



# **A New Era of Treatment Options for Chronic Idiopathic Thrombocytopenic Purpura**

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# Disclosures

- Jane Pruemer, PharmD, BCOP, FASHP has no real or apparent conflict of interest
- Julianna A. Burzynski, PharmD, BCPS, BCOP has no real or apparent conflicts of interest to report

# Learning Objectives

- Describe the epidemiology of idiopathic thrombocytopenic purpura (ITP) and the pathophysiology underlying disease progression in chronic ITP
- Discuss the limitations of current agents used to treat chronic ITP
- Understand the mechanisms of monoclonal antibodies and thrombopoietic agents as used in ITP treatment
- Summarize recent clinical findings for newly developing therapies for chronic ITP



# **Epidemiology, Pathophysiology, and Initial Management of Chronic ITP**

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# Outline: Epidemiology, Pathophysiology, and Initial Management of Chronic ITP

- Epidemiology
- Clinical symptoms and diagnosis of ITP
- Differences between pediatric and adult ITP
- Overview of first-line therapies for the management of chronic ITP
- Comparison of ASH Guidelines (1996) with the British Committee for Standards in Haematology (BCSH) (2003) for the management of ITP

# Historic Viewpoint of ITP

- 1950: 2 hematology fellows (Harrington and Hollingsworth) at Barnes Hospital, St. Louis
- Proposal: cause of ITP was a factor in the blood that destroyed platelets
- Harrington was infused with patient's blood
- Within a few hours, his platelet count dropped, resulting in a seizure
- For 4 days, he experienced thrombocytopenia with bruises and petechiae
- By day 5, his platelet count began to return to normal

# Epidemiology of ITP

- An autoimmune disease characterized by low platelets (less than  $30 \times 10^9/L$ ) and mucocutaneous bleeding that ranges in severity from mild to life-threatening
- Estimated annual incidence of approximately 1 per 10,000 to 1 per 1000 persons
- Women are affected more commonly than men (2–3:1)
- Patients typically present in early adulthood
- An estimated 200,000 individuals in the United States have developed ITP

Cines DB, Blanchette VS. *N Engl J Med.* 2002;346:995-1002.

Psaila B, Bussel JB. *Hematol Oncol Clin North Am.* 2007;21:743-59.

Platelet Disorder Support Association. Available at: <http://www.pdsa.org/itp-information/index.html>. Accessed 5/12/2008.

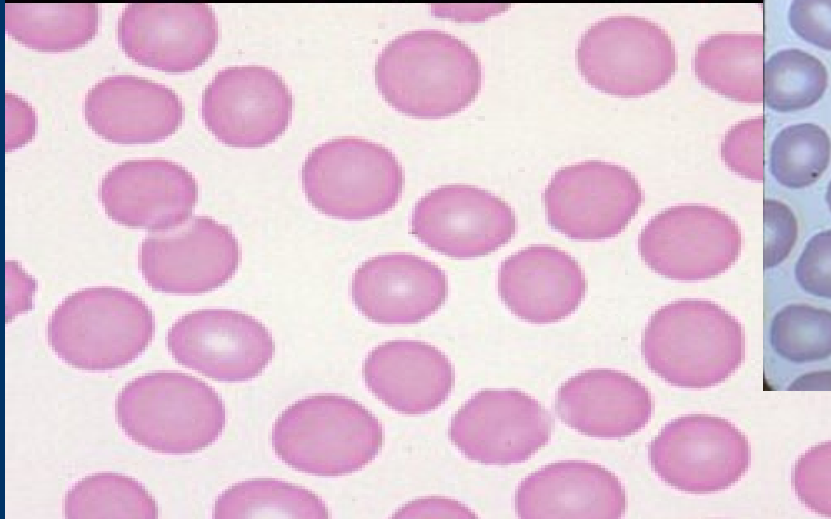
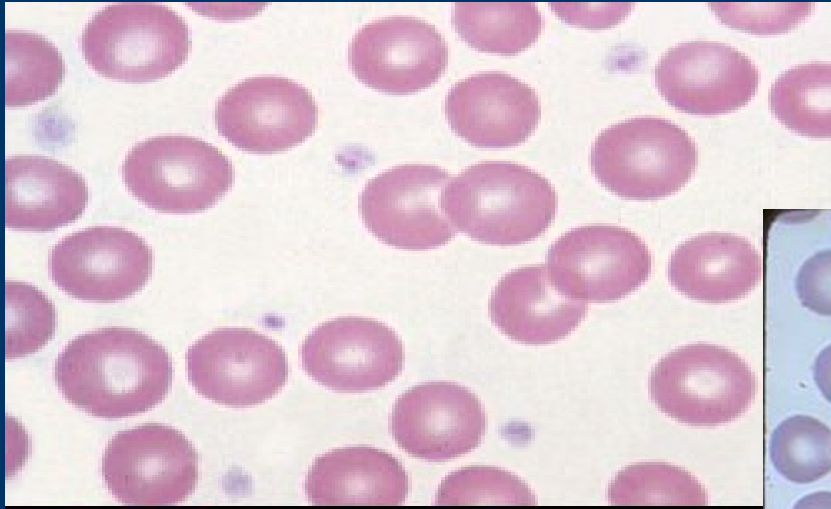
# Pathogenesis of Chronic ITP

- Chronic ITP is an autoimmune disorder in which the patient's immune system reacts with a platelet autoantigen, resulting in thrombocytopenia due to immune-mediated platelet destruction and/or suppression of platelet production
- Platelet membrane proteins become antigenic and stimulate the immune system to produce autoantibodies and cytotoxic T cells
- Autoantibodies against platelet GP IIb-IIIa and/or GP 1b-IX can be detected in the majority of patients

# Pathogenesis of Chronic ITP

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# Peripheral Blood Smear: Normal vs Patient With ITP



# Clinical Symptoms and Diagnosis of ITP

- Some patients will present with asymptomatic thrombocytopenia
- Others present with bleeding symptoms
- Hallmark of ITP = mucocutaneous bleeding that manifests as purpura (petechiae, ecchymosis), epistaxis, menorrhagia, or oral mucosal, gastrointestinal, or rarely, intracranial hemorrhage
- Rate of fatal bleeding estimated at 0.02 to 0.04 cases per patient year; highest (0.13 cases per patient year) among patients >60 years of age

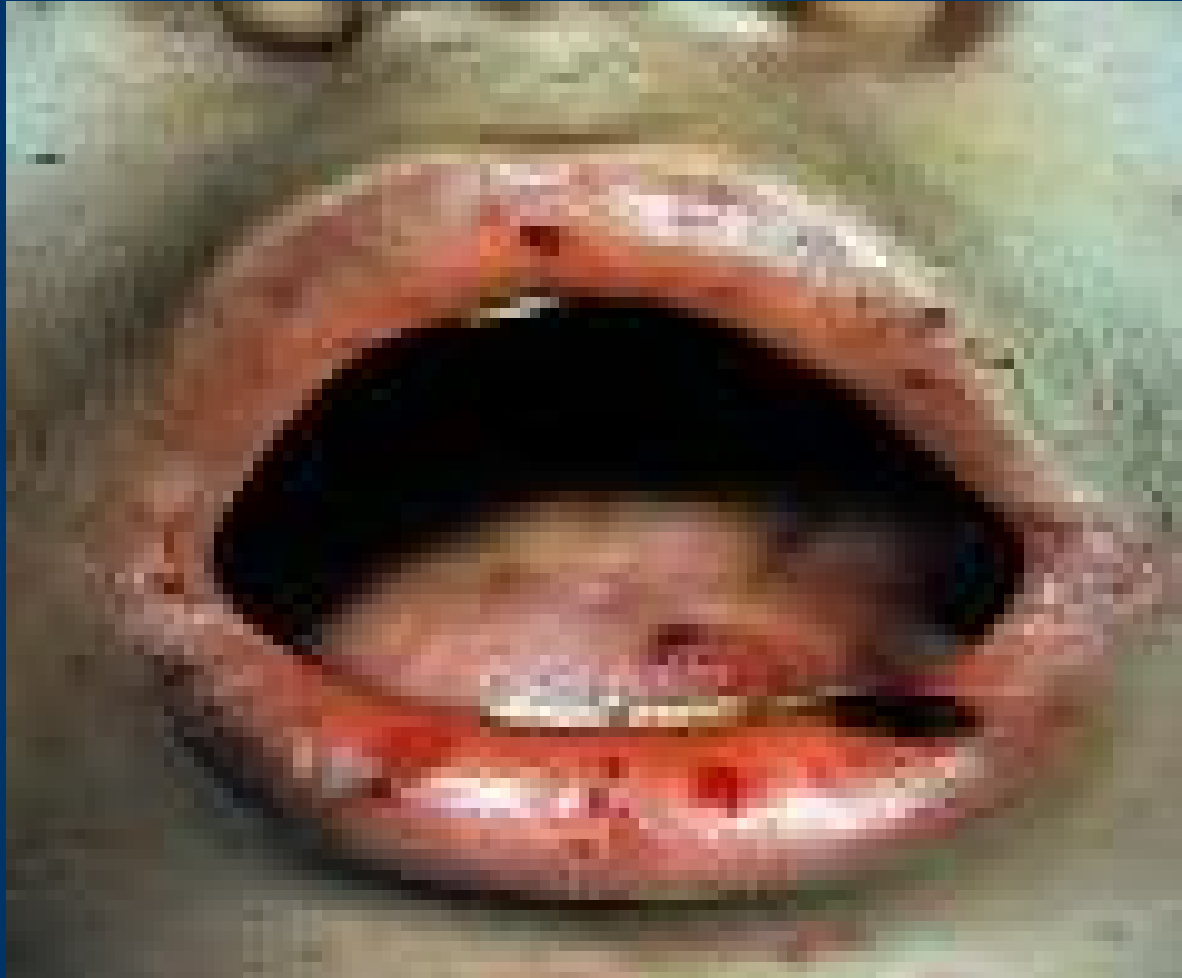
# Differences Between Pediatric and Adult ITP

- Pediatric ITP is most commonly considered acute ITP; seen in children aged 2 to 10 years
- Most children recover within 6 months, with or without treatment
- Chronic ITP mostly affects adults
- Chronic ITP persists for more than 6 months and requires treatment because it rarely spontaneously resolves

# Child With Bruises From ITP



# “Wet” Purpura in a Child With ITP



# First-Line Therapies for the Management of Chronic ITP

- The standard practice is to initiate treatment of ITP with oral prednisone or prednisolone at a dose of 1mg/kg per day as suggested by both ASH and BCSH guidelines
- Treatment regimens used, duration of full-dose treatment (3–6 weeks), and the mode of tapering (fast or slow), are diverse
- There are no randomized controlled studies comparing corticosteroids with no treatment
- There is no evidence of a beneficial effect of corticosteroid treatment on morbidity or mortality or on the rate of sustained remission

# IVIg or High-Dose Methylprednisolone, With or Without Oral Prednisone, for Adults With Untreated Severe ITP

- Randomized, multicenter trial of 122 adults with platelet count  $\leq 20 \times 10^9/L$
- Randomized to receive either IVIG or high-dose methylprednisolone on days 1 to 3, and then randomized to receive either oral prednisone or placebo on days 4 to 21

IVIg = intravenous immunoglobulin.

Godeau B, et al. *Lancet*. 2002;359:23-9.

# IVIg or High-Dose Methylprednisolone, With or Without Oral Prednisone, for Adults With Untreated Severe ITP

	IVIg (n = 56)	Methylpred (n = 60)	<i>P</i> Value
No. days platelets >50 x 10 <sup>9</sup> /L	18	14	<i>P</i> = 0.02
Patients with platelets >50 x 10 <sup>9</sup> /L on day 2	7%	2%	<i>P</i> = 0.04
Patients with platelets >50 x 10 <sup>9</sup> /L on day 7	79%	60%	<i>P</i> = 0.04

Methylpred = high-dose methylprednisolone.

Godeau B, et al. *Lancet*. 2002;359:23-9.

# IVIg or High-Dose Methylprednisolone, With or Without Oral Prednisone, for Adults With Untreated Severe ITP

- During the second treatment period, prednisone was more effective than placebo for all endpoints:
  - Number of days with platelet count  $>50 \times 10^9/L$
  - Highest platelet count after treatment
  - Platelet count at day 21
- The percent of remissions, however, was similar for all 4 groups of patients after 1 year of follow-up
- IVIg, steroids, or both, do not modify the natural history of ITP and support the assumption that a short course of prednisone has only a delaying action

# IVIg for the Treatment of Chronic ITP

- Costly
- Rapidly elevates the platelet count in 80% of patients
- Effect is transient, and by 3 to 4 weeks or less, the platelet count returns to pretreatment levels
- Adverse effects: allergic reactions, fever, renal failure with some sucrose-based formulations, headache, aseptic meningitis, and thromboembolic events

# IVIg for Adults With ITP

- Randomized study of 37 adults who were to undergo surgery
- 1 g/kg vs 0.5 g/kg
- 1 g/kg was more effective than lower dose and led to a significant increase in the platelet count in more than 60% of patients
- In nonresponders to lower dose, a subsequent infusion of 1 to 1.5 g/kg on day 3 was effective

# Anti-D Immunoglobulin for Chronic ITP

- Anti-D is a polyclonal antibody against the Rho(D) blood antigen
- Infusion of Rh immune globulin induces an increase in platelet count in nonsplenectomized Rh+ patients with ITP
- Anti-D was not considered in the ASH or BCSH guidelines as there was insufficient evidence for recommendation at the time

# Anti-D for Chronic ITP

- Retrospective report
- N = 261 patients (124 children, 137 adults)
- Patients were treated with IV anti-D at a dose of 25 mcg/kg or 50 mcg/kg on day 1, which could be repeated on days 3 and 4
- 7 days following the initial infusion, the mean platelet count was  $82 \times 10^9/L$  in 75 patients
- 72% had a platelet count  $>20 \times 10^9/L$  on day 7

# Splenectomy for Chronic ITP

- Splenectomy was first proposed as a therapy for ITP more than 90 years ago
- A retrospective analysis by Kojouri et al of pooled case series showed that a complete response was reported for 66% of 2623 adult patients with a follow-up of 1 to 153 months
- However, there are additional reports of continuing relapses during long-term follow-up (after 4–8 years)

# Summary of Early Therapies for the Treatment of Chronic ITP

- Oral prednisone remains the first-line treatment of ITP in adults with minor or mild bleeding
- The optimal duration of steroid therapy remains unknown
- IVIG should be reserved for patients with very low platelet counts and significant bleeding. The recommended dose of 2 g/kg over 2 days could be reduced to 1 g/kg in a single infusion unless the patient has life-threatening bleeding
- Anti-D may have a place in therapy for newly diagnosed ITP or persistent ITP prior to splenectomy
- A controlled study is needed in adults to compare IVIG and anti-D

# Guidelines for the Management of Chronic ITP

- American Society of Hematology – 1996
- British Committee for Standards in Haematology – 2003

# Summary of American Society of Hematology Guidelines – 1996

- Patients with platelet counts greater than  $20 \times 10^9/L$  should be managed as outpatients if they are asymptomatic or have only minor purpura
- Patients with counts exceeding  $50 \times 10^9/L$  do not routinely require treatment
- Hospitalization may be appropriate for patients with a platelet count less than  $20 \times 10^9/L$  or who have significant mucous membrane bleeding

# Summary of American Society of Hematology Guidelines – 1996

- Initial therapy with corticosteroids is the first-line treatment for chronic ITP
- In cases of severe or life-threatening bleeding, appropriate regimens include high-dose methylprednisolone, IVIG, and platelet transfusions
- IVIG is inappropriate as the initial treatment for patients with counts less than  $30 \times 10^9/L$  and who are asymptomatic or who have only minor purpura

# Summary of American Society of Hematology Guidelines – 1996

- Splenectomy should not be considered at an early stage for patients who have no bleeding symptoms
- Splenectomy may be appropriate if the platelet count remains below  $30 \times 10^9/L$  after 4 to 6 weeks of medical treatment

# Summary of American Society of Hematology Guidelines – 1996

- When symptoms of ITP persist after primary treatment with corticosteroids and splenectomy, further therapy is recommended for patients with platelet counts below  $30 \times 10^9/L$  and who have active bleeding
- Recommended therapies for above cases include IVIG, corticosteroids, and accessory splenectomy

# Summary of British Committee for Standards in Haematology – 2003

## ■ First-line therapy

- There is no indication for therapy in adults without bleeding symptoms or with a platelet count above  $30 \times 10^9/L$  unless they are undergoing a procedure likely to cause blood loss, such as surgery, dental extraction, or childbirth
- First-line therapy includes oral corticosteroids and IVIG

# Summary of British Committee for Standards in Haematology – 2003

## ■ First-line therapy

- Corticosteroids should be rapidly tapered and withdrawn, particularly in patients who fail to respond to treatment after 4 weeks
- IVIG is the first-line therapy for patients in whom the platelet count has to be rapidly increased because of symptoms or predictable bleeding (eg, surgery, pregnancy/labor, or operative dentistry)

# Summary of British Committee for Standards in Haematology – 2003

- Second-line therapy
  - Splenectomy should be considered as the major second-line therapy
  - Patients who fail oral corticosteroids and splenectomy are considered to have refractory ITP
    - Methylprednisolone is useful as a second-line therapy
    - It may be used in combination with IV cyclophosphamide or IVIG

# Summary of British Committee for Standards in Haematology – 2003

- Second-line therapy
  - Accessory splenectomy
  - Therapeutic options to consider for non-urgent cases
    - High-dose IVIG
    - Vinca alkaloids
    - Anti-D immunoglobulin
    - Danazol
    - Azathioprine
    - Cyclosporine

# Summary of British Committee for Standards in Haematology – 2003

- Second-line therapy
  - Therapeutic options for low platelet count and bleeding
    - Campath-1H<sup>®</sup> (alemtuzumab)
    - Rituximab
  - Mycophenolate mofetil
  - Not recommended
    - IFN- $\alpha$
    - Protein A columns
    - Plasmapheresis
    - Liposomal doxorubicin

IFN- $\alpha$  = interferon alpha.

British Committee for Standards in Haematology General Haematology Task Force. *Br J Haematol.* 2003;120:574-96.

# Summary of British Committee for Standards in Haematology – 2003

- Emergency treatment
  - To increase the platelet count rapidly in extreme emergencies, transfusion of random donor platelets is appropriate

# Summary/Conclusions

- Described the epidemiology of ITP and the pathophysiology underlying disease progression in chronic ITP
  - Platelet membrane proteins become antigenic and stimulate the immune system to produce autoantibodies and cytotoxic T cells
- Discussed the use of current agents used to treat chronic ITP, as recommended by ASH and BCSH
  - Corticosteroids
  - IVIG
- Discussed the limitations of these agents



# New Options After First-Line Therapy for Chronic ITP

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# Lecture Objectives

- Discuss the limitations of current agents used to treat chronic ITP
- Understand the mechanisms of monoclonal antibodies and thrombopoietic agents as used in ITP treatment
- Summarize recent clinical findings for newly developing therapies for chronic ITP

# Relapsed/Refractory ITP

## Options for Therapy

### Immunosuppression

Danazol

Azathioprine

Cyclophosphamide

Vinca alkaloids

Combination chemotherapy

Cyclosporine

Interferon

### Monoclonal Antibody

Rituximab

GMA 161

### Thrombopoietin Agonist

Romiplostim

Eltrombopag

AKR-501

# Epidemiology

- 30%–40% of patients fail splenectomy<sup>1</sup>
  - 26% are “refractory” to other salvage therapies
  - Less than 10% of all ITP cases are “refractory”
- Mortality related to refractory ITP<sup>2</sup>
  - 6% – 15%
  - Multiple factors influence
    - Age
    - Range of platelet counts included
    - Study time frame
    - Follow-up duration

1. McMillan R, Durette C. *Blood*. 2004;104:956-60.

2. Godeau B, et al. *Curr Opin Hemat*. 2007;14:535-56.

# Postsplenectomy Systematic Review

Treatment	n	CR	PR	NR
Cyclophosphamide	28	39%	29%	32%
Cyclosporine	8	38%	58%	12%
Autologous PBSCT	9	33%	22%	45%
Rituximab	35	23%	43%	34%
Azathioprine	53	19%	66%	15%
Dexamethasone	46	11%	43%	46%
Vinca alkaloid	34	6%	50%	44%
Interferon	28	4%	39%	57%
Danazol	52	0%	71%	29%

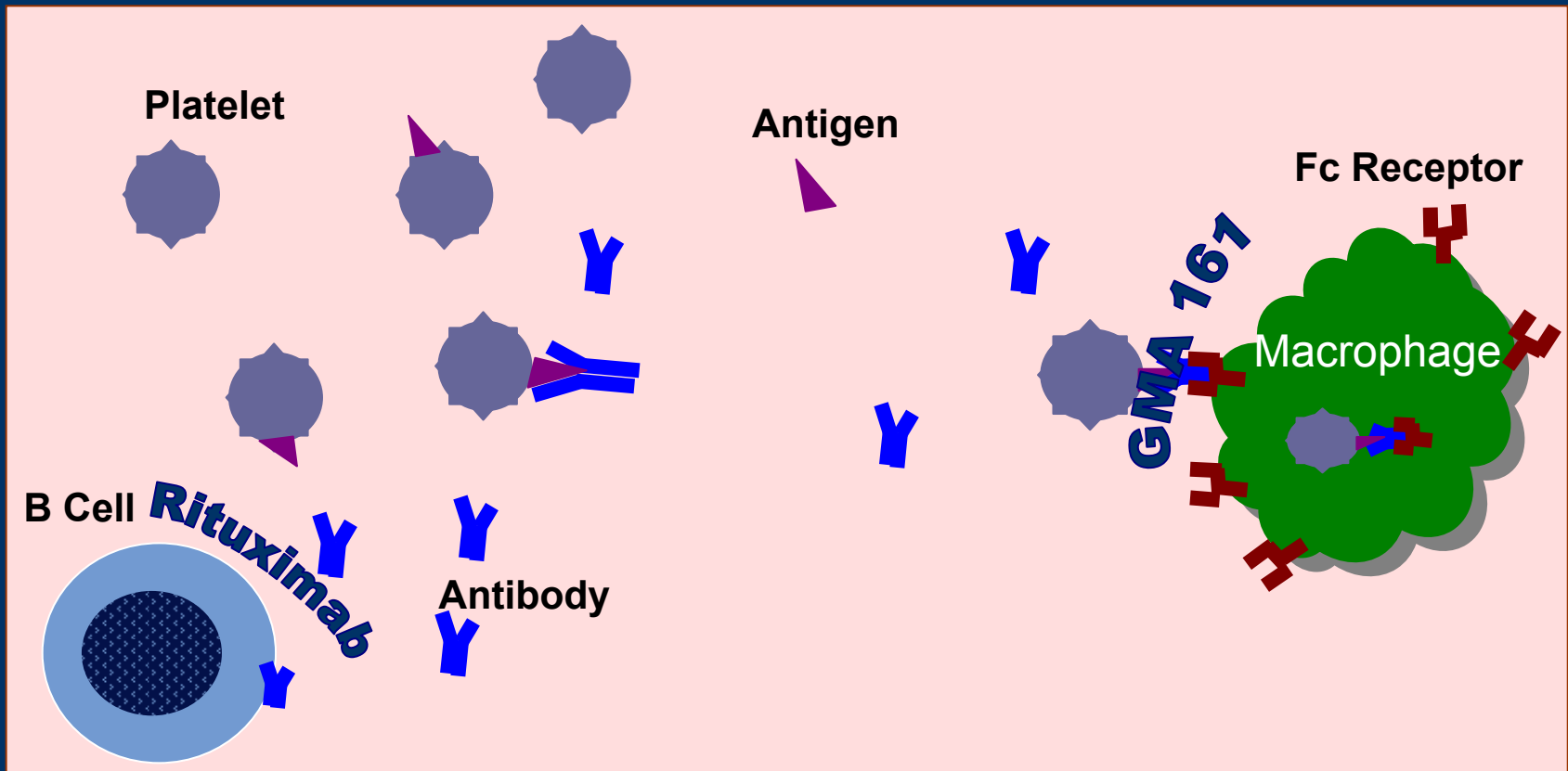
CR = complete response ; PR = partial response; NR = no response; PBSCT = peripheral blood stem cells.

Vesely SK, et al. *Ann Intern Med.* 2004;140:112-20. Reprinted with permission.

# Adverse Effects

Treatment	Response Duration	Adverse Effects
Cyclophosphamide <sup>1</sup>	2–84 mo	Myelosuppression, ? 2° malignancy
Cyclosporine <sup>2</sup>	6–48 mo	Headache, myalgia, hypertension
Autologous PBSCT <sup>3</sup>	9–42 mo	Myelosuppression, ? 2° malignancy
Rituximab <sup>4</sup>	3–94 mo	Infusion reaction
Azathioprine <sup>5</sup>	7–182 mo	Hepatotoxicity, myelosuppression
Dexamethasone <sup>6,7</sup>	2–12 mo	Psychiatric, edema, hyperglycemia
Vinca alkaloid <sup>8</sup>	1–5 mo	Neuropathy
Interferon <sup>9</sup>	3.5–24 mo	Flu-like symptoms, myelosuppression
Danazol <sup>10</sup>	3–182 mo	Edema, virilization

# Monoclonal Antibody Mechanism of Action



# Rituximab Systematic Review

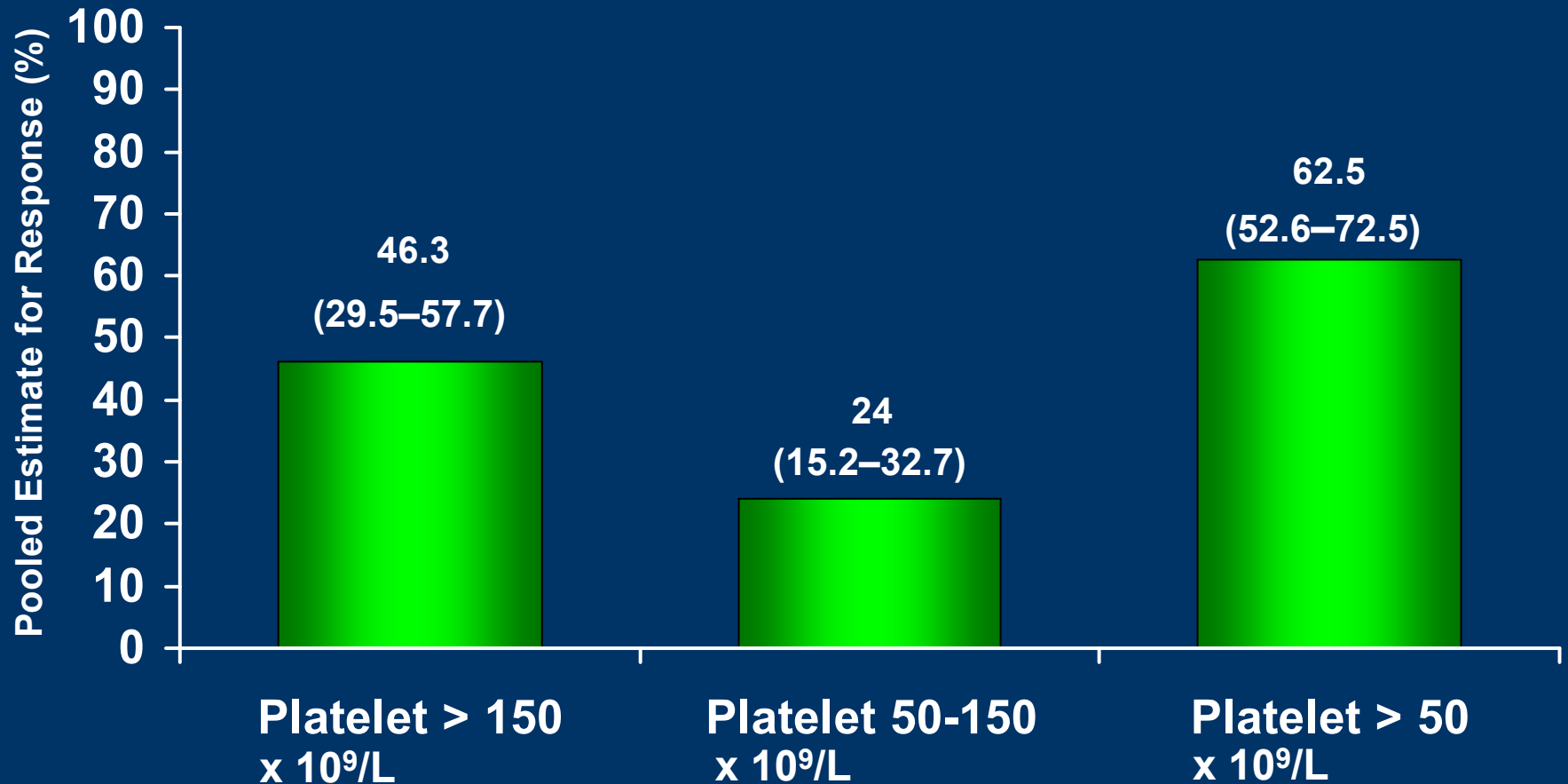
- 19 reports for efficacy (n = 313)
- 29 reports for safety (n = 306)

## Patient Demographics

Age range, y	16–89
ITP duration, mo	1–360
Prior corticosteroids	99.0%
Prior splenectomy	50.5%
Immunosuppression	Not described

# Rituximab Systematic Review

## Efficacy

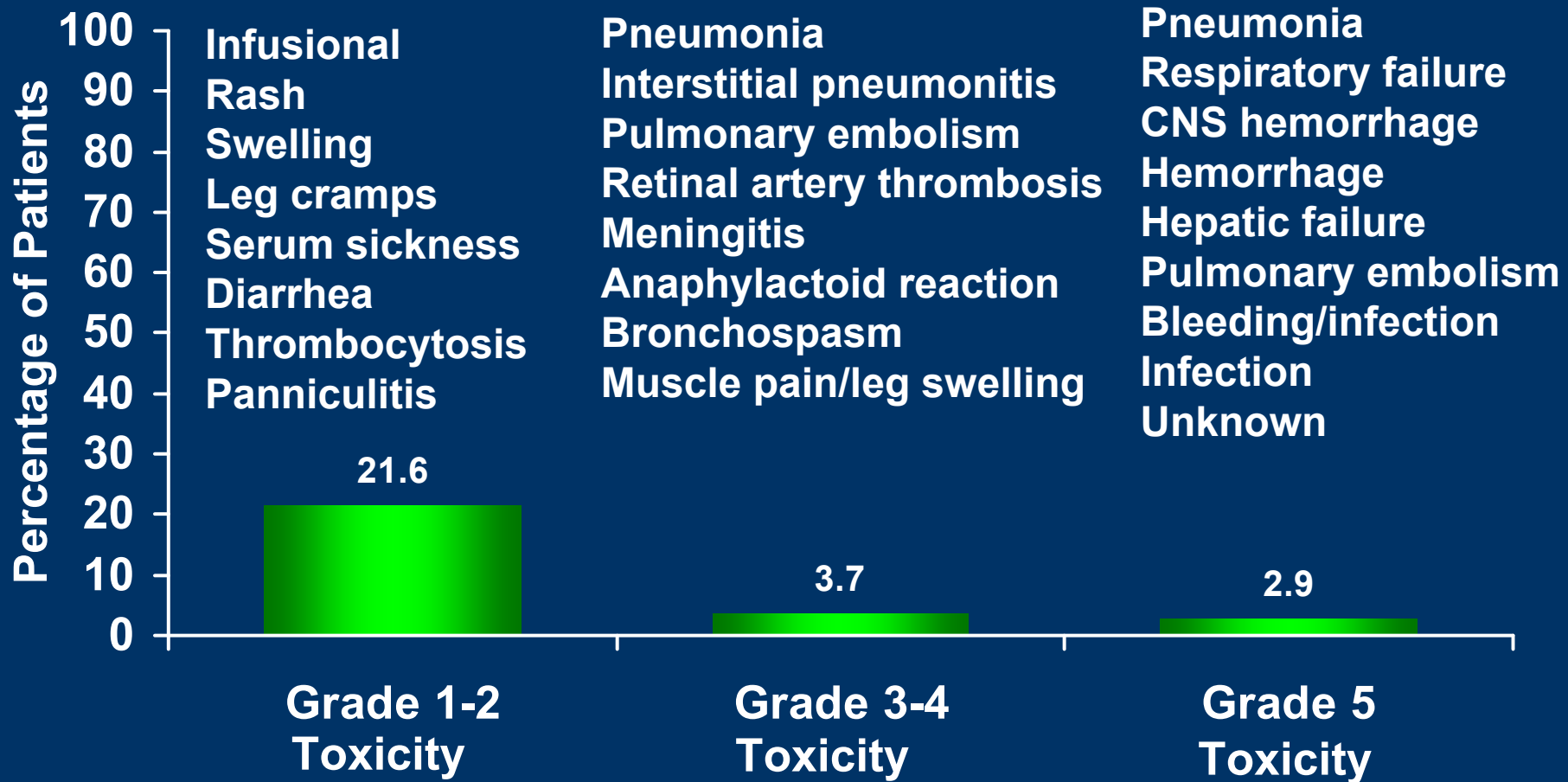


# Rituximab Systematic Review

- Time to response
  - Median 5.5 weeks
  - Range 2–18 weeks
- Response duration
  - Median 10.5 months
  - Range 6.3–41 months
- Follow-up
  - Median 9.5 months
  - Range 2–25 months
- Predictors of response
  - Duration of ITP
  - Time from diagnosis to rituximab administration
  - Younger age
  - Complete response

# Rituximab Systematic Review

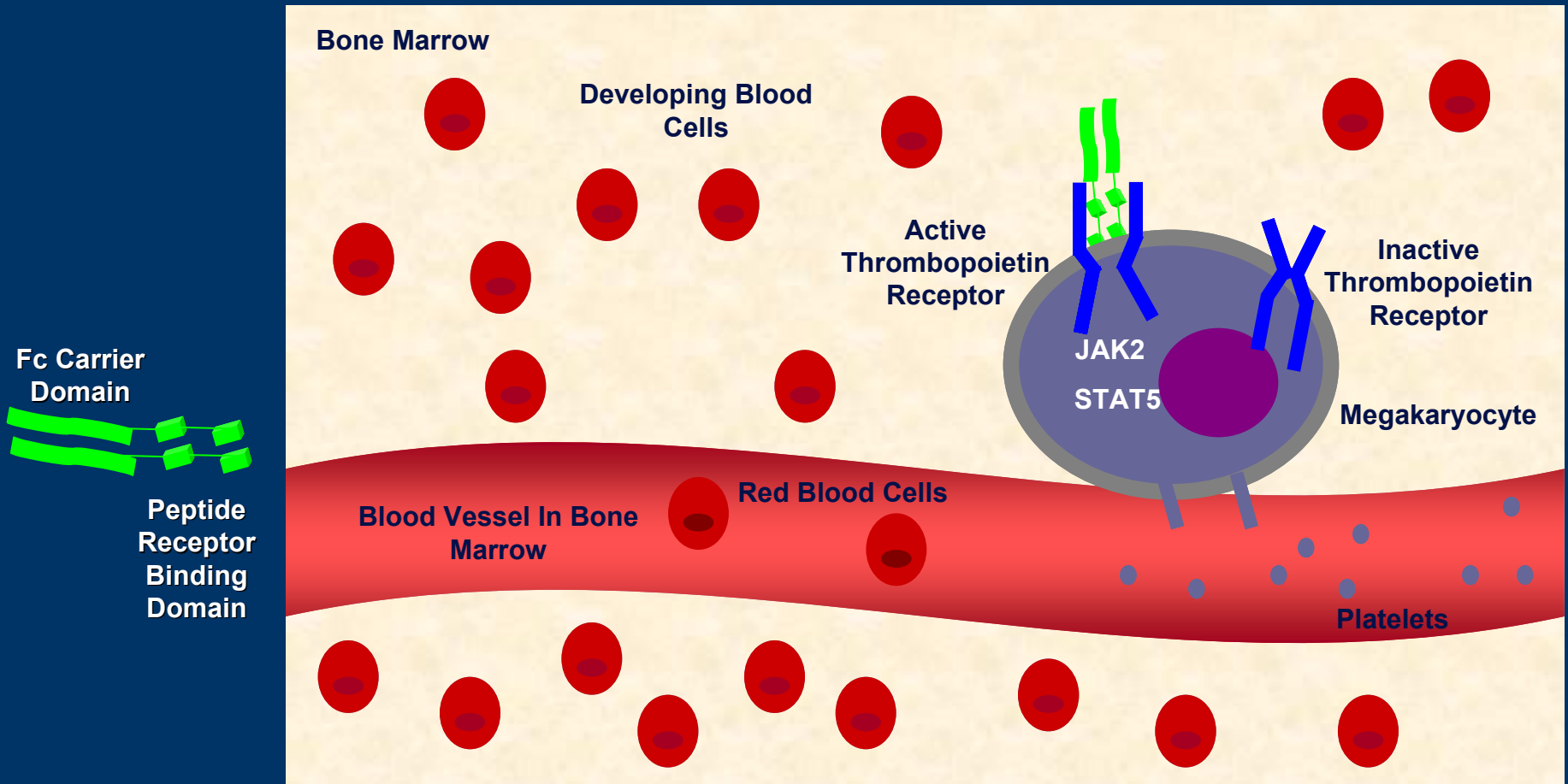
## Adverse Events



# Clinical Trials in ITP

- Few randomized, prospective controlled trials
  - None show prevention of bleeding or death
- Most case series are single-center reports
  - Results not reproducible at other centers
- Heterogeneous patient population
  - Not all patients were refractory to splenectomy
  - Some patients had platelet counts  $>30,000 \times 10^9/L$
- Small number of patients in each report
- The complete response rate is low

# Romiplostim, Nplate™



Bussel J, et al. *N Engl J Med.* 2006;355:1672-81; Geddis AE, et al. *Science.* 2007;317:1689-90; Kuter DJ. *Blood.* 2007;109:4607-16.

# Romiplostim in Chronic ITP<sup>1</sup>

## ■ Inclusion

- Chronic ITP defined by ASH Guidelines<sup>2</sup>
- Baseline platelet  $<30 \times 10^9/L$  (3 counts)
- Concomitant stable doses of azathioprine, corticosteroids, and danazol were allowed

## ■ Primary objective

- Durable platelet  $\geq 50 \times 10^9/L$  for 6 of 8 weeks
- No rescue therapy in past 24 weeks

## ■ Secondary objective

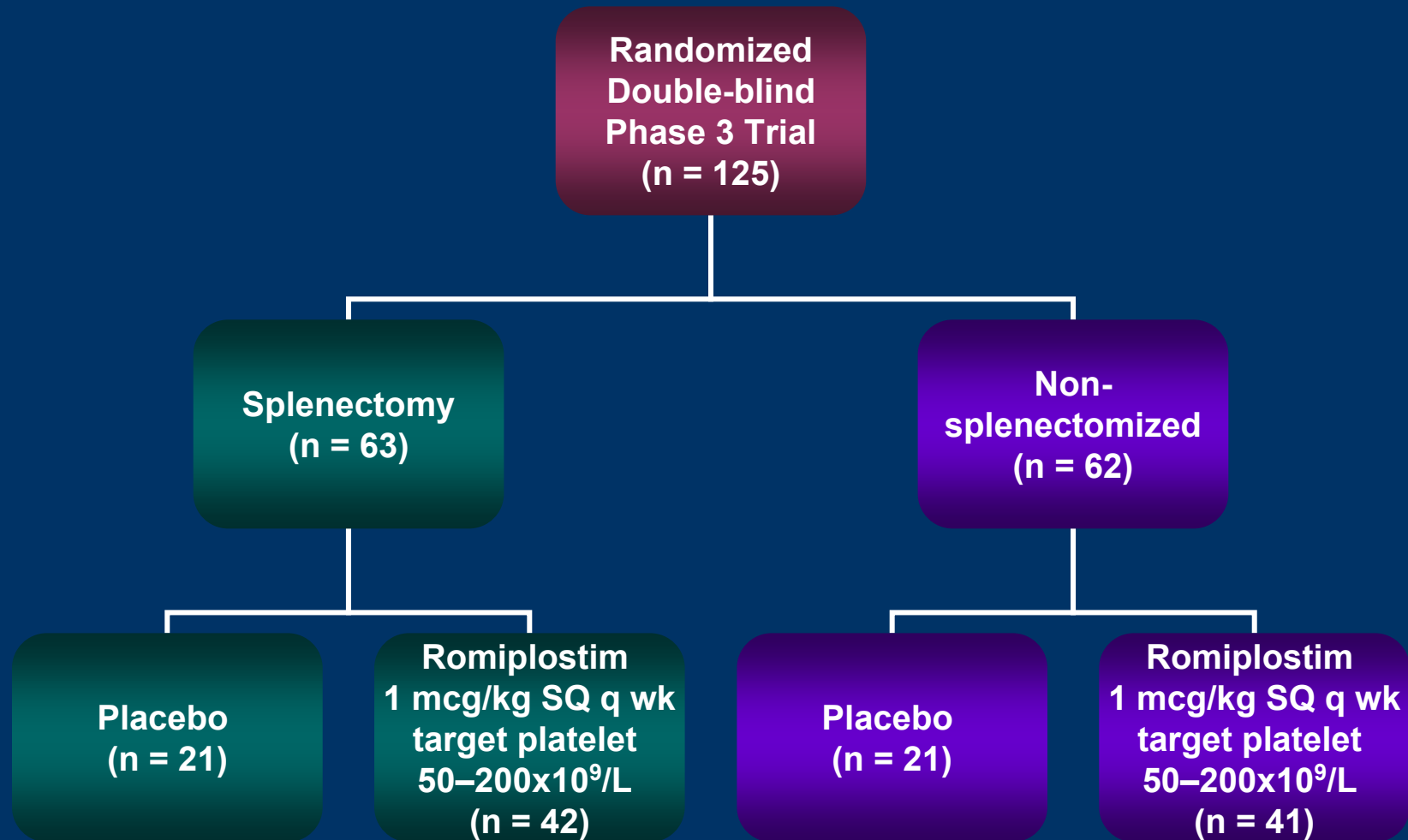
- Safety
- Decrease concomitant therapy for ITP

ASH = American Society of Hematology.

1. Kuter DJ, et al. *Lancet*. 2008;371:395-403.

2. George, et al. *Blood*. 1996;88: 3-40.

# Romiplostim in Chronic ITP



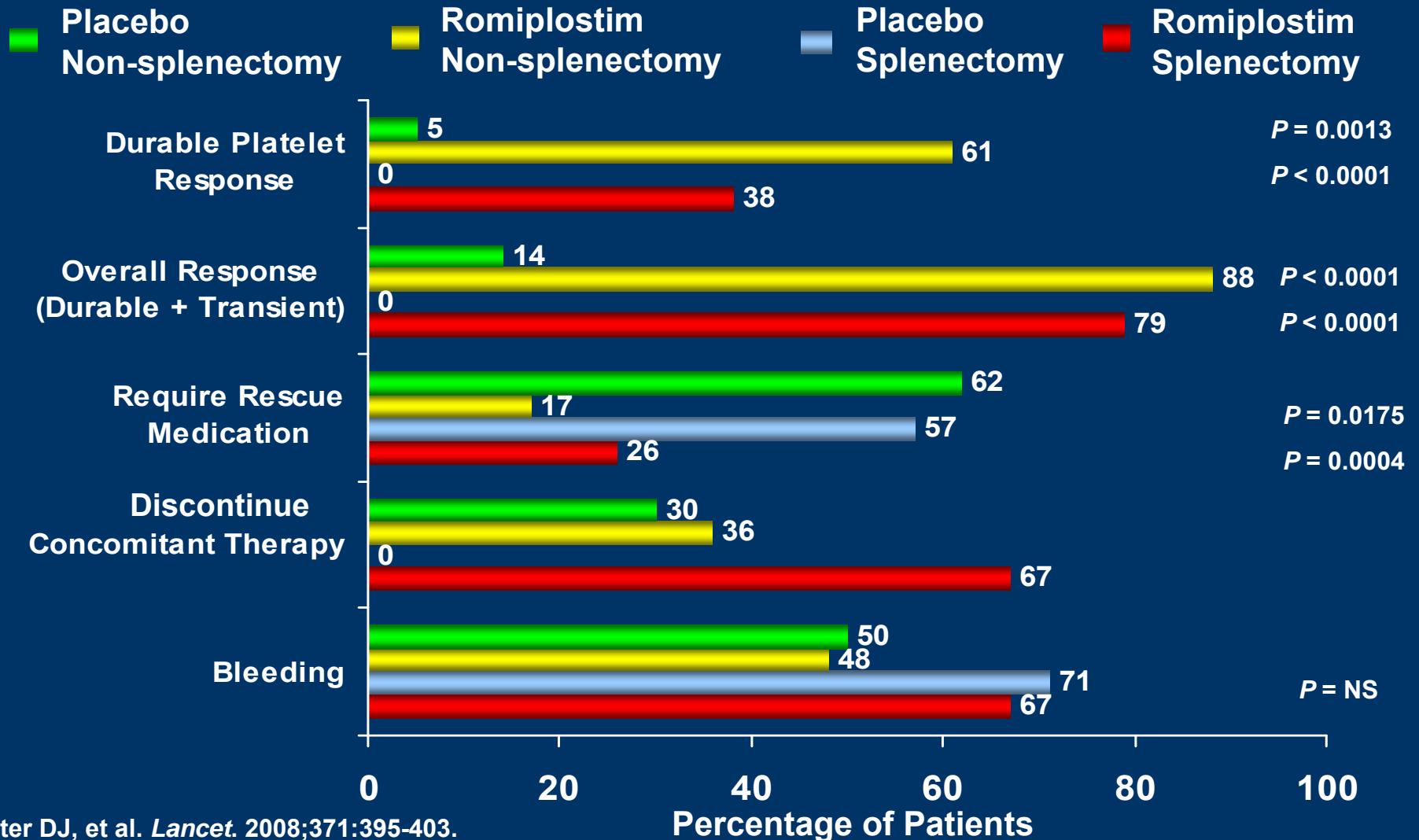
SQ = subcutaneously.

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

# Romiplostim in Chronic ITP

	Splenuetomized		Non-Splenuetomized	
	Placebo (n = 21)	Romiplostim (n = 42)	Placebo (n = 21)	Romiplostim (n = 42)
Age range, y	56 (26–72)	51 (27–88)	46 (23–88)	51 (21–80)
Baseline platelet (x10 <sup>9</sup> /L)	15 (2–28)	14 (3–29)	19 (5–31)	19 (2–29)
Duration of ITP, y	8.5	7.75	1.6	2.2
≥3 prior therapies	20 (95%)	39 (93%)	5 (24%)	15 (37%)
Patients on concurrent medication for ITP	6 (29%)	12 (29%)	10 (48%)	11 (27%)

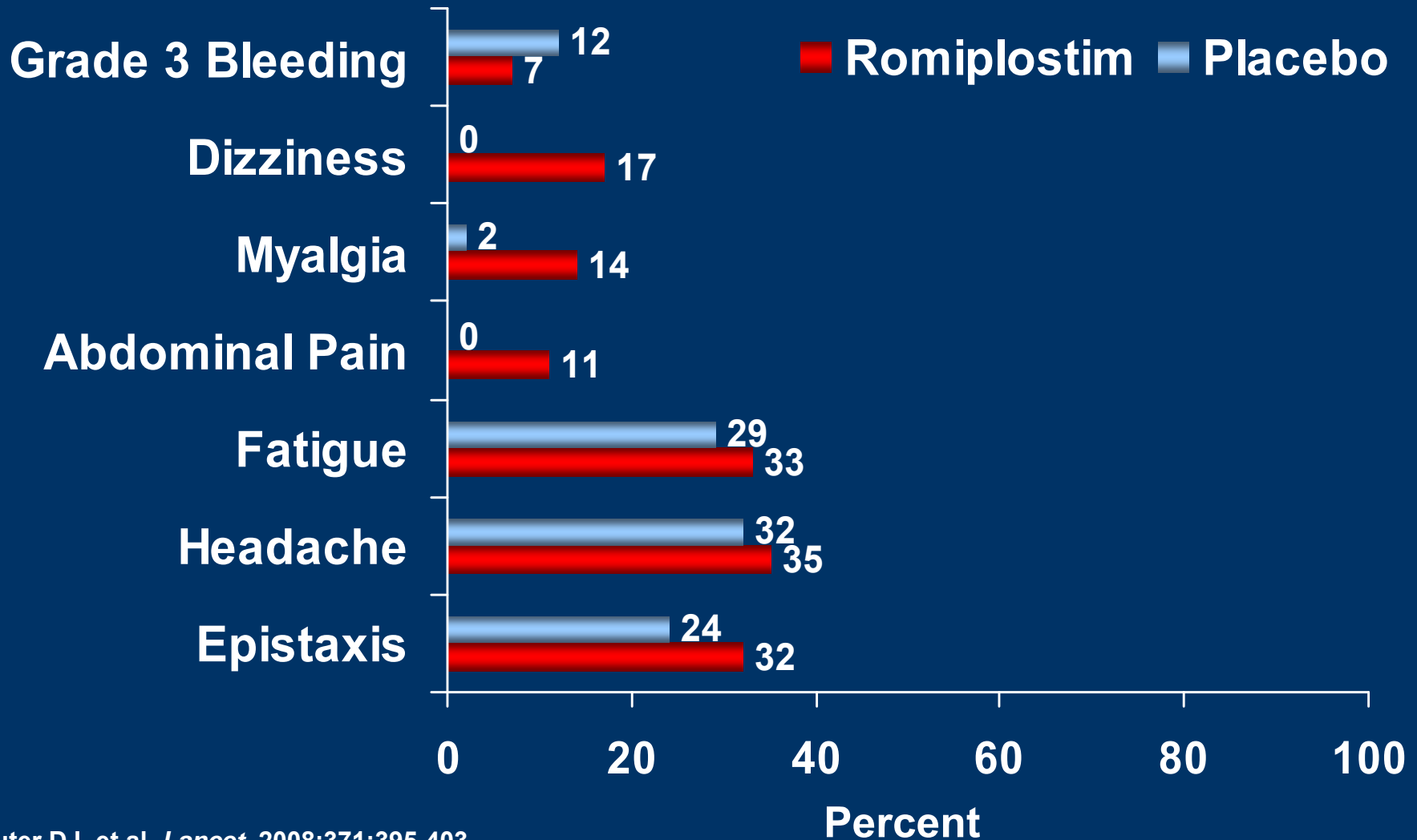
# Romiplostim Efficacy



# Romiplostim Adverse Effects

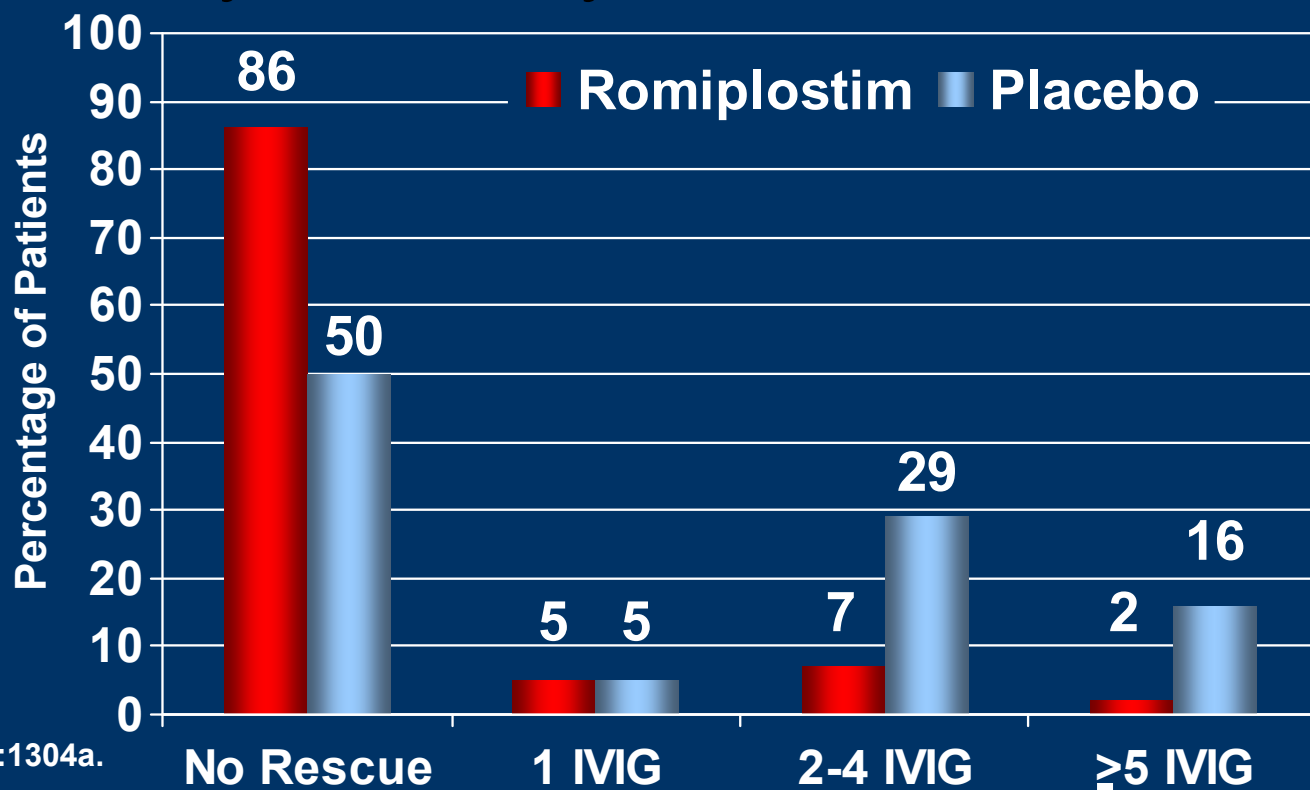
<b>Fatal or Treatment-related SAE</b>	<b>Placebo (n = 41)</b>	<b>Romiplostim (n = 84)</b>
Cerebral hemorrhage	1	0
Atypical pneumonia	1	0
Pulmonary embolism	1	0
Intracranial hemorrhage (died 2 weeks after discontinued)	0	1
Elevated bone marrow reticulin (not consistent with diagnosis of myelofibrosis improved after discontinued)	0	1
Thrombosis	0	2

# Romiplostim Adverse Effects



# Immunoglobulin Use in ITP Patients Receiving Romiplostim

- Immunoglobulin as rescue
  - Bleeding/wet purpura platelet count  $<10 \times 10^9/L$
  - When medically necessary

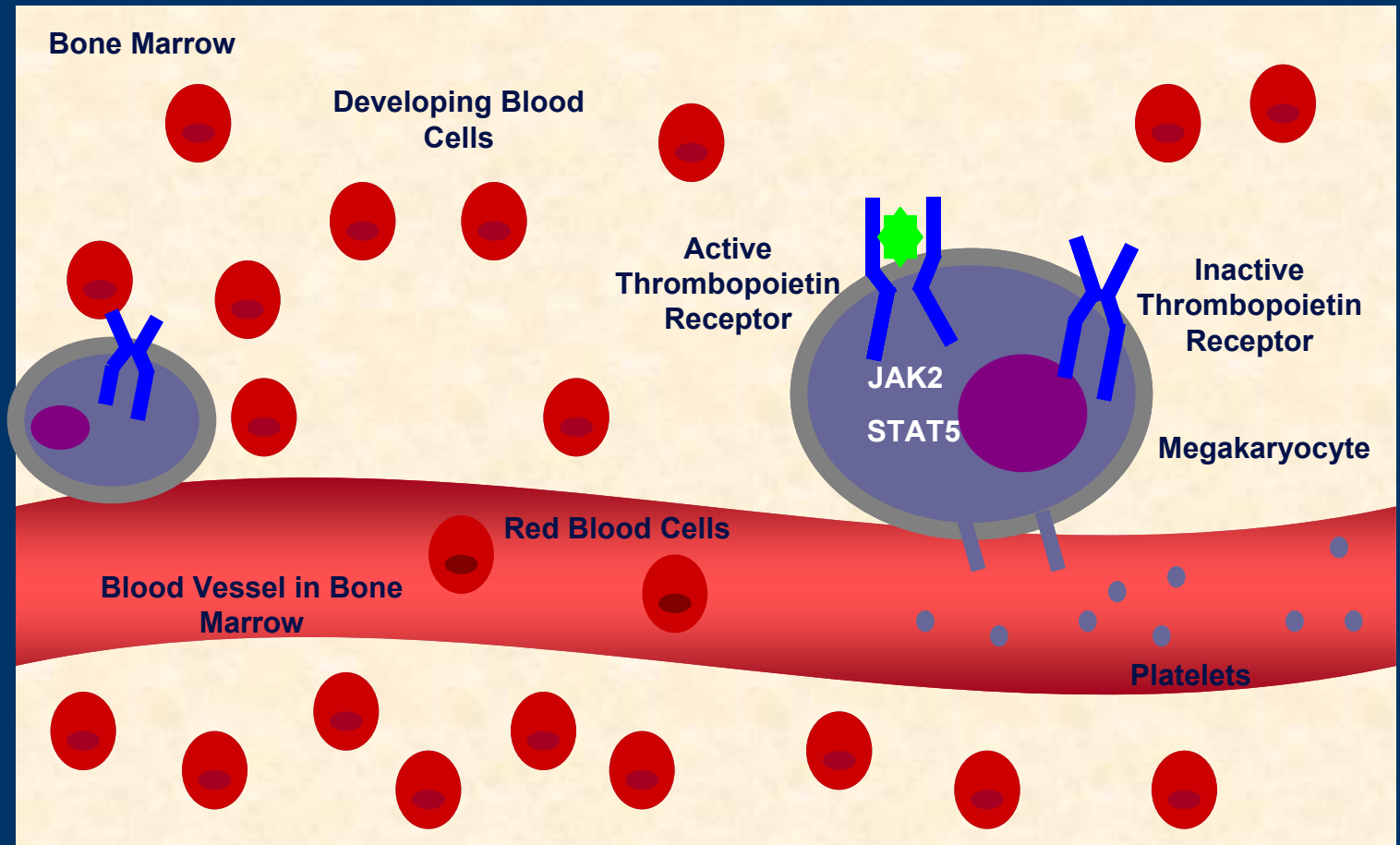


# Eltrombopag, Promacta®



Nonpeptide  
Thrombopoietin  
Receptor  
Agonist

**AKR-501**



Bussel J, et al. *N Engl J Med.* 2006;355:1672-81.

Geddis AE, et al. *Science.* 2007;317:1689-90.

Kuter DJ. *Blood.* 2007;109:4607-16.

# Eltrombopag for Chronic ITP

## ■ Inclusion Criteria

- Age over 18 years
- 6-month history of ITP
- At least 1 prior therapy
- Platelet count  $<30 \times 10^9/L$

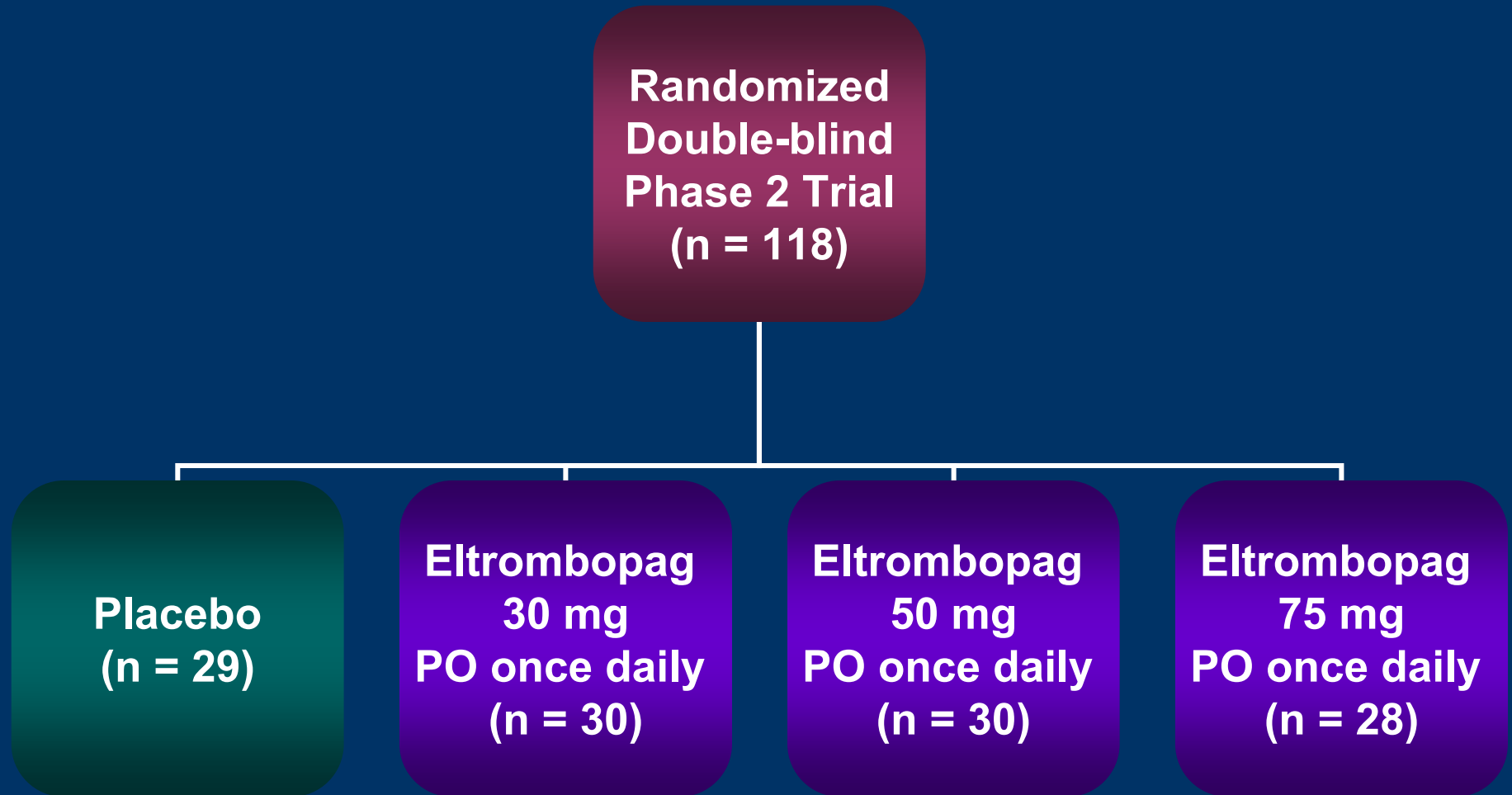
## ■ Primary Objective

- Platelet  $>50 \times 10^9/L$  on day 43

## ■ Secondary Objective

- Safety, health-related quality of life, bleeding

# Eltrombopag for Chronic ITP



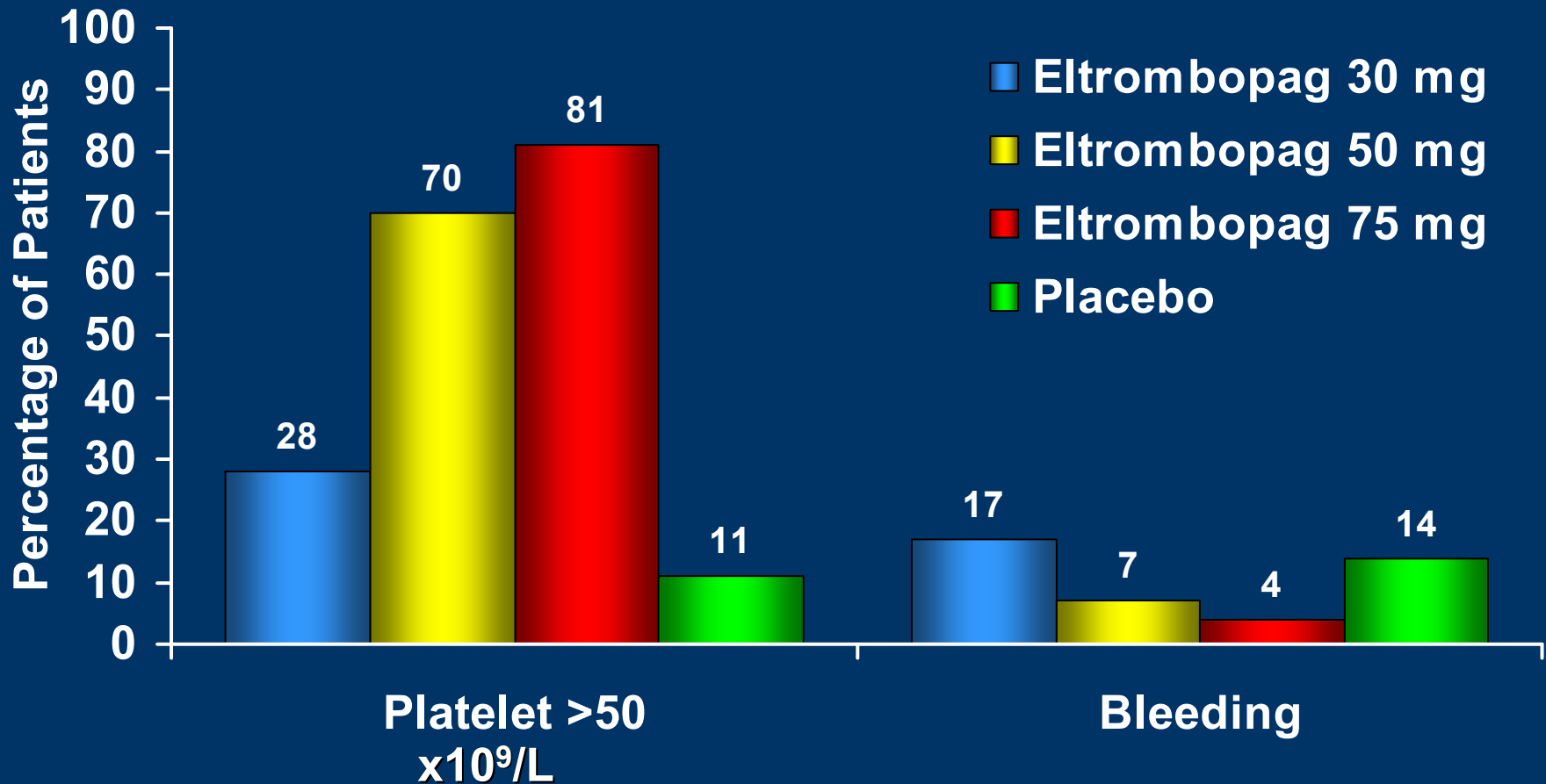
PO = by mouth.

Bussel J, et al. *N Engl J Med.* 2007;357:2237-47.

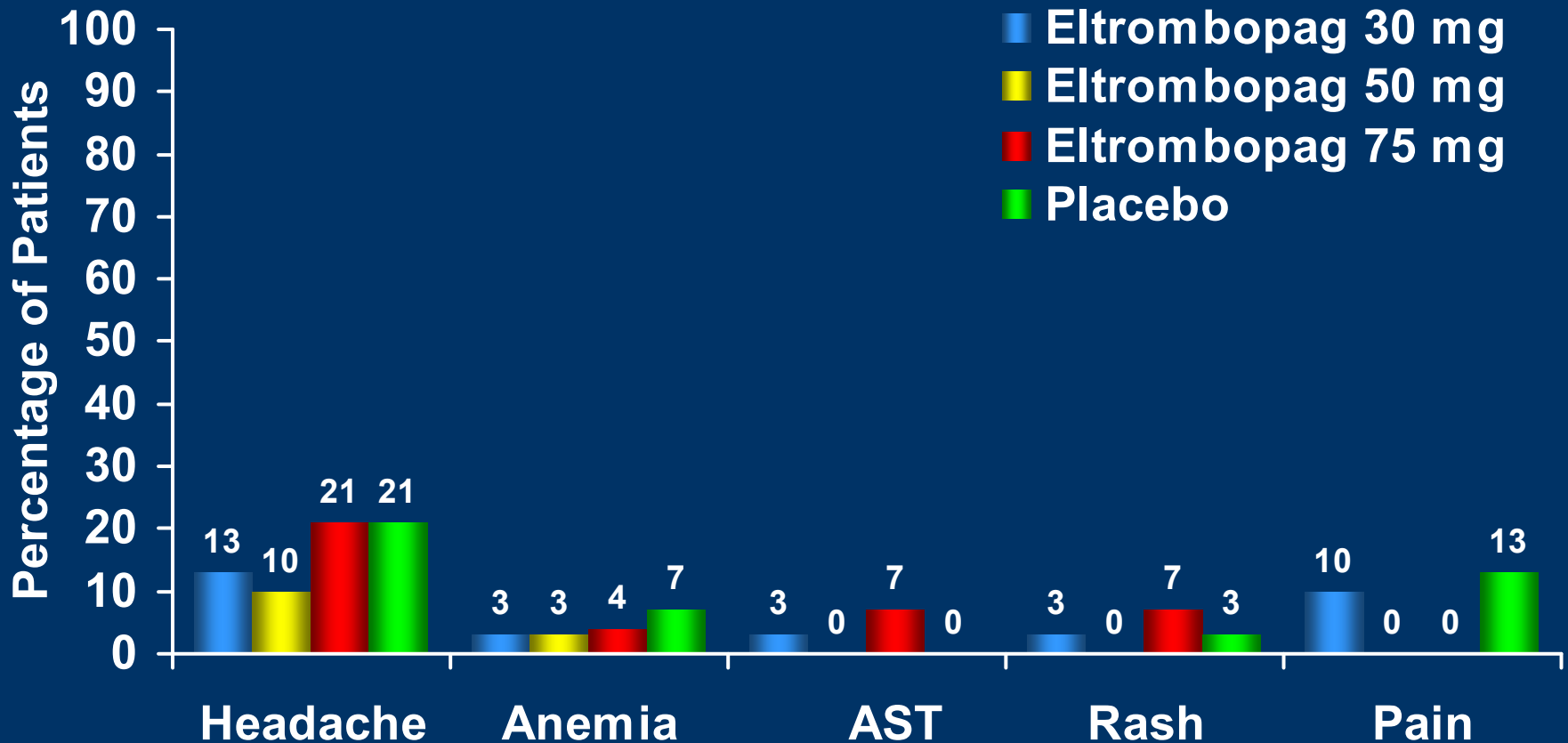
# Eltrombopag for Chronic ITP

	Placebo (n = 29)	Eltrombopag 30 mg (n = 30)	Eltrombopag 50 mg (n = 30)	Eltrombopag 75 mg (n = 28)
Age range, y	42 (18-85)	51 (23-79)	45 (23-81)	55 (18-85)
Platelet $\leq 15 \times 10^9/L$	48%	50%	40%	54%
Splenectomy	48%	50%	50%	39%
Concomitant medication for ITP	21%	33%	40%	36%
$\geq 3$ prior therapies	48%	57%	60%	39%

# Eltrombopag Efficacy



# Eltrombopag Adverse Effects



AST = aspartate aminotransferase.

Bussel J, et al. *N Engl J Med.* 2007;357:2237-47.

# Eltrombopag EXTEND Study

## Stage 1

4-week washout; eltrombopag 50–75 mg/day  
(n = 109)

## Stage 2

Tapering and/or discontinue ITP concomitant meds

## Stage 3

Titration eltrombopag (25–75 mg) to maintain platelet counts

Platelet >  
50 x 10<sup>9</sup>/L

## Stage 4

Treat with eltrombopag as long as patient benefits

# Eltrombopag for Chronic ITP

- Platelets  $>50 \times 10^9/L$  80%
- Platelets  $>400 \times 10^9/L$  19%
- Sustained platelets  $>50 \times 10^9/L$ 
  - x 10 weeks 54%
  - x 25 weeks 24%
- Discontinued all immunosuppression 35%
- Serious adverse events 13%
- Thromboembolism in 3 patients

# Chronic ITP Summary

## Platelet $< 30 \times 10^9/L$

**Prednisone**  
**Methylprednisolone**  
**Dexamethasone**

**Intravenous Immune Globulin**  
**Rho D Immune Globulin**

**Persistent, Chronic ITP**  
**for 6 months**

**Splenectomy**  
**SR = 60–70 %**

**Rituximab**  
**SR = 40%**

**Cyclophosphamide**  
**CR = 39%**  
**Cyclosporine**  
**CR = 38%**

**Romiplostim**  
**SR = 49%**  
**Eltrombopag**  
**SR = 24%**

**Danazol**  
**Azathioprine**  
**Vinca Alkaloid**  
**PR = 50 – 71%**