Is the allogeneic stem cell transplantation still an option for PNH therapy?

Austin Kulasekararaj
King's College Hospital and King's College London

Disclosures

Research support (to institute)	Celgene/BMS, Novartis
Speaker's fees	Alexion, Amgen, Biocryst, Celgene/BMS, Novartis, Pfizer, Regeneron, Roche, Samsung, Sobi
Scientific advisory board	Agios, Alexion, Amgen, Biocryst, Celgene/BMS, Novartis, Novo Nordisk, Pfizer, Regeneron, Roche, Samsung, Silence Therapeutics, Adrax, Sobi

Is the allogeneic stem cell transplantation still an option for PNH ?

Yes

British Journal of Haematology, 1973, **24**, 743.

Paroxysmal Nocturnal Haemoglobinuria and Refractory Marrow Failure Treated by Marrow Transplantation

RAINER STORB, ROBERT S. EVANS, E. DONNALL THOMAS, C. DEAN BUCKNER, REGINALD A. CLIFT, ALEXANDER FEFER, PAUL NEIMAN AND STEPHEN E. WRIGHT

Department of Medicine, University of Washington School of Medicine, Veterans Administration Hospital, and the United States Public Health Service Hospital, Seattle, Washington

(*Received 29 August* 1972; *accepted for publication 2 October* 1972)

Haemolytic PNH

- 21year old male
- New diagnosis of haemolytic PNH 2008
- LDH 2241 (NR <240), Hb 82 g/L
- Symptomatic of haemolysis, with no thrombosis

- Identical Twin Brother (monozygotic)- Fit and well

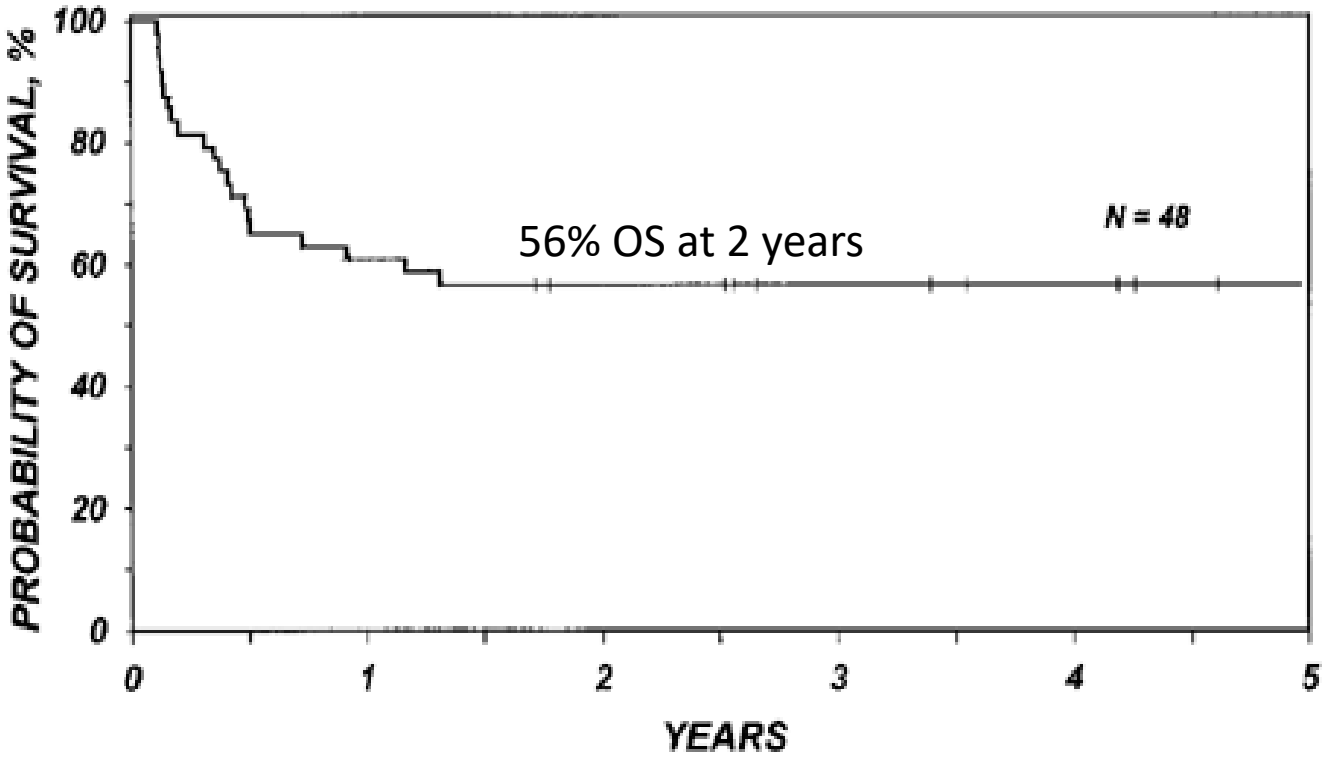
- what is the best treatment option?

HSCT vs Anti-complement therapy

HSCT in PNH

British Journal of Haematology, 1999, **104**, 392–396

1978-1995 (n=57)-CIBMTR



Bone marrow transplants for paroxysmal nocturnal haemoglobinuria

Radovan Sašo,[2] Judith Marsh,[2] Lidija Čevreska,[3] Jeffrey Szer,[4] Robert Peter Gale,[5] Philip A. Rowlings,[1] Jakob R. Passweg,[6] Melodee L. Nugent,[1] Lucio Luzzatto,[7] Mary M. Horowitz and Edward C. Gordon-Smith[2] [1]*International Bone Marrow Transplant Registry, Health Policy Institute,*

Two recipients of identical twin transplants remain alive 8 and 12 years after treatment.

Haemolytic PNH

- 21 year old male
- New diagnosis of haemolytic **PNH 2008**
- LDH 2241 (NR <240), Hb 82 g/L
- Symptomatic of haemolysis, with no thrombosis
- Identical Twin Brother (monozygotic)- Fit and well
- what is the best treatment option?

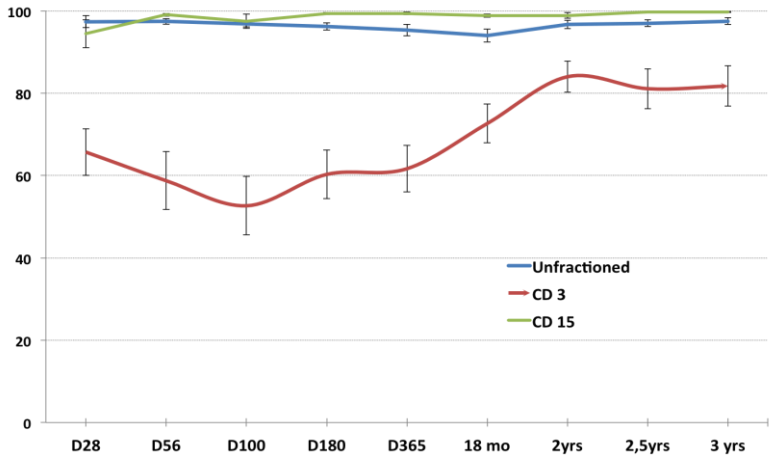
HSCT vs Anti-complement therapy

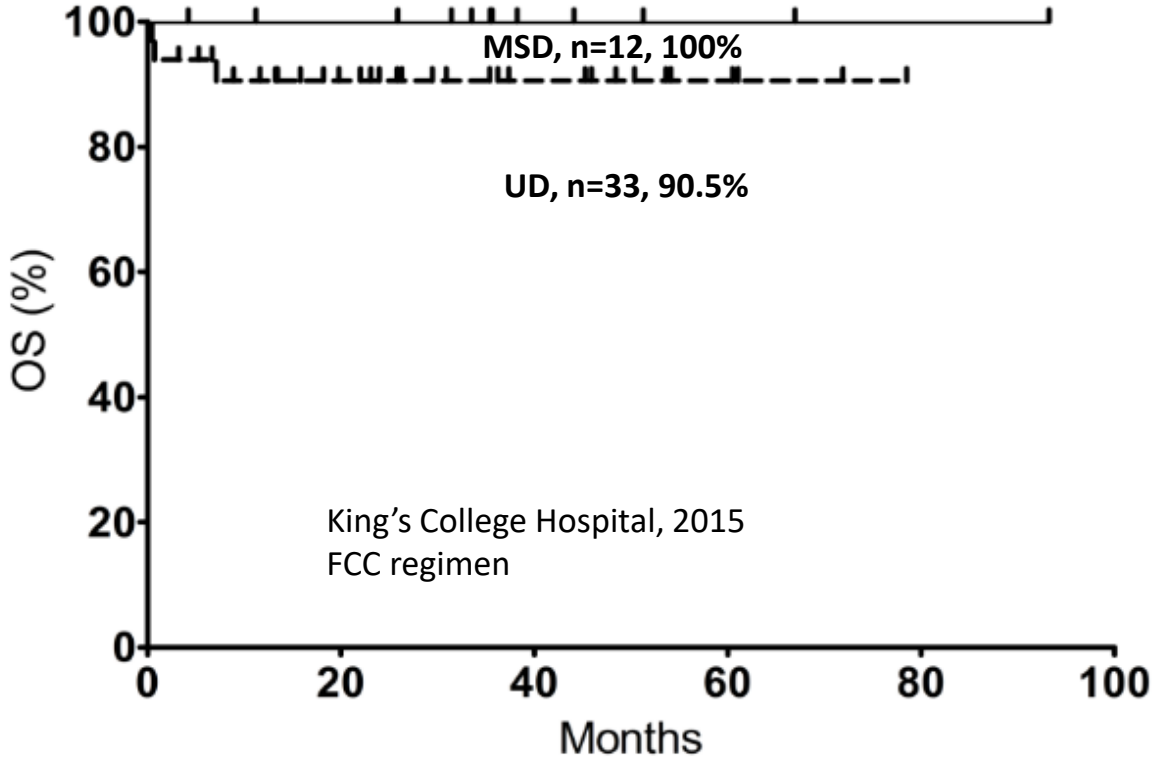
- No treatment
- Took 6 years to convince him and now on Ecu---Ravulizumab (since 2014)
- Total cost- Euro 3.82 million (per decade)

HSCT in Aplastic Anaemia

Study design
Multi-centre, retrospective

Regimen (‘FCC’)
Fludarabine 30mg/m2 x 4
CY 300mg/m^2 x 4
Alemtuzumab 60mg (40-100)
Post graft: ciclosporin

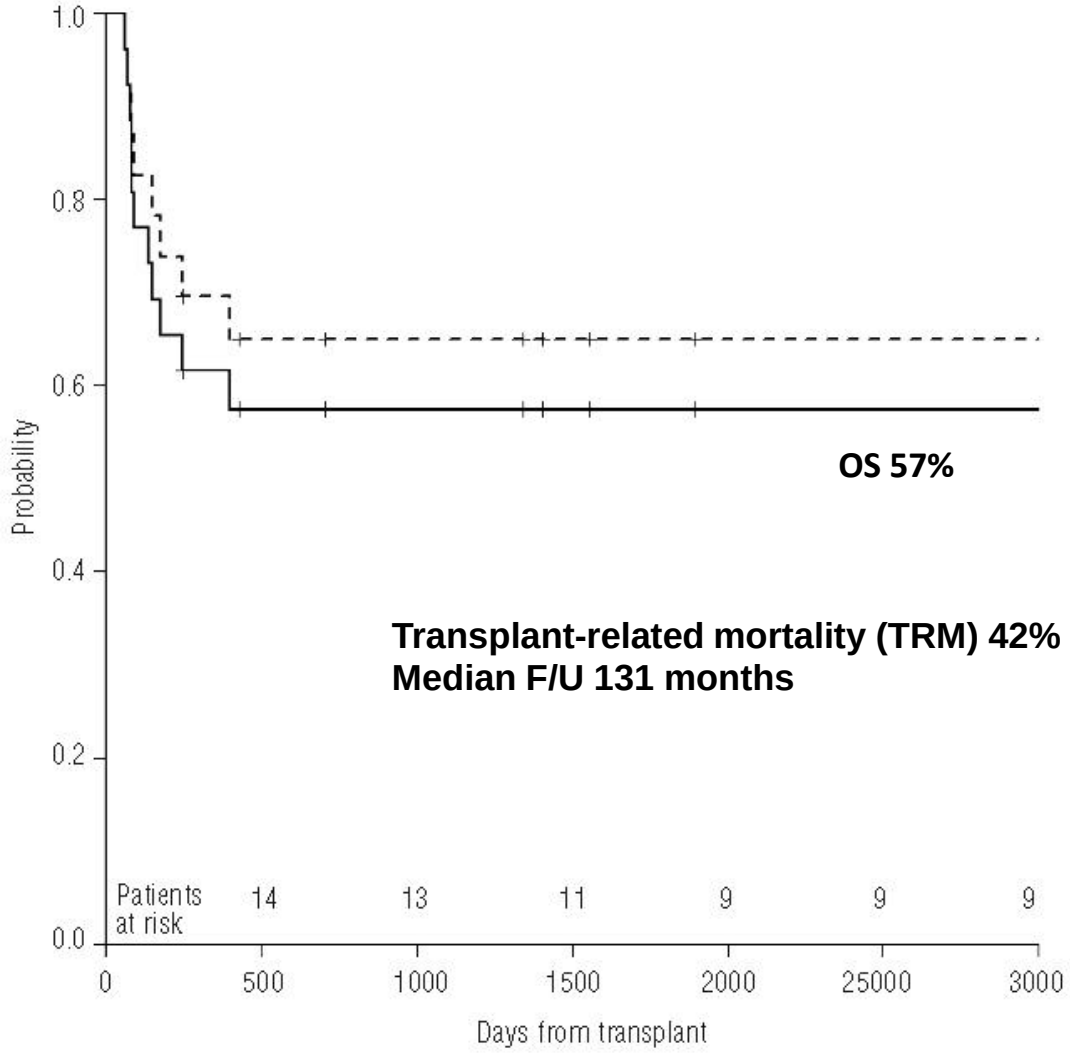




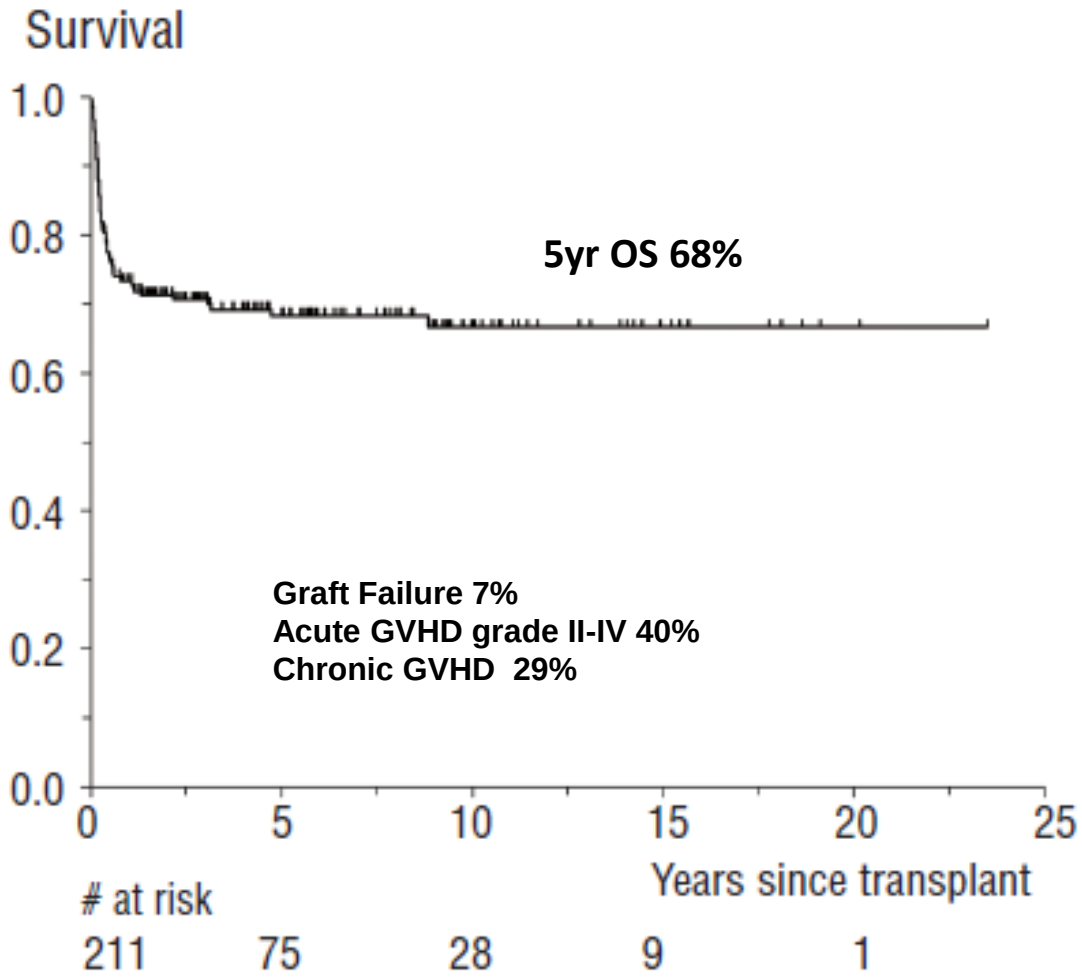
King’s College Hospital, 2015
FCC regimen

Sheth et al, Blood Advances, 2019

HSCT in PNH

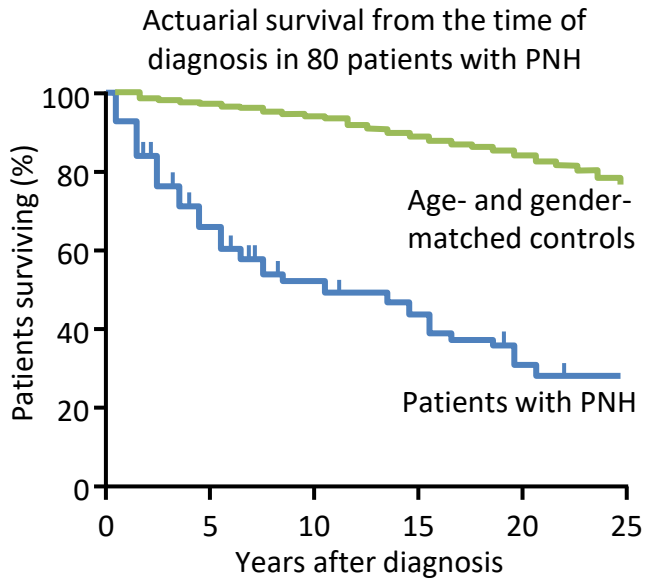


Santarone, Haematologica 2010

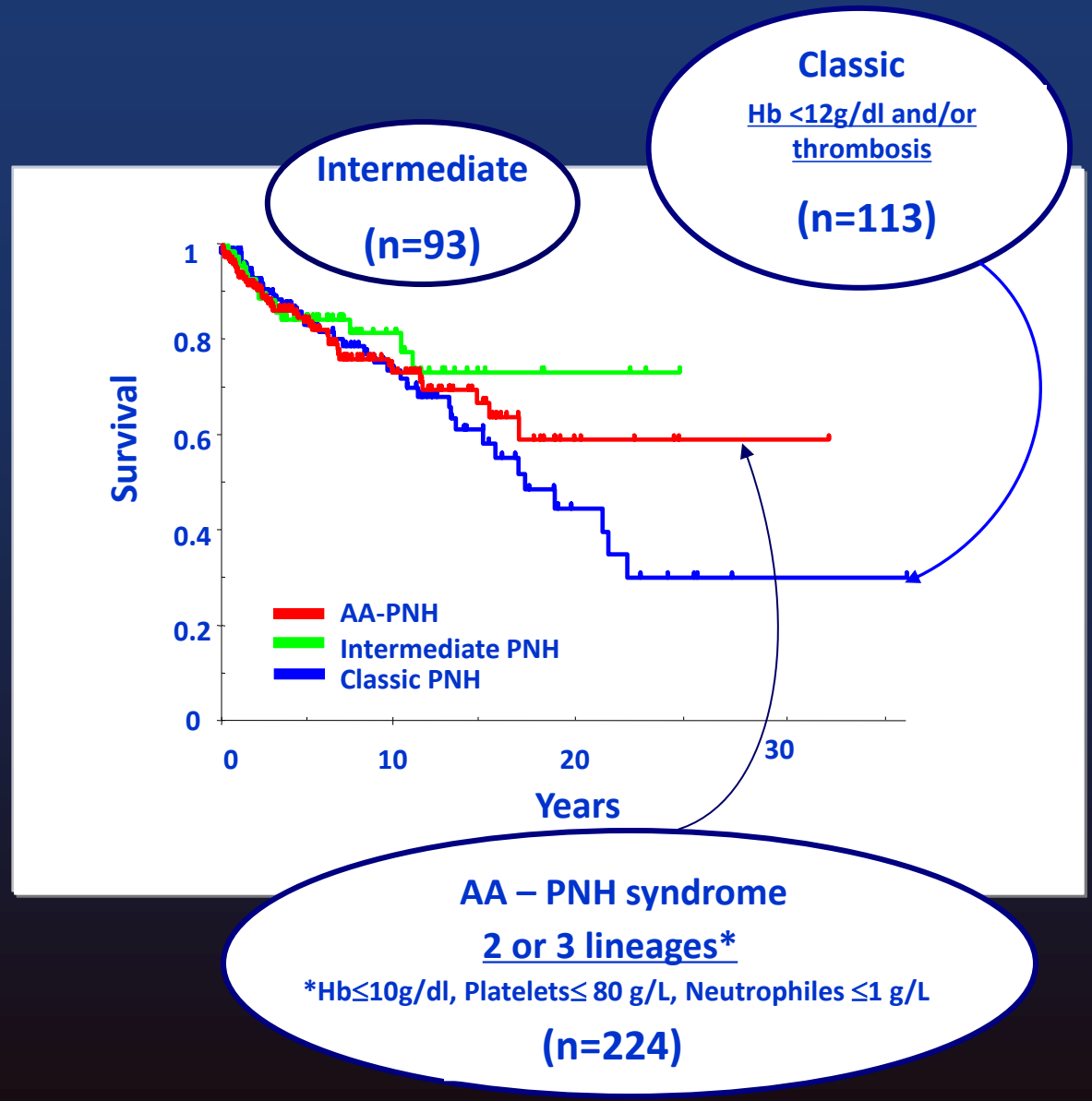


Peffault de Latour, Haematologica 2012

Mortality With Best Supportive Care In Hemolytic PNH Patients



French cohort (n=460)



Socié et al, *Lancet* 1996; Peffault de Latour, RP et al, *Blood.* 2008;112(8):3099-3106.

Mortality With Transplantation In Hemolytic PNH Patients (1978-2007)

median age 30 years, 2/3rd HLA-identical

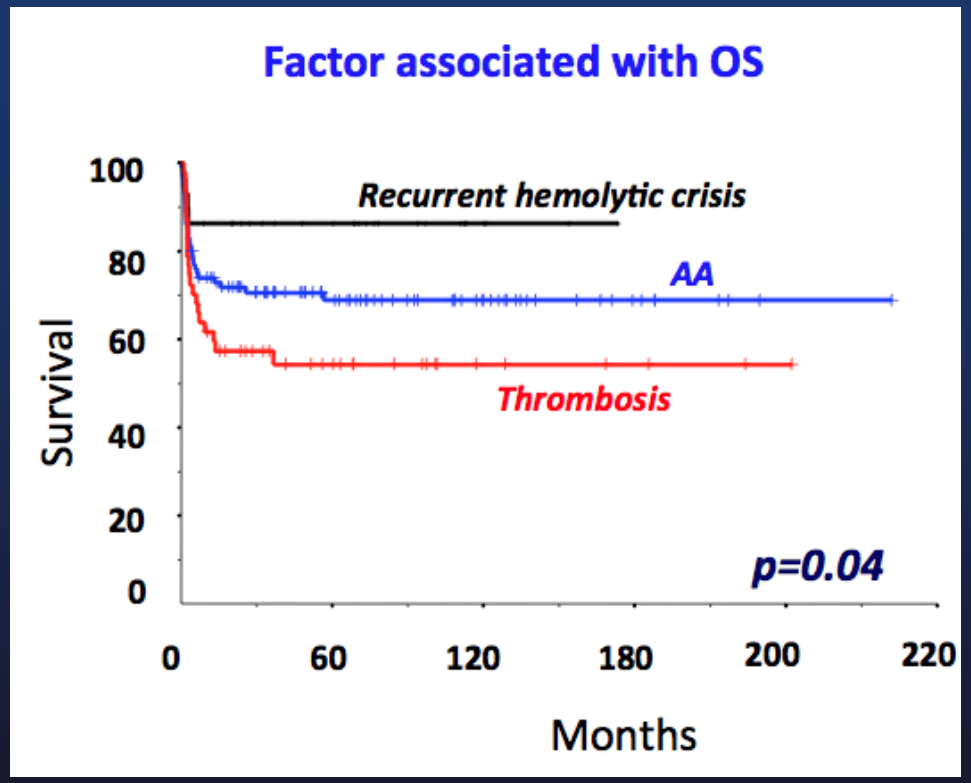
EBMT cohort (n=211)

-**Hemolytic (n=64)**
-Aplastic anemia (n=100)
-Thrombosis (n=47)

Transplantation

-**GvHD**
- Acute, CI = 65%
- Chronic, CI = 45%

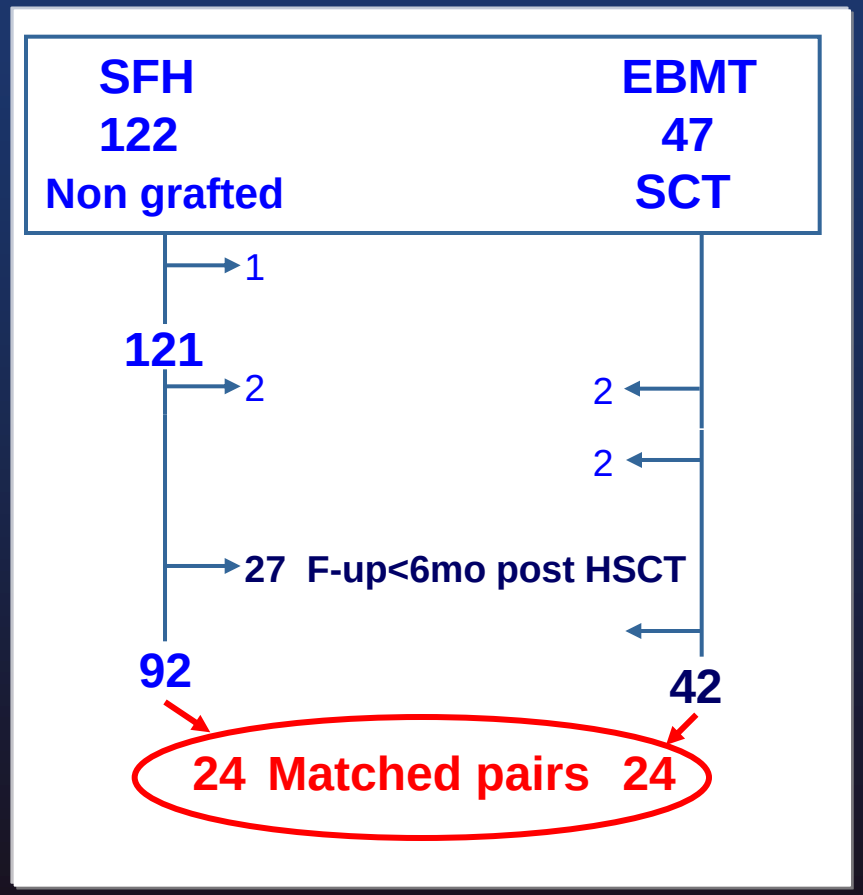
-**Causes of death (n=64)**
- GvHD
- Infections



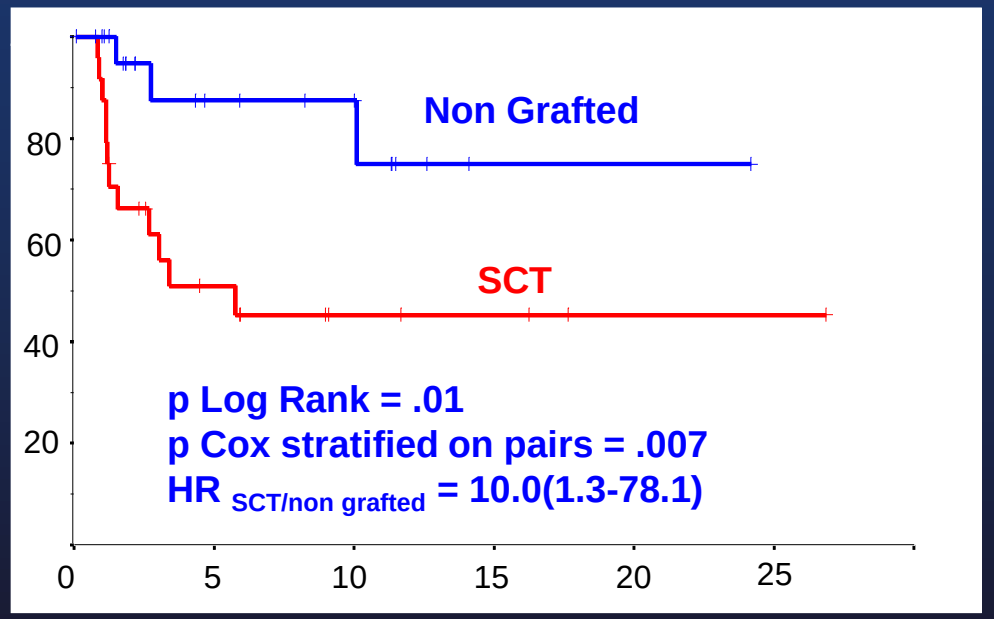
RHC-recurrent haemolytic crisis (HR 1)
AA-aplastic anaemia with no TE (HR 2.4)
TE-thromboembolism (HR 3.7)

Peffault de Latour, et al. *Haematologica.* 2012

Thrombosis and Transplantation



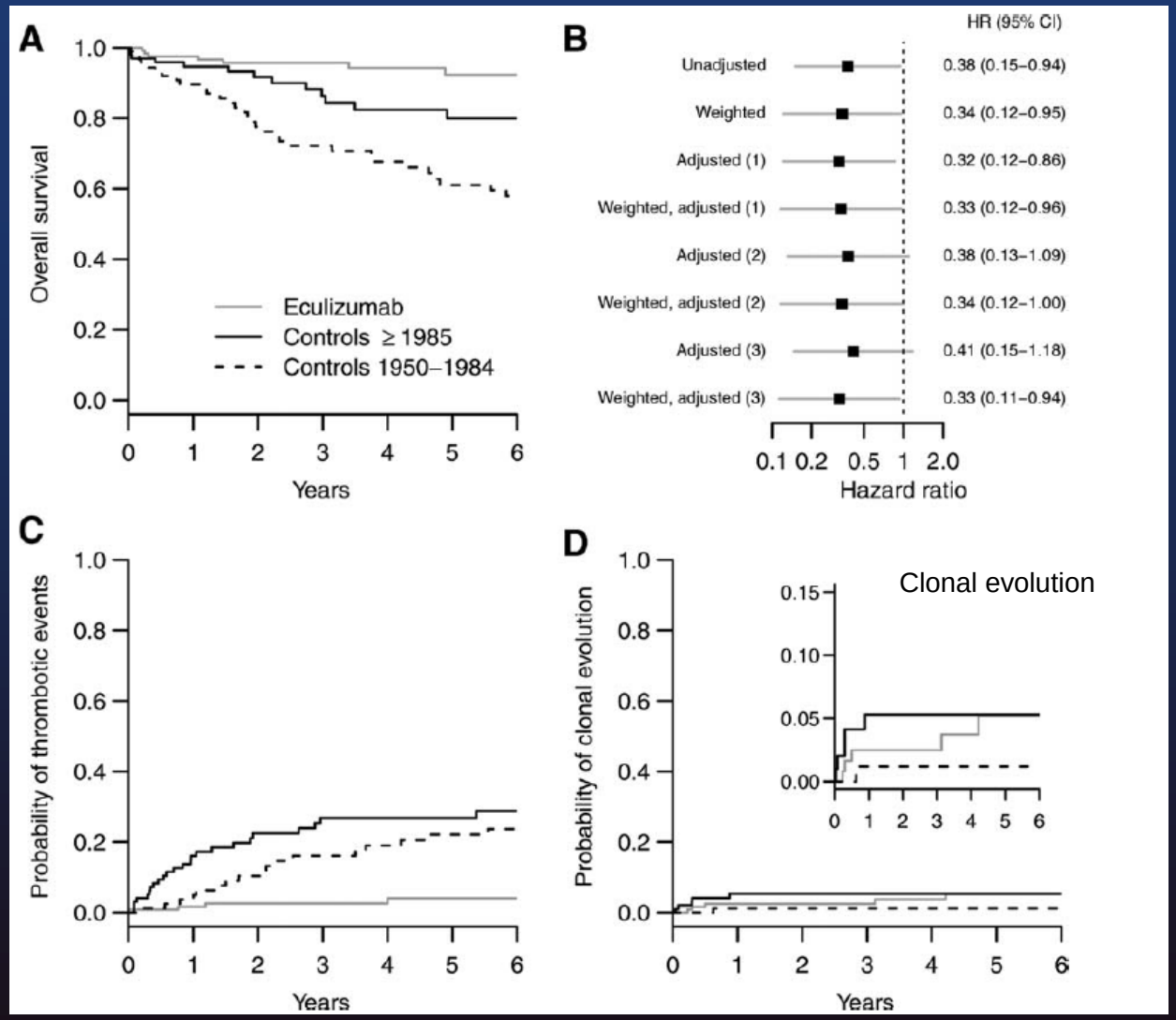
Overall Survival (OS)

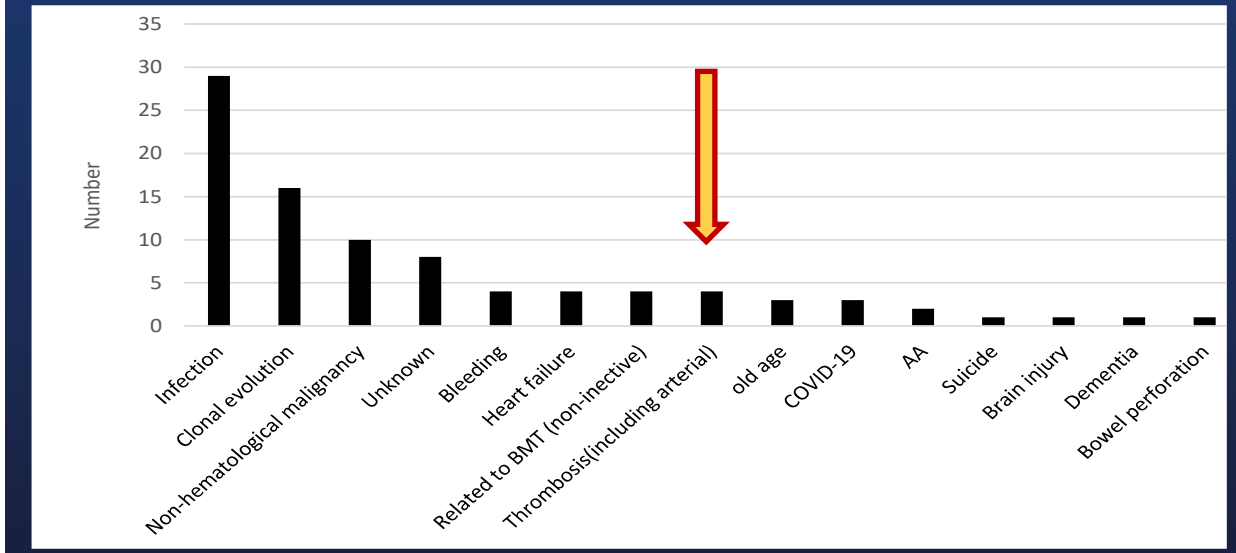


Time since thrombosis (year)

Peffault de Latour *et al*, *Haematologica* 2012

Thrombosis and eculizumab/ravulizumab





Loschi et al. American Journal of Hematology 2016

Peffault de Latour et al. *Blood* 2008; 112:3099-3106.

Kelly et al. *Blood* 2024.

How to transplant if anti-complement therapy is not available?

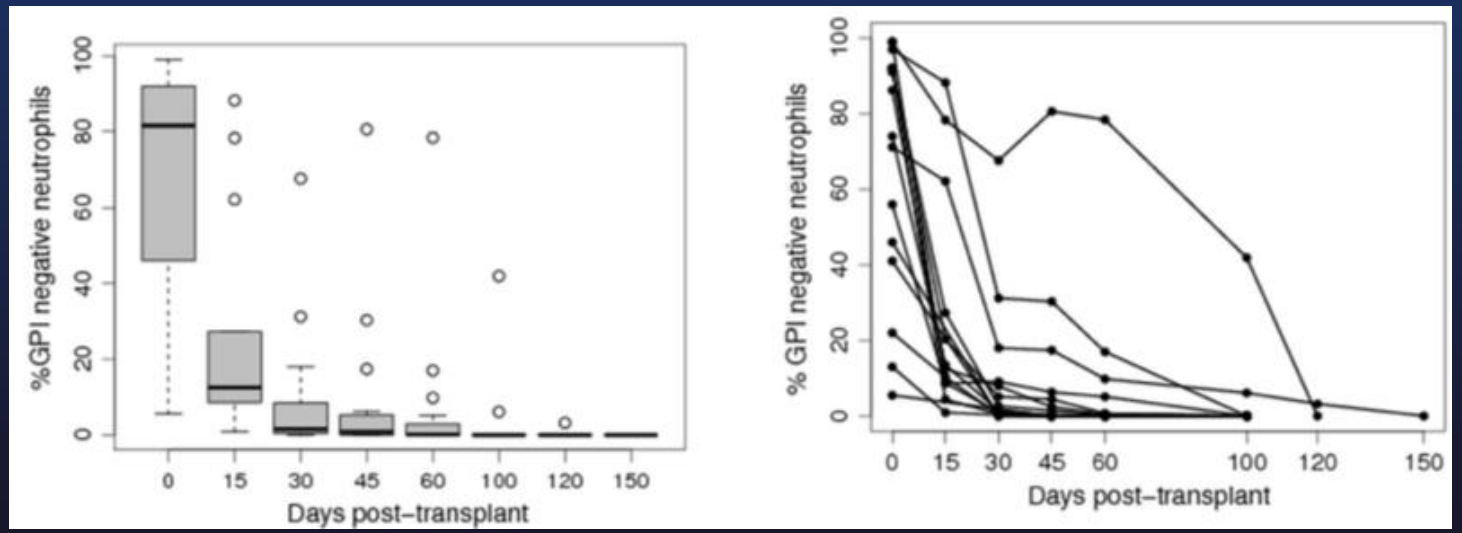
Bone marrow failure, patient preference or drug unavailability

- Patients, N=17; median age of **31** (range 20–42 years)
- Median percentage of **GPI-negative neutrophils pre-transplant was 81.6%** (range 5.5%–99%).
- **Indications** for transplant included:
  - 10 patients with PNH- BMF (2 with cytogenetic evidence for evolution to myelodysplastic syndrome)
  - 3 with thrombotic events;
  - 4 uncontrolled hemolysis
- Patients received a T-cell replete G-CSF PBSC from a sibling after **RIC regimen** (Cy 60 mg/kg/d D-7 and -6 and flu 25 mg/m2/d D-5 to -1). Horse ATG + CSA + MMF (Mtx) as GvHD prophylaxis

Pantin, et al. *BBMT.* 2014

How to transplant if anti-complement therapy is not available?

- All patients engrafted with full donor chimerism
- The cumulative incidence of grade 2–4 acute GVHD was 47.1% (n=8) and the cumulative incidence of chronic GVHD was 70.6% (n=11)



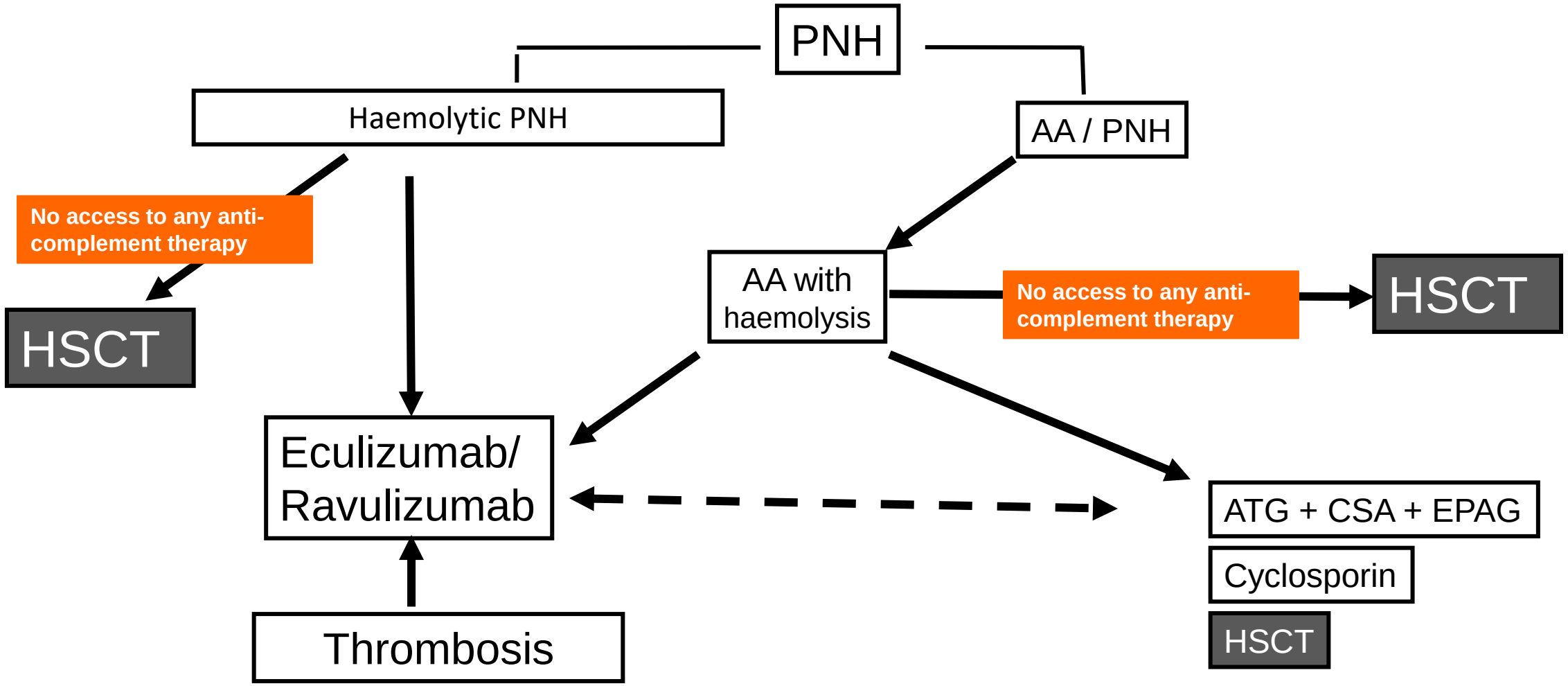
- With a median follow-up of 6 years (range 2.6–11 years), 15 patients (87.8%) are alive

Pantin, et al. *BBMT.* 2014

HSCT in PNH- No anti-complement therapy

Article	No. of Cases	Sex F/M	Age, yr (range)	Diagnosis	Disease Duration, mo, median (range)	Donor Source	Conditioning Regimen	aGVHD/ cGVHD, n	Follow-Up mo, median (range)	No. of Deaths	Causes of Death, %	Survival, %
Santarone et al. (2010) [28]	26	10/16	32 (22-60)	NA	33 (3-208)	MRD, 22 MUD, 2 Haplo, 2	NMA, 11 MAC, 15	10/10	131 (30-204)	11	Infection, 15.4 GVHD, 11.5 Multiorgan failure, 7.7 Others, 7.7	10-yr DFS, 57
Peffault de Latour et al. (2012) [12]	211	106/105	30 (23-39)	Classic, 85 AA/PNH, 103 Others, 23	20 (7-59)	MRD, 136 MUD, 74 Others, 1	MAC 70 NMA 74 Others, 67	85/57	61	64	Infection, 16.6 GVHD, 8.5 Hemorrhage, 5.7 Multiorgan failure, 3.3 Other, 3.8	5-yr OS, 68
Pantin et al. (2014) [29]	17	4/13	31 (20-42)	Classic, 11 AA/PNH, 6	NA	MRD, 17	NMA, 17	8/11	67.2 (5.5-132)	2	Digestive ulcer, 5.9 aGVHD, 5.9	6-yr OS, 87.8
Tian et al. (2016) [26]	18	3/15	25 (13-54)	Classic, 14 AA/PNH, 4	15 (3-240)	Haplo, 10 MRD, 5 MUD, 3	MAC, 18	9/10	20 (14-85)	1	Infection, 5.6	1.7-yr OS, 94.4
Kamranzadeh et al. (2017) [13]	13	3/10	27.5 (18-47)	Classic, 13	41.3 (5-132)	NA	MAC, 13	9/11	21 (1-159)	3	GVHD, 23.1	13-yr OS, 74.07
Lee et al. (2017) [20]	33	12/21	34 (13-56)	Classic, 7 AA/PNH, 26	8.9 (1.2-212.9)	MRD, 24 MUD, 7 Haplo, 2	NMA, 6 MAC, 27	9/6	57 (6-151.3)	4	Infection, 6.1 aGVHD, 3.0 Hemorrhage, 3.0	5-yr OS, 87.9
Cooper et al. (2019) [11]	55	37/18	32.1 (14- 66.9)	Classic, 17 AA/PNH, 38	1.3 (0.1-30.3)	MRD, 20 MUD, 28 UCB, 3 Syng, 2 Haplo, 2	MAC, 26 RIC, 27 NCR, 2	41/26	NA	19	Infection, 16.4 Hemorrhage, 7.3 GVHD, 1.8 Multiorgan failure, 1.8 Others, 7.3	5-yr OS, 70
Liu et al. (2019) [19]	44	18/26	28.5 (6-54)	Classic, 15 AA/PNH, 29	6 (3-240)	Haplo, 25 MRD, 15 MUD, 4	MAC, 29 NMA, 15	12/8	36 (4~132)	4	Infection, 4.5 aGVHD, 2.3 Thrombotic microangiopathy, 2.3	3-yr OS, 90.4
Nakamura et al. (2020) [16]	42	19/23	32.5 (16-64)	NA	28.6 (3.1-451.5)	NA	MAC, 7 RIC, 32 Unknown, 3	9/7	79.5 (9.6-227.5)	11	Infection, 7.1 Graft failure, 7.1 Hemorrhage, 4.8 Others, 7.1	6-yr OS, 74
Markiewicz et al. (2020) [17]	78	NA	29 (12-65)	Classic, 27 AA/PNH, 51	12 (1-127)	MRD, 19 MUD, 49 Others, 10	MAC, 5 RTC/RIC, 73	39/22	61.2 38.4	10	Infection, 5.1 GVHD, 2.6 Graft failure, 1.3 Hemorrhage, 1.3 Unknown, 2.6	3-yr OS, 88.9 3-yr OS, 85.1

AA/PNH Management



Slide courtesy Régis Peffault de Latour , modified

Concurrent treatment of AA and PNH

Concurrent treatment of aplastic anemia/paroxysmal nocturnal hemoglobinuria syndrome with immunosuppressive therapy and eculizumab: a UK experience

haematologica 2018; 103:e345

Morag Griffin,[1] Austin Kulasekararaj,[2] Sheyans Gandhi,[2] Talha Munir,[1] Stephen Richards,[1] Louise Arnold,[1] Nana Benson-Quarm,[2] Nicola Copeland,[1] Isabel Duggins,[2] Kathryn Riley,[1] Peter Hillmen,[1] Judith Marsh[2] and Anita Hill[1]

N=25

LETTER TO THE EDITOR

Combined intensive immunosuppression and eculizumab for aplastic anemia in the context of hemolytic paroxysmal nocturnal hemoglobinuria: a retrospective analysis

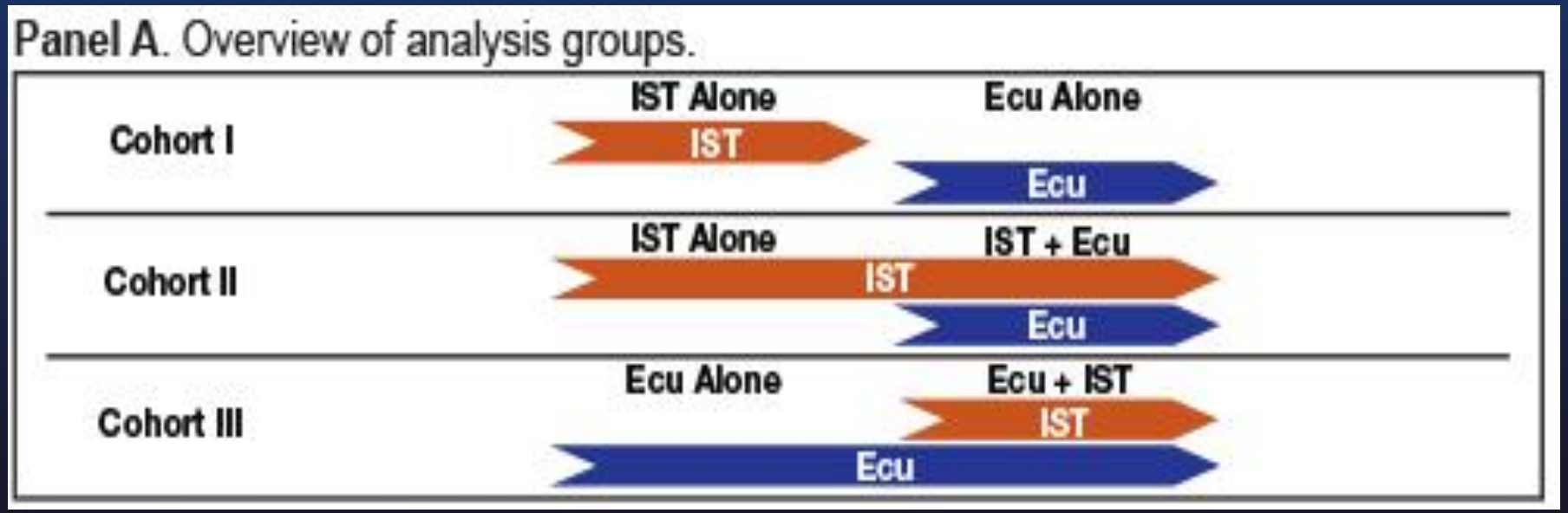
Bone Marrow Transplantation (2018) **53,** 105–107

N=9

PNH patients with coexistent BMF (AA/MDS) can have IST (ATG/CSA/Campath) with eculizumab either concurrently or sequentially without any deleterious effects

NO CHANGE IN THE EFFECTIVENESS OF IMMUNOSUPPRESSIVE THERAPY IN PATIENTS WITH PNH AND AA RECEIVING CONCOMITANT ECULIZUMAB

Anita Hill[1]; Régis Peffault de Latour[2]; Austin G. Kulasekararaj[3]; Morag Griffin[4]; Robert A. Brodsky[5]; Jaroslaw P. Maciejewski[6]; Amanda Wilson[7]; Philippe Gustovic[8]; Hubert Schrezenmeier[9]



N=88

N=162

N=33

EHA 2019 and Acta Haematologica, 2022, in press

Evolution to AA, MDS or AML under eculizumab

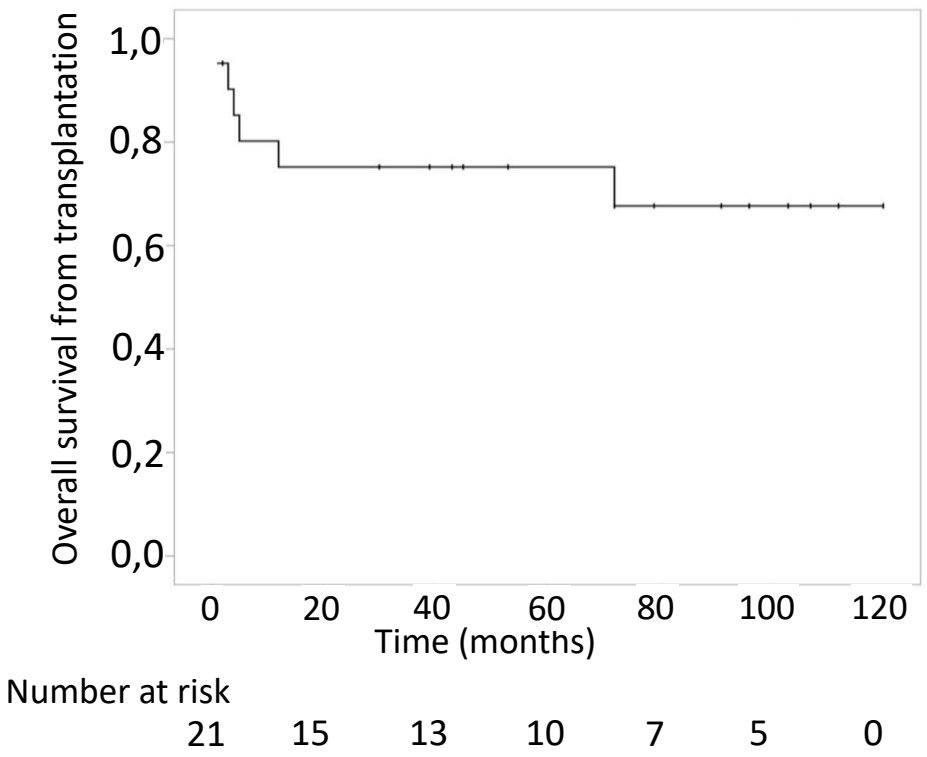
Hematopoietic Stem Cell Transplantation For Patients With Paroxysmal Nocturnal Hemoglobinuria Previously Treated With Eculizumab: A Retrospective Study Of 21 Patients From SFGM-TC Centers

Nicolas Vallet[1], Flore Sicre de Fontbrune[2], Michaël Loschi[3], Deborah Desmier[4], Alban Villate[1], Fiorenza Barraco[5], Patrice Chevallier[6], Louis Terriou[7], Ibrahim Yakoub-Agha[7], Annalisa Ruggeri[8], Mohamad Mohty[8], Natacha Maillard[4], Pierre-Simon Rohrlich[9], Patrice Ceballos[10], Stéphanie Nguyen[11], Xavier Poiré[12], Gaëlle Guillerm[13], Reza Tabrizi[14], Jonathan Farhi[15], Raynier Devillier[16], Marie-Thérèse Rubio[17], Gérard Socié[2] and Régis Peffault de Latour[2]⇑ on behalf of the Société Francophone de Greffe de Moelle et Thérapie Cellulaire

- Retrospective study, 2007-2017, patients going to HSCT while on eculizumab
- 21 Patients:
  - Aplastic anemia, n=10
  - Clonal evolution, n=1
  - Hemolytic patients, n=8
  - Thrombosis, n=2

Vallet, et al. Haematologica. 2018

Evolution to AA, MDS or AML under eculizumab



Overall survival 70%

Causes of death

-GvHD

-Infections

Last dose of eculizumab should be done during/ just prior to start of the. conditioning regimen

Among the 16 patients at risk, cGvHD was not observed

(EBMT study -cGvHD of 29% at 2 years)

Vallet, et al. Haematologica. 2018

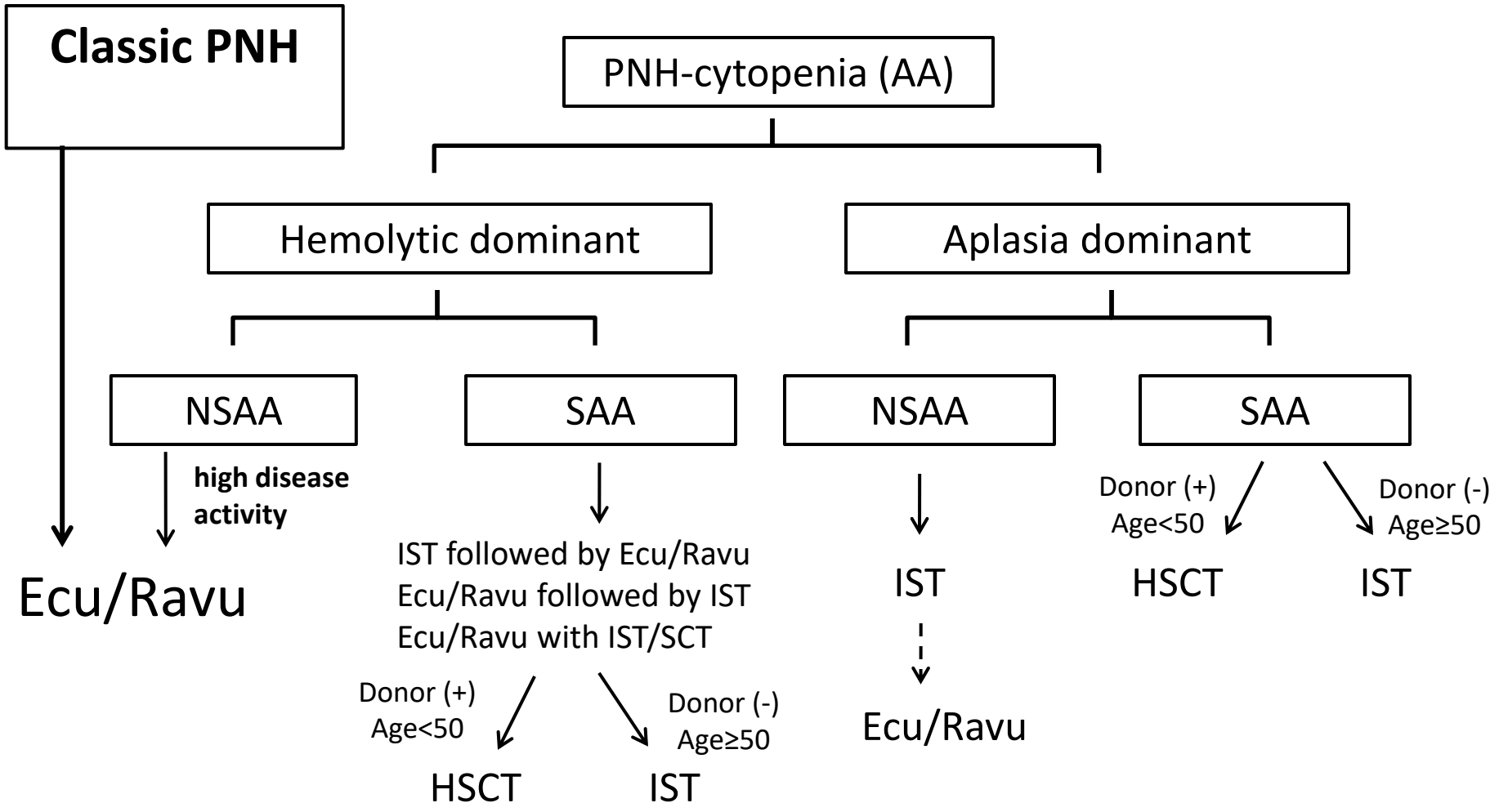
Eculizumab with HSCT in PNH

Article	No. of Cases	Sex, F/M, n	Age, yr, median (range)	Indication for HSCT	Disease Duration, mo, median (range)	Donor Source	Conditioning Regimen	Pre-HSCT Eculizumab Dose	Post-HSCT Eculizumab Dose	aGVHD/ cGVHD, n	Follow-Up, mo, median (range)	Deaths, n	Cause of Mortality	Relapse Rate, %
Cooper et al. (2018) [11],*	7	5/2	27.8 (14.9~54.9)	Clonal evolution to MDS, 3; progressed to BMF, 3; hemolytic attacks during eculizumab, 1	2.9 (1~30.3)	MRD, 1 MUD, 5 UCB, 1	MAC, 5 RIC, 2	Three patients 900~1200 mg every 2 wk until HSCT, 1 patient 600 mg on day -9, and 1 patient 600 mg every 7 d for 2 mo	One patient 600 mg on days -9, -1, +5, +12, and +19; one patient 900 mg on days -1, +12, +26, and +40*	5/4	27.6 (2.4~82.8)	0	NA	NA
DeZern et al. (2018) [7]	8	4/4	24.5 (17-47)	Progressed to BMF	NA	MRD, 5 MUD, 3	NMA	600 mg every 7 ± 2 d for 4 doses, then 900 mg every 7 ± 2 d, then maintenance dose of 900 mg every 14 ± 2 d	None	0	37 (2~83)	0	NA	NA
Vallet et al. (2018) [18]	21	NA	NA	Clonal evolution to MDS; recurrent thrombosis; AA/PNH; transfusion- dependent classical PNH	NA	MRD, 10 MUD, 8 Syng, 2 Haplo, 1	NMA, l8 MAC, 2 NCR, 1	600 mg weekly for 4 wk, then 900 mg (maintenance dose) every 14 d	Three patients 900~1200 mg every 2 wk until HSCT; 1 patient 600 mg on day -9 and 1 patient 600 mg every 7 d for 2 mo	7/0	45 (1~120)	6	Infection, 3 GVHD, 2 MDS transformation, 1	1 (4.8)
Mei et al. (2019) [30]	8	2/6	42 (25~63)	Progressed to BMF	NA	MRD, 4 MUD, 4	RIC	600 mg every 7 ± 2 d for 4 doses, then 900 mg for 7 ± 2 d, then 900 mg every 14 ± 2 d (maintenance dose)	Eight patients accepted 1~3 doses of eculizumab within 30 d post-HSCT	4/5	36 (1~86)	3	Infection, 2 Evolution to MDS, 1	0

AML indicates acute myelogenous leukemia.

* Cooper et al reported 55 cases, among them 7 patients were treated with eculizumab pre- or peri-HSCT.

Proposed algorithm for the management of PNH and PNH/AA



IST; immunosuppressive therapy, HSCT; stem cell transplantation

Modified and based on BCSH guideline (Kulasekararaj, BJH 2024)

Transplant for PNH (no access to anti-complement therapy)

NO

YES

- To all patients
- Caution with Thrombotic PNH
- GVHD risk exists
- ?role of short access to complement inhibition pre-HSCT

Transplant for PNH (availability of complement inhibition)

NO

- Sub-optimal response to Ecu/Ravu
  EVH, residual haemolysis and residual anaemia
- Refractory to Ecu/Rav
  - C5 polymorphism
- Thrombotic PNH

YES

- Concurrent symptomatic BMF
  - coexisting AA (even NSAA?)
  - Relapse of AA
  - Progression to MDS and/or AML
- Young/adolescents with hPNH???
  - Syngeneic donor
  - Sibling donor
  - Pharmaco-economic rationale? (even in countries with access)

Paroxysmal Nocturnal Haemoglobinuria Service

Research Nurses: Nicola Houghton, Nora Youngs, Tapiwa Zhakata

Leeds Teaching Hospitals NHS Trust

Level 3, Bexley Wing
St James' University Hospital
Beckett Street
Leeds LS9 7TF
Tel: 0113 206 8625