San Giuseppe Moscati - Avellino
Azienda Ospedaliera di Rilievo Nazionale e di Alta Specializzazione

1ST SYMPOSIUM ON INNOVATIVE THERAPIES IN HEMATOLOGY

Avellino, Hotel de la Ville
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Future opzioni terapeutiche per la porpora trombocitopenica immune: una terapia per tutti?

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Disclosures Monica Carpenedo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Amgen					X	X	
Argenx						X	
Grifols					X	X	
Novartis					X	X	
Sanofi					X		
Sobi					X		

ITP: unresolved issues

- How to increase first line response
- How to achieve a stable response after first line failure/relapse
- How to manage multirefractory patients

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Streght and limitation of current First Line Therapy in ITP

» STRENHGTS

✓ Availability

✓ Cost

✓ Rapid response in most patient

» LIMITATION

✓ Side effects

✓ Low % of stable & long term response (20-30%)

MMF + steroid as First Line Therapy in ITP: the FLIGHT Trial

Prednisone 1 mg/kg x 4 days, 40 mg/d x 2 wks, 20 mg/d x 2 wk, 10 mg x 2 wk, 5 mg/d x 2 wks, 5 mg EOD x 2 wks

OR

Dexamethasone 40 mg/d x 4 days x n pulses (at the discretion of clinician)

+/- (random open label)

MMF 500 mg BID x 2 wks -- > 1gr BID x 6 months -> taper and stop if CR or lowest dose to keep safe plt count

Newly ITP, no previous tx

12 months observation

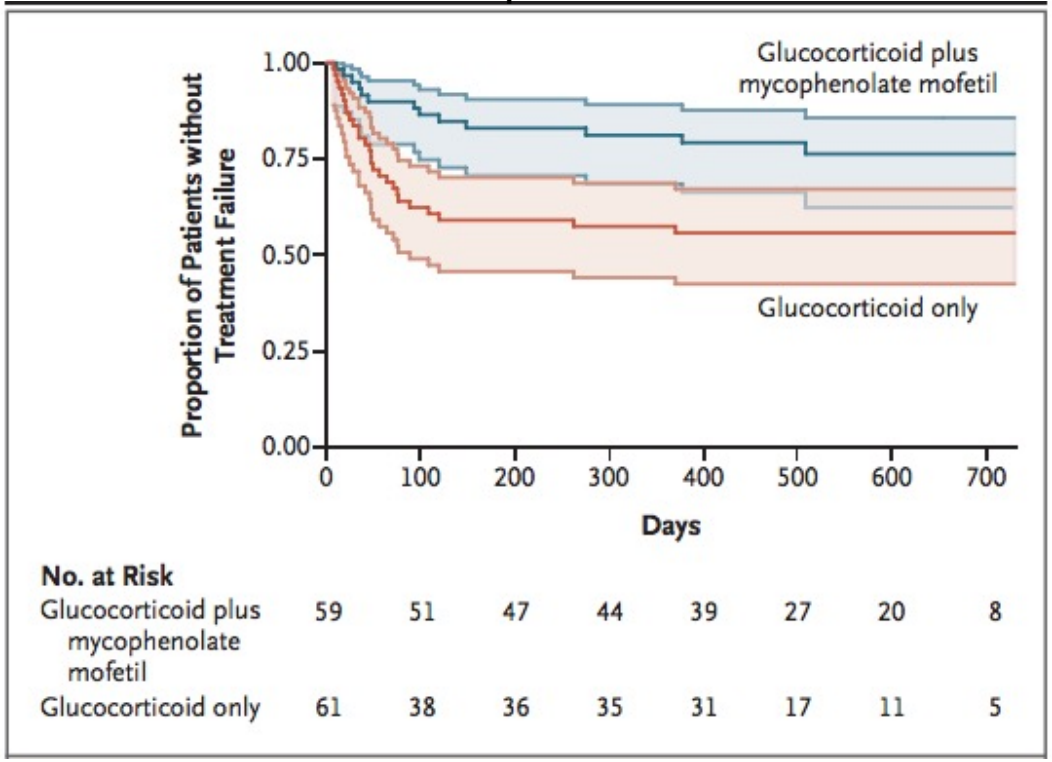
Primary end point: treatment failure (plt < 30 x 10^9/L and or need of 2 nd line

Data on QoL

Bradbury C et al , NEJM 2021

Primary and point: failure of 1st line

N= 120 pts



44 failure:
13 (22%) in MMF + steroid
27 (44%) in steroid alone

HR 0.41 (95%CI, 0.21- 0.80)
P=0.008

More fatigue in MMF group

Bradbury C et al , NEJM 2021

Variable	Mycophenolate Mofetil plus Glucocorticoid (N=59)	Glucocorticoid Only (N=61)	Relative Risk Ratio (95% CI)
Platelet level >30×10^9/liter and twice the level at baseline within 2 weeks after randomization — no. (%)	30 (50.8)	29 (47.5)	1.06 (0.74–1.54)
Platelet level >100×10^9/liter within 2 weeks after randomization — no. (%)	21 (35.6)	21 (34.4)	1.04 (0.63–1.68)
Platelet level >30×10^9/liter and twice the level at baseline in response to first-line treatment — no. (%)	55 (93.2)	46 (75.4)	1.23 (1.05–1.45)
Platelets >100×10^9/liter in response to first-line treatment — no. (%)	54 (91.5)	39 (63.9)	1.43 (1.17–1.76)
Patients with disease refractory to first-line treatment — no. (%)	4 (6.8)	15 (24.6)	
Median time to platelet level of >30×10^9/liter and twice the level at baseline (IQR) — days†‡	14 (6–57)	18 (5–55)	
Median time to platelet level of >100×10^9/liter (IQR) — days†§	38 (6–65)	46 (6–58)	
Treatment side effects — no. (%)			
Infection	14 (23.7)	14 (23.0)	
Weight gain	17 (28.8)	21 (34.4)	
Neutropenia	0	4 (6.6)	
Difficulty sleeping	12 (20.3)	17 (27.9)	
Mood change or psychiatric disorder	18 (30.5)	21 (34.4)	
Steroid-induced diabetes	1 (1.7)	2 (3.3)	
Steroid-induced hypertension	2 (3.4)	2 (3.3)	
Diarrhea or other gastrointestinal symptom	20 (33.9)	15 (24.6)	
Patients with bleeding episode — no. (%)	14 (23.7)	15 (24.6)	

Bradbury C et al , NEJM 2021

More on other combo tx as first line

» Oseltamivir (sialidase inhibitor): phase 2 trial (NCT01965626):

- Dexa ± O: at day 14 Response 86 vs. 66%; OR 3.18; *P* = 0.030); at 6 months 53 vs. 30%; OR 2.17; *P* = 0.032); at 10 months similar response in the 2 groups

» Dexa ± ATRA (China): OR @6 mo 3.1; p=0.0017 (68% vs 41%); no longer follow up

» Coming soon in Milan: **RODEX Study** (EudraCT No.: 2021-006970-22):

- A multicentre, randomized, open-label study of romiplostim plus dexamethasone vs dexamethasone in patients with newly diagnosed primary immune thrombocytopenia

ITP: unresolved issues

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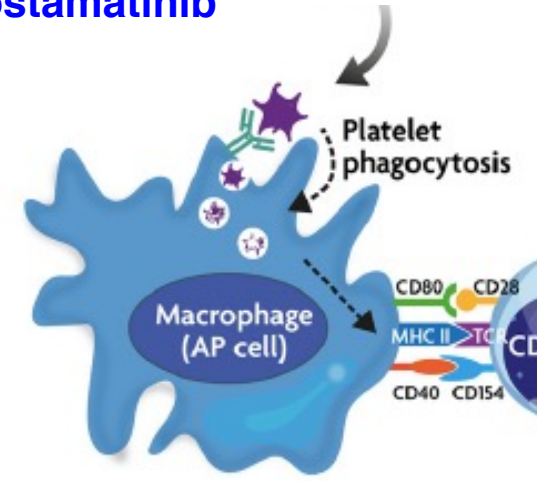
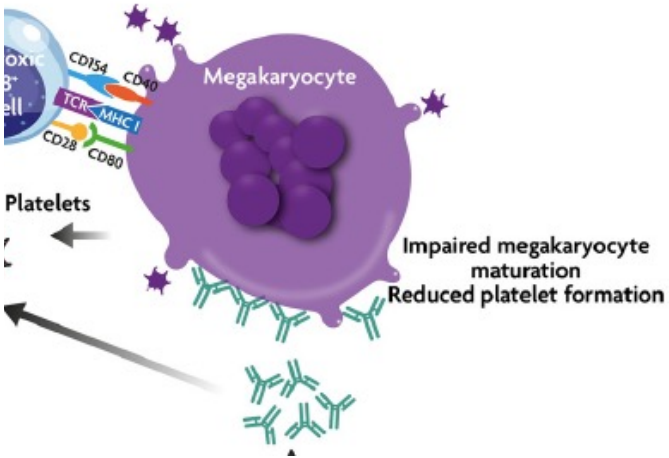
Already available drugs

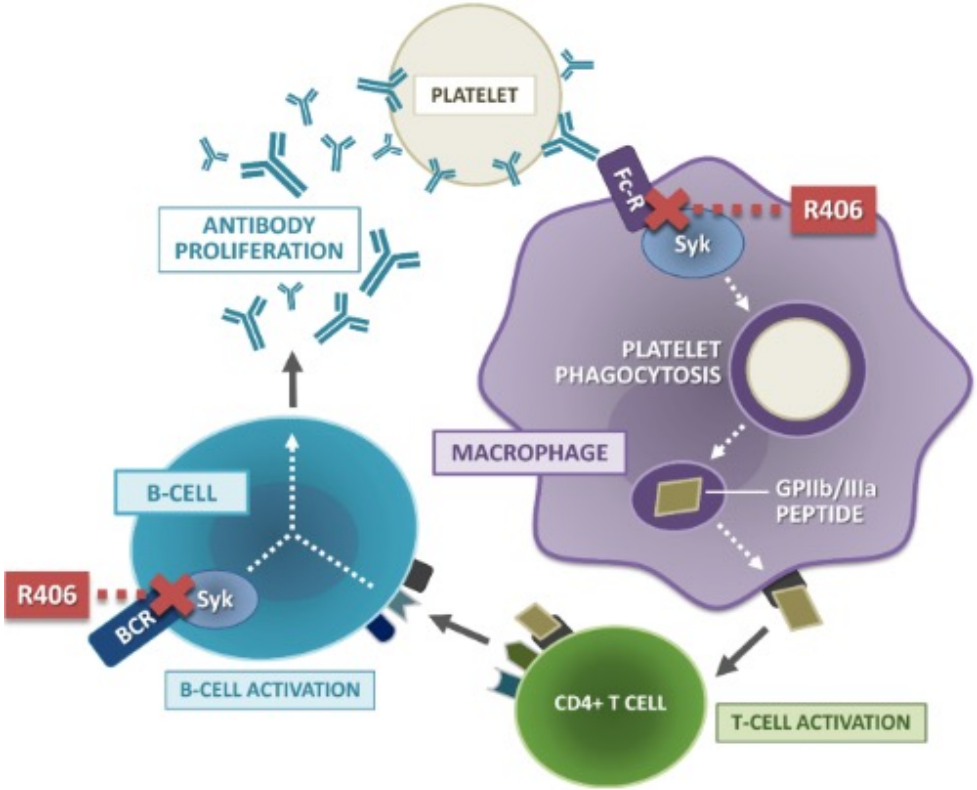
Fostamatinib



Avatrombopag



Fostamatinib



- Fostamatinib is a small molecule prodrug

- Its major active metabolite R406 is a potent and relatively selective, orally available inhibitor of Syk

- R406 reduces macrophage destruction of opsonized platelet and inhibits signal transduction of B-cell receptors

Main efficacy results of FIT studies (randomized vs placebo, dose finding)

Allowed concomitant azathioprin, steroid < 20 mg prednison or danazol

	FIT-1 ($N=76$)		FIT-2 ($N=74$)	
	Fostamatinib ($N=51$)	Placebo ($N=25$)	Fostamatinib ($N=50$)	Placebo ($N=24$)
Outcomes *n* (%)				
Stable platelet response (primary outcome)	9 (18)	0 (0) $P=0.03$	8 (16)	1 (4) $P=$NS
*Overall response	19 (37)	2 (8) $P<0.01$	24 (48)	5 (21) $P<=0.05$
Rolled over into FIT-3 at week 12	28 (55)	22 (88)	33 (66)	19 (79)
Completed 24 24-week study	12 (24)	1(4)	13 (26)	2 (8)

*Post hoc analysis for overall response (one or more platelet count $\geq 50 \times 10^9$/L during weeks 0–12) in FIT-1 and FIT-2. Pooling the two studies 43% of patients on fostamatinib vs. 14% on placebo ($P=0.0006$) reached overall response, data derived from Bussel et al. [17]

Safety data in FIT studies

Relevant common (≥5% of cases) adverse reactions occurring at higher rate or increased severity compared to placebo in a pooled analysis of exposed patients in FIT-1 and FIT-2

Adverse reactions (%)	Fostamatinib $N=102$			Placebo $N=48$		
	Mild (%)	Moderate (%)	Severe (%)	Mild (%)	Moderate (%)	Severe (%)
Diarrhea	21	10	1	13	2	0
Hypertension[&]	17	9	2	10	0	2
Dizziness	8	2	1	6	2	0
Chest pain	2	3	1	2	0	0
Neutropenia[$]	3	2	1	0	0	0
ALT and/or AST elevation*	>3–<5×ULN (%) 1	>5–<10×ULN (%) 5	>10×ULN (%) 1	>3–<5×ULN (%) 0	>5–<10×ULN (%) 0	>10×ULN (%) 0

[&]Hypertensive crisis in 1% of patients; [$]febrile neutropenia in 1%;*alanine aminotransferase (*ALT*) and/or aspartate aminotransferase (*AST*) elevation above 3 to 10× upper limit of normal (ULN)

4 fatal AEs (pneumonia, sepsis, plasma cell myeloma and endocarditis), none considered by the investigator to be related to treatment

Efficacy of fostamatinib is related to n of previous therapies

Boccia R et al, BJH 2020

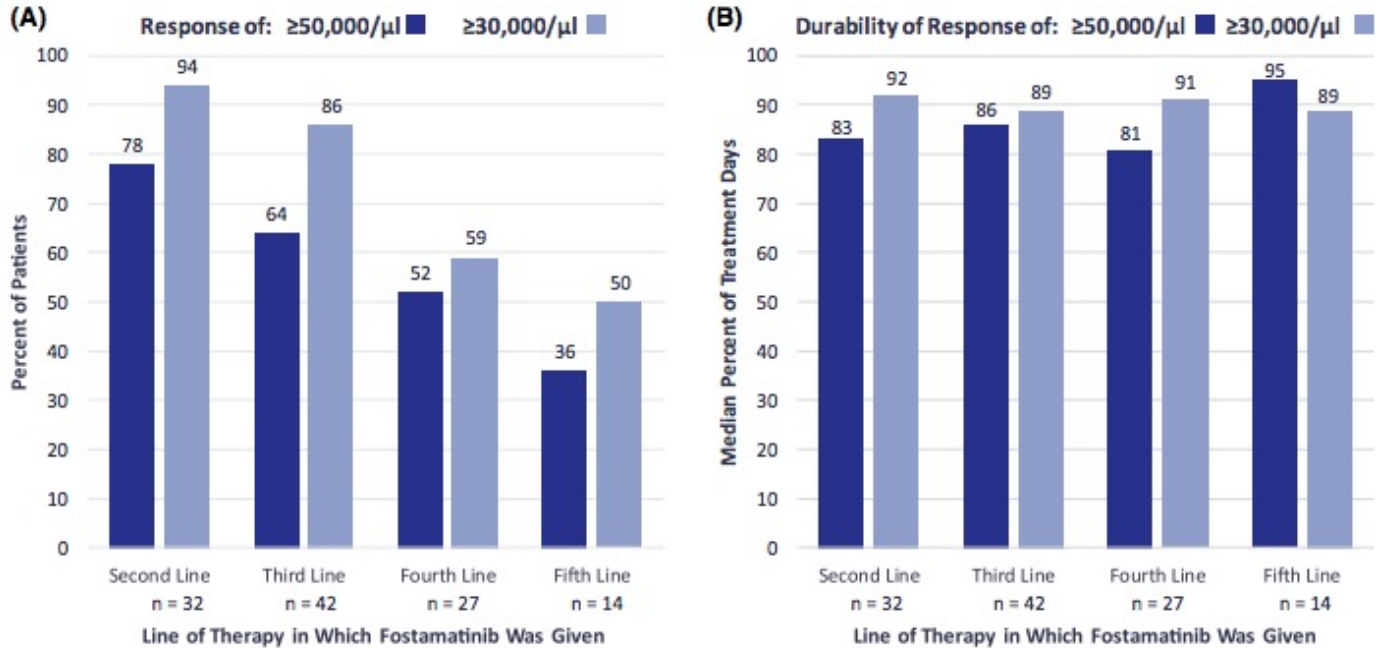


Fig 1. Response rate and durability of response in patients receiving fostamatinib as second-line, third-line, fourth-line, or fifth-line therapy. (A) Response, defined as ≥1 platelet count ≥50 000/µl (dark blue) or ≥30 000/µl (light blue) at any visit (not within 4 weeks of rescue therapy). (B) Durability of response: median percent of treatment days that patients maintained a response of ≥50 000/µl (dark blue) or ≥30 000/µl (light blue), with loss of response at the first of two platelet counts <30 000/µl or <20 000/µl, respectively, at least four weeks apart or use of rescue therapy. Thirty patients who received fostamatinib as sixth-line to tenth-line therapy are not shown. [Colour figure can be viewed at wileyonline library.com]

Thrombotic risk of fostamatinib

Table 1. Baseline patient characteristics and risk factors for thromboembolic events (TEEs).

Baseline characteristics	All patients *N* = 146
Patients with ⩾1 risk factor for TEE, *n* (%)	127 (87)
Patients with multiple risk factors for TEE, *n* (%)	85 (58)
Number of TEE risk factors, median (range)	2 (0–7)
Age ⩾65 years, *n* (%)[a]	37 (25)
Body mass index ⩾30 (%)	43 (29)
Medical history	
Diabetes (%)	15 (10)
Cancer[b] (%)	7 (5)
Cardiovascular disease, excluding hypertension (%)	37 (25)
Hypertension (%)	51 (35)
Prior ITP treatments	
Splenectomy (%)	51 (35)

[a]Fifteen (10%) males were over age 65 years.
[b]Breast cancer in three, endometrial cancer in two, colorectal cancer, non-melanoma skin cancer in five.
ITP, immune thrombocytopenia.

Despite TEE risk factors in many of the 146 patients treated with fostamatinib for up to 5 years with **229 patient-years total**, only one minor **(0.7%) TEE** was observed*.

TEE risk in TPO-RA:
- 2.7 per 100 pts-yrs eltrombopag
- 3.1-3.9 per 100 pts-yrs romiplostim

* 1 mild TIA

Cooper N et al, Ther Adv Hematol 2021

Case report

Sustained response off therapy after fostamatinib: A chronic refractory ITP case report

Giuseppe Auteri [a,b,*], Mattia Biondo [a,b], Camilla Mazzoni [a,b], Marta Venturi [a,b], Andrea Davide Romagnoli [a,b], Simona Paglia [a], Michele Cavo [a,b], Nicola Vianelli [a], Francesca Palandri [a]

Heliyon, 2023,

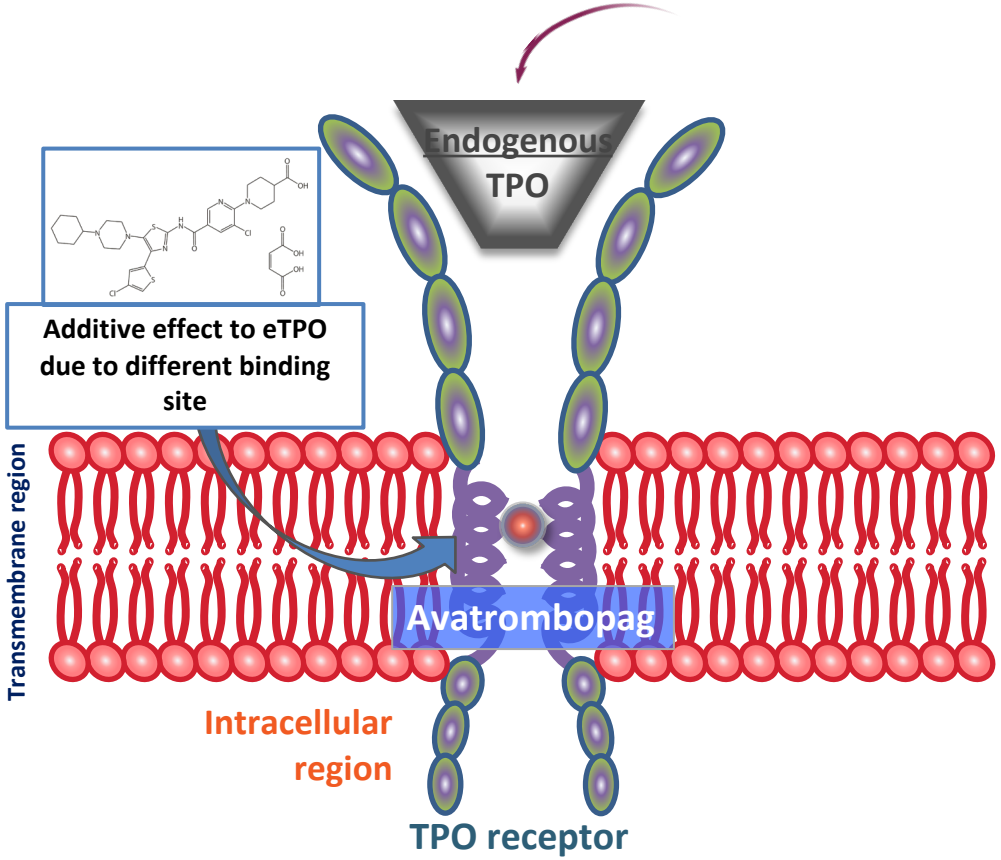
bjh short report

Long-term sustained response to fostamatinib in two patients with chronic refractory immune thrombocytopenia (ITP)

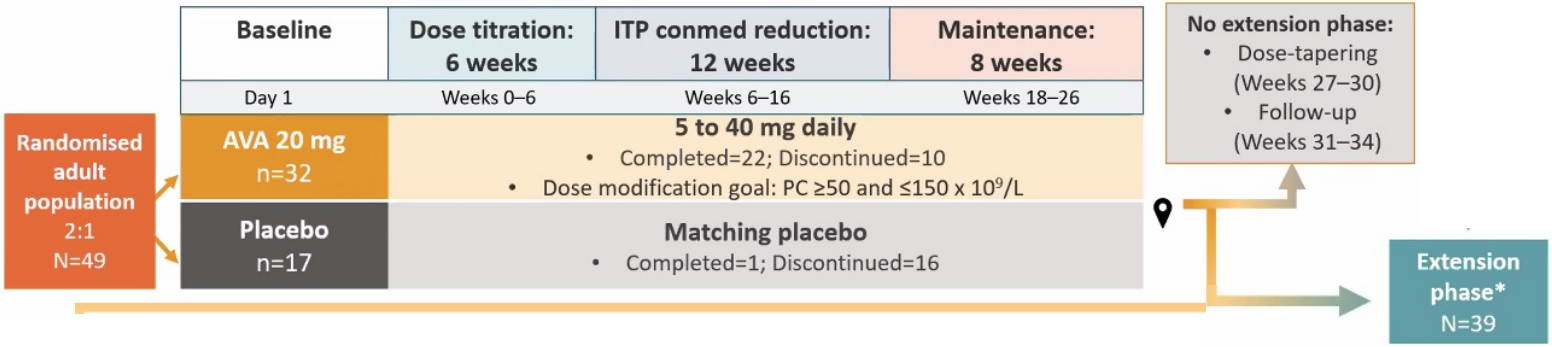
Lee et al , BJH 2020

Avatrombopag

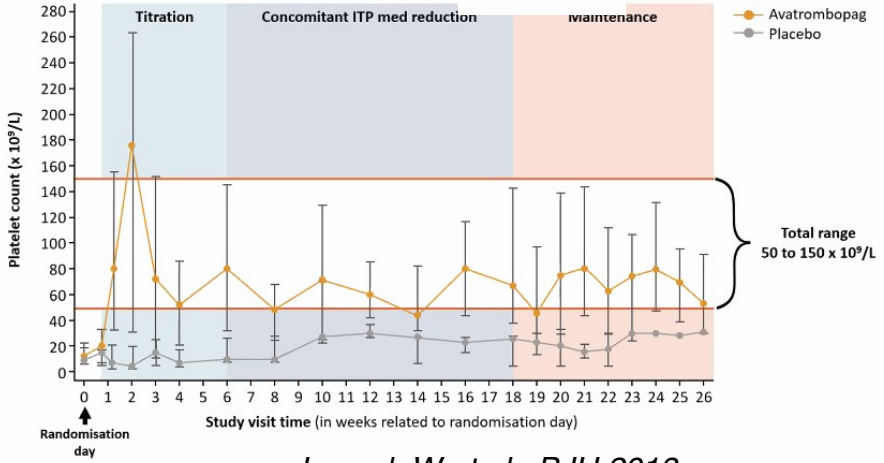
- Avatrombopag stimulated megakaryocyte colony formation in a concentration-dependent fashion in human cord blood CD34+ cells
- The combination of avatrombopag plus rhTPO resulted in an increase greater than either avatrombopag or rhTPO alone
- No food restriction



Avatrombopag: phase 3 study

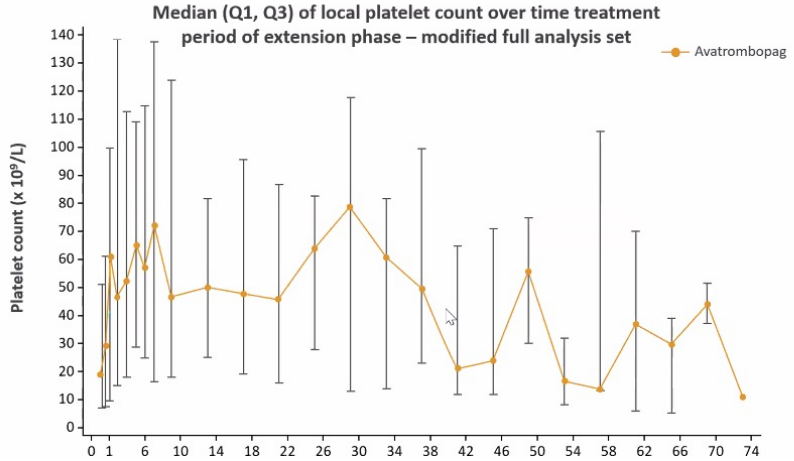


Primary endpoint	• **Cumulative number of weeks of platelet response** (defined as platelet count ≥50 × 10^9/L) during 6 months of treatment in the absence of rescue therapy
Secondary / exploratory endpoints	• **Platelet response at day 8** • Proportion of patients with reduction in concomitant ITP medications from baseline
Additional endpoint of interest	• **Durable platelet response** (defined as proportion of patients in the last 8 weeks (weeks 18–26) of 6-month treatment period with ≥6 weekly platelet counts ≥50 × 10^9/L)
Safety / tolerability	• Evaluate the safety and tolerability of long-term therapy with avatrombopag in participants with chronic ITP • Severity of AEs were graded by the investigator using the CTCAE



Jurczak W et al , BJH 2018

Extension study efficacy[1]



- Overall platelet response in the core study was **generally maintained throughout the extension** up until ~Week 36
- Beyond Week 38, platelet response was noted to be lower and more variable*

Subjects	AVATROMBOPAG 32	PLACEBO 17	p value
PRIMARY: cumulative number of weeks of platelet response	**12.4**	0.0	p<0.0001
SECONDARY: responders to avatrombopag on Day 8, (%)	**65.5**	0	p<0.001
SECONDARY: Proportion of patients with reduction in concomitant ITP medications from baseline, (%)	**33.3**	0	P=0.1348
Durable platelet response (defined as proportion of patients in the last 8 weeks (weeks 18–26) of 6-month treatment period with ≥6 weekly platelet counts ≥50 × 10^9/L), (%)	**34.4**	0	P = 0.009

Jurczak W et al , BJH 2018

Avatrombopag: data of interest

* **More than half (57.1%)** of patients on chronic corticosteroids **reduced or discontinued corticosteroids**

*

Incidence of bleeding events during 6-month treatment	Placebo (N=17)	Avatrombopag (N=32)
Yes, n (%)	9 (52.9)	14 (43.8)
No, n (%)	8 (47.1)	18 (56.3)
P-value	0.5394	

- **All bleeding events were WHO Grade 1**, except for three patients in the avatrombopag treatment group who experienced **Grade 2 (N=2)** or **Grade 3 (N=1)** bleeding events
  - The WHO Grade 3 bleeding event (epistaxis) was also reported as an AE of special interest

Jurczak W et al , BJH 2018

Safety profile of clinical trials for avatrombopag in chronic ITP

Authors	Study	Patients with grade 3-4 TEAE	Patients with SAE	Patients requiring discontinuation	Thromboembolic events
Bussel et al *(Blood 2014)*	Phase II trial (n = 64)	26 (40.6%)	12 (18.8%)	10 (15.6%)	4 (6.3%): iliac DVT, stroke, superficial thrombosis, MI + retinal artery occlusion
Jurczak et al *(BJH 2018)*	Phase III trial (n = 32)	6 (18.8%) vs 0 (0% placebo)	9 (28.1%) vs 1 (5.9% placebo)	3 (9.4%)	3 (9.4%: DVT, PE, stroke) + 1 jugular vein thrombosis

TAEA: treatment-emergent adverse event; SAE: serious adverse event, DVT: deep vein thrombosys; PE: pulmonary embolism; MI: Myocardial infarction

Avatrombopag in real life

- **Multicentre**, **observational study** of consecutive **adult patients with ITP who switched from eltrombopag or romiplostim to avatrombopag** for any reason between July 2019 and December 2020. Data were collected retrospectively
  - Patients ≥18 years of age with a diagnosis of primary or secondary ITP were included if they had been on **avatrombopag treatment for at least two months** with no more than a one-month gap between stopping eltrombopag or romiplostim and starting avatrombopag.

Baseline characteristics	Total population	Effectiveness	Convenience	Adverse event
Total patients	*N* = 44	*n* = 14	*n* = 23	*n* = 7
Male, *n* (%)	21 (48)	9 (64)	9 (39)	3 (43)
White, *n* (%)	30 (68)	10 (71)	15 (65)	5 (71)
Primary ITP, *n* (%)	25 (57)	7 (50)	13 (57)	5 (71)
Age				
Median (range), years	61 (21, 87)	66.5 (39, 81)	59 (21, 87)	59 (34, 76)
Duration of ITP until AVA initiation				
Median (range), months	49 (2, 550)	73 (6, 404)	43 (2, 550)	85 (16, 124)
# Unique prior ITP therapies before AVA				
Median (range)	4 (2, 10)	7 (3, 10)	4 (2, 8)	4 (2, 8)
Previous TPO-RA				
Romiplostim, ratio (%)	33 (75)	10 (71)	21 (91)	2 (29)
Eltrombopag, ratio (%)	10 (23)	4 (29)	1 (4)	5 (71)
Romiplostim/eltrombopag, ratio (%)	1 (2)	0 (0)	1 (4)	0 (0)

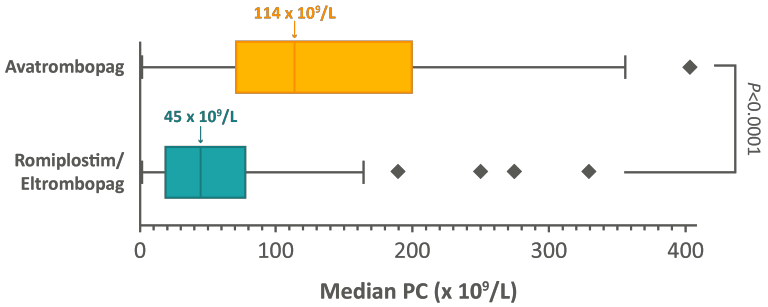
Abbreviations: AVA, avatrombopag; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist.

*Mean dose ROM 8 mcg/kg/week
*Mean dose ELT 75 mg/die

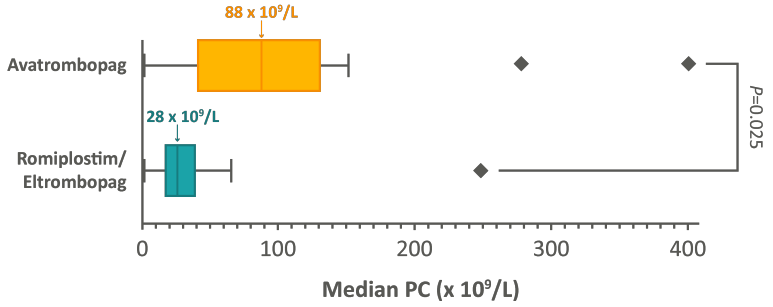
Al-Samkari et al. Br J Haematol 2022

Platelet response after switching to avatrombopag from romiplostim or eltrombopag: real word data

Median PC[b], all patients (N=44)



Median PC[a], patients who switched due to ineffectiveness of romiplostim/eltrombopag (n=14)



Response at least once in absence of rescue	Total population	Effectiveness	Convenience	Adverse event
PC ≥ 50 000, ratio (%)	41/44 (93)	12/14 (86)	23/23 (100)	6/7(86)
PC ≥ 100 000, ratio (%)	38/44 (86)	10/14 (71)	22/23 (96)	6/7 (86)

Abbreviation: PC, platelet count.

[a]Patients requiring rescue therapy had their platelet counts disqualified for the purposes of response assessment for eight weeks (corticosteroids), four weeks [intravenous immunoglobulin (IVIG) or anti-RhD immune globulin], or one week (platelet transfusion) from the time of receipt of rescue therapy.

Al-Samkari et al. Br J Haematol 2022

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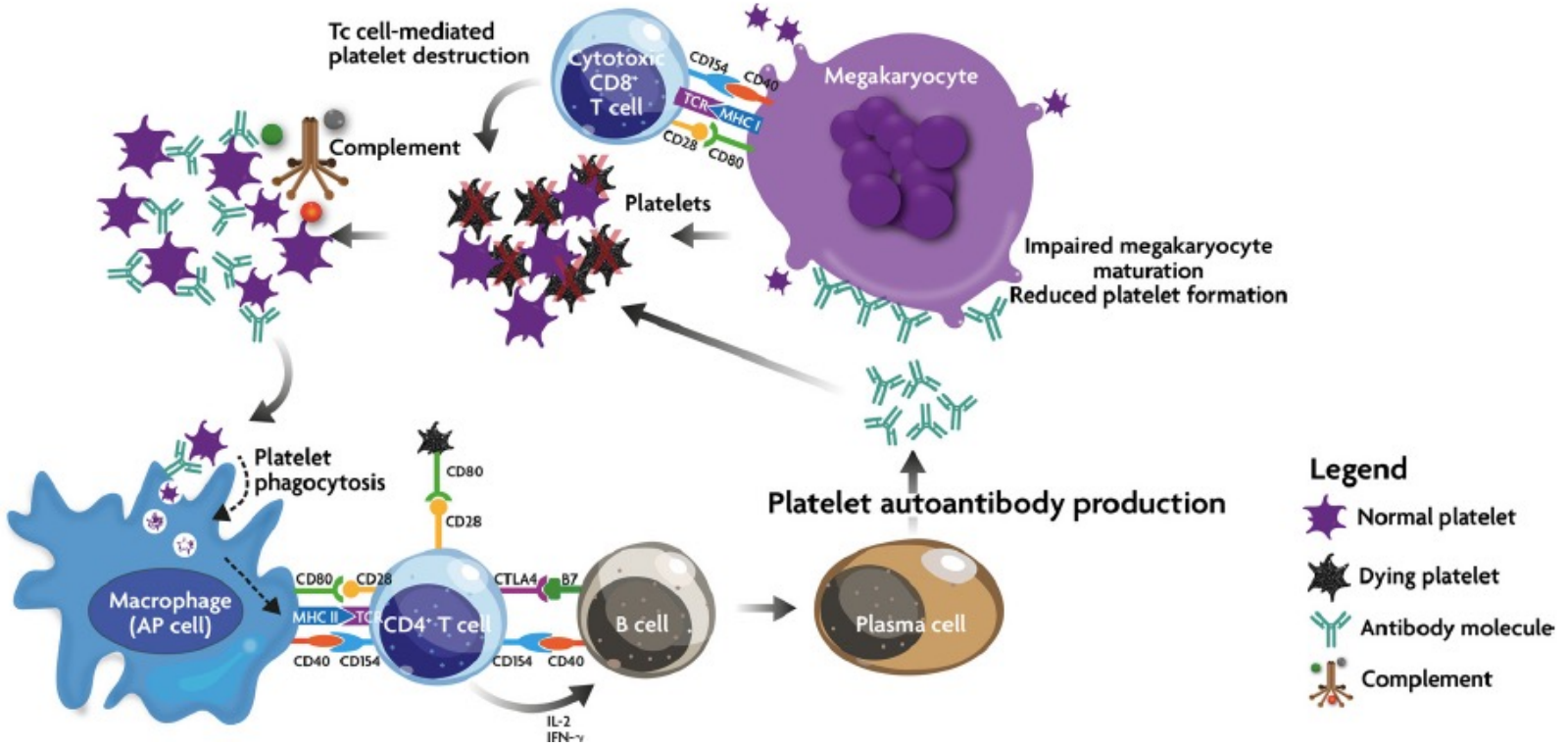
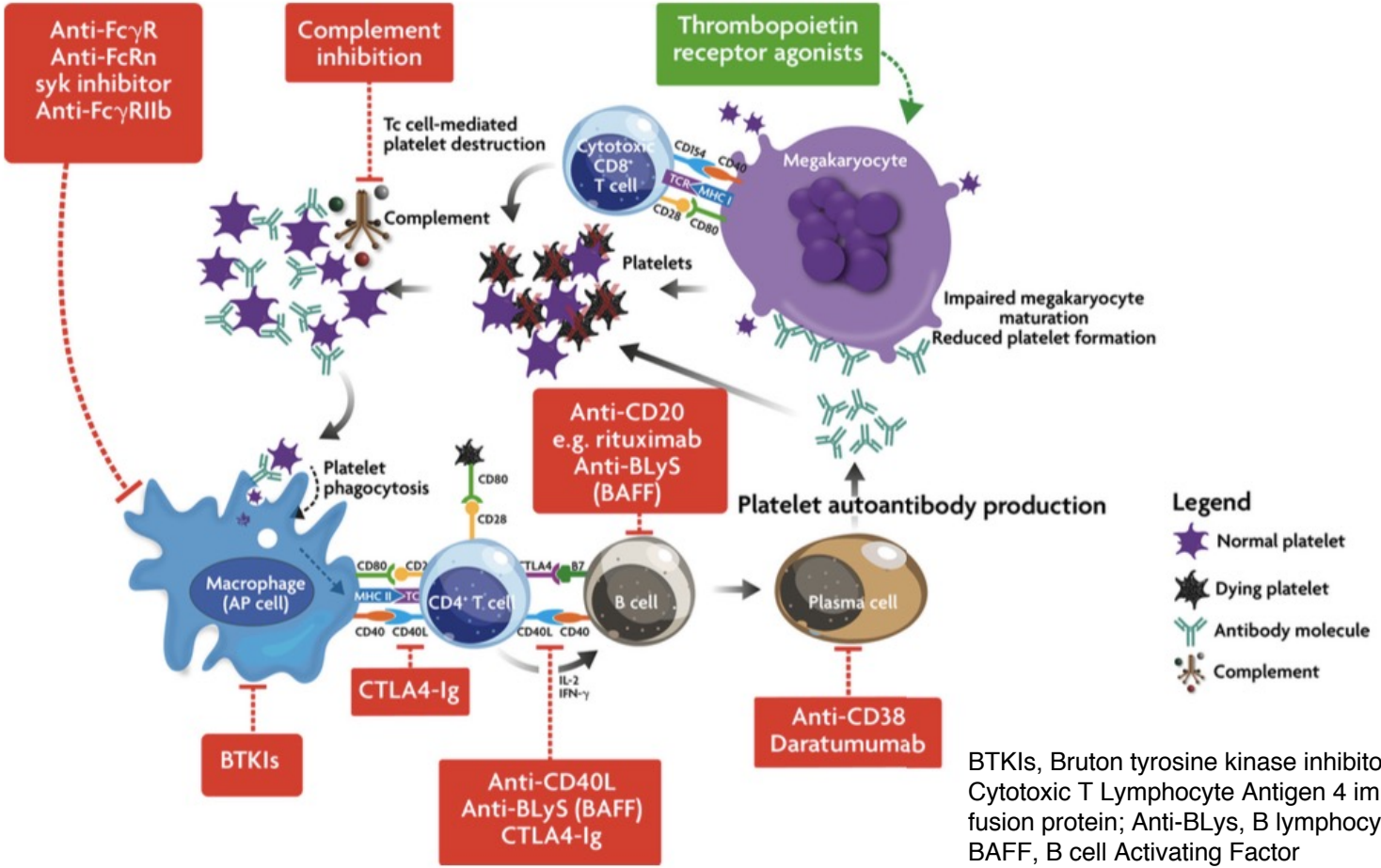

Tc cell-mediated platelet destruction
Cytotoxic CD8+ T cell
CD154
CD40
TCR
MHC I
CD28
CD80
Megakaryocyte
Complement
Platelets
Impaired megakaryocyte maturation
Reduced platelet formation
Platelet phagocytosis
CD80
CD28
Platelet autoantibody production
Macrophage (AP cell)
CD80
CD28
MHC II
TCR
CD4+ T cell
CTLA4
B7
CD40
CD154
CD154
CD40
B cell
Plasma cell
IL-2
IFN-γ
Legend
Normal platelet
Dying platelet
Antibody molecule
Complement



BTKIs, Bruton tyrosine kinase inhibitors; CTLA4-Ig, Cytotoxic T Lymphocyte Antigen 4 immunoglobulin G1 fusion protein; Anti-BLys, B lymphocyte stimulator; BAFF, B cell Activating Factor

New therapies under developement

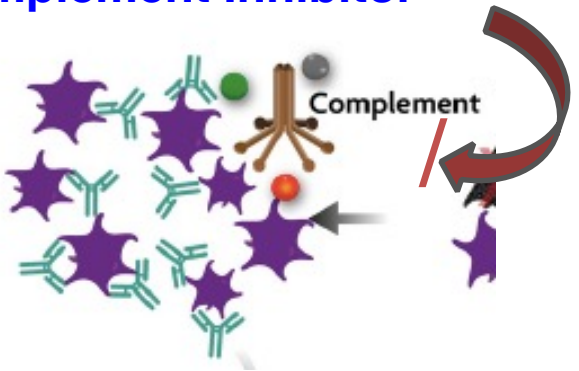
Novel therapy	Mechanism of action	Drugs evaluated in ITP*
Anti-CD40 ligand antibody	Reduces production of anti-platelet antibody	IDEC-131, hu5c8, letolizumab
Anti-CD38 antibody	Inhibits plasma cell production of anti-platelet antibody	Mezagitamab (TAK-079), daratumumab
Immunoproteasome inhibitors	Reduce production of anti-platelet antibody	KZR-616
Neonatal Fc receptor (FcRn) inhibitors	Increase clearance of anti-platelet antibody	IVIG, efgartigimod, rozanolixizumab
Staphylococcal Protein A	Inhibits macrophage phagocytosis	PRTX-100
Hypersialylated immunoglobulin G	Blocks macrophage FcR and reduces phagocytosis	M254
Recombinant Fc multimers	Bind macrophage FcR and reduce phagocytosis	PF067553471 (GL-2045), stradomers
Bruton kinase inhibitors	Reduce macrophage function	Rilzabrutinib (PRN1008)
Complement inhibitors	Antibody inhibits C1s activity	Sutimlimab
Platelet desialylation inhibitors	Inhibit platelet neuraminidase activity	Oseltamivir
New TPO receptor agonists	Stimulate megakaryocyte growth	Hetrombopag
Low-level laser light	Prevents megakaryocyte apoptosis	810 nm laser light

ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; FcR, Fc receptor; TPO, thrombopoietin.

*For many novel therapies there are other members of the drug class being investigated in other diseases; shown here are those for which ITP has been a focus of research.

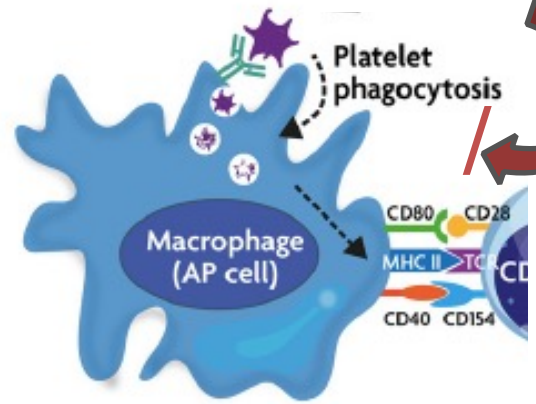
New therapies under developement

Complement Inhibitor

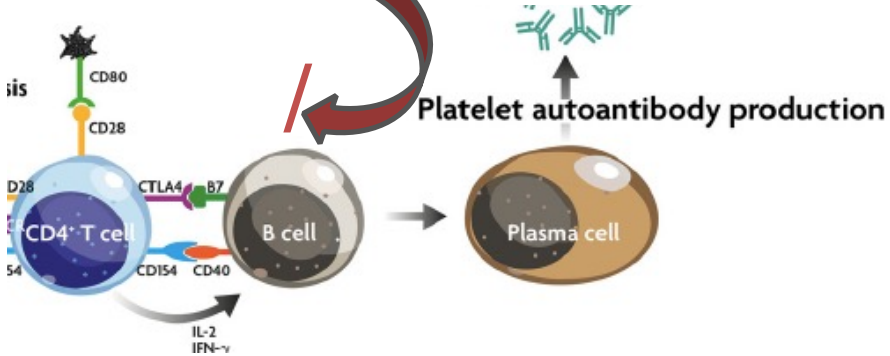


FcRn Inhibitors

BTK Inhibitor

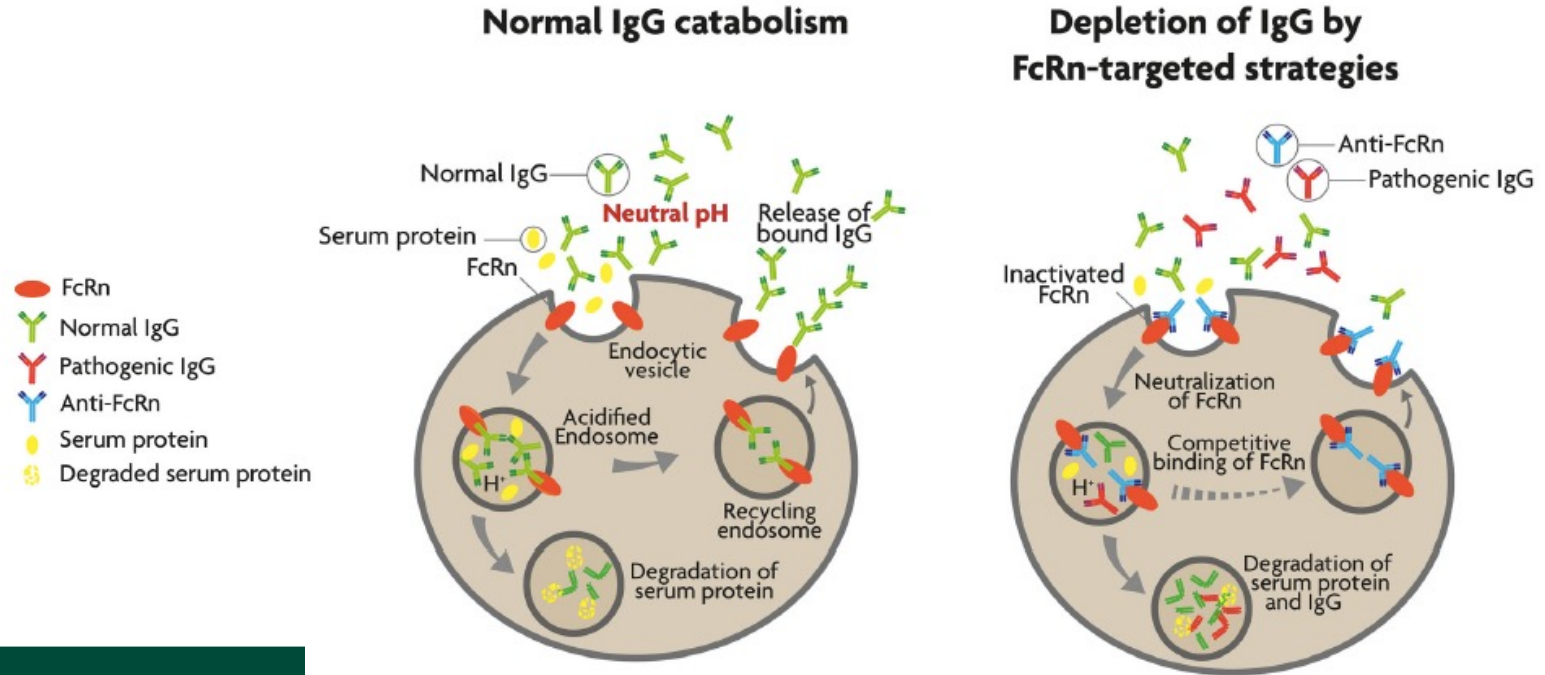


BAFF Inhibitors



Neonatal Fc receptor inhibitors ("medical plasmapheresis")

- Able to mediate the transfer of IgG between mother and fetus
- It binds multimeric IgG in the form of immune complexes to dendritic cells
- Is reponsible for the long circulatory half-lives of IgG and albumin

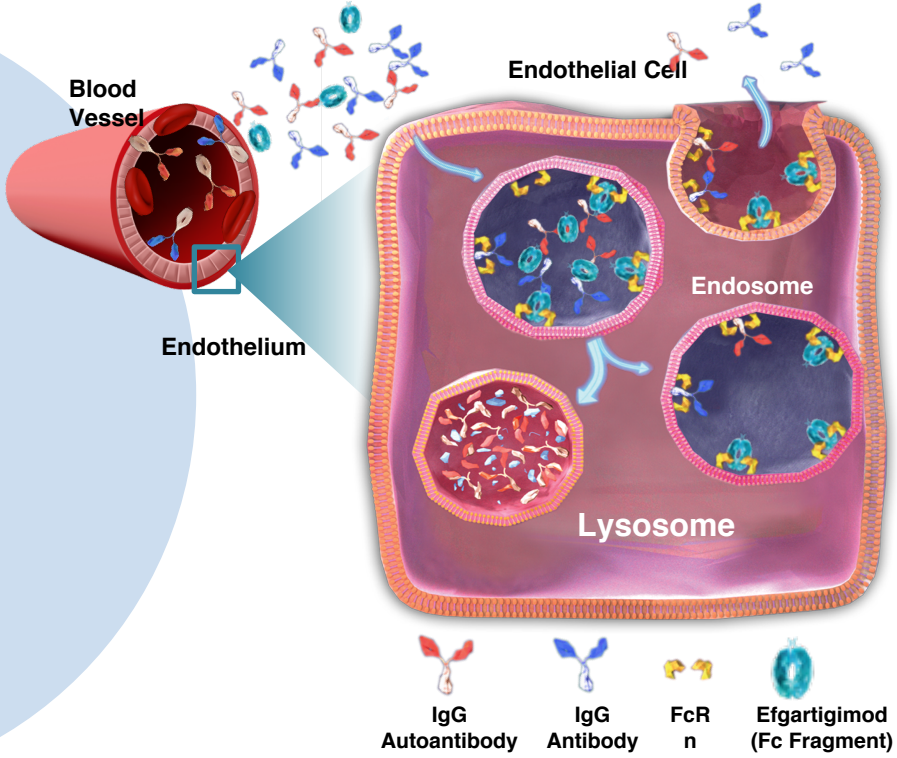


Drugs:

- Efgartigimod
- (Rozanolixizumab)
- Nipocalimab
- IMVT-1401

Efgartigimod Mechanism of Action: Competitive Inhibition of FcRn

- The neonatal Fc receptor (FcRn) recycles immunoglobulin G (IgG), extending its half-life and serum concentration[1]
- Efgartigimod is a human IgG1 Fc fragment, a natural ligand of FcRn, engineered for increased affinity for FcRn[2]
- Efgartigimod was designed to outcompete endogenous IgG, preventing recycling and promoting lysosomal degradation of IgG (without impacting IgG production) leading to[2-5]:
  - Targeted reduction of all IgG subtypes
  - No impact on IgM or IgA
  - No reduction in albumin levels
  - No increase in cholesterol
- Efgartigimod is approved for the treatment of generalized myasthenia gravis (gMG) in patients positive for anti-acetylcholine receptor (AChR) antibodies in the US and in patients with an insufficient response to steroids or nonsteroid immunosuppressive therapies in Japan



AChR = acetylcholine receptor; FC = crystallizable fragment; FcRn = neonatal Fc receptor; gMG = generalized myasthenia gravis; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M.

1. Sesarman A, et al. *Cell Mol Life Sci.* 2010;67(15):2533-2550. 2. Ulrichts P, et al. *J Clin Invest.* 2018;128(10):4372-4386. 3. Vaccaro C, et al. *Nat Biotech.* 2005;23(10):1283-1288. 4. Howard JF Jr, et al. *Lancet Neurol.* 2021;20(7):526-536. 5. Nixon AE, et al. *Front Immunol.* 2015;6:176.

ADVANCE STUDY

PLENARY ABSTRACTS | NOVEMBER 15, 2022

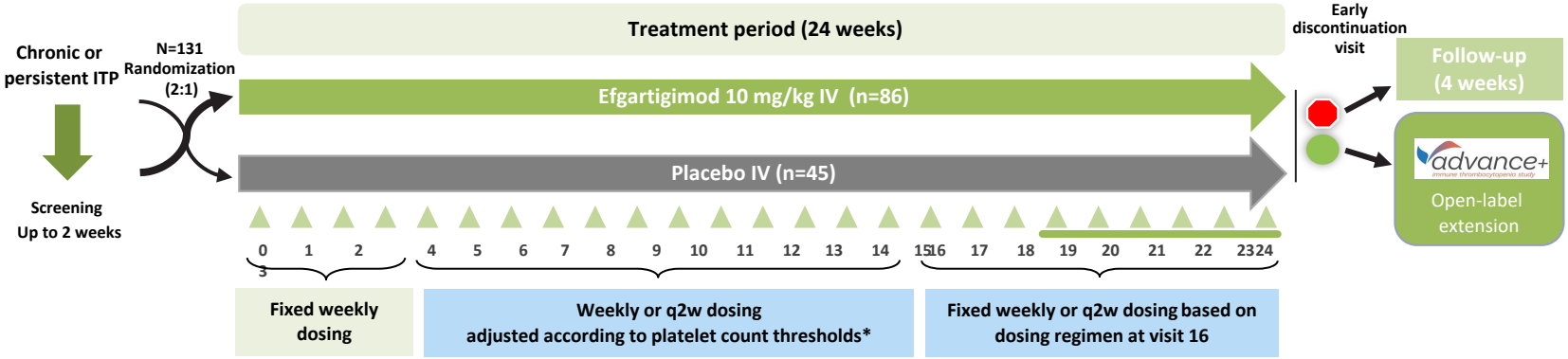
Efficacy and Safety of Intravenous Efgartigimod in Adults with Primary Immune Thrombocytopenia: Results of a Phase 3, Multicenter, Double-Blinded, Placebo-Controlled, Randomized Clinical Trial (ADVANCE IV)

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

Blood (2022) 140 (Supplement 1): 6–8.

ADVANCE IV (NCT04188379): Study Design

Phase 3, Multicenter, Double-blinded, Placebo-controlled, Randomized Clinical Trial



Eligibility criteria

- Age ≥18 years
- Chronic or persistent ITP : Diagnosis supported by a response to a prior ITP therapy
- 2 platelet counts of $<30\times10^9$/L during screening
- At least 2 prior ITP treatments or 1 prior and 1 concurrent treatment
- Concurrent ITP therapy† permitted at stable dose and frequency at study entry and throughout study

*q2w if $\geq100\times10^9$/L for 3 of 4 visits or $\geq100\times10^9$/L for 3 consecutive visits; weekly if $<100\times10^9$/L on 2 consecutive visits, $<30\times10^9$/L at 1 visit or rescue therapy received.
†Concurrent oral corticosteroids, oral immunosuppressants, dapsone, danazol, fostamatinib, and oral thrombopoietin receptor agonists (not romiplostim).
q2w = every other week; ITP = immune thrombocytopenia; IV = intravenously.

Baseline Characteristics Indicate the Majority of Participants Had Multiple Prior Therapies and Long-standing ITP

	Efgartigimod* (n=86)	Placebo* (n=45)
Age, mean, years (SD)	46.9 (16.6)	51.7 (17.9)
Female, n (%)	47 (54.7)	24 (53.3)
Time since diagnosis, mean, years (SD)	10.3 (12.1)	11.1 (13.1)
Patients with chronic / persistent ITP, n	78 / 8	40 / 5
Platelet count, 10^9/L mean (SD)	17.3 (10.2)	14.2 (9.2)
Patients with history of splenectomy, n (%)	32 (37.2)	17 (37.8)
World Health Organization (WHO) bleeding score, n (%)		
No bleeding	44 (51.2)	16 (35.6)
Grade 1	38 (44.2)	25 (55.6)
≥Grade 2	4 (4.7)	4 (8.9)
Patients with ≥3 prior ITP therapies, n (%)	59 (68.6)	29 (64.4)
Concurrent ITP therapy types at baseline, n (%)		
Corticosteroids	22 (25.6)	12 (26.7)
Oral TPO-RA	20 (23.3)	9 (20.0)
Other immunosuppressants	8 (9.3)	6 (13.3)
None	43 (50.0)	23 (51.1)

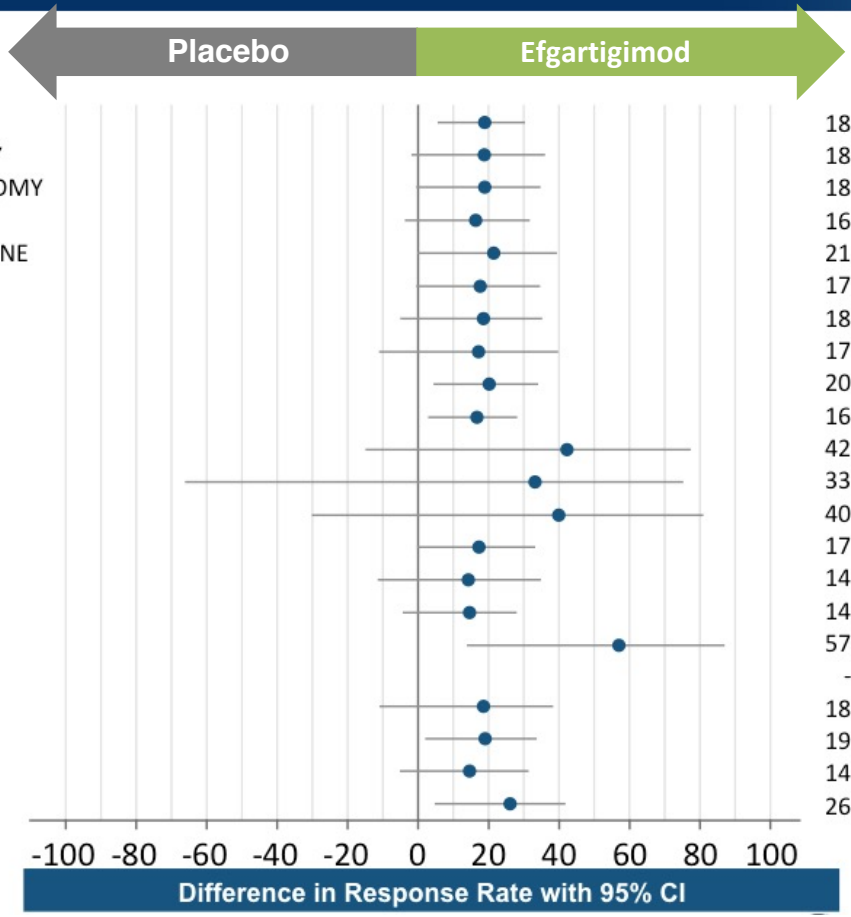
[a]Safety Analysis Set.

ITP = immune thrombocytopenia; SD = standard deviation; TPO-RA = thrombopoietin receptor agonists; WHO = World Health Organization.

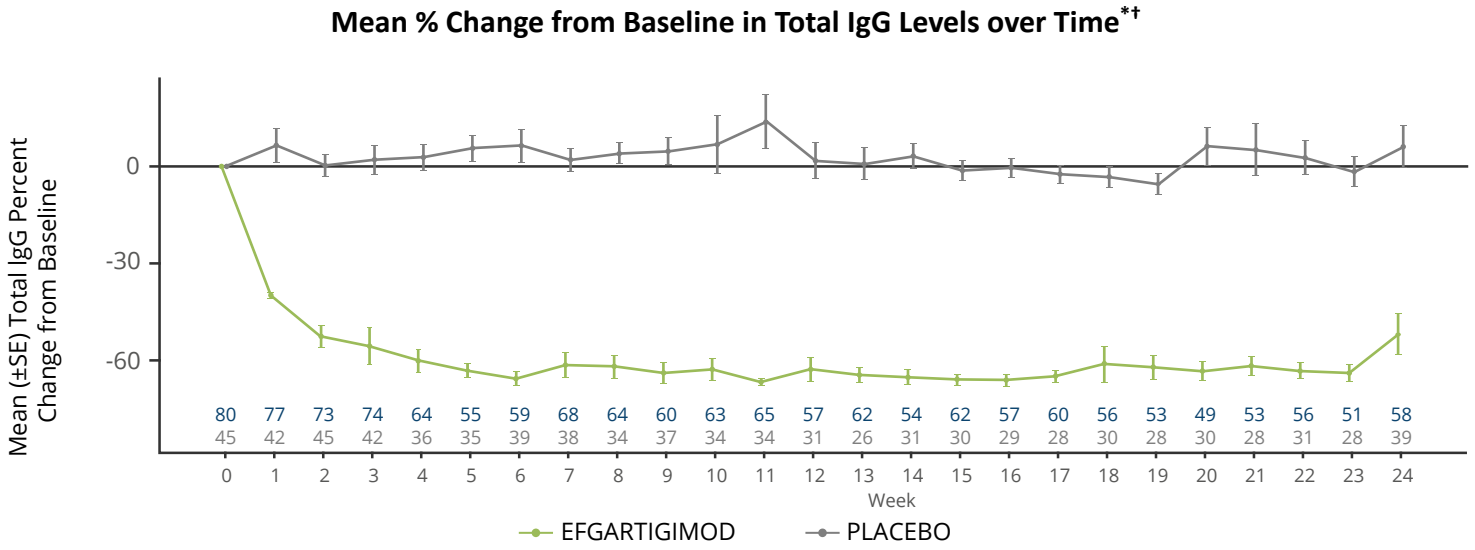
Efficacy Endpoints: Primary and All Platelet-related Secondary Endpoints Were Met*

Endpoint†	Efgartigimod	Placebo	*P*-value
Primary endpoint			
Proportion with sustained platelet count response, n/N (%)‡ ≥50×10^9/L in ≥4/6 visits during weeks 19-24, in the absence of intercurrent events†	17/78 (21.8%)	2/40 (5.0%)	**0.0316**
			Key secondary endpoints
Number of cumulative weeks of disease control, Mean (SD)‡ Number of weeks with platelet counts ≥ 50 x 10^9/L	6.1 (7.66)	1.5 (3.23)	**0.0009**
Sustained platelet count response, n/N (%)§ ≥ 50x10^9/L in ≥4/6 visits during weeks 19-24	22/86 (25.6%)	3/45 (6.7%)	**0.0108**
Number of visits with a WHO Bleeding Score ≥ 1, Mean (SD)§	6.2 (6.39)	8.3 (8.01)	0.8287
Durable sustained platelet count response, n/N (%)§ ≥ 50x10^9/L in ≥6/8 visits during weeks 17-24	19/86 (22.1%)	3/45 (6.7%)	0.0265

hierarchical testing procedure, nominal *p*-values are always less than 0.05 for platelet-based endpoints.
†Analyzed on Full Analysis Set.
‡Chronic population.
§Chronic + persistent population.
SD = standard deviation; WHO = World Health Organization.


Placebo
Efgartigimod
All Patients OVERALL 18.9 (5.3, 30.7)
Splenectomy History HISTORY OF SPLENECTOMY 18.8 (-1.9, 35.8)
NO HISTORY OF SPLENECTOMY 18.9 (-1.0, 35.2)
Baseline ITP Therapies ITP THERAPY AT BASELINE 16.4 (-4.0, 32.0)
NO ITP THERAPY AT BASELINE 21.5 (0.1, 39.6)
Baseline Platelet Count <15x10⁹/L 17.6 (-0.8, 34.8)
≥15x10⁹/L 18.6 (-5.0, 35.4)
Prior ITP Therapies <3 17.1 (-11.1, 39.9)
≥3 20.3 (4.4, 33.9)
Time Since Diagnosis CHRONIC ITP 16.8 (3.1, 28.5)
PERSISTENT ITP 42.5 (-14.6, 77.4)
Region UNITED STATES 33.3 (-65.9, 75.5)
JAPAN 40.0 (-30.3, 81.1)
EU/EEA/EFTA 17.1 (0.7, 33.5)
REST OF THE WORLD 14.2 (-11.5, 35.0)
Age Group 18 - <65 YEARS 14.6 (-4.5, 27.9)
65 - <75 YEARS 57.1 (14.0, 87.1)
≥75 YEARS - -
Prior Rituximab YES 18.7 (-11.0, 38.4)
NO 19.0 (1.9, 34.1)
Prior TPO-RA YES 14.7 (-5.1, 31.5)
NO 26.3 (4.6, 42.1)
-100 -80 -60 -40 -20 0 20 40 60 80 100
Difference in Response Rate with 95% CI

Efgartigimod Resulted in Targeted Reduction of IgG Levels*



- Mean IgG levels decreased steadily over the first 4 weeks of treatment, which was sustained across time and aligned with platelet count responses
  - After the initial decrease in IgG, mean maximum reductions from baseline remained >60% throughout the trial

*Full Analysis Set. †Errors bars are standard errors around the least squares (LS) means.
IgG = immunoglobulin G; SE = standard error.

Efgartigimod Was Well-Tolerated in Patients With ITP and Consistent With Other Efgartigimod Studies[1-5]

	Efgartigimod (n=86)	Placebo (n=45)
Patients with event, n (%)		
≥1 TEAE	80 (93.0)	43 (95.6)
≥1 serious TEAE	7 (8.1)	7 (15.6)
≥1 TEAE leading to discontinuation of study drug	4 (4.7)	1 (2.2)
≥1 treatment-related TEAE according to PI	15 (17.4)	10 (22.2)
≥1 serious treatment-related TEAE according to PI	0	0
AESI: Any bleeding event	61 (70.9)	39 (86.7)
AESI: Any infection event	25 (29.1)	10 (22.2)
Infusion-related reaction event	10 (11.6)	5 (11.1)
Most common TEAEs, n (%)		
Asthenia	6 (7.0)	0 (0.0)
Fatigue	4 (4.7)	1 (2.2)
Headache	14 (16.3)	6 (13.3)
Petechiae	13 (15.1)	12 (26.7)
Hypertension	5 (5.8)	0 (0.0)
Nausea	5 (5.8)	2 (4.4)
Haematuria	14 (16.3)	7 (15.6)
Purpura	7 (8.1)	4 (8.9)

AESI = adverse event of special interest (defined per protocol); ITP = immune thrombocytopenia; PI = principal investigator; TEAE = treatment-emergent adverse event.

1. Howard JF Jr, et al. *Neurology*. 2019;92(23):e2661-e2673. 2. Howard JF Jr, et al. *Lancet Neurol*. 2021;20(7):526-536. 3. Newland AC, et al. *Am J Hematol*. 2020;95:178-187. 4. Goebeler M, et al. *Br J Dermatol*. 2021. doi:10.1111/bjd.20782.

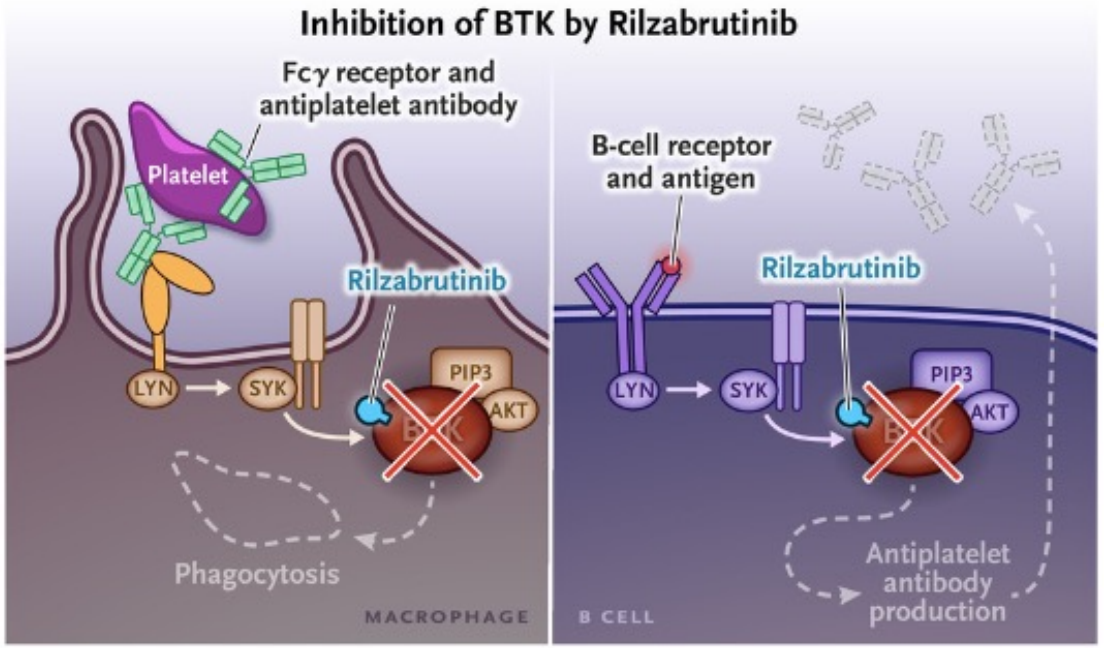
ADVANCE plus STUDY: Open Label Extension

» More @ EHA 2023, Frankfurt 8-10 June 2023

LONG-TERM SAFETY AND EFFICACY OF EFGARTIGIMOD IN PATIENTS WITH PRIMARY IMMUNE THROMBOCYTOPENIA: INTERIM RESULTS OF THE ADVANCE+ STUDY

Rilzabrutinib (oral, reversible, covalent inhibitor of BTK)

- The BTK pathway is critical for the FcϒRreceptor (FcϒR)-signalling pathway in phagocytic and antigen presenting cells
- Inhibition of BTK would reduce macrophage phagocytosis of platelets but it might also accomplish significant immunosuppression with reduction of pathogenic antibody production



ORIGINAL ARTICLE

Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia

Intrapatient dose escalation of oral rilzabrutinib over a period of 24 weeks
- starting dose: 200 mg once daily, maximum 400 mg bid

- rilzabrutinib had no effect on platelet aggregation

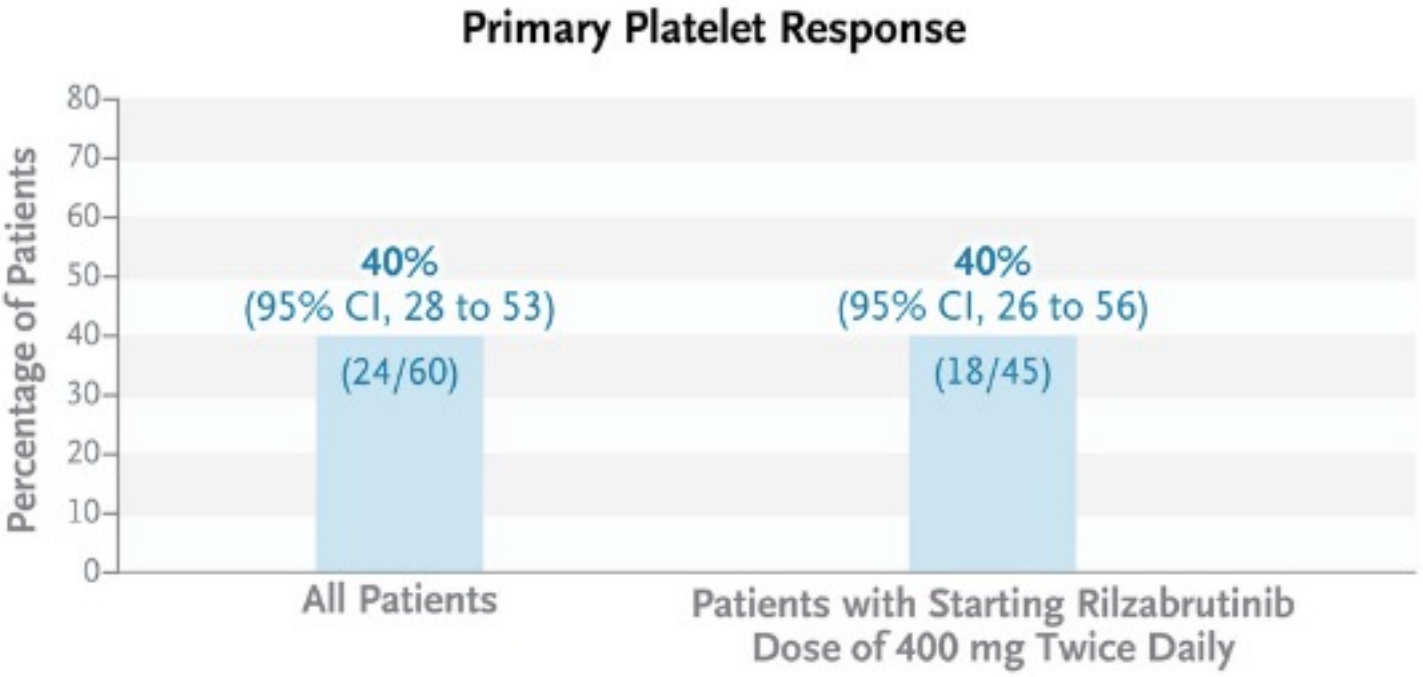
- Stable dose of steroids or TPO-RA were allowed

Table 1. Characteristics of the Patients at Baseline (Safety Population).*

Characteristic	All Patients (N=60)	Patients with Starting Rilzabrutinib Dose of 400 mg Twice Daily (N=45)
Median age (range) — yr	50 (19–74)	49 (19–74)
Sex — no. (%)		
Male	26 (43)	18 (40)
Female	34 (57)	27 (60)
Median baseline platelet count (range) — $\times 10^3/mm^3$	15 (2–33)	15 (2–33)
Median duration of ITP (range) — yr†	6.3 (0.4–52.5)	6.1 (0.4–52.5)
Median no. of different previous ITP therapies (range)‡	4 (1–17)	4 (1–17)
Previous splenectomy — no. (%)‡	15 (25)	11 (24)
Most common previous ITP therapies — no. (%)‡		
Glucocorticoid	55 (92)	42 (93)
Thrombopoietin-receptor agonist§	35 (58)	24 (53)
Intravenous immune globulin	26 (43)	21 (47)
Rituximab	24 (40)	22 (49)
Fostamatinib	8 (13)	7 (16)

Kuter D et al, NEJM 2022

PRIMARY ENDPOINT: at least two consecutive platelet counts (separated by ≥5 days) of at least $50\times10^{9/L}$ and an increase from baseline of at least 20×109/L without the use of rescue medication



Kuter D et al, NEJM 2022

Subgroup efficacy analysis

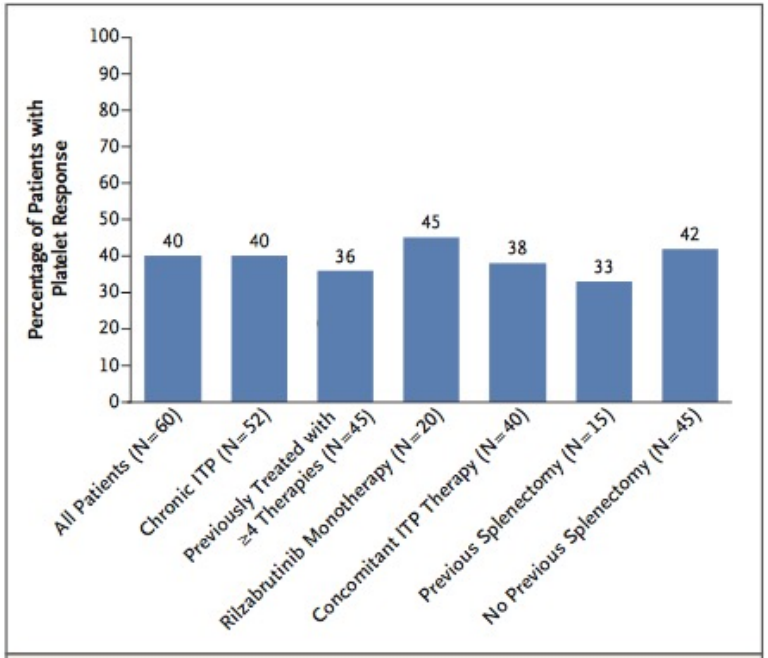
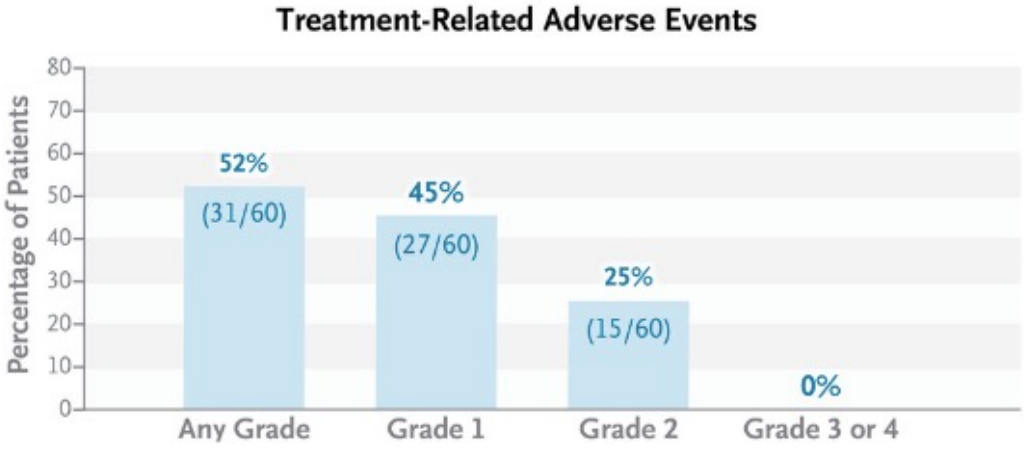


Figure 2. Subgroup Analysis of Primary Platelet Response.

Shown are the percentages of patients who met the primary end point of platelet response. Chronic immune thrombocytopenia (ITP) was defined as

Treatment-related adverse events



Kuter D et al, NEJM 2022

Adverse events

Table 2. Adverse Events According to Grade in All 60 Patients.

Event	Adverse Events Due to Any Cause				Treatment-Related Adverse Events*			
	Any Grade	Grade 1	Grade 2	Grade 3 or 4	Any Grade	Grade 1	Grade 2	Grade 3 or 4
	number of patients (percent)							
Any adverse event	48 (80)	43 (72)	30 (50)	8 (13)†	31 (52)	27 (45)	15 (25)	0
Diarrhea	22 (37)	19 (32)	3 (5)	0	19 (32)	16 (27)	3 (5)	0
Nausea	21 (35)	18 (30)	3 (5)	0	18 (30)	16 (27)	2 (3)	0
Fatigue	12 (20)	10 (17)	2 (3)	0	6 (10)	5 (8)	1 (2)	0
Abdominal distention	6 (10)	6 (10)	0	0	4 (7)	4 (7)	0	0
Vomiting	4 (7)	3 (5)	1 (2)	0	3 (5)	2 (3)	1 (2)	0

* Adverse events were reported after the first dose of rilzabrutinib. Relatedness of the adverse event to treatment was determined by the investigators. The treatment-related adverse events listed here are those that occurred in at least 5% of the patients.

† Eight patients had an adverse event of grade 3 or 4 that was due to any cause and that was considered by the investigators to be unrelated to rilzabrutinib treatment. Multiple events may have occurred in a single patient. These events included grade 3 anemia (in two patients); grade 3 abnormal alanine aminotransferase level, contusion, gastrointestinal hemorrhage, hematoma, ITP, myelofibrosis, and thrombocytopenia (in one patient each); and grade 4 Evans syndrome and thrombocytopenia (in one patient each).

Kuter D et al, NEJM 2022

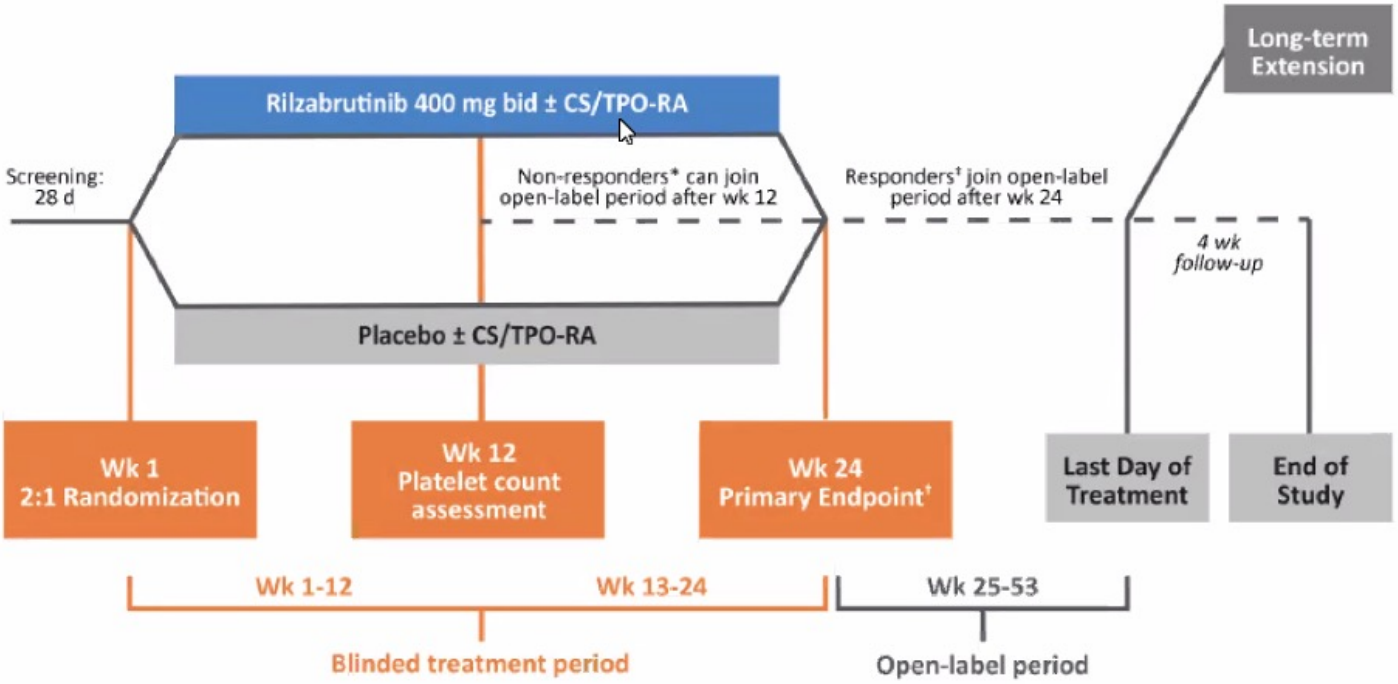
ONGOING

Phase III Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial of the Oral BTK Inhibitor Rilzabrutinib in Adults and Adolescents with Persistent or Chronic ITP

LUNA3 Phase III Study Design

Primary ITP Patients

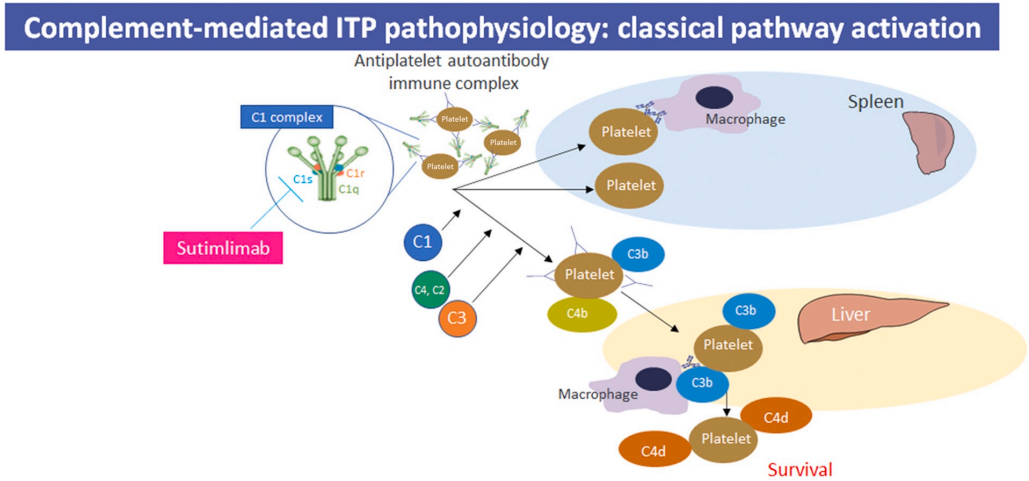
- Persistent or chronic
- n=194 adults aged ≥18 y with primary ITP >3 mo
- n=30 adolescents aged 12-17 y with primary ITP >6 mo

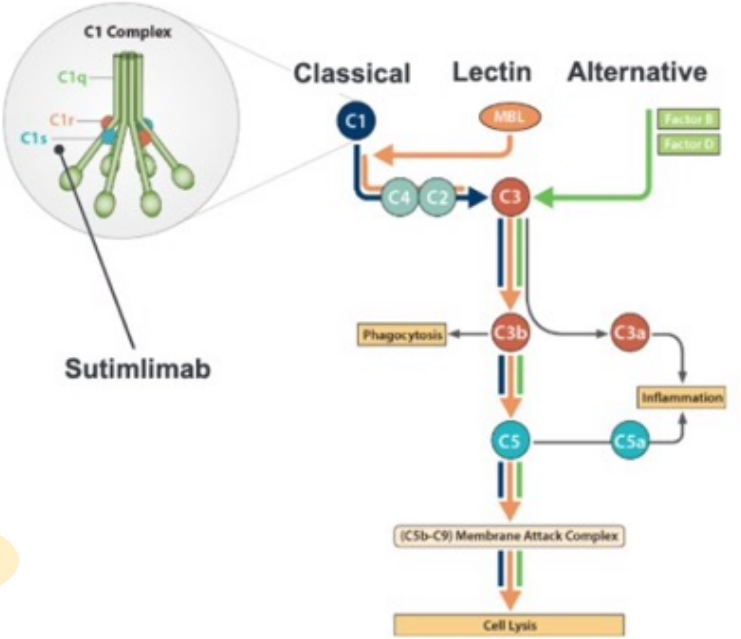


*Non-responder: platelet counts <30×10^9/L or <20×10^9/L above baseline on two consecutive visits.
†Primary endpoint: platelet counts ≥50×10^9/L for ≥8 of the last 12 wk of the 24-wk blinded treatment period without rescue medication.
‡Responder: platelet counts ≥50×10^9/L or ≥30×10^9/L and at least doubled from baseline at ≥50% of visits without rescue therapy during the last 8 wk of the open-label period.

Sutimlimab

- Humanized mAb that inhibits C1s, preventing classical complement pathway activity
- Inhibition of C1s prevents activation of C3 via the classical CP, leaving the lectin and alternative pathways intact





Safety and efficacy of classical complement pathway inhibition with sutimlimab in chronic immune thrombocytopenia

Broome C et al. Blood Adv 2023

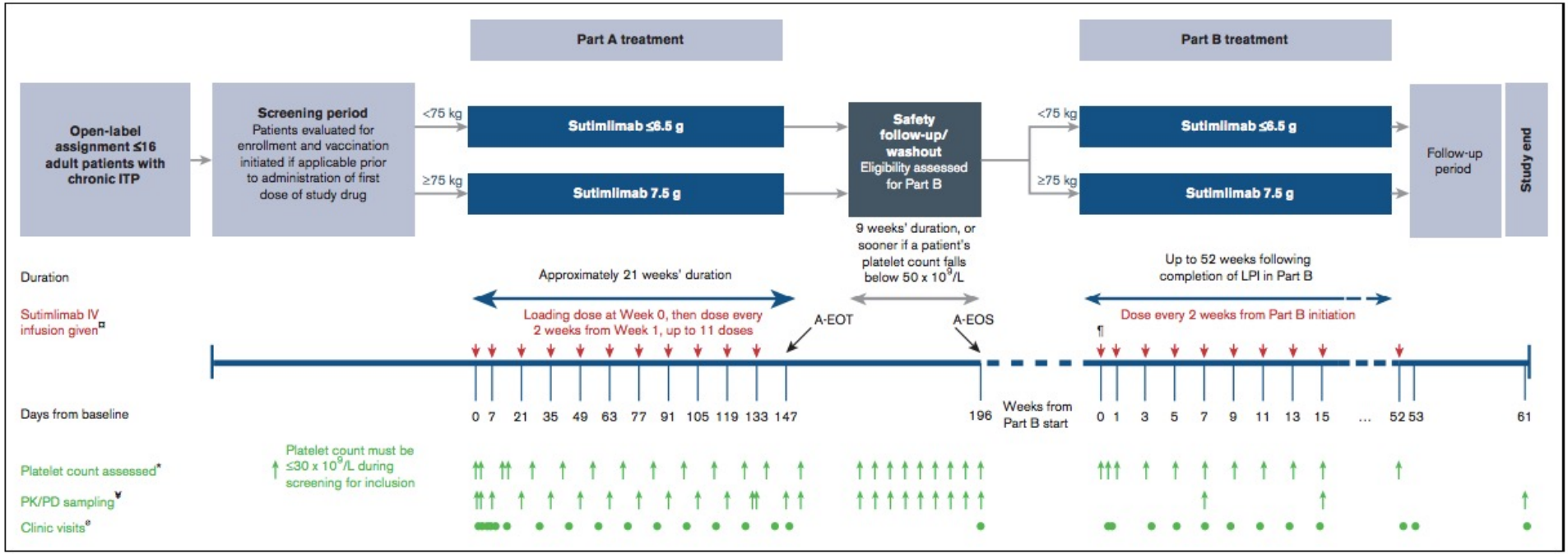
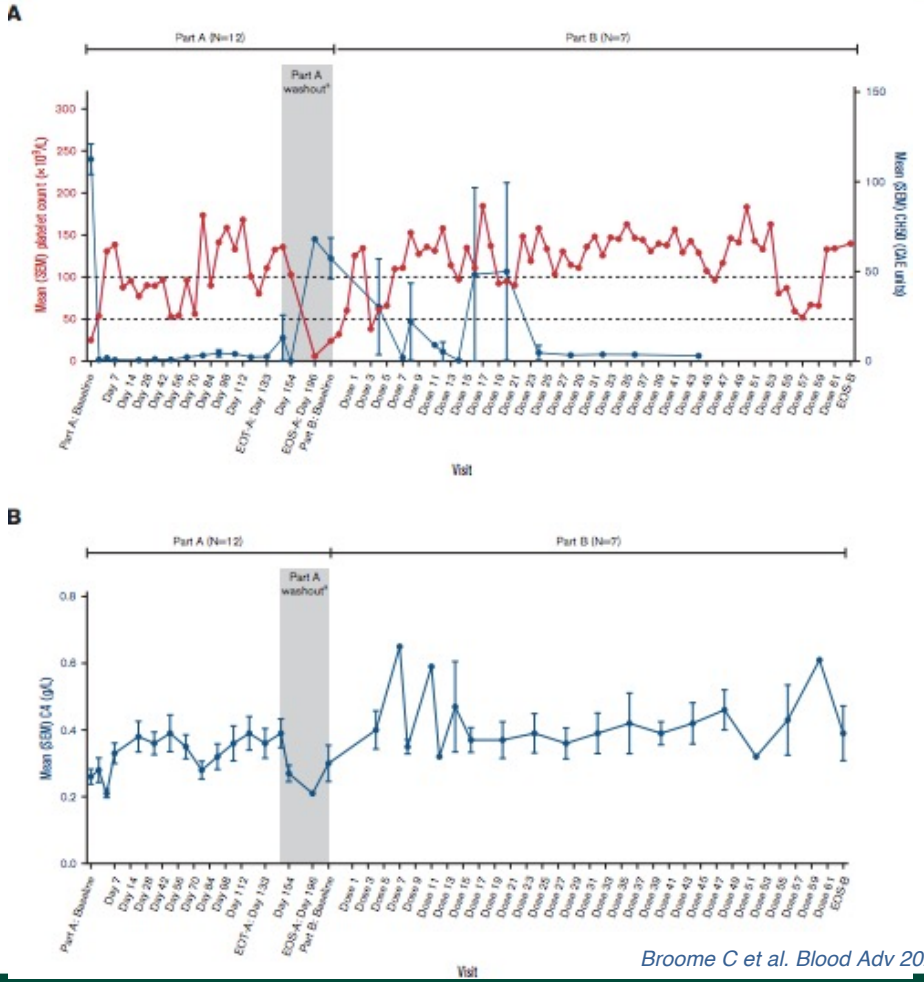


Table 1. Patient demographic and baseline disease characteristics

Baseline characteristics, (N = 12)	
Age, median (range) y	41.5 (27-66)
Sex, female, n (%)	9 (75.0)
Race, n (%)	
White	8 (66.7)
Black or African American	3 (25.0)
Asian	1 (8.3)
Weight, kg [n = 11], mean (range)	78.3 (57-114)
Disease duration at screening, y [n = 7], median (range)	4.7 (2.0-36.4)
Platelet count,* median (range), $\times 10^9$/L	19 (1-57)
Number of prior treatments, median (range)	5.5 (2-10)
Prior treatment received, n (%)	
Rituximab	10 (83.3)
Corticosteroids	8 (66.7)
TPO-RA	
Romiplostim	8 (66.7)
Eltrombopag	8 (66.7)
IVIg	7 (58.3)
Fostamatinib	2 (16.7)
Rilzabrutinib†	1 (8.3)
Prior splenectomy, n (%)	4 (33.3)



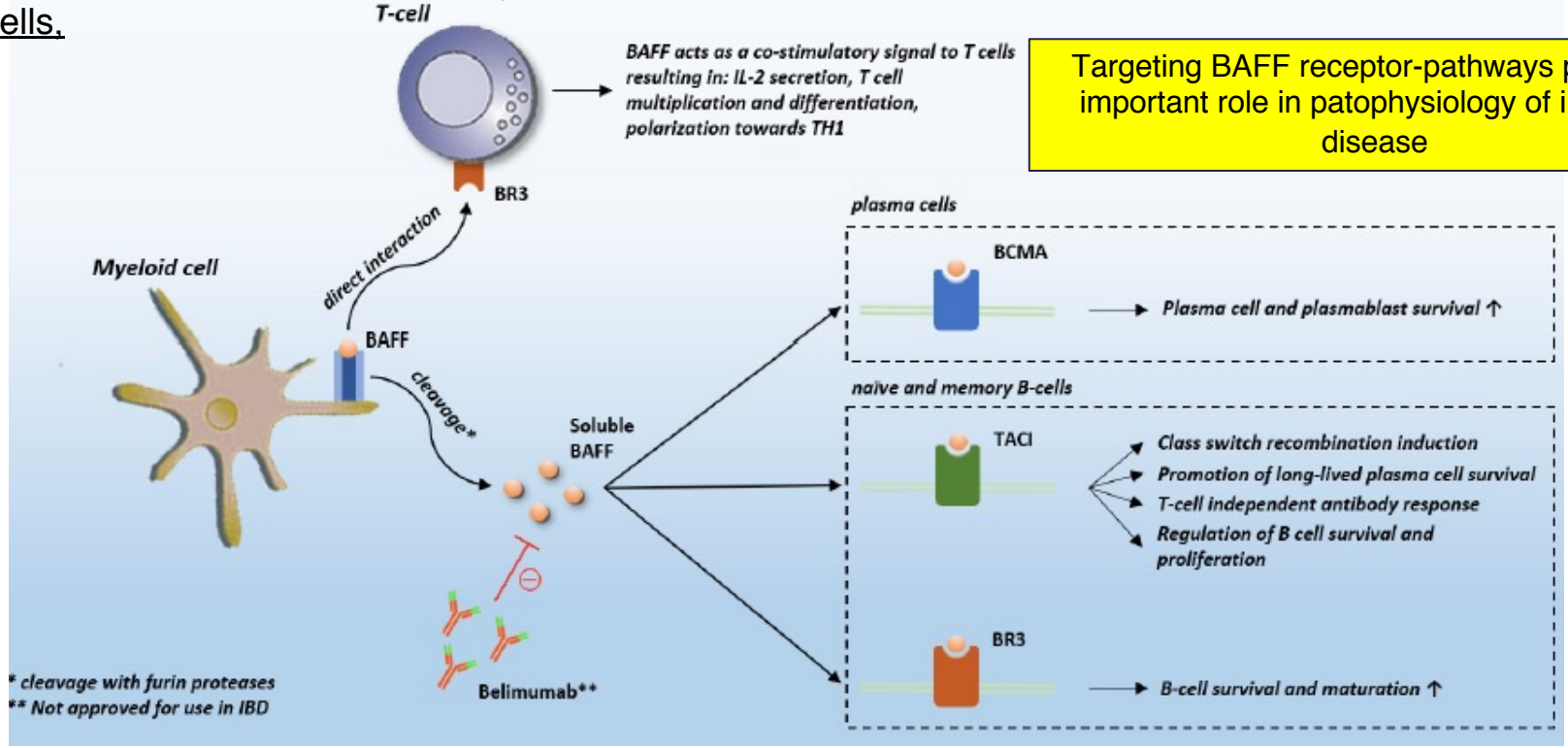
Broome C et al. Blood Adv 2023

Summary: sutimlimab in ITP first data

- 12 ITP pts : Median (range) prior ITP medications was 4 (2-10)
- 42% of patients responded
- 4 (33%) patients achieved a platelet count ≥50x 10^9/l on ≥70% of visits
- NO significant SAE (no thombosis, no infectious, no death)

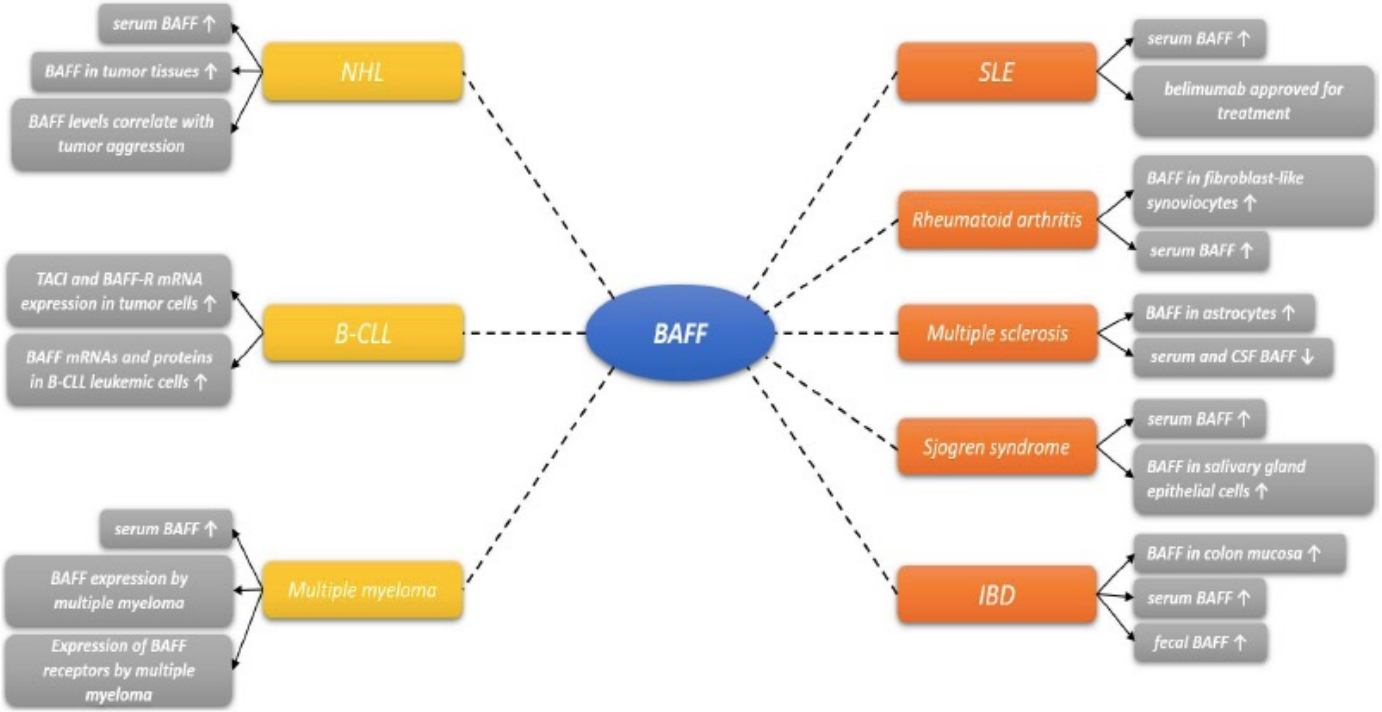
Role of BAFF and BAFF receptors in immunological diseases

- B cell activating factor belonging to the TNF family (BAFF) is a B cell survival factor essential for B cell maturation
- BAFF transmits a B cell survival signal important for B cell development and interacts with three receptors on B cells,



Targeting BAFF receptor-pathways plays an important role in patophysiology of immune disease

Involvement of BAFF in many diseases

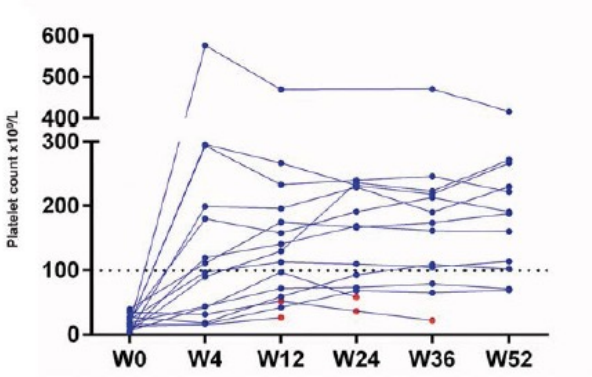


- BAFF levels are elevated in a range of autoimmune disorders, including primary biliary cholangitis, SLE, rheumatoid arthritis, coeliac disease, Sjögren's syndrome, systemic sclerosis, myasthenia gravis and correlate with autoantibody titres

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

Matthieu Mahévas,[1,2,3] Imane Azzaoui,[1,3*] Etienne Crickx,[1,2,3*]

A



B

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

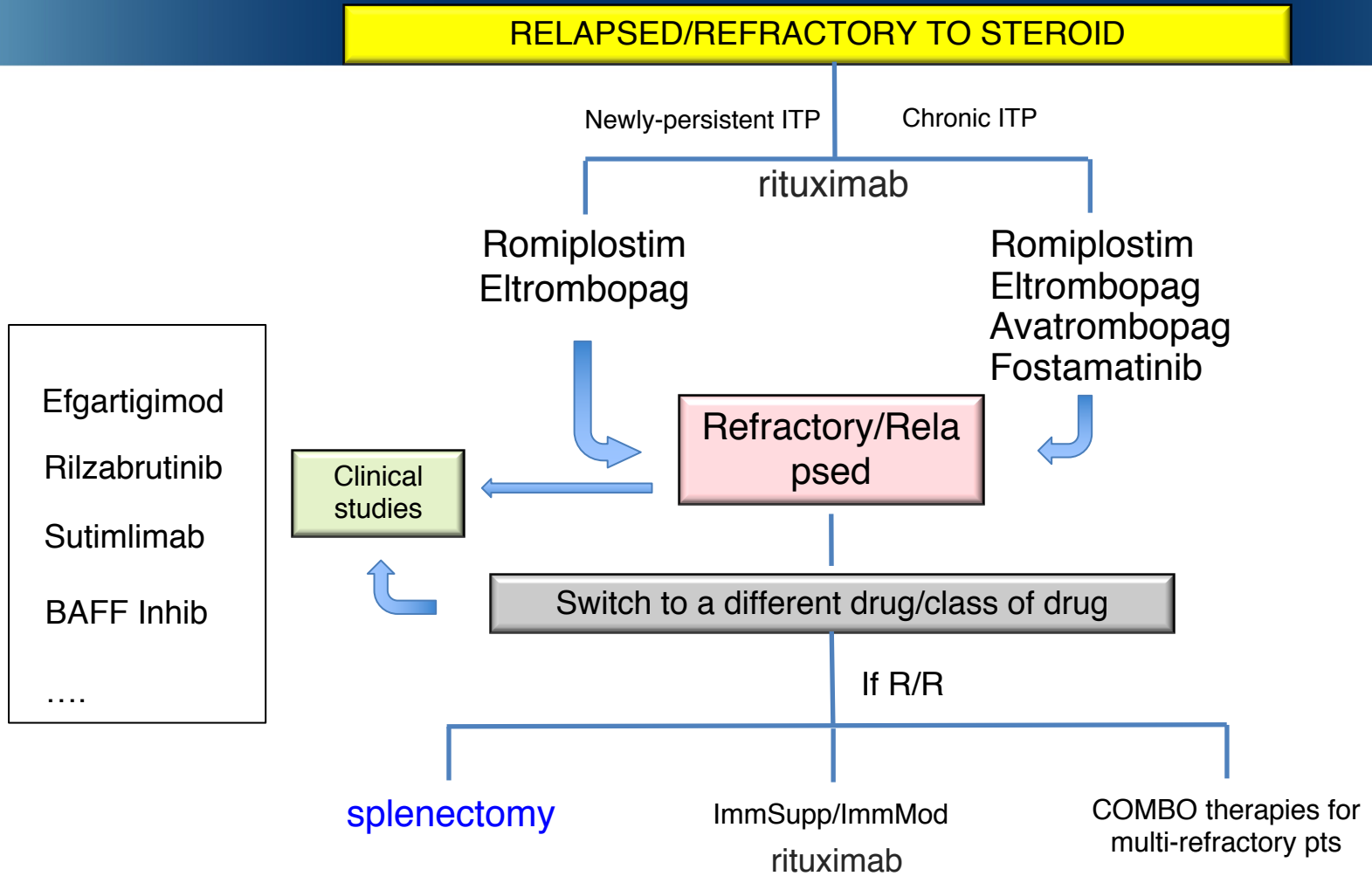
15 ITP R/R non splenectomized
RTX 1000 mg (2 weeks apart) +
Belimumab 10 mg/kg per 5 admn

At W52, 12 (80%) patients achieved an overall response, including ten (66.7%) with complete response

Hematologica 2021

Ianalumab

- Ianalumab is a BAFF-R antibody
- Ianalumab has two modes of action: a direct lysis of B cells by antibody-dependent cellular cytotoxicity, and BAFF receptor blockade that interrupts BAFF-mediated signalling for B-cell maturation, proliferation, and survival.
- Studies in ITP and wAIHA are in development


RELAPSED/REFRACTORY TO STEROID
Newly-persistent ITP
Chronic ITP
rituximab
Romiplostim
Eltrombopag
Romiplostim
Eltrombopag
Avatrombopag
Fostamatinib
Efgartigimod
Rilzabrutinib
Sutimlimab
BAFF Inhib
….
Clinical studies
Refractory/Relapsed
Switch to a different drug/class of drug
If R/R
splenectomy
ImmSupp/ImmMod
rituximab
COMBO therapies for multi-refractory pts

New drugs, new questions..

- TPO-RA switch: is it advisable to switch all 3 available drugs before switching to fostamatinib?
- After failure of one/two TPO-RA → fostamatinib - -> but in case of failure or limited response is it advisabale to switch again to a TPO-RA? A different one?
- Is it possibile to combine fostamatinib & TPO-RA ? (regulatory gap)

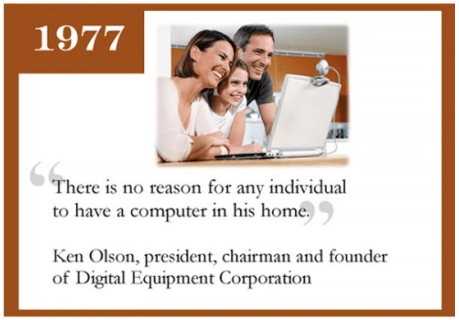
Qualcosa è cambiato…

1977

"There is no reason for any individual to have a computer in his home."

Ken Olson, president, chairman and founder of Digital Equipment Corporation

Vorrei che qualcosa cambiasse nei prossimi X anni…



Recommendations for diagnosis of primary ITP in children and adults

1. The diagnosis of ITP is based principally on the exclusion of other causes of isolated thrombocytopenia using patient history, physical examination, blood count, and evaluation of the peripheral blood film (to exclude other hemato[illegible] conditions, including hereditary thrombocyto and pseudothrombocytopenia). If therapy is ad tered, platelet count should be closely monitor response as a diagnostic aid.

Recommendations for subsequent therapy strategy

1. There are many medical therapy options with few AEs.
2. Not all therapies are available in all countries; thus, the recommendations should be modified based on available resources and patient preference.
3. Some medical options may require ongoing continued treatment.
4. Up to one third of patients may remit in 1 year,[113] and up to 80% may remit in 5 years.[114,115] If possible, splenectomy should be deferred for ≥1 year to allow for remission.[113,115]