Not So Benign Hematology

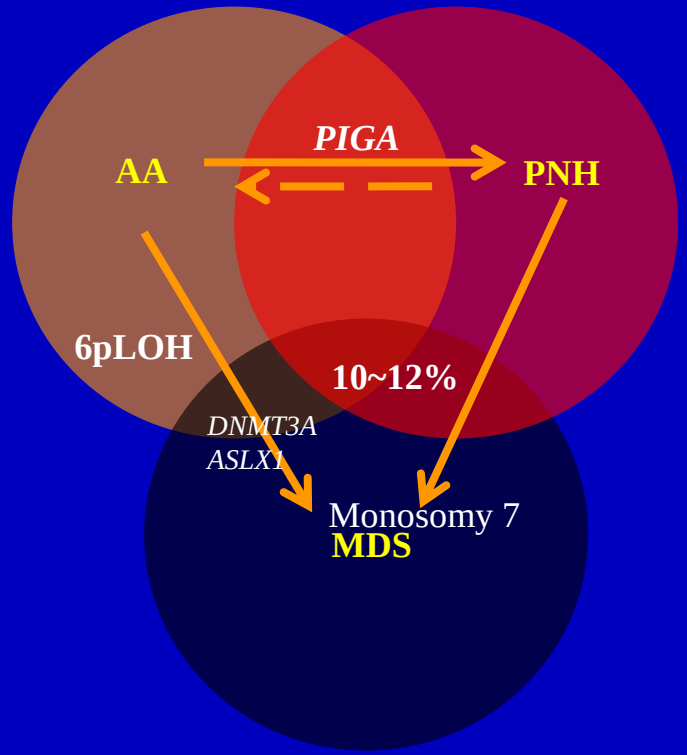
Robert A. Brodsky, MD
Johns Hopkins Family Professor of Medicine and Oncology
Division Chief Hematology

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

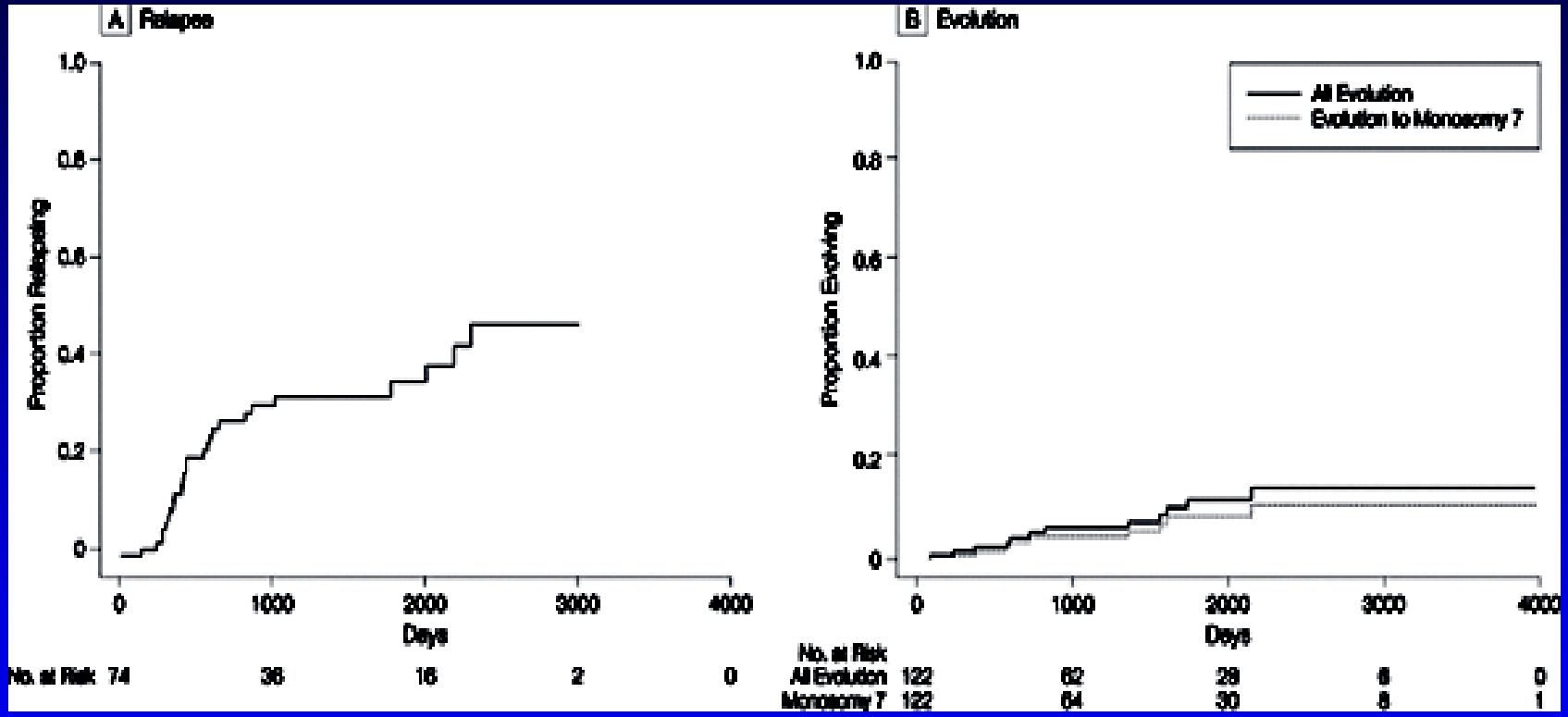
Severe Aplastic Anemia

- 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

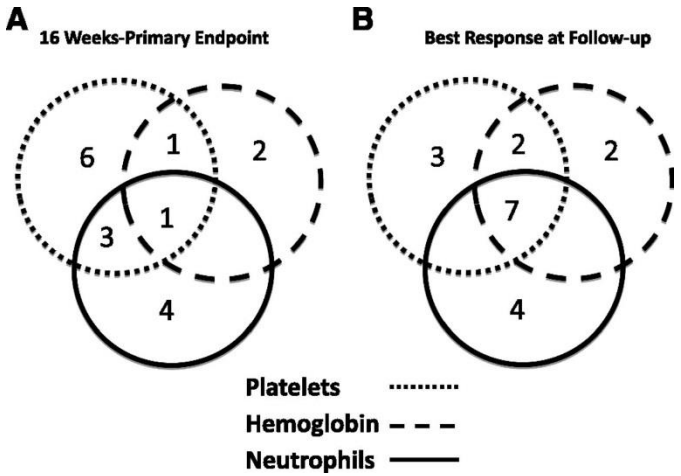


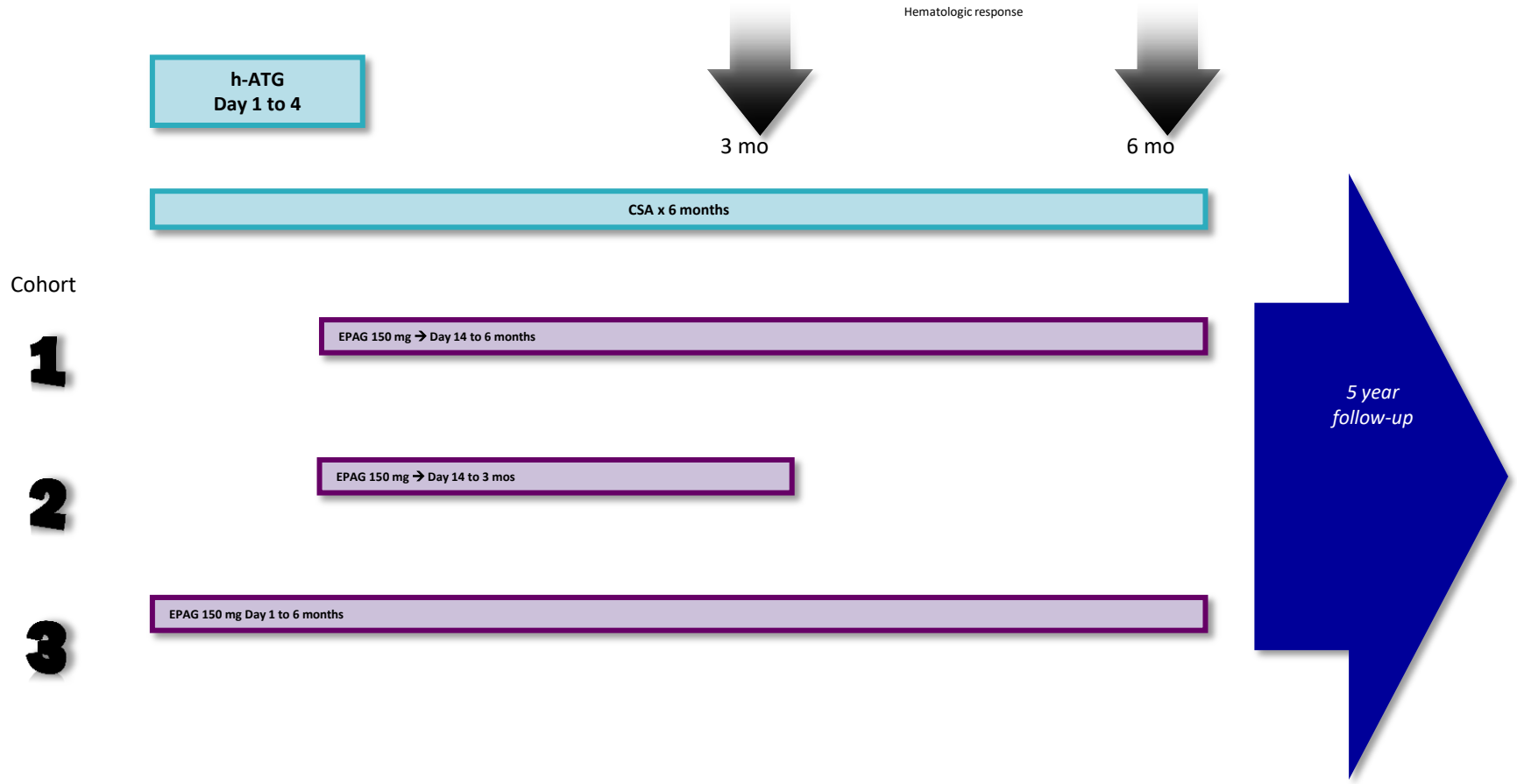
Table 2. Characteristics of patients who evolved while on eltrombopag

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.

Ronan Desmond et al. Blood 2014;123:1818-1825

ELTROMBOPAG ADDED TO STANDARD IMMUNOSUPPRESSION AS FIRST TREATMENT IN APLASTIC ANEMIA



Townsley, DM et al, *NEJM* 2017; 376:1540-50.

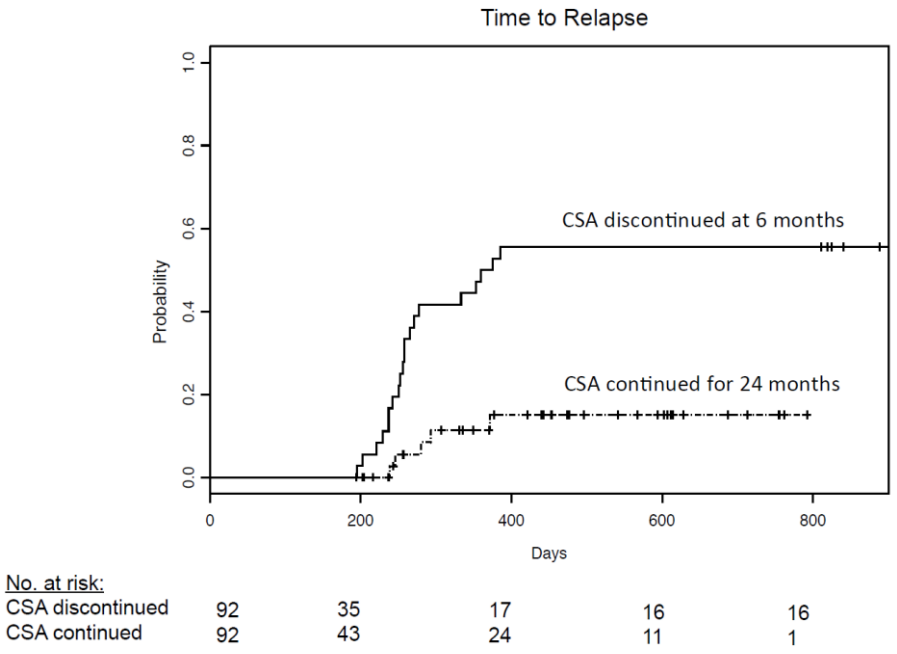
ATG/CSA/EPAG: Response Rates

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

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



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*

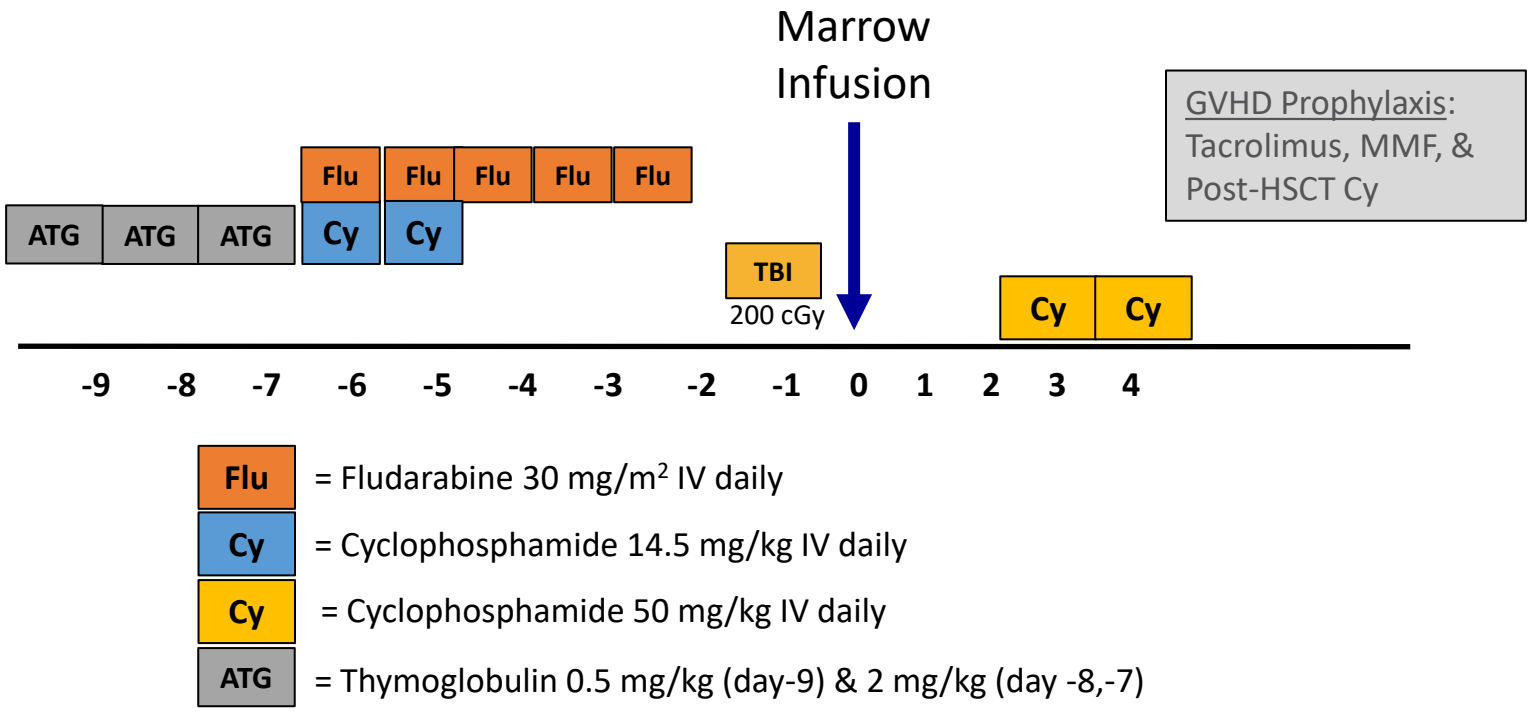
Reduced intensity haploidentical BMT with post-transplant Cyclophosphamide (CY)

- **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



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 2nd 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

Updated internal data and DeZern et al. BBMT 017

JOHNS HOPKINS MEDICINE

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

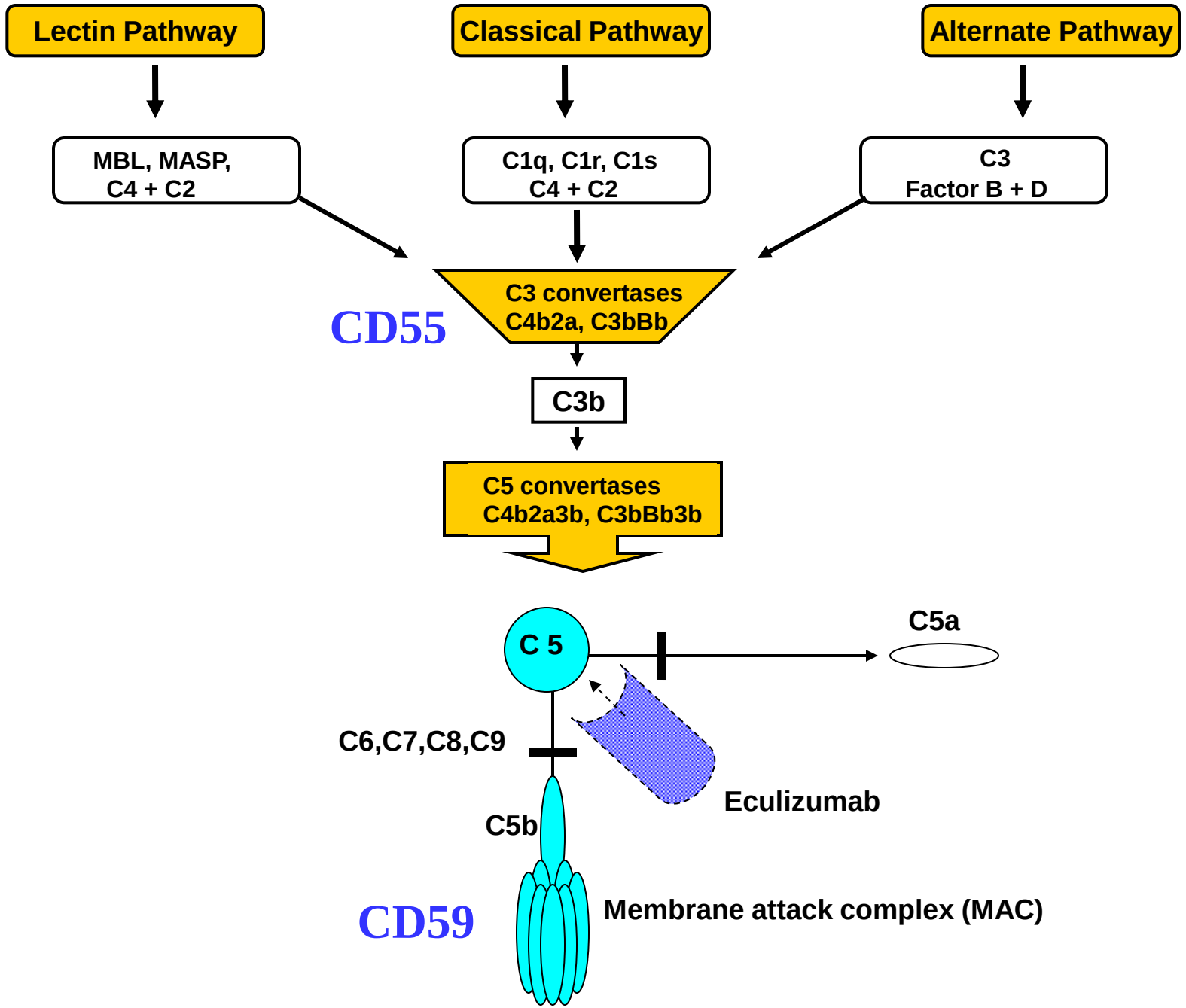
Biology

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

PNH

Pathogenesis of hemolytic anemia

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

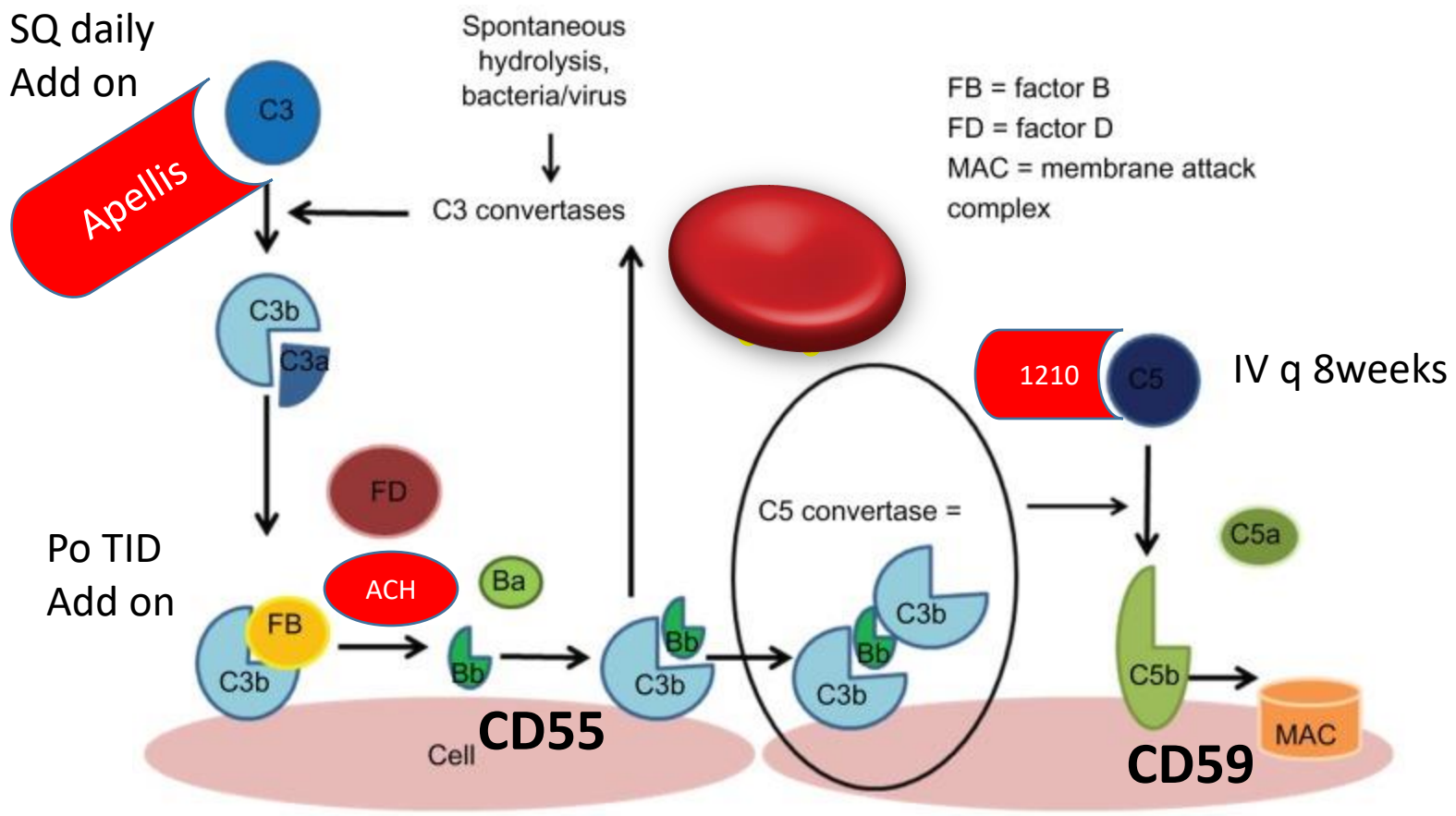

Lectin Pathway
Classical Pathway
Alternate Pathway
MBL, MASP,
C4 + C2
C1q, C1r, C1s
C4 + C2
C3
Factor B + D
CD55
C3 convertases
C4b2a, C3bBb
C3b
C5 convertases
C4b2a3b, C3bBb3b
C 5
C5a
C6,C7,C8,C9
Eculizumab
C5b
CD59
Membrane attack complex (MAC)

Limitations of Eculizumab

- **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**

Hillmen et al, NEJM 2006, 355:1233-43
Brodsky et al, Blood 2008, 111: 1840-47

Next Generation Complement Inhibitors

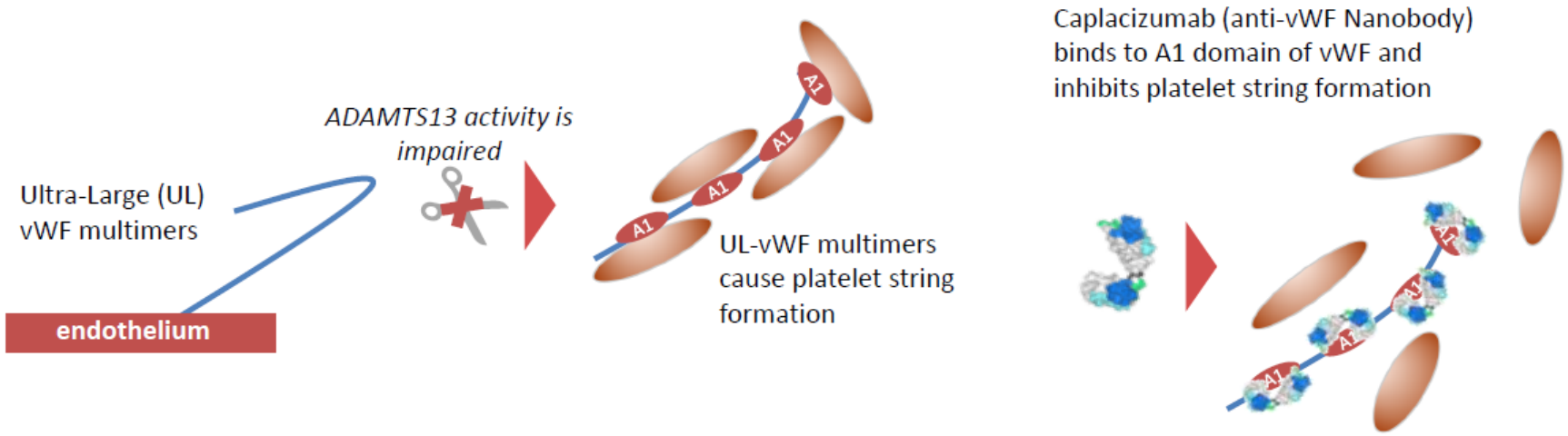


Caplacizumab

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

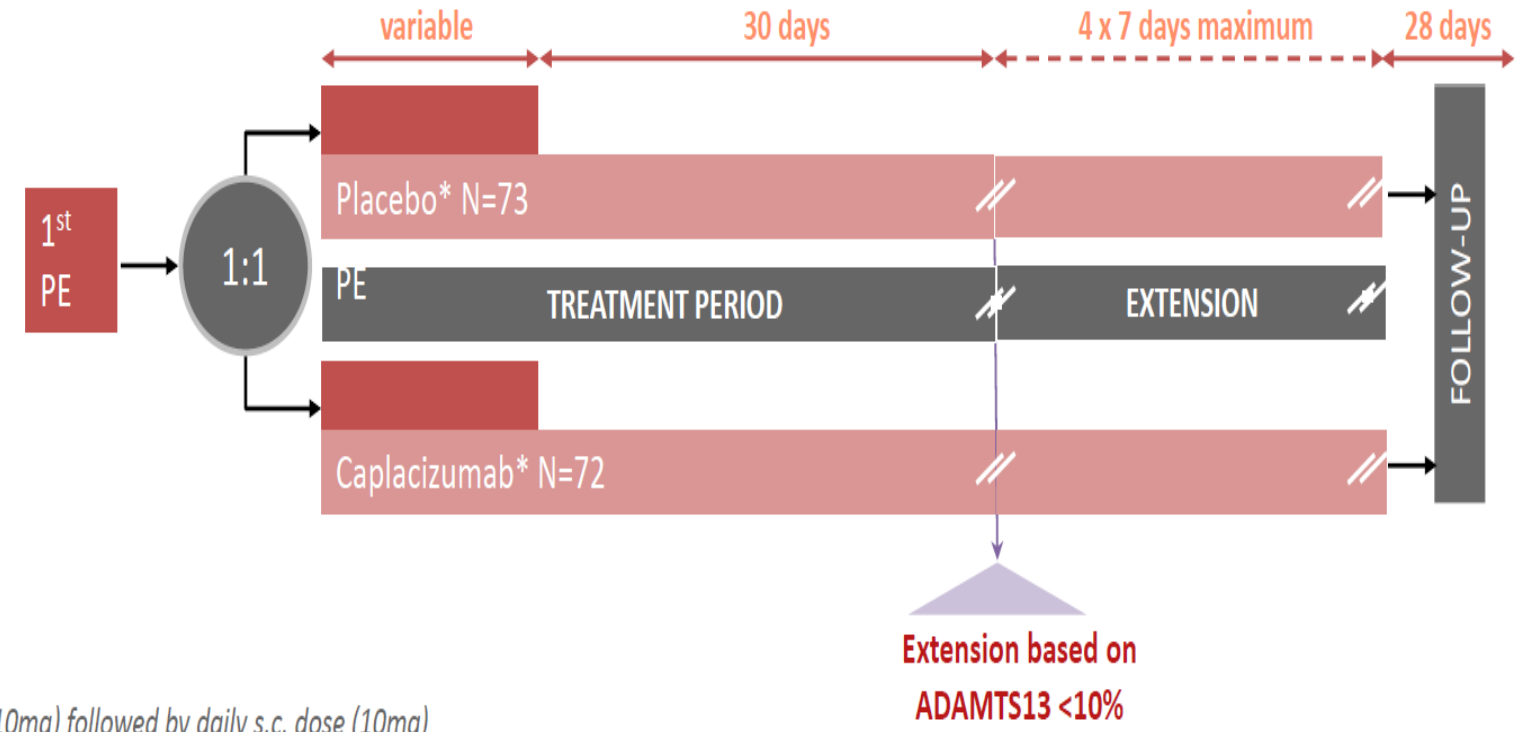
Caplacizumab



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

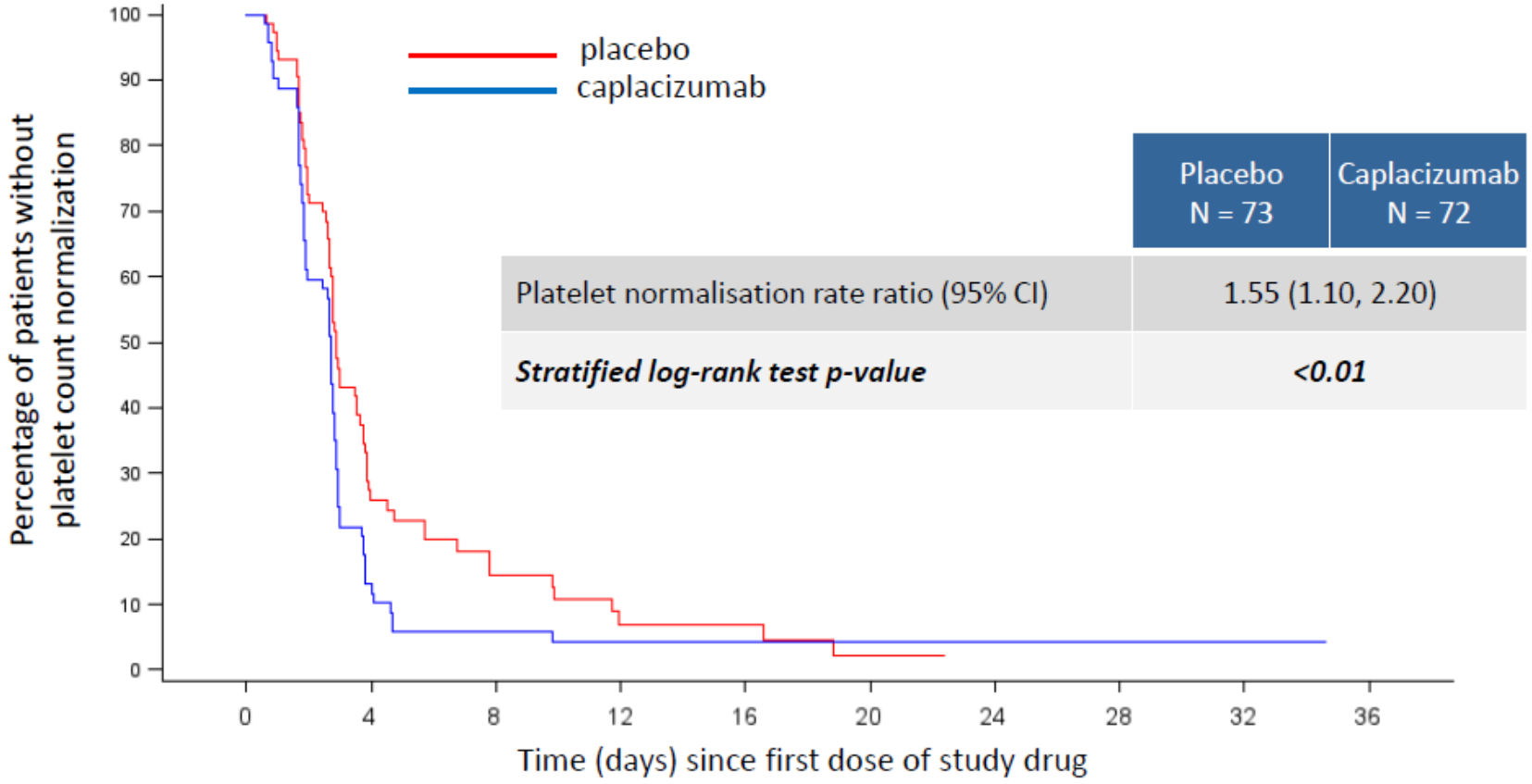
- Randomized, double-blind, placebo-controlled, multi-national study



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

PE = plasma exchange

Primary Endpoint: Time to PLT Response



	Placebo N = 73	Caplacizumab N = 72
Platelet normalisation rate ratio (95% CI)		1.55 (1.10, 2.20)
Stratified log-rank test p-value		***<0.01***

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

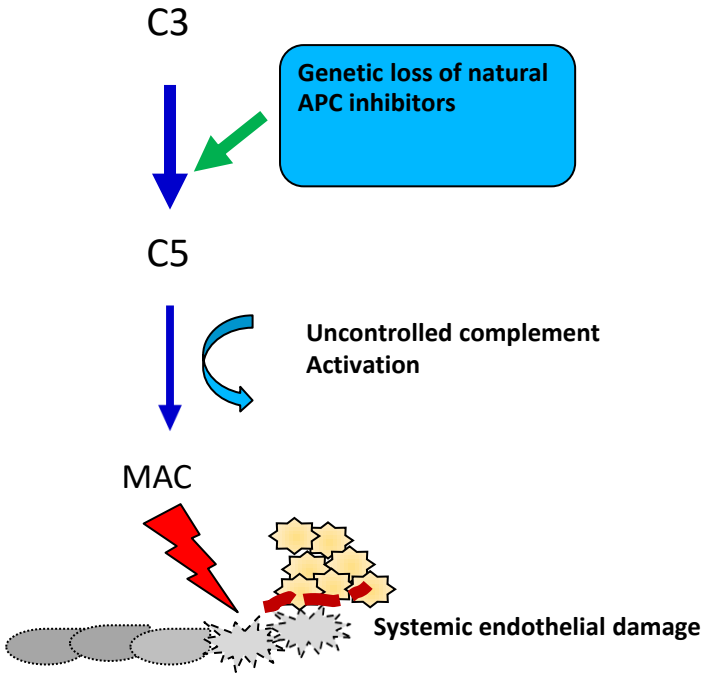
- Shortens time to plt normalization
- Improved **Composite** Endpoint
  - Death, **exacerbation of TTP**, or major thromboembolic event
- Prevention of relapse when treatment extended until resolution of underlying disease
- Reduced use of PLEX and ICU stays

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



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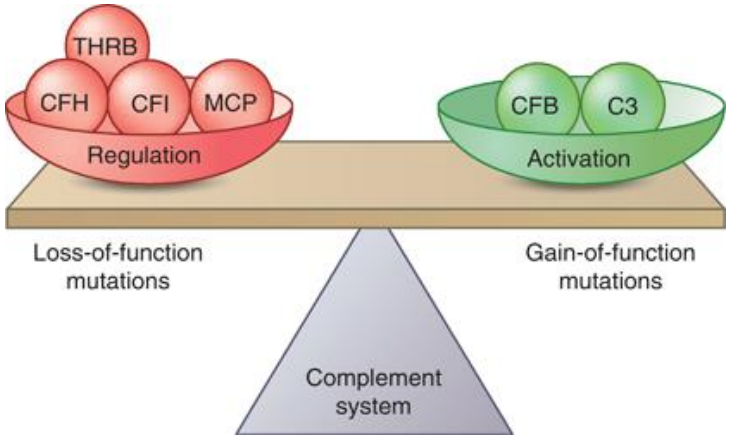

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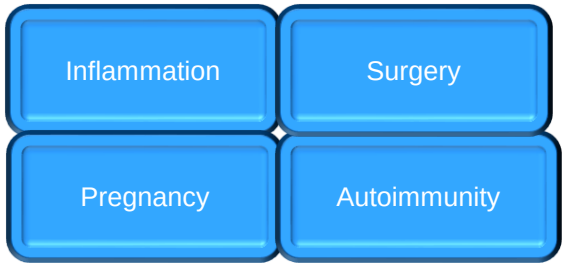


aHUS: Genetics

- 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)

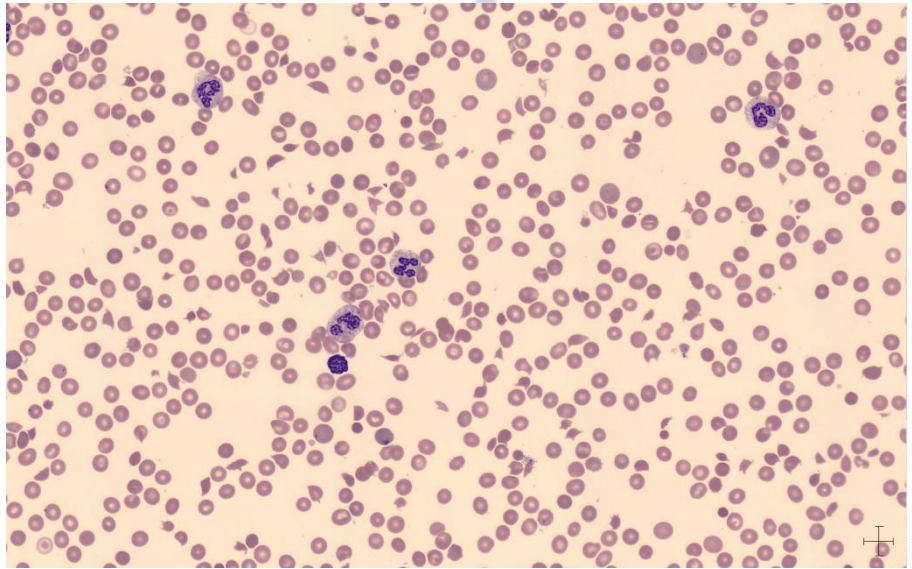
Suspected TMA

- ADAMTS13 activity
- shiga-toxin

Plasma exchange (x4-5)

?

Poor response and ADAMTS13%>10%



?

Consider aHUS diagnosis

Initiate eculizumab treatment

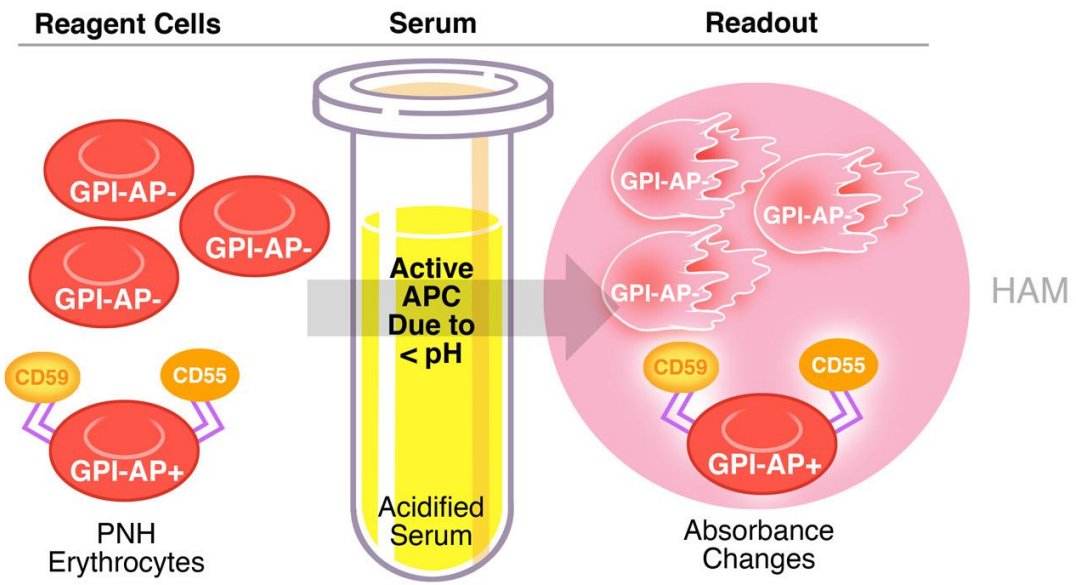
Adapted from Cataland SR, Wu HM. Blood Reviews. 2014

aHUS: Clinical Conundrums

1. Diagnosis of exclusion

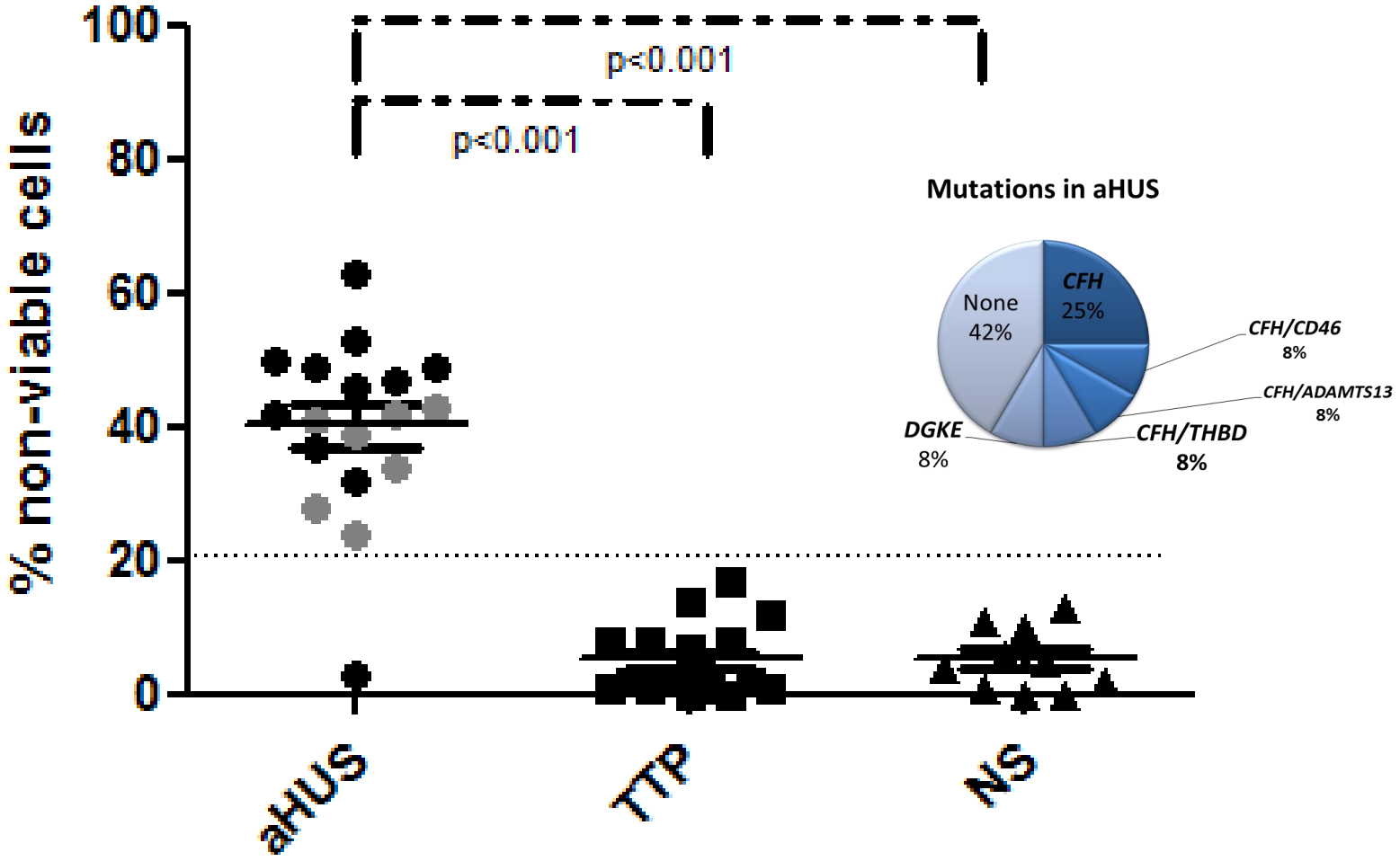
2. Expense
   - Eculizumab ~ 750K a year for aHUS
   - Is lifelong administration required?

Modified Ham test in aHUS



Gavriilaki E, et al. Blood 2015 125:3637-3646

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

Merrill et al, Blood 2017; 130:368-72

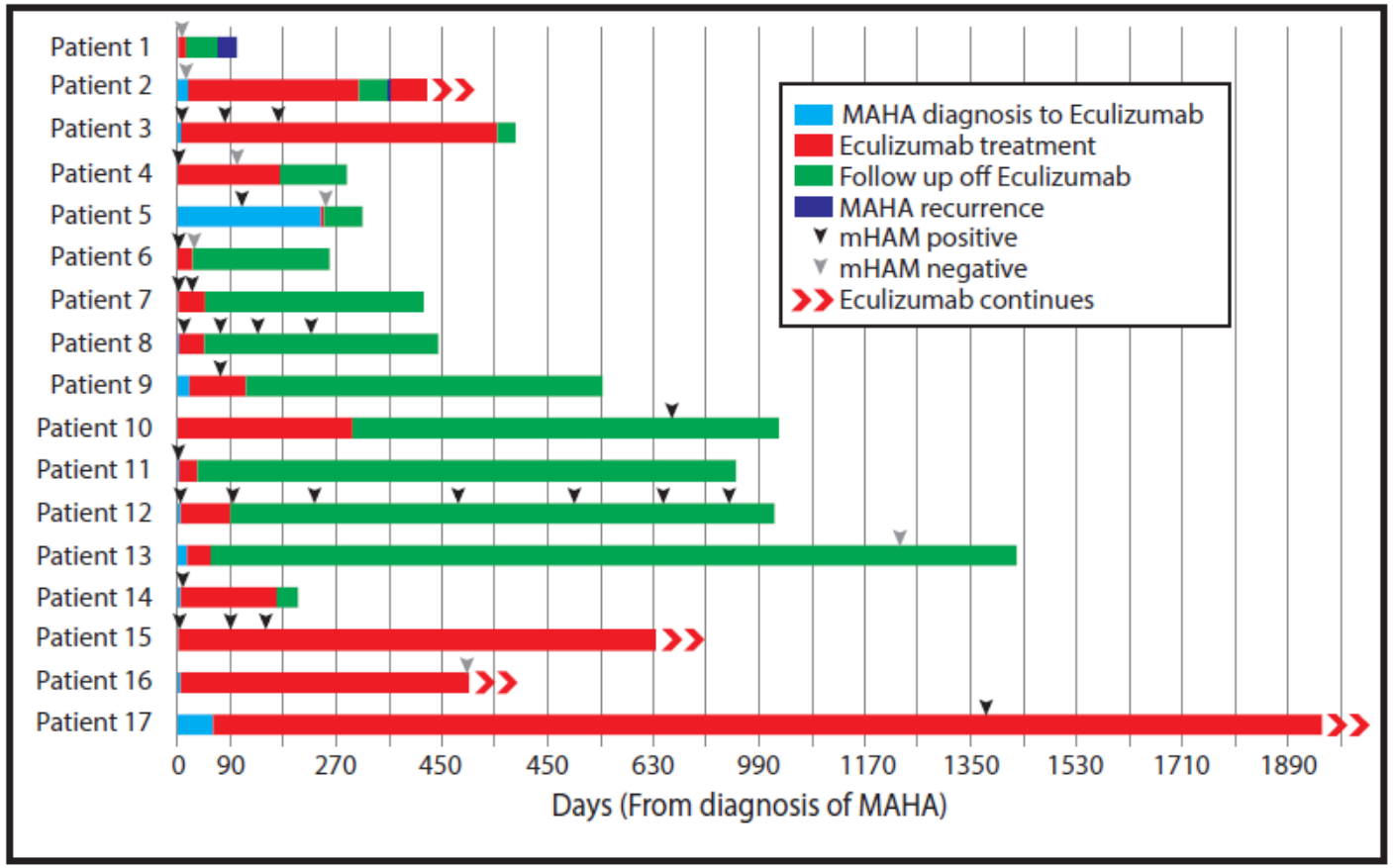
Eculizumab Cessation Offered to aHUS patients in CR with Mitigation of Putative Trigger

- 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

Merrill et al, Blood 2017; 130:368-72

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