2ND meeting of the European Research Consortium on ITP

NEW INSIGHTS INTO IMMUNE THROMBOCYTOPENIA

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How BTK inhibition may change the therapeutic approach in ITP

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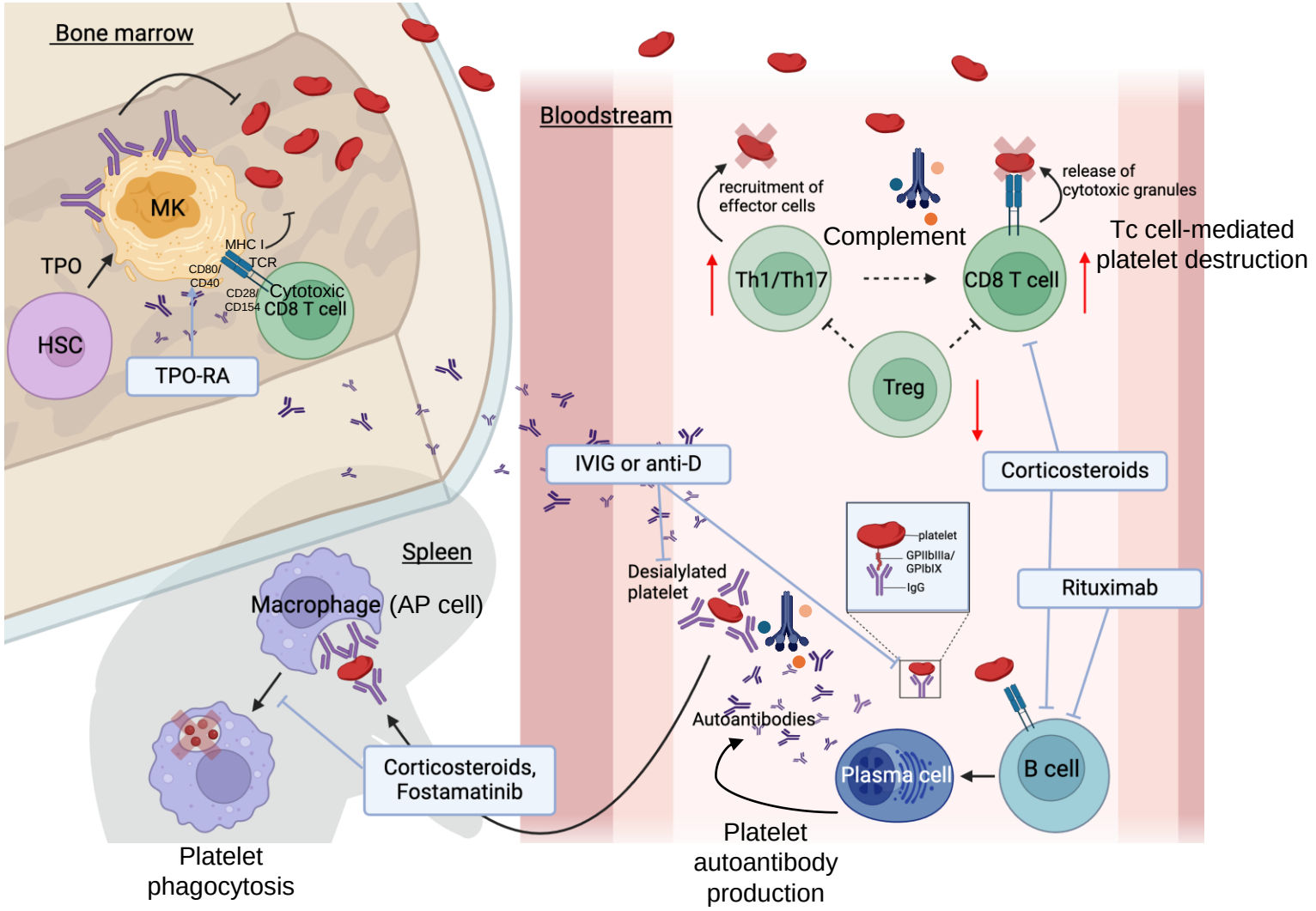
Disclosures of

Nichola Cooper

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis	x					x	
Sanofi						x	
Griffols	x					x	
Argenx	x					x	
Takenda						x	
Sobi						x	

Why is BTK inhibition useful in ITP?



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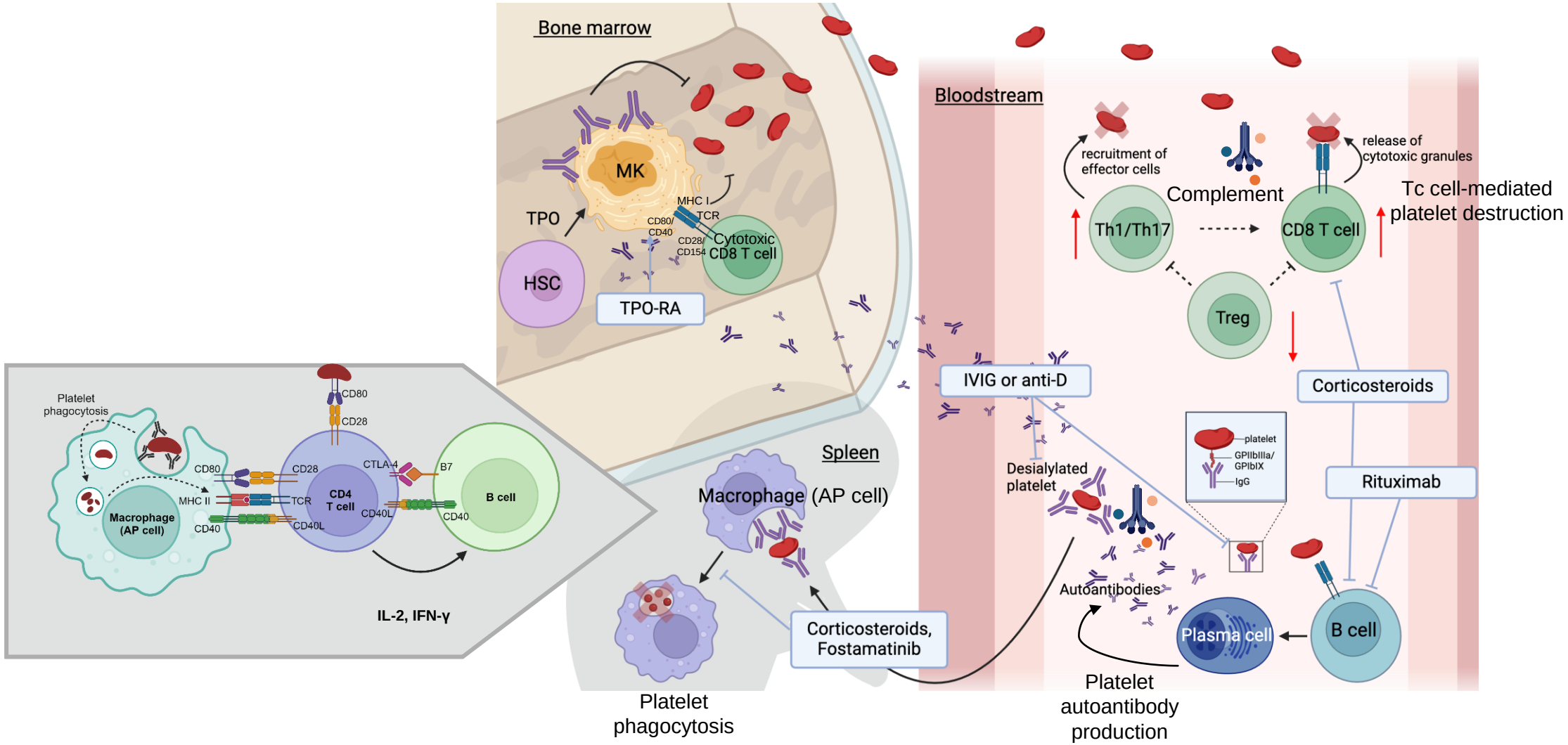
Why is BTK inhibition useful in ITP?



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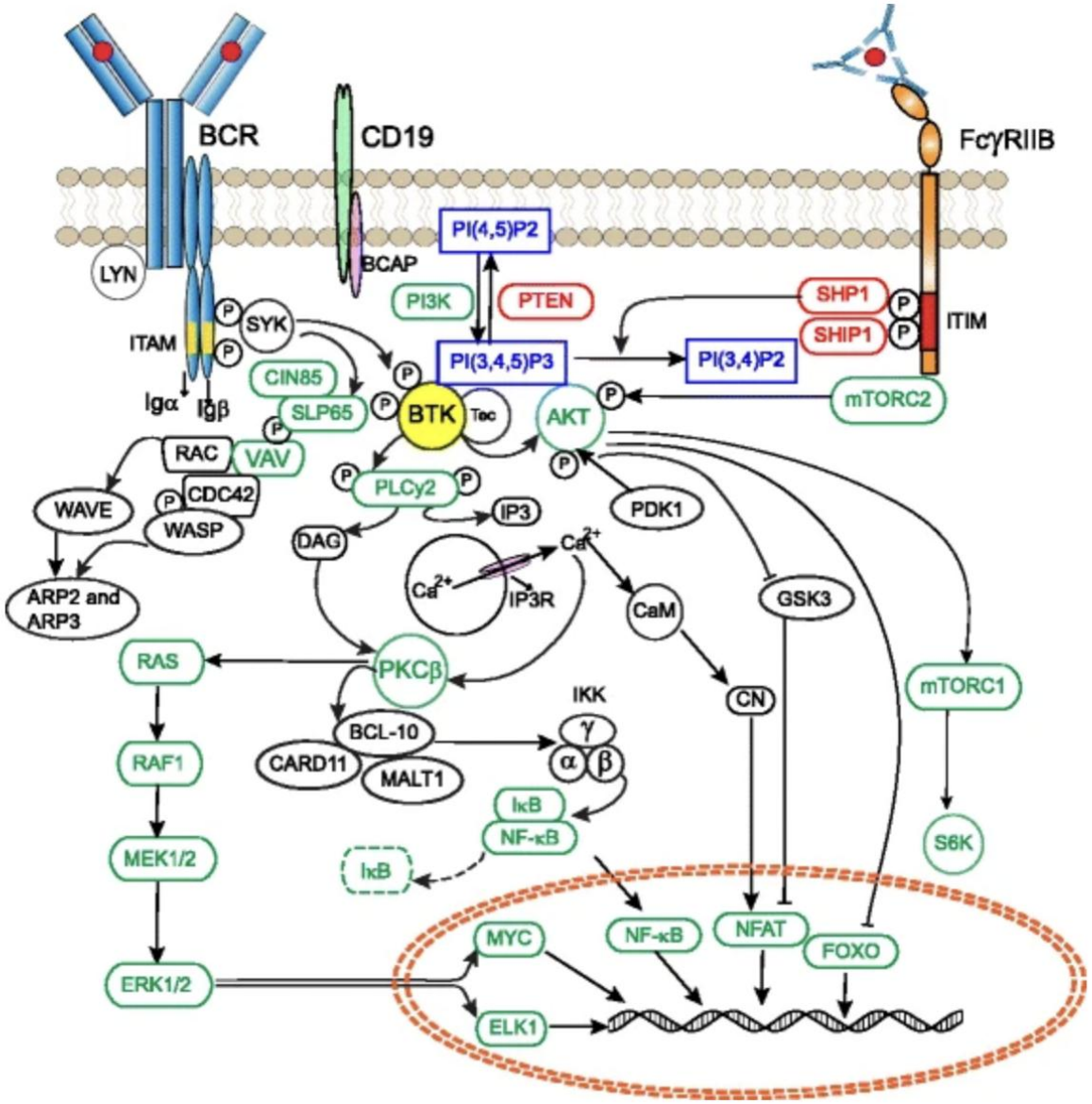
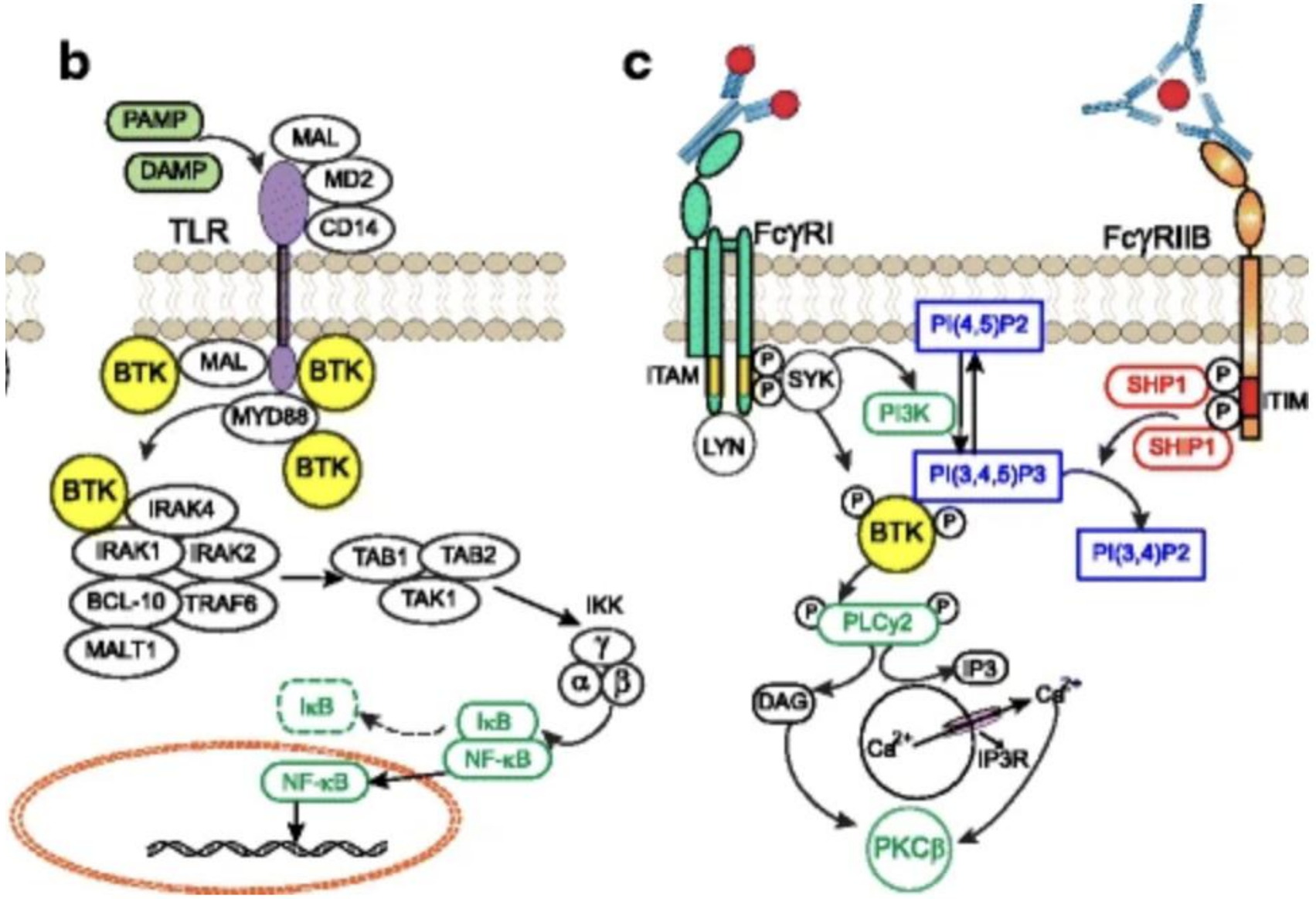
BTK is central to B cell activation



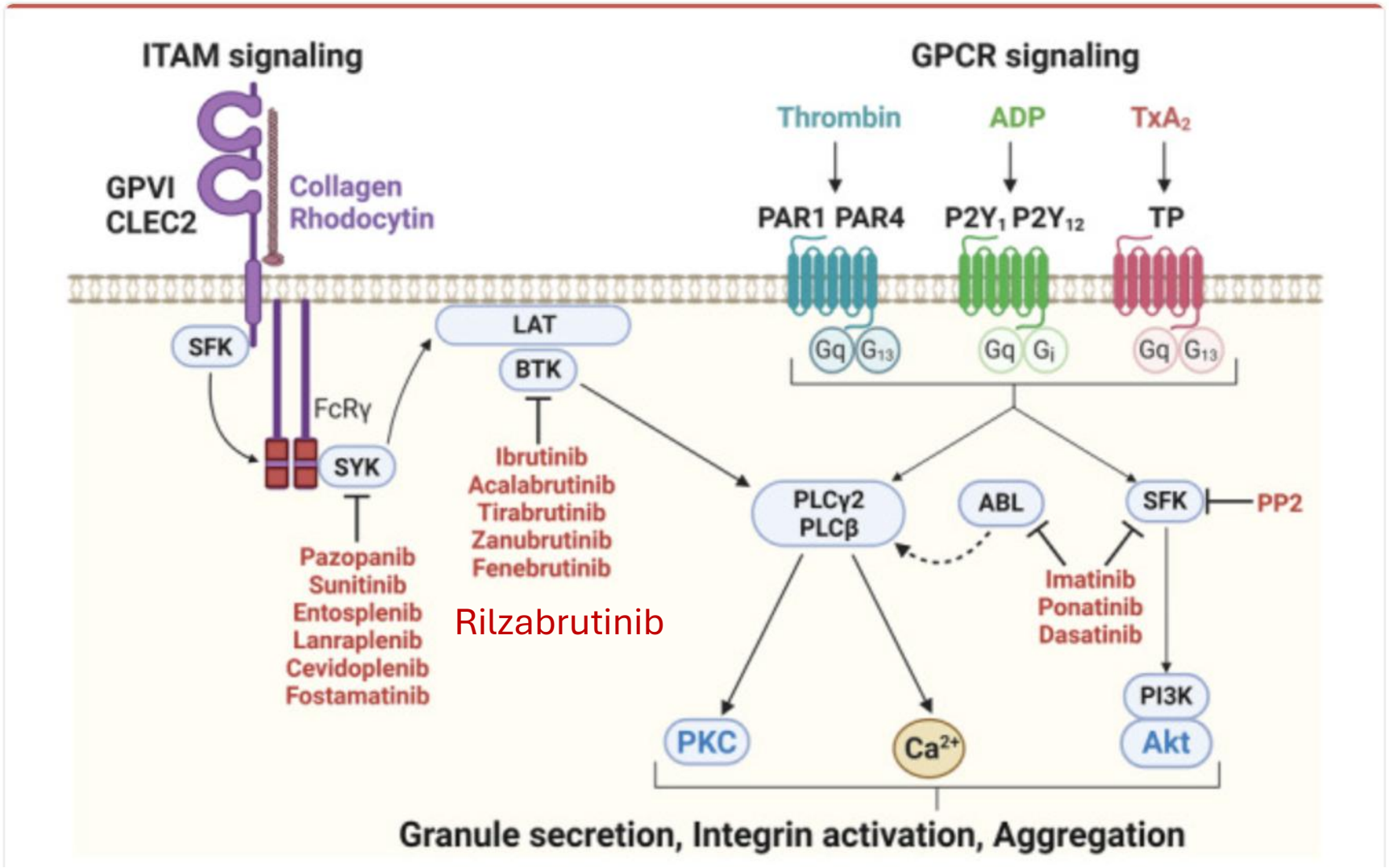
Singh et al Molecular cancer 2018

BTK also central to TLR and FcR activation



Singh et al Molecular cancer 2018

BTK also central in platelet activation



Zheng et al Am J Physiol Cell Physiol 2022

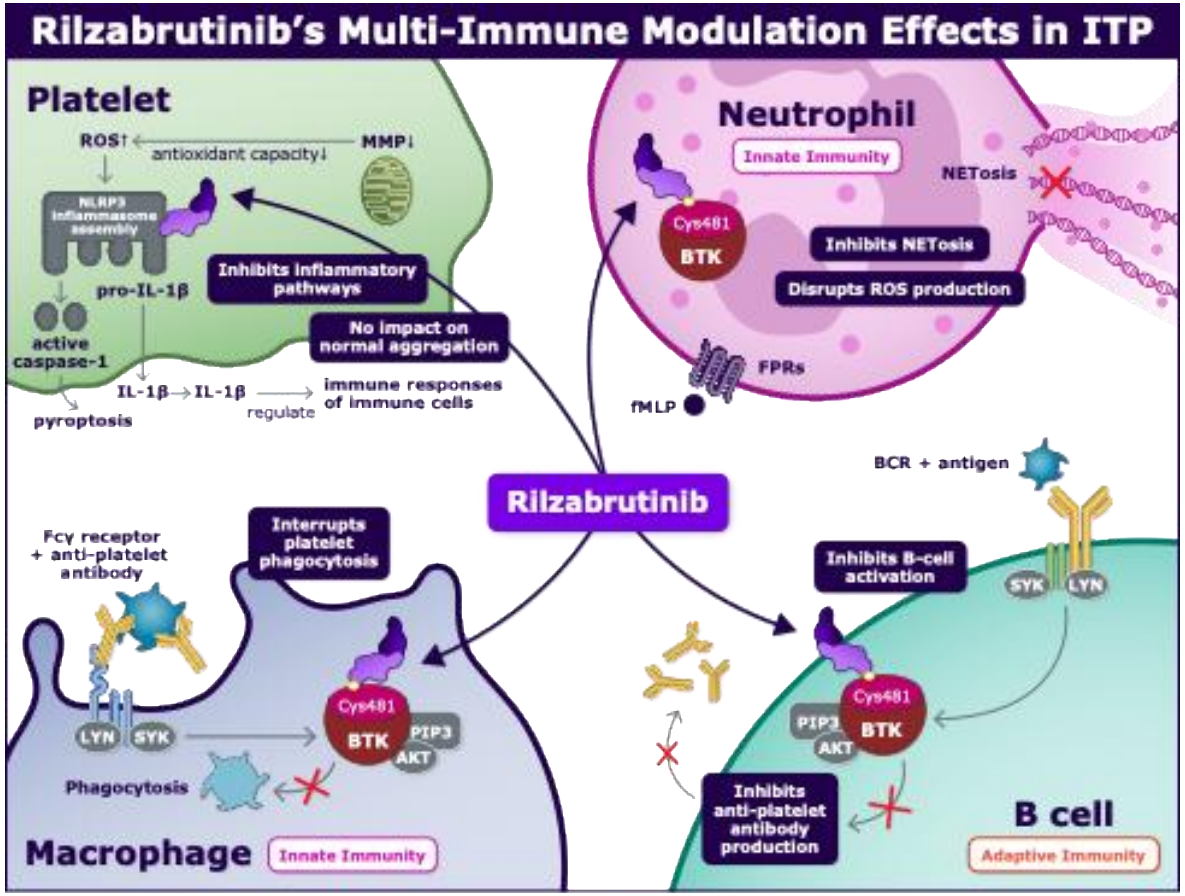
Key features of rilzabrutinib in platelets

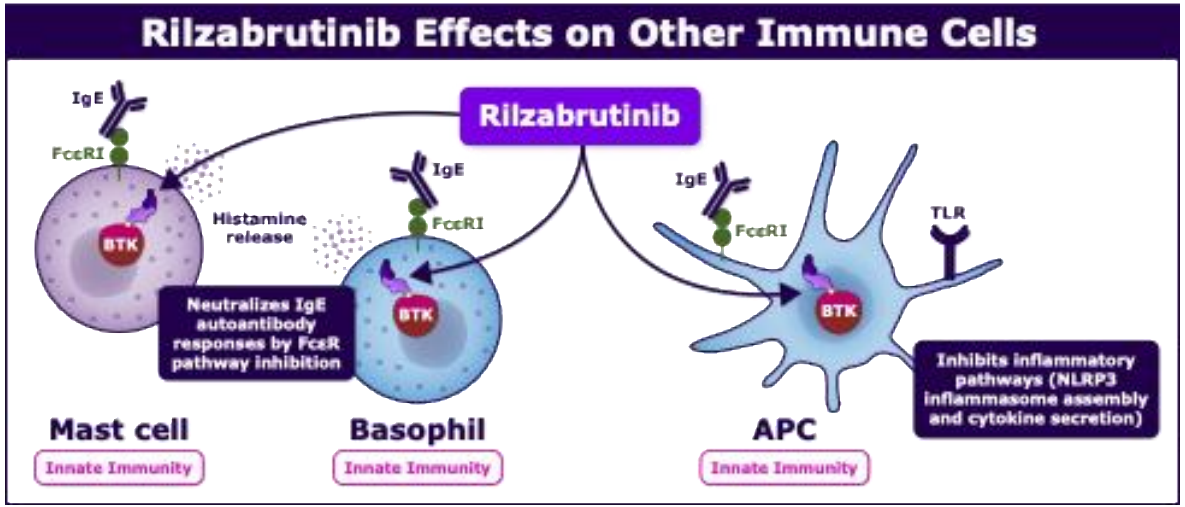
- Targets the ATP-binding domain of BTK through a non-covalent bond-dominated mode making it reversible
- (Unlike traditional covalent BTK inhibitors, which cause sustained suppression of BTK function through irreversible binding),
- Retain the functions of pathways such as G protein-coupled receptors
- Potently inhibits CLEC-2-mediated platelet activation but avoids off-target inhibition of SFKs, thereby preventing bleeding risks associated with SFKs inhibition
- Can reduce venous thrombosis in mice

Liu et al Drug Des Devel Ther 2025

Immune Modulation Mechanisms of Action with Rilzabrutinib[1,2]

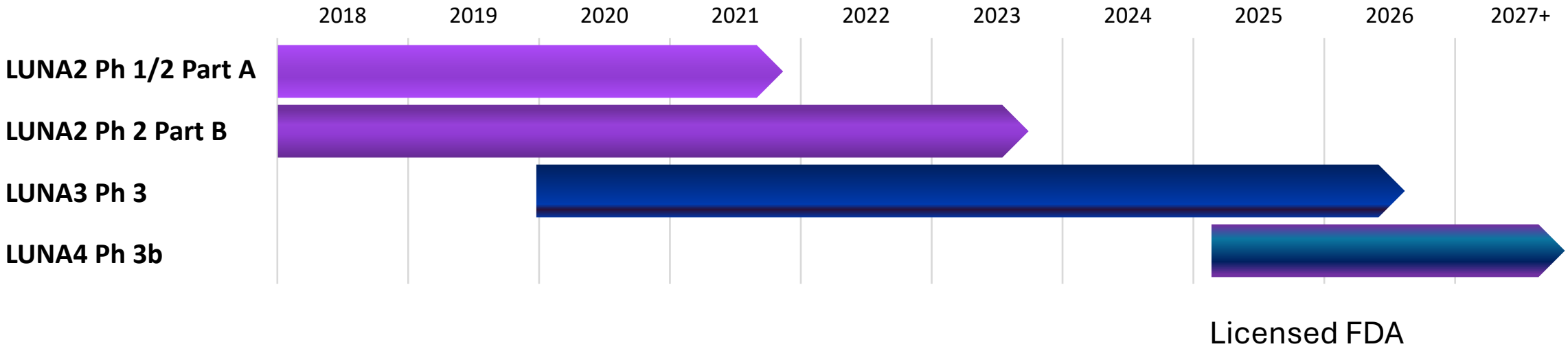
- Inhibits **B-cell** activation and decreases autoantibody production
- Prevents Fcγ receptor-mediated phagocytosis in **macrophages** in the spleen and liver
- Inhibits NLRP3 inflammatory pathways and CLEC-2–mediated **platelet** function and prevents thromboinflammation
- Inhibits NETosis in **neutrophils** and disrupts ROS production (which also prevents thromboinflammation)
- No impact on platelet aggregation
- Can also inhibit mast cells, basophils and APCs





1. Langrish CL, et al. *J Immunol*. 2021;206:1454-1468. 2. Daak A, et al. *Blood.* 2024;144:2482-2483.

Clinical Trials of Rilzabrutinib in ITP



Luna2: phase 2 results

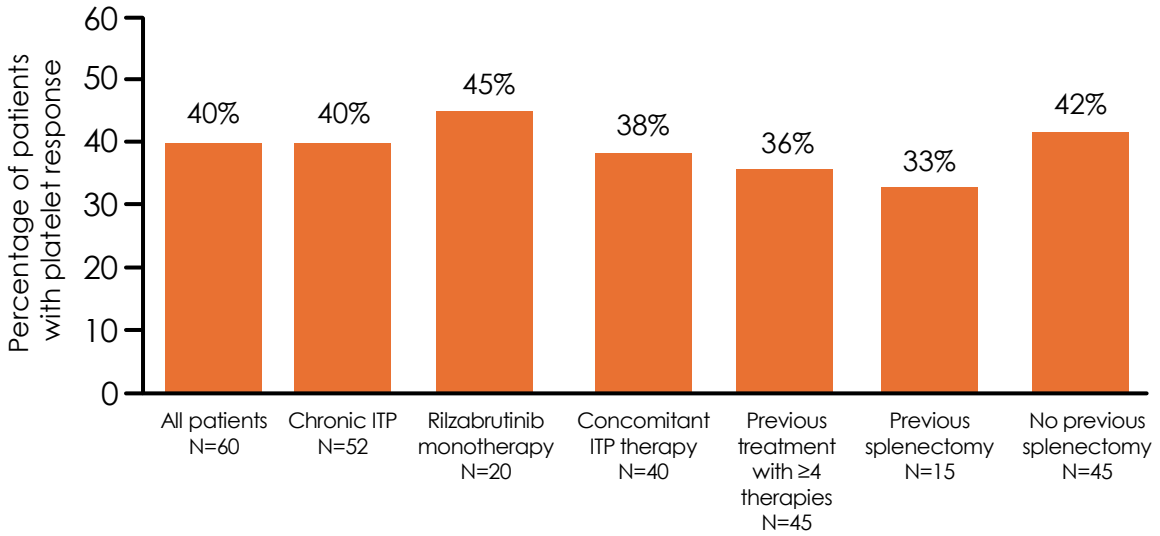
Platelet response in 43% of patients with previously treated persistent or chronic ITP

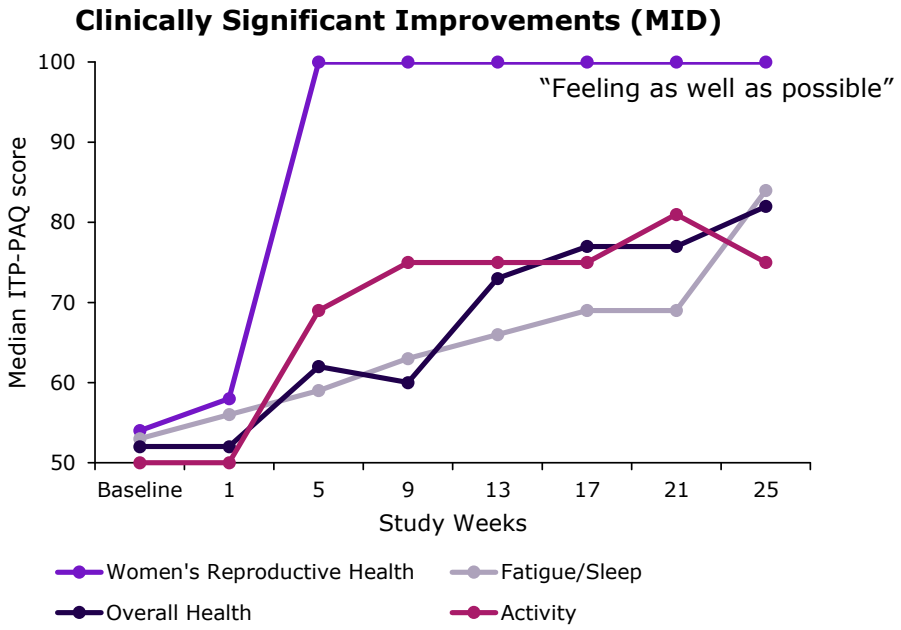
Well tolerated

No increase in bleeding

No increase in thrombosis

Improved HRQoL (ITP-PAQ) including fatigue



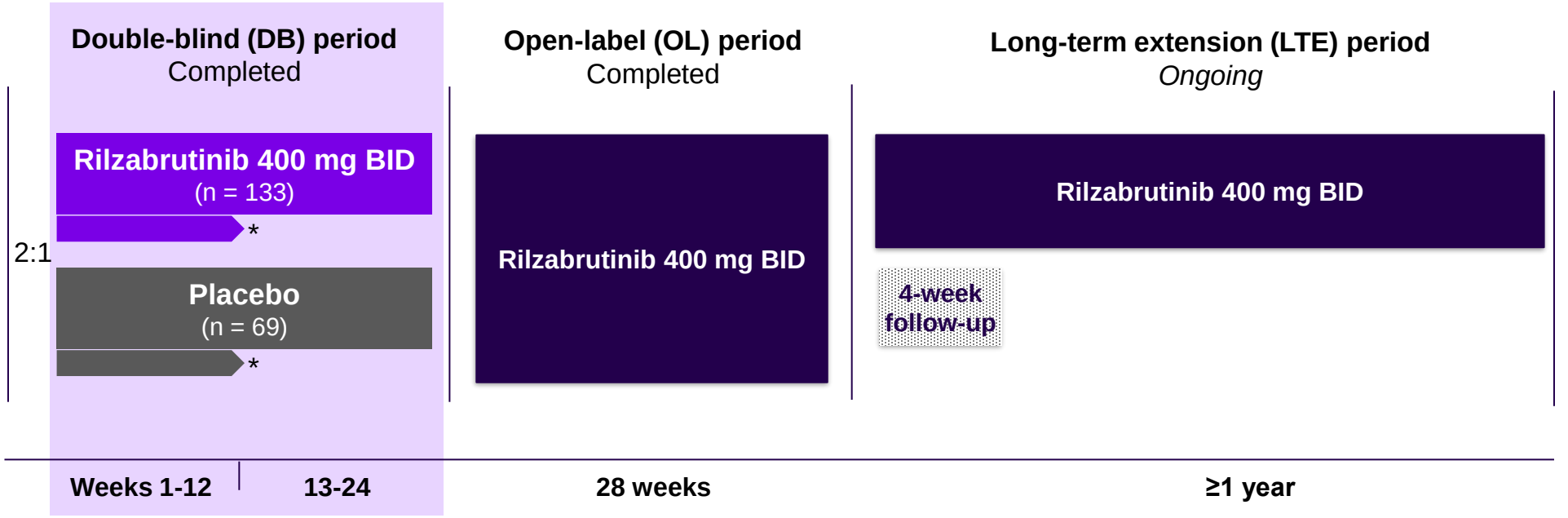


Kuter DJ, et al. *N Engl J Med*. 2022;386:1421-1431, Kuter DJ, et al. *Blood Adv.* 2024;8:1715-1724, Cooper N, et al. *Am J Hematol*. 2025;100:439-449.

LUNA 3 Study Design

Adults with persistent/chronic primary ITP

- Prior IVIg/anti-D or CS
- Qualifying platelets <30×10^9/L
- Allowed stable concomitant CS and/or TPO-RA

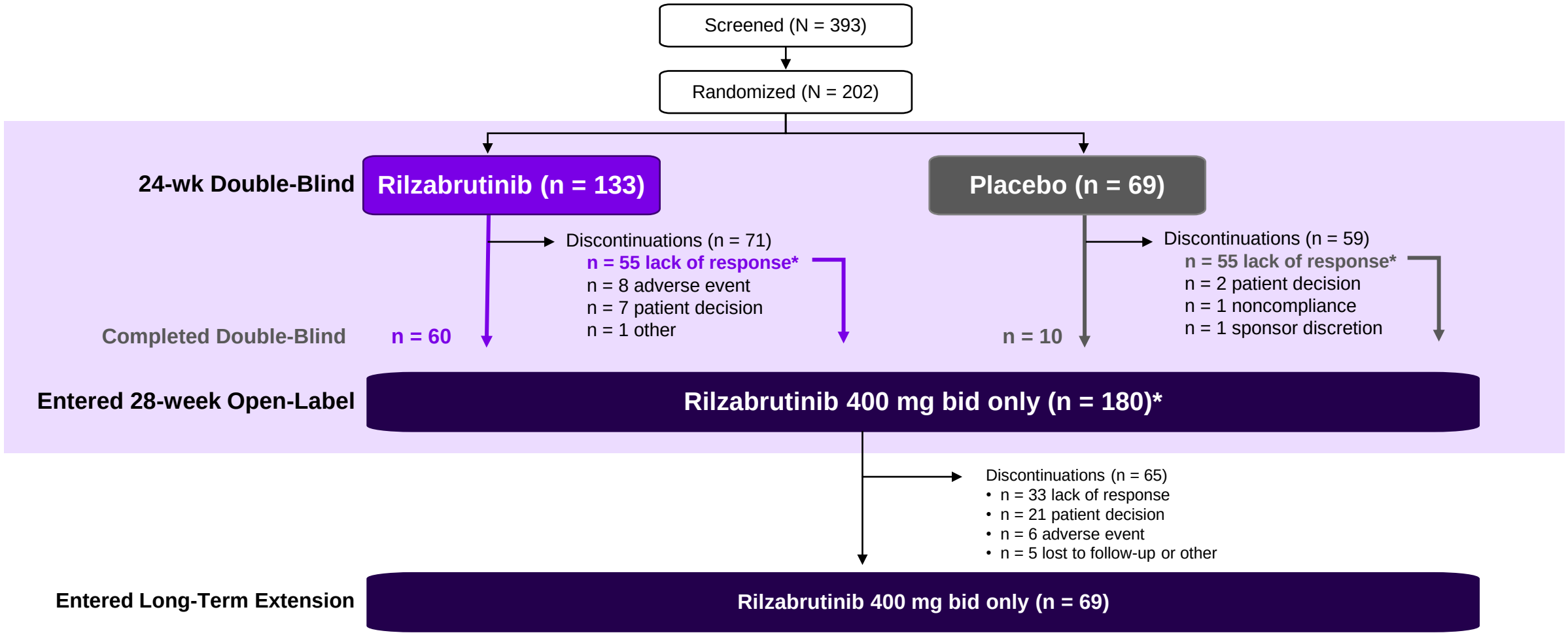


Double-blind period analyses

- **Durable response**
- **ITP-PAQ**

NCT04562766; EudraCT 2020-002063-60. BID, twice daily; CS, corticosteroids; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.
*Non-responders: option to discontinue or proceed to OL on rilzabrutinib only. Some non-responder patients may have had >12 weeks of treatment during the DB period.

LUNA3 RCT: Patient Disposition



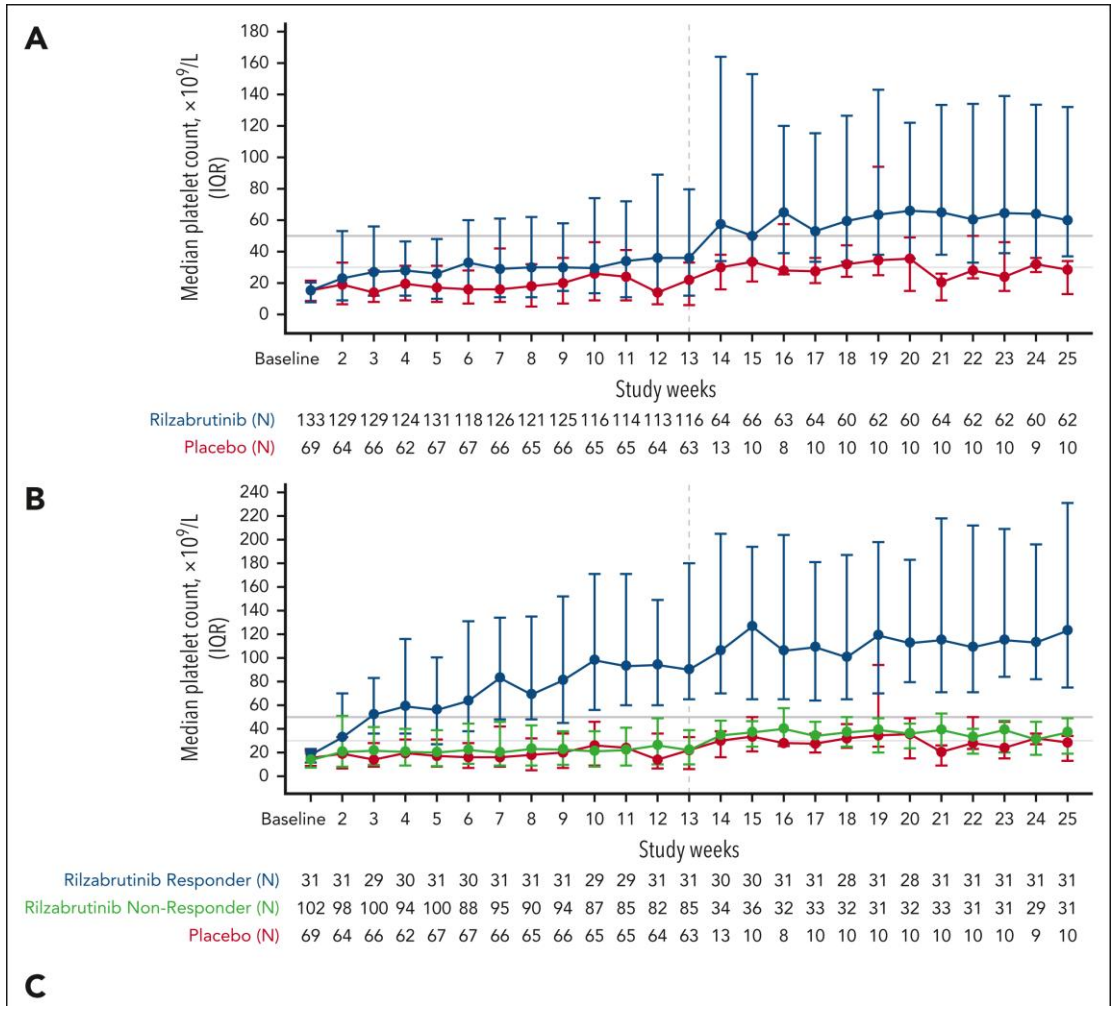
Data cutoff 15 Oct 2024. *Included n = 115 rilzabrutinib and n = 65 placebo total patients from the double-blind period. Patients with lack of response per protocol could transition to open-label directly on rilzabrutinib or discontinue the study.

Baseline Characteristics and Prior/Concomitant Therapy Luna 3

Characteristic	Double blind period Rilzabrutinib and Placebo (N = 202)
Median age, years (range)	47 (18-80)
Female, n (%)	127 (63)
Median duration of ITP, years (range)	7.7 (0.3-52.2)
Median platelet count, $\times 10^9$/L (range)	15 (1-54)
Median number of unique prior ITP therapies (range)	4 (1-15)
Number of prior ITP therapies, n (%)	
1 to 4	109 (54)
≥5	93 (46)
Splenectomy, n (%)	56 (28)
Rilzabrutinib study treatment	
Monotherapy	76 (38)
Plus concomitant CS and/or TPO-RA	126 (62)

David J. Kuter et al Blood, 2025

Luna 3: RCT of rilzabrutinib results



Primary end point, durable platelet response (platelet count ≥50 × 10^9/L for ≥two-thirds of ≥8 of the last 12 of 24 weeks without rescue therapy),

31 (23%) rilzabrutinib vs 0 placebo patients (P < .0001)

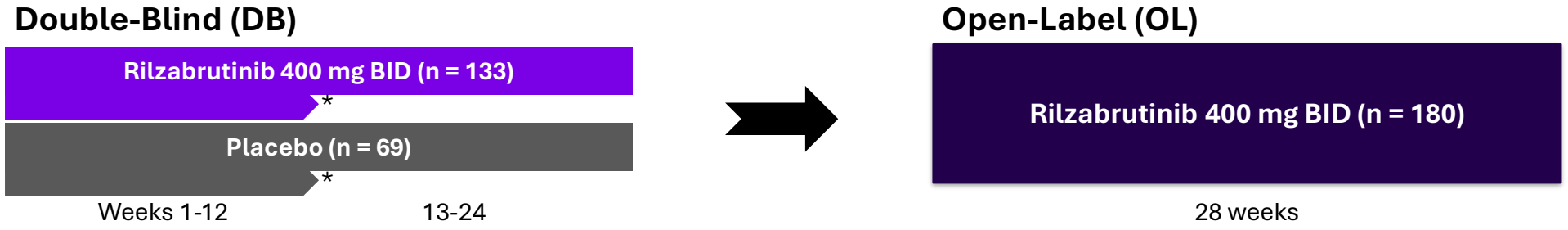
Median time to first platelet response 15 days in rilzabrutinib responders.

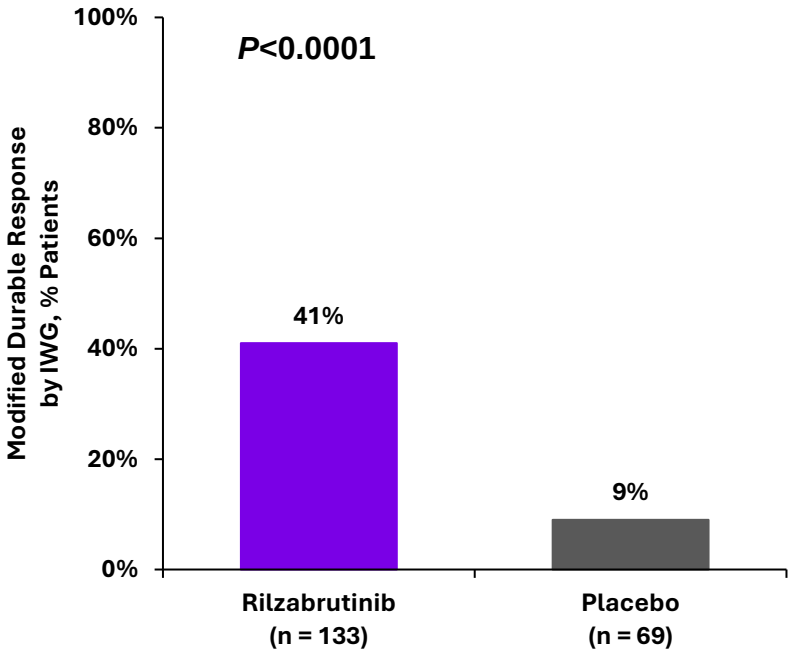
Rilzabrutinib significantly reduced rescue therapy use by 52% (P = .0007)

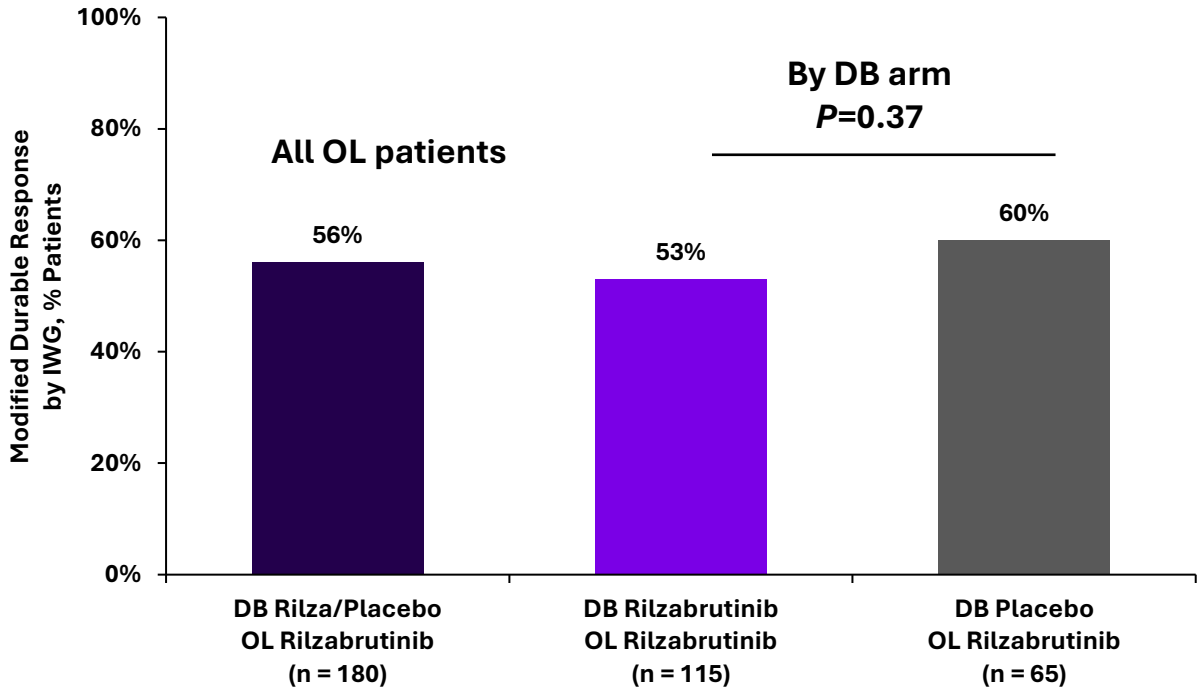
Improved week 25 bleeding scores (P = .0006)

David J. Kuter et al Blood, 2025, Figure 2.

Modified Durable Response by International Working Group definition (platelets > 30 and double baseline)





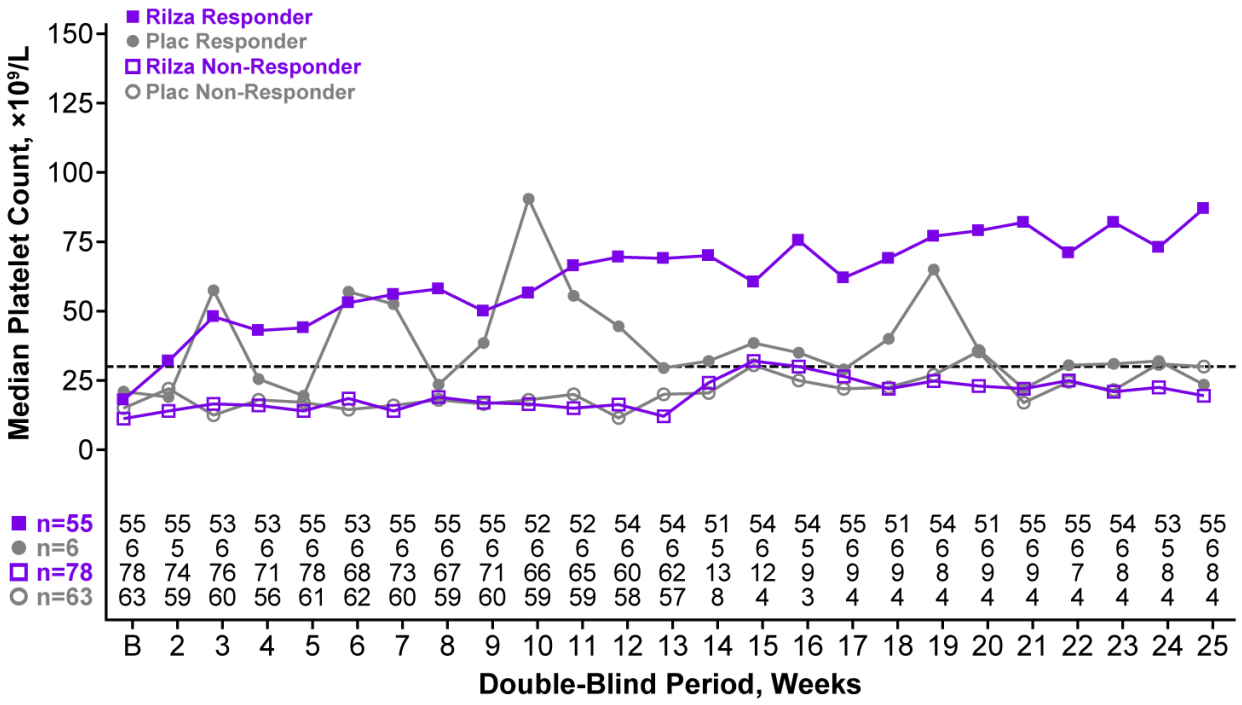


Data cutoff 15 Oct 2024. *Non-responders could discontinue or proceed to open-label on rilzabrutinib only.
Modified durable response by IWG: Platelet count ≥30×10^9/L and at least doubled from baseline absent bleeding for ≥50% of assessments during DB and OL periods.

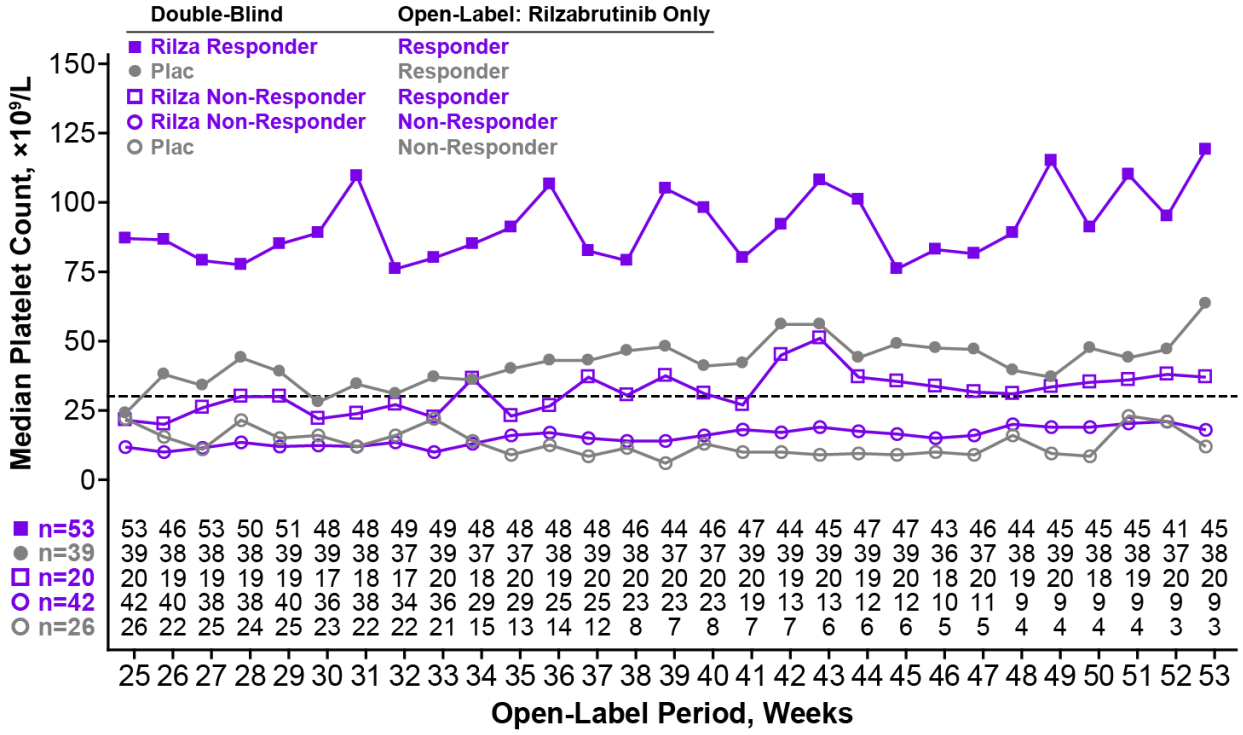
Platelet Counts by Response: DB and OL Periods

- Median platelet counts were maintained or increased for rilzabrutinib responders and increased in some non-responders

A. Double-blind



B. Open-Label

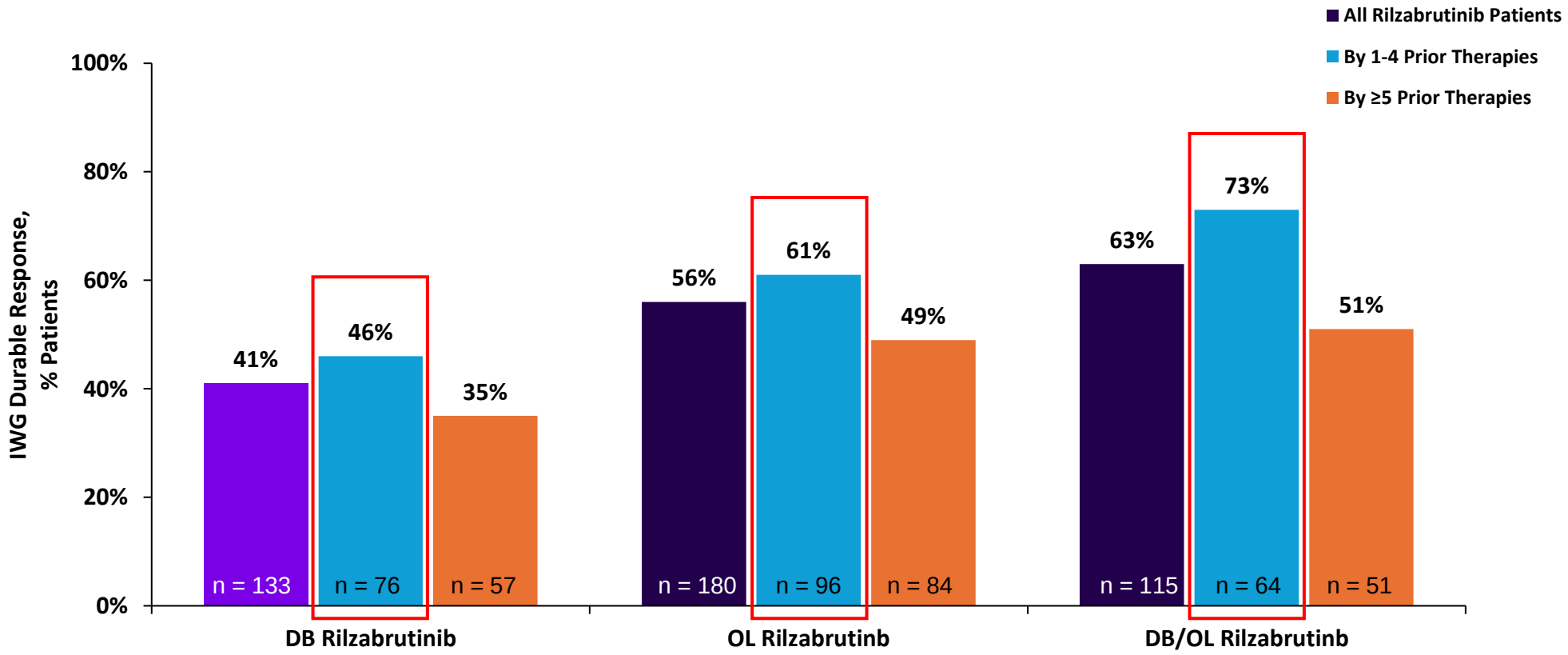


Data cutoff 15 Oct 2024. Plac, placebo; Rilza, rilzabrutinib.
Note: 2 rilzabrutinib responder patients from the DB period did not enter the OL period.

Ghanima EHA 2025

Modified Durable Response by IWG: Number of Prior Therapies

- Higher responses were seen among patients receiving rilzabrutinib across periods, with a trend favoring patients with fewer prior ITP therapies



Data cutoff 15 Oct 2024.

Conclusions luna 3

- Primary end point (platelet >50 for >2/3rds of >8 of the 12 weeks)
  - 23% of rilzabrutinib vs 0% placebo
- Modified durable responses by IWG (platelet > 30 and double base line):
  - 41% rilzabrutinib vs 9% placebo during the double-blind period
  - Improved with continued treatment and the addition of rilzabrutinib in the open-label period (56% all patients) – some late responders
- Trend for higher responses in patients with fewer prior ITP therapies

Univariate Analyses of Platelet Response

- Associations with higher overall response:
  - Female sex (*P*=0.009),
  - Baseline platelet count ≥15x10^9/L (*P*<0.0001), and
  - No prior therapy with TPO-RA (*P*=0.03) or rituximab (*P*=0.01)
- Associations with higher sustained response
  - Baseline platelet count ≥15x10^9/L (*P*=0.005)
  - No prior TPO-RA (*P*=0.04) or splenectomy (*P*=0.02)
- No significant association with response was seen for patients receiving concomitant corticosteroids or TPO-RA during the study

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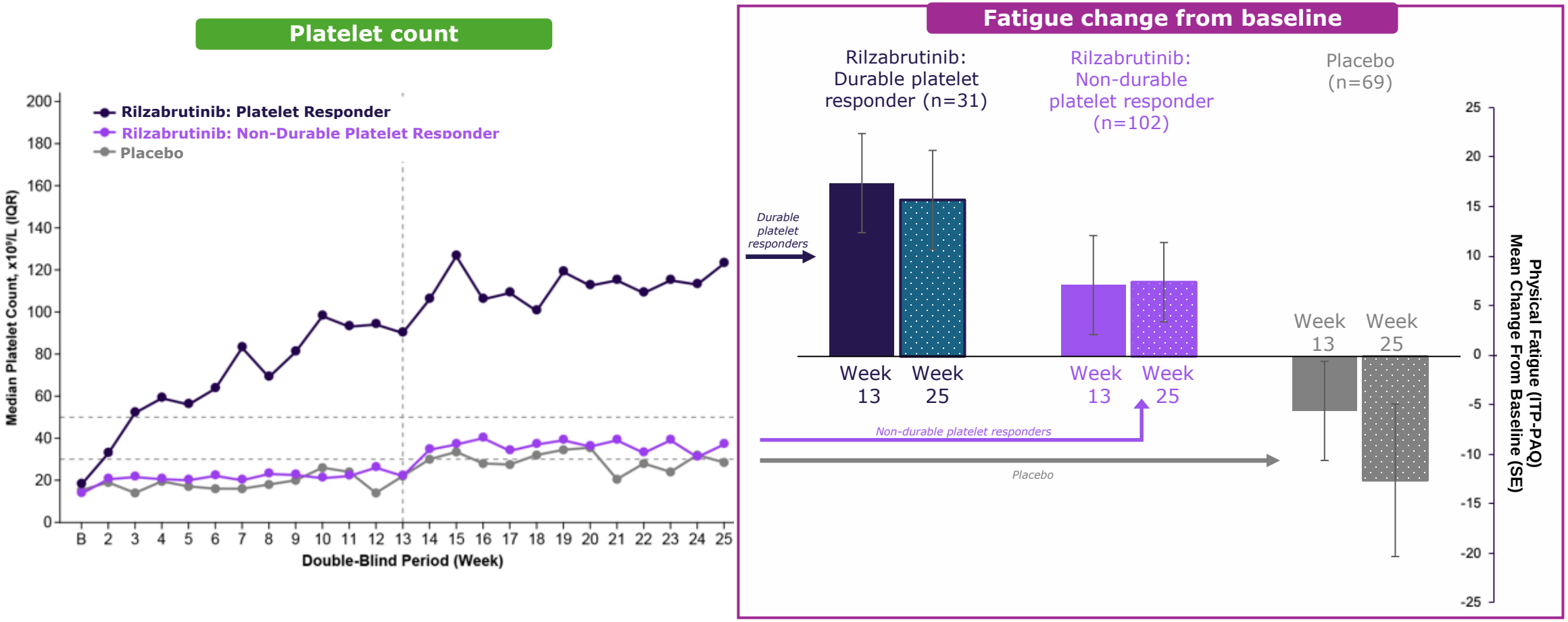
Rilzabrutinib Improved Fatigue at Weeks 13 and 25 in Durable and Non-Durable Platelet Responders[1]



Investigational agents mentioned in this slide have not been evaluated or approved by any regulatory agency.
[a]LUNA3 was a Phase 3, multicenter, placebo-controlled, parallel group trial; patients received rilzabrutinib 400 mg twice daily or placebo for the 24-week double-blind period. Serious adverse events occurred in 9% of patients receiving rilzabrutinib and 12% of patients receiving placebo. [b]Data cut-off 14 March 2024.

BTK, Bruton's tyrosine kinase; DB, double-blind; IQR, interquartile range; ITP, immune thrombocytopenia; ITP-PAQ, Immune Thrombocytopenia patient Assessment Questionnaire; OL, open-label; SE, standard error.

1. Kuter DJ, et al. American Society of Hematology (ASH) Congress, San Diego, December 7–10, 2024. Oral Presentation.

Ghanima EHA 2025

ITP-PAQ Women's Reproductive Health Results

- Overall ITP-PAQ WRH domain changes from baseline were improved with rilzabrutinib with mean changes from baseline at weeks 13 and 25, but the domain MID was not met
- **WRH item level for rilzabrutinib-treated patients**
  - Clinically meaningful improvements (ie, 3.3-point change[26]) in respective heavy menstrual bleeding (item 35) and bleeding duration (item 36) were seen with rilzabrutinib at weeks 13 and 25
  - Likelihood of getting pregnant (item 38) and giving birth (item 39) improved with rilzabrutinib at weeks 13 and 25
- **WRH item level for placebo-treated patients**
  - Meaningful item-level changes at week 13 were only observed for placebo in pain (item 37) and likelihood of getting pregnant (item 38)

26. Mathias SD, et al. *Curr Med Res Opin*. 2009;25:375-383.

Lambert et al ASH 2025

ITP-PAQ WRH Item-Level Changes From Baseline Based on Durable Response Status With Rilzabrutinib

- At week 25, durable responders with rilzabrutinib treatment showed meaningful improvement[26] from baseline above MID in all 6 items 35-40
- Non-durable responders with rilzabrutinib showed improvements from baseline above MID at week 25 in
  - heavy menstrual bleeding (item 35),
  - likelihood of getting pregnant (item 38) and giving birth (item 39)
  - Improvement was also shown in heavy menstrual bleeding at week 13 (item 35)
- No placebo patients were durable responders; overall and individual item levels changes at weeks 13 and 25

26. Mathias SD, et al. *Curr Med Res Opin*. 2009;25:375-383.

Lambert et al ASH 2025

Changes from Baseline in ITP-PAQ WRH Overall and by Item-Specific Domains at Weeks 13 and 25

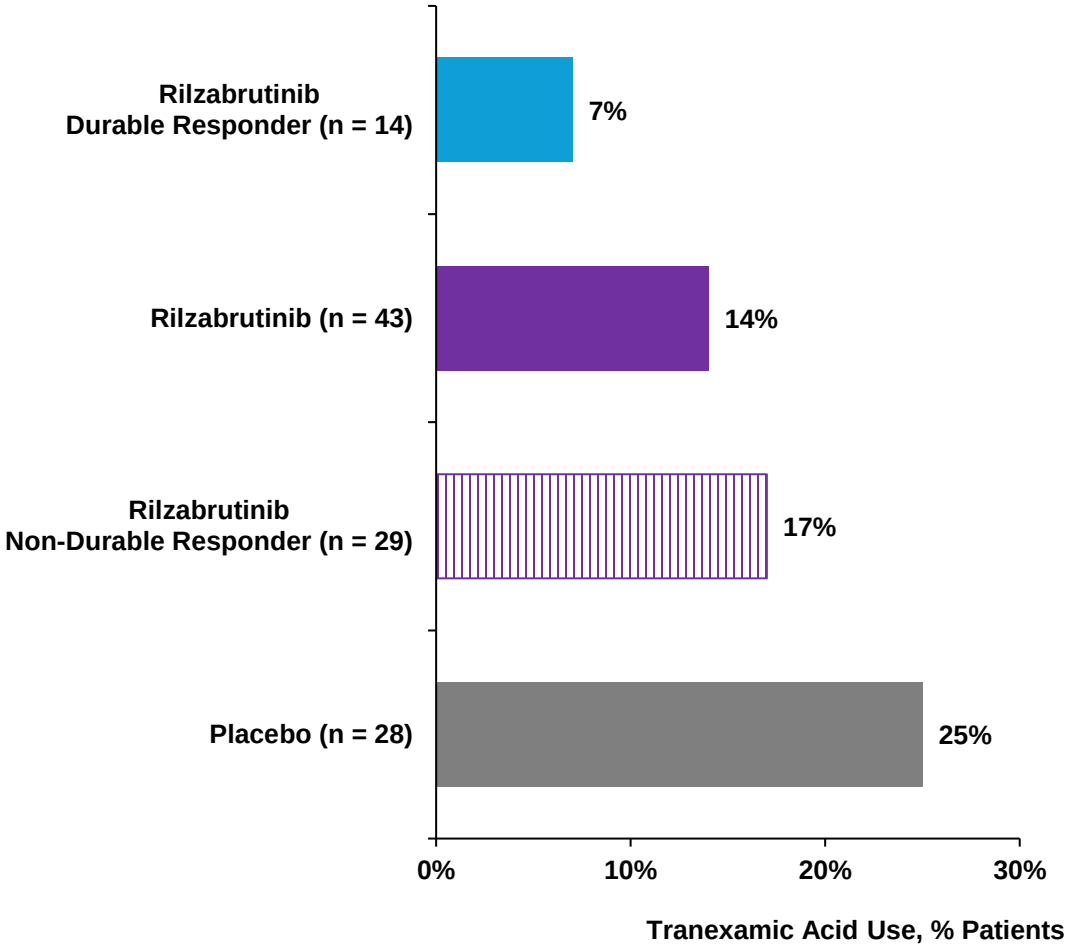
ITP-PAQ Domain/Item	MID Reference*	Rilzabrutinib			Placebo		
		Baseline, Mean (SD) (n = 43)	Mean (SD) Change from Baseline at		Baseline, Mean (SD) (n = 27-28)	Mean (SD) Change from Baseline at	
			Week 13 (n = 39)	Week 25 (n = 22)		Week 13 (n = 25)	Week 25 (n = 2)
Overall women's reproductive health	8-12	69 (26)	3.5 (23.3)	6.6 (20.6)	59 (26)	0.4 (19.1)	-16.7 (5.9)
Item 35: Heavy menstrual bleeding	3.3	58 (38)	7.1 (35.3)*	9.1 (32.3)*	56 (31)	1.0 (28.4)	0 (0)
Item 36: Bleeding duration	3.3	64 (38)	4.5 (34.4)*	10.2 (40.6)*	63 (36)	-9.0 (36.0)	-25.0 (70.7)
Item 37: Pain	3.3	80 (27)	0.6 (25.3)	1.1 (22.5)	77 (26)	4.0 (20.0)*	-37.5 (17.7)
Item 38: Likelihood of getting pregnant	3.3	68 (40)	3.9 (39.5)*	7.95 (34.8)	45 (45)	6.0 (36.3)*	0 (0)
Item 39: Likelihood of giving birth	3.3	67 (41)	3.2 (35.9)	9.1 (35.0)*	46 (44)	2.0 (33.0)	0 (0)
Item 40: Likelihood to adopt	3.3	77 (38)	1.9 (35.1)	2.3 (31.7)	71 (35)	-2.0 (16.0)	-37.5 (53.0)

ITP-PAQ, Immune Thrombocytopenic Purpura - Patient Assessment Questionnaire; MID, minimal important difference; repr, reproductive; SD, standard deviation; WRH, women's reproductive health.
*8-12–point improvement on the ITP-PAQ WRH domain was considered the minimum important difference (MID), translating to a 3.3-point change/item for menstrual symptom/fertility items. ITP-PAQ score ranges from 0 worst to 100 best.

Lambert et al ASH 2025

Use of Tranexamic Acid by Double-Blind Treatment and Durable Response

- Use of tranexamic acid during the double-blind period was lower in rilzabrutinib durable responders than non-durable responders (rilzabrutinib or placebo)



Tranexamic acid is an antifibrinolytic agent used to treat heavy menstrual bleeding, including critical bleeds in ITP

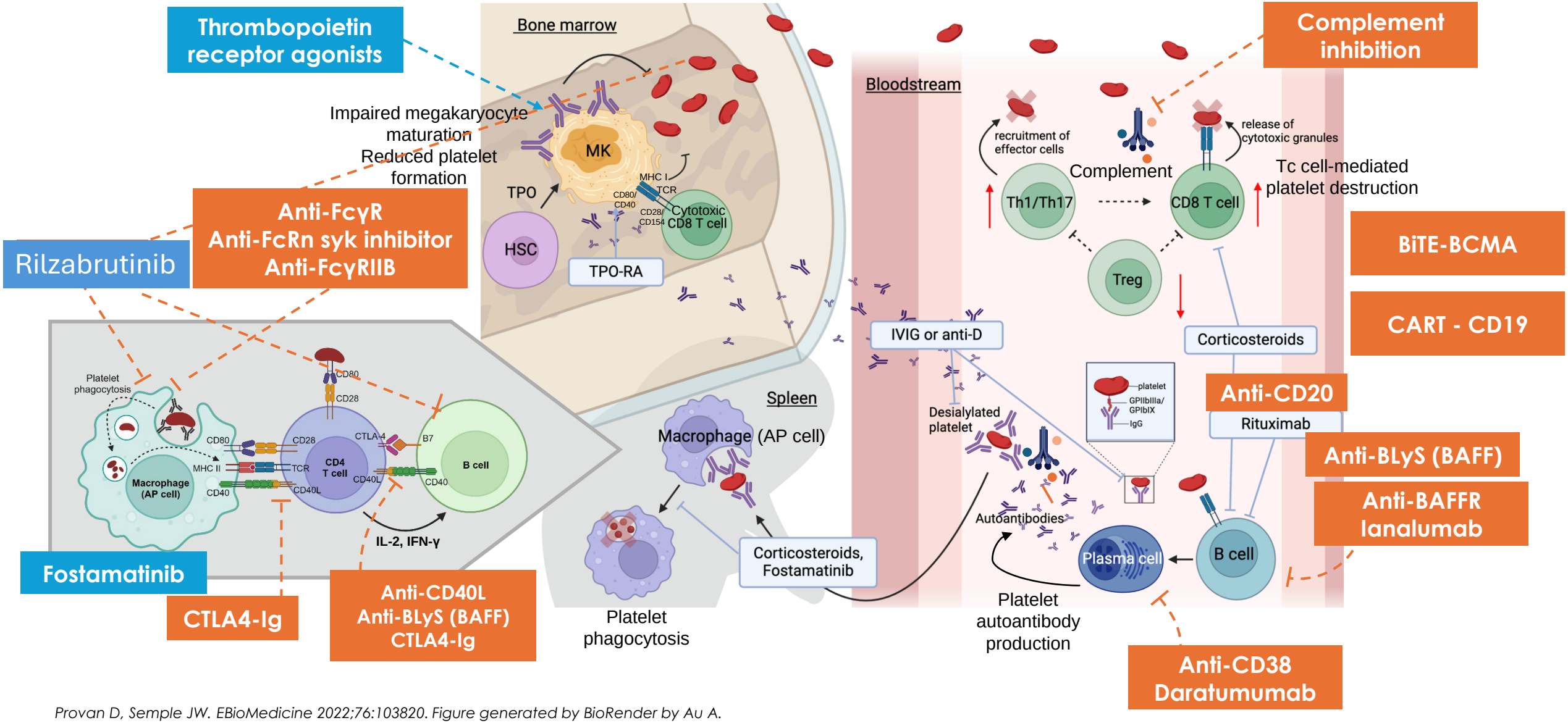
Lambert et al ASH 2025

Clinical Studies of Rilzabrutinib

- **Phase 1-2 LUNA2:** Rilzabrutinib showed rapid and durable platelet responses, improved HRQoL (fatigue) and bleeding score, well-tolerated safety in previously treated adults with persistent/chronic ITP[1-3]
- **Phase 3 LUNA3:** Established superiority over placebo in all disease aspects during the double-blind (DB) period, confirmed improvement in HRQoL including fatigue, and improved female health QoL[4-6]
- **Phase 3b LUNA4:** Evaluating early immune modulation with rilzabrutinib in patients with primary ITP who failed first line treatment[7]
- **August 2025**: Rilzabrutinib **approved by the FDA for the treatment of adults with persistent/chronic ITP who had an insufficient response to previous treatment[8]**

1.Kuter DJ, et al. *N Engl J Med*. 2022;386:1421-1431. 2. Kuter DJ, et al. *Blood Adv.* 2024;8:1715-1724. 3. Cooper N, et al. *Am J Hematol*. 2025;100:439-449. 4. Kuter DJ, et al. *Blood.* 2025;145:2914-2926. 5. Kuter DJ, et al. *Res Pract Thromb Haemost*. 2025; 9(suppl 2):311-312 (abstract PB0376). 6. Ghanima W, et al. *HemaSphere*. 2025;9(S1):490-491 (abstract S310). 7. Clinicaltrials.gov NCT07007962.
8. Wayrilz™ (rilzabrutinib) prescribing information. Genzyme Corporation (A Sanofi Company). Cambridge, MA. Aug 2025.

What is the place of BTKi in ITP?



Provan D, Semple JW. EBioMedicine 2022;76:103820. Figure generated by BioRender by Au A.

Other BTK inhibitors in clinical trial in ITP

- Orelobrutinib
- Pirtobrutinib

Conclusions Rilzabrutinib

- Superior platelet response compared to placebo
- No bleeding (? Reduced bleeding)
- No thrombotic complications
- Improved Quality of life
- Improved fatigue

- Is there a particular role of BTK inhibition in patients with fatigue, and those with thrombotic risks?
- Trials of first line use needed to establish whether it can reduce the development of chronic disease