Paroxysmal Nocturnal Hemoglobinuria & Aplastic Anemia

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Disclosures

- Advisory Board Honoraria: Alexion, Takeda, Sobi, Novartis, Sanofi, Roche
- Travel Support: Alexion, Sobi
- Speaking Honoraria: Alexion, Roche
- Clinical Trial Involvement
  - Alexion (ALXN1210-301, ALXN2040-301)
  - Apellis (APL2-307)

Objectives

- Explore the clinical presentation(s) and diagnostic approach to PNH and Aplastic anemia
- Discuss the current standard of care treatment for PNH and AA in Canada
- Present data on recent clinical trials of new complement inhibitors for PNH

Background

Aplastic Anemia

Aplastic Anemia

- A hematopoietic stem cell disorder associated with decreased hematopoiesis (blood cell making capacity)
- Misnomer “Aplastic Pancytopenia”
- Classification and prognosis in AA are related to the depth of cytopenias in the peripheral blood
- Severity drives the therapeutic decisions and management
- In Western countries the incidence is approximately two per million/year
- Half of cases of AA occur in the first three decades of life
- “Bone marrow failure” is an umbrella term which captures AA, MDS, or BM replacement by tumor or fibrosis

Pathophysiology

Loss of hematopoietic stem cells by :

- Autoimmune mechanisms (inappropriate immune system activation)
- Direct injury to HSCs (eg, by drugs, chemotherapy, radiation)
- Infections
- Pregnancy
- Idiopathic (40-70%)

Presentation

Pancytopenia with inappropriately low reticulocyte response

- Anemia → fatigue, shortness of breath, pallor, syncope, headache
- Thrombocytopenia → bleeding, bruising, petechiae
- Neutropenia → infections, fever, mouth sores

Classification of AA

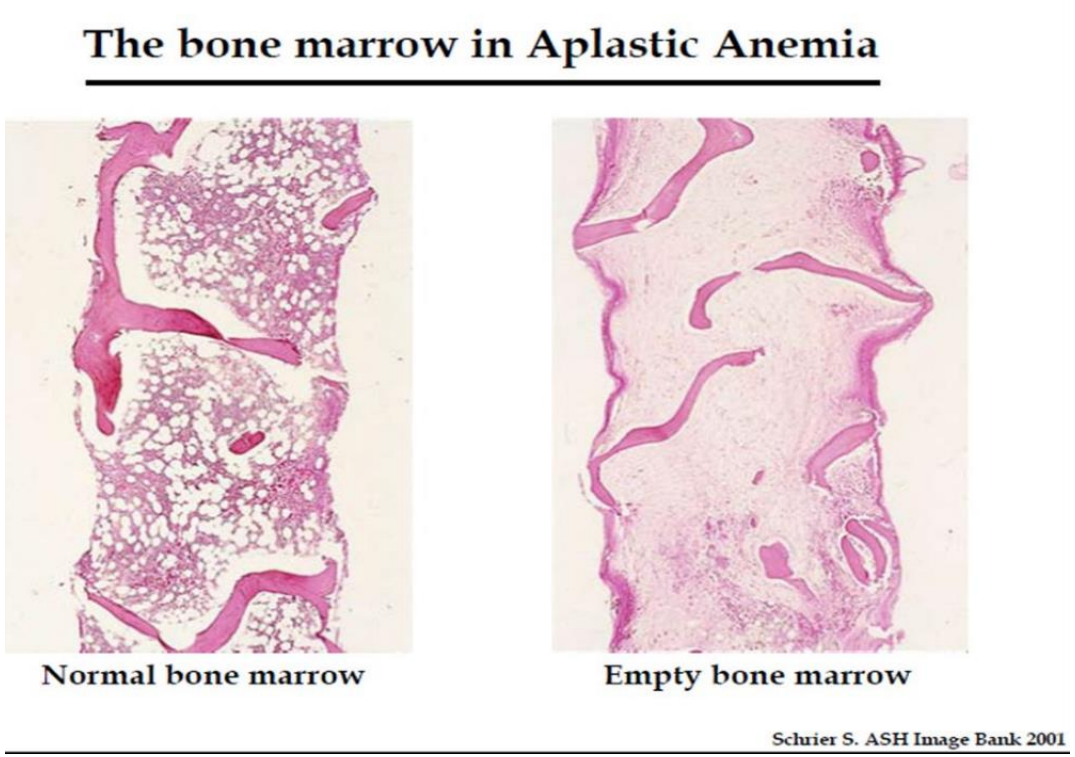
Table 19-1 Classification of aplastic anemia by severity

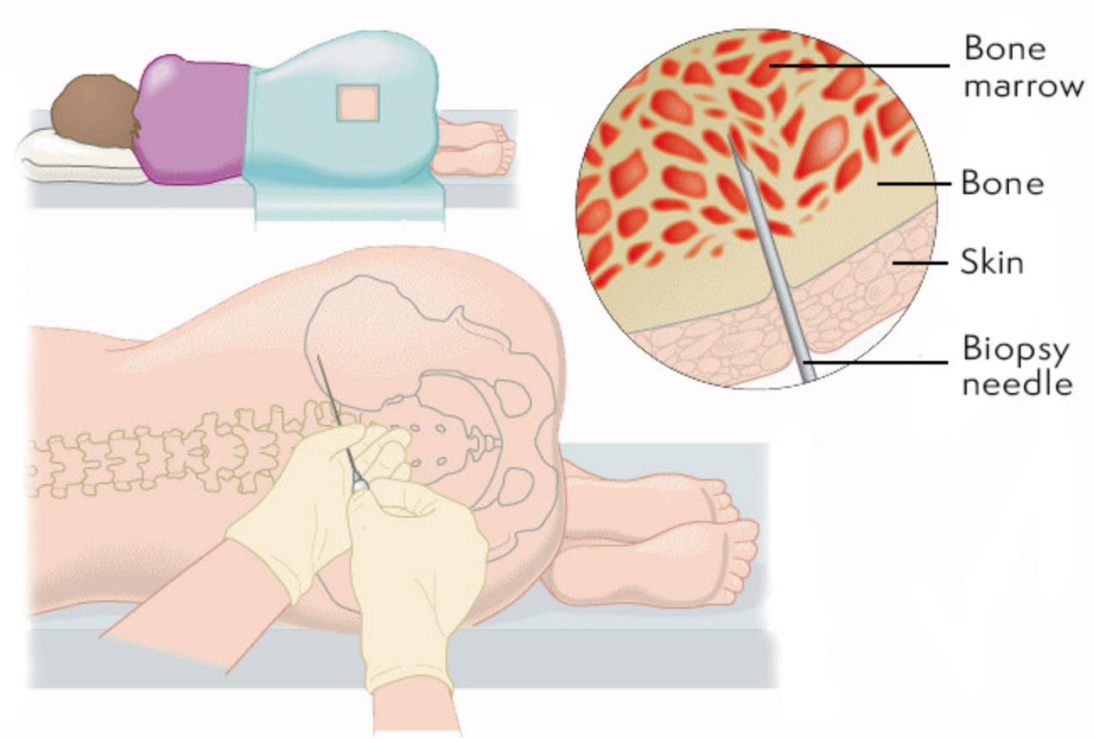
Peripheral blood cytopenias	Nonsevere (moderate) aplastic anemia (not meeting criteria for severe disease)	Severe aplastic anemia (any two of three)	Very severe aplastic anemia (meets criteria for severe disease and absolute neutrophils <200)
Bone marrow cellularity	<25%	<25%	<25%
Absolute neutrophil count		$<0.5\times10^9$/L	$<0.2\times10^9$/L
Platelet count		<20,000/μL	
Reticulocyte count		<1.0% corrected or <60,000/μL	

*Very severe aplastic anemia is reserved for patients who fulfill criteria for SAA but with an absolute neutrophil count of $<0.2\times10^9$/L.

Altman, JK. et al. *American Society of Hematology Self-Assessment Program. 2022.*
DOI: https://doi.org/10.1182/ashsap8

Diagnosis





[1]ASH image bank
2https://lymphoma-action.org.uk/about-lymphoma-tests-diagnosis-and-staging/bone-marrow-biop

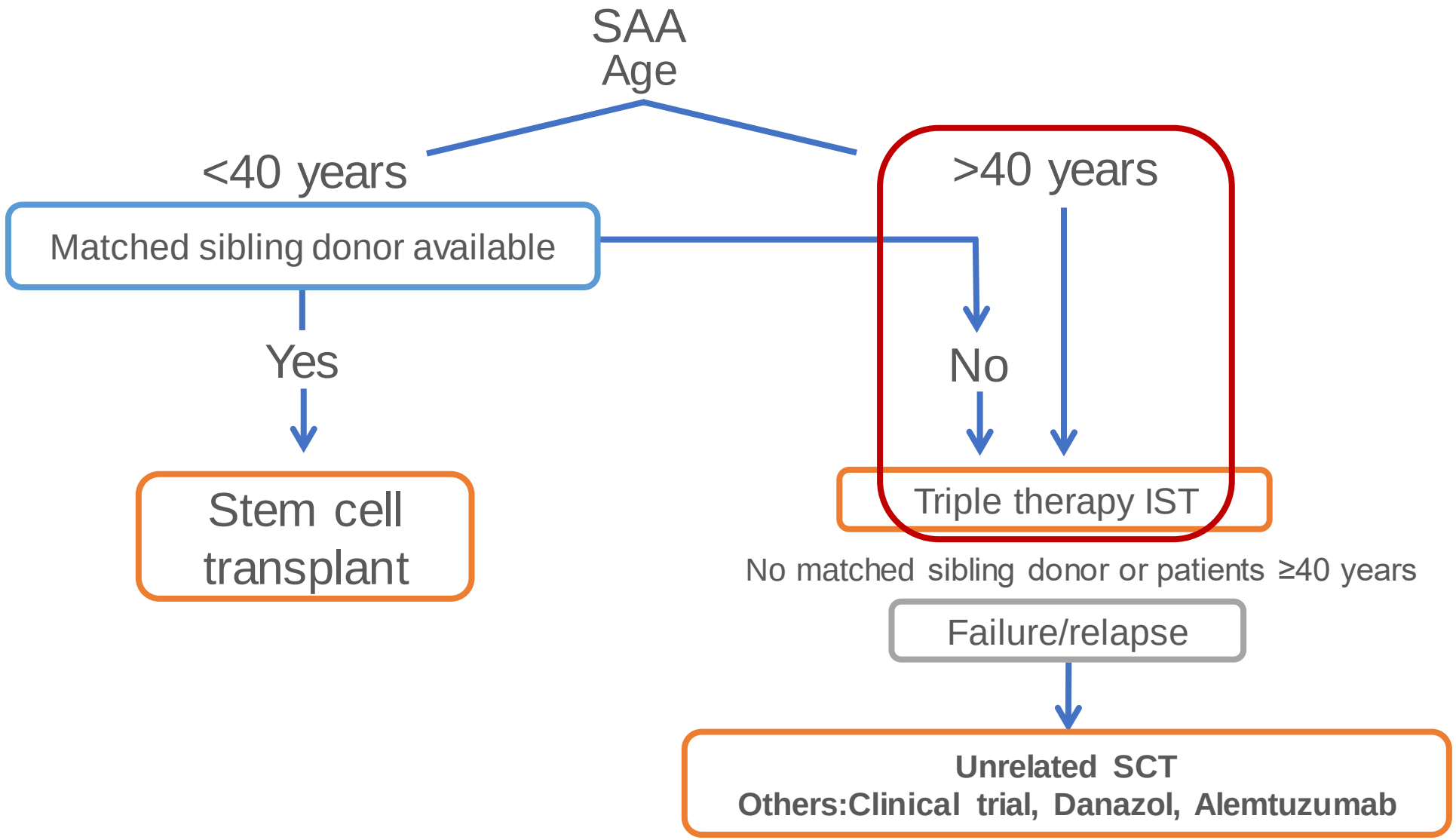
Supportive Management

- Transfusions of blood products to keep platelet count > 10, hemoglobin > 70-80g/l
- Attempt to limit transfusions in transplant eligible patients if possible
- Blood donations from close family/siblings should be avoided in order to minimize the risk of transplant rejection secondary to immune response to donor
- Patients may require iron chelation from iron overload from repeated pRBCS (typically >6-10 units)
- Prophylaxis→fungal, bacterial, viral
- No benefit with G-CSF or EPO

Prognosis

- Without treatment, almost all patients with SAA or very severe AA eventually will succumb to infection or to bleeding complications
- Untreated, SAA has a one-year mortality of over 70 %
- Prompt diagnosis is key to initiate supportive care measures and definitive treatment with either immunosuppression or transplant
- In patients with moderate AA, it is reasonable to observe patients for several weeks to months to better define the tempo and trajectory of the disease.
- A subset of patients will exhibit spontaneous remission of cytopenias, while others evolve to severe AA (SAA)

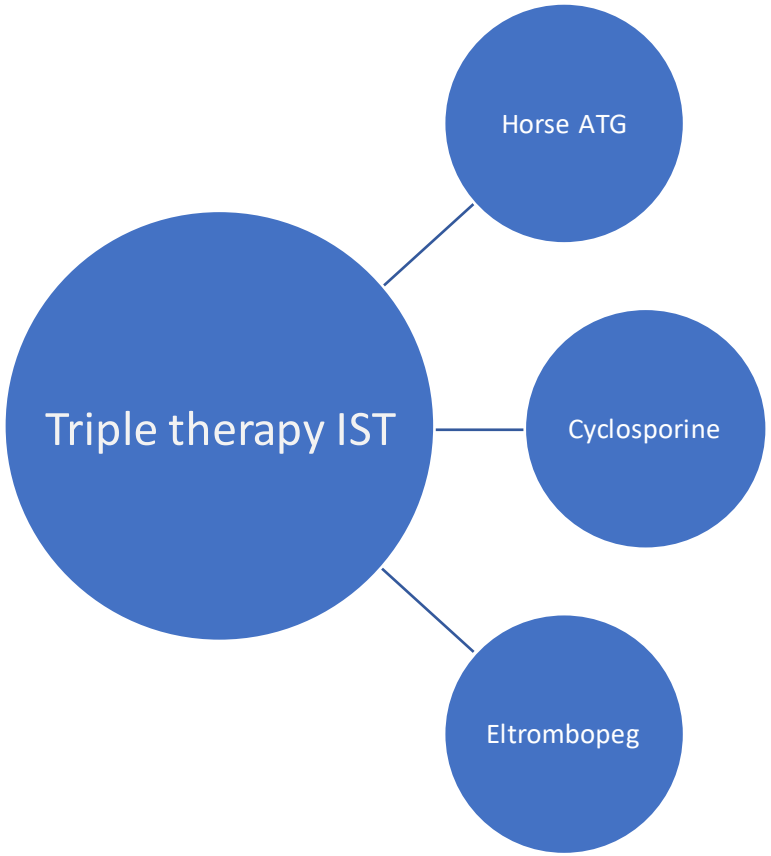
Treatment options for severe AA



Marsh JCW *et al. Br J Haematol* 2009;147:43–70

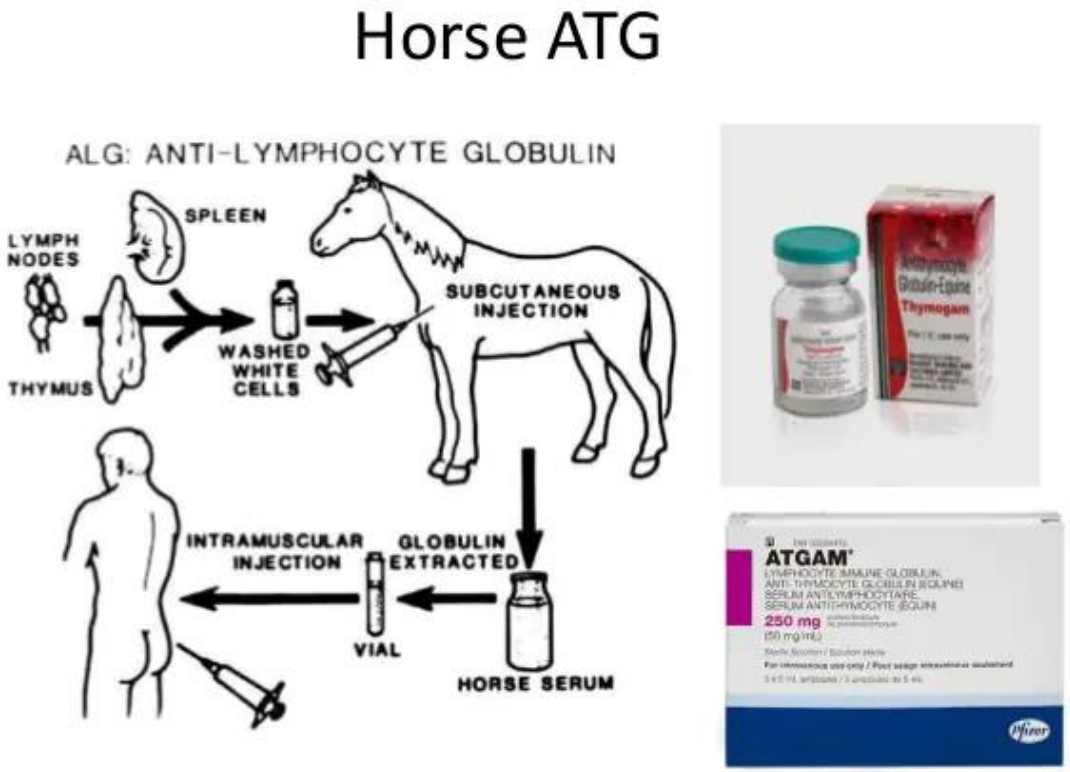
Immunosuppression

- Funding varies from province to province
- Standard of care is horse ATG + Cyclosporine at minimum
- Preferred regimen (if funding allows) is triple therapy immunosuppression
- 52% complete response at 12 months, ORR 68% at 6 months and 2-year OS is 90%
- Transfusion independence and improvement of neutropenia take 1-3 months
- Compared with hATG plus CsA, triple IST achieves superior responses (CR, ORR, earlier first response and time to transfusion independence) with equivalent toxicity



De Latour P. *et. al. N Engl J Med.* 2022;386(1):11

Patel BA *et. al. Blood.* 2022;139(1):34



Horse ATG

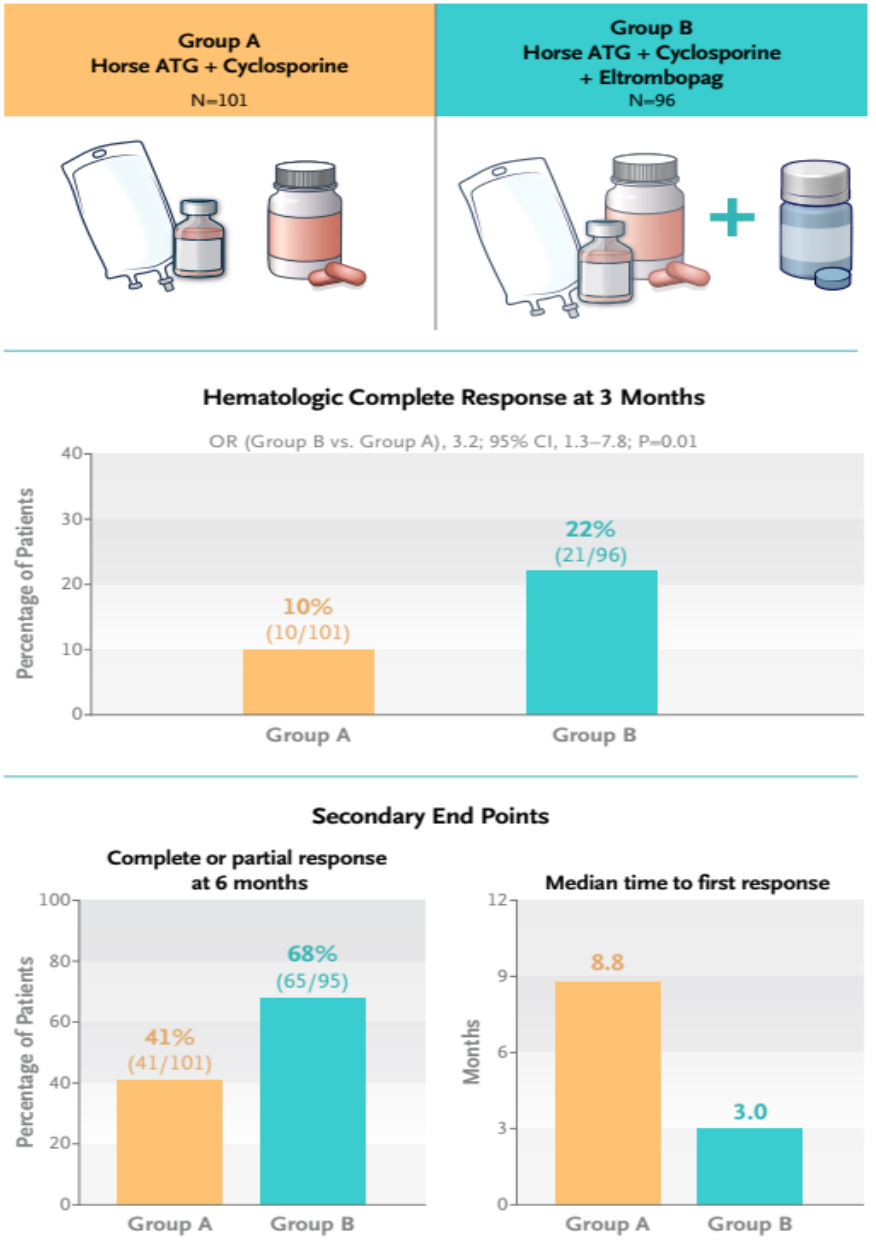
- IV infusion given over 4-18 hours x 4 days in hospital
- Given with steroids to prevent serum sickness
- Serum sickness can occur up to 14 days following infusion
- Risk of infusion reaction which presents with fever, rash, chills/rigors, BP changes, fluid retention

Cyclosporine

- Oral medication, derived from fungus, reduces T cell proliferation and inflammatory cytokines.
- Twice daily to target trough level of 200 to 400 ng/mL
- CsA may cause renal dysfunction, hypertension, and magnesium wasting
- Tremor, hypertrichosis, gingival hyperplasia and neurotoxicity can also be seen
- Usually patients require minimum of 6-12 months of CsA with slow taper

Addition of Eltrombopeg

- First-generation TPO-R agonist
  - Binds to the transmembrane domain of TPO-R, acting in synergy with TPO to stimulate hematopoiesis
- First trialled in refractory SAA patients with 40% response rates observed
- Starting dose is 150mg orally once daily, but may be dose reduced in Asian patients
- Most common side effects include skin rashes, nausea, cough, diarrhea, headache, fatigue and liver dysfunction
- Concern that eltrombopeg can stimulate clonal evolution so need close monitoring of the CBC and peripheral blood smear with repeat bone marrow if clinical concern



De Latour P. *et. al. N Engl J Med.* 2022;386(1):11

Treatment of Moderate AA

- Treatment is indicated for MAA when ongoing transfusion support is required affecting the patient's ability to participate in activities of daily life
- Treatment may also be started following 6-10 units of pRBCs to avoid the consequences of iron overload
- There is no consensus on management of MAA, and treatment decisions are usually individualized
- lower-intensity immunosuppression and eltrombopeg are equally acceptable based on the favorable balance of efficacy and side effects relative to high-risk stem cell transplant or intensive triple therapy immunosuppression.

Treatment of the less-fit, frail AA patient

- Informed by the patient's values and care philosophy
- Generally lower-intensity therapy and/or supportive care
- Options include single agent Eltrombopeg or Cyclosporine
- Anabolic steroids such as danazol, and Anti-CD52 monoclonal antibody treatment Alemtuzumab have been used

Olson TS & Dunbar CE. (2023). Treatment of Aplastic anemia in Adults. In Rosmartin. *Uptodate*. Retrieved Apr 01, 2023

Transplant in Aplastic Anemia

Allogeneic stem cell transplantation (SCT) can cure AA, but transplantation is associated with the potential for significant short- and long-term morbidity and mortality

SCT replaces the immune system which is responsible for the initial attack on the bone marrow as well as restores the supply of hematopoietic stem cells

Outcomes are determined by recipient age, donor availability and match of donor and conditioning regimens used

Generally, first line therapy for children and adults <40

Conclusions

- Aplastic anemia is a benign but life-threatening bone marrow condition
- Need for treatment and type of treatment is determined by the severity of the cytopenias
- Upfront immunosuppression with triple therapy horse ATG, cyclosporine and eltrombopeg has proven to result in superior CR rates and more brisk time to response than dual IST
- Hematopoietic stem cell transplant remains the only curative therapy for AA
- Space in the treatment landscape for new therapies
- Questions remain re: treatment for moderate AA, pregnancy, elderly or medically frail

Paroxysmal Nocturnal Hemoglobinuria

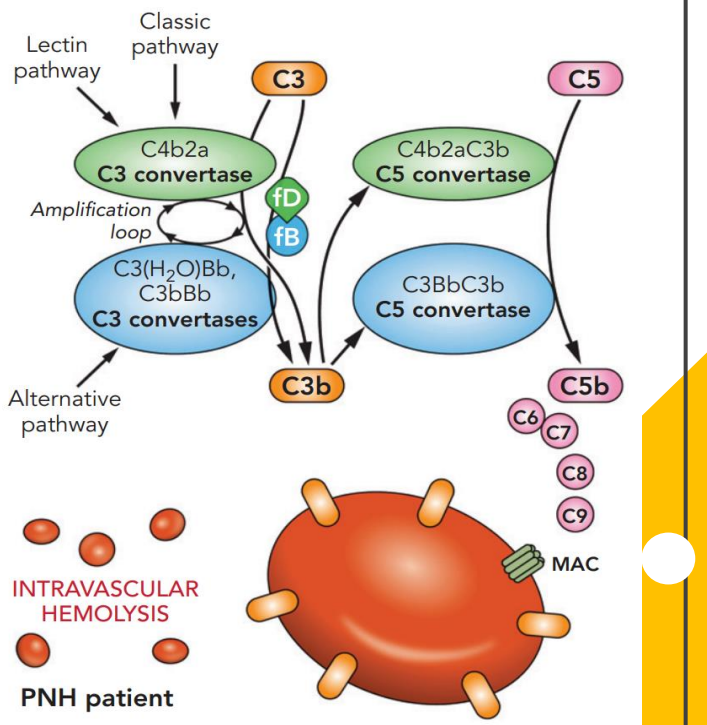
Paroxysmal Nocturnal Hemoglobinuria

- Acquired, ultra-rare, benign clonal abnormality of hematopoietic stem cells
- Prevalence is estimated to be between 0.5-2 per million people/yr
- It was named because of the belief that hemolysis (red blood cell break down) and eventual hemoglobinuria (free hemoglobin in urine) occurred:
  - Intermittently (paroxysmal)
  - With greater frequency during the night (nocturnal)
- It can affect any age group, but mostly commonly presents in the 3rd decade
- No pattern with regards to geography, race, ethnicity, or sex

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***

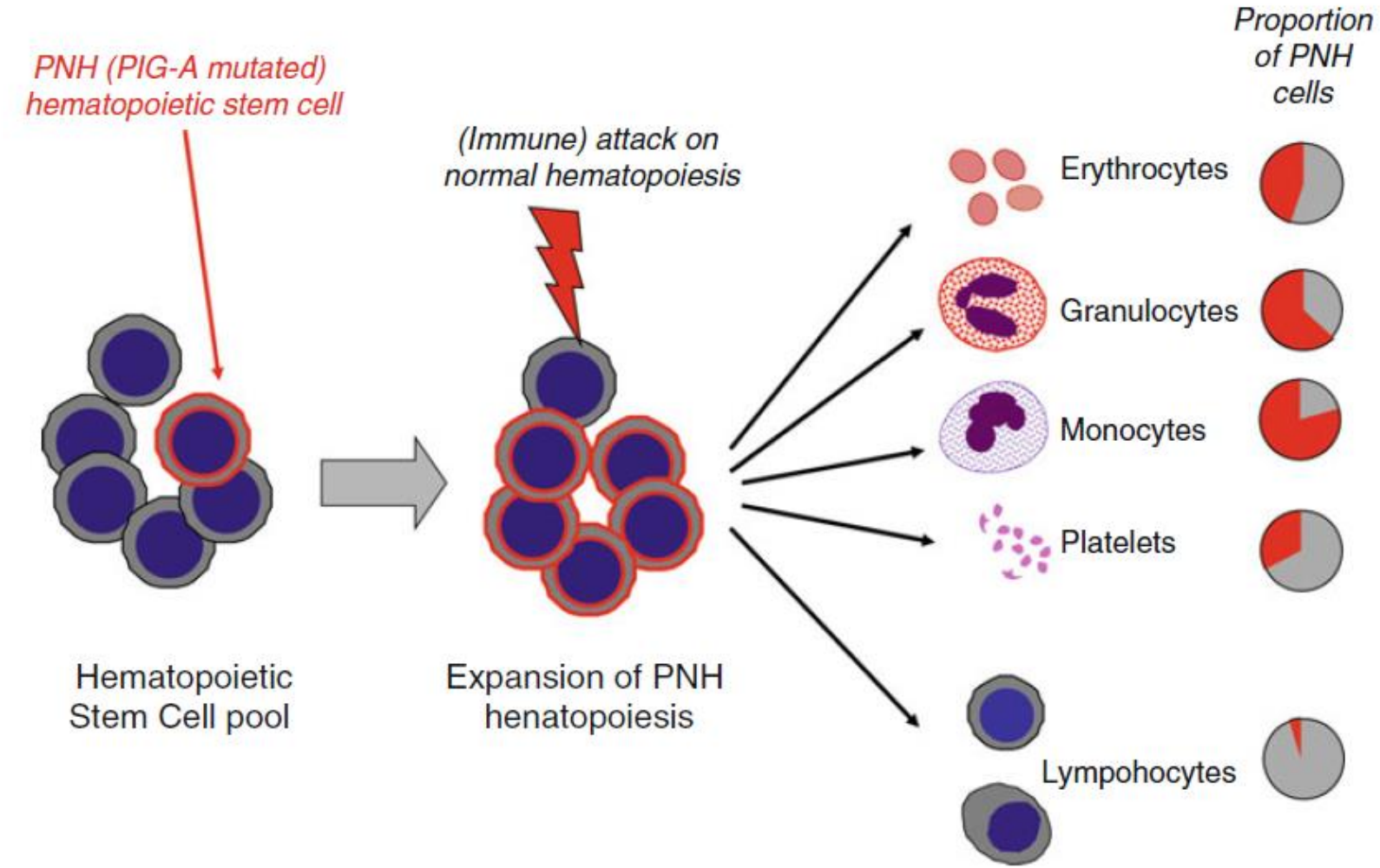
Paroxysmal Nocturnal Hemoglobinuria

- The primary defect in PNH is in the *PIG-A* gene located on the X chromosome leading to absence of GPI-linked complement "chaperones" CD55/59
- The mechanism for the gene mutation is unclear
- Leads to uncontrolled, unregulated activation of immune system's complement cascade
- It can arise *de novo* (spontaneous) or in the setting of an underlying bone marrow failure disorder
  - Aplastic Anemia
  - Myelodysplastic Syndrome
  - Other myeloid neoplasms



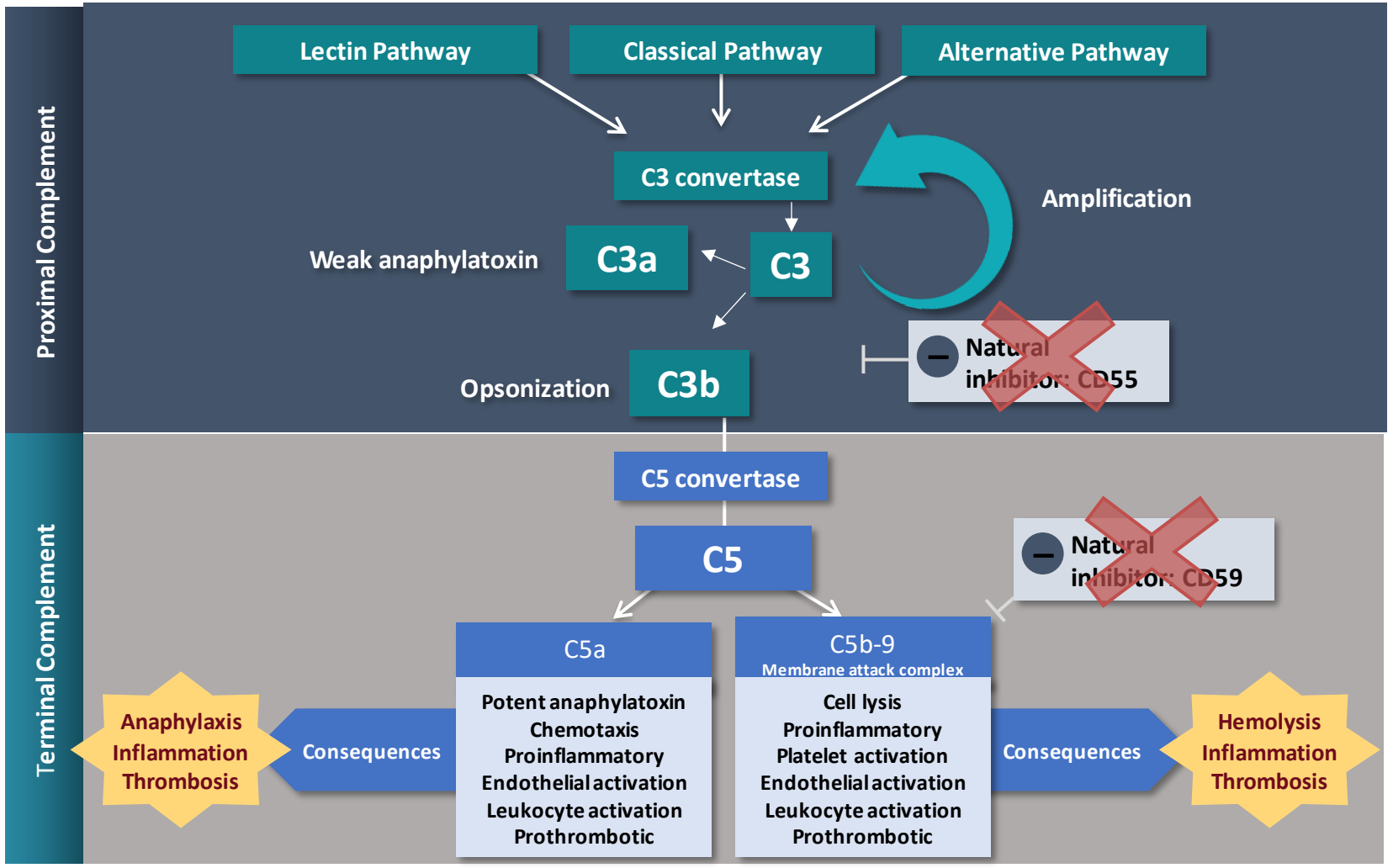
Brodsky RA (2015) *Blood*
Luzzatto L (2016) *F1000 Research*
Hill A *et al.* (2017) *Nat Dis Prim*
Patriquin CJ *et al.* (2019) *Eur J Hematol*

Clonal Selection and Expansion



Luzzatto L (2016) *F1000 Research*
Hill A *et al.* (2017) *Nat Dis Prim*

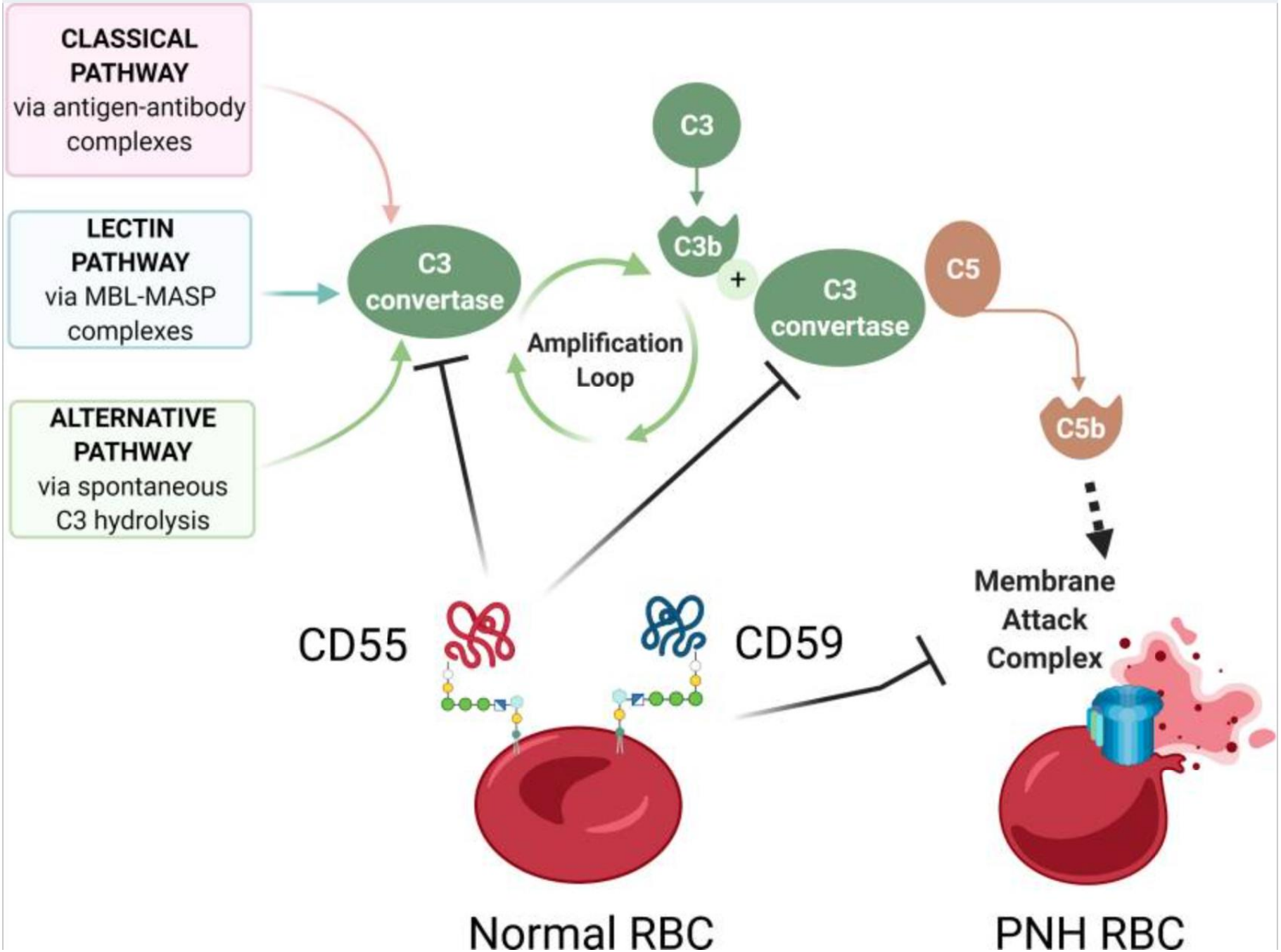
Missing Complement Regulatory Proteins Lead to Uncontrolled Complement Activation



PNH, paroxysmal nocturnal hemoglobinuria.

1. Walport MJ. *N Engl J Med.* 2001;344(14):1058-1066. **2.** Murphy K. *Janeway's Immunobiology.* 8th ed. New York, NY: Garland Science; 2012:37-73. **3.** Kelly R, et al. *Ther Clin Risk Manag.* 2009;5:911-921.

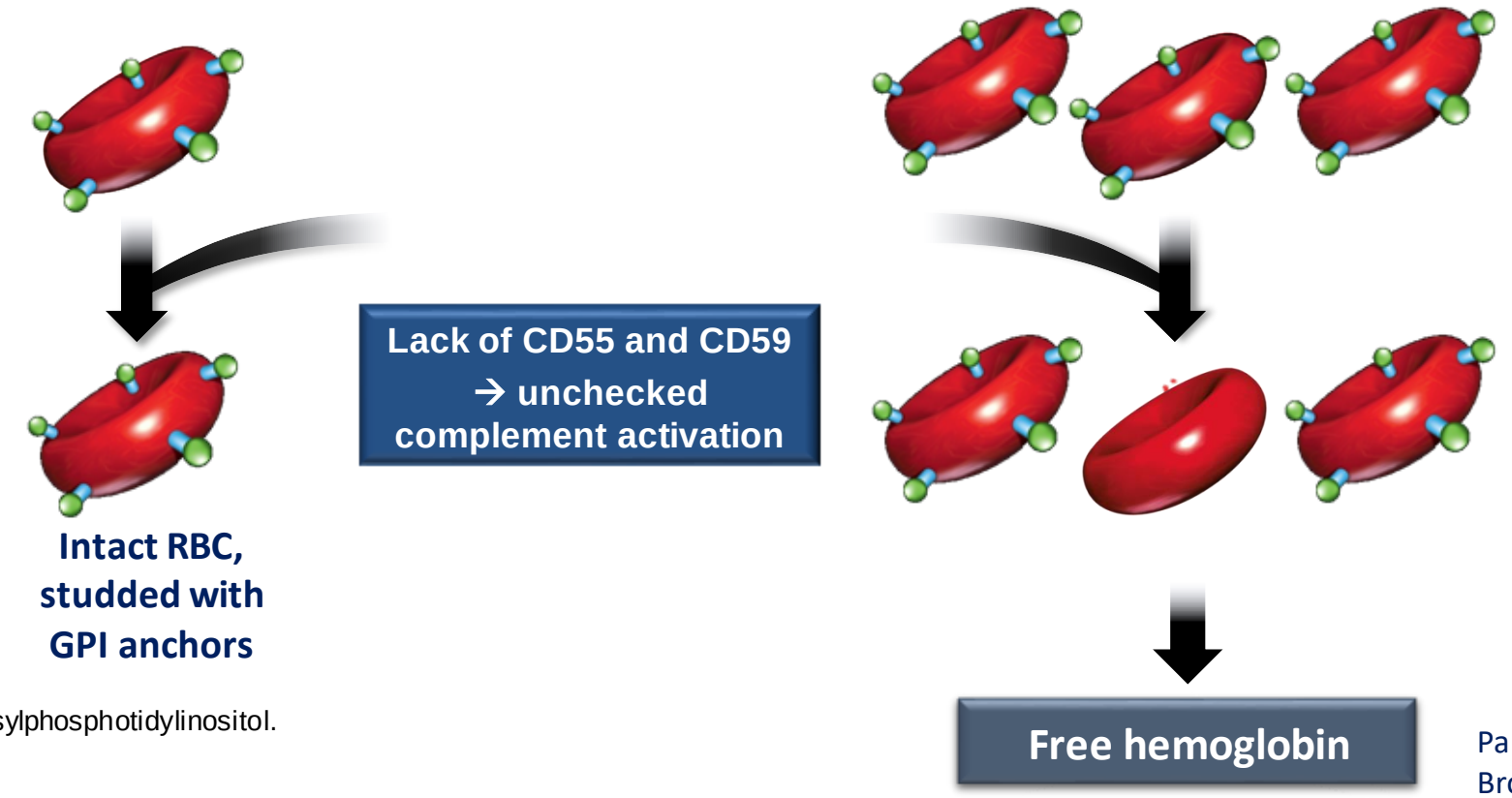
COMPLEMENT


CLASSICAL PATHWAY
via antigen-antibody complexes
LECTIN PATHWAY
via MBL-MASP complexes
ALTERNATIVE PATHWAY
via spontaneous C3 hydrolysis
C3
C3b
C3 convertase
Amplification Loop
+
C3 convertase
C5
C5b
Membrane Attack Complex
CD55
CD59
Normal RBC
PNH RBC

Unchecked Complement Activation

Typically RBCs are shielded from complement destruction by "chaperone" GPI-anchored proteins, namely CD55 & CD59

Without their complement chaperones, PNH RBCs are vulnerable to destruction



GPI = glycosylphosphotidylinositol.

Parker C et al., 2005.
Brodsky R *in* Hoffman et al.2005
Rother RP et al., 2005
Socié G et al., 1996
Hill A et al., 2007

Clinical signs and symptoms of PNH vary in presentation and severity

Significant impact on **morbidity:**

Hemoglobinuria[1,2]

- Hemolysis causes dark colored urine, which is most prominent in the morning in ~45% of patients

Fatigue[2,3]

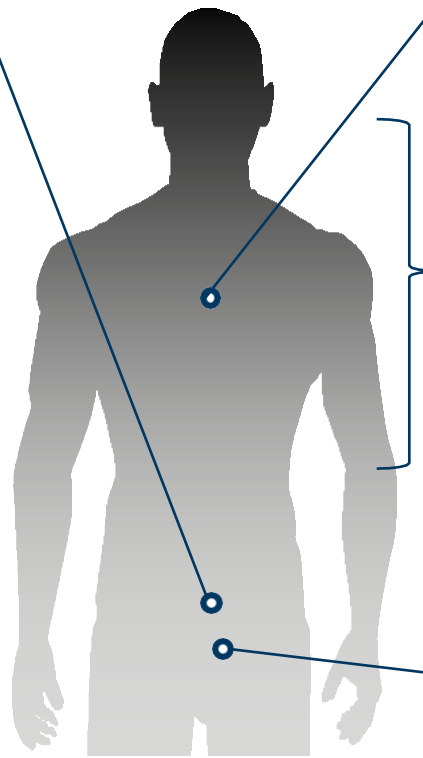
- ~80% of patients experience fatigue, which can be disabling during periods of hemoglobinuria

Smooth muscle dystonia[2,4]

- Can present as dysphagia (in 17% of patients), abdominal pain (35%), or erectile dysfunction (24%)

Anemia[1]

- Premature destruction of RBCs can result in hemolytic anemia that is worsened by the underlying bone marrow dysfunction



Significant impact on **survival:**

Pulmonary hypertension[2,5]

- ~50% of patients have evidence of PH at baseline
- Dyspnea, a sign of PH, occurs in 45% of cases

Thrombotic events[1,6]

- Occur in up to 44% of cases
- Symptoms depend on the location of the blood clot
  - Liver: jaundice, abdominal pain
  - Stomach: abdominal pain, bloating
  - Cerebral vein: headache, cognitive problems
  - Lungs: shortness of breath, heart palpitations

Chronic kidney disease[7,8]

- 65% of patients with PNH have chronic kidney disease, which is associated with early mortality

PH, pulmonary hypertension; PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell.

1. National Organization for Rare Disorders. Paroxysmal nocturnal hemoglobinuria. https://rarediseases.org/rare-diseases/paroxysmal-nocturnal- hemoglobinuria/ [Accessed January 30, 2021]; 2. Schrezenmeier H, et al. Ann Hematol 2020;99:1505–14; 3. John Hopkins Medicine. Paroxysmal nocturnal hemoglobinuria (PNH). https://www.hopkinsmedicine.org/kimmel_cancer_center/types_cancer/paroxysmal_nocturnal_hemoglobinuria_PNH.html [Accessed January 30, 2021]; 4. Kelly R, et al. Ther Clin Risk Manag 2009;5:911–21; 5. Hill A, et al. Br J Haematol 2010;149:414–25; 6. Hill A, et al. Blood 2013;121:4985–96; 7. Hillmen P, et al. Am J Hematol 2010;85:553–9; 8. Jang JH, et al. J Korean Med Sci 2016;31:214–21.

Presentation

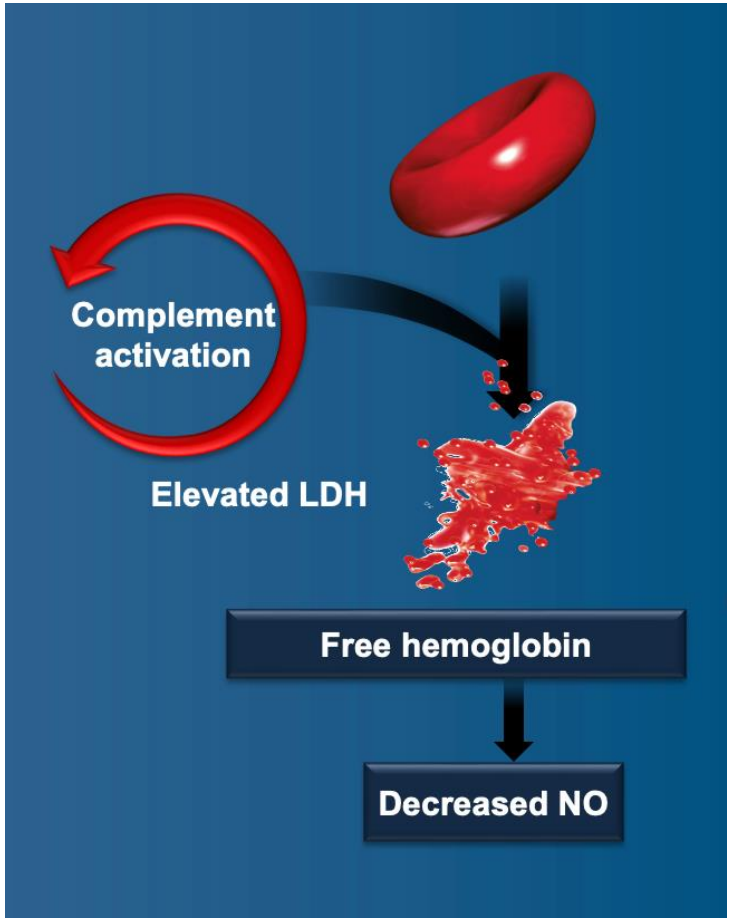
Classical triad

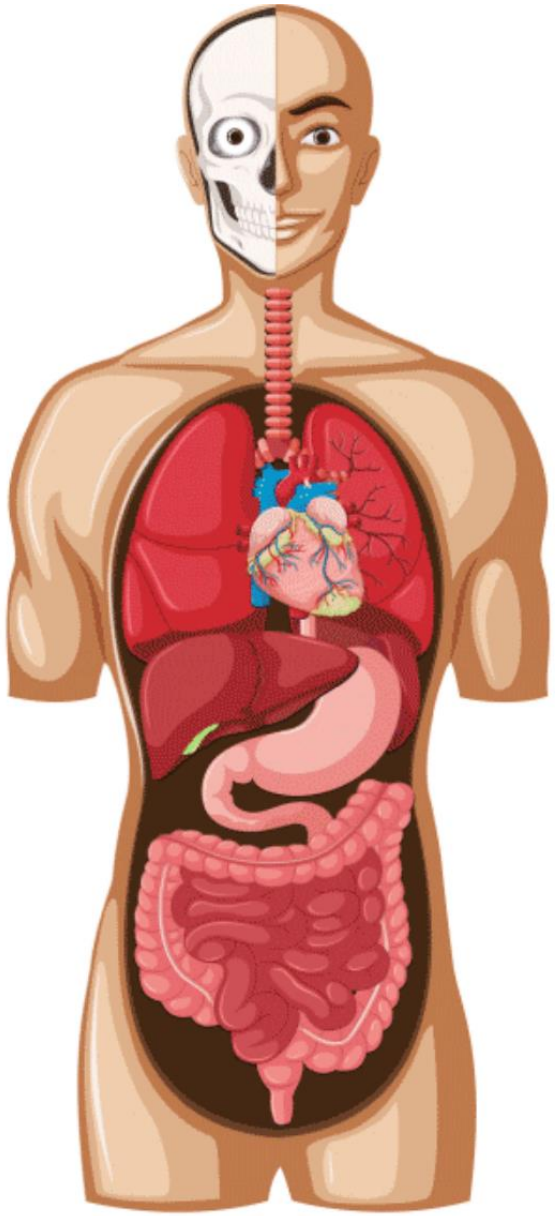
- DAT-neg hemolysis, thrombosis, bone marrow failure

Common clinical features

- Fatigue
- Dark urine
- Jaundice
- Chest pain
- Shortness of breath
- Abdominal pain
- Kidney Dysfunction
- Smooth muscle dysfunction (ex. pHTN, dysphagia (difficulty swallowing), erectile dysfunction)
- Thrombosis

Presentation



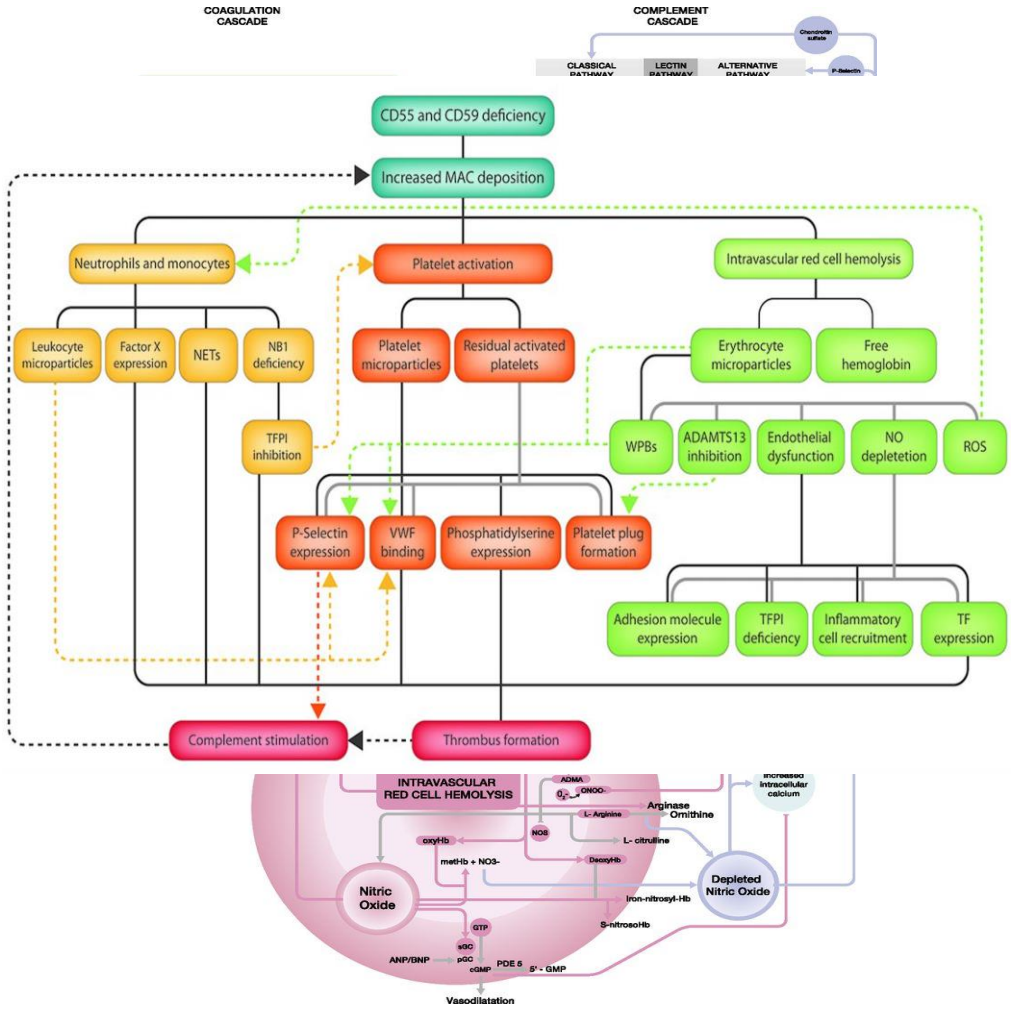


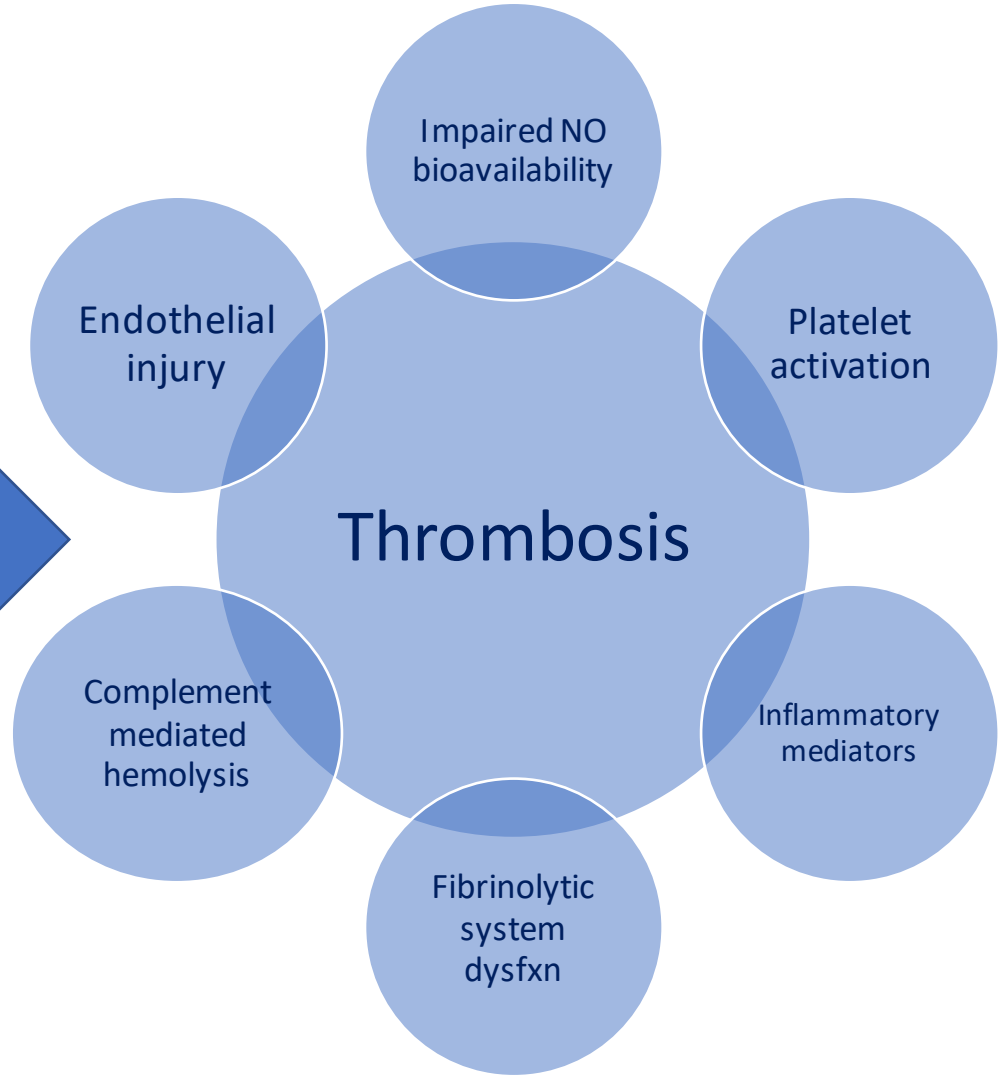
- Most symptoms of PNH are directly attributed to anemia secondary to blood cell breakdown
- Some symptoms indirectly associated to the release of free hemoglobin
- Possible to have hemolysis without anemia if the bone marrow can compensate
- Urine will will pink/dark red but with test negative for red blood cells
- Most patients with PNH clones >50% will be symptomatic but some patient may experience symptoms even if clone is smaller
- Higher rates of hemolysis increase thrombotic risk

Schrezenmeir et al.Haematologica. 2014.;99(5):922-9.
Meyers G et al. *Blood*. 2007;110(11): Abstract :3683.

Thrombosis and PNH

Thrombosis and PNH





Complex interplay of the coagulation and complement cascade

Hill A *et al.* (2013) *Blood*
Peacock-Young et al. (2018) Haematologica

Clinical Presentation of Thromboembolism

- Thrombotic events (TEs) occur in 30-45% of patients
  - Increased involvement of atypical sites but typical-sites ie. DVT & PE also occur
  - Hepatic (Budd Chiari) & cerebral vein thromboses may be the impetus for PNH diagnosis

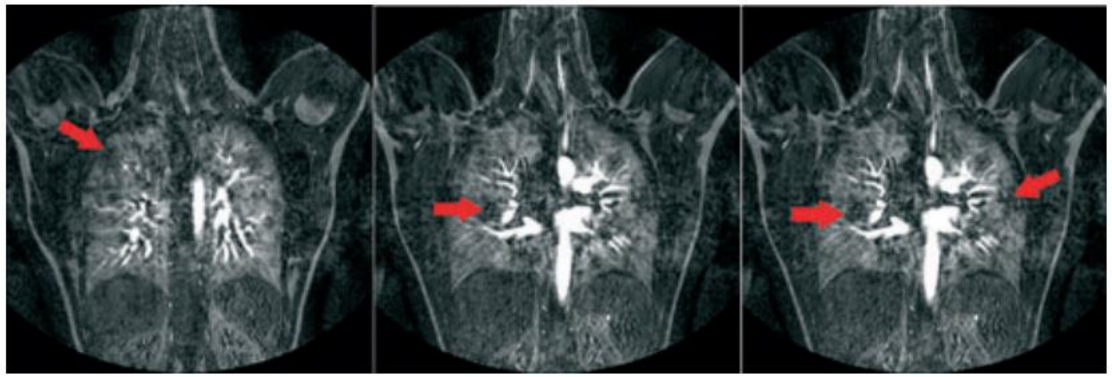
- Leading cause of mortality (40-70%) in untreated/undertreated
  - First recognized thrombosis can be fatal, and increased risk of death 5-10 fold
  - RR (VTE) ~ 62
  - Pts may have chronic, subclinical thrombosis which may go unnoticed

De Stefano V et al., 2002
Hillmen P *et al.* (2007) *Blood*
Hill A *et al.* (2012) *BJH*
Hill A *et al.* (2013) *Blood*
Peacock-Young et al. (2018) Haematologica

Table II. MRI findings in ten patients with paroxysmal nocturnal haemoglobinuria (bold numbers in bottom row are median values).

Age (years)	Disease duration (years)	PNH neutrophil clone size (%)	LDH (u/l)*	Transfused	Primary warfarin	Pulmonary defects	Myocardial damage	RVEF (%)†
18	1	84	2047	Yes	No	Yes	No	35
21	3	95	5815	No	Yes	Yes	No	42
23	6	100	4879	Yes	Yes	Yes	No	49
26	<1	89	2267	Yes	No	No	No	38
27	1	92	3365	No	Yes	No	No	42
36	2	64	1016	No	Yes	No	No	38
38	4	71	2066	No	No	No	No	39
42	19	99	3429	No	No	Yes	No	44
50	<1	99	7339	Yes	Yes	Yes	Yes	41
70	1	78	865	Yes	No	Yes	Yes	54
32	**2**	**91**	**2816**					**42**

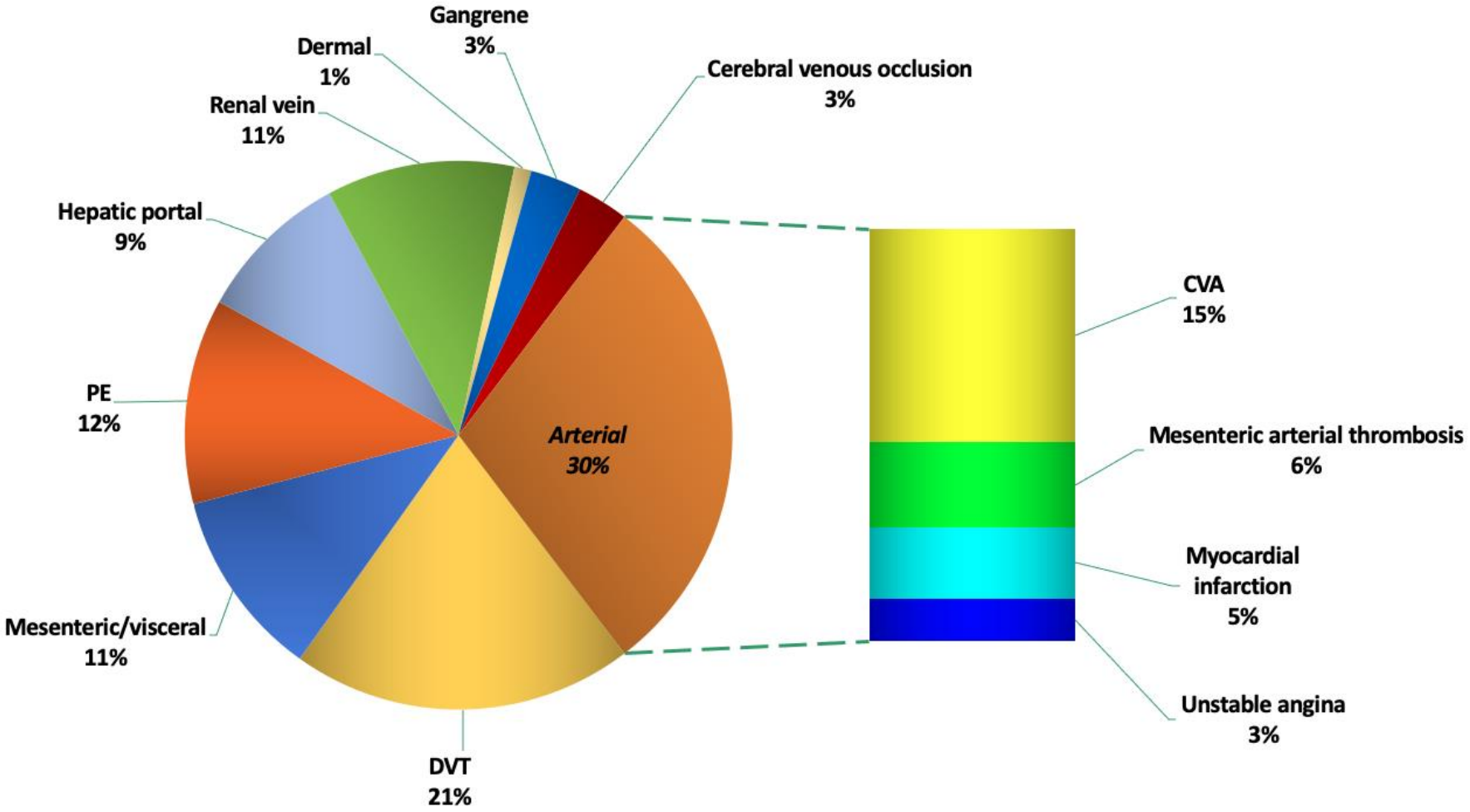
MRI, magnetic resonance imaging; PNH, paroxysmal nocturnal haemoglobinuria.
*LDH, lactate dehydrogenase: normal range; 160–430 u/l.
†RVEF, right ventricular ejection fraction: normal range; 48–63%).



60% had sub-clinical PE and 20% had evidence of myocardial scarring!

Hill A *et al.* (2012) *Br J Haem*

Distribution of Thrombosis in PNH



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

Diagnosis

Blood work

- CBC with differential
- Bilirubin
- LDH
- Reticulocyte count
- Haptoglobin
- Creatinine
- Blood smear
- DAT (Coombs test)

Urine Studies

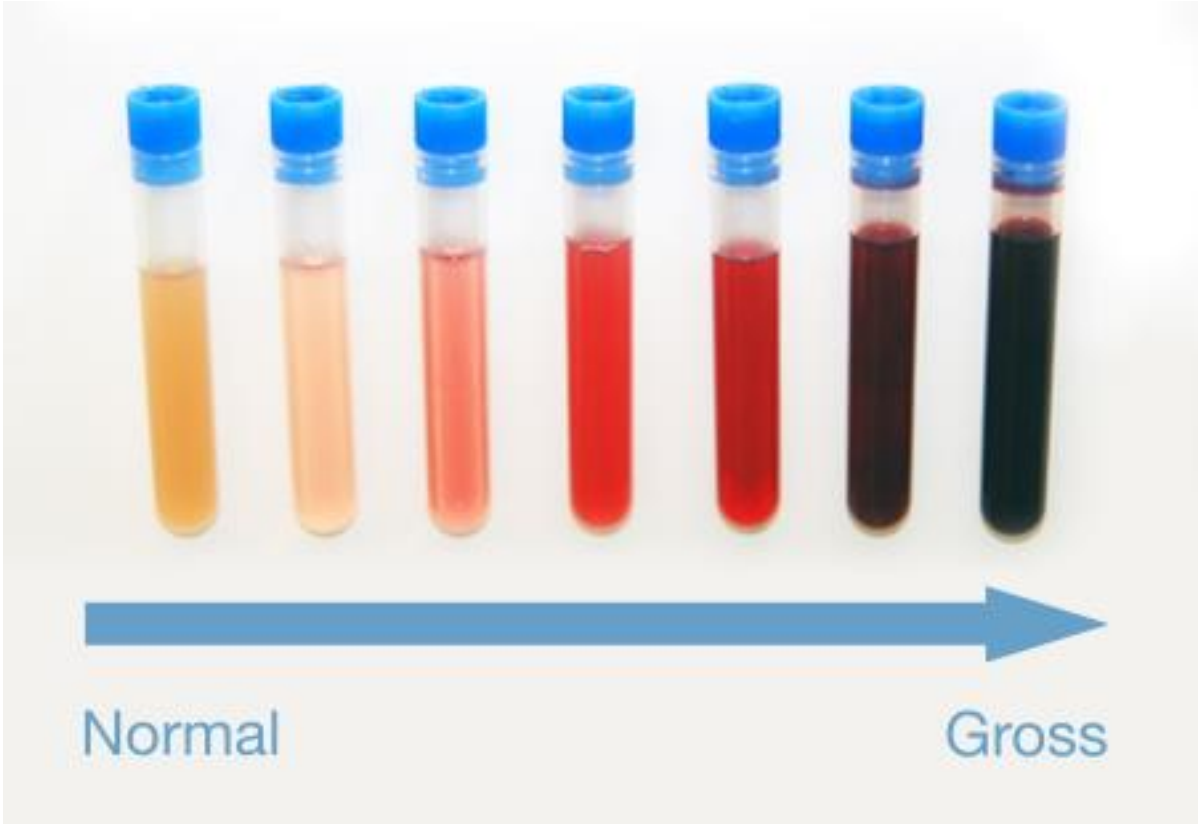
- Hemoglobinuria
- Hemosiderinuria

Bone Marrow Biopsy

- If cytopenias concerning for bone marrow failure

Flow Cytometry

- Identify the GPI-AP deficient peripheral blood cells



Flow Cytometry

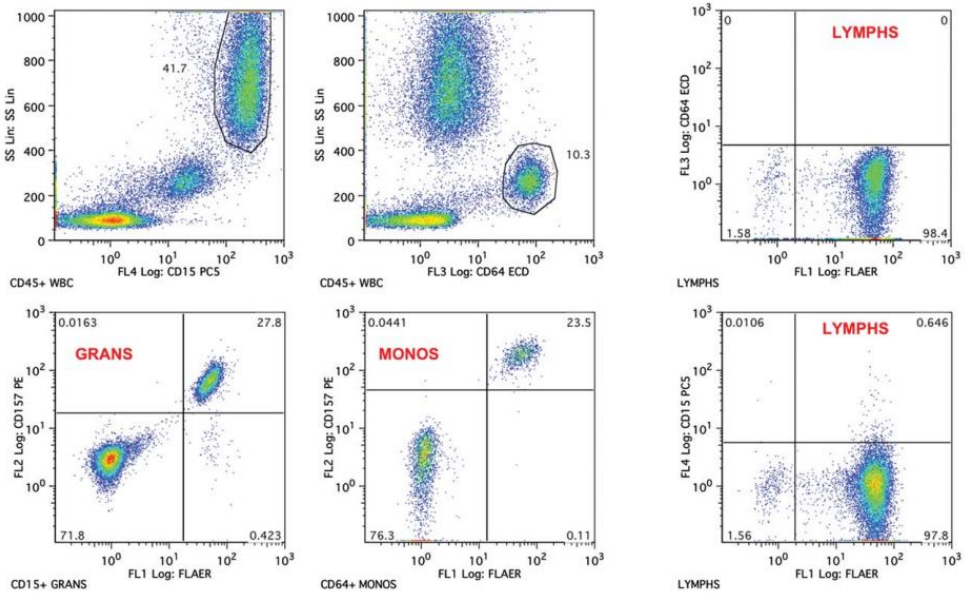
Laser-based technique which detects the expression of surface (and intracellular) molecules to identify and characterize various cell populations

- FLAER (fluorescent labeled aerolysin)
- Absence of CD55, CD59
- Degree of GPI-deficiency is variable:

  Type I RBCs: normal GPI expression

  Type II RBCs: partial GPI expression

  Type III RBCs: no GPI expression



- WBC (monocytes, granulocytes) are the ideal cell line to assess PNH clone size

→The life span of WBC is preserved (RBC lifespan affected by hemolysis, <20 days)

→Not affected by RBC transfusion

Borowitz et al. Cytometry B Clin Cytom. 2010;78(4):211

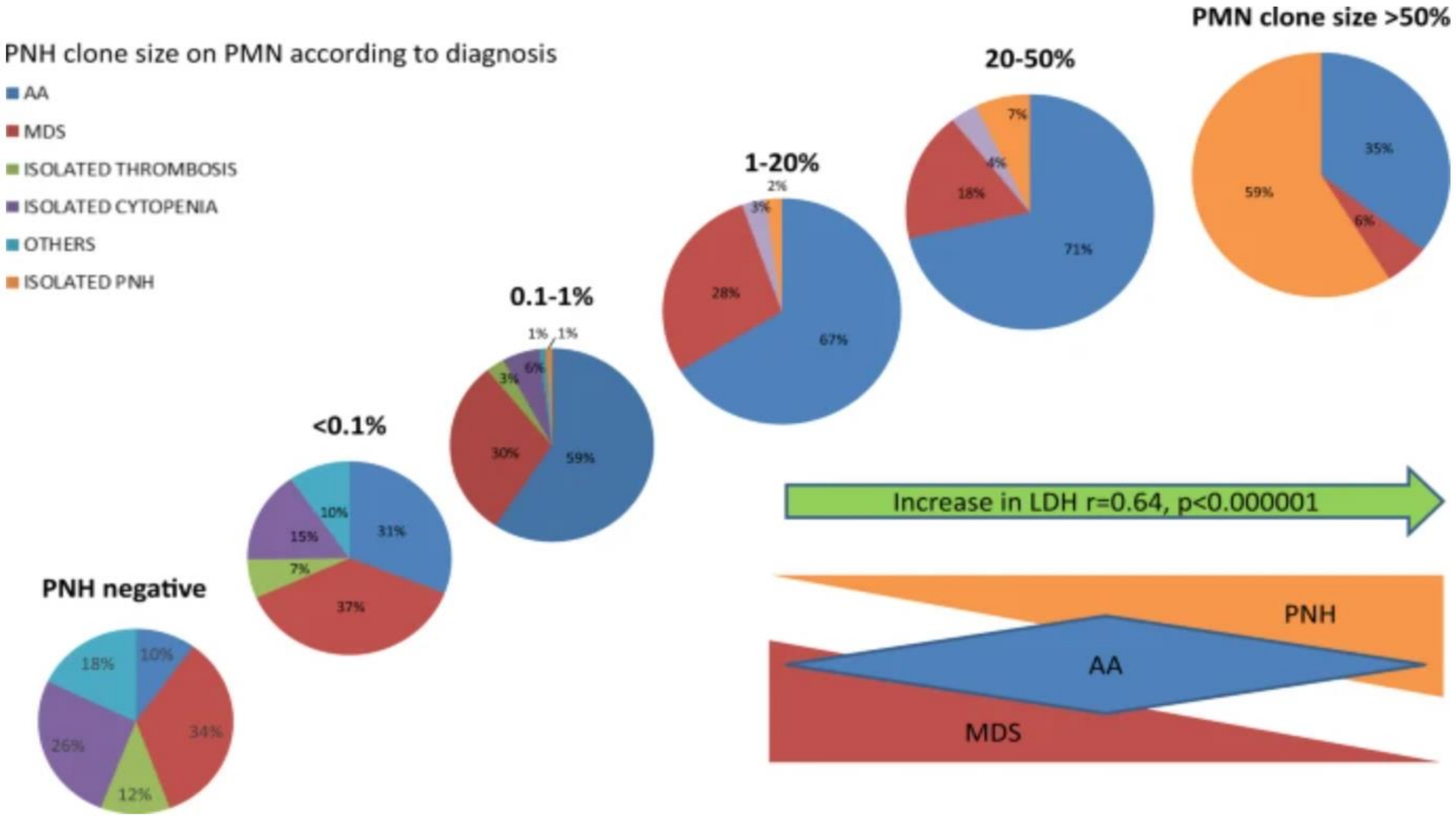
Parker et al. Blood 2005;106:3699-3709

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

Classification of PNH

Classification	Hemolysis	Bone Marrow Findings	Flow Cytometry
Classical PNH	Florid hemolysis! (Dark/red urine, jaundice, thrombosis, renal dysfunction, smooth muscle dysfxn etc.)	-Cellular marrow with erythroid hyperplasia -No karyotypic abnormalities	Large population (>50%) PNH WBC clone
PNH in the setting of bone marrow failure	Yes-Mild	-Evidence of a concomitant bone marrow failure syndrome -cytogenetic abnormalities	Variable, PNH WBC clone, usually <50%
Sub-clinical	No	-Unremarkable or early evidence bone marrow failure syndrome	-PNH WBC clone <10%

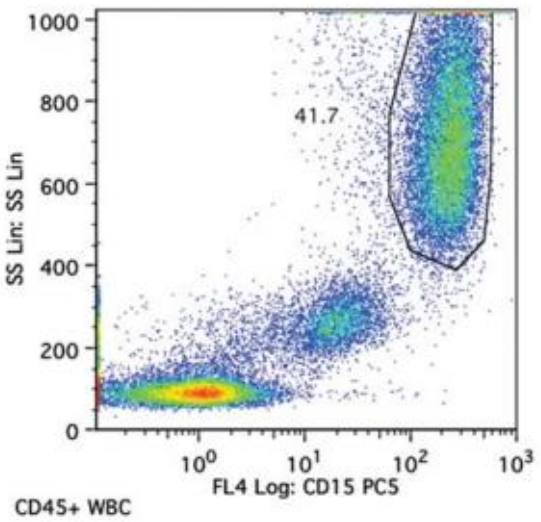
Brodsky RA. Blood 2021; 137(10):1304-1309.

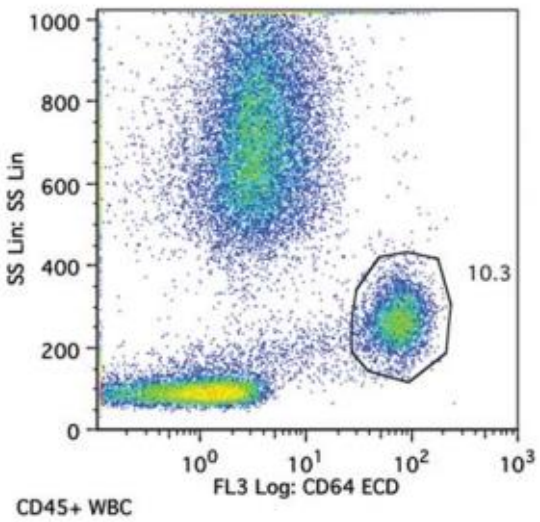


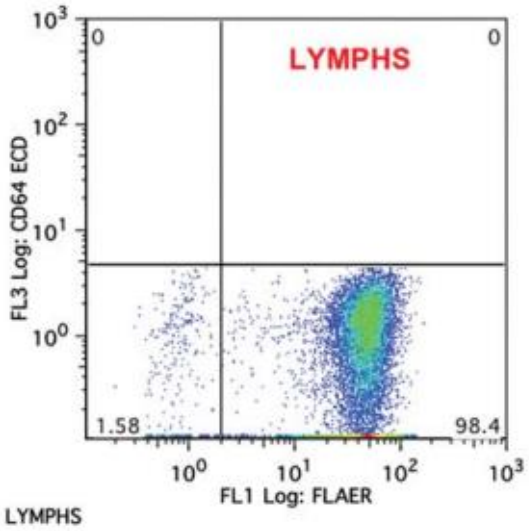
MDS cases mostly presented with small (<10%) and very small clones (<1%), while classical PNH with large clones (>50%), and AA cases mainly medium clones (10–50%). LDH significantly increase along with clone size ($p < 0.00001$).

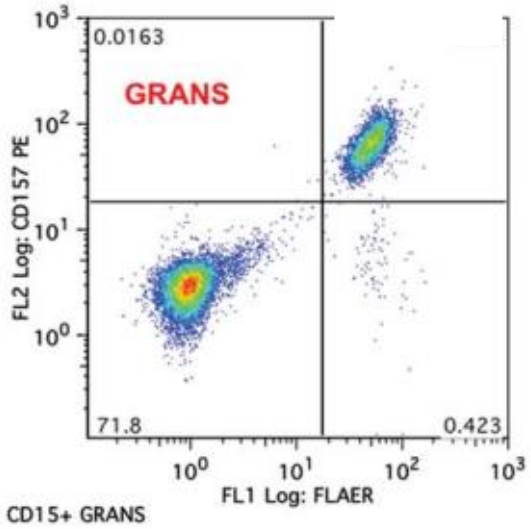
Fattizzo, B. et al. *Leukemia.* 2021.35, 3223–3231.

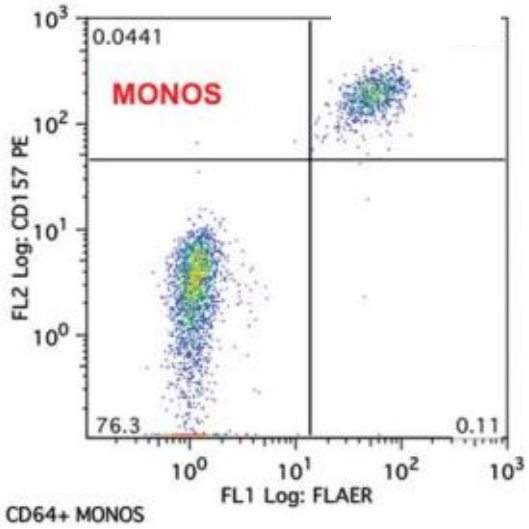
Flow Cytometry Plots

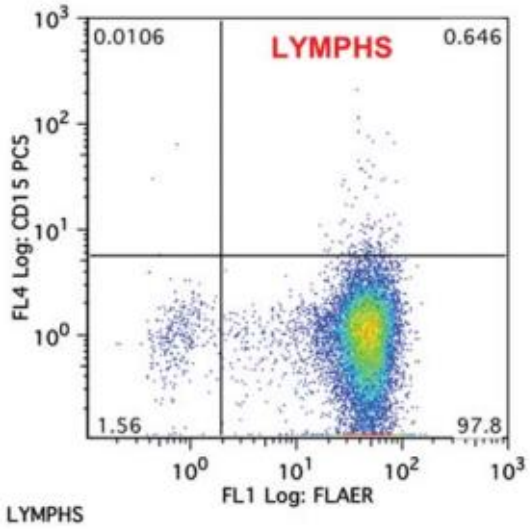






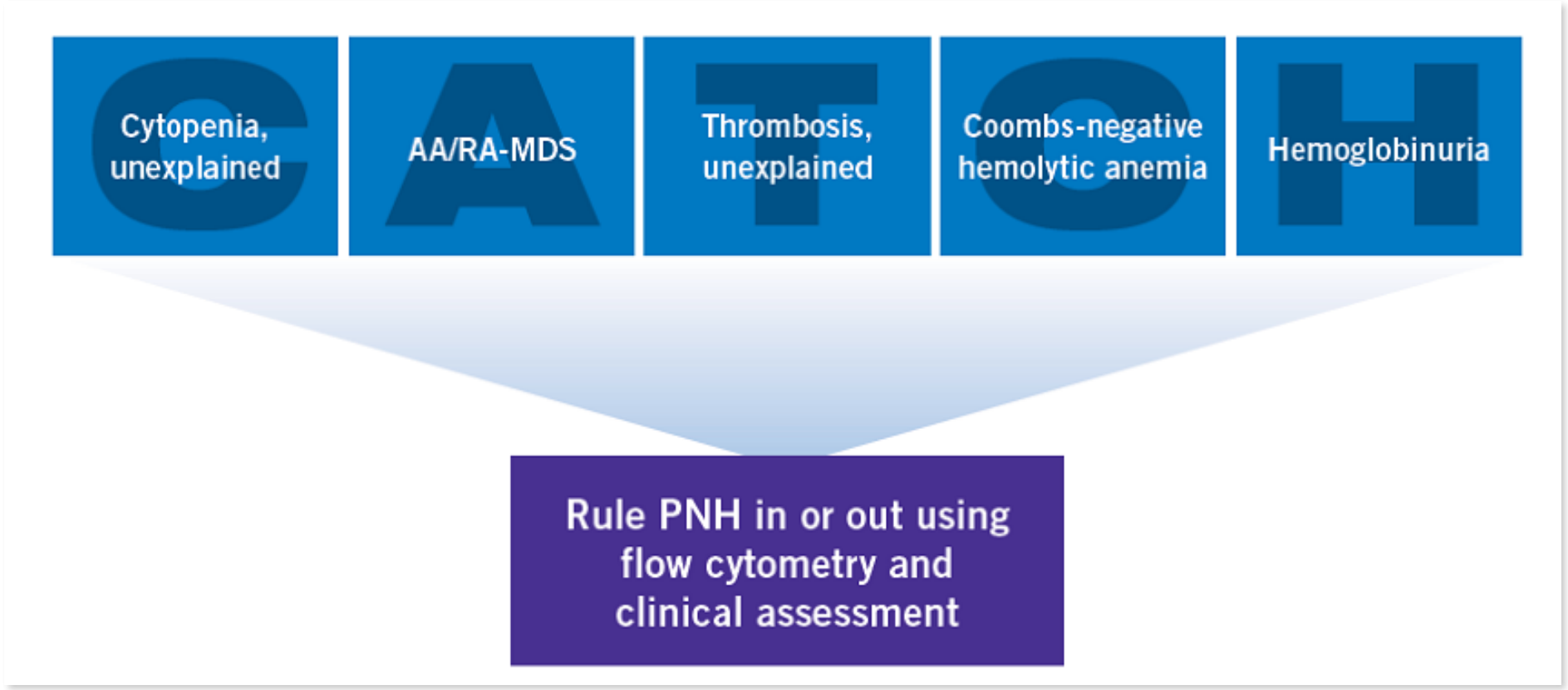






Sutherland DR *et al*. (2014) *Clin Cytometry*

Putting it all Together…



Early diagnosis of PNH to paramount to optimize patient management and outcomes!

Movalia M *et al.* (2011) *ASH 2011 Abstract #1033*

Patriquin CJ *et al.* (2019) *Eur J Hematol*

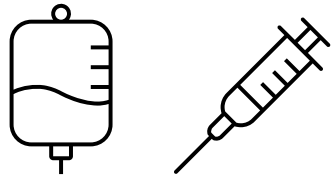
PNH Treatment

Management of PNH

- Supportive Care
  - Transfusion support- packed red blood cells
  - Hematinic support (folate, iron)
  - Analgesia
- Thrombosis
  - Primary prophylaxis if unable to start complement inhibitor
  - Therapeutic anticoagulation if history of thrombosis
- Allogeneic stem cell transplant
  - Reserved for BMF-predominant presentations
  - Almost never employed for classical PNH
- Complement inhibition

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

Eculizumab



- Monoclonal antibody to C5 that prevents cleavage of C5 to C5b, preventing the formation of terminal complement complex which is essential in the pathogenesis of PNH.
- In 2007, the US FDA approved eculizumab for use in PNH based on its efficacy in two phase 3 clinical trials (SHEPERD, TRIUMPH)
- In 2010 Soliris priced as the most expensive drug in the world, at approximately US$645,000 annually in the United States (2010), €430,000 in the UK, and $500,000 in Canada (2014).

Eculizumab dosing schedule

	Induction phase				Maintenance phase				
Week →	1	2	3	4	5	6	7	8	9
Dose (mg)	600	600	600	600	900	X	900	X	900

q14d

Brodsky et al. Blood. 2008;111(4):1840-1847.
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*

Eculizumab

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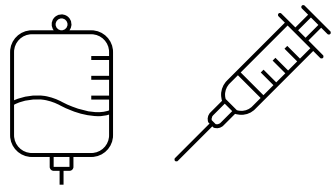

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Socié G *et al.* (2019) *BJH*

Safety Profile

BLACK BOX WARNING

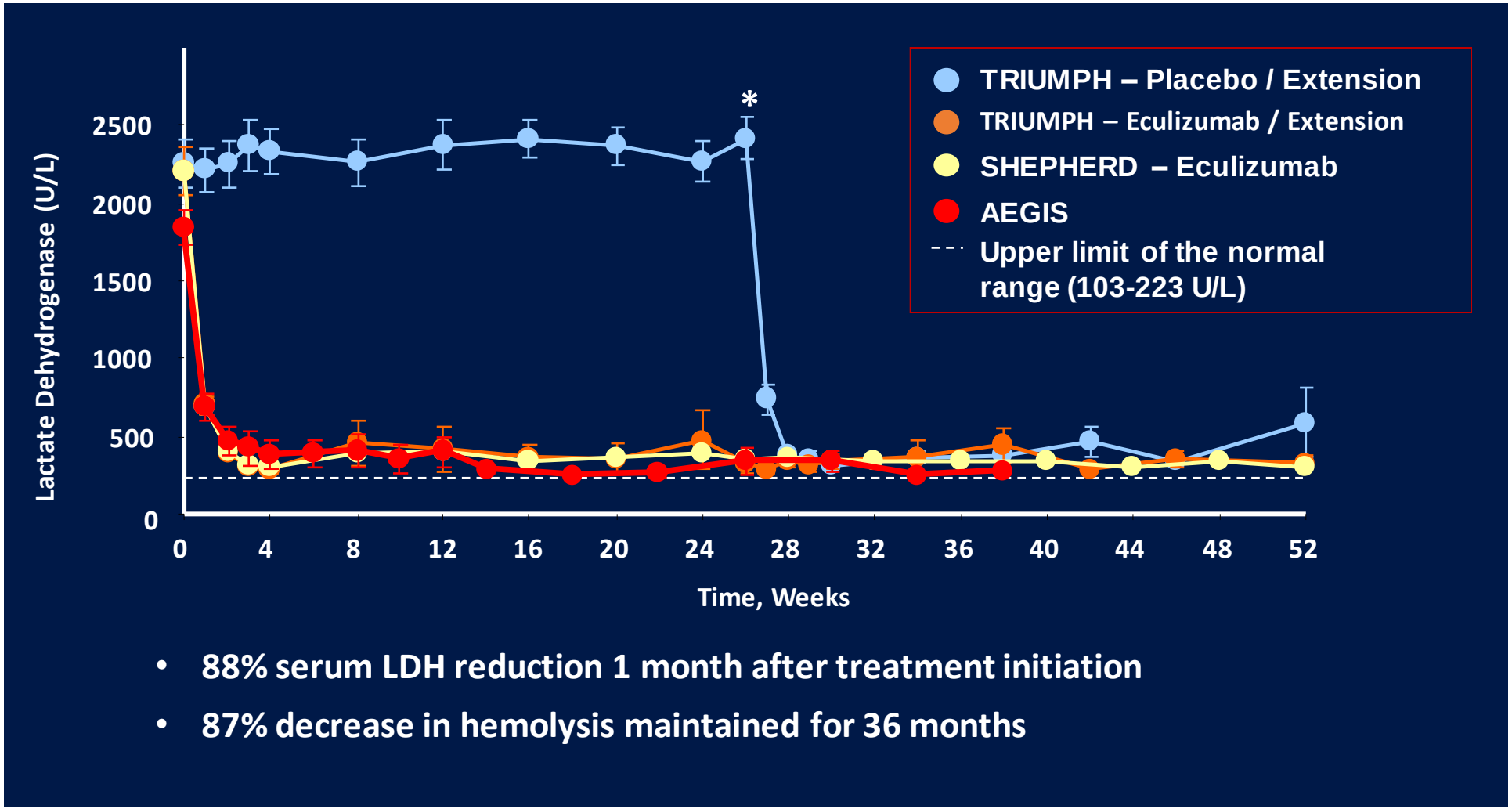
"Life-threatening and fatal meningococcal infections have occurred in patients treated with eculizumab. Meningococcal infection may become rapidly life-threatening or fatal if not recognized and treated early."

- **Meningococcal vaccination (ACWY + MenB) mandatory at initiation and q3-5 years thereafter**
- Anti-meningococcal antibiotics required until 14+ days post-vaccine
- May consider additional encapsulated bacteria vaccinations

<u>Other side effects</u>

- Headache in ~50% of patients following infusion
- Nasopharyngitis/URTI
- Back Pain
- Nausea

Reduced Intravascular Hemolysis with Eculizumab



- 88% serum LDH reduction 1 month after treatment initiation
- 87% decrease in hemolysis maintained for 36 months

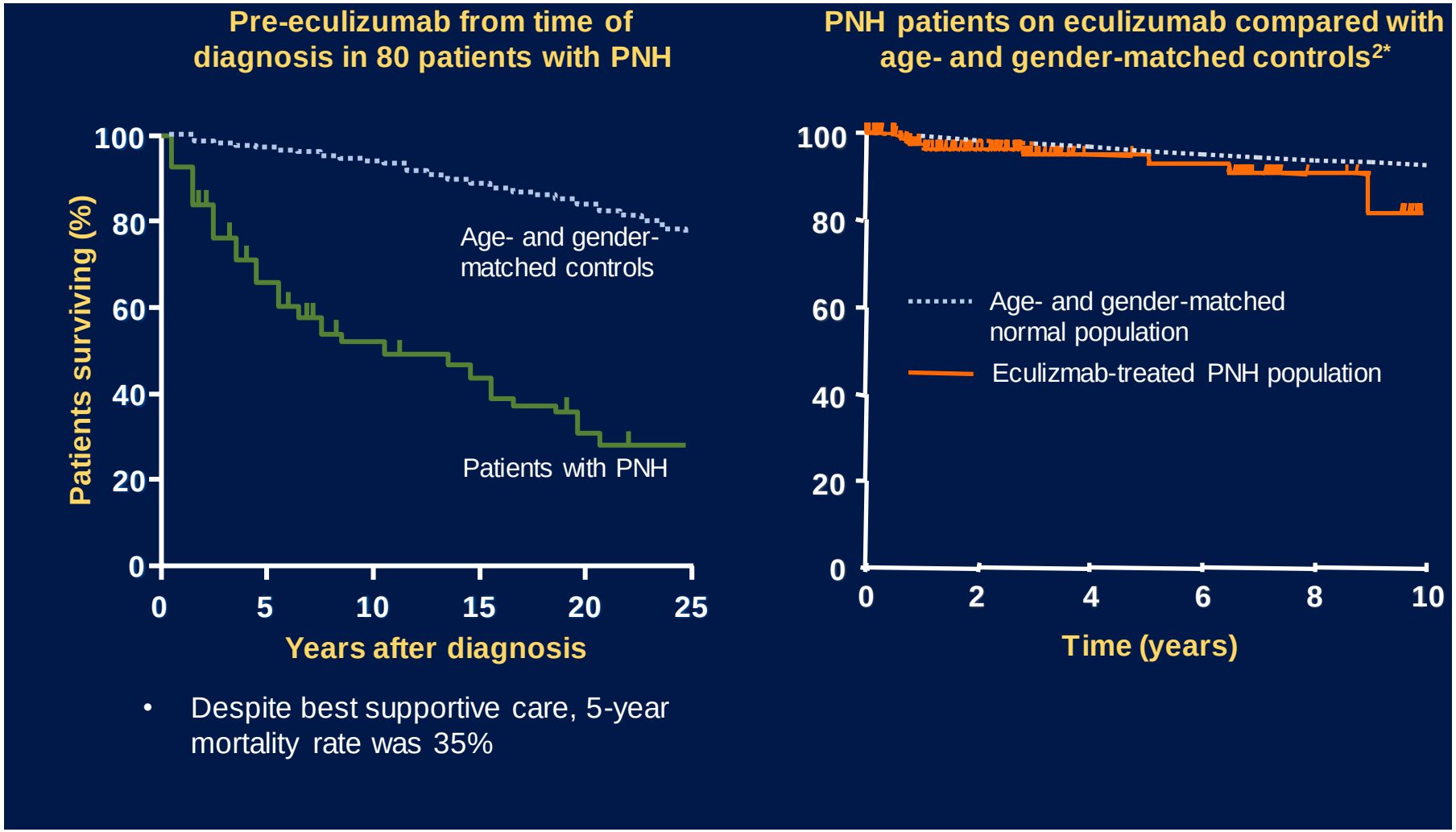
Hillmen P *et al.* (2006) *NEJM*

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

Brodsky RA *et al.* (2008) *Blood*

Kanakura Y *et al.* (2011) *Int J Hematol*

Eculizumab Improves Survival



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

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

Eculizumab Therapy Expectations

In 1 week
- Reduction in hemolysis (as measured by LDH)[1]

Between 2 and 3 weeks
- Improvement in quality of life[2]

Between 2 and 6 months
- Reduction in transfusions[2]
- Stabilization of hemoglobin levels[2]

>6 months
- Continued improvement in quality of life[2,5]
- Achieved maximum concentration of red blood cells[4]

At 36 months
- Continued reduction in hemolysis (as measured by LDH) was sustained[6]
- Prevention of TE was maintained[6]

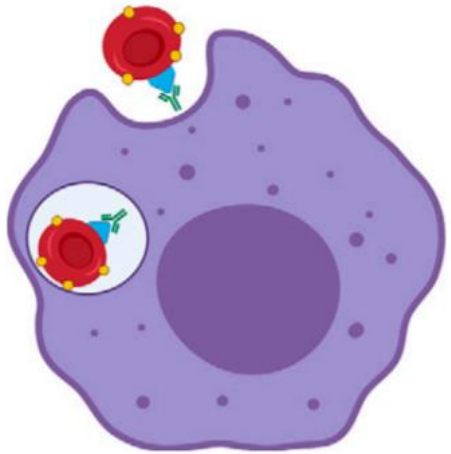
At 8 years
- Sustained and well-tolerated efficacy; improved survival[8]

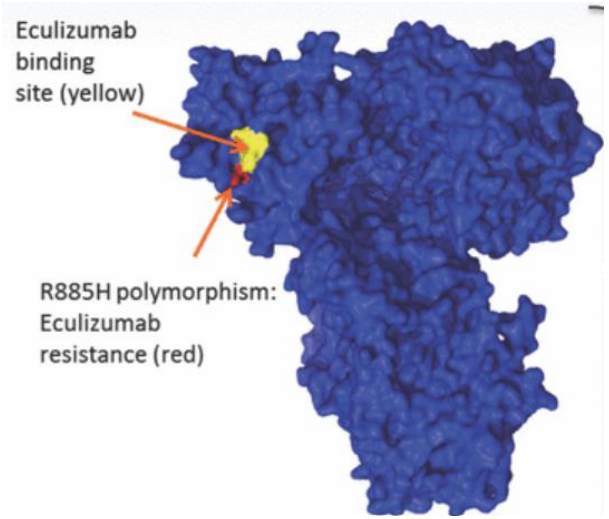
Hillmen P et al., 2006 & 2007.
Brodsky RA et al., 2008
Hill A et al., 2010.
Hillmen P et al., 2010
Kelly RJ et al., 2011
Hillmen P et al. 2013
Soliris® (eculizumab) Product Monograph, 2013

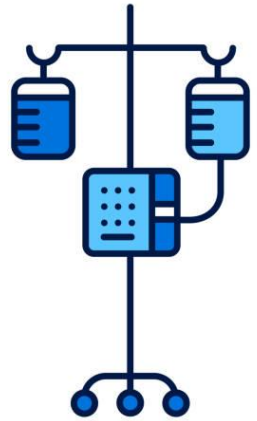
Novel Therapies

Why do we need them?

- Complications
  - Incomplete complement blockade
  - C5 polymorphisms/Eculizumab resistance
  - C3-mediated extravascular escape hemolysis!
  - Infection risk mitigation
- Convenience
  - Administration schedules (q2week indefinitely, doc?!)
  - Route of administration
  - Accommodating travel plans
- Competition
  - Drive down drug costs $$
  - Motivate more rigorous trial methodology and better understanding of complement diseases







Eculizumab does not treat bone marrow failure and does not decrease the PNH clone!

Images from: Brodsky R (2021) *Blood*
https://sec.report/Document/0001104659-17-021374/
https://www.alamy.com/stock-photo/oval-pills.html?page=2

Logistics of administering C5i

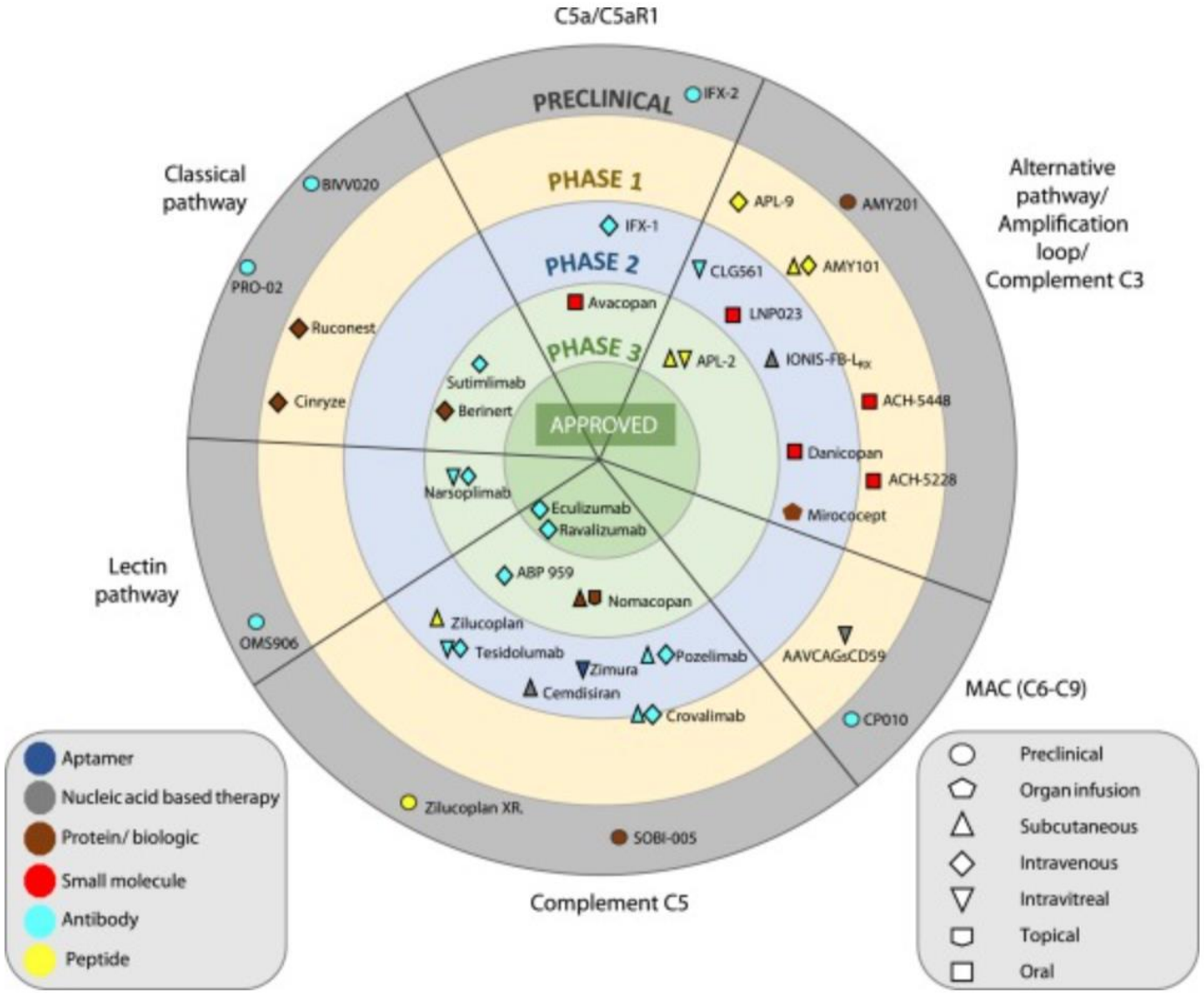
- Most patients must travel to local infusion clinic q2weeks for therapy.
- Some patients who live remotely may need to travel by plane or boat to access therapy
- Repetitive veni-puncture can be challenging for minority of patients and may require definitive central or peripheral vein access (Picc, port-a-cath)
- The need for fortnightly infusions may restrict prolonged or international/remote travel
- Approximately 40% of patients receiving eculizumab therapy suffer from significant residual anaemia (<100g/l) and many remain transfusion dependent

Debureaux PE et al. (2021). Bone Marrow Transplant
Risitano AM et al. Front Immunol 2019;10:1157
Hillmen et al 2021

FDA Approved Complement Inhibitors

Complement inhibitor	Trade Name	**Company**	**Target**	**Mechanism of Action**	**Modality**	**Treatment Schedule**	**Date of Approval**
Pegcetacoplan	Empaveli	Apellis	C3	Peptide	SC inj	Twice weekly	May 2021
Eculizumab	Soliris	Alexion	C5	mAb	IV	q2weeks	May 2007
Ravulizumab	Ultomiris	Alexion	C5	mAb	IV	q8weeks	December, 2018

Complement Inhibitors in Development



1. Monoclonal antibodies
2. Peptide inhibitors
3. Decoy receptors

Zelek, WM et al. 2019. *Molecular immunology*

Upcoming Therapies in PNH

CLINICAL TRIALS AND OBSERVATIONS

Ravulizumab (ALXN1210) vs eculizumab in adult patients with PNH naive to complement inhibitors: the 301 study

Jong Wook Lee,[1] Flore Sicre de Fontbrune,[2] Lily Wong Lee Lee,[3] Viviani Pessoa,[4] Sandra Gualandro,[5] Wolfgang Füreder,[6] Vadim Ptushkin,[7] Scott T. Rottinghaus,[8] Lori Volles,[8] Lori Shafner,[8] Rasha Aguzzi,[8] Rajendra Pradhan,[8] Hubert Schrezenmeier,[9,10] and Anita Hill[11]

CLINICAL TRIALS AND OBSERVATIONS

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

Austin G. Kulasekararaj,[1] Anita Hill,[2] Scott T. Rottinghaus,[3] Saskia Langemeijer,[4] Richard Wells,[5] F. Ataulfo Gonzalez-Fernandez,[6] Anna Gaya,[7] Jong Wook Lee,[8] Emilio Ojeda Gutierrez,[9] Caroline I. Piatek,[10] Jeff Szer,[11] Antonio Risitano,[12] Shinji Nakao,[13] Eric Bachman,[3] Lori Shafner,[3] Andrew I. Damokosh,[3] Stephan Ortiz,[3] Alexander Röth,[14] and Regis Peffault de Latour[15-17]

12-Month Analysis of a Phase 2 Study of Iptacopan (LNP023) Monotherapy for Paroxysmal Nocturnal Hemoglobinuria

Jun-Ho Jang, Lily LL Wong, Bor-Sheng Ko, Sung-Soo Yoon, Katie Li, Izabela Rozenberg, Prasanna K Nidamarthy, Raghav Chawla, Guido Junge, Eng Soo Yap

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pegcetacoplan versus Eculizumab in Paroxysmal Nocturnal Hemoglobinuria

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

Vol. 106 No. 12 (2021): December, 2021 > Danicopan: an oral complement factor D inhibitor for...

ARTICLES

Danicopan: an oral complement factor D inhibitor for paroxysmal nocturnal hemoglobinuria

Antonio M. Risitano, Austin G. Kulasekararaj, Jong Wook Lee, Jaroslaw P. Maciejewski, Rosario Notaro, Robert Brodsky, Mingjun Huang, Michael Geffner, Peter Browett

Vol. 106 No. 12 (2021): December, 2021 https://doi.org/10.3324/haematol.2020.261826

Complement Inhibitors in development

Complement inhibitor	Company	Target	Mechanism of Action	Modality	Treatment Schedule	Phase		
Pozelimab	Regeneron	C5	mAb			III		
Crovalimab	Roche-Chugai Pharma	C5	mAb			III		
Tesidolumab	Novartis	C5	mAb			II		
Danicopan (ACH-4471)	Achillion	Factor D	Small molecule			III		
Vemircopan (ACH-5228)	Achillion	Factor D	Small molecule			II		
Iptacopan	Novartis		Small molecule			III		

Ravulizumab (Ultomiris)

-C5 Inhibitor which binds same epitope as Eculizumab

Benefits:

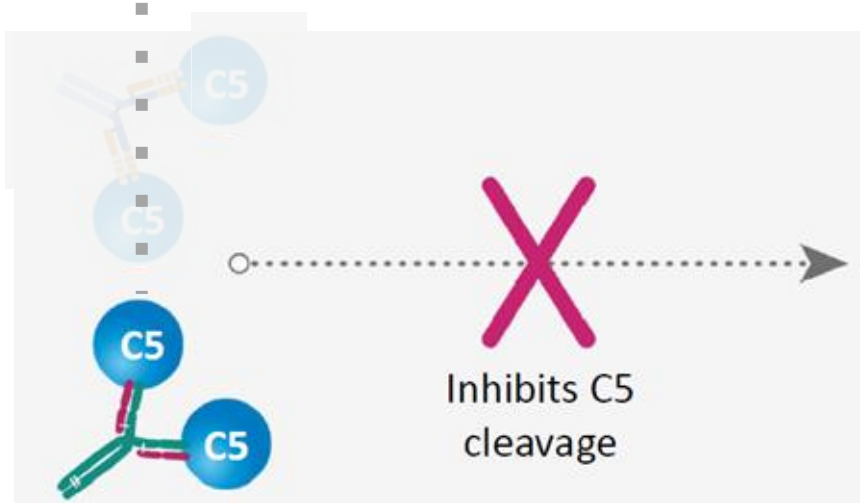
1. Reduces frequency of trough exposure

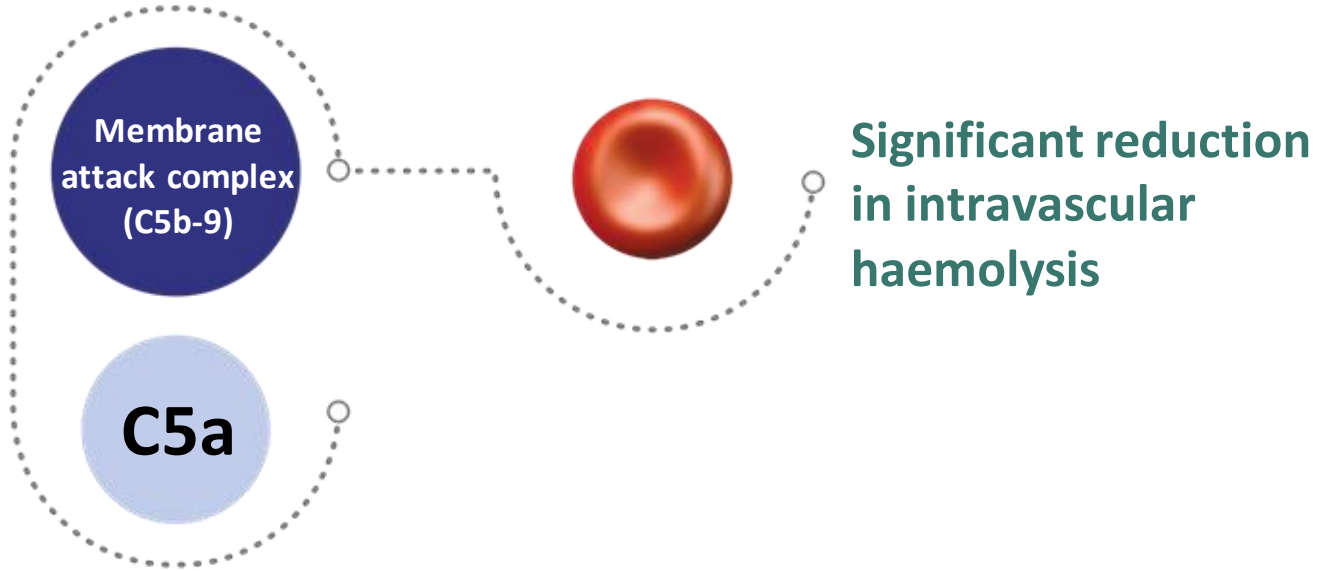
2. Increased interval between infusions (q8weeks vs q2weeks) secondary to longer half life

2. Reduced annual cost

ULTOMIRIS® binds with higher affinity to C5 increasing its half-life compared with Soliris®[1–5]

Increased affinity for FcRn at endosomal pH





Significant reduction in intravascular haemolysis

ULTOMIRIS®

Binds with high affinity to C5

Affinity for C5 at endosomal pH 6 is reduced, promoting endosomal C5 release

GPI, glycosylphosphatidylinositol; PNH, paroxysmal nocturnal haemoglobinuria; RBC, red blood cell.

1. Röth A, et al. Blood Adv. 2018;2:2176–2185; 2. Sheridan D, et al. PLoS One. 2018;13: e0195909; 3. Rother R, et al. Nat Biotechnol. 2007;25:1256–1264; 5. Soliris® Product Monograph, Alexion Pharmaceuticals, Inc. October 2019; 6.ULTOMIRIS® (ravulizumab) Product Monograph. Alexion Pharmaceuticals, Inc., Jan. 6, 2023;

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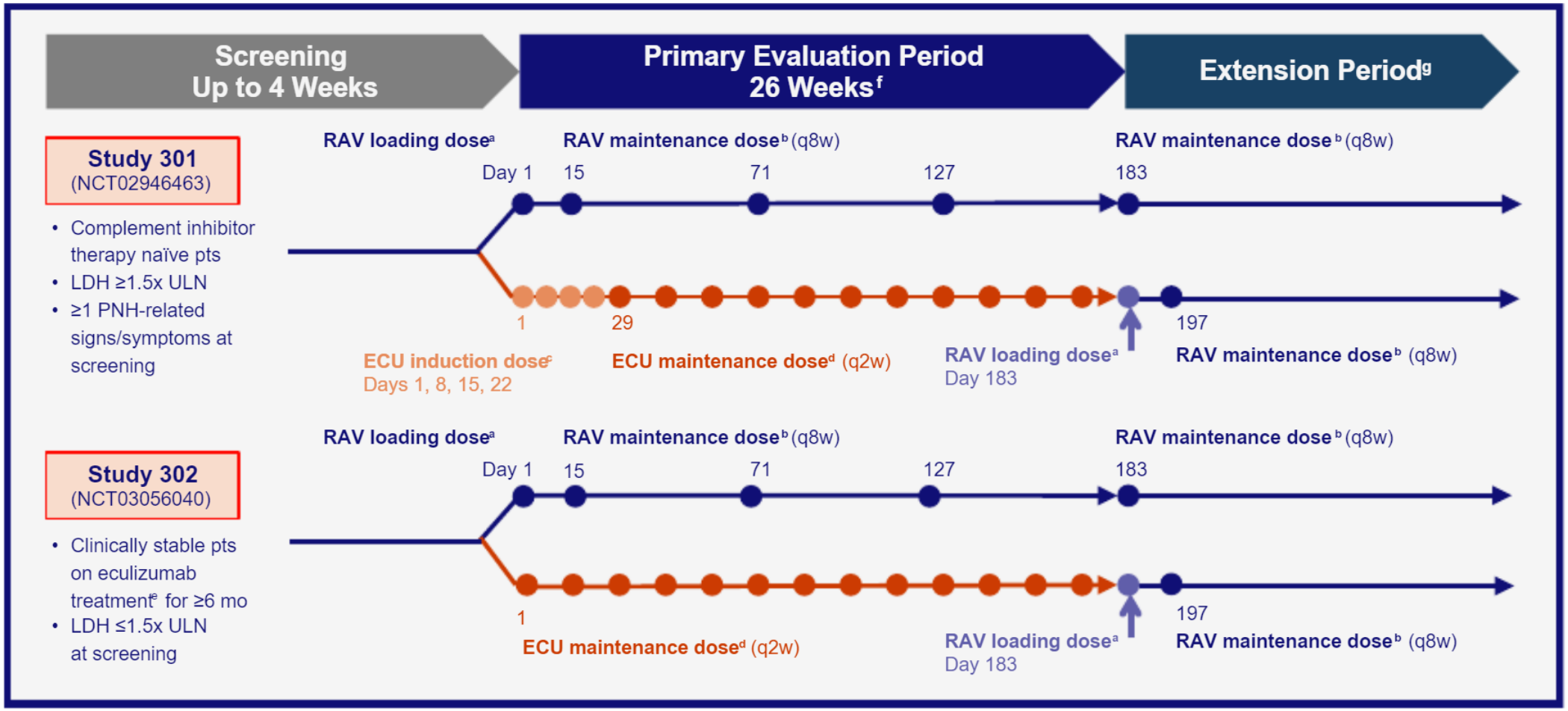
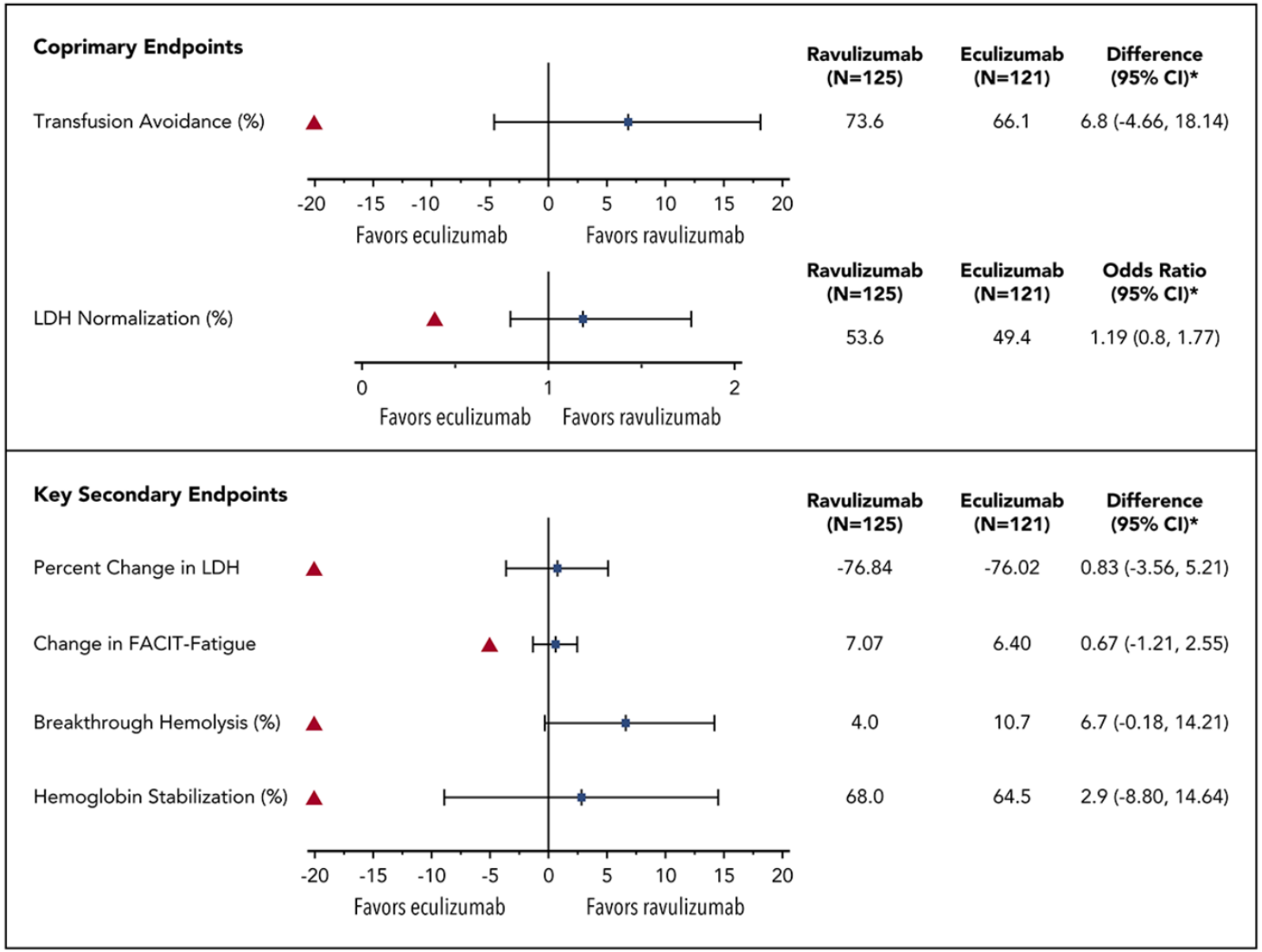
ALXN1210-301/302 Trials



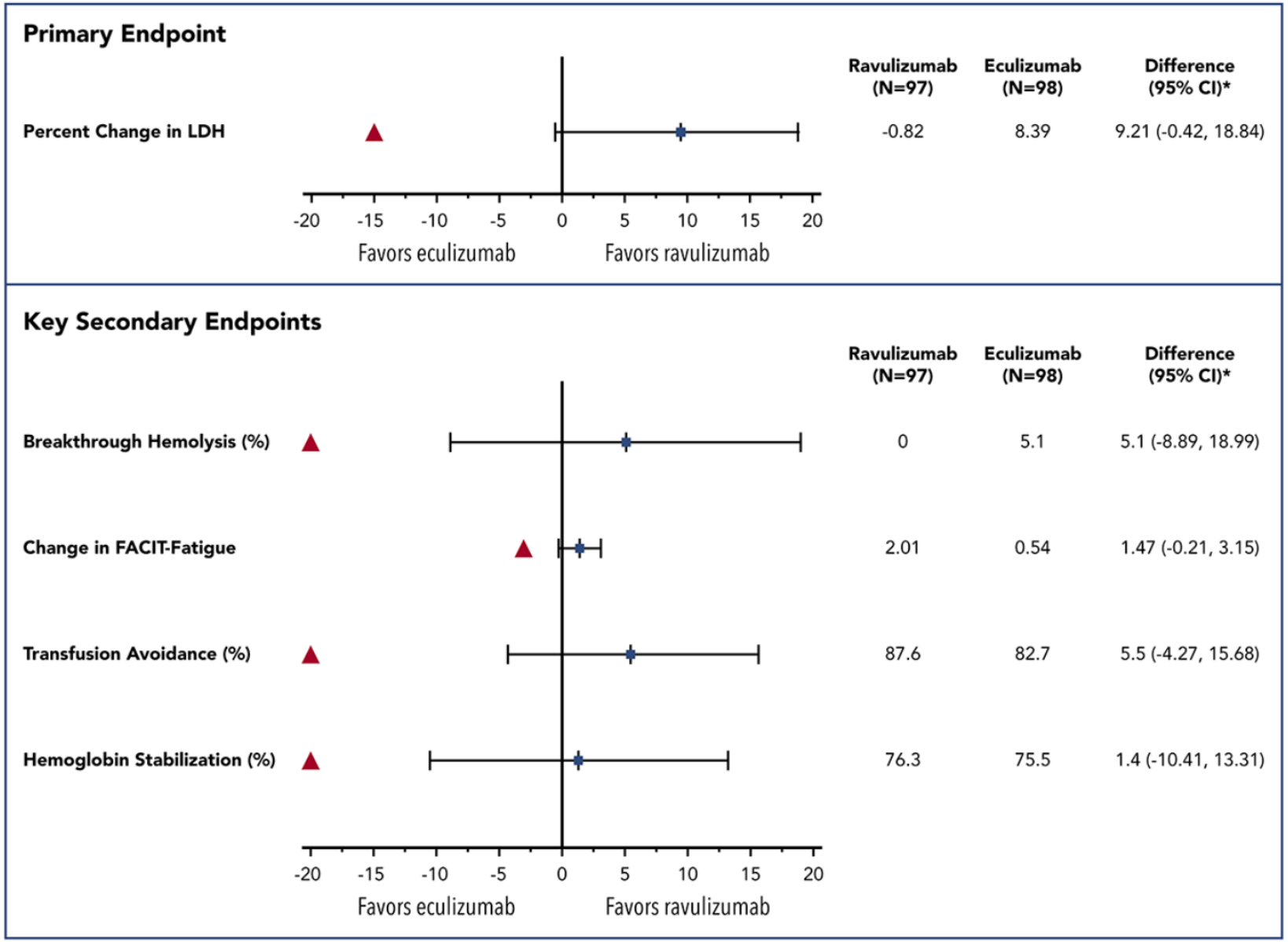
Lee JW *et al.* (2019) *Blood*
Kulasekararaj AG *et al.* (2019) *Blood*
Peffault de Latour R *et al.* (2020) *BJH*

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



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

Efficacy of Ravulizumab and Eculizumab in PNH Patients Stable on Eculizumab



Patients treated with ravulizumab had a low incidence of breakthrough hemolysis events

Fewer patients experienced breakthrough hemolysis after patients switched from eculizumab to ravulizumab

No breakthrough hemolysis events were associated with free C5 ≥0.5 µg/mL while on ravulizumab

Schrezenmeier H, et al. *Ther Adv Hematol*. 2020;11:1-14.

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

Patients preferred ravulizumab for its improved symptom control (including fatigue), over an extended period

93% of patients **prefer ravulizumab** to eculizumab (**p < 0.001**)
6% have no preference, 1% prefer eculizumab

88% of patients prefer ravulizumab based on their **overall quality of life** (**p < 0.001**)
11% have no preference, 1% prefer eculizumab

98% of patients prefer ravulizumab based on their **being able to plan activities** (**p < 0.001**)
2% have no preference, 0% prefer eculizumab

64% of patients preferred ravulizumab based on **fatigue control**
32% have no preference, 4% prefer eculizumab

- 95 patients enrolled in the switch study (302s) and with exposure to both ravulizumab and eculizumab completed a patient preference questionnaire
- Patients were significantly **able to better plan and enjoy their lives** while receiving treatment with ravulizumab than with eculizumab
  - Mean of agreement with the statement "**while I was receiving treatments, I was able to enjoy life"**: 3.62 for ravulizumab vs. 2.81 for eculizumab* ($p < 0.001$)*
  - Large effect size (0.93, normative standard for the effect size: large ≥ 0.80)

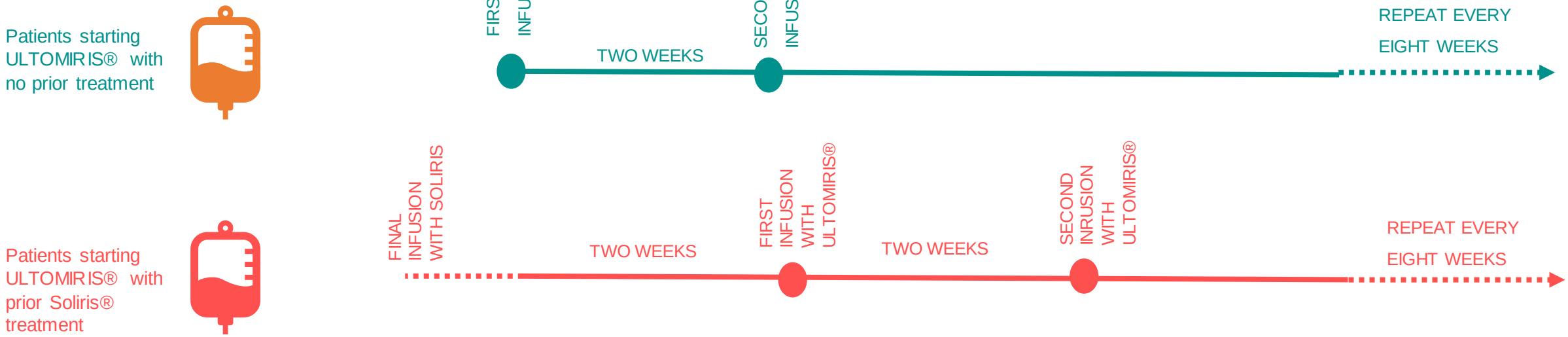
*Mean of responses on an agreement scale of 0 = "Not at all" to 4 = "Very much". Normative standards for effect sizes: 0.20 ≤ small < 0.50; 0.50 ≤ medium < 0.80; large ≥0.80

Patients with experience of both products show a clear preference for ravulizumab

Peipert JD, et al, PLoS One, 2020;15(9):1-12 https://doi.org/10.1371/journal.pone.0237497

ULTOMIRIS® infusions

The recommended dosing regimen for adults with PNH consists of a loading dose followed by more than 7 maintenance doses per year[1]



Ultomiris® (ravulizumab) Product Monograph. Alexion Pharmaceuticals, Inc., Jan 6 2023;

Pegcetacoplan (PEG)

- Pegcetacoplan (PEG) is the first approved C3 inhibitor for US adults with PNH and EU adults with PNH who are anemic after treatment with a C5 inhibitor for ≥3 months.

- Benefits

1. Can inhibit both intravascular and extravascular hemolysis.
2. It is administered SC twice weekly

- Most common side effects include injection site reactions and diarrhea

Image from https://www.drugs.com/history/empaveli.html

Pegcetacoplan has been **assessed in several clinical trials**

Phase 1

Phase 1 Single Ascending Dose (SAD)

To investigate the safety, tolerability, PK, and PD of **escalating single doses** of **SC** pegcetacoplan in **healthy volunteers**

Phase 1 Multiple Ascending Dose (MAD)

To investigate the safety, tolerability, PK and PD of **escalating multiple doses** of **SC** pegcetacoplan in **healthy volunteers**

Phase 1 Single Ascending Dose (SAD) for IV administration

To investigate the safety, PK and PD of **escalating single doses** of **IV** pegcetacoplan in **healthy volunteers**

Phase 1b/2

Phase 1b PHAROAH

To investigate the safety, tolerability, PK and PD of **SC** pegcetacoplan as an **add-on therapy to SoC** for PNH patients who **remained anaemic during treatment with eculizumab**

Phase 1b PADDOCK

To investigate the safety, tolerability, preliminary efficacy and PK of **monotherapy SC** pegcetacoplan in PNH patients who are **complement inhibitor-naïve**

Phase 2a PALOMINO

To investigate the safety, tolerability, preliminary efficacy and PK of **monotherapy SC** pegcetacoplan in PNH patients who are **complement inhibitor-naïve**

Phase 3

Phase 3 PEGASUS

To investigate the efficacy of **SC** pegcetacoplan in patients with PNH who had **haemoglobin levels of <10.5 g/dL in comparison to eculizumab**. It was a superiority study for haemoglobin and non-inferiority for additional parameters such as transfusion avoidance and other haematological profiles

Phase 3 PRINCE

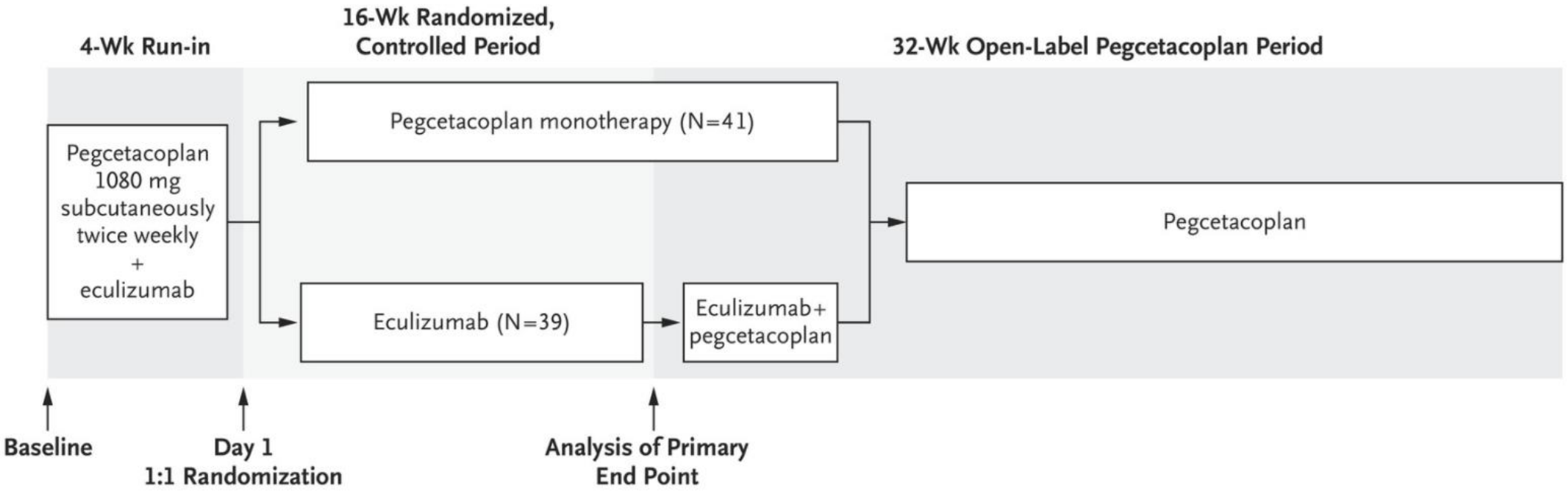
To investigate the efficacy and safety of **SC** pegcetacoplan in PNH patients **in comparison to SoC excluding complement inhibitors**

Phase 3 Extension Study (307 Study)

To investigate the **long-term safety and efficacy of pegcetacoplan** treatment in adult PNH patients that previously participated in a pegcetacoplan trial

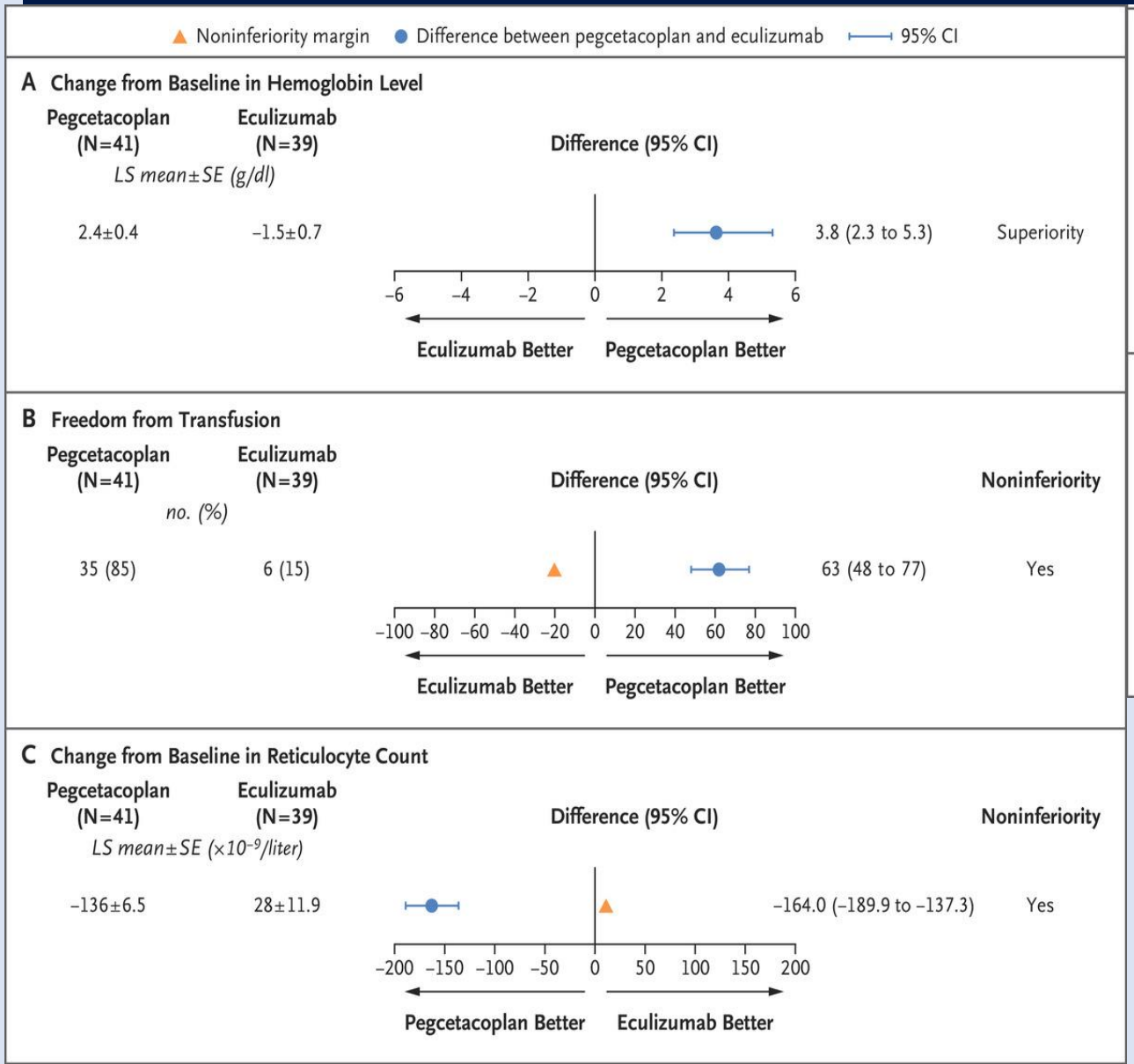
Slide prepared by Sobi

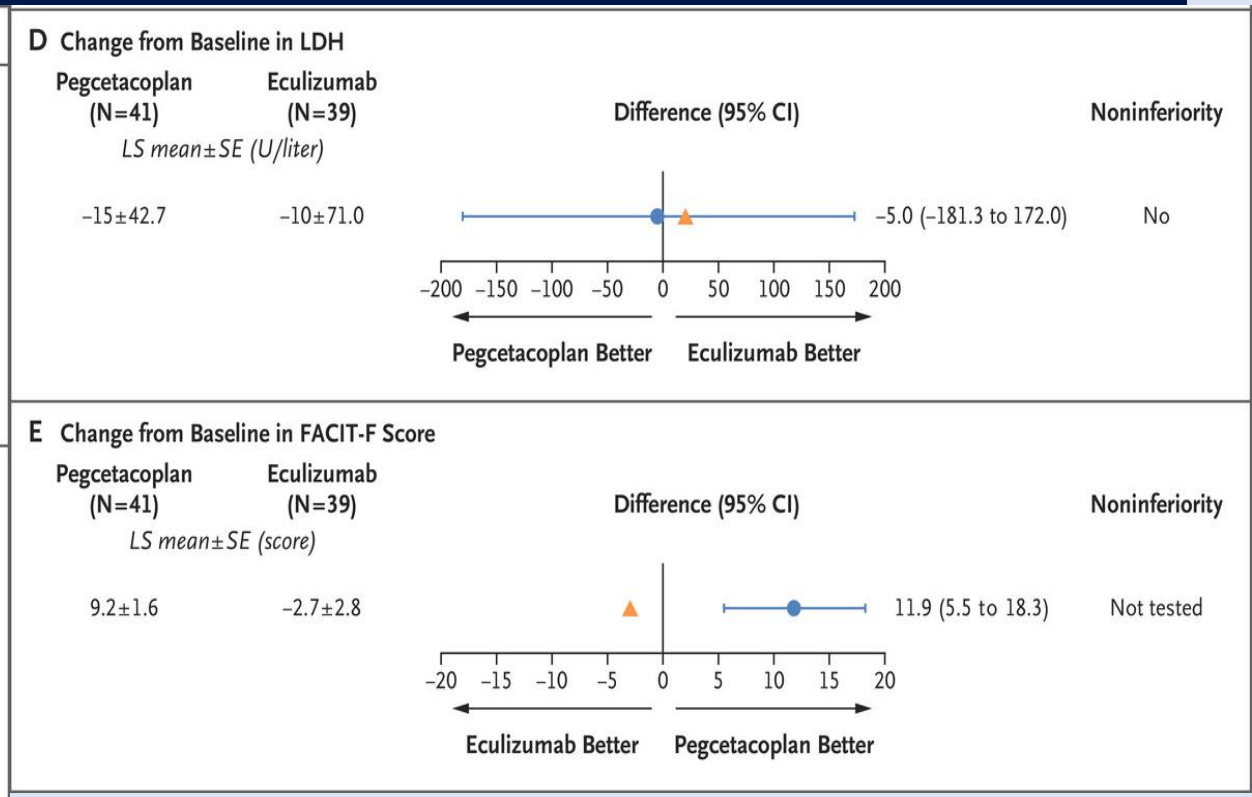
PEGASUS Phase 3 Trial Design



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

PEGASUS Phase 3 Trial Outcomes





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

Poster 1248: Long-Term Safety and Efficacy of Pegcetacoplan Treatment in Adults with Paroxysmal Nocturnal Hemoglobinuria

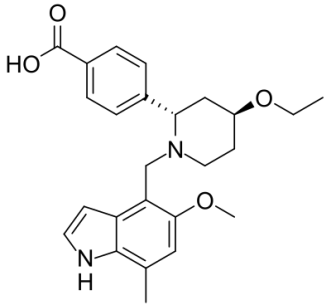
Christopher J. Patriquin, MD, MSc, FRCPC*, Andrija Bogdanovic, MD, PhD, MSc, Morag Griffin, FRCPath, MRCP, Richard Kelly, BSc, MD, Jaroslaw P. Maciejewski, MD, PhD, FACP, Brian Mulherin, MD, Regis Peffault De Latour, Alexander Roeth, MD, Veena Selvaratnam[1], Jeffrey Szer, MBBS, FRACP, Jessica Savage, MD, MHS, Regina Horneff, PhD, Lisa Tan, Michael Yeh, MD, MBA, MPH and Jens Panse, MD*

Health Canada approved as of December 9th, 2023 with PSP launched in March 2023!

Results

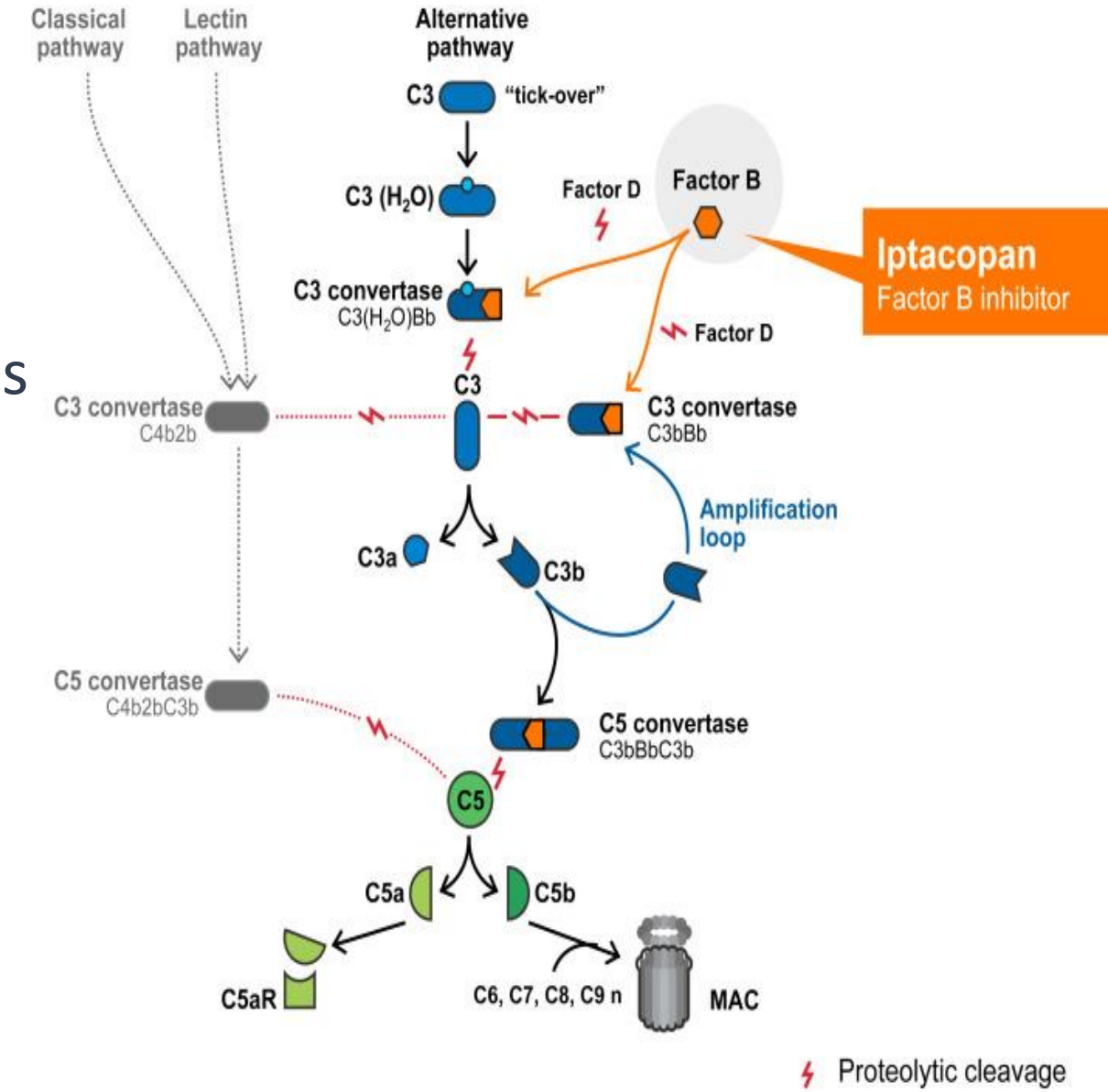
- Report the long-term safety and efficacy data from 48-week follow-up of Study 307, the open-label extension study for patients previously enrolled in pegcetacoplan clinical trials for a total of 137 patients (Phase 1& 1b: PHAROAH (n=4), PADDOCK (n=15); Phase 2a: PALOMINO (n=4); Phase 3: PEGASUS (n=64), PRINCE (n=50).
- Demonstrated robust and sustained improvements in Hg, LDH and fatigue in patients with PNH.
- Transfusions needs were improved, with 83.2% of patients achieving transfusion independence (n= 114/137)
- The long-term safety data is comparable to that reported in previous clinical trials.
- Breakthrough hemolysis is a potential downside but being evaluated in a separate study through either intensive SC or IV dosing of PEG.
- Health Canada approved as of December 9th, 2023 with PSP launched in March 2023!

Iptacopan



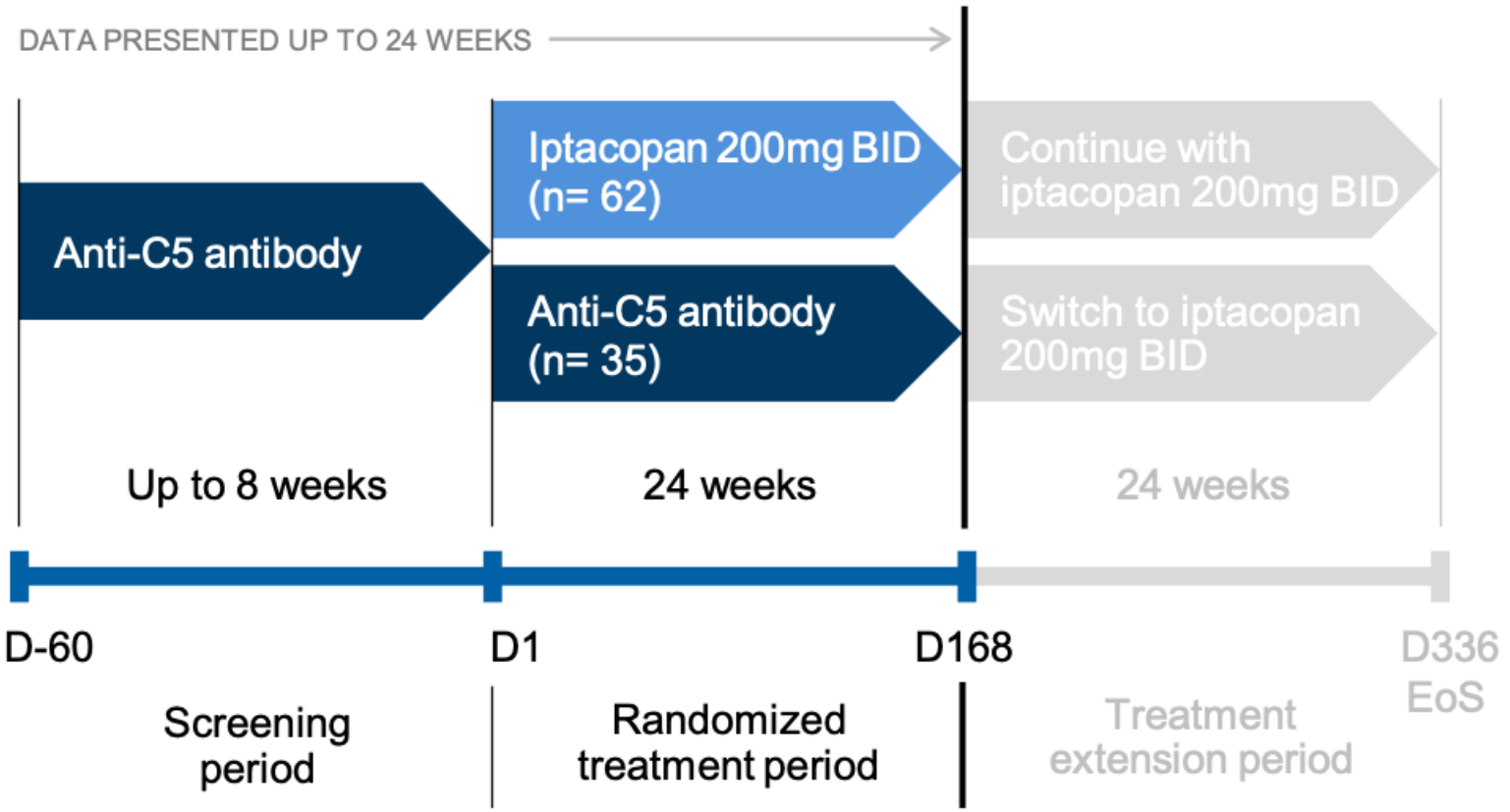
- Iptacopan is a first-in-class, oral, selective factor B inhibitor which targets the complement system proximally via the alternative pathway

- By targeting the complement cascade proximally, both intravascular and extravascular hemolysis is controlled.



1. Schubart A et al. Proc Natl Acad Sci USA 2019;116:7926–31.
2. Risitano AM et al. Lancet Haematol 2021;8:e344–54
3. Image from https://en.wikipedia.org/wiki/Iptacopan

Study design



PNH = Paroxysmal Nocturnal Hemoglobinuria Hb = Hemoglobin RBC = Red Blood Cell BID = twice a day EoS = End of Study

- Adult PNH pts (n=97) with mean Hg <100 g/L on stable SoC therapy (ECU/RAV) for ≥6 months were randomized 8:5 to receive iptacopan monotherapy or to continue SoC for 24 weeks.

- Randomization was stratified by prior SoC therapy and RBC transfusions in the preceding 6 months.

- **Primary end points:**
  - ≥20 g/L Hg increase from baseline
  - Hg ≥120 g/L
  (each in the absence of pRBCs)

- **Secondary end points:**
  - Transfusion independence
  - FACIT- fatigue scores
  - Absolute reticulocyte count and LDH
  - Breakthrough hemolysis
  - Major adverse events
  - Safety

Primary End Points

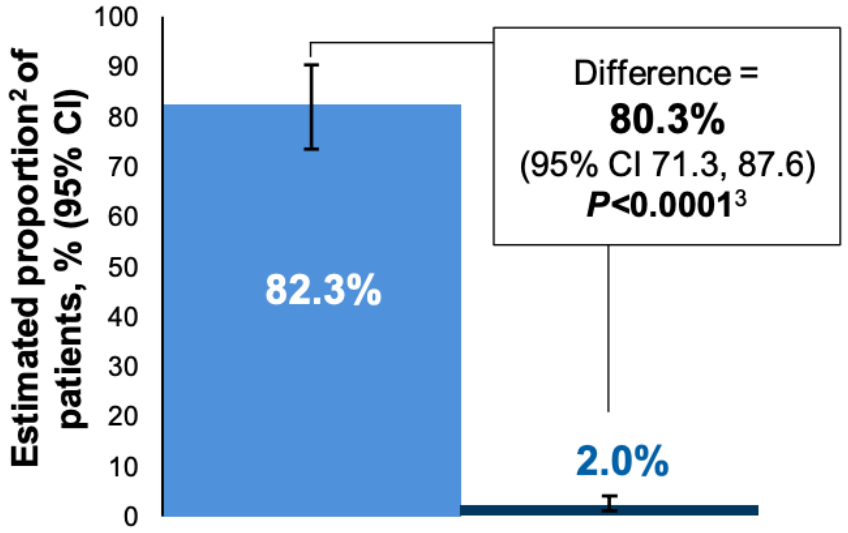
Increase from baseline in Hb of ≥ 2 g/dL
in the absence of RBC transfusions

Observed

51/60[1] patients treated with **iptacopan**

0/35 patients treated with **SoC**

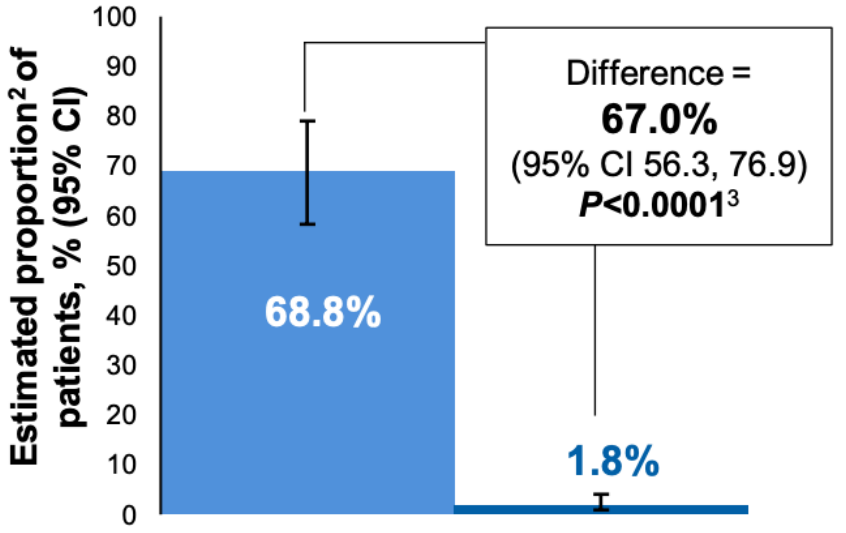
Population estimate



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

42/60[1] patients treated with **iptacopan**

0/35 patients treated with **SoC**

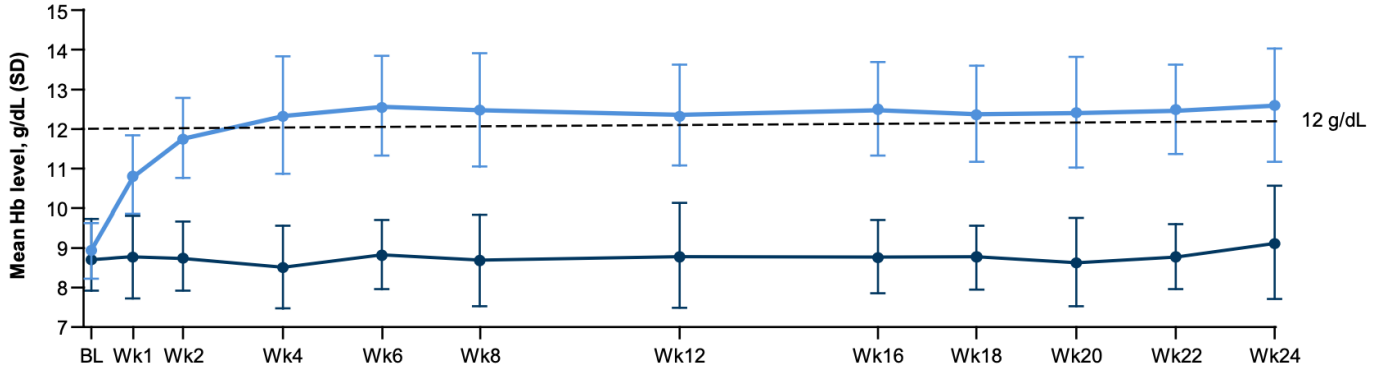


1. 2/62 patients in the iptacopan arm had missing data between Days 126 and 168 so were not evaluable based on observed data. 2. Marginal proportions, differences in marginal proportions and 95% CIs were calculated using a logistic regression model using the Firth correction that adjusted for baseline covariates and accounted for missing data and the possibility of no patients meeting the primary endpoint criteria in the SoC arm; consequently, the treatment effect of iptacopan is underestimated and the treatment effect of SoC is overestimated. Marginal proportions reflect the population average probability of a patient meeting the primary endpoint criteria. 3. P values are two-sided and unadjusted. CI, confidence interval

Image from Ipatcopan ASH Update, Investor Presentation. Novartis.com

Iptacopan monotherapy was superior to SoC at increasing Hb level from baseline and reducing patient reported fatigue

Mean Hb (SD) over time during the 24-week randomized treatment period[3]

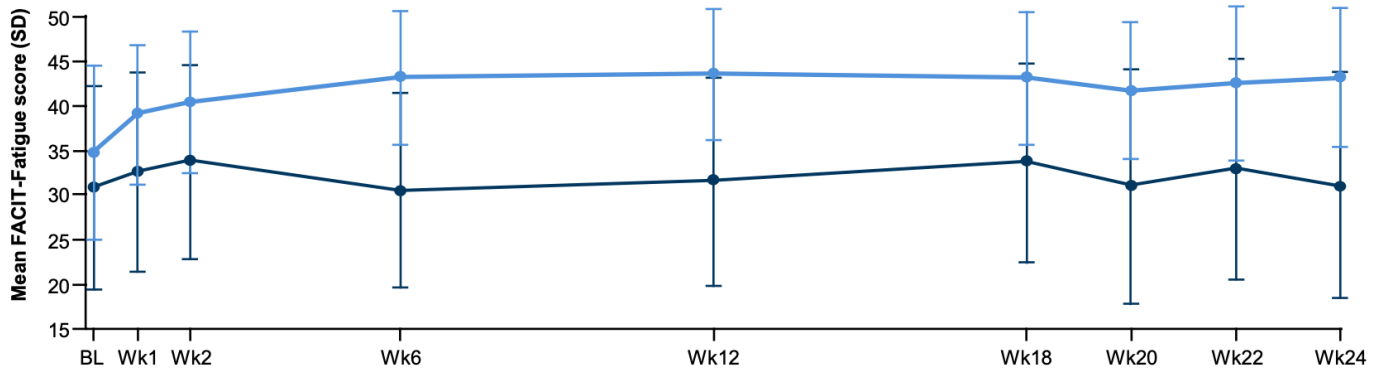


Patients with available data							Study visit					
Iptacopan	62	61	59	60	59	59	60	59	59	59	57	61
Anti-C5 SoC	35	29	27	32	32	31	33	28	34	32	32	34

Adjusted mean Hb change from baseline[1] (95% CI) was +3.59 (3.32, 3.86) g/dL for iptacopan vs −0.04 (−0.42, 0.35) g/dL for SoC, with a difference of +3.63 (3.18, 4.08) g/dL (P<0.0001[2]).

1. Between Days 126 and 168 (excluding values within 30 days of RBC transfusion). 2. A repeated measures model, adjusting for covariates including baseline Hb, was used for comparisons between the treatment arms. P value is two-sided and unadjusted. 3. Includes post-transfusion data. 2/62 patients in the iptacopan arm and 21/35 patients in the SoC arm had RBC transfusions between Days 14 and 168. BL = baseline Wk = week

Mean FACIT-Fatigue score (SD) during the 24-week randomized treatment period



Patients with available data					Study visit				
Iptacopan	62	60	57	61	57	58	59	56	60
Anti-C5 SoC	33	27	28	32	29	29	28	28	30

Adjusted mean change from baseline[1] in FACIT-Fatigue score (95% CI) was +8.59 (6.72, 10.47) for iptacopan vs +0.31 (−2.20, 2.81) for SoC, with a difference of +8.29 (5.28, 11.29) (P<0.0001[2])

1. Between Days 126 and 168. 2. A repeated measures model, adjusting for covariates including baseline FACIT-Fatigue score, was used for comparisons between the treatment arms. P value is two-sided and unadjusted.

Image from Ipatcopan ASH Update, Investor Presentation. Novartis.com

Most common TEAEs (≥4 patients in either arm)[1]

n (%)	Iptacopan 200mg bid N=62	Anti-C5 SoC N=35
Any TEAE	**51 (82.3)**	**28 (80.0)**
Mild / Moderate / Severe, %	**32.3 / 45.2 / 4.8**	**37.1 / 34.3 / 8.6**
Headache	10 (16.1)	1 (2.9)
Diarrhea	9 (14.5)	2 (5.7)
Nasopharyngitis	7 (11.3)	2 (5.7)
Nausea	6 (9.7)	1 (2.9)
COVID-19	5 (8.1)	9 (25.7)
Urinary tract infection	5 (8.1)	1 (2.9)
Arthralgia	5 (8.1)	1 (2.9)
Abdominal pain	4 (6.5)	1 (2.9)
Increased blood LDH	4 (6.5)	3 (8.6)
Dizziness	4 (6.5)	0
Breakthrough hemolysis	2 (3.2)	6 (17.1)

- No discontinuation of Iptacopan due to TEAEs
- No death or meningitis caused by encapsulated bacteria
- Serious TEAEs: 9.7% vs 14.3%
- Serious TEAE of TIA, considered to be unrelated to Iptacopan

- <u>Hemolysis as serious TEAEs</u>

Iptacopan:

- None

SoC:

- Breakthrough hemolysis (n=1)
- Extravascular hemolysis (n=1)

Conclusions and Considerations

- Complement inhibitors (proximal and distal) continue to be costly and delays into entering public funding models are expected
- With potential multiple modalities of treatment (PO, SC, IV) becoming available in the future, important to prioritize patient preferences to optimize QoL and compliance
- Cases of serious or fatal meningococcal infections have been reported in patients treated with complement inhibitors and vaccination mandatory
- Must consider special patient populations ie. Pregnancy, concurrent MDS, etc
- Role for combination therapy with proximal and distal complement blockade
- Exciting time for PNH community with evolving treatment landscape!

Questions?

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