PNH: Understanding Your Disease and Treatment Options

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PNH: What's in a Name

- It is not paroxysmal[1]
  - Even in the absence of symptoms, destructive progression of hemolysis is ongoing
- It is not nocturnal[1]
  - Hemolysis in PNH is subtle and constant, 24 hours a day
- Hemoglobinuria is a less commonly seen complication
  - ¾ patients present without hemoglobinuria[2]

1. Rother R *et al. Nature Biotechnology* 2007;25,11:1256–1264;
2. International PNH Interest Group. *Blood.* 2005;106:3699–3709.

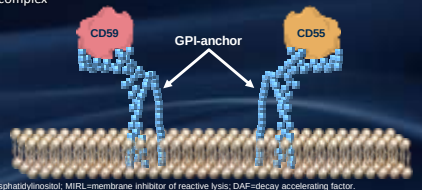
2

The Defect in PNH

PNH clones are defined as PNH cells with a deficiency of proteins that require a GPI anchor for attachment to the cell membrane[1]

CD59 (MIRL)
- Forms a defensive shield for red blood cells (RBCs) from complement-mediated lysis
- Inhibits the assembly of the membrane attack complex

CD55 (DAF)
- Prevents formation and augments instability of the C3 convertases, attenuating the complement cascade



GPI = glycerophosphatidylinositol; MIRL=membrane inhibitor of reactive lysis; DAF=decay accelerating factor.
1. Borowitz MJ *et al. Cytometry B Clin Cytom* 2010;78:211–230.
Adapted from: Johnson RJ *et al. J Clin Pathol: Mol Pathol* 2002;55:145–152; Brodsky R. Paroxysmal nocturnal hemoglobinuria. In: R Hoffman *et al*, eds. *Hematology - Basic Principles and Practices*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005;419–427.

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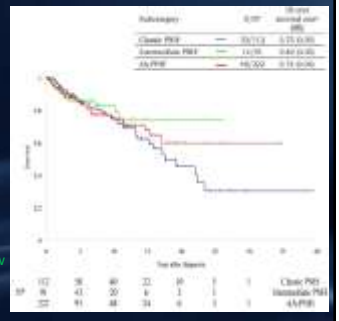
PNH Classification

- **Classic PNH**
  - Intravascular hemolysis
    - Reticulocytosis
    - Increased LDH
    - Increased indirect bilirubin
    - Low haptoglobin
- **PNH + Bone Marrow Disorder**
  - Intravascular hemolysis + AA/MDS/Myelofibrosis
- **Subclinical PNH**
  - No clinical/lab evidence of hemolysis
  - Detected by very sensitive flow cytometric analysis
  - In association with AA/MDS

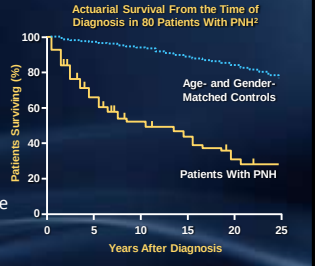


Parker et al. *Blood* 2005;106:3699-3709
de Latour et al. *Blood* 2008;112:3099-3106

4

Paroxysmal Nocturnal Hemoglobinuria (PNH): A Chronic, Systemic, and Life-Threatening Disease

- Prevalence: 15.9 / million[1]
- Diagnosed at all ages
  - Median age early 30s[3,4]
- Progressive disease[2–4]
  - Uncontrolled complement activation underlies the morbidities and mortality
- Despite best supportive care
  - 5 year mortality: 35%[2]



The expected survival of an age- and gender-matched control group is shown for comparison (Hillmen *et al.* 1995)

1. Hill A *et al. Blood* 2006;108:290a. Abstract 985; 2. Hillmen P *et al. N Engl J Med* 1995;333:1253–1258;
3. Nishimura JI *et al. Medicine* 2004;83:193–207; 4. Socié G *et al. Lancet* 1996;348:573–577.

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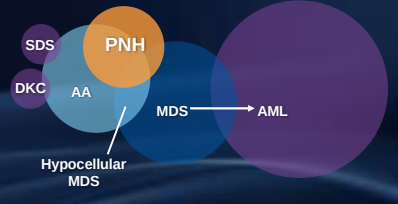
PNH and Other BMF Syndromes

PNH overlaps with BMF syndromes, and the predominant clinical characteristics can evolve over time[1,2]



AML, acute myelogenous leukaemia; AA, aplastic anaemia; DKC, dyskeratosis congenita; MDS, myelodysplastic syndrome; SDS, Shwachman-Diamond syndrome.
Young NS, et al. *Blood* 2006;108(8):2509-2519. 2. Weinzierl EP, et al. *Am J Clin Pathol.* 2013;139(1):9-29.

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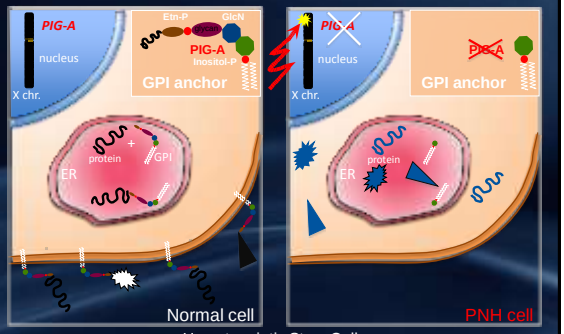
Paroxysmal Nocturnal Hemoglobinuria
Pathogenesis



Hematopoietic Stem Cells

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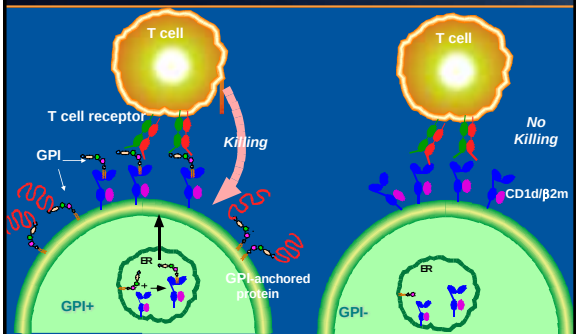
Hypothesis: GPI-specific, CD1d-restricted T cells responsible for selection of PNH cells



Karadimitris and Luzzatto, *Leukemia* 2001

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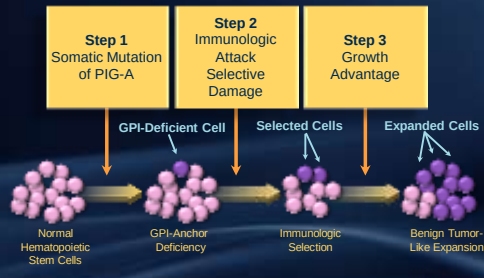
Expansion of the PNH Clone Is Necessary to Result in Clinical PNH



- Expansion may be due to another somatic mutation
- The need for both selection and expansion may explain the rarity of PNH

Adapted from: Inoue N *et al. Int J Hematol* 2003;77:107.

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The Role of Complement

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The Complement System: Always on, Strongly Amplified, Dependent on Natural Regulators

The complement system is a vital component of the natural (innate) protective immune system[1]

- Complement is activated by three mechanisms (classical, alternative, and lectin) which allow the system to respond to inflammatory, infectious, ischemic, necrotic, as well as foreign and self antigens
- Always 'on' to allow rapid immune response[1]
  - Rapid amplification leads to powerful and destructive immune reactions[2]
  - Natural inhibitors of complement keep amplification in check and prevent uncontrolled complement activation[2]

1. Holers VM *et al. Immunol Rev* 2008;223:300–316; 2. Zipfel PF *et al. Curr Opin Nephrol Hypertens* 2010;4:372–378.

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Factors That Amplify Complement Activation

Glovsky MM *et al. Ann Allergy Asthma Immunol* 2004;93:513–523; Rubio MT *et al. Bone Marrow Transplant* 2008;41(Suppl. 1):S220. Abstract P766; Mastellos D *et al. Immunologic Res* 2003;3:367–385; Mergenhagen STE *et al. J Infect Dis* 1973;128:S86: Chenoweth DE *et al. N Engl J Med* 1981;304:497–503: Giradi G. *Am J Reprod Immunol* 2008:59:183–192.

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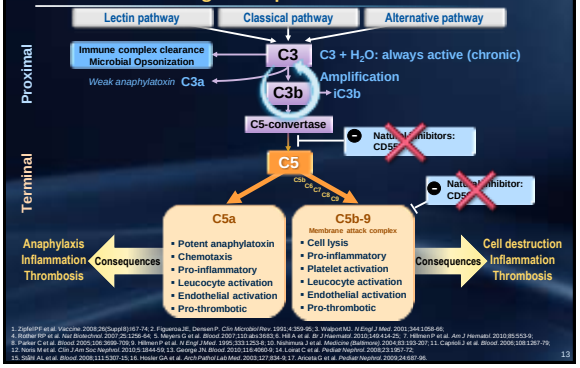
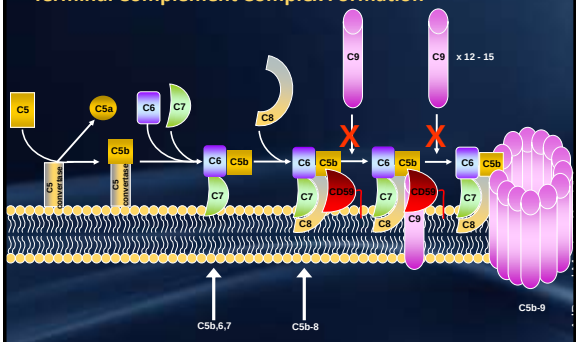
Chronic Uncontrolled Complement Activation Leads to Devastating Consequences in PNH



1. Zipfel PF *et al. Vaccine* 2008;26(Suppl 8):H67–74; 2. Figueroa JE, Densen P. *Clin Microbiol Rev* 1991;4:359–95; 3. Walport MJ. *N Engl J Med* 2001;344:1058–66; 4. Rother RP *et al. Nat Biotechnol* 2007;25:1256–64; 5. Meyers G *et al. Blood* 2007;110:abs3683; 6. Hill A *et al. Br J Haematol* 2010;149:414–25; 7. Hillmen P *et al. Am J Hematol* 2010;85:553–9; 8. Parker C *et al. Blood* 2005;106:3699–709; 9. Hillmen P *et al. N Engl J Med.* 1995;333:1253–8; 10. Nishimura J *et al. Medicine (Baltimore)* 2004;83:193–207; 11. Capitoli J *et al. Blood.* 2006;108:1267–79; 12. Nona M *et al. Clin J Am Soc Nephrol.* 2010;5:1844–59; 13. George JN. *Blood.* 2010;116:4060–9; 14. Loirat C *et al. Pediatr Nephrol.* 2009;23:1957–72; 15. Stănă AL *et al. Blood.* 2008;111:5307–15; 16. Hosler GA *et al. Arch Pathol Lab Med.* 2003;127:834–9; 17. Aricata G *et al. Pediatr Nephrol.* 2009;24:687–98.

Absence of CD59 Allows Terminal Complement Complex Formation



Adapted from: Cellular and Molecular Immunology AK Abbas, AH Litchman and JS Pober, 3rd Edition. 1991 WB Saunders; Philadelphia.

Historically Viewed as a Hemolytic Anemia

Normal red blood cells (RBCs) are protected from complement attack by a shield of terminal complement inhibitors

Without this protective complement inhibitor shield, PNH RBCs are destroyed

Complement Activation

Lack of Bound CD55, CD59 Leads to Uncontrolled Complement Activation

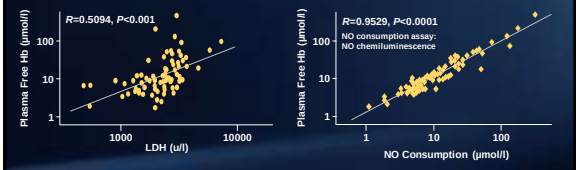
Intact RBC

Reduced Red Cell Mass

Free Hemoglobin

1. International PNH Interest Group. *Blood* 2005;106:3699–3709. 2. Brodsky R Paroxysmal Nocturnal Hemoglobinuria. In: *Hematology - Basic Principles and Practices*. 4th ed. R Hoffman, EJ Benz, S Shattil *et al.* eds. Philadelphia, PA: Elsevier Churchill Livingstone;2005;419–427. 3. Rother RP *et al. JAMA* 2005;293:1653–1662. 4. Socie G *et al. Lancet* 1996;348:573–577. 5. Hill A *et al. Br J Haematol* 2007;137:181–192.

Hemolysis Leads to NO Consumption in PNH Patients



- LDH significantly correlates with free hemoglobin (Hgb)[1]
  - Confirms LDH as a biomarker for hemolysis
  - LDH ≥1.5x at diagnosis had a 4.8-fold greater mortality[2]
- Free Hgb significantly correlates with NO consumption
  - Hgb is in reduced state and reactive with NO

1. Hill A *et al. Br J Haematol* 2010;149:414–425; 2. Lee JW *et al.* ASH 2011. Abstract 3166.

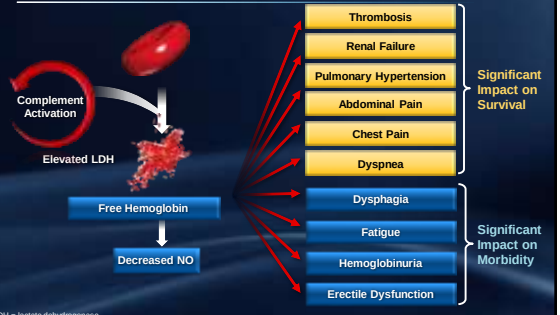
Consequences of Nitric Oxide (NO) Depletion

Reduced Nitric Oxide Can Cause

- Smooth muscle dystonias[1]
  - Vascular constriction – pulmonary and systemic hypertension, erectile dysfunction[2]
  - Gastrointestinal contractions – dysphagia, abdominal pain
- Platelet activation and aggregation[1–4]
  - Platelet hyperreactivity
  - Hypercoagulability

1. Rother R *et al. JAMA* 2005;293:1653–1662; 2. Hill A *et al. Br J Haematol* 2010;149:414–425; 3. Weitz I. *Thrombosis Res* 2010;125:S106–S107; 4. Helley D *et al. Haematologica* 2010;95:574–581.

Chronic Uncontrolled Complement Activation Leads to Devastating Consequences



LDH = lactate dehydrogenase.

1. International PNH Interest Group. *Blood* 2005;106:3699–3709; 2. Brodsky R. Paroxysmal nocturnal hemoglobinuria. In: R Hoffman *et al.* eds. *Hematology - Basic Principles and Practices*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005:419–427; 3. Rother RP *et al. JAMA.* 2005;293:1653–1662; 4. Socie G *et al. Lancet* 1996;348:573–577; 5. Hill A *et al. Br J Haematol* 2007;137:181–192; 6. Lee JW *et al. Hematologica* 2010;95(s2): Abstracts 505 and 506; 7. Hill A *et al. Br J Haematol* 2010;149:414–425; 8. Hillmen P *et al. Am J Hematol* 2010;85:553–559.

Historical Management of PNH

Supportive care options do not impact progression and risk for severe morbidities and mortality[1]

- Transfusions[1] – risk of iron overload
- Anticoagulants[1] – ineffective in many patients
- Red cell supplements[1] – may expand clone and elevate hemolysis
- Steroids/androgen hormones[1] – adverse events

Although BMT is the only potentially curative therapy for PNH, BMT is associated with significant morbidities and mortality[2,3]

- In a study examining PNH patients (n=23)[2]
  - 50% chronic GVHD; 42% acute GVHD[3]
  - Transplant-related mortality was 42%
- BMT has a significant impact on quality of life (QoL) post-transplant[4,5]

1. International PNH Interest Group. *Blood* 2005;106:3699–3709; 2. Santaraone S *et al. Haematologica* 2010;95:983–988; 3. de Latour PF *et al.* EBMT 2009:Abstract 316; 4. Bieri S *et al. Bone Marrow Transplant* 2008;42:819–827; 5. Fraser CJ *et al. Blood* 2006;108:2867–2873.

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Morbidities and Mortality in PNH

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Thrombosis

Thrombosis Is the Leading Cause of Death in PNH[1]

- Accounts for 40–67% of deaths[2]
  - First thrombotic event (TE) can be fatal[2,3]
  - First TE increases risk for death 5- to 10-fold[2]
- Up to 44% of patients experience clinical thrombotic events[2]
- Occurs in typical and atypical sites[4]
- Is not adequately managed with anticoagulation[2]
- All patients with PNH are at risk for thrombosis[2]

1. International PNH Group *et al. Blood* 2005;106:3699–3709; 2. Hillmen *et al. Blood* 2007;110:4123–4128; 3. Audebert HJ *et al. J Neurol* 2005;252:1379–1386; 4. Lee JW *et al. Hematologica* 2010;95(s2): Abstract 506.

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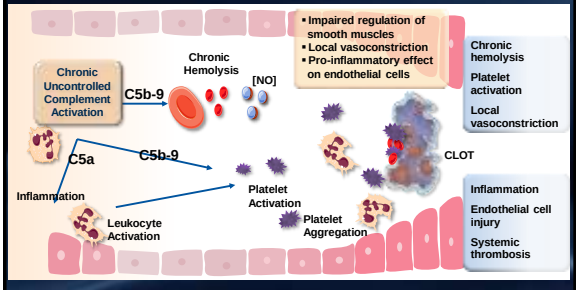
Thrombosis

Chronic Uncontrolled Complement Activation Leads to Vasoconstriction and Thrombosis

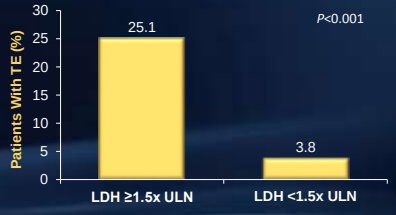


Adapted from: Gladwin MT *et al. Free Rad Biol & Med* 2004;36:707–717; Rother RP *et al. JAMA* 2005;293:1653–1662.

22

Thrombosis

The Incidence of TE is Increased in Patients with Elevated LDH at Diagnosis



- Univariate analysis showed that the incidence of TE was significantly increased in patients with LDH ≥1.5x ULN at diagnosis (43/171; 25.1%) compared with patients with LDH <1.5x ULN (2/53; 3.8%; OR 8.57)

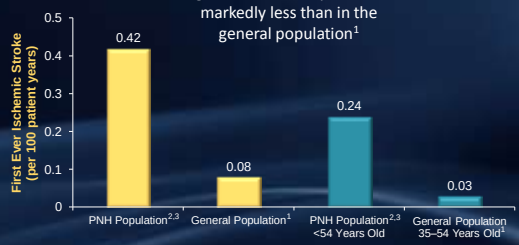
Data from South Korean National Registry. Lee JW *et al.* Presented at the 54th Annual Meeting of the American Society of Hematology: December 8–11, 2012; Atlanta, GA. Abstract 1273.

23

Thrombosis

Risk of First Ever Ischemic Stroke (FEIS) Elevated in PNH

Age of FEIS in PNH patients is markedly less than in the general population[1]



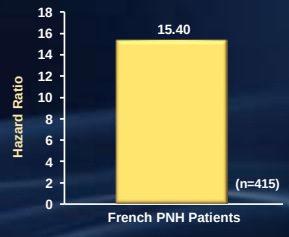
1. Gostynski M *et al. J Neurol* 2006;253:86–91; 2.Hillmen P *et al. Blood* 2007;110:4123–4281; 3. Data on file. Alexion Pharmaceuticals, Inc.

24

Thrombosis

Thrombosis is Associated With Risk of Early Mortality

TE increases risk of death 15-fold over patients with no TE



- TE was an independent prognostic factor related to poor survival (HR 15.4; 95% CI 9.3–25.4; *P*<0.001) in a large cohort of French PNH patients

de Latour RP *et al. Blood* 2008;112:3099–3106.

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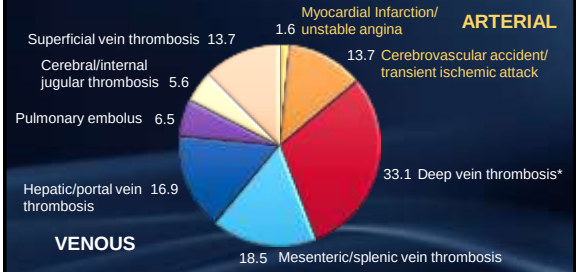
Thrombosis

Thrombosis Occurs in Both Typical and Atypical Sites*



*124 events, 63 patients

*Includes 18.5% lower extremity and 14.5% other (inferior vena cava, bilateral lower extremity, pelvic, ureter, axillary, subclavian, and brachiocephalic veins).

Hillmen P *et al. Blood* 2007;110:4123–4128.

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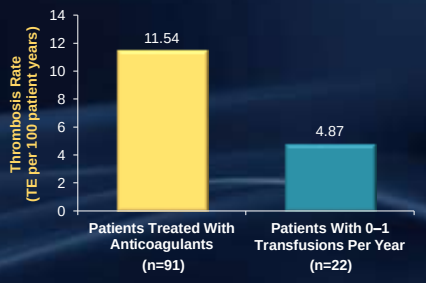
Thrombosis

PNH Patients are at Risk of Thrombosis Despite Anticoagulation or Minimal Transfusion Requirements



Hillmen P *et al. Blood* 2007;110:4123–4128.

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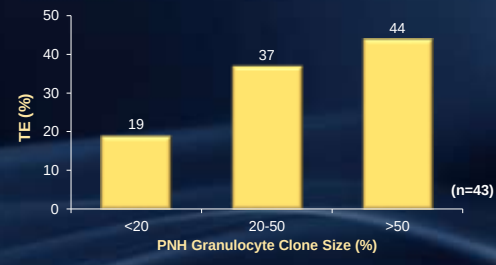
Thrombosis

Thrombosis Can Occur Regardless of Clone Size



Data from South Korean National Registry.
Lee JW *et al. Hematologica* 2010;95(s2): Abstract 505.

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Chronic Kidney Disease

Chronic Kidney Disease: Morbidity and Mortality in PNH

- Kidney failure is the cause of 8–18% of PNH-related deaths[1]
- 80% of PNH patients (median age of 31.5 years) had MRI evidence of significant renal hemosiderosis[2,3]
  - Marked hemosiderin deposits in the proximal renal tubule are a common feature in all autopsy and biopsy reports dealing with PNH
  - Demonstrable by MRI even when no overt hemoglobinuria is seen

1. Hillmen P, et al. *Am J Hematol* 2010;85:553–559; 2. Brodsky R. Hematology: Paroxysmal nocturnal hemoglobinuria. In: R Hoffman et al, eds. *Hematology - Basic Principles and Practices*. 4th ed. Philadelphia, PA: Elsevier Churchill Livingstone 2005;419–427. 3. Hill A. et al. *Blood* 2006;108: Abstract 979.

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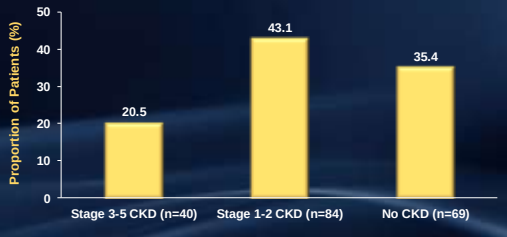
Chronic Kidney Disease

64% of PNH Patients Exhibit Clinical Chronic Kidney Disease (CKD)



1. Hillmen P *et al. Am J Hematol* 2010;85:553–559.

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Chronic Kidney Disease

Kidney Disease in PNH: Conclusions

- Kidney failure is the cause of 8–18% of PNH-related deaths[1]
- Kidney disease in PNH is caused by complement-mediated hemolysis[2,3]
- 64% of patients with PNH exhibit chronic kidney disease at any one time[4]
- Kidney disease is underappreciated in PNH[4]

1. Nishimura JI *et al. Medicine* 2004;83:193–207; 2. Clark DA *et al. Blood* 1981;57:83–89; 3. McKeage K. *Drugs* 2011;71:2327–2345; 4. Hillmen P *et al. Am J Hematol* 2010;85:553–559; 5. Kim JS *et al. Hematologica* 2011;96(s2): Abstract 271.

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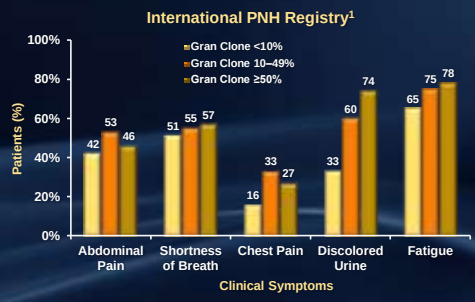
Common Symptoms of PNH

Clone Size Does Not Correlate to Symptom Severity



1. Urbano-Ispizua A *et al. Hematologica* 2010;95(s2): Abstract 1022.

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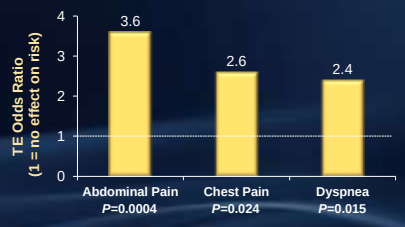
Common Symptoms of PNH

Common PNH Symptoms are Associated With TE



Elevated LDH (≥1.5× ULN) in combination with abdominal pain, chest pain, and dyspnea are associated with a higher risk of TE

Study description: a retrospective analysis of the medical charts of 286 PNH patients in a South Korean National Registry.
Lee JW *et al. Hematologica* 2010;95(s2): Abstracts 505 and 506.

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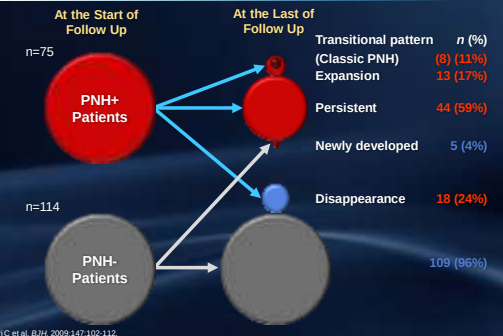
PNH Clonal Expansion in an AA Representative Population



Sugimori C et al. *BJH.* 2009;147:102-112.

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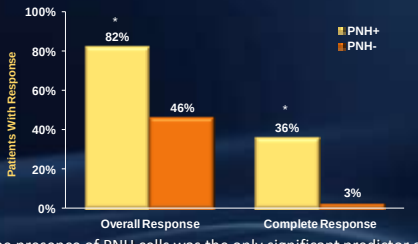
AA

Immunosuppressive Therapy (IST) Has Increased Efficacy in AA Patients With PNH Cells



- The presence of PNH cells was the only significant predictor of response to IST in 140 AA patients ($P<0.01$) in multivariate analysis[2]

Complete response (CR) was defined as hemoglobin normal for age, neutrophil count more than 1.5 × 10^9/L, and platelet count more than 150 × 10^9/L; Partial response (PR) was defined as transfusion independent and no longer meeting criteria for severe disease in patients with severe AA.[1] Overall response = CR + PR

*P value = complete response, P=0.03; Overall response, P<0.001.

1. Sugimori C *et al. Blood* 2006;107:1308–1314; 2. Sugimori C *et al. Exp Hematol* 2007;35:13–20.

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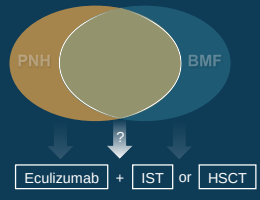
Management of Patients With Overlapping Signs and Symptoms

- Some patients may present with elements of both PNH and BMF, with the clinical picture evolving over time[1]
- Targeted treatments should address both haemolysis and BMF[1,2]

Treatment algorithm[3-5]



1. Luzzatto L, et al. *Br J Haematol.* 2011;153(6):709-720. 2. Parker CJ. *Hematology Am Soc Hematol Educ Program.* 2011;2011:21-29. 3. de Latour R, et al. *Rev Med Interne.* 2010;31(3):200-207.

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36

RA-MDS

Evidence of PNH Cells in RA-MDS

EXPLORE TRIAL Patient Population Description	RA-MDS (n=1293)
PNH cells/clone (Grans + RBC type III) > 0.01%	17.16% (222 / 1293)
WBC PNH clone ≥ 1%	1.54% (20 / 1293)
Clone ≥1% and LDH > ULN	40.0% (8 / 20)
WBC PNH Clone size ≥ 1%	
Mean clone	32.19% (n=20)

- Interim Results from EXPLORE, a Multi-center Prevalence Study of PNH Clone Size in Patients with AA, MDS, and other BMF

Galili N *et al.* Poster presentation at: American Society of Clinical Oncology 45th Annual Meeting; May 29–June 2, 2009; Orlando, FL.

37

Unexplained Cytopenias

Patients With Unexplained Cytopenias are at High Risk for PNH[1]

Test the Following Cytopenic Patients for PNH[5,6]

Unexplained Cytopenia
- After thorough work-up

Cytopenia and Evidence of Hemolysis
- LDH
- Haptoglobin
- Reticulocyte count (with or without anemia)

Cytopenia With Any of These Coexisting Findings
- Thrombosis
- Anemia
- Coombs-negative hemolytic anemia
- Bone marrow failure disorder
- Hemoglobinuria (dark colored urine)

*0.01% PNH cell threshold.

1. Movalia MK *et al. Blood* 2011;118: Abstract 1033; 2. Barzi A, Sekeres MA. *Clev Clin J Med* 2010;77:37–44; 3. Jordan MB *et al. Blood* 2011;118:4041–4052; 4. Moreno C *et al. Blood* 2010;116:4771–4776; 5. Borowitz MJ *et al*; Clinical Cytometry Society. *Cytom B Clin Cytom* 2010;78B:211–230; 6. Brodsky RA. *Blood* 2009;113:6522–6527.

38

How Do You Test for PNH?

39

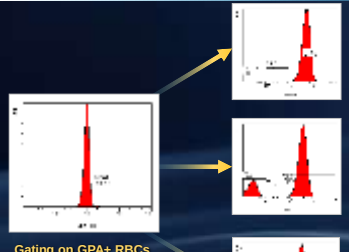
Standard Diagnostic Test for PNH

- Flow cytometry performed on peripheral blood
- Granulocytes and at least one additional cell line should be evaluated
  - RBCs
  - Monocytes
- Quantitative results
  - Optimal–high sensitivity analysis: ≥0.01%
  - Routine analysis: ≥1%
- Easy to understand PNH reports
- Use more than one reagent against GPI-anchored proteins

Borowitz MJ *et al.*; Clinical Cytometry Society. *Cytom B Clin Cytom* 2010;78B:211–230.

40

Testing for PNH in RBCs



Patient 1:
Normal RBCs with normal CD59 expression (Type I cells)

Patient 2:
PNH clone with complete CD59 deficiency (Type III cells)

Patient 3:
PNH clone with complete CD59 deficiency (Type III cells) and partial CD59 deficiency (Type II cells)

GPA = glycophorin A.
Data Source: Dahl-Chase Diagnostic Services.

41

Why Look Beyond RBCs for PNH?

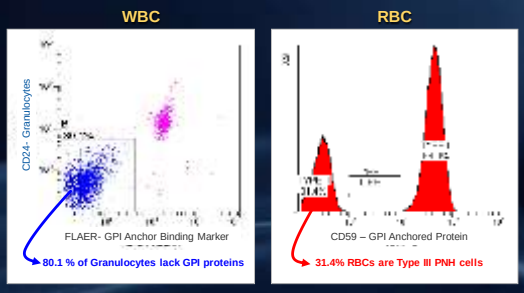
- Granulocytes provide more accurate representation of PNH clone size[1]
- Percentages of PNH RBCs may be affected by:
  - Hemolysis
  - Blood transfusion

PNH reports should provide quantitative results expressing clone size on both granulocytes and RBCs

1. Borowitz MJ *et al*; Clinical Cytometry Society. *Cytom B Clin Cytom* 2010;78B:211–230.

42

PNH Patient With an 80% WBC Clone Size and 31% RBC Clone Size Indicating Hemolysis



Data Source: Dahl-Chase Diagnostic Services.

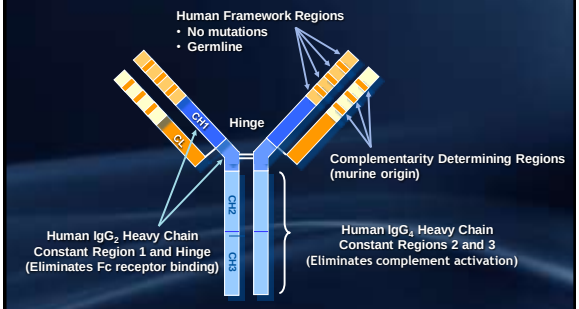
ICCS Recommendations for Follow-Up Testing of Patients With an Identified PNH Clone

- Annual monitoring[1]
  - Stable patients
  - Patients with aplastic anemia and small PNH clone
  - Patients with refractory cytopenia with unilineage dysplasia (RCUD) and small PNH clone
- More frequent monitoring to evaluate for expanding clones
  - Patients with changing symptoms or lab values
  - Patients in early stages of treatment

1. Borowitz MJ *et al.*; Clinical Cytometry Society. *Cytom B Clin Cytom* 2010;78B:211–230.

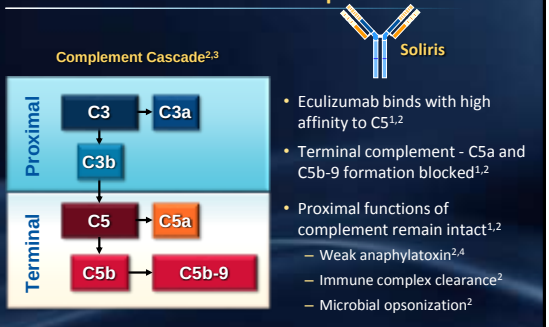
Treatment of PNH with Complement Inhibitor Eculizumab

Eculizumab (soliris) Humanized First in Class Anti - C5 Antibody



Rother R et al. Nat Biotech 2007;25:1256

Eculizumab Blocks Terminal Complement[1,2]



- Eculizumab binds with high affinity to C5[1,2]
- Terminal complement - C5a and C5b-9 formation blocked[1,2]
- Proximal functions of complement remain intact[1,2]
  - Weak anaphylatoxin[2,4]
  - Immune complex clearance[2]
  - Microbial opsonization[2]

Please see full prescribing information for Soliris® (eculizumab).
1. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012; 2. Rother RP *et al. Nature Biotech* 2007;25:1256–1264; 3. Walport MJ. *N Engl J Med* 2001;344:1058–1066; 4. Figueroa JE, Densen P. *Clin Microbiol Rev* 1991;4:359–395.

Clinical Trials With Eculizumab

Pilot Study – *NEJM* 2004
N=11
Primary endpoint: reduction of hemolysis

TRIUMPH – *NEJM* 2006
Pivotal Phase III, Double-Blind, Placebo-Controlled Trial, N=87

SHEPHERD – *Blood* 2008
Broader patient population, including those receiving minimal transfusions or with thrombocytopenia, N = 97

Long-Term Extension Trial Hillmen *Blood* 2007
Evaluated long-term safety, efficacy and effect on thrombosis; Placebo patients switched to eculizumab
N=187

Please see full prescribing information for Soliris® (eculizumab).
Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012.

Eculizumab is a Chronic Treatment for a Chronic Disease

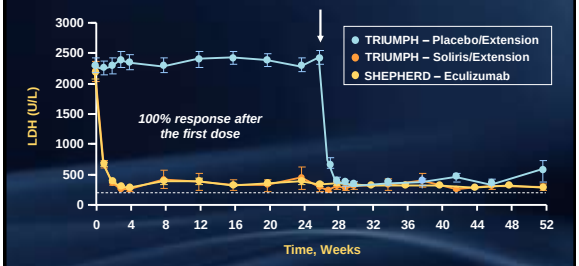
Soliris PNH Dosing Schedule											
Pretreatment		Induction Phase				Maintenance Phase					
≥2 weeks before induction	Week →	1	2	3	4	5	6	7	8	9	q14d
Neisseria meningitidis vaccination	Soliris dose, mg	600	600	600	600	900	X	900	X	900	

Dose within ±2 days.

- In clinical trials all patients were vaccinated against *Neisseria meningitidis*[1]
- Concomitant medications allowed:
  - Steroids, immunosuppressant drugs, anti-clotting agents and hematinics[2]
- Eculizumab should be administered via IV infusion within 25-45 minutes every 7 days during induction and every 14 days during maintenance[1]
- Eculizumab dose adjustment to every 12 days may be necessary for some patients to maintain LDH reduction[1]

Please see full prescribing information for Soliris® (eculizumab).
1. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012. 2. Hillmen P *et al. N Engl J Med* 2004;350:552–559.
49

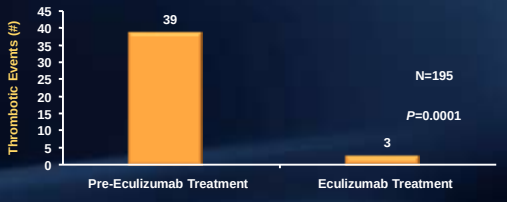
86% Reduction in LDH: TRIUMPH and SHEPHERD



- TRIUMPH placebo patients switched to Eculizumab after Week 26
- All TRIUMPH patients entered the long-term extension study

P<0.001 at all measured time points.
Please see full prescribing information for Soliris® (eculizumab). Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012.
Hillmen P *et al. Blood* 2007;110:4123–4128.
50

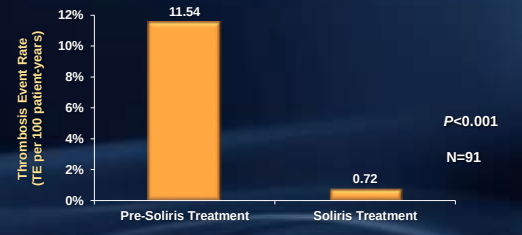
92% Reduction in Thrombotic Events



- 63% of patients received concomitant anticoagulants[1]
- The effect of anticoagulant withdrawal was not studied[2]
- Events observed in both venous and arterial sites[3]
- There were fewer thrombotic events with Eculizumab treatment than during the same period of time prior to treatment[2]

Please see full prescribing information for Soliris® (eculizumab).
1. Brodsky R *et al. Blood* 2008;111:1840–1847; 2. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012;
3. Hillmen P *et al. Blood* 2007;110:4123–4128.
51

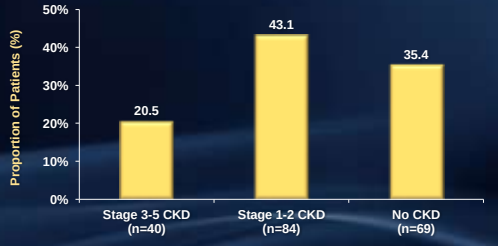
Eculizumab Reduced Thrombosis in Patients Treated with Anticoagulants[1]



94% reduction in event rate with Eculizumab

*Excludes patients on antiplatelet agents.
Please see full prescribing information for Soliris® (eculizumab). Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012.
1. Hillmen P *et al. Blood* 2007;110:4123–4128.
52

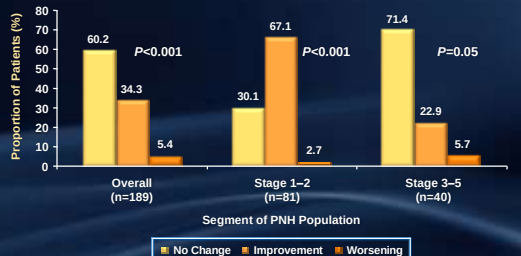
64% of Patients Exhibit Chronic Kidney Disease (CKD)[1]



59% of patients with minimal (0–1) transfusion history had CKD (n=22)

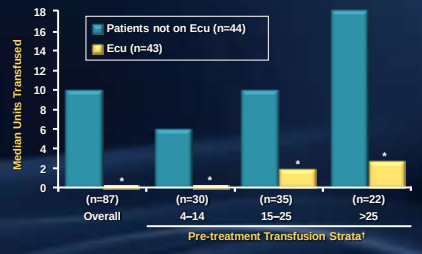
1. Hillmen P *et al. Am J Hematol* 2010;85:553–559.
53

Renal Function With Eculizumab in Different Baseline PNH Populations – 18 Months[1]



Please see full prescribing information for Soliris® (eculizumab). Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012.
1. Hillmen P *et al. Am J Hematol* 2010;85:553–559.
54

73% Reduction in Mean Units Transfused Across All Subgroups: TRIUMPH

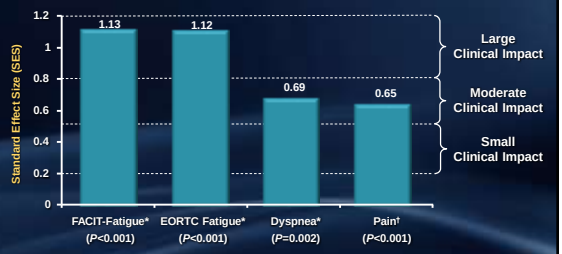


- 51% of Ecu patients achieved transfusion independence vs 0% of patients not on Ecu[1]
- Patients with concomitant bone marrow dysfunction may continue to require transfusions[2]

*P<0.001.
†Transfusion data obtained during 12 months before treatment; values were normalized for a 6-month period.
Please see full prescribing information for Soliris® (eculizumab). Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012.
1. Hillmen P *et al. N Engl J Med* 2006;355:1233–1243; 2. Schubert J. *Br J Haematol* 2008;142:263–272.

55

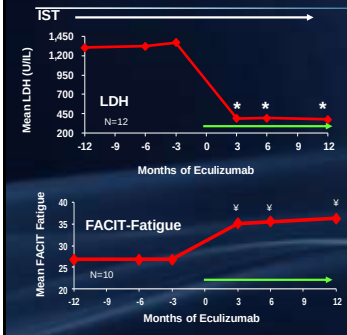
Eculizumab Treatment Results in Large and Clinically Meaningful Improvements in Patient-Reported Outcomes



Please see full prescribing information for Soliris® (eculizumab). Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012.
1. Brodsky R *et al. Blood* 2006;108: Abstract 3770; 2. Data on file. Alexion Pharmaceuticals. 3. Weitz I, et al. *Internal Medicine Journal* 2012. Accepted Article; doi: 10.1111/j.1445-5994.2012.02924.x

56

Eculizumab Reduces Hemolysis and Improves Fatigue in IST-Treated Patients



- IST: Severe hemolysis
- Ecu: Significant and sustained reduction in hemolysis
- IST: Severe fatigue
- Ecu: Significant and sustained reduction in fatigue
- Demonstrates effectiveness of treatment with Eculizumab to reduce hemolysis and fatigue in AA patients despite concomitant IST treatment

* *P*<0.01 when prior and post months compared. . *P*<0.05 when prior and post months compared.
Schrezenmeier et al Blood 2009

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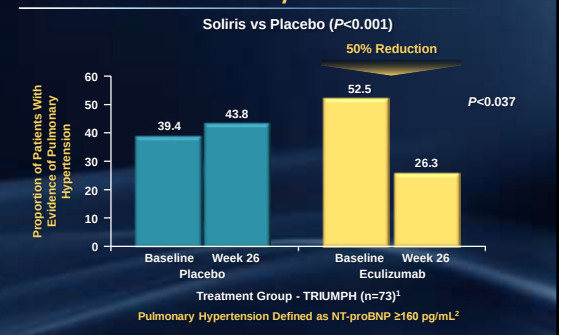
Reduction of Pulmonary Hypertension With Eculizumab as Measured by NT-ProBNP



Please see full prescribing information for Soliris® (eculizumab). Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012.
1. Hill A *et al. Br J Haematol* 2012;158:409–414. 2. Machado *et al. JAMA*. 2006.

58

Recommendations for Monitoring PNH Patients on Eculizumab

- Monthly
  - Complete Blood Count
  - Reticulocyte count
  - Serum LDH
- Yearly
  - PNH Flow Cytometry
- If Evidence of Extravascular Hemolysis (anemia and increased retic)
  - Direct Antiglobulin Test

Brodsky et al.. *Blood* 2014;124:2804–2811.

59

Summary of Clinical Efficacy[1–5]

- 86% sustained reduction in hemolysis as measured by LDH
  - Maintained over a 36 month treatment period[1–3]
- 92% reduction in thrombotic events
- 73% reduction in transfusion requirements across all patient populations
- 78% clinically meaningful improvement in fatigue
  - Sustained improvement in overall quality of life
- Patients treated with eculizumab experienced improvement in CKD and pulmonary hypertension
  - Eculizumab provided a rapid and durable effect on dyspnea, a key marker of hemolysis-induced PHT

Please see full prescribing information for Soliris® (eculizumab).
1. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012 . 2. Hillmen P *et al. N Engl J Med* 2006;355:1233–1243;
3. Brodsky R *et al. Blood* 2010;116: Abstract 4237; 4. Hillmen P *et al. Blood* 2007;110:4123–4128; 5. Socie G *et al. Blood* 2007;110: Abstract 3672.
4. Szer J *et al.* In: Abstracts of the 54th Annual Meeting of the American Society of Hematology (ASH). December 8–11, 2012, Atlanta, GA; Abstract #1260. Appears in *Blood* 2012;120(21).

60

Summary of Clinical Efficacy and Safety[1–5]

- In a multicenter analysis eculizumab showed a major impact on survival in PNH; survival is comparable to age- and gender-matched controls
  - Eculizumab significantly reduced hemolysis, the underlying cause of morbidity and mortality in PNH
  - Significant reductions in AEs were observed suggesting good tolerability and a favorable risk/benefit ratio over the long term

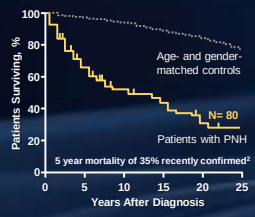
Please see full prescribing information for Soliris® (eculizumab).

1. Soliris® (eculizumab) Summary of Product Characteristics. Alexion Europe SAS; 2012. 2. Hillmen P *et al. N Engl J Med* 2006;355:1233–1243; 3. Brodsky R *et al. Blood* 2010;116: Abstract 4237; 4. Hillmen P *et al. Blood* 2007;110:4123–4128; 5. Socie G *et al. Blood* 2007;110: Abstract 3672. 4. Szer J *et al.* In: Abstracts of the 54th Annual Meeting of the American Society of Hematology (ASH). December 8–11, 2012, Atlanta, GA; Abstract #1260. Appears in *Blood* 2012;120(21).

61

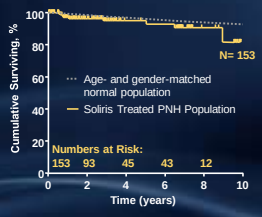
Paroxysmal Nocturnal Hemoglobinuria: Compelling Long Term Clinical Benefits in PNH Patients

Pre-Soliris from Time of Diagnosis in 80 Patients With PNH[1,2]



- Despite best supportive care - 5 year mortality: 35%[1]

Survival of PNH Patients Treated With Soliris Compared With the Normal UK Population[3]



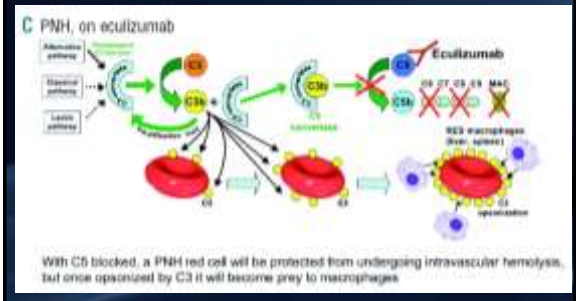
1. Hillmen P et al. *N Engl J Med.* 1995;333:1253-1258. 2. Kelly RJ et al. *Blood.* 2011;117:6786-6792 3. Hillmen et al. *Br Jnl Haematol.* 2013;162:62-73

62

Role of Complement 3 in Continued Extravascular Hemolysis

63

Complement Cascade Regulation and Erythrocytes



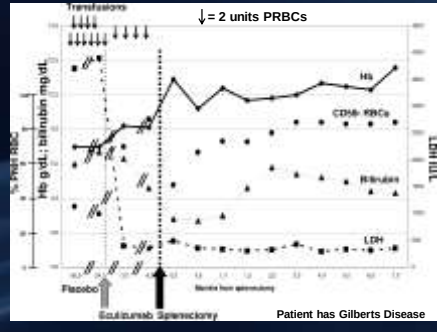
Lucio Luzzatto et al. Haematologica 2010;95:523-526

64

Role of Splenectomy

65

Hemoglobin Normalization after Splenectomy



Risitano et al. *Blood* 2008;112:449-451

66

Novel Complement Inhibitors

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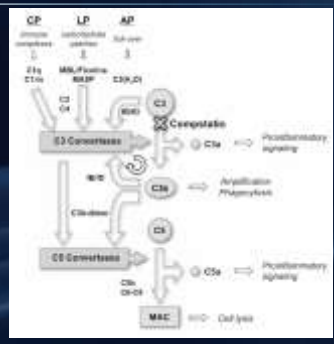
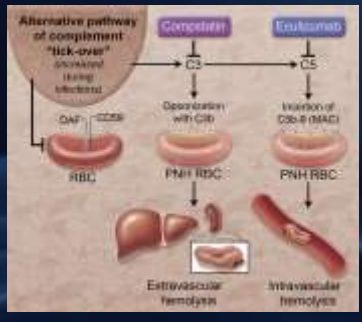
Complement Cascade



Ricklin and Lambris *Adv Exp Med Biol*. 2008;632:273-292

68

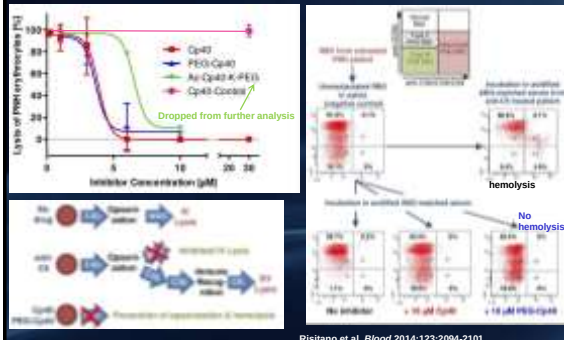
Complete Attack in PNH



Joshua M. Thurman *Blood* 2014;123:1975-1976

69

Effect of C3 inhibitors on hemolysis and C3 fragment deposition on PNH erythrocytes.



Risitano et al. *Blood* 2014;123:2094-2101

70

Novel Complement Inhibitors

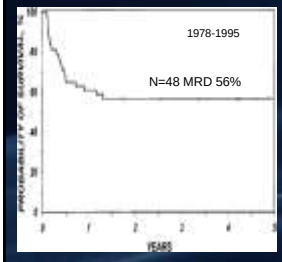
- ALXN 1210—C5 antibody prolonged half life administered every 8 weeks.
- AMY 101/APL-2-compstatin analog. Synthetic peptide that inhibits C3
- Coversin-small molecule protein derived from a tick that inhibits C5, daily subq dosing
- ACH-4471-oral agent. Small molecule inhibits factor D. C3 proactivator convertase. Early phase 1 trials. Active independent of C5 inhibitor
- OMS-721—complement inhibitor lectin pathway, IV, monoclonal antiobdy tartes MASP-2
- ALN-CC5-RNAi C5 inhibitor

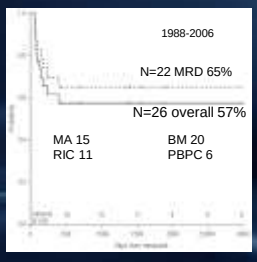
71

Transplantation for PNH

72

HCT for PNH Long Term Results

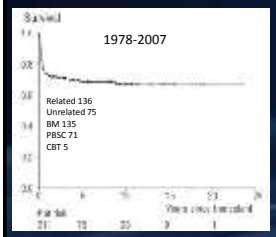


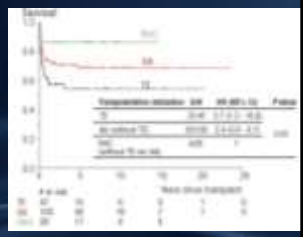


Sašo et al *Br J Haematol*. 1999:104;392-396

Santarone et al. *Haematologica* 2010:95;983-988

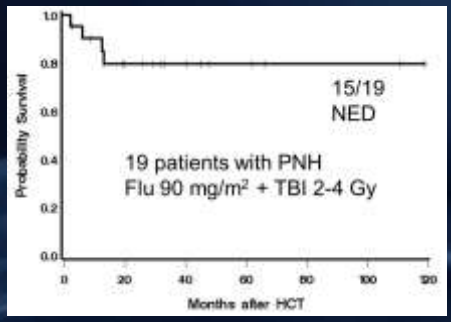
HCT for PNH





De Latour Haematologica 2012;97:1666-1673

RIC HCT for PNH



Farah et al. ASH 2011 abstract 2047

Meningitis Vaccine in PNH

Meningitis Vaccines

- Meningitis A, C, Y, W-135 (Quadrivalent Vaccines)
  - MenHibrix (Hib-Men CY-TT) BIVALENT children 6 weeks-18 mos
  - Menveo (Men ACWY-CRM) 2 months-55 years of age
  - Menactra (Men ACWWY-D) 9 months-55 years of age
  - Menomune (MPSV4) polysaccharide
    - allergic reactions
    - Older than 55
    - No mucosal immunity
    - Duration of immunity less than 3 years—no memory T cells

Current ACIP Recommendations for Complement Deficiencies

People with persistent complement component deficiencies[78]		
• for age 2 through 18 months	Give MCV4-CRM or Hib-MenCY at ages 2, 4, 6 and 12–15 months	Give MCV4 booster after 3 years followed by boosters every 5 years thereafter
• for children age 7 through 23 months who have not initiated a series of MCV4-CRM or Hib-MenCY	Give 2 doses, separated by 3 months, of MCV4-CRM (if age 9–23 months)[1] or MCV4-D (if age 9–23 months)	
• for ages 2 through 55 years	Give 2 doses of MCV4, 2 months apart	Boost every 5 years with MCV4[11]
• for age 56 years and older	Give 2 doses of MCV4, 2 months apart	Boost every 5 years with MCV4[11]

ACIP=Advisory Committee on Immunization Practices

Distribution of Meningitis Serotype in Norway

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Meningitis Vaccines

- Meningitis A, C, Y, W-135 (Quadrivalent Vaccines)
  - MenHibrix (Hib-Men CY-TT) BIVALENT children 6 weeks-18 mos
  - Menveo (Men ACWY-CRM) 2 months-55 years of age
  - Menactra (Men ACWWY-D) 9 months-55 years of age
  - Menomune (MPSV4) polysaccharide
    - allergic reactions
    - Older than 55
    - No mucosal immunity
    - Duration of immunity less than 3 years—no memory T cells
- Meningitis B
  - Bexsero (Novartis) 10-25 years of age
    - 2 dose series (0 and 1-6 months)
  - Trumenba (Pfizer) 10-25 years of age
    - 3 dose series (0,2, and 6 months)

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Meningitis Vaccines

- Meningitis X
  - North America, Europe, Australia and West Africa
  - No commercially available vaccine

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Laboratory Analsysis in PNH

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Chemistry panel in PNH

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Hematology panel in PNH

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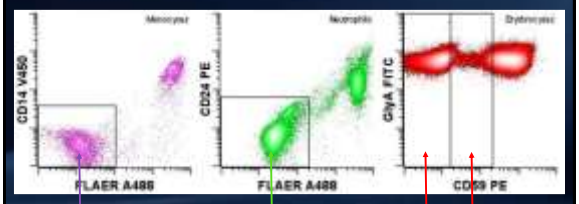
PNH Flow Testing



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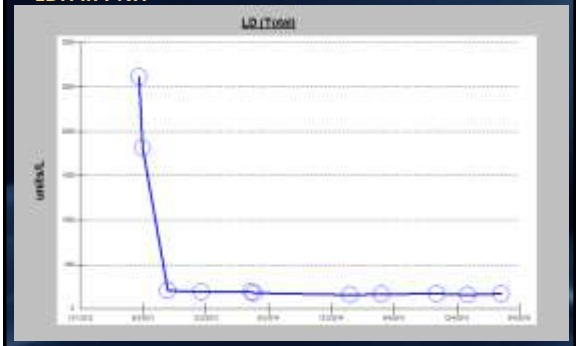
LDH in PNH



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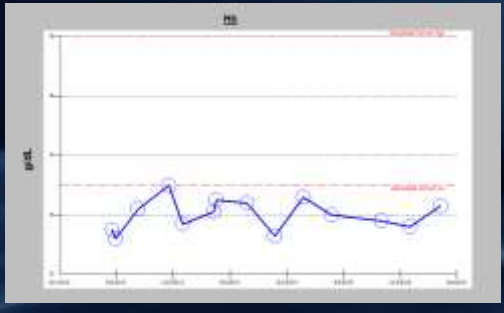

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