UCLouvain

Aplastic anemia and paroxysmal nocturnal hemoglobinuria (PNH)

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INSTITUT ROI ALBERT II
CANCER ET HÉMATOLOGIE
Cliniques universitaires SAINT-LUC
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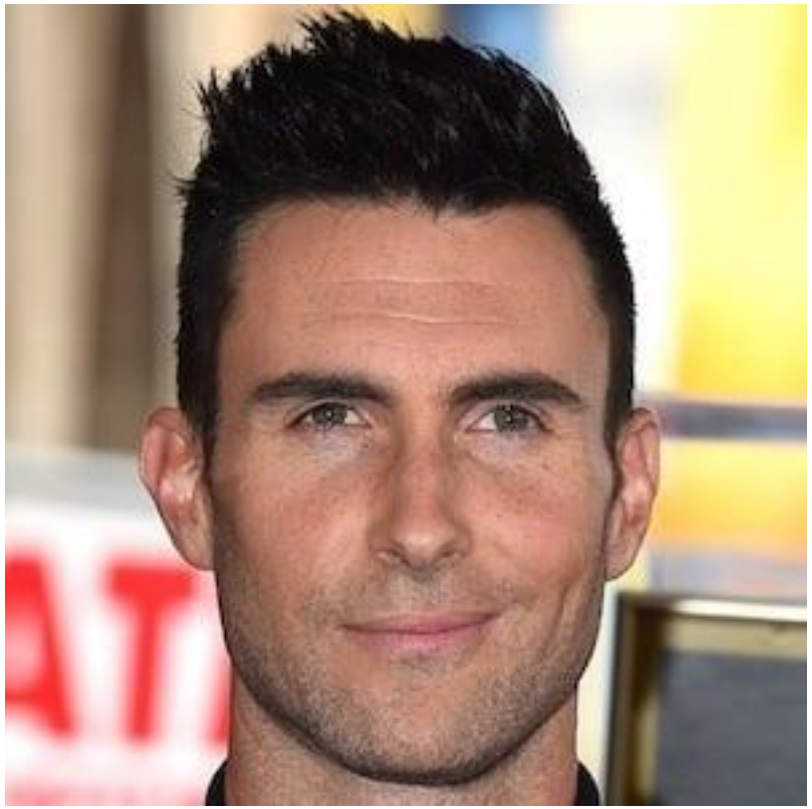
Middle-aged man with pancytopenia



This is a fiction

Adam (45 yo) is complaining about fatigue and easy bruising for the past 3 weeks

Hgb 7.6 g/dL
Rc 20 x 10^9/L
WBC 1.2 x 10^9/L
Neutros 0.25 x 10^9/L
Plts 18 x 10^9/L

Normal LDH, normal bilirubin and LFT, normal coagulation test

No medical history and no family history

2 brothers and 2 sisters.

3 kids from 8 yo to 1 yo.

No current medication

Aplastic Anemia : definition and severity

DEFINITION

Hypocellular BM
No dysplasia

At least 2 criteria:
Hg < 10 g/dL
Plts < 50 x 10^9/L
Neutros < 1.5 x 10^9/L

CAMITA CRITERIA

SAA

- Marrow cellularity <25%
- At least 2 of the followings
  - Neutros < 0.5 x 10^9/L
  - Plts < 20 x 10^9/L
  - Rc < 60 x 10^9/L

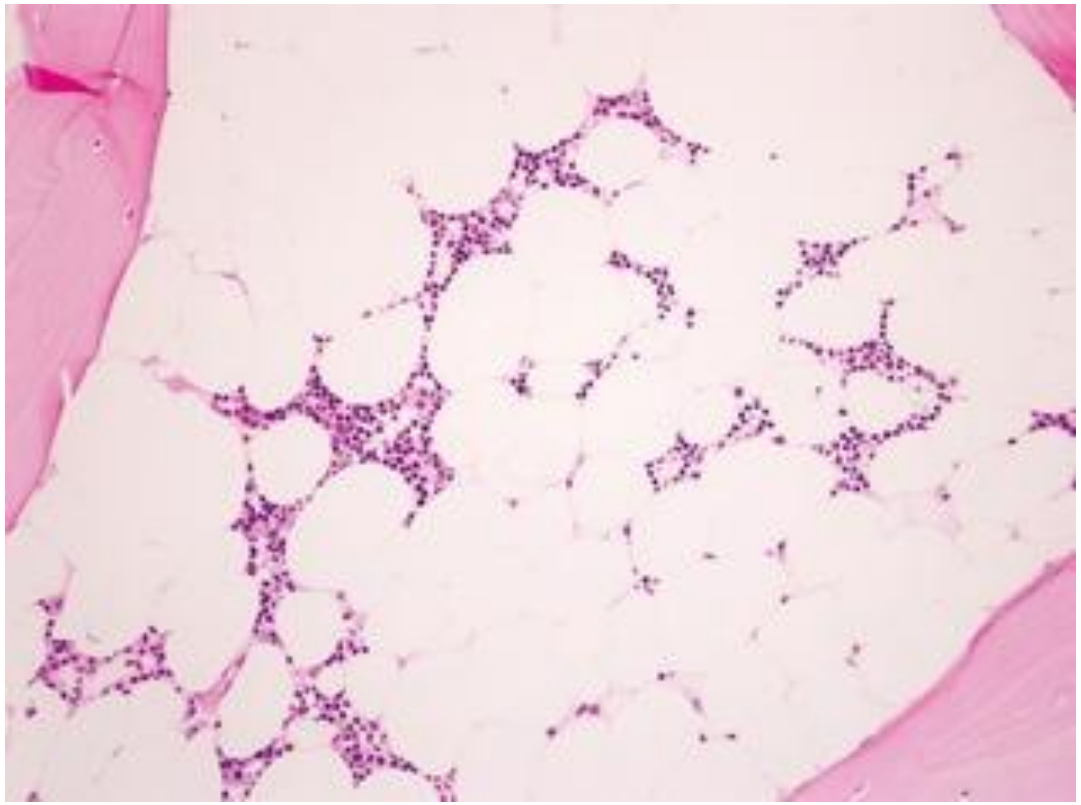
VSAA

Same as SAA
But Neutros < 0.2 x 10^9/L

NSAA

AA with no criteria for SAA and VSAA

BONE MARROW



Aspirate to evaluate dysplasia (Hypocellular MDS)

Biopsy to assess cellularity

No dysplasia among megacaryocytes and granulocytes

No blasts

Sometimes hot pockets

Small lymphocytic infiltrates

Cytogenetics and FISH: del13q and +8 common

MEDICATIONS AND SEROLOGY

Chart 33-3 Substances Associated With Aplastic Anemia

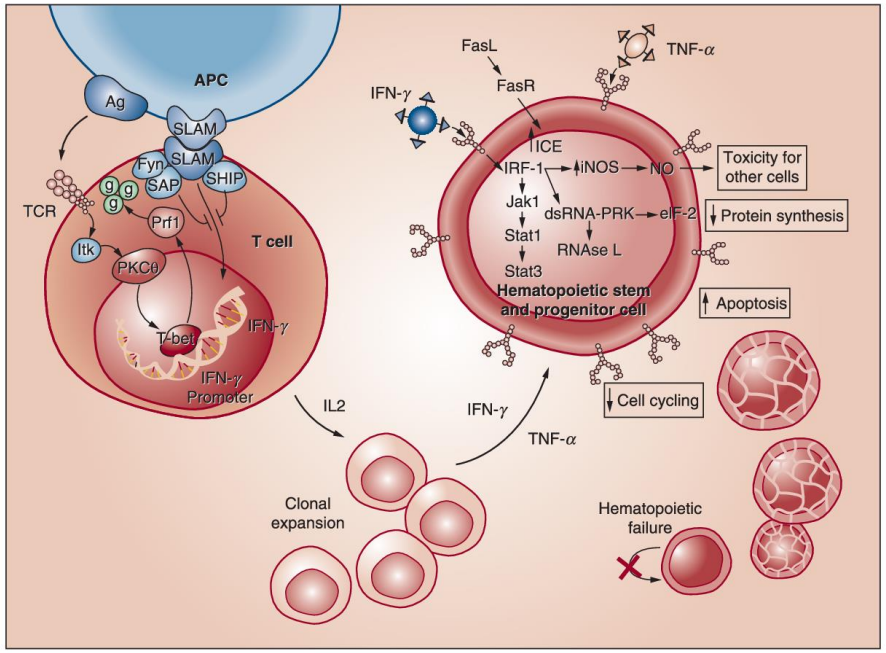
Analgesics
Antiseizure agents (mephenytoin, triethadione*)
Antihistamines
Antimicrobials*
Antineoplastic agents (alkylating agents, antitumor antibiotics, antimetabolites)
Antithyroid medications
Benzene*
Chloramphenicol*
Gold compounds*
Heavy metals
Hypoglycemic agents
Insecticides
Organic arsenicals*
Phenylbutazone*
Phenothiazines
Sulfonamides*
Sedatives

*Most common.

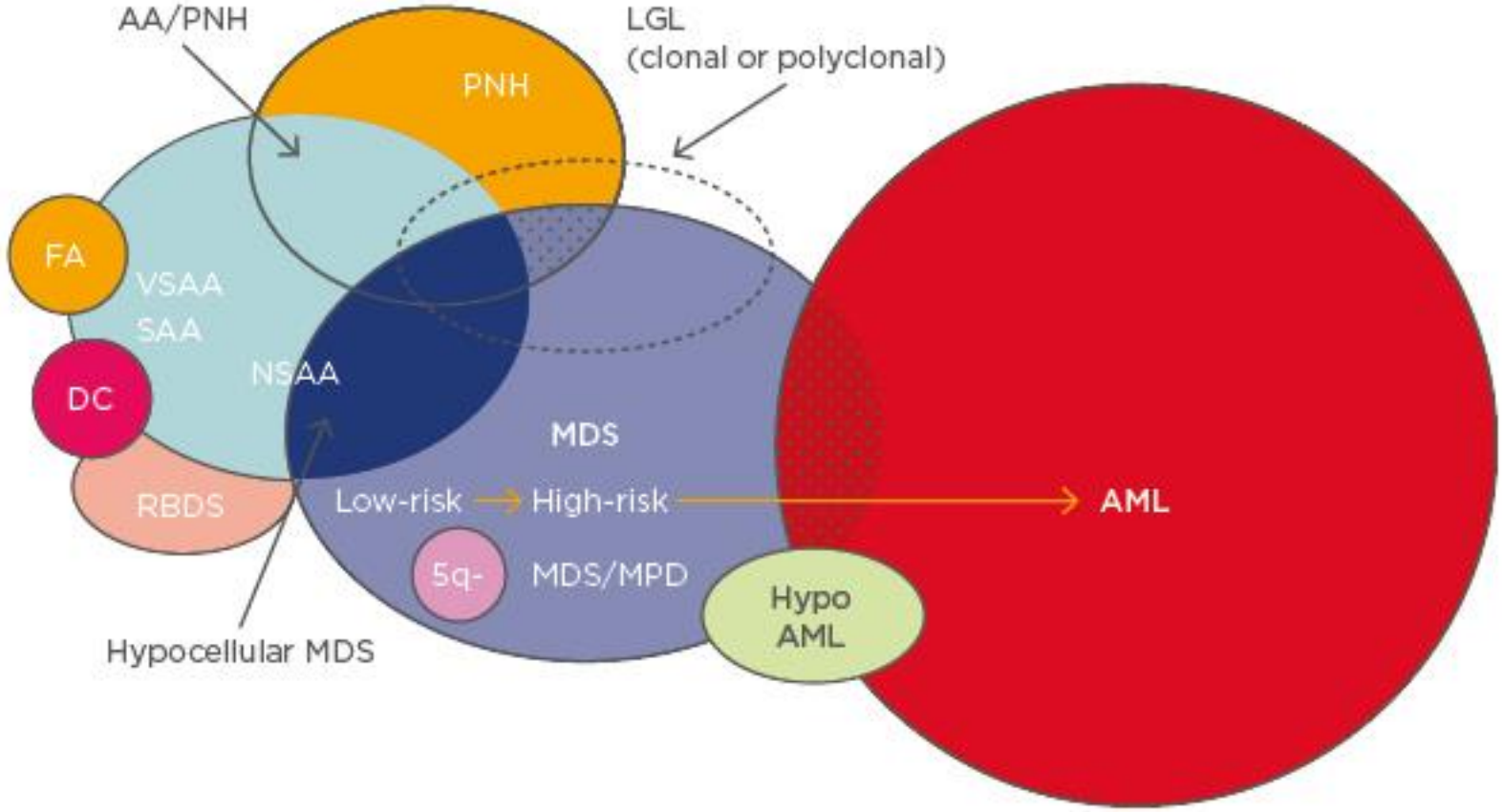
Pathology	Virus	Comments	Reference
Pancytopenia	EBV	Self-resolving	(20)
	HCV	Afffected by medication	(21)
Aplastic anemia	Parvovirus B19	Driven by infection of erythroid progenitors	(22, 23)
	EBV, CMV, VZV, HHV, HIV, HAV, and HCV	Driven by a strong antiviral T cell response and ensuing cytokine production	(24, 25)
	Dengue	Mechanism unknown	(26)
HLH	CMV	Driven by the ensuing antiviral immune response rather than the virus itself	(27, 28)
	Parvovirus B19		(22)
	Dengue		(29, 30)
	HAV		(31)
	HIV (acute)		(32)
Lymphoproliferative disorders and malignancies	EBV	Infectious mononucleosis and chronic active EBV disease	(20)
	HCV	Acute myeloid leukemia, primary myelodysplastic syndrome	(21)

In this table, we summarize the viruses that can contribute to particular type of pathology in human BM.

PHYSIOPATHOLOGY



-1. Immune pathogenesis of apoptosis of CD34 multipotential hematopoietic cells in acquired aplastic anemia. Antigens are presented to T lymphocytes



HYPOPLASTIC MDS

Table 4 Integrated cyto-histologic/genetic score (hg-score)

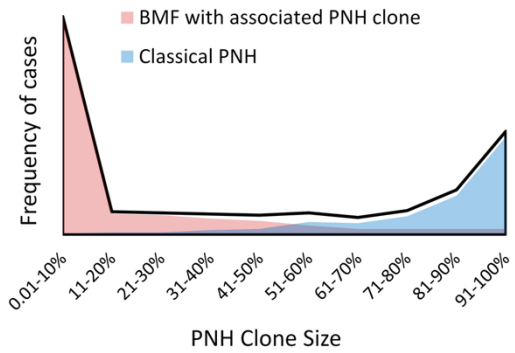
Cytological/histological variables	Score
Requisite criteria	
Bone marrow blasts AND/OR CD34 + cells ≥5%	2
Bone marrow blasts AND/OR CD34 + cells 2–4%	1
Fibrosis grade 2–3	1
Dysmegakaryopoiesis	1
Co-criteria	
Ring sideroblasts ≥15%	2
Ring sideroblasts 5–14%[a]	1
Severe dysgranulopoiesis	1
Karyotype (co-criterion)	
Presumptive cytogenetic abnormality[a]	2
Somatic mutation (co-criterion)	
Specific mutation pattern[b]	1

Bono Leukemia 2019

Defining cytogenetic abnormalities
Complex karyotype (≥3 abnormalities)
5q deletion or loss of 5q due to unbalanced translocation
Monosomy 7, 7q deletion, or loss of 7q due to unbalanced translocation
11q deletion
12p deletion or loss of 12p due to unbalanced translocation
Monosomy 13 or 13q deletion
17p deletion or loss of 17p due to unbalanced translocation
Isochromosome 17q
idic(X)(q13)
Defining somatic mutations
ASXL1
BCOR
EZH2
SF3B1
SRSF2
STAG2
U2AF1
ZRSR2

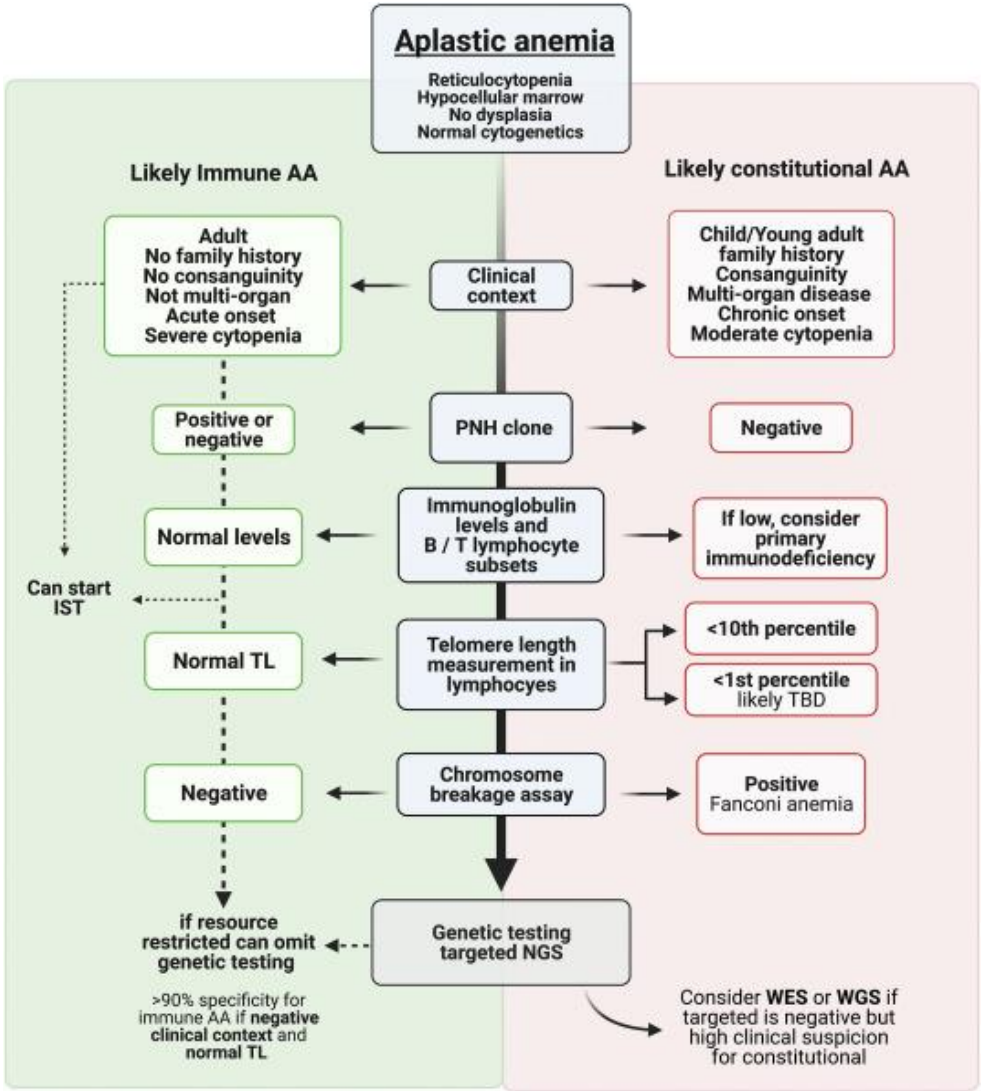
Khoury Leukemia 2022

ACQUIRED versus CONSTITUTIONAL



PNH > 1%

OTHER TESTS
Vitamin B12 and folates
LFTs
ANA and anti-dsDNA
Abdominal US



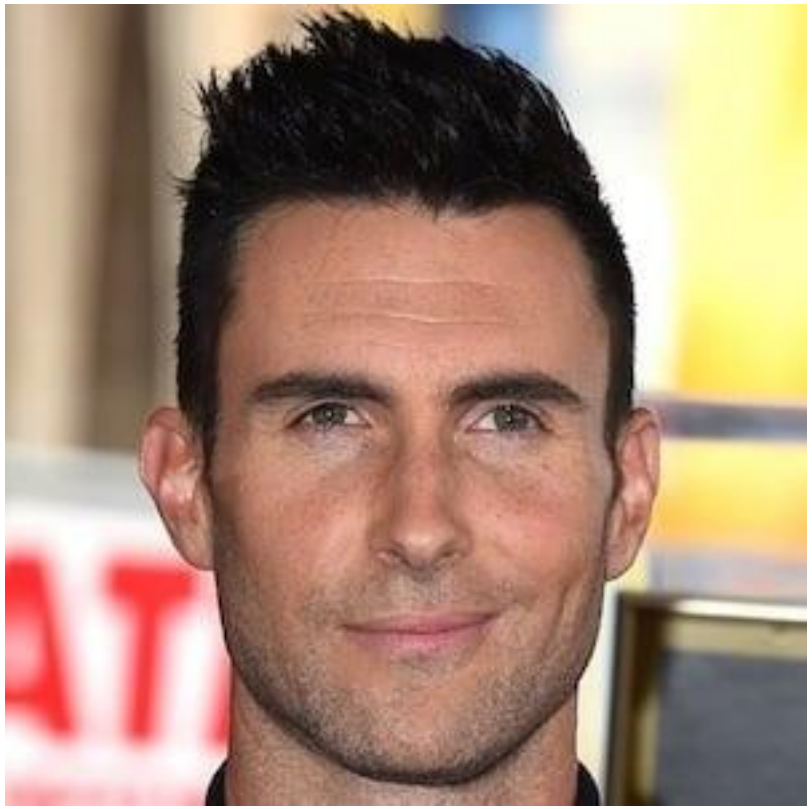
Excess HbF

FCM

Temolere length – FLOW-FISH

Chromosomal breakage

ADAM, 45 yo, with aplastic anemia



This is a fiction

Hgb 7.6 g/dL
Rc 20 x 10^9/L
WBC 1.2 x 10^9/L
Neutros 0.25 x 10^9/L
Plts 18 x 10^9/L

BM: 20% marrow cellularity, no dysplasia

Normal LDH, normal bilirubin and LFT, normal coagulation test, normal vitamin B12 and folate

No medical history and no family history

2 brothers and 2 sisters. All are haplo-identical

No current medication or toxic

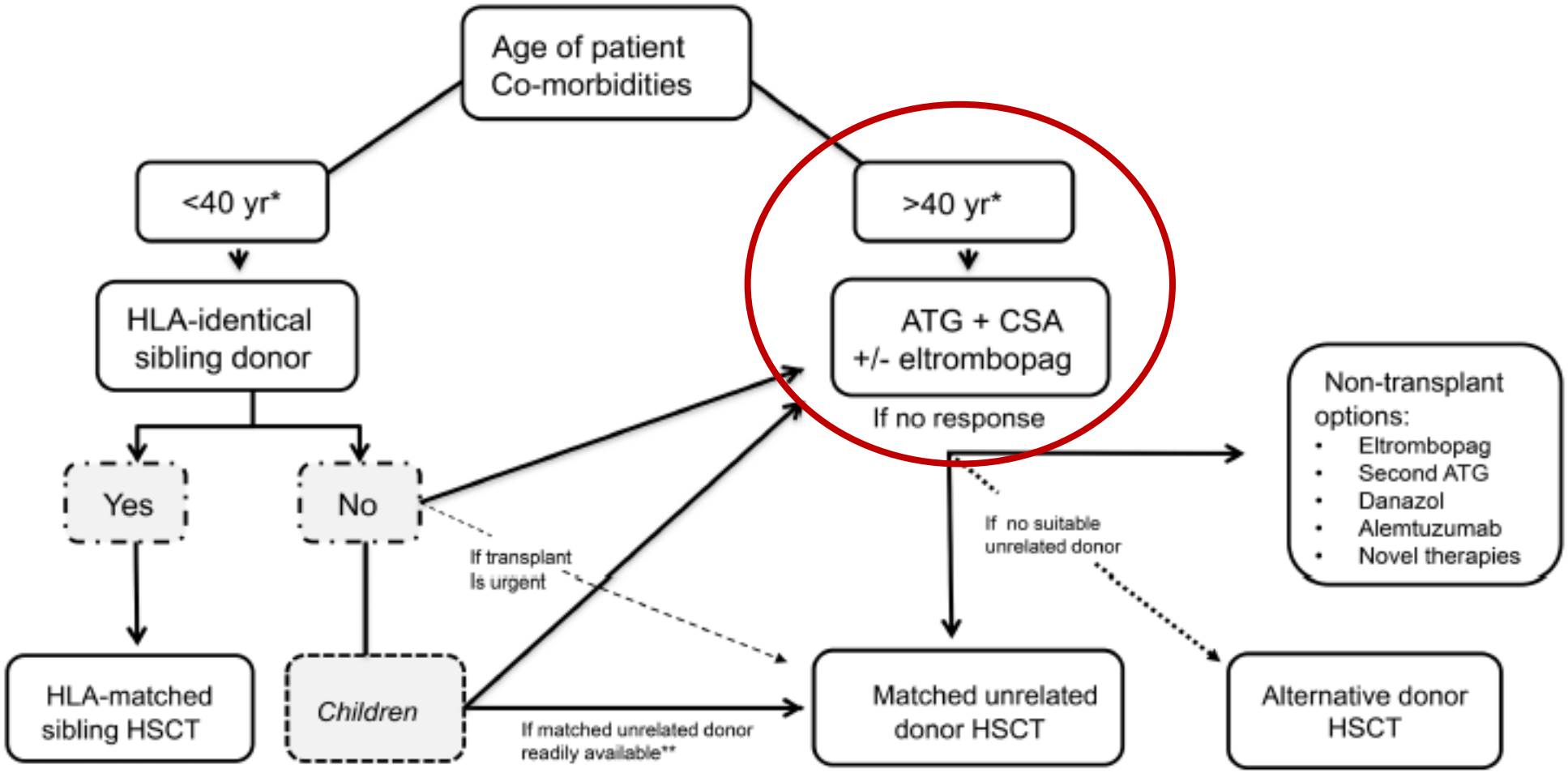
PNH 2% on granulocytes

Telomere length 20%, No DNA breakage

Cytogenetics: +8

→ SAA

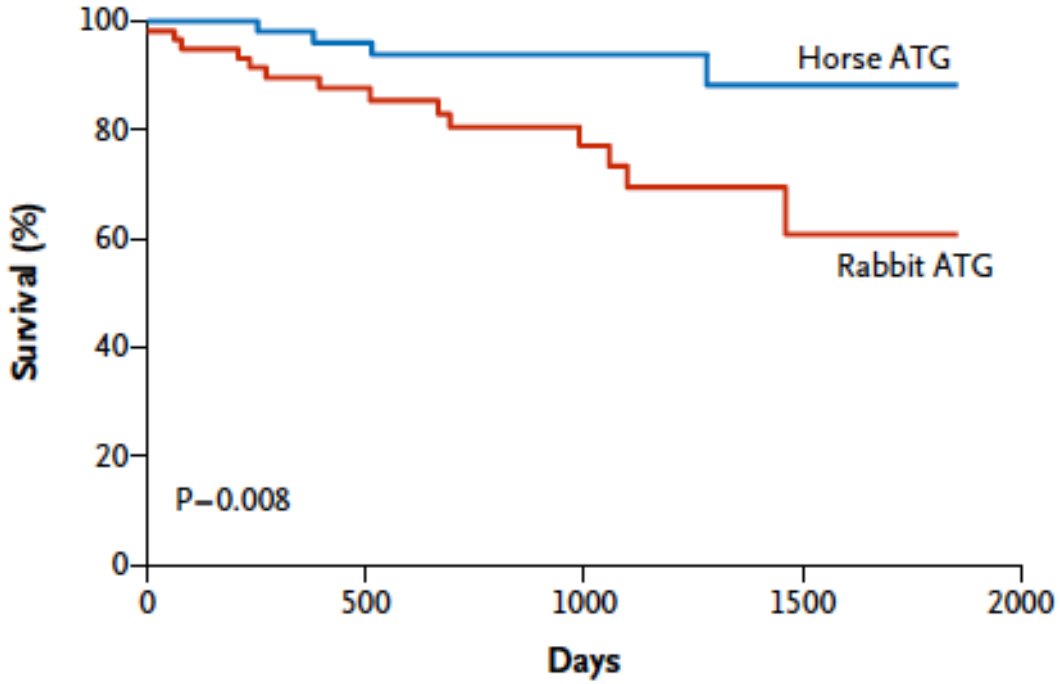
TREATMENT ALGORITHM in AA



Kulasekararaj BJH 2024

IMMUNOSUPPRESSIVE THERAPY IN AA

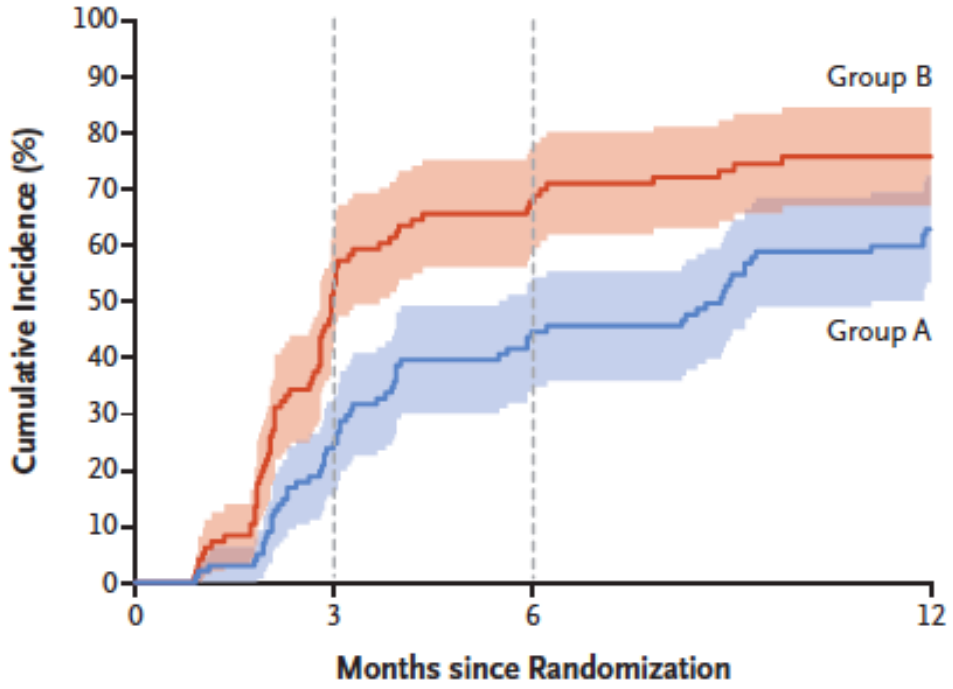
ATG + CsA



No. at Risk				
Horse ATG	60	44	27	12
Rabbit ATG	60	41	22	6

Scheinberg NEJM 2011

hATG + CsA + EPAG

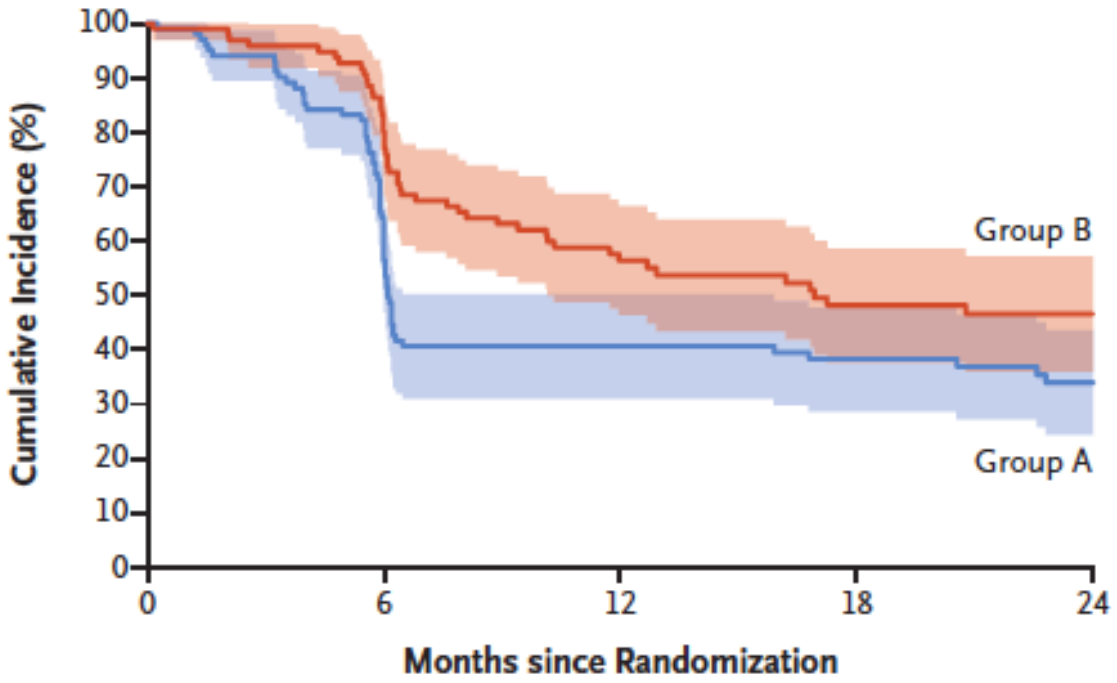


No. at Risk			
Group B	96	25	4
Group A	101	40	14

Peffault NEJM 2022

IMMUNOSUPPRESSIVE THERAPY IN AA

hATG + CsA + EPAG



No. at Risk					
Group B	96	76	45	31	15
Group A	101	60	38	30	10

Peffault NEJM 2022

G-CSF not recommended
hATG 40 mg/kg x 5 days
CsA 150-250 during 9-12 months, then taper every 3 months
EPAG 150 mg starting day 14 or day 1 for 6 months
Steroids for serum sickness prophylaxis

RELAPSE 30-40% at 5 years

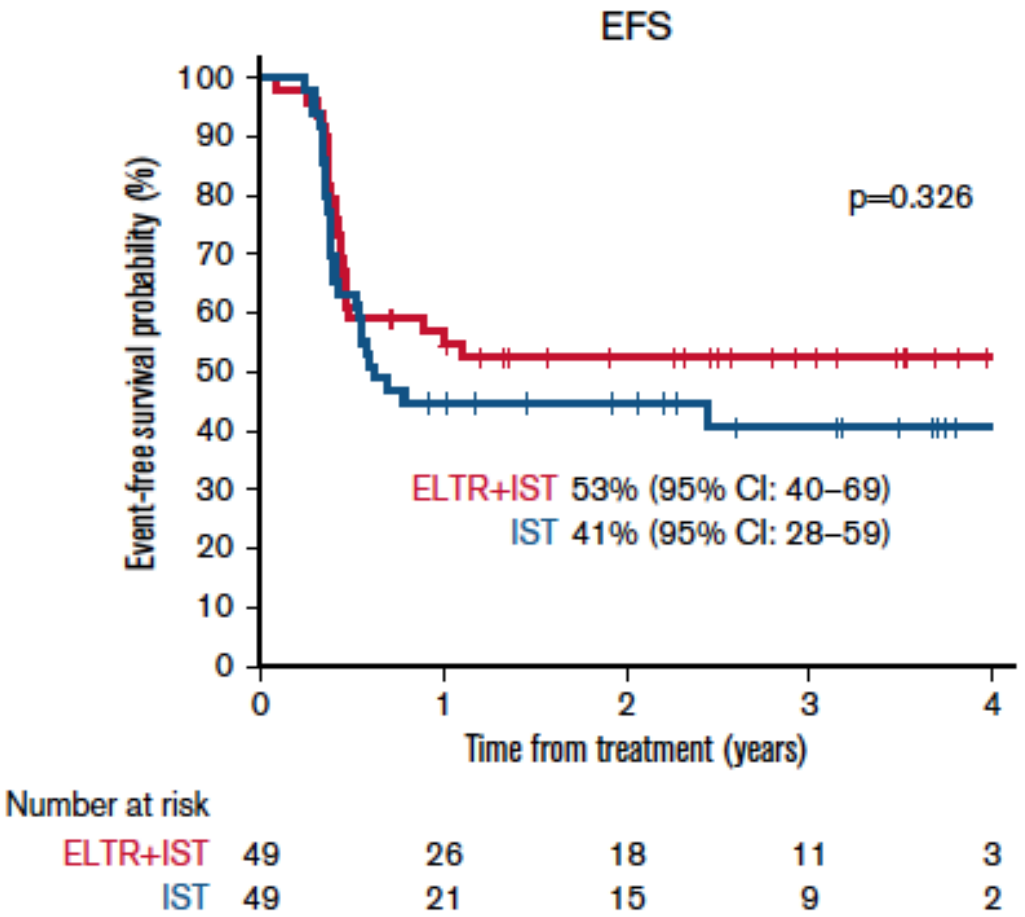
CLONAL EVOLUTION 10-15% at 10 years - BM

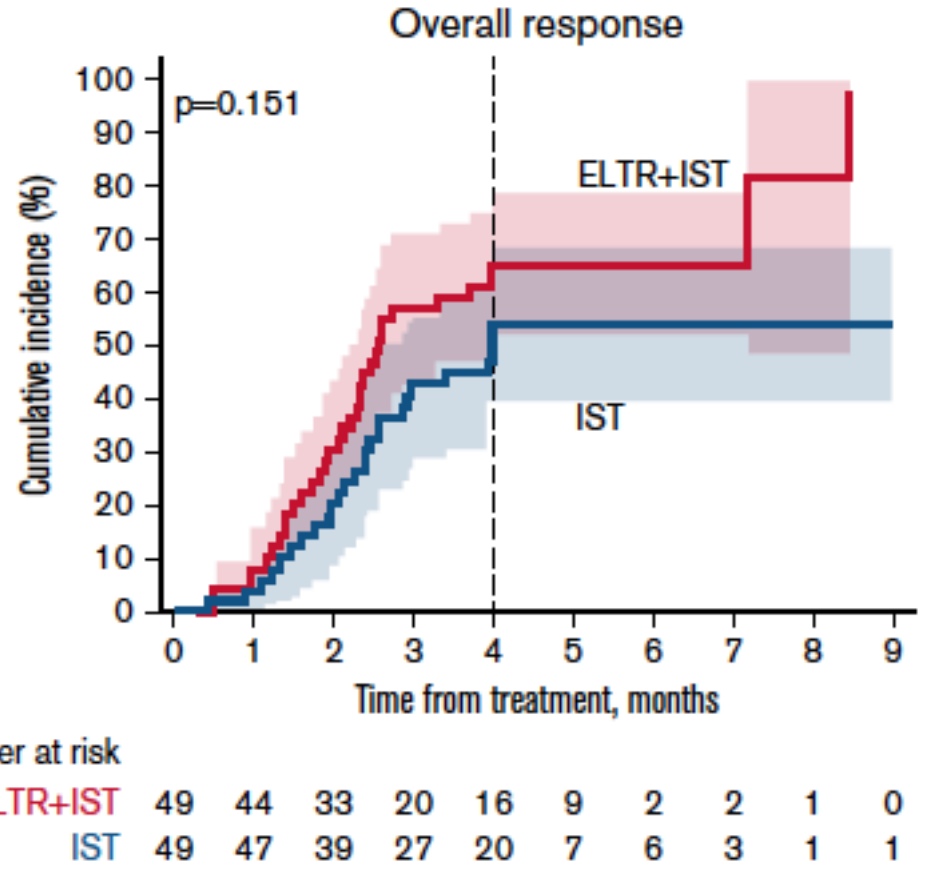
PNH expansion

Anti-herpes prophylaxis during IST
Bactrim no recommended

Restrictive blood transfusion – irradiated RBC

IMMUNOSUPPRESSIVE THERAPY IN CHILDREN



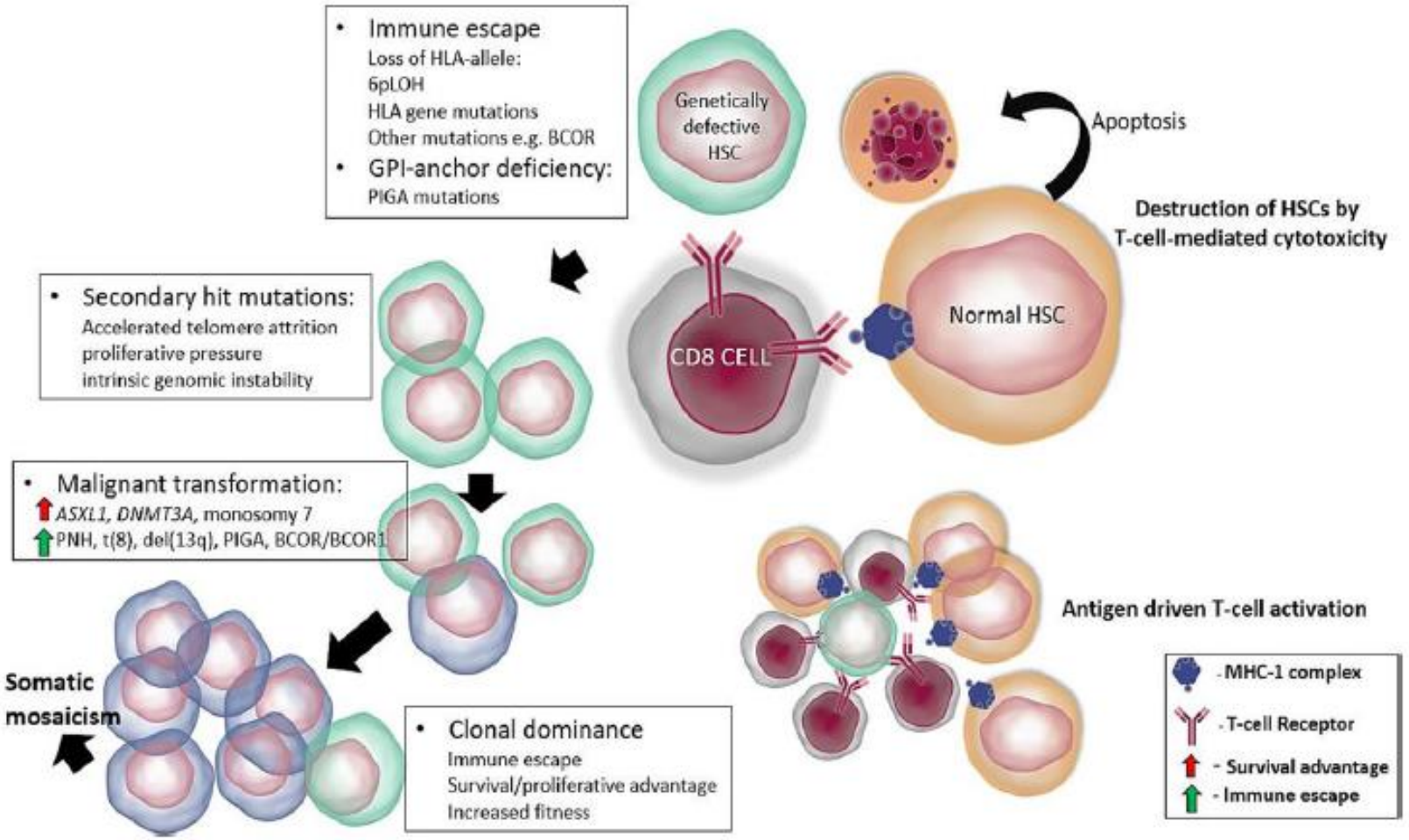


Goronkova BloodAdv 2023

IMMUNE ESCAPE AND CLONAL EVOLUTION IN AA

ADAPTATIVE

BCOR
BCOL1
PIGA
+8
Del13q
6pUPD



Boddu Eur J of Haematology 2019

MALADAPTATIVE

ASXL1
DNMT3A
RUNX1
TP53
SRSF2
Abn 7q

Younger female with pancytopenia

This is a fiction

Admitted to the ER with gums bleeding

Hgb 8.2 g/dL
Rc 35 x 10^9/L
WBC 0.9 x 10^9/L
Neutros 0.15 x 10^9/L
Plts 9 x 10^9/L

Normal LFTs, coagulation, vitamine B12 and folates

BM: 15% marrow cellularity, no dysplasia, normal KT

PNH 5% on granulocytes

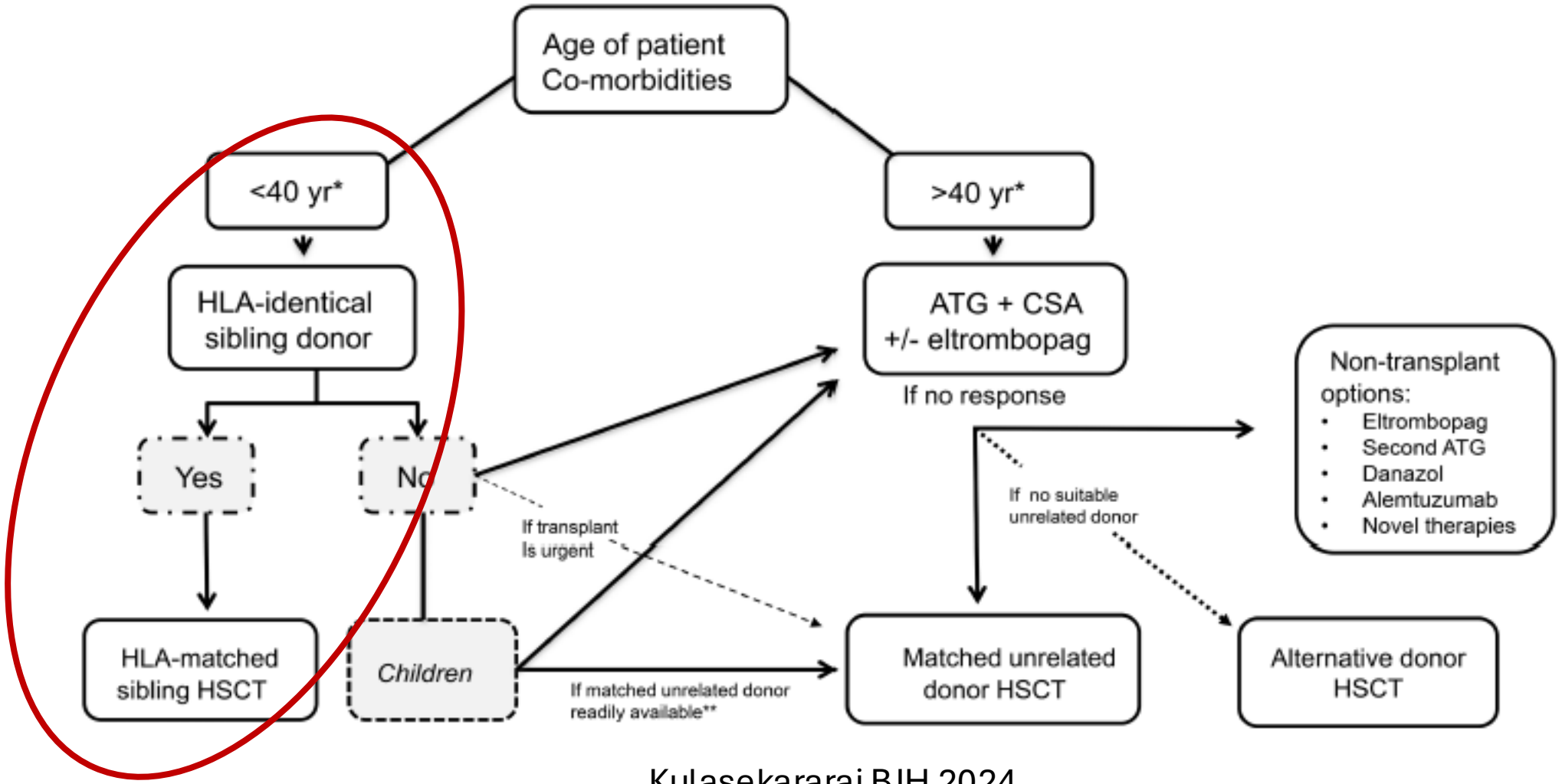
No personnel and family history

No medication

Telomere length 40%, no DNA breakage

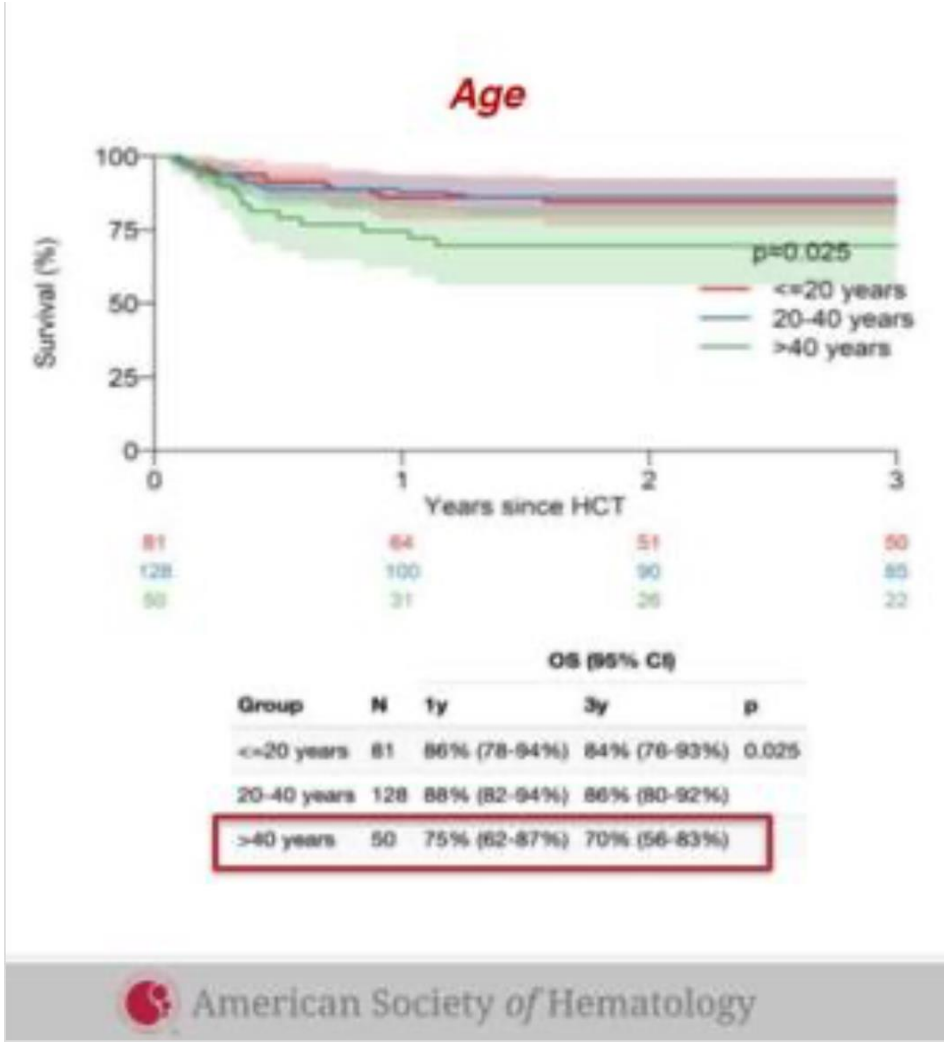
→ VSAA

TREATMENT ALGORITHM in AA

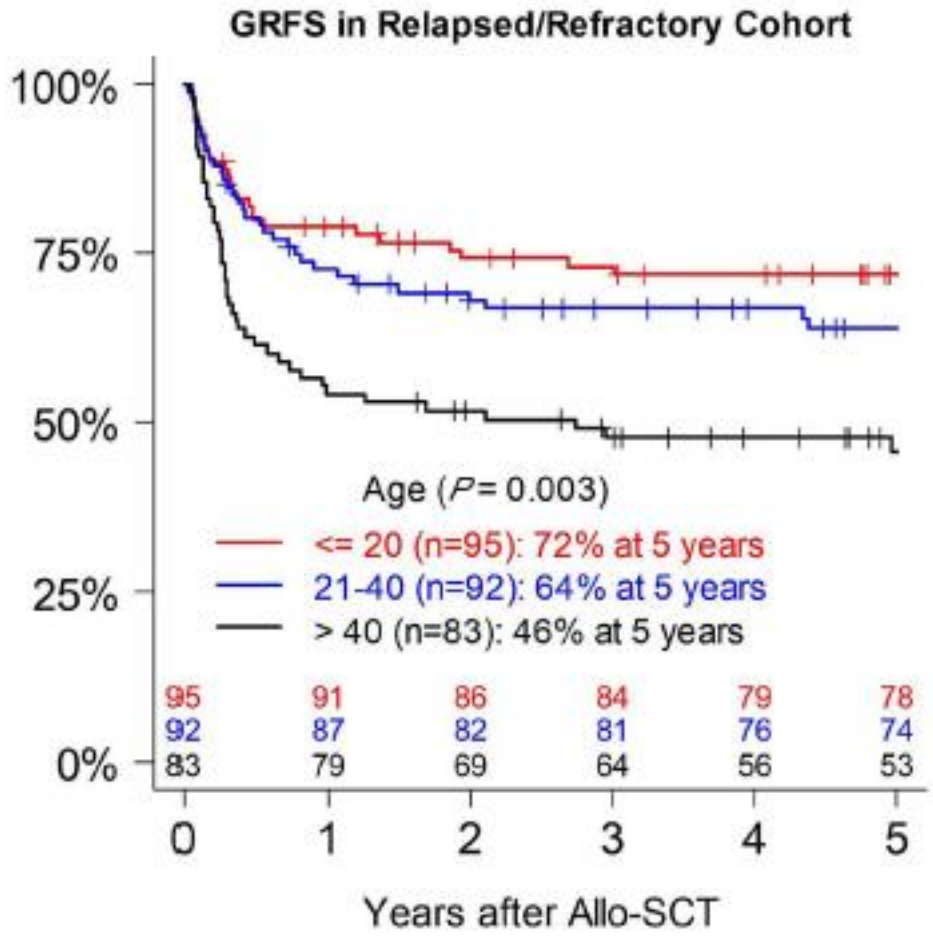


Kulasekararaj BJH 2024

ALLOGENEIC TRANSPLANTATION IN AA

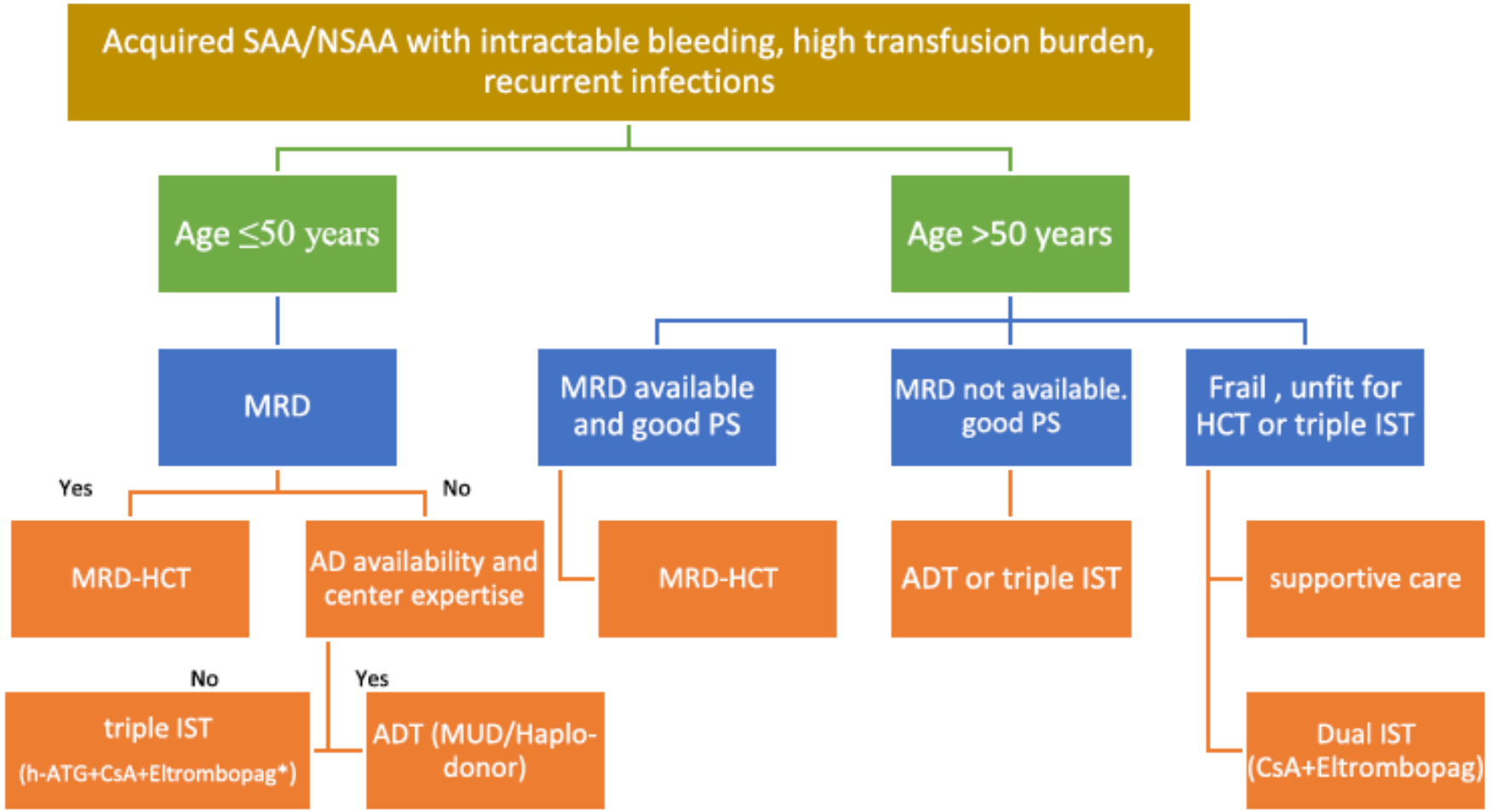


Risitano ASH 2024



Devillier Haematologica 2023

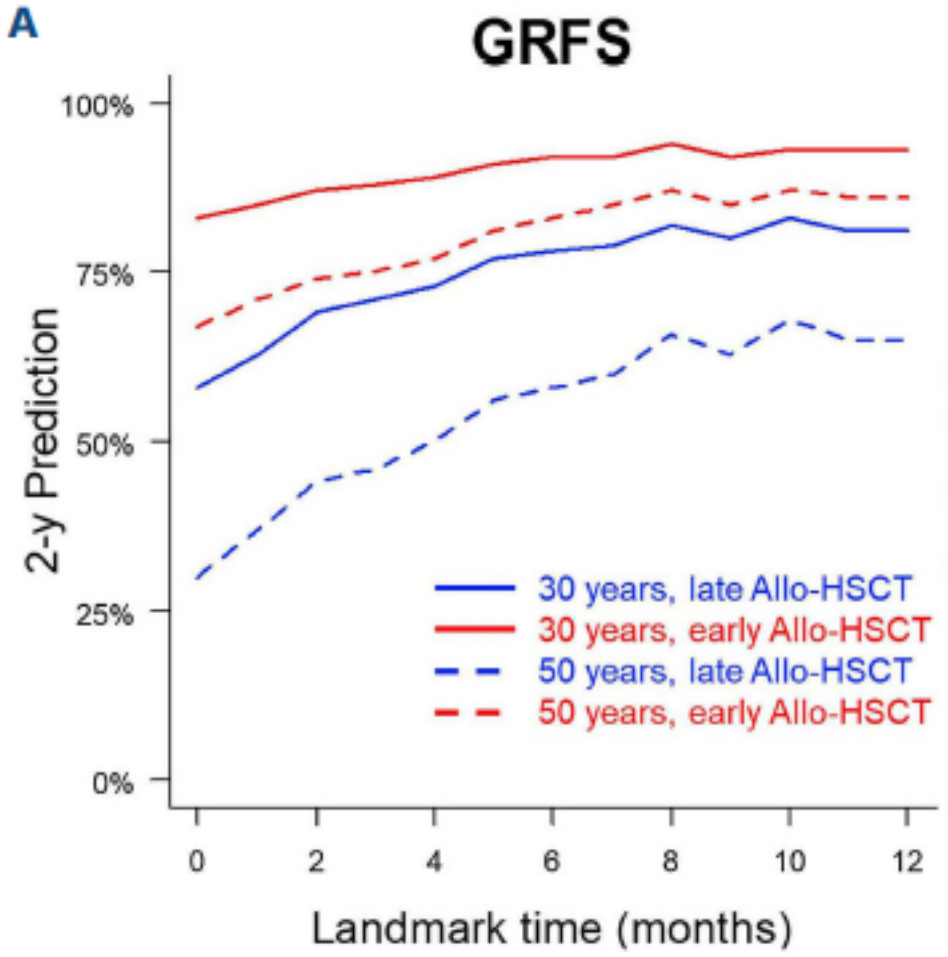
ASTCT Guidelines



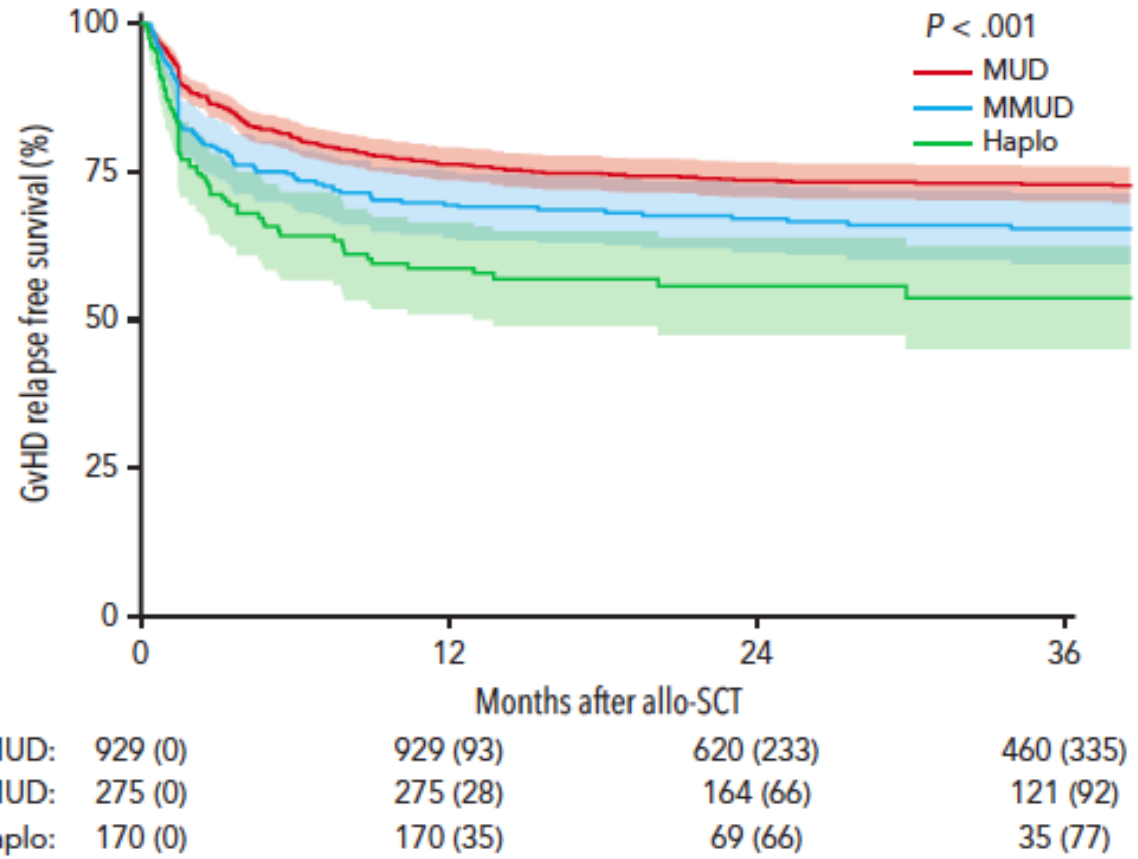
Iftikhar TCT 2024

MRD=matched-related donor

ALLOGENEIC TRANSPLANTATION IN AA

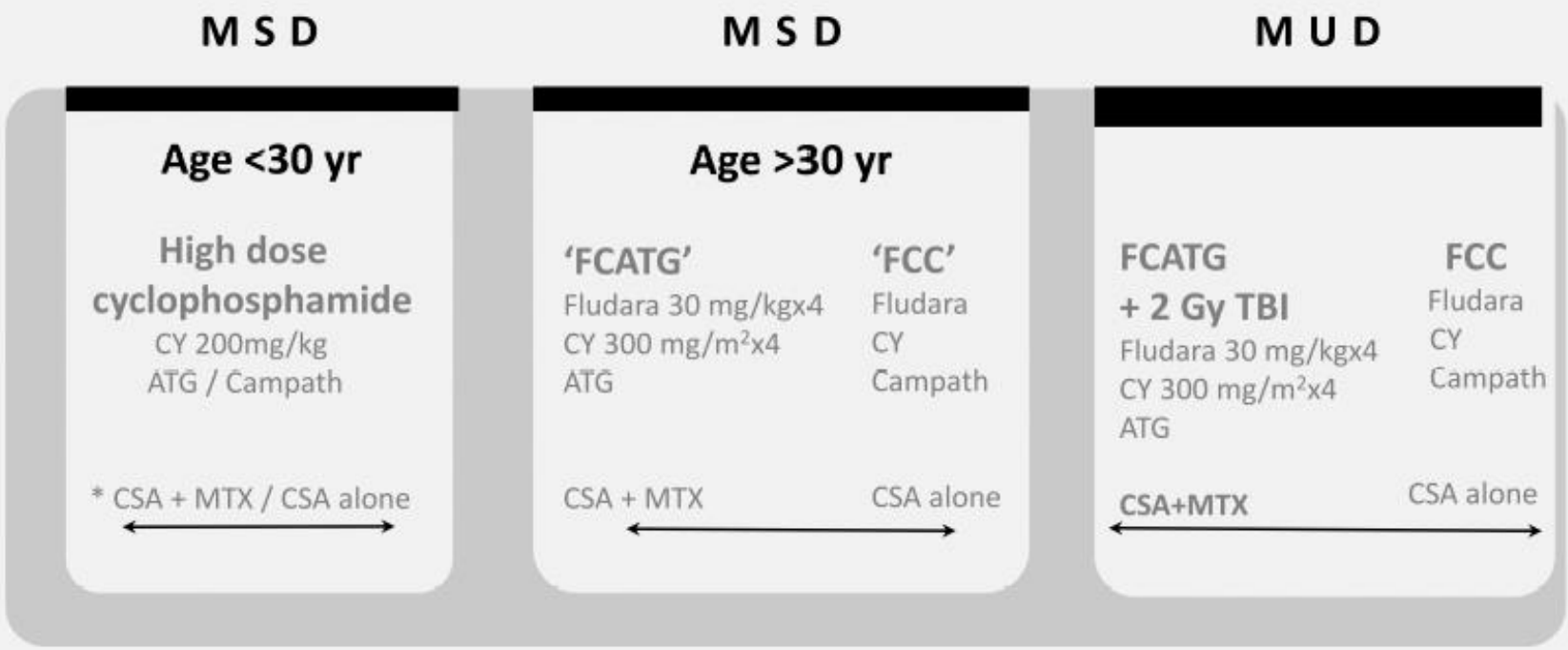


Devillier Haematlogica 2023



Montoro Blood 2024

ALLOGENEIC TRANSPLANTATION IN AA



Immunosuppressive, non-myeloablative regimens

Stem cell source and dose:

- BM for ATG-based regimens
- PB (or BM) for Campath regimens
- Low dose is associated with graft failure

***Post-graft immune suppression:**

- For 9 months, then 3 months taper to prevent late graft failure
- Keep CSA levels >250 µg/l*

Conditioning regimen for second transplants: fludarabine, ATG and CSA

Kulasekararaj BJH 2024

50 yo male with mild pancytopenia

This is a fiction

Hgb 8.7 g/dL
Rc 45 x 10^9/L
WBC 2 x 10^9/L
Neutros 0.9 x 10^9/L
Plts 40 x 10^9/L

BM: 25% cellularity, no dysplasia, normal KT

Normal LFTs, coagulation, vitamine B12 and folates → NSAA

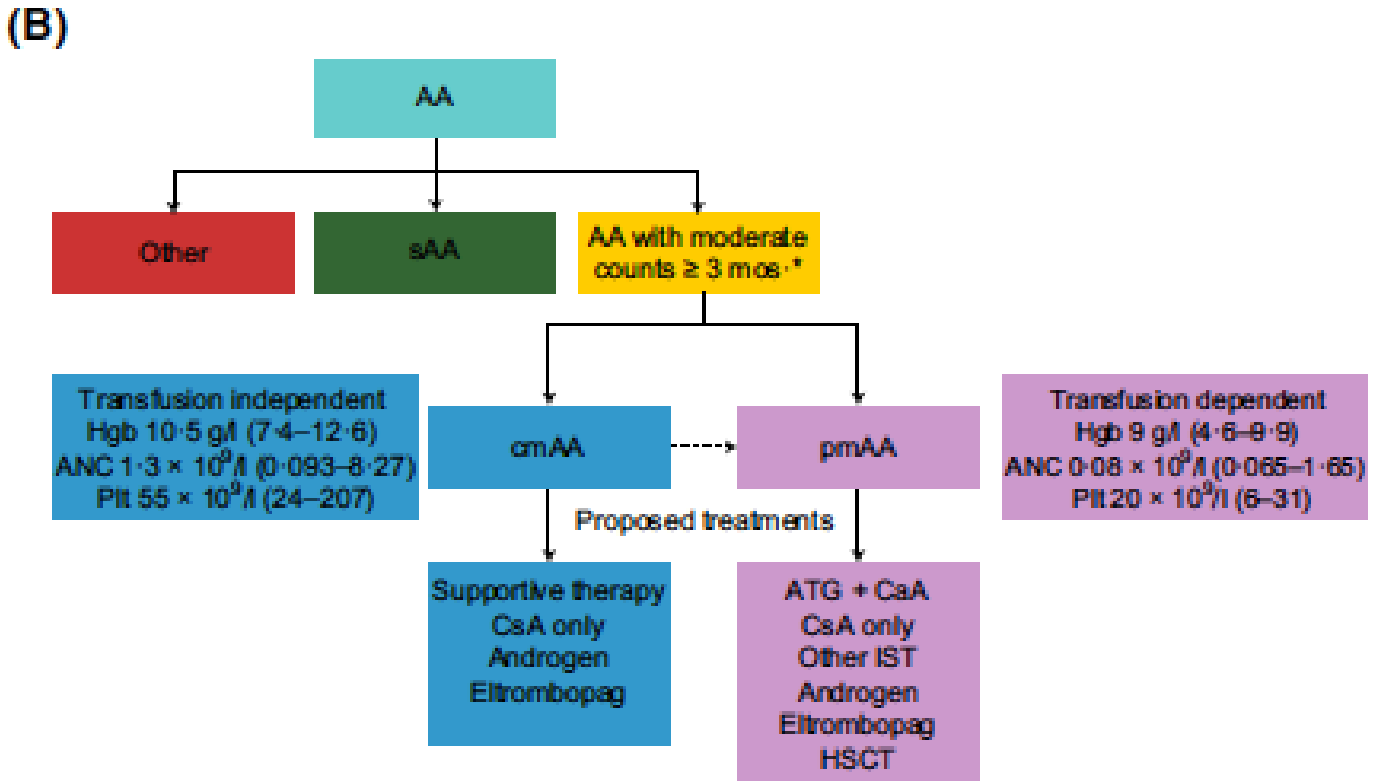
No personal or family history

No medication or toxic

Normal telomere length and no DNA breakage

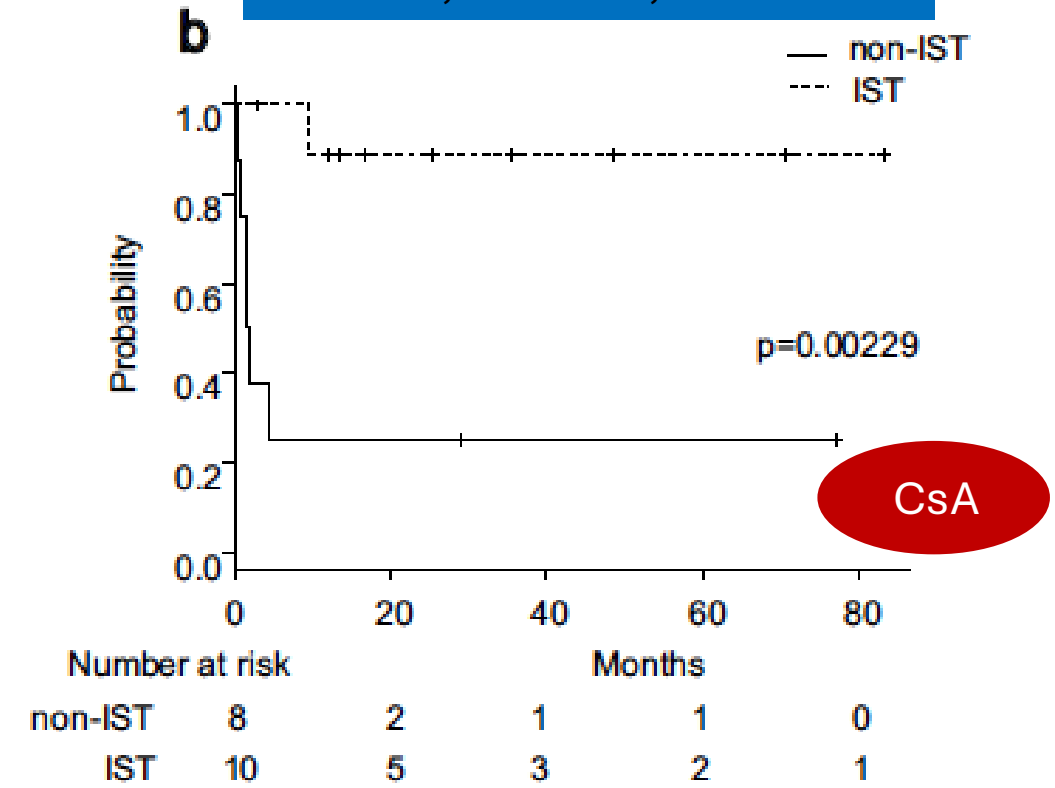
No PNH clone

TREATMENT OF NSAA



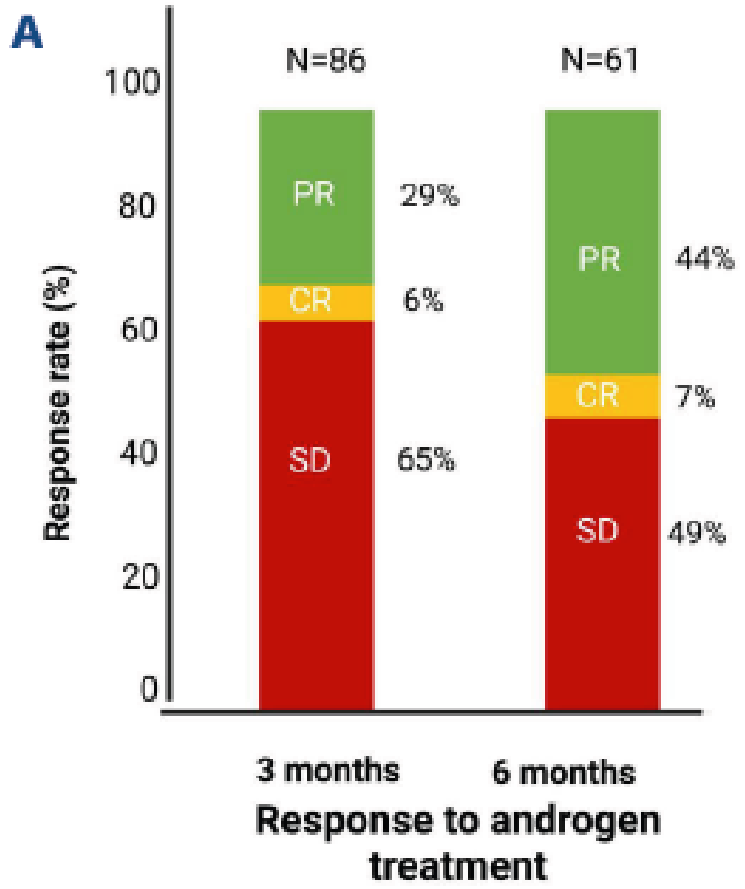
Patel BJH 2020

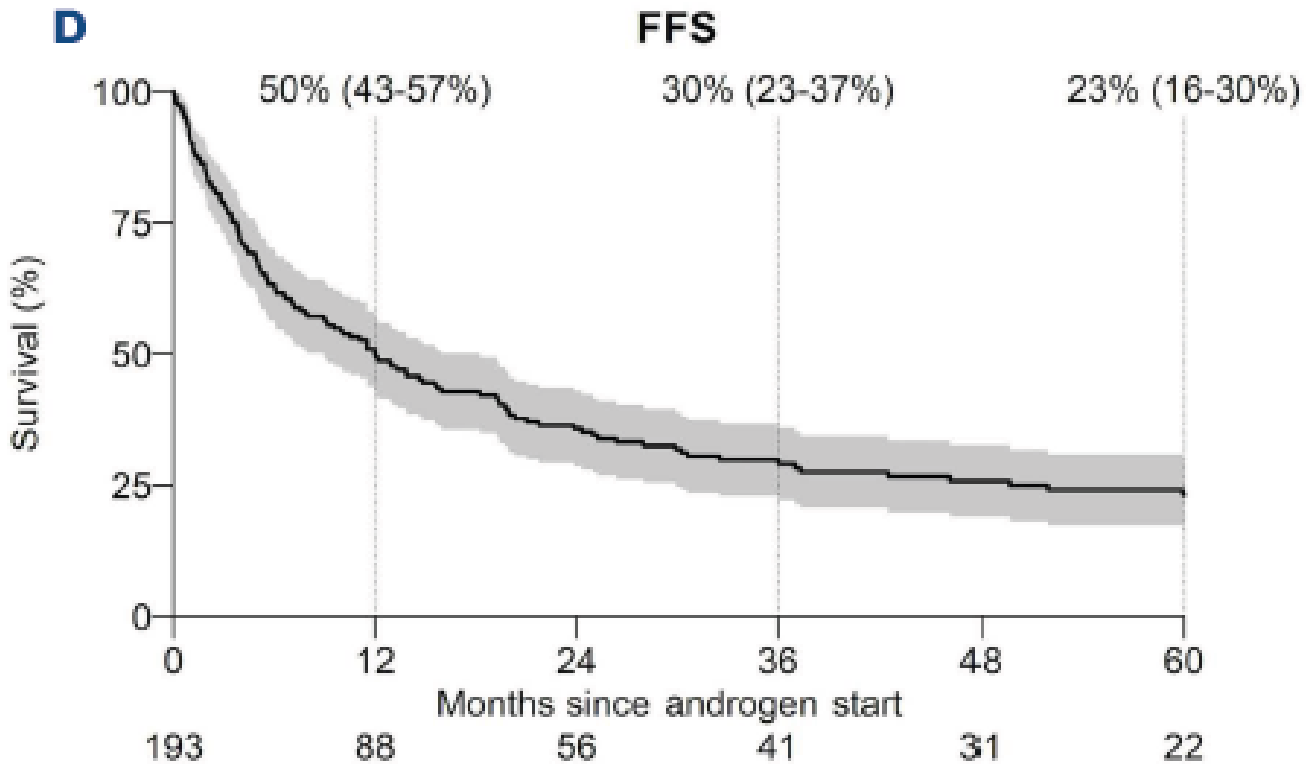
Rc < 60K, Plts<50K, neutros>1K



Matsuda Intern Med 2019

ANDROGENS IN AA





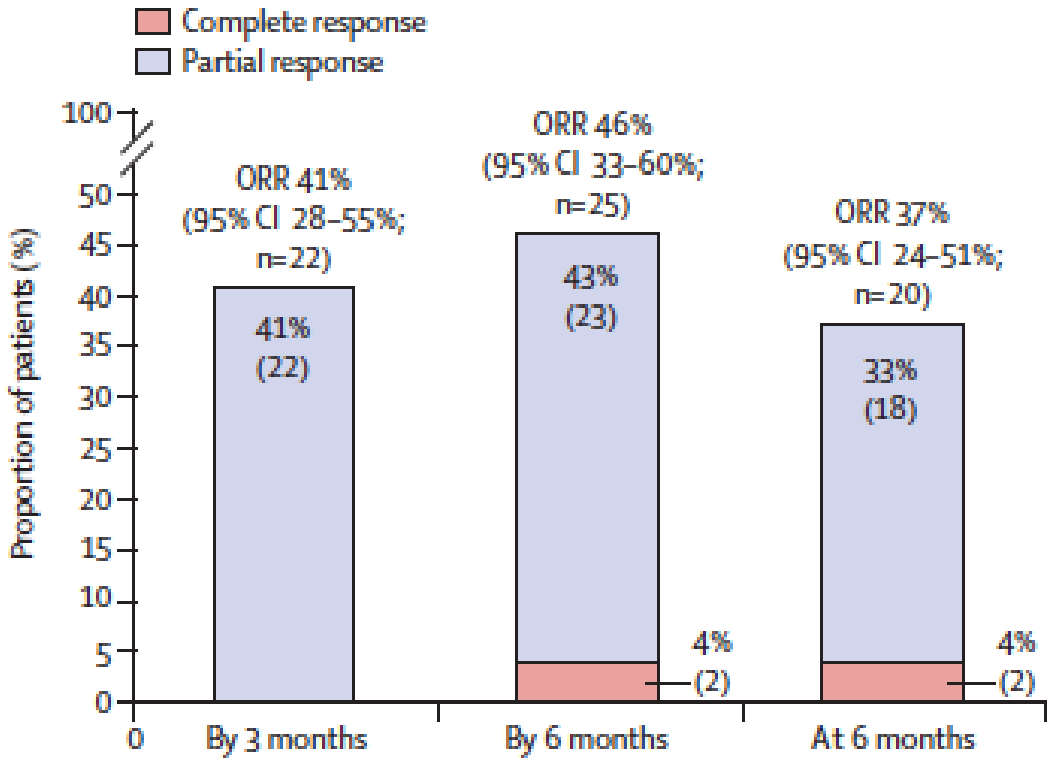
PSA
Liver MRI

Danazol
400 mg BID

Pagliuca Haematologica 2024

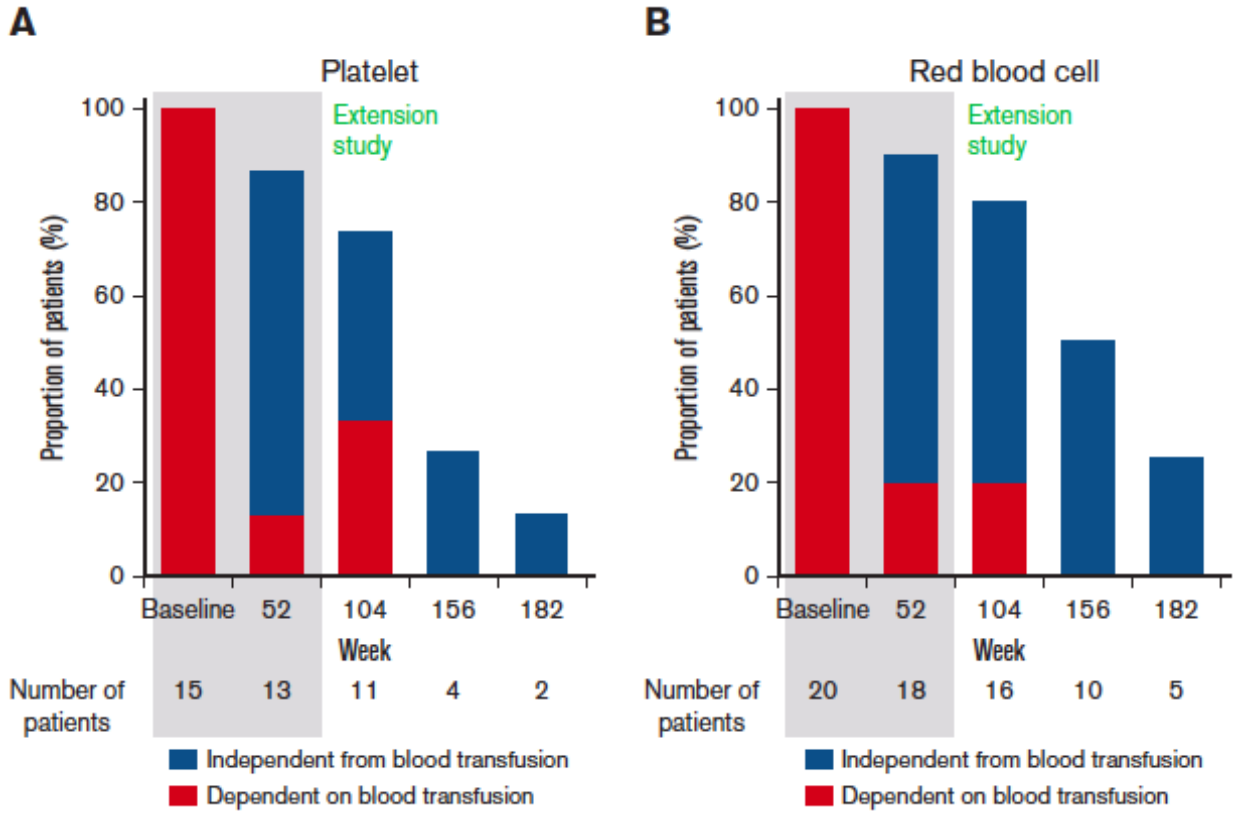
ALTERNATIVE THERAPIES in AA

CsA + EPAG



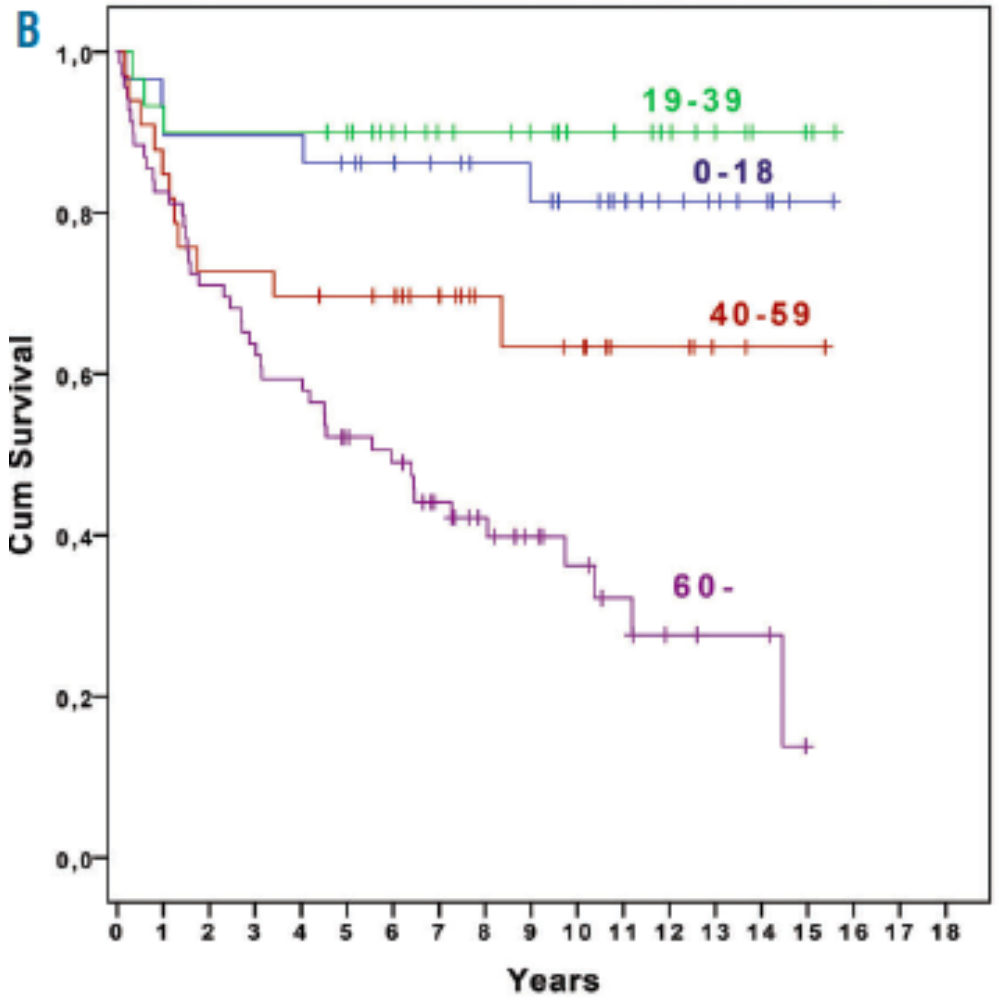
Scheinberg Lancet Heamato 2024

ROMIPLOSTIM



Miltani BloodAdv 2024

AA in ELDERLY



Vaht Haematologica 2017

ATG + CsA as first line
PFT and echocardiography

Alternatives:
CsA+EPAG
Danazol
CsA
Romiplostim
No SCT beyond 60 yo?

20 yo female with recurrent abdominal pain

This is a fiction

April : abdominal pain

- Splenomegaly
- Acute EBV infection
- Thrombocytopenia, LDH 1338

May : acute torsion-like abdominal pain

- Gastroscopy : oesophagitis

May : temporal headache, speech and behavior disorders

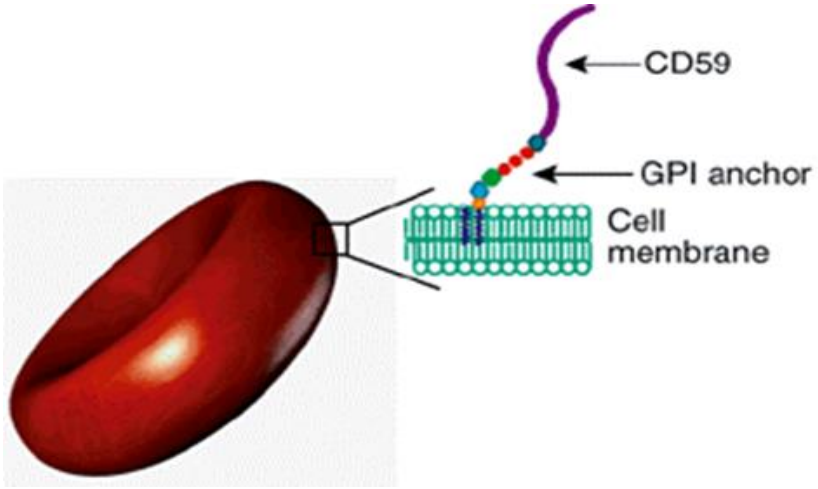
- MRI: cortical venous thrombosis with left temporal venous infarction and hemorrhagic transformation
- RF : pill
- R/ Sintrom

→ PNH

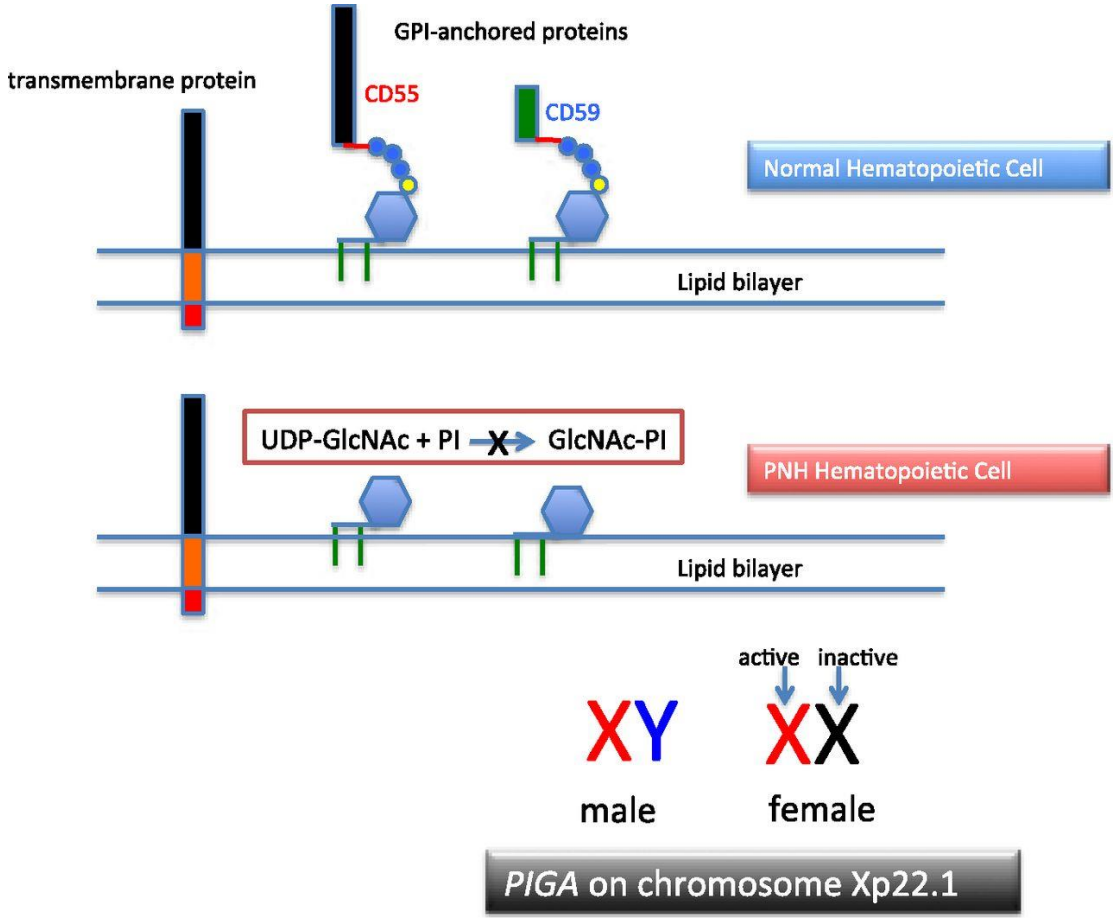
June : acute abdominal pain

- Thrombocytopenia
- Regenerative anemia (ARC 150.000)
- Undetectable Haptoglobin, elevated bilirubin
- Coombs negative, no schizocyte

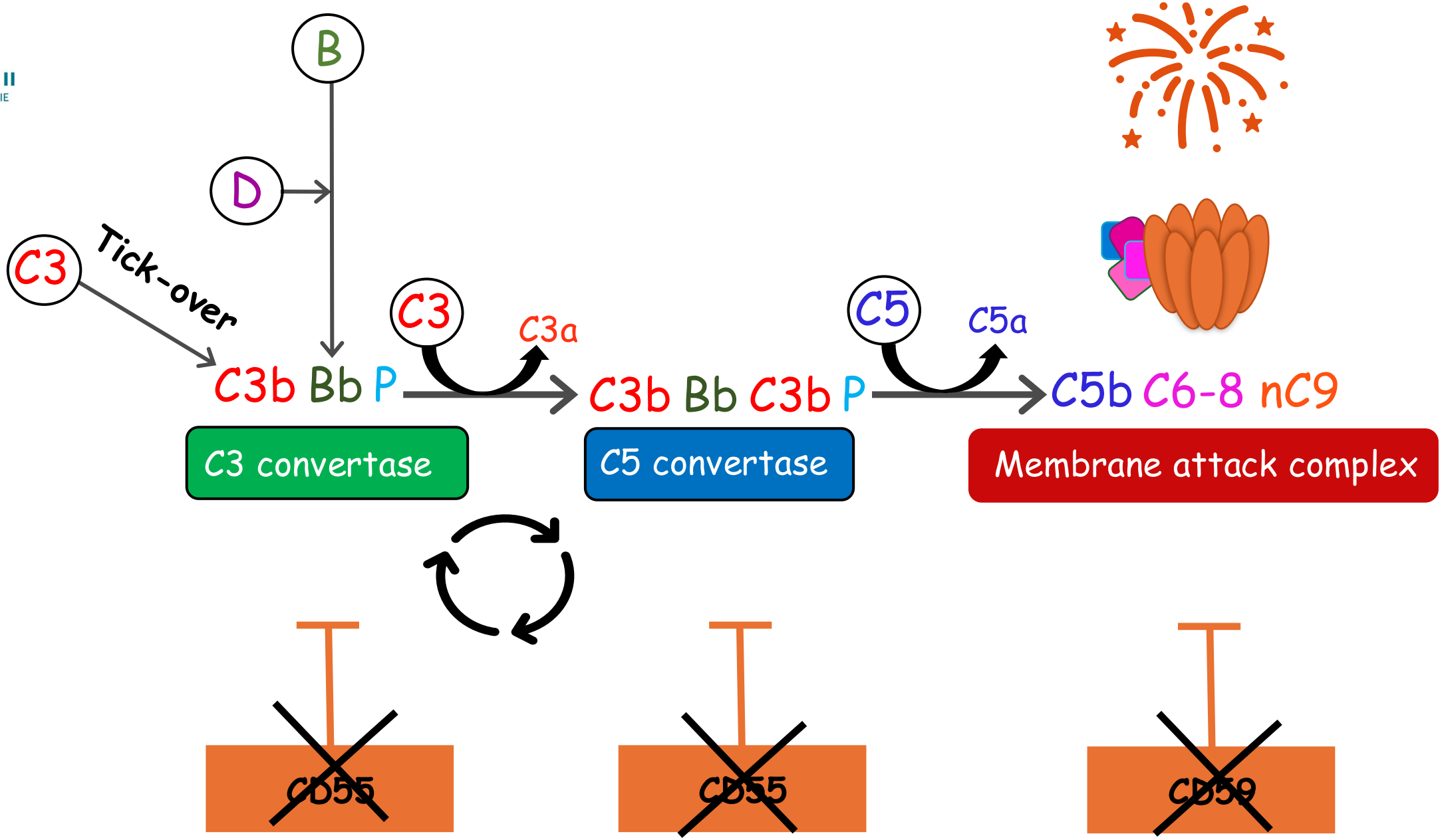
PNH physiopathology : PIGA mutation



Red Blood Cells
Platelets
White Blood Cells



Brodsky *Blood* 2015, Parker *Blood* 2016, Risitano et al *Front Immunol* 2019



Brodsky *Blood* 2015, Parker *Blood* 2016, Risitano et a *Front Immunol* 2019, Lee et al *Exp Rev Clin Parmacol* 2022, Risitano *Immunol Rev* 2022

PNH : Symptoms

Adapted from Brodsky 2005, Rother et al *JAMA* 2005

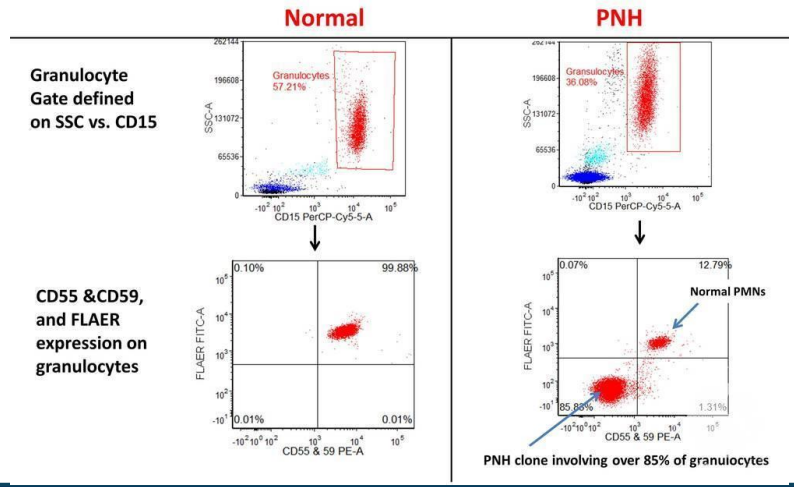
PNH : diagnosis

When : CATCH criteria

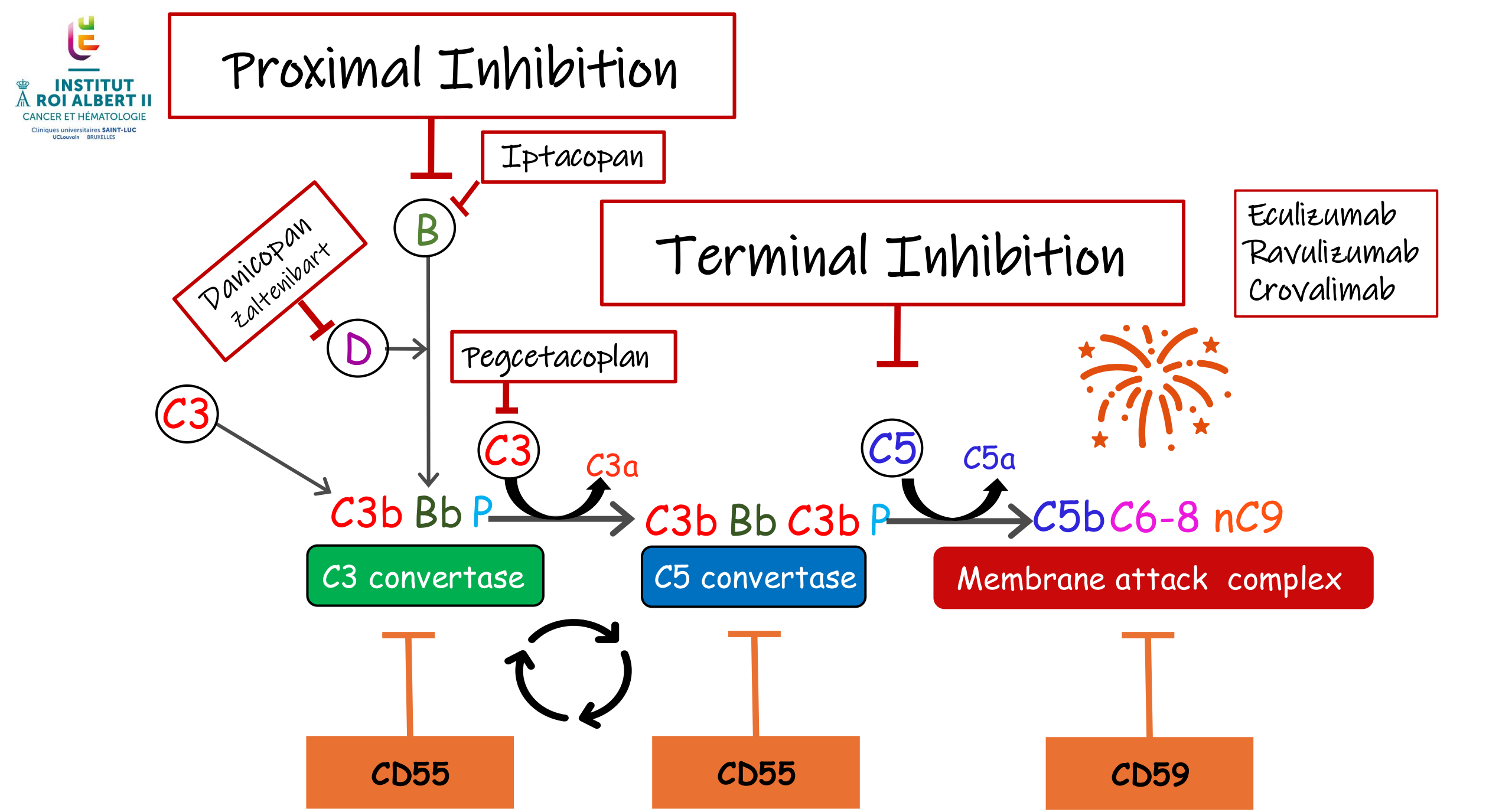
- Unexplained **C**ytopenia
- **A**plastic anemia, hypoplastic MDS
- Unprovoked and/or unusal site **T**hrombosis
- **C**oombs-negative hemolysis
- Unexplained **H**emoglobinuria

How : Flow cytometry

- At least 2 markers (CD55, CD59, Flaer)
- At least 2 cell lineages
  - Type III : RBC totally deficient in GPI anchor
  - Type II : RBC partially deficient in GPI anchor
  - Type I : normal RBC

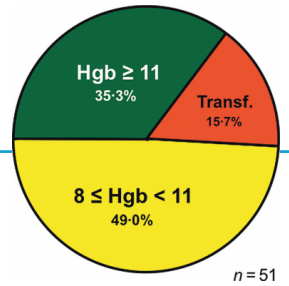


Patriquin et al *Eur J Hematol* 2019, Brodsky et al *Blood* 2009


Proximal Inhibition
Iptacopan
B
Danicopan
Zaltenibart
D
Terminal Inhibition
Eculizumab
Ravulizumab
Crovalimab
Pegcetacoplan
C3
C3
C3a
C5
C5a
C3b Bb P
C3b Bb C3b P
C5b C6-8 nC9
C3 convertase
C5 convertase
Membrane attack complex
CD55
CD55
CD59

PNH : Terminal inhibition

	Eculizumab Soliris®	Ravulizumab ALXN1210 Ultomiris®	Crovalimab RO7112689 SKY59	Coversin (Nomacopan)	Pozelimab REGN 3918	Zilucopan	Cemdisiran ALN-CC5	Tesidolumab LFG316
Chemistry	mAb	mAb	mAb	Tick saliva protein	mAb	Macrocyclic peptide	RNAi	mAb
Target	C5	C5	C5	C5	C5	C5	Liver C5 mRNA	C5
Route	IV	IV, (SC)	IV, SC	SC	IV, SC	SC	SC	IV
Frequency	1/W x 4, 1/2W	Every 8 weeks	Every 4 weeks	BID	1/W		Weekly-monthly	Biweekly/ monthly
Comments		FcRn sweeping technology Same epitope	FcRn and C5 sweeping technology Other epitope	Bifunctional activity inhibiting C5 + Leukotriene		Not taken foward in Ph. III	Inadequate in monotherapy	



Kulasekararaj et al, Am J Hematol 2023

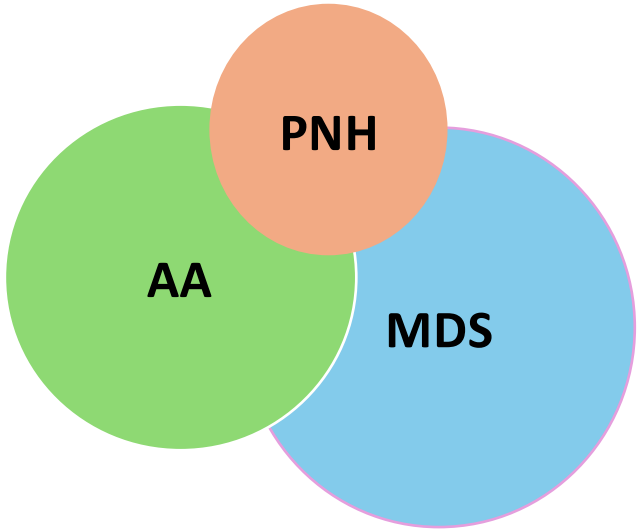
Non inferior
Reimbursed

Meningococcal vaccination

Adapted from Peffault de Latour, 2019

PNH : persistent anemia

AA-related

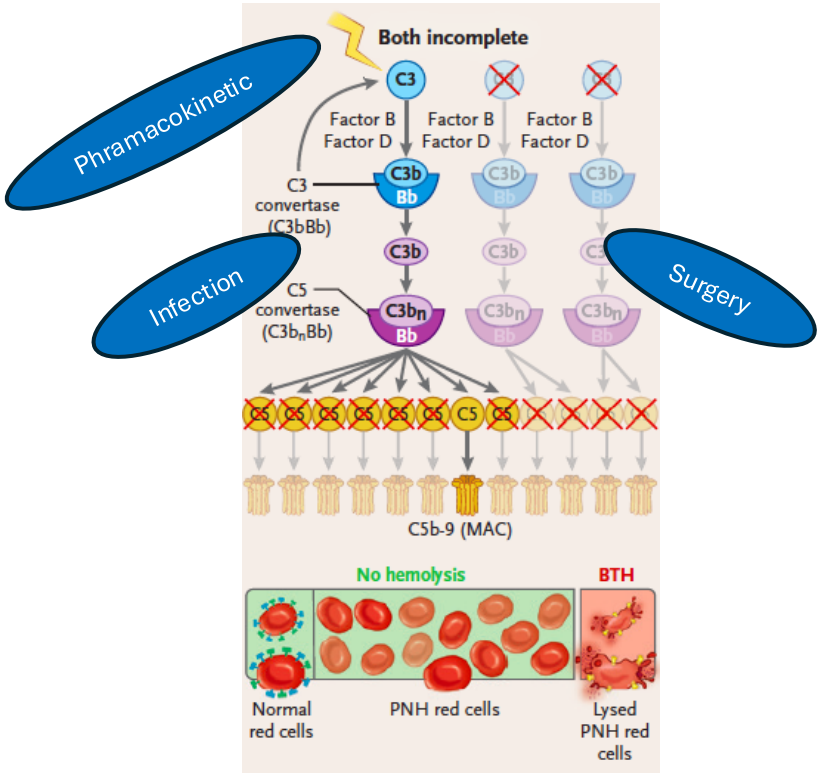


Ferritin/folates/Vit B12

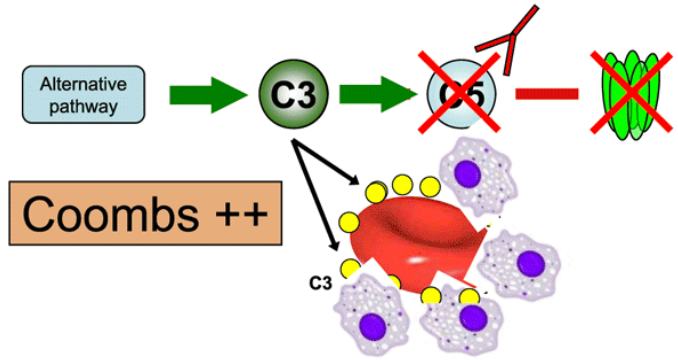
BM/18m

BTH

Chronic/Acute, LDH > 2 ULN, PNH symptoms, Hgb drop



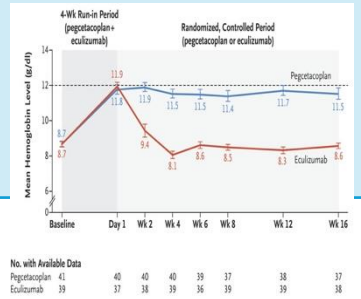
EVH



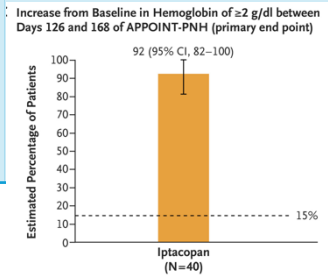
10-30%
C3d by Flow or C3d Coombs
LDH ≤ 1.5 ULN
Rc ≥ 100 x 10^9/L

PNH : proximal inhibition

	Apellis - Sobi	Alexion	Novartis	Omeros
	Pegcetacoplan APL-2	Danicopan ALXN2040	Iptacopan LNP023	Zaltenibart **OMS 906**
Chemistry	Cyclic peptide pegylated	Small molecule	Small molecule	MoAB targeting MASP-3
Target	C3	Factor D	Factor B	**ProFactor D**
Administration	SC	oral	oral	**SC**
Frequency	Twice/W	TID	BID	**1/4W**



Add-on

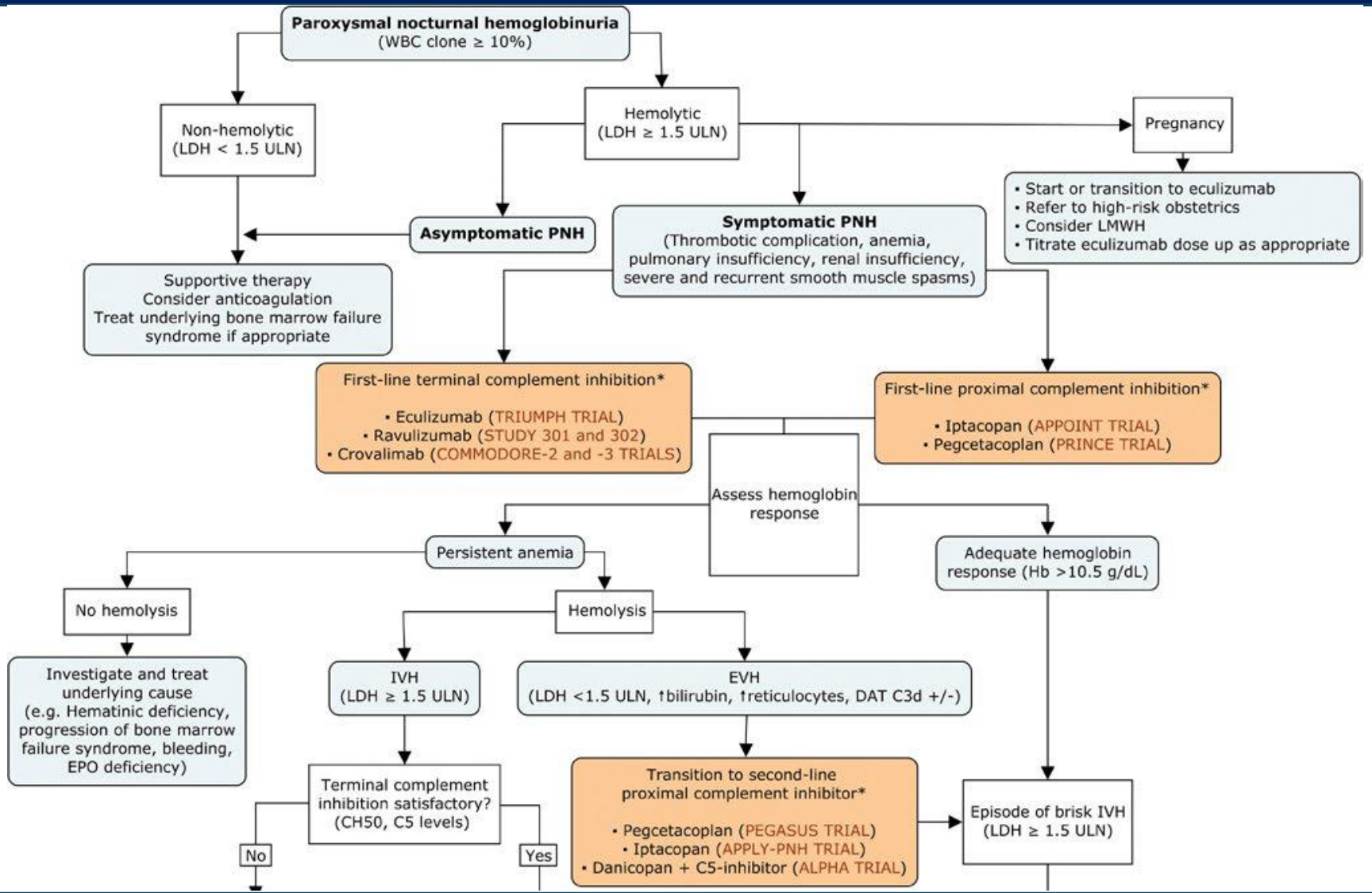


Vaccines
MenB+PCV+HIB

Kulasekararaj et al, Am J Hematol 2023; Karnabeda et al *Blood* ASH 2023

Adapted from Peffault de Latour, 2019

PNH Management



Bienz ASH 2025

References

1. A. Kulasekararaj, J. Cavenagh, I. Dokal et al. Guidelines for the diangosis and management of aplastic anemia: A British Society fo Haematology Guideline. Br J Haematol. 2024;204:784-804

2. P. Scheinberg. Progress in medical therapy in aplastic anemia: why it took so long? Int Journal of Hemato. 2024;119:248-254

3. R. Iftikhar, Z. DeFilipp, A. DeZern et al. Allogeneic Hematopoetic Cell Transplantation for the Treatment of Severe Aplastic Anemia: Evidence-based Guidelines from the American Society of Transplantation and Cellular Therapy. TCT. 2024:30;1155-1170

4. A. Risitano and R. Peffault de Latour. Br J Haematol. 2022:196;288-303

5. R. Notaro and L. Luzzato. New Eng J Med. 2022:387;160-166