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Initial Management of ITP: Diagnosis and Treatment Considerations Guidelines Review

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How Do We Define ITP?

By Association

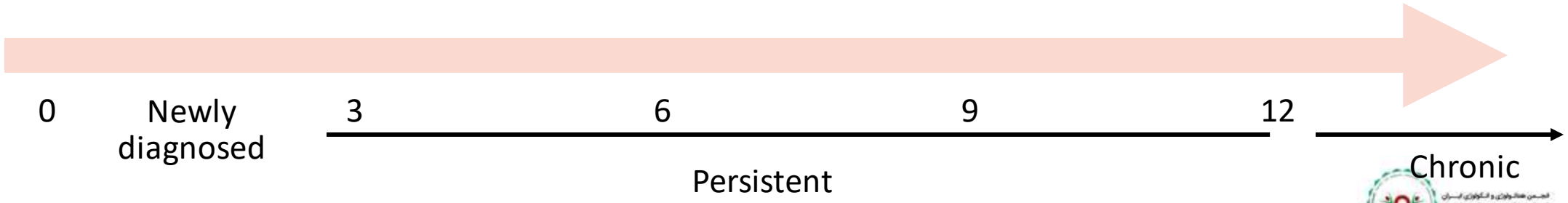
Primary ITP

- Isolated thrombocytopenia (not caused by or associated with another disorder)
- Platelet count < 100,000/µL
- 80% of all cases

Secondary ITP

- All other immune-mediated thrombocytopenia
  - Infection-associated (HCV, HIV, *H pylori*, CMV), immunodeficiency (CVID, WAS), autoimmune disorders (SLE, others), lymphoproliferative (CLL, others), drug induced

By Chronicity



Rodeghiero. Blood. 2009;113:2386.

What Are the Goals of ITP Treatment?

- Treatment goals should be individualized to the patient and the phase of the disease
- Treatment should prevent severe bleeding episodes
- In general, treatment should maintain a target platelet level > 20-30 x 10^9/L at least for symptomatic patients, though this should be dictated by the patient's lifestyle and expectations
- Treatment-related toxicity should be minimized
- Treatment should optimize health-related quality of life

Should ITP therapy be targeted toward inducing a remission?

Provan. Blood Adv. 2019;3:3780.

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Does This Patient Require Treatment for ITP?

- **ASH guideline**: For adults with newly diagnosed ITP and a platelet count < 30 x 10^9/L, who are asymptomatic or have minor mucocutaneous bleeding, corticosteroids are suggested vs observation (conditional recommendation)[1]
- **IC guideline**: Treatment rarely indicated for patients with platelet counts > 20 x 10^9/L in the absence of bleeding due to platelet dysfunction or another cause[2]

1. Neunert. Blood Adv. 2019;3:3829. 2. Provan. Blood Adv. 2019;3:3780.

Should This Patient Be Admitted to the Hospital? ASH Guidance

- In adults with **newly diagnosed ITP and a platelet count of < 20 x 10^9/L** who are asymptomatic or have minor mucocutaneous bleeding, **admission to the hospital** vs outpatient management suggested
- In adults with an **established diagnosis of ITP and a platelet count of < 20 x 10^9/L** who are asymptomatic or have minor mucocutaneous bleeding, **outpatient management** vs admission to the hospital suggested
- In **adults with a platelet count of ≥ 20 x 10^9/L who are asymptomatic** or have minor mucocutaneous bleeding, **outpatient management** vs admission to the hospital suggested

Neunert. Blood Adv. 2019;3:3829.

Initial Treatment of ITP: Guidelines

ASH Guideline[1]

- In adults with newly diagnosed ITP, **a short course of prednisone** (**≤ 6 wks,** including treatment and taper) is recommended vs a prolonged course
- In adults with newly diagnosed ITP, either **prednisone** (0.5-2.0 mg/kg/day) or **dexamethasone** (40 mg/day for 4 days) is suggested as the type of corticosteroid

IC Guideline[2]

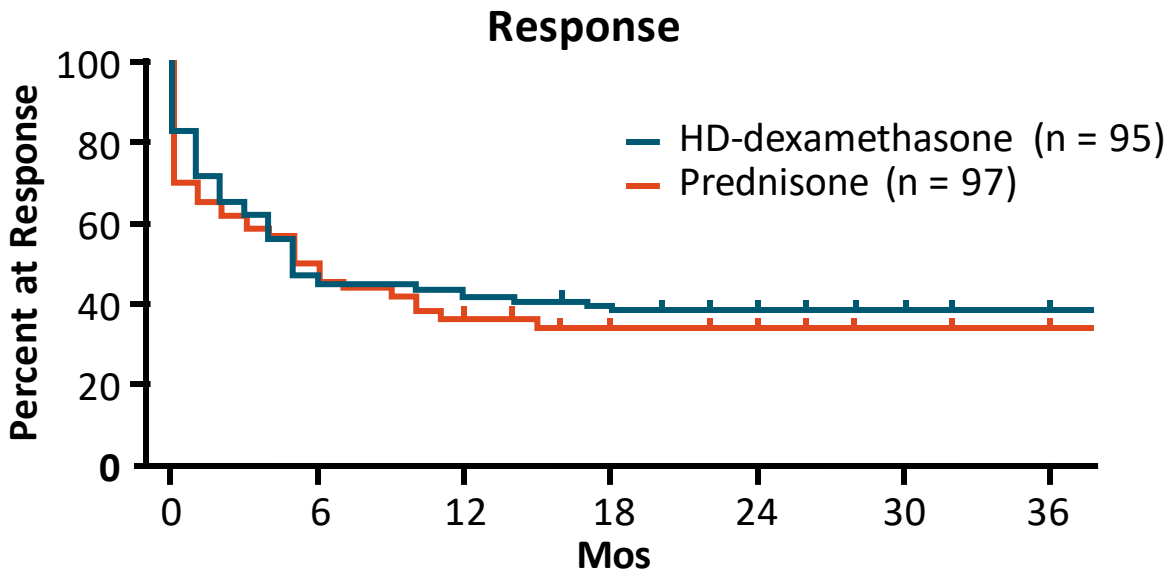
- Corticosteroids are the standard initial treatment for adults with ITP who need treatment: **predniso(lo)ne** at 1 mg/kg* for 2 wks, to a maximum of 3 wks, or **dexamethasone** 40 mg/day for 4 days, repeated up to 3 times
- If response, predniso(lo)ne should be tapered, with the aim to stop by **6 wks** (max. 8 wks), even if the platelet count drops during the taper
- If no response to initial dose within 2 wks, predniso(lo)ne should be tapered rapidly over 1 wk and stopped

*Maximum dose 80 mg, even in patients weighing > 80 kg.

1. Neunert. Blood Adv. 2019;3:3829. 2. Provan. Blood Adv. 2019;3:3780.

Initial Therapy of ITP: Dexamethasone vs Prednisone

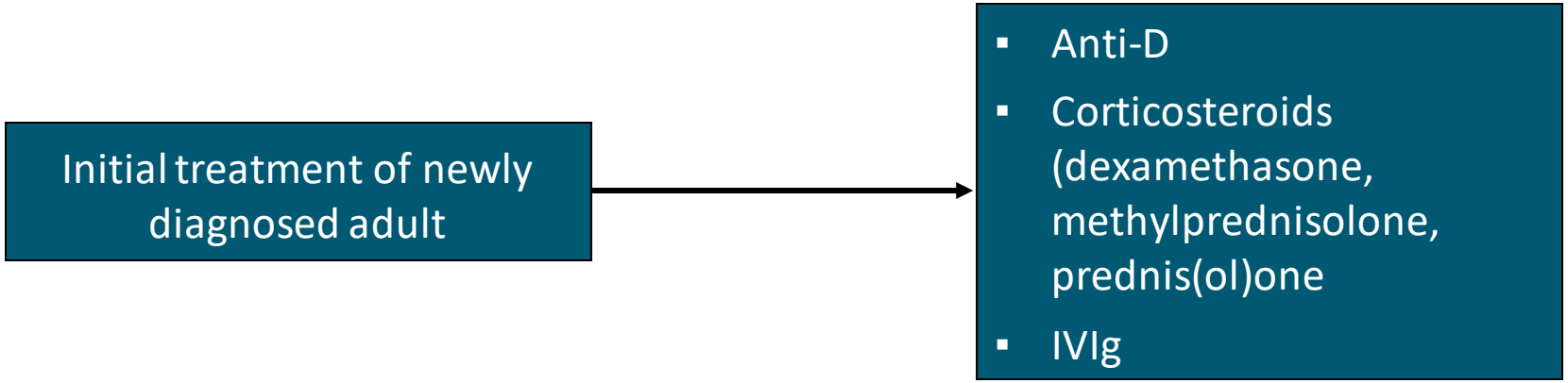
- Prospective randomized trial of **HD-dexamethasone** (40 mg/day x 4 days for 1-2 cycles) vs **prednisone** (1 mg/kg for 4 wks, then taper) for treating adult ITP (N = 192)
- Dexamethasone vs prednisone
  - Higher initial response rate (82.1% vs 67.4%)
  - Higher CR (50.5% vs 26.8%)
  - Shorter time to response
  - No difference in sustained response (40% vs 41.2%)
- Extent of initial response correlates with sustained response



Dexamethasone might be a better choice for a severely thrombocytopenic patient; otherwise, no efficacy advantage of one over the other

Wei. Blood. 2016;127:296.

Additional Treatments for Newly Diagnosed ITP



- **IVIg**
  - Generally reserved for more severe thrombocytopenia
  - Dose 2.0 g/kg over 2-5 days
  - 65% achieve platelets counts > 100 x 10^9/L; 85% > 50 x 10^9/L
  - Most responses transient; 30% become refractory
- **Anti-D**
  - For Rh+, nonsplenectomized patients, generally with severe thrombocytopenia
  - 70% response rate, average duration 21 days
  - Average drop in Hb = 0.8 gm/dL
  - Black box warning for severe hemolysis and DIC (incidence ~ 1/20,000)

Provan. Blood Adv. 2019;3:3780.

Can Remission Be Achieved With First-line Therapy?

- **ASH guideline**: In adults with newly diagnosed ITP, corticosteroids alone vs rituximab and corticosteroids suggested for initial therapy*[1]
- **IC guideline**: TPO receptor agonists and rituximab are not considered initial therapies[2]

But could some patients possibly achieve remission if given more aggressive therapy early in the course of ITP?

*Conditional recommendation based on very low certainty in the evidence of effects.

1. Neunert. Blood Adv. 2019;3:3829. 2. Provan. Blood Adv. 2019;3:3780.

Defining Responses in Newly Diagnosed ITP

- Quality of response
  - **CR**: platelet count > 100 x 10^9/L and absence of bleeding
  - **Response**: platelet count ≥ 30 x 10^9/L and ≥ 2-fold increase from baseline with absence of bleeding
  - **NR**: platelet count < 30 x 10^9/L or < 2-fold increase from baseline platelet count or bleeding
  - **Loss of CR or response**: platelet count < 100 x 10^9/L or bleeding (from CR) or platelet count < 30 x 10^9/L or < 2-fold increase from baseline platelet count or bleeding (from response)
- Timing of assessment of response
  - Variable, depends on the type of treatment
- Duration of response
  - Measured from the achievement of CR or response to loss of CR or response
  - Measured as the proportion of the cumulative time spent in CR or response during the period under examination as well as the total time observed from which the proportion is derived

But what would we consider a remission in ITP?

Rodeghiero. Blood. 2009;113:2386.

Remission in Adult ITP

- **No widely accepted definition**
  - No platelet count cutoff, distinction between on or off treatment responses, or documentation of how long off treatment needed to define remission
- **Guideline definitions:**
  - ASH: platelet count ≥ 100 x 10^9/L at 12 mos
  - ICR: platelet count ≥ 30 x 10^9/L in the absence of ITP-specific treatment

- **Incidence of spontaneous remission in ITP is not carefully studied**
  - Stasi et al, AJM 1995[1]
    - 8 of 87 untreated patients (9.2%) followed for ≥ 6 mos
    - 25 of 134 (18.7%) steroid-treated patients achieved off-treatment response for > 6 mos (only 2 of 19 with ITP > 6 mos)
  - Pizzuto et al, Blood 1984[2]
    - 9 of 934 untreated patients (~ 0.9%)
    - 39% of steroid treated patients with ITP < 6 mos vs 14% of steroid treated patients with ITP > 6 mos

1. Stasi. Am J Med. 1995;98:436. 2. Pizzuto. Blood. 1984;64:1179.

Problems With All Guidelines for ITP

- Rare disease
- Lack of data in ITP
- Few comparative trials
- Treatments vs treatment algorithms
- No new data for older treatments

- Almost all are expert opinion (Level C)
  - ASH “evidence” based
    - “Very low certainty of the evidence”
    - Only 2 of 11 recommendations “strong” but lacking evidence
      - Don’t treat if platelets > 30 x 10^9/L
      - Don’t use corticosteroids for > 6 weeks

Summary

- Corticosteroids remain the preferred initial therapy for ITP
- However, both spontaneous and corticosteroid-induced "remissions" are uncommon in adult ITP patients
- Suggestive data that the use of rituximab or TPO-RAs as a component of initial therapy may improve the rate of ITP remission
- Corticosteroids are overused in ITP; their use should be limited to 6 wks of initial therapy, and they should not be used repeatedly or at a prolonged basis in relapsing or "steroid-dependent" ITP
- New approaches to initial treatment of ITP continue to emerge

Applying Guidelines to Practice

What to do after corticosteroids?

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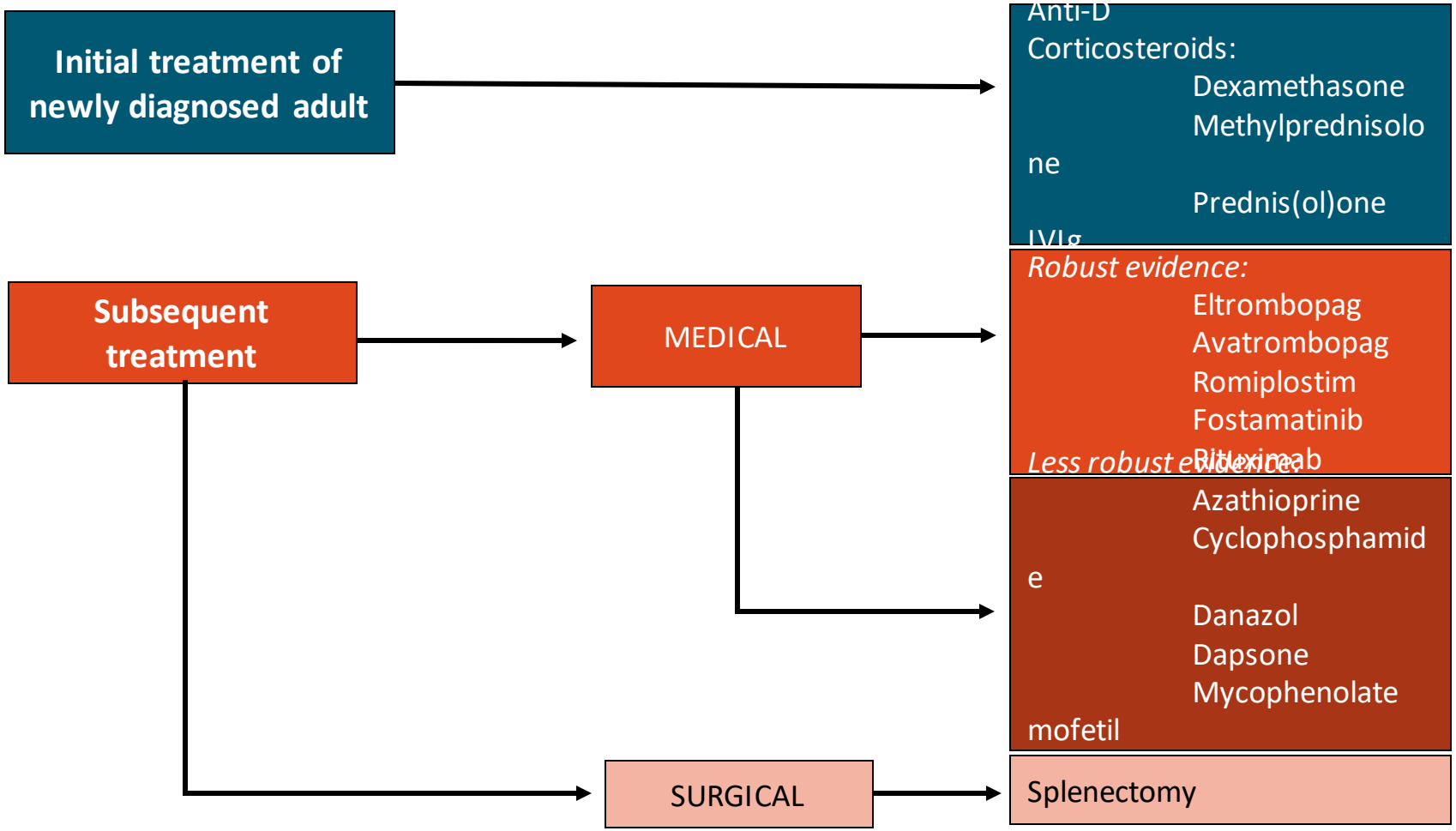
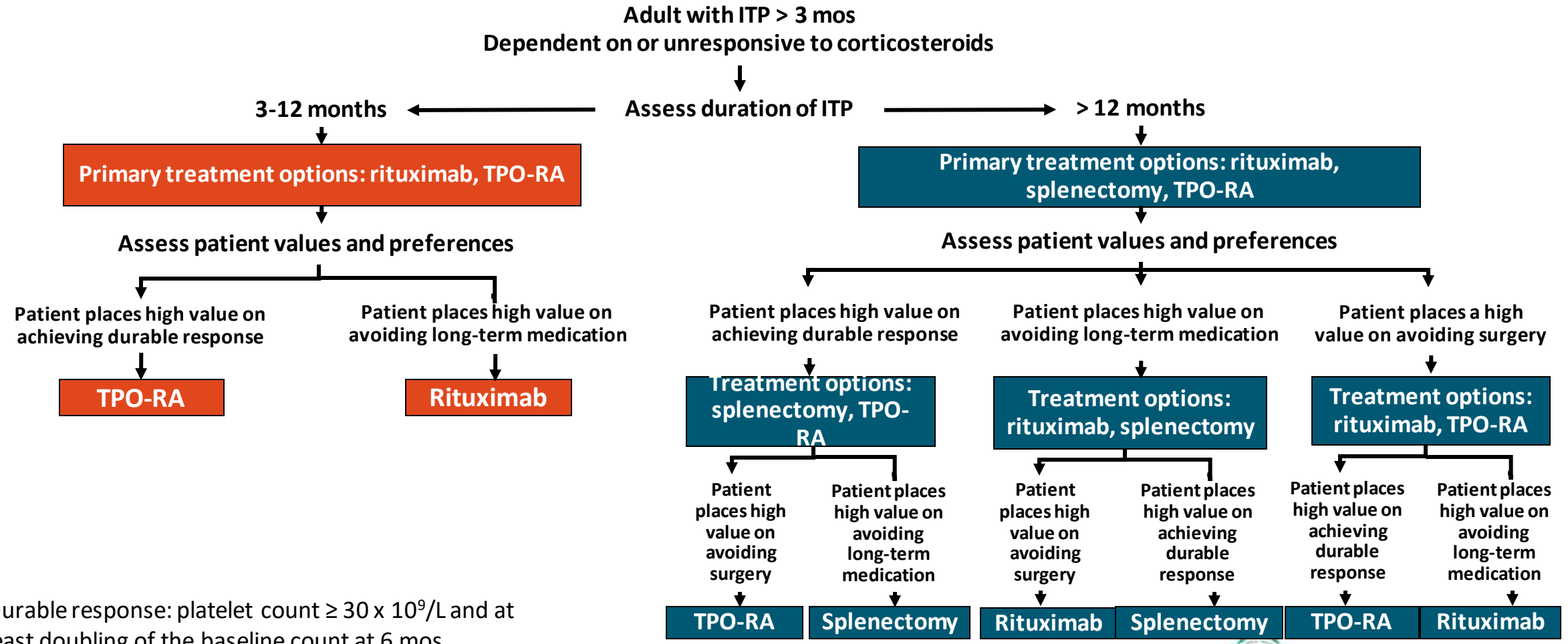
IC Treatment Algorithm



Provan. Blood Advances. 2019;3:3780.

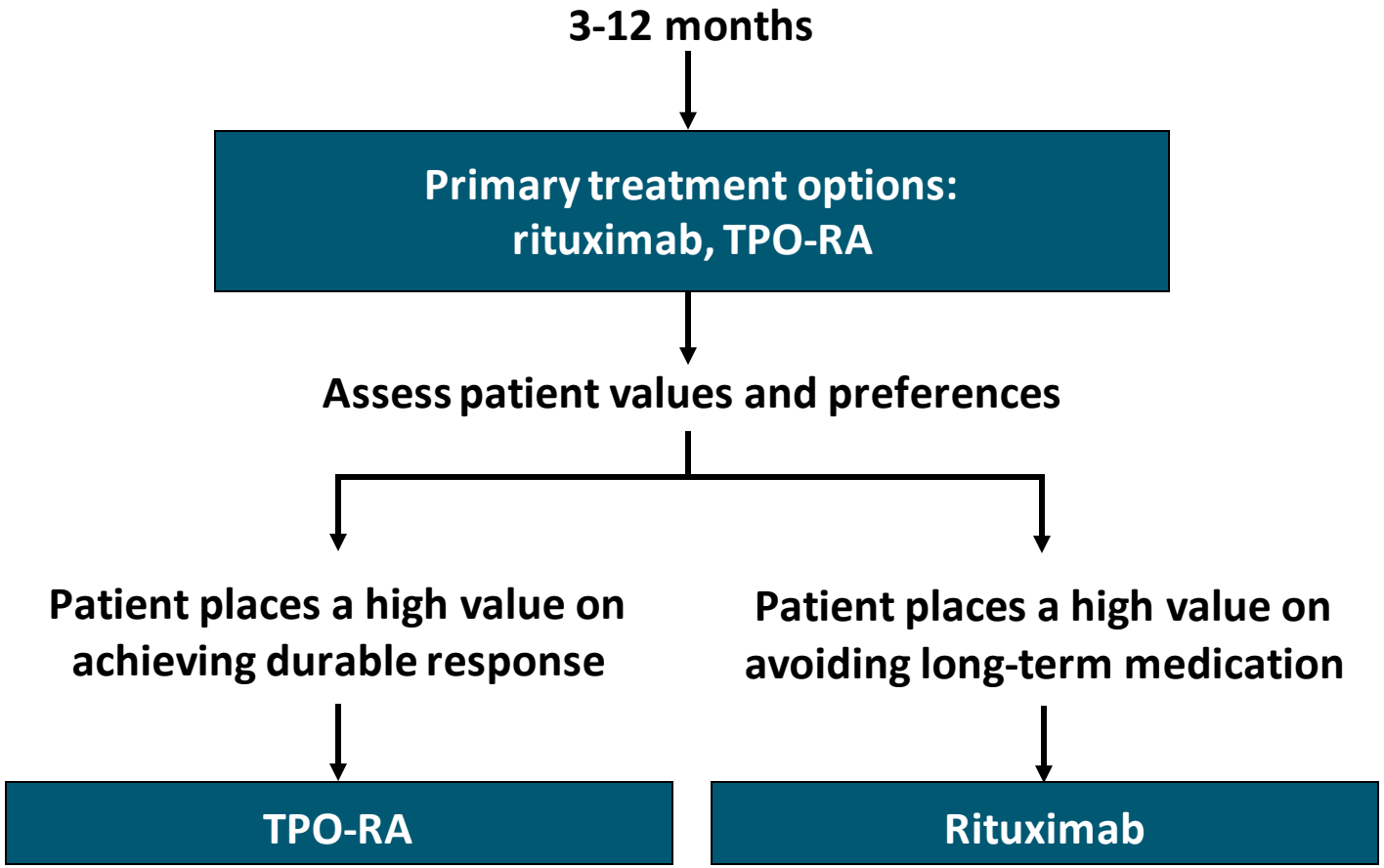
ASH Treatment Algorithm



Durable response: platelet count ≥ 30 x 10^9/L and at least doubling of the baseline count at 6 mos.

Neunert. Blood Advances. 2019;3:3829.

ASH Treatment Algorithm



Durable response: platelet count ≥ 30 x 10^9/L and at least doubling of the baseline count at 6 months.

Neunert. Blood Advances. 2019;3:3829.

What Does “Patient Values and Preferences” Mean?

- Fear and anxiety over “low platelet count”
- Acceptance of a “low platelet count”
- Tolerance of minor bleeding
- Activity level
- Acceptance of chronic therapy
- Desire to avoid corticosteroids
- Desire to avoid splenectomy
- Desire to “get it all over”
- Desire for pregnancy

Patient assessment > physician assessment

Major Consensus Issues

- Medical therapy preferred to surgical therapy for 12-24 months
  - TPO-RAs generally favored over rituximab
- Early (> 3 months) use of medical therapy, especially TPO-RAs
  - No reason to wait for chronic phase to use TPO-RA, rituximab
- Minimize/eliminate use of corticosteroids other than for initial therapy and “rescue”
- Older therapies (MMF, azathioprine) if resources limited
- Reassess diagnosis at each decision point
- Reassess indications for treatment at each decision point
- Assess “patient values and preferences” in decisions

Second-line Treatment Options: Mechanisms of Action

- TPO-RA: increase platelet production
- Rituximab: reduce antiplatelet antibody?
- Fostamatinib: kinase inhibitor; reduce platelet clearance by macrophages

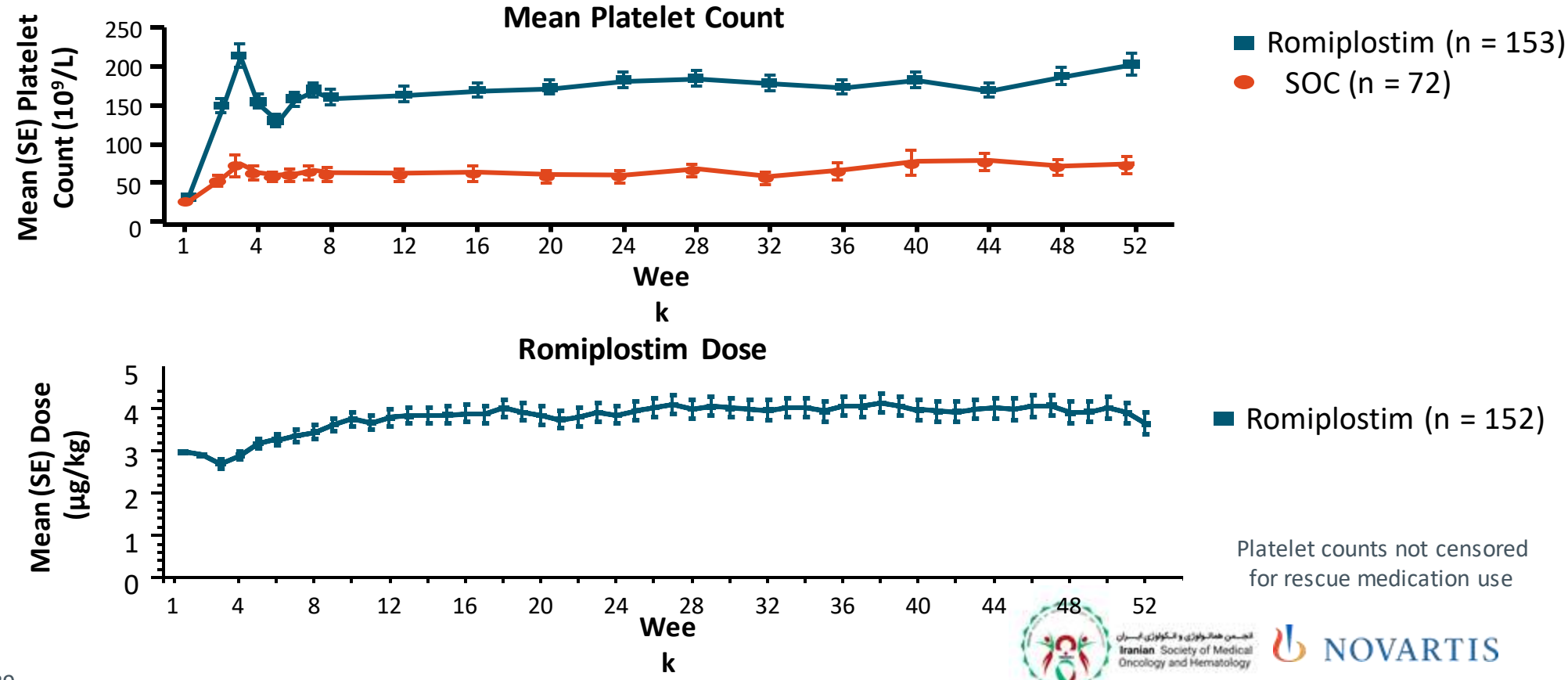
“Second-line” Treatment Options: TPO-RAs

Agent	FDA Indications for Treating Thrombocytopenia in Adults With ITP
Avatrombopag	▪ Patients with chronic ITP who have had an insufficient response to a previous treatment
Eltrombopag	▪ Patients with chronic ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy and are at increased risk for bleeding
Romiplostim	▪ Patients with ITP who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy

Avatrombopag PI. Eltrombopag PI. Romiplostim PI.

Romiplostim vs Standard of Care for Patients With ITP

- Randomized phase III trial of **romiplostim** vs medical **SOC** for treating adults with ITP who had no previous splenectomy (N = 234)

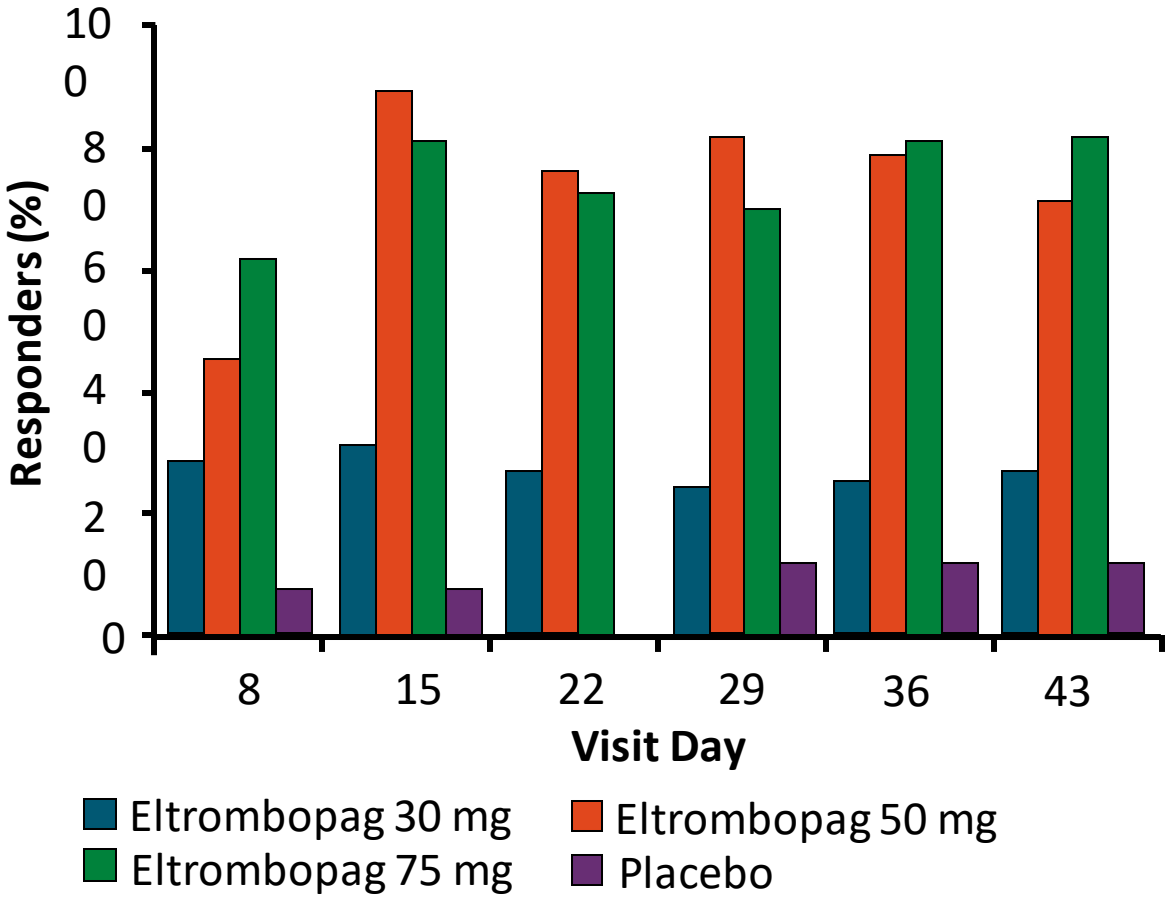


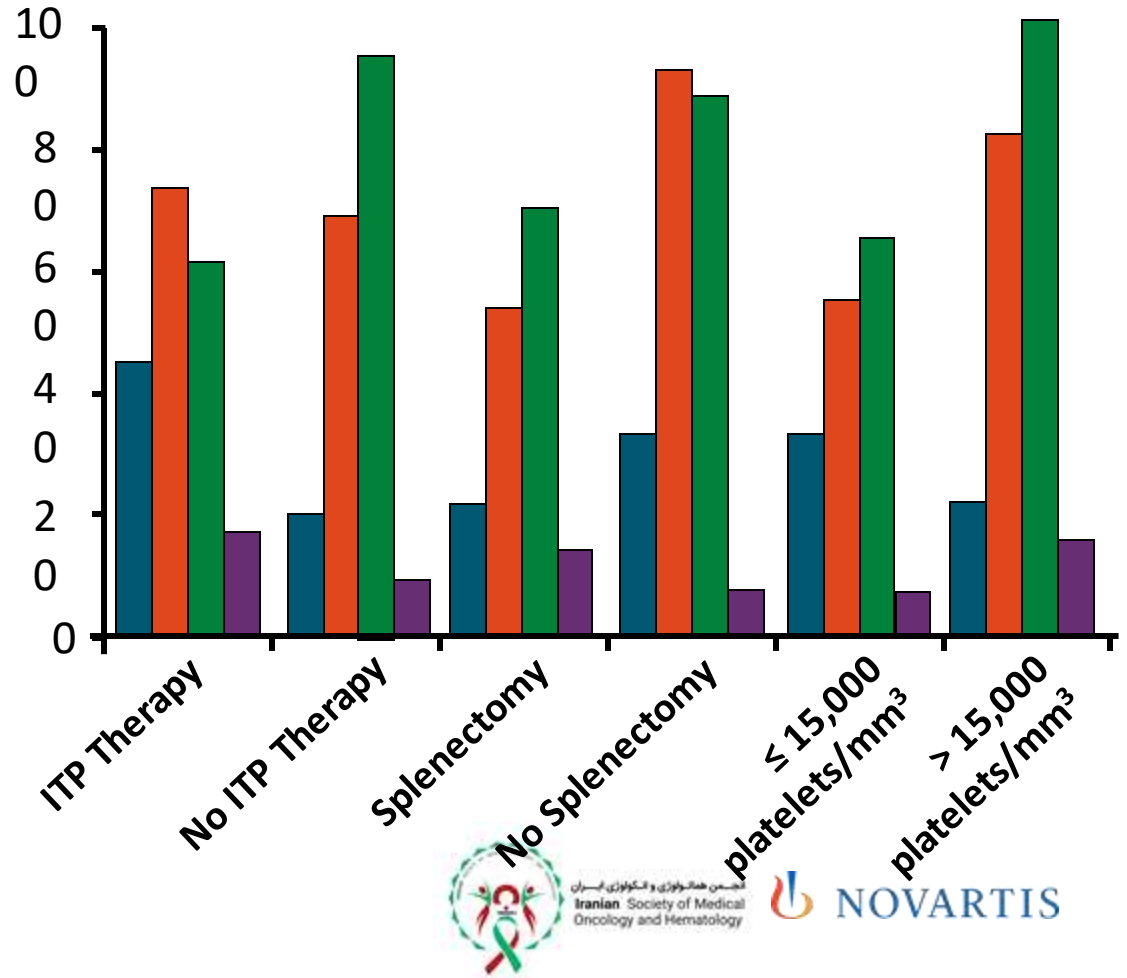
Platelet counts not censored for rescue medication use

Kuter. NEJM. 2010;363:1889.

Eltrombopag in Chronic ITP

- Randomized phase II study of **eltrombopag vs placebo** for patients with R/R chronic ITP (N = 118)





Bussel. NEJM. 2007;357:2237.

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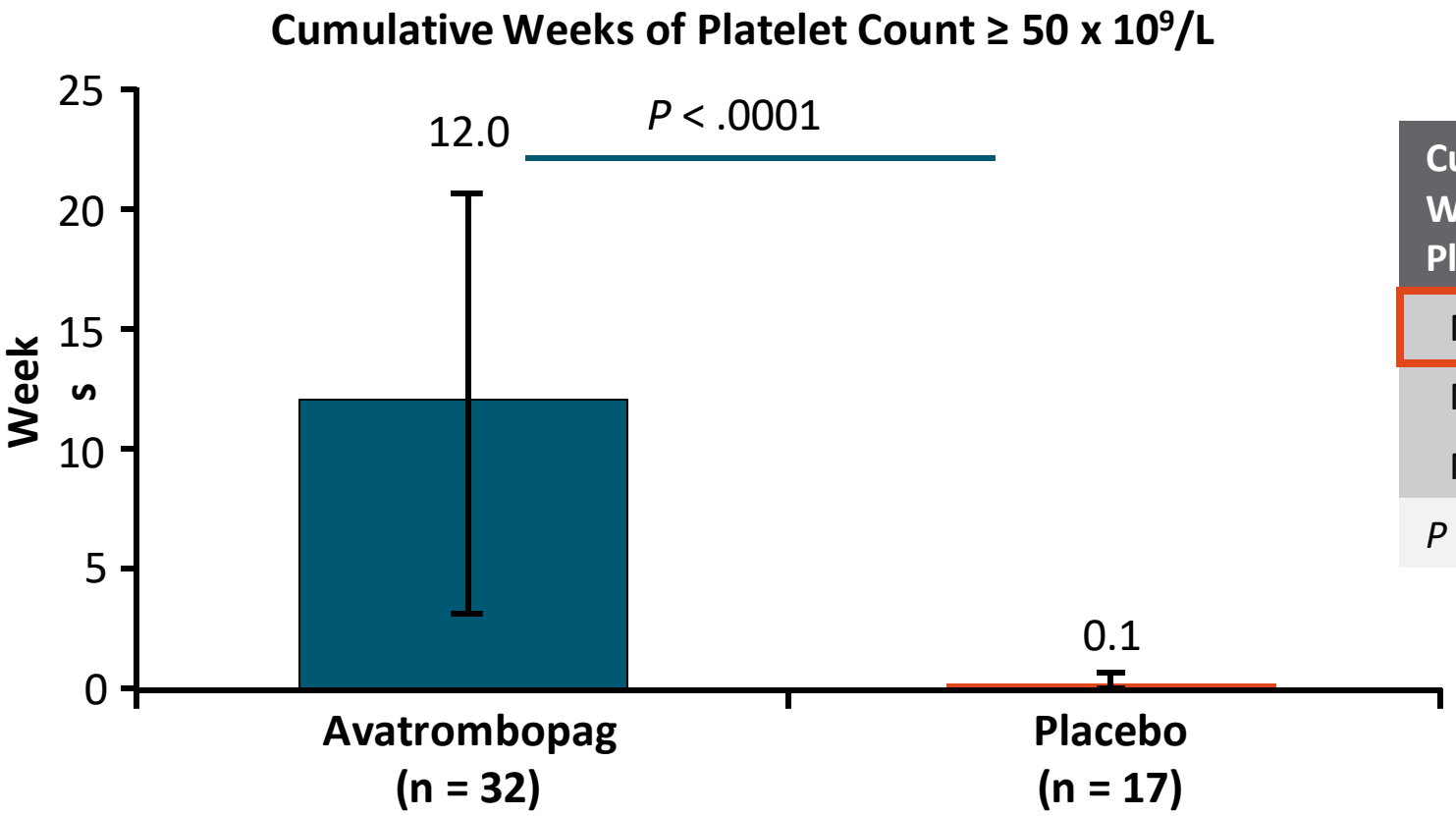
Avatrombopag vs Placebo in Chronic ITP: Platelet Responses

- Randomized, double-blind phase III study of **avatrombopag** vs **placebo** for adults with previously treated chronic ITP (N = 49)



Cumulative No. of Weeks With Platelet Response	Avatrombopag (n = 32)	Placebo (n = 17)
Median	12.4	0
Mean (SD)	12.0 (8.75)	0.1 (0.49)
Min, max	0, 25	0, 2
P value	< .0001	

Jurczak. Br J Haematol. 2018;183:479.

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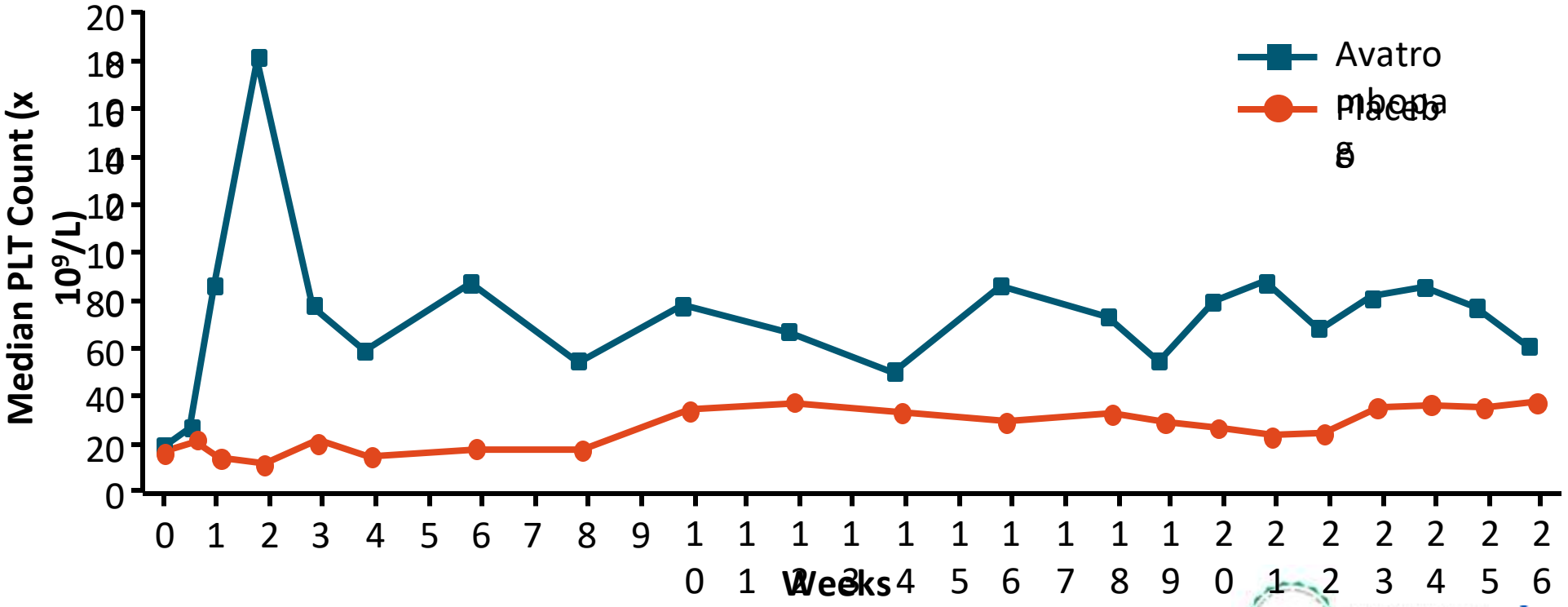
Avatrombopag vs Placebo in Chronic ITP: Platelet Counts Over Time

- Median platelet count higher with **avatrombopag** vs **placebo** beginning at Day 8 (80.5 vs 8.0 x 10^9/L)



Jurczak. Br J Haematol. 2018;183:479.

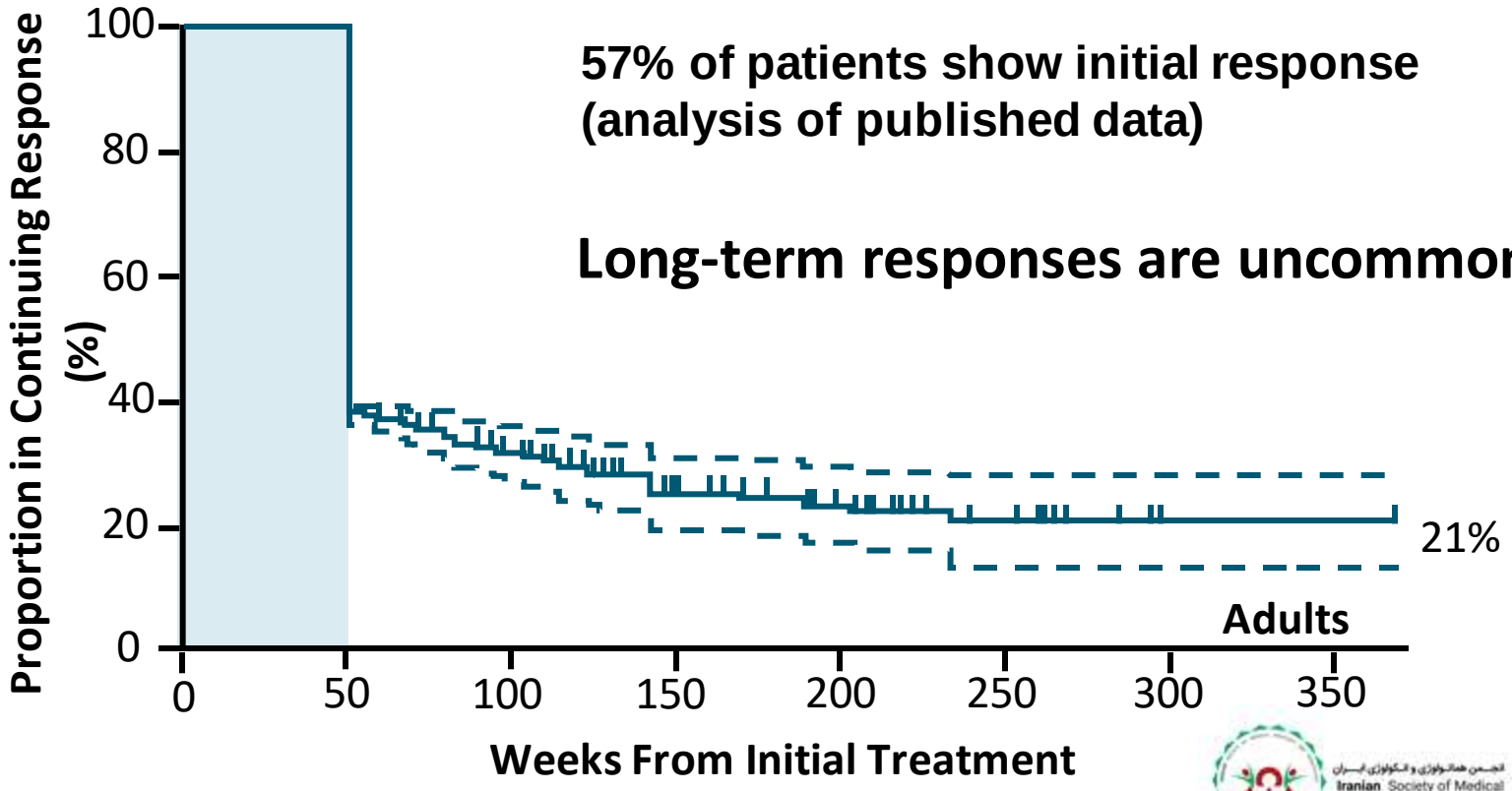
Potential Adverse Consequences of Thrombopoietin Receptor Agonists

- Thrombocytosis
- Thrombosis
- Stimulation of leukemia cell growth
- Autoantibody formation
- Elevated LFTs (eltrombopag only)
- Reduction in threshold for platelet activation
- Rebound worsening of thrombocytopenia
- Increased bone marrow reticulin

Avatrombopag PI. Eltrombopag PI. Romiplostim PI.

Rituximab: Long-term Responses

- Follow up of patients with ITP who were treated with **rituximab** and achieved a response (N = 138 from 7 centers)



Patel. Blood. 2012;119:5989.

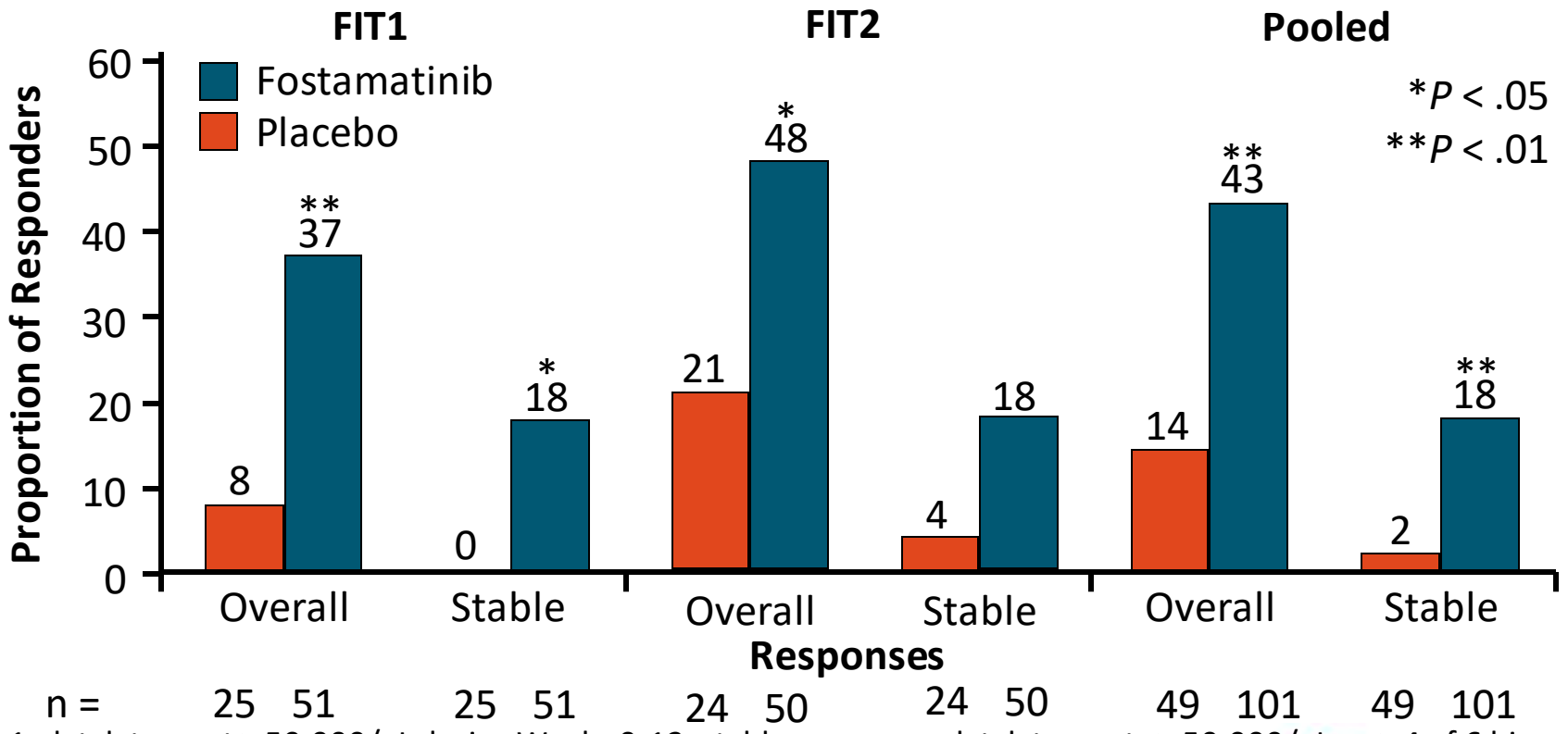
Potential Adverse Consequences of Rituximab Treatment

- Infusion reactions
- Mucocutaneous reactions
- Hypogammaglobulinemia
- Immunosuppression
- Delayed neutropenia
- Hepatitis B reactivation
- Progressive multifocal leukoencephalopathy
- Inability to respond to vaccinations (eg, influenza, probably COVID-19)

Rituximab PI.

Fostamatinib: Response Rates in ITP

- Analysis of 2 phase III trials of **fostamatinib** vs **placebo** for treating adult patients with ITP (N = 150)



Overall response: ≥ 1 platelet count ≥ 50,000/µL during Weeks 0-12; stable response: platelet counts ≥ 50,000/µL on ≥ 4 of 6 biweekly clinic visits during Weeks 14-24.

Bussel. Am J Hematol. 2018;93:921.

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Applying Guidelines to Practice

What about splenectomy?

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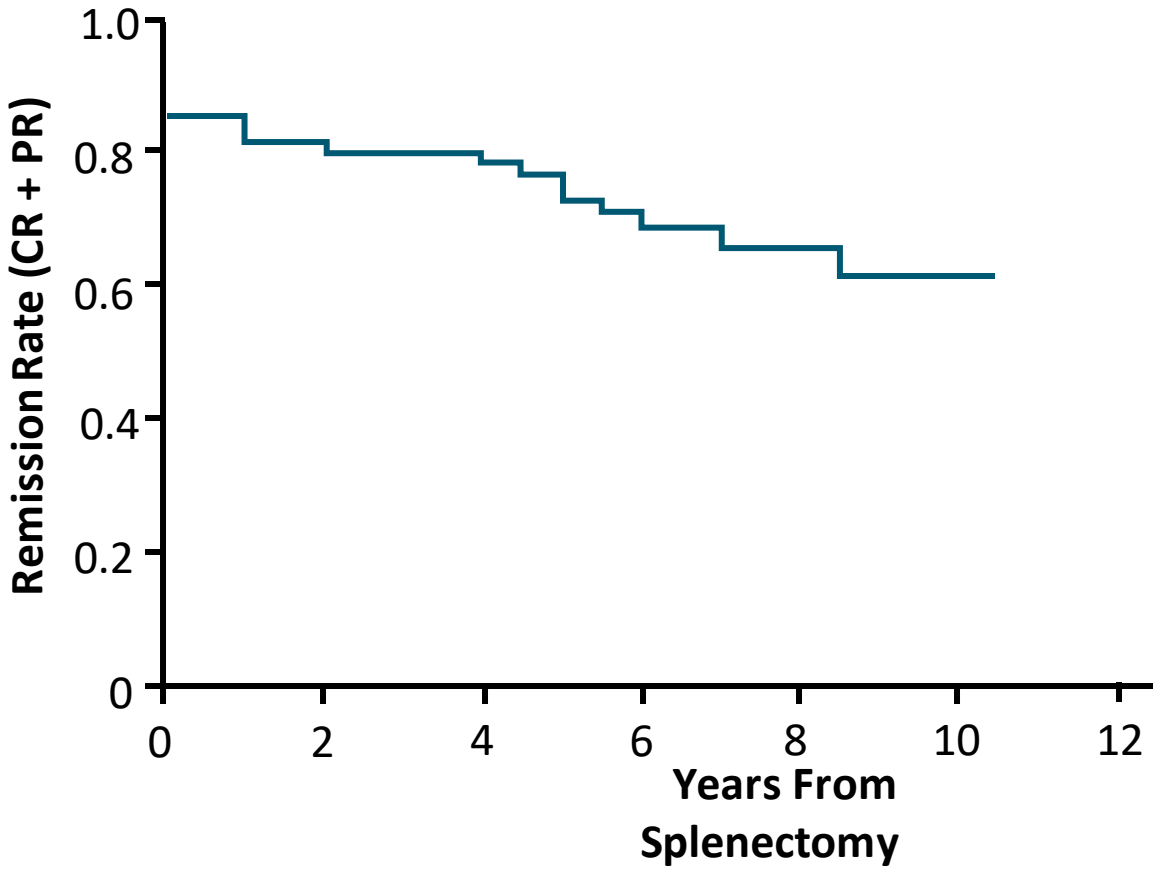
Splenectomy: Long-term Outcome



- Early response rate ~ 80%
- Responses usually rapid
- 15% relapse rate in first year, more later
- Laparoscopic splenectomy results in less morbidity
- Predictors of response controversial
- Immunize with pneumococcal, Hib, meningococcal vaccine

Schwartz. Am J Hematol. 2003;72:94.

Increased Risk of VTE and Sepsis After Splenectomy for ITP

AE, %	Cumulative Incidences	
	Splenectomy (n = 1762)	No Splenectomy (n = 8214)
Abdominal VTE*	1.6	1.0
VTE	4.3	1.7
Sepsis	11.1[†]	10.1

AE	HR (95% CI)	
	< 90 Days	≥ 90 Days
Abdominal VTE*	5.4 (2.3-12.5); *P* < .0001	1.5 (0.9-2.6); *P* = .1252
VTE	5.2 (3.2-8.5); *P* < .0001	2.7 (1.9-3.8); *P* < .0001
Sepsis	3.3 (2.4-4.6); *P* < .0001	1.6 (1.3-2.0); *P* < .0001[‡] 3.1 (2.2-4.4); *P* = .0016[§]

*Mesenteric, portal, or hepatic veins. [†]2.6% < 90 days and 8.8% ≥ 90 days. [‡]0-1 comorbidities. [§]2+ comorbidities.

Boyle. Blood. 2013;121:4782.

What About Splenectomy?

- Rarely needed
- If possible, delay for 12-24 months to allow disease to mitigate or remit
- Bone marrow biopsy in truly “refractory” patient
- Indium-labeled autologous platelet scanning if available
- Laparoscopic procedure preferred
- Appropriate patient education necessary as to AEs with the procedure (infection, thrombosis) and remission rate

Matzdorff. Oncol Res Treat. 2018;41(suppl 5):1. Provan. Blood Adv. 2019;3:3780.
Neunert. Blood Adv. 2019;3:3829. Kashiwagi. Int J Hematol. 2020;111:329.

Summary: How to Treat ITP

- Many ITP patients do not need treatment
- Initial treatment is prednisone/IVIg
- Splenectomy works, but rarely needed to treat ITP
  - Increased rate of VTE, infection
- Not all adult ITP will become/remain chronic

- Give medical therapy a chance before splenectomy
  - Rituximab occasionally gives long-term treatment-free response
  - TPO receptor agonists highly effective
    - Low rate of AEs, improve HRQoL
    - May not need to "be forever"
  - Fostamatinib may be considered
  - Don't forget danazol, azathioprine, dapsone, MMF, cyclosporine
- Lots of new ITP treatments being developed