



2ND meeting of the European Research Consortium on ITP

NEW INSIGHTS INTO IMMUNE
THROMBOCYTOPENIA



Paris Crowne Plaza Paris République

April 23-24, 2026



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How BTK inhibition may change the therapeutic approach in ITP

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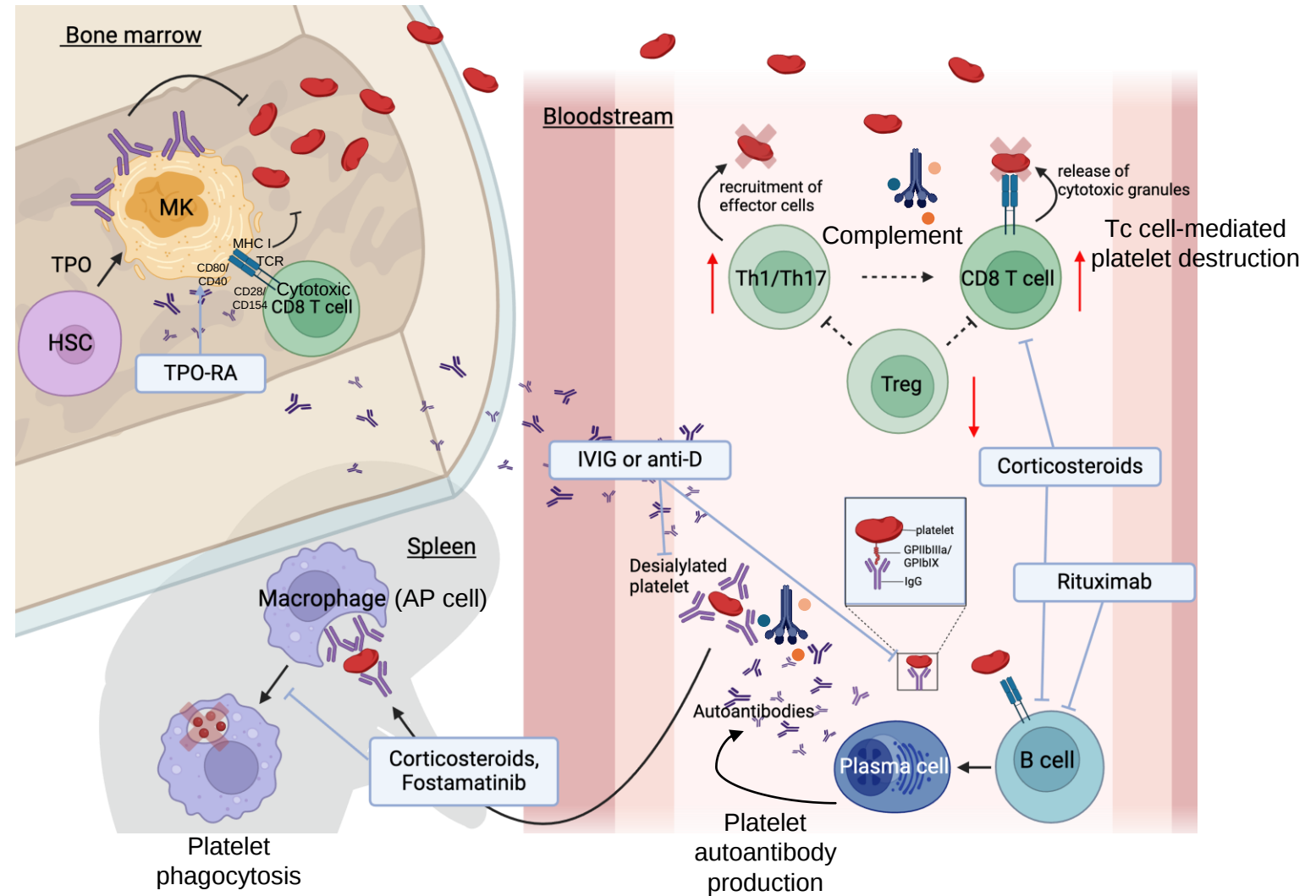
Disclosures of

Nichola

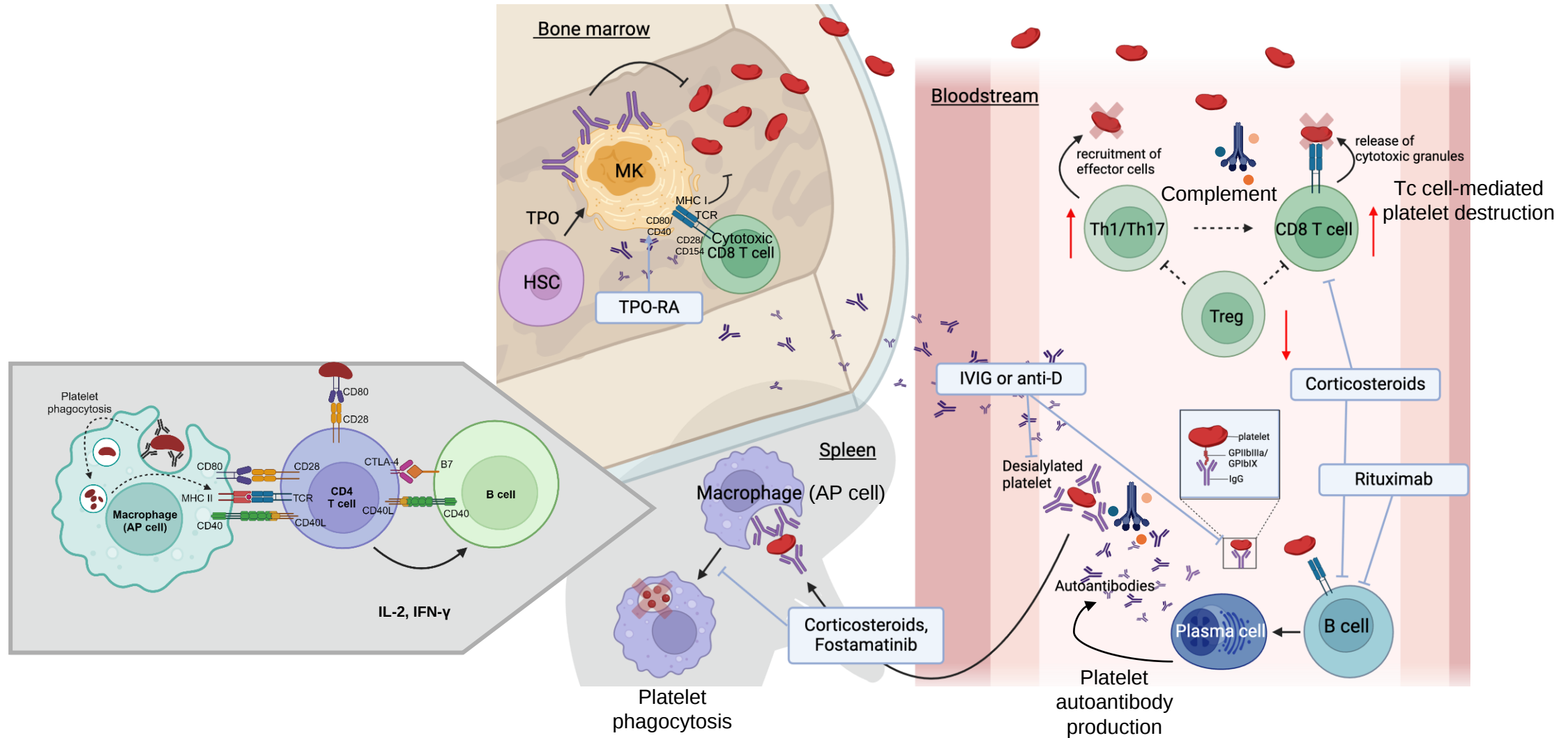
Cooper

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	

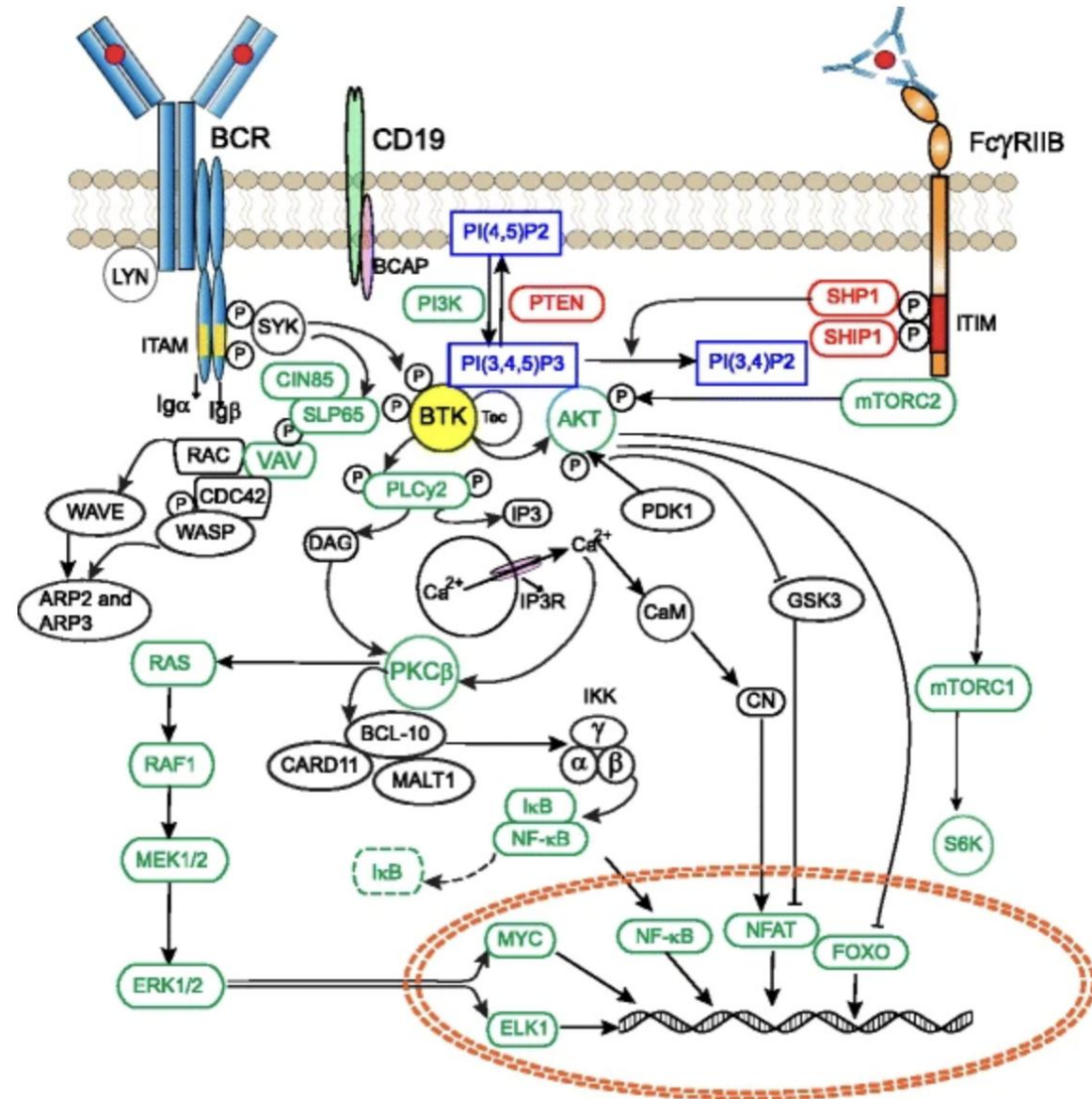
Why is BTK inhibition useful in ITP?



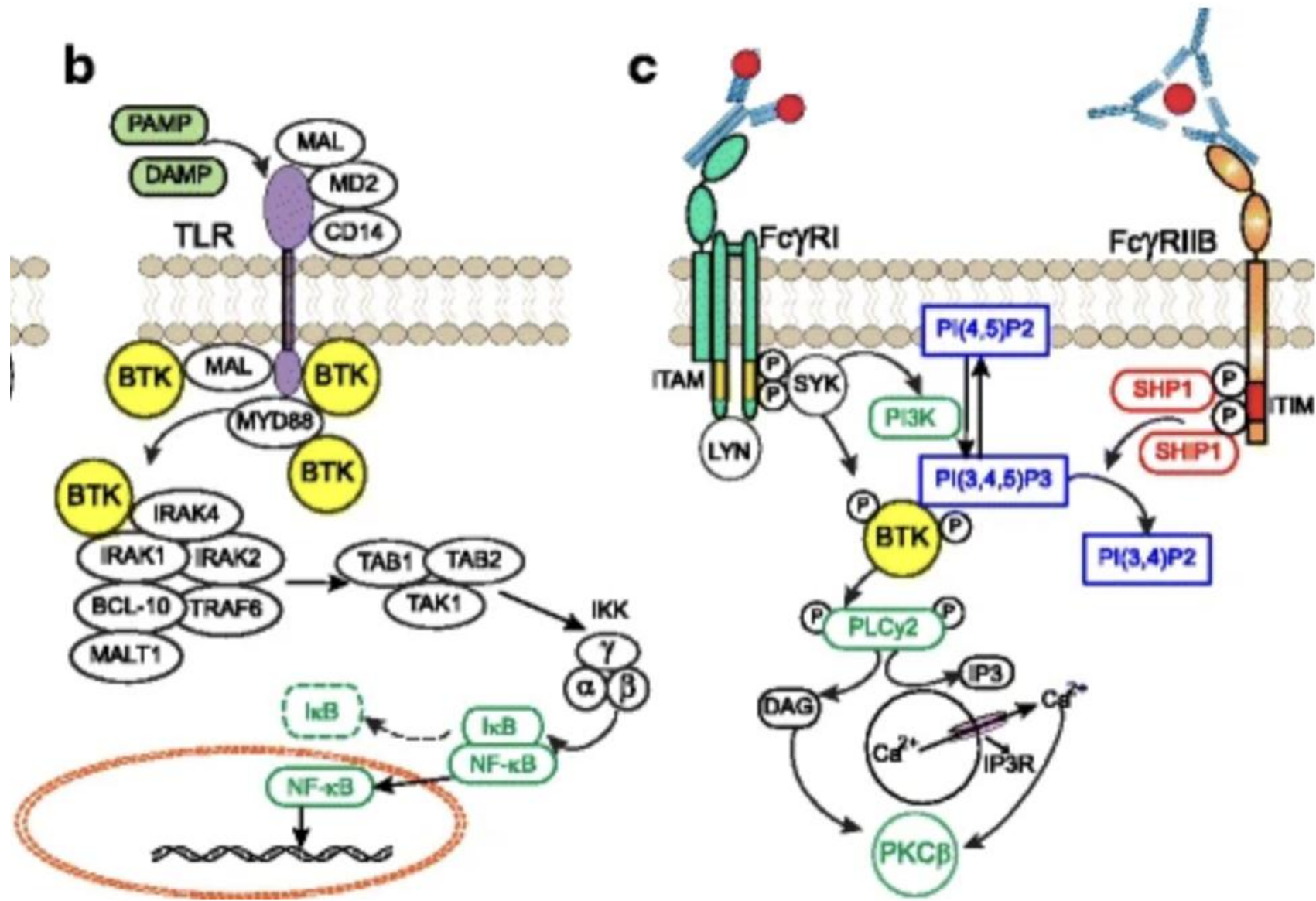
Why is BTK inhibition useful in ITP?



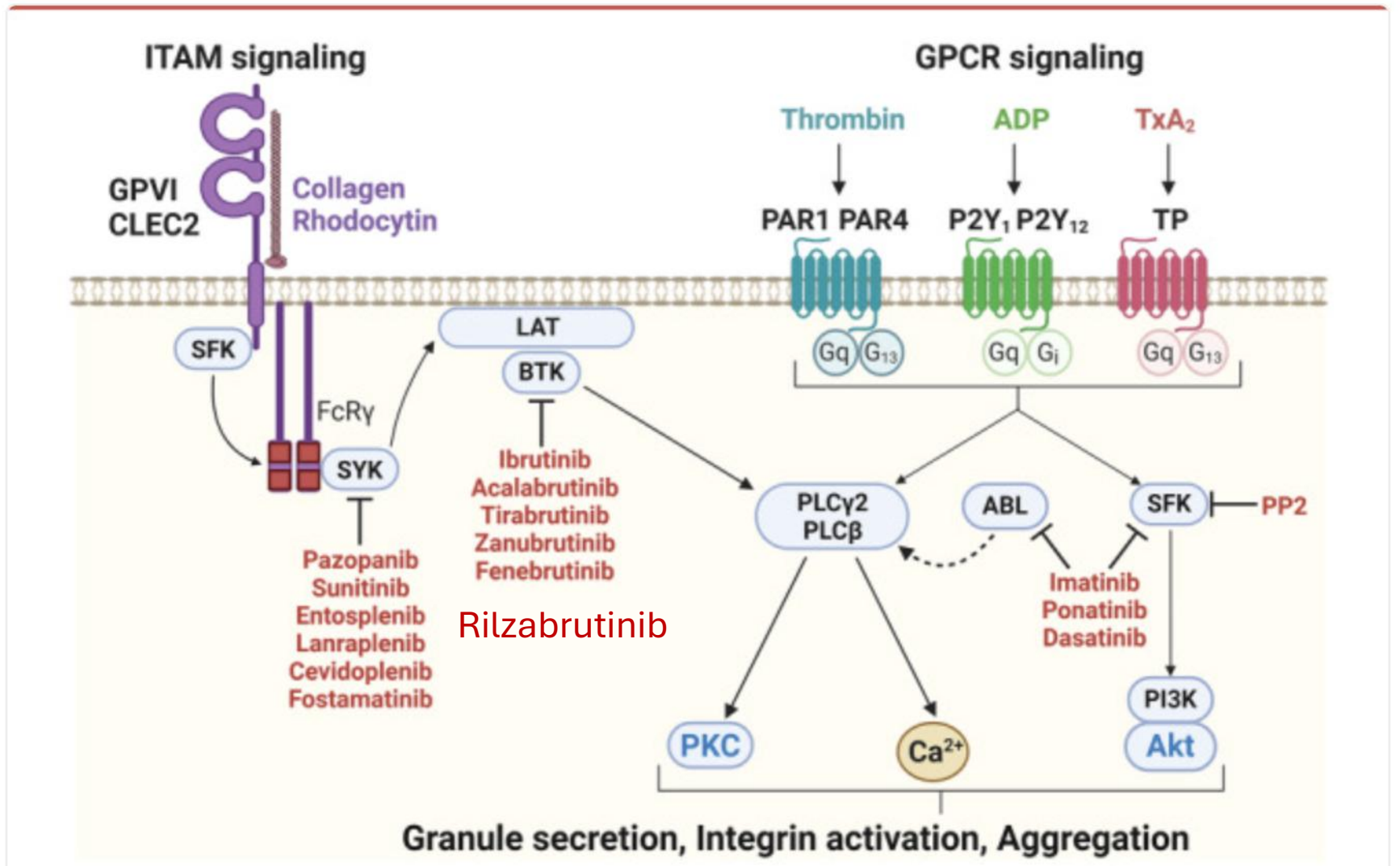
BTK is central to B cell activation



BTK also
central to
TLR and
FcR
activation



BTK also
central in
platelet
activation



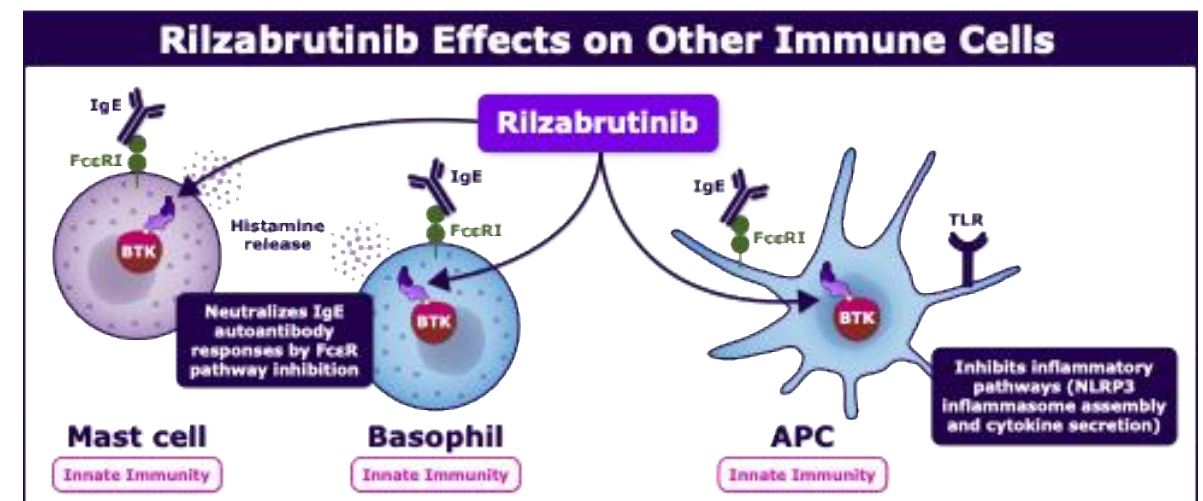
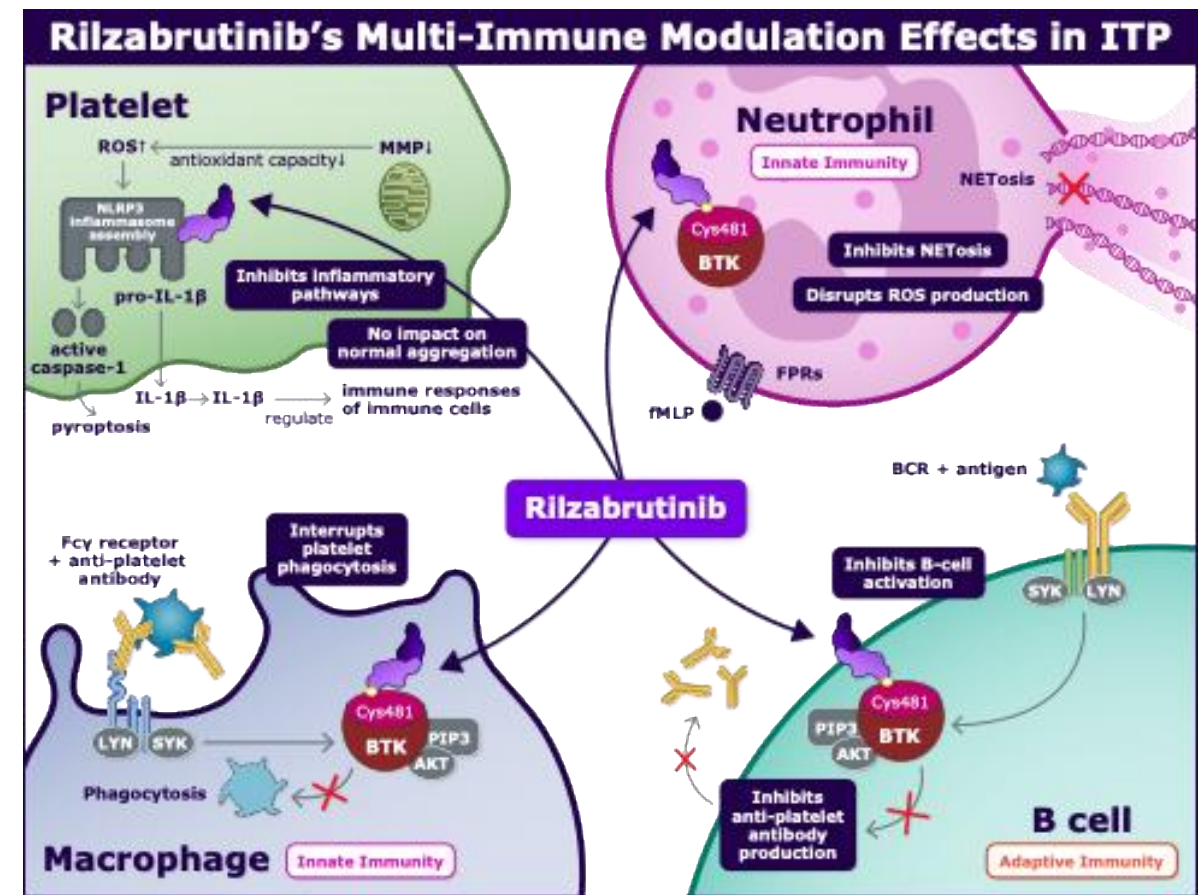
Key features of rilzabrutinib in platelets

- 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

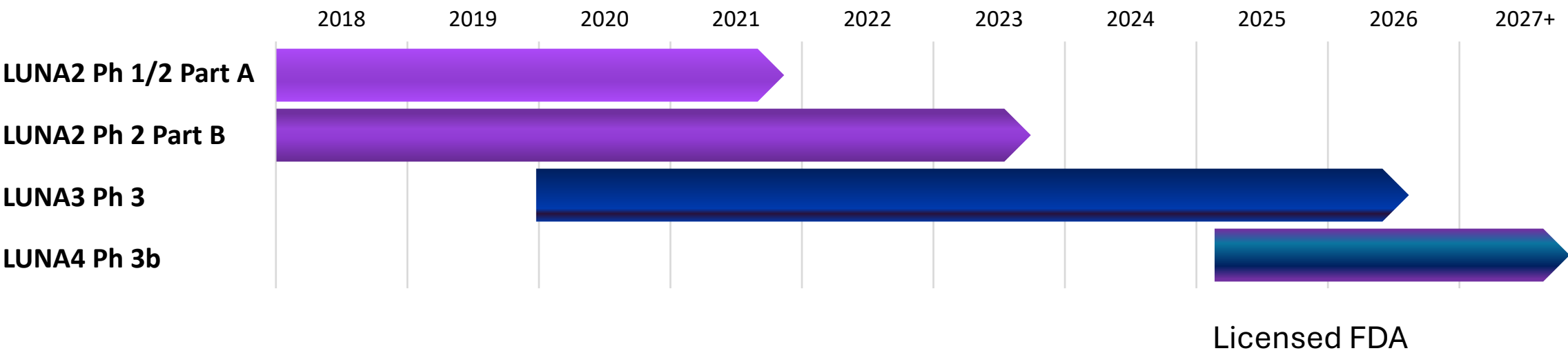
Immune Modulation Mechanisms of Action with Rilzabrutinib^{1,2}

- 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

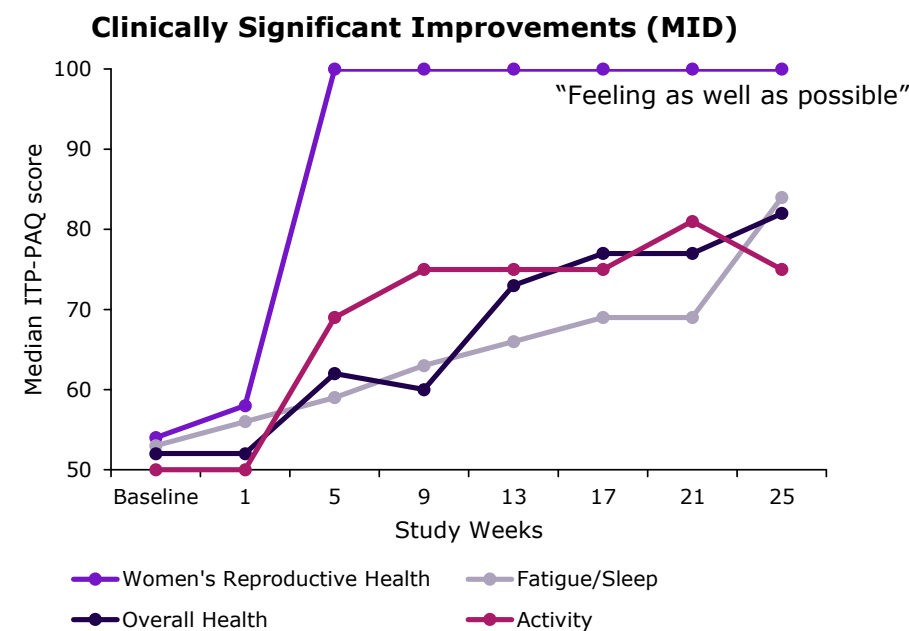
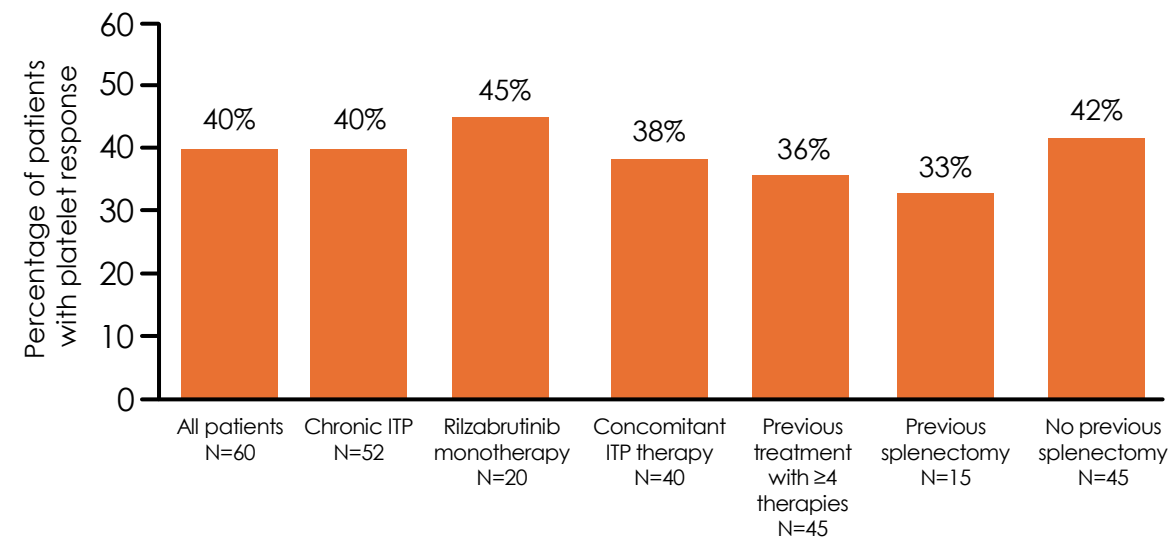
Platelet response in 43% of patients with previously treated persistent or chronic ITP

Well tolerated

No increase in bleeding

No increase in thrombosis

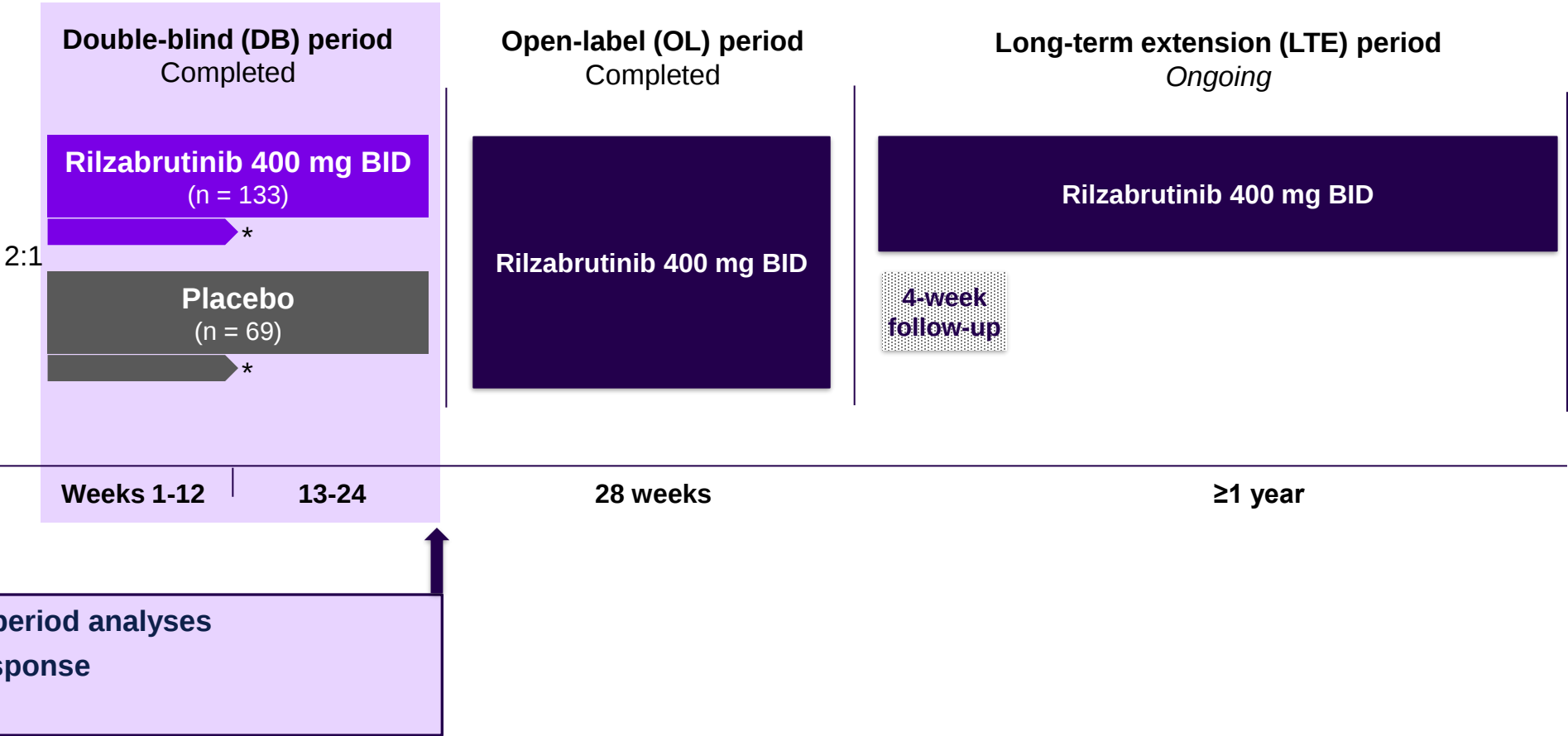
Improved HRQoL (ITP-PAQ) including fatigue



LUNA 3 Study Design

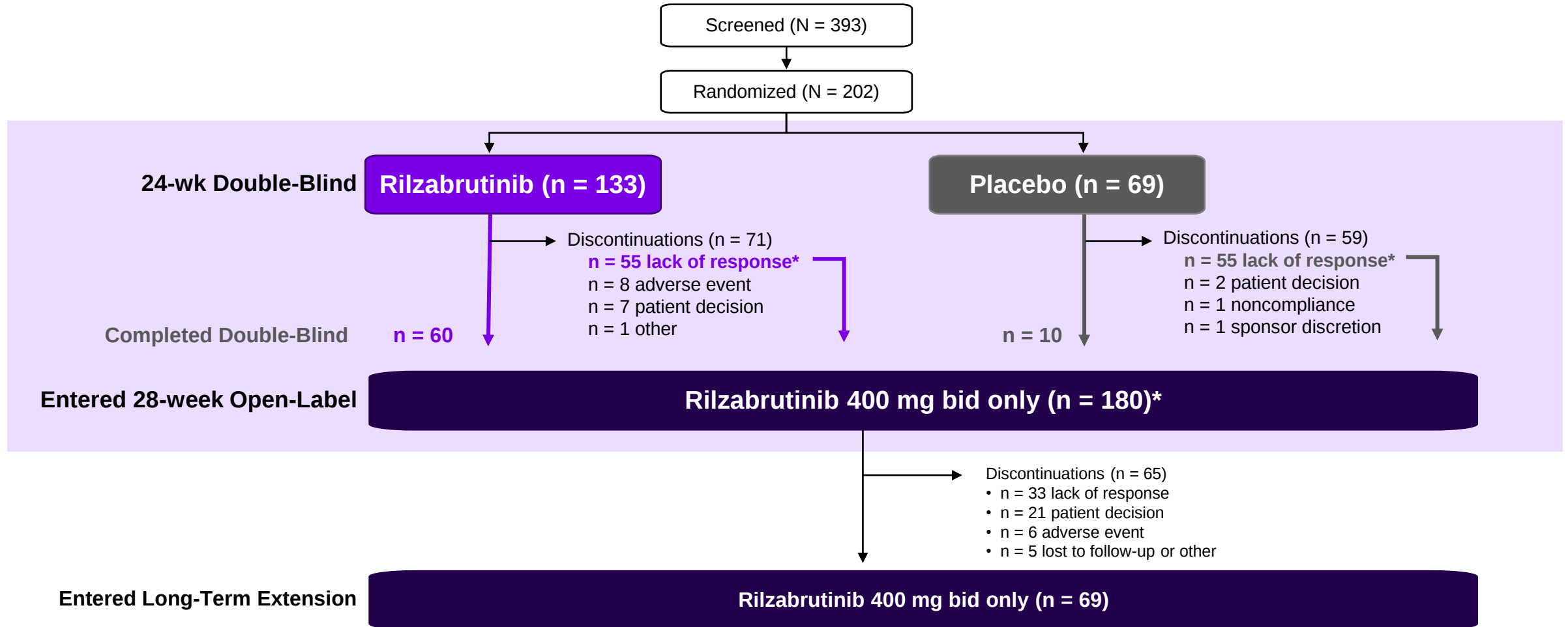
Adults with persistent/chronic primary ITP

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



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

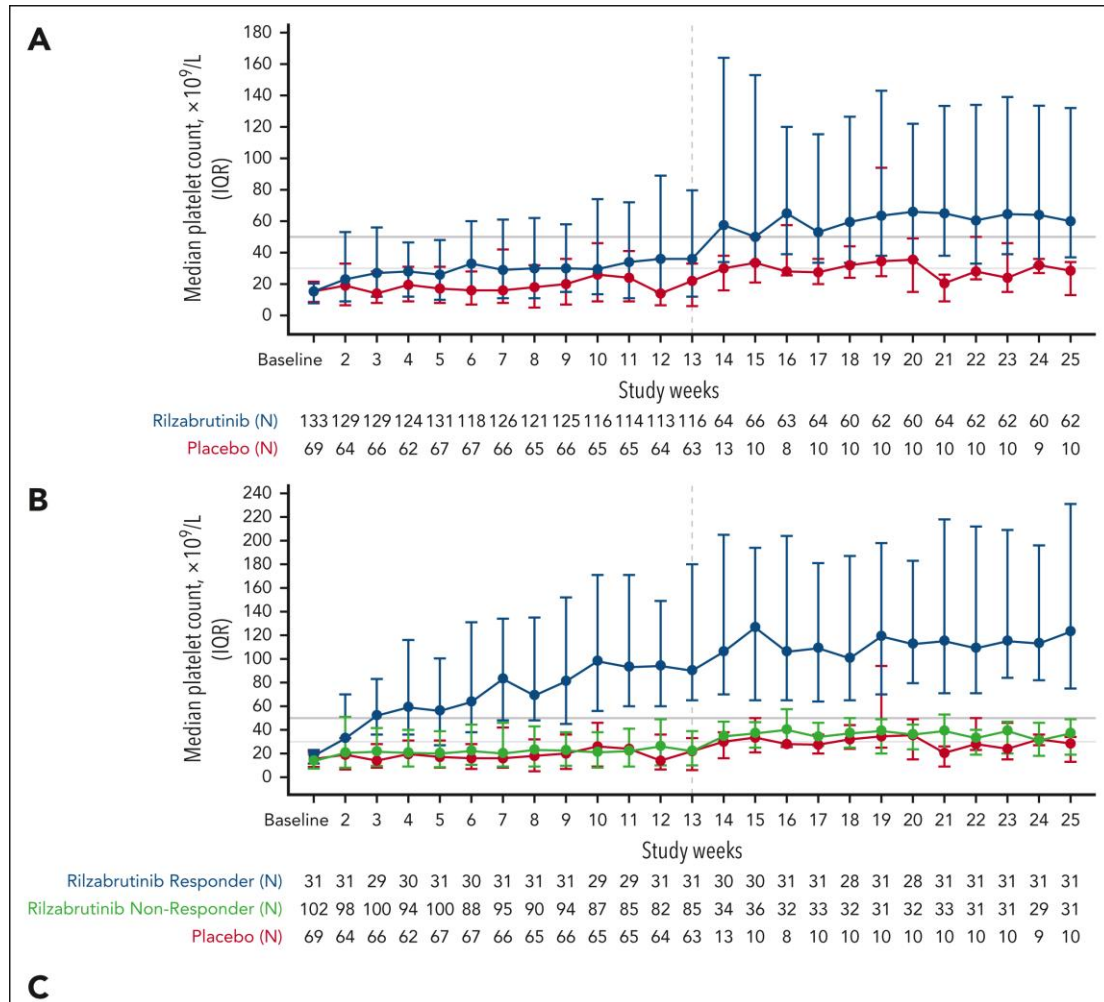


Baseline Characteristics and Prior/Concomitant Therapy

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, $\times 10^9/\text{L}$ (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)

Luna 3: RCT of rilzabrutinib results



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

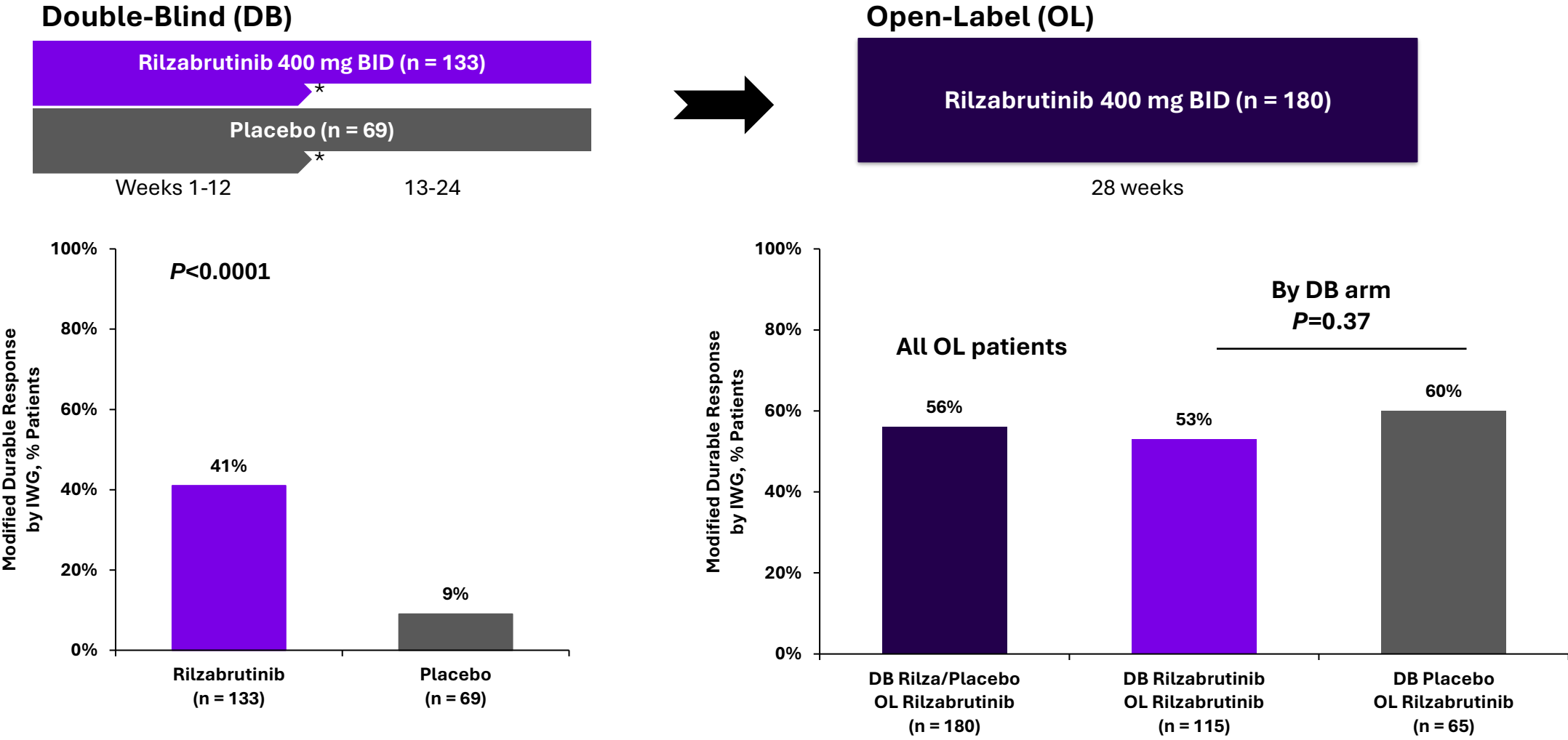
31 (23%) rilzabrutinib vs 0 placebo patients ($P < .0001$)

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 ($P = .0006$)

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

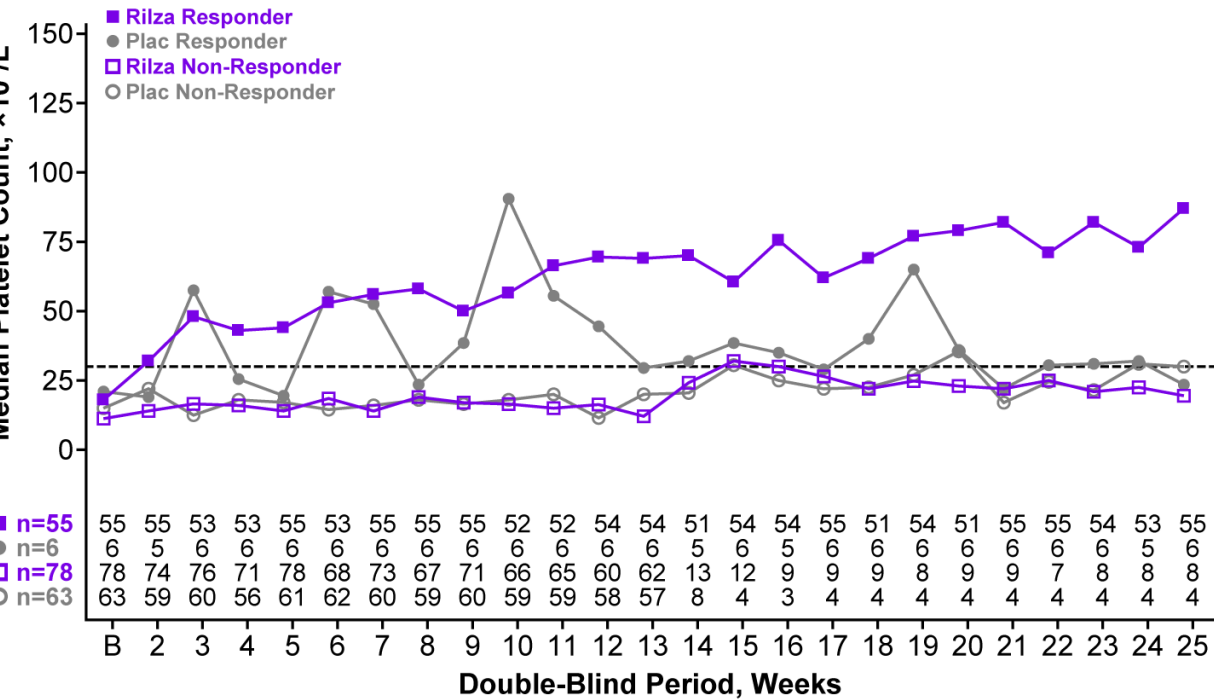


Data cutoff 15 Oct 2024. *Non-responders could discontinue or proceed to open-label on rilzabrutinib only.
Modified durable response by IWG: Platelet count $\geq 30 \times 10^9/L$ and at least doubled from baseline absent bleeding for $\geq 50\%$ of assessments during DB and OL periods.

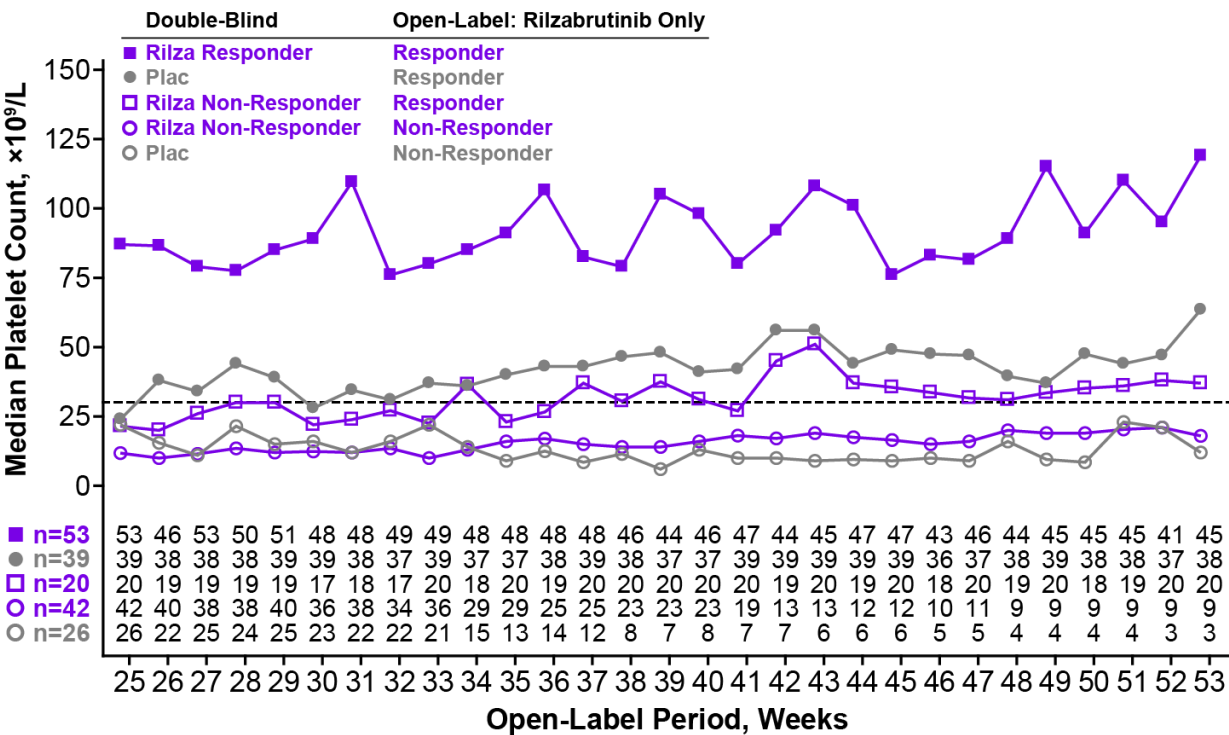
Platelet Counts by Response: DB and OL Periods

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

A. Double-blind



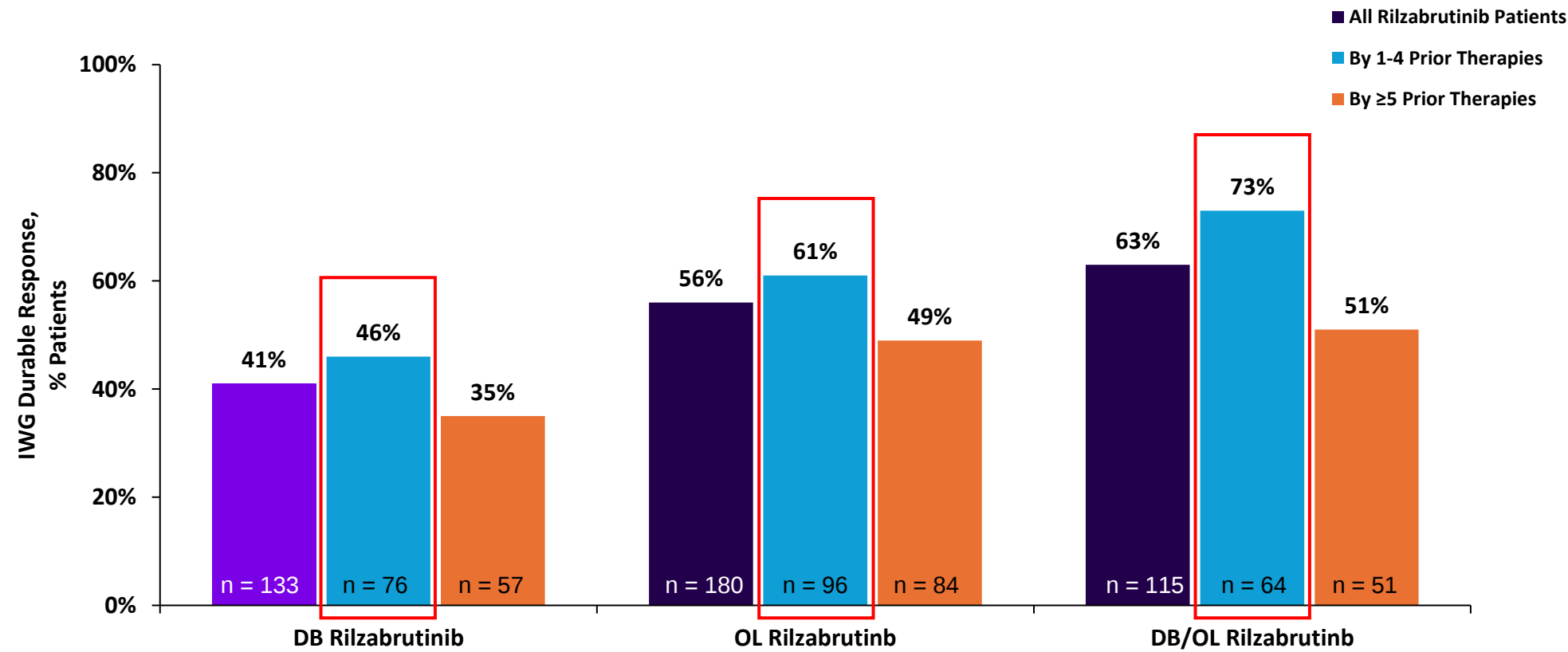
B. Open-Label



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

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



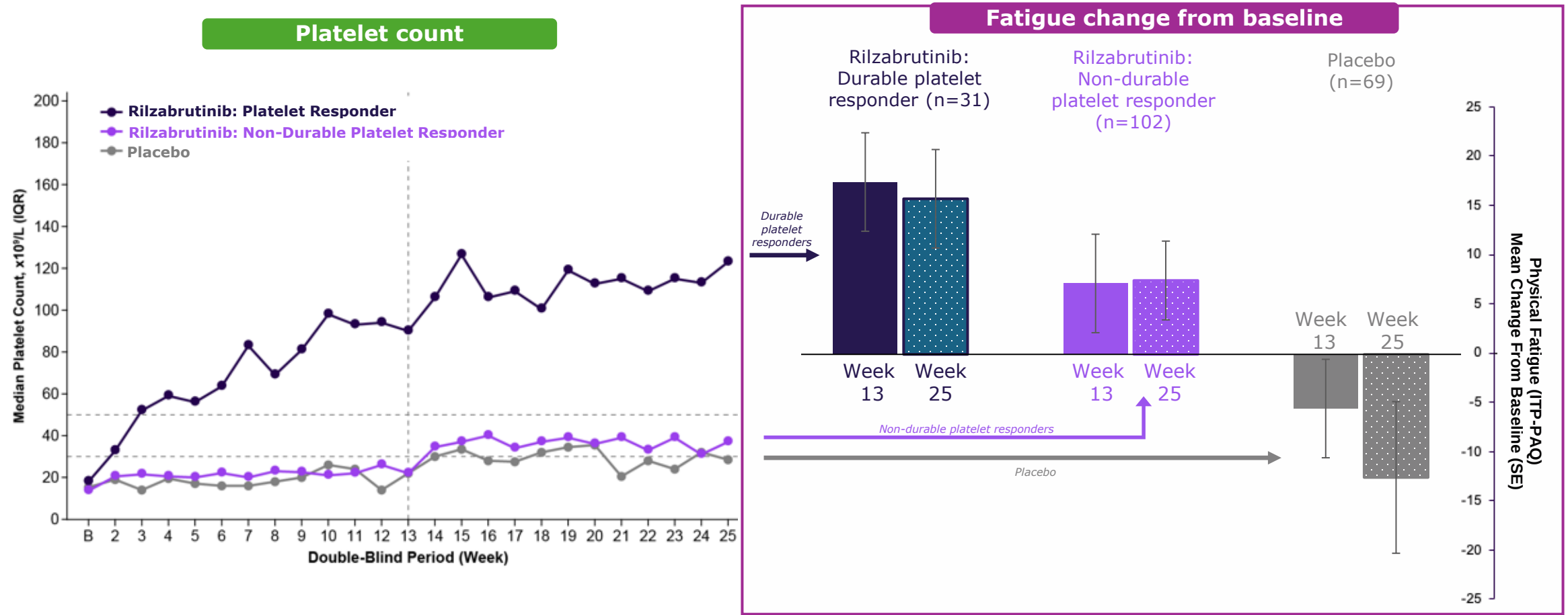
Conclusions luna 3

- Primary end point (platelet >50 for $>2/3$ 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 $\geq 15 \times 10^9/\text{L}$ ($P<0.0001$), and
 - No prior therapy with TPO-RA ($P=0.03$) or rituximab ($P=0.01$)
- Associations with higher sustained response
 - Baseline platelet count $\geq 15 \times 10^9/\text{L}$ ($P=0.005$)
 - 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

Rilzabrutinib Improved Fatigue at Weeks 13 and 25 in Durable and Non-Durable Platelet Responders¹



Investigational agents mentioned in this slide have not been evaluated or approved by any regulatory agency.
^aLUNA3 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. ^bData 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.

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 change²⁶) 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)

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 improvement²⁶ 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.

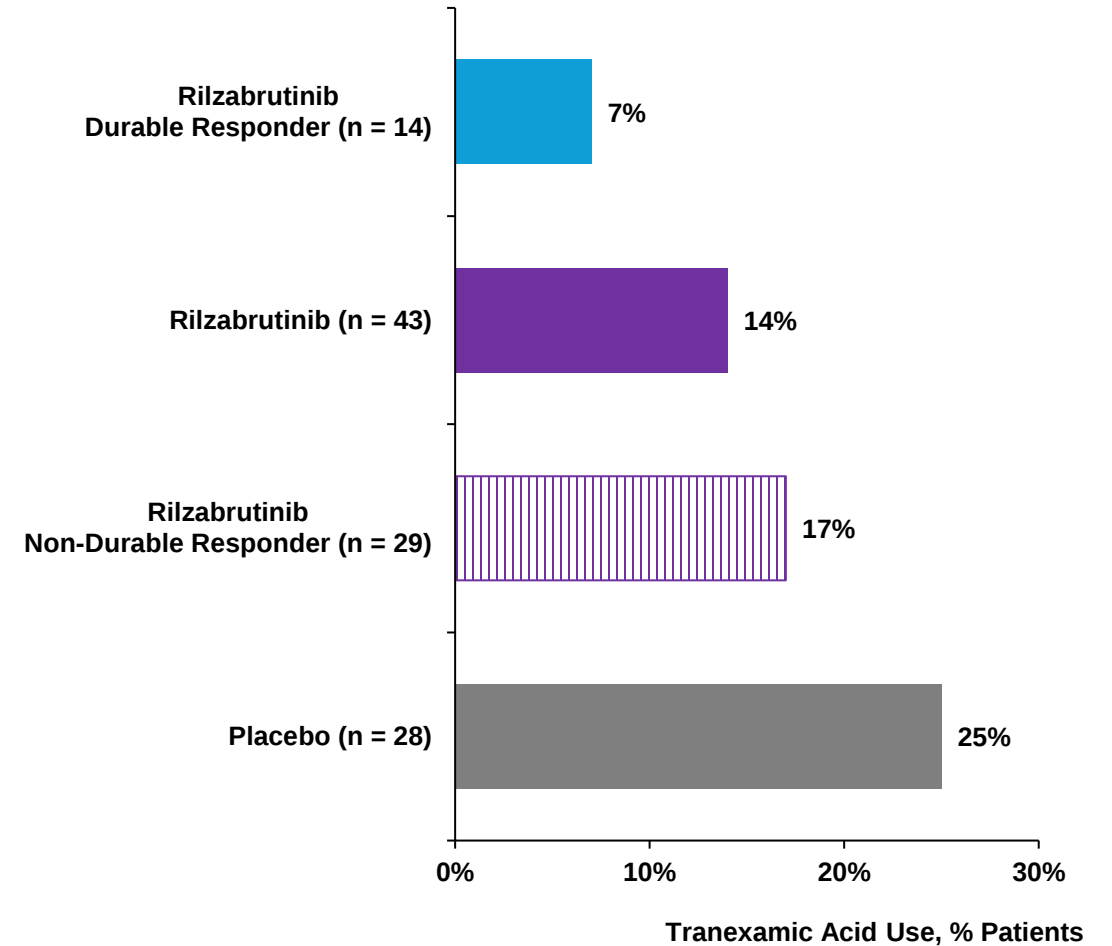
Changes from Baseline in ITP-PAQ WRH Overall and by Item-Specific Domains at Weeks 13 and 25

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.

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

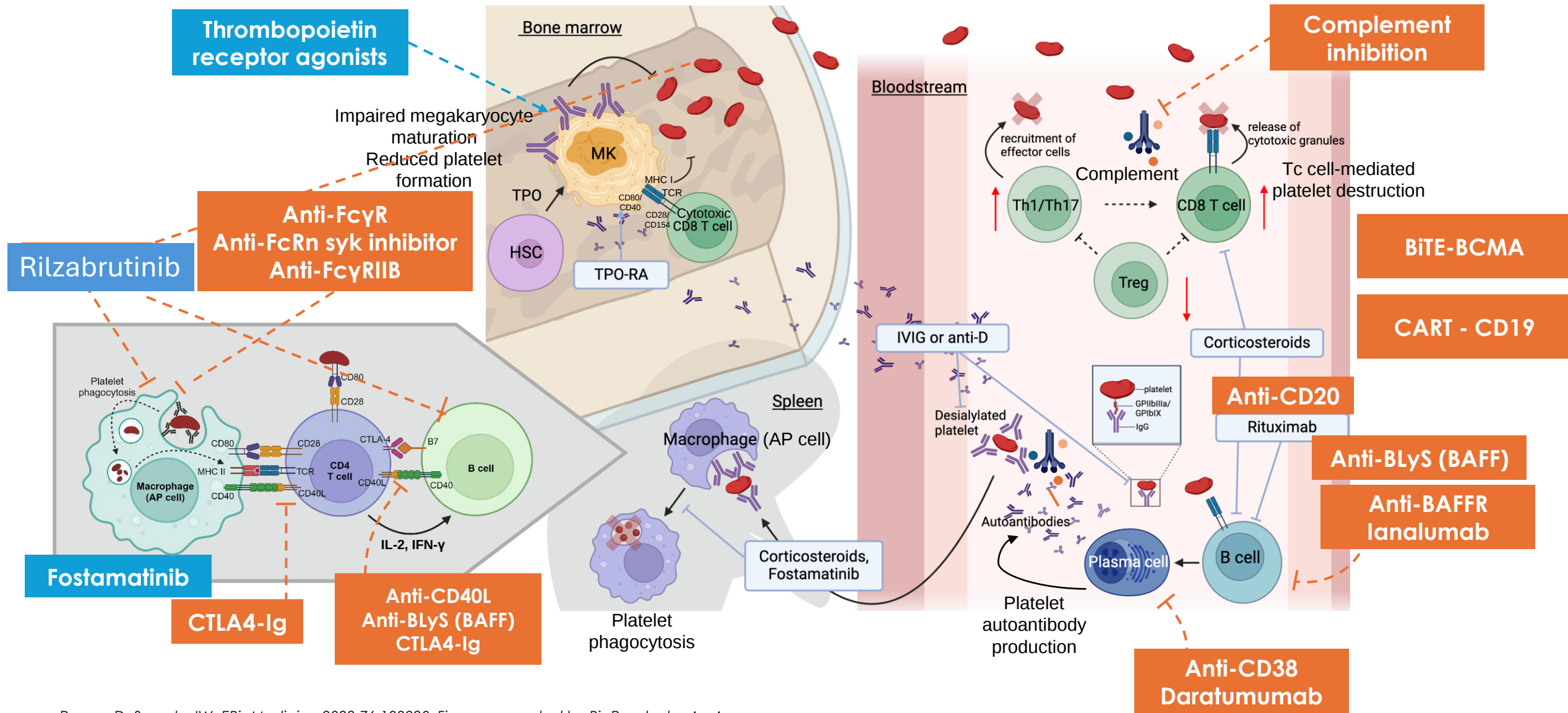
- Use of tranexamic acid during the double-blind period was lower in rilzabrutinib durable responders than non-durable responders (rilzabrutinib or placebo)



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 ITP¹⁻³
- **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 QoL⁴⁻⁶
- **Phase 3b LUNA4:** Evaluating early immune modulation with rilzabrutinib in patients with primary ITP who failed first line treatment⁷
- **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

What is the place of BTKi in ITP?



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