Classical treatment of PNH: when complement inibitors were (or are) not available

Hubert Schrezenmeier

Institute of Transfusion Medicine, University of Ulm
And Institute of Transfusion Medicine and Immunogenetics, University Hospital Ulm
and German Red Cross Blood Transfusion Service Baden-Württemberg-Hessen

Disclosures of Hubert Schrezenmeier

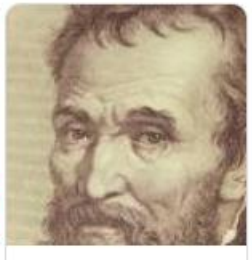
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Alexion Astra Zeneca Rare Diseases	X				X	X	
Amgen Inc.						X	
Omeros Inc.						X	
Sanofi						X	
SOBI						X	
Novartis					x	X	

all payments to the institution i.e. University Hospital Ulm, Germany

Classical treatment of PNH:
when complement inibitors were (or are) not available

an e-mail from Florence ….

Dear Hubert,
I hope to find you well. I am writing to invite you to a meeting that will be held in **Florence** on 3 and 4 October 2024.












YES !!

Classical treatment of PNH:
when complement inibitors were (or are) not available

Dear Hubert, an e-mail from Firenze ….

I hope to find you well. I am writing to invite you to a meeting that will be held in Florence on 3 and 4 October 2024.
















The title of the meeting is “PNH: at the crossroads of somatic mutations, clonal expansion and immunity”: I hope you could attend and give a talk on **“Classical treatment of PNH: when complement inhibitors were (or are) not available”** (the title is still tentative).

I would be very happy if you could attend a meeting that is intended to be not only a workshop with most of the PNH experts, but above all a sort of friendly reunion of PNH community.
Thank you very much, best wishes, Rosario

Classical treatment of PNH:
when complement inibitors were (or are) not (yet) available


Lorenzo de' Medici
1449–1492


Michelangelo
1475–1564


Leonardo da Vinci
1452–1519


Donatello
1386–1466


Galileo Galilei
1564–1642


Niccolò Machiavelli
1469–1527


Amerigo Vespucci
1451–1512


Cosimo de' Medici
1389–1464

Non è saggio difendere ciò a cui si deve comunque rinunciare.

It is not wise to defend what you have to lose anyway.

N.Macchiavelli, History of Firence

The prohibitively high price of eculizumab and related drugs is of great concern. With others and personally on many occasions I have publicly deplored that price makes these drugs inaccessible to at least two-thirds of PNH patients in the world.
This anomaly ought to be corrected.

L.Luzzatto, 2022

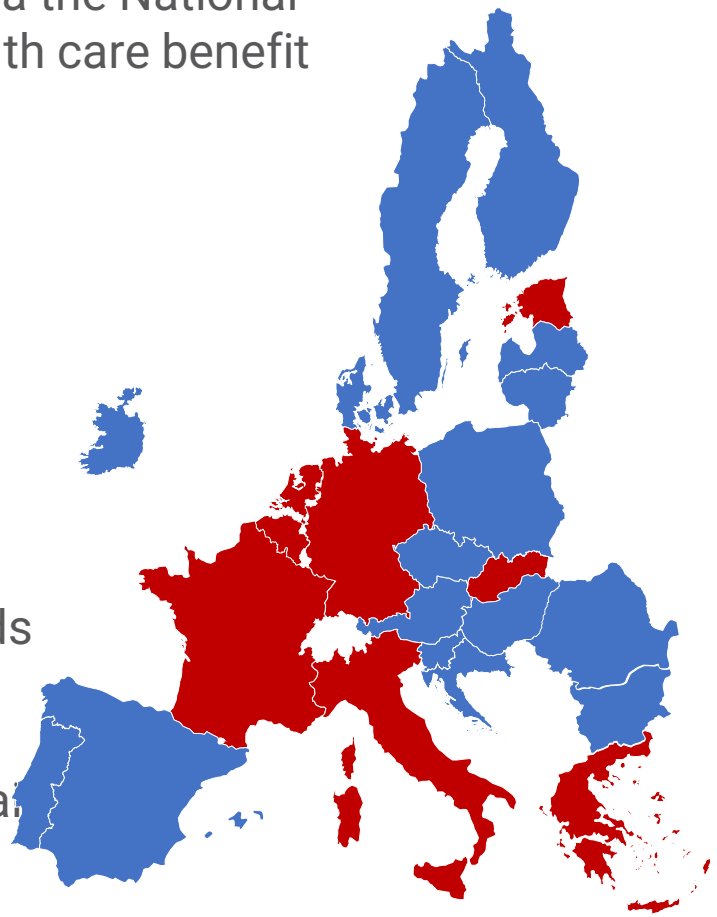
95% affirmed its availability in their country (19 out of 20 EU MS)

Eculizumab

Available in all centers and reimbursed via the National standard health care benefit package:

- Belgium
- Denmark
- Estonia
- France
- Germany
- Greece
- Italy
- Netherlands
- Slovakia

NOT at all ava
- Bulgaria

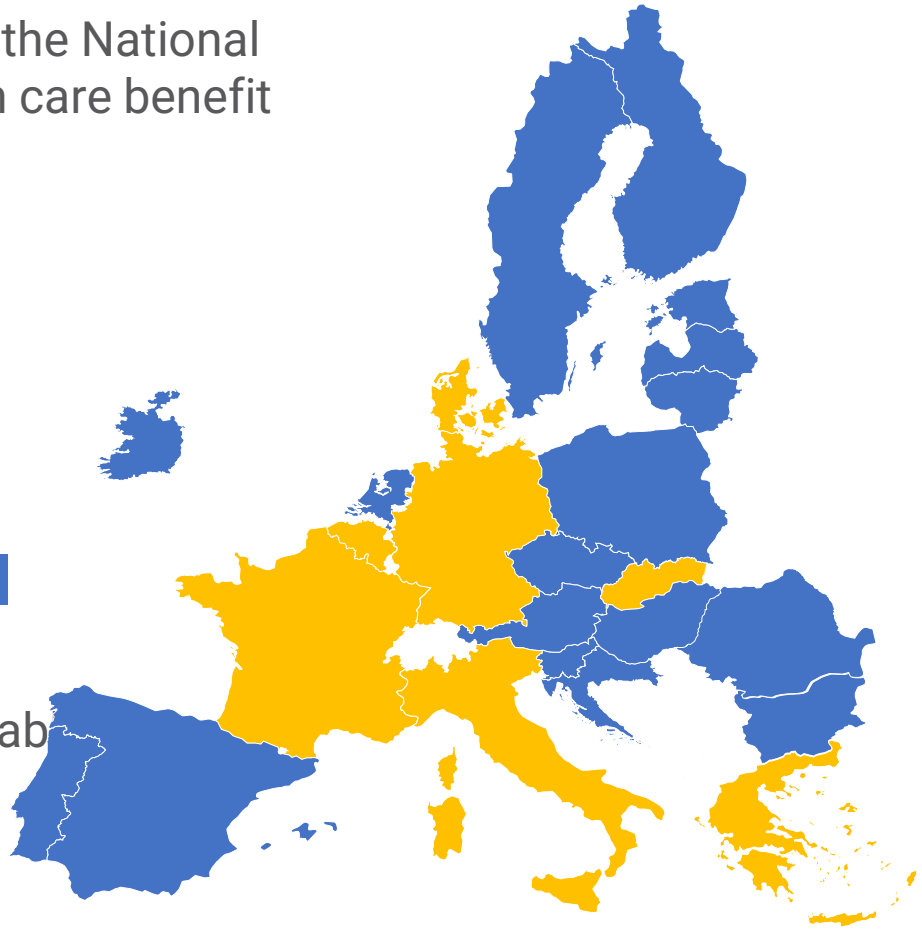


Ravulizumab

Available in all centers and reimbursed via the National standard health care benefit package:

- Belgium
- Denmark
- France
- Germany
- Greece
- Italy
- Slovakia

NOT at all availab
- Bulgaria
- Estonia
- Netherland
- Romania
- Portugal



Classical treatment of PNH: when complement inibitors were (or are) not available

Supportive / non-curative approaches:

- Supportive measures to ameliorate anemia
- Treatment of hemolysis
- Prevention of thrombosis
- Treatment of thrombosis
- Treatment of infections

Curative approach:

- Allogeneic stem cell transplantation

Expert opinion, case reports / case series, retrospective analysis, registry data

Management of PNH – if complement inhibitors are not available

Diagnosis and management of paroxysmal nocturnal hemoglobinuria

Charles Parker, Mitsuhiro Omine, Stephen Richards, Jun-ichi Nishimura, Monica Bessler, Russell Ware, Peter Hillmen, Lucio Luzzatto, Neal Young, Taroh Kinoshita, Wendell Rosse, and Gerard Socié, for the International PNH Interest Group

Blood 2005

Check for updates

Received: 1 February 2018 | Revised: 21 May 2018 | Accepted: 22 May 2018

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Management of PNH – if complement inhibitors are not available

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Paroxysmale nächtliche Hämoglobinurie (PNH)

Autoren: Jörg Schubert, Peter Bettelheim, Tim Henrik Brümmendorf, Pascale Olivia Burmester, Ulrike Göbel, Britta Höchsmann, Jens Panse, Alexander Röth, Hubert Schrezenmeier, Georg Stüssi

Management of PNH – Supportive measures in patients with hemolysis and anemia

- **Folic acid**: 5 mg /day (increase erythropoietic activity)

- **Red blood cell transfusion**: leukodepleted (!) RBC
  no washing required

restrictive transfusion strategy – but based on the patient's anemia symptoms

transfuse if Hb < 7-8 g/dl **and** clinical symptoms of anemia
no fixed threshold for transfusion, symptoms of anemia / concomitant disorder prevail

Paroxysmal nocturnal hemoglobinuria and the transfusion of washed red cells

A myth revisited

M. E. BRECHER AND H. F. TASWELL

which originated the recommendation for using WRBCs. The posttransfusion increment in hemoglobin concentration in patients receiving ABO-identical packed RBCs was comparable to that in patients receiving frozen or washed RBCs. These findings indicate that the use of WRBCs is unnecessary and that patients with PNH should be transfused with group-specific blood and blood products. **TRANSFUSION** 1989;29:681–685.

Management of PNH – Supportive measures in patients with hemolysis and anemia

- **Folic acid**: 5 mg /day (increase erythropoietic activity)

- **Red blood cell transfusion**: leukodepleted (!) RBC
  no washing required

  restrictive transfusion strategy – but based on the patient's anemia symptoms

  transfuse if Hb < 7-8 g/dl **and** clinical symptoms of anemia
  no fixed threshold for transfusion, symptoms of anemia / concomitant disorder prevail

- Patient **not on complement inhibitor therapy**:
  hemoglobinuria and hemosiderinuria may cause iron deficiency
  → **iron substitution** (oral 200 to 400 mg/d) if there is evidence of iron deficiency

Management of PNH –
Treatment of patients with hemolysis if complement inhibitors are not available

Diagnosis and management of paroxysmal nocturnal hemoglobinuria

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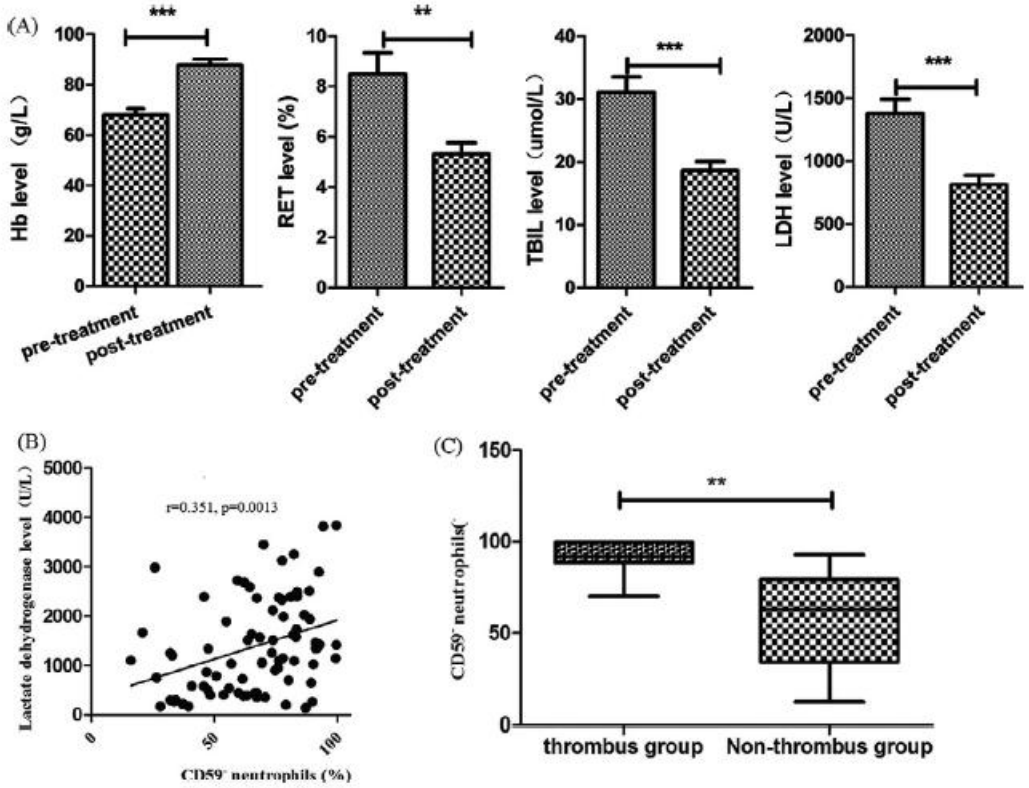
Blood 2005

- **Corticosteroids** ?
  - 0.25 to 1.0 mg/kg KG in acute hemolytic exacerbations (Parker et al., IPIG-Recommendations Blood 2005); controversial !! (*„Corticosteroids as treatment, for both chronic hemolysis and acute hemolytic exacerbations, is a subject of debate, and some members of the International PNH Interest Group do not advocate the use of steroids in PNH in any circumstances*")
  - No long-term use to control chronic hemolysis
- **Androgens** ?
- **Eythropoietin ?**
- **Splenectomy ?**

Management of PNH –
Treatment of patients with hemolysis if complement inhibitors are not available

- **Corticosteroids** ?

  n= 92 patients (64 classical PNH, 17 AA-PNH, 11 subclinical PNH)
  methylprednisolone 1 mg/kg, if Hb < 6 g/dl: in addition EPO, 100 – 150 IU/kg qod
  Median treatment duration: 7.5 months



„Glucocorticoid is still the first-line treatment for PNH patients to control hemolytic attack" ?

But:

- No control group –
  not even a period with / without corticosteroids
  in the same patients
- Stopping rules for corticosteroids unclear
- „post-treatment" not defined
- Further follow-up (without steroids): not reported

Fu et al., J.Clin.Lab.Anal. 2020, 34, e23008

Management of PNH –
Treatment of patients with hemolysis if complement inhibitors are not available

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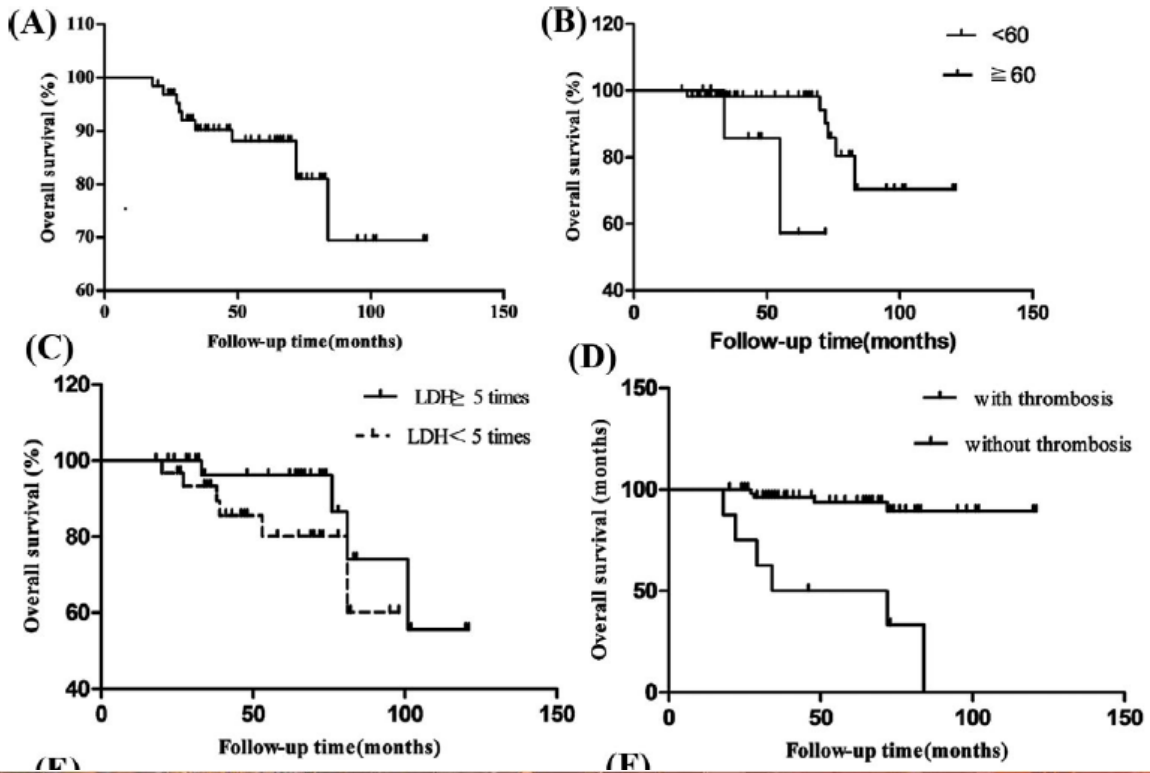

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- Stopping rules for corticosteroids unclear
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- Further follow-up (without steroids): not reported

16 Lost to follow up; 22/76 died within 10 yrs. of FU

Fu et al., J.Clin.Lab.Anal. 2020, 34, e23008

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Treatment of patients with hemolysis if complement inhibitors are not available

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  - No long-term use to control chronic hemolysis
- **Androgens** ?
  - *Androgen therapy, either alone or in combination with steroids, has been used successfully to treat the anemia of PNH.*[39,40]
- **Eythropoietin ?**
- **Splenectomy ?**

Management of PNH
- Erythropoietin -

Patients n	EPO dose	Hb Response		Transfusion requirement		GPI clone GPI-def. erythrocytes		Author, year
		pre	post	pre	post	pre	post	
3	500 U/kg three times a week	5.6 7.0 5.6	>10 >10 >11	2-3 RBC/mo 2-3 RBC/mo	no no		only Ham Test available: no change	Bourantas, 1994
2	150 U/kg/day	8.8 7.4	12.6 14.2	RBC transf.	no			Balleari, 1996
1	150 U/kg/day	7.5	11	2 RBC /mo	no	67%	27%	Astori, 1997
6 (7)	150 U/kg/day		4 pts.: NR 1 resp: +1.5 g/dl		1 pt. transfusion independent			Boschetti, 2004

EPO levels:
high in PNH (386 mU/ml in PNH compared to 136 mU/ml in iron deficiency anemia, ***McMullin et al., Br.J.Haematol. 1996***

Management of PNH – if complement inhibitors are not available

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5.3 | Classic PNH

5.3.1 | Historical treatment

In the past, management of PNH mainly consisted of supportive measures including red blood cell transfusions, folate supplements, androgens and corticosteroid administration. However, the long-term side-effects (eg, corticosteroids) and the poor efficacy limit their use.[6]

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Short-term steroids may be considered in haemolytic episode

Management of PNH – if complement inhibitors are not available

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3. We suggest that extravascular hemolysis, which can occur in patients receiving eculizumab, be identified by a newly positive DAT (C3d+). Treatment with *corticosteroids* or splenectomy can be considered but the risks and benefits of either approach must be weighed carefully.

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Classical treatment of PNH: when complement inibitors were (or are) not available

Supportive / non-curative approaches:

- Supportive measures to ameliorate anemia
- Treatment of hemolysis
- Prevention of thrombosis
- Treatment of thrombosis
- Treatment of infections

Curative approach:

- Allogeneic stem cell transplantation

Management of PNH –
- Risk of thrombosis / Prophylaxis of thrombosis -

Hall, 2003	Peffault de Latour, 2008	Lee, 2013	Höchsmann, 2023	Gurnari, 2024
UK data n=163 pts	**SFH Registry n=224 pts**	**Korean Registry N=301 pts**	**Int. PNH-Registry 57 / 189 pts**	**4 US centers n=267**
granulocyte PNH clone > 50% / ≤ 50%: 10-yr risk: 44% vs. 5.8%	granulocyte PNH clone > 50% (HR 3.2)		**Granulocyte clone > 30% (OR 4.9)**	Granulocyte clone size > 70% (OR 3.3) RBC clone size >20% (OR 2.5) **PNH type II dominant phenotype (OR 4.1)** PIGA VAF > 15% (OR 3.4), ≥ 2 mutations
		LDH ≥ 1.5xULN (OR 7.0)	**LDH ≥ 1.5 ULN +** ≥ 4 HDA-criteria (OR 11.8) **2-3 HDA criteria (OR 6.2)**	LDH > 400 (OR 3.5)
		LDH ≥ 1.5 ULN + …. Abdominal pain (17.8) Chest pain (19.0) Dyspnea (2.9) Hemoglobinuria (10.3)	Abdominal pain (OR 5.0), dysphagia (OR 3.0), hemoglobinuria (OR 2.7)	
	Warfarin use (HR 5.2)		Recent anticoag. (OR 4.8)	
	Thrombosis at dx (HR 3.2)		History of TE (OR 3.6)	
	Age >55 yrs (HR 1.8)			
	Use of transfusions (HR 1.7)			Retics > 80 G/L (OR 2.2) AST > 40 U/L (OR 2.3) D-Dimer > 1.000 mg/L (OR 3.2)

Management of PNH –
Treatment of patients if complement inhibitors are not available
- Risk of thrombosis / Prophylaxis of thrombosis -

Association of thrombosis risk with …

- Clone size (in particular granulocyte clone size), no clear threshold
  Caveat: also patients with low granulocyte clone size can develep thrombosis
  (Gurnari et al., Blood 2024; Schrezenmeier et al, Ann Hematol 2020; Griffin et al., Haematologica 2019)

- Hemolytic activitiy (as inidcated by LDH)

- Clinical signs of hemolysis (sign of NO depletion ?)

- D-Dimer elevation

- previous thrombosis

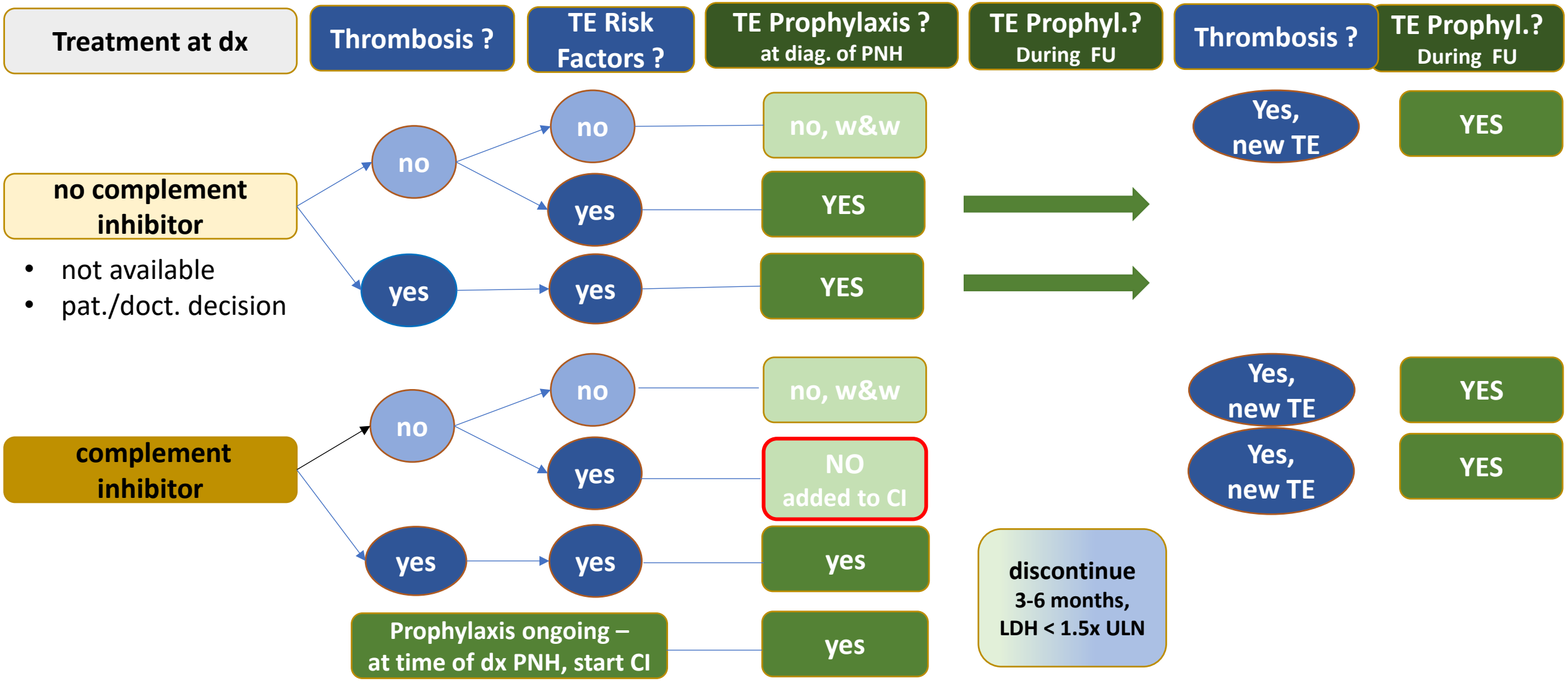
Management of PNH –
Treatment of patients if complement inhibitors are not available
- Prophylaxis of thrombosis: type of anticoagulant ? -

Prophylactic anticoagulation with

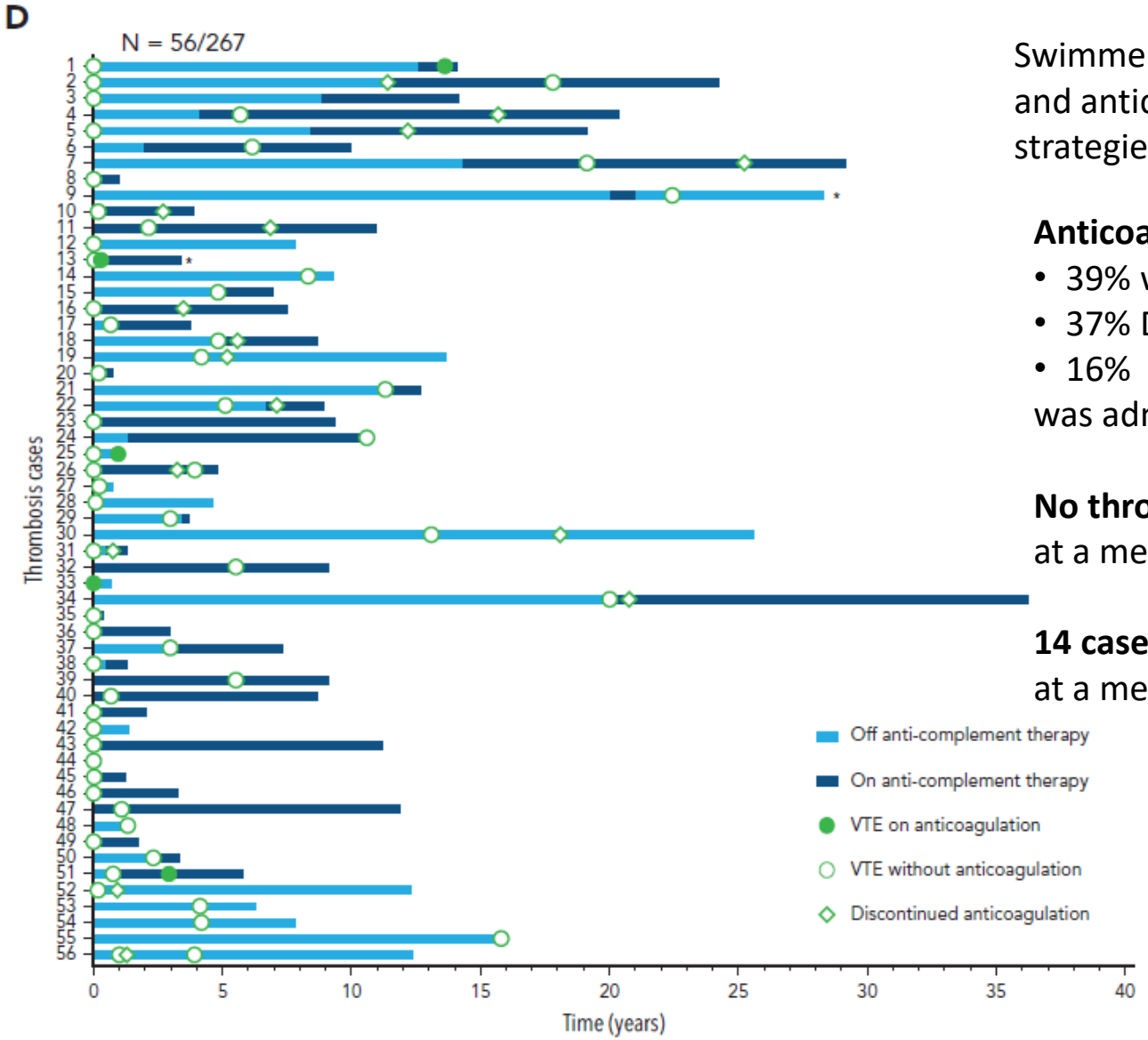
- Vitamin K antagonists (warfarin, coumarin)
- Low molecular weight heparin
- Direct oral anticoagulants (DOACS)

- Which prophylaxis is better ? No clinical trials – knowledge gap !

- Thrombosis prophylaxis in PNH: for whom and for how long ? – a personal view



- PNH-related thrombosis in the era of novel therapies: a 2043-patient-year analysis -



Swimmer plot illustrates the longitudinal follow-up, and anticomplement and anticoagulation strategies in patients experiencing TEs in our cohort.

Anticoagulation

- 39% warfarin
- 37% DOACs
- 16% low-molecular weight heparin

was administered for a median of 29 months (interquartile range [IQR], 9-61.8).

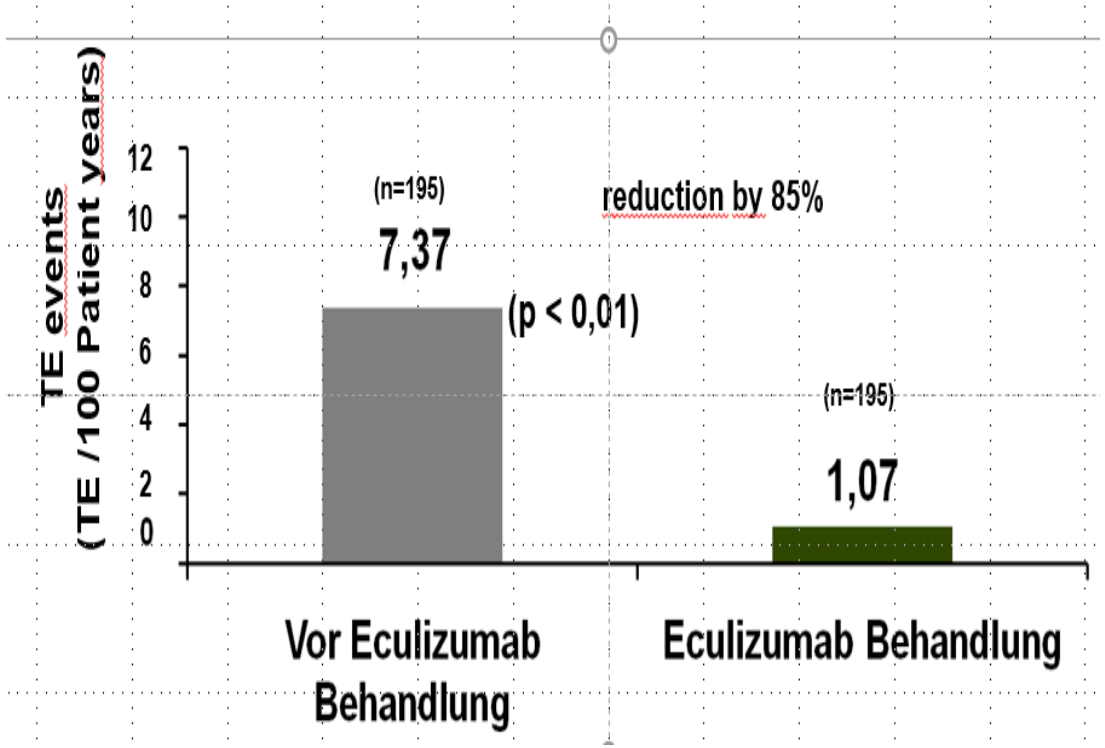
No thrombotic recurrence was observed in **19 patients treated with DOACs*** at a median observation of 17.1 months (IQR, 8.9-45)

14 cases discontinued anticoagulation without TE recurrence at a median time of 51.4 months (IQR, 29.9-86.8)**

Gurnari et al., Blood 2024, 144:145

(*Dragoni et al, Thromb J 2018)
(** Gerber et al., Am J. Hematol 2022)

PNH-related thrombosis: effect of eculizumab



Hillmen, Blood 2007, 110: 4123

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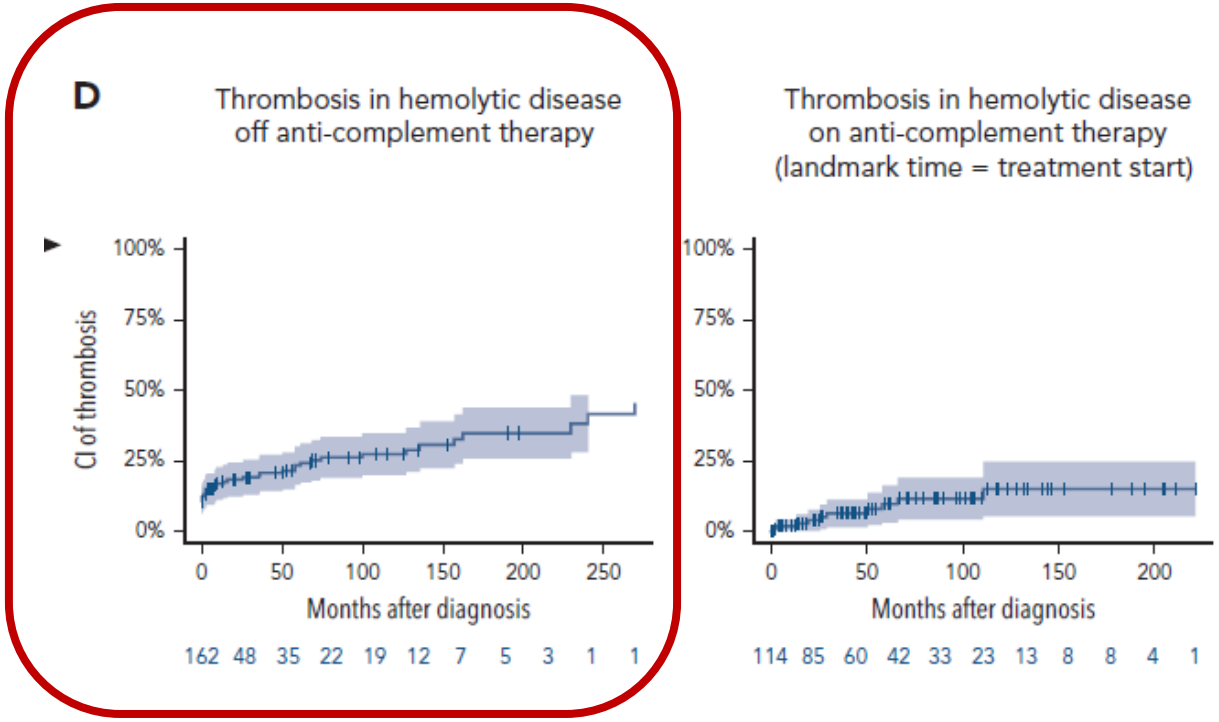
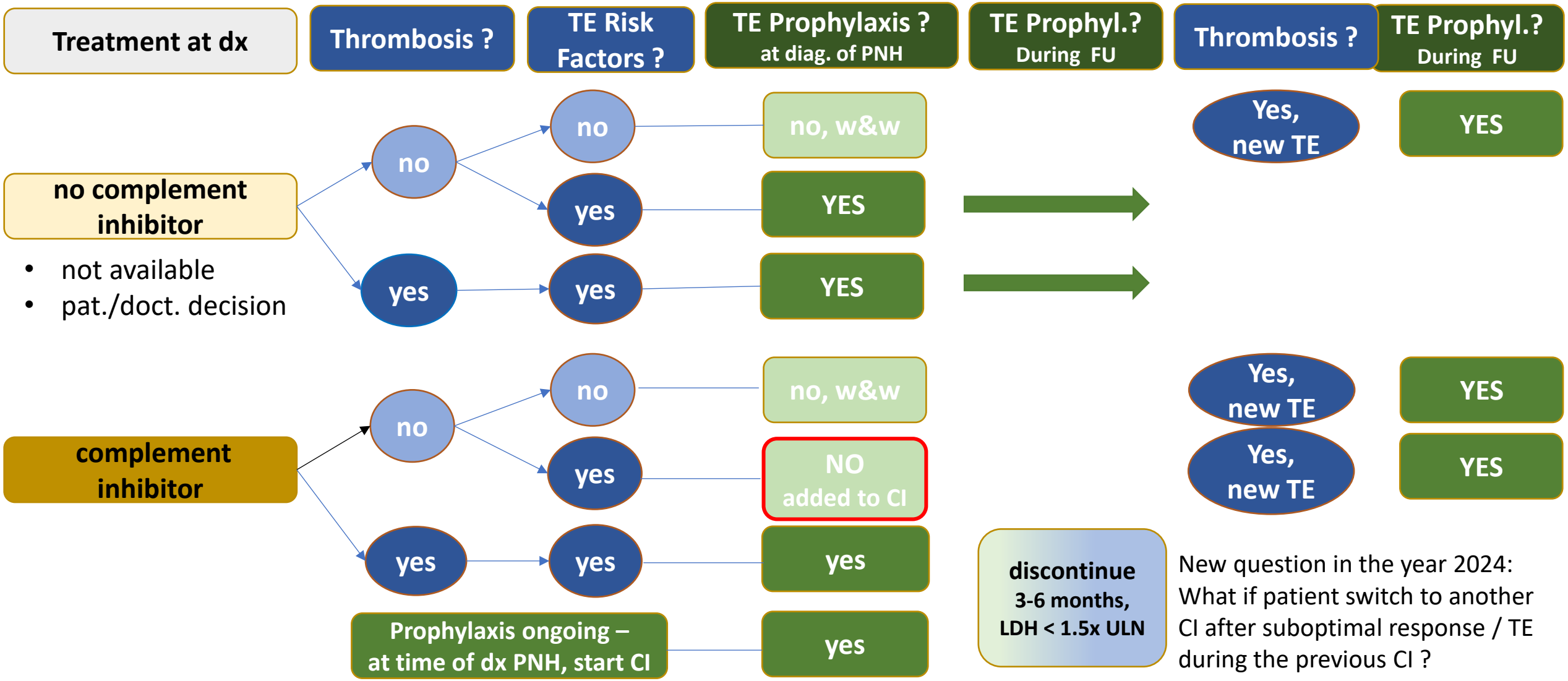


2 years:
the incidence of thrombosis was 18.3% (12.8%-24.7%) in untreated (death and anticomplement treatment initiation as competing events) vs 3.9% (1.3%-9.1%) upon therapy commencement (landmark time = treatment start, death as competing event).

Gurnari, Blood 2024, 144:145

Thrombosis prophylaxis in PNH: for whom and for how long ? – a personal view



New question in the year 2024: What if patient switch to another CI after suboptimal response / TE during the previous CI ?

Thrombolytic therapy

Table 1B. Patients who received thrombolytic therapy: clinical course.

Pt	Presentation of thrombotic episode	Sites of thrombosis	Estimated onset before tPA	Total n. of courses of tPA[a]	N. of admissions for tPA	Sites of hemorrhage	Initial radiological response[b]	Long-term treatment after tPA	Eventual outcome[c]	Current status	N. of years of follow-up[d]
1	Massive ascites, deep jaundice	HV, PV, IVC, SV	6 wks	5	1	Flank	PR	Warfarin	CR	Excellent	4.5
2	Abd pain and HA	PV, SV, IVC, HV, SS	1 wks	3	2	None	CR	LMWH→ fondaparinux, eculizumab	CR	Excellent	7.5
3	Abd pain	PV, HV	4 wks	2	1	Subcutaneous	nCR	Warfarin, eculizumab	nCR	Excellent	7
4	Vomiting, distention jaundice	TVS, JV, IVC, RV, HV, SMV	2 wks	3	1	SDH	nCR	NA	Died	Died	--
5	Renal failure	RV, JV, IVC,SCV	Few wks	2	1	Vaginal bleeding	Impr	Warfarin, LMWH, eculizumab	nCR	Excellent	13
6	Abd pain	HV	Few wks	3.5	1	SDH, mesenteric	PR	NA	CR[e], Died	Died	--
7	Abd pain	HV	Few wks	1.5	3	Pleural effusion, epistaxis	CR	Fondaparinux, eculizumab	Partial Budd Chiari	Excellent	4
8	Budd-Chiari	IVC, HV	Few days	4	4	CNS	PR	LMWH[g] eculizumab	Recurrent relapses	Good	4
9	Budd-Chiari	PV, HV	1 month	3	1	Psoas muscle	PR	Fondaparinux, eculizumab	PR	Died[f]	1

Abd: abdominal; wks: weeks; HV: hepatic vein; PV: portal vein; SV: splenic vein; JV: jugular vein; SMV: superior mesenteric vein; RV: renal vein; TVS: transverse sinus; SS: sagittal sinus; SCV: subclavian vein; CR: complete resolution; PR: partial resolution; nCR: near complete resolution; Impr: improvement; SDH: subdural hematoma; LMWH: low molecular weight heparin; HA: headache. [a]Total number of 24 h infusions administered during initial presentation; [b]initial response during first hospitalization; [c]eventual radiologic outcome of initial thrombosis; [d]years of clinical follow-up after the initial tPA infusion, [e]patent on post- mortem examination [f]elevated WBC, progression to chronic neutrophilic leukemia associated with acquired JAK2 mutation, treatment with decitabine, iron overload; [g]LMWH was discontinued after his bleeding complications, and he has been stable on eculizumab since then.

Araten et al, Haematologica 2012, 97(3)

Thrombolytic therapy

Table 2. Summary of the literature on thrombolytic therapy in patients with PNH.

Pt	Year	Author	Age	M/F	Sites of thrombosis	Regimen	Radiologic outcome	Clinical outcome
1	1985	Sholar	33	F	HV, IVC	Streptokinase 7500 U/h then 5000 U/h (total of 72 h); second course 2 months later: urokinase 250,000 U bolus then 250,000 U over 12 h	Complete resolution	Good, 2 years follow-up
2	1985	Sholar	33	M	HV, IVC	Streptokinase 250,000 U loading dose then 100,00 units/hour (48 h infusion) route not specified	Complete resolution	Good outcome, 2 years follow-up
3	1992	Kwan	47	F	Budd Chiari Syndrome	tPA iv, 100 mg over 3 h	Not determined	Marked clinical improvement, then bleeding complications, ultimately died
4	1992	Ishiguchi	42	F	IVC, Hepatic veins	Urokinase, catheter-directed, 360,000 U over 35 min, then 240,000 U/day	Partial response	Marked clinical improvement, doing well at 14 month follow-up
5	1993	Frawley	50	M	IVC, HV, SMV	Streptokinase 40,000 U/h catheter-directed into IVC then tPA 5mg x 3 then 7 mg/h via hepatic veins	Partial response	Died after CHOP chemotherapy
6	1994	McMullin	33	F	HV, IVC	Systemic iv tPA 0.25 mg/kg for 2 days	Restored flow	Good outcome, follow-up 6 years post-treatment
7	1994	McMullin	22	F	HV	0.25 mg/kg tPA iv over 3 h, then tPA catheter-directed into hepatic artery (12 mg over 24 h), then 12 mg over 24 h iv, then 50 mg over 24 h	Normal flow in hepatic veins	Good outcome, 2 year follow-up
8	2003	D'Amico	32	M	HV, IVC	Intravenous tPA dose not specified	No	Complicated by HITT
9	2003	Hauser	38	F	HV, IVC	Systemic iv infusion: 25 mg tPA over 3 h, then 25 mg over 21 h x 2 infusions	PR then CR after 2nd infusion	Death from mesenteric thrombosis 4 months later
10	2003	Tsatalas	35	M	HV	tPA, route and dose not specificied	Stable disease	Clinically well after 14 month follow-up
11	2006	Kuo	27	M	RHV, MHV	Urokinase catheter-directed into hepatic veins 125,000 U/h per vein (5 million U/36 h)	Complete	Good outcome after BMT
12	2006	Kuo	34	M	IVC, HV	Urokinase 7.45 million units/47 h catheter-directed localized infusion	Complete	Alive
13	2006	Kuo	14	F	Middle HV	Urokinase, catheter-directed, into hepatic vein: 2.9 million U/24 h	Near CR	Death from complications of subsequent BMT
14	2007	Shindo	39	F	IVC	Urokinase 1000 U/h for 1 week, route not specified	Complete resolution	Subsequent death from complications of aplastic anemia
15	2009	Yin	52	F	SMV, portal vein	500,000 U urokinase, catheter-directed	Some improvement	Clinical improvement

HV: hepatic vein; IVC: inferior vena cava; SMV: superior mesenteric vein; RHV: right hepatic vein; BMT: bone marrow transplantation.

Araten et al, Haematologica 2012, 97(3)

Classical treatment of PNH: when complement inibitors were (or are) not available

Supportive / non-curative approaches:

- Supportive measures to ameliorate anemia
- Treatment of hemolysis
- Prevention of thrombosis
- Treatment of thrombosis
- Treatment of infections

Curative approach:

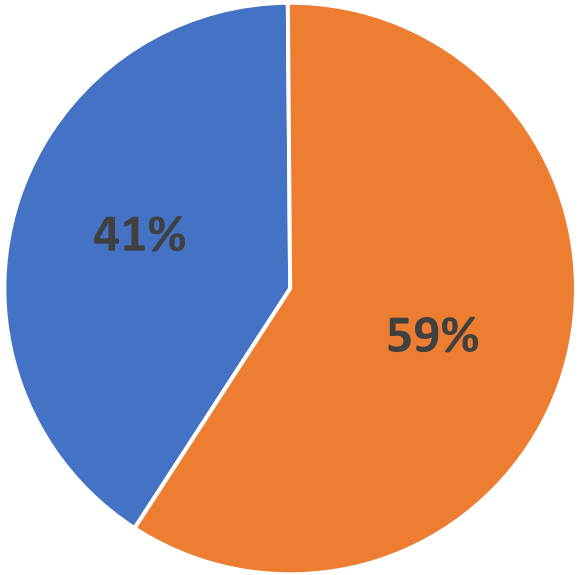
- Allogeneic stem cell transplantation

Stem Cell Transplantation for PNH (since 2010, > 5 pts.)

Pat.N	Age (yrs)	Diagnosis Indication for Transplant			Int. Dx-SCT (mo.)	Donor Source			Author, Year
		Classic PNH	AA/PNH	Other		MRD	MUD	Haplo/Other	
26	32			23	33	22	2	2 / 0	Santarone, 2010
211	30	85	103		20	136	74	0 / 1	Peffault de Latour, 2012
17	31	11	6			17			Pantin, 2014
6	37	0	6		5	6			Schcolnik-Cabrera,2015
18	25	14	4		15	5	3	10 / 0	Tian, 2016
13	28	13			41	2			Kamranzadeh, 2017
33	34	7	26		9	24	7	2 / 0	Lee, 2017
55	32	17	38		1	20	28	2 / 5	Cooper, 2019
44	29	15	29		6	15	4	25 / 0	Liu, 2019
42	33				29				Nakamura, 2020
78	29	27	51		12	19	49	10 / 0	Markiewicz, 2020
32	22	8	24		18		15	17 / 0	Lu, 2022
575		197	287			266	182	68 / 6	TOTAL

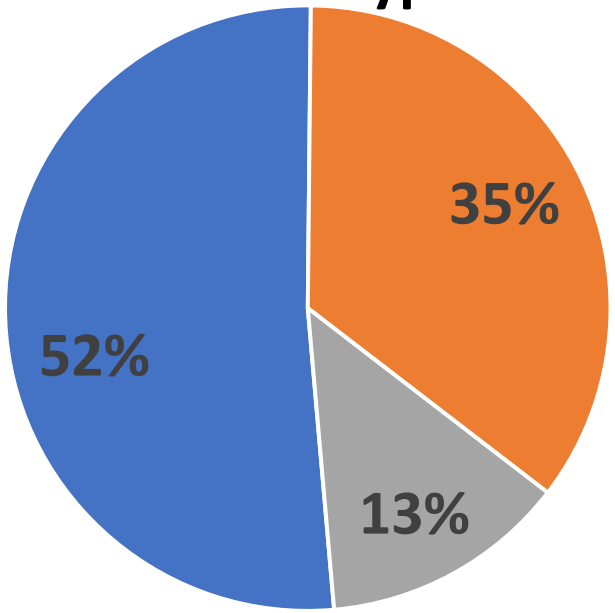
Stem Cell Transplantation for PNH (since 2010, > 5 pts.)

PNH classification



classical PNH AA/PNH syndrome

Donor Type



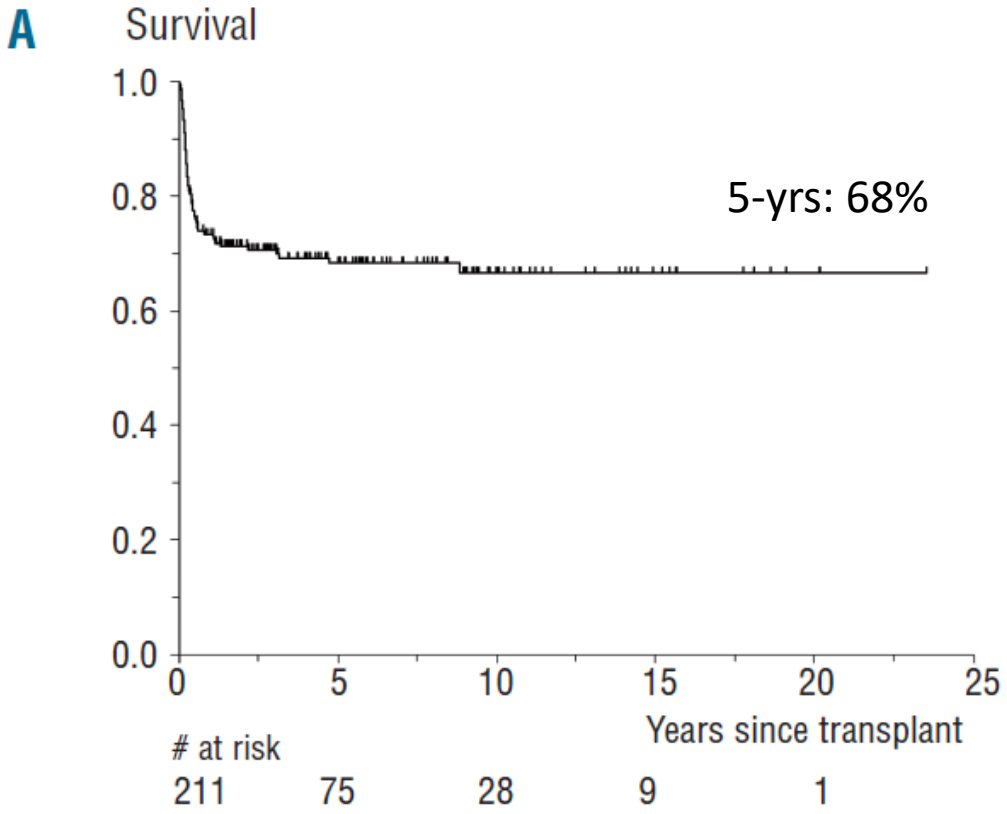
MFD MUD Haplo

Stem Cell Transplantation for PNH (since 2010, > 5 pts.)

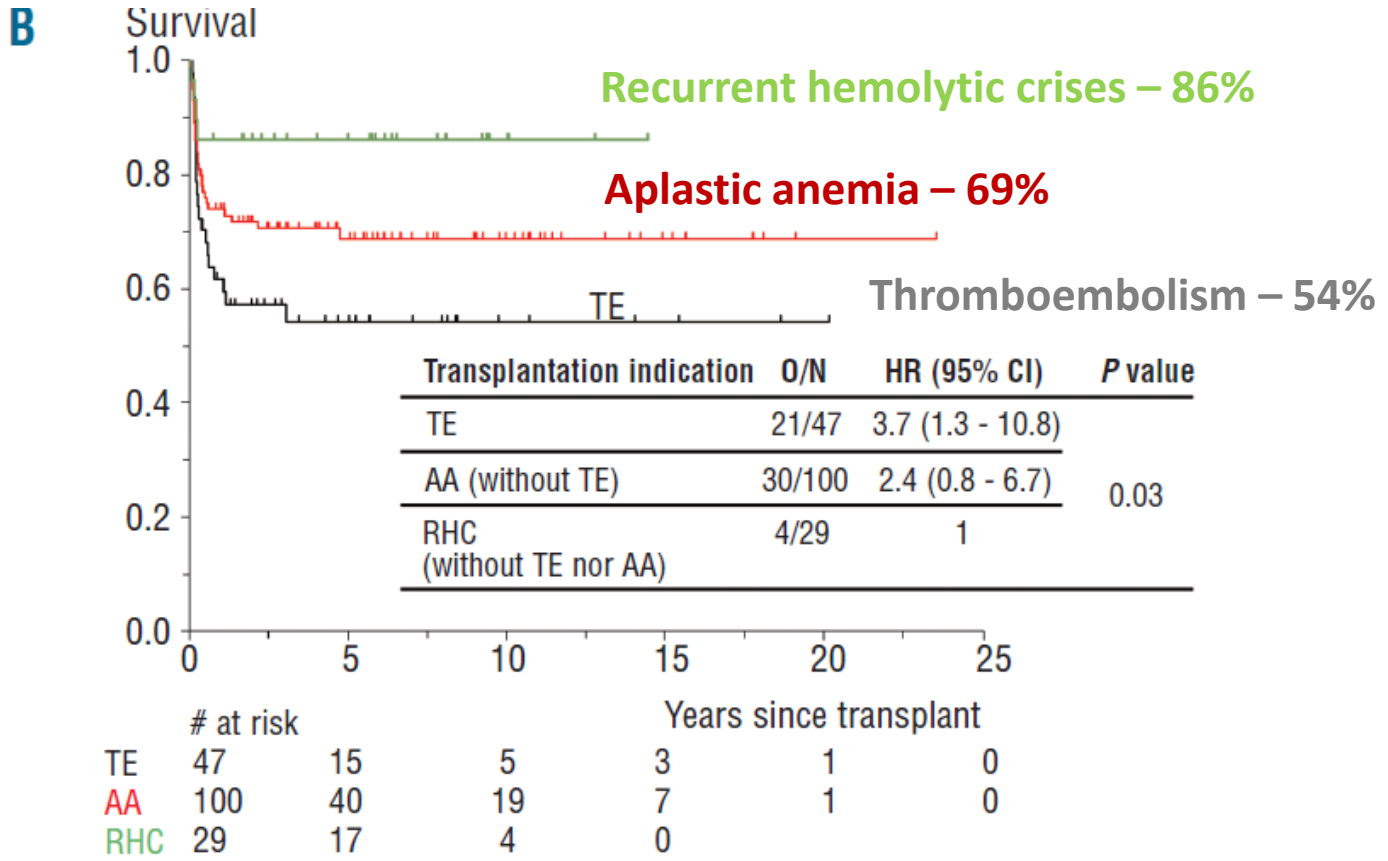
Pat.N	Conditioning regimens			GvHD		Survival			Author, Year
	Non-myeloablative	Myelo-ablative	Other/ missing	acute	chronic	No. of death	Survival (time, OS/DFS)	Survival %	
26	11	15		10	10	11	10-yr DFS	57	Santarone, 2010
211	70	74	67	85	87	64	5-yr OS	68	Peffault de Latour, 2012
17	17	0		8	11	2	6-yr OS	88	Pantin, 2014
6	6	0		1	22	1	8-yr OS	83	Schcolnik-Cabrera,2015
18	0	18		9	10	1	1.7-yr OS	94	Tian, 2016
13	13	13		9	11	3	13-yr OS	74	Kamranzadeh, 2017
33	6	27		9	6	4	5-yr OS	88	Lee, 2017
55	27	26	2	41	26	19	5-yr OS	70	Cooper, 2019
44	15	29		12	8	4	3-yr OS	90	Liu, 2019
42	7	32	3	8	7	11	6-yr OS	74	Nakamura, 2020
78	73	5		39	22	10	3-yr OS	88 / 85	Markiewicz, 2020
32	5	27				5	3-yr OS	83	Lu, 2022

Allogeneic Stem Cell Transplantation for PNH

Overall



by indication

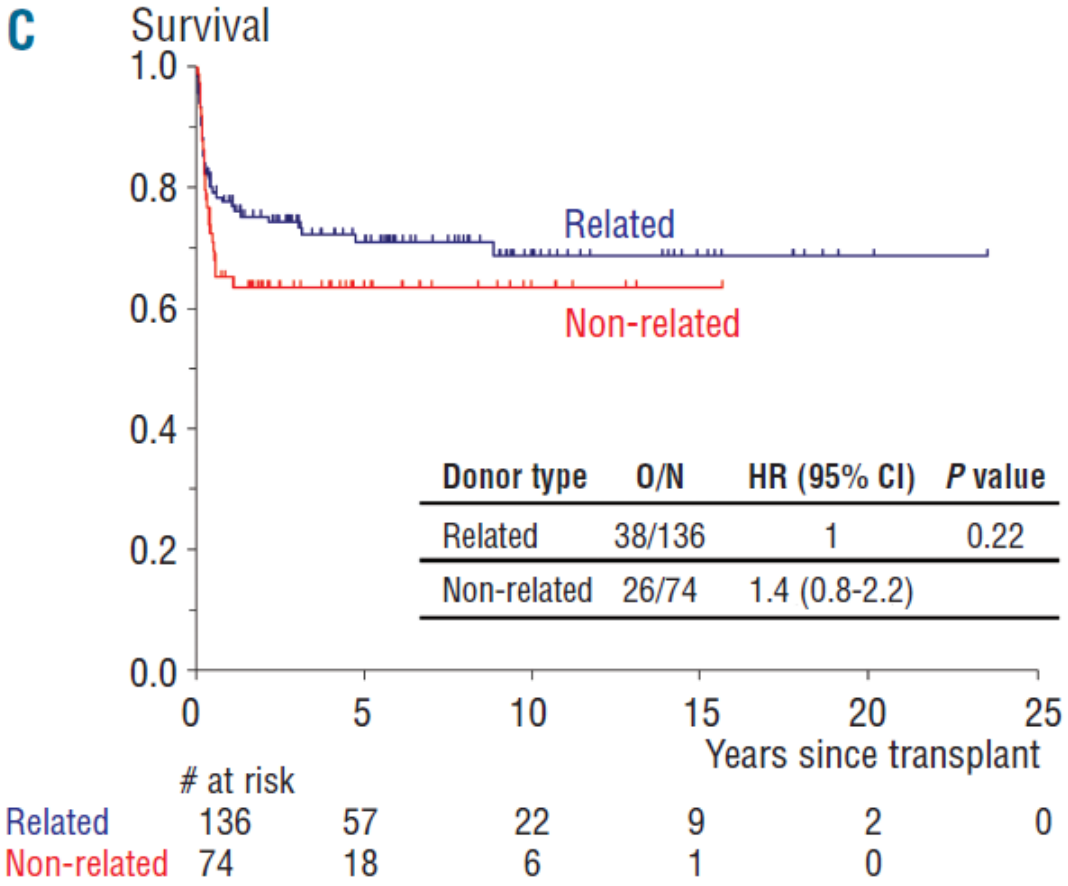


Transplantation indication	O/N	HR (95% CI)	*P* value
TE	21/47	3.7 (1.3 - 10.8)	
AA (without TE)	30/100	2.4 (0.8 - 6.7)	0.03
RHC (without TE nor AA)	4/29	1	

Peffault de Latour, Schrezenmeier, Haematologica 2012, 97: 1666-1673

Allogeneic Stem Cell Transplantation for PNH

donor type: related vs. unrelated - causes of death .



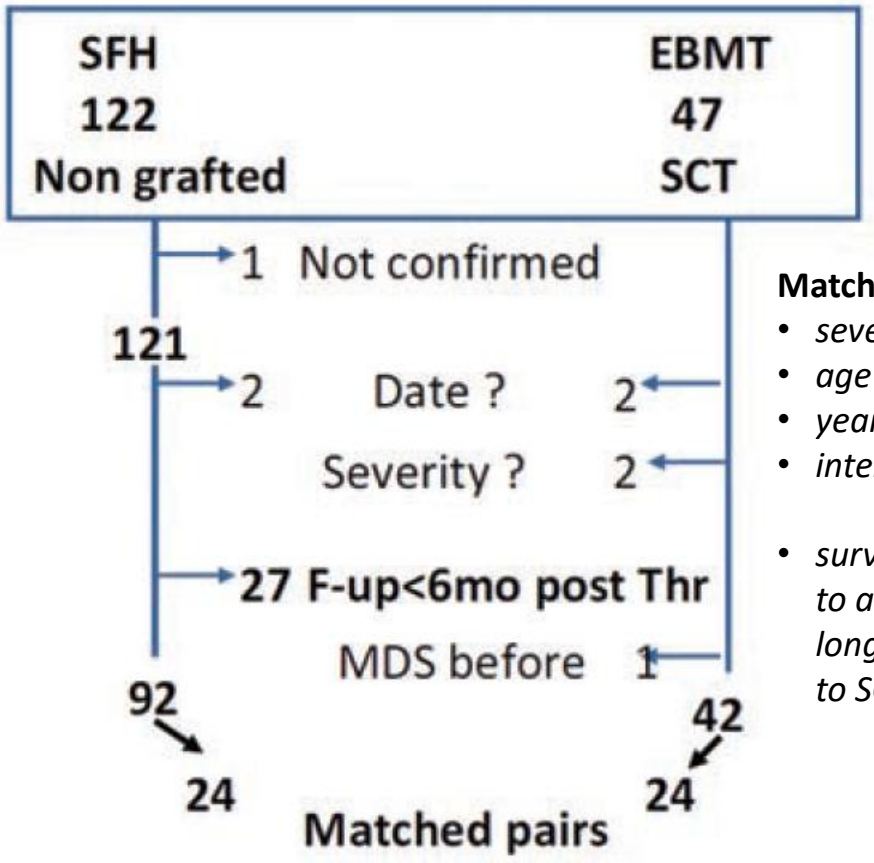
Causes	n
Infections	35
Bacterial	9
Fungal	9
Viral	6
Unknown	2
Graft-*versus*-host disease	18
Hemorrhage	12
Multiorgan failure	7
Other*	8

**Toxicity for five patients, one rejection, one lymphoproliferative disorder and one case of renal failure.*

Peffault de Latour, Schrezenmeier, Haematologica 2012, 97: 1666-1673

Allogeneic Stem Cell Transplantation for PNH (EBMT / SFH)

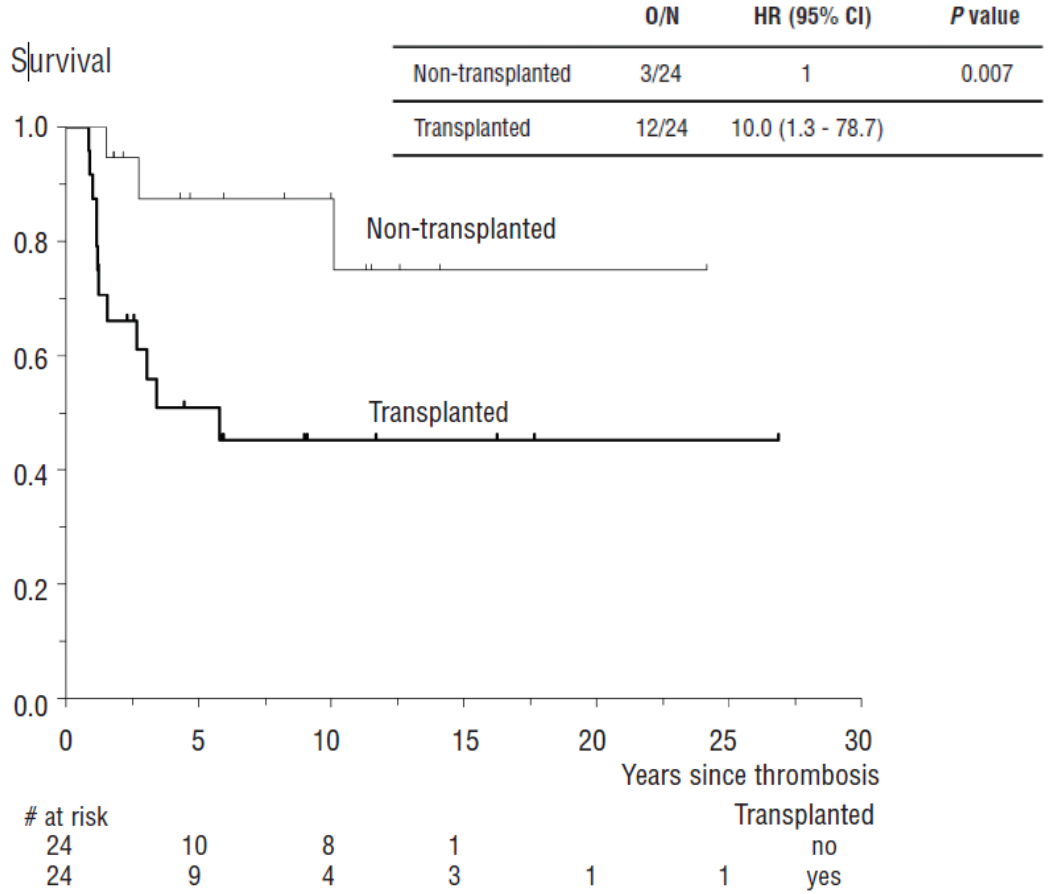
PNH with thromboembolism - comparison of matched pairs (n=24)



Matching:

- *severity of the complication*
- *age at complication*
- *year of complication*
- *interval PNH dx and compl.*

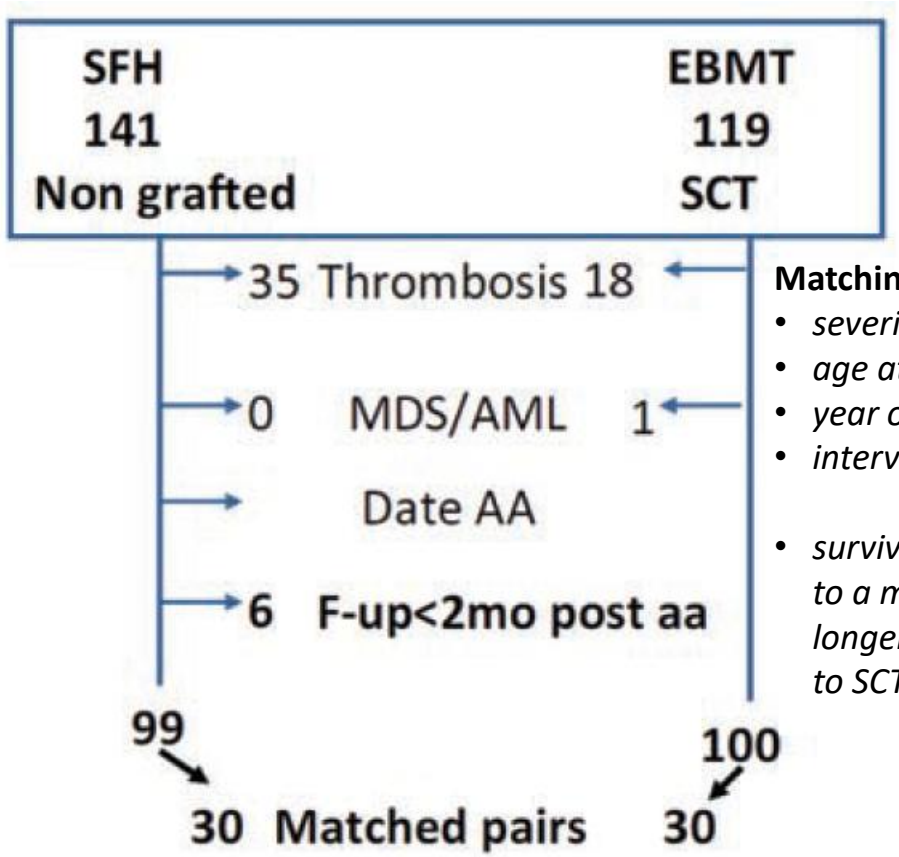
- *survival time from complication to a matched non-SCT patient longer than the time from complication to SCT for matched patient*



Peffault de Latour, Schrezenmeier, Haematologica 2012, 97: 1666-1673

Allogeneic Stem Cell Transplantation for PNH (EBMT / SFH)

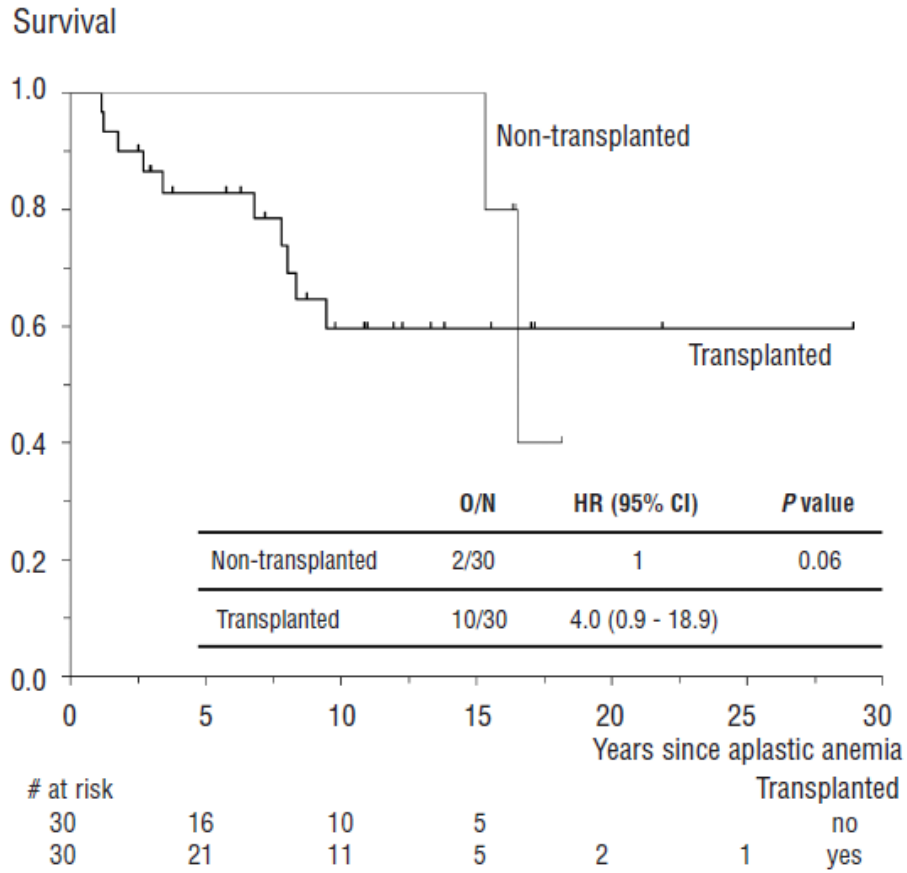
AA/PNH without thromboembolism - comparison of matched pairs (n=30)



Matching:

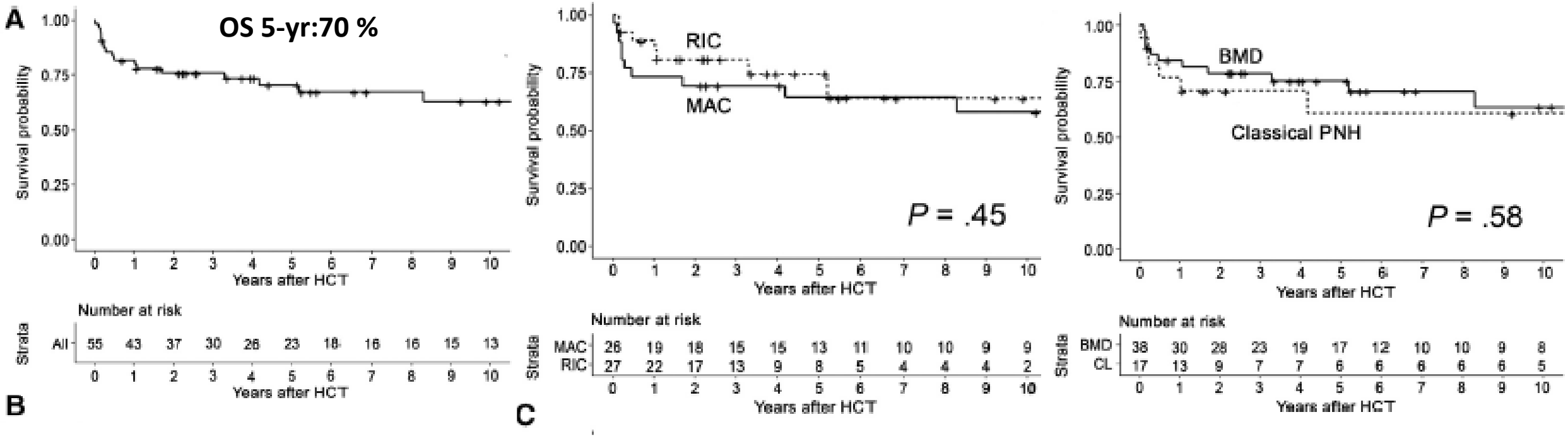
- *severity of the complication*
- *age at complication*
- *year of complication*
- *interval PNH dx and compl.*

- *survival time from complication to a matched non-SCT patient longer than the time from complication to SCT for matched patient*



Peffault de Latour, Schrezenmeier, Haematologica 2012, 97: 1666-1673

Allogeneic Hematopoietic Stem Cell Transplantation for PNH
- Single Center Experience Seattle FHCRC -

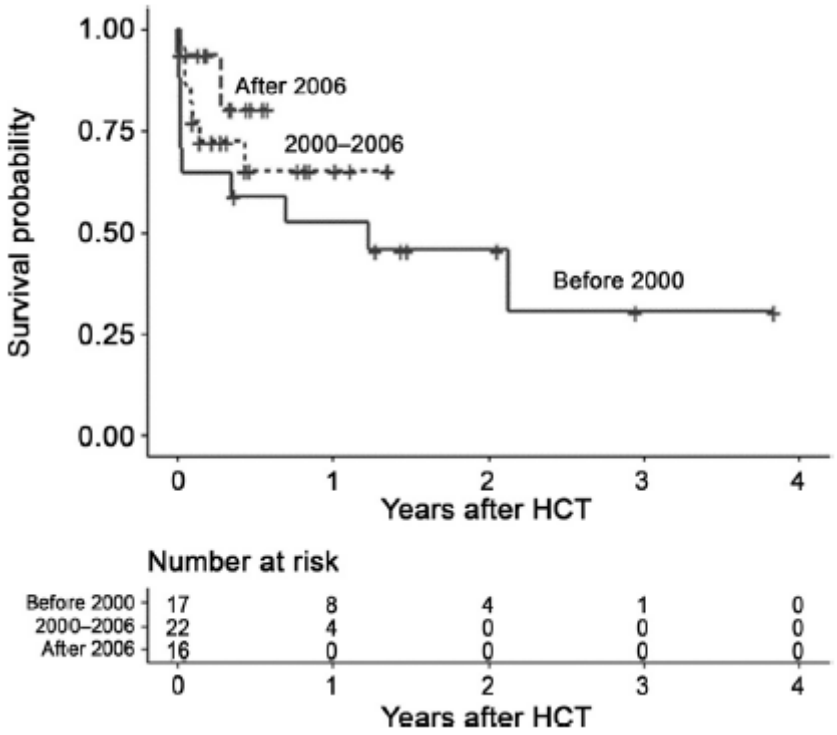


Period: 1971-2015
N = 17 (31%) classic PNH
N = 38 (69%) AA/PNH
Age: 31 (median; range 14 - 67 years)

Interval Dx - transplant: 15 (1 – 360 months)
Conditioning: 47% myeloablative, 49% reduced conditioning
Stem cell source: 46% PBSC, 47% BM
Donor type: 36% identical siblings, 36% MUD, 6% UCB
Engraftment: 93%
)

Cooper et al
Biol Blood Marrow Transplant
2019, 1331-1339

Allogeneic Hematopoietic Stem Cell Transplantation for Paroxysmal Nocturnal Hemoglobinuria- Single Center Experience Seattle FHCRC -



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Age: 31 (median; range 14 - 67 years)

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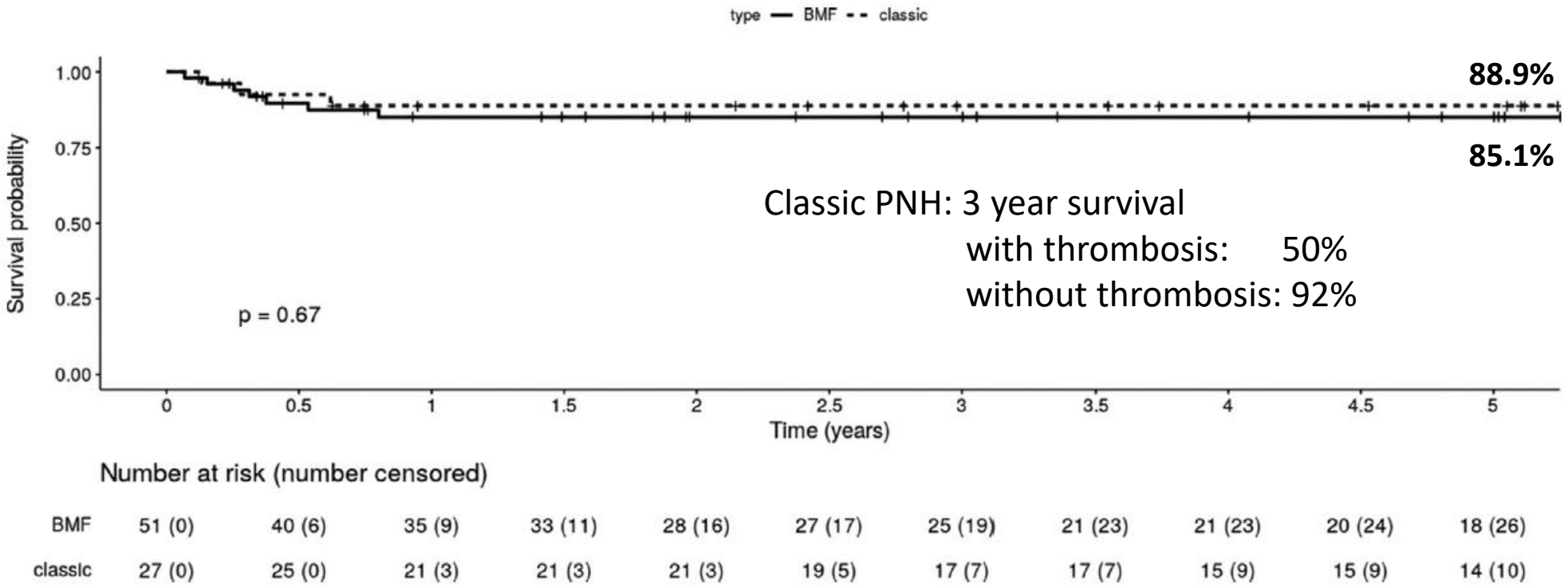
Stem cell source: 46% PBSC, 47% BM
Donor type: 36% identical siblings, 36% MUD, 6% UCB
Engraftment: 93%
)

Cooper et al
Biol Blood Marrow Transplant
2019, 1331-1339

Allogeneic Hematopoietic Stem Cell Transplantation for Paroxysmal Nocturnal Hemoglobinuria Multicenter Analysis by the Polish Adult Leukemia Group



Classic PNH: 3 year survival
with thrombosis: 50%
without thrombosis: 92%

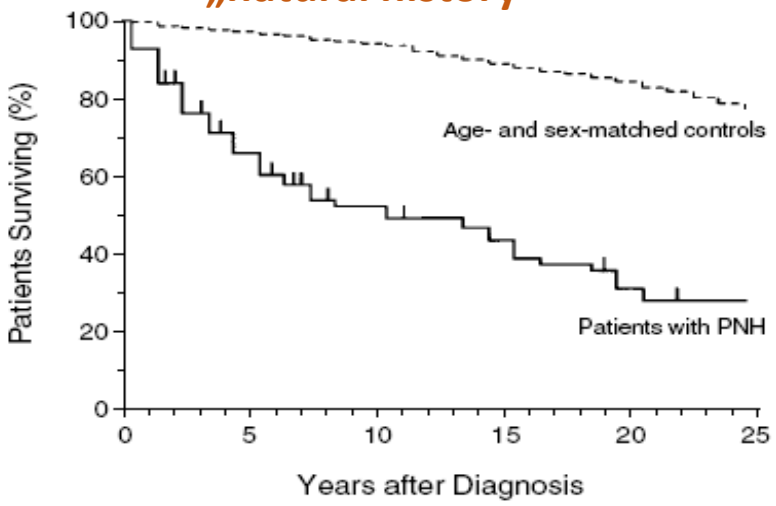
Period: 2002-2016
N = 27 classic PNH
N = 51 AA/PNH
Age: 29 (median; range 12- 65 years)

Interval Dx - transplant: 12 montsh (1 – 27 months)
Conditioning: 94% reduced conditioning (66% with Treosulfan)
Stem cell source: 72% PBSC, 27% BM
Donor type: 24% identical siblings, 63% MUD, 13% MMUD
Engraftment: 96%
)

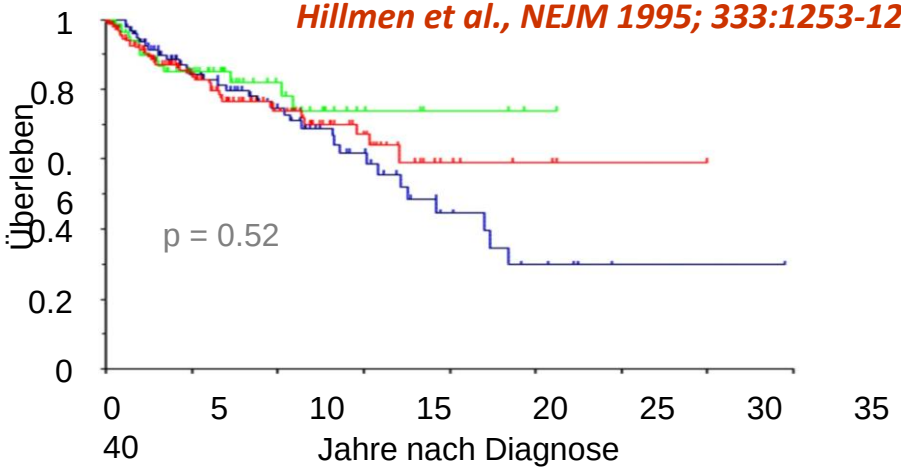
Markiewicz et al Biol Blood Marrow Transplant 2020, 1833-1839

Allogeneic Hematopoietic Stem Cell Transplantation for PNH
- a matter of alternative options and comparison -

„natural history“

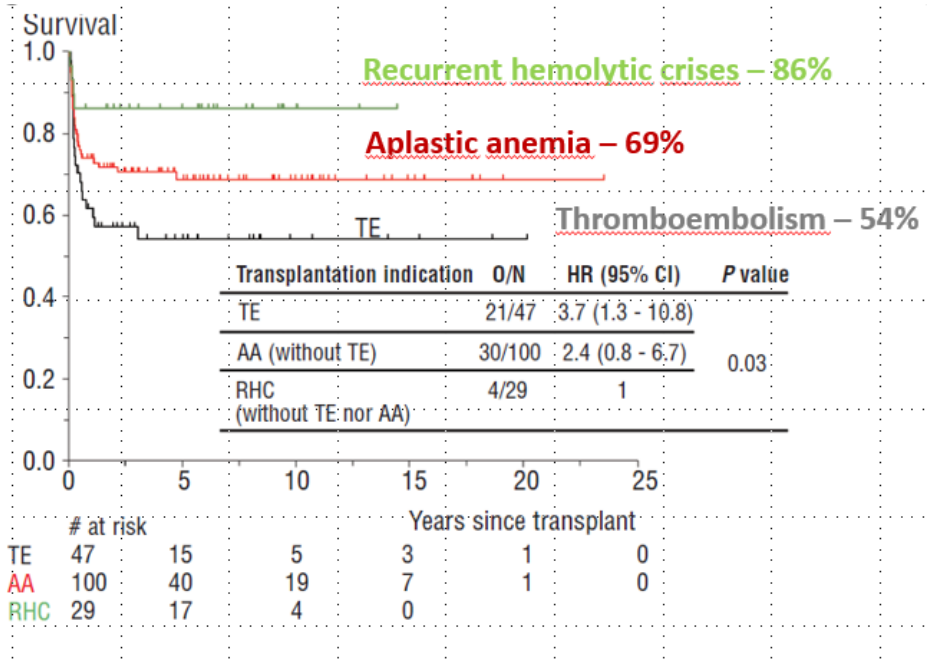


Hillmen et al., NEJM 1995; 333:1253-1258;



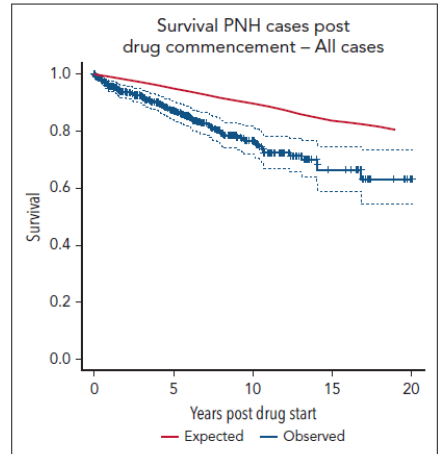
Peffault de Latour et al., Blood 2008;112:3099-3106

SCT



Peffault de Latour, Schrezenmeier, et al. Haematologica 2012, 97: 1666-1673

Long-term C5-Inhib.



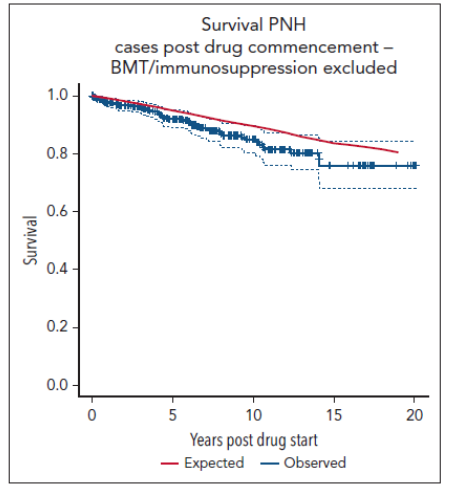


Figure 2. OS of patients with PNH, excluding those with clonal evolution or treatment for AA.

Kelly et al., Blood 2024, 143: 1157

Stem Cell Transplantation for PNH (since 2010, > 5 pts.)

Pat.N	Conditioning regimens			GvHD		Survival			Author, Year
	Non-myeloablative	Myelo-ablative	Other/ missing	acute	chronic	No. of death	Survival (time, OS/DFS)	Survival %	
26	11	15		10	10	11	10-yr DFS	57	Santarone, 2010
211	70	74	67	85	87	64	5-yr OS	68	Peffault de Latour, 2012
17	17	0		8	11	2	6-yr OS	88	Pantin, 2014
6	6	0		1	22	1	8-yr OS	83	Schcolnik-Cabrera,2015
18	0	18		9	10	1	1.7-yr OS	94	Tian, 2016
13	13	13		9	11	3	13-yr OS	74	Kamranzadeh, 2017
33	6	27		9	6	4	5-yr OS	88	Lee, 2017
55	27	26	2	41	26	19	5-yr OS	70	Cooper, 2019
44	15	29		12	8	4	3-yr OS	90	Liu, 2019
42	7	32	3	8	7	11	6-yr OS	74	Nakamura, 2020
78	73	5		39	22	10	3-yr OS	88 / 85	Markiewicz, 2020
32	5	27				5	3-yr OS	83	Lu, 2022

Allogeneic Hematopoietic Stem Cell Transplantation for PNH
- Conclusion -

- **Indication for SCT**: if **complement inhibitors** are ….

  …. available (for long-term treatment):
  SCT is <u>not</u> the treatment of choice for patients with classical PNH (with hemolysis or thromboembolism)

  …. not available at all:
  SCT is a <u>valid option</u> for PNH patients: elimination of PNH clone, acceptable toxicity and long-term survival

  …. Temporarily available
  SCT remains a valid option for PNH patients – C5i (eculizumab) as a „bridge to transplant“ may improve outcome
  → more studies needed

- **Prognostic factors**:
  - Good: hemolytic PNH Poor: thromboembolic events

- No consensus on **conditioning regimens** – good results in newer studies with reduced intensitiy conditioning
- Relapse of PNH after SCT does not seem to be the problem.

- **Donor Type**: Similar outcome after MFD vs. MUD and haplo SCT

Stem Cell Transplantation with eculizumab: bridge to transplant ?

Pat.N	Eculizumab dosing – prior to SCT	Eculizumab Post SCT	a/c GVHd And Survival			Author, Year
			acute	chronic	No. of death	
7	900 to 1.200 mg, every 2 wks. Until SCT (n=3) 600 mg prior to SCT (n=1) 600 mg every 7 d for 2 mo. (n=1)	Variabel	5	4	0	Cooper, 2018
8	600 mg every 7 d (4 doses), then 900 mg every 14 days	None	0	0	0	deZern, 2018
21	600 mg, every 7 days (4 doses), then 900 mg every 14 days	variable	7	0	6	Vallet, 2018
8	600 mg,very 7 days (4 doses), then 900 mg every 14 days	1 – 3 dose within 3 weeks post SCT	4	5	3	Mei, 2019

Pat.N	Conditioning regimens			Author, Year
	Non-myeloablative	Myelo-ablative	Other/ missing	
7	2	5		Cooper, 2018
8	8	0		deZern, 2018
21	18	2	1	Vallet, 2018
8	8	0		Mei, 2019


Paroxysmal Nocturnal Hemoglobinuria:
at the crossroads of somatic mutations, clonal expansion and immunity
Florence, October 3-4, 2024
Grand Hotel Baglioni

Questions ?

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Stem Cell Transplantation for PNH

Pat. No.	Age (yrs)	Diagnosis Indication for Transplant			Int. Dx-SCT (mo.)	Donor Source			Author, Year
		Classic PNH	AA/PNH	Other		MRD	MUD	Haplo/Other	
7	25	3	4		30	7			Raiola, 2000
26	32			23	33	22	2	2 / 0	Santarone, 2010
211	30	85	103		20	136	74	0 / 1	Peffault de Latour, 2012
17	31	11	6			17			Pantin, 2014
6	37	0	6		5	6			Schcolnik-Cabrera,2015
18	25	14	4		15	5	3	10 / 0	Tian, 2016
13	28	13			41	2			Kamranzadeh, 2017
33	34	7	26		9	24	7	2 / 0	Lee, 2017
55	32	17	38		1	20	28	2 / 5	Cooper, 2019
44	29	15	29		6	15	4	25 / 0	Liu, 2019
42	33				29				Nakamura, 2020
78	29	27	51		12	19	49	10	Markiewicz, 2020
32	22	8	24		18		15	17	Lu, 2022

Stem Cell Transplantation for PNH

Pat. No.	Age (yrs)	Diagnosis Indication for Transplant			Int. Dx-SCT (mo.)	Donor Source			Author, Year
		Classic PNH	AA/PNH	Other		MRD	MUD	Haplo/Other	
7	28	3	4		30	7			Raiola, 2000
26	32			23	33	22	2	2 / 0	Santarone, 2010
211	30	85	103		20	136	74	0 / 1	Peffault de Latour, 2012
17	31	11	6			17			Pantin, 2014
6	37	0	6		5	6			Schcolnik-Cabrera,2015
18	25	14	4		15	5	3	10 / 0	Tian, 2016
13	28	13			41	2			Kamranzadeh, 2017
33	34	7	26		9	24	7	2 / 0	Lee, 2017
55	32	17	38		1	20	28	2 / 5	Cooper, 2019
44	29	15	29		6	15	4	25 / 0	Liu, 2019
42	33				29				Nakamura, 2020
78	29	27	51		12	19	49	10	Markiewicz, 2020
32	22	8	24		18		15	17	Lu, 2022