GIORNATE EMATOLOGICHE VICENTINE

X edizione

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Palazzo Bonin Longare - Vicenza

Nuovi orizzonti fisiopatologici e terapeutici nell'ITP

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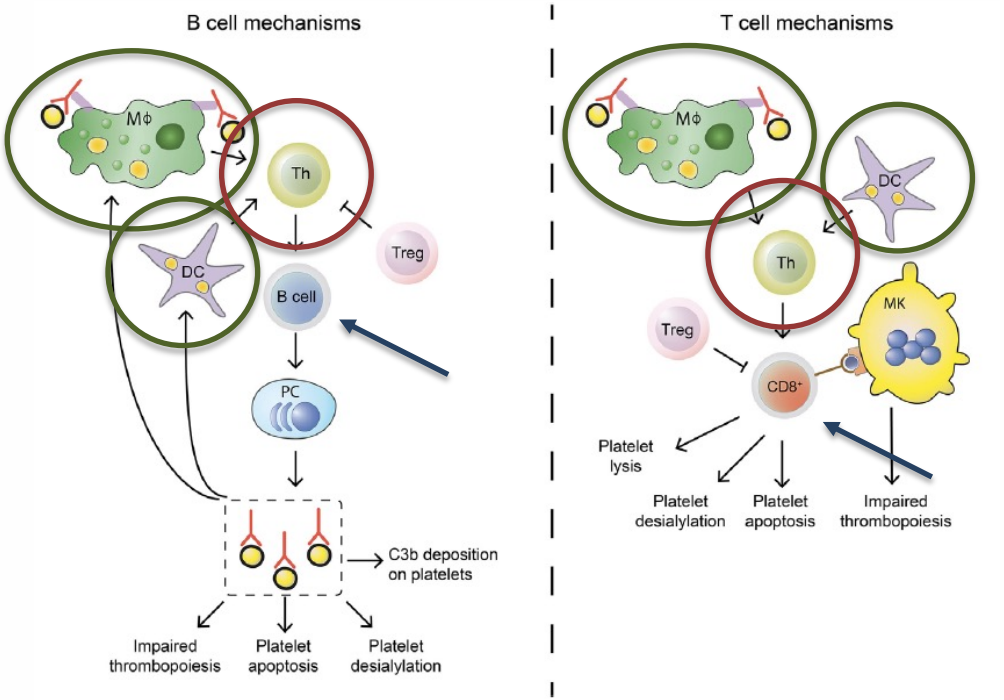
UCO Ematologia - Trieste

Disclosures of Name Surname

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

Breakdown of immune tolerance to platelet antigens



Macrophages and dendritic cells can present antigens to Th cells

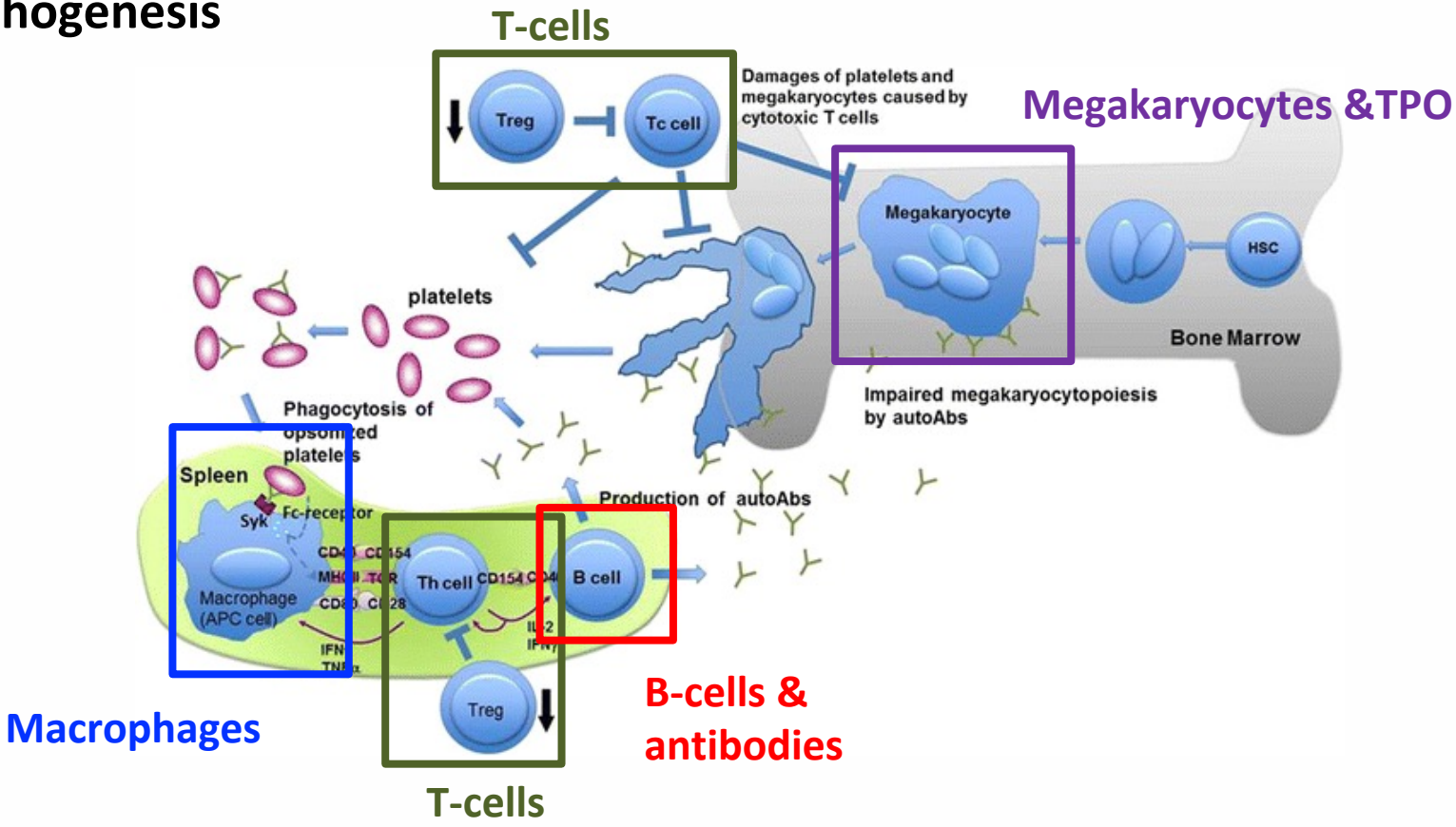
- B-cell activation
- Cytotoxic T cell activation

Platelet phagocytosis
Platelet lyisis
Platelet desyalilation
Impaired Mkpoiesis

Dysfunctional regulatory T and B cells

Adapted from Swinkels et al Frontiers in Immunology 2018

ITP pathogenesis



Kashiwagi et al International Journal of Hematology 2013

Megakaryocytes &TPO

- **Cytotoxic T cell-attack**:

CD8+ T cell co-culture with MKs results in fewer platelet production[1]

- **Autoantibodies**:

Plasma from patients with antiplatelet antibodies in vitro reduces the total number of MKs, inhibites MK maturation[2] and proplatelet formation[3]

- **Apoptosis**:

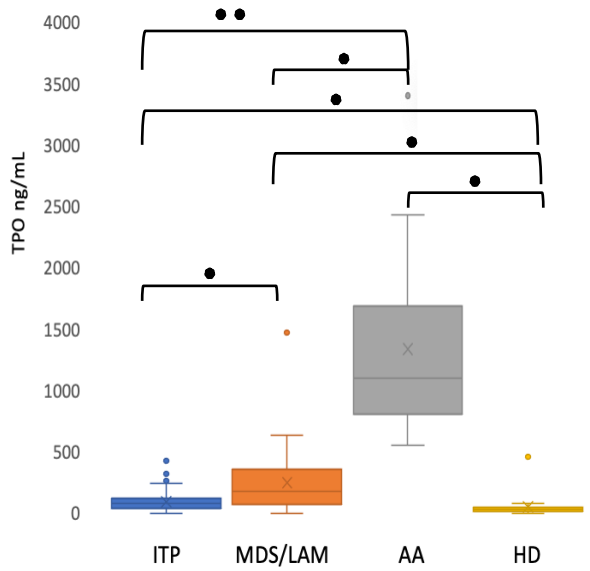
Abnormal apoptotic features in ITP patients → dysmegakaryocytopoiesis and reduced platelet production[4-6]

- **Abnormal autophagy**[7]

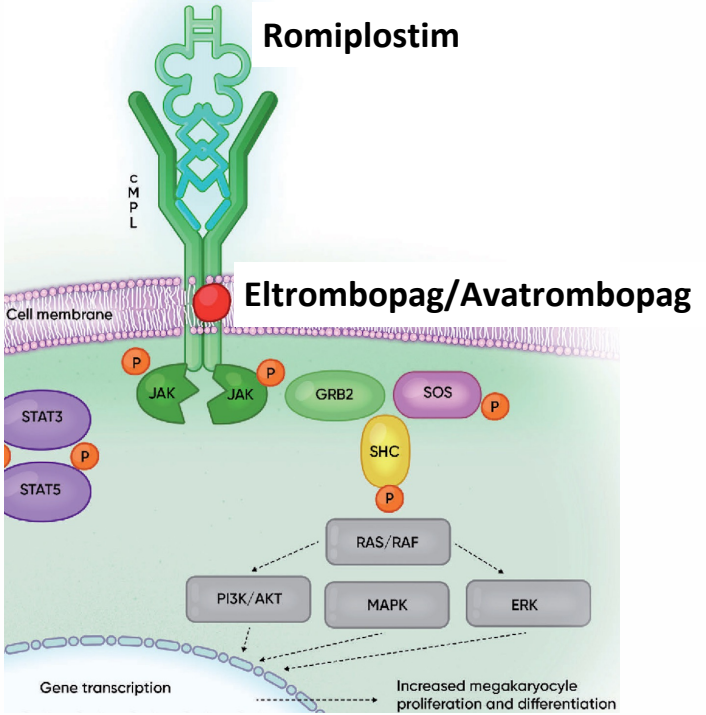
- **Mesenchymal stem cell deficiency**[8]

1. Li S, et al. *Br J Haematol.* 2007;139:605–611; 2. McMillan et al. Blood 2004; 3.Iraqi et al. Haematologica 2015; 4. Houwerzijl et al Blood 2004; 5. Yang et al. Blood 2010; 6. Vrbensky et al Platelets 2018; 7..Rui-Jie Sun et al. Cancer Cell 2019 8. Zhang et al. Autoimmunity 2014

Inadequate TPO levels in patients with ITP



TPO-mimetics



Ghanima W et al. Haematologica 2019

TPO-mimetics in ITP

Short-term activity: 70-80%

Long-term activity: 50-60%

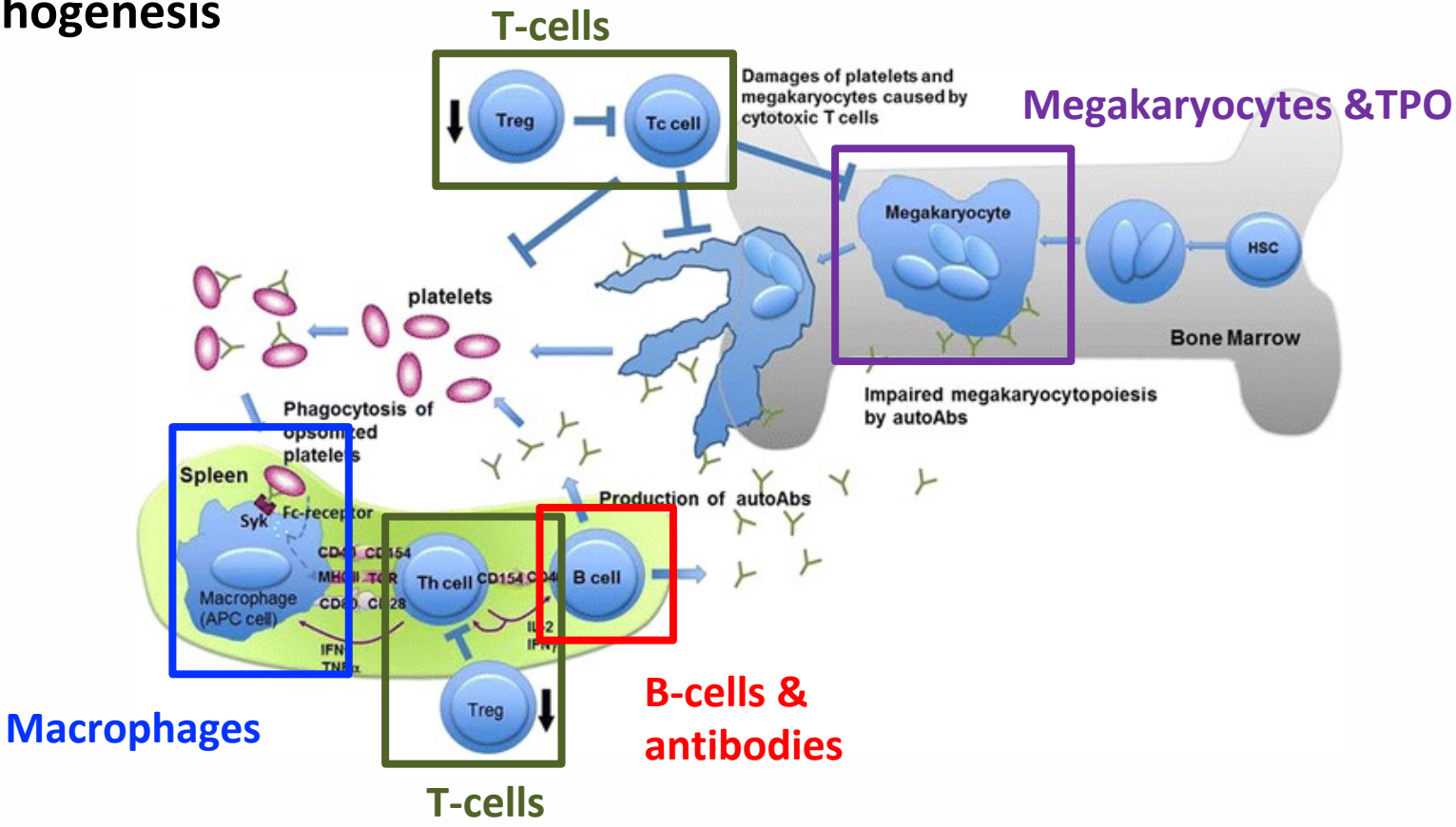
Sustained response off-treatment: 30%

How can they be improved?

Study	Number of pts	ITP duration before starting TPO-RA	PLT count required to start tapering	Type of TPO-RA	Pts in sustained remission (n, % of all pts)	Median follow-up (months)
Newland BJH 2016	75	< 6 months	≥50x10^9	Romiplostim	24 (32%)	6
Lucchini BJH 2020	51	ND 43%; P 57%	≥30x10^9	Eltrombopag	13 (25%)	6
Guillet Blood 2023	48	P 38%; C 62%	≥100x10^9	83% Elt 17% Romi	25 (52%)	12
Cooper N EHA 2022 abs	105	n/a	≥70x10^9	Eltrombopag	32 (30%)	12

Ghanima W et al. Haematologica 2019

ITP pathogenesis



Kashiwagi et al International Journal of Hematology 2013

B-cells & antibodies

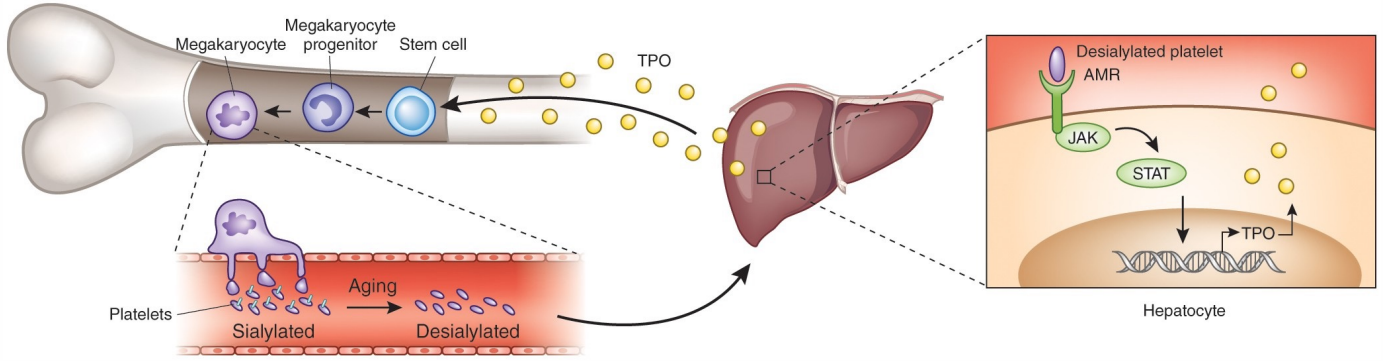
Anti-platelet antibodies are produced by a restricted number of B-cell clones, who underwent somatic hypermutation (CD4+-T cell-driven specific antigen response)[1]

Autoantibodies mediate platelet clearance by:

- Fc-dependent manner: phagocytosis, apoptosis, complement activation
- Fc-independent manner: desyalilation[2,3]

1. Roark et al. Blood 2002 2. Kile nat.med 2015 3.Grozovsky et al. Nat Med 2015

B-cells & antibodies - desialylation



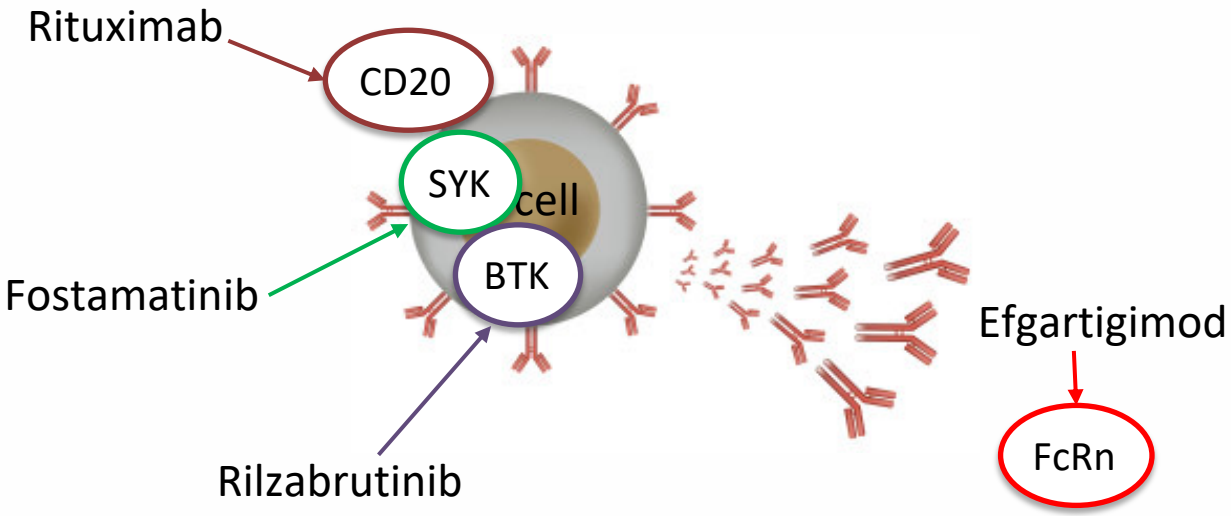
Desialylation can be triggered by antiplatelet antibodies, both GPIbIX and GPIIb/IIIa:

- Enhanced platelet cleareance[1]
- Impaired platelet production[2]

Therapeutic target ?

1. Li et al. Nat Commun. 2015; 2. Marini et al *Haematologica*. 2021

B-cells & antibodies



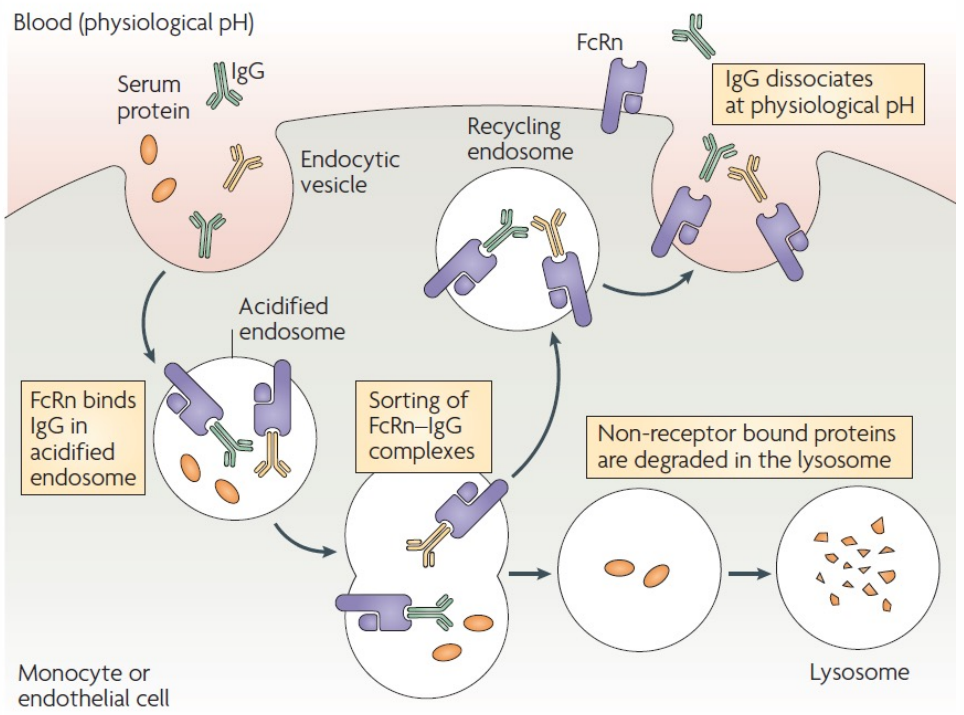
1. Roark et al. Blood 2002 2. Kile nat.med 2015 3.Grozovsky et al. Nat Med 2015

FcRn inhibitor

Functions:

- Mediates maternal IgG transport – confering passive immunity
- Protect monomeric IgG and degrade multimeric immune complexes-IgG for antigen presentation
- Critical role in albumin homeostasis
- Increased IgG half-life (28 days vs 1-2 days) in FcRn deficient mice

→ It's involved in IgG recycling, preventing their degradation



Roopenian DC, et al. Nat Rev Immunol. 2007

blood®

Efficacy and Safety of Intravenous Efgartigimod in Adults with Primary Immune Thrombocytopenia: Results of a Phase 3, Multicenter, Double-Blinded, Placebo-Controlled, Randomized Clinical Trial (ADVANCE IV)

Catherine M. Broome, Vickie McDonald, Yoshitaka Miyakawa, Monica Carpenedo, David J. Kuter, Hanny Al-Samkari, James B. Bussel, Marie Godar, Jaume Ayguasanosa, Kristof De Beuf, Francesco Rodeghiero, Marc Michel, Adrian C. Newland

Patients with persistent or chronic R/R ITP randomized to receive 2:1 Efgartigimod vs placebo for 24 weeks.

- Weekly administration for 4 weeks, then adjusted according to platelet counts.

Primary Endpoint: sustained platelet response: PLT of ≥50×10^9/L in ≥4 of 6 visits between weeks 19 and 24 without intercurrent events

131 patients (118 chronic, 13 persistent)

Heavily pretreated (67.2% had ≥3 prior ITP therapies)

blood®

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Endpoint	Population	Efgartigimod	Placebo	P value
Sustained platelet count response (primary endpoint)	Chronic	17/78 (21.8%)	2/40 (5%)	0.031*
Incidence of WHO bleeding events (WHO ≥1)**	Overall	6.2	8.3	0.828
Durable sustained response	Overall	19/86 (22.1%)	3/45 (6.7%)	0.026*

** Number of visits with WHO ≥1 (mean)

- Platelet response usually rapid (after 1 week)
- **Response according to IWG criteria: 51.2% of efgartigimod-treated patients vs 20% in placebo group.**
- Sustained platelet response achieved in 90% (9/10) of patients who reached and maintain the qw2 fixed dosing.

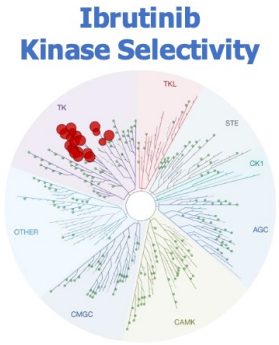
Broome et al. 2022 ASH Abstract

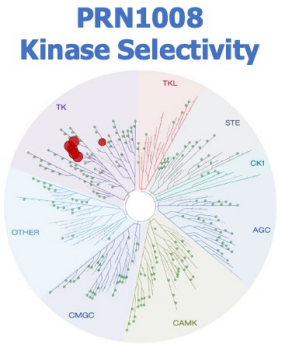
BTK inhibitor

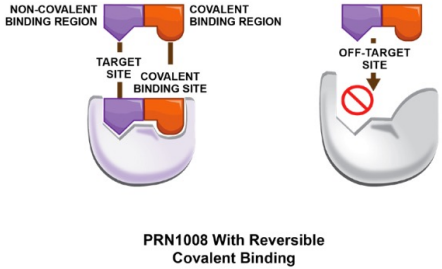
Rilzabrutinib (PRN1008) is an oral, **reversible covalent** Bruton's tyrosine kinase (BTK) inhibitor.

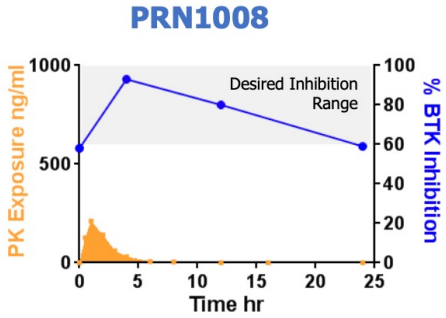
BTK is present in the signalling pathways of most types of white blood cells except for T cells and plasma cells.

Rilzabrutinib does not inhibit collagen-activated platelet aggregation









Langrish CL et al. *Blood.* 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia

David J. Kuter, M.D., Merlin Efraim, M.D., Jiri Mayer, M.D., Marek Trněný, M.D.,

Phase 1/2 open-label study
60 chronic ITP patients

Median duration of disease 6.3 years (range 0.4-52.5)

Intrapatient dose escalation, from 200 mg once daily to 400 mg twice daily.

Primary endpoints:
- Safety
- Platelet responses (at least two consecutive platelet counts of ≥50x10^3/mmc)

Treatment-Related Adverse Events*

	Any Grade	Grade 1	Grade 2	Grade 3 or 4
Any adverse event	31 (52)	27 (45)	15 (25)	0
Diarrhea	19 (32)	16 (27)	3 (5)	0
Nausea	18 (30)	16 (27)	2 (3)	0
Fatigue	6 (10)	5 (8)	1 (2)	0
Abdominal distention	4 (7)	4 (7)	0	0
Vomiting	3 (5)	2 (3)	1 (2)	0

Mostly grade 1-2 and transient

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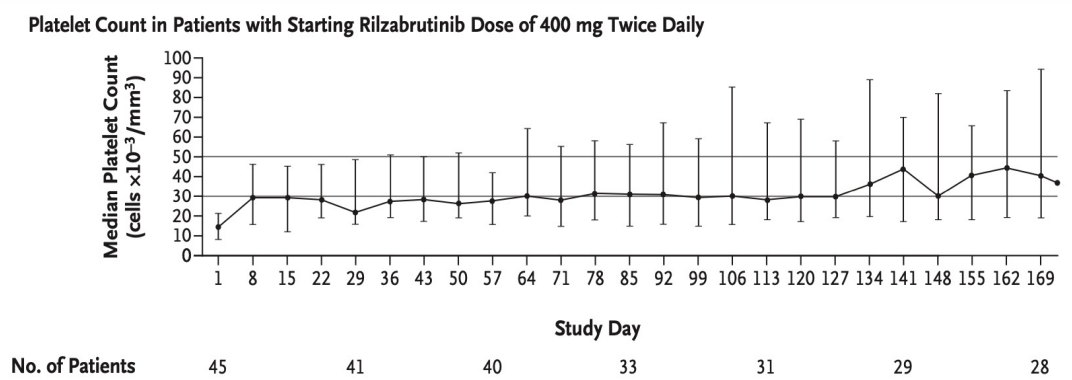
Primary endpoint: 24 of 60 patients (**40%**) had **at least two consecutive platelet counts of ≥50x10³/mmc**

Median time to first platelet count > 50×10³/mmc: 11.5 days

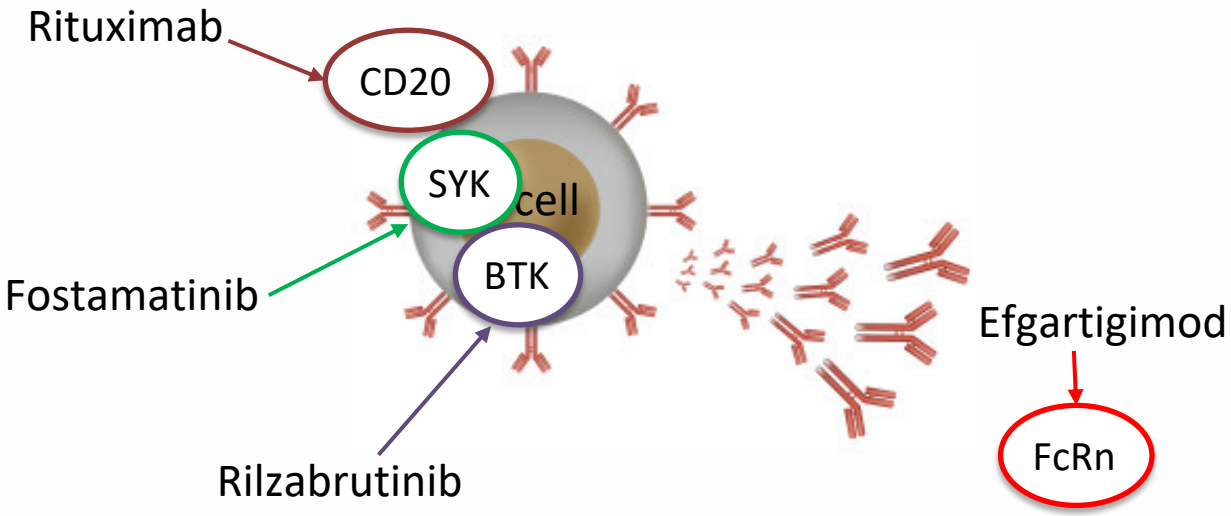
40/60 patients received concomitant medication: TPO-RAs (24 pts) and glucocorticoids (23 pts)

→ Phase 3 placebo-randomized study ongoing



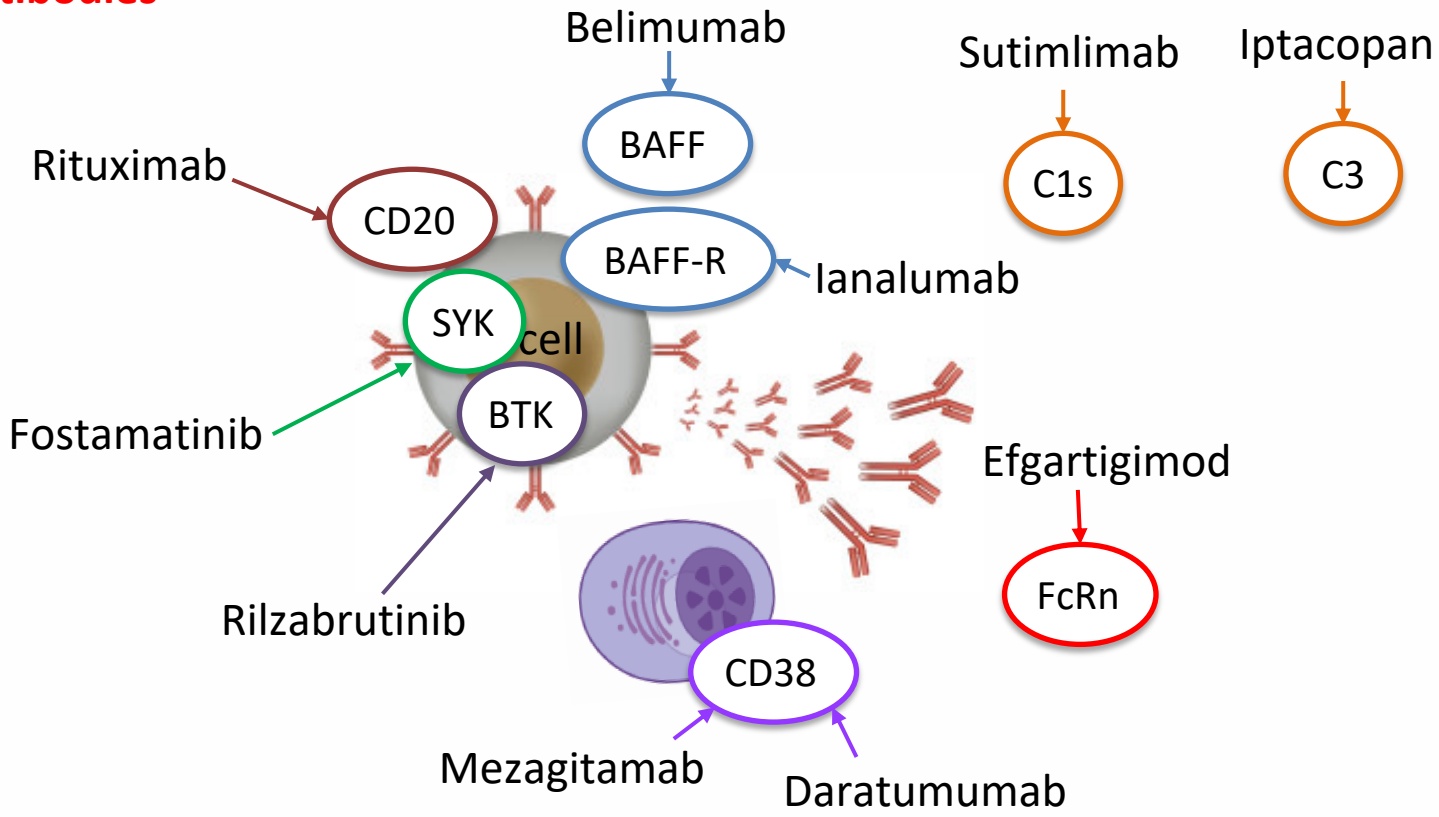
Kuter D et al. NEJM 2022

B-cells & antibodies



1. Roark et al. Blood 2002 2. Kile nat.med 2015 3.Grozovsky et al. Nat Med 2015

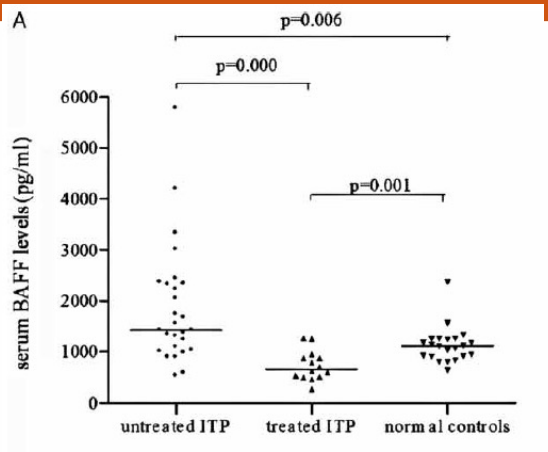
B-cells & antibodies

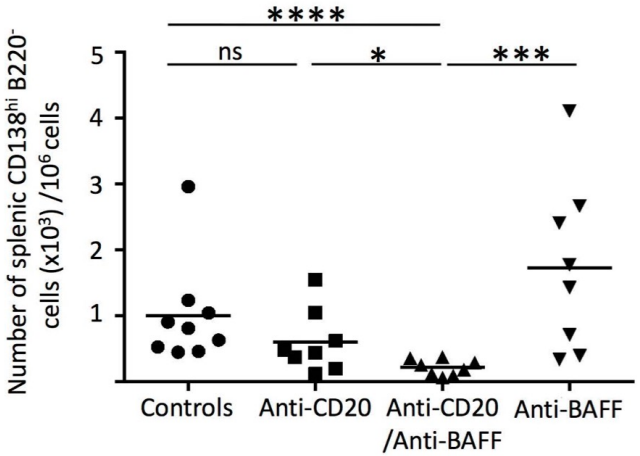


1. Roark et al. Blood 2002 2. Kile nat.med 2015 3.Grozovsky et al. Nat Med 2015

B-cells - 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

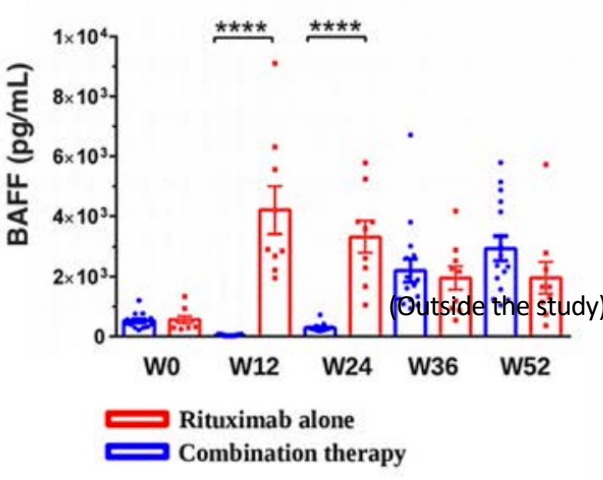
Single arm, prospective, Phase 2 tiral in patients with persistent or chronic ITP

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.

Safety:
- No infusion-related reactions reported with belimumab
- No severe infections
- No severe hypogammaglobulinemia, although significant decrease in IgG and IgM titres. No changes in IgA titres.



(Outside the study)

Reduced BAFF levels at W12, which returned to baseline at W24

Mahevas et al. Haematologica 2021

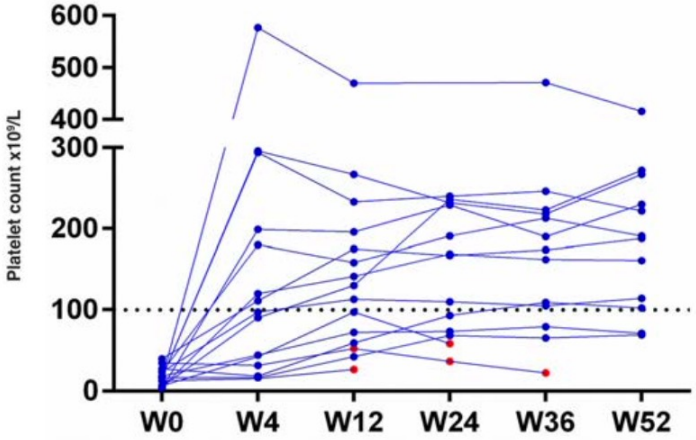
Efficacy, safety and immunological profile of combining rituximab with belimumab for adults with persistent or chronic immune thrombocytopenia: results from a prospective phase IIb trial

Efficacy.

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

Among responders, one patient in CR relapsed after a follow-up of 18 months.

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



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

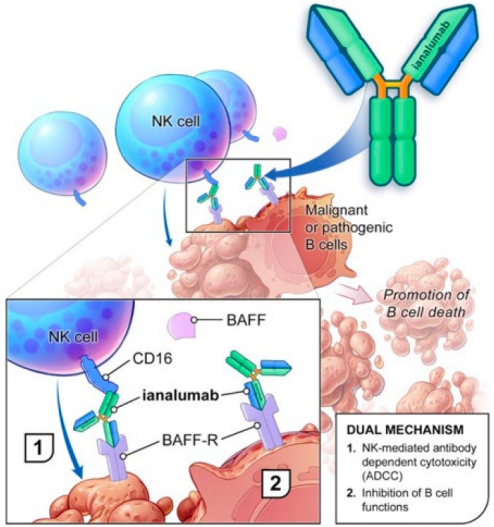
Mahevas et al. Haematologica 2021

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 tested in 12 clinical trials incuding nearly 500 subjects (Sjogren, SLE, autoimmune hepatitis, CLL..)[3]:

- Infusion-related reactions
- Rapid and sustained circulating B-cell depletion
- Median time to B-cell recovery: several months

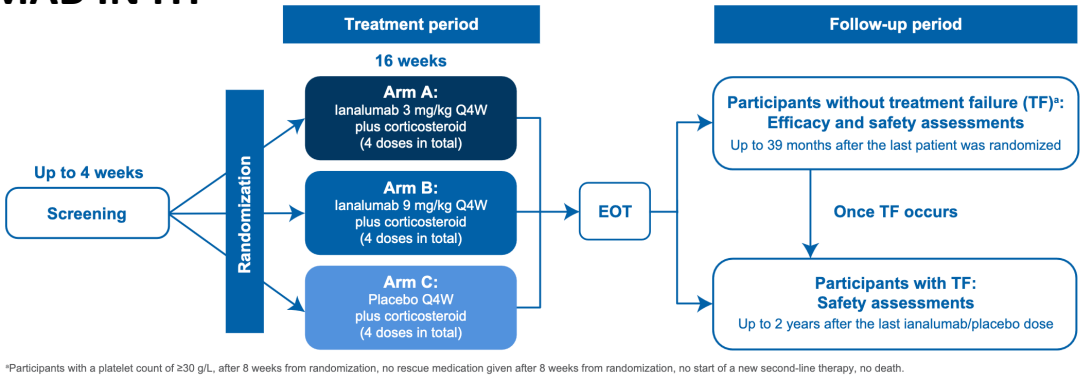
Promising results in a phase 2 study in patients with Sjogren syndrome in terms of efficacy and safety, no increase in infections[2].

1. Droner T et al. Ann Rheum Dis. 2019. 2. Bowman SJ et al. Lancet 2022. 3. Novartis unpublished data

IANALUMAB IN ITP

VAY736I12301

A phase III, randomized, double-blind study of ianalumab (VAY736) versus placebo in addition to first-line corticosteroids in primary immune thrombocytopenia (VAYHIT1)

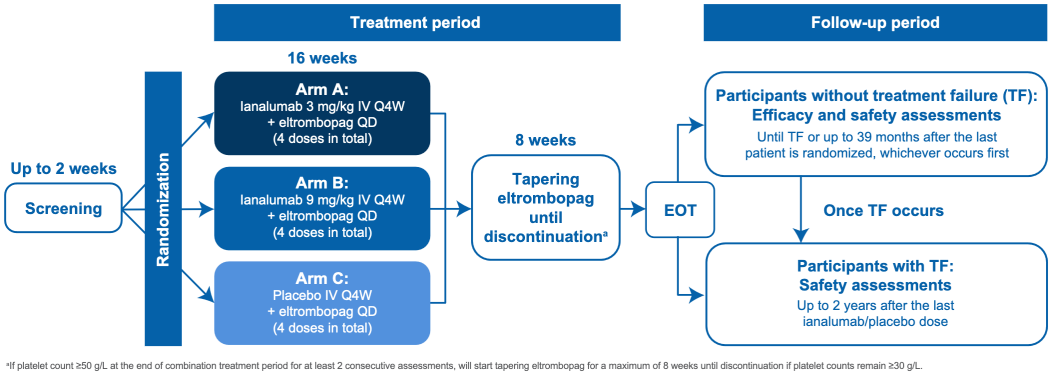


[a]Participants with a platelet count of ≥30 g/L, after 8 weeks from randomization, no rescue medication given after 8 weeks from randomization, no start of a new second-line therapy, no death.

Primary endpoint: time from randomization to treatment failure

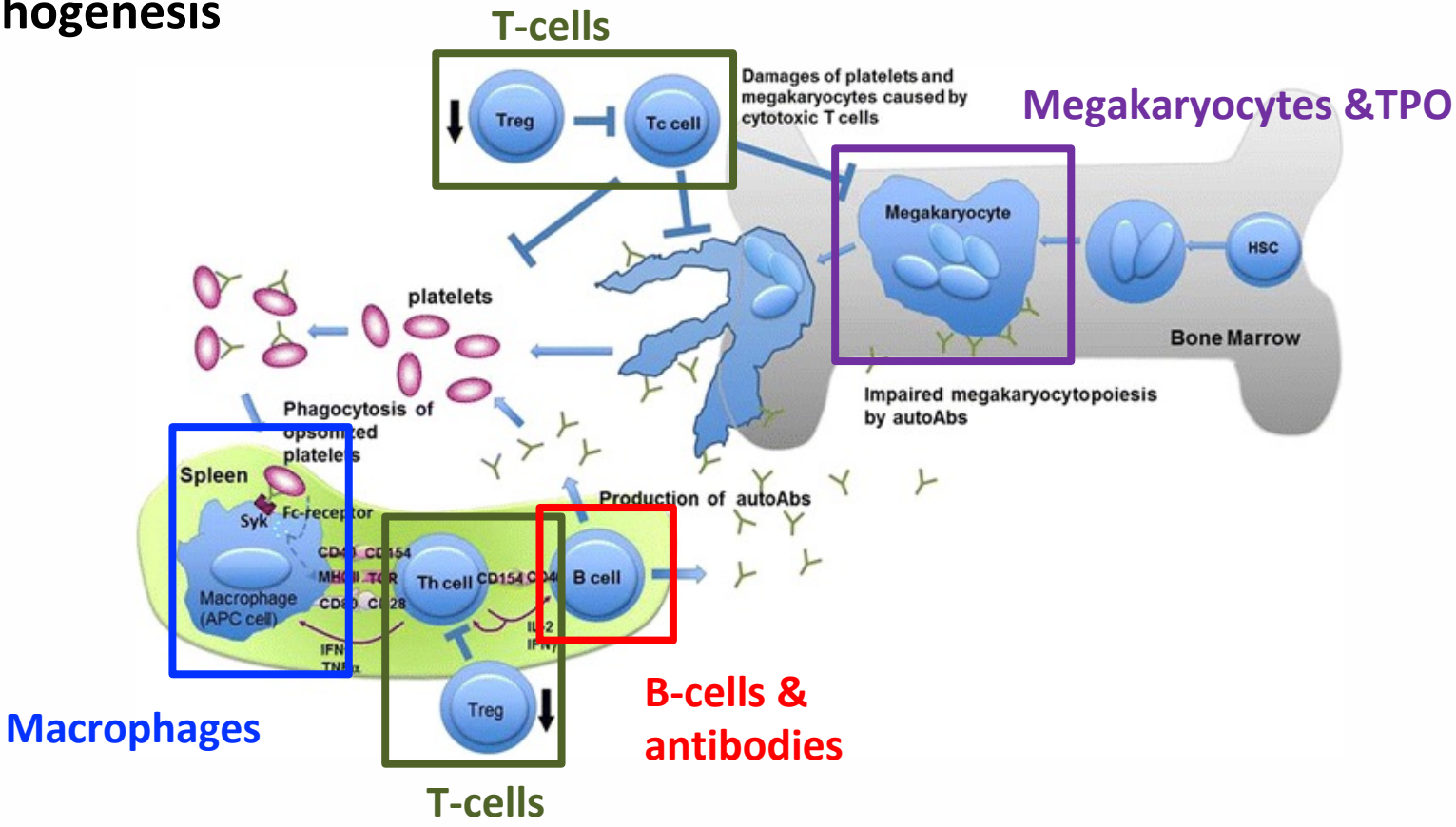
VAY736Q12301

A phase 3 randomized, double-blind study of ianalumab (VAY736) versus placebo in addition to eltrombopag in patients with primary immune thrombocytopenia (ITP) who had an insufficient response or relapsed after first line steroid treatment (VAYHIT2)



[a]If platelet count ≥50 g/L at the end of combination treatment period for at least 2 consecutive assessments, will start tapering eltrombopag for a maximum of 8 weeks until discontinuation if platelet counts remain ≥30 g/L.

ITP pathogenesis



Kashiwagi et al International Journal of Hematology 2013

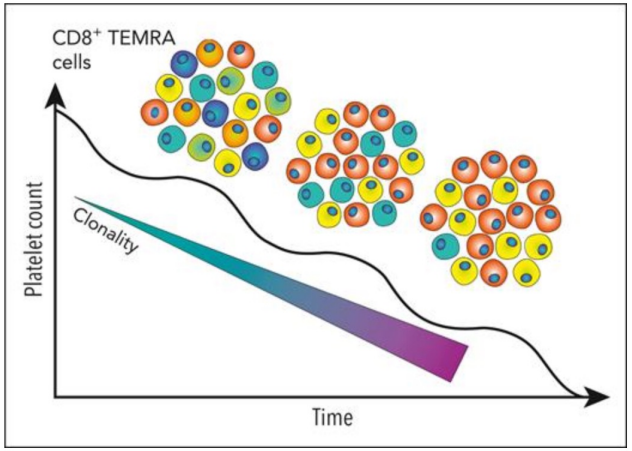
T-cells

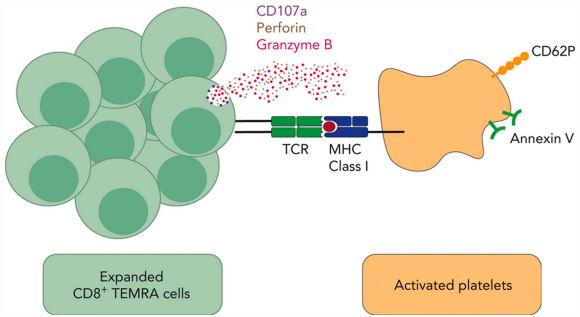
Patients with chronic ITP have a clonal expansion of a particular subset of CD8+ T cells: terminally-differentiated effector memory (TEMRA) T cells, that display features of activation.

Patients with more refractory disease have a greater expansion of T-cell clones.

TEMRA cells are inversely correlated with platelet count

When co-cultured with platelets, these cells promote platelet activation and apoptosis





Malik A et al. Blood 2023; Lazarus & Semple, Blood 2023

- Personalized therapy
- Combination therapy

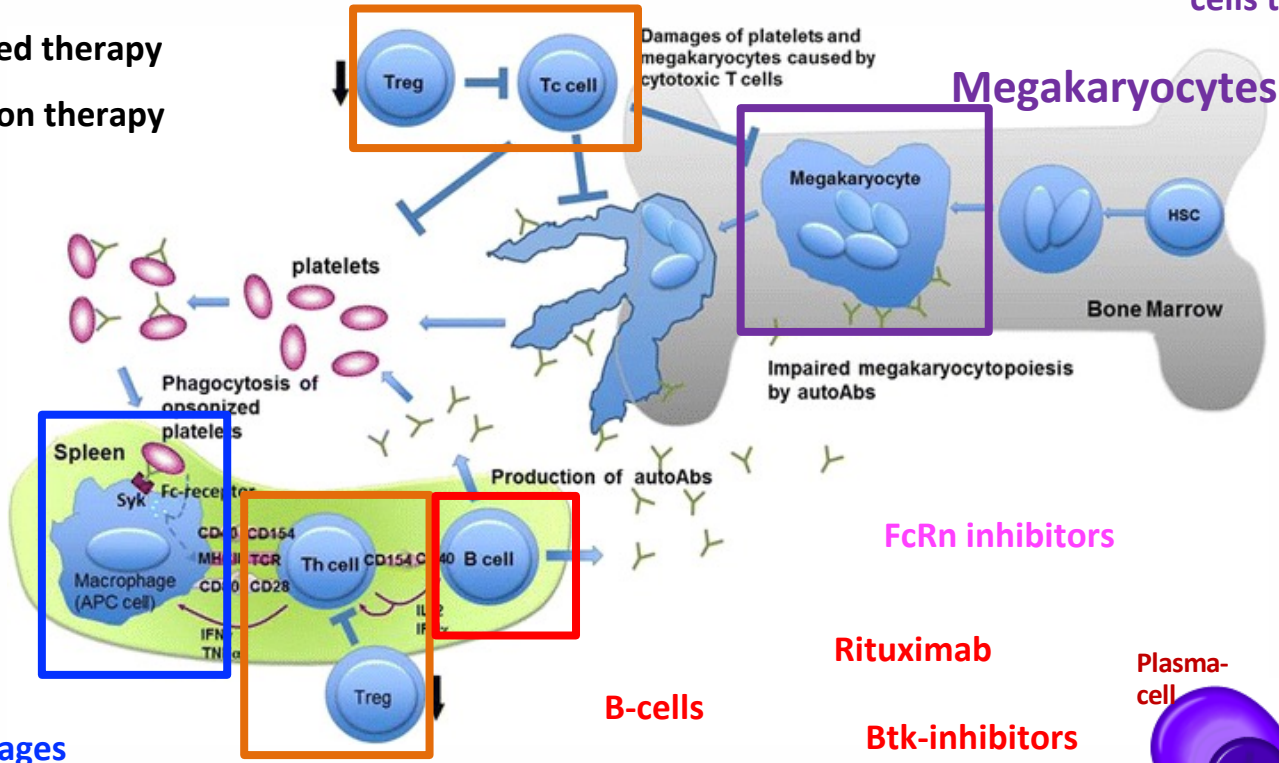
T-cells

TPO-RAs

Mesenchymal stem cells transplantation

Megakaryocytes

Autophagy:
Chloroquine
Rapamycin
Syrolimus
Decitabine



Complement-inhibitors

FcRn inhibitors

Fostamatinib

Rituximab

Plasma-cell

Anti-CD38

Macrophages

B-cells

Btk-inhibitors

Proteosome-inhibitors

T-cells

BAFF-Ibhibitors

Kashiwagi et al International Journal of Hematology 2013