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# Transfusion Medicine and Apheresis

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University of Pennsylvania  
Pennsylvania, PA

# Disclosures

*In compliance with ACCME policy, ASH requires disclosures to the session audience:*

## **Speaker**

Vijay Bhoj, MD, PhD

## **Disclosures**

**Royalties:** Cabaletta Bio.

**Discussion of off-label drug use:** Not applicable



# Learning Objectives

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**Upon participation in this activity, attendees will be able to:**

- Review newer treatment options for autoimmune hemolytic anemias
- Understand challenges of transfusing blood in autoimmune hemolytic anemias
- Summarize management of platelet refractoriness

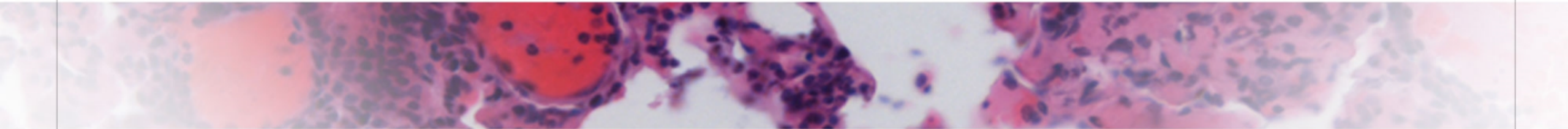
## ARS Case-1

- **65 F with a recent covid-19 infection presents with SOB, fatigue and headache. Her Hb is 6.5 g/dl and retics are 15%. Which of the following is suggestive of immune hemolytic anemia?**
  - A. LDH of 1100 IU/L**
  - B. Haptoglobin of <5**
  - C. Total bilirubin of 1.9 mg/dL**
  - D. DAT 4+**





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**Evaluating patients with autoimmune hemolytic anemia  
in the transfusion service and immunohematology reference  
laboratory: pretransfusion testing challenges and  
best transfusion-management strategies**

Sue T Johnson, MSTM, MLS(ASCP)SBB<sup>CM</sup>  
Director, Clinical Education & Transfusion Medicine Program  
Versiti & Marquette University  
Milwaukee, WI

# Autoimmune Hemolytic Anemias

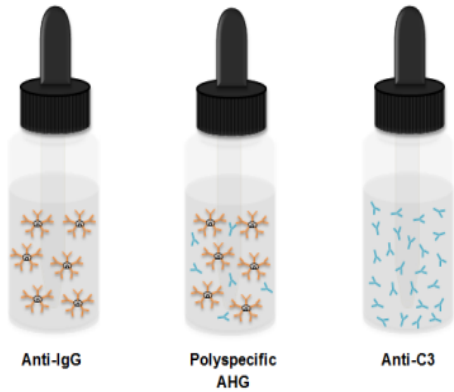
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- Evidence of hemolysis
- Positive Coombs test
- 80% warm antibody: IgG antibody that reacts to protein antigens **mainly Rh** on RBC surface at core body temperature
- 20% cold antibody: IgM antibody that reacts to polysaccharide antigens **mainly I/i antigen** on RBC surface at temperatures below core body temperature in peripheral structures

# Typical Antibody Screening Results for Autoantibodies and Alloantibodies

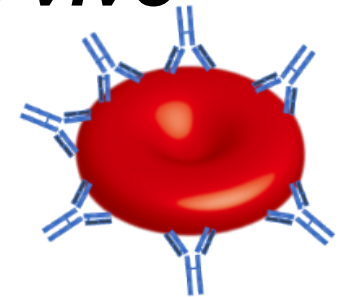
	No Antibody Detected			Alloantibody Detected			Warm Autoantibody			Cold Autoantibody		
Reagent Red Cells	IS	37C	IAT	IS	37C	IAT	IS	37C	IAT	IS	37C	IAT
1	0	0	0	0	0	0	0	0	3+	4+	3+	1+
2	0	0	0	0	0	3+	0	0	3+	4+	3+	1+
3	0	0	0	0	0	0	0	0	3+	4+	3+	1+
Autocontrol*	0	0	0	0	0	0	0	0	4+	4+	3+	1+

# Case 1 - Direct Antiglobulin Test (DAT)



AHG Reagent	IS/RT
Polyspecific AHG	4+
Anti-IgG	4+
Anti-C3	3+
Control	0

- Detects IgG and/or C3 binding to patient RBCs *in vivo*
  - ~100 – 500 molecules of IgG
  - ~ 400 – 1,100 molecules of C3
- Indirectly detects IgM by C3 binding



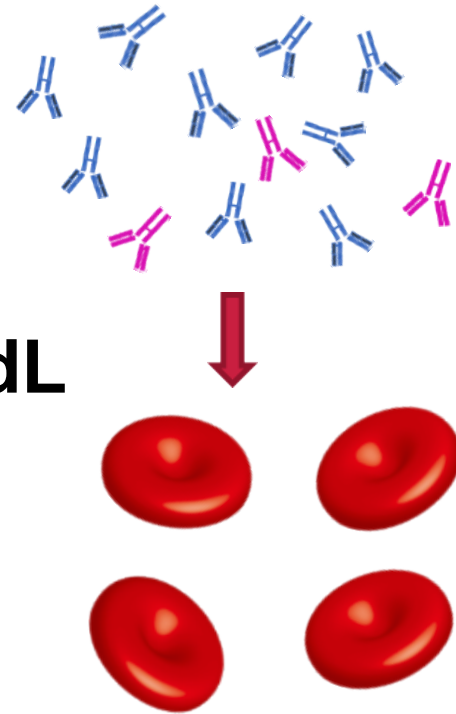
# Interpretation of a positive DAT

DAT	Elution	Conclusion
IgG only or IgG with low C3d	Reacts with all cells	WAIHA
IgG only with recent Tx	Reacts with a few select cells	AlloAb
IgG only	Negative	Drug induced
C3d only	Negative	Cold AIHA



# Autologous Adsorption vs. Allogeneic Adsorption

- Remove autoantibody to leave alloantibody free
- Transfusion history is key
  - Recent - in last 3 months
  - Ever?
- Availability of patient's RBCs
  - Patient's Hgb <5 g/dL, our patient 4.4 g/dL
  - Small pediatric patient
  - **May take several hours to days!!**



Allogeneic Donor Red Cells

## ARS Case-2

- **65 WF with a chronic WAIHA for last 3 years has failed steroid, rituximab, and is blood transfusion dependent every month, with Hb in 7-9g/dL range with <5% retics affecting her QOL. Which of the following options is/are appropriate next step therapy?**
  - A. Aggressive weekly plasma exchange
  - B. A trial of IVIG
  - C. Erythropoietin stimulating agent
  - D. Fostamatinib



# **Phase 3, Randomized, Double-blind, Placebo-controlled, Global Study (FORWARD) of Fostamatinib for the Treatment of Warm Antibody Autoimmune Hemolytic Anemia**

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**Presented by: David Kuter, MD, PhD<sup>1</sup>  
Co-Authors: Caroline Piatek, MD<sup>2</sup>, Khalil Saikali, PhD<sup>3</sup>,  
and Wolfgang Dummer, MD<sup>3</sup>**

<sup>1</sup>Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA;

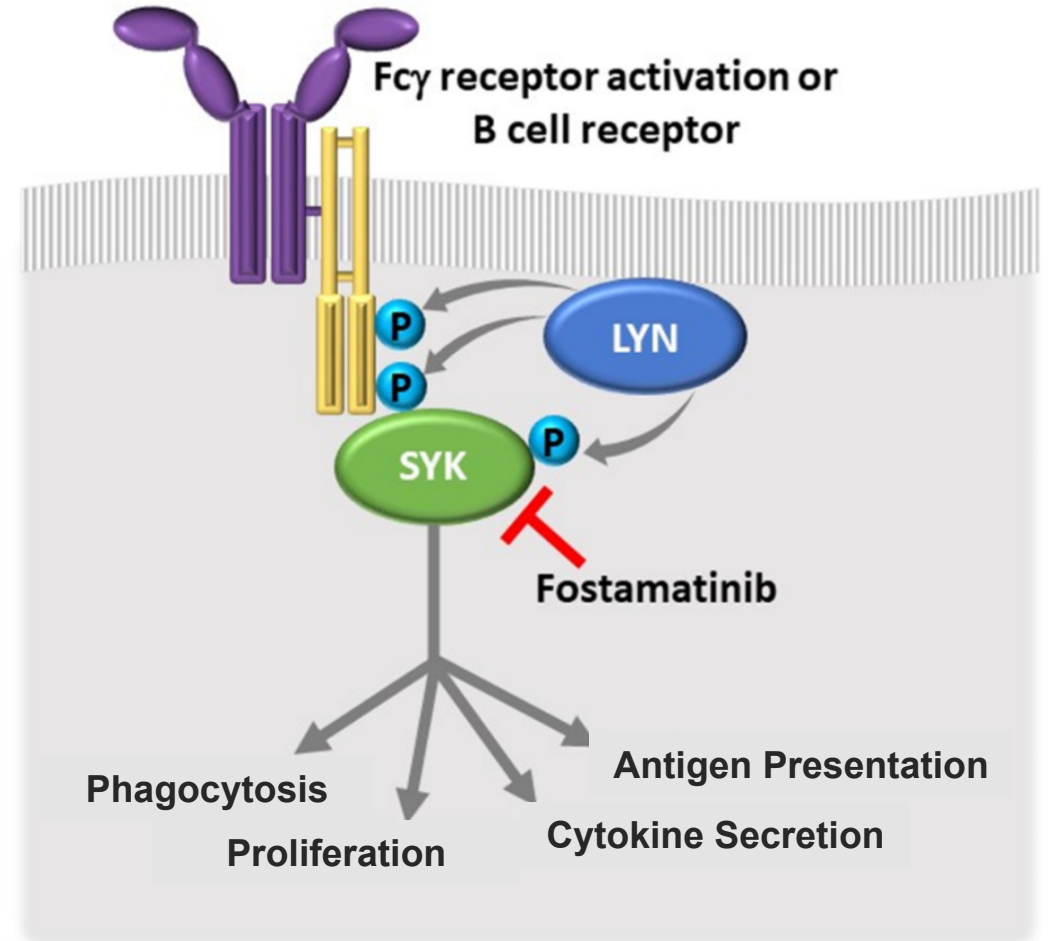
<sup>2</sup>University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA;

<sup>3</sup>Rigel Pharmaceuticals, Inc., South San Francisco, CA, USA

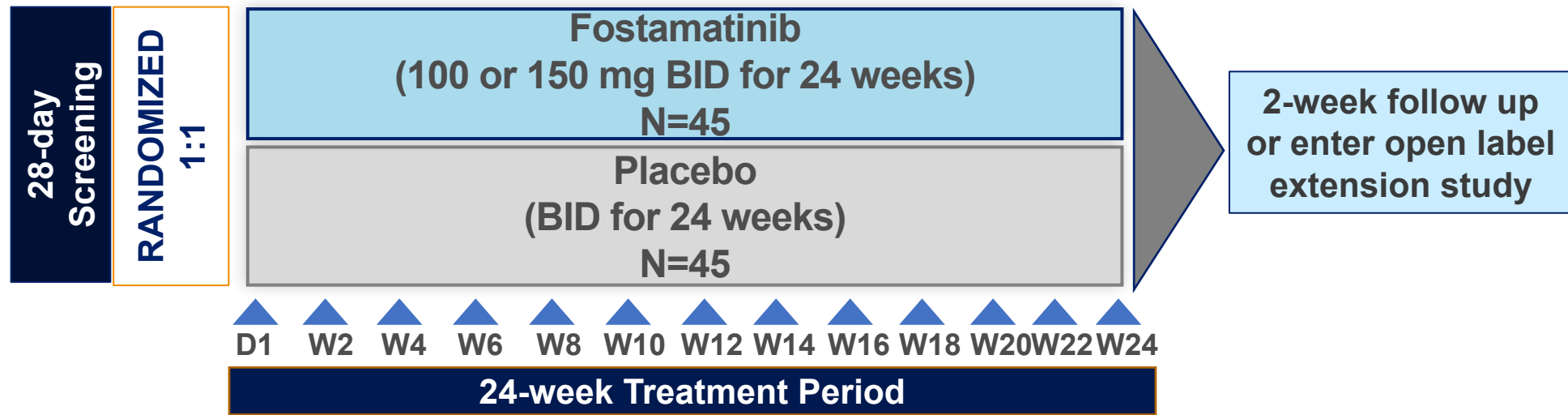
**Presented at the American Society of Hematology Conference, December 10-13, 2022**

# Background

- **Fostamatinib, a spleen tyrosine kinase inhibitor, blocks destruction of red blood cells and decreases B cell activation thereby reducing antibody production and epitope spreading.**
- **Fostamatinib is approved for immune thrombocytopenia and is under investigation for warm AIHA.**



# Study Design – FORWARD (NCT04138927)



- A Phase 3 randomized, double-blind, placebo-controlled clinical study
- 90 patients with wAIHA who had failed at least one prior treatment
- The primary endpoint was a durable Hgb response of  $\geq 10$  g/dL with an increase from baseline of  $\geq 2$  g/dL on 3 consecutive visits during the 24-week treatment period.

# Primary Efficacy Endpoint: Durable Hgb Response

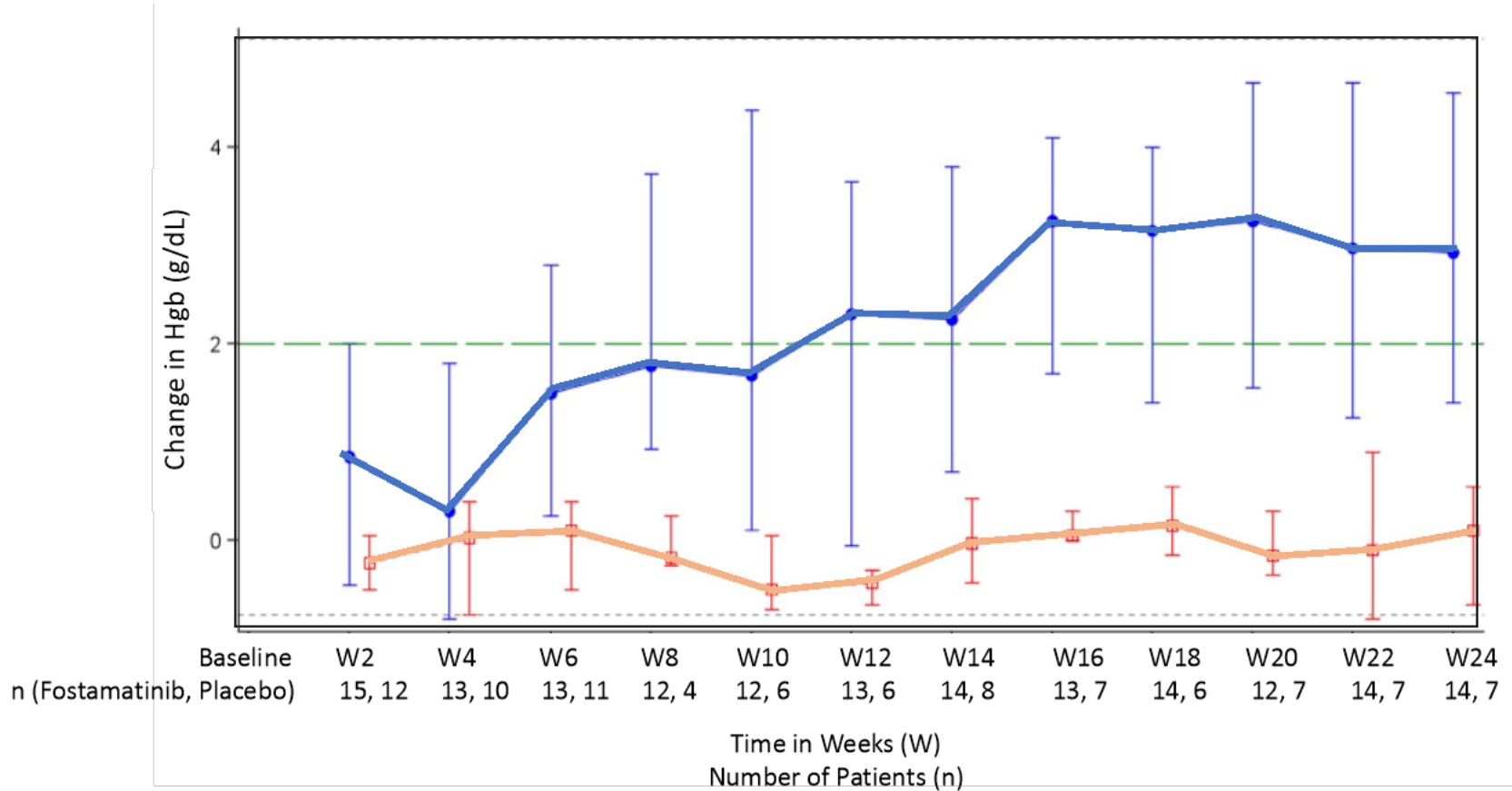
	ITT Population		U.S., Canada, Australia and Western Europe*		Eastern Europe**	
	Fostamatinib (N=45)	Placebo (N=45)	Fostamatinib (N=25)	Placebo (N=28)	Fostamatinib (N=20)	Placebo (N=17)
<b>Prespecified Analysis</b>	16 (35.6%)	12 (26.7%)	9 (36.0%)	3 (10.7%)	7 (35.0%)	9 (52.9%)
<b>P-Value</b>	P= 0.398		P=0.030		P=0.304	
<b>Reanalysis</b>	15 (33.3%)	6 (14.0%)	8 (32.0%)	0 (0)	7 (35.0%)	6 (40.0%)
<b>P-Value</b>	P=0.0395		P=0.0021		P=0.7664	

\*Western Europe (Austria, Germany, Spain, France, Italy, Belgium, U.K. Netherlands, and Norway)

\*\*Eastern Europe (Bulgaria, Czech Republic, Russia, Ukraine, Georgia, Belarus, and Serbia).

- The primary endpoint was not met in the overall population but was significant in US, Canada, Australia and Western Europe.
- The reanalysis showed the primary endpoint was met in the overall population as well as the US, Canada, Australia and Western Europe.

# Median Change in Hemoglobin Over 24 Weeks (ITT; U.S./Canada/Australia and Western Europe)



- **Reanalysis: Hgb values were censored if potentially impacted by rescue therapy received during the screening and treatment periods**

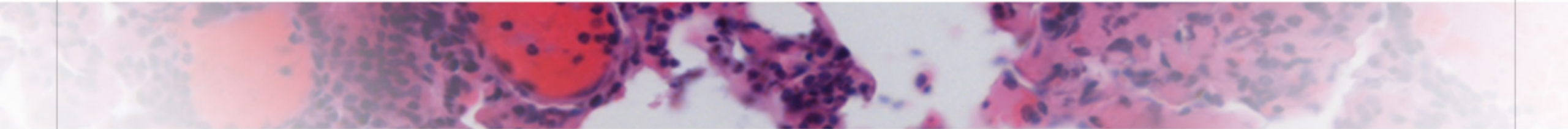
# Conclusions

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- **The primary endpoint of durable Hgb response was not met in the overall population but was significant in US, Canada, Australia and Western Europe.**
- **The reanalysis showed significant efficacy results in the overall population as well as the US, Canada, Australia and Western Europe.**



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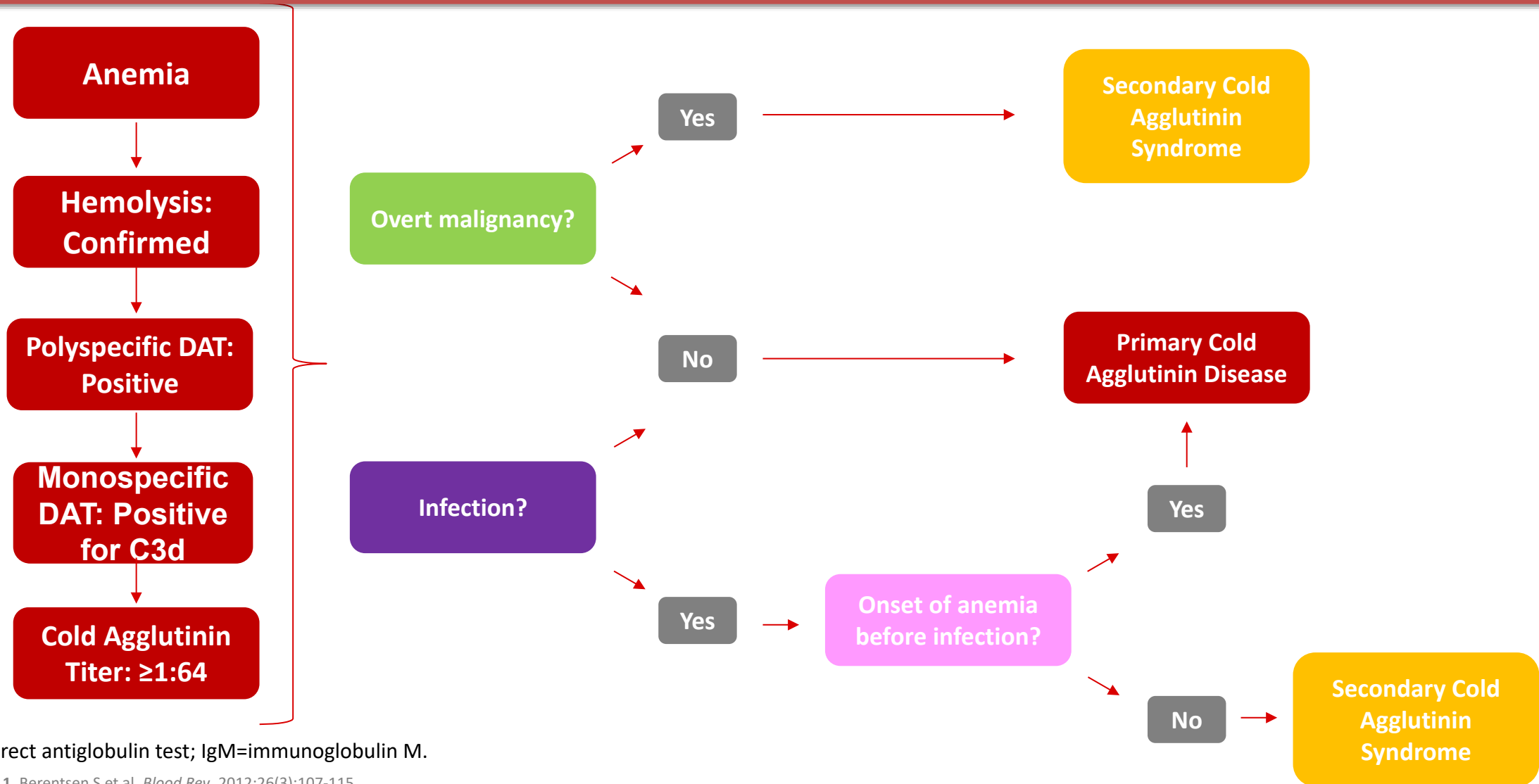
# Cold Agglutinin Disease

**Catherine Broome MD**  
**Associate Professor of Medicine**  
**MedStar Georgetown University Hospital**  
**Lombardi Cancer Center**

# Cold Agglutinin Disease(CAD)

- **CAD is generally diagnosed in 6<sup>th</sup>, 7<sup>th</sup> and 8<sup>th</sup> decade**
- **Slightly more common in women.**
- **An estimated prevalence of 5–20 cases per million.**
- **Diagnosis –**
  - **Presence of cold agglutinins, 90% IgM rarely IgG or IgA,**
  - **Hemolysis +/-**
  - **Circulatory symptoms +/-**
  - **Associated with an underlying, microscopic, clonal (MYD88 L265P mutation negative) low grade B cell lymphoproliferative disorder.**

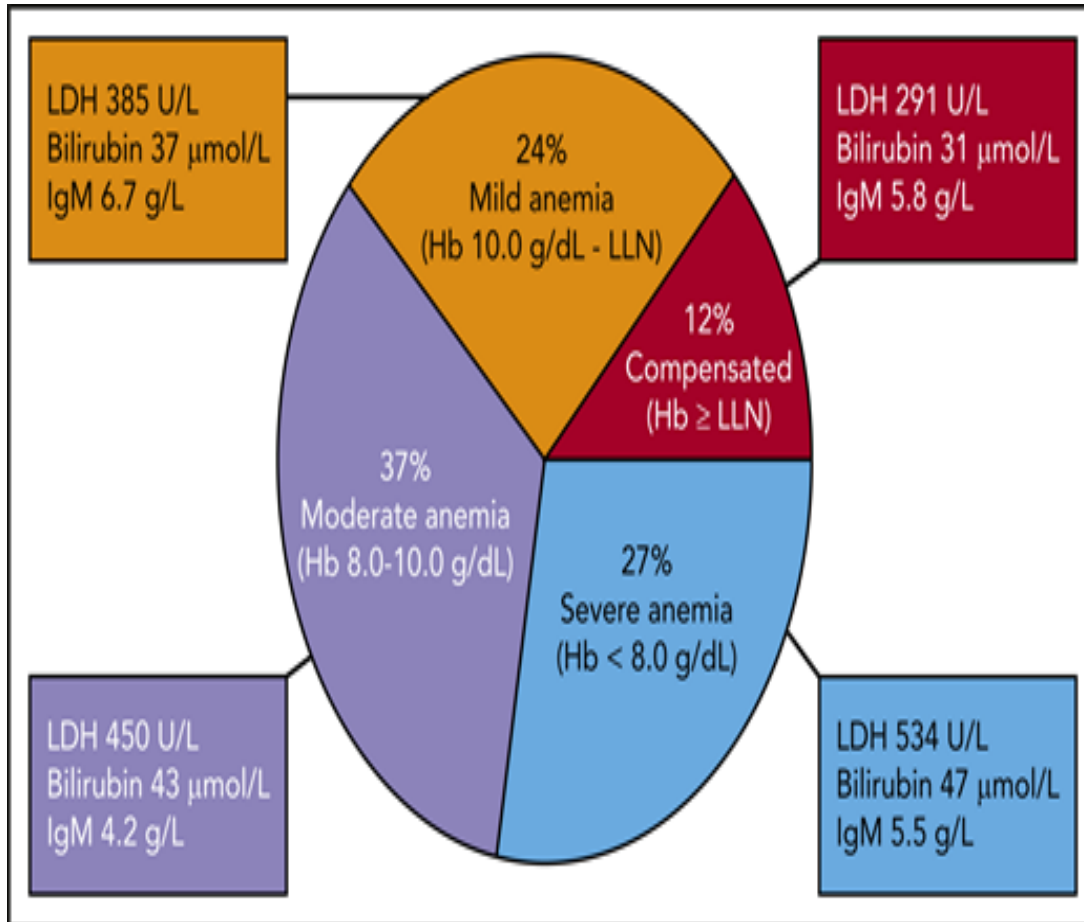
# Cold Agglutinin Disease(CAD) vs Cold Agglutinin Syndrome(CAS)



DAT=direct antiglobulin test; IgM=immunoglobulin M.

Reference: 1. Berentsen S et al. *Blood Rev.* 2012;26(3):107-115.

# Anemia in CAD



**64% of patients with CAD have baseline Hgb less than 10g/dL**

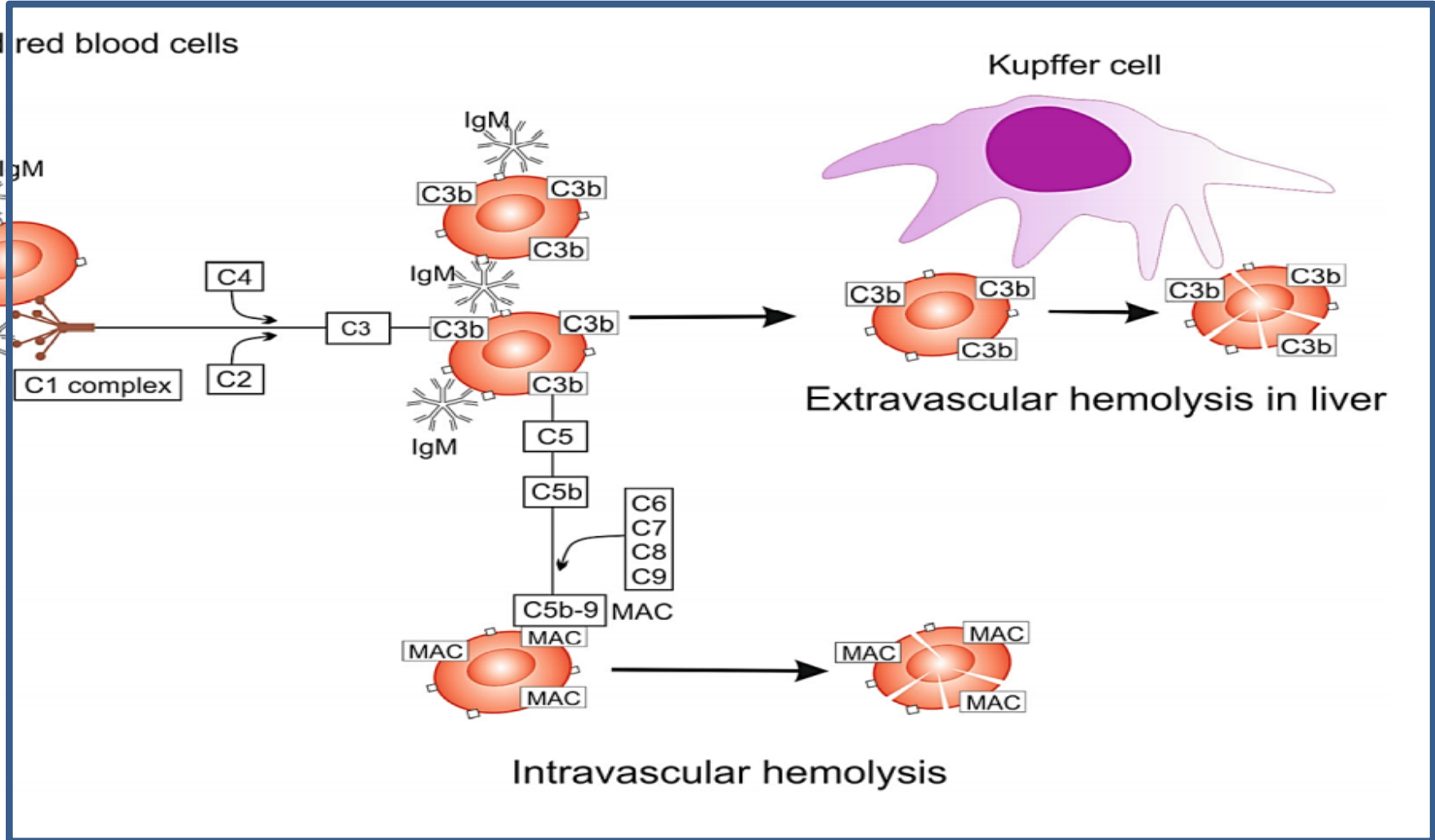
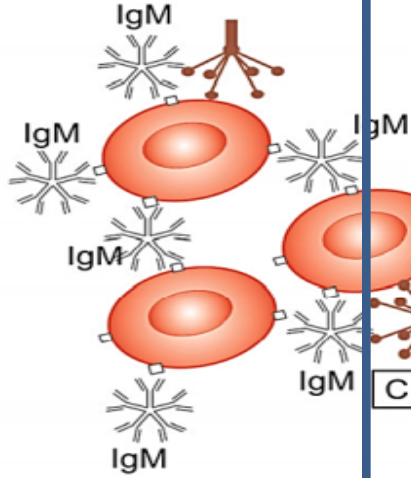
**Even patients with a normal Hgb have evidence of ongoing hemolysis**

**The level of IgM(cold agglutinin) does not linearly correlate with degree of anemia**

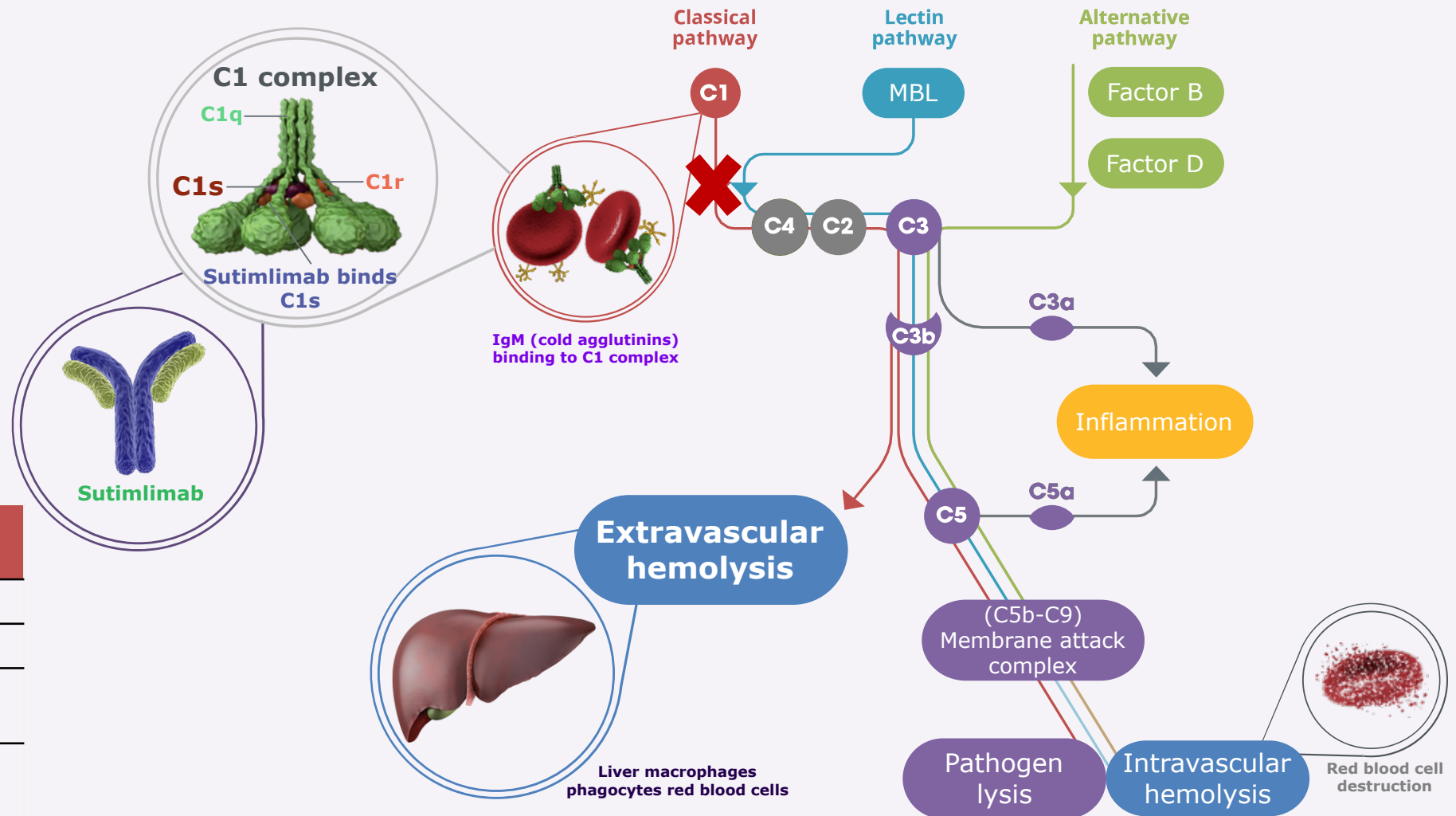
Sigbjørn Berentsen, How I treat cold agglutinin disease, Blood, 2021

# Hemolysis in CAD

Cold antibody coated red blood cells



# Sutimlimab, an Investigational Drug, Selectively Targets Complement C1s Inhibiting Classical Complement Pathway Activation<sup>1,2</sup>



<b>Sutimlimab</b> (formerly BIVV009) <sup>3</sup>
Humanized monoclonal Ab
IgG <sub>4</sub> (S241P; L248E)
Designed to <b>inhibit the classical complement pathway</b>
Designed to leave the lectin and alternative pathways intact

Ab, antibody; C, complement protein; Ig, immunoglobulin; MAC, membrane attack complex; MBL, mannose-binding lectin. Jäger U, et al. *Blood*. 2019; 133(9):893–901. Figure adapted with permission of the American Society of Hematology.

1. Murphy K. *Janeway's Immunobiology*. 8th ed. New York, NY: Garland Science; 2012; 2. Jäger U, et al. *Blood*. 2019; 133(9):893–901;

3. Bartko J, et al. *Clin Pharmacol Ther*. 2018;104(4):655–63.



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## Sutimlimab Provides Sustained Improvements in Patient-Reported Outcomes and Quality of Life in Patients with Cold Agglutinin Disease: Open-label Extension of the Randomized, Phase 3 CADENZA Study

Alexander Röth<sup>1</sup>, Catherine M. Broome<sup>2</sup>, Wilma Barcellini<sup>3</sup>, Bernd Jilma<sup>4</sup>, Quentin A. Hill<sup>5</sup>, David Cella<sup>6</sup>, Tor Henrik Anderson Tvedt<sup>7</sup>, Masaki Yamaguchi<sup>8</sup>, Irina Murakhovskaya<sup>9</sup>, Michelle Lee<sup>10</sup>, Frank Shafer<sup>10</sup>, Marek Wardęcki<sup>11</sup>, Jennifer Wang<sup>12</sup>, Ronnie Yoo<sup>12</sup>, Jerome Msihid<sup>13</sup>, Ilene C. Weitz<sup>14</sup>

<sup>1</sup>Department of Hematology and Stem Cell Transplantation, West German Cancer Center, University Hospital Essen, University of Duisburg-Essen, Essen, Germany; <sup>2</sup>Division of Hematology, MedStar Georgetown University Hospital, Washington, DC, USA; <sup>3</sup>Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; <sup>4</sup>Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria; <sup>5</sup>Leeds Teaching Hospitals NHS Trust, Leeds UK; <sup>6</sup>Department of Medical Social Sciences, Center for Patient-Centered Outcomes, Institute for Public Health and Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; <sup>7</sup>Section for Hematology, Department of Medicine, Haukeland University Hospital, Bergen, Norway; <sup>8</sup>Ishikawa Prefectural Central Hospital, Japan; <sup>9</sup>Department of Hematology and Oncology, Albert Einstein College of Medicine/Montefiore Medical Center, Bronx, NY, USA; <sup>10</sup>Sanofi, Bridgewater, NJ, USA; <sup>11</sup>Sanofi, Warsaw, Poland; <sup>12</sup>Sanofi, Cambridge, MA, USA; <sup>13</sup>Sanofi, Chilly-Mazarin, France; <sup>14</sup>Keck School of Medicine of USC, Los Angeles, CA, USA

*Medical writing and editing support was provided by David Campbell, of Lucid Group Communications Ltd., and was funded by Sanofi*

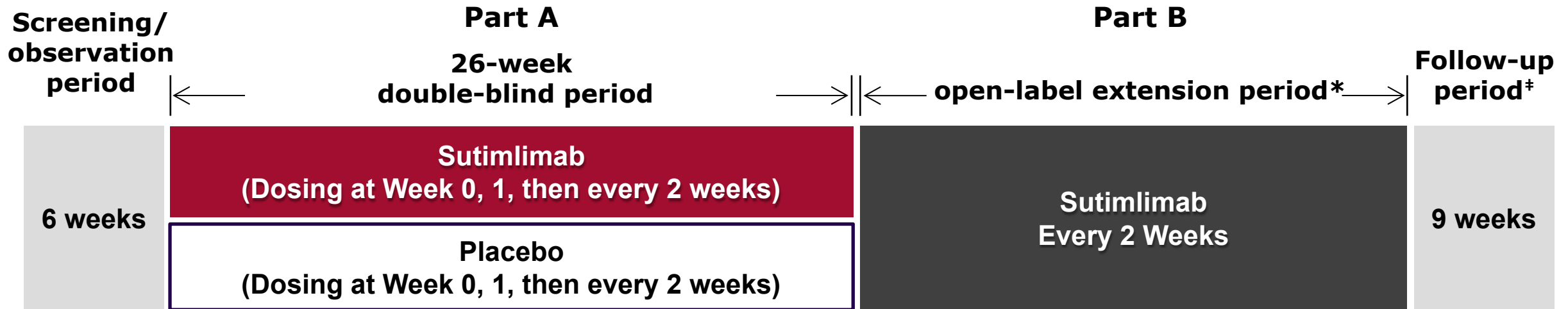


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# **Sustained Complement C1s Inhibition with Sutimlimab in Patients With Cold Agglutinin Disease Results in Continued Efficacy During Part B of the Randomized Placebo Controlled Phase 3 CADENZA Study (NCT03347422)**

Alexander Röth, Sigbjørn Berentsen, Wilma Barcellini, Shirley D'Sa, Bernd Jilma, Marc Michel, Ilene C. Weitz, Masaki Yamaguchi, Jun-ichi Nishimura, Josephine M.I. Vos, Joan Cid, Michael Storek, Nancy Wong, Ronnie Yoo, Jennifer Wang, Deepthi S. Vagge, Marek Wardęcki, Frank Shafer, Michelle Lee, Catherine M. Broome

# CADENZA Study Design



Full eligibility criteria for CADENZA have been previously described<sup>1</sup>

For efficacy and safety results of Part B, visit poster 1201

- In the open-label extension Part B, all patients who had completed Part A were eligible to receive **biweekly doses of sutimlimab** at 6.5 g (if <75 kg) or 7.5 g (if ≥75 kg), continuing until 1 year after the last patient completed Part A
- **PRO endpoints** included Functional Assessment of Chronic Illness Therapy-Fatigue (**FACIT-Fatigue**), Patient Global Impression of Change (**PGIC**), Patient Global Impression of [Fatigue] Severity (**PGIS**), 12-Item Short Form Health Survey (**SF-12**), and EuroQol visual analogue scale (**EQ VAS**)<sup>2</sup>

\*The duration of the open-label extension was variable; the minimum time was 1 year from the last patient completing Part A, to a maximum time of approximately 2 years.

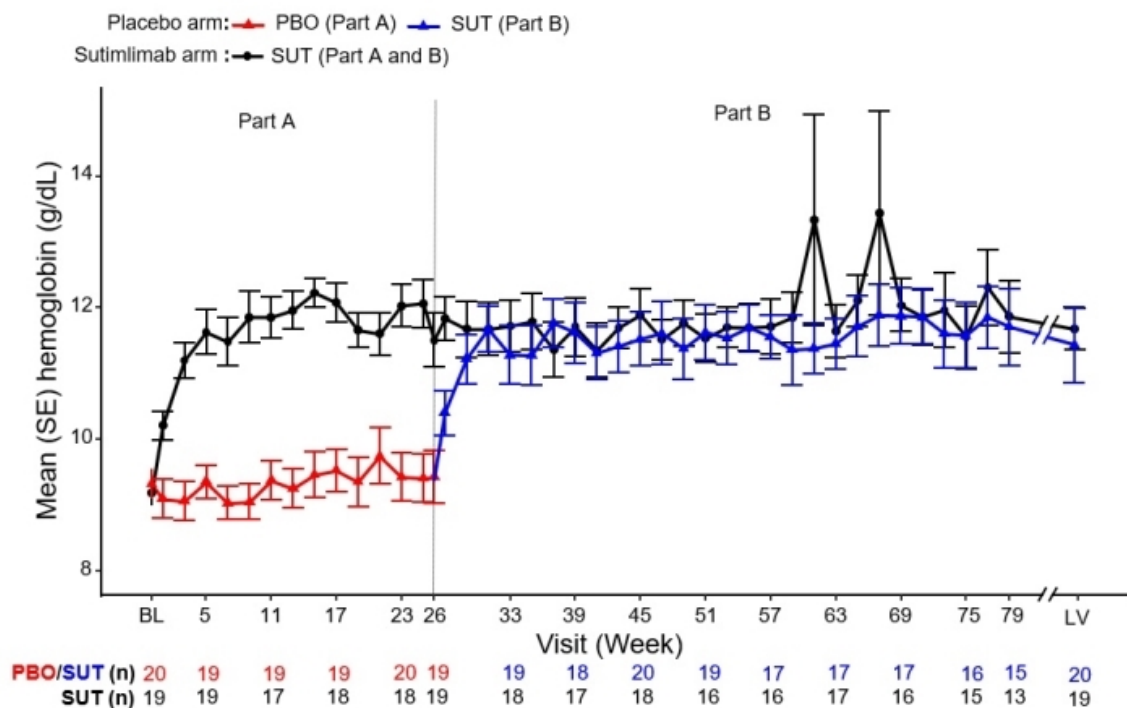
†Only on-treatment data from Part B are reported in this presentation, and not from the 9-week follow-up period

PRO, patient reported outcome.

1. Röth A, et al. *Blood*. 2022 Sep 1;140(9):980-991. 2. ClinicalTrials.gov Identifier: NCT03347422.



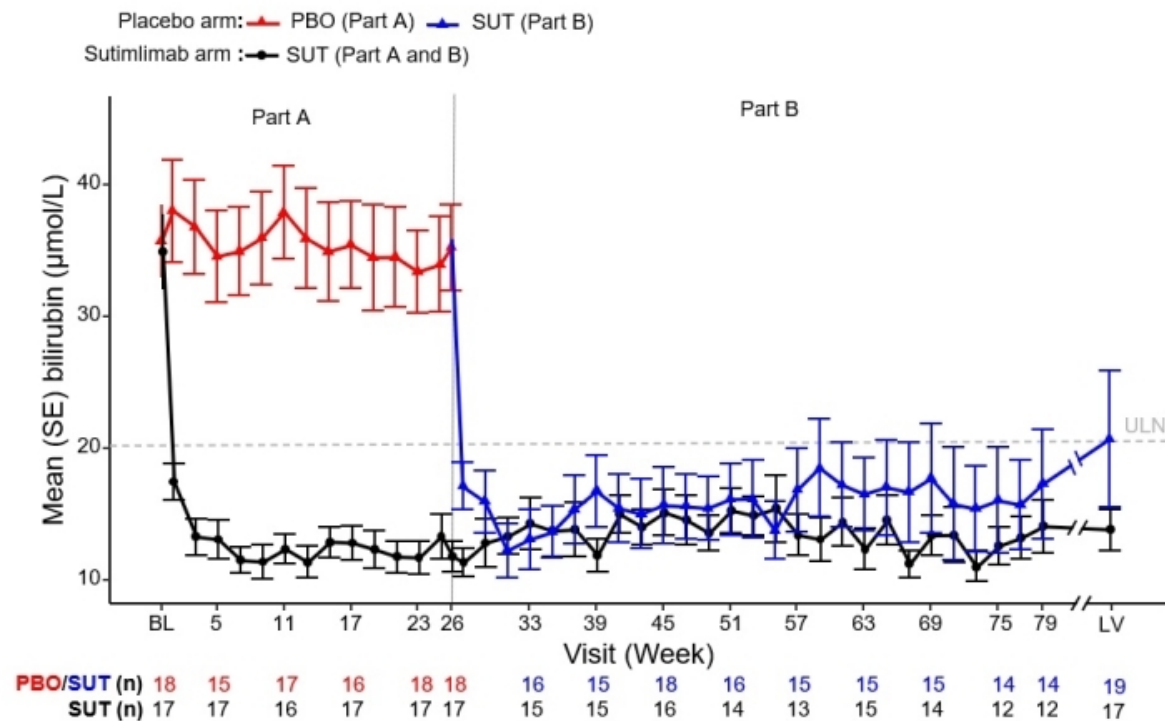
# Sustained Hematological Response with Long-term Sutimlimab



## Hemoglobin

- Sutimlimab treatment rapidly improved hemoglobin levels
- In Part B, improvements were sustained in patients previously treated with sutimlimab, while patients previously treated with placebo saw rapid and comparable increases in hemoglobin levels

BL, baseline; LV, last available on-treatment value; PBO, placebo; SE, standard error; SUT, sutimlimab; ULN, upper limit of normal



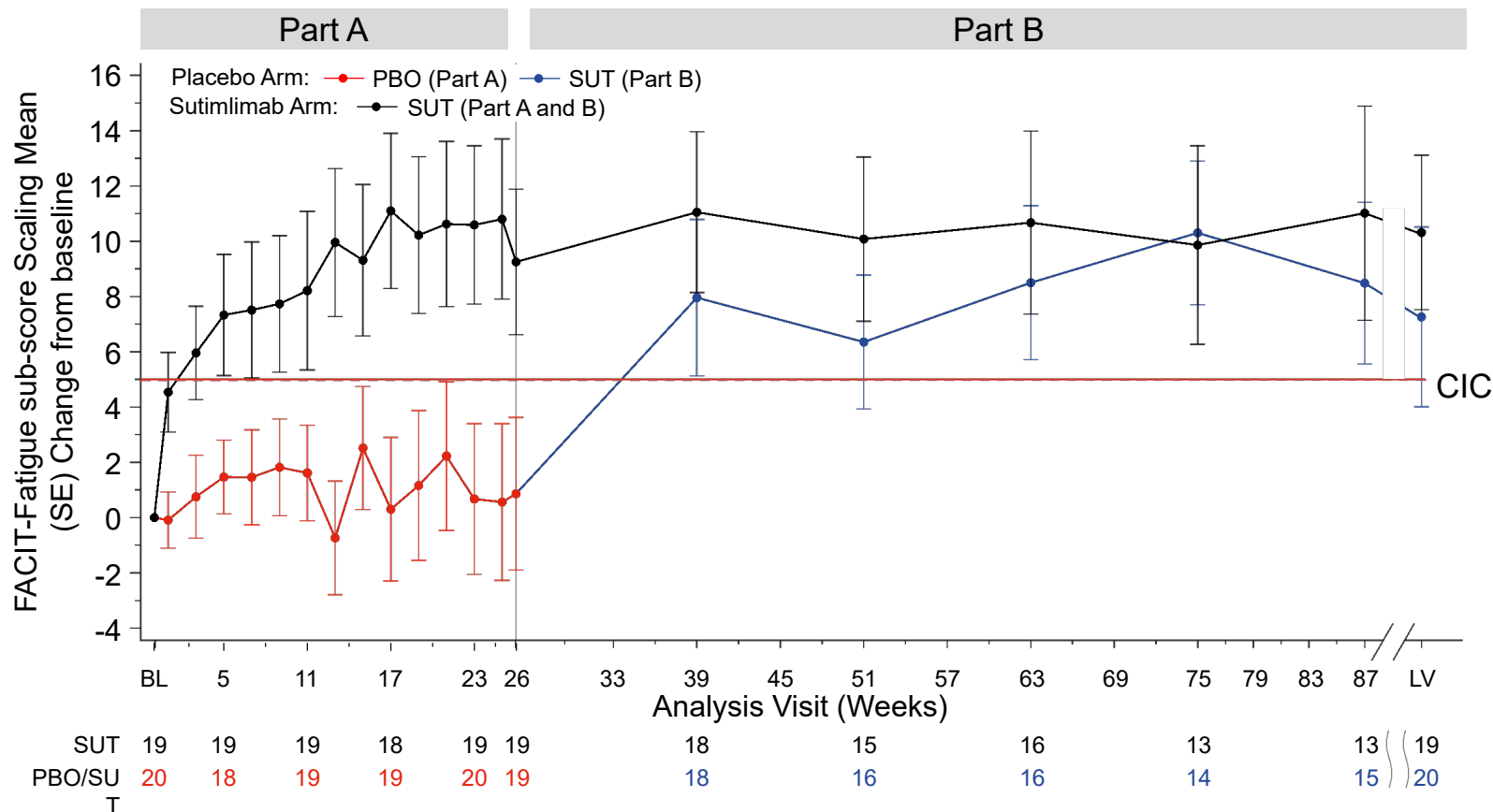
## Bilirubin

- Mean total bilirubin was normalized with sutimlimab treatment in Part A and sustained through to LV in Part B; similar decreases were observed for patients previously treated with placebo when they started receiving sutimlimab in Part B



# Rapid and Sustained Improvement in FACIT-Fatigue Score with Long-term Sutimlimab

FACIT-Fatigue Score: Mean Change from Baseline



- In patients previously treated with placebo the mean (SE) change was 8.0 (2.8) points, by first assessment after switch, exceeding the CIC<sup>a</sup> of 5 points
- At the last on-treatment visit (LV) the mean (SE) change for all patients (N=39) was 8.8 (2.1) points

<sup>a</sup>The clinically important change (CIC) reflects the smallest score change that indicates a meaningful treatment benefit for individual patients. <sup>1</sup>

BL, baseline; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LV, last available on-treatment visit; PBO, placebo; SE, standard error; SUT, sutimlimab.

1. Hill Q, et al EHA 2021; EP1179.





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# Reticulocytes are an Unappreciated Risk Factor for RBC Alloimmunization at the Donor and Recipient Levels



Tiffany Thomas, Annie Qiu, Christopher Kim, Dominique Gordy, Anabel Miller, Maria Tredicine, Elizabeth Stone, Monika Dzieciatkowska, Eldad Hod, Angelo D'Alessandro, Steven Spitalnik, James Zimring, Imo Akpan, John Luckey, **Krystalyn E. Hudson**

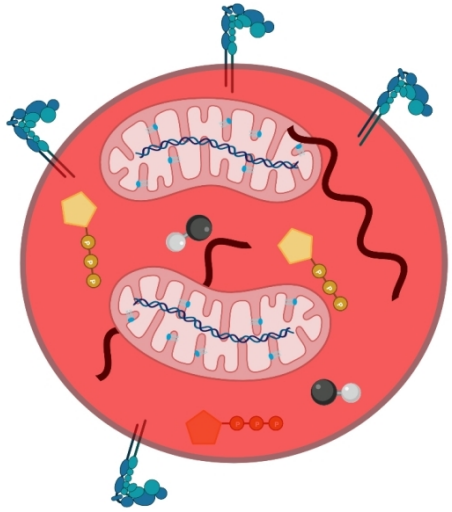


NIH NHLBI R01HL133325 (KEH); NIH NHLBI R01HL148151 (SLS)

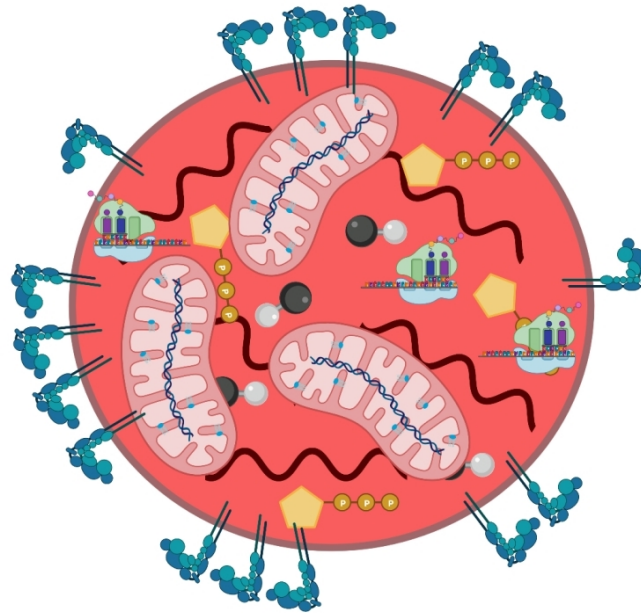
# Reticulocytes contain immunogenic components

## Damage-associated molecular patterns (DAMPs)


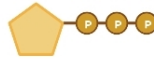


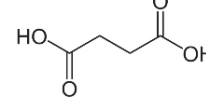


Reticulocytes



Stress Reticulocytes



>100% Larger  
Less Deformable

-  Mitochondrial DNA
-  ATP
-  Cardiolipin
-  Reactive oxygen species
-  Succinate
-  RNA
-  Integrins

Mitochondria

Reticulocytes

Stress Reticulocytes



# Hypothesis: Reticulocytes modulate RBC alloimmunization

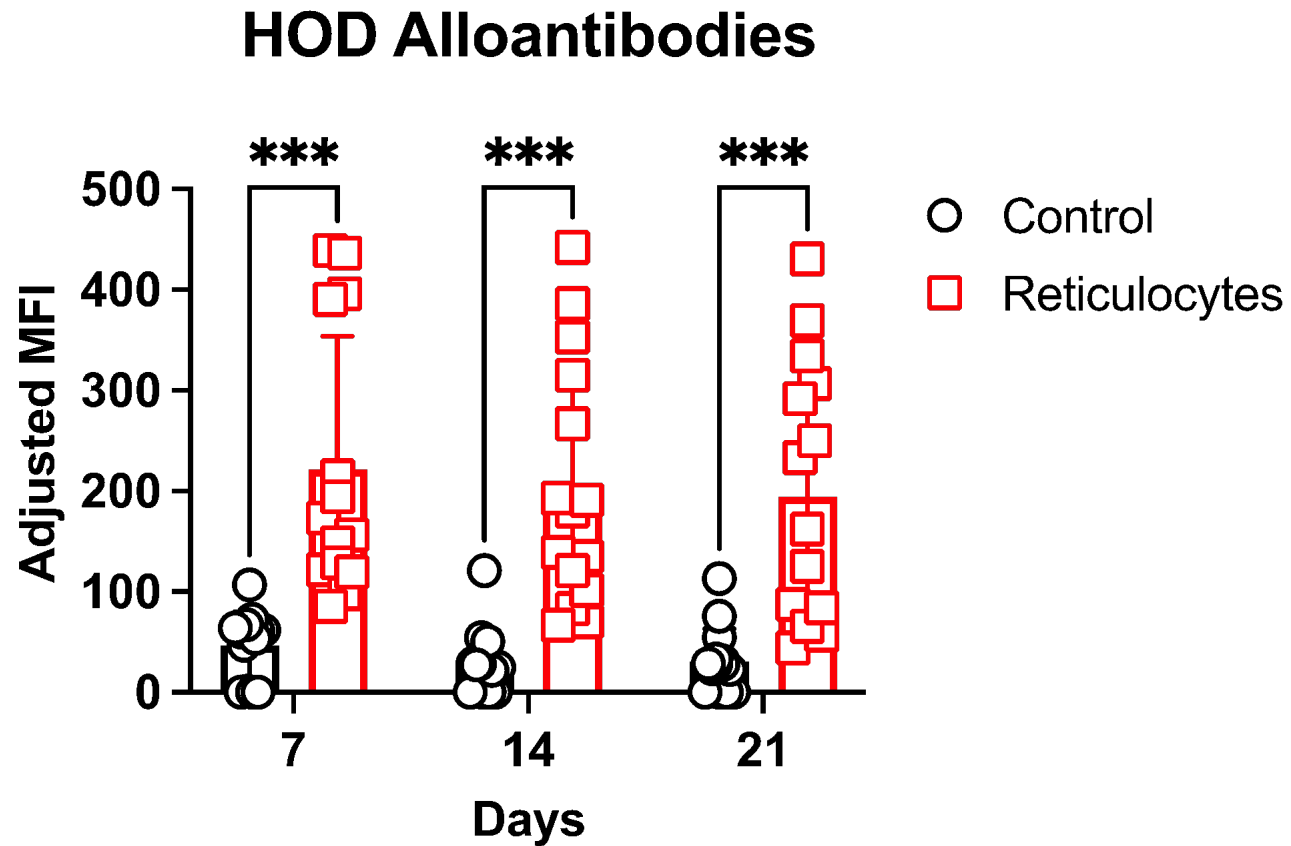
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- **Mitochondria elicit Type I IFNs**
- **Association between Type I IFNs and RBC Alloimmunization**
- **(Donors) Repeat volunteer blood donors have higher reticulocyte frequencies**
- **(Recipients) Patients with hemolytic anemias are at highest risk for RBC alloimmunization**

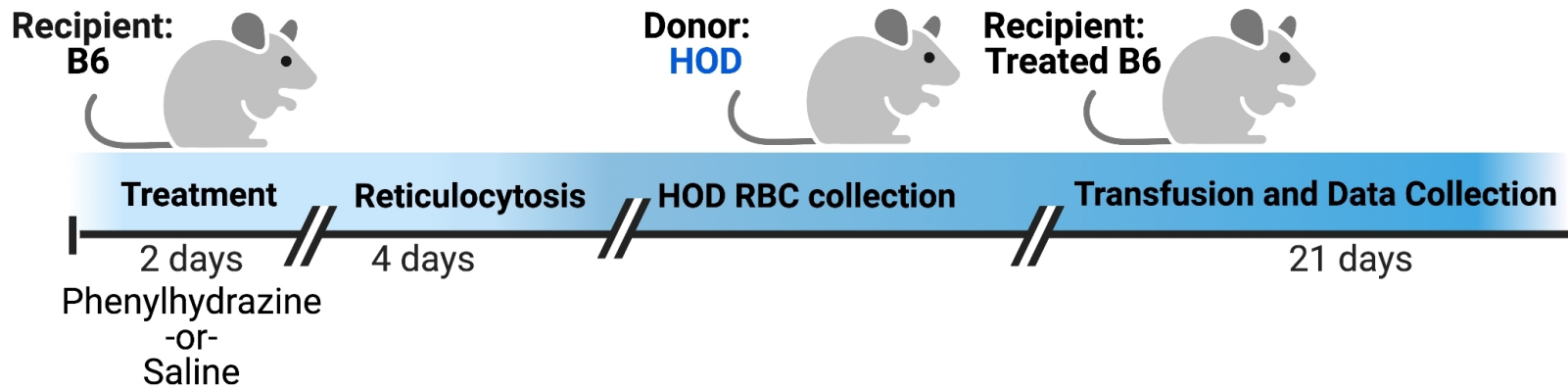


# Transfusion of reticulocyte-rich RBCs increases RBC alloimmunization and alloantibodies

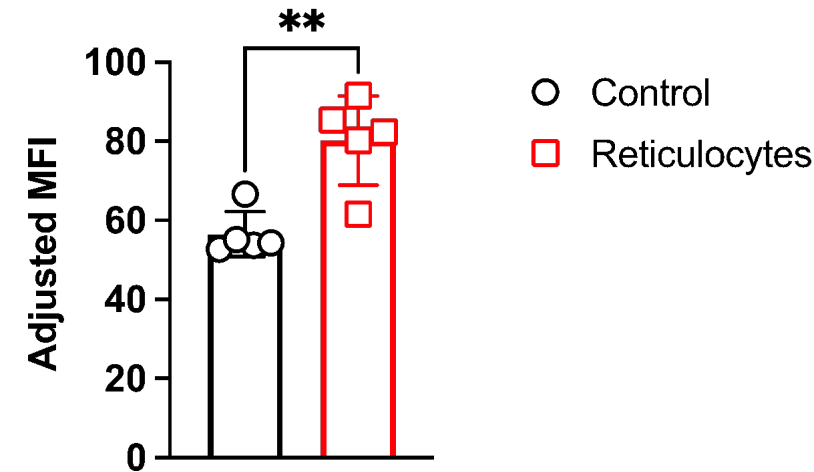
6 day storage



# Transfusion recipients with increased reticulocytes are primed to make alloantibodies



## HOD Alloantibodies



# Summary and Implications

- **Transfusion of RBC donor units with elevated reticulocyte frequencies**
  - **increased RBC alloimmunization rates and alloantibody levels**
  - **RBC donor units can have as few as 5% reticulocytes to observe effect**
- **Transfusion of RBC to patients with high reticulocytes also induces alloantibodies**
- **Implications regarding: donation intervals, screening units for reticulocyte %, especially for patients with hemolytic anemias**

## ARS Case-3

**A 65-year-old male is undergoing chemotherapy for AML and receiving frequent RBC and platelet transfusion support. The clinical team is concerned about a lack of platelet count increase after transfusion.**

**What is the first step in the workup when suspicious of platelet refractoriness?**

- A. Order Panel Reactive Antibody Test (PRA)
- B. Request ABO-matched platelets from blood bank
- C. Request cross-match compatible platelets from blood bank
- D. Perform two platelet transfusions with 15-60min post platelet counts to calculate corrected count increment (CCI)

# Platelet Transfusion - Refractoriness

**Definition: Corrected Count Increment (CCI) <7500 on  
two (consecutive) occasions  
15-60min after transfusion**

$$\text{CCI} = \frac{\text{Platelet increment (platelets/uL)} \times \text{BSA (m}^2\text{)} \times 10^{11}}{\text{Platelet Dose (usually } 3 \times 10^{11}\text{)}}$$

**Acceptable CCI is > 5000**



# Refractoriness – Mechanism

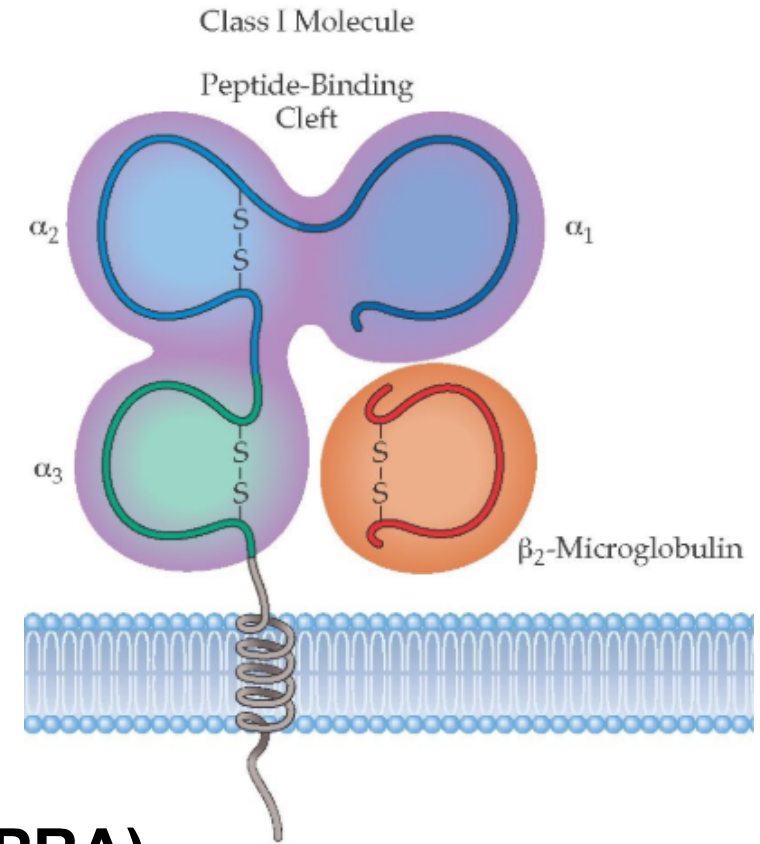
- >60min: Non-immune (most common)
- 15-60min: Immune
- Immediate / Non-immune: Splenomegaly
  - Drugs
    - Commonly cause immune-mediated thrombocytopenia:

Heparin, quinine, quinidine, phenytoin, procainamide, cephalosporin, linezolid, penicillin, rifampin, sulfonamides, vancomycin, ranitidine, abciximab, eptifibatide, tirofiban



# Refractoriness – HLA alloimmunization

- **HLA alloimmunization**
  - **Platelets express class I HLA molecules (A and B >>C)**
  - **Recipient antibodies to class I HLA mediates clearance**
- **Risks for alloimmunization:**
  - **Pregnancies, past transfusions, organ transplantation**
- **Order PANEL REACTIVE ANTIBODY (PRA)**
- **Order HLA type of patient**



# Alternative therapeutic approaches?

## Successful Desensitization of Severe Alloimmune Platelet Refractoriness and Provision of Permissive Platelet Transfusions with a Novel IgG-Targeted Enzyme Therapeutic

*Adnan Qamar<sup>1\*</sup>, Laurie Pearson<sup>2</sup>, John Junping Xin<sup>1</sup>, Andreas Klein<sup>2</sup> and Jensyn Cone Sullivan<sup>1</sup>*

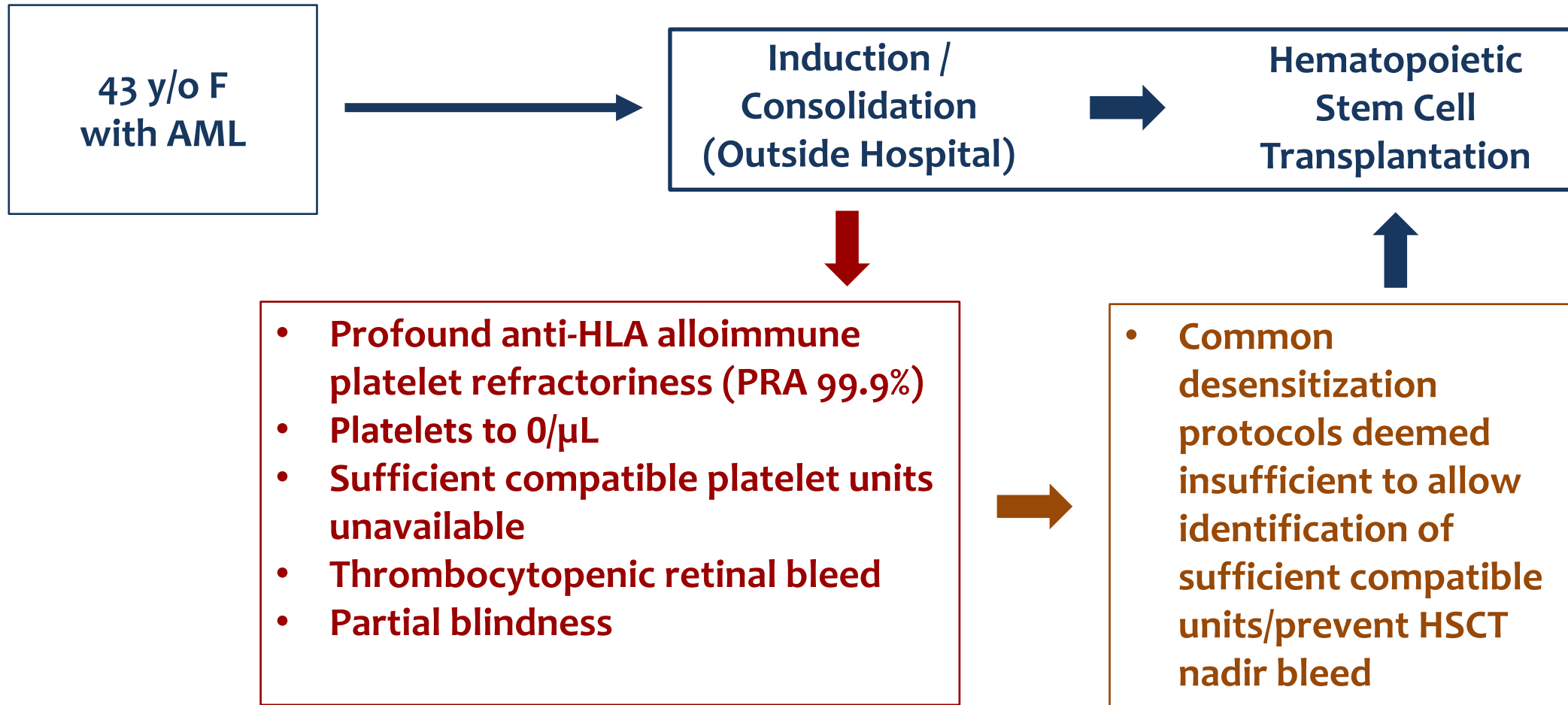
<sup>1</sup>Department of Pathology & Laboratory Medicine, Tufts Medical Center, Boston, MA, USA

<sup>2</sup>Department of Internal Medicine – Division of Hematology & Oncology, Tufts Medical Center, Boston, MA, USA

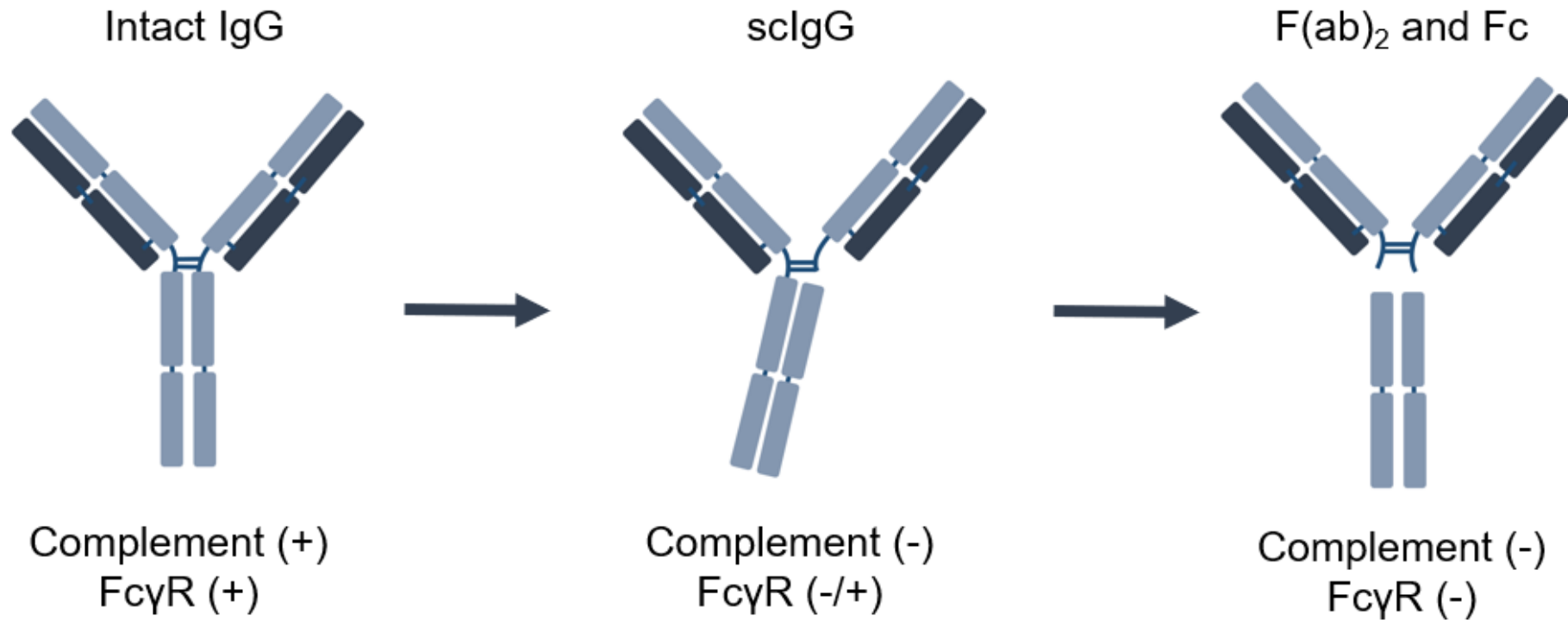
*\*Presenter*



# Background: Patient Case



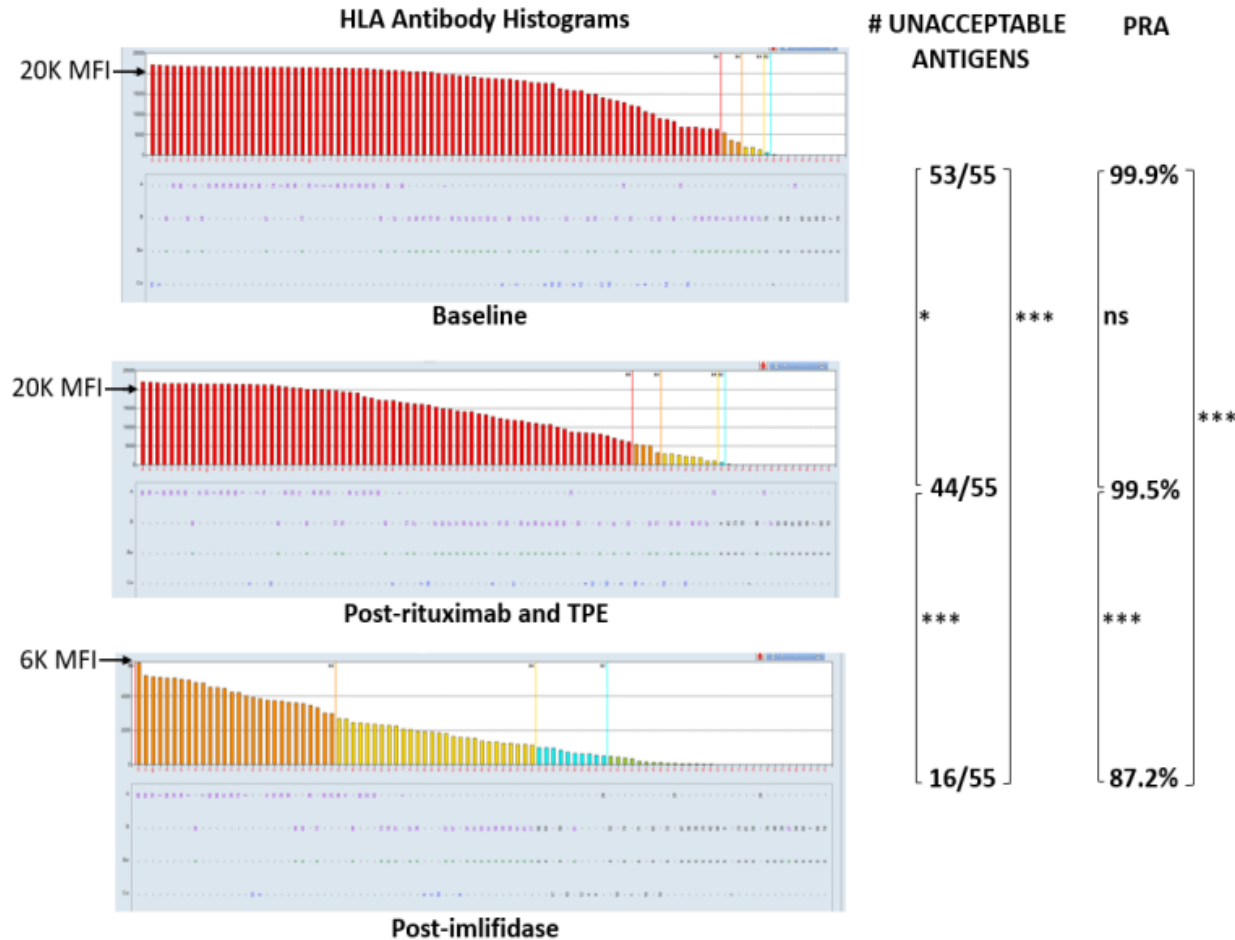
# Background: Imlifidase



- *S. pyogenes*-isolated cysteine protease
- Specifically cleaves/inactivates human IgG
- Used to desensitize highly-alloimmunized renal transplant recipients
- ?Potential to desensitize profoundly alloimmune platelet refractory patients



# Post-Imlifidase Decrease in Unacceptable Antigens and PRA

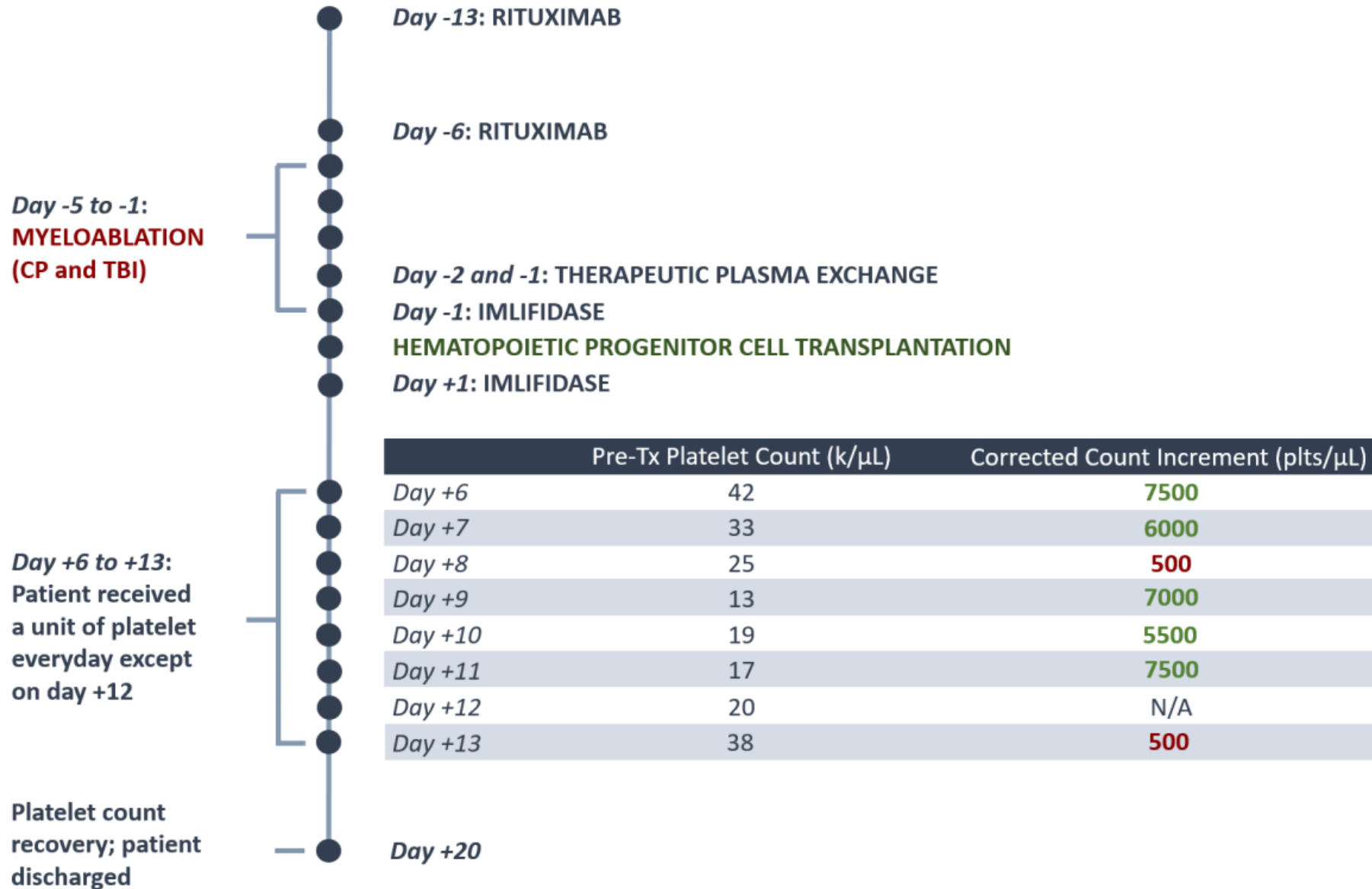


## HLA antibody levels in MFI throughout desensitization regimen

TPE = therapeutic plasma exchange, MFI = mean fluorescent intensity, HLA = human leukocyte antigen, PRA = panel reactive antibody. ns = not significant, \*  $P \leq 0.05$ , \*\*  $P \leq 0.01$ , \*\*\*  $P \leq 0.001$ .



# Peri-HSCT Conventional and Imlifidase Desensitization; Resultant Platelet Response



# CONCLUSION

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- **Imlifidase is a potentially powerful method to rapidly desensitize profound alloimmune platelet refractoriness, expand compatible platelet supply and promote good platelet transfusion response**



# What happens to HLA antibodies over time?

## **Serial HLA-Antibody Testing Identifies Waning Calculated Panel Reactive Antibodies (cPRA) In Platelet Transfusion Refractory Patients with Hematologic Malignancies**

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## **INTRODUCTION**

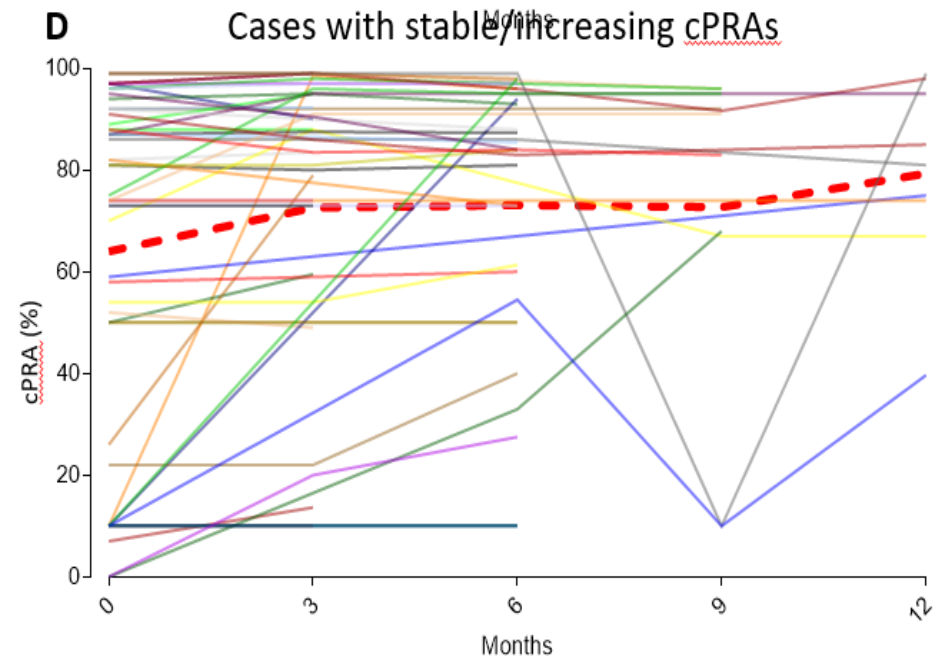
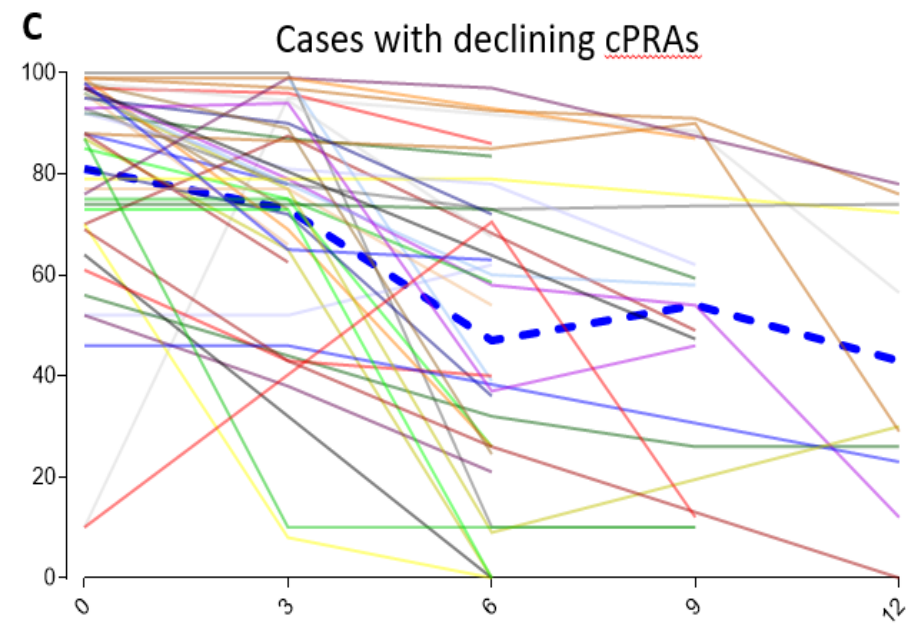
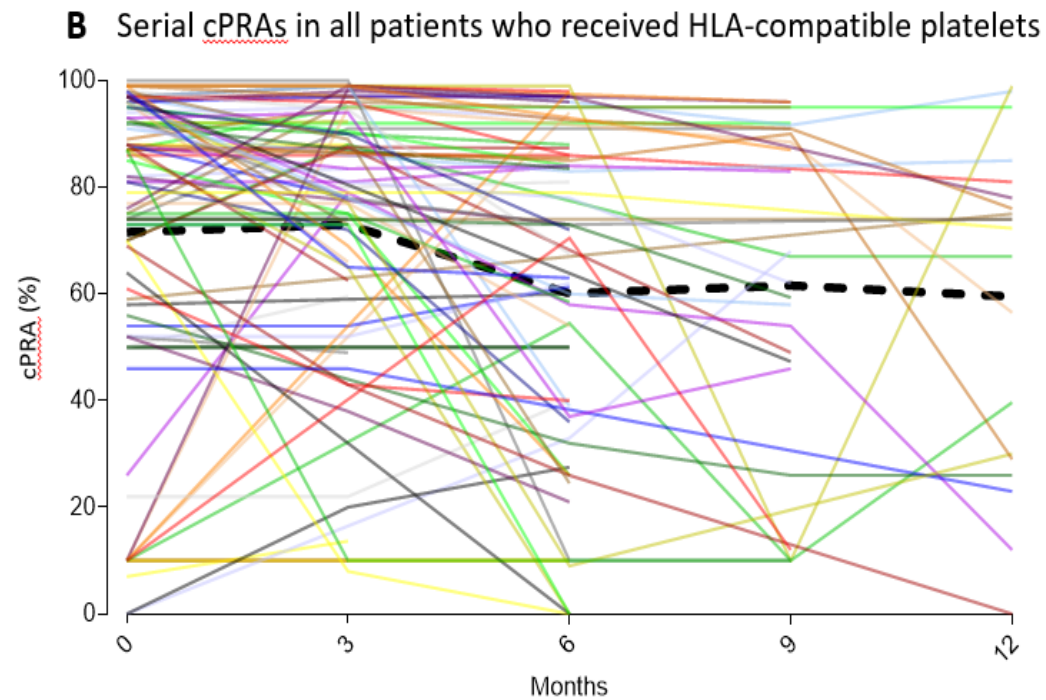
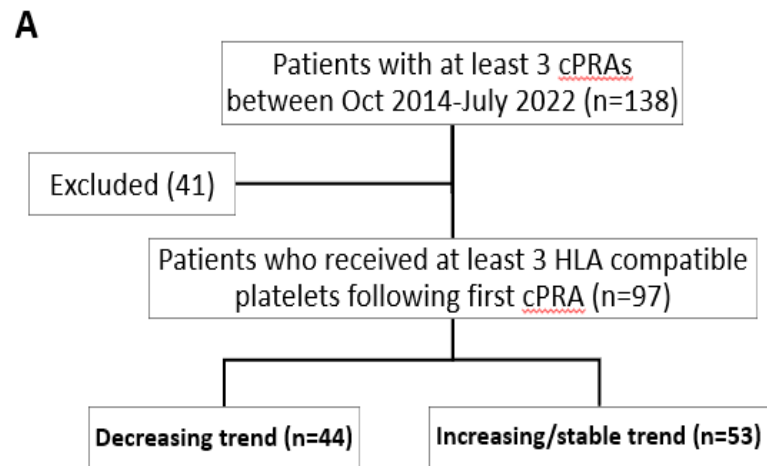
- **Serial testing for HLA antibodies every 1-2 months in all patients who receive HLA compatible products**

## **METHODS**

- **Retrospective review from October 2014 to July 2022. Patients who had at least 3 serial HLA antibody identification tests over the course of 1 year due to platelet refractoriness.**
- **We identified ones who required 3 or more HLA-compatible platelet transfusions during the same year (Figure A).**

# RESULTS

- **97 patients, mean age was 57 years.**
- **Majority Caucasian (81%) and female ,(80%)**
- **The mean number of HLA compatible and pooled/random donor platelets transfused during the study period were 30 ( $\pm$  29) and 28 ( $\pm$  51) units, respectively.**
- **1/3 of the women (26/78) had previous history of pregnancy.**
- **Overall, the average cPRAs declined significantly from 72% to 60% by 6 months ( $p=0.01$ ) (Figure B).**



Clinical features	Decreasing cPRA (n=44)	Increasing/Steady (n=53)	p-value
Age in years (mean ± SO)	56± 15	56± 15	NS
Race (Caucasian)	86%	73%	NS
Sex (Female)	77%	83%	NS
ABO (Group O)	46%	50%	NS
Average first PRA	80%	64%	NS
Prior pregnancies	30% (10/34)	40% (17/44)	NS
# HLA compatible products	30	29	NS
# Random donor products	35	21	NS
Compatible/mismatched platelets	3.9 : 1	6.8 : 1	NS
Diagnosis	61% AML	45% AML	NS
Allogeneic stem cell Tx.	60% (26/44)	40% (22/53)	0.07



# CONCLUSIONS

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- **Periodic assessment of HLA antibodies demonstrated a significant decline in cPRA in HLA alloimmunized patients despite chronic HLA-compatible platelet transfusions.**
- **Data showed that more than half of the HLA-alloimmunized patients will lose their antibodies before 12 months.**
- **Proactive periodic HLA antibody testing may help broaden the limited donor pool.**



## Take Home Message

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- **ESA and fostamatinib can be used in WAIHA**
- **Restrictive blood transfusion in AIHA and SCA**
- **Platelet refractoriness – imlifidase and CSA**

