1ST SYMPOSIUM ON
INNOVATIVE THERAPIES IN HEMATOLOGY
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Targeted therapies for AIHA and CAD

Wilma Barcellini, MD
UOS Fisiopatologia delle Anemie, UOC Ematologia
Fondazione IRCCS Ca' Granda,
Ospedale Maggiore Policlinico
Università di Milano

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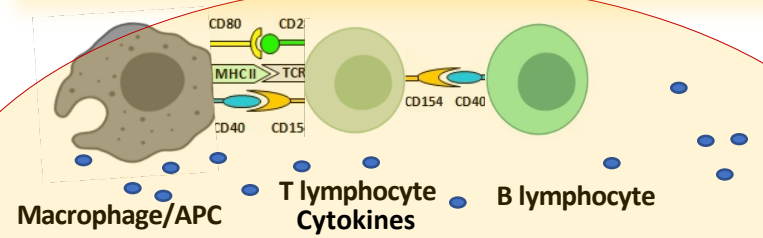
Università degli Studi di Milano

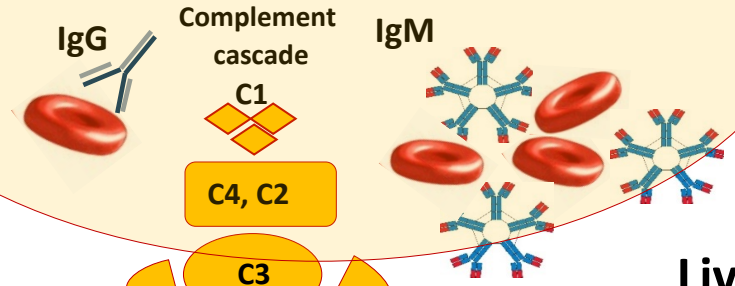
Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico

Autoimmune hemolytic anemia (AIHA): a complex pathogenesis and not only periphery….

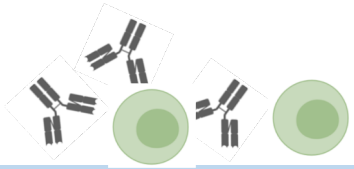
- **Genetic background**
- (HLA-linkage, IGHV, CTLA-4, LT-α, cytokine gene polymorphisms)
- **Immune-deficiencies**
- **Infections**
- **Neoplasms**
- **Drugs (CPI)**
- **Hematologic treatments (HSCT)**

Autoimmune activation (breakdown of both central and peripheral self-tolerance)



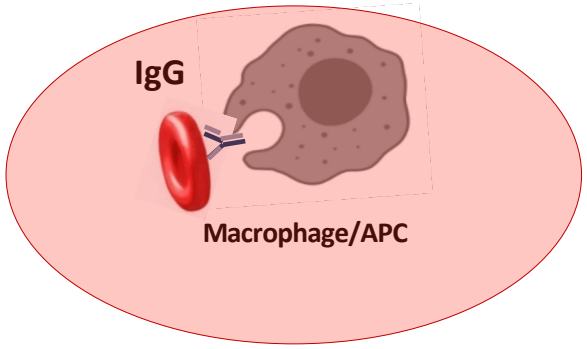


- **Molecular mimicry**
- **Emergence of forbidden clones**
- **Polyclonal B-cell activation**
- **Generation of neoantigens**
- **Immune dysregulation**



Autoimmune attack (Ab, T cytotoxic) against BM precursors (erythroblast?)

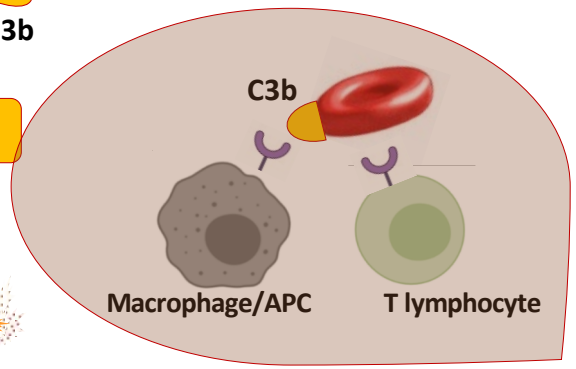
Spleen



Extravascular hemolysis (AIHA) PLT destruction (ITP)

Intravascular hemolysis

Liver



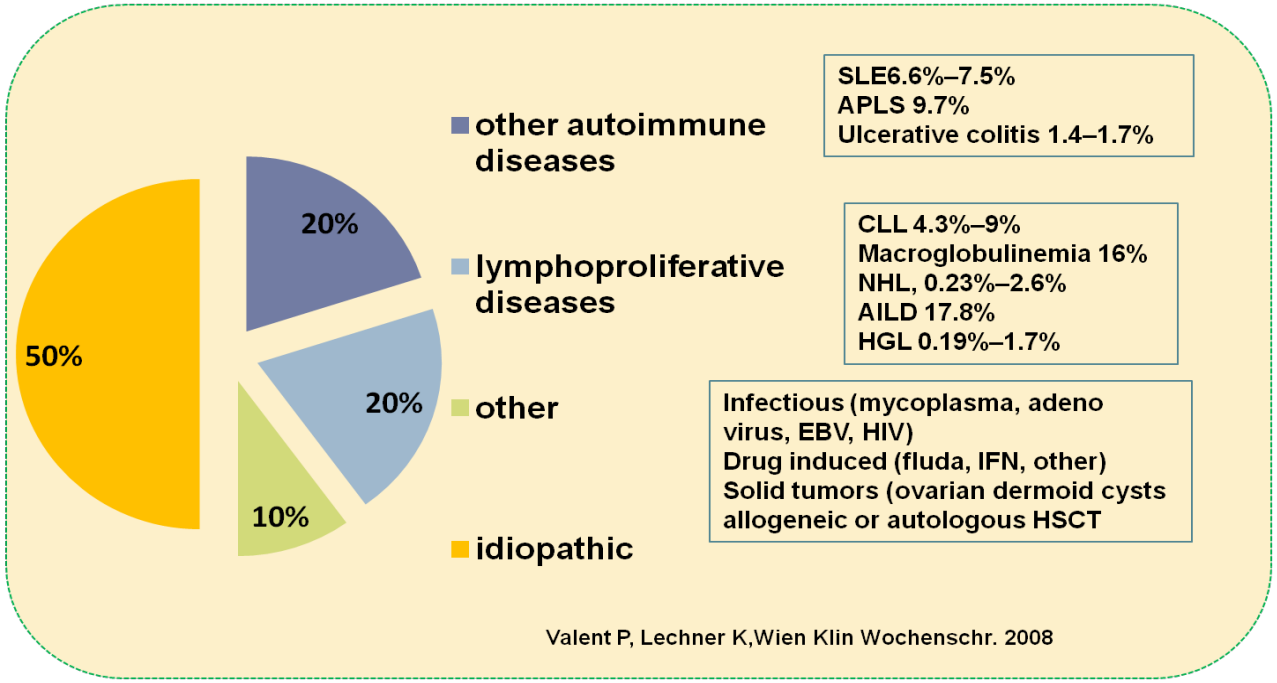
Extravascular hemolysis PLT destruction (ITP)

Inadequate BM compensation

Fattizzo B & Barcellini W, Exp Rev Clin Immunol 2022, modified

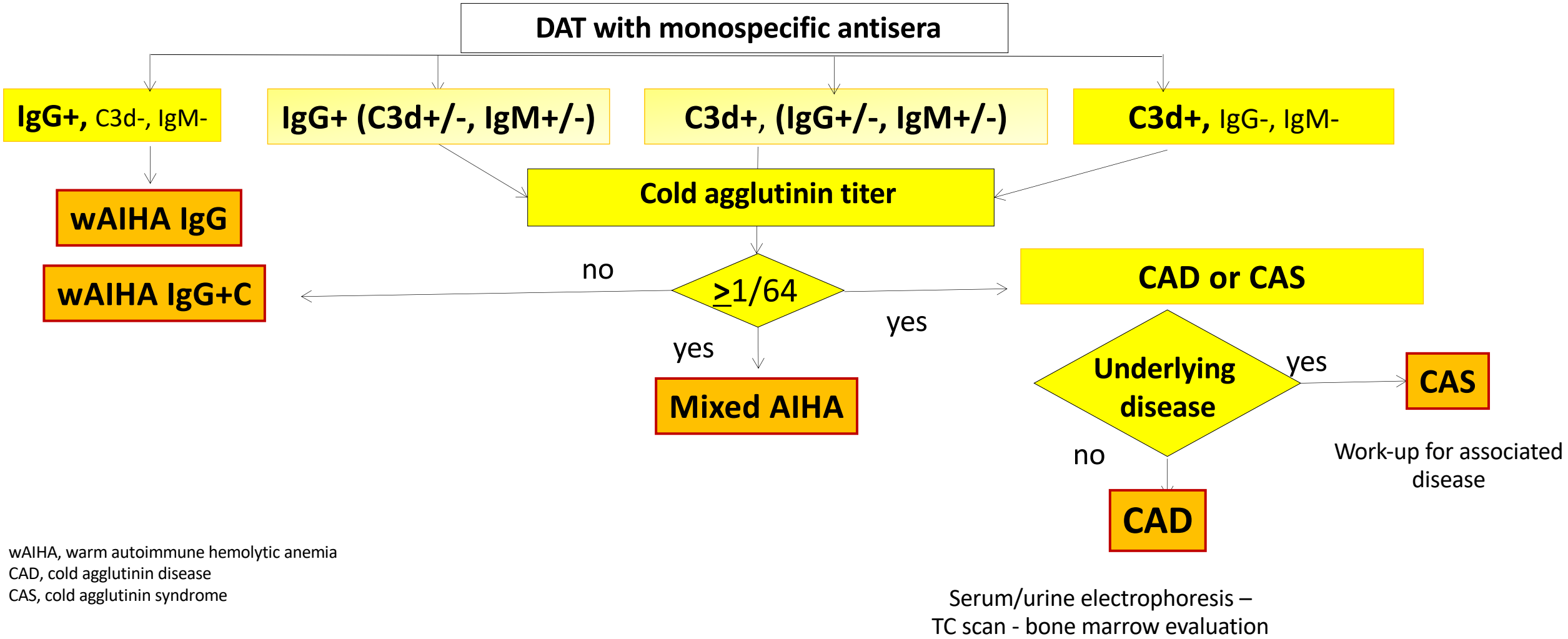
Autoimmune hemolytic anemia (AIHA): some highlights…

- estimated incidence 1-3 per 10^5/year, prevalence of 17:100,000
- heterogeneous condition (from fully compensated to life-threatening)
- "warm" IgG mediated (wAIHA), 60-70%, DAT + IgG (+/-weak C), extravascular hemolysis (spleen)
- "cold" IgM-mediated (CAD), 20-25%, DAT + C, high titer cold agglutinins, extravascular hemolysis (liver), intravascular in severe forms
- Mixed (5-10%), DAT negative (5-10 %)
- Primary and secondary cases (diagnostic work-up: TC, BM biopsy, autoimmune markers, endogenous EPO levels, consider confounders of hemolytic markers)
- Thrombotic complications (11-20% of cases) associated with Hb levels <6 g/dL at onset, intravascular hemolysis, previous splenectomy
- Infections (not only therapy-related, underlying immunodeficiency?)
- Acute renal failure, Evans Syndrome, mortality (3-4%)



Barcellini W. Expert Rev Clin Immunol. 2018; Jaeger U. Blood Rev 2019; Berentsen S & Barcellini W, NEJM 2020; Berentsen S. Blood 2021; Barcellini & Fattizzo, Blood 2021.

Diagnostic Algorithm of AIHA



wAIHA, warm autoimmune hemolytic anemia
CAD, cold agglutinin disease
CAS, cold agglutinin syndrome

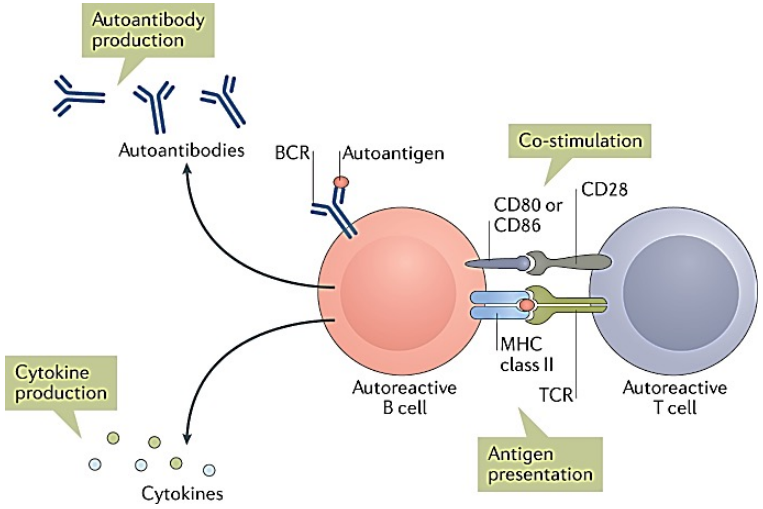
Berentsen S, Barcellini W. NEJM 2021

Standard therapies for warm AIHA (wAIHA) and cold agglutinin disease (CAD).

TREATMENT	RESPONSE RATES %	COMMENTS
		wAIHA
Steroids	**75–80**	**Curative in 20–30% only**; short-term side effects (mood swings, psychosis); long-term side effects (diabetes, hypertension, infections, osteoporosis, cushingoid syndrome)
Rituximab	**80–90**	**Durable responses 30-50%; re-treatment equally effective**; well-established safety profile
Splenectomy	**80**	Potentially curative; unsuitable for elderly; surgical complications; thrombotic risk; life-long immune suppression; infection prophylaxis required
Azathioprine/Cyclophospamide	**40–60**	**Steroid-sparing agent**; myelosuppression; infections; secondary malignancy; toxicity
Cyclosporin A	**40–60**	**Steroid-sparing**; possible dose adjustment; hypertension; infections; nephrotoxicity
Mycophenolate Mofetil	**80–100**	**Steroid-sparing**; particularly effective in children; good safety profile; mild myelosuppression
Danazol	**40**	**Steroid-sparing** agent; low effectiveness in refractory cases; long-term hepatotoxicity
IVIG	**40**	Particularly used in pediatric settings (60%); low toxicity; indicated in pot-infective forms
		CAD
Steroids	**15–30**	**Effective only at high and unacceptable dose**; short- and long-term side effects
Rituximab	**50**	**Mostly partial and short-lasting responses. Re-treatment equally effective**; well-established safety profile
Rituximab/fludarabine	**75**	**Sustained remissions (median response duration 6.5 years); hematologic and infectious toxicity**
Rituximab/Bendamustine	**70**	Sustained remissions; infectious complications
Recombinant erythropoietin	**50-70**	**Effective in wAIHA and CAD, cute or R/R cases particularly with reticulocytopenia**

Fattizzo B & Barcellini W, Exp Rev Clin Immunol 2022, modified

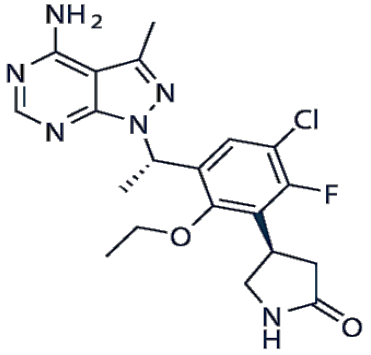
B-cell/ plasmacell directed therapies in AIHA



- B cells produce antibodies, serve as antigen-presenting cells (APCs) and produce cytokines.
- B cell-targeting strategies include
  - B cell depletion,
  - blockade of activation checkpoints
  - inhibition of pro-inflammatory cytokines
  - triggering of B cell inhibitory checkpoints and trafficking blockade

- Bortezomib, a proteosoma inhibitor, in association with dexamethasone or rituximab, observational multicenter studies, heterogeneous and mainly secondary AIHAs, ORR 70-80%, known toxicities
- Daratumumab, an anti-CD38 MoAb, several case reports in wAIHA and CAD
- Ibrutinib, an oral Bruton tyrosine kinase inhibitor (BTKi), mainly case reports and secondary AIHAs. A Phase 2 trial in association with rituximab ongoing
- Rilzabrutinib, an oral BTKi. A Phase 1 trial in wAIHA ongoing
- Isatuximab, an anti-CD38 MoAb, a Phase 1 trial in wAIHA ongoing
- Ianalumab, an anti-BAFF (B-cell activating factor). A Phase 2/3 randomized placebo-controlled study in wAIHA ongoing

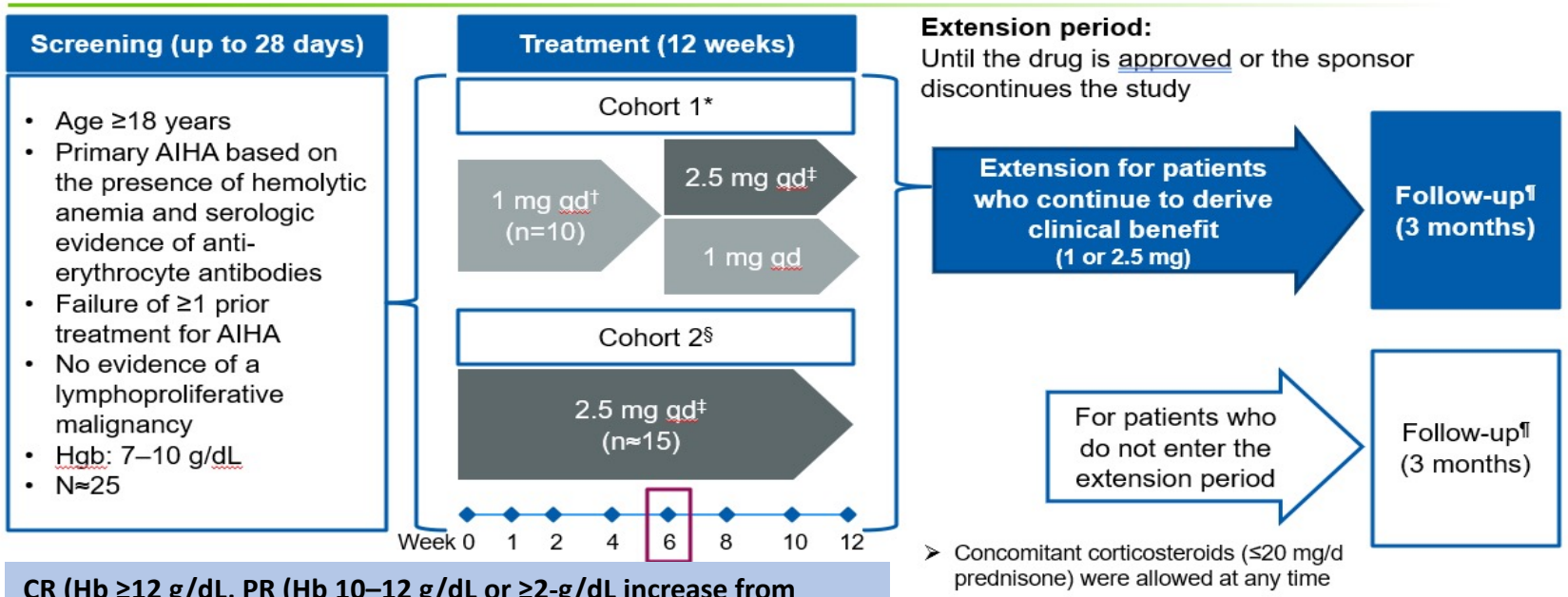
PI3Kδ inhibitor parsaclisib



LONG-TERM EFFICACY AND SAFETY RESULTS FROM AN ONGOING OPEN-LABEL PHASE 2 STUDY OF PARSACLISIB FOR THE TREATMENT OF AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)

Barcellini W. , Murakhovskaya I, Terriou L, et al- S286 – EHA 2022 oral presentation

Study Design



CR (Hb ≥12 g/dL, PR (Hb 10–12 g/dL or ≥2-g/dL increase from baseline at any visit from Weeks 6–12

- **25 pts enrolled, 16 wAIHA, 6 CAD, 3 mixed**
- **Mean (SD) Hb at baseline 8.9 (0.8) g/dL**
- **Disease duration > 5 yrs in 40%**
- **Previous therapies: rituximab 76%, transfusion(s) 36%, splenectomy 12%, other 36%**
- **20 pts (80%) completed 12 wk of treatment.**
- **Mean parsaclisib exposure 334 (range, 7–819) days.**

PI3Kδ inhibitor parsaclisib

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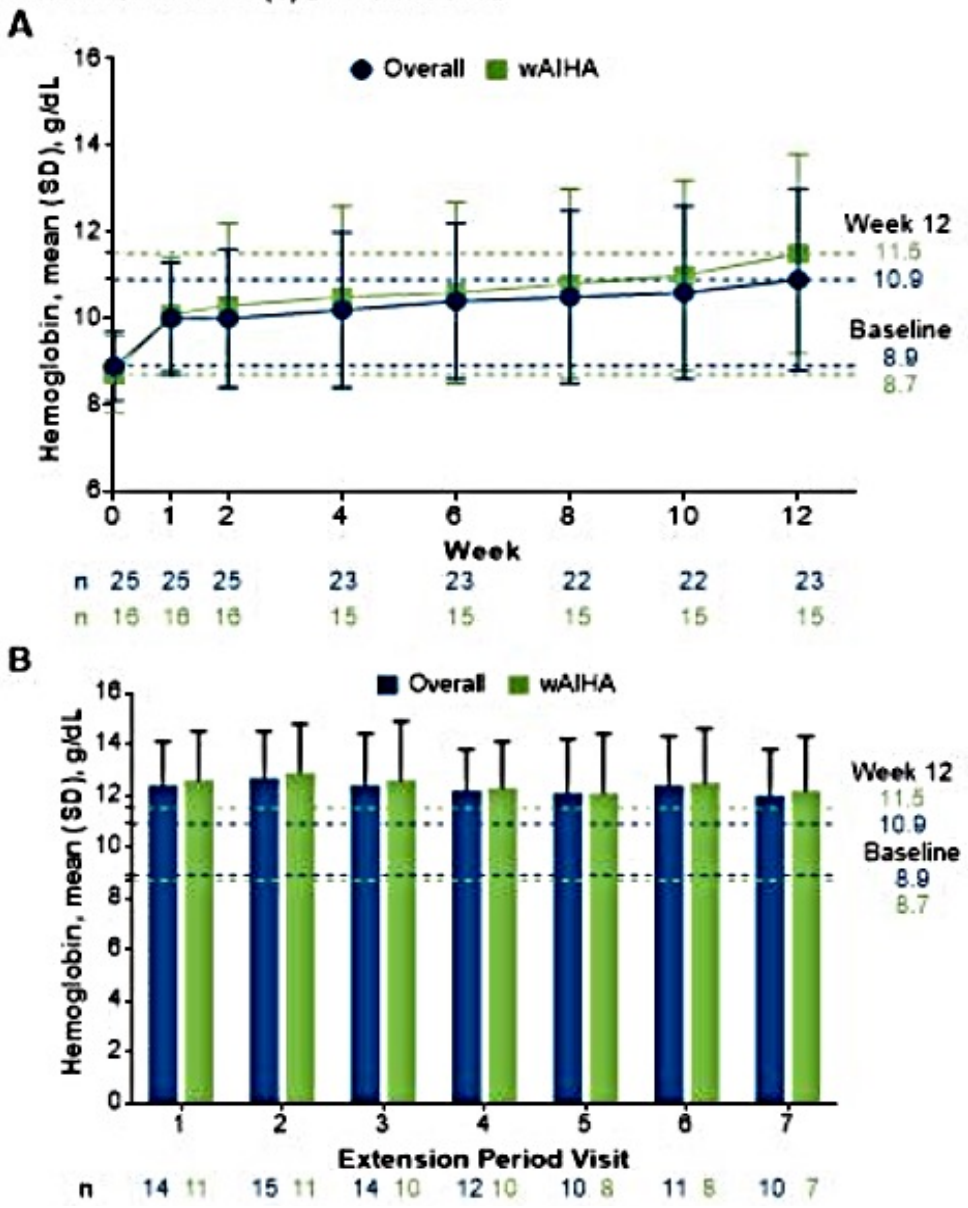
- Overall, **16 pts (64%) had a response, of whom 8 pts (32%) achieved CR and at any visit from wk 6–12**.
- Among pts **with wAIHA (n=16), 14 completed 12 wk of treatment, and 12 (75%) achieved a response, of whom 8 pts (50%) a CR**
- **Safety**: **TEAEs occurred in 21 pts (84%);** Gr ≥3 AEs and SAEs were each reported in 9 pts (53%). Treatment-related AEs: diarrhea and rash, CMV reactivation, psoriasis. One fatal TEAE (acute respiratory failure in the extension period due to COVID) was deemed unrelated to parsaclisib.

Parsaclisib resulted in rapid Hb improvements (as early as Week 2) that increased over 12 weeks of treatment and were sustained through the extension period.

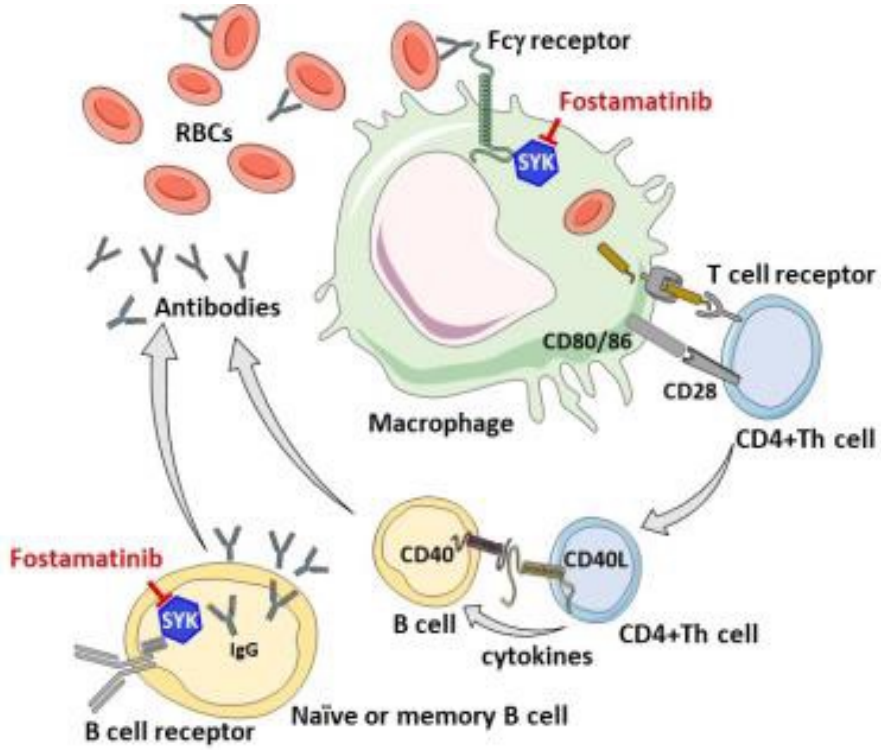
A randomized, controlled phase 3 trial in wAIHA is now recruiting (NCT05073458)

Figure. Mean Hemoglobin Levels by Study Visit During the (A) Initial 12-Week Treatment Period and (B) Extension Period



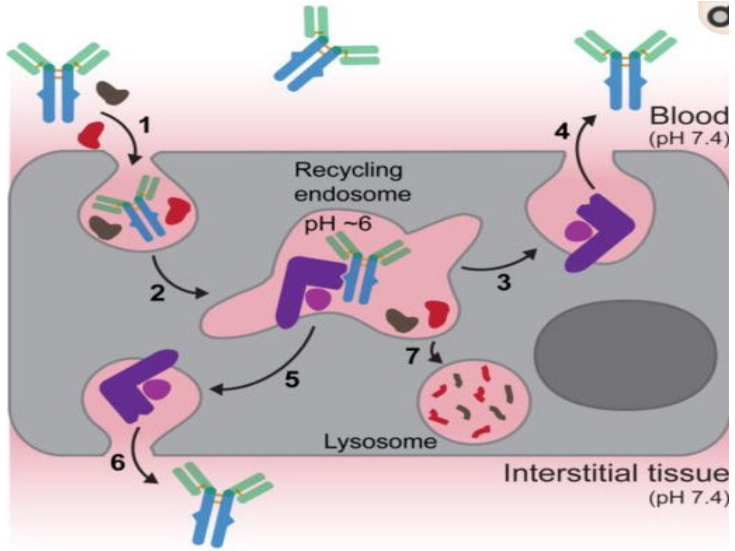
Fostamatinib, an oral spleen tyrosine kinase (SYK) inhibitor

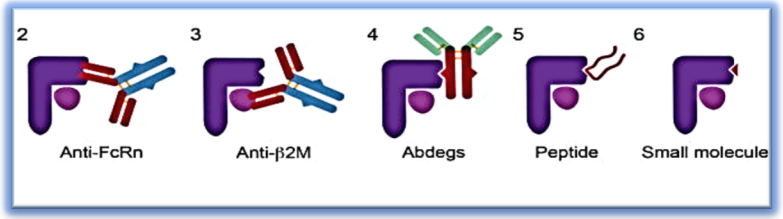
- **Fostamatinib is a potent oral SYK inhibitor, approved for immune thrombocytopenia (ITP), following 2 randomized, placebo-controlled trials in persistent and chronic disease**
- **One of the key pathogenic mechanism of wAIHA is RBC phagocytosis and destruction mediated by Fcg receptor-bearing macrophages in a spleen tyrosine kinase (SYK) dependent pathway**
- In wAIHA, the drug **may prevent RBC phagocytosis and thus RBCs destruction, and also prevent autoantibody production by B cells by inhibiting antigen presentation and differentiation of B cells in antibody-producing plasmacells**
- **The SOAR study is an open-label, Phase 2 multicenter study that evaluated the response to fostamatinib in adult patients with wAIHA (NCT02612558):** 25 pts (20 primary), 48% responded with sustained Hb increase
- **The FORWARD study, is a randomized, double-blind, phase 3 study; 90 pts enrolled:** preliminary results seem to indicate that the **primary endpoint of durable Hb response was not met in fostamatinib arm compared to placebo**. However, a post-hoc analysis showed that lower responses were observed in Eastern European countries, deserving **further data analysis**



Anti-neonatal Fc receptor

- Firstly described about 50 years ago, the Fc-Rn is responsible for the salvage of IgG from catabolism
- FcRn is structurally homologous to the MHC Class I heterodimeric receptor family, and is expressed by several cells including macrophages, monocytes, B cells, and dendritic cells·
- Blocking Fc-Rn may increase IgG clearance (including pathogenic autoantibodies), resulting in reduced IgG
- High dose IVIg can saturate FcRn and accelerate the clearance of endogenous IgG (another mechanism of action in AIHA, together with masking Fc mediated ADCC)
- Several Fc-Rn blocking strategies are under investigation in various autoimmune diseases: anti-FcRn heavy and light chain antibodies (2, 3), Fc-engineered IgGs that that have increased affinity for FcRn (4), peptides (5) and small molecules (6) that compete with IgG for binding to FcRn.





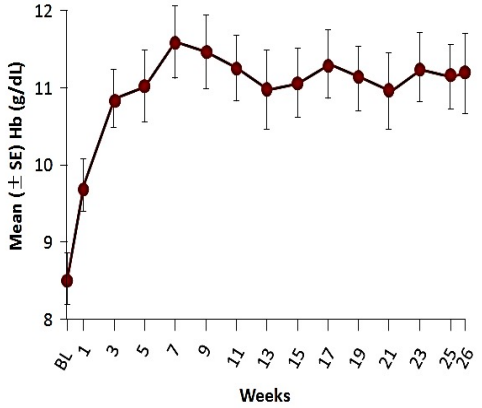
Trials ongoing

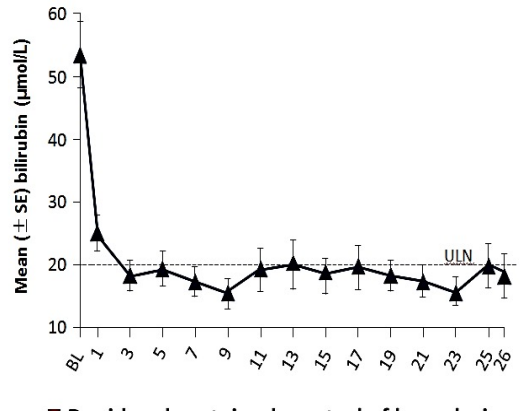
Efficacy and Safety of M281 (nipocalimab) in Adults With Warm Autoimmune Hemolytic Anemia. ClinicalTrials.gov Identifier: NCT04119050

A Phase 3 Study to Evaluate the Safety and Efficacy of Efgartigimod PH20 Subcutaneous in Adult Patients With Primary Immune Thrombocytopenia (ADVANCE SC+) ClinicalTrials.gov Identifier: NCT04812925

Complement inhibition in CAD

- **Sutimlimab, a MoAb against complement protein C1s (prospective trial) administered iv every 2weeks induced**
- **a rapid Hb response and normalization of hemolysis; 83% (20/24) had ≥ 1 g Hb increase; 2.6 g/dL mean Hb increase**
- **Inhibited activity of the classic complement pathway, with concomitant normalization of C4 levels**
- **the drug is safe (lectin and alternative pathways remain intact), but discontinuation results in reappearance of hemolysis and anemia**





Röth A, NEJM 2021; Berentsen S & Barcellini W. NEJM 2021; Roth A, Blood 2022

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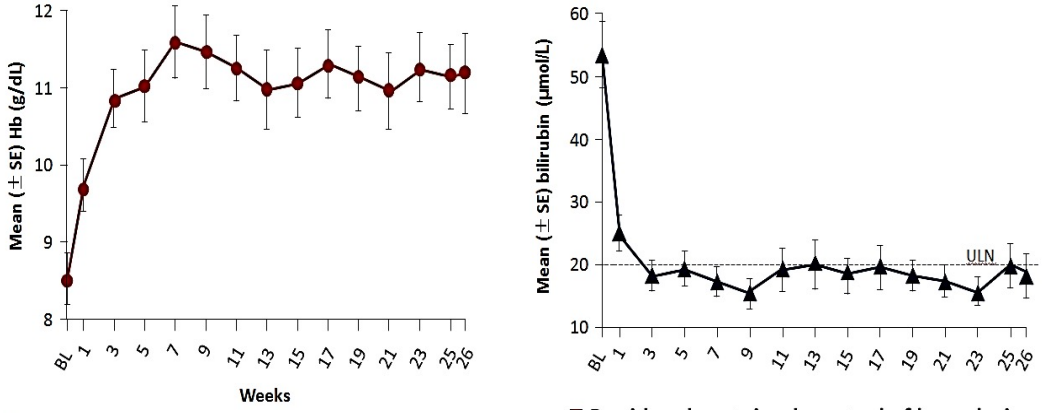
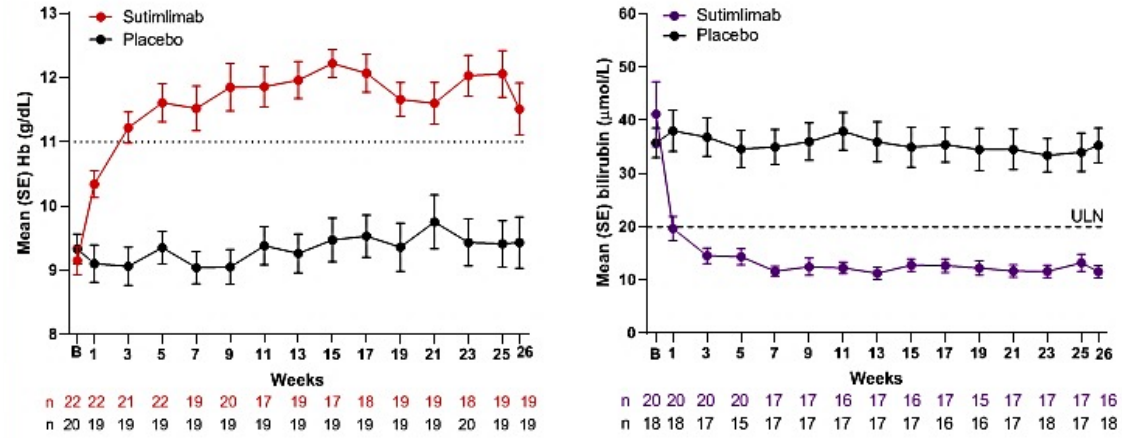
- **In prospective, randomized placebo-controlled trials, Sutimlimab confirmed rapid and sustained increase in Hb, control of hemolysis and improvements in QoL, compared with placebo**





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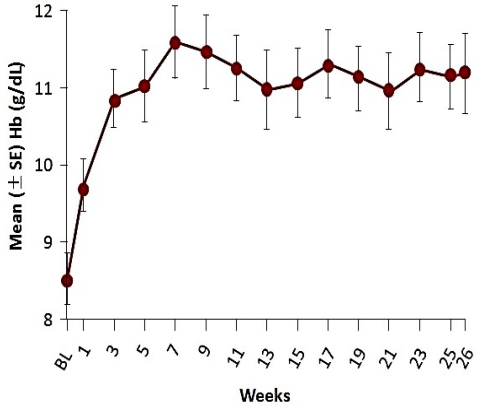
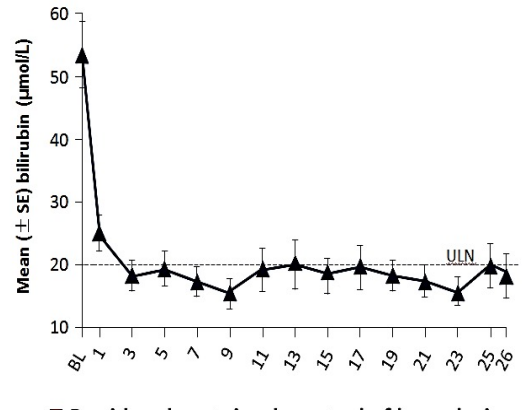
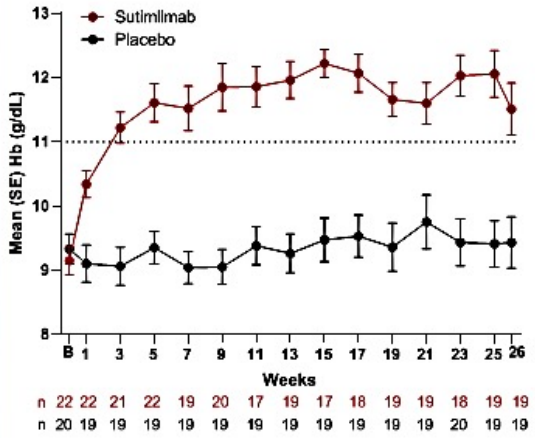
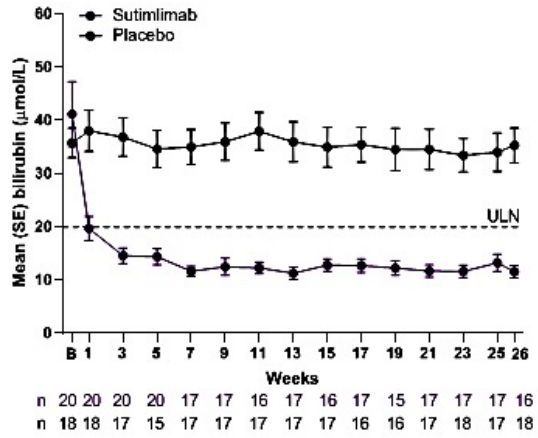








- Unlike most B-cell–directed therapies, which are given for brief intervals, complement inhibition will probably have to be continued indefinitely to maintain its effect.
- This approach will provide a therapeutic option for patients in whom B-cell–directed therapy has failed or is contraindicated. The much shorter time to a response may be particularly helpful in patients with severe anemia and those in acute crisis.

Röth A, NEJM 2021; Berentsen S & Barcellini W. NEJM 2021; Roth A, Blood 2022

Complement inhibition in wAIHA

Multicenter Study > Am J Hematol. 2018 Sep;93(9):E243-E246. doi: 10.1002/ajh.25212. Epub 2018 Aug 25.

Predictors of refractoriness to therapy and healthcare resource utilization in 378 patients with primary autoimmune hemolytic anemia from eight Italian reference centers

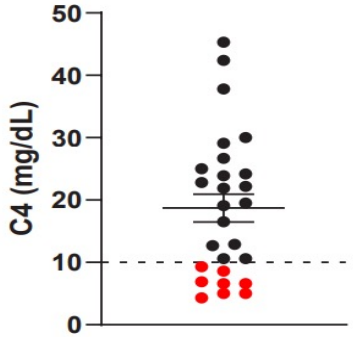
Wilma Barcellini [1], Anna Zaninoni [1], Bruno Fattizzo [1], Juri Alessandro Giannotta [1], Monia Lunghi [2],

- 1/3 of wAIHA display complement positivity at DAT evaluation (i.e. IgG+C+)
- IgG+C+ wAIHAs represent an unmet need
- Display lower Hb and higher LDH versus IgG+
- More frequently required 2 lines or more (58% vs 38%)
- More frequently experienced infectious or thrombotic complications

Evidence of Classical Complement Pathway Involvement in a Subset of Patients with Warm Autoimmune Hemolytic Anemia

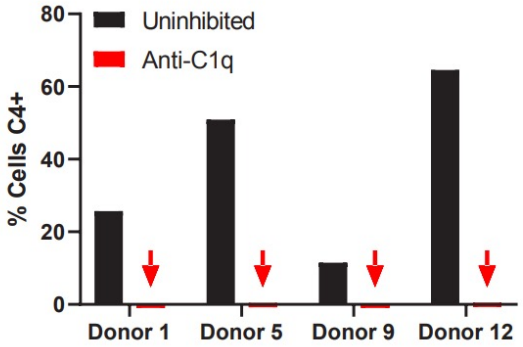
Jeffrey Teigler, Julian Low, Shawn Rose, Ellen Cahir-Mcfarland, Ted Yednock, Hendrik Kroon, Sanjay Keswani, Ronald Go, Wilma Barcellini

blood



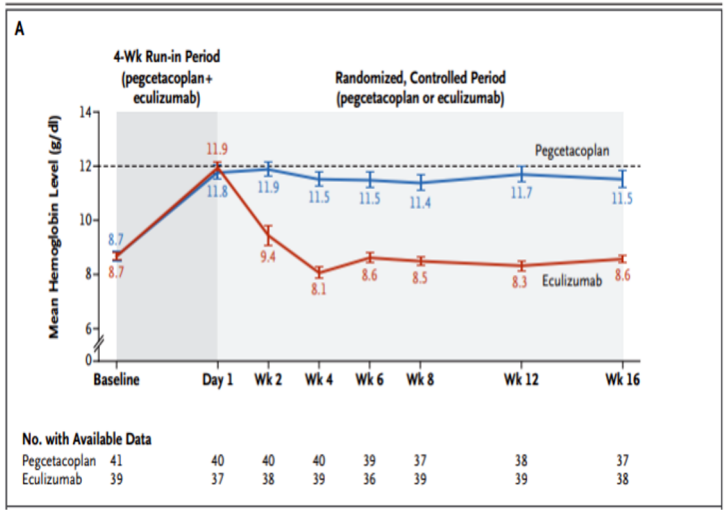
- ~50% of w AIHA display complement deposition on RBC
- ~30% displayed C4 levels below the lower limit of normal
- Addition of an inhibitory antibody against C1q fully blocked deposition of C4 on RBCs indicating dependence of the classical complement pathway

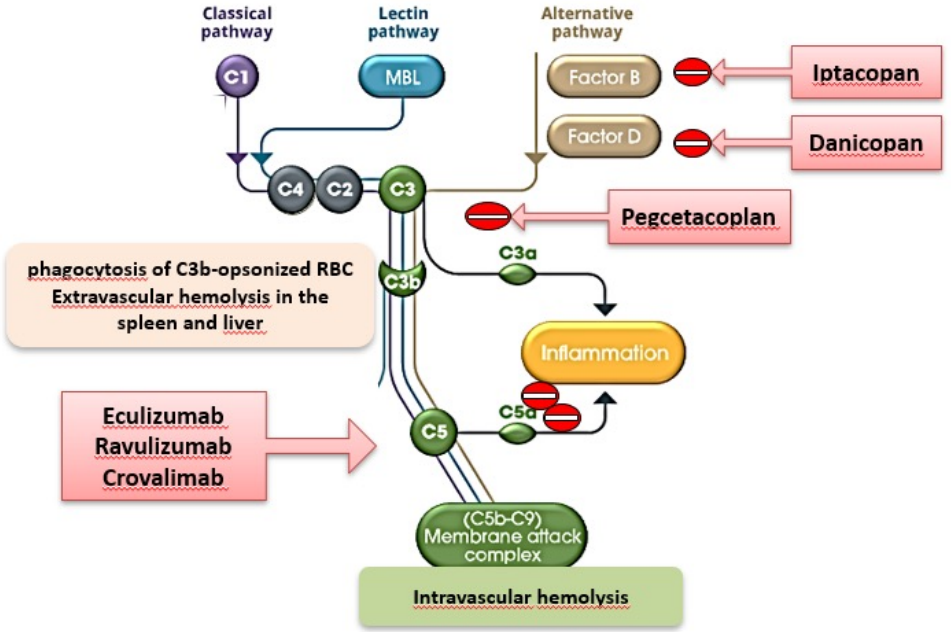
Blockade of C4 Deposition in wAIHA Sera on Healthy Human RBC by Anti-C1q



Other complement inhibitors

In PNH patients with suboptimal response to eculizumab, Pegcetacoplan, a pegylated peptide targeting proximal complement protein C3, induced increase of mean Hb level of 3.84 g/dL, 85% transfusion independence, improvement of FACIT –Fatigue scores





Trial ongoing

Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ANX005 in Participants With Warm Autoimmune Hemolytic Anemia (wAIHA). ClinicalTrials.gov Identifier: NCT04691570

A Study to Evaluate the Efficacy and Safety of Pegcetacoplan in Patients With Cold Agglutinin Disease (CAD). ClinicalTrials.gov Identifier: NCT05096403

Basket Study to Assess Efficacy, Safety and PK of Iptacopan (LNP023) in Autoimmune Benign Hematological Disorders (ITP, CAD). ClinicalTrials.gov Identifier: NCT05086744

New drugs for autoimmune hemolytic anemias (AIHA)

Understanding the physiopathology of AIHA paved the way to targeted therapies even in this context beyond steroids and rituximab

	Mechanism	Route of Administr.	Study Phase	Setting
B-cell directed therapies				
Ofatumumab	Anti-CD20	IV	Case report	Secondary AIHA
Alemtuzumab	Anti-CD52	SC	Case reports	Secondary AIHA
Daratumumab	Anti-CD38	IV	Case reports	wAIHA/CAD/Secondary
Isatuximab	Anti-CD38	SC	Phase 1	wAIHA
Ibrutinib	BTKi	Oral	Case reports, Phase 2 plus R	Secondary AIHA
Rilzabrutinib	BTKi	Oral	Phase 1	wAIHA
Venetoclax	Bcl2i	Oral	Case reports	Secondary AIHA
Parsaclisib	PI3Kδi	Oral	Phase 2, Phase 3	wAIHA/CAD
Complement inhibitors				
Eculizumab	Anti-C5	IV	Case reports and Phase 2	CAD/Mixed AIHA
Sutimlimab	Anti-C1s	IV	Phase1b and 3	CAD
Pegcetacoplan	Anti-C3/C3b	SC	Phase1/2 and Phase 3	CAD/wAIHA
ANX005	Anti-C1q	IV	Phase1	wAIHA IgG+C
IgG-mediated phagocytosis inhibitors				
Fostamatinib	Syki	Oral	Phase2	wAIHA
Nipocalimab	Anti-FcRn	IV- SC	Phase2	wAIHA

Fattizzo & Barcellini, Expert Rev Clin Immunol 2022, modified

Standard therapies:

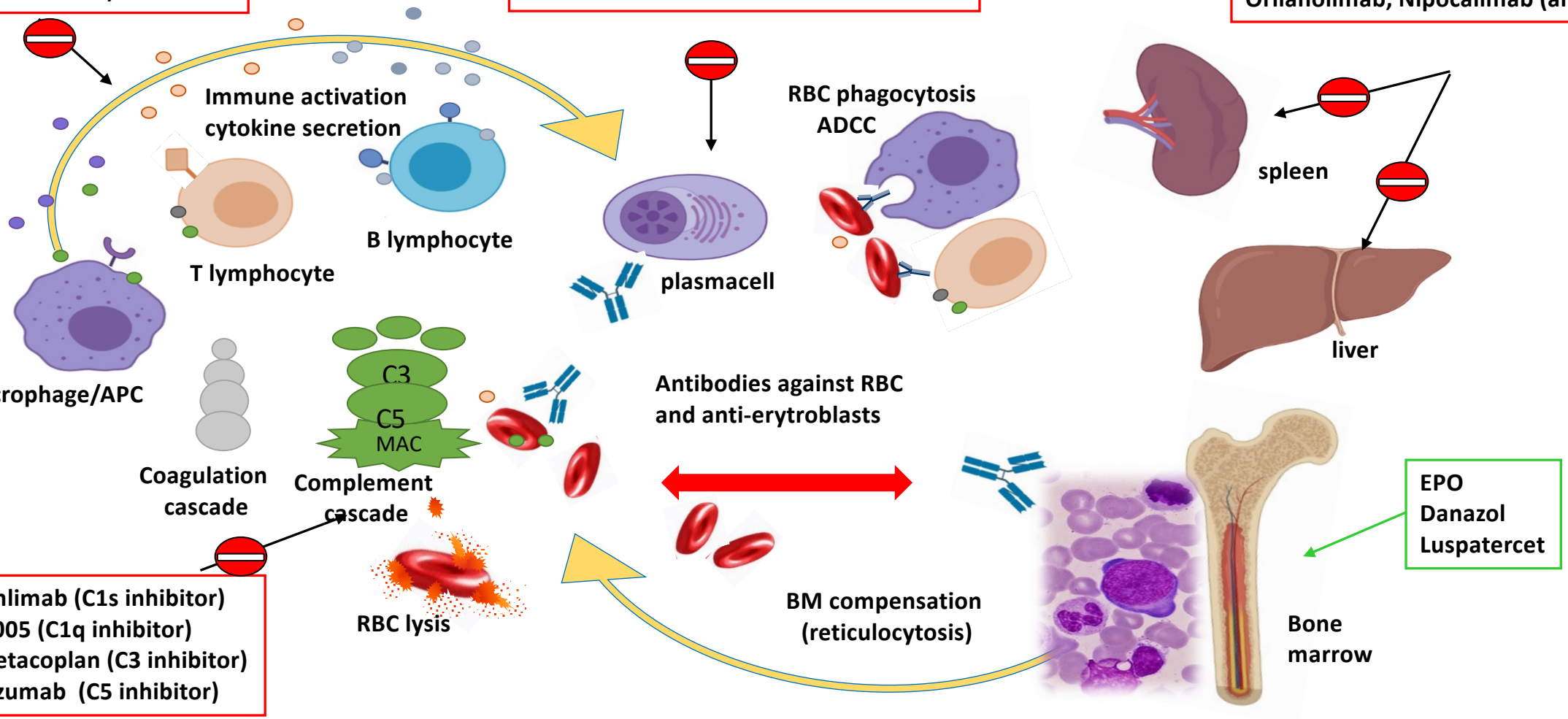
steroids — azathioprine, cyclosporine, cyclophosphamide — splenectomy

Target therapies:

Alemtuzumab (anti-CD52)
MMF (purine synthesis inhibitor)
Sirolimus (anti-mTOR)

Rituximab (anti-CD20)
Bortezomib (proteosome inhibitor)
Daratumumab, isatuximab (anti-CD38)
Parsaclisib, Idelalisib (PI3Kδ inhibitor)
Ibrutinib, rilzabrutininb (BTK inhibitor)
Belimumab (BAFF-April system inhibitor)

Fostamatinib (Syk inhibitor)
Orilanolimab, Nipocalimab (antiFcRn)



EPO
Danazol
Luspatercet

Sutimlimab (C1s inhibitor)
ANX005 (C1q inhibitor)
Pegcetacoplan (C3 inhibitor)
Eculizumab (C5 inhibitor)

Clinical evolution of idiopatic cytopenias (ITP/AIHA/CIN) in ICUS/IDUS/BMF

Received: 29 November 2016 | Accepted: 1 December 2016
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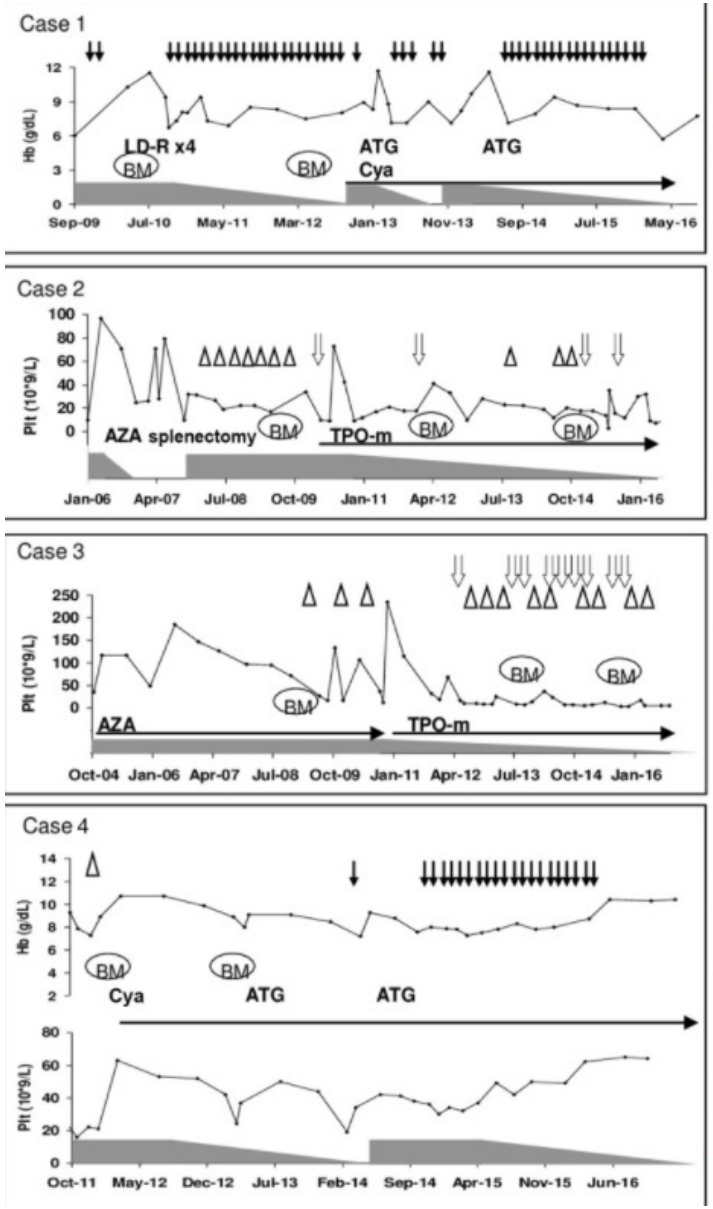
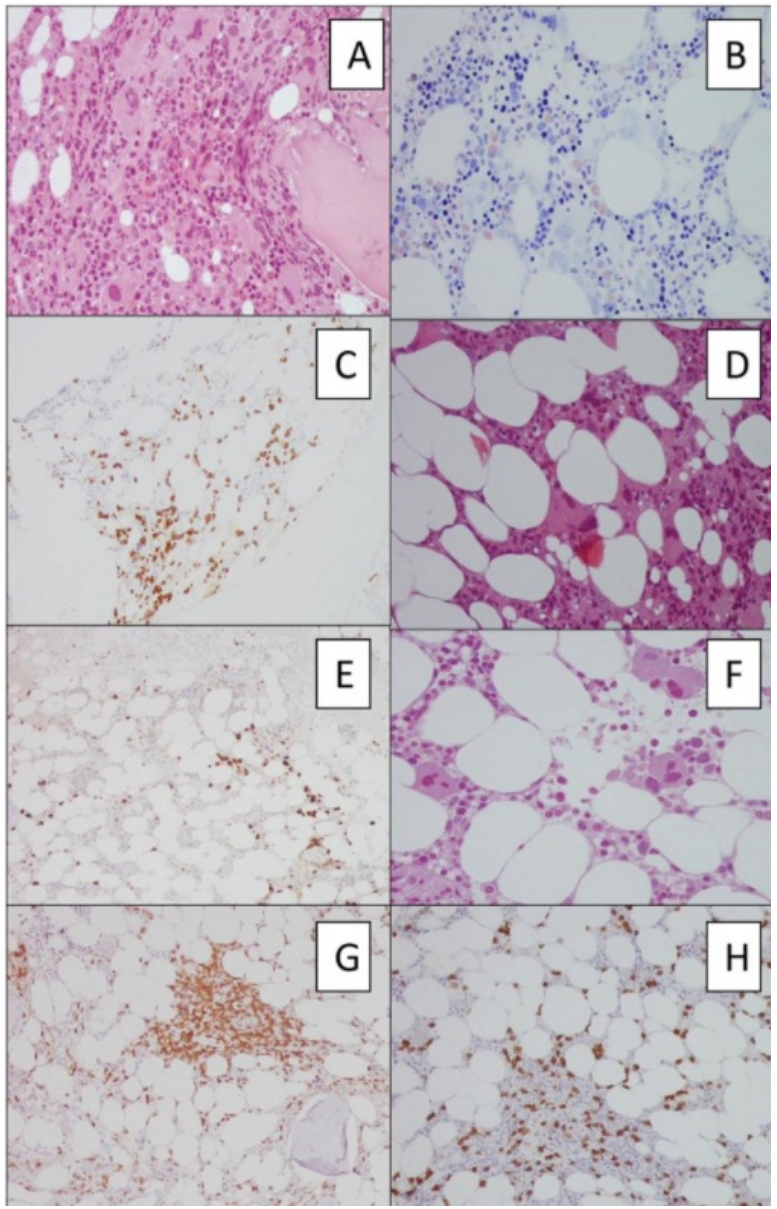
AJH WILEY

Clinical evolution of autoimmune cytopenias to idiopathic cytopenias/ dysplasias of uncertain significance (ICUS/IDUS) and bone marrow failure syndromes

Barcellini W, Fattizzo B, Zaninoni A, et al
Am J Hematol. 2017

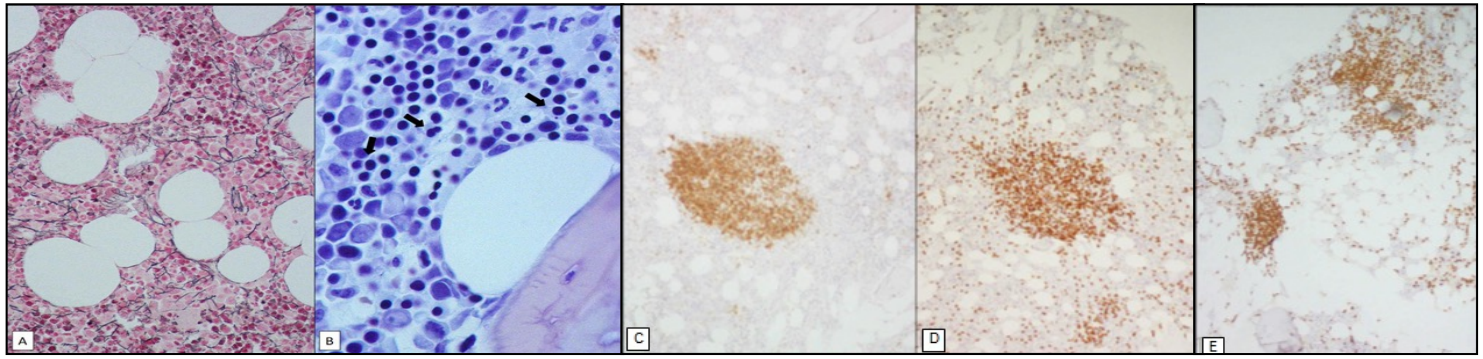
- **5 paradigmatic cases of refractory/ relapsing autoimmune cytopenias, AIHA, ITP, and CIN, that evolved to IDUS/bone marrow failure syndromes over time**
- **BM features: (A) megakaryocytes clustering in loose aggregates, with dysmorphic and hypolobulated nuclei; (B) megaloblastic changes, increased number of proerytroblasts; (C, E, G, H) infiltration of lymphoid T-cells**





Negative prognostic impact of bone marrow fibrosis and dyserytrhopoiesis in AIHA

STUDY GROUP	MF0 N=30	MF≥1 N=17
Hb, g/dL,	7.4 (3.5-13.1)	8 (2-11)
LDH x UNL	1.27 (0.4-7)	1 (0-3)
Ret x10^3/mmc	113 (13-275)	157 (58-284)*
Bone marrow characteristics		
Cellularity, %	52.5 (25-90)	65(20-99)**
Normo, N (%)	12 (40)	2 (12)
Hypo, N (%)	2 (7)	1 (6)
Hyper, N (%)	16 (53)	14 (82)*
Diserythropoiesis N (%)	16 (53)	14 (82)*
Lymphoid infiltrate		
T-cell, N (%)	8 (26)	2 (12)
B-cell, N (%)	4 (13)	3 (18)
Mixed, N (%)	10 (30)	10 (59)



(A) **loose network of reticulin fibers with many intersections (MF-1), (B) The hyperplastic erythropoietic series shows some grade of dyserytropoiesis**

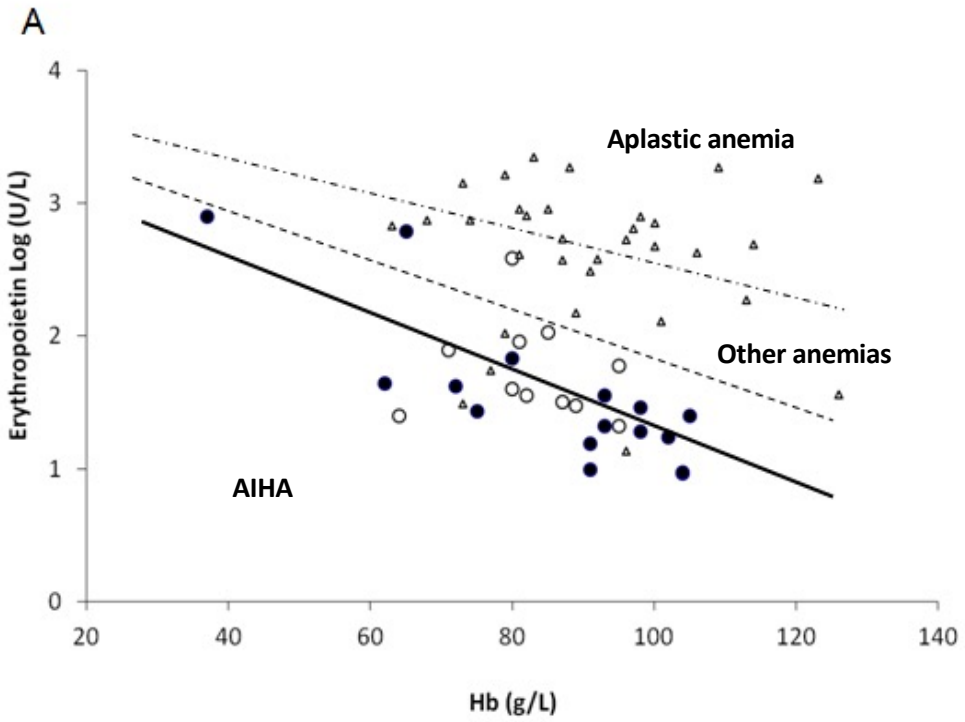
(C) centro-lacunar lymphoid aggregate predominantly composed of CD20-positive small B lymphocytes
(D) small CD3-positive T lymphoid cells
(E) focal and interstitial lymphoid infiltrate composed mainly of CD3+ small T-lymphoytes

- Reticulinic fibrosis (MF1) is present in 36% of AIHA cases and correlates with the presence of a hypercellular dyserythropoietic bone marrow, and a higher rate of relapse and treatment requirement
- These chronic refractory cases may show clinical/pathologic features similar to low-risk myelodysplastic syndromes and recently described idiopathic cytopenia/dysplasia of unknown significance (ICUS/IDUS)

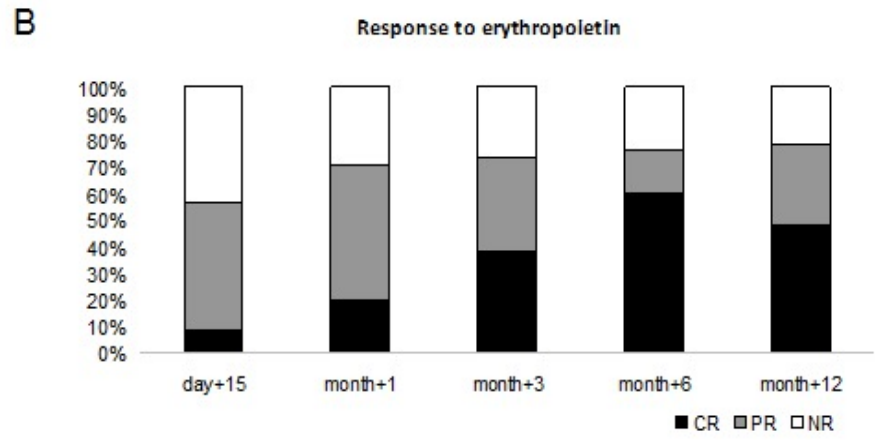
Barcellini, AJH 2016, Fattizzo et al, AJH 2018

Predictors of Response to Erythropoietin in AIHA

- 48 AIHA cases (4 cases 2ndary)
- 37% of patients showed severe anemia (Hb<8 g/dL) and 53% active hemolysis (LDH >1.5 xULN); almost all subjects showed inadequate reticulocyte counts
- 71% started EPO because of non-response to ongoing treatment (steroid 23, rituximab 9, immunosuppressor 8, sutimlimab 1)
- At EPO initiation, 88% had inadequate endogenous EPO levels considering Hb



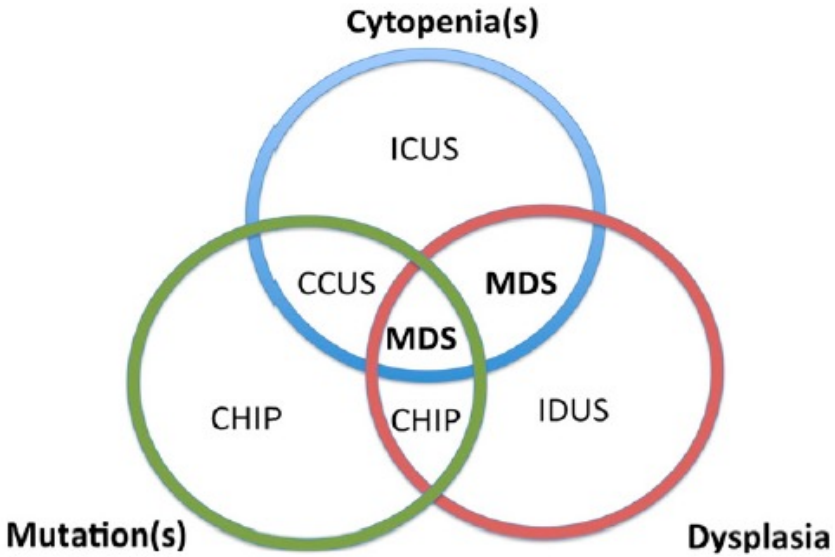
- EPO is effective in roughly 70% of chronic refractory AIHA cases, independently from antibody thermal characteristics/isotype and underlying disease
- Predictors of response were severe anemia and low levels of endogenous EPO, shorter disease duration, and a lower burden of previous treatments
- These data suggest an early use of EPO in this setting in order to overcome inadequate bone marrow compensatory ability



Fattizzo B, Michel M, Zaninoni A, Giannotta J, Guillet S, Frederiksen H, Vos JMI, Mauro FR, Jilma B, Patriarca A, Zaja F, Hill A, Berentsen S, Barcellini W. Haematologica. 2021

Fattizzo et al, Haematologica 2020

ICUS, IDUS, CCUS, CHIP…



Common (>50) variants, n		Less common (10-49) variants, n		Uncommon (5-9)
DNMT3A	403	*TP53*	33	*GNAS*
TET2	72†	*JAK2*	31	*BRCC3*
ASXL1	62†	*SF3B1*	27	*CREBBP*
		GNB1	22	*NRAS*
		CBL	12	*RAD21*
		SRSF2	11	*SETDB1*
		PPM1D	†	*U2AF1*
				SETD2

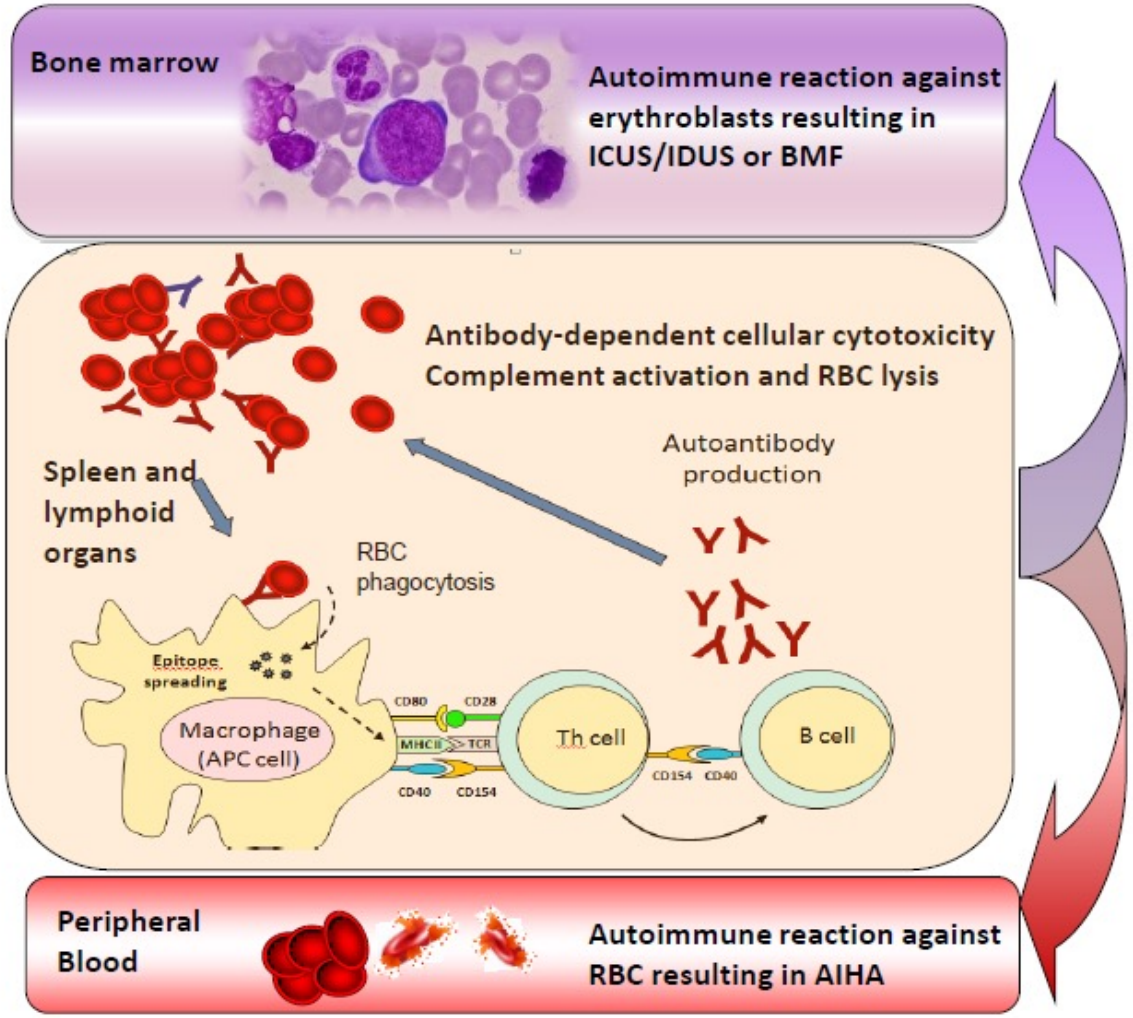
More than 10% of the general population over age 70 yrs carries mutations

Pre-MDS	Major diagnostic features and criteria
ICUS	Peripheral cytopenia(s)[a], MDS criteria not fulfilled, no MDS-related mutation[b] found, no or only mild (<10%) dysplasia, blast cells <5%[c]
CCUS	Peripheral cytopenia(s)[a], MDS criteria not fulfilled, one or more MDS-related mutations[b] found, no or only mild (<10%) dysplasia, blast cells <5%[c]
IDUS	No peripheral cytopenia[a], MDS criteria not fulfilled, no MDS-related mutation[b] found, dysplasia in ≥10% of neutrophilic, erythroid, and/or megakaryocytes found, blast cells <5%[c]
CHIP	No peripheral cytopenia[a], MDS criteria not fulfilled, one or more MDS-related mutations[b] found, no or only mild (<10%) dysplasia, blast cells <5%[c]

MDS, myelodysplastic syndromes; ICUS, idiopathic cytopenia of undetermined significance; CCUS, clonal cytopenia of undetermined significance; IDUS, idiopathic dysplasia of undetermined significance; CHIP, clonal hematopoiesis of indeterminate potential. [a] Cytopenia of any degree counts as a criterion, but the cytopenia must persist for at least 4 months. [b] Mutations may be de-

Valent P. Pathobiology 2019;86:30–38; Steensma DP. Blood Advances 2018 2:3404-3410

Peripheral (erythrocytes) and central (erythroblasts) immune attack in AIHA



- In AIHA the immune attack is mainly directed against peripheral erythrocytes, which dominates the clinical picture
- In cases with severe onset the immune attack is also directed against bone marrow precursors (reticulocytopenia)
- In chronic/relapsing AIHA there is a shift towards a preferential erythroblast-directed autoimmunity, possibly leading to idiopathic cytopenia of uncertain significance (ICUS), idiopathic dysplasia of uncertain significance (IDUS) or bone marrow failure (BMF) syndromes over time
- An immune attack versus bone marrow precursors is observed also immune thrombocytopenia (ITP), and chronic idiopathic neutropenia (CIN)
- Anti-erythroblast antibodies are found also in about 50% of early MDS (RA and RARS)

Barcellini et al, Haematologica 2007, AJH 2016 & Expert Rev Hematol 2017, Zaninoni et al. Transfusion 2016, Fattizzo et al, AJH 2018,

PNH: an intriguing story…

Leukemia
https://doi.org/10.1038/s41375-021-01190-9

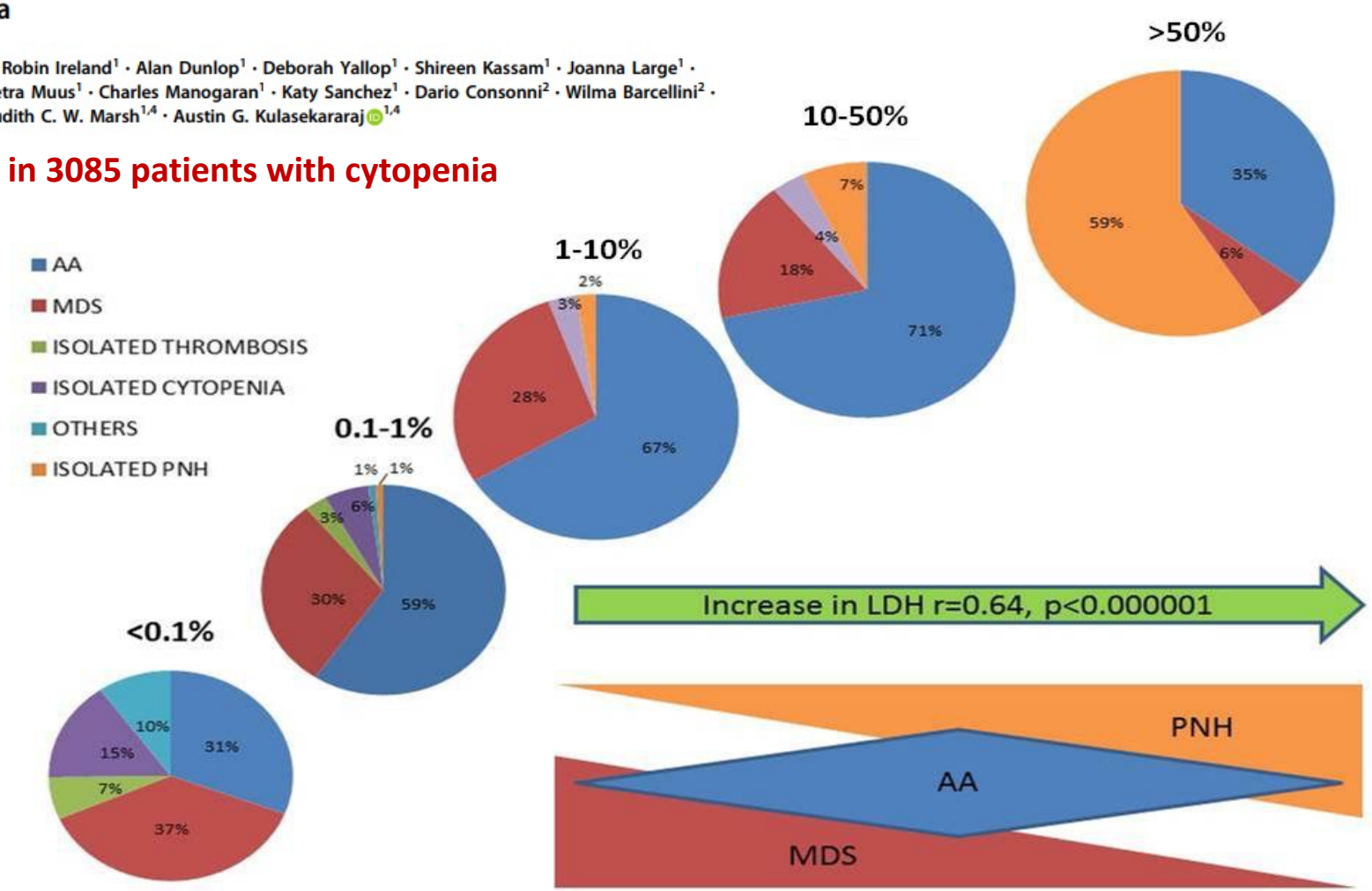
ARTICLE

Myelodysplastic syndrome

Clinical and prognostic significance of small paroxysmal nocturnal hemoglobinuria clones in myelodysplastic syndrome and aplastic anemia

Bruno Fattizzo[1,2,3] · Robin Ireland[1] · Alan Dunlop[1] · Deborah Yallop[1] · Shireen Kassam[1] · Joanna Large[1] · Shreyans Gandhi[1] · Petra Muus[1] · Charles Manogaran[1] · Katy Sanchez[1] · Dario Consonni[2] · Wilma Barcellini[2] · Ghulam J. Mufti[1,4] · Judith C. W. Marsh[1,4] · Austin G. Kulasekararaj[1,4]

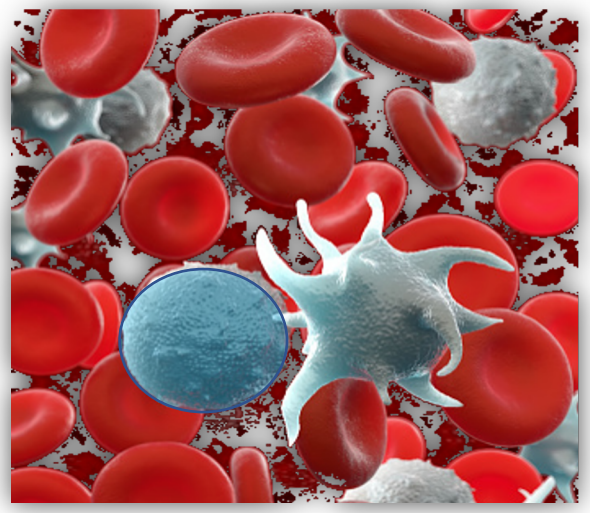
PNH clones in 3085 patients with cytopenia



- classical PNH with large clones (>50%)
- AA cases mainly medium clones (10-50%)
- MDS cases mostly presented with small (<10%) and very small clones (<1%)
- LDH significantly augmented along with clone size increase
- Thrombotic complications were more frequent in patients with larger clones (7 to 21%, p<0.0001)

- **PNH positivity correlates with better response to IST and HSCT in MDS and AA,**
- **The presence of at least 0.01% PNH clone correlated with better survival**

Small PNH clones: the immunological scar of an immune attack against BM precursors



- **37% of AIHA displayed a small PNH clone.**
- **PNH+AIHA pts had aprominent hemolytic pattern, and a higher thrombotic risk**
- **PNH+AIHA pts showed reduced levels of IFN-γ and IL-17 compared to PNH- cases**
- **TEST PNH clone!**

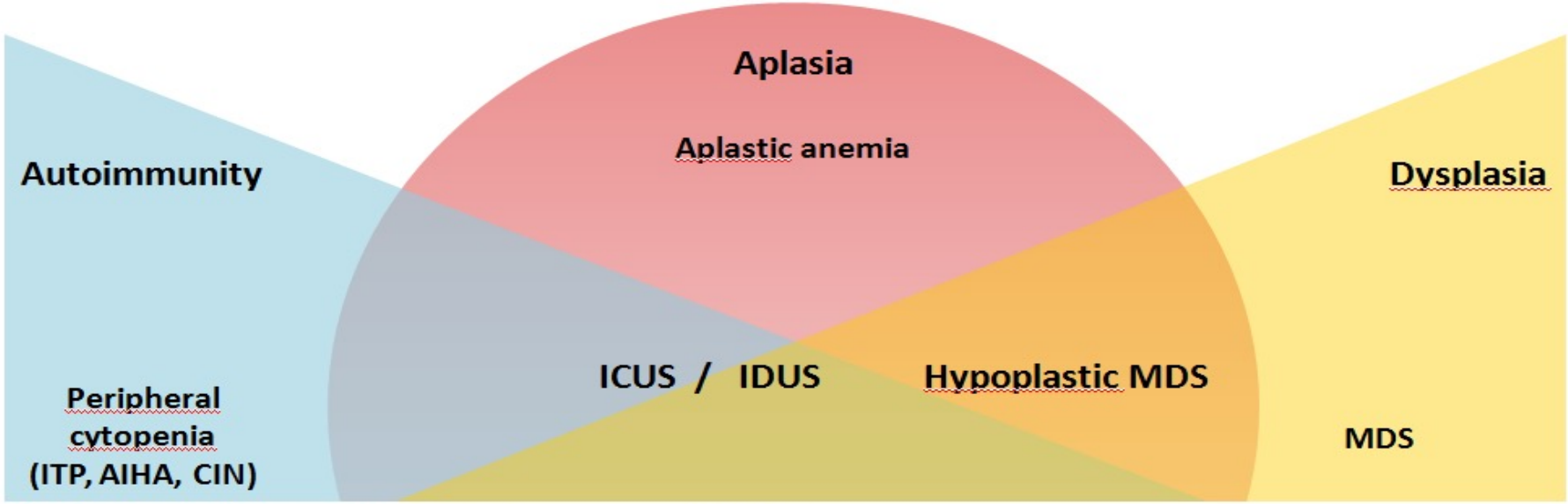
Hypomegakaryocytic thrombocytopenia (HMT): an immune-mediated bone marrow failure characterized by an increased number of PNH-phenotype cells and high plasma thrombopoietin levels.
Saito C, et al Br J Haematol. 2016 Oct;175(2):246-251.

Hypomegakaryocytic thrombocytopenia and increased number of PNH-phenotype cells - an emerging subgroup of myelodysplastic syndrome showing frequent response to immunosuppression.
Rafferty M, et al. Br J Haematol. 2018 Jul;182(1):152-154.

Minor populations of paroxysmal nocturnal hemoglobinuria-type cells in patients with chronic idiopathic neutropenia.
Damianaki A, et al. Eur J Haematol. 2016 Dec;97(6):538-546.

Small Paroxysmal Nocturnal Hemoglobinuria Clones in Autoimmune Hemolytic Anemia: Clinical Implications and Different Cytokine Patterns in Positive and Negative Patients.
Fattizzo B, Giannotta J, Zaninoni A, Kulasekararaj A, Cro L, Barcellini W.
Front Immunol. 2020 Jun 4;11:1006.

Immune cytopenias, MDS, AA: a disease spectrum and common pathogenic mechanisms?



- AIHA has a complex pathophysiology involving immune dysregulation both in peripheral blood, spleen and bone marrow
- Differential diagnosis is challenging and periodic re-evaluation of the patient (bone marrow biopsy) from the "pathogenetic" point of view is important to avoid improper therapy
- Relapsing/refractory cases shows bone marrow features similar to ICUS/IDUS, two recently recognized provisional conditions that may evolve to MDS or BMF
- Bone marrow dyserythropoiesis/fibrosis and high endogenous EPO levels predict poor response to therapy
- Targeted therapies (possibly in combination) are advisable, as pathogenetic mechanism are variably involved in the different patients, and change over time

FONDAZIONE IRCCS
CÀ GRANDA
OSPEDALE MAGGIORE
POLICLINICO

UNIVERSITÀ DEGLI STUDI
DI MILANO

Paola Bianchi
Francesca Binda
Francesca Cavallaro
Bruno Fattizzo
Valeria Ferla
Elisa Fermo
Valeria Ferri
Juri Giannotta
Anna Gregorini
Anna Marcello
Giulia Milesi
Tommaso Radice
Veronica Sciumbata
Giulia Soverini
Viviana Valli
Cristina Vercellati
Anna Zaninoni
Agostino Cortelezzi
Alberto Zanella

Questions: wilma.barcellini@policlinico.mi.it