Current treatment strategy for PNH

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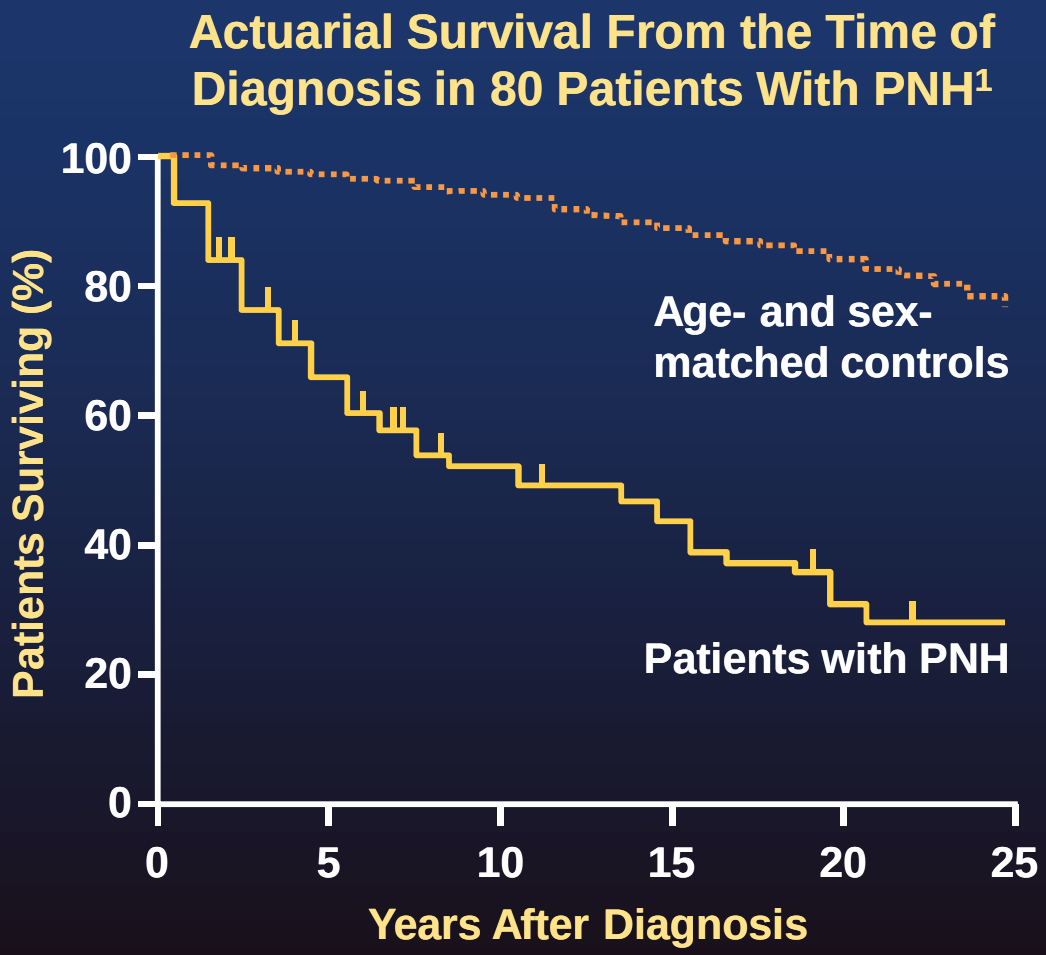
Acknowledgments

- Michael Brown
- Petra Muus for case reports

Paroxysmal Nocturnal Haemoglobinuria: A Chronic Disabling and Life-Threatening Disease

- 5 year mortality: 35%[2]
- Diagnosed at all Ages – Median age early 30's[3,4]
- Quality of life diminished[5]
- Progressive disease[5]



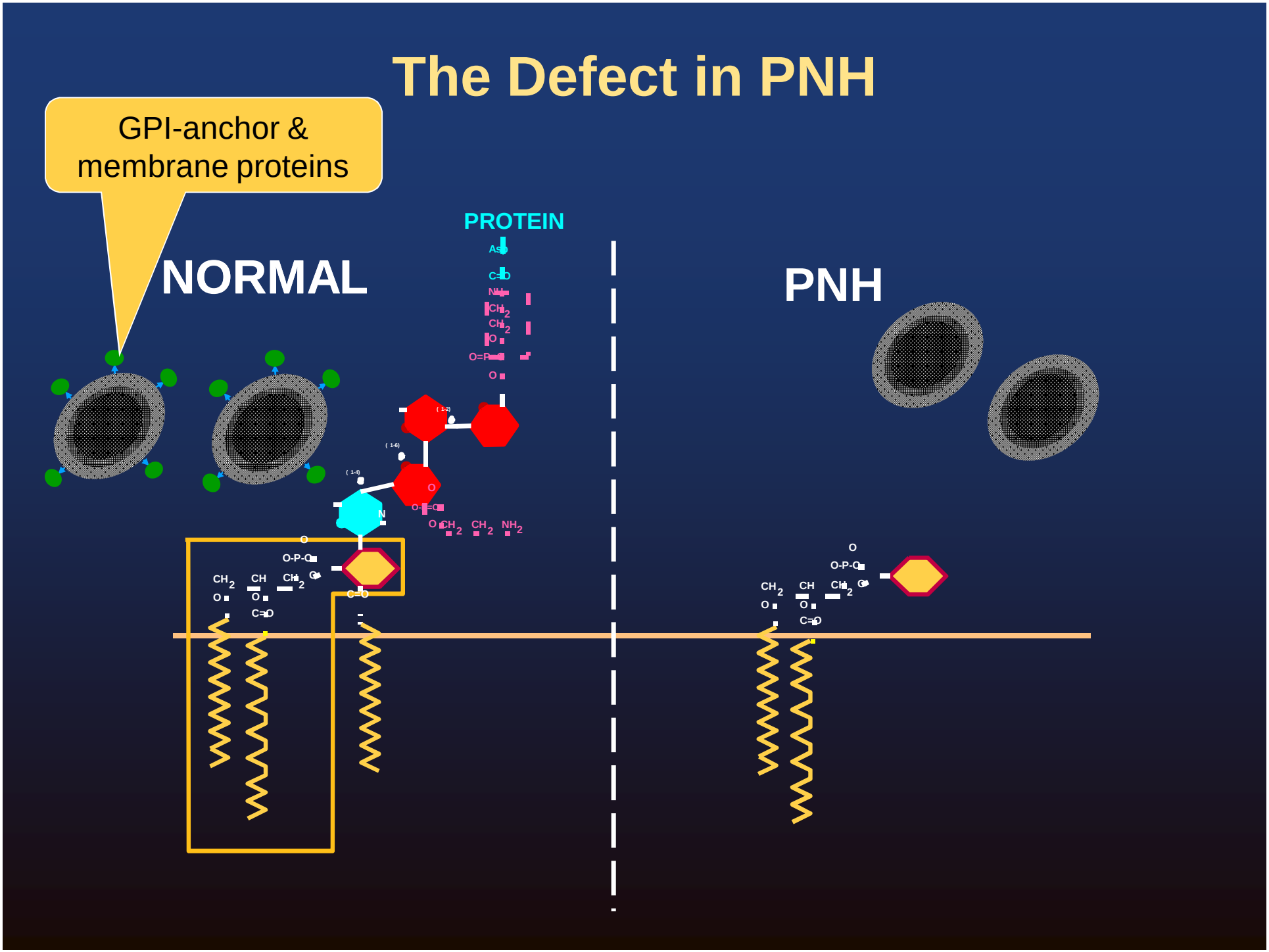
2. Hillmen, et al. *N Engl J Med.* 1995;333:1253-1258.
3. Nishimura JI, et al. *Medicine*. 2004;83:193-207. 4. Socié G et al. *Lancet*. 1996;348:573-77. 5. Hill A et al. *Br J Haematol.* 2007;137:181-92.

Paroxysmal Nocturnal Hemoglobinuria

- It's not paroxysmal
  - Even in the absence of symptoms, destructive progression of haemolysis is ongoing
- It's not nocturnal
  - Haemolysis in PNH is subtle and constant, 24 hours a day
- Haemoglobinuria is a less commonly seen complication
  - ¾ patients present without haemoglobinuria[1]

1. International PNH Interest Group. *Blood.* 2005;106:3699-3709.

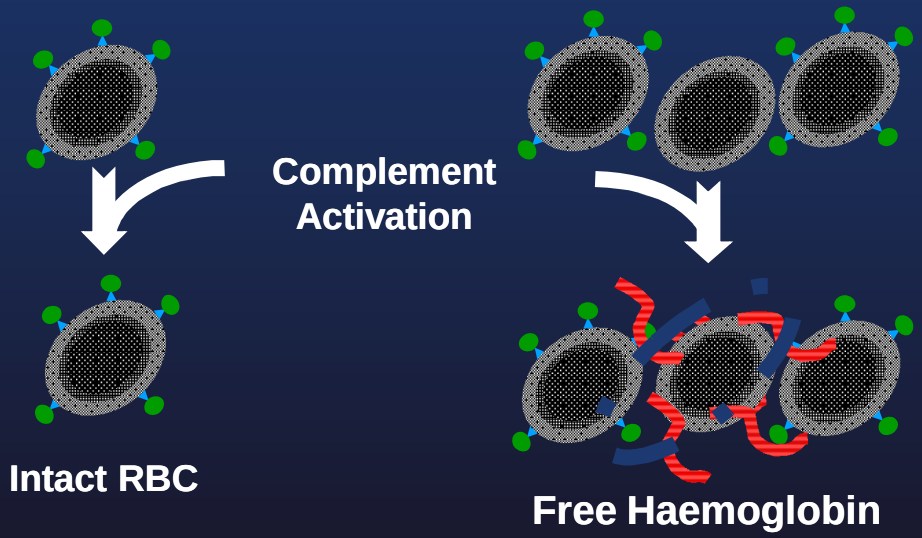
The Defect in PNH



Historically Viewed as a Hemolytic Anemia

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

Without this protective complement inhibitor shield, PNH red blood cells are destroyed



Anemia

International PNH Interest Group. *Blood.* 2005;106:3699-3709.; 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; p. 419-427; Rother RP et al. *JAMA.* 2005;293:1653-1662; Socie G et al. *Lancet.* 1996;348:573-577; Hill A et al. *Br J Haematol.* 2007;137:181-92.

Haemolysis leads to Free Hb and Nitric Oxide Depletion

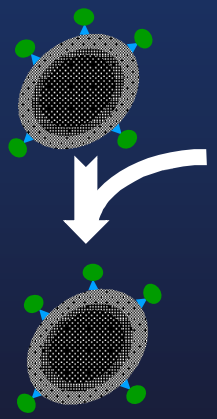
- Red blood cell destruction during haemolysis releases cell-free haemoglobin
- Cell-free haemoglobin scavenges NO
- Reduced nitric oxide can cause:
  - Vasoconstriction
  - Thrombosis
    - Platelet hyperreactivity
    - Impaired fibrinolysis
    - Hypercoagulability

Rother R. et al. *JAMA.* 2005; 293: 1653-1662

PNH is a Progressive Disease of Chronic Hemolysis

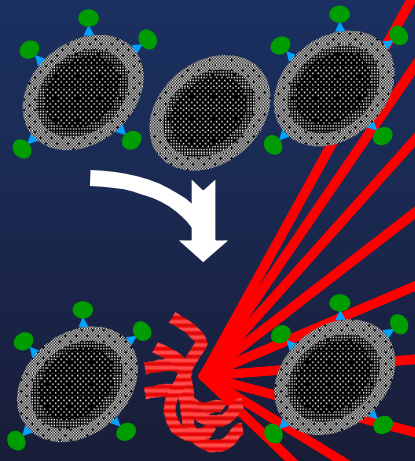
Normal red blood cells are protected from complement attack by a shield of terminal complement inhibitors

Without this protective complement inhibitor shield, PNH red blood cells are destroyed



Intact RBC

Complement Activation



Free Hemoglobin

- Thrombosis
- Chronic Kidney Disease
- Pulmonary Hypertension

Significant Impact on Survival

- Haemoglobinuria
- Dysphagia
- Abdominal Pain
- Anaemia
- Fatigue
- Dyspnoea

Significant Impact on Morbidity

- Anaemia

International PNH Interest Group. *Blood.* 2005;106:3699-3709; 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; p. 419-427; Rother RP et al. *JAMA.* 2005;293:1653-1662; Socie G et al. *Lancet.* 1996;348:573-577; Hill A et al. *Br J Haematol.* 2007;137:181-92.

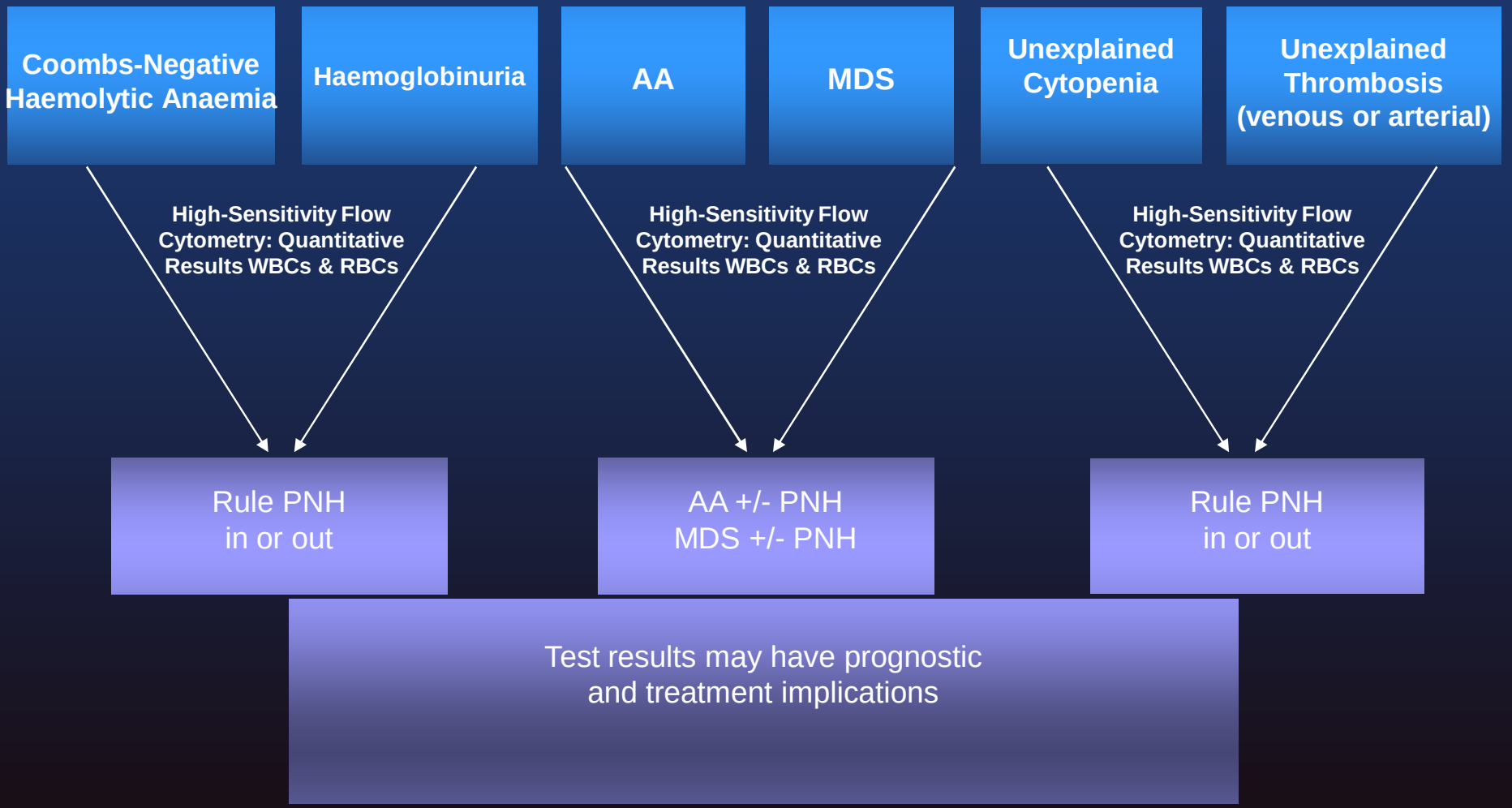
PNH Can Be Challenging to Diagnose

Delays in diagnosis range from 1 to more than 10 years[1]

Clinical Signs or Symptoms	Incidence Rate (%)
Thrombosis	40%[1]
Dyspnoea	66%[2]
Chronic Kidney Disease	64%[3]
Abdominal Pain	57%[2]
Anaemia	88%[4]
Fatigue, impaired QOL	96%[2]
Haemoglobinuria (at presentation)	**26%[5]**
Dysphagia	41%[2]
Erectile Dysfunction	47%[2]

1. Hillmen P et al. *N Engl J Med*. 1995;333:1253-8.
2. Meyers G et al. *Blood*. 2007;110(11):Abstract 3683.
3. Hillmen P et al. *Blood* (ASH Annual Meeting Abstracts). 2007;110:abstract 3678.
4. Nishimura J et al. *Medicine*. 2004;83(3):193-207.
5. Parker C et a. *Blood.* 2005;106(12):3699-3709.

Diagnostic Pathway for PNH



International PNH Interest Group. *Blood*. 2005;106:3699-3709

Historical Management of PNH

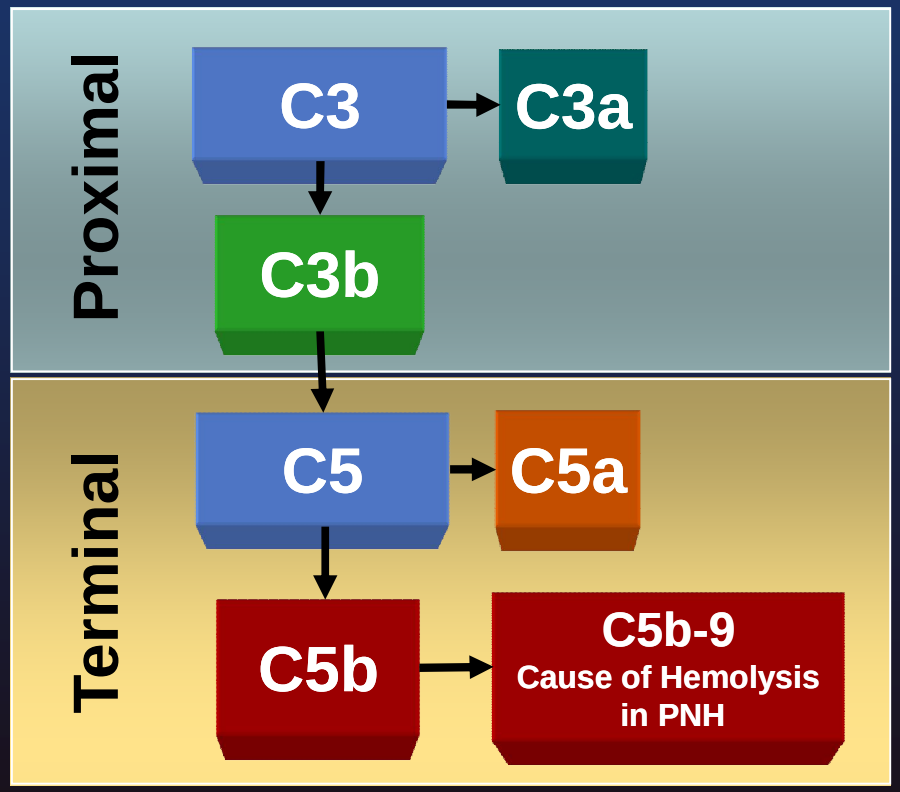
Palliative options do not impact progression and risk for severe morbidities and mortality

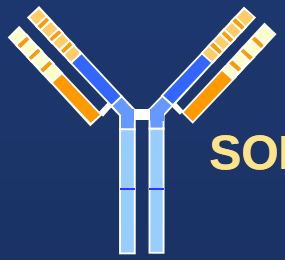
- Transfusions
  - Risk of iron overload
  - Transient treatment of anaemia
- Anticoagulants
  - Risk of hemorrhage
  - Ineffective in many patients*
- Red cell supplements
  - ESAs may expand clones and increase haemolysis
  - Folic acid, iron, erythropoiesis-stimulating agents
- Steroids/androgen hormones
  - No controlled clinical trials

International PNH Interest Group. *Blood.* 2005;106:3699-3709.
*Hillmen P et al. *Blood.* 2007;110:4123-8.

ESA=erythropoietin stimulating agents

Eculizumab Blocks Terminal Complement





SOLIRIS®

- Eculizumab binds with high affinity to C5
- Terminal complement activity is blocked
- Proximal functions of complement remain intact
  - **Weak anaphylatoxin**
  - **Immune complex clearance**
  - **Microbial opsonization**

Figueroa JE, Densen P. *Clin Microbiol Rev*. 1991;4(3):359-395.
Walport MJ. *N Engl J Med*. 2001;344(14):1058-66.
SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009. Rother RP et al. *Nature Biotech*. 2007;25(11):1256-64.

Eculizumab PNH Clinical Studies

AEGIS–
N = 29
Primary endpoint: reduction of hemolysis

AEGIS–
N = 27
Primary endpoint: long-term safety and efficacy

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

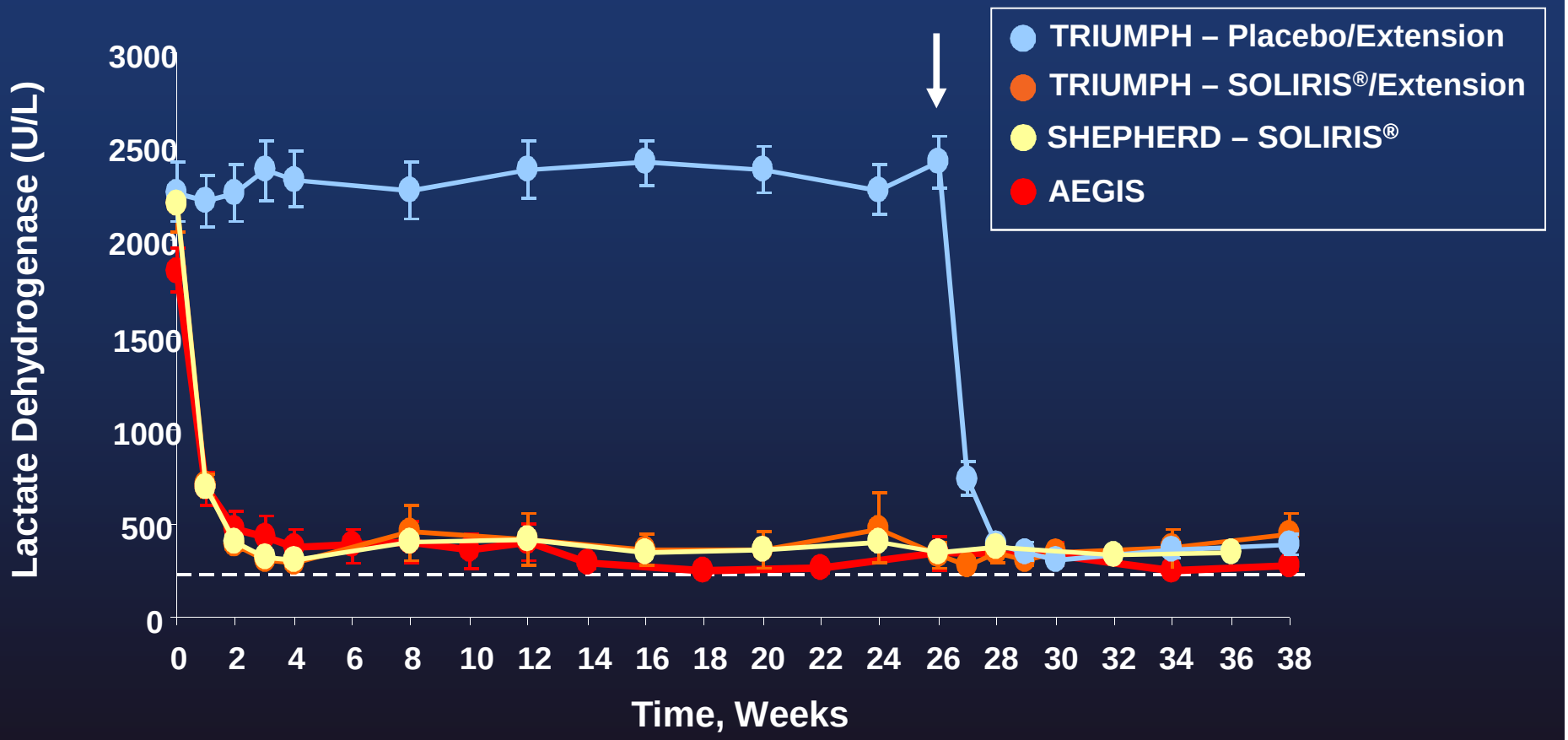
Pilot Study – *NEJM*. 2004
N = 11
Primary endpoint: reduction of hemolysis

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

Baseline Demographics

Parameter	AEGIS Eculizumab N = 29	Multinational Eculizumab N = 140	Multinational Placebo N = 44
Sex- Female	15 (52%)	72 (51.4%)	29 (65.9%)
Mean age (SD)	47 (12.4)	42 (14.6)	38.4 (13.4)
≥ 65 years	1 (3.4%)	13 (9.3%)	2 (4.5%)
History of AA	11 (37.9%)	36 (25.7%)	12 (27.3%)
History of MDS	2 (6.9%)	3 (2.1%)	0
Comcomitant antithrombotic	9 (31.0%)	83 (59.0%)	19 (43.2%)
Concomitant steroids	14 (48.3%)	49 (35.0%)	14 (31.8%)
History of TE	5 (17.2%)	58 (41.4%)	8 (18.2%)
Pretreatment LDH levels	1814	2125	2258

Consistent 86% Reduction in LD

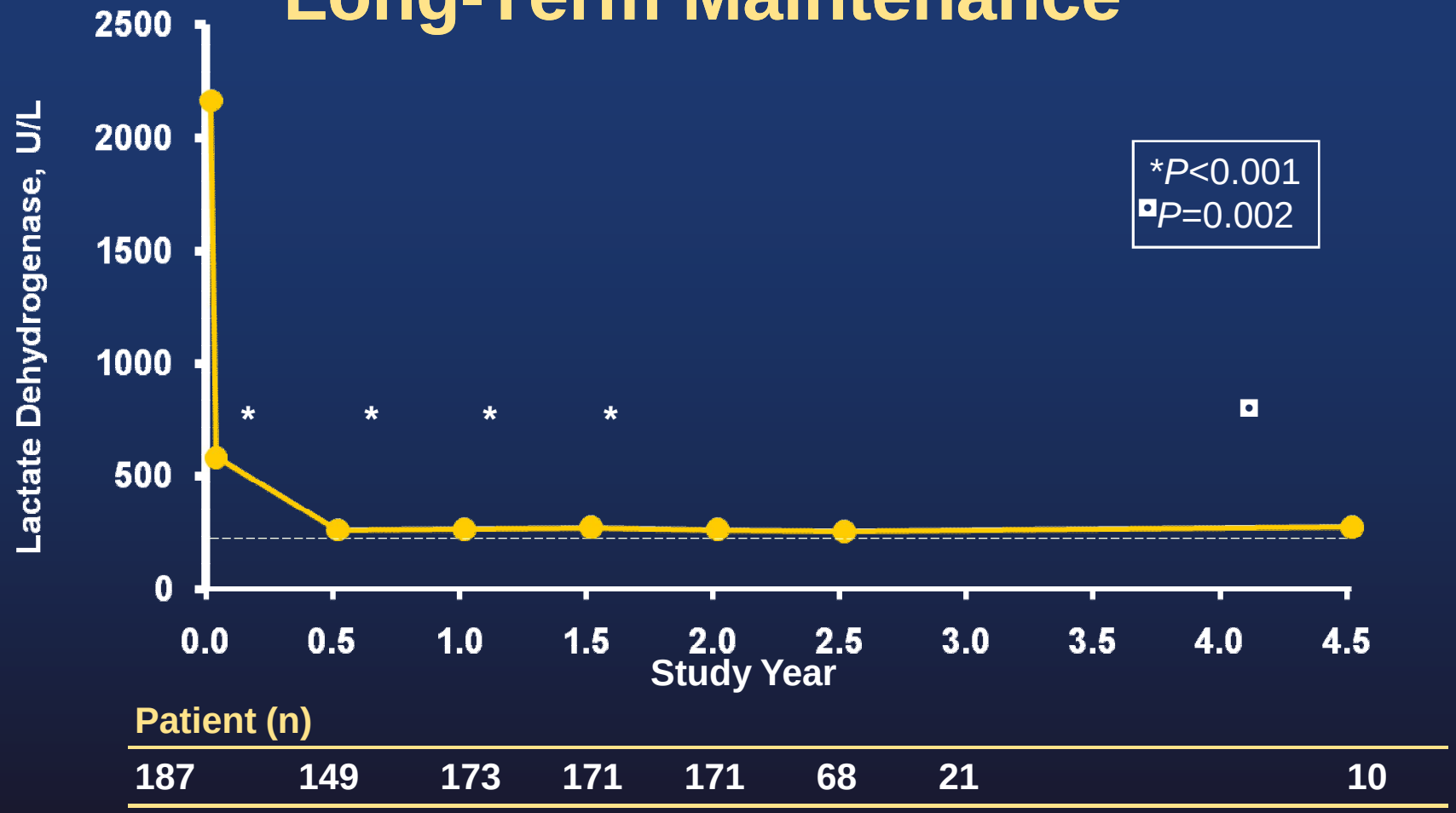


→ **TRIUMPH placebo patients switched to SOLIRIS® after week 26. All TRIUMPH patients entered the long-term extension study.**

P<0.001 at all measured time points.

Hillmen P et al. *Blood*. 2007;110(12):4123-8.

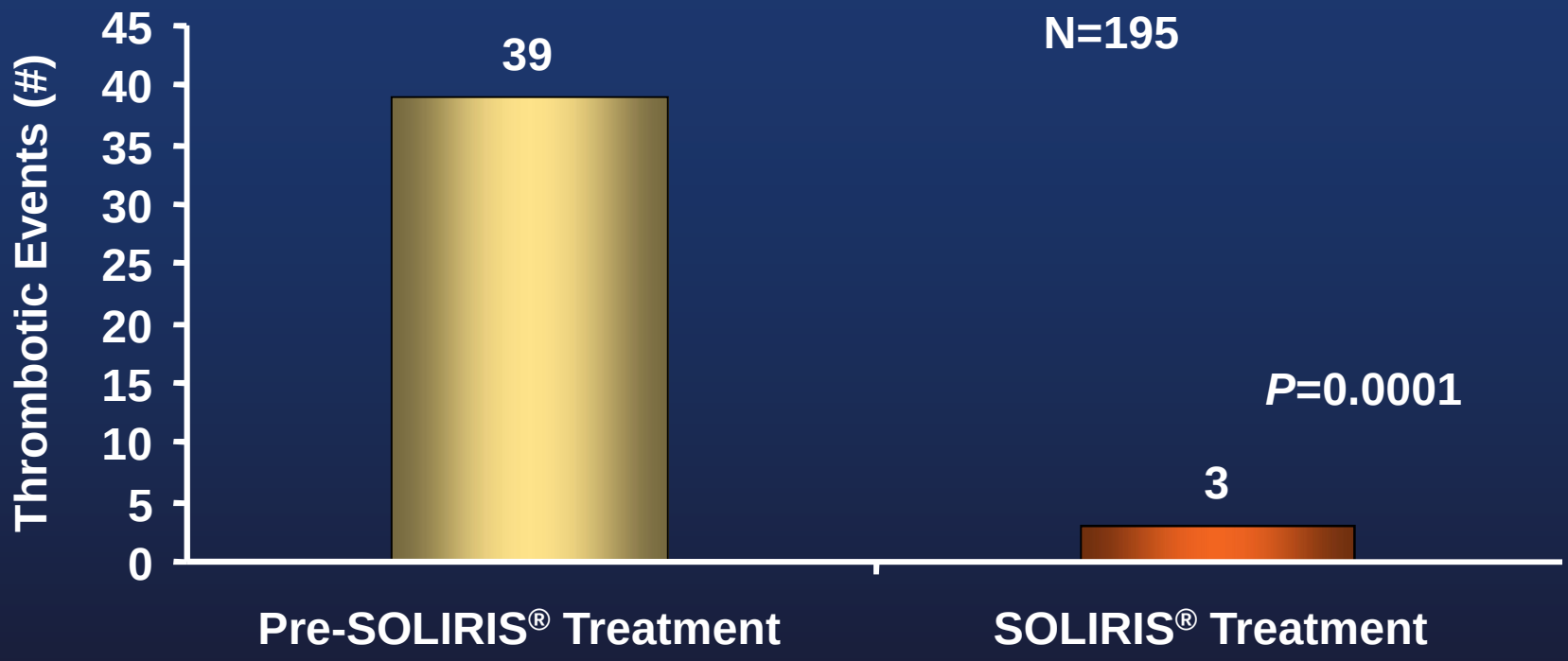
Long-Term Maintenance



- All TRIUMPH patients entered the long-term extension study
- All patients sustained a reduction in hemolysis as measured by LDH
  - Patients followed for up to 54 months
- 10 patients who participated in the pilot study demonstrated sustained reduction in LDH out past 5 years

Socié G et al. Blood. 2007;110(11): Abstract 3672. SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009.

92% Reduction in Thrombotic Events[1]



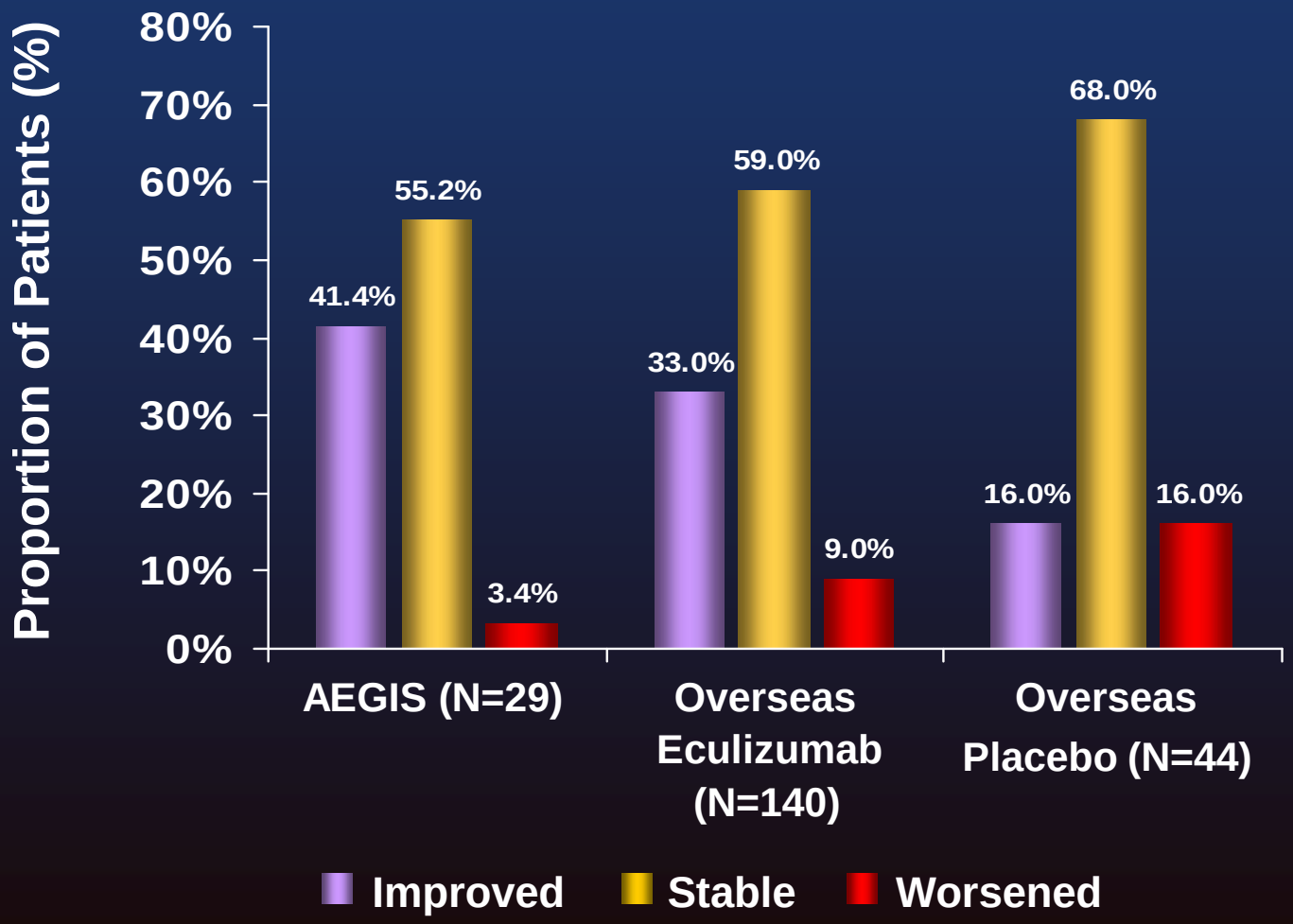
- 63% of patients received concomitant anticoagulants[2]
- The effect of anticoagulant withdrawal was not studied[3]
- Events observed in both venous and arterial sites[1]

PI: There were fewer thrombotic events with SOLIRIS® treatment than during the same period of time prior to treatment.

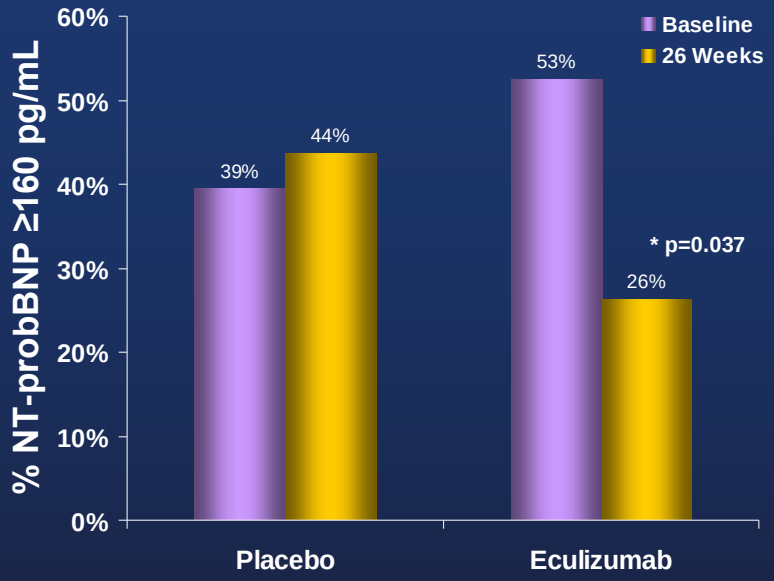
1.Hillmen P, et al. *Blood*. 2007;110:4123-4128. 2. Brodsky R et al. Blood. 2008;111(4):1840-47.
3.SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009.

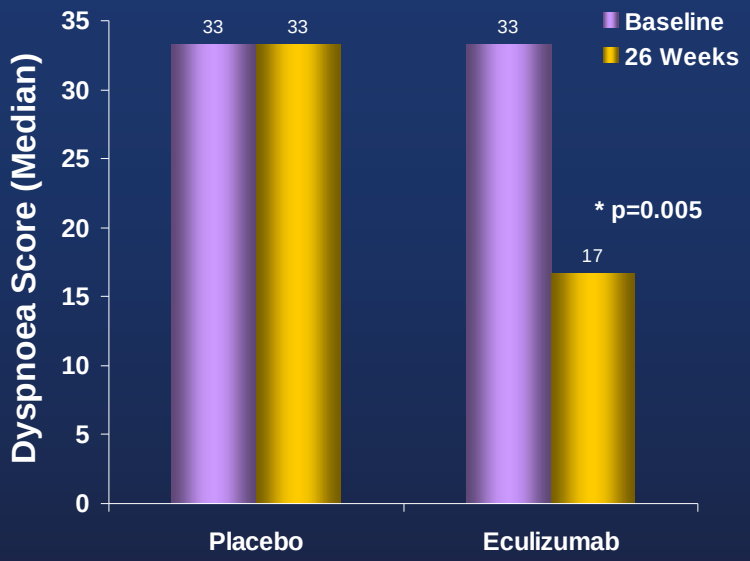
Improvement in CKD Following Eculizumab Treatment

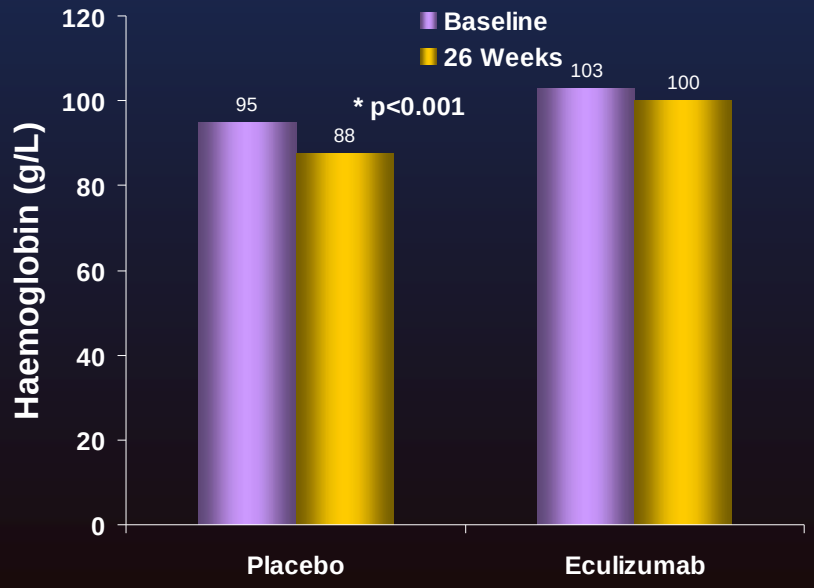
Improvement has been maintained out to 18 months



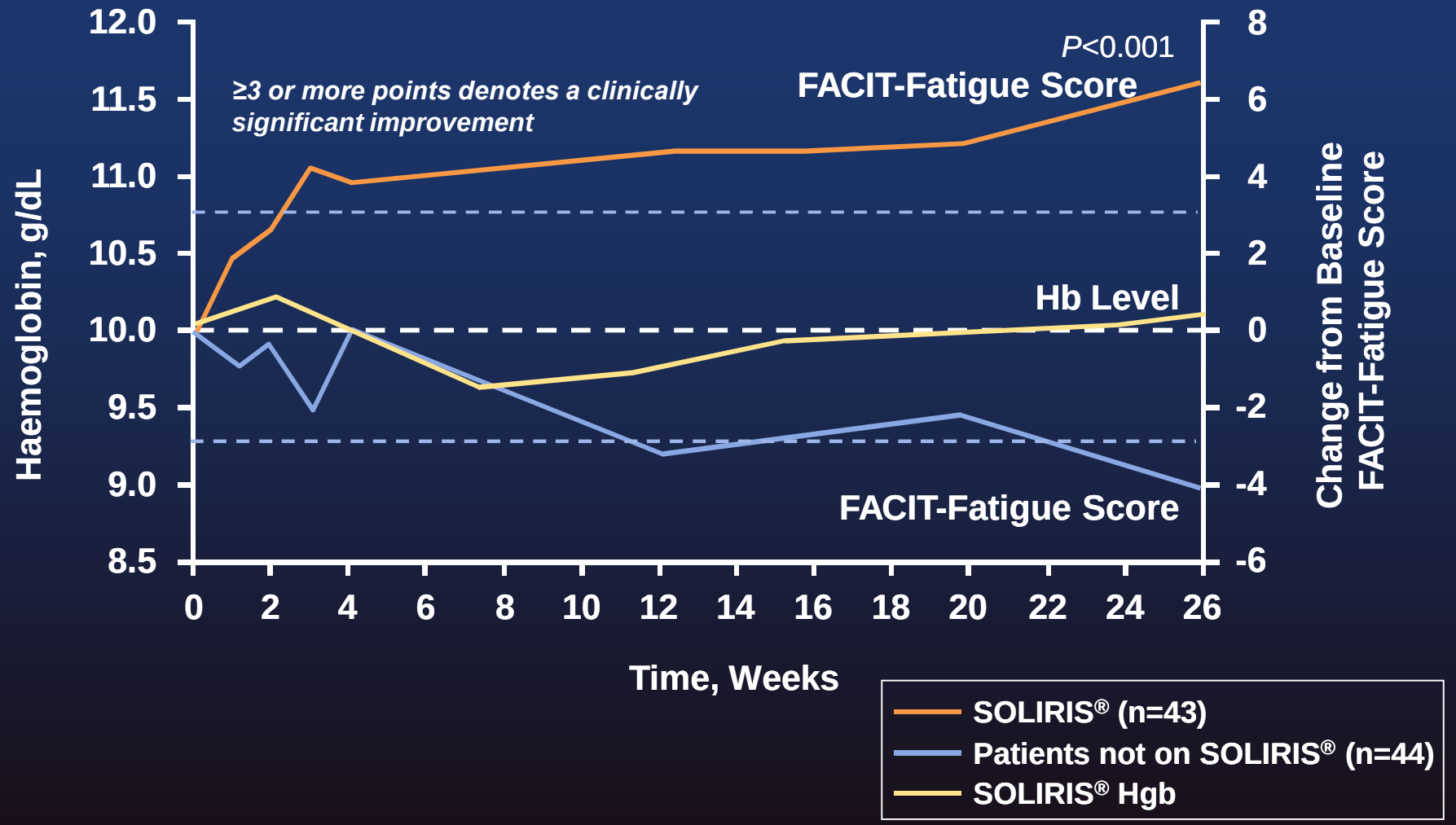
Change in NT-proBNP and Dyspnoea Independent of Haemoglobin





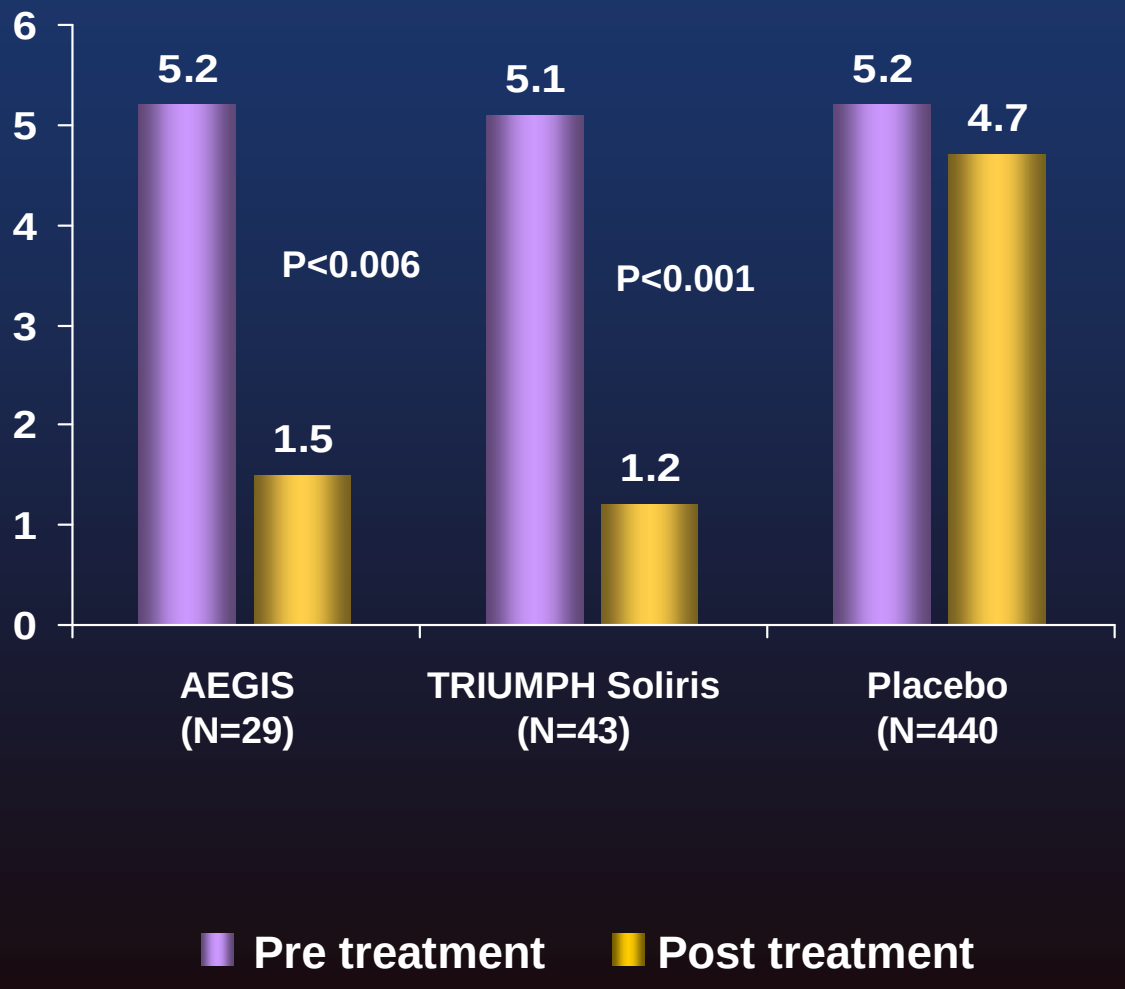


Improvement in Fatigue Occurred Independent of Haemoglobin Response



FACIT = Functional Assessment of Chronic Illness Therapy; Adapted from: Hillmen P et al. *NEJM*. 2006;355:1233-43.; Data on file. Alexion Pharmaceuticals; 2009. 1. Brodsky RA et al. *Blood Rev*. 2008; 22: 65-74. 2. Hill A et al. *Haematologica*. 2008; 93 (Suppl 1): 359. Abstract 0904. 3. Brodsky RA et al. Blood. 2008;111:1840-1847.

Control of Haemolysis
Reduced RBC Transfusion Requirements



- AEGIS
- 71% reduction from 5.2 to 1.5 mean units
- 66% of transfusion dependent patients became transfusion independent

Evidence of PNH Disease Burden in 44 Never-Transfused PNH Patients*

Parameter	Measure
LDH Median (range)	**1,463 U/L (180 – 5950)**
	% of Patients
Evidence of Thromboembolism (n=43)	**28%**
Thromboembolism event rate	**7.57/100 patient years**
Evidence of Impaired Quality of Life (n=39)	**87%**

- 15% of this patient cohort had LDH levels <500 U/L, indicating PNH patients with low levels of haemolysis experience impaired QoL and risk of TE
- TE event rate identical for clone size <50% or ≥ 50%

*** Post-marketing setting; AU, IT, FR, NL, US**

Muus P. ASH 2009. Abstract 4029

Global Improvements in Never-Transfused Patients with PNH Treated with Eculizumab

Measure	Pre-Soliris Treatment	During Soliris Treatment	P-value
LD (median U/L) (n=27 pts)	1,603	380	< 0.001
Impaired Quality of Life (n=11 pts)	91%	0	NA
TE events (n=36 pts)	11	0	NA
TE Free survival at 3 years (n = 36 pts)	68%	100%	0.01

(a) TE events reported as present or absent prior and during eculizumab treatment; NA = Not Applicable

- Despite no transfusions; increase in haemolysis, TE events, impaired QoL pre-treatment early mortality
- Treatment reduced haemolysis, improved QoL and survival.

Muus, Blood 2009; 114:4029

Summary of Efficacy

- PNH is a progressive and life-threatening disease
- Haemolysis is central to the morbidities of PNH
- Current treatments have not demonstrated a safe and effective treatment option to address haemolysis
- Eculizumab targets terminal complement cascade to inhibit haemolysis.
- Benefits include reduction in TE events, PHT risk, transfusions, fatigue and improvement in CKD.

SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009.
Data on file. Alexion Pharmaceuticals; 2009.

Important Safety Information About SOLIRIS®

Warning

WARNING: SERIOUS MENINGOCOCCAL INFECTION

- Eculizumab **increases the risk of meningococcal infections**
  - **Vaccinate patients with a meningococcal vaccine at least 2 weeks prior to receiving the first dose of** Eculizumab
  - **Revaccinate according to current medical guidelines for vaccine use**
  - **Monitor patients for early signs of meningococcal infections, evaluate immediately if infection is suspected, and treat with antibiotics if necessary**

SOLIRIS™ (eculizumab) [package insert]. Alexion Pharmaceuticals; 2007.

Serious Adverse Events: Clinical Trial Experience

- Meningococcal infections are the most important adverse events that may be experienced by patients receiving SOLIRIS®
- In clinical studies, 2 out of 196 patients developed serious meningococcal infections while receiving treatment with Soliris
  - Both patients had been vaccinated

SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009.
Data on file. Alexion Pharmaceuticals; 2009.

Adverse Reactions Reported in ≥ 5% of Eculizumab -Treated Patients in TRIUMPH

	Patients, n (%)	
Reaction	SOLIRIS (n = 43)	Placebo (n = 44)
Headache	19 (44)	12 (27)
Nasopharyngitis	10 (23)	8 (18)
Back pain	8 (19)	4 (9)
Nausea	7 (16)	5 (11)
Fatigue	5 (12)	1 (2)
Cough	5 (12)	4 (9)
Herpes simplex virus infections	3 (7)	0
Sinusitis	3 (7)	0
Respiratory tract infection	3 (7)	1 (2)
Constipation	3 (7)	2 (5)
Myalgia	3 (7)	1 (2)
Pain in extremity	3 (7)	1 (2)
Influenza-like illness	2 (5)	1 (2)

SOLIRIS™ (eculizumab) [package insert]. Alexion Pharmaceuticals; 2007.

Safety: Warnings and Precautions

- Patients with systemic infections should be administered eculizumab with caution

- Patients who discontinue eculizumab must be monitored closely for signs of serious hemolysis
  - In clinical trials, 16 of 196 PNH patients discontinued eculizumab treatment; no serious hemolysis was observed

SOLIRIS™ (eculizumab) [package insert]. Alexion Pharmaceuticals; 2007.

Safety: Warnings and Precautions (cont)

- LD levels may be used to monitor haemolysis
  - SOLIRIS® dose adjustment to every 12 days may be necessary for some patients to maintain LDH reduction

- The effect of withdrawal of anticoagulant therapy during SOLIRIS® treatment has not been established. Therefore, treatment with SOLIRIS® should not alter anticoagulant management.

SOLIRIS® (eculizumab) [package insert]. Alexion Pharmaceuticals; 2009.

Case Examples

Case 1: 41 F

- 1989 fatigued and anaemic for several yrs:
- PNH (84%)

- Supportive: prednisone, ESA
- 35 units of red cells per yr (Hb 40-80 g/L)
- Intelligent, clerk till 1998 then unable to work

2003 TIA: antihypertensive treatment and aspirin

2004 CVA: warfarin and Plavix

- Persistent spastic paresis right leg and paresis right arm.

Case 1: 41 F

- March 2005 : mencevax ACW135Y start eculizumab

- Haemoglobinuria resolved
- Hb 90- 105 g/L
- Transfusion: 0 - 2x/yr (infection-related)

- No new vascular events.

- More energy, active, got drivers license, travels.

Case 2: 58M

1991 fatigued, Hb 67 g/L

1992 PNH: fatigue, hemoglobinuria, erectile dysfunction, abdominal pain, dysphagia.

Transfusions 1x/6wk(3mo), rarely thereafter.

Bookkeeper, part-time work, no social life

2005: clone size 97%

No thrombosis and no prophylaxis

Hb 95-110 g/L, 1 transfusion in 2 yrs,

LDH 2500-5000 U/L

QoL 14 yr: minimal

Case 2: 58M

9/2005: Mencevax ACW135Y and start eculizumab (Shepherd, later extension study)

Recovery of erectile function

Hb 130-150 g/L

LD normal

No thrombosis

Fit, not fatigued, active social life, travels.

Efficacy of eculizumab in patients with 0 or 1 transfusions/yr pre-treatment (n=22)

Endpoints	Pre-treatment	Change at 52 Weeks	Improvement (%)	*P* Value
Median LD, U/L	1991.5	-1737.5	87%	< 0.001
Median FACIT-Fatigue Score *	27.0	11.0	41%	< 0.001
Median EORTC-Fatigue Score #	55.6	-22.2	40%	< 0.001
Median EORTC-Global Health Score*	50.0	25.0	50%	< 0.001
Thrombosis, Events per 100 pt-yrs	4.87	0.00	100%	0.06

* Positive score change is an improvement; # Negative score change is an improvement

Case 3: untransfused 49M

- PNH 2003
- Attacks of “not feeling well”, followed by severe crampy abdominal pain followed by dark urine and extreme fatigue .
- 3 days absent from work. No complaints in between crises. Never thrombosis.
- Prednisone 5 mg/d, 30mg/d during crises, folic acid, iron supplements
- Thrombosis prophylaxis.

Case 3 49M

- Hb 100-130 g/L untransfused , MCV 95, retics 44
- LD 1574-3260 U/L (n<450). Haptoglobin undetectable, bilirubin 26-33 µmol/L
- PNH clone: 80% granulocytes CD55 and CD59 negative.
- BM: hypercellular, erythroid hyperplasia.

Case 3 49M

- Crises every 2 weeks
- Interfered with family life and work

- Ample discussion and consideration:
- Mencevax ACW135Y and start eculizumab June 2008.

- Since then: no abdominal pain,
- Did not miss a day from work, family life OK
- Hb improved and stabilized, LDH normal.

PNH/AA and PNH/MDS overlap syndromes

12% AA patients have abnormal cytogenetic clones in the absence of MDS

(Appelbaum et al 1989, Tichelli et al 1996, Gupta et al 2006).

50% of AA patients have small PNH clones

(Dunn et al 1999, Socié et al 2000, Sugimore et al 2005)

Patients may have evidence of bone marrow failure and large PNH clones

Routine LDH and Hb may not be representative of the degree of intravasular hemolysis during episodes of complement activation.

Is there a place for eculizumab in PNH with another BM disease?

78yr, PNH 2009, clone (WBC) : 27% to 60%, to 75%

Transfusion-dependent, platelets 25x10^9/L, WBC 3.3x10^9/L,

LDH 1400-2100 U/L.

BM 35% cellularity, blasts < 5%, some dysplasia.

Cytogenetics: -7 ! MDS (RA) + PNH

Why Eculizumab ?

Clone > 50% and expanding,

Haemolysis, Transfusion dependent,

Exhaustion

Anticoagulation relatively contra-indicated

Less transfusion dependent; LDH 650 U/L BM unchanged

Is there a place for eculizumab in PNH with another BM disease?

67yr PNH 1982,

09 / 2009: proven visceral thrombosis

History: DVT 1983, Budd Chiari ≤ 2005 and transient renal failure.

Recent: 5 Units Tx/6wks, clone size 90%

Hb 7.0 g/dL , Plts $20x10^9$/L, WBC$1.2x10^9$/L,

4% blasts, LDH 2600 - 4100 U/L,

BM : blasts 9%, cytogen. +8, -11. **PNH + MDS**

Why eculizumab?

Proven visceral thrombosis and GI haemorrhage

Bowel healed on conservative treatment ; Reduced transfusion requirement . Subsequently transformed to AML

Is there a place for eculizumab in PNH with another BM disease?

23 yr AA: PNH clone 55%

Cyclosporin

Visceral thrombosis small bowel

AA + PNH

Why eculizumab?

Large clone, active haemolysis

Active Visceral thrombosis

Low platelet count

bowel healed without surgery,

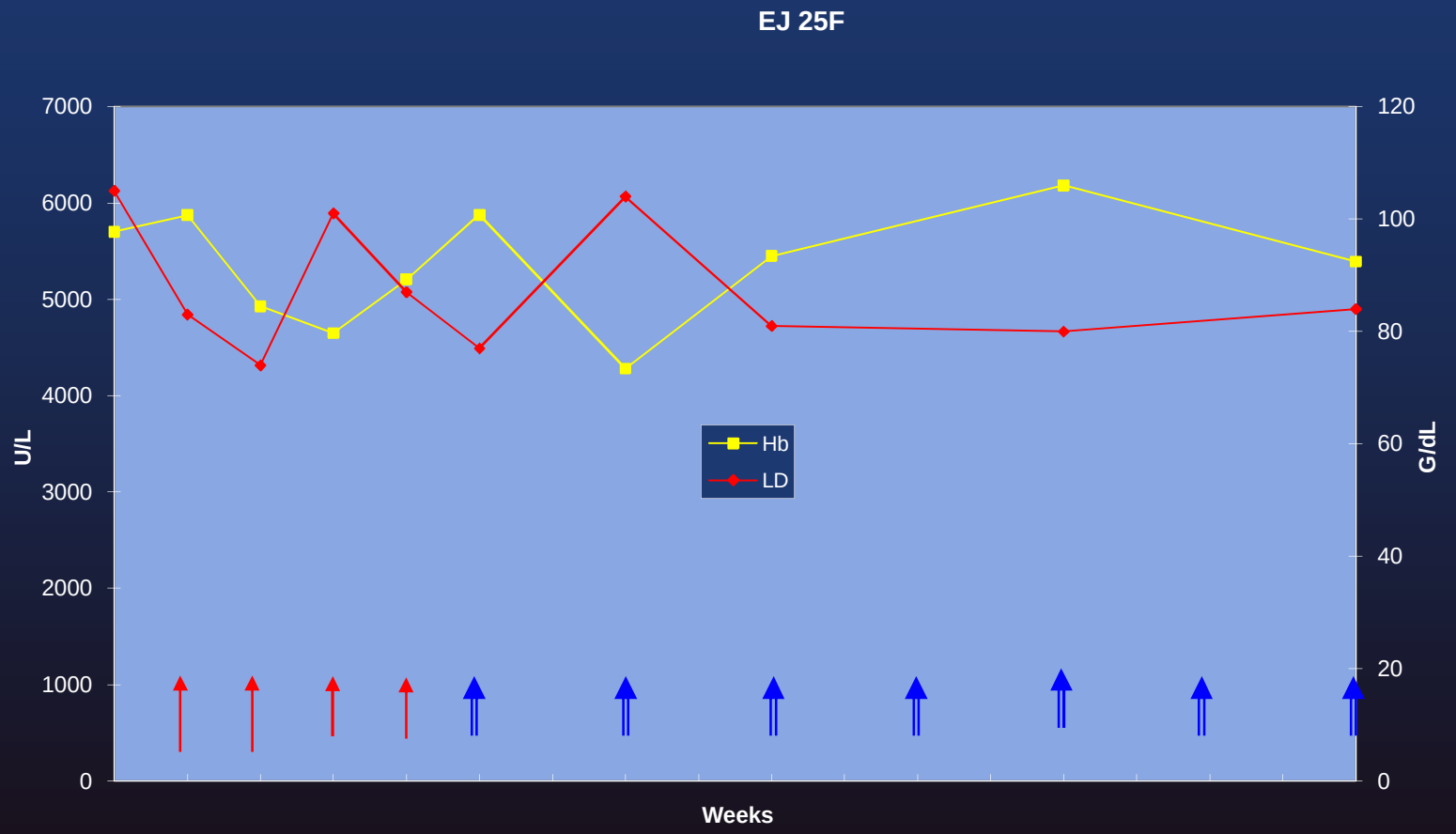
reduced transfusion requirement,

still low counts at +6mo on cyclosporin

Patient in evolution

- 31F Spontaneous DVT 1998
- May 2003 PNH diagnosed
  - Symptomatic anaemia and icterus
  - 2-3 weekly transfusions
- Jan 2005
  - Referred -> TRIUMPH study
  - First study drug infusion 9/2/05

Initial progress



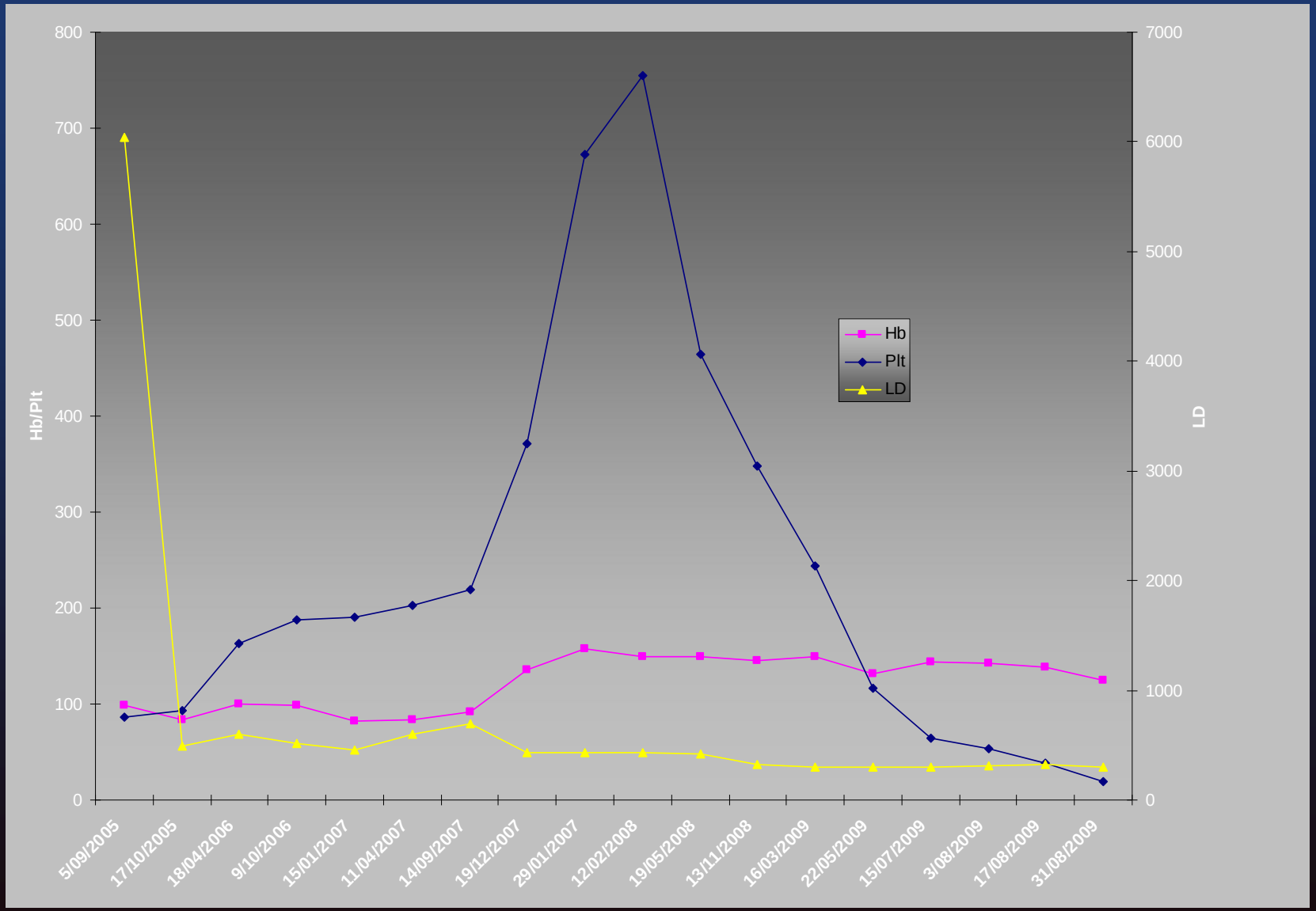
Progress

- Stopped infusions 19/8/05: no impact on transfusion requirement
- Commenced extension study 6/9/05
  - Mild headache after first infusion
  - Felt better over 4 weeks
- November 2005
  - Transfusion requirement reduced (approx q4-6 weeks) but not absent.
  - Dosing interval contracted to 12 daily and improved: 6-8 weekly transfusion.
- Bone marrow biopsy

Progress

- December 2005
  - Commenced darbepoetin 100mcg/week: 12 months
    - Serum epo 420
  - Hb normalised: no transfusions after 12/06

EJ Progress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12/02/2008
19/05/2008
13/11/2008
16/03/2009
22/05/2009
15/07/2009
3/08/2009
17/08/2009
31/08/2009

Summary

- Haemolytic PNH
- No response to placebo
- Good control with 12 daily eculizumab
  - ?short exposure to darbepoetin
- Transient thrombocytosis
  - JAK2 neg
- Remission of PNH
- Thrombocytopenia
- Evolution to AML

Eculizumab era

- Place for allo-SCT?
- Thrombosis prophylaxis still indicated?
- Better survival?
- Use in AA-PNH?
- Follow up of clone size.

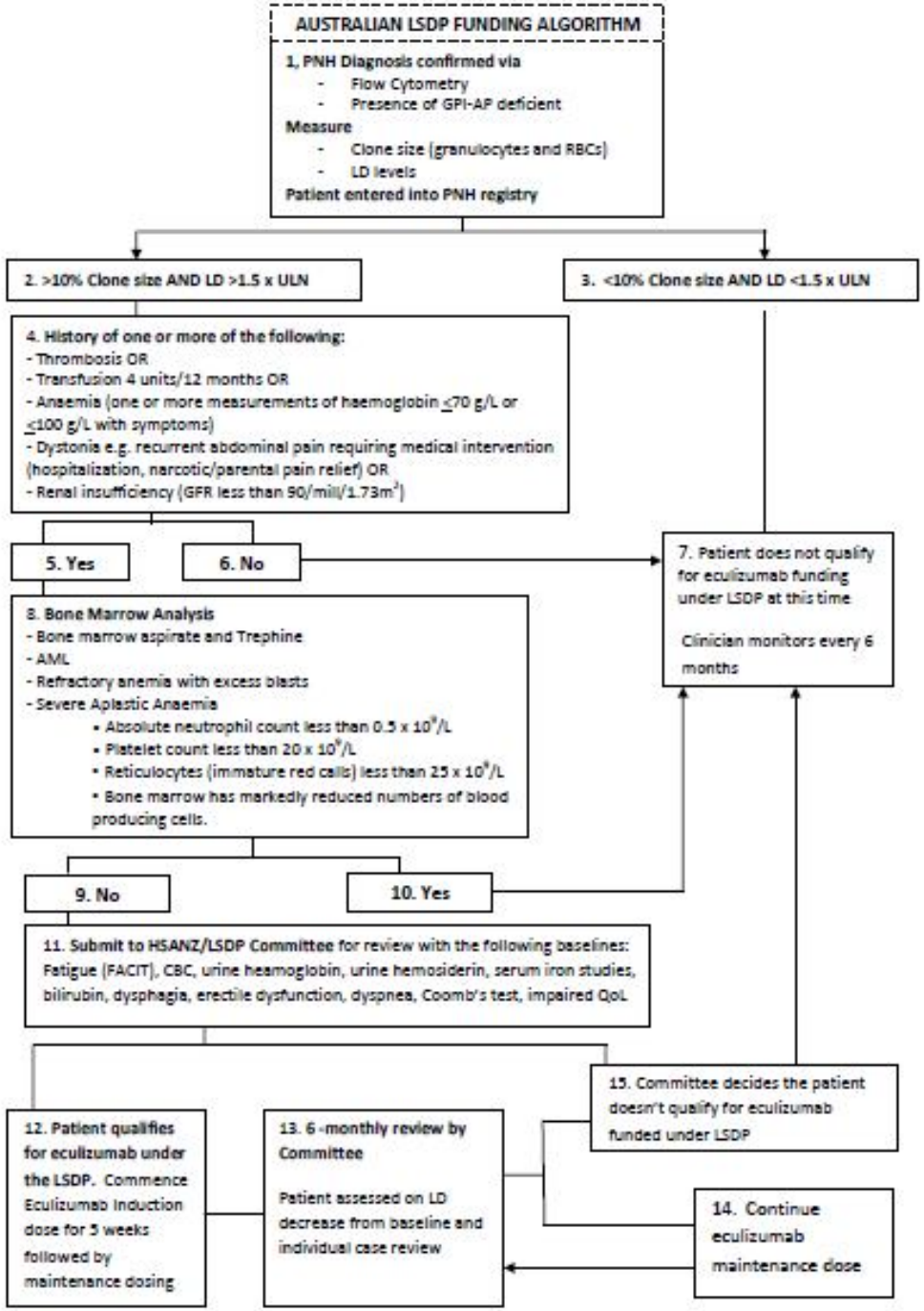
Importance of international PNH registry study

- Application in aHUS / hyperhemolysis?

- Global, observational, non-interventional study to collect real world safety, effectiveness and QoL data
  - Open to all physicians treating patients with PNH regardless of therapy
- Objectives:
  - Database for publications to enhance understanding of disease and improve outcomes
  - Promote evidence-based medicine
- Current enrollment:
  - Over 500 patients enrolled
  - Participation in 14 countries, including the United States, Argentina, Denmark, Netherlands, Belgium, Australia, France, New Zealand, Germany, and Taiwan
- Enrollment information: www.pnhsource.com

Conclusions

- PNH is an ultraorphan, life-threatening disease
- Importance of sophisticated diagnostics
- Therapy is now available in some parts of the world and is life-transforming for most patients who are exposed to it. This therapy has also resulted in an increased understanding of the clinical manifestations of the disease.
- Haemolytic PNH deserves treatment on its own rights, independent of co-existent conditions
- Individual patient reports are of particular value in this disease


AUSTRALIAN LSDP FUNDING ALGORITHM
1, PNH Diagnosis confirmed via
- Flow Cytometry
- Presence of GPI-AP deficient
Measure
- Clone size (granulocytes and RBCs)
- LD levels
Patient entered into PNH registry
2. >10% Clone size AND LD >1.5 x ULN
3. <10% Clone size AND LD <1.5 x ULN
4. History of one or more of the following:
- Thrombosis OR
- Transfusion 4 units/12 months OR
- Anaemia (one or more measurements of haemoglobin ≤70 g/L or ≤100 g/L with symptoms)
- Dystonia e.g. recurrent abdominal pain requiring medical intervention (hospitalization, narcotic/parental pain relief) OR
- Renal insufficiency (GFR less than 90/min/1.73m²)
5. Yes
6. No
7. Patient does not qualify for eculizumab funding under LSDP at this time
Clinician monitors every 6 months
8. Bone Marrow Analysis
- Bone marrow aspirate and Trephine
- AML
- Refractory anemia with excess blasts
- Severe Aplastic Anaemia
• Absolute neutrophil count less than 0.5 x 10⁹/L
• Platelet count less than 20 x 10⁹/L
• Reticulocytes (immature red cells) less than 25 x 10⁹/L
• Bone marrow has markedly reduced numbers of blood producing cells.
9. No
10. Yes
11. Submit to HSANZ/LSDP Committee for review with the following baselines: Fatigue (FACIT), CBC, urine heamoglobin, urine hemosiderin, serum iron studies, bilirubin, dysphagia, erectile dysfunction, dyspnea, Coomb's test, impaired QoL
15. Committee decides the patient doesn't qualify for eculizumab funded under LSDP
12. Patient qualifies for eculizumab under the LSDP. Commence Eculizumab induction dose for 5 weeks followed by maintenance dosing
13. 6-monthly review by Committee
Patient assessed on LD decrease from baseline and individual case review
14. Continue eculizumab maintenance dose