

# **Paroxysmal Nocturnal Hemoglobinuria in bone marrow failure**

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Form A: no conflicts of interest to declare.



**대한혈액학회 Korean Society of Hematology**

# **COI disclosure**

*Name of author : Jun Ho Jang*

**I have no personal or financial interests to declare:**

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# Contents

1. The overlapping relationship between PNH and bone marrow failure disorders
2. The Mortality of PNH in the context of BMF
3. Mechanisms of PNH clonal expansion
4. Management of PNH in the context of BMF

# **The overlapping relationship between PNH and bone marrow failure disorders**

# Relationship between PNH and BMF disorders

- While there is a close association between PNH and BMF, they are distinguished based on predominant clinical features<sup>1,2</sup>

**PNH**

Continuous destruction of RBCs (ie, hemolysis)<sup>2</sup>

**BMF**

Diminished production of RBCs, WBCs, and platelets (ie, pancytopenia)<sup>3</sup>

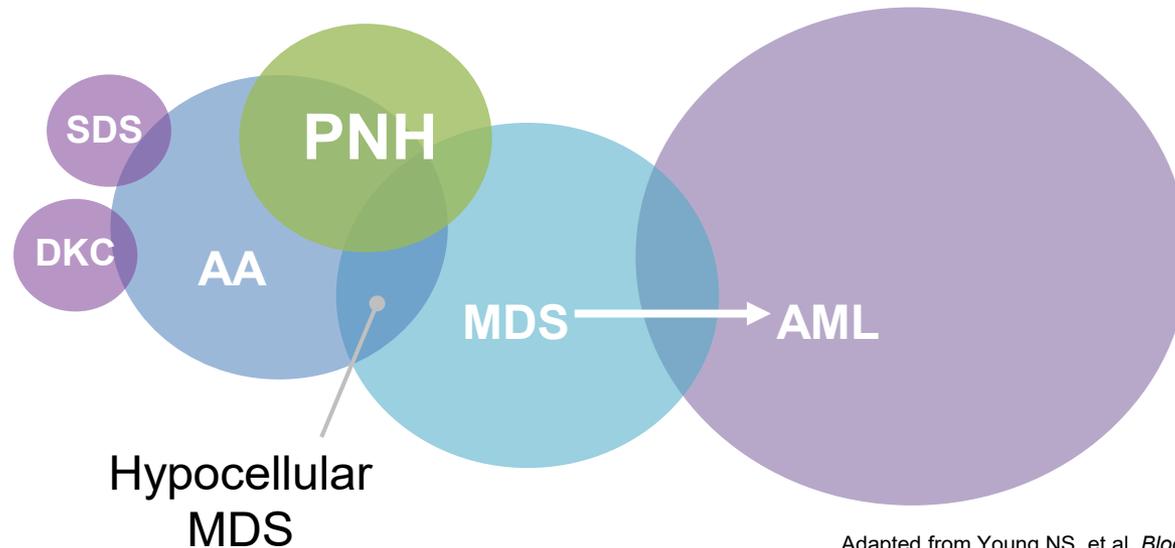
- Each condition may progress independently and require a distinct clinical management and treatment approach<sup>2,4</sup>
- Cytopenias due to PNH and BMF often present concurrently, but are the result of distinct blood disorders<sup>5</sup>

BMF, bone marrow failure; RBC, red blood cell; WBC, white blood cell.

1. Brodsky RA. *Blood* 2009;113(26):6522–6527; 2. Luzzatto L, et al. *Br J Haematol* 2011;153(6):709–720; 3. Weinzierl EP, et al. *Am J Clin Pathol* 2013;139(1):9–29; 4. Sugimori C, et al. *Br J Haematol* 2009;147(1): 102–112; 5. Young NS, et al. *Hematology Am Soc Hematol Educ Program* 2000:18–38.

# PNH and other BMF syndromes

- PNH overlaps with BMF syndromes, and the predominant clinical characteristics can evolve over time<sup>1,2</sup>



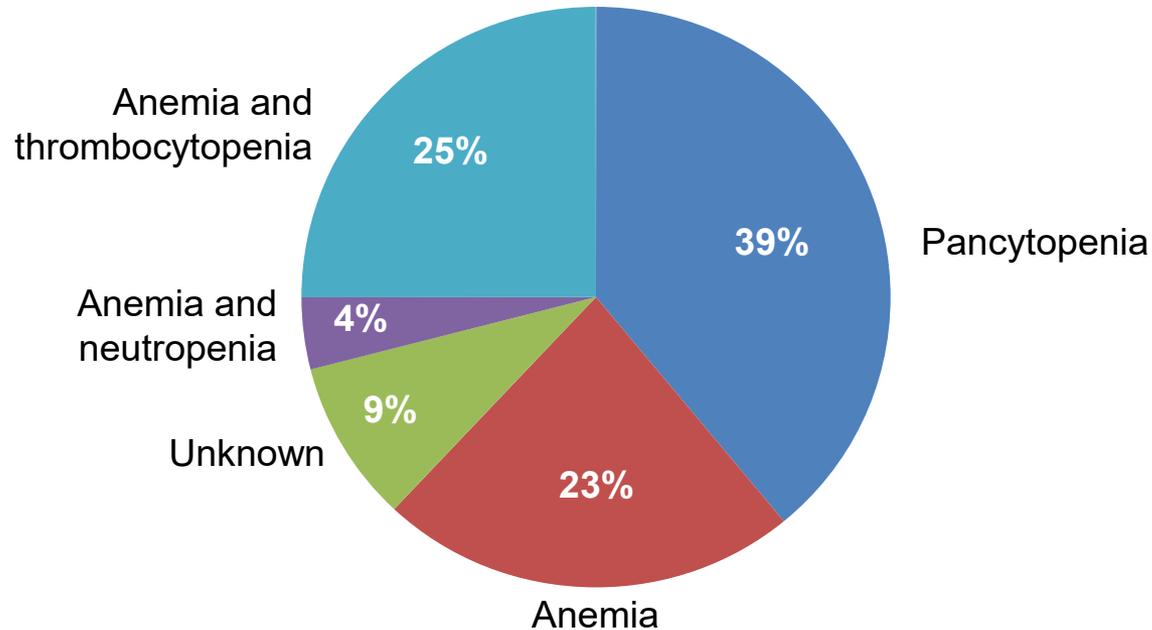
- Patients who develop PNH have an element of BMD either before or at the time of diagnosis<sup>3,4</sup>
  - Typically aplastic anemia
  - Occasionally myelodysplastic syndrome
  - Bone Marrow Dysfunction NOS

AA, aplastic anemia; AML, acute myelogenous leukemia; BMF, bone marrow failure; DKC, dyskeratosis congenita; HSCs, hematopoietic stem cells; MDS, myelodysplastic syndrome; *PIG-A*, phosphatidylinositol glycan complementation class-A; SDS, Shwachman-Diamond syndrome.

1. Young NS, et al. *Blood* 2006;108(8):2509–2519; 2. Weinzierl EP, et al. *Am J Clin Pathol* 2013;139(1):9–29; 3. Sugimori C, et al. *Br J Haematol* 2009;147(1):102–112; 4. Raza A, et al. *Cytometry B Clin Cytom* 2014;86(3): 175–182;

# Patients with PNH often have peripheral blood abnormalities

**91% of patients with PNH present with cytopenias<sup>1</sup>**



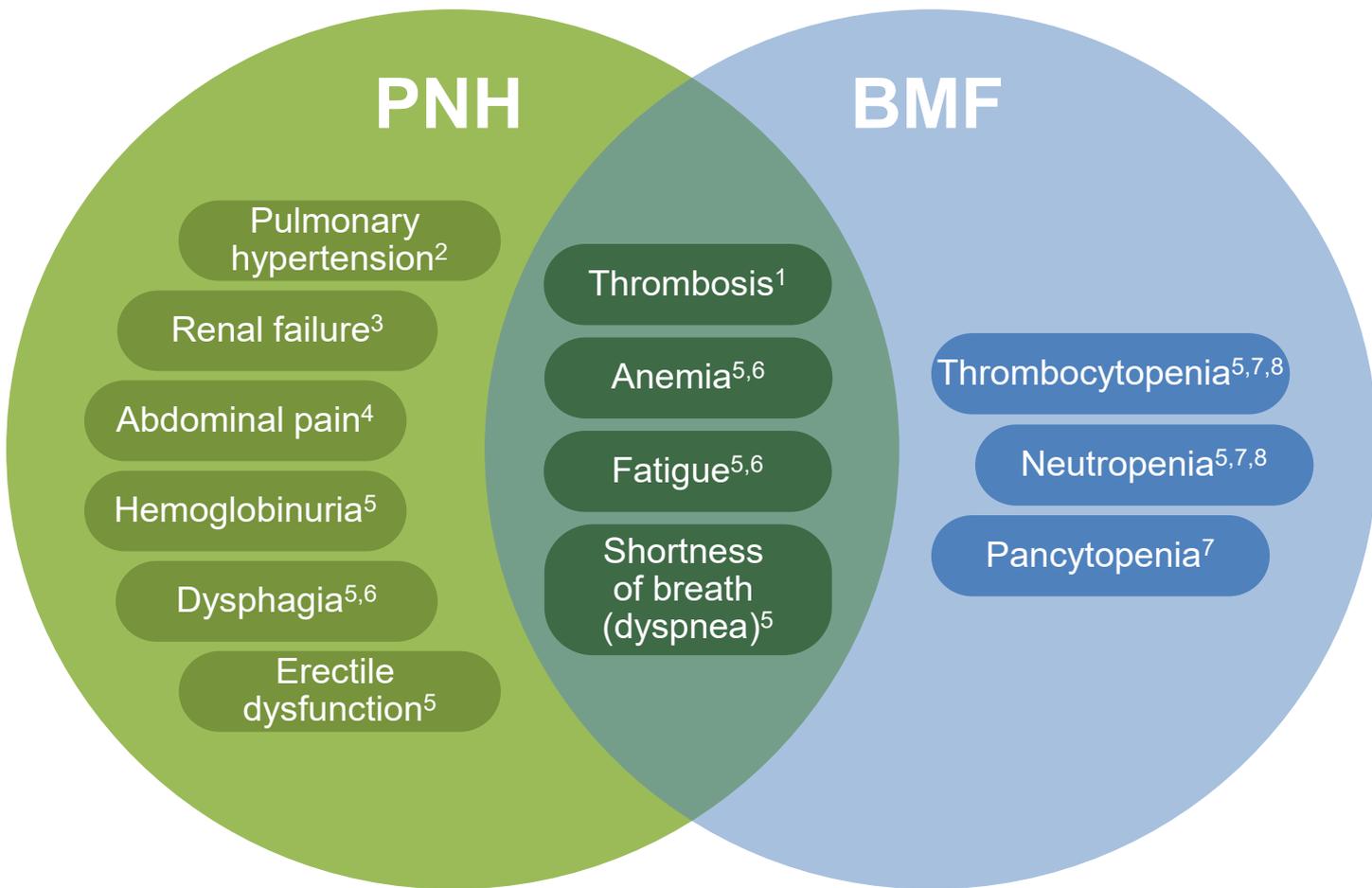
Adapted from Peffault de Latour R, et al. *Blood* 2008;112(8):3099–3106.

Cytopenias due to BMF and PNH are distinct blood disorders that often present concurrently<sup>2</sup>

1. Peffault de Latour R, et al. *Blood* 2008;112(8):3099–3106;

2. Young NS, et al. *Hematology Am Soc Hematol Educ Program* 2000:18–38.

# Patients with PNH and BMF may have an overlapping set of signs and symptoms

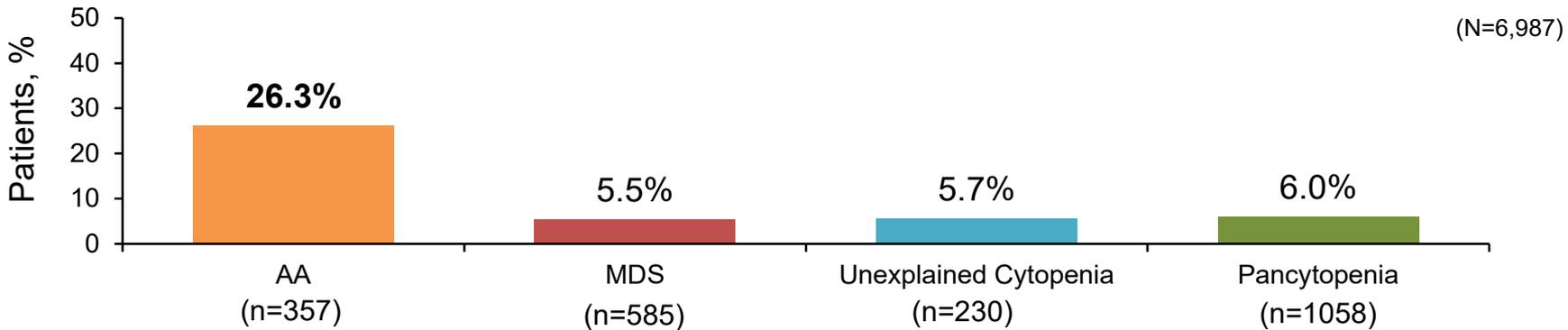


1. Hill A, et al. *Blood* 2013;121(25):4985–4996; 2. Hill A, et al. *Br J Haematol* 2012;158(3):409–414;
3. Hillmen P, et al. *Am J Hematol* 2010;85(8):553–559; 4. Lee JW, et al. *Haematologica* 2010;95(suppl 2):506;
5. Hill A, et al. *Br J Haematol* 2007;137(3):181–192; 6. Brodsky RA, et al. *Lancet* 2005;365(9471):1647–1656;
7. Weinzierl EP, et al. *Am J Clin Pathol* 2013;139(1):9–29; 8. Parker CJ. *Hematology Am Soc Hematol Educ Program* 2016;2016(1):208-216.

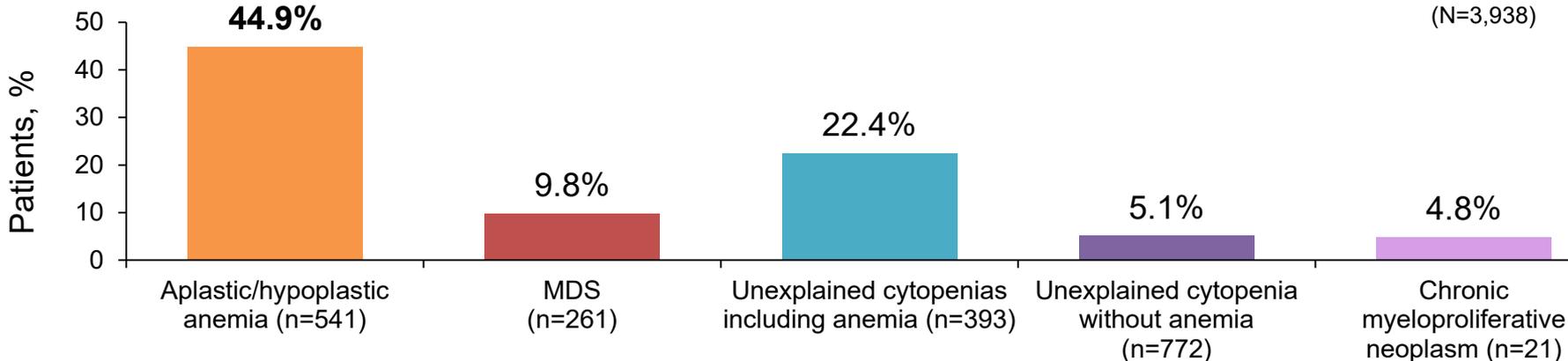
# GPI-AP deficient cells in patients with BMF

: Percentage of patients with >0.01% GPI-AP deficient cells based on diagnosis

## Incidence of PNH Clones in Patients with ICD-9 Diagnostic Code at single center (US)<sup>1</sup>



## Prospective study of flow cytometry blood samples in Spain and Brazil.<sup>2</sup>



Adapted from Morado M, et al. *Cytometry B Clin Cytom* 2017;92(5):361–370.

MDS, myelodysplastic syndrome; ICD, International Classification of Diseases.

1. Movalia MK, et al. *Blood*. 2011;118(21). Abstract 1033. 2. Morado M, et al. *Cytometry B Clin Cytom* 2017;92(5):361–370.

# GPI-AP deficient cells in patients with MDS

- The study assessed HS-FCM assay for PNH clones in 136 patients with various BMD  
(MDS (n=110), MDS/MPD (n=15), CIMF (n=5) and AML (n=6))
- PNH+ clone** in nine patients who represented **8% of the 110 MDS cases** and **12% (9/75)** of the MDS cases with lower than 5% blasts.  
(all of whom had low-grade MDS with less than 5% blasts)

**Table 1.** Patients' clinicopathological characteristics and disease categorization.

Diagnosis	Patients (n)	Sex male/female	Median age (years)	Abnormal cytogenetics <sup>1</sup> (%)	PNH clone (n)	Median overall survival (months)	Median follow-up (months)	Alive/dead (n)
5q- syndrome	5	1:4	68.0	100	1	NR	19.0	4/1
RA	17	13:4	63.0	29.4	6	NR	18.7	15/2
RCMD	37	20:17	68.0	44.1	2	NR	19.4	24/13
RARS	9	5:5	66.0	22.2	0	NR	20.4	8/1
RCMD-RS	6	4:2	69.0	16.7	0	NR	18.9	6/0
RAEB-1	13	7:6	68.0	66.7	0	NR	16.8	7/6
RAEB-2	13	8:5	71.0	54.0	0	15.5	14.8	5/8
MDS-U	10	5:5	66.5	40.0	0	NR	17.0	8/2
CIMF	5	3:2	74.0	40.0	0	NR	16.2	3/2
CMML <sup>2</sup>	5	3:2	68.0	40.0	0	17.0	16.6	2/3
Other MDS/MPD <sup>3</sup>	10	6:4	70.0	70.0	0	NR	16.2	7/3
AML	6	4:2	69.0	60.0	0	5.5	5.2	2/4
Total	136	77:59	68.0	45.0	9	NR	19.0	91/45

RA: refractory anemia; RCMD: refractory anemia with multilineage dysplasia; RARS: refractory anemia with ringed sideroblasts; RAEB: refractory anemia with excess blasts; MDS-U: myelodysplastic syndrome, unclassifiable; CMML: chronic myelomonocytic leukemia; MPD: myeloproliferative syndrome; AML: acute myeloid leukemia; NR: not reached; <sup>1</sup>Cytogenetic analysis was not available in four MDS cases (three RCMD and one RAEB-1) and one case of AML; <sup>2</sup>CMML cases include four cases of CMML-1 and one case of CMML-2; <sup>3</sup>Other MDS/MPD besides CMML cases were three cases of atypical chronic myelogenous leukemia, one RARS with marked thrombocytosis, and six MDS/MPD, unclassifiable.

# GPI-AP deficient cells in patients with MDS

- The bone marrow cellularity and blast percentage in PNH+ MDS patients were significantly lower than those in the PNH-negative MDS patients.

**Table 3.** Clinical and laboratory comparison of patients with low grade myelodysplastic syndrome with or without a PNH clone.

Patient	PNH+ (n=9)	PNH- (n=65)	p
Male:female	7:2	39:36	0.174
Age, mean (years)	65 (33-82)	66 (23-100)	0.716
Hemoglobin, mean (g/dL)	11.2 (7-13.2)	10.7 (7.3-14.8)	0.450
ANC, mean ( $\times 10^9/L$ )	1.9 (1.1-8.3)	2.7 (0.3-14.6)	0.360
Platelets, mean ( $\times 10^9/L$ )	125 (14-330)	180 (6-349)	0.299
MCV, mean (fL)	94.5 (82.3-114.6)	101.8 (63.5-118.2)	0.152
Reticulocytes, mean (%)	3.0 (1.2-3.9)	2.2 (0.2-7.7)	0.143
BM cellularity, mean (%)	37 (10-60)	59 (5-100)	0.017
BM blasts, median (%)	0.7 (0-1)	1.5 (0-4.8)	0.039
Abnormal cytogenetics (%)	22	44	0.292
AML transformation	0	4	1.000
OS, median (months)	NR	NR	

ANC: absolute neutrophil count; MCV: median corpuscular volume; BM: bone marrow; AML: acute myeloid leukemia; OS: overall survival; NR: not reached.

- PNH is more likely to be detected in MDS patients who:
  - Present with marrow failure
  - Are less likely to transform into leukemia
  - Have refractory anemia; the most common subtype associated with clonal expansion

# The Incidence of BMF in patients with PNH

- 701 (43.5%) of the patients had been diagnosed with AA among 1610 enrolled patients (International PNH Registry)

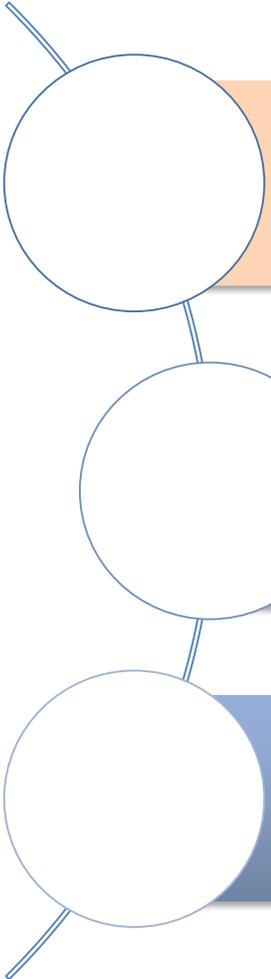
	Ever diagnosed BMD*
<b>Aplastic anemia</b>	<b>701 (43.5%)</b>
Myelodysplastic syndromes	93 (5.8%)
Myelofibrosis	7 (0.4%)
Acute myeloid leukemia	6 (0.4%)

\* Bone marrow disorder

- 40 % of patients had PNH with AA and 6% of patients had PNH with MDS was reported in Korean PNH registry.

	Ever diagnosed BMD
Aplastic anemia	121 (40.2 %)
Myelodysplastic syndromes	19 (6.3%)

# Guidelines for the diagnosis and monitoring of PNH in AA and MDS by flow cytometry



Recommended to perform PNH screening in all patients with AA, even in the absence of hemolysis, and in certain MDS patients

AA patients may progress to hemolytic PNH; serial monitoring is important as this may be presaged by an increase in the PNH clone size

- Annual monitoring may be sufficient, but any change in clinical or hematologic parameters requires more frequent monitoring

Small PNH clones can be reliably detected in many patients with AA and MDS; the prognostic value remains controversial

# **The mortality of PNH in the context of BMF**

# Severity of PNH-Cytopenia

## Definition of the severity of aplastic anemia and PNH-Cytopenia<sup>1</sup>

Severe AA BM cellularity <25%, or 25–50% with <30% residual hemopoietic cells\*

2/3 of the following:

neutrophil count <0.5 x 10<sup>9</sup>/L

platelet count <20 x 10<sup>9</sup>/L

reticulocyte count <20 x 10<sup>9</sup>/L

Very severe AA As for severe AA, but neutrophils <0.2 x 10<sup>9</sup>/L

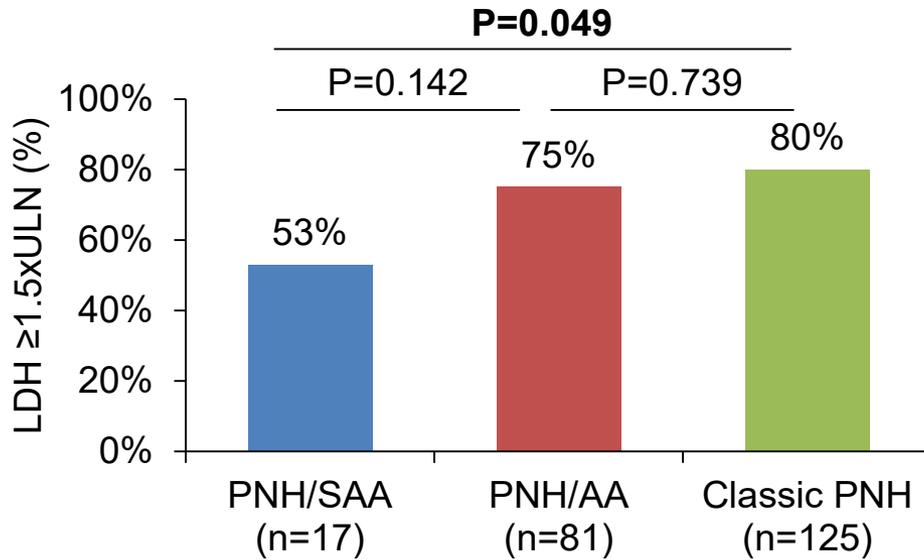
Non-severe AA Patients not fulfilling the criteria for severe or very severe AA

\* Patients were identified by the evidence of at least 2 of the following 3 hematological values at PNH diagnosis

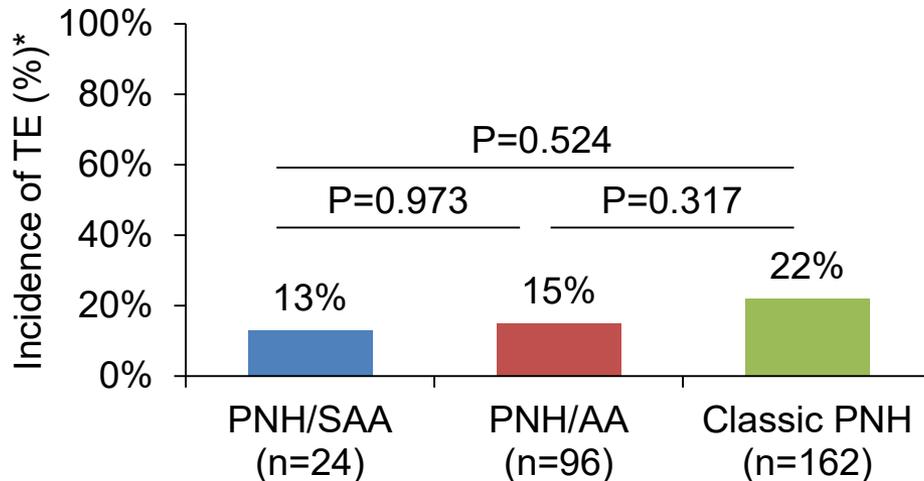
- I. **PNH/SAA:** Hb ≤ 8 g/dL, ANC < 0.5 x 10<sup>9</sup>/L, PLT < 20x10<sup>9</sup>/L
- II. **PNH/AA:** Hb ≤ 10 g/dL; ANC: 0.5~1.5 x10<sup>9</sup>/L, PLT: 20~100x10<sup>9</sup>/L
- III. **Classic PNH:** Not enough to meet the above mentioned criteria

1. Marsh JC, et al. *Br J Hematol* 2009;147:43-70.  
2. Kim JS, et al. *Ann Hematol* 2016;95(1):125–33.

# Patients with PNH and BMF may have an overlapping set of characteristics



Elevated hemolysis (LDH  $\geq 1.5$  fold x ULN) between three groups



TE occurred in all patients with PNH regardless of type of PNH

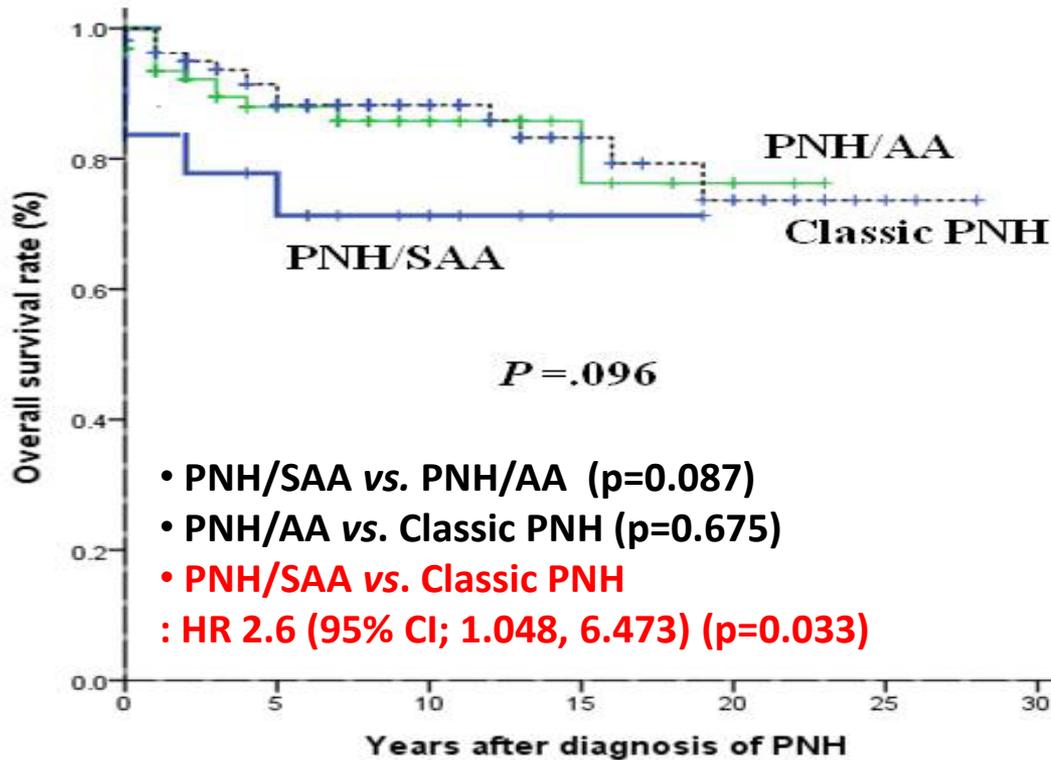
\*TE per patient.

LDH, lactate dehydrogenase; ULN, Upper Limit of Normal; SAA, severe aplastic anemia.

1. Kim JS, et al. *Ann Hematol* 2016;95(1):125-33.

# PNH/SAA had significantly poor survival compared to classic PNH

- Overall survival was significantly lower in the PNH/SAA subgroup than in the classic PNH subgroup (P=0.033).

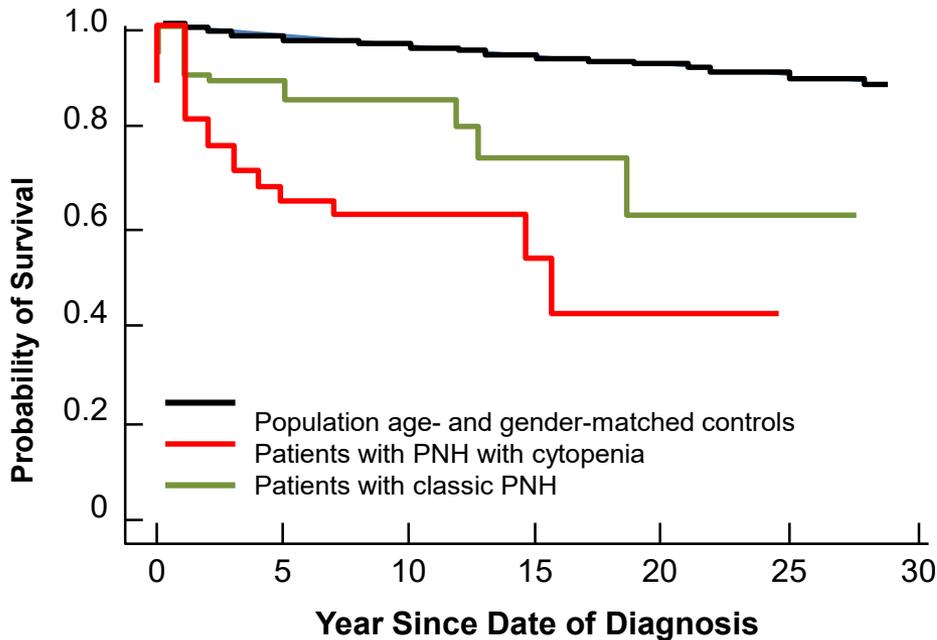


\* Patients were identified by the evidence of at least 2 of the following 3 hematological values at PNH diagnosis

- PNH/SAA:** Hb  $\leq$  8 g/dL, ANC  $<$   $0.5 \times 10^9/L$ , PLT  $<$   $20 \times 10^9/L$
- PNH/AA:** Hb  $\leq$  10 g/dL; ANC:  $0.5 \sim 1.5 \times 10^9/L$ , PLT:  $20 \sim 100 \times 10^9/L$
- Classic PNH:** Not enough to meet the above mentioned criteria

# The survival of PNH patients with cytopenia compared with age- and gender-matched general population

- Patients with cytopenia had a mortality rate 6.2-fold greater than the age- and gender-matched general population (SMR=6.2; 95% CI, 4.7-9.3;  $P < 0.001$ ).



Patient population	SMR vs. age- and sex-matched general population	
	SMR (95% CI)	P value
Total PNH patients (n = 301)	3.89 (2.73-5.05)	< 0.001
Classic PNH (n = 157)	4.4 (2.72-6.23)	< 0.001
PNH-Cytopenia (n = 107)	6.2 (4.71-9.34)	< 0.001

**Study Description:** A retrospective analysis of 301 Korean patients with PNH, age- and gender-matched with the general population, was performed to systemically identify the clinical symptoms and signs predictive of mortality.

# Significant predictors of mortality in PNH Patients

- Univariate analyses showed that significant predictors of mortality were TE ( $P < 0.001$ ), IRF ( $P = 0.001$ ), LDH  $\geq 1.5 \times$  ULN ( $P = 0.009$ ), **PNH-cytopenia ( $P = 0.023$ )**, abdominal pain ( $P = 0.026$ ), and dyspnea/chest pain ( $P = 0.026$ )
- Multivariate analyses showed that significant predictors of mortality were TE ( $P < 0.001$ ), IRF ( $P = 0.029$ ), **PNH- cytopenia ( $P = 0.020$ )**.

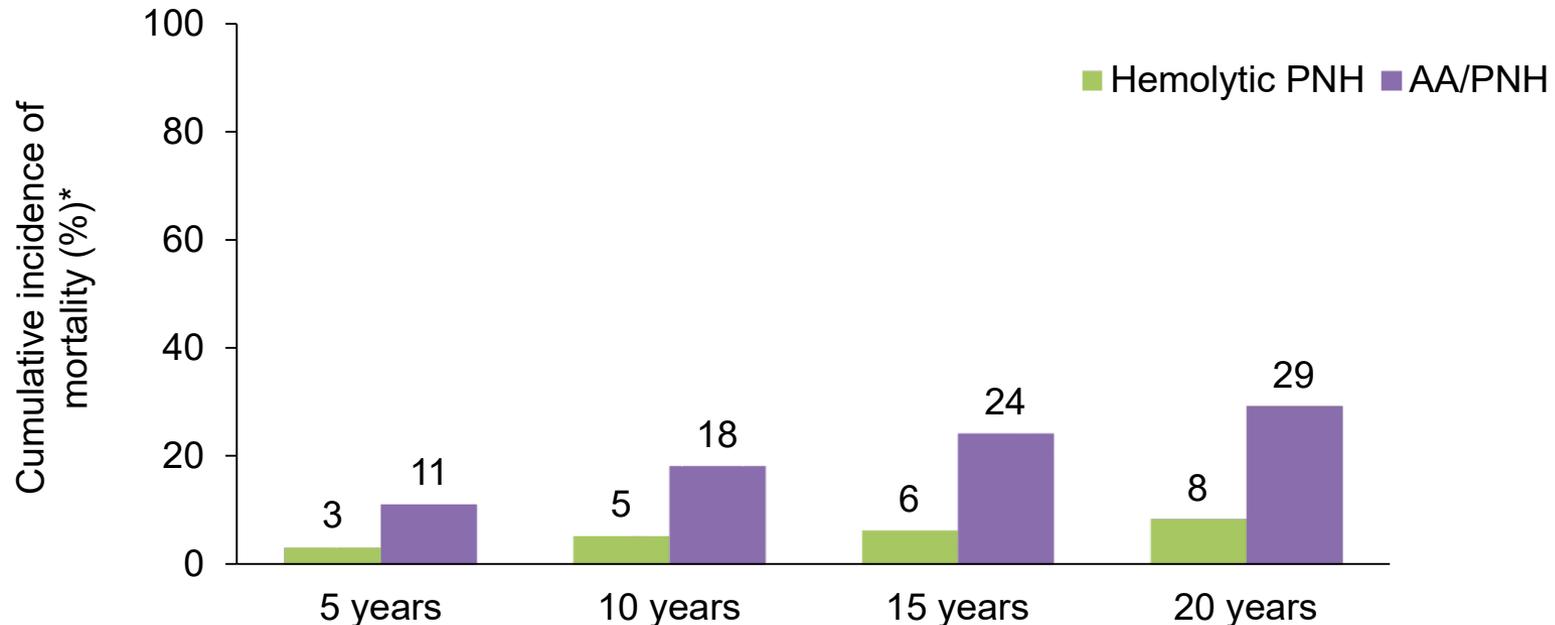
Table 2. Univariate and multivariate analysis of risk factors of mortality

Risk factors for mortality	Univariate analysis		Multivariate analysis	
	<i>P</i> value	Odds ratio (95% CI)	<i>P</i> value	Odds ratio (95% CI)
TE	< 0.001	8.42 (4.15-17.08)	< 0.001	7.110 (3.052-16.562)
IRF	0.001	3.41 (1.66-7.02)	0.029	2.953 (1.116-7.818)
PNH-cytopenia	0.023	2.17 (1.11-4.21)	0.020	2.547 (1.159- 5.597)
LDH $\geq 1.5 \times$ ULN	0.009	4.99 (1.15-21.70)	0.159	3.204 (0.633-16.230)
Abdominal pain	0.026	2.10 (1.08-4.08)	0.162	1.828 (0.785-4.256)
Dyspnea/Chest pain	0.026	2.09 (1.086-4.024)	0.855	1.077 (0.487-2.381)
Hemoglobinuria	0.636	0.86 (0.45-1.63)	0.073	0.449 (0.187-1.077)
Clone size	0.391	1.01 (0.99-1.02)	0.744	0.995 (0.967-1.024)

CI, confidence interval; IRF, impaired renal function; LDH, lactate dehydrogenase; TE, thromboembolism; ULN, upper limit of normal.

# Patients with AA/PNH have a higher mortality compared with hemolytic PNH patients<sup>1</sup>

- Study of patients enrolled in the International PNH Registry
  - Hemolytic PNH: 35 deaths among 698 patients (5%)
  - AA-PNH syndrome: 44 deaths among 374 patients (12%)



\*Cumulative incidence for mortality based on competing risks method (Fine and Gray<sup>2</sup>), where BMT is competing risk.

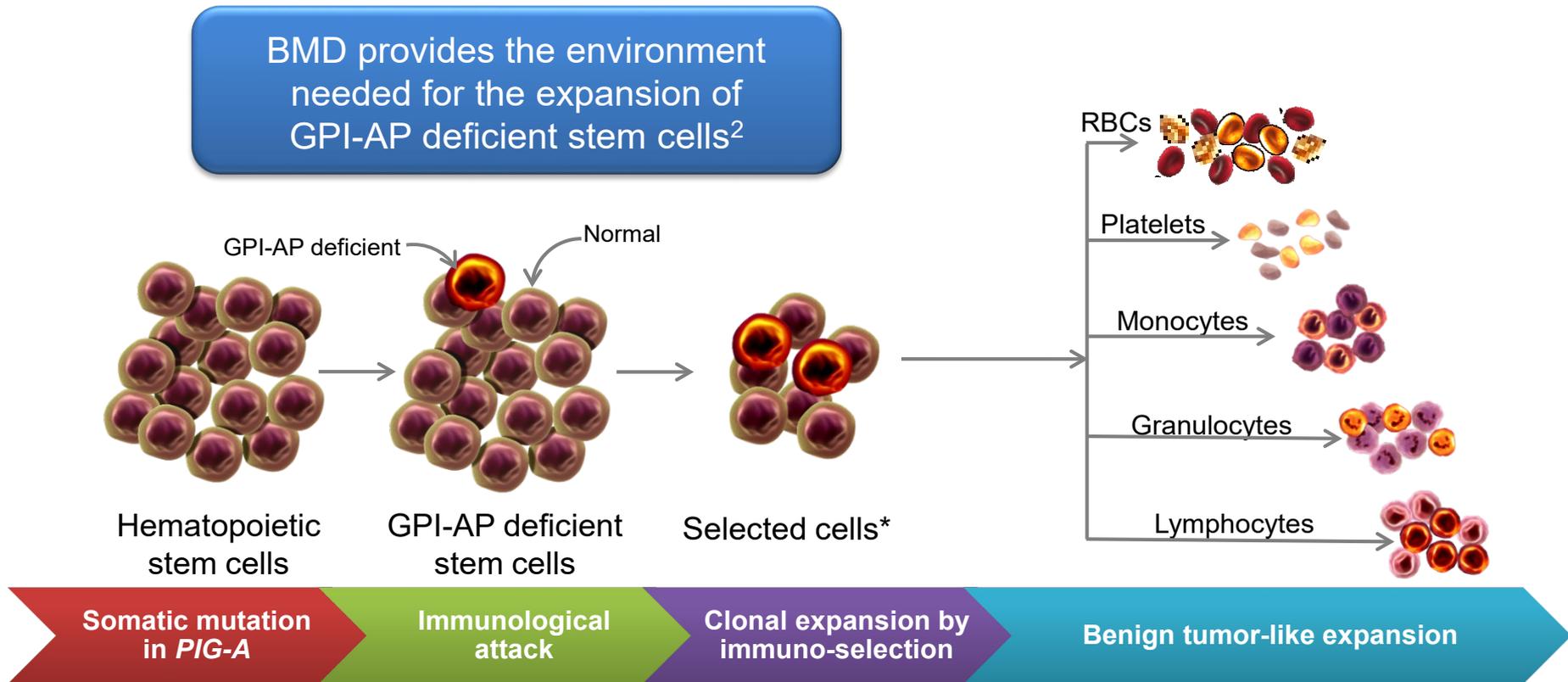
AA, aplastic anemia; BMT, bone marrow transplantation.

1. Socié G, et al. *Intern Med J* 2016;46(9):1044–1053

# **Mechanisms of PNH clonal expansion**

# PNH is a disease of the bone marrow

- GPI-AP deficient hematopoietic stem cells are selected in pathologic bone marrow, leading to populations of circulating blood cells that also lack GPI-AP



RBC, red blood cell.

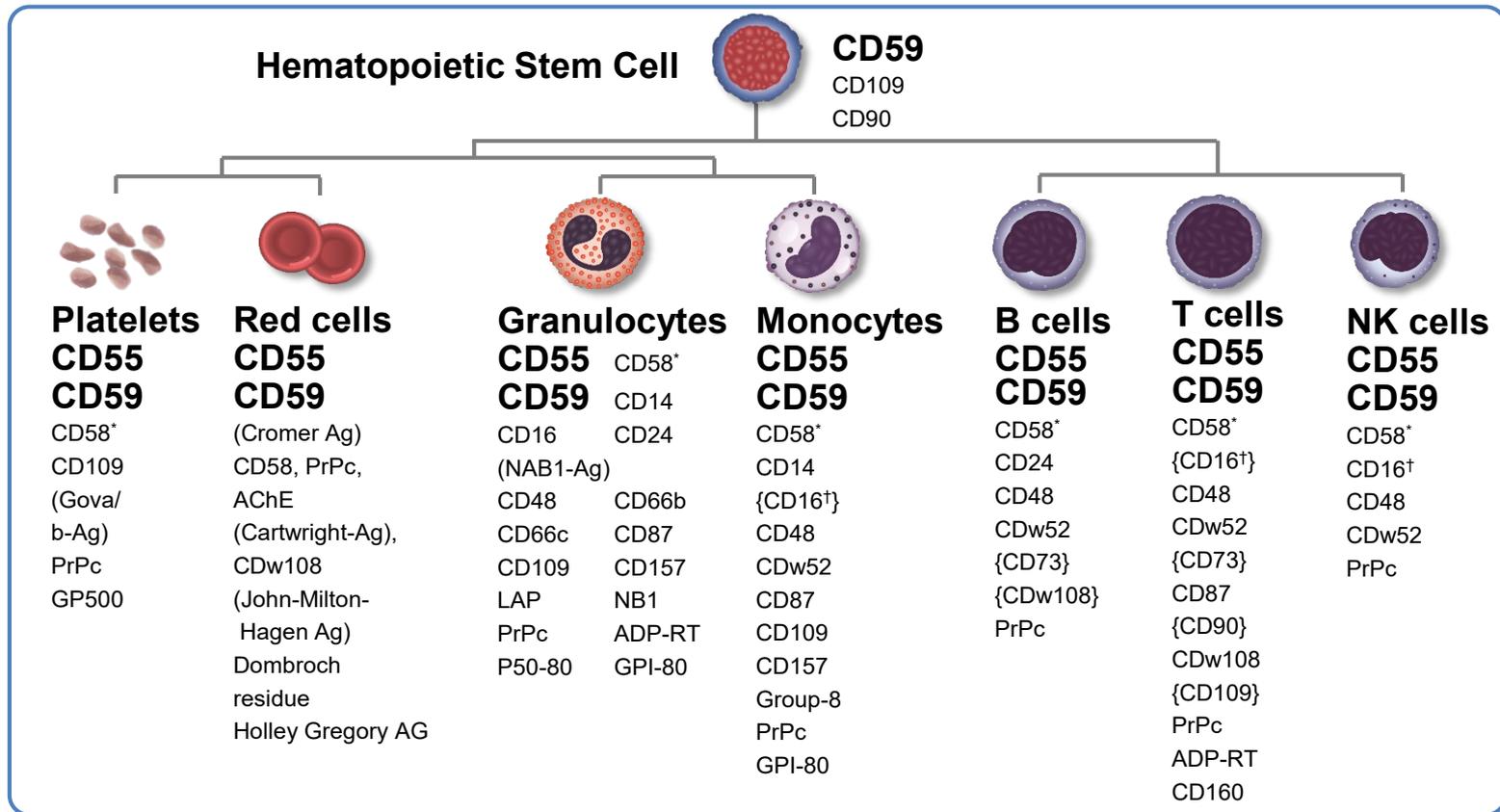
\*Clones presumed to have a conferred growth advantage, in addition to the *PIG-A* mutation, resulting in GPI-AP deficiency.

1. Inoue N, et al. *Int J Hematol* 2003;77(2):107–112; 2. Kelly R, et al. *Ther Clin Risk Manag* 2009;5:911–921.

# Blood cells in PNH are missing GPI-anchored proteins

- All blood cell lineages carry the same mutation, indicating that PIG-A mutations occur in hematopoietic progenitor cells

## GPI-anchored proteins expressed on normal cells of hematopoietic origin



ACHe, acetylcholinesterase; ADP-RT, mono ADP-ribosyl transferase; LAP, leukocyte alkaline phosphatase; NK, natural killer; PrPc, prion protein.

\*Both GPI-anchored and transmembrane form; <sup>†</sup>Transmembrane-anchored isoform; {blood group antigens}; (Expression upon activation or only in a subset of cells).

# Proposed mechanisms of clonal expansion of PNH cells

The mechanism of expansion of the GPI-AP deficient clone in PNH is not fully understood; the following hypotheses have been proposed:

## Selective advantage of PNH clones

**Hypothesis 1:** PNH clones expand by negative selection against normal HSCs<sup>1,2</sup>

The GPI anchor may be the target of immune attack in patients with PNH

**Hypothesis 2:** Mutations (other than that of *PIG-A*) provide PNH clones with a selective advantage over normal HSCs<sup>2,3</sup>

Research has demonstrated:

- Rearrangements involving the *HMGA2* gene in two patients with PNH<sup>3</sup>
- Mutations in other genes than that of *PIG-A* as initial clonal events in PNH<sup>4</sup>

HSCs, hematopoietic stem cells.

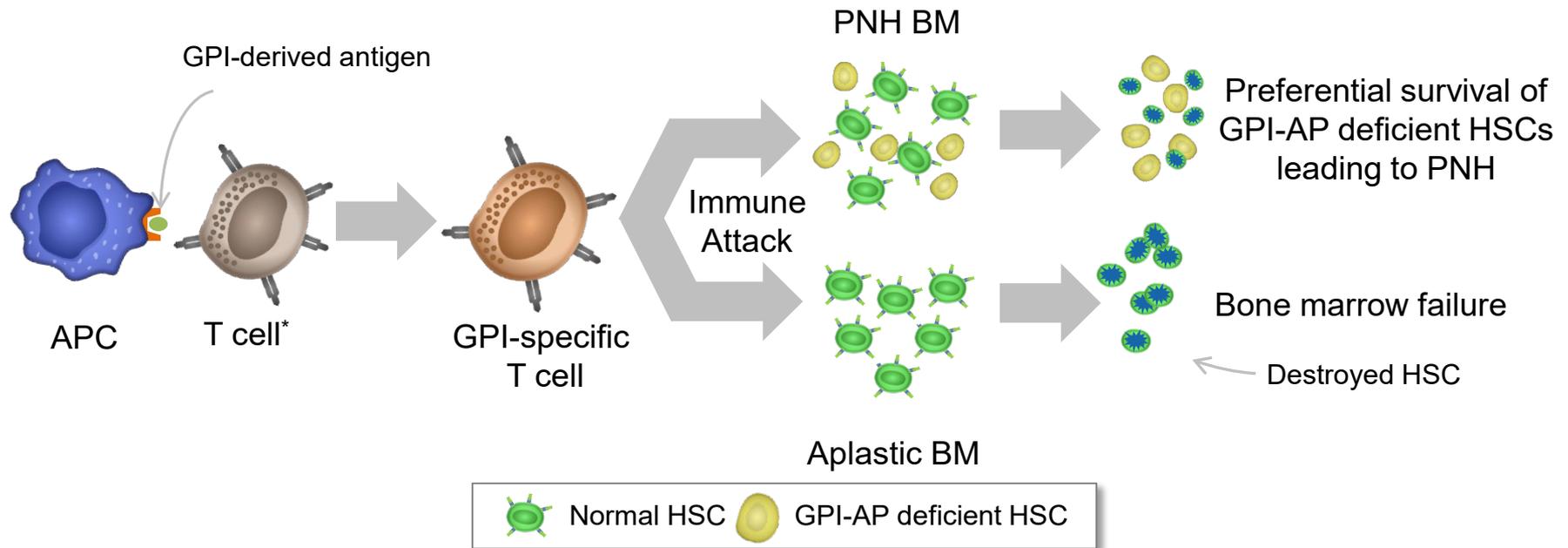
1. Gargiulo L, et al. *Blood* 2013;121(14):2753–276; 2. Hill A, et al. *Nat Rev Dis Primers* 2017;3:17028.

3. Inoue N, et al. *Blood* 2006;108:4232–4236; 4. Dingli D, et al. *PNAS* 2008;105:18496–18500.

# Hypothesis 1: The GPI anchor may be the target of immune attack in patients with PNH<sup>1</sup>

- GPI-AP deficient cells in PNH may preferentially survive due to a T-cell-mediated autoimmune process that targets GPI-positive but not GPI-negative HSCs
- Elevated numbers of GPI-reactive T cells\* have been observed in patients with PNH

## Potential mechanism of immune attack in PNH



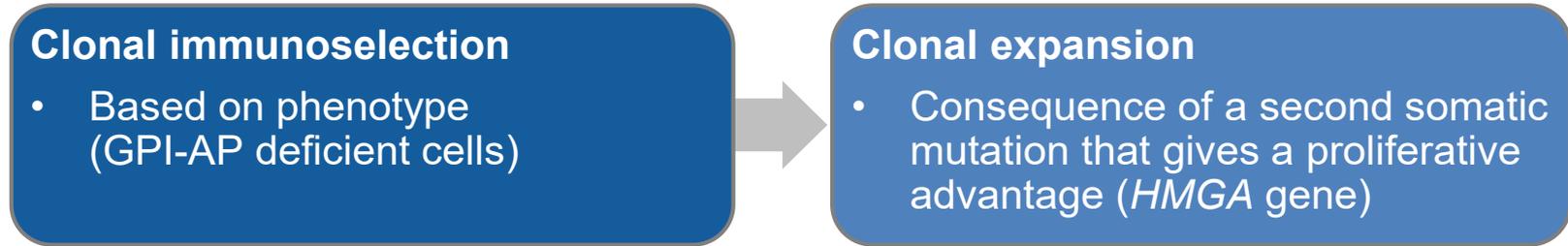
\*CD1d-restricted T cells expressing an invariant TCR $\alpha$  chain.

APC, antigen-presenting cells; BM, bone marrow; HSC, hematopoietic stem cell.

1. Gargiulo L, et al. *Blood* 2013;121(14):2753–2761.

# Hypothesis 2: A second mutation provides PNH clones with a proliferative advantage

## 2-step process:<sup>1</sup>



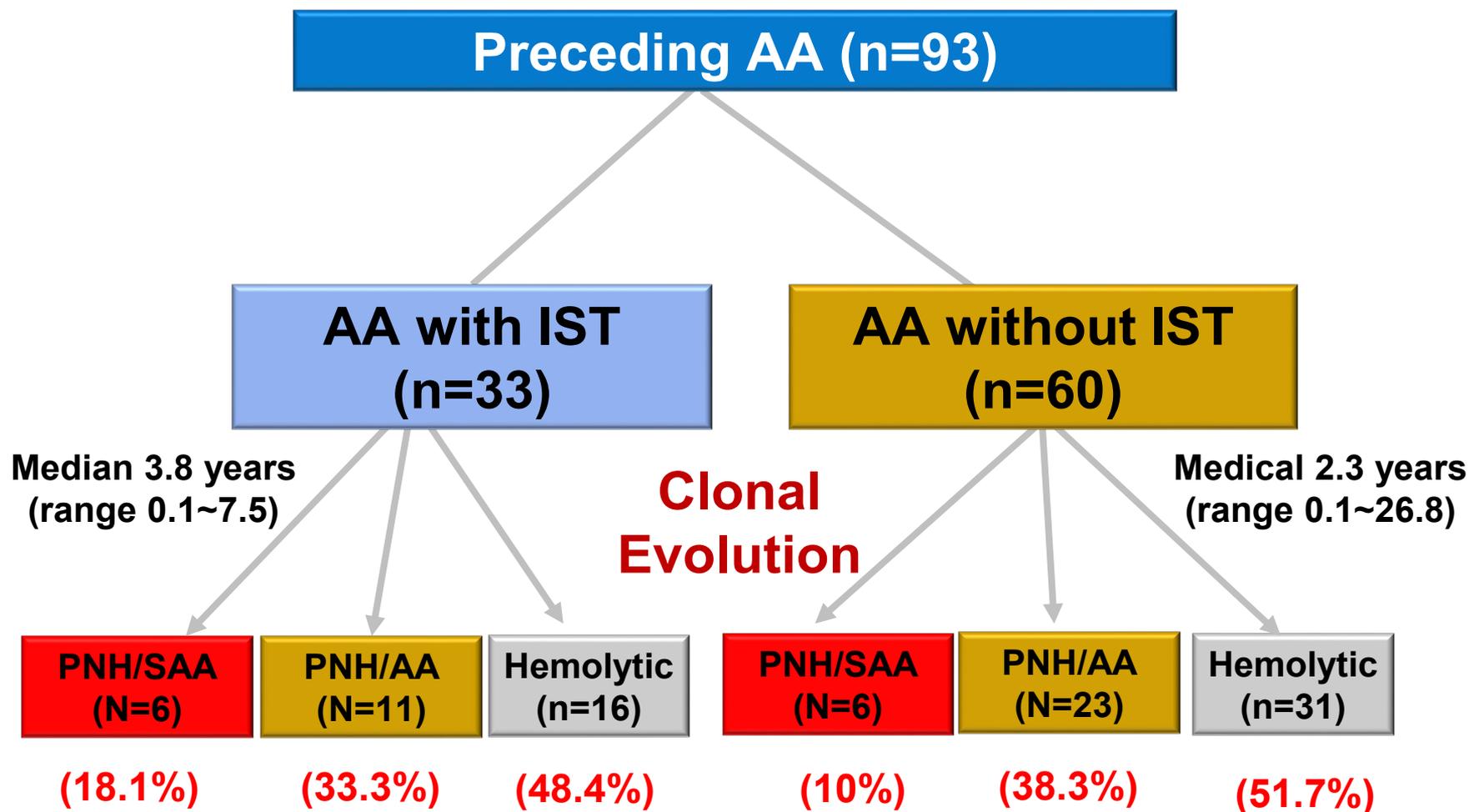
## *HMGA* gene:<sup>1</sup>

- Deregulated in a number of benign mesenchymal tumors
- 2 patients with PNH demonstrated GPI-AP deficient cells displaying aberrant expression of *HMGA2*

## Considerations:<sup>2</sup>

- A study did not reveal an increase in *HMGA2* mRNA, suggesting this is not a major mechanism to explain clonal expansion in PNH (N=42)
- It remains possible that another, presently unrecognized mutation or survival factor, is required for clonal expansion in PNH

# Clonal evolution from preceding AA to PNH according to the immunosuppressive therapy

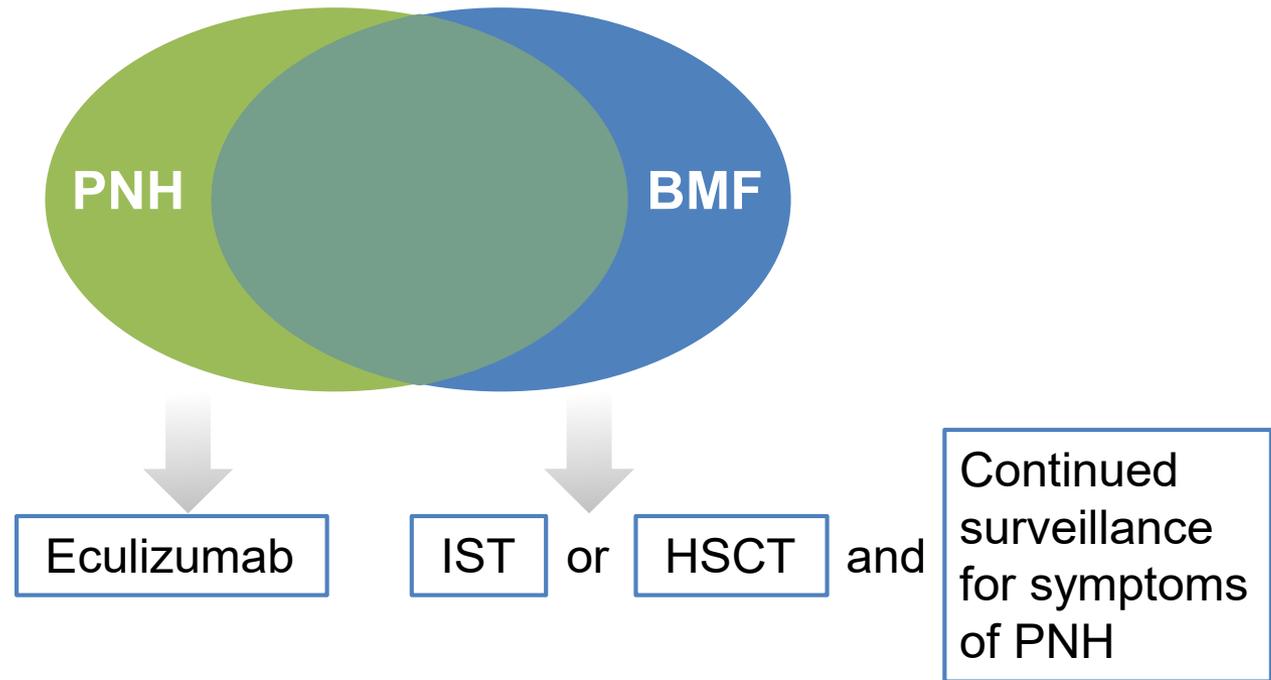


# **Management of PNH in the context of BMF**

# Patients with concurrent PNH and BMF: Two distinct diseases with two different treatments

- PNH and BMF are distinct diseases with significant morbidity and mortality<sup>1,2</sup>
- Each condition may progress independently and require a distinct clinical management and treatment approach<sup>3,4</sup>

## Treatment algorithm<sup>3-5</sup>



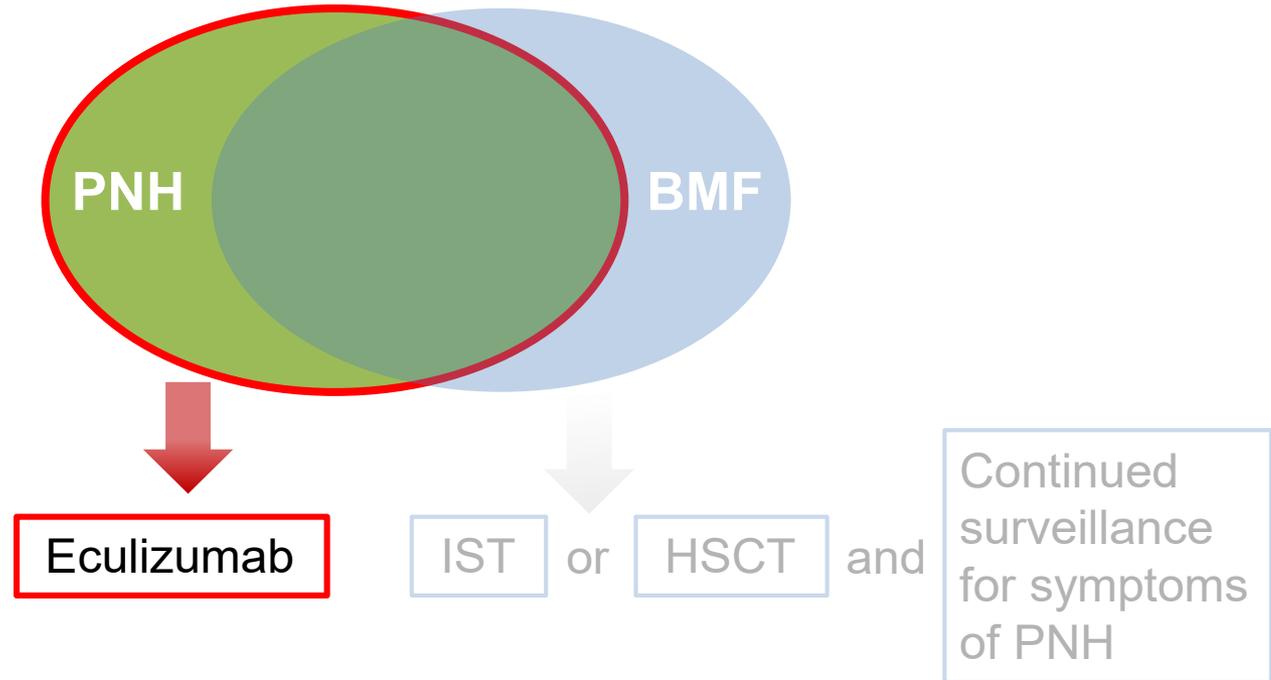
HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy.

1. Gerds AT, et al. *Curr Hematol Malign Rep* 2012;7(4):292–299; 2. Rachidi S, et al. *Eur J Intern Med* 2010;21(4):260–267; 3. Parker CJ. *Hematology Am Soc Hematol Educ Program* 2011;2011:21–29; 4. Luzzatto L, et al. *Br J Haematol* 2011;153(6):709–720; 5. Peffault de Latour R, et al. *Rev Med Interne* 2010;31(3):200–207.

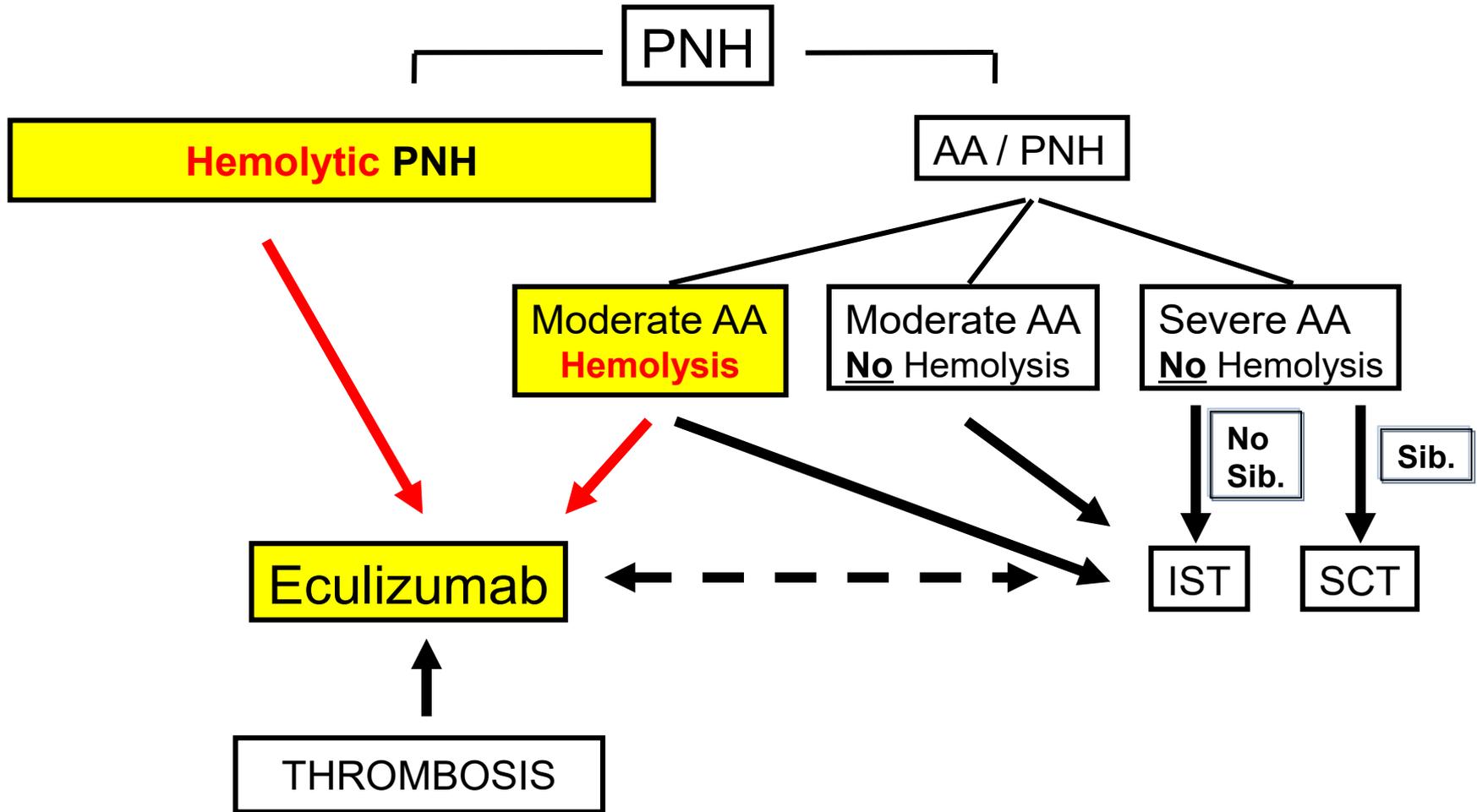
# Management of patients with PNH

- In patients with PNH and associated symptoms (eg, fatigue, thromboses), treatment should focus on controlling hemolysis<sup>1,2</sup>

## Treatment algorithm<sup>3,4</sup>



# Management of patients with PNH



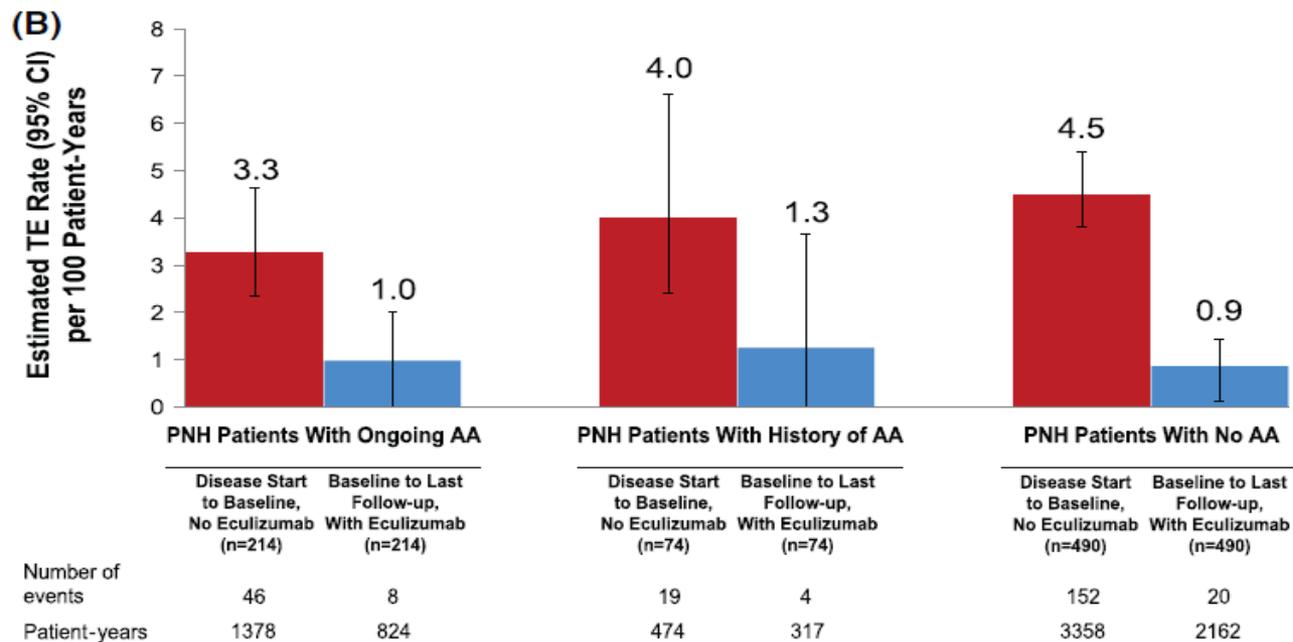
AA, aplastic anemia; ATG, antithymocyte globulin; HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy; MRD, matched related donor; PNH, paroxysmal nocturnal hemoglobinuria.

a. Indications for treatment are severe AA (2 in 3 blood counts, including absolute neutrophil count  $<500/\mu\text{L}$ , absolute reticulocyte count  $<60,000/\mu\text{L}$ , and platelet count  $<20,000/\mu\text{L}$ ) or in cases of moderate AA, where the patient needs transfusion support or has infectious complications because of a low neutrophil count. b. The presence of a PNH clone in this setting highlights the underlying autoimmune-mediated process in favor of an idiopathic AA and not an inherited disorder, and should also make physicians think about thrombosis upon suggestive clinical signs, because PNH is a known predisposition to thrombosis complications. Clearly, complement inhibitory therapy has no effect on the BM-failure component of the disease and should not be used in this situation. c. The level of hemolysis is indicated by lactate dehydrogenase (LDH). Significant hemolysis is considered  $>2$  times LDH. d. Exceptional cases of AA-PNH syndrome with significant intravascular hemolysis may require HSCT or IST treatment of BM failure and eculizumab for the hemolysis, and should be discussed on a case-by-case basis.

1. Peffault de Latour R. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):90-98

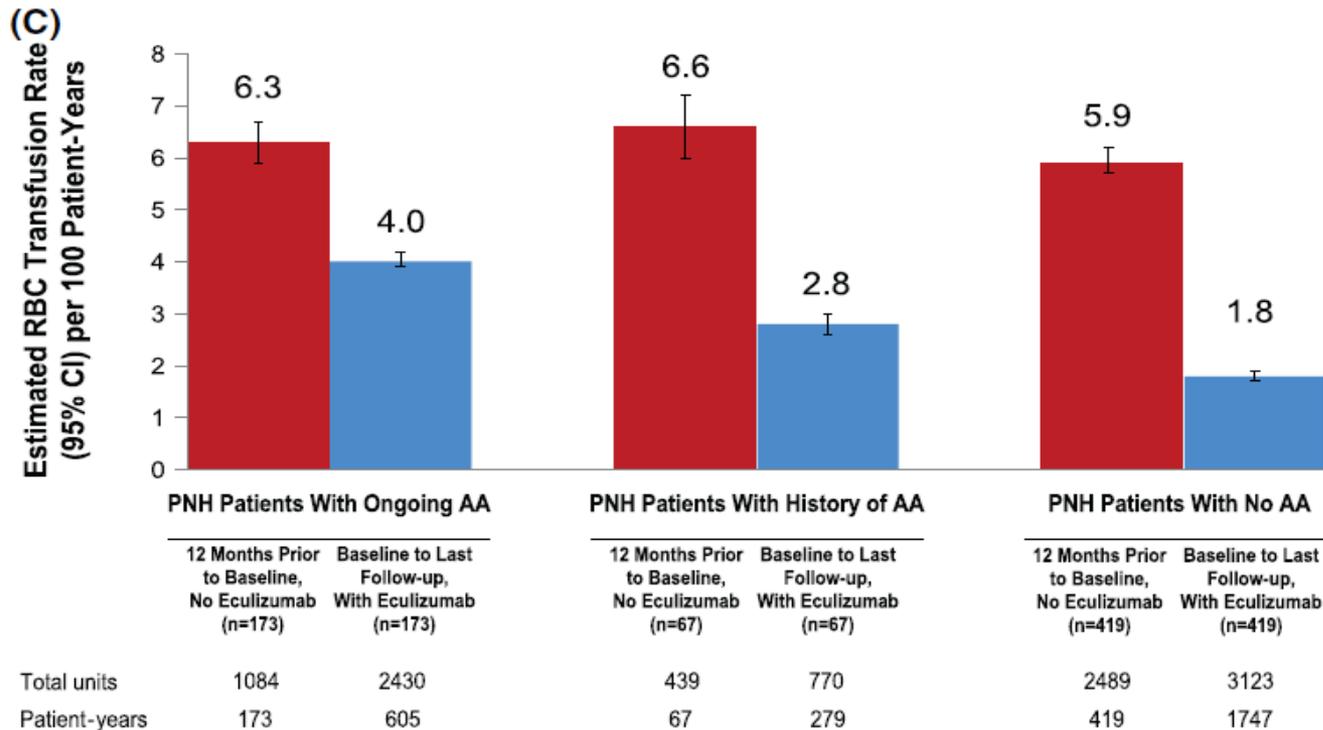
# Effectiveness of Eculizumab in patients with PNH with or without aplastic anemia: International PNH Registry

- The rates of TEs decreased from  $\geq 3.3$  events per 100 patient-years prior to baseline to  $\leq 1.3$  events per 100 patient-years after baseline in all 3 groups.
- Treatment with Eculizumab was associated with significant improvement in rates of TEs, regardless of AA status



# Effectiveness of Eculizumab in patients with PNH with or without aplastic anemia: International PNH Registry

- Treatment with Eculizumab was associated with significant improvement in rates of RBC transfusions, regardless of AA status

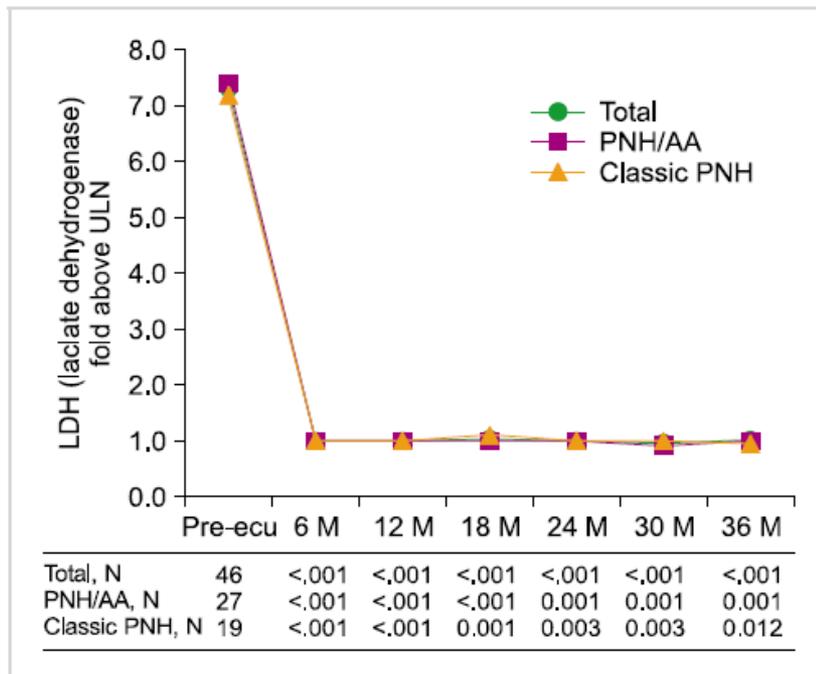


# Efficacy of eculizumab in PNH patients with or without aplastic anemia

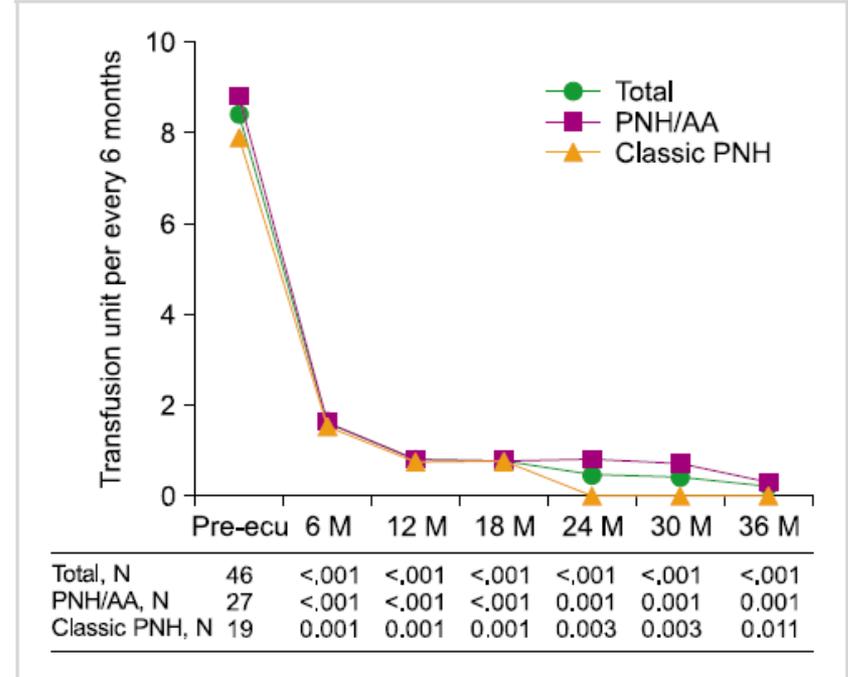
## : prospective study of a Korean PNH cohort

- Treatment with eculizumab induced rapid and consistent inhibition of hemolysis to near normal levels in all patients after 36 months of follow-up
- The mean number of packed RBC units transfused was significantly reduced regardless of AA. (8.5 units → 1.6 units)

Reduction in hemolysis after Eculizumab

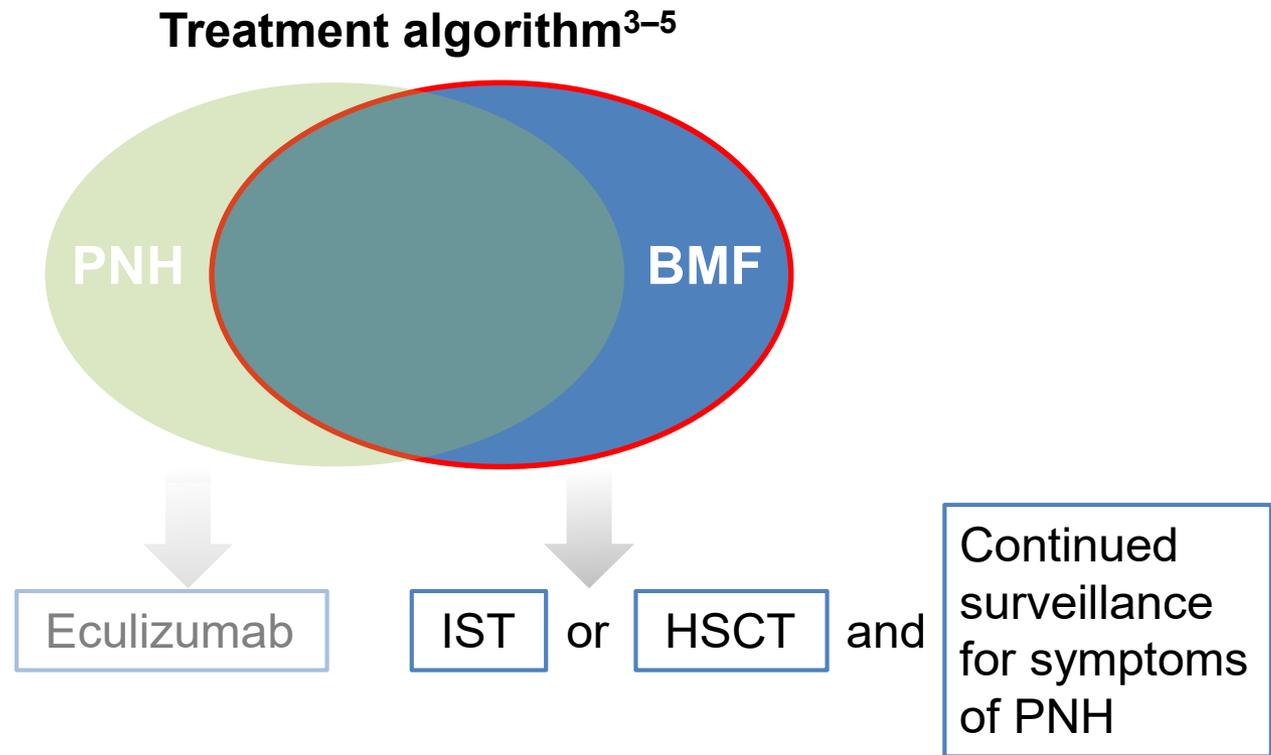


Reduction of transfusion requirement after Eculizumab



# Management of patients with PNH and BMF without hemolysis

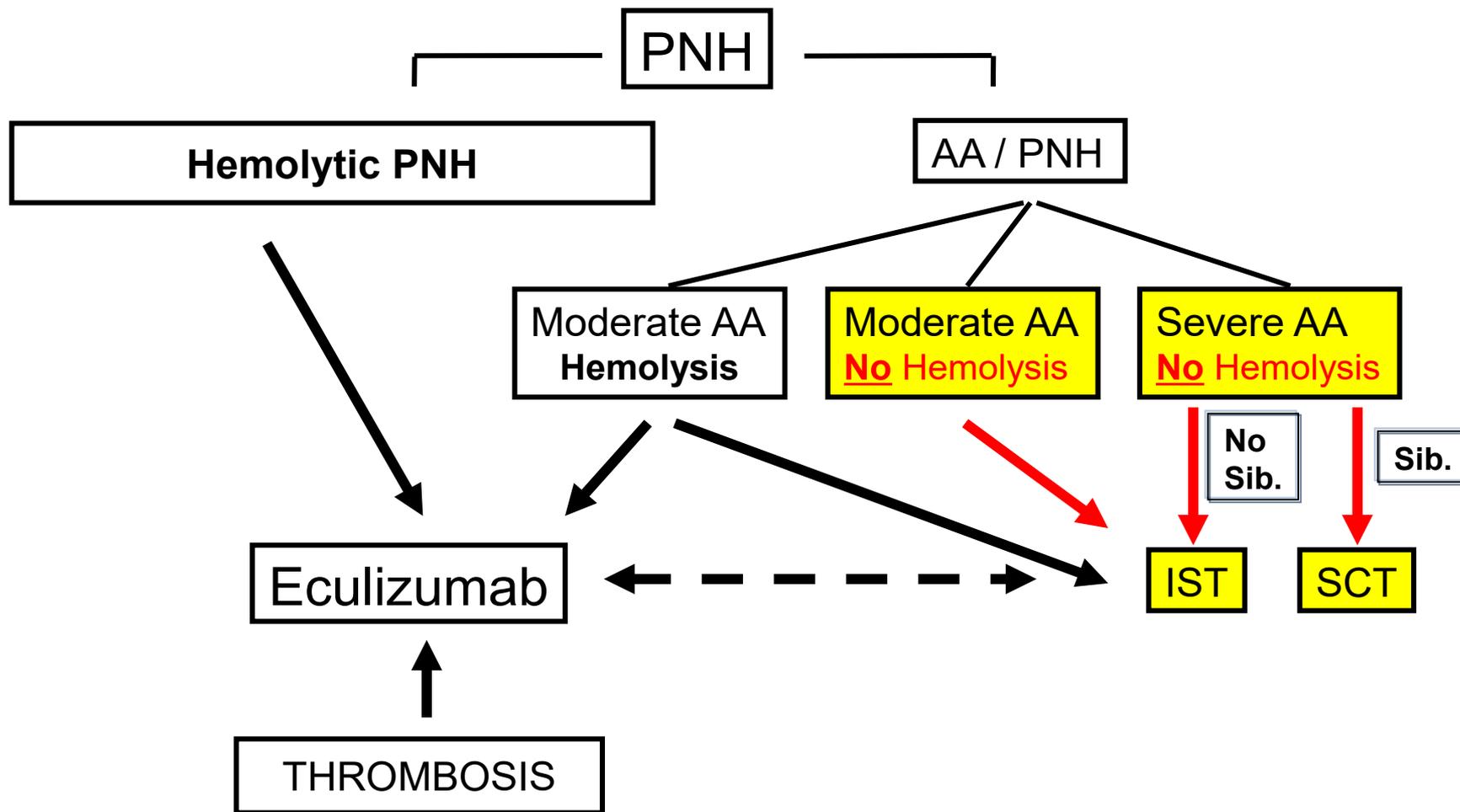
- In patients who are asymptomatic for PNH, interventions should focus on underlying bone marrow dysfunction<sup>1,2</sup>



HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy.

1. Brodsky RA. *Blood* 2009;113(26):6522–6527; 2. Parker CJ. *Hematology Am Soc Hematol Educ Program* 2016;2016(1):208–216; 3. Parker CJ. *Hematology Am Soc Hematol Educ Program* 2011;2011:21–29; 4. Peffault de Latour R, et al. *Rev Med Interne* 2010;31(3):200–207; 5. Luzzatto L, et al. *Br J Haematol* 2011;153(6):709–720.

# Management of patients with PNH and BMF without hemolysis



AA, aplastic anemia; ATG, antithymocyte globulin; HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy; MRD, matched related donor; PNH, paroxysmal nocturnal hemoglobinuria.

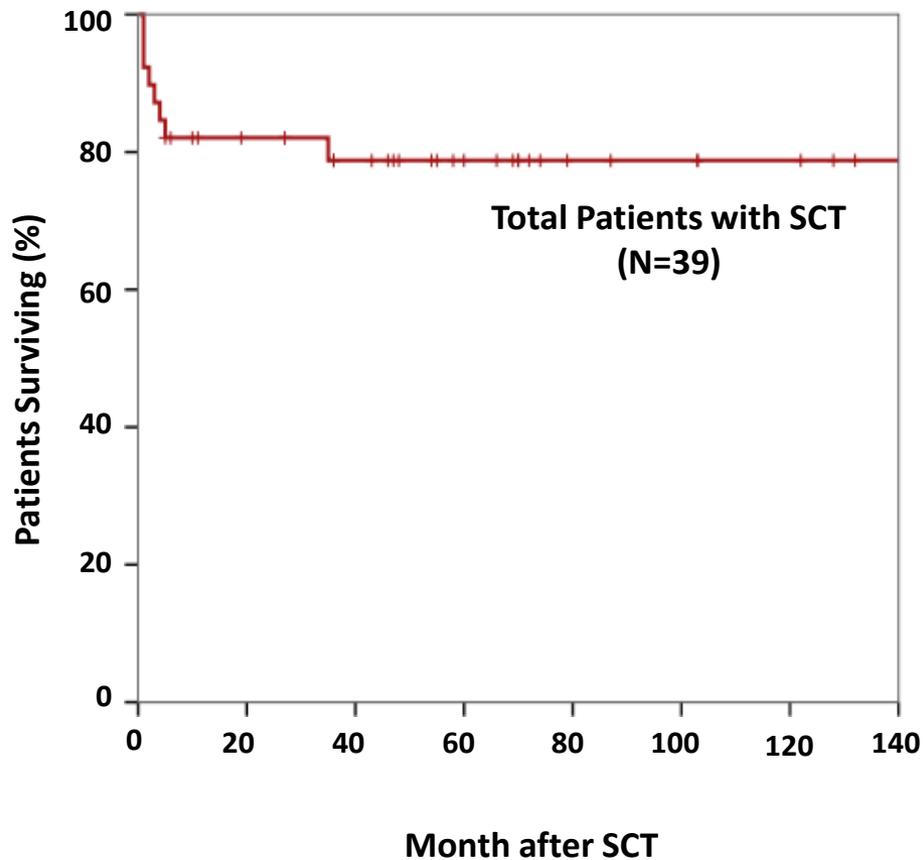
a. Indications for treatment are severe AA (2 in 3 blood counts, including absolute neutrophil count  $<500/\mu\text{L}$ , absolute reticulocyte count  $<60,000/\mu\text{L}$ , and platelet count  $<20,000/\mu\text{L}$ ) or in cases of moderate AA, where the patient needs transfusion support or has infectious complications because of a low neutrophil count. b. The presence of a PNH clone in this setting highlights the underlying autoimmune-mediated process in favor of an idiopathic AA and not an inherited disorder, and should also make physicians think about thrombosis upon suggestive clinical signs, because PNH is a known predisposition to thrombosis complications. Clearly, complement inhibitory therapy has no effect on the BM-failure component of the disease and should not be used in this situation. c. The level of hemolysis is indicated by lactate dehydrogenase (LDH). Significant hemolysis is considered  $>2$  times LDH. d. Exceptional cases of AA-PNH syndrome with significant intravascular hemolysis may require HSCT or IST treatment of BM failure and eculizumab for the hemolysis, and should be discussed on a case-by-case basis.

1. Peffault de Latour R. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):90-98

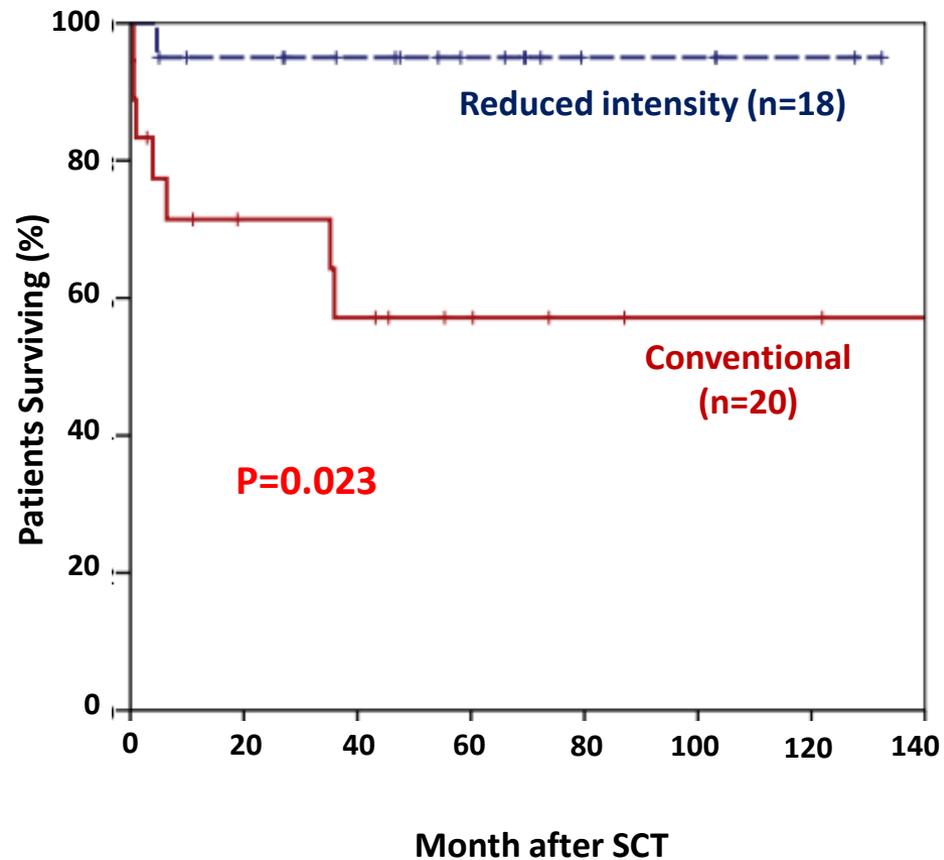
# Patients Survival with SCT:

Patients with RIST had a better survival than those with conventional conditioning.

## Overall Survival



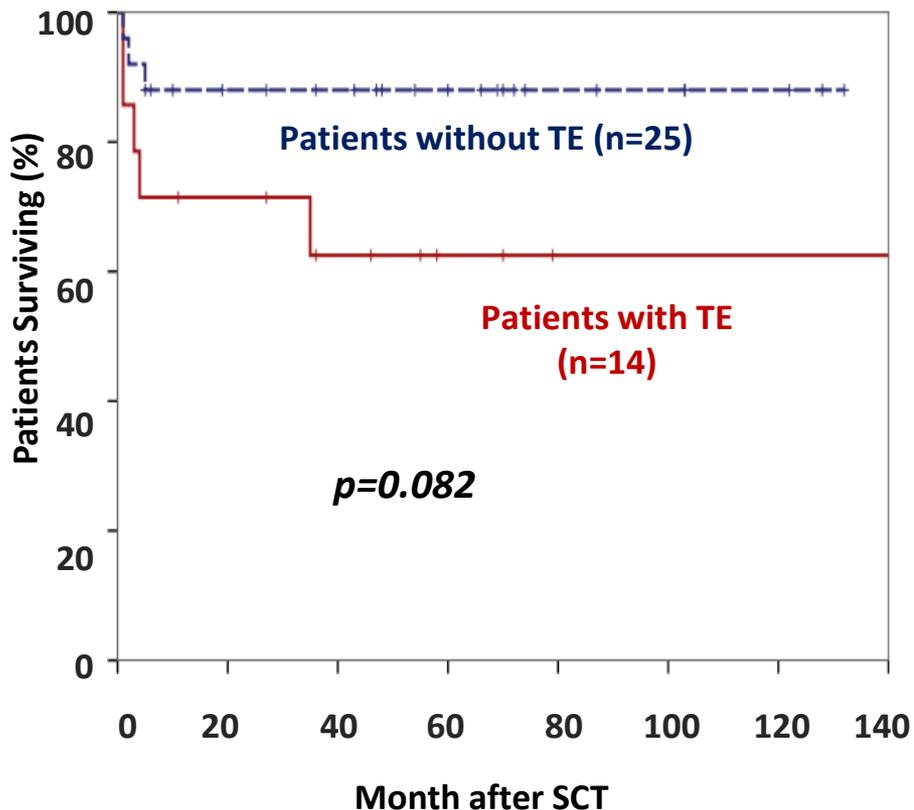
## Survival with Conditioning Regimen



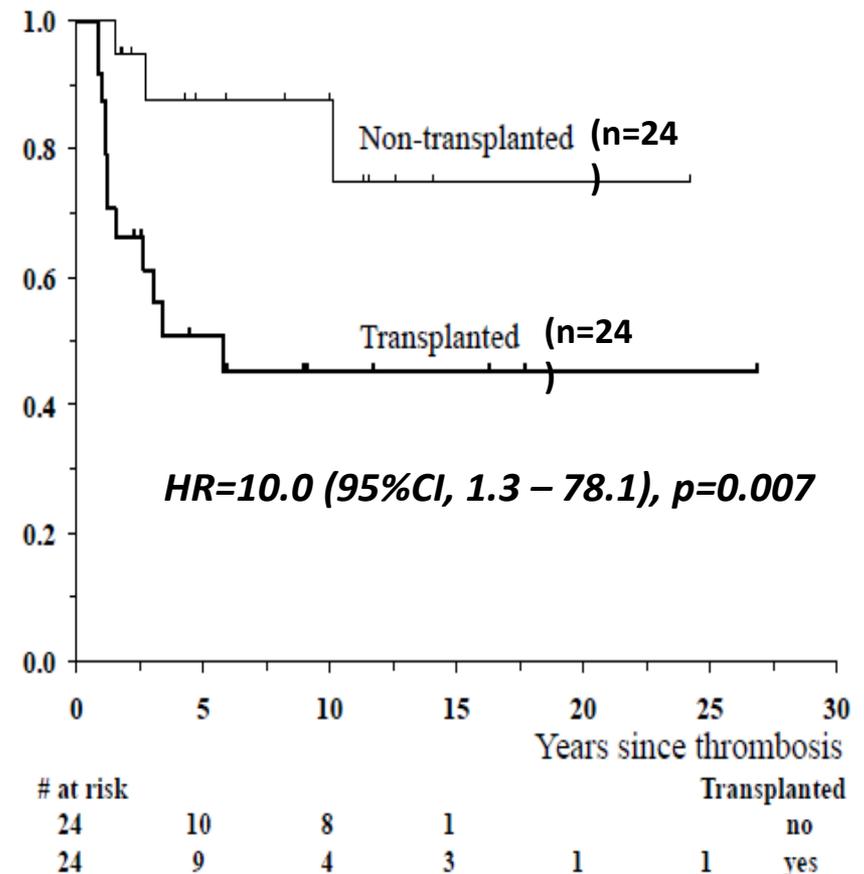
# Survival with evidence of TE with SCT:

## Previous history of thrombosis confers worse outcomes of survival in patients undergoing all-SCT for PNH.

Survival in SCT patients with TE vs. Non-TE<sup>1</sup>



Survival in TE patients with transplanted vs. non-transplanted patients<sup>2</sup>

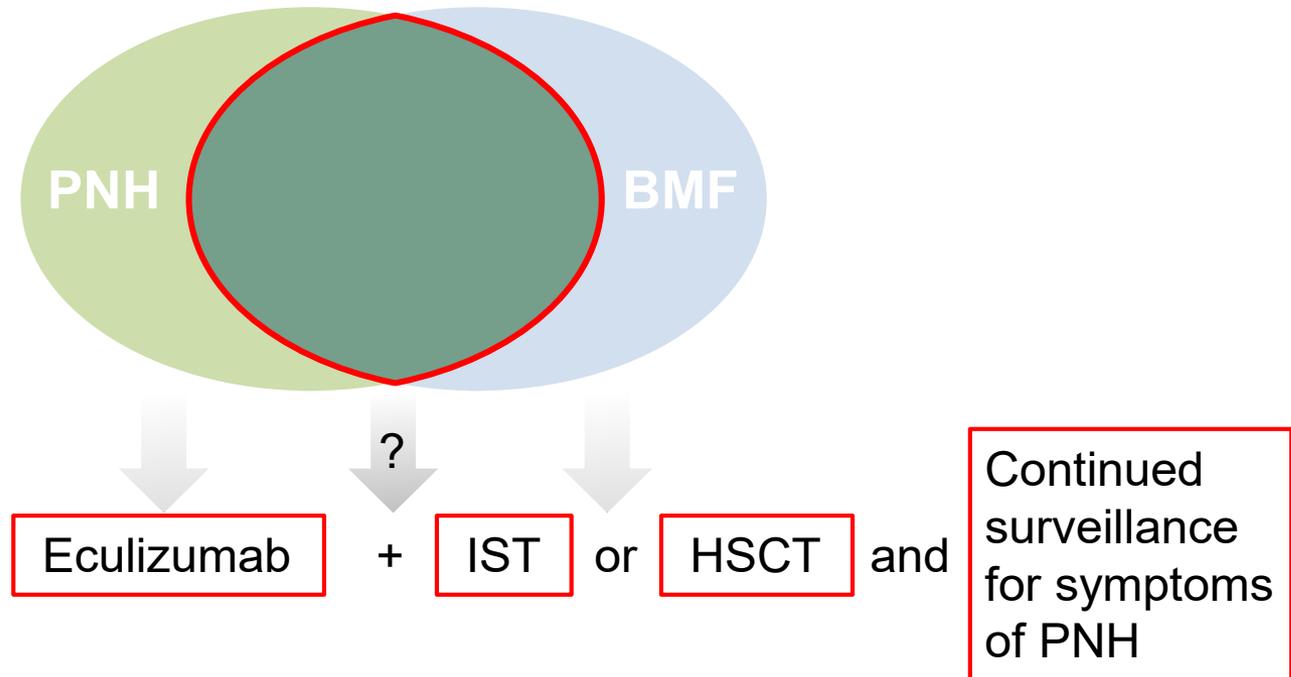


1. Jang JH et al, APBMT 2012 2. De Latour et al. Haematologica, Epub. 2012

# Management of patients with concurrent active PNH and BMF

- Some patients may present with elements of both PNH and BMF, with the clinical picture evolving over time<sup>1</sup>
- Targeted treatments should address both hemolysis and BMF<sup>1,2</sup>

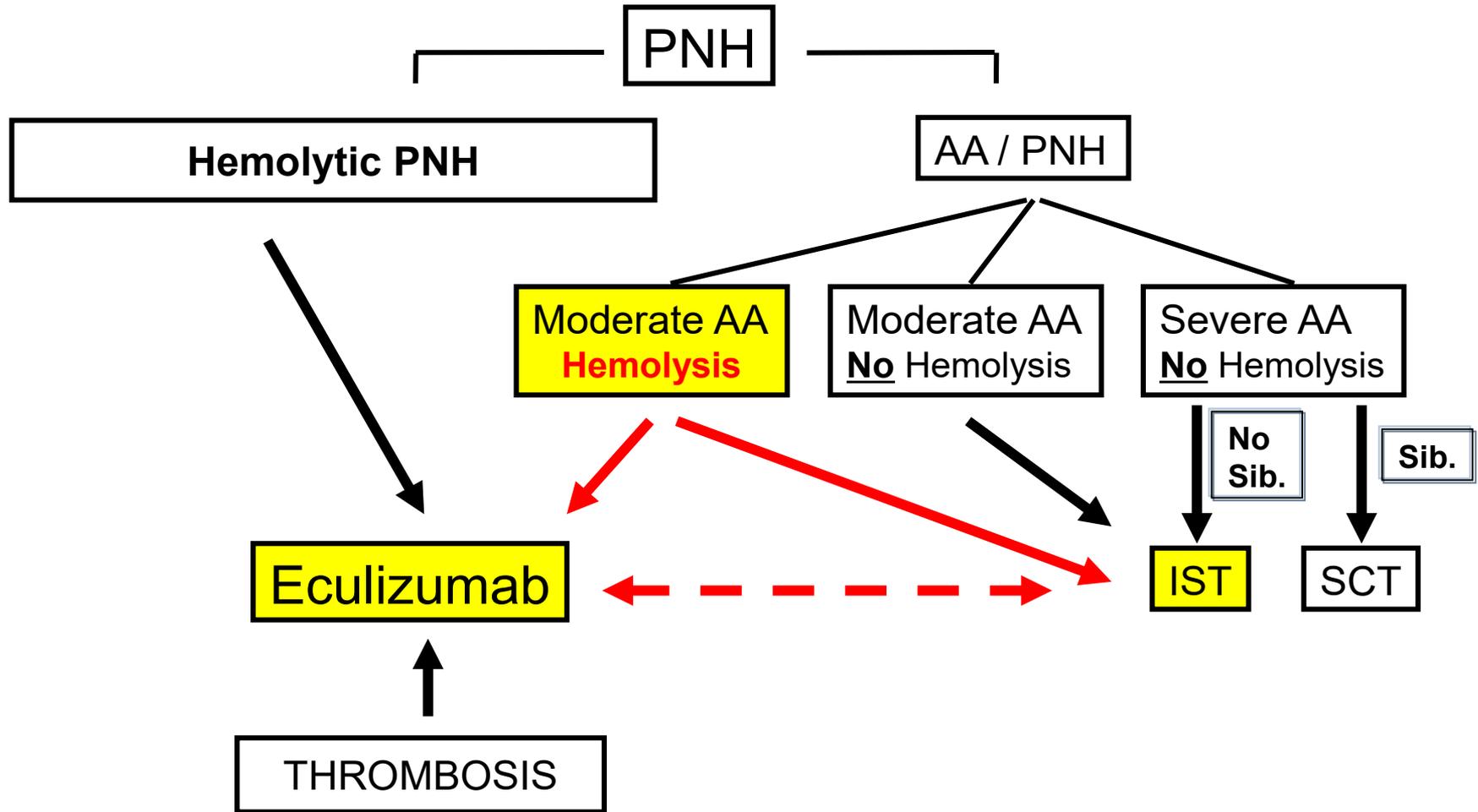
## Treatment algorithm<sup>1,3</sup>



HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy.

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

# Management of patients with concurrent active PNH and BMF



AA, aplastic anemia; ATG, antithymocyte globulin; HSCT, hematopoietic stem cell transplantation; IST, immunosuppressive therapy; MRD, matched related donor; PNH, paroxysmal nocturnal hemoglobinuria.

a. Indications for treatment are severe AA (2 in 3 blood counts, including absolute neutrophil count  $<500/\mu\text{L}$ , absolute reticulocyte count  $<60,000/\mu\text{L}$ , and platelet count  $<20,000/\mu\text{L}$ ) or in cases of moderate AA, where the patient needs transfusion support or has infectious complications because of a low neutrophil count. b. The presence of a PNH clone in this setting highlights the underlying autoimmune-mediated process in favor of an idiopathic AA and not an inherited disorder, and should also make physicians think about thrombosis upon suggestive clinical signs, because PNH is a known predisposition to thrombosis complications. Clearly, complement inhibitory therapy has no effect on the BM-failure component of the disease and should not be used in this situation. c. The level of hemolysis is indicated by lactate dehydrogenase (LDH). Significant hemolysis is considered  $>2$  times LDH. d. Exceptional cases of AA-PNH syndrome with significant intravascular hemolysis may require HSCT or IST treatment of BM failure and eculizumab for the hemolysis, and should be discussed on a case-by-case basis.

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# Patients with concurrent PNH and AA or MDS require multiple therapeutic approaches

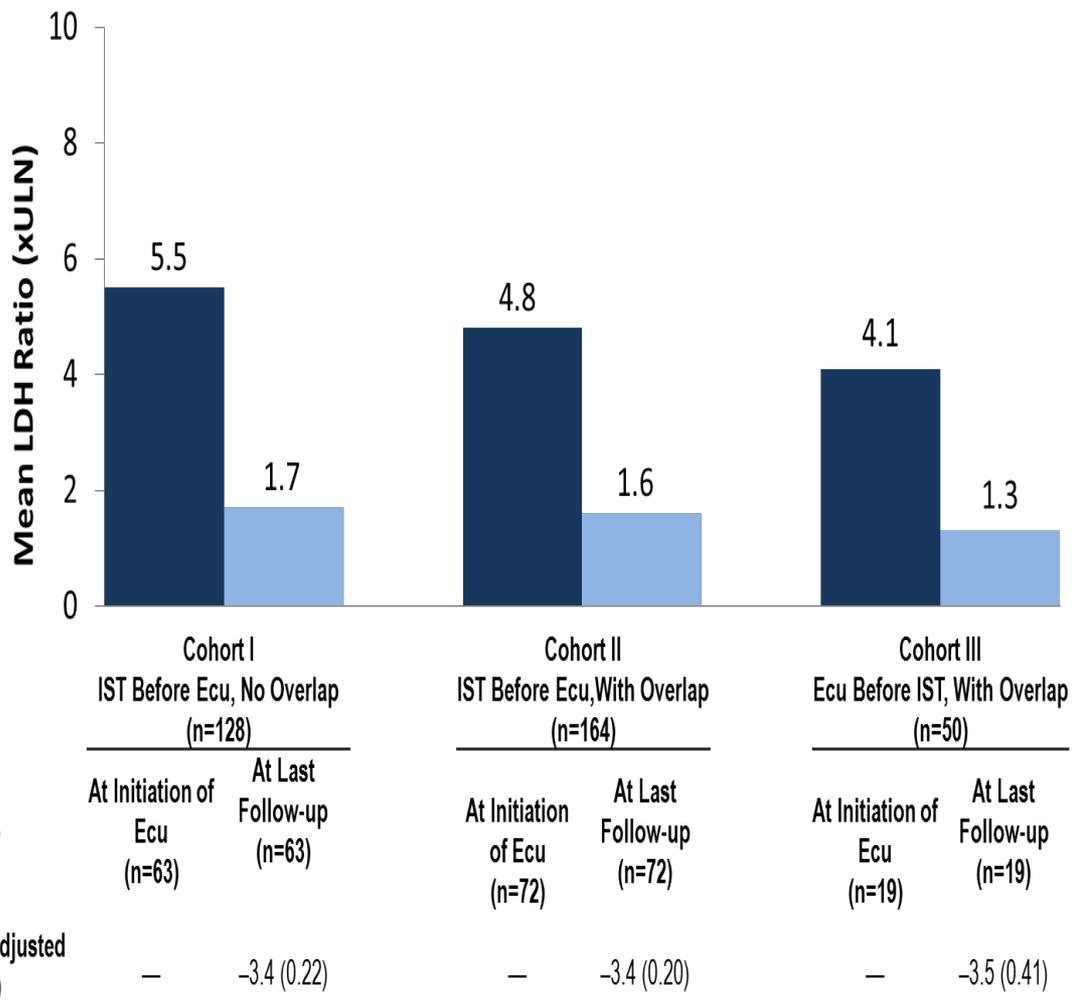
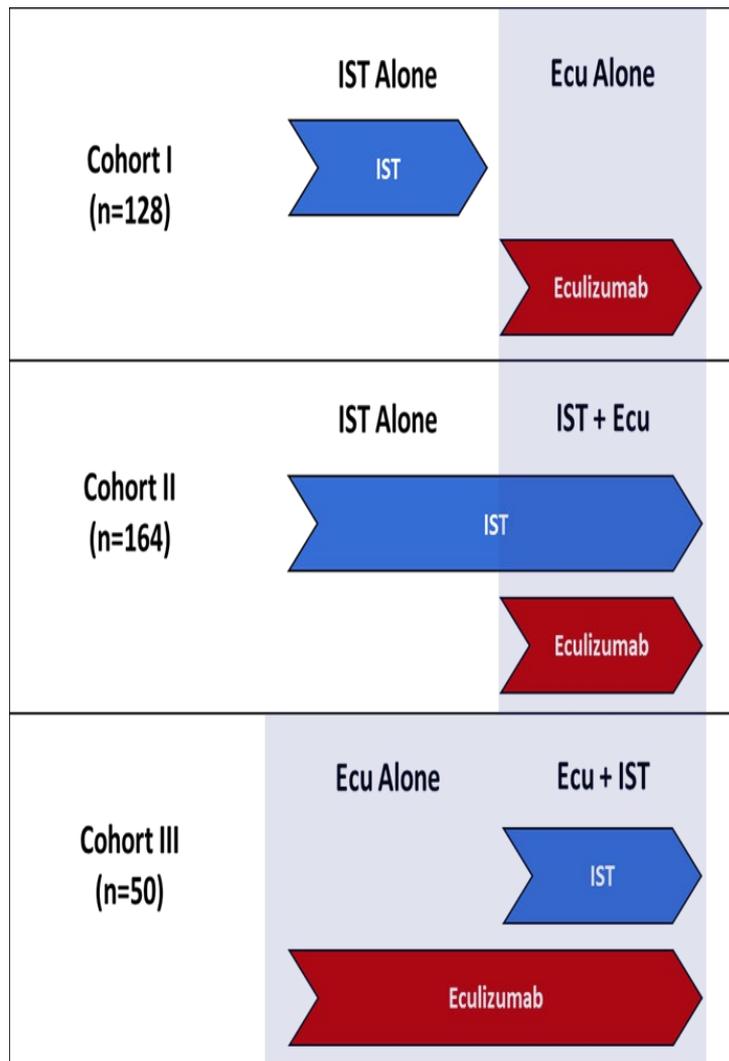
## If treated with immunosuppressive therapy alone, patients with concomitant BMF and PNH can continue to experience hemolysis<sup>1</sup>

- PNH results in RBC hemolysis, while AA / MDS impedes the production of all blood cells including RBCs<sup>2,3</sup>
- In a retrospective analysis of 207 AA patients with a detectable PNH clone and treated with IST alone:<sup>4</sup>
  - **14.5%** showed an increase in clone size
  - **3%** showed evidence of hemolysis and thrombosis

## PNH and AA can be treated concomitantly<sup>1</sup>

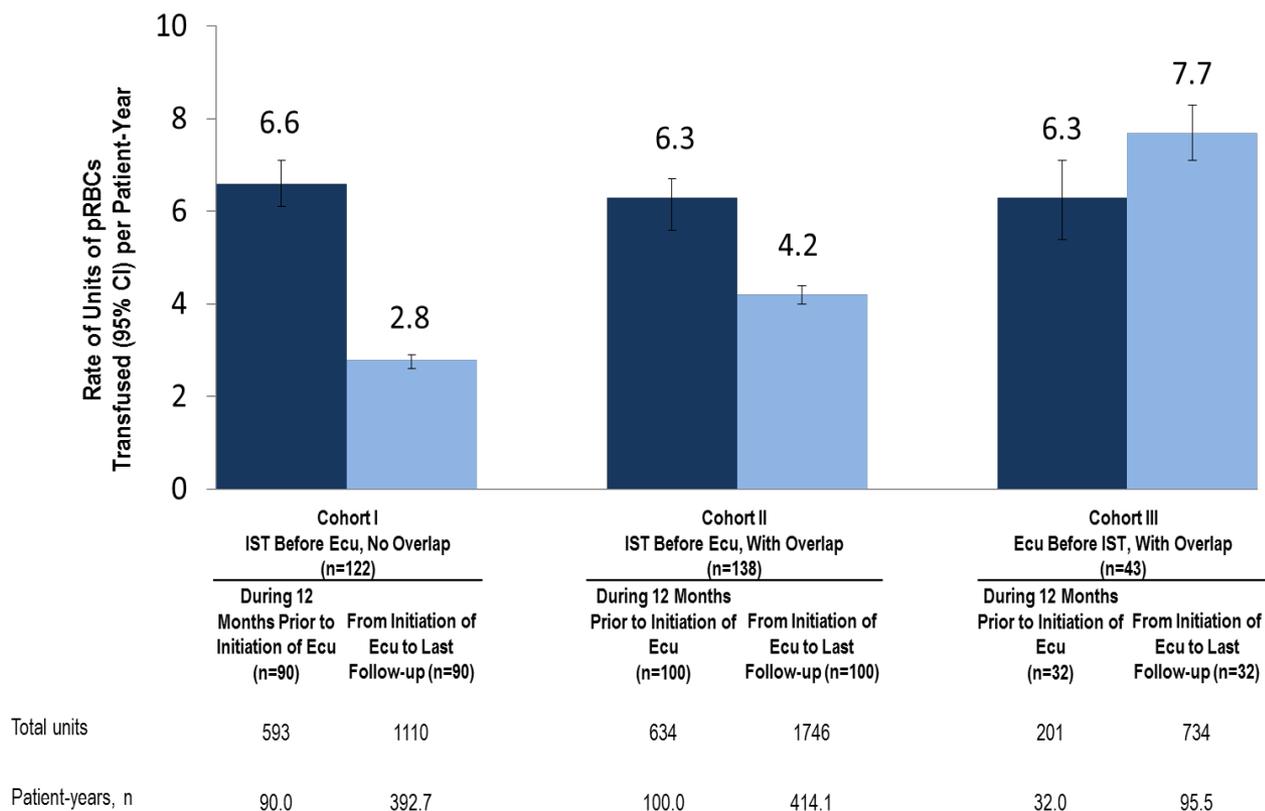
- Eculizumab is an effective treatment for PNH, while immune modulating agents can be used to treat AA and MDS<sup>3,5-7</sup>

# Effectiveness of Eculizumab in PNH patients receiving concomitant immunosuppressive therapy : International PNH Registry



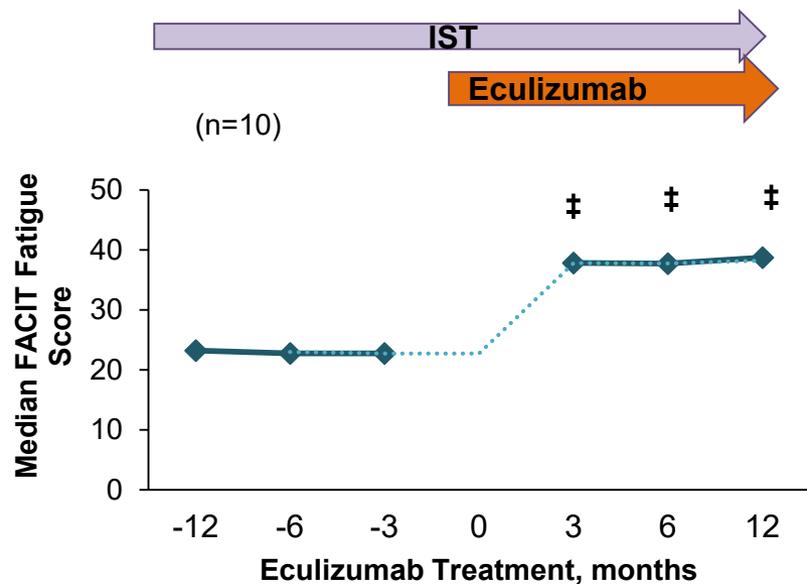
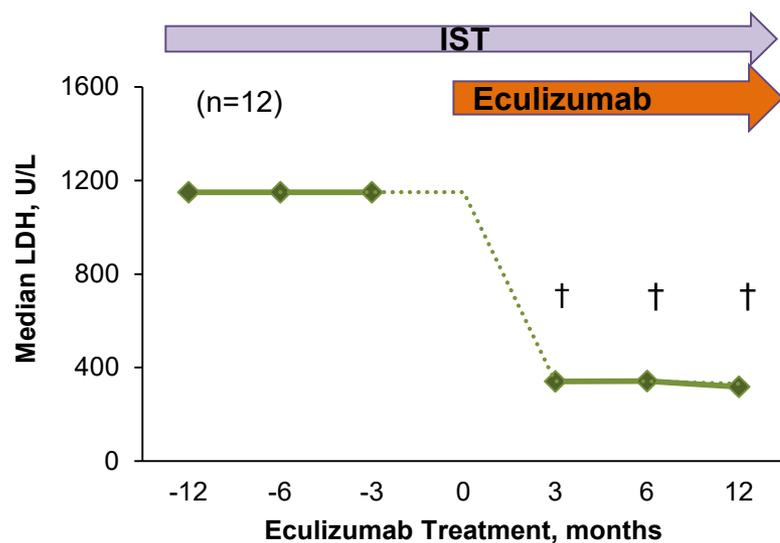
# Effectiveness of Eculizumab in PNH patients receiving concomitant immunosuppressive therapy : International PNH Registry

- Differences in RBC transfusions were observed according to the cohorts, possibly reflecting underlying AA.



# Concomitant Use of Eculizumab and IST

- IST alone is insufficient to prevent PNH-related haemolysis and QoL issues
- Eculizumab in addition to IST results in significant and sustained
  - Reduction in hemolysis
  - Improvement in FACIT fatigue scores\*



FACIT, Functional Assessment of Chronic Illness Therapy; LDH, lactate dehydrogenase.

This study is a post hoc review of the PNH clinical trial database (n=195) to evaluate the efficacy and safety of eculizumab in a population of patients (n=17) receiving concomitant IST. Group 1 included patients on eculizumab during ongoing IST therapy. Group 2 included patients on IST therapy during eculizumab treatment.

\*A change in FACIT-fatigue of  $\geq 3$  is considered clinically meaningful.

† $P < 0.01$  when prior and post months were compared.

‡ $P < 0.05$  when prior and post months were compared.

Schrezenmeier H, et al. *Blood*. 2009;114(22):Abstract 3012.

# Post-allogeneic Hematopoietic Stem Cell Transplantation Eculizumab as prophylaxis against hemolysis and thrombosis for patients with PNH

- 8 patients who underwent alloHCT for PNH who had received at least 1 dose of eculizumab within 30 days of transplantation
  - 6 patients engrafted well: no hemolysis, thrombotic events
  - 1 patient with underlying aplastic anemia failed to engraft.
  - 1 patient experienced steroid-refractory grade IV acute GVHD and died of a fungal infection.
  - No infections associated with encapsulated bacteria occurred in any of 8 patients

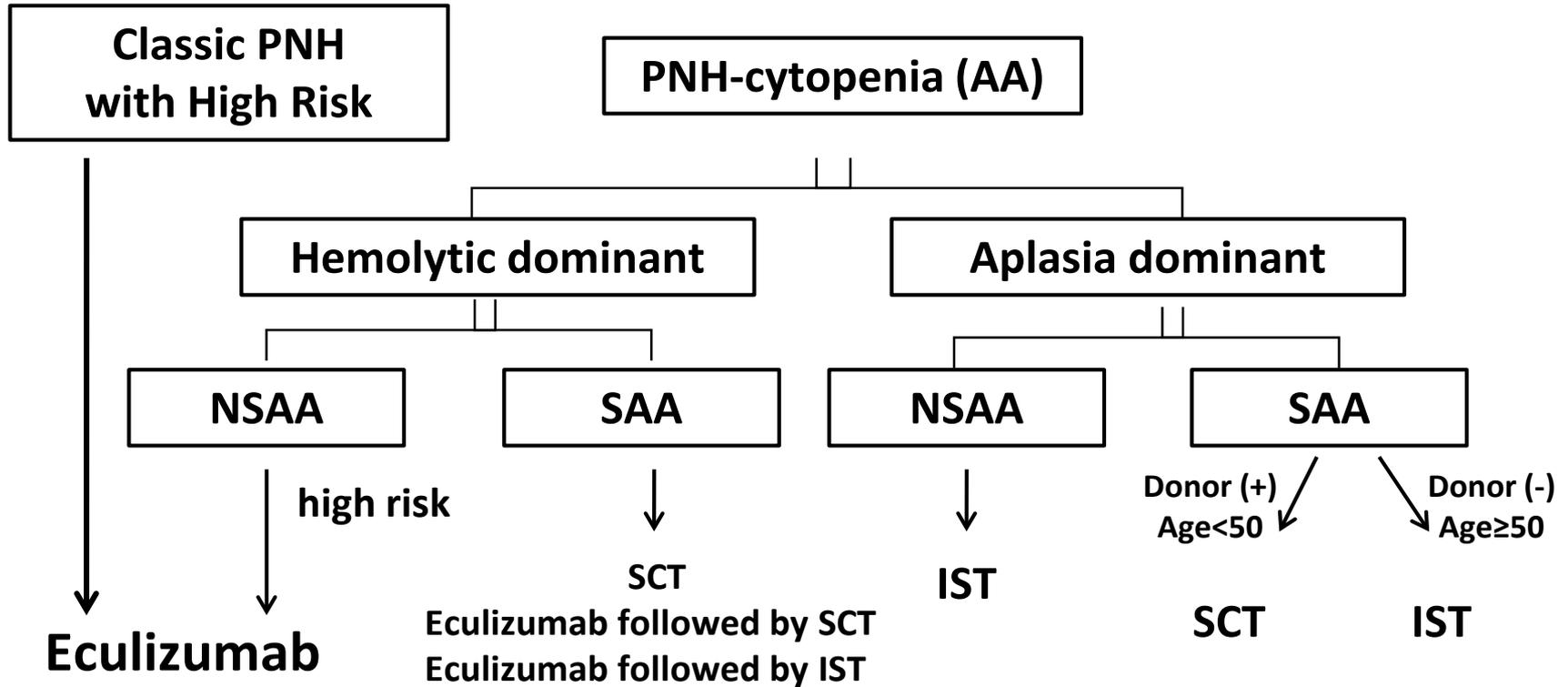
**Table 1**  
Demographics and Clinical Characteristics

Patient	Age, yr	Sex	Disease	Donor	Conditioning	Source	Day of Last Pre-HCT Eculizumab Dose	Pre-HCT PNH Clone Size (% gran/RBC)	Days to Neutrophil Engraftment	Days to Platelet Engraftment	Eculizumab Post-HCT (Days Given)	Follow-Up, mo
1	60	Male	AA	Sibling	Cy/ATG	BM	Unknown	36/0	28	21	+3, +17	51
2	25	Male	AA	Sibling	Flu/Cy/ATG	BM	-13	6/NA	20	18	+2, +16	52
3	32	Male	AA	Sibling	Cy/ATG	BM	-14	23/NA	NA	NA	+2, +23, +30	1
4	29	Female	AA	MUD	Flu/Mel	PBSCs	-18	70/30	12	11	+7	86
5	38	Male	MDS	Sibling	Flu/Mel	BM	-21	68/6	15	15	+8, +22	6
6	58	Female	MDS	MUD	Flu/Mel	PBSCs	-1	60/10	12	10	+6, +13	59
7	63	Male	MDS	MUD	Flu/Mel	PBSCs	-12	89/10	14	N/A	+2	3
8	46	Male	PMF	MUD	Flu/Mel	BM	-11	73/12	23	23	+2, +16, +30	20

Cy indicates cyclophosphamide; ATG, antithymocyte globulin; Flu, fludarabine; BM, bone marrow; NA, not applicable; MUD, matched unrelated donor; Mel, melphalan; PBSCs, peripheral blood stem cells; PMF, primary myelofibrosis.

- Eculizumab given immediately post-allogeneic hematopoietic cell transplantation (HCT) as thrombosis prophylaxis is feasible.
- Post-HCT eculizumab does not seem to increase infections due to encapsulated bacteria.

# Proposed algorithm for the Management of Classic PNH and PNH/AA (Korea)



*Thank you*