Day in Complement | 20 September 2025

Optimizing PNH Management

New Treatments, New Discussions, New Decisions

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Disclosures

Consultancy Honouraria: *Alexion, Apellis, BioCryst, Novartis, Roche, Sanofi, Sobi, Takeda*

Speaking Honouraria: *Alexion, Sobi*

Clinical Trial Involvement:

- *Alexion (ALXN1210-301, -302, -311, -HSCT-313, ALXN2040-301, ALXN2050)**
- *Apellis (APL2-302, -307)**
- *BioCryst (BCX9930 – REDEEM-1, REDEEM-2)**
- *Regeneron (ACCESS-1)**
- *Roche (COMMUTE-a)**
- *Amgen (ABP959)†*
- *Novartis (LNP023)†*

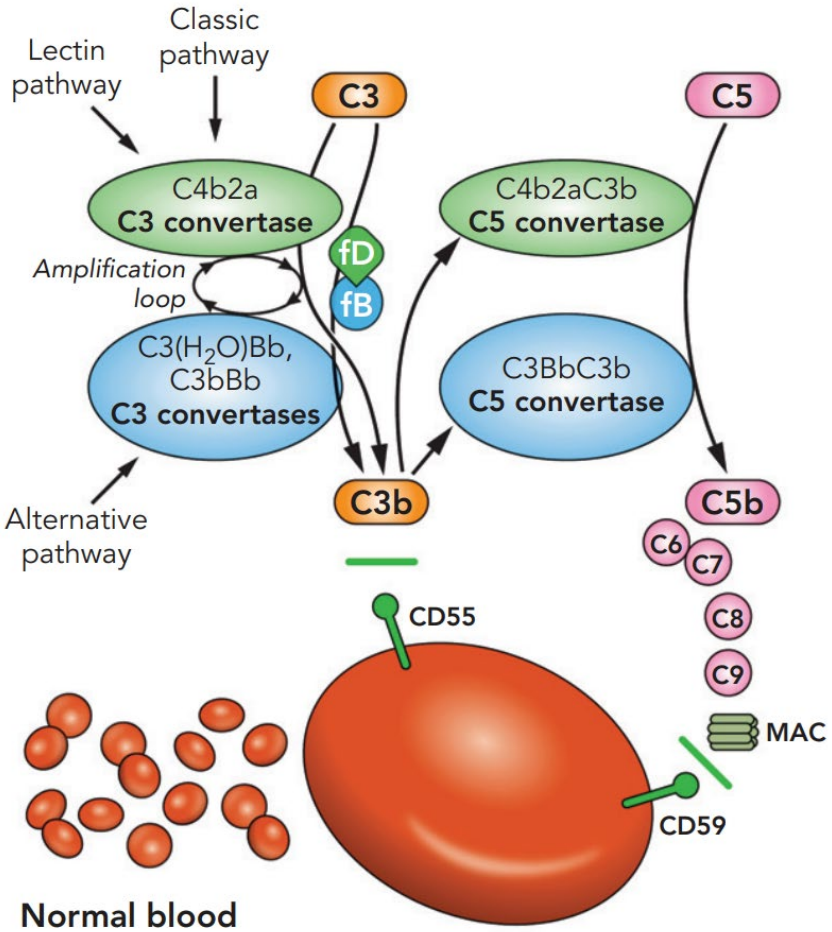
**** Site Principal Investigator***
† Member, Data Monitoring Committee

Objectives

- Review the pathophysiology of paroxysmal nocturnal hemoglobinuria (PNH)
- Explore the clinical presentation, recognition, and diagnosis of PNH
- Describe the impact of complement inhibition
- Present a treatment algorithm reflective of the Canadian landscape

Paroxysmal Nocturnal Hemoglobinuria

- Acquired clonal abnormality of HSCs (*PIGA*)
  - 1-5 per million/year, 15 per million population
  - Absent complement regulators CD55 & CD59
- Classical triad
  - DAT-negative hemolysis, thrombosis, BMF
- Common clinical features
  - Chest pain, dyspnea, abdominal pain, renal failure
  - Smooth muscle dystonia (ex. pHTN, dysphagia, ED)
  - Fatigue, impaired QoL



Brodsky RA (2015) *Blood*
Luzzatto L (2016) *F1000 Research*
Hill A *et al.* (2017) *Nat Dis Prim*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

Paroxysmal Nocturnal Hemoglobinuria

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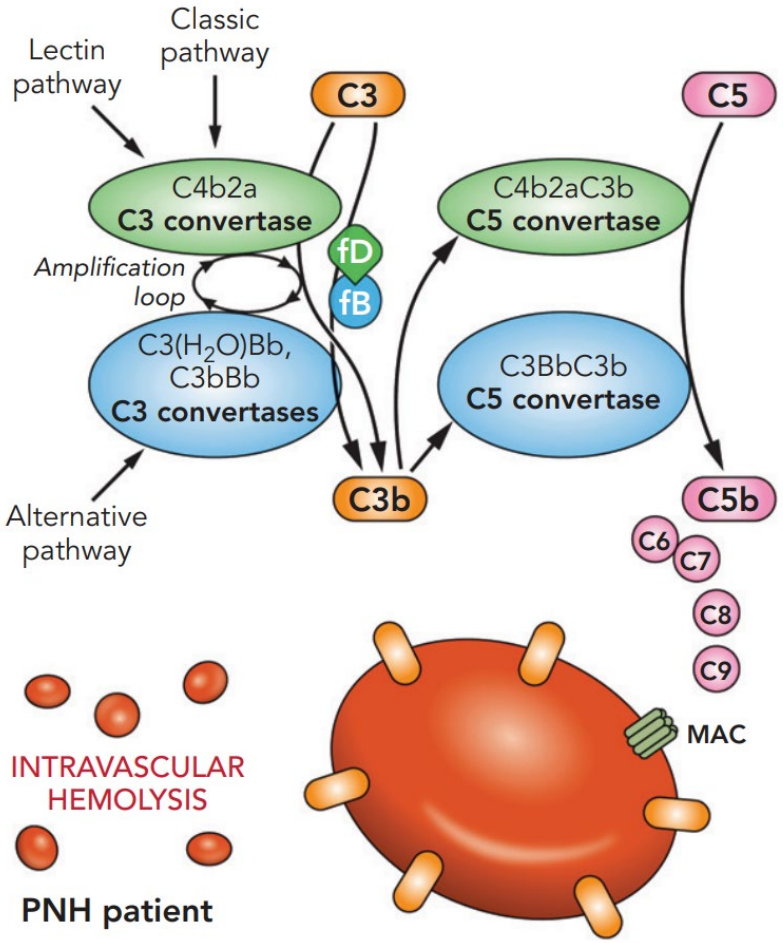

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Luzzatto L (2016) *F1000 Research*
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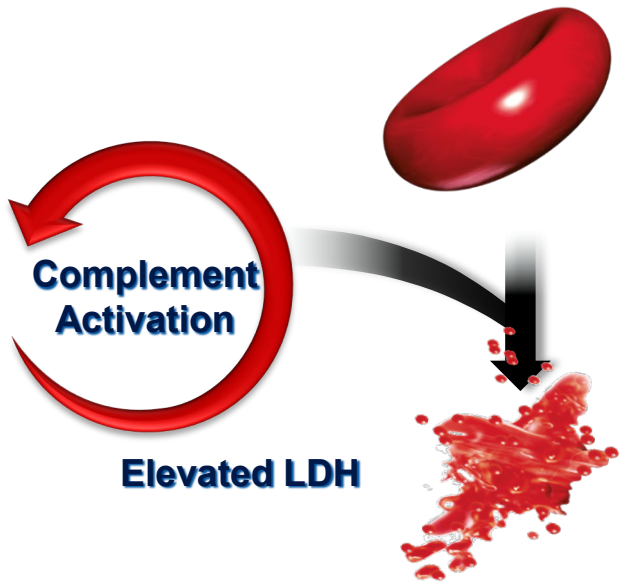
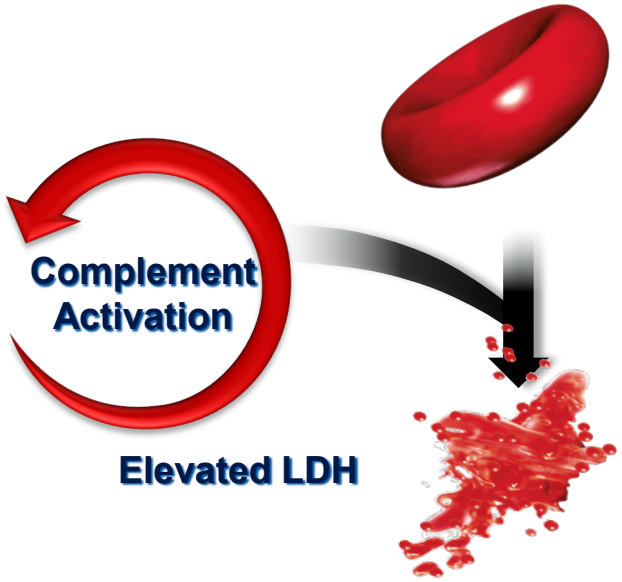
Uncontrolled Complement in PNH

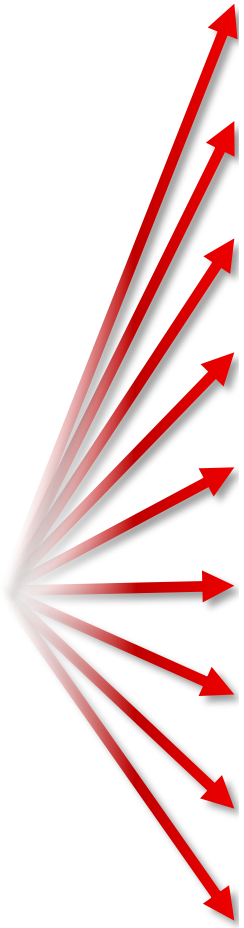


Presenting symptom/sign[b]	All patients with PNH clone	Patients on eculizumab	Patients not on eculizumab
Elevated LDH ≥ 1.5 × ULN	43/107 (40.2%)	33/37 (89.2%)	10/70 (14.3%)
LDH ratio × ULN, mean (SD)	2.9 (3.6)	5.9 (4.5)	1.2 (1.2)
Granulocyte clone			
<10%	45/97 (46.4%)	1/32 (3.1%)	44/65 (67.7%)
10% to <50%	19/97 (19.6%)	3/32 (9.4%)	16/65 (24.6%)
≥50%	33/97 (34.0%)	28/32 (87.5%)	5/65 (7.7%)
Erythrocyte clone >10%	33/94 (35.1%)	25/31 (80.6%)	8/63 (12.7%)
Transfusion dependence	64/116 (55.2%)	21/24 (87.5%)	43/92 (46.7%)
BMF syndrome (%)			
AA	73/147 (49.7)	17/64 (26.6)	56/83 (67.5)
MDS	20/147 (13.6)	7/64 (10.9)	13/83 (15.7)
History of TE (%)			
Venous	16/144 (11.1)	12/65 (18.5)	4/79 (5.1)
Arterial	2/143 (1.4)	2/65 (3.1)	0/78 (0.0)
Abdominal pain	55/126 (43.7)	27/41 (65.9)	28/85 (32.9)
Dysphagia	22/126 (17.5)	11/41 (26.8)	11/85 (12.9)
Dyspnea	71/126 (56.3)	24/41 (58.5)	47/85 (55.3)
Pulmonary hypertension	3/140 (2.1)	2/66 (3.0)	1/74 (1.4)
Hemoglobinuria	49/125 (39.2)	31/41 (75.6)	18/84 (21.4)
Fatigue	111/126 (88.1)	40/41 (97.6)	71/85 (83.5)
ED in males	13/58 (22.4)	4/18 (22.2)	9/40 (22.5)

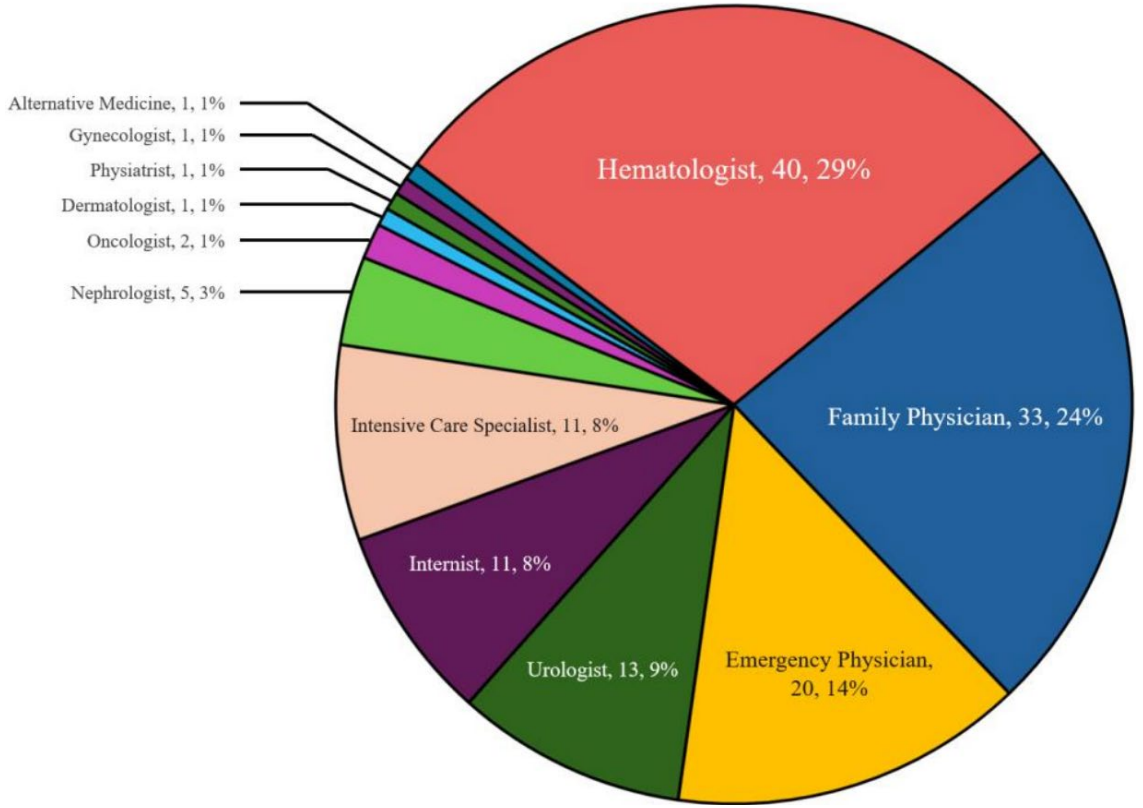
Hill A *et al.* (2005) *Haematologica*
Lee JW *et al.* (2010) *Haematologica*
Hillmen P *et al.* (2010) *Am J Hematol*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

Uncontrolled Complement in PNH



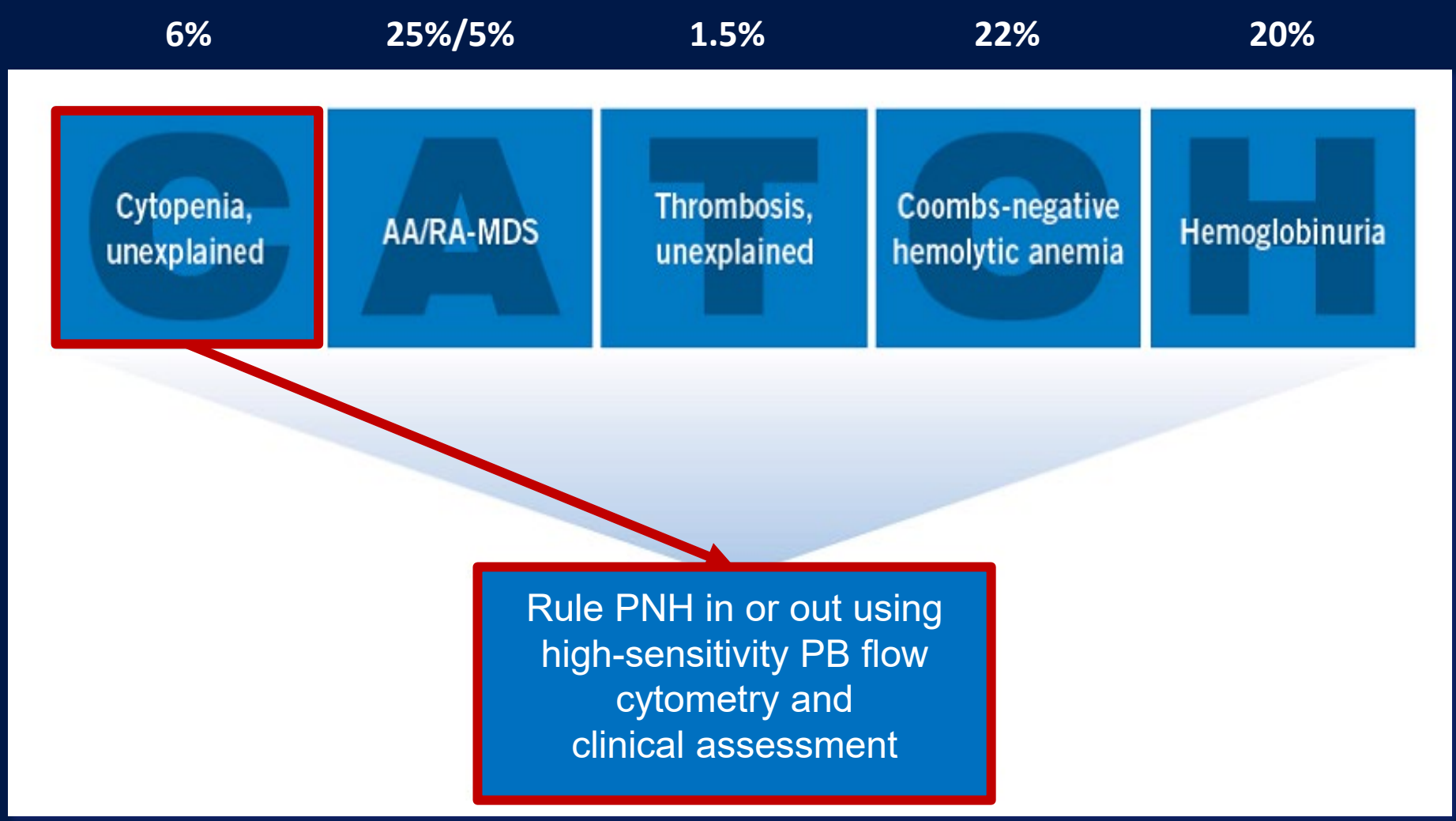


Rho, Yang, Chow & Patriquin, *in press*.



Hill A *et al.* (2005) *Haematologica*
Lee JW *et al.* (2010) *Haematologica*
Hillmen P *et al.* (2010) *Am J Hematol*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

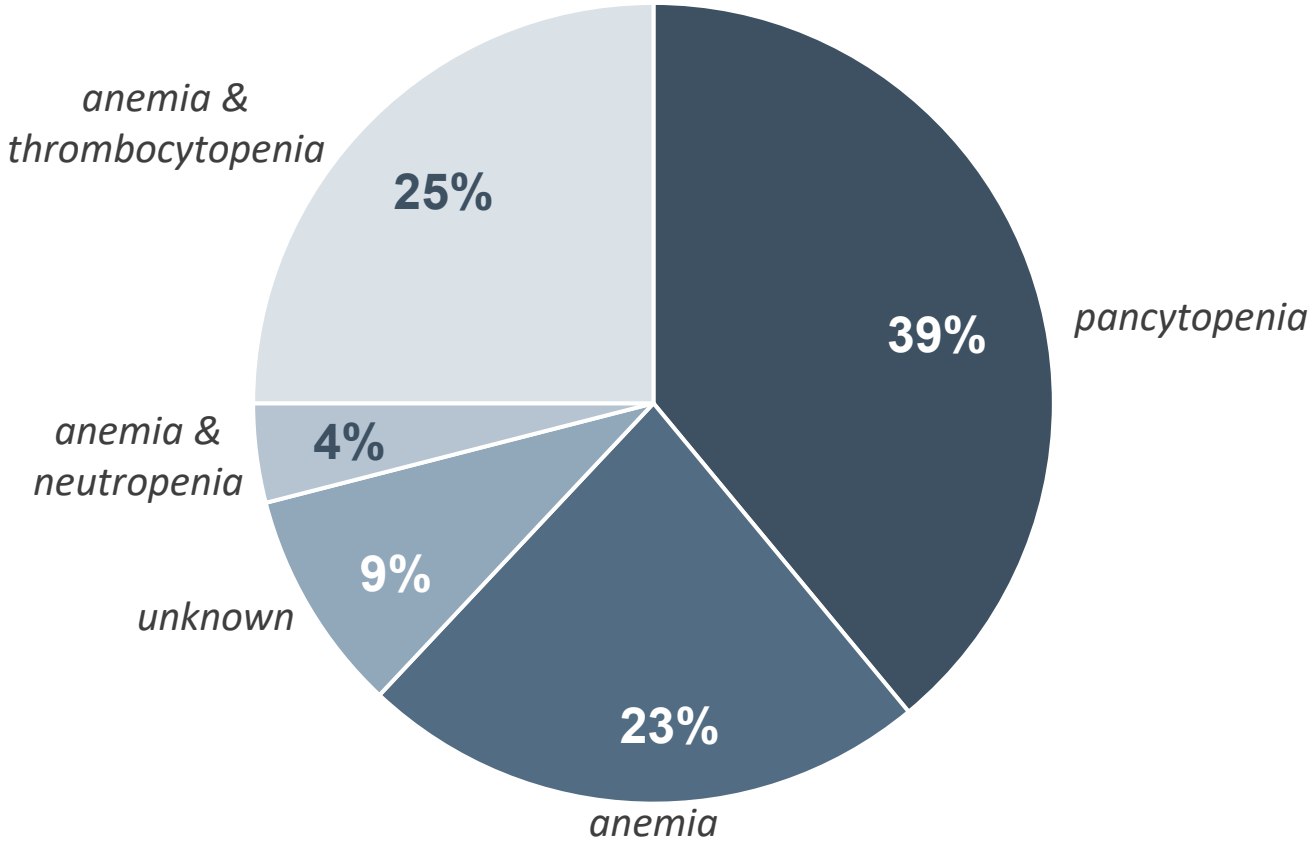
DIAGNOSIS OF PNH



Movalia M *et al.* (2011) *ASH 2011 Abstract #1033*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

Cytopenias in PNH

91% of patients with PNH clones present with cytopenia(s)



In a Canadian study only

10.4%

of patients with unexplained cytopenias were tested for PNH, despite potential indicators of hemolysis in **24.2%** of all cytopenic patients

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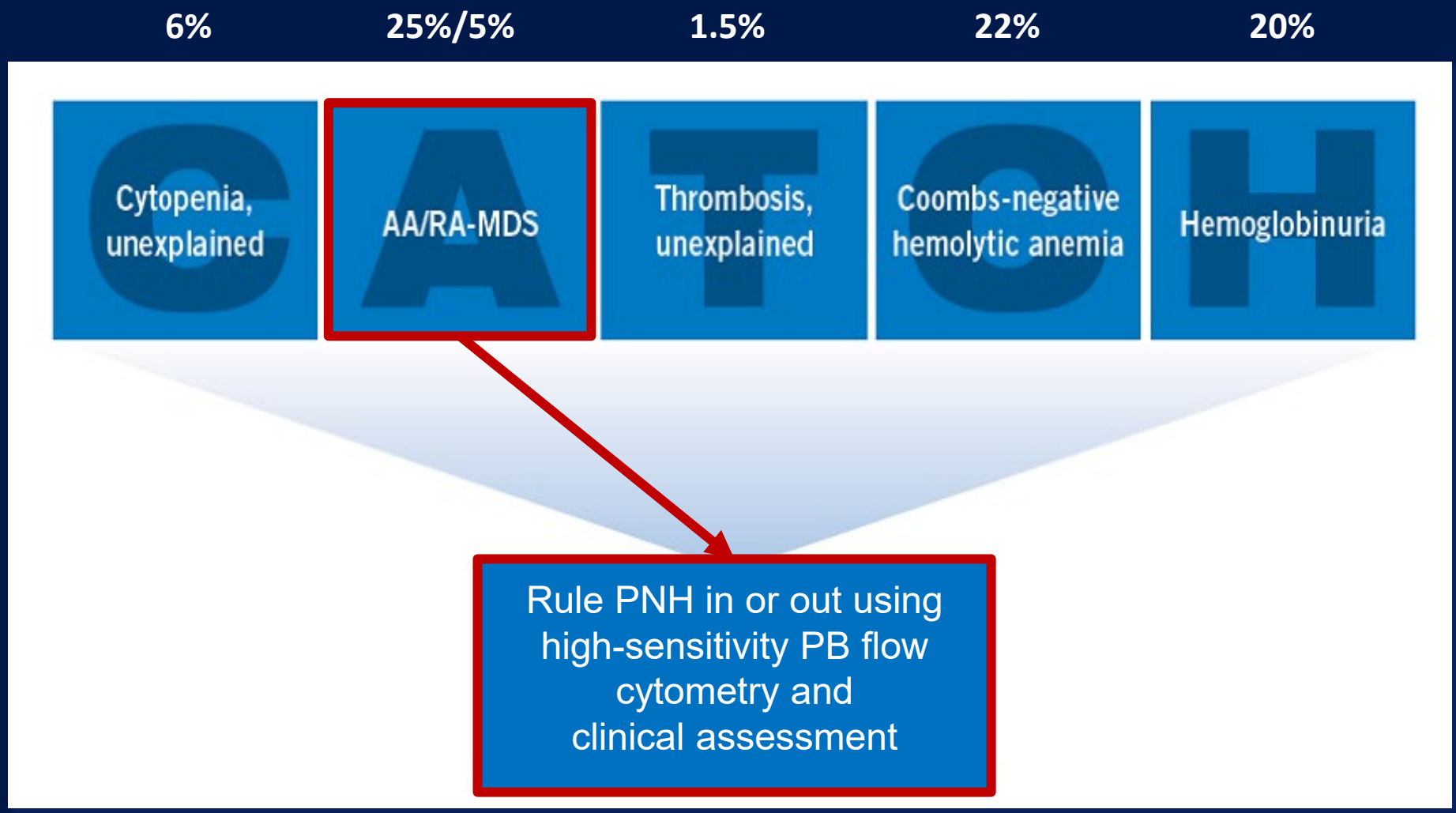
CANADIAN PNH NETWORK

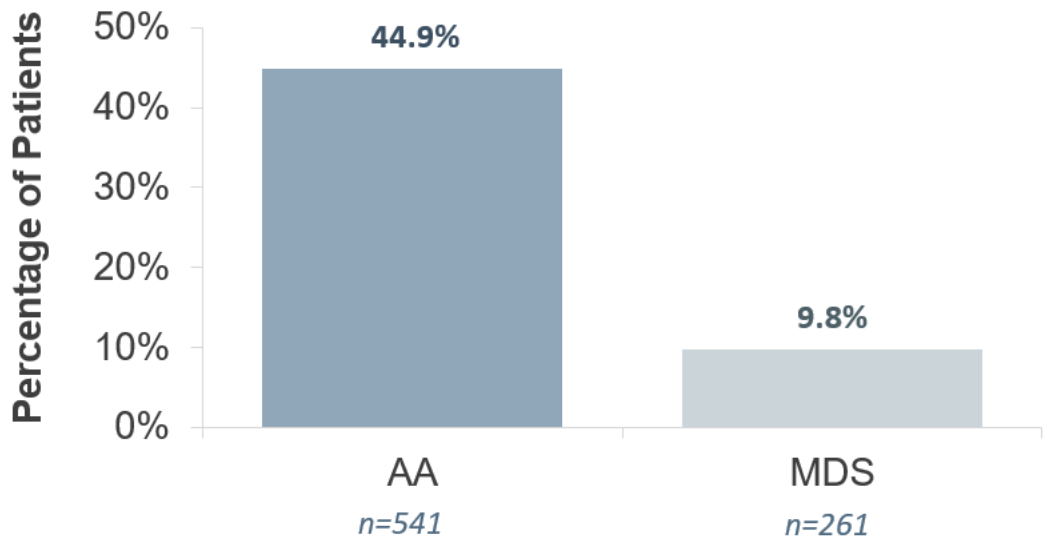
Peffault de Latour R *et al*. (2008) *Blood*
England J *et al.* (2016) Poster presented at EHA 2016 # E1011



Movalia M *et al.* (2011) *ASH 2011 Abstract #1033*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

Bone Marrow Failure & PNH

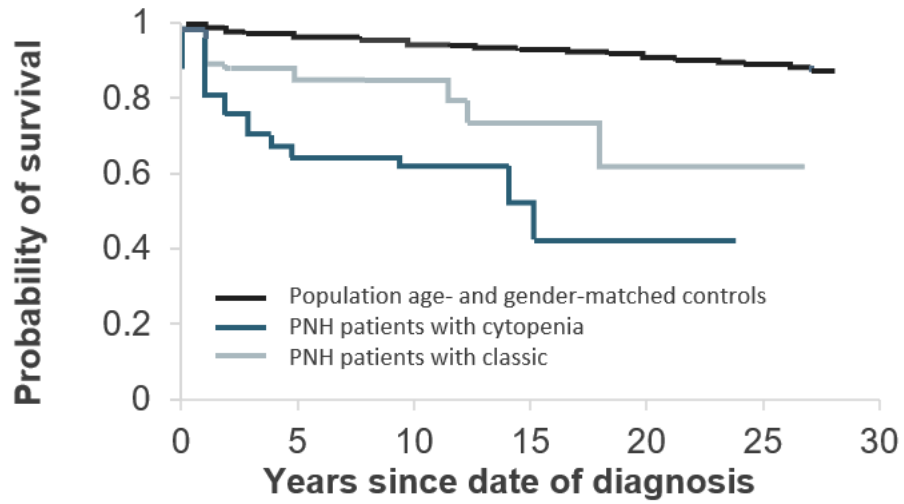
Percentage of Patients With >0.01% PNH Cells



MDS: In a Canadian center only **7% (11/152)** of patients diagnosed with MDS since 2009 have had PNH testing done

Presenting BMF in the International PNH registry

BMF syndrome %	International PNH registry	Canadian patients
AA	2206/4201 (52.5)	73/147 (49.7)
Other BMF (incl. MDS)	424/4201 (10.1)	20/147 (13.6)



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CANADIAN PNH NETWORK

Morado M *et al.* (2017) *Cytometry B Clin Cytom*
Wong SA *et al.* (2018) *Curr Oncol*
Schrezenmeier H *et al.* (2020) *Ann Hematol*
Patriquin CJ *et al.* (2019) *Eur J Haematol*

Bone Marrow Failure & PNH

Testing for GPI-deficient cells by high-sensitivity flow cytometric analysis at diagnosis of AA is recommended by:

International PNH Interest Group

"Patients with aplastic anemia [should be screened] at diagnosis…"

International Clinical Cytometry Society

Clinical indications for PNH include: "Evidence of bone marrow failure", including "suspected or proven aplastic or hypoplastic anemia."

British Committee for Standards in Haematology

"Patients should be screened for PNH at the diagnosis of AA."

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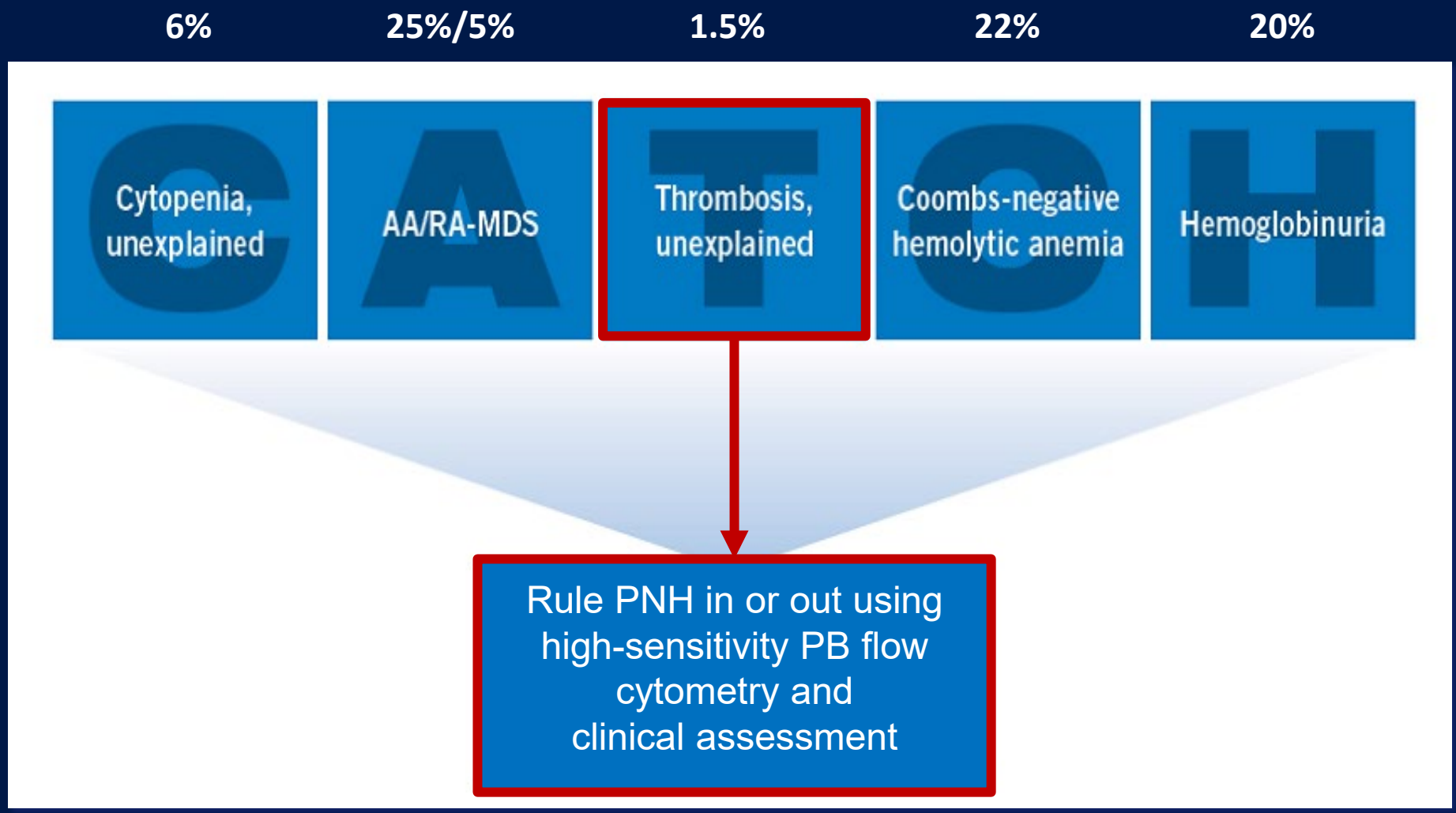
CANADIAN PNH NETWORK

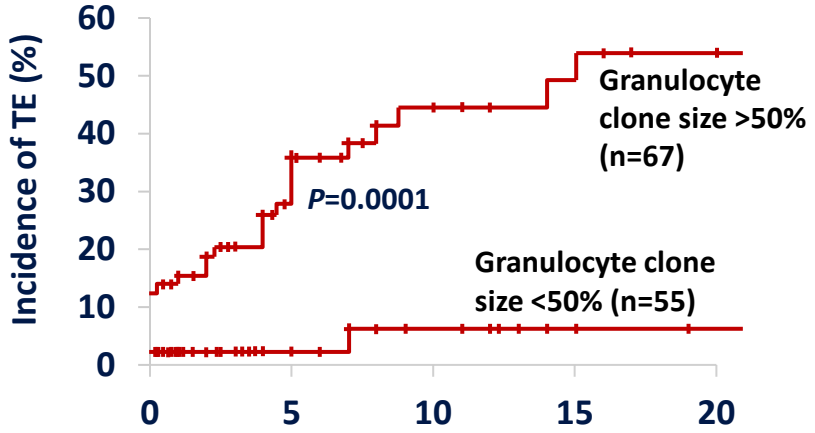
Parker C *et al.* (200) *Blood*
Borowitz MJ *et al.* (2010) *Cytometry B Clin Cytom*
Killick SB *et al.* (2016) *Br J Haematol*
Schrezenmeier H,*et al.* (2020) *Ann Hematol*



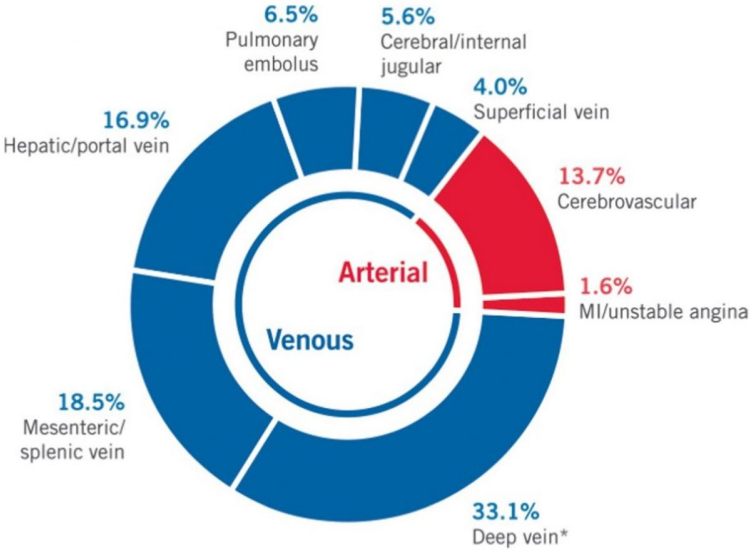
Movalia M *et al.* (2011) *ASH 2011 Abstract #1033*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

Clinical Presentation & Thromboembolism Risk

"We can safely say that PNH is the most vicious acquired thrombophilic state known in medicine" ~ L. Luzzatto



- Thrombosis in 30-45% (10% at diagnosis)
- Leading cause of mortality (40-67%)
- Atypical (visceral, CNS) & typical sites
- Multiple sites in 20% of patients



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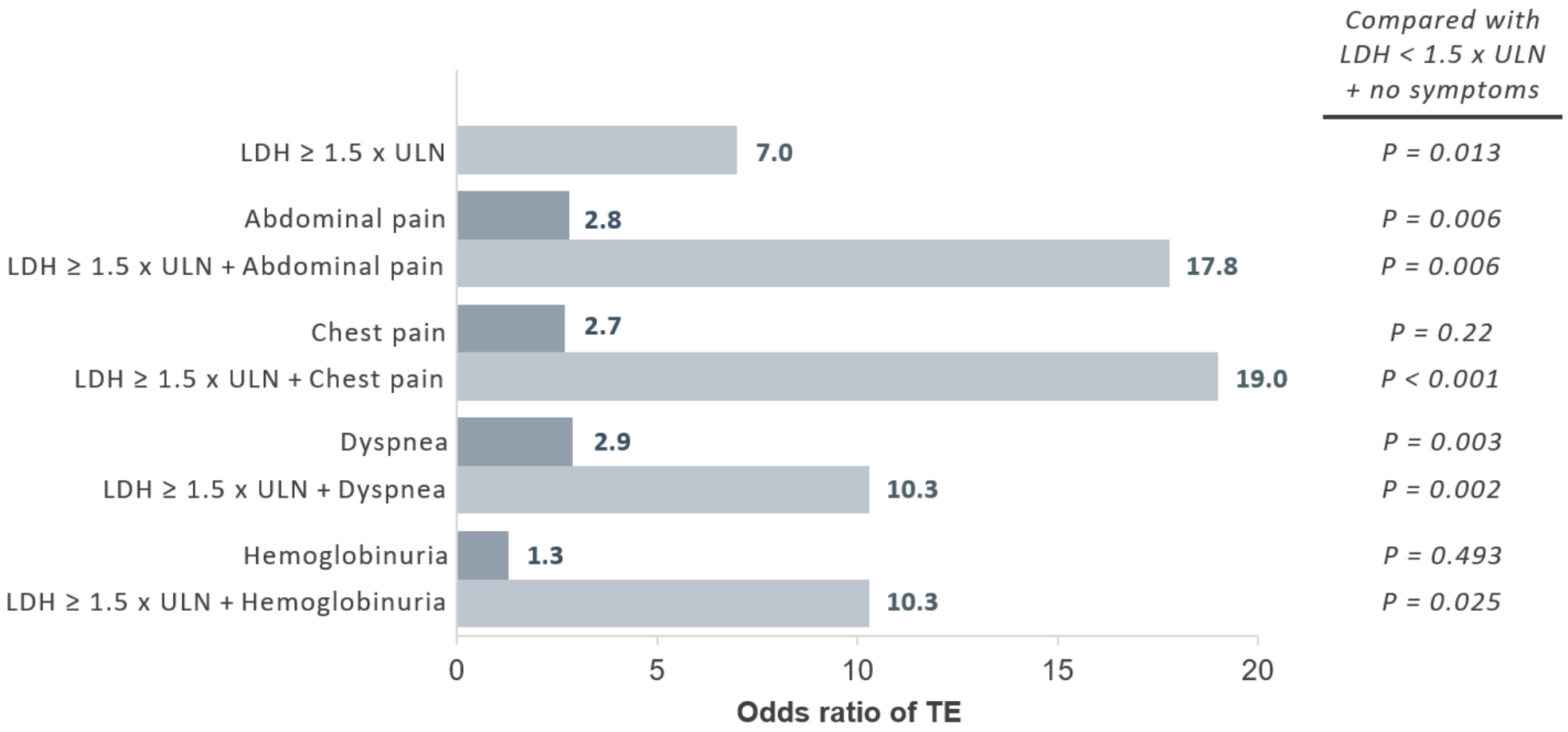
CANADIAN PNH NETWORK

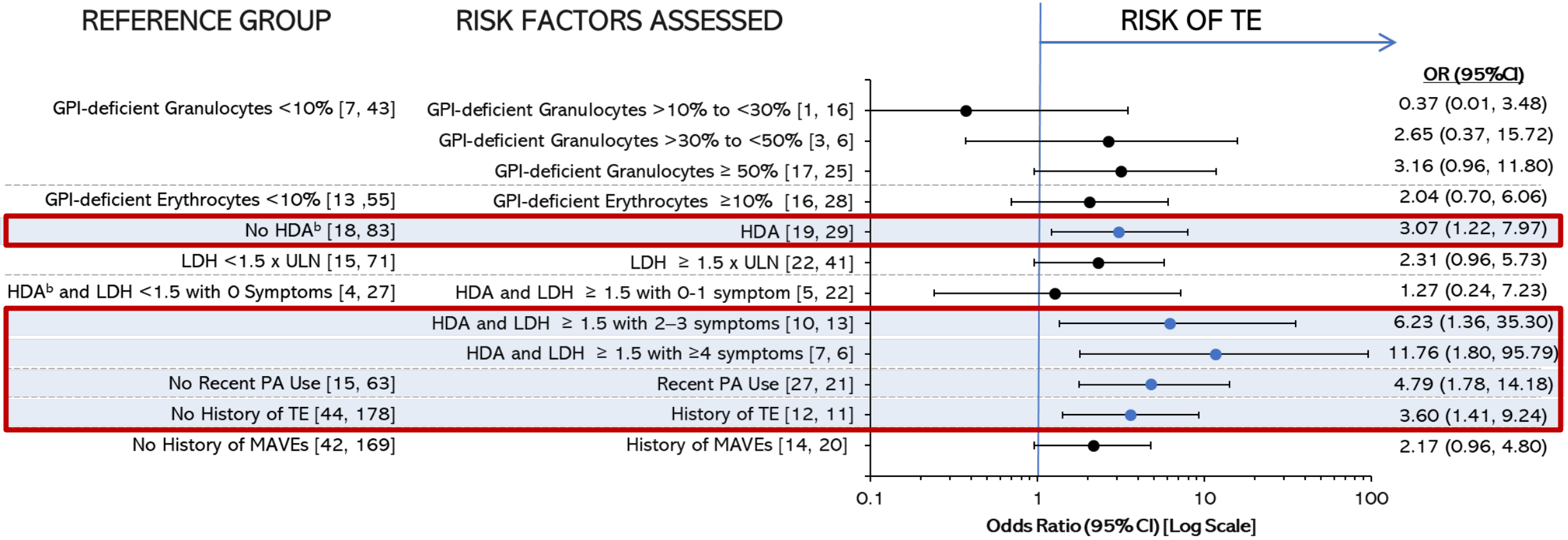
De Stefano V *et al.* (2002) *Haematologica*
Hill A *et al.* (2006) *Blood*
Hillment P *et al.* (2007) *Blood*
Hall C *et al.* (2003) *Blood*

VTE Risk & LDH Elevation



Lee JW *et al.* (2013) *Int J Hematol*

Risk Factors – LDH, HDA, and Prior TE



**HDA = hemolysis (LDH ≥1.5 x ULN) plus one or more of: fatigue, hemoglobinuria, abdominal pain, dyspnea, anemia, thromboembolism (TE) or other major adverse vascular event (MAVE), dysphagia or erectile dysfunction.*

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CANADIAN PNH NETWORK

Höchsmann B *et al.* (2023) *Annals of Hematology*

Thrombophilia Testing Algorithm

RECOMMENDATION

PDF

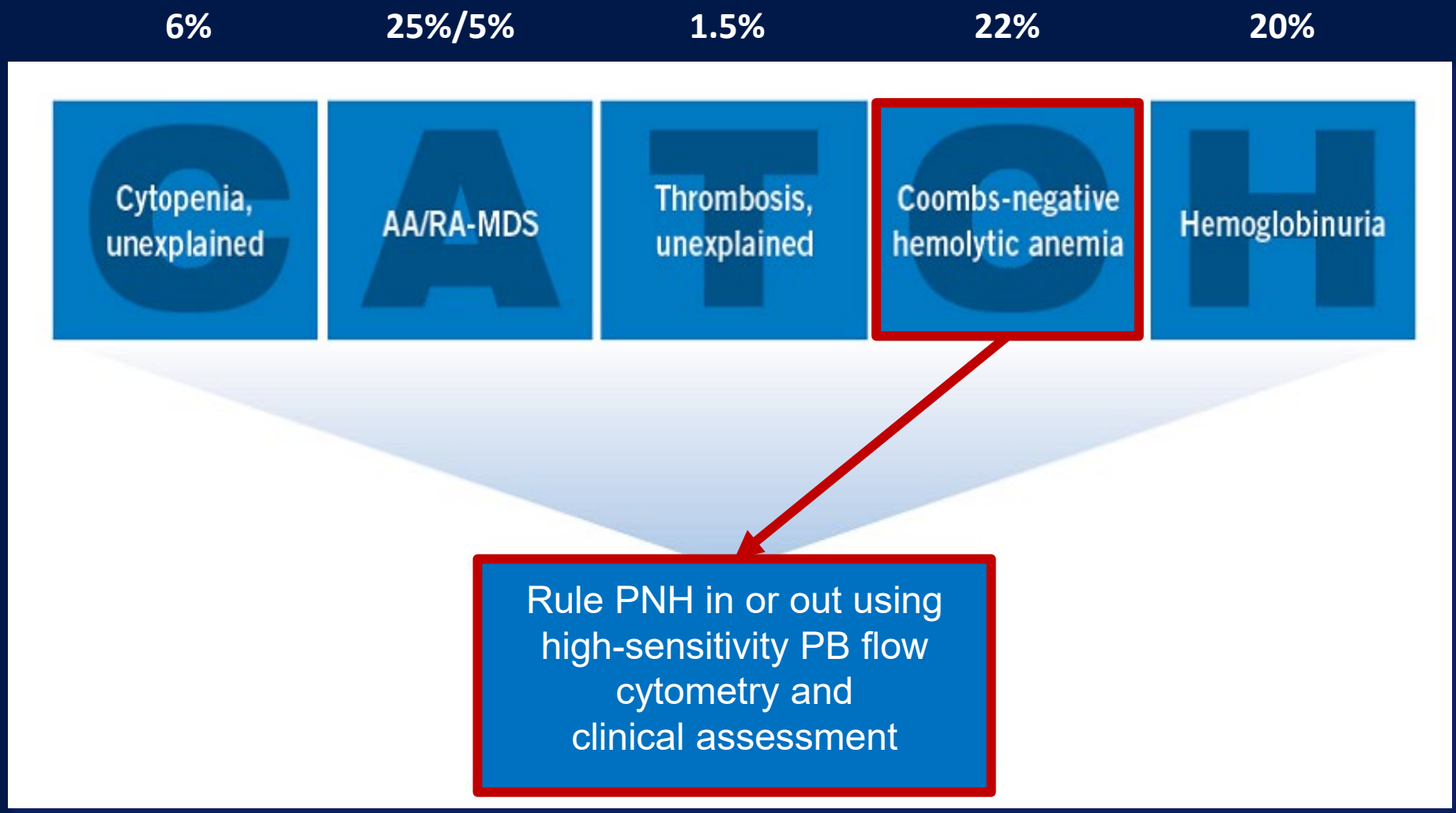
Consider thrombophilia testing* WITH specialist consultation if 1 or more of:

- Concomitant arterial disease
- Young age (<50 years old)
- Strong family history, i.e. first-degree family members affected at <50 years old
- CBC abnormalities (e.g. anemia, thrombocytopenia, thrombocytosis, polycythemia), consider MPN ? APS ? PNH ? HIT ?
- Autoimmune disease

Consider APS testing, especially in the case of arterial or recurrent events, and/or recurrent pregnancy loss. If abnormal results, repeat testing in 12 weeks, then refer.

Anticoagulants can interfere with many thrombophilia tests. Is your patient on anticoagulants? Click here for more information.

* *Only consider thrombophilia testing if the test results will make a difference in how you manage the patient.*



Movalia M *et al.* (2011) *ASH 2011 Abstract #1033*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

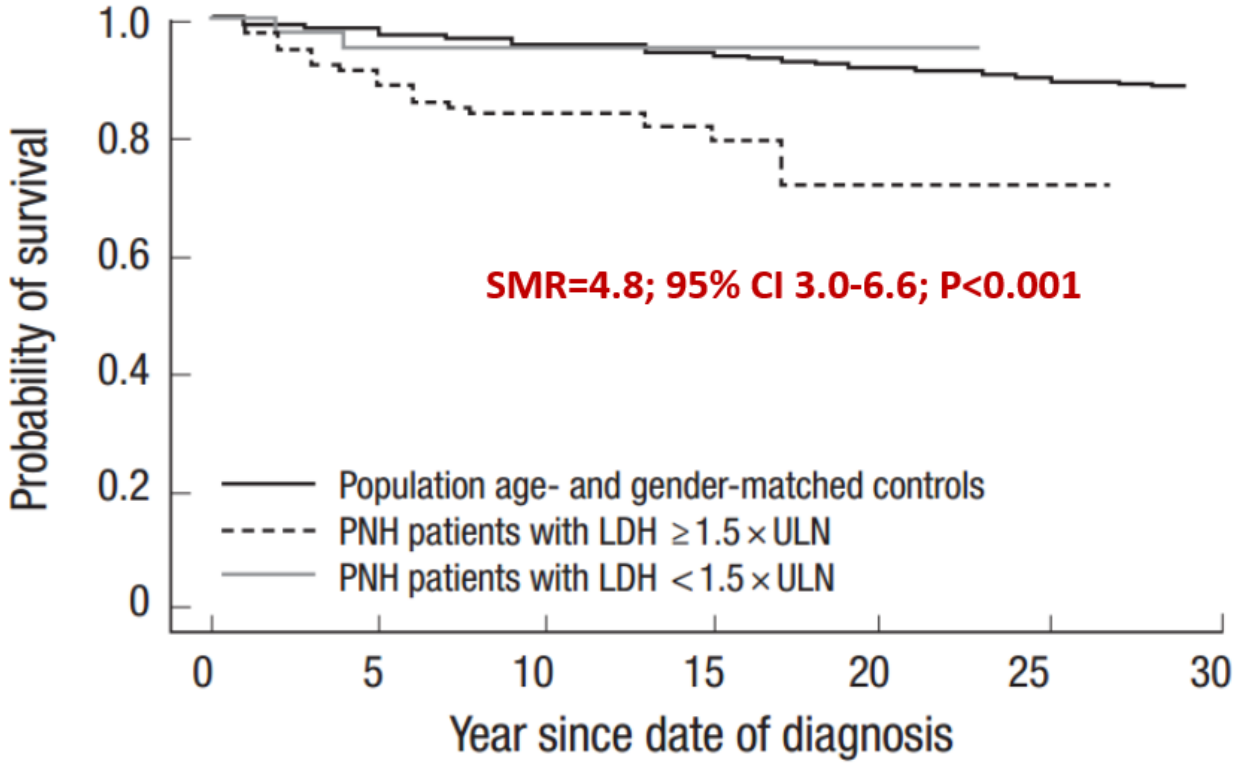
Intravascular Hemolysis Risk & PNH

18.6%

(n=382)

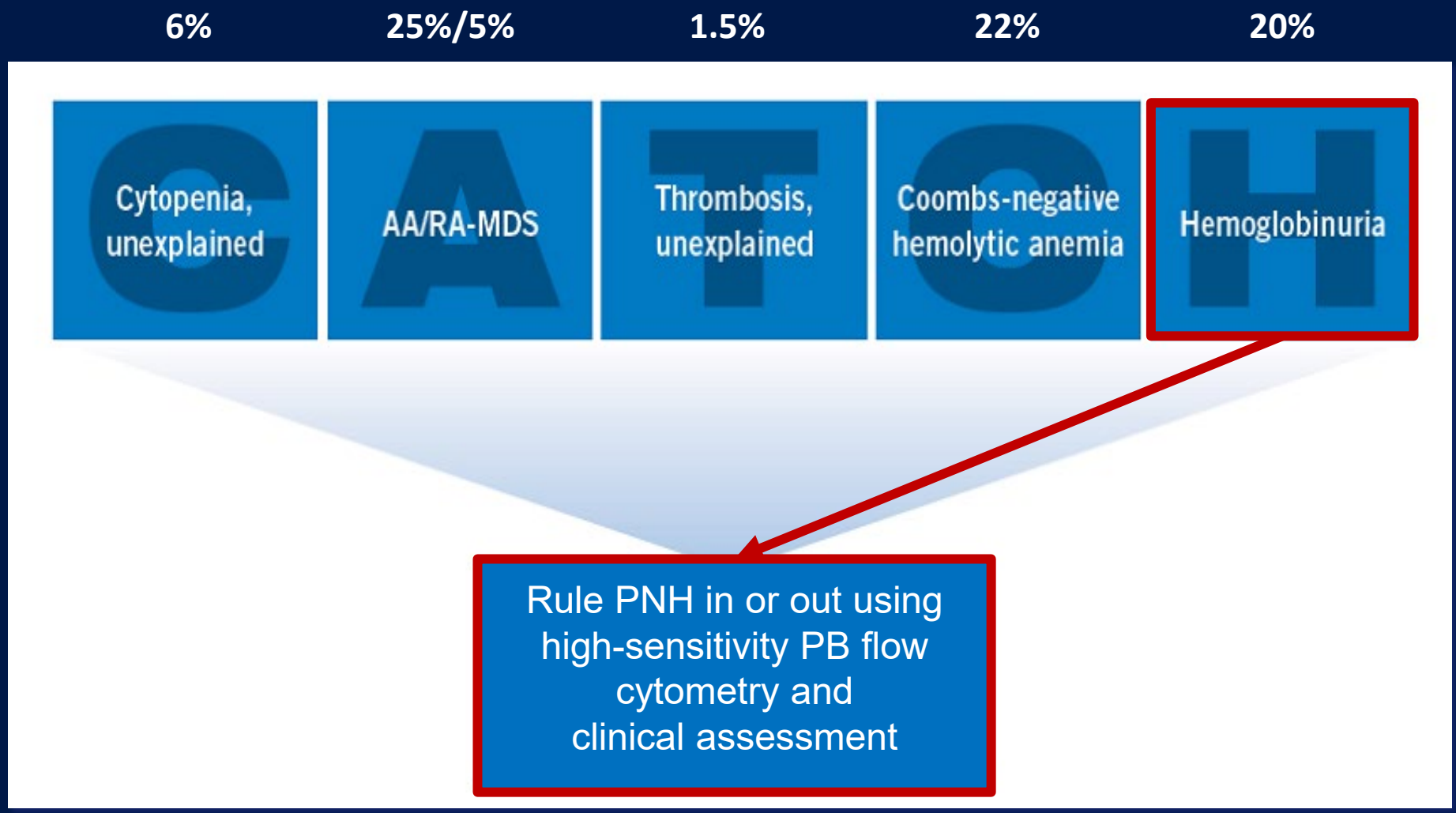
of patients screened for PNH because of hemolytic anemia had a PNH clone of >0.01%

Elevated hemolysis significantly increases the risk of mortality



Morado M *et al.* (2017) *Cytometry B Clin Cytom*

Jang J *et al.* (2016) *J Kor Med Sci*

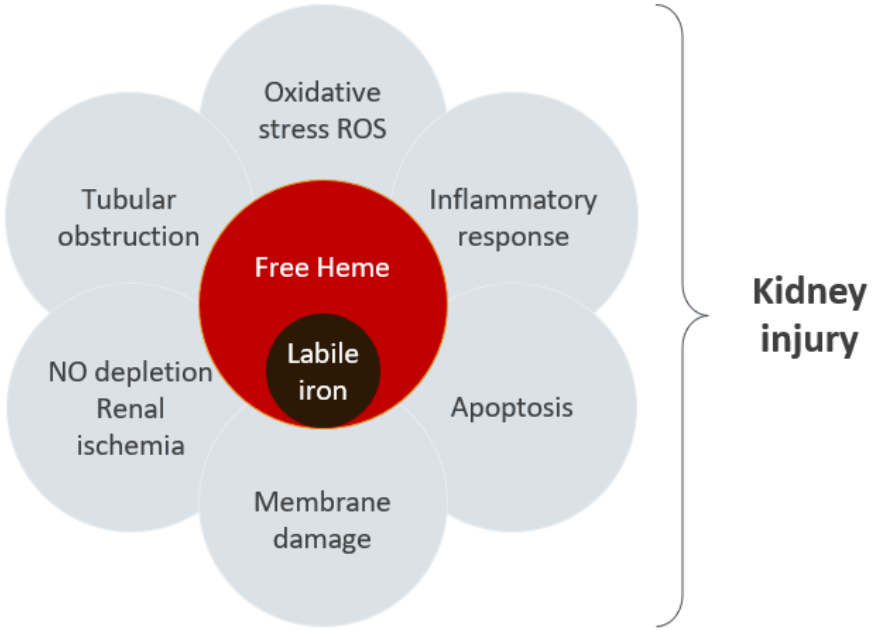


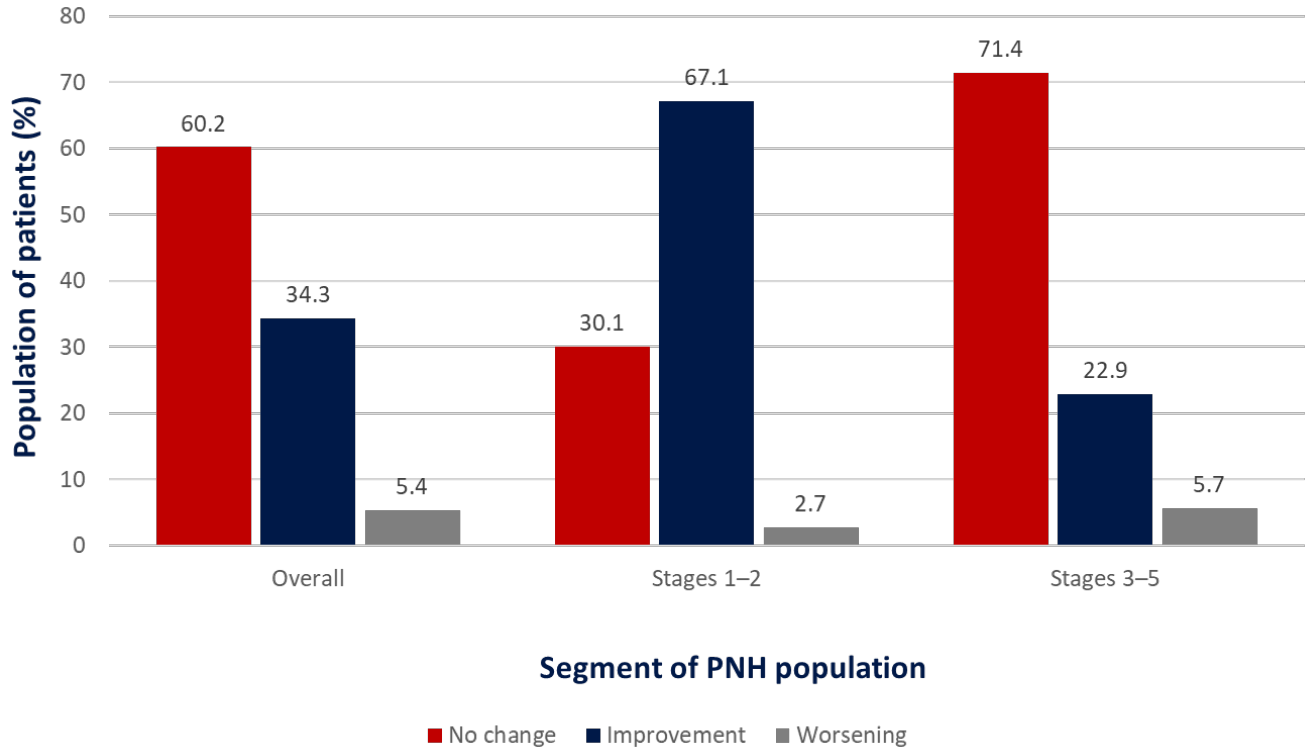
Movalia M *et al.* (2011) *ASH 2011 Abstract #1033*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

Hemoglobinuria & Renal Injury in PNH

42.8% of patients in the international PNH registry had impaired renal function at baseline

Mechanisms of renal involvement in PNH





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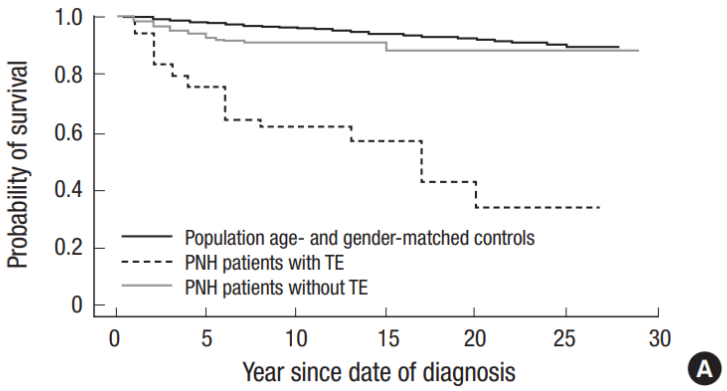
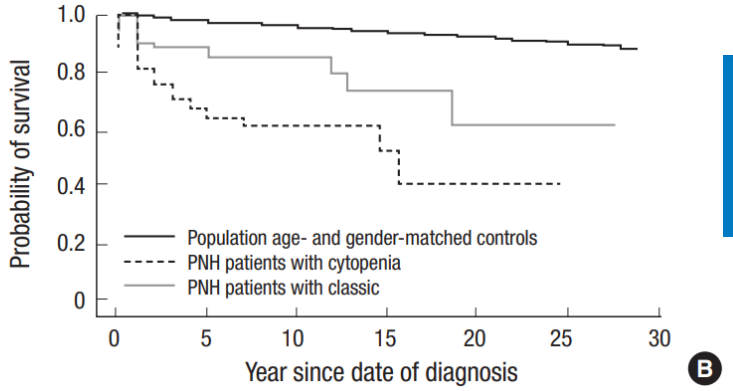
Hillmen P *et al.* (2010) *Am J Hematol*
Schrezenmeir H *et al.* (2020) *Ann Hematol*
Kokoris *et al.* (2018) *Hematology*

Factors Associated with Increased PNH Mortality

Thrombosis, unexplained

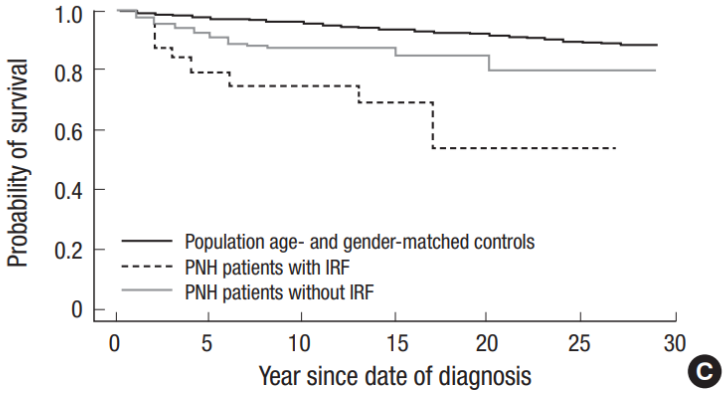


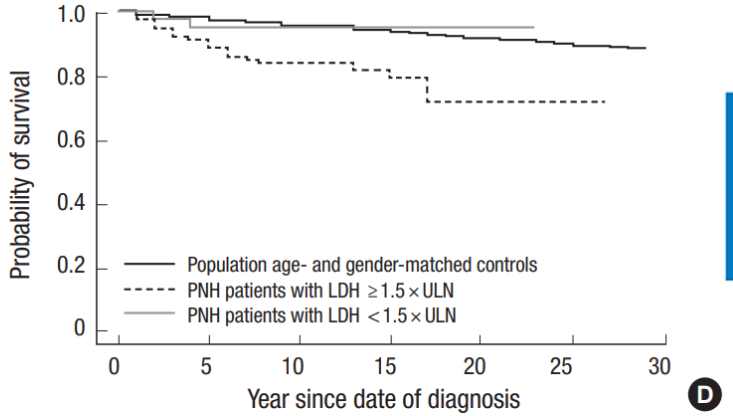


Cytopenia, unexplained

AA/RA-MDS

Hemoglobinuria





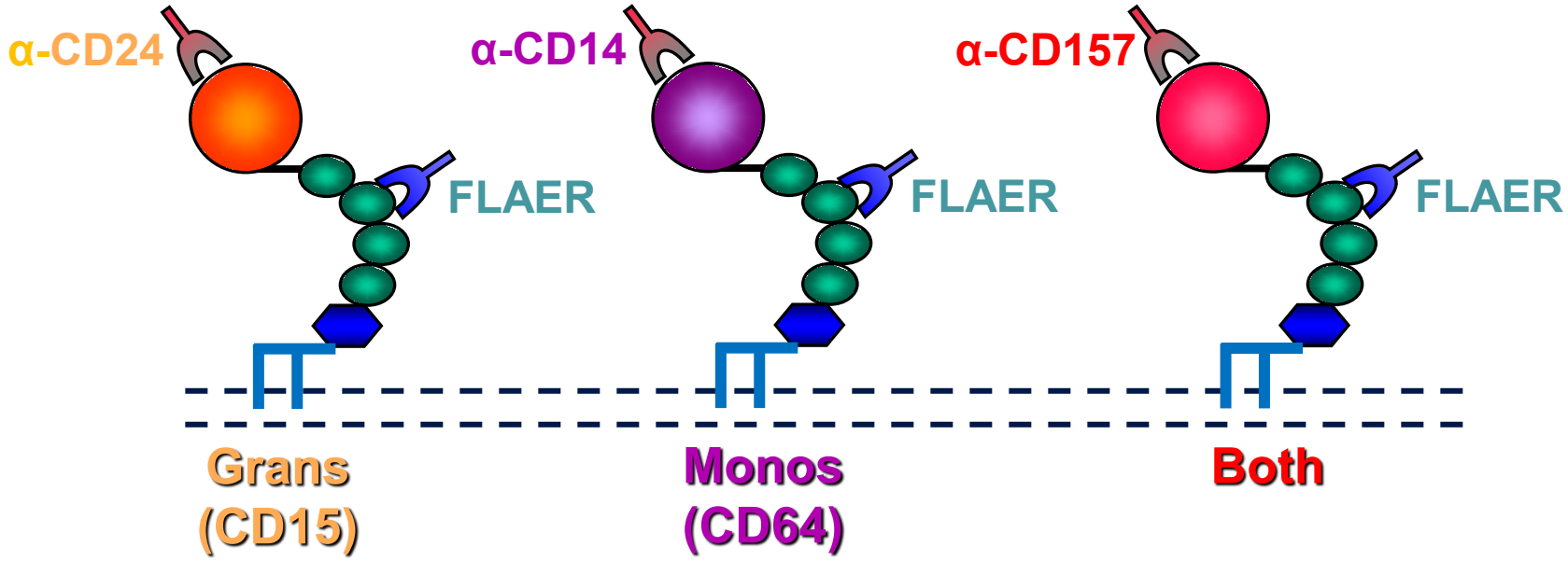
Coombs-negative hemolytic anemia

Fig. 2. Kaplan-Meier survival of PNH patients compared with age- and gender-matched general population. (**A**) Patients with TE had a 14-fold higher mortality rate compared with the general population (standard mortality ratio [SMR] = 13.9; 95% confidence interval [CI], 8.2-19.6; $P < 0.001$). (**B**) Patients with cytopenia had a mortality rate 6.2-fold greater than the age- and gender-matched general population (SMR = 6.2; 95% CI, 4.7-9.3; $P < 0.001$). (**C**) Patients with impaired renal function (IRF) had a mortality rate 7.8-fold greater than the age- and gender-matched general population (SMR = 7.8; 95% CI, 3.9-11.8; $P < 0.001$). (**D**) PNH patients with lactate dehydrogenase (LDH) ≥1.5 times the upper limit of normal (ULN) had a 5.0-fold greater risk for mortality compared with patients with LDH <1.5×ULN (95% CI, 1.15-21.70; $P = 0.009$). PNH patients with LDH ≥1.5×ULN had a 4.8-fold higher mortality rate compared with the general population (SMR = 4.8; 95% CI, 3.0-6.6; $P < 0.001$).

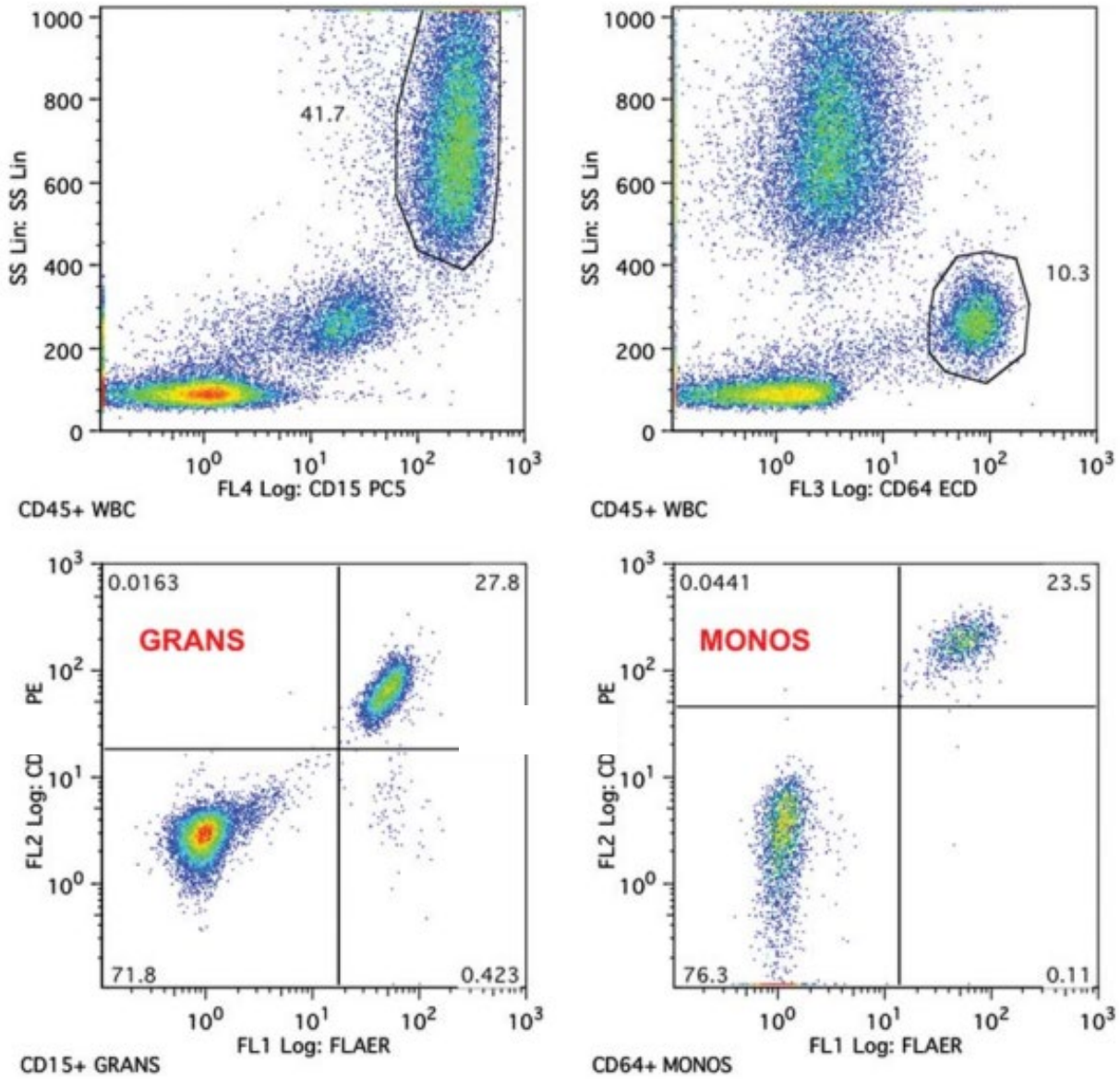
Jang JH *et al.* (2016) *J Korean Med Sci*

High Sensitivity Flow Cytometry

1. Identify relevant cell population(s)
2. Demonstrate GPI-negativity in ≥2 lineages



Brodsky RA (2009) *Blood*
Sutherland DR et al. (2012) *Cytometry Part B*
Sutherland DR *et al.* (2014) *Cytometry Part B*
Slide courtesy of Prof. R Sutherland



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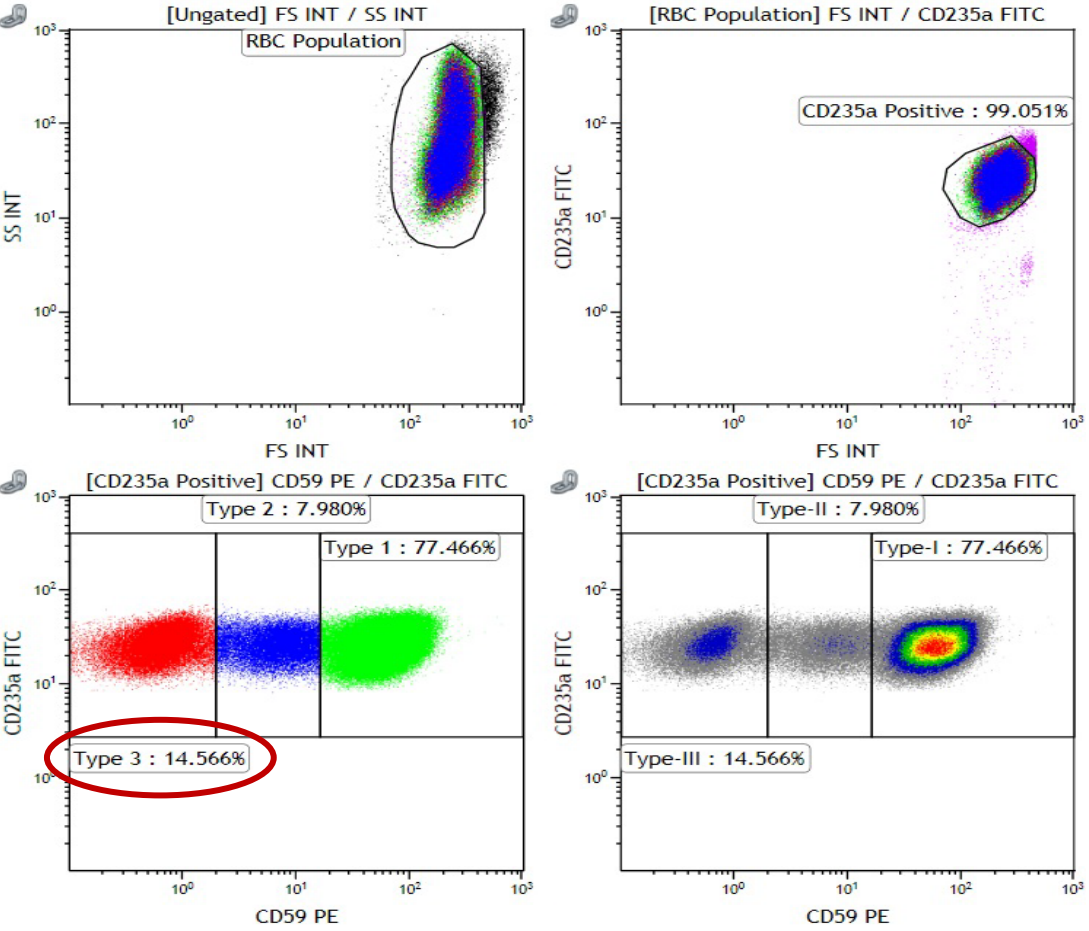
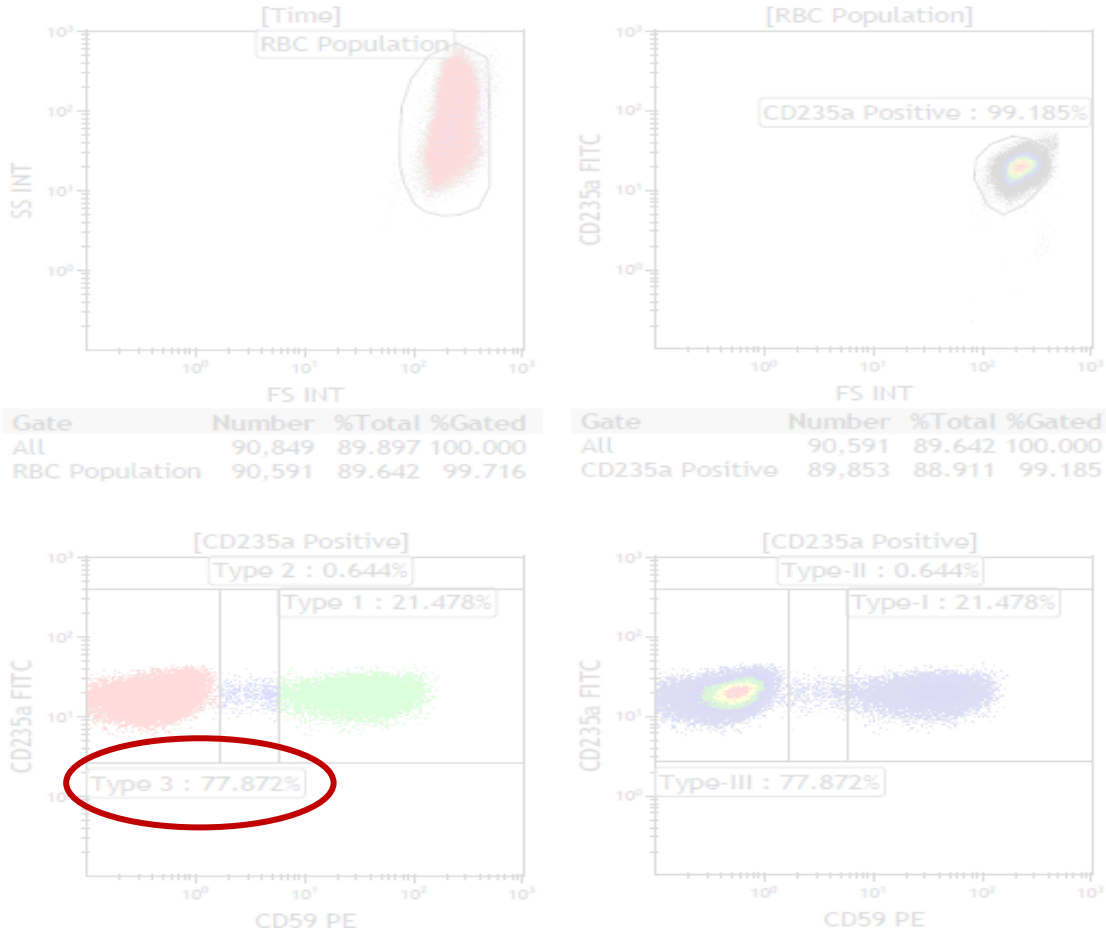
Sutherland DR *et al*. (2014) *Clin Cytometry*

RBC Flow Cytometry (*naïve → treatment*)



Treatment



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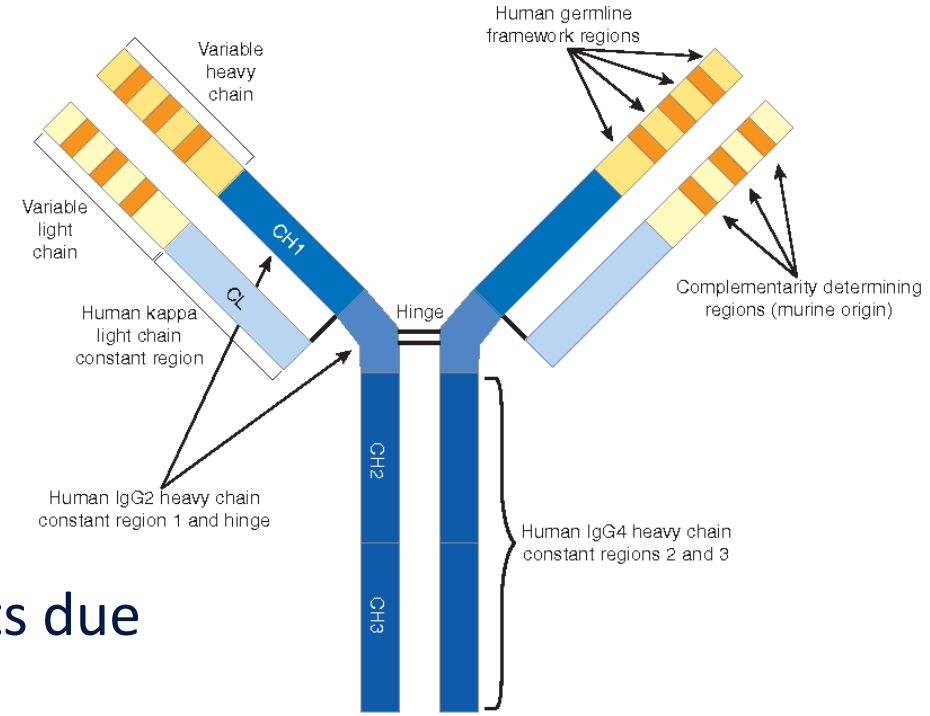
CANADIAN PNH NETWORK

Slide courtesy of M. Keeney (London Health Sciences)

TREATMENT OF PNH

Upfront Management of PNH

- Supportive Care
  - Transfusions, hematinics (folate, iron), analgesia
- Allogeneic stem cell transplant
  - Reserved for BMF-predominant presentations
  - Avoid HSCT for thrombotic patients
- **Complement inhibition**
  - Continuous protection required while PNH clone exists due to the chronic, persistent risks from hemolysis



Legendre C *et al.* (2013) *NEJM*
Patriquin CJ & KHM Kuo (2019) *TMR*
Socié G *et al.* (2019) *BJH*

Management of PNH with Eculizumab

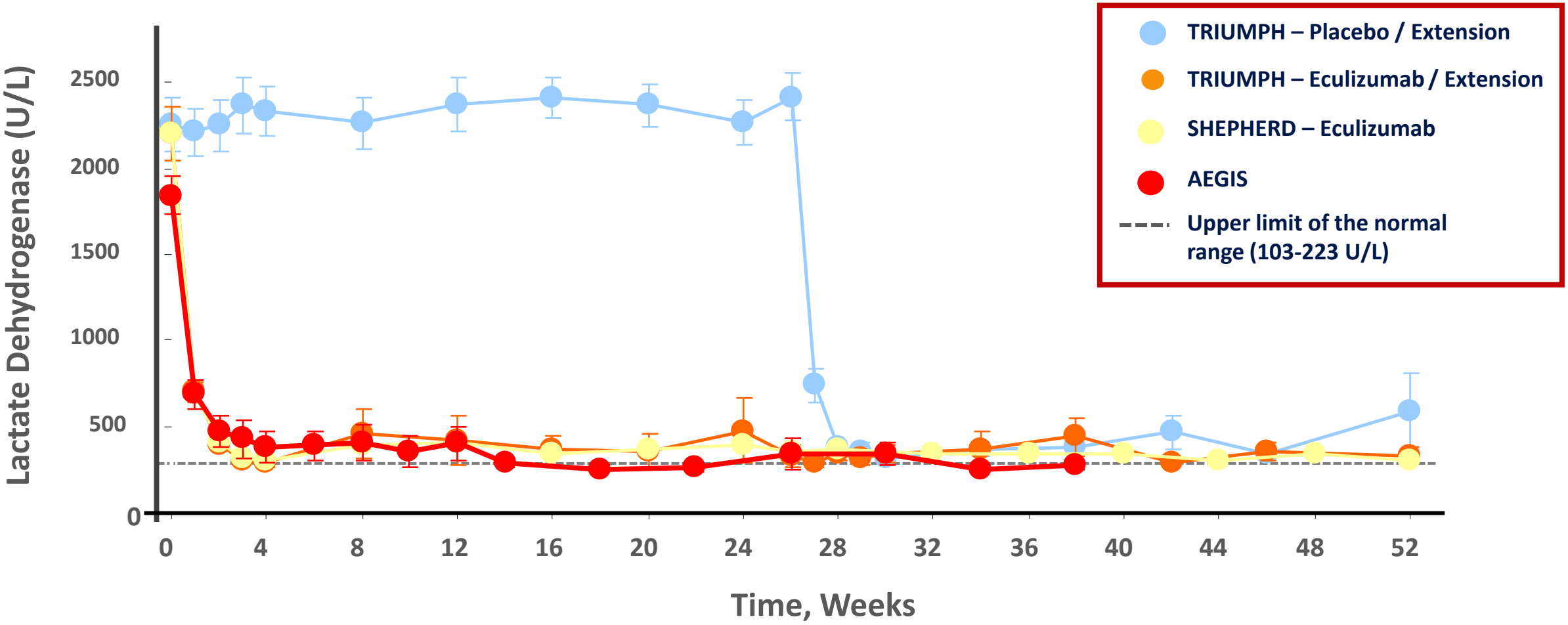
Eculizumab dosing schedule										
Pretreatment		**Induction phase**				**Maintenance phase**				
2 weeks before induction**	Week →	1	2	3	4	5	6	7	8	9
Neisseria meningitidis vaccination	Dose (mg)	600	600	600	600	900	X	900	X	900

q14d

- ***Meningococcal vaccination (ACWY + MenB) mandatory***
- *Anti-meningococcal antibiotics required until 14+ days post-vaccine*
- *May consider additional encapsulated bacteria vaccinations*

Kelly RJ *et al.* (2015) *NEJM*
Hallstensen RF *et al.* (2015) *Immunobiology*
Sarno L *et al.* (2019) *J Nephrol*
Socié G *et al.* (2019) *BJH*

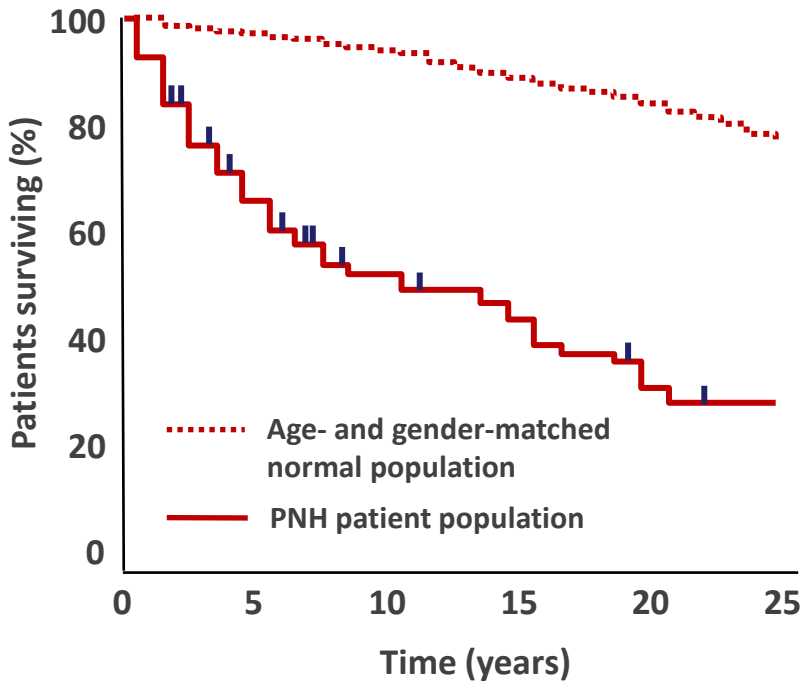
Reduced Intravascular Hemolysis with Eculizumab



Hillmen P *et al.* (2006) *NEJM*
Brodsky RA *et al.* (2008) *Blood*
Kanakura Y *et al.* (2011) *Int J Hematol*

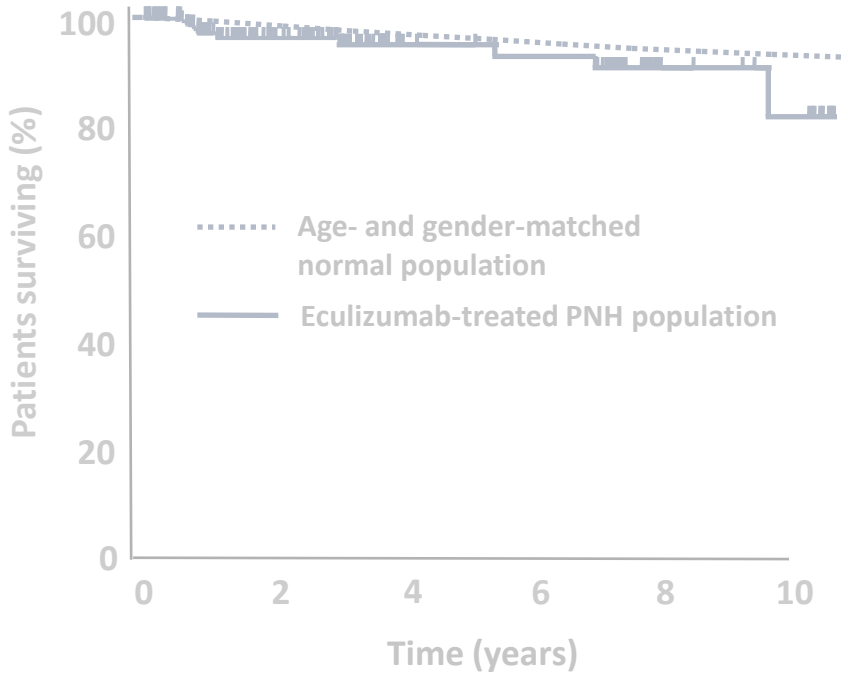
Eculizumab Improves Overall Survival

Pre-eculizumab from time of diagnosis in 80 patients with PNH



Despite best supportive care, 5-year mortality rate was 35%

PNH patients on eculizumab compared with age- and sex-matched controls



Overall survival >90% over 10 years, with deaths mostly due to BMF

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CANADIAN PNH NETWORK

Hillmen P *et al.* (1995) *NEJM*
Kelly RJ *et al.* (2011) *Blood*

Terminal Complement Blockade Reduces TE Risk

85% RRR

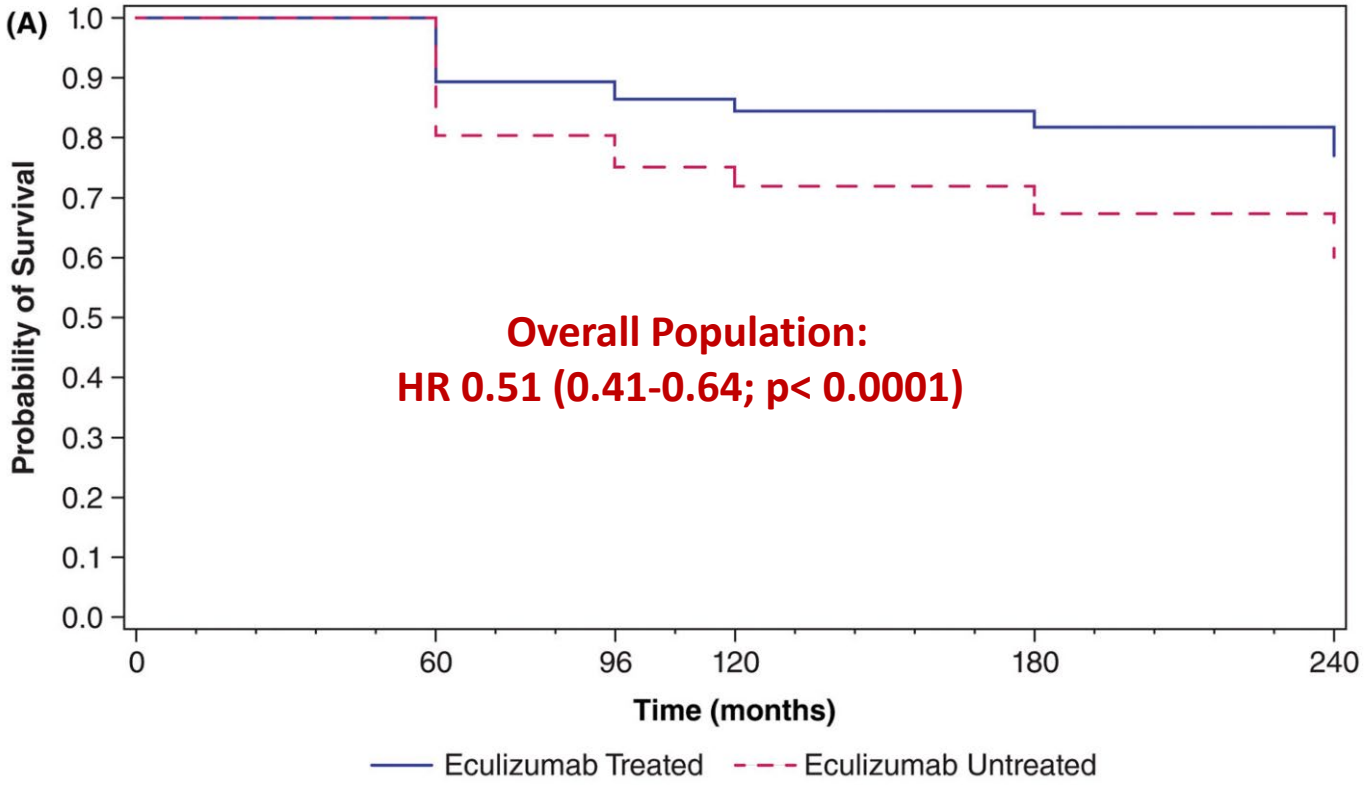
Table 3. Thromboembolism events in patients with and without eculizumab

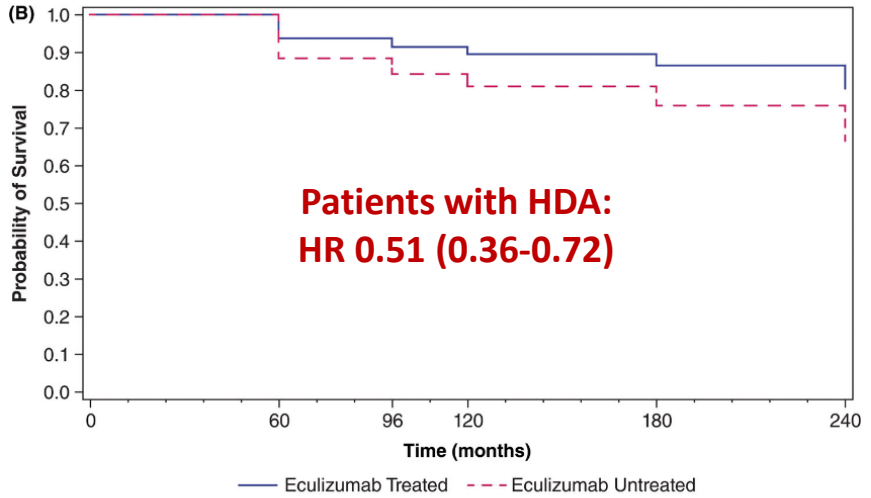
TE events	Pilot*	TRIUMPH		SHEPHERD	Extension† (all studies)
		Placebo group	Eculizumab group		
Before treatment					
Patients, no.	11	44	43	97	195
TE events, no.	5	11	16	91	124
Patient-years, no.	161.7	470.4	309.0	718.3	1683.4
TE event rate, no. per 100 patient-years	3.09	2.34	5.18	12.67	7.37
Eculizumab treatment‡					
Patients, no.	11	44	43	97	195
TE events, no.	0	1	0	2	3§
Patient-years, no.	34.2	22.9	21.8	96.9	281.0
TE event rate, no. per 100 patient-years	0.00	4.38	0.00	2.06	1.07‖

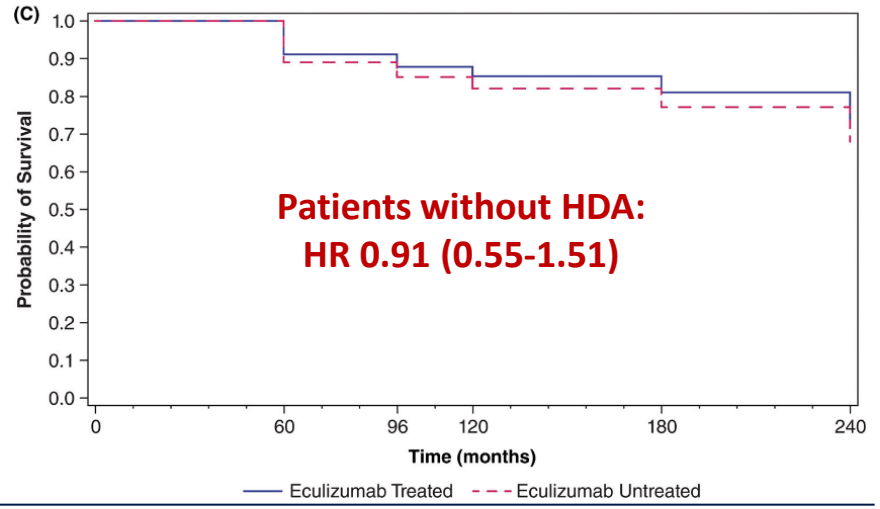
*Includes a 1-year and a 2-year extension study.
†Includes TRIUMPH placebo-treated patients who transitioned to eculizumab treatment in the phase 3 extension study.
‡Three of 195 patients began anticoagulant treatment during eculizumab, 2 of whom started the treatment after a TE event.
§The 3 TE events occurring during eculizumab treatment included 2 events during SHEPHERD and 1 event during the extension.
‖$P < .001$ for comparisons of eculizumab treatment versus before treatment, signed rank test.

Hillmen P *et al.* (2007) *Blood*

Eculizumab Improves Overall Survival







Treated *vs.* untreated time TE risk, HR 0.40 (0.26–0.62)

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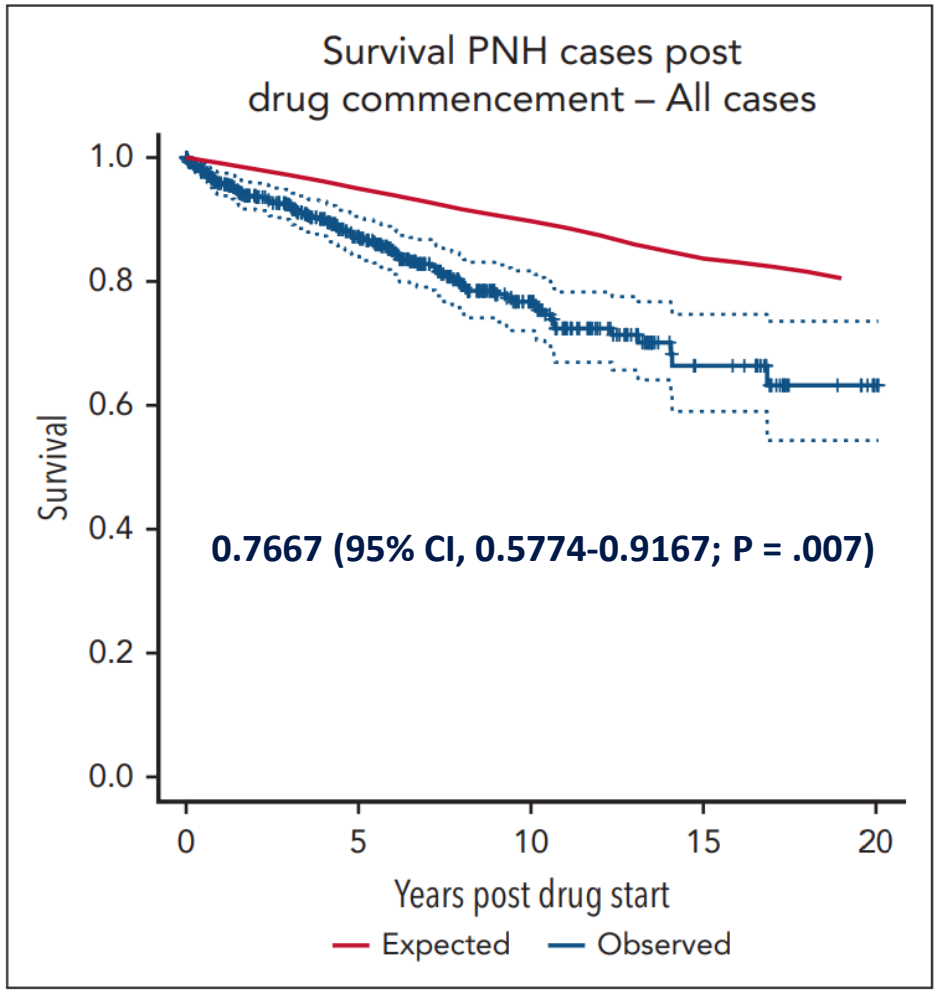
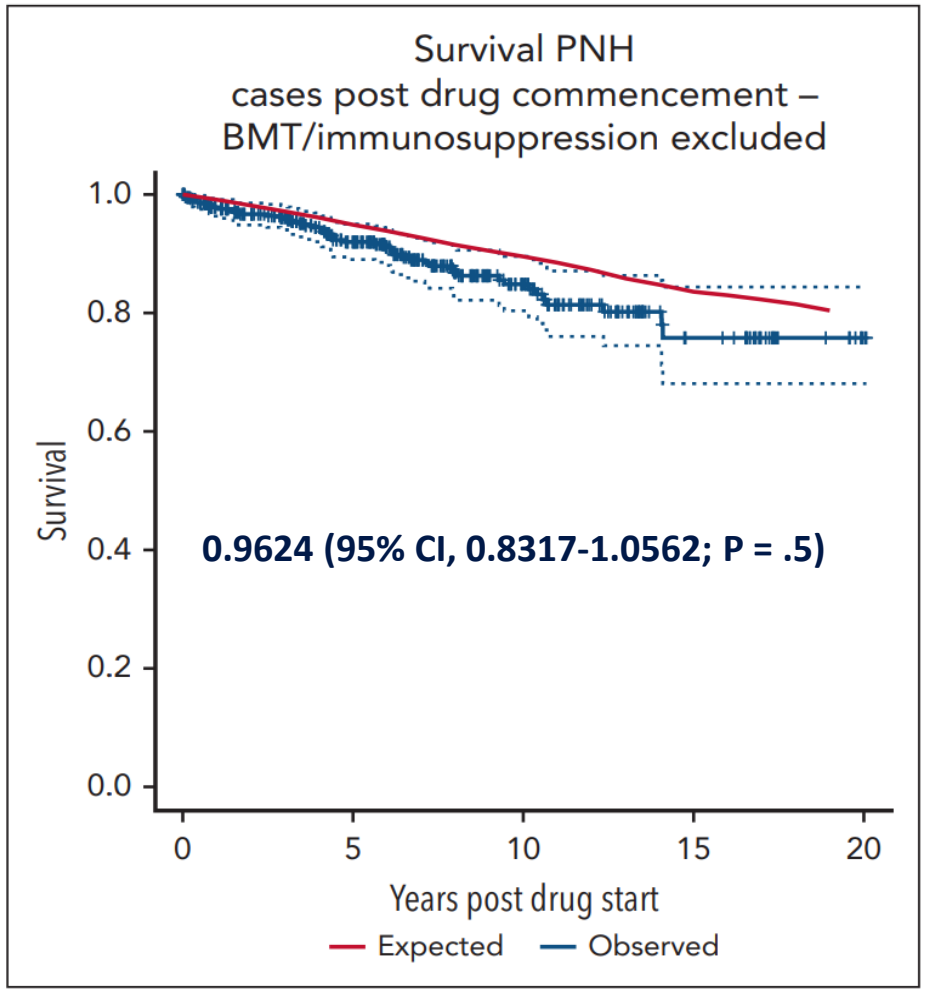
Terriou L *et al.* (2023) *Eur J Haematol*

Overall Survival with C5 Inhibition





Kelly RJ *et al.* (2024) ***Blood***

APPROVED THERAPIES BEYOND ECULIZUMAB

Why Do We Need New Treatments?

Met Needs

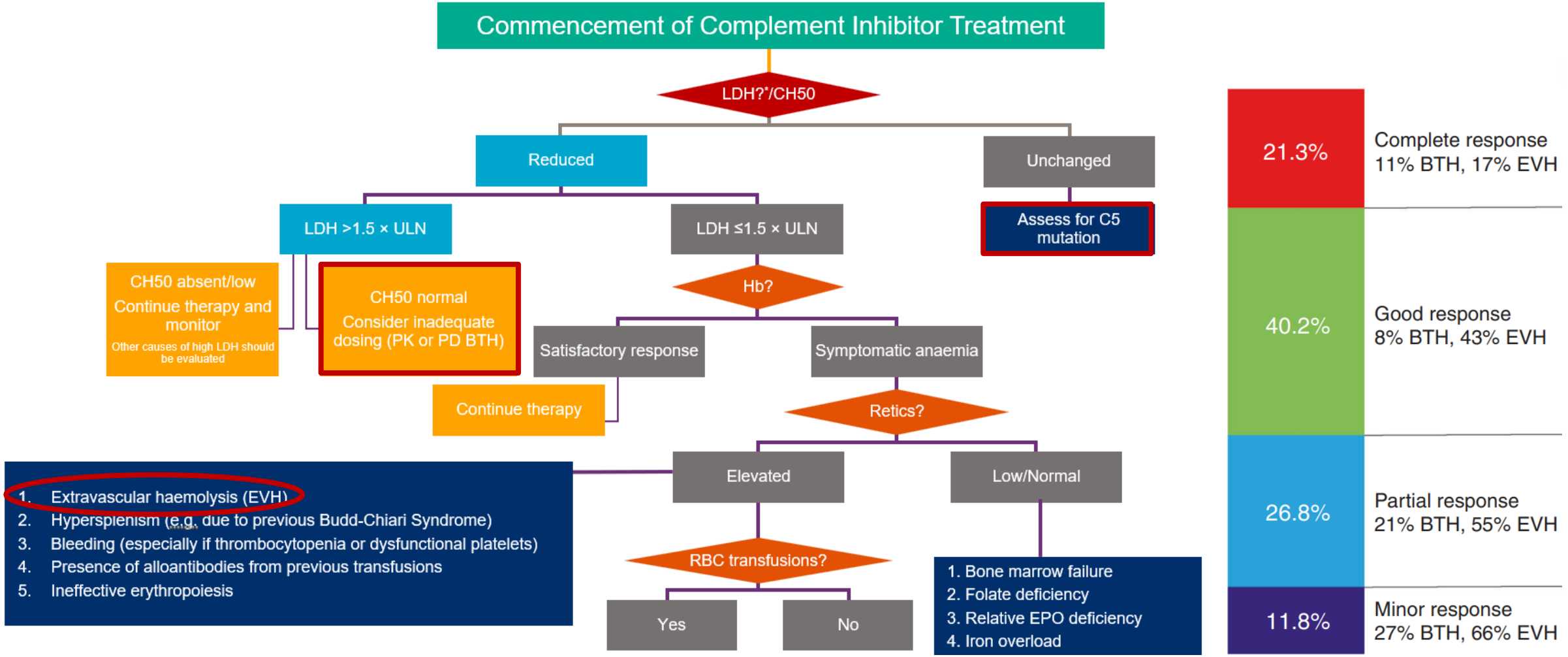
- IVH blockade
- Reduced thrombosis risk
- Minimised end-organ damage
- Increased overall survival
- Improved pregnancy outcomes

Unmet Needs

- Correct the anemia of EVH
- Improve quality of life
- Reduce treatment burden
- Biomarker availability
- Validate BTH management

Summarised in: Oliver M & Patriquin CJ (2023) *J Blood Medicine*

Evaluating a PNH Patient on C5 Inhibition



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Kulasekararaj AG et al. (2021) *Am J Hemato*
Debureaux PE *et al.* (2021) *BMTI*

C5 Inhibition Drives Extravascular Escape

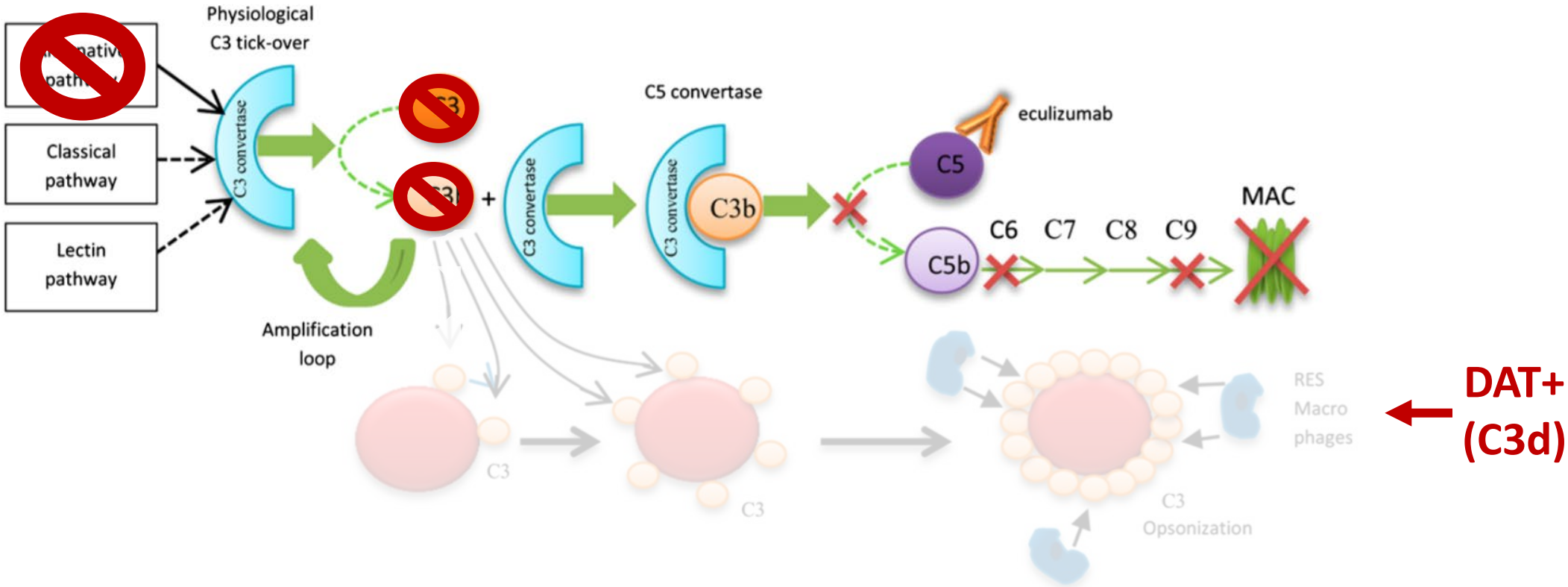

Image from: Devalet B *et al.* (2014) *J Extracell Vesicles*

Complement Inhibitors for PNH Treatment

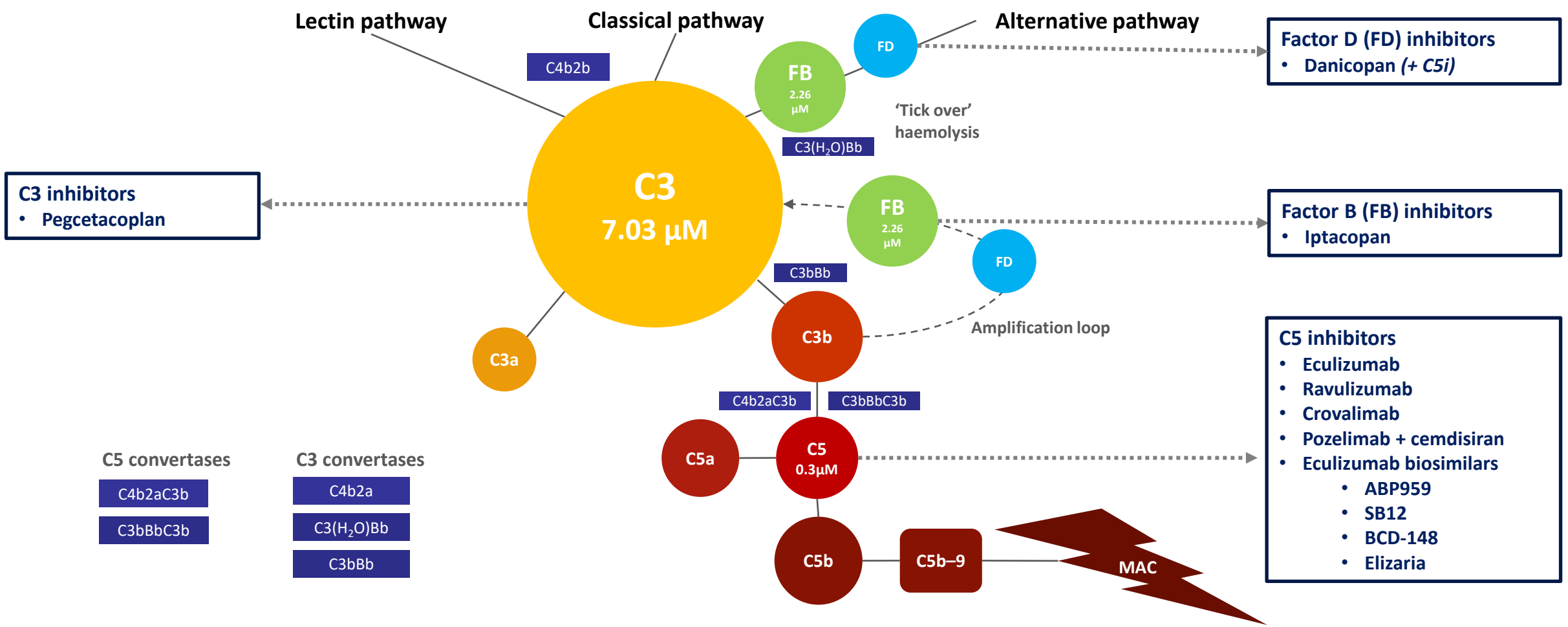

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Image modified from: Kulasekararaj AG & Lazana I (2023) *Am J Hematol*

Complement Inhibitors for PNH Treatment

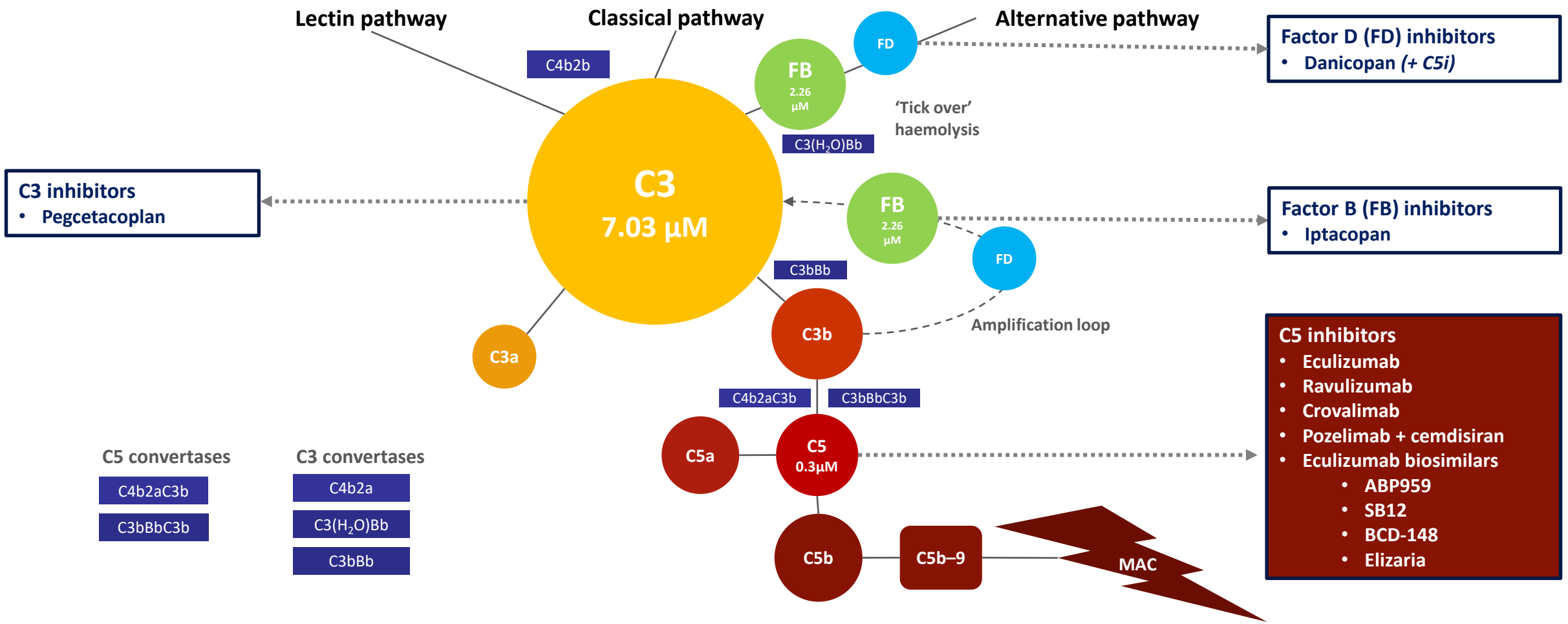

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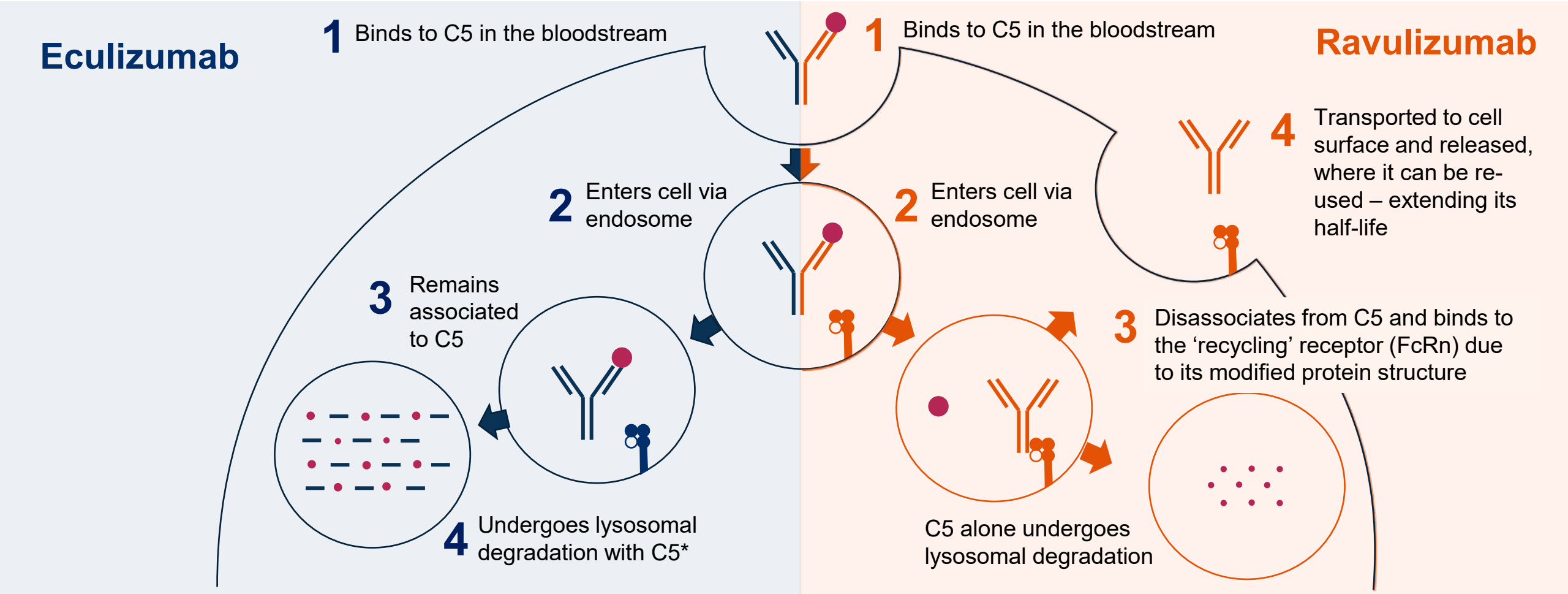
Image modified from: Kulasekararaj AG & Lazana I (2023) *Am J Hematol*

Eculizumab vs. Ravulizumab

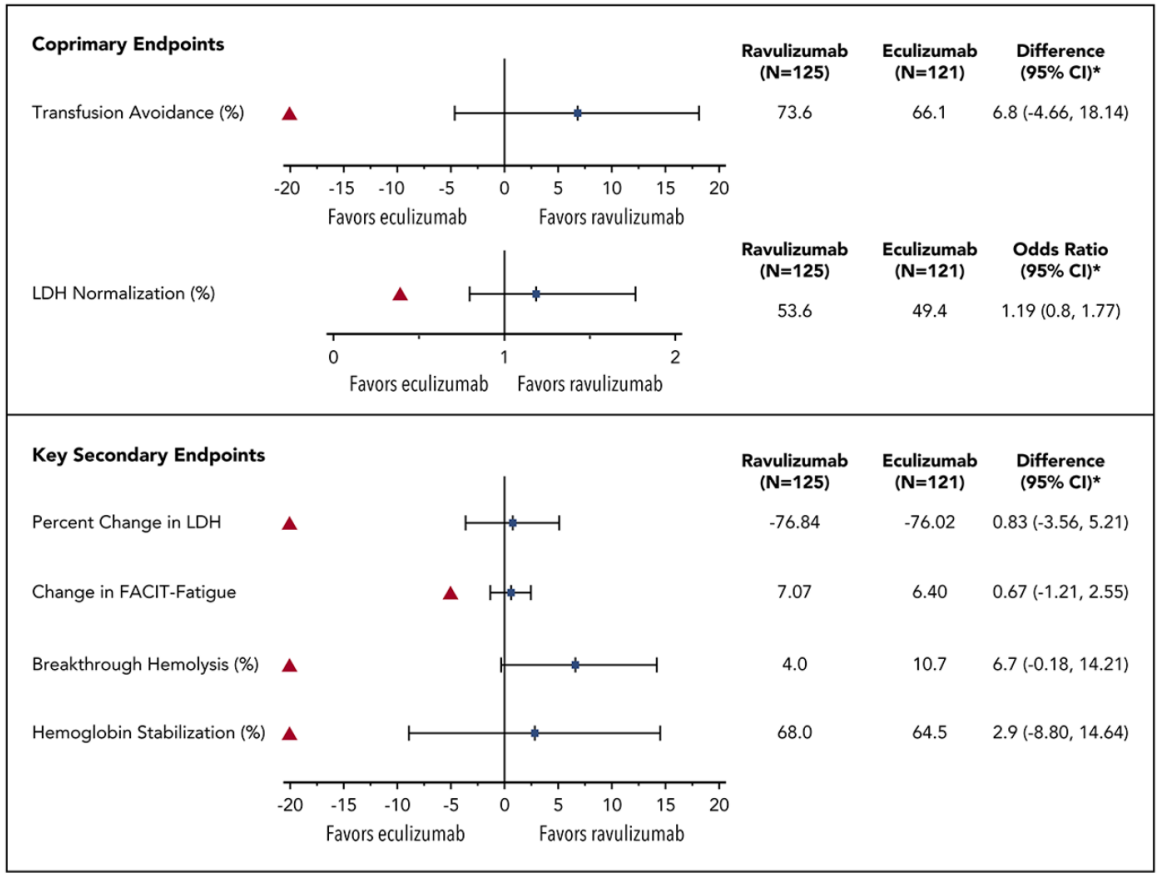


Tanaka K et al. (2021) *Pediatr Nephrol*

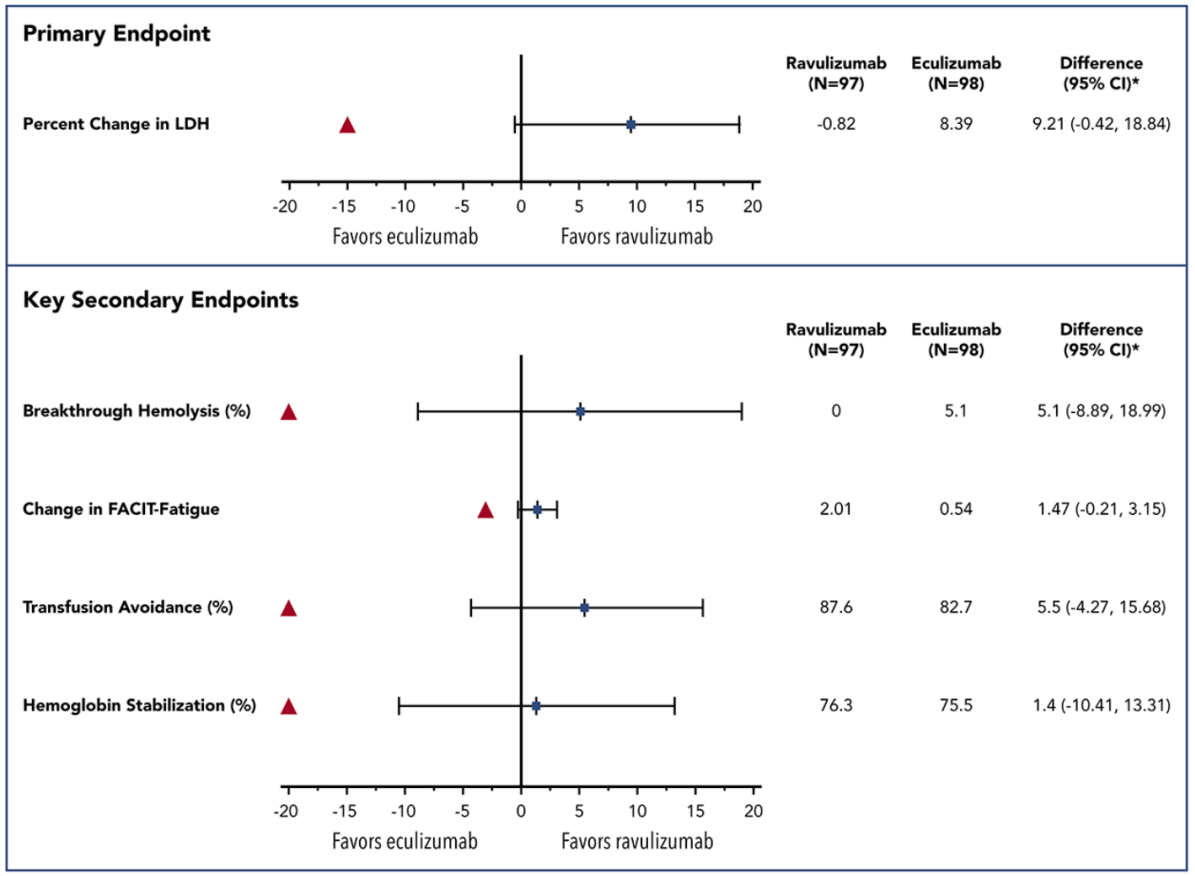
Sheridan D *et al.* (2018) *PLoS One*

IVH Control Non-Inferior with Ravulizumab

Efficacy of Ravulizumab and Eculizumab in Complement Inhibitor–Naive PNH Patients



Efficacy of Ravulizumab and Eculizumab in PNH Patients Stable on Eculizumab



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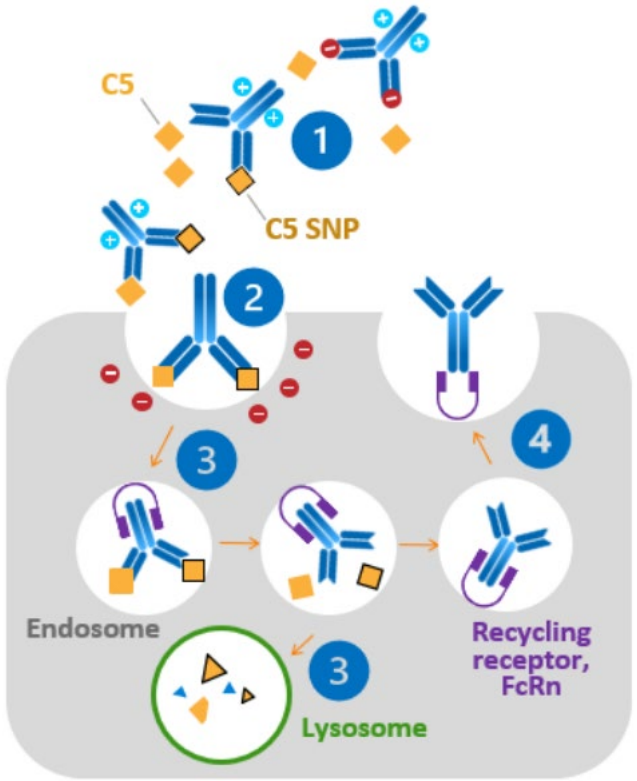
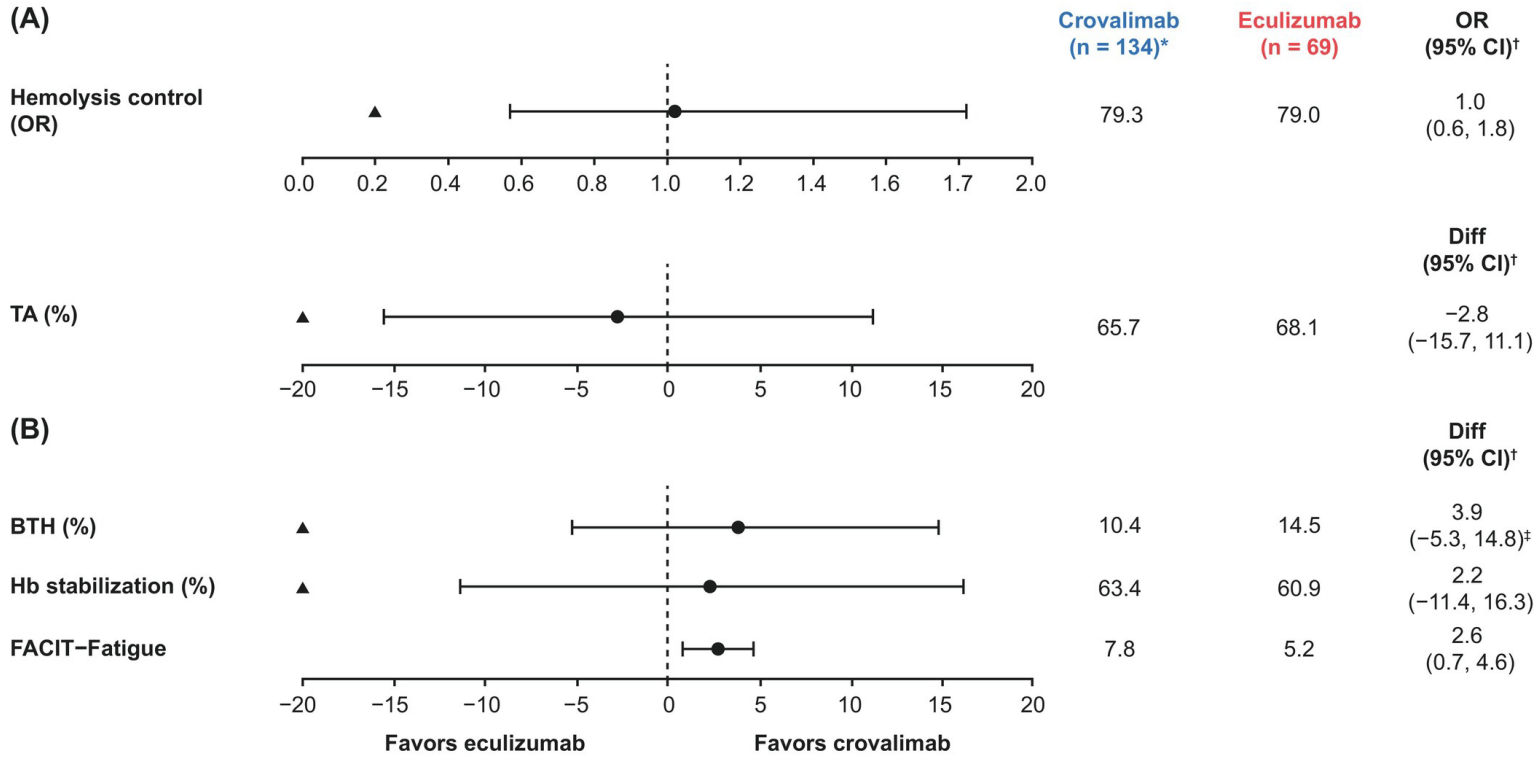
Lee JW *et al.* (2019) *Blood*
Kulasekararaj AG *et al.* (2019) *Blood*

IVH Control Non-Inferior with Crovalimab





Röth A *et al.* (2024) *Am J Hematology*

Complement Inhibitors for PNH Treatment

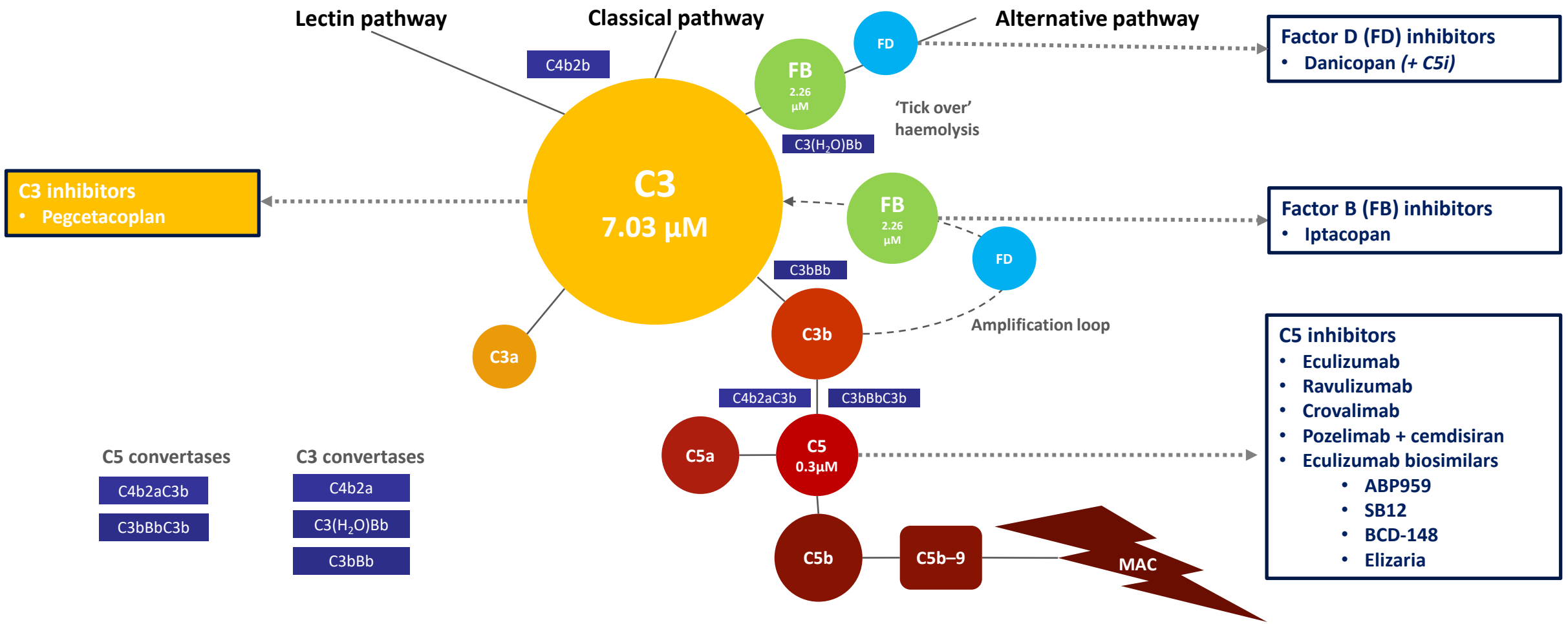
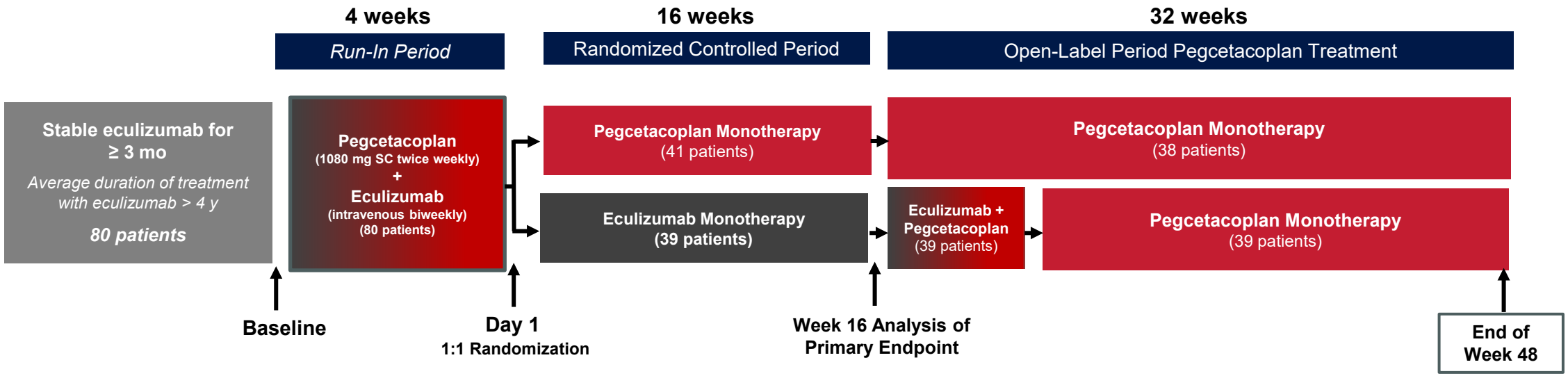


Image modified from: Kulasekararaj AG & Lazana I (2023) *Am J Hematol*

PEGASUS: Subcutaneous C3 Inhibition



Study Design	
Population	Patients ≥ 18 years of age with PNH and Hb < 10.5 g/dL despite stable treatment with eculizumab (≥ 3 months)
Primary endpoint	Change from baseline in Hb level at week 16

Week 48 Endpoints	
Secondary endpoints	• Change from baseline in Hb levels, LDH levels, ARC, and FACIT-F • Freedom from transfusions
Safety endpoints	Incidence and severity of TEAEs
Treatment groups	• **Pegcetacoplan to pegcetacoplan:** Patients received peg during the randomized period and continued through week 48 of the OLP • **Eculizumab to pegcetacoplan:** Patients received ecu during the randomized period and switched to peg during OLP after run-in

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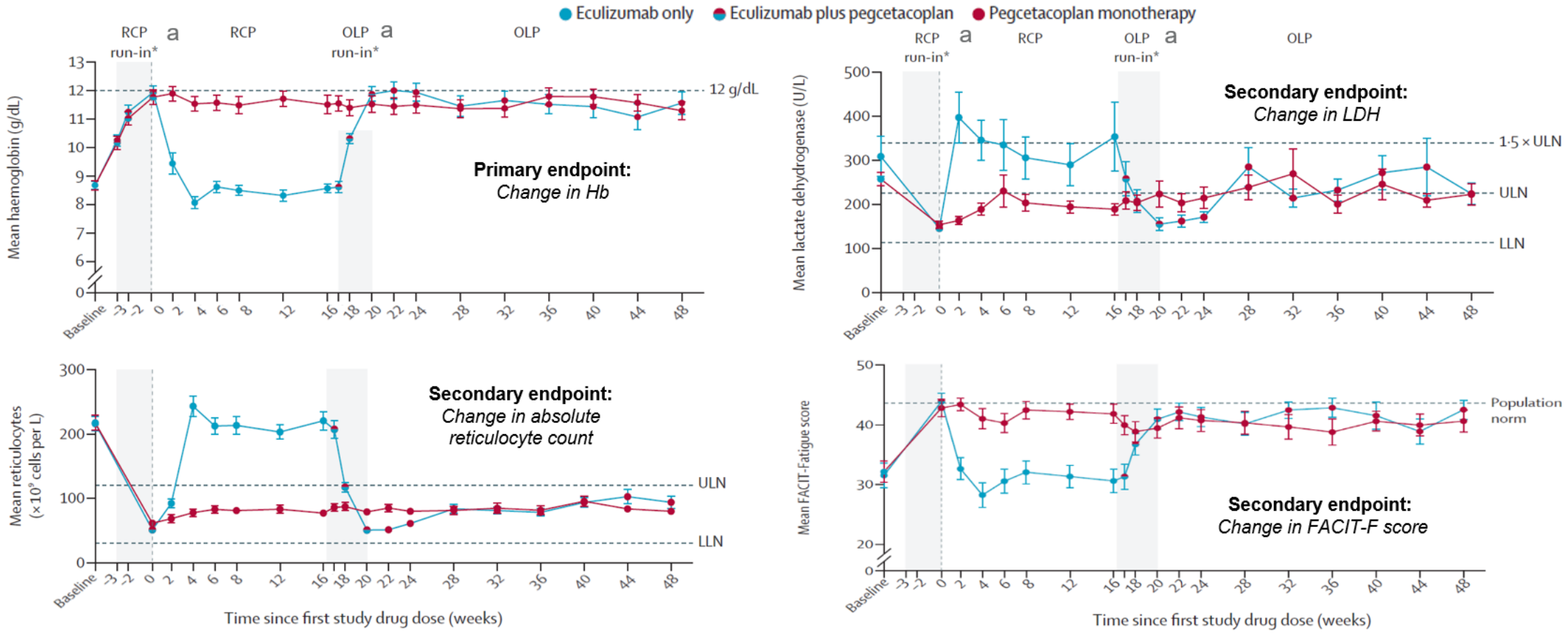
Hillmen P *et al.* (2021) *NEJM*

PEGASUS: Subcutaneous C3 Inhibition



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Hillmen P *et al.* (2021) *NEJM*

Complement Inhibitors for PNH Treatment

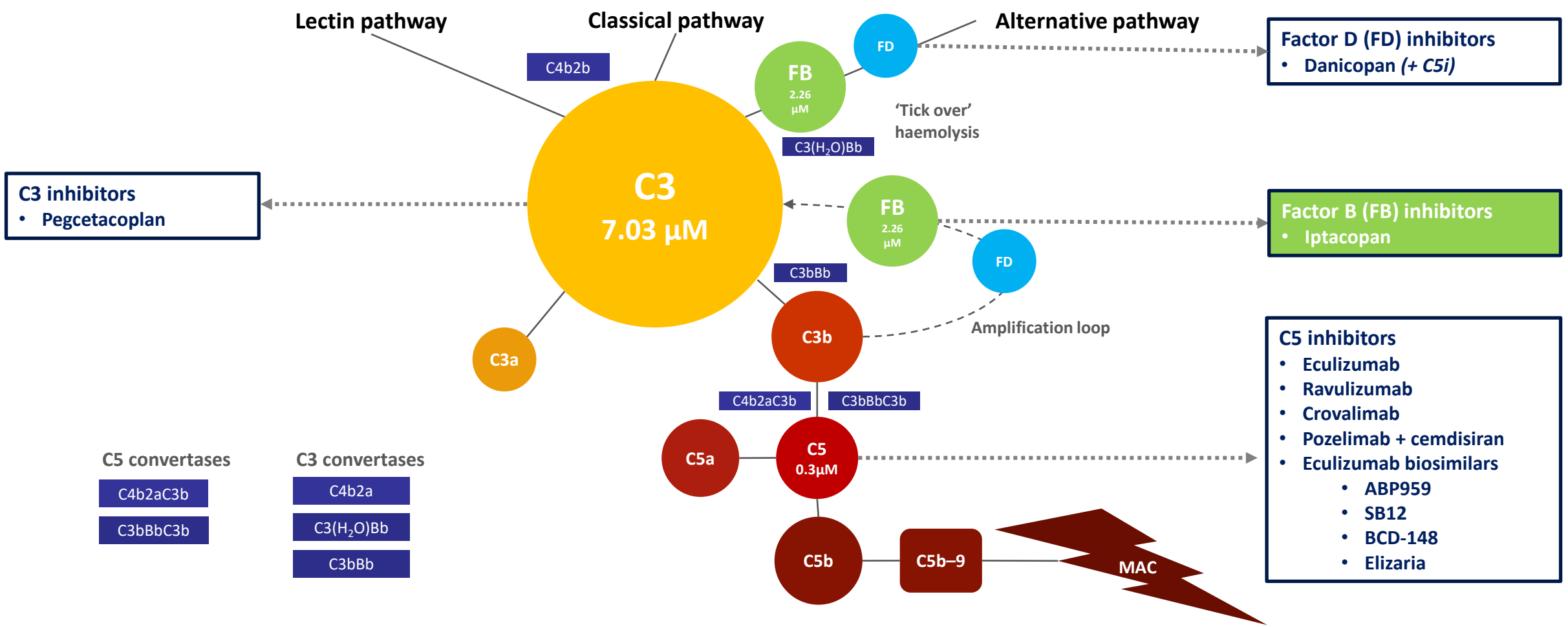

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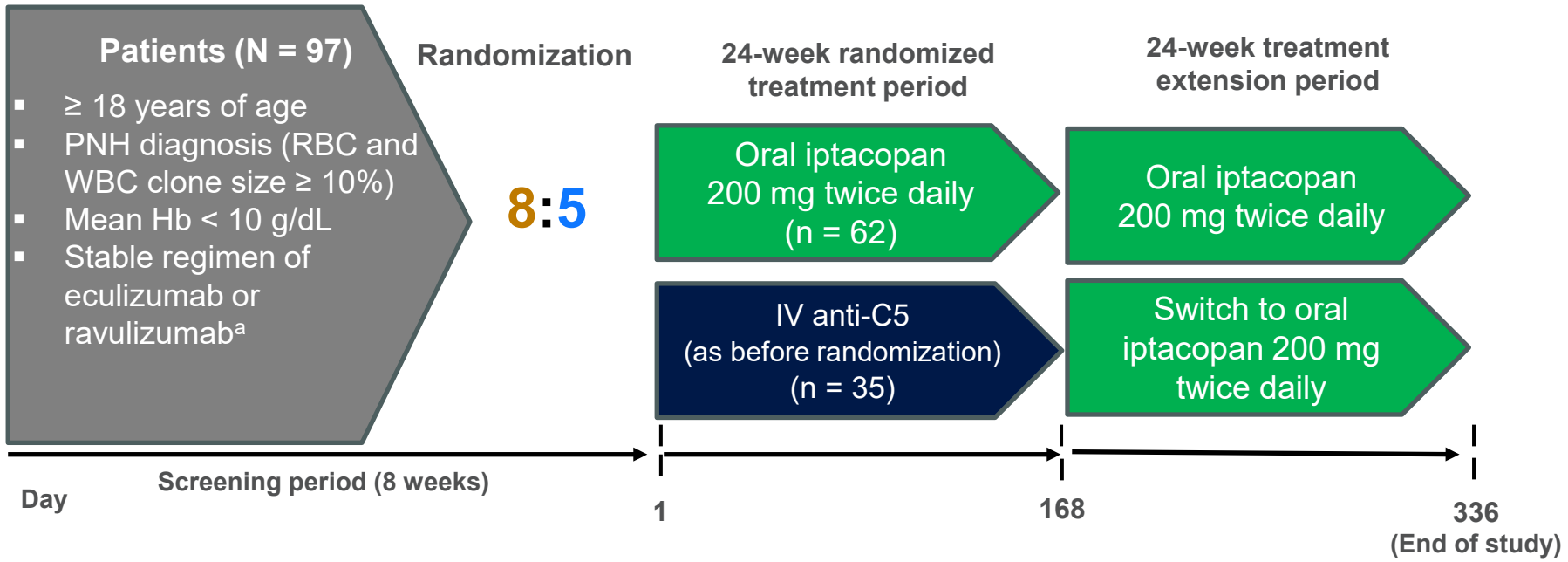
Image modified from: Kulasekararaj AG & Lazana I (2023) *Am J Hematol*

APPLY-PNH: Oral Factor B Inhibition

Open-label, Randomized, Active Comparator Controlled Multicenter, Phase III Trial Investigating Iptacopan Monotherapy in Adult Patients With PNH and Residual Anemia Despite SOC Therapy (NCT04558918)



Primary Endpoints

- Hematological response defined as an increase from baseline in Hb of ≥ 2 g/dL[c] in the absence of RBC transfusions[d]
- Hematological response defined as Hb ≥ 12 g/dL[c] in the absence of RBC transfusions[d]

Secondary Endpoints

- Transfusion avoidance[d]
- Change from baseline[c]:
  - Hb levels[e]
  - FACIT-Fatigue scores
  - ARC
  - LDH levels
- Occurrences of clinical breakthrough hemolysis and MAVEs[f]
- Safety[f]

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Peffault de Latour R *et al.* (2024) *NEJM*

APPLY-PNH: Oral Factor B Inhibition

Increase From Baseline in Hb of ≥ 2 g/dL Between Days 126 and 168 of APPLY-PNH

Hb ≥ 12 g/dL Between Days 126 and 168 of APPLY-PNH

Observed:

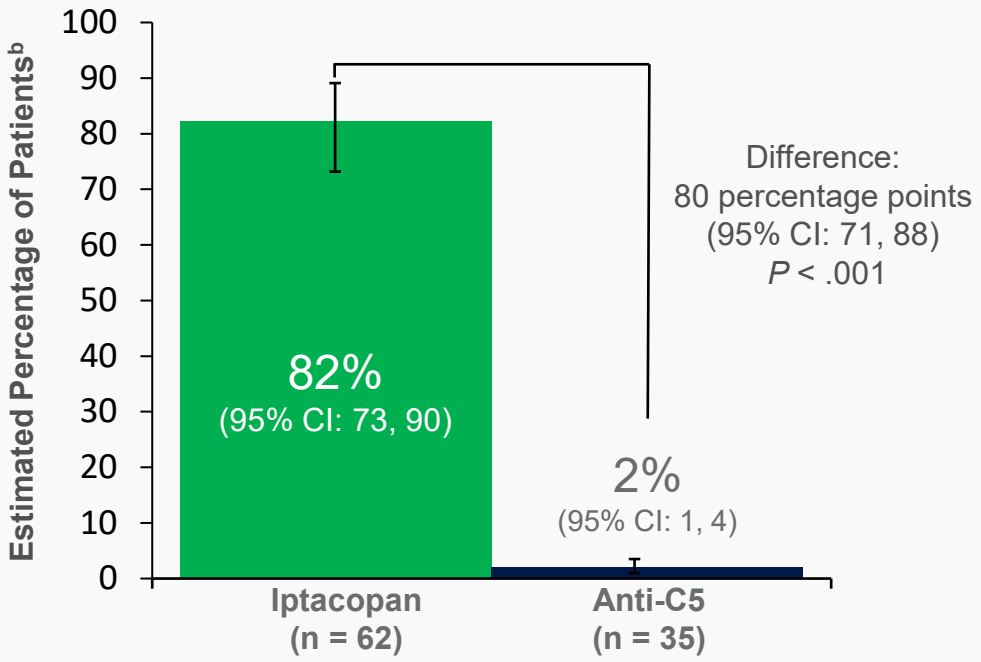
51/60 patients treated with iptacopan

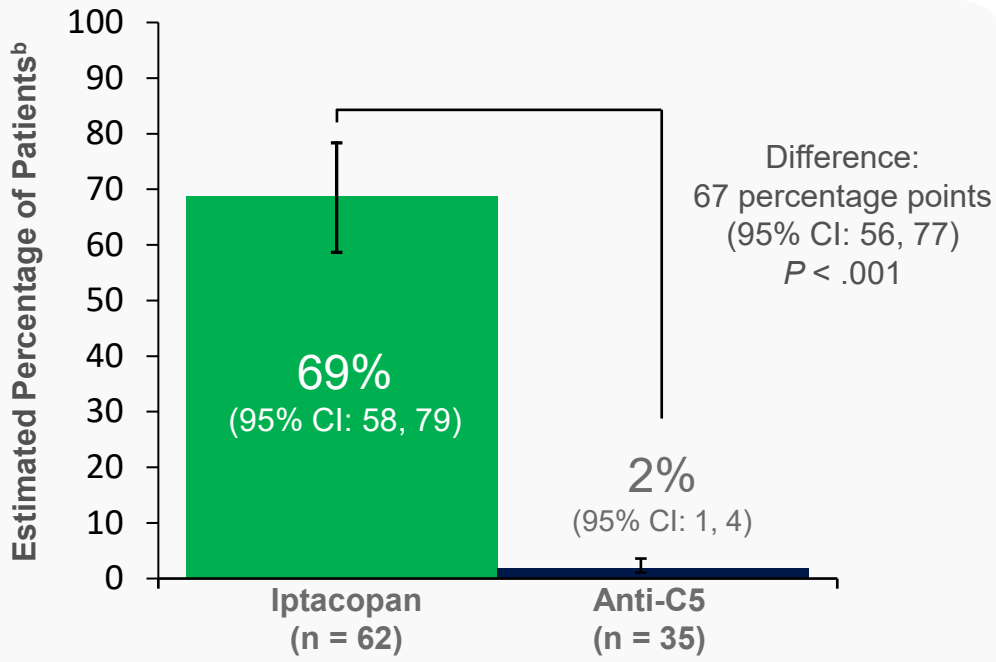
0/35 patients treated with anti-C5 therapy

42/60 patients treated with iptacopan

0/35 patients treated with anti-C5 therapy

Population estimate:





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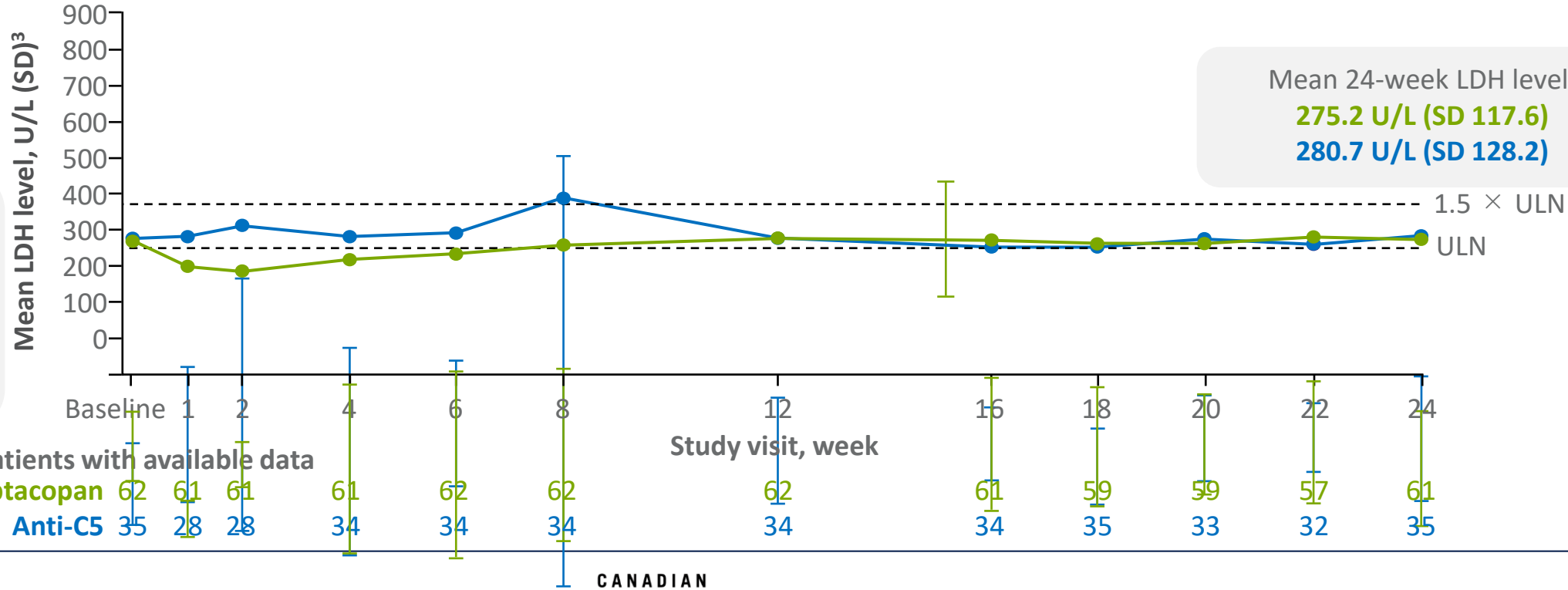
Peffault de Latour R *et al.* (2024) *NEJM*

APPLY-PNH: Oral Factor B Inhibition

- Adjusted geometric mean ratio to baseline in LDH (95% CI) **0.96 (0.90, 1.03) for iptacopan** vs **0.98 (0.89, 1.07) for anti-C5**
- **Most patients** (92.8%) had **LDH ≤ 1.5 × ULN at baseline** because of control by anti-C5 therapy
- After switching to iptacopan monotherapy from anti-C5 therapy, **IVH control was maintained**

Mean baseline LDH level:[3]
269.1 U/L (SD 70.1)
272.7 U/L (SD 84.8)



Mean 24-week LDH level:
275.2 U/L (SD 117.6)
280.7 U/L (SD 128.2)

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Peffault de Latour R *et al.* (2024) *NEJM*

Complement Inhibitors for PNH Treatment

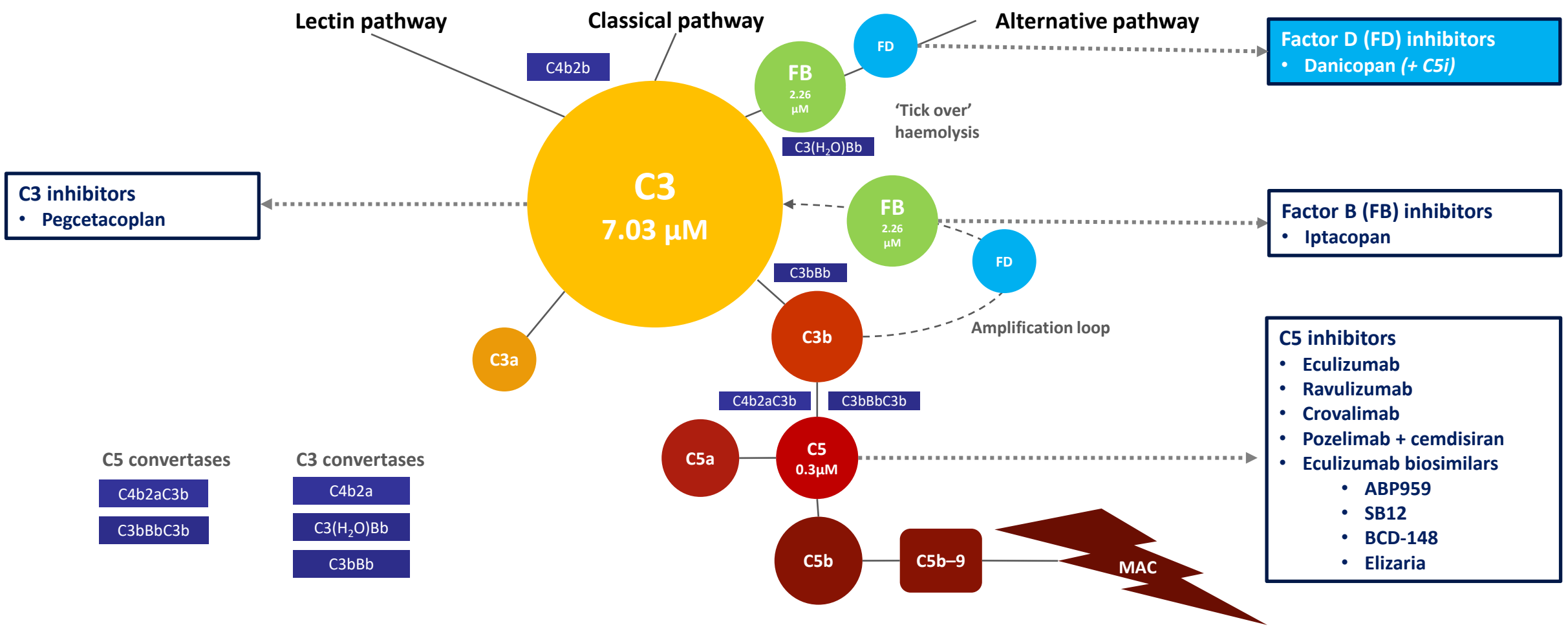
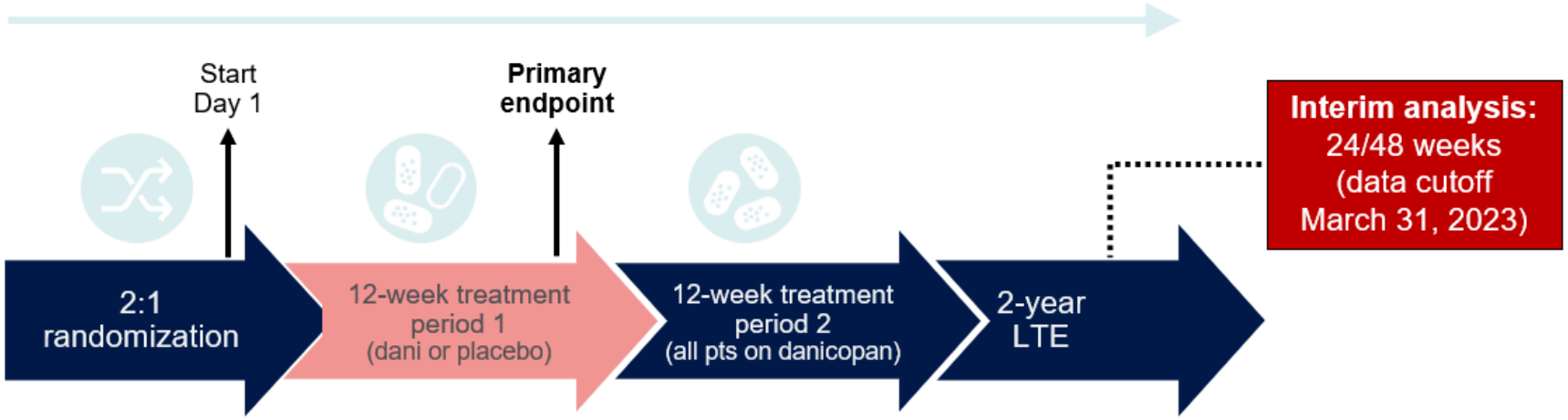


Image modified from: Kulasekararaj AG & Lazana I (2023) *Am J Hematol*

ALPHA Trial: Factor Inhibition + C5 Inhibition



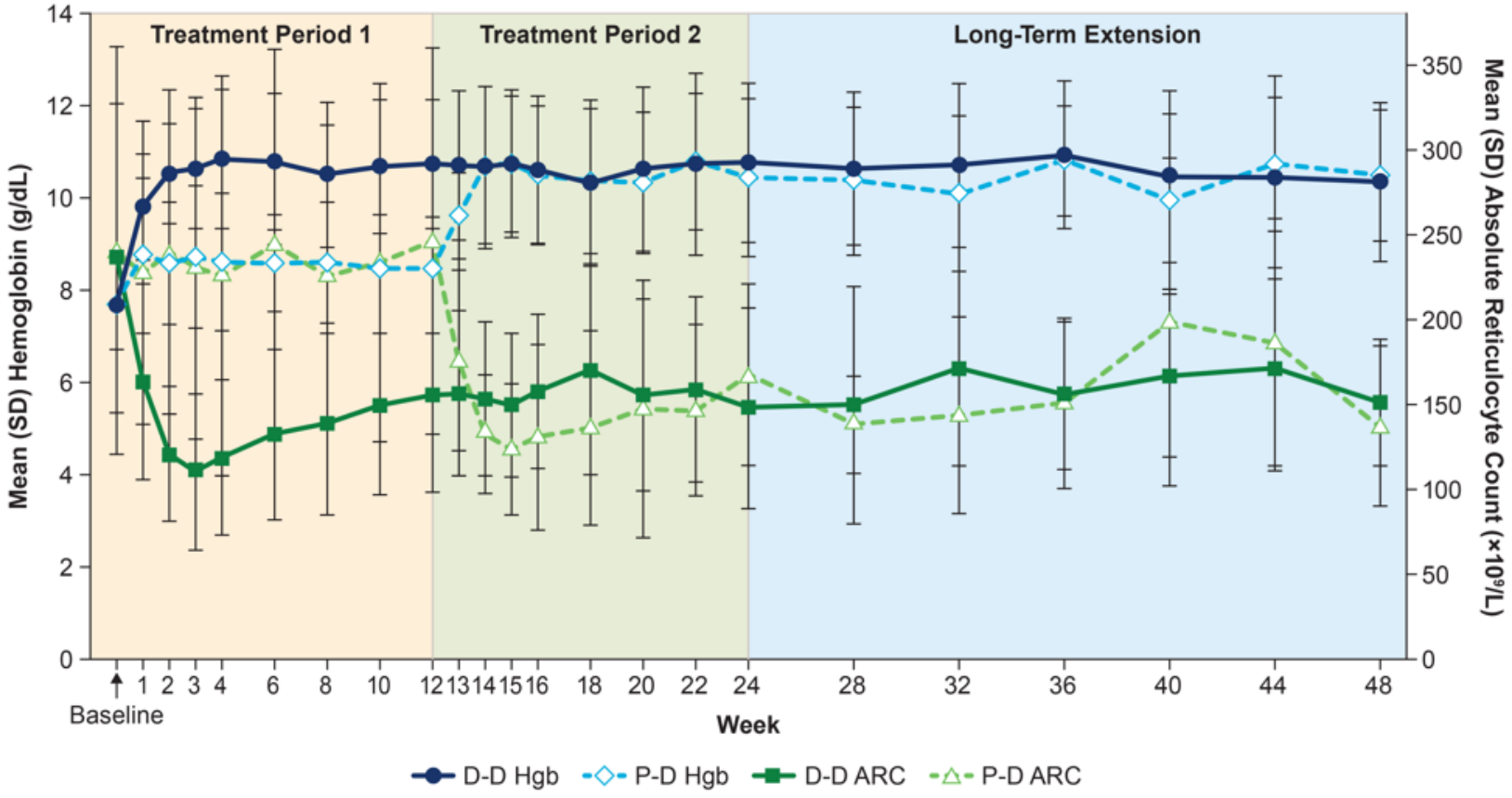
Key Inclusion Criteria	Efficacy Measures
▪ Aged ≥ 18 years with diagnosis of PNH ▪ csEVH (Hb ≤ 9.5 g/dL, ARC ≥ 120 x 10^9/L) ▪ ≥ 6 months of treatment with eculizumab or ravulizumab	▪ Change from baseline in Hb, ARC, and LDH (weeks 12, 24 and 48) ▪ Hb increase ≥ 2 g/dL in the absence of transfusion (week 24) ▪ Transfusion avoidance (weeks 12-24)
Dosing	**Safety**
▪ Danicopan 150 mg 3 times daily ▪ Dose escalation up to 200 mg 3 times daily was permitted based on clinical response (Hb levels and/or transfusion)	▪ TEAEs and laboratory abnormalities (throughout)

Lee JW *et al.* (2023) *The Lancet Haematology*

ALPHA Trial: Factor Inhibition + C5 Inhibition

LSM (SEM) change in Hgb at Week 12
D-D: 2.94 (0.21) g/dL
P-D: 0.50 (0.31) g/dL

LSM (SEM) change in Hgb at Week 24
D-D: 3.17 (0.30) g/dL
P-D: 2.26 (0.34) g/dL



LSM (SEM) change in ARC at Week 12
D-D: –83.8 (8.93) × 10^9/L
P-D: 3.5 (12.68) × 10^9/L

LSM (SEM) change in ARC at Week 24
D-D: –80.2 (8.75) × 10^9/L
P-D: –65.2 (12.74) × 10^9/L

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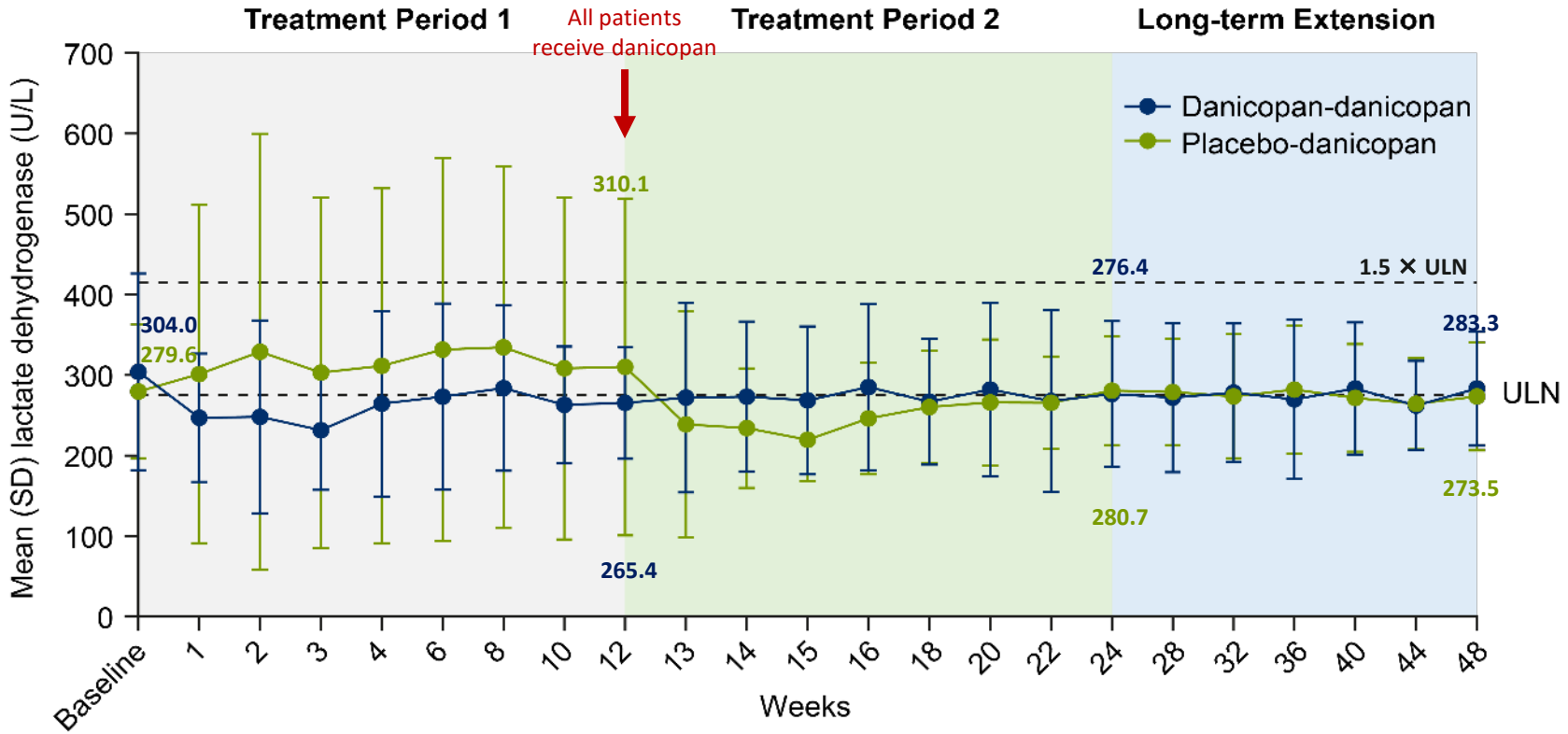
Lee JW *et al.* (2023) *The Lancet Haematology*

ALPHA Trial: Factor Inhibition + C5 Inhibition



Mean LDH levels were **maintained** from week 12 to 48 and were **near normal** in both treatment groups

Week	BL	1	2	3	4	6	8	10	12	13	14	15	16	18	20	22	24	28	32	36	40	44	48
Danicopan-danicopan, n	56	51	57	54	56	54	54	51	52	53	53	51	54	54	49	54	52	51	48	47	46	43	36
Placebo-danicopan, n	25[a]	25	26	24	22	25	24	25	25	23	23	22	24	23	24	24	23	23	22	20	21	20	20

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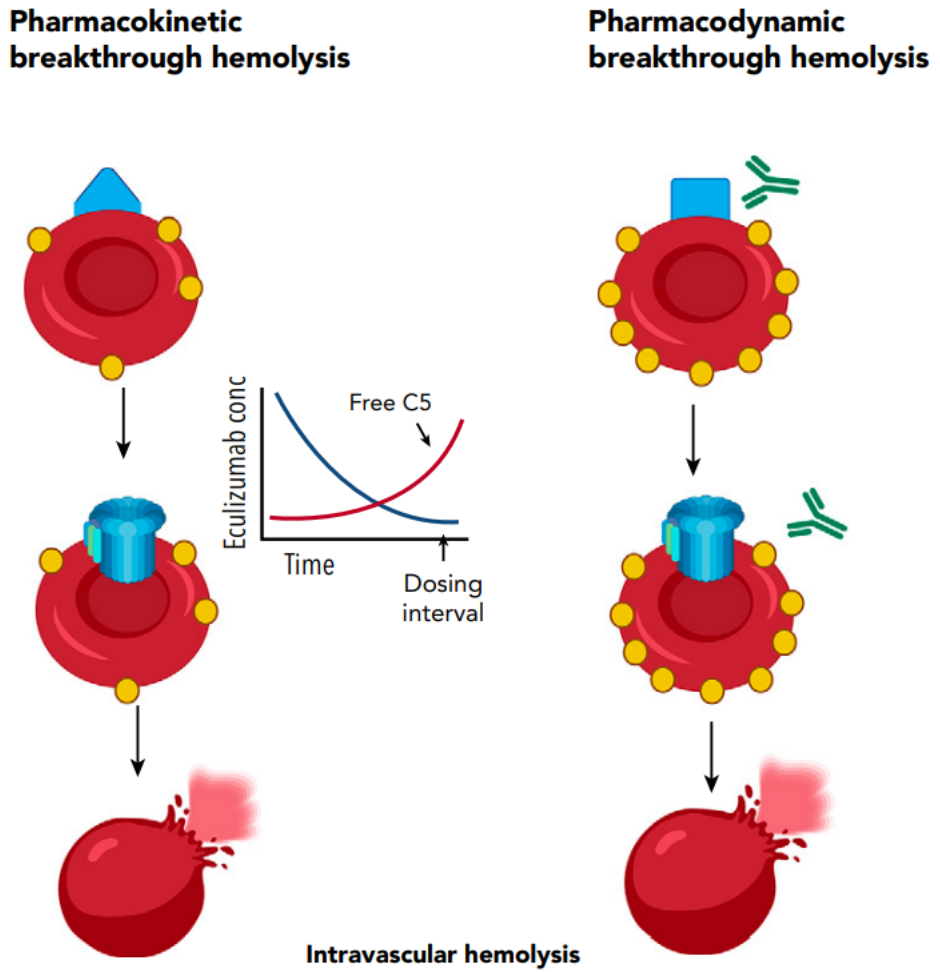
CANADIAN PNH NETWORK

Lee JW *et al.* (2023) *The Lancet Haematology*

BREAKTHROUGH HEMOLYSIS

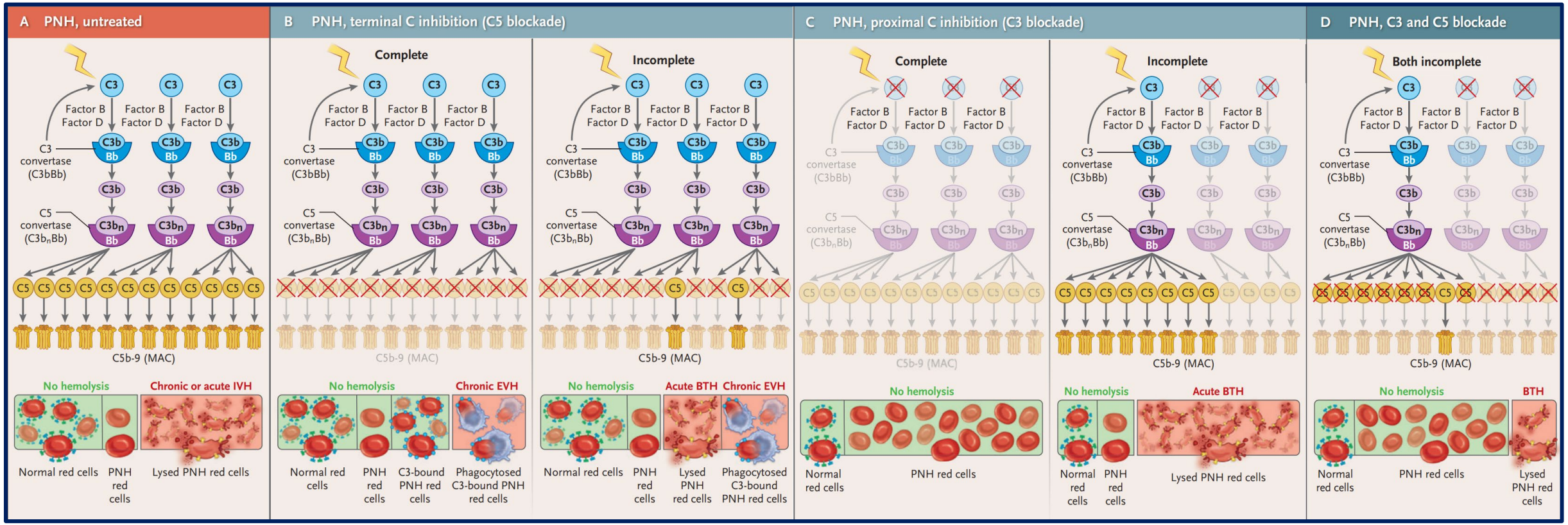
Breakthrough Hemolysis Definitions & Etiology

- Return of IVH and signs/symptoms of PNH
  - Anemia, fatigue, dark urine, abdo pain, etc.
  - Thrombosis, AKI, pancreatitis, pulmonary HTN
- Pharmacokinetic (PK) BTH
  - Insufficient dosing to inhibit complement
  - Nearing the end of each dosing cycle
- Pharmacodynamic (PD) BTH
  - Triggered by complement-amplifying conditions (e.g. infections, vaccines)
  - Rarely predictable (counselling is crucial)



Brodsky RA *et al.* (2021) *Blood*
Oliver M & Patriquin CJ (2023) *J Blood Med*

Variable Theoretical BTH Risk by Target



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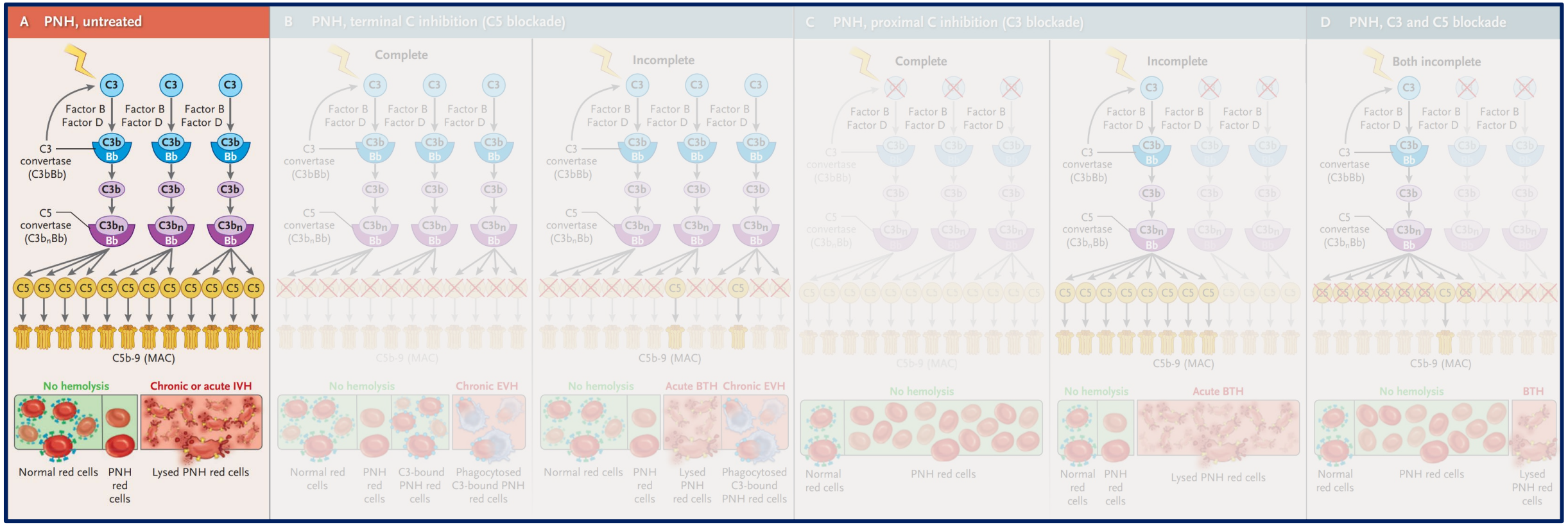
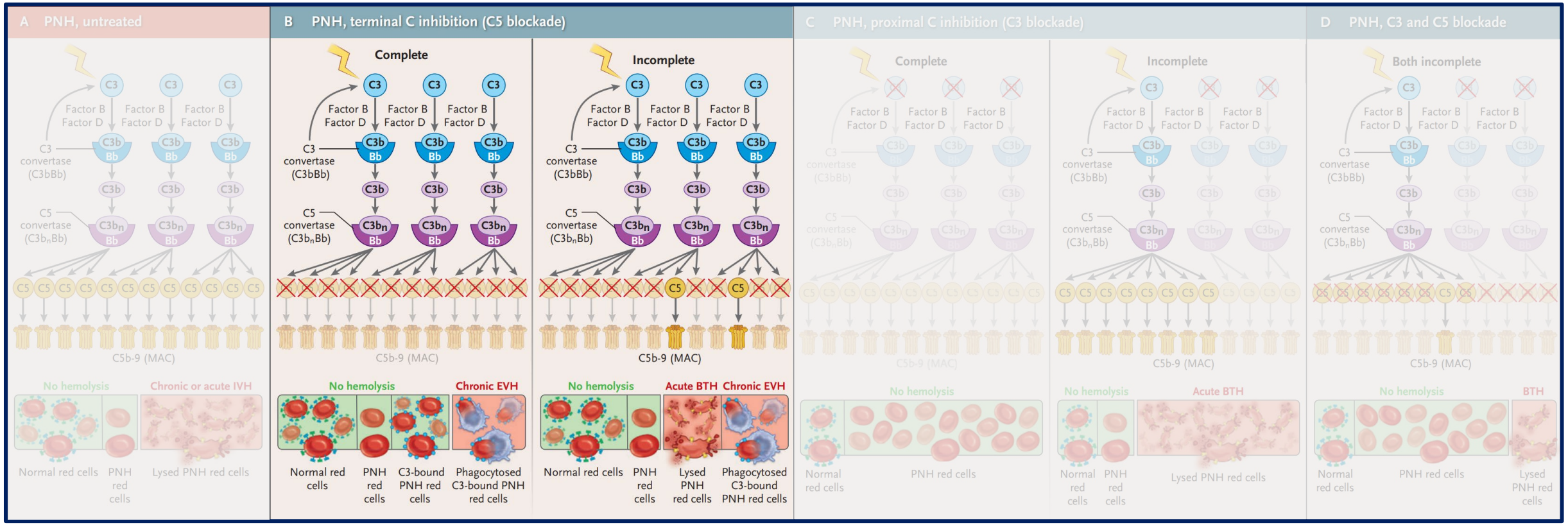
Notaro R & Luzzatto L (2022) *NEJM*

Variable Theoretical BTH Risk by Target



Notaro R & Luzzatto L (2022) *NEJM*

Variable Theoretical BTH Risk by Target



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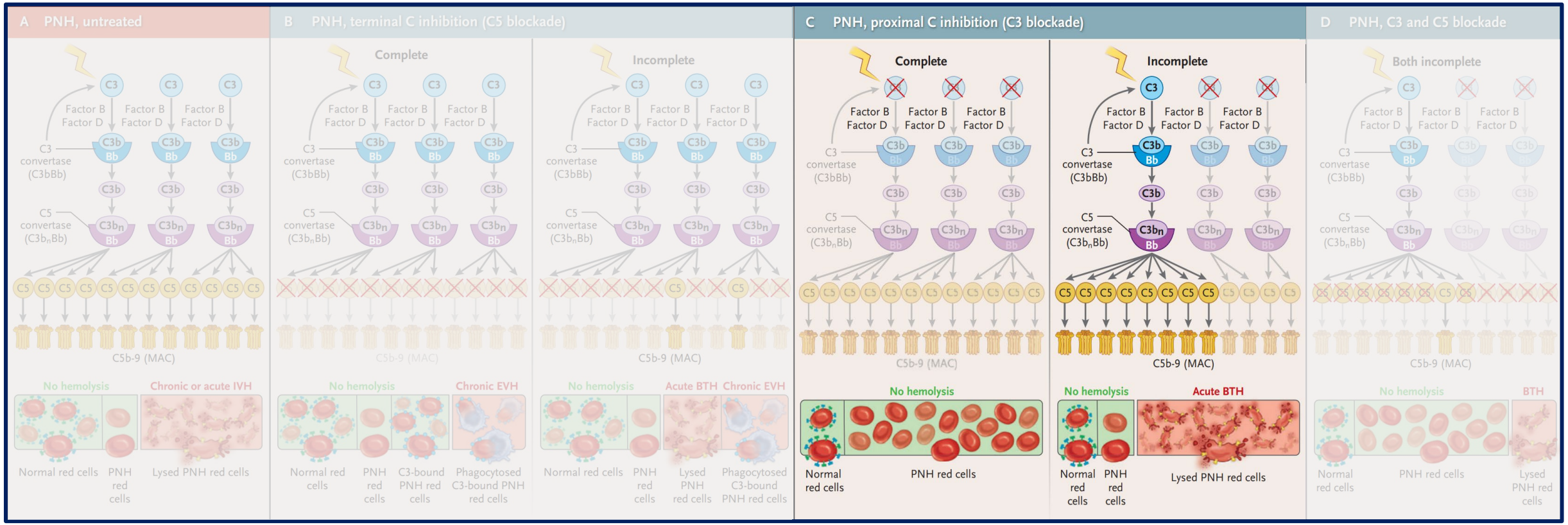
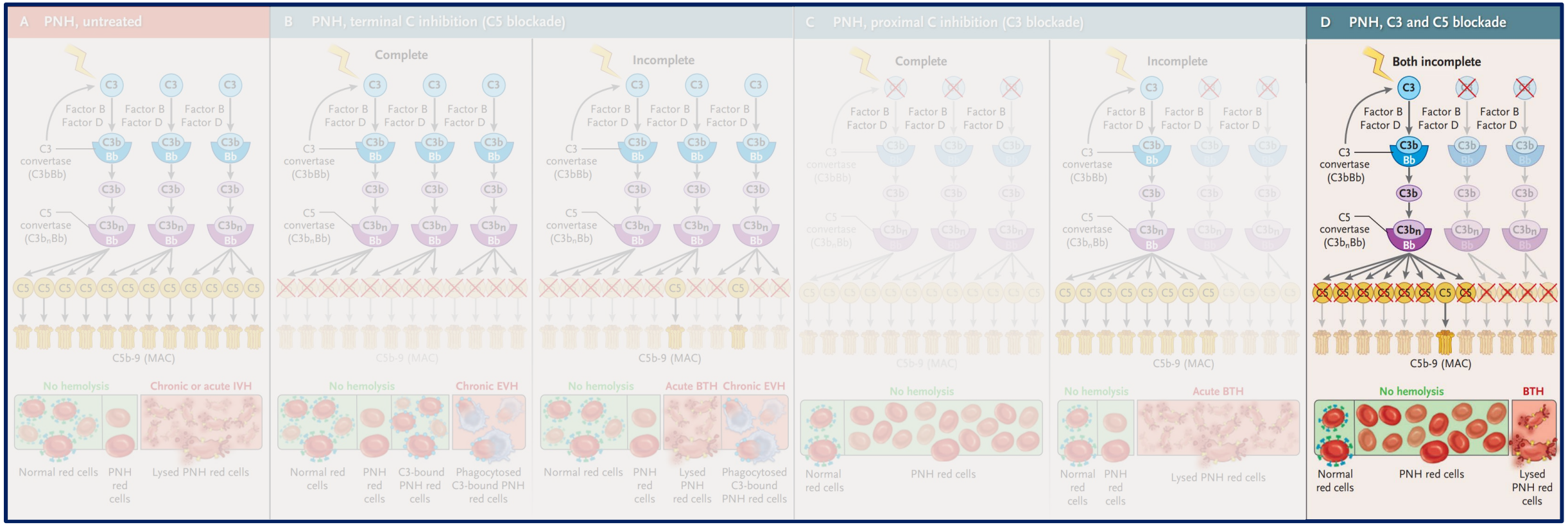
Notaro R & Luzzatto L (2022) *NEJM*

Variable Theoretical BTH Risk by Target



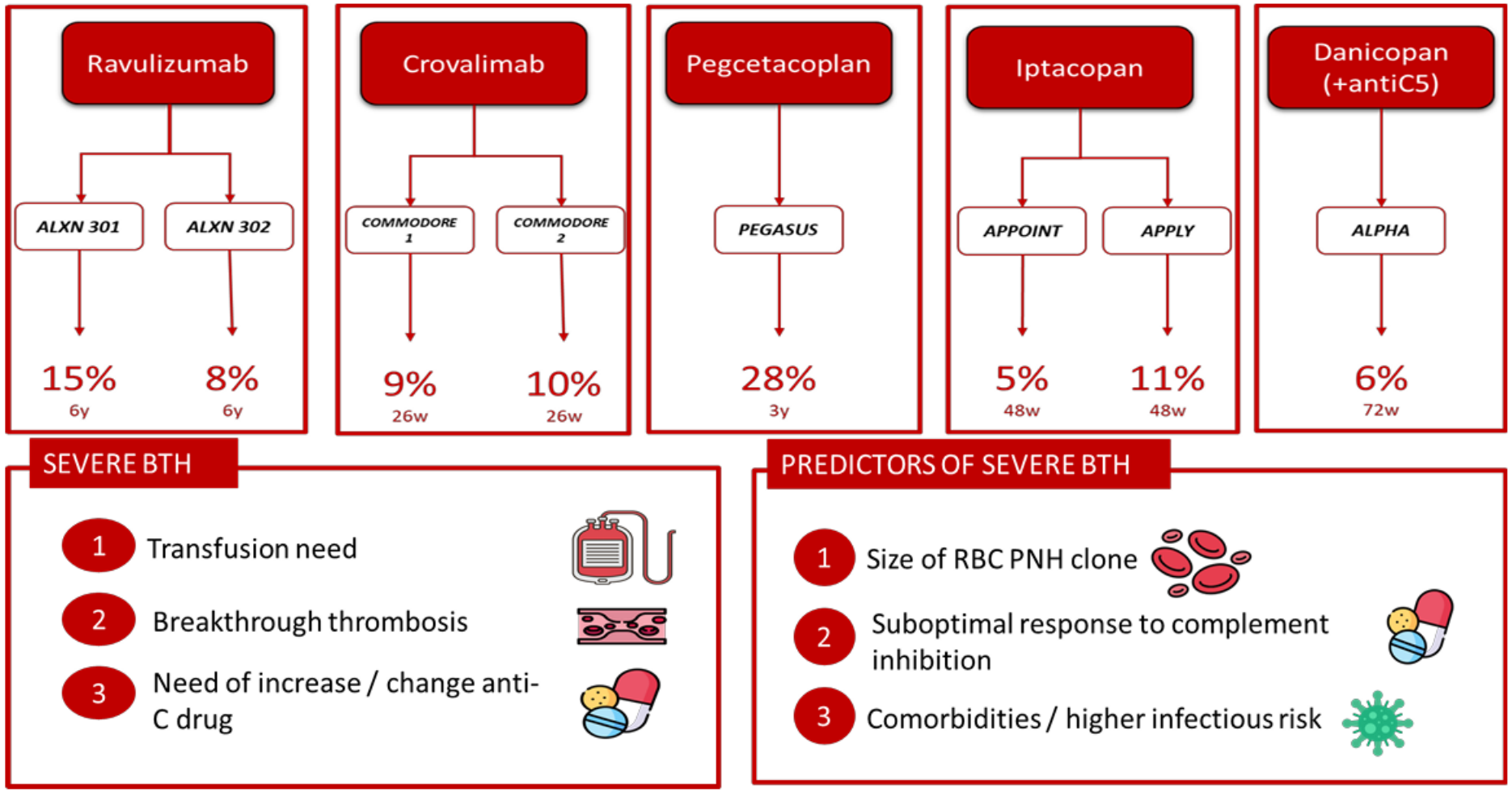
Notaro R & Luzzatto L (2022) *NEJM*

Variable Theoretical BTH Risk by Target



Notaro R & Luzzatto L (2022) *NEJM*

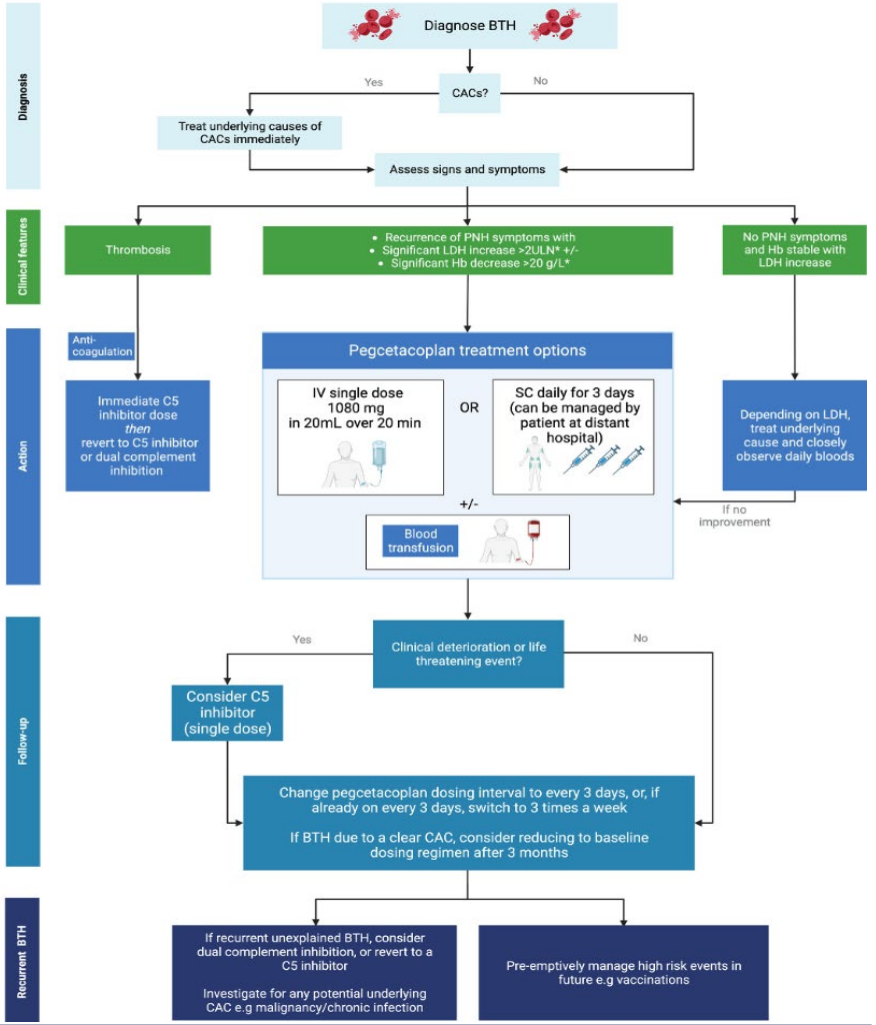
Breakthrough Hemolysis Across Therapies



Fattizzo B *et al.* (2025) *Blood*

Breakthrough Hemolysis Management

- A universal definition remains elusive
  - International consensus planned (IPIG, ASH)
- Severity Assessment
  - LDH increase (x ULN), manifestations, TE, etc.
- Unknowns
  - Risk factors (e.g. C5i dose, transfusions, LDH)
  - Funding of additional doses?
  - Utility of additional doses?
  - Availability of rescue C5i?



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Oliver M & Patriquin CJ (2024) *J Blood Medicine*
Griffin M *et al.* (2024) *Am J Hematology*
Dingli D *et al.* (2024) *Hematology*

NEW DISCUSSIONS, NEW DECISIONS

Treatment Pathways for PNH: Patient Selection

Complement inhibitor-naïve patients with at least of the following:

- Clinically significant intravascular hemolysis
- Pregnancy (even if naïve)
- New thrombosis
- Severe IVH with end-organ damage (e.g. AKI/CDK, PH)

Terminal Complement (C5) Blockade (1L)

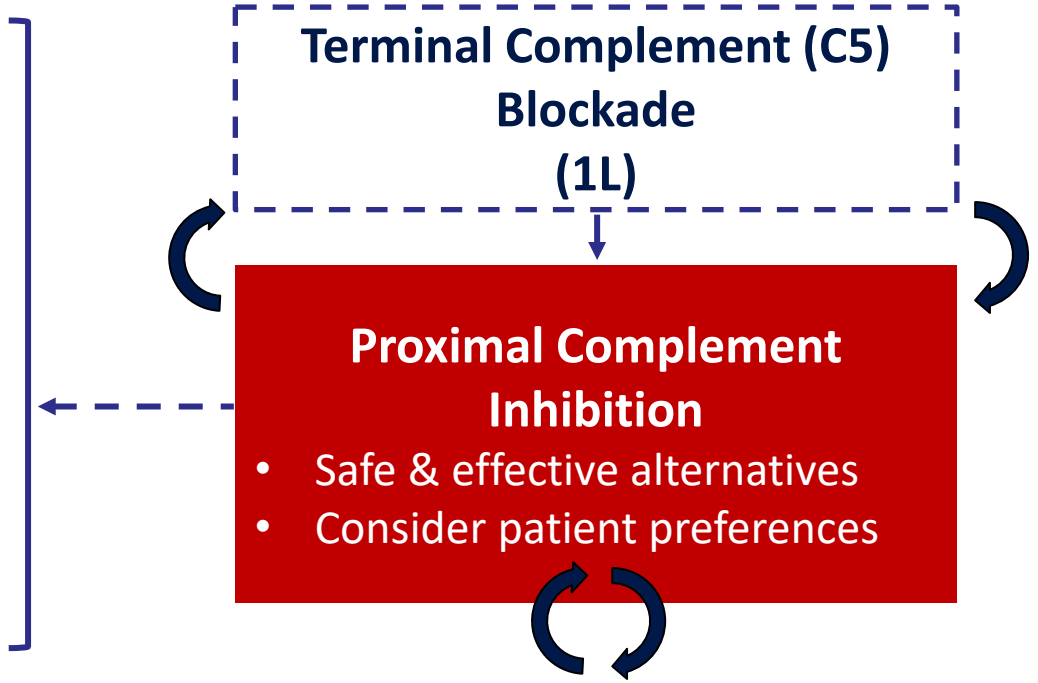
Proximal Complement Inhibition
- Safe & effective alternatives
- Consider patient preferences

Oliver M & Patriquin CJ (2023) *J Blood Med*

Treatment Pathways for PNH: Patient Selection

Proximal (dual) inhibition should be considered for the following:

- Inadequate response to C5i after ≥3-6 months
- Intolerance to C5 inhibition
- Route & frequency choice
- Breakthrough hemolysis risk
- Jurisdictional availability



Criteria or parameters which would best reflect clinical response remain to be fully defined.

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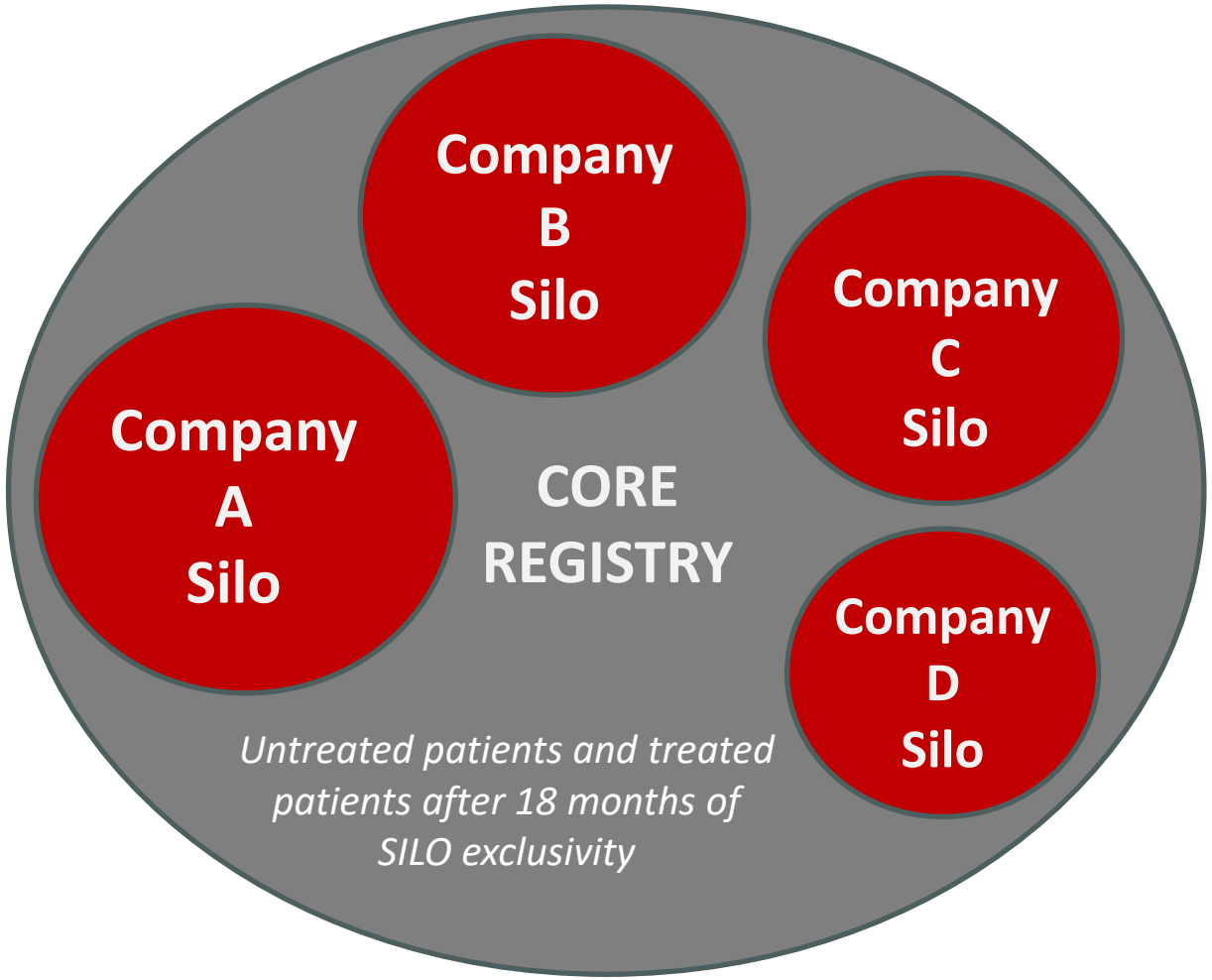
Oliver M & Patriquin CJ (2023) *J Blood Med*

A New Tool – The IPIG PNH Registry



- All PNH patients enter CORE Registry
- Industry supports CORE & SILO areas
- Common variables for patients in any SILO eventually enter the CORE
- Potential areas of inquiry:
  - *Drug changes & combinations*
  - *Infrequent events (rate, management, etc)*
  - *Breakthrough hemolysis*
  - *Outcomes in vulnerable groups*
  - *Role of biomarkers*

WRAPPING UP

Take-Home Messages

- PNH is a rare hemolytic anemia presenting with common signs/symptoms
  - *Maintain a high index of suspicion and low threshold for testing (CATCH criteria)*
- Uncontrolled terminal complement activity drives natural history
  - *Thrombosis, renal failure, abdominal pain, and death associated with elevated LDH*
  - *Terminal inhibition may unmask clinically significant EVH, drive anemia, impair QoL*
- PNH is a chronic condition requiring long-term treatment and monitoring
  - *Newer treatment strategies must improve upon established efficacy and safety*
  - *Proximal/dual inhibition allows us to improve Hb, QoL, and align with lifestyle*
  - *Members of the Canadian PNH Network are always available to help (PNHnetwork.ca)*

SAVE THE DATE!

TORONTO COMPLEMENT CONFERENCE SEPT 24-26, 2026

Friday, September 25 to Saturday, September 26, 2026
In-person and hybrid registration available – *opening Spring 2026*
Toronto, Ontario

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The end.

Questions? Comments?

Christopher.Patriquin@uhn.ca

www.PNHnetwork.ca

Thrombosis Canada Thrombophilia Algorithm
https://ThrombosisCanada.ca/tools/?calc=ThrombophiliaAlgorithm