POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

Novità dal Meeting della Società Americana di Ematologia

Piastrinopenie

Francesco Zaja - Trieste

Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

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Pier Luigi Zinzani

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DICHIARAZIONE

Francesco Zaja

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(Novartis, Argenx)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(Novartis, Amgen, Grifols, Sobi)**
- Partecipazione ad Advisory Board **(Novartis, Amgen, Grifols, Sobi, Argenx)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

Outlines

1. **BTK inhibition in ITP. Rilzabrutinib:**
   - **2 abstracts: Outcome and QoL**
2. **TPO-RAs in ITP and CIT/CAR-T:**
   - **3 abstracts:**
     - **Avatrombopag in newly diagnosed and persistent ITP**
     - **Avatrombopag in combination with Fostamatinib**
     - **TPO-RAs in CIT/CAR-T**
3. **APRIL-BAFF inhibitors in ITP**
4. **CAR-T in ITP mouse models**

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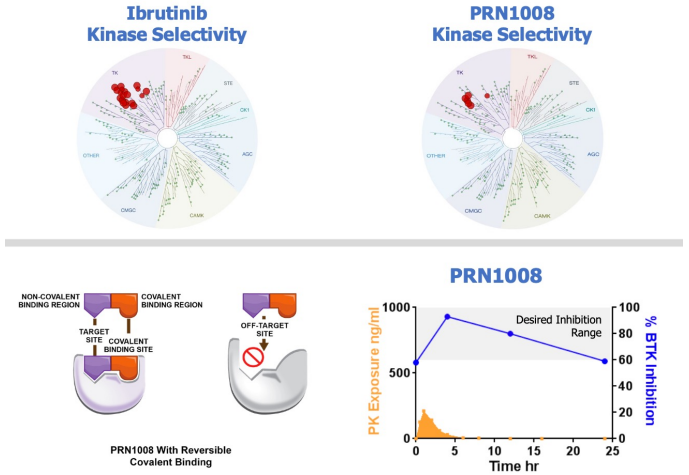
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia

David J. Kuter, M.D., Merlin Efraim, M.D., Jiri Mayer, M.D., Marek Trněný, M.D.,

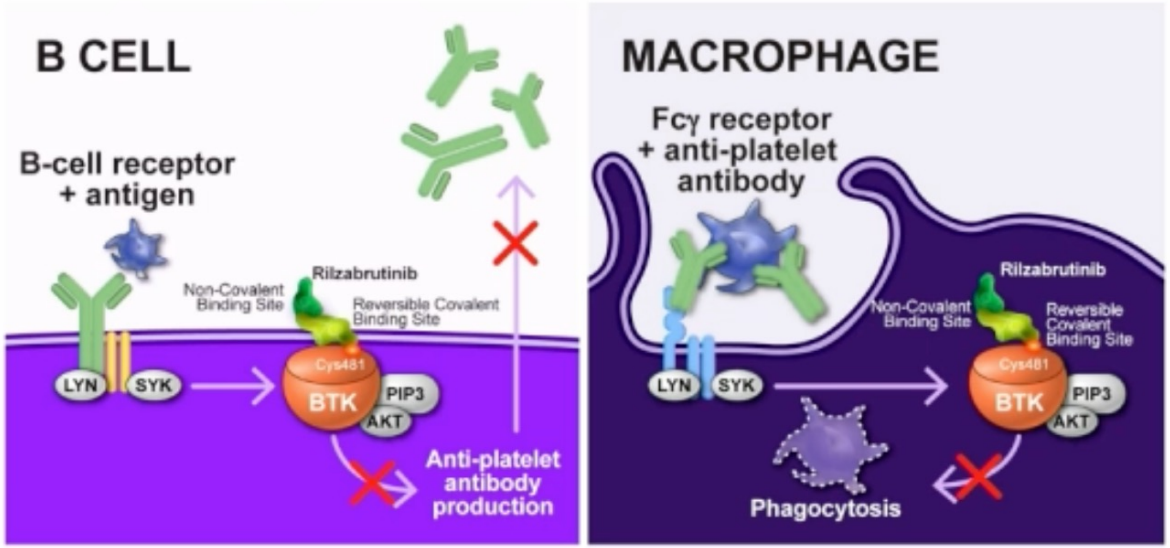


- Rilzabrutinib is an oral, **reversible covalent** Bruton's tyrosine kinase (BTK) inhibitor
- BTK is present in the signalling pathways of most types of WBC except for T-cells and plasma cells.
- Rilzabrutinib does not inhibit collagen-activated platelet aggregation

N Engl J Med 2022;386:1421-31.

Bruton Tyrosine Kinase Inhibitor Rilzabrutinib Is Specifically Designed for Immune-Mediated Diseases

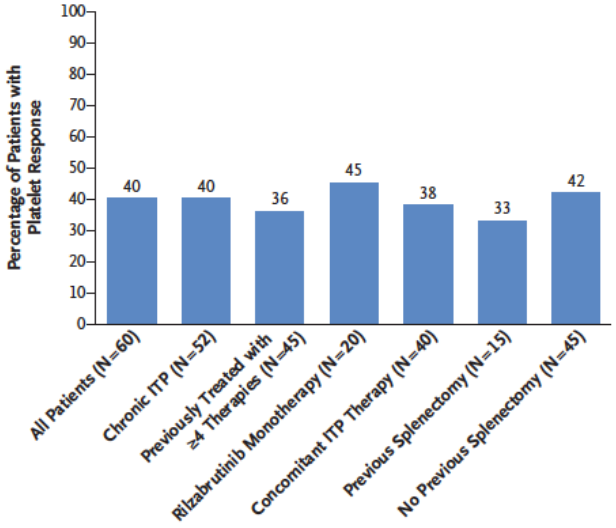
- Rilzabrutinib mediates ITP therapeutic effects through dual mechanisms of action[1,2]
  - Inhibition of B-cell activation
  - Interruption of platelet phagocytosis by FcγR in spleen and liver

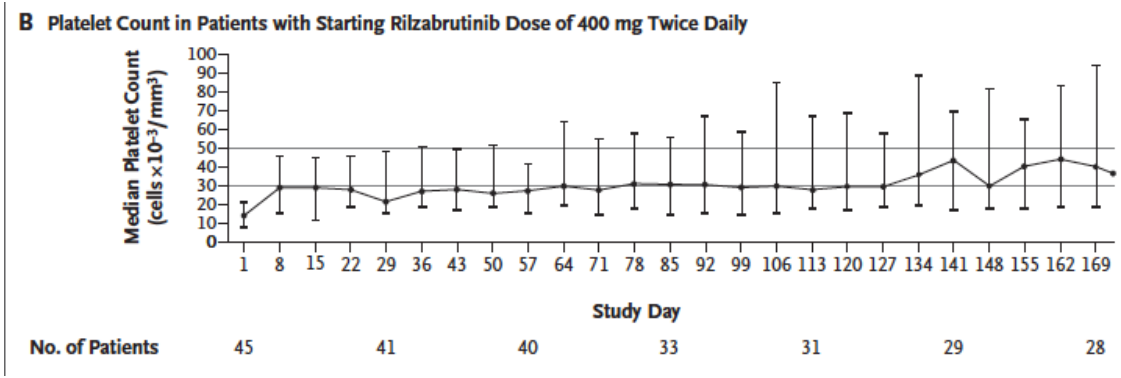


1. Langrish C, et al. *J Immunol*. 2021;206:1454-1468. 2. Kuter DJ, et al. *Ther Adv Hematol*. 2023;14:1-14. Copyright © 2023 (Sage Pub). DOI:10.1177/20406207231205431.

Primary endpoint: PLT response in patients starting on 400 mg bid (n = 45)

- Median treatment duration was 168 days (range 10-188) for the main treatment period and LTE
- **18 patients (40%)** initiating 400 mg bid rilzabrutinib met the primary endpoint, defined as
  - ≥2 consecutive platelet counts ≥50×10^9/L and
  - increased ≥20×10^9/L and
  - no use of rescue medication in the 4 weeks prior to the latest elevated platelet count
- 16 of these 18 patients showed clinically relevant platelet counts of ≥50×10^9/L at any point in the first 8 weeks of study treatment





D Kuter et al. New Engl J Med 2022;386:1421-1431

INITIAL REPORT OF PART B PHASE 1/2 EFFICACY AND SAFETY RESULTS FOR BRUTON TYROSINE KINASE INHIBITOR RILZABRUTINIB IN PATIENTS WITH RELAPSED IMMUNE THROMBOCYTOPENIA

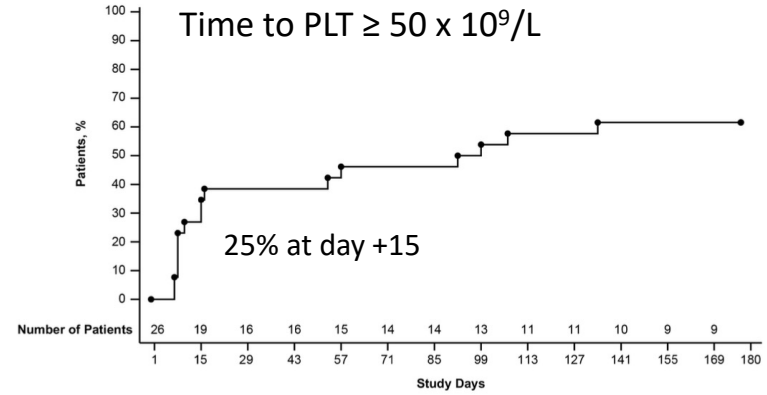
Nichola Cooper,[1] A. J. Gerard Jansen,[2] Robert Bird,[3] Jiří Mayer,[4] Michelle Sholzberg,[5] Michael D. Tarantino,[6] Mamta Garg,[7] Paula F. Ypma,[8] Vickie McDonald,[9] Charles Percy,[10] Milan Košťál,[11] Isaac Goncalves,[12] Lachezar H. Bogdanov,[13] Terry B. Gernsheimer,[14] Remco Diab,[15] Mengjie Yao,[16] Ahmed Daak,[17] and David J. Kuter[18]

[1]Hammersmith Hospital, London, United Kingdom; [2]Erasmus MC, University Medical Center, Rotterdam, Netherlands; [3]Princess Alexandra Hospital, Woolloongabba, Australia; [4]Masaryk University Hospital, Brno, Czech Republic; [5]St Michael's Hospital, Li Ka Shing Knowledge Institute, University of Toronto, Toronto, Ontario, Canada; [6]Bleeding and Clotting Disorders Institute, University of Illinois College of Medicine-Peoria, Peoria, IL, USA; [7]Leicester Royal Infirmary, Leicester, United Kingdom; [8]HagaZiekenhuis, Den Haag, Netherlands; [9]Barts Health NHS Trust, The Royal London Hospital, London, United Kingdom; [10]NHS Foundation Trust, University Hospitals Birmingham, Birmingham, United Kingdom; [11]Fourth Department of Internal Medicine and Hematology, Faculty of Medicine, University Hospital of Hradec Králové, Hradec Králové, Czech Republic; [12]Royal Melbourne Hospital and Peter MacCallum Cancer Centre, Parkville, Australia; [13]Clinic of Hematology, University Hospital, Pleven, Bulgaria; [14]University of Washington and Fred Hutchinson Cancer Center, Seattle, WA, USA; [15]Sanofi, Rotkreuz, LU, Switzerland; [16]Sanofi, Bridgewater, NJ, USA; [17]Sanofi, Cambridge, MA, USA; [18]Hematology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Baseline Demographics and Characteristics

	Patients (N = 26)
Median age, y (range)	57 (20-75)
Female, n (%)	**16 (62)**
Median platelet count at baseline, $\times 10^9$/L (range)	13 (2-24)
Median duration of ITP, y (range)*	**10.3 (0.7-48.2)**
Median number of unique prior ITP therapies (range)†	**6 (3-19)**
Most common prior ITP therapies, n (%)	
Corticosteroids	26 (100)
TPO-RA	22 (85)
Immunosuppressants (including cyclophosphamide)	21 (81)
IVIg	21 (81)
Rituximab	13 (50)
Splenectomy	**12 (46)**
Fostamatinib	4 (15)

A



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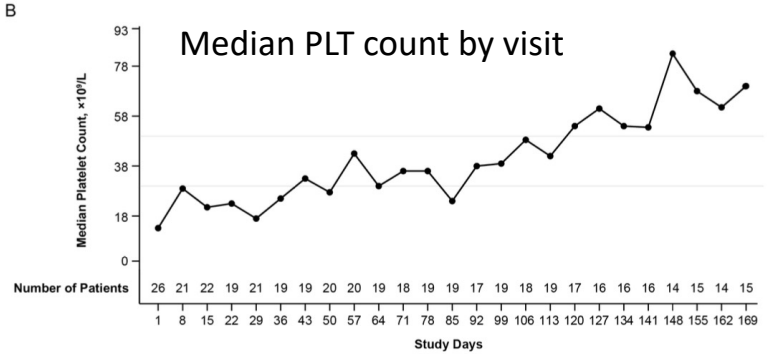
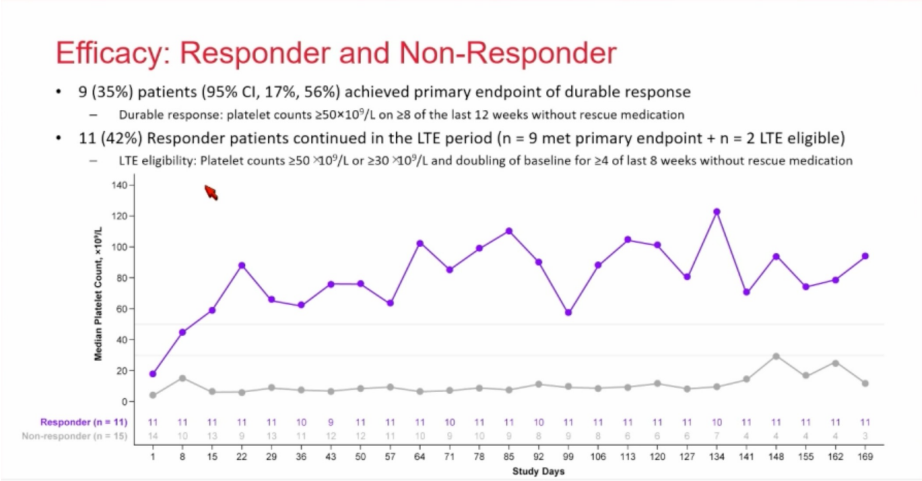
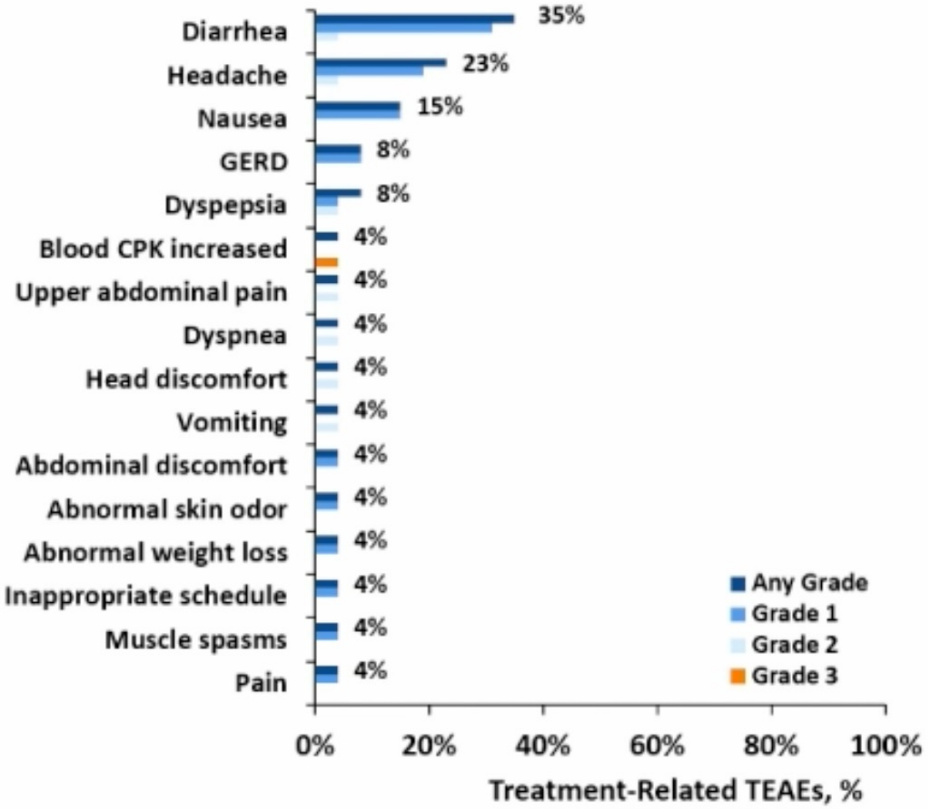


Primary endpoints: safety and durable PLT response defined as platelet counts ≥50x10⁹/L on ≥8 of the last 12 weeks of rilzabrutinib without rescue medication. Achieved in **35%** of patients.



35% durable response

Safety in Main Treatment Period (24 Weeks)



- Median treatment duration was 167 d (range, 7-169); 99% median compliance
- 85% any-cause TEAEs
  - 12% SAEs: none were treatment related per investigators and all resolved
- 62% treatment-related TEAEs, mainly grade 1 or 2
- No related grade ≥2 bleeding/thrombotic events or infections, SAEs, or deaths in main or LTE periods

THE EFFECTS OF RILZABRUTINIB, AN ORAL BRUTON TYROSINE KINASE INHIBITOR, ON BLEEDING SYMPTOMS AND HEALTH-RELATED QUALITY OF LIFE IN PATIENTS WITH IMMUNE THROMBOCYTOPENIA

Michael D. Tarantino,[1] A. J. Gerard Jansen,[2] Nichola Cooper,[3] Imene Gouia,[4] Mengjie Yao,[5] Ahmed Daak,[6] and David J. Kuter[7]

[1]The Bleeding and Clotting Disorders Institute, University of Illinois College of Medicine-Peoria, Peoria, IL, USA; [2]Erasmus MC, University Medical Center, Rotterdam, Netherlands; [3]Hammersmith Hospital, London, United Kingdom; [4]Sanofi, Gentilly, France; [5]Sanofi, Bridgewater, NJ, USA; [6]Sanofi, Cambridge, MA, USA; [7]Hematology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Safety: Bleeding Events During Main Treatment Period

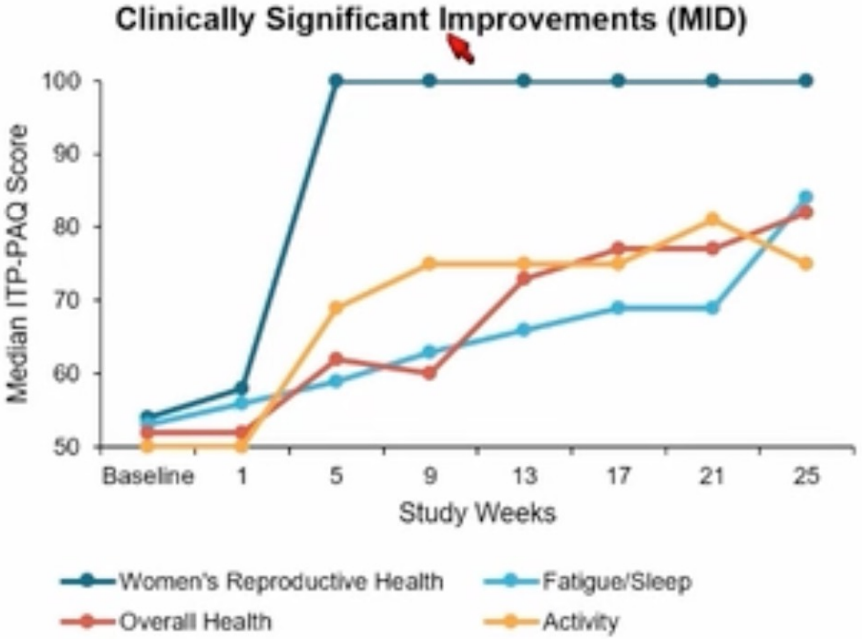
- There were no treatment-related bleeding events
- 4 patients (15%) had grade ≥2 bleeding events due to any cause
  - All events were recovered/resolved; none were considered related to treatment by the investigator
  - Grade 3 post-procedural hemorrhage was an SAE leading to dose interruption on day 123; patient later entered the LTE

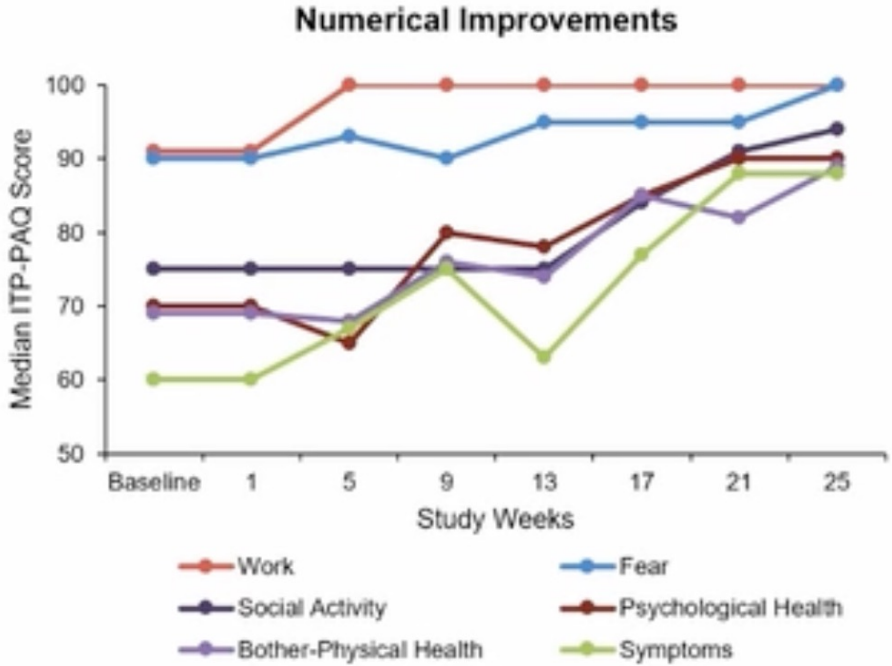
Bleeding events, n (%)	TEAEs Due to Any Cause				Treatment-Related TEAEs			
	Any Grade	Grade 1	Grade 2	Grade 3	Any Grade	Grade 1	Grade 2	Grade 3
Contusion	5 (19)	3 (12)	2 (8)	0	0	0	0	0
Epistaxis	2 (8)	1 (4)	1 (4)	0	0	0	0	0
Post-procedural hemorrhage	1 (4)	0	0	1 (4)	0	0	0	0
Blood urine present	1 (4)	0	1 (4)	0	0	0	0	0
Gingival bleeding	1 (4)	1 (4)	0	0	0	0	0	0

Data cutoff: 31 Jan 2023. SAE, serious adverse event; TEAE, treatment-emergent adverse events.

ITP-PAQ HRQOL Scores Over Time

- Improvements in HRQOL scores were observed early in the study





LUNA 2 Part B Efficacy and Safety Conclusions

- Rilzabrutinib 400 mg bid demonstrated rapid and durable platelet responses in heavily treated primary ITP, with a well-tolerated safety profile during the main treatment and LTE periods

Efficacy

- **Durable response**: 35% of patients achieved primary platelet response
- **Rapid response**: median time to first platelet count $\geq 50 \times 10^9$/L among LTE patients was 15 d
- 11 patients are ongoing in LTE

Safety

- No related grade 3/4 TEAEs, SAEs, or deaths
- No related TEAEs led to treatment discontinuation
- No related grade ≥2 bleeding/thrombotic events or infections, or other safety signals associated with BTK inhibitor drug class (ie, neutropenia, atrial fibrillation)
- No new safety observations in the LTE

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Avatrombopag for Adults with Early Versus Chronic ITP

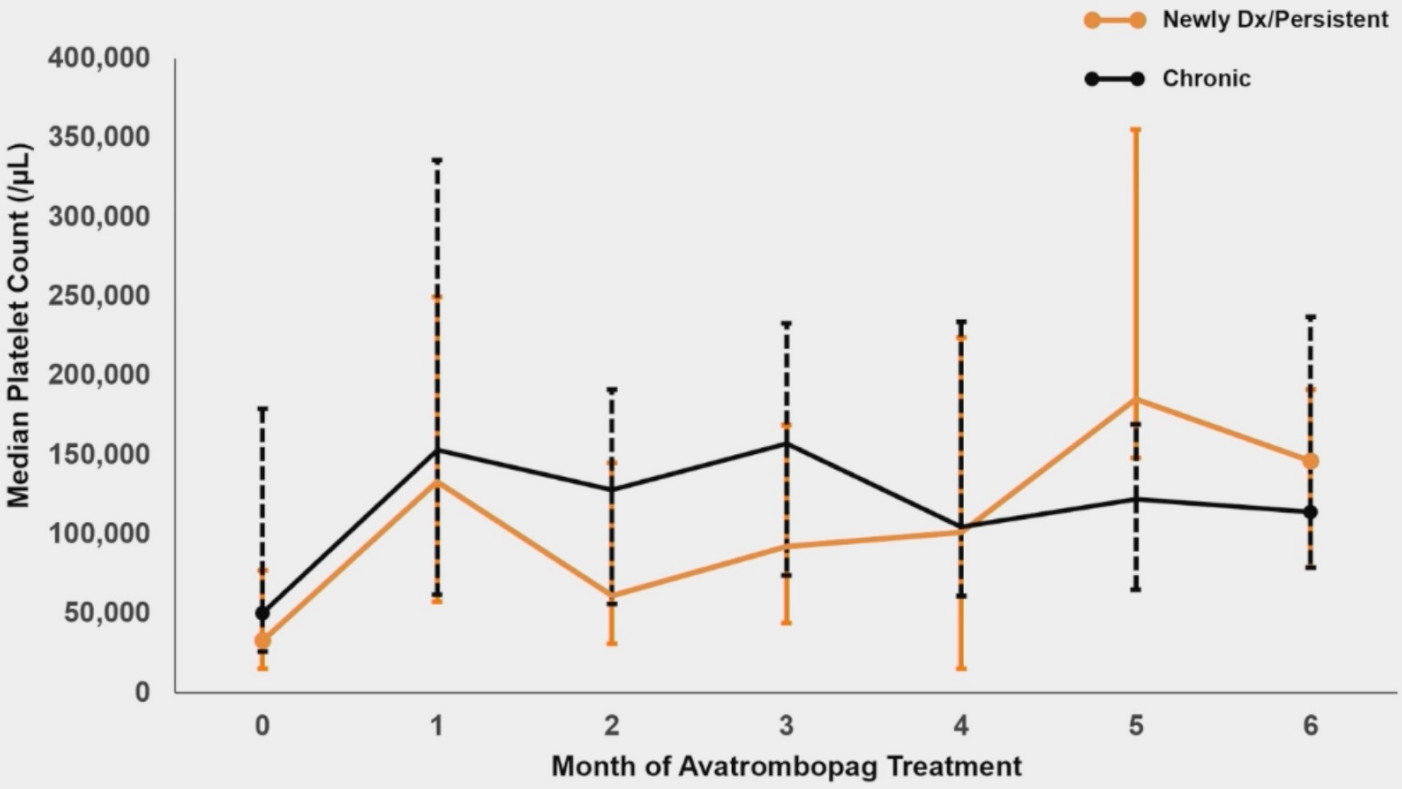
- multicenter, observational cohort study of all adult patients with primary or secondary ITP
- 4 US hospitals
- to compare outcomes of 75 patients with newly diagnosed or persistent ITP versus patients with chronic ITP

Virk Z et al. ASH 2023 abstract 392

Results: Platelet Outcomes

Outcome	Newly Dx/ Persistent ITP N = 23	Chronic ITP N = 52	*P* value
Response, n (%)	19 (91)	46 (96)	0.58
Response fraction, mean (95% CI)	0.74 (0.59-0.89)	0.84 (0.76-0.92)	0.16
Complete response, n (%)	18 (86)	39 (81)	0.78
Complete response fraction, mean (95% CI)	0.54 (0.36-0.72)	0.66 (0.55-0.78)	0.26

Results: Platelet Outcomes



Results: Safety

- Thrombocytosis similar (44% in the newly diagnosed/persistent ITP group and 40% in the chronic ITP group)
- No patient had arterial TE
- No patient in the newly diagnosed/persistent group had VTE; 1 patient in chronic group had a VTE
- No patient in the newly diagnosed/persistent group discontinued AVA due to an adverse event or safety concern
- Rate of TE in entire cohort (83.0 patient-years of AVA exposure) was 1.2 thromboembolic events per 100 patient-years
  - Considerably lower than prior phase 2 and 3 clinical trials of AVA in ITP (which together documented 11 thromboembolic events occurring over 72.4 patient-years of AVA exposure, or 15.2 thromboembolic events per 100 patient-years)

Avatrombopag Plus Fostamatinib Combination Efficacy and Safety in Patients with ITP

- retrospective, multicenter, international, observational, non-interventional study
- Spain and Norway
- 16 of 55 patients (29%) NR after at least two weeks of AVA
- In 6 of 16 FOS was combined to AVA 280 mg/weekly

Patient	Initial weekly dose of FOS * (mg)	Type of Response	Time from combination to platelets>30x10^9/L (days)	Time from combination to platelets>100x10^9/L (days)	Follow up since combination start (days)	Last weekly dose of FOS (mg)	Last weekly dose of AVA (mg)	Platelet count in last visit (x10^9/L)
1	1400	CR	3	5	45	1400	60	383
2	2100	CR	42	112	313	2100	280	145
3	1400	CR	4	4	232	1400	60	160
4	2100	CR	24	31	159	700	60	102
5	2100	R	26	NCR	277	2100	280	44
6	2100	CR	32	153	192	2100	140	129

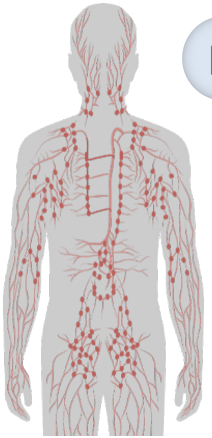
AVA: Avatrombopag; FOS: Fostamatinib; NCR: Non complete response

Mingot Castellano CE et al ASH 2023 abstract 2596

Chemotherapy-induced Thrombocytopenia: Current Treatment Strategies

Backgrounds

- CIT grade 3-4 affects 15-20% solid tumor patients (up to 70%)
- Reduction, dose delay of chemotherapy may negatively affect outcomes
- There are no established guidelines for CIT treatment
- NCCN Guidelines Ver. 1.2024: Romiplostim is Grade 2A recommendation in the management of CIT



Potential treatment options for CIT

- Dose delay/reduction
- Platelet transfusion
- TPO-RAs

Dose Delay/reduction of chemotherapy could result in suboptimal treatment outcomes, and risk of suboptimal OS and PFS.

The role of platelet transfusion is limited in patients with solid tumors and CIT given its cost, limited availability, and short duration of effect

Active management of CIT with TPO-RAs is likely to improve oncologic outcomes, although additional data are needed.
Phase 3 trials are ongoing.

Kuter DJ. Haematologica. 2022;107:1243-1263. Published 2022.

TPO-RAs in Chemotherapy induced thrombocytopenia (CIT)

Reference	TPO-RAs			
Wilkins et al Abs	ROM	Impact on OS from date of first exposure to Romiplostim	Solid tumors	- no OS advantage with Romiplostim - lack of OS benefit across PLT count
Chen et al Abs 1505	AVA	Efficacy and safety	30 ALL children	- shorter G3-4 thrombocytopenia (3.36±1.77 days vs. 4.7±2.46 days, P=0.019) - shorter time to platelet recovery (7.9±2.63 days vs. 9.76±2.77 days, P=0.01)
Chen et al Abs 2862	AVA 40 mg	Efficacy and safety	24 AL adults	- apparently positive results

Use of Eltrombopag for Post-CAR T Cytopenias: A Multi-Institutional Experience

- 185 patients with NHL and MM were included in this retrospective analysis
- 163 (88%) experienced thrombocytopenia or leukopenia at day +30 post-CAR T
- **42 patients** met institutional criteria for ELT treatment and initiated therapy
- Median time to initiation of ELT was **33 days** (range 28-50) from infusion
- Median duration for the use of ELT was **63 days** (range 32-172)
- No statistically significant differences in bleeding events in the ELT vs non-ELT groups
- No reported cases of DVT/PE after initiating ELT
- The use of ELT safe without any significant toxicities of thrombosis or MDS

Wesson et al ASH 2023 abstract 2136; Eur J Hematol 2023

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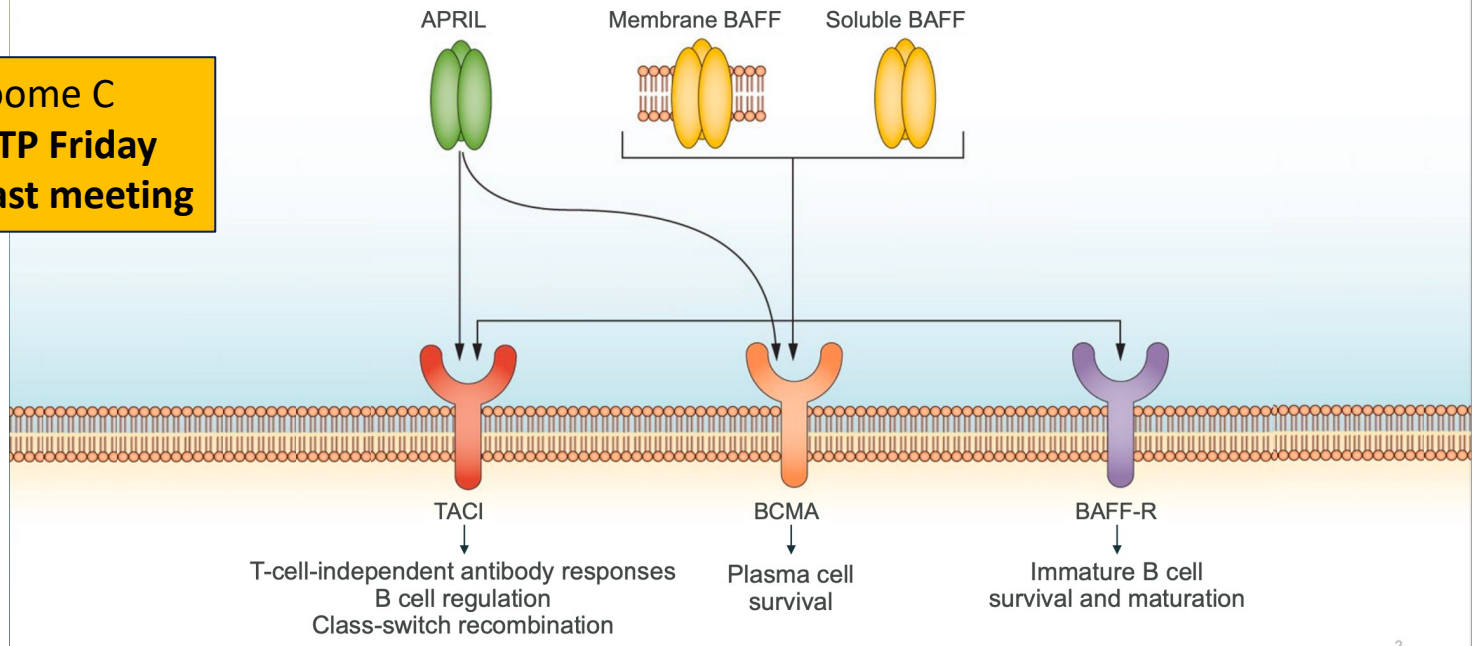
Broome C
ASH ITP Friday breakfast meeting

APRIL and BAFF are TNF-family cytokines that play key roles in B cell maturation, proliferation and survival



BAFF and APRIL are upregulated in ITP, and APRIL levels negatively correlate with platelet counts. Inhibition of BAFF and APRIL may block the activation, differentiation and/or survival of B cells, particularly antibody-secreting cells, as well as T cells and innate immune cells that drive the pathogenesis of autoimmune cytopenias, including ITP

Rituximab + belimumab in ITP

Efficacy

- ORR at week 12: 87% (13/15), with 60% CR
- **ORR at week 52: 80% (12/15), with 66% CR**

Among responders, one patient in CR relapsed after a follow-up of 18 months

Safety:

- No infusion-related reactions with belimumab
- No severe infections
- No severe hypogammaglobulinemia, although significant decrease in IgG and IgM titres

Outcome at W12	Outcome at W24	Outcome at W36	Outcome at W52
9 CR	9 CR	10 CR	10 CR
4 R	4 R	2 R	2 R
2 NR	2 NR	3 NR	3 NR

Phase 3 clinical trial ongoing (RITUX-PLUS 2)

Rituximab + scBelimumab vs Rituximab + placebo

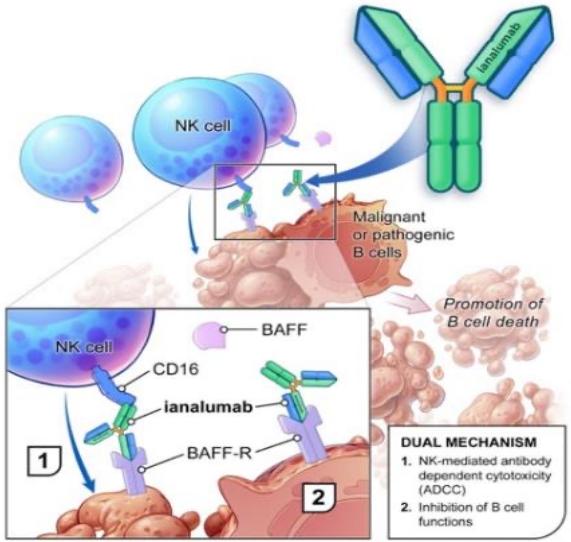
AE, adverse event; NR, no response.

Mahévas M, et al. Haematologica 2021

Ianalumab

Ianalumab has a novel dual MoA

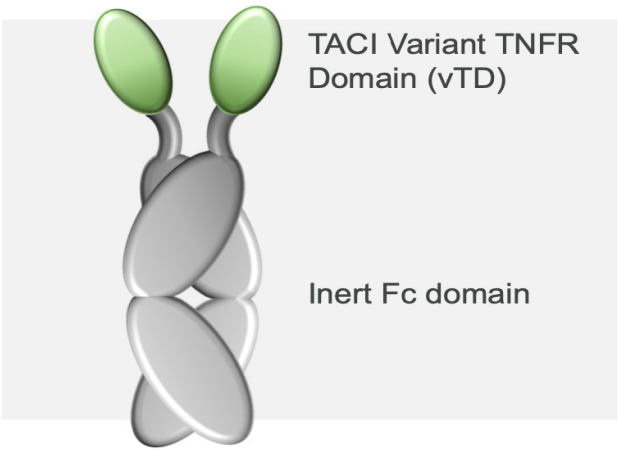
1. Direct ADCC-mediated depletion of B cells
2. Blockade of BAFF-R-mediated signaling, involved in B-cell differentiation, proliferation and survival



VAI736 program in ITP

Povetacicept

(TACI vTD-Fc; ALPN-303)



Modified TACI-Fc fusion protein

Dual BAFF and APRIL inhibition

RUBY-4

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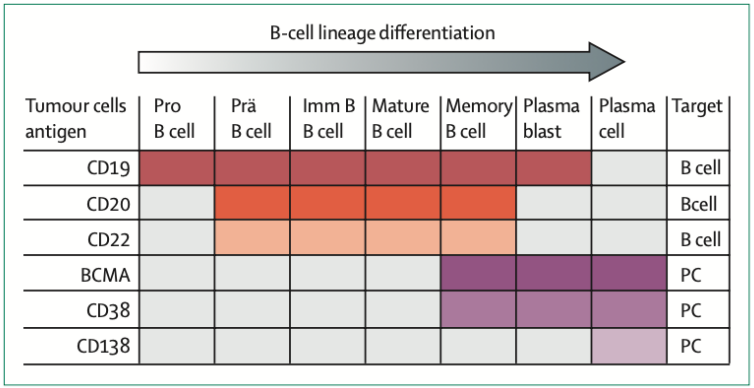
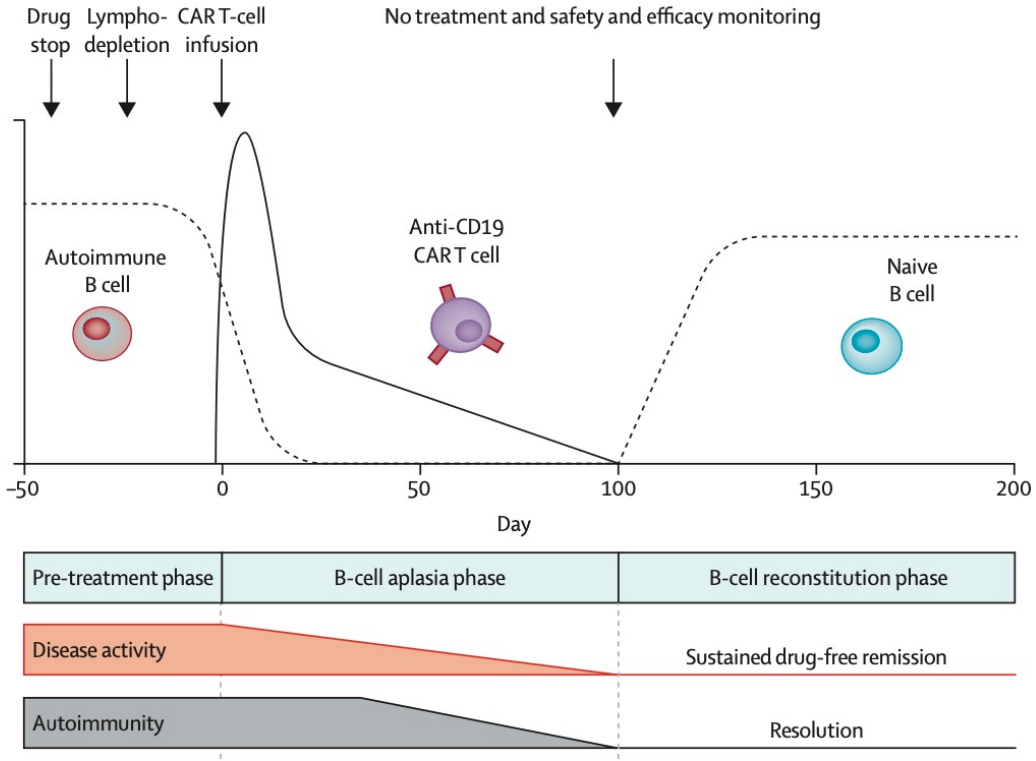
CAR T-cell therapy in autoimmune diseases

Georg Schett, Andreas Mackensen, Dimitrios Mougiakakos

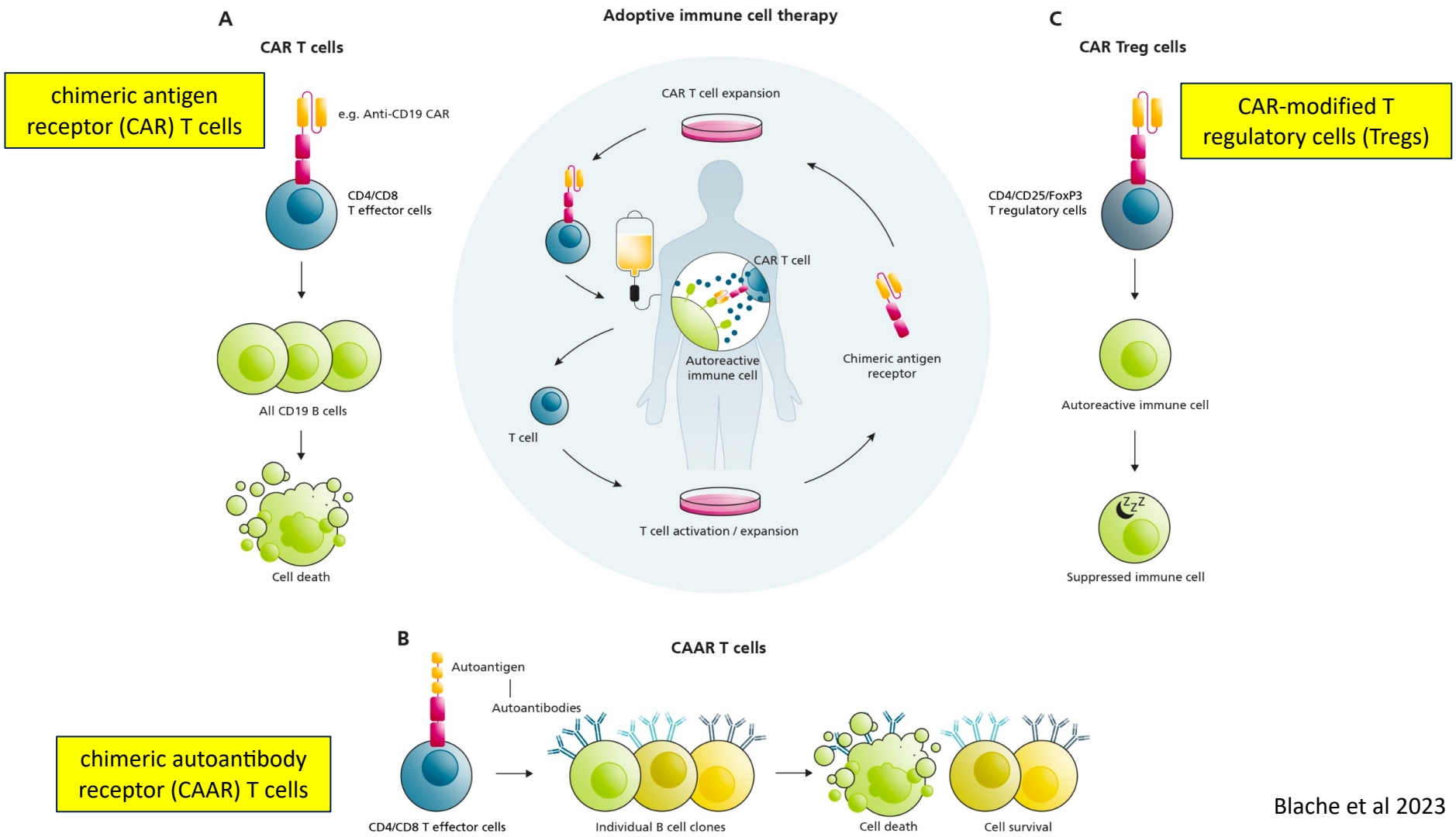
Despite the tremendous progress in the clinical management of autoimmune diseases, many patients do not respond to the currently used treatments. Autoreactive B cells play a key role in the pathogenesis of autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. B-cell-depleting monoclonal antibodies, such as rituximab, have poor therapeutic efficacy in autoimmune diseases, mainly due to the persistence of autoreactive B cells in lymphatic organs and inflamed tissues. The adoptive transfer of T cells engineered to target tumour cells via chimeric antigen receptors (CARs) has emerged as an effective treatment modality in B-cell malignancies. In the last 2 years treatment with autologous CAR T cells directed against the CD19 antigen has been introduced in therapy of autoimmune disease. CD19 CAR T cells induced a rapid and sustained depletion of circulating B cells, as well as in a complete clinical and serological remission of refractory systemic lupus erythematosus and dermatomyositis. In this paper, we discuss the evolving strategies for targeting autoreactive B cells via CAR T cells, which might be used for targeted therapy in autoimmune diseases.

Schett et al Lancet 2023





Schett et al Lancet 2023



Blache et al 2023

The Therapeutic Potential of CD19 CAR-T Cells in Active ITP Murine Models

Yun Wang, Fengjiao Han, Qiuyu Guo, Qi Feng, Jun Peng, Ming Hou, Miao Xu*

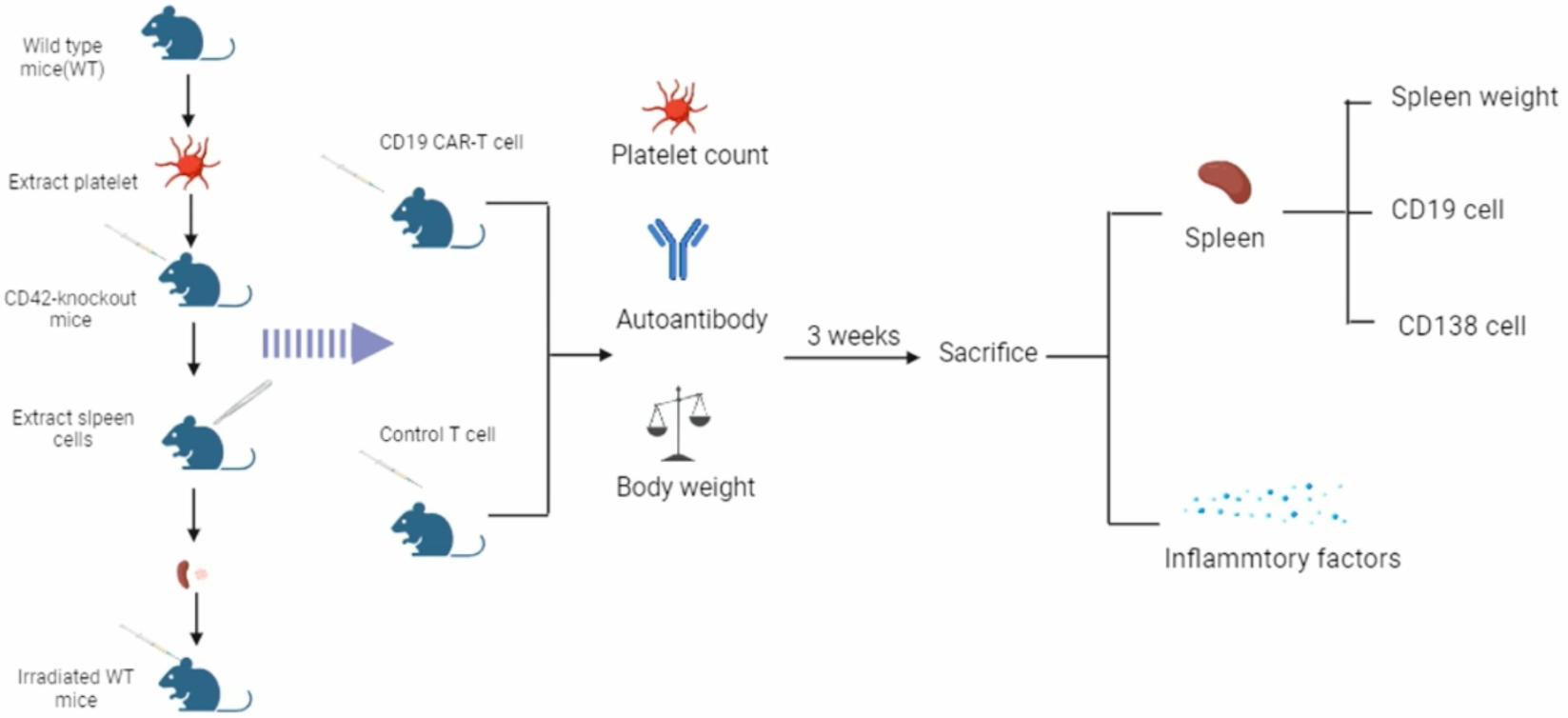
Affiliations: Department of Hematology, Cheeloo College of Medicine, Qilu Hospital of Shandong University, Jinan, China

ASH 2023 Abstract 688

Presenter: Yun Wang, MSc Candidate

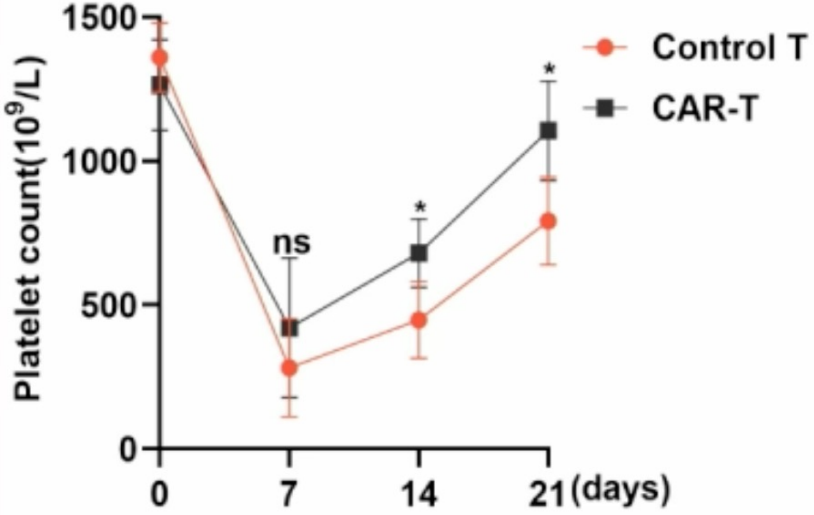
Dec 11th, 2023

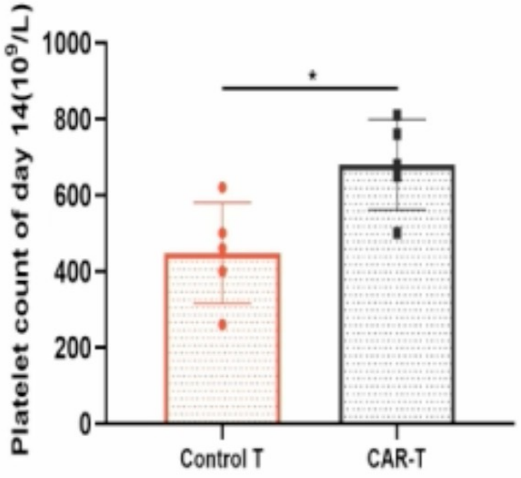
Methods

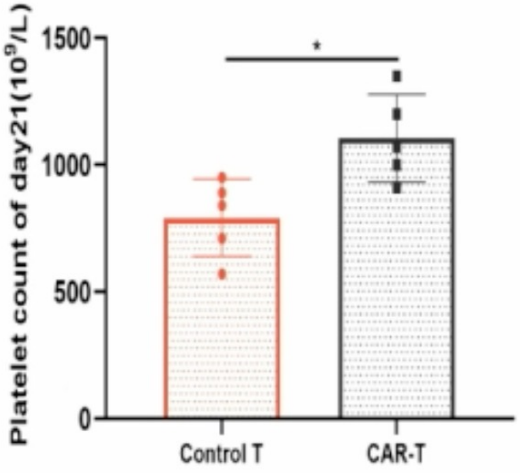

Wild type mice(WT)
Extract platelet
CD42-knockout mice
Extract sIpeen cells
Irradiated WT mice
CD19 CAR-T cell
Control T cell
Platelet count
Autoantibody
Body weight
3 weeks
Sacrifice
Spleen
Spleen weight
CD19 cell
CD138 cell
Inflammtory factors
Active ITP murine models
In vivo experiment
In vitro experiment

Results

- **Platelet count**



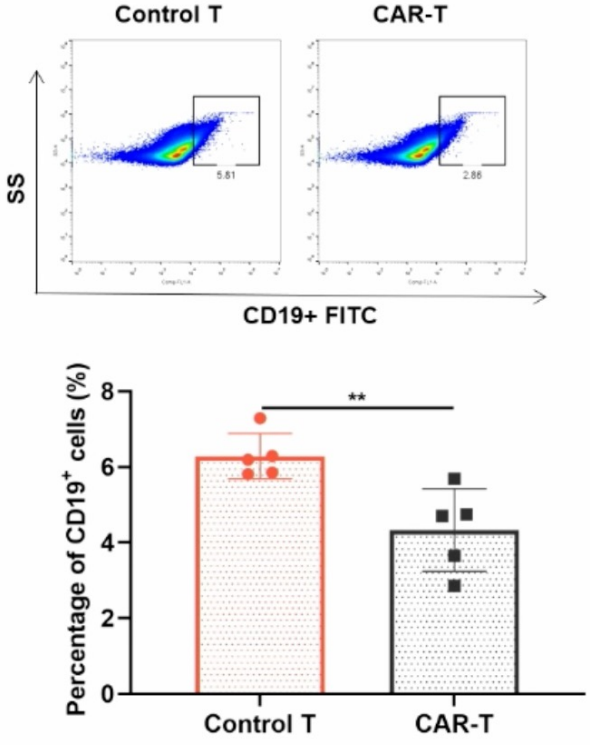




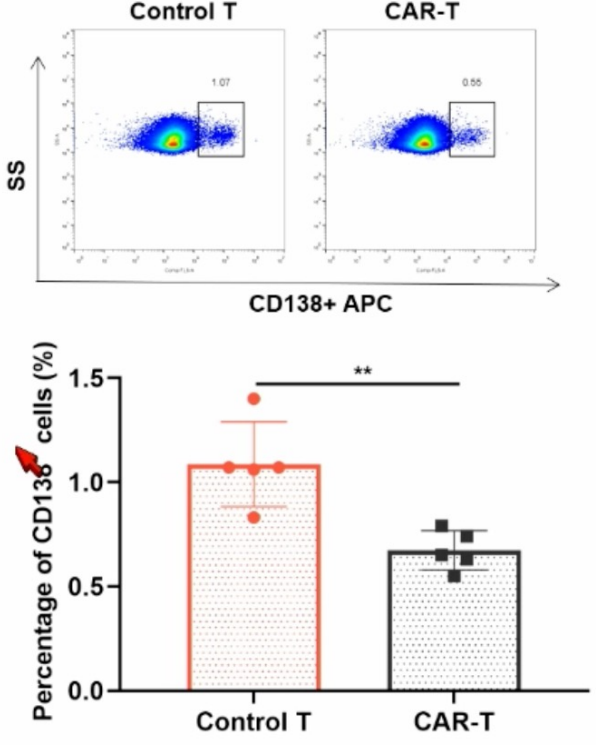
(n =5; *$p < 0.05$; ns: not significant)

Results

- **CD19**



- **CD138**



(**$p < 0.01$; ns: not significant)

Conclusion:

- This study demonstrates the effectiveness of CD19 CAR-T cell therapy in treating thrombocytopenia by suppressing plasma and B cells in a mouse model of active ITP
- These findings provide valuable insights into the potential therapeutic application of CD19 CAR-T cell immunotherapy for ITP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