POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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Immune Thrombocytopenia (ITP)

UOC Ematologia, IRCCS Azienda Ospedaliero-Universitaria di Bologna/ UOC Ematologia, Azienda Sanitaria Universitaria Giuliano Isontina, Trieste

Disclosures of Nicola Vianelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
				NONE			

Principali «appuntamenti» scientifici relativi all'ITP in San Diego 2024

- ITP breakfast PDSA (Platelet Disorder Support Association)
- Sessione Educazionale
- 12 oral +1 oral Plenary Session
- 38 poster

Educational 1: Waleed Ghanima, MD, PhD
Østfold Hospital Gralum, Norway
Insights on Treatment of Adult ITP: Algorithm for Management and Role of Multimodal Therapy

Educazional 2: Michele P. Lambert, MD
Children's Hospital of Philadelphia, Philadelphia, PA
On the Horizon: Upcoming New Agents for the Management of ITP

Educational 3: Annemarie E Fogerty, M.D.
Massachusetts General Hospital Boston, MA
ITP in Pregnancy: Diagnostics and Therapeutics in 2024

ITP breakfast PDSA (Platelet Disorder Support Association)

Living under the sword of Damocles

Giuseppe Auteri Hematology Unit, University of Ferrara, Ferrara, Italy
Laura Ricci President of DOCEAT, Firenze, Italy
Barbara Lovrencic, president AIPIT aps Caprino Veronese, Italy

“Why” of this project?

In recent years, scientific studies have highlighted the significant negative impact of ITP on the quality of life of those affected.

Anxiety stemming from platelet count instability causes individuals with ITP to live with a constant sense of having the Sword of Damocles hanging over their heads.

Cooper et al. Am J Hematol. 2021 Feb 1;96(2):188-198,
Giordano P, Lassandro G, di Meo NA,Palladino V, Lovrencic B, Spinelli M and Jankovic M (2019) A Narrative Approach to Describe QoL in Children With Chronic ITP. Front. Pediatr. 7:163. doi: 10.3389/fped.2019.00163

Psychological Support in ITP Care

Standard care often overlooks psychological support.

Patients express the need for support from different sources, especially at the time of diagnosis/relapse.*

The “Living under the Sword of Damocles” (jan-dec 2024)

Key Objectives:

- Alleviate anxious-depressive symptoms in ITP patients.
- Provide targeted support to caregivers.
- Raise awareness of the psychological burden of ITP among hematologists bringing new understanding of patients experience

**Kruse A, Kruse C, Potthast N, Milligan K, Bussel JB. Mental Health and Treatment in Patients with Immune Thrombocytopenia (ITP); Data from the Platelet Disorder Support Association (PDSA) Patient Registry. Blood. 13 novembre 2019;134(Supplement_1):2362*

Patient (20) group specific results

We have found qualitative outcomes:

1. **normalize the disease**, finding a renewed balance and ability to integrate the ITP into daily life;
2. **a better understanding** of what the **disease** looks like **in their bodies** and a significant improvement in managing anticipatory anxiety;
3. feeling more **supported** and understood by those around them
4. being **able to share** with those who have the same experience, reducing the feeling of loneliness (independently of gender, age, ITP phase);
5. **applying learned tools** to divert daily or obsessive attention away from the platelet count and the fear of the relapses.

Caregivers (11)

Physicians (10) specific results

The following awareness emerged:

1. the **importance** of having **psychological support** as they work alongside patients and their caregivers through the various stages of disease and, especially, chronicity;
2. recognize their **own emotions** and use them as a **personal resource,** for their teams and patients;
3. **share strategies** for dealing with patients' anger and aggression;
4. **optimize** follow up visits for more constructive limited available **time**
5. awareness to **seek** new approaches to guide **patients to embrace the care of the entire team** and not just of the referring hematologist.

Sanquin

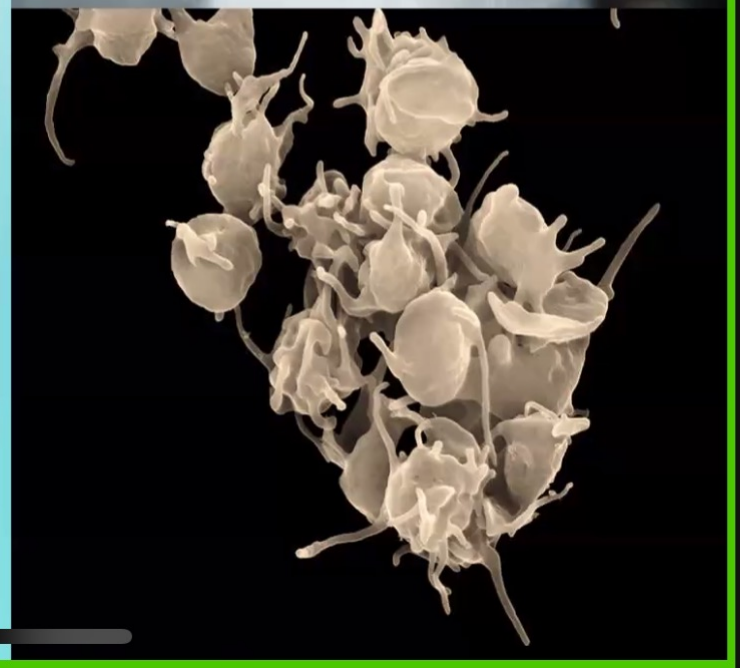
The intestinal flora: the key to unraveling heterogeneity in ITP?

Rick Kapur, MD, PhD, MSc

Sanquin, Amsterdam, The Netherlands

ASH ITP Breakfast Meeting,
San Diego, December 6, 2024

For Life.

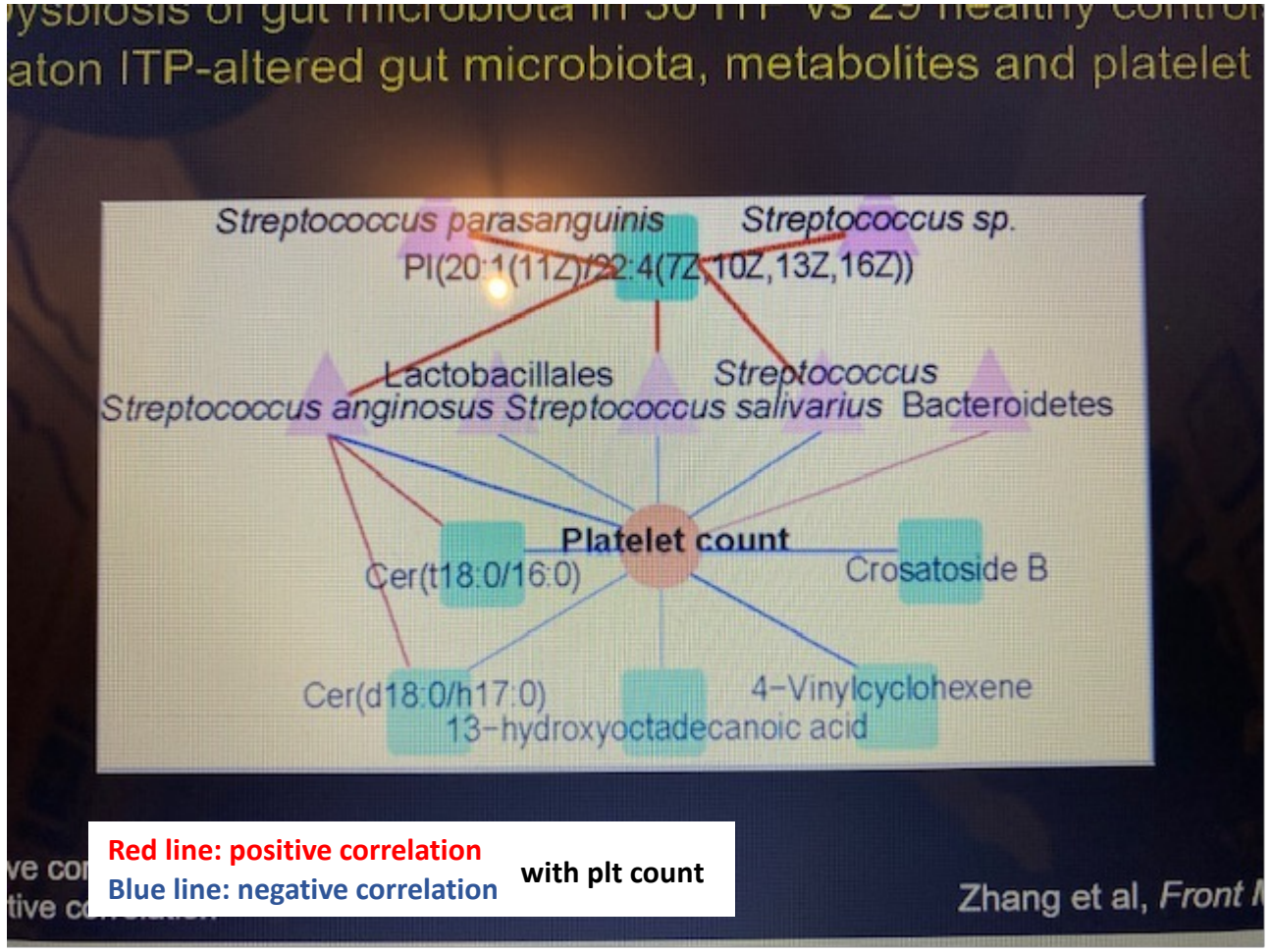


Gut microbiota and ITP: studies so far

Study	Patients	Finding
- Jiang et al, *Int J Hematol* 2024 - Li et al, *Front Microbiol* 2024 - Guo et al, *Front Microbiol* 2023	Mendelian randomization study	Several microbial taxa are potentially causally linked to ITP
Wang et al, *Hematology* 2023	40 ITP vs 33 healthy controls	Intestinal flora alterations in ITP patients caused by inflammation
Rui et al, *Front Cell Infect Microbiol* 2023	37 ITP vs 36 healthy controls	More abundant bacteria genera, specifically pseudomonas, in ITP patients
Yu et al, *Front Med* 2022	29 ITP vs 33 healthy controls	Relationship between microbiota and fatty metabolism in ITP
Wang et al, *Sci China Life Sci*, 2021	99 ITP vs 52 healthy controls	Corticosteroid-resistant ITP patients displayed a distinct gut microbiome
Zhang et al, *Front Microbiol*, 2020	30 ITP vs 29 healthy controls	Dysbiosis of gut microbiota and metabolome in ITP
Liu et al, *Thromb Res* 2020	9 ITP vs 10 healthy controls	Distinct microbiota dysbiosis in ITP characterized by alterations in biodiversity and composition

Gut Microbiome and Metabolome Were Altered and Strongly Associated With Platelet Count in Adult Patients With Primary Immune Thrombocytopenia

Zhang X et al Front in Microb 2020



- The findings of this study showed that the **alterations of ITP gut microbiota were mainly due to enrichment of Lactobacillus, Streptococcus and their members**, as well as **depletion of Bacteroides** and their members.
- In addition, fecal metabolomes of ITP patients comprised ITP-enriched Cer (t18:0/16:0) and the ITP-depleted lysoPE (14:0/0:0) and were significantly different from those of HCs.
- **Lactobacillales and its members**, including Streptococcus (p = 1.73E-06), S. anginosus (p = 2.00E-06) and S. salivarius (p = 8.95E-06) were **highly negatively (blue lines)** correlated with platelet counts, while **Bacteroidetes** (p = 4.92E-06) were **highly positively (red lines)** correlated with platelet count.
- Meanwhile, **lipids and lipid-like molecules Cer** (t18:0/16:0) (p = 1.67E- 06), **13-hydroxyoctadecanoic acid** (p = 3.10E-06), Cer (d18:1/17:0) (p = 3.62E-06), **Crosatoside B** (p = 3.76E-06) and **4-Vinylcyclohexene** (p = 9.11E-07) were highly negatively **(blue lines)** correlated with platelet count.
- **The intestinal flora and its metabolites may play a key role in the development of ITP.**

- Overall, these results may contribute to research in pathogenesis research, diagnosis and treatment of ITP.

Gut microbiota and ITP: early phase

- Observational cross-sectional studies only
- Various selection criteria ITP patients (Chinese vs ASH guidelines)
- Limited selection criteria healthy controls (diet, lifestyle, medications etc)
- Only comparison to healthy controls, lack of non-ITP thrombocytopenic group
- No focus on therapeutic responses (comparing responders to non-responders)
- No focus on newly diagnosed ITP vs chronic ITP
- No focus on childhood ITP
- No mechanistic experiments related to cellular ITP pathophysiology

Gut microbiota and ITP: conclusions

- ITP is characterized by a high degree of unexplained heterogeneity
- Early ITP studies have described a perturbed intestinal microbiota in ITP
- We hypothesize that the intestinal microbiota plays a role in ITP pathophysiology
- Analyzing gut microbiota may potentially aid in diagnostic and clinical management
- Further intestinal microbiota characterization is needed in ITP

Schoenaker et al, *Blood Rev 2024, in press*

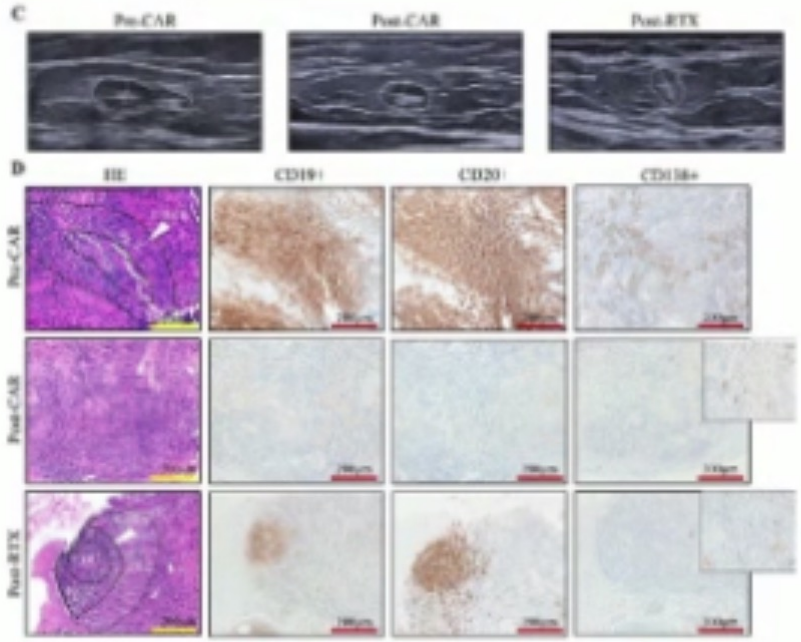
Gut microbiota and ITP: research agenda

- Characterization of gut microbiome using well-defined clinical cohorts of ITP patients and controls
- Investigating how a perturbed intestinal microbiome may mechanistically influence the heterogeneous pathophysiology in ITP patients
- Exploring the potential of personalized treatment using fecal microbiota transplantation in ITP patients

A perturbed intestinal microbiome may, at least in part, be responsible for the heterogeneity in ITP and its analysis may hold promise for improving diagnostic and clinical management.

Schoenaker et al, *Blood Rev 2024, in press*

Reason ② —— CAR T-cell therapy induces deep tissue depletion of B cells



B-cell lineage differentiation

Tumour cells antigen	Pro B cell	Pre B cell	Imm B B cell	Mature B cell	Memory B cell	Plasma blast	Plasma cell	Target
CD19								B cell
CD20								Bcell
CD22								B cell
BCMA								PC
CD38								PC
CD138								PC

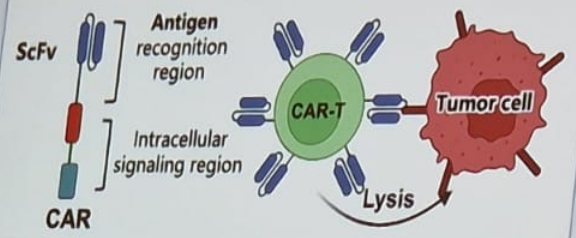
In SLE patients, compared to RTX treatment, CD19-CAR-T cell therapy **results in the complete depletion of the B cell maturation compartment**, including the disappearance of the follicular dendritic cell (FDC) network and T follicular helper (TFH) cells, along with a reduction in B cell proliferation (<90%).

Our exploration② —— Application of CAAR-T therapy in ITP

Chimeric Antigen Receptor (CAR)

Target head: **scFv** that binds to tumor cell surface antigens

Purpose: Specific killing of malignant clones of B cells

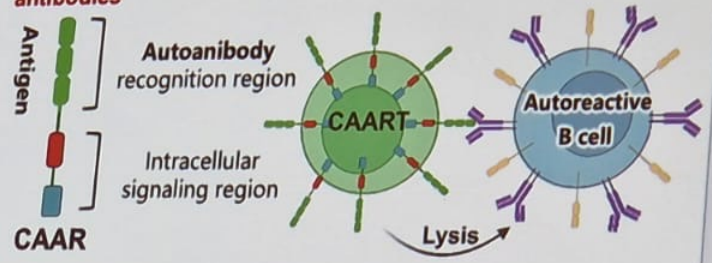


VS

Chimeric Autoantibody Receptor (CAAR)

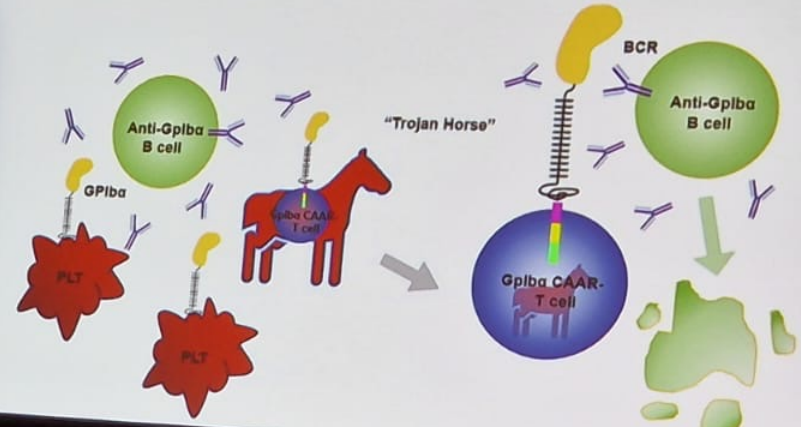
Target head: **Antigens** recognized by the autoreactive B cell receptor (BCR)

Purpose: Accurately destroy B cells that secrete specific antibodies



Trojan horse

Camouflaging CAAR-T cells targeting the GPIbα molecule associated with refractory relapsed ITP as platelets to recognize and eliminate autoreactive B cells secreting specific antibodies.



Our exploration① —— Clinical Trials of CAR-T at our center

Name	Type	Indication	Mechanism	Target
PRG-1801	CAR-T cells	ITP	Remove autoantibody-producing memory B cells, plasmoblasts, and plasma cells	BCMA
IASO-782	Fully Human Antibody	ITP AIHA	Clear CD19+ B cells and plasma cells by ADCC and ADCP	CD19

Car-T nelle piastrinopenie secondarie a malattie autoimmuni (Lupus, Sclerosi sistemica, Miastenia gravis, etc) e nelle ITP primarie

PRO

- **Risultati molto promettenti (in primis anti-CD19 e anti-BCMA)**
- **Attività profonda e prolungata per marcata deplezione dei cloni autoreattivi**
- **Remissione libera da terapie immunosoppressive**
- **Impatto favorevole su QoL**
- **Costi ? (Terapia one shot vs. terapie croniche…)**

Heng Mei

CONTRO

- **Disponibilità non immediata (leucoaferesi e manufacturing)**
- **Costi ? (Procedura e terapie di supporto costose)**
- **Tossicità (sebbene profilo di safety molto buono) quali CRS, ICANS, IEC-HS* (simil-HLH), ICAHT* (tossicità ematologica)**
- **Rischio infettivo**
- **Seconde neoplasie (?)**
- **Target eterogenei per patogenesi eterogenee; quale il migliore? (anti CD19? BCMA? GP1bα?)**

Nichola Cooper

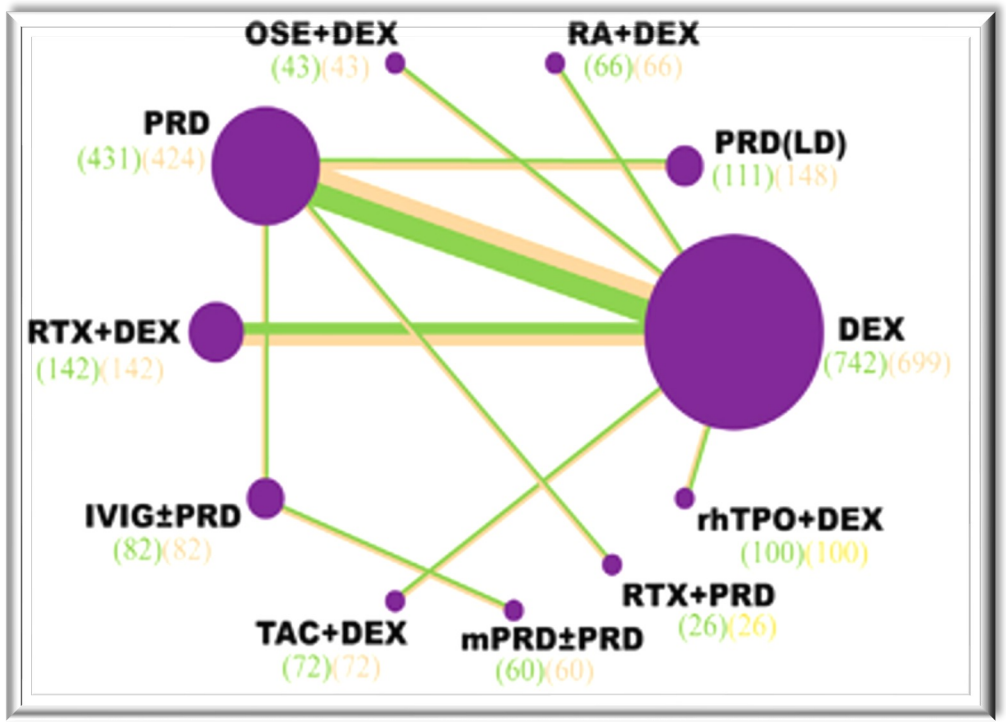
***HLH**: Linfoistiocitosi emofagocitica; **ICATH**: immune effector cell-associated hematotoxicity

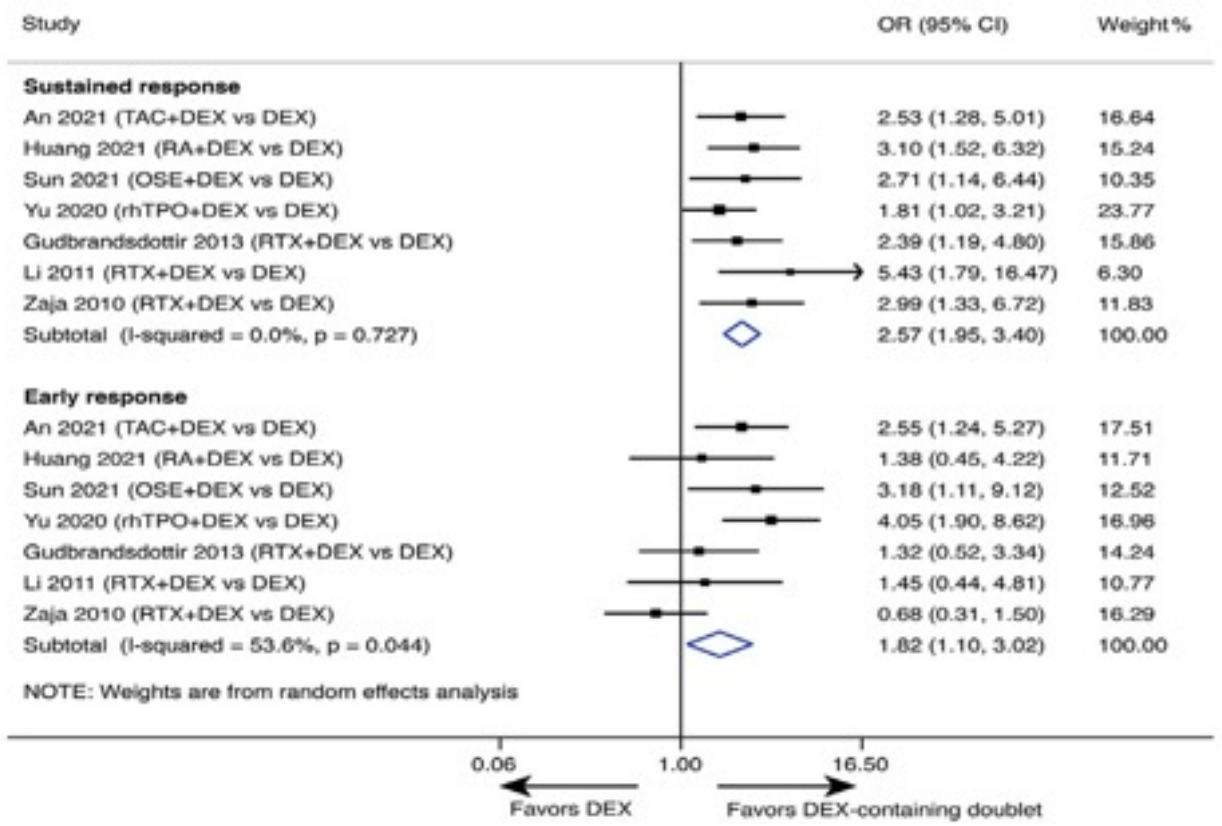
Insights on treatment of ITP: Algorithm for Management And Role of Multi-Modal Therapy

Waleed Ghanima[1], Adam Cuker[2], Marc Michel[3]

1. Østfold Hospital, Norway and Institute of Clinical Medicine, University of Oslo, Norway
2. Department of Medicine and Department of Pathology & Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
3. Department of Internal Medicine and Clinical Immunology, Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris, Université Paris-Est Créteil, Créteil, France.

Combination therapies improve early and sustained response rates in **newly diagnosed** ITP





Early Response: OR 1.82; 95% CI 1.10–3.0
Sustained Response: OR 2.57; 95% CI 1.95–3.4

Courtesy by Ghanima

DEX, dexamethasone; IVIG, intravenous gammaglobulin; mPRD, methylprednisolone; OR, odds ratio; OSE, oseltamivir; RA, all-trans retinoic acid; rhTPO, recombinant human thrombopoietin; RTX, rituximab; TAC, tacrolimus.

Wang et al. eClinicalMedicine 2023

Two ongoing trials currently evaluating the efficacy of TPO-RA + dexamethasone as **upfront therapy**

NCT04346654 Eltrombopag + DEX (XPAG-ITP)	NCT05325593 Romiplostim + DEX (RODEX)
Phase 2, multiceter, randomized (1:1), open-label study. Efficacy and Safety of Eltrombopag + DEX as first-line in adults patients with newly diagnosed primary ITP	Open label, randomized (1:1), phase 3 study. Compare romiplostim plus DEX vs DEX alone in patients with newly primary ITP

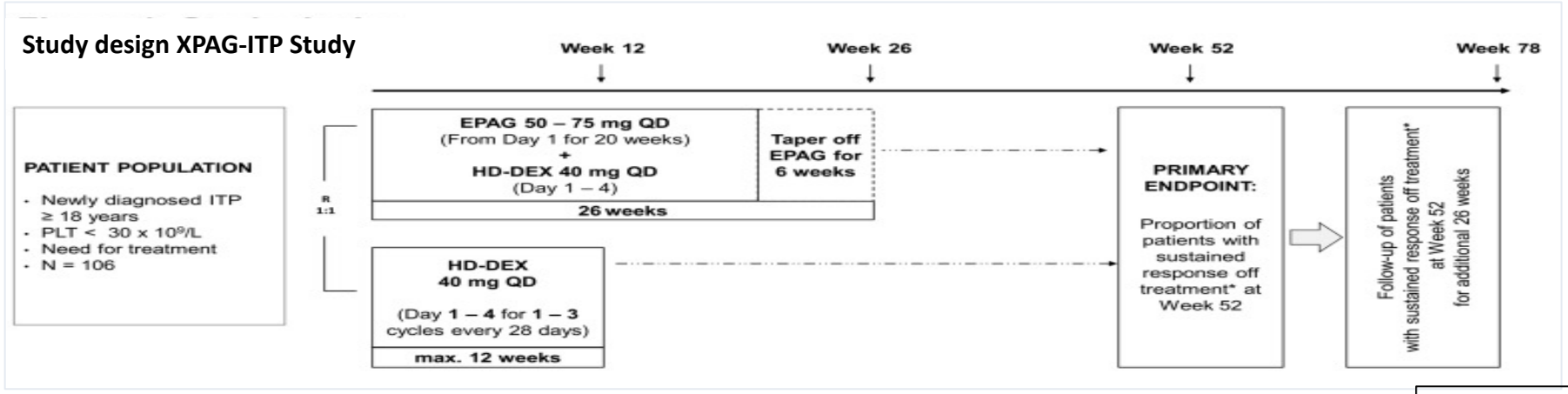
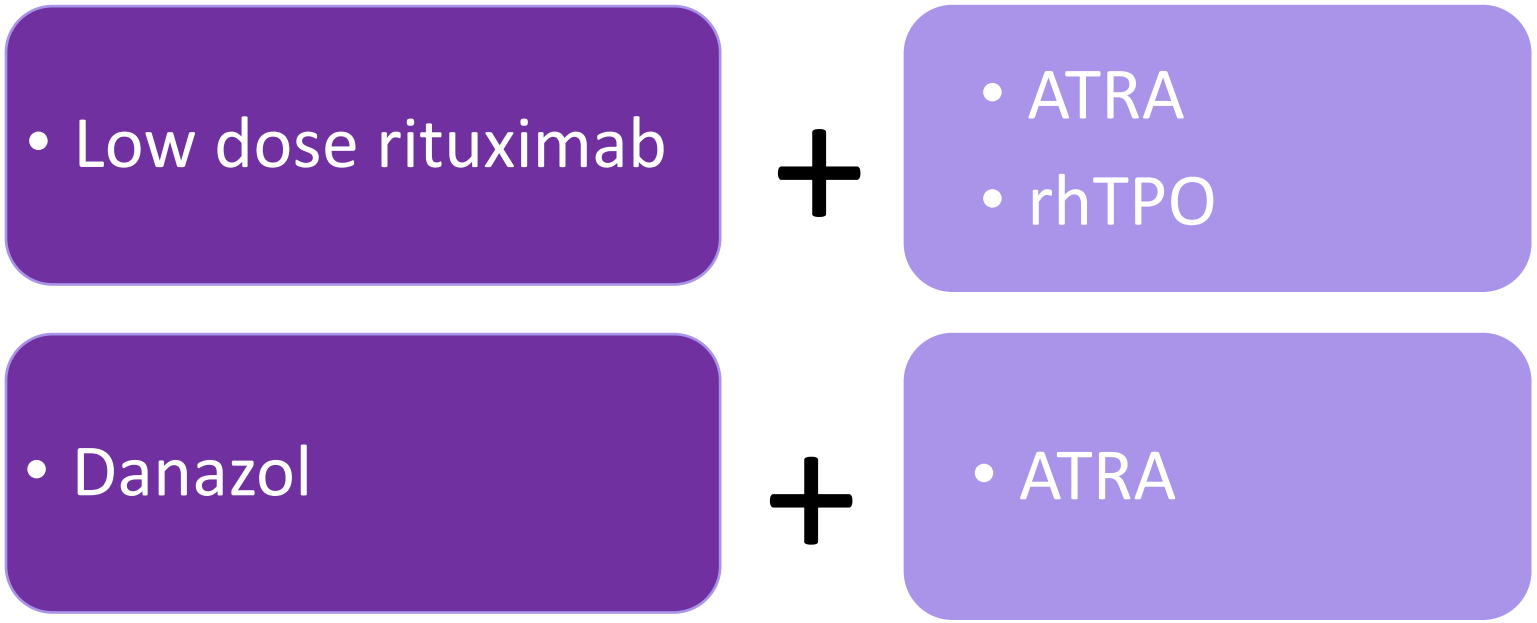


Figure from Zhuo et al. Blood 2021. EPAG: eltrombopag. HD-DEX: High-dose dexamethasone

Courtesy by Ghanima

Multi-modal combinations in the second line

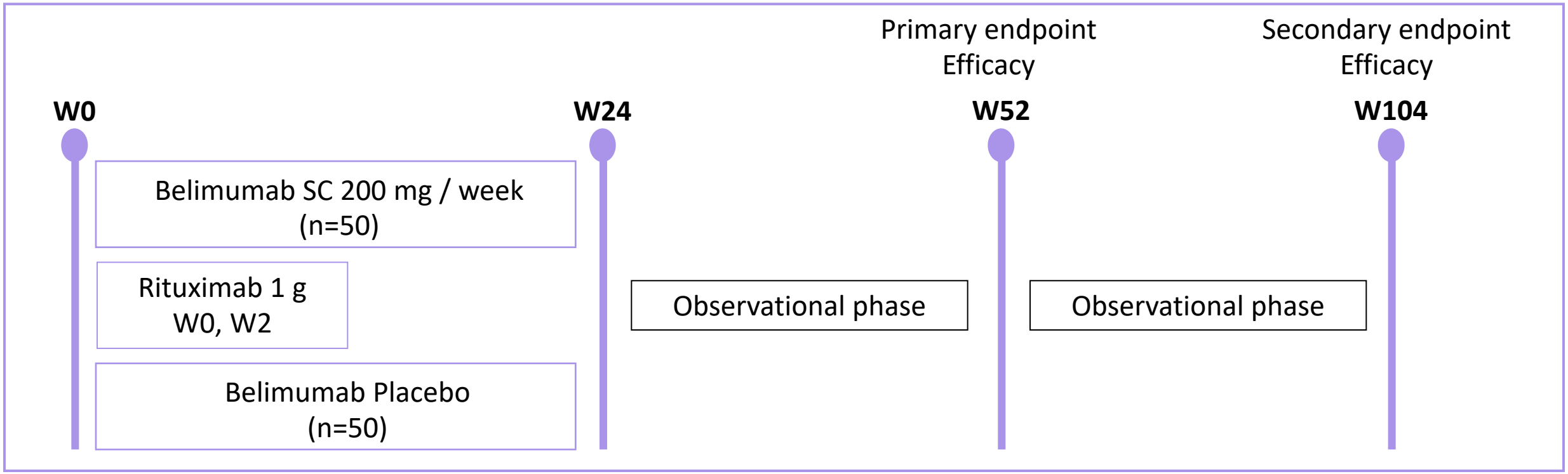


Courtesy by Ghanima

RITUX-PLUS 2 compares the efficacy of rituximab/belimumab vs rituximab/placebo in adults with persistent /chronic ITP

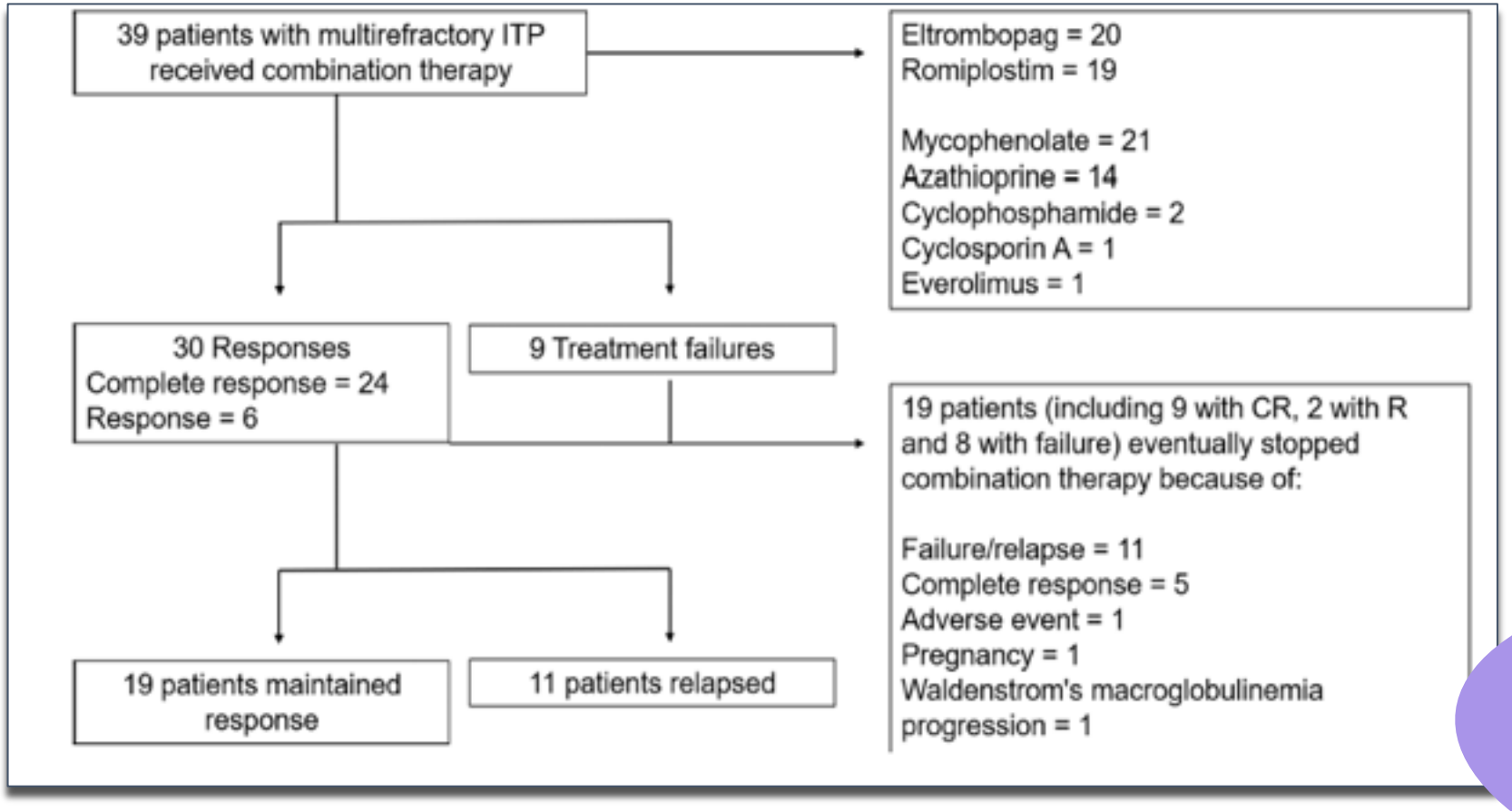
Courtesy by Ghanima

The combination of rituximab and belimumab was shown to be effective providing initial response in 87% in a single arm study of 15 patients



Mahévas M. *et al.* Haematologica 2020.

Multi-refractory ITP: combining immunosuppressive drugs with TPO-RA - an update on the French experience



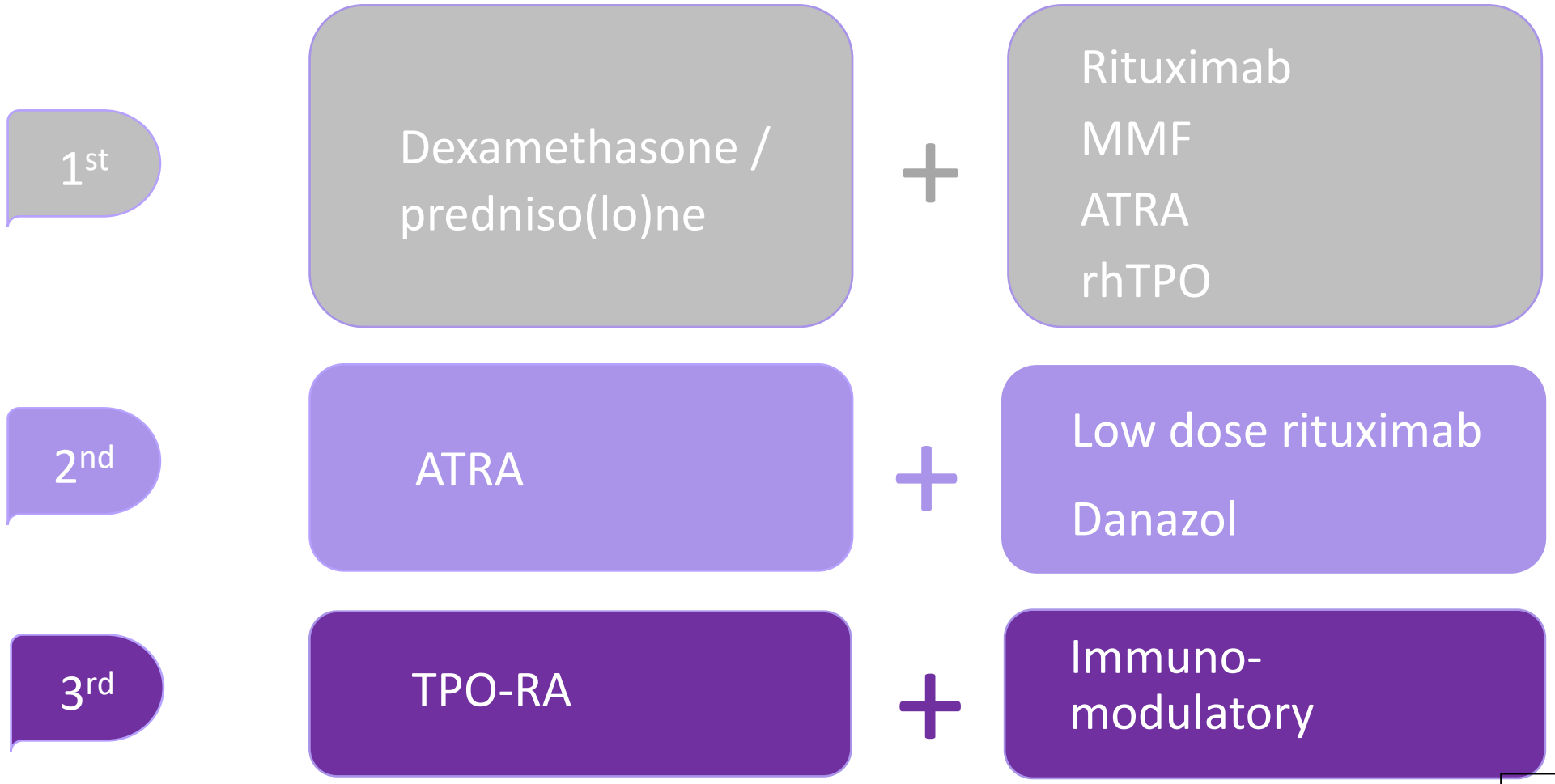
- 77% achieved at least a response
- After a median follow--up of 21 months
  - 63% in response
  - 37% relapsed

Multi-refractory defines as failure to response to rituximab, romiplostim and eltrombopag, and splenectomy (except if splenectomy was contra-indicated or refused by the patient)

Crickx et al. Br J Haematol. 2023

Courtesy by Ghanima

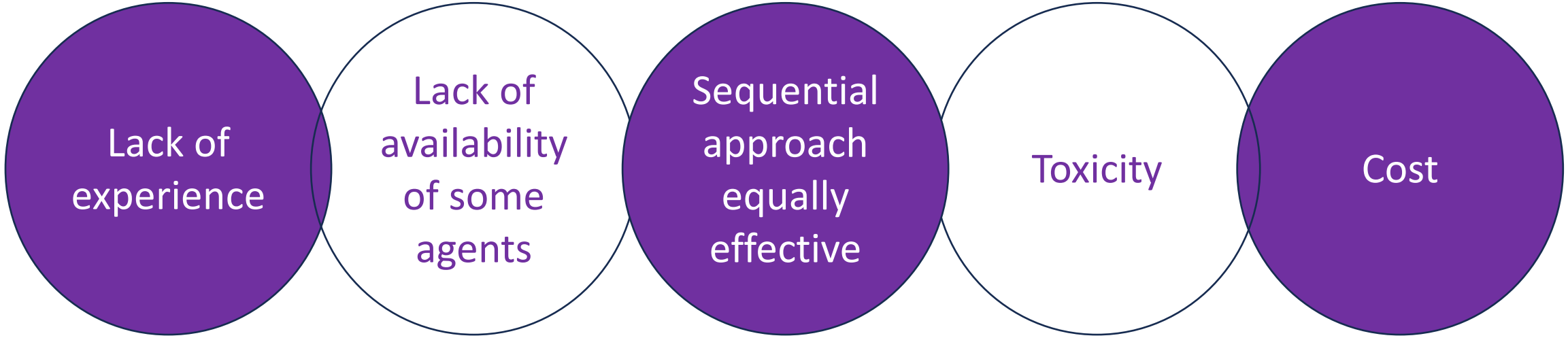
Most multi-modal combination therapy approaches have shown prolongation of sustained response rates



Courtesy by Ghanima

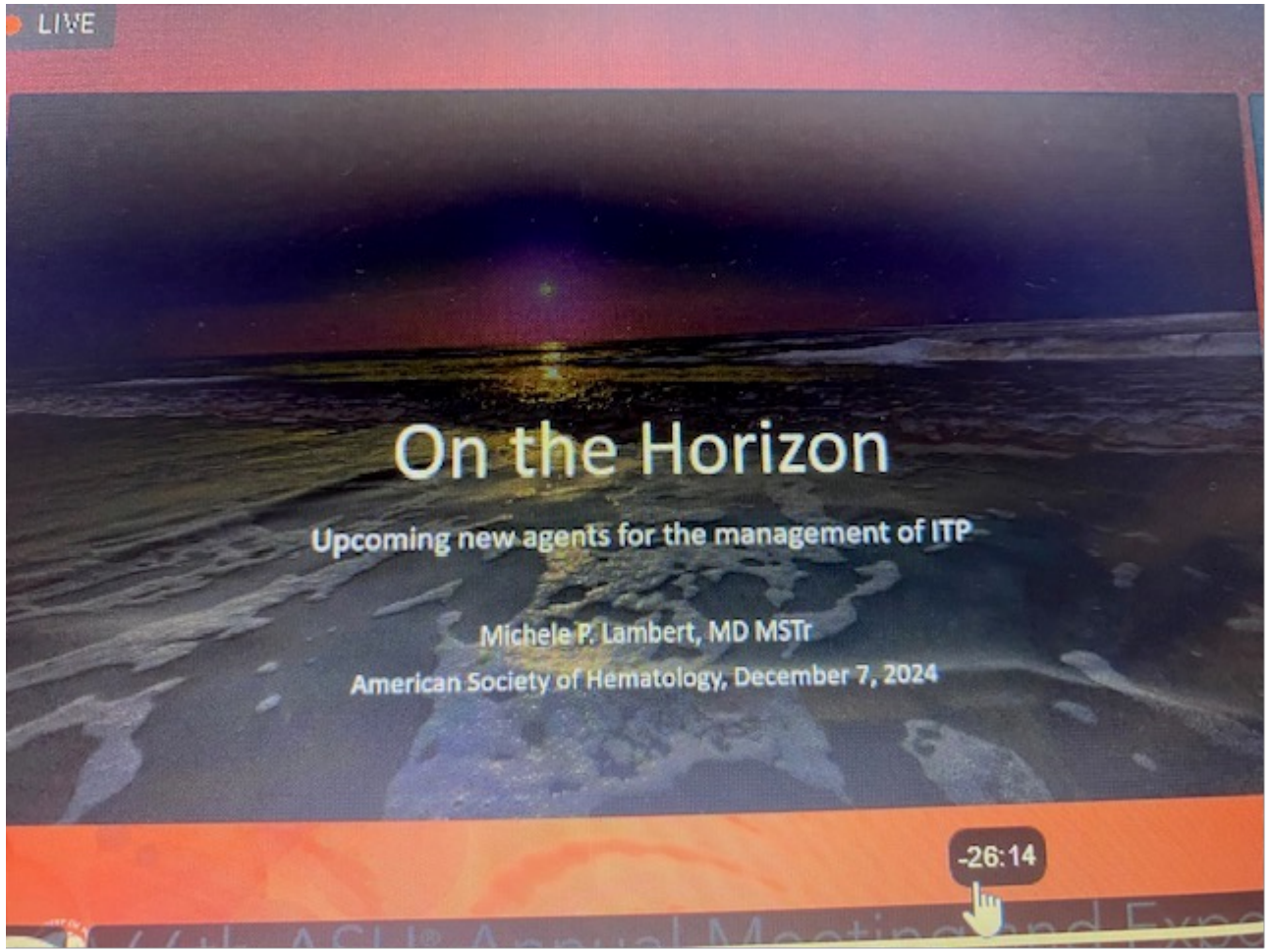
Despite encouraging results, and apart from refractory ITP, the use of multi-modal combinations remains very limited

Multiple reasons for limited use of combination therapies



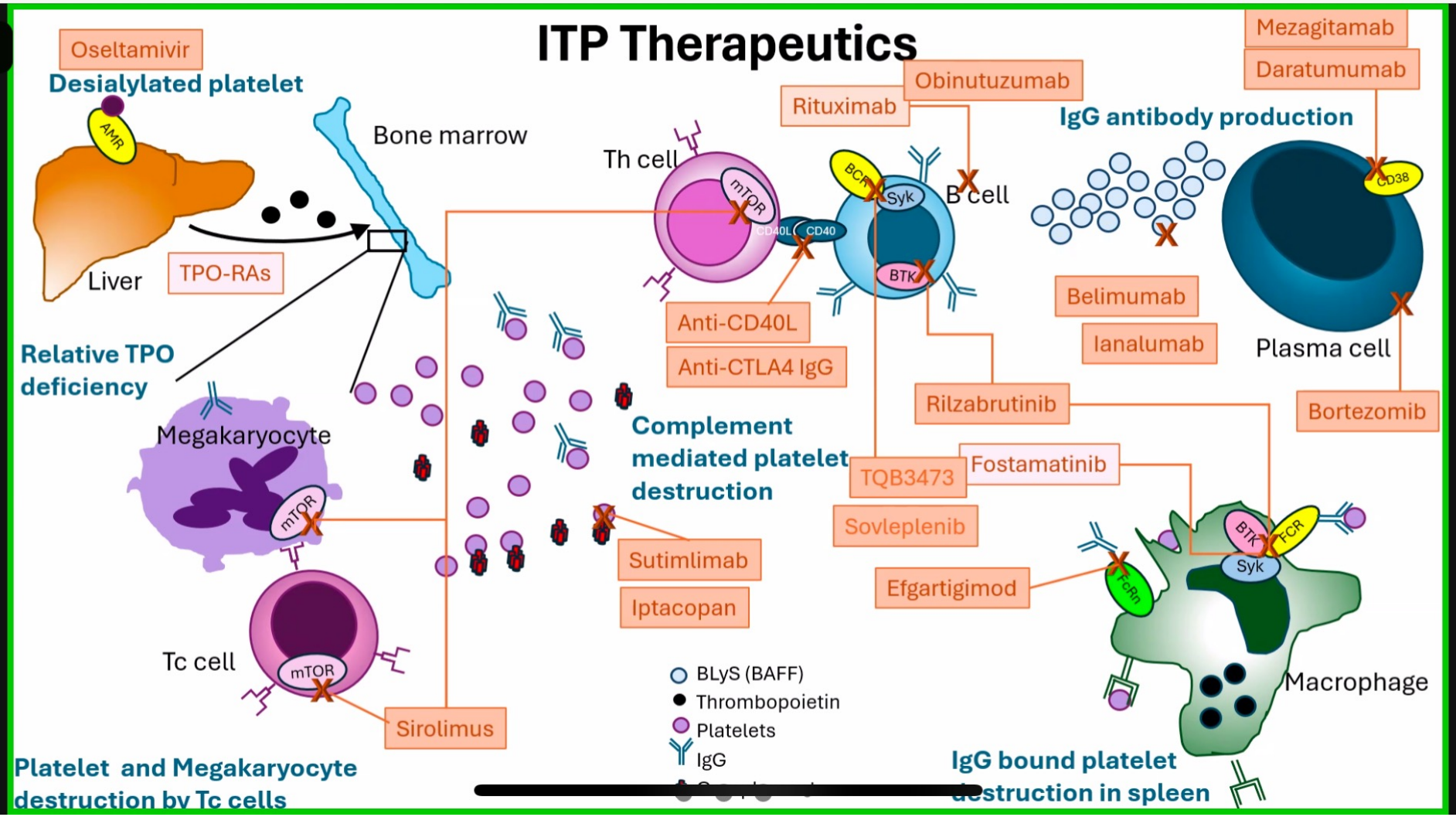
Courtesy by Ghanima

Ongoing trials on multi-modal combination may change the therapeutic landscape in the future



Educazionale: Michele P. Lambert, MD
Children's Hospital of Philadelphia
Philadelphia, PA

On the Horizon: Upcoming New Agents for the Management of ITP



Plasma cell inhibition: Anti-CD38

- Targets CD38 expressing plasma cells
- Reports of use of daratumumab and now open-label, phase 2 dose escalation study
- Current study (phase 2) of TAK-079 (Mezagitamab)
- CM313 phase 1-2 study recently reported

Anti-CD38 mAb in ITP

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BJHaem BRITISH JOURNAL OF HAEMATOLOGY — British Society for Haematology

SHORT REPORT

The early and rapid response to daratumumab in children with chronic refractory immune thrombocytopenia from a referral single centre of China

Yu Hu, Zhifa Wang, Jingyao Ma, Nan Wang, Jinxi Meng, Shuyue Dong, Zhenping Chen, Xiaoling Cheng, Runhui Wu

First published: 03 June 2024 | https://doi.org/10.1111/bjh.19553 IF: 5.1 Q1 | Citations: 1

Yu Hu and Zhifa Wang have contributed equally to this work and share first authorship.

BJHaem BRITISH JOURNAL OF HAEMATOLOGY — British Society for Haematology

LETTER TO THE EDITOR

Long-term complete remissions of refractory severe idiopathic immune thrombocytopenia treated with daratumumab: A case series

T. Strüßmann, J. Heinz, R. Wäsch, J. Jung, M. Engelhardt, J. Duyster, J. Finke, J. Duque-Afonso, R. Marks

First published: 28 July 2024 | https://doi.org/10.1111/bjh.19660 IF: 5.1 Q1

J. Duque-Afonso and R. Marks contributed equally as senior authors.

ELSEVIER — Blood Cells, Molecules, and Diseases

Volume 99, March 2023, 102724

Short communication

Daratumumab as a novel treatment option in refractory ITP

Ilze Vernava [a], Clemens A. Schmitt [a b c d e]

blood — **2021 ASH abstract**

Daratumumab As a Treatment for Adult Immune Thrombocytopenia: A Phase II Study with Safety Run-in (the DART Study)

Galina Tsykunova, Pal André Holme, Hoa Thi Tuyet Tran, Tor Henrik Anderson Tvedt, Ludvig Andre Munthe, Marc Michel, Henrik Frederiksen, James B Bussel, David J. Kuter, Waleed Ghanima

Check for updates

Blood (2021) 138 (Supplement 1): 2088.

https://doi.org/10.1182/blood-2021-151410 IF: 21.0 Q1

1. Hu Y, et al. Br J Haematol. 2024 Jul;205(1):300-305.
2. Strüßmann T, et al. Br J Haematol. 2024 Oct;205(4):1618-1621.
3. Vernava I, Schmitt CA. Blood Cells Mol Dis. 2023 Mar;99:102724.
4. Galina Tsykunova, et al. Blood 2021; 138 (Supplement 1): 2088.

CM313 for Treating ITP

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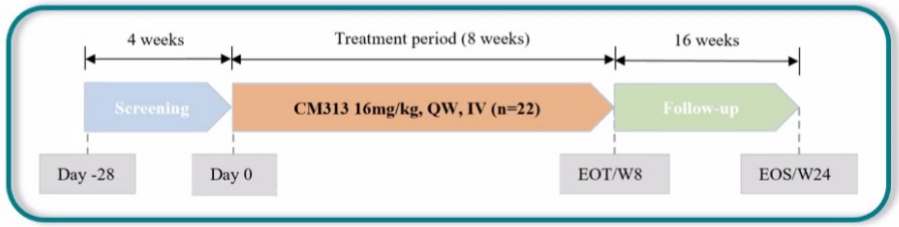
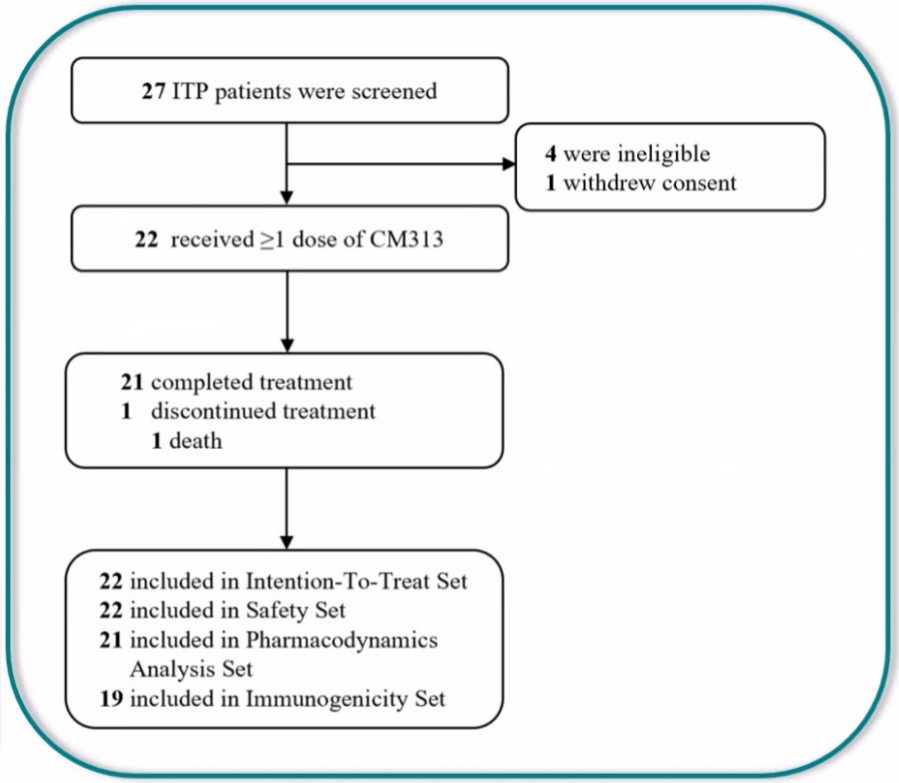
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Novel Anti-CD38 Monoclonal Antibody for Treating Immune Thrombocytopenia

Yunfei Chen, M.D., Yanmei Xu, M.D., Huiyuan Li, M.D., Ting Sun, M.D., Xuan Cao, M.D., Yuhua Wang, M.D., Feng Xue, M.D., Wei Liu, M.D., Xiaofan Liu, M.D., Huan Dong, M.D., Rongfeng Fu, M.D., Xinyue Dai, M.D., Wentian Wang, M.D., Yueshen Ma, M.S., Zhen Song, M.S., Ying Chi, M.D., Mankai Ju, M.D., Wenjing Gu, M.D., Xiaolei Pei, M.D., Renchi Yang, M.D., and Lei Zhang, M.D.





Chen Y, et al. N Engl J Med. 2024 Jun 20;390(23):2178-2190.

Treatment outcomes

山东大学齐鲁医院 QILU HOSPITAL OF SHANDONG UNIVERSITY | 山东大学第一临床学院

Table S4. Treatment Outcomes

Outcomes*	Total Patient (N=22)	95% CI
Primary endpoint#, n (%)	21 (95)	[77.2, 99.9]
PLT ≥ 50 × 10^9/L at least once within 12 weeks, n (%)	21 (95)	[77.2, 99.9]
PLT ≥ 30 × 10^9/L with a ≥ 2-fold increase from the baseline count (≥ 2 consecutive measurements) within 8 weeks, n (%)	21 (95)	[77.2, 99.9]
Time to the first PLT ≥ 30 × 10^9/L, median (range), weeks£	1 (1-3)	-
Time to the first PLT ≥ 50 × 10^9/L, median (range), weeks£	1 (1-3)	-
Cumulative response duration of PLT ≥ 30 × 10^9/L within 24 weeks¶, median (IQR), weeks	24 (17-24)	-
Cumulative response duration of PLT ≥ 50 × 10^9/L within 24 weeks, median (IQR), weeks	23 (17-24)	-
Durable sustained platelet count response rate‡, n (%)	14 (64)	[40.7, 82.8]
Overall response (OR) rate at week 8§, n (%)	18 (82)	[63.7, 97.0]
OR rate at week 12§, n (%)	19 (86)	[69.6, 98.8]
OR rate at week 24§, n (%)	14 (64)	[43.0, 85.4]
OR rate within 24 weeks§, n (%)	21 (95)	[77.2, 99.9]
Complete response (CR) rate within 24 weeks, n (%)	20 (91)	[70.8, 98.9]
Partial response (PR) rate within 24 weeks, n (%)	1 (5)	[0.1, 22.8]

Primary Outcomes:

- **Efficacy after CM313 treatment within 8 weeks**
- **Safety of CM313**

A total of 21 of the 22 patients (95%) had two or more consecutive platelet counts of at least 50×10^9 per liter during the 8-week treatment period, with a median cumulative response duration of 23 weeks (interquartile range, 17 to 24).

Secondary Outcomes:

- Other efficacy evaluation
- Duration from treatment initiation to platelet count ≥30×10^9/L and ≥50×10^9/L
- Cumulative weeks of platelet ≥30×10^9/L and platelet ≥50×10^9/L
- Number of subjects with clinically significant bleeding
- Measurements of platelet glycoprotein autoantibodies
- Measurements of immunoglobulin quantification
- Measurements of various subsets of immune cells

Chen Y, et al. N Engl J Med. 2024 Jun 20;390(23):2178-2190.

Summary

Conclusion:

- CD38 monoclonal antibody significantly increased the proportion and enhanced the immunosuppressive functions of Tregs.
- CD38 monoclonal antibody potentially reprograms the immunosuppressive function of Tregs by inhibiting Sirt-1, which provides a novel target for the management of ITP.
- This study suggested versatile mechanisms of anti-CD38 therapy in autoimmune disorders and rationalized its long-term efficacy in patients with ITP.

Unpublished data.

Immune Mechanism: B and T cell directed therapies

- Several therapies targeting anti-platelet antibodies:
  - Anti-CD20 antibodies (rituximab and similar)
  - BLyS (BAFF) inhibitors
  - BTK inhibitors
  - Syk inhibitors
  - Anti-plasma cell therapies
  - Anti-FcRN
- T cell directed therapies
  - Sirolimus
  - Anti CD40/CD40L

711 Preliminary Efficacy and Safety Results of TQB3473, a Novel Syk Inhibitor, in Adult Patients with Immune Thrombocytopenia (ITP), Hu Zhou et al.

- **Overall, 21/36 (58.3%) achieved responses** (at least 1 platelet counts >50x10^9/L within 12 weeks without rescue medication), and the response rate was 0, 63.0% and 66.7% at 400mg, 600mg and 800mg/day, respectively.
- **The overall durable response** (platelets counts >50x10^9 /L for at least 4 of 6 scheduled visits) rate was **30.6%**, which was 0, **33.3%** and 33.3% at 400mg /day, **600mg /day** and 800mg/day, respectively **(treatment duration 24 weeks)**
- **Median time to first platelet counts >50x10^9/L** for patients responded at 600mg /day was **25 days** (3-70). In primary responders, **platelet counts >50x10^9/L were maintained for 89% of visits**.

712 Updated Outcome from Biomarker MSC-C5b-9-Guided All-Trans Retinoic Acid Treatment for Resistant/Recurrent ITP: A Multicenter, Randomized, Open-Label, Phase 3 Clinical Trial, Menglin Li et al.

- Previous clinical trials firstly confirmed the efficacy and safety of all-trans retinoic acid (ATRA) in the treatment of ITP and revealed that MSC-C5b-9 may be a stratification marker for evaluating the efficacy of ATRA (Lancet Haematol,2021; Blood,2022).
- **Multicenter, randomized clinical trial; 96 patients were enrolled, including 29 (30%) MSC-C5b-9-positive patients.**
- **ATRA 10mgx2/day x 12w combined with eltrombopag vs elt alone (control) based on MSC-C5b-9 for the treatment of steroid-resistant/recurrent ITP.**
- **There was no significant difference in the complete response rate or response rate (IR and ER) between the two groups (p>0.05).**
- **Notably, among the MSC-C5b-9-negative patients, the ATRA group had a significantly higher CR rate and better treatment efficacy compared with the control group (p=0.008, p=0.038).**
- **Among all the patients, SR was achieved in 64.5% of patients in the ATRA group compared with 33.3% of patients in the control group (p=0.015) at 18 months after enrollment.**
- **Among the MSC-C5b-9-negative patients, SR was achieved in 72% of patients in the ATRA group, whereas it was achieved in 23.8% of patients in the control group (p=0.003) at 18 months after enrollment.**

713 Avespa Study: Effectiveness and Safety of Avatrombopag in Immune Thrombocytopenia (ITP). a Real-World Study of the Spanish ITP Group (GEPTI), Maria Cristina Pascual Izquierdoet al. al.

- **268 pts recruited from 28 Spanish hospitals and followed for a median of 47 months**
- **When AVA treatment started, 193, 46 and 29 had severe (PC <50x10^9 /L), moderate (50- 100x10^9 /L) and mild (>100x10^9 /L) ITP, respectively. Prior to switching to AVA 197 (73%) and 106 (40%) patients had used >2 and >3 lines of treatment, respectively.**
- **In the severe ITP group, 154/193 (79.8%) and 20/193 (10.4%) patients achieved CR (PC>100x10^9 /L) and R (PC>50x10^9 /L), respectively.**
- **Among 129/193 (67%) severe ITP patients who were still on AVA at their last visit, 87 (67.4%) and 26 (20.1%) had CR and R, respectively.**
- **Severe ITP patients reached R and CR in 13 (7-21) and 14 (9-35) days, respectively.**
- **65% of pts did not experience any AE, and - 9/268 (3.3%) pts experienced a thromboses, none fatal; 40/268 (15%) discontinued for thrombocytosis.**
- **At the end of follow-up, 185/268 (69%) pts were still on AVA treatment (stability of response).**

Efficacy and Safety of Oral Bruton Tyrosine Kinase Inhibitor Rilzabrutinib in Adults With Previously Treated Immune Thrombocytopenia: A Phase 3, Placebo-Controlled, Parallel-Group, Multicenter Study (LUNA 3)

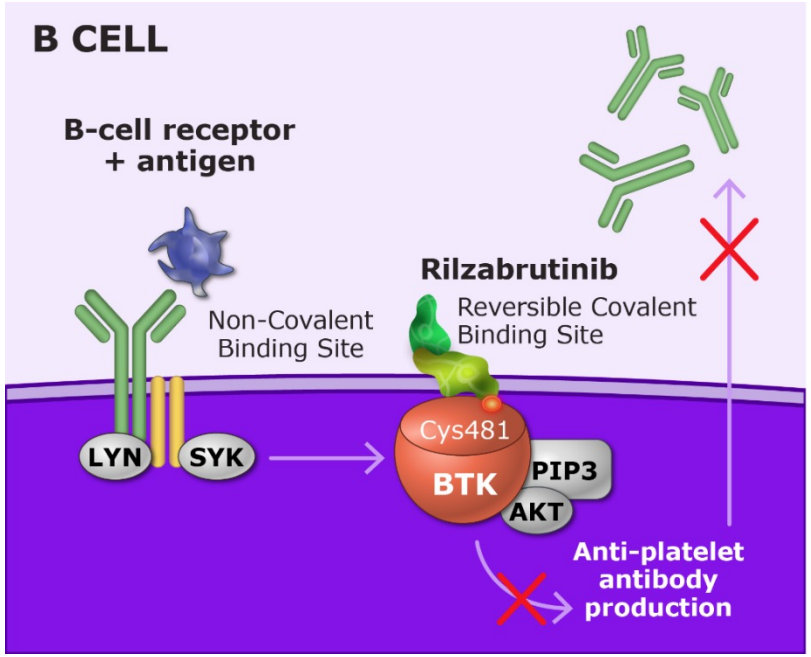
David J. Kuter,[1] Waleed Ghanima,[2] Nichola Cooper,[3] Howard A. Liebman,[4] Lei Zhang,[5] Yu Hu,[6] Yoshitaka Miyakawa,[7] Luisa Elena Morales Galindo,[8] Ana Lisa Basquiera,[9] Chuen Wen Tan,[10] Güray Saydam,[11] Marie Luise Hütter-Krönke,[12] Chatree Chai-Adisaksopha,[13] David Gómez Almaguer,[14] Huy Tran,[15] Ho-Jin Shin,[16] Maria Cristina Pascual Izquierdo,[17] Ilya Kirgner,[18] Elisa Lucchini,[19] Ganna Kuzmina,[20] Sylvain Audia,[21] Matias Cordoba,[22] Remco Diab,[23] Mengjie Yao,[24] Michelle J. Lee,[22] and Ahmed Daak[22] (LUNA 3 Trial Group)

[1]Hematology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Østfold Hospital Trust, Grålum, Norway and Institute of Clinical Medicine, University of Oslo, Oslo, Norway; [3]Hammersmith Hospital, London, United Kingdom; [4]University of Southern California, Los Angeles, CA, USA; [5]Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin, China; [6]Wuhan Xie'he Hospital, Wuhan, China; [7]Department of Hematology, Saitama Medical University, Saitama, Japan; [8]IC La Serena Research SpA, La Serena, Chile; [9]Hospital Privado Universitario de Córdoba-Instituto Universitario de Ciencias Biomédicas de Córdoba (IUCBC), Cordoba, Argentina; [10]Department of Hematology, Singapore General Hospital, Singapore; [11]Internal Medicine and Hematıology, Faculty of Medicine, Ege University, İzmir Türkiye; [12]Department of Hematology, Oncology and Tumorimmunology, Charité - Universitätsmedizin Berlin, Freie Universität Berlin and Humboldt Universität zu Berlin, Berlin, Germany; [13]Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand; [14]Hospital Universitario Dr. Jose Eleuterio Gonzalez, Monterrey, Mexico; [15]Peninsula Private Hospital, Frankston, Victoria, Australia; [16]Division of Hematology-Oncology, Department of Internal Medicine, Biochemical Research Institution, Pusan National University Hospital, Pusan National University School of Medicine, Busan, Republic of Korea; [17]Instituto de Investigación Gregorio Marañon, Madrid, Spain; [18]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [19]UCO Ematologia, Azienda Sanitaria Universitaria Giuliano-Isontina, Trieste, Italy; [20]Municipal Enterprise Kryvyi Rih City Clinical Hospital #2 of Kryvyi Rih City Council, SI Dnipropetrovsk Medical Academy under the Ministry of Health of Ukraine, Kryvyi Rih, Ukraine; [21]CHU Dijon Bourgogne - Hopital Francois Mitterrand, Dijon, France;

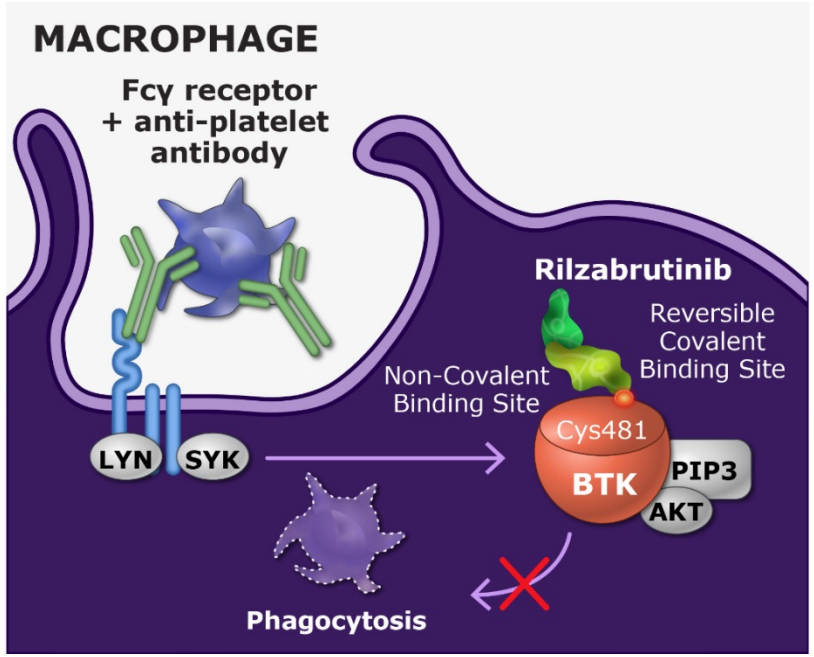
#5

Rilzabrutinib is an Oral, Reversible, Potent BTK Inhibitor

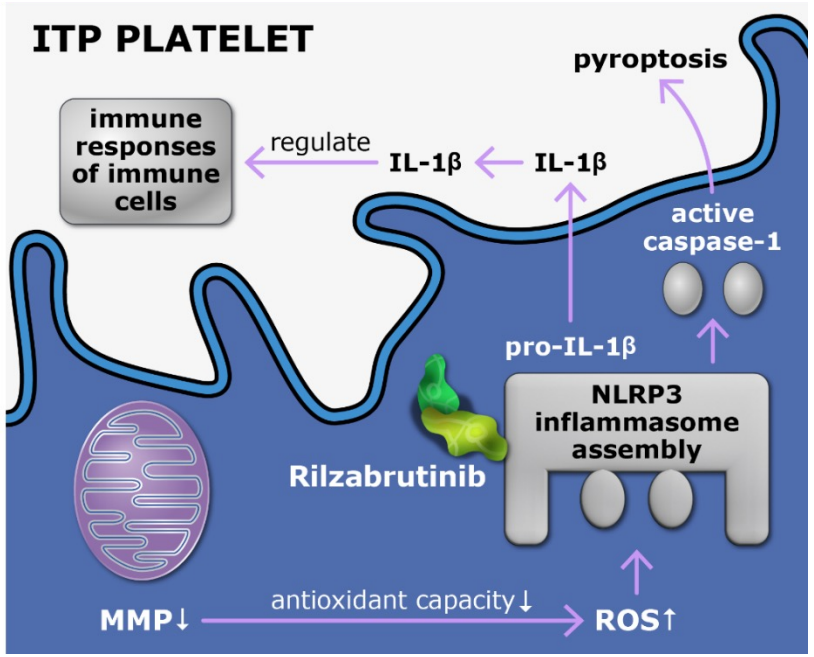
Inhibition of B cell activation



Interruption of platelet phagocytosis by FcγR in spleen and liver



Inhibition of inflammatory pathways in ITP platelets



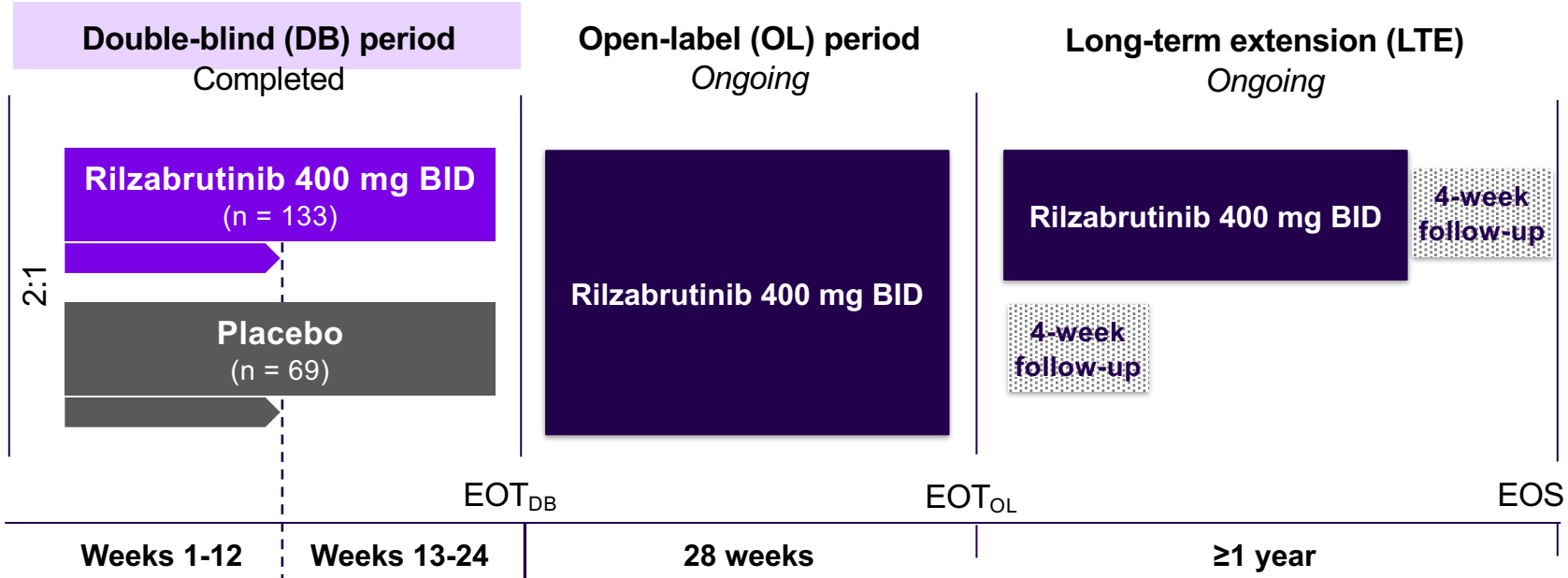
BTK inhibition impacts different mechanisms that target key aspects of ITP disease pathophysiology[1-4]

1. Kuter DJ, et al. *Ther Adv Hematol*. Copyright © 2023, © SAGE Publications. 2023;14. doi: 10.1177/20406207231205431. 2. Langrish CL, et al. *J Immunol*. 2021;206(7):1454-1468.
3. Wang S, et al. *Thromb Res*. 2021;199:1-9. 4. Daak A, et al. *Blood* (ASH). 2024;abstract 2482.

LUNA 3 Study Design

Adult patients (*pediatric ongoing*)

- Age ≥18 years
- Persistent or chronic primary ITP
- Prior IVIg/anti-D or CS but not sustained
- Qualifying platelet counts <30×10^9/L
- Allowed stable concomitant CS and/or TPO-RA



Median number prior therapy before trial: 4

Platelet response (week 13)

- Platelet count ≥50×10^9/L or ≥30–<50×10^9/L and doubled from baseline
- Non-responders: option to discontinue or proceed to open-label on rilzabrutinib only

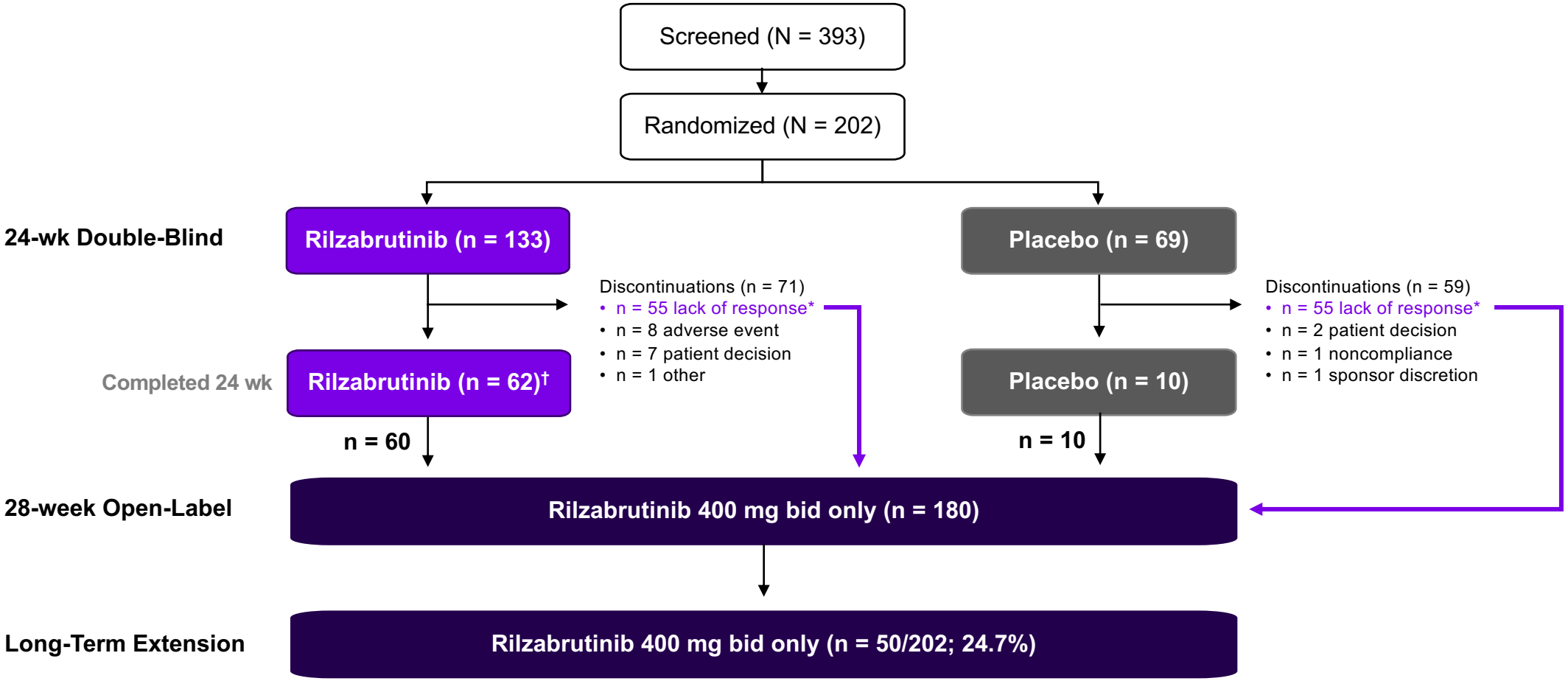
Durable response (week 25)

Primary endpoint

- Platelet count ≥50×10^9/L for ≥ two-thirds of last 12 weekly (8/12) visits in the absence of rescue therapy

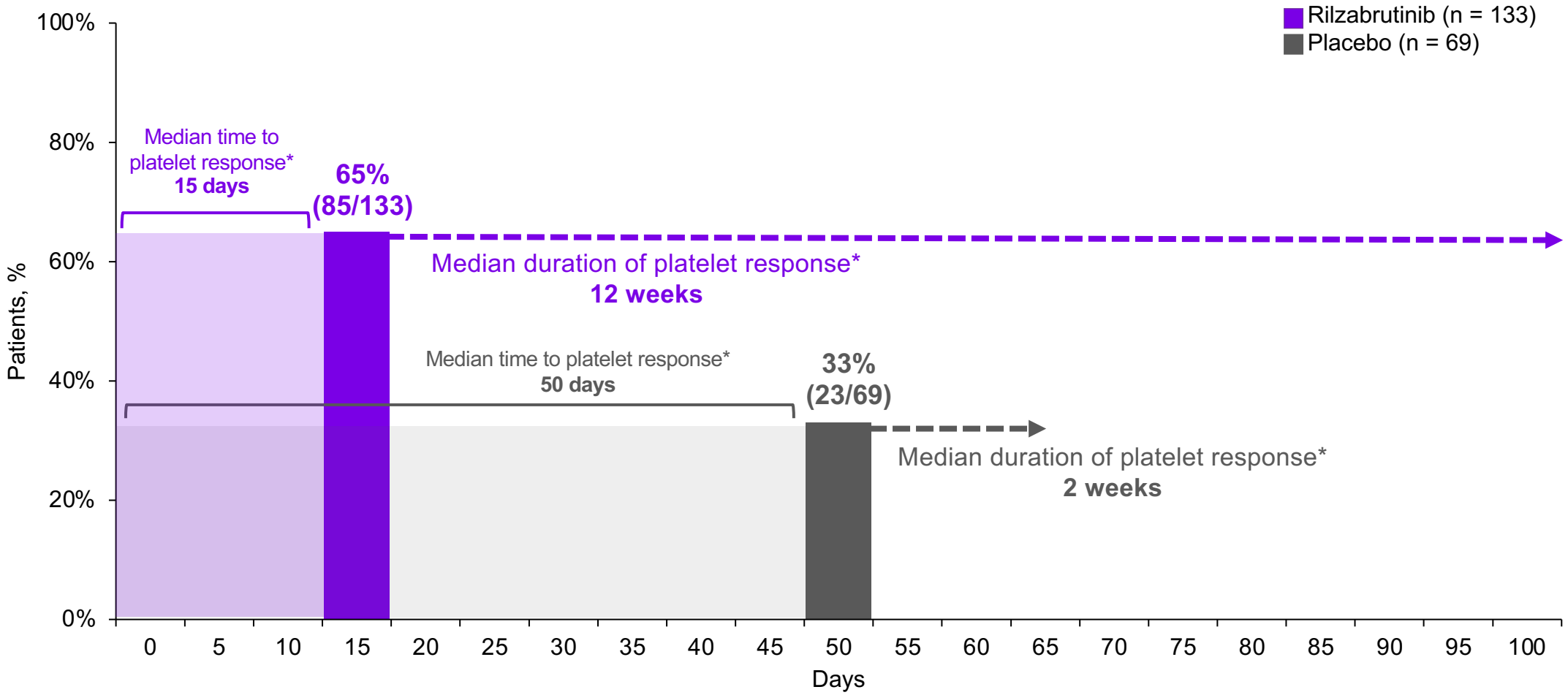
NCT04562766; EudraCT 2020-002063-60.

Patient Disposition



Data cutoff 14 March 2024.
*Lack of response per protocol (including receipt of rescue medication week >8). Week 12 non-responders could transition to open-label directly on rilzabrutinib or discontinue the study.
†Two additional rilzabrutinib patients had not yet entered the open-label period.

Initial Platelet Response (within the first 12 weeks)
Platelet count >50×10^9/L or 30-<50×10^9/L and at least doubled from baseline

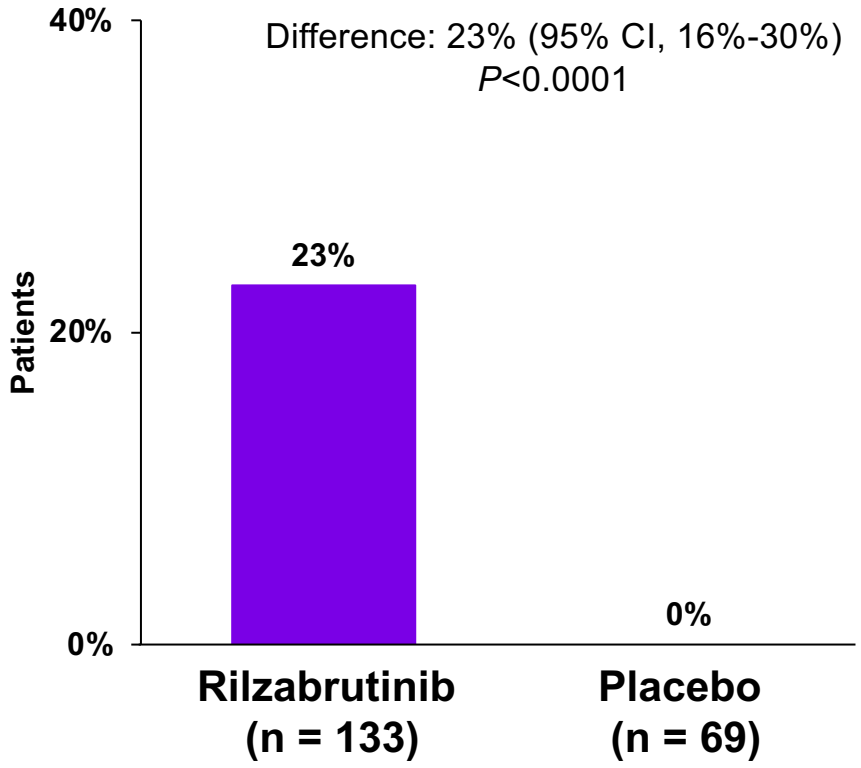


Data cutoff 14 March 2024.

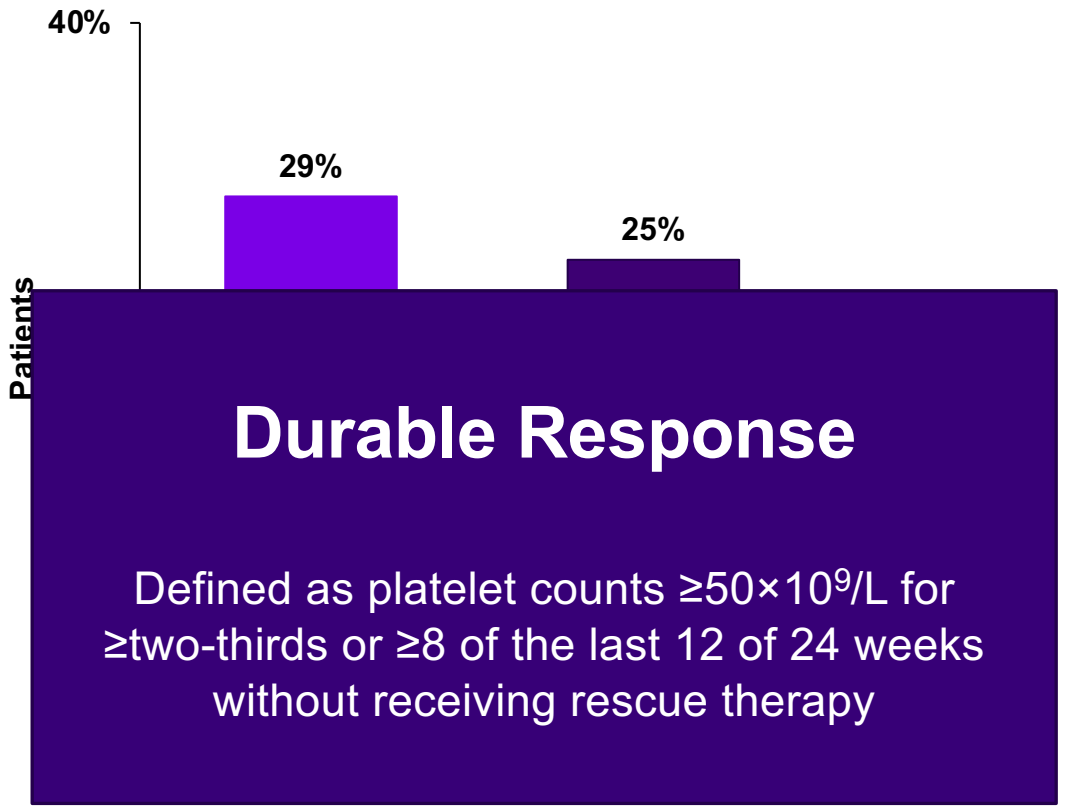
*Response was at any **during the double-blind period.** Time to and duration of platelet response values were **in patients achieving response at any point during the double-blind period.**

Durable Platelet Response

Durable Response
Week 25 Primary Endpoint Was Met



Durable Response
Double-blind + Open-label at data cutoff



Data cutoff 14 March 2024.

*Included 133 rilzabrutinib and 60 placebo patients from double-blind and all patients receiving rilzabrutinib during the open-label period.

LUNA 3 Conclusions

Rilzabrutinib had superior durable platelet response vs placebo

All secondary endpoints were significantly improved with rilzabrutinib

– Significantly earlier time to first platelet counts, higher number of weeks at platelet count thresholds, fewer patients requiring rescue therapy, and improved fatigue, HRQoL, and bleeding scores

Rilzabrutinib significantly improved fatigue, even among non-durable platelet responders

Mainly low-grade AEs observed with rilzabrutinib, with no BTK inhibitor class effects

Rilzabrutinib led to rapid and durable platelet responses, improved HRQoL, and was generally well-tolerated in difficult to treat adults with ITP

POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

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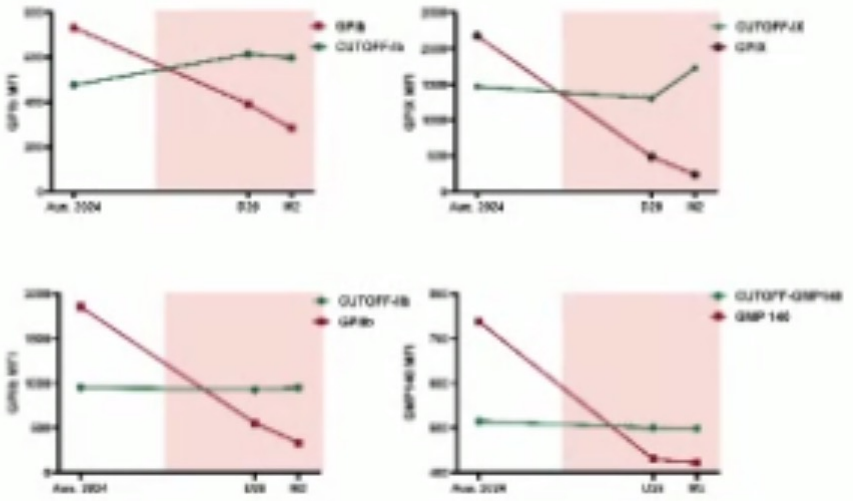
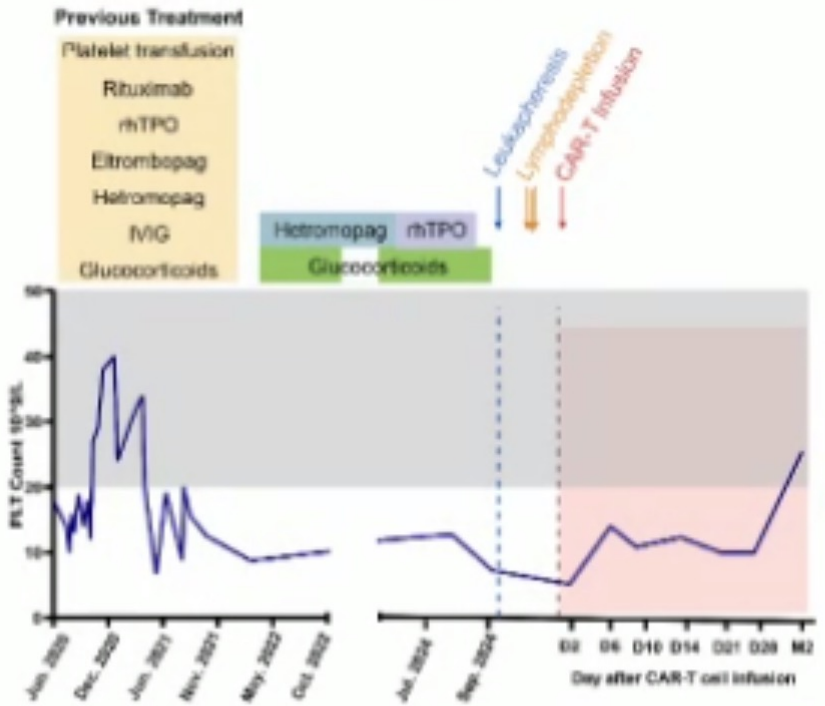
The evaluation of efficacy





- On Day 28, the patient's anti-platelet glycoprotein antibodies turned negative, and the patient's platelet count showed a sustained upward trend.

Avatrombopag plus Fostamatinib for treatment of patients with **multi-refractory ITP**

Courtesy by Ghanima

Retrospective, multicenter, international, observational study

N=18

Median 5 treatments prior to combination

OR 83%

15/18 Overall response; 8/15 CR

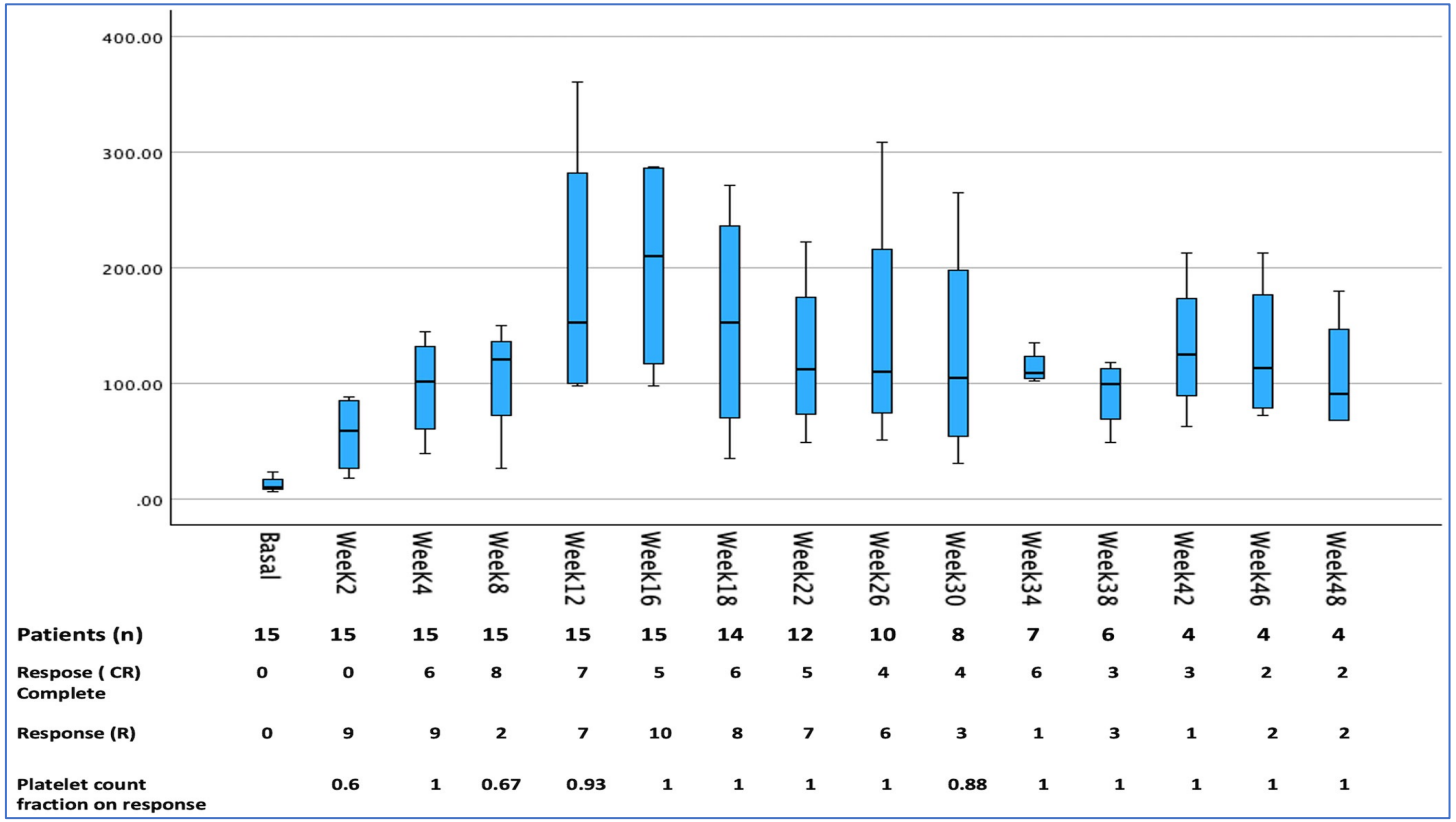
15 days

(range: 8–35 days)
Median time to response

Relapse 27%

Relapsed during dose tapering

Platelet count response and evolution in responding patients



	Basal	WeeK2	WeeK4	Week8	Week12	Week16	Week18	Week22	Week26	Week30	Week34	Week38	Week42	Week46	Week48
Patients (n)	15	15	15	15	15	15	14	12	10	8	7	6	4	4	4
Respose (CR) Complete	0	0	6	8	7	5	6	5	4	4	6	3	3	2	2
Response (R)	0	9	9	2	7	10	8	7	6	3	1	3	1	2	2
Platelet count fraction on response		0.6	1	0.67	0.93	1	1	1	1	0.88	1	1	1	1	1

[a] Response PC 30-100 x 10^9/L and complete response PC >100 x 10^9/L. AVA,

Mingot Castellano BJH 2024

Inhibiting NFκB: Bortezomib

- Proteosome inhibitor targeting NFκB
- Case reports and small case series reporting responses in refractory patients
- Biology study in murine models (Thromb haemost 2018)
- Two clinical trials open looking at bortezomib +/- rituximab
  - phase 2 single arm open label
  - Phase 3 randomized trial of combination vs rituximab alone

Immune Mechanism: Anti-platelet antibodies

- Several therapies targeting anti-platelet antibodies:
  - Anti-CD20 antibodies (rituximab and similar)
  - BLyS (BAFF) inhibitors
  - BTK inhibitors
  - Syk inhibitors
  - Anti-plasma cell therapies
  - Anti-FcRN