Púrpura Trombocitopénico Inmune

Desafíos Terapéuticos

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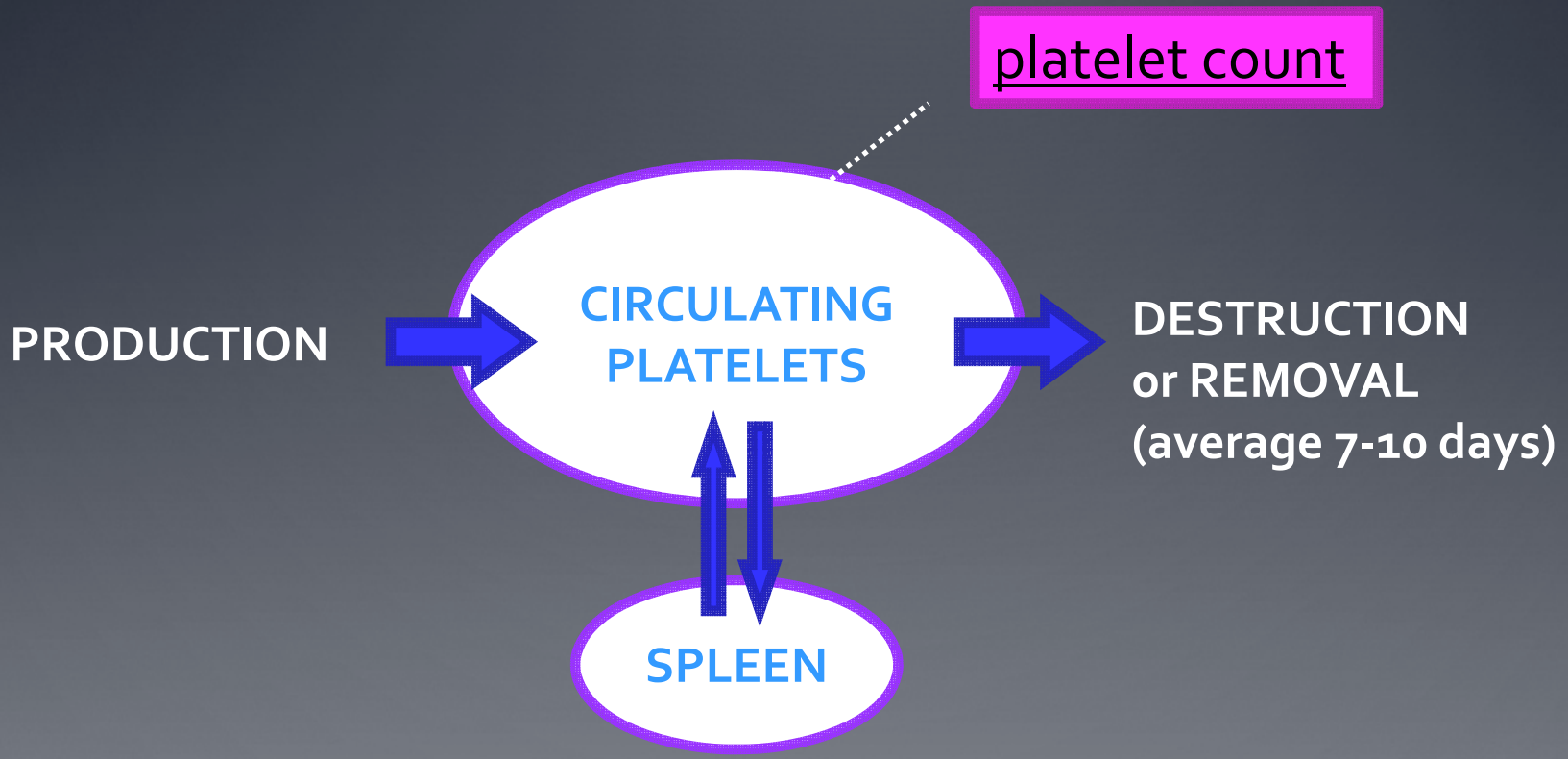
Clínica Las Condes

Platelets

1. Cell fragment without nucleus
2. Cytoplasmic fragments of megakarycytes
3. Spheric shape, diameter between **1 - 4µm** and 1µm in thickness
4. Newly formed platelets are bigger and have higher haemostatic activity than mature circulating platelets
5. First step of haemostasis constituting "white" clot and during the entire coagulation process

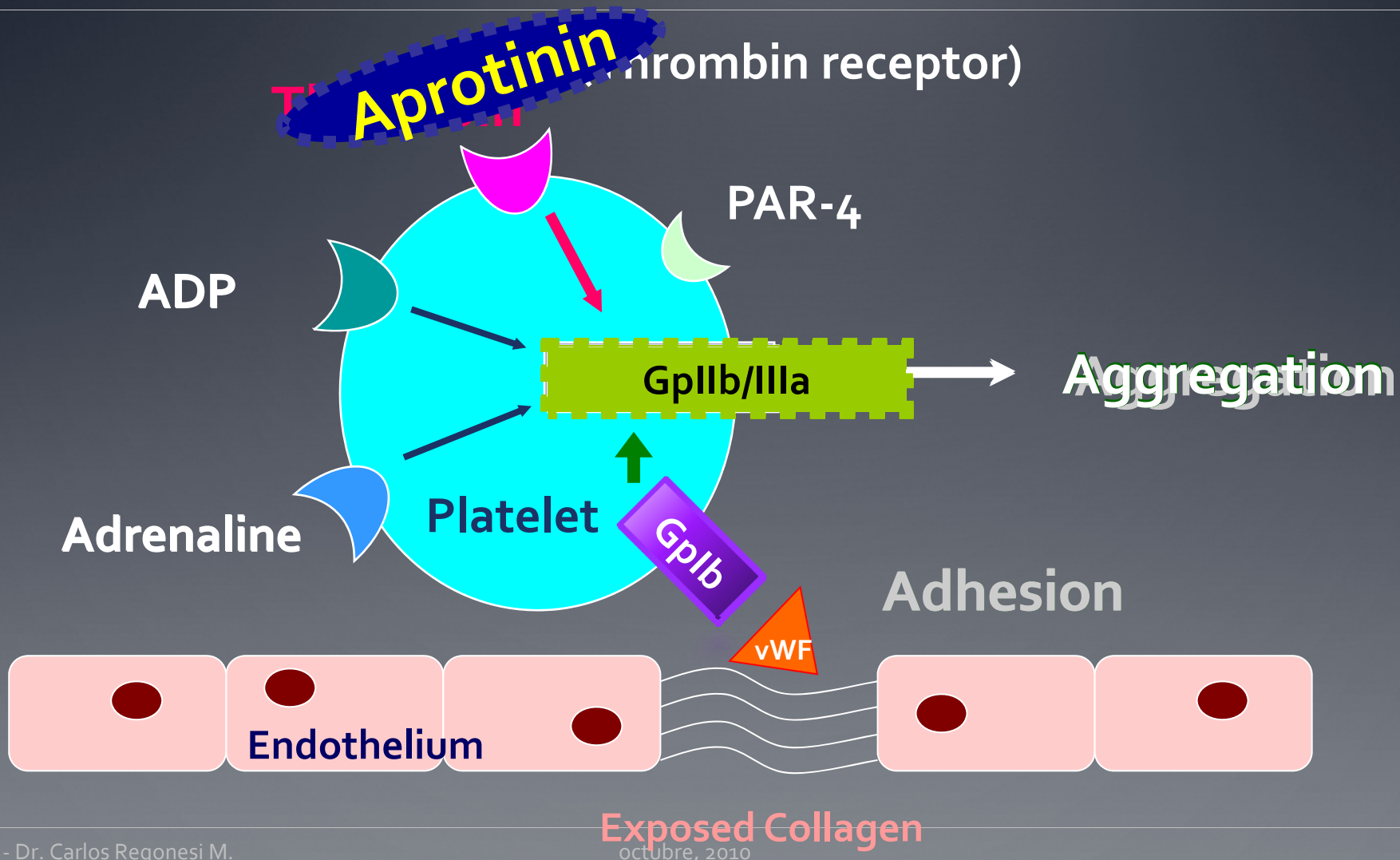
Platelets in the circulation: Influx, efflux, and redistribution



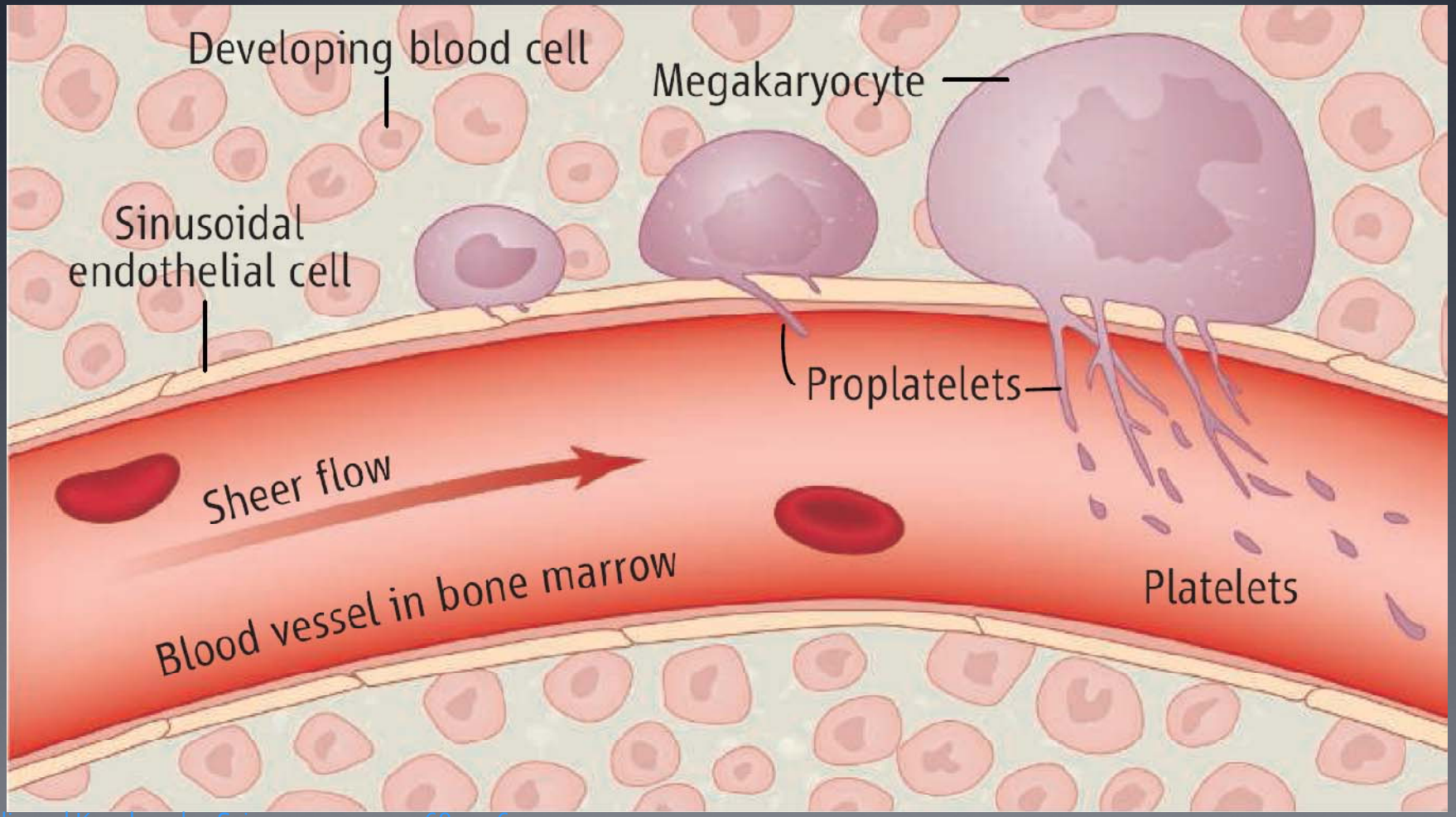
Contents of Platelets

	Content	Function
α-Granule	Fibrinogen	Adhesion, aggregation, coagulation
	Fibronectin	Adhesion
	Vitronectin	Adhesion
	von Willebrand factor	Adhesion
	Thrombospondin	Adhesion, aggregation, cell proliferation
	Platelet-derived growth factor	Growth of smooth muscle
	Transforming growth factor-β	Control of cellular proliferation
	Platelet factor 4	Growth
	Factor V	Coagulation
	High-molecular-weight kininogen	Coagulation
	Factor XI	Coagulation
	Protein S	Anticoagulation
	Plasminogen-activator inhibitor-1	Coagulation
Dense (δ) granule	Adenosine diphosphate	Platelet activation and recruitment
	Adenosine triphosphate	Leukocyte activation
	Serotonin	Vascular tone
	Calcium	Activation and coagulation

Platelet Activation



Formation and Release of Platelets



Geddis and Kaushansky. Science 2007; 317:1689 - 1691

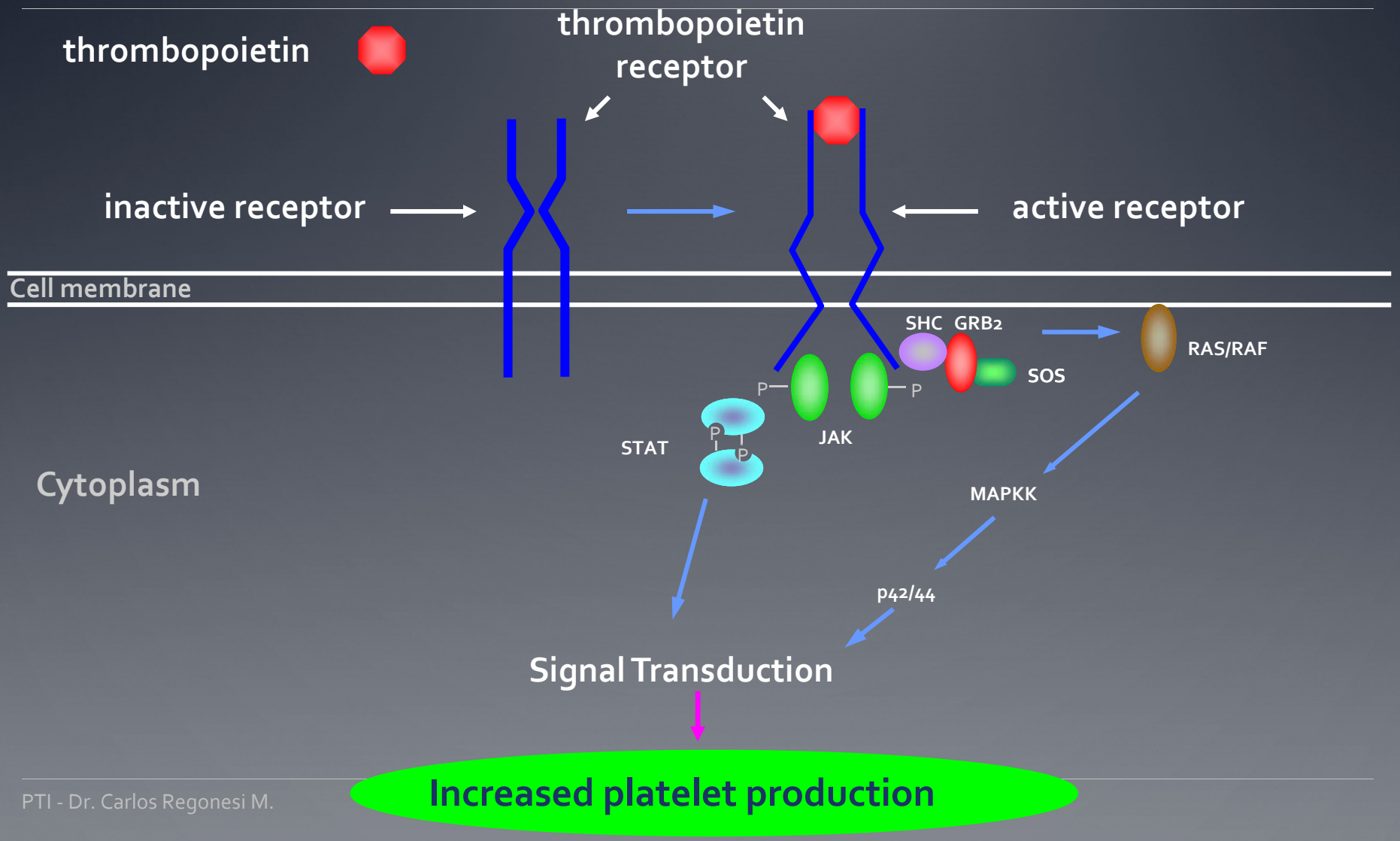
Thrombopoeisis

- Estimated one megakaryocyte produces approx. **1000-5000 platelet a day**
- In adults, normal platelet production **~35,000-50,000/microL** (i.e.,100 x 109/day).
- Can be increased 10 times if megakaryocytes are stimulated
- Average adult human must produce $1x10^{11}$ platelets daily
- Thrombopoeisis dependant on marrow microenvironment
- Cell surface and soluble hematopoietic growth factors

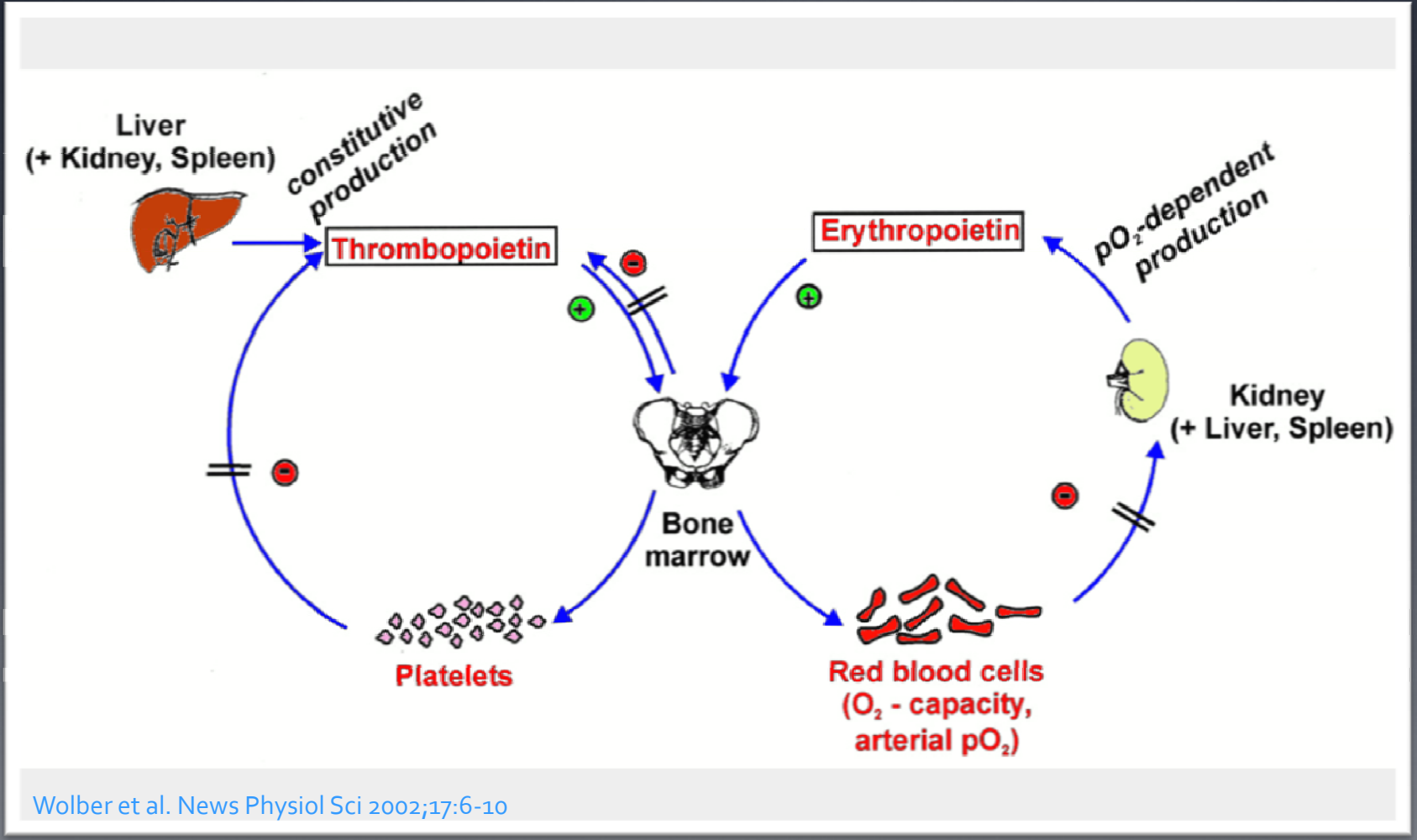
Thrombopoeisis

- Endothelial cells: big role in the cellular microenvironment
- Fibronectin engagement of integrin $\alpha 4\beta 1$ stimulates megakaryopoiesis
- Vitronectin engagement of integrin $\alpha V\beta 3$ enhances platelet formation
- Many hematopoietic growth factor: (IL)-3, GM-CSF, IL-6, IL-11
- The 2 most important SCF and Tpo
- The liver is the richest source of Tpo production

TPO acts through c-Mpl (TPO-receptor)



Different regulation of plasma TPO concentrations



Wolber et al. News Physiol Sci 2002;17:6-10

Evaluation of the thrombocytopenic patient

- **Always** review the blood smear and visit the patient!!!
  - Pseudothrombocytopenia? Platelets and white cells abnormal?
  - Identify abnormalities that might suggest a specific cause of thrombocytopenia (splenomegaly, skeletal deformities, etc)
- **Consider** the clinical setting and history!!!
  - Pregnant women
  - Patients on medications (eg, heparin)
  - Recent infection
  - Relatives with thrombocytopenia
- **Ask** for additional tests only if consistent with the above findings!!!
  - Beware: thrombocytopenia may be the first manifestation of HIV and may occur early in the infection

ITP

- Acquire auto-inmune disease
- Platelet destruction
- Impaired megakaryocyte maturation
- Impaired platelet production
- 30 new cases per million annually
- Most common in women and elderly patients
- Signs of bleeding usually minor
- #1 cause of isolated thrombocytopenia in otherwise healthy young persons

ITP in the 21st Century: Plenty of New Information

- Terminology
- Definition
- Epidemiology
- Pathophysiology
- Treatment

Old Terminology

ITP = Idiopathic Thrombocytopenic Purpura

- The defining condition is purpura
- Absence of recognizable causes and unknown pathophysiology

New Terminology

ITP = Primary Immune Thrombocytopenia

- The defining condition is thrombocytopenia
  - Bleeding symptoms are absent or minimal in a large proportion of cases
- Emphasis on the immune-mediated mechanisms of the thrombocytopenia
- The acronym ITP was retained because of:
  - Its widespread use
  - Its utility for literature searches

Rodeghiero F, et al. *Blood.* 2009;113(11):2386-2393.

ITP in the 21st Century: Plenty of New Information

- Terminology
- **Definition**
- Epidemiology
- Pathophysiology
- Treatment

ITP: Definition

- Isolated thrombocytopenia with otherwise normal CBC and peripheral smear
- No other conditions or factors that can cause (or be associated with) thrombocytopenia

Rodeghiero F, et al. *Blood.* 2009;113(11):2386-2393.

Old Definition of Thrombocytopenia

Platelet count less than $150 \times 10^9/L$

- Based on statistical definition of normality

Rodeghiero F, et al. *Blood.* 2009;113(11):2386-2393.

New Definition of Thrombocytopenia

Platelet count less than $100 \times 10^9/L$

- Based upon a prospective cohort of otherwise healthy subjects with a platelet count between 100 and $150 \times 10^9/L$
  - Showed that the 10-year probability of developing more severe thrombocytopenia (persistent platelet count below $100 \times 10^9/L$) is only 6.9%

Rodeghiero F, et al. *Blood.* 2009;113(11):2386-2393.

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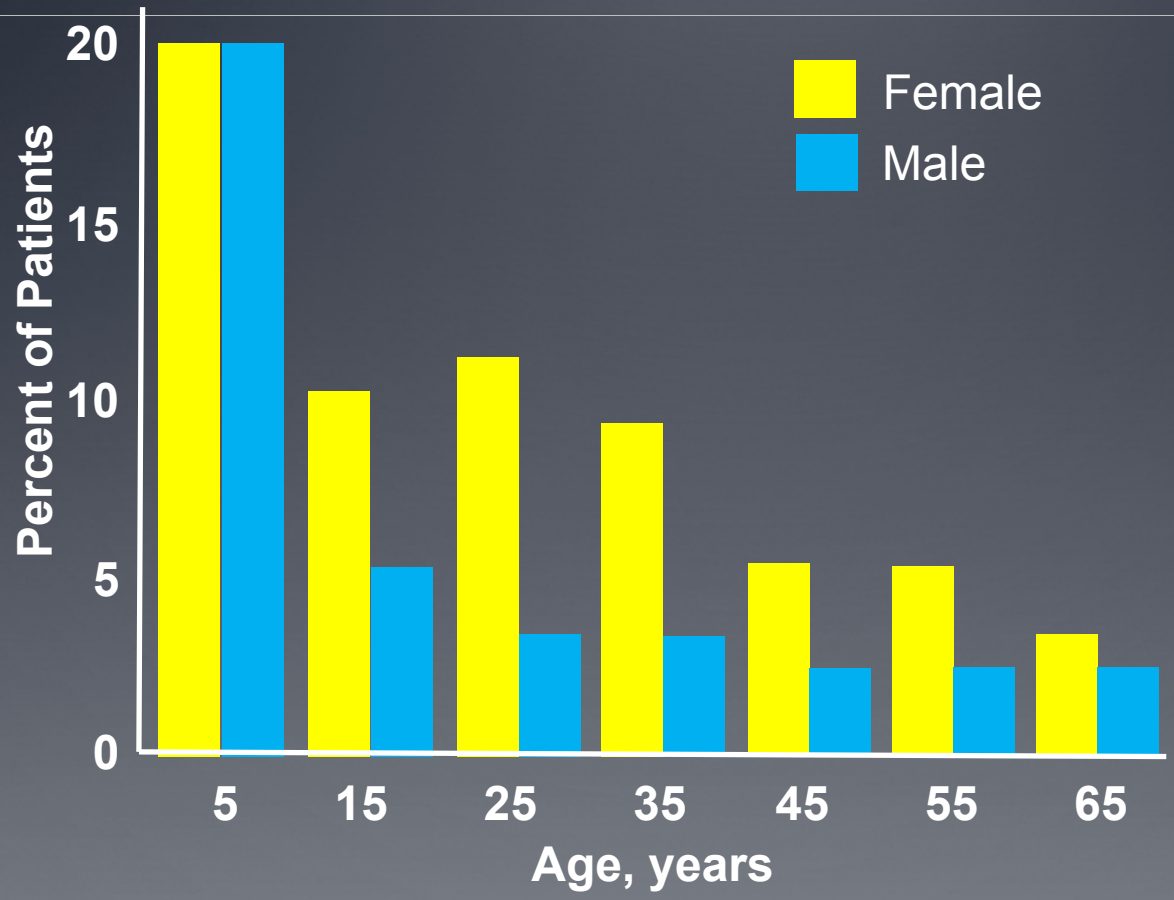
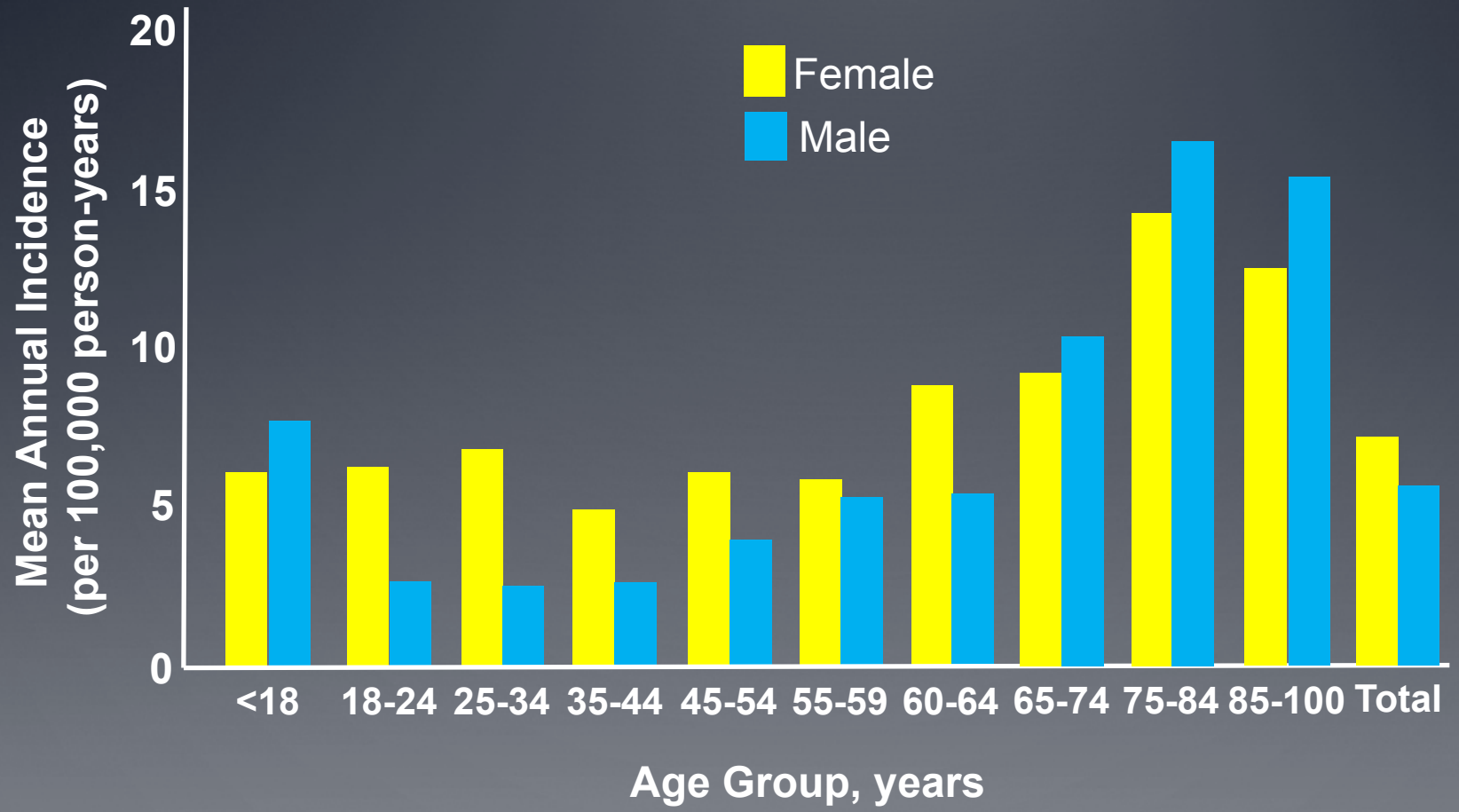
Demographics of ITP: 1960-1985



Incidence rate is 1-12.5/10^5/yr

George JN, et al. *Williams Hematology*, 5th ed, McGraw-Hill, New York, 1995:1315-1355.

Demographics of ITP: 1990-2005



Schoonen WM, et al. *Br J Haematol*. 2009;145(2);235-244.

ITP in the 21st Century: Plenty of New Information

- Terminology
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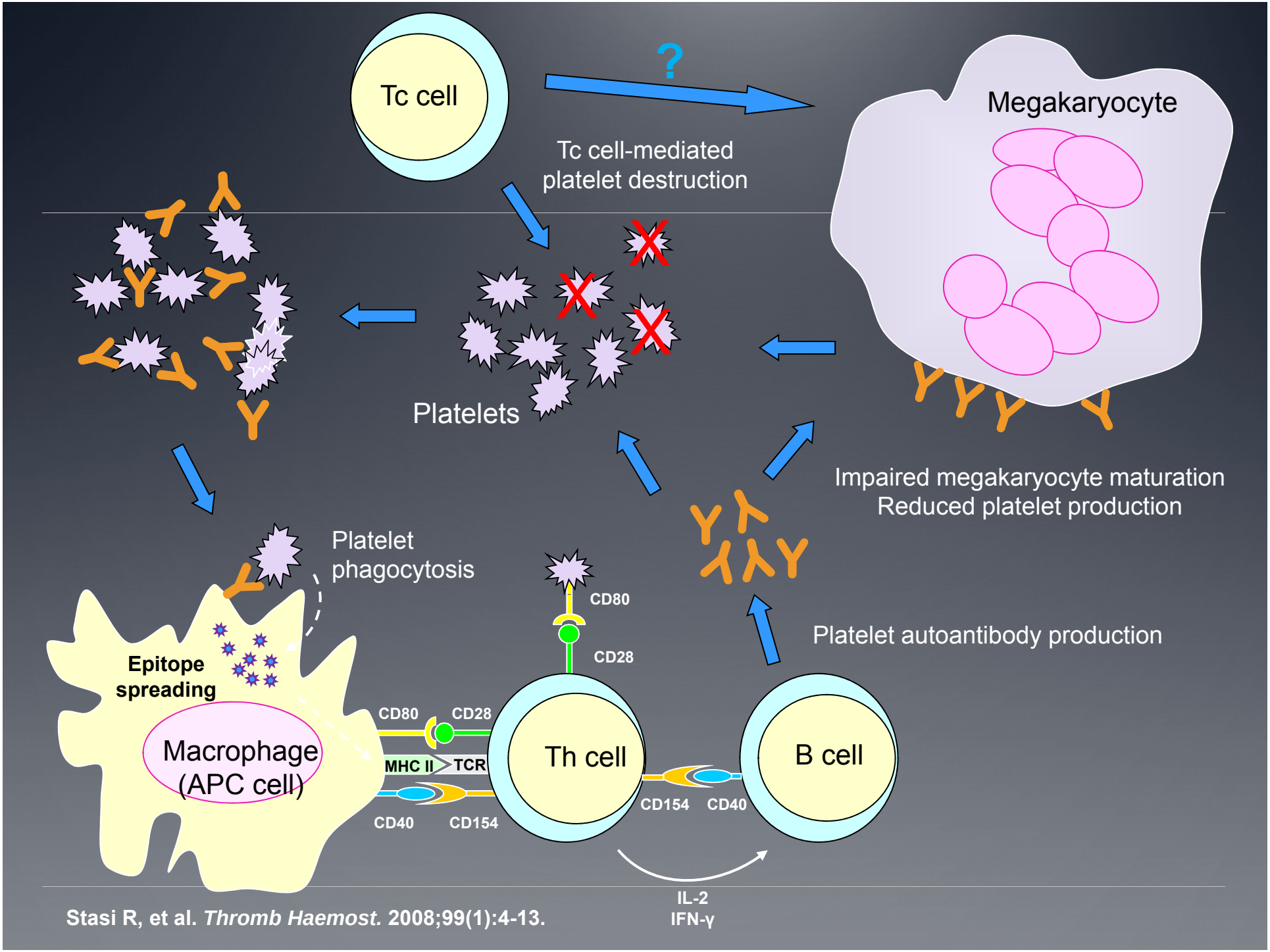
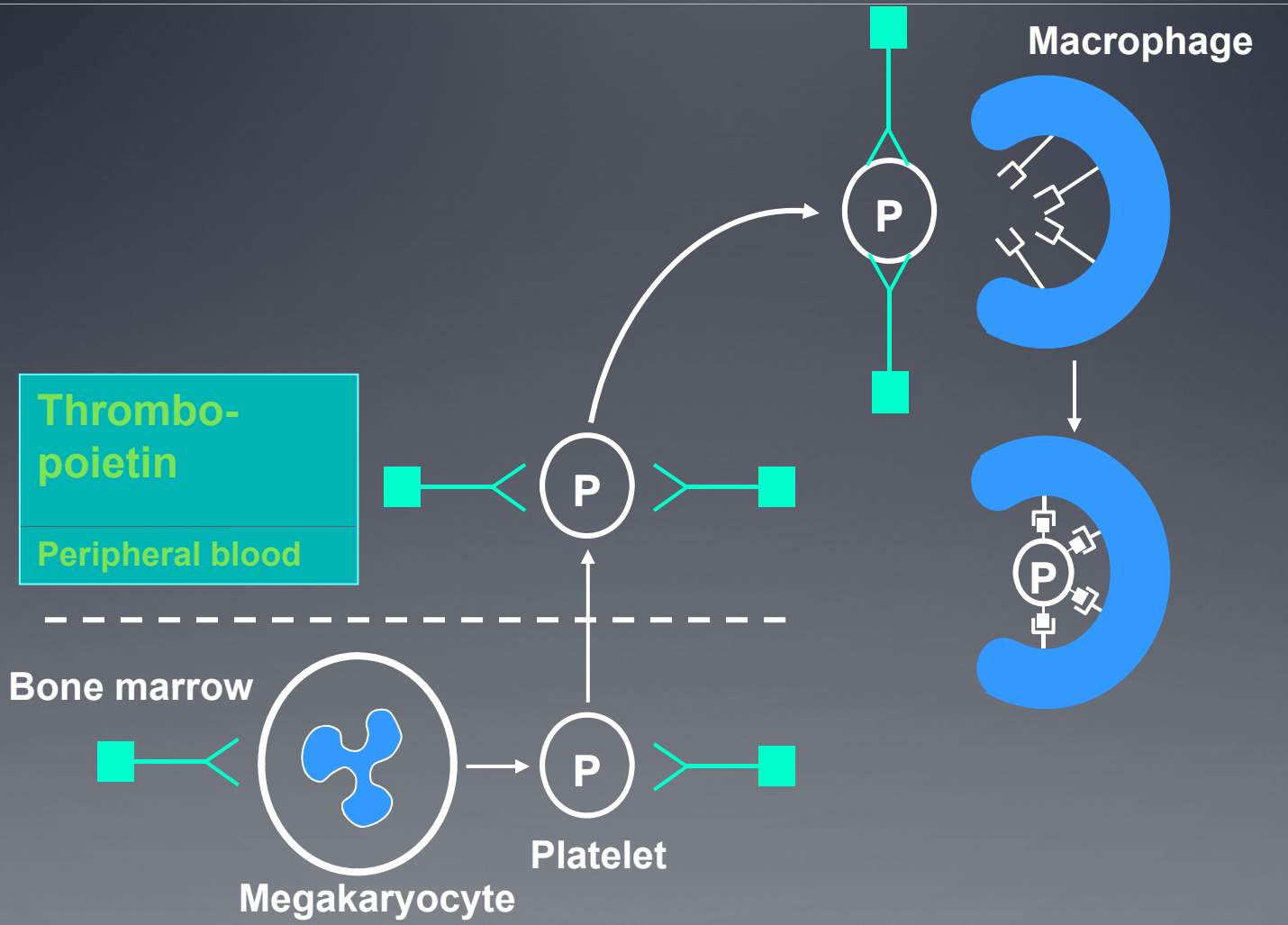
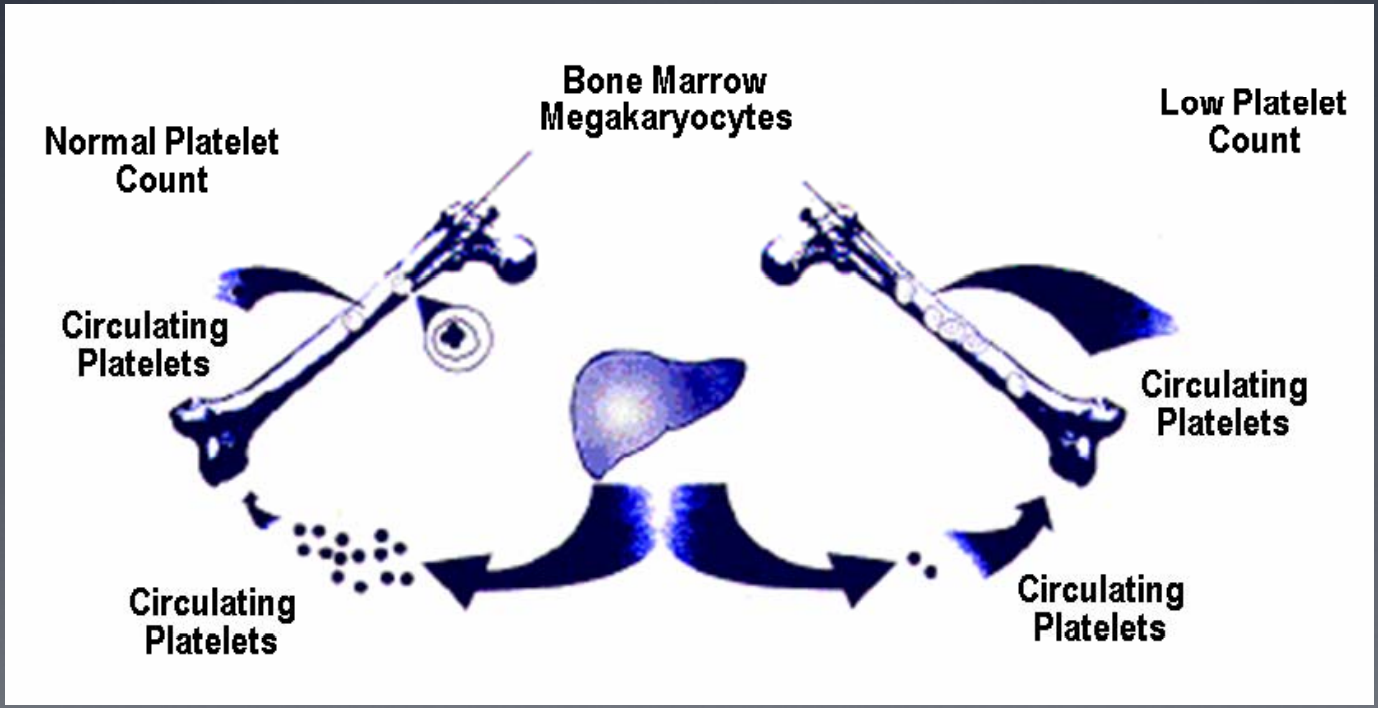


Stasi R, et al. *Thromb Haemost.* 2008;99(1):4-13.

Pathophysiology of ITP

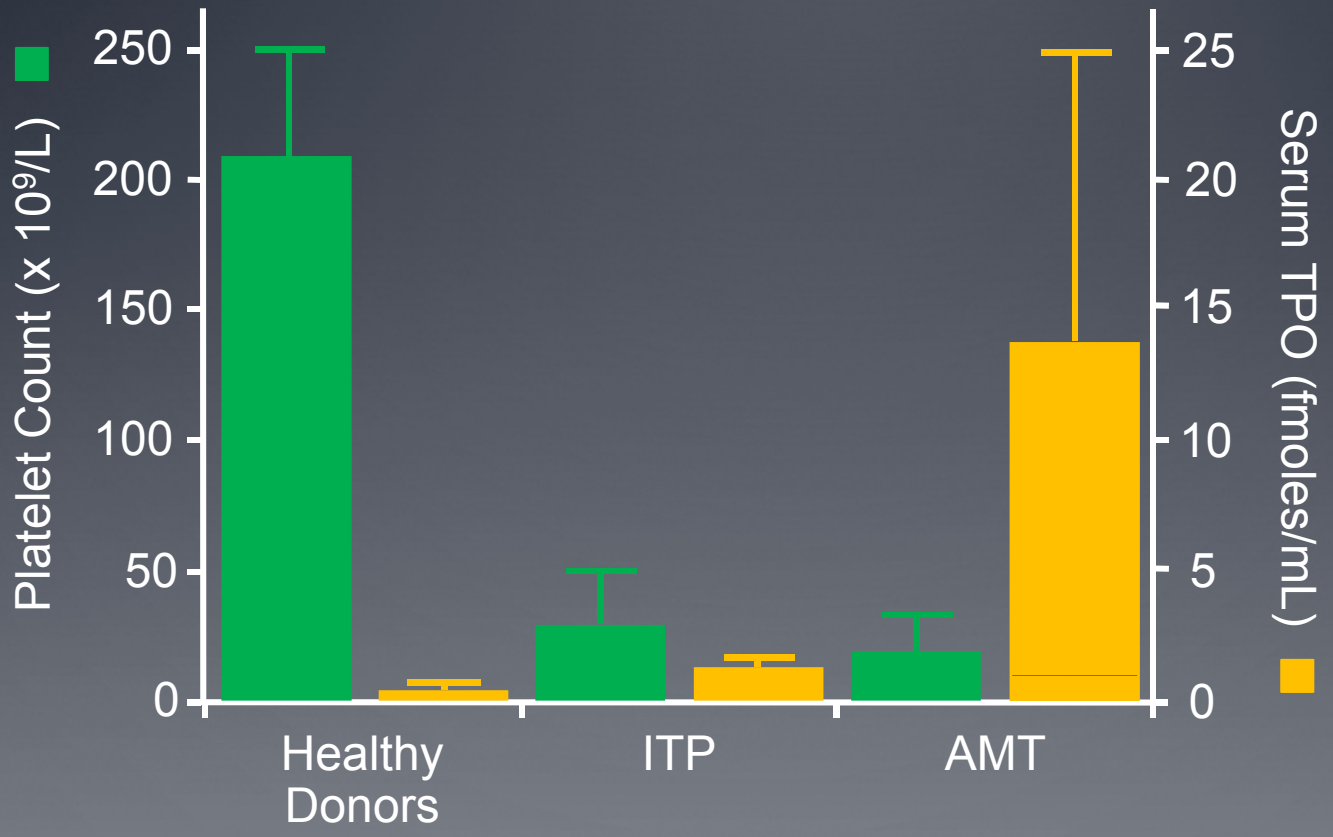


Thrombopoietin Physiology



Kuter DJ, et al. *Proc Natl Acad Sci U S A*. 1994;91:11104-11108.

Thrombopoietin Levels in ITP



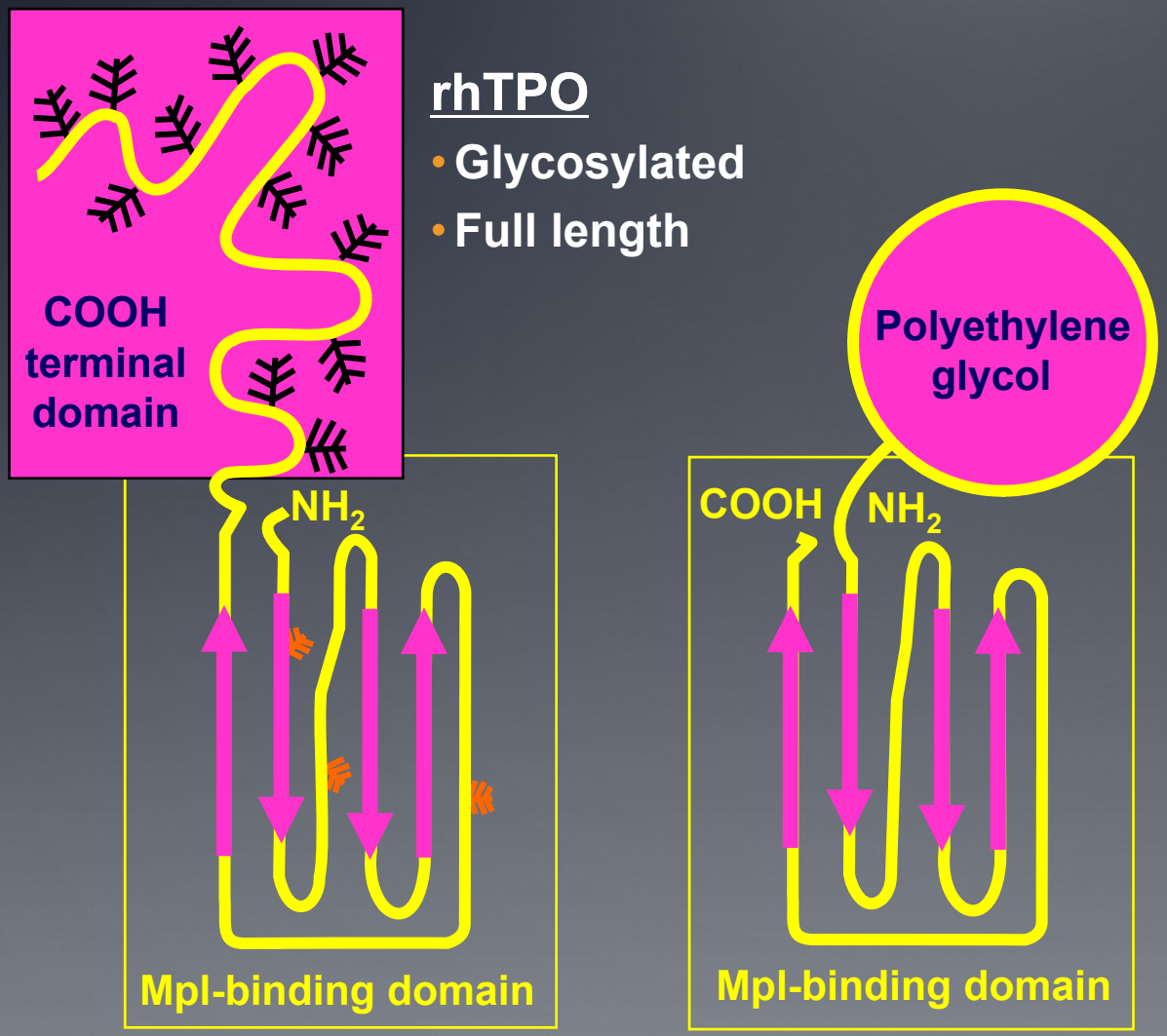
Mukai HY, et al. *Thromb Haemost.* 1996;76:675-678.

Platelet Production Is Suboptimal in ITP Patients

- Autoantibodies inhibit megakaryocyte growth and promote apoptosis[1,2]
- Autologous ^{111}In-platelet studies show platelet production ≤ normal in 2/3 pts
- TPO levels normal in 75% of ITP patients (relative TPO deficiency)
- Damaged or dysfunctional megakaryocytes in marrow[3]

1. Chang M, et al. *Blood.* 2003;102(3):887-895. 2. McMillan R, et al. *Blood.* 2004;103(4):1364-1369. 3. Houwerzijl EJ, et al. *Blood.* 2004;103(2):500-506.

rhTPO and PEG-rHUMGDF



rhTPO

- Glycosylated
- Full length

PEG-rHuMGDF

- Not glycosylated
- Truncated
- Additional polyethylene glycol moiety

Kuter DJ, et al. *Blood.* 2002;100(10):3457-3469.

ITP: Pathophysiology

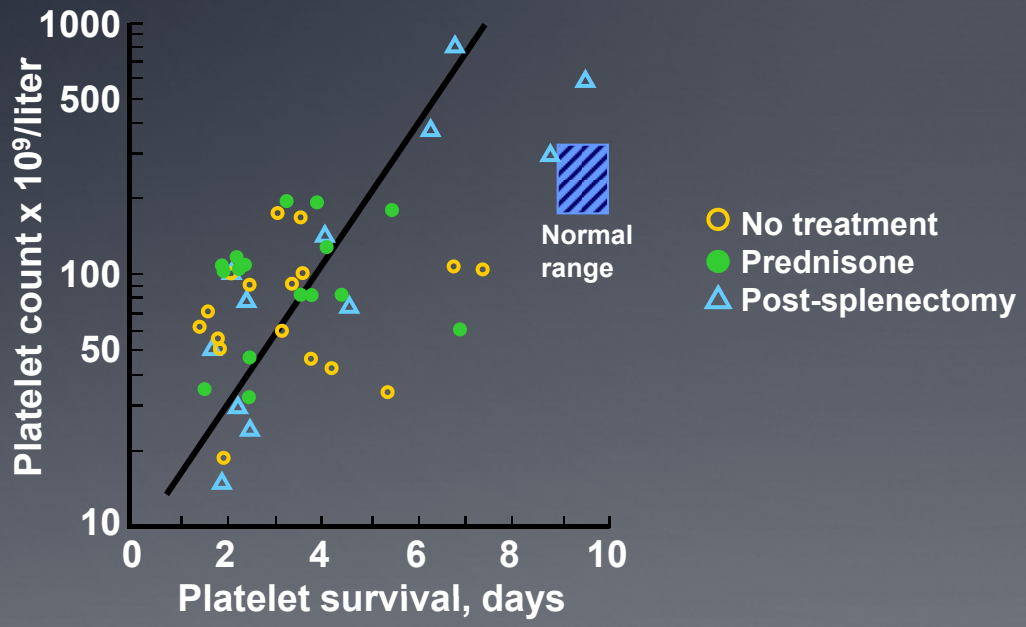
- Mechanisms of platelet destruction
- Role of antibodies (B cells)
- Role of T cells
- Triggering factors: Infections

Stasi R, et al. *Thromb Haemost.* 2008;99(1):4-13.

Platelet Kinetics in ITP

Decreased Platelet Survival

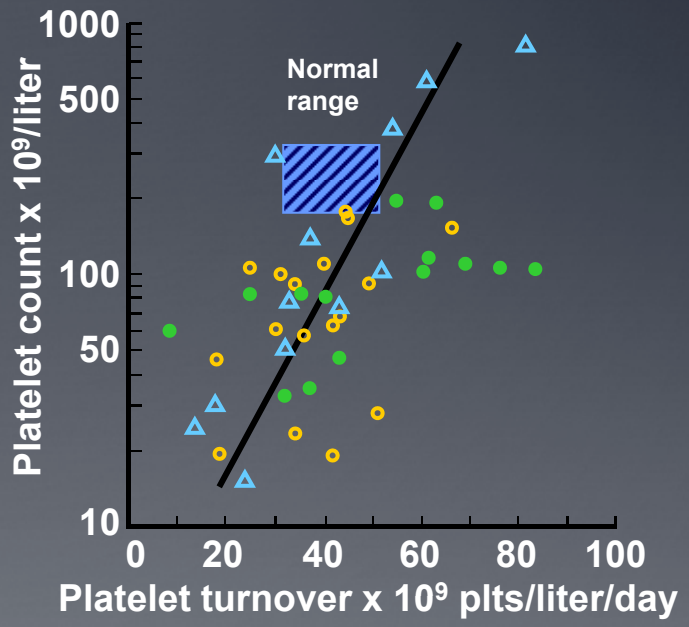
Radiolabeled <u>autologous</u> platelets



<u>Heterologous</u> platelets are cleared much faster (minutes-hours)

Impaired Platelet Production

Production ≈ Platelet count / Platelet survival



Most patients have <u>inappropriately low or normal</u> rates of platelet production

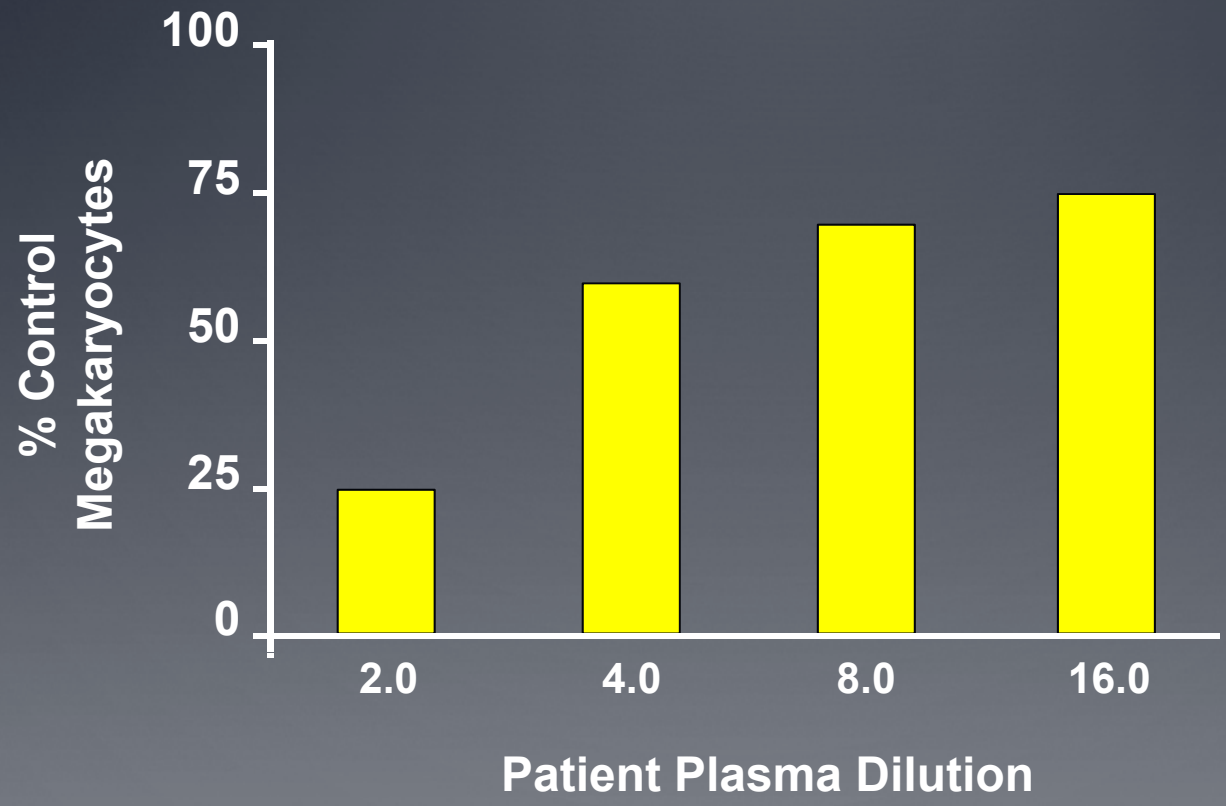
Ballem PJ, et al. *J Clin Invest*. 1987;80(1):33-40.

Mechanisms of Thrombocytopenia in ITP

Increased platelet destruction

Decreased platelet production

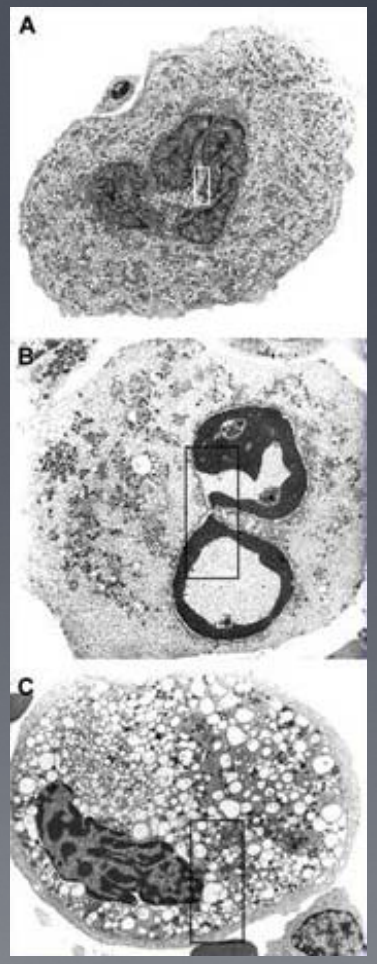
Megakaryocyte Production by ITP Plasma Dilutions



McMillan R, et al. *Blood.* 2004;103(4):1364-1369.

Megakaryocytes in the Bone Marrow

- Electron micrographs, showing normal megakaryocytes (A) versus the apoptotic damaged megakaryocytes (B, C) present in the bone marrow of patients with ITP



Houwerzijl EJ, et al. *Blood.* 2004;103(2):500-506.

ITP: Clinical features

- occurs in any age or sex, but typically young female
- can be preceded by viral infection (particularly in children)
- signs and symptoms depend on platelet count
- onset usually insidious in adults

ITP: Diagnostic work-up

- **ITP IS A DIAGNOSIS OF EXCLUSION**
- **No** sensitive and specific test for ITP
- History and physical examination
- CBC with differential
- Peripheral smear
  - Pseudothrombocytopenia (caused by platelet clumping)
  - Giant platelets in congenital thrombocytopenia
  - Schistocytes in TTP, DIC or hemolysis
  - Megathrombocytes (large, immature platelets) common in ITP

ITP: Diagnostic work-up

- **Careful** examination of medication list
- **HIV and hepatitis C** serologies in patients with risk factors
- **H. pylori** testing in countries with a high background prevalence
- **Thyroid** function tests
- Bone marrow biopsy in selected patients
- **Avoid** unnecessary testing!!!

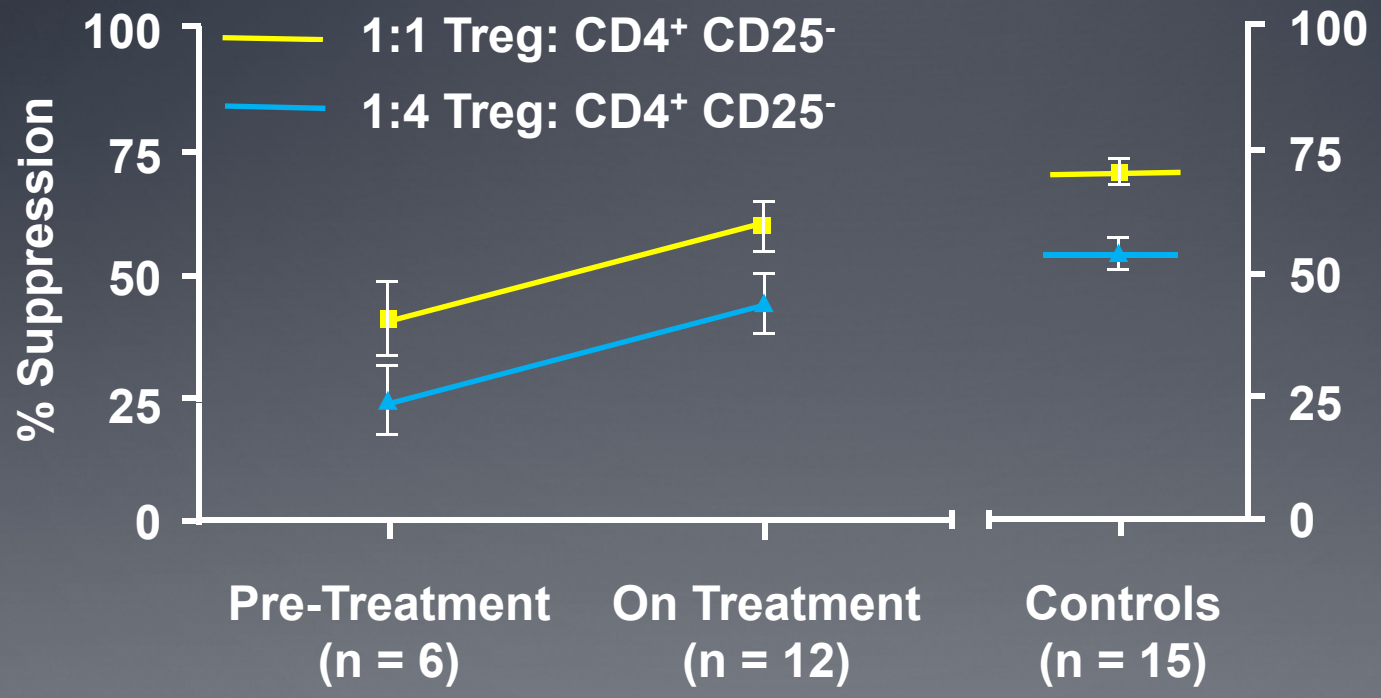
ITP: Diagnostic work-up

- Anti-platelet antibodies
  - Did not differentiate between pts with and without ITP in multiple retrospective studies
  - Sensitivity 49-66%
  - Specificity 78-92%
  - PPV 80-83%
- Not recommended by ASH and BCSH guidelines

ITP: Bone marrow aspirate/biopsy

- Indicated to evaluate for MDS
- Indications:
  - Age > 60
  - Other abnormal cell lines (WBC or RBC)
  - Lack of response to treatment (before splenectomy)
  - Red flags: Fever, weight loss, bone pain

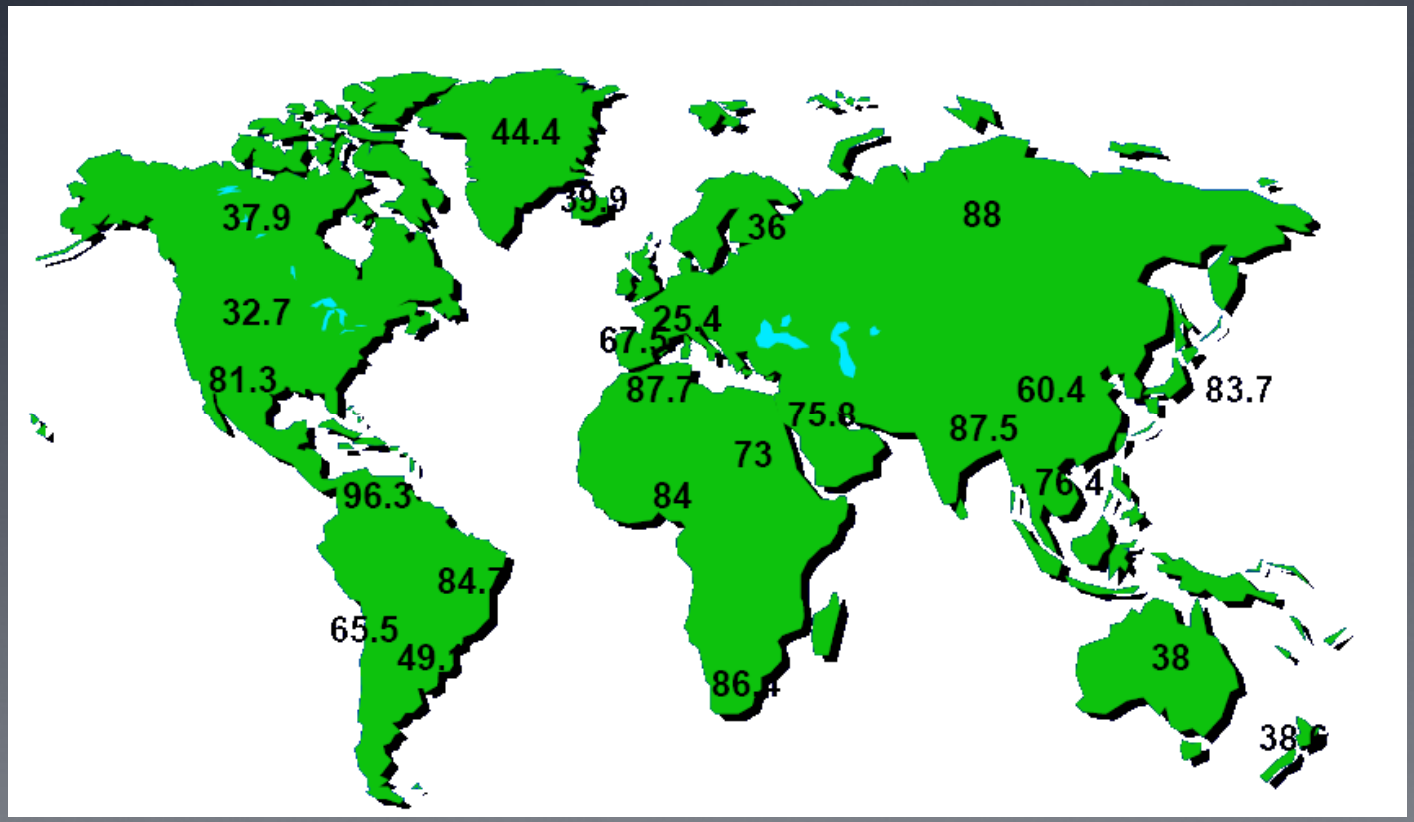
Improved Regulatory T Cell Activity in Patients with Chronic ITP Treated with Thrombopoietic Agents



Bao W, et al. *Blood*. 2009;114: Abstract 684.

Etiology: Helicobacter pylori Infection

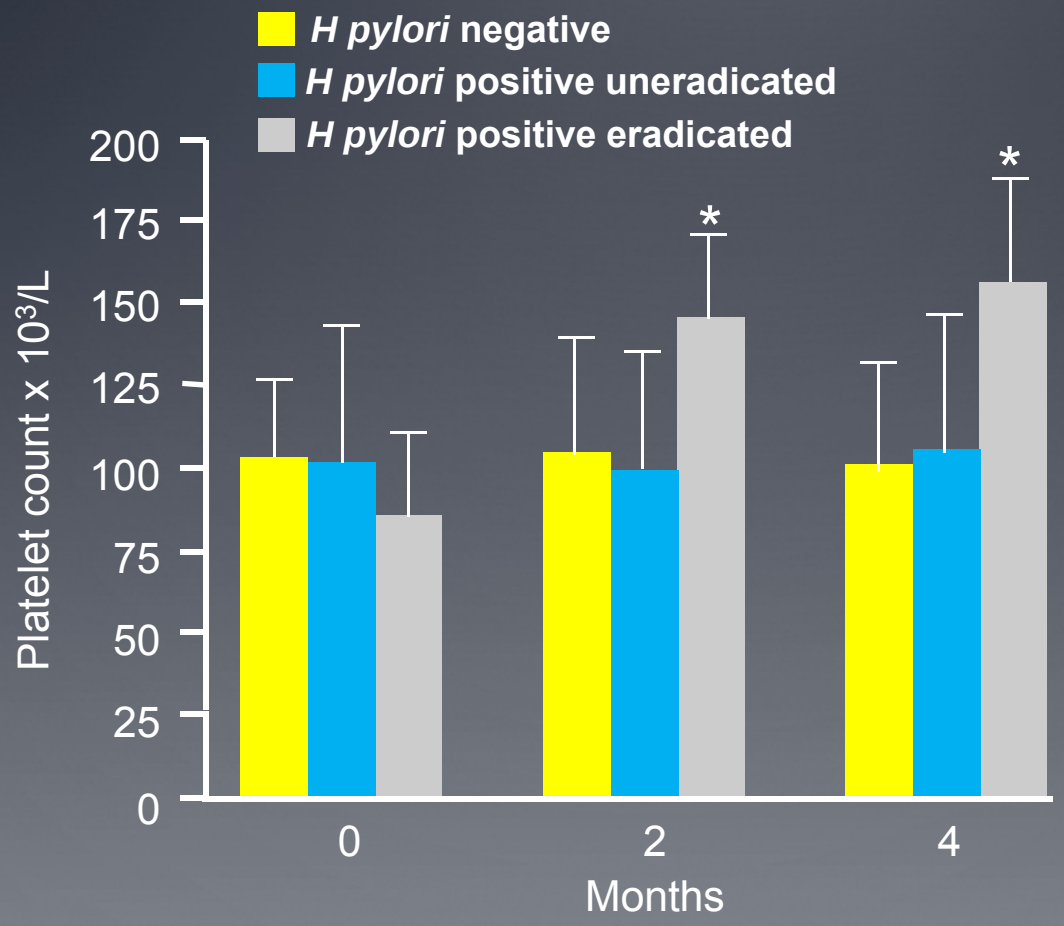
Micro-aerophilic, Gram-negative, slow-growing, spiral-shaped, flagellated bacterium



Marshall BJ, et al. *Med Clin North Am*. 2005;89(2):313-344.

H pylori Infection and ITP

Platelet counts in patients with autoimmune thrombocytopenia



Data are mean (SD)
*** *P*<.05 compared with initial count**

Gasbarrini A, et al. *Lancet.* 1998;352(9131):878.

Triggering Factors: *H pylori*

Country	Prevalence of HP Infection	Bacterial Eradication[a]	Platelet Response[b]
Japan	67.3%	83.2%	56.2%
Europe	57.6%	87.3%	41.5%
United States	21.6%	97%	17.2%
Other countries	70.8%	92.1%	58.6%

UK: Prevalence 47%, response rate in severe ITP <10%

The platelet response rate varies in different geographical areas

[a]Results are expressed as the total number of patients with bacterial eradication from among the total number of treated patients.
[b]Complete or partial response among patients with successful eradication.

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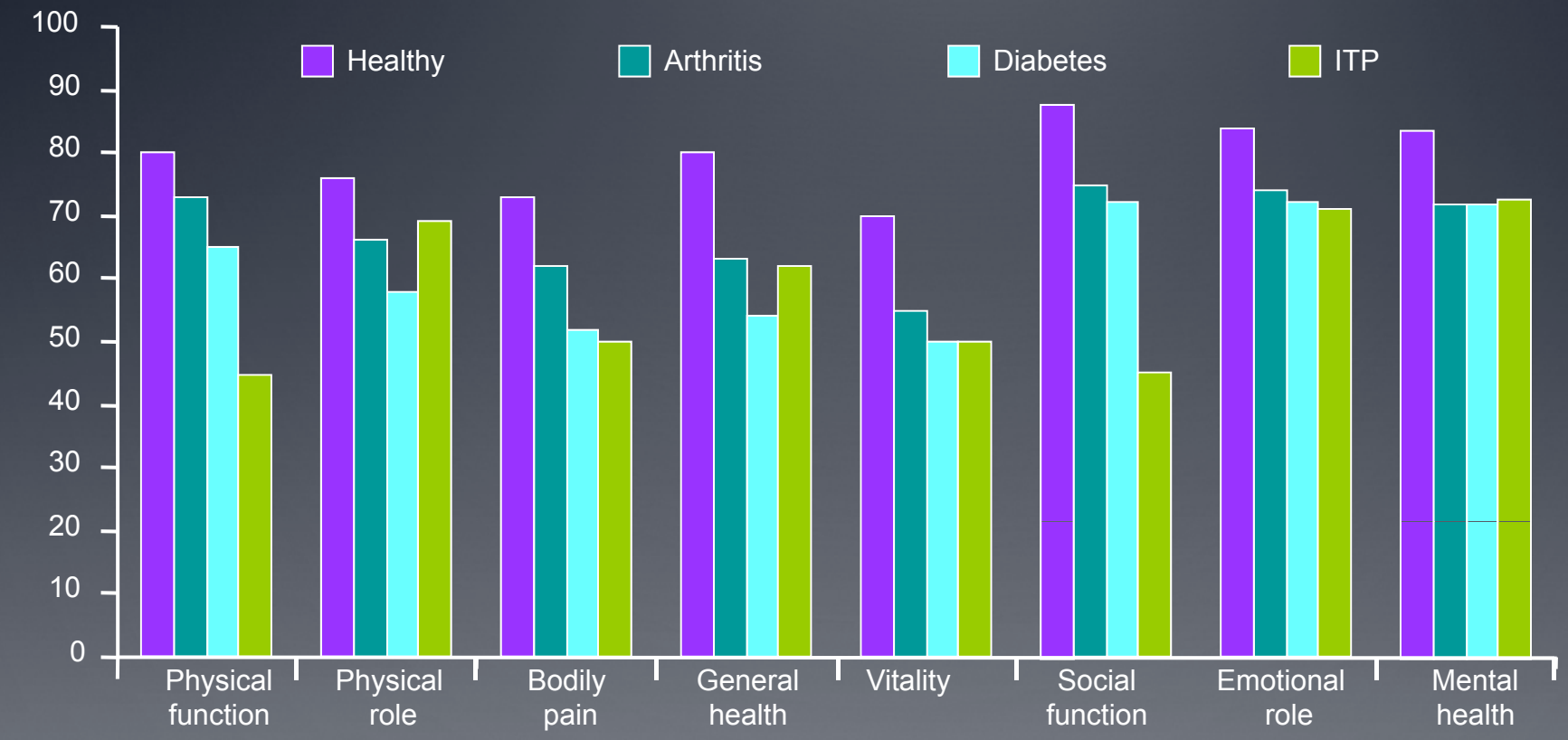
Impact of ITP on quality of life in relation to other chronic conditions



All scores range from 0 to 100.
Higher scores indicate better health-related quality of life (HRQoL)

Adapted from: Bussel J et al. Presented at: 45th ASH Annual Meeting; Dec 6–9, 2003; San Diego, CA, USA. Data on file, Amgen

The 3 categories of ITP* patients

1. Those who must or should be treated.
   - Active bleeding
   - OR
   - Platelet count <10 x 109/L

2. Those for whom treatment is controversial.
   - No bleeding or mild bleeding tendency
   - AND
   - Platelet count 10–30 x 109/L

3. Those for whom there is no need for treatment except in special circumstances (eg surgery).
   - No bleeding nor bleeding tendency
   - AND
   - Platelet count >30 x 109/L

*ITP, idiopathic thrombocytopenic purpura

Stasi & Provan. *Mayo Clin Proc* 2004;79:504–522

Management of the bleeding patient

- How severe is bleeding?
  - Life-threatening (eg intracranial haemorrhage, gastric haemorrhage [melena]) → see 'Emergency treatment'
  - Not life-threatening
    - Severe (eg metrorrhagia, unstoppable epistaxis) → see 'Emergency treatment'
    - Mild to moderate (eg petechiae, ecchymoses, gingival bleeding) → see 'Standard treatment'

Emergency treatment

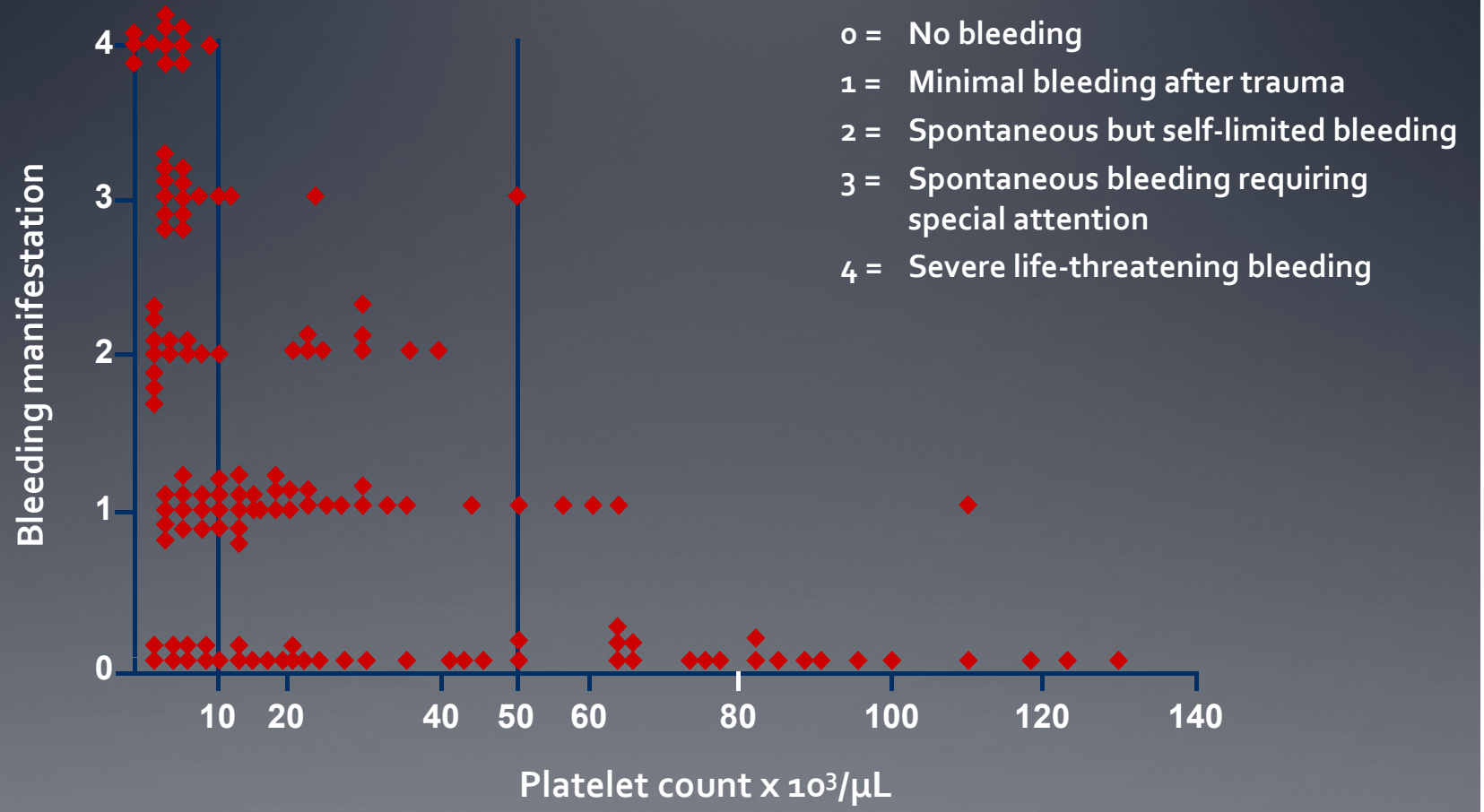
- Intravenous immunoglobulin
  - 1 g/kg, repeated the following day if the platelet count remains <50 x 109/L
- High-dose methylprednisolone
  - 1 g/day for 3 days (not for those with gastric haemorrhage)
- Platelet transfusions
  - 10 U every 4–6 hours or 3 U/hour
- Recombinant activated factor VII (rFVIIa)
  - Anecdotal reports

Stasi et al. *Thromb Haemost* 2008;99:4–13

If not bleeding, when should we treat ITP patients?

- Disease considerations
- Patient considerations
- Treatment considerations

Disease considerations: platelet count and bleeding in ITP



Lacey & Penner. *Semin Thromb Hemost* 1977;3:160–174

Disease considerations: natural history of chronic ITP in adults

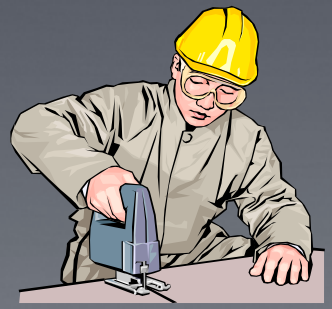
- **Variable and unpredictable**
- **Spontaneous remissions ~10%**; most often occur in patients with mild ITP[1]
- **85%** of patients achieve a platelet count >30 x 109/L **without any treatment[2]**
- **Overall mortality risk** relative to the general population 1.3, but 4.2 in those who have platelet counts persistently <30 x 109/L 2 years after diagnosis[2]

1. Stasi et al. *Am J Med* 1995;98:436–442
2. Portielje et al. *Blood* 2001;97:2549–2554

Patient considerations

- **Risk** of fatal haemorrhage **greatest in older patients**:[1]
  - 0.4% per year in patients <40 years
  - 1.2% per year in patients 40–60 years
  - 13% per year in patients >60 years
- **Energetic lifestyles** require **'safer'** platelet counts

Platelet >20–30 x 10^9/L



Platelet >50 x 10^9/L

Platelet >80 x 10^9/L

Cohen et al. *Arch Intern Med* 2000;160:1630–1638

Treatment considerations

- Only **a few treatments** are truly **evidence based** and approved by EMEA
- Long-term **side effects** for new agents are not currently known
- **Treatment** of ITP may be more **dangerous** than the disease itself:[1]
  - 6 patients out of 152 died
  - 2 died from haemorrhage
  - 4 died from infections probably treatment related

1. Portielje et al. *Blood* 2001;97:2549–2554

Recommendation for 'safe' platelet counts in adults

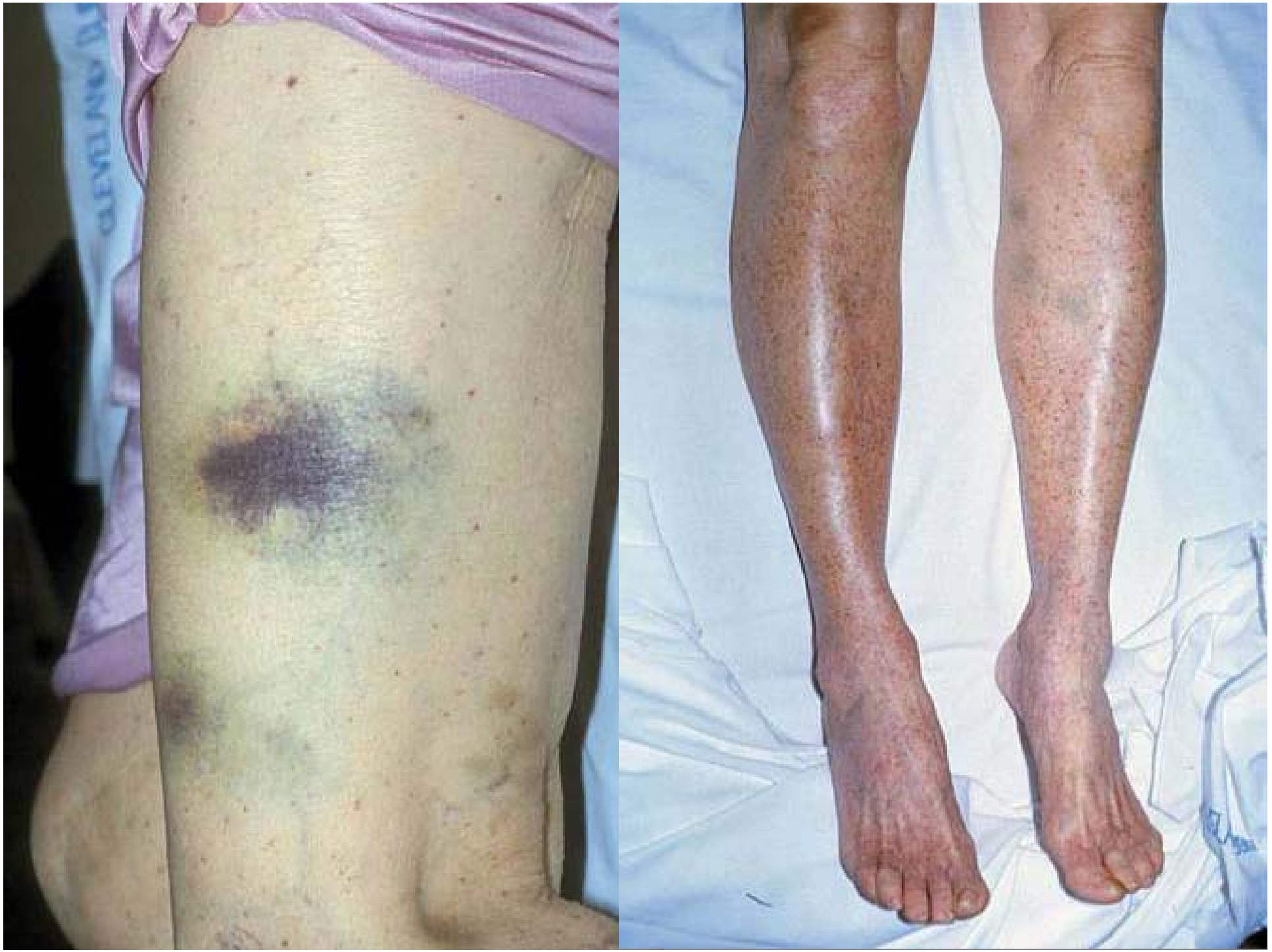
- Dentistry ≥10 x 109/L
- Extractions ≥30 x 109/L
- Regional dental block ≥30 x 109/L
- Minor surgery ≥50 x 109/L
- Major surgery ≥80 x 109/L
- Obstetrics:
  - Vaginal delivery ≥50 x 109/L
  - Caesarean section ≥80 x 109/L

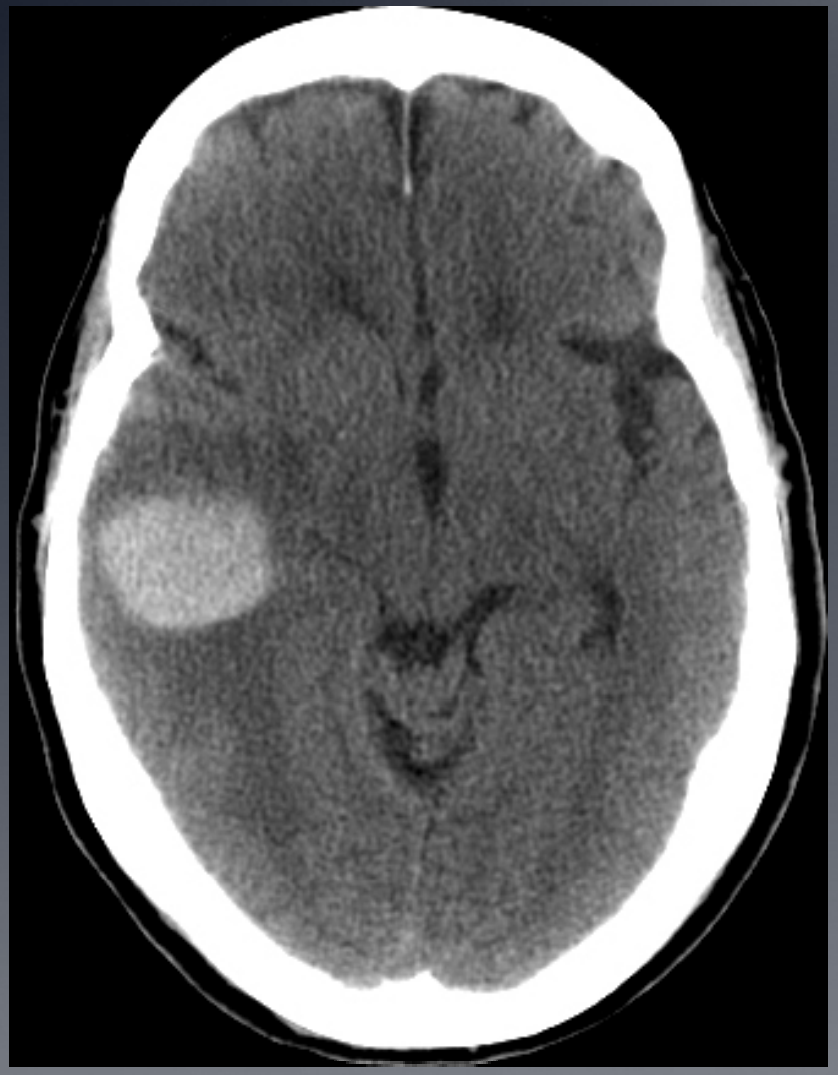
BCSH Guidelines. *Br J Haematol* 2003;120:574–596

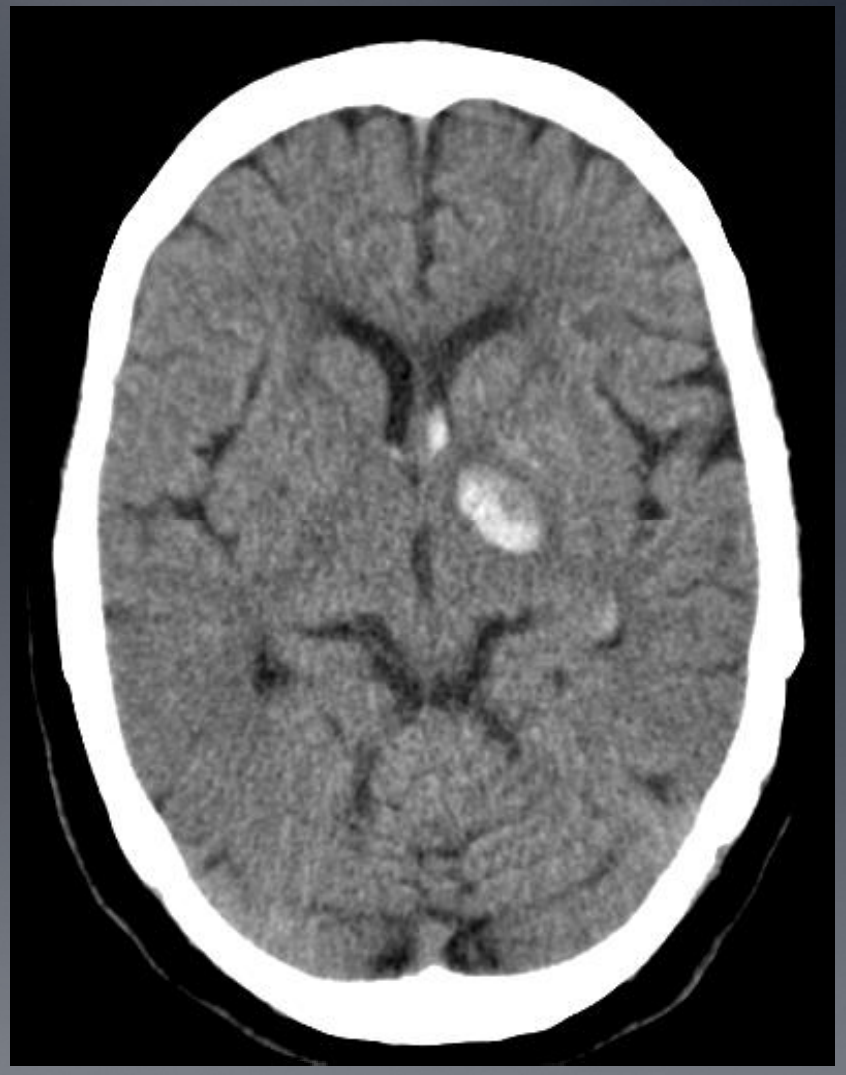
ITP: Treatment Goals in the 21st Century

- Prevention of bleeding
- Improvement of QOL

Stasi R, et al. *Thromb Haemost.* 2008;99(1):4-13.







First-line therapy in newly-diagnosed ITP

- **Corticosteroids**
  - Prednisone 1–2 mg/kg/day for 4 weeks given orally as single or divided doses → CR ~70%, sustained responses ~15%1
  - High-dose dexamethasone 40 mg/day for 4 consecutive days → ~85% good initial OR, sustained responses >50%2
- **Early management for those unresponsive to steroids**
  - IV immunoglobulin (IVIg) 0.5–1 g/kg/day for 1 or 2 days → rapid but transient responses ~80% of cases (generally recommended for patients with critical bleeding)1
  - IV anti-D 50–75 µg/kg for 1 day → responses ~70% of cases1

NB: The repeated use of either maintenance IVIg or maintenance anti-D globulin allows approximately 40% of adults with ITP to avoid splenectomy

*CR, complete response; IV, intravenous; Ig, immunoglobulin; OR, overall response

1. Stasi et al. *Thromb Haemost* 2008;99:4–13
2. Cheng et al. *N Engl J Med* 2003;349:831–836

Splenectomy in ITP

- Generally **accepted criteria** for splenectomy include:[1]
  - Severe thrombocytopenia (platelet count <10 x 109/L)
  - A high risk of bleeding for platelet counts <30 x 109/L
  - The requirement of continuous glucocorticoid therapy to maintain safe platelet counts
- **Complete response** (platelets >150 x 109/L) rate of **66%**[2]
- **Sustained responses** (>5 years) **64%**[2]
- No pre-operative characteristic **predictive of response**[2]
- **Mortality** rate with laparoscopic splenectomy **0.2%**[2]
- **Lifelong** infection risk
- Current trend is to **defer splenectomy** and offer medical treatment

1. Stasi et al. *Thromb Haemost* 2008;99:4–13
2. 2. Kojouri et al. *Blood* 2004;104:2623–2634

Defining chronic refractory ITP

- The patient has **failed** to respond to splenectomy
- AND
- The platelet count is **<30,000/µL**

Stasi et al. *Thromb Haemost* 2008;99:4–13

Long-term outcomes in adults with chronic ITP after splenectomy failure

- 105 patients with refractory ITP; median follow-up 110 months
- 30% patients remained unresponsive to treatment
  - 16% died of ITP (bleeding, 11 patients; therapy complications, 6 patients)
  - 14% died of unrelated causes

McMillan & Durette. *Blood* 2004;104:956–960

Interventional measures: non-selective therapies*

- Oral/IV dexamethasone
- IV methylprednisolone
- Danazol
- Dapsone
- Azathioprine
- Vinca alkaloids
- IV cyclophosphamide
- Cyclosporine
- Combination chemotherapy
- Interferon-α
- Mycophenolate Mofetil

- Osteoporosis, psychosis etc
- Diabetes, fluid retention
- Weight gain, hirsutism, LFTs abnormal
- Haemolysis
- Immunosuppression, LFTs abnormal
- Neuropathy
- Leukaemia, cytopenia, teratogenic
- Nephrotoxic, immunosuppression
- Leukaemia, myelosuppression
- Thrombocytopenia

BUT: No real evidence of which/when to use or in which order[1]

LFTs - liver function tests;
Staph - staphylococcal

*Many of which are utilised in an off-label setting

1. Stasi & Provan. *Mayo Clin Proc* 2004;79:504–522

Interventional measures: targeted therapies*

- Thrombopoietin receptor stimulators**
- Syk inhibitors
  - R788 (tamatinib fosdium)
- Antibody therapies
  - Campath-1H (anti-CD52)
  - Anti-CD40 ligand (anti-CD154)
  - GMA161 (anti-CD16)
  - Rituximab
- Co-stimulatory blockade CTLA-4-Ig
- Staphylococcal protein A (PRYX-100)

Refractory ITP: Interventional Measures

OLD

- Non-selective therapies
  - Azathioprine Corticosteroids Cyclophosphamide Cyclosporine Mycophenolate mofetil Vincristine

NEW

- Antibody therapies
  - Rituximab
- Thrombopoietin receptor agonists
  - Eltrombopag
  - Romiplostim

Rituximab* in chronic ITP

- Zaja F.; BLOOD, 8 APRIL 2010, VOLUME 115, N 14
- Randomized trial in previously untreated patients
- Dexamethasone vs. Dexamethasone plus rituximab
- Sustained response after 6 months of treatment
  - 36% vs. 63%

Thrombopoietic Growth Factors

First-generation thrombopoietic growth factors
Recombinant human thrombopoietins
rhTPO
PEG-rHuMGDF
Recombinant TPO fusion proteins
Promegapoietin (TPO/IL3 fusion protein)
Second-generation thrombopoietic growth factors
TPO peptide mimetics
Fab 59
*AMG 531 (Romiplostim) (Lancet Feb 2008)
Peg-TPOmp
TPO nonpeptide mimetics
*Eltrombopag (SB497115, Promacta) (NEJM Nov 2007)
AKR-501
TPO agonist antibodies
Minibodies [VB22B sc(Fv)2]
Domain subclass-converted TPO agonist antibodies (MA01G4G344)

- Improved platelet recovery after non-myeloablative chemotherapy
- Improved platelet counts in 7/9 ITP patients
- Healthy subjects developed antibodies cross-reacting with endogenous Tpo and became thrombocytopenic

Kuter DJ. New thrombopoietic growth factors. Blood 2007;109:4607

Second Generation Thrombopoietin (TPO) Receptor Agonists in ITP

- Peptide TPO Receptor Agonist
  - *Romiplostim (AMG531) - *Nplate*®
  - Fab59, PEG TPOmp
- Nonpeptide TPO Receptor Agonist
  - *Eltrombopag - *Revolade/Promacta*®
  - AKR501, LGA-4665, S-888711
- TPO agonist antibodies
  - Minibodies (VB22B sc(Fv)2), MA01G4G344

*eltrombopag and romiplostim FDA / EMEA approved

Studies with Romiplostim in ITP

- Phase I: Open label study of 24 subjects treated in groups of 4 at six dose levels: 0.2, 0.5, 1.0, 3.0, 6.0, 10.0 µg/kg SQ
- Phase II: Double-blind, placebo-controlled trial of 1 or 3 µg/kg romiplostim (16 subjects) vs placebo (4 subjects)
- Phase II: Double-blind, placebo-controlled trial in 22 children on romiplostim and 5 placebo divided by age
- Phase III: Double-blind, placebo-controlled trial of romiplostim vs placebo in patients with or without splenectomy
- Phase III: Romiplostim vs standard of care in ITP with or without splenectomy
- Extension Study (213): Open label safety and efficacy study of long-term weekly treatment of subjects from Phase 1-3

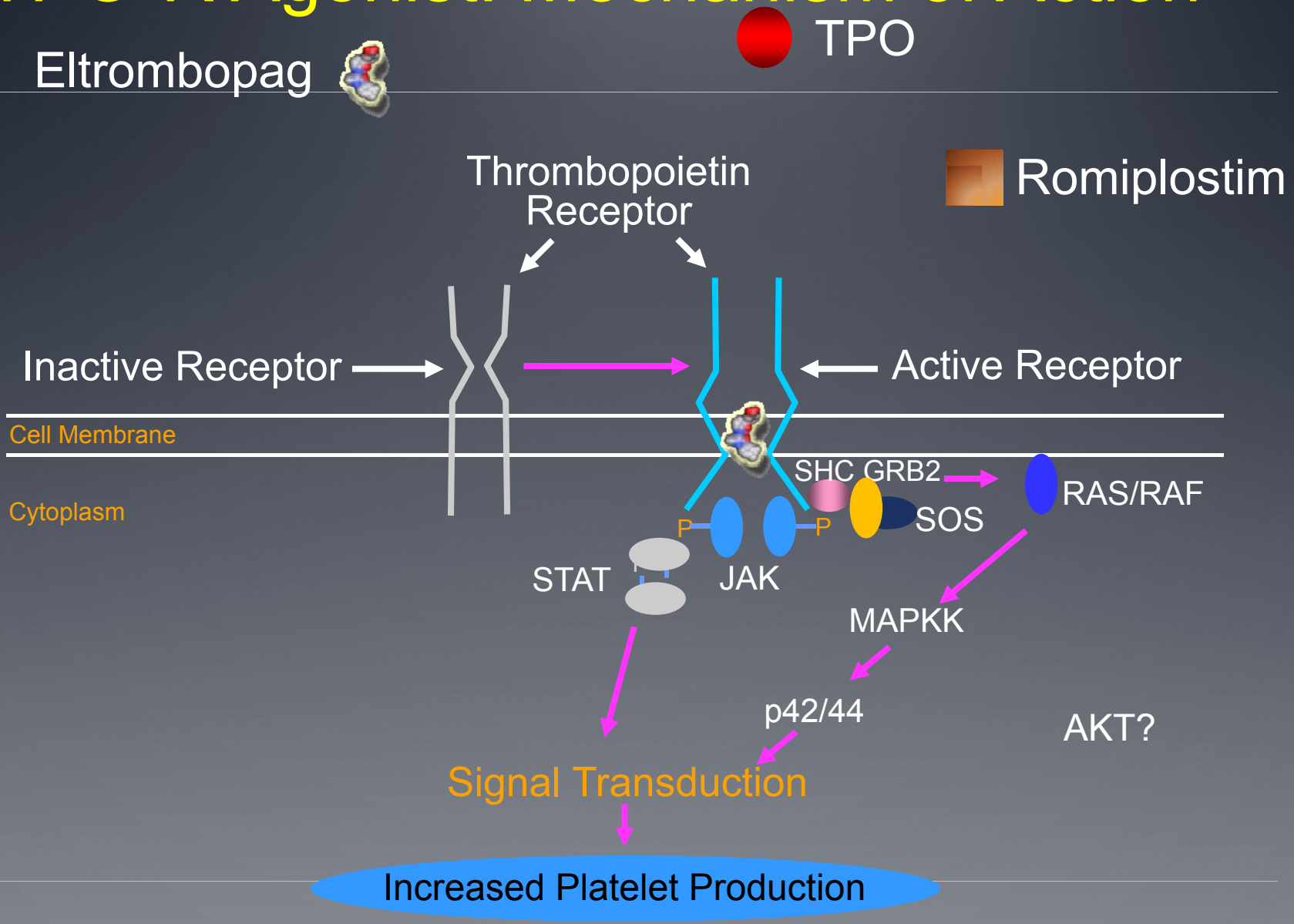
Bussel JB, et al. *N Engl J Med.* 2006;355:1672-1681. Newland A, et al. *Br J Haematol.* 2006;135:547-553. Kuter DJ, et al. *Lancet.* 2008; 371:395-403. Bussel JB, et al. *Blood.* 2009;114: Abstract 681. Kuter DJ, et al. *Blood.* 2009:114: Abstract 679. Buchanan GR, et al. *Blood.* 2009;114: Abstract 680.

Studies with Eltrombopag in ITP

- Phase II/III: Double-blind, placebo-controlled trials
  - 773A: placebo or 30, 50, 75 mg daily for 6 weeks
  - 773B: placebo or 50 mg daily for 6 weeks
- Phase II: REPEAT – three cycles of 6 weeks each of active, open-label treatment
- Phase III: RAISE – double-blind, placebo-controlled trial for 6 months of variable doses of eltrombopag vs placebo in patients with or without splenectomy
- Extension Study: EXTEND Open label safety and efficacy study of long-term weekly treatment of subjects from Phase II-III
- Phase II: (Ongoing): PETIT Study of eltrombopag in children with persistent and chronic ITP in 3 age cohorts

Bussel JB, et al. *N Engl J Med.* 2007;357:2237-2247. Bussel JB, et al. *Blood.* 2009;112: 3431. Saleh et al. *Blood.* 2009;114: Abstract 682. Stasi R, et al. *Haematologica.* 2009;94(Suppl 2):231. http://www.clinicaltrials.gov/ct2/show/NCT00908037?term=PETIT&rank=1.

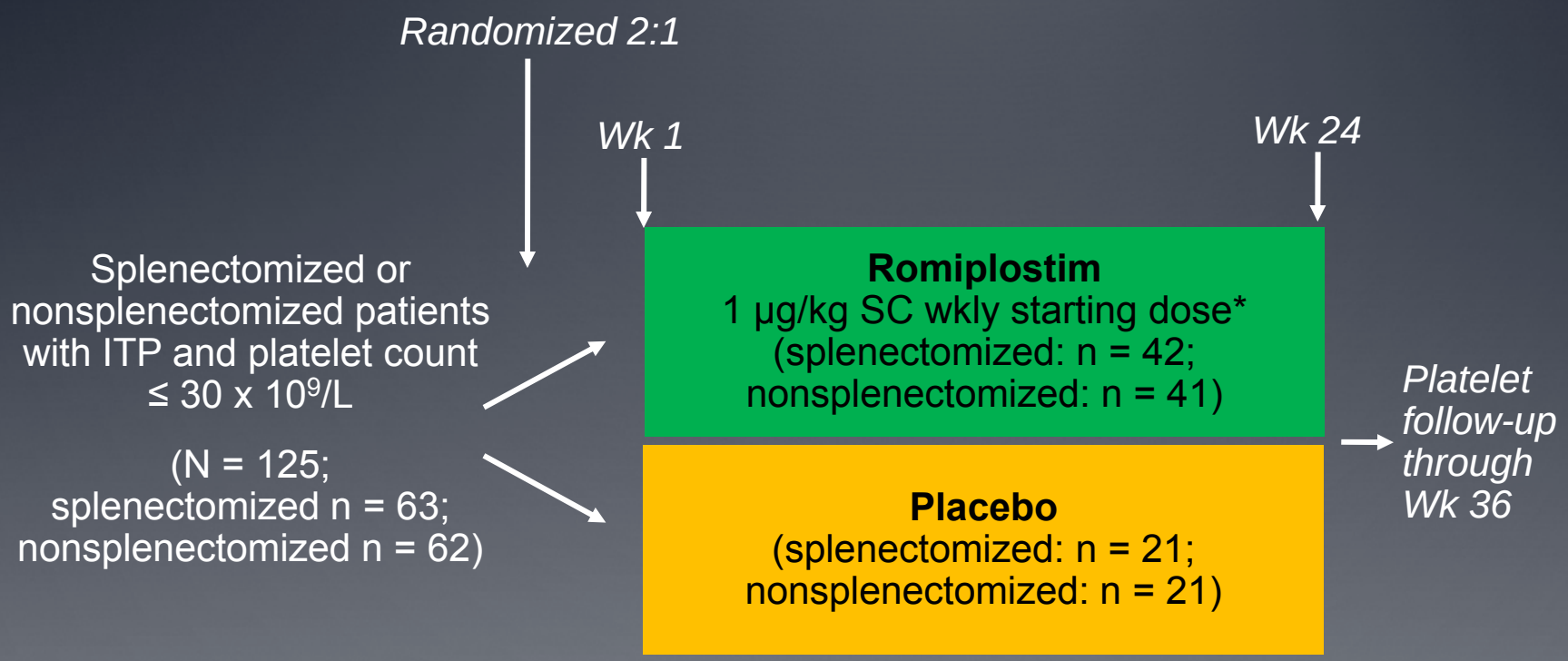
TPO-R Agonist: Mechanism of Action



Romiplostim

- No sequence homology with endogenous TPO
- Fusion protein of Fc and TPO mimetic peptides
- Stimulates platelet production by same mechanism as TPO
- Recycled by FcRn on endothelial cells
- Administered as weekly subcutaneous injections
  - Titrations between 1–10 µg/Kg (adjustable based on platelet count)

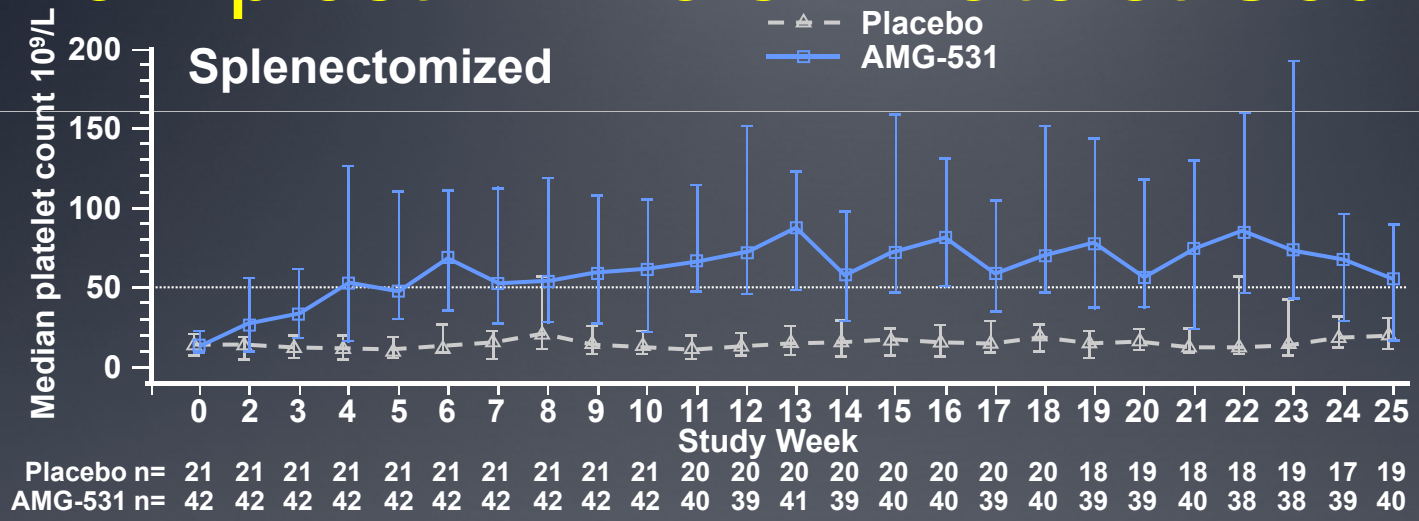
Romiplostim: Parallel Phase III Trials in Chronic ITP

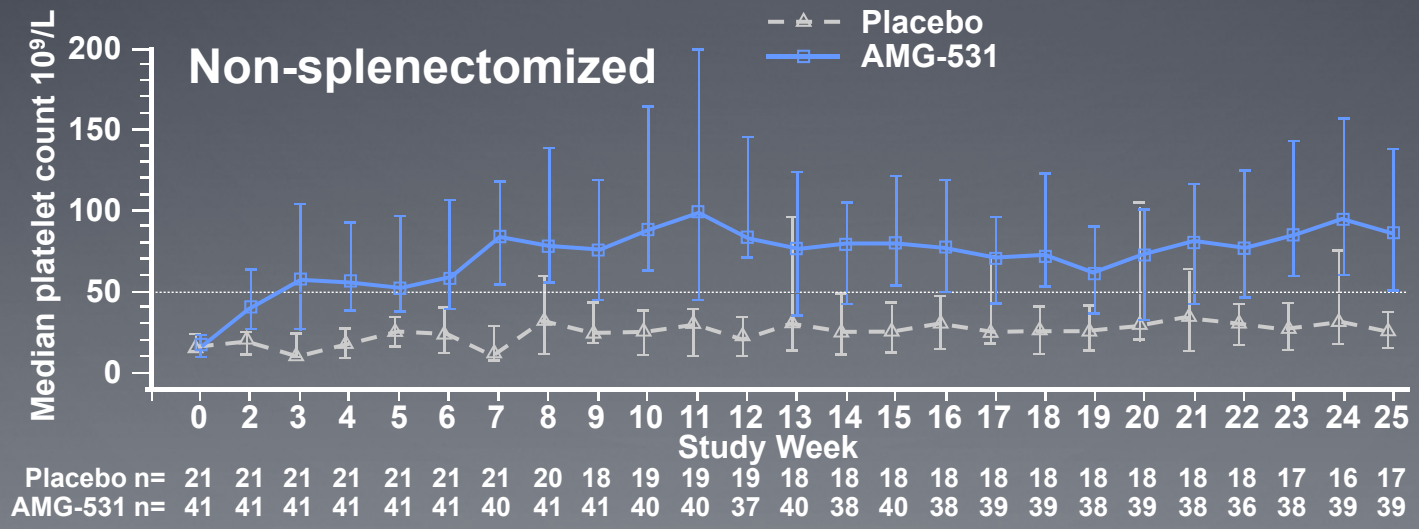


*Individual dose adjustment based on wkly platelet count. Reductions in concurrent ITP therapies allowed when platelet counts > 100 x 10^9/L. Rescue medications allowed.

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

Romiplostim Trials : Platelet Count

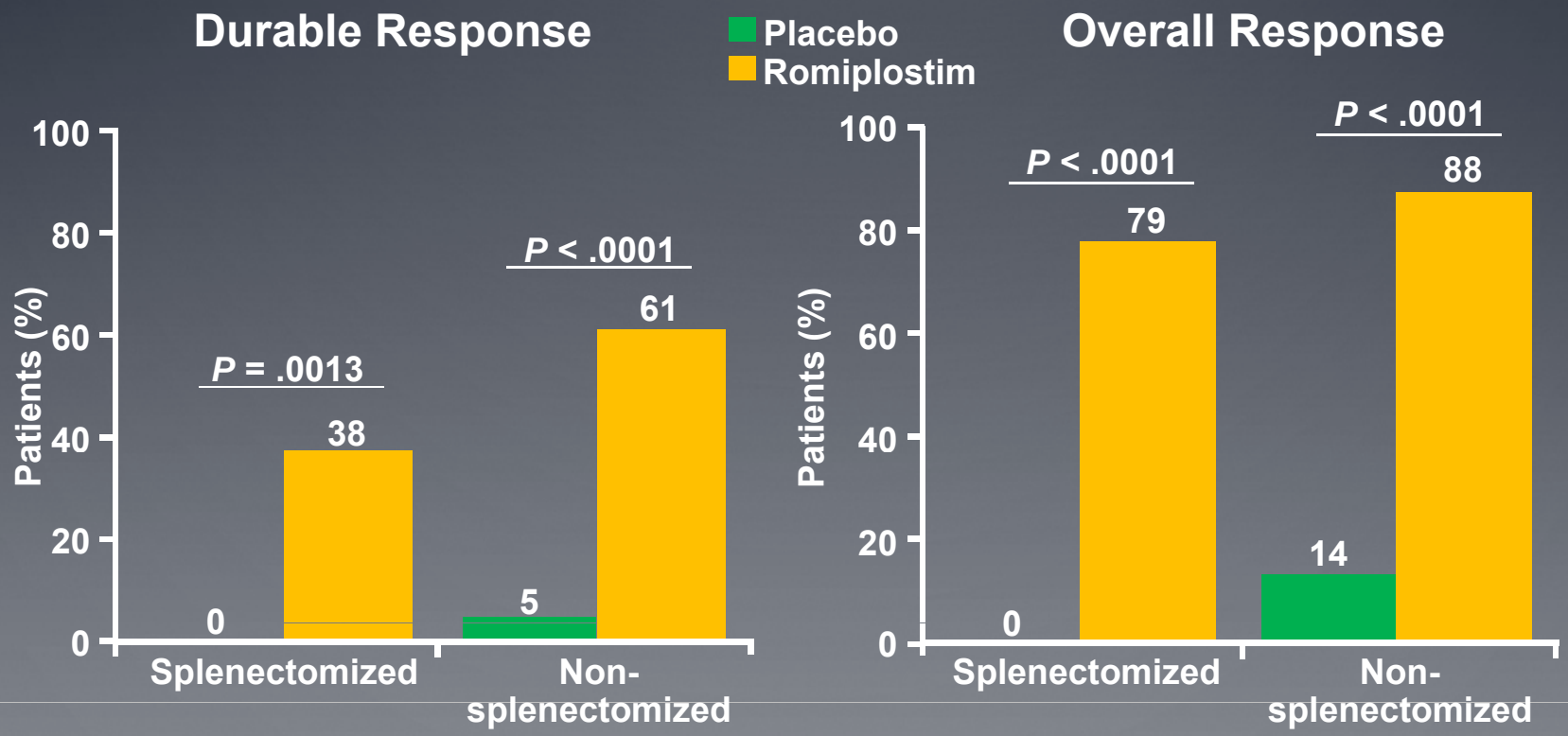




Kuter DJ, et al. *Lancet.* 2008;371:395-403.

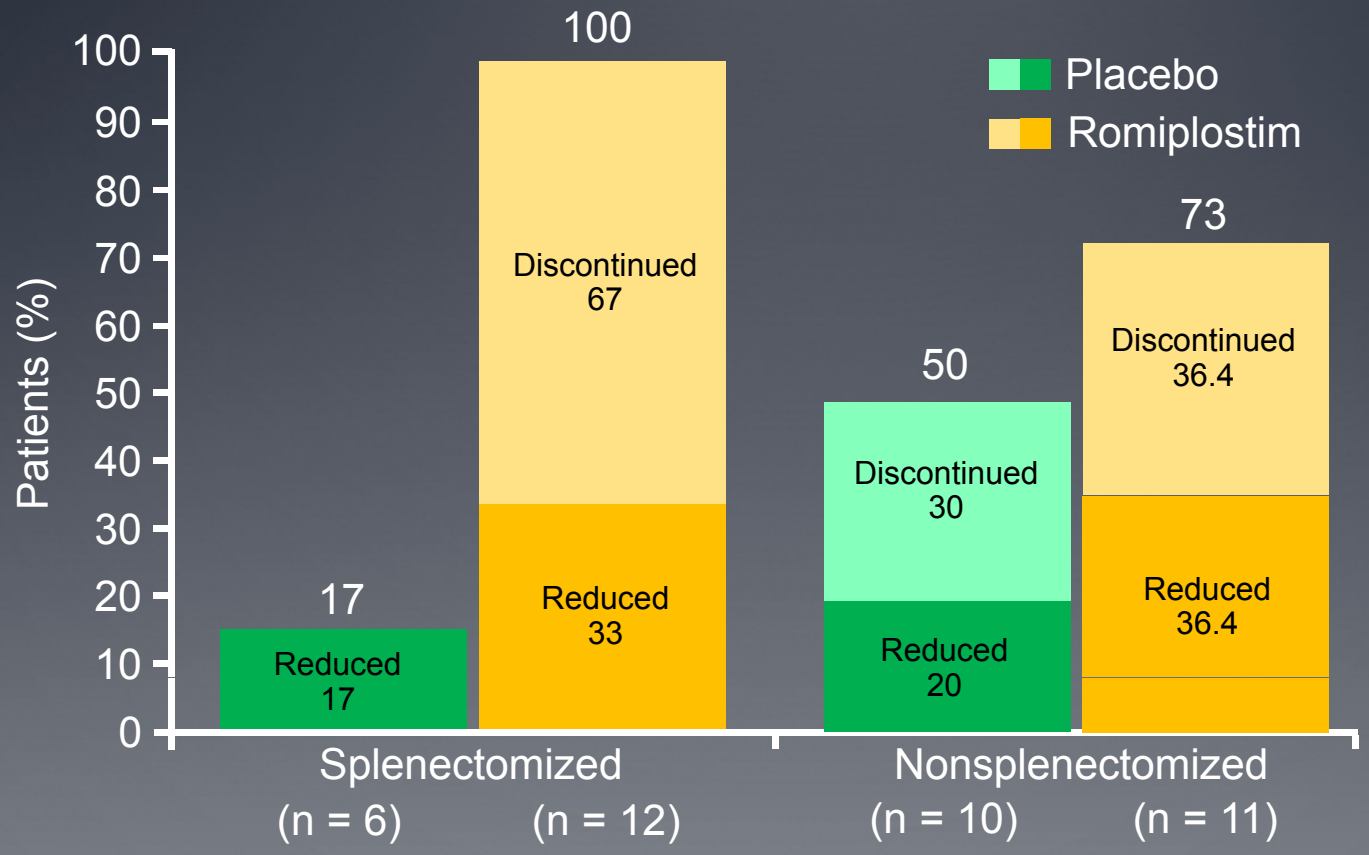
Romiplostim: Platelet Response Outcomes in Chronic ITP

- Durable platelet response: at least 6 weekly platelet responses during the last 8 weeks of treatment in the absence of rescue medication at any time during the treatment period
  - Weekly platelet response: a platelet count of ≥50 x 10^9/L on the weekly scheduled dose day from week 2 to week 25



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

Romiplostim: Reduction or Discontinuation of Concurrent ITP Therapy



Patients discontinued or reduced by > 25% concurrent ITP therapy

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

Long-term Open-label Extension Study Design

SCREENING

Romiplostim starting dose:
1 µg/kg or last dose on prior study‡

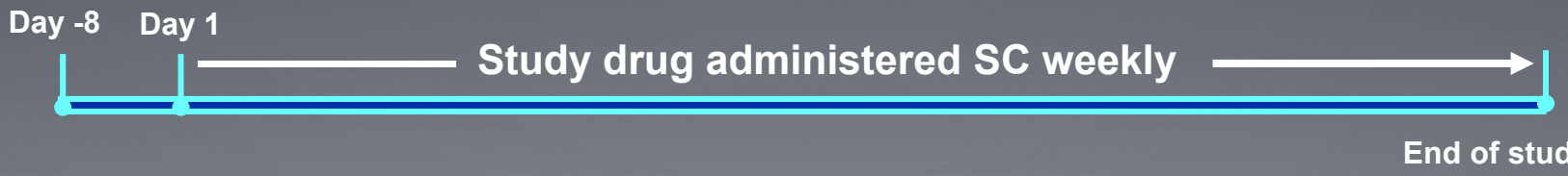
Individual dose adjustment based on platelet count

Maximum dose 10 µg/kg

Reductions in concurrent ITP therapies allowed when platelet counts > 50 x 10^9/L

Rescue medications allowed

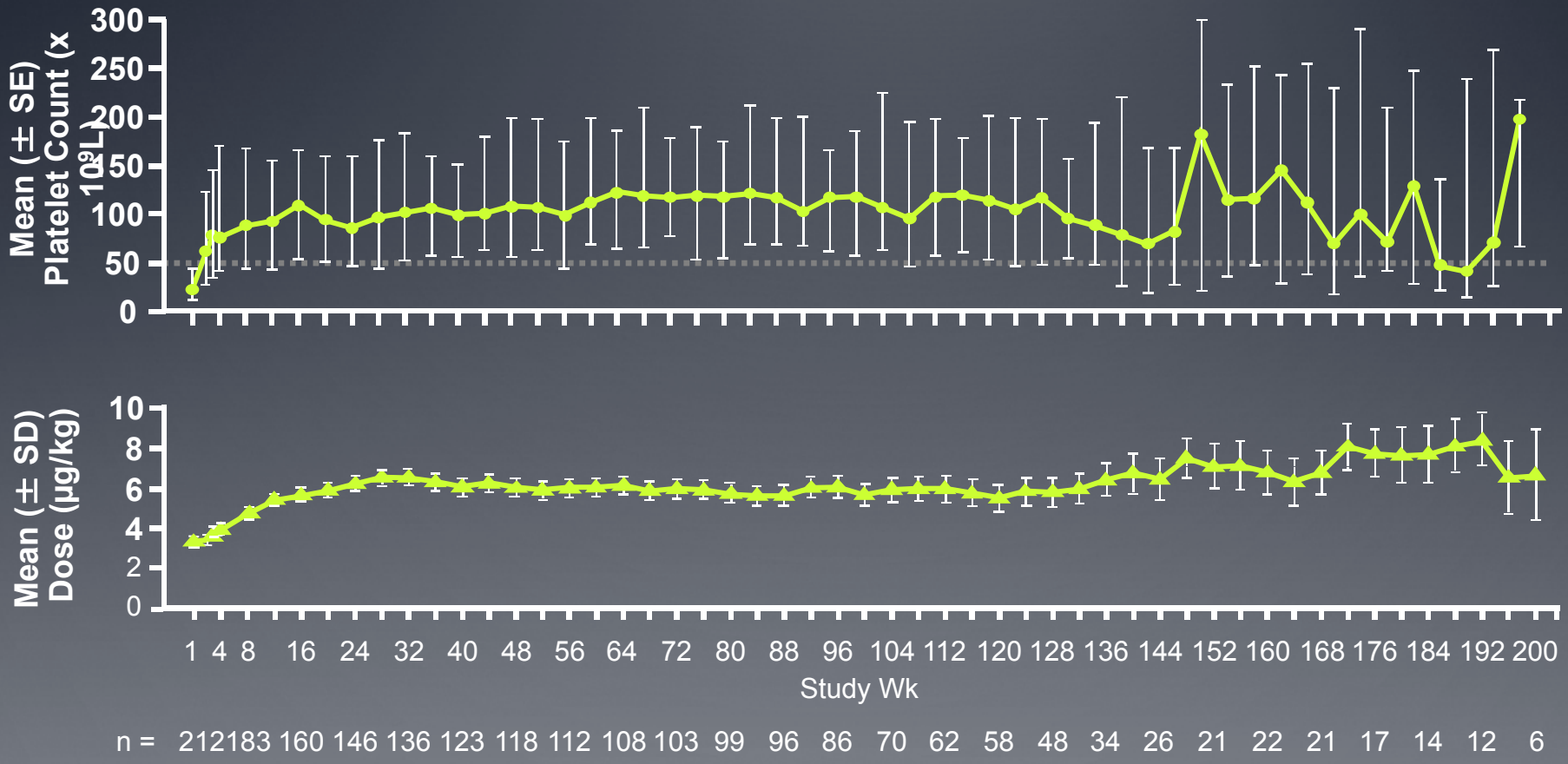
INTERIM ANALYSIS



‡Romiplostim administered at 1 µg/kg if >24 weeks since prior romiplostim dose

Terebelo et al. Annual Chicago Supportive Conference 2008; poster; Bussel et al. *Blood* 2008; doi:10.1182

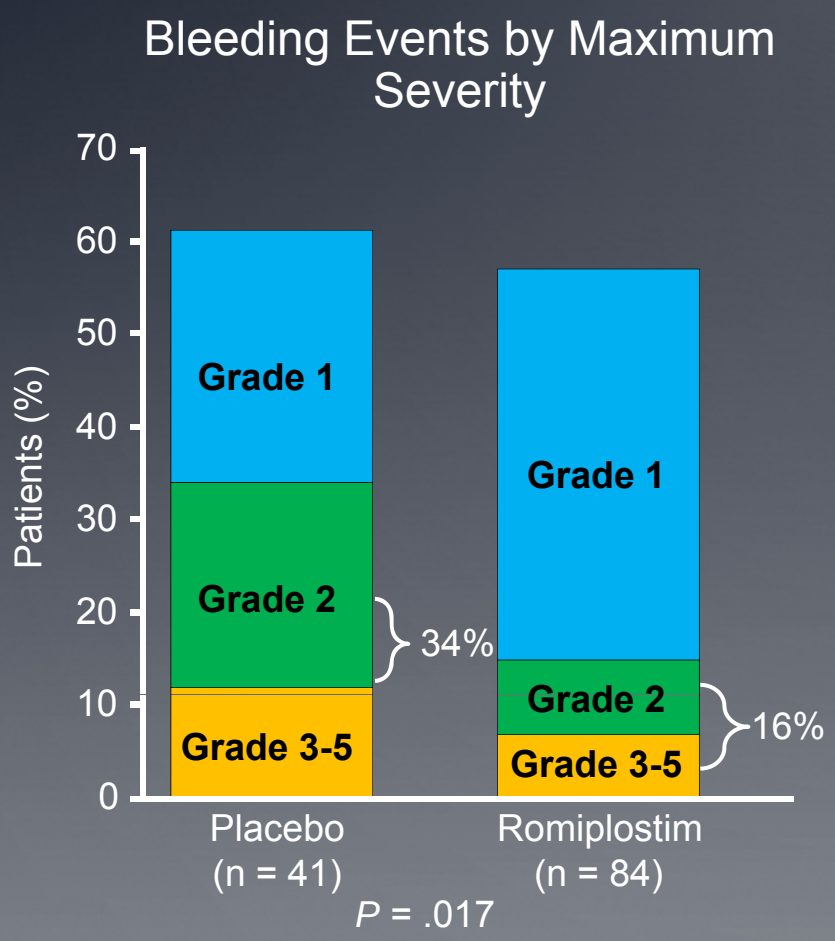
Mean Platelet Count and Romiplostim Dose Over 204 Wks

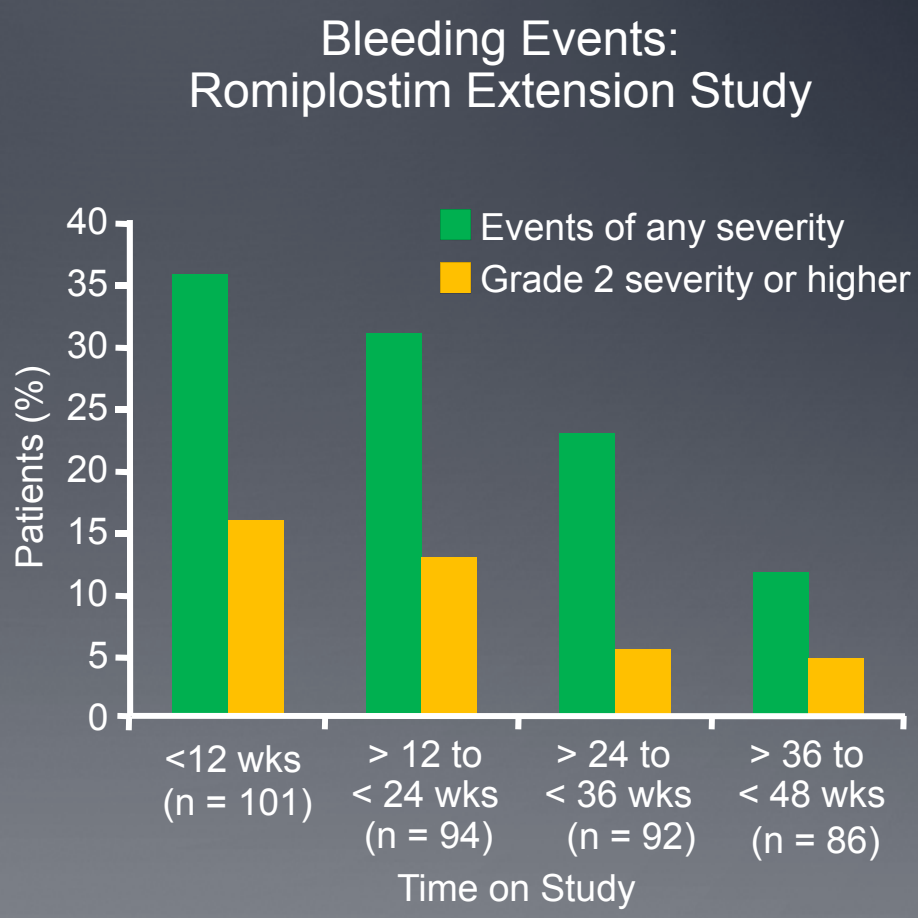


Platelet counts within 8 wks after receiving any rescue medications were excluded

Bussel JB, et al. *Blood*. 2009;113(10):2161-2171.

Long-term Use of Romiplostim: Bleeding Events

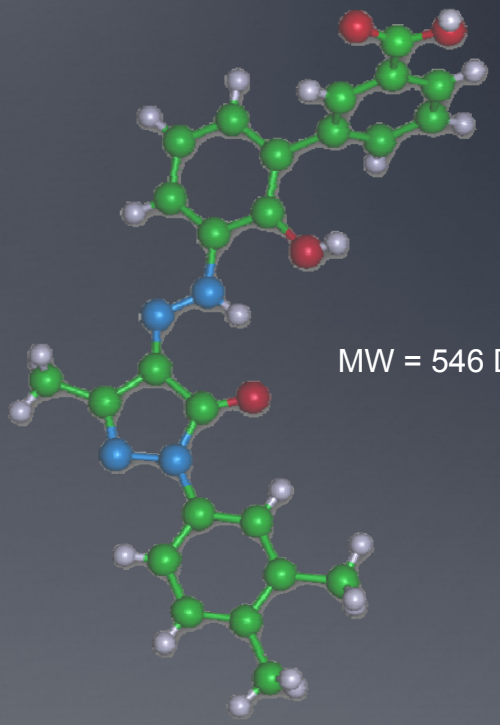




Tarantino M, et al. *Blood* 2008;112: Abstract 3422.

Eltrombopag

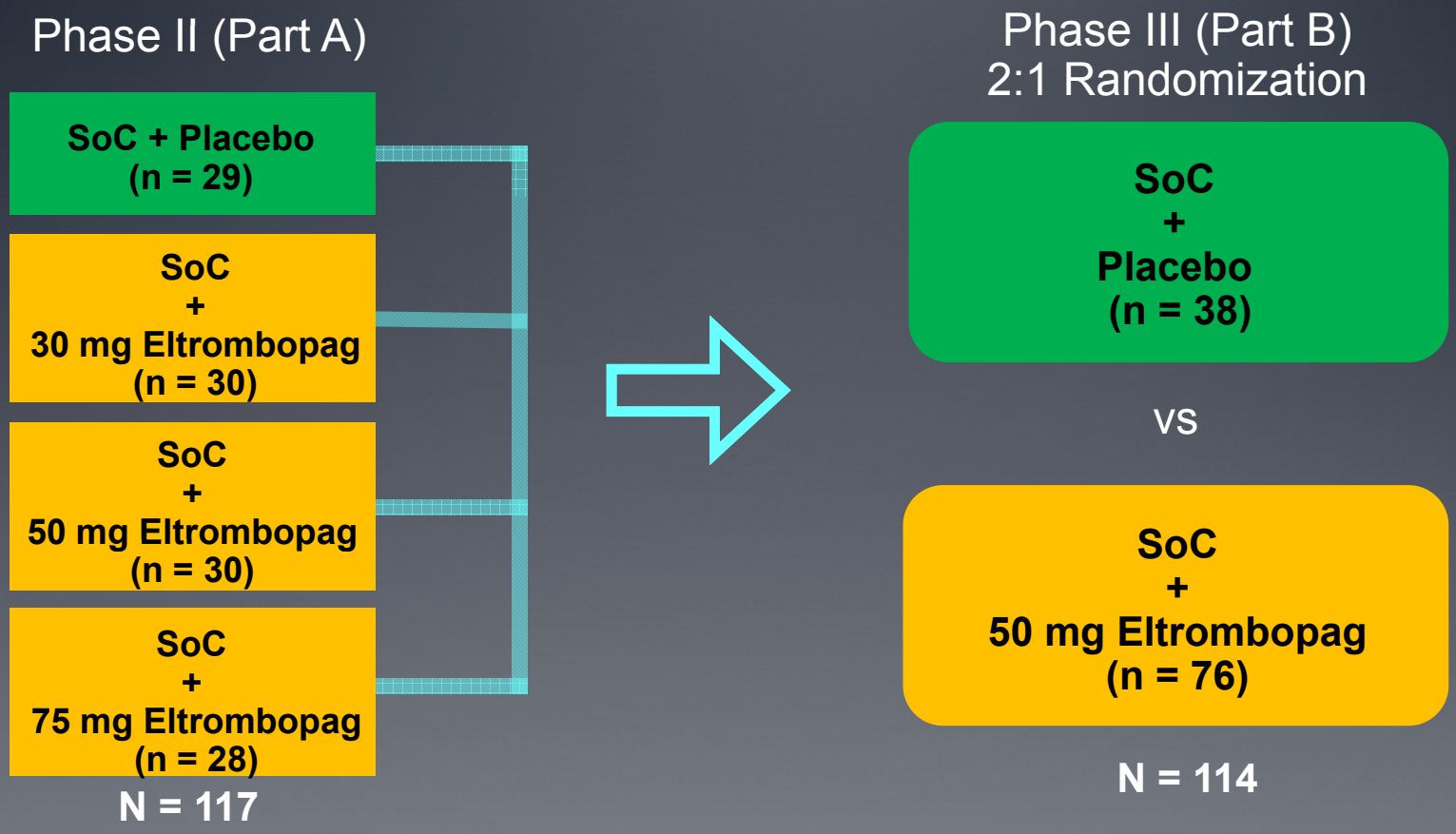
- Small molecule, non-peptide thrombopoietin receptor agonist
- Dose-dependent increases in normally functioning platelets
- Does not prime platelet activation
- Once daily oral dose: 50mg
  - Adjusted between 25mg and 75mg as needed
  - AUC 70% to 80% higher in East Asian patients
  - Should be taken 4hrs before or after any calcium containing products or mineral supplements containing polyvalent cations



MW = 546 Da

Erickson-Miller CL, et al.*Stem Cells* 2009;27: 424–30; Bussel JB, et al.*N Engl J Med* 2007;357(22):2237–47;Stasi R, et al. *Drugs* 2008;68(7):901–12;Jenkins et al. *Blood*.2007;109(11):4739-4741; Garnock-Jones KP, et al. Drugs 2009; 69(5): 567–76.

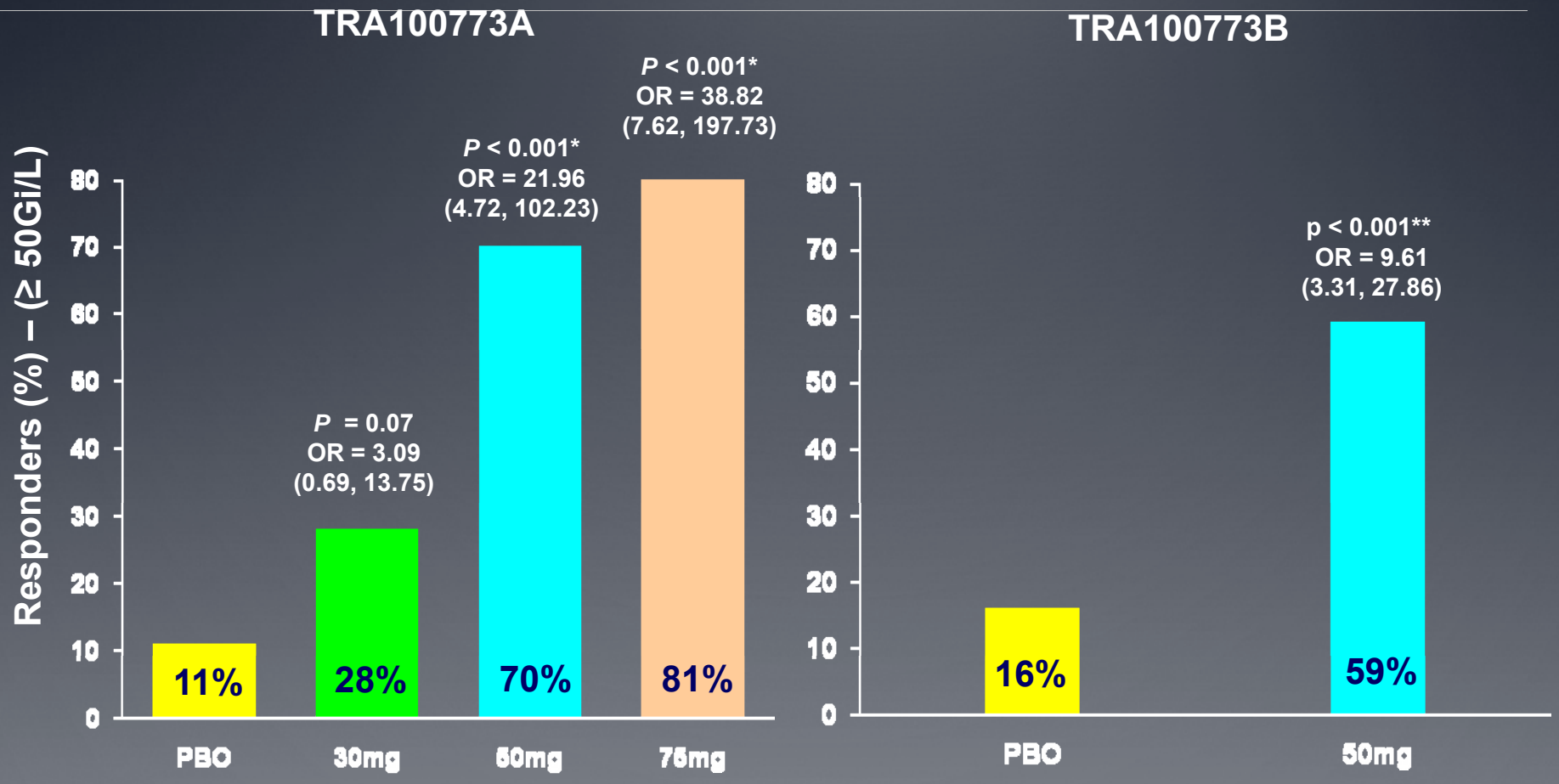
Phase III Eltrombopag Treatment of Chronic ITP



Randomization stratified on basis of concomitant ITP therapy, splenectomy status, platelet count > or ≤ 15 x 10^9/L

Bussel JB, et al. *N Engl J Med* 2007; 357: 2237–47. Bussel JB, et al. *Lancet* 2009; 373(9664): 641–8.

Primary Endpoint 773A & B: Elevation of Platelet Counts



*1-sided *P* value. odds ratio (OR)
eltrombopag / placebo

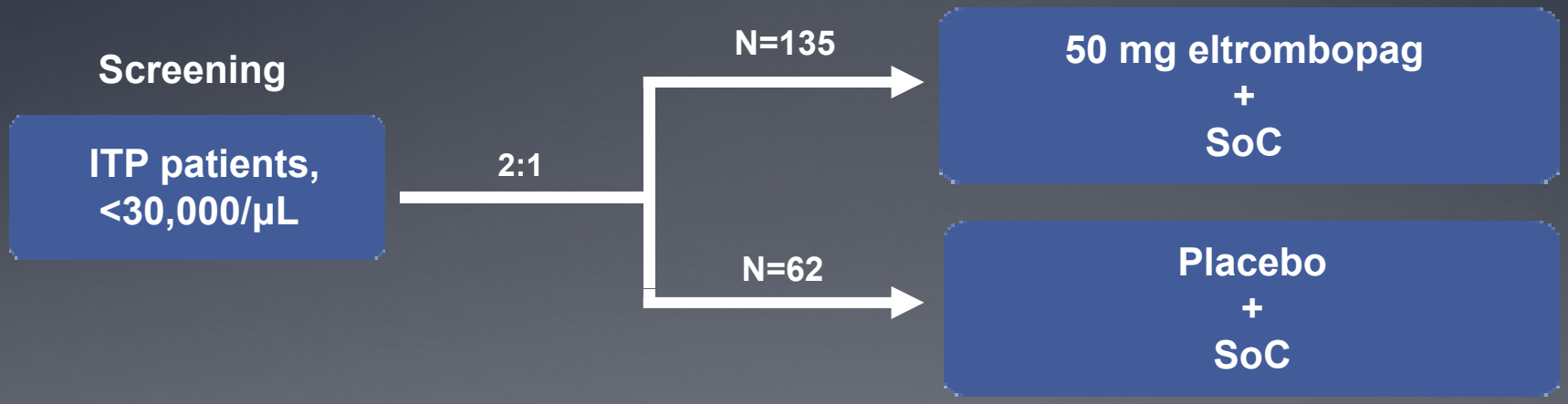
**2-sided *P* value, OR, odds ratio
eltrombopag / placebo

Bussel JB, et al. *N Engl J Med* 2007; 357: 2237–47. Bussel JB, et al. *Lancet* 2009; 373(9664): 641–8.

Eltrombopag: RAISE Study

PHASE III RAndomized Placebo-controlled ITP Study with Eltrombopag

Primary endpoint: odds of responding with a platelet count 50,000 to 400,000/μL during the 6-month treatment period



Randomization stratification:

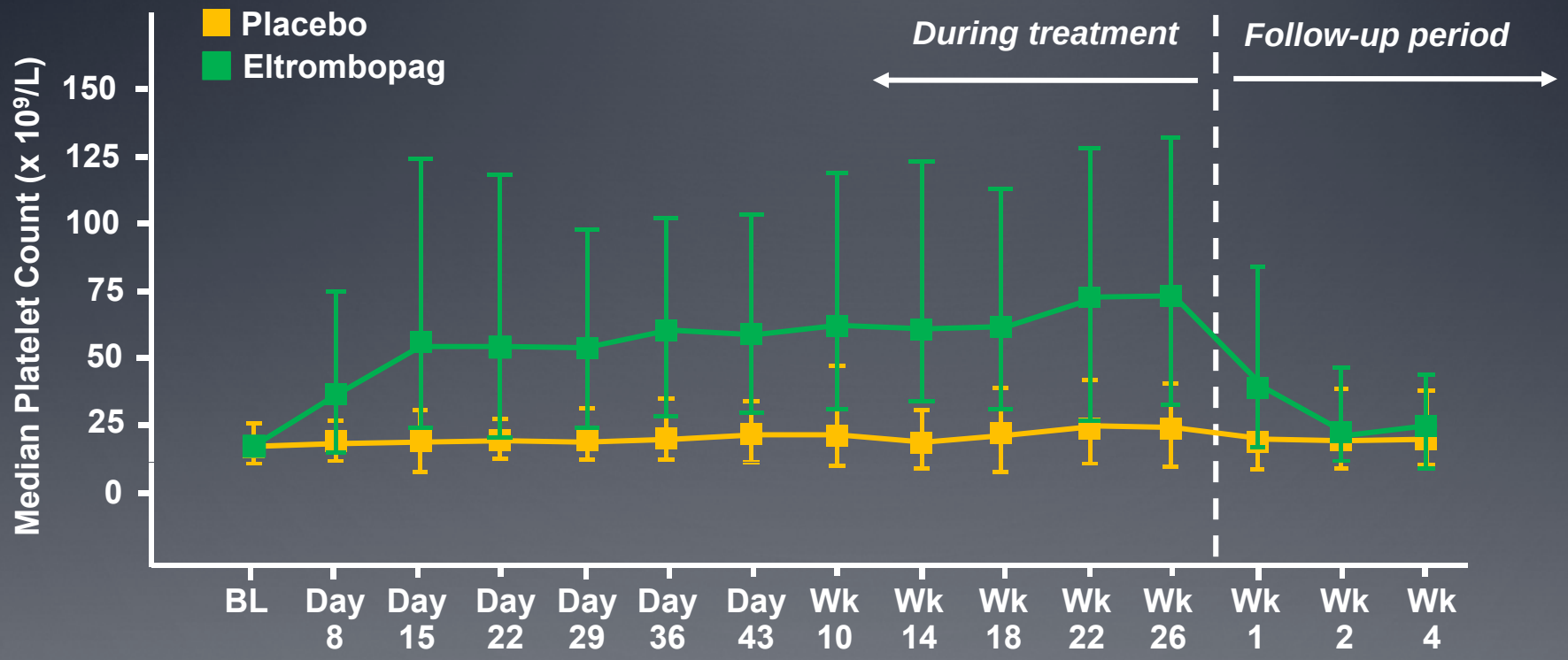
- Splenectomy status
- Concomitant maintenance ITP therapy
- Baseline platelet counts ≤15 000/μL or >15 000/μL

6-month treatment period

SoC=standard of care

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

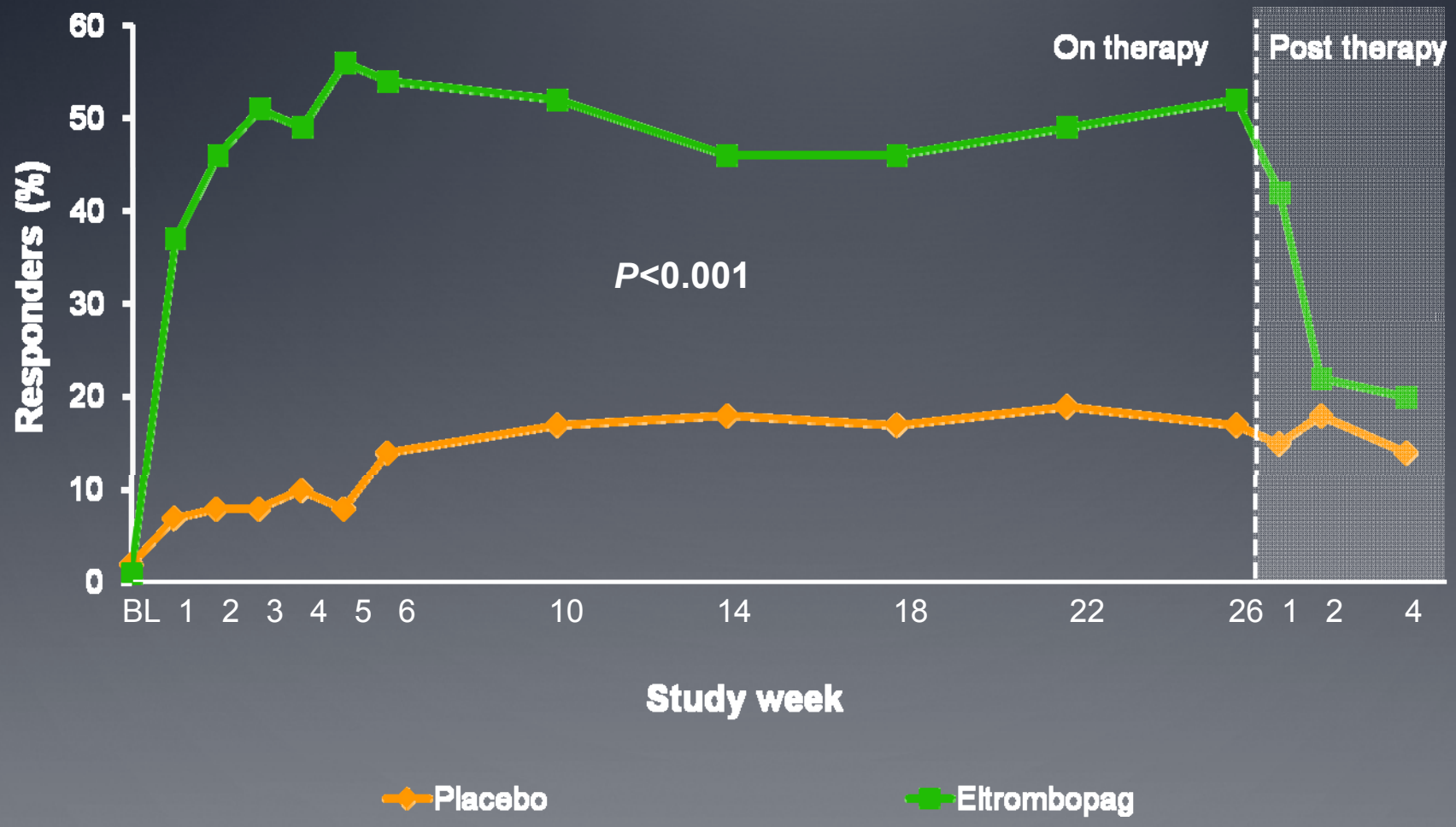
Eltrombopag: Phase III RAISE Study
Platelet Response



Eltrombopag was effective regardless of concomitant ITP therapy, splenectomy status or baseline platelet count

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

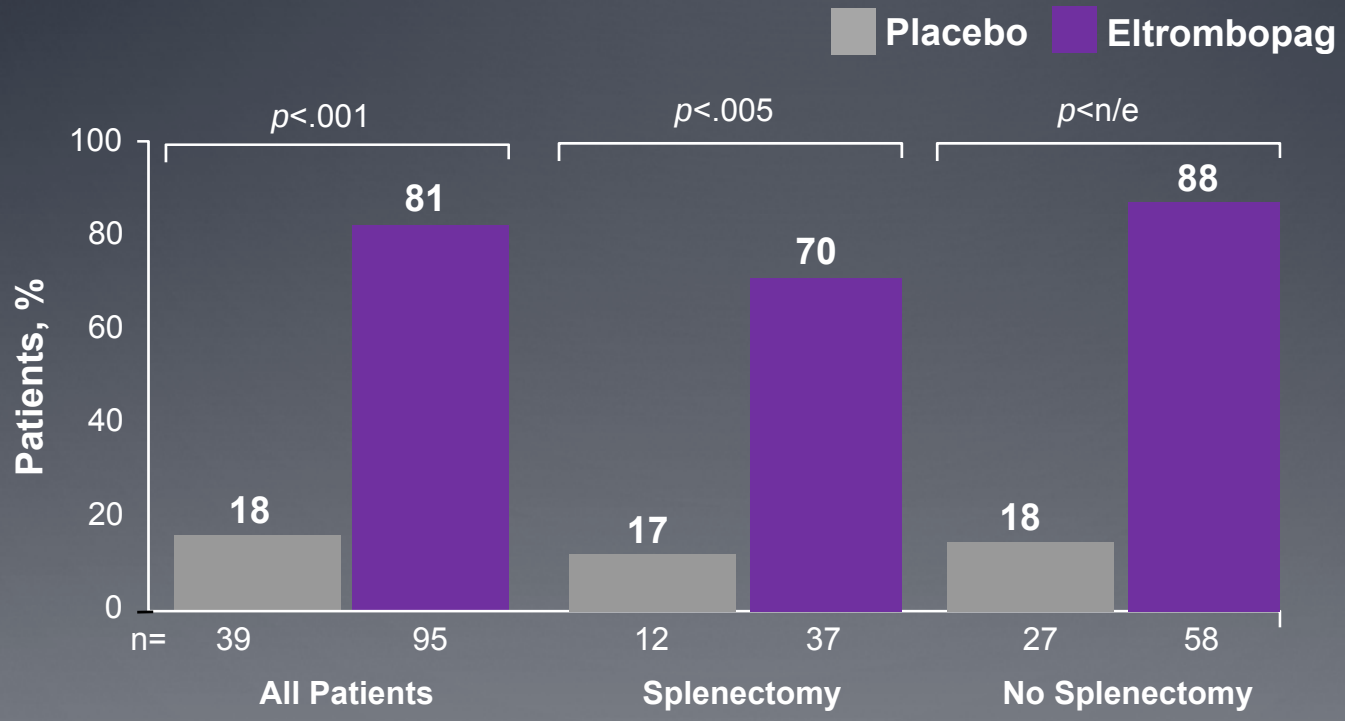
Significant Number of Patients Achieved Platelets between 50,000 and 400,000/μL with Eltrombopag



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

Eltrombopag: Overall Platelet Response*

Overall response: Four or more weekly platelet responses **(platelets ≥50,000/µL and ≤400,000/µL)** at any time during the study

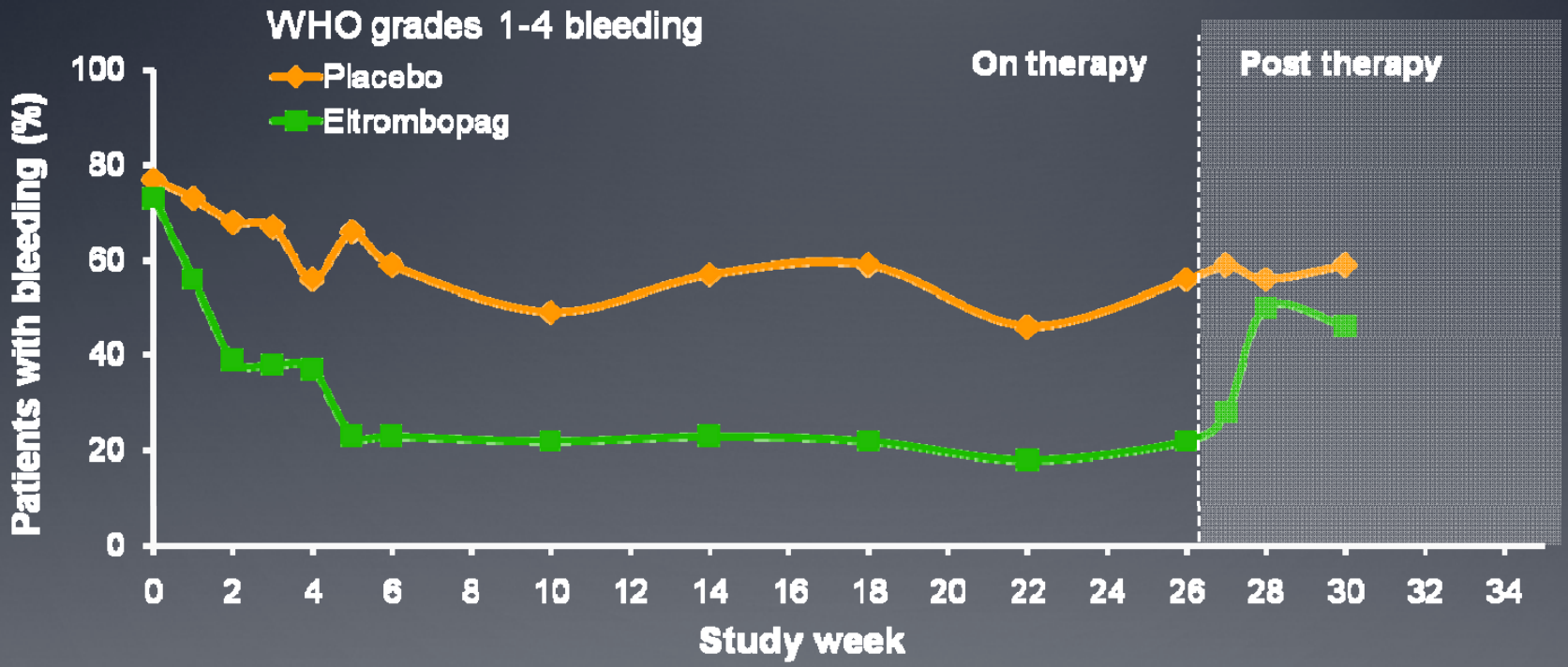


***Post hoc analysis**

n/e = not estimable

Stasi R, et al. *Haematologica* 2009; 94(Suppl 2): 231.

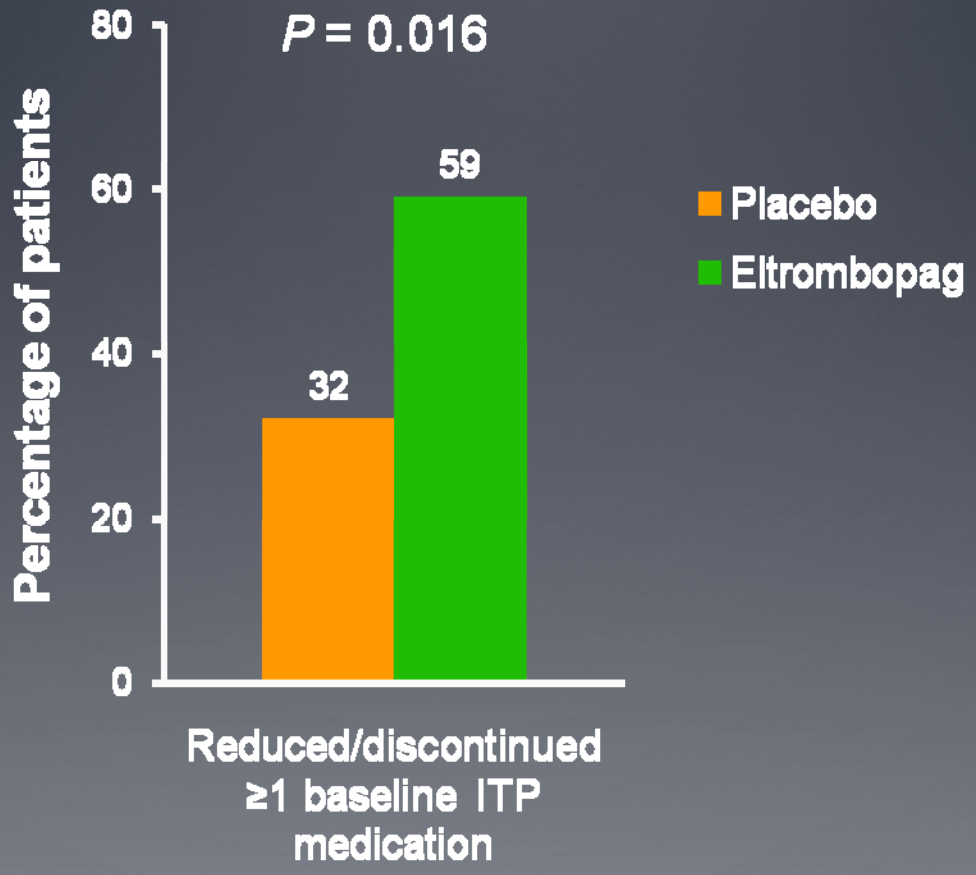
Eltrombopag Significantly Reduces Bleeding



Reduced the incidence of bleeding (WHO grades 1–4) and clinically significant bleeding (WHO grades 2–4) from baseline by approximately 50% from day 15 throughout the 6-month treatment period

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

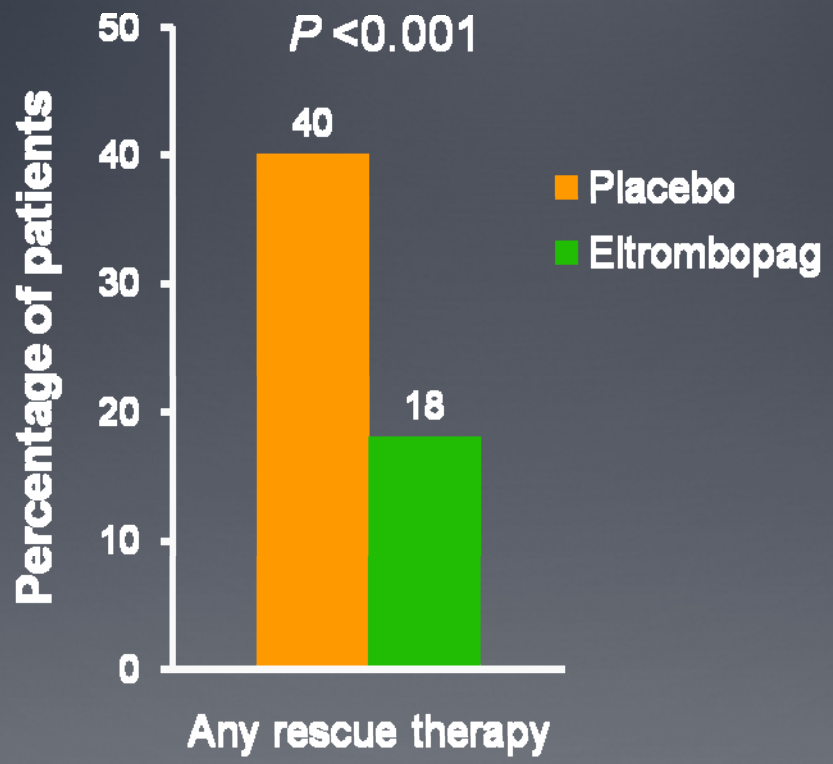
Eltrombopag: Reduction or Discontinuation of Concurrent ITP Therapy



Primarily a reduction in the use of corticosteroids

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

Eltrombopag: Reductions in Use Of ITP Rescue Medication



Odds ratio = 0.33 (95% CI = 0.16–0.64).

Primarily a reduction in the use of corticosteroids

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

Eltrombopag Improved Patient Health-Related Quality of Life

Patient-Reported Outcome: Instrument and Domain	Average Effect of Eltrombopag on Score Δ from BL		
	Estimate score Δ	95% CI	P value
SF-36v2			
Physical role	5.4	0.5-10.3	.030
Bodily pain	5.1	-0.5-10.6	.074
Vitality	3.9	0.1-7.7	.045
Social Function	4.1	-0.6-8.9	.089
Emotional role	5.4	0.8-10.1	.023
PCS	1.3	-0.2-2.9	.092
MCS	2.1	0.2-4.0	.030
FACT-Fatigue	1.6	-0.2-3.5	.082
FACT-Th (6 selected items)	1.5	0.5-2.5	.004

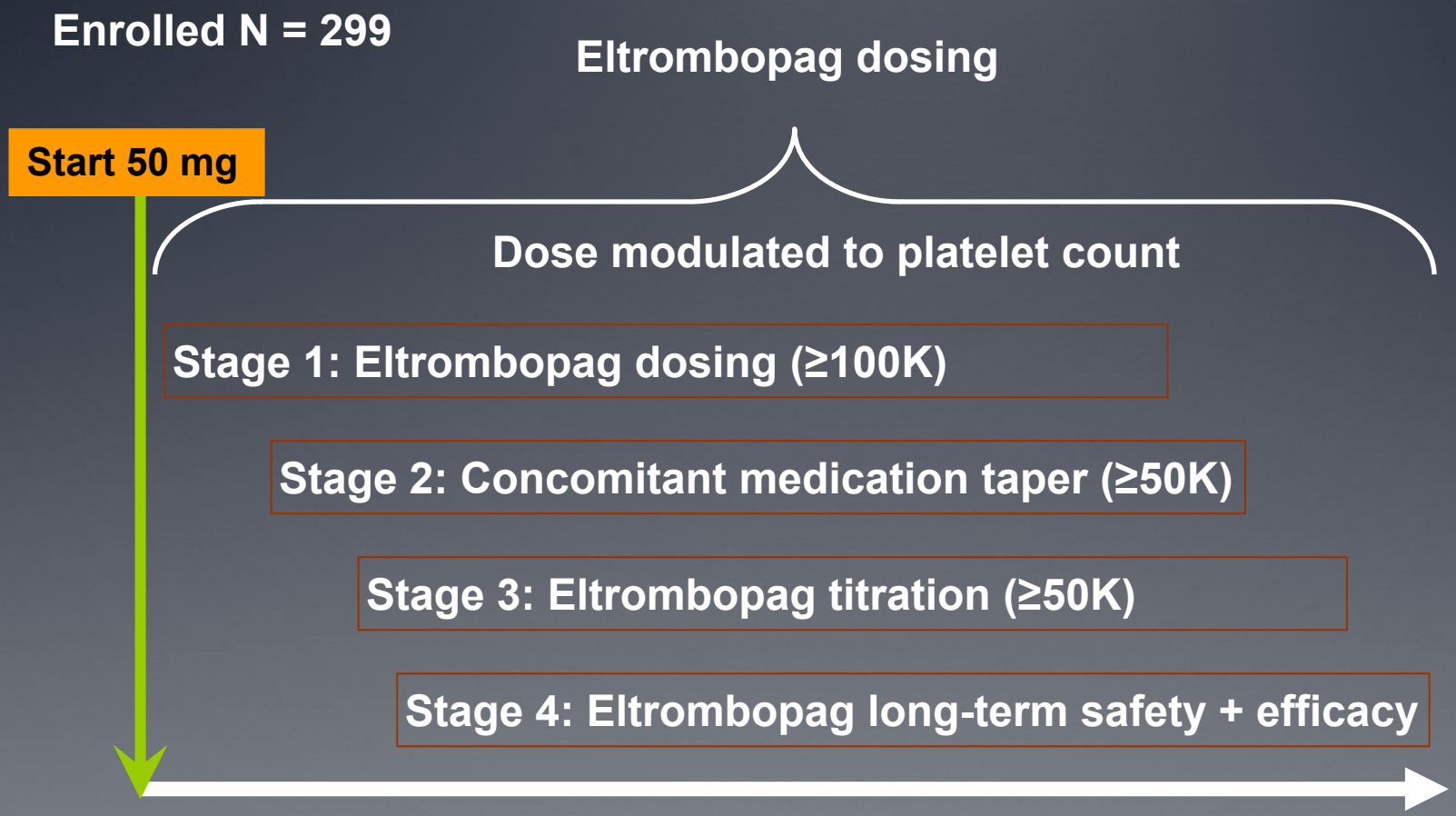
Patients treated with eltrombopag experienced less fatigue as evidenced by improvements in the vitality domain of the SF-36v2, the FACIT-Fatigue, and the 6 items of the FACT-Th.

- **Less fatigue with eltrombopag therapy**: improvements in the vitality domain of the SF-36v2, the FACIT-Fatigue, and the 6 items of the FACT-Th

Adapted from Bussel JB, et al. *Haematologica.* 2009; 94(Suppl 2): 0233.

EXTEND: Open-Label Extension Study

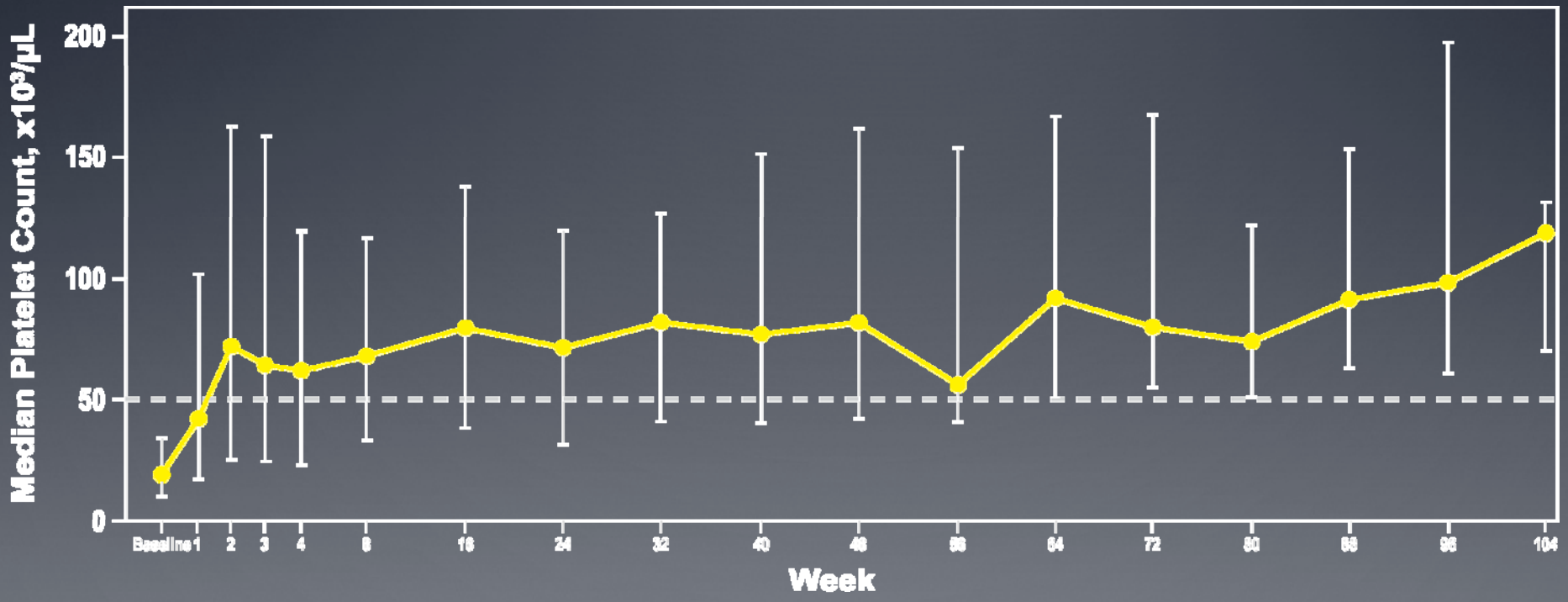
Chronic ITP patients previously enrolled in eltrombopag studies



Saleh et al. *Blood.* 2009;114: Abstract 682.

EXTEND: Durable Platelet Count Elevation

- **79% of patients achieved a platelet count of > 50 x 10^9/L at least once and 78% of these patients maintained platelets > 50 x 10^9/L for over 50% of their time in the study.**



# patients	299	271	241	161	118	97	76	47	31	22	17	17	16	8	5

Saleh et al. *Blood.* 2009;114: Abstract 682.

Common Side Effects of Romiplostim and Eltrombopag

- Generally well tolerated
- AEs were mostly mild to moderate
- Dizziness, myalgia and abdominal pain more common with romiplostim than with placebo
- Nausea and vomiting were more common with eltrombopag than with placebo

Kuter DJ, et al. *Lancet.* 2008;371(9610):395-403. Cheng G, et al. *Blood.* 2008;112: Abstract 400.

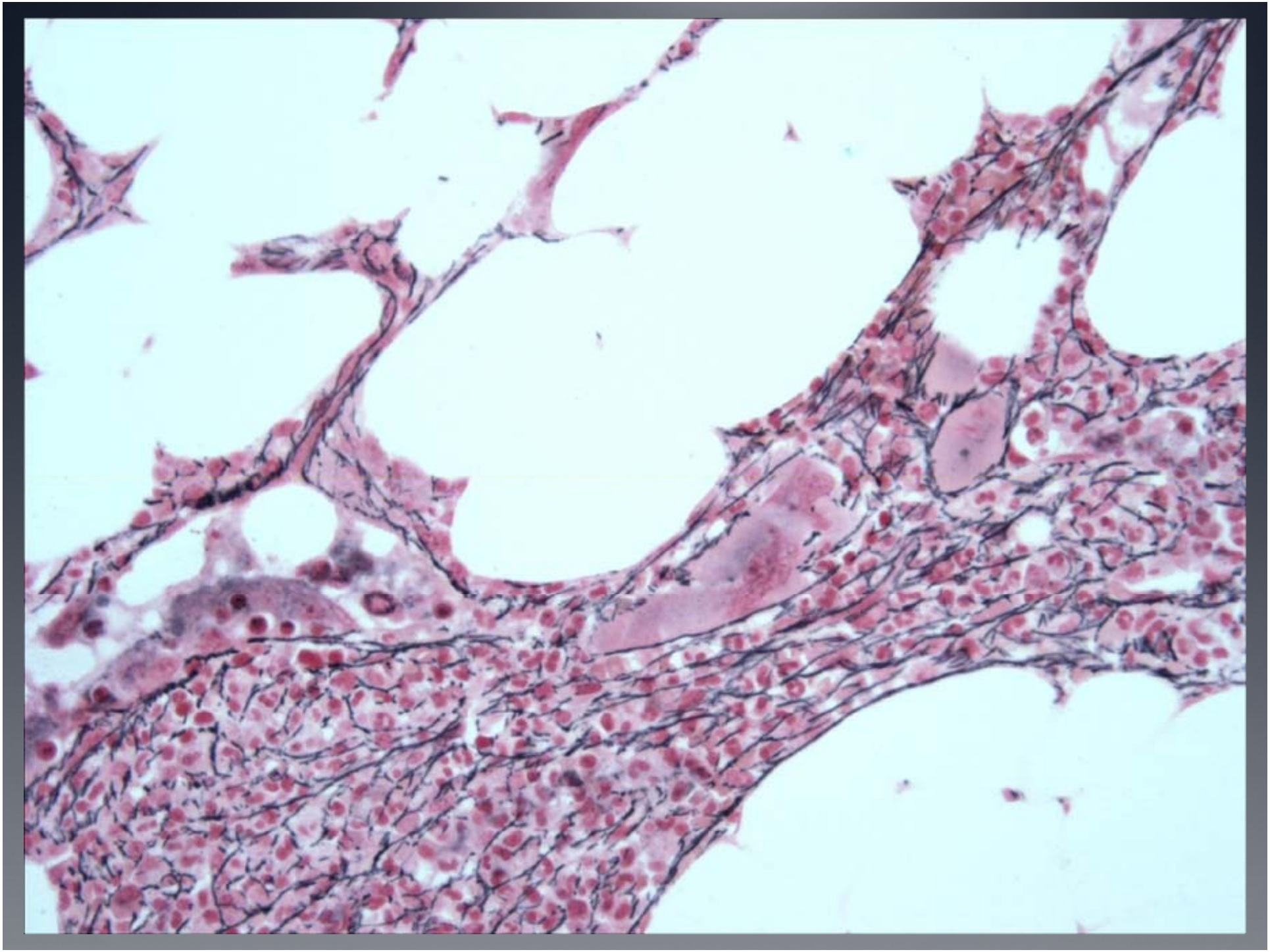
Potential Adverse Consequences of Thrombopoietic Growth Factors

- Thrombocytosis
- Autoantibody formation
- Stem cell depletion
- Reduced threshold for platelet activation
- Stimulation of tumor growth
- Interactions with other cytokines
- Headache
- Hepatobiliary laboratory abnormalities
- Rebound worsening of thrombocytopenia
- Increased bone marrow reticulin or collagen
- Thrombosis
- Stimulation of leukemia cell growth

Thromboembolic Events (TEE)

- In double-blind, placebo-controlled studies, no statistically significantly increased risk of TEE with both agents
- TEE in long-term studies:
  - Romiplostim 4.9%[1]
  - Eltrombopag 3.8%[2]
- No correlation seen between peak platelet count and TEEs

1. Bussel JB, et al. *Blood*. 2009;113:2161-2171. 2. Bussel JB, et al. *Blood*. 2009;114: Abstract 2423.



Increased Bone Marrow Reticulin

- Normals and patients with ITP prior to treatment may have detectable reticulin in the bone marrow[1]

- Reversible in 9 AML subjects with rhTPO-related increase[2]
- 10/271 romiplostim patients[3-4]
  - Many at high doses (6/10 received ≥ 10 µg/kg)
  - Many with minimal response to drug
  - Decreased in 3 with subsequent bone marrow biopsies
- 19/117 eltrombopag patients had bone marrow examination
  - 5 reticulin increased, 2 collagen increased[5]

1. Kuter DJ, et al. Br J Haematol. 2007;139(3):351-62. 2. Douglas VK, et al. *Am J Clin Pathol.* 2002;117:844-850 3. Bussel JB, et al. *Blood.* 2009;113(10):2161-2171. 4. Kuter DJ, et al *Lancet*. 2008;371(9610):395-403. 5. US FDA ODAC Briefing Document. Available at: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4366b1-02-GSK.pdf.

Key Summary of TPO-R Agonist Benefits

- Raises and sustains platelet count in more than 60% of patients
- Reduction in bleeding
- Reduction/discontinuation of concomitant ITP or rescue ITP medication
- Well tolerated safety profile – ongoing long term effects of TPO-R agonists need to be monitored
- Robust clinical data for romiplostim SC weekly and eltrombopag once daily oral tablet in the treatment of chronic ITP

Use of TPO-R Agonists in ITP: Questions for the Present and the Future

- How fast can one increase the count
- Do the different agents work in the same patients or are responses different
- Do you give these agents indefinitely or may improvement be seen
- Are there additive effects or synergy with other treatments

Conclusions

- New terminology: Primary immune thrombocytopenia
- New definition of thrombocytopenia: Plt < 100 x 10^9/
- New epidemiologic data: ITP ↑ with increasing age
- New concepts on pathophysiology
  - Thrombocytopenia is due both to increased platelet destruction and impaired platelet production
  - Both B-cells and T-cell activity disregulated
- New treatment options:
  - Second-generation thrombopoietic agents