

Case #3—Immune Thrombocytopenia: Shifting Focus in Management

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Summary of Case

- **Young female**
- **Dry purpura mainly (petechiae & bruising)**
- **Mild nosebleeds**
- **Platelets $9 \times 10^9/L$**
- **Standard treatment with prednisone 1mg/kg/d**

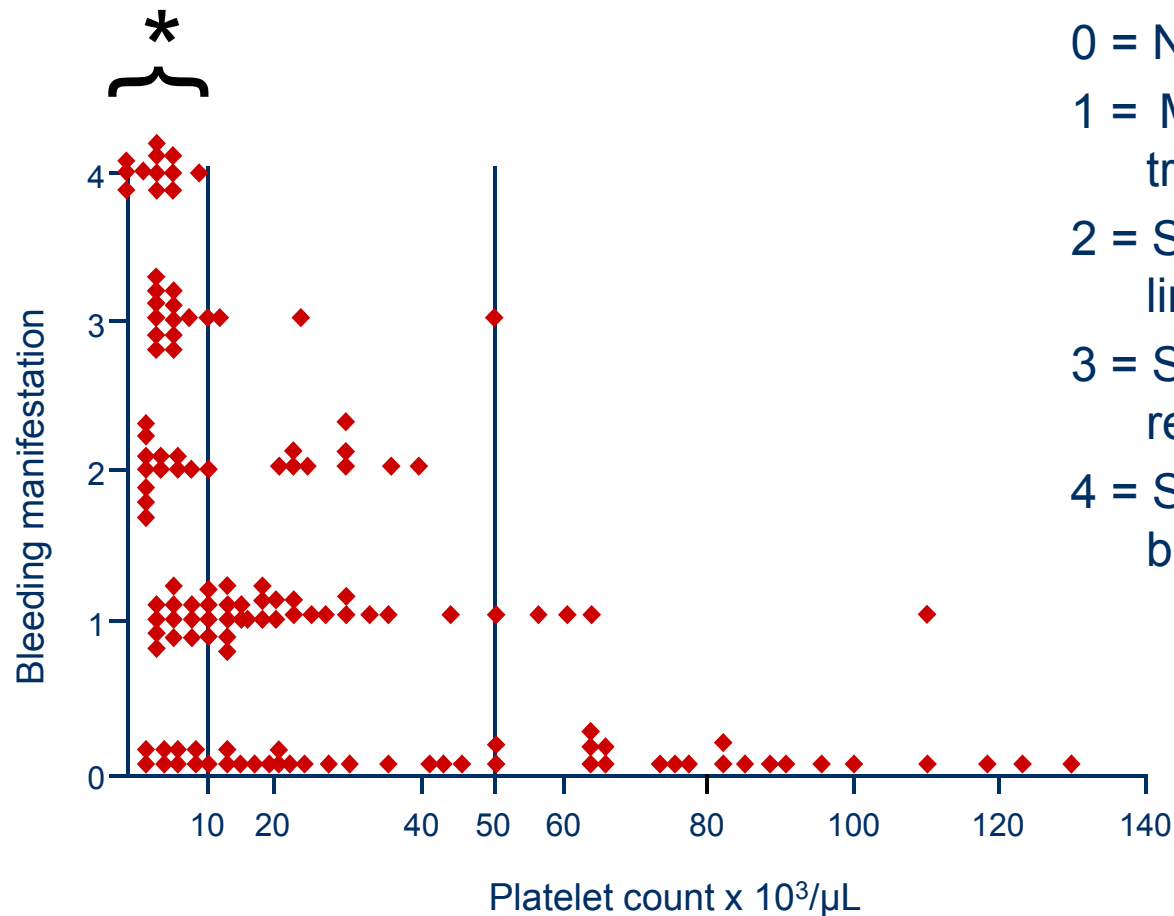
Rh(D) neg – irrelevant in EU

Summary of Case

- **Good response to steroids**
- **Typical drop in platelets as steroids reduced**
- **Classical side effects from steroid treatment**
- **Eventual drop in platelets to $15 \times 10^9/L$**
- **No mucocutaneous bleeding**

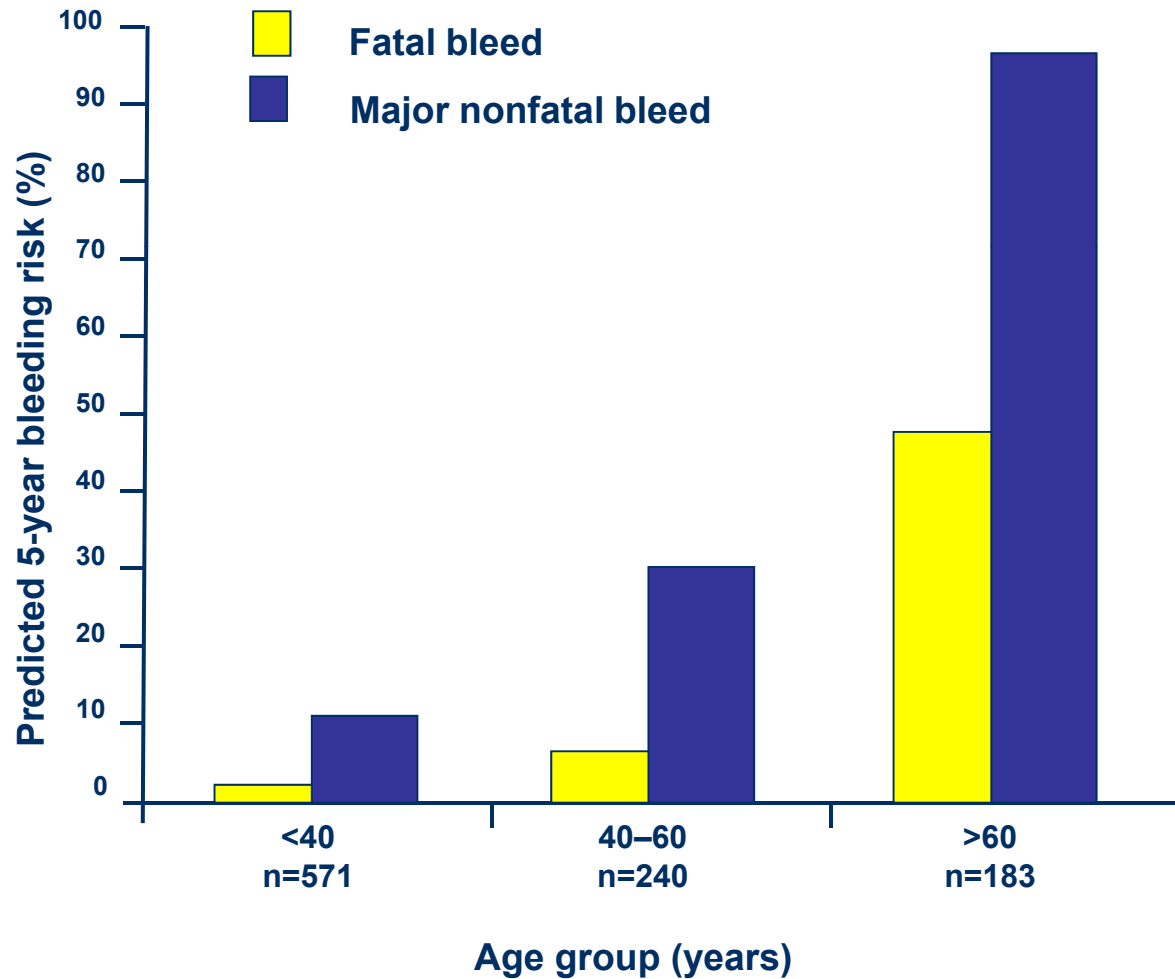
Is she low or high risk for major bleeding?

Platelet Count vs Bleeding



- 0 = No bleeding
- 1 = Minimal bleeding after trauma
- 2 = Spontaneous but self-limited bleeding
- 3 = Spontaneous bleeding requiring special attention
- 4 = Severe life-threatening bleeding

Age vs Bleeding



Is She Low-Risk or High-Risk Overall?

- **Low-risk**
- **Observation** reasonable, rescue if required
- **IVIg** not indicated unless bleeding
 - Does not need platelets $>30 \times 10^9/L$
- **Rituximab** – too soon
 - And dose too high (100mg/week x 4)
- **Azathioprine** – not yet, and $>3-4$ months
- Laparoscopic **splenectomy** - no

Splenectomy?

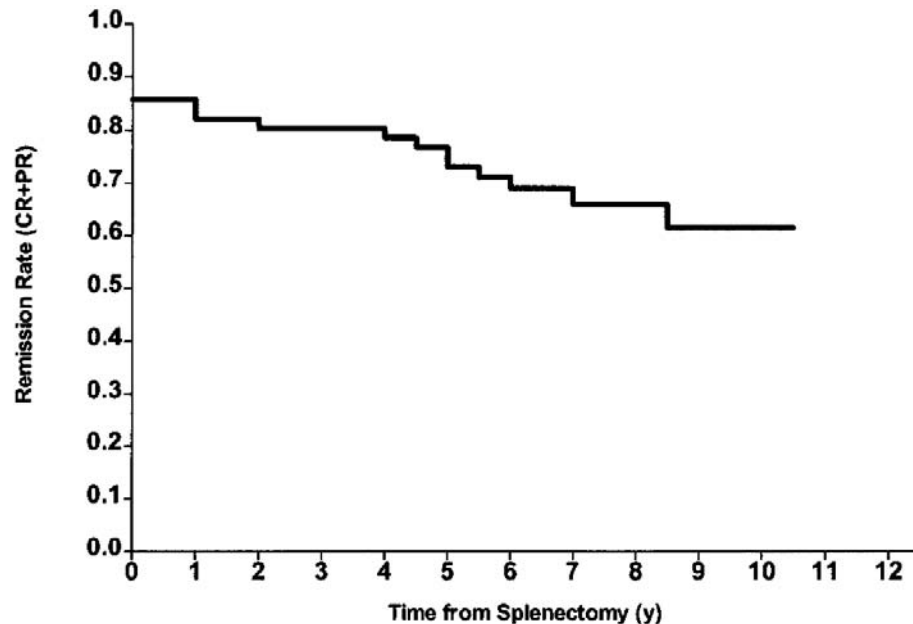


Fig. 1. Kaplan–Meier curve of remission rate (CR+PR) in 56 adults with ITP following splenectomy.

Effective in 2/3

BUT

Not risk-free

Invasive

Relapses

Complications, incl OPSI

Most patients can avoid

Progress

Had laparoscopic splenectomy

Platelets $220 \times 10^9/L \rightarrow 15 \times 10^9/L$ days later

What Would I Now Recommend?

Observation	Reasonable, plts $15 \times 10^9/L$ (+ TXA)
Dexamethasone	Maybe, but lower dose (side effects)
IVIg	If bleeds
Romiplostim	Possibly
Rituximab	Possibly, but low dose 100mg/week
Azathioprine	Prefer mycophenolate (MMF)
Eltrombopag	Possibly

Main Questions

Does she need treatment?

What treatment?

What Would I Recommend?

Observe

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graph TD; A[Observe] --> B[MMF]; B --> C[Romiplostim/Eltrombopag]; C --> D[Rituximab];
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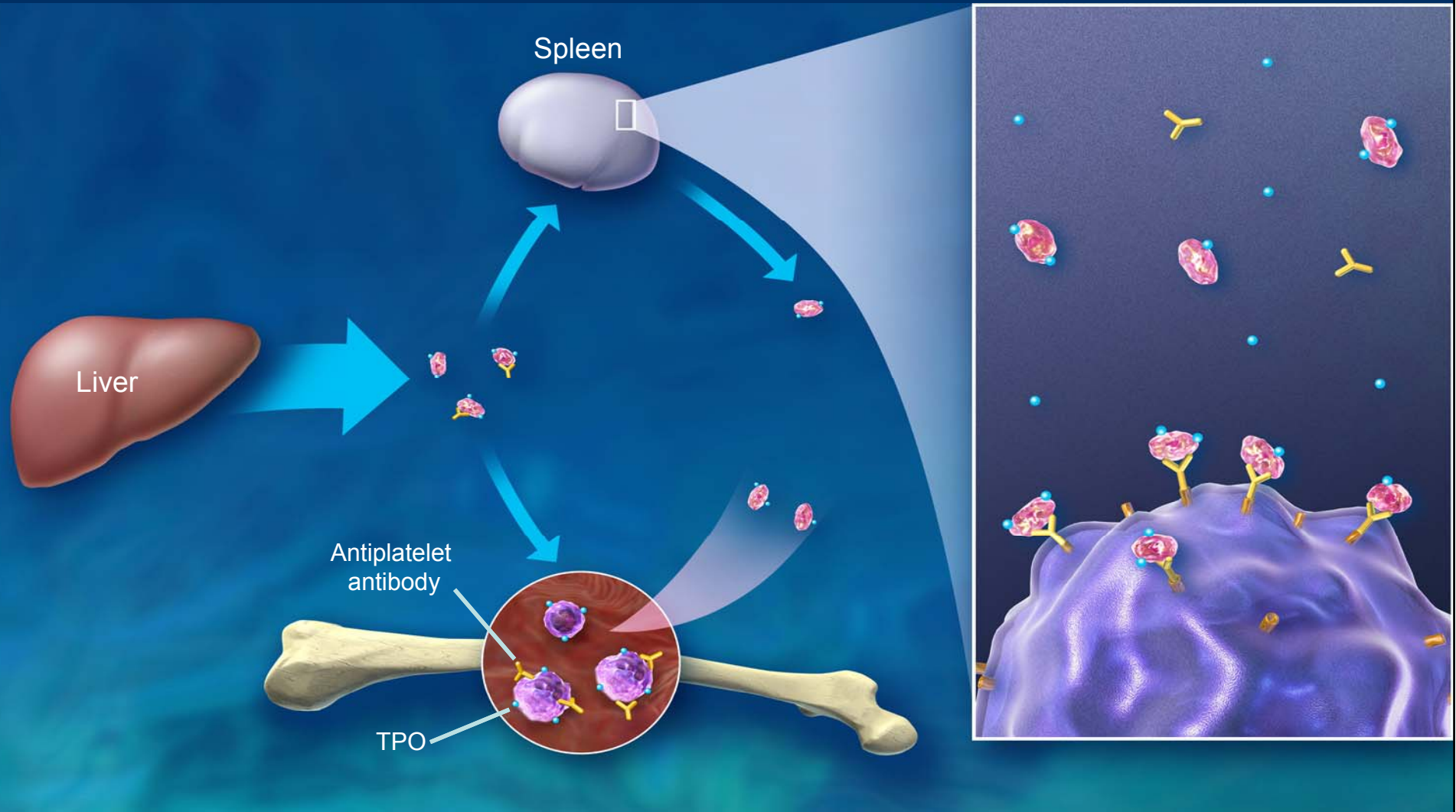
MMF

Romiplostim/Eltrombopag

Rituximab

ITP is more than just platelet destruction

ITP – A Disease of Accelerated Destruction and Suboptimal Production of Platelets

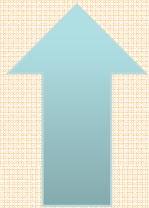


Blue arrow represents amount of free or unbound TPO in the system

Evolving Concept of ITP

Traditional model

Accelerated platelet
destruction



Current treatments

Gernsheimer TB, et al. *Hematology*. 2008;1:219-226. Cines DB, et al. *N Engl J Med*. 2002;346(13):995-1008.
McMillan R, et al. *Blood*. 2004;103(4):1364-1369. Chang M, et al. *Blood*. 2003;102(3):887-895. Stoll D, et al. *Blood*.
1995;65(3):584-588. Heyns A du P, et al. *Blood* 1986;67(1):86-92. Ballem PJ, et al. *J Clin Invest* .1987;80(1):33-40.

What's Wrong With Standard Therapies?

- Corticosteroids, immunosuppressants, etc.

Pros

Cheap
Familiar

Cons

Low efficacy
Few RCTs
Side effects
Morbidity & mortality ↑
Only ↓ destruction

New treatments developed

Thrombopoietin-Receptor (TPO-R) Agonists

Romiplostim

Subcut once weekly

Slow action

Useful for 2nd-line, maintenance,
pre-procedure

Not useful for emergency Rx

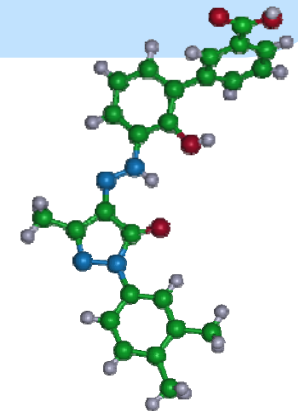
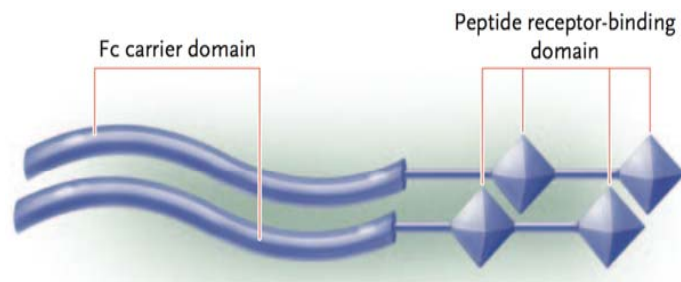
Eltrombopag

Oral once daily

Slow action

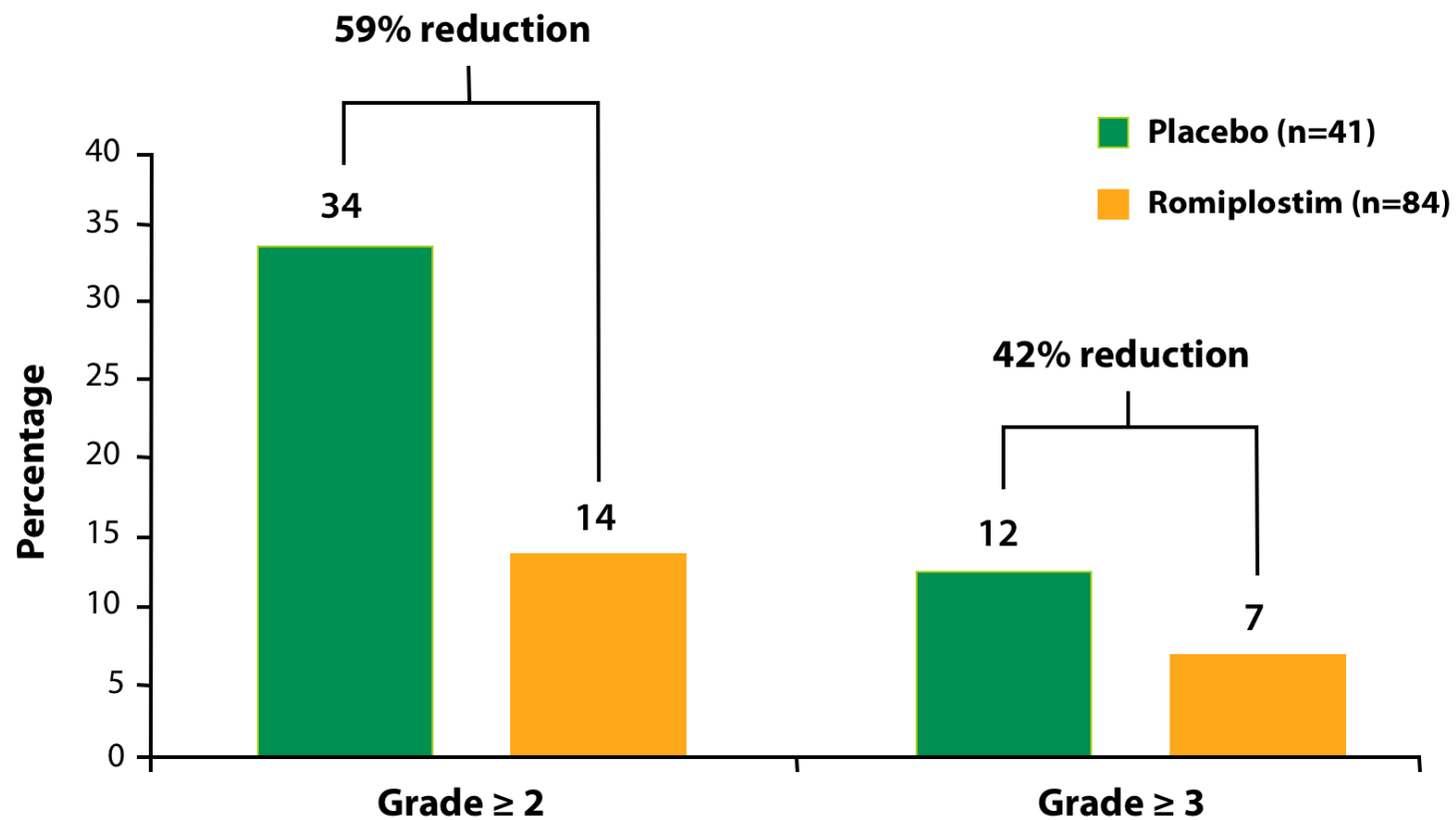
Useful for 2nd-line, maintenance,
pre-procedure

Not useful for emergency Rx



Clinical benefit?

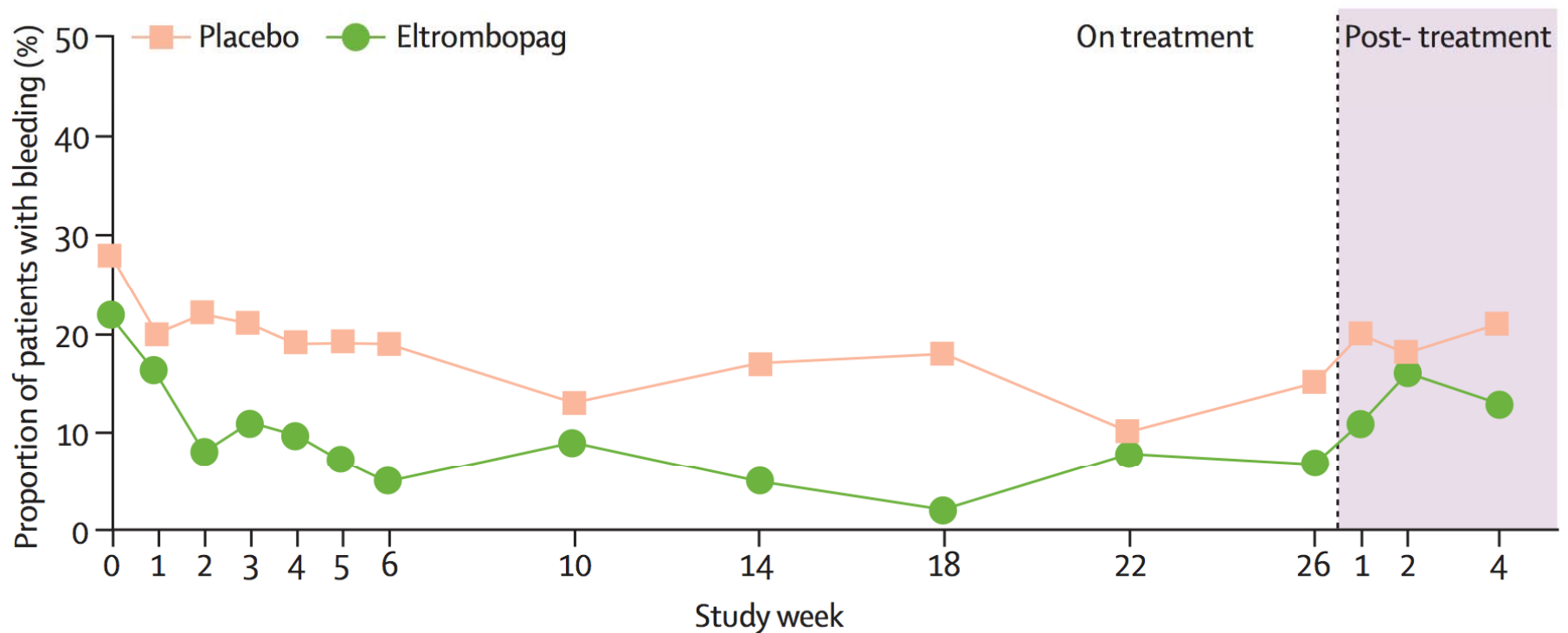
Romiplostim: Bleeding Events



Severity grades according to MedDRA 9.0 definition

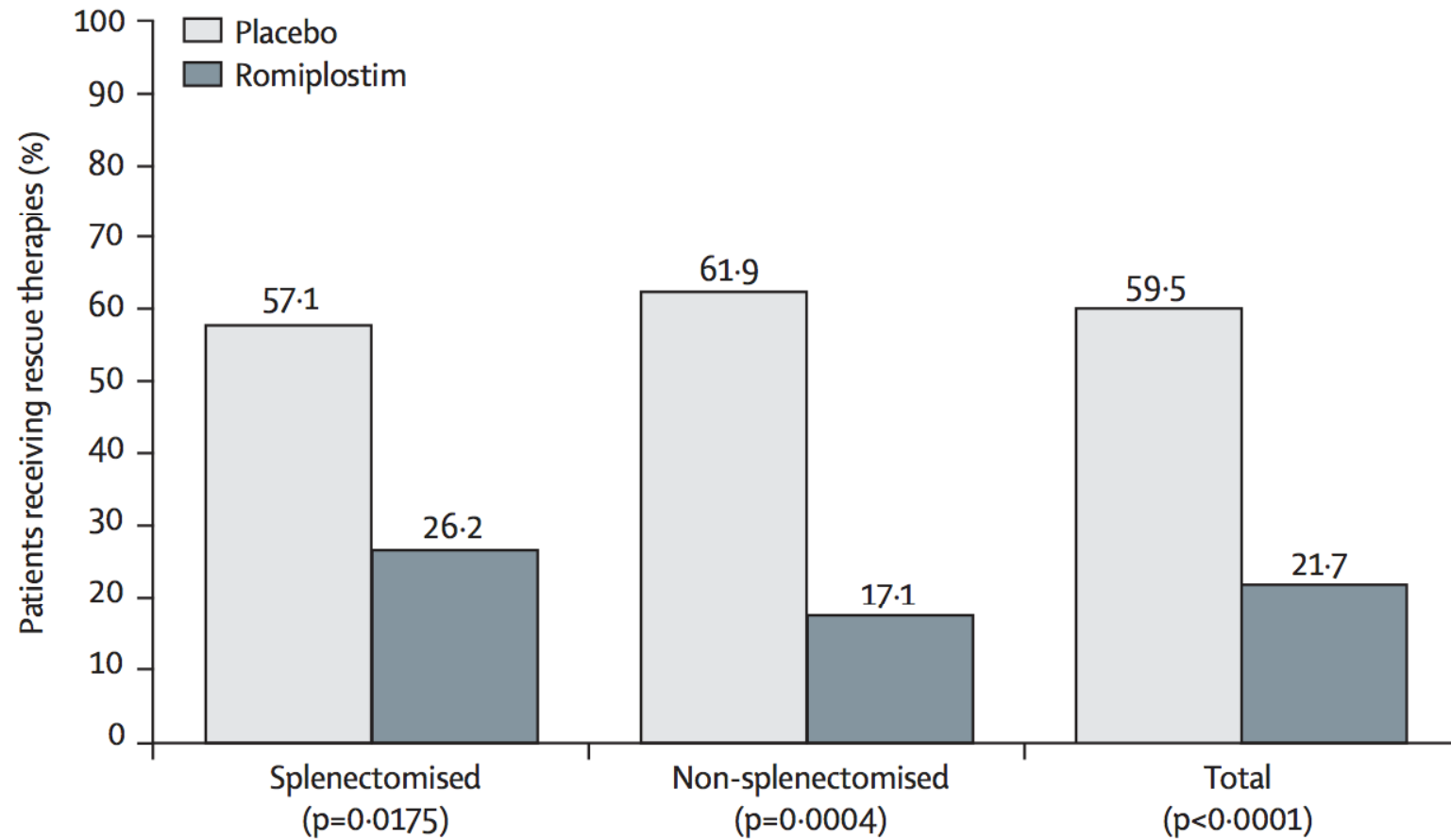
Eltrombopag: Bleeding Events

Grade 2-4 Bleeding



Cheng, et al. *Lancet*. In press.

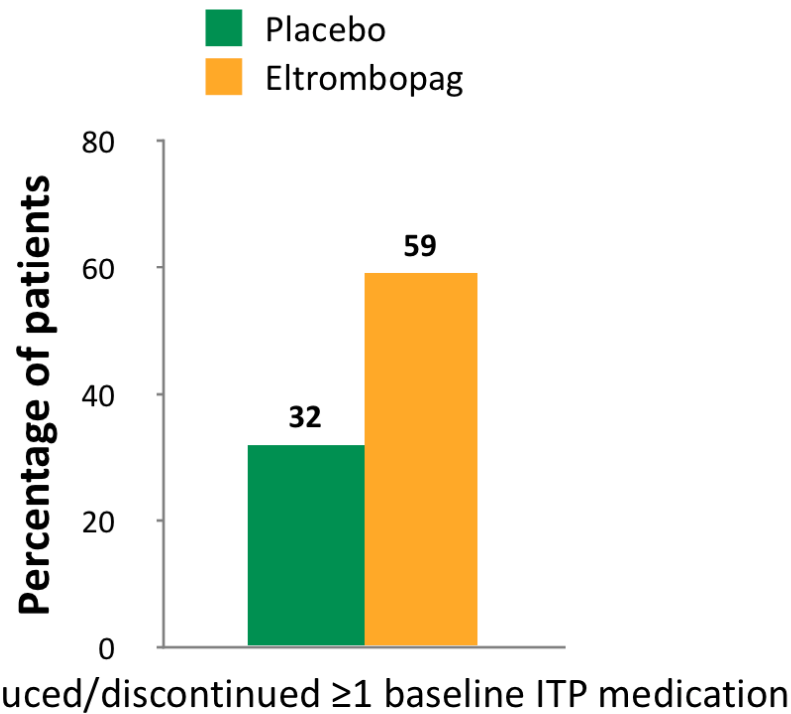
Romiplostim: Use of Rescue Rx



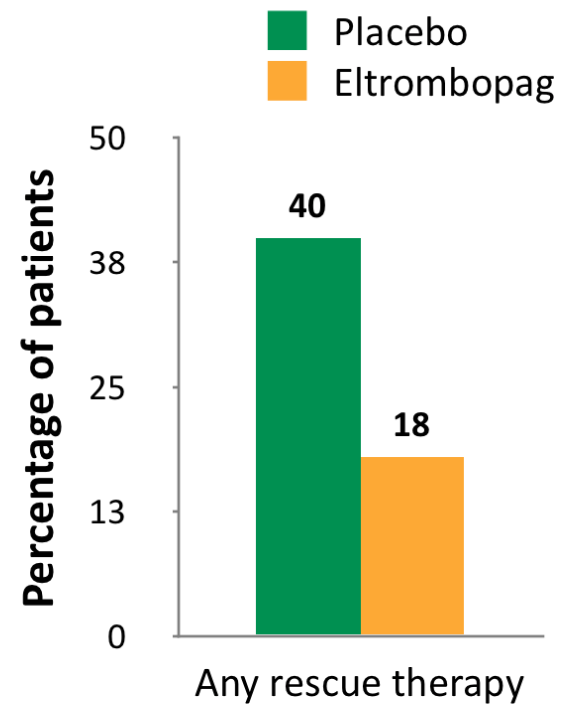
Kuter DJ, et al. *Lancet*. 2008;371(9610):395-403.

Eltrombopag: Baseline ITP Rx and Rescue

Baseline medication



Rescue therapy



Cheng G, et al. *Blood*. 2008;112: Abstract 400.
Cheng, et al. *Lancet*. In press.

Thrombopoietin-Receptor (TPO-R) Agonists

Clinically beneficial

Impressive efficacy

↑ **platelets**

↓ **bleeding**

↓ **need for rescue**

No immune suppression/steroid etc

When to use?

The new International Consensus

The Need for Updated Guidance

- Previous guidelines increasingly outdated:
 - American Society of Hematology (1996)¹
 - British Committee for Standards in Haematology (2003)²
- Clinical developments:
 - Greater understanding of the disease
 - Changes in practice
 - New published data^{3,4}
 - Novel classes of therapeutic agents

1. George J, et al. *Blood*. 1996;88(1):3-40. 2. Provan D, et al. *British Journal of Haematology*. 2003;120(4):574-596.
3. Kuter DJ, et al. *Lancet*. 2008;371(9610):395-403. 4. Bussel JB, et al. *Lancet*. 2009;373(9664):641-648.

Aims of New Guidance

- Improved diagnostic accuracy
- Individualize treatment
- Remove ineffective/toxic treatments

blood

Prepublished online Oct 21, 2009;
doi:10.1182/blood-2009-06-225565

International consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan, Roberto Stasi, Adrian C. Newland, Victor S. Blanchette, Paula Bolton-Maggs, James B. Bussel, Beng H. Chong, Douglas B. Cines, Terry B. Gernsheimer, Bertrand Godeau, John Grainger, Ian Greer, Beverley J. Hunt, Paul A. Imbach, Gordon Lyons, Robert McMillan, Francesco Rodeghiero, Miguel A. Sanz, Michael Tarantino, Shirley Watson, Joan Young and David J. Kuter

Treatment of ITP in adults

Who Should Be Treated?

Factors to take into account:

Bleeding

Activity and lifestyle

Patient preferences & concerns

Tolerance of side effects

Platelet counts

Final judgments: based on individual circumstances

First-Line

Steroids

dexamethasone

methylprednisolone

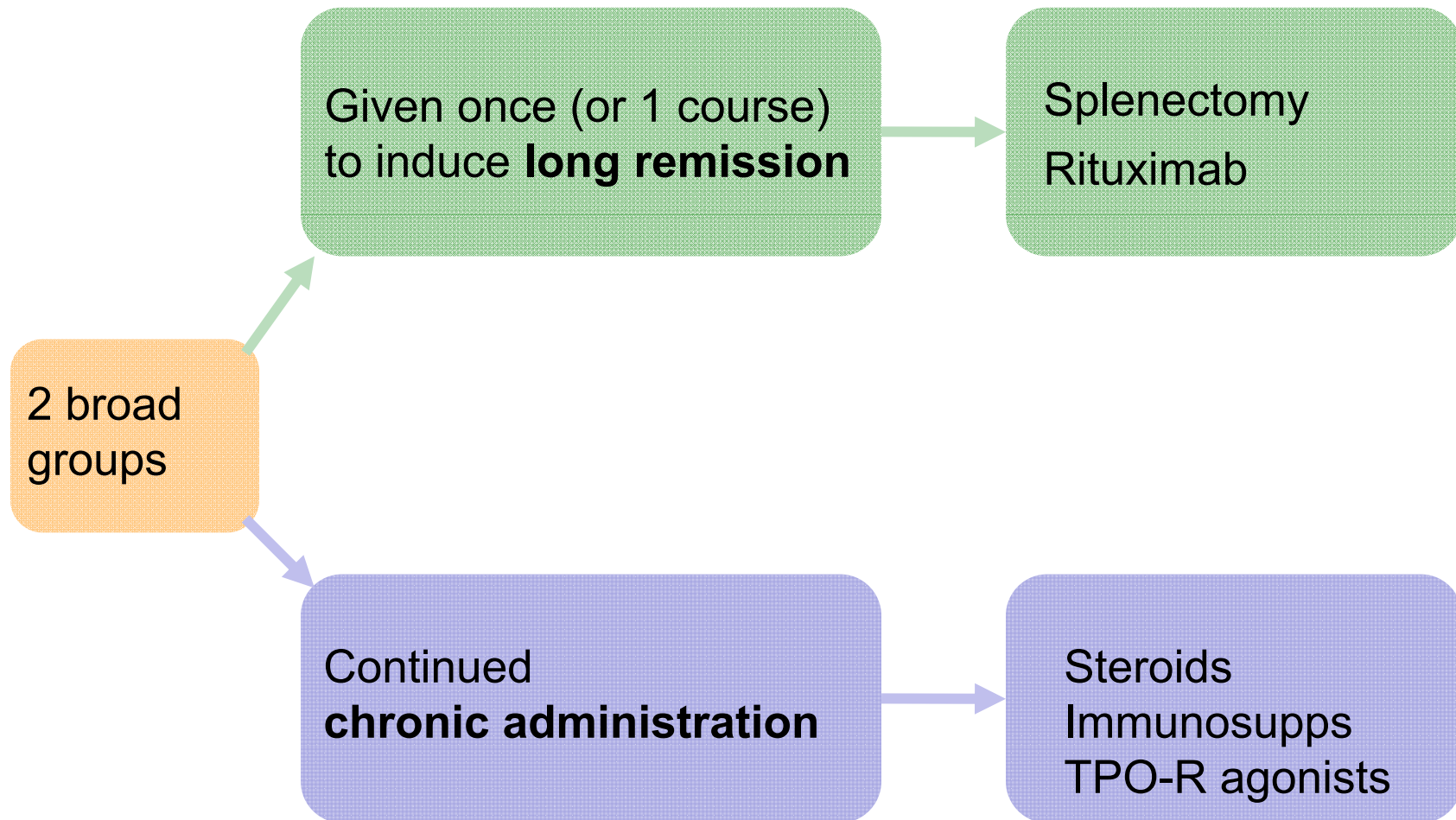
prednis(ol)one

IVIg

~~Anti-D*~~

* Not available in EU

Recommendations For Second-Line Therapy



Second-Line Therapy

Azathioprine
Cyclophosphamide
Cyclosporin A
Danazol
Dapsone
Mycophenolate mofetil
Rituximab
Splenectomy
TPO-R agonists
Vinca alkaloids

Grade B

Grade C

Grade A

Second-Line Therapy

Azathioprine
Cyclophosphamide
Cyclosporin A
Danazol
Dapsone
Mycophenolate mofetil
Rituximab
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TPO-R agonists
Vinca alkaloids

Grade B

Grade C

Grade A

Recommendations for Patients Failing First-Line and Second-Line Therapy

- ~20% patients (+10–20% splx responders relapse)
- **Options**

Patient may tolerate low counts



Choose no medical treatment

Patient may have problems



Discuss alternative Rx

May not be ITP (remains diagnosis of exclusion)



Look for other diagnosis

Patients Failing 1st-Line and 2nd-Line

Rx options with sufficient data

TPO-R agonists

Rx options with minimal data and potential for considerable toxicity

Alemtuzumab-1H

Combination of 1st-line and 2nd-line Rxs

Combination chemotherapy

Hemopoietic stem cell transplantation

Therapies Whose Use Is Not Justified

- Ineffective or too toxic
 - Colchicine
 - Interferon- α
 - Protein A immunoadsorption columns
 - Plasmapheresis
 - Vitamin C
 - rVIIa

Summary and Outlook

Better understanding of ITP

Focus shifted away from platelet *destruction*

TPO-R agonists developed: enhance *production*

BUT most patients need little treatment

Treatment should be individualized

Consensus-based recommendations provide guidance for diagnosis and treatment