

SINTOMA symposium

Paroxysmal Nocturnal hemoglobinuria

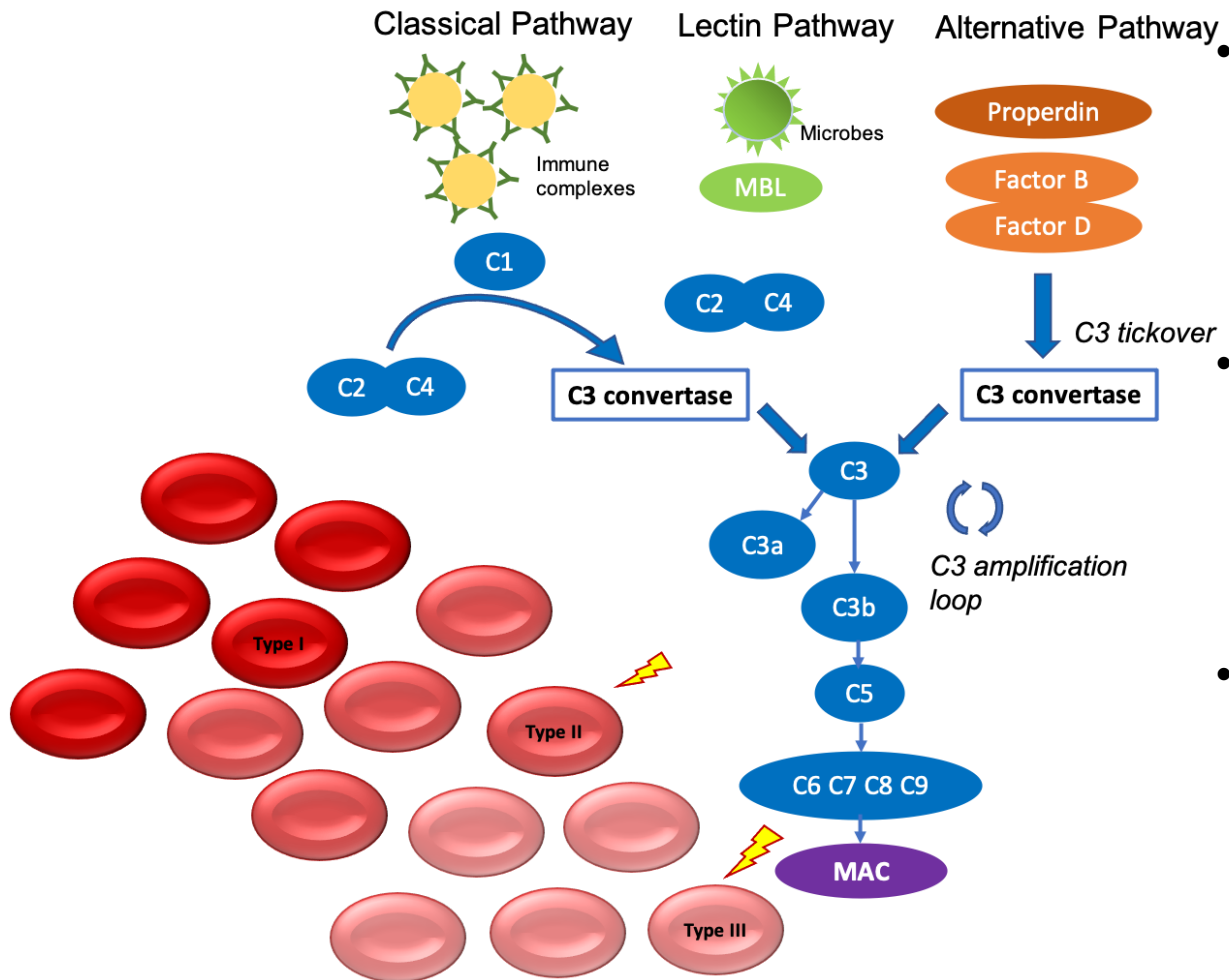


Bruno Fattizzo

Department of Oncology and Hemato-oncology, University of Milan, Italy

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

Paroxysmal nocturnal hemoglobinuria: bone marrow failure and hemolysis

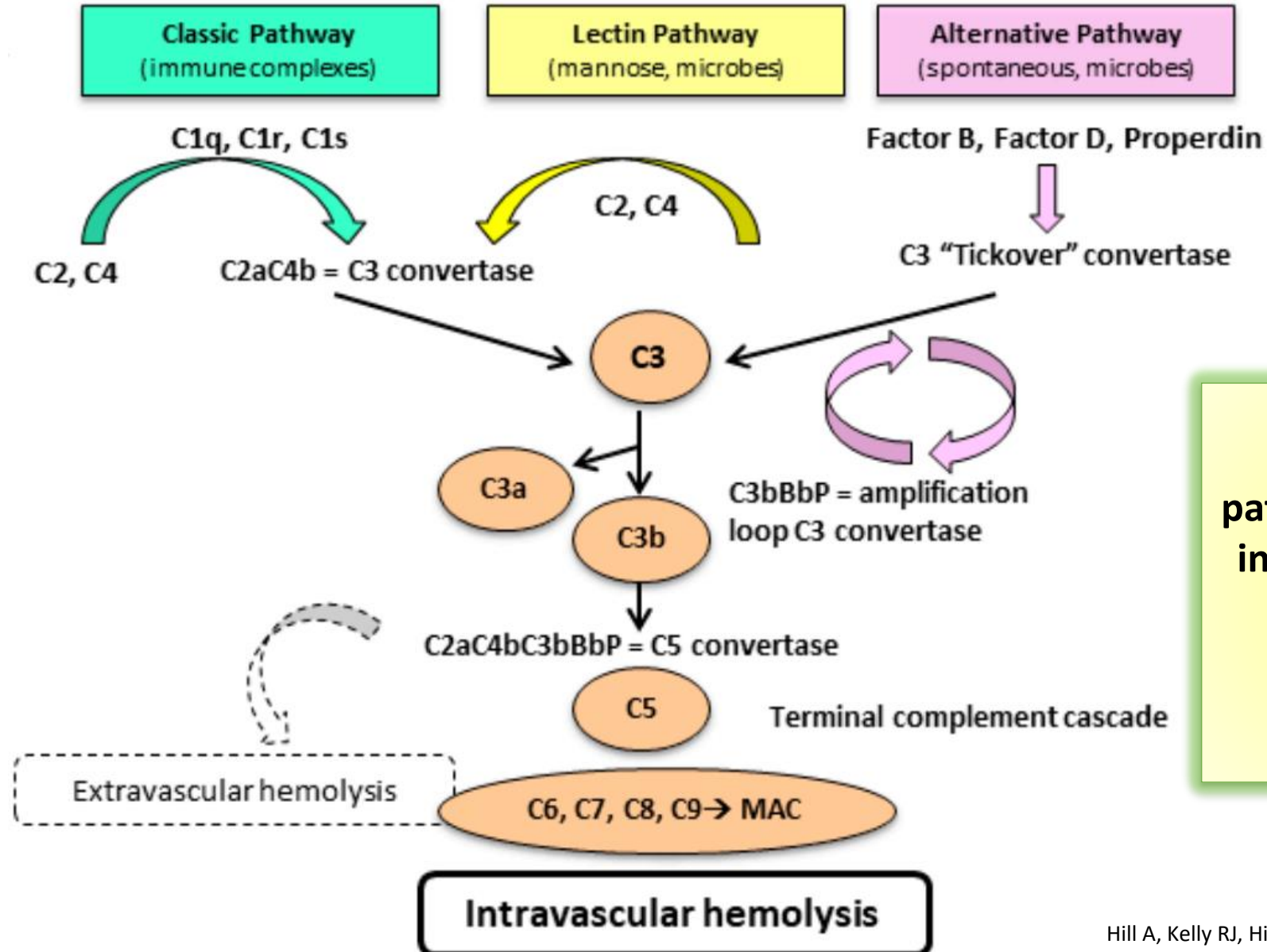


Paroxysmal nocturnal hemoglobinuria (PNH) is characterized by the acquisition of the somatic mutation of *PIGA* gene encoding for GPI-anchor.

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.

How does hemolysis occur?



IVH is the main pathogenetic mechanism in untreated PNH being associated with symptoms and thrombosis

Which is the main cause of morbidity and mortality in untreated PNH?

1. Hemolysis
2. Anemia
3. Thrombosis
4. Leukemic evolution
5. infections



Clinical consequences

ANEMIA

Asthenia, fatigue,
pallor, jaundice,
malaise

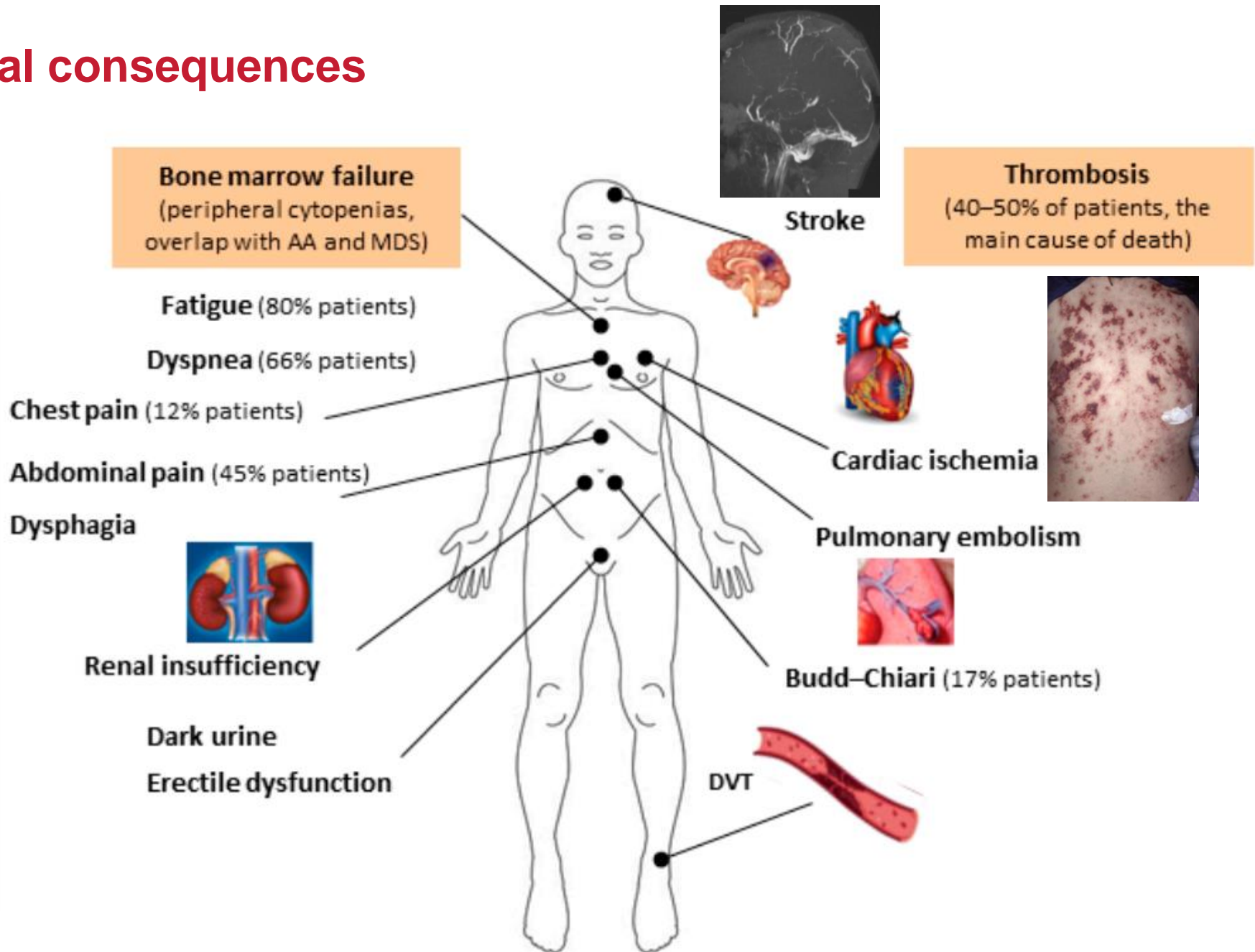
CHRONIC HEMOLYSIS

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

BMF

Infections, bleeding

THROMBOSIS



How do you measure disease activity?

1. bilirubin
2. Hb
3. LDH
4. thrombosis
5. PNH related symptoms
6. Need of transfusion



Heterogeneity of clinical presentation in untreated PNH: The International PNH Registry

PNH patients, particularly those with large PNH clone size, may present with high disease activity (HDA)

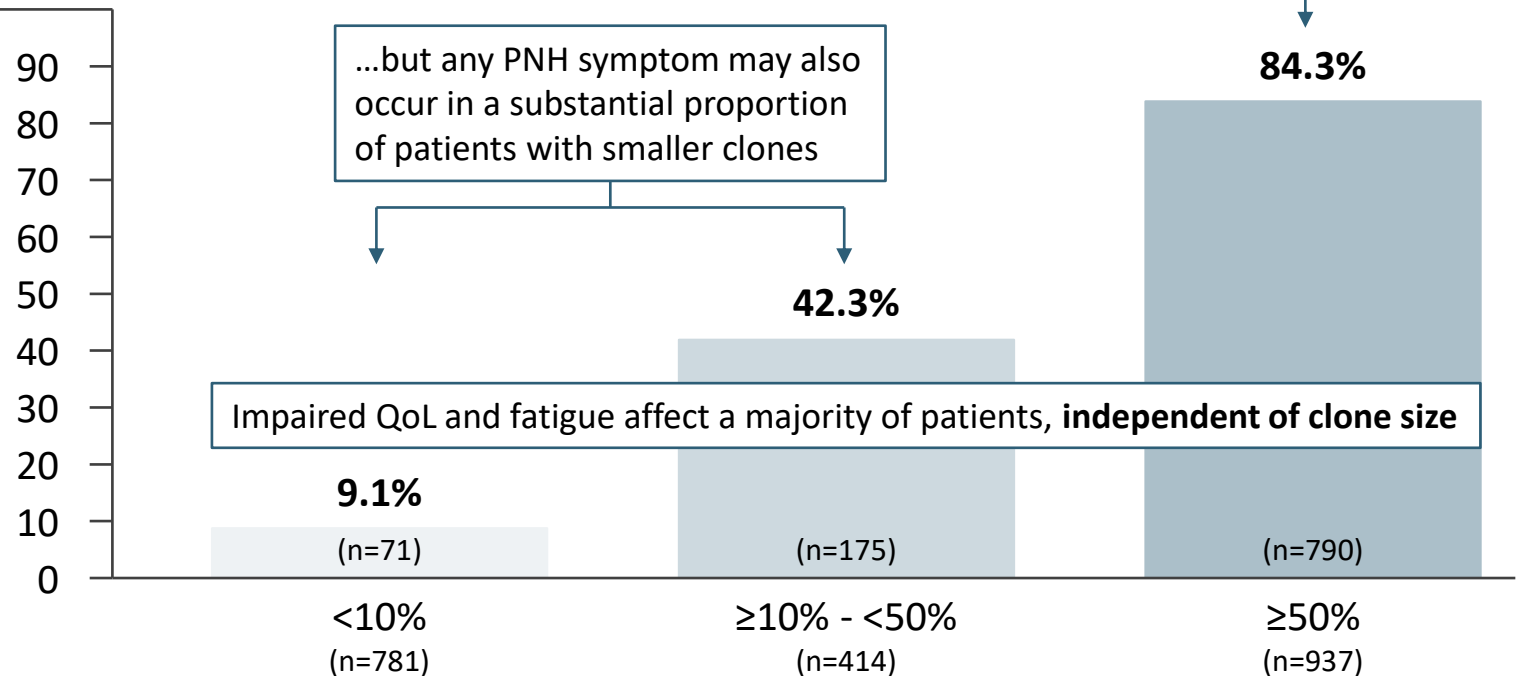
Patients with HDA (%)



LDH $\geq 1.5 \times$ ULN, a marker of intravascular haemolysis²



History of ≥ 1 PNH symptom

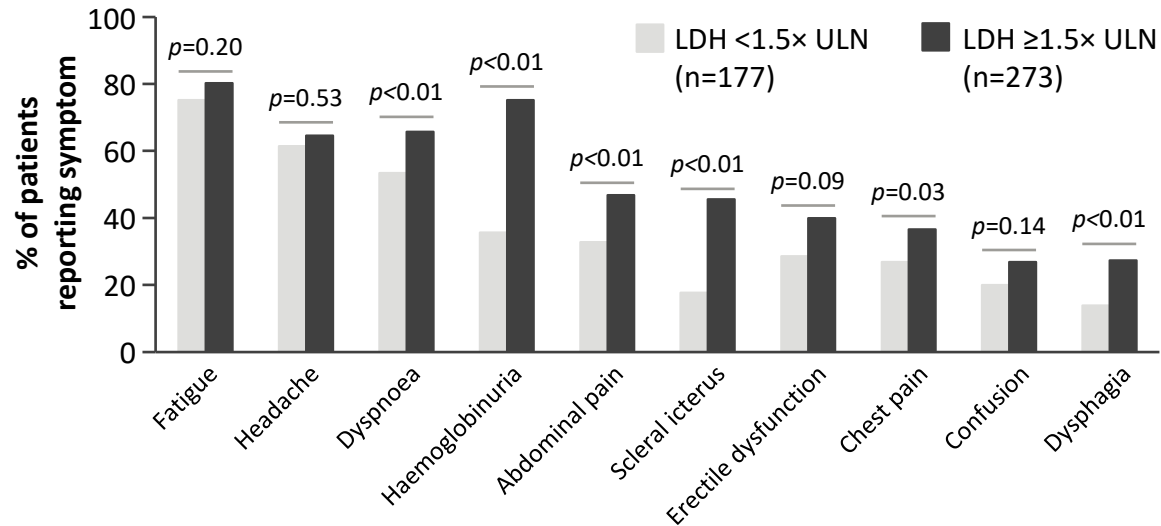


GPI, glycosylphosphatidylinositol; HDA, high disease activity; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; QoL, quality of life; ULN, upper limit of normal.
1. Schrenzenmeier et al. *Ann Hematol* 2020 2. Kulasekararaj et al. *Blood Rev* 2023.

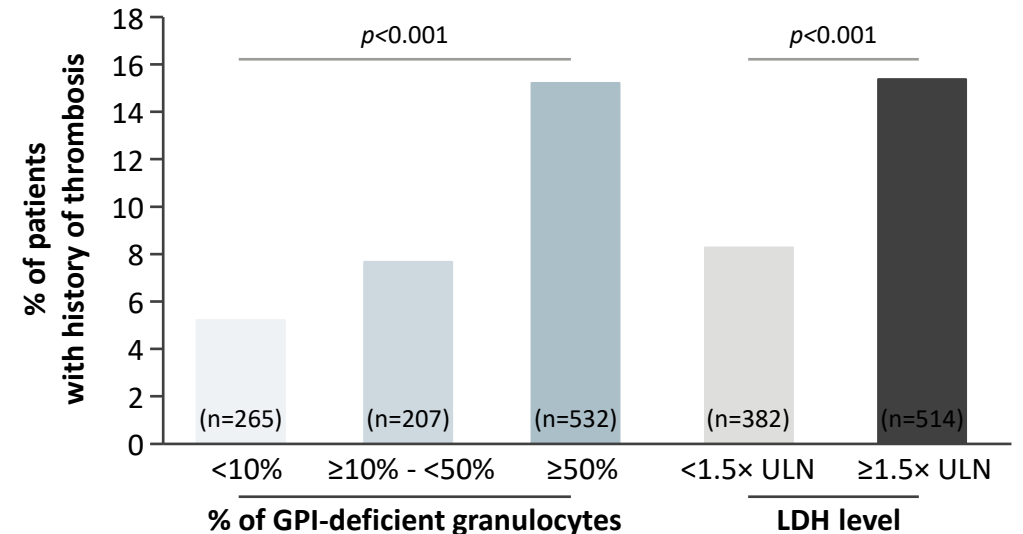
% GPI-deficient granulocytes at baseline

Elevated LDH, an indicator of high disease activity and IVH, is associated with symptom burden and thrombosis risk

Elevated LDH is associated with increased prevalence of many PNH symptoms in untreated patients¹



Elevated LDH is associated with a history of thrombosis, the leading cause of death in PNH¹



Supported by retrospective analysis of untreated patients in the Korean PNH Registry:

The presence of IVH at diagnosis is associated with life-threatening thrombosis, poor quality of life, and early mortality^{2,3}

GPI, glycosylphosphatidylinositol; IVH, intravascular haemolysis; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria; ULN, upper limit of normal.

1. Schrenzenmeier et al. *Haematologica* 2014 2. Jang et al. *J Korean Med Sci* 2016 3. Kim et al. *ASH* 2010; abstract 4241.

Current therapy with complement inhibitors

- **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 extravascular hemolysis due to C3 deposition.**
- **Proximal complement inhibition (C3)** with **pegcetacoplan** for suboptimal responders (***residual anemia after >3 months on C5i***) ***in Europe vs for all in USA***
- Several novel inhibitors are under investigation in clinical trials in the last 5-7 years.

Clinical vignette– F 41 years



Diagnosis of classic PNH

Tx+ Iron + vitamins
LMWH

Renal thrombosis

Accepted ECU
> Hb 8.8 g/dL

Doctor, will I keep on with this IV drug every 14 days?

- The patient went from transfusion dependence before ECU
- To moderate anemia under ECU and frequent BTH (PK? PD?)

Doctor, I feel better but I'm always at the day care facility!

I keep seeing dark urine before every eculizumab dosing!



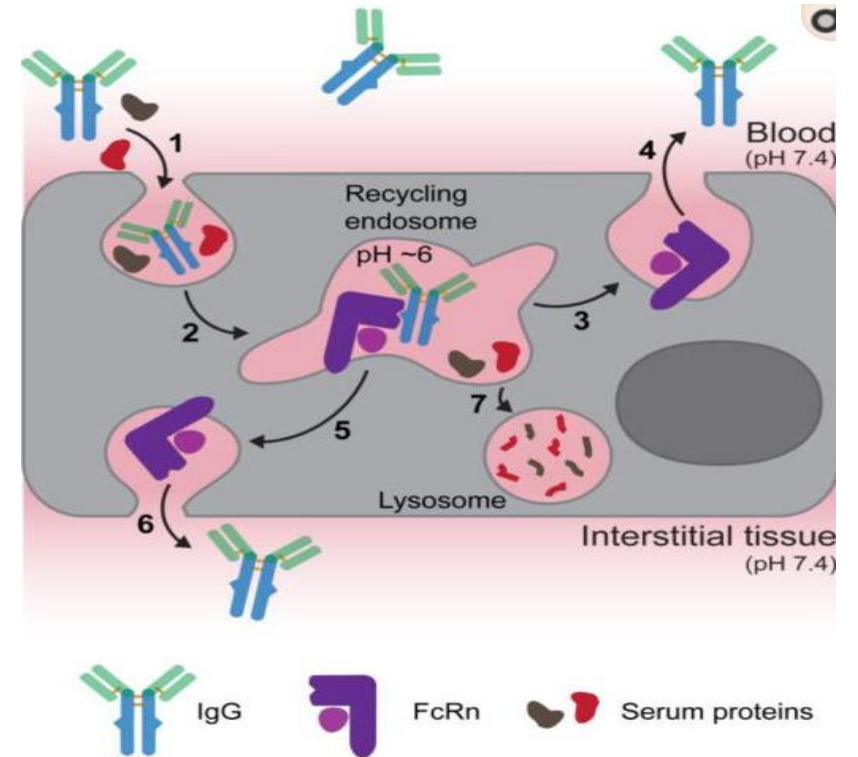
Ravulizumab

Modification of eculizumab for increased half-life

Histidine substitution at two positions within the first and second heavy chain complementarity-determining regions of eculizumab generates a novel mAb

This extends its PK and PD in the presence of human C5 in a mouse model

Additional modifications were made to the Fc region from eculizumab to further increase the half-life by increasing its affinity for FcRn



- The neonatal Fc Receptor (Fc-Rn) was firstly described about 50 years ago, and is responsible for the salvage of IgG from catabolism
- FcRn is structurally homologous to the MHC Class I heterodimeric receptor family, and is expressed by several cells including macrophages, monocytes, B cells, and dendritic cells.
- Ab recycling by FcRn engineering protect Ab from degradation
- Conversely, blocking Fc-Rn may increase IgG clearance (including pathogenic autoantibodies), resulting in reduced IgG

**Ravulizumab has a half-life ~4x longer than eculizumab
Administration every 8 weeks!**

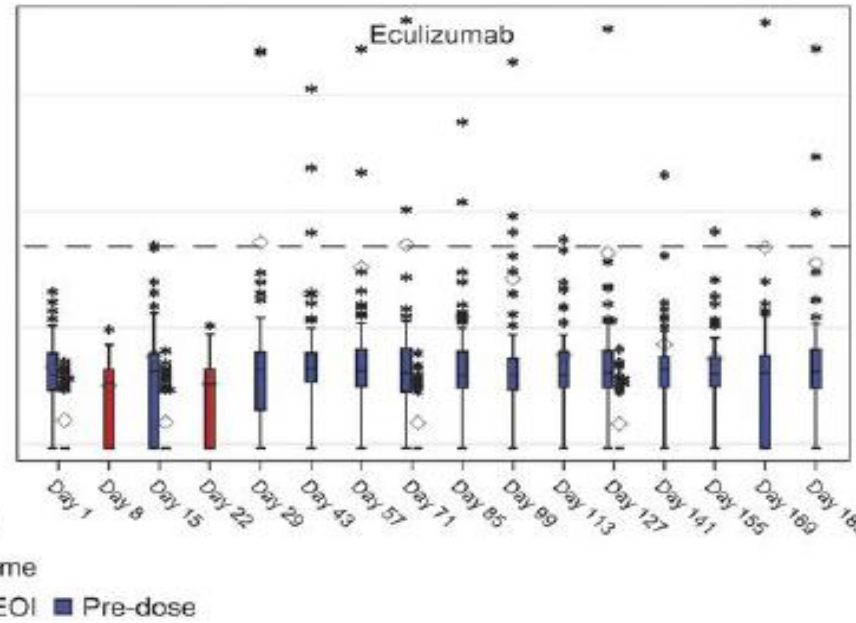
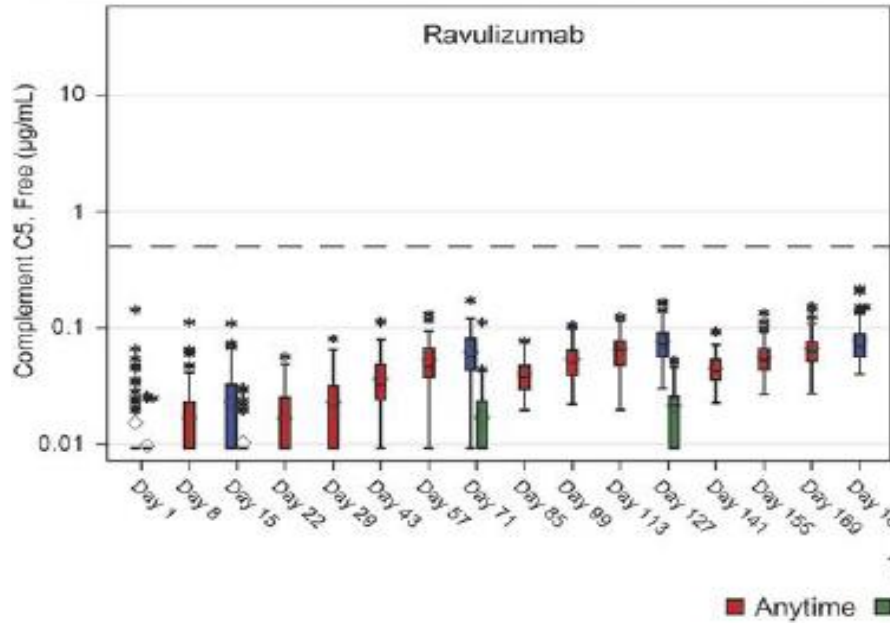
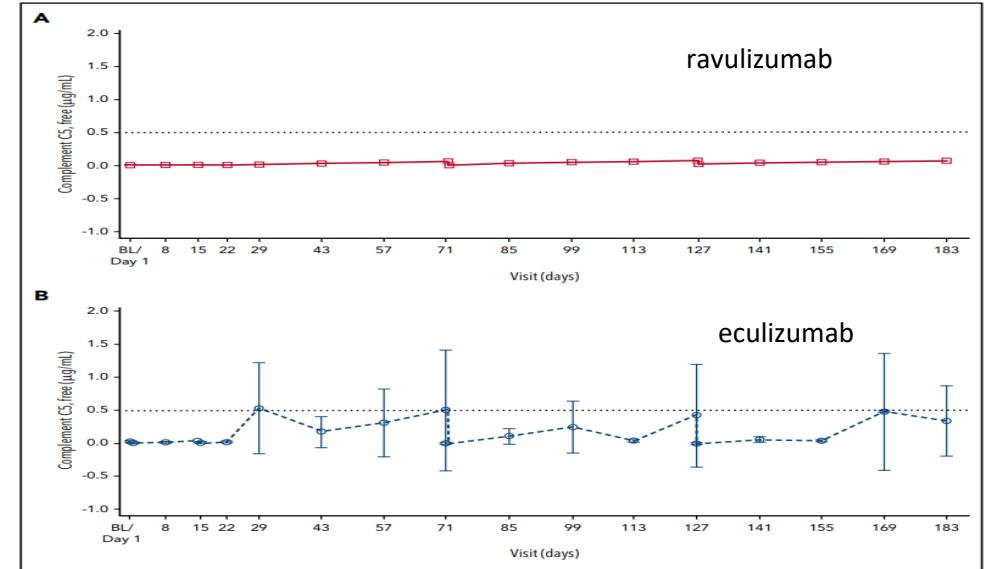
Ravulizumab vs eculizumab

Ravulizumab (ALXN1210) vs eculizumab in C5-inhibitor-experienced adult patients with PNH: the 302 study

Austin G. Kulasekararaj,¹ Anita Hill,² Scott T. Rottinghaus,³ Saskia Langemeijer,⁴ Richard Wells,⁵ F. Ataulfo Gonzalez-Fernandez,⁶ Anna Gaya,⁷ Jong Wook Lee,⁸ Emilio Ojeda Gutierrez,⁹ Caroline I. Piatek,¹⁰ Jeff Szer,¹¹ Antonio Risitano,¹² Shinji Nakao,¹³ Eric Bachman,³ Lori Shafner,³ Andrew I. Damokosh,³ Stephan Ortiz,³ Alexander Röth,¹⁴ and Regis Peffault de Latour¹⁵⁻¹⁷

Mean serum free C5 concentrations were suppressed to $<0.5 \mu\text{g/mL}$ by the end of the first infusion and at all subsequent visits for all patients receiving ravulizumab

This threshold was not consistently met in the eculizumab group



Safety

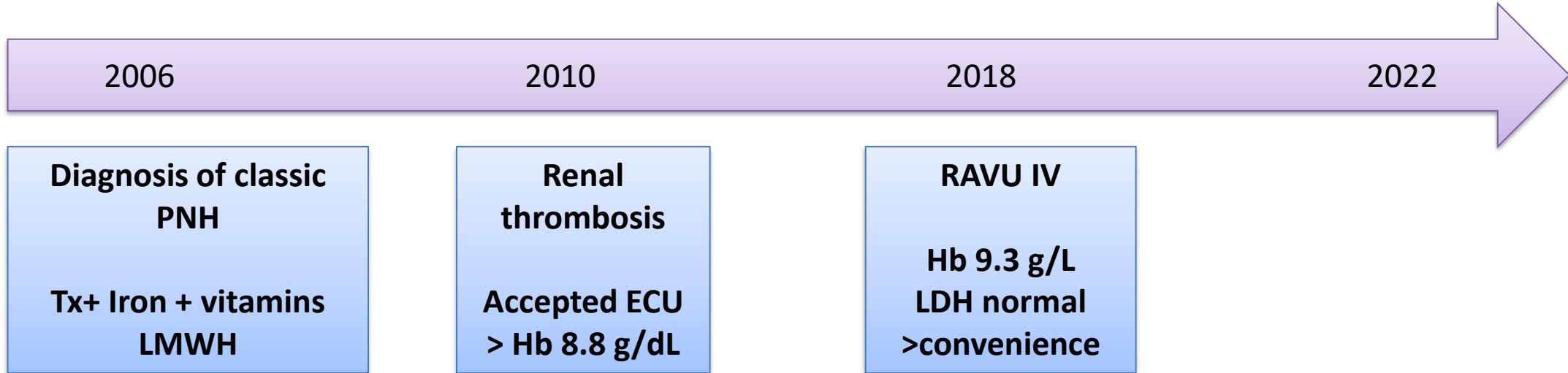
The most frequently reported AE was headache (26.8% and 17.3% in ravulizumab and eculizumab)

SAEs observed in 4 ravulizumab and 8 eculizumab

No cases of meningococcal infections observed.

No treatment-emergent antidrug antibodies in patients treated with ravulizumab

Clinical vignette – F 41 years



- The patient went from transfusion dependence before ECU
- To moderate anemia under ECU and frequent BTH (PK? PD?)
- To moderate anemia with no BTH under RAVU IV

Shall we consider proximal inhibitor?

Would you give a proximal complement inhibitor?

1. No, the patient is well with herself
2. Yes, Hb is still below 10 g/dl
3. Only in case of recurrent BTH
4. Only in case of transfusion and increased unconjugated bilirubin
5. Only if direct antiglobulin test is positive for complement





Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition? A Position Paper From the SAAWP of the EBMT

OPEN ACCESS

Antonio M. Risitano^{1,2*}, Serena Marotta^{1,2}, Patrizia Ricci¹, Luana Marano¹, Camilla Frieri¹, Fabiana Cacace¹, Michela Sica³, Austin Kulasekararaj^{4,5}, Rodrigo T. Calado⁶, Phillip Scheinberg⁷, Rosario Notaro⁸ and Regis Peffault de Latour^{9,10} on behalf of the Severe Aplastic Anemia Working Party of the European group for Bone Marrow Transplantation

Edited by:
John D. Lambris,
University of Pennsylvania,

How can we assess response to therapy? At what time? 6 months versus 3 months

TABLE 1 | Tentative classification of hematological response to anti-complement agents in PNH.

Response category	Red blood cell transfusions	Hemoglobin level	LDH level* [‡]	ARC*
Complete response	None	≥12 g/dL	≤1.5x ULN	and ≤150,000/μL [§]
Major response	None	≥12 g/dL	>1.5x ULN	or >150,000/μL [§]
Good response	None	≥10 and <12 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure [°]
Partial response	None or occasional (≤2 every 6 months)	≥8 and <10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure [°]
Minor response [#]	None or occasional (≤2 every 6 months) Regular (3–6 every 6 months) Reduction by ≥50% [^]	<8 g/dL <10 g/dL <10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure [°]
No response [#]	Regular (>6 every 6 months)	<10 g/dL	A. ≤1.5x ULN B. >1.5x ULN	Rule out bone marrow failure [°]

→ Anemia

≥ moderate

→ Transfusions

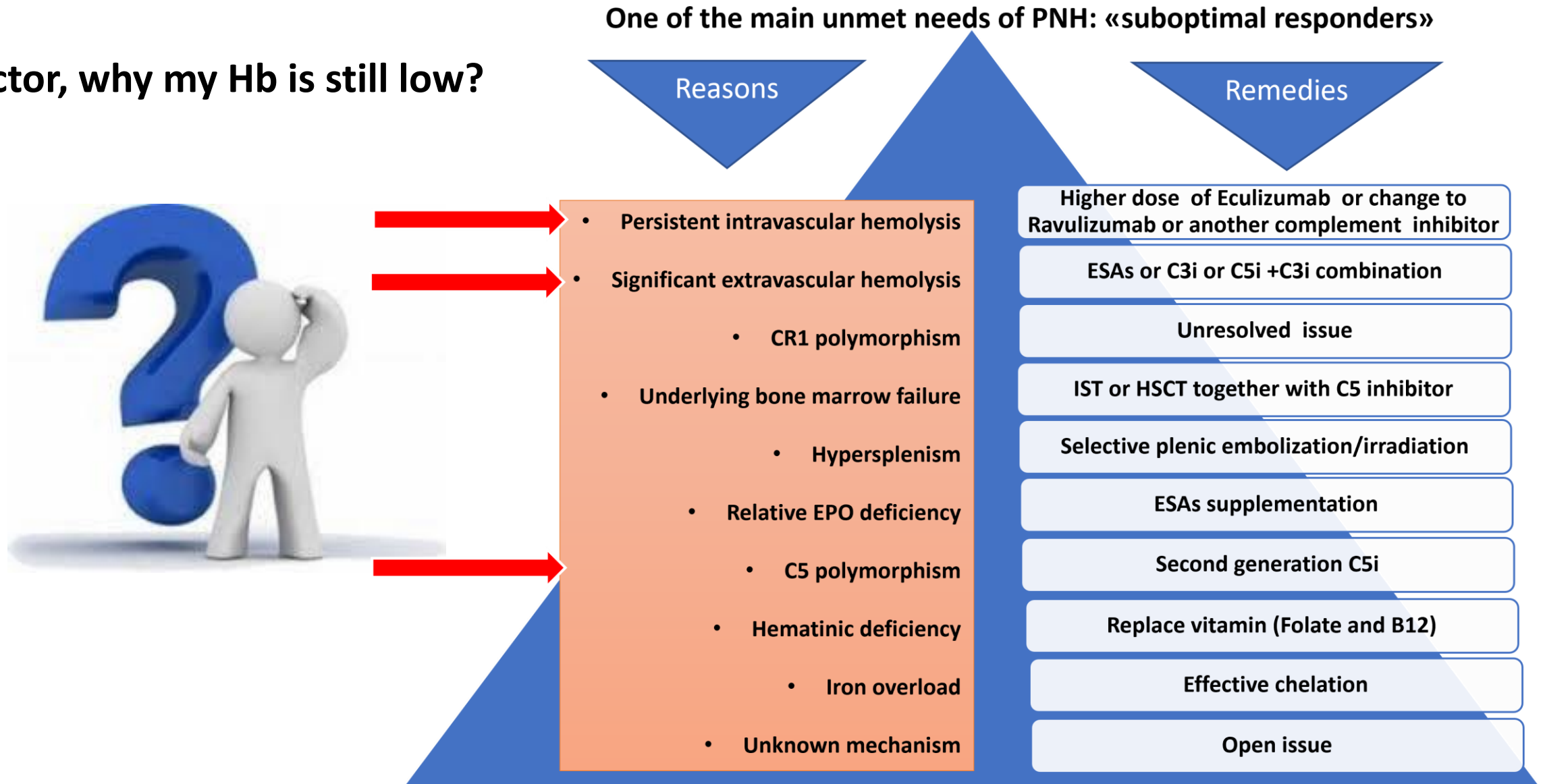
from little to

regular

LDH, lactate dehydrogenase; ULN, upper limit of the normal; ARC: absolute reticulocyte count. *Response categories are mostly based on red blood cell transfusion and hemoglobin level, but LDH and ARC serve as ancillary indicators to discriminate between complete and major response, as well as within suboptimal response categories. [‡]A. and B. indicate subcategories without or with residual significant intravascular hemolysis, respectively. [§]To rule out increased erythropoietic response to compensate ongoing hemolysis; the value of 150,000/μL is a tentative index based on 1.5x ULN (which in most laboratories is set at 100,000/μL). [°]To assess the relative contribution of the degree of bone marrow failure to any response less than complete: a value of ARC below 60,000/μL could be a tentative index to establish such a contribution; bone marrow investigation may be appropriate. [^]For patients with previous transfusion history (with a pre-treatment follow up of at least 6 months). [#]For patients who do not accept red blood cell transfusions, minor response can be defined based on hemoglobin level ≥6 and <8 g/dL, and no response based on hemoglobin <6 g/dL. All hemoglobin, LDH and ARC values should be assessed based on the median value over a period of 6 months.

Several causes of “suboptimal response” to be considered

Doctor, why my Hb is still low?



Crovalimab: C5 inhibitor active on C5 polymorphisms and very convenient



CLINICAL TRIALS AND OBSERVATIONS

The complement C5 inhibitor crovalimab in paroxysmal nocturnal hemoglobinuria

Alexander Röth,¹ Jun-ichi Nishimura,² Zsolt Nagy,³ Julia Gaál-Weisinger,³ Jens Panse,⁴ Sung-Soo Yoon,⁵ Miklos Egyed,⁶ Satoshi Ichikawa,⁷

- **Crovalimab is unique: its properties allow for subcutaneous (SC) injections once every 4 weeks**
- **can be self-administered**
- **binds to C5 mutational variants.**
- **Efficacy and safety confirmed in the Phase I/II COMPOSER trial (NCT03157635; Röth et al, Blood. 2020) conducted in patients with PNH, with or without prior anti-C5 treatment.**
- **During the OLE LDH maintained at $\leq 1.5 \times$ ULN, transfusion avoidance 83%-92% of patients and haemoglobin stabilisation was reached in 79%-88% of patients across each 24-week interval.**
- **Five BTH events occurred with none leading to withdrawal**

- The Phase 3 single-arm COMMODORE 3 study → complement inhibitor-naive patients
- **78% achieved hemolysis control → 1 BTH**

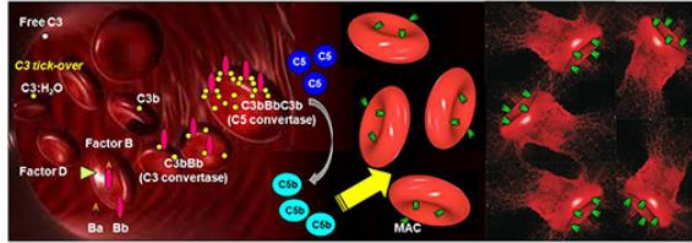
Röth et al, Blood 2020

Röth et al, Eur J Hematol 2023

Liu et al, AJH 2023

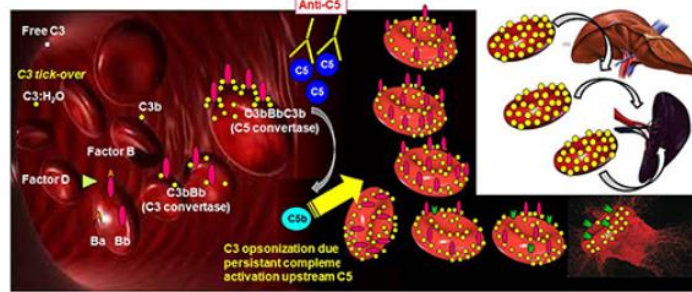
Iatrogenic Extravascular hemolysis → Proximal complement inhibitors

PNH erythrocytes in absence of anti-complement treatment



MAC-mediated massive intravascular hemolysis

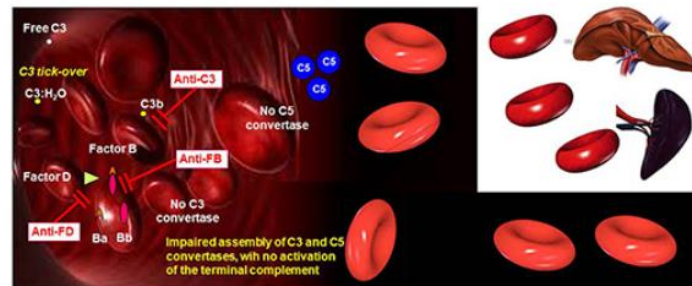
PNH erythrocytes on terminal complement inhibitors



C3-mediated extravascular hemolysis

Residual MAC-mediated intravascular hemolysis (i.e., PK or PD breakthrough)

PNH erythrocytes on proximal complement inhibitors (+/- terminal inhibitors?)



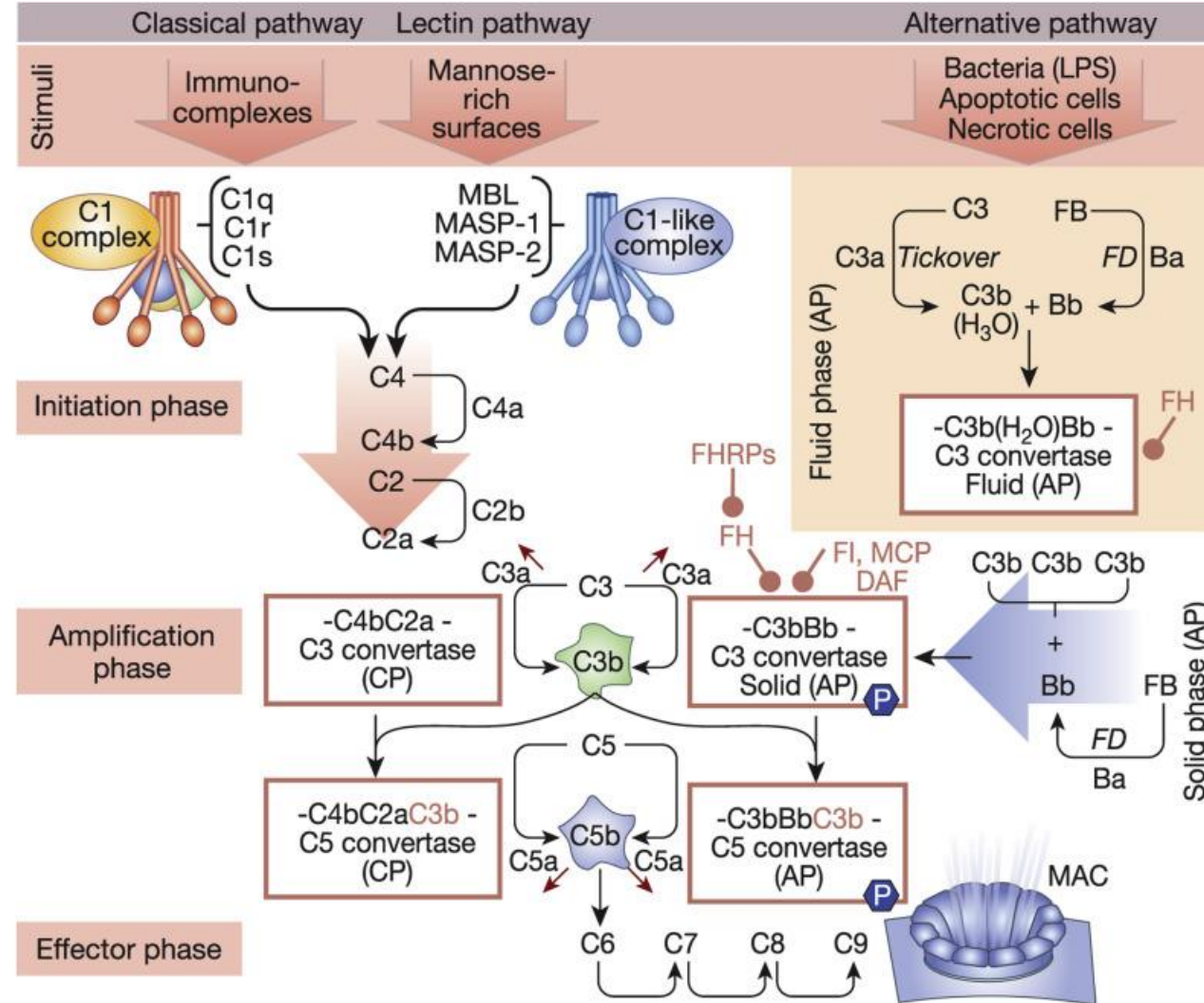
Normal life-span of PNH erythrocytes

- Anti-C5 agents:**
- mAbs: eculizumab, ravulizumab, SKY59, LFG316, ABP959, REGN3918
 - RA101495
 - Coversin
 - ALNCC5

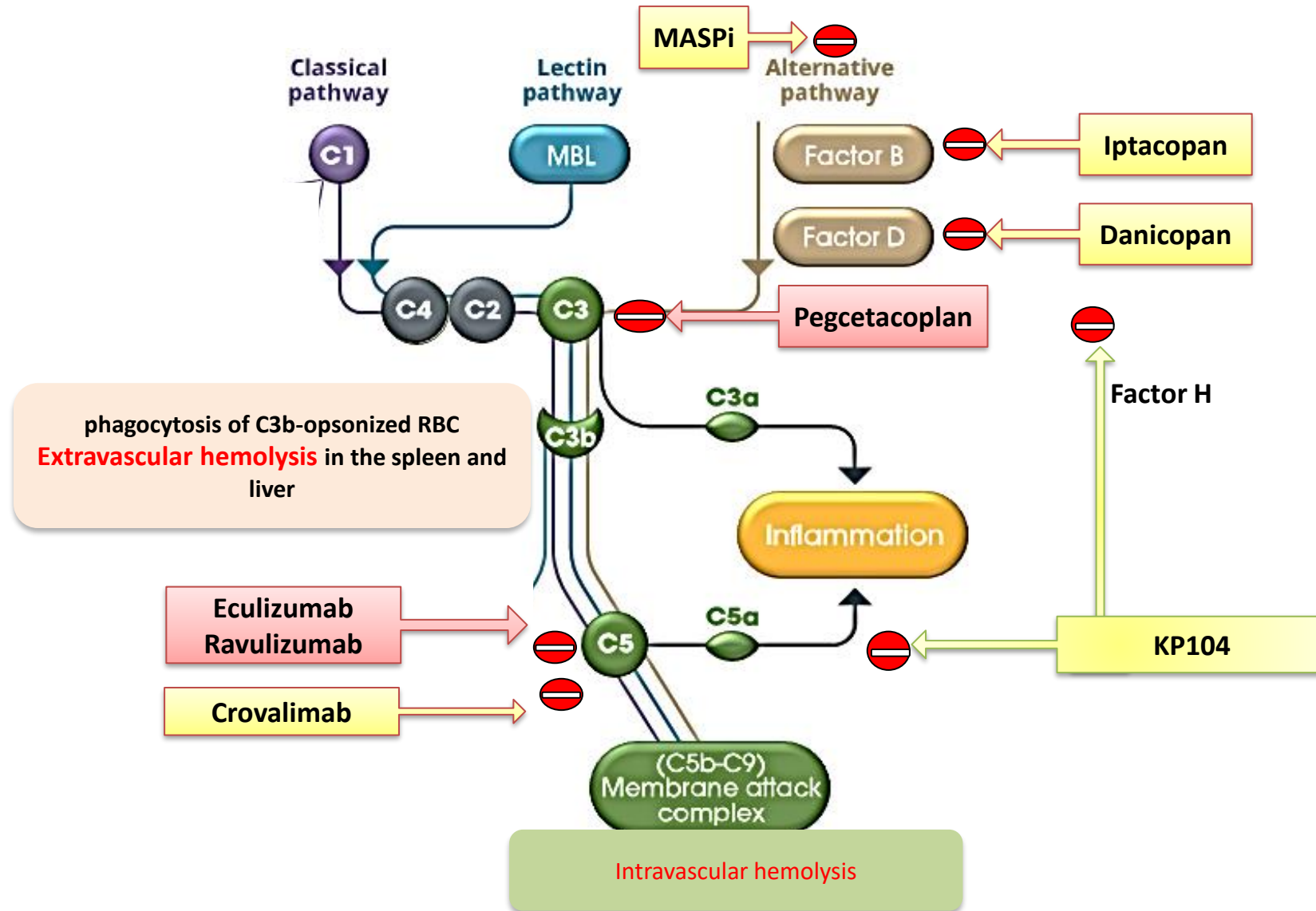
- Anti-C3 agents:**
- AMY-101
 - APL-2

- Anti-FD agents:**
- ACH4471

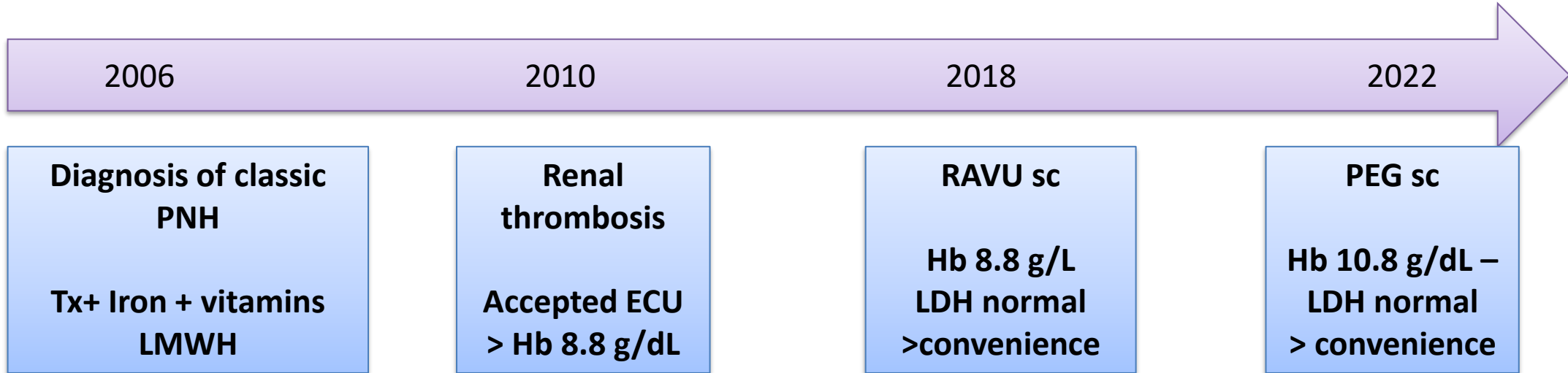
- Anti-FB agents:**
- LNP023



The panorama of PNH therapy involves terminal and proximal inhibitors



Clinical vignette – F 41 years



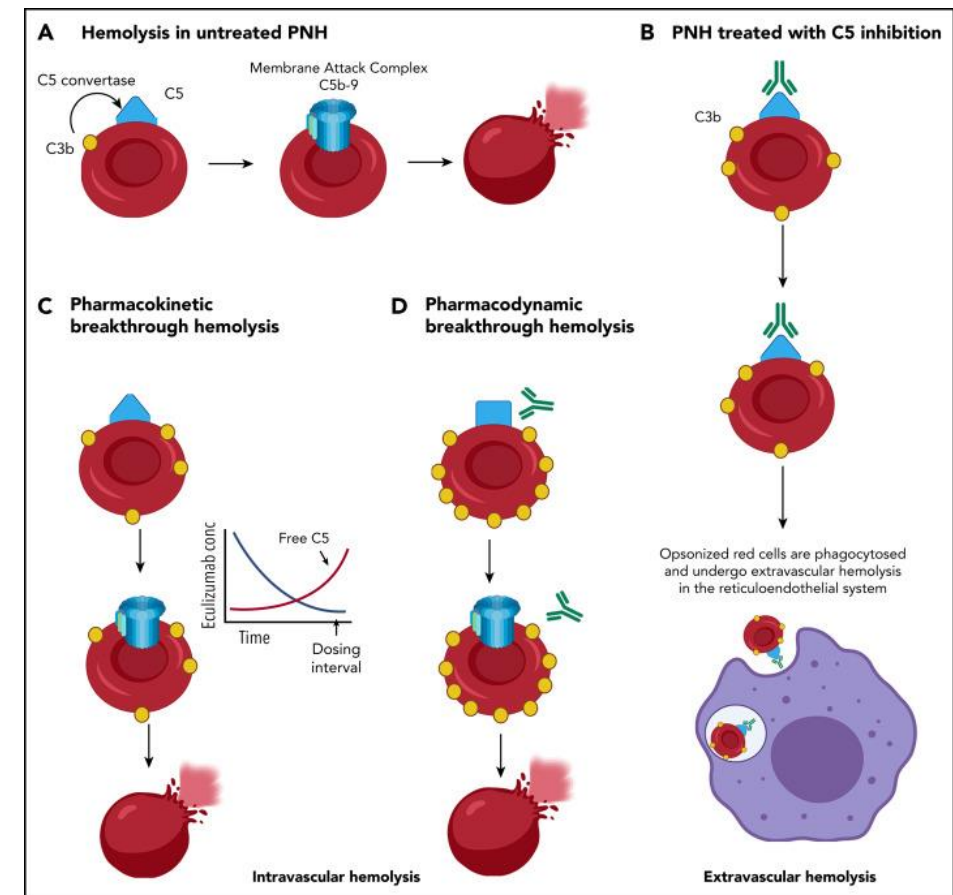
- The patient went from transfusion dependence before ECU
- To moderate anemia under ECU and frequent BTH (PK? PD?)
- To moderate anemia and no BTH under RAVU IV
- To mild anemia and markedly improved QoL since switching to PEG but ...

Doctor, I fee generally better, but why dark urine are round the corner again?

Precipitating conditions & breakthrough hemolysis

Any complement amplifying condition (**infections, traumas, surgery, pregnancy, vaccines**, etc.) may result in increased hemolytic rate with:

- Worsening of dark urine and PNH symptoms
- Worsening of anemia and possible transfusion need
- Increased free Hb release and risk of thrombosis
- **If the patient is on Ci hemolytic flares are called BTH**



	Timing	Frequency	Concomitant conditions	Free C5	Eculizumab plasma level	Mechanism	Intervention
Pharmacokinetic breakthrough	>7–10 days from previous dosing	Recurrent	Usually none*	Always >0.5–1 $\mu\text{g/mL}$	Inadequate	Residual free C5 available for steady-state (normal) C5 convertase activity	Decrease interval of dosing (10–12 days) or increase dose of eculizumab (1,200 mg)
Pharmacodynamic breakthrough	Any time	Sporadic	Infectious events (both bacterial and viral, such as common seasonal viruses) or any event leading to inflammation (i.e., surgery, possible comorbidities)	Usually $\leq 0.5\text{--}1 \mu\text{g/mL}$ (but it may occur with any free C5 plasma level)	Adequate	Massive complement activation leading to excess C5 convertase activity, which might displace C5 from eculizumab	None (treat the underlying cause triggering complement activation)



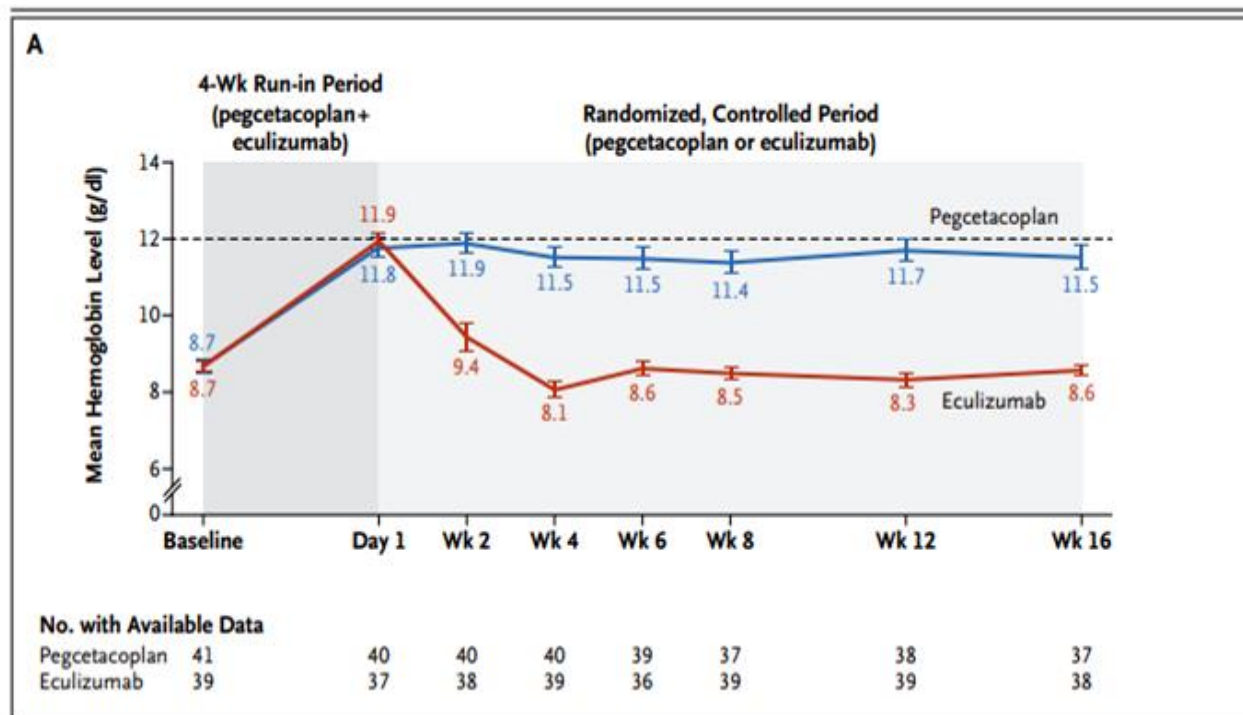
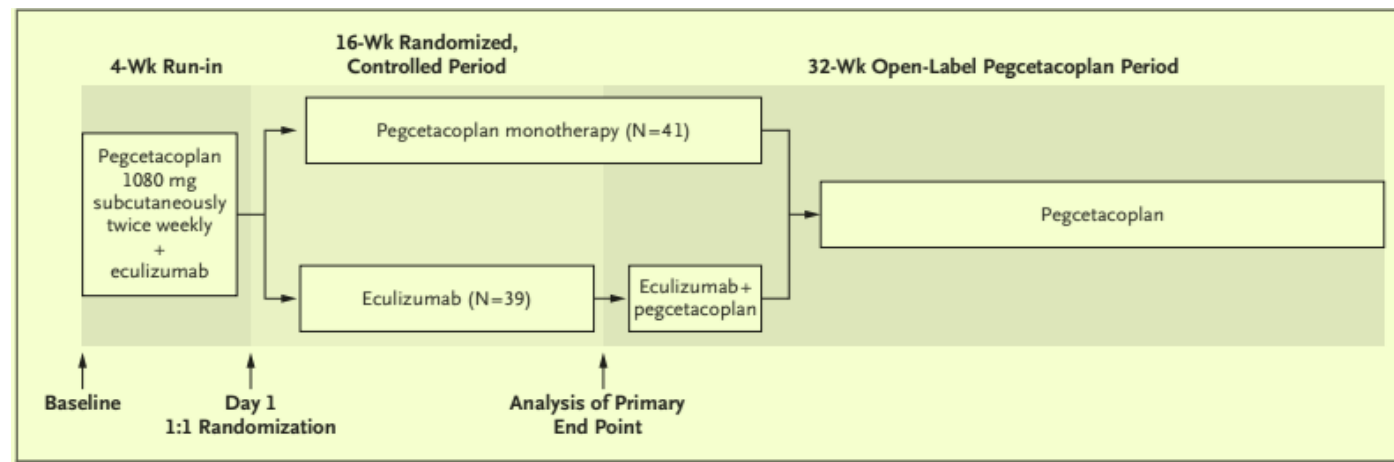
Would you switch the patient to an oral agent?

1. Yes, monotherapy to improve convenience
2. Yes, as add on to anti-C5 to prevent BTH and improve Hb
3. No
4. Only in case of transfusion need
5. Only in case of persistent extravascular hemolysis

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Jeff Szer, M.B., B.S., Ilene Weitz, M.D., Alexander Röth, M.D., Britta Höchsmann, M.D., Jens Panse, M.D., Kensuke Usuki, M.D., Ph.D., Morag Griffin, B.M.Sc., M.B., Ch.B., Jean-Jacques Kiladjian, M.D., Ph.D., Carlos de Castro, M.D., Hisakazu Nishimori, M.D., Ph.D., Lisa Tan, R.N., Mohamed Hamdani, M.S., Pascal Deschatelets, Ph.D., Cedric Francois, M.D., Ph.D., Federico Grossi, M.D., Ph.D., Temitayo Ajayi, M.D., Antonio Risitano, M.D., Ph.D., and Régis Peffault de la Tour, M.D., Ph.D.

Pegcetacoplan (anti-C3 – sc x2/week)

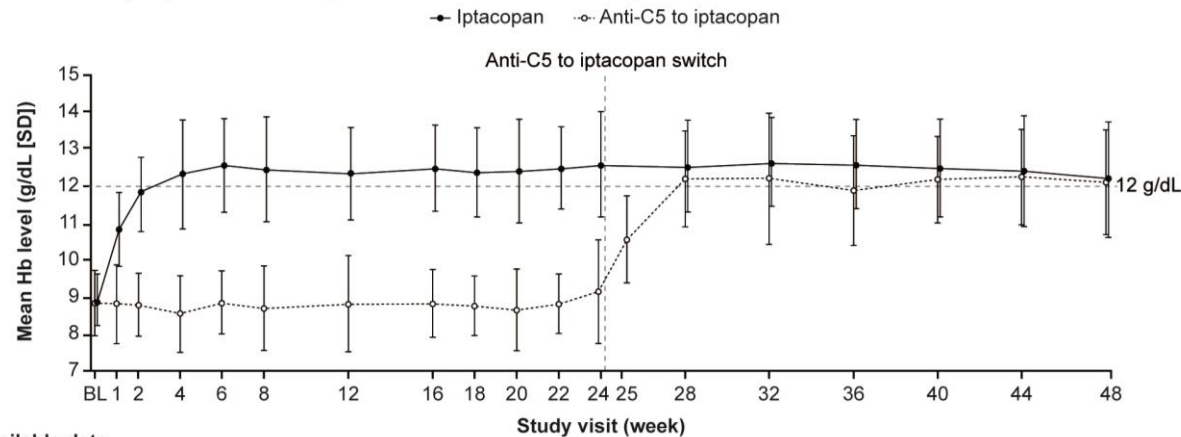


- **Pegcetacoplan, a pegylated peptide targeting proximal complement protein C3, was superior to eculizumab in:**
- **Change in Hb level from baseline to week 16, with an adjusted mean difference of 3.84 g per deciliter ($P < 0.001$); 35 patients**
- **85% receiving pegcetacoplan no longer required transfusions vs 15% in eculizumab.**
- **breakthrough hemolysis (BTH) was observed in 10% (pegcetacoplan) vs 23% (eculizumab)**
- **FACIT –Fatigue scores improved from baseline in the pegcetacoplan group.**
- **The most common adverse events in the pegcetacoplan and eculizumab groups were injection site reactions (37% vs. 3%), diarrhea (22% vs. 3%), headache (7% vs. 23%), and fatigue (5% vs. 15%).**
- **There were no cases of meningitis in either group.**

Iptacopan (factor B inhibitor – oral BID)

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

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



Pts with available data	BL	1	2	4	6	8	12	16	18	20	22	24	25	28	32	36	40	44	48
Iptacopan	62	61	59	60	59	59	60	59	59	59	57	61	—	56	59	59	57	57	59
Anti-C5 to iptacopan	35	29	27	32	32	31	33	28	34	32	32	34	27	28	32	31	29	30	30

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		Adjusted mean change from baseline (95% CI) at Week 48	Adjusted mean difference in change from baseline (95% CI): Week 48 vs Week 24
	Iptacopan N=62	Anti-C5 to iptacopan N=35		
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)

- 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

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

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



Letters to Blood

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. Brodsky¹

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. Boshkos¹, Kaila R. Fives², Davong D. Phrathep³, Kevin D. Healey², Miten Patel⁴

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

With proximal inhibitors

> % PNH-RBCs are spared

If blockade is incomplete activation is exponential → possible severe BTH

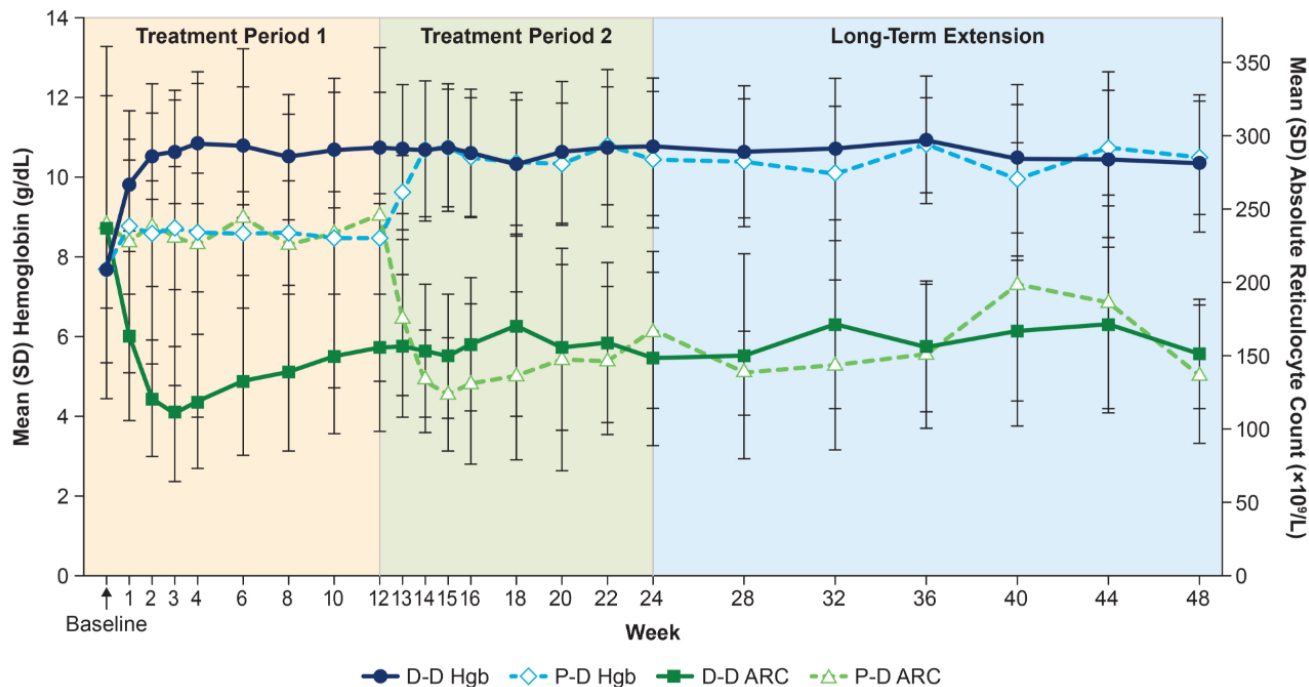
How to manage? Combination therapy?

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 (factor D inhibitor – oral T1D + anti-C5)

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

- 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 $120 \times 10^9/L$) - 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).

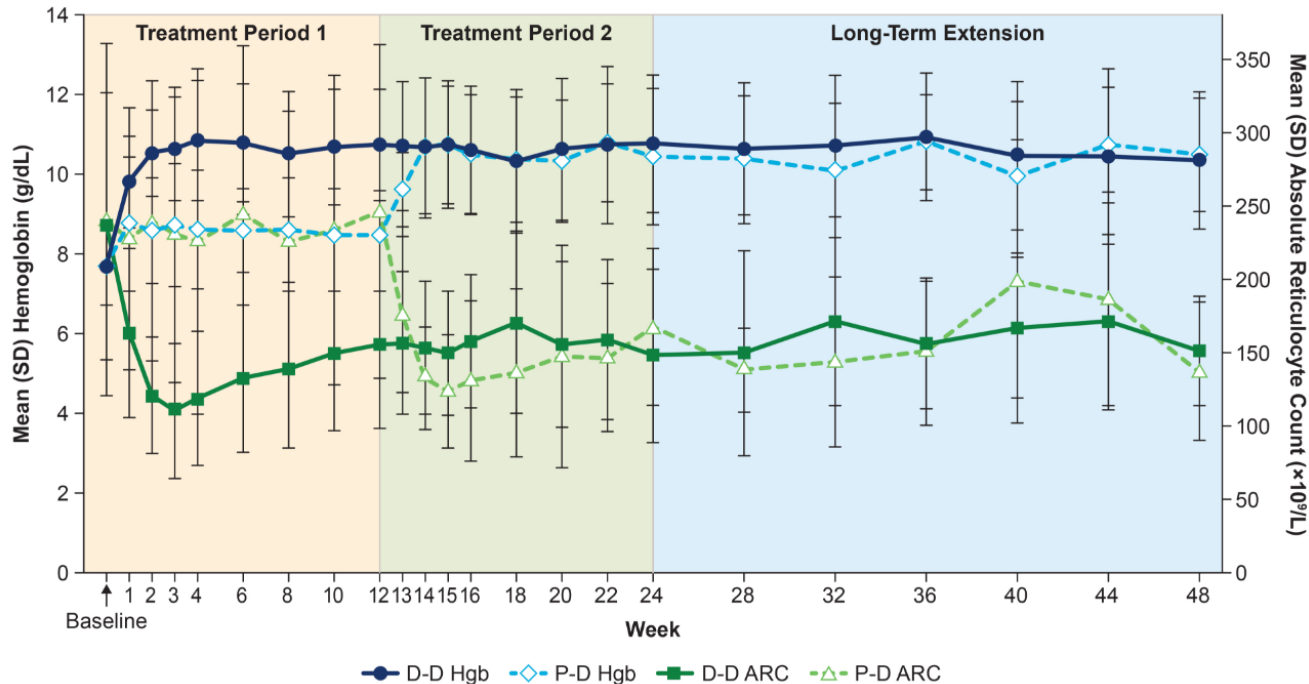


- **Hgb ≥ 2 g/dL was 46% in Dan-Dan and 35% in the Pbo-Dan**
- **Transfusion avoidance was 78% in Dan-Dan and 90% in Pbo-Dan.**
- **compliance was 98.8%**
- No deaths, meningococcal infections
- **4 BTH, only 1 with LDH $>2 \times ULN$ related to COVID-19.**

Danicopan (factor D inhibitor – oral T1D + anti-C5)

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

- 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 120x10⁹/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).



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

ASH highlights

→ Efficacy/safety at 48w

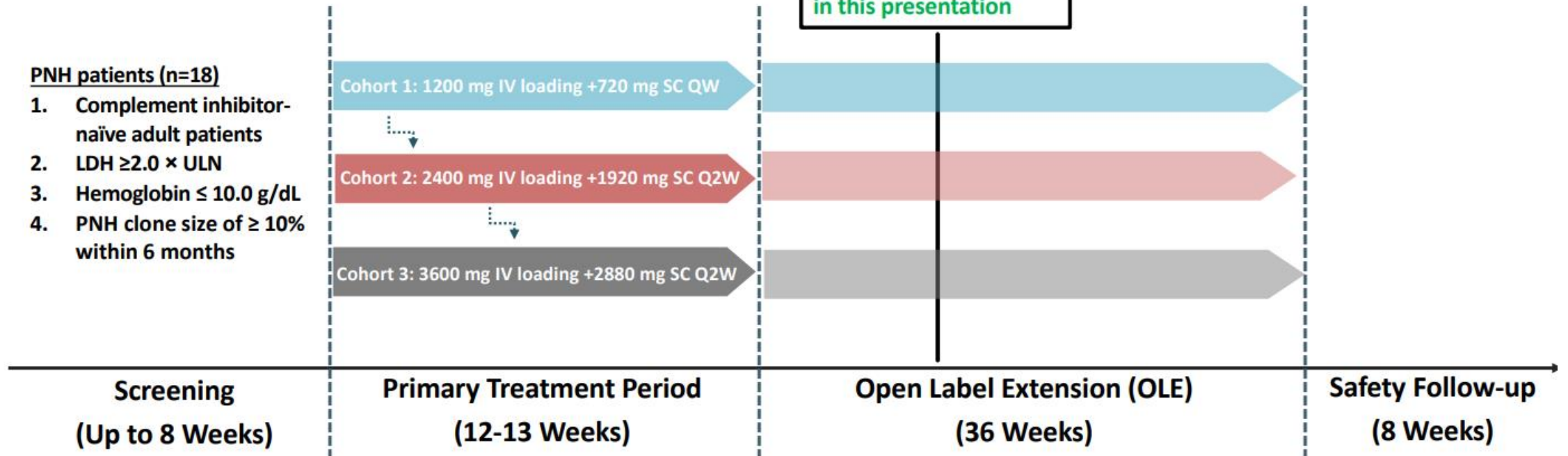
→ Same benefit in switch arm

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



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

American Society of Hematology 2023 – Fengkui Zhang et al



PNH patients (n=18)

1. Complement inhibitor-naïve adult patients
2. LDH $\geq 2.0 \times$ ULN
3. Hemoglobin ≤ 10.0 g/dL
4. PNH clone size of $\geq 10\%$ within 6 months

- **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

Conclusions

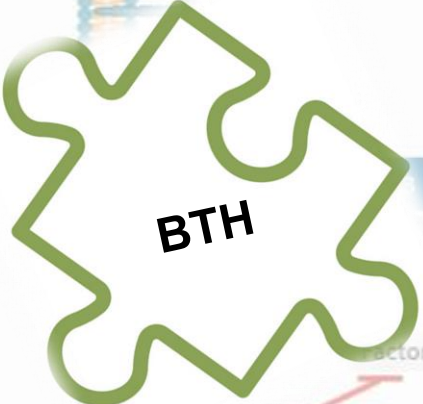
- PNH is characterized by complement mediated intravascular hemolysis
- The alternative pathway is the main responsible as it is homeostatically active and induces chronic hemolysis
- Thrombosis may occur in 40-60% of untreated subjects
- Precipitating factors may induce overactivation of complement and hemolytic flares (including BTH)
- Complement inhibitors anti-C5 improve hemolysis and anemia, reduce thrombotic risk and reconstitute survival to that of the general population
- Knowing the pathophysiology of residual anemia aids to overcome this unmet need (i.e. extravascular hemolysis and proximal complement inhibitors)
- EVH may be targeted with proximal inhibitors including novel agents such as pegcetacoplan, iptacopan and danicopan

Emerging treatments



Complement pathways and Inhibitors

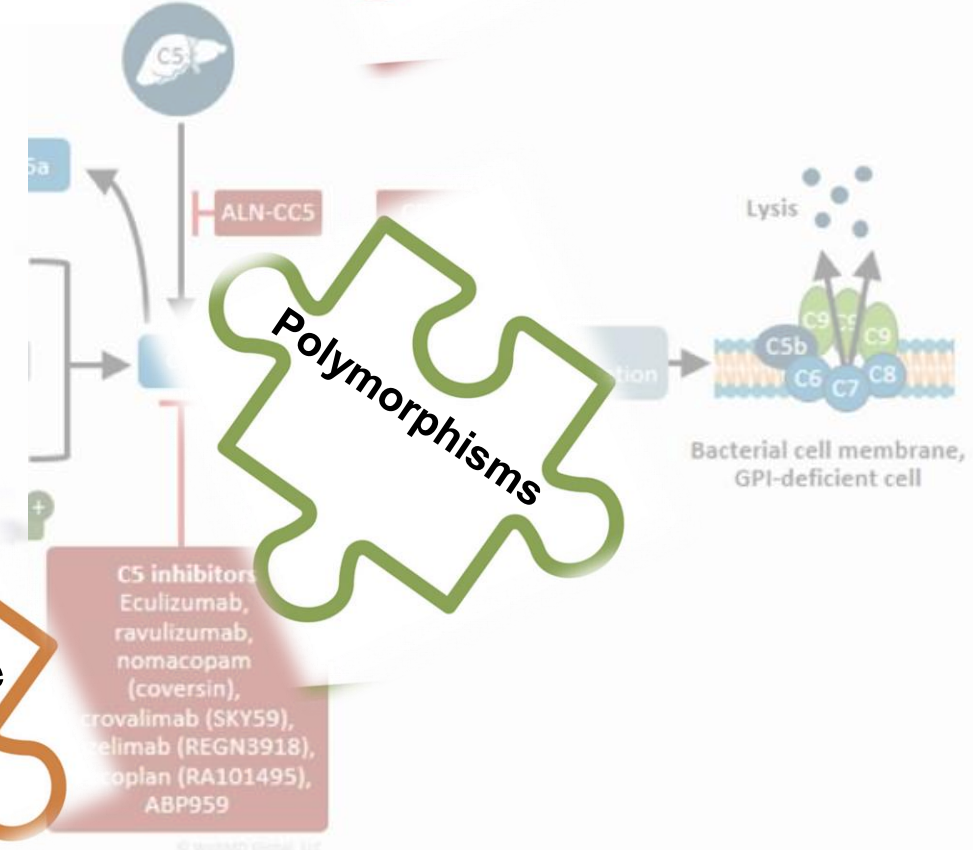
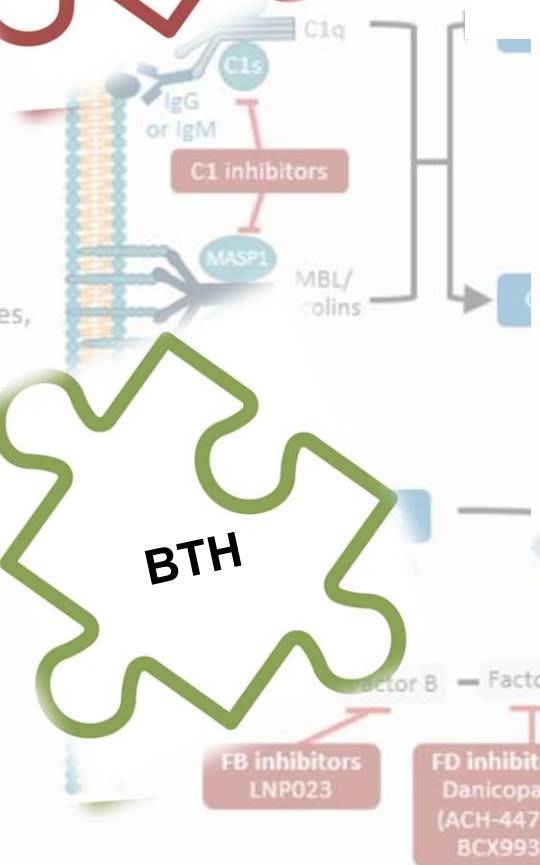
Doctor, which is the best drug for me?



Classical
Antigen-antibody complexes

Lectin
Microbial carbohydrates, MBL, MASP1/2

Alternative
Endotoxin, bacterial cell walls, tickover



FB inhibitors
LNPO23

FD inhibitors
Danicopan (ACH-4471),
BCX9930

CD55, CR1
Factor H

C5 inhibitors
Eculizumab, ravulizumab, nomacopam (coversin), trovalimab (SKY59), belimumab (REGN3918), koplan (RA101495), ABP959

Thank you!

Bruno Fattizzo

Department of Oncology and Hemato-oncology, University of Milan, Italy

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