Immune Thrombocytopenia

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- Royalties
  - Up to Date
- Research Funding
  - Novartis

Objectives

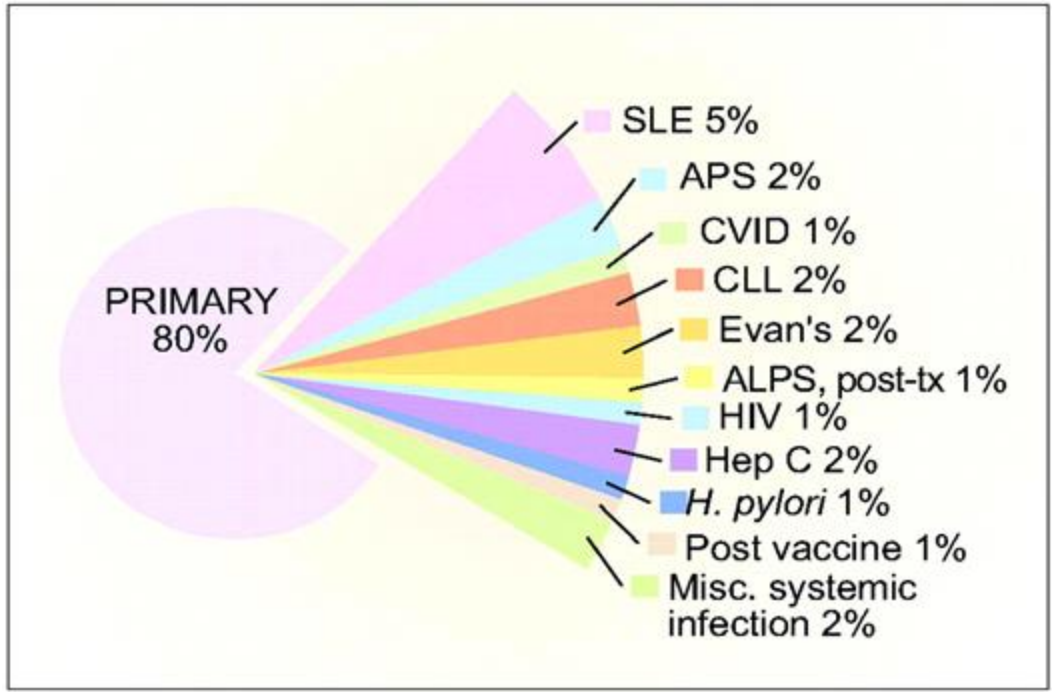
1. Review the pathophysiology of ITP
2. Discuss the diagnosis of ITP
3. Outline first- line management
4. Provide an overview of second- line treatment strategies
5. Highlight third-line agents and novel agents in development

Epidemiology and Pathophysiology

Module 1

Immune Thrombocytopenia

- An autoimmune disorder
  - Isolated thrombocytopenia: platelet count < 100 × 10^9/L
  - The absence of other causes or disorders that may be associated with thrombocytopenia
  - Remains a diagnosis of exclusion
- Increased risk of bleeding
  - Bleeding is very heterogeneous
- Can be primary or secondary

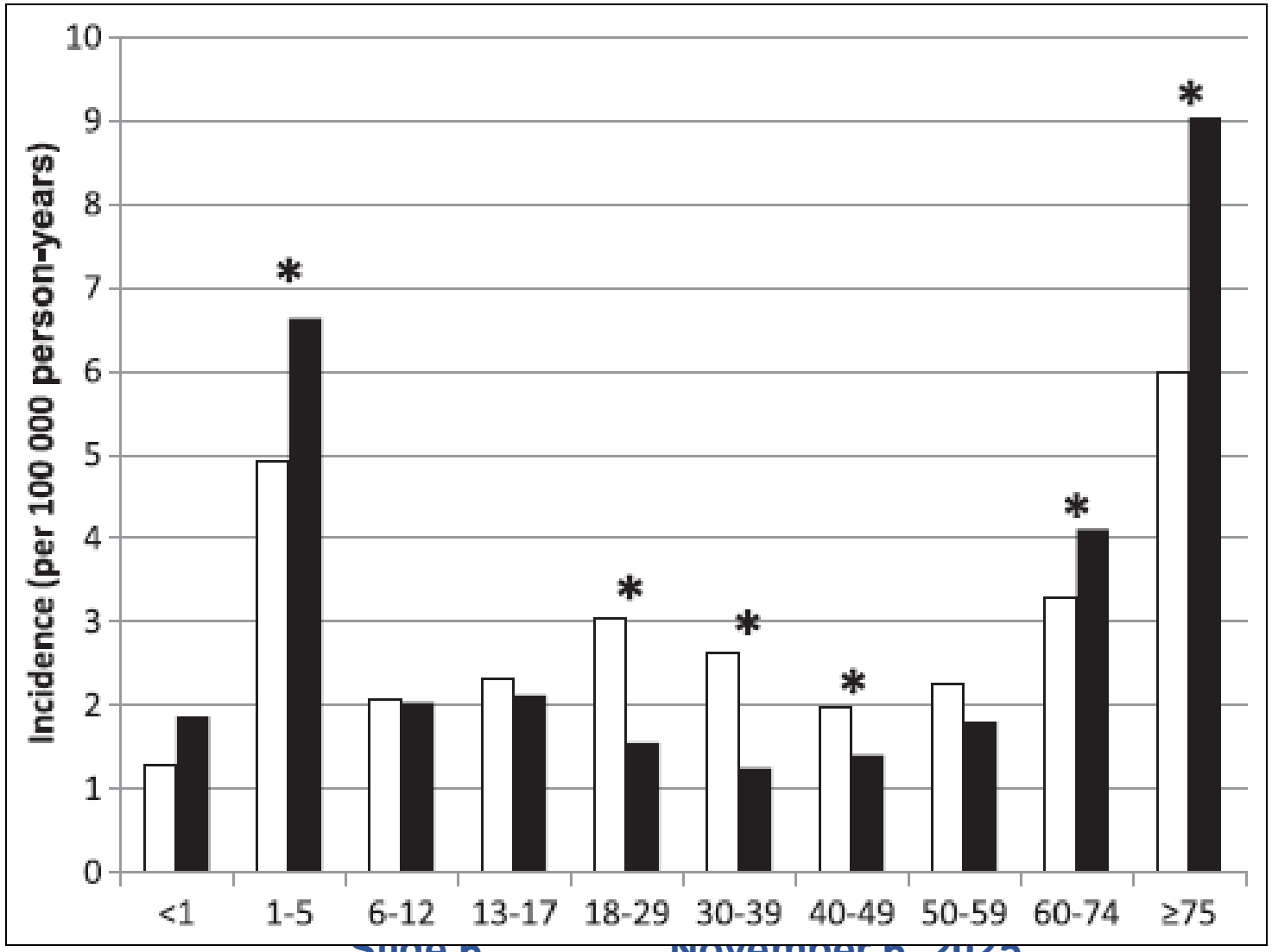


SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; CVID, common variable immune deficiency; CLL, chronic lymphocytic leukemia; APLS, autoimmune lymphoproliferative syndrome; post-tx, post-bone marrow or solid organ transplantation

Cuker A. *Hematology Am Soc Hematol Educ Program*. 2010
Rodeghiero F, et al. *Blood.* 2009

Epidemiology

Annual incidence: 1.6-3.9 per 100,000 person-years

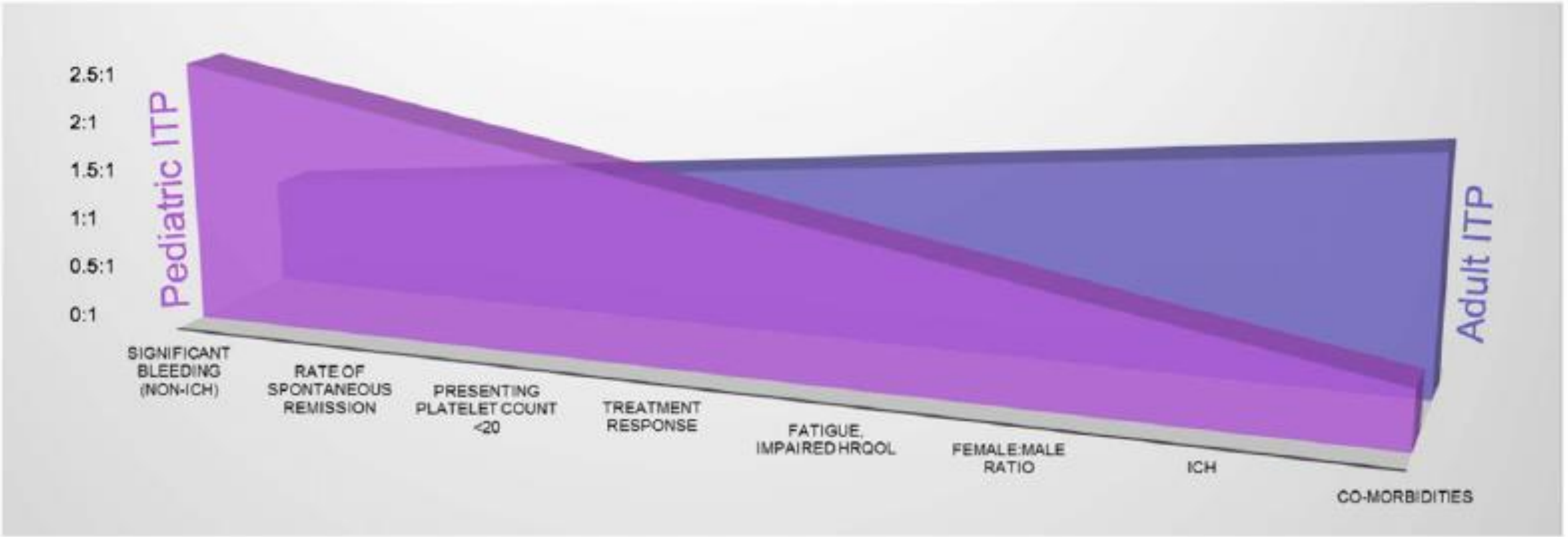


= Females

= Males

*Statistically significant differences among males and females (α = 5%)

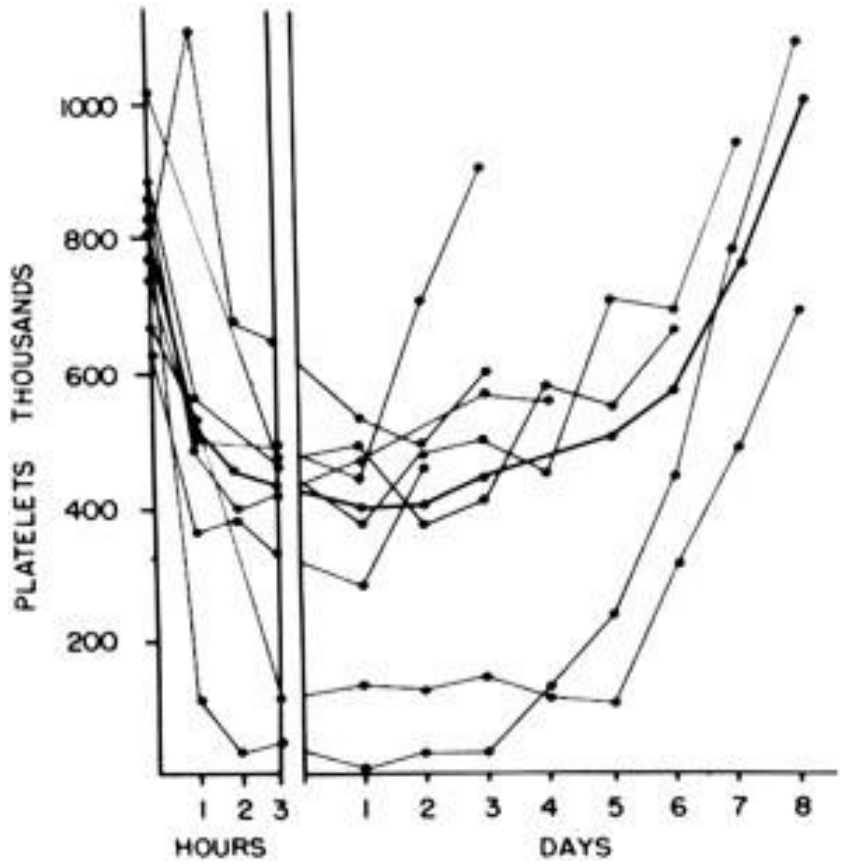
Moulis G, et al. *Blood. 2014*

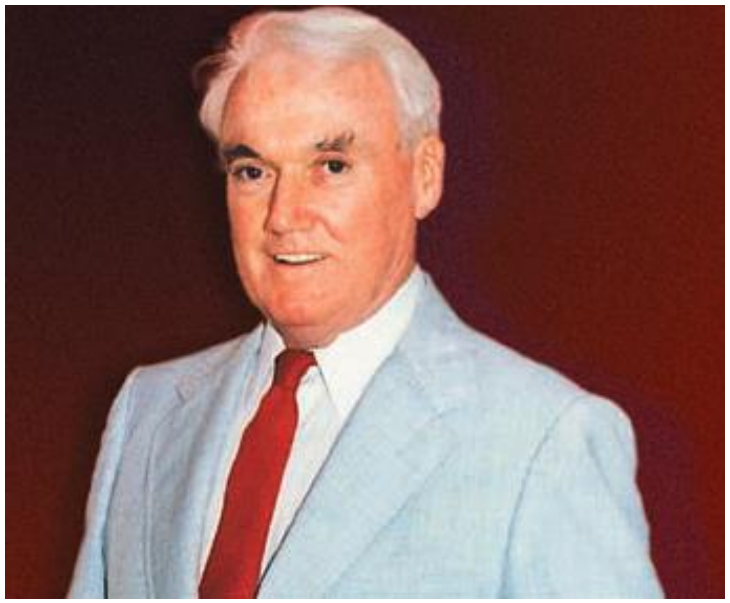


Despotovic. *Hematology Am Soc Hematol Educ Program* 2018

Pathogenesis

- Dr. Harrington and Dr. Hollingsworth in 1950
  - Injected blood from a patient with ITP
  - Developed severe thrombocytopenia
  - Bone marrow showed normal number of megakaryocytes



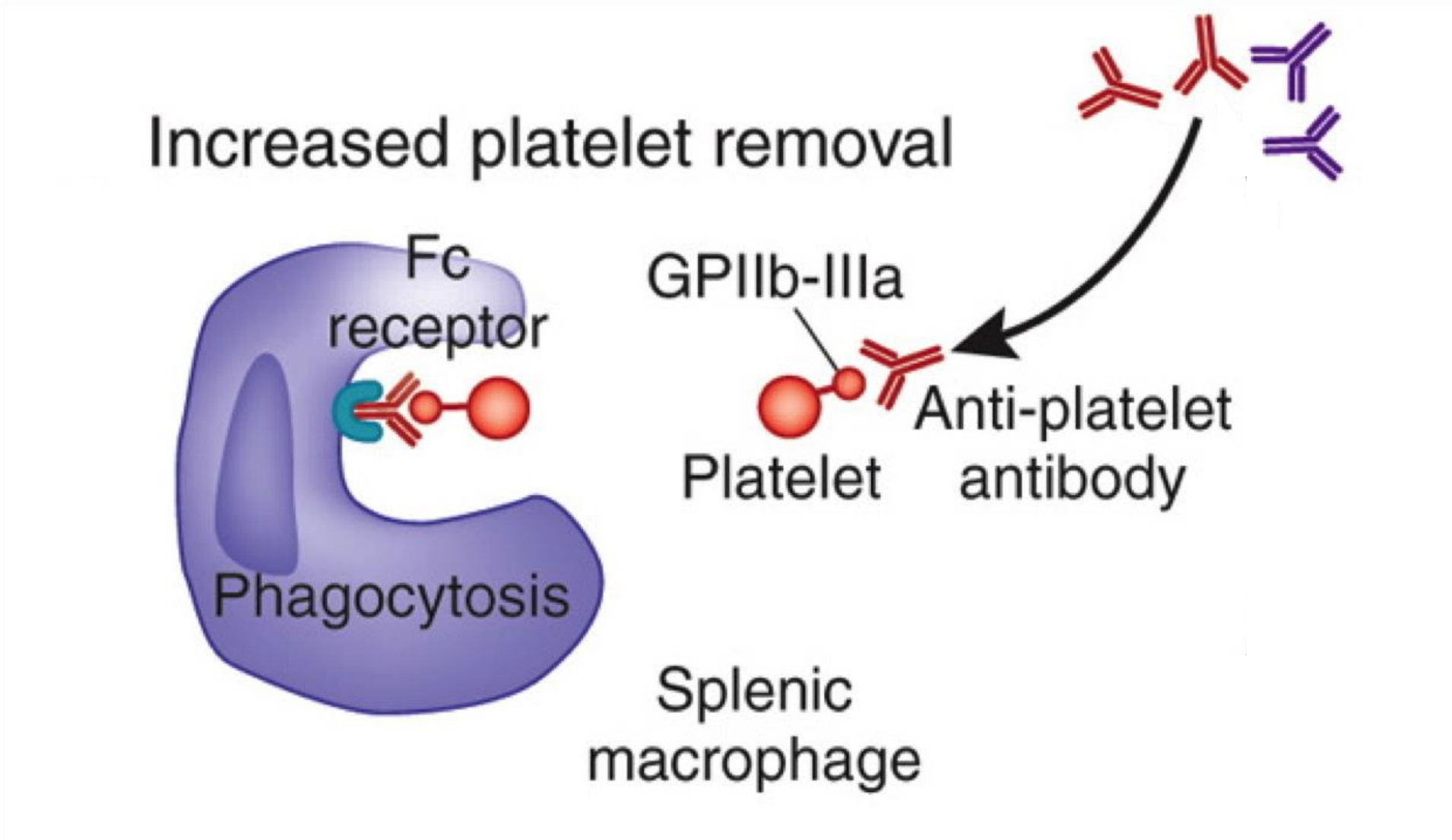


"This experiment, one of the most important ever to be performed in the field of hematology….changed the meaning of the "I" in ITP from idiopathic to immune"

- Schwartz, 2007, NEJM

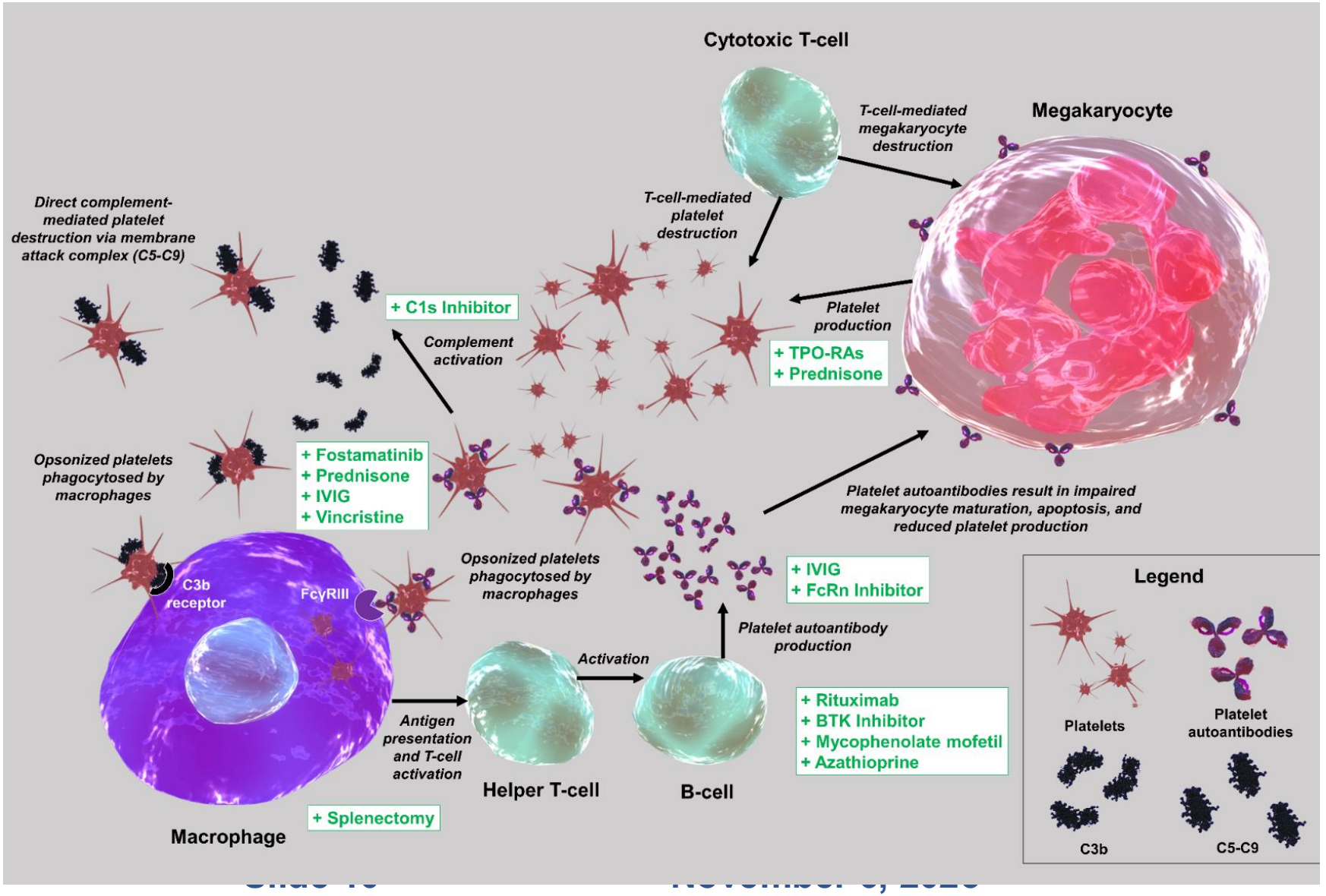
Harrington et al. J Lab Clin Med 1951

Pathogenesis: Then…..



Wei and Jackson Nat Med 2008

Pathogenesis Now….

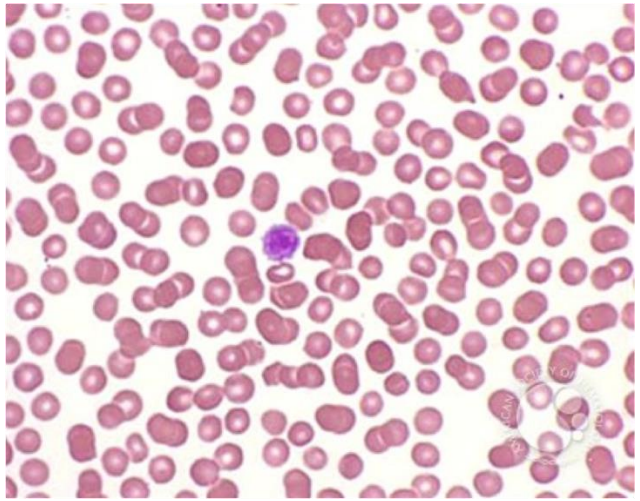


Al-Samkari H, Kuter DJ. Semin Thromb Hemost.2020

Diagnosis
Module 2

Diagnosis

- **A diagnosis of exclusion:**
  - Defined as a platelet count of less than 100 × 10^9/L
  - Absence of red and white cell abnormalities
  - Anemia if significant bleeding present
  - Pay attention to red cell indices

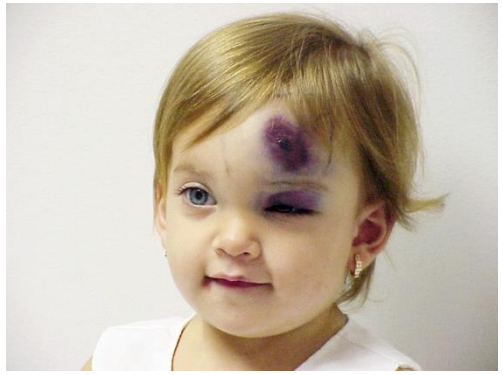


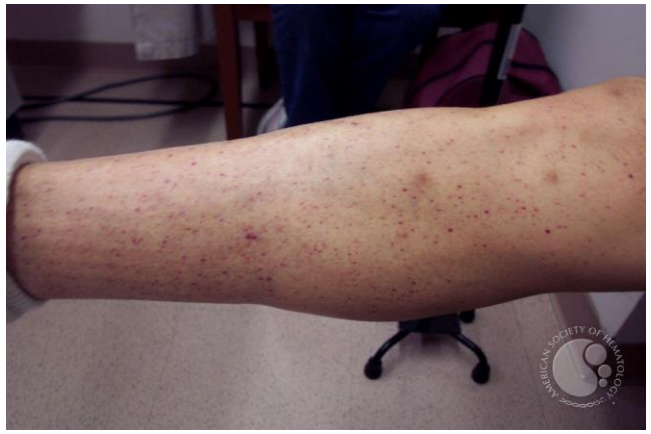
- Peripheral blood smear
  - Few large to normal platelets present
  - No red or white cell abnormalities
- HCV and HIV testing is recommended for all patients
- Bone marrow examination
  - Not necessary in patients presenting with typical ITP
  - Age and failure of response to standard therapy are a debated factors

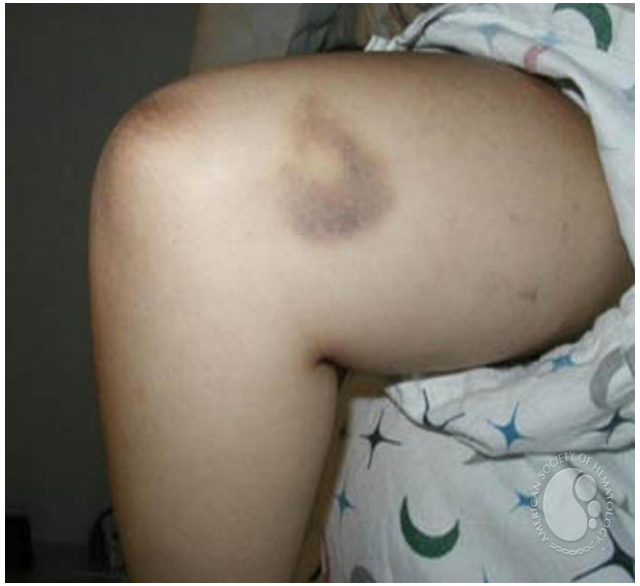
ITP: Clinical Manifestations

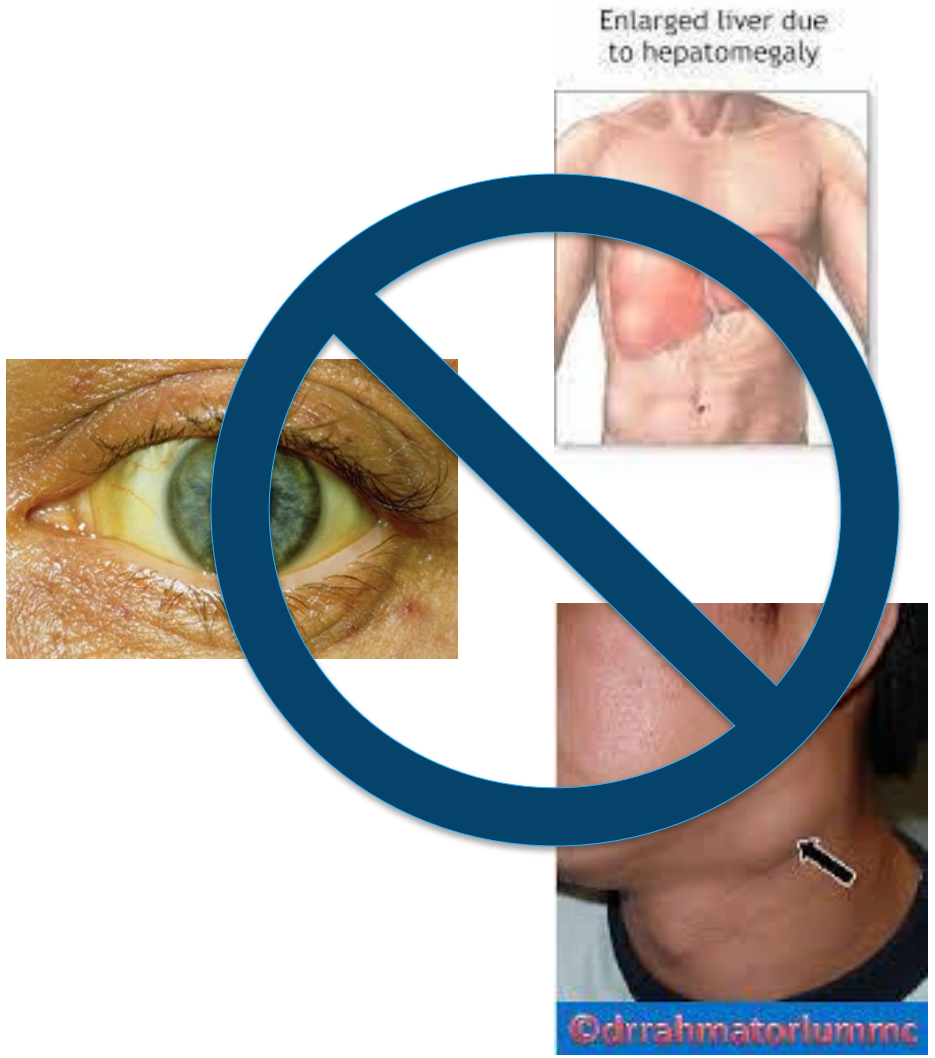
- Bleeding
  - Substantial inter-individual variation in bleeding phenotype
  - Mucocutaneous bleeding is most common manifestation
  - Spontaneous intracranial hemorrhage (ICH) is rare, especially when platelet count is >20 x 10^9/l
  - Advanced age, prior bleeding, anti-platelet/anticoagulants are independent risk factors
- Impact on health-related quality of life (HRQoL)
  - Fatigue, worry about bleeding, reduced activities
- Possible increase in thrombotic events

ITP Physical Examination









Terminology

- Newly Diagnosed ITP: ≤ 3 months
- Persistent ITP: 3-12 months
- Chronic ITP: > 12 months
- Relapsing ITP:
  - Episodes of ITP separated by periods of remission or ITP that requires treatment for remission
- Severe ITP

Rodeghiero et al. Blood, 2009

Treatment

- The goal of treatment is to achieve normal hemostasis, not to reach a normal platelet count
- Additional considerations beyond the platelet count should be considered:
  - Age
  - Upcoming surgery
  - Comorbidities associated with a risk of bleeding
  - Anti-platelet medications or anticoagulation
  - Social concerns about distance from the hospital, ability to follow-up, etc
  - Additional symptoms such as fatigue and assessment of health-related quality of life

First-line Treatment
Module 3

Upfront Management of ITP

	Dose	Time to Response	Side Effects
Observation and Education	Time	1 week - indefinite	Bleeding
Corticosteroids	**Adults:** Prednisone (0.5 to 2.0 mg/kg/day) or dexamethasone (40 mg/day for 4 days) **Children:** 2-4 mg/kg PO divided BID for 5-7 days	3-4 days	Mood changes Hypertension Hyperglycemia Gastritis
IVIG	0.8-1.0 gm/kg IV for one dose Up to 2gm/kg max	24-48 hours	Infusion reaction Headache/Aseptic meningitis Thrombosis FDA Black box warning for renal failure
Anti-D Immunoglobulin (WinRho)	50-75 mcg/kg IV for one dose	24-48 hours	Hemolysis (2.0 gram decrease in Hgb) FDA Black box warning for fatal intravascular hemolysis

2019 ASH Guidelines: Adult Newly Diagnosed

Recommendation	Population	Intervention	Comparator	Strength	Certainty in the evidence
1a	Platelet Count < 30 x 10^9/l Asymptomatic or minor bleeding	Corticosteroids	Observation	Conditional	Very low
1b	Platelet Count ≥ 30 x 10^9/l Asymptomatic or minor bleeding	Corticosteroids	Observation	Strong	Very low
2a	Platelet Count < 20 x 10^9/l Asymptomatic or minor bleeding	Inpatient (new patient)	Outpatient (established patient)	Conditional	Very low
2b	Platelet Count ≥ 20 x 10^9/l Asymptomatic or minor bleeding	Inpatient	Outpatient	Conditional	Very low
3	Requiring corticosteroids	Prolonged corticosteroids	Short course of corticosteroids	Strong	Very low
4	Requiring corticosteroids	Prednisone	Dexamethasone	Conditional	Very low
5	Requiring treatment	Corticosteroids	Corticosteroids plus rituximab	Conditional	Very low

Neunert et al. Blood Adv, 2019

ASH Guidelines: Adult ITP Newly Diagnosed

- Also carried forward recommendations from the 2011 ASH Guidelines:
  - IVIG be used with corticosteroids when a more rapid increase in platelet count is required (grade 2B)
  - Either IVIG or anti-D (in appropriate patients) be used as a first-line treatment if corticosteroids are contraindicated (grade 2C)
  - If IVIG is used, the dose should initially be 1 g/kg as a 1-time dose; this dosage may be repeated if necessary (grade 2B)

Good Practice Statement

- The treating physician should ensure the patient is adequately monitored for potential corticosteroid side effects regardless of the duration or type of corticosteroid selected. This includes close monitoring for hypertension, hyperglycemia, sleep and mood disturbances, gastric irritation or ulcer formation, glaucoma, myopathy, and osteoporosis.
- Given the potential impact of corticosteroids on mental health, the treating physician should conduct an assessment of health-related quality of life (depression, fatigue, mental status, etc.) while patients are receiving corticosteroids.

Neunert et al. Blood Adv, 2019

Prednisone or High Dose Dexamethsone

- Primary aim: 6-month response rates
- Response at 6 months did not vary
  - Overall response 54% vs 43%
  - Complete response 37% vs 21%
- Increase in OR by day 14 with dexamethasone
- No effect of high cumulative dose
- Adverse event rates:
  - 24 per 100 patients in the dexamethasone group
  - 46 per 100 patients in the prednisone group

Mithoowani et al. Lancet Haematolo 2016

2019 ASH Guidelines: Pediatric Newly Diagnosed

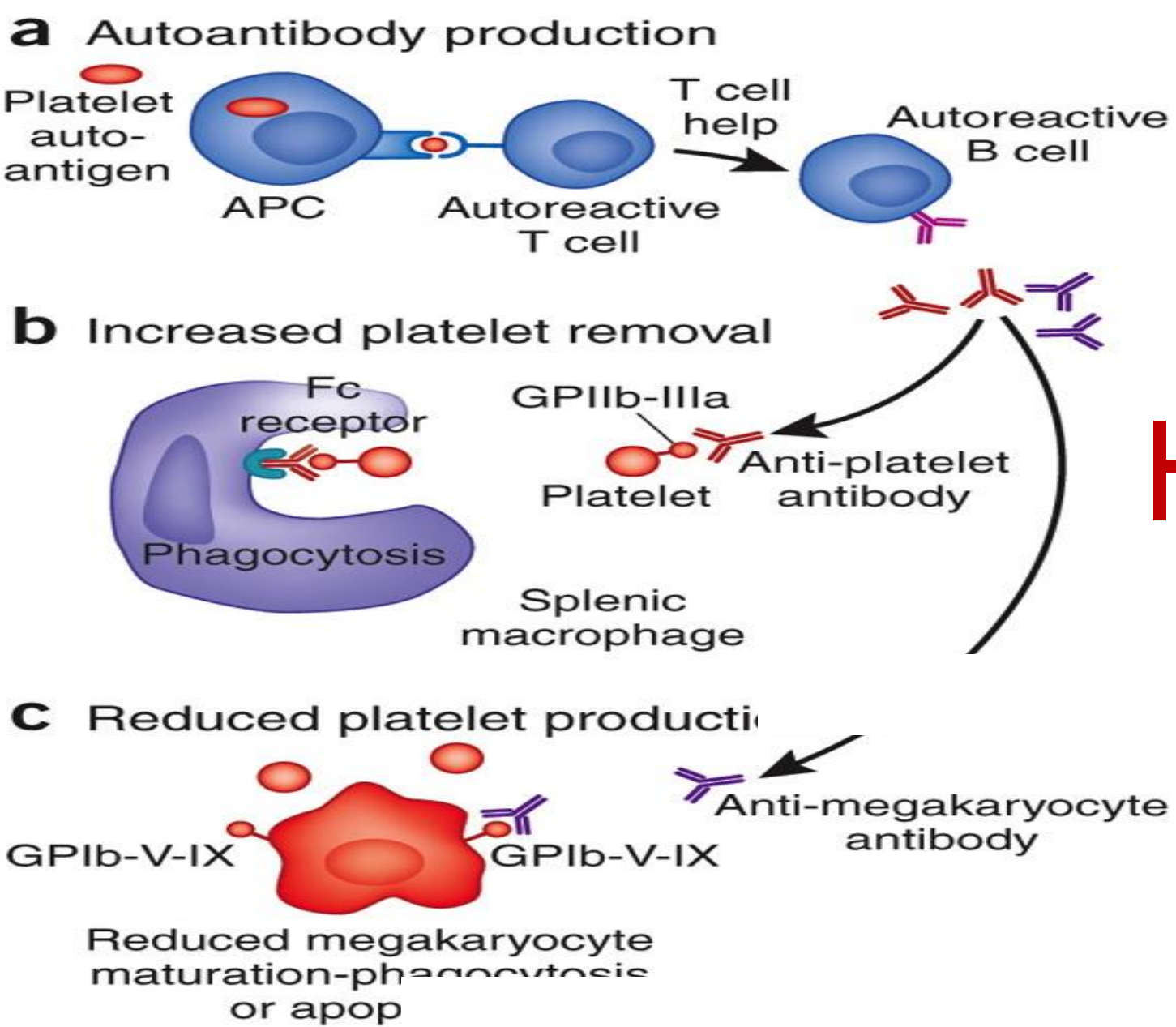
Recommendation	Population	Intervention	Comparator	Strength	Certainty in the evidence
10a/b	All newly diagnosed	Inpatient	Outpatient	Conditional	Very low
11	No or mild bleeding	Corticosteroids	Observation	Conditional	Very low
12	No or mild bleeding	IVIg	Observation	Strong	Moderate
13	No or mild bleeding	Anti-D immunoglobulin	Observation	Strong	Moderate
14	Non-life-threatening mucosal bleeding or impaired HRQoL	Prolonged corticosteroids	Short course corticosteroids	Strong	Very low
15	Non-life-threatening mucosal bleeding or impaired HRQoL	Prednisone	Dexamethasone	Conditional	Very low
16	Non-life-threatening mucosal bleeding or impaired HRQoL	Corticosteroids	Anti-D immunoglobulin	Conditional	Low
17	Non-life-threatening mucosal bleeding or impaired HRQoL	Anti-D immunoglobulin	IVIg	Conditional	Low
18	Non-life-threatening mucosal bleeding or impaired HRQoL	Corticosteroids	IVIg	Conditional	Low

Neunert et al. Blood Adv, 2019

Augmented First Line Therapy

- Dexamethasone + Rituximab
- Dexamethasone + TPO-RAs
  - Mostly eltrombopag
  - PINES trial in children
- Corticosteroids + MMF (FLIGHT trial)

Subsequent Treatment
Module 4



Rituximab

BTK inhibitors

Splenectomy and Fostamatinib

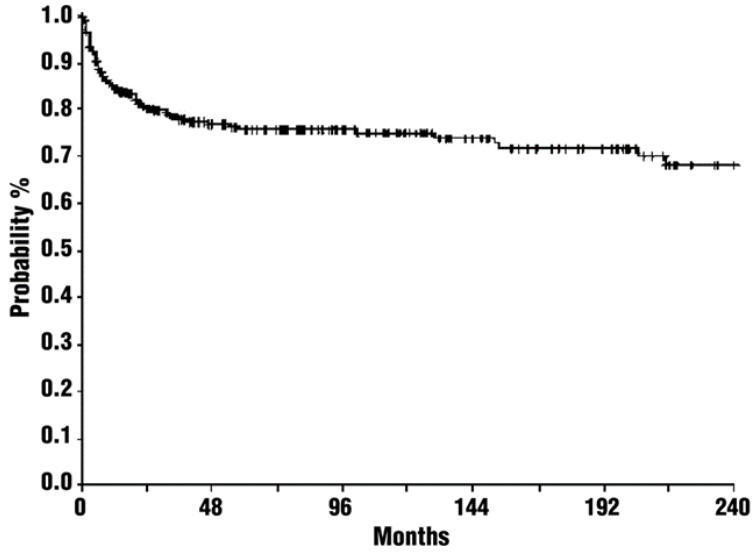
Thrombopoeitin Receptor Agonists (TPO-RAs)

2025

Wei and Jackson Nat Med 2008

Splenectomy

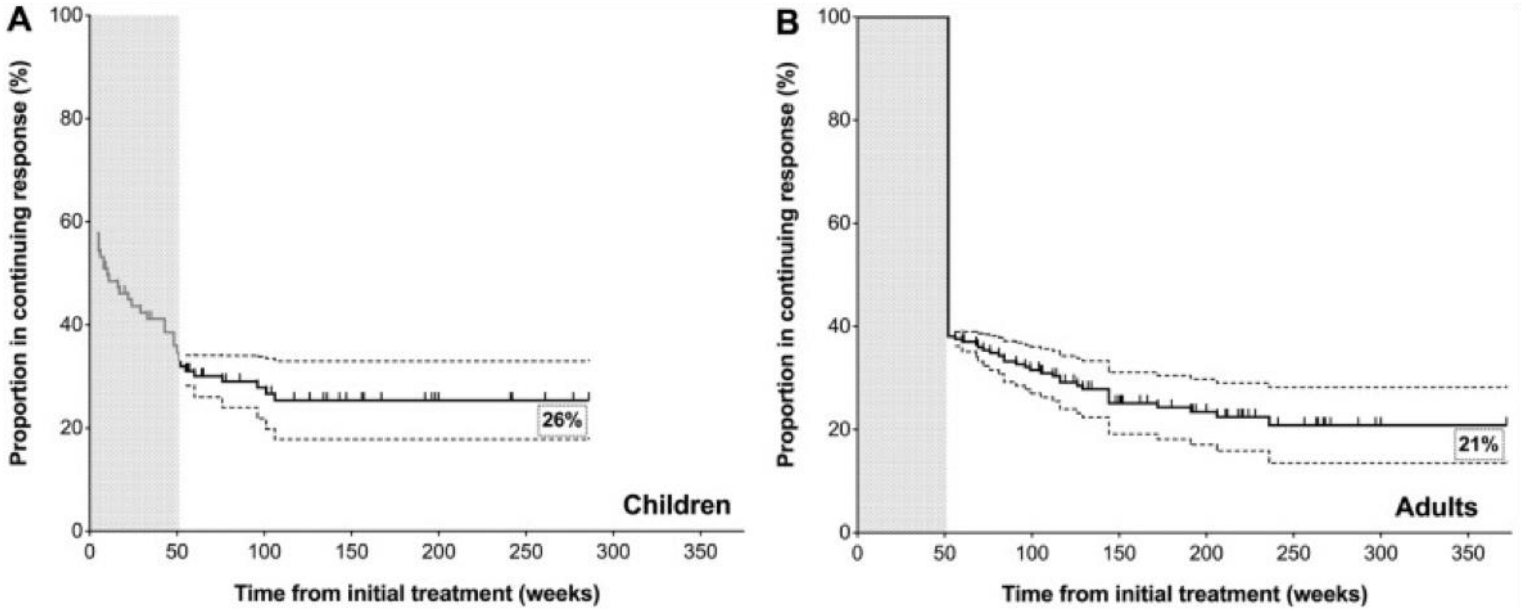
- Response:
  - Remission in 2/3 of patients
- Need to vaccinate against encapsulated organisms
  - Monitor titers and revaccinate for pneumococcus and HIB every 3-5 years
  - Life-long fever precautions and antibiotic prophylaxis
- Potential Thrombosis Risk



Ghanima W et al. Blood 2012; Stasi R, Provan D. Mayo Clin Proc 2004, Crary and Buchanan Blood 2009

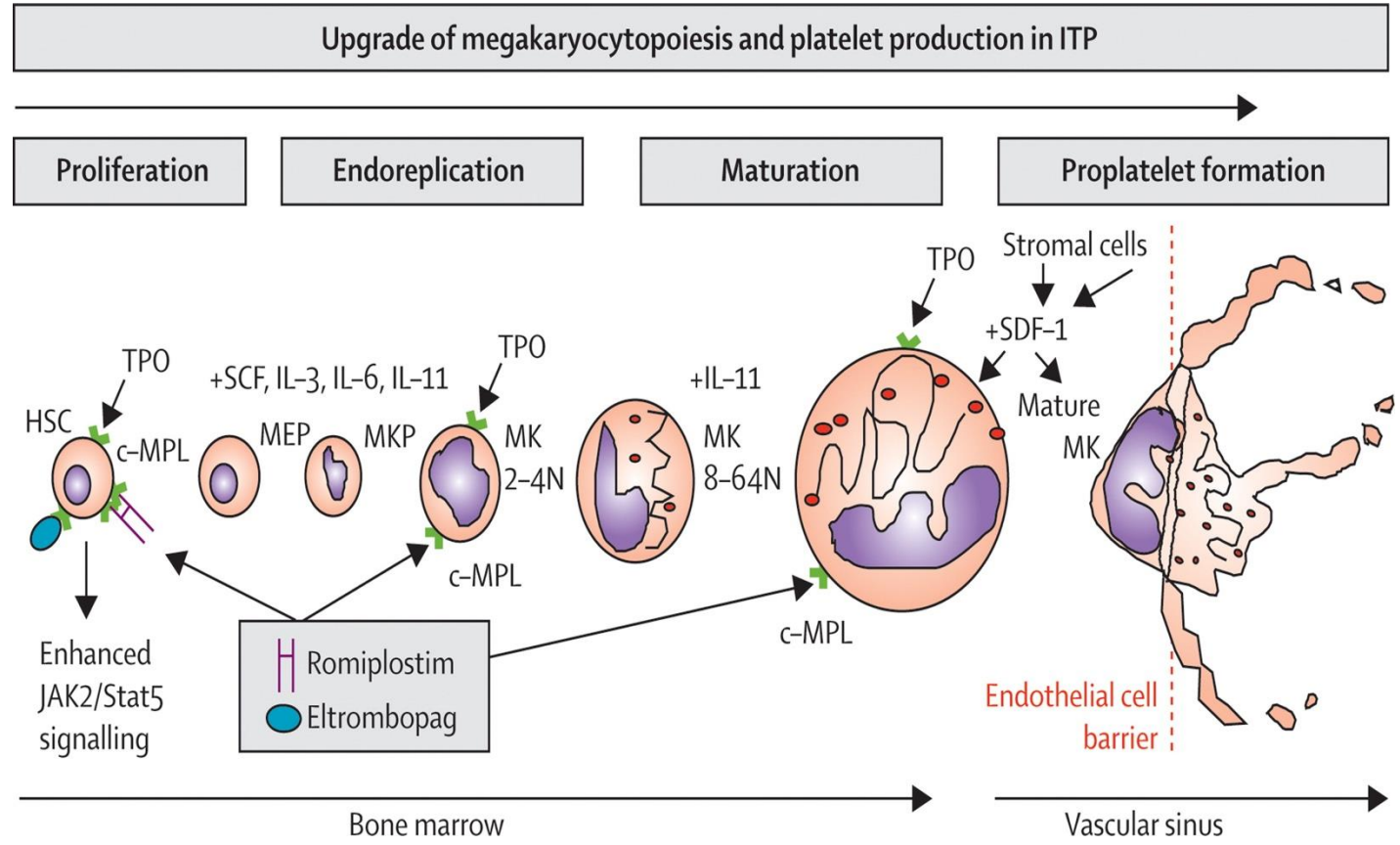
Rituximab

- Early remission rates
  - Adults: 57-63%
  - Pediatric: 57% -68%
- Sustained remission rates remain lower



Arnold et al. Int Med 2007;Patel et al Blood 2012; Liang et al PloS one 2012

Thrombopoietin



http://thelancet.com/cms/attachment/2001001856/2003729871/gr1_lrg.jpg

- Prevents megakaryocyte apoptosis
- Induces mobilization of stem cells
- Megakaryocyte proliferation/differentiation
- JAK/STAT activation

Gernsheimer, The Oncologist 2009

TPO-RAs

- Romiplostim, eltrombopag, avathrombopag, and lusutrombopag
  - Discontinuation results in thrombocytopenia
  - Reports suggest no cross-resistance
- Increase platelet count, decrease bleeding, reduce additional medications, and improve health-related quality of life (HRQoL)
- Sustained drug free response following use
  - Immune tolerance?
  - Restore T and B regulatory cells

Polverelli Brit J of Haematol 2013; D'Arena Blood 2013; Ghadaki et al. Transfusion 2013

TPO-RAs

- Bone marrow reticulin and transformation
  - EXTEND study: No grade 3 reticulin, symptoms of bone marrow dysfunction, or blast counts >3%

- Thromboembolic events
  - Event rate of 3.17-4.16 per 100 patient years
  - No increased risk in meta-analysis of romiplostim

- Eltrombopag hepatotoxicity
  - 10% of patients had drug induced liver insufficiency
  - Reversible with drug discontinuation

Saleh et al. Blood 2013; Kuter et al. British journal of haematology 2013; Cines et al. Haematologica 2017

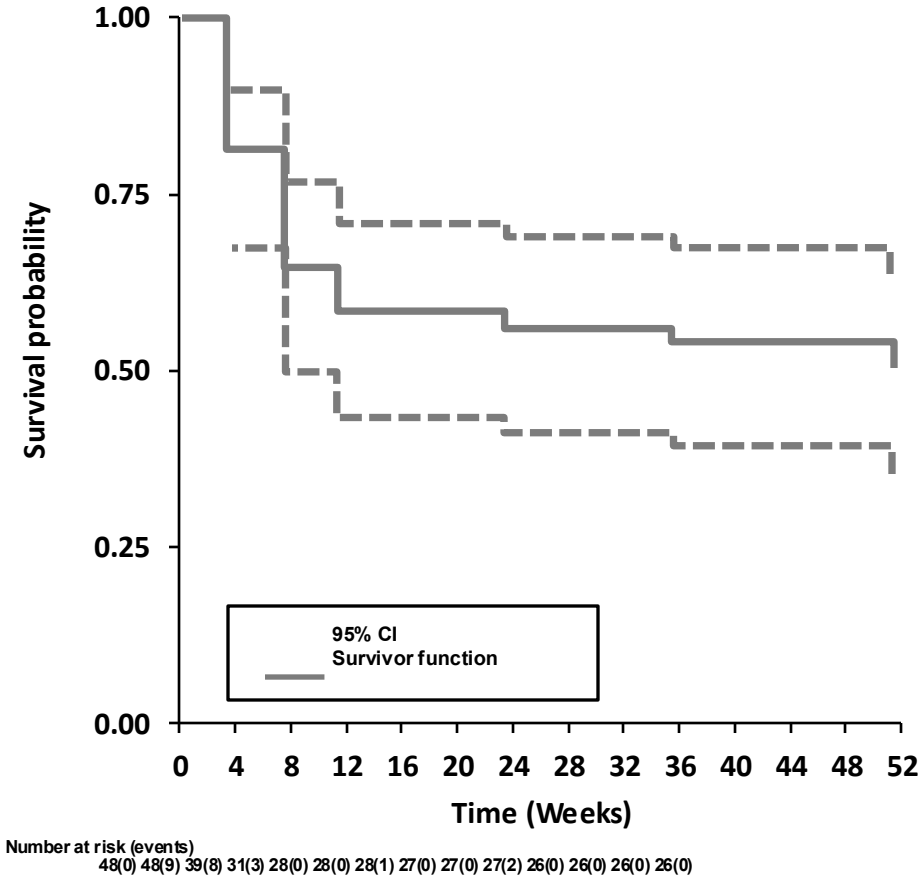
TPO-RAs

- STOPAGO: a nationwide prospective multicenter2 year interventional study

- 49 patients
  - Persistent (n=2) or chronic (n=47)
  - Median age of 58.5 years IQR (41 to 73)

- A number of patients with chronic ITP demonstrated a sustained off-treatment remission after discontinuation
  - Initially achieve a stable CR

- Relapses are mainly observed within the first weeks after discontinuation



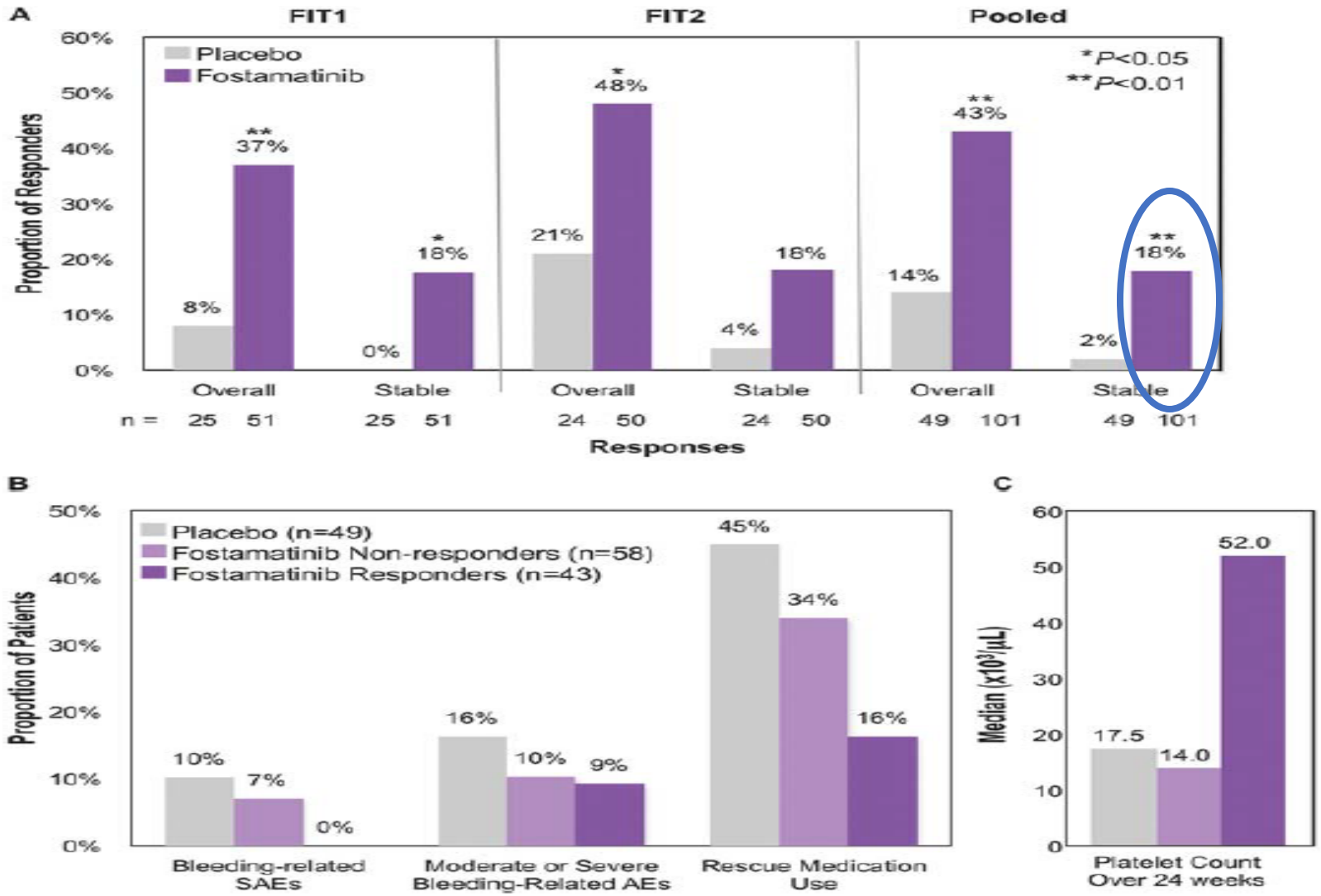
Mahevas M, et al. ASH 2021. 583.
Newland AC, et al. ASH 2011 3157.

Fostamatinib

- Phase III clinical studies (n=146)
  - 2 randomized controlled trials and 1 open-label extension study
  - Dose: 100mg BID PO and increased to 150mg BID
- Overall response (n=101): 43% versus 14% placebo
  - Second-line therapy: 25/32 (78%) had an overall platelet response
- The most commonly reported AEs
  - Diarrhea, hypertension, nausea, vomiting, dizziness, and transaminitis
  - Resolved or were managed by dose reduction or dose interruption

Busell et al. Am J Haem 2018

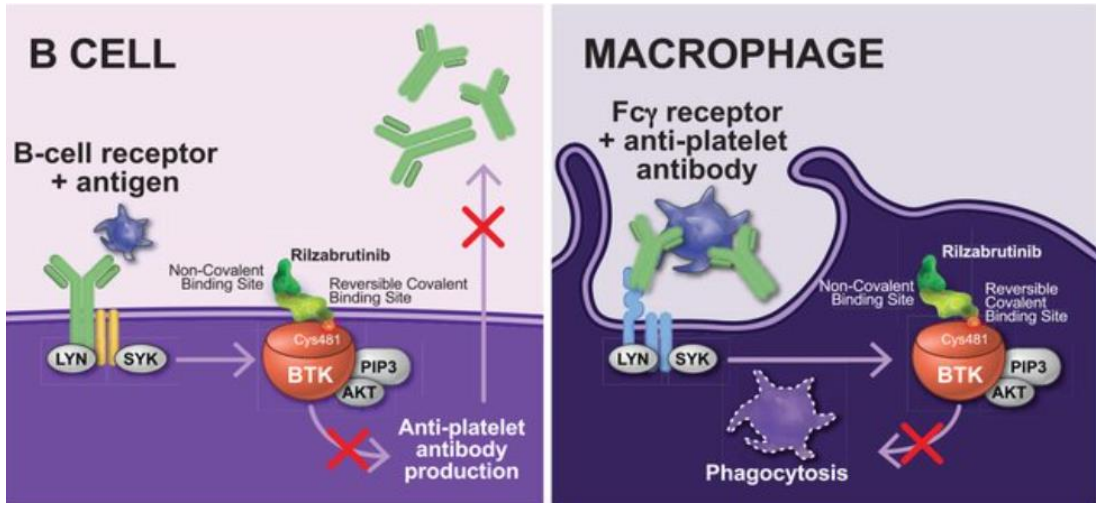
Fostamatinib



Open label extension study: 17% had a stable response

Busell et al. Am J Haem 2018, Busell et al. Am J Haem 2019

Rilzabrutinib



Durable response:
Achieved in 23% of rilzabrutinib patients vs 0% placebo (*P*<0.0001)

Overall platelet response:
65% rilzabrutinib vs 33% placebo

B cells, plasma cells	Monocyte, macrophage	Mast cells, basophils	Neutrophils	T cells
Blocks B-cell receptor Inhibits plasma cell differentiation and antibody production	Blocks IgG-mediated FcgR activation, phagocytosis, inflammatory mediators	Blocks IgE-mediated FceR activation and degranulation	Inhibits activation, adhesion, recruitment, oxidative burst	No effect
BTK inhibition				

IgG, immunoglobulin G

Kuter DJ, et al. *Ther Adv Hematol*. 2023;14:20406207231205431; Langrish CL, et al. *J Immunol*. 2021;206(7):1454-1468.

Rilzabrutinib: LUNA 3 Trial

- Dose: 400mg BID
- 24 week randomized trial followed by a 28 week open label
- 31 patients (23%) vs 0 (0%) placebo patients met the primary endpoint ($p < 0.0001$)
  - ≥2 consecutive platelet counts ≥50 x 10^9/L for ≥ two thirds of ≥ 8 weeks of the last 12 of 24 weeks without rescue therapy
- Median time to response was 15 days
- Improved fatigue from weeks 13 through 25
- Primary side effects:
  - Most AEs were grade ½
  - Diarrhea and nausea (23%)
  - One case of a pulmonary embolism that resulted in discontinuation

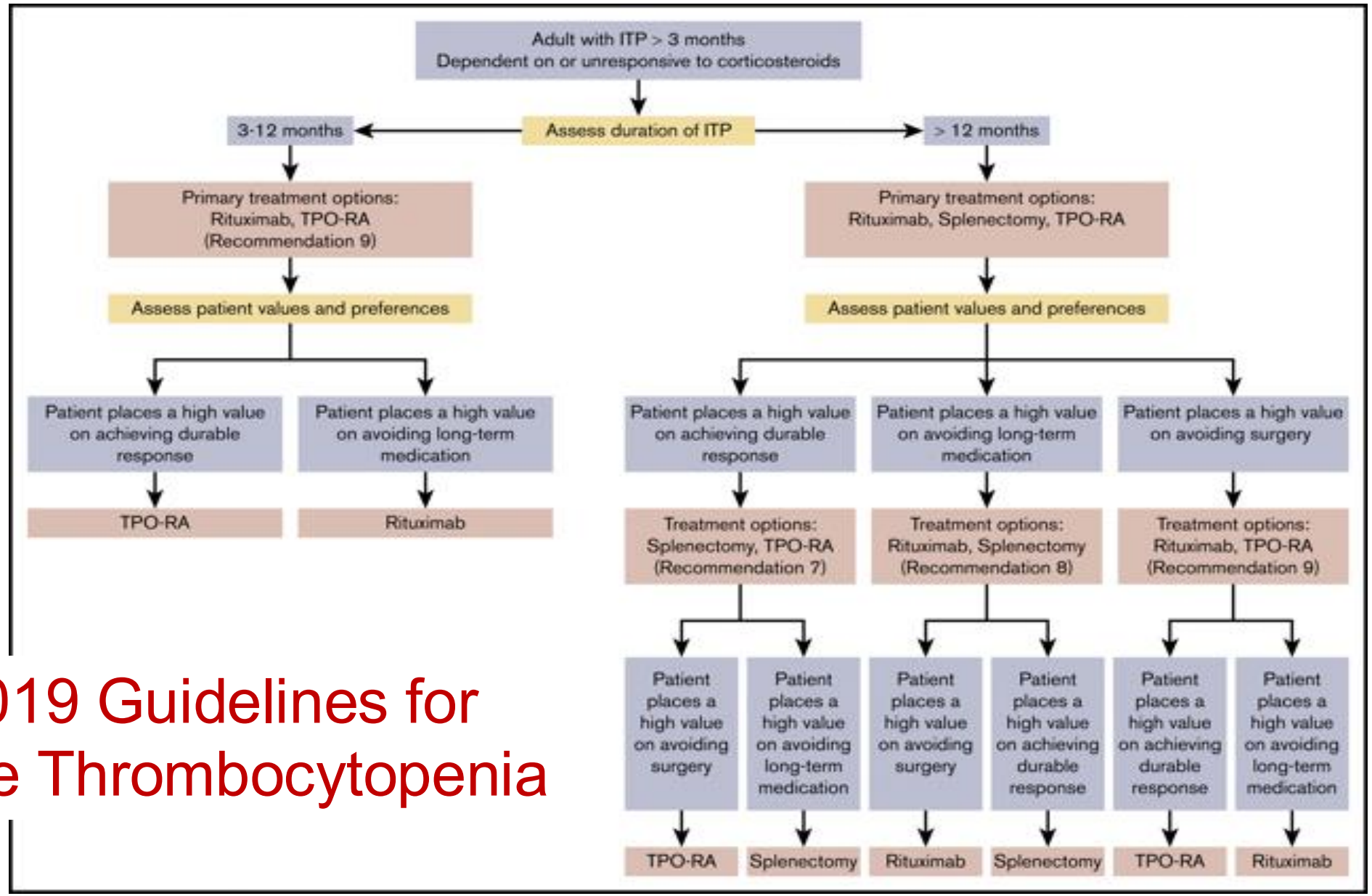
Kuter D et al. *Blood*. 2025

Durable Response

	TPO-RAs: Romiplostim	TPO-RAs: Eltrombopag	TPO-RAs: Avatrombopag	Splenectomy
Response	38%	60%	34.4%	53%
Definition as per the study	PC ≥ 50 x 10^9/l for ≥ 6 of the last 8 weeks	PC ≥ 50 - 400 x 10^9/l for ≥ 6 of the last 8 weeks	PC ≥ 50 x 10^9/l for ≥ 6 of the last 8 weeks	PC ≥ 30 x 10^9/l and at least doubling at 6 mths

	Rituximab	Fostamatinib	Rilzabrutinib
Response	46.8%	18%	23%
Definition as per the study	PC ≥ 100 x 10^9/l at 24 weeks	PC ≥ 50 x 10^9/l for ≥ 4 of 6 biweekly counts weeks 14-24	PC ≥ 50 x 10^9/l for ≥ two thirds of ≥ 8 of the last 12-24 weeks

ASH 2019 Guidelines for Immune Thrombocytopenia



Neunert et al. Blood,Adv 2019

2019 ASH Pediatric ITP Guidelines

In children with ITP who have non-life-threatening mucosal bleeding and/or diminished health-related quality of life and do not response to first-line treatment:

***Suggests* the use of TPO-RAs rather than rituximab.**

***Suggests* TPO-RAs rather than splenectomy.**

***Suggests* rituximab rather than splenectomy.**

All conditional recommendations based on very low certainty in the evidence of effects.

Good Practice Statement

- The choice of second-line treatment should be individualized based on duration of ITP, frequency of bleeding episodes requiring hospitalization or rescue medication, comorbidities, adherence, medical and social support networks, patient values and preferences, cost, and availability.
- Patient education and shared decision-making are encouraged.
- If possible, splenectomy should be delayed for as long as possible after diagnosis because of the potential for spontaneous remission.

Neunert et al. Blood Adv, 2019

Additional and Novel Therapies

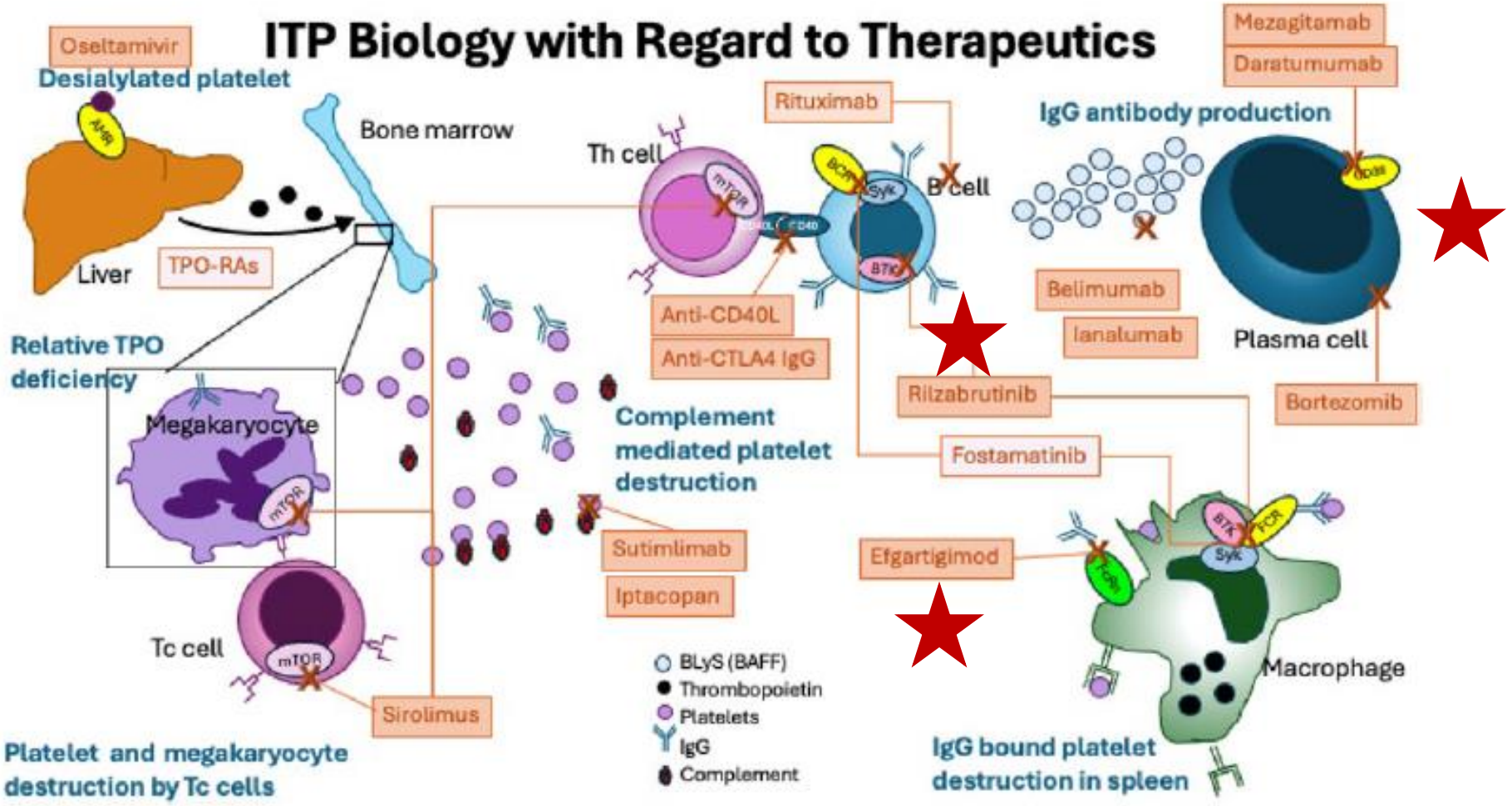
Module 5

Other ITP Therapies

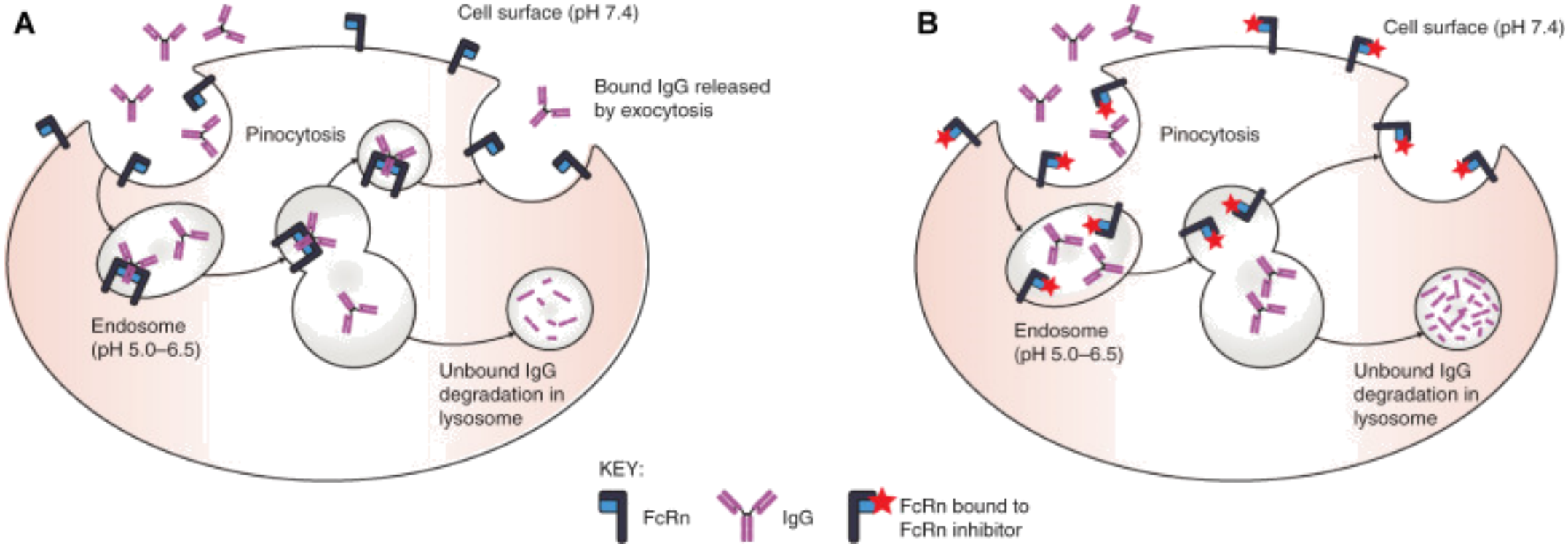
Drug	No. of studies	Response within 7 days		Response within 1 month		Durable Response		Remission	
		Unweighted	Weighted (95% CI)	Unweighted	Weighted (95% CI)	Unweighted	Weighted (95% CI)	Unweighted	Weighted (95% CI)
Azathioprine	3	_____	_____	27% 21/77 N=2	30% (1-95%) N=2	59% 55/94 N=2	58% (45-70%) N=2	40% 21/53 N=1	NA
Cyclophosphamide	4	_____	_____	34% 17/50 N=2	34% (3-91%) N=2	58% 46/80 N=2	57% (46-68%) N=2	48% 19/40 N=2	45% (25-67%) N=2
Cyclosporine A	5	21% 7/34 N=2	21% (10-39%) N=2	48% 52/109 N=4	48% (38-58%) N=4	32% 22/69 N=3	32% (21-47%) N=3	27% 21/79 N=3	27% (18-37%) N=3
Danazol	9	_____	_____	33% 191/582 N=7	38% (26-52%) N=7	59% 137/231 N=5	57% (38-74%) N=5	5% 1/21 N=1	NA
Dapsone	5	_____	_____	50% 133/265 N=5	50% (39-60%) N=5	22% 33/147 N=3	21% (7-47%) N=3	13% 12/89 N=2	13% (6-27%) N=2
Mycophenolate mofetil	4	14% 7/50 N=2	15% (7-28%) N=2	48% 48/100 N=4	48% (37-60%) N=4	61% 43/71 N=3	61% (49-71%) N=3	23% 16/71 N=3	22% (8-48%) N=3
Vinca alkaloids	14	71% 67/95 N=3	71% (52-85%) N=3	66% 268/407 N=13	65% (57-72%) N=13	33% 60/182 N=6	28% (13-50%) N=6	25% 52/206 N=5	26% (20-33%) N=5

Neunert et al. Blood Adv, 2019

Emerging Therapies



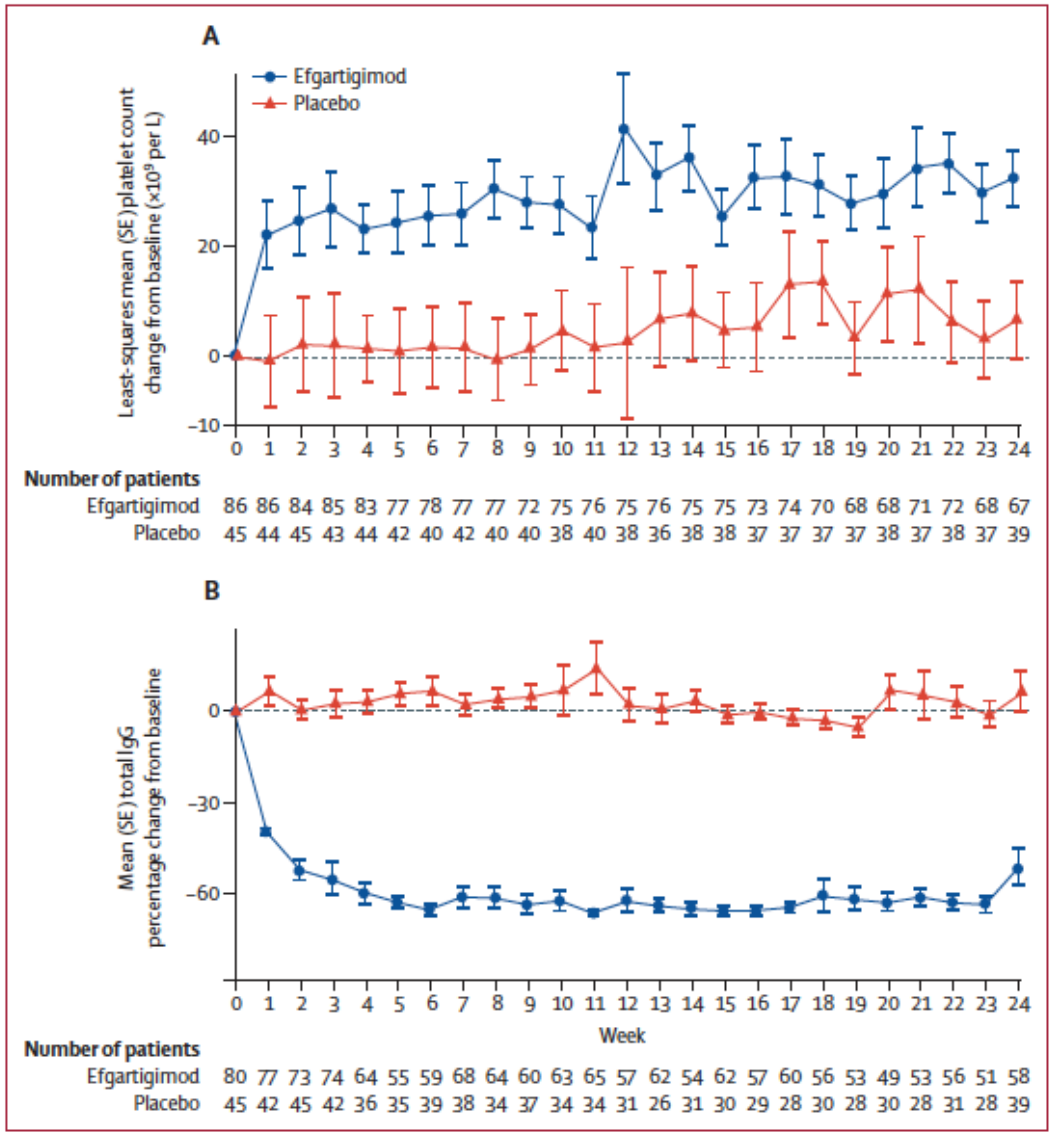
Neonatal Fc Receptor Antagonists



Patel DD, Bussel JB. *J Allergy Clin Immunol.* 2020;146(3):467-478.

Efgartigimod: ADVANCE IV TRIAL

- Efgartigimod (10 mg/kg) or placebo intravenously for 4 weeks
  - Once per week or every other week for 24 weeks
- Primary endpoint: sustained platelet count response (≥50 × 10^9 for at least 4 of the last 6 weeks).
  - 22% (17/78) receiving efgartigimod versus 5% (2/40) of those receiving placebo
- Well tolerated
- ADVANCE-SC
  - Did not show similar efficacy



Other Emerging Therapies

Emerging Therapy	Mechanism of Action	Emerging Therapy	Mechanism of Action
Anti-CD20 Targeting Therapies		**CD40/CD154 Blockade**	
Veltuzumab	Humanized monoclonal antibody	Ruplizumab (hu5c8)	Anti-CD154 antibody
Obinutuzumab	Type II antibody with increased ADCC	Letolizumab (BMS-986004)	Fc-modified anti-CD154 antibody
Plasma Cell Targeting Therapies		BI655064	Humanized antagonistic anti-CD40 monoclonal antibody
Bortezomib	Proteasome inhibitor	**IL-2 Signaling Modulation**	
KZR-616	Proteasome inhibitor	Low dose IL-2	Expansion of Treg/restoration of immunosuppressive properties
Daratumumab	Anti-CD38 monoclonal IgG_1 antibody	**Epigenetic Modulation**	
Mezagitamab (TAK-079)	Anti-CD38 antibody	Chidamide	Histone deacetylase
Inhibition of Platelet Desialylation		Low dose decitabine	Demethylating agent
Oseltamivir	Inhibits neuraminidase		

ADCC, Antibody-dependent cellular cytotoxicity; IL-2, Interleukin 2.

Audia S, Bonnotte B. *J Clin Med*. 2021
https://clinicaltrials.gov/ct2/show/NCT04278924

Conclusions

- ITP remains a diagnosis of exclusion
- Management of ITP in both adults and children is based on the clinical symptoms and consideration of additional risk factors
- There are a lack of randomized trials to guide management
- Exciting new drug development may provide treatment options for the most refractory patients