Taking a Deep Data Dive Into PNH: Focus on New and Emerging Agents

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Learning Objectives

- Explain the pathogenesis of paroxysmal nocturnal hemoglobinuria (PNH) and the importance of targeting the proximal as well as terminal complement system pathways
- Evaluate recently released efficacy and safety findings from clinical trials of new and emerging treatments for PNH
- Integrate a patient-focused strategy when selecting and monitoring treatments for PNH

Brief Review of PNH

Articles Discussed

- Cançado RD, Araújo A da S, Sandes AF, et al. Consensus statement for diagnosis and treatment of paroxysmal nocturnal haemoglobinuria. *Hematol Transfus Cell Ther*. 2021;43:341-348.
- Fattizzo B, Serpenti F, Giannotta JA, Barcellini W. Difficult cases of paroxysmal nocturnal hemoglobinuria: diagnosis and therapeutic novelties. *J Clin Med*. 2021;10:948.
- Schrezenmeier H, Röth A, Araten DJ, et al. Baseline clinical characteristics and disease burden in patients with paroxysmal nocturnal hemoglobinuria (PNH): updated analysis from the International PNH Registry. *Ann Hematol*. 2020;99:1505-1514.

Defining/Quantifying PNH

- **P**aroxysmal = sudden onset
- **N**octurnal = occurring at night (or in the morning after awakening)
- **H**emoglobinuria = blood in urine due to hemolysis

Most patients don't present this way and, in International PNH Registry (N=4,439), only 45% present with hemoglobinuria

- Prevalence: **Rare!** 10–20 million, worldwide
- Median age of onset: Early to mid 30s; men and women equally
- Mortality if untreated: 35% in 5 years; 50% in 10 years

Cançado RD, et al. *Hematol Transfus Cell Ther.* 2021;43:341-348; Schrezenmeier H, et al. *Ann Hematol.* 2020;99:1505-1514.

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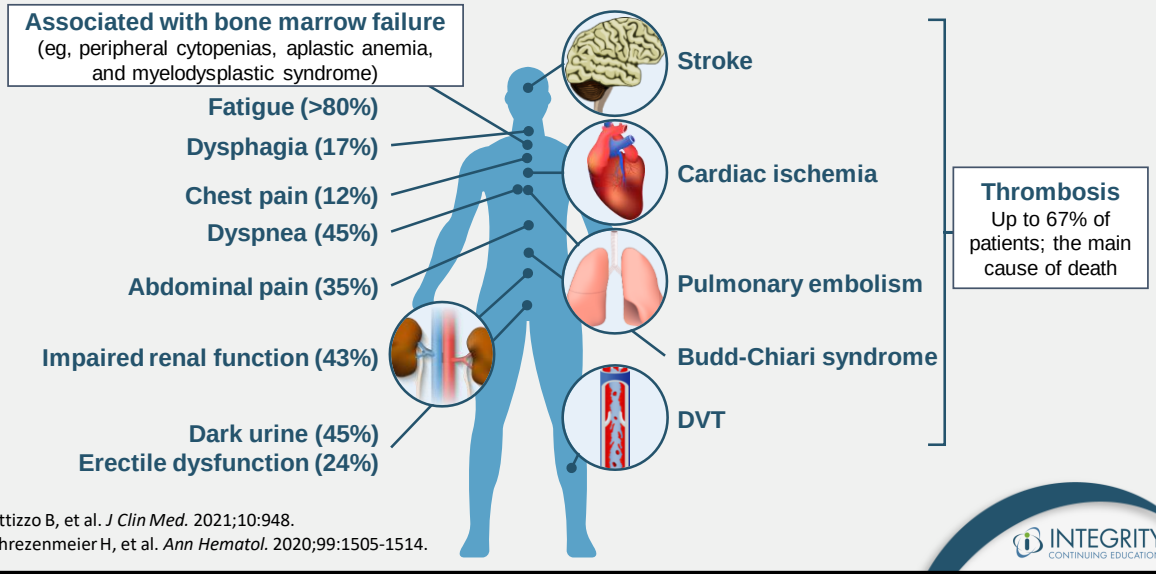
Heterogeneous Clinical Characteristics



Fattizzo B, et al. *J Clin Med.* 2021;10:948.
Schrezenmeier H, et al. *Ann Hematol.* 2020;99:1505-1514.

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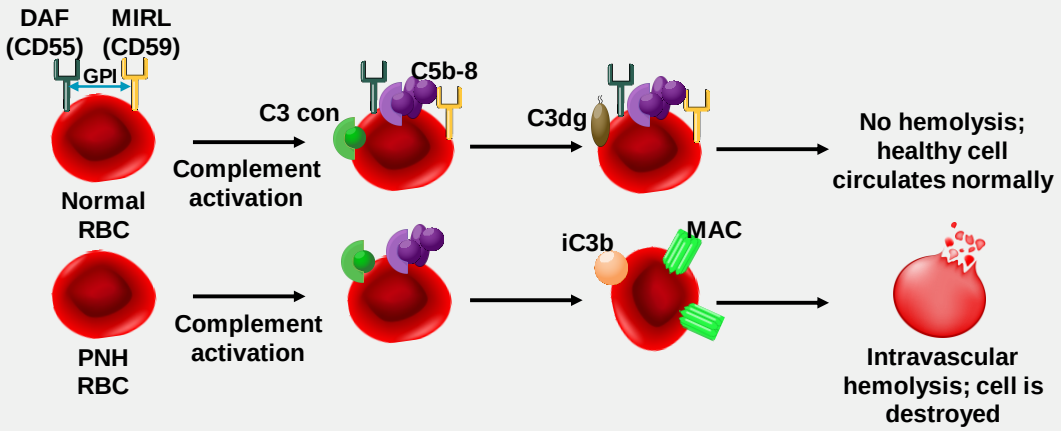
Pathogenesis of PNH

Articles Discussed

- Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. *Blood*. 2021;137:1304-1309.
- Lee JW, Brodsky RA, Nishimura J-I, Kulasekararaj AG. The role of the alternative pathway in paroxysmal nocturnal hemoglobinuria and emerging treatments. *Expert Rev Clin Pharmacol*. 2022;15:851-861.
- Wong RSM. Safety and efficacy of pegcetacoplan in paroxysmal nocturnal hemoglobinuria. *Ther Adv Hematol*. 2022;13:20406207221114673.

Complement Activation in Normal and PNH RBCs



CD, cluster of differentiation; con, convertase; DAF, decay-accelerating factor; GPI, glycophosphatidylinositol; MAC, membrane attack complex; MIRL, membrane inhibitor of reactive lysis; RBCs, red blood cells.

Brodsky RA. *Blood.* 2021;137:1304-1309.

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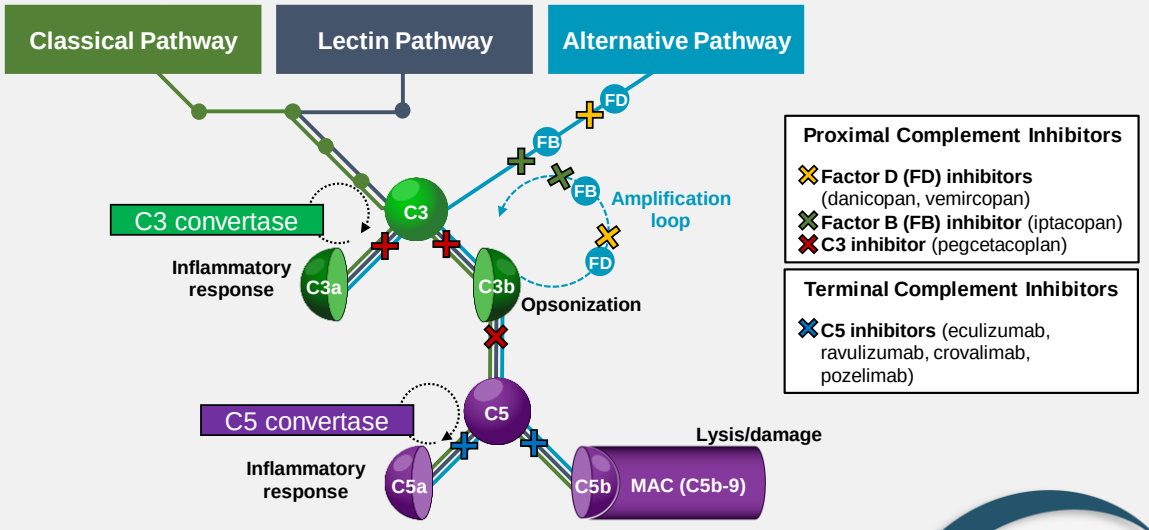
Complement Cascade Pathways, Treatment Targets



Lee JW, et al. *Expert Rev Clin Pharmacol.* 2022;15:851-861.

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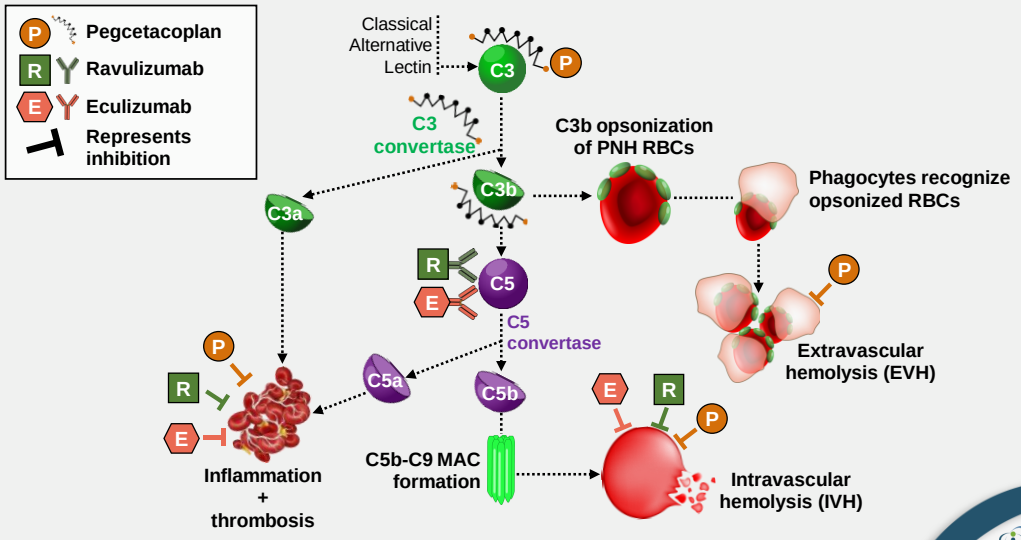
Breakthrough IVH and EVH



Wong RSM. *Ther Adv Hematol.* 2022;13:20406207221114673.

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C3 Inhibition

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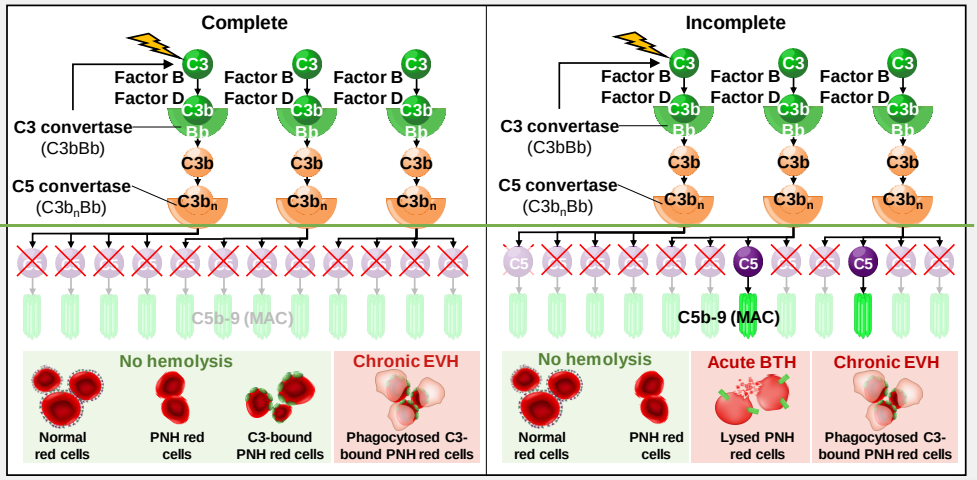
Articles Discussed

- Brodsky RA. How I treat paroxysmal nocturnal hemoglobinuria. *Blood*. 2021;137:1304-1309.
- Notaro R, Luzzatto L. Breakthrough hemolysis in PNH with proximal or terminal complement inhibition. *N Engl J Med*. 2022;387:160-166.
- Hillmen P, Szer J, Weitz I, et al. Pegcetacoplan versus eculizumab in paroxysmal nocturnal hemoglobinuria. *N Engl J Med*. 2021;18:384:1028-1037.
- Peffault de Latour R, Szer J, Weitz IC, et al. Pegcetacoplan versus eculizumab in patients with paroxysmal nocturnal haemoglobinuria (PEGASUS): 48-week follow-up of a randomised, open-label, phase 3, active-comparator, controlled trial. *Lancet Haematol*. 2022;9:e648-e659.
- Wong R, Fishman J, Wilson K, et al. Comparative effectiveness of pegcetacoplan versus ravulizumab and eculizumab in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria: a matching-adjusted indirect comparison. *Adv Ther*. 2023;40:1571-1589.
- Wong RSM, Navarro-Cabrera JR, Comia NS, et al. Pegcetacoplan controls hemolysis in complement inhibitor-naïve patients with paroxysmal nocturnal hemoglobinuria. *Blood Adv*. 2023 Feb 27. [Online ahead of print]

Results of Incomplete C5 Inhibition

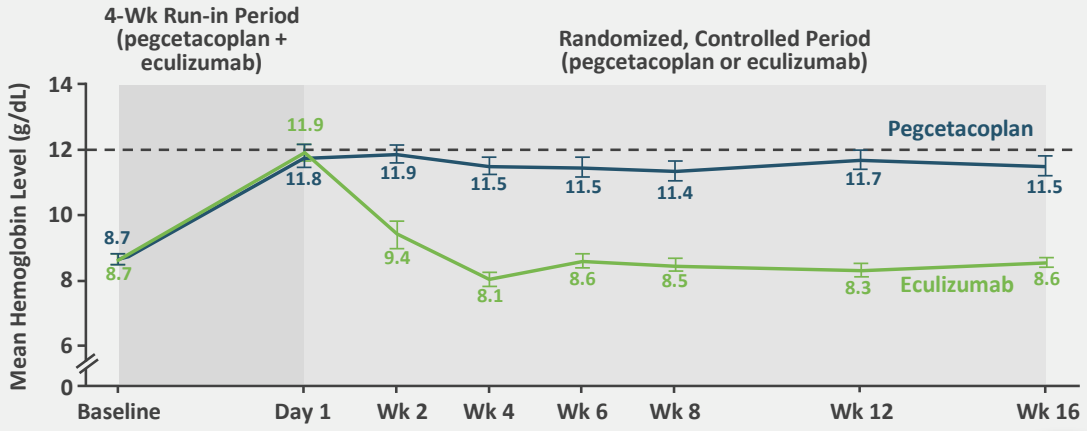


BTH, breakthrough hemolysis.

Notaro R, Luzzatto L. *N Engl J Med.* 2022;387:160-166.

PEGASUS: 16-Week Trial

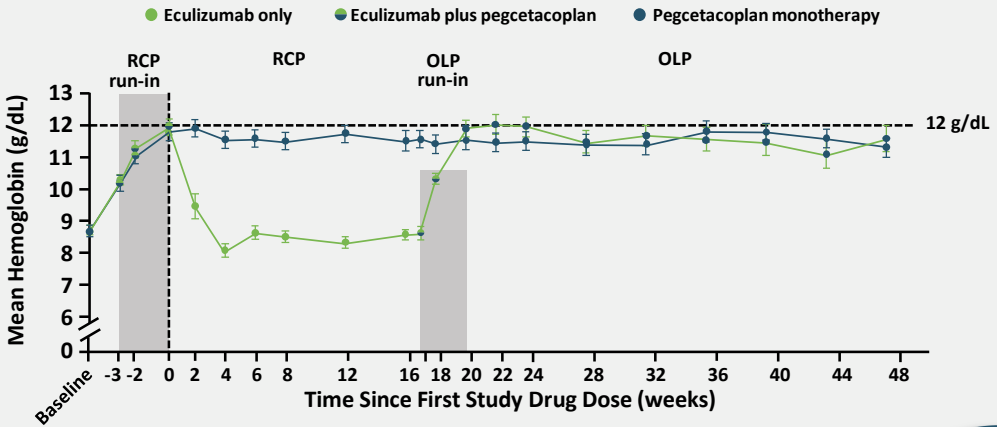
Phase 3, patients with hemoglobin <10.5 g/dL after ≥3 months of eculizumab (N=80)



Hillmen P, et al. *N Engl J Med.* 2021;18:384-1028-1037.

PEGASUS: 48-Week Follow-Up

Patients who stayed on PEG vs those who switched from ECU to PEG, weeks 16–48 (N=77)

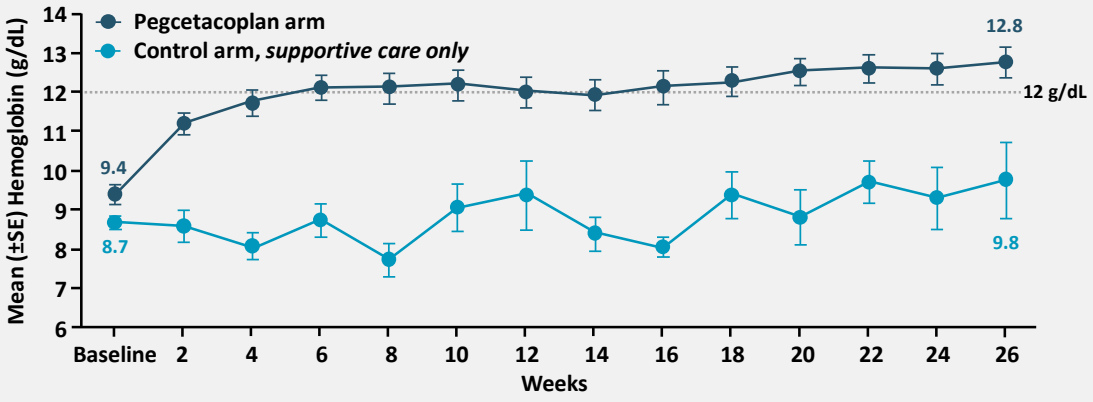


OLP, open-label period; RCP, randomized controlled period.

Peffault de Latour R, et al. *Lancet Haematol.* 2022;9:e648-e659.

PRINCE: Pegcetacoplan vs Supportive Care

Phase 3 trial in complement inhibitor naïve patients (N=53)



Wong RSM, et al. *Blood Adv.* 2023 Feb 27. [Online ahead of print]

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Emerging Treatments for PNH

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Article Discussed

- Liu H, Xia L, Weng J, et al. Results from the first phase 3 crovalimab (C5 inhibitor) study (COMMODORE 3): efficacy and safety in complement inhibitor-naive patients with paroxysmal nocturnal hemoglobinuria (PNH). *Blood.* 2022;140(Suppl 1):714-716.
- Kelly R, Houghton N, Munir T, et al. Phase 2, open-label study evaluating the safety and efficacy of combination pozelimab and cemdisiran therapy in patients with paroxysmal nocturnal hemoglobinuria who switch from eculizumab. *Blood*. 2022;140(Suppl 1):8174-8175.
- Peffault de Latour R, Roeth A, Kulasekararaj A, et al. Oral monotherapy with iptacopan, a proximal complement inhibitor of factor B, has superior efficacy to intravenous terminal complement inhibition with standard of care eculizumab or ravulizumab and favorable safety in patients with paroxysmal nocturnal hemoglobinuria and residual anemia: results from the randomized, active-comparator-controlled, open-label, multicenter, phase III APPLY-PNH study. *Blood*. 2022;140(Suppl 2):LBA-2.
- Kulasekararaj AG, Lazana I. Paroxysmal nocturnal hemoglobinuria: where are we going? *Am J Hematol*. 2023;98(Suppl4):S33-S43.

Emerging Treatments: C5 Inhibitors in Phase 3

Drug Name	Trial Name	Study ID #	Pts	Patient Population	Completion Date
Crovalimab	COMMODORE 1	NCT04432584	190	CI-experienced patients*	September 2029
	COMMODORE 2	NCT04434092	214	CI-naive patients*	June 2028
	COMMODORE 3	NCT04654468	51	CI-naive patients	February 2028
Pozelimab + cemidisiran†	ACCESS-1	NCT05133531	148	CI-naïve patients‡	March 2027
	ACCESS-EXT	NCT05744921	300	Long-term safety & efficacy§	March 2028

*Being tested against eculizumab. †Cemdisiran is an RNA interference therapeutic that targets C5. ‡Being tested against ravulizumab. §Up to 108 weeks.

CI, complement inhibitor.

Source: ClinicalTrials.gov, May 15, 2023.

Crovalimab: COMMODORE 3 Trial

Phase 3, C5-inhibitor naïve patients (N=51)

	Crovalimab (N=51)
Proportion of patients with hemolysis control, mean [95% CI], %	78.7 [67.8–86.6]
Transfusion avoidance, n (%) [95% CI]	26 (51) [36.8–65.1]
Breakthrough hemolysis, n (%) [95% CI]	2 (3.9) [0.7–14.6]
Stabilized hemoglobin, n (%) [95% CI]	26 (51) [36.8–65.1]
FACIT-fatigue score, mean [95% CI]	
Baseline	31.8 [29.3–34.3]
Week 2	38.4 [36.6–40.3]
Week 17	40.5 [38.6–42.5]
Absolute change from baseline through Week 17	8.8 [6.0–11.6]

CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy.

Liu H, et al. *Blood.* 2022;140(Suppl 1):714-716.

Emerging Treatments: Factor B Inhibitor

Drug Name (former name)	Trial Name* Study ID #	Phase	Pts	Patient Population	Completion Date
Iptacopan (LPN023)	APPOINT-PNH NCT04820530	3	40	Monotherapy in CI-naïve patients	April 2023
	APPLAUSE NCT05630001	3	50	Monotherapy in CI-experienced patients†	January 2025
	NCT04747613	3	250	Long-term monotherapy safety/tolerability‡	June 2026

*If assigned. †Studying patients who switch from stable C5 regimen. ‡Assessing proportion of adverse events in 60-month time frame.

CI, complement inhibitor.

Source: ClinicalTrials.gov, May 15, 2023.

Emerging Treatments: Factor D Inhibitors

Drug Name (fomer name)	Trial Name* Study ID #	Phase	Pts	Patient Population	Completion Date
Danicopan (ALXN2040)	ALPHA NCT04469465	3	86	Add-on for C5 inhibitor patients w/ EVH	December 2023
	NCT05389449	3	100	Long-term safety & efficacy as C5 add-on therapy†	February 2027
Vemircopan (ALXN2050)	NCT04170023	2	29	Monotherapy in CI-naïve & CI-experienced‡	October 2026

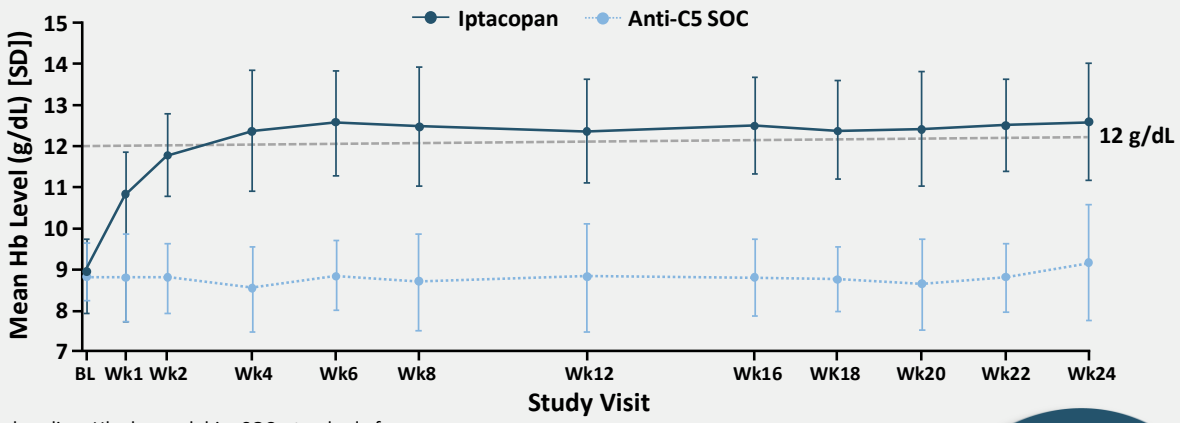
*If assigned. †Add-on treatment to eculizumab or ravulizumab with 3-year time frame. ‡Patients taking eculizumab included if they continued to experience anemia and reticulocyte levels above ULN.

CI, complement inhibitor; ULN, upper limit of normal.

Source: ClinicalTrials.gov, May 15, 2023.

APPLY-PNH: Iptacopan vs Supportive Care

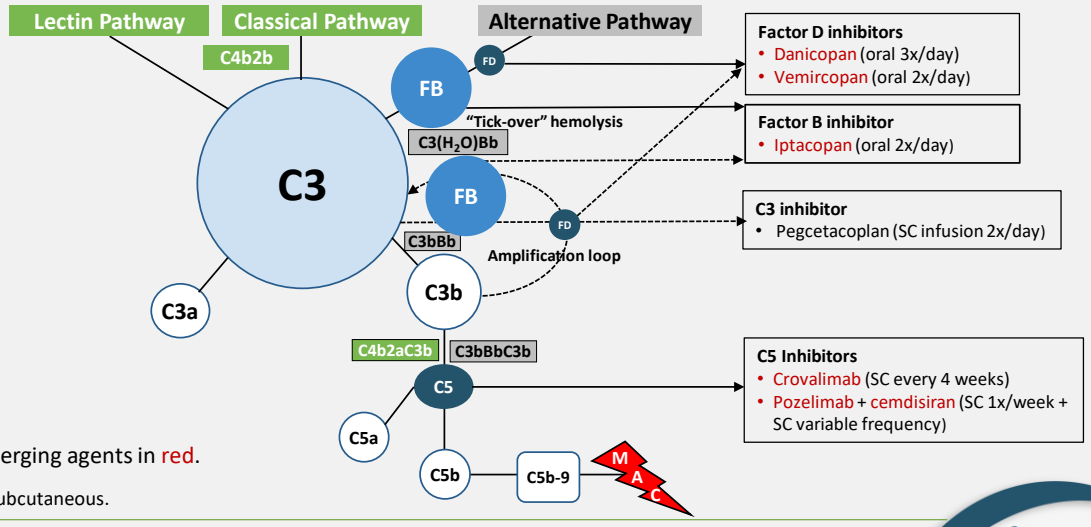
Phase 3, patients with hemoglobin <10.5 g/dL after ≥6 months on standard of care (N=97)



BL, baseline; Hb, hemoglobin; SOC, standard of care.

Peffault de Latour, et al. *Blood.* 2022;140(Suppl2):LBA-2.

Emerging* C3 and C5 Complement Inhibitors



*Emerging agents in red.

SC, subcutaneous.

Kulasekararaj AG, Lazana I. *Am J Hematol.* 2023;98(Suppl 4):S33-S43.

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The Management of PNH

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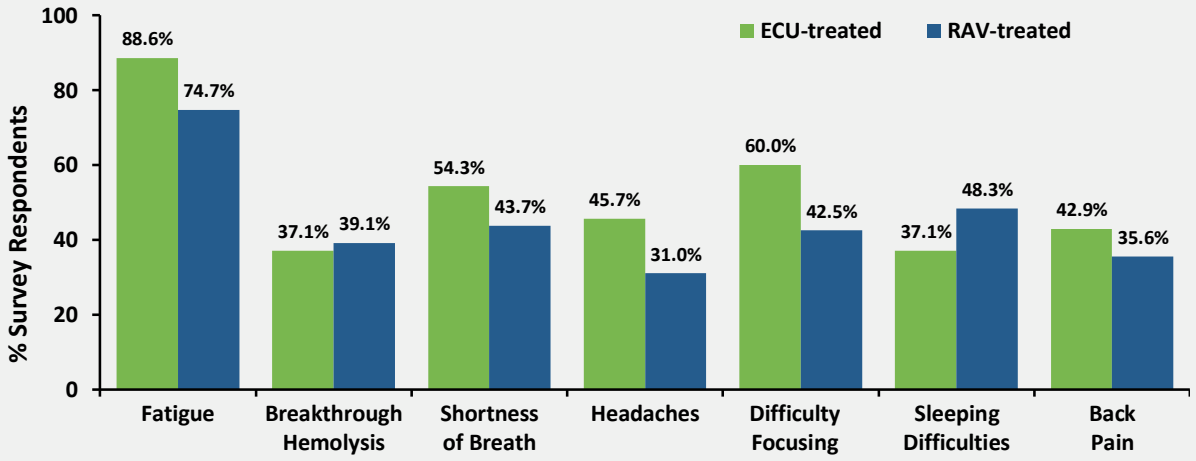
Article Discussed

- Dingli D, Matos JE, Lehrhaupt K, et al. The burden of illness in patients with paroxysmal nocturnal hemoglobinuria receiving treatment with the C5-inhibitors eculizumab or ravulizumab: results from a US patient survey. *Ann Hematol*. 2022;101:251-263.
- Daly RP, Jalbert JJ, Keith S, Symonds T, Shamma J. A novel patient-reported outcome instrument assessing the symptoms of paroxysmal nocturnal hemoglobinuria, the PNH-SQ. *J Patient Rep Outcomes*. 2021;5:102.
- Risitano AM, Peffault de Latour R. How we('ll) treat paroxysmal nocturnal hemoglobinuria: diving into the future. *Br J Haematol*. 2022;196:288-303.
- Szlendak U, Budziszewska B, Spychalska J, Drozd-Sokołowska J, Patkowska E, Nowak J. Paroxysmal nocturnal hemoglobinuria: advances in the understanding of pathophysiology, diagnosis, and treatment. *Pol Arch Intern Med*. 2022;132:16271.

Patient Survey Measuring Disease Burden



ECU, eculizumab; RAV, ravulizumab.

Dingli D, et al. *Ann Hematol.* 2022;101:251-263.

Patient Survey Measuring Disease Burden

PNH Symptoms
Fatigue
Abdominal pain
Headaches
Shortness of breath
Difficulty swallowing
Erectile dysfunction
Hemoglobinuria
Cardiovascular symptoms (eg, chest pain, irregular heartbeat)
Cognitive symptoms (eg, confusion, poor concentration, dizziness)
Bruising/bleeding
Back pain
Leg pain

PNH Symptoms

Impacts on Illness Perceptions
eg, losing control of own body, visible symptoms remind me I'm sick

Impact on Work/School Life
eg, problems with work, no flexibility in planning studies

Overall Quality of Life
eg, normal rhythm of life affected, missing something in life, future prospects

Preoccupation With Disease
eg, thoughts center around disease, disease center of life

Emotional Impacts
eg, fear, loss of lightheartedness, stress, helplessness

Physical Impacts
eg, trouble walking, jogging, standing

Impacts on ADLs
eg, problems getting household work done

Impacts on Relationship
eg, support from family/friends

ADLs, activities of daily living.

Daly RP, et al. *J Patient Rep Outcomes.* 2021;5:102.

Patient Survey Measuring Disease Burden

Type of Reponses	RBC Transfusions	Hemoglobin	Hemolysis Indicators and Hemolytic Crises
Complete response	No	≥13 g/dL (men); ≥12 g/dL (women)	LDH ≤1.5 × ULN and RET ≤150 G/l; no episodes of hemolytic crisis
Major response	No	≥13 g/dL (men); ≥12 g/dL (women)	LDH >1.5 × ULN and/or RET >150 G/l; only subclinical episodes of hemolytic crisis
Good response	No	≥10 and <13 g/dL (men) or ≥10 and <12 g/dL (women)	Any value of LDH and RET, only subclinical hemolytic crisis (excluding bone marrow failure)
Partial response	No or occasional (≤2 every 6 months)	≥8 and <10 g/dL	—
Minor response	No or occasional (≤2 every 6 months)	<8 g/dL	—
	Regularly (3–6 every 6 months)	<10 g/dL	
	Reduction by ≥50%	<10 g/dL	
No response	Regularly (>6 every 6 months)	<10 g/dL	—

LDH, lactate dehydrogenase; RET, reticulocytes.

Risitano AM, Peffault de Latour R. *Br J Haematol.* 2022;196:288-303.
Szlendak U, et al. *Pol Arch Intern Med.* 2022;132:16271

Program Summary

Program Summary

- Physicians need to be aware of PNH and its pathogenesis
- Pegcetacoplan is the only currently available C3 inhibitor
  - Considerations about when to start it
  - Differences between IVH and EVH
- Emerging C5 inhibitors and Factor B and Factor D, which work through the proximal alternative pathway, may fill unmet needs if/when they are approved
- Multidisciplinary patient-centric management approach is necessary