants receiving pomalidomide and 10% receiving placebo (Table 3).

Key Secondary Efficacy Outcomes—Improvement in the HHT-QoL score was substantially greater at 24 weeks in the pomalidomide compared to the placebo group (−2.7 [95% CI −3.4 to −1.9] versus −1.2 [95% CI, −2.1 to −0.3]; mean difference, −1.4 [95% CI, −2.6 to −0.3]). This improvement was maintained through the 4-week post treatment visit (Table 2, Figure 2B, Tables S3.1 and S3.2). The remaining key secondary outcomes showed greater improvement in the pomalidomide group at 24 weeks (Table 2). Daily self-reported epistaxis duration, reported for 82% (87/106) of active participants at 24

weeks, was highly variable with no treatment group differences noted (Table 2, Table-Figure S4.1). However, post-hoc analyses that weighted bleeding duration by the reported intensity (Supplemental Methods) identified reduced weighted bleeding duration in pomalidomide-treated participants across all time points: at 24 weeks: −12.2 weighted intensity-minutes [95% CI −17.1 to −7.3] versus −3.3 [95% CI, −9.5 to 2.8], mean difference −8.9 [95% CI, −16.5 to −1.2]), Table 2, Table-Figure S4.2. Group differences in red blood cell transfusions and iron infusions were most apparent in a post-hoc evaluation encompassing weeks 12–24 of treatment: RBC transfusions were administered to 9% of participants in the pomalidomide group compared to 18% in the placebo group, and the median amount of iron infused (mg per 4 weeks) was 0 (IQR 0–340) in the pomalidomide group and 333 mg (IQR 0–500) in the placebo group (Table 2, Table S5). The Neuro-QoL Satisfaction with Social Roles and Activities score demonstrated the greatest improvement in the pomalidomide compared to the placebo group at the 4-week post-treatment visit (mean difference, 2.6 [95% CI, 0.1 to 5.2], Table 2, Tables S6.1 and 6.2–Figure S6.

Other Secondary Efficacy Outcomes—Other secondary efficacy outcomes are described in Table 2 and Tables-Figures S7–S15. Most did not demonstrate a notable treatment group difference at 24 weeks, but several had a strong treatment group difference at 4 weeks post-treatment, as follows: PROMIS Fatigue score (mean difference, −5.5 [95% CI, −8.7 to −2.3], Tables S8.1 and S8.2–Figure S8), hemoglobin (mean difference, 1.09 [95% CI, 0.38 to 1.80] g/dL, Table-Figure S10), hematocrit (mean difference, 2.41% [95% CI, 0.51% to 4.32%], Table-Figure S11). Proportional changes in MCV (Table-Figure S13), and MCHC (Table-Figure S14) were also observed.

No differences were seen in use of concomitant medications (e.g., tranexamic acid or epsilon-aminocaproic acid) or interventional procedures between the pomalidomide and placebo groups (Tables 2, S15).

Adverse Events

Drug doses were reduced to 3 mg or 2 mg in 37% of pomalidomide participants versus 4% of placebo (Table-Figure S16). The major toxicity was neutropenia (44% in the pomalidomide group vs 10% in the placebo group, p<0.001, Tables 3, Table-Figure S17.1, Tables S18.1–S18.7). The mean change in absolute neutrophil count (ANC) from baseline to week 24 was −1710 (95% CI −2030 to −1390) /μL in the pomalidomide group compared to −20 (95% CI −420, 380) /μL in the placebo group (P<0.001, Table-Figure S17.1). Three pomalidomide participants (3%) developed an ANC <500/μl; none were associated with infection. Neutropenia was reversible with dose reduction or temporary discontinuation of pomalidomide. No significant difference in platelet counts was noted in pomalidomide versus placebo treated patients (Table S17.2). Other adverse events more common in the pomalidomide group included constipation (47% vs 18%) and rash (35% vs 10%). Adverse events of grade 3 (severe) or higher occurred more often in the pomalidomide group (47% vs 24%). Four venous thromboembolic events (4%) occurred in the pomalidomide group (2 provoked distal DVT, 2 unprovoked subsegmental pulmonary emboli) versus 1 venous thromboembolic event (2%) in the placebo group (portal vein thrombosis) (Table S18.3). Participants with drug permanently stopped due to adverse events, interrupted but

not stopped, and dose reduced but not interrupted in the pomalidomide group compared to placebo were 16% vs 2% (p=0.01), 40% vs 14% (p=0.002) and 13% vs 0 (p=0.01) respectively (Tables 3, S18.4–S18.6).

Discussion

This randomized double-blind trial demonstrated that pomalidomide resulted in a significant improvement in the epistaxis severity score and substantially improved disease specific HRQoL.[6] These improvements occurred despite a strong placebo effect that dissipated following discontinuation of blinded study drug. Additional objective measures, including incidence of blood transfusion, quantity of infused iron, hemoglobin, hematocrit, MCV and MCHC were all directionally consistent with these outcomes. The benefits of pomalidomide were most apparent over the second twelve weeks of the study, not dependent on HHT genotype or epistaxis severity and persisted during the four weeks after treatment discontinuation.

Pomalidomide is structurally related to other IMiD family drugs, particularly thalidomide. These agents share similar properties, including therapeutic efficacy in multiple myeloma. Compared to thalidomide, however, pomalidomide displays an improved safety profile, with a lower incidence of cytopenias and peripheral neuropathy.[36] Given that fatigue and thrombosis have been observed in populations with multiple myeloma receiving IMiDs and are relevant in HHT, the low and similar rates of these adverse events in treatment and placebo arms suggest feasibility for the use of pomalidomide in HHT.

Pomalidomide was generally associated with low grade toxicities. The most notable adverse event was neutropenia that was generally mild, not associated with opportunistic infections, and promptly reversible with dose modification. We observed no reduction in efficacy in patients in whom the pomalidomide dose was decreased, suggesting that, as with thalidomide, lower doses of pomalidomide may be similarly efficacious in HHT with fewer adverse events.[17]

HHT is characterized by mutations in *ENG*, *ACVRL1* or *SMAD4* in more than 90% of patients. These genes encode proteins involved in signaling through the TGF-β/BMP pathway and the beneficial effects of pomalidomide in HHT might reflect reversal of angiogenic dysregulation by bypassing or reversing abnormalities in TGF-β/BMP signaling. We found that the Epistaxis Severity Score improved similarly in patients with either *ENG* or *ACVRL1* mutations. In a seven patient pilot study, participants treated with thalidomide underwent biopsy of nasal telangiectasia before and after treatment. Examination of post-treatment biopsies did not demonstrate inhibition of endothelial cell proliferation, but rather enhanced mural cell coverage of the vasculature.[20]

Participants treated with pomalidomide demonstrated increases in hemoglobin and hematocrit. These occurred despite a substantial decrease in intravenous iron infusions and red cell transfusions.

We observed a persistent reduction in the Epistaxis Severity Score below baseline in the four weeks following pomalidomide treatment, accompanied by further improvement in the

HHT-specific quality-of-life score, hemoglobin, and hematocrit. These results suggest that pomalidomide effects may extend beyond the duration of treatment in HHT, and that the failure to more substantially increase hemoglobin levels during treatment may represent a component of bone marrow suppression by pomalidomide at the 4 mg daily dosing regimen used in this study.

The efficacy of pomalidomide compared to bevacizumab in HHT can only be discerned by head-to-head trials. Retrospective reports of intravenous bevacizumab enrolled patients with a higher mean Epistaxis Severity Score than our study, though the reduction in Epistaxis Severity Score in pomalidomide treated patients with Epistaxis Severity Score ≥ 6 compared to those in series of bevacizumab is similar.[15] An advantage of pomalidomide, unlike bevacizumab, is that it is an oral medication and might be more convenient for patients without access to infusion centers. Whether pomalidomide or bevacizumab are more effective in patients with different types of bleeding or sites of arteriovenous malformations is uncertain and will need to be determined in future studies. Since pomalidomide and bevacizumab may have different mechanisms of action, they may have additive or synergistic activity in severe cases of HHT.

Strengths of this study include double-blind treatment, adequate power for the primary outcome, broad inclusion criteria, and thorough collection of secondary outcomes. Evidence of efficacy based on changes in the Epistaxis Severity Score led to early study termination, resulting in reduction from the planned sample size, thus impacting power for secondary outcome analyses. A potential weakness of the study is that similar efficacy might have been observed with lower doses of pomalidomide with less toxicity. In addition, Black patients were underrepresented.

Though our study provides evidence of efficacy and safety of pomalidomide for HHT-related epistaxis, whether similar effects are evident in patients with GI bleeding, or pulmonary, liver or brain arteriovenous malformations is uncertain. Moreover, defining mechanisms of action of pomalidomide in HHT will require additional studies. Most importantly, however, PATH-HHT demonstrates efficacy of a new agent for HHT that may provide improved quality of life for this population for whom no approved therapies exist.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

We thank the patients and their families for their participation in the trial, personnel at the study sites and coordinating centers for their contributions to the trial, Cure HHT for assistance with participant recruitment, and members of the Data and Safety Monitoring Board for their oversight (Supplement). Pomalidomide and matching placebo were kindly donated by Bristol-Meyers-Squibb. The manuscript was drafted by H. Al-Samkari, S Thomas, and K.McCrae.

Funding/Support

The project was funded by the National Heart Lung and Blood Institute, under grants UG3HL140097 (K. McCrae, Cleveland Clinic, clinical coordinating center) and U24HL140090 (S. Thomas, RTI, data coordinating center).

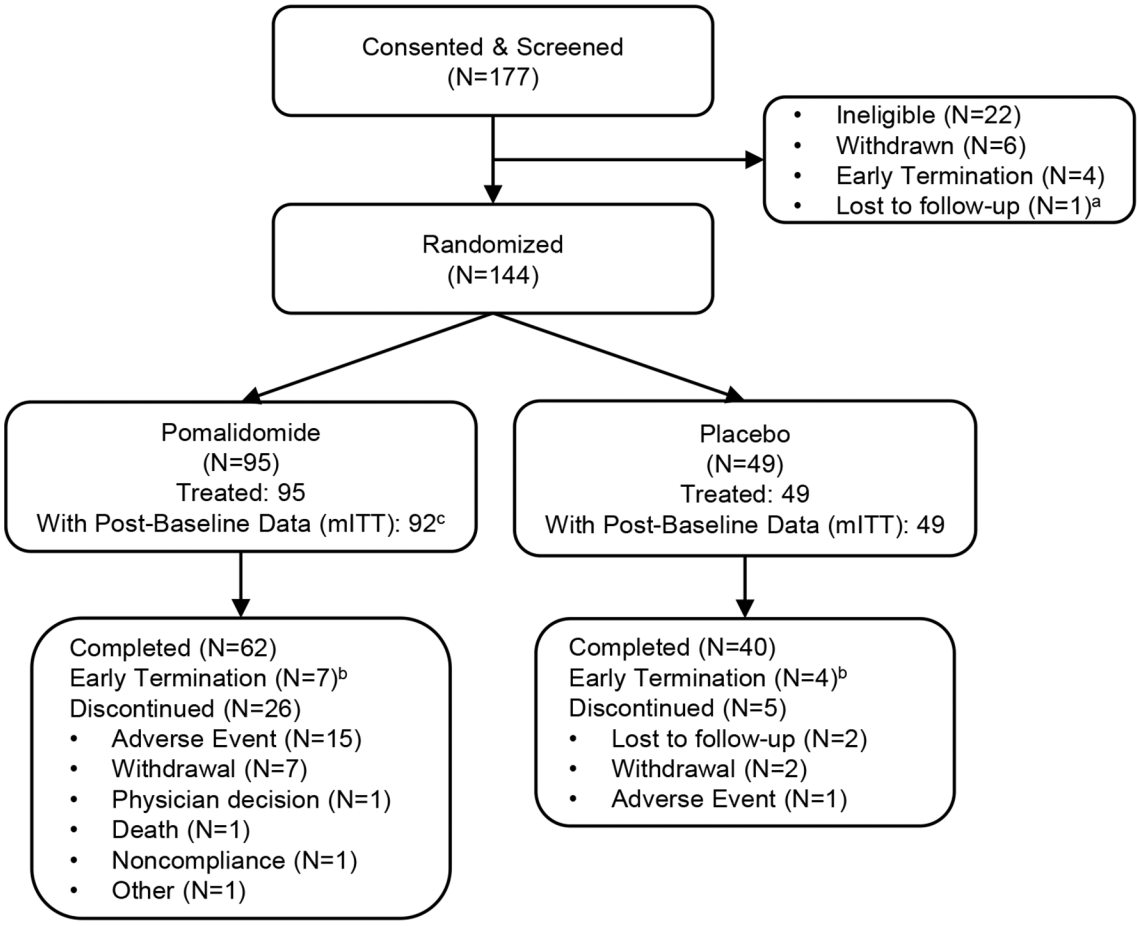
H. Al-Samkari is funded by the National Heart, Lung, and Blood Institute (1K23HL159313). All of the authors report funding from the National Heart Lung and Blood Institute.

National Heart Lung and Blood Institute (NHLBI) provided study oversight via recommendations from the Data Safety Monitoring Board. Bristol Myers Squibb (BMS) did not participate in the design or conduct of the study. Neither NHLBI nor BMS participated in collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

References

1. Chowdhury FN, et al. , Links Between Strokes and Hereditary Hemorrhagic Telangiectasia: A Population-Based Study. Can J Neurol Sci, 2019. 46(1): p. 44–50. [PubMed: 30520389]
2. Kritharis A, Al-Samkari H, and Kuter DJ, Hereditary hemorrhagic telangiectasia: diagnosis and management from the hematologist's perspective. Haematologica, 2018. 103(9): p. 1433–1443. [PubMed: 29794143]
3. Al Tabosh T, et al. , Hereditary hemorrhagic telangiectasia: from signaling insights to therapeutic advances. J Clin Invest, 2024. 134(4).
4. OS AA, Friedman CM, and White RI Jr., The natural history of epistaxis in hereditary hemorrhagic telangiectasia. Laryngoscope, 1991. 101(9): p. 977–80. [PubMed: 1886446]
5. Faughnan ME, et al. , Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. Ann Intern Med, 2020. 173(12): p. 989–1001. [PubMed: 32894695]
6. Kasthuri RS, et al. , Development and performance of a hereditary hemorrhagic telangiectasia-specific quality-of-life instrument. Blood Adv, 2022. 6(14): p. 4301–4309. [PubMed: 35877137]
7. Chaturvedi S, et al. , Depression and post-traumatic stress disorder in individuals with hereditary hemorrhagic telangiectasia: A cross-sectional survey. Thromb Res, 2017. 153: p. 14–18. [PubMed: 28314138]
8. Kasthuri RS, et al. , Prevalence and predictors of anemia in hereditary hemorrhagic telangiectasia. Am J Hematol, 2017.
9. Kjeldsen AD and Kjeldsen J, Gastrointestinal bleeding in patients with hereditary hemorrhagic telangiectasia. Am J Gastroenterol, 2000. 95(2): p. 415–8. [PubMed: 10685743]
10. Shovlin CL, et al. , The European Rare Disease Network for HHT Frameworks for management of hereditary haemorrhagic telangiectasia in general and speciality care. Eur J Med Genet, 2022. 65(1): p. 104370. [PubMed: 34737116]
11. Donaldson JW, et al. , Complications and mortality in hereditary hemorrhagic telangiectasia: A population-based study. Neurology, 2015. 84(18): p. 1886–93. [PubMed: 25862798]
12. Han C, et al. , VEGF neutralization can prevent and normalize arteriovenous malformations in an animal model for hereditary hemorrhagic telangiectasia 2. Angiogenesis, 2014. 17(4): p. 823–830. [PubMed: 24957885]
13. Cirulli A, et al. , Vascular endothelial growth factor serum levels are elevated in patients with hereditary hemorrhagic telangiectasia. Acta Haematol, 2003. 110(1): p. 29–32. [PubMed: 12975554]
14. Peng HL, et al. , Thalidomide Effects in Patients with Hereditary Hemorrhagic Telangiectasia During Therapeutic Treatment and in Fli-EGFP Transgenic Zebrafish Model. Chin Med J (Engl), 2015. 128(22): p. 3050–4. [PubMed: 26608985]
15. Al-Samkari H, et al. , An international, multicenter study of intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study. Haematologica, 2021. 106(8): p. 2161–2169. [PubMed: 32675221]
16. Dupuis-Girod S, et al. , Efficacy and safety of intravenous bevacizumab on severe bleeding associated with hemorrhagic hereditary telangiectasia: A national, randomized multicenter trial. J Intern Med, 2023. 294(6): p. 761–774. [PubMed: 37592715]
17. Invernizzi R, et al. , Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol, 2015. 2(11): p. e465–73. [PubMed: 26686256]
18. Thalidomide (Thalomid) Prescribing Information. 2021, FDA US.

19. D'Amato RJ, et al. , Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci U S A, 1994. 91(9): p. 4082–5. [PubMed: 7513432]
20. Lebrin F, et al. , Thalidomide stimulates vessel maturation and reduces epistaxis in individuals with hereditary hemorrhagic telangiectasia. Nat Med, 2010. 16(4): p. 420–8. [PubMed: 20364125]
21. Shovlin CL, et al. , Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). Am J Med Genet, 2000. 91(1): p. 66–7. [PubMed: 10751092]
22. Hoag JB, et al. , An epistaxis severity score for hereditary hemorrhagic telangiectasia. Laryngoscope, 2010. 120(4): p. 838–43. [PubMed: 20087969]
23. POMALYST U.S. Prescribing Information. 2023, Bristol Myers Squib.
24. Cella D, et al. , Neuro-QOL: brief measures of health-related quality of life for clinical research in neurology. Neurology, 2012. 78(23): p. 1860–7. [PubMed: 22573626]
25. Gershon RC, et al. , Neuro-QOL: quality of life item banks for adults with neurological disorders: item development and calibrations based upon clinical and general population testing. Qual Life Res, 2012. 21(3): p. 475–86. [PubMed: 21874314]
26. Pilkonis PA, et al. , Item banks for measuring emotional distress from the Patient-Reported Outcomes Measurement Information System (PROMIS(R)): depression, anxiety, and anger. Assessment, 2011. 18(3): p. 263–83. [PubMed: 21697139]
27. Garcia SF, et al. , Standardizing patient-reported outcomes assessment in cancer clinical trials: a patient-reported outcomes measurement information system initiative. J Clin Oncol, 2007. 25(32): p. 5106–12. [PubMed: 17991929]
28. Davis S, Chapter 5. Mixed models for repeated measures with categorical time effects (MMRM). in Clinical trials with missing data : a guide for practitioners, O'Kelly M and Ratitch B, Editors. 2014, John Wiley & Sons Inc.: Chichester, West Sussex.
29. Ratitch B, O'Kelly M, and Tosiello R, Missing data in clinical trials: from clinical assumptions to statistical analysis using pattern mixture models. Pharm Stat, 2013. 12(6): p. 337–47. [PubMed: 23292975]
30. Ratitch B, Chapter 6: Multiple Imputation, in Clinical trials with missing data : a guide for practitioners, O'Kelly M and Ratitch B, Editors. 2014, John Wiley & Sons Inc.: Chichester, West Sussex.
31. O'Kelly M and Ratitch B, Chapter 8: Analyses under missing-not-at-random assumptions, in Clinical trials with missing data : a guide for practitioners, O'Kelly M and Ratitch B, Editors. 2014, John Wiley & Sons Inc.: Chichester, West Sussex.
32. Stokes ME, Davis CS, and Koch GG, Categorical data analysis using the SAS system. 2nd ed. 2000, Cary, NC: SAS Institute. viii, 626 p.
33. SAS, version 9.4 SAS Institute Inc.: Cary, NC.
34. Hasan Albitar HA, et al. , Healthcare Utilization and Costs associated with Hereditary Hemorrhagic Telangiectasia Patients in a Large US Claims Database. Mayo Clin Proc Innov Qual Outcomes, 2021. 5(1): p. 55–64. [PubMed: 33718784]
35. Yin LX, et al. , The minimal important difference of the epistaxis severity score in hereditary hemorrhagic telangiectasia. Laryngoscope, 2016. 126(5): p. 1029–32. [PubMed: 26393959]
36. Richardson PG, et al. , Phase 1 study of pomalidomide MTD, safety, and efficacy in patients with refractory multiple myeloma who have received lenalidomide and bortezomib. Blood, 2013. 121(11): p. 1961–7. [PubMed: 23243282]
37. Cohen J, Statistical power analysis for the behavioral sciences. 2nd ed. 1988, Hillsdale NJ: L. Erlbaum Associates. xxi, 567 p.
38. Kozlowski AJ, et al. , Evaluating Individual Change With the Quality of Life in Neurological Disorders (Neuro-QoL) Short Forms. Arch Phys Med Rehabil, 2016. 97(4): p. 650–654 e8. [PubMed: 26740062]
39. Yost KJ, et al. , Minimally important differences were estimated for six Patient-Reported Outcomes Measurement Information System-Cancer scales in advanced-stage cancer patients. J Clin Epidemiol, 2011. 64(5): p. 507–16. [PubMed: 21447427]
40. Meaningful Change for PROMIS®. 2024; Available from: https://www.healthmeasures.net/score-and-interpret/interpret-scores/promis/meaningful-change.



mITT = modified Intent-to-Treat

[a] Due to the timing of randomization, one participant was randomized but was lost to follow-up prior to their baseline visit

[b] Ongoing participants at the time the study was stopped due to interim analysis. All participants completed at least up through week 12.

[c] One participant died from an unrelated serious adverse event prior to attending the 4-week visit and two participants discontinued after less than two weeks due to adverse events (one not drug-related, one drug-related rash) and had no post-baseline efficacy data .

Figure 1.
Consort Diagram

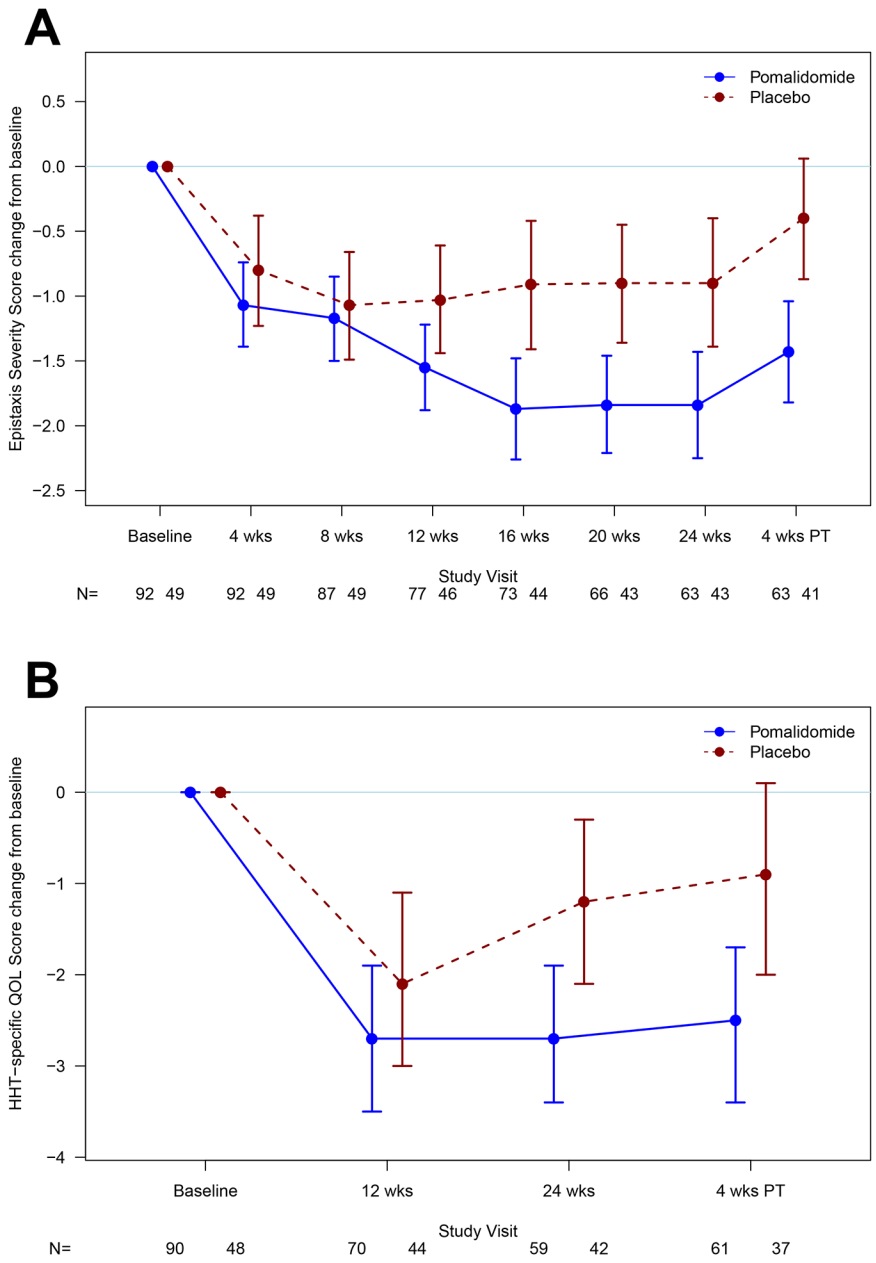


Figure 2.

Model-estimated Mean Change (95% CI) from Baseline in the Epistaxis Severity Score (Panel A) and the HHT-specific QOL (Panel B) by Treatment Group.

Estimates and 95% confidence intervals are from the mixed model for repeated measures. The Epistaxis Severity Score (ESS) ranges from 0–10 with higher scores indicating worse condition in the prior 4 weeks. The minimal important difference is 0.71. The HHT-specific QOL score ranges from 0 to 16 with higher scores indicating more limitations due to HHT in the prior 4 weeks.

Table 1.

Characteristics of the Patients at Baseline – All Randomized and Treated Patients

Characteristic	Total (N=144)	Pomalidomide (N=95)	Placebo (N=49)
Mean Age (SD) - years	58.8 (12.2)	58.8 (13.0)	58.7 (10.7)
Female Sex - no. (%)	69 (48)	45 (47)	24 (49)
Non-white Race - no. (%)	15 (11)	9 (10)	6 (13)
Hispanic/Latino Ethnicity - no. (%)	5 (3)	2 (2)	3 (6)
Genetic Mutations - no. (%)[a]	n=134	n=88	n=46
ENG	50 (37)	37 (42)	13 (28)
ACVRL1	69 (51)	38 (43)	31 (67)
SMAD4	1 (1)	1 (1)	0 (0)
None identified	14 (10)	12 (14)	2 (4)
Any HHT involvement other than epistaxis - no. (%)	103 (72)	69 (73)	34 (69)
GI bleeding - no. (%)	53 (37)	34 (36)	19 (39)
Brain - no. (%)	15 (10)	9 (9)	6 (12)
Liver - no. (%)	35 (24)	25 (26)	10 (20)
Lungs - no. (%)	58 (40)	42 (44)	16 (33)
Pulmonary hypertension - no. (%)	9 (6)	4 (4)	5 (10)
High output heart failure - no. (%)	3 (2)	2 (2)	1 (1)
Received a red blood cell transfusion in past 6 months - no (%)	28 (19)	20 (21)	8 (16)
Emergency room visit in past 6 months - no (%)	25 (17)	16 (17)	9 (18)
Received an Iron infusion in past 6 months - no (%)	121 (84)	79 (83)	42 (86)
Amount of iron Infused, n, median (Q1–Q3) − (mg/4 wks)[b]	107	69	38
	170 (100 – 375)	170 (85 – 375)	170 (125 – 340)
Taking oral iron – no. (%)	63 (44)	42 (44)	21 (43)
Mean Hemoglobin (SD) - g/dL	11.5 (2.3)	11.4 (2.4)	11.8 (2.1)
Median Ferritin (Q1–Q3) − ng/mL	57 (24 – 147)	54 (23 – 165)	64 (28 – 127)
Anemia - no. (%)	99 (69)	66 (69)	33 (67)
Mean Epistaxis Severity Score (SD) in the prior 4 weeks[c]	5.0 (1.5)	4.9 (1.5)	5.2 (1.4)
Epistaxis Severity Score >=6 - no. (%)	29 (20)	17 (18)	12 (24)
Mean HHT-specific QOL Score (SD)[d]	6.3 (3.1)	5.8 (2.9)	7.1 (3.4)
Median epistaxis duration in past 4 wks (Q1–Q3) − min/day[e]	11.7 (5.8 – 20.6)	11.1 (4.0 – 19.1)	12.4 (7.1 – 26.6)
Mean Neuro-QoL™ Satisfaction with Social Roles and Activities T-score (SD)[f]	45.2 (6.2)	45.4 (6.3)	44.7 (6.0)
Mean PROMIS® Emotional Distress-Depression T-score (SD)[g]	50.3 (9.8)	49.3 (9.8)	52.4 (9.6)
Mean PROMIS® Fatigue T-score (SD)[h]	56.4 (10.3)	55.8 (10.1)	57.7 (10.8)

HHT denotes heredity hemorrhagic telangiectasia, SD standard deviation, QOL quality of life, min minutes, wks weeks

[a]Genetic mutations include “known pathogenetic mutation” and “likely pathogenetic variant”.

[b]Total iron infused (mg) is calculated from amounts reported in the prior 24 weeks at screening. Some data was not available.

[c] The Epistaxis Severity Score ranges from 0–10 with higher scores indicating worse condition in the prior 4 weeks at baseline. Inclusion criteria were based on screening ESS.[22]

[d] The HHT-specific QOL score ranges from 0 to 16 with higher scores indicating more limitations due to HHT in the prior 4 weeks.[6]

[e] The daily epistaxis duration is calculated as the total duration of all reported nose bleeding events in a day, averaged across all days reported in a 4-week smartphone diary.

[f] The Neuro-QoL™ Satisfaction with Social Roles and Activities Short Form (V1.1) T-score has a value of 50 representing the average general US population, with a standard deviation of 10, and with higher scores indicating more satisfaction.[24, 25]

[g] The PROMIS® Emotional Distress-Depression Short Form (V1.0) T-score has a value of 50 representing the average general US population, with a standard deviation of 10, and with higher scores indicating more depression.[26]

[h] The PROMIS® Fatigue Short Form (V1.0) T-score has a value of 50 representing the average general US population, with a standard deviation of 10, and with higher scores indicating more fatigue.[27]

Table 2.

Efficacy Outcomes at 24 weeks – Modified Intent-to-Treat (mITT) Population

Change from Baseline to 24 weeks unless otherwise indicated	Pomalidomide (N=92) Model Estimate (95% CI)	Placebo (N=49) Model Estimate (95% CI)	Estimated Mean Difference (95% CI)	p-value
Primary				
Epistaxis Severity Score[A, D]	−1.84 (−2.25, −1.43)	−0.90 (−1.39, −0.40)	−0.94 (−1.57, −0.31)	0.004
Key Secondary				
HHT-specific QOL Score[B,E]	−2.7 (−3.4, −1.9)	−1.2 (−2.1, −0.3)	−1.4 (−2.6, −0.3)	-
Amount of Iron Infused (mg/4 wks) through 24 weeks – n, median (Q1-Q3)[B, F, G]	92, 170 (0 – 408)	49, 204 (33 – 341)	−32 (−107, 43)	-
Amount of Iron Infused (mg/4 wks) 12–24 weeks – n, median (Q1-Q3)[C, F, G]	74, 0 (0 – 340)	45, 333 (0 – 500)	−115 (−230, 0)	-
Received any packed red blood cells transfusion through 24 weeks – n (%)[B, H]	15/92 (16)	11/49 (22)	Relative risk 0.73 (0.36, 1.46)	-
Received any packed red blood cells transfusion 12–24 weeks – n (%)[C, H]	7/74 (9)	8/45 (18)	Relative risk 0.53 (0.21, 1.37)	-
Daily epistaxis duration in past 4 wks-min/day[B, I]	−6.1 (−10.7, −1.6)	−3.7 (−9.4, 2.0)	−2.4 (−9.6, 4.7)	-
Intensity-weighted Daily epistaxis duration in past 4 weeks (Winsorized) - min/day[C, I]	−12.2 (−17.1, −7.3)	−3.3 (−9.5, 2.8)	−8.9 (−16.5, −1.2)	-
Neuro-QoL™ Satisfaction with Social Roles and Activities T-score[B, J]	2.8 (1.2, 4.5)	1.6 (−0.4, 3.6)	1.3 (−1.2, 3.8)	-
Other Secondary				
PROMIS® Emotional Distress-Depression T-score[C, K]	−2.3 (−4.2, −0.5)	−3.4 (−5.6, −1.2)	1.1 (−1.7, 3.8)	-
PROMIS® Fatigue T-score[C, L]	−1.5 (−3.7, 0.6)	−1.0 (−3.5, 1.6)	−0.6 (−3.8, 2.7)	-
Received any iron infusion or blood transfusion through 24 weeks – n (%)[C, M]	68/92 (74)	37/49 (76)	Relative risk 0.96 (0.71, 1.21)	-
Required endoscopic intervention through 24 weeks – n (%)[C, H]	8/92 (9)	5/49 (10)	Relative risk 0.85 (0.29, 2.47)	-
Transferrin saturation (%)– n, median (Q1-Q3)[C, G]	58, 2 (−5 – 13)	39, 1 (−5 – 16)	0 (−7, 7)	-
Ferritin (ng/mL)– n, median (Q1-Q3)[C,G]	61, 5 (−30 – 67)	42, −1 (−42 – 51)	3 (−35, 41)	-
Hemoglobin– g/dL[C]	0.32 (−0.10, 0.75)	0.05 (−0.46, 0.56)	0.27 (−0.37, 0.92)	-
Hematocrit - %[C]	0.40 (−0.81, 1.60)	−0.23 (−1.69, 1.24)	0.62 (−1.22, 2.47)	-
MCV -fL[C]	3.21 (1.94, 4.49)	1.08 (−0.46, 2.62)	2.13 (0.17, 4.09)	-
MCHC -g/dL[C]	0.55 (0.21, 0.89)	0.12 (−0.29, 0.53)	0.44 (−0.08, 0.95)	-

CI denotes confidence interval, HHT heredity hemorrhagic telangiectasia, QOL quality of life, MCV mean corpuscular volume, MCHC mean corpuscular hemoglobin concentration. N.S, non-significant

The modified Intent-to-Treat population includes all randomized and treated patients with post-baseline efficacy data.

Normal lower limit for laboratory assessments is as follows: transferrin saturation (%): 15 male, 10 female; ferritin ng/mL:30.3 male, 14.7 female; hemoglobin g/dL 13 male, 11.5 female; hematocrit % 39 male, 36 female; MCV 80 fL, MCHC 30.5 g/dL.

Unless otherwise noted, estimates and p-values are from a general linear model for repeated measurements with fixed effects for baseline value, pooled clinical site, treatment, time period as a categorical predictor, and interaction between treatment and time period, with a heterogeneous Toeplitz correlation structure for the within-participant measures across time periods.

A Statistical significance of the primary outcome is p=0.0425 based on Lan-DeMets alpha spending functions with O'Brien-Fleming boundaries for two interim analyses conducted at 54% and 80%. The study was halted due to reaching the efficacy criteria (p=0.023) at the 80% interim.

B Statistical significance of 5 key secondary outcomes is assessed with the Hochberg modification to the Bonferroni procedure. In this case, statistical significance is evaluated at p= 0.01. None of the outcomes met this significance level, therefore p-values are not provided.

C All other outcomes are for descriptive purposes, therefore p-values are not provided.

D The Epistaxis Severity Score (ESS) ranges from 0–10 with higher scores indicating worse condition in the prior 4 weeks. The minimal important difference is 0.71.[22, 35] Cohen's D effect size at 24 weeks (estimated mean difference between groups divided by the standard deviation), is 0.57.[37]

E The HHT-specific QOL score ranges from 0 to 16 with higher scores indicating more limitations due to HHT in the prior 4 weeks.[6]

F Iron infused (mg) is the total in 4 weeks, averaged across all visits reported through 24 weeks. Patients with no infusions have a value of zero.

G Treatment difference and 95% CI are from a Hodges-Lehman shift estimate. P-values are from a rank analysis of covariance with adjustment for baseline measurements and pooled clinical site.

H Relative risk for receiving a packed red blood cells transfusion or receiving endoscopic intervention are unadjusted.

I The daily epistaxis duration is the sum of all reported nose bleeding durations in a day, averaged across all days reported in a 4-week smartphone diary. See Supplemental Methods in the Supplementary Appendix for detailed description of derivation of Intensity-weighted Daily epistaxis duration.

J The Neuro-QoL™ Satisfaction with Social Roles and Activities Short Form (V1.1) T-score has a value of 50 representing the average general US population, with a standard deviation of 10, and higher scores indicating more satisfaction. The minimal detectable change is 3.7 T score points.[24, 25, 38]

K The PROMIS® Emotional Distress-Depression Short Form (V1.0) T-score has a value of 50 representing the average general US population, with a standard deviation of 10, and with higher scores indicating more depression.[26]

L The PROMIS® Fatigue Short Form (V1.0) T-score has a value of 50 representing the average general US population, with a standard deviation of 10, and with higher scores indicating more fatigue.[27] The minimum clinically important difference (MCID) ranges from 3–5 T score points[39, 40]

M Relative risk for receiving an iron infusion or blood transfusion is from a nonlinear transformation of logistic regression with adjustment for receiving a blood transfusion or iron infusions totaling at least 250 mg in the 24 weeks prior to screening.

Table 3.

Safety Outcomes – All Randomized and Treated Patients

Outcome	Pomalidomide (N=95)	Placebo (N=49)	p-value
Patients with Adverse Events of Special Interest – N (%)			
Constipation	45 (47)	9 (18)	<.001
Fatigue	42 (44)	17 (35)	0.27
Neutropenia	42 (44)	5 (10)	<.001
Rash[A]	33 (35)	5 (10)	0.002
Tremor[B]	8 (8)	0 (0)	0.04
Venous thromboembolism[C]	4 (4)	1 (2)	0.50
Thrombocytopenia	4 (4)	0 (0)	0.15
Peripheral neuropathy[D]	3 (3)	0 (0)	0.21
Arterial thromboembolism	0 (0)	0 (0)	1.00
Patients with other medically relevant Adverse Events of at least moderate severity and at least possibly related to study drug – N (%)			
Dyspnea[E]	4 (4)	0 (0)	0.15
Muscle spasms	2 (2)	1 (2)	0.98
Alanine aminotransferase increased	1 (1)	0 (0)	0.47
Mouth ulceration	1 (1)	0 (0)	0.47
Tachycardia	1 (1)	0 (0)	0.47
Peripheral edema	0 (0)	0 (0)	1.00
Patients with any Serious Adverse Event – n (%)	22 (23)	8 (16)	0.34
Patients with any Bleeding Serious Adverse Event – n (%)	6 (6)	5 (10)	0.50
Epistaxis	2 (2)	2 (4)	0.61
GI	1 (1)	3 (6)	0.11
Unspecified	3 (3)	0 (0)	0.55
Patients with any Grade 3+ Adverse Event[F]– n (%)	45 (47)	12 (24)	0.01
Strongest action taken for an Adverse Event per patient – n (%)			
Drug withdrawn	15 (16)	1 (2)	0.01
Drug interrupted	38 (40)	7 (14)	0.002
Dose reduced	12 (13)	0 (0)	0.009
Platelets (K/uL) change from baseline at 24 weeks – n, median (Q1-Q3)[G]	62, −38 (−75 – 21)	42, 9 (−22 – 27)	0.07
Platelets categories for Thrombocytopenia[H]– n (%)			0.26
>= 1.45 K/uL (normal)	83 (90)	44 (90)	
1.00 – <1.45 K/uL	7 (8)	2 (4)	
0.50 – <1.00 K/uL	1 (1)	3 (6)	
< 0.50 K/uL	1 (1)	0 (0)	
Mean neutrophils change from baseline at 24 weeks – K/uL – model estimate (95% CI)	−1.71 (−2.03, −1.39)	−0.02 (−0.42, 0.38)	<.001
Neutrophils categories for Neutropenia[H]– n (%)			<.001
>= 150 K/uL (normal)	33 (36)	44 (90)	

Outcome	Pomalidomide (N=95)	Placebo (N=49)	p-value
100 – <150 K/uL	32 (35)	4 (8)	
50 – <100 K/uL	24 (26)	1 (2)	
< 50 K/uL	3 (3)	0 (0)	
Hemoglobin < 6.5 mg/dL – n (%)	3 (3)	3 (6)	0.42

CI denotes confidence interval, K 1,000.

Normal lower limit for laboratory assessments is as follows: platelets (K/uL): 150; neutrophils (K/uL): 1.45

Adverse events occurred any time during the 24-week treatment period or the 4-week post-treatment follow-up period. Patients are counted once per row. P-values comparing proportion of patients with adverse events and hemoglobin < 6.5 are from a chi-square test or Fisher's exact test for small cell counts. All p-values are for descriptive purposes.

[A] Rash combines MedDRA terms "rash", "rash papular", "rash pruritic", "rash maculo-papular", "rash erythematous", "rash macular", and "urticaria".

[B] Two reported tremor events were of moderate severity; all others were reported as mild.

[C] Venous thromboembolism combines MedDRA terms "portal vein thrombosis", "deep vein thrombosis", and "pulmonary embolism".

[D] Peripheral neuropathy combines MedDRA terms "neuropathy peripheral" and "peripheral sensory neuropathy".

[E] Dyspnea combines MedDRA terms "dyspnoea" and "dyspnoea at rest".

[F] Grade 3+ adverse event refers to any event that was classified as severe, life-threatening, or fatal.

[G] P-values for platelet change from baseline are from a rank analysis of covariance with adjustment for baseline value and pooled clinical site.

[H] Categories for platelets and neutrophils are based on the lowest (worst) recorded laboratory value during the 24-week treatment period or 4-week post-treatment follow-up period. P-values are from a Mean Score Chi-square test with modified midrank scores.

[I] Estimates and p-values for neutrophils change from baseline are from a general linear model for repeated measurements with fixed effects for baseline value, pooled clinical site, treatment, time period as a categorical predictor, and interaction between treatment and time period, with a heterogeneous Toeplitz correlation structure for the within-participant measures across time periods.