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POSTER ABSTRACTS

508.BONE MARROW FAILURE: ACQUIRED

Ravulizumab Provides Durable Control of Intravascular Hemolysis and Improves Survival in Patients with Paroxysmal Nocturnal Hemoglobinuria: Long-Term Follow-up of Study 301 and Comparisons with Patients of the International PNH Registry

Austin Kulasekararaj, MD PhD MPH[1], *Hubert Schrezenmeier, MD*[2,3], *Kensuke Usuki, MD PhD*[4], *Aleksander Kulagin*[5], *Sandra Fatima Gualandro, MDPhD*[6], *Rosario Notaro*[7,8], *Masayo Ogawa, MD*[9], *Ji Yu*[10], *Ami Patel, PhD*[9], *Yogesh Patel*[9], *Wolfgang Füreder*[11], *Regis Peffault De Latour*[12], *Jong-Wook Lee, MD*[13]

[1] Department of Haematological Medicine, King's College Hospital NHS Foundation Trust, London, United Kingdom
[2] German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen and University Hospital Ulm, Ulm, Germany
[3] University of Ulm, Ulm, Germany
[4] NTT Medical Center Tokyo, Tokyo, Japan
[5] 5RM Gorbacheva Research Institute, Pavlov University, St Petersburg, RUS
[6] Division of Haematology, University of São Paulo Medical School, Sao Paulo, Brazil
[7] Istituto Per Studio, La Prevenzione E La Rete Oncologica (ISPRO), Florence, ITA
[8] Haematology, Azienda Ospedaliero Universitaria Careggi, Florence, Italy
[9] Alexion, AstraZeneca Rare Disease, Boston, MA
[10] Alexion, AstraZeneca Rare Disease, Boston
[11] Department of Internal Medicine I, Division of Hematology and Hemostaseology, Medical University of Vienna, Vienna, Austria
[12] Hôpital Saint-Louis„ Paris, France
[13] Department of Hematology, Seoul St. Mary's Hospital Catholic University of Korea, Seoul, South Korea

Background: Paroxysmal nocturnal hemoglobinuria (PNH) is a rare chronic blood disorder characterized by uncontrolled terminal complement activation, leading to intravascular hemolysis (IVH), major adverse vascular events (MAVEs; including thrombotic events), organ damage and increased morbidity and mortality. Where available, ravulizumab is considered the standard of care for patients with PNH, providing immediate, complete and sustained inhibition of terminal complement activity. In study 301 (NCT02946463), complement component 5 (C5) inhibitor-naïve patients with PNH reported elevated levels of lactate dehydrogenase (LDH) and low hemoglobin (Hb) concentrations at baseline, alongside a history of MAVEs and need for transfusions. In such patients, ravulizumab provides durable control of IVH, reported for up to 2 years.
Objectives: To report ravulizumab treatment outcomes for up to 6 years in C5 inhibitor-naïve patients with PNH from study 301 and compare survival with untreated patients of the International PNH Registry (NCT01374360).
Methods: C5 inhibitor-naïve patients with PNH and high-disease activity (HDA; LDH level $\geq$ 1.5 $\times$ the upper limit of normal [ULN] and at least one sign or symptom of PNH) (N = 246) were randomized to receive ravulizumab or eculizumab. After the primary evaluation period (26 weeks), patients received ravulizumab for the 5-year open-label extension (OLE) period. LDH level change from baseline, the proportion of patients experiencing MAVEs, and transfusion avoidance were evaluated. Cox-proportional hazards regression analyses compared survival of patients treated with ravulizumab with untreated patients with HDA and clone size $\geq$ 5% at PNH Registry enrollment. Covariates comprised age at PNH diagnosis, gender, Hb concentration, estimated glomerular filtration rate, PNH clone size, transfusion history and medical history of MAVEs and bone marrow disease at baseline (i.e., date of ravulizumab treatment initiation [study 301] or PNH Registry enrollment). Transfusion history ($p = 0.05$), age at PNH diagnosis and gender were included in the final adjusted model.
Results: Ravulizumab treatment data were available for 244/246 patients (median [range] follow-up: 46.8 [0.4-69.3] months). At baseline, all 246 patients had LDH levels > 1.5 $\times$ ULN; at 26 weeks, 87.1% of patients achieved LDH levels $\leq$ 1.5 $\times$ ULN, which was maintained in 79.3% of patients at last follow-up (day 2045 [n/N = 42/53]; highest proportion reported at day 225 [n/N = 92/97; 94.9%]). At baseline, 17.1% of patients had a history of MAVEs (MAVE rate: 3.4 per 100 patient-years [PYs]). The proportion of ravulizumab-treated patients who experienced MAVEs was low throughout the study (n = 11 [4.5%], 13 events, MAVE rate: 1.4 per 100 PYs), with 9 patients (3.7%) reporting MAVEs during the OLE (11 events, MAVE rate: 1.3 per 100 PYs).

Prior to randomization (≤ 6 months of study entry), 24.8% of patients did not need transfusions; at 26 weeks, this increased to 73.6% and was maintained in 53.9% of patients for the entire OLE with the highest proportion not requiring transfusions reported during the final 6 months of the OLE (75.7%). In addition, units transfused reduced from 1019 prior to randomization to 110 during the final 6 months of the OLE. Overall, 33 patients (13.4%) discontinued ravulizumab treatment during the entire study period (30 [12.2%] during the OLE). Reasons for discontinuation were death (n = 8), patient choice (n = 7), physician decision (n = 5), pregnancy (n = 4), adverse event (n = 3), lost to follow-up (n = 1) and other (n = 5). When compared with 413 untreated patients, ravulizumab was associated with an adjusted survival probability (95% confidence interval [CI]) of 84.1% (77.4, 91.3) at 4 years (hazard ratio [95%CI]: 0.14 (0.06, 0.32), $p < 0.001$; **Figure 1**) and mortality was 3.5-fold lower than that observed in untreated patients in the PNH Registry.

Conclusions: This study reports the longest duration of ravulizumab treatment exposure in C5-inhibitor-naïve patients with PNH (925.7 PYs) to date. For up to 6 years, ravulizumab provided effective long-term control of IVH, evidenced by the maintenance of LDH ≤ 1.5 × ULN and low incidence of MAVEs and death. No new safety signals were identified and ravulizumab improved survival compared with untreated patients in the PNH Registry, further supporting the use of ravulizumab as the first-line treatment of choice for patients with PNH, where available.

Disclosures Kulasekararaj: *Achillion:* Consultancy; *Akari Therapeutics:* Consultancy; *Celgene/BMS:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *Samsung:* Consultancy; *Novartis:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees; *F. Hoffmann-La Roche Ltd:* Consultancy, Membership on an entity's Board of Directors or advisory committees; *Amgen:* Honoraria, Membership on an entity's Board of Directors or advisory committees; *BioCryst:* Consultancy; *Alexion, AstraZeneca Rare Disease:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Schrezenmeier:** *Roche:* Other: honoraria (to University of Ulm) ; *Apellis:* Other: honoraria (to University of Ulm) ; *Sobi:* Honoraria, Other: travel support, Research Funding; *Novartis:* Honoraria, Other: travel support, Research Funding; *Alexion, AstraZeneca Rare Disease:* Honoraria, Other: travel support, Research Funding; *Sanofi:* Other: honoraria (to University of Ulm). **Usuki:** *Abbvie:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Alnylam Japan:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; *Alxion:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees, Research Funding; 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*Novartis:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Alexion:* Membership on an entity's Board of Directors or advisory committees, Research Funding. **Notaro:** *Alexion:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *Novartis:* Membership on an entity's Board of Directors or advisory committees; *SOBI:* Membership on an entity's Board of Directors or advisory committees, Speakers Bureau; *SAMSUNG BIOEPIS:* Membership on an entity's Board of Directors or advisory committees. **Ogawa:** *Alexion, AstraZeneca Rare Disease:* Current Employment. **Yu:** *Alexion, AstraZeneca Rare Disease:* Current Employment. **Patel:** *Alexion, AstraZeneca Rare Disease:* Current Employment, Current equity holder in publicly-traded company. **Patel:** *Alexion, AstraZeneca Rare Disease:* Current Employment. **Füreder:** *Sobi:* Honoraria; *Novartis:* Honoraria; *BioCryst:*

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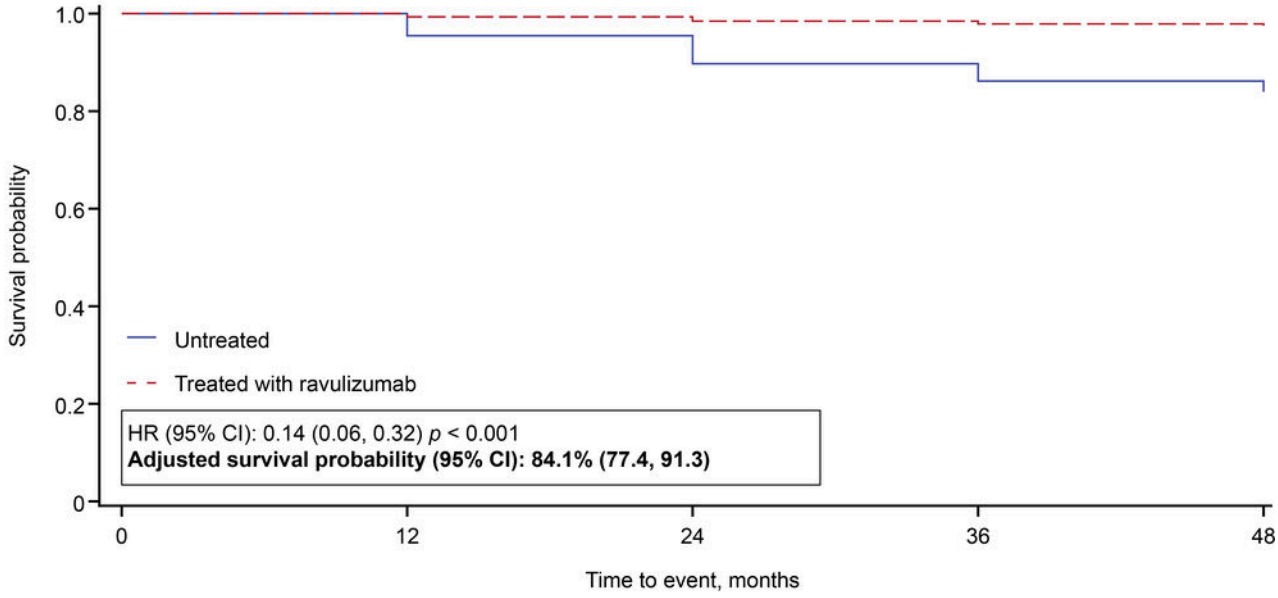
Figure 1. Adjusted survival analysis of ravulizumab-treated and untreated patients with PNH



Covariates included in the final adjusted model include age at PNH diagnosis, sex and transfusion history at baseline.
CI, confidence interval; HR, hazard ratio; PNH, paroxysmal nocturnal hemoglobinuria.

Figure 1

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