Emerging Therapies in Immune Thrombocytopenia

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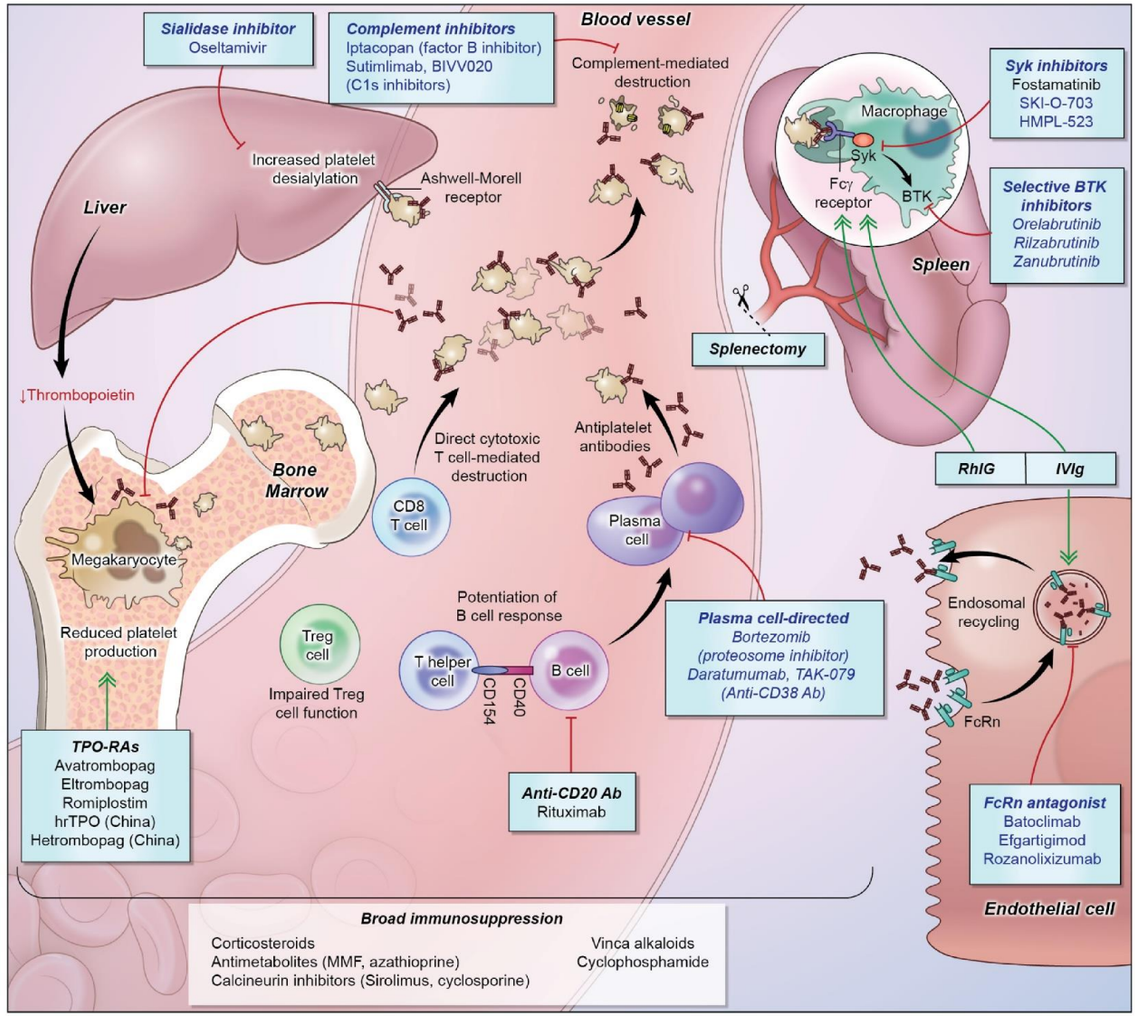
Disclosures of Hanny Al-Samkari

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Agios, Amgen, Novartis, Sobi	X		X				
Vaderis	X						
Sanofi, Pharmacosmos, argenx, Alnylam			X				

ITP: From Steroids, Splenectomy & Salvage to Numerous Targeted Therapies in Two Decades

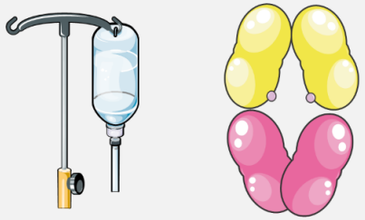


Jiang et al., *Transfusion Med Reviews* 2022

The Major Types of ITP Therapies Under Investigation

Efgartigimod

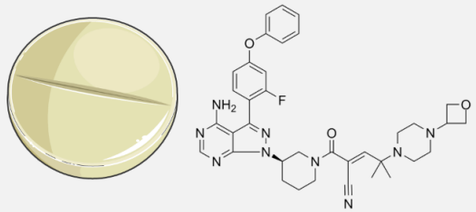
Neonatal Fc Receptor Antagonist



Status: Completed Phase 3
ADVANCE IV Study (Intravenous): Positive
ADVANCE SC Study (Subcutaneous): Negative

Rilzabrutinib

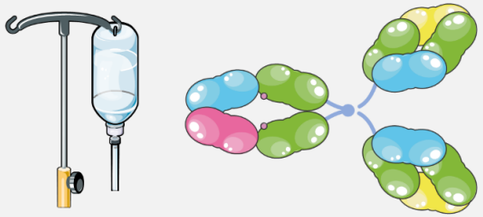
Bruton's Tyrosine Kinase Inhibitor



Status: Completed Phase 3 (Adults)
LUNA 3 Study (Adult Portion): Positive
LUNA 3 Study (Pediatric Portion): Ongoing

Ianalumab

BAFF Receptor Antagonist



Status: Ongoing Phase 2 and Phase 3
VAYHIT1 (1st Line + Steroids): Ongoing
VAYHIT2 (2nd Line + Eltrombopag): Ongoing
VAYHIT3 (Later line): Ongoing

Povetacicept

BAFF and APRIL Antagonist

Status: Ongoing Phase 2
RUBY-4 Study (Basket Trial): Ongoing

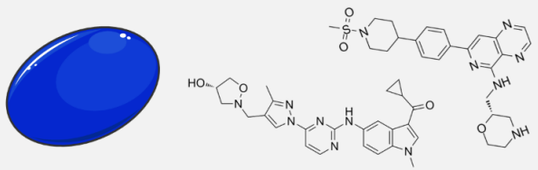
Anti-CD38 Antibodies

Mezagitamab, Daratumumab, CM313

Status: Completed and Ongoing Phase 2
TAK-079-1004 (Mezagitamab, SC): Positive
2022-CM313-ITP (CM313, IV): Positive

Novel SYK Inhibitors

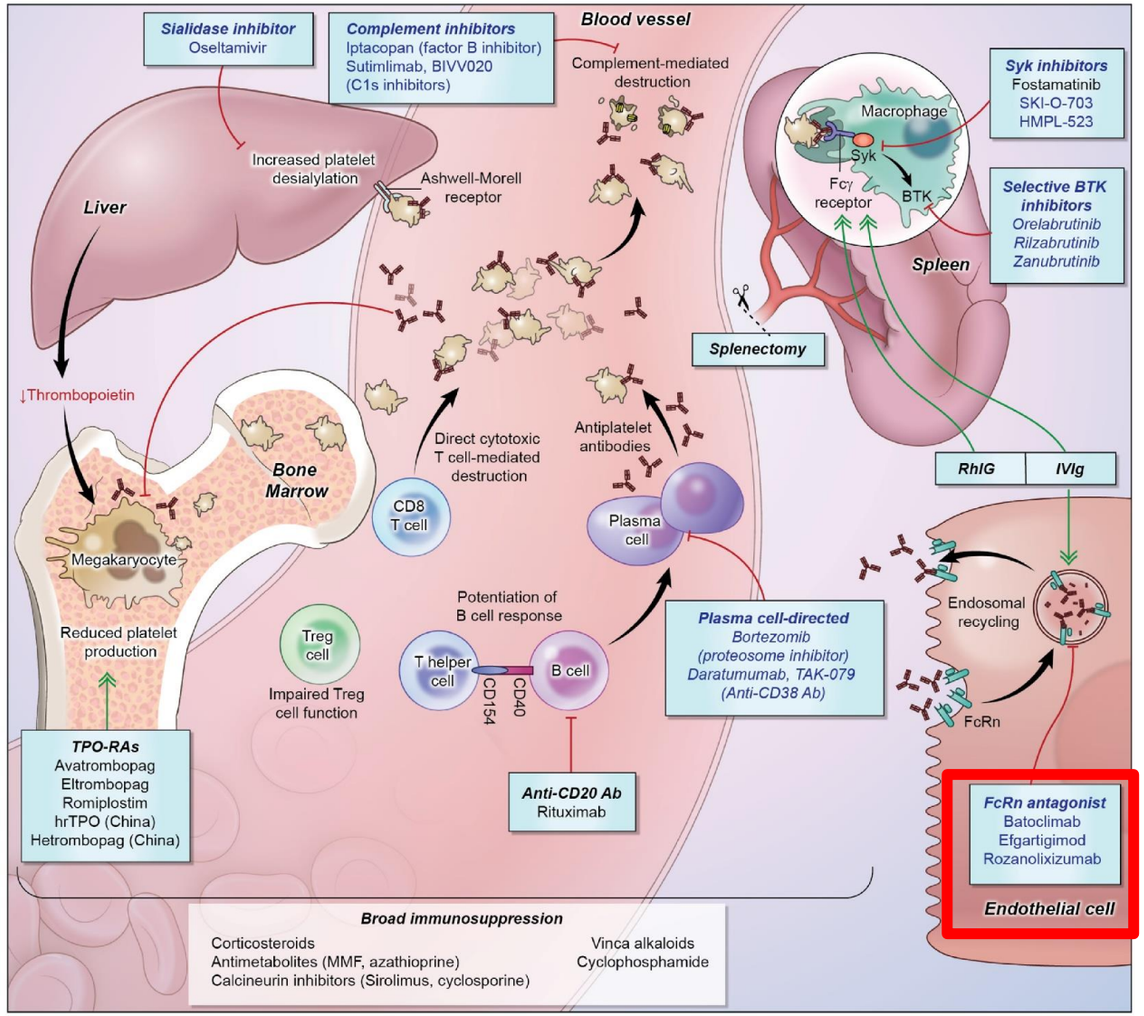
Sovleplenib and Cevidoplenib



Status: Completed Phase 2 and Phase 3
Sovleplenib Phase 2: Positive
ESLIM-1 (Sovleplenib Phase 3): Positive
Cevidoplenib Phase 2: Positive

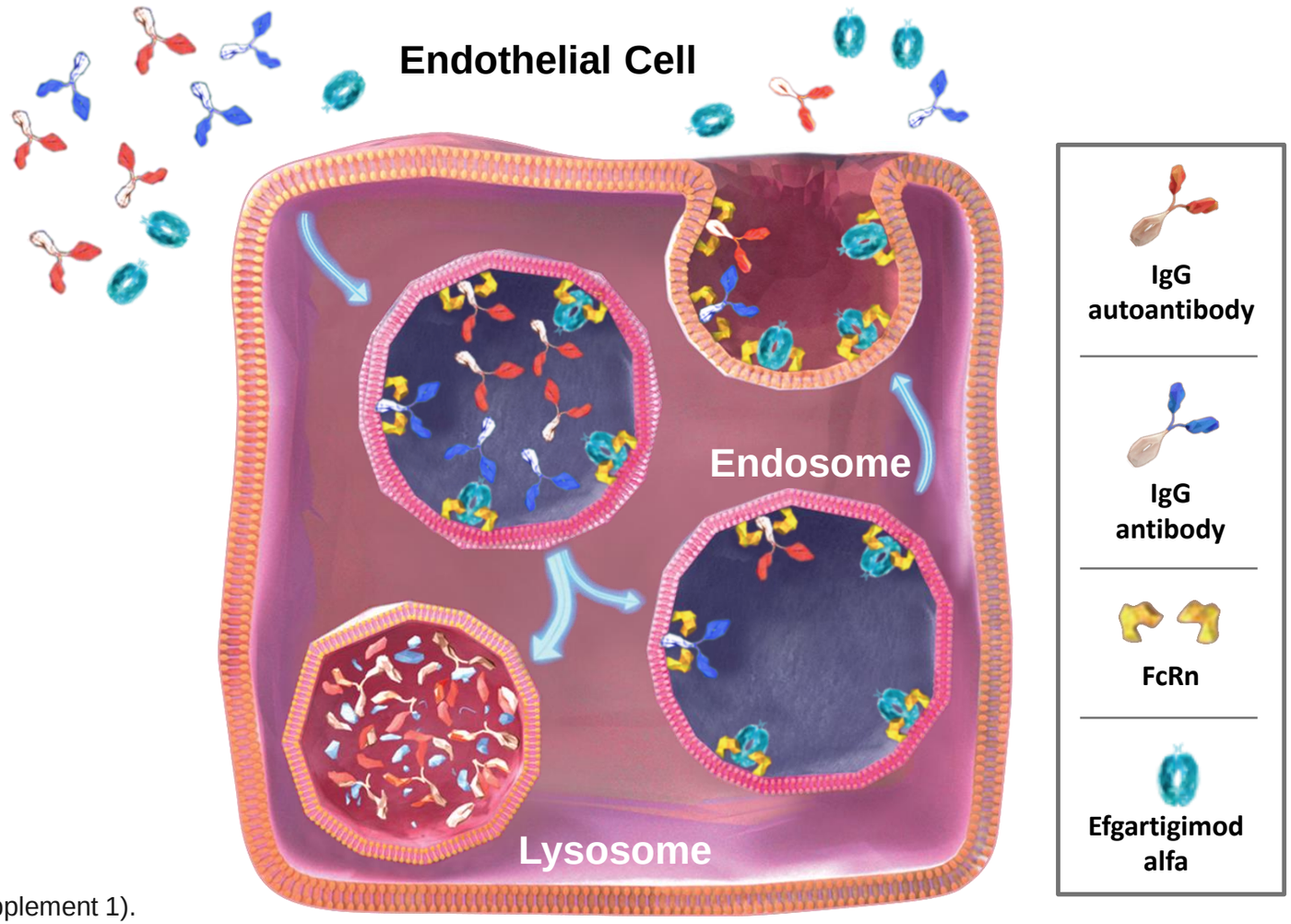
Al-Samkari H. *Amer J Hematol* 2024

Novel Agents for ITP: Neonatal Fc Receptor Antagonists



Jiang et al., *Transfusion Med Reviews* 2022

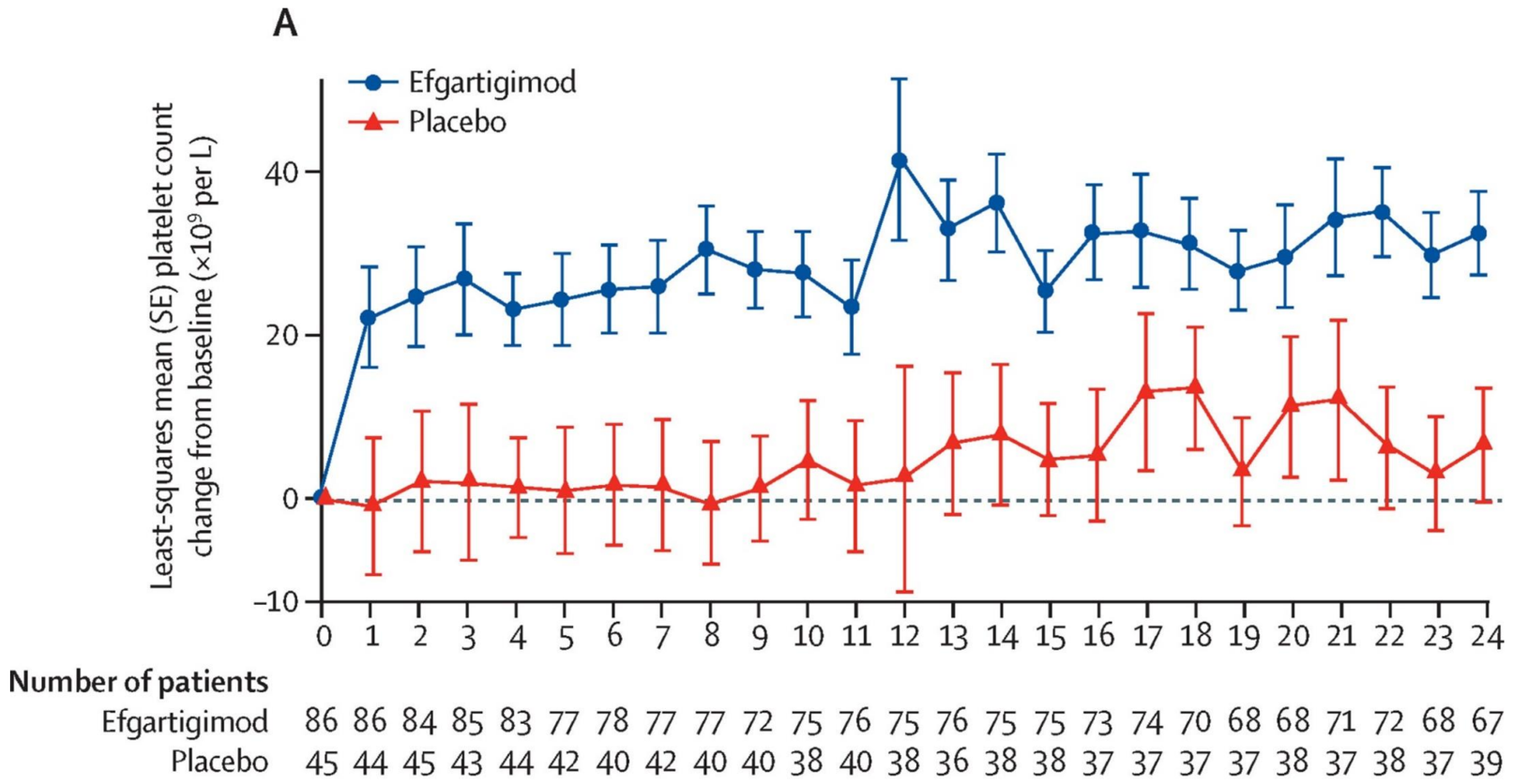
Efgartigimod Competitively Inhibits FcRn



Broome et al., Blood (2022) 140 (Supplement 1).

Efgartigimod Phase 3 Study (ADVANCE IV) Platelet Counts

Platelet Counts Over Time



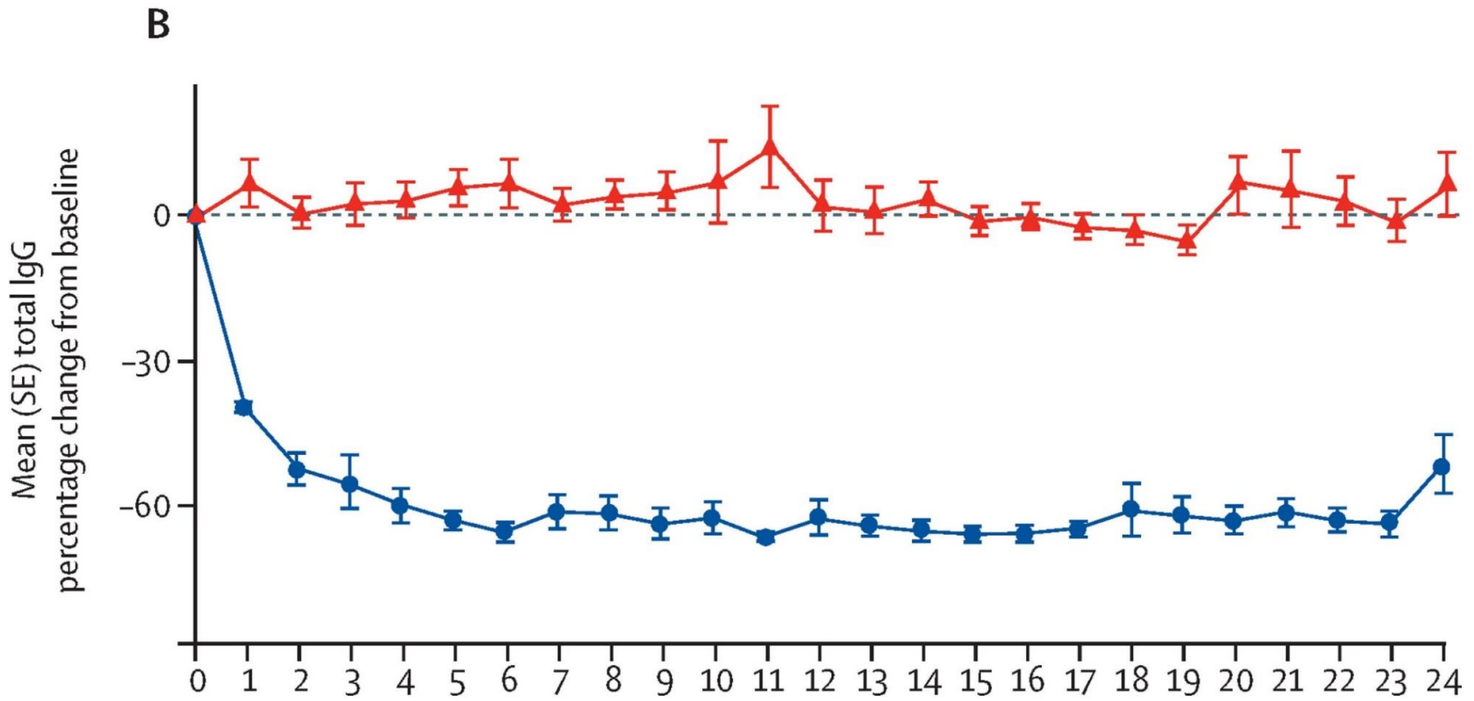
33 (38.4%) of efgartigimod treated participants compared to **5 (11.1%) placebo** reached a platelet count of 30X10^9 platelets at week 1

Sustained platelet count response achieved in **90%** (9/10) of participants who switched from weekly to every other week dosing

Broome et al., *The Lancet* 2023

Efgartigimod Phase 3 Study (ADVANCE IV) IgG Levels Fell 60%

Mean % Change from Baseline in Total IgG Levels over Time



Number of patients																									
Efgartigimod	80	77	73	74	64	55	59	68	64	60	63	65	57	62	54	62	57	60	56	53	49	53	56	51	58
Placebo	45	42	45	42	36	35	39	38	34	37	34	34	31	26	31	30	29	28	30	28	30	28	31	28	39

Broome et al., *The Lancet* 2023

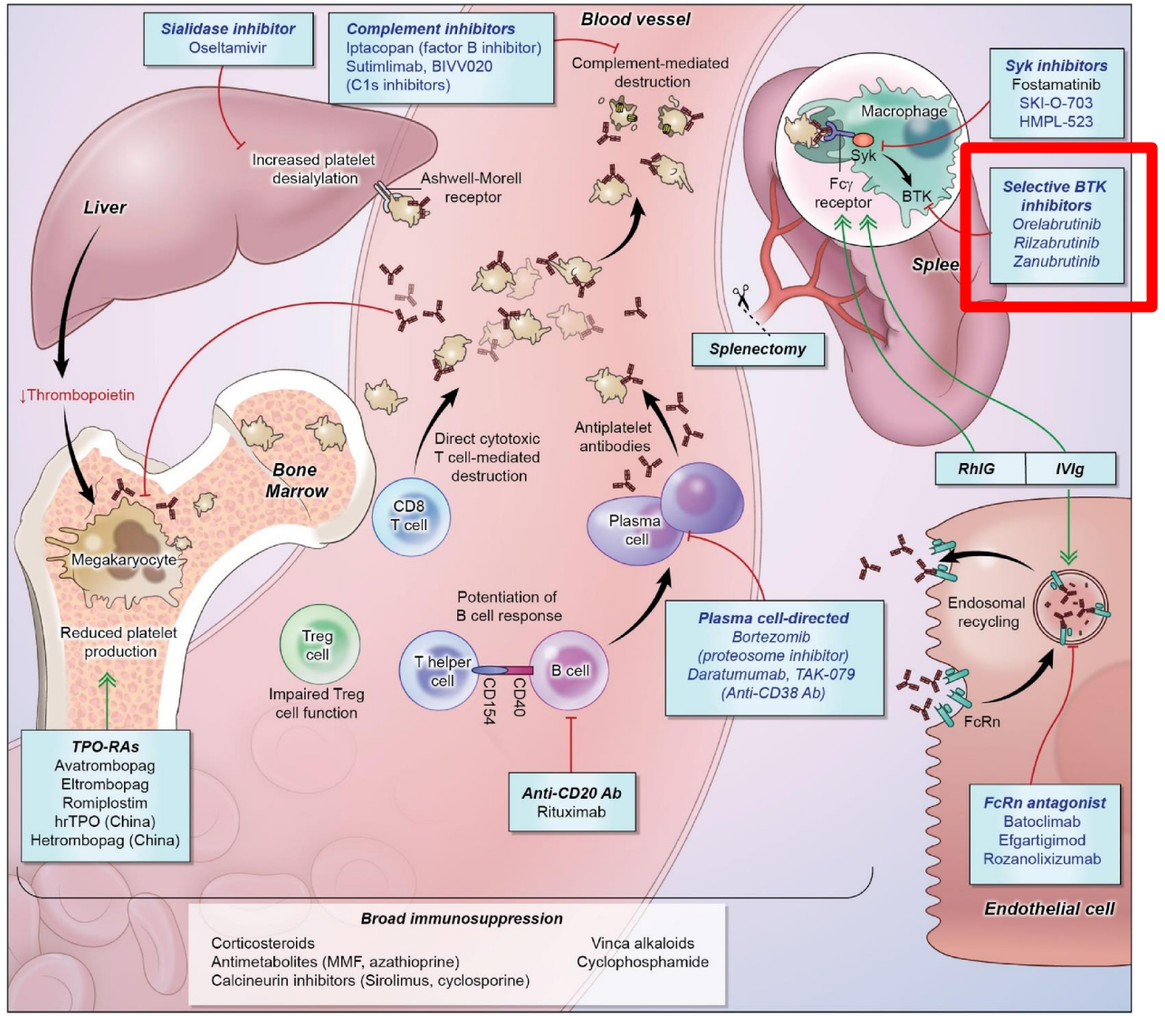
Efgartigimod Phase 3 Study (ADVANCE IV) Endpoints

Endpoint[b]	Efgartigimod	Placebo	P-value
Primary endpoint			
Proportion with sustained platelet count response, n/N (%)[c] Platelet count of ≥50×10^9/L for at least 4 of the 6 visits between weeks 19 and 24, in the absence of intercurrent events[b]	17/78 (21.8%)	2/40 (5.0%)	**0.0316***
Key secondary endpoints			
Number of cumulative weeks of disease control, Mean (SD)[c] 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 (%)[d] ≥ 50 x 10^9/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)[d]	6.2 (6.39)	8.3 (8.01)	0.8287
Durable sustained platelet count response, n/N (%)[d] ≥ 50 x 10^9/L in ≥6/8 visits during weeks 17-24	19/86 (22.1%)	3/45 (6.7%)	0.0265

[a] All endpoints were statistically tested in a fixed sequence to maintain an overall statistical significance level or alpha value of 5%. Although endpoints were subjected to a hierarchical testing procedure nominal p-values are always less than than 0.05 for platelet-based endpoints
[b] Analyzed on Full Analysis Set
[c] Chronic population (per protocol)
[d] Chronic + persistent population (per protocol)

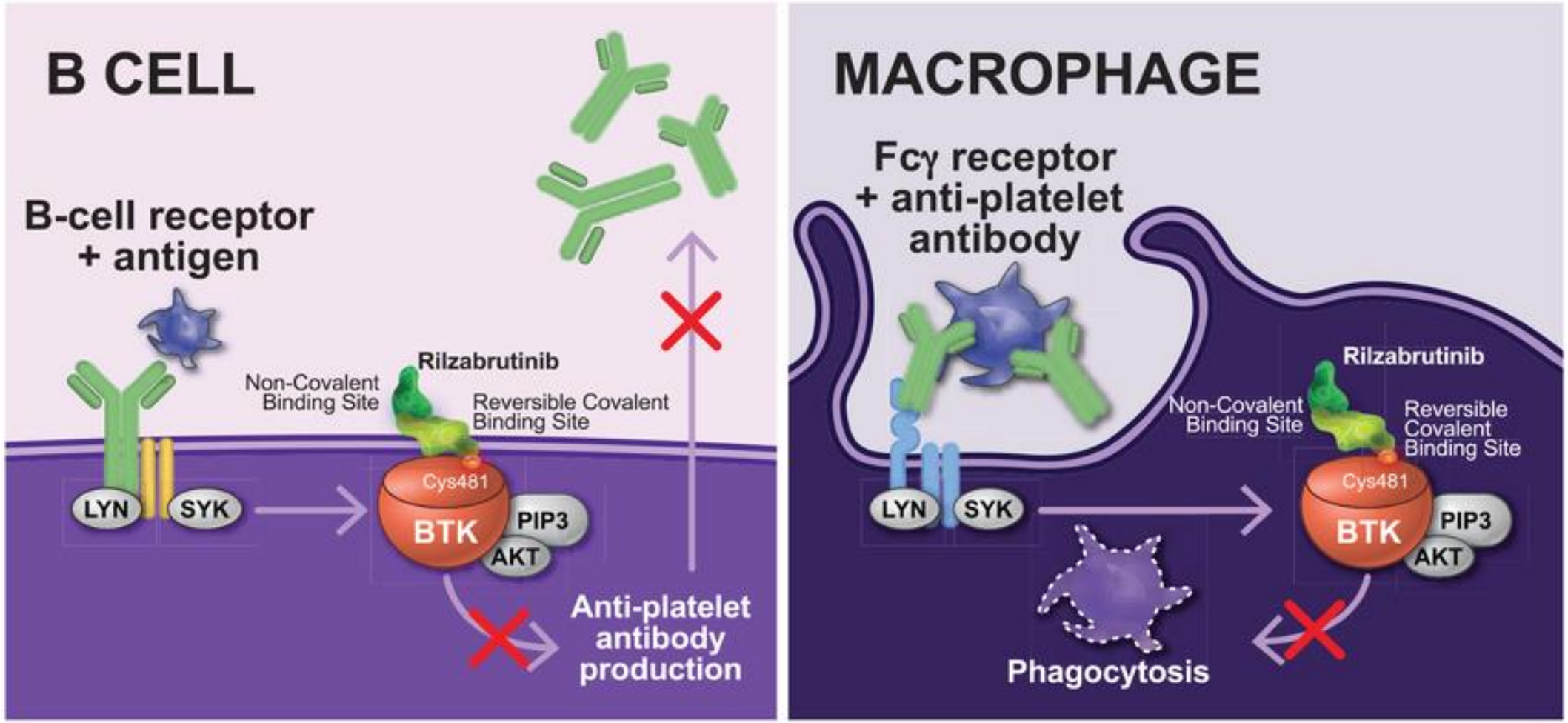
Broome et al., *The Lancet* 2023

Novel Agents for ITP: Bruton's Tyrosine Kinase Inhibitors



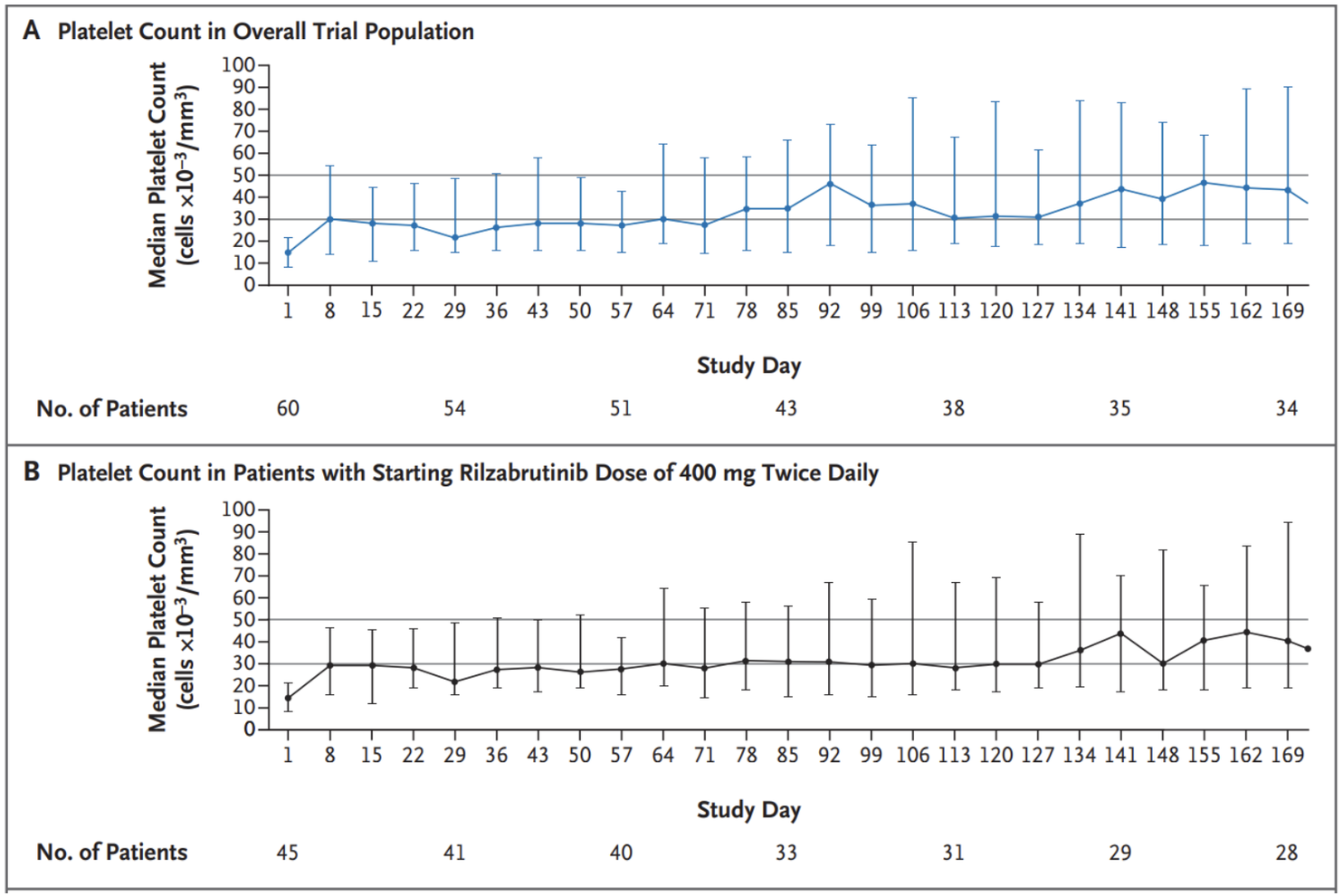
Jiang et al., *Transfusion Med Reviews* 2022

Effects of BTK Inhibition



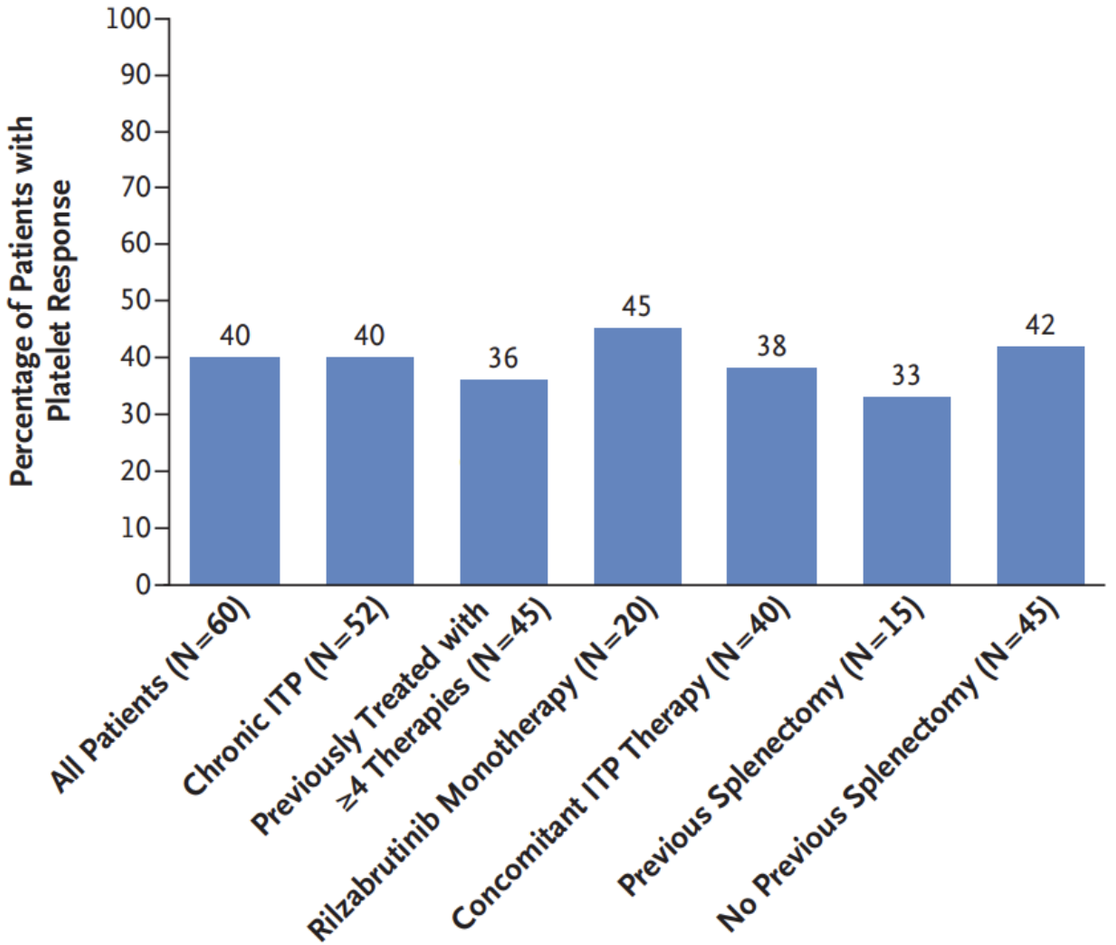
Kuter et al., *Ther Adv Hematol* 2023

BTK Inhibitor for ITP: Rilzabrutinib



Kuter et al., *New Engl J Med* 2022

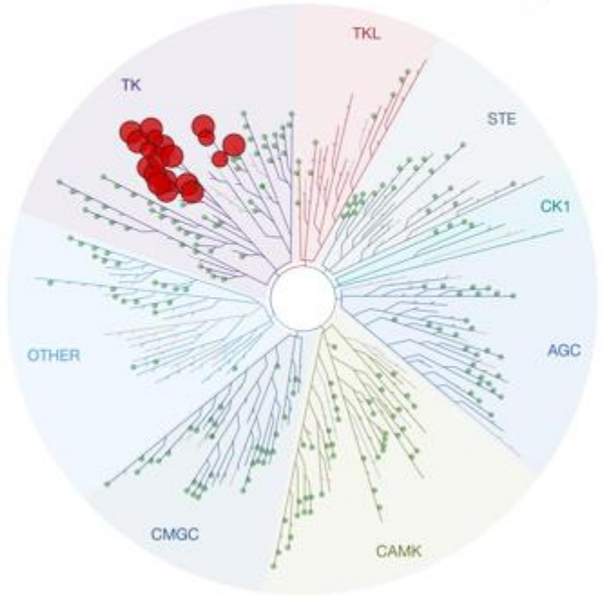
BTK Inhibitor for ITP: Rilzabrutinib



Kuter et al., *New Engl J Med* 2022

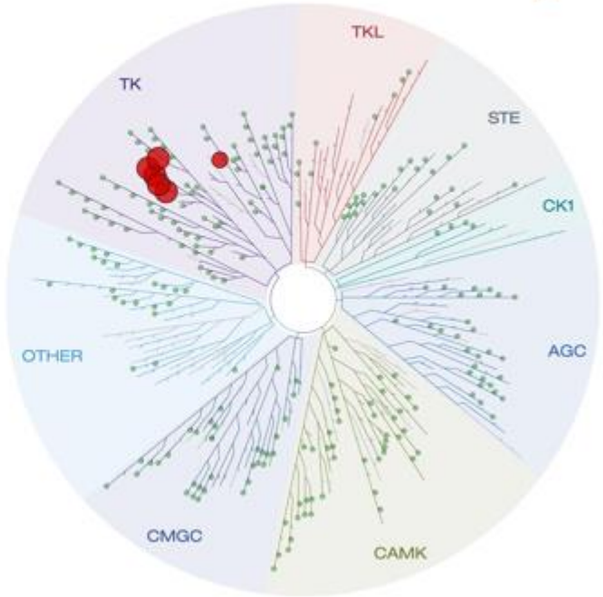
BTK Inhibitor for ITP: Rilzabrutinib

Ibrutinib Kinase Selectivity



21 kinases inhibited >90%

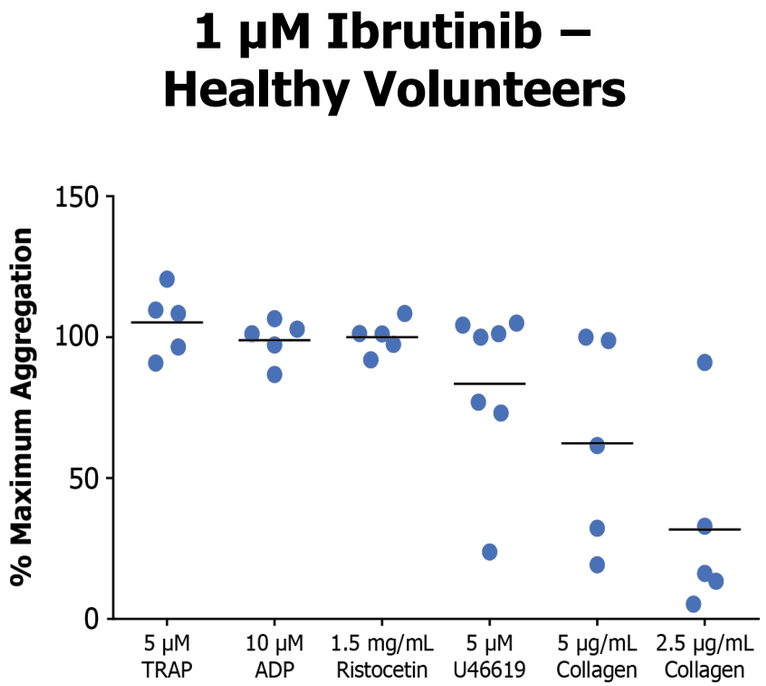
PRN1008 Kinase Selectivity

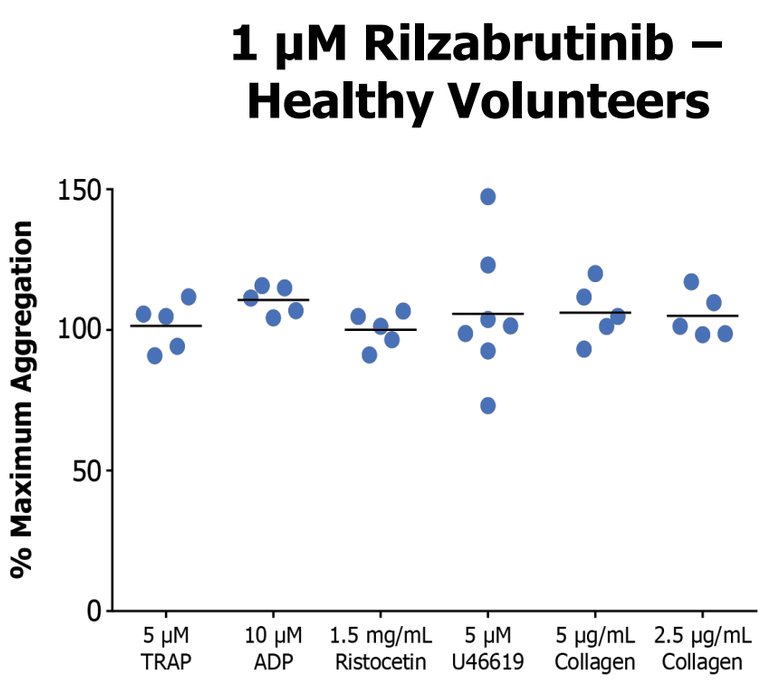


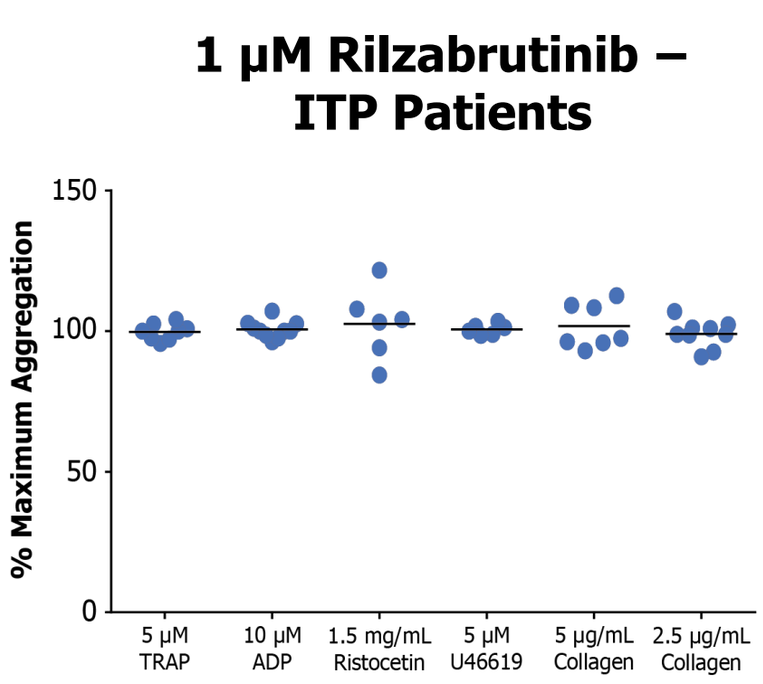
6 kinases inhibited >90%

Kuter et al., *Blood* 2020

BTK Inhibitor for ITP: Rilzabrutinib



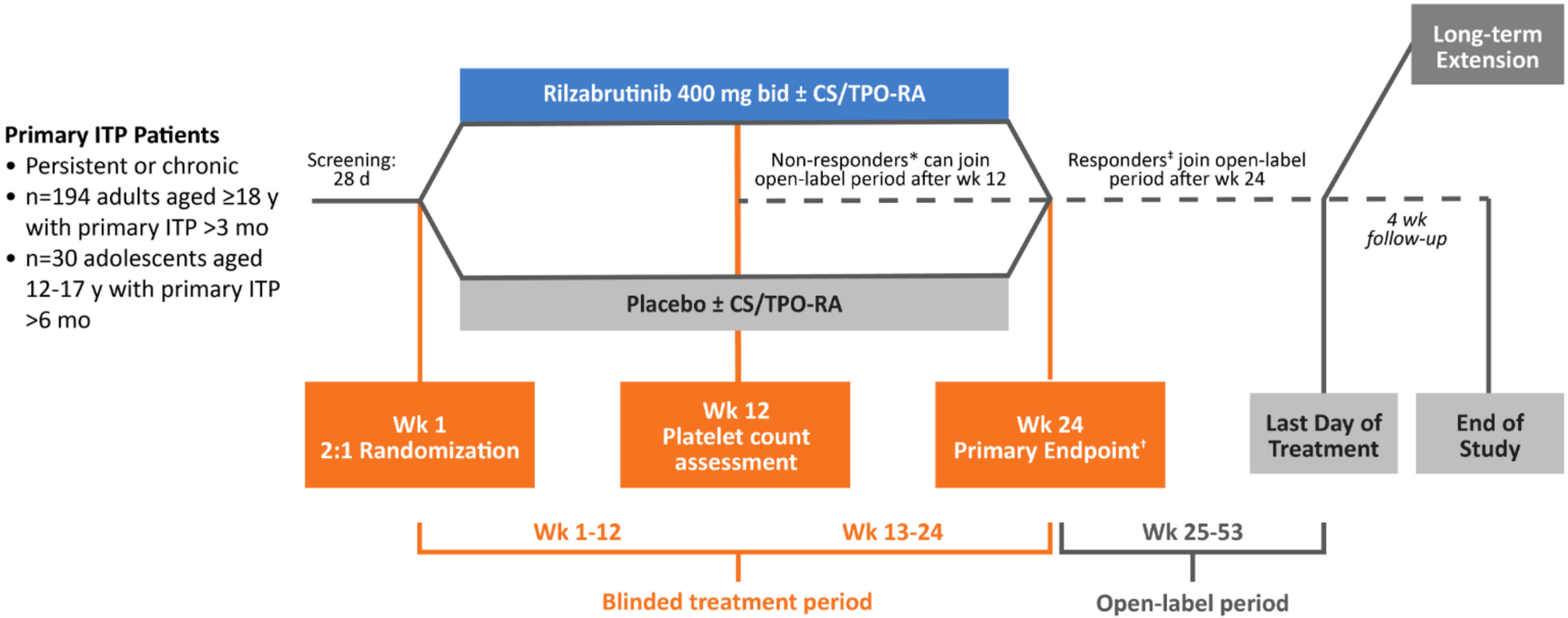




Kuter et al., *Blood* 2020

BTK Inhibitor for ITP: Rilzabrutinib

Figure. LUNA3 Phase III Study Design



*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.

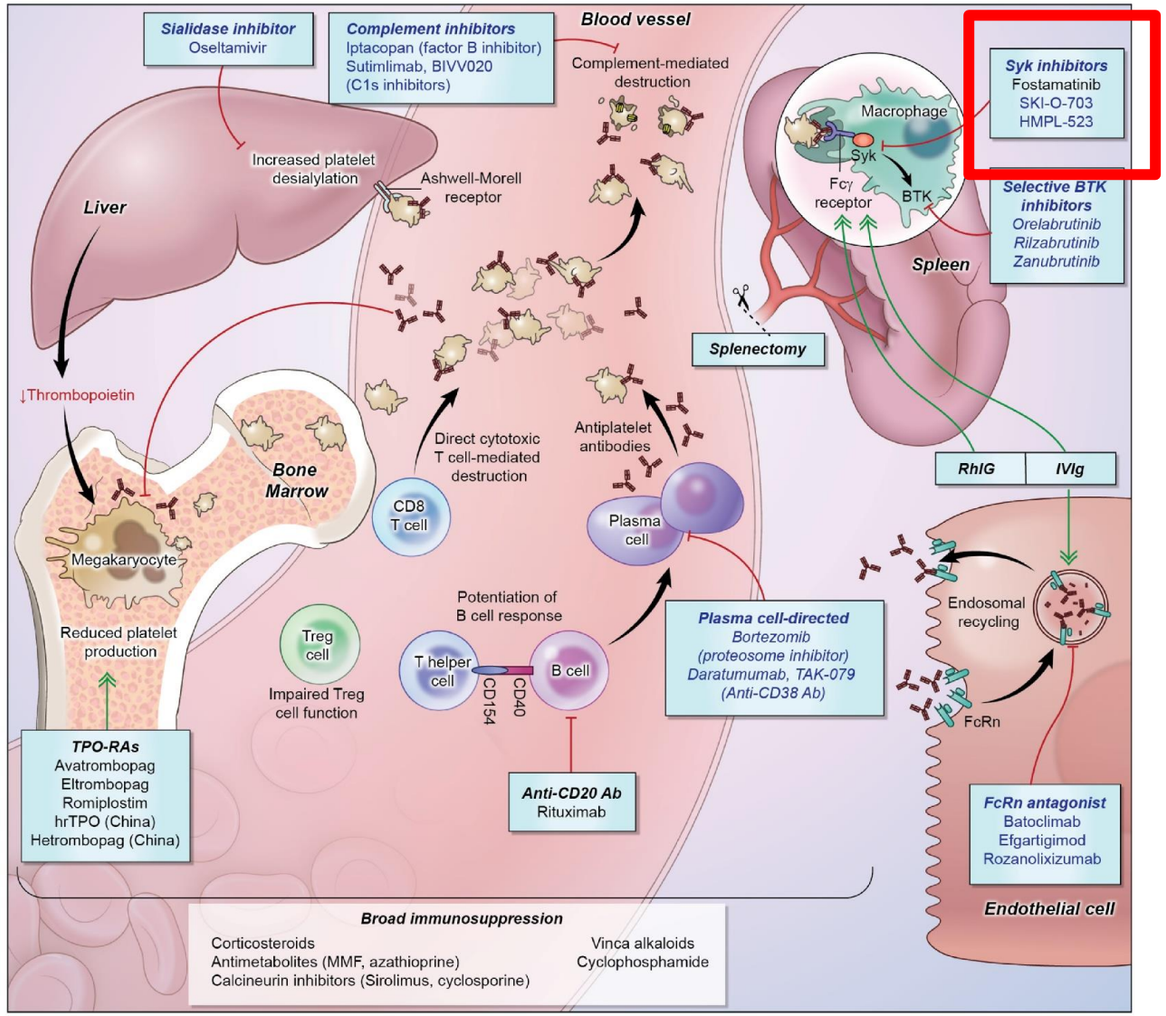
Kuter et al., *Blood* 2021

BTK Inhibitor for ITP: Rilzabrutinib

- LUNA 3 Adult ITP Results presented at ASH 2024 Plenary Session
- N=133 randomized to rilzabrutinib, N=69 randomized to placebo, similar baseline characteristics
  - Median 5 prior ITP therapies, median duration of ITP 8.1 years
- Platelet response achieved in 65% RIL, 33% PBO
- Durable response achieved in 29% RIL
- 52% rescue therapy in RIL arm vs PBO arm
- Significant and clinically meaningful improvements in physical fatigue (ITP-PAQ)
- More diarrhea, nausea, and headache in RIL vs. PBO

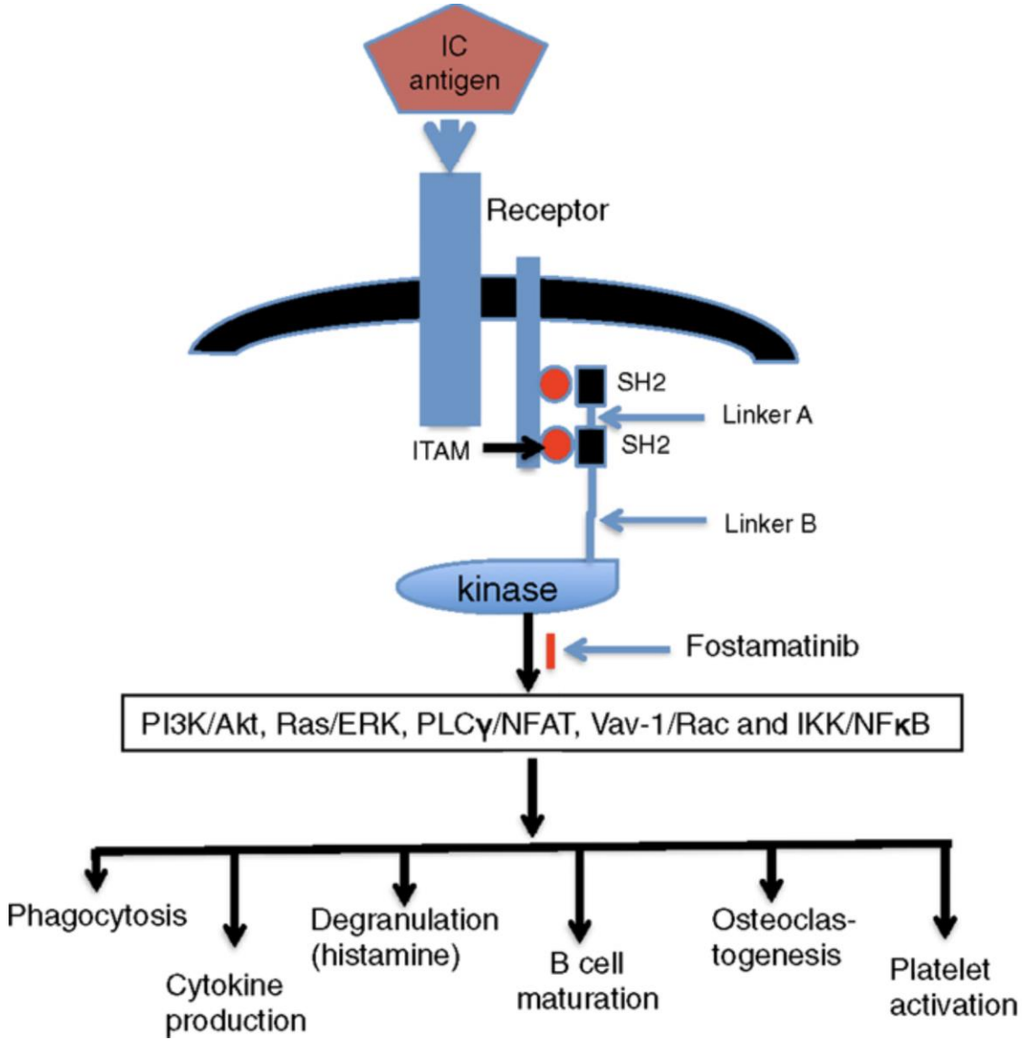
Kuter et al., *ASH Plenary Session* 2024

Novel Agents for ITP: Novel SYK Inhibitors



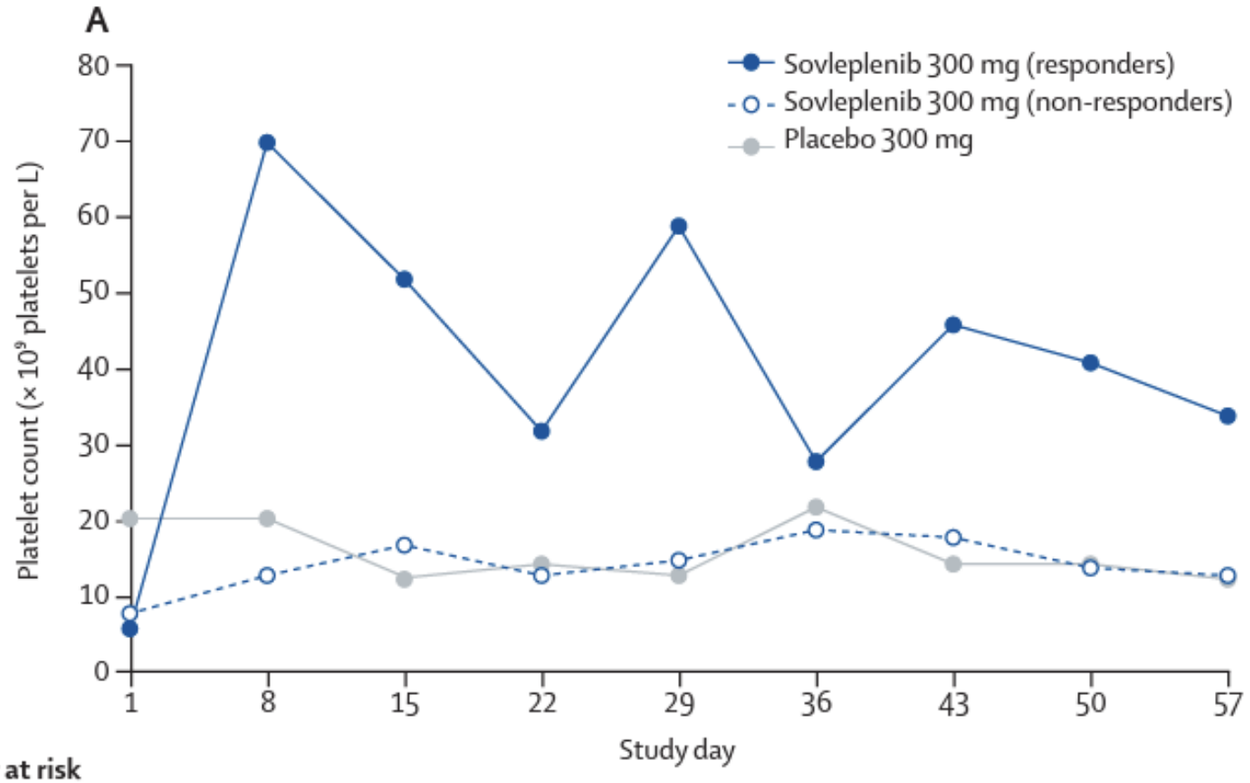
Jiang et al., *Transfusion Med Reviews* 2022

Inhibition of the Spleen Tyrosine Kinase



Deng et al., *Frontiers in Immunology* 2016

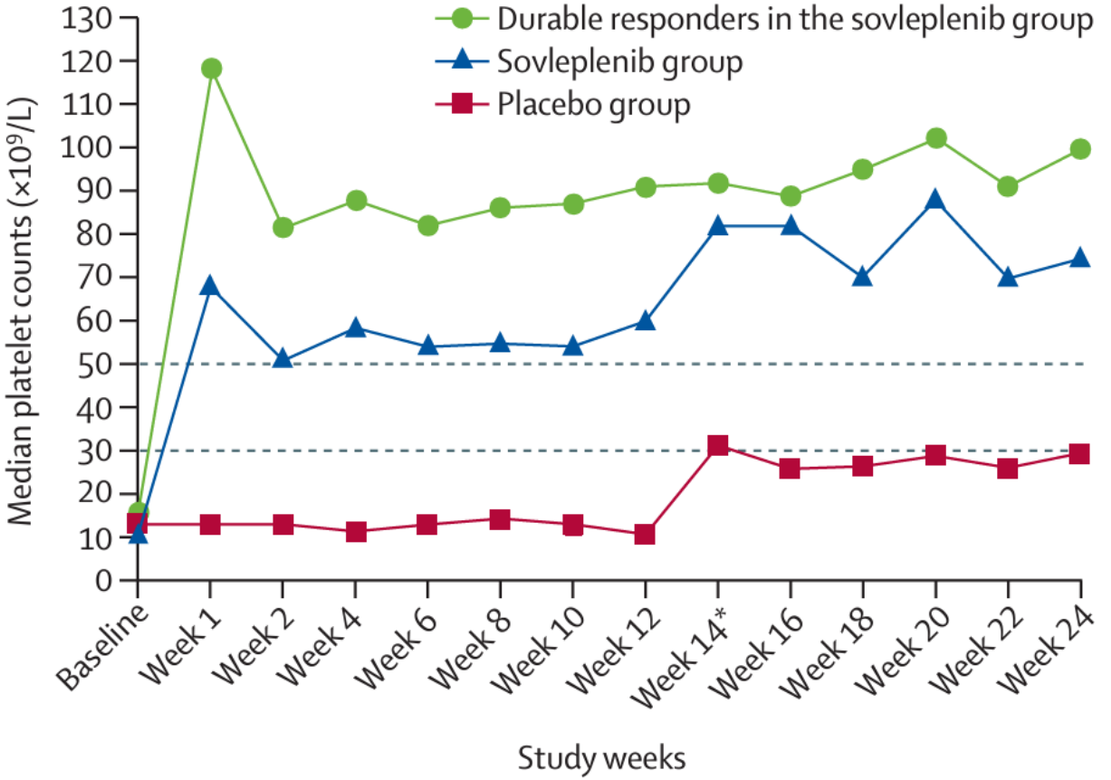
Sovleplenib in ITP: Phase 2 Study



Number at risk									
Sovleplenib 300 mg (responders)	11	11	11	11	11	11	11	11	11
Sovleplenib 300 mg (non-responders)	5	5	5	5	4	4	4	4	4
Placebo 300 mg	4	4	4	4	4	4	4	4	4

Liu et al., *Lancet Haematol* 2023

Sovleplenib in ITP: Ph3 ESLIM-1 Study



Durable responders in the sovleplenib group	61	19	60	59	60	61	59	60	60	61	59	61	61	61
Sovleplenib group	126	41	114	110	109	111	109	105	83	83	84	85	85	84
Placebo group	62	22	54	52	47	50	47	49	8	8	8	8	8	8

Hu et al., *Lancet Haematol* 2024

Sovleplenib in ITP: Ph3 ESLIM-1 Study

	Sovleplenib group (n=126)	Placebo group (n=62)	Difference between treatment groups (95% CI)	p value
Primary endpoint				
Durable response rate*	61 (48%)	0	48% (40–57)	<0·0001
Secondary endpoints				
Overall response rate in 0–12 weeks*	86 (68%)	9 (15%)	53% (42–65)	<0·0001
Overall response rate in 0–24 weeks*	89 (71%)	10 (16%)	54% (43–66)	<0·0001
Patients with a platelet count of <15 × 10^9/L at baseline†				
Patients with a platelet count of ≥30 × 10^9/L and an increase of ≥20 × 10^9/L from baseline in 0–12 weeks*	55 (73%)	8 (22%)	52% (36–68)	<0·0001
Patients with a platelet count of ≥30 × 10^9/L and an increase of ≥20 × 10^9/L from baseline in 0–24 weeks*	56 (75%)	8 (22%)	53% (37–69)	<0·0001
Patients with two consecutive platelet counts of ≥30 × 10^9/L and a platelet count doubling from the baseline in 0–24 weeks*	92 (73%)	4 (6%)	67% (57–76)	<0·0001
Patients who received rescue treatment in the 24-week period	28 (22%)	22 (35%)	–13% (–27 to 0)	0·0451
Patients who received concomitant treatment for anti-immune thrombocytopenia at baseline‡				
Patients who reduced or discontinued baseline concomitant treatment for anti-immune thrombocytopenia in 0–24 weeks	11 (27%)	2 (10%)	16% (–3 to 35)	0·1471
Time to response (from treatment initiation to first platelet count ≥50 × 10^9/L), days§	8 (8–12)	30 (24–46)	NA	NA
WHO bleeding scale score in 0–12 weeks	0·586 (0·0766)	0·786 (0·0838)	–0·199 (–0·324 to –0·075)	0·0019
WHO bleeding scale score in 0–24 weeks	0·555 (0·0743)	0·786 (0·0813)	–0·231 (–0·351 to –0·110)	0·0002

Data are n (%), median (IQR), or least square mean (SE), unless otherwise specified. NA=not applicable. SE=standard error. *Not caused by rescue treatment during the treatment period. †75 patients in the sovleplenib group and 37 in the placebo group. ‡41 patients in the sovleplenib group and 20 in the placebo group. §Results are from patients who initially signed informed consent form version 3.0 and above and had a response.

Hu et al., *Lancet Haematol* 2024

Sovleplenib in ITP: Ph3 ESLIM-1 Study

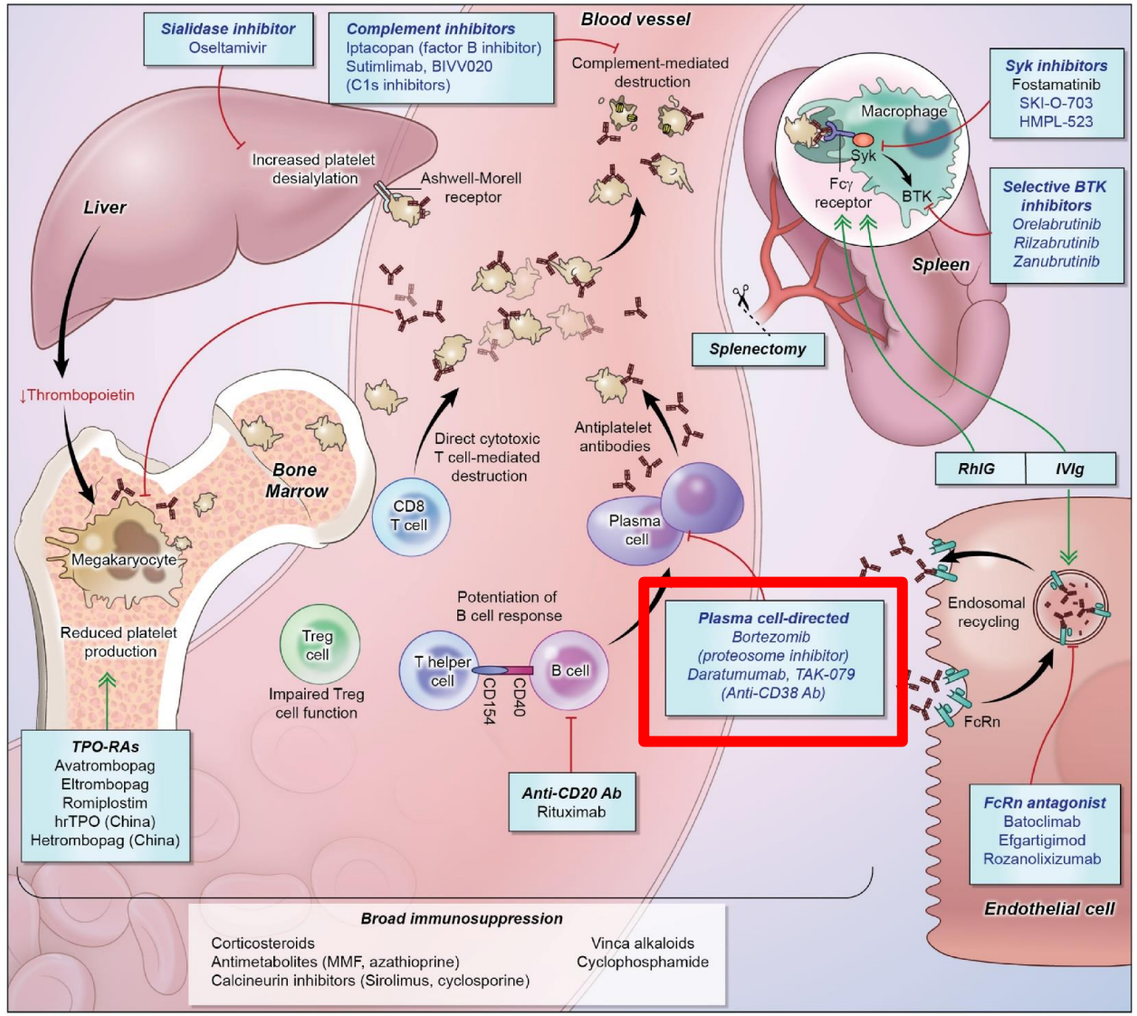
	Sovleplenib (n=126)			Placebo (n=62)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
Any treatment-emergent adverse event	93 (74%)	19 (15%)	13 (10%)	38 (61%)	7 (11%)	8 (13%)
Upper respiratory tract infections	34 (27%)	2 (2%)	0	6 (10%)	0	0
Blood lactate dehydrogenase increased	30 (24%)	0	0	4 (6%)	0	0
COVID-19 infection	29 (23%)	1 (1%)	0	8 (13%)	0	0
Haemorrhage subcutaneous	24 (19%)	0	0	8 (13%)	0	0
Hyperuricaemia	23 (18%)	0	0	3 (5%)	0	0
Hypokalaemia	22 (17%)	0	1 (1%)	3 (5%)	0	0
Rash	21 (17%)	1 (1%)	0	1 (2%)	0	0
Anaemia	20 (16%)	2 (2%)	1 (1%)	4 (6%)	4 (6%)	0
Aspartate aminotransferase increased	20 (16%)	0	0	1 (2%)	0	0
Occult blood positive	20 (16%)	0	0	9 (15%)	0	0
Abnormal liver function	17 (13%)	0	0	2 (3%)	0	0
Alanine aminotransferase increased	16 (13%)	3 (2%)	0	1 (2%)	0	0
Gingival bleeding	16 (13%)	0	0	7 (11%)	0	0
Neutrophil count decreased	15 (12%)	4 (3%)	0	0	0	0
Blood creatine phosphokinase increased	14 (11%)	0	0	2 (3%)	0	0
Hypertension	11 (9%)	4 (3%)	0	3 (5%)	0	0
Headache	9 (7%)	0	0	5 (8%)	1 (2%)	0
Leukopenia	7 (6%)	1 (1%)	0	1 (2%)	0	0
Neutropenia	7 (6%)	1 (1%)	0	1 (2%)	0	0

Hu et al., *Lancet Haematol* 2024

Cevidoplenib in ITP

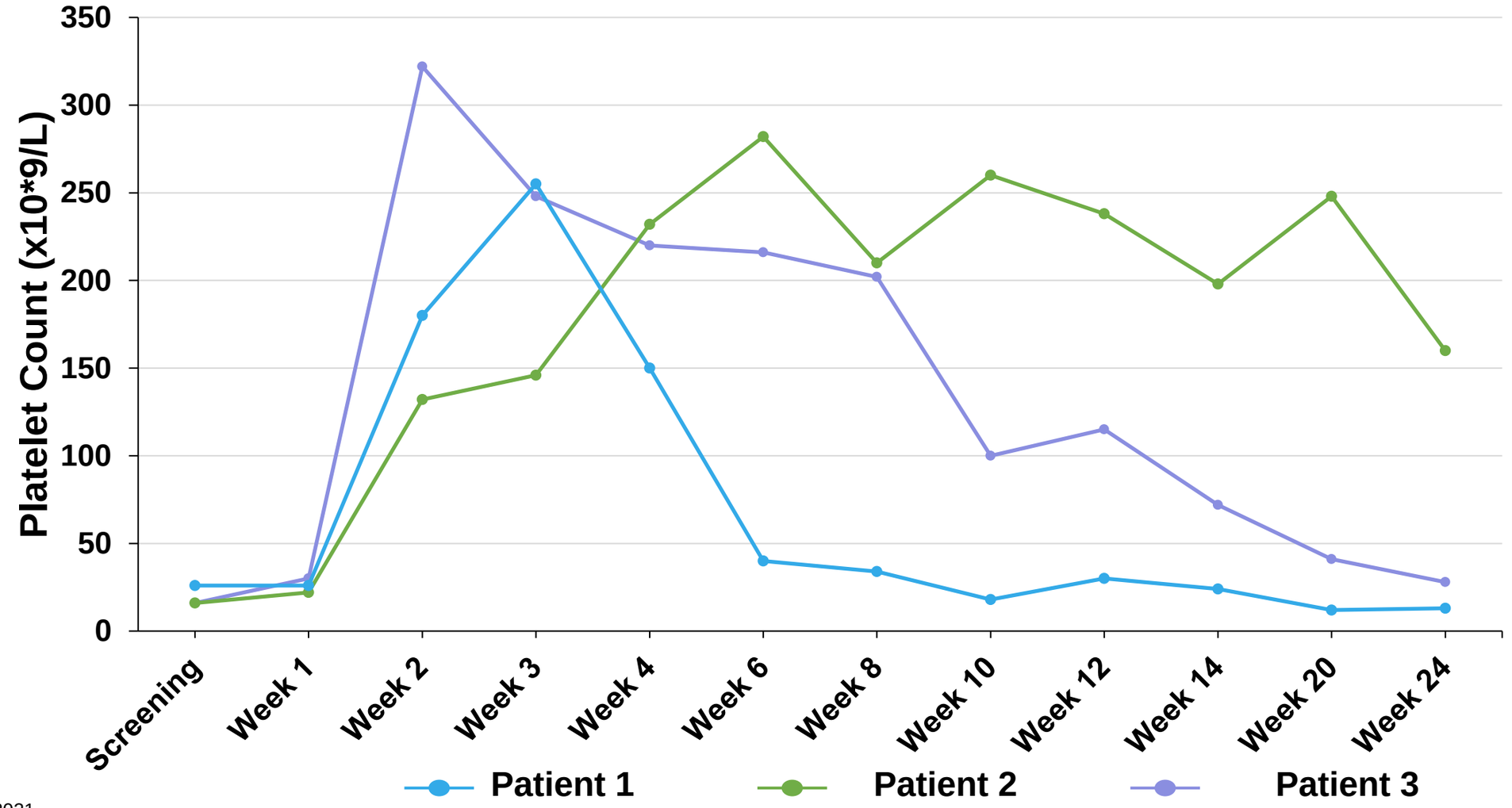
- International randomized phase 2 trial (NCT04056195) has been completed
- Positive topline results announced in press release form
- Full results from this trial are awaited

Novel Agents for ITP: Anti-CD38 Antibodies



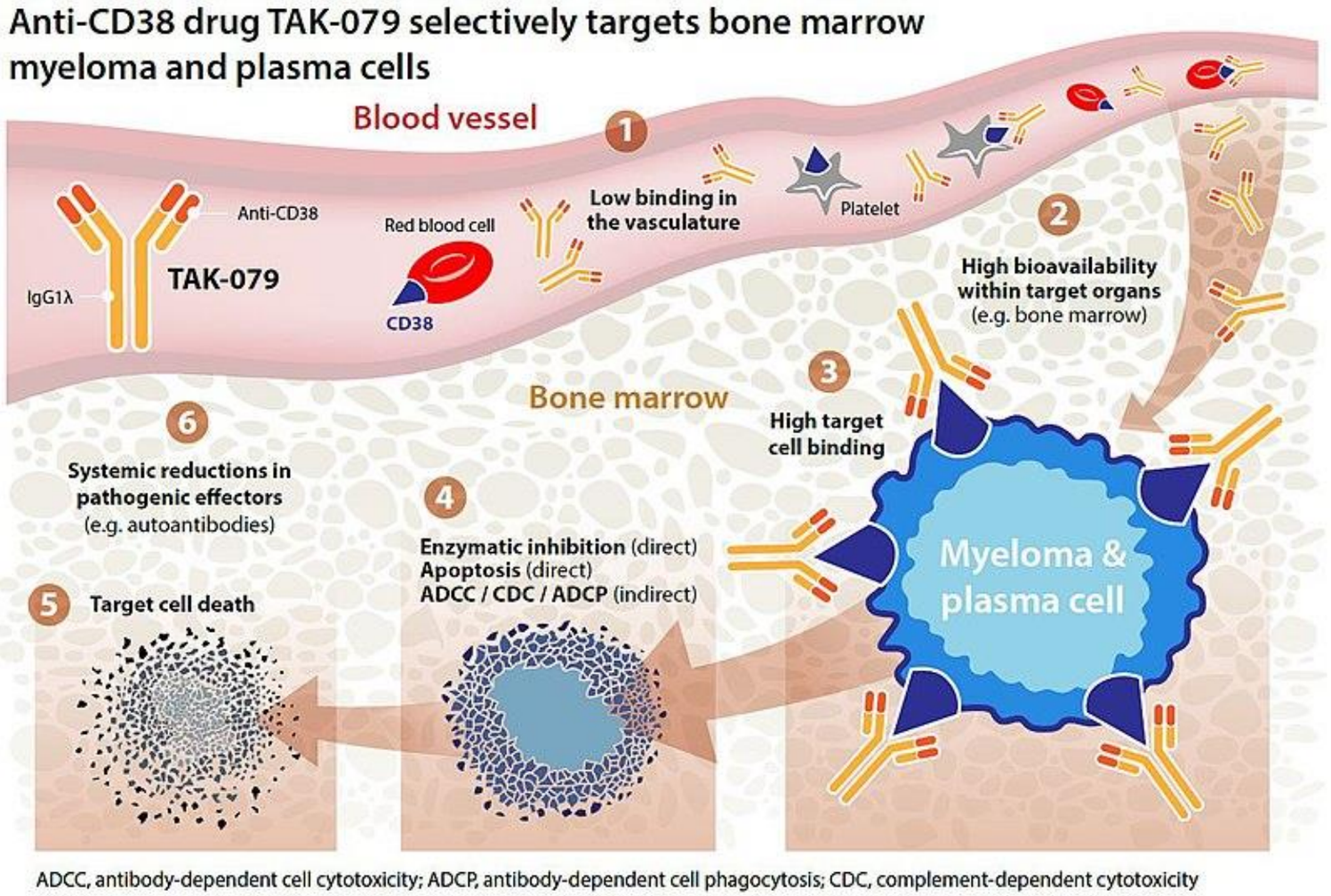
Jiang et al., *Transfusion Med Reviews* 2022

Daratumumab to Treat ITP



Tsykunova et al., *Blood* 2021

Mezagitamab (TAK-079) to Treat ITP



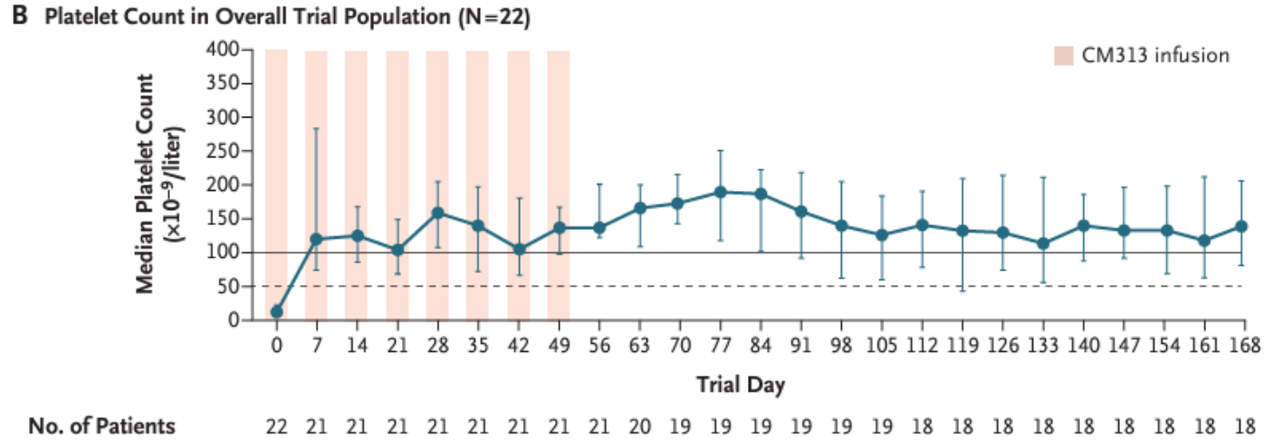
Kuter et al., ISTH 2024

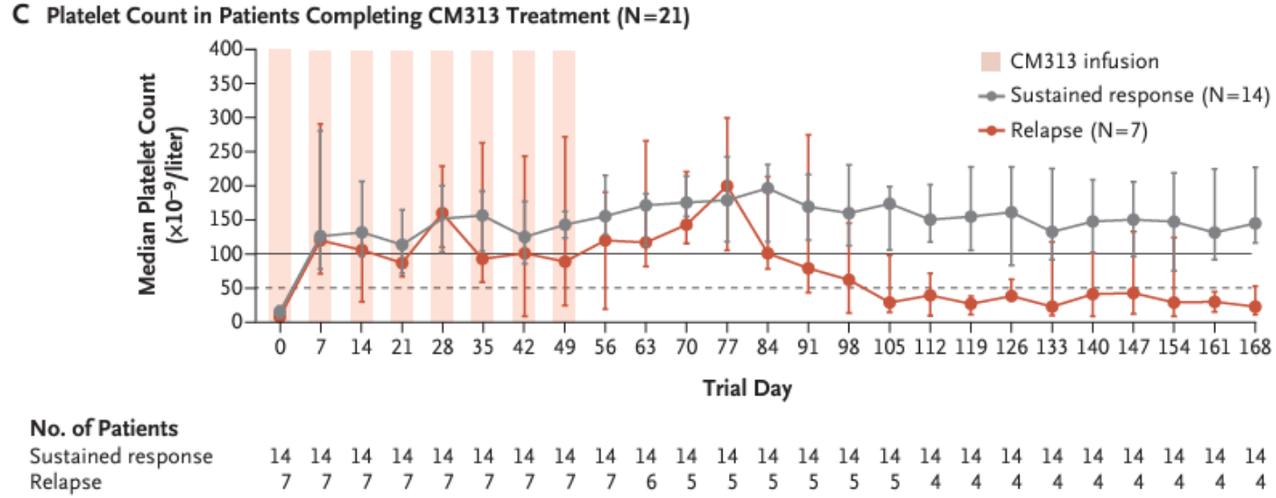
ISTH June 2024: Positive phase 2 randomized, PBO-controlled mezagitamab study in ITP

Response rate ~80%, favorable side-effect profile

Ph3 ongoing

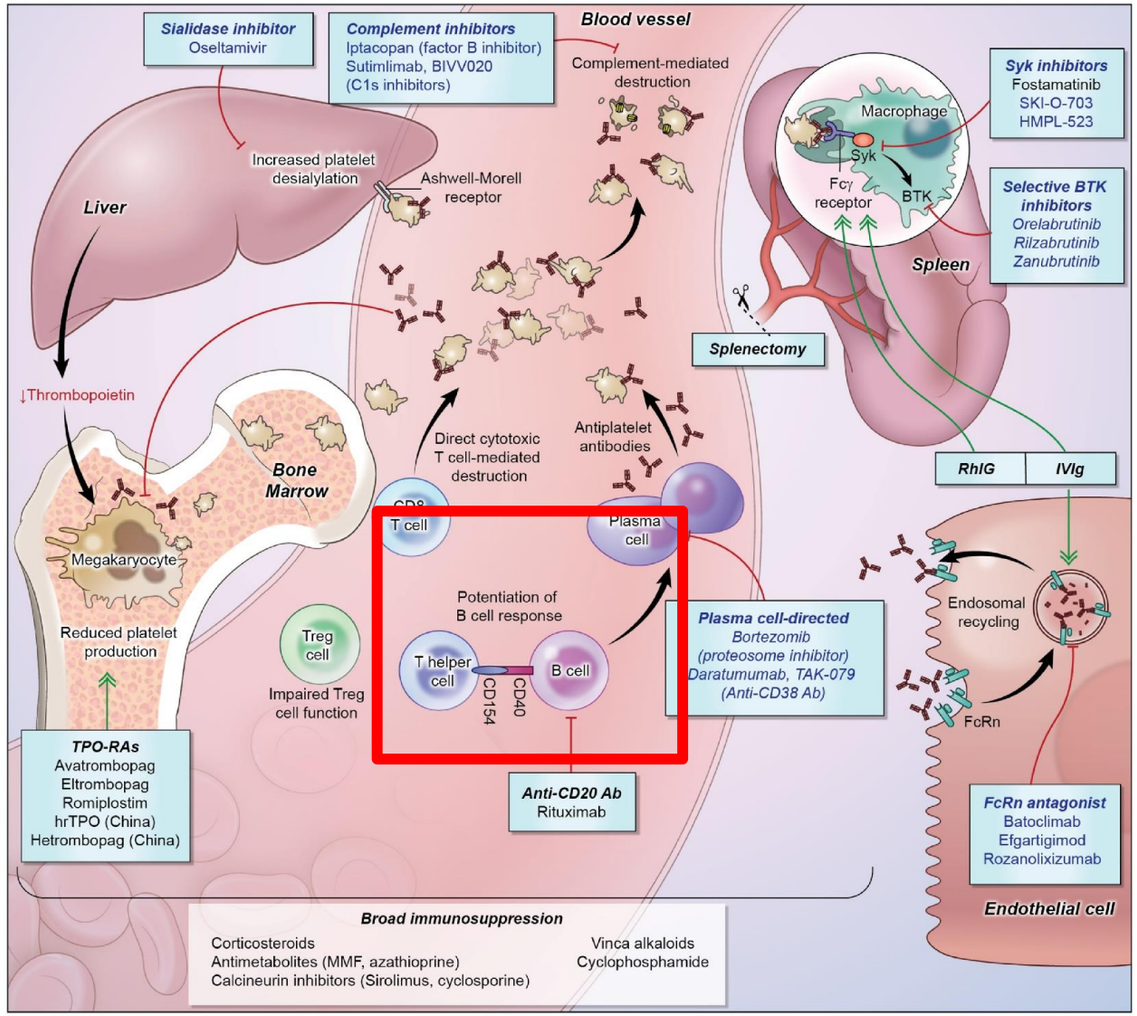
CM313 to Treat ITP





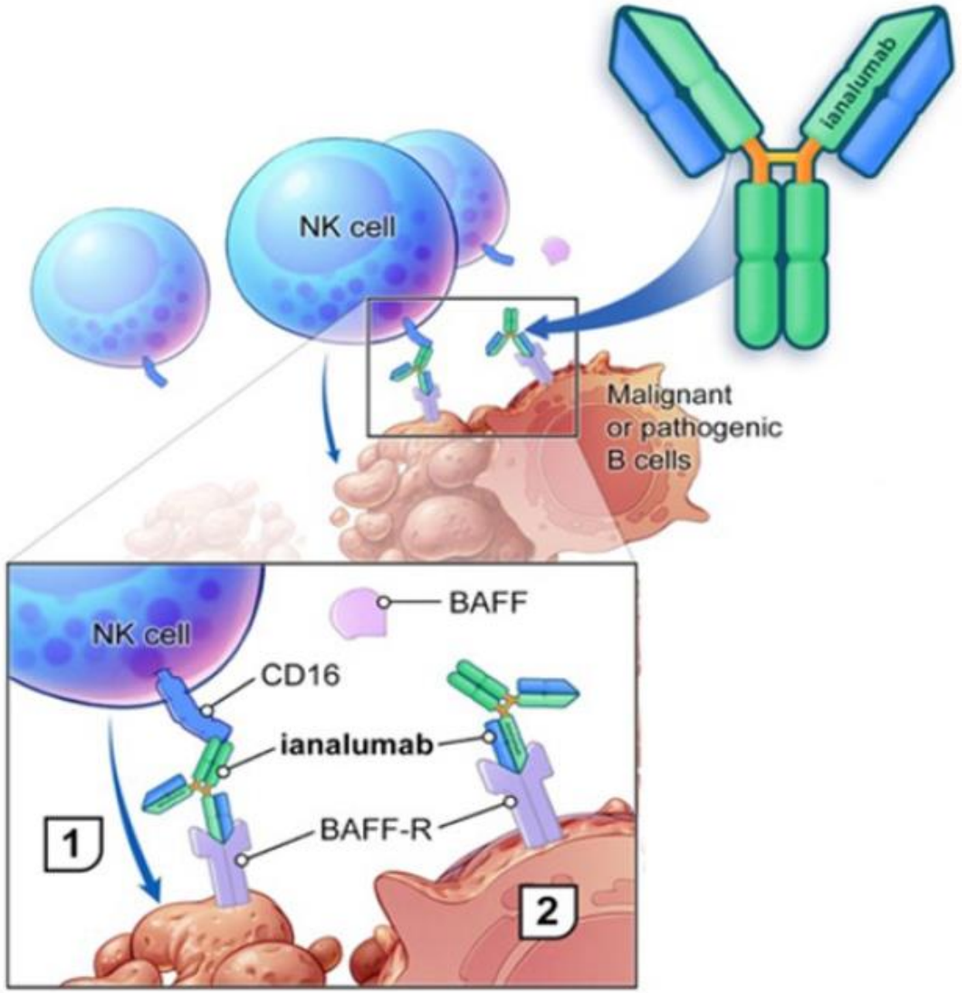
Chen et al., *NEJM* 2024

Novel Agents for ITP: BAFF-R and BAFF/APRIL Inhibition



Jiang et al., *Transfusion Med Reviews* 2022

Ianalumab (VAY736) in ITP



Dual mechanism of action:

1) BAFF-R blockade

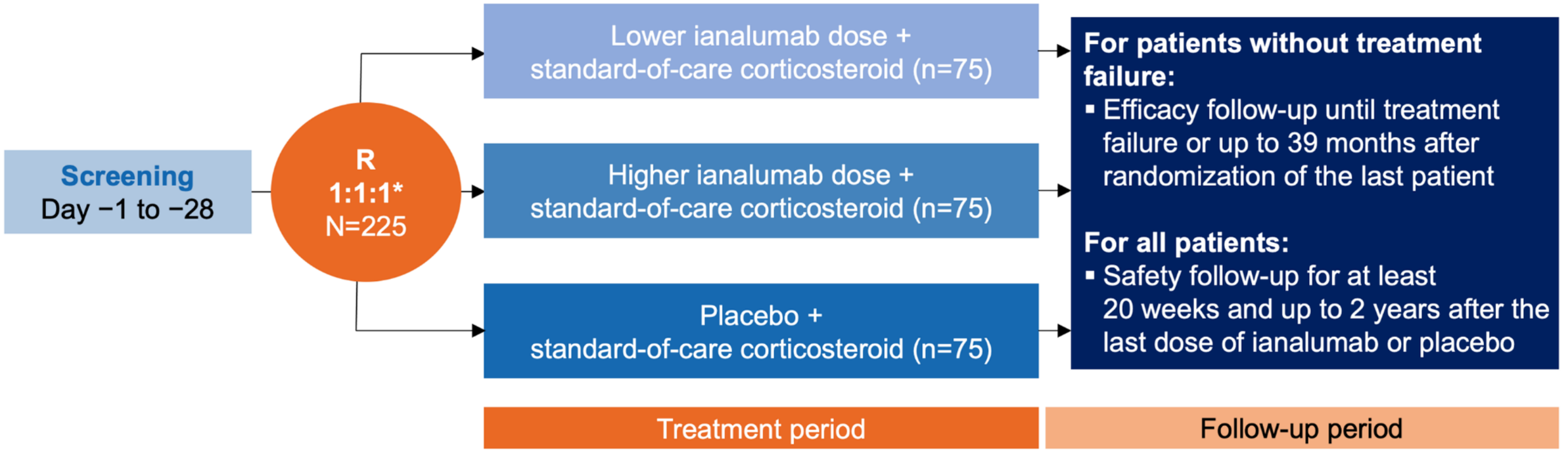
- Prevents activation and differentiation of B-cells and induction of long-lived plasma cells
- May overcome rebound/resistance mechanisms (including loss of CD20, BAFF-driven B-cell hyperactivation)

2) Enhanced ADCC-mediated B-cell depletion

- Provides more potent, sustained B-cell depletion in blood and tissues

Ianalumab (VAY736) in ITP: VAYHIT1 Study

Figure. VAYHIT1 study design

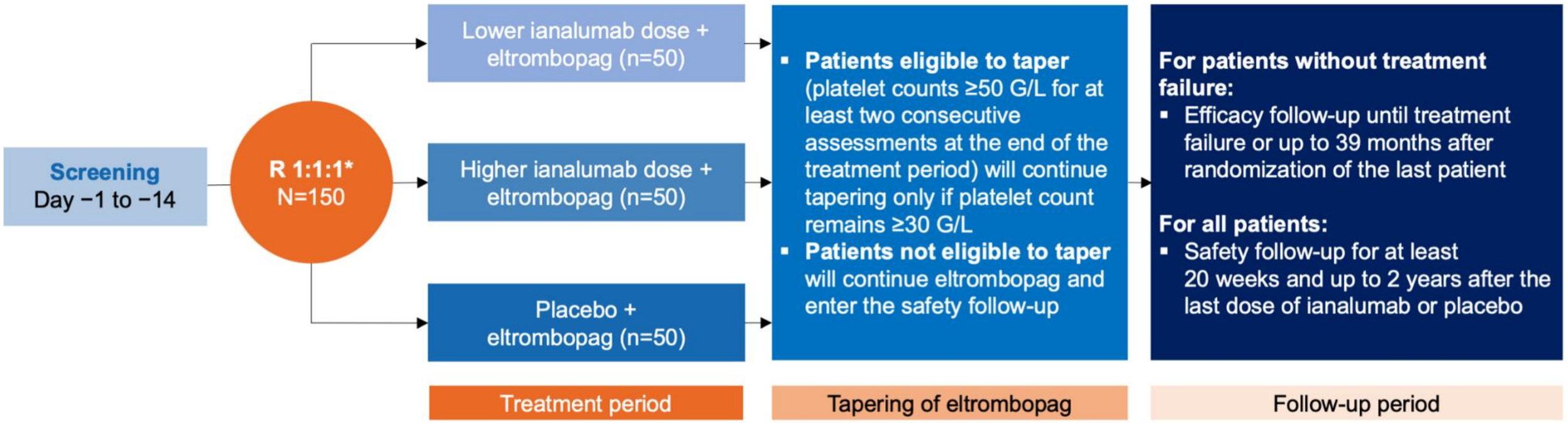


*Randomization will be stratified by the type of first-line corticosteroid treatment (predniso[lo]ne or dexamethasone)
R, randomization

Cooper et al. *HemaSphere* 2023

Ianalumab (VAY736) in ITP: VAYHIT2 Study

Figure. VAYHIT2 study design



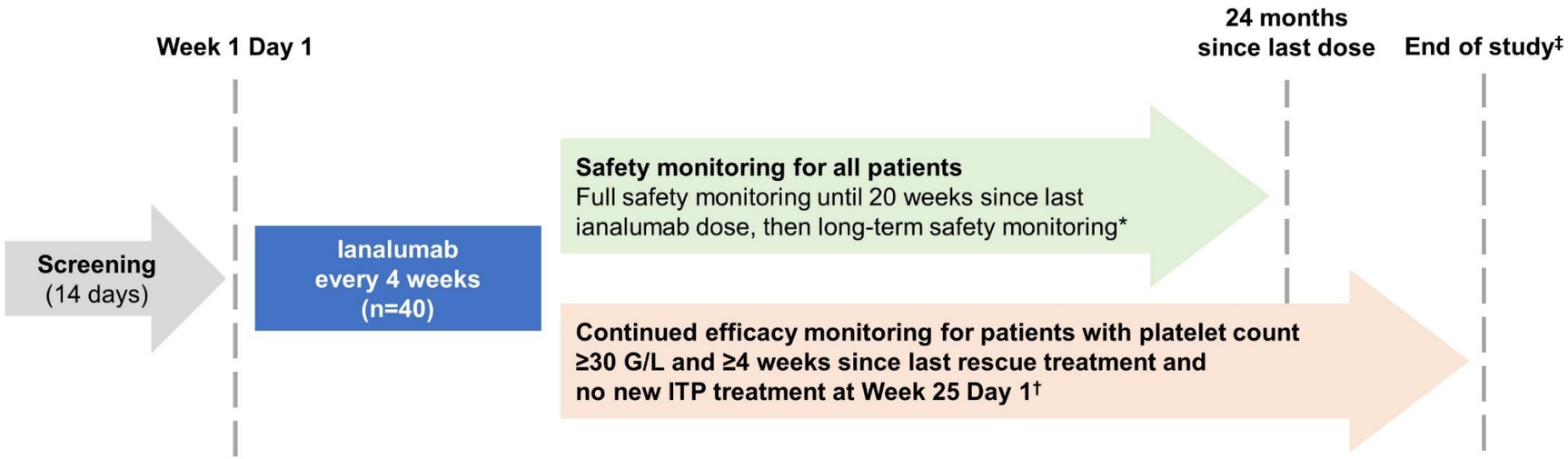
*Randomization will be stratified by the time since ITP diagnosis (newly diagnosed versus persistent and chronic ITP)
ITP, immune thrombocytopenia; R, randomization

Zaja et al. *HemaSphere* 2023

Ianalumab (VAY736) in ITP: VAYHIT3 Study

VAYHIT3 Study Design

Figure. VAYHIT3 trial design



*Long-term safety monitoring includes only the collection of AEs and SAEs potentially related to B-cell depletion or assessed by the investigator as related to AMPs and SAEs assessed by the investigator as possibly related to ianalumab. If a different B-cell-depleting therapy starts, AEs and SAEs assessed by the investigator as related to AMPs and SAEs assessed by the investigator as possibly related to ianalumab will be collected; †Efficacy monitoring will end if, after Week 25 Day 1, the patient's platelet count is <30 G/L, they start a new line of ITP therapy or they require a rescue treatment; ‡The study will end once all patients have completed 24 months of safety follow-up since their last dose of ianalumab or discontinued from the study earlier

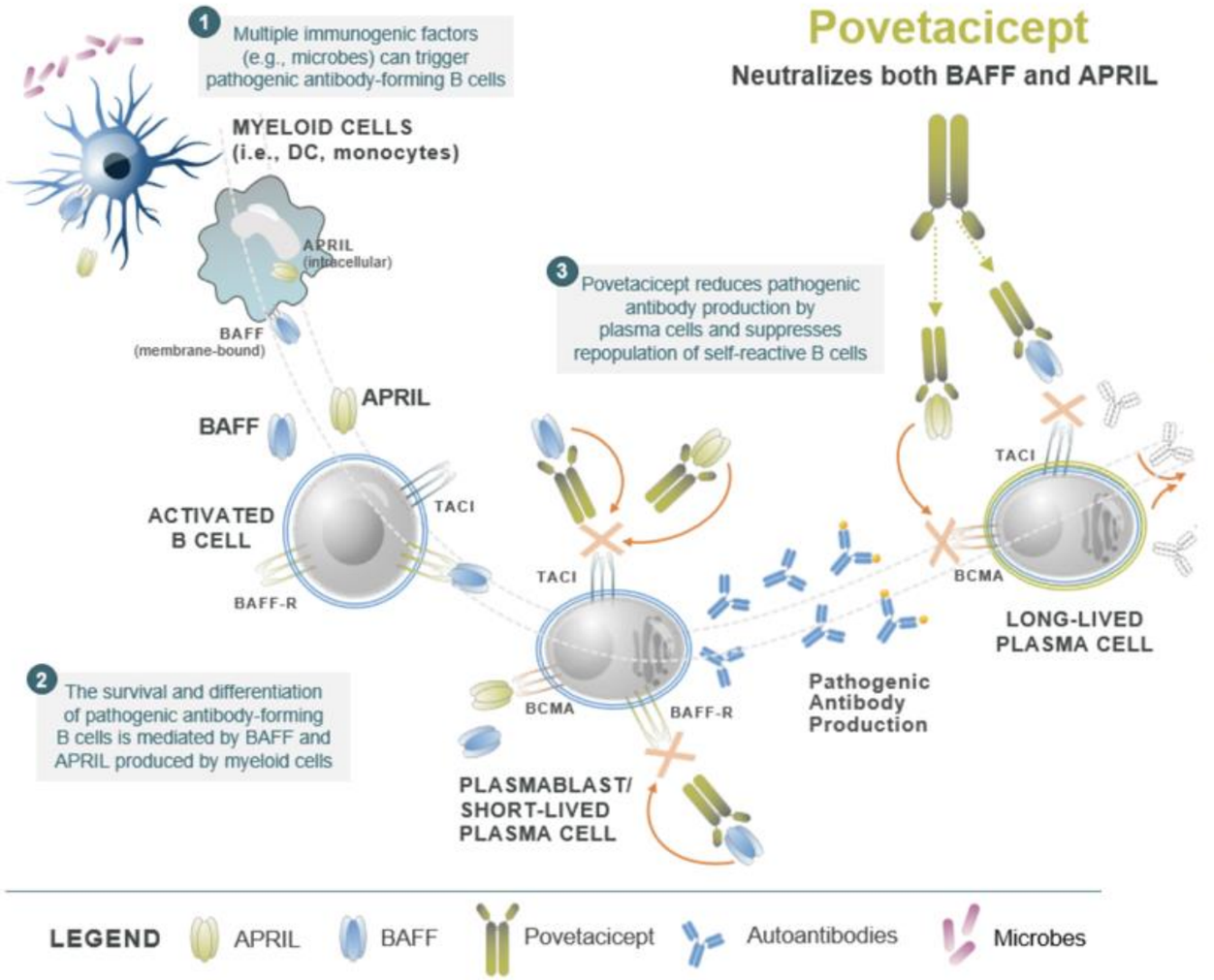
AE, adverse event; AMP, auxiliary medicinal product; ITP, immune thrombocytopenia; SAE, serious adverse event

VAYHIT3 Interim Results ASH Abstract

- 39 patients enrolled by data interim analysis cutoff date, 10 completed 6 months of therapy (or discontinued by data cutoff)
- 8 completed 4 infusions, 2 discontinued
- Median time from diagnosis 3 years, but heavily pretreated
- 5 patients (50%) achieved confirmed response (Plt ≥50K at ≥2 assessments at least 7 days apart), 4 of which achieved this within the first 8 weeks
- Mild-to-moderate infections and infusion reactions noted

Kuter et al., *ASH* 2024

Povitacicept (ALPN-303) in ITP



Blair et al., *ACR Convergence* 2023

Povitacicept (ALPN-303) in ITP: RUBY-4 Study

RUBY-4: Phase 1b Autoimmune Cytopenia Basket

Study Populations

- Adults; active cytopenia
- ITP ≥ 3 months; sustained plt < 30,000 / mL; ≥ 2 prior treatments
- wAIHA or CAD ≥ 3 months; sustained Hb ≤10 g/dL; ≥ 2 prior treatments
- Stable immuno-suppression, if applicable
- Excluded: Secondary cytopenia (e.g., systemic autoimmune disease, infection, malignancy), Evans Sx

ITP: 240 mg SC Q4W (N=7-14)

Warm AIHA: 240 mg SC Q4W (N=7-14)

Cold Agglutinin: 240 mg SC Q4W (N=7-14)

- Open-Label, 2-Stage Fleming Design
- Primary treatment of 24 weeks, optional 24 week extension
- Consider dose de-escalation based on safety/tolerability

AIHA Autoimmune Hemolytic Anemia
ITP Immune Thrombocytopenia

Study Endpoints

- Disease activity – response and durable response; use of rescue therapy
- Change in disease-related antibodies, e.g., anti-platelet, anti-RBC
- Safety, PK, ADA
- PD/biomarkers – Soluble ligands (APRIL, BAFF); serum IgG, IgA, IgM; circulating B cell subsets

Questions?