PNH: to transplant or not to transplant?

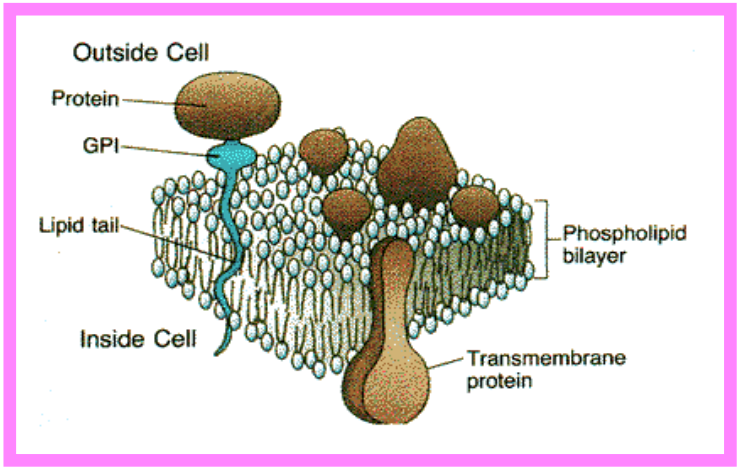
Anna Paola Iori

UMBERTO I
POLICLINICO DI ROMA
Ematologia

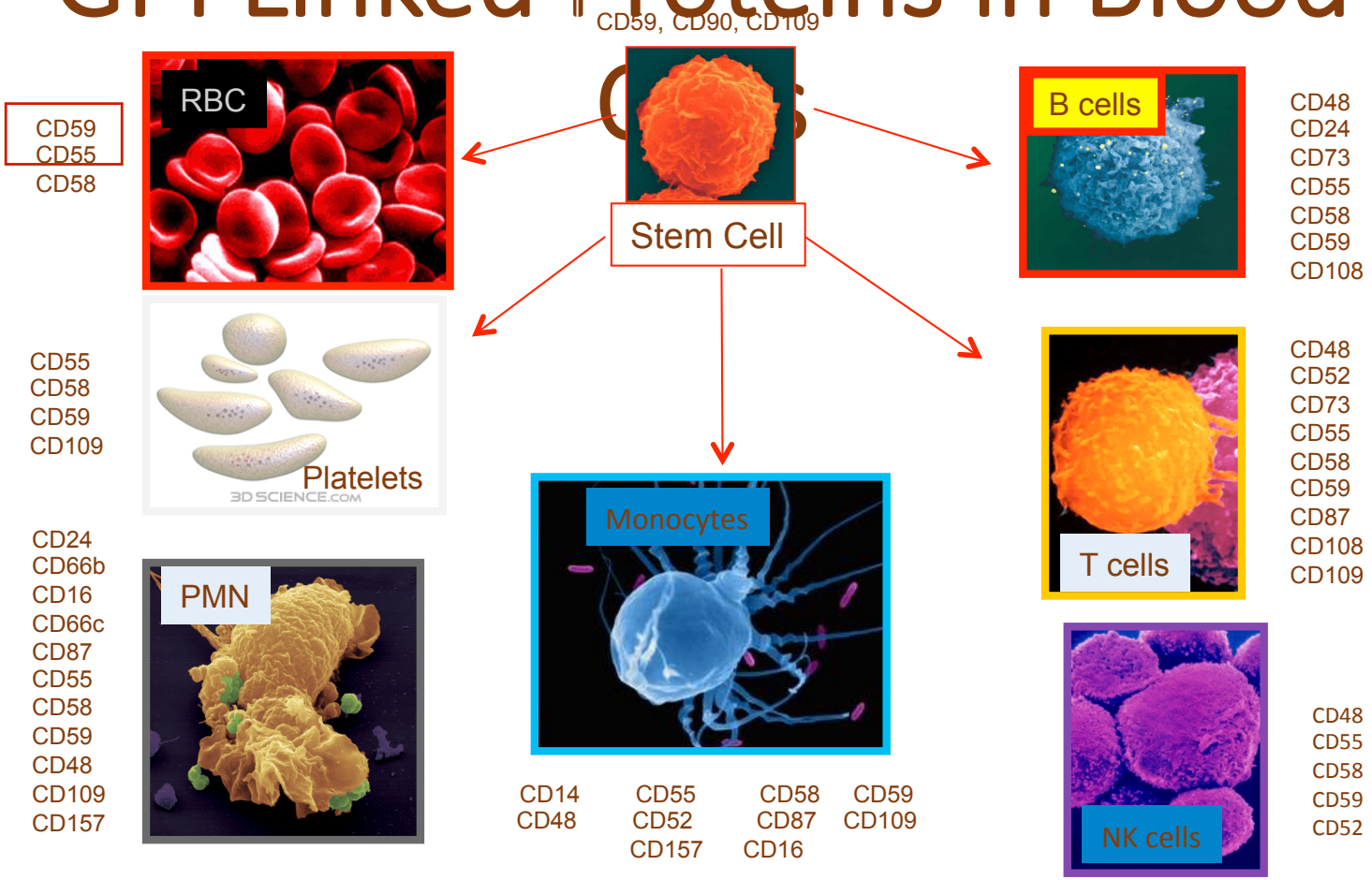
Paroxysmal nocturnal hemoglobinuria (PNH)

EPIDEMIOLOGY: rare disease (1-5 per million/year)

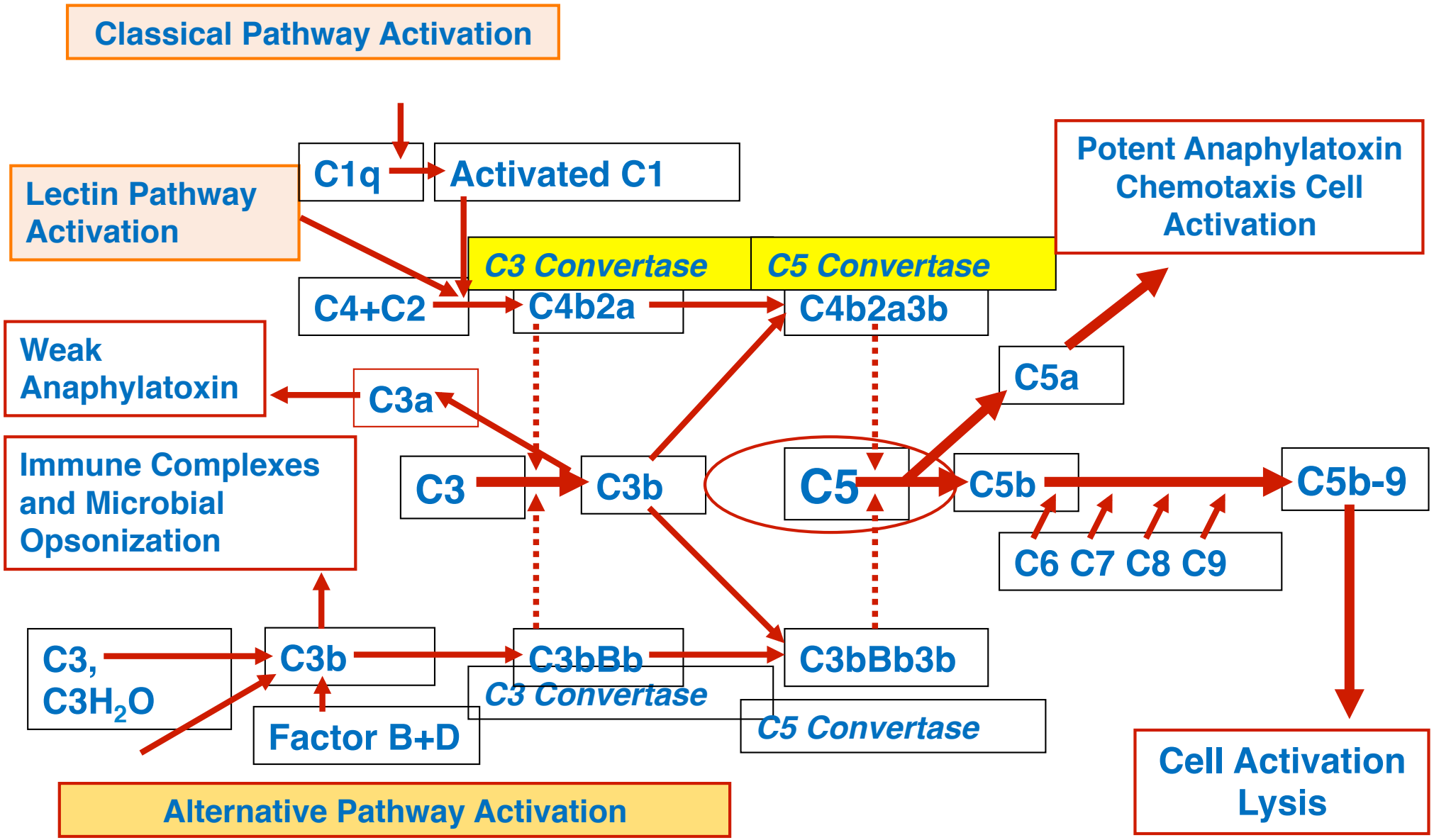
- **Clonal disease of HSC**
- **Acquired somatic mutation of the X – chromosome gene PIG-A**
- **Lack of expression of the GPI-anchored proteins on HSC**



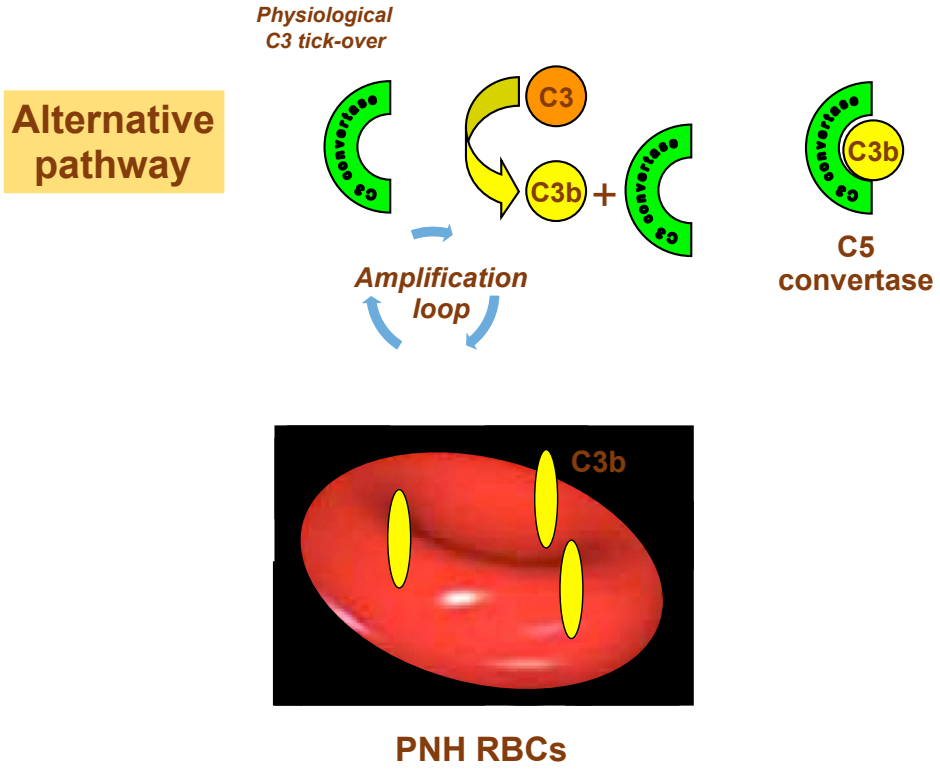
GPI Linked Proteins in Blood



Complement Activation

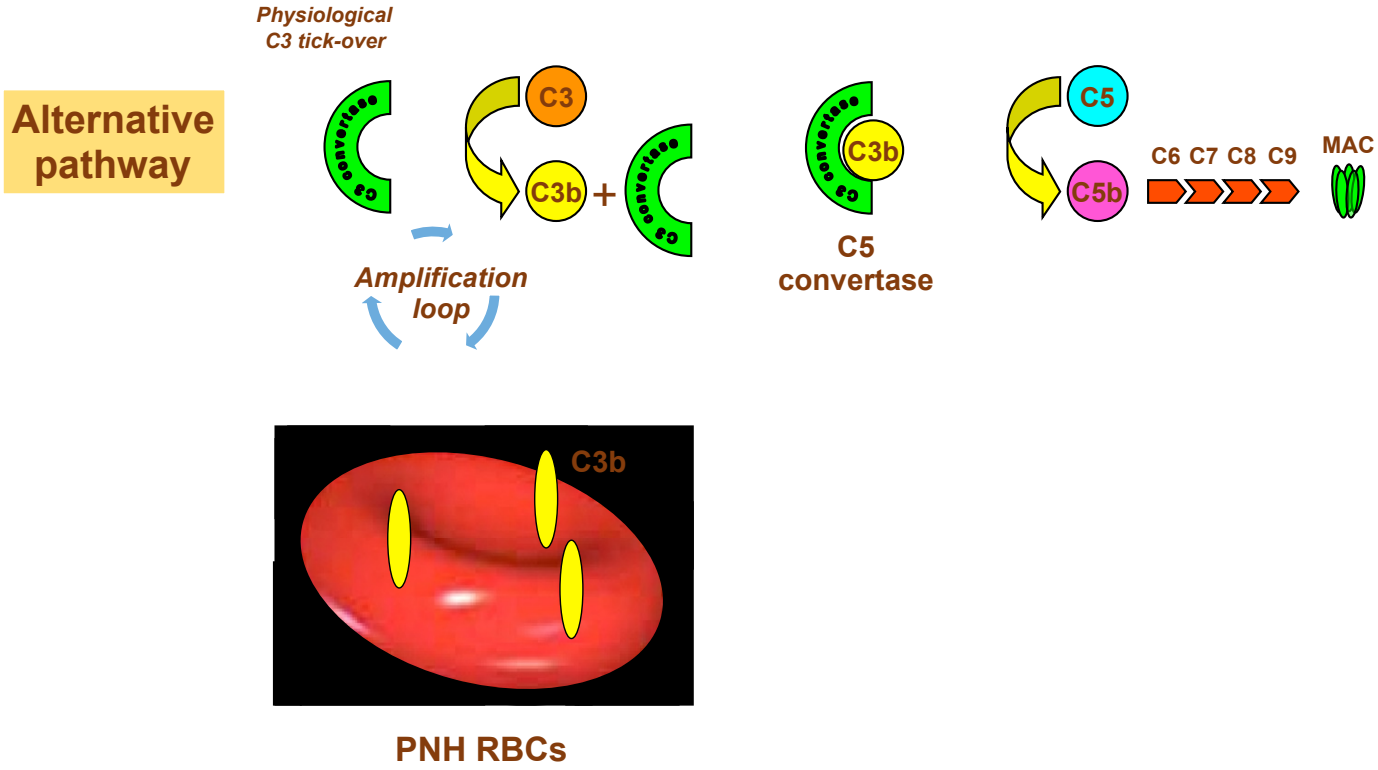


THE COMPLEMENT CASCADE REGULATION IN PNH



Courtesy of Antonio Risitano

THE COMPLEMENT CASCADE REGULATION IN PNH



Courtesy of Antonio Risitano

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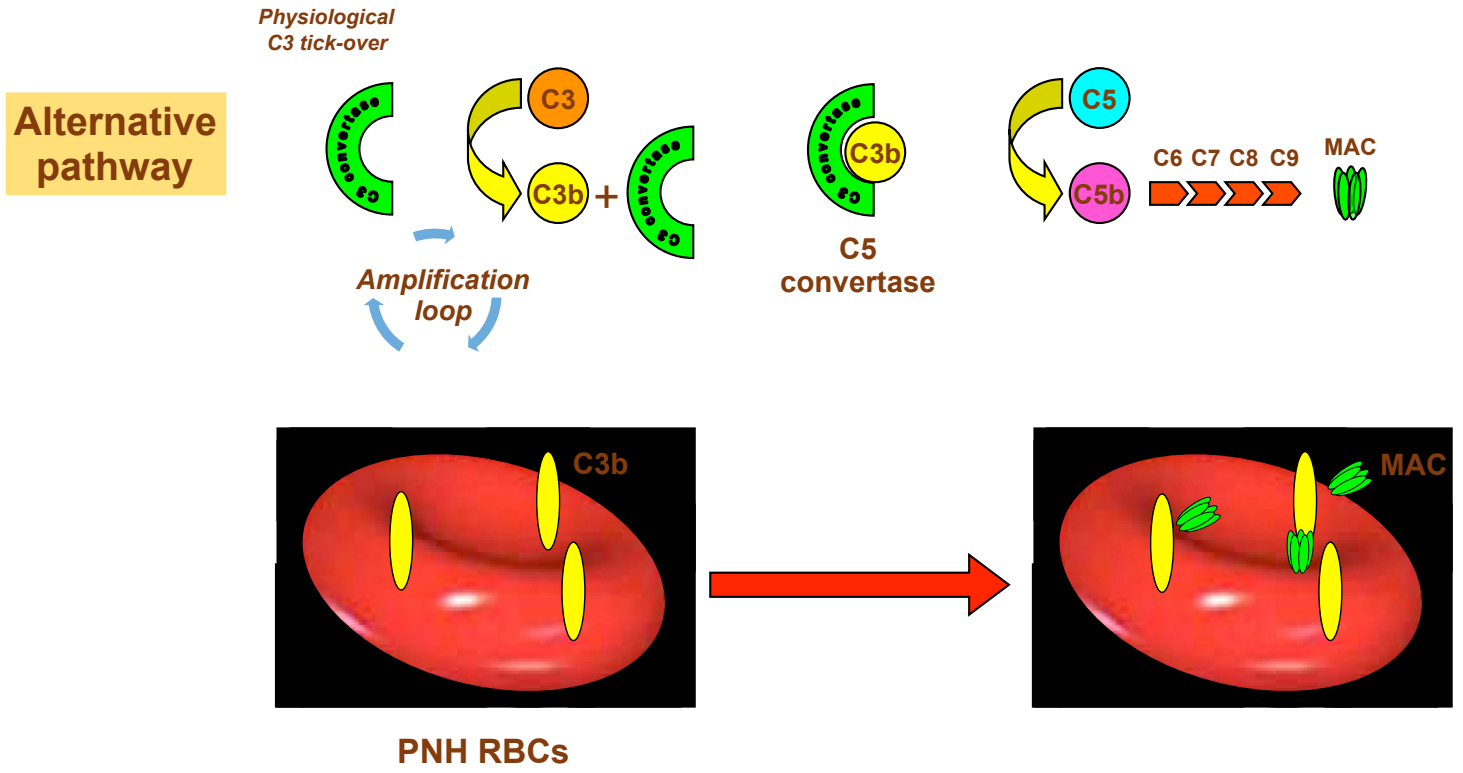
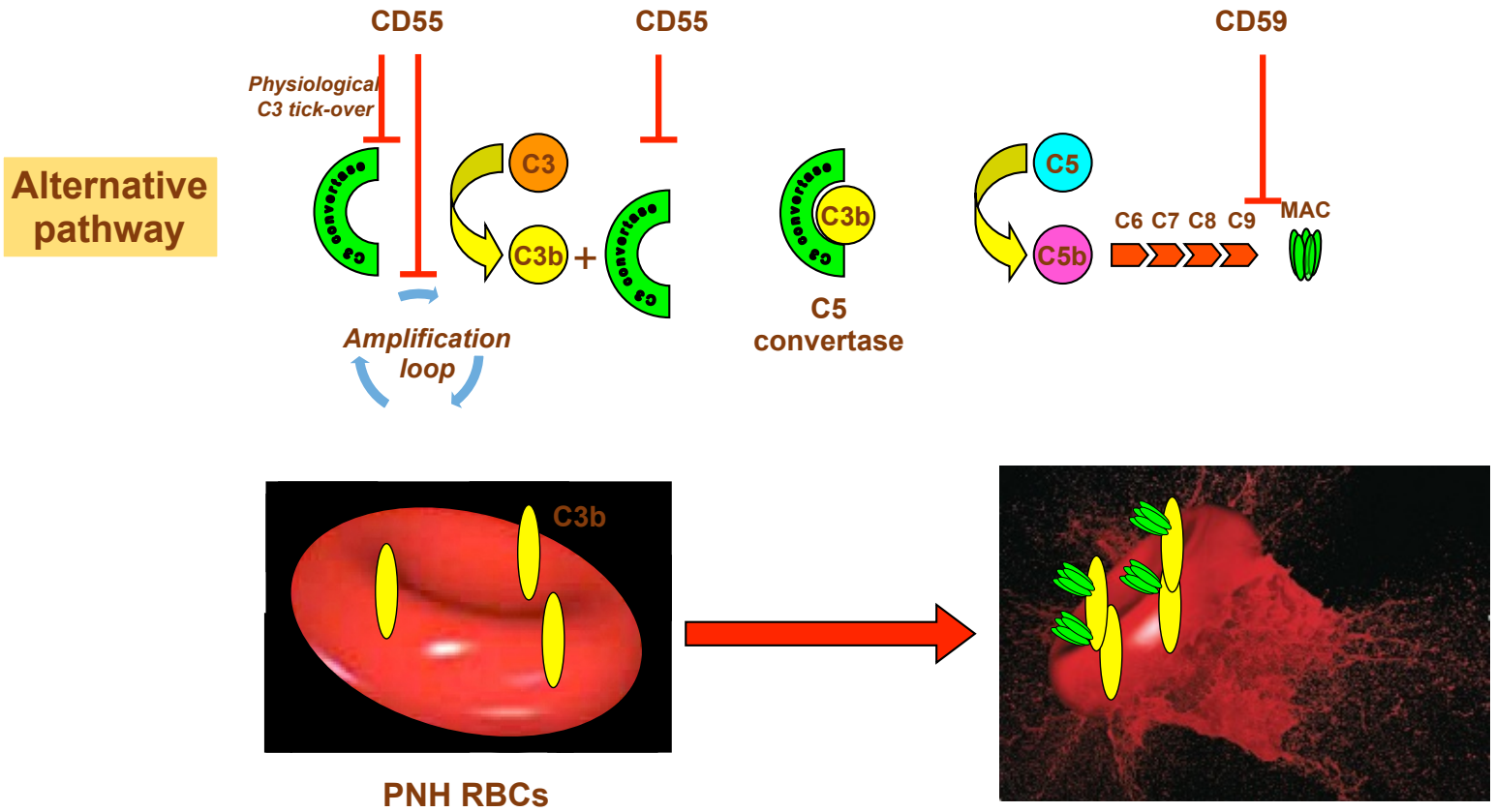


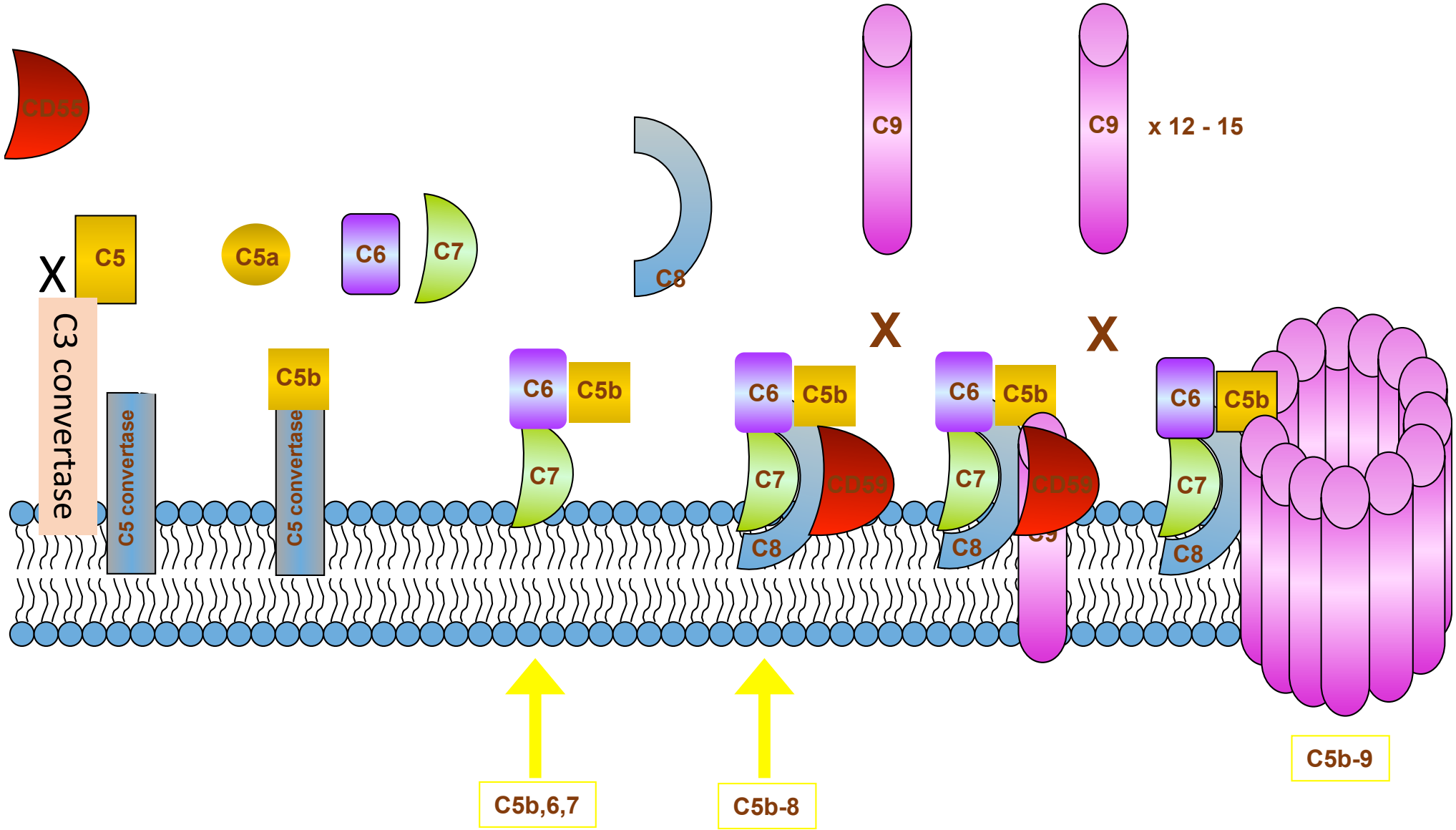
Courtesy of Antonio Risitano

THE COMPLEMENT CASCADE REGULATION IN PNH



Courtesy of Antonio Risitano

Complement on normal Red cell

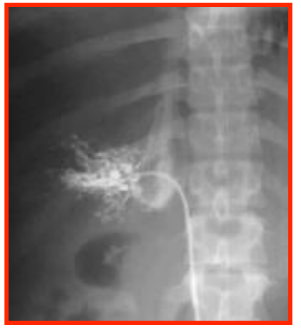


Adattato da Cellular and Molecular Immunology AK Abbas, AH Litchman and JS Pober, 3rd Edition. 1991 WB Saunders; Philadelphia.

THE CLINICAL TRIAD OF PNH

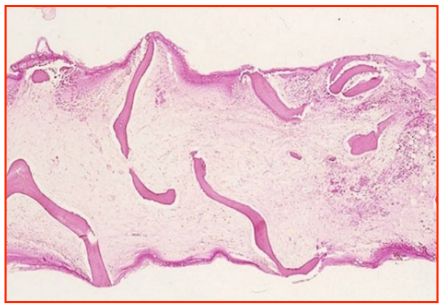
1. Chronic hemolytic anemia with paroxistic crises

   Intravascular hemolysis, complement mediated



2. Propensity to thromboembolisms

   Often at unusual site, especially veins
   (cerebral veins, hepatic veins, splenic vein)



3. Variable cytopenia

   Stigmata of marrow failure, possible
   overlapping with aplastic anemia (AA/PNH)

NATURAL HISTORY OF PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

PETER HILLMEN, M.B., CH.B., PH.D., S.M. LEWIS, M.D., MONICA BESSLER, PH.D., LUCIO LUZZATTO, M.D., AND JOHN V. DACIE, M.D.

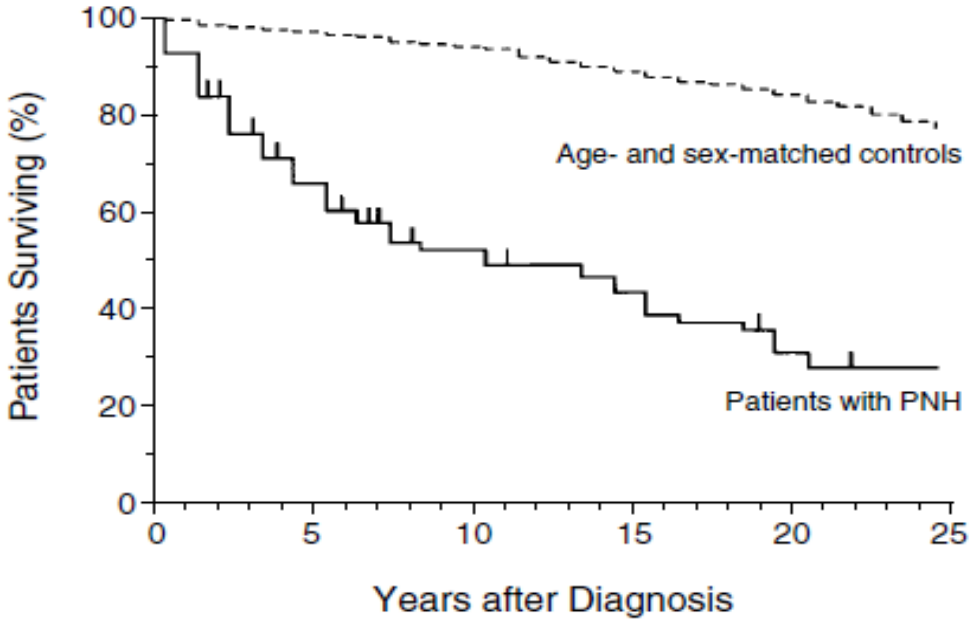


Figure 2. Actuarial Survival from the Time of Diagnosis in 80 Patients with PNH.

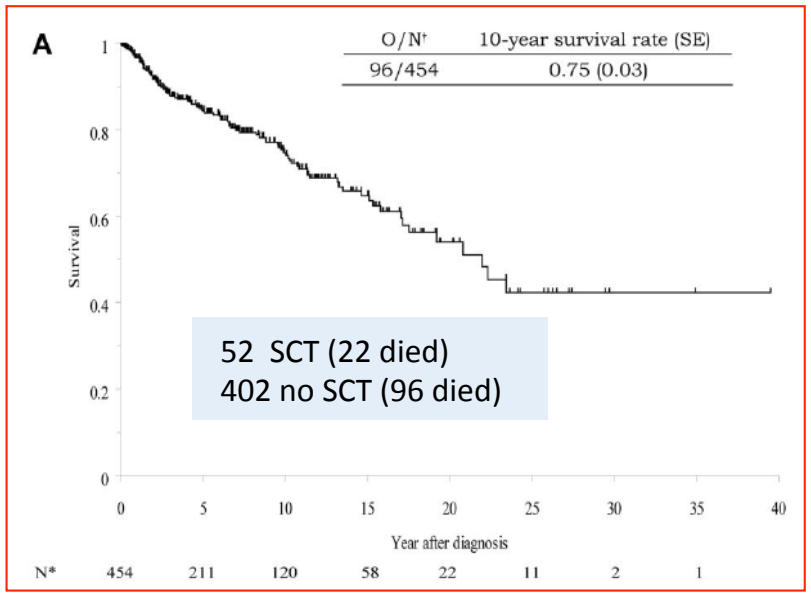
The median survival was 10 years. The expected survival of an age- and sex-matched control group is shown for comparison.

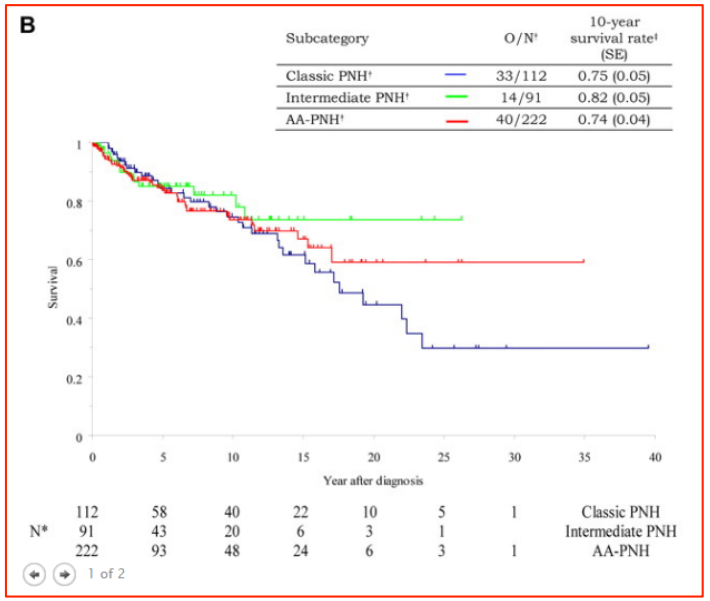
Blood 2008

Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories

Régis Peffault de Latour,[1] Jean Yves Mary,[2] Célia Salanoubat,[3] Louis Terriou,[4] Gabriel Etienne,[5] Mohamad Mohty,[6] Sophie Roth,[7] Sophie de Guibert,[8] Sebastien Maury,[9] Jean Yves Cahn,[10] and Gerard Socié,[1] on behalf of the French Society of Hematology and of the French Association of Young Hematologists

French cohort (n=460)





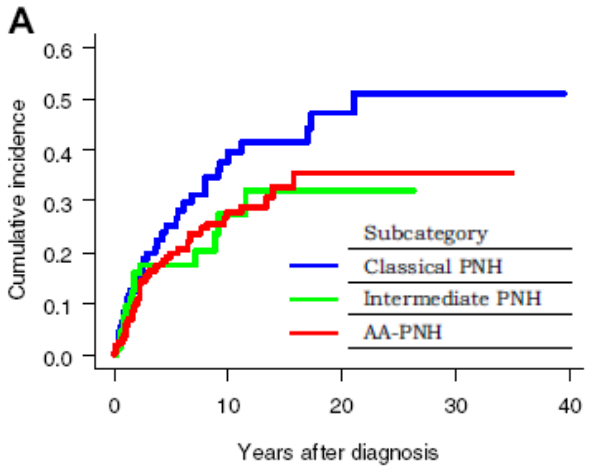
- Classic PNH: intravascular hemolysis with Hb< 12 g/dl and /or thrombosis at diagnosis but no evidence of bone marrow failure: PMN > 1.5 x 10^9 cells/L and PLTS120 >109 cells/L,
- AA-PNH: at least, 2 or 3 cytopenias (Hb≤10 g/dL, PLTS ≤80x10^9/L, PMN ≤ 1x10^9 /L).
- Intermediate PNH: who did not fulfill the last 2 subcategories'

NATURAL HISTORY OF PNH

Impact of thrombosis on survival

Table 4. Independent prognosis factors in the 3 subcategories of PNH

Factors	Classic PNH, n = 109	AA-PNH syndrome, n = 221	Intermediate PNH, n = 90
Period, 1985 or after	**3.6 (1.3-10.3), .010**	0.89 (0.74)†	**4.1 (1.0-16.9), .045**
Age at diagnosis			
Between 40 and 55 y	**5.4 (1.9-15.7), <.001**		
More than 40 y		1.7 (0.11)†	
More than 55 y	**21.4 (6.6-68.7), <.001**		**5.7 (1.4-23.3), .020**
Thrombocytopenia			**0.16 (0.04-0.60), .007**
Androgens/danazol	**0.17 (0.03-0.88), .013**		
Immunosuppressive treatment*		**0.33 (0.11-0.99), .026**	
Transfusions before 1996		**2.7 (1.3-5.6), .007**	
Evolution to*			
Bicytopenia or pancytopenia	**7.3 (2.5-21.5), <.001**	**NA‡**	2.5 (0.29)†
Thrombosis	**7.8 (3.4-17.8), <.001**	**33.0 (14.3-76.2), <.001**	**17.6 (4.5-68.5), <.001**
Malignant disease (MDS/AML)	2.2 (0.68)†§	**48.8 (15.9-149.6), <.001**	**38.5 (4.5-327.9), .003**



Thrombosis is the main cause of death as well as the complication with the largest impact on quality of life and survival of PNH patients, regardless the specific PNH subcategory

De Latour et al, Blood 2008

Blood 2008

Paroxysmal nocturnal hemoglobinuria: natural history of disease subcategories

Régis Peffault de Latour,[1] Jean Yves Mary,[2] Célia Salanoubat,[3] Louis Terriou,[4] Gabriel Etienne,[5] Mohamad Mohty,[6] Sophie Roth,[7] Sophie de Guibert,[8] Sebastien Maury,[9] Jean Yves Cahn,[10] and Gerard Socié,[1] on behalf of the French Society of Hematology and of the French Association of Young Hematologists

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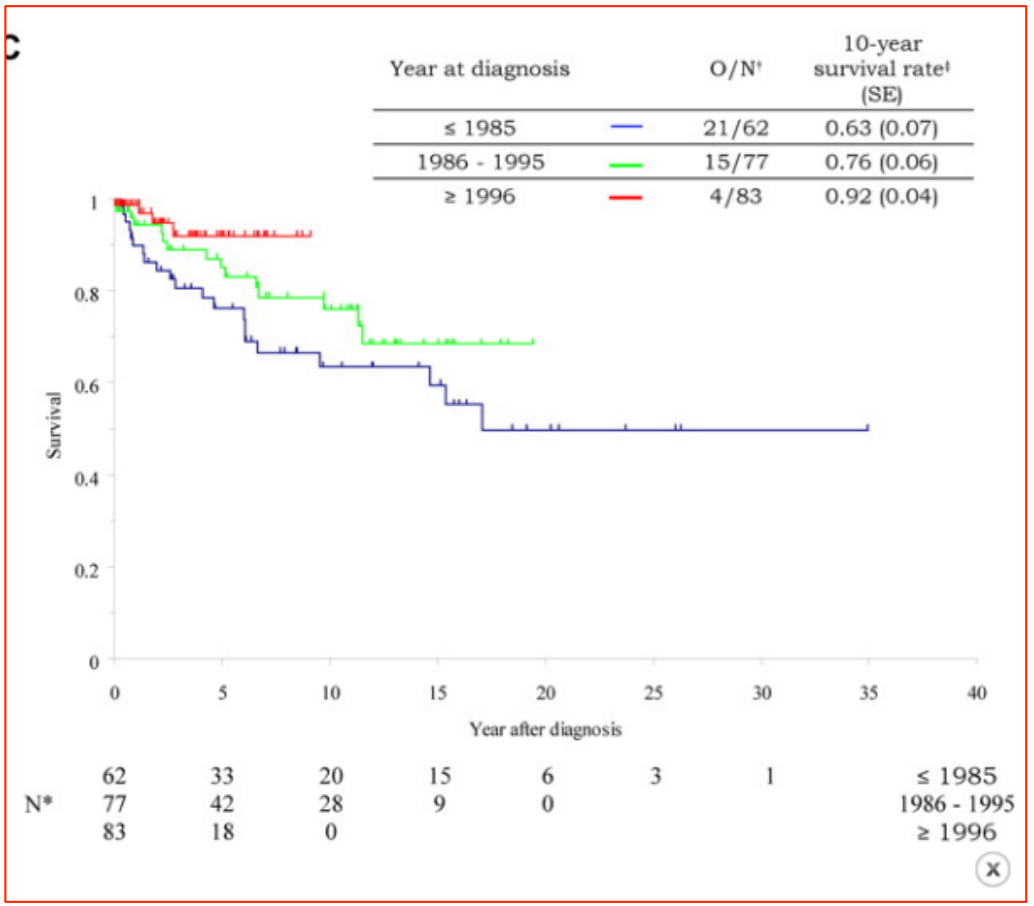


Therapeutic approach

Supportive therapy

- Iron support
- Red blood cell transfusions // iron chelation
- Ev Idratation 
- Corticosteroids
- Antocoagulant therapy

(vitamin K antagonist; LMWH)

Manageable Symptoms Mild PNH

Severe PNH

Curative therapy

- Allogeneic – HSCT (sib)

Life threatening status

SAA, high trasfusion requirement, severe / recurrent thrombosis

ISST

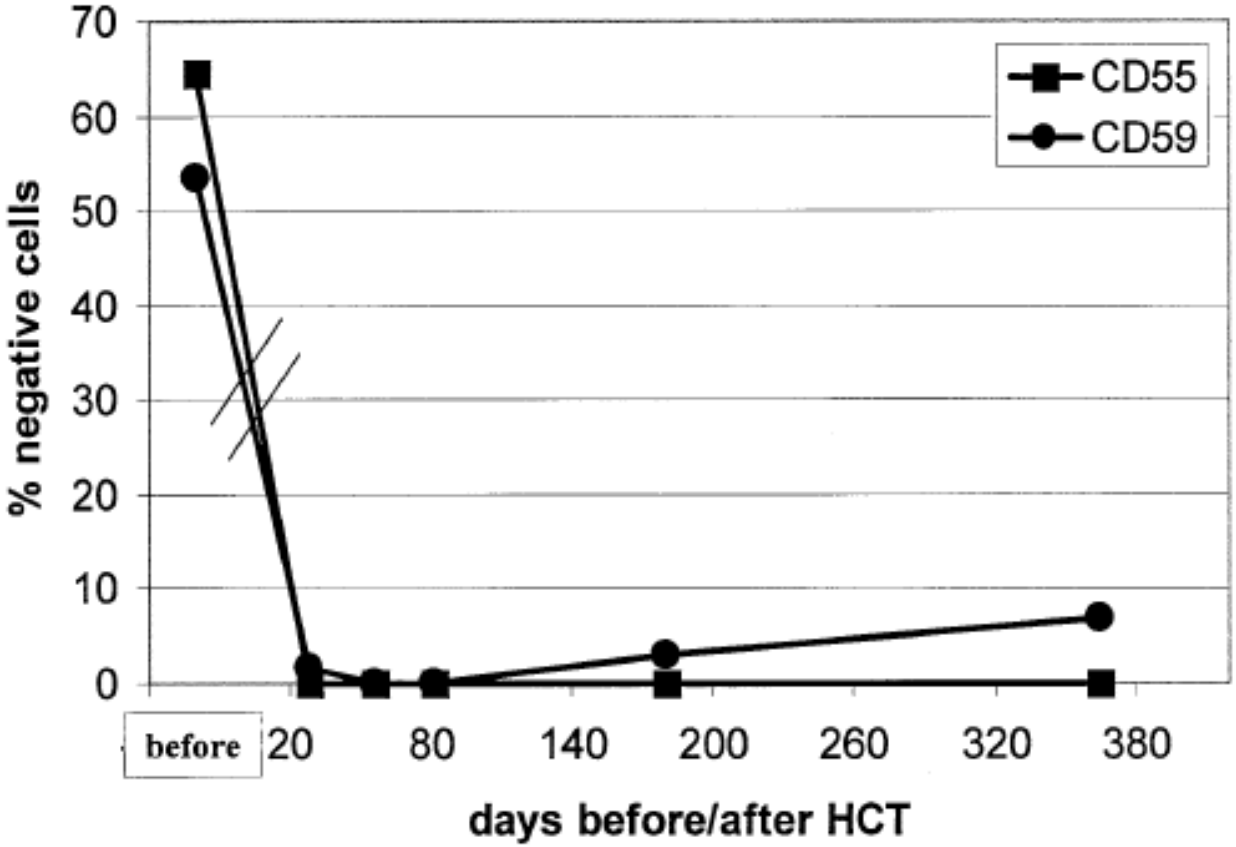
Biology of Blood and Marrow Transplantation 9:689-697 (2003)

1083-8791/03/0911-0004$30.00/0
doi:10.1016/S1083-8791(03)00264-7

ASBMT
American Society for Blood and Marrow Transplantation

Hematopoietic Cell Transplantation from Related and Unrelated Donors after Minimal Conditioning as a Curative Treatment Modality for Severe Paroxysmal Nocturnal Hemoglobinuria

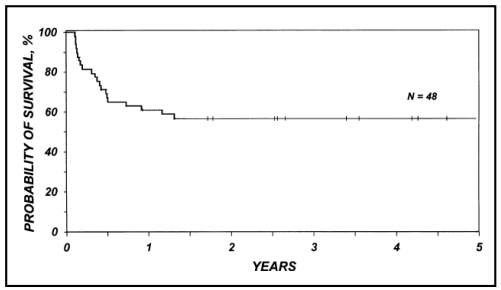
U. Hegenbart,[1] D. Niederwieser,[1] S. Forman,[2] E. Holler,[3] S. Leiblein,[1] L. Johnston,[4] W. Pönisch,[1] E. Epner,[5] R. Witherspoon,[6,7] K. Blume,[4] R. Storb[6,7]



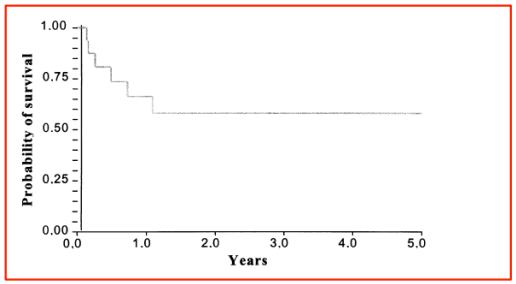
7 pts
Fludara 90mg/m2
TBI 200

Transplant expericences

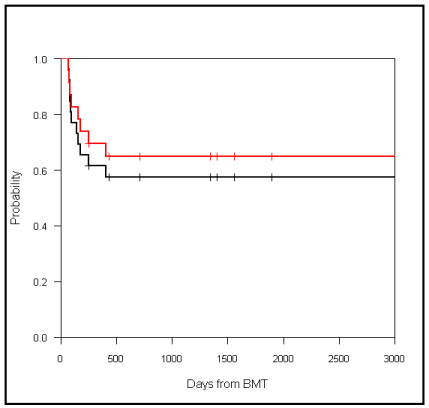
Ref	N°	Conditioning	OS	GVHD
Saso BJH 1999 IBMTR	48 sib 6 MUD 1 aplo 2 Syn	BuCY 53% TBI 21%	5yrs OS 56% (MUD 1/7 alive)	AGVHD II-IV:34% ECGVHD:33%
Bemba BJH 1999 France	16 sib	CyTBI 6 % CyTAI 50% Cybased 43%	5yrs OS 58%	AGVHD II-IV 50% ECGVHD11%
Santarone Haematol 2010 GITMO	22 sib 2 MUD 1 aplo 1 MMR	BuCy 58% RIC 42%	5yrs OS 57%	AGVHD 42% ECGVHD 16%



Saso BJH, 1999



Bemba BJH,1999



Santarone Haematol 2010

SCT and PNH: an EBMT retrospective study

haematologica | 2012; 97(11)

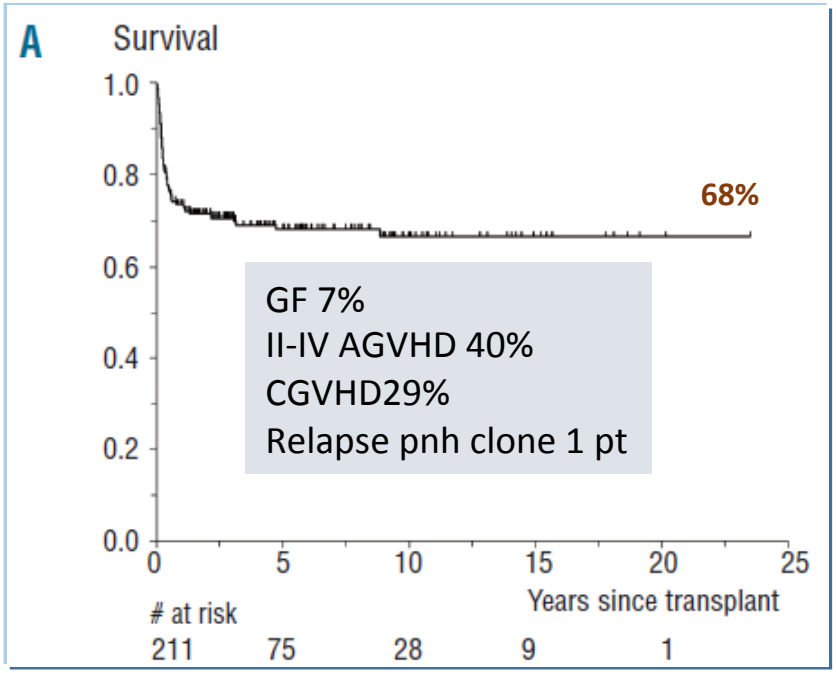
Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria

by Régis Peffault de Latour, Hubert Schrezenmeier, Andrea Bacigalupo, Didier Blaise, Carmino A. de Souza, Stephane Vigouroux, Roelf Willemze, Louis Terriou, Andre Tichelli, Mohamad Mohty, Sophie de Guibert, Judith Marsh, Jakob Passweg, Jean Yves Mary, and Gerard Socie

211 SCT for PNH from the EBMT database (1978-2007)

Table 1. Characteristics of patients and their transplants (n=211).

Characteristics	n/N (%) or median (IQR[a]), N
Indications for SCT[w]	
Severe aplastic anemia	118/191 (62%)
Recurrent severe hemolytic crises	64/191 (70%)
Thrombosis[§]	47/191 (25%)
Mesenteric veins	17
Budd Chiari	14
Central nervous system	6
Pulmonary embolism	3
Deep vein thrombosis	2
Myelodysplastic syndrome/acute myeloid leukemia	13/191 (7%)
Donor type	
HLA-identical sibling	136/210 (65%)
Source of stem cells[«]	
Bone marrow	135/210 (64%)
Peripheral blood stem cells	71/210 (34%)
Conditioning regimen	
Cyclophosphamide + busulfan	47/144 (33%)
Cyclophosphamide + total body irradiation (≥ 8 Gray)	22/144 (15%)
Cyclophosphamide + anti-thymocyte globulin	32/144(22%)
Fludarabine-based regimen	42/144 (29%)



GF 7%
II-IV AGVHD 40%
CGVHD29%
Relapse pnh clone 1 pt

SCT and PNH: an EBMT retrospective study

haematologica | 2012; 97(11)

Allogeneic stem cell transplantation in paroxysmal nocturnal hemoglobinuria

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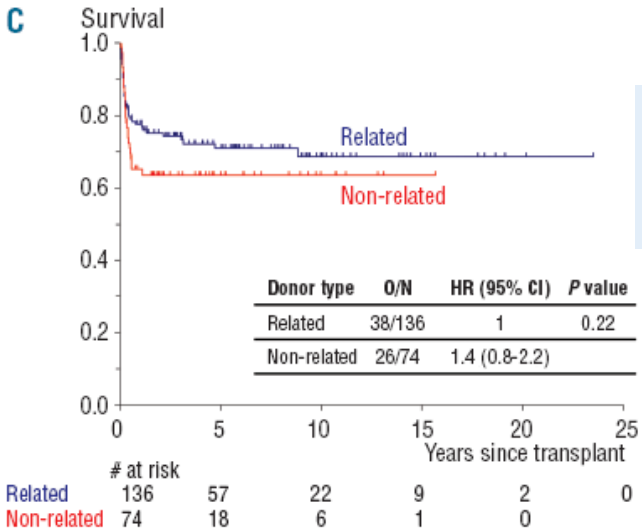
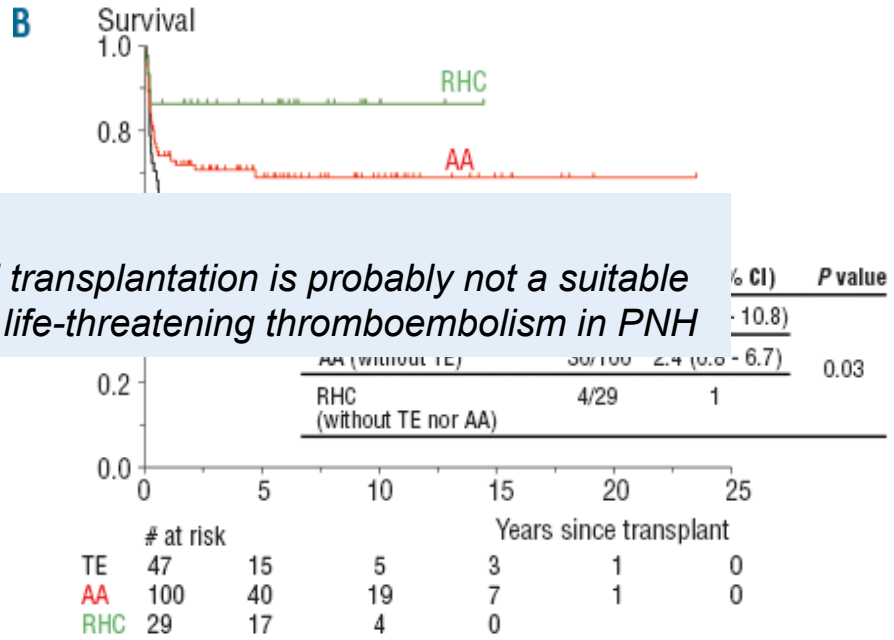




Conclusions

Allogeneic stem cell transplantation is probably not a suitable treatment option for life-threatening thromboembolism in PNH

No Difference in AA pts if SCT in upfront or after ISS (16pts)
No Difference in AA pts for stem cell source but BM < CGVHD

Biology of Blood and Marrow Transplantation 2014
journal homepage: www.bbmt.org

RIC and PNH
The NIH experience

Long-Term Outcome of Fludarabine-Based Reduced-Intensity Allogeneic Hematopoietic Cell Transplantation for Debilitating Paroxysmal Nocturnal Hemoglobinuria

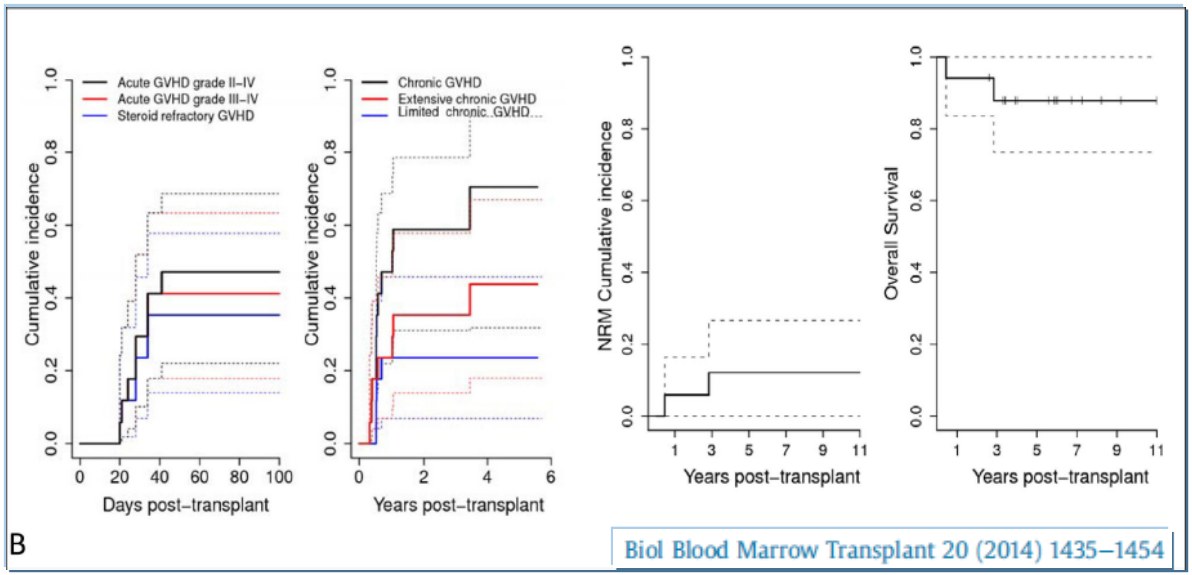
Jeremy Pantin [1,2], Xin Tian [3], Nancy Geller [3], Catalina Ramos [1], Lisa Cook [1], Elena Cho [1], Phillip Scheinberg [1,4], Sumithira Vasu [1,5], Hahn Khuu [6], David Stroncek [6], John Barrett [1], Neal S. Young [1], Theresa Donohue [1], Richard W. Childs [1,*]

N=17; indication to SCT:
- **BMF (10)**
- **hemolysys (4)**
- **thrombosis (3)**

✓**Conditioning: CTX 120 mg/kg (-7/-6), Flu 125 mg/m2 (-5/-1)**

✓**Immunosuppression: hATG (40x4), CsA, MTX (or MMF)**

✓**HLA-matched siblings (1 mother); SCT source PBSC**



Biol Blood Marrow Transplant 20 (2014) 1435–1454

Haploidentical hematopoietic stem cell transplant in paroxysmal nocturnal hemoglobinuria

Hong Tian, Liming Liu, Jia Chen et al

Leukemia &Lymphoma 2016; Vol 57, N= 4, 835-841

N° 18 (2007-2013)/ Haploidentical 10 pts

Median age 25 yrs (13-54)

Subcathegory:

- Hemolitic TD 5
- Cytopenia TD 4
- Cytopenia 1

Stem cell source:

- PB
- BM + PB 9

Conditioning regimen:

- Cytarabine: 4 g/m2 -5 to -2
- ATG 2,5 mg/Kg -5-2
- Busulfan (4mg/Kg/day) -8 to-6
- CY 1,8 g/m^2 -5-4
- Simustine (Me-CCNU; 250 mg/m2) -3

GVHD prophylaxis

CSA, MFM, MTX

Follow up(months)status

Alive 9/10

Median 17 months (14-29)

Dead 16 months (Infection)

GVHD

Acute II-III 4

Chronic 7

Limited 5

Extensive 1

Editorial Leukemia & Lymphoma

Flore Sicre de Fontbrune & Regis Peffault de Latour

haematologica | 2012; 97(11)

SCT and PNH: an EBMT retrospective study

Case-control comparison between SCT and best supportive care

SCT (n=211, 1978-2007, EBMT) vs best care (n=402, 1950-2005, French Registry).

Table 1. Characteristics of patients and their transplants (n=211).

Characteristics	n/N (%) or median (IQR[φ]), N
Indications for SCT[γφ]	
Severe aplastic anemia	118/191 (62%)
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Cyclophosphamide + total body irradiation (≥ 8 Gray)	22/144 (15%)
Cyclophosphamide + anti-thymocyte globulin	32/144 (22%)
Fludarabine-based regimen	42/144 (29%)

Table 2. Characteristics of non-transplanted patients.

Characteristics	n/N (%) or median (IQR[φ]), N
Gender, female	222/402[θ] (55%)
Age at diagnosis, years	36 (25-51)
Clone size	30 (15-52), 132
Complications	
Aplastic anemia	59/402
Thrombosis	106/402
Budd Chiari	44
Central nervous system	33
Deep vein thrombosis	31
Pulmonary embolism	7
Myelodysplastic syndrome/acute leukemia	21/402
Treatment	
Immunosuppressive treatment (≥1)[γ]	96/402 (24%)

No pt received eculizumab

haematologica | 2012; 97(11)

SCT and PNH: an EBMT retrospective study

APLASTIC ANEMIA

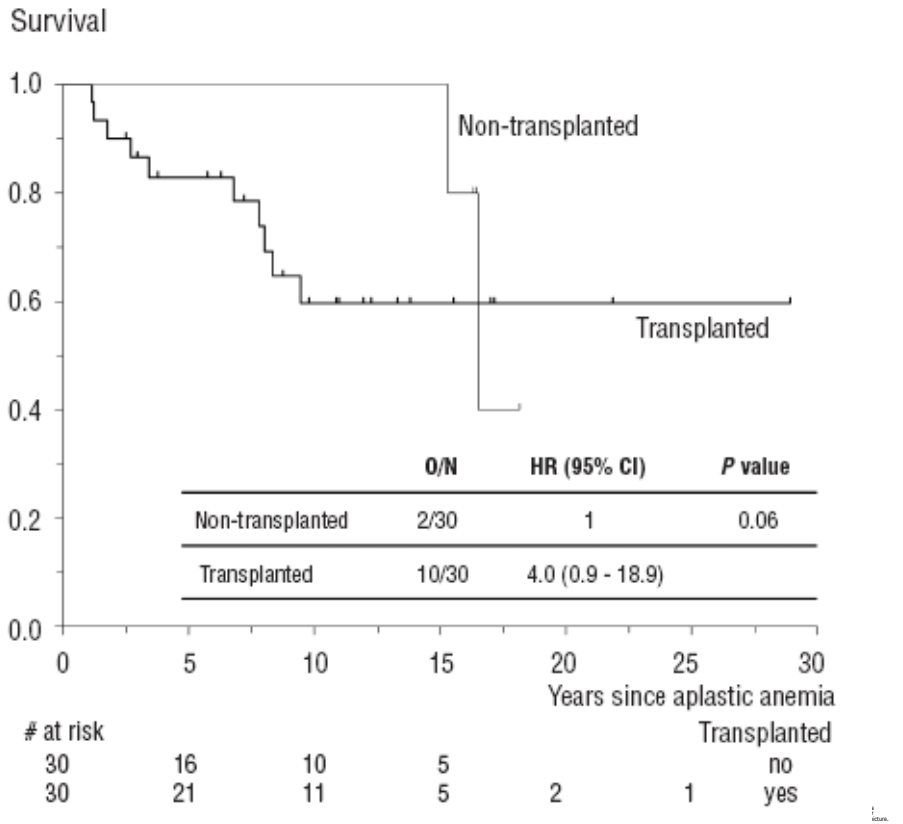
One to one matching between transplanted and non-transplanted patients
30 matched pairs of transplanted vs non-transplanted pts

No statistically significant difference:

Possible benefit

IST over SCT?

Best results with SCT in sAA, SIB, > 2002



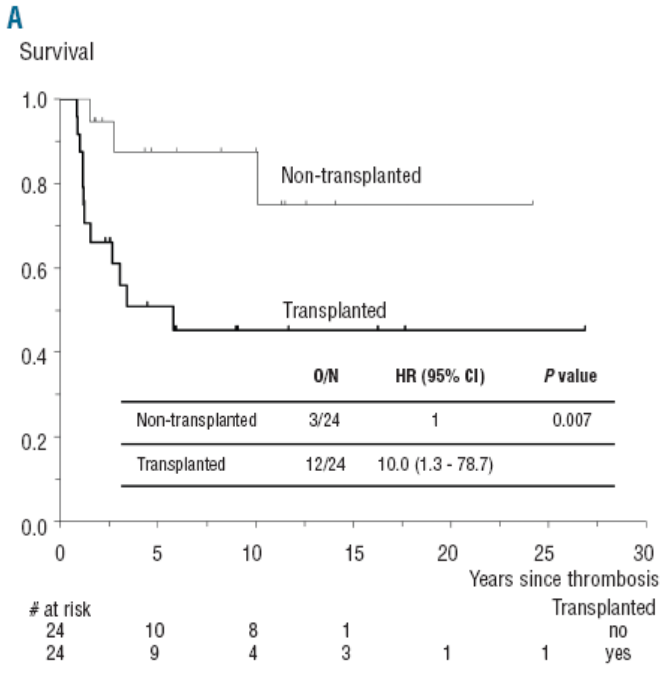
haematologica | 2012; 97(11)

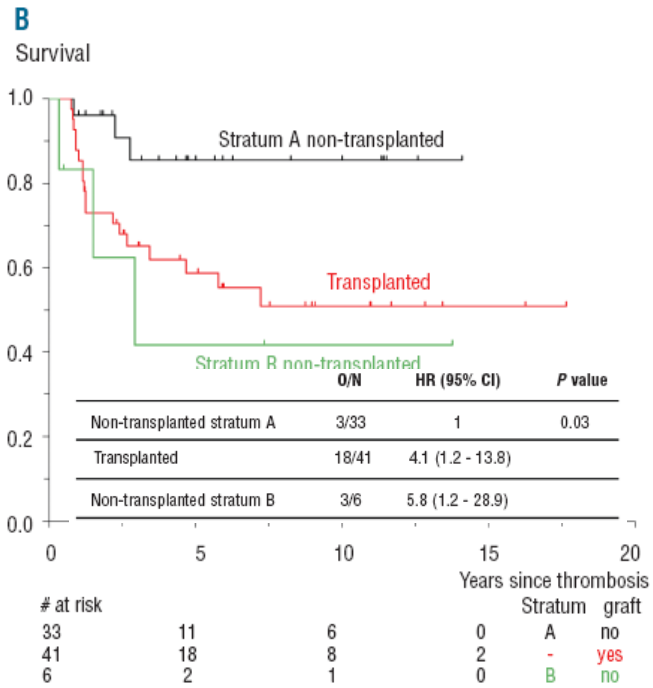
SCT and PNH: an EBMT retrospective study

THROMBOTIC EVENT

Global matching

stratum A : non SCT, age <30 years and delay ≥ 3 months, or delay < 3 months between PNH and TE event
stratum B: non SCT, age ≥ 30 years and delay ≥ 3 months





Pilot Study – *NEJM* 2004; N = 11

TRIUMPH – *NEJM.* 2006; Phase III Trial, N = 87

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Eculizumab was licensed by the Food and Drug Administration in March 2007 and by the European Medicines Agency in June 2007 for the treatment of PNH

blood

2008 111: 1840-1847
Prepublished online Nov 30, 2007;
doi:10.1182/blood-2007-06-094136

Multicenter phase 3 study of the complement inhibitor eculizumab for the treatment of patients with paroxysmal nocturnal hemoglobinuria

Robert A. Brodsky, Neal S. Young, Elisabetta Antonioli, Antonio M. Risitano, Hubert Schrezenmeier, Jörg Schubert, Anna Gaya, Luke Coyle, Carlos de Castro, Chieh-Lin Fu, Jaroslaw P. Maciejewski, Monica Bessler, Henk-André Kroon, Russell P. Rother and Peter Hillmen

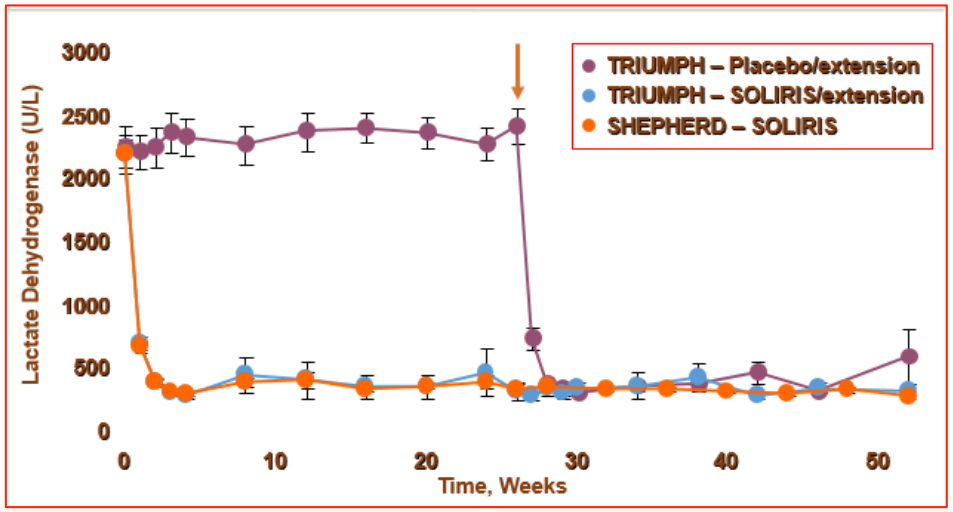
blood

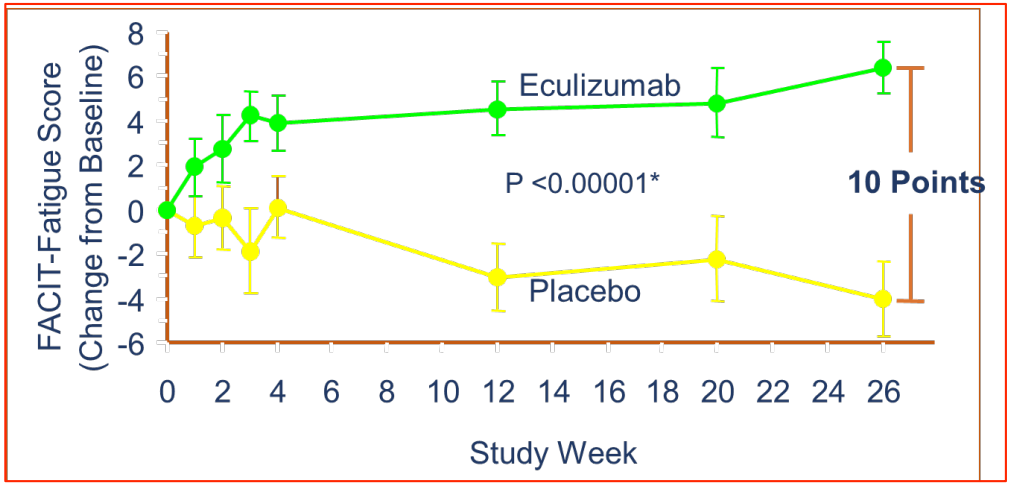
2007 110: 4123-4128
Prepublished online Aug 16, 2007;
doi:10.1182/blood-2007-06-095646

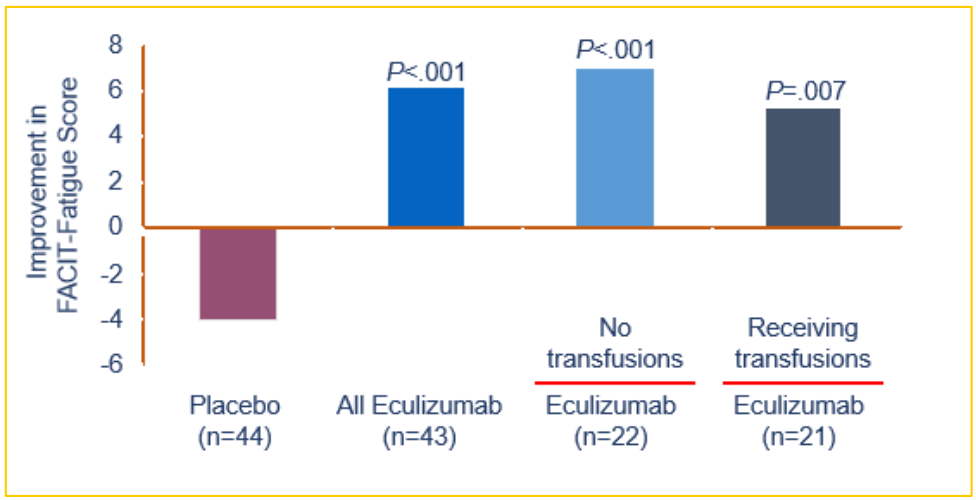
Effect of the complement inhibitor eculizumab on thromboembolism in patients with paroxysmal nocturnal hemoglobinuria

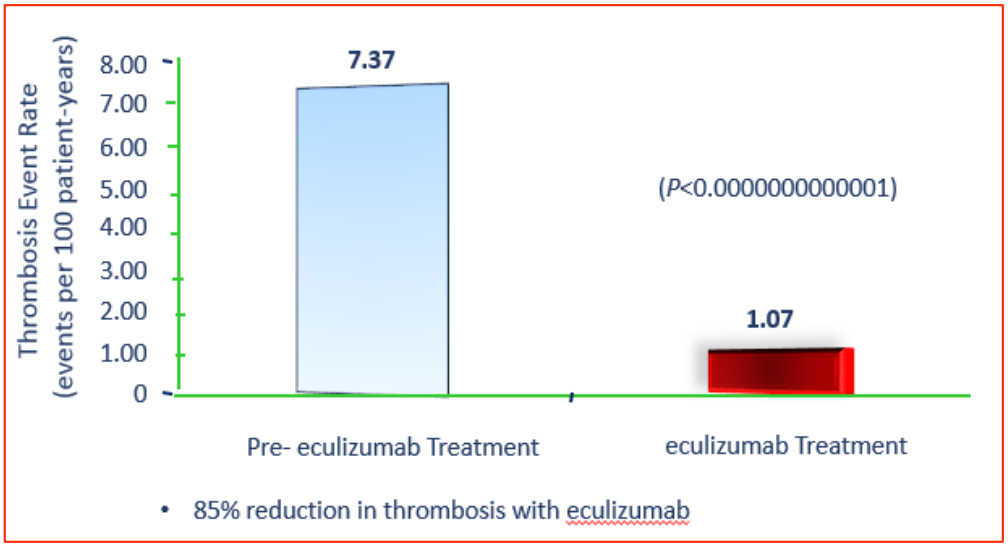
Peter Hillmen, Petra Muus, Ulrich Dührsen, Antonio M. Risitano, Jörg Schubert, Lucio Luzzatto, Hubert Schrezenmeier, Jeffrey Szer, Robert A. Brodsky, Anita Hill, Gerard Socié, Monica Bessler, Scott A. Rollins, Leonard Bell, Russell P. Rother and Neal S. Young

Eculizumab effect on PNH patients

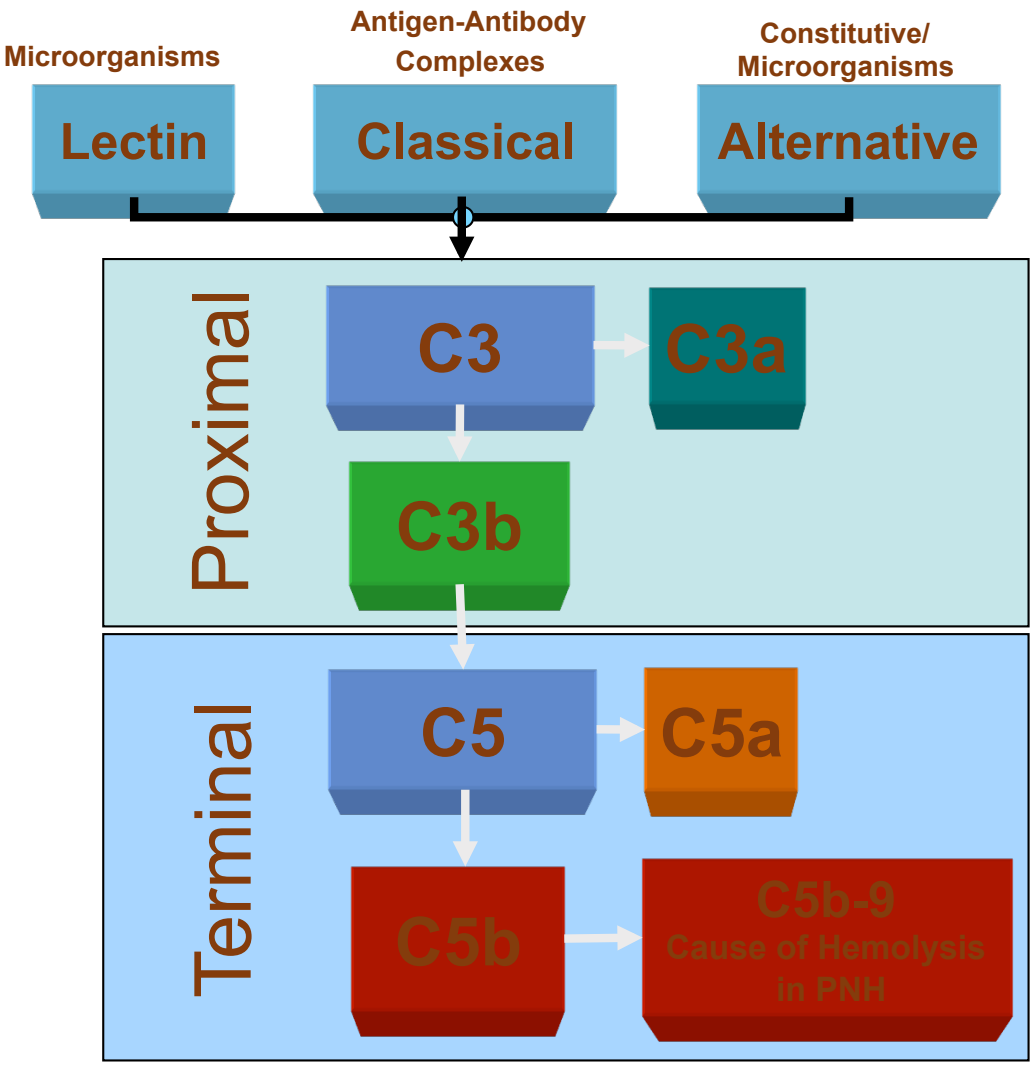


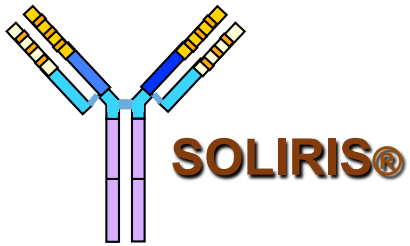






New Era
SOLIRIS® Blocks Terminal Complement





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

Figueroa, et al. *Clin Microbiol Rev*. 1991;4:359-395.
Walport. *N Engl J Med*. 2001;344:1058.

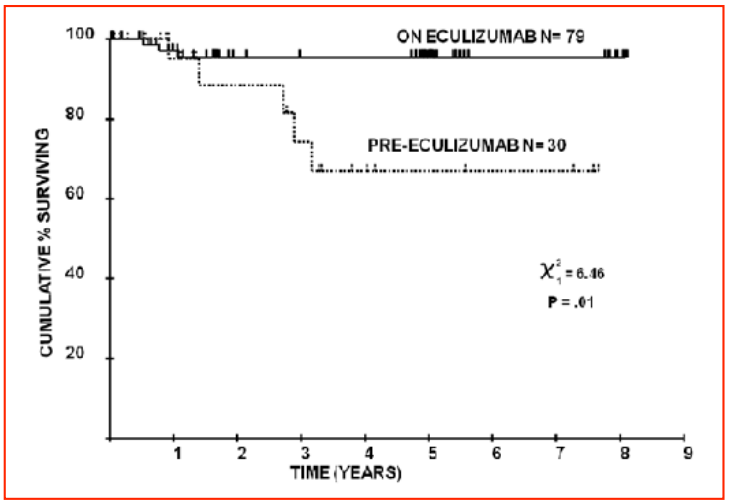
ECULIZUMAB AND PNH: EFFECTS ON SURVIVAL

blood

Long term treatment with eculizumab in paroxysmal nocturnal hemoglobinuria: sustained efficacy and improved survival

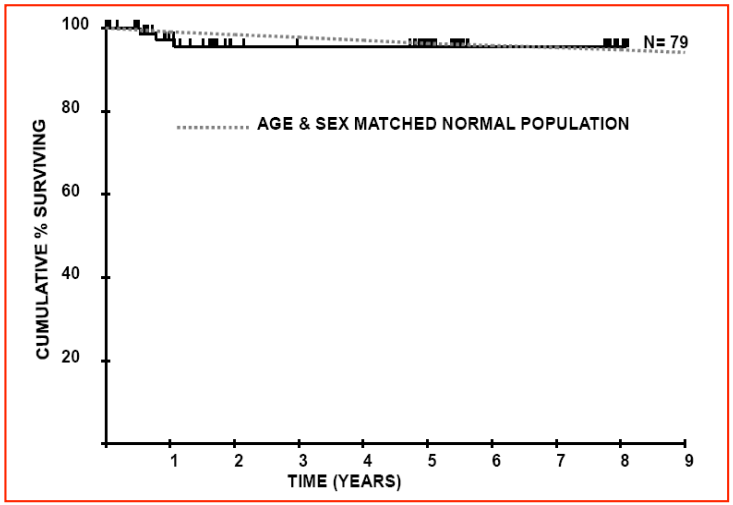
Richard J Kelly, Anita Hill, Louise M Arnold, Gemma L Brooksbank, Stephen J Richards, Matthew Cullen, Lindsay D Mitchell, Dena R Cohen, Walter M Gregory and Peter Hillmen

Untreated vs Ecu-treated PNH



OS of 30 pts with PNH assessed between 1997 and 2004 who fulfilled the criteria for treatment with eculizumab was also compared with the treated patient group

Treated PNH vs normal population



OS on eculizumab was compared with age- and sex-matched control averages obtained using 2001 United Kingdom census data from the United Kingdom Office of National Statistics.

RESEARCH ARTICLE

Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study

Michael Loschi,[1,2] Raphael Porcher,[3] Fiorenza Barraco,[4] Louis Terriou,[5] Mohamad Mohty,[6] Sophie de Guibert,[7] Beatrice Mahe,[8] Richard Lemal,[9] Pierre-Yves Dumas,[10] Gabriel Etienne,[10] Fabrice Jardin,[2] Bruno Royer,[11] Dominique Bordessoule,[12] Pierre Simon Rohrlich,[13] Luc Mathieu Fornecker,[14] Celia Salanoubat,[15] Sebastien Maury,[16] Jean-Yves Cahn,[17] Laure Vincent,[18] Thomas Sene,[19] Sophie Rigaudeau,[20] Stephanie Nguyen,[21] Anne-Claire Lepretre,[22] Jean-Yves Mary,[23,24] Bernadette Corront,[25] Gerard Socie,[1,24,*] and Regis Peffault de Latour[1,24,*]

Variable	Historical controls (*N* = 191)	Controls ≥ 1985 (*N* = 100)	Eculizumab (*N* = 123)	Standardized diff. (%)[a]	
				Unweighted	Weighted
Male gender—no. (%)	83 (43)	40 (40)	55 (45)	9.5	2.0
Age at inclusion (years) —median (IQR)	38 (27 to 52)	40 (29 to 51)	42 (31 to 60)	17.1	3.2
No. > 55 years (%)	44 (23)	23 (23)	39 (32)	19.5	2.9
Age at diagnosis (years) —median (IQR)	38 (26 to 51)	38 (27 to 50)	37 (24 to 49)	6.6	9.1
Time from diagnosis to inclusion (years) – median (IQR)	0.0 (0.0 to 1.1)	0.0 (0.0 to 1.7)	2.3 (0.5 to 7.0)	63.8	19.1
Flow cytometry—no. (%)	61 (32)	61 (61)	105 (94)	-	-
No. missing	1	0	11		
GPI-negative cells (%)—median (IQR)	46.0 (27.5 to 71.5)	46.0 (27.5 to 71.5)	80.5 (60.8 to 93.5)	-	-
No. missing	148	57	21		
No. > 50%	20 (47)	20 (47)	81 (79)	-	-
Presentation at inclusion					
Classic PNH—no. (%)	109 (61)	51 (54)	80 (87)	38.7	7.1
No. missing	13	6	31		
Previous aplastic anemia—no. (%)	54 (28)	25 (25)	43 (35)	21.8	3.5
Clinical symptoms					
Abdominal pain—no. (%)	56 (30)	27 (27)	53 (43)	32.3	5.6
Thrombosis—no. (%)	95 (50)	60 (60)	70 (57)	6.2	2.3
Infections—no. (%)	27 (14)	12 (12)	15 (12)	<1.0	1.8
Peripheral blood abnormalities – no. (%)					
None	40 (23)	28 (30)	25 (25)	12.0	6.2
Anemia only	80 (46)	34 (37)	58 (57)	29.7	4.3
Anemia and thrombocytopenia	24 (14)	12 (13)	12 (12)	8.8	28.5
Anemia and neutropenia	2 (1)	1 (1)	3 (3)	15.0	22.5
Pancytopenia	28 (16)	18 (19)	4 (4)	44.4	52.5
No. missing	17	7	21		
Follow-up—median years (IQR)	9.4 (2.2 to 15.9)	5.1 (1.8 to 11.4)	4.5 (2.4 to 5.6)	-	-

[a] Standardized differences are calculated as the absolute value of the mean difference between the controls > 1985 and eculizumab groups, divided by the pooled standard deviation. They are given for both the unweighted sample (characteristics presented in the table) and the weighted sample. Values presented are pooled over the imputed datasets.

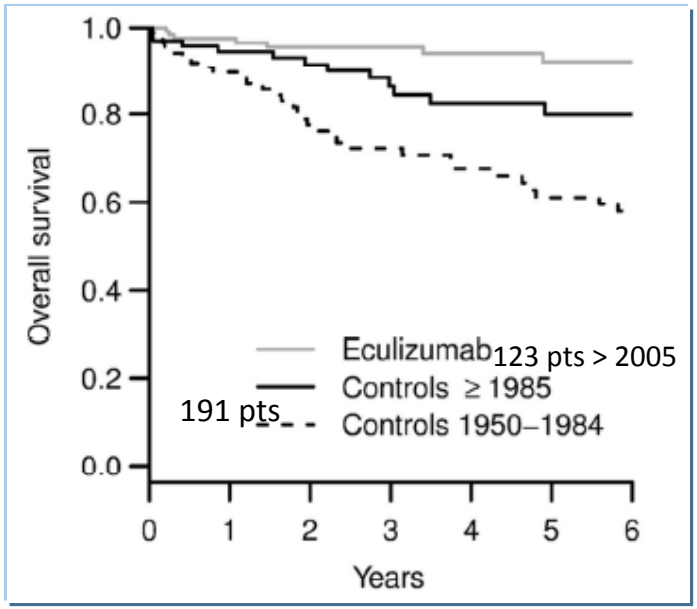
RESEARCH ARTICLE

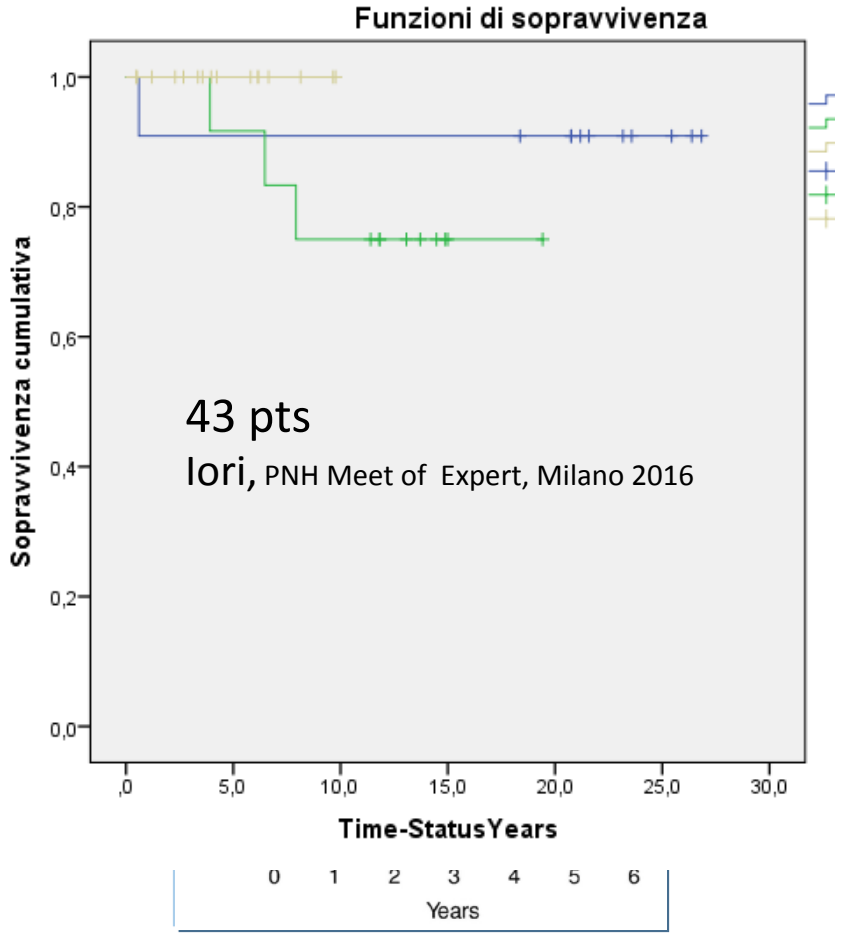
AJH

Impact of eculizumab treatment on paroxysmal nocturnal hemoglobinuria: a treatment versus no-treatment study

Michael Loschi,[1,2] Raphael Porcher,[3] Fiorenza Barraco,[4] Louis Terriou,[5] Mohamad Mohty,[6] Sophie de Guibert,[7] Beatrice Mahe,[8] Richard Lemal,[9] Pierre-Yves Dumas,[10] Gabriel Etienne,[10] Fabrice Jardin,[2] Bruno Royer,[11] Dominique Bordessoule,[12] Pierre Simon Rohrlich,[13] Luc Mathieu Fornecker,[14] Celia Salanoubat,[15] Sebastien Maury,[16] Jean-Yves Cahn,[17] Laure Vincent,[18] Thomas Sene,[19] Sophie Rigaudeau,[20] Stephanie Nguyen,[21] Anne-Claire Lepretre,[22] Jean-Yves Mary,[23,24] Bernadette Corront,[25] Gerard Socie,[1,24]* and Regis Peffault

Control group: PNH patients with indication to eculizu (clinically meaningful hemolysis and/or thrombosis)





Caution

The Soliris® increases the risk of meningococcal infection

- Vaccination before starting the drug
- Revaccination periodically according to the guidelines for meningococcal vaccination
- Patient monitoring for early signs of infection (antibiotics)
- Administration with caution in patients with infections in place

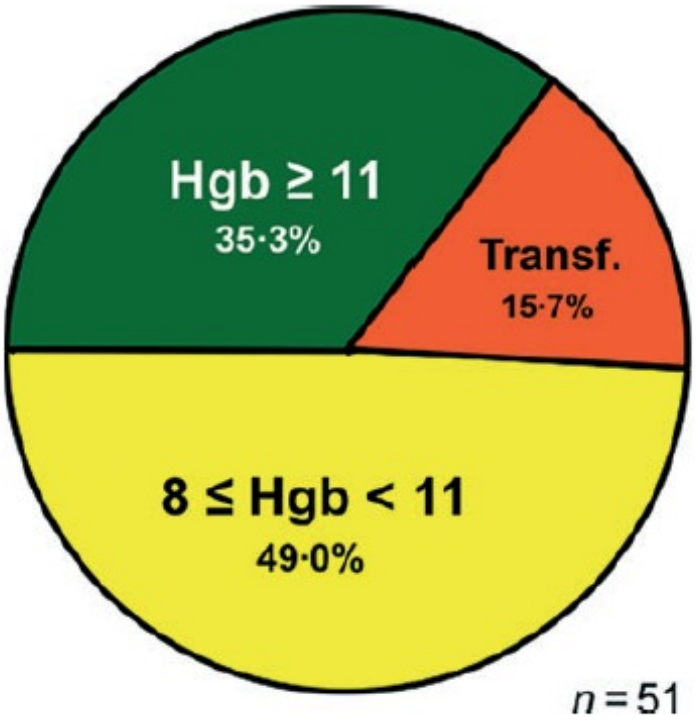
Patients who discontinue the Soliris®should be closely monitored for the onset of severe hemolysis

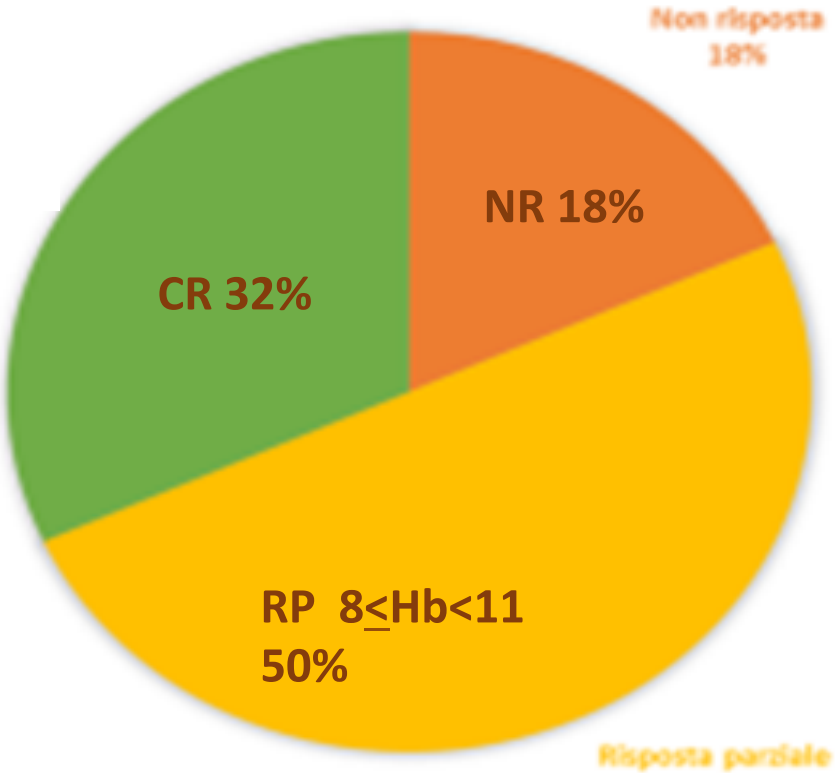
Eculizumab response

bjh state of the art review

Management of Paroxysmal Nocturnal Haemoglobinuria: a personal view

Lucio Luzzatto,[1] Giacomo Gianfaldoni[2] and Rosario Notaro[3]





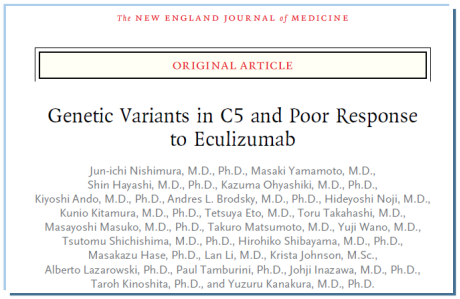
N 22

British Journal of Haematology, 153, 709–720 2011

Iori AP, Milano 2016

Genetics of response to eculizumab in PNH: C5

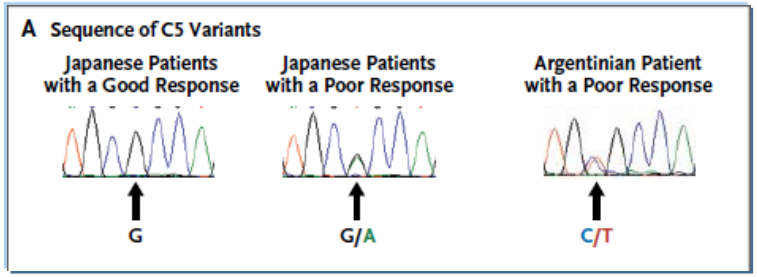
Rare C5 mutation may result in resistance (Nishimura et al, NEJM 2014)


The NEW ENGLAND JOURNAL of MEDICINE

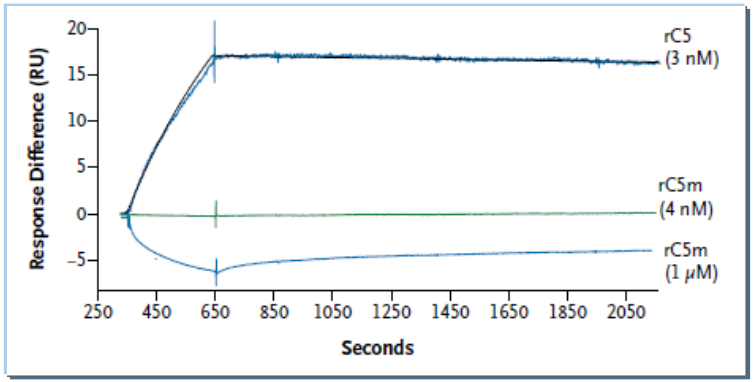
ORIGINAL ARTICLE

Genetic Variants in C5 and Poor Response to Eculizumab

Jun-ichi Nishimura, M.D., Ph.D., Masaki Yamamoto, M.D., Shin Hayashi, M.D., Ph.D., Kazuma Ohyashiki, M.D., Ph.D., Kiyoshi Ando, M.D., Ph.D., Andres L. Brodsky, M.D., Ph.D., Hideyoshi Noji, M.D., Kunio Kitamura, M.D., Ph.D., Tetsuya Eto, M.D., Toru Takahashi, M.D., Masayoshi Masuko, M.D., Ph.D., Takuro Matsumoto, M.D., Yuji Wano, M.D., Tsutomu Shichishima, M.D., Ph.D., Hirohiko Shibayama, M.D., Ph.D., Masakazu Hase, Ph.D., Lan Li, M.D., Krista Johnson, M.Sc., Alberto Lazarowski, Ph.D., Paul Tamburini, Ph.D., Johji Inazawa, M.D., Ph.D., Taroh Kinoshita, Ph.D., and Yuzuru Kanakura, M.D., Ph.D.

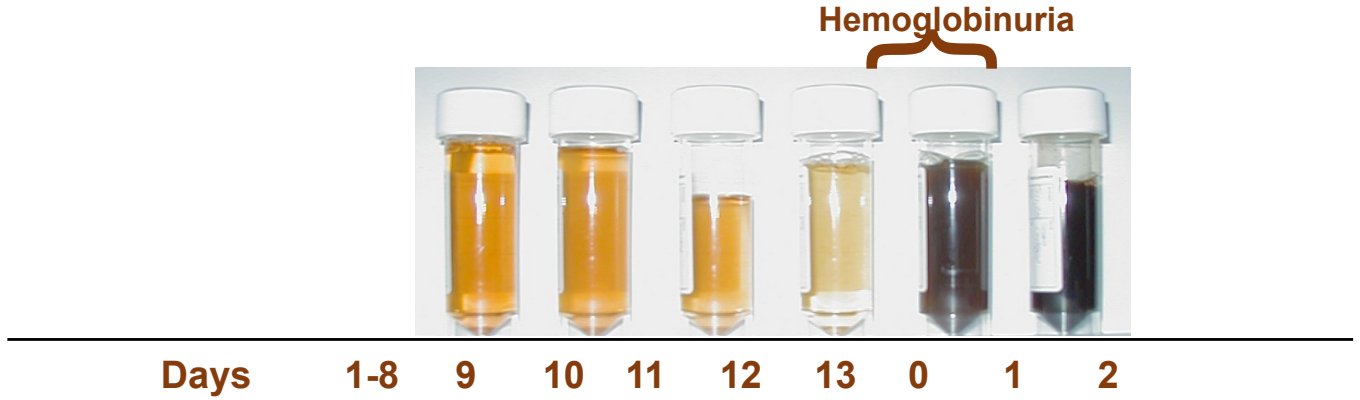


- **Polymorphisms of C5 at Arg 885**
  - Single heterozygous missence **(p.Arg885His)** mutation (generating a new *ApaLI* restriction site) found in 11 out 11 Japanese PNH patients lacking any response to eculizumab (n=345; 3,3%)
  - also found in healthy Japanese population (allelic frequence 3,5%)
  - A similar mutation **(p.Arg885Cys)** was found in a non-responder from Argentina (Asian ancestry)
- The mutation affected the binding to eculizumab



"BREAKTHROUGH" hemolysis during eculizumab treatment

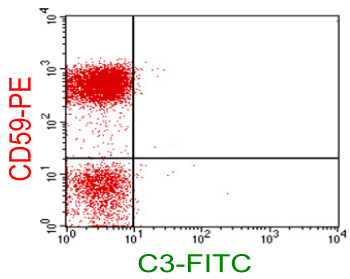
Pharmacokinetic breakthrough

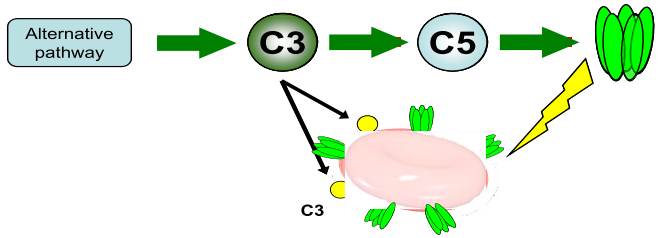


EXTRAVASCULAR HEMOLYSIS

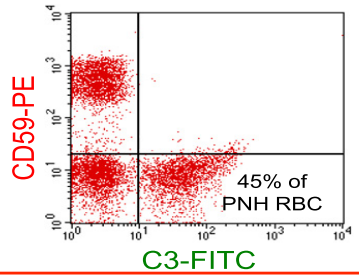
Risitano et al. Blood, 2009

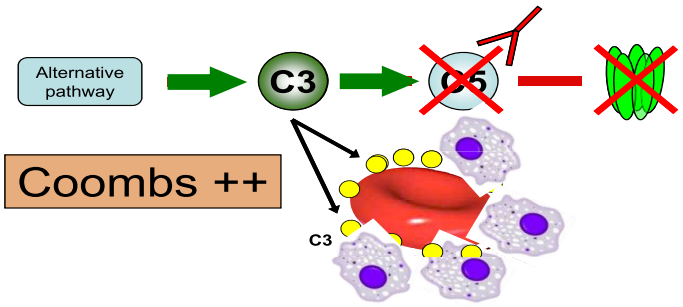
Untreated PNH patient





PNH patient on Eculizumab





Two procedures: pros and cons

HSCT	
Pros • **Curative approach**	**Cons** • TRM (>30%) • GVHD/QoL (30-40%)
Eculizumab	
Pros • **QoL** /PREGNANCY • **Increase OS**/Reduction of Thrombosis	**Cons**

ALEXION Study 1210-PNH 302

Selective Splenic artery embolization

TT30, Compstatin, Mini FH, AntiFD, Anti FB

PNH: to transplant or not to transplant?

We/patients wish to be cured even if risking mortality/worse quality of life
or we/pts wish
to have a good quality of life?

Initial assessment (>3 months)

Severe PNH

Mild PNH

Main problem: pancytopenia

Main problem: severe haemolysis;

Follow-up (living with PNH)

<40-50 yrs

HLA-identical donor?

Worsening

Stable

Main problem: Thrombysis

No

Yes

> 40yrs

ALG+CyA

Allo-HSCT

ECULIZUMAB

Supportive management

+/- Eltrombopag

??Very Young??

If eculizumab is not available:East/Middle est Europe, Africa

If response to eculizumab is not satisfaying: persistent transfusion-dependency

(even if novel treatment strategies may become available in the near future; shared decision with patient)

Iron support
Vitamin
Renal/Lung monitoring

Adapted by Luzzatto, BJH 2010


Grazie