APLASIE MEDULLAIRE
centre de référence

Inhibiteurs Proximaux & HPN

Quels patients sont éligibles ?

MaRIH
Filière de santé Maladies Rares ImmunoHématologiques

Journée annuelle CRMR CeRAMIC, 3 Octobre 2025

centre de référence
maladies rares

Liens d’interêts

- Grants ou contrats APHP : Alexion (AstraZeneca Rare Disease), Novartis, Sobi & Pfizer
- Honoraires individuels : Alexion (AstraZeneca Rare Disease), Novartis, Pfizer, Sobi & Jazz Pharma
- Congres ou transports : Novartis & Sobi

AMM

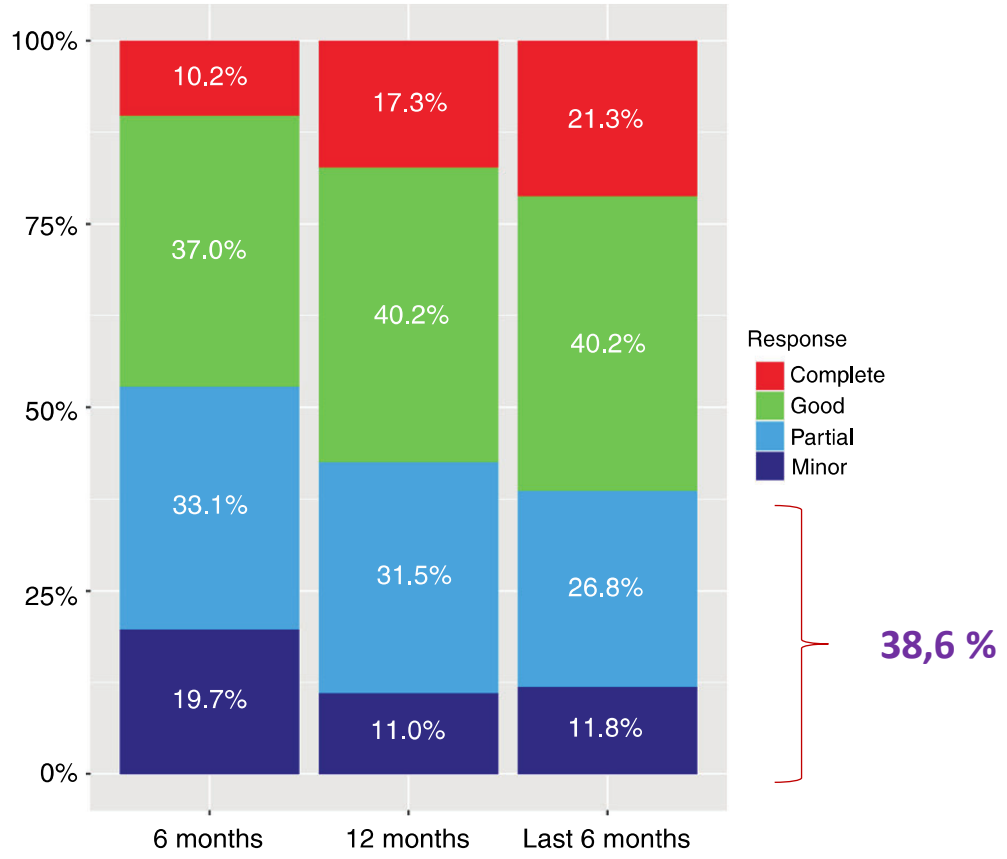
- Pegcetacoplan : traitement de l'HPN chez les patients adultes anémiques après un traitement par un inhibiteur de complément C5 pendant au moins 3 mois, uniquement en cas de taux d'Hb < 10,5 g/dl.
- Iptacopan : le traitement des patients adultes atteints d'HPN et présentant une anémie hémolytique symptomatique après un traitement par inhibiteur du complément C5 pendant au moins 6 mois.
- Danicopan : en association avec le ravulizumab ou l'eculizumab dans le traitement des patients adultes atteints d'HPN présentant une anémie hémolytique symptomatique après un traitement par inhibiteur du complément C5 pendant au moins 6 mois

HPN 1ère ligne : Inhibiteurs terminaux – Eculizumab/Ravulizumab

Etude internationale multicentrique (Paris, Naples/Avellino, London, Florence, São Paulo, and Ribeirão Preto)

160 patients HPN traités par eculizumab
Médiane de durée 5,8 ans (0.5–14.5)
(10% < 18 mois)
Censurés : nouvel anti C (35) ou HSCT (2)
Issue étude

- 83 % : 900 mg / 14 jours
- 17% : 1200 mg ou intervalle < 14 jours



Debureaux, PE. Bone marrow transplant 2021

HPN 1ère ligne : Inhibiteurs terminaux – Eculizumab/Ravulizumab

509 pts with **PNH eculizumab / ravulizumab** Mai 2002 & Juillet 2022

474 pts ECU (16% dose > 900) dt 237 switch RAVU (2021)

35 pts RAVU d'emblée

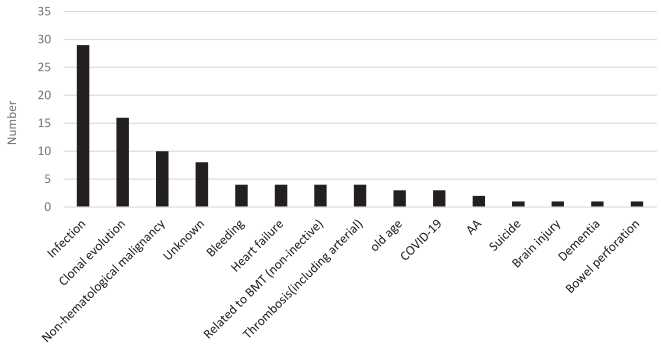
20% des pts Hb « normale »

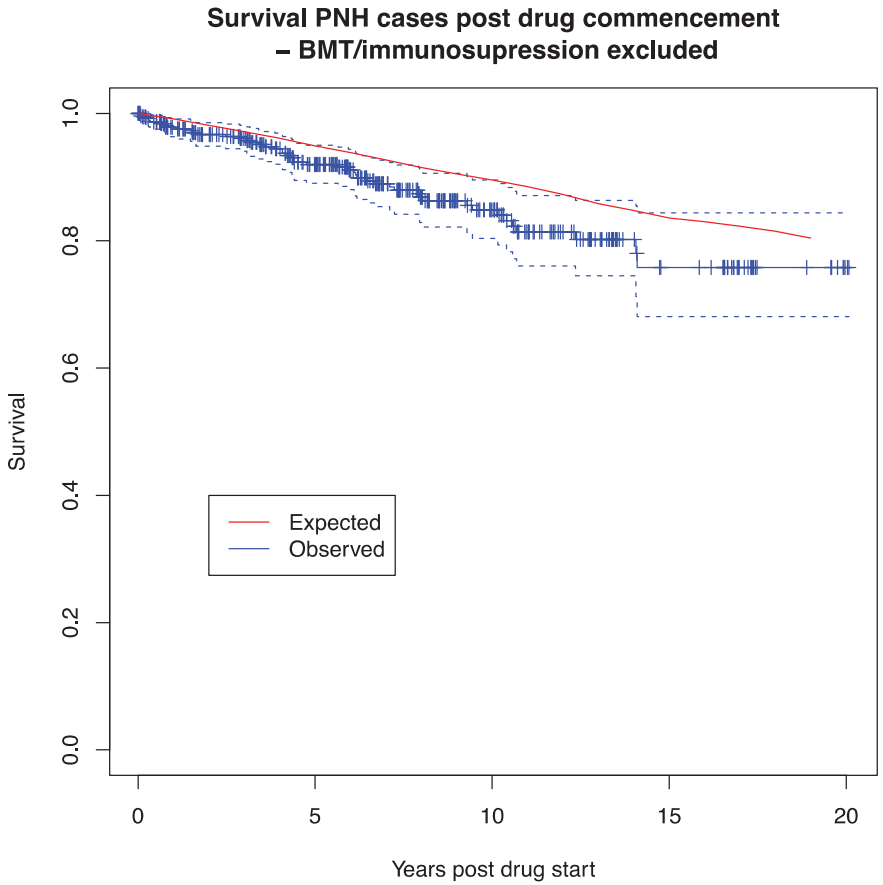
27% toujours transfusés

11 cas septicemie à Meningo / 10 pts dont 1 fatale

23 pts thrombose sous traitement

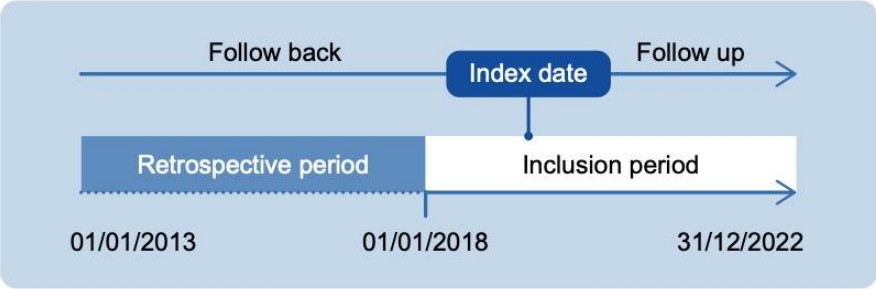
20 pts (3.9%) arrêt car clone HPN < 10%





Kelly, R. Blood 2024

HPN 1ère ligne : Inhibiteurs terminaux – Eculizumab/Ravulizumab

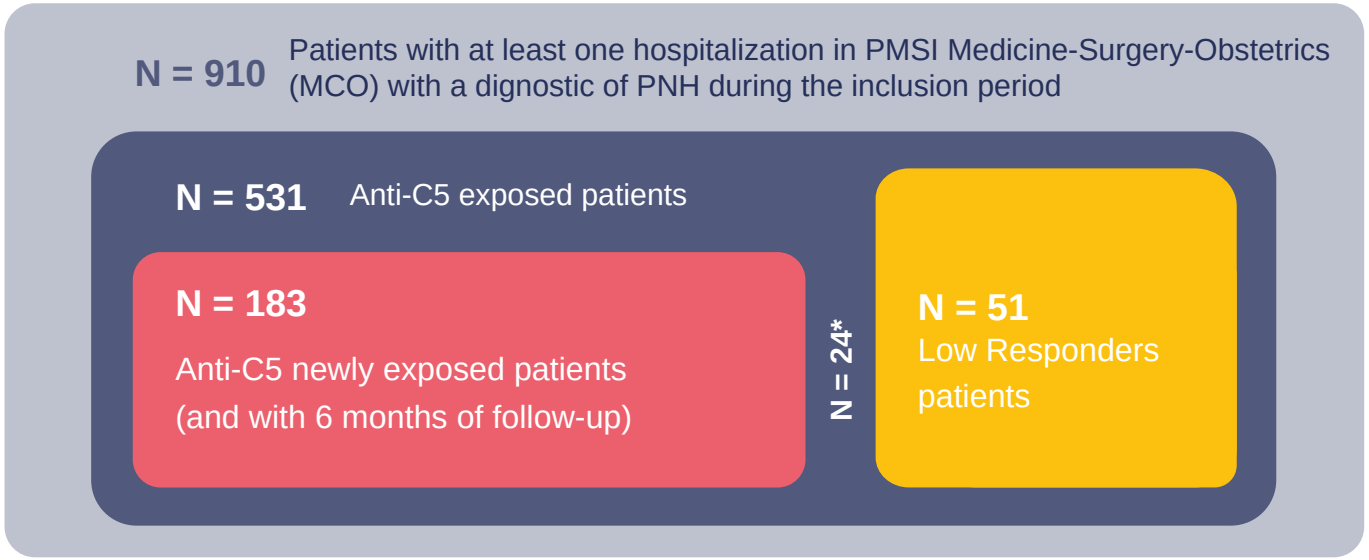


Patients exposed to anti-C5 drugs: Patients with at least one dispencing of anti-C5 drugs during the extraction period.

Newly exposed: patient not exposed to anti-C5 during the retrospective period.

Low Responders: Patients exposed to an anti-C5 who have had either a switch to an anti-C3 (outside clinical trials), or an increase in the number of transfusions: at least 2 consecutive transfusions over a one-year period starting 6 months after initiation of anti-C5.

Alcazer, V. ISPOR 2024 : abstract

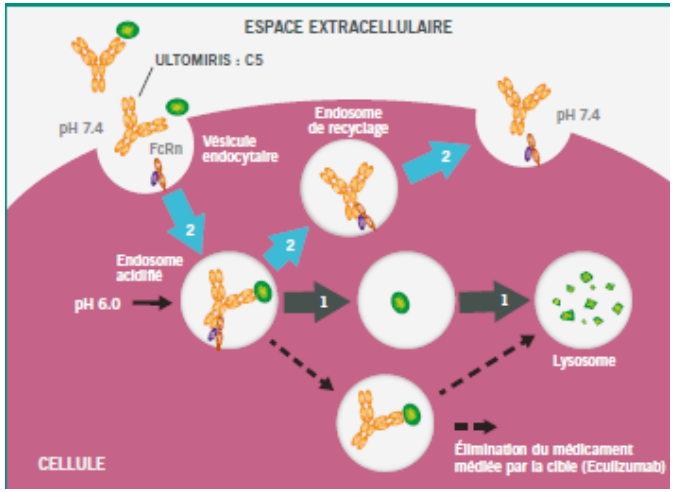


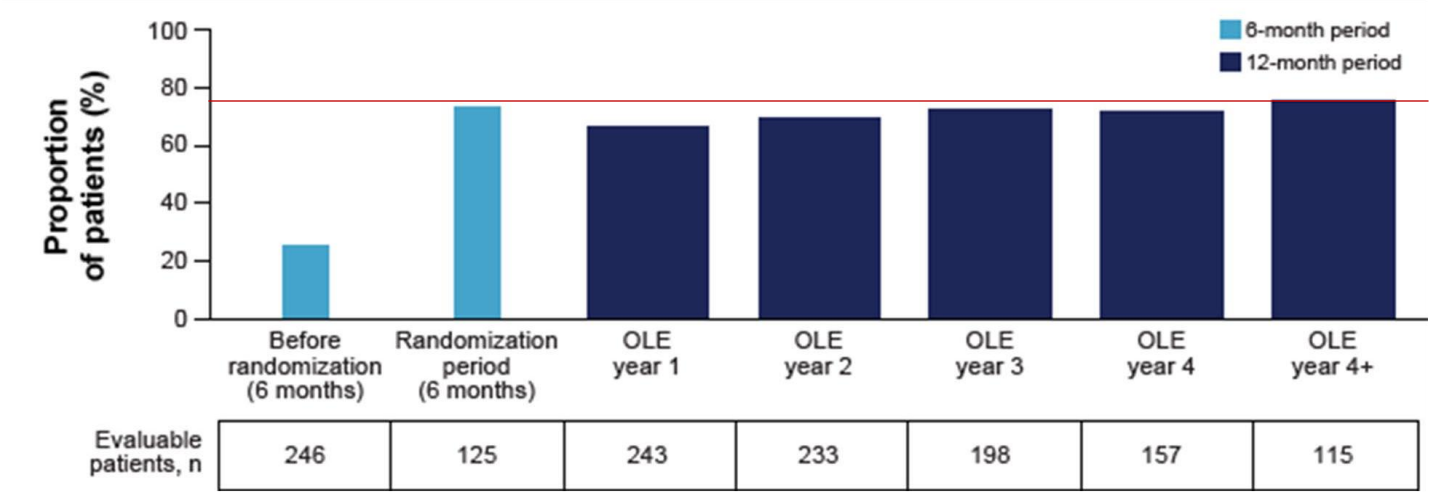
*Anti-C5 newly exposed & low responders patients

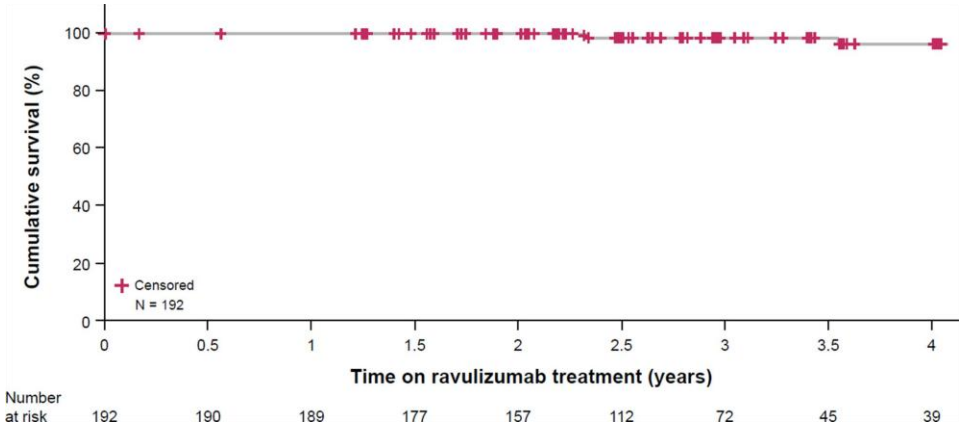
N	183	51
Transfusions	**Newly exposed**	**Low responders**
Patients with transfusions	N=85 46.5%	N=50* 98.0%
Mean number of transfusions (all causes)	3.8 (± 9.0)	7.8 (± 9.3)
Patients with transfusions (PNH causes)	N=54 29.5%	N=50* 98.0%
Mean number of transfusions (PNH causes)	1.3 (± 4.1)	5.02 (± 6.8)

*patients requiring antiC3 were considered as low responder independantly of the numbers of transfusions.

HPN 1ère ligne : Inhibiteurs terminaux – Eculizumab/Ravulizumab

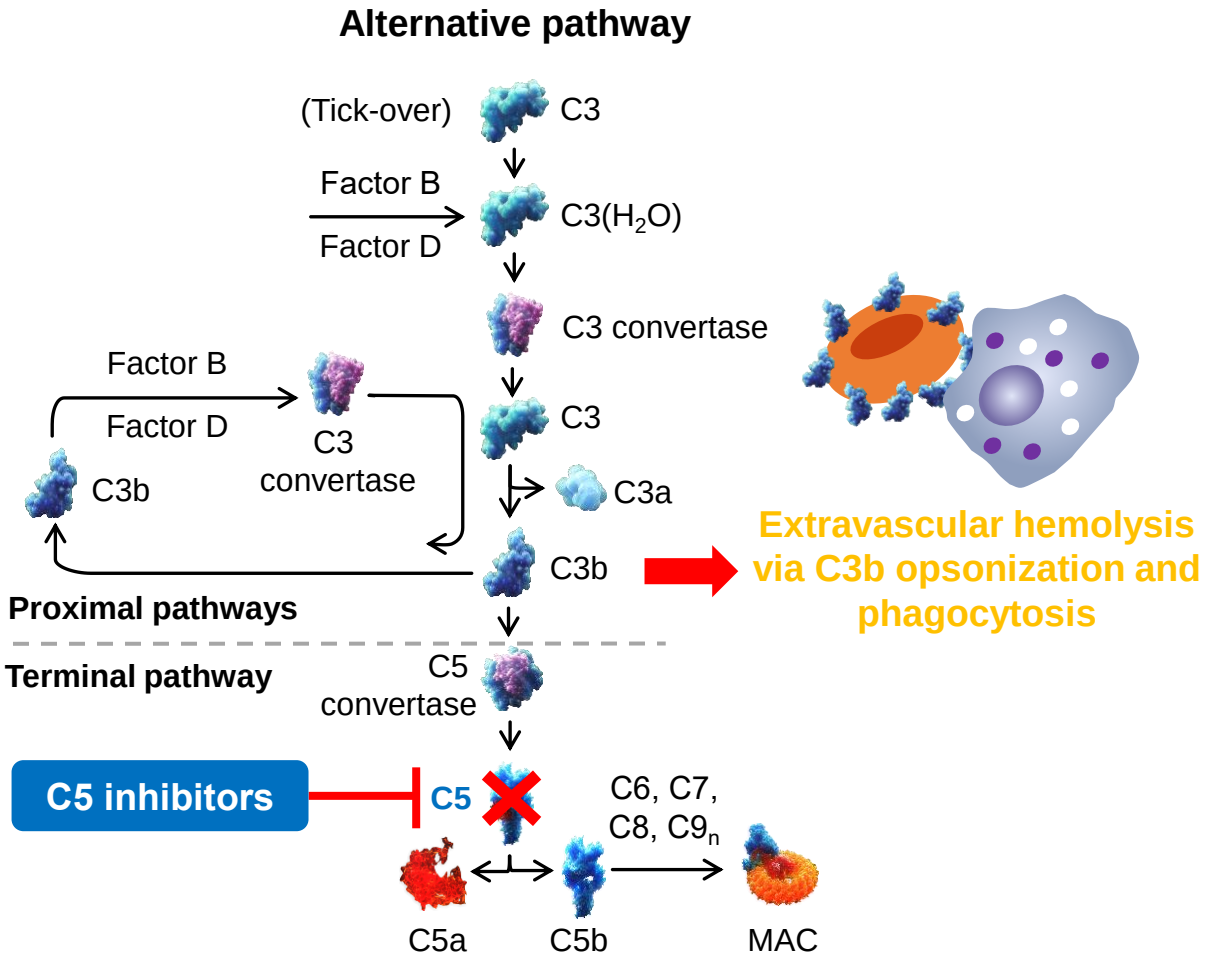


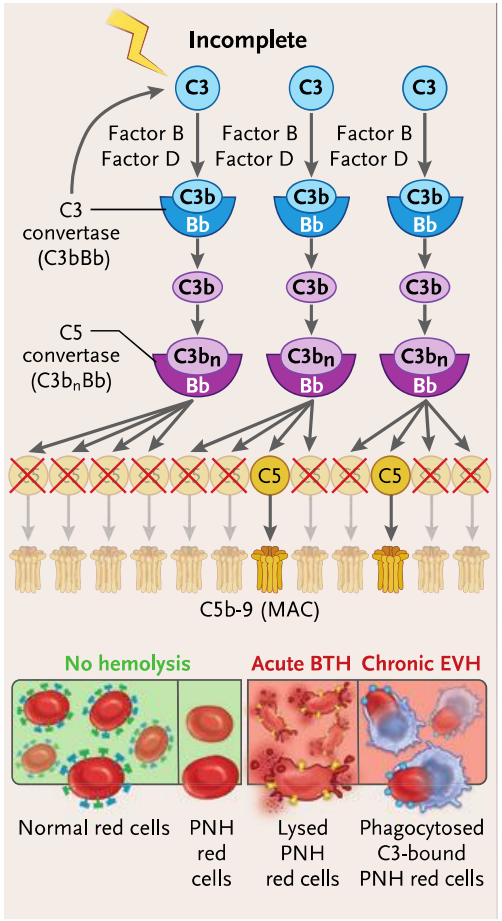




Kulasekararaj, A. Annals of Hematology 2025

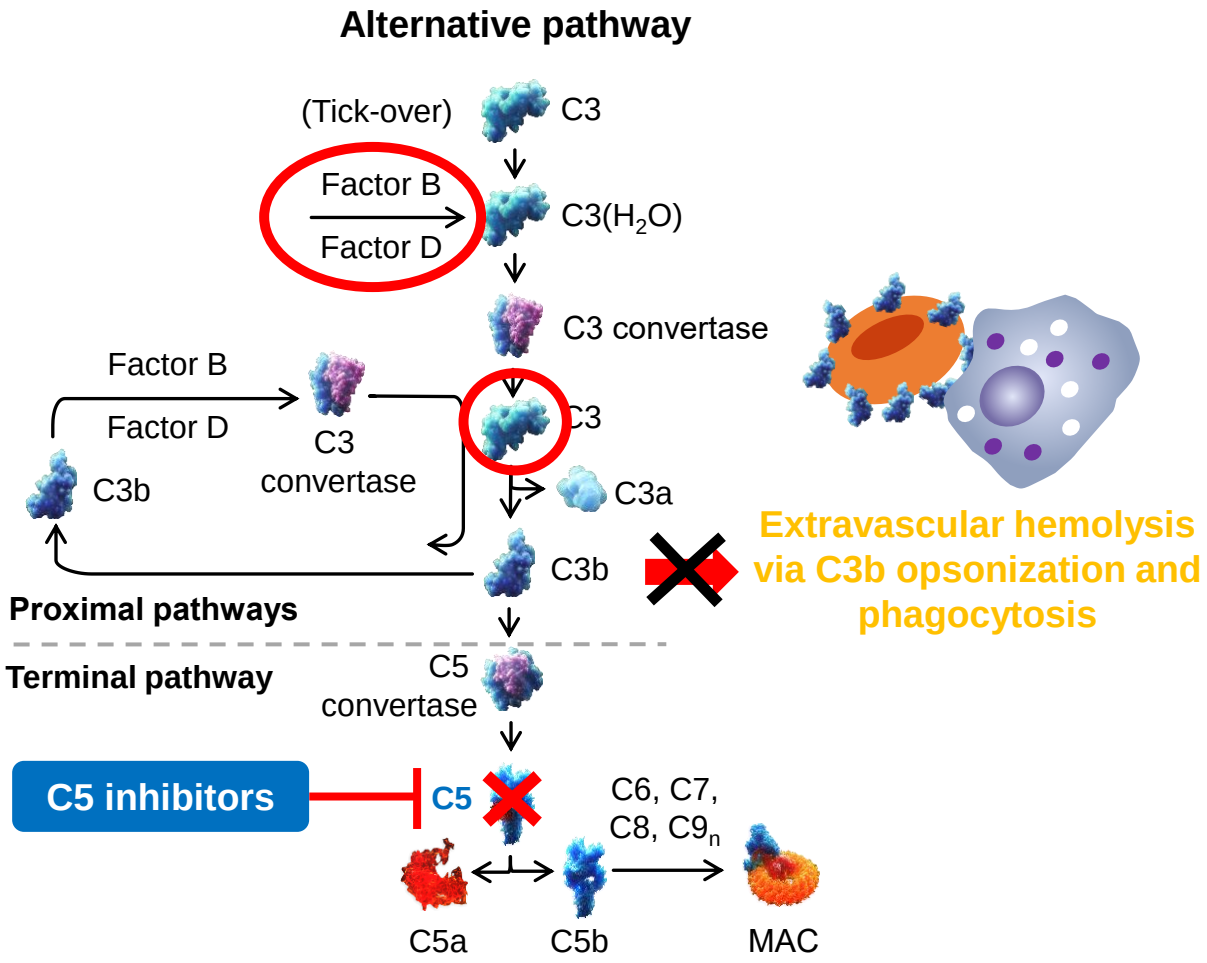
Hémolyse extravasculaire – Conséquence





Notaro & Luzzatto, NEJM 2022

Inhibiteur Proximaux – Impacts



Extravascular hemolysis via C3b opsonization and phagocytosis

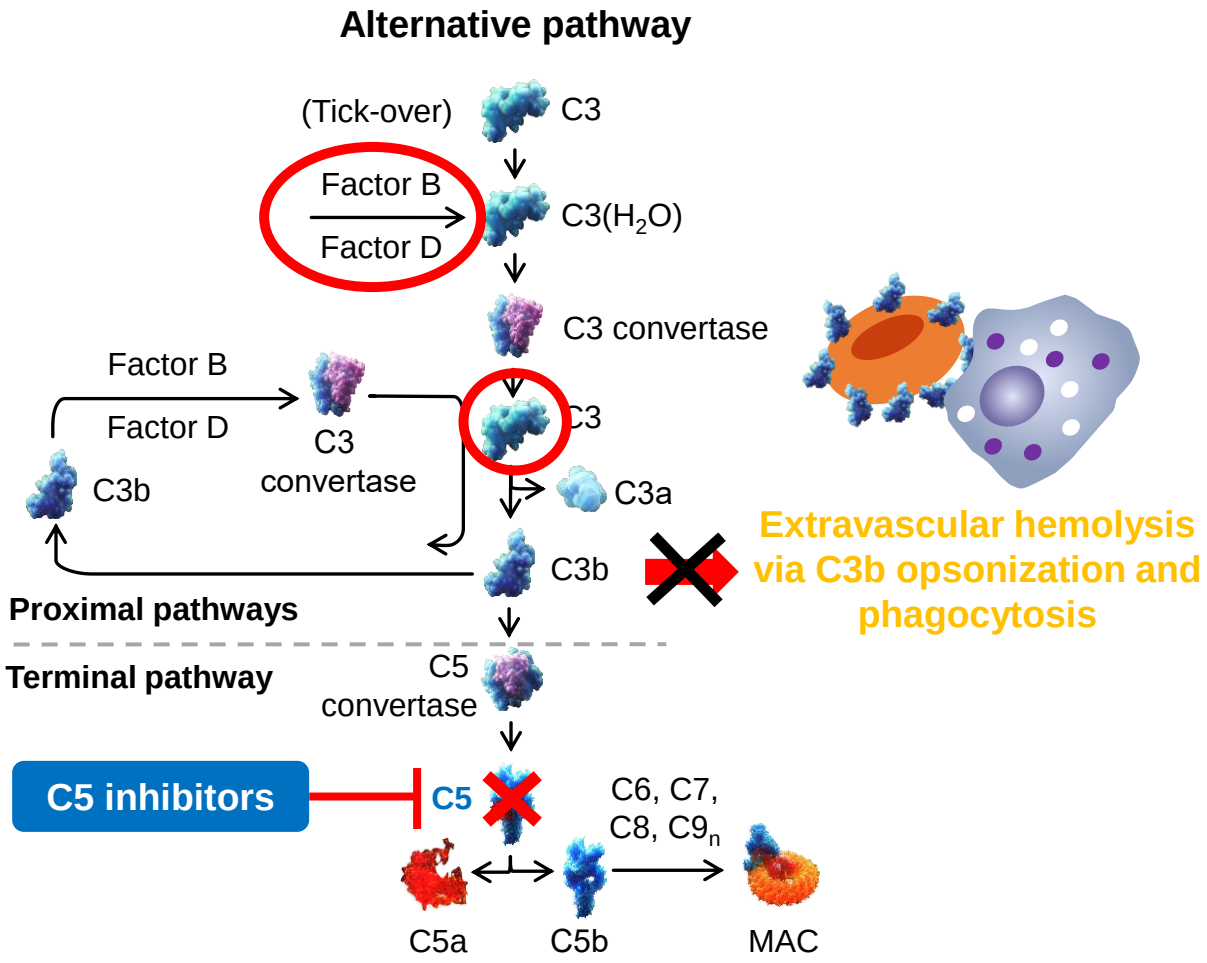
Inhibiteur Proximaux - AMM

Anti C3 : Aspavelli, SC x 2 à 3 / semaines

Anti Facteur B : Ipactopan, PO x 2 / jour

Anti Facteur D : Voydeya, PO x 3 / jour + anti C5

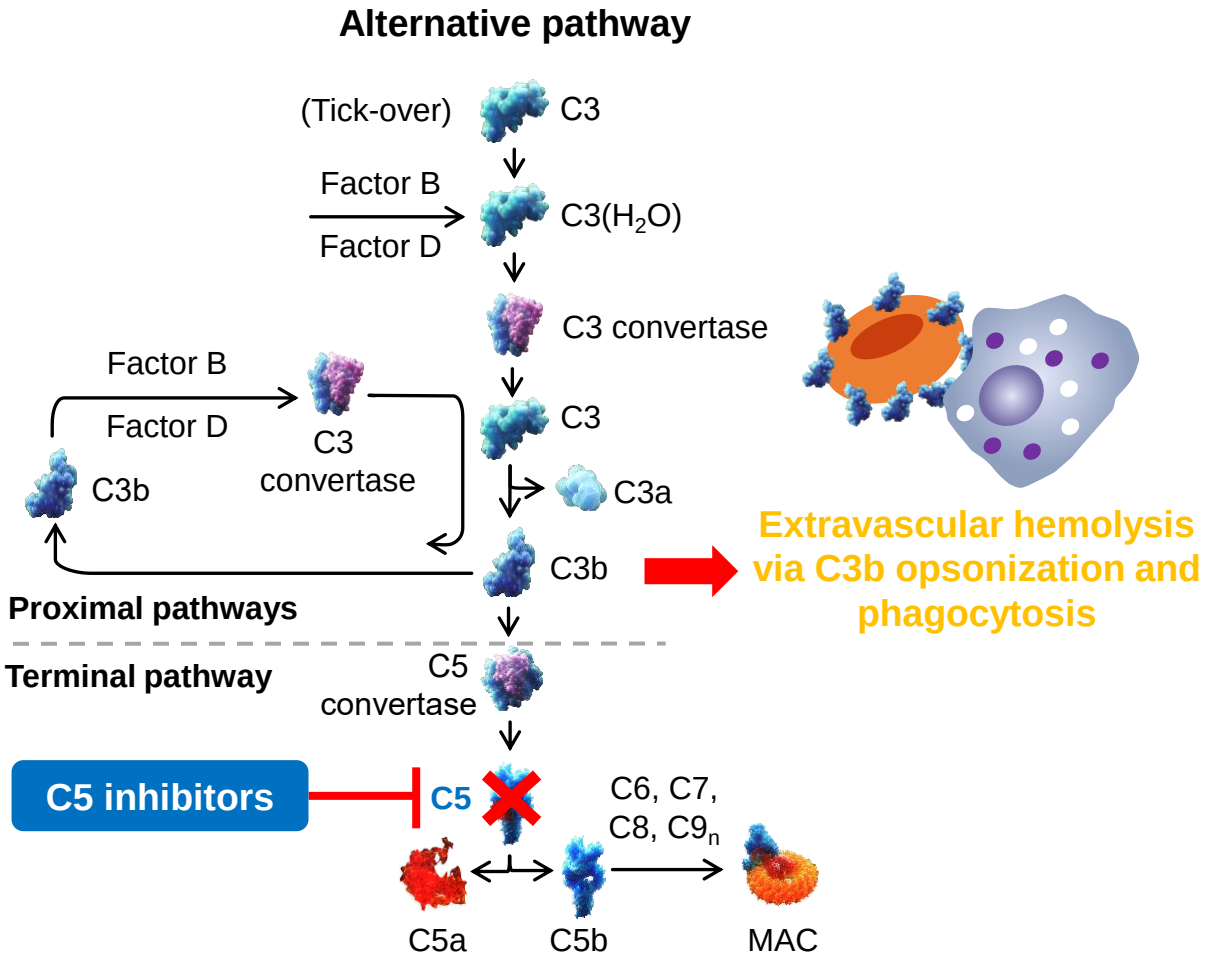
Inhibiteur Proximaux – Impacts



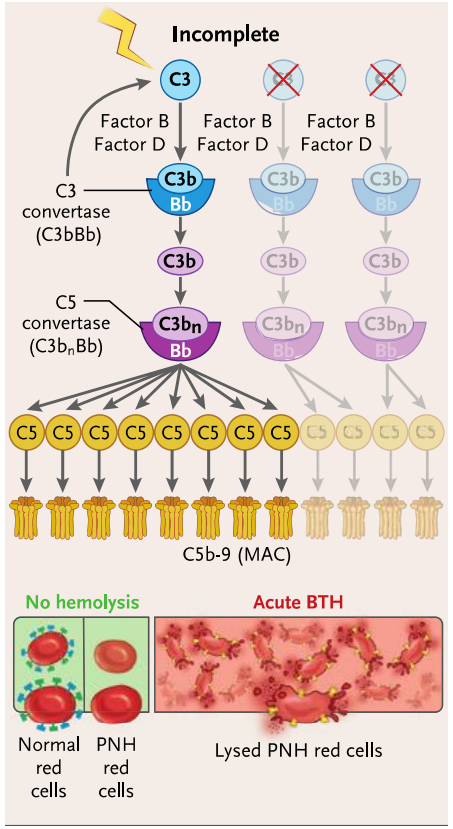
Extravascular hemolysis via C3b opsonization and phagocytosis

- ↑ **Hémoglobine**
- ↓ **réticulocytes**
- ↓ **GR CD59-C3b+**
- ↑ **taille du clone érythrocytaire**
- → **clone PNN & mono**

Hémolyse extravasculaire – Conséquence



Extravascular hemolysis via C3b opsonization and phagocytosis



Notaro & Luzzatto, NEJM 2022

Iptacopan

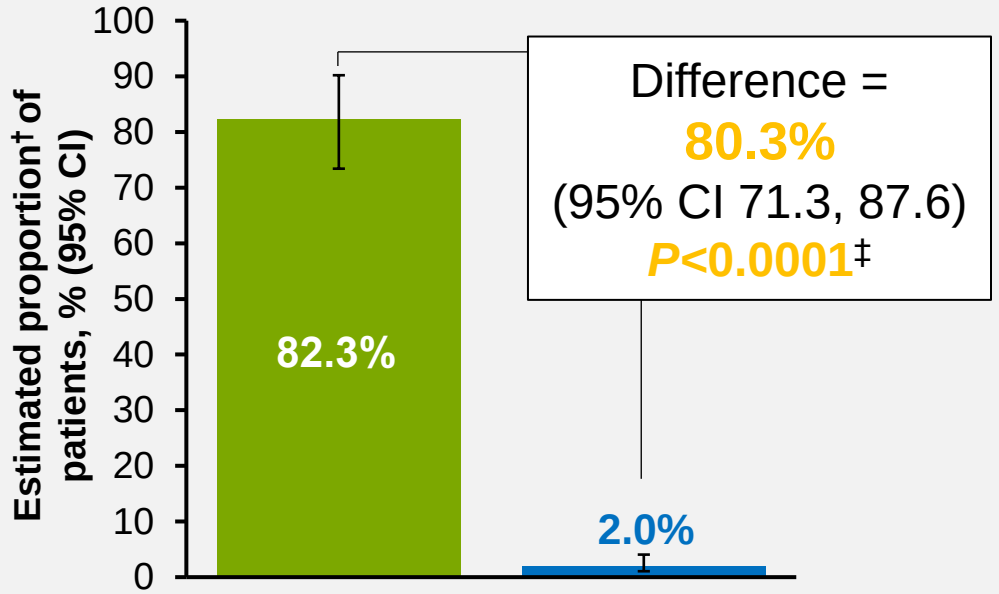
Increase from baseline in Hb of ≥2 g/dL in the absence of RBC transfusions

Observed

51/60* patients treated with **iptacopan**

0/35 patients treated with **anti-C5**

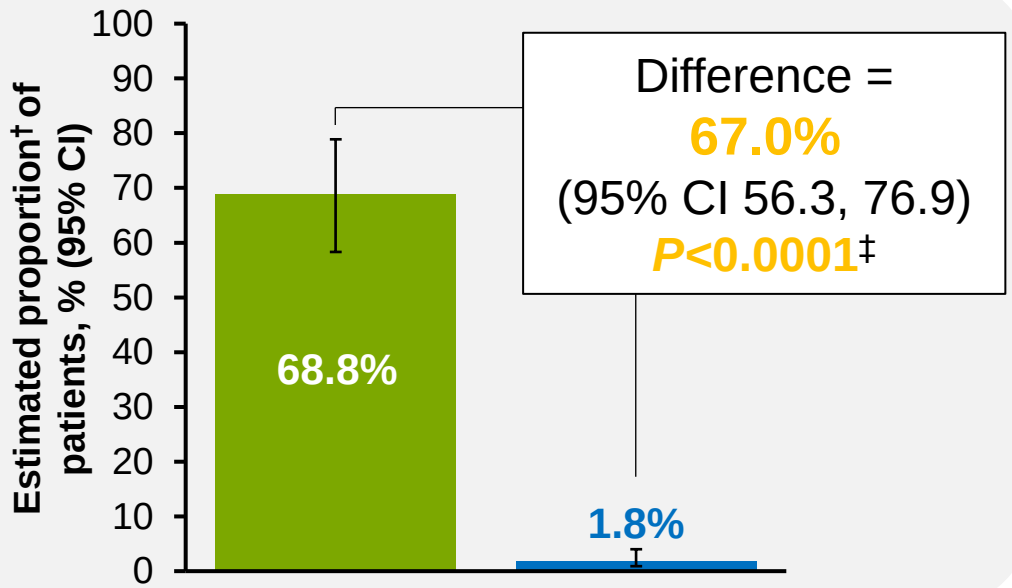
Population estimate



Hb ≥12 g/dL in the absence of RBC transfusions

42/60* patients treated with **iptacopan**

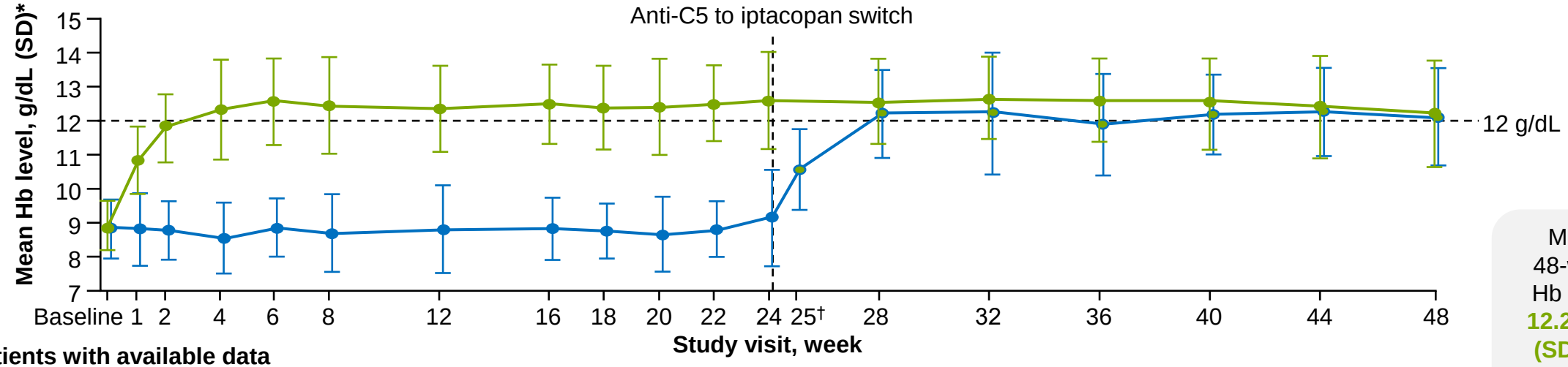
0/35 patients treated with **anti-C5**



*2/62 patients in the iptacopan arm had missing data between Days 126 and 168 so were not evaluable based on observed data; †Marginal proportions, differences in marginal proportions and 95% CIs were calculated using a logistic regression model using the Firth correction that adjusted for baseline covariates and accounted for missing data and the possibility of no patients meeting the primary endpoint criteria in the anti-C5 arm; consequently, the treatment effect of iptacopan is underestimated and the treatment effect of anti-C5 is overestimated. Marginal proportions reflect the population average probability of a patient meeting the primary endpoint criteria; ‡*P* values are two-sided and unadjusted.
CI, confidence interval

Iptacopan

Mean baseline Hb level:
8.9 g/dL (SD 0.7)
8.9 g/dL (SD 0.9)



Mean 48-week Hb level:
12.2 g/dL (SD 1.6)
12.1 g/dL (SD 1.4)

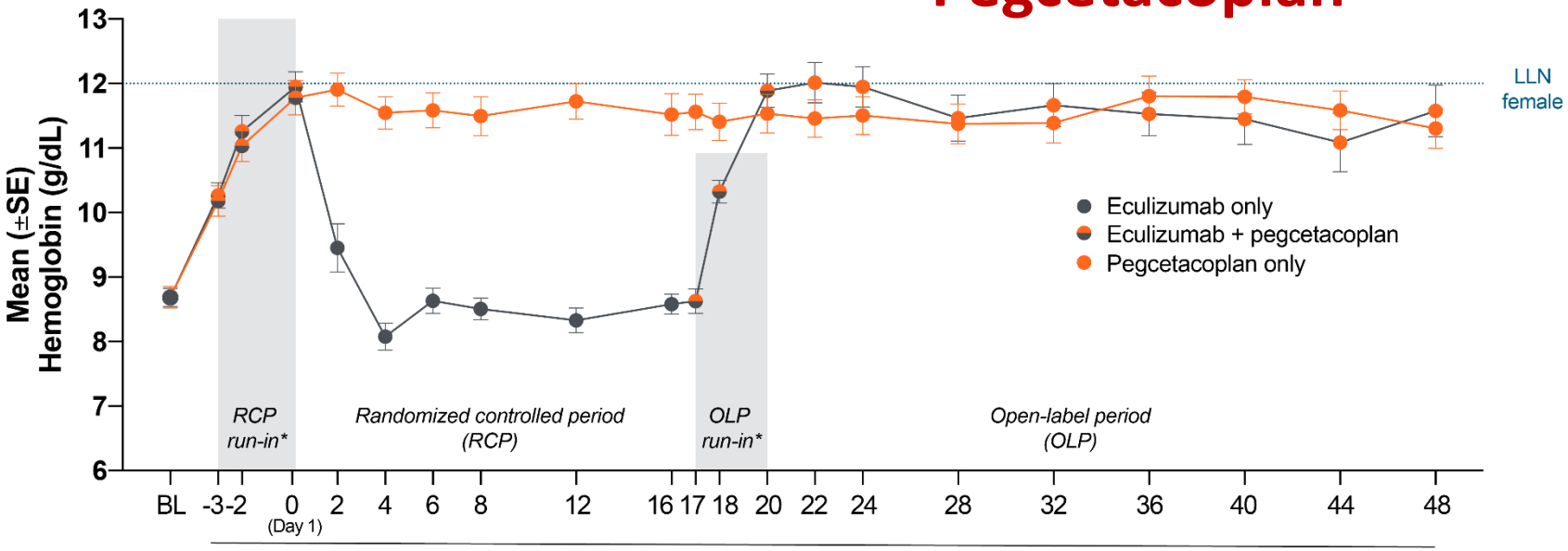
Patients with available data

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

	Treatment arm	Adjusted mean change from baseline at Week 48 (95% CI)	Adjusted mean difference in change from baseline (95% CI): Week 48 versus Week 24[§]
Change from baseline in Hb level (g/dL)[‡]	Iptacopan	**+3.35** (3.04, 3.67)	**−0.41** (−0.80, −0.01)
	Anti-C5 to iptacopan	**+3.36** (2.94, 3.79)	**+3.02** (2.49, 3.56)

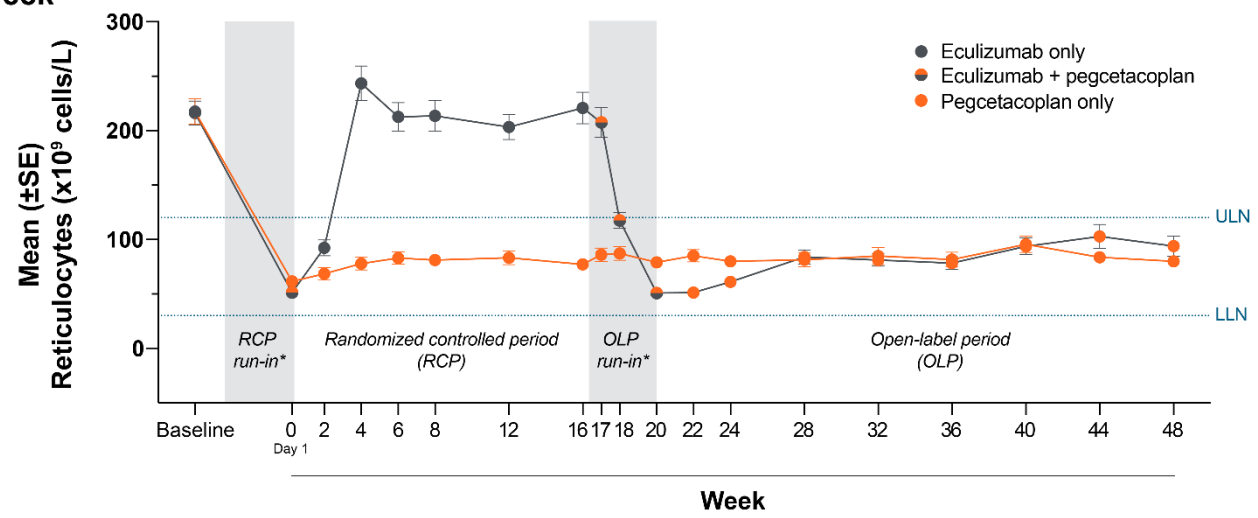
Risitano *et al. Lancet Haem* 2025

Pegcetacoplan



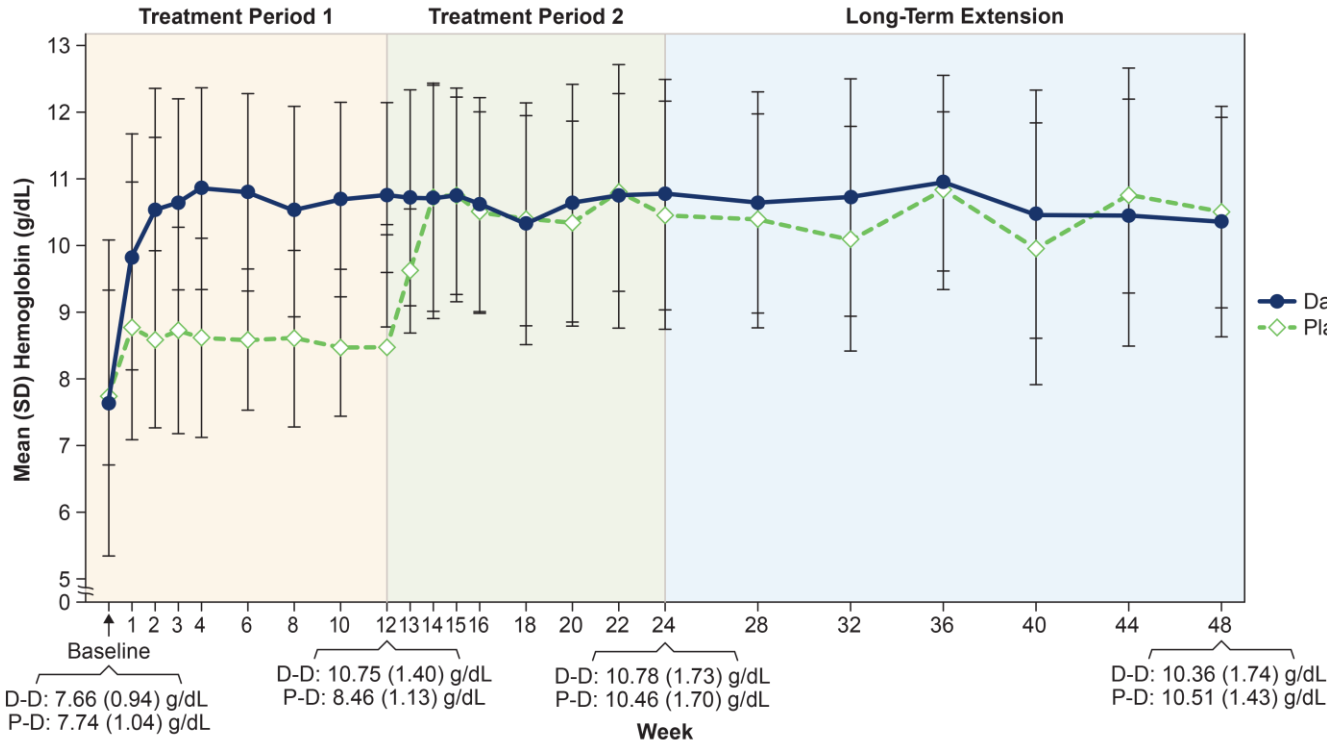
Freedom from Transfusions

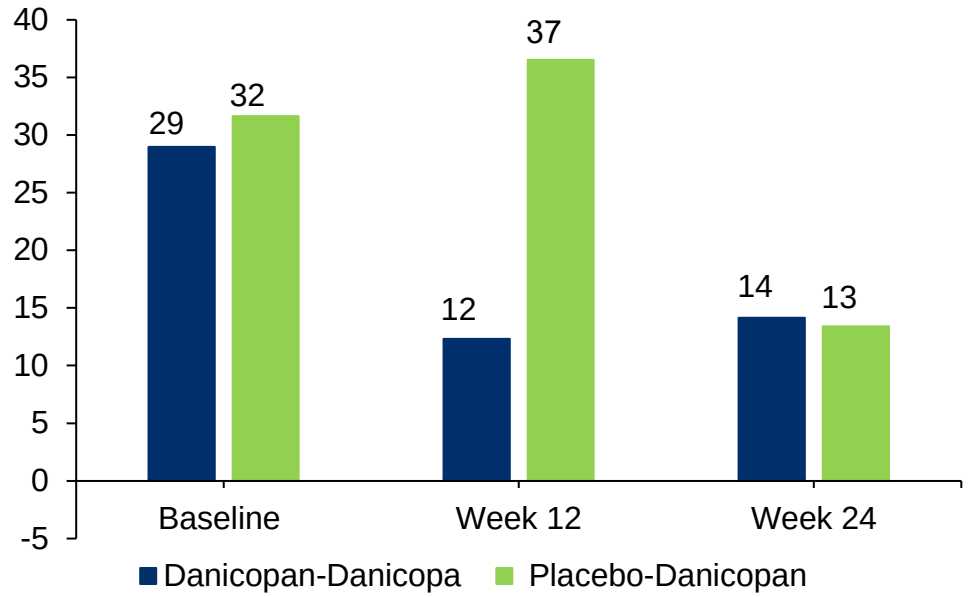
Change from Baseline in Hemoglobin Levels (g/dL)	Week 16	Week 48
PEG-to-PEG, Mean (SD)	2.73 (1.99) n=37	2.47 (1.72) n=33
ECU-to-PEG, Mean (SD)	−0.15 (0.92) n=38	2.93 (2.09) n=30



Peffault de Latour *et al. Lancet Haem* 2021

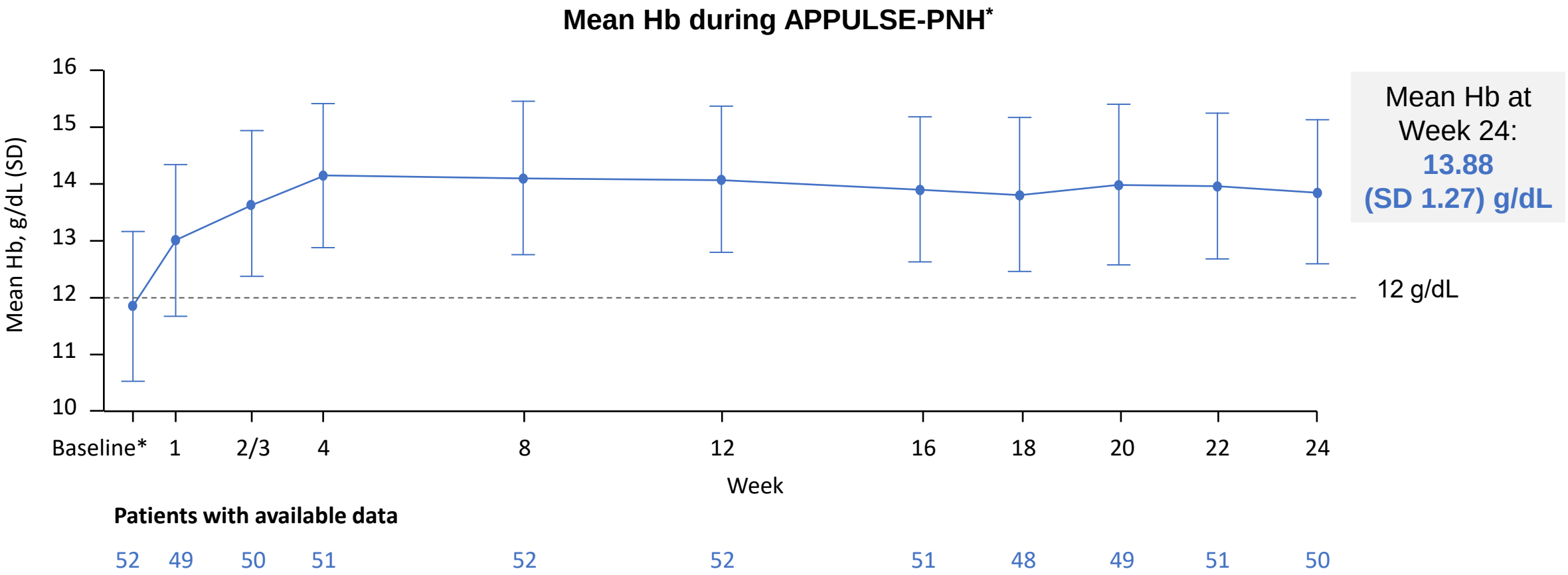
Danicopan + antiC5





Kulasekararaj *et al. Blood* 2025

Iptacopan – Hb > 10 g/dL



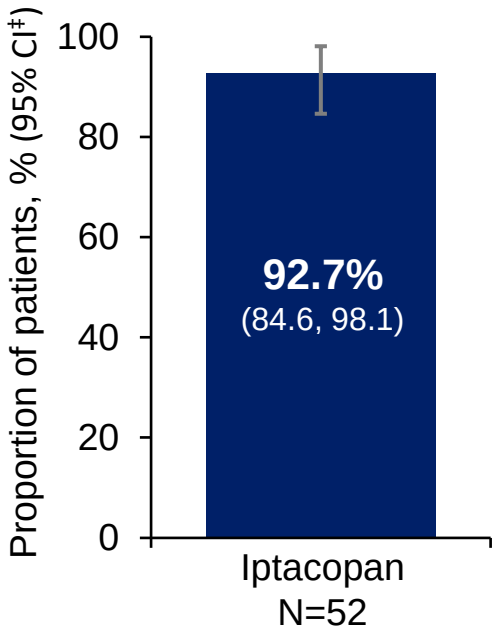
Kulasekararaj *et al. EHA* 2025 : abstract

Iptacopan – Hb > 10 g/dL

At **baseline**, **38.5%** patients (20/52) had **Hb ≥12 g/dL** in the absence of RBC transfusions 6 months prior to screening

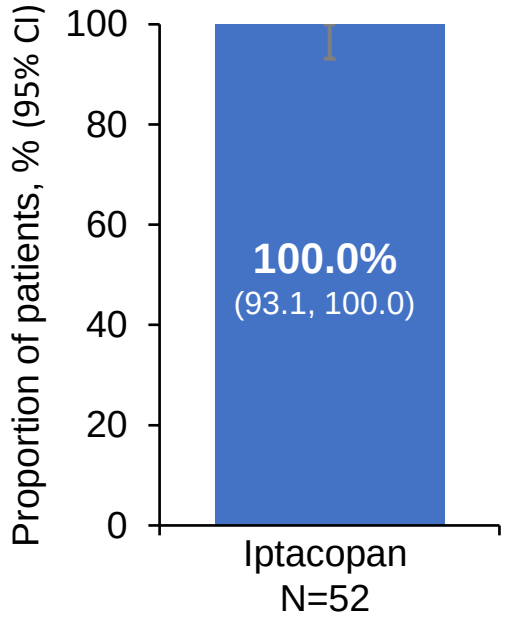
Patients achieving Hb ≥12 g/dL
between Day 126 and 168* in the absence of RBC transfusions between Day 1 and 168†

48/51 patients with non-missing data*



RBC transfusion avoidance
between Day 1 and 168†

52/52 patients

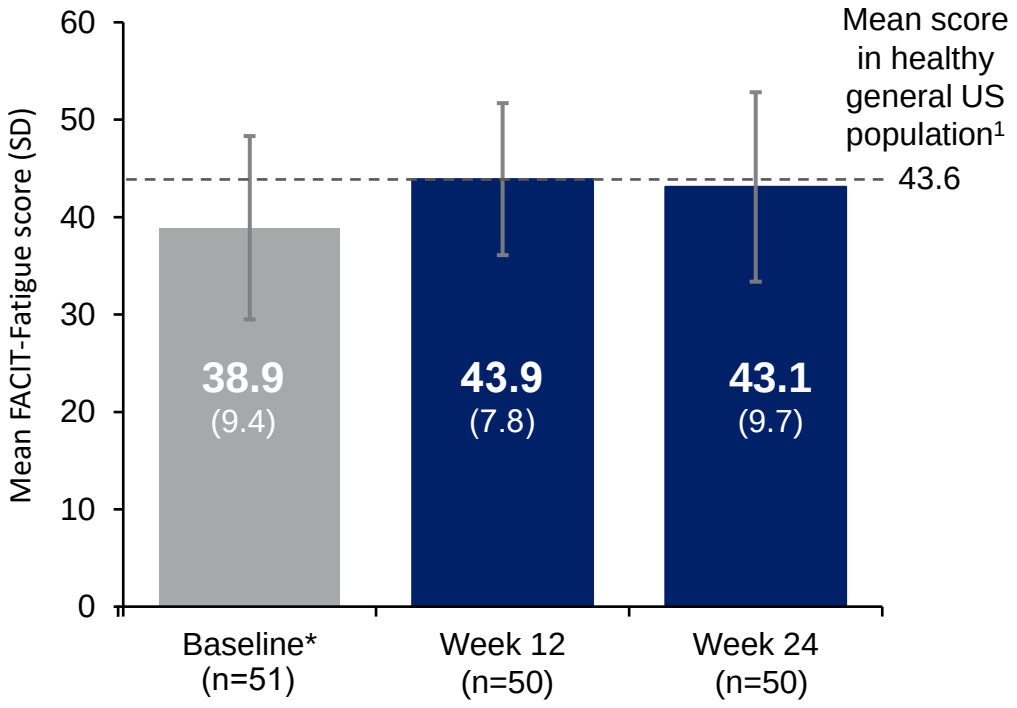


Kulasekararaj *et al. EHA* 2025 : abstract

Iptacopan – Hb > 10 g/dL

Adjusted mean change from baseline* in FACIT-Fatigue score at Day 168 was **+4.29 (95% CI 1.74, 6.85)**†

Mean FACIT-Fatigue score during APPULSE-PNH



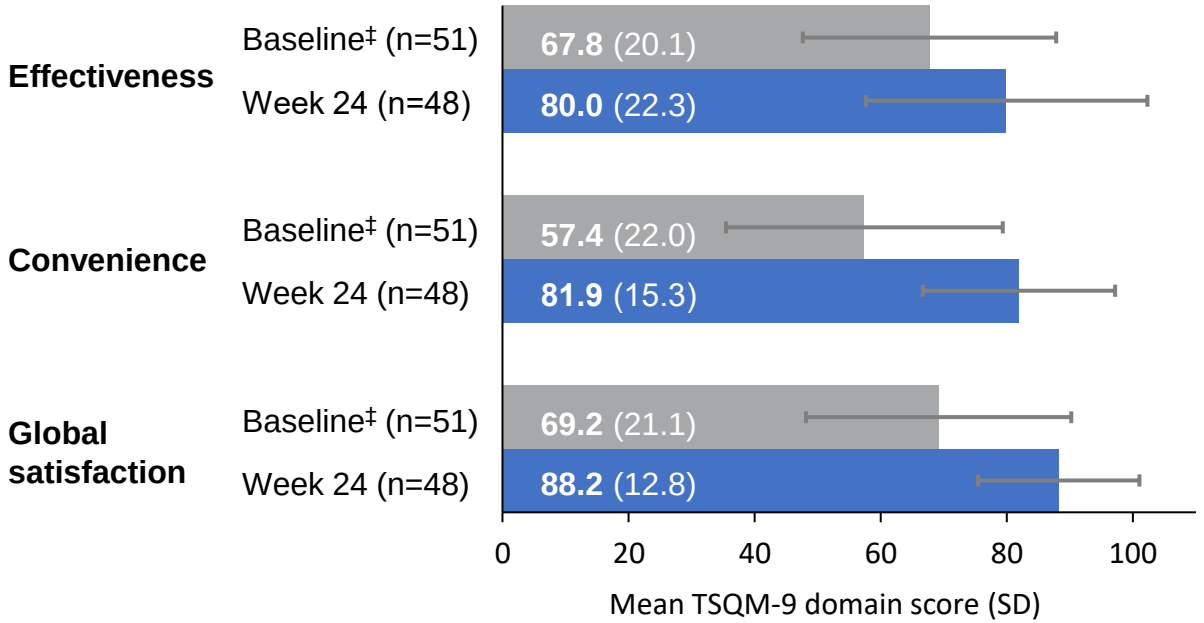
Adjusted mean (95% CI) changes from baseline‡ in TSQM-9 domains at Day 168 were:†

+12.54 (5.58, 19.49) for effectiveness

+23.86 (17.62, 30.10) for convenience

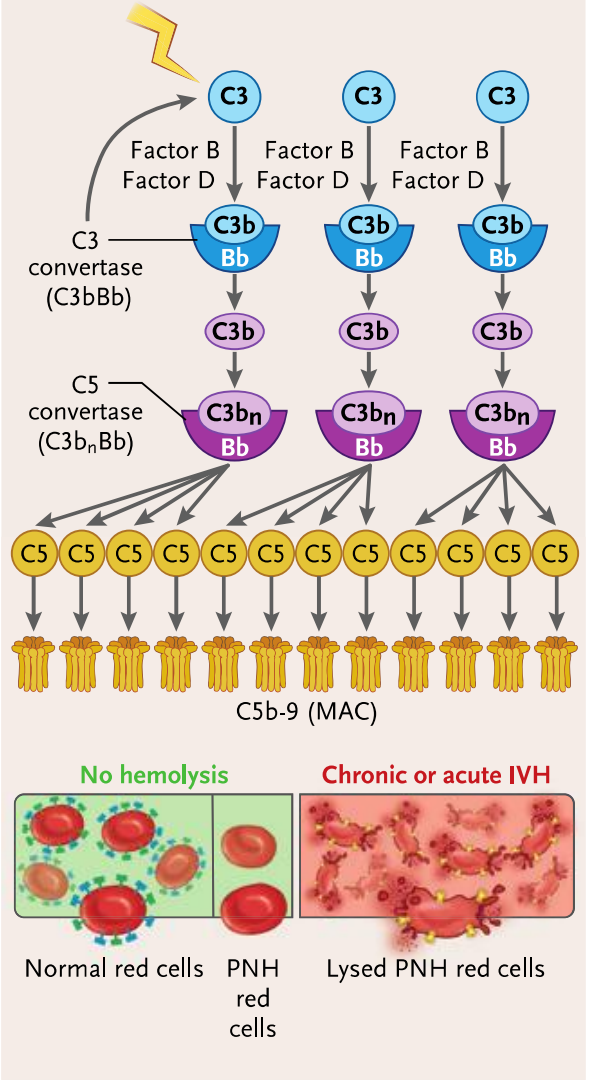
+18.53 (12.87, 24.19) for global satisfaction

Mean TSQM-9 scores during APPULSE-PNH

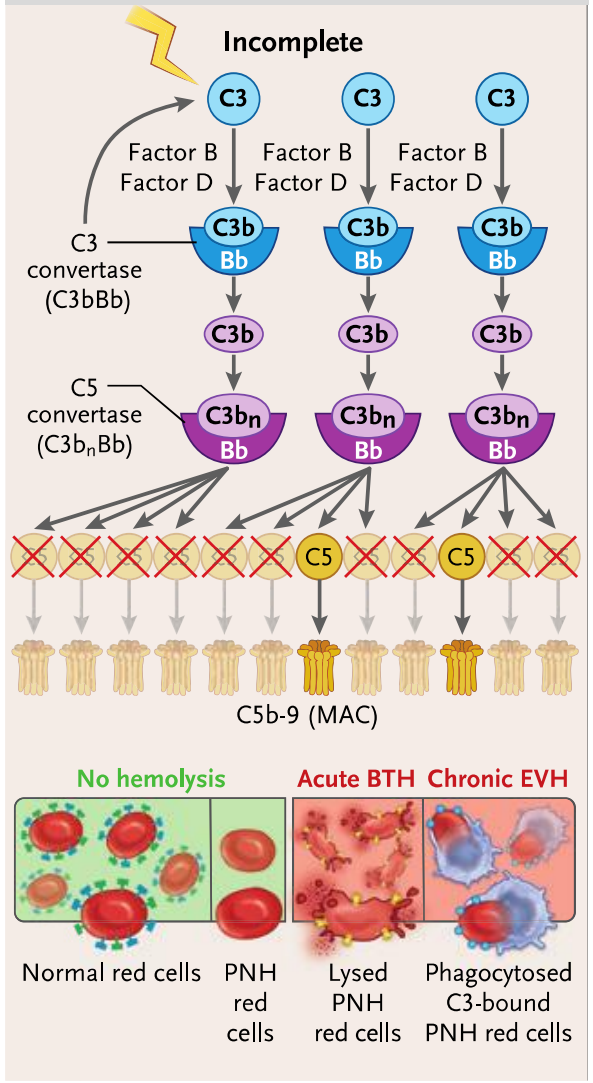


Kulasekararaj *et al. EHA* 2025 : abstract

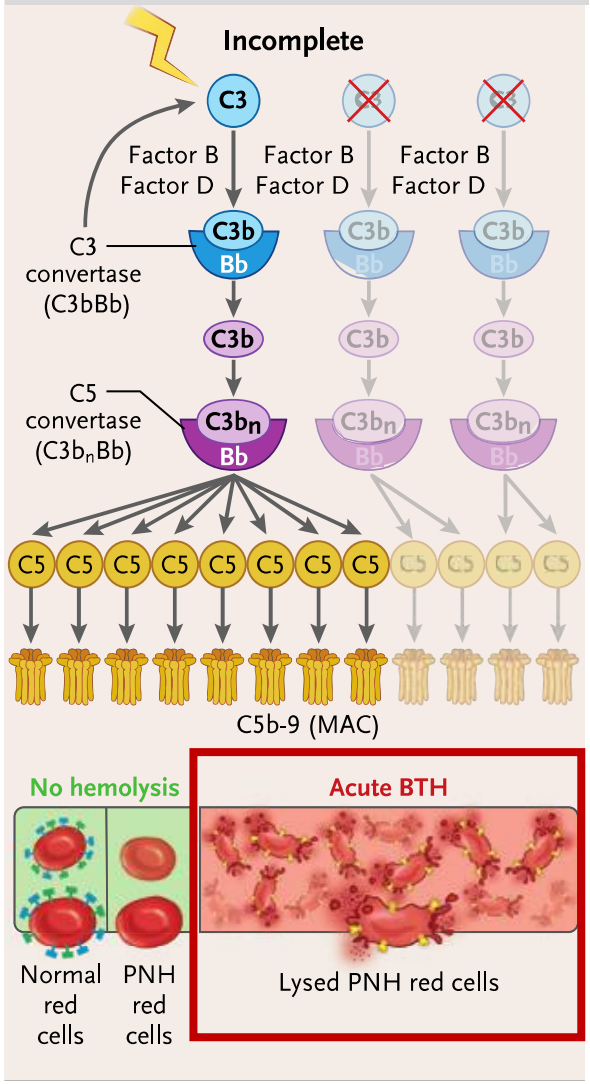
Sans traitement



Blocage incomplet C5



Blocage incomplet C3



↑ clone érythrocytaire
-
½ vie courte

Notaro & Luzzatto, NEJM 2022

Long-term Safety and Efficacy of Pegcetacoplan Treatment in Adults with Paroxysmal Nocturnal Hemoglobinuria

Patient disposition and exposure

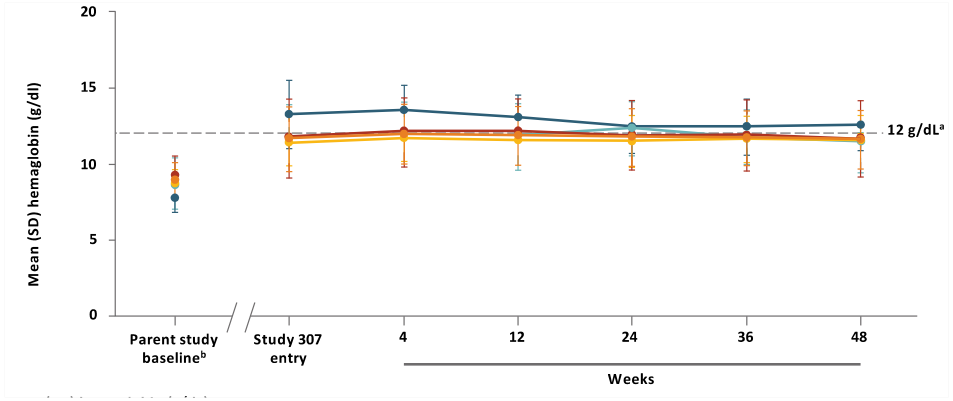
- Overall, 137 of 145 patients (94%) who completed a pegcetacoplan trial entered the 307 open-label extension study
- All 137 patients had received at least 1 dose of pegcetacoplan (ITT population) and were included in this analysis
- At data cutoff (August 27, 2021), 107 patients had received at least 48 weeks of pegcetacoplan in the 307 extension trial

Table 1. Hemoglobin and LDH Normalization[a] at Week 48

	PHAROAH N=4	PALOMINO N=4	PADDOCK N=15	PEGASUS N=64	PRINCE N=50	Total N=137
Hemoglobin normalization (number of evaluable patients[b])	n=4	n=4	n=14	n=57	n=28	n=107
>12 g/dL, n (%)	1 (25.0)	2 (50.0)	6 (42.9)	23 (40.4)	14 (50.0)	46 (43.0)
≥sex-specific LLN[c], n (%)	1 (25.0)	2 (50.0)	5 (35.7)	20 (35.1)	9 (32.1)	37 (34.6)
LDH normalization (number of evaluable patients[d])	n=4	n=4	n=14	n=57	n=27	n=106
≤ULN[e], n (%)	3 (75.0)	3 (75.0)	8 (57.1)	43 (75.4)	18 (66.7)	75 (70.8)

[a]Hemoglobin normalization was defined as a hemoglobin level greater than the LLN for females (12.0 g/dL) or greater than or equal to the sex-specific LLN. Normalization of LDH was defined as an LDH level less than or equal to the ULN. [b]Patients with data available from the specified visit and no transfusions during the prior 60 days. [c]Hemoglobin LLN: 13.6 g/dL (males), 12.0 g/dL (females). [d]Patients with data available from the specified visit. [e]LDH ULN: 226 U/L. LDH, lactate dehydrogenase; LLN, lower limit of normal; ULN, upper limit of normal.

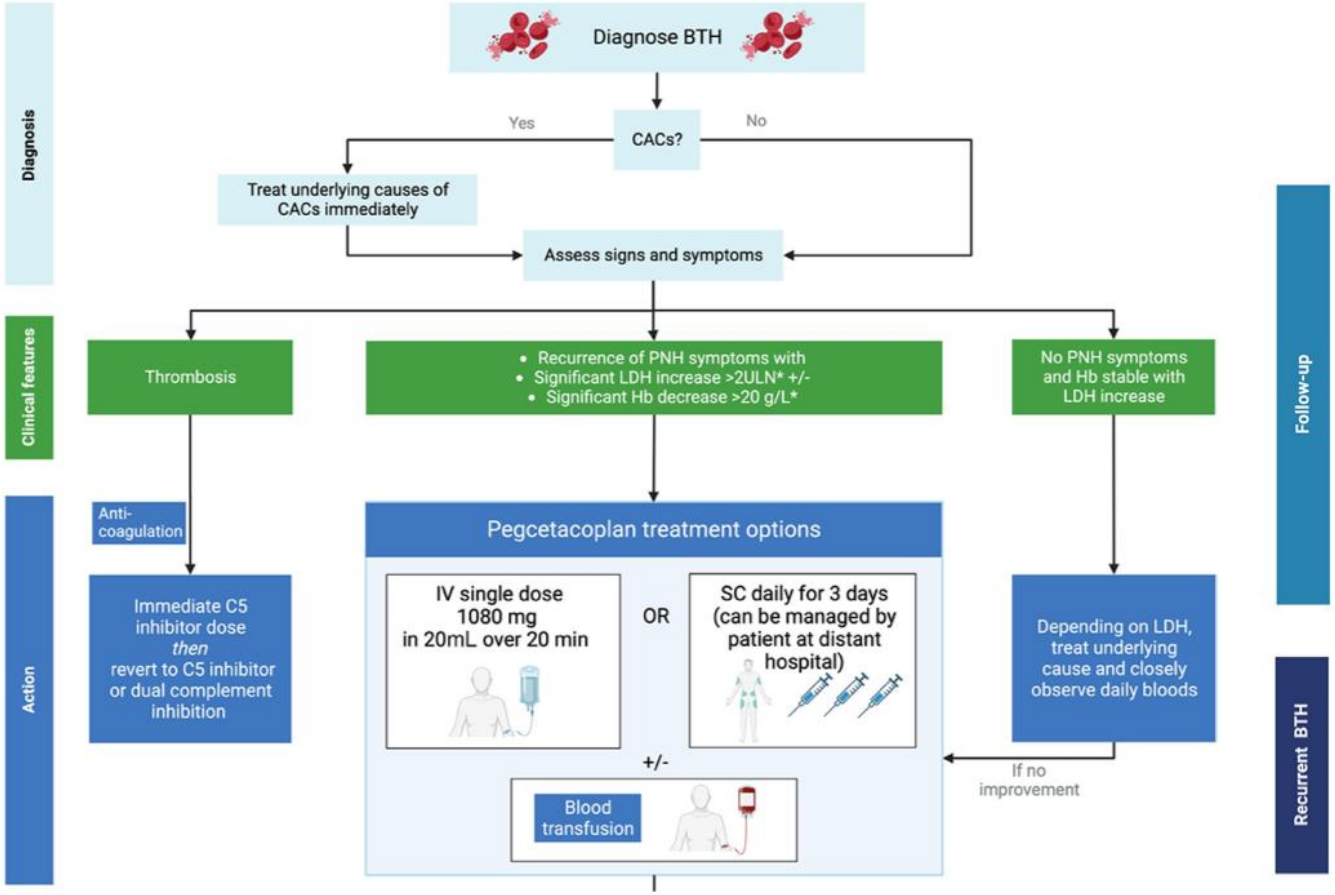
Patriquin et al. Adv Ther 2024

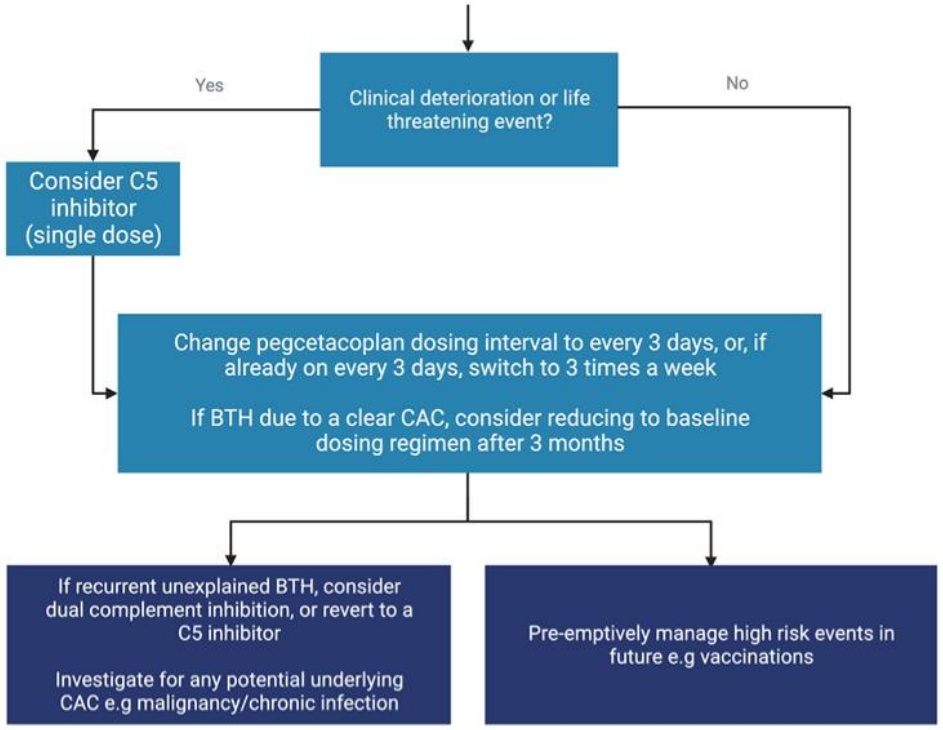


n (%)	PHAROAH N=4	PALOMINO N=4	PADDOCK N=15	PEGASUS N=64	PRINCE N=50	Total N=137
Any AE	4 (100.0)	2 (50.0)	12 (80.0)	60 (93.8)	23 (46.0)	101 (73.7)
AEs related to pegcetacoplan	0	1 (25.0)	3 (20.0)	13 (20.3)	5 (10.0)	22 (16.1)
Any serious AE	1 (25.0)	1 (25.0)	3 (20.0)	16 (25.0)	6 (12.0)	27 (19.7)
Serious AEs related to pegcetacoplan	0	0	0	0	0	0
Serious AEs in ≥5% of patients overall						
Hemolysis	0	1 (25.0)	0	9 (14.1)	1 (2.0)	11 (8.0)
AEs leading to study discontinuation[b]	0	0	0	2 (3.1)	1 (2.0)	3 (2.2)
AEs leading to death[c]	0	0	0	0	1 (2.0)	1 (0.7)

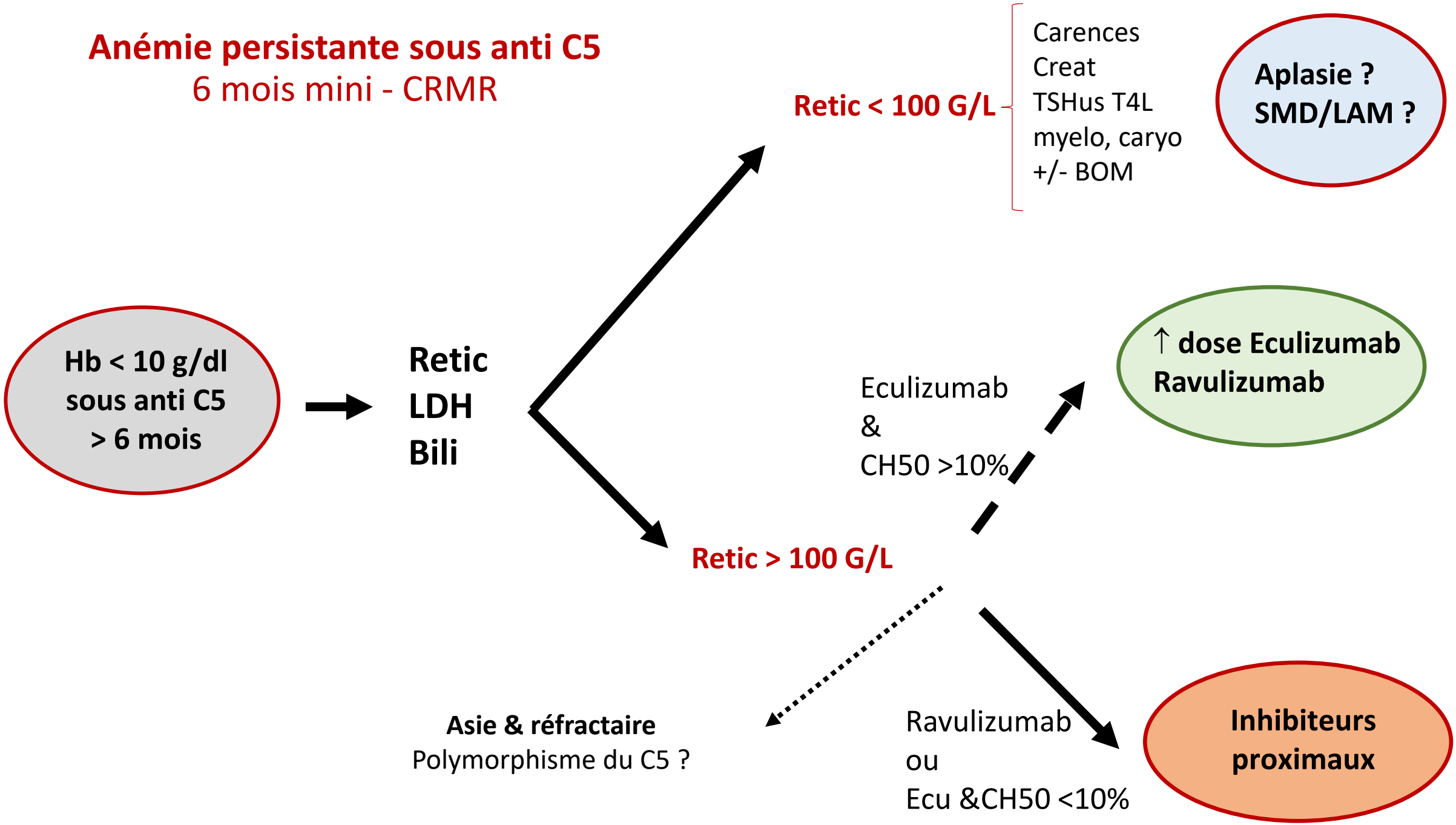
Real-world experience of pegcetacoplan in paroxysmal nocturnal hemoglobinuria

Cohorte UK + France : 48 patients traités par PEG





Griffin, et al. Am J Hematol 2024


Anémie persistante sous anti C5
6 mois mini - CRMR
Hb < 10 g/dl
sous anti C5
> 6 mois
Retic
LDH
Bili
Retic < 100 G/L
Carences
Creat
TSHus T4L
myelo, caryo
+/- BOM
Aplasie ?
SMD/LAM ?
Retic > 100 G/L
Eculizumab
&
CH50 >10%
↑ dose Eculizumab
Ravulizumab
Asie & réfractaire
Polymorphisme du C5 ?
Ravulizumab
ou
Ecu &CH50 <10%
Inhibiteurs
proximaux

Quels patients éligibles aux inhibiteurs proximaux

- Oui si Hb < 10 g/dL et retic > 100 G/L
- Asthénie malgré Hb > 10 : rôle de l'anémie à questionner ??
- Choix du proximal selon profil patient :
  - Contraintes professionnelles, personnelles
  - Risque d'oubli en monothérapie (compliance, compréhension…)
  - Interactions médicamenteuses éventuelles
  - Choix du patient
- Arrêt recommandé en cas de grossesse
- ETP ++++

FU long termes inhibiteurs proximaux

- Incidence cumulée d'accidents hémolytique
- Infections
- Risques méconnus : Dysimmunité ? Cancers ?

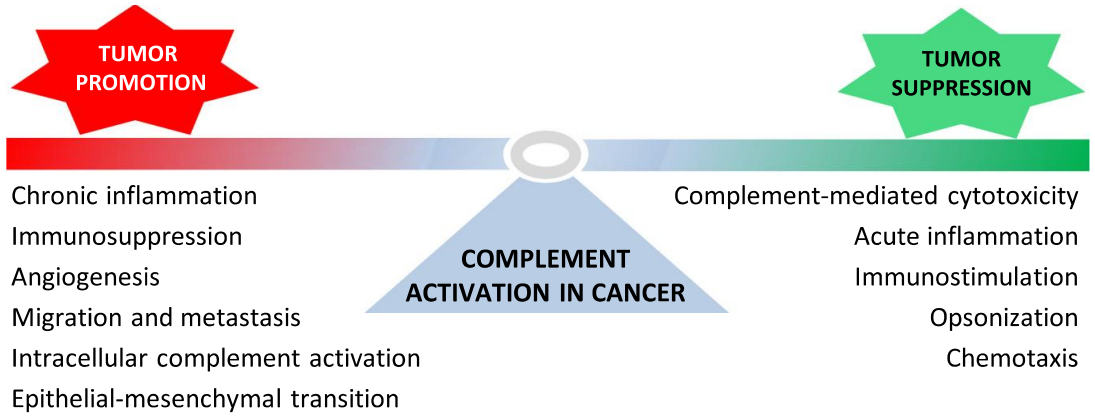


Fig. 1. Dual action of complement activation in cancer.

Ajona, et al. Seminars in Immunology 2025

Inhibiteurs proximaux – questions résiuels

- Facteurs individuels favorisant l'HEV ?
- Biomarqueurs précoces ?
- Biomarqueurs pour choix de l'inhibiteur proximal ?
- Biomarqueurs suivi inhibiteur proximal ?
- Intérêt du dosage des inhibiteurs proximaux ?

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COMplement Expertise and Therapeutics

CRMR Aplasies médullaires acquises et constitutionnelles

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