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International PNH Interest Group

Intravascular and Extravascular Hemolysis in Treated PNH: When do we see them and what do we do about them

Case #2: hemolysis "*around*" proximal inhibitors

Antonio M. Risitano, M.D., Ph.D.
Chair of the Severe Aplastic Anemia Working Party of the EBMT
Chair of the International PNH Interest Group

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Excellence in science
European Group for Blood and Marrow Transplantation

Discloures

- Alexion: consultancy, honoraria, speaker bureau, advisory committees
- Eli Lilly: honoraria (DSMB)
- Novartis: Advisory boards
- Sobi: honoraria, speaker bureau
- Takeda: consultancy, honoraria, speaker bureau
- Specialised Therapeutics: advisory committee

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Please scan the QR code to participate in the Audience Response and Q&A

A young patient with PNH (in 2018)

- 34 y.o. male with negligible medical history (no family history for anemia or any hematological disorder; normal blood counts in 2002)
- In 2018 moderate anemia, without further hematological abnormality (Hb 9.3, WBC 6.700, ANC 4.200, Plt 349.000
- Second-level hematological screening
  - Mild iron deficiency (ferritin 21; transferrin saturation 11%)
  - No vitamin deficit (folate and B12)
  - ARC 312K, MCV 101 **>>>> Hyper-regenerative anemia**
  - LDH 631 (≈2.5x ULN)
  - Total bilirubin 2.0 mg/dL (indirect 1.2 mg/dL)
- Hemolytic anemia (apparently acquired)
  - Coombs test negative

A young patient with PNH (in 2018)

- Coombs-negative acquired hemolytic anemia
  - Flow cytometry: GPI-negative population in all blood lineages (14% erythrocytes, 46% granulocytes, 49% monocytes)
- **Diagnosis of hemolytic (classical) PNH**
  - No thrombosis
  - No sign of bone marrow failure (trephine biopsy: slightly hypercellular due to increased erytropoiesis); normal karyotype 46XY; NGS not performed
- **Eculizuman started due to worsening of anemia** (Hb 8.1), with mild symptoms/signs (fatigue, asthenia, sporadic abdominal pain, dark urines)
  - @6m: Hb 8.5, LDH 274, ARC 261K, Bil T 1.9, ANC 4700; 3 pRBC units
  - @1: Hb 8.9, LDH 265, ARC 312K, Bil T 2.0, ANC 3800; 4 pRBC units
  - @2y: Hb 8.3, LDH 312, ARC 394K, Bil T 2.3, ANC 4100; 9 pRBC units/year
  - @3y: Hb 8.1, LDH 285, ARC 355K, Bil T 2.1, ANC 4300; 11 pRBC units/year

Question #1

What therapeutic approach would you choose in this PNH patient still transfusion-dependent despite of eculizumab treatment (back to 2022)?

1. Watch & wait: continue the same treatment (eculizumab 900 mg every 14 days)
2. Switch to an off-label eculizumab schedule (900 mg every 10-12 days) or dose (1200 mg every 14 days)
3. Switch to a long-acting C5 inhibitor (ravalizumab or crovalimab)
4. Enroll in a clinical trial with proximal inhibitors
5. Bone marrow transplantation

A young patient with PNH (in 2022)

- Considered for trials with pegcetacoplan, danicopan, vemircopan and iptacopan
  - Screened for the **vemircopan monotherapy NCT04170023 trial**

    A phase 2, open-label clinical trial of vemircopan monotherapy in patients with PNHto explore whether inhibiting the complement alternative pathway via factor D is safe and effective for patients with PNH.
- **Vemircopan treatment started** on Oct 20th 2022
  - Initial treatment dose 120 mg BID
  - @6m: Hb 12.5, LDH 299, ARC 156K, Bil T 0.6, ANC 3900; no transfusions
  - @1y: Hb 13.3, LDH 313, ARC 140K, Bil T 0.4, ANC 3500; no transfusions
    - PNH populations: erythrocytes 87% (C3+ <1%), granulocytes 93%
-
  -
  -

The factor D inhibitor vemircopan in PNH

blood advances

American Society of Hematology
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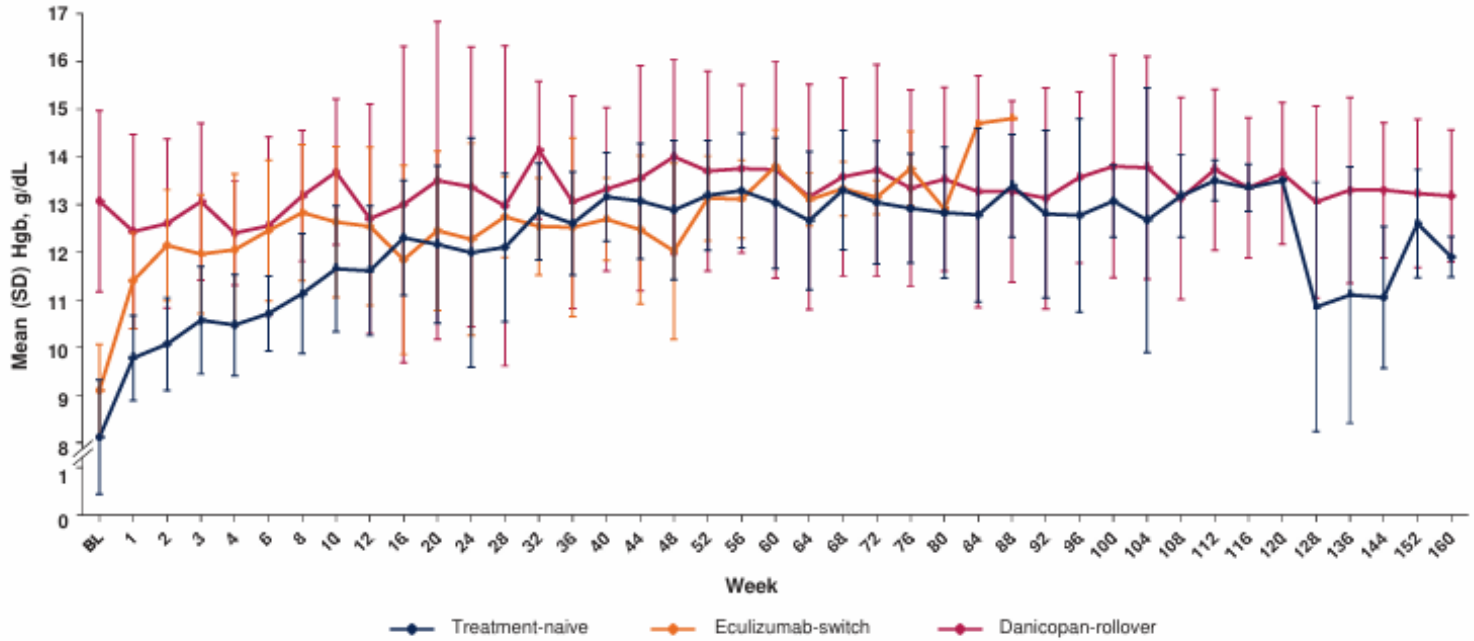
Washington, DC 20036
Phone: 202-776-0544 | Fax 202-776-0545
bloodadvances@hematology.org

Efficacy and Safety of Vemircopan as Monotherapy in Patients With Paroxysmal Nocturnal Hemoglobinuria

Tracking no: ADV-2025-017731R1

Figure 1



Week	BL	12	24	36	48	60	72	84	96	108	120	144	160
Treatment-naive	12	11	11	11	8	11	10	10	9	5	2	2	2
Eculizumab-switch	11	10	11	11	11	4	2	1	0	0	0	0	0
Danicopan-rollover	6	6	6	6	5	6	6	6	6	4	2	4	4

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B. Individual LDH Values Over Time – Eculizumab-Switch

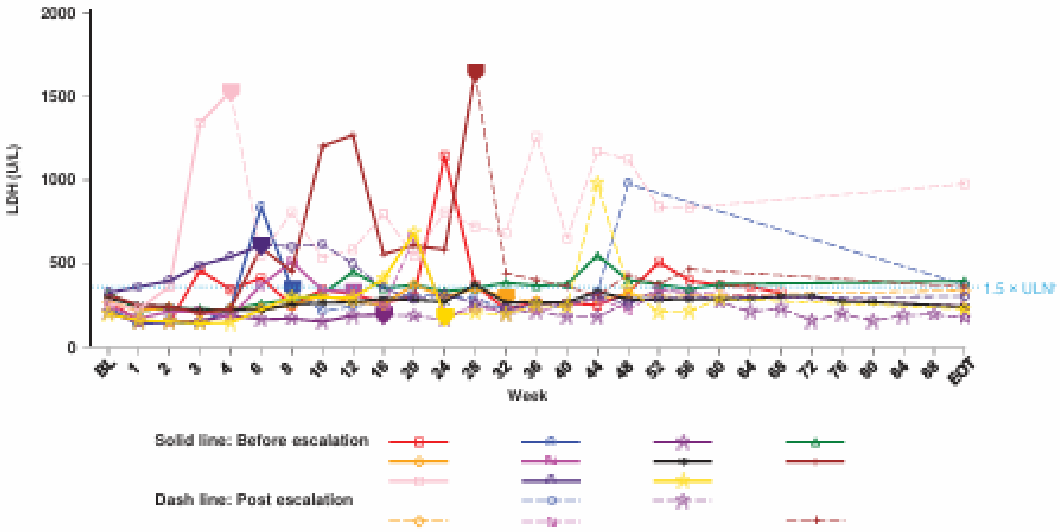
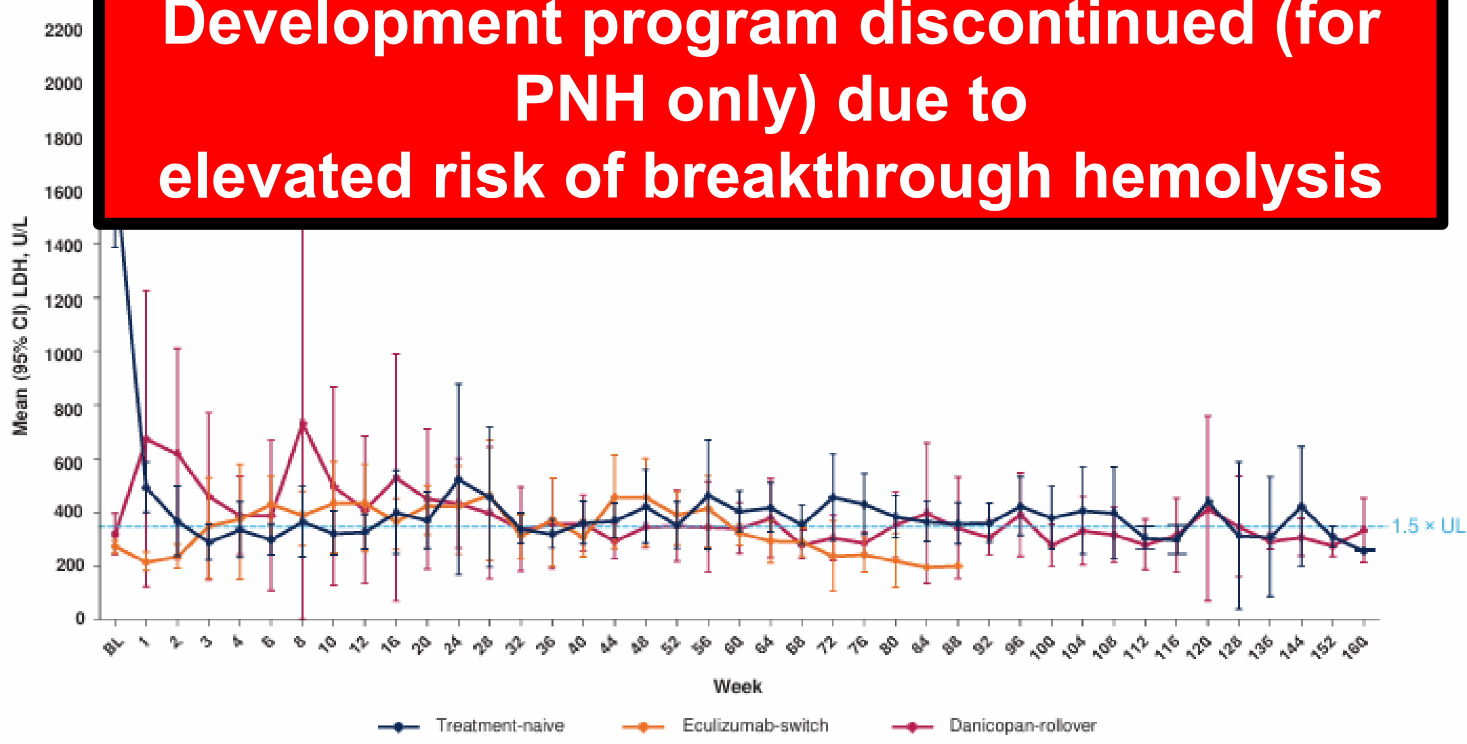


Figure 2



Development program discontinued (for PNH only) due to elevated risk of breakthrough hemolysis

Week	BL	12	24	36	48	60	72	84	96	108	120	144	160
Treatment-naive	12	11	12	12	10	12	11	11	9	6	1	2	2
Eculizumab-switch	11	11	11	11	11	5	2	1	0	0	0	0	0
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A young patient with PNH (in 2022)

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  - @1y: Hb 13.3, LDH 313, ARC 140K, Bil T 0.4, ANC 3500; no transfusions
    - PNH populations: erythrocytes 87% (C3+ <1%), granulocytes 93%
- **Vemircopan to be discontinued due to early study termination**
  - How to move forward with the treatment of this patient?
  - Patient to be switched (back) to commercially available treatment

Question #2

Is there any relevant concern in this PNH patient switching back from a proximal inhibitor to a terminal inhibitor?

1. Risk of massive intravascular hemolysis due to pharmacokinetic reasons (PK BTH)?
2. Risk of massive intravascular hemolysis due to pharmacodynamic reasons (PD BTH)?
3. Risk of massive extravascular hemolysis due to large mass of susceptible C3- PNH RBCs?
4. Risk of mild extravascular hemolysis due to small mass of C3+ PNH RBCs?
5. No concern: a proper terminal blockade should mitigate any risk of clinically meaningful hemolysis

PNH patients switching (back) from proximal to terminal inhibitors

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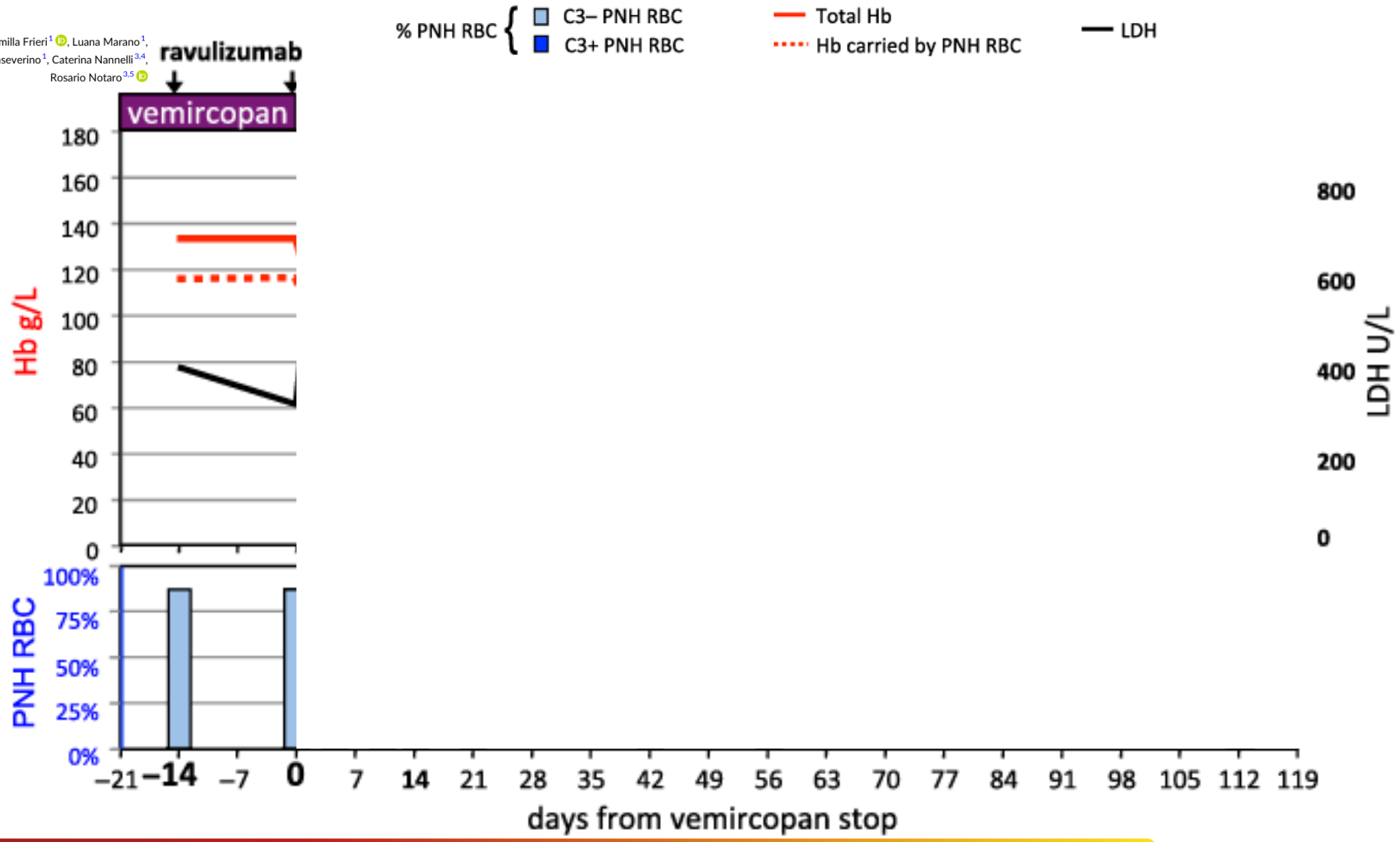
Massive hemolysis in paroxysmal nocturnal hemoglobinuria after switching from proximal complement inhibitor to anti-C5 therapy: A lesson not to be forgotten

Antonio M. Risitano[1,2], Camilla Frieri[1], Luana Marano[1], Eleonora Urciuoli[1], Ada Sanseverino[1], Caterina Nannelli[3,4], Rosario Notaro[3,5]

- ✓ Excellent hematological response on FD-inhibitor monotherapy
  - Risk-mitigation strategy in case of discontinuation
- ✓
  -
- ✓



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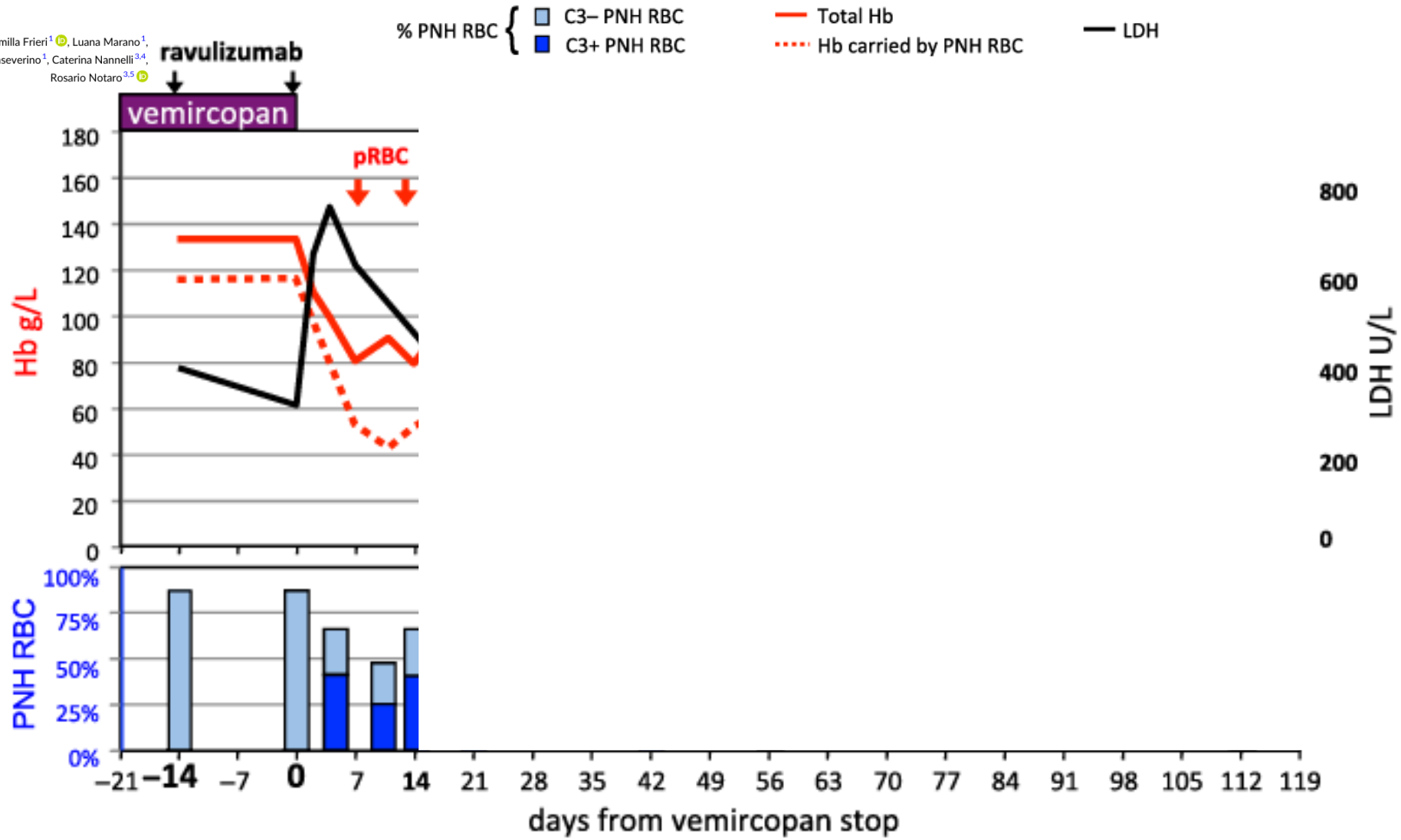
- ✓ Excellent hematological response on FD-inhibitor monotherapy
  - Risk-mitigation strategy in case of discontinuation
- ✓ Massive hemolysis at time of FD-inhibitor discontinuation (despite of proper anti-C5)
  - Intravascular vs extravascular
- ✓



Hemolysis and PNH

1. Intravascular hemolysis (IVH)

- The (only) one typical of untreated disease
- Chronic with acute exacerbations (the "*paroxysms*")

2. Extravascular hemolysis (EVH)

- Iatrogenic only, during treatment with terminal inhibitors
- Mainly chronic (rare acute exacerbations)

3. Breakthrough hemolysis (BTH)

- Iatrogenic only, during treatment with any inhibitor
- Acute event by definition; usually IVH
- Pharmacokinetic vs pharmacodynamic
- Terminal vs proximal inhibitors
  - ✓ ***"Rebound hemolysis"*** **(switching back from proximal to terminal inhibitors): acute/subacute, mixed IVH + EVH**

4. Residual hemolysis

- Iatrogenic only, during treatment with any inhibitor
- Chronic, low grade
- Mechanisms? Drug-dependent? Others?

Risitano AM, personal opinion

Genetics and response to eculizumab in PNH: CR1

CR1 polymorphism associated with poor response (Rondelli, Haematolol 2014)

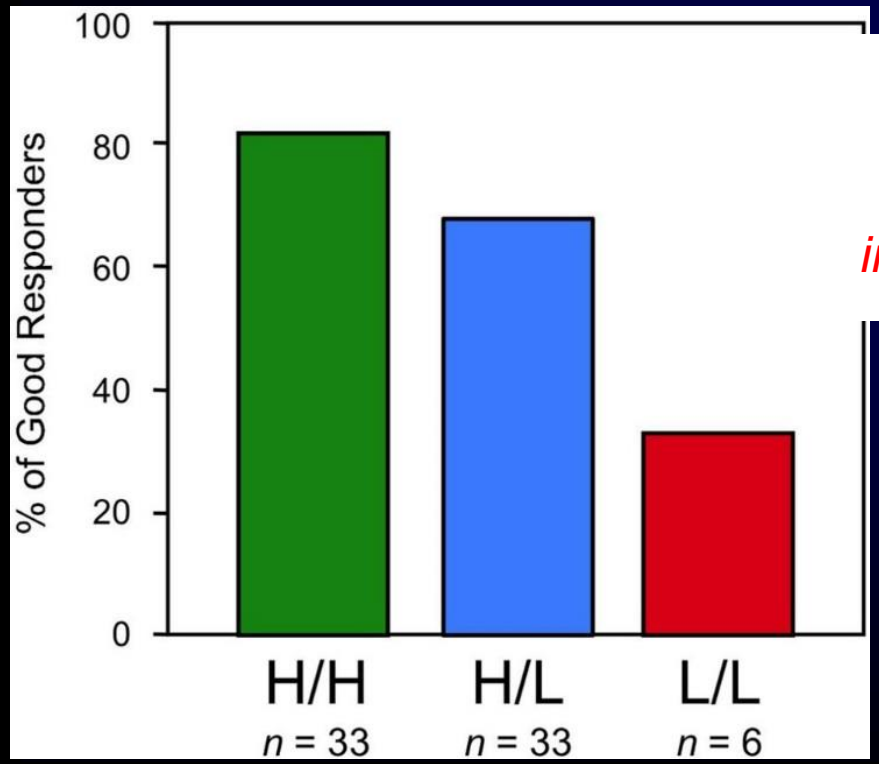
Rosario Notaro

Articles — Red Cell Biology & its Disorders

Polymorphism of the *complement receptor 1* gene correlates with the hematologic response to eculizumab in patients with paroxysmal nocturnal hemoglobinuria

Tommaso Rondelli,[1] Antonio M. Risitano,[2]* Régis Peffault de Latour,[3]* Michela Sica,[1] Benedetta Peruzzi,[1] Patrizia Ricci,[2] Wilma Barcellini,[4] Anna Paola Iori,[5] Carla Boschetti,[4] Veronica Valle,[5] Veronique Frémeaux-Bacchi,[6] Maria De Angioletti,[1,7] Gerard Socie,[3,8] Lucio Luzzatto,[9] and Rosario Notaro[1]

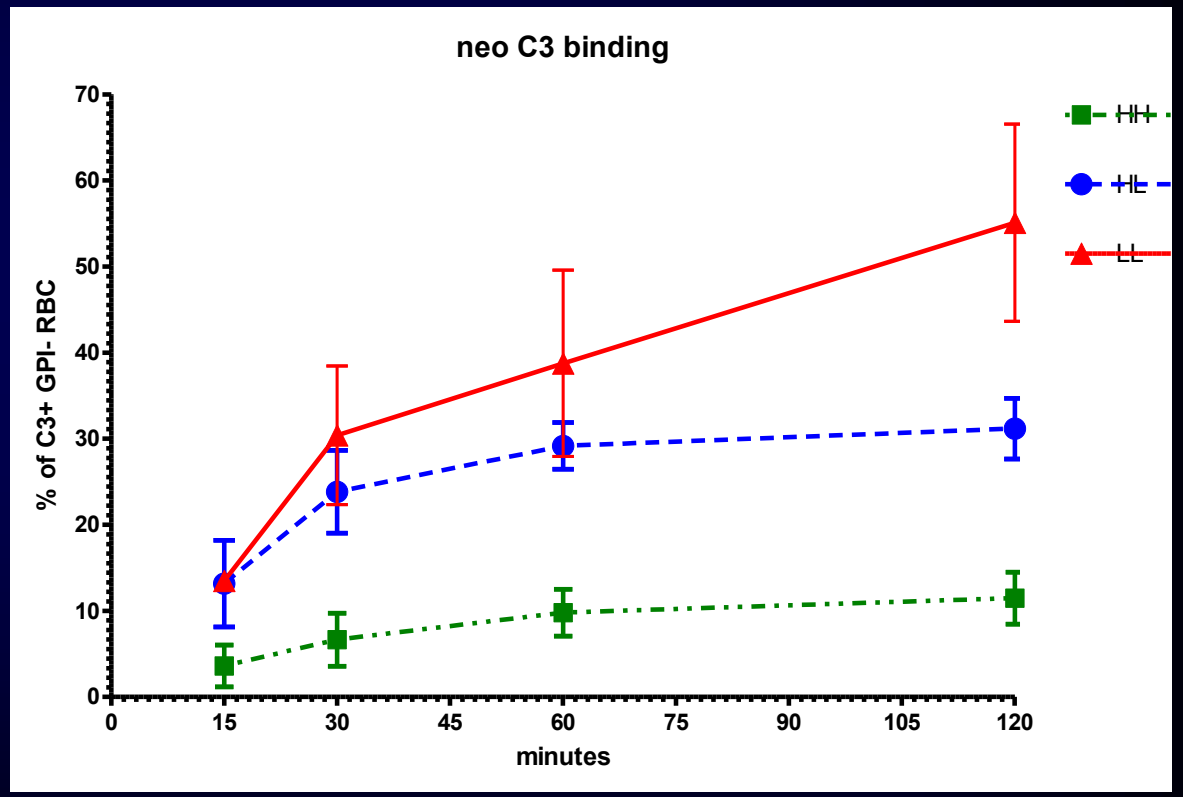
CR1 Hind III RFLP polymorphism was associated with a lower chance of transfusion independency to eculizumab (p=0.016)



Good response: transfusion independency

A French-Italian study on 72 patients

Kinetics of C3 deposition on PNH RBCs exposed to complement activation



Dose effect of the hypomorphic CR1 variant on kinetics of C3 deposition on PNH cells in vitro (heterozygous subjects have slight faster C3 deposition

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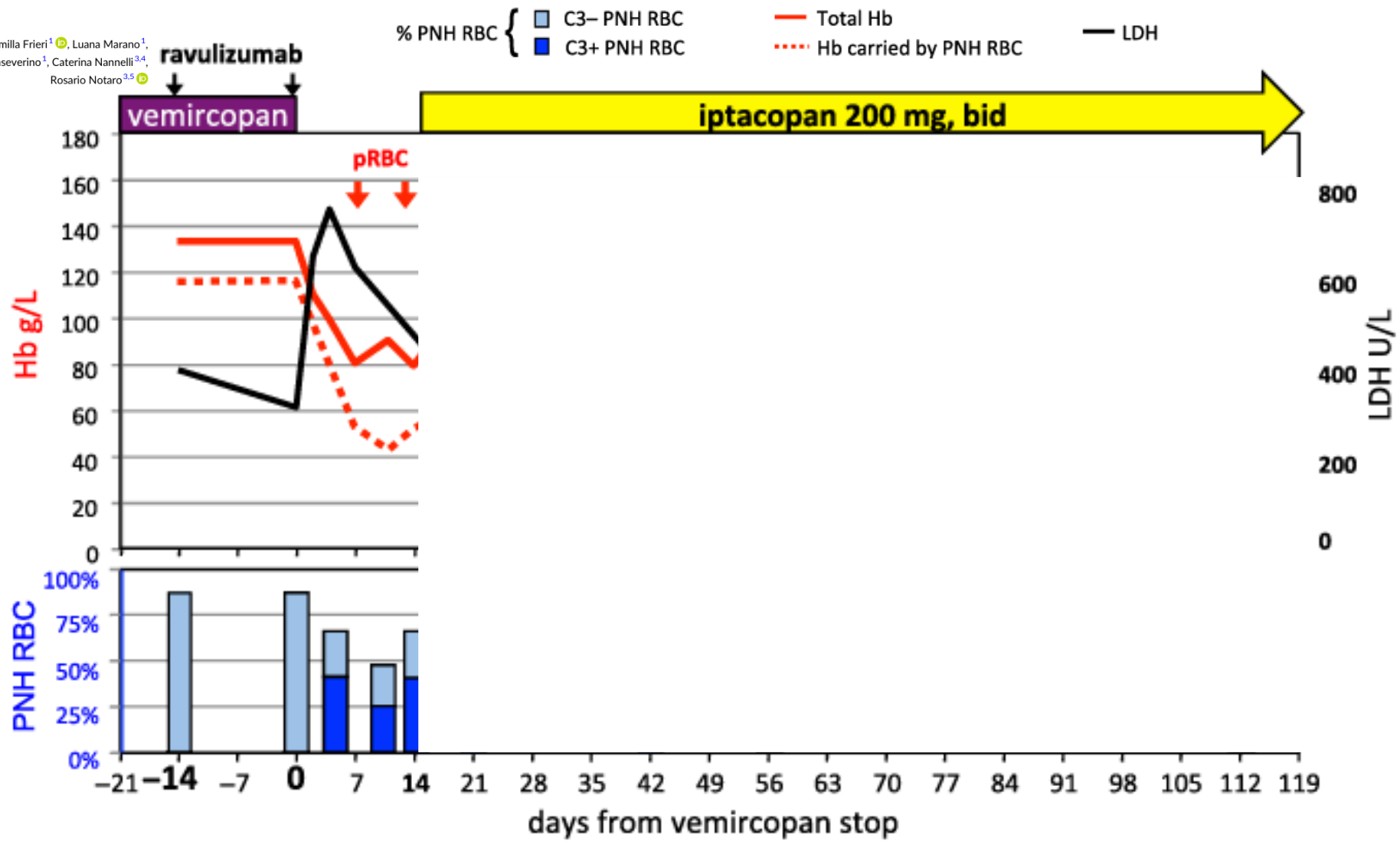

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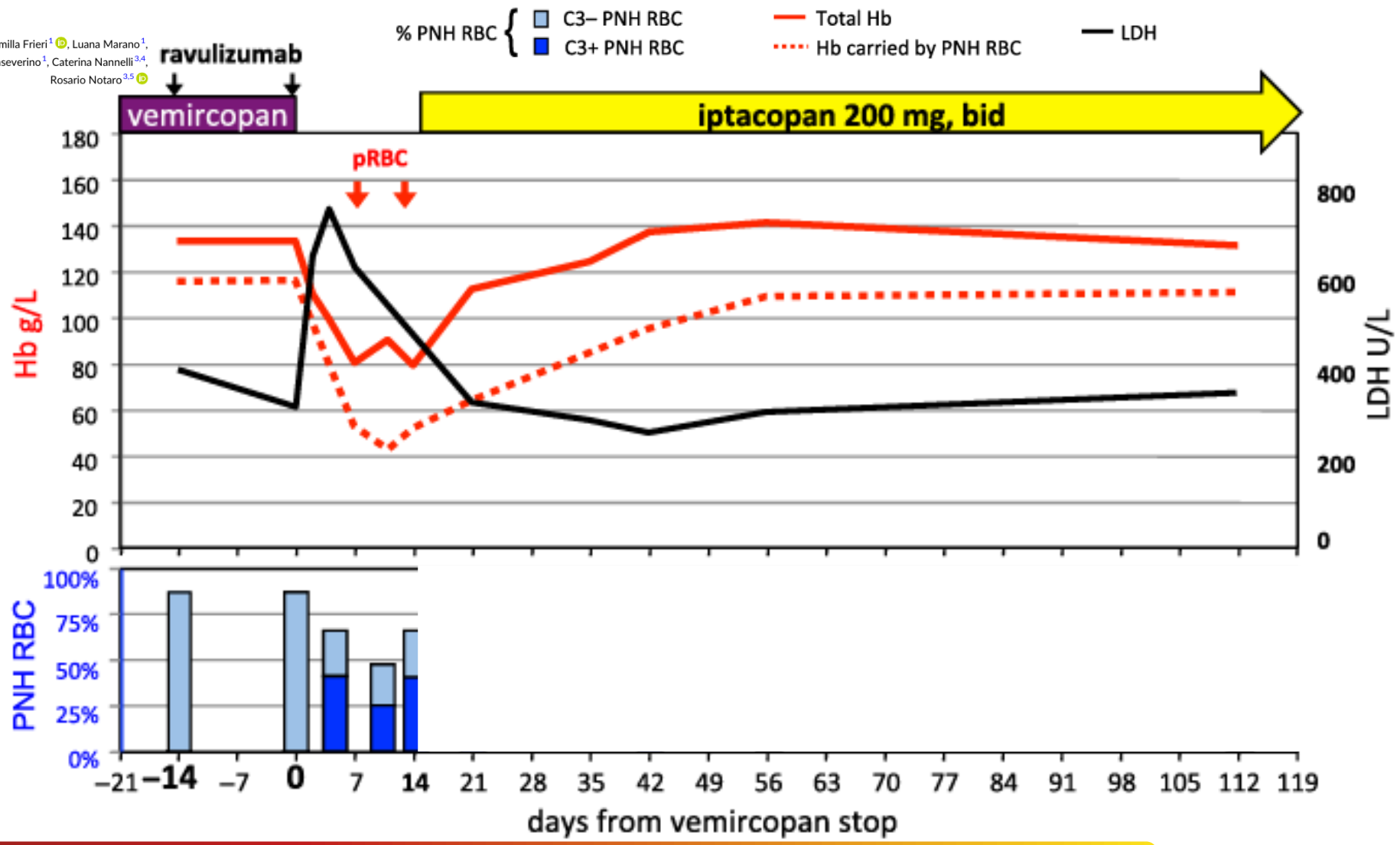

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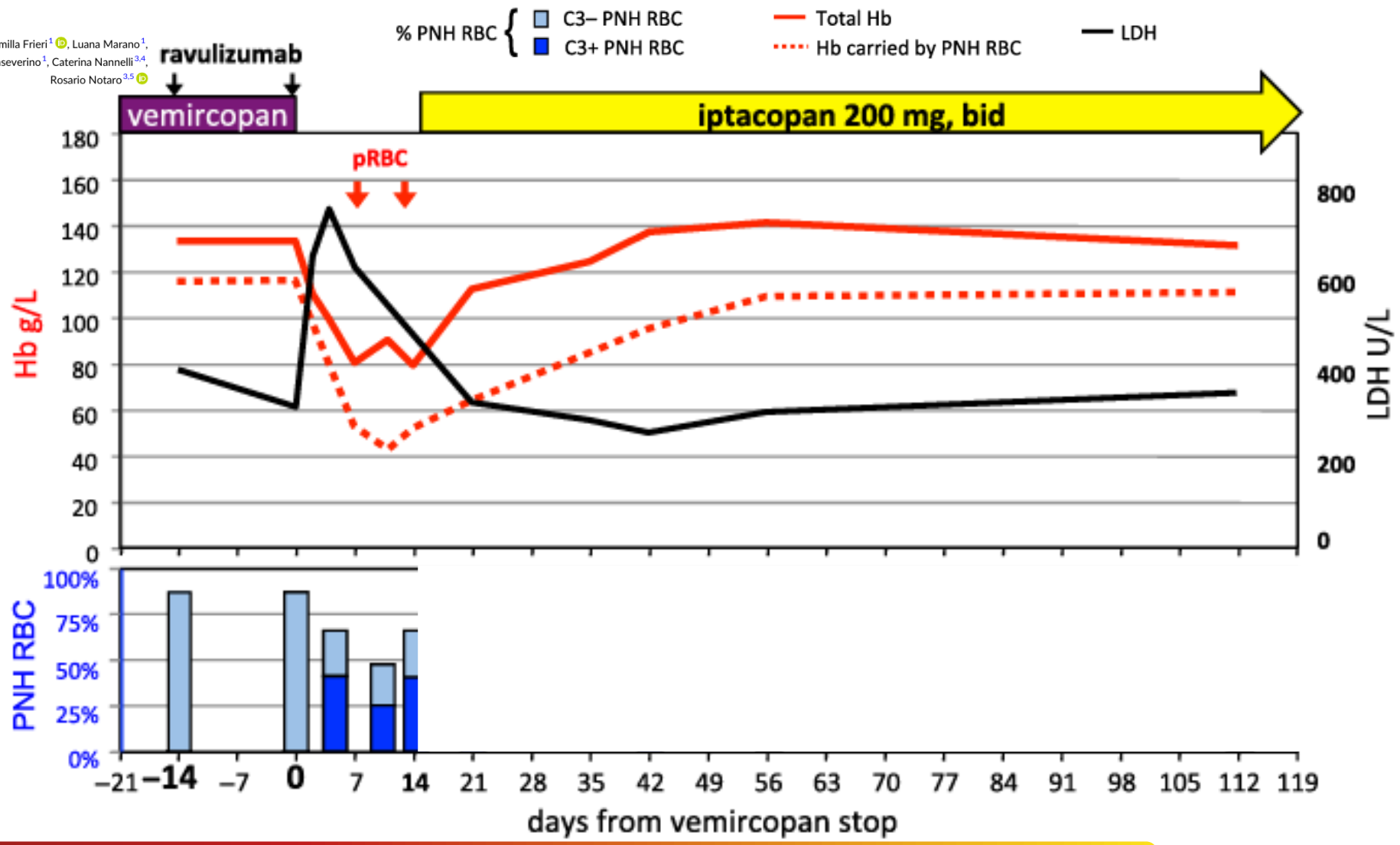

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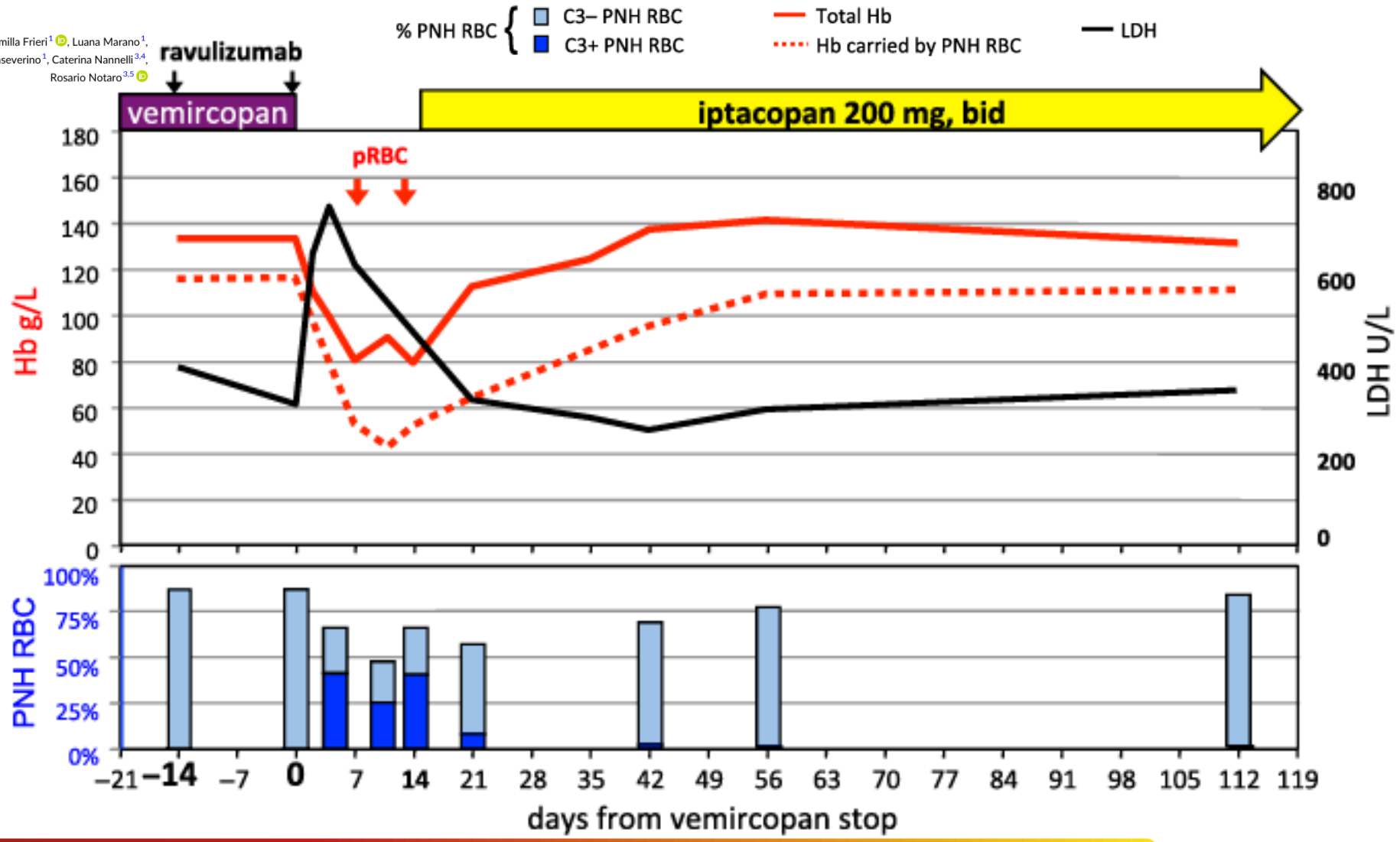
- ✓ Excellent hematological response on FD-inhibitor monotherapy
  - Risk-mitigation strategy in case of discontinuation
- ✓ Massive hemolysis at time of FD-inhibitor discontinuation (despite of proper anti-C5)
  - Intravascular vs extravascular
- ✓ Rescued by reintroduction of a proximal inhibitor (FB-inhibitor)

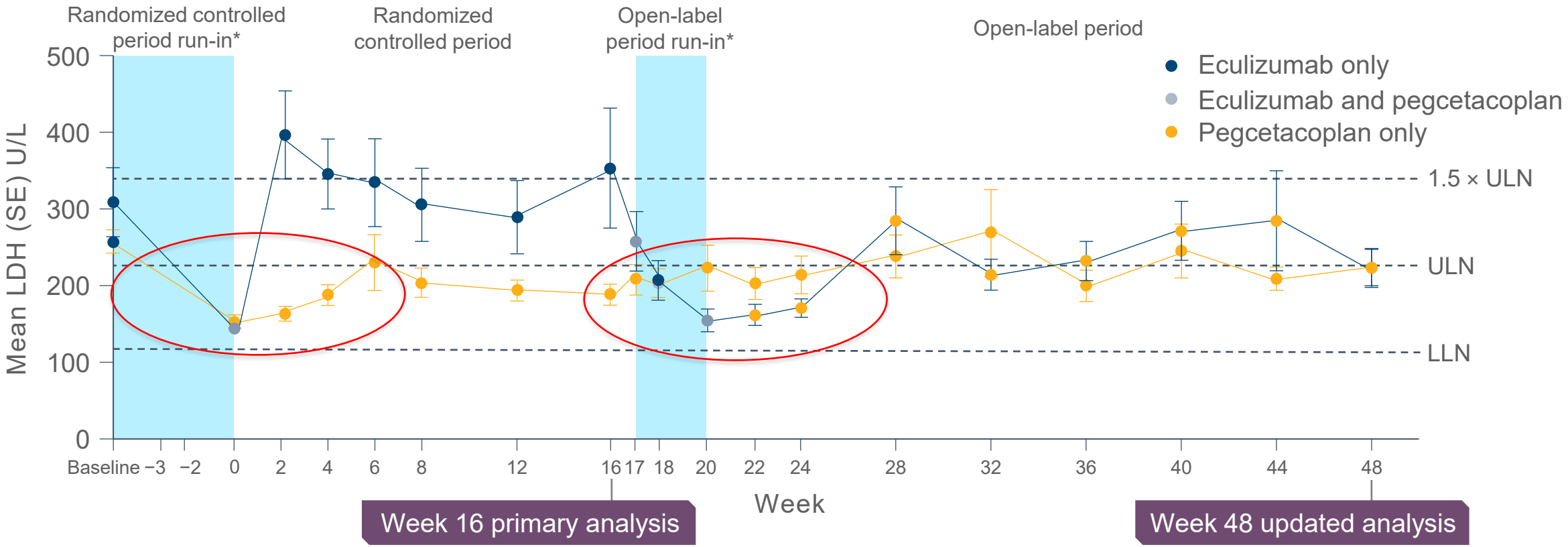


Question #3

What are the clinical implications of mild, continuous LDH increase (1.5-2 times the ULN) in this patient on proximal inhibitor in monotherapy?

1. Pharmacokinetic breakthrough hemolysis (PK BTH): consider treatment modification
2. Phamacodynamic breakthrough hemolysis (PD BTH): consider treatment modification
3. Clinically meaningful intravascular residual chronic hemolysis due to suboptimal complement inhibition: consider treatment modification
4. Low-grade intravascular residual chronic hemolysis with negligible clinical relevance: treatment modification not needed
5. Clinically meaningful extravascular residual chronic hemolysis due to suboptimal complement inhibition: consider treatment modification

By Week 48, there was no significant difference in mean LDH levels between treatment arms in PEGASUS



At **Week 16**, **non-inferiority was not shown** for change from baseline in **LDH level** with pegcetacoplan versus eculizumab[1]

At **Week 48**, by which point all patients were receiving pegcetacoplan only, there was **no significant difference** in mean **LDH levels** between treatment groups (nominal ***P*=0.80**)[2]

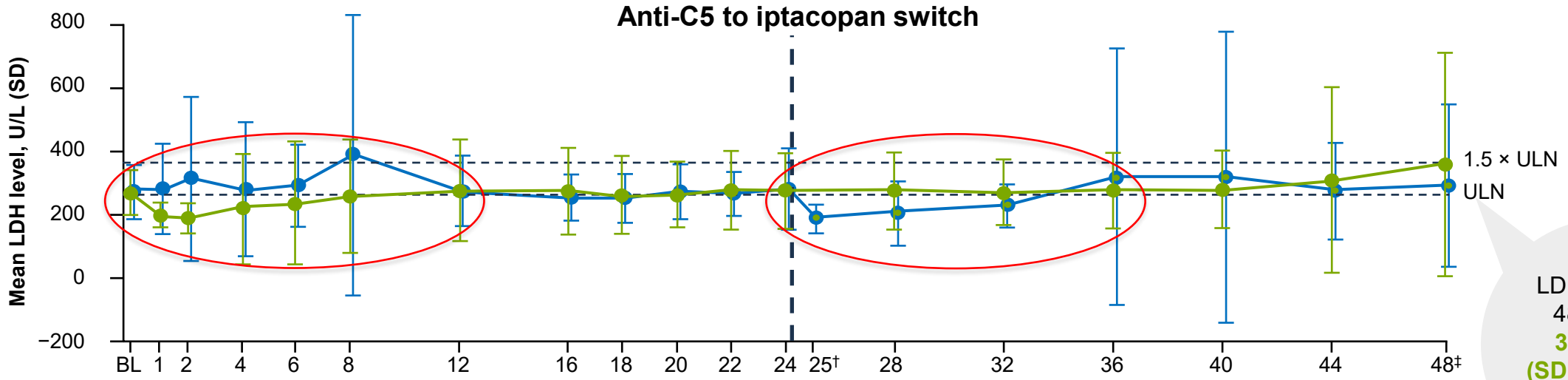
Figure adapted from Peffault de Latour R *et al. Lancet Haematol* 2022;9:e648–59

*All observed/uncensored for transfusion data. LDH, lactate dehydrogenase; LLN, lower limit of normal; ULN, upper limit of normal

1. Hillmen P *et al. N Engl J Med* 2021;384:1028–37; 2. Peffault de Latour R *et al. Lancet Haematol* 2022;9:e648–59

Mean LDH levels were generally maintained at <1.5 × ULN in both treatment arms

- Mean **LDH levels** at **Week 48** were **consistent** with **baseline levels** in **both arms**, as shown by Week 48 geometric adjusted mean ratios to baseline that were close to 1.0 (**iptacopan arm**: **1.11** [95% CI 1.02, 1.22]; **anti-C5-to-iptacopan arm**: **0.99** [0.88, 1.11])*
- Mean **LDH levels** at **Week 48** were also **consistent** with the levels at **Week 24** in both arms (geometric adjusted mean ratio for Week 48 vs Week 24: **iptacopan arm**, **1.12** [95% CI 1.00, 1.25]; **anti-C5-to-iptacopan arm**, **0.99** [0.85, 1.15])*

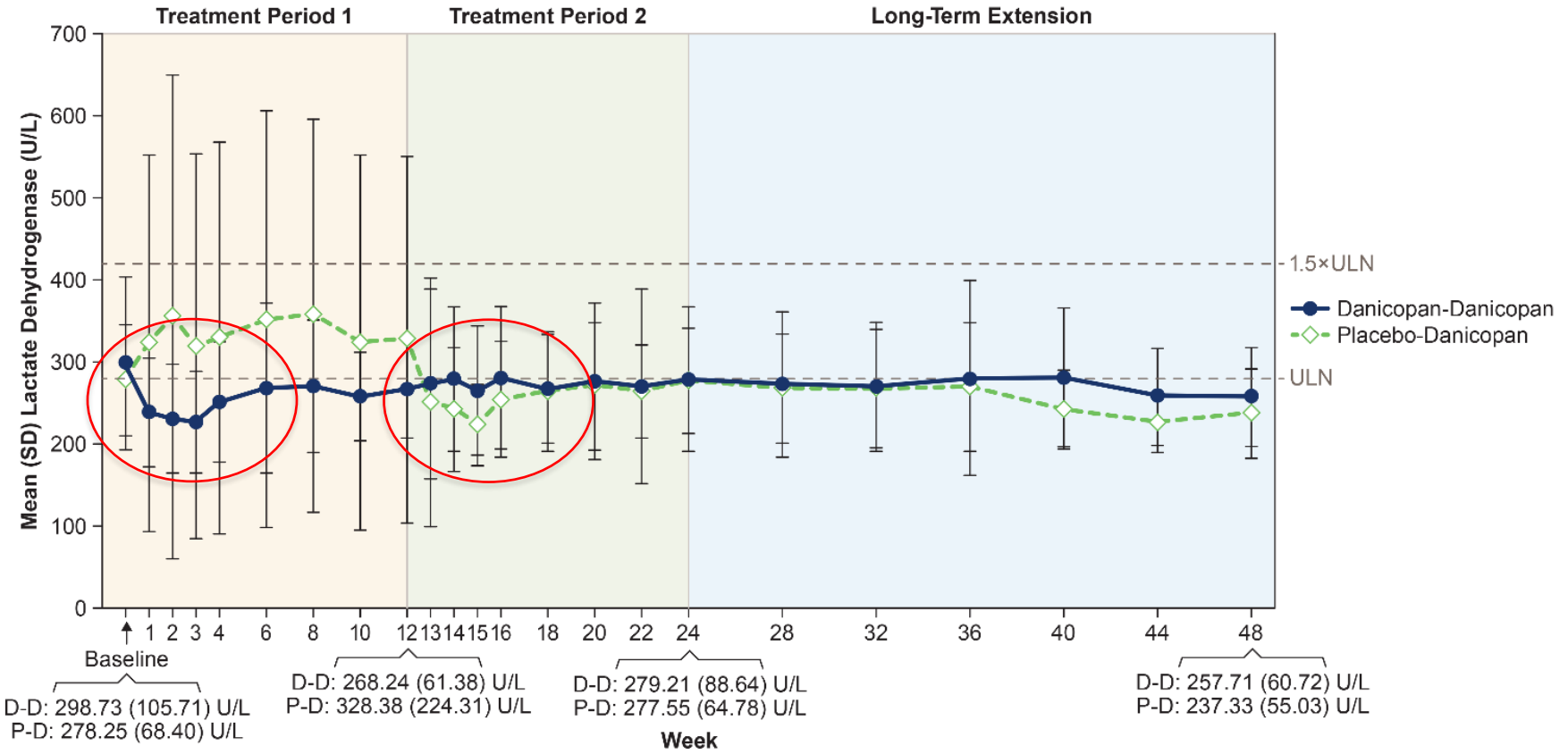


Patients with available data	BL	1	2	4	6	8	12	16	18	20	22	24	25†	28	32	36	40	44	48‡
Iptacopan	62	61	61	61	62	62	62	61	59	59	57	61	–	58	60	59	56	58	61
Anti-C5 to iptacopan	35	28	28	34	34	34	34	34	35	33	32	35	32	31	34	32	33	31	33

Mean LDH levels at 48 weeks: **358.3 U/L (SD 351.0)** and **293.8 U/L (SD 256.8)**

*Log-transformed ratio to baseline was analyzed using a mixed model of repeated measures that adjusted for covariates, including baseline LDH; †At Week 25, LDH data were only available for one patient in the iptacopan arm (LDH level: 348.0 U/L); this was not a scheduled visit in the protocol for the iptacopan arm but was for the anti-C5-to-iptacopan arm. The value in the iptacopan arm is not plotted on the graph as one patient cannot be representative of the whole treatment group; ‡Variability in LDH level in the iptacopan arm at Week 48 was driven by a few outliers.
LDH, lactate dehydrogenase; SD, standard deviation; ULN, upper limit of normal.

LDH Levels Were Maintained Across 48 Weeks in Both Treatment Arms



Week	BL	1	2	3	4	6	8	10	12	13	14	15	16	18	20	22	24	28	32	36	40	44	48
D-D, n	42	37	42	41	41	40	39	37	41	39	41	39	40	41	36	40	38	38	33	30	27	22	21
P-D, n	20	20	21	20	18	21	20	21	21	19	19	18	20	19	20	20	20	19	16	13	13	12	12

LSM (SEM) change at Week 12
- D-D: –23.49 (8.29) U/L
- P-D: –2.92 (11.91) U/L

LSM (SEM) change at Week 24
- D-D: –17.79 (13.73) U/L
- P-D: –6.03 (18.77) U/L

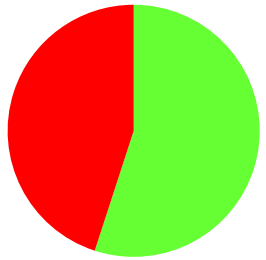
BL, baseline; D-D, danicopan-danicopan; LDH, lactate dehydrogenase; LSM, least squares mean; P-D, placebo-danicopan; ULN, upper limit of normal.

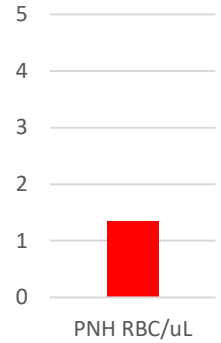
Based on a data cutoff of 20 Sept 2022

Residual hemolysis during anti-complement treatment

The dogma of LDH

LDH	Residual complement activity*	*Hb (RBC/uL)*	*% PNH RBC*	**PNH RBC mass**
1,5x ULN	**1 + 0.5**	**10%**	*10 g/dL (3x10⁶)*	*45%*
1,33x ULN	**1 + 0.33**			

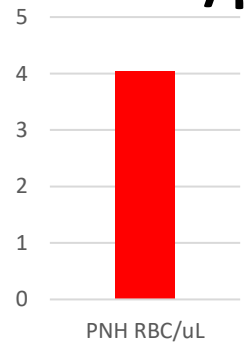




1.35x10⁶/µL

On terminal inhibitors

LDH	Residual complement activity*	*Hb (RBC/uL)*	*% PNH RBC*	**PNH RBC mass**
2,5x ULN	**1 + 0.5 x3**	**10%**	*15 g/dL (4.5x10⁶)*	*90%*
2x ULN	*1 + 0.33 x3*			



4.05x10⁶/µL

x3

On proximal inhibitors

**the effect may be different depending on the target due to the amplification*

Take home messages: hemolysis "*around*" proximal inhibitors

- ✓Proximal inhibitors lead to very large PNH RBC mass (which eventually is the best proof of their higher therapeutic efficacy)
- ✓In presence of such large PNH RBC mass it is essential that therapeutic blockade is complete and sustained
- ✓If/when therapeutic inhibition is loss patients are obviously at risk of clinically meaningful (or even catastrophic) massive hemolysis
  - PK and PD characteristics of individual inhibitors may account for the frequency and the severity of such events
  - When this happens terminal inhibitors are not be a perfect mitigation strategy, because "rebound hemolysis" may be both intravascular and extravascular
- ✓Subtle residual complement activity may result in mild LDH increase which documents minimal residual hemolysis that remains clinically negligible
- ✓The association of all these therapeutic scenarios with the thrombotic risk remains to be elucidated, but preliminary data suggest that "breakthrough thromboembolisms" are at least not more frequent than on terminal inhibitors

Understanding complement amplification

Therapeutic implications

1. Amplification within the complement cascade is due to enzymatic activity exerted by the C3/C5 convertase
2. C5 inhibitors act downstream complement amplification; then triggers of complement amplifications (commonly defined as *"complement amplifying conditions, CAC"* *amplifying conditions, CAC"*) may overcome the therapeutic C5 blockade
   - Different molecul… …se and C5 conformational change
   - Therapeutic anti-… …levels result in massive BTH)
3. All proximal inhibit… … due to the concept that any loss of inhibiti…
   - When there is a l… …ug level) CAC might result in massive …
     - Add-on anti-C5 agents are an obvious risk-mitigation strategy
   - But if the inhibition is complete and sustained (eg, the target is saturated) even CAC would not overcome the therapeutic blockade (which is upstream), resulting in negligible residual hemolysis (add-on anti-C6 not needed)

PK and PD data remain missing for most (if not all) proximal complement inhibitors

Complement biomarkers might be useful to track the deepness of therapeutic inhibition and correlate it with clinical events

Combined complement inhibition in vitro

Anti-C5 + proximal inhibitor (TT30)

DOI: 10.1111/imr.13137

INVITED REVIEW

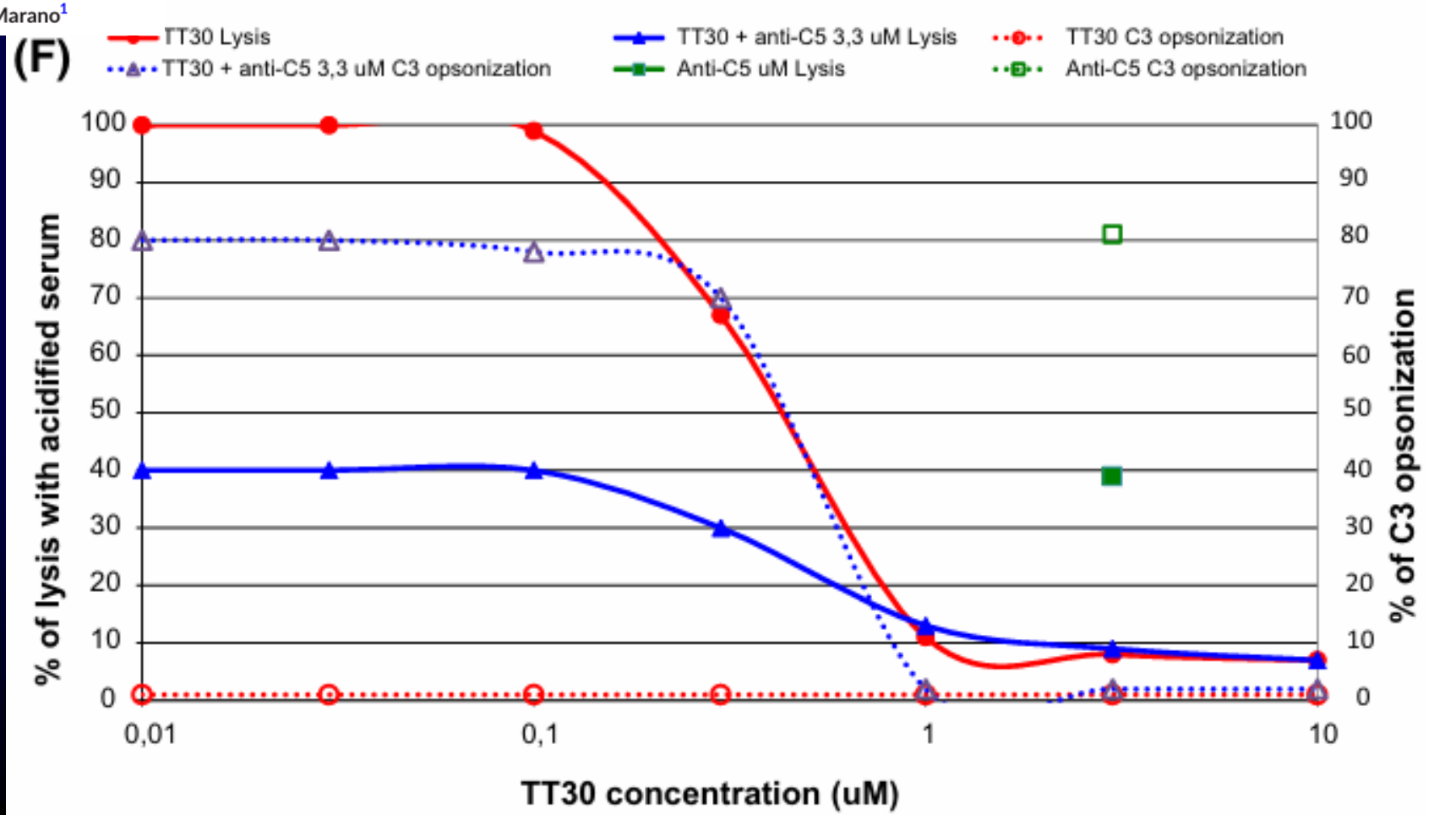
Immunological Reviews WILEY Immunological Reviews. 2023;313:262–278.

The complement alternative pathway in paroxysmal nocturnal hemoglobinuria: From a pathogenic mechanism to a therapeutic target

Antonio M. Risitano[1,2,3] | Camilla Frieri[1] | Eleonora Urciuoli[1] | Luana Marano[1]

TT30 and anti-C5 eculizumab (at fixed dose, 3.3 µM)

- ✓ In presence of anti-C5, the contribution of the proximal inhibitors is better seen as inhibition of C3 opsonization, which becomes evident at doses overlapping to those of the dose-response in absence of anti-C5
- ✓ At the same concentration, the additive (and not synergic) effect on lysis also appears, leading to full inhibition of lysis (while at suboptimal concentration the effect on lysis was entirely driven by the anti-C5).



IPIG
International PNH Interest Group

A CASE OF EXTRAVASCULAR HEMOLYSIS

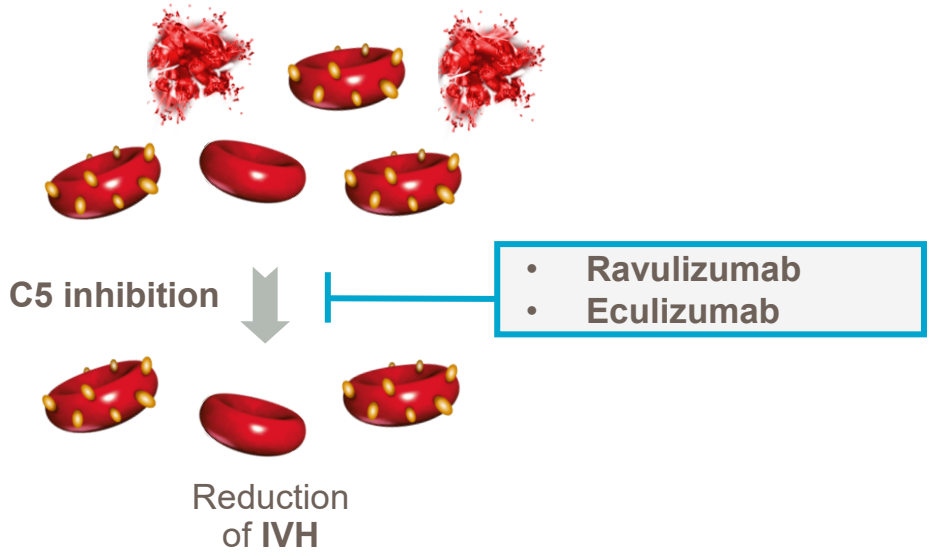
Jeff Szer AM MBBS FRACP.
Secretary of the International PNH Interest Group
Chair of IPIG Registry

IPIG

Blocking terminal complement activation

C5 inhibitor is the current standard of care in patients diagnosed with PNH where available[1]

- Reduce **IVH**[2,3]
- Reduce transfusions[2]
- Improve symptoms[2,3]
- Reduce thrombotic events[2,3]
- Reduce organ damage[2,3]
- Improve morbidity[2,3]



Terminal complement activation leading to IVH is the major contributor to morbidity associated with PNH, and therefore terminal complement inhibition and IVH control is necessary to mitigate disease[1,5,6]

Inhibition with eculizumab/ravulizumab is the standard of care for inhibiting terminal complement activity and reducing the morbidity related to terminal complement activity and IVH in patients with PNH[1]

IVH, intravascular haemolysis; LDH, lactate dehydrogenase; PNH, paroxysmal nocturnal haemoglobinuria.

1. Kulasekararaj AG, et al. *Ther Adv Hematol.* 2022;13. doi:10.1177/20406207221091046; 2. Hillmen P, et al. *Br J Haematol.* 2013;162(1):62–73; 3. Kulasekar al. *HemaSphere.* 2023;7(S3):1427–1428;
4. Kulasekararaj A, et al. *Eur J Haematol.* 2022;109(2):205–214; 5. Brodsky RA. Paroxysmal nocturnal hemoglobinuria. In: Hoffman R, et al, eds. 2005:419–4
A, et al. *Br J Haematol.* 2007:137(3):181–192.

Chronic and acute intravascular haemolysis in PNH[1]

Untreated PNH[1]

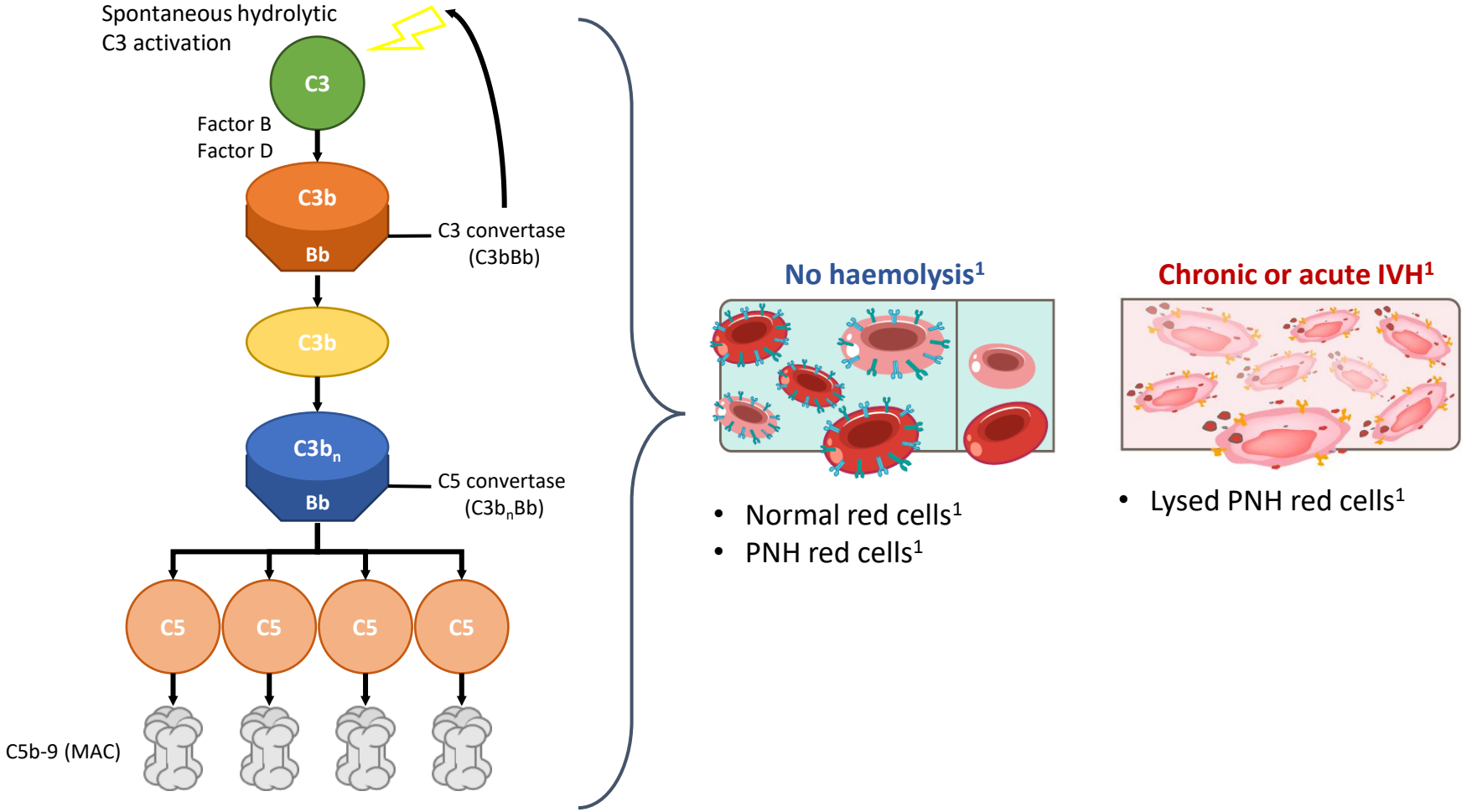
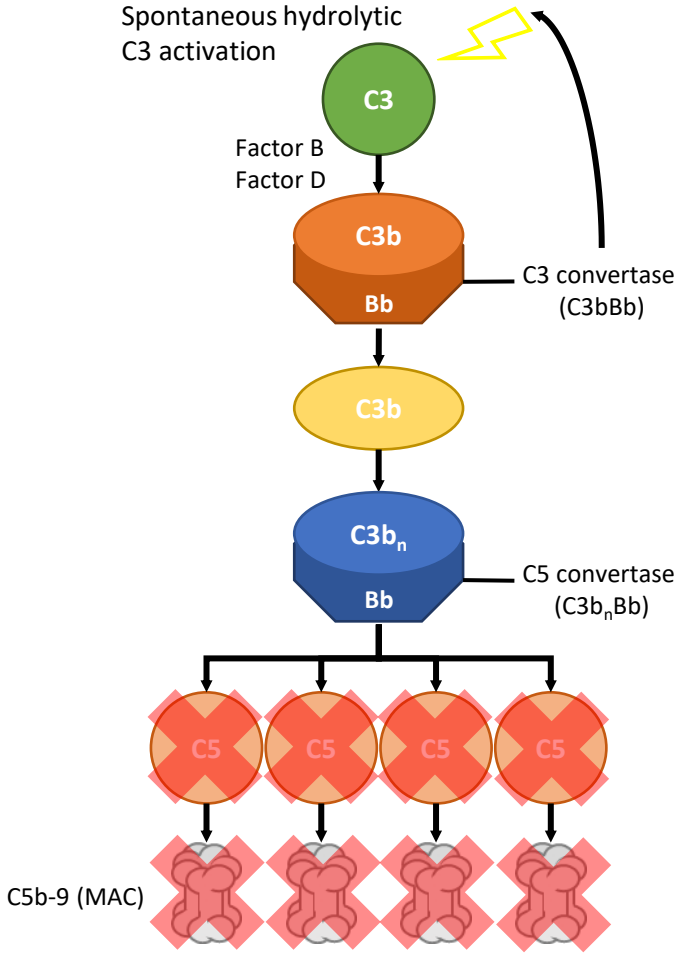


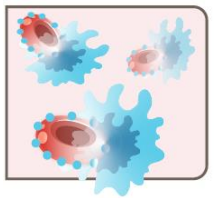
Figure adapted from Notaro R et al. *N Engl J Med* 2022.
IVH, intravascular haemolysis; MAC, membrane-attack complex; PNH, paroxysmal nocturnal haemoglobinuria.
1. Notaro R et al. *N Engl J Med* 2022;387:160–166.

Chronic extravascular haemolysis[1]

PNH with complete complement C5 blockade[1]

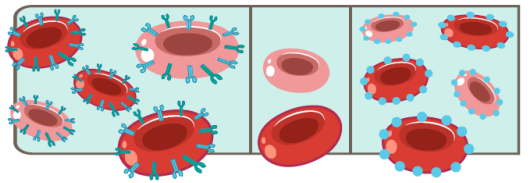


Chronic EVH[1]



- Phagocytosed C3-bound PNH red cells[1]

No haemolysis[1]

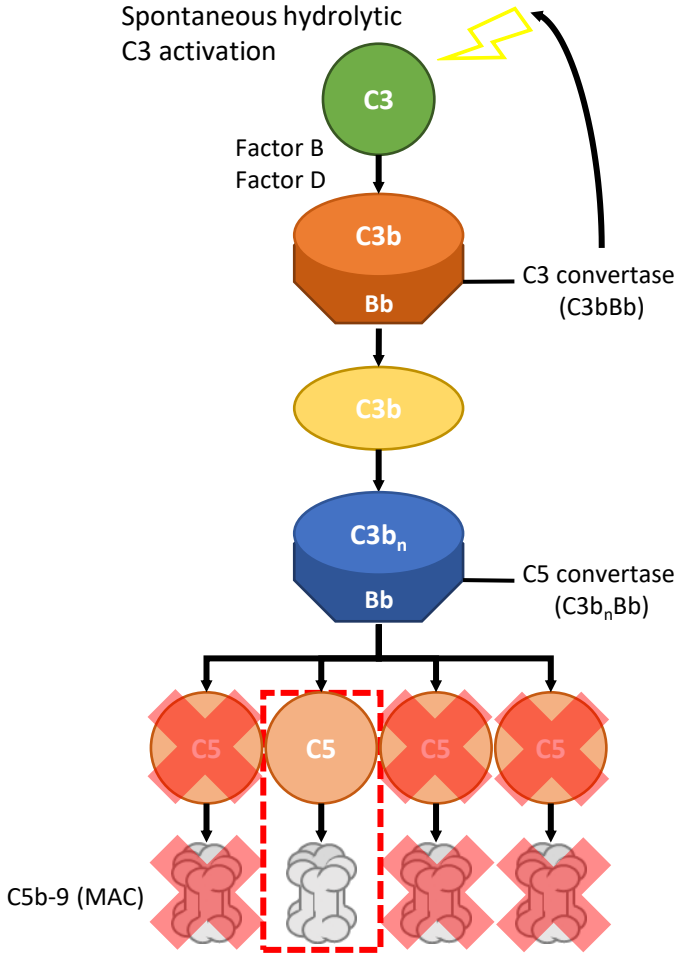


- Normal red cells[1]
- PNH red cells[1]
- C3-bound PNH red cells[1]

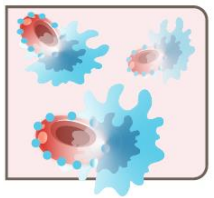
Figure adapted from Notaro R et al. *N Engl J Med* 2022.
EVH, extravascular haemolysis; MAC, membrane-attack complex; PNH, paroxysmal nocturnal haemoglobinuria.
1. Notaro R et al. *N Engl J Med* 2022;387:160–166.

Breakthrough intravascular haemolysis[1]

PNH with incomplete complement C5 blockade[1]



Chronic EVH[1]



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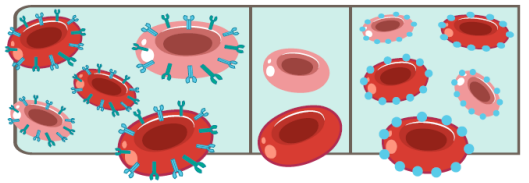
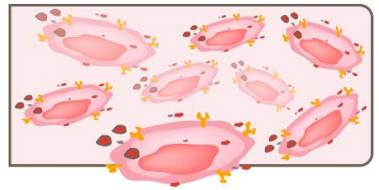


- Normal red cells[1]
- PNH red cells[1]

Acute BTH[1]



- Lysed PNH red cells[1]

Figure adapted from Notaro R et al. *N Engl J Med* 2022.

BTH, breakthrough haemolysis; EVH, extravascular haemolysis; MAC, membrane-attack complex; PNH, paroxysmal nocturnal haemoglobinur

1. Notaro R et al. *N Engl J Med* 2022;387:160–166.

Breakthrough intravascular haemolysis

- Breakthrough intravascular haemolysis refers to the ***return of haemolytic disease activity*** in patients treated with a complement inhibitor[1]

- Symptoms include anaemia, smooth muscle dystonia and thrombosis[2]

- Breakthrough intravascular haemolysis can be identified by:[2]
  - A ***sudden reappearance of signs and symptoms*** of intravascular haemolysis, possibly including haemoglobinuria[2]
  - A marked ***increase in LDH*** and a sharp ***decrease in haemoglobin***[2]

Patient case: Presentation and blood test results

- 44-year-old female presented to her GP in October 2010 (age 44 years) with:
  - 3 months of progressive severe lethargy, nausea and very dark urine
  - Able to work (office) but exhausted before end of each day
  - Recent onset of abdominal pain (for past 3 days)
  - Blood tests done and referral made:

Full Blood Count (Whole Blood)

Hb	***102L***	g/L	115-150
WCC	4.4	x10^9/L	4.0-11.0
PLT	148	x10^9/L	140-400
RCC	***2.81L***	x10^12/L	3.80-5.10
PCV	***0.30L***	L/L	0.35-0.45
MCV	***106.3H***	fL	80.0-96.0
MCH	***36.4H***	pg	27.0-33.0
MCHC	343	g/L	320-360
RDW	***18.9H***	%	11.0-15.0
Retics %	***3.74H***	%	0.5-2.0
Retics	105.1	x10^9/L	20-110

White Cell Differential

Neut	***1.8L***	x10^9/L	2.0-8.0
Lymph	2.3	x10^9/L	1.2-4.0
Mono	0.2	x10^9/L	0.1-1.0
Eos	0.0	x10^9/L	0.0-0.5
Baso	0.0	x10^9/L	0.0-0.1

11R011038 31/01/11 15:50
Film Comment : Mild macrocytic anaemia with occasional elongated cells, rare fragmented red cells, rare spherocytes and moderate polychromasia. Mild neutropenia and borderline thrombocytopenia.

ALT	***53H***
AST	***107H***
Bili Total	***23H***
T. Protein	74
LD	***2820H***

PNH SCREEN - Red Blood Cells

Type I	47.6	%
Type II	40.7	%
Type III	11.1	%

- Granulocytes

FLAER/CD24	92.0	%-DEFICIENT

- Monocytes

FLAER/CD14	81.8	%-DEFICIENT

- RESULT

PNH Result	Pos

31/01/11 11R011038
PNH Flow Results: Utilising CD235a/CD59 markers on red cells, approximately 41% of red cells are Type II GPI deficient cells and 11% are Type I GPI deficient cells.
FLAER/CD24 identifieds that 92% of neutrophils are GPI deficienct.
FLAER/CD14 staining of monocytes identifies 82% of monoctes as GPI deficient.
PNH Diagnosis: PNH clone identified affecting red cells, granulocytes and monocytes.

Patient case: Assessments and treatment

- Computed tomography scan of the abdomen revealed portal vein thrombosis (PVT)
  - Anticoagulant therapy was initiated and the PVT-related symptoms resolved
- No transfusions (Hb 80–100 g/L, NR:115–155)
- Bone marrow: subtle dyserythropoiesis.
  - Cytogenetics: 46XX
  - Myeloid NGS gene panel: no variants

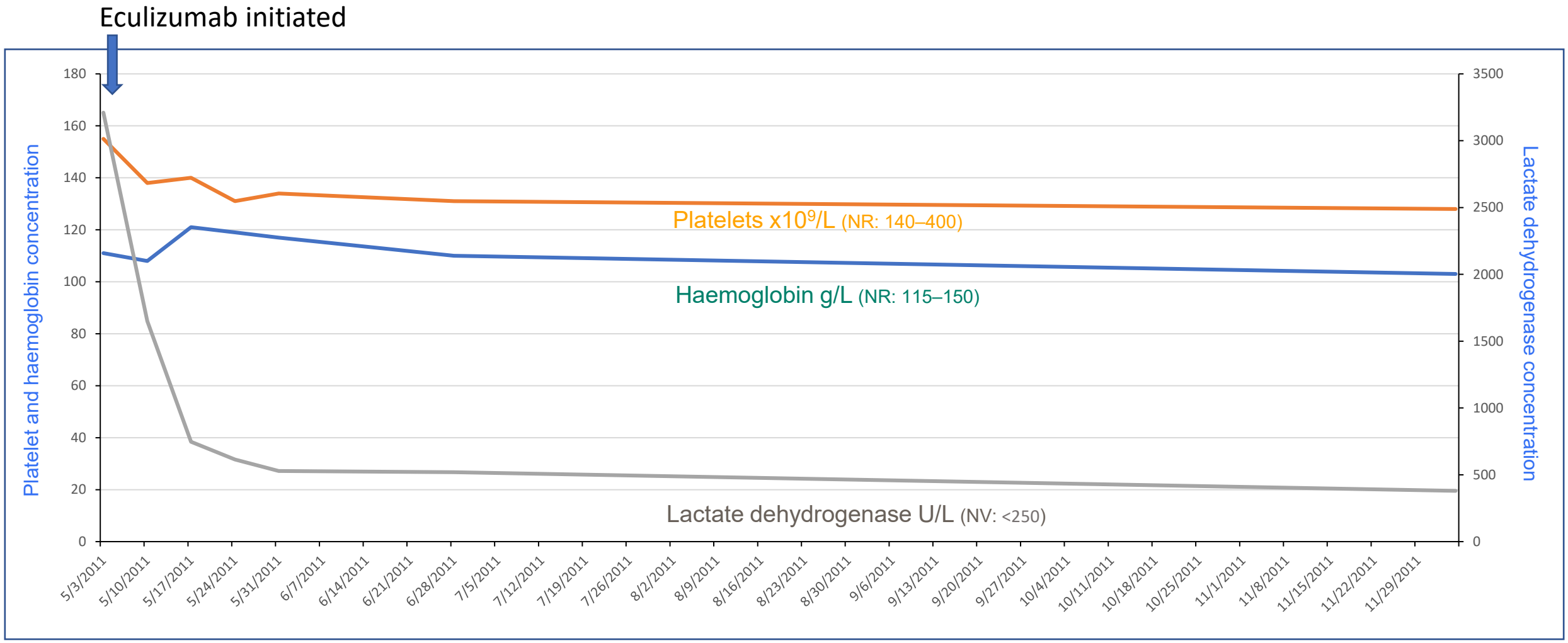
Is therapy indicated?

a) YES
b) NO
c) MAYBE

What happened next

- Eculizumab commenced 3 May 2011 based on LDH, clone size, and anaemia (multiple readings <100 g/L) along with portal vein thrombosis

Patient case: Response to treatment with eculizumab

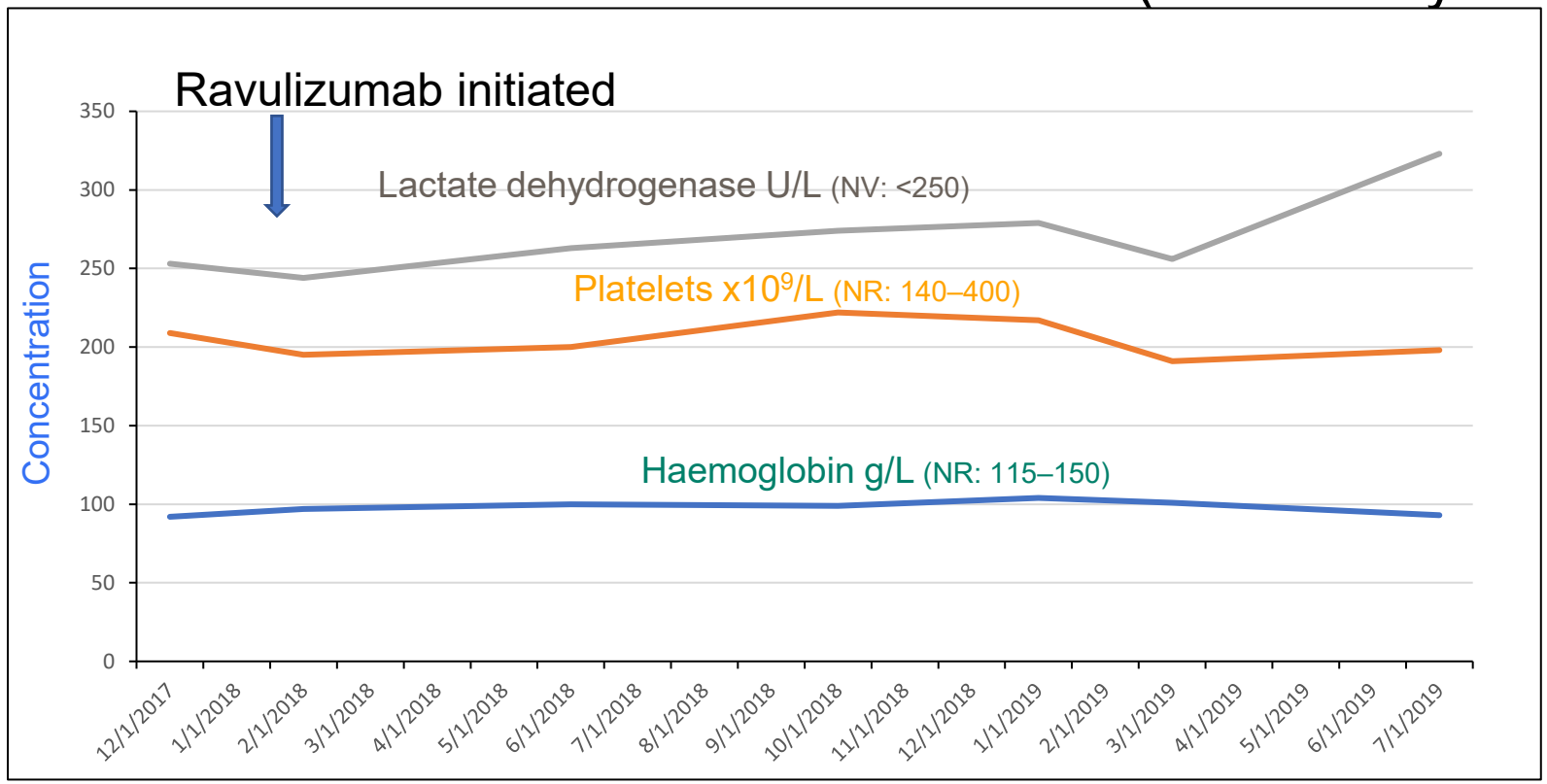


Patient case: Symptoms

- Most symptoms settled within 6 weeks of beginning eculizumab
- Fatigue much less
- Workday much easier to accommodate
- 1 June 2016
  - Hb 106 g/L (NR: 115–150), Plt 181 x 10^9/L (140–400), LDH 228 U/L (NV <250), DAT+ (C3d)
  - Type 3 RBC: 38.8%
  - Very keen to reduce interval of infusion

Patient case: 302 study treatment

- Day 1: patient randomised to eculizumab arm (8 August 2017)
- Day 183: patient received first dose of ravulizumab (8 February 2018)



Patient case:
Latest laboratory results

• Hb	99	(115-155 G/L)
• Neutrophils	1.1	(2.0-8.0x10^9/L)
• Platelets	125	(150-400x10^9/L)
• Reticulocytes	164	(20-100x10^9/L)
• DAT	2+ C3d	
• LDH	265	(120-250 U/L)
• BR	27	(<21μmol/L)
• AST	26	(<31U/L)
• ALT	16	(5-35U/L)

Patient case:
Latest high-sensitivity flow cytometry results

PNH Screen Analysis

Clinical Details:	PNH on Ravulizumab		
Antibody Panel:	CD15, 45, FLAER, 235a, 157, 59, 64.		
Number of events:	CD45+ WBC: 197,000		Red Cells: 451,000
Test Sensitivity:	WBC: btn 10^{-4} - 10^{-3} RBC: 10^{-4}		
Red Cell:	Type I	29.89	%
	Type II	12.460	%
	Type III	57.650	%
Mature Granulocytes:	FLAER/157	98.000	% deficient
Monocytes:	FLAER/157	97.000	% deficient
Conclusion:	Persistent PNH red cell & white cell clones which appear stable.		

Patient case: summary

- Patient remains stable on ravulizumab for >7 years
- Asymptomatic and excellent quality of life
- Only impact of participating in the 302 study was the reduced number of treatments per unit time
- Note the high proportion of Type III red cells
- She remains anaemic

What is this and what would you do?

Is the anemia caused by

a) Bone marrow failure
b) Chronic bleeding
c) Breakthrough hemolysis
d) Extravascular hemolysis

What is this and what would you do?

Extravascular hemolysis in this case is best managed by

a) Switch to a proximal complement inhibitor
b) Addition of a proximal complement inhibitor to ravulizumab
c) Allogeneic stem cell transplantation
d) MICLO*

*Masterly Inactivity with Cat-Like Observation

Conclusion

- Extravascular hemolysis (EVH) is an iatrogenic disorder in patients with PNH treated with a terminal complement inhibitor
- EVH may cause symptoms such as fatigue and a return of, increase of or persistence of transfusion requirement
- Not all EVH needs active management.

IPIG
International PNH Interest Group

THANK YOU!

Proximal inhibitors: Are we understanding better?

Régis Peffault de Latour, MD, PhD

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French network for rare immunological & hematological disorders (MaRIH)
Severe aplastic anemia working party of EBMT (SAAWP EBMT)
Hôpital Saint-Louis, Paris, France

MaRIH
Filière de santé Maladies Rares ImmunoHématologiques

APLASIE MEDULLAIRE
centre de référence

Disclosures

- **Expert consultant / speaker:** Alexion, Amgen, Apellis, Jazz, Novartis, Pfizer, Roche & Samsung
- **Research grant:** Alexion, Novartis & Pfizer

Mr B (DOB: March 31th 1984)

- **Administrative officer, 1 daughter, no previous medical history**
- **PNH history:**
  - **2011:**
    - Hemolytic PNH with abdominal pain & RBC transfusions
    - Hb: 7.5 g/dL; reticulocytes 180 G/L; Platelets: 190 G/L; Neutrophils: 1.8 G/L
    - LDH: 4N
    - **> Treated initially with Eculizumab**

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    - LDH: 4N
    - **> Treated initially with Eculizumab**
  - **2011-2014:**
    - No clinical symptom of intravascular hemolysis but still transfused monthly in RBC
    - LDH 2.5N / CH50 > 20% before next dose
    - **> Increase Eculizumab at 1200 mg every 2 weeks in June 2014**

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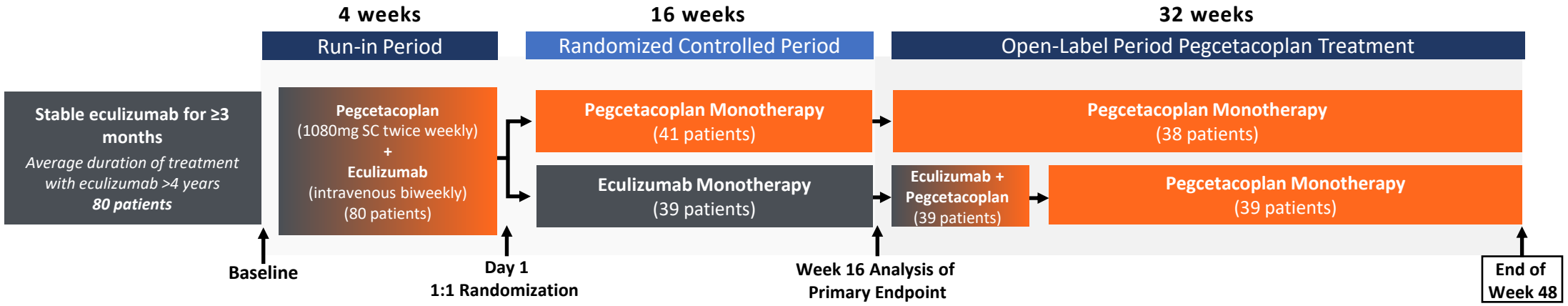
    - **> Treated initially with Eculizumab**
  - **2011-2014:**
    - No clinical symptom of intravascular hemolysis but still transfused monthly in RBC
    - LDH 2.5N / CH50 > 20% before next dose
    - **> Increase Eculizumab at 1200 mg every 2 weeks in June 2014**
  - **2019**:
    - Still transfused once a month in RBC / LDH 1.5N / Reticulocytes 320 G/L
    - **> Decision for inclusion in the PEGASUS clinical trial (anti-C3)**

Mr B (DOB: March 31th 1984)



Study Design	
Population	Patients ≥18 years of age with PNH and hemoglobin <10.5 g/dL despite stable treatment with eculizumab (≥ 3 months)
Primary Endpoint	Change from baseline in hemoglobin level at Week 16
Week 48 Endpoints	
Efficacy Endpoints	• Change from baseline in hemoglobin levels, LDH levels, ARC, and FACIT-Fatigue score at Week 48 • Freedom from transfusions
Safety Endpoints	Incidence and severity of TEAEs
Treatment Groups	• **PEG-to-PEG**: Patients received pegcetacoplan during the randomized controlled period and continued through Week 48 of the open-label period • **ECU-to-PEG**: Patients received eculizumab during the randomized controlled period and switched to pegcetacoplan during the open-label period after a 4-week run-in

Peffault de Latour *et al,* Lancet Haematology 2021

Mr B (DOB: March 31th 1984)

- **Feeling extremely well under antiC3 / Transfusion independance**

Hémogramme (*)
Cytométrie de flux, Impédance, Photométrie, SYSMEX XN

				10/03/2025
Hématies	4.68	T/L	(4,28–6,00)	5,14
Hémoglobine	15,1	g/dL	(13,4–16,7)	16,5
Hématocrite	43,3	%	(39,0–49,0)	47,7
V.G.M	93	fL	(78–98)	93
T.C.M.H	32,3	pg	(26,0–34,0)	32,1
C.C.M.H	34,9	%	(31,0–36,5)	34,6
I.D.R	13,2	%	(11,2–15,9)	13,3

Formule sanguine (*)
Mesure par fluorocytometrie,a diffraction optique SYSMEX XN

					10/03/2025
Leucocytes			5,39 G/L	(4,00–11,00)	6,03
Polynucléaires neutrophiles	56,4	%	3,04 G/L	(1,80–6,90)	3,35
Polynucléaires éosinophiles	1,1	%	0,06 G/L	(0,02–0,63)	0,06
Polynucléaires basophiles	0,7	%	0,04 G/L	(<0,11)	0,04
Lymphocytes	29,9	%	1,61 G/L	(1,00–4,80)	1,77
Monocytes	11,9	%	0,64 G/L	(0,18–1,00)	0,80

Mr B (DOB: March 31th 1984)

- **Feeling extremely well under antiC3 / Transfusion independance**

Numération plaquettaire (*)

				10/03/2025
Plaquettes (Mesure par variation d'impédance SYSMEX XN)	130	G/L	(150–400)	132
Volume Plaquettaire Moyen	9,7	fl	(6,8–12,2)	9,4

Commentaire : Absence de caillot contrôlée

Réticulocytes (*)

				10/03/2025
Réticulocytes (Mesure par fluorocytométrie à diffraction optique SYSMEX XN)	2,36	%		2,17
soit	110,4	G/L	(25,0–100,0)	111,5
Teneur en hémoglobine du réticulocyte	33,3	pg	(31,2–36,2)	33,9

				10/03/2025
LDH (Lactate Deshydrogénase) (*) (Technique Test UV ROCHE)	220	U/L	(135–225)	235
Urée (*) (Technique cinétique ROCHE)	0,40	g/L	(0,17–0,49)	0,51
	6,66	mmol/L	(2,83–8,16)	
Créatinine (*) (Technique enzymatique ROCHE)	128	µmol/L		146
	14,5	mg/L		

Mr B (DOB: March 31th 1984)

- **Doing great with Pegcetacoplan**
- **December 2019 – cholecystitis with peritonitis:**
  - Massive breakthrough hemolysis with ICU admission
  - Hb: 5.5 g/dL; reticulocytes 300 G/L; Platelets: 30 G/L; Neutrophils: 0.5 G/L
  - Dialysis for acute kidney failure / mechanical ventilation
  - Documented infections to E Coli, K Oxytoca et E Cloacae
  - Deep vein thrombosis + Budd Chiari syndrome + Mesenteric veins thrombosis
  - **> Decision to stop Pegcetacoplan and back to treatment by Eculizumab**

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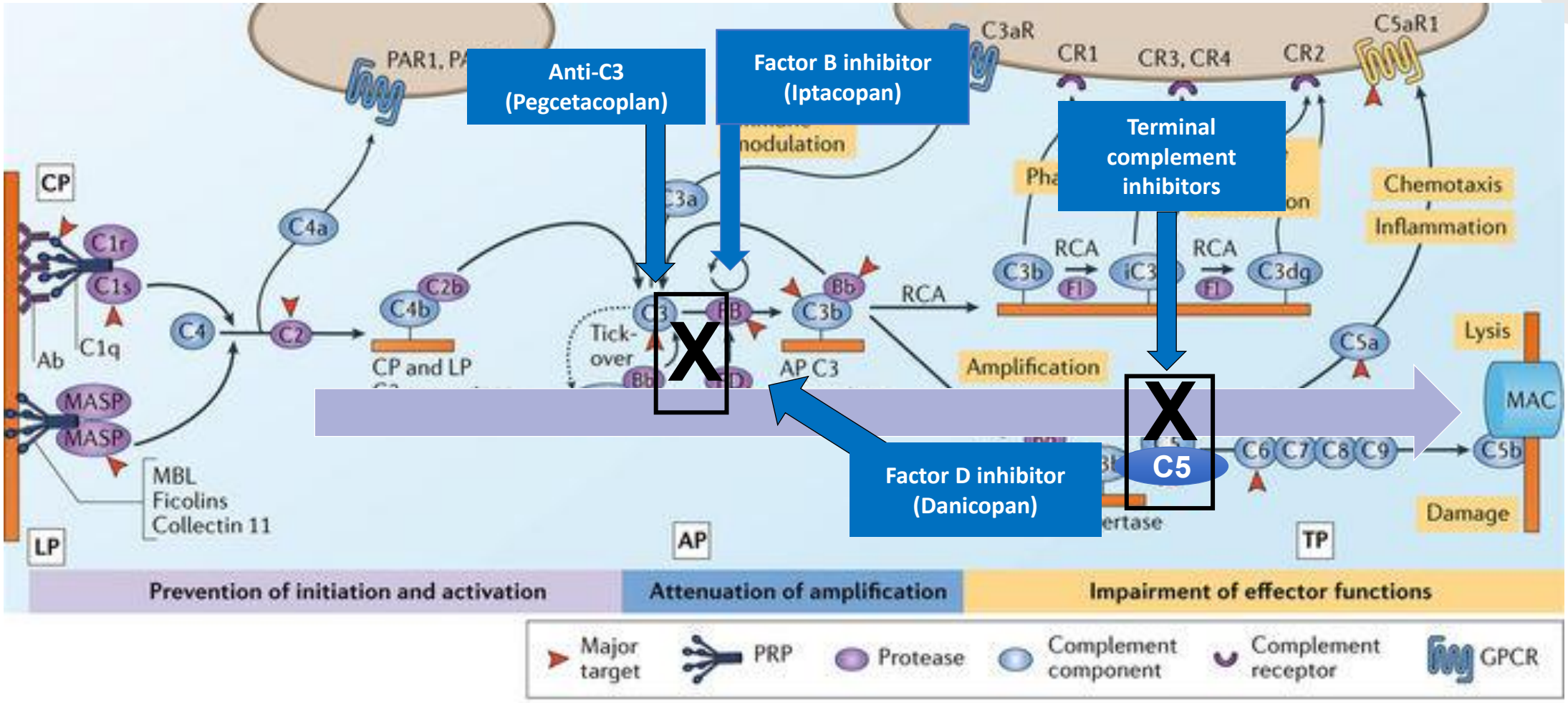
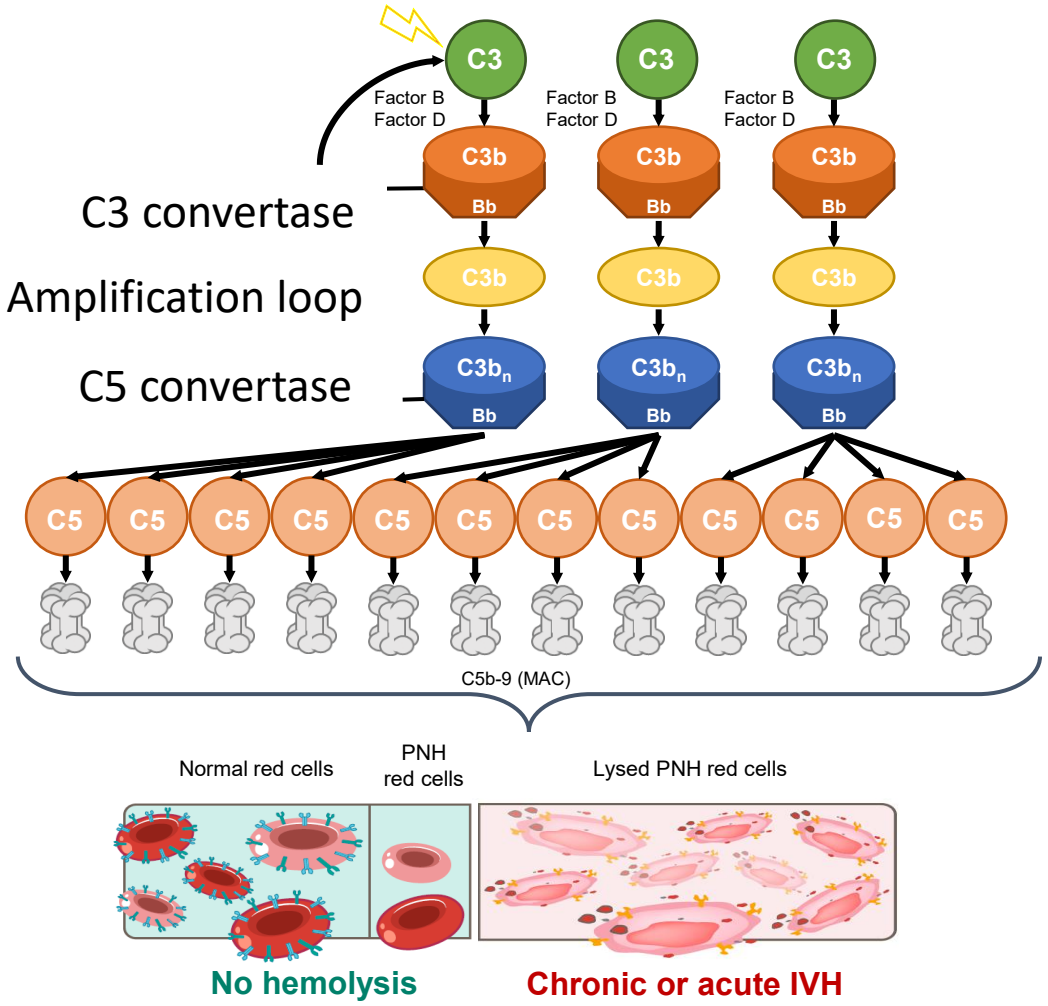
  - Deep vein thrombosis + Budd Chiari syndrome + Mesenteric veins thrombosis
  - **> Decision to stop Pegcetacoplan and back to treatment by Eculizumab**
- **March 2021:**
  - Finally discharged from the hospital
  - Back to initial hematological situation (monthly transfusion in RBC)
  - **> Decision to switch to Ravulizumab in June 2022**

Terminal - Proximal complement inhibitors



Untreated PNH



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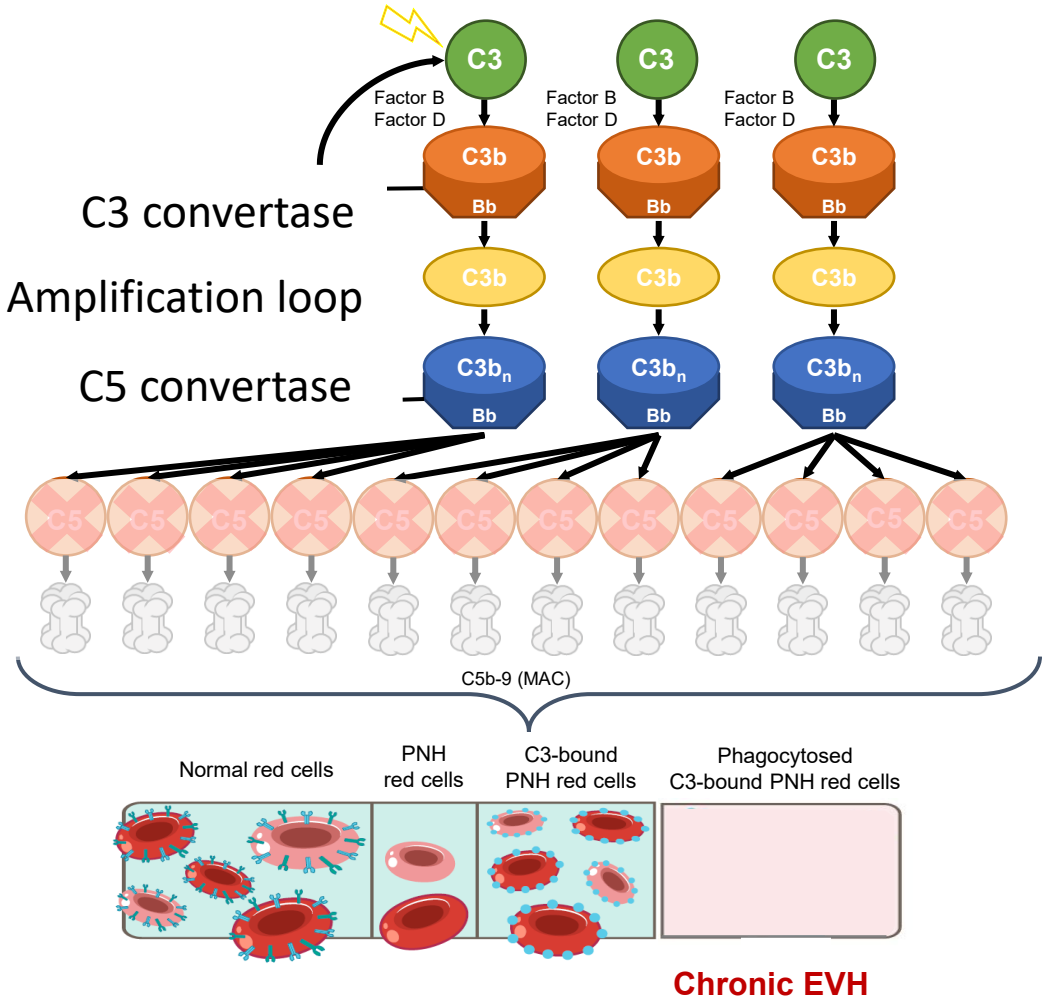
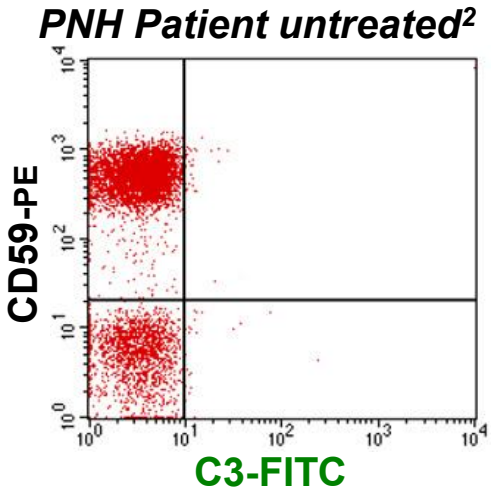
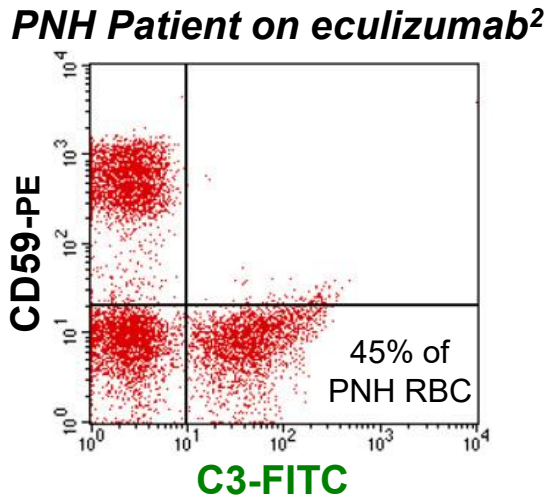
1. Notaro R, Luzzatto L. *N Engl J Med.* 2022;387(2):160–166.

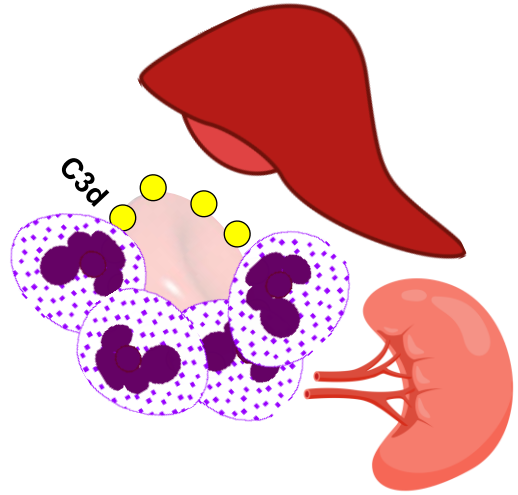
C5 blockade, C3 binding and *de novo* iatrogenic extravascular hemolysis







~30–40% of patients on terminal complement inhibition can develop clinically significant EVH[3–5]



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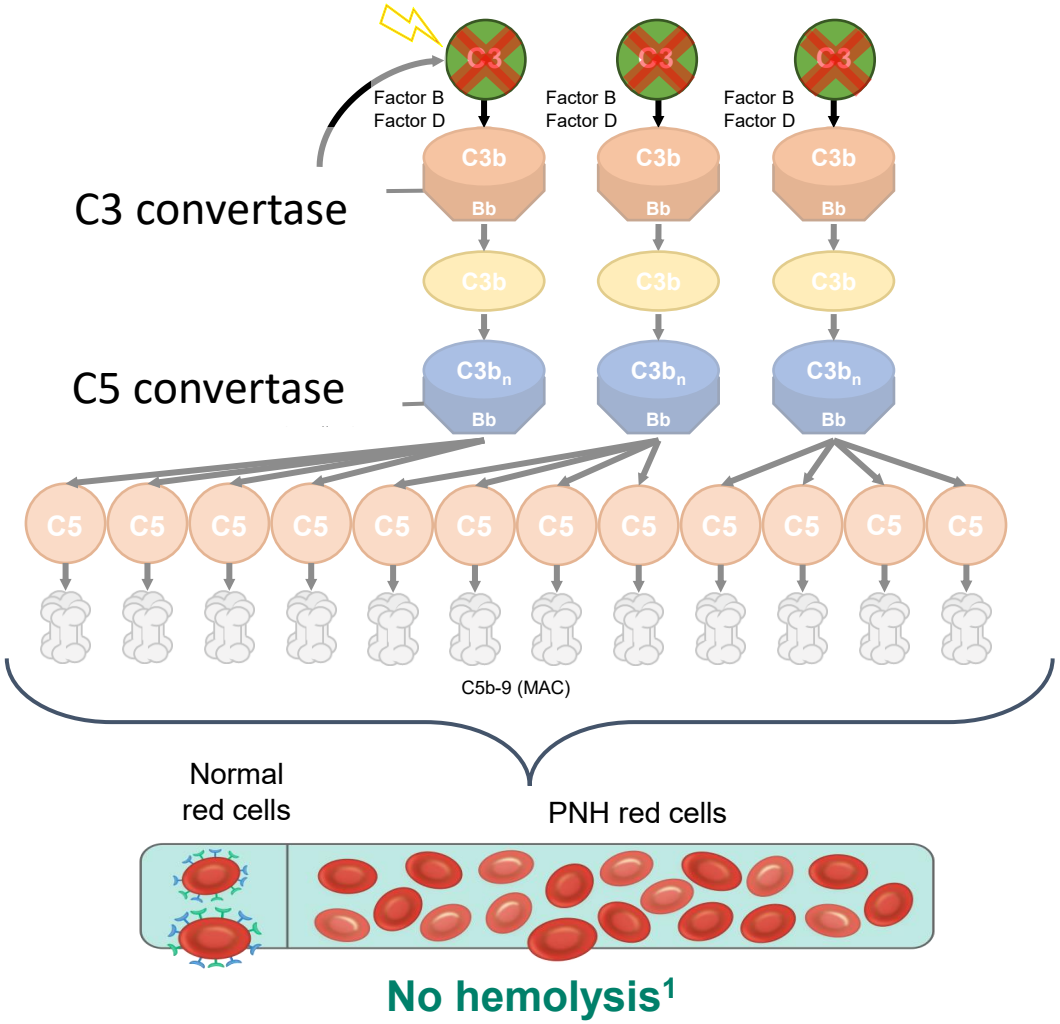
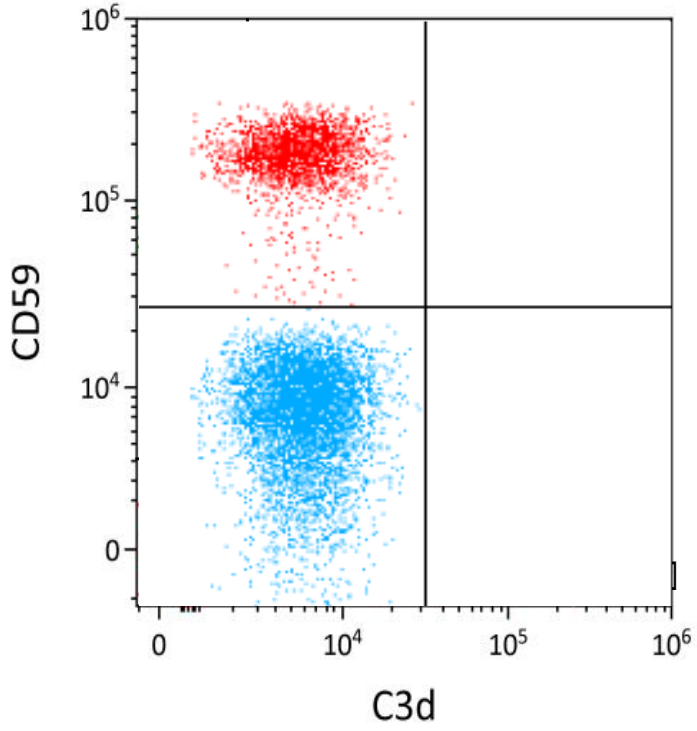
EVH, extravascular haemolysis; MAC, membrane-attack complex; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell.

1. Notaro R, Luzzatto L. *N Engl J Med.* 2022;387(2):160–166; 2. Figures from personal library of Dr Notaro; 3. Risitano AM et al. *Blood* 2009;113(17):4094-4100;
4. Kulasekararaj A et al. Presentation at EHA 2023. Abstract PB2056. *Hemasphere* 2023; 7(Suppl): e35238f0; 5. Dubureaux PE et al. *Bone Marrow Transplant.* 2021;56(10):2600–2602.

Complete proximal complement inhibition in PNH

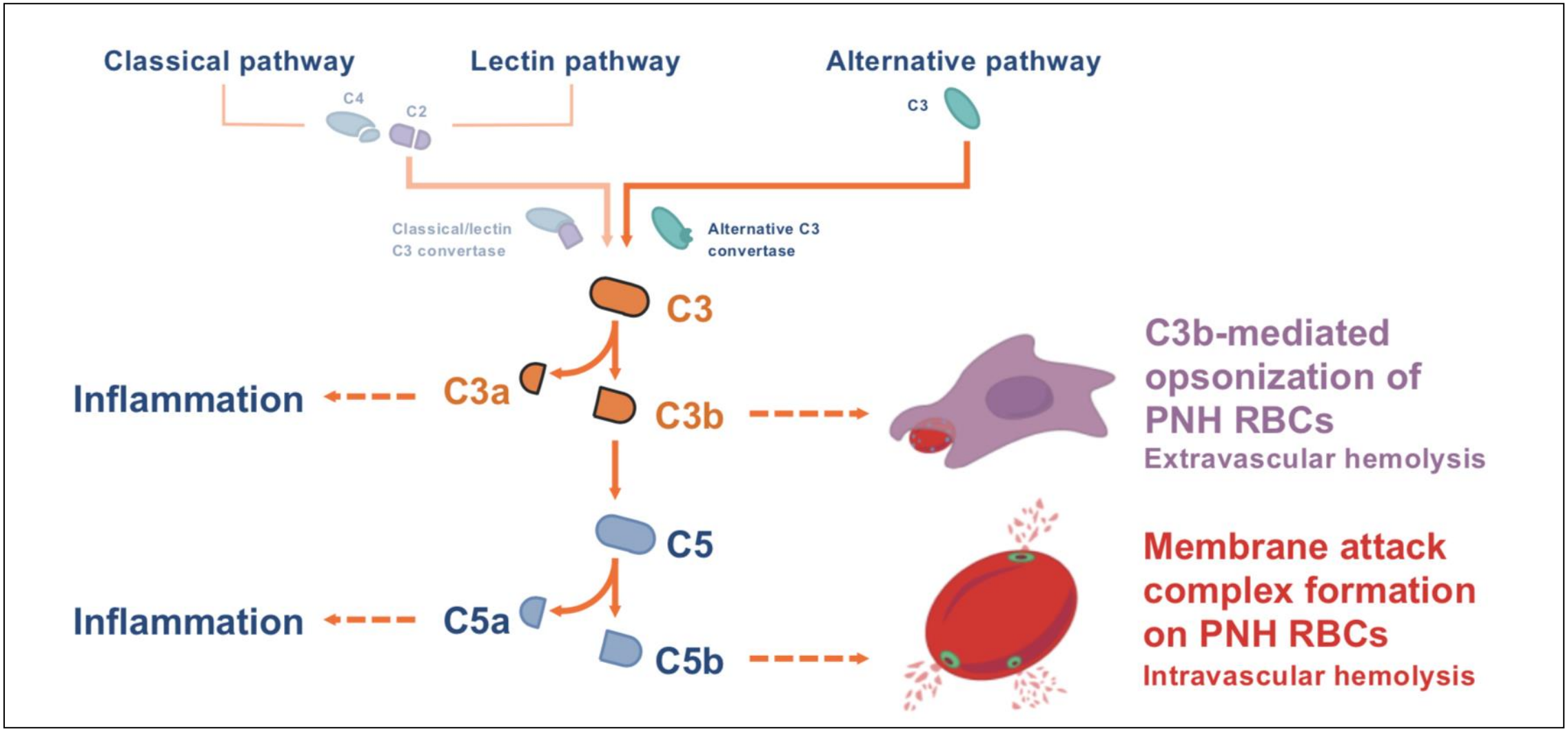


Patient treated with proximal complement inhibitor[2]

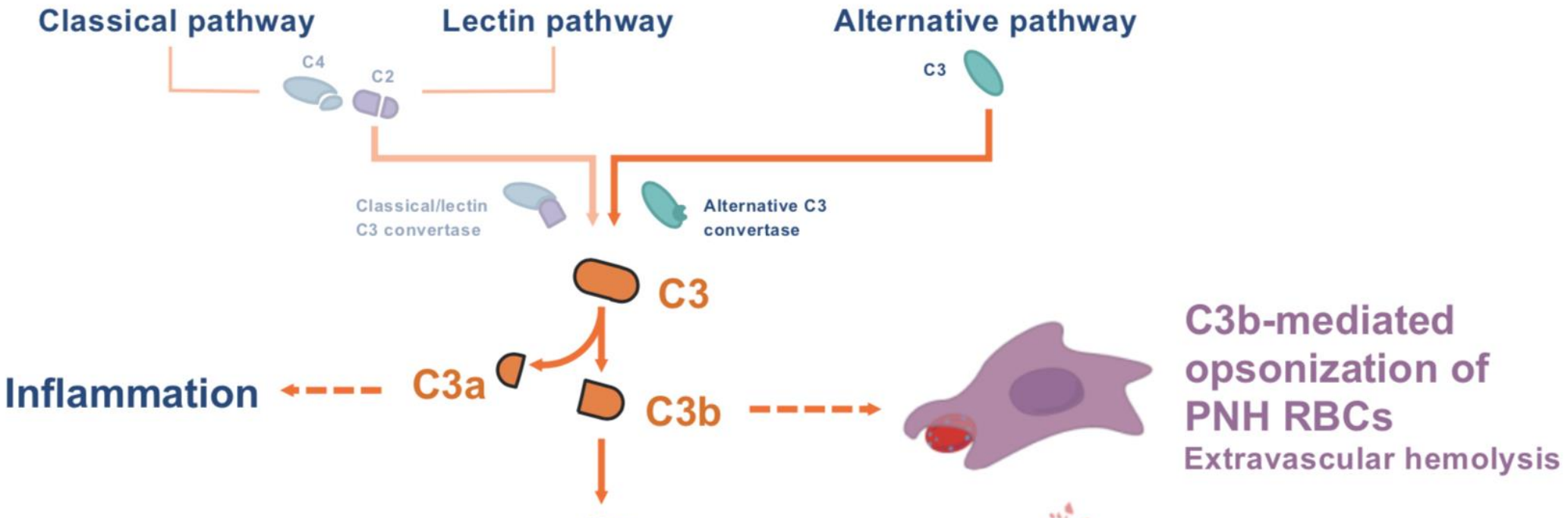


BTH, breakthrough haemolysis; EVH, extravascular haemolysis; MAC, membrane-attack complex; PNH, paroxysmal nocturnal haemoglobinuria.
1. Figure adapted from Notaro R et al. *N Engl J Med* 2022;387:160–166; 2. Figure from personal library of Dr Rosario Notaro.

Extra-vascular hemolysis

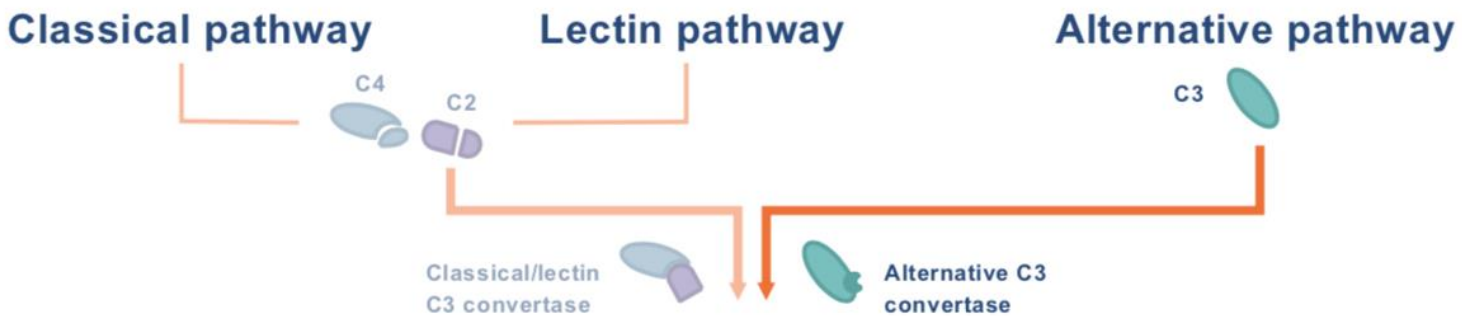


Extra-vascular hemolysis



C5 inhibition

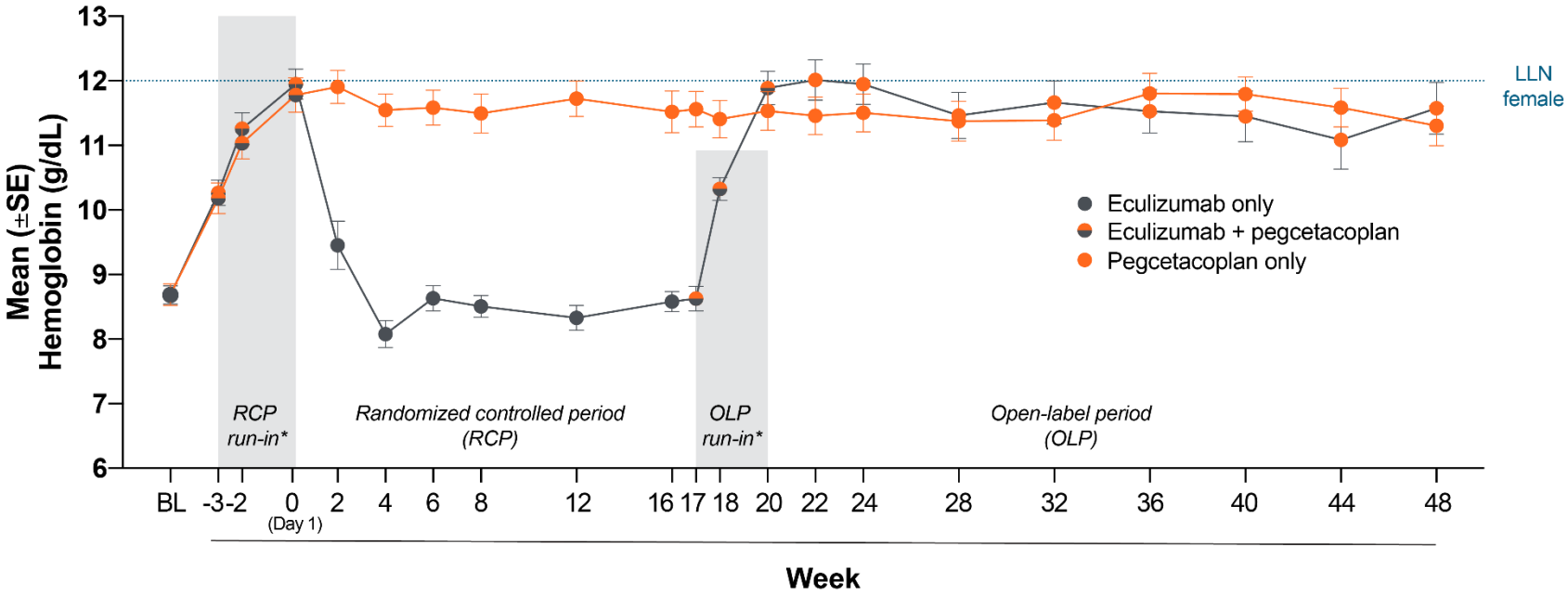
Extra-vascular hemolysis



Proximal inhibition

C5 inhibition

PEGASUS clinical trial (80 patients)
Anti-C3 (Pecetacoplan) – sustained efficacy



*Pegcetacoplan run-in periods: 1) before randomization, for both PEG-to-PEG and ECU-to-PEG treatment groups; and 2) before the open-label period, for the ECU-to-PEG treatment group only
All observed/uncensored for transfusion data

Change from Baseline in Hemoglobin Levels (g/dL)	Week 16	Week 48
PEG-to-PEG, Mean (SD)	2.73 (1.99) n=37	2.47 (1.72) n=33
ECU-to-PEG, Mean (SD)	−0.15 (0.92) n=38	2.93 (2.09) n=30

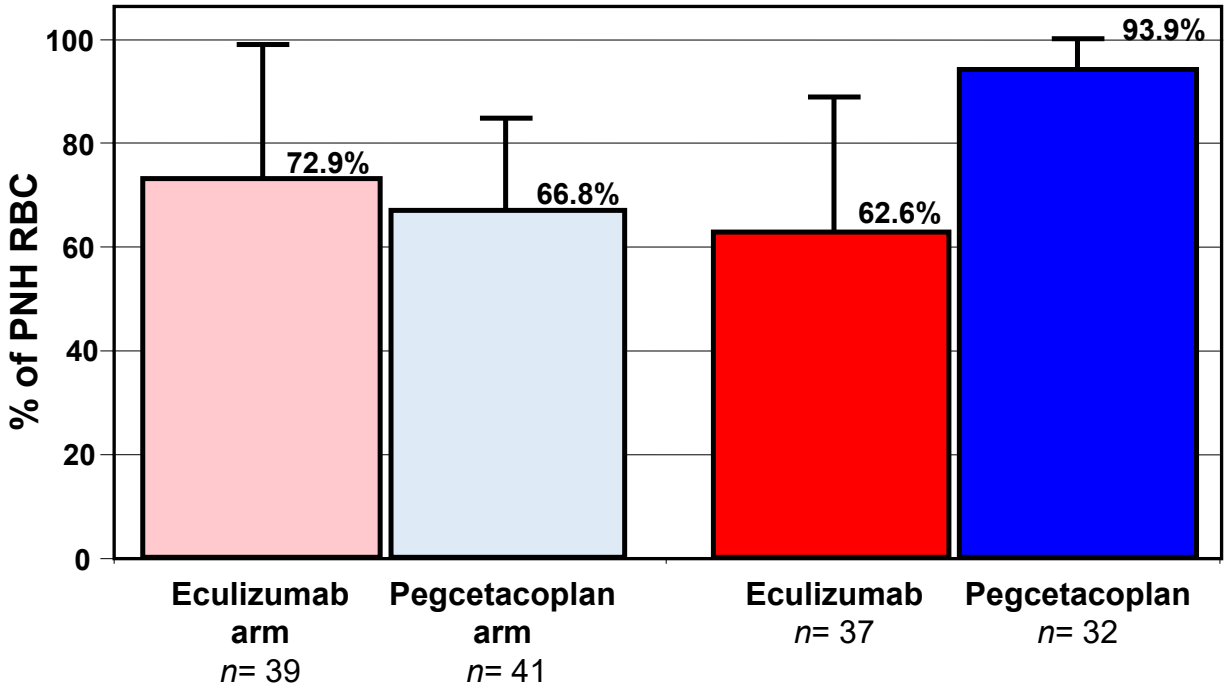
Using all available data regardless of transfusion events.

- **Sustained hemoglobin levels in the PEG-to-PEG** group from Week 16 through Week 48 (no significant difference in hemoglobin levels between Week 16 and Week 48 in the PEG-to-PEG group; p=0.14[a])
- **Significant improvement in hemoglobin levels in the ECU-to-PEG** group from Week 16 through Week 48 (p<0.0001[a])

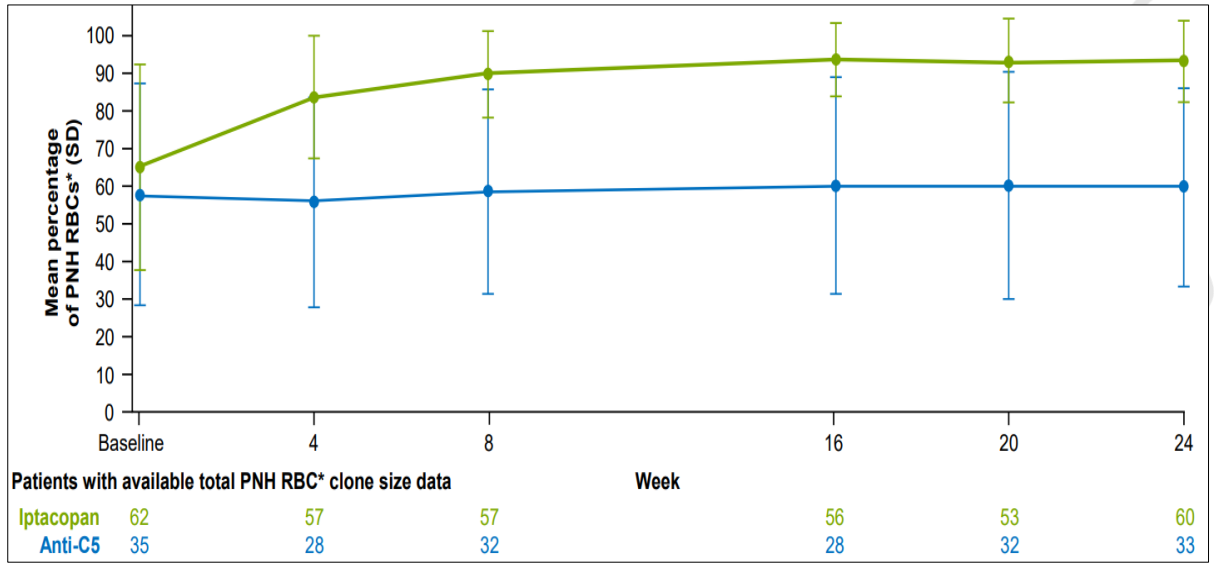
Peffault de Latour et al. *Lancet Haematology* 2021

Proportion of PNH red cells on proximal inhibitors

Pegcetacoplan: Pharmacodynamic endpoints from 16-week randomised period of PEGASUS trial[1a]



Iptacopan: Mean total PNH RBC* clone size (SD) during the 24-week randomised treatment period of APPLY-PNH trial[2b]



*Type II + type III PNH RBCs

[a]PEGASUS is a Phase III open-label, controlled trial to assess the efficacy and safety of pegcetacoplan compared with eculizumab in adults with PNH and haemoglobin levels <10.5 g/dL despite eculizumab therapy. After a 4-week run-in phase in which all patients received pegcetacoplan plus eculizumab, patients were randomised to subcutaneous pegcetacoplan monotherapy (41 patients) or intravenous eculizumab (39 patients) for the 16-week randomized, controlled period.[1]

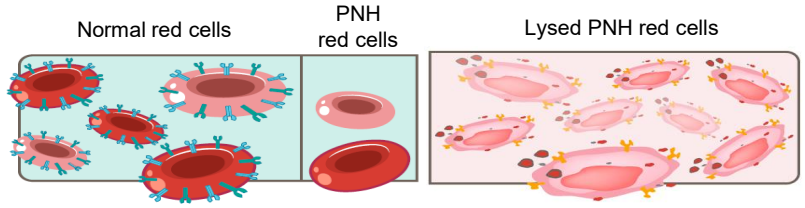
[b]APPLY-PNH is a Phase III, randomised, open-label trial to evaluate the efficacy and safety of twice-daily, oral iptacopan monotherapy (200 mg) for the treatment of PNH compared to anti-C5 therapies (eculizumab or ravulizumab) in adult patients presenting with residual anaemia despite a stable regimen of anti-C5 treatment in the last six months prior to randomisation.[4]

Ecu, eculizumab; IPTA, iptacopan; Pegcet. pegcetacoplan; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell; SD, standard deviation.

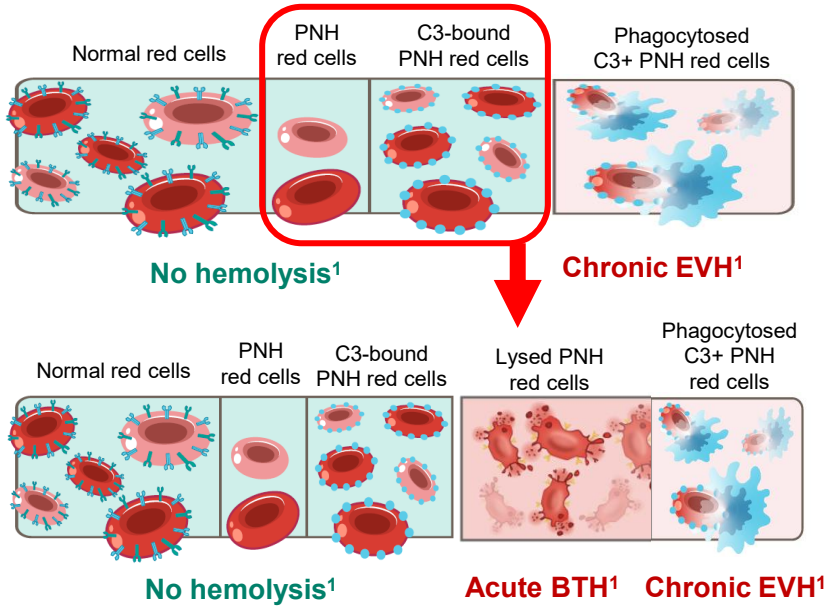
1. Hillmen P et al. *N Engl J Med.* 2021;384(11):1028-1037 (Supplementary Appendix); 2. Risitano AM et al. Oral presented at the European Hematology Association 2023 Congress, held in Frankfurt, Germany and virtually on 8–11 June 2023;
3. Aspaveli EU SmPC; 4. Peffault de Latour R et al. *NEJM* 2024

Breakthrough hemolysis (clinical level)

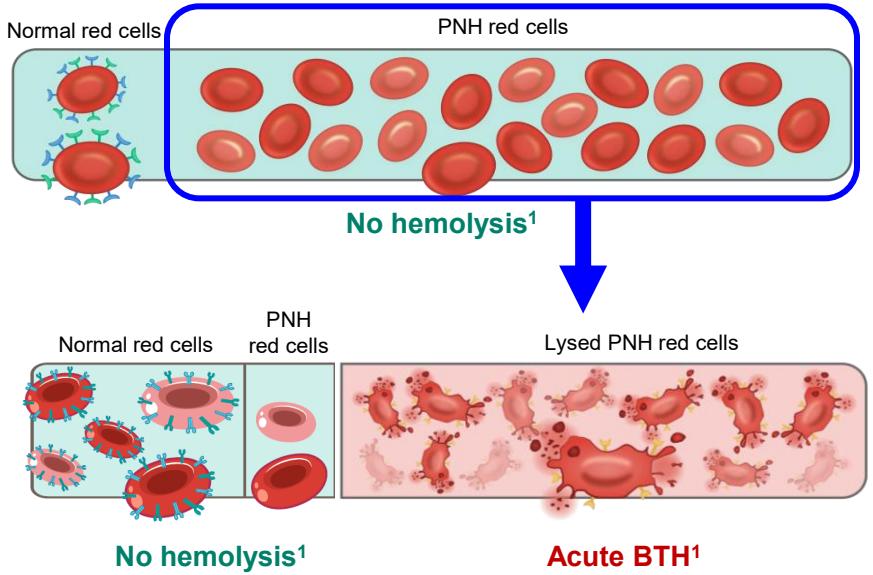
Untreated PNH



Incomplete Terminal inhibition



Incomplete Proximal inhibition



Figures adapted from Notaro R et al. *N Engl J Med* 2022[1]
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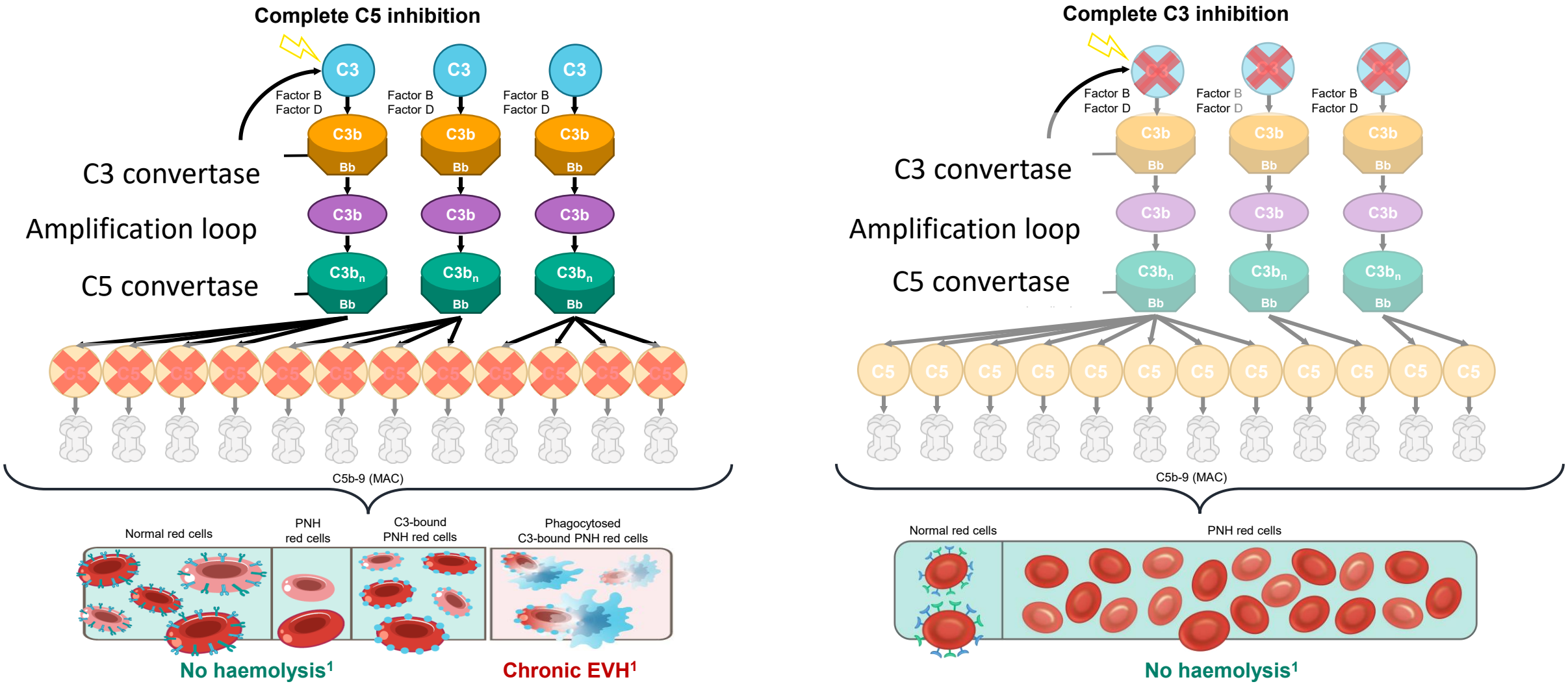
1. Notaro R, Luzzatto L. *N Engl J Med.* 2022;387(2):160–166.

Breakthrough hemolysis (complement level)



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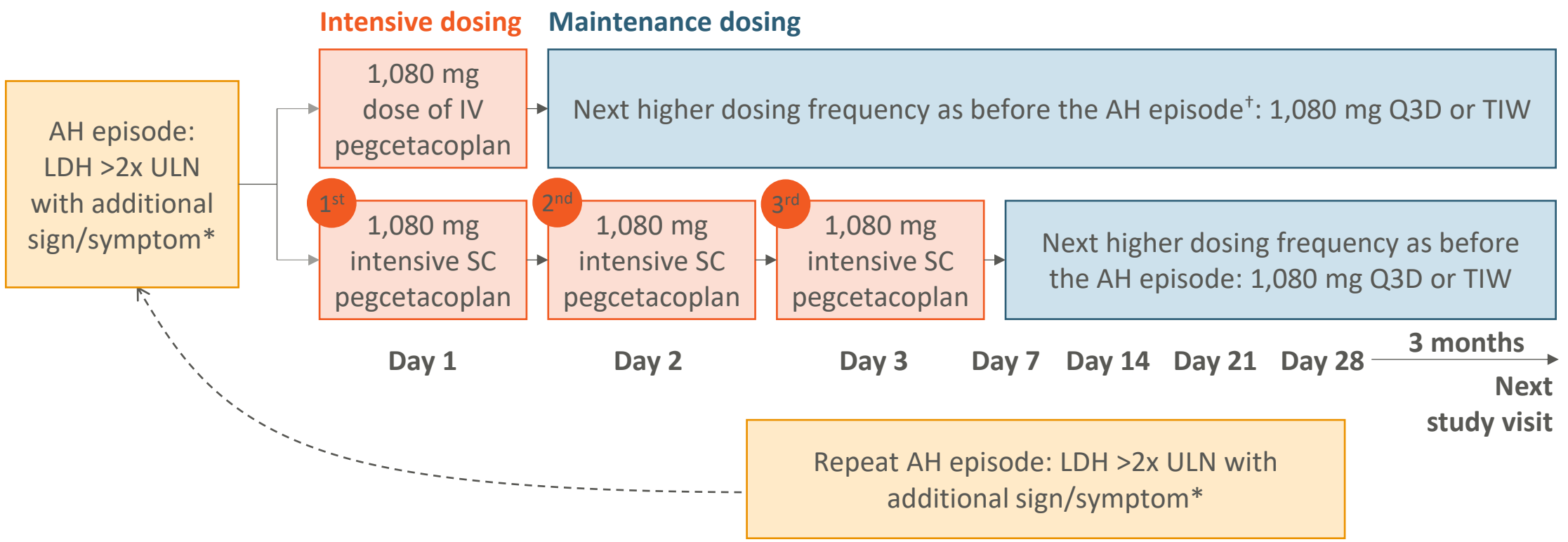
1. Notaro R, Luzzatto L. *N Engl J Med.* 2022;387(2):160–166.

307 Acute hemolytic sub-study
Intensive pegcetacoplan treatment regimens

Patients who had an acute hemolytic (AH) event warranting acute intervention (determined by investigator) were eligible to receive intensive pegcetacoplan dosing

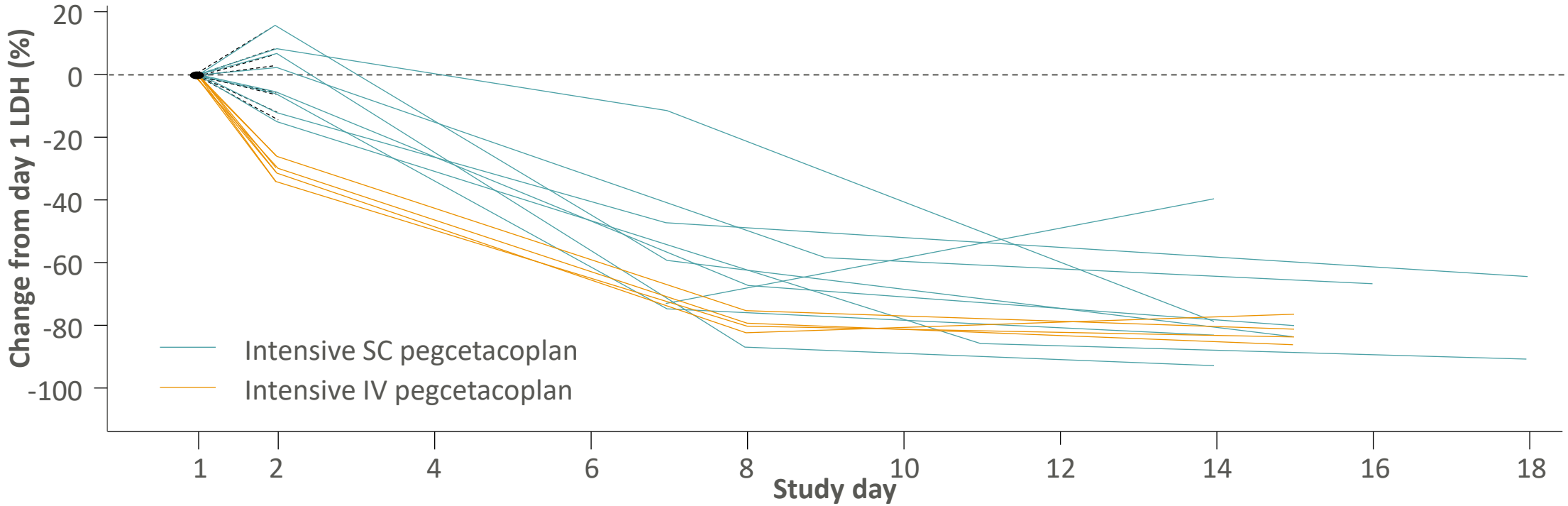


* e.g., decreased haemoglobin, haemoglobinuria, or fatigue.
† Maintenance dosing could not exceed 1,080 mg TIW.
AH, acute haemolysis; IV, intravenous; LDH, lactate dehydrogenase; Q3D, every 3 days; SC, subcutaneous; TIW, 3 times weekly; ULN, upper limit of normal.

Griffin et al. *Blood Advances* 2024

307 Acute hemolytic sub-study
Intensive pegcetacoplan treatment regimens

Overall, 13 out of 137 patients (aged 20 to 72 years) in the OLE received intensive pegcetacoplan treatment at the time of analysis (PEGASUS: n=10; PRINCE: n=2; PADDOCK: n=1)



- **LDH decreased** within the first week, with 9/13 patients (69%), achieving LDH <2x ULN* at day 14-19
- **Mean time to resolution** of AH event was **18.8 days** (as reported by investigator)
- After the initial drop, **haemoglobin levels improved** for all patients **regardless** of **transfusion status**

*LDH ULN: 226 U/L.
AH, acute haemolysis; IV, intravenous; LDH, lactate dehydrogenase; SC, subcutaneous; ULN, upper limit of normal.

Griffin et al. *Blood Advances* 2024

Real world experience

Retrospective analysis – UK & France - May 2019 and August 2023

48 patients **currently or previously treated with pegcetacoplan** were included

EVH on C5 inhibitors was the **indication for switch to pegcetacoplan** (eculizumab n=29; ravulizumab n=16; others n=3)

12/48 patients had **participated in PEGASUS**, continuing treatment after trial completion

73% of patients **required blood transfusion** within the previous 12 months

20.2 **months** was the mean **duration of pegcetacoplan** treatment

22/48 patients had a **history of aplastic anemia**

Largest real-world cohort of PNH patients treated with pegcetacoplan in second line

EVH, extravascular haemolysis; PNH, paroxysmal nocturnal haemoglobinuria.

Griffin et al. *AJH* 2024

Real world experience

Retrospective analysis – UK & France - May 2019 and August 2023

	Start of pegcetacoplan (patients with data available)	3 months post pegcetacoplan (patients with data available)	Mean change (patients with paired data available)
Mean hemoglobin, g/dL	9.1 (47/48)	11.6 (42/48)	**+2.2** (41/48)
Mean reticulocyte count, $\times 10^9$/L	205 (38/48)	107 (30/48)	**-133** (28/48)
Mean LDH, ×ULN	0.82 (44/48)	0.87 (41/48)	**-0.2** (37/48)

Rapid increase in hemoglobin, reduction in reticulocytes and maintained LDH confirm that **pegcetacoplan** is able to **address both intra- and extravascular hemolysis**

EVH, extravascular haemolysis; PNH, paroxysmal nocturnal haemoglobinuria.

Griffin et al. *AJH* 2024

Real world experience

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Mean LDH, ×ULN	0.82 (44/48)	0.87 (41/48)	-0.2 (37/48)

BTH events were manageable - successful clinical management included daily SC pegcetacoplan for 3 days, single eculizumab doses and/or blood transfusions

No drug discontinuation

EVH, extravascular haemolysis; PNH, paroxysmal nocturnal haemoglobinuria.

Griffin et al. *AJH* 2024

Mr B (DOB: March 31th 1984)

- **Initially randomized to Pegcetacoplan**
- **November 2019 – cholecystitis with peritonitis:**
  - Massive breakthrough hemolysis with ICU admission
  - Hb: 5.5 g/dL; reticulocytes 300 G/L; Platelets: 30 G/L; Neutrophils: 0.5 G/L
  - Dialysis for acute kidney failure / mechanical ventilation
  - Documented infections to E Coli, K Oxytoca et E Cloacae
  - Deep vein thrombosis + Budd Chiari syndrome + Mesenteric veins thrombosis
  - **> Decision to stop Pegcetacoplan and back to treatment by Eculizumab**
- **March 2021:**
  - Finally discharged from the hospital
  - Back to initial hematological situation (monthly transfusion in RBC)
  - **> Decision to switch to Ravulizumab in June 2022**
- **June 2023: agreed to resume Pegcetacoplan (commercial access) and doing well since then**

Conclusion

- Clinically significant EVH in 30/40% of patients under C5 inhibition who will benefit from proximal blockade
- If proximals, possible severe breakthrough hemolysis
  - Patient compliance is mandatory under treatment
  - Information / education with patients is essential
  - Be ready to react quickly
- Particular situations with no (very few) experience with proximal complement inhibitors: pregnancy etc
- Long term follow-up needed
  - Infections
  - Auto-immune disease
  - Cancers

Thank You!

The French Reference Center for aplastic anemia and PNH in Paris

Saint-Louis Hospital

Robert Debré Hospital

Institute of Hematology, IUH St-Louis

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N Vasquez, W. Cuccuini, J Soulier (Fanconi team),

C Kannengiesser, E Lainey, L Da Costa (Telomeres team)

Véronique Frémeaux-Bacchi, Magali Legarf-Tavernier, Oriane Wagner-Ballon (PNH team)

APLASIE MEDULLAIRE centre de référence

MaRIH
Filière de santé Maladies Rares ImmunoHématologiques

SFGM TC
Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

2016 EBMT
European Society for Blood and Marrow Transplantation