POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
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15-16-17 Febbraio 2024

Emoglobinuria Parossistica Notturna (EPN)

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Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico e
Università degli Studi di Milano

Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
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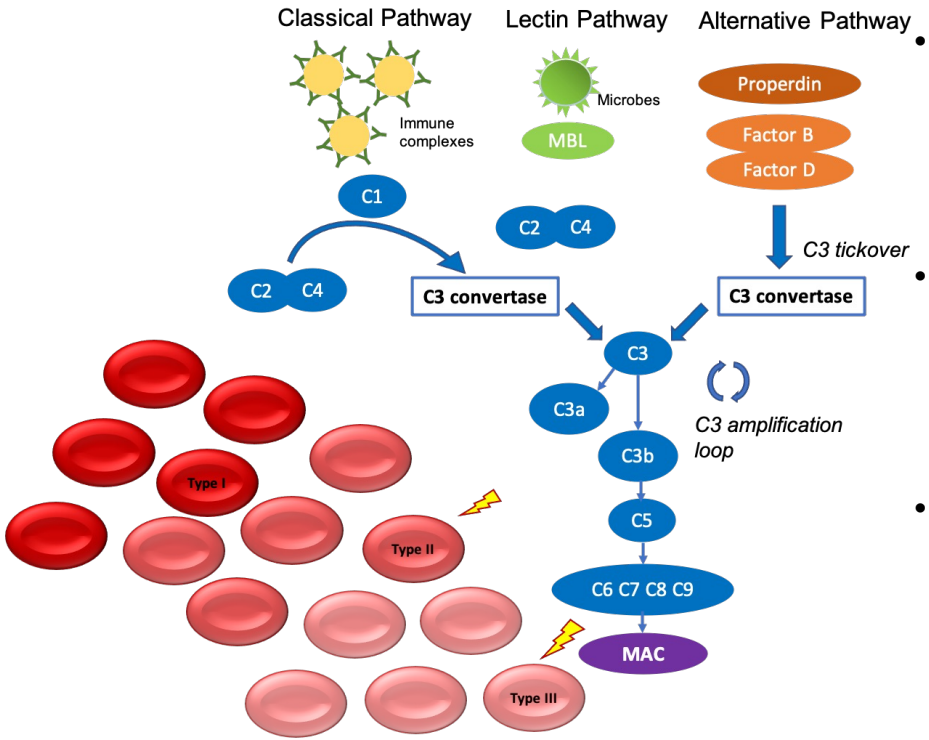
Janssen					X	X	
Novartis			X			X	
Roche			X				
Sobi					X	X	

Paroxysmal nocturnal hemoglobinuria: bone marrow failure and hemolysis



- Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by the acquisition of the somatic mutation of *PIGA* gene encoding for GPI-anchor.
- GPI-anchored molecules include the complement inhibitors CD55 and CD59 that will be therefore deficient on GPI-negative cells.
- GPI-neg erythrocytes are sensitive to complement mediated lysis.

Risitano AM et al, AJH 2018; Kulasekararaj A et al, AJH 2023

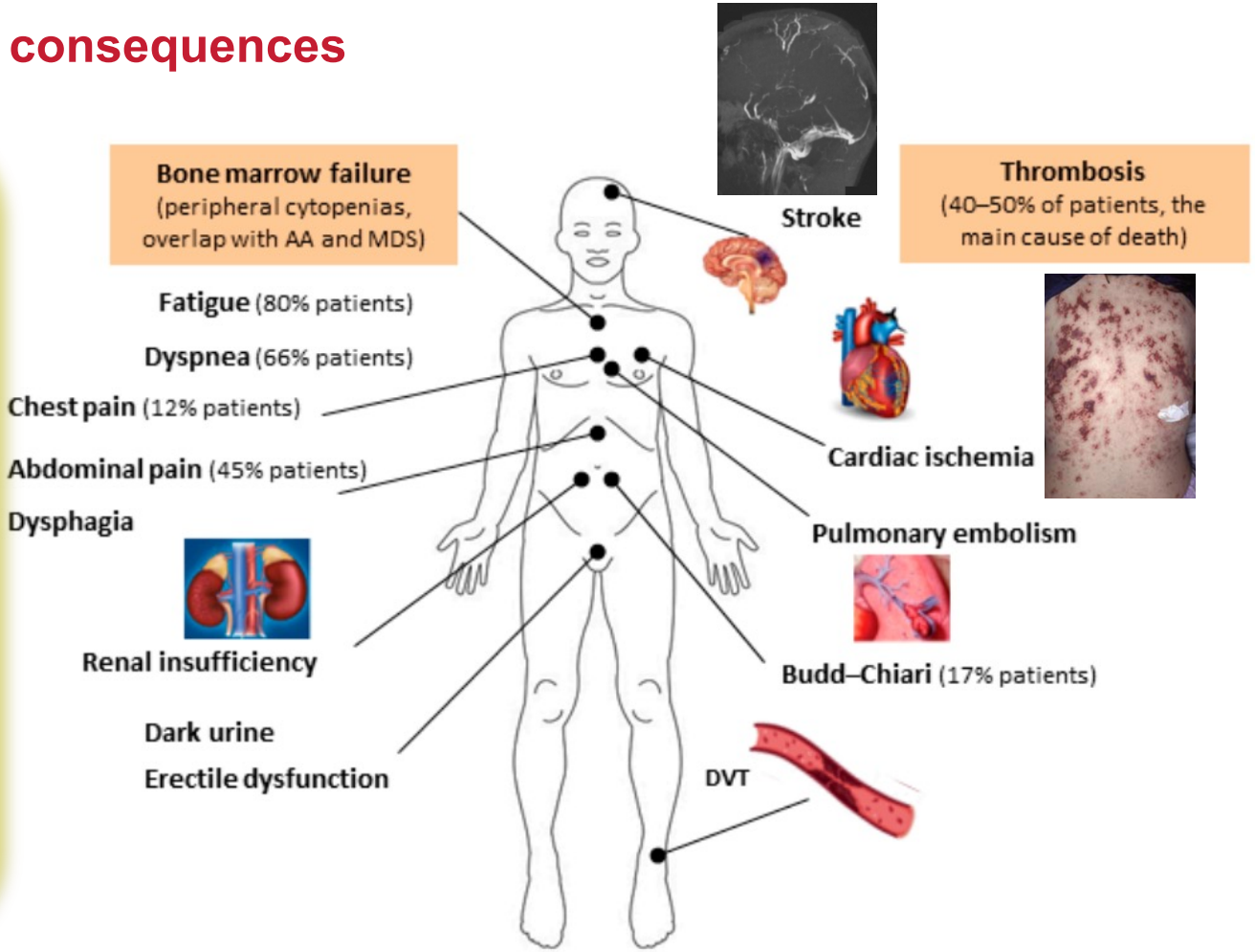
Clinical consequences

ANEMIA
Asthenia,fatigue, palor, jaundice, malaise

CHRONIC HEMOLYSIS
microthrombi and vasospasms:
Dark urine and abdominal pain, dysphagia, erectile dysfunction, pulmonary hypertension

BMF
Infections, bleeding

THROMBOSIS



Fattizzo B et al, JCM 2021

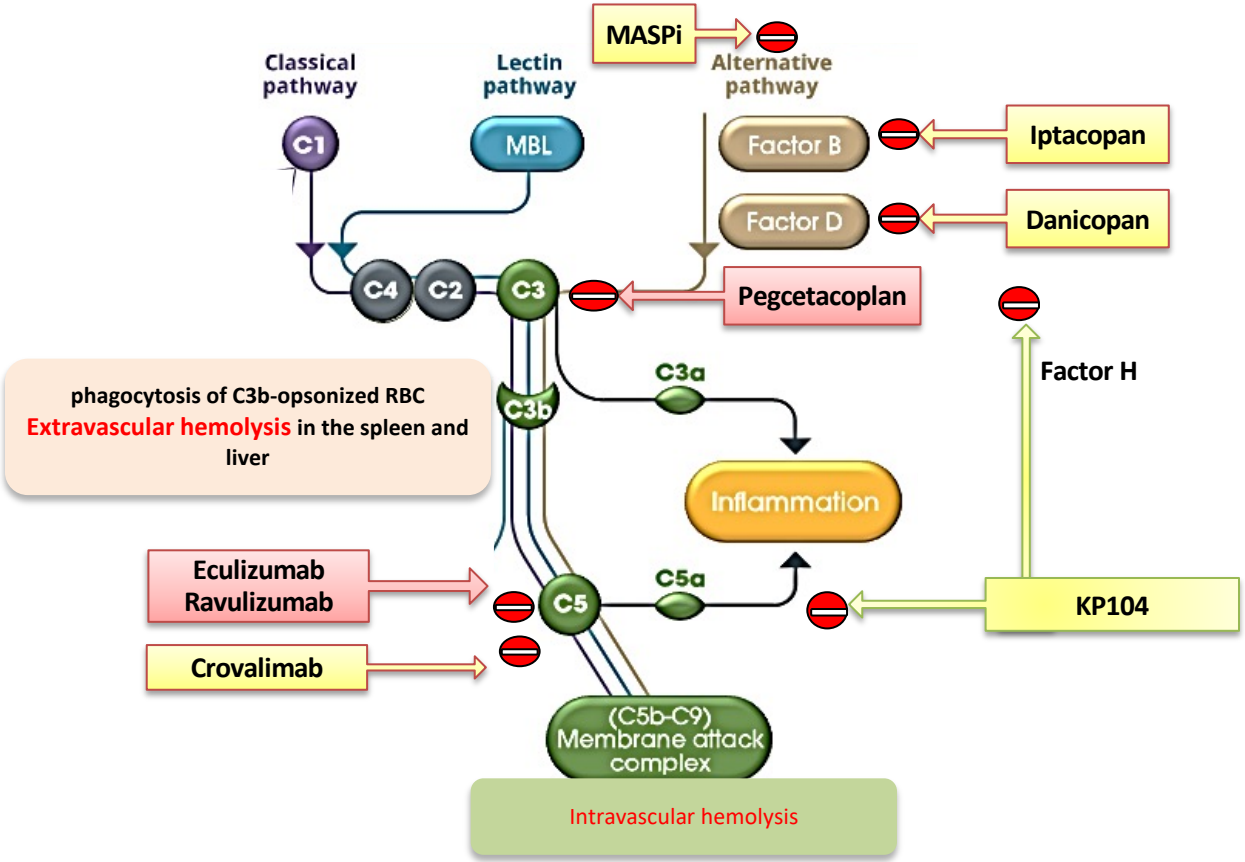
Current PNH therapy in Europe

- **Terminal complement inhibition (C5)** with **eculizumab and ravulizumab**.
- Patients need to receive infusions every 2 weeks or every 8 weeks
- High medicalization, vaccines required
- Not all patients respond due to various causes including
  - ❖inadequate bone marrow compensation,
  - ❖ **residual C5 activation →BTH,**
  - ❖C5 polymorphisms,
  - ❖**persistent extravascolar hemolysis due to C3 deposition**.

- **Proximal complement inhibition (C3)** with **pegcetacoplan** for suboptimal responders ***(residual anemia after >3 months on C5i)***
- Several novel inhibitors are under investigation in clinical trials in the last 10 years.

Risitano AM et al, AJH 2018; Kulasekararaj A et al, AJH 2023

The panorama of complement inhibitors involves terminal ad proximal inhibitors



508. Bone Marrow Failure: Acquired: Unraveling the Future of PNH Therapy From Clinical Trials

571 Factor B Inhibition with Oral Iptacopan Monotherapy Demonstrates Sustained Long-Term Efficacy and Safety in Anti-C5-Treated Patients (pts) with Paroxysmal Nocturnal Hemoglobinuria (PNH) and Persistent Anemia: Final 48-Week Results from the Multicenter, Phase III APPLY-PNH Trial

Antonio M Risitano, MD, PhD[1,2], *Austin Kulasekararaj, MD, MBBS, FRCPath, MRCP*[3,4,5], *Alexander Röth, MD*[6],

572 KP104, a Bifunctional C5 Antibody/Factor H Fusion Protein, Effectively Controls Both Intravascular and Extravascular Hemolysis: Interim Results from a Phase 2 Study in Complement Inhibitor-Naïve PNH Patients

Fengkui Zhang[1*], *Li Zhang*[1*], *Chen Yang*[2*], *Chunrong Wang*[3*], *Changhe Yue*[3*], *Hui Yan*[3*], *Jay Ma*[4*], *Helen Fu*[5*], *Chaomei He*[5*], *Ping Tsui*[5*], *Jingtao Wu*[5*], *Richard Lee*[5*], *Wenru Song*[5] *and Bing Han*[2*]

573 OMS906, a Novel Alternative Pathway MASP-3 Inhibitor, Normalizes Hemoglobin Levels and Increases Clone Size in Treatment-Naïve PNH Patients

Oksana Karnabeda, MD[1,2*], *Valentyn Moskalenko, MD, PhD*[1*], *Zoreslava Lysak, MD*[1*], *Narinder Nangia, PhD*[3*], *Charlotte A. Osborne*[3*], *J. Steve Whitaker, MD*[3*], *Eleni Gavriilaki, MD, PhD*[4] *and* ***Jens Panse, MD***[5,6]

574 Efficacy and Safety Is Maintained in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria Receiving Pegcetacoplan for up to 3 Years

Carlos M de Castro, MD[1], *Brian Mulherin, MD*[2,3*], *Christopher J. Patriquin*[4*], *Veena Selvaratnam, MBBS, FRCPath*[5*], *Raymond SM Wong, FRCP*[6], *Richard J. Kelly, BSc, MD*[7*], *Lisa Tan*[8,9*], *Peter Hillmen, MD*[10*], *Dale Zhang*[11*], *Jessica Savage*[11*] *and Regis Peffault De Latour*[12,13*]

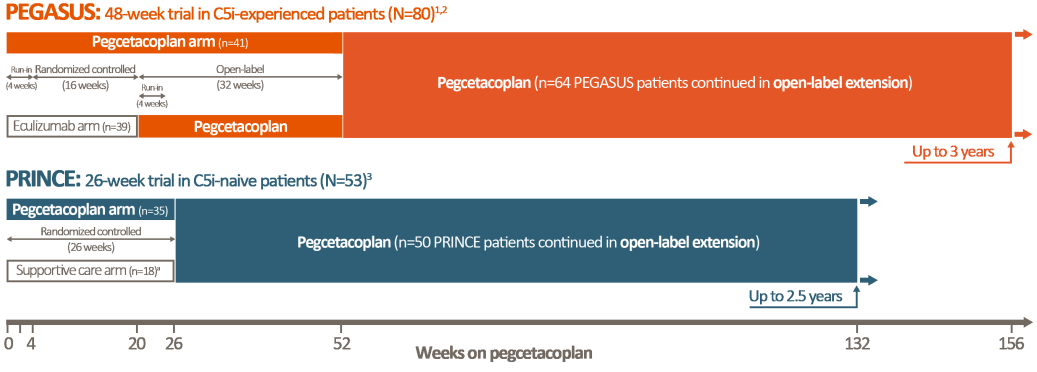
575 Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH): Pooled Results from the Phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 Studies

Alexander Röth, MD[1], *Rong FU, MD*[2*], *Guangsheng He*[3*], *Hazza A Alzahrani*[4*], *Sheng-Chieh Chou*[5*], *Yosr Hicheri*[6*], *Maciej Kazmierczak, MD*[7*], *Viviane Lacorte Recova*[8*], *Michihiro Uchiyama*[9*], *ANA Maria Vladareanu*[10*], *Leigh Beveridge, MBBS, FRACP*[11], *Simon Buatois*[12*], *Muriel Buri*[12*], *Dayu Shi*[13*], *Nadiesh Balachandran*[14*], *Sasha Srekovic*[11*] *and Phillip Scheinberg, MD*[15]

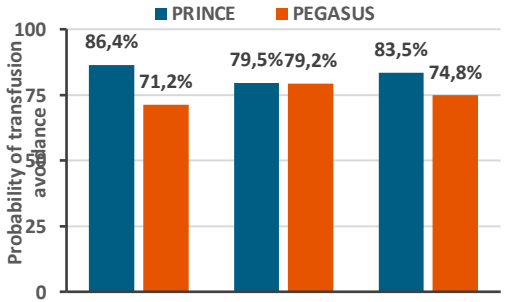
576 Danicopan As Add-on Therapy to Ravulizumab or Eculizumab Versus Placebo in Patients with Paroxysmal Nocturnal Hemoglobinuria and Clinically Significant Extravascular Hemolysis: Phase 3 Long-Term Data

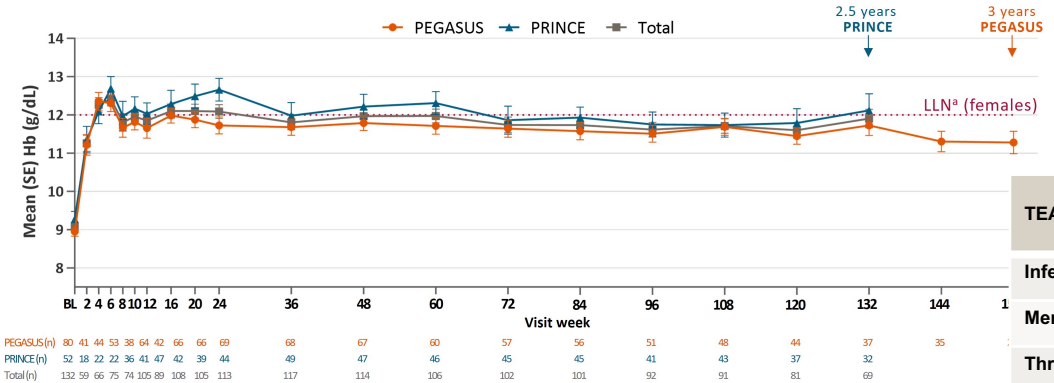
Austin Kulasekararaj, MD, MBBS, FRCPath, MRCP[1], *Morag Griffin, FRCPath, MRCP*[2*], *Caroline I Piatek, MD*[3], *Jamile Shammo, MD*[4], *Jun-Ichi Nishimura, MD, PhD*[5], *Christopher J. Patriquin*[6*], *Hubert Schrezenmeier, MD*[7], *Anna Gaya, MD*[8*], *Yogesh Patel*[9*], *Peng Liu*[9*], *Gleb Filippov, MD*[9*], *Flore Sicre De Fontbrune*[10*], *Antonio M Risitano. MD. PhD*[11] *and Jona-Wook Lee. MD*[12]

Efficacy and Safety Is Maintained in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria receiving Pegcetacoplan for up to 3 Years – Carlos De Castro



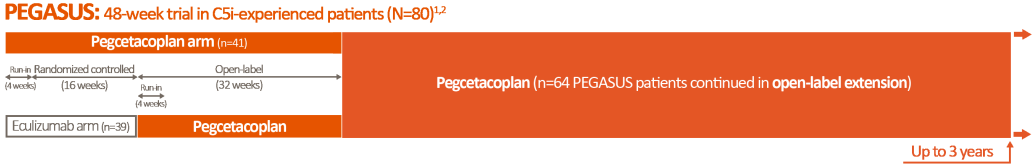
- **Hb rapidly improved and LDH decreased** and were maintained stable for up to 3 years
- **>70% transfusion free** at 3 years
- FACIT-fatigue score increased to levels similar to the general population
- **BTH 30%**

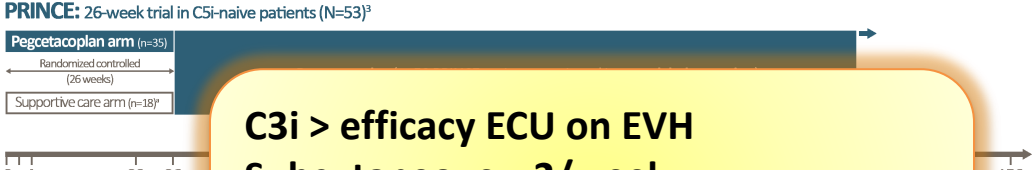




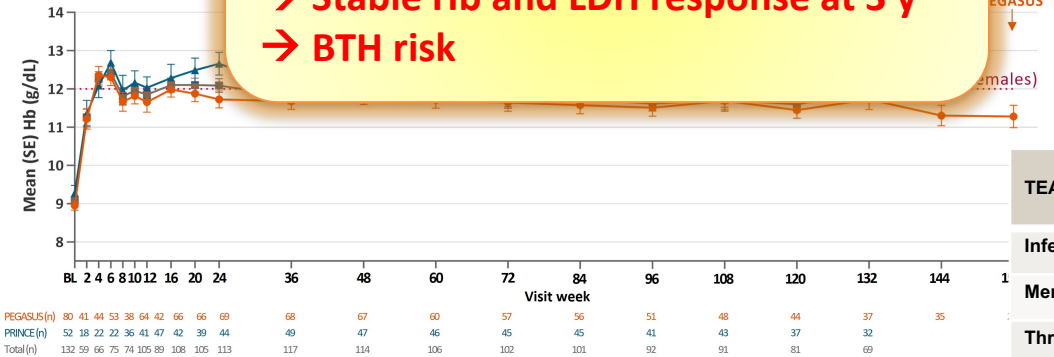
TEAEs of special interest, n (%)	PEGASUS population (N=80)	PRINCE population (N=52)
Infections	**63 (78.8)**	**35 (67.3)**
Meningitis	**0**	**0**
Thrombosis	**3 (3.8)**	**0**
Breakthrough hemolysis[a]	**23 (28.8)**	**16 (30.8)**
Patients with 1/2 events	14 (17.5) / 4 (5.0)	10 (19.2) / 3 (5.8)

Efficacy and Safety Is Maintained in Adult Patients with Paroxysmal Nocturnal Hemoglobinuria receiving Pegcetacoplan for up to 3 Years – Carlos De Castro





C3i > efficacy ECU on EVH
Subcutaneous x 2/week
ASH highlights
→ Stable Hb and LDH response at 3 y
→ BTH risk



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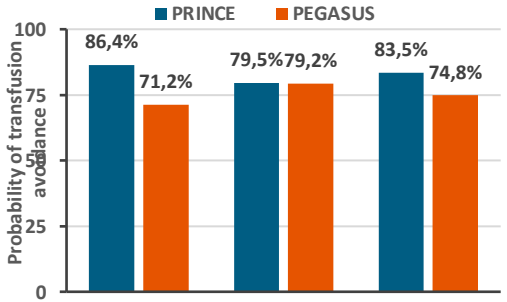

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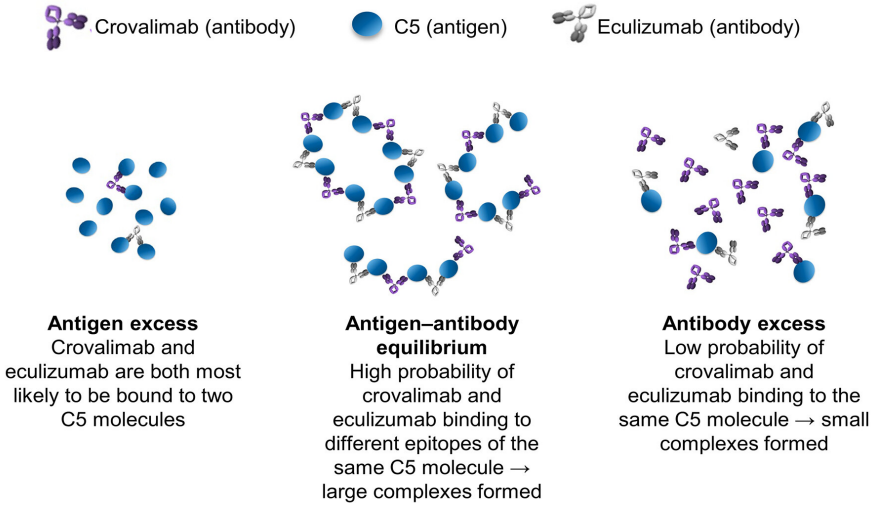
Safety of Crovalimab Versus Eculizumab in Patients with Paroxysmal Nocturnal Hemoglobinuria (PNH): Pooled Results from the Phase III COMMODORE 1, COMMODORE 2, and COMMODORE 3 Studies – A. Roth

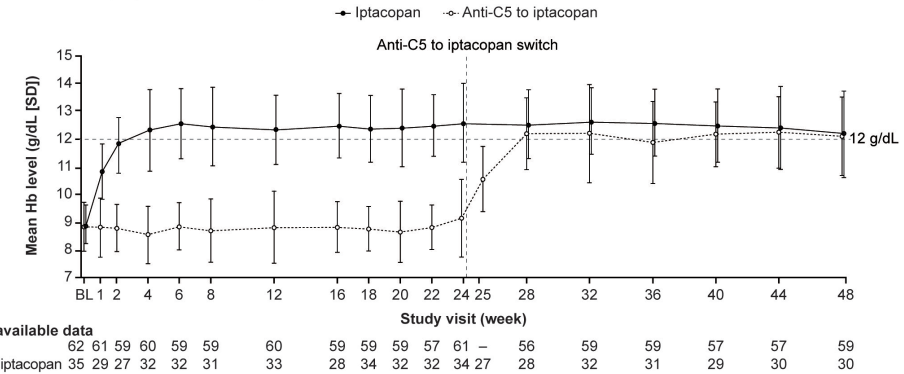
C5i = efficacy ECU
Subcutaneous/4 weeks
ASH highlights
→ same safety as ECU
→ drug-target-drug syndrome

- Crovalimab is a novel anti-C5 recycling antibody that allows for low-volume, s**ubcutaneous (SC) self-administration every 4 weeks** (q4w).
- Pooled analysis of phase 3 studies of Crova (377) vs ecu (111) in C5-naïve or treated PNH
- There were **522 adverse events (AEs) per 100 pt years** in crova pts and **583 in ecu** pts. **No meningococcal infections**.
- **18% of crova switched pts developed complexes formed with ECU → Type III hypersensitivity after a median of 1.6 weeks (range, 0.7–4.4)** and lasting 1.9 weeks (0.4–34.1).
- Most frequently (≥5%) **arthralgia (9%) and rash (6%); Grade 3 in 7% of switched pts**.



Factor B Inhibition with Oral Iptacopan Monotherapy Demonstrates Sustained Long-Term Efficacy and Safety in Anti-C5-Treated Patients (pts) with Paroxysmal Nocturnal Hemoglobinuria (PNH) and Persistent Anemia: Final 48-Week Results from the Multicenter, Phase III APPLY-PNH Trial – AM Risitano

Figure. Mean Hb level (SD) over time during the entire 48-week treatment period of APPLY-PNH



- **Mean Hb levels at Wk 48 were 12.2 and 12.1 g/dL** in the iptacopan and anti-C5-to-iptacopan arms
- **Transfusion avoidance 93.5 and 94,1%**
- **6/62 pts on iptacopan arm had BTH**
- 3 pts had major adverse vascular events:2 TIAs and 1 portal vein thrombosis
- **Most frequent TEAEs were COVID-19** (29.0% of pts), **headache** (19.4%), diarrhea (16.1%) and nasopharyngitis (14.5%).
- **No deaths, nor infectious TEAEs**

Table. Summary of efficacy parameters after the entire 48-week treatment period of APPLY-PNH, including comparison of data at Week 48 vs Week 24

Parameter	Arm	*Iptacopan N=62 Anti-C5 to iptacopan N=35*	*Adjusted mean change from baseline (95% CI) at Week 48*	*Adjusted mean difference in change from baseline (95% CI): Week 48 vs Week 24*
Change from baseline* in Hb level (g/dL)†	Iptacopan		**+3.35** (3.03, 3.66)	**–0.41** (–0.80, –0.01)
	Anti-C5 to iptacopan		**+3.36** (2.93, 3.79)	**+3.02** (2.48, 3.56)
Change from baseline‡ in FACIT-F score	Iptacopan		**+9.80** (8.04, 11.56)	**+0.73** (–1.14, 2.60)
	Anti-C5 to iptacopan		**+10.96** (8.58, 13.34)	**+10.79** (8.12, 13.47)

FBi > efficacy ECU on EVH
Oral x 2/day
ASH highlights
→ Efficacy/safety at 48w
→ Same benefit in switch arm

Doctor, no more dark urine and jaundice with novel drugs?

RAVU reduced PK BTH
but PD BTH may still occur even with novel drugs

TO THE EDITOR:

COVID-19 vaccines induce severe hemolysis in paroxysmal nocturnal hemoglobinuria

Gloria F. Gerber,[1] Xuan Yuan,[1] Jia Yu,[1] Benjamin A. Y. Cher,[2] Evan M. Braunstein,[1] Shruti Chaturvedi,[1] and Robert A. Brodsky[1]

Breakthrough Hemolysis Associated With COVID-19 Vaccination and Active COVID-19 Infection in a Patient With Paroxysmal Nocturnal Hemoglobinuria Maintained on Pegcetacoplan: A Case Report

Mitchell C. Boshkos [1], Kaila R. Fives [2], Davong D. Phrathep [3], Kevin D. Healey [2], Miten Patel [4]

→**PEGCETACOPLAN** → 10% in phase 3, 30% after 3 year
→**IPTACOPAN** → 0% in phase 1-2, 10% in phase 3 48 w
→**DANICOPAN** → 17% in phase 2

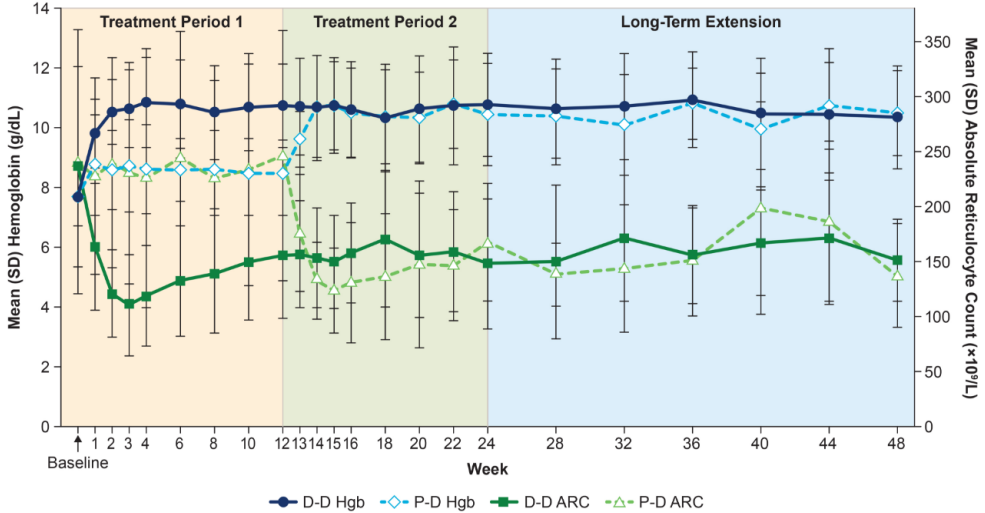
With proximal inhibitors
> % PNH-RBCs are spared
If blockade is incomplete activation is exponential → possible severe BTH

How to manage? Combination therapy?

Boshkos et al, Cureus, 2023
Hillmen et al, NEJM 2021
Risitano et al, Lancet Hem 2022
Jang et al, Blood Adv 2022
Kulasekararaj et al, Blood 2022
Notaro & Luzzatto NEJM 2022

Danicopan As Add-on Therapy to Ravulizumab or Eculizumab Versus Placebo in Patients with Paroxysmal Nocturnal Hemoglobinuria and Clinically Significant Extravascular Hemolysis: Phase 3 Long-Term Data – A. Kulasekararaj

- first-in-class oral factor D inhibitor danicopan as add-on treatment to Rav or Ecu
- Phase 3 in PNH with EVH (Hb <9.5 g/dL and Ret 120x10^9/L) - NCT04469465
- 12-wk data (double-blind): superiority of Dan vs Pbo in Hb increase and transfusion avoidance.
- **Open-label 24-wk (TP2) and ongoing long-term extension (LTE) data are presented.**
- Primary endpoint was change from baseline (CFB) at wk 12 in Hgb.
- Secondary endpoints: Hgb ≥2 g/dL and transfusion avoidance through wk 24
- 86 pts were randomized; 60 completed TP2 (Dan n=40; Pbo n=20).



- **Hgb ≥2 g/dL was 46% in Dan-Dan and 35% in the Pbo-Dan**
- **Transfusion avoidance was 78% in Dan-Dan and 90% in Pbo-Dan.**
- **compliance was 98.8%**
- No deaths, meningococcal infections
- **4 BTH, only 1 with LDH >2×ULN related to COVID-19.**

Danicopan As Add-on Therapy to Ravulizumab or Eculizumab Versus Placebo in Patients with Paroxysmal Nocturnal Hemoglobinuria and Clinically Significant Extravascular Hemolysis: Phase 3 Long-Term Data – A. Kulasekararaj

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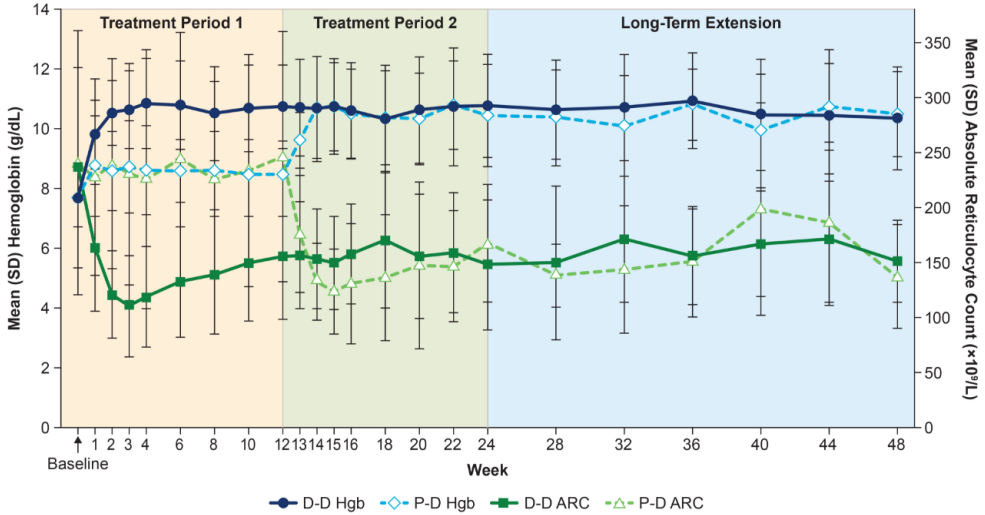
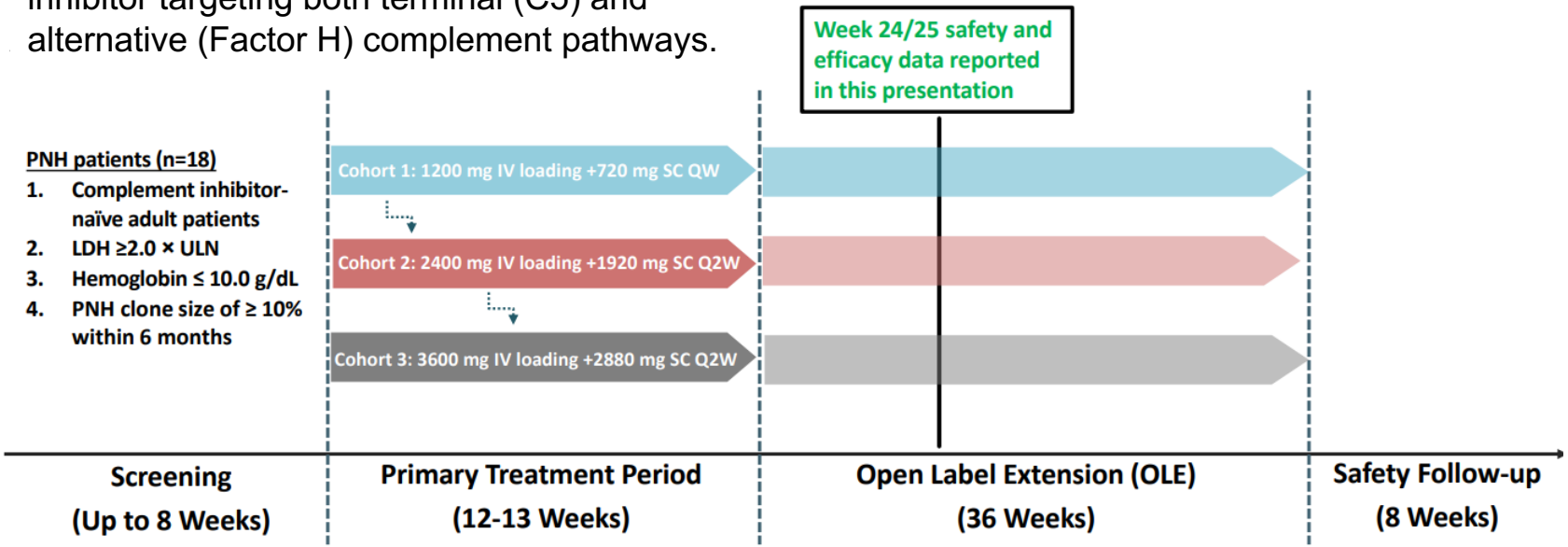


FDi > efficacy ECU on EVH but >BTH
Oral x 3/day + ECU/RAVU

ASH highlights
→ Efficacy/safety at 48w
→ Same benefit in switch arm

KP104, A Bifunctional C5 Antibody/Factor H Fusion Protein, Effectively Controls Both Intravascular and Extravascular Hemolysis: 24/25-Week Results From An Ongoing Phase 2 Study In Complement Inhibitor-naïve Patients with PNH - Fengkui Zhang et al

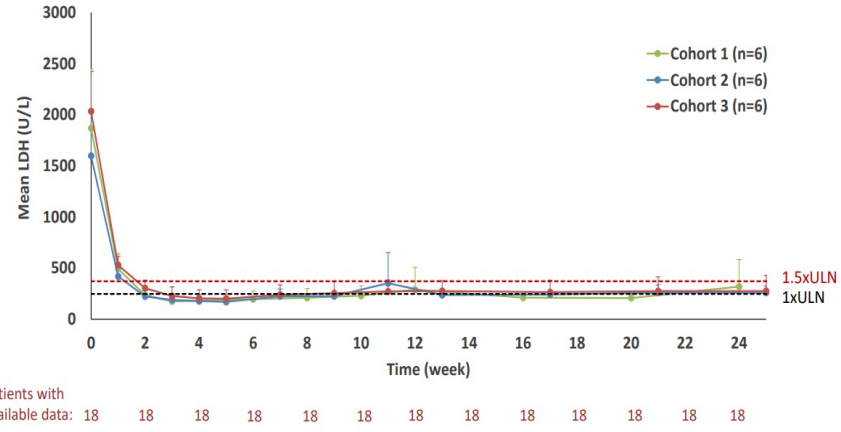
KP104 is a potent, first-in-class bifunctional inhibitor targeting both terminal (C5) and alternative (Factor H) complement pathways.

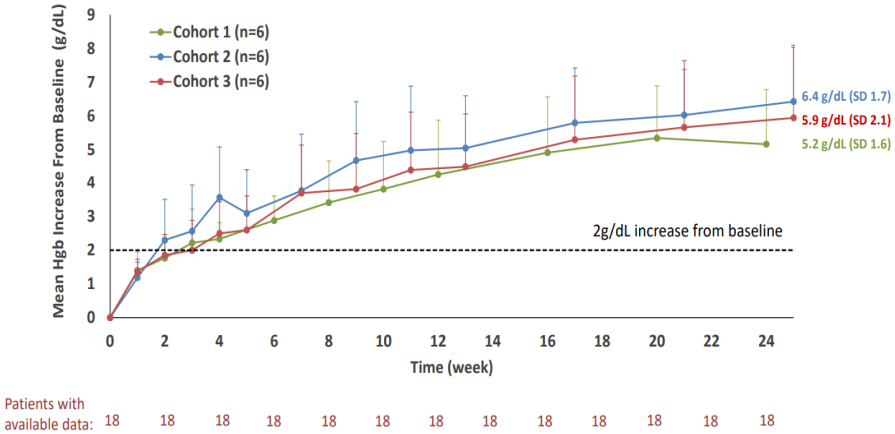


- **Primary Endpoints**: safety, tolerability, and efficacy (% subjects achieving **≥ 2 g/dL increase** in hemoglobin (Hgb) level from baseline in the absence of RBC transfusion through the treatment period)
- **Secondary Endpoints**: change from baseline in LDH and Hgb levels, transfusion avoidance, and FACIT-Fatigue score

KP104 Met All the Pre-specified Key Clinical Efficacy Endpoints Across All Three Cohorts (N=18) at the End of 24/25 Weeks of Treatment Period

Hb Increase of ≥ 2 g/dL from baseline (18/18)	100%
RBC Transfusion Avoidance (18/18)	100%
Hb Normalization ≥ 12 g/dL (10/18)	56%
FACIT-Fatigue Score Clinically Meaningful Improvement (18/18)	100%
LDH <1.5x ULN (15/18)	83%
Free of BTH (17/18)	94%
LDH <1x ULN (13/18)	72%
Safe and well-tolerated without ≥ Grade 3 TEAEs (18/18)	100%





Emerging Treatments for PNH

Griffin M, et al. *Ther Adv Rare Dis*. 2020;1:1-12.

Thank You!

Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan, Italy

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