

# **Not So Benign Hematology**

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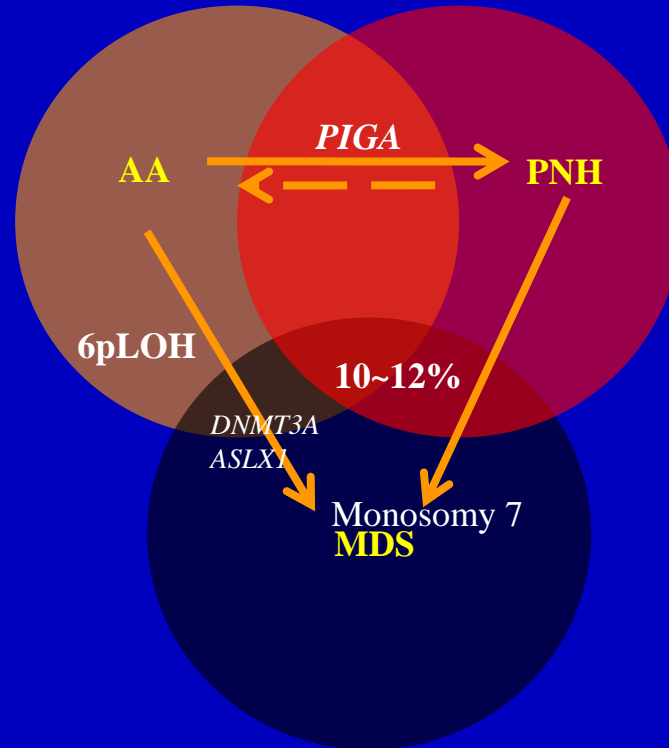
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**Division Chief Hematology**

# Disclosures

- Dr. Brodsky serves as a Scientific Advisory Board member to:
  - Alexion Pharmaceuticals
  - Achillion Pharmaceutical
  - Apellis Pharmaceuticals
- Grant funding:
  - NHLBI
  - Alexion

# Acquired SAA is an Acute and Chronic Disease



➤ Autoimmune attack on stem cells  
Predisposes to clonal  
escape/malignancy

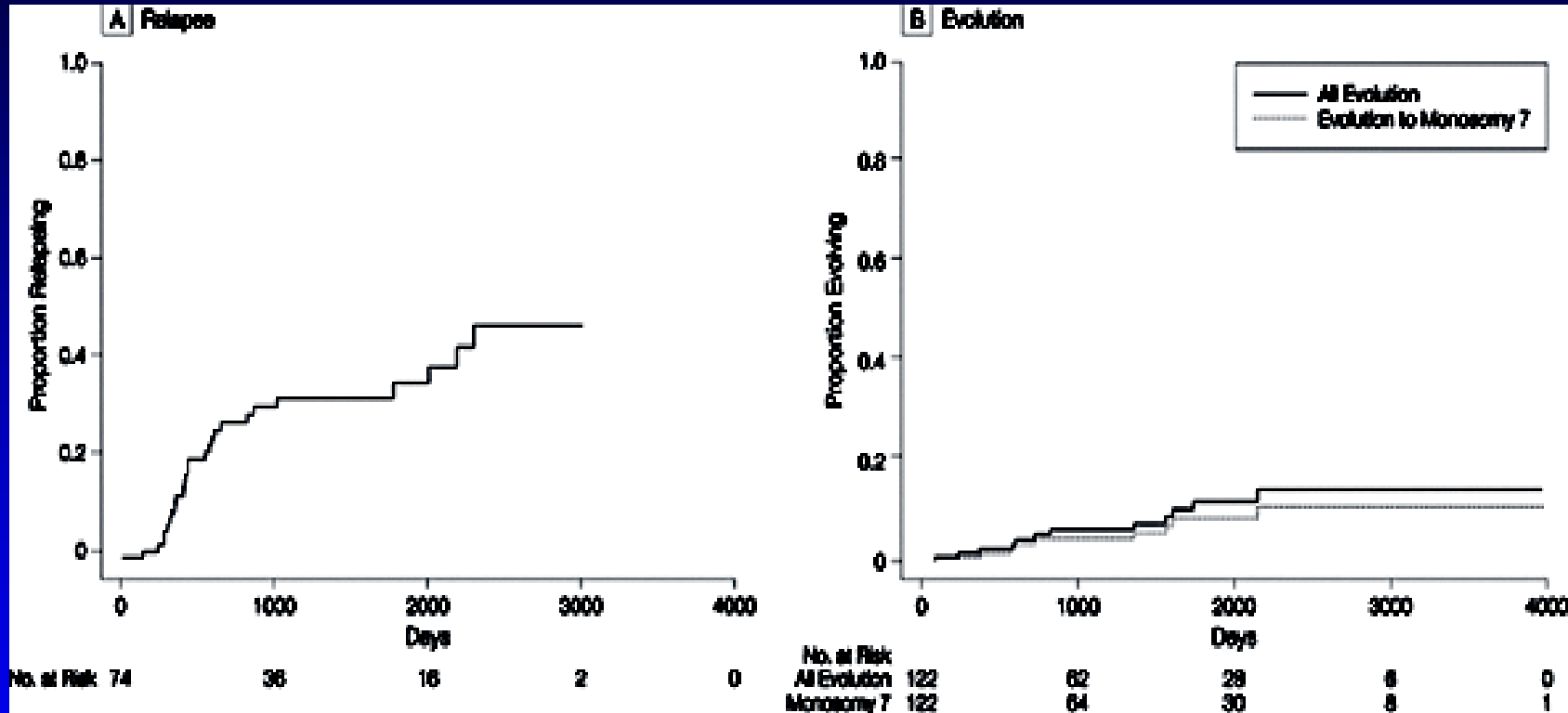
➤ Clonality often present at Dx

# Severe Aplastic Anemia

- **First line therapy**
  - BMT
  - IST (ATG/CSA) +/- eltrombopag
  
- **Refractory Disease (poor response/prognosis)**
  - Eltrombopag
  - Alternative donor BMT
  - Other IST

# ATG/CSA: Late complications

Rosenfeld et. al, Jama 2003;289: 1130-35



Risk of relapse > 40% in responders

Risk of clonal evolution

**30% failure-free survival**

# Eltrombopag in Refractory SAA

43 patients  
Just 17 remained  
on drug

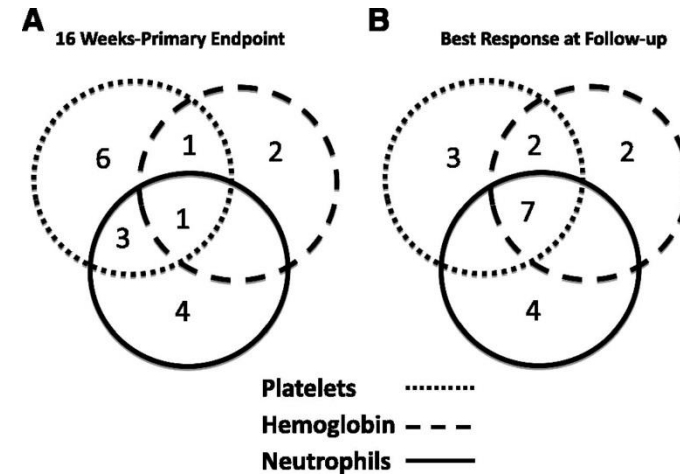
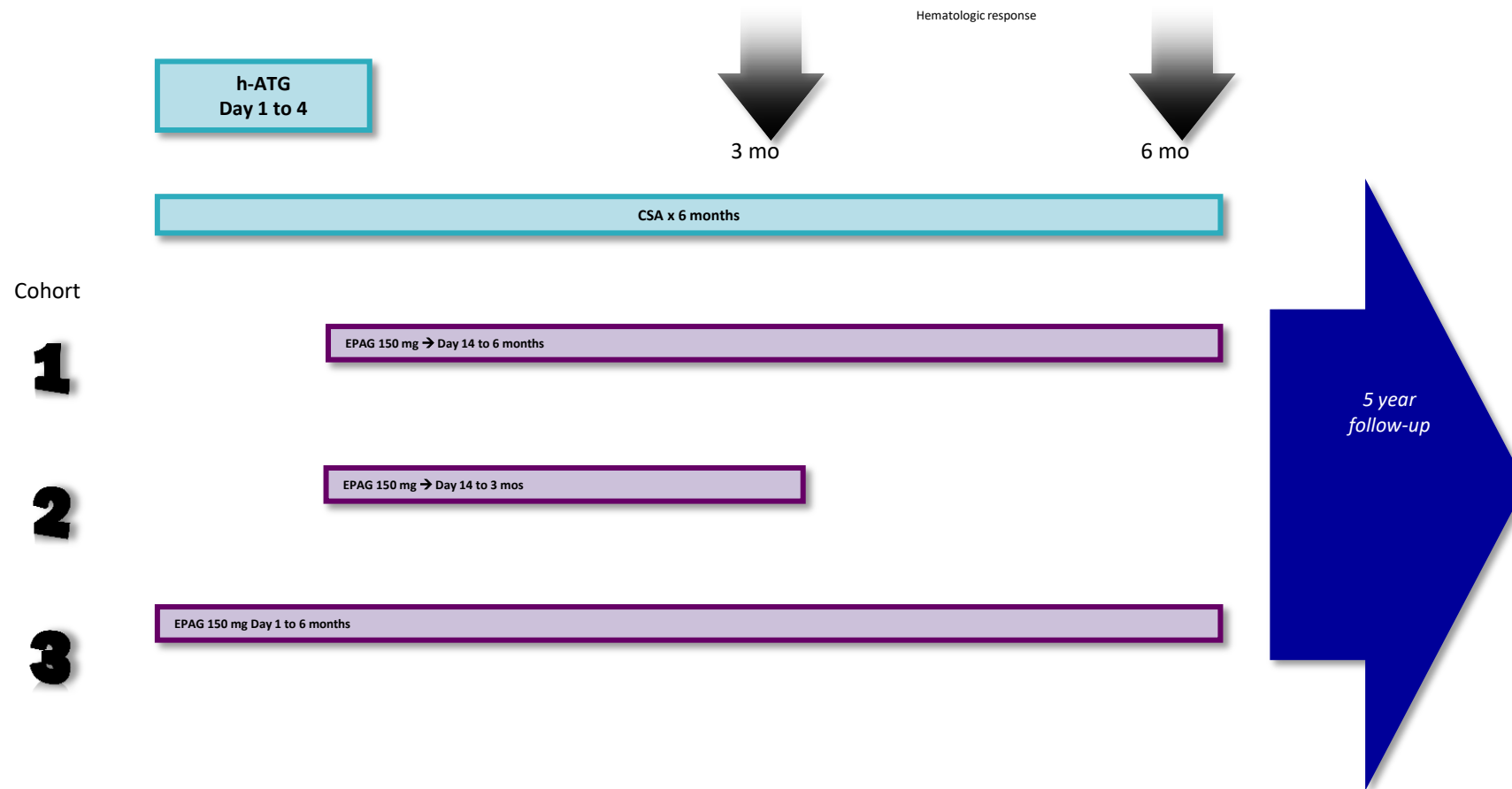


Table 2. Characteristics of patients who evolved while on eltrombopag

Patient #	Age (y)	Response	Baseline	At evolution	Time on eltrombopag (mo)	Dysplasia	Outcome	Time posttransplant (mo)
7	60	NR	46XY[20]	-7[20]	3	N	Died of progressive cytopenias	N/A
8	18	NR	46XX[6]	+8[9]/46XX[11]	3	N	Transplanted successfully	31
19	20	NR	46XY[20]	-7[5]t(1;16) [3]/46XY[12]	3	N	Transplanted successfully	18
26	67	R	46XY[20]	del(13)[19]/46XY[1]	13	Mild dyserythropoeisis	Transplanted	8
31	41	NR	46XY[20]	+21[3]/46XY[17] -7[2]/46XY[19]	3 6	Mild dyserythropoeisis	Awaiting transplant	N/A
32	66	R	46XY[20]	46XYdel13q[2]/46XY[18]	9	N	Under observation	N/A
36	23	NR	46XY[20]	-7[5],XY[15]	3	N	Transplanted successfully	3
42	17	NR	No metaphases	+1,der(1;7) [4]/46XY[16]	3	N	Transplanted successfully	4

N/A, not applicable; NR, nonresponder; R, responder.

# ELTROMBOPAG ADDED TO STANDARD IMMUNOSUPPRESSION AS FIRST TREATMENT IN APLASTIC ANEMIA



# ATG/CSA/EPAG: Response Rates

	Cohort 1 N=30	Cohort 2 N=31	Cohort 3 N=31	All Cohorts N=92	Historic IST N=388*
	N (%)	N (%)	N (%)		
<b>3 months</b>				<b><u>86/92</u></b>	
OR	23 (77)	24 (77)	<b>23/25 (92)</b>	<b>81%</b>	<b>60%</b>
CR	5 (17)	8 (26)	<b>11/25 (44)</b>	<b>28%</b>	<b>8%</b>
<b>6 months</b>				<b><u>81/92</u></b>	
OR	24 (80)	27 (87)	<b>19/20 (95)</b>	<b>86%</b>	<b>63%</b>
CR	10 (33)	8 (26)	<b>12/20 (60)</b>	<b>37%</b>	<b>12%</b>

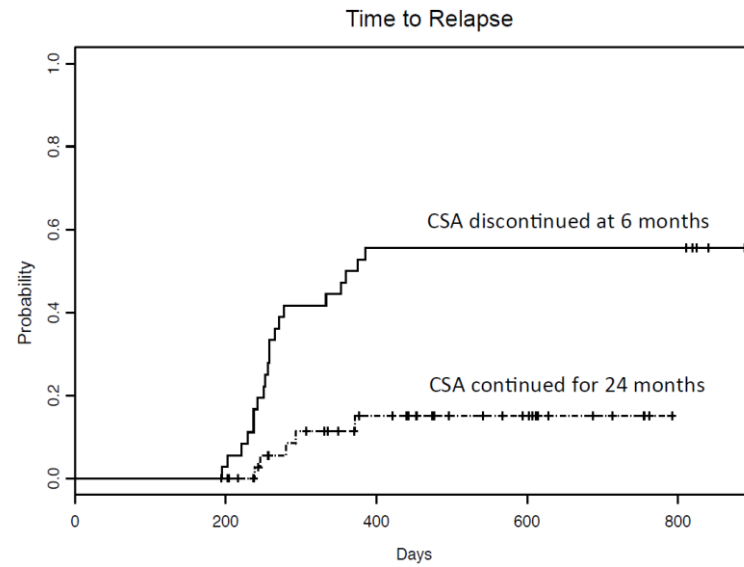
## Supplemental methods:

The protocol was amended starting with subject # 46 on cohort 2, so that cyclosporine was continued at a fixed daily dose, 2mg/kg/day, for an additional 18 months in order to prevent relapse.



# Supplemental Figure 4

Median follow-up 23 months



No. at risk:

CSA discontinued	92	35	17	16	16
CSA continued	92	43	24	11	1

## Cytogenetic abnormality of unclear significance

68	CR	3	46, XX, del(13)(q12q22)[cp3]/46,XX[17]	No	Cytogenetics normalized
39	CR	30	48, XX +6 +15 [2]/ 46,XX[18]	No	CR stable

## Chromosome 7 abnormality

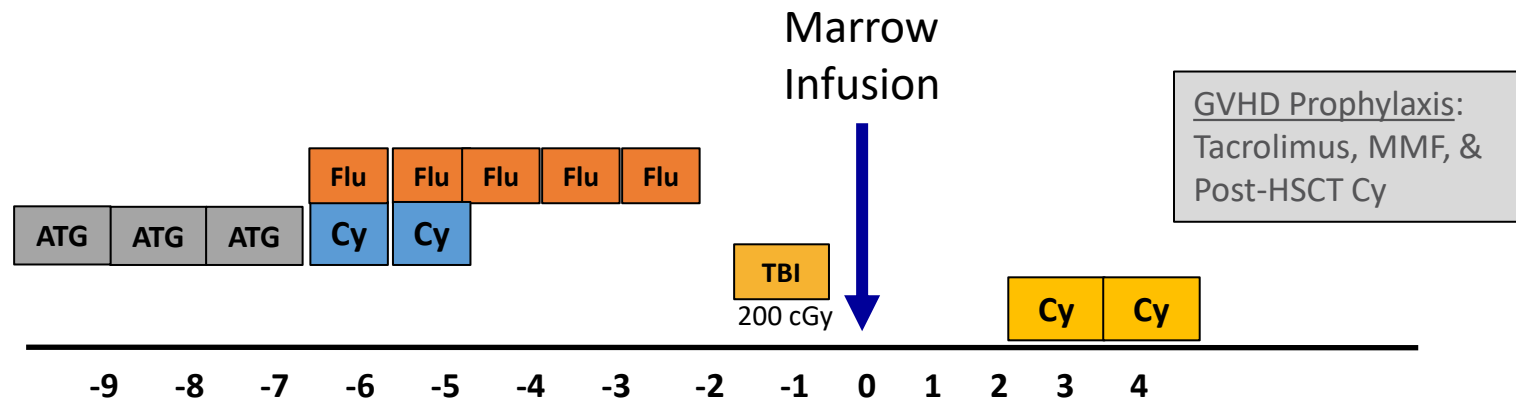
64	PR	3	45,XX,t(3:3)(q21;q26),-7[3]/ 46, XX[17]	Yes	AML, death post-HSCT*
72	PR	30	45, XY, -7[20]	Yes	PR stable
48	CR	6	46,XX,del(7)(p13p15)[3]/46,XX[19]	No	HSCT
61	PR	6	45, XX,-7[7]/46,XX[16]	Yes	Awaiting HSCT
16	NR	3	45, XY,-7[6]/46,XY[14]	No	HSCT*

## Reduced intensity haploidentical BMT with post-transplant Cyclophosphamide (CY)

- **Mitigates GVHD**
- **Allows for greater use of alternative donors (haplo BMT)**
  - **No difference for engraftment or GVHD btw matched sibs and HLA-haplo identical donors**
- **Average person in US has >4 HLA haplo-identical donors**

# HLA Haplo-identical BMT for Refractory SAA

## DeZern et al, Johns Hopkins



- Flu** = Fludarabine 30 mg/m<sup>2</sup> IV daily
- Cy** = Cyclophosphamide 14.5 mg/kg IV daily
- Cy** = Cyclophosphamide 50 mg/kg IV daily
- ATG** = Thymoglobulin 0.5 mg/kg (day-9) & 2 mg/kg (day -8,-7)

# Alternative donor BMT with PTCy Cures Refractory SAA

- **21 patients with refractory SAA (median f/u 24 mos (range 3-72))**
  - Median age: 33 years (range 5-69)
  - 15/21 had evidence of clonality (PNH and/or cytogenetic abnormality)
  - 18 haplo 1 mmURD(9/10) 2 URD (10/10)
- **Rapid and consistent engraftment**
  - ANC 15 days                      Reds 25 days                      Platelets 28 days
  - Day 60 chimerism 100% in 20/21 patients
    - One primary graft failure (engrafted with 2<sup>nd</sup> BMT from different donor)
- **Excellent Disease Free Survival**
  - All 21 alive, transfusion-independent, without clonality (KPS 100)
  - Acute GVHD grade II-IV 2/21 (9.5%)
  - Extensive chronic GVHD 0/21
  - All off IST

# Conclusions

- **Eltrombopag appears to increase early response rate when added to ATG/CSA**
  - data too early on relapse/clonality/survival
  - adds >100K to cost
- **Post-transplant Cy safely expands the donor pool in SAA**
  - Patients with refractory SAA should be referred for BMT (BMTCTN 1502)
  - Frontline indications for BMT likely to expand

# Paroxysmal Nocturnal Hemoglobinuria

## Biology

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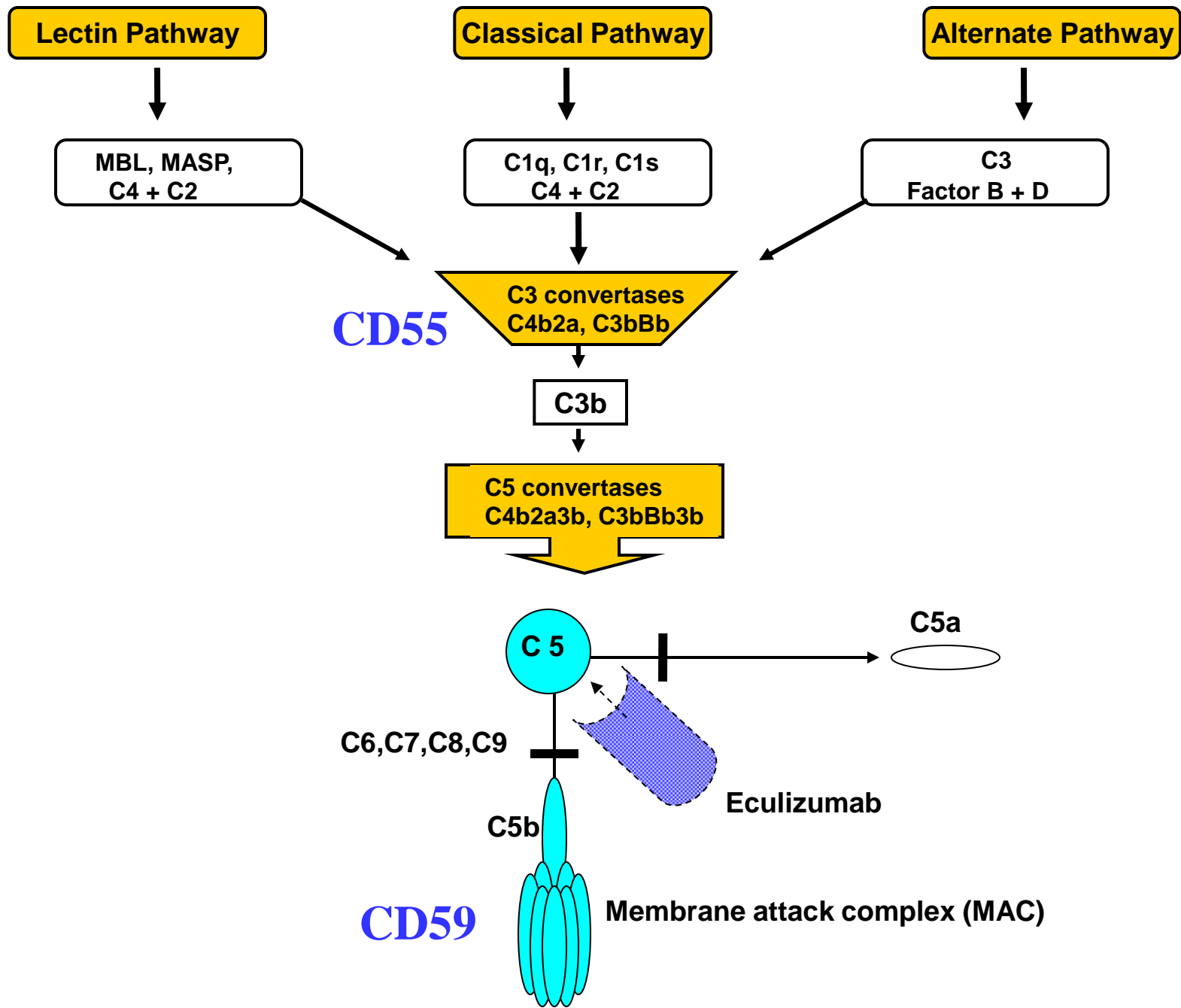
- **Acquired Clonal Hematopoietic Stem Cell Disease**
- ***PIGA* mutation**
  - X(p22.1)
- **PIGA gene product necessary for 1<sup>st</sup> step in the biosynthesis of GPI anchors**
- **PNH cells have deficiency or absence of all GPI anchored proteins**

# PNH

## Pathogenesis of hemolytic anemia

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- **CD59**
  - Prevents incorporation of C9 into C5b-8; thus, MAC does not form
- **CD55**
  - Block C3 convertase
- **Protect cells from complement-mediated destruction**



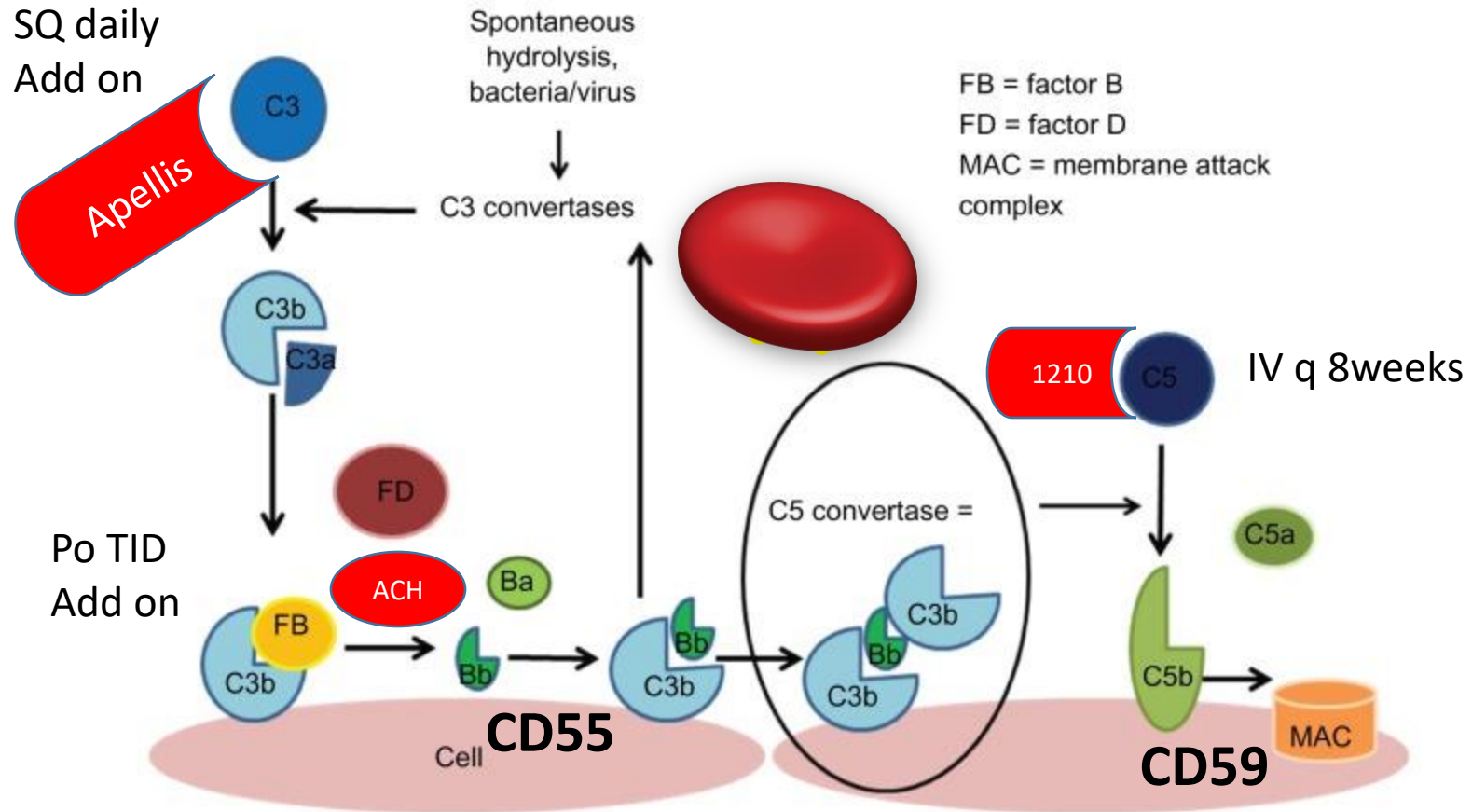


## Limitations of Eculizumab

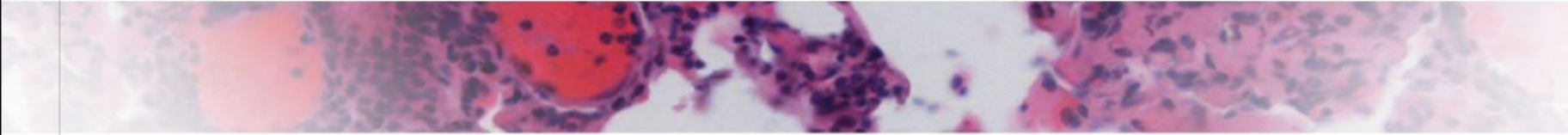
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- **Drawbacks**
  - Risk for meningitis (1K to 2K increased risk or 0.5%/yr)
  - Lifelong therapy intravenous therapy q 14 days
  - Cost (> 400K a year)
  - Up to 20% patients experience symptomatic extravascular hemolysis and require intermittent transfusions

# Next Generation Complement Inhibitors



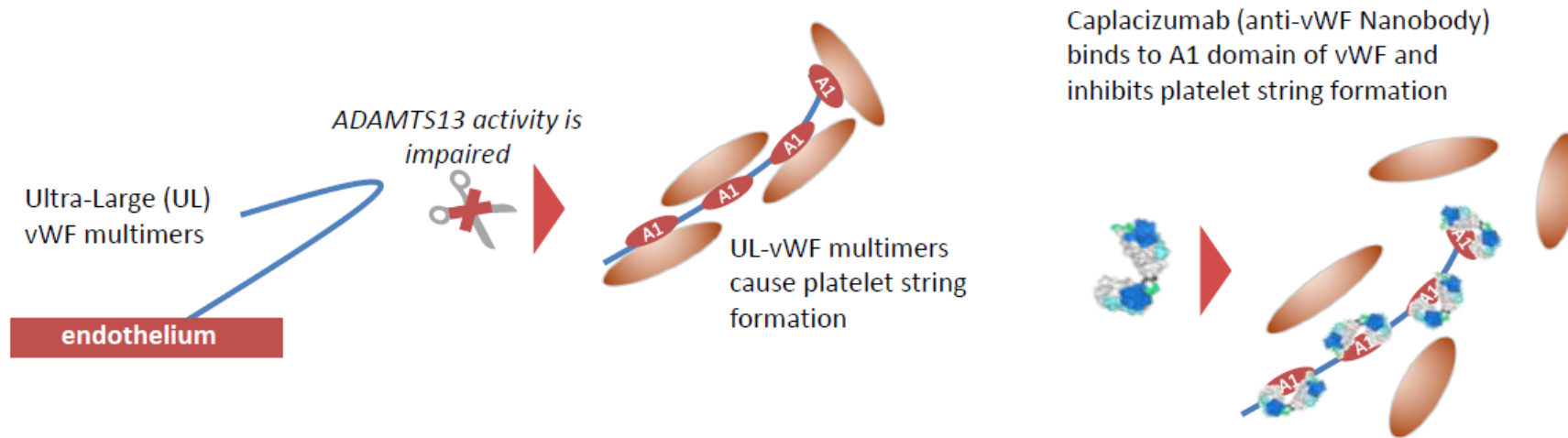
# Caplacizumab



## Results of the Randomized, Double-Blind, Placebo-Controlled, Phase 3 Hercules Study of Caplacizumab in Patients with Acquired Thrombotic Thrombocytopenic Purpura

**Marie Scully**, Spero Cataland, Flora Peyvandi, Paul Coppo, Paul Knoebl, Johanna A. Kremer Hovinga, Ara Metjian, Javier de la Rubia, Katerina Pavenski, Filip Callewaert, Debjit Biswas, Hilde De Winter, Robert K. Zeldin  
*for the HERCULES Investigators*

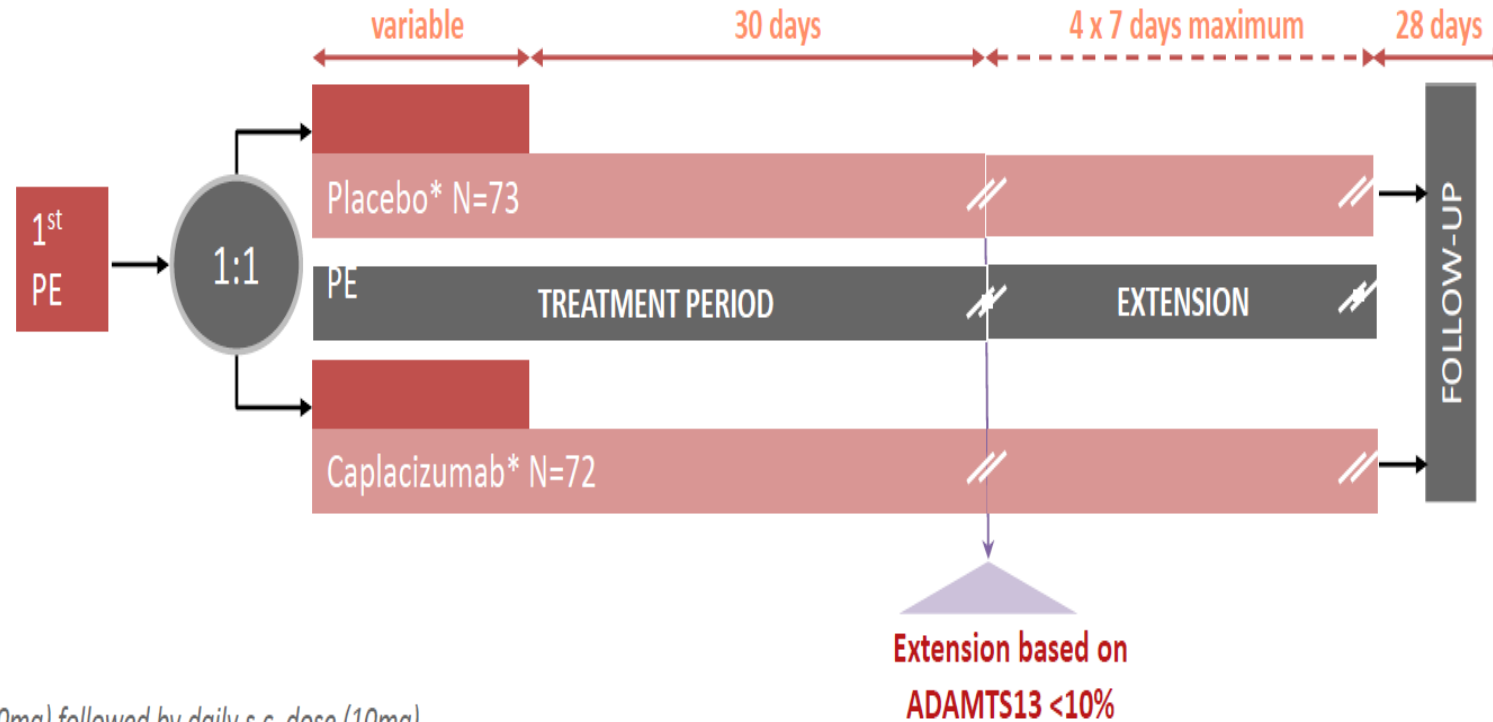
# Caplacizumab



**Caplacizumab blocks the binding of vWF to platelets which has an immediate effect on platelet aggregation and the ensuing formation of microthrombi**

# Caplacizumab - Phase III HERCULES study design

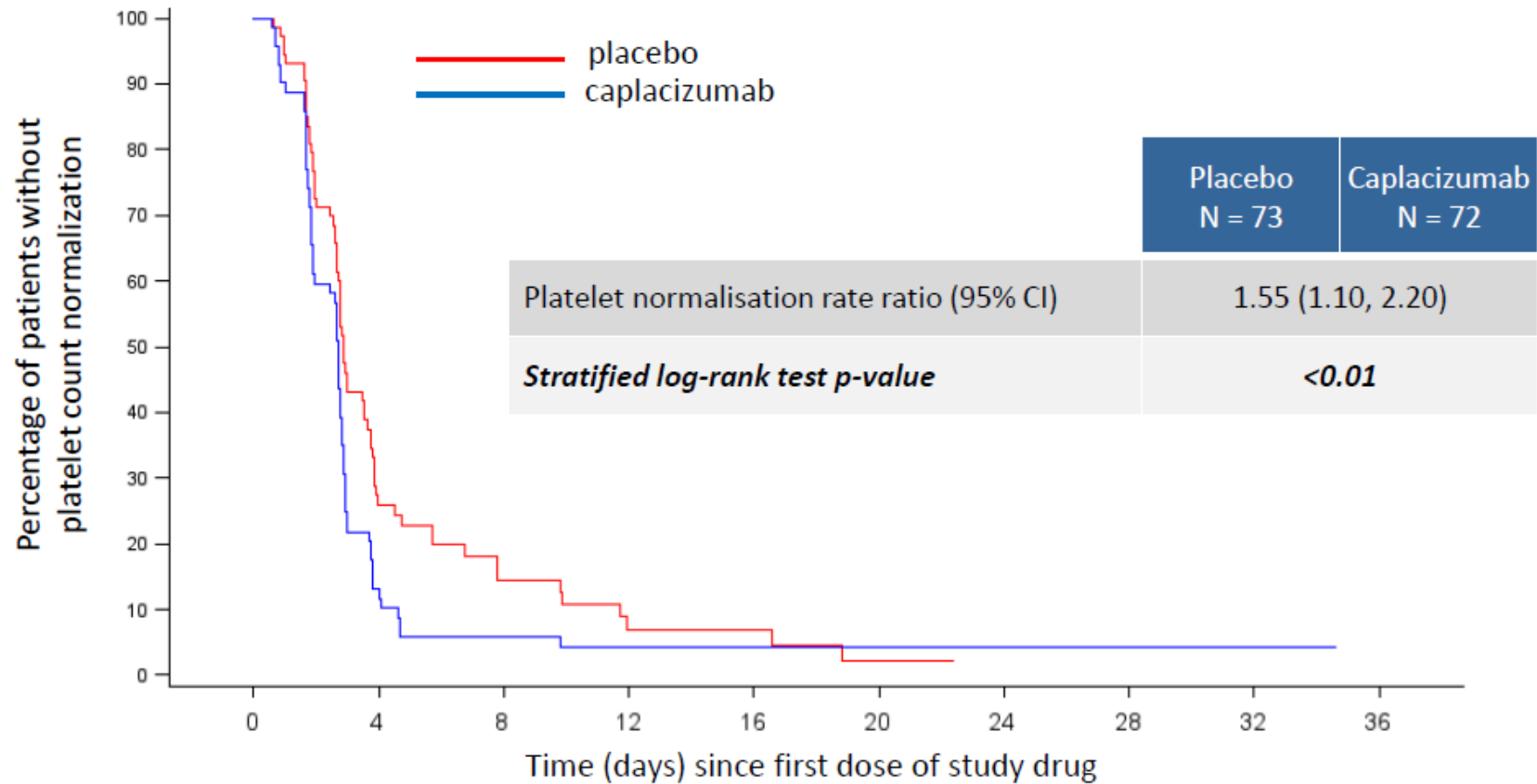
- Randomized, double-blind, placebo-controlled, multi-national study



\* i.v. bolus (10mg) followed by daily s.c. dose (10mg)

PE = plasma exchange

# Primary Endpoint: Time to PLT Response



# Caplacizumab Decreases Vol of PLEX and Days in ICU

## Other secondary endpoints

Plasma exchange parameters, duration of ICU stay and overall hospitalization

Overall study drug treatment period (mean±SE)	Placebo N=73	Caplacizumab N=71	% relative reduction
Number of days of Plasma Exchange	9.4±0.8	5.8±0.5	↓38%
Volume of plasma (L)	35.9±4.2	21.3±1.6	↓41%
Number of days in Intensive Care Unit	9.7±2.1 (n=27)	3.4±0.4 (n=28)	↓65%
Number of days in Hospital	14.4±1.2	9.9±0.7	↓31%

# Conclusions

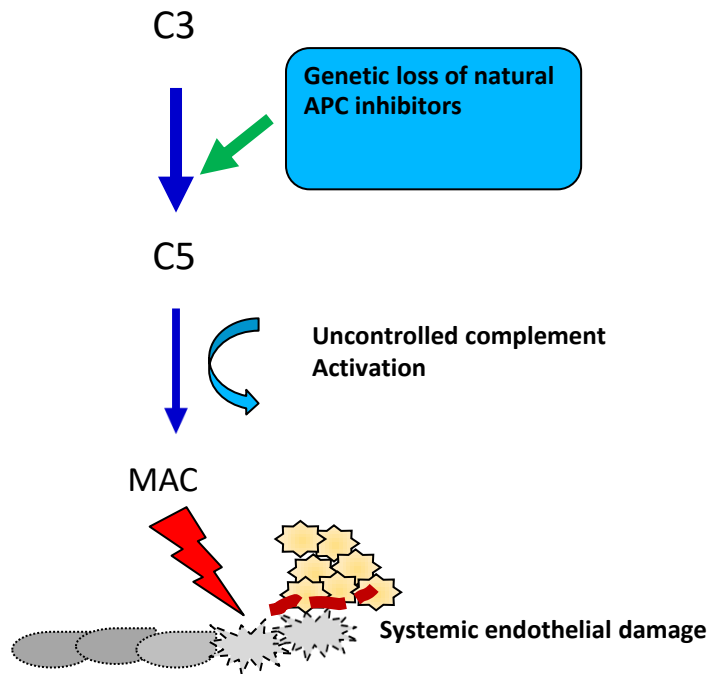
- Shortens time to plt normalization
- Improved **Composite** Endpoint
  - Death, **exacerbation of TTP**, or major thromboembolic event
- Prevention of relapse when treatment extended until resolution of underlying disease
- Reduced use of PLEX and ICU stays



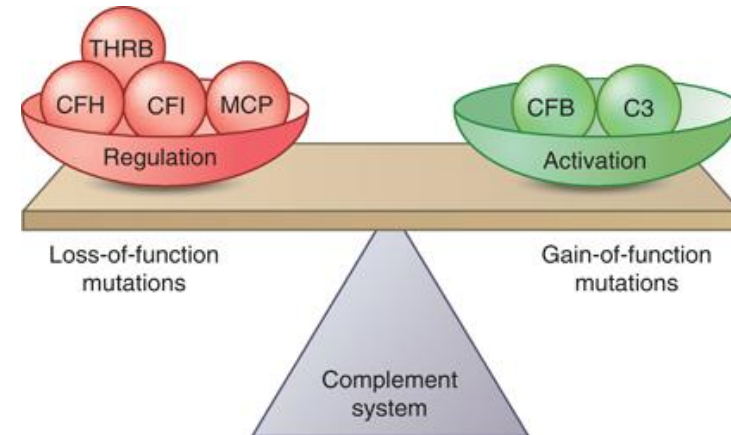
# Caplacizumab: Lots of Questions

- Where does this fit in treatment paradigm?
  - First line? Refractory? Relapse? Maintenance?
- Cost?

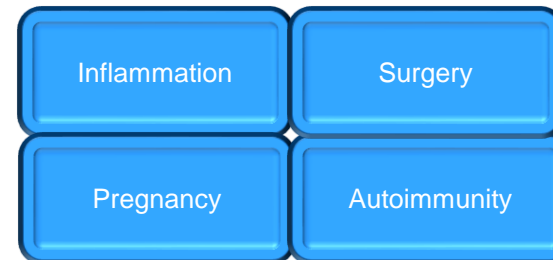
# Atypical Hemolytic Uremic Syndrome: excessive activation of the APC



1



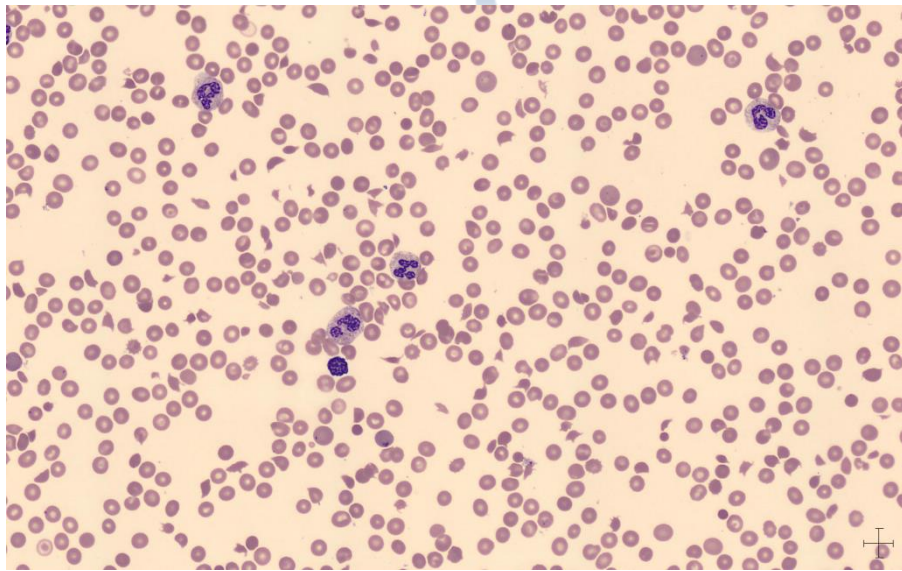
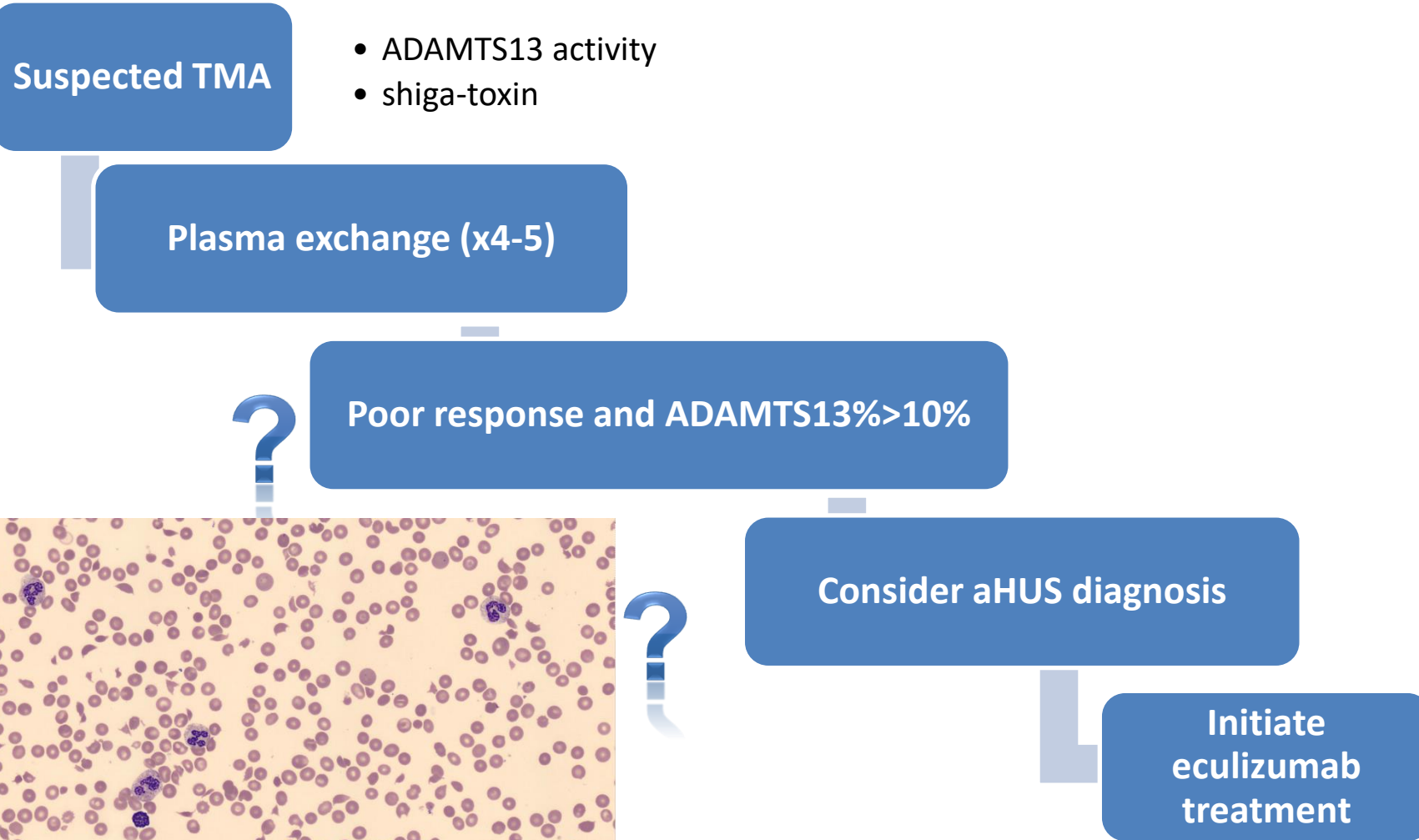
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# aHUS: Genetics

- Germline mutations involving APC genes 50-60% cases
  - ~20% have 2 or more mutations, often heterozygous
- Majority are sporadic rather than familial
  - Even in familial forms penetrance is incomplete
- **KEY CONCEPT:** Genetic mutations in APC regulator genes PREDISPOSE but do NOT cause aHUS

# Atypical hemolytic uremic syndrome (aHUS)



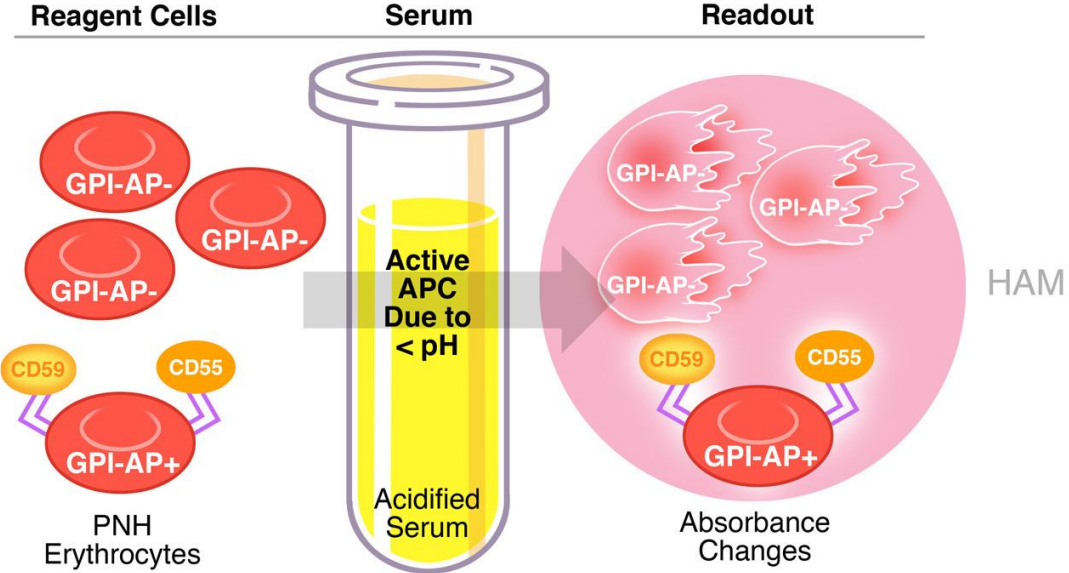
# aHUS: Clinical Conundrums

## 1. Diagnosis of exclusion

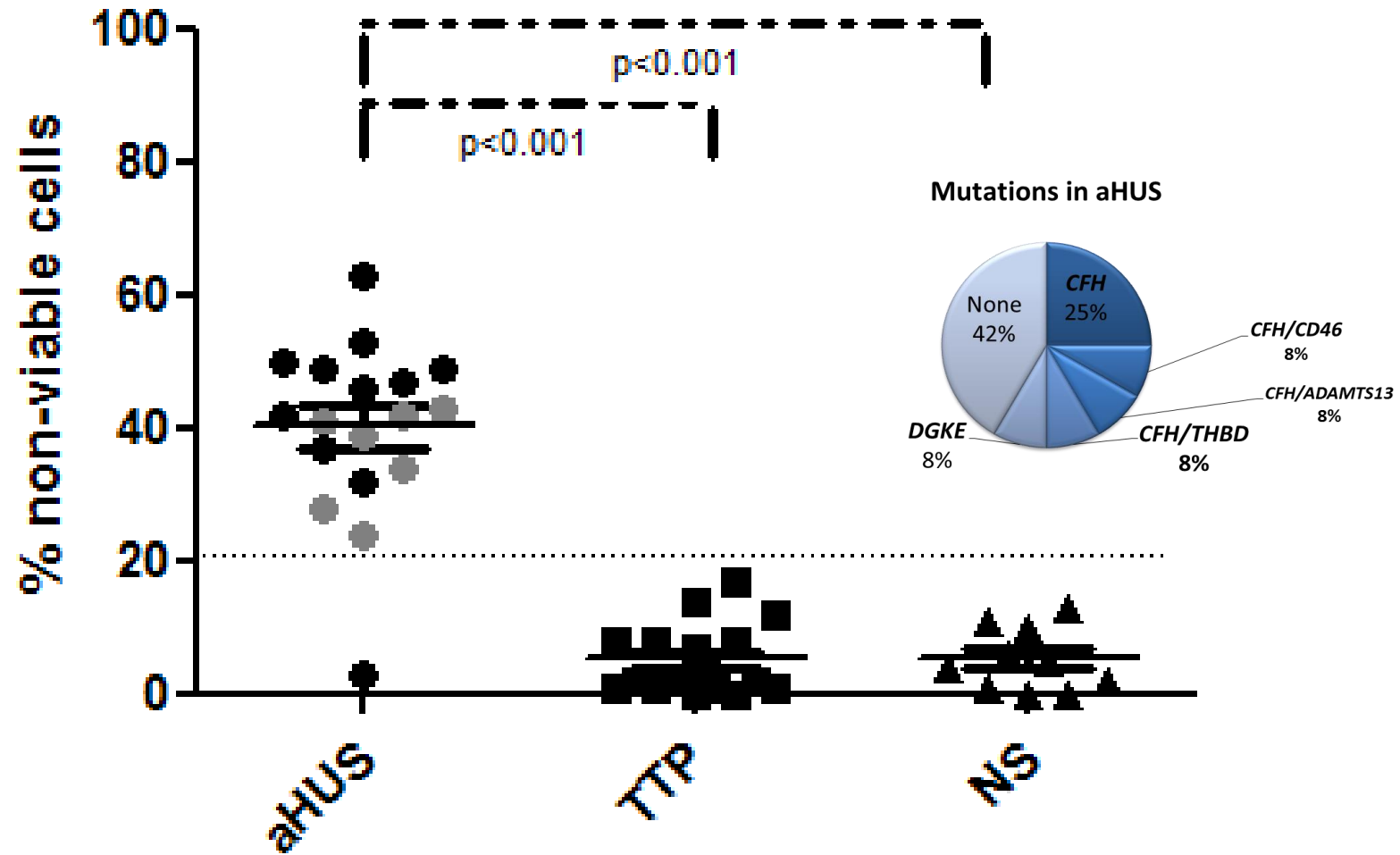
## 2. Expense

- Eculizumab ~ 750K a year for aHUS
- Is lifelong administration required?

# Modified Ham test in aHUS



# Modified Ham Can Distinguish aHUS from TTP



● aHUS on eculizumab

# Eculizumab Cessation in aHUS

- 17 patients (76% female, 70% white)
  - ADAMTS13: 60% (15-102); Hgb 8.3 (3.3-13.3)
- Initial PLEX 64%. All with active aHUS at initiation of ecu
- Median duration of ecu: 90 (14-545) days before stopping ecu
- 2 deaths: 1 while on ecu; 1 with non-adherence

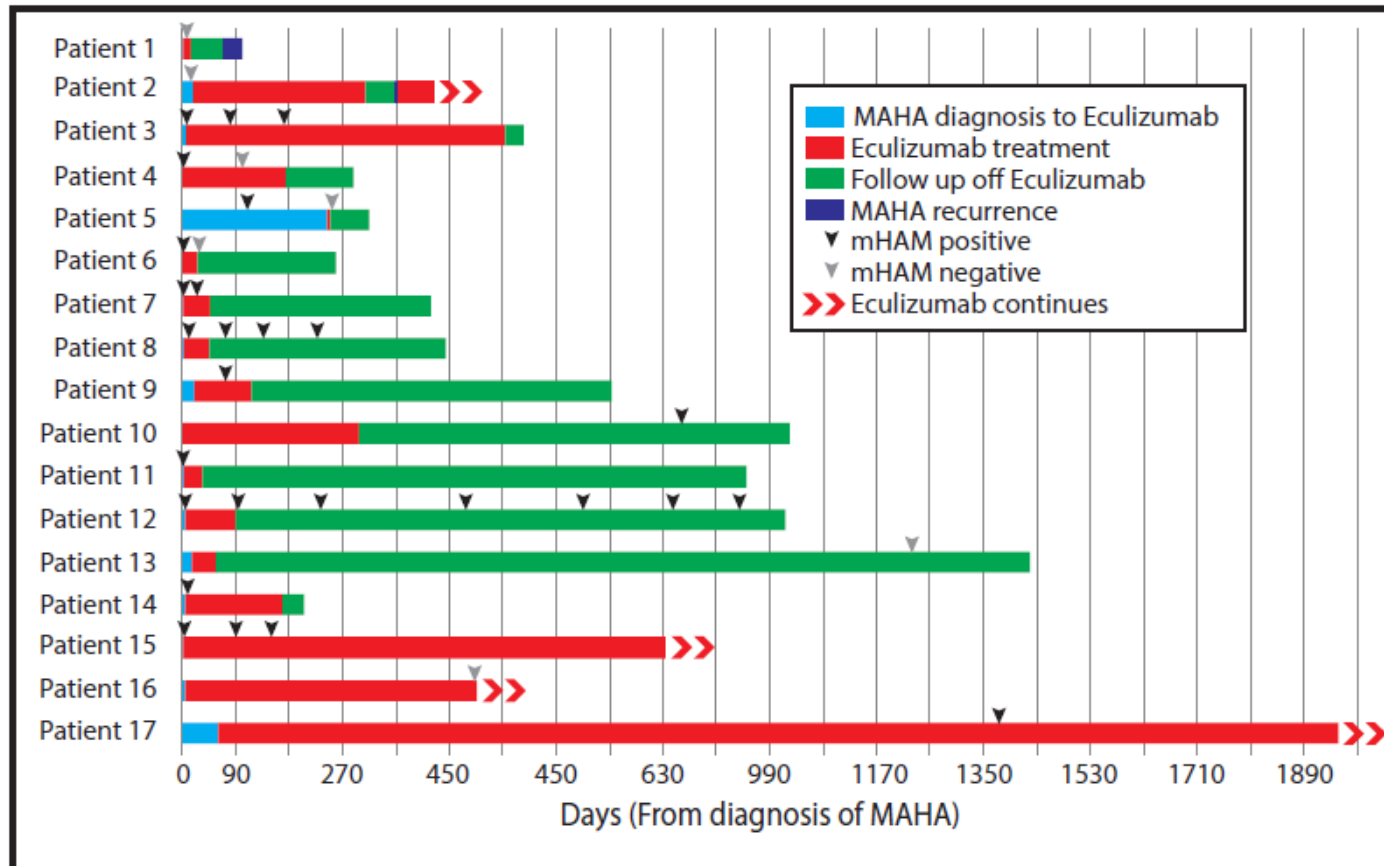


## Eculizumab Cessation Offered to aHUS patients in CR with Mitigation of Putative Trigger

- 15 patients stopped ecu
  - 13 planned
  - 2 Non-adherence
- Relapses: 3 (20%)
  - 2 non-adherent patients
  - **1 planned (7%)**
  - No patient required resumption of dialysis

# Eculizumab can be Discontinued in Most aHUS Patients

Must discuss with patient



Decision points:

- Mutations
- Trigger
- Compliance

Labs

- Cbc, retic, LDH, comp, PBS, CRP
- 2weeks post last dose
- Weekly x 4
- Biweekly x 2
- Monthly x 4

**Approx cost 25K/dose (650K/yr)**  
**Savings > \$13 million**

# Take Home

- **SAA: IST vs BMT**
  - Exciting clinical trials of IST and BMT
  - BMT advancing faster; solves problem of relapse and clonality
- **PNH:**
  - Novel complement inhibitors under development
- **TTP:**
  - Caplacizumab: nanobody that binds A1 domain of vWF
- **aHUS:**
  - Most patients do not require lifelong eculizumab to maintain remissions