45° Convegno Nazionale di Studi di Medicina Trasfusionale

Rimini | 29-31 maggio 2024

SIMTI

Anemia emolitica immunomediata e nuovi farmaci

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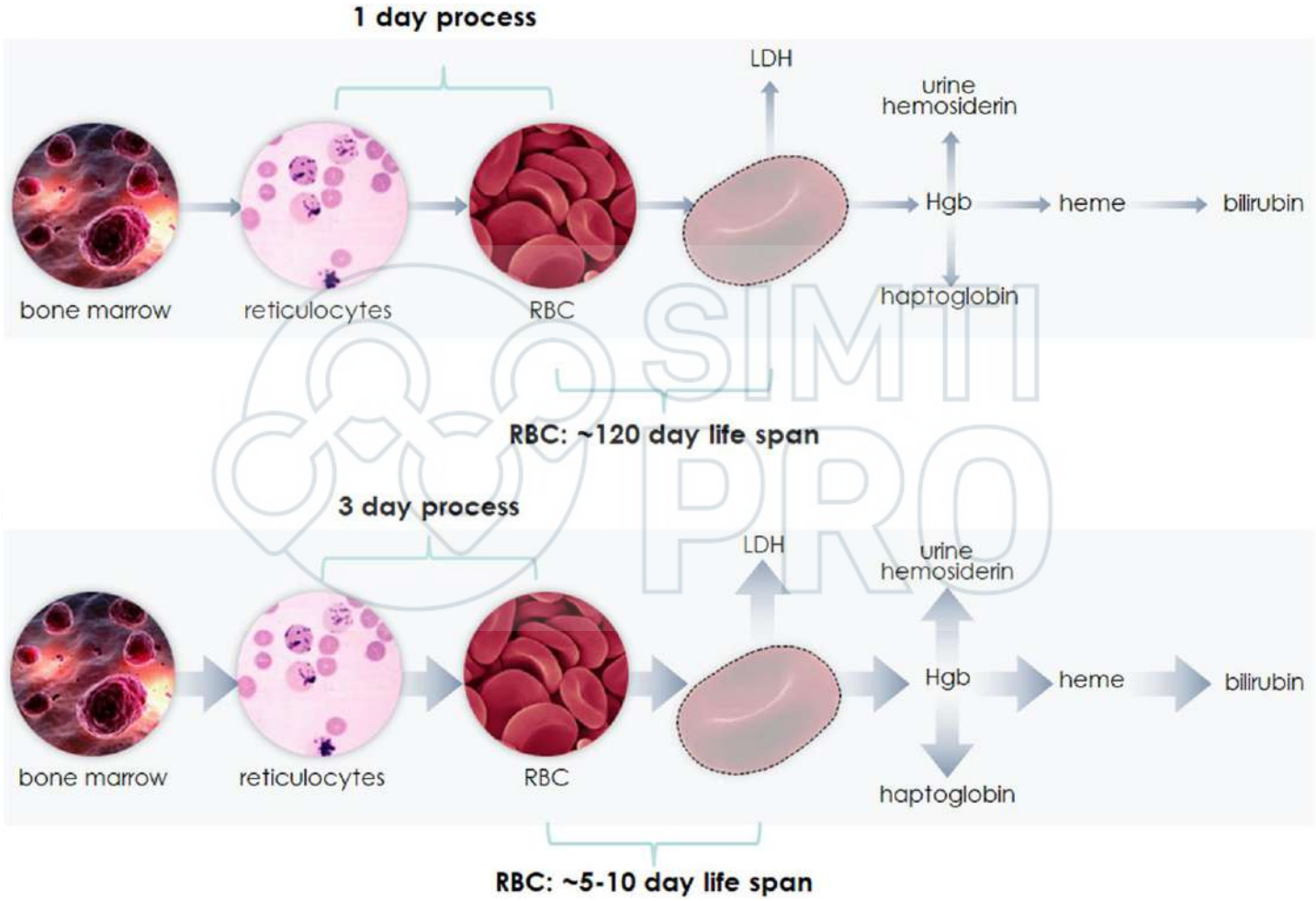
NO DISCLOSURES FOR THIS TALK

Red cell production and catabolism in states of normal or accelerated cell turnover



Kuter DJ. Blood 2022

Immune-mediated hemolytic anemia

Pathogenesis

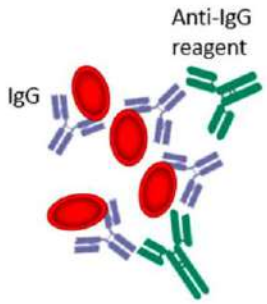
- **caused by autoantibodies directed against erythrocyte self-antigens, with or without complement activation.**
- **estimated incidence 1-3 per 10^5/year, prevalence of 17:100,000**
- **heterogeneous condition (from fully compensated to life-threatening)**

		Autoantibody characteristics			*DAT positivity*	*In vivo hemolysis (RBC sequestration)*
		Class	*Optimal T of reaction (range)*	*Specificity*		
1. ***Warm AIHA***	***60-70%***	**IgG** (possible complement fixation, IgG1 and IgG3)	37°C (0-40)	Rh system	**IgG or IgG+ (weak) C**	**Extravascular** (spleen)
2. ***Cold AIHA***						
2a. Cold agglutinin disease (CAD)	***20-25%***	**IgM** (common complement fixation)	4°C (4-34)	I/i system	**C**	**Intravascular and extravascular** (**liver**/spleen)
2b. Paroxysmal Cold Hemoglobinuria (PCH)	***1-5%***	**IgG** (common complement fixation)	Reacts at 4°C and hemolyses at 37°C	P antigen	**Positive Donath-Landsteiner test**	**Intravascular and extravascular**
3. ***Mixed AIHA***	***5-10%***	**warm IgG** and **cold IgM**	4°C and 37°C		**IgG+high titer cold IgM**	**Extravascular/ Intravascular (spleen /liver)**

Barcellini W. 2015; Berentsen S. 2015; Barcellini W. 2015; Berentsen S. 2016; Barcellini W; 2018; Berentsen S. Br J Haematol. 2018; Jaeger U, Blood Rev 2019.

Immune-mediated hemolytic anemia

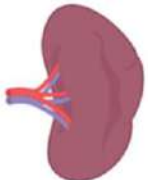
Warm-antibody vs Cold-antibody AIHA



IgG auto Abs weakly activate complement, do not agglutinate spontaneously

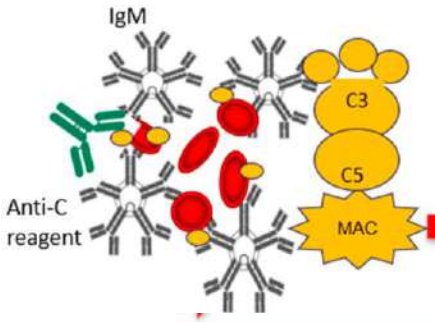
Agglutination occurs with anti-IgG reagent

DAT + IgG



extravascular hemolysis by phagocytosis of IgG-opsonized RBC in the spleen (wAIHA)

- Polyclonal antibodies
- May occur as primary or secondary disease
- Complement-mediated hemolysis less likely



IgM auto Abs agglutinate RBC and strongly activate complement, Spontaneously agglutinate RBC

DAT + C

intravascular hemolysis by membrane attack complex (MAC)

extravascular hemolysis by phagocytosis of C3b-opsonized RBC in the liver (CAD)

- Most often monoclonal for presence of clonal B-cell lymphoproliferative disorder
- Hemolysis is complement-mediated hemolysis (classical pathway)

Immune-mediated hemolytic anemia

Major determinants of clinical severity of AIHA

- ✓ Autoantibody class, thermal amplitude
- ✓ Efficiency in activating complement
- ✓ Activity of immune system (spleen, liver and lymphoid organs)
- ✓ Efficacy of the bone marrow compensatory response

- Extravascular hemolysis: 17 ml RBCs/hr = 420 ml RBCs/24hr

- Intravascular hemolysis: 200ml RBCs in 1 hr

Immune-mediated hemolytic anemia

Goals of therapy for wAIHA

- Normalization of hemoglobin is rarely required.

- Aim to stable Hgb level over 10 g/dL, resolution of symptoms, and transfusion independence

- Avoid the side effects of corticosteroids, with chronic prednisone dosage never exceeding 5 mg/d

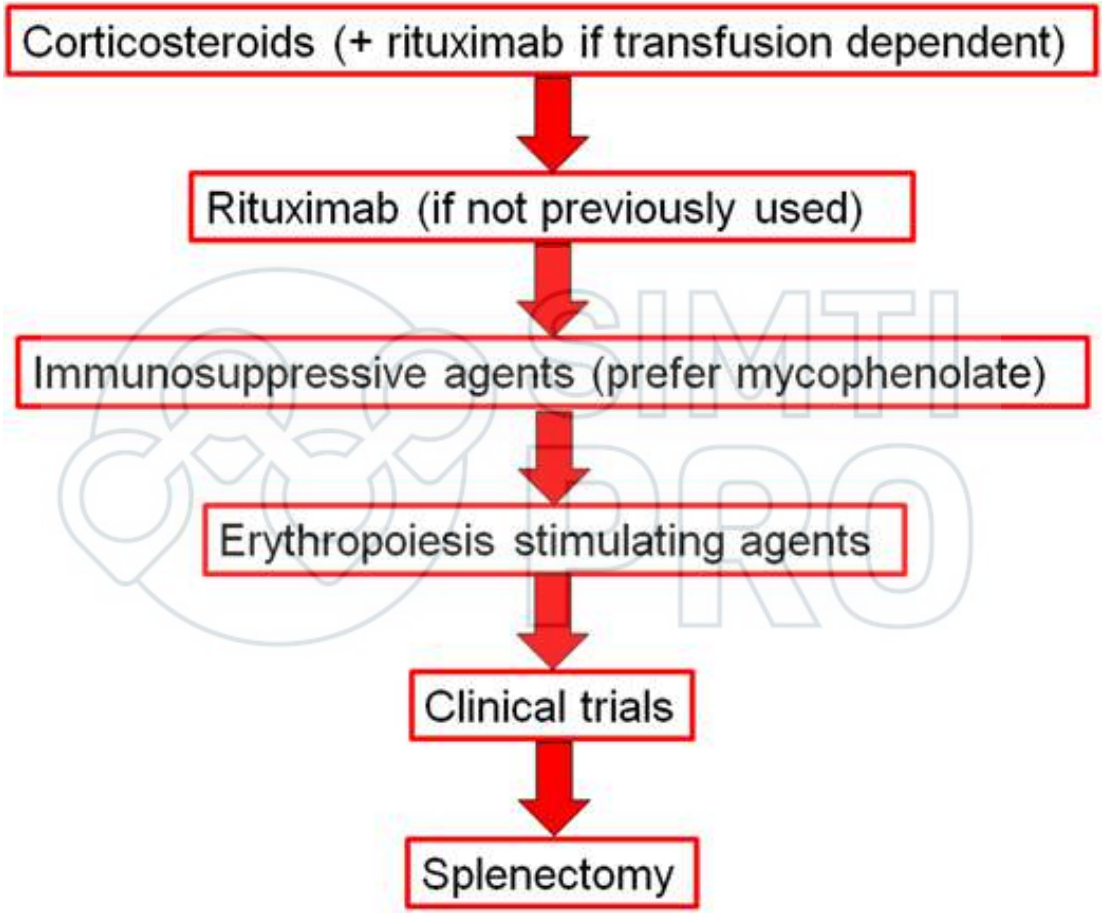
- Definition of response: an increase in Hgb by more than 2 g/dL or normalization of Hgb without a biochemical resolution of hemolysis, along with an absence of transfusion for the last 7 days

- Complete response (CR): normalization of Hgb, no evidence of hemolysis (normal bilirubin, LDH, haptoglobin, and reticulocytes), and the absence of transfusions

Jäger U et al. *Blood Rev.* 2020

Immune-mediated hemolytic anemia

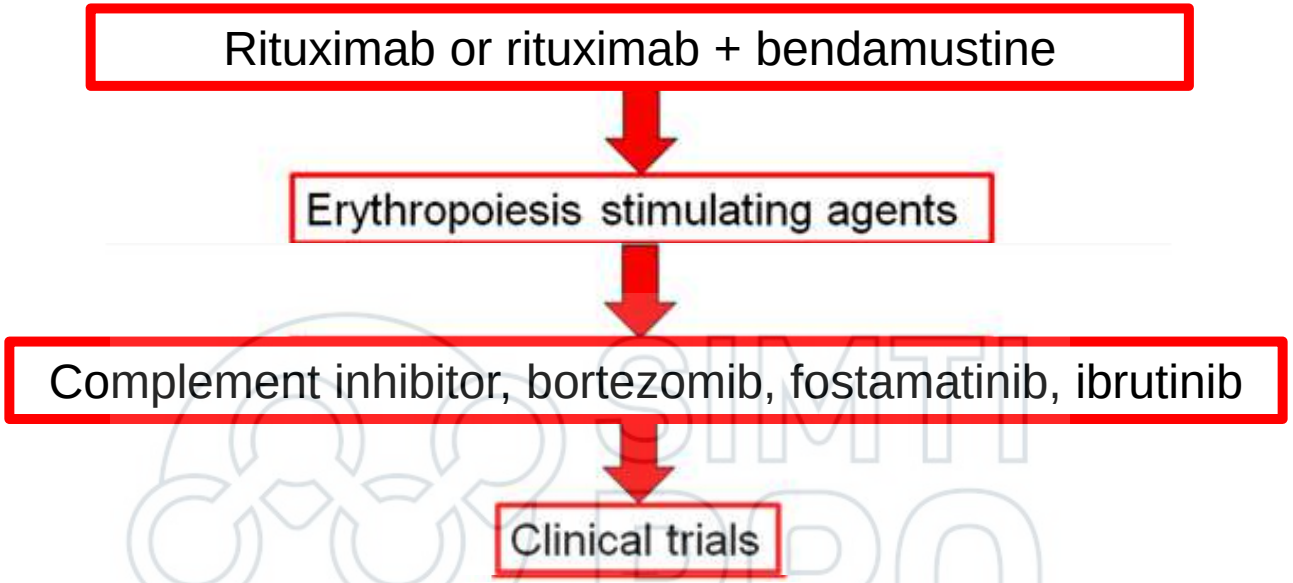
Current treatment of wAIHA



- Steroids effective in 80% if cases but relapse in 50% within 1 year
- Rituximab: durable remission rate 70 % percent

Immune-mediated hemolytic anemia

Current treatment of cold AIHA

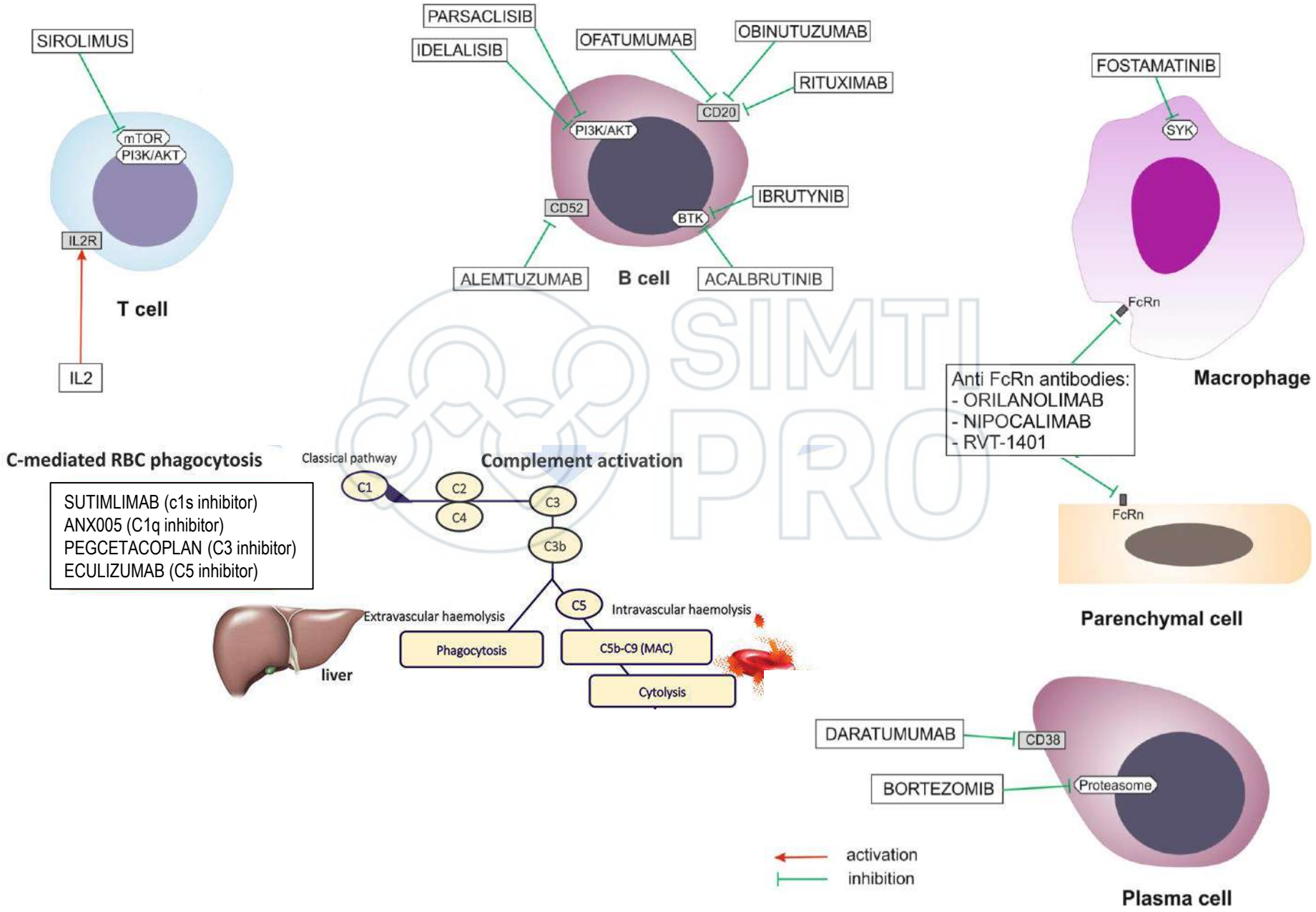


- Patients with mild anemia or compensated hemolysis and no clinical symptoms do not benefit from treatment
- CAD should not be treated with corticosteroids
- Splenectomy is ineffective
- Rituximab: PR rate of ~50%, few CRs, median response duration of 6.5 to 11 months
- Rituximab + bendamustine: response rate at 78%, 53% CR at long term
- Complement inhibitors not effective for ischemic symptoms

Schöllkopf C et al. *Leuk Lymphoma* 2006; .Berentsen S. et al. *Blood* 2004; Berentsen S. et al. Blood 2017 & 2020

WARM AIHA
New agents

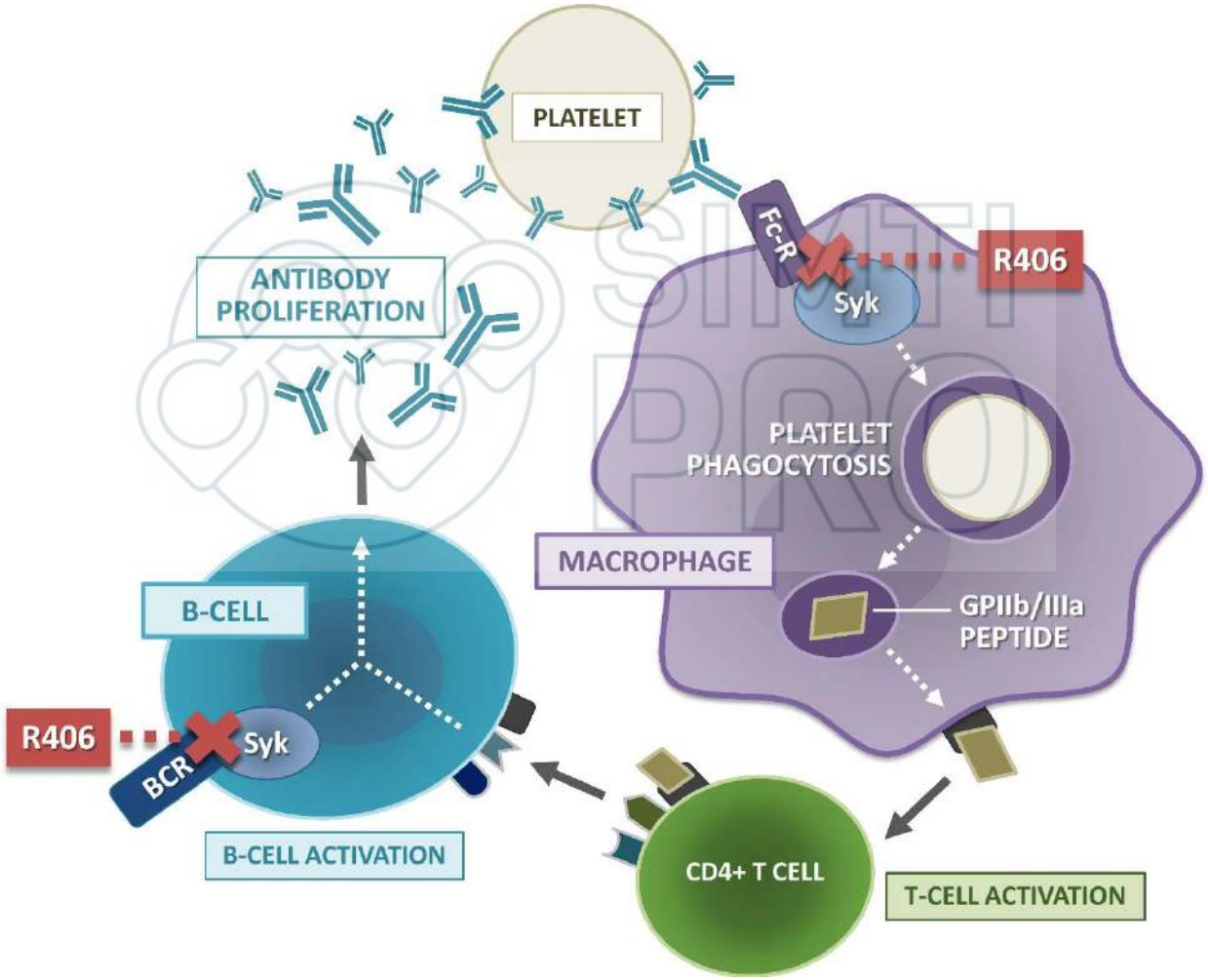
New agents for the treatment of autoimmune hemolytic anemia



Novel agents in treatment of wAIHA

Drug/Class	Mechanism	Indication	Study
Monoclonal Antibodies			
Alemtuzumab	Anti-CD52	Secondary AIHA	Case reports
Daratumumab	Anti-CD38	HSCT-AIHA	Case reports
Ofatumumab	Anti-CD20	Secondary AIHA	Case reports
Ianalumab	Anti-BAFF	Primary of secondary wAIHA	Phase 3
Povetacicept	Anti-APRIL/BAFF	Primary wAIHA, CAD, ITP	Phase 1b
Obexelimab	Anti-CD19	Primary or secondary wAIHA	Phase 3
B-cell receptor pathway and FcγR signaling inhibitors			
Ibrutinib	BTKi	Secondary AIHA	Case reports
Rilzabrutinib	BTKi	Primary, secondary wAIHA	Phase 2
Venetoclax	Bcl2	Secondary AIHA	Case reports
IgG-mediated Phagocytosis Inhibitors			
Fostamatinib	Syk inhibitor	wAIHA	**Phase 2,3**
Sovleplenib	Syk inhibitor		**Phase 2/3**
Nipocalimab	FcRn MoAB	wAIHA	**Phase 2/3**
Orilanolimab	FcRn MoAB	wAIHA	Phase 2
Complement inhibitors			
Annexion-005	C1q inhibitor	wAIHA, CAD	Phase 1/2
Eculizumab	C5 inhibitor	CAD/Mixed AIHA	Case reports, Phase 2
Pegcetacoplan	C3/C3b inhibitor	wAIHA, CAD	Phase 1/2
Bortezomib	Proteosome Inhibitor	WAIHA, CAD	Case reports, Phase 2

SPLEEN TYROSINE KINASE (SYK) INHIBITORS
FOSTAMATINIB



Paik J. *Drugs* 2021

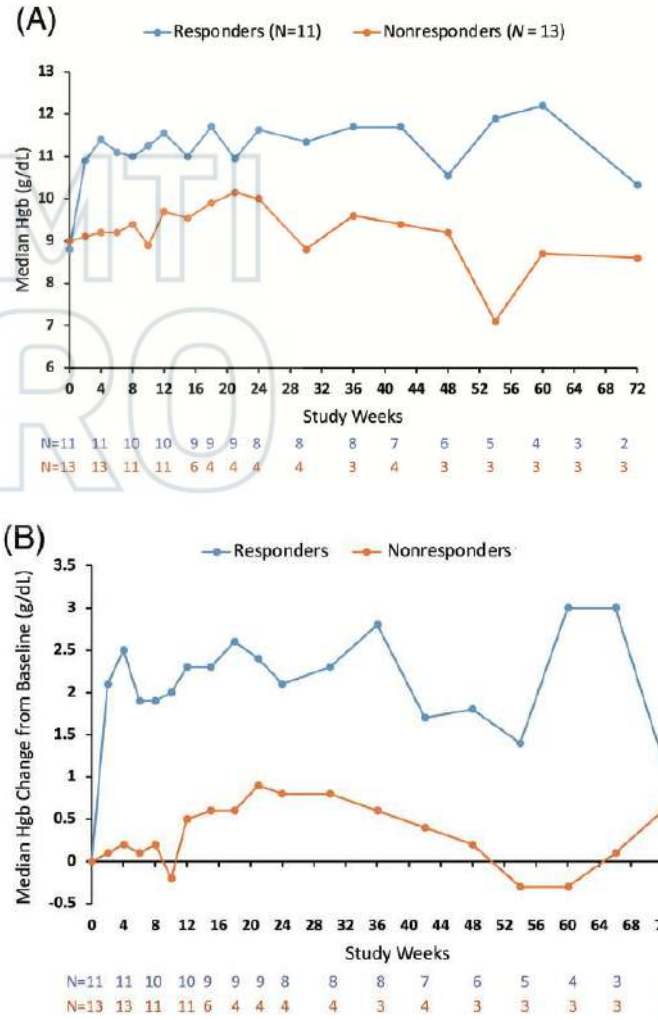
SPLEEN TYROSINE KINASE (SYK) INHIBITORS

FOSTAMATINIB

Fostamatinib for the treatment of warm antibody autoimmune hemolytic anemia: Phase 2, multicenter, open-label study

SOAR study

- 26 patients treated with fostamatinib at 150 mg BID
- Primary endpoint:Hb level of >10 g/dL and ≥2 g/dL the baseline Hb
- 21 of 24 patients (50%) achieved the primary endpoint
- Post-analysis ≥1.5 g/dL in Hb from baseline) met by 15 of 24 patients (63%)



Kuter ey al. Am J Hematol. 2022

SPLEEN TYROSINE KINASE (SYK) INHIBITORS

FOSTAMATINIB

Phase 3, Randomized, Double-Blind, Placebo-Controlled, Global Study (FORWARD) of Fostamatinib for the Treatment of Warm Antibody Autoimmune Hemolytic Anemia

David J. Kuter, Caroline I. Piatek, Khalil Saikali, Wolfgang Dummer

- Approved for ITP April 17, 2018
- AIHA Orphan Drug designation

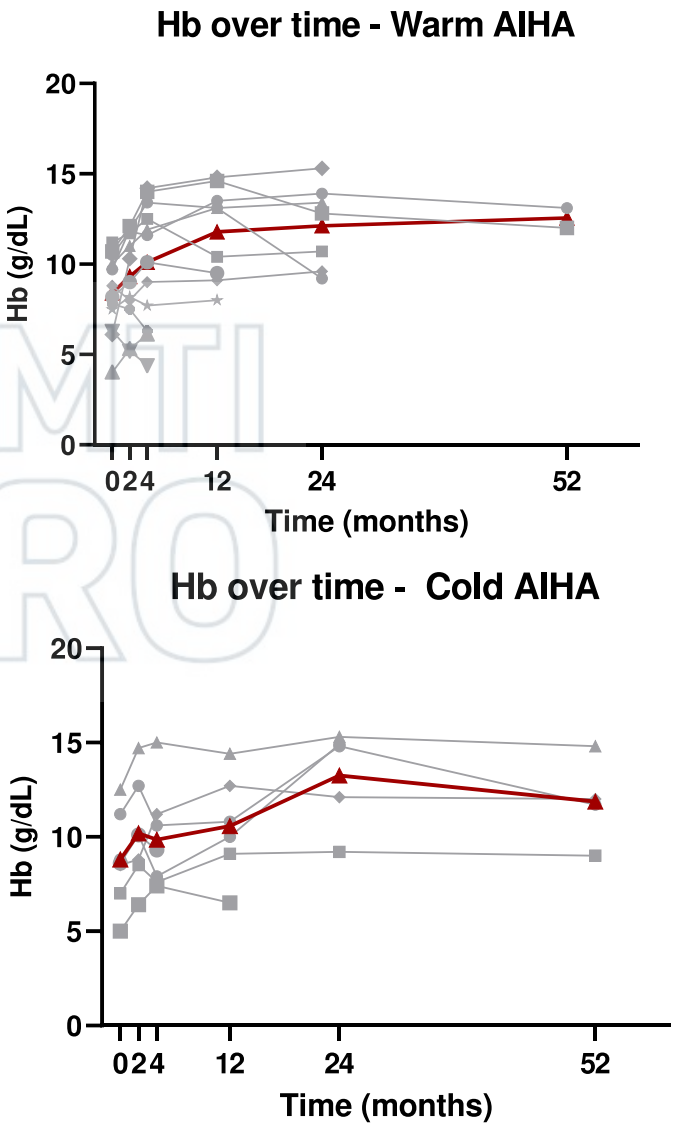
- FORWARD study is 24-week Phase 3 RCT (N=90)
- Primary endpoint: Hgb > 10 g/dL and ≥ 2 g/dL from baseline
- Overall response rate: 35.8% in fostamatinib group vs 26.7% in placebo group.
- Reanalysis: 33% in fostamatinib group vs 14.0% in placebo group. (Two patients removed from placebo group who did not have evidence of hemolysis)
- High placebo response rate observed (esp in Eastern Europeans)

Regions	Durable hemoglobin response, n (%)		
Treatment group	Fostamatinib	Placebo	p-value
Overall population – prespecified analysis	16/45 (35.6%)	12/45 (26.7%)	P=0.398
Overall population, n (%) – reanalysis	15/45 (33.3%)	6/43 (14.0%)	P=0.0395
U.S., Canada, Australia, Western Europe – reanalysis	8/25 (32.0%)	0/28 (0)	P=0.021
Eastern Europe – reanalysis	7/20 (34.0%)	6/15 (40.0%)	NS

Kuter D et al. *Blood.* 2022; 140 (suppl 1): 2438-2439.

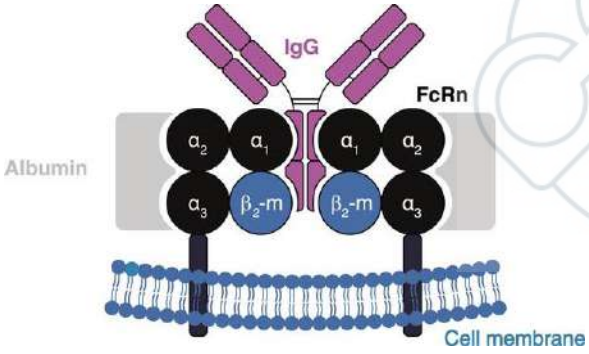
ANTI-CD38 ANTIBODIES
DARATUMUMAB

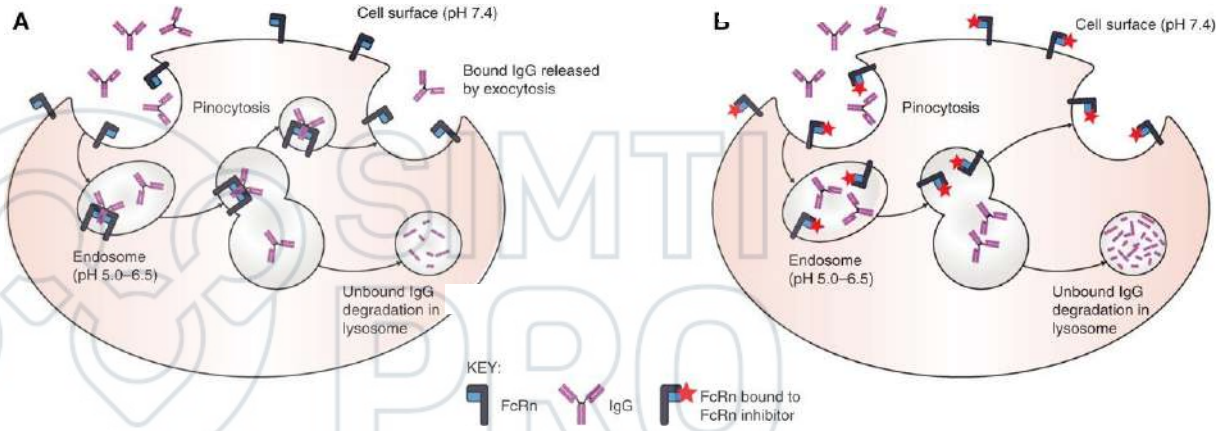
- Multinational retrospective observational study of 19 patients with AIHA with or without ITP
- Daratumumab 16 mg/kg weekly, 4 or 8 doses
- Overall complete Hb response:
  - wAIHA patients 6/12 (50%)
  - cAIHA patients 4/7 (57%), complete Hb response in 3 patients
- Infections reported in 4/19 (21%) patients, including three of grade 3 and one of grade 1



Jalink M et al. Blood Advances 2024

FcRn Inhibition





- MHC class I FcγR
- IgG transplacental transport
- IgG recycling and transport
- Albumin recycling and transport

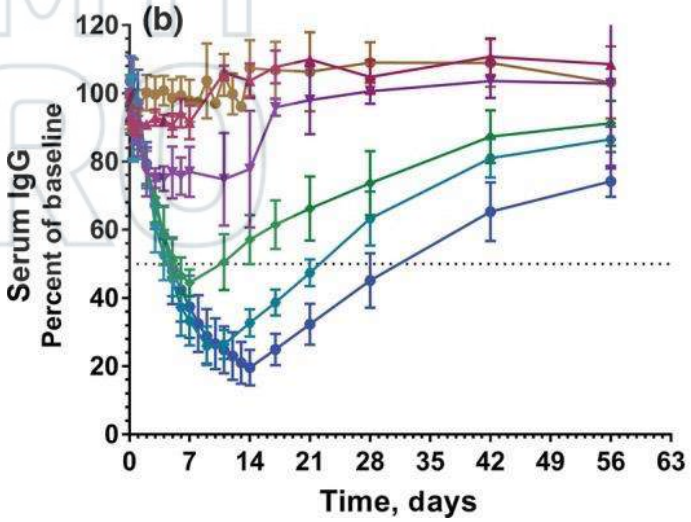
Ling LE et al. Clin Pharmacol Ther. 2019; 105: 1031-1039.
Patel DD, Bussel JB. J. Allergy Clin. Immunol. 2020; 146(3): 467-478.

FcRn INHIBITORS
NIPOCALIMAB

Energy Trial in Warm Autoimmune Hemolytic Anemia (wAIHA): Design of a Phase 2/3 Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nipocalimab, an FcRn Blocker

Irina Murakhovskaya, Bruno Fattizzo, Tarek Ebrahim, Kristen Sweet, Cathye Shu

- AIHA Orphan Drug designation
- **Vivacity-MG: Phase 2 trial in myasthenia gravis**
  substantial and rapid reductions in serum total and pathogenic IgG autoantibodies which were correlated statistically significantly with symptom improvement (P<0.0001).
- Open-label phase 2 UNITY trial
  positive results from the treatment of pregnant adults at high risk for severe hemolytic disease of the fetus and newborn (HDFN).
- ENERGY trial is 24-week Phase 2/3 RCT (N=111)
- Primary endpoint: durable response of improvement in Hgb
- Enrolment is ongoing.

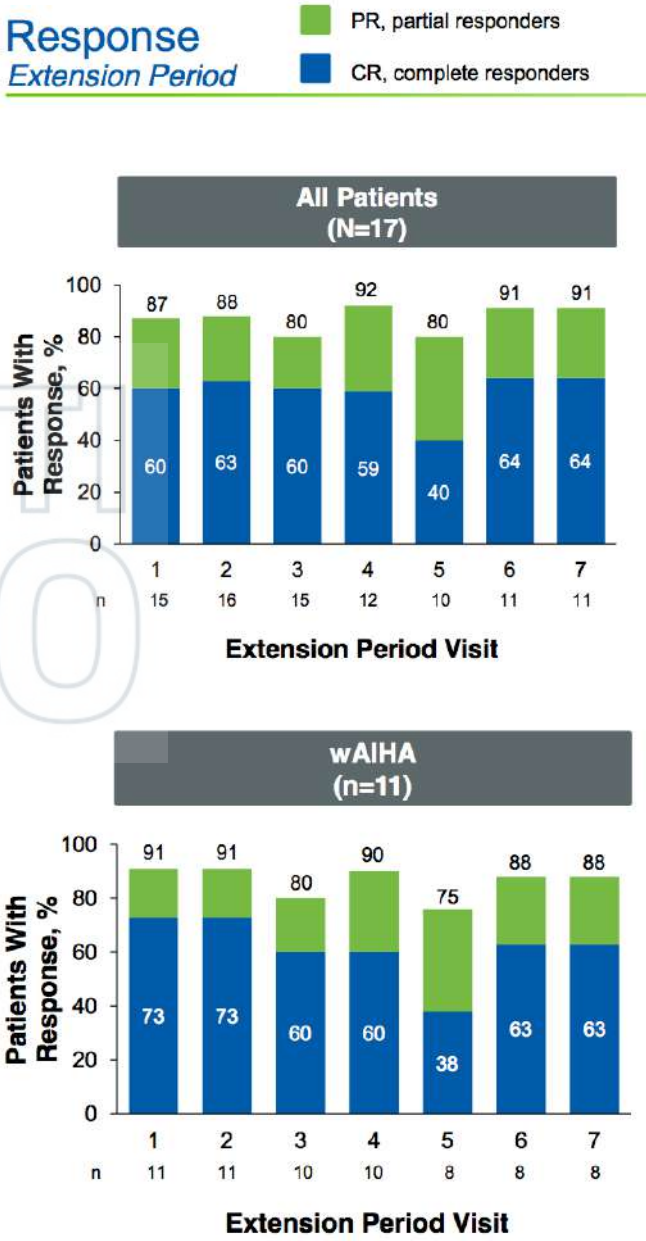


Murakhovskaya I et al. *Blood.* 2022; 140 (suppl 1): 2443-2444.
Murakhovskaya et al *EHA 2021, NORD 2021*. Figure provided by Author.

PI3Kδ INHIBITORS
PARSACLISIB

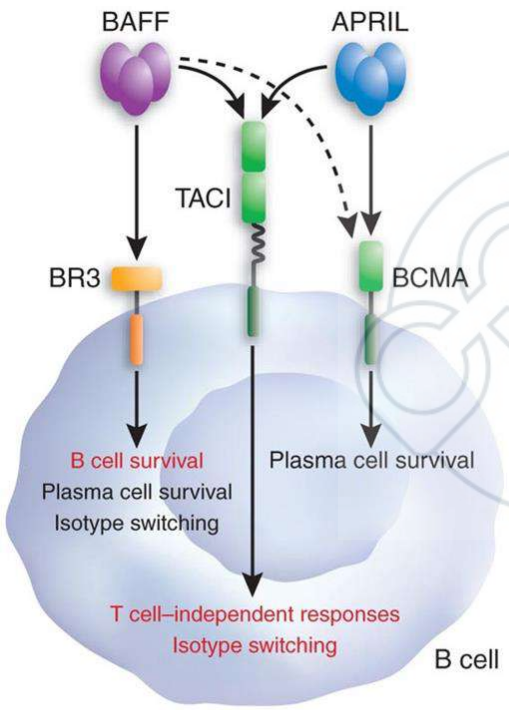
25 pts

- 16 pts (64%) wAIHA, 6 (24%) CAD, 3 (12%) mixed AIHA
- Overall response: CR in 8 pts (32%), PR in 16 pts (64%) from wk 6–12
- Among pts with wAIHA, 12 (75%) achieved PR
- Gr ≥3 AEs and SAEs (diarrhea, rash, psoriasis, CMV reactivation) were each reported in 9 pts (53%)
- 2 pts (12%) had TEAEs leading to parsaclisib discontinuation.



HemaSphere 2022

B-CELL ACTIVATING FACTOR - BAFF INHIBITION



- BAFF-mediated signaling needed for B cell maturation, proliferation and survival
- Elevated levels of BAFF have been detected in the serum of patients with various B-cell-mediated autoimmune disorders

- IANALUMAB
  - Monoclonal antibody against the BAFF receptor
  - B cell depletion via direct lysis of B cells
  - BAFF receptor blockade
- POVETACICEPT
  - Inhibition of BAFF and the proliferation inducing ligand April
  - Reduces antibody-secreting cells

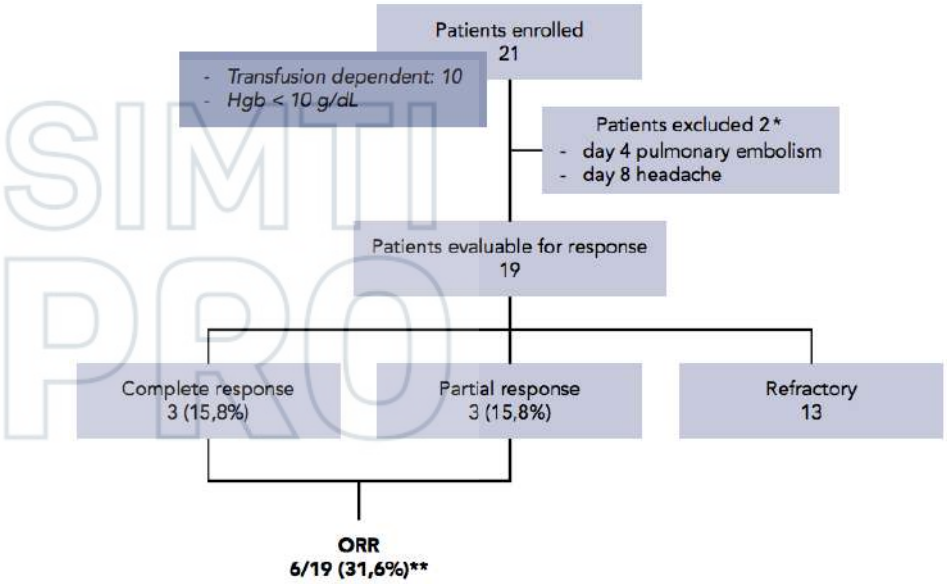
Bowman SJ et al. Lancet 2021; 399; 161-171.
https://www.alpineimmunesciences.com/alpn-303/

COLD AIHA
New agents

Short course of bortezomib in anemic patients with relapsed cold agglutinin disease: a phase 2 prospective GIMEMA study

Giuseppe Rossi,[1] Doriana Gramegna,[1] Francesca Paoloni,[2] Bruno Fattizzo,[3] Francesca Binda,[3] Mariella D'Adda,[1] Mirko Farina,[1] Elisa Lucchini,[4] Francesca Romana Mauro,[5] Flavia Salvi,[6] Monia Marchetti,[7] Paola Fazi,[2] Francesco Zaja,[4] and Wilma Barcellini[3]

- Single course of bortezomib (1.3 mg/sqm IV on days 1, 4, 8, 11)
- Four of 6 responding patients maintained the response after a median follow-up of 16 months
- One patient relapsed after 1 year and obtained a second remission with bortezomib
- All patients were alive at last follow-up except 1 who died of septic shock during off treatment
- Median hemoglobin levels (g/L) before and after treatment were 85 and 114 in responding patients, and 88 and 92 in nonresponding patients



Blood 2018

blood

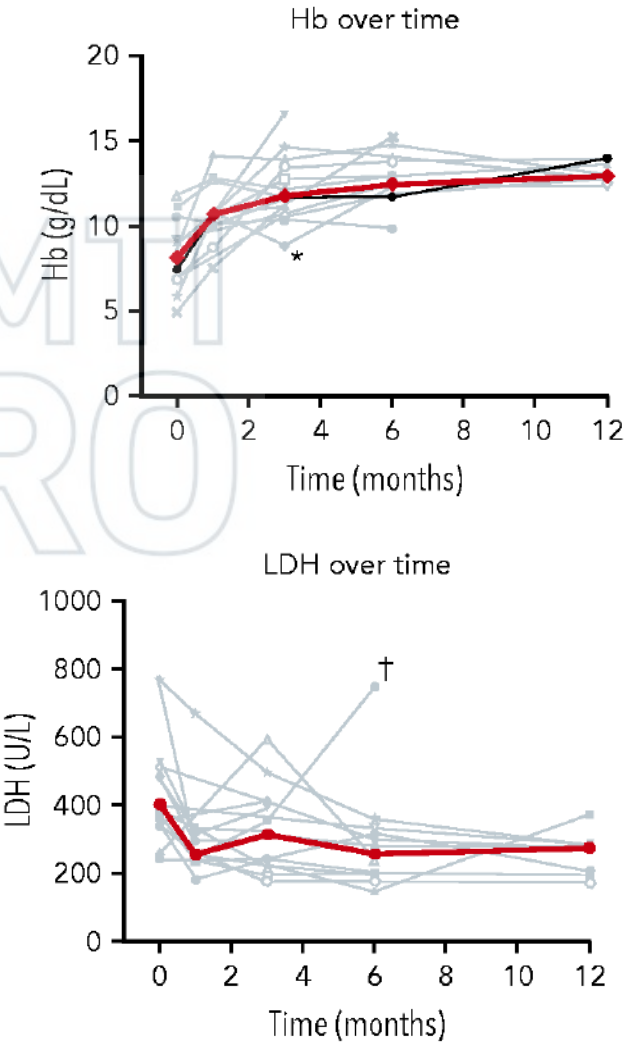
Effect of ibrutinib treatment on hemolytic anemia and acrocyanosis in cold agglutinin disease/cold agglutinin syndrome

Marit Jalink,[1,2] Sigbjørn Berentsen,[3] Jorge J. Castillo,[4] Steven P. Treon,[4] Marjan Cruijsen,[5] Bruno Fattizzo,[6,7] Ramona Cassin,[6] Despina Fotiou,[8] Efstathios Kastritis,[8] Masja De Haas,[9,10] Liesbeth E. M. Oosten,[9] Henrik Frederiksen,[11] Andrea Patriarca,[12] Shirley D'Sa,[13] and Josephine M.I. Vos[2,10,14]

- 15 patients with cAIHA (4 primary CAD, 5 WM, 5 CLL, 1 SLL
- Median number of prior therapies was 3

12 CR and 1 PR

- All transfusion-dependent patients became transfusion independent



Jalink M. et al. Blood 2021

CONCLUSIONS – UNMET CLINICAL NEEDS

- Rituximab remains the drug with the longest response duration in both wAIHA and CAD experiences, and novel drugs struggle to compare it. (and rituximab can be repeated at 1–2-year intervals in case of relapse)

- Endpoint of treatment should be 'relapse free survival' or 'duration of response' as endpoints for evaluating treatment efficacy in modifying disease course.

- Many novel drugs need to be administered indefinitely and do not shut down autoimmunity

- The acute AIHA phase represents in fact an unmet clinical need, since it is marked by the highest rate of complications, need of ICU admission, and mortality, and rituximab is a relatively slow-acting agent.

- T-cell compartment still not a target.