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COMPREHENSIVE CANCER CENTER

Anxiety Inducing Hematologic Disorders: Managing the Patient with Cold Agglutinin Disease, Thrombotic Thrombocytopenic Purpura and Paroxysmal Nocturnal Hemoglobinuria

PATIENT CARE
RESEARCH
EDUCATION
COMMUNITY

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NCI CCC *A Comprehensive Cancer Center Designated by the National Cancer Institute*

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Disclosures

- Alexion: Research Funding, Honoraria
  Alpine: Research Funding, Honoraria, Membership on an entity's advisory committees
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  Electra: Research Funding, Honoraria
  Novartis: Research Funding, Honoraria
  Regenx bio: Other
  Sanofi: Research Funding, Honoraria

CAD: Background

Cold agglutinin disease (CAD) is a **rare blood disorder** accounting for ~25% of autoimmune hemolytic anemia (AIHA) cases, with an estimated incidence of **0.5–1.9 cases per million persons in a year**[1–3]

In CAD, antigen-IgM complexes on RBCs bind complement protein C1, resulting in **activation of the classical complement pathway**, leading to **chronic hemolytic anemia**

CAD is a **chronic** disease, with profound **fatigue**, frequent need of **transfusions**, increased **thromboembolic and mortality risk**, and unfavorable impact on **patient-reported outcomes**

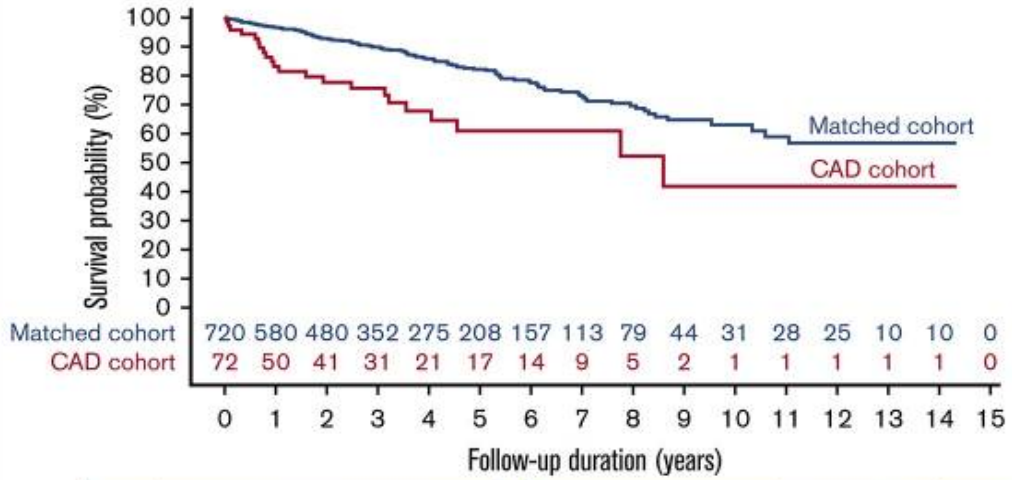
Cold agglutinin syndrome (CAS) may be secondary to an underlying disease such as infection, overt malignant or autoimmune conditions.[8] The **distinction between CAD and CAS** is pivotal for proper treatment.

QoL, quality of life.

1. Mullins M, *et al. Blood Adv*. 2017;1(13):839–848; 2. Berentsen S, *et al. Blood* 2020;136(4);480–488; 3. Hansen DL, *et al. Clinical Epidemiol* 2020:12;497–508; 4. Broome CM, et al. *Res Pract Thromb Haemost*. 2020;4(4):628–635; 5. Kamesaki T, *et al. Int J Hematol*. 2020;112(3):307–315; 6. Bylsma LC, *et al. Blood Adv.* 2019;3(20):2980–85; 7. Hansen DL, *et al. Eu J Hem*. 2022;00:1–11. doi:10.1111/ejh.13764 [Epub ahead of print]; 8. Berentsen S, *et al. J Blood Med.* 2019;10:93–103.

Mortality in CAD

Survival probability between patients with cold agglutinin disease (CAD) vs a general population matched cohort between 1999–2013 in Denmark

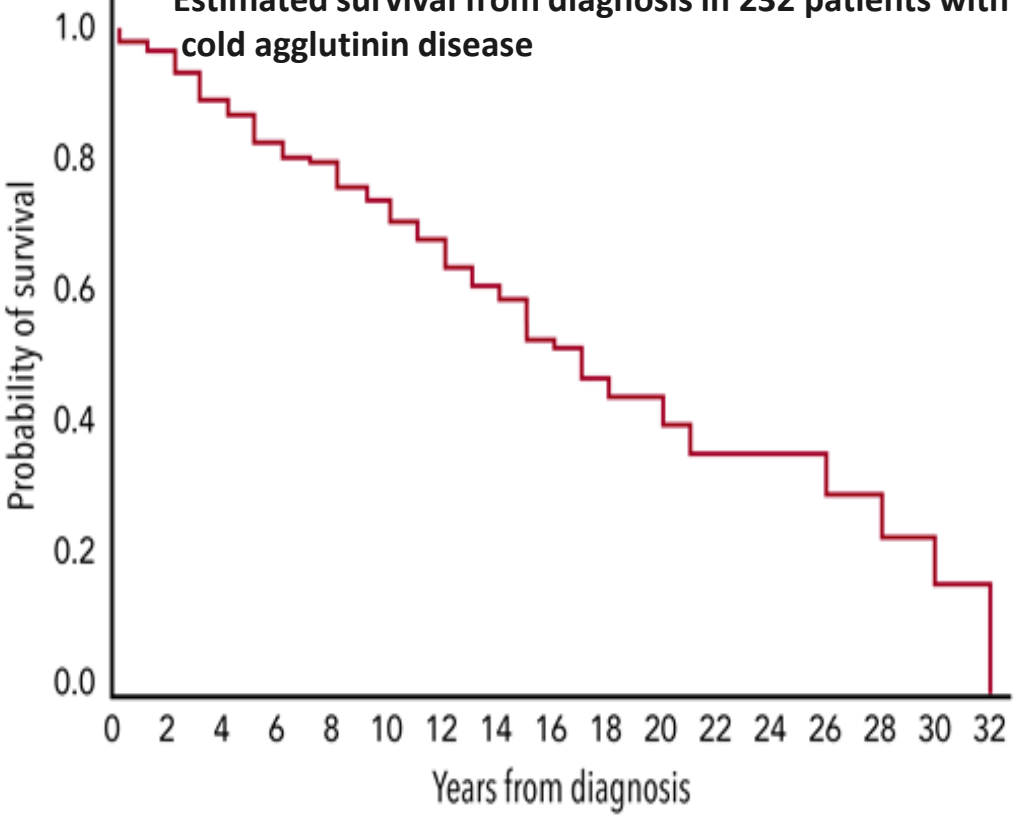


Year	Survival probability	
	CAD cohort	Matched cohort
1	83%	97%
3	75%	89%
5	61%	82%

Mortality risk	Adjusted HR* (95% CI)	*P*-value
Entire follow-up period	1.84 (1.10-3.06)	0.020
First 5 years after diagnosis/cohort entry	2.27 (1.32-3.89)	0.003

CI, confidence interval; HR, hazard ratio.
*Adjusted for Charlson comorbidity index score.

Estimated survival from diagnosis in 232 patients with cold agglutinin disease



Occurrence, thromboembolic risk, and mortality in Danish patients with cold agglutinin disease
Lauren C Bylsma , Anne Gulbech Ording , Adam Rosenthal , Buket Öztürk , Jon P Fryzek , Jaime Morales Arias , Alexander Röth , Sigbjørn Berentsen 2019 Oct 22;3(20):2980-2985. blood advances
Cold agglutinin disease revisited: a multinational, observational study of 232 patients Sigbjørn Berentsen et al. B*lood* (2020) 136 (4): 480–488.

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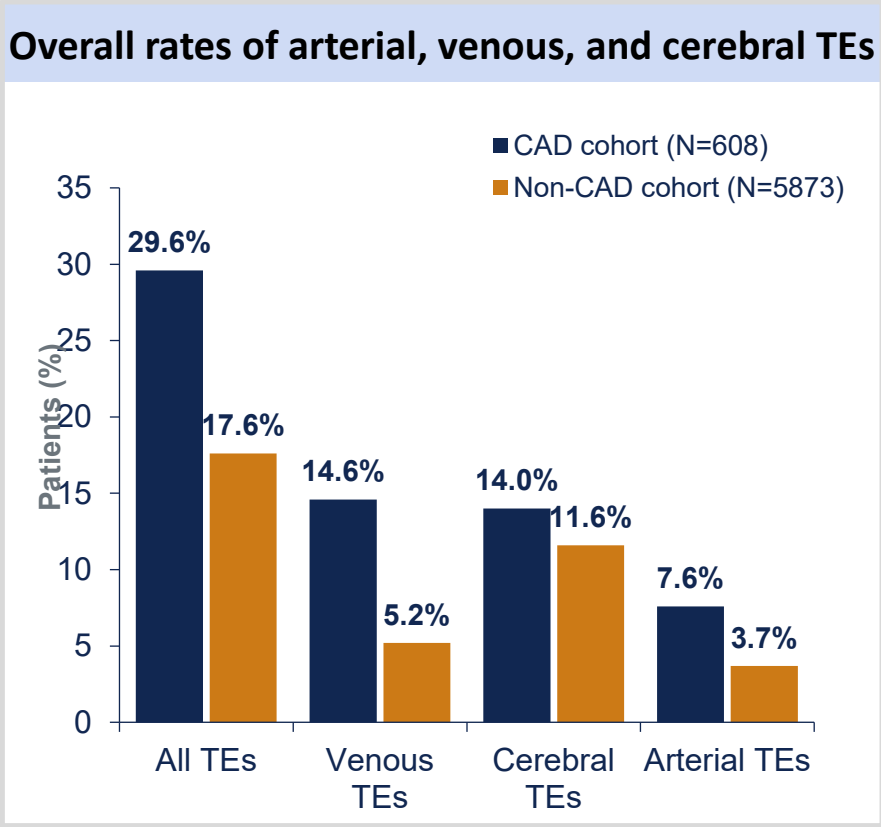
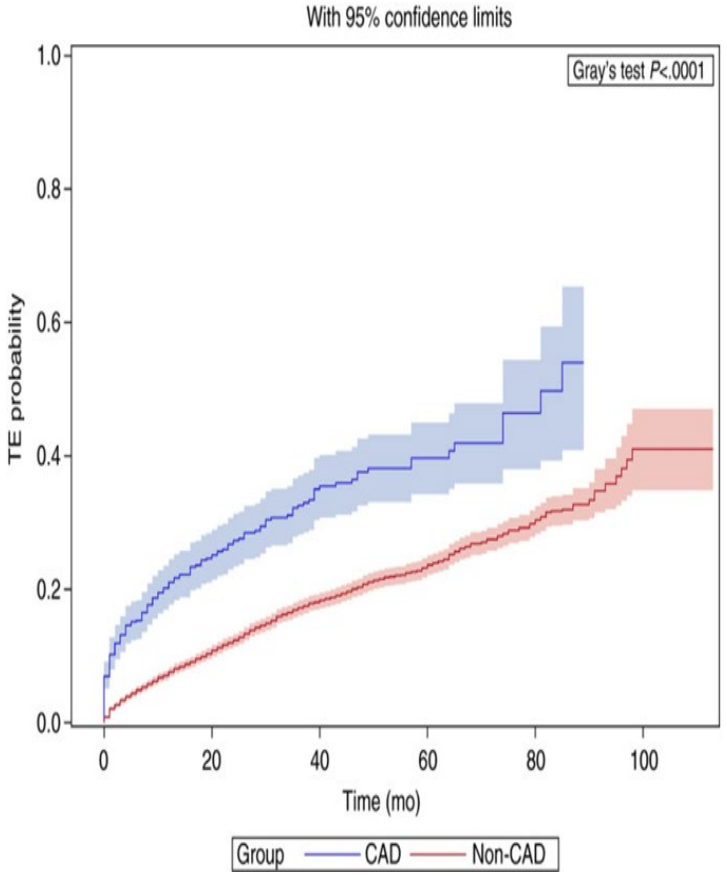
Thrombosis in CAD



Number of TEs	Patients with CAD, n (%)	Patients without CAD, n (%)	HR[a] (95% CI)	Adjusted HR[b] (95% CI)
All CAD	N = 608	N = 5873	2.36 (2.01-2.76)	1.94 (1.64-2.30)
0	428 (70.4)	4840 (82.4)		
1+	180 (29.6)	1033 (17.6)		
Primary CAD	n = 425	n = 4126	2.25 (1.84-2.75)	1.80 (1.46-2.22)
0	311 (73.2)	3446 (83.5)		
1+	114 (26.8)	680 (16.5)		



608 patients with CAD and 5,873 matched comparison patients were identified from 2006 to 2016
Higher incidence of ≥1 TE in patients with CAD versus the comparison cohort (adjusted HR 1.94; P<0.0001)
26.8% of patients with primary CAD and NO comorbidities experienced 1 or more TEs compared to 16.5% of comparator cohort

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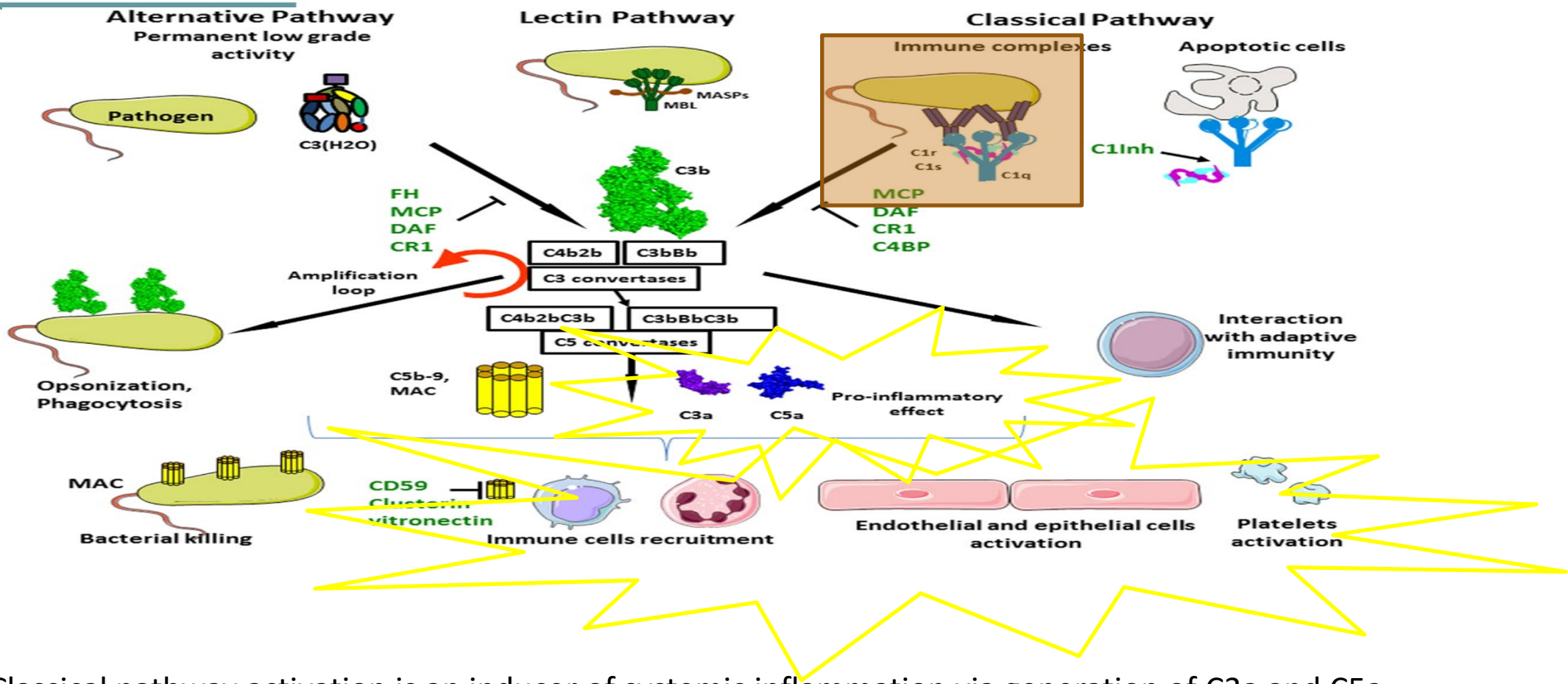
Catherine M. Broome, MD, Julia M. Cunningham, MD, [...], and Adam Rosenthal, PhD Res Pract Thromb Haemost. 2020 May; 4(4): 628–635.

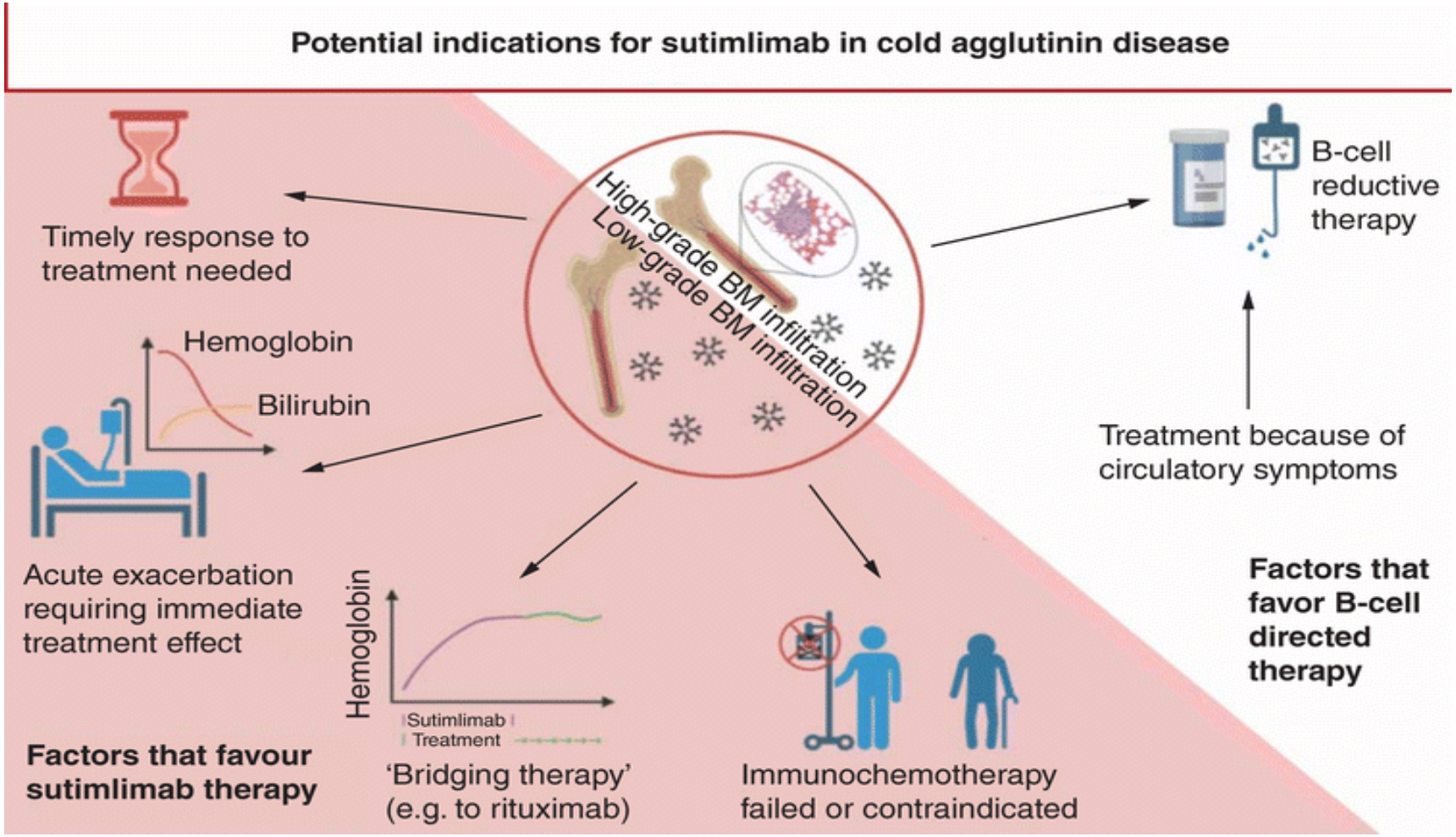
Complement Activity and Inflammation



Classical pathway activation is an inducer of systemic inflammation via generation of C3a and C5a, recruitment of neutrophils, endothelial cell activation and platelet activation

Nicolas S. Merle et al Complement system part II: role in immunity Front. Immunol., 26 May 2015

Considerations When Choosing Therapy for CAD



BM = bone marrow.

Berentsen et al, 2022.

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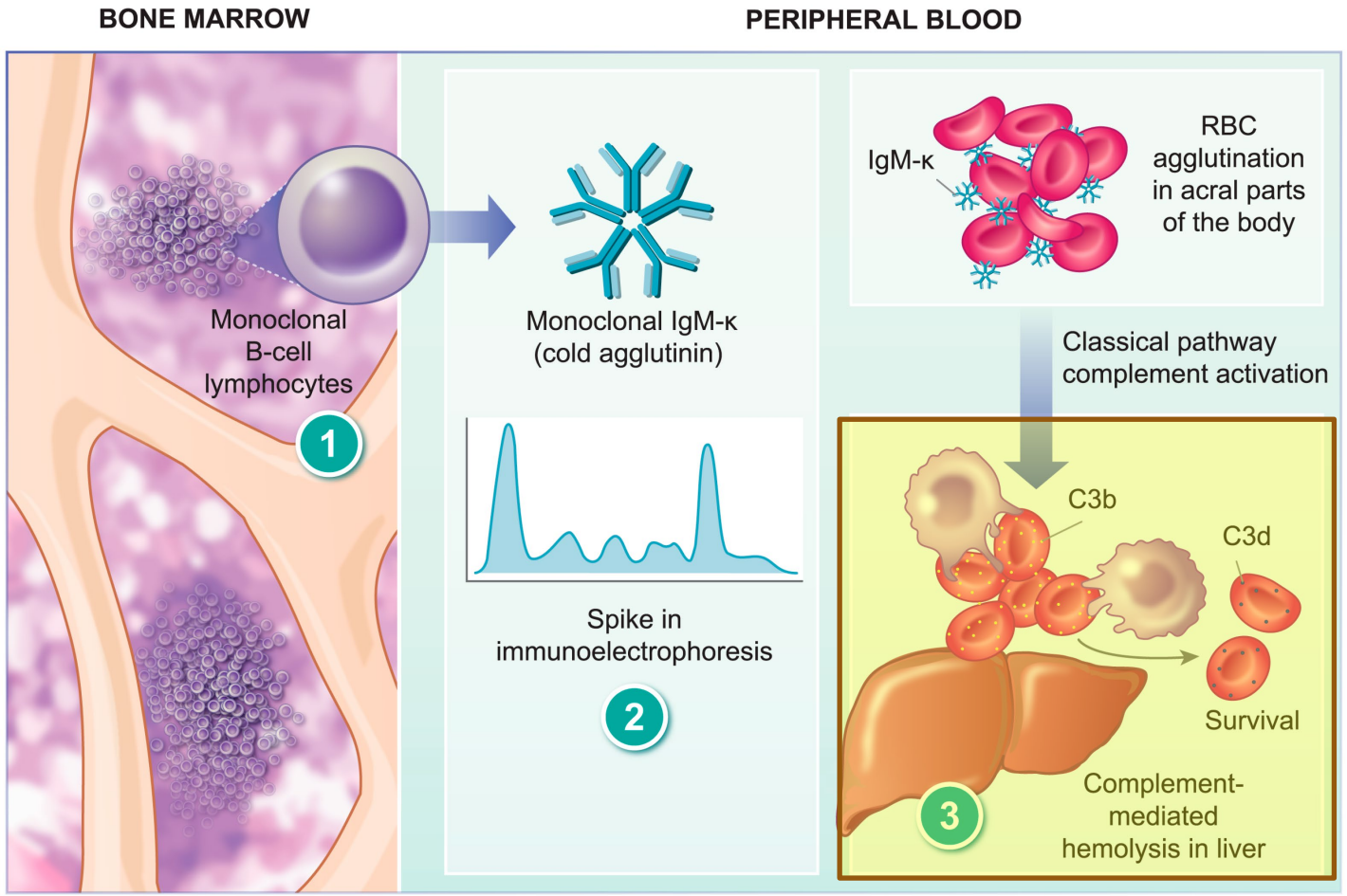
Complement Directed Therapy in CAD



Climent, F et al. Hemato **2022**, *3*(1), 163-173;

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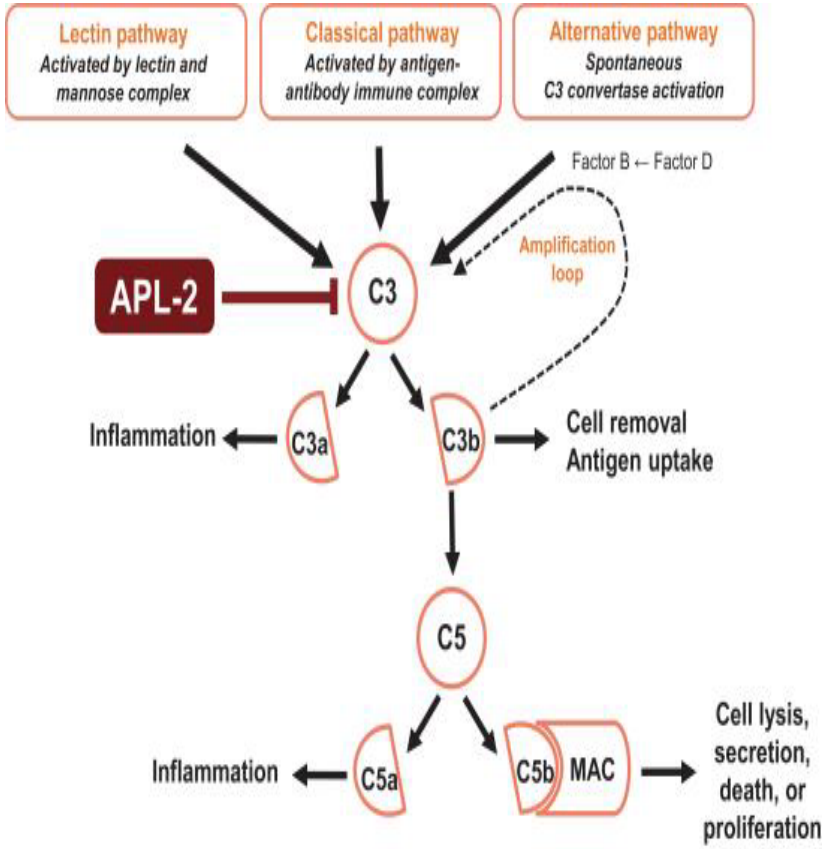
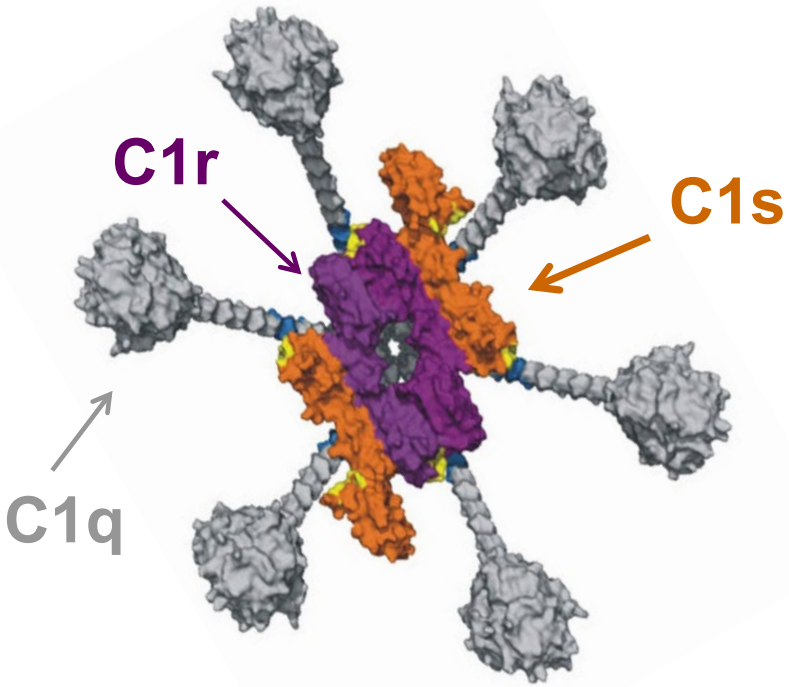
Pegcetacoplan(APL2)

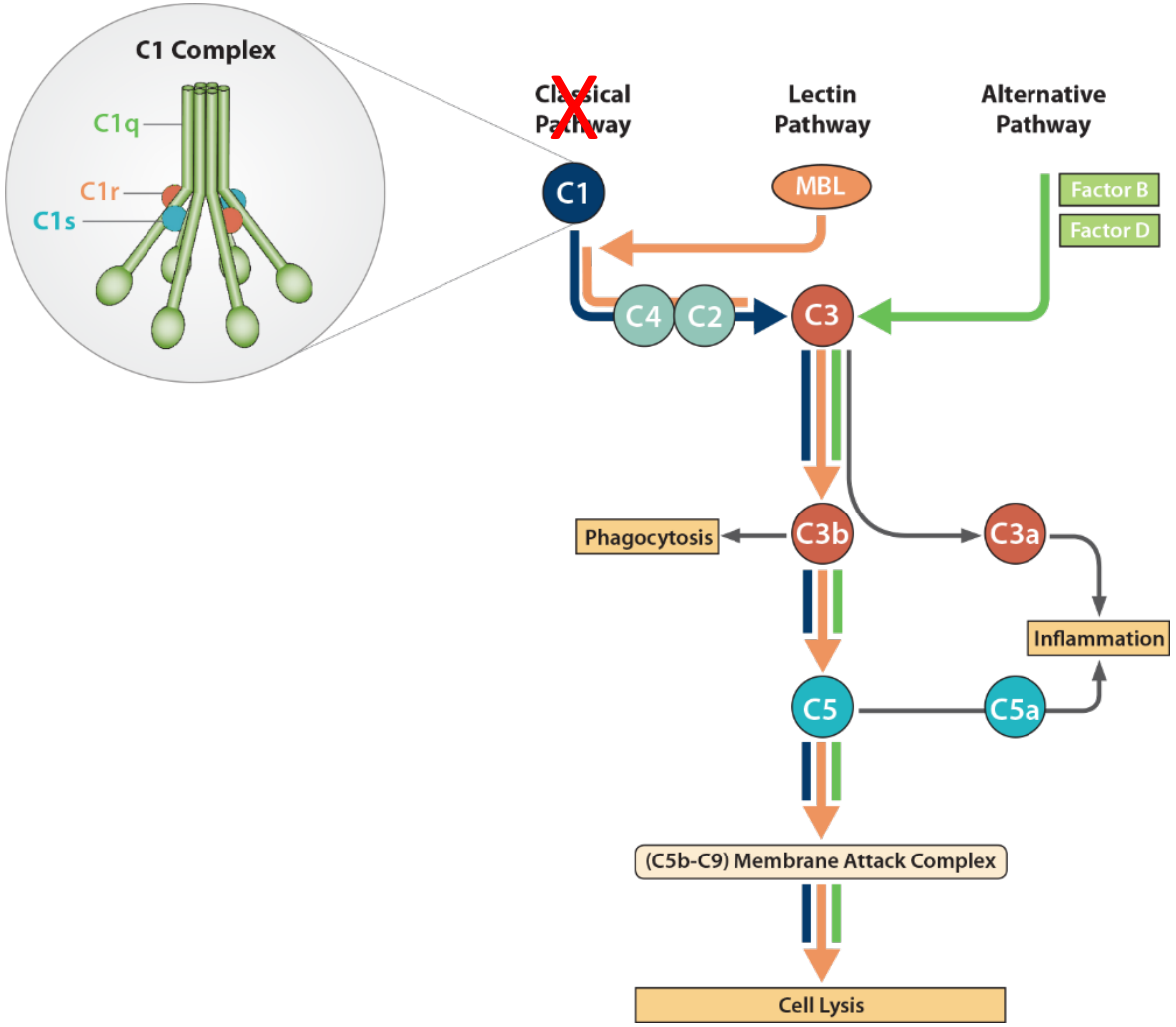


- Phase 2 ,48 week open label trial in patients with primary AIHA
- 12 patients enrolled with CAD
- Pegcetacoplan 270mg/d SQ or 360mg/d SQ
- Interim analysis at day 56
- Mean Hgb increased from 8.7 to 12.1g/dL
- Mean LDH, reticulocyte count and indirect bilirubin returned to normal
- 75% experienced >/= 1 AE
- Pegcetacoplan increases Hgb in CAD
- Reduces intra and extravascular hemolysis
- Appears safe and well tolerated

Gertz, M et al Br J Haematol 2019:185 :24

Sutimlimab Inhibits C1s, Preventing Classical Pathway Activity





1. Delves PJ et al. *Roitt's Essential Immunology*. 13th ed. Oxford, UK: Wiley Blackwell; 2017. 2. Abbas AK, Lichtman AH, Pillai S. Effector mechanisms of humoral immunity. In: Abbas AK, Lichtman AH, Pillai S, eds. *Cellular and Molecular Immunology*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2015:265-288.

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Sutimlimab established efficacy and safety in the CARDINAL and CADENZA trials[1–4]

Cardinal STUDY

- A phase 3, global, multicenter, open-label, single-arm trial of sutimlimab
- Included patients with CAD and a recent history of transfusion (N=24)
- **Duration:** 26-week treatment period (Part A) + a long-term safety and durability of response extension phase (Part B) for an additional 24 months*
- **Dosing:** IV, weight-based dosing at Days 0 and 7, then biweekly of 6.5 g (<75 kg) or 7.5 g (≥75 kg)

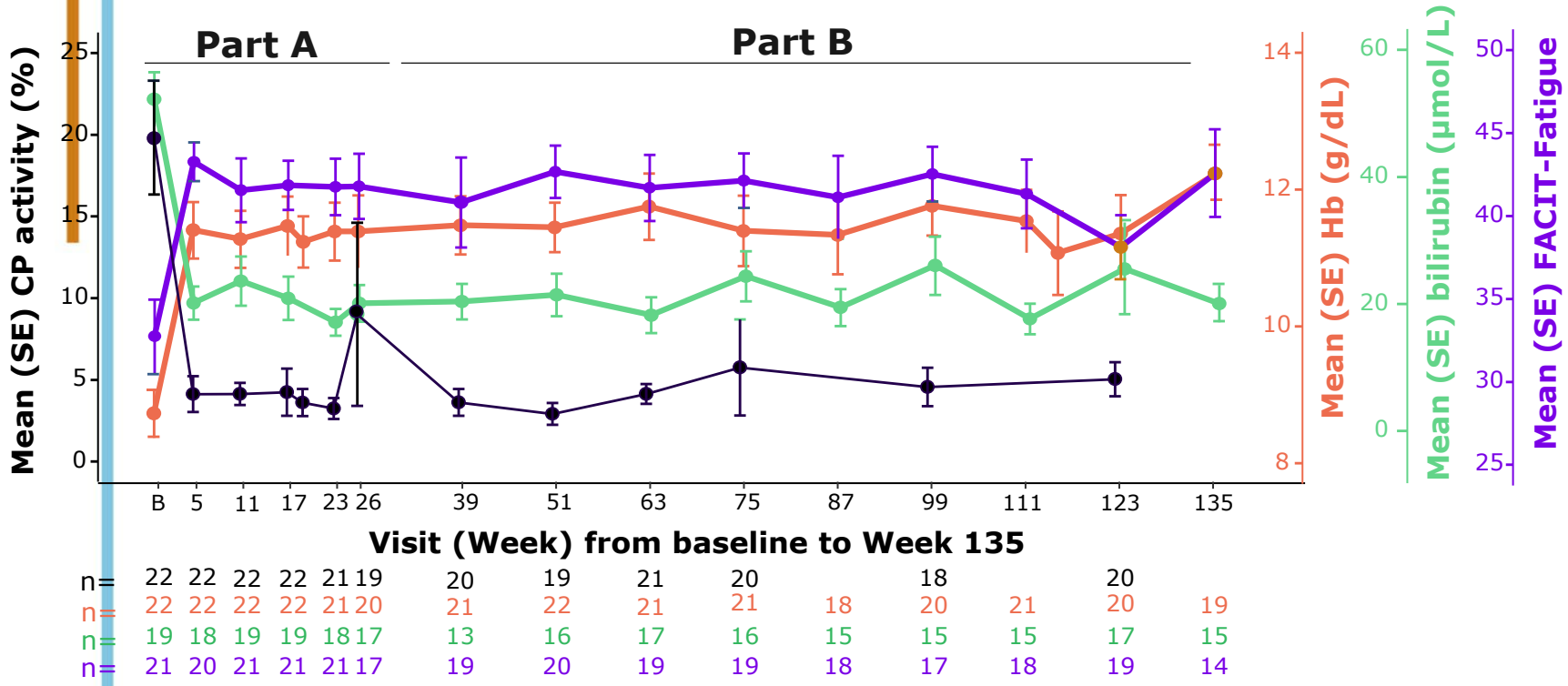
Cadenza STUDY

- A phase 3, placebo-controlled, global, multicenter, randomized, double-blind trial of sutimlimab
- Included patients with CAD without recent history of transfusion (N=42)
- **Duration:** 26-week treatment period (Part A) + long-term safety and durability of response extension phase (Part B) for an additional 12 months*
- **Dosing:** IV, weight-based dosing at Days 0 and 7, then biweekly of 6.5 g (<75 kg) or 7.5 g (≥75 kg)

***1-year or 2-year follow-up starts after the last patient finishes Part A of the clinical studies.**

CAD, cold agglutinin disease; IV, intravenous. 1. Sutimlimab (ENJAYMO). Prescribing information. Genzyme Corporation. Available at: https://products.sanofi.us/enjaymo/enjaymo.pdf. [Last accessed: November 2023]; 2. Röth A, *et al. Blood*. 2022;140(9):980–91; 3. Röth A, *et al. N Engl J Med*. 2021;384(14):1323–34; 4. Data on file. Sanofi.

CARDINAL: Hematological markers, QoL assessment, and complement pathway activity[1,2]



Improvements in:

- **bilirubin**
- **FACIT-Fatigue score**
- **Hb**

correlated with near-complete inhibition of **CP activity**

Sustained treatment with sutimlimab continues to inhibit hemolysis and improve anemia and QoL. Effects on bilirubin, Hb, and FACIT-Fatigue were maintained throughout the treatment period

CP, complement pathway; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; Hb, hemoglobin; QoL, quality of life; SE, standard error

1. Sutimlimab (ENJAYMO). Prescribing information. Genzyme Corporation. Available at: https://products.sanofi.us/enjaymo/enjaymo.pdf. [Last accessed: September 2023];
2. Röth A, *et al. Am J Hematol*. 2023;98(8):1246–53.

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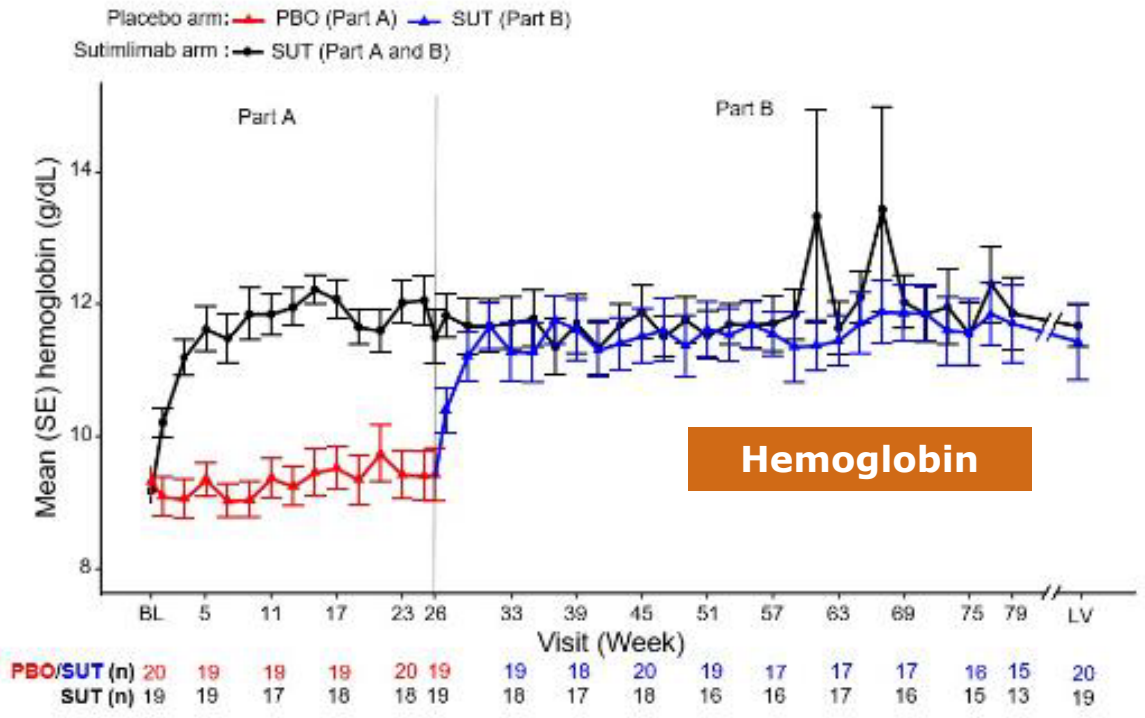
CADENZA: Hematological markers from baseline to last available on-treatment value (1/3)

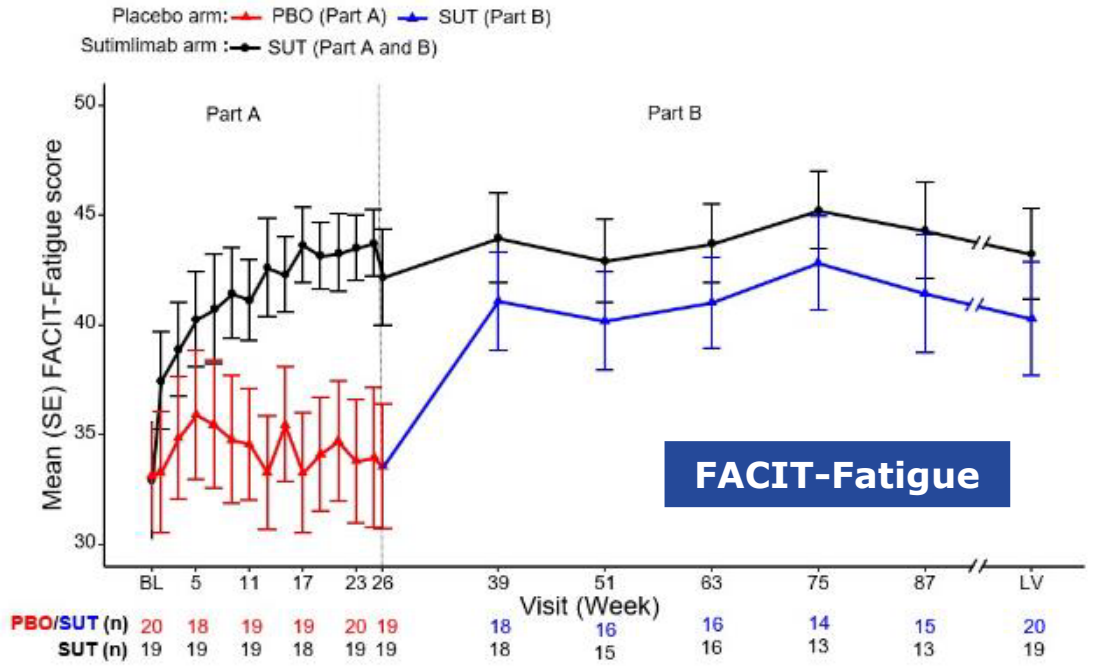


- Sutimlimab treatment rapidly improved Hb levels
- In Part B, increased Hb levels were sustained in patients previously treated with sutimlimab, while patients previously treated with placebo had rapid and comparable increases

Improvements in Hb and bilirubin correlated with normalisation of C4 and near-complete inhibition of CP activity, which were maintained through the end of treatment

BL, baseline; CP, complement pathway; Hb, hemoglobin; PBO, placebo; SE, standard error; SUT, sutimlimab; ULN, upper limit of normal.
Röth A, et al. ASH, New Orleans, 10–13 December 2022. Oral presentation S31.

CADENZA: FACIT Fatigue from baseline to last available on-treatment value (3/3)



FACIT-Fatigue

- In patients previously treated with sutimlimab, mean FACIT-Fatigue improvement observed in Part A was sustained in Part B
- In patients previously treated with placebo, mean FACIT-Fatigue score increased to comparable levels after sutimlimab treatment was initiated
- At the last on-treatment visit (LV), mean (SE) change for all patients (N=39) was 8.8 (2.1) points[2]

Improvements in Hb and bilirubin correlated with normalisation of C4 and near-complete inhibition of CP activity, which were maintained through the end of treatment

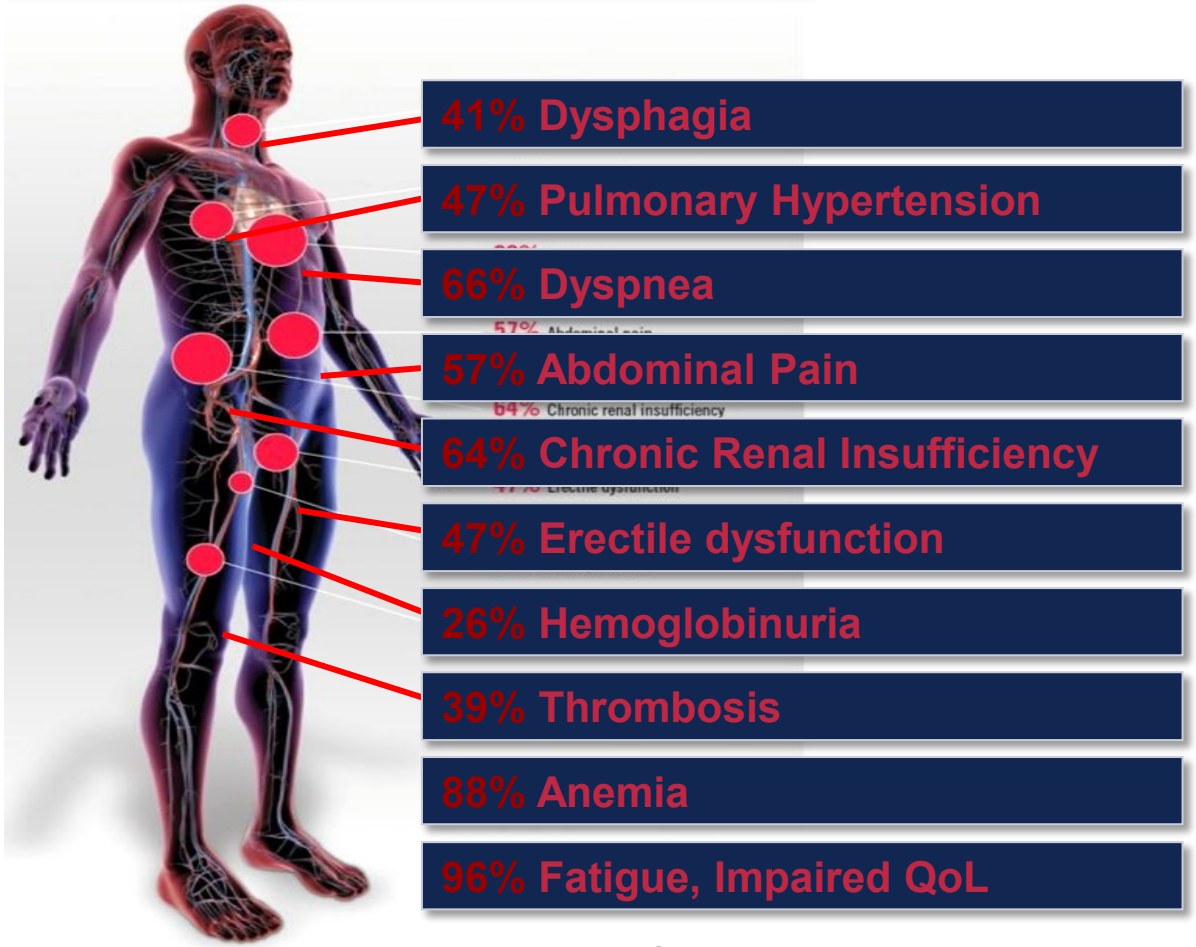
BL, baseline; CIC, clinically important change; CP, complement pathway; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; LV, last available on-treatment value; PBO, placebo; SE, standard error; SUT, sutimlimab. Figure reproduced with permission from: Röth A, et al. ASH, New Orleans, 10–13 December 2022. Oral presentation S31.

1. Röth A, et al. ASH, New Orleans, 10–13 December 2022. Oral presentation S31; 2. Röth A, et al. ASH, New Orleans, 10–13 December 2022. Oral presentation: S121.

Paroxysmal Nocturnal Hemoglobinuria

Common Symptoms in Patients With PNH

PNH Symptom Incidence Rate (%)



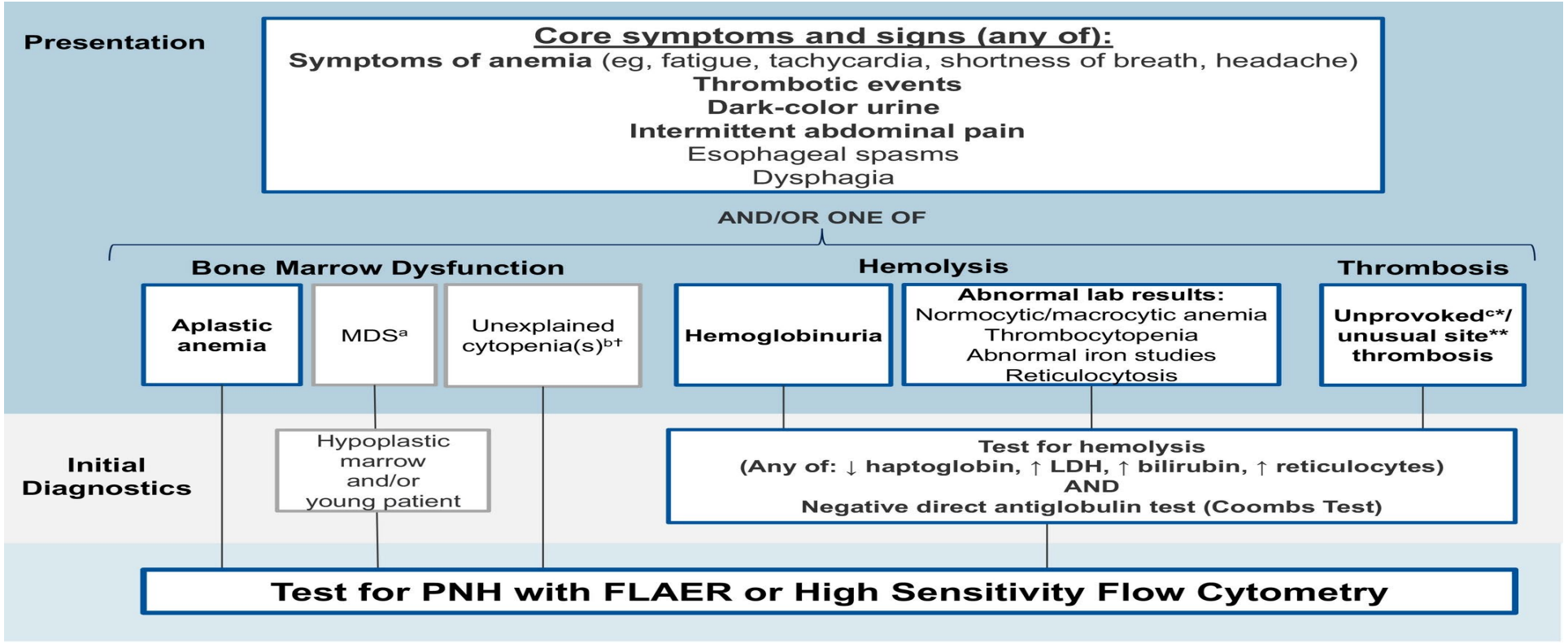
- 41% Dysphagia
- 47% Pulmonary Hypertension
- 66% Dyspnea
- 57% Abdominal Pain
- 64% Chronic Renal Insufficiency
- 47% Erectile dysfunction
- 26% Hemoglobinuria
- 39% Thrombosis
- 88% Anemia
- 96% Fatigue, Impaired QoL

Characterized by signs and symptoms of hemolysis or red blood cell breakdown.

Meyers G et al. *Blood*. 2007;110(11):Abstract 3683.3. 2. Hill A et al. *Br. J. Hematol.* 2010;149(3):414-425. 3. Hillmen P et al. *Am. J. Hematol*. 2010; 85:553-559. 4. International PNH Interest Group. *Blood.* 2005;106(12):3699-3709.

5. Hillmen P et al. *N Engl J Med*. 1995;333:1253-8. 6. Nishimura J et al. *Medicine.* 2004;83(3):193-207

Diagnostic Algorithm for PNH



[a] Parker 2005; [b]Peffault de Latour 2008, Brodsky 2009, Valent 2012; [c] NICE 2015
†An unexplained persistent cytopenia in patients in whom (minimal) diagnostic criteria for MDS are not fulfilled
*DVT and/or PE in a patient with no antecedent major clinical risk factor for VTE that is not provoked by surgery, trauma, immobilization, hormonal therapy (oral contraceptive or hormone replacement therapy) or active cancer.
**Unusual sites include hepatic veins (Budd-Chiari syndrome), other splanchnic veins (portal, splenic), cerebral vein, and dermal veins.

Based on Delphi Panel Consensus

Röth, A, Maciejewski, J, Nishimura, J-I, Jain, D, Weitz, JI. Screening and diagnostic clinical algorithm for paroxysmal nocturnal hemoglobinuria: Expert consensus. *Eur J Haematol*. 2018; 101: 3– 11. https://doi.org/10.1111/ejh.13059

Therapy for PNH

Curative

Allogeneic stem cell transplant

Noncurative

Supportive care-transfusions, folic acid supplementation, treat other complications when

they occur

Prophylactic Anticoagulation

Other Therapy corticosteroids, androgens, erythropoietin, cyclophosphamide, treatment

of infections

Targeted Therapy complement inhibition, gene therapy

Effects of Uncontrolled or Excessive Complement Activation

- Lysis of red blood cells-HEMOLYSIS[1]
- Activation of platelets[2,3]
- Endothelial activation, especially in the kidneys[4]
- Cytokine activation[1,5]
- Result: hemolysis, venous thrombosis, microvascular thromboses, and potential renal effects[1,2,4-6]

RBC = red blood cell.

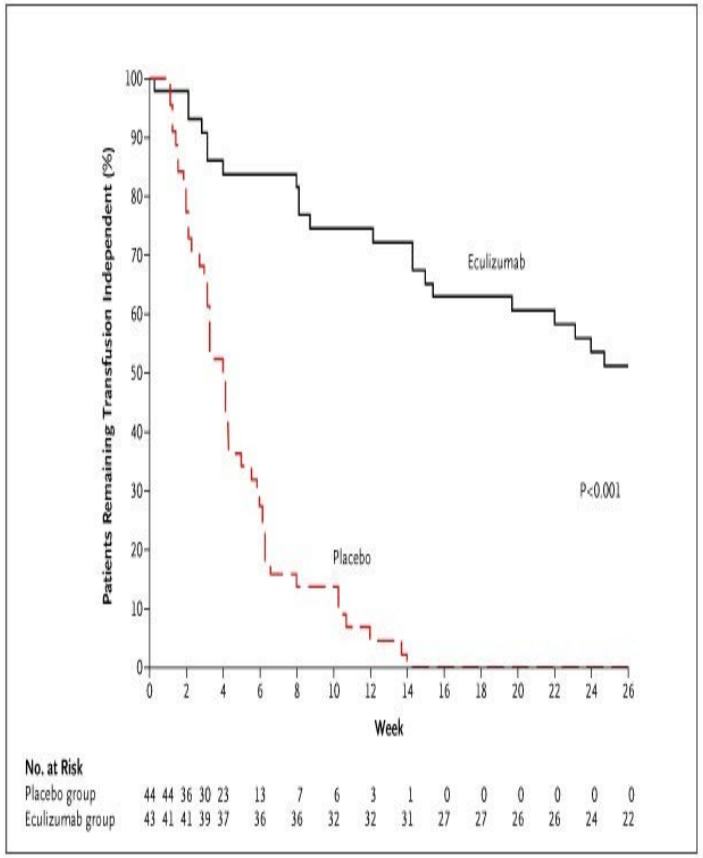
1. Figueroa JE, Densen P. *Clin Microbiol Rev*. 1991;4:359-395. 2. Wiedmer T, et al. *Blood*. 1993;82:1192-1196. 3. Sims PJ, et al. *J Biol Chem*. 1989;264:19228-19235. 4. Fang CJ, et al. *Br J Haematol*. 2008;143:336-348. 5. Gao L, et al. *Clin Exp Immunol*. 2006;144:326-334. 6. Walport MJ. *N Engl J Med*. 2001;344:1058-1066.

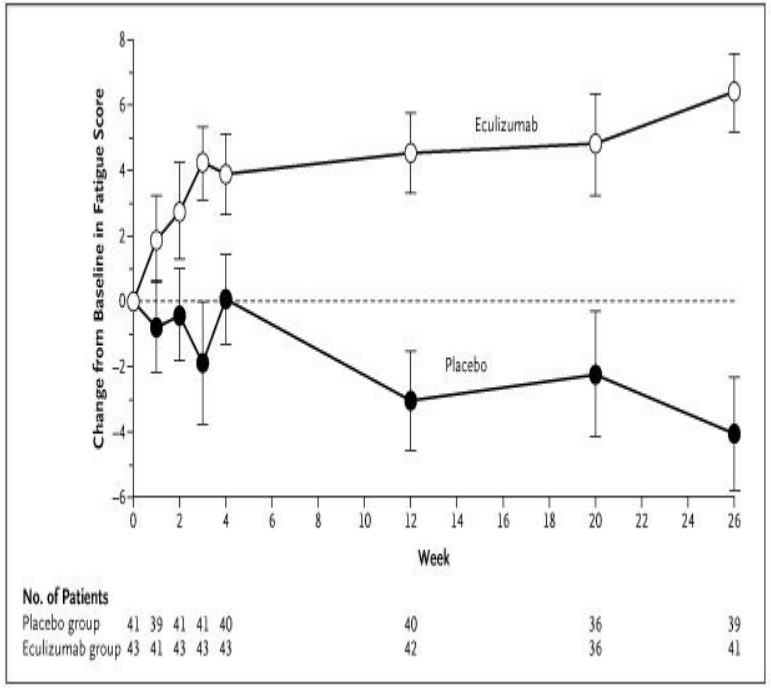
C5 Inhibition with Eculizumab for PNH

Table 2. Stabilization of Hemoglobin Levels and the Number of Units of Packed Red Cells Transfused during Treatment.*

Primary End Point	Before Treatment†		During Treatment		P Value
	Placebo Group	Eculizumab Group	Placebo Group	Eculizumab Group	
Patients with stabilized hemoglobin levels (%)	NA	NA	0	49	<0.001‡
Packed red cells transfused (units/patient)					
Median	8.5	9.0	10	0	<0.001§
Interquartile range	7–12.5	6–12	6–16	0–6	
Mean	9.7±0.7	9.6±0.6	11.0±0.8	3.0±0.7	
Total	417	413	482	131	

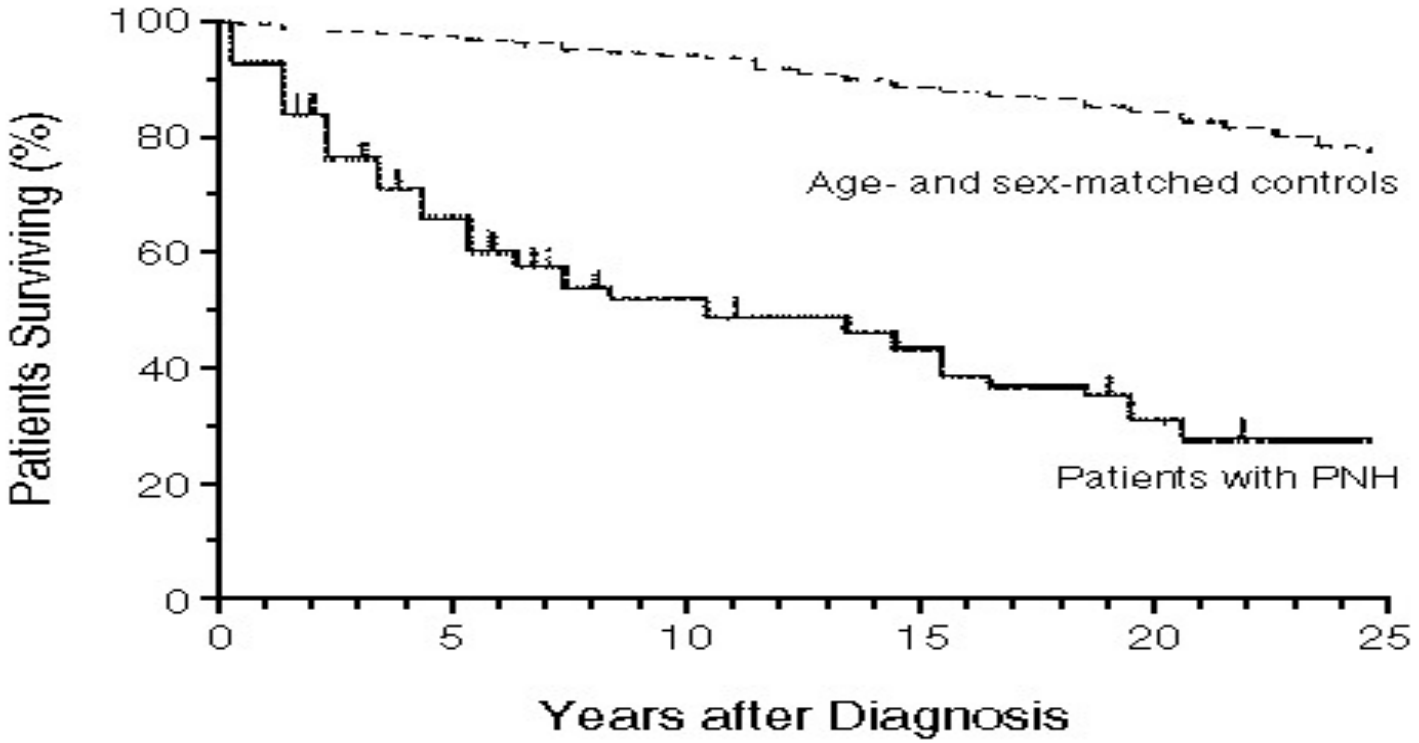
* Plus–minus values are means ±SE. NA denotes not applicable.
† Transfusion data obtained during 12 months before treatment were normalized to a value equivalent to the value for a 6-month period.
‡ The P value is for the comparison between groups during treatment, calculated with the use of a two-tailed Fisher's exact test.
§ The P value is for the comparison between groups during treatment, calculated with the use of the Wilcoxon rank-sum test.





The Complement Inhibitor Eculizumab in Paroxysmal Nocturnal Hemoglobinuria
Peter Hillmen, et al. September 21, 2006N Engl J Med 2006; 355:1233-1243
DOI: 10.1056/NEJMoa061648

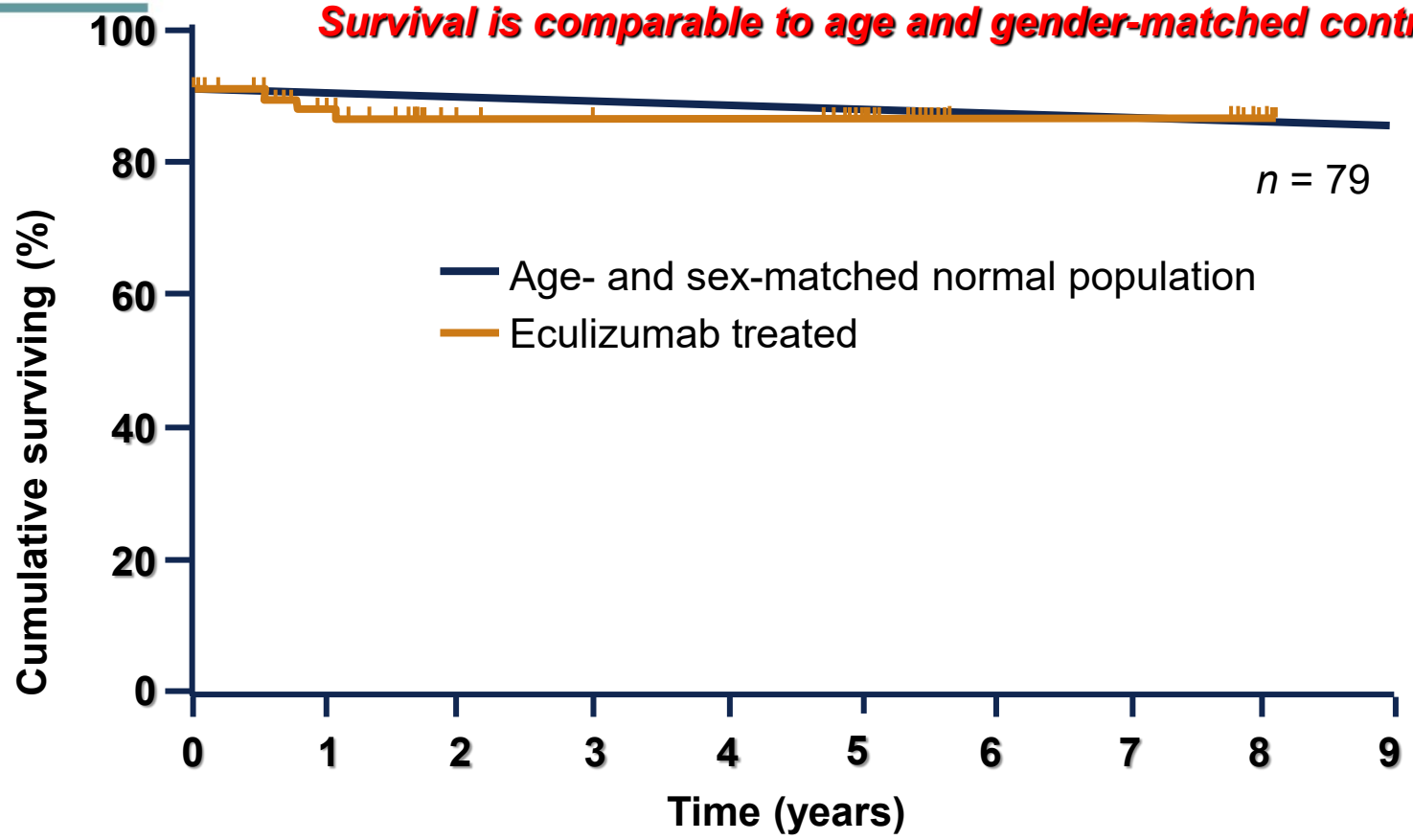
Natural History of PNH



Natural History of Paroxysmal Nocturnal Hemoglobinuria
Peter Hillmen et al. November 9, 1995
N Engl J Med 1995; 333:1253-1258
DOI: 10.1056/NEJM199511093331904

Eculizumab Has a Major Impact on Survival in PNH

Survival is comparable to age and gender-matched control population out to 8 years



- 96% (76/79) patient survival
- There was no difference in mortality between patients on eculizumab and the normal population (*P*=0.46)

Kelly RJ et al. *Blood.* 117:6786-6792, June 2011

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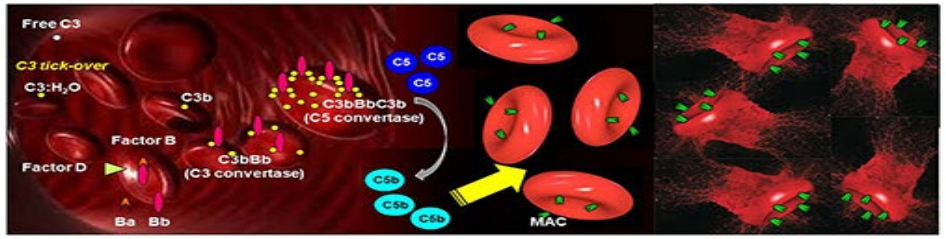
PNH on C5 Inhibition

A

PNH erythrocytes in absence of anti-complement treatment

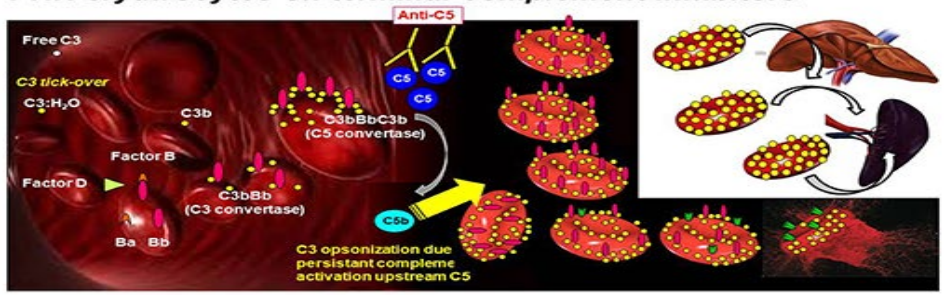


MAC-mediated massive intravascular hemolysis

B

PNH erythrocytes on terminal complement inhibitors

Anti-C5 agents:
- mAbs: eculizumab, ravulizumab, SKY59, LFG316, ABP959, REGN3918
- RA101495
- Coversin
- ALNCC5



C3-mediated extravascular hemolysis

Residual MAC-mediated intravascular hemolysis (i.e., PK or PD brekthrough)

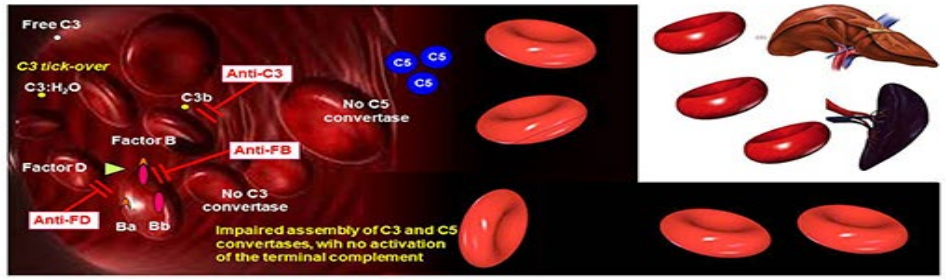
C

PNH erythrocytes on proximal complement inhibitors (+/- terminal inhibitors?)

Anti-C3 agents:
- AMY-101
- APL-2

Anti-FD agents:
- ACH4471

Anti-FB agents:
- LNP023



Normal life-span of PNH erythrocytes

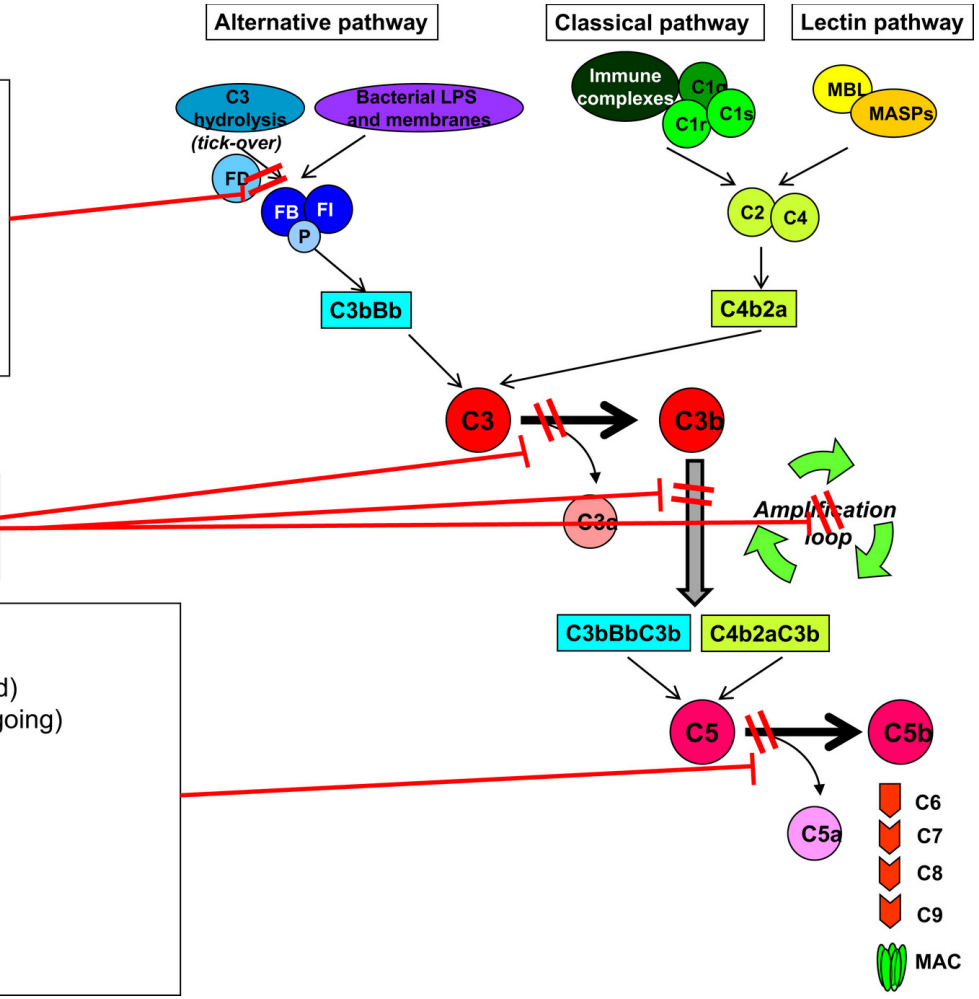
Front. Immunol., 14 June 2019Sec. Molecular Innate Immunity Volume 10 - 2019 | https://doi.org/10.3389/fimmu.2019.01157 Anti-complement Treatment for Paroxysmal Nocturnal Hemoglobinuria: Time for Proximal Complement Inhibition

Complement Inhibitors in PNH

C Alternative Pathway inhibitors:
- **FH-based proteins (IV/SC)**
  - TT30 (Ph1, stopped)
- **FD inhibitors (oral)**
  - ACH-4471/danicopan (Ph2, completed)
  - BCX-9930 (Ph1/2, ongoing)
- **FB inhibitors (oral)**
  - LNP023 (Ph2, ongoing)

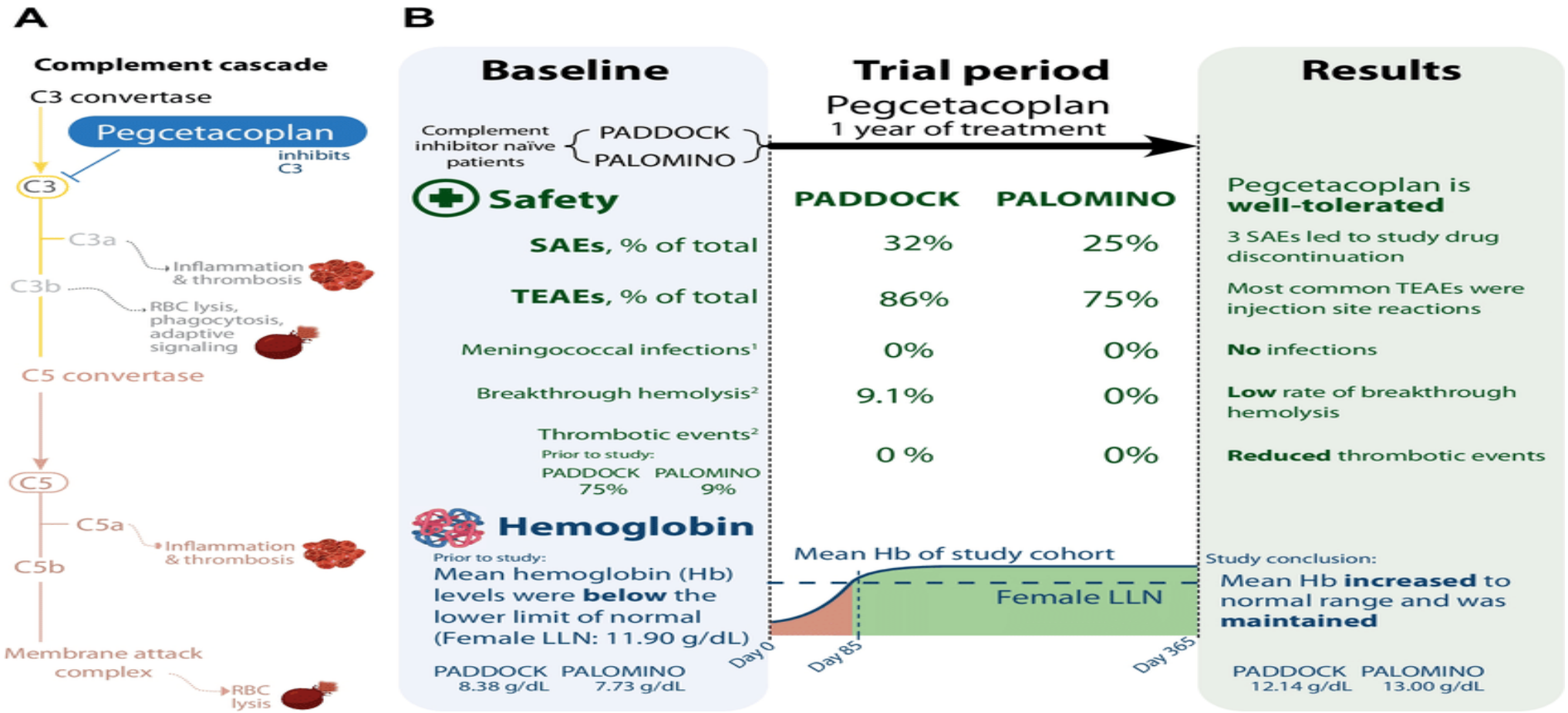
C3 inhibitors (SC):
- APL-2/pegcetacoplan (Ph3, completed)
- AMY-101 (Ph1, completed)

Novel anti-C5 agents:
- **mAb**
  - ALXN1210/ravulizumab (Ph3, completed)
  - SKY59/RO711269/crovalimab (Ph3, ongoing)
  - LFG316 (Ph2, ongoing)
  - REGN3918 (Ph2, ongoing)
  - Biosimilars
- **Small molecules (SC/oral)**
  - RA101495 (Ph2, completed)
  - Coversin (Ph1/2, ongoing)
- **siRNA**
  - ALNCC5 (Ph2, stopped)



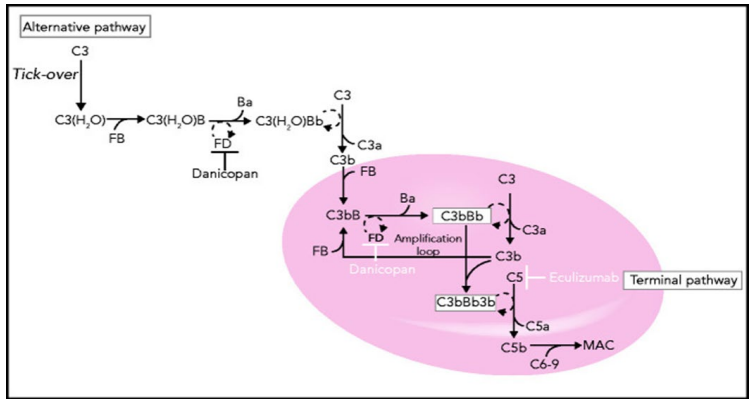
Luzzatto, L. and Karadimitris, A. (2020), Paroxysmal nocturnal haemoglobinuria (PNH): novel therapies for an ancient disease. Br. J. Haematol., 191: 579-586. https://doi.org/10.1111/bjh.17147

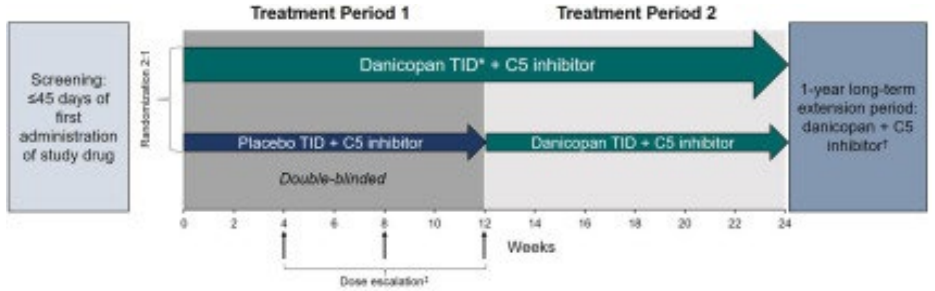
Pegcetacoplan in PNH



Wong RSM. Safety and efficacy of pegcetacoplan in paroxysmal nocturnal hemoglobinuria. Therapeutic Advances in Hematology. 2022;13. doi:10.1177/20406207221114673

Danicopan-Oral Factor D Inhibitor



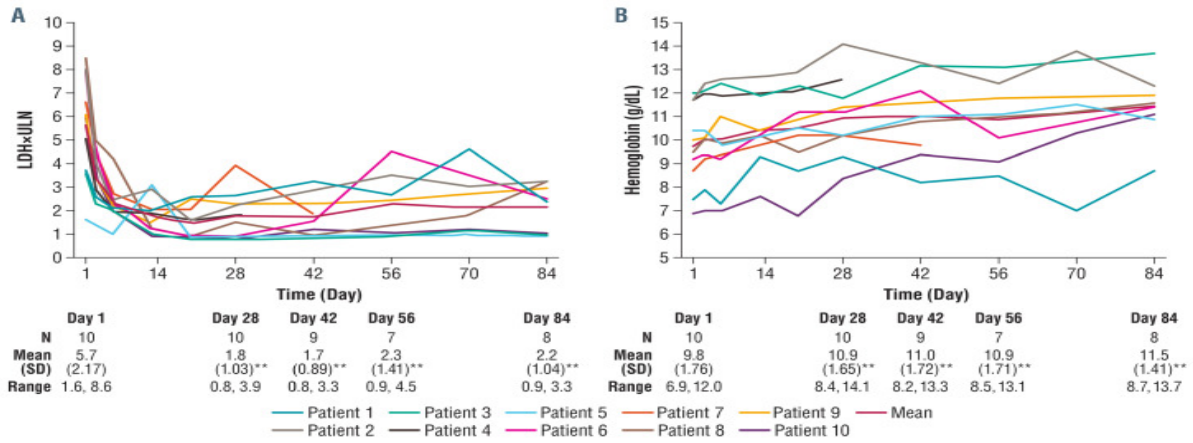


TID, three times daily

*The starting dose of danicopan is 150 mg TID. Patients with alanine aminotransferase (ALT) or direct bilirubin screening values >1.5x upper limit of normal (ULN) will start at 100 mg TID.

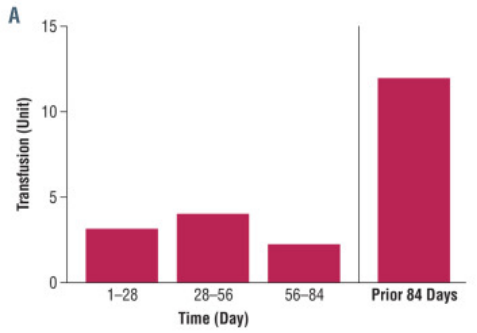
†After completion of the study, patients may enter the long-term extension period at the same danicopan dose they were receiving at week 24, plus continue their C5 inhibitor therapy. During the long-term extension, patients may switch from their day 1 C5 inhibitor therapy to any other approved C5 inhibitor (not permitted during Treatment Period 1 or Treatment Period 2).

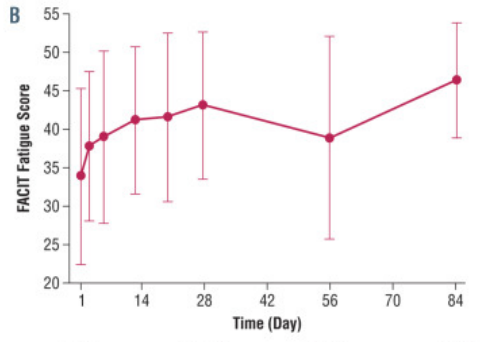
‡Dose escalation may occur based on safety and clinical effect at protocol-specified timepoints up to a dose of 200 mg TID; dose escalations after week 12 will be made on a patient-by-patient basis at the discretion of the principal investigator.



	Day 1	Day 28	Day 42	Day 56	Day 84
N	10	10	9	7	8
Mean (SD)	5.7 (2.17)	1.8 (1.03)**	1.7 (0.89)**	2.3 (1.41)**	2.2 (1.04)**
Range	1.6, 8.6	0.8, 3.9	0.8, 3.3	0.9, 4.5	0.9, 3.3

	Day 1	Day 28	Day 42	Day 56	Day 84
N	10	10	9	7	8
Mean (SD)	9.8 (1.76)	10.9 (1.65)**	11.0 (1.72)**	10.9 (1.71)**	11.5 (1.41)**
Range	6.9, 12.0	8.4, 14.1	8.2, 13.3	8.5, 13.1	8.7, 13.7



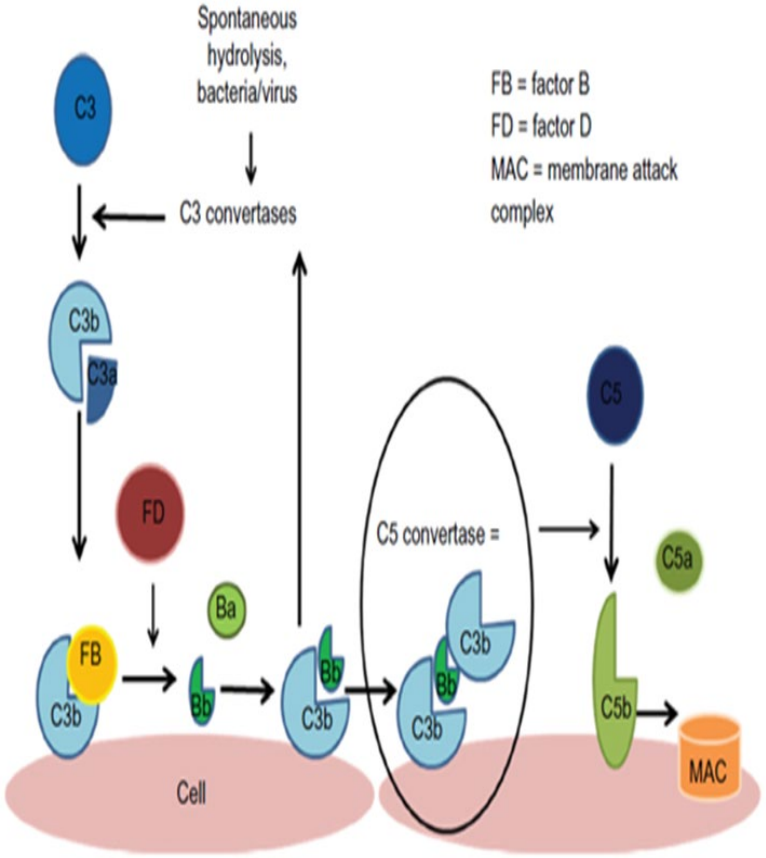


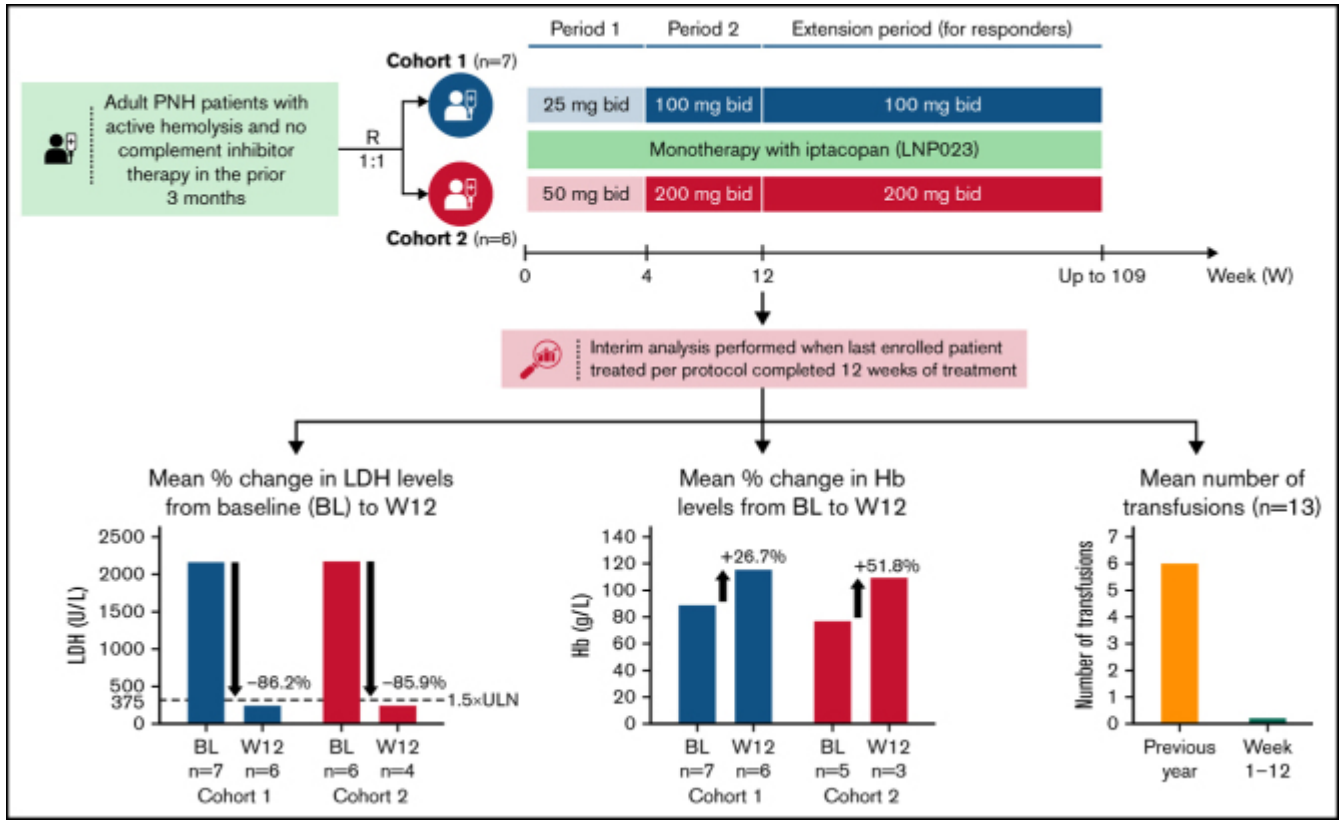
	Day 1	Day 28	Day 56	Day 84
N	10	10	7	8
Mean (SD)	34 (11.5)	43 (9.6)*	39 (13.2)*	47 (7.5)**
Range	20, 49	23, 52	18, 51	31, 52

Risitano AM, Kulasekararaj AG, Lee JW, Maciejewski JP, Notaro R, Brodsky R, Huang M, Geffner M, Browett P. Danicopan: an oral complement factor D inhibitor for paroxysmal nocturnal hemoglobinuria. Haematologica. 2021 Dec 1;106(12):3188-3197. doi: 10.3324/haematol.2020.261826. PMID: 33121236; PMCID: PMC8634185.

Georgetown | Lombardi

Iptacopan-Oral Factor B Inhibitor





Jang JH, Wong L, Ko BS, Yoon SS, Li K, Baltcheva I, Nidamarthy PK, Chawla R, Junge G, Yap ES. Iptacopan monotherapy in patients with paroxysmal nocturnal hemoglobinuria: a 2-cohort open-label proof-of-concept study.

Blood Adv. 2022 Aug 9;6(15):4450-4460. doi: 10.1182/bloodadvances.2022006960. PMID: 35561315; PMCID: PMC9636331.

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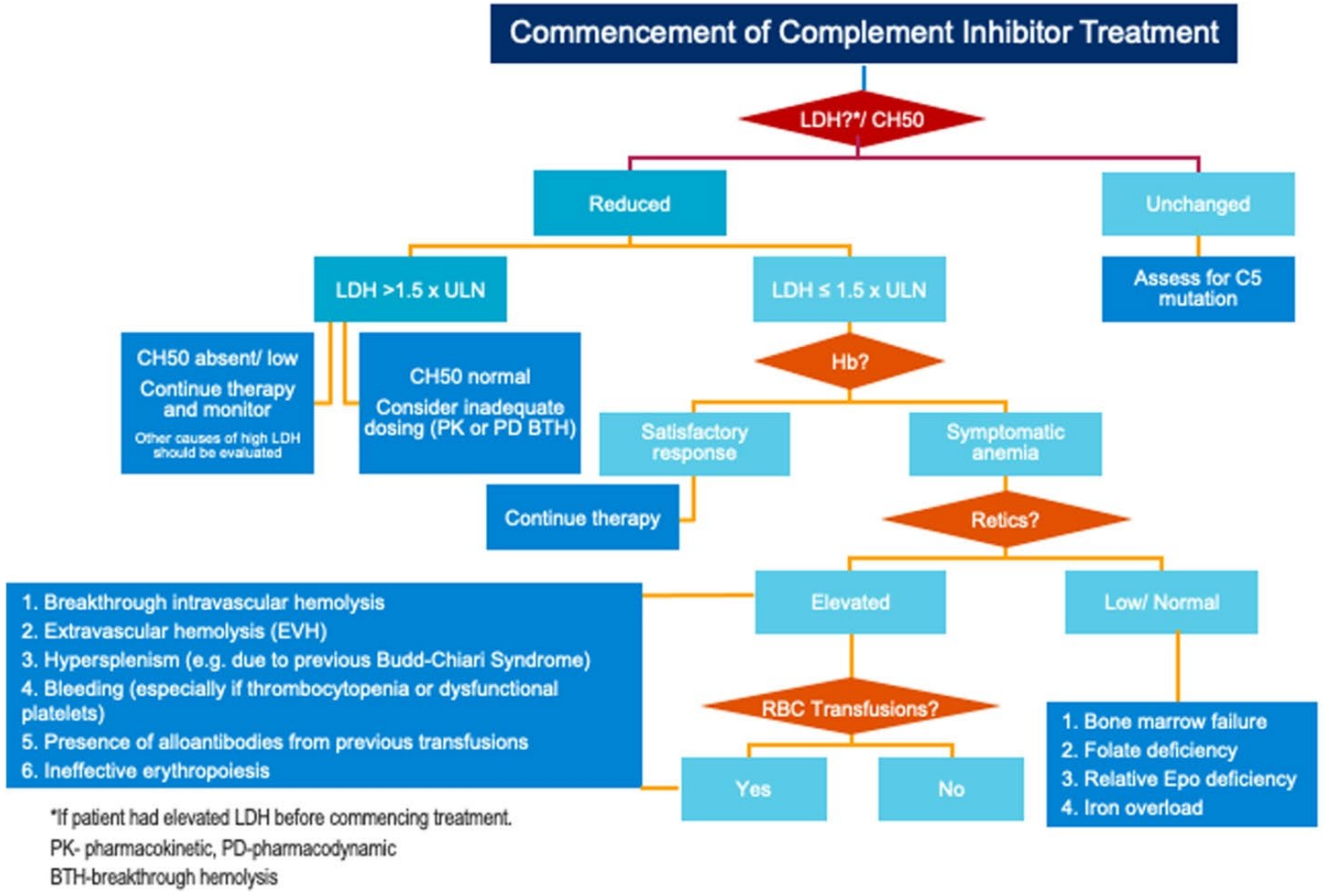
Complement inhibition PNH

ASSESSMENT OF PATIENTS ON A COMPLEMENT INHIBITOR



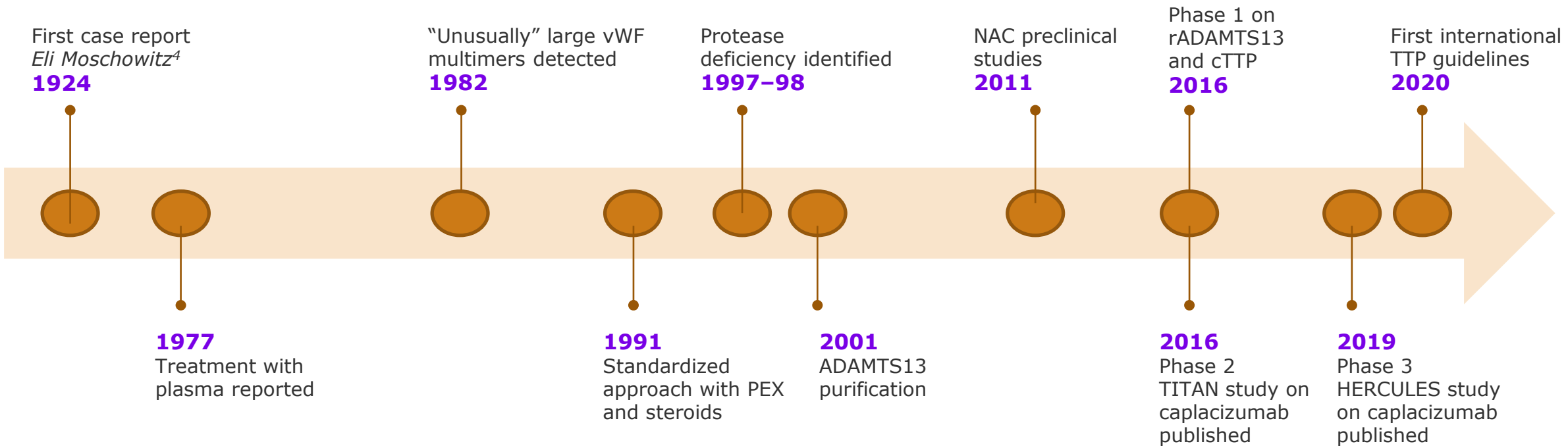
Causes of anemia on C5 inhibition	Suggested Action if symptomatic +/- transfusion dependent
LOW/ NORMAL RETICULOCYTE COUNT	
Bone Marrow Failure e.g. AA or MDS	Follow parallel concomitant recommendations for the underlying bone marrow failure
Folate deficiency	Folic acid supplementation
Relative erythropoietin deficiency	Exogenous erythropoietin supplementation
Iron overload	Iron chelation therapy
ELEVATED RETICULOCYTE COUNT	
Breakthrough intravascular hemolysis	Resolution of activating event/ additional dose of complement inhibitor/ dose adjustment
Clinically significant extravascular hemolysis	Consider proximal complement inhibition in clinical trials
Hypersplenism	Splenic embolization in selected cases
Bleeding	Directed to cause
Alloantibodies	Blood transfusion recommendations
Ineffective erythropoiesis e.g. MDS	Follow parallel concomitant recommendations for the underlying bone marrow failure

AA- aplastic anemia, MDS-myelodysplastic syndrome

Kulasekararaj, A.G., Brodsky, R.A. and Hill, A. (2021), Monitoring of patients with paroxysmal nocturnal hemoglobinuria on a complement inhibitor. Am J Hematol, 96: E232-E235. https://doi.org/10.1002/ajh.26176

Thrombotic Thrombocytopenic Purpura

Evolution of Therapeutic Strategies and Knowledge[1–3]



~100 years from the first case: evolution prognostic, morbidity, quality of life

Adapted with permission from: Masias C, et al. *Res Pract Thromb Haemost*. 2017;2(1):19–6.

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; cTTP, congenital thrombotic thrombocytopenic purpura; NAC, N acetylcysteine; PEX, plasma exchange; rADAMTS13, recombinant ADAMTS13; vWF, von Willebrand factor.

1. Masias C, et al. *Res Pract Thromb Haemost*. 2017;2(1):19–6; 2. Zheng XL, et al. *J Thromb Haemost*. 2020;18(10):2496–502; 3. Scully M, et al. *N Engl J Med*. 2019;380(4):335–46;
4. Moschcowitz E. *Proc NY Pathol Soc*. 1924;24:21–4.

Preclinical TTP Diagnosis Scores

PLASMIC SCORE[1–3]

Parameter	Score
Platelet count <30 x10^9 /L	+1
Serum creatinine level <2.0 mg/dL	+1
Evidence of hemolysis: Indirect bilirubin >2.0 mg/dL *or* reticulocyte count >2.5% *or* undetectable haptoglobin	+1
No active cancer in previous year	+1
No history of solid organ or stem cell transplantation	+1
INR <1.5	+1
MCV <90 fL (<9.0 x 10^{-14}/L)	+1
Likelihood of severe ADAMTS13 deficiency	**Low risk – 0 to 4**: 0–4% **Intermediate risk – 5**: 5–24% **High risk – 6 to 7**: 62–82%

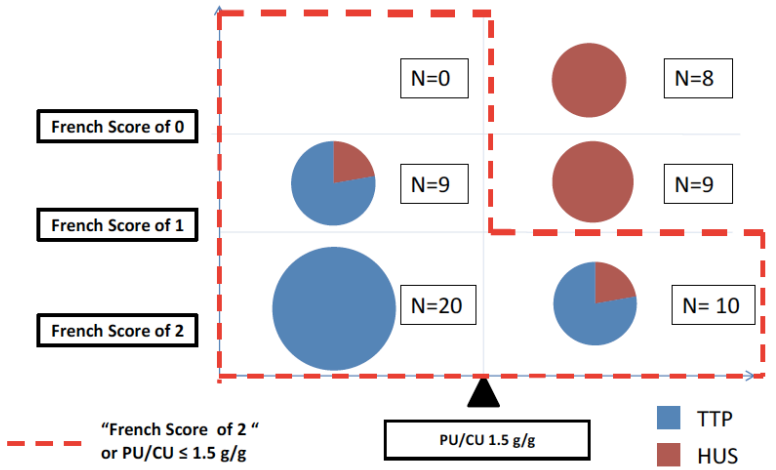
FRENCH SCORE[1–3]

Parameter	Score
Platelet count <30 x10^9 /L	+1
Serum creatinine level <2.0 mg/dL	+1
Prediction of severe ADAMTS13 deficiency (activity <10%) based on score	**0**: 2% **1**: 70%

New Score: French score 2 plus or 1 plus ratio <1.5 g/g sensitivity to 99.6% (95% CI: 93, 100)[4]

TTP versus HUS:

- French Score and proteinuria/creatinine in urine
- Ratio <1.5 g/g, **77% sensitivity** (95% CI: 63, 94)
- Ratio <1.5 g/g, **90% specificity** (95% CI: 71, 100)



ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; CI, confidence interval; HUS, hemolytic and uremic syndrome; INR, prothrombin time; MCV, mean corpuscular volume; PU/CU, proteinuria/creatininuria ratio; TTP, thrombotic thrombocytopenic purpura. Tables reproduced with permission from Elsevier. Figure reproduced with permission from: Burguet L, et al. *J Clin Med*. 2022;11(3):648. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8836555/. Copyright © 2022 by the authors. Licenced under CC BY-NC-ND 4.0 DEED https://creativecommons.org/licenses/by/4.0/.

1. Coppo P, et al. *Res Pract Thromb Haemost*. 2019;3(1):26-37; 2. Zheng XL, et al. *J Thromb Haemost*. 2020;18(10):2486–95; 3. Bendapudi PK, et al. *Lancet Haematol*. 2017;4(4):e157–e164; 4. Burguet L, et al. *J Clin Med*. 2022;11(3):648.

New TTP Outcomes Definitions

Category	Outcomes	Definition	Management Implications
Remission	Clinical remission	Sustained clinical response with either no TPE and no anti-vWF therapy for ≥30 days or with attainment of ADAMTS13 remission (partial or complete), whichever occurs first	**Post-remission implications** • ADAMTS13 remission (partial or complete) is always accompanied by clinical remission • However, clinical remission may occur with or without an ADAMTS13 remission • Patients in clinical remission who do not achieve an ADAMTS13 remission or who experience an ADAMTS13 relapse are at increased risk of clinical relapse • In such patients, pre-emptive immunosuppression (e.g., rituximab) may be used to attain an ADAMTS13 remission, thereby reducing the risk of clinical relapse
	Partial ADAMTS13 remission	ADAMTS13 activity ≥20% to <LLN	
	Complete ADAMTS13 remission	ADAMTS13 activity ≥LLN	
Relapse	Clinical relapse	After a clinical remission, platelet count decreases to $<150x10^9$/L (with other causes of thrombocytopenia ruled out), with or without clinical evidence of new ischemic organ injury. A clinical relapse must be confirmed by documentation of severe ADAMTS13 deficiency	
	ADAMTS13 relapse	After an ADAMTS13 remission (partial or complete), the ADAMTS13 level decreases to <20%	

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; LLN, lower limit of normal; TPE, therapeutic plasma exchange; vWF, von Willebrand factor; TTP, thombotic thromboctyopenic purpura. Table reproduced with permission from Elsevier.

Cuker A, et al. *Blood*. 2021;137(14):1855–61.

Treatment Strategies for TTP

Treatments aim to prevent production of *and/or* eliminate autoantibodies, supplement ADAMTS13, and prevent thrombus formation

Immunomodulators: Elimination of antibodies

- **T cell:** *ciclosporin A, mycofenolate, azathioprin*
- **B cell:** *rituximab*
- **Plasma cell:** *steroids, bortezomib*
- Plasma exchange
- Splenectomy

ADAMTS13 Supplement

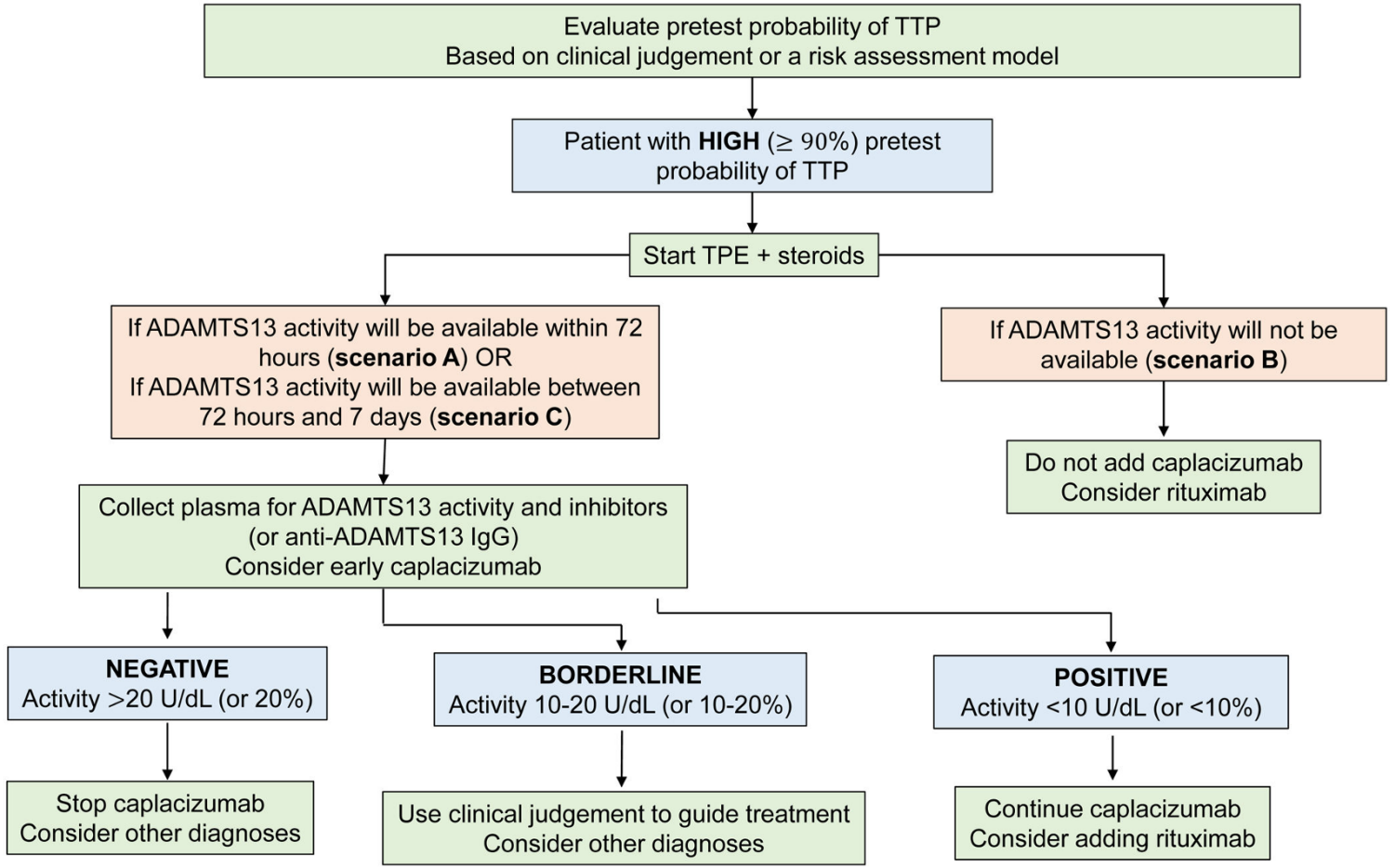
- Plasma exchange
- Recombinant ADAMTS13 (trial)

Inhibition: Platelet/vWF

- Caplacizumab
- N-acetilcistein
- Aptamer

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; TTP, thombotic thromboctyopenic purpura; vWF, von Willebrand factor.
Coppo P, et al. *Res Pract Thromb Haemost*. 2019;3(1[26-37]

Guidelines for TTP: International Society of Thrombosis and Hemostasis (ISTH)



ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; IgG, immunoglobulin G; TTP, thombotic thromboctyopenic purpura.

Zheng XL, et al. *J Thromb Haemost.* 2020;18(10):2486–95.

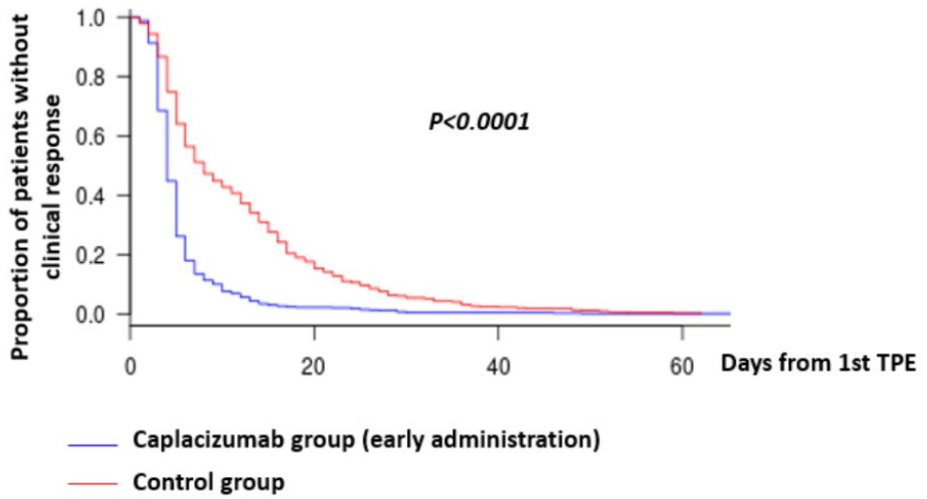
The Capla 500+ Project: An International, Real-World Study (TTP-IWG)

To understand the optimal timing of frontline caplacizumab initiation, and the impact on unfavorable outcomes and mortality

Caplacizumab group	Control group	Primary endpoint
Treated with daily TPE, caplacizumab and immunosuppression with corticosteroids ± rituximab (N=942)	Randomly selected in a 2:1 ratio, treated with TPE and immunosuppression (N=495)	3-month survival post first TPE

- **3-month survival post first TPE was 98.6% versus 93.3%** (p<0.0001), between caplacizumab and control groups, respectively
- Failure to achieve clinical response was **5x less likely in the caplacizumab group** compared to the control group (95% CI, 0.1-0.37, p<0.0001)
- Unfavorable outcomes were **infrequent** with early caplacizumab initiation (within 3 days), and time to clinical response in survivors was **half the time** compared to control group survivors (p<0.0001)
- Caplacizumab-related AEs occurred in 220 patients (23%)

Cumulative daily rate of event (clinical response)-free survival after first TPE within 3 months

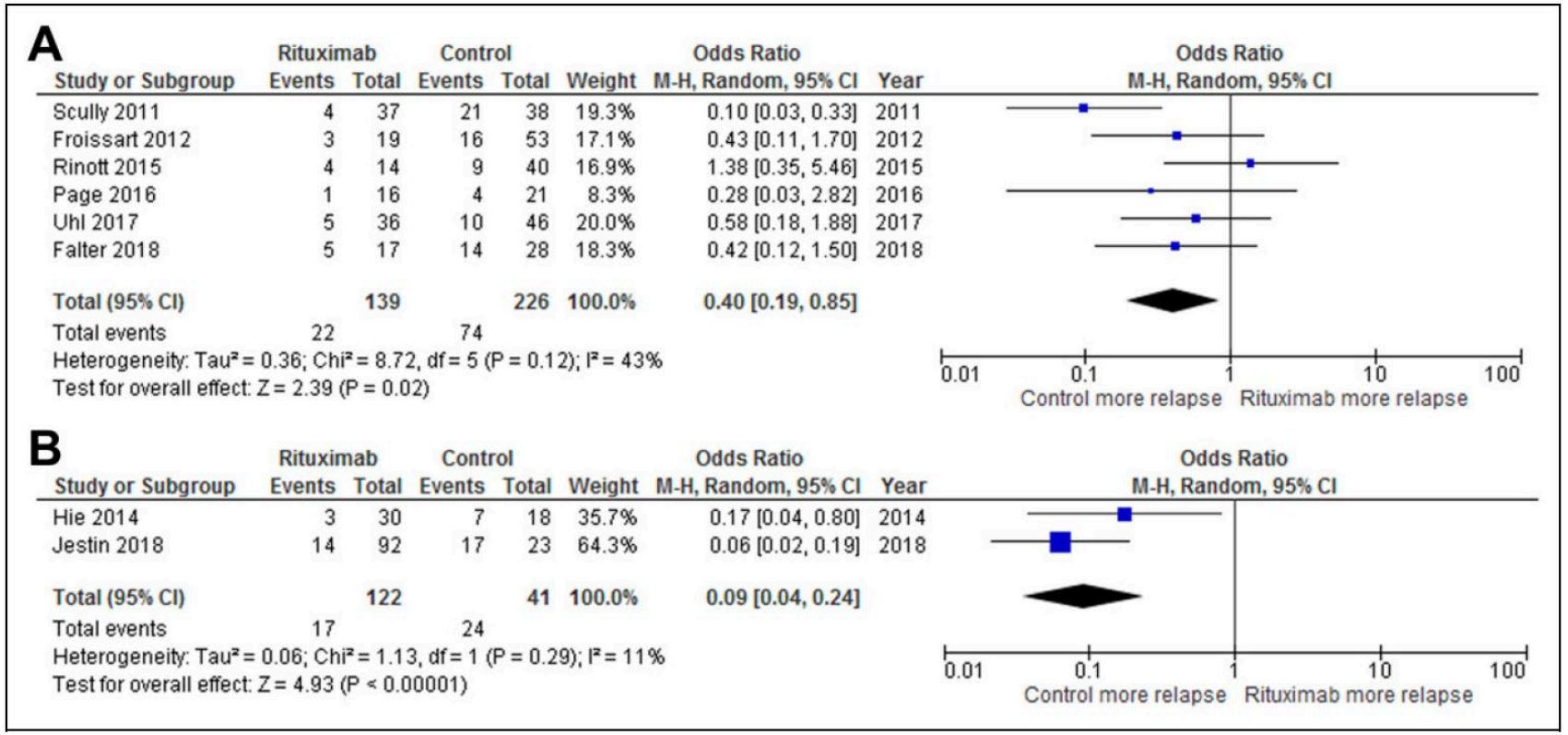


Timely addition of caplacizumab to TPE and immunosuppression prevents unfavorable outcomes during the acute phase of iTTP, and alleviates burden of care at the potential expense of rare, major bleeding events

•Adult patients from 10 countries; †Random selection between 2015–2018. AE, adverse event; CI, confidence interval; iTTP, immune thrombotic thrombocytopenia purpura; TPE, therapeutic plasma exchange; TTP-IWG, Thrombotic Thrombocytopenic Purpura International Working Group. Figure reproduced with permission from: Coppo P, et al. The 65th Annual Meeting of American Society of Hematology (ASH), San Diego, CA, USA, Dec 8–10, 2023. Poster 2636.

How Can We Reduce the Risk of Relapse?

Rituximab reduces the risk of relapse as first-line prophylaxis:



Note: Rituximab is not indicated for the treatment of immune thrombotic thrombocytopenic purpura (iTTP).

CI, confidence interval; M-H, Mantel-Haenszel.

MAYARI Study

The **efficacy and safety of caplacizumab in combination with immunosuppressive therapy without first-line therapeutic plasma exchange** is currently being evaluated in adults with iTTP…

MAYARI

Status:
Currently recruiting

A **Phase 3, single-arm, open-label, multicenter** study in adults experiencing an **acute episode of iTTP**

Anticipated **study duration** per participant without a recurrence while on therapy is **maximum 24 weeks**

- (i.e., approximately 1 day for screening + maximum 12 weeks of treatment for the presenting episode + 12 weeks of follow-up)

iTTP, immune thrombotic thrombocytopenia purpura.

Gunawardena S, et al. ASH, New Orleans, December 10-13, 2022.