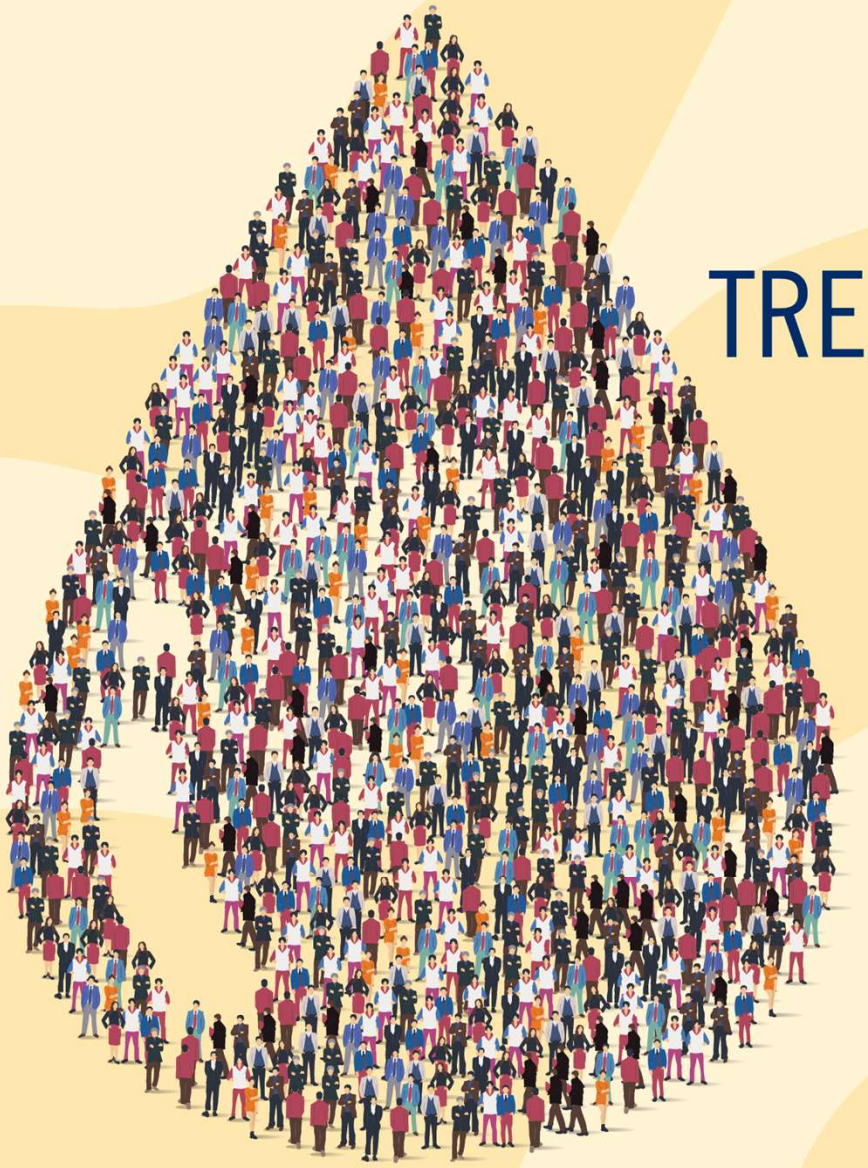


TREATING ITP:

Working Together to Improve Outcomes

ISTH International Society on Thrombosis and Haemostasis

Platelet Disorder Support Association
Empowering ITP Patients

Today's Panel of Experts

INTRODUCTION
Caroline Kruse
President and CEO
Platelet Disorder Support Association – PDSA
Cleveland, OH
USA

Scan for CME Information

MODERATOR
Nichola Cooper, MA, MBBS, FRCP, FRCPath, MD
Professor of Immune Hematology
Department of Immunology and Inflammation - Faculty of Medicine
Imperial College Healthcare NHS Trust
London, England
UK

David J. Kuter, MD, DPhil
Chief of Hematology
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School
Boston, MA
USA

Terry Gernsheimer, MD
Professor of Hematology (Emerita)
University of Washington
The Fred Hutch Cancer Center
Seattle, Washington
USA

Stephanie Sanford, APRN
Hematology/Oncology Nurse Practitioner
North Shore Cancer Center
Massachusetts General Hospital
Boston, MA
USA

Learning Objectives

- Demonstrate understanding of the impact of cITP on patients
- Outline for a patient the benefits and risks of current treatment approaches for cITP
- Address common patient concerns regarding emerging cITP treatment options

Housekeeping

- All learners have arrived muted
- Use the “Raise Hand” option to speak
- Use the Q & A function for questions
- Contact The France Foundation via chat if you are having issues and/or technical questions
- This meeting will be recorded

Today's Agenda

Welcome and Introductions (Caroline Kruse, President and CEO, PDSA)

Knowledge Check Questions (Nichola Cooper, MD)

The True Impact of ITP: What Our Patients Teach Us (Terry Gernsheimer, MD)

Current Approaches to Managing ITP (Stephanie Sanford, APRN)

Navigating Advancements in the Therapeutic Management of Persistent/Chronic ITP (David Kuter, MD)

Key Takeaways

Question and Answer (Moderated by Nichola Cooper, MD)

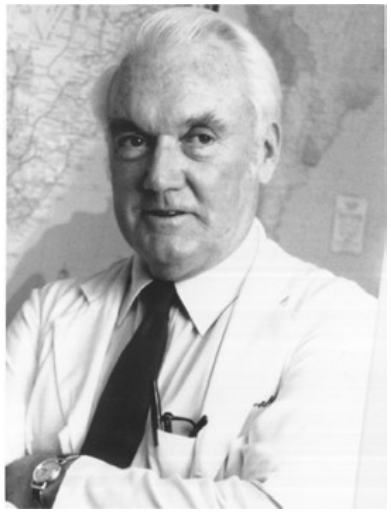
The True Impact of ITP: What Our Patients Teach Us

Terry Gernsheimer, MD

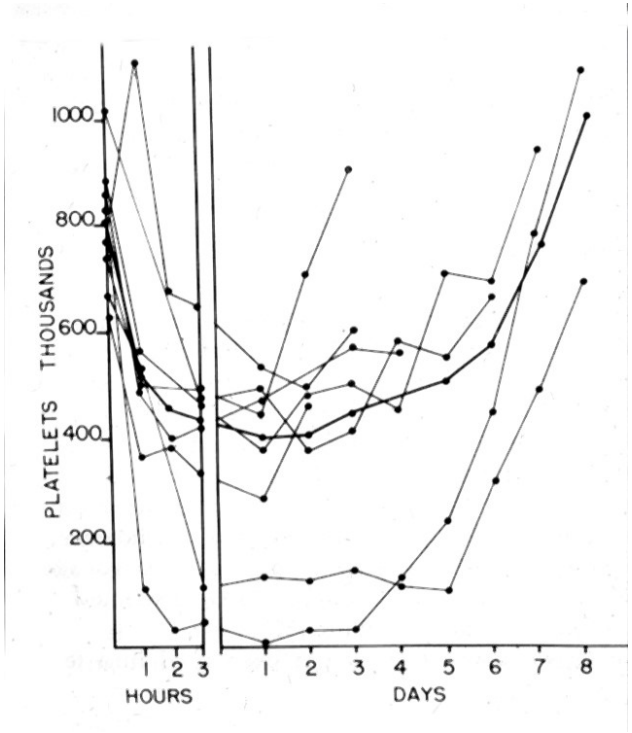
Meet Brenda

Patient Video Clip: Overall Experience with ITP (Burden of Disease)

ITP Is an Immune Disorder of Increased Platelet Destruction



1923-1992
WJ Harrington



The Harrington–Hollingsworth experiment established the autoimmune nature of ITP

Harrington WJ, et al. *J Lab Clin Med.* 1951;38:1-10.

ITP Is Also a Disorder of Impaired Platelet Production

TPO receptor

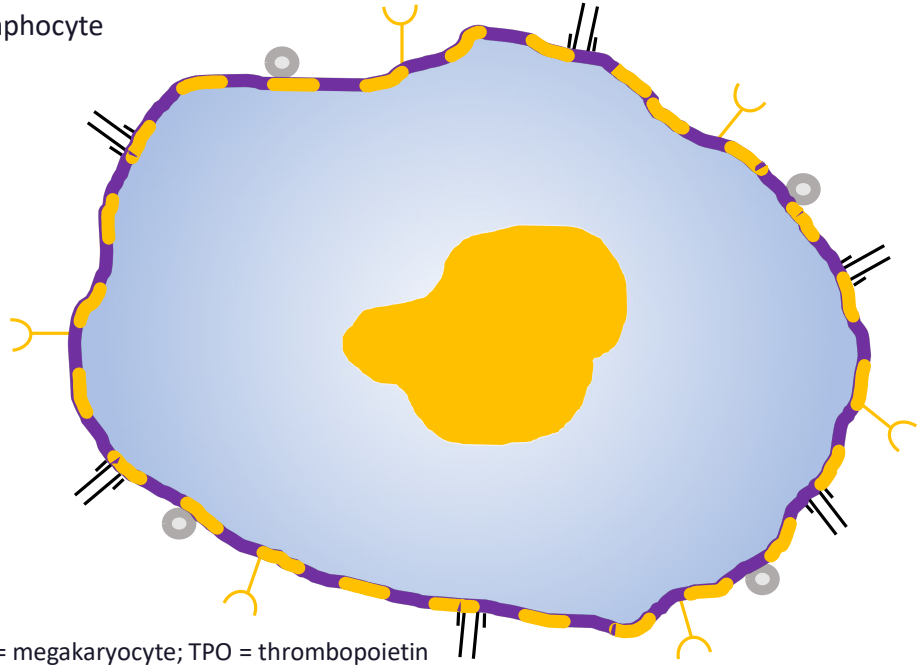
Antiplatelet antibody

Antiplatelet lymphocyte

Antiplatelet antibody attacks Mk

Lymphocyte attacks Mk

Mk undergoes apoptosis



ITP = immune thrombocytopenia; Mk = megakaryocyte; TPO = thrombopoietin

Jinna S, Khandhar PB. Thrombocytopenia. [Updated 2023 Jul 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542208/

ITP Is a Clinical Diagnosis

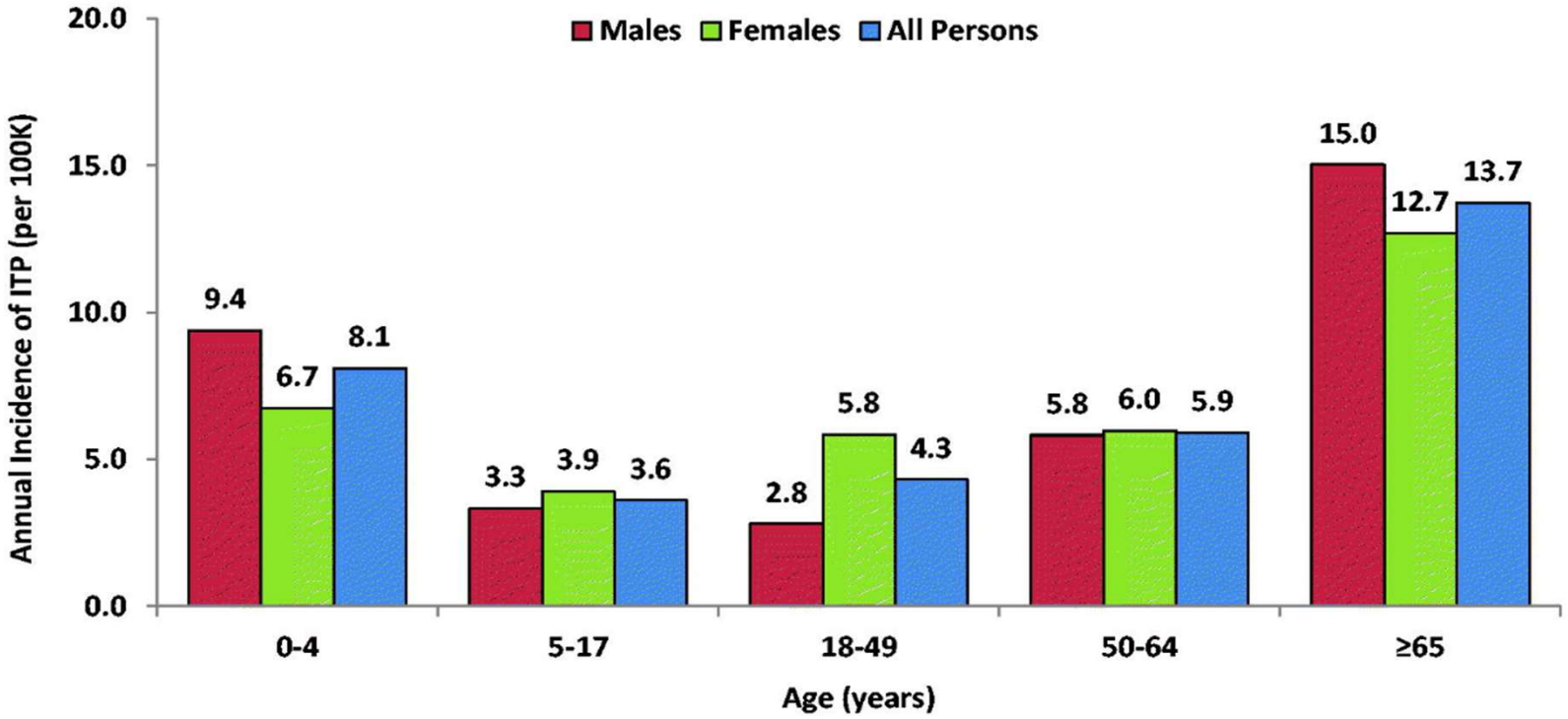
- Platelet count < 100 x 10^9/L
- No other causes of thrombocytopenia
- Primary vs. secondary
- Staging scheme may not reflect any difference in pathophysiology
- Staging system
  - Newly diagnosed: Months 0-3
  - Persistent ITP: Months > 3-12
  - Chronic ITP: Months > 12
- Bone marrow rarely needed
  - Patient unresponsive to corticosteroid/IVIG
  - Other cytopenias

- **Staging definitions may be helpful in comparing therapies in clinical research**
- **No "test" to document patient has ITP**

IVIG, intravenous immunoglobulin

Rodeghiero F, *et al. Blood*. 2009;113:2386–93; Provan D, *et al. Blood Advances.* 2019;3:3780–817; Neunert C, *et al. Blood Advances.* 2019;3:3829–3866.

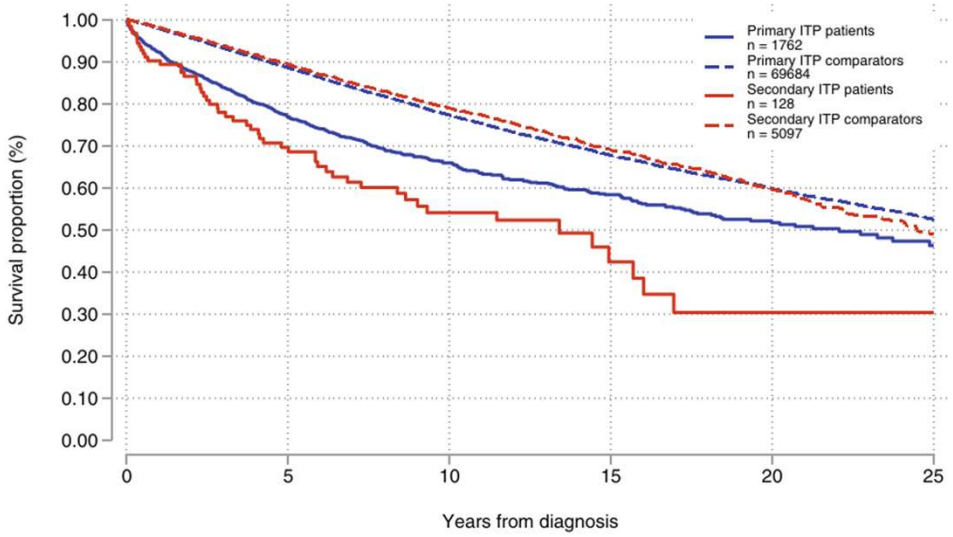
Annual Incidence of ITP in the US by Age and Sex



D Weycker, et al. *J Med Econ*. 2020;23(2):184-92.

Natural History of ITP

- Average age (range) at diagnosis: 32 (0-72) years
- Average (range) disease duration: 12.5 (0-69) years
- 20%-45% of adults achieve complete remission by 6 months
- Patients with persistently low platelet counts < 30 x 10^9 have a 4.2-fold higher mortality risk
- Overall survival for primary ITP reduced 5.1 years



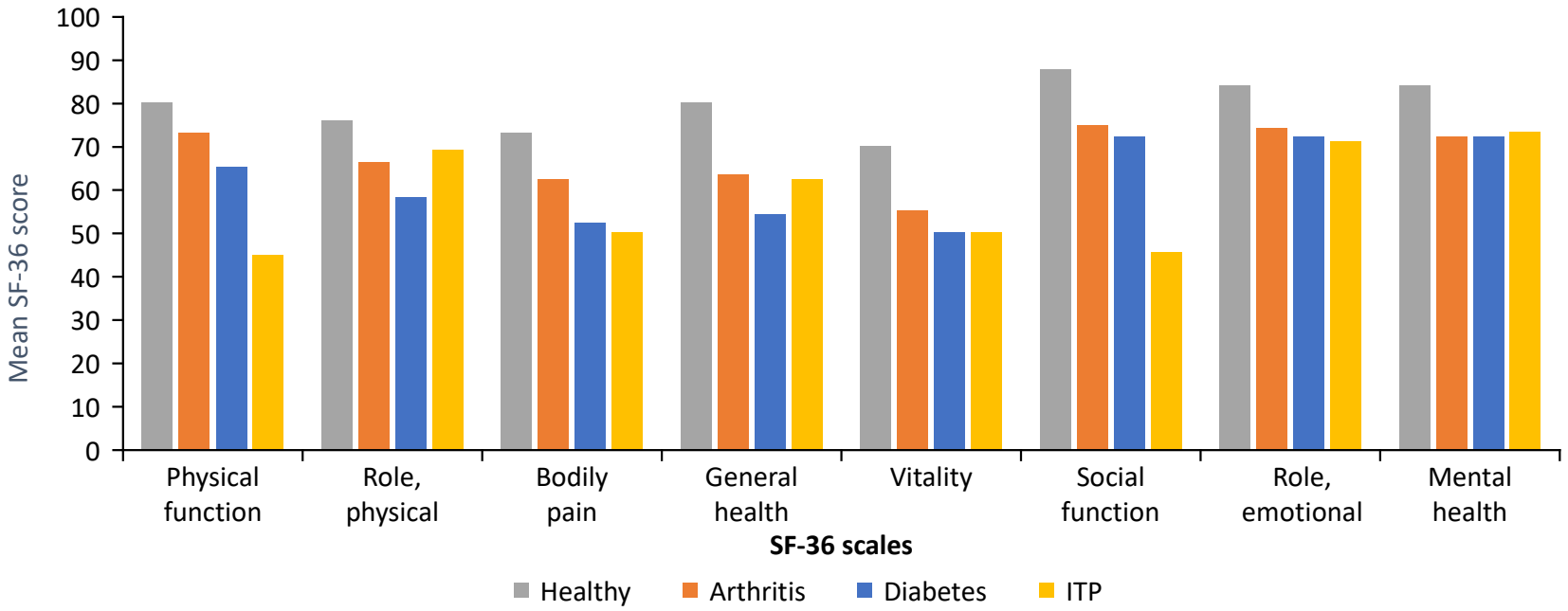
Kruse A, et al. *Blood.* 2018;132(suppl 1):4979. Portielje JE, et al. *Blood*. 2001;97:2549–54; Neunert C, et al. *Blood Adv.* 2019;3(23):3829-3866; Mannering N, et al. *Transfusion*. 2023 Feb;63(2):415-426.

Presenting Symptoms of ITP in Adults

- Bleeding:[1,2]
  - Intracranial hemorrhage (ICH): 1.4%[1]
  - Hemorrhage: 12%[2]
  - Purpura: 59%[2]
  - Asymptomatic 29%[2]
- Fatigue: 94%[1]
- Thromboembolism: 8% of patients with ITP had a thromboembolism prior to diagnosis[1]
- Cognitive dysfunction: ~ 50%[3]
- 80% of adults with ITP will develop chronic ITP[1]

1. Neunert C, et al. *Blood Adv*. 2019;3(23):3829-3866; 2. Neylon AJ, et al. *Br J Haematol.* 122;2003:966–974; 3. Kuter DJ, et al. *Br J Haematol.* 2024;205(1):291-299.

Patients With ITP Have Lower QoL



No simple tool for assessing QoL in ITP

SF-36 = Short-Form 36-Item Questionnaire

McMillan R, *et al. Am J Hematol*. 2007;83(2):150–4; Bussel J, *et al. Abstract presented at ASH.* 2006

Thank You

Current Approaches to Managing ITP

Stephanie Sanford, APRN

Case Introduction

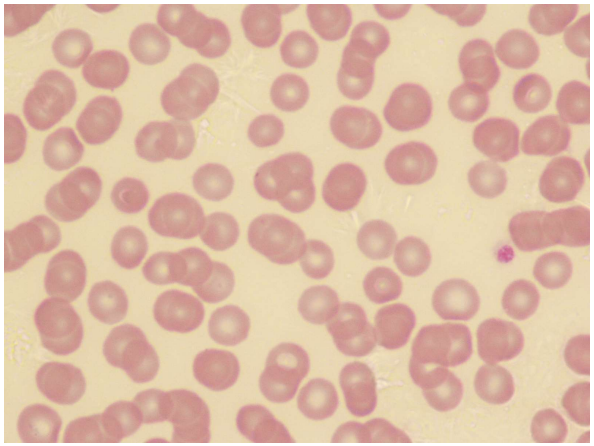
Amanda

27 years of age

- School teacher, 4-year-old son
- No medications

Admitted with:

- Generalized purpura
- Palatal petechiae
- Frequent nosebleeds
- Heavy menstrual bleeding
- Platelet count 8 x 10^9/L



Hb (g/dL)	10.1
WBC (x 10^9/L)	4.2
ANC (x 10^9/L)	3.1

Indications for Treatment in ITP

- Treatment may not be indicated for asymptomatic patients with platelets 20-30 x 10^9/L
- But treatment may be indicated in patients with platelet counts below 50 × 10^9/L with bleeding due to:
  - Platelet dysfunction
  - Another hemostatic defect
  - Trauma
  - Surgery
  - Clear comorbidities for bleeding
  - Mandated anticoagulation therapy or aspirin therapy
  - Profession or lifestyle predisposing to trauma

Provan D, et al. *Blood Adv.* 2019;3(22):3780-3817; Neunert C, et al. *Blood Adv.* 2019;3(23):3829-3866.

Assessing Treatment Goals

Treatment should:

- Prevent severe bleeding episodes
- Maintain a target platelet level of at least 30-50 x 10^9/L in patients with increased risk of bleeding or comorbidities
- Have minimal toxicity
- Optimize HRQoL

HRQoL = health-related quality of life

Provan D, et al. *Blood Adv*. 2019;3:3780–3817; Neunert C, et al. *Blood Adv.* 2019;3(23):3829-3866.

Overview of Management Options

Clinical Situation	Therapeutic Options
Initial treatment for ITP	Corticosteroids: dexamethasone, methylprednisolone, prednis(ol)one Intravenous immunoglobulin Anti-D (where available)
Subsequent therapy with adequate clinical trial data	Thrombopoietin-receptor agonists Fostamatinib Rituximab Splenectomy Mycophenolate mofetil
Subsequent therapy (with minimal clinical trial data)	Vinca alkaloids Sirolimus Cyclosporin A Cyclophosphamide Danazol Dapsone Azathioprine

Provan D, et al. *Blood Adv*. 2019;3:3780–3817; Neunert C, et al. *Blood Adv.* 2019;3(23):3829-3866; Bradbury CA, et al. *N Engl J Med.* 2021;385(10):885-895.

Patient Video: Initial Treatment and Side Effects

Benefit Risk Profile of Currently Available Therapies (1/2)

Therapy	Benefits	Risks
Corticosteroids	• Rapid platelet count increase in many patients • Familiar and low-cost option	• Acute toxicities (fatigue, insomnia, irritability, hyperactivity, etc.) • Multiple toxicities associated with extended therapy (weight gain, cataracts, diabetes, etc.)
Immunoglobulins	• Rapid increase in platelet counts • Useful for acute bleeding episodes	• Short-term efficacy • Potential for allergic reactions • Headaches and aseptic meningitis (with IVIG) • Hemolysis (more commonly with anti-D)
TPO-RAs	• Durable platelet response • Reduced bleeding events • Improved QoL • Suitable for long-term management	• Potential for elevated hepatic enzymes (eltrombopag) • Need for regular monitoring • Possible rebound thrombocytopenia upon rapid dose decrease or discontinuation • Low risk for bone marrow reticulin

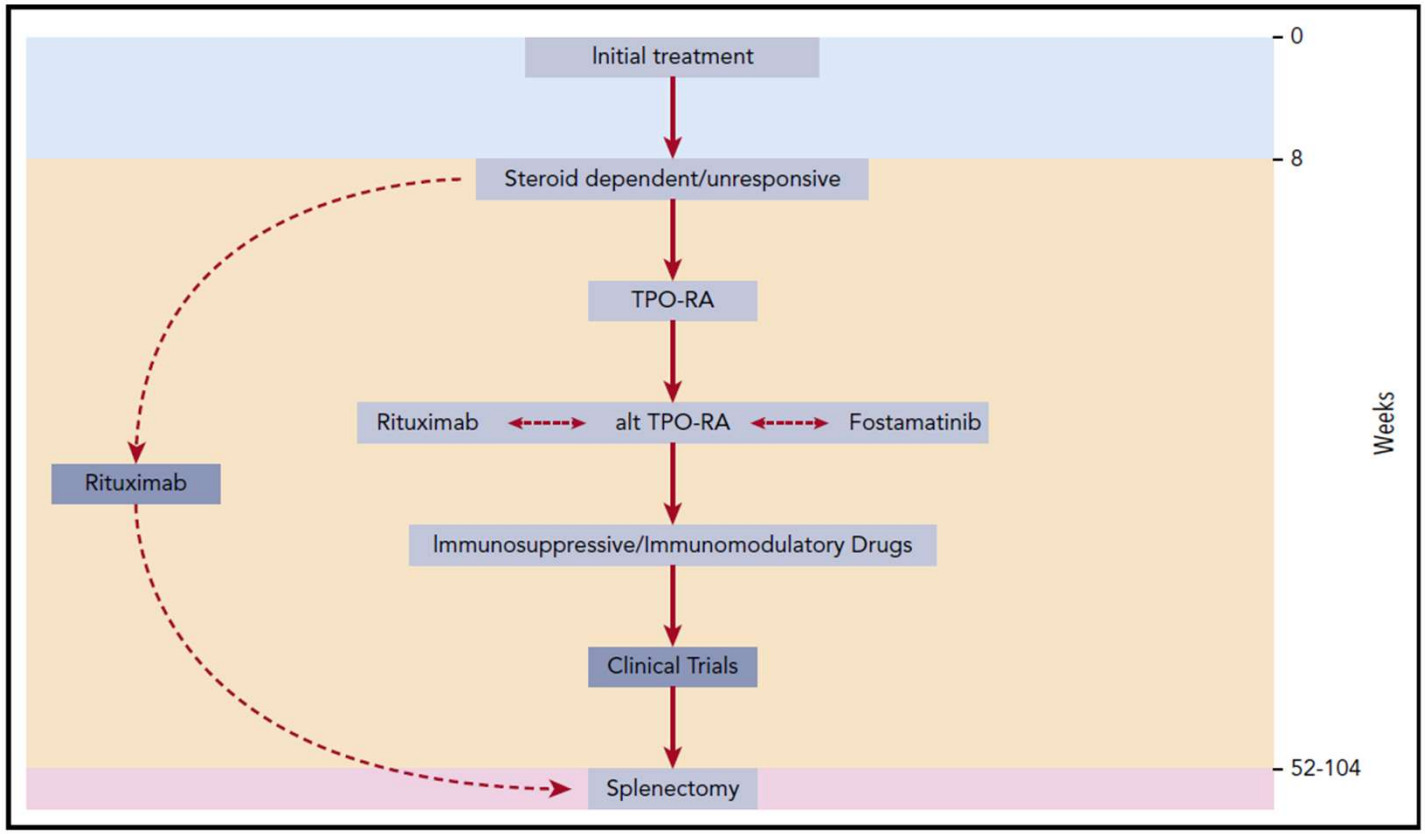
Cuker A, et al. *Res Pract Thromb Haemost*. 2021;5(6):e12592; Guo Y, et al. *Front Immunol*. 2018;9:1299; Neunert CE. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):400-405. Lozano ML, et al. *Sci Rep*. 2019;9(1):16680; Wang L, et al. *Sci Rep*. 2016;6:39003.

Benefit Risk Profile of Currently Available Therapies (2/2)

Therapy	Benefits	Risks
Rituximab	• Leads to long-term remission in some patients	• Decreased vaccine response • Prolonged lymphopenia • Increased risk of infection
Fostamatinib	• Novel mechanism of action (Syk inhibitor) • Effective in some patients refractory to other treatments	• Gastrointestinal side effects • Hypertension • Potential for liver function abnormalities
Splenectomy	• Leads to long-term remission in some patients without need for ongoing therapy	• Surgical complications • Long-term increased risk of infection • Long-term increased risk of thrombosis • Decreased vaccine responsiveness

Deshayes S, et al. *Am J Hematol*. 2019;94(12):1314-1324; ElSaied DG, et al. *EJIM*; 2024;36(60); Neunert CE. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):400-405; Bussel JB, et al. *Am J Hematol.* 2019;94(5):546-553.

Current Clinical Practice Algorithm



Ghanima W, et al. *Blood*. 2021;137(20):2736-2744.

Initial Treatment of ITP

International consensus report

Prednisone
1 mg/kg/day
for 2 weeks
(max 3 weeks)

Dexamethasone
40 mg/day
for 4 days
(max 3 cycles)

IVIG/anti-D
In case of bleeding, high risk of bleeding, corticosteroid contraindication, or surgery

No response → Taper over 1 week

Platelets > 50×10^9/L → Taper and stop at 6 weeks (max 8 weeks). Begin second-line therapy if required.

- **Low long-term remission rate**
- **Multiple toxicities associated with extended corticosteroid therapy**

Provan D, et al. *Blood Adv*. 2019;3:3780–3817.

Factors Influencing Treatment Indication and Choice of Therapy

Patient-related factors

- Patient characteristics
- Concomitant medication
- Patient preference
- Comorbidities
- Compliance
- Lifestyle/work
- Sports

External factors

- Financial restrictions
- Regulatory restrictions
- Guidelines
- Availability of treatment
- Physician preference

Treatment-related factors

- Response
- Tolerance
- Schedule

Disease-related factors

- Risk of bleeding
- Platelet count
- Phase of disease
- Symptoms

Ghanima W, et al. *Blood*. 2021;137(20):2736-2744; Neunert C, et al. *Blood Adv*. 2019;3(23):3829-3866; Liu XG, et al. *J Hematol Oncol*. 2023;16(1):4. Matzdorff A, et al. *Oncol Res Treat*. 2018;41 Suppl 5:1-30. Pietras NM, et al. [Updated 2024 May 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562282/

Shared Decision-Making (SDM)

- ITP treatment decisions are complex due to:
  - Multiple second-line treatment options available, each with different benefits and risks
  - Lack of comparative trials between treatments
  - Variability in how patients respond to, and tolerate, different therapies
- Engaging in shared decision-making for ITP management:
  - Improves patient understanding of their condition and treatment options
  - Increases patient satisfaction with care
  - Enhances adherence to chosen treatments
- PDSA has patient- and clinician-focused materials and infographics to help facilitate SDM

PDSA, Platelet Disorder Support Organization

Grace RF, et al. *Am J Hematol*. 2018;93(7):882-888; Neunert C, et al. *Blood Adv*. 2020 Jan 28;4(2):252; https://itpsupport.org.uk/the-new-itp-discussion-guide/

Case Study: 1st Line Therapy

Amanda

27 years of age

Started on 1 mg/kg prednisone oral daily

She returns to the clinic 2 weeks later with the following:

- Generalized purpura reduced
- Petechiae resolved
- Reports insomnia

- Platelet count 80 x 10^9/L

Hb (g/dL)	12.2
WBC (x 10^9/L)	9.1
ANC (x 10^9/L)	8.3

Begin to taper steroids?

Case Study: 1st Line Therapy

Amanda

27 years of age

Tapered steroids over 4 weeks to 20 mg/daily

She returns to the clinic with the following:

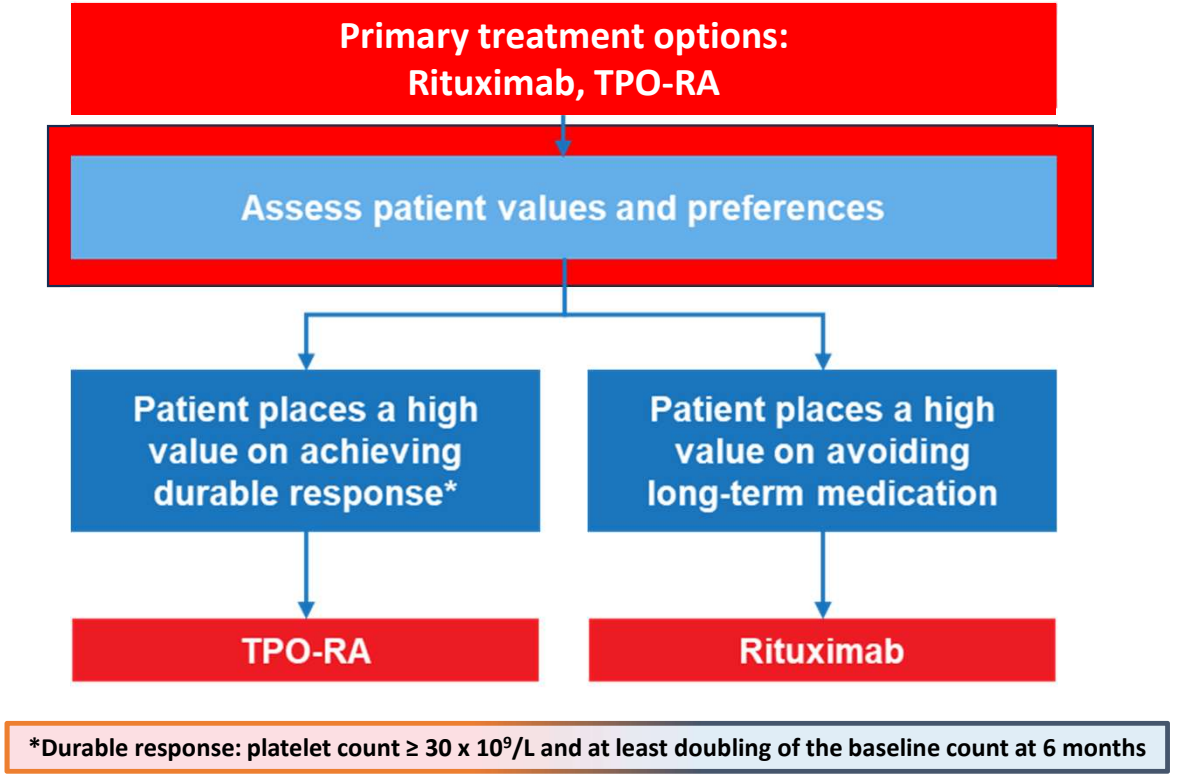
- Generalized purpura reduced
- Occasional nose bleeds
- Weight gain
- Heavy menstrual flow
- Reports insomnia

- Platelet count 20 x 10^9/L

Hb (g/dL)	12.3
WBC (x 10^9/L)	6.8
ANC (x 10^9/L)	4.2

What would you do next?

Treatment Options for Unresponsive or Steroid-Dependent Patients



Neunert C, et al. *Blood Adv*. 2019;3(23):3829-3866.

Patient Video: Subsequent Treatments (Rituximab, Dexamethsone + AEs)

Challenges Managing ITP

Managing ITP is associated with many challenges due to:

- Lack of evidence in general and comparative studies
- Available therapies have limited efficacy and variable toxicity
- Low long-term remission rates (except for splenectomy)
- Lack of tools for measuring QoL
- Lack of biomarkers

Assessing patient values and preferences

- Discrepancy between patients' and physicians' experiences, perception, and needs
- Assess **patients' perception** of treatment goals, values, and preferences
- Allow for **shared decision-making**

Mingot-Castellano ME, et al. *Pharmaceuticals (Basel)*. 2022;15(7):779. Provan D. *VJHemOnc.* Accessed August 29, 2024. https://www.youtube.com/watch?v=MuO8tGOsCv8&t=1s; Gresele P. *VJHemOnc.* Accessed August 29, 2024. https://www.youtube.com/watch?v=8R2AUBuFWno

Case Study: 2nd Line Therapy

Amanda

27 years of age

Started on 50 mg oral eltrombopag daily
Increased to 75 mg after platelet count did not rise by week 3

6 weeks later, she returns to the clinic with the following:

- Reduced purpura
- Fewer nosebleeds reported
- Heavy menstrual bleeding ongoing
- Fatigue

- Platelet count 20 x 10^9/L

Hb (g/dL)	12.5
WBC (x 10^9/L)	4.2
ANC (x 10^9/L)	2.5

What should be the next step for the management of Amanda?

Thank You

Navigating Advancements in the Therapeutic Management of Persistent/Chronic ITP

David Kuter, MD

Case Study: After 2nd Line Therapy

Amanda

27 years of age

- Declined splenectomy
- Continued eltrombopag
- Received a course of rituximab

2 months later, she returns to the clinic with the following:

- Reduced purpura
- No change in nosebleeds reported
- Mild improvement in heavy menstrual bleeding

- Platelet count 29 x 10^9/L

Hb (g/dL)	12.0
WBC (x 10^9/L)	4.9
ANC (x 10^9/L)	4.2

What should be the next step for the management of Amanda?

Novel Therapies in Clinical Trials

Name	Drug class	Phase	Administration Route
Sovleplenib	Syk inhibitor	3	Oral/daily
Cevidoplenib (SKI-O-703)		2	Oral/twice daily
Efgartigimod	FcRn inhibitor	**3**	**IV/weekly**
STSA-1301		1	SubQ/once
Rilzabrutinib	BTK inhibitor	**3**	**Oral/daily-twice daily**
Orelabrutinib		3	Oral/daily
Daratumumab	Plasma cell therapy (anti-CD38)	2	IV/weekly
Mezagitamab		**2**	**IV/weekly**
CM313		2	IV/weekly
Sutimlimab	Complement inhibition	1	SubQ/weekly
Ianalumab	BAFF-R inhibitor	3	IV/monthly
PF-06835375	CXCR5 inhibitor	2	SubQ/monthly

Therapies in bold will be discussed further in this presentation

BAFF= B-cell activating factor; BTK = bruton tyrosine kinase; CXCR5 = chemokine receptor type 5; FcRn = neonatal fragment crystallizable; IV = intravenous; SubQ = subcutaneous

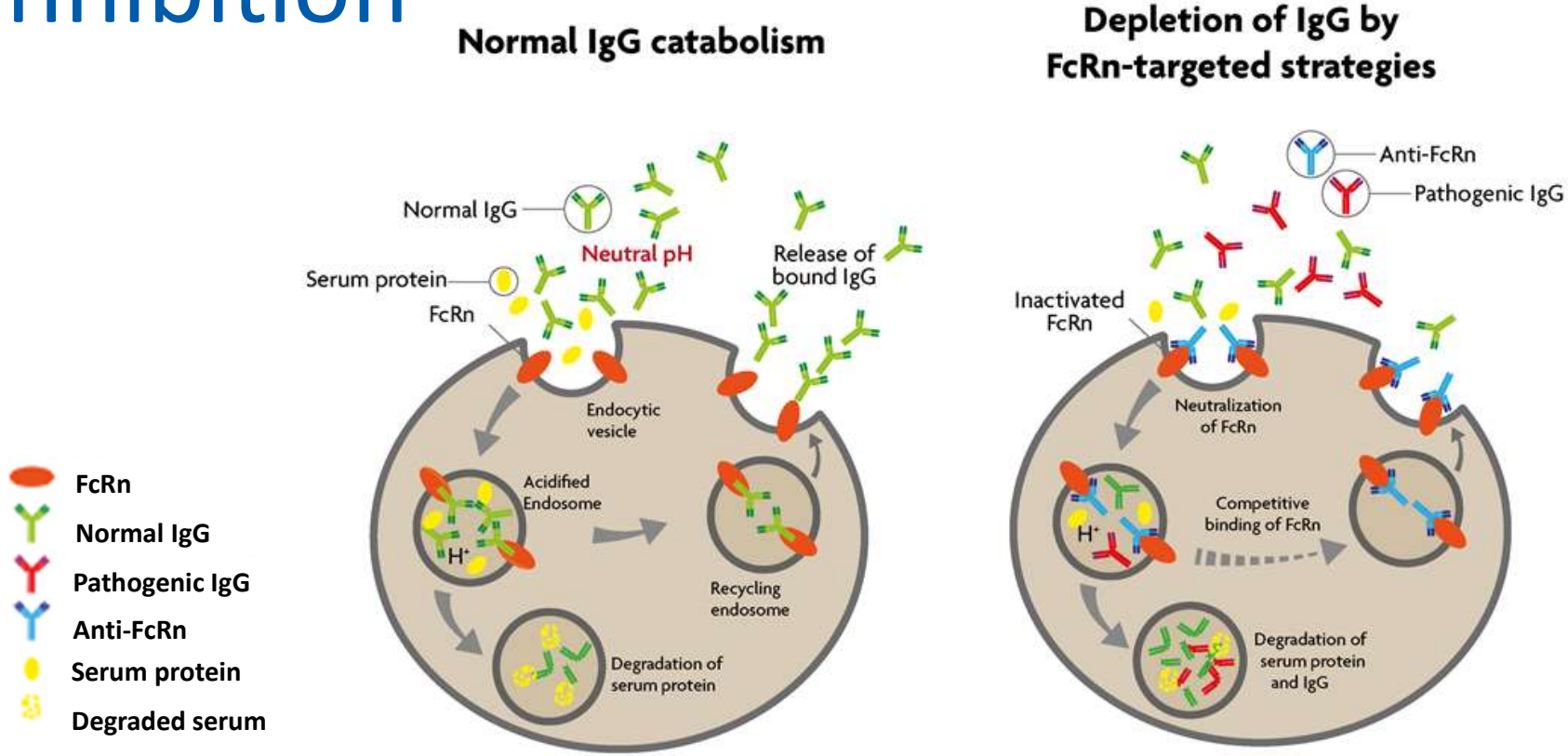
Clinicaltrials.gov

Characteristics of Patients Usually Entered in Clinical Trials

- Clinical trials for novel ITP therapies vary but typically include the following general eligibility criteria:
  - Confirmed diagnosis of primary ITP according to standard guidelines
  - Inadequate response to or relapse after prior ITP treatments including:
    - Corticosteroids
    - Immunoglobulins
    - Other standard therapies
  - Platelet count below a certain threshold, commonly < 30 x 10^9/L
  - Adult patients (usually 18 years or older, though some trials investigate pediatric patients)
  - No active, uncontrolled bleeding
  - Absence of other causes of thrombocytopenia
  - Not pregnant or breastfeeding
  - No secondary causes of ITP
  - Did not recently receive other experimental therapy
  - No anti-B cell therapy in the past 3-6 months

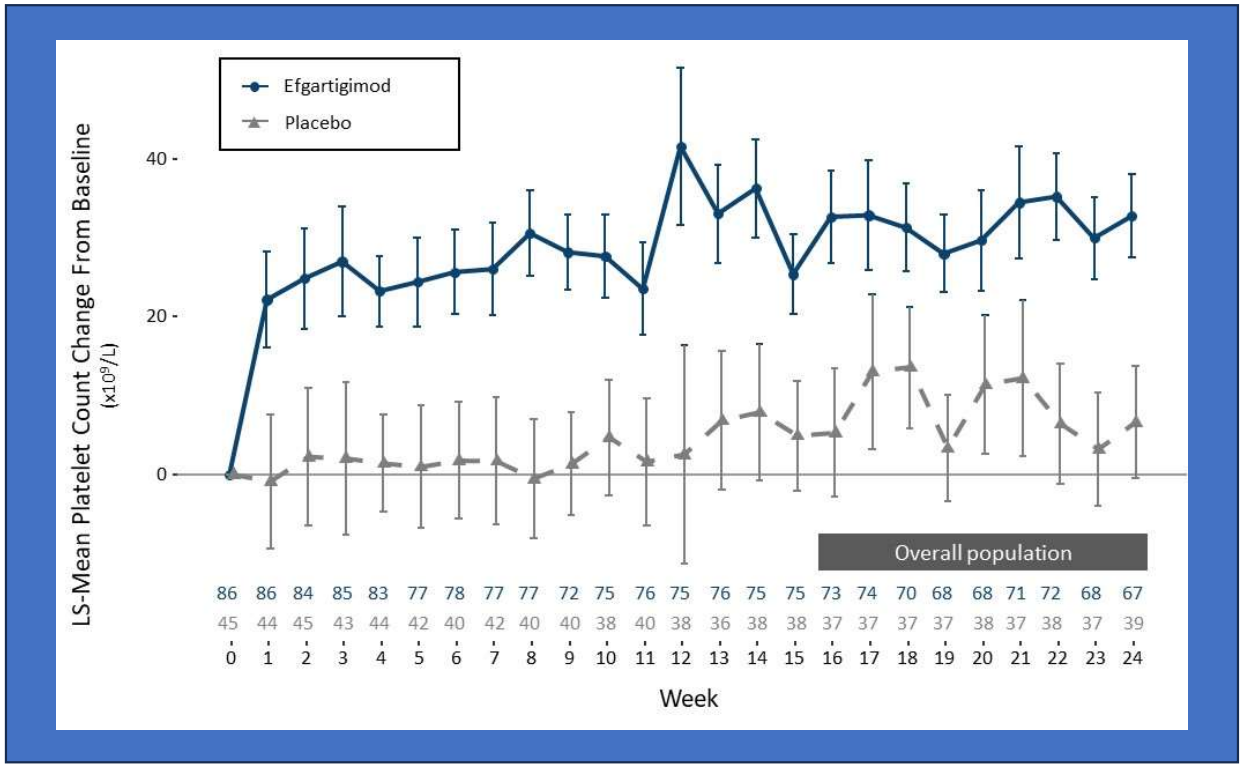
Singh A, et al. *J Clin Med*. 2021;10(4):789; Vianelli N, et al. *Ann Hematol*. 2022;101(5):963-978. Provan D, et al. *Blood Adv.* 2019;3(22):3780-3817.

Mechanism of Action of FcRn and Its Inhibition



Kuter DJ. *Br J Haematol*. 2022 Mar;196(6):1311-1328.

Efgartigimod: ADVANCE Study–Platelet Response

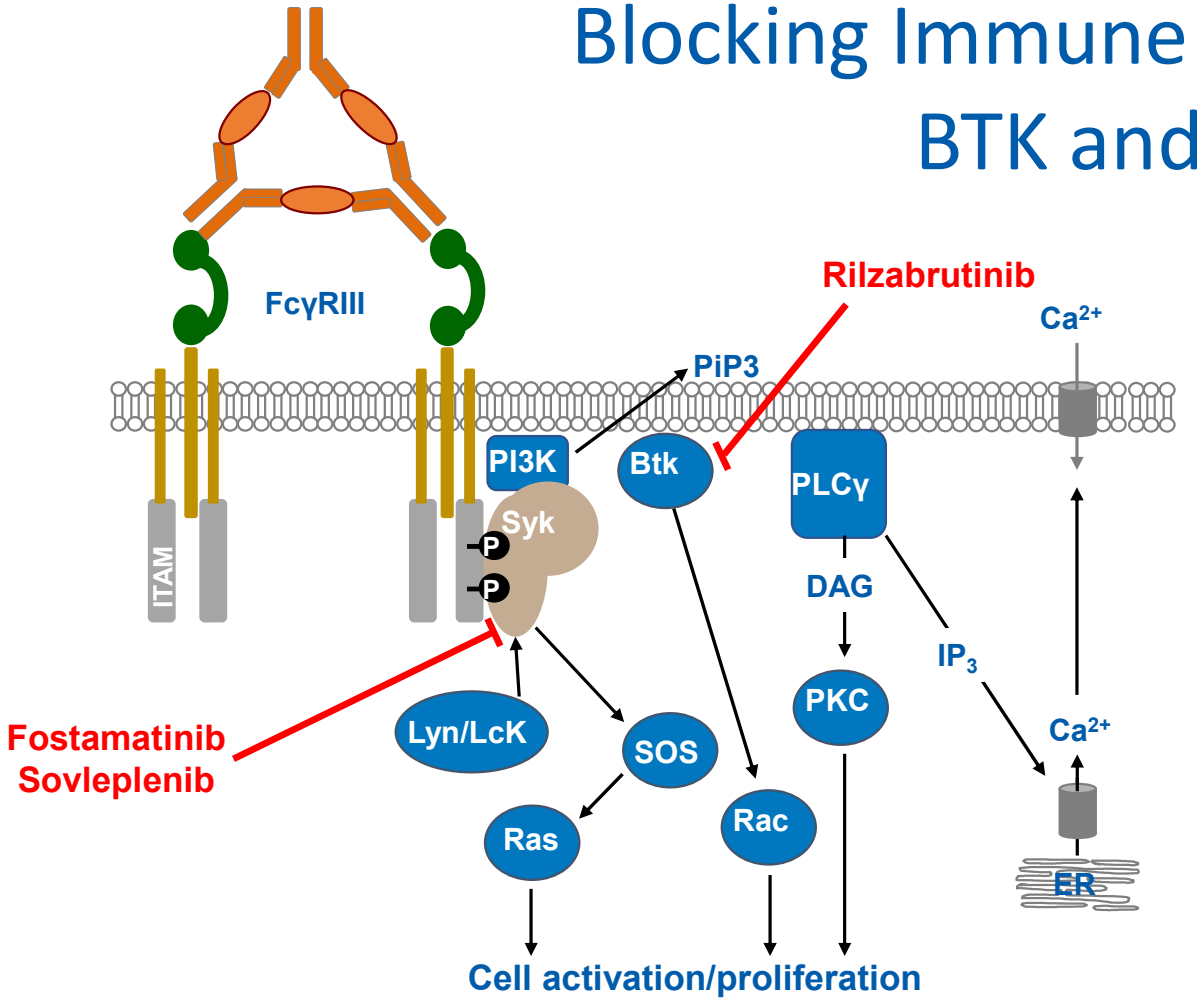


- **Primary endpoint: Sustained platelet count response*** achieved in **21.8%** (17/78) of efgartigimod patients compared with **5%** (2/40) of placebo patients (**P = 0.0316**)
- **33 (38.4%) of efgartigimod-**treated participants compared to **5 (11.1%) placebo** recipients reached a platelet count of 30 X 10^9 platelets at week 1

* Platelet count $\geq$ 50 x 10^9/L in 4 of 6 visits weeks 19-24

C Broome, et al. *Lancet.* 2023;402:1648-1659.

Blocking Immune Cell Signaling: BTK and Syk Inhibitors

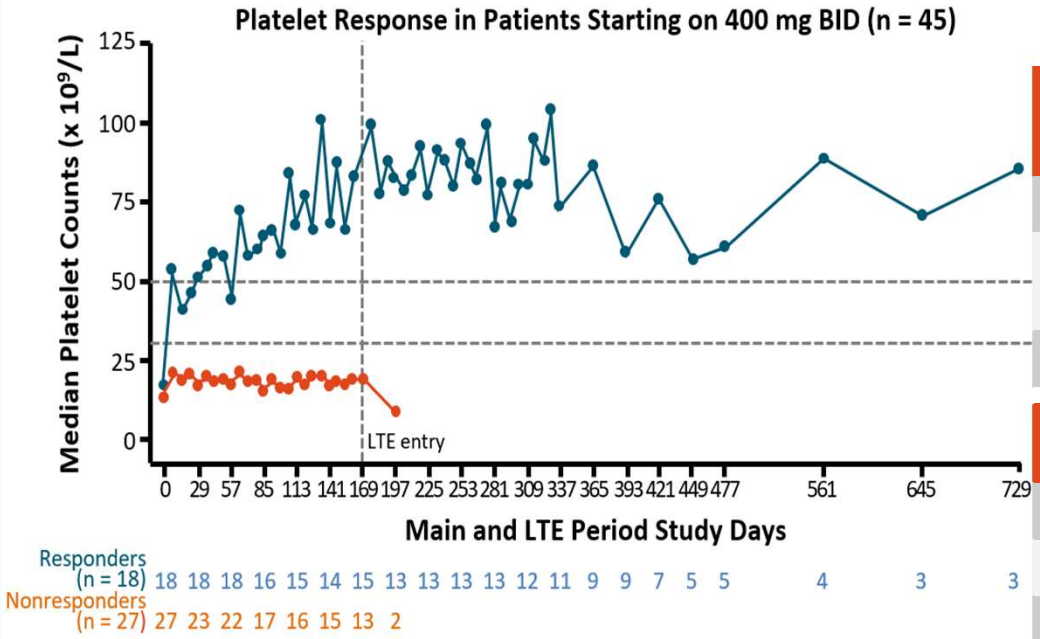


Btk = Bruton's tyrosine kinase; ER = endoplasmic reticulum; ITAM = immunoreceptor tyrosine-kinase-based activation motifs; PI3K = phosphatidylinositol-3 kinase; PLCγ = phospholipase C γ; Syk = spleen tyrosine kinase.

Adapted from: Nimmerjahn F, Ravetch J. *Ann Rev Immunol.* 2008;26:513–33.

Rilzabrutinib Phase I/II Trial in Previously Treated ITP: Platelet Responses With 400 mg BID

- Median treatment duration: 168 days (range: 10-188) for the main treatment period and LTE
- 18 patients (40%) initiating 400 mg BID rilzabrutinib met the primary endpoint: ≥2 consecutive platelet counts ≥50 x 10^9/L and increased ≥20 x 10^9/L without use of rescue medication in the 4 wk prior to the latest elevated platelet count
- 16 of these 18 patients showed clinically relevant platelet counts of ≥50x10^9/L at any point in the first 8 wk of study treatment



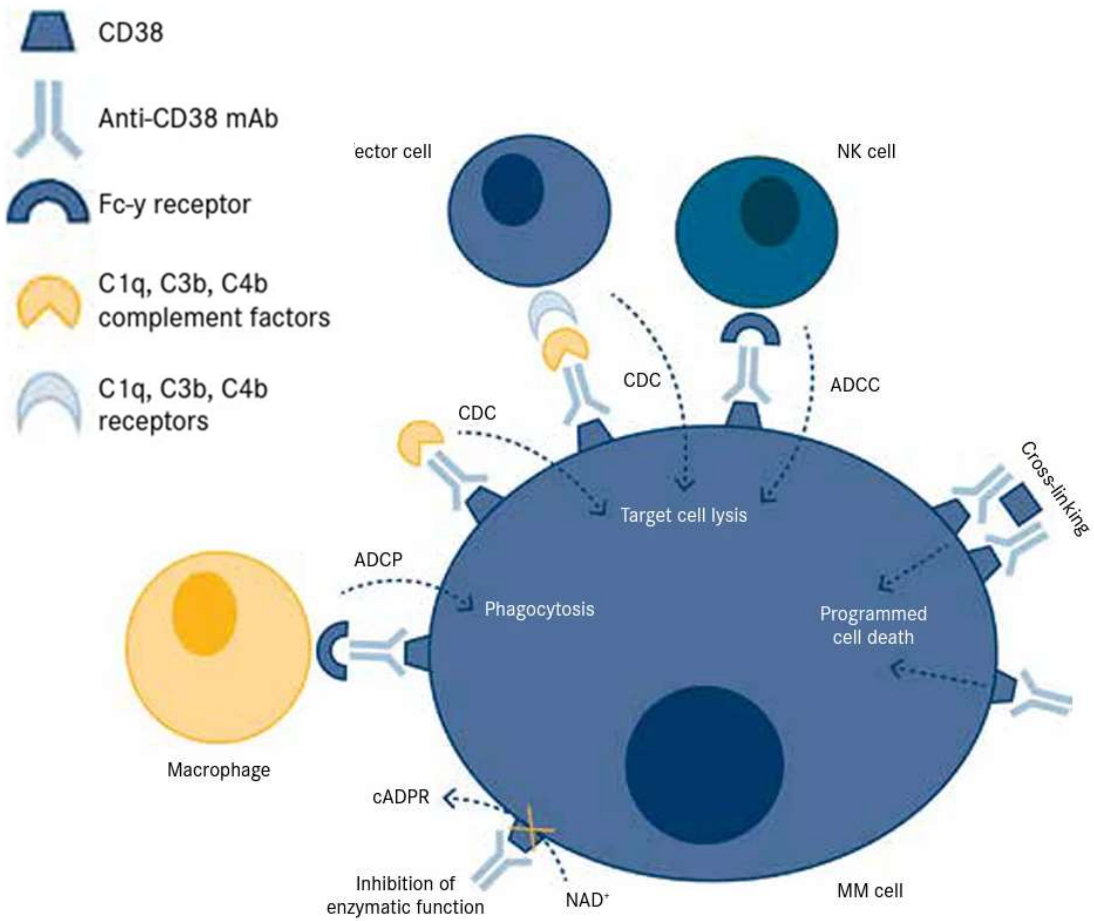
Primary Efficacy Responders Platelet Counts (n = 18)	Median No. of Wk	Duration of Response, Median % Wk
≥30 x 10^9/L	20.5	95
≥30 x 10^9/L with ≥20 x 10^9/L above baseline	18	86
≥50 x x10^9/L	14	72

Select TRAE (n = 60), n (%)	Gr 1	Gr 2	Gr 3/4
Diarrhea	16 (27)	3 (5)	0
Nausea	16 (27)	2 (3)	0
Fatigue	5 (8)	1 (2)	0

Kuter. NEJM. 2022;386:1421. Kuter. EHA 2022. Abstr S291.

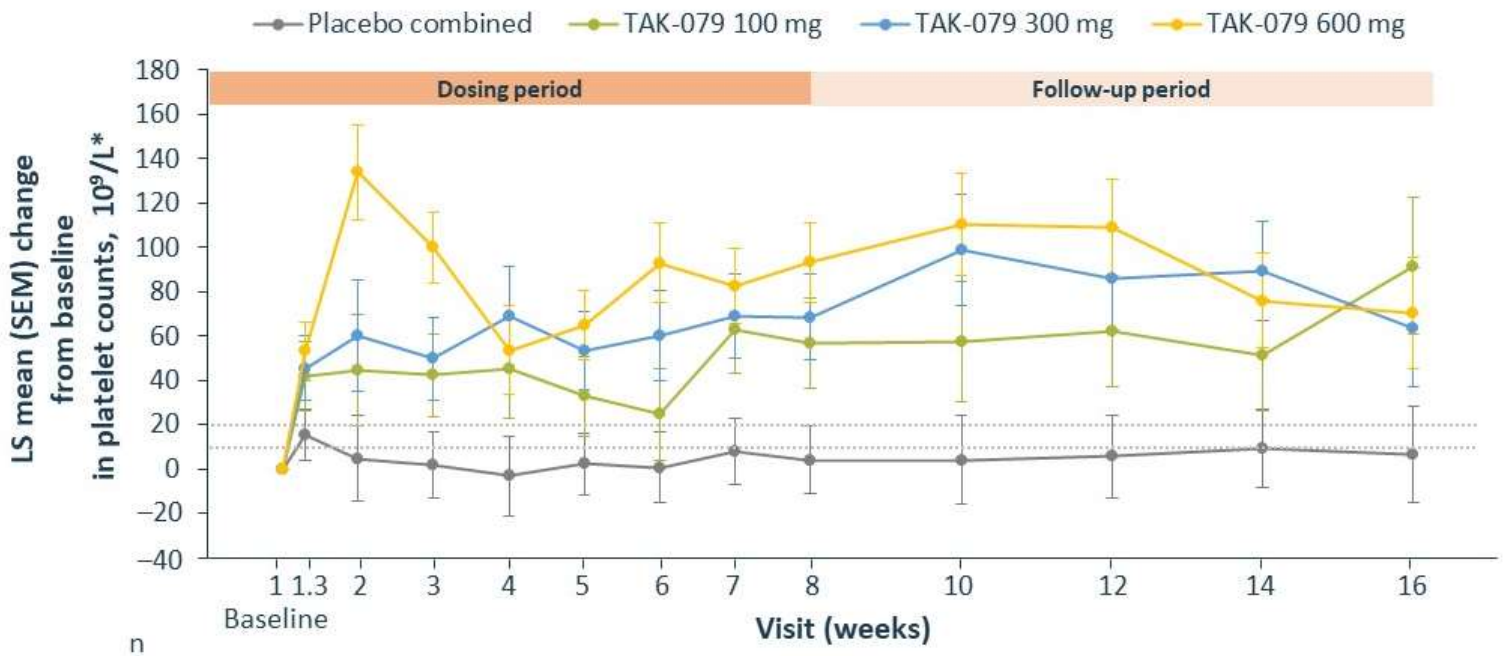
CD38

- Primitive multifunctional enzyme on cell surface
- Plasma cells, B and T cells, NK cells, many others
- Enzyme
  - NADase activity
  - Alters Ca^{2+} flux in many cells
- Receptor
  - Activator of B and T cells
- Loss of function mutations: immune deficiency



Morandi F, et al. *Frontiers Immunol*. 2018, 9:2722.

Mezagitamab (TAK-079): Anti-CD38



n												
Placebo combined	12	13	13	13	13	13	13	12	12	12	12	11
TAK-079 100 mg	7	8	8	8	7	6	7	7	5	5	5	5
TAK-079 300 mg	8	8	8	8	8	8	8	8	8	8	8	8
TAK-079 600 mg	10	11	9	10	10	8	9	9	9	9	8	9

DJ Kuter, et al. Oral Presentation. Presented at the 2024 International Society of Thrombosis and Hemostasis. Bangkok, June 22-26.

Key Takeaways

- Shared decision-making is essential in the management of ITP, and treatment should be tailored to the patient's preferences and symptoms
- Treatment may not be indicated above a platelet count > 30 x 10^9 in the absence of bleeding symptoms or risk
- Patients failing multiple approved or recognized therapies should be considered for clinical trials

Panel Discussion and Q & A Session

Thank You to Our Supporters

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