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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Categorization of Hematological Responses to Oral Iptacopan Monotherapy in Anti-C5-Treated Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) and Persistent Anemia in the Phase III APPLY-PNH Trial and Complement Inhibitor-Naïve Patients in the Phase III APPOINT-PNH Trial

Antonio M Risitano, MDPhD[1,2], Bing Han, MDPhD[3], Austin Kulasekararaj, MD PhD MPH[4,5,6], Yasutaka Ueda[7], Phillip Scheinberg, MD[8], Carlos de Castro[9], Jaroslaw P. Maciejewski, MD, PhD, FACP[10], Josefin Snellman[11], Ranjan Tiwari[12], Marion Dahlke, MD[11], Régis Peffault de Latour[13,14]

[1] AORN Moscati, Avellino, Italy
[2] University of Naples Federico II, Naples, Italy
[3] Department of Hematology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China
[4] King's College Hospital NHS, London, United Kingdom
[5] National Institute for Health and Care Research and Wellcome King's Research Facility, London, United Kingdom
[6] King's College London, London, United Kingdom
[7] Osaka University Graduate School of Medicine, Suita, Japan
[8] Hospital A Beneficência Portuguesa, São Paulo, Brazil
[9] Duke University School of Medicine, Durham, NC
[10] Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH
[11] Novartis Pharma AG, Basel, Switzerland
[12] Novartis Healthcare Pvt. Ltd, Hyderabad, India
[13] French Reference Center for Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria, Paris, France
[14] Assistance Publique Hôpitaux de Paris, Université Paris Cité, Paris, France

Background: PNH is an ultrarare disease characterized by complement-mediated hemolysis and consequent anemia. Iptacopan is the first oral, selective complement inhibitor that targets factor B to inhibit the alternative pathway proximally in the complement system. Iptacopan monotherapy led to normal/near normal hemoglobin (Hb) values and transfusion avoidance in the majority of complement inhibitor-naïve patients and anti-C5-treated patients with persistent anemia in the Phase III APPOINT-PNH (NCT04820530) and APPLY-PNH (NCT04558918) trials, respectively, with iptacopan achieving its primary endpoints and demonstrating superiority to anti-C5 treatment in APPLY-PNH.
Aim: To apply hematological response categories, adapted from Risitano *et al.* in *Front Immunol* 2019, to the data from APPLY-PNH (baseline and Week 24 data) and APPOINT-PNH (Week 24 data).
Methods: APPLY-PNH enrolled adult PNH patients with a mean Hb level <10 g/dL who had been receiving eculizumab or ravulizumab for ≥6 months. Patients were randomized 8:5 to receive iptacopan monotherapy 200 mg twice daily or to continue their anti-C5 regimen for 24 weeks. APPOINT-PNH enrolled complement inhibitor-naïve adult PNH patients, with a mean Hb level <10 g/dL and lactate dehydrogenase (LDH) >1.5 × upper limit of normal (ULN); patients received iptacopan monotherapy 200 mg twice daily. Using central laboratory data, hematological responses were categorized primarily based on Hb levels (at baseline and between Days 126 and 168) and the need for packed red blood cell transfusions (in the 6 months prior to baseline and between Days 14 and 168). LDH levels and absolute reticulocyte counts were ancillary indicators to discriminate between complete and major responses. In the original definition of the response categories, absolute reticulocyte count was used to rule out patients with bone marrow failure; however, for this analysis, as patients with laboratory evidence of bone marrow failure were excluded from APPLY-PNH and APPOINT-PNH, absolute reticulocyte count was not used to define the suboptimal categories (ie good, partial, minor and no response categories). Week 24 categories were defined as follows: complete response - median Hb ≥12 g/dL, no transfusions, and both median LDH ≤1.5 × ULN and median absolute reticulocyte count ≤150,000/μL between Days 1 and 168; major response - median Hb ≥12 g/dL, no transfusions, and either LDH >1.5 × ULN or absolute reticulocyte count >150,000/μL between Days 1 and 168; good response - median Hb ≥10 and <12 g/dL and no transfusions; partial response - median Hb ≥8 and <10 g/dL and ≤2 transfusions; minor response - median

Hb <8 g/dL and ≤2 transfusions; or median Hb <10 g/dL and 3-6 transfusions; or median Hb <10 g/dL and a reduction in transfusions by ≥50% between Days 14 and 168 compared with the number of transfusions received in the 6 months prior to baseline; no response - median Hb <10 g/dL and >6 transfusions.

Results: Sixty-two patients received iptacopan and 35 patients received anti-C5 treatment in the APPLY-PNH trial; 40 patients received iptacopan in the APPOINT-PNH trial. There were no baseline differences between patients in the iptacopan arm and patients in the anti-C5 arm of the APPLY-PNH trial, with most patients having a partial hematological response to complement inhibitor treatment at baseline (62.9% [39/62] of patients in the iptacopan arm and 62.9% [22/35] in the anti-C5 arm; Figure 1). At Week 24, most iptacopan-treated patients in the APPLY-PNH trial achieved a complete response (71% [44/62] of patients versus 0% in the anti-C5 arm; Figure 1). Most patients in the APPOINT-PNH trial also achieved a complete response to iptacopan (62.5% [25/40] of patients; Figure 2). As expected, at Week 24, none of the patients in the anti-C5 arm of APPLY-PNH achieved complete or major hematological responses, with most continuing to maintain a partial hematological response (54.3% [19/35] of patients).

Conclusions: This *post hoc* analysis of the APPLY-PNH and APPOINT-PNH trial data demonstrates that the majority of patients achieved complete or major hematological responses during treatment with iptacopan monotherapy, highlighting the ability of both complement inhibitor-naïve patients and anti-C5-treated patients with persistent anemia to achieve transfusion avoidance and improvement of Hb to normal/near normal levels with iptacopan.

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Figure 1. Hematological responses of patients in the APPLY-PNH trial at baseline and Week 24 of the treatment period

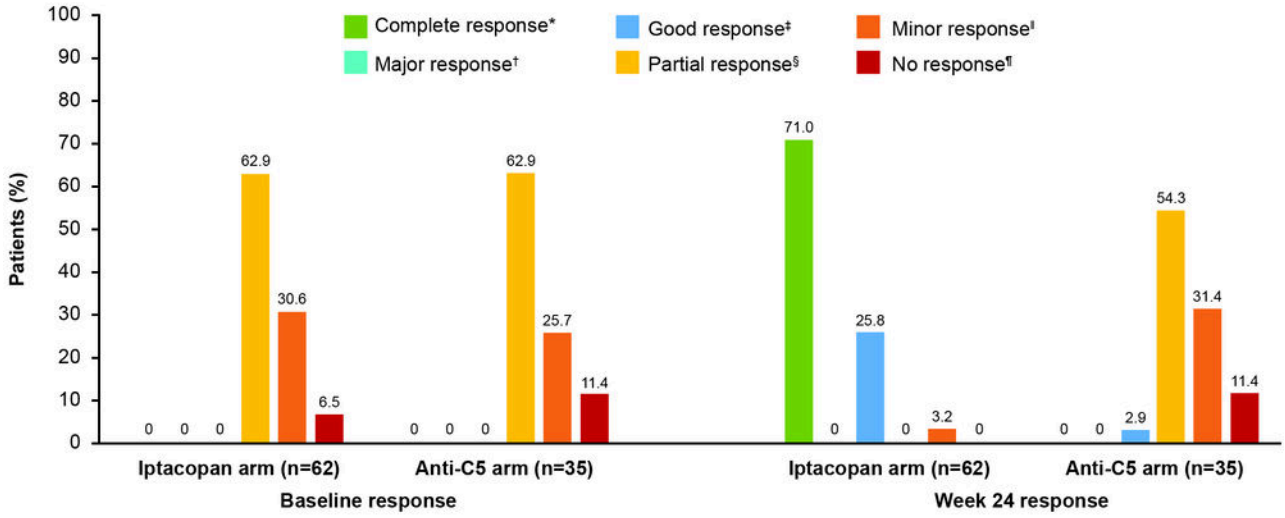
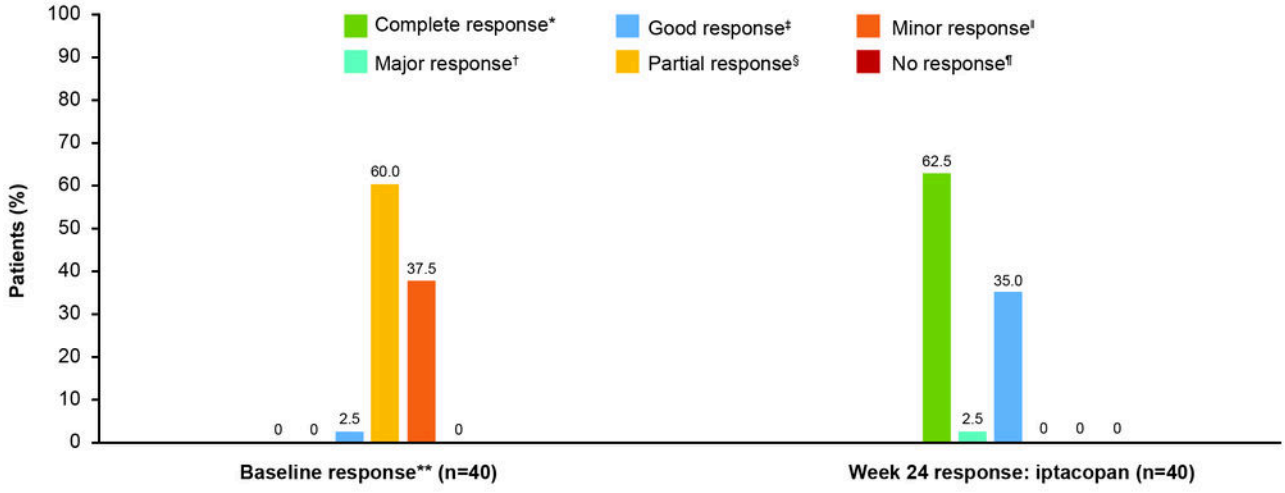


Figure 2. Hematological responses of patients in the APPOINT-PNH trial at baseline and Week 24 of the treatment period**



*The criteria for complete response at baseline were no transfusions in the last 6 months, Hb ≥12 g/dL, LDH ≤1.5 × ULN and absolute reticulocyte count ≤150,000/μL. The criteria for complete response at Week 24 were no transfusions between Days 14 and 168, median Hb ≥12 g/dL between Days 126 and 168, median LDH ≤1.5 × ULN between Days 1 and 168 and median absolute reticulocyte count ≤150,000/μL between Days 1 and 168; †The criteria for major response at baseline were no transfusions in the last 6 months, Hb ≥12 g/dL and either LDH >1.5 × ULN or absolute reticulocyte count >150,000/μL. The criteria for major response at Week 24 were no transfusions between Days 14 and 168, median Hb ≥12 g/dL between Days 126 and 168, and either median LDH >1.5 × ULN between Days 1 and 168 or median absolute reticulocyte count >150,000/μL between Days 1 and 168; ‡The criteria for good response at baseline were no transfusions in the last 6 months and Hb ≥10 and <12 g/dL. The criteria for good response at Week 24 were no transfusions between Days 14 and 168 and median Hb ≥10 and <12 g/dL between Days 126 and 168; §The criteria for partial response at baseline were ≤2 transfusions in the last 6 months and Hb ≥8 and <10 g/dL. The criteria for partial response at Week 24 were ≤2 transfusions between Days 14 and 168 and median Hb ≥8 and <10 g/dL between Days 126 and 168; ‖The criteria for minor response at baseline were either ≤2 transfusions in the last 6 months and Hb <8 g/dL; or 3–6 transfusions in the last 6 months and Hb <10 g/dL. The criteria for minor response at Week 24 were either ≤2 transfusions between Days 14 and 168 and median Hb <8 g/dL between Days 126 and 168; or 3–6 transfusions between Days 14 and 168 and median Hb <10 g/dL between Days 126 and 168; or reduction in transfusions by ≥50% between Days 14 and 168 compared with the number of transfusions received in the last 6 months prior to baseline and median Hb <10 g/dL between Days 126 and 168; ¶The criteria for no response at baseline were >6 transfusions in the last 6 months and Hb <10 g/dL. The criteria for no response at Week 24 were >6 transfusions between Days 14 and 168 and median Hb <10 g/dL between Days 126 and 168; **Baseline categorization was applied although patients in APPOINT-PNH had not received prior complement inhibitor treatment
Hb, hemoglobin; LDH, lactate dehydrogenase; ULN, upper limit of normal

Figure 1

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