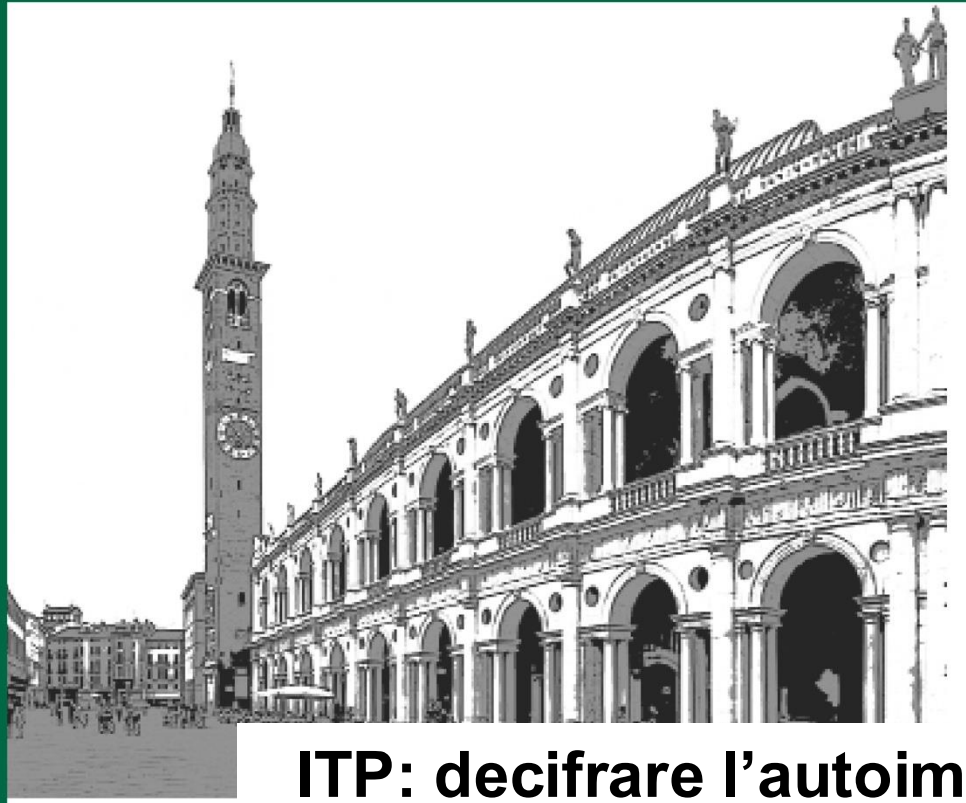


GIORNATE EMATOLOGICHE VICENTINE

XI edizione

9-10 Ottobre 2025
Palazzo Bonin Longare - Vicenza

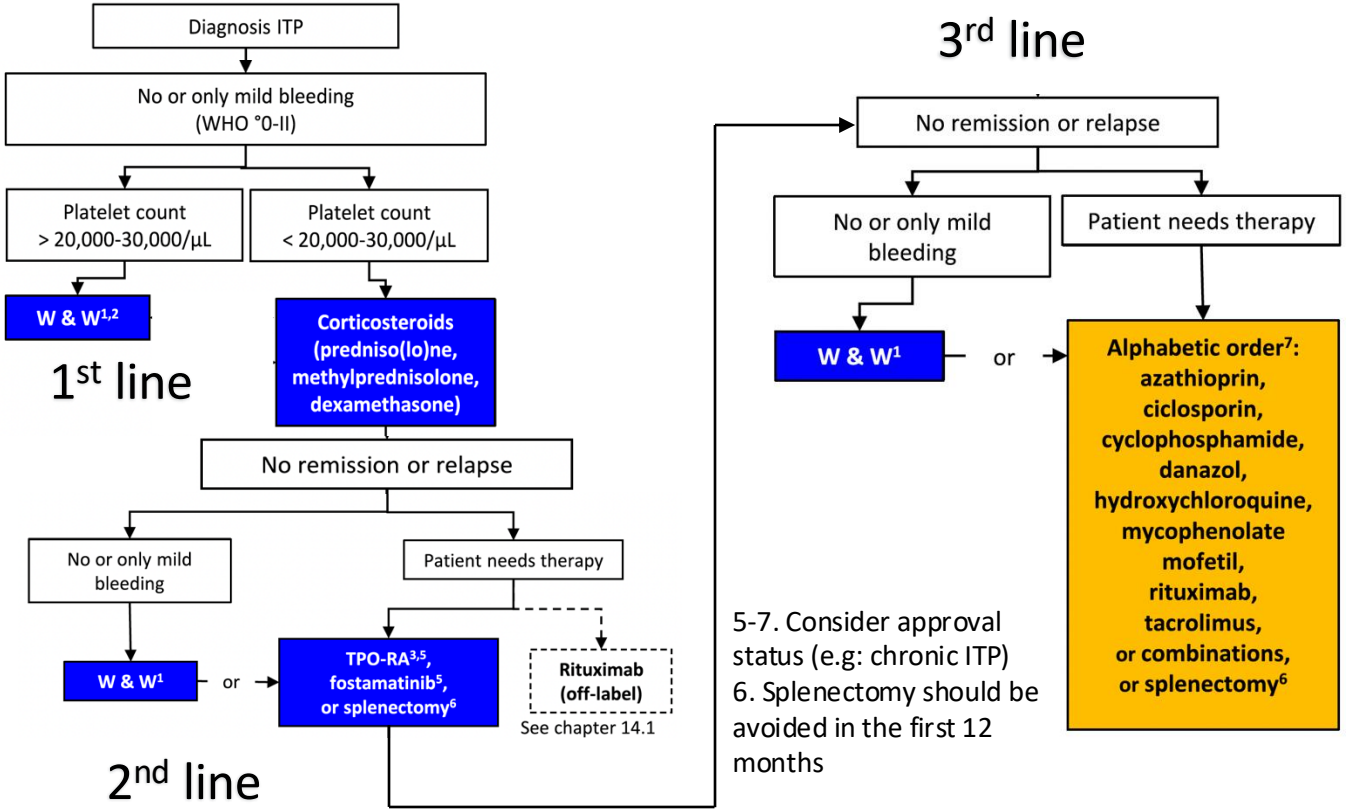
ITP: decifrare l'autoimmunità per creare nuovi percorsi di terapia

Elisa Lucchini
UCO Ematologia - Trieste

Disclosures of Elisa Lucchini

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Roche							x
Amgen							x

German guidelines[1]



5-7. Consider approval status (e.g: chronic ITP)
6. Splenectomy should be avoided in the first 12 months

Rituximab off-label in Germany

Spanish guidelines[2]

«Fostamatinib is particularly suitable as a first option for second-line treatment in patients with high thromboembolic risk»

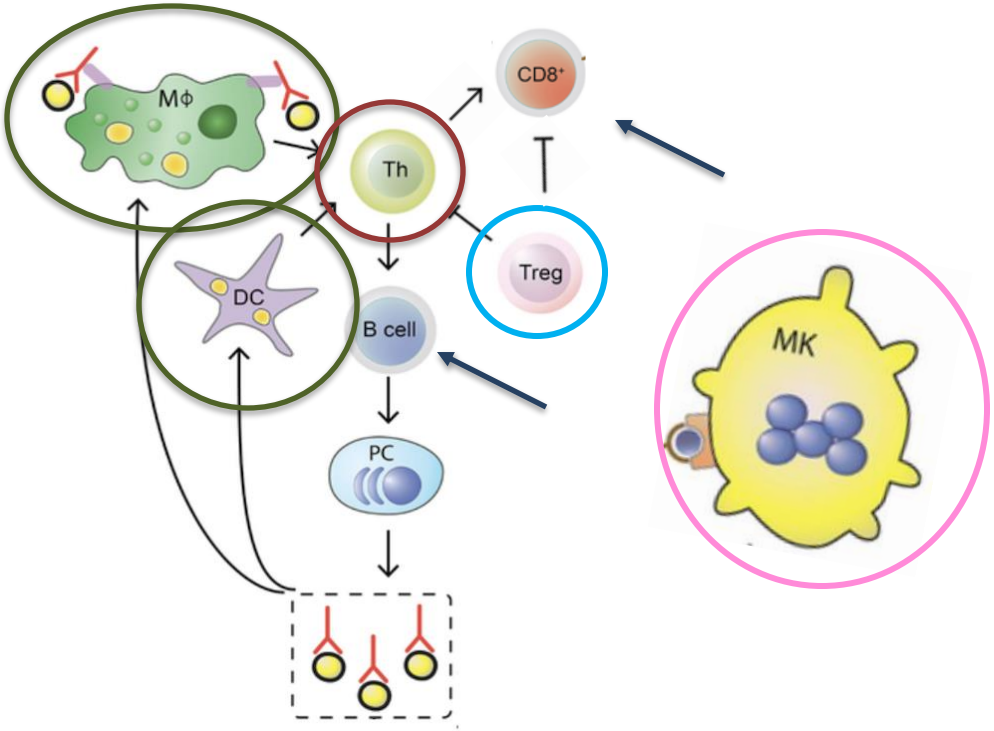
«Rituximab should be the secondary scenario in second-line options»

«There is no clear recommendation about how refractory patient treatments should be managed»

1.Adapted from Matzdorff et al. 2023

2.Mingot-Castellano et al. 2023

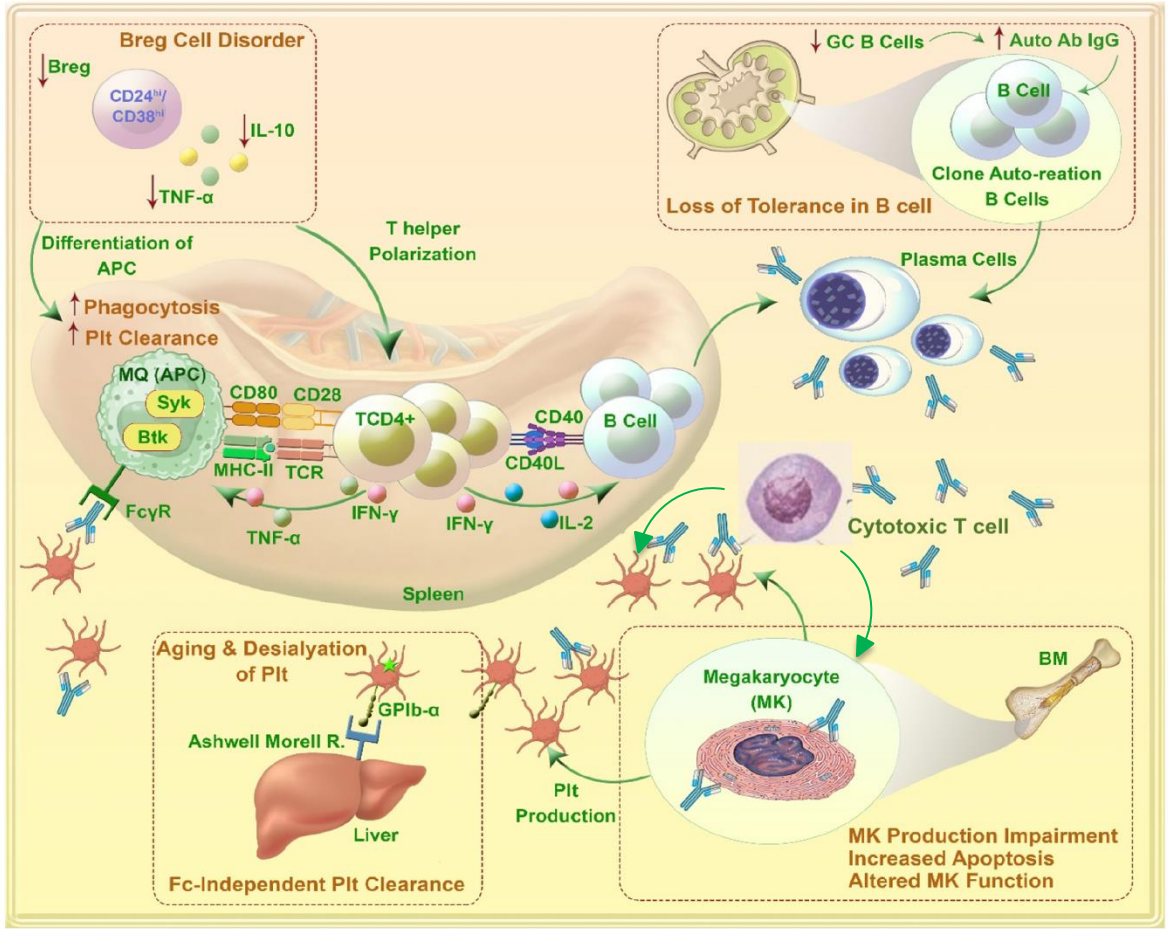
BREAKDOWN OF IMMUNE TOLERANCE TO PLATELET ANTIGENS



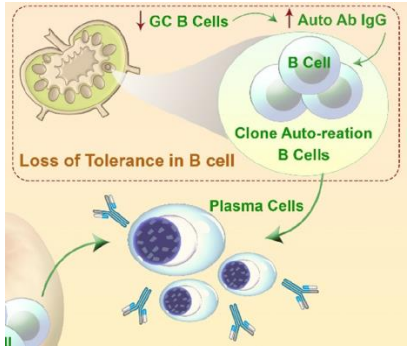
Macrophages and dendritic cells can present antigens to Th cells

- B-cell activation
- Cytotoxic T cell activation
- Dysfunctional regulatory T and B cells
- Impaired Mkpoiesis

Adapted from Swinkels et al Frontiers in Immunology 2018



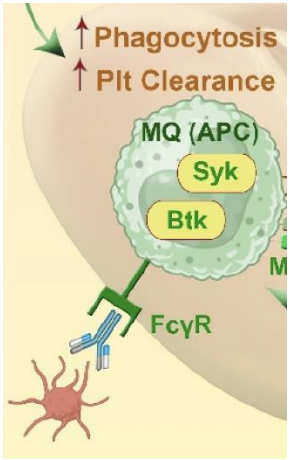
Adapted from Delshad et al. Thrombosis Research 2024



Anti-platelet antibodies are produced by a restricted number of B-cell clones, who underwent somatic hypermutation (CD4+-T cell-driven specific antigen response)[1]

- Mainly directed against GPIIbIIIa and GPIbIX BUT
- Only found in 20-60% of patients with chronic ITP (assay limits? Other specificities?)[2]
- Targeting highly conserved epitopes on both GPIIbIIIa and GPIbIX[3]

1. Roark et al. Blood 2002; 2. Kiyomizu K et al. Blood 2012; 3. He et al. 1995. 4.Kile nat.med 2015 5.Grozovsky et al. Nat Med 2015



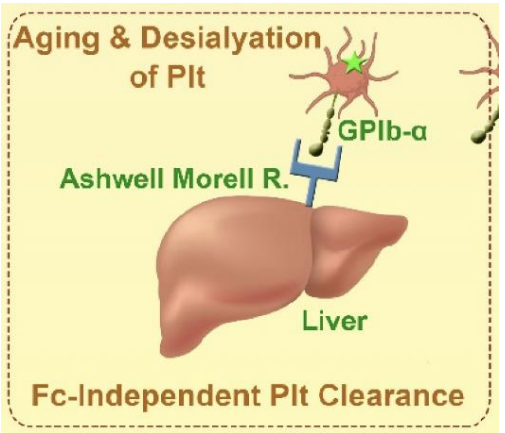
Antibody-mediated platelet clearance

Fc-dependent

Fc-independent

Phagocytosis (ADCP)
Cytotoxicity (ADCC)
Apoptosis
Complement activation

Desialylation[1,2]
Receptor cross-linking



Therapeutic target: Oseltamivir (sialidase inhibitor)

1.Kile nat.med 2015 2.Grozovsky et al. Nat Med 2015

Dexamethasone plus oseltamivir versus dexamethasone in treatment-naive primary immune thrombocytopenia: a multicentre, randomised, open-label, phase 2 trial [1]

THE LANCET
Haematology

Treatment: dexamethasone 40 mg/day for 4 days +/- oseltamivir 75 mg twice a day for 10 days

Endpoints: 14-days ORR and 6 months ORR

96 patients enrolled, 47 dexa + oseltamivir vs 49 dexa

Initial ORR: 86% vs 66% (p=0.030)
6-months ORR: 53% vs 30% (p=0.032)

Original Article

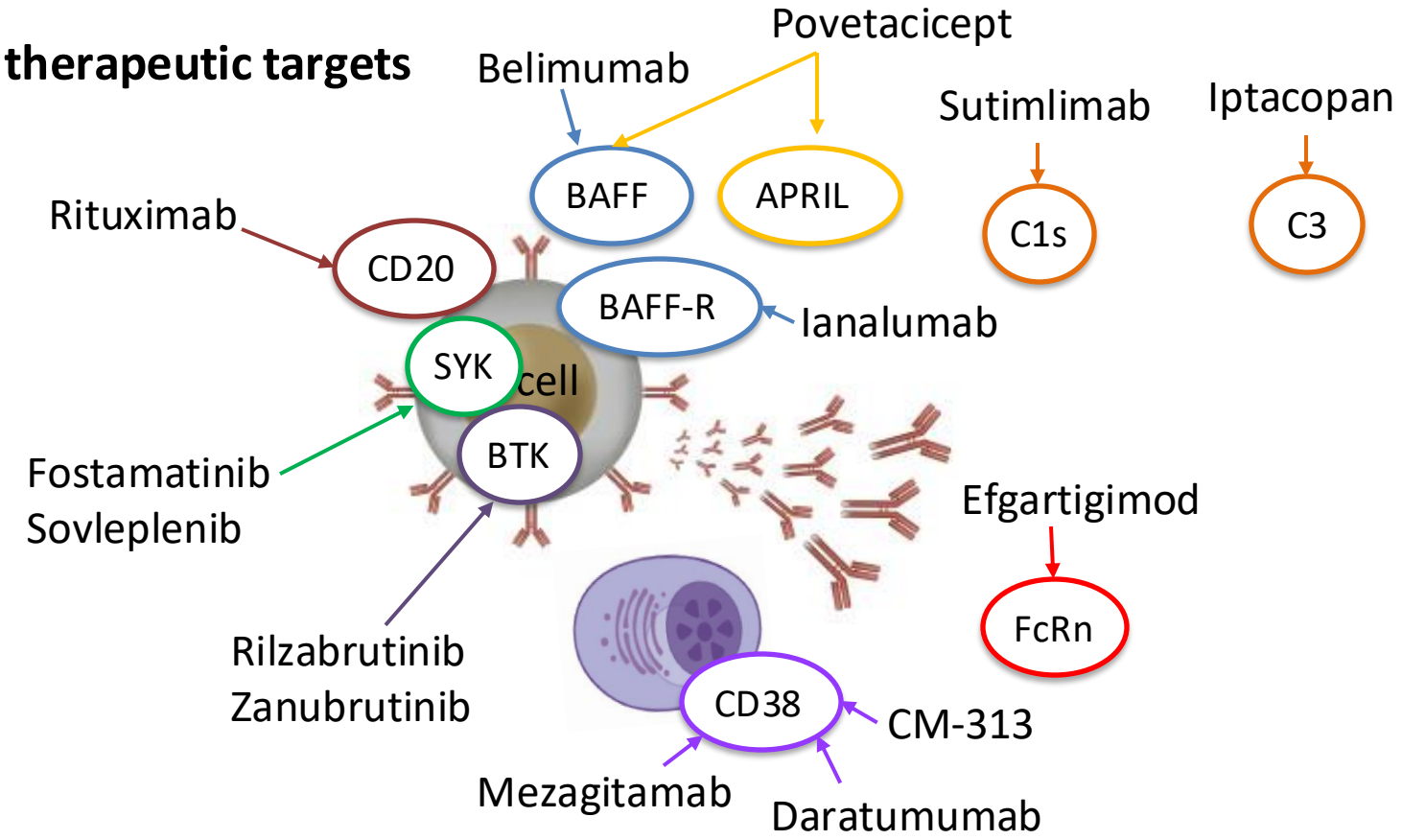
Multirefractory primary immune thrombocytopenia; targeting the decreased sialic acid content

Nuria Revilla, Javier Corral, Antonia Miñano, Maria Eva Mingot-Castellano, Rosa Maria Campos,

10 patients with remarkable loss of platelet terminal sialic acids were treated with oseltamivir, alone or in combination with TPO-RA or immunosuppressive therapy.
66% of patients responded.

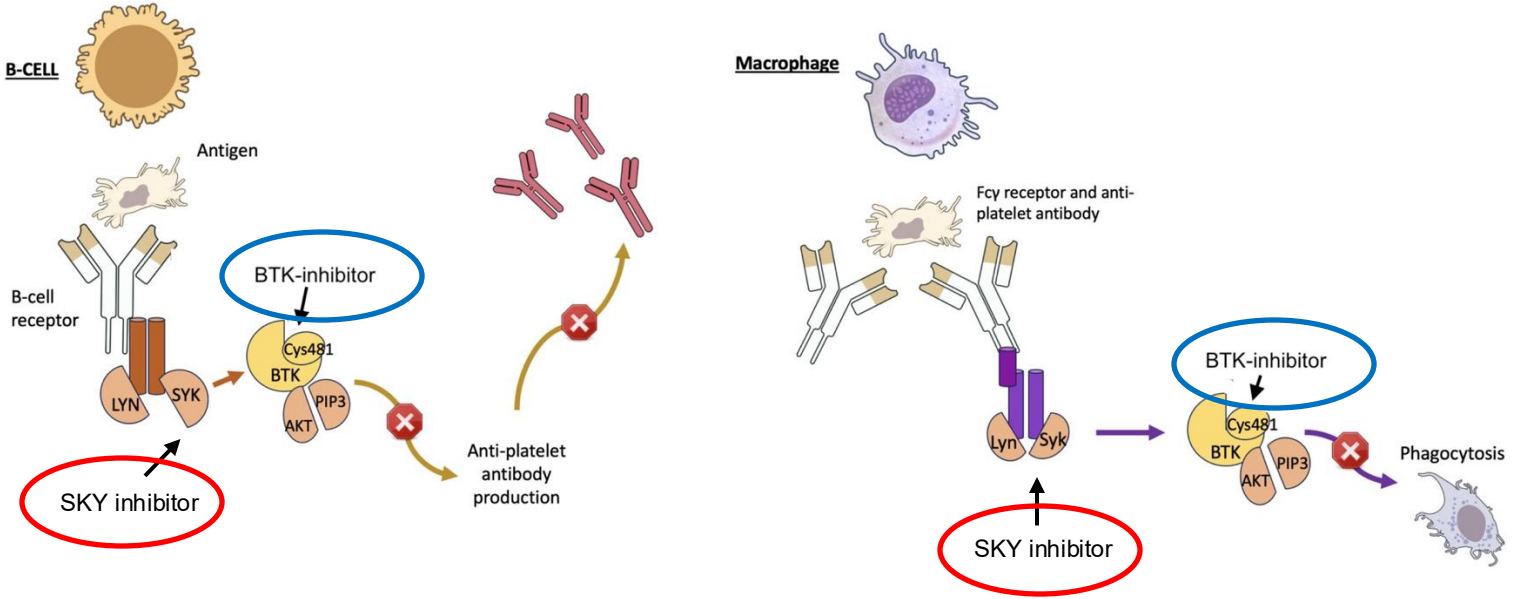
1.Sun L et al. Lancet Haematol 2021;8;e289-e298

B-cells as therapeutic targets



SYK and BTK-inhibition

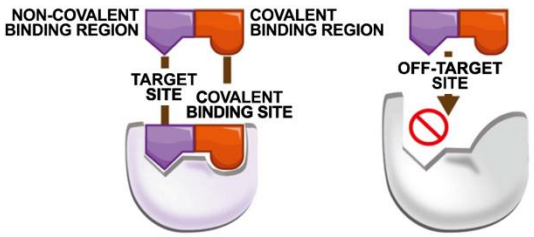
Reduces autoantibody production and impairs macrophage function and phagocytosis.



Adapted from Labanca C et al. EJH 2025

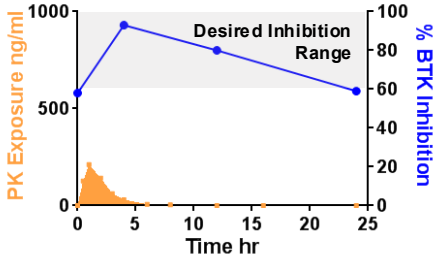
Kuter D et al Blood. 2025; Langrish et al. J Immunol 2021

Safety and efficacy of rilzabrutinib vs placebo in adults with immune thrombocytopenia: the phase 3 LUNA3 study



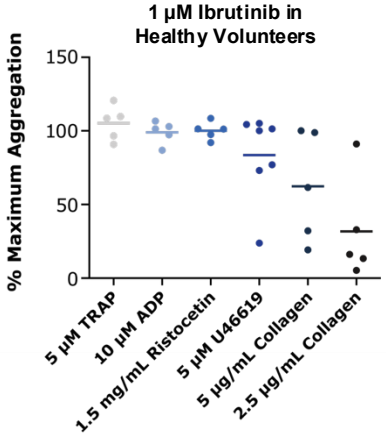
Selective/Reversible

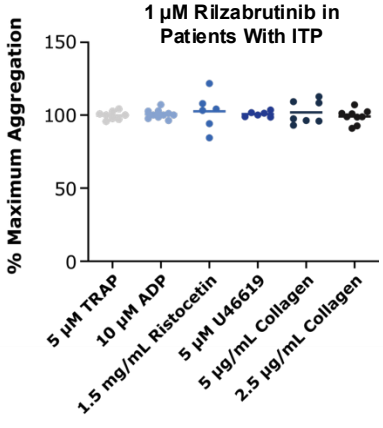
Precise Inhibition; No Permanent Modification of Proteins and Peptides



Durable BTK Inhibition With Low Exposure

Potential Optimized Clinical Benefit





No Inhibition of Platelet Aggregation

Potential Reduced Risk of Bleeding

Efficacy and Safety of the Bruton's Tyrosine Kinase Inhibitor Zanubrutinib in Immune Thrombocytopenia

Qiu-Sha Huang[1,2,3,4] | Hai-Xia Fu[1,2,3,4] | Chen-Cong Wang[1,2,3,4] | Xiao-Lu Zhu[1,2,3,4] | Yun He[1,2,3,4] | Jin Wu[1,2,3,4] | Qi Chen[1,2,3,4] | Peng Zhao[1,2,3,4] | Zhuo-Yu An[1,2,3,4] | Kai-Yan Liu[1,2,3,4] | Xiao-Jun Huang[1,2,3,4] | Xiao-Hui Zhang[1,2,3,4]

Zanubrutinib: irreversible, covalent BTK-inhibitor

Phase 2, open-label; primary ITP 18-70 yrs relapsed/refractory to corticosteroids

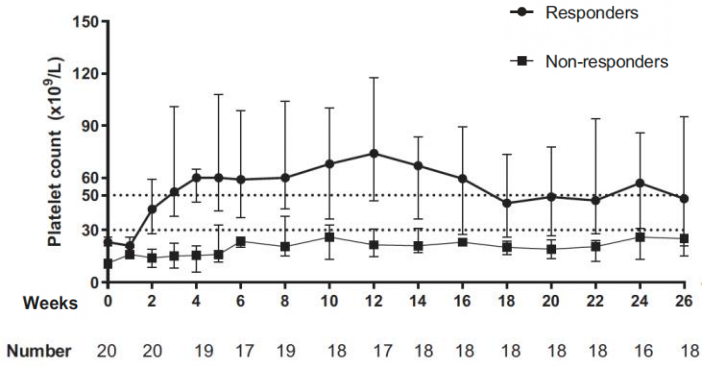
Treatment: zanubrutinib 80 mg/day for 6 weeks

20 patients enrolled; median number of previous therapies: 4 (3-6)

11 pts (55%) achieved an overall response (>30x10^9/L)

Sustained response (at 6 months) 35%

No bleeding events during zanubrutinib treatment



Huang et al. AJH 2025

LONG-LIVED PLASMA CELLS

Research article

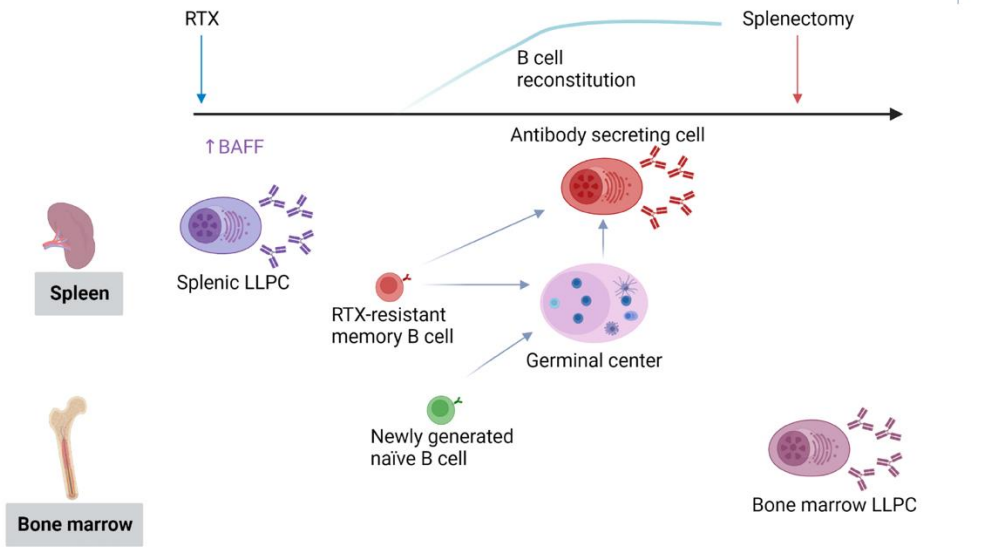
B cell depletion in immune thrombocytopenia reveals splenic long-lived plasma cells

Matthieu Mahévas,[1,2] Pauline Patin,[1] François Huetz,[1,3] Marc Descatoire,[1] Nicolas Cagnard,[4]

REVIEW

BJHaem BRITISH JOURNAL OF HAEMATOLOGY

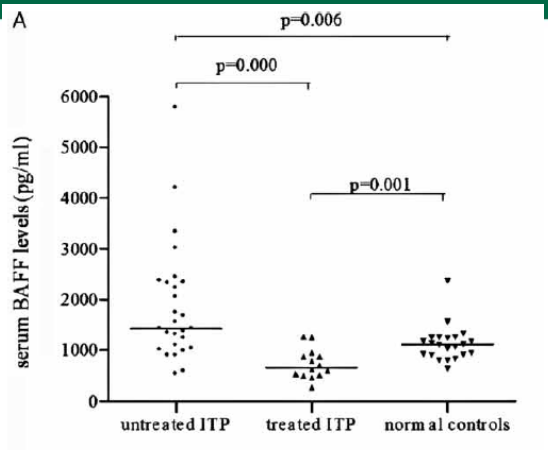
B cells and antibodies in refractory immune thrombocytopenia

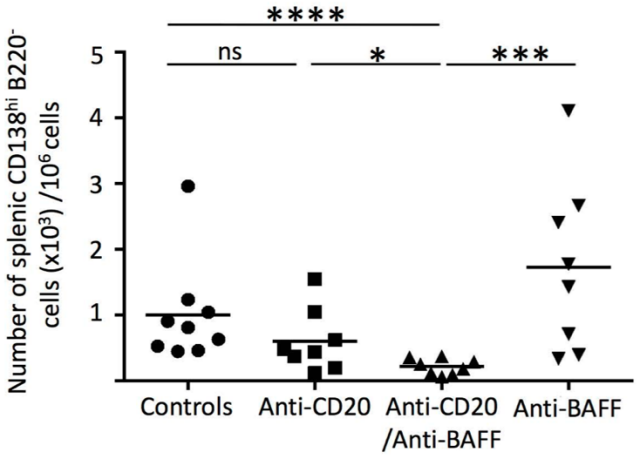


Mahévas M, et al. J Clin Invest 2013; Roeser A et al. BJH 2023

BAFF

- Serum BAFF levels are higher in untreated ITP patients compared with controls and treated patients[1]
- B-cell depletion promotes the differentiation of long-lived plasma-cells[2]
- BAFF plays a major role for long-lived plasma cell survival after B-cell depletion therapy[3]
- Combining anti-CD20 and anti-BAFF reduces the number of splenic plasmacells[3]





1. Zhou e al. Autoimmunity 2009. 2. Mahévas M et al. J Clin Invest 2013 3. Thai et al. Blood 2018

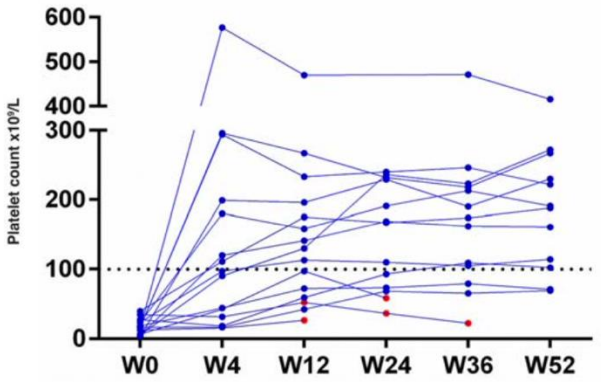
Efficacy, safety and immunological profile of combining rituximab with belimumab for adults with persistent or chronic immune thrombocytopenia: results from a prospective phase IIb trial

Single arm, prospective, Phase 2 tiral in patients with persistent or chronic ITP

Treatment:
- Rituximab 1000 mg, 2 weeks apart
- Belimumab 10 mg/kg, intravenous at Day 0, week 2, week 4, week 8 and week 12.

Primary endpoint: overall response at week 52 according to IWG criteria.
15 patients enrolled.

Efficacy.



Outcome at W12	Outcome at W24	Outcome at W36	Outcome at W52
9 CR	9 CR	10 CR	10 CR
4 R	4 R	2R	2 R
2 NR	2 NR	3NR	3 NR

- ORR at week 12: 86.7% (13/15), with 60% CR
- **ORR at week 52: 80% (12/15), with 66% CR**

→ Phase 3 clinical trial ongoing (RITUX-PLUS 2)
Rituximab + scBelimumab vs Rituximab + placebo

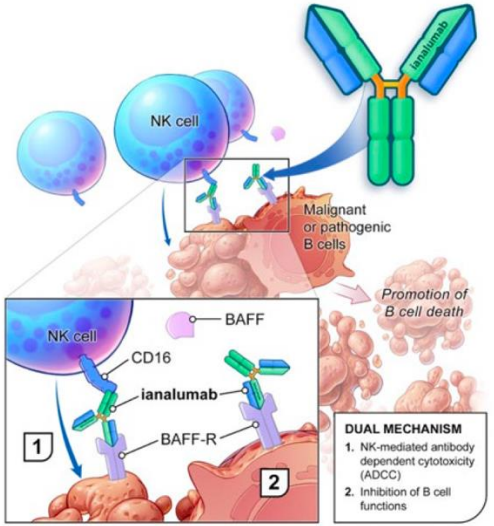
Mahevas et al. Haematologica 2021

IANALUMAB

Anti BAFF-R monoclonal antibody[1]:

- B cell depletion by ADCC
- Better NK cell recruitment
- Blocks BAFF:BAFF-R signaling by targeting BAFF-R on plasmablasts, naive and mature B cells

} Expected to deliver deeper B-cell depletion and long-term disease remission



Ianalumab in ITP:

- First-line: phase III, randomized, double-blind study of Ianalumab vs placebo added to standard first-line therapy
- Second-line: phase III, randomized, double-blind study of eltrombopag + Ianalumab/placebo in patients who failed or relapsed after first-line therapy
- ≥ 3 lines: phase II study, open-label, Ianalumab in patients already treated with corticosteroids and a TPO-RA

1. Droner T et al. Ann Rheum Dis. 2019.

A Phase 2 Study of Ianalumab in Patients with Primary Immune Thrombocytopenia Previously Treated with at Least Two Lines of Therapy: Interim Results from VAYHIT3

David J Kuter, Tomas Jose Gonzalez Lopez, Karolin Trautmann-Grill, Mathias J. Rummel, Philip Young-Ill Choi, Alessandra Borchiellini, Muhlis Cem Ar, Huyen Tran, Tienan Zhu, Jae-Ho Yoon, Nichola Cooper, Thomas Stauch, Pinar Tarkun, Fabienne Le Gac, Alex Allepuz, Patrick Urban, Renxin Lin, Charlotte A. Bradbury

Treatment: Ianalumab 9 mg/kg every 4 weeks for 4 doses

Primary endpoint: ***confirmed response (ConfR)*** = platelet count ≥50x10^9/L at two or more consecutive assessments at least 7 days apart between week 1 and 25.

39 patients enrolled; interim analysis of 10 patients. 60% had received ≥6 prior lines of therapy
2/10 discontinued treatment earlier

ConfR achieved in 50% of cases: 2 patients in monotherapy, 8 patients in combination with TPO-RA

1. Kuter D et al. ASH 2024 oral presentation

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

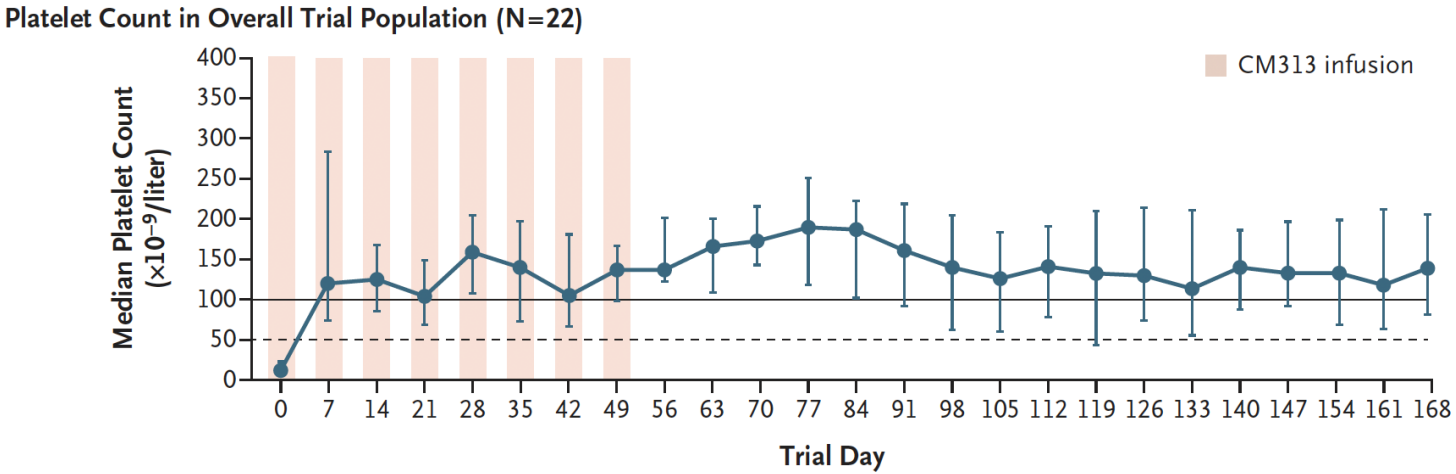
A Novel Anti-CD38 Monoclonal Antibody for Treating Immune Thrombocytopenia

22 pts enrolled
Median number of previous treatments: 4 (3-7)

- CM-313; phase 1-2 study.
- IV, 16 mg/kg for 8 weeks

95% responded (two consecutive plt count ≥50.000/mmc)

No correlation between anti-platelet antibodies and respose



Chen Y et al. NEJM 2024

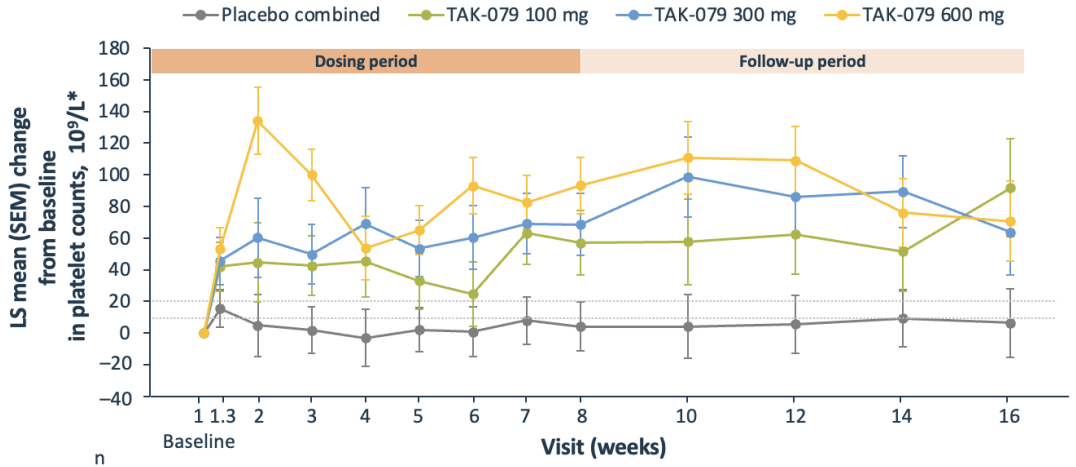
Safety, tolerability, and efficacy of mezagitamab (TAK-079) in chronic or persistent primary immune thrombocytopenia: Interim results from a phase 2, randomized, double-blind, placebo-controlled study

Platelet response:

- **600 mg: 90.9%**
- 300 mg: 62.5%
- 100 mg 66.7%
- Placebo: 23.1%

41 patients with persistent/chronic ITP

Randomized to receive mezagitamab (3 different doses) or placebo <u>for 8 weeks</u>, subcutaneously



n											
Placebo combined	12	13	13	13	13	13	13	12	12	12	12	11
TAK-079 100 mg	7	8	8	8	7	6	7	7	5	5	5	5
TAK-079 300 mg	8	8	8	8	8	8	8	8	8	8	8	8
TAK-079 600 mg	10	11	9	10	10	8	9	9	9	9	8	9

Kuter D et al. ISTH 2024

SAFETY AND EFFICACY of DARATUMUMAB in ITP

blood advances

Phase 2, open-label study of patients with primary ITP who failed corticosteroids and at least 1 between TPO-RAs and Rituximab

Treatment: Daratumumab 1800 mg sc weekly
Safety run-in → cohort 1 (8 doses) and cohort 2 (10 doses)

Primary endpoint: platelet response ≥$50x10^9$ at week 12 or 16

21 patients enrolled; median number of previous therapies: 4 (2-11)
Previous rituximab 76%
Previous splenectomy 24%

Tsykunova G et al. Blood Advances 2025

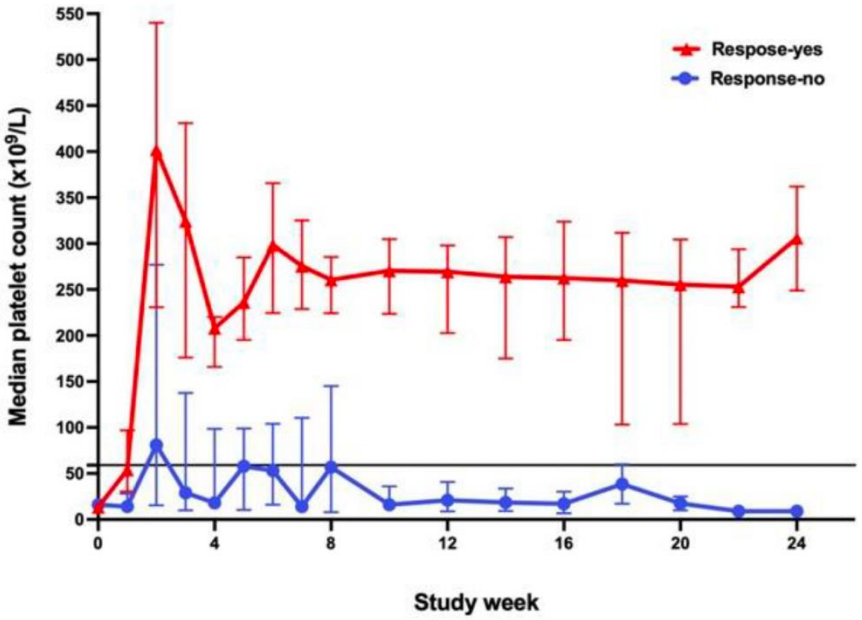
SAFETY AND EFFICACY of DARATUMUMAB in ITP

blood advances

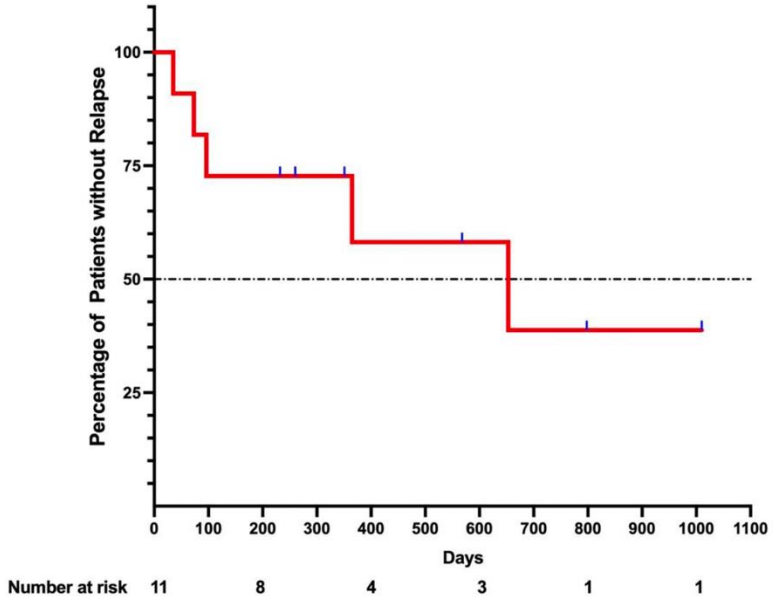
Primary endpoint (at week 12 or 16): met in 48%

Sustained response (at week 24): 38%

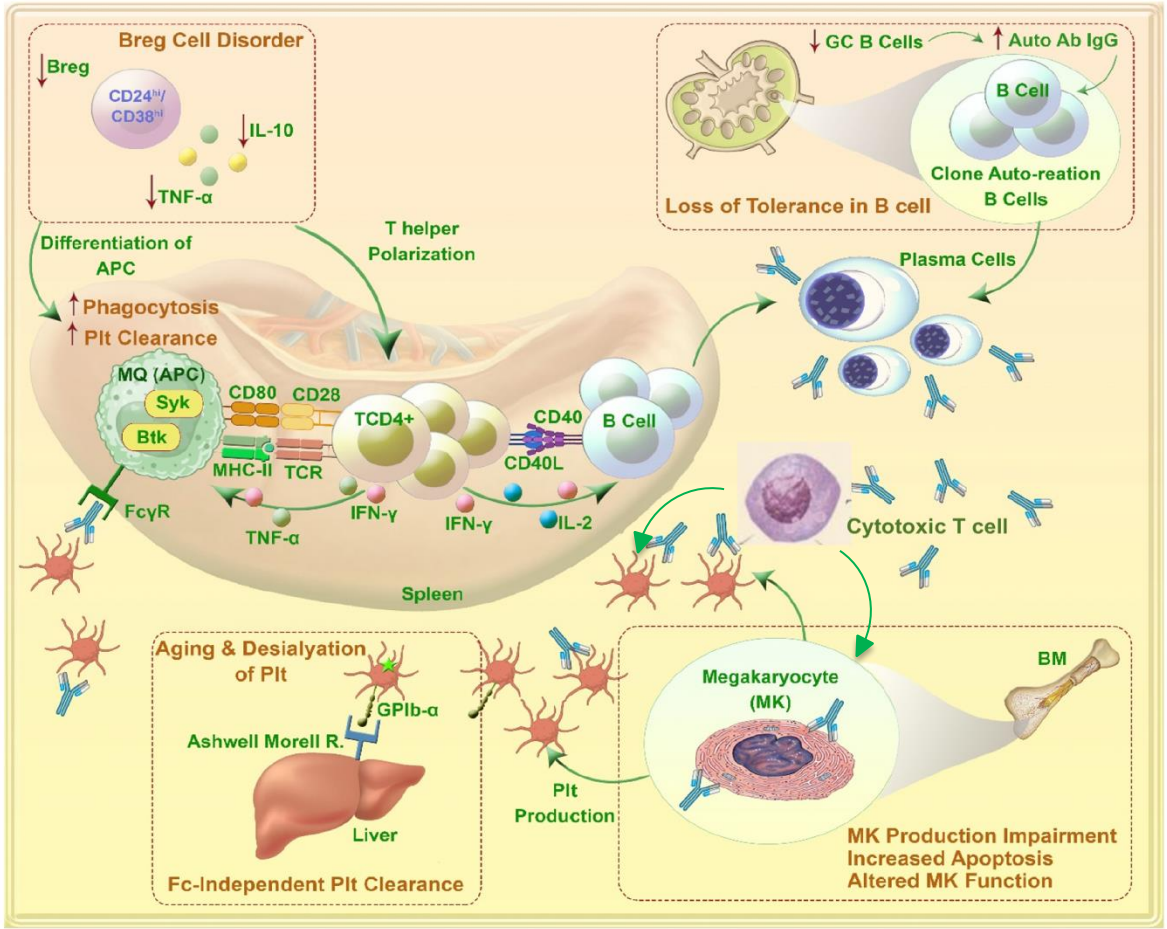
«Overall» response (≥50x10^9/L at least once): 86%



Median duration of response 21.5 months



Tsykunova G et al. Blood Advances 2025



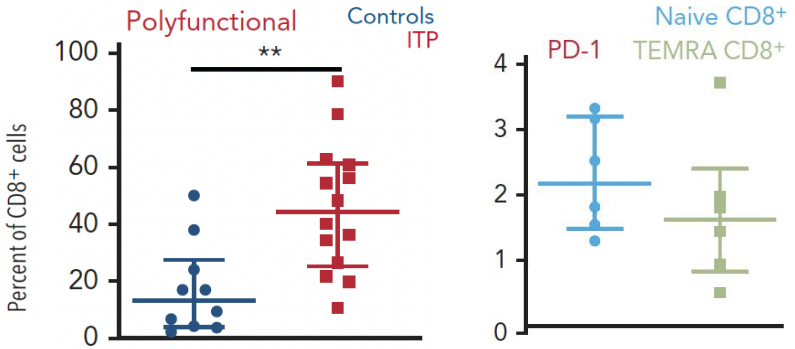
T-cells abnormalities in ITP:

- Increased ratio Th1/Th2 ($CD4^+$) (↑ IL-2 and INF-γ; ↓ IL-10)
- ↑ IL-17: proinflammatory cytokine
- ↑ IL-22 and Th22 cells: inflammatory cytokine; effects on epithelial cells
- ↑ follicular T-helper
- **Cytotoxic T cells**
- **T-reg cell deficiency**

Adapted from Delshad et al. Thrombosis Research 2024

The role of CD8$^+$ T-cell clones in immune thrombocytopenia

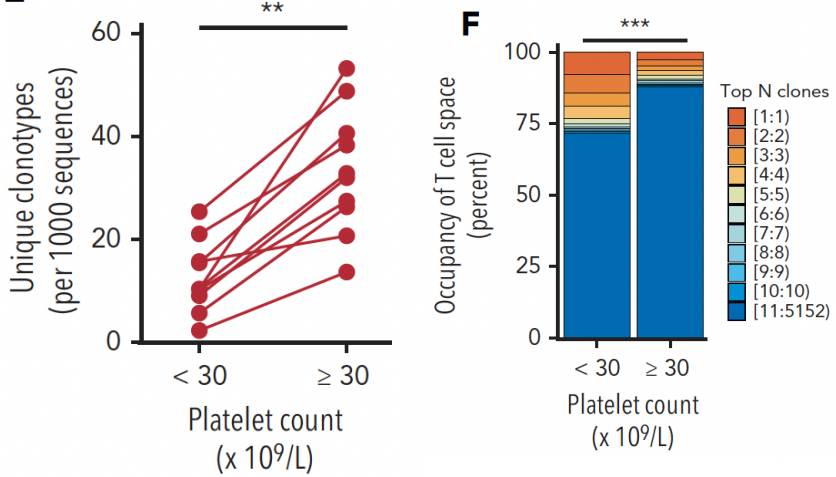
- Expanded population of terminally differentiated CD8+ T cells (TEMRA) in ITP patients compared to controls, and especially in patients with active disease (plt count < 30x10^9/L).
- TEMRA cells of ITP patients secrete IFN-gamma, TNF-alfa and granzyme B and normal levels of PD-1
- Higher numbers of T cell clones in ITP patients compared to controls; private clones (unique to individual patients); no shared clones across patients



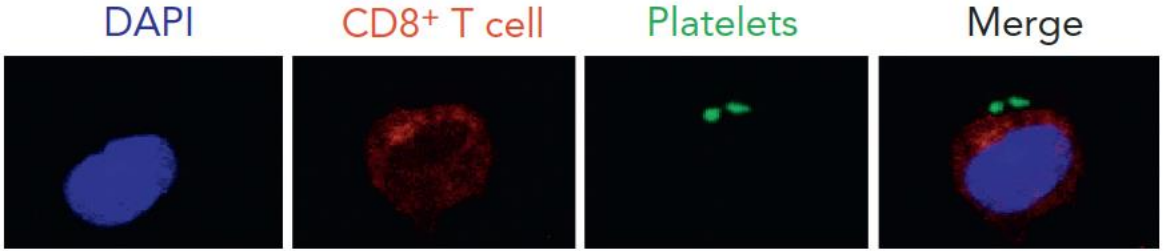
Malik A et al. Blood 2023

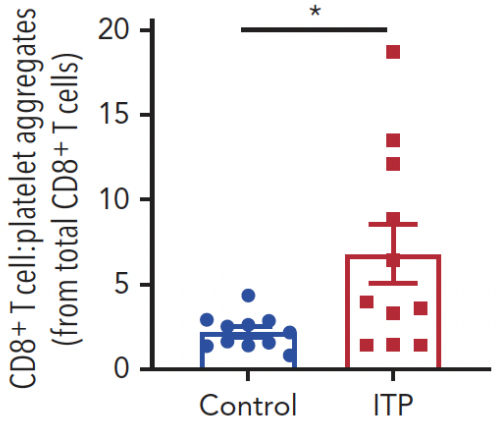
The role of CD8$^+$ T-cell clones in immune thrombocytopenia

- Expanded clones and reduced T-cell repertoire diversity when plt count was lower
- Expanded clones belong to the TEMRA cells



- Co-culture of CD8+T cells with autologous platelets → stable T-cell-platelet aggregates





Malik A et al. Blood 2023

Target therapies

B-cells/phagocytosis		Plasmacells	Antibodies	Complement
Fixed duration	**Continuous**	**Fixed duration**	**Continuous**	**Continuous**
Rituximab	Fostamatinib	Daratumumab	Efgartigimod	Sutimlimab
Ianalumab	Rilzabrutinib	CM-313		Iptacopan

? How to chose ?

TPO-RAs
Mainly continuous
Eltrombopag
Romiplostim
Avatrombopag

ATRA	Decitabine	Splenectomy	Combinations
Fixed duration	**Fixed duration**	**Fixed duration**	**Ideally fixed duration**

«broad spectrum» therapies

fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GIMEMA BIO-ITP study (ITP1222)

Studio multicentrico, biologico, prospettico, non farmacologico, con l'obiettivo di caratterizzare i pazienti con ITP da un punto di vista biologico.

- ITP adulti (età ≥18 anni) con ITP primitiva da avviare a terapia di prima linea
- Pazienti non precedentemente trattati (o entro 24h dall'avvio della terapia di prima linea)
- Esclusi i pazienti con ITP secondaria

I campioni di sangue periferico, di midollo osseo e di feci saranno raccolti **prima dell'inizio del trattamento**, **dopo il trattamento** (a 30 e a 180 giorni) e all'eventuale recidiva, così **per ogni eventuale nuova linea di terapia**.

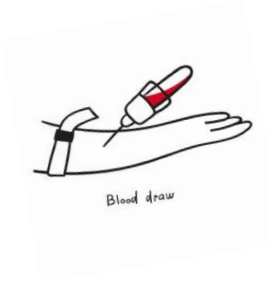
fondazione GIMEMA onlus
per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

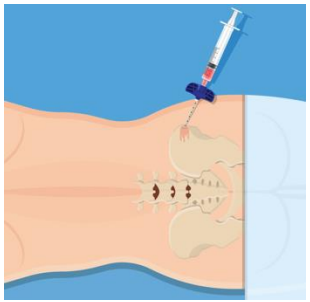
GIMEMA BIO-ITP study (ITP1222)

Sangue periferico
Anticorpi anti-piastrine
Profilo citochine Sottopopolazioni linfocitarie Complemento
Parametri piastrinici
TPO
Desialilazione e apoptosi
Clonalità B e T
Pannello genetico per autoimmunità / malattie linfoproliferative

Midollo (non mandatorio)
Stessi test eseguiti su sangue periferico

Campione di feci
Microbiota fecale*





Centri coinvolti nello studio: **23**

Centri aperti all'arruolamento: **15**

Data apertura arruolamento dello studio: **27/11/2023**

Numero totale dei pazienti eleggibili : **49**

UCO Ematologia, Trieste

Prof Francesco Zaja

Dr. Mario Ballerini
Dr.ssa Laura Ballotta
Dr.ssa Manuela Caizzi
Dr.ssa Eleonora De Bellis
Dr. Giovanni De Sabbata
Dr. Davide Griguolo
Dr.ssa Sara Mohamed
Dr.ssa Monica Poiani
Dr. Eugenio Sbisà
Dr.ssa Rossella Stella
Dr.ssa Cristina Ancora (Med in formazione)
Dr. Matteo Turoldo

UNIVERSITÀ DEGLI STUDI DI TRIESTE

ASUGI Azienda Sanitaria Universitaria Giuliano Isontina
REGIONE AUTONOMA FRIULI VENEZIA GIULIA