Patients

Webinars

AA and PNH

Topic On Focus

EuroBloodNet

PNH understanding the disease and the tretaments

Dr Flore Sicre de Fontbrune
National French Reference Center for AA and PNH
Saint Louis Hospital - APHP
ERN-EuroBloodNet
Paris – FRANCE
14 december 2022

Co-funded by
the Health Programme
of the European Union

PNH SUPPORT

PNH GLOBAL ALLIANCE

lichterzellen
Stiftung zur Hilfe bei PNH/AA

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Alexion Pharma

Sobi

Novartis

- **30-35min presentation (30 slides max) + 15 min Q&A session**
- **Microphones will be muted by host to avoid back noise**
- **Please, stop your video to improve internet conexion**
- **Send your questions during the presentation through the chat**

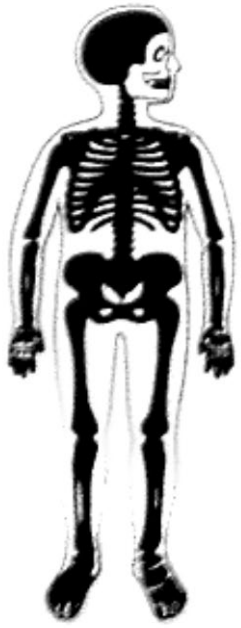
1. PNH pathophysiology and clinical manifestations
2. Link between PNH and AA
3. Treatments and supportive care

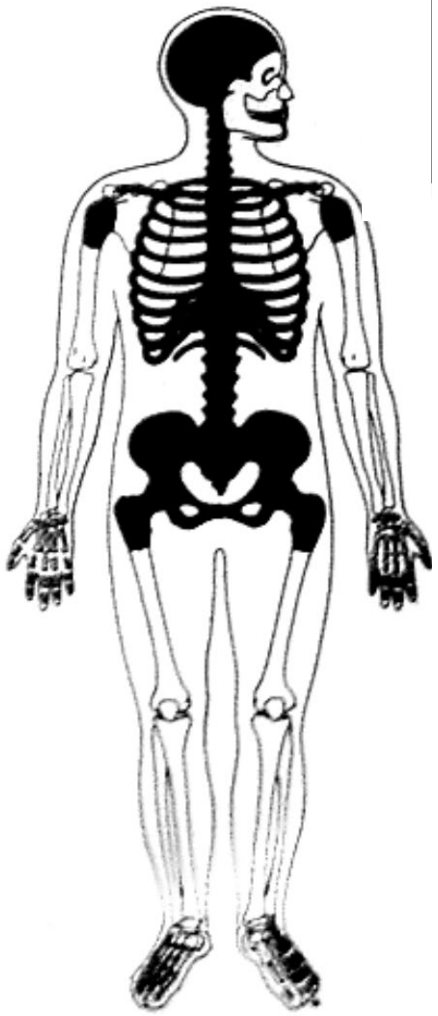
	Lifespan	Daily production
 Érythrocytes	120 days	200 10^9
 Leucocytes	2-10 days	50-100 10^9
 Thrombocytes	10 days	100 10^9

Érythrocytes

Leucocytes

Thrombocytes





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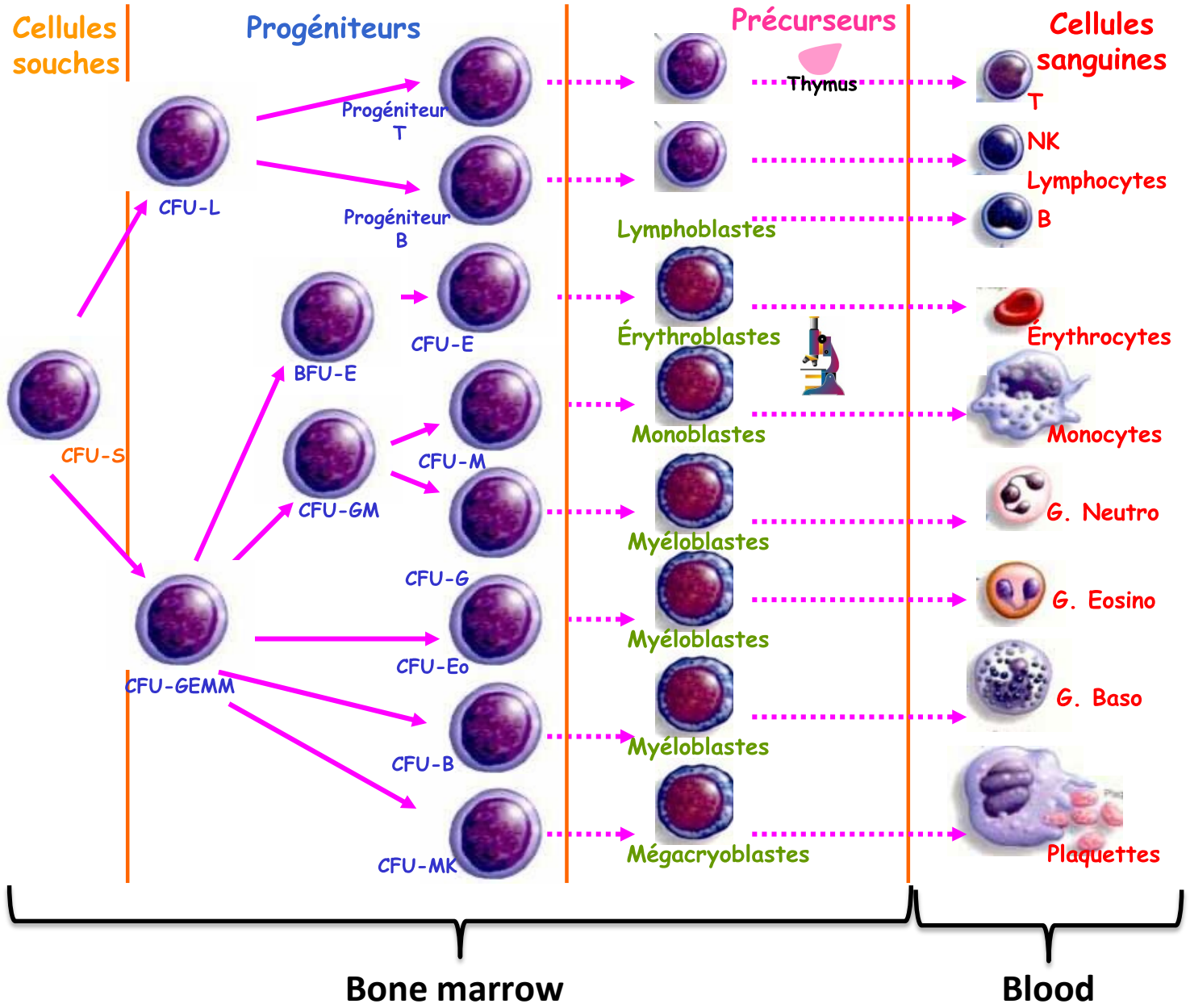
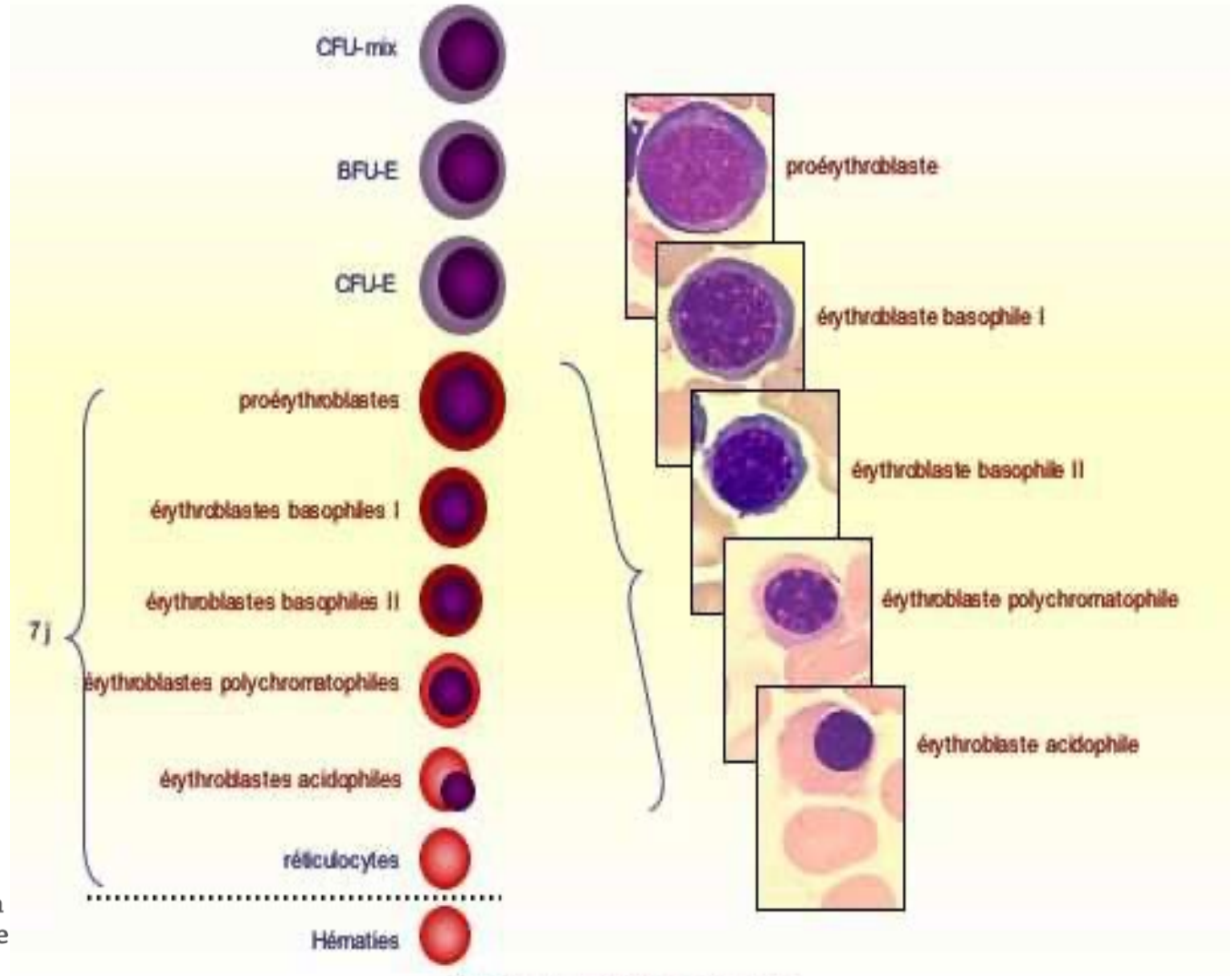
Hematopoietic stem cells



Normal Erythropoiesis



EPO

IRON

Vitamins
- B6
- B12
- B9

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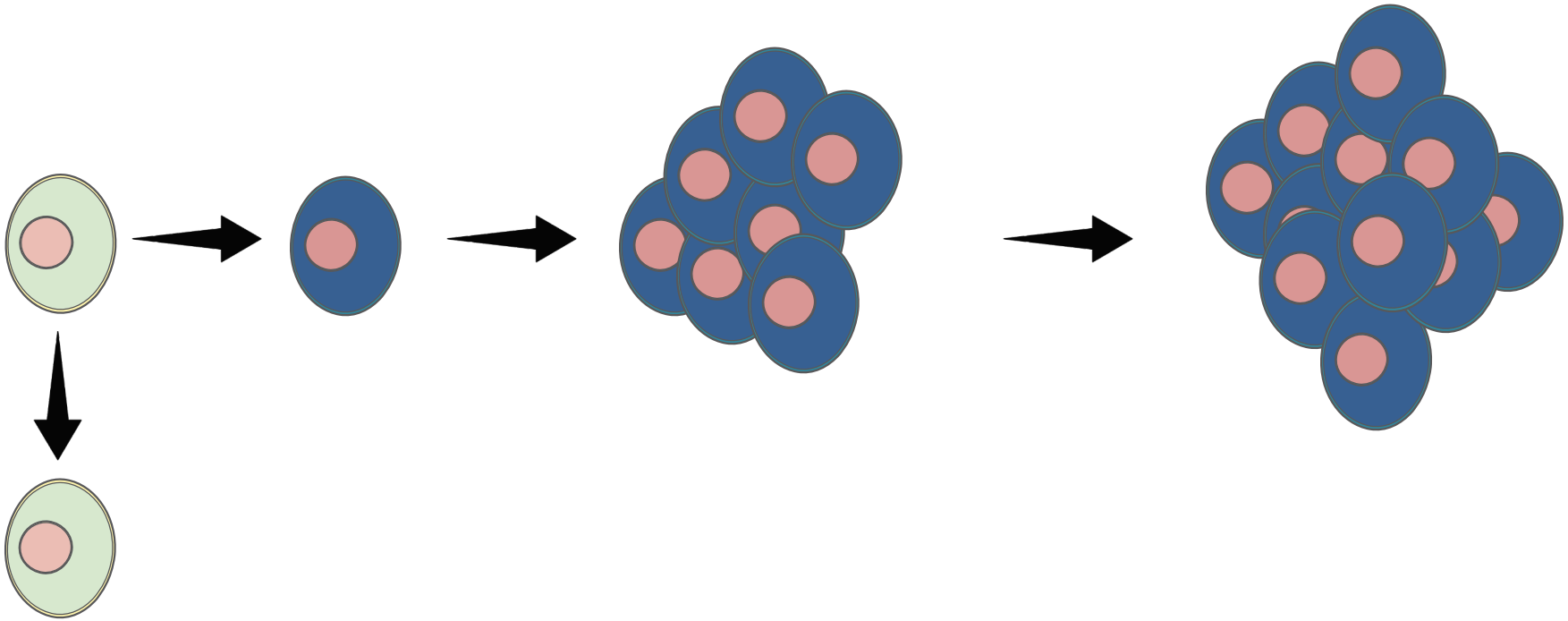
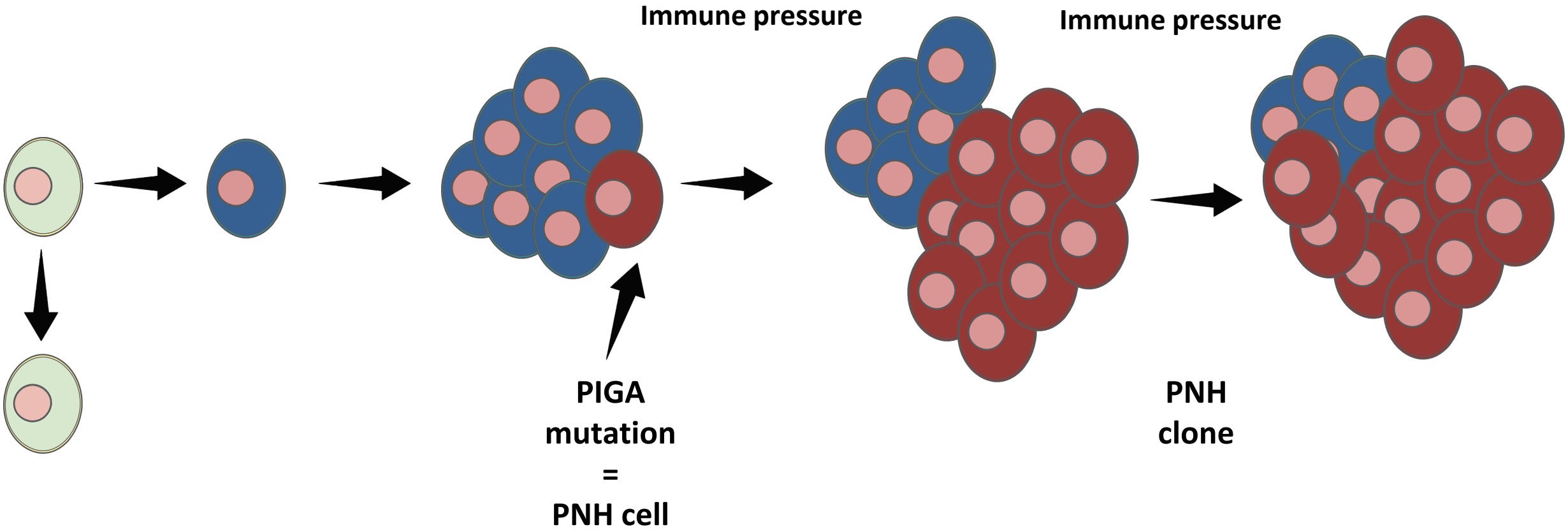
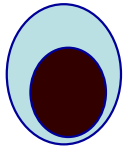
Hematopoiesis in PNH

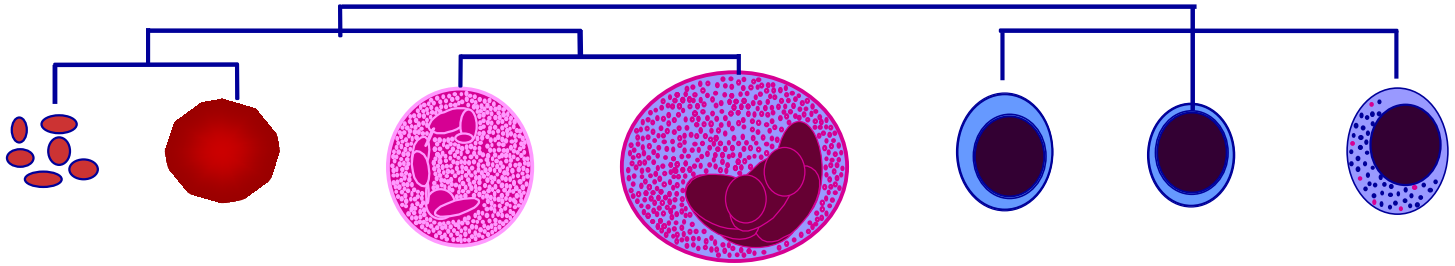



Immune pressure
Immune pressure
PIGA mutation = PNH cell
PNH clone

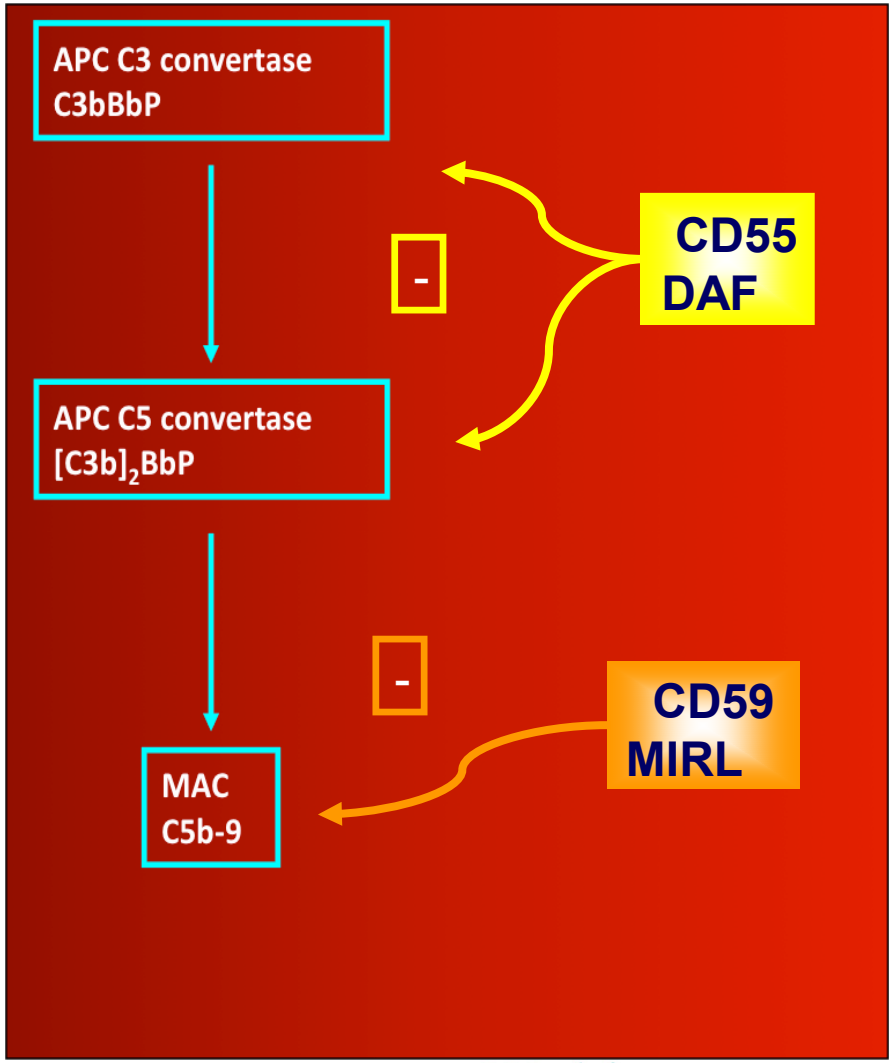
Hematopoietic Stem Cell



CD59, CD109
CD90



Platelets	Red Cells	Granulocytes	Monocytes	B Cells	T Cells	NK Cells
CD55	**CD55, CD59**	**CD55** CD58	**CD55**	**CD55**	**CD55**	**CD55**
CD58	(Cromer Ag)	**CD59** CD14	CD58	CD58	CD58	CD58
CD59	CD58, PrPc,	CD16 CD24	CD59	**CD59**	**CD59**	**CD59**
CD109	AChE	(NAB1- **Ag)**	CD14	CD24	{CD16}	CD16
(Gova /b- Ag)	(Cartwrigt-Ag)	CD48 CD66b	{CD16}	CD48	CD48	CD48
PrPc	CDw108	CD66c CD87	CD48	CDw52	CDw52	CDw52
GP500	(John-Milton	CD109 CD157	CDw52	{CD73}	{CD73}	PrPc
	- Hagen Ag)	LAP NB1	CD87	{CDw108}	CD87	
	Dombroch	PrPc ADP-RT	CD109	PrPc	{CD90}	
	residue	p50-80 GPI-80	CD157		CDw108	
	Holley Gregory AG		Group-8		{CD109}	
			PrPc		PrPc	
			GPI-80		ADP-RT	



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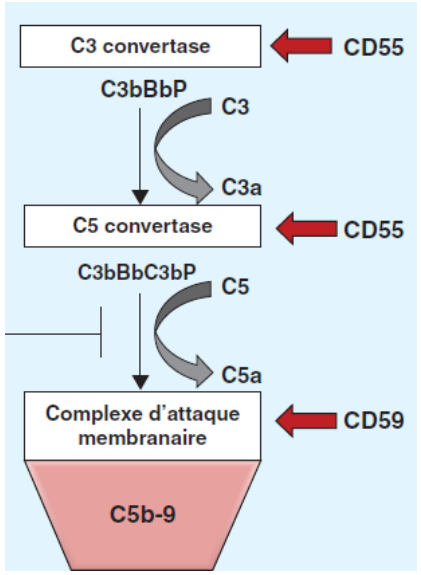
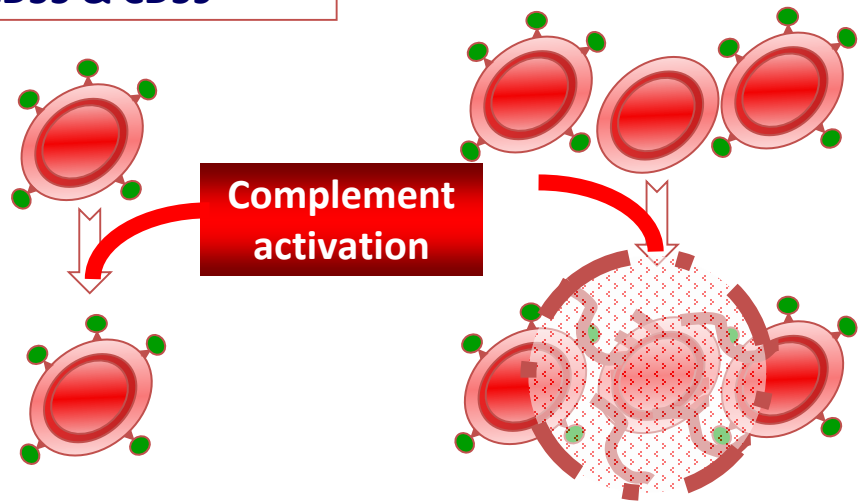


Normal RBC prevent C mediated hemolysis by 2 GPI anchored proteins CD55 & CD59

PNH RBC lysis in case of C activation



- Thrombosis
- Kidney failure
- Hemoglobinuria
- Pulmonary HT
- Free Hb
- Abdominal pain
- Asthenia
- Dyspnea
- Anaemia
- Erectile dysfonction
- Dysphagia

Rother R et al; Discovery and development of the complement inhibitor ecuizumab for the treatment of paroxysmal nocturnal hemoglobinuria. Nature Biotechnol 2007; 25 : 1256-1263

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Manifestations of PNH

Characteristic	n/N (%) or median (IQR*), N
Sex, female	250/460 (54.3%)
Age at diagnosis, y	34.2 (24.2-48.4)#, 460
Diagnostic test	
Flow cytometry†	215/459 (46.8%)
Size of PNH clone (%)	30 (14-50), 159
GPI-negative cells more than 50%	37/159 (23%)
Presentation	
Aplastic anemia preceding	106/460 (23.0%)
Signs and symptoms	
Clinical symptoms	
Abdominal pain	83/456 (18.2%)
Thrombosis‡	33/457 (7.2%)
Infections	69/453 (15.2%)
Peripheral blood abnormalities	
Anemia alone	102/447 (22.8%)
Anemia and thrombocytopenia	113/447 (25.3%)
Anemia and neutropenia	18/447 (4.0%)
Pancytopenia at diagnosis	175/447 (39.1%)

Complications	n/N (%)	10-year cumulative incidence rate, % (95% CI)
Bicytopenia or pancytopenia	36/231 (atrisk)§	19.2 (12.9-25.2)
Recurrent abdominal pain crisis	138/451 (30.2)	NA
Infections*	185/453 (40.8)	NA
Thrombosis	116/454‖	30.7 (25.4-35.9)¶
Budd-Chiari syndrome	49 (43)	
Central nervous system	35 (31)	
Limbs	31 (27)	
Other sites	29 (25)	
Myelodysplastic syndrome†	21/454	5.2 (2.9%-7.6%)
Acute leukemia†	8/454	2.4 (0.7%-4.0%)
Deaths‡	96/454	
Central nervous system (SCN) vascular complications	23	NA
Infectious diseases	23	NA
Budd-Chiari syndrome	21	NA
Malignant disorders	9	NA
Other causes	17	NA

Peffault de Latour et al. Blood 2008

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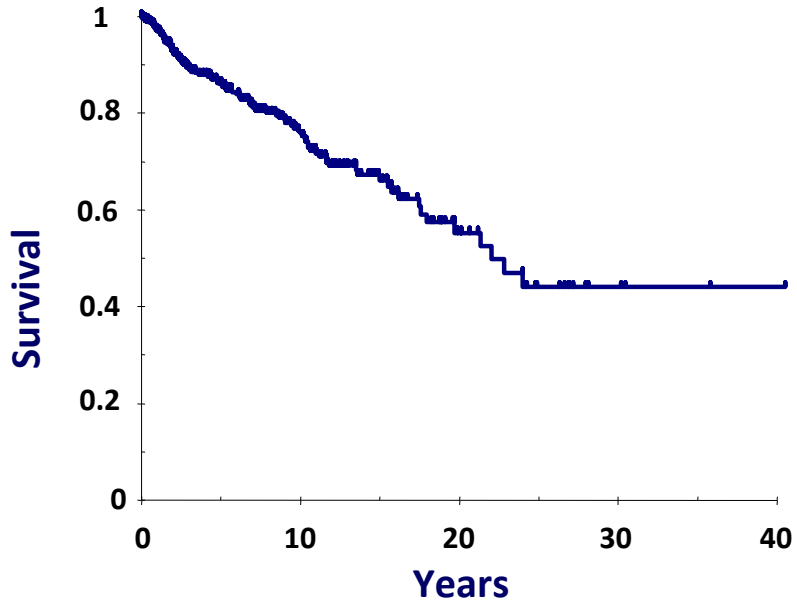
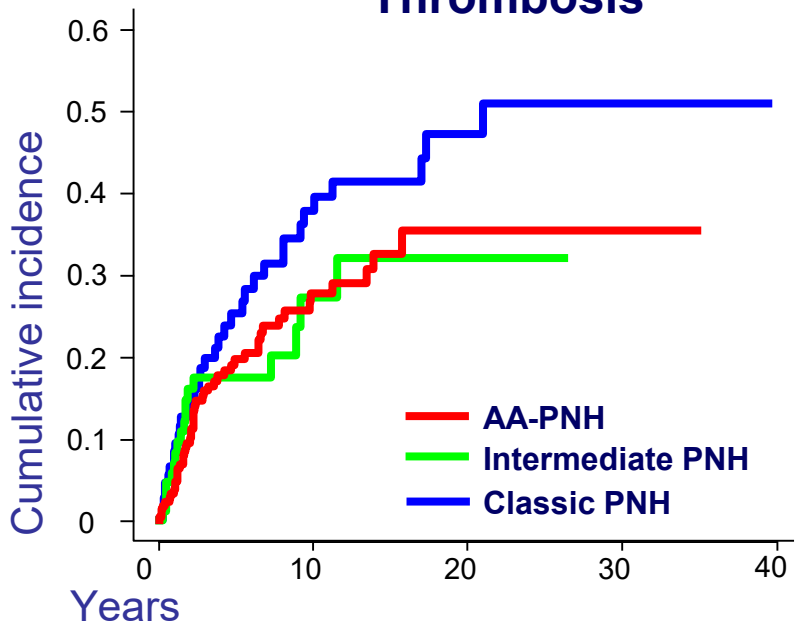
Median follow-up: 6.8 +/- 0.5 years



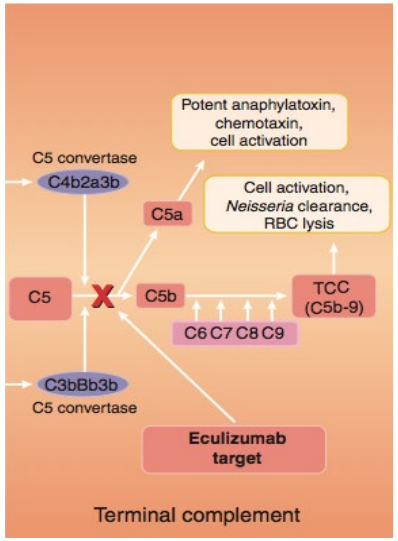
median survival time: 22.1 +/- 2.2 years

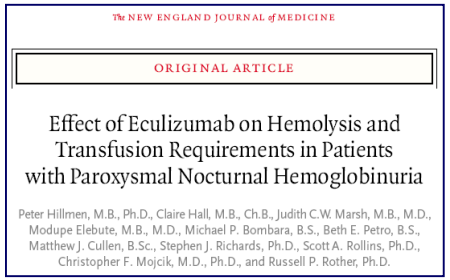
Thrombosis



Thrombosis is the main cause of death in PNH

Treatment of PNH

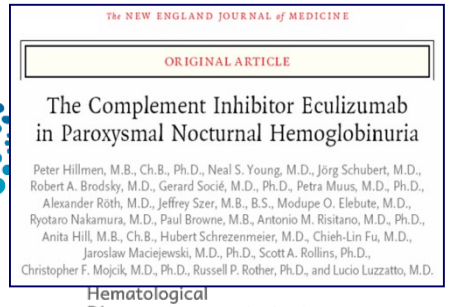



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effect of Eculizumab on Hemolysis and Transfusion Requirements in Patients with Paroxysmal Nocturnal Hemoglobinuria

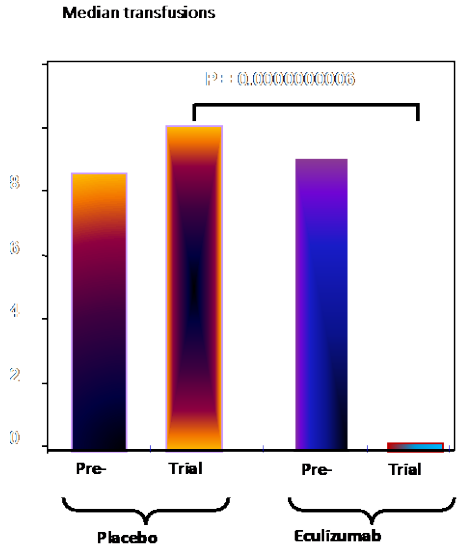
Peter Hillmen, M.B., Ph.D., Claire Hall, M.B., Ch.B., Judith C.W. Marsh, M.B., M.D., Modupe Elebute, M.B., M.D., Michael P. Bombara, B.S., Beth E. Petro, B.S., Matthew J. Cullen, B.Sc., Stephen J. Richards, Ph.D., Scott A. Rollins, Ph.D., Christopher F. Mojcik, M.D., Ph.D., and Russell P. Rother, Ph.D.

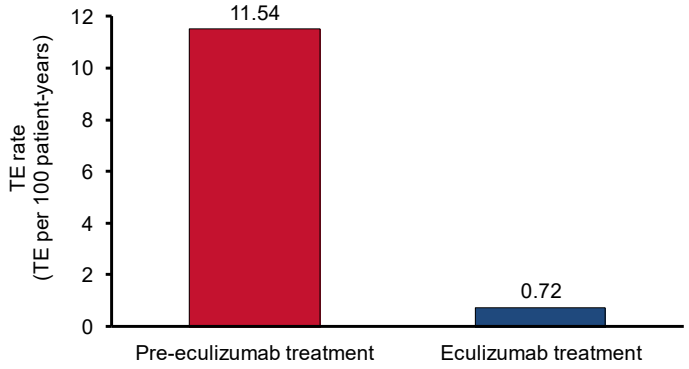

The NEW ENGLAND JOURNAL of MEDICINE

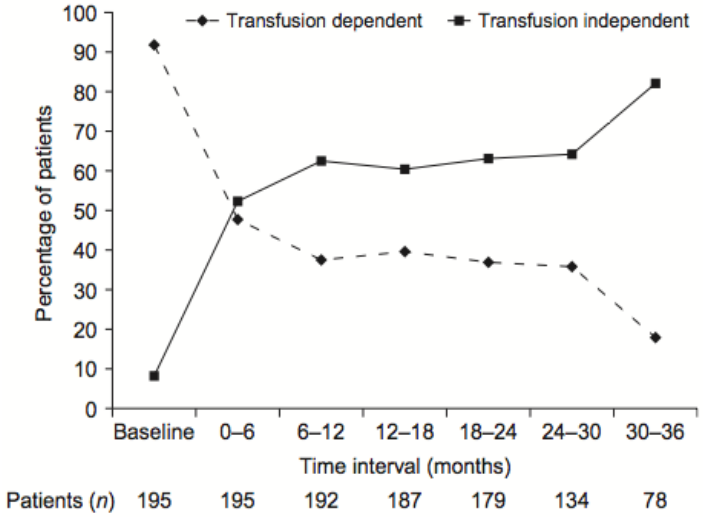
ORIGINAL ARTICLE

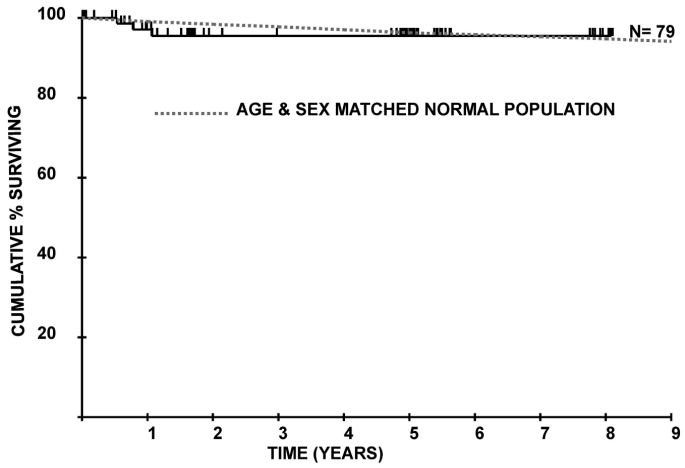
The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

Peter Hillmen, M.B., Ch.B., Ph.D., Neal S. Young, M.D., Jörg Schubert, M.D., Robert A. Brodsky, M.D., Gerard Socié, M.D., Ph.D., Petra Muus, M.D., Ph.D., Alexander Röth, M.D., Jeffrey Szer, M.B., B.S., Modupe O. Elebute, M.D., Ryotaro Nakamura, M.D., Paul Browne, M.B., Antonio M. Risitano, M.D., Ph.D., Anita Hill, M.B., Ch.B., Hubert Schrezenmeier, M.D., Chieh-Lin Fu, M.D., Jaroslaw Maciejewski, M.D., Ph.D., Scott A. Rollins, Ph.D., Christopher F. Mojcik, M.D., Ph.D., Russell P. Rother, Ph.D., and Lucio Luzzatto, M.D.

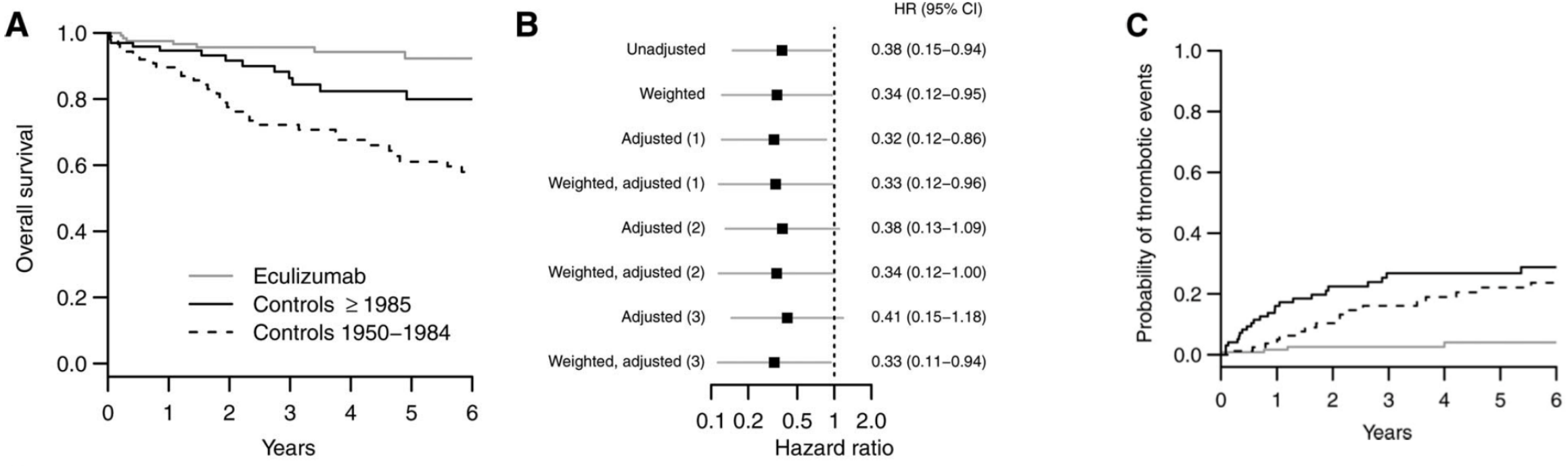








Hillmen et al, NEJM 2004 ; Hillmen et al, NEJM 2006 ; Kelly et al, Blood 2011



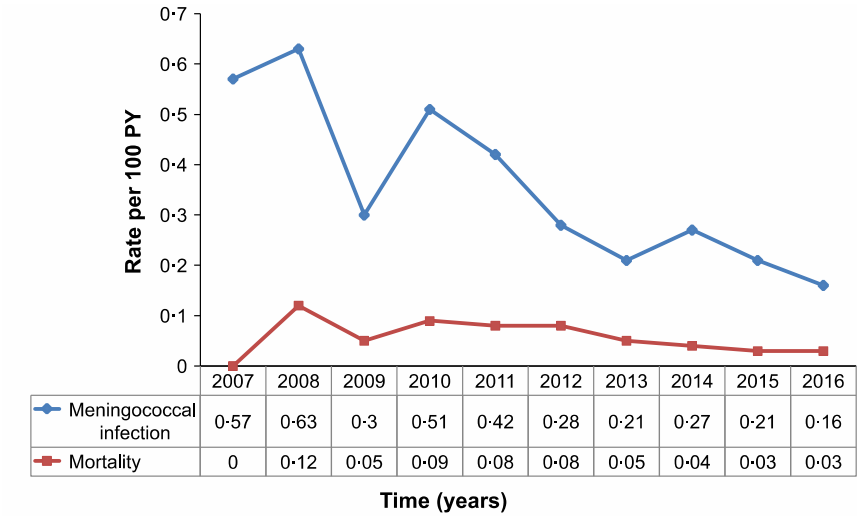
Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study

Loschi, Am J hematol 2016

Impact of Eculizumab therapy on QoL

- IV infusions every 14 days
- Home delivery not available in all districts and countries
- Impact on professional career
- Impact on high school training
- Impact on holidays and travels

MedDRA preferred term	Spontaneous number of AEs per 100 PY		Solicited number of AEs per 100 PY		Total
	Serious	Nonserious	Serious	Nonserious	
Haemoglobin decreased	2·4	0·9	12·7	3·4	19·4
Fatigue	0·4	1·7	1·6	3·9	17·6
Pyrexia	1·6	0·9	3·9	3·3	9·7
Headache	0·6	1·0	1·4	6·2	9·2
Haemolysis	2·7	0·5	3·5	2·3	9·0
Dyspnoea	0·5	0·6	1·8	4·3	7·2
Abdominal pain	0·7	0·6	2·1	3·7	7·1
Platelet count decreased	0·6	0·5	3·7	2·2	7·1
Transfusion	0·6	0	5·0	0·2	5·8



	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
Meningococcal infection	0·57	0·63	0·3	0·51	0·42	0·28	0·21	0·27	0·21	0·16
Mortality	0	0·12	0·05	0·09	0·08	0·08	0·05	0·04	0·03	0·03

Socié et al, BJH 2019

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Anti C5 therapies indications

- **PNH clone upper than 10% and**
- Haemolysis with RBC transfusions requirement
- Thrombosis
- **PNH clone upper than 50% and**
- Biological haemolysis activity
- Clinical symptoms of dystonia

Treatments goals

- Transfusion independency
- Thrombosis avoidance

International multicentric study (Paris, Naples/Avellino, London, Florence, São Paulo, and Ribeirão Preto)

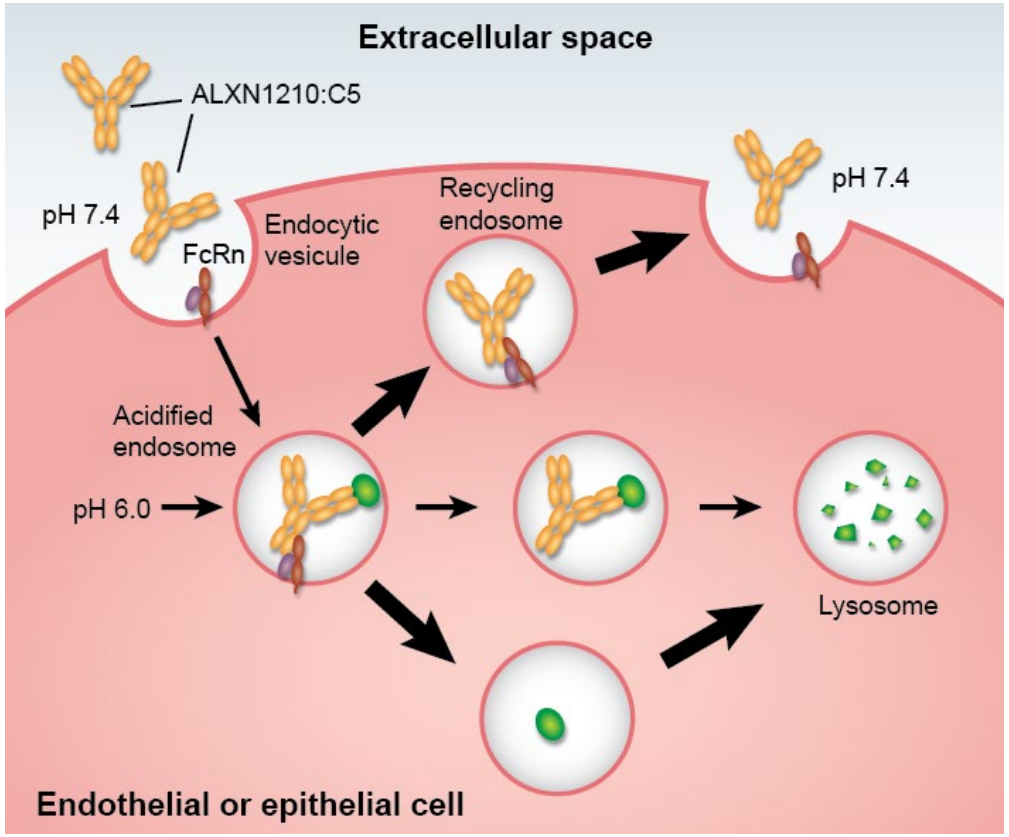
160 PNH pts receiving eculizumab
Median treatment duration 5.8 y (0.5–14.5) (10% < 18 months)
Censored : new anti C (35) or HSCT (2)
At the end of the study

- 83 % : 900 mg / 14 d
- 17% : 1200 mg or interval < 14 d

38,6 %

Complete response = No Tf, Hb > 12
Good response = No Tf, 10 < Hb < 12
Partial response = Occasional Tf, 8 < Hb < 10
Minimal response = Regular Tf

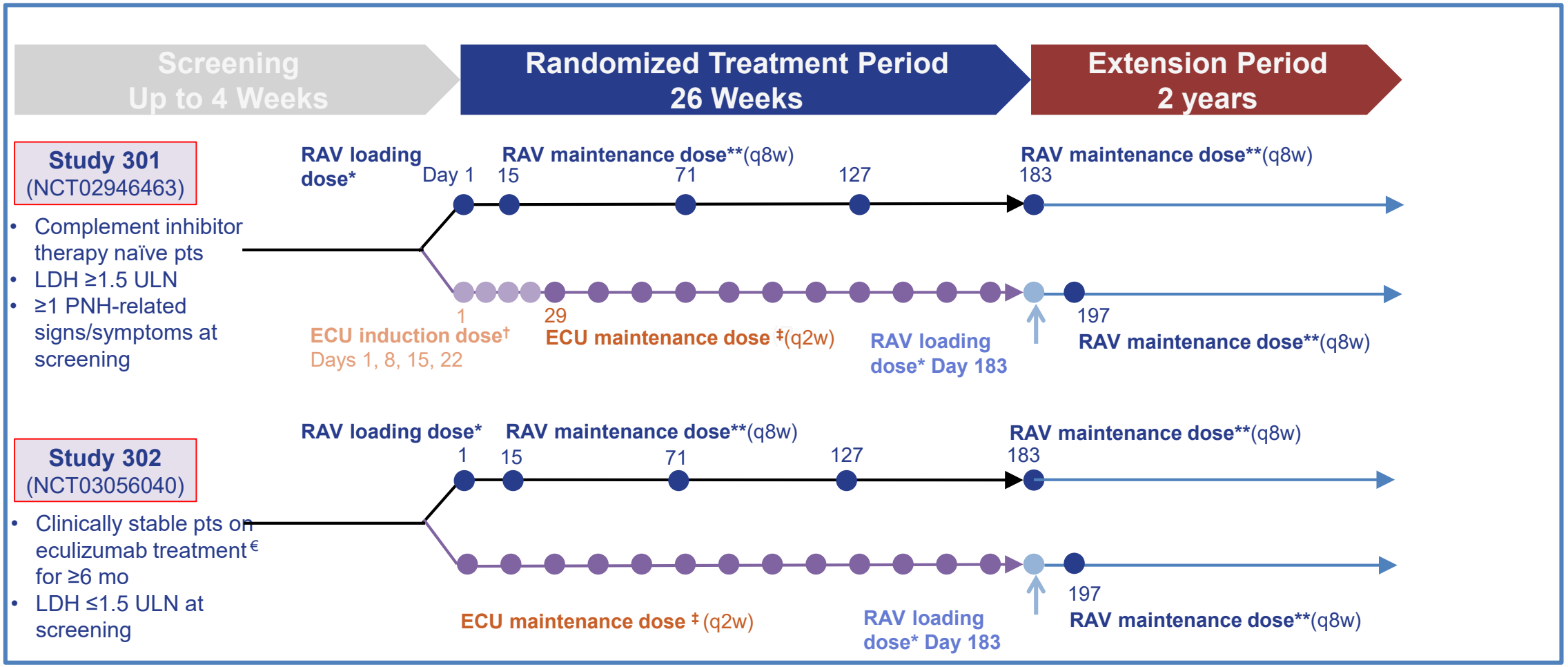
Debureaux et al, BMT 2021



Immediate, complete, sustained reduction of free C5 activity ≥99%

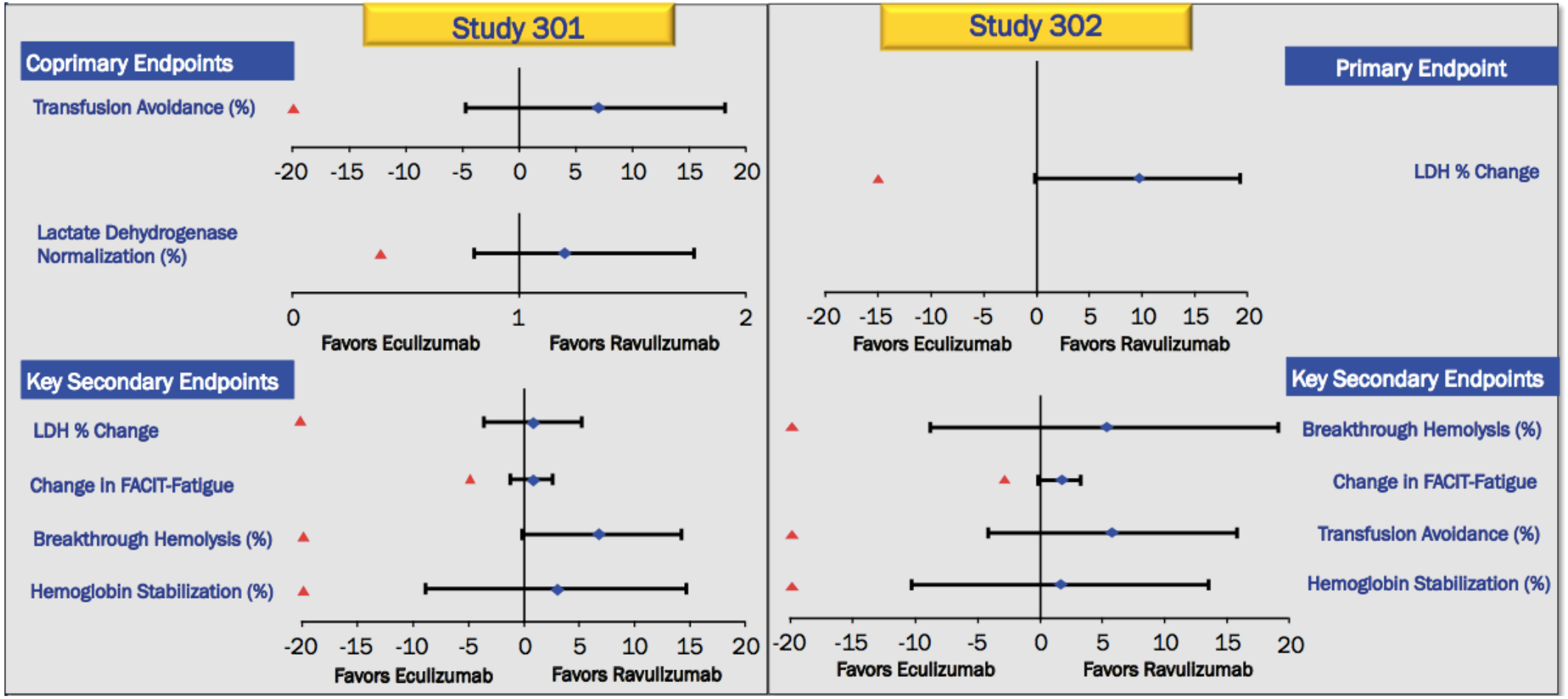
- High affinity Anti-C5 monoclonal antibody
- Derived from eculizumab through targeted engineering designed to:
  - Enhance Fc receptor recycling
  - Increase half-life
  - Maintain favorable safety and tolerability profile

Lee et al, Blood 2018 ; Kulasekaraj et al, Blood 2018

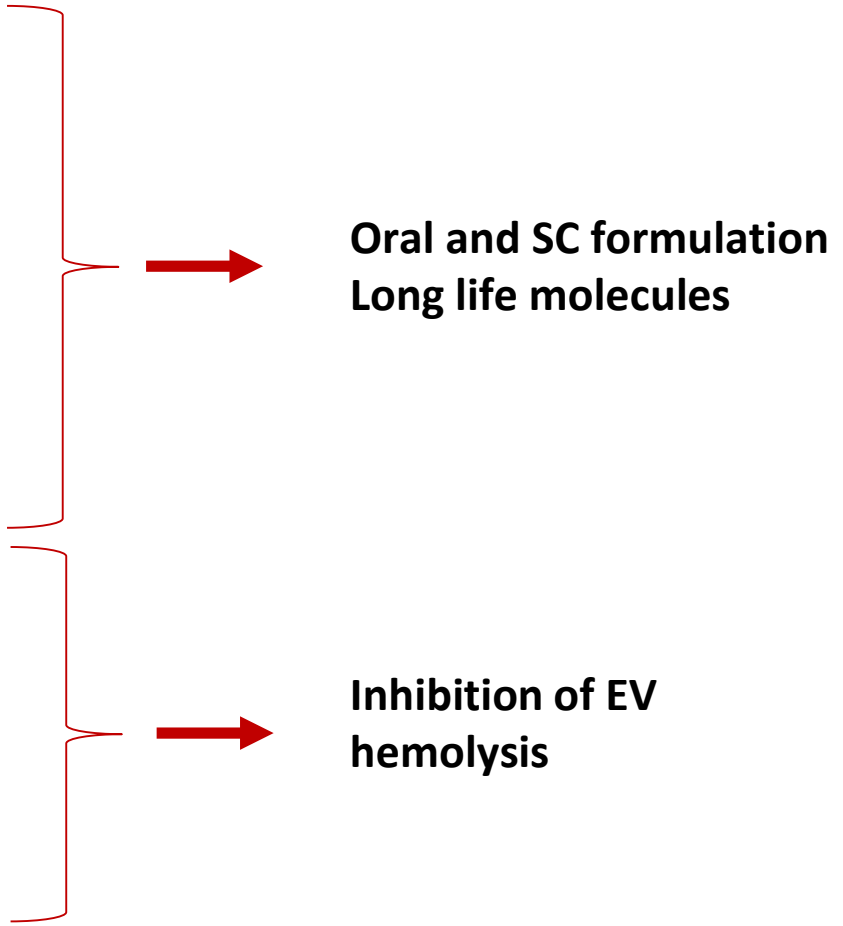


Lee et al, Blood 2018 ; Kulasekaraj et al, Blood 2018

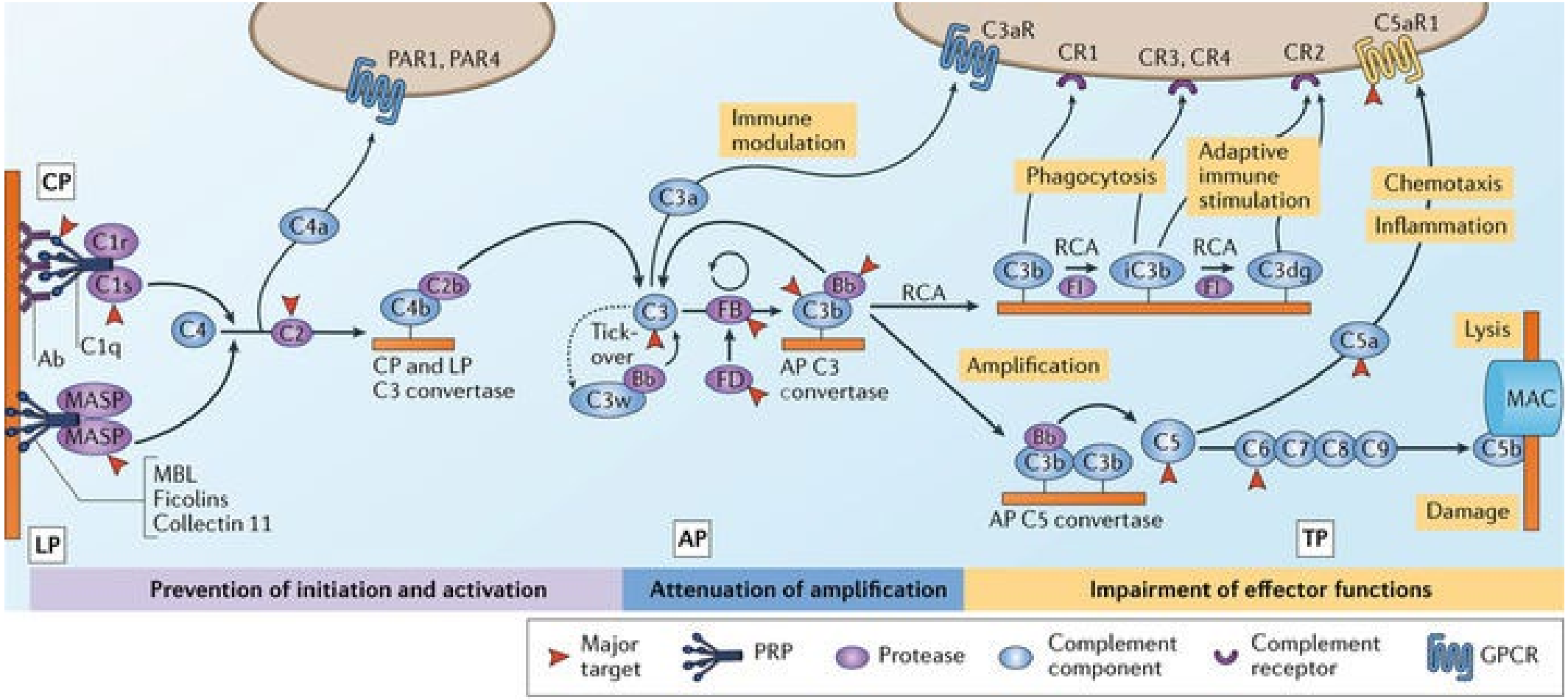
New Treatments of PNH : Ravulizumab



Lee et al, Blood 2018 ; Kulasekaraj et al, Blood 2018


Oral and SC formulation
Long life molecules
Inhibition of EV hemolysis
cholecystitis, thrombosis

New Target of PNH treatments



Nature Reviews | Nephrology

Ricklin , Nat Rev Nephrol 2018

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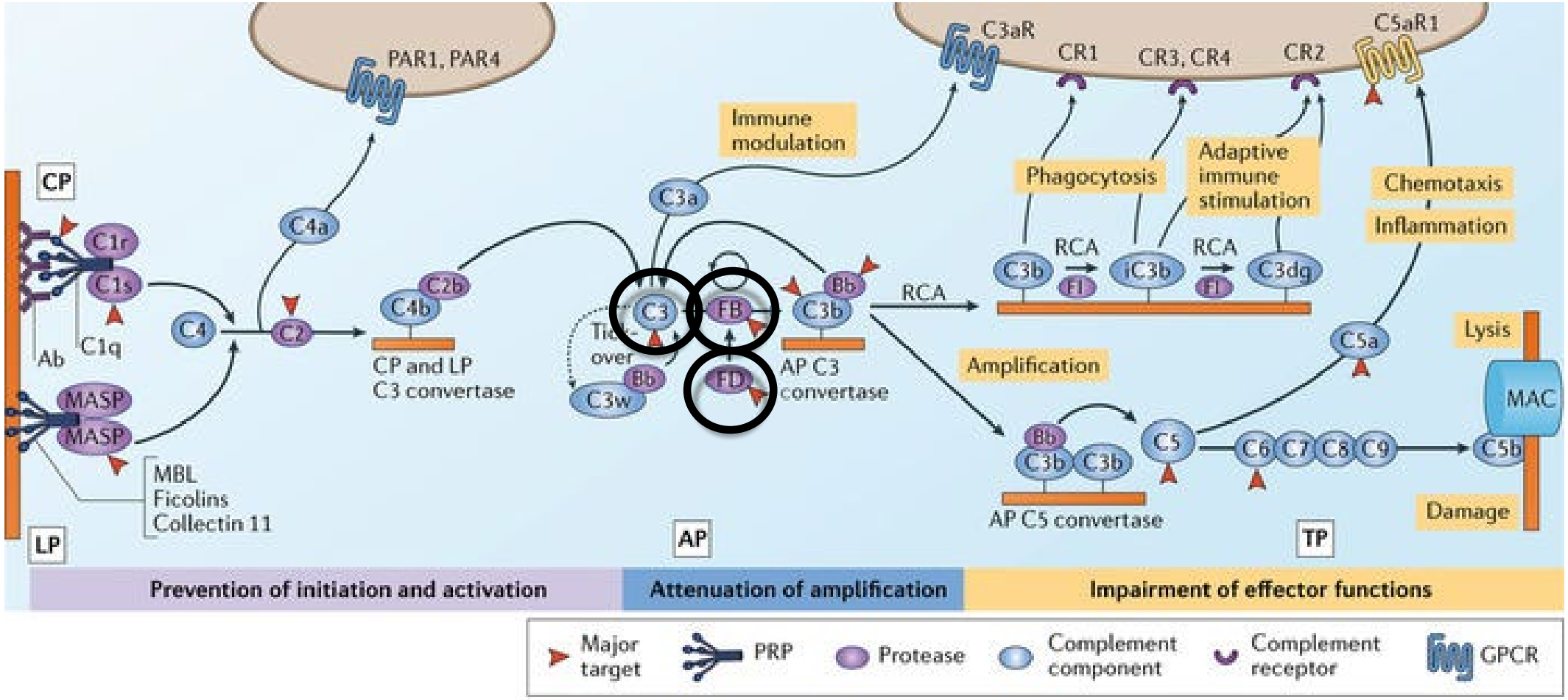
New Target of PNH treatments



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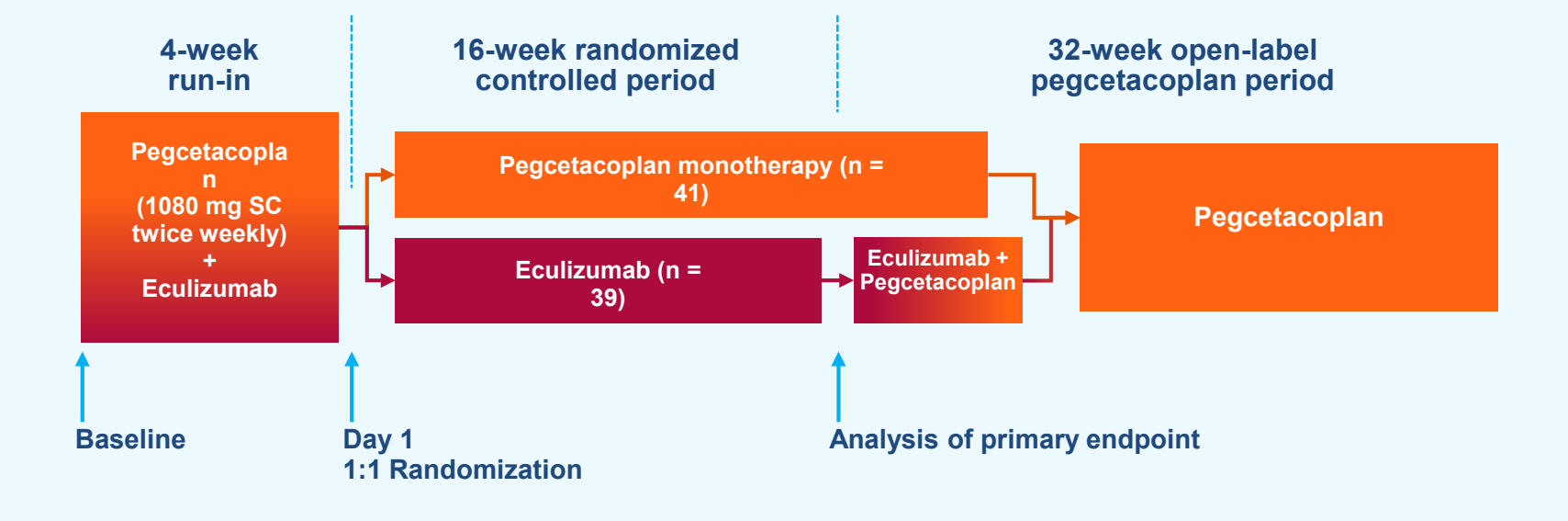
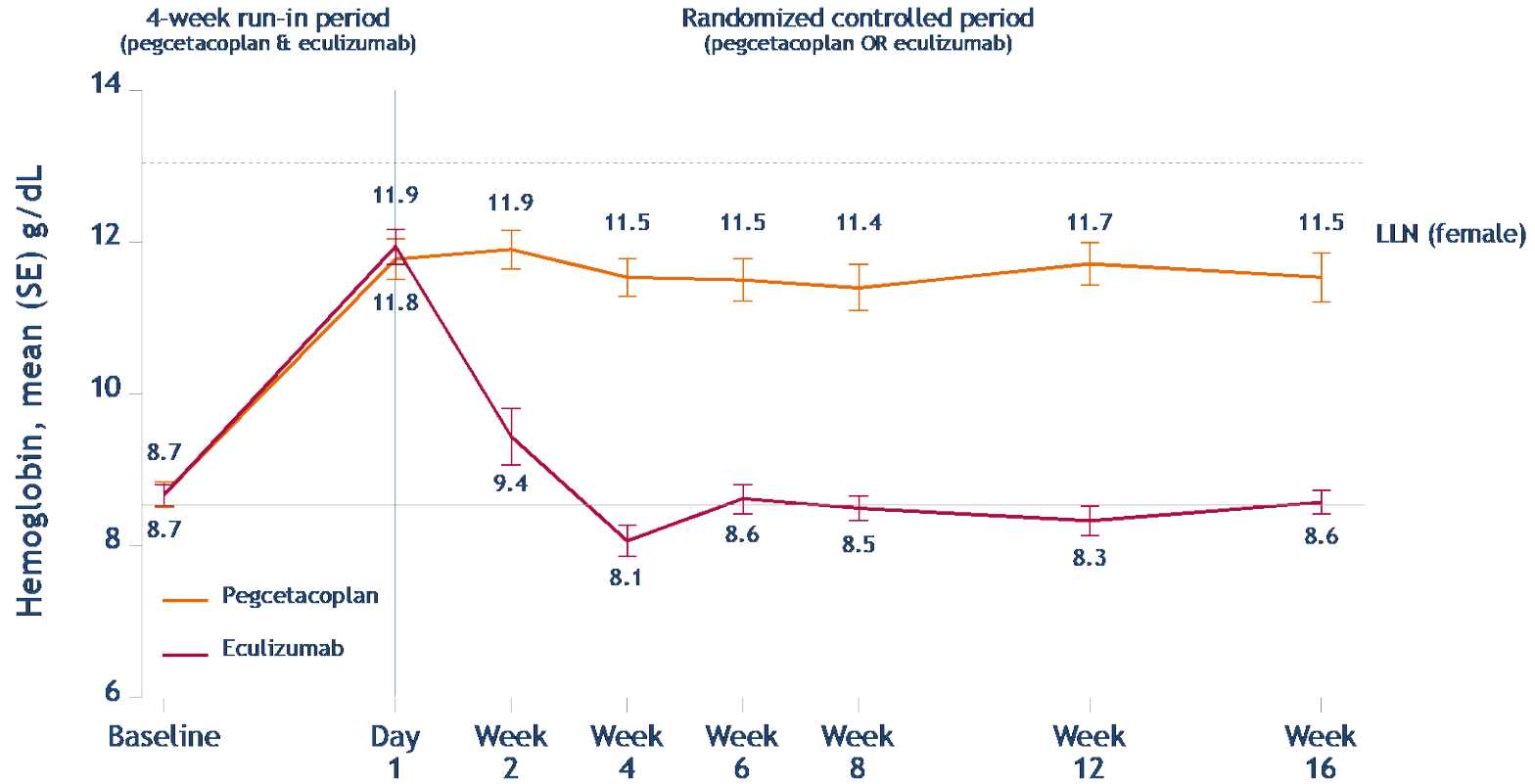
Pegcecatoplan

- C3 Inhibitor
- SC
- Eculi > 3 mois,
- Hb < 10,5, retic > N



Hemoglobin, mean (SD) g/dL	8.69 (1.08)	8.68 (0.89)
≥4 transfusions in previous 12 months, n (%)	21 (51.2)	23 (59.0)
Reticulocyte count, mean (SD) ×10⁹/L	217.5 (75.0)	216.2 (69.1)
LDH level, mean (SD) U/L [NRR: 113–226]	257.5 (97.6)	308.6 (284.8)

Hillmen, *NEJM 2021*

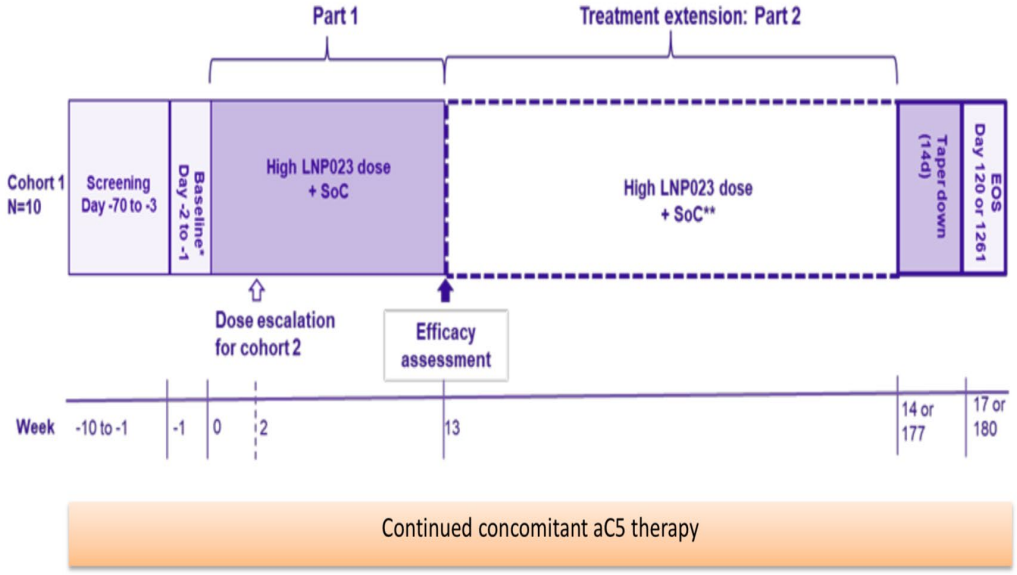


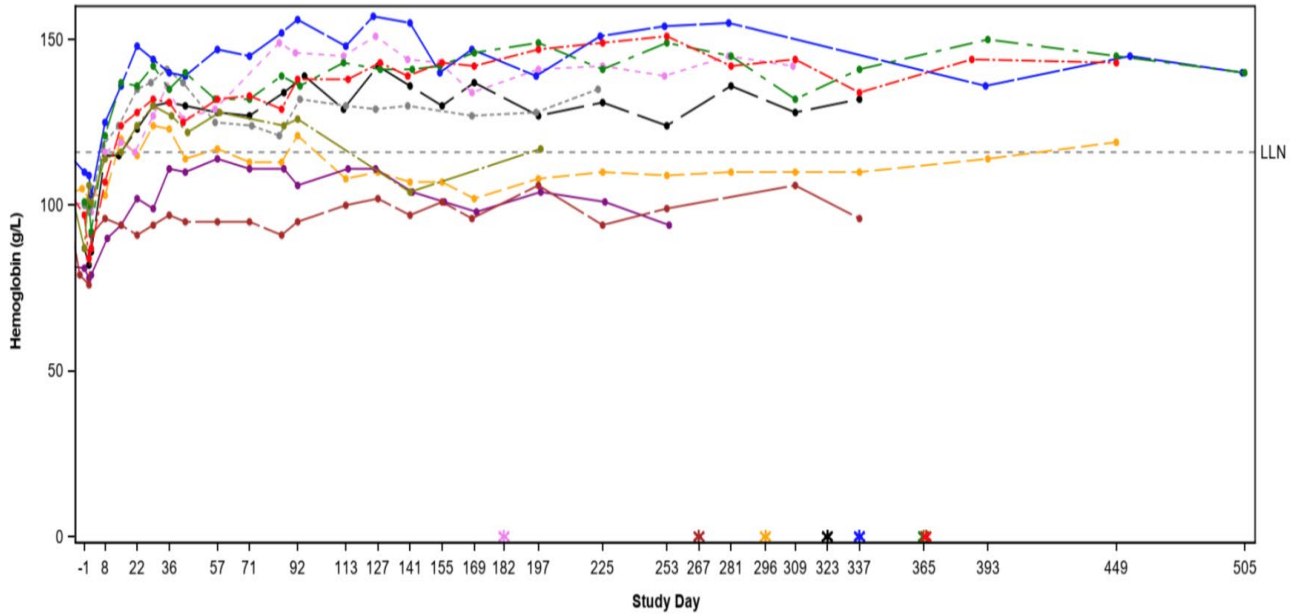
Hillmen, *NEJM 2021*

Iptacopan

- Factor B Inhibitors
- Oral
- Eculi > 6 mois,
- Hb < 10,5, retic > N

Risitano, *Lancet 2021*





100% Transfusion free

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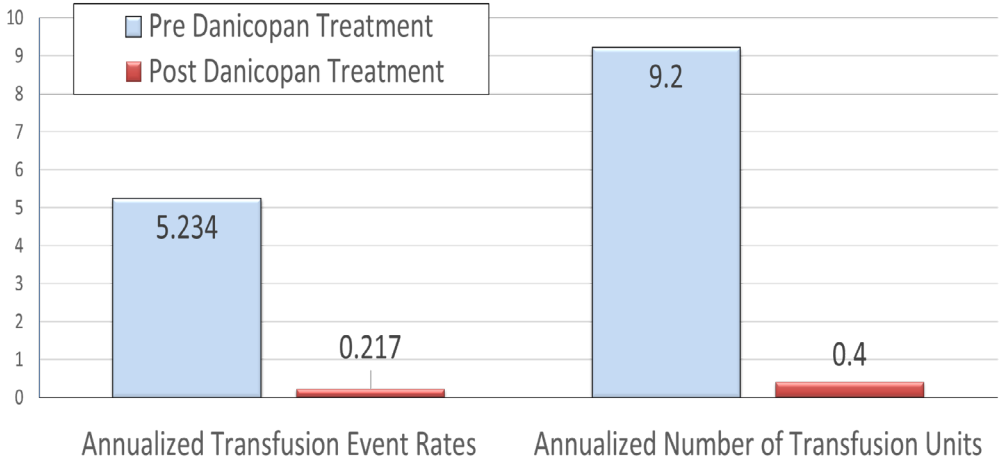
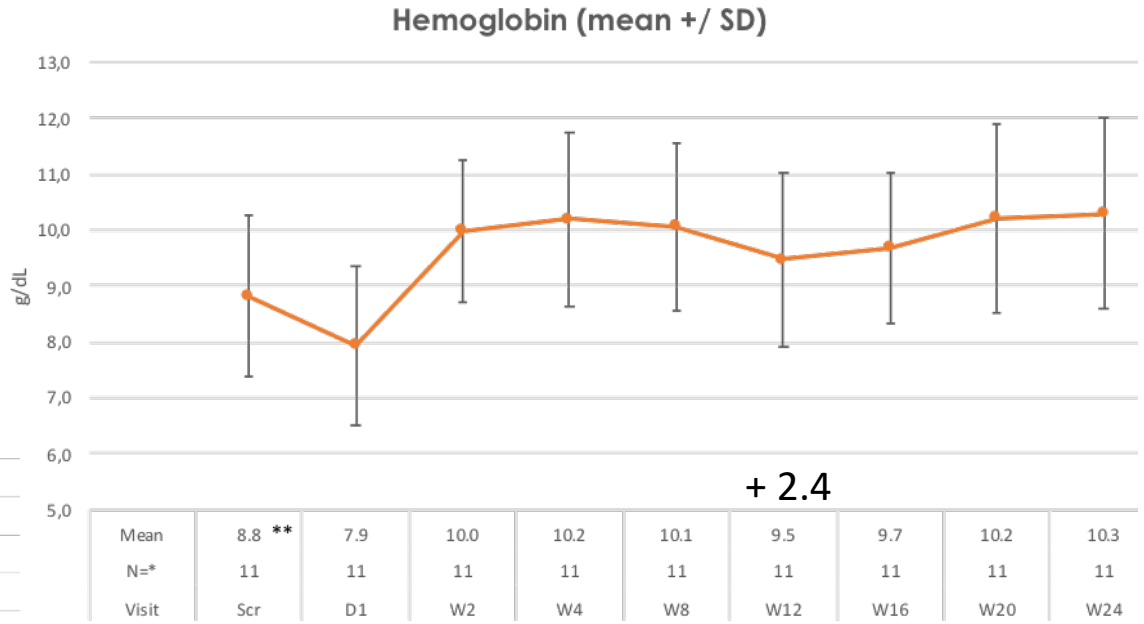
- Danicopan
- Oral Factor D inhibitor
- Eculi > 6 months,
- Hémolysis with transfusion needs
- Bithérapie avec eculizumab





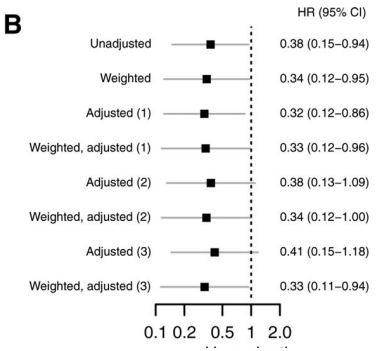
Kulasekararaj et al. Blood (2019) 134 (Supplement_1): 3514. https://doi.org/10.1182/blood-2019-124748.

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

Patients Webinars
AA and PNH
Topic On Focus
EuroBloodNet

- **All complement inhibitors are associated with a risk of encapsulated bacterial infections**
  - Vaccinations against Meningococcus, Pneumococcus and Haemopilus Influenzae
  - Vaccination against Flu
  - Daily antibiotics prophylaxis
  - Intravenous antibiotic injection in case of fever

- **Bone marrow in PNH is abnormal and there is a risk of evolution to AA and myeloid malignancies**



- **Pregnancies in PNH and AA are associated with an increased risk of complications for mothers and babies**

1. **PNH is associated with hemolysis and thrombosis**
2. **Only complement inhibitors prevent hemolysis and thrombosis**
3. **PNH and AA are strongly associated**

Discussion