Romiplostim

Oncologic Drugs
Advisory Committee

12 March 2008

Agenda

Background and Introduction	**Joseph Miletich, MD, PhD** **Research & Development, Amgen Inc.**
Thrombopoietin (TPO) and Management of Immune Thrombocytopenic Purpura (ITP)	**David Kuter, MD, DPhil** **Professor, Department of Medicine, Harvard Medical School, Director, Clinical Hematology, Massachusetts General Hospital**
Romiplostim in ITP: Efficacy and Risk Assessment	**Dietmar Berger, MD, PhD** **Global Clinical Development, Amgen Inc.**
Risk Management Program and Closing Remarks	**Paul Eisenberg, MD, MPH** **Global Regulatory Affairs & Safety, Amgen Inc.**

Thrombopoietin (TPO): The Elusive Platelet Growth Factor

nature

Nature 369, 519 - 520 (16 June 1994)

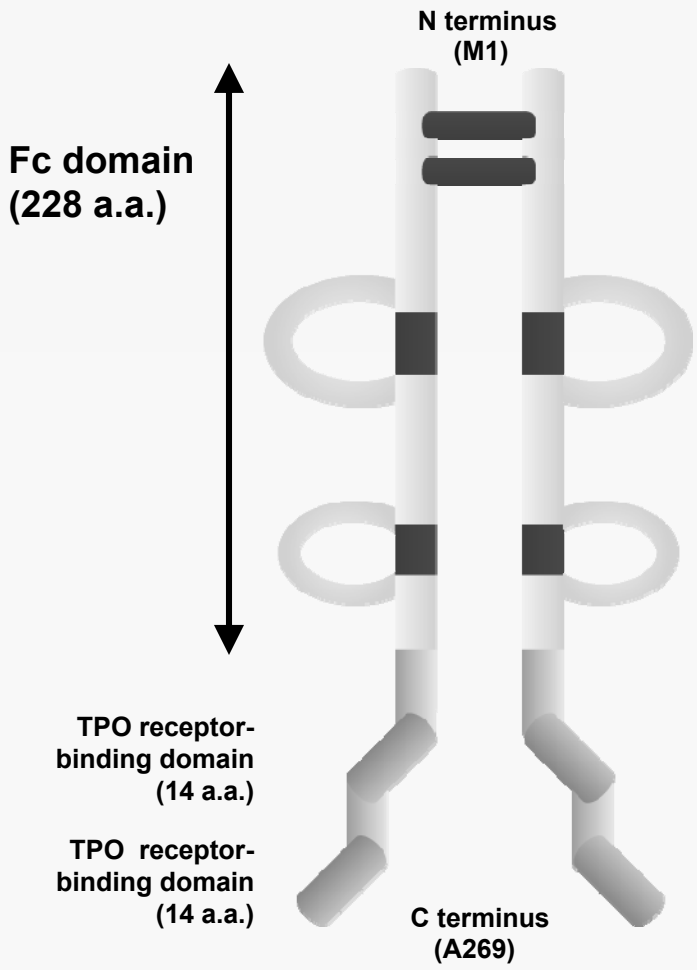
Thrombopoietin — at last

Donald Metcalf, MD, PhD

- **Sequenced and/or isolated by 5 groups in 1994**
- **Established as the major megakaryocyte/platelet growth factor**
- **Trials with two recombinant molecules based on TPO sequence. Neutralizing antibodies cross-reacted with endogenous TPO**
- **Evidence of efficacy in Immune Thrombocytopenic Purpura (ITP)**

Romiplostim Stimulates Platelet Production Through Binding to the TPO Receptor

- **Not based on TPO sequence**
- **Novel peptide binds to and stimulates receptor**
- **Fc-peptide fusion protein, (peptibody) produced in *E. coli***



Amgen Has Consulted with FDA on Romiplostim Development in ITP

- **Immune Thrombocytopenic Purpura (ITP) is an orphan disease**
- **Efficacy demonstrated for primary and secondary endpoints in two pivotal trials**
- **Risk Management Program proposed, including a formal risk minimization action plan (RiskMAP)**

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ITP

- **Definition of ITP**
  - **Isolated thrombocytopenia**
  - **Exclusion of other causes of thrombocytopenia**
- **Characteristics**
  - **Autoantibodies to platelet glycoproteins**
  - **Platelet destruction and impaired platelet production**
  - **Thrombocytopenia, bruising, bleeding**
  - **Treatments: immunosuppressive or immunomodulatory (including splenectomy)**
- **Epidemiology**
  - **Incidence 1.6-3.3 / 100,000 adults / yr**
  - **Prevalence 9.5 / 100,000 adults**

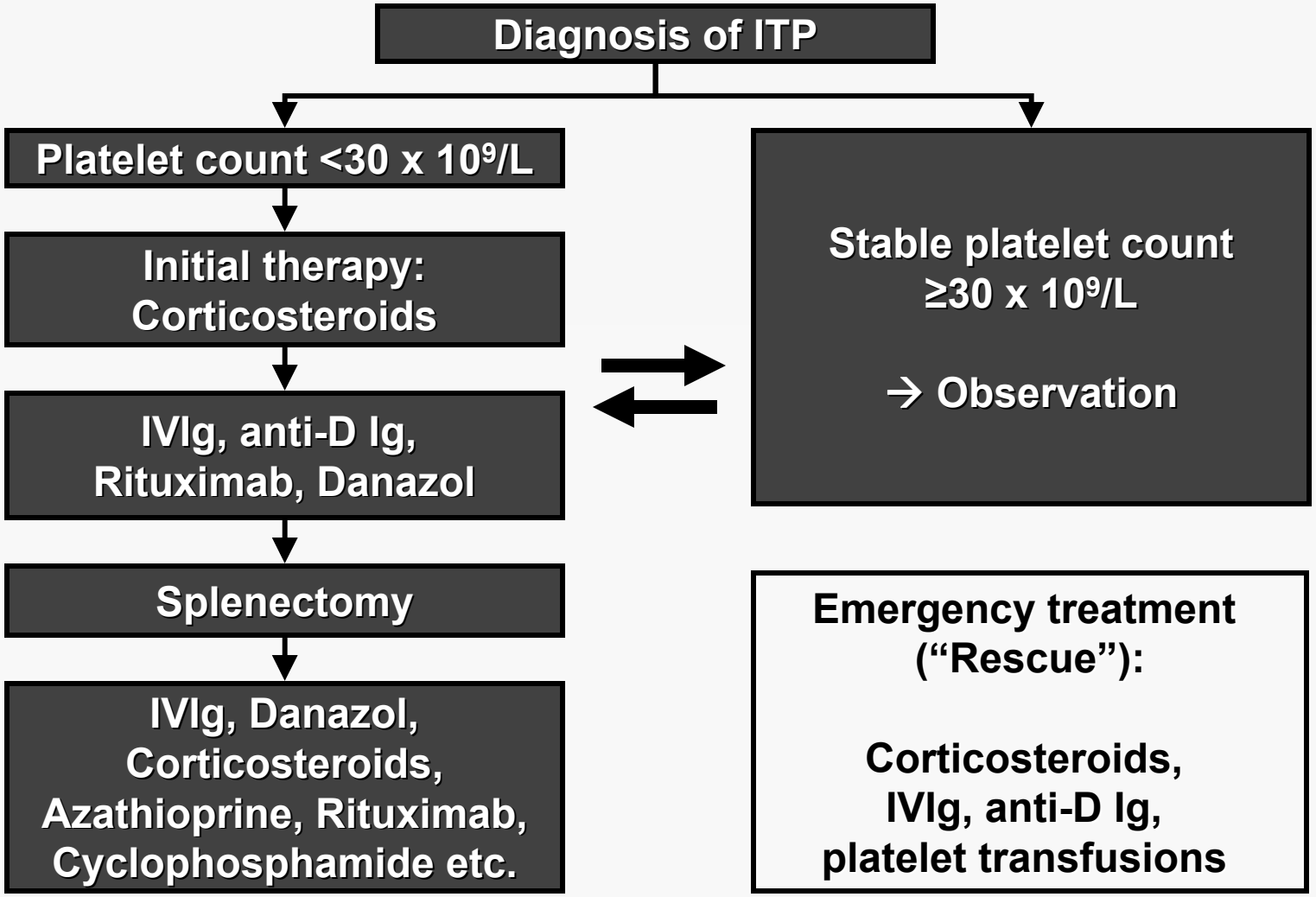
Adapted from Cines & Blanchette, 2002

ITP Diagnosis and Treatment Per ASH Guidelines

- **Diagnosis**
  - **History, physical exam, blood counts and peripheral blood smear required**
  - **No confirmatory test; anti-platelet antibody not informative**
  - **No routine bone marrow biopsy performed, aspirate recommended in patients >60 or prior to splenectomy**
  - **Confirmed by clinical response to corticosteroids**
- **Treatment**
  - **Indicated for platelet counts <20-30 x 10^9/L or <50 x 10^9/L with significant mucosal bleeding or risk factors for bleeding**
  - **Goal is platelet count >50 x 10^9/L**

George et al., 1996

Current Treatment Options for ITP: All Target Platelet Destruction



Most products not approved for treatment of ITP

Current ITP Medical Therapies Have Risk for Serious Consequences

Corticosteroids	**Depression/psychosis, diabetes, hypertension, adrenocortical suppression, osteoporosis, cataracts, life-threatening infection**
Anti-D Ig	**Anaphylaxis, intravascular hemolysis, infection transmission**
IV Ig	**Anaphylaxis, infusion reactions, infection transmission**
Rituximab	**Fatal infusion reaction, severe mucocutaneous reaction, progressive multifocal leukoencephalopathy, hepatitis B reactivation with fulminant hepatitis**
Danazol	**Lipoprotein alterations, androgenic effects**
Azathioprine	**Immunosuppression, increased risk of neoplasia, serious infection, pancytopenia, hematologic toxicity**
Cyclophosphamide	**Renal failure, heart failure, impaired fertility and mutagenesis, carcinogenesis**

Individual product prescribing information

Considerations for Splenectomy in ITP

- **Laparotomy**
  - **Mortality: 48/4955 (1.0%)**
  - **Morbidity: 318/2465 (12.9%)**
- **Laparoscopy**
  - **Mortality: 3/1301 (0.2%)**
  - **Morbidity: 88/921 (9.6%)**
- **Relapse rate: 30-40%**
- **Long-term risk: increased susceptibility to bacterial infection**

Kojouri et al., 2004

Bleeding Risk in ITP Patients

- **Review of 17 studies including 1817 ITP patients**
- **Non-fatal, severe bleeding not analyzed**
- **49 cases of fatal hemorrhage**
- **Fatal bleeding risk calculated as 1.6 – 3.9% per patient year**
- **Increased risk with higher age groups (>60 years)**

Cohen et al., 2000

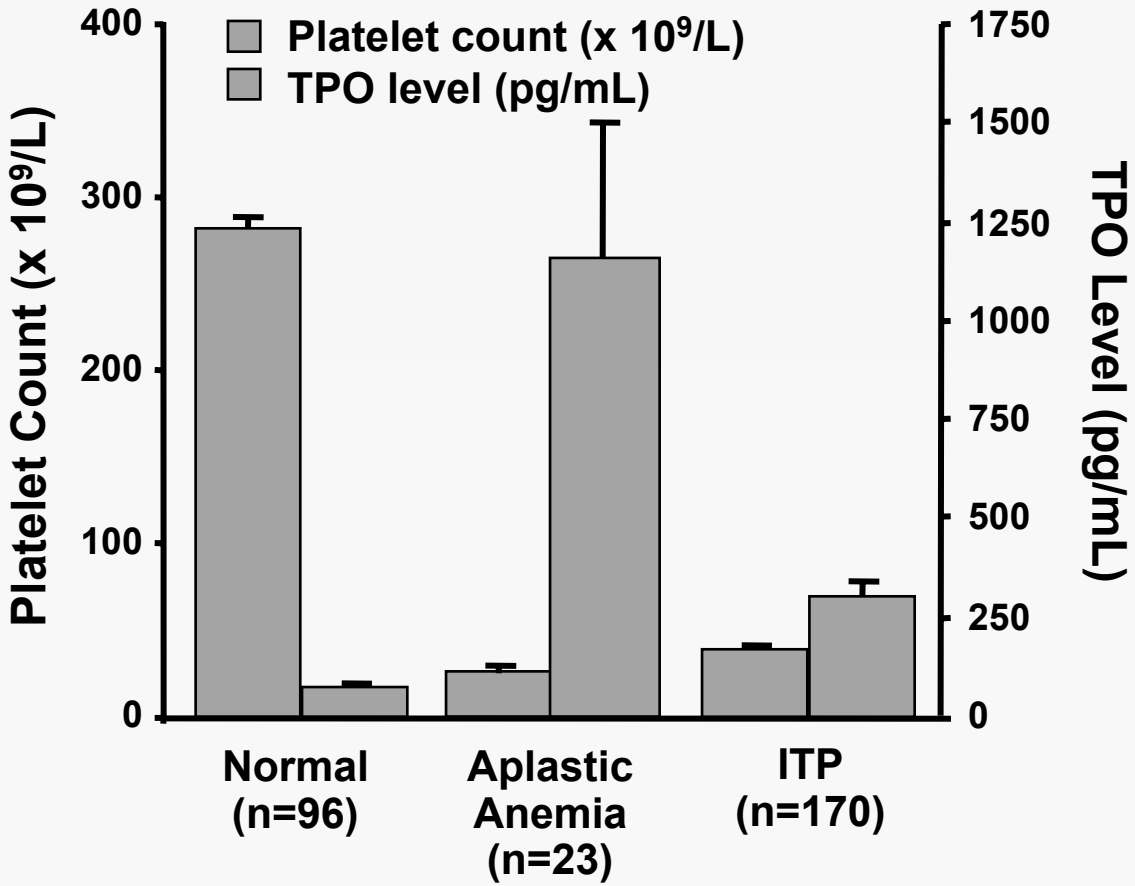
Fatal Events in Adult Patients with Refractory ITP

- **Largest prospective study in refractory adult ITP (n=105)**
- **Median follow-up 110 months (mean 143 months)**
- **Multiple treatments: corticosteroids, danazol, azathioprine, cyclophosphamide, combination therapies**
- **11 patients (10%) died of bleeding**
- **6 patients (6%) died of treatment-related AEs**

McMillan and Durette, 2004

Mechanisms for Inadequate Platelet Production in ITP

- **TPO levels normal in 75% of ITP patients[1]**
- **Platelet production reduced or normal in 2/3 of ITP patients[2-4]**
- **Autoantibody inhibition of megakaryocyte growth and induction of early apoptosis[5-6]**



[1]Kuter, et al., 1997. [2]Stoll, et al., 1985. [3]Heyns et al., 1986 [4]Ballem et al.,1987. [5]McMillan, et al,. 2004. [6]Chang M, et al., 2003.

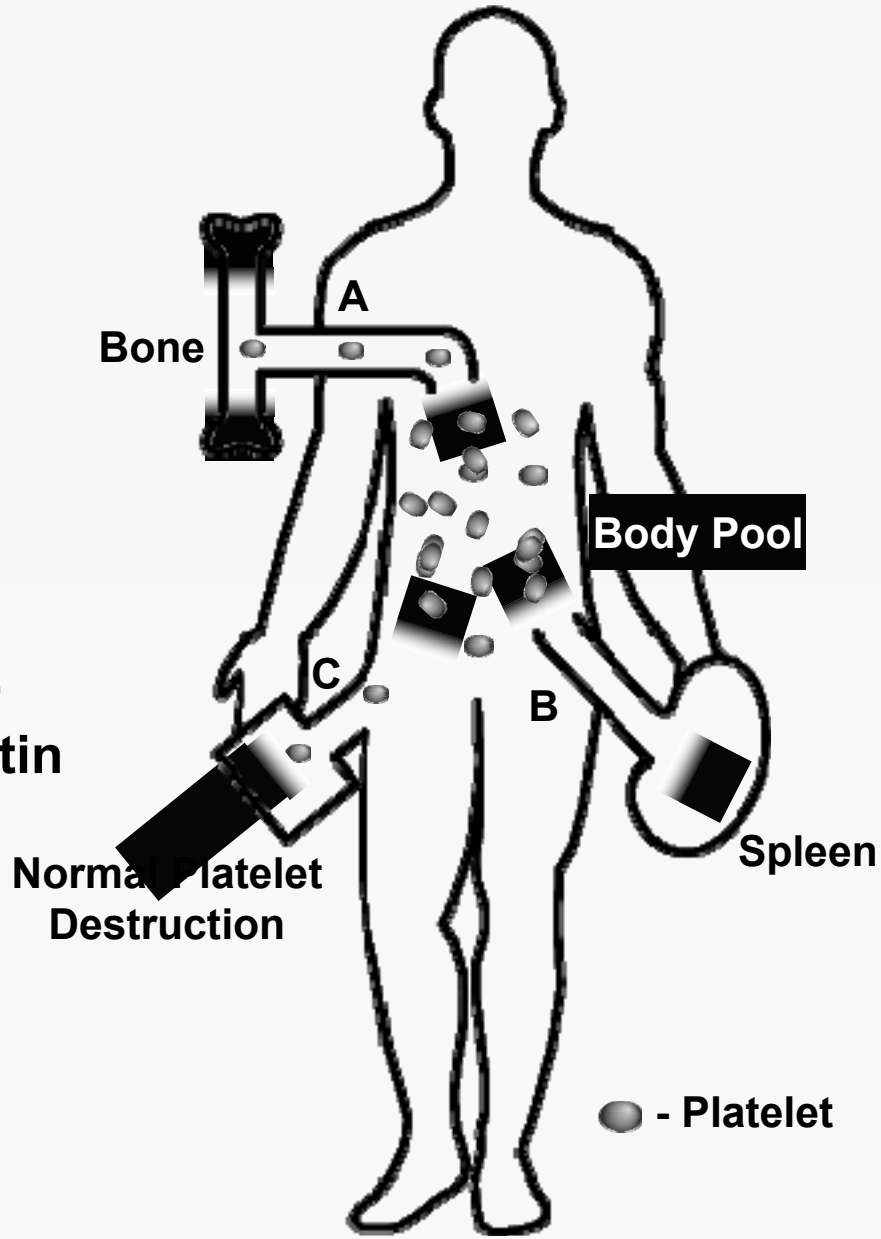
Normal

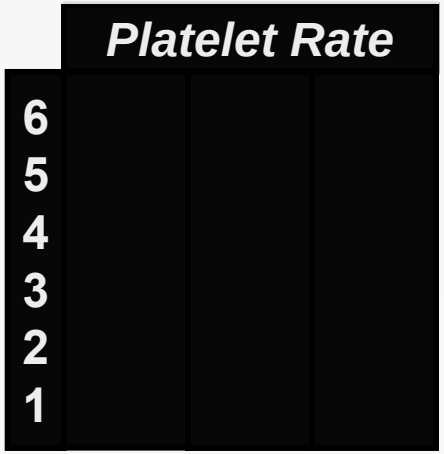
Onset ITP

Chronic ITP
Old Model

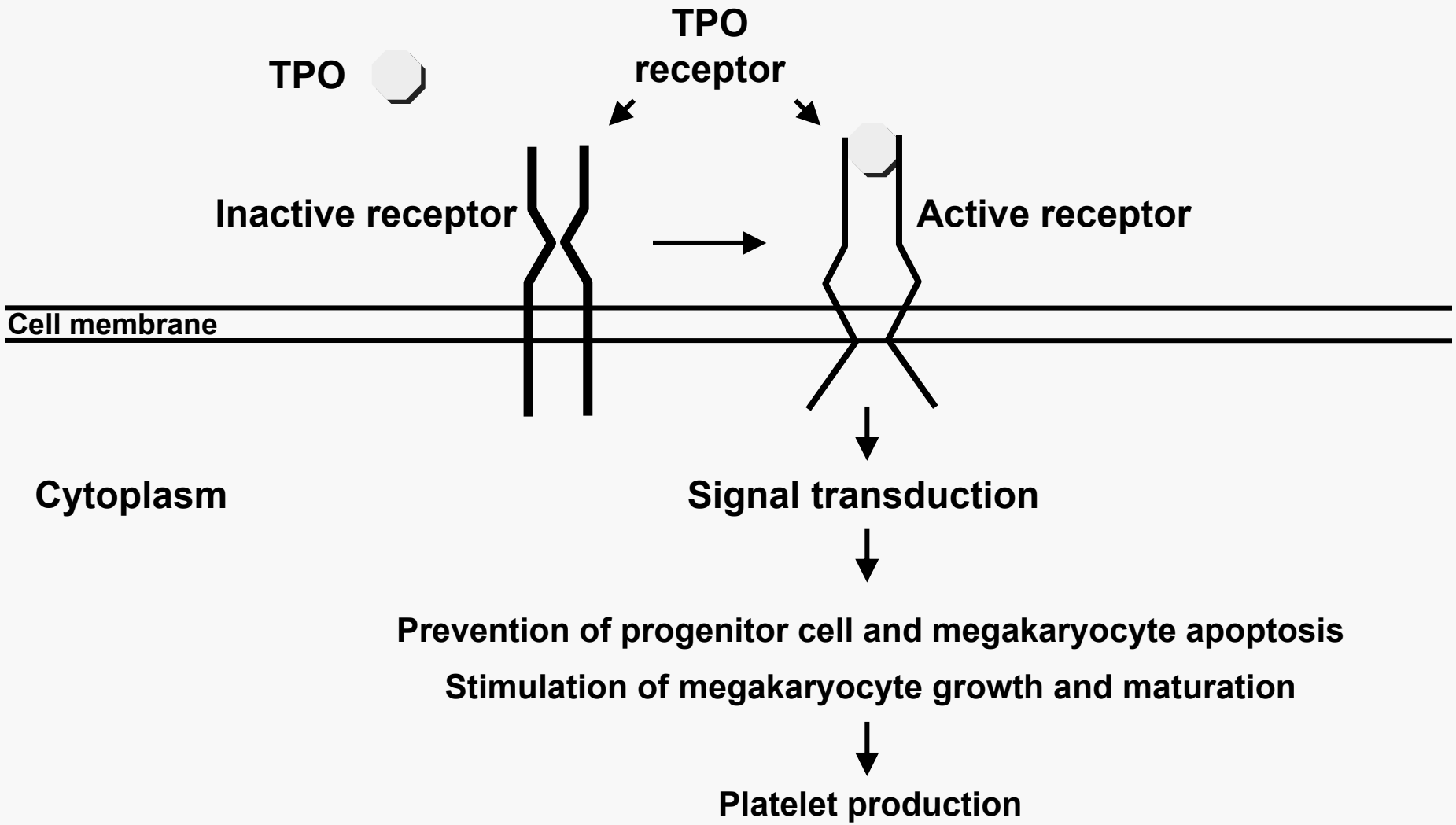
Chronic ITP
New Model

Chronic ITP +
Thrombopoietin



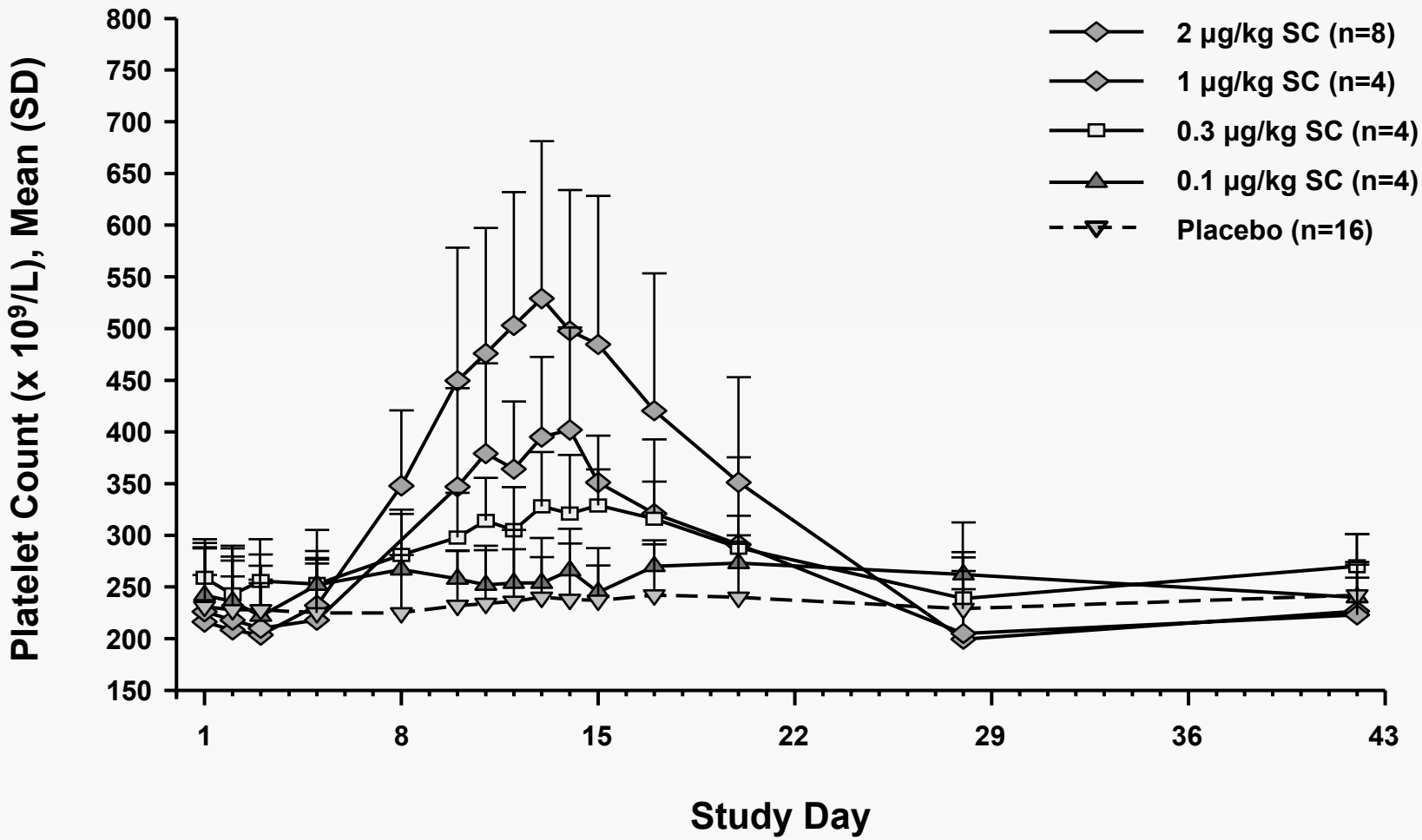


TPO Mechanism of Action



Kuter, 2007

Platelet Response to a Single Dose of Romiplostim in Healthy Subjects

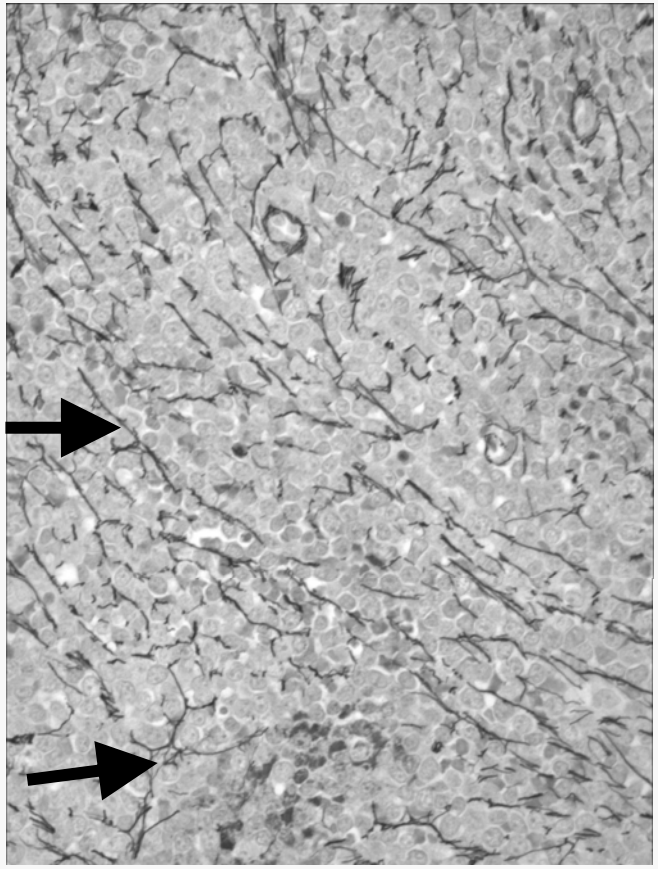


Wang et al., 2004

Theoretical Concerns Regarding Pharmacologic Administration of Thrombopoietic Factors

- **Thrombocytosis**
- **Thrombosis**
- **Stimulation of tumor growth**
- **Stimulation of leukemia cell growth**
- **Autoantibody formation**
- **Increased bone marrow reticulin**

Reticulin: A Normal Bone Marrow Component

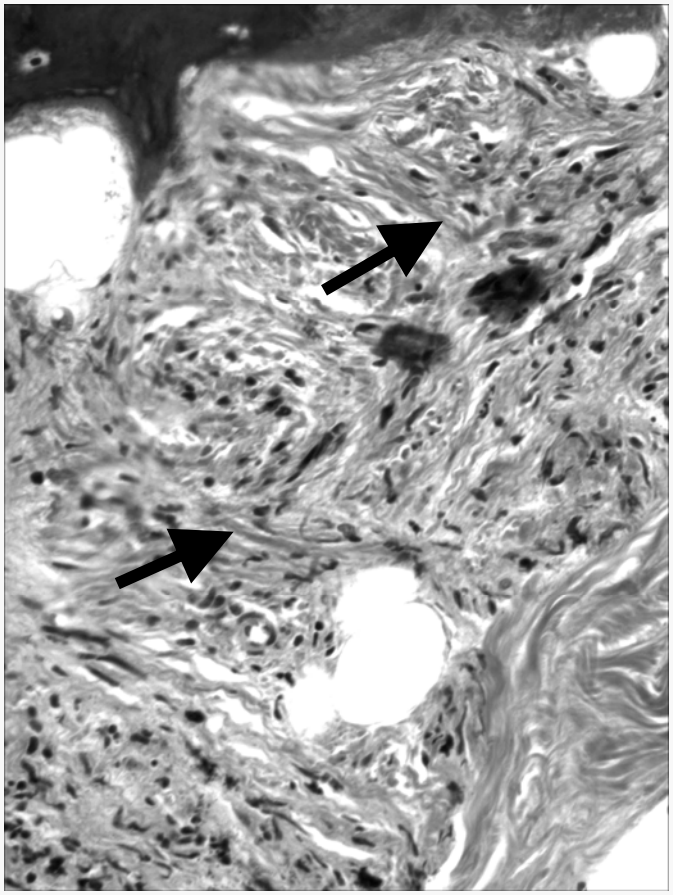


Bone marrow reticulin stain
Grade 2

- **Silver stains bind hexoses around reticulin**
- **Grades 0-2 in normal and ITP subjects**
- **Grades 3-4 may be abnormal**
- **Increased in many infectious, inflammatory, oncologic disorders, with GM-CSF, IL-3, IL-11**
- **Reversible**
- **Does not affect blood counts**

Kuter et al., 2007; Bauermeister et al., 1971

Collagen: Pathological in Bone Marrow



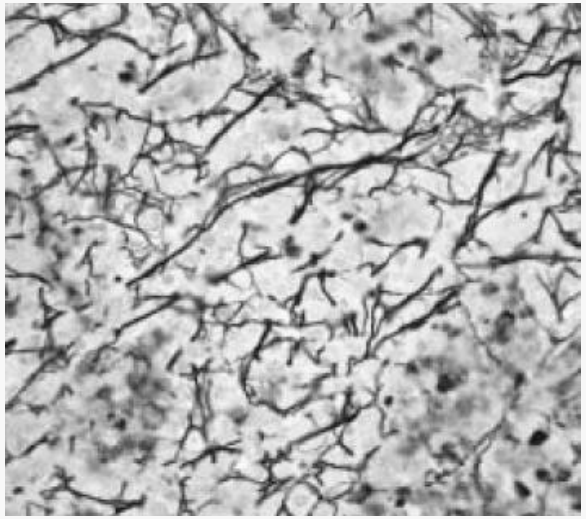
Bone marrow collagen (trichrome) stain

- **Trichrome stain**
- **May be accompanied by reticulin staining (Grade 4)**
- **Associated with clonal malignant disorders (metastatic cancer, hairy cell leukemia, myeloproliferative disorders)**
- **Reversible with treatment of clonal disorders**
- **Underlying clonal disease accounts for blood count abnormalities**

Kuter et al., 2007; Bauermeister et al., 1971

Increased Reticulin in TPO Treated AML Patients is Reversible

- **AML induction chemotherapy patients treated with TPO (2.5 µg/kg/d IV, up to 21 doses) + GM-CSF**
  - **8/9 had increased reticulin**
  - **2/6 controls (GM-CSF alone) had increased reticulin**
  - **Fully reversible in 30 d (range: 13-42 d)**



Reticulin stain x600

Douglas et al., 2002

Summary

- **ITP is a disease of accelerated platelet destruction and suboptimal platelet production**
- **Thrombocytopenia in ITP may lead to severe clinical consequences, including life-threatening bleeding**
- **Current treatments of ITP are often unsuccessful**
- **TPO is the major regulator of platelet production**
- **In ITP, circulating TPO levels are inadequate, and TPO administration can lead to platelet production**

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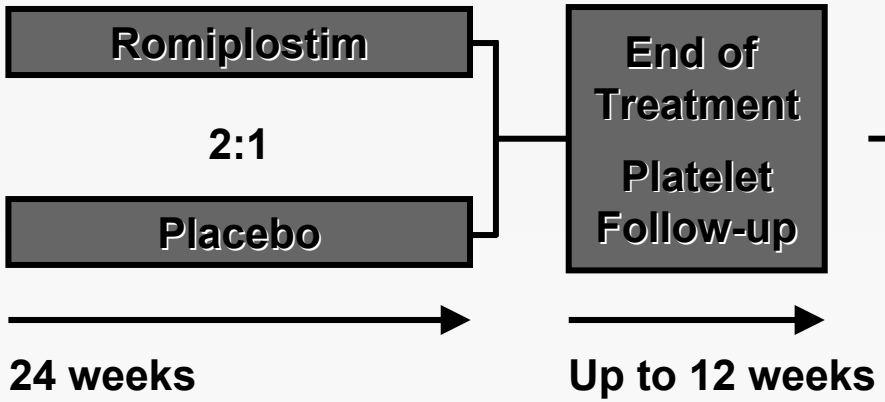
Overview of Clinical Study Program and Exposure at 120-Day Update

- **11 studies in ITP, n=308**
- **2 studies in healthy subjects, n=78**
- **1 study in MDS, n=44**
- **1 study in chemotherapy-induced thrombocytopenia n=21**

Duration of Romiplostim Exposure in ITP (Weeks)	n (%)
≥1	271 (100)
≥26	153 (56)
≥52	114 (42)
≥104	36 (13)

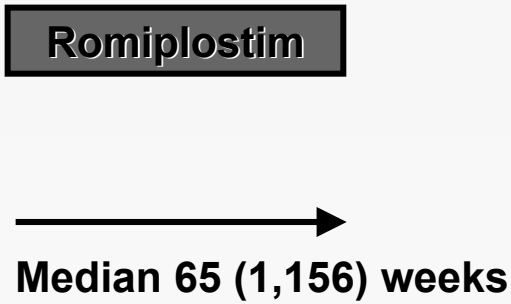
Romiplostim Study Designs in ITP

2 Randomized, Controlled, Phase 3 Studies



- 20030105: Splenectomized (n=63)
- 20030212: Non-splenectomized (n=62)
- Platelet count ≤30 x 10^9/L
- Romiplostim starting dose 1 µg/kg QW, dose adjustment by platelet count
- Concurrent and rescue ITP medication allowed

Long-term Extension Study



- 20030213: Ongoing, open-label (n=143)
- Similar design

Phase 3 Dosing Regimen Based on Early Clinical Studies

- **1 µg/kg starting dose supported by**
  - **Minimum active dose in healthy subjects**
  - **33% ITP subjects achieved 50 x 10^9/L within 1 week after dose**
  - **No ITP subjects exceeded 450 x 10^9/L**
- **1 week dosing interval supported by phase 2 data**
- **Individual dose adjustment required due to**
  - **Platelet count variability at baseline and on treatment**
  - **Platelet count variability between subjects at a given dose**

Primary Efficacy Endpoint

- **Incidence of durable platelet response**
  - **≥6 weekly platelet counts ≥50 x 10^9/L during last 8 weeks of 24 week treatment period**
  - **In absence of rescue medication at any time during study**
- **Platelet count ≥50 x 10^9/L clinically recognized as target at which risk of bleeding is minimized**

Secondary Efficacy Endpoints

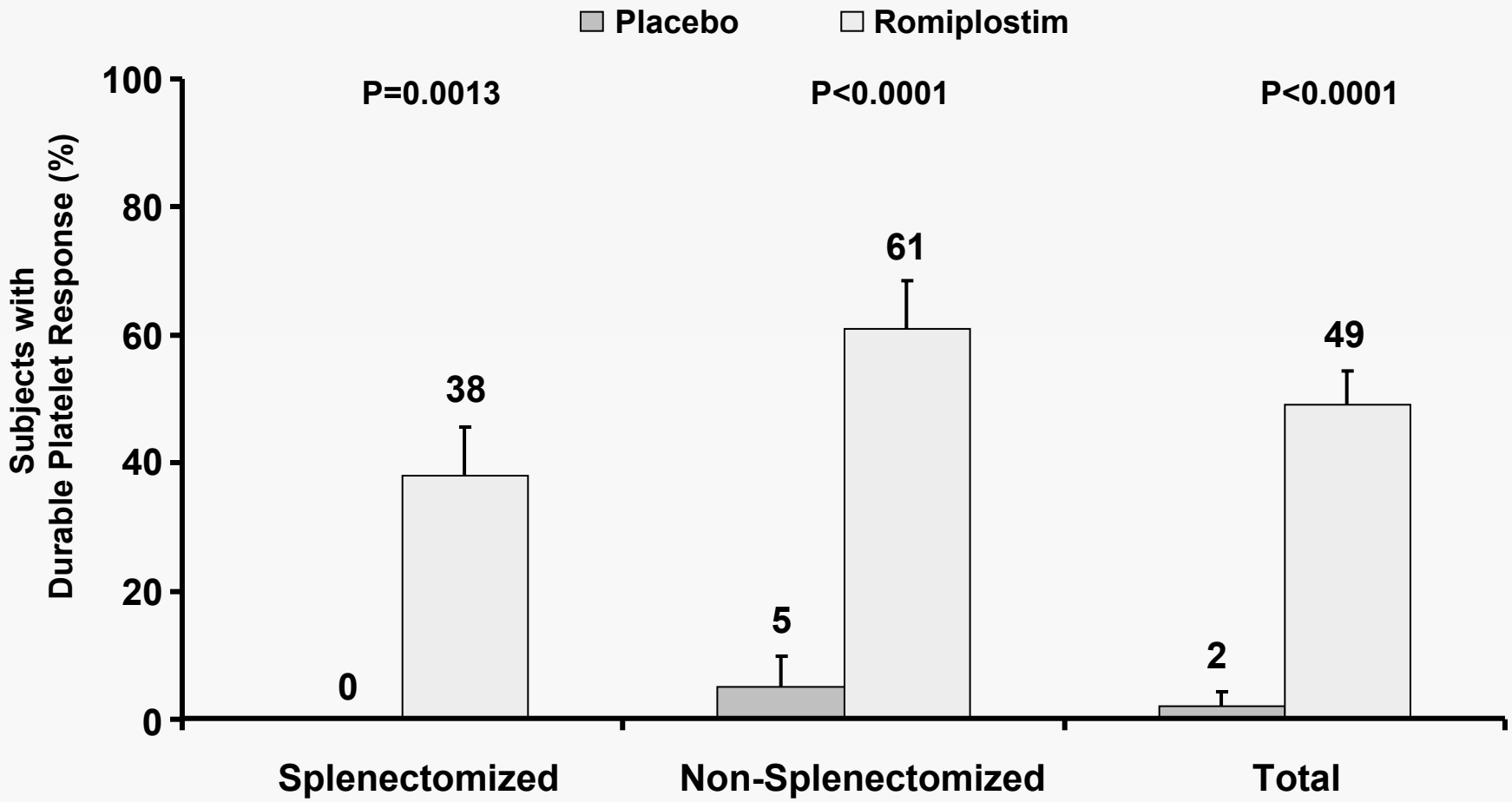
- **Overall platelet response**
  - **≥4 weekly platelet responses during 24 week treatment period**
  - **Platelet counts excluded within 8 weeks of rescue**
- **Number of weekly platelet responses**
- **Proportion of subjects requiring rescue medication**
- **Discontinuation/reduction of concurrent ITP medications**
- **Patient reported outcomes**

Patient Demographics

		Splenectomized		Non-Splenectomized	
		Placebo n=21	Romiplostim n=42	Placebo n=21	Romiplostim n=41
Age (years)	Mean (SD)	54 (13)	51 (16)	55 (22)	53 (16)
Female	n (%)	11 (52)	27 (64)	16 (76)	27 (66)
Platelet count (x 10^9/L)	Mean (SD)	14 (8)	15 (8)	19 (8)	17 (8)
Number of prior therapies*	Median (min, max)	6 (3,10)	6 (3,9)	3 (1,7)	3 (1,7)

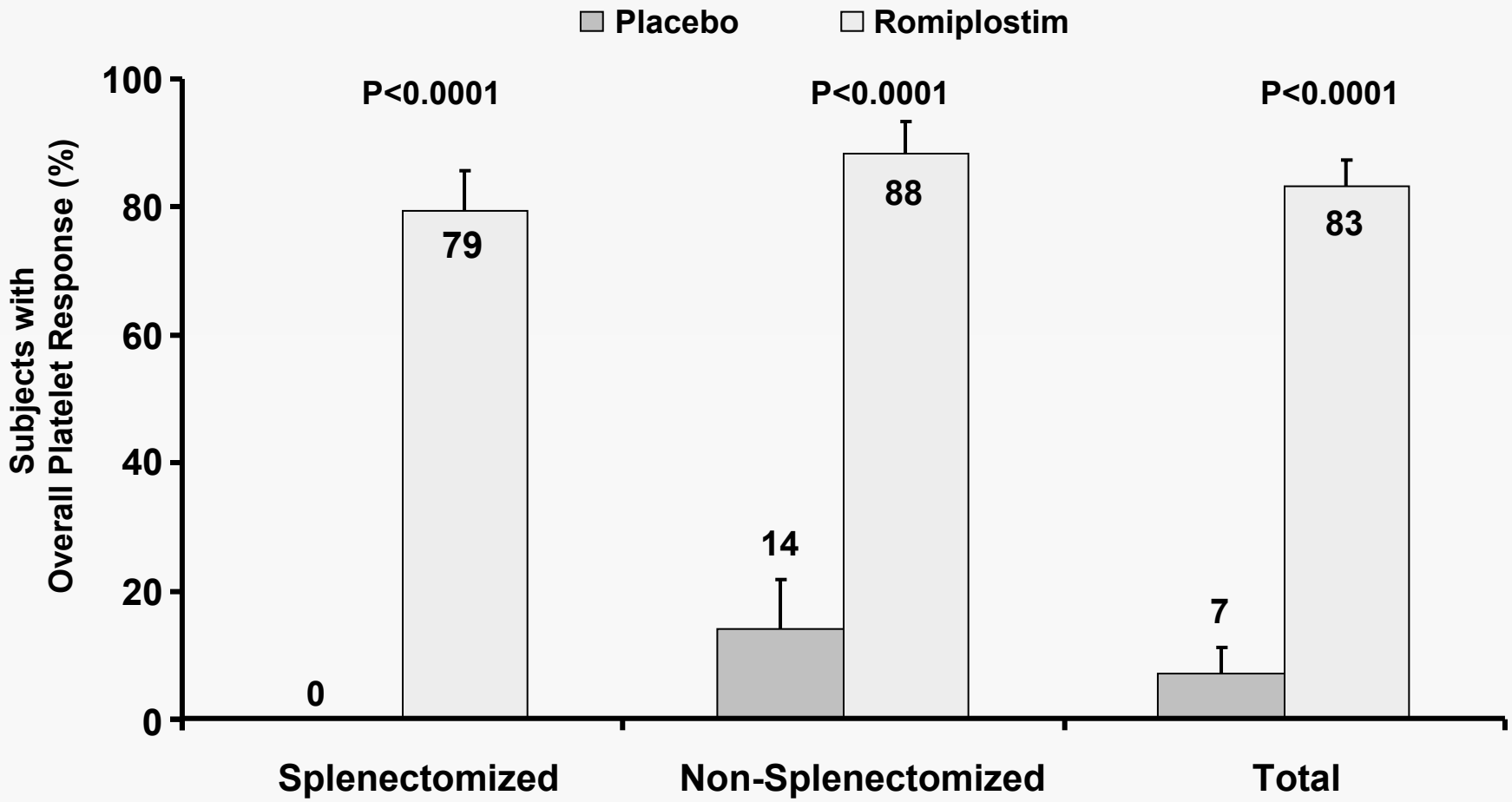
Five most frequently used prior medical therapies: corticosteroids, IVIg, rituximab, anti-D Ig, cyclophosphamide (P3 studies)

Primary Endpoint: Subject Incidence of Durable Platelet Response



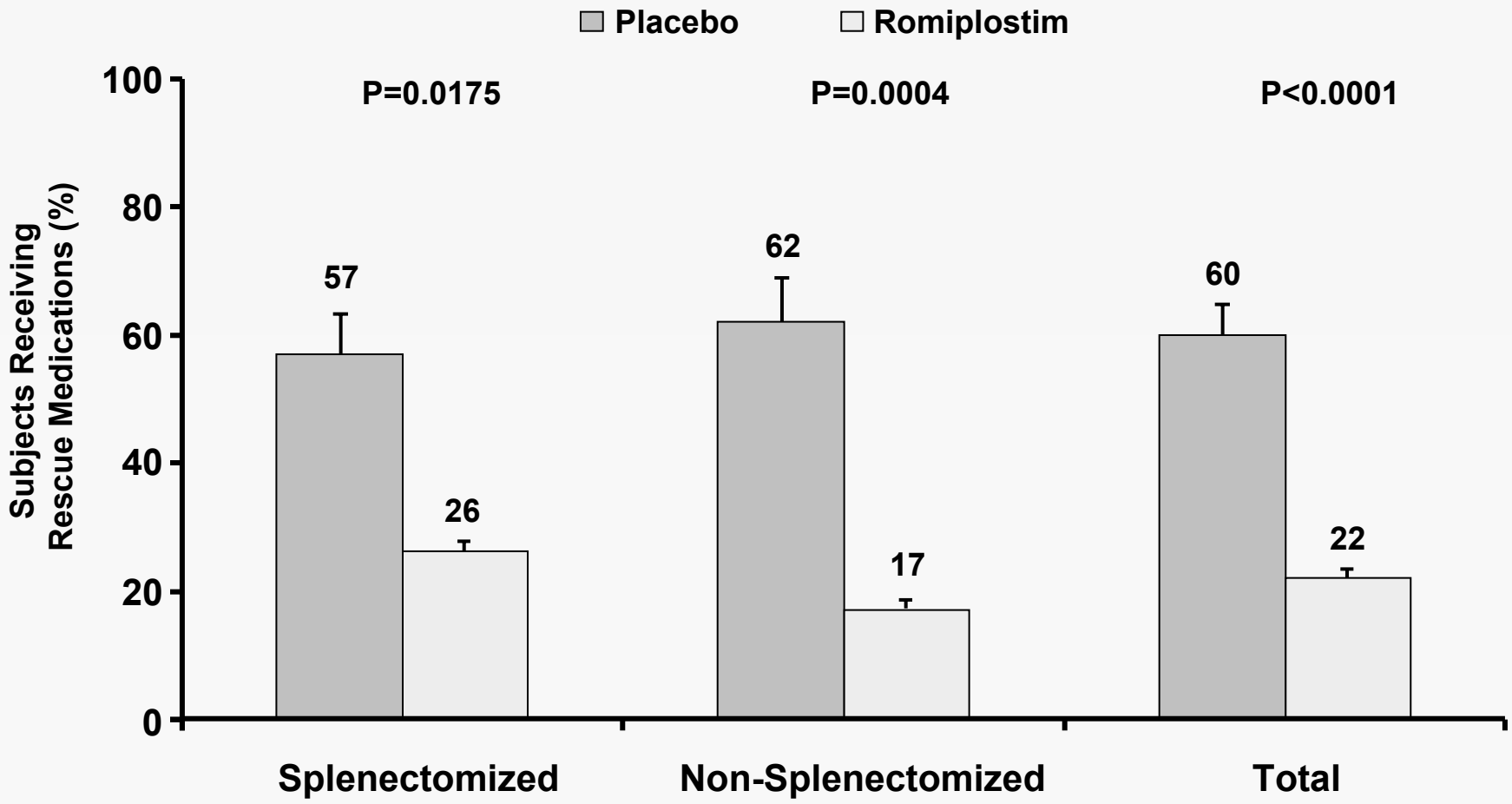
Durable platelet response: ≥6 weekly platelet counts ≥50 x 10^9/L during last 8 weeks of treatment period, in absence of rescue medication. Error bars represent standard error.
Kuter et al., 2008
(P3 studies)

Secondary Endpoint: Subject Incidence of Overall Platelet Response



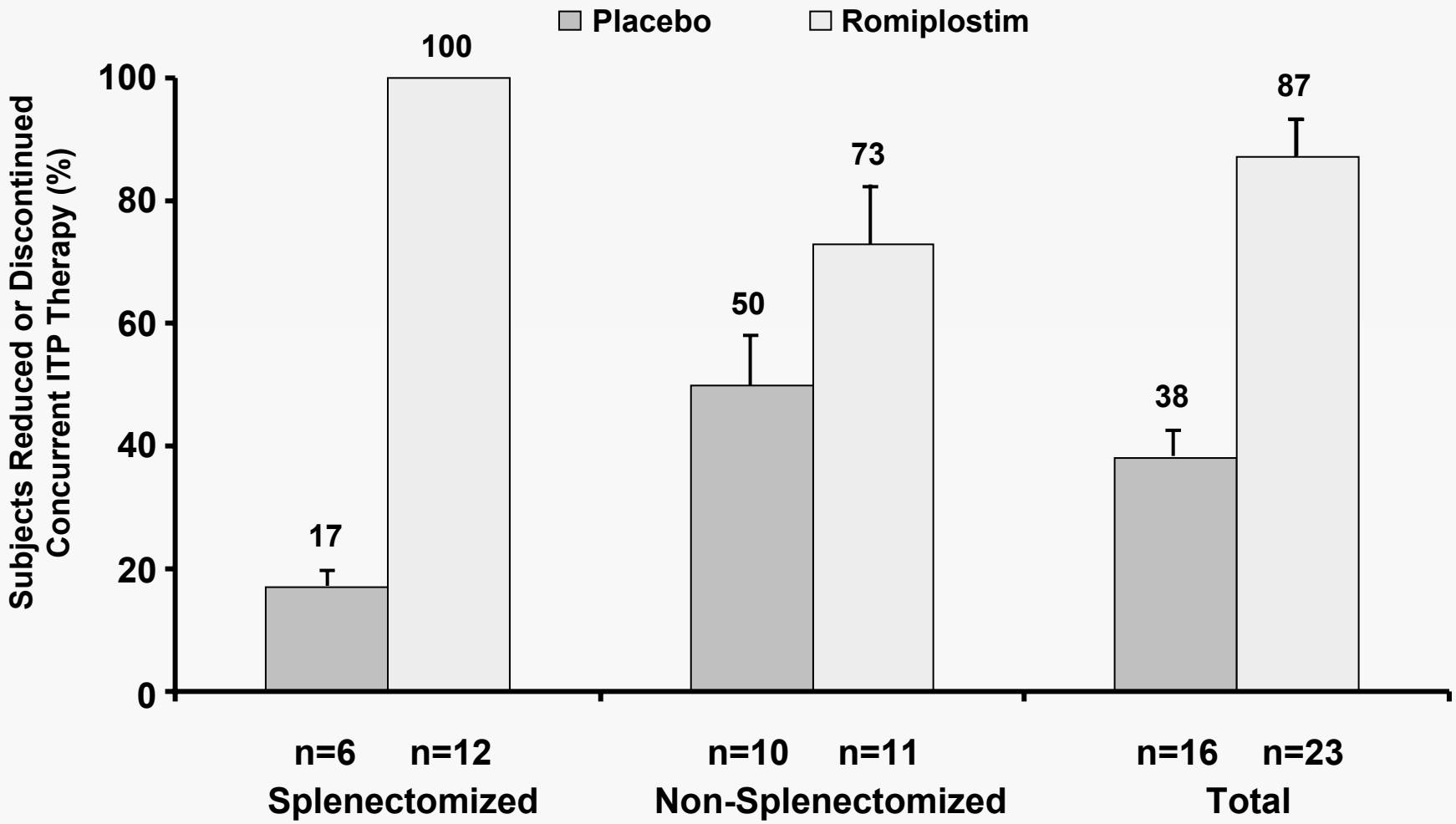
Overall platelet response: ≥4 weekly platelet counts ≥50 x 10^9/L during treatment period, platelet counts excluded within 8 weeks of rescue medication. Error bars represent standard error.
Kuter et al., 2008
(P3 studies)

Secondary Endpoint: Subject Incidence of ITP Rescue Medication Use



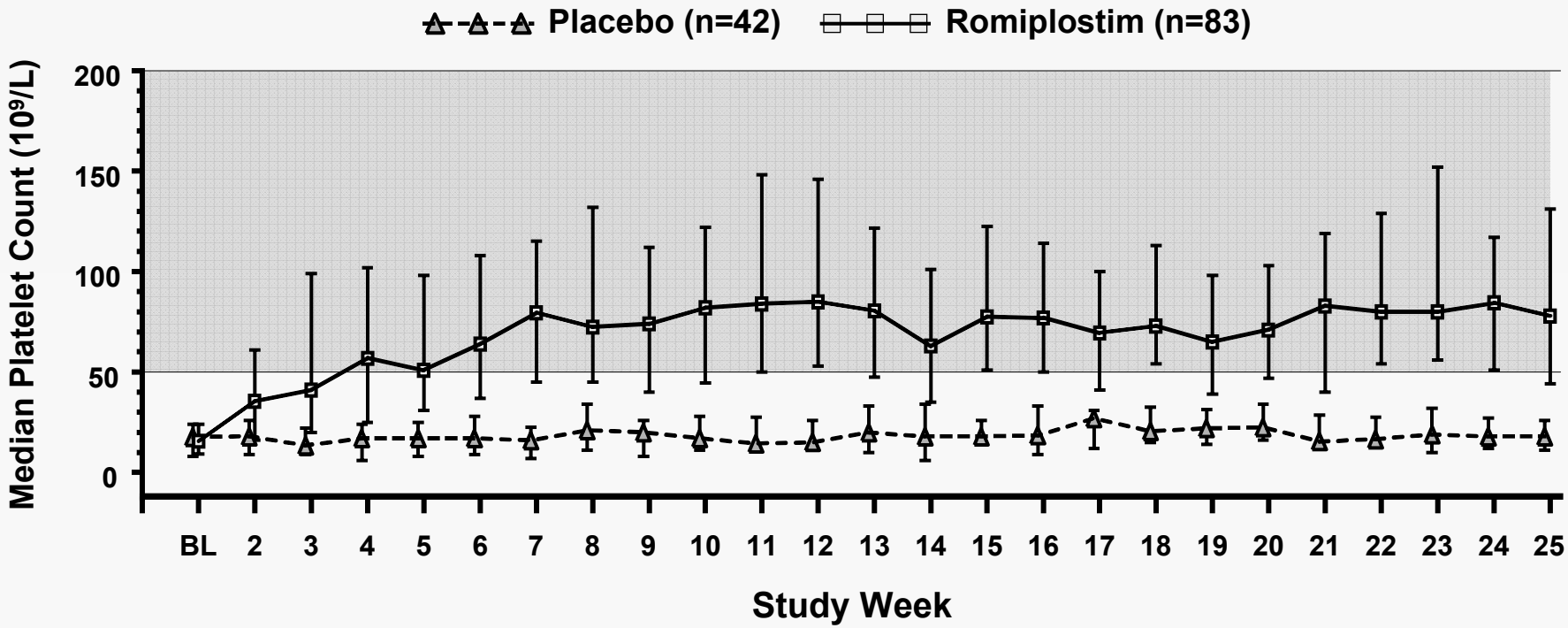
*Any medical intervention administered to increase platelet counts (corticosteroids, IVIg, anti-D Ig, platelet transfusions, cyclosporine). Error bars represent standard error.
(P3 studies)

Secondary Endpoint: Reduction and Discontinuation of Concurrent ITP Therapies



Patients discontinued or reduced by > 25% concurrent ITP therapy. Analysis based on subjects with concurrent ITP medications at baseline. Error bars represent standard error.
(Long term extension study)

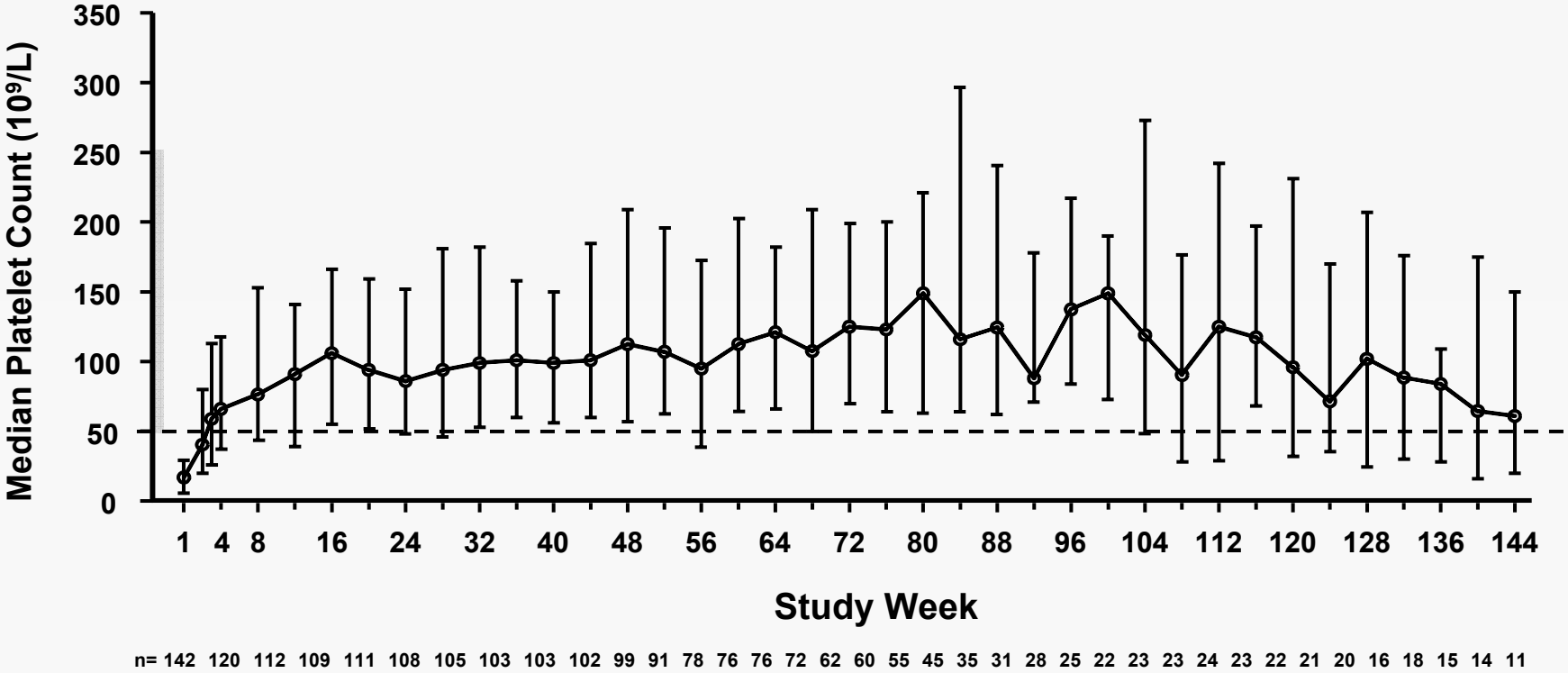
Romiplostim Maintained Median Platelet Counts in an Effective Range



Placebo n=	42	39	33	23	18	19	20	19
Romiplostim n=	83	78	77	71	72	66	67	69

Platelet counts within 8 weeks of rescue medication excluded as per Statistical Analysis Plan.
Error bars represent Q1, Q3.
(P3 studies)

Romiplostim Maintained Median Platelet Counts in Long-term Extension Study



Platelet counts within 8 weeks after receiving any rescue medications were excluded as per Statistical Analysis Plan.
Error bars represent Q1, Q3.
(Long term extension study)

Efficacy Conclusions

- **Romiplostim patients showed significant improvement in platelet count responses compared to placebo**
- **Romiplostim patients used less rescue medication**
- **Romiplostim patients were able to reduce or discontinue concurrent ITP therapies**
- **Majority of patients treated in long-term extension study experienced sustained weekly platelet responses**

Overall Summary of Adverse Events (AEs)

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Subjects with AEs	**39 (95)**	**84 (100)**
All SAEs	**8 (20)**	**14 (17)**
Life-threatening	**1 (2)**	**3 (4)**
Deaths	**3 (7)**	**1 (1)**
Withdrawals due to AE	**1 (2)**	**3 (4)**

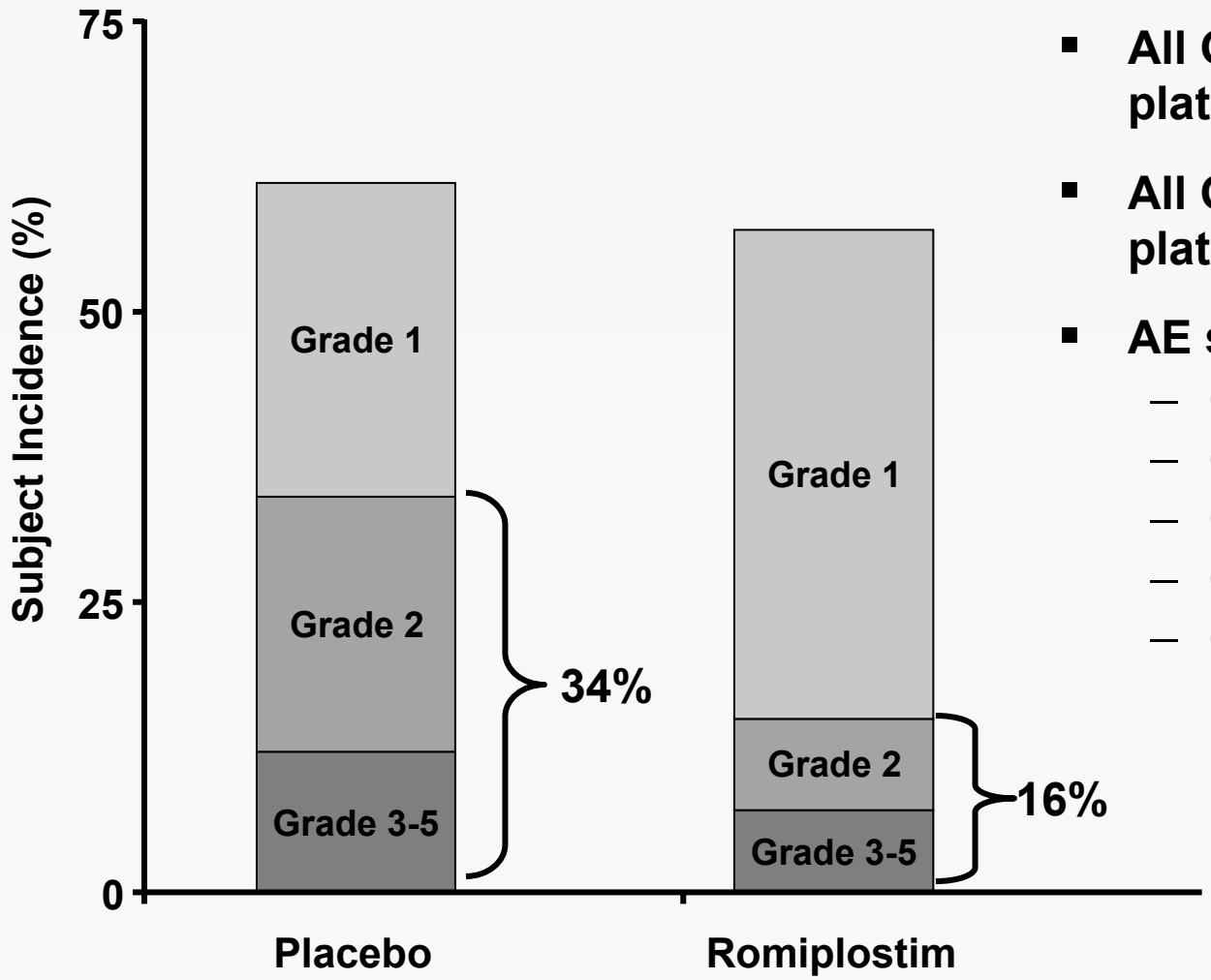
(P3 studies)

AEs with ≥5% Higher Incidence: Majority were Mild or Moderate, Transient, Non-serious

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Epistaxis	10 (24)	27 (32)
Arthralgia	8 (20)	22 (26)
Dizziness	0 (0)	14 (17)
Insomnia	3 (7)	13 (15)
Myalgia	1 (2)	12 (14)
Pain in extremity	2 (5)	11 (13)
Abdominal pain	0 (0)	9 (11)
Shoulder pain	0 (0)	7 (8)
Dyspepsia	0 (0)	6 (7)
Paraesthesia	0 (0)	5 (6)

(P3 studies)

Fewer Subjects With Grade ≥ 2 Bleeding Adverse Events With Romiplostim



- All Grade ≥2 occurred at platelet counts <50 x 10^9/L
- All Grade ≥3 occurred at platelet counts <20 x 10^9/L
- AE scale used
  - Grade 1: mild
  - Grade 2: moderate
  - Grade 3: severe
  - Grade 4: life-threatening
  - Grade 5: fatal

(P3 studies)

Events of Interest

- **Thrombocytopenia after cessation of treatment**
- **Bone marrow reticulin**
- **Neutralizing antibodies**
- **Thromboembolic events**
- **Neoplasms**

Thrombocytopenia After Cessation of Treatment

- **Thrombocytopenia expected after cessation of romiplostim treatment**
- **Phase 1 and 2 studies: AE of severe thrombocytopenia after cessation of treatment in 4/57 subjects (transient)**
- **Thrombocytopenia after cessation of treatment may lead to severe bleeding, particularly in the presence of anti-platelet agents**
  - **One case of fatal intracerebral hemorrhage**

Bone Marrow Reticulin

- **Bone marrow ancillary study (20050123): 10 ITP patients**
- **Spontaneous AE reporting: 10/271 (3.7%) romiplostim-treated ITP patients**
- **Bone marrow expert panel**
  - **Hematologists and hematopathologists (B. Bain, G. Mufti, D. Kuter, R. Hasserjian)**
  - **Reviewed bone marrow samples and reticulin data (study 20050123, 10 spontaneously reported cases)**

Bone Marrow Panel Consensus Statement

- **Potentially insufficient exposure to observe all possible romiplostim effects**
- **Bone marrow effects included hypercellularity, increased reticulin, and megakaryocyte clustering with hyperchromatic nuclei**
- **Patients experiencing these findings tended to be exposed to high doses of drug (>10 µg/kg)**
- **Findings often improved or disappeared after stopping drug**
- **Baseline history may have confounded findings in several patients**
- **No evidence romiplostim causes hematological neoplasms**

Immunogenicity

- **Immunogenicity assays**
  - **Screening assays (biacore) detect low and high affinity binding antibodies to romiplostim (400 ng/mL) or TPO (200 ng/mL)**
  - **Cell-based bioassays detect neutralizing antibodies to romiplostim or TPO**
- **Immunogenicity in preclinical studies**
  - **Binding and neutralizing antibodies to MGDF in animal models led to thrombocytopenia**
  - **Binding and neutralizing antibodies to romiplostim in animal models did not cross-react with TPO and did not lead to thrombocytopenia**

Immunogenicity

	Pre-dose Binding Antibodies n (%)	Post-dose Binding Antibodies n (%)	Post-dose Neutralizing Antibodies n (%)
Anti-romiplostim antibodies			
Romiplostim (n=225)	17 (8)	23 (10)	1 (0.4)
Placebo (n=45)	2 (4)	2 (4)	0 (0)
Anti-TPO antibodies			
Romiplostim (n=225)	12 (5)	12 (5)	0 (0)
Placebo (n=45)	2 (4)	4 (9)	0 (0)

(ITP Studies: 20000137, 20010218, 20030105, 20030212, 20030213, 20040209, 20050102)

Thromboembolic Events

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Thromboembolic AEs	1 (2)	2 (2)
Cerebrovascular accident	0 (0)	1 (1)
Peripheral embolism	0 (0)	1 (1)
Pulmonary embolism	1 (2)	0 (0)

ITP Safety Set (n=271): 12 subjects with thromboembolic events: DVT (3), PE (3), Portal vein thrombosis (2), thrombophlebitis (2), thrombosis (2), myocardial infarction (2)

(P3 studies)

Neoplasms

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Neoplasm AEs	**5 (12)**	**2 (2)**
B-cell lymphoma	0 (0)	1 (1)
Basal cell carcinoma	0 (0)	1 (1)
Benign ovarian tumor	1 (2)	0 (0)
Fibroma	1 (2)	0 (0)
Lung neoplasm	1 (2)	0 (0)
Metastases to liver	1 (2)	0 (0)
Multiple myeloma	1 (2)	0 (0)
Uterine leiomyoma	1 (2)	0 (0)

Uterine leiomyoma and benign ovarian tumor in the same subject
(P3 studies)

Individual Cases from Other ITP Studies

- **901002: 63 y/o male**
  - **Enrolled on study 20040209 (01/2006)**
  - **At month 7, AE of splenomegaly**
  - **Bone marrow biopsy (month 8): bone marrow fibrosis**
  - **Baseline biopsy (month -3): del (20q), reticulin +, sclerotic bone, consistent with MDS/MPD**
- **90502: 75 y/o female**
  - **Enrolled on study 20040209 (05/2006)**
  - **At month 6, AE of aplastic anemia, after treatment with azathioprine, steroids, IVIg and rituximab**
  - **Pre-existing macrocytosis**

Study 20030159: Romiplostim in Disease-related Thrombocytopenia in MDS

- **Phase I/II single arm dose escalation study**
- **44 subjects with low/int-1 risk MDS**
- **Platelet response in 54% of patients**
  - **Fewer transfusions and bleeding events**
- **Progression to AML: 2 subjects**
- **Increase in IPSS score: 3 subjects**
- **Transient blast cell increase: 6 subjects**
- **Further clinical studies planned in disease-related and treatment-related thrombocytopenia in MDS**

Safety Conclusions

- **Majority of AEs mild to moderate and transient**
- **Bleeding events grade ≥2 more frequent in placebo (34%) than romiplostim patients (16%)**
- **Thromboembolic and neoplasm events similar for placebo and romiplostim groups**
- **Thrombocytopenia after cessation of treatment and increase of bone marrow reticulin are identified risks of romiplostim in ITP**
- **Risk Management Program**
  - **Risk Minimization Action Plan (RiskMAP)**

Agenda

Background and Introduction	**Joseph Miletich, MD, PhD** **Senior Vice President, Research & Development, Amgen Inc.**
Thrombopoietin (TPO), and Management of Immune Thrombocytopenic Purpura (ITP)	**David Kuter, MD, DPhil** **Professor, Department of Medicine, Harvard Medical School, Director, Clinical Hematology, Massachusetts General Hospital**
Romiplostim in ITP: Efficacy and Risk Assessment	**Dietmar Berger, MD, PhD** **Executive Director Global Clinical Development, Amgen Inc.**
Risk Management Program and Closing Remarks	**Paul Eisenberg, MD, MPH** **Senior Vice President Global Regulatory Affairs & Safety, Amgen Inc.**

Overview of Risk Management Program

- **Safety experience from clinical program**
  - **Identified and potential risks**
- **Proposed Risk Management Program**
  - **Risk assessment (pharmacovigilance, targeted studies)**
  - **Risk minimization (labeling, RiskMAP)**
- **Components of RiskMAP**
  - **Targeted education**
  - **Controlled Distribution Program**
  - **Safety registry**
- **Overall assessment of Benefit:Risk**

Risks Addressed in Risk Management Program

Identified Risks

- **Reoccurrence of thrombocytopenia after cessation of treatment**
- **Increased bone marrow reticulin**

Risks Addressed in Risk Management Program

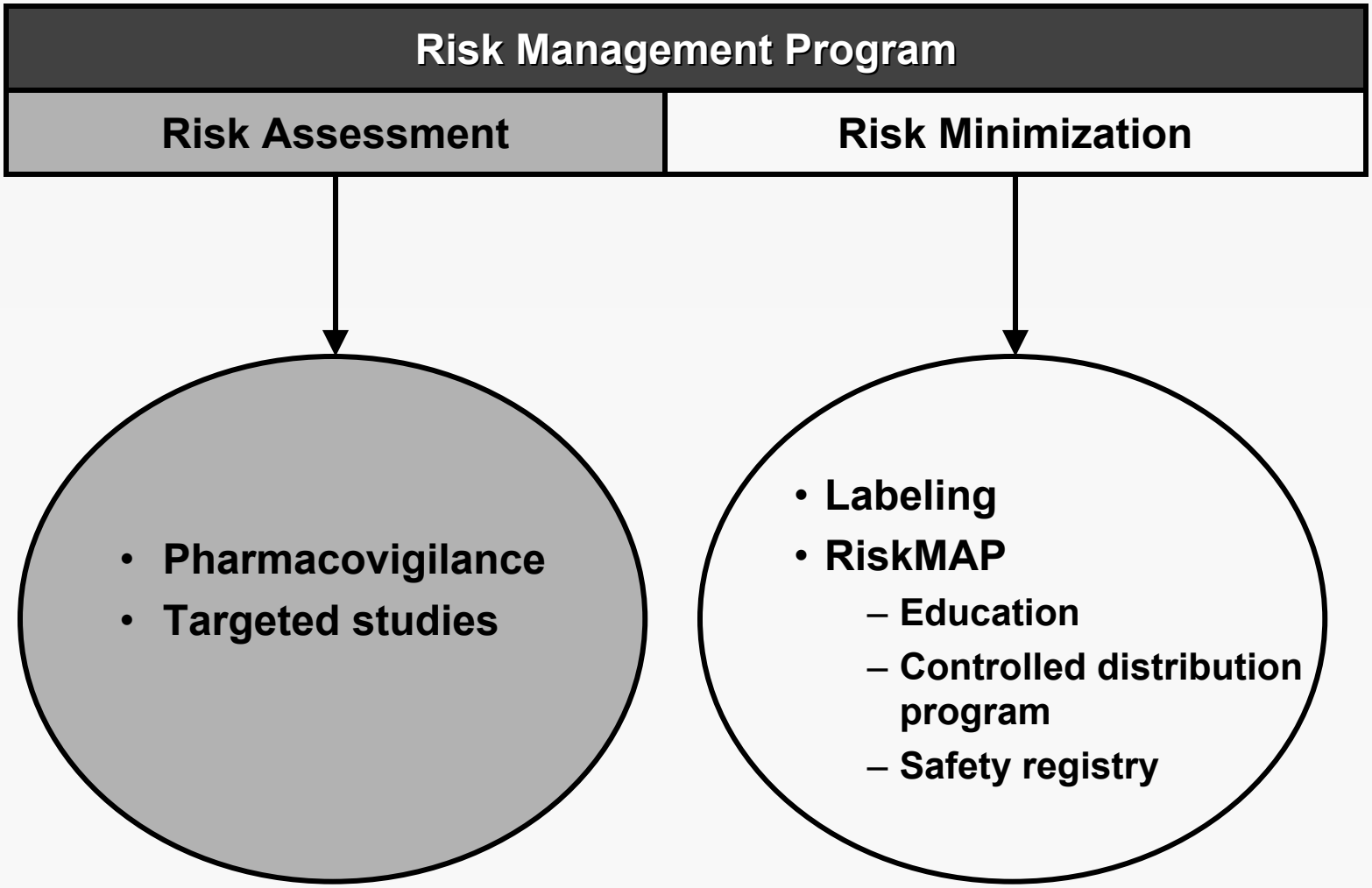
Identified Risks

- **Reoccurrence of thrombocytopenia after cessation of treatment**
- **Increased bone marrow reticulin**

Potential Risks

- **Thrombotic / thromboembolic complications**
- **Neutralizing antibodies that cross react with eTPO**
- **Progression of existing hematopoietic malignancies**
- **Progression of reticulin to irreversible fibrotic state**
- **Use in indications where benefit:risk has not been adequately studied**
- **Medication errors**

Risk Management Program



Risk Assessment: Observational Studies

- **Retrospective epidemiologic study**
  - **Define prevalence of bone marrow reticulin and fibrosis in ITP patients using Danish National Health Registry Database**
  - **Data on 3,000 patients with ITP and over 600 with ITP >6 months from 1996 to 2006**
  - **Extensive bone marrow biopsy data**
- **Prospective study to monitor incidence of increased bone marrow reticulin and bone marrow fibrosis**
  - **Longitudinal assessment of bone marrow reticulin and clinical sequelae in romiplostim treated patients**
  - **All adult patients with ITP in Denmark, Sweden, and Finland between January 1, 2009 and December 31, 2019**

Risk Assessment: Long-term Open Label Prospective Study

- **Longitudinal evaluation of changes in bone marrow morphology in romiplostim-treated ITP subjects (n~200)**
- **Key endpoints**
  - **Increase in bone marrow reticulin and collagen after 24 and 60 months of romiplostim exposure**
  - **Incidence of post-treatment thrombocytopenia**
  - **Incidence of antibody development after 24 and 60 months of romiplostim exposure**
- **Assessment of incidence of hematological malignancies and thromboembolic adverse events**

Risk Minimization: Labeling

Identified Risks	Prescribing Information	
Reoccurrence of thrombocytopenia	✓	Warning
Increased bone marrow reticulin	✓	Max dose 10µg/kg

Risk Minimization: Labeling

Identified Risks	Prescribing Information	
Reoccurrence of thrombocytopenia	✓	Warning
Increased bone marrow reticulin	✓	Max dose 10 µg/kg
Potential Risks		
Off-label use	✓	Indication-ITP only
Neutralizing antibodies	✓	Warning, contact info
Thromboembolic events	✓	Maintain platelet count $\geq 50 \times 10^9$/L and minimize excursions > 200×10^9/L
Progression of reticulin to irreversible fibrotic state	✓	Warning
Progression of existing hematopoietic malignancies	✓	Warning
Medication errors	✓	Administered by HCP

Risk Minimization Action Plan (RiskMAP)

- **Strategic safety program designed to meet specific goals and objectives in minimizing product risks while preserving benefits**
- **Uses tools that**
  - **Are evidence-based**
  - **Allow appropriate product access**
  - **Consider stakeholder input, technology, practice settings**
- **3 categories of tools**
  - **Targeted education and outreach**
  - **Reminder systems**
  - **Controlled distribution**
- **Effectiveness of tools is monitored and periodically reported to FDA**

Guidance for Industry. Development and Use of Risk Minimization Action Plans. U.S. Department of Health and Human Services. FDA. CDER. CBER. March 2005

Overview of Romiplostim RiskMAP

- **Goal**
  - **Appropriate use in ITP**
  - **Assess identified and potential risks associated with use of romiplostim**
- **Objectives**
  - **Patient and physician education on risk profile and appropriate use**
  - **Long term monitoring of identified and potential risks**
  - **Limit off-label use**
- **Proposed RiskMAP based on feedback from stakeholders and FDA**

Proposed Indications and Usage

- **Indicated for treatment of thrombocytopenia in adult patients with chronic ITP**
  - **Who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins**
  - **Who are splenectomized and have an insufficient response to splenectomy**

RiskMAP Tools: Patient Management Program

- **Targeted education and outreach**
  - **Product labeling / Medication Guide**
  - **Provider Education Training Kit**
    - **ASH guidelines**
    - **ITP diagnosis checklist**
- **Reminder systems**
  - **Medication Guide**
  - **Pre-use checklist**
  - **6 month reconfirmation of diagnosis**
- **Controlled Distribution Program**
  - **Patient/physician consent to enter program**
  - **Ships only to physicians for treatment of enrolled ITP patients**
  - **Tracking database/safety registry**

RiskMAP:
Controlled Distribution Program (CDP)

Step 1

Patient **Heme/Onc**

Educates patient
1. **Medication Guide**
2. **Inform on CDP**

Complete and sign program enrollment form

Case manager enters patient into program

RiskMAP Tool: Program Enrollment Questionnaire

Patient demographics and physician attestation to chronic ITP diagnosis

Patient consent for program participation
(Includes sharing of medical and safety data)

Physician information

Patient attestation of Medication Guide review

AMGEN

Program Enrollment Questionnaire

nt Information and Physician Certification of Diagnosis

_____ Patient Initials: _____

ender: ☐M ☐F Weight: _____ kg

m is a thrombopoietin (TPO) mimetic indicated f tre of
ocytopenia in adult patients with chronic immune tic)
mbocytopenic purpura (ITP):

- Who are non-splenectomized and have an in t res nse or are intolerand to corticosteroids and/or immunoglo
- Who are splenectomized and have an insufficient e to splenectomy.

I certify that I am prescribing Romiplos patient atment chronic ITP as described in the prescrib n

Prescriber's signature: _____

2. Physician Inform

Full Name (print): _____

Phone: e-mail _____

Physi n Sig _____ Date: ___/___/___

3. Co r Pa tion in the Romiplostim Patient Management Pro ram

I consent nta d by the Romiplostim case manager and to the sharing of my medical nt information within the patient management program for Romiplostim a mgen.

Patient signature _____ Date _____

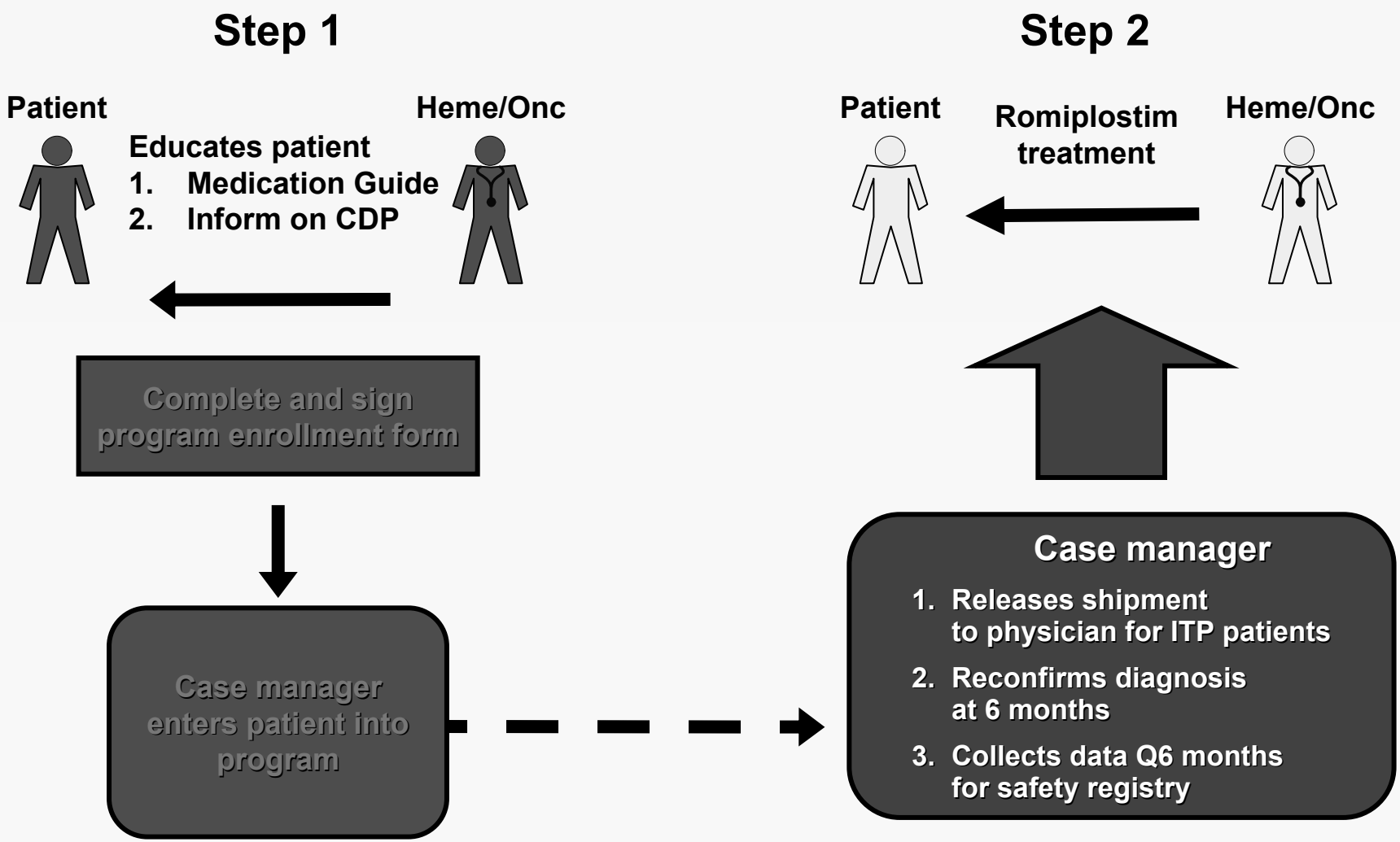
4. Patient Confirmation of Medication Guide Receipt

Prior to receiving my first dose of Romiplostim therapy, my health care provi shared with me the Romiplostim Medication Guide and patient education kit a described the benefits and risks of Romiplostim therapy.

Patient signature _____ Date _____

DRAFT

RiskMAP: Controlled Distribution Program (CDP)



RiskMAP Summary

Identified Risks	RiskMAP Activities		
	Education	Safety Registry	Controlled Distribution
Reoccurrence of thrombocytopenia	✓	✓	
Increased bone marrow reticulin	✓	✓	
Potential Risks			
Off-label use	✓		✓
Neutralizing antibodies	✓	✓	
Thromboembolic events	✓	✓	
Progression of reticulin to irreversible fibrotic state	✓	✓	
Progression of existing hematopoietic malignancies	✓	✓	
Medication errors	✓	✓	

Closing Remarks

- **ITP carries the risk of serious bleeding**
- **Safety and efficacy of current therapies are inadequate and few are approved**
- **Romiplostim is a novel and effective therapy for chronic treatment of ITP with potential to decrease risk of serious bleeding**
- **Amgen has proposed a robust Risk Management Program**
  - **Additional targeted studies**
  - **Comprehensive RiskMAP**

Romiplostim

Oncologic Drugs
Advisory Committee

12 March 2008

Agenda

Background and Introduction	**Joseph Miletich, MD, PhD** **Research & Development, Amgen Inc.**
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Thrombopoietin (TPO): The Elusive Platelet Growth Factor

nature

Nature 369, 519 - 520 (16 June 1994)

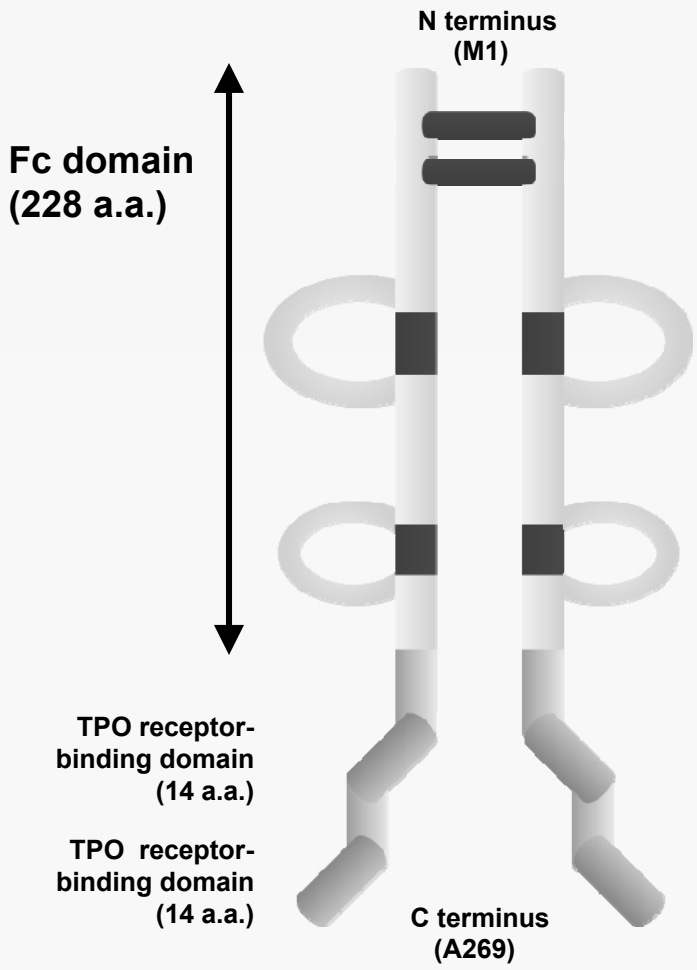
Thrombopoietin — at last

Donald Metcalf, MD, PhD

- **Sequenced and/or isolated by 5 groups in 1994**
- **Established as the major megakaryocyte/platelet growth factor**
- **Trials with two recombinant molecules based on TPO sequence. Neutralizing antibodies cross-reacted with endogenous TPO**
- **Evidence of efficacy in Immune Thrombocytopenic Purpura (ITP)**

Romiplostim Stimulates Platelet Production Through Binding to the TPO Receptor

- **Not based on TPO sequence**
- **Novel peptide binds to and stimulates receptor**
- **Fc-peptide fusion protein, (peptibody) produced in *E. coli***



Amgen Has Consulted with FDA on Romiplostim Development in ITP

- **Immune Thrombocytopenic Purpura (ITP) is an orphan disease**
- **Efficacy demonstrated for primary and secondary endpoints in two pivotal trials**
- **Risk Management Program proposed, including a formal risk minimization action plan (RiskMAP)**

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ITP

- **Definition of ITP**
  - **Isolated thrombocytopenia**
  - **Exclusion of other causes of thrombocytopenia**
- **Characteristics**
  - **Autoantibodies to platelet glycoproteins**
  - **Platelet destruction and impaired platelet production**
  - **Thrombocytopenia, bruising, bleeding**
  - **Treatments: immunosuppressive or immunomodulatory (including splenectomy)**
- **Epidemiology**
  - **Incidence 1.6-3.3 / 100,000 adults / yr**
  - **Prevalence 9.5 / 100,000 adults**

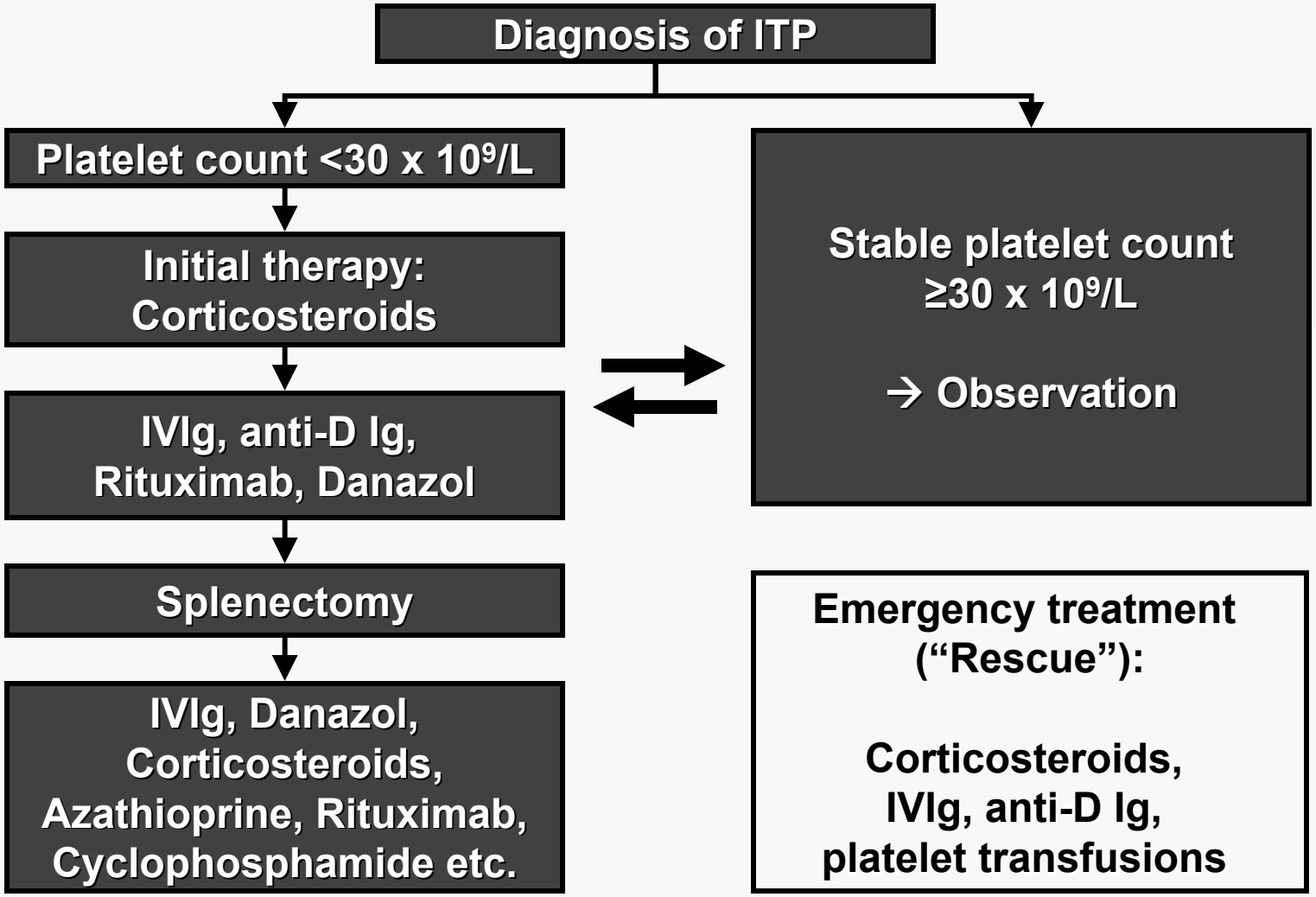
Adapted from Cines & Blanchette, 2002

ITP Diagnosis and Treatment Per ASH Guidelines

- **Diagnosis**
  - **History, physical exam, blood counts and peripheral blood smear required**
  - **No confirmatory test; anti-platelet antibody not informative**
  - **No routine bone marrow biopsy performed, aspirate recommended in patients >60 or prior to splenectomy**
  - **Confirmed by clinical response to corticosteroids**
- **Treatment**
  - **Indicated for platelet counts <20-30 x 10^9/L or <50 x 10^9/L with significant mucosal bleeding or risk factors for bleeding**
  - **Goal is platelet count >50 x 10^9/L**

George et al., 1996

Current Treatment Options for ITP: All Target Platelet Destruction



Most products not approved for treatment of ITP

Current ITP Medical Therapies Have Risk for Serious Consequences

Corticosteroids	**Depression/psychosis, diabetes, hypertension, adrenocortical suppression, osteoporosis, cataracts, life-threatening infection**
Anti-D Ig	**Anaphylaxis, intravascular hemolysis, infection transmission**
IV Ig	**Anaphylaxis, infusion reactions, infection transmission**
Rituximab	**Fatal infusion reaction, severe mucocutaneous reaction, progressive multifocal leukoencephalopathy, hepatitis B reactivation with fulminant hepatitis**
Danazol	**Lipoprotein alterations, androgenic effects**
Azathioprine	**Immunosuppression, increased risk of neoplasia, serious infection, pancytopenia, hematologic toxicity**
Cyclophosphamide	**Renal failure, heart failure, impaired fertility and mutagenesis, carcinogenesis**

Individual product prescribing information

Considerations for Splenectomy in ITP

- **Laparotomy**
  - **Mortality: 48/4955 (1.0%)**
  - **Morbidity: 318/2465 (12.9%)**
- **Laparoscopy**
  - **Mortality: 3/1301 (0.2%)**
  - **Morbidity: 88/921 (9.6%)**
- **Relapse rate: 30-40%**
- **Long-term risk: increased susceptibility to bacterial infection**

Kojouri et al., 2004

Bleeding Risk in ITP Patients

- **Review of 17 studies including 1817 ITP patients**
- **Non-fatal, severe bleeding not analyzed**
- **49 cases of fatal hemorrhage**
- **Fatal bleeding risk calculated as 1.6 – 3.9% per patient year**
- **Increased risk with higher age groups (>60 years)**

Cohen et al., 2000

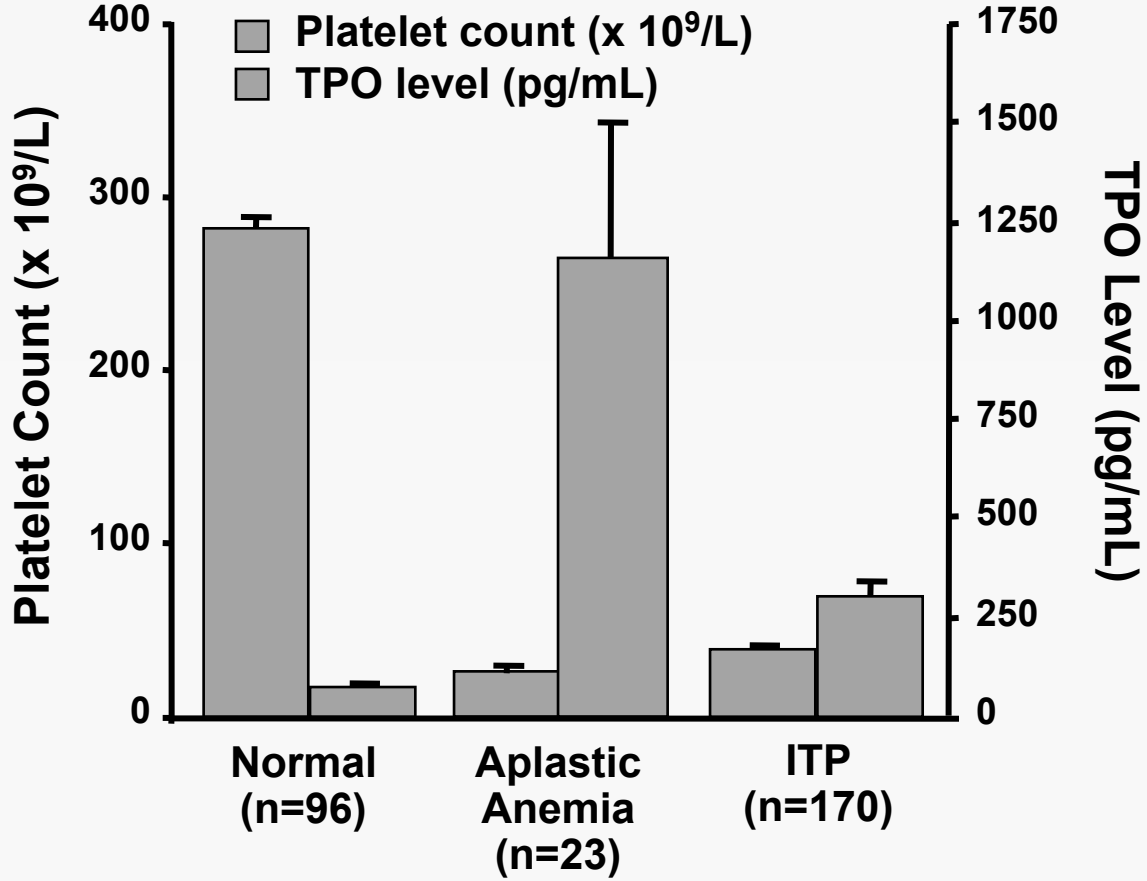
Fatal Events in Adult Patients with Refractory ITP

- **Largest prospective study in refractory adult ITP (n=105)**
- **Median follow-up 110 months (mean 143 months)**
- **Multiple treatments: corticosteroids, danazol, azathioprine, cyclophosphamide, combination therapies**
- **11 patients (10%) died of bleeding**
- **6 patients (6%) died of treatment-related AEs**

McMillan and Durette, 2004

Mechanisms for Inadequate Platelet Production in ITP

- **TPO levels normal in 75% of ITP patients[1]**
- **Platelet production reduced or normal in 2/3 of ITP patients[2-4]**
- **Autoantibody inhibition of megakaryocyte growth and induction of early apoptosis[5-6]**



[1]Kuter, et al., 1997. [2]Stoll, et al., 1985. [3]Heyns et al., 1986 [4]Ballem et al.,1987. [5]McMillan, et al,. 2004. [6]Chang M, et al., 2003.

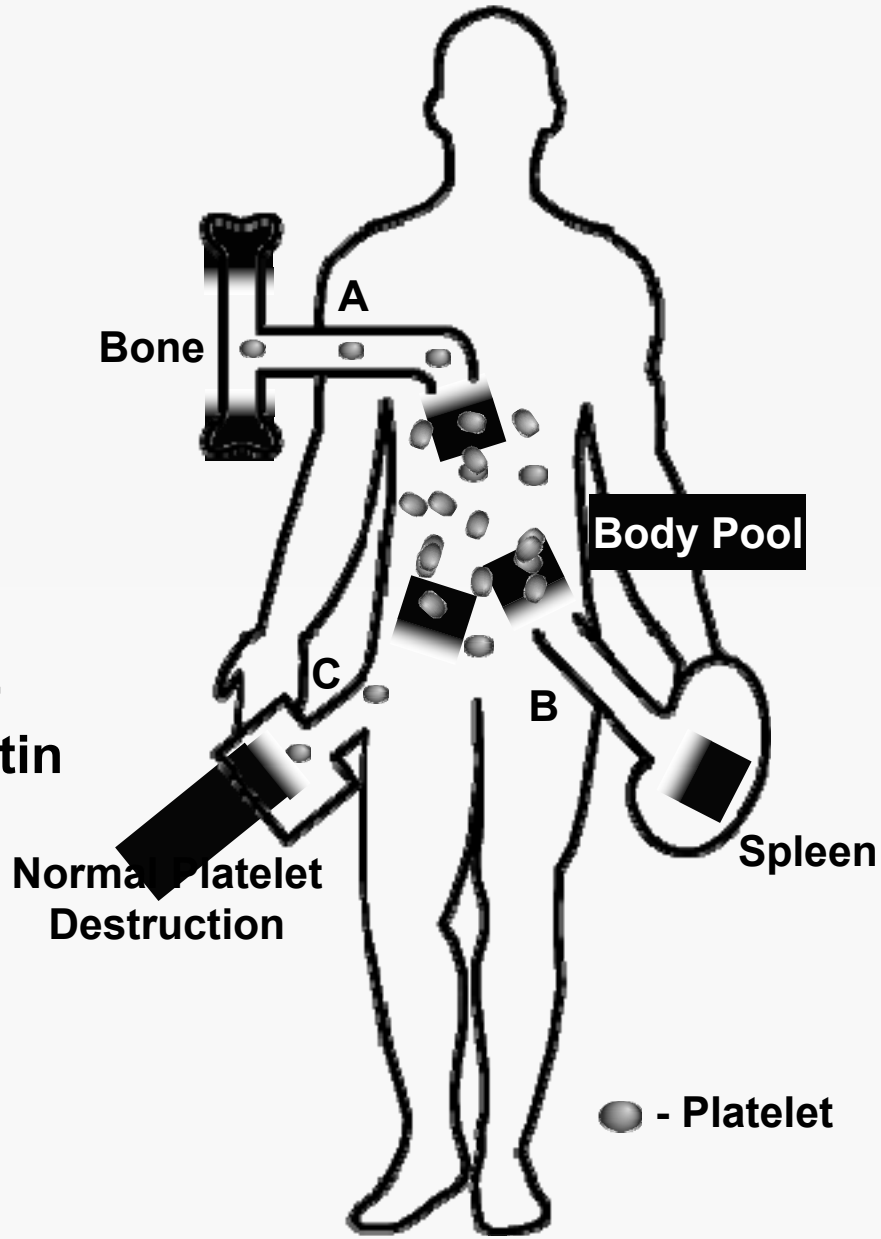
Normal

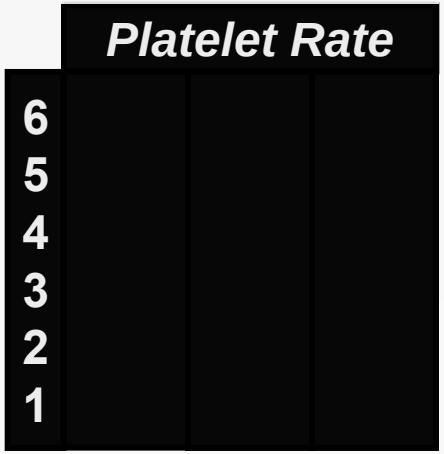
Onset ITP

Chronic ITP
Old Model

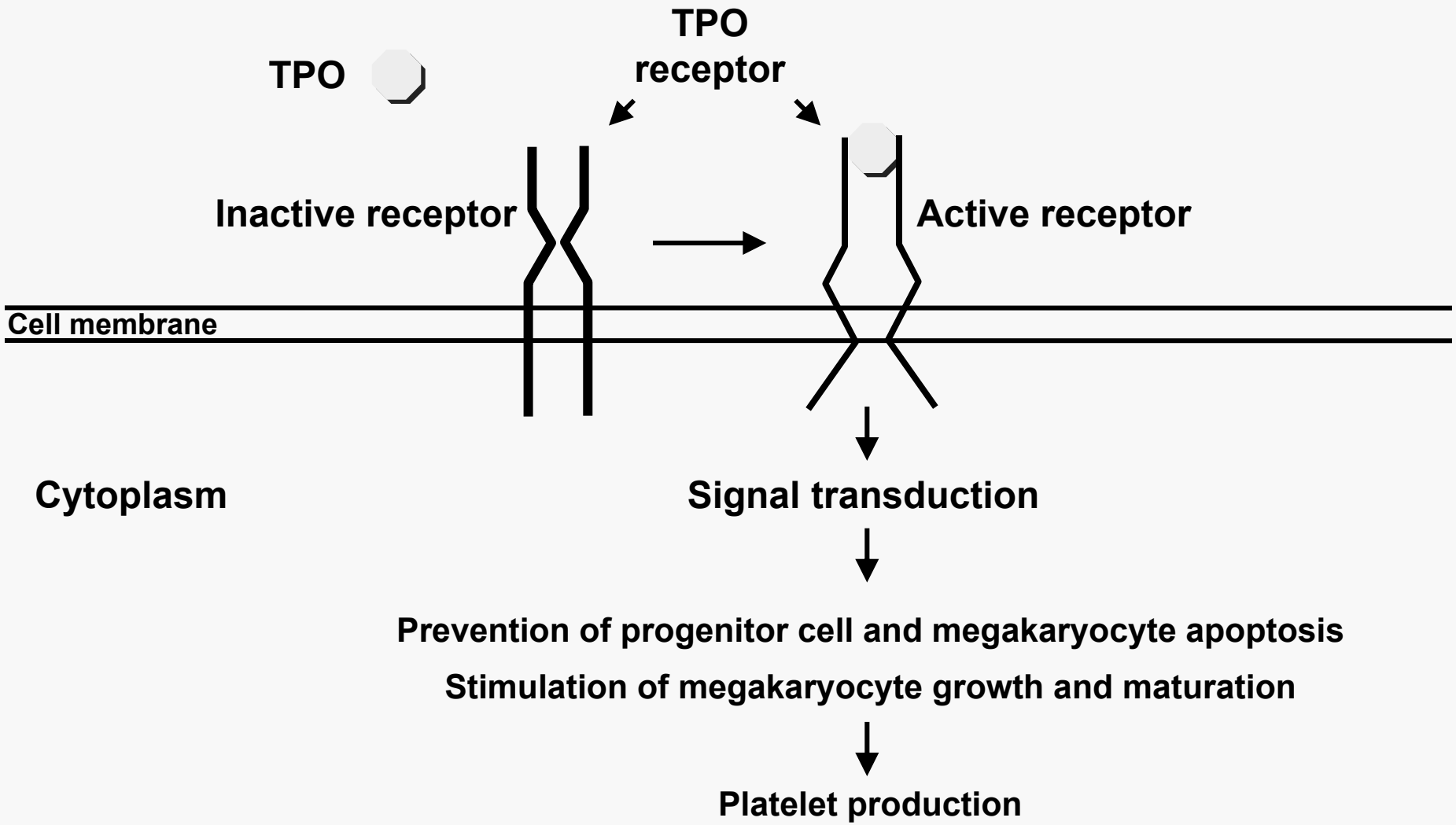
Chronic ITP
New Model

Chronic ITP +
Thrombopoietin



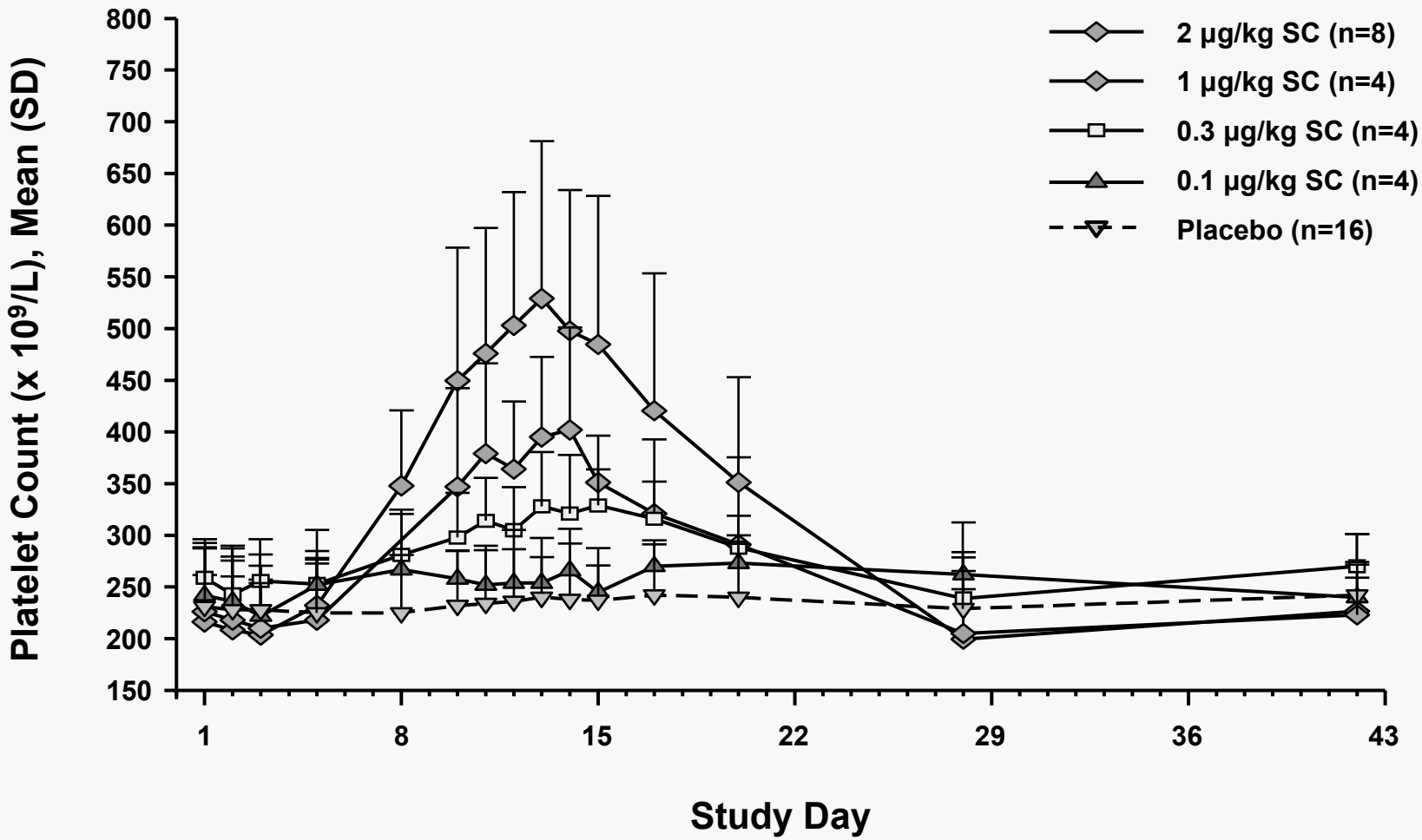


TPO Mechanism of Action



Kuter, 2007

Platelet Response to a Single Dose of Romiplostim in Healthy Subjects

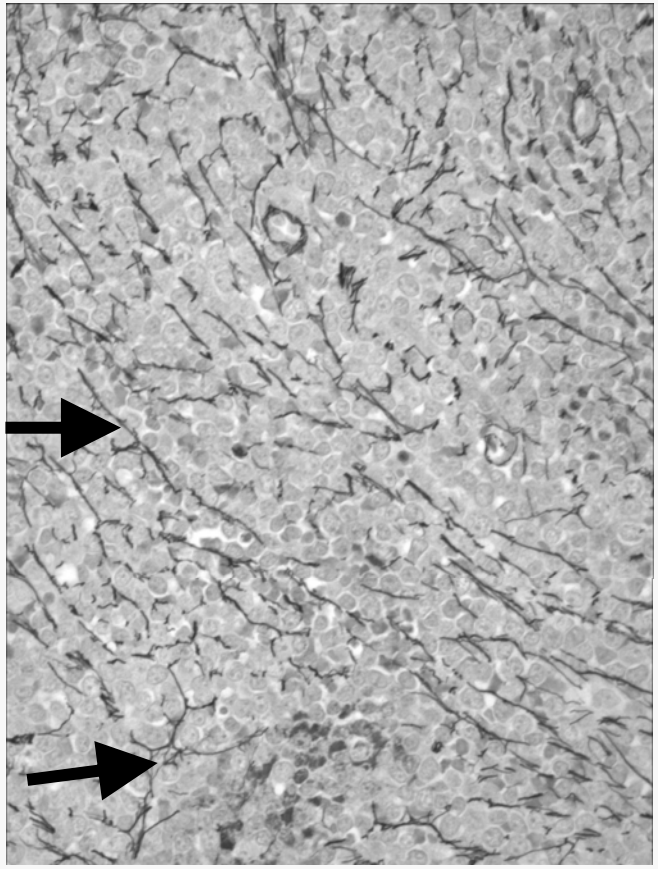


Wang et al., 2004

Theoretical Concerns Regarding Pharmacologic Administration of Thrombopoietic Factors

- **Thrombocytosis**
- **Thrombosis**
- **Stimulation of tumor growth**
- **Stimulation of leukemia cell growth**
- **Autoantibody formation**
- **Increased bone marrow reticulin**

Reticulin: A Normal Bone Marrow Component

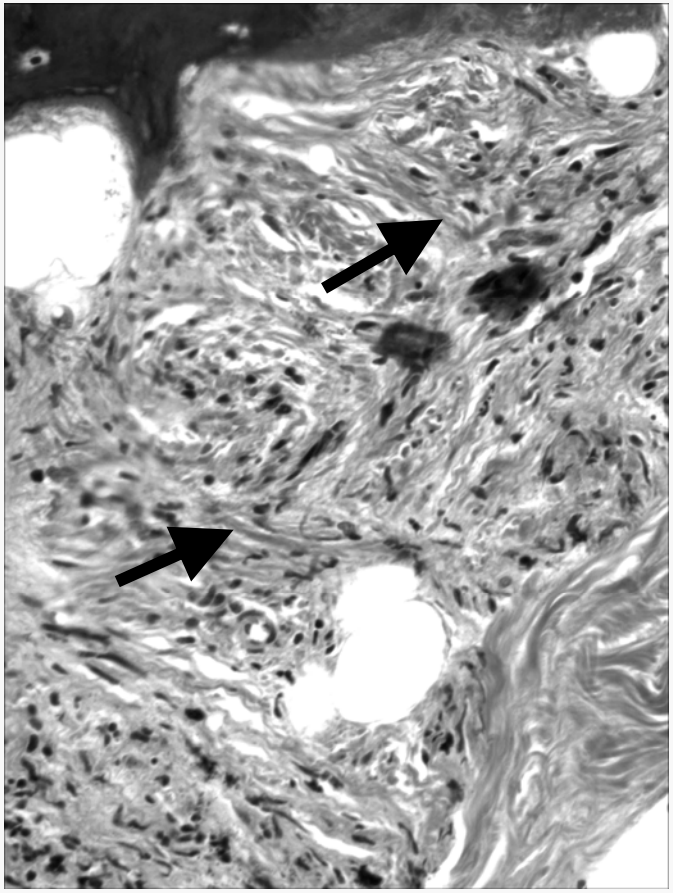


Bone marrow reticulin stain
Grade 2

- **Silver stains bind hexoses around reticulin**
- **Grades 0-2 in normal and ITP subjects**
- **Grades 3-4 may be abnormal**
- **Increased in many infectious, inflammatory, oncologic disorders, with GM-CSF, IL-3, IL-11**
- **Reversible**
- **Does not affect blood counts**

Kuter et al., 2007; Bauermeister et al., 1971

Collagen: Pathological in Bone Marrow



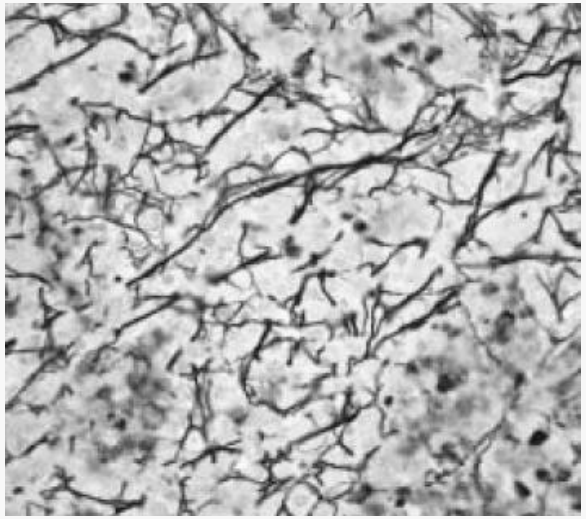
Bone marrow collagen (trichrome) stain

- **Trichrome stain**
- **May be accompanied by reticulin staining (Grade 4)**
- **Associated with clonal malignant disorders (metastatic cancer, hairy cell leukemia, myeloproliferative disorders)**
- **Reversible with treatment of clonal disorders**
- **Underlying clonal disease accounts for blood count abnormalities**

Kuter et al., 2007; Bauermeister et al., 1971

Increased Reticulin in TPO Treated AML Patients is Reversible

- **AML induction chemotherapy patients treated with TPO (2.5 µg/kg/d IV, up to 21 doses) + GM-CSF**
  - **8/9 had increased reticulin**
  - **2/6 controls (GM-CSF alone) had increased reticulin**
  - **Fully reversible in 30 d (range: 13-42 d)**



Reticulin stain x600

Douglas et al., 2002

Summary

- **ITP is a disease of accelerated platelet destruction and suboptimal platelet production**
- **Thrombocytopenia in ITP may lead to severe clinical consequences, including life-threatening bleeding**
- **Current treatments of ITP are often unsuccessful**
- **TPO is the major regulator of platelet production**
- **In ITP, circulating TPO levels are inadequate, and TPO administration can lead to platelet production**

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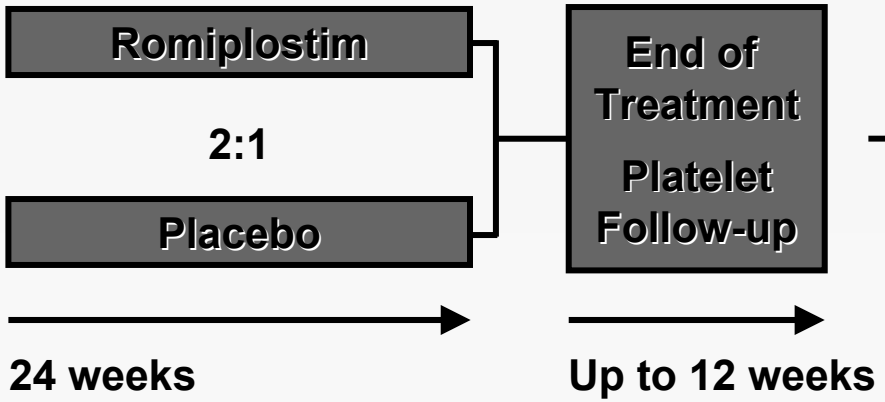
Overview of Clinical Study Program and Exposure at 120-Day Update

- **11 studies in ITP, n=308**
- **2 studies in healthy subjects, n=78**
- **1 study in MDS, n=44**
- **1 study in chemotherapy-induced thrombocytopenia n=21**

Duration of Romiplostim Exposure in ITP (Weeks)	n (%)
≥1	271 (100)
≥26	153 (56)
≥52	114 (42)
≥104	36 (13)

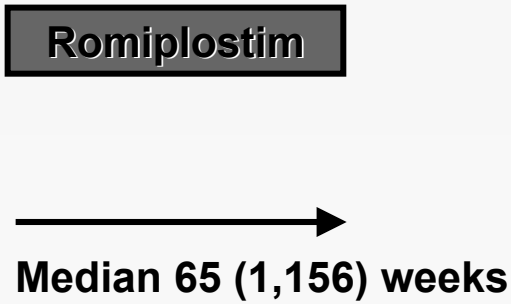
Romiplostim Study Designs in ITP

2 Randomized, Controlled, Phase 3 Studies



- 20030105: Splenectomized (n=63)
- 20030212: Non-splenectomized (n=62)
- Platelet count ≤30 x 10^9/L
- Romiplostim starting dose 1 µg/kg QW, dose adjustment by platelet count
- Concurrent and rescue ITP medication allowed

Long-term Extension Study



- 20030213: Ongoing, open-label (n=143)
- Similar design

Phase 3 Dosing Regimen Based on Early Clinical Studies

- **1 µg/kg starting dose supported by**
  - **Minimum active dose in healthy subjects**
  - **33% ITP subjects achieved 50 x 10^9/L within 1 week after dose**
  - **No ITP subjects exceeded 450 x 10^9/L**
- **1 week dosing interval supported by phase 2 data**
- **Individual dose adjustment required due to**
  - **Platelet count variability at baseline and on treatment**
  - **Platelet count variability between subjects at a given dose**

Primary Efficacy Endpoint

- **Incidence of durable platelet response**
  - **≥6 weekly platelet counts ≥50 x 10^9/L during last 8 weeks of 24 week treatment period**
  - **In absence of rescue medication at any time during study**
- **Platelet count ≥50 x 10^9/L clinically recognized as target at which risk of bleeding is minimized**

Secondary Efficacy Endpoints

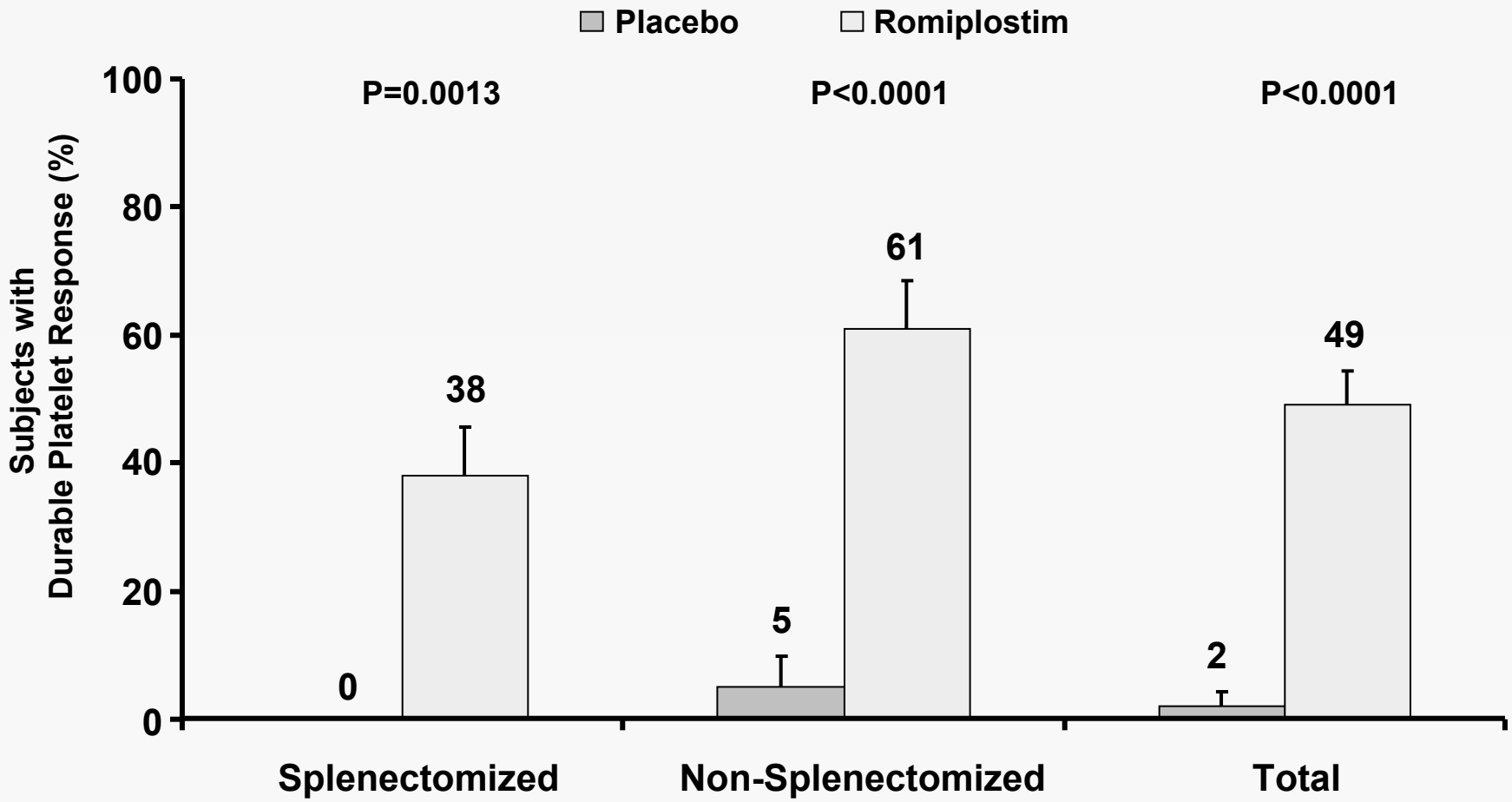
- **Overall platelet response**
  - **≥4 weekly platelet responses during 24 week treatment period**
  - **Platelet counts excluded within 8 weeks of rescue**
- **Number of weekly platelet responses**
- **Proportion of subjects requiring rescue medication**
- **Discontinuation/reduction of concurrent ITP medications**
- **Patient reported outcomes**

Patient Demographics

		Splenectomized		Non-Splenectomized	
		Placebo n=21	Romiplostim n=42	Placebo n=21	Romiplostim n=41
Age (years)	Mean (SD)	54 (13)	51 (16)	55 (22)	53 (16)
Female	n (%)	11 (52)	27 (64)	16 (76)	27 (66)
Platelet count (x 10^9/L)	Mean (SD)	14 (8)	15 (8)	19 (8)	17 (8)
Number of prior therapies*	Median (min, max)	6 (3,10)	6 (3,9)	2 (1,7)	3 (1,7)

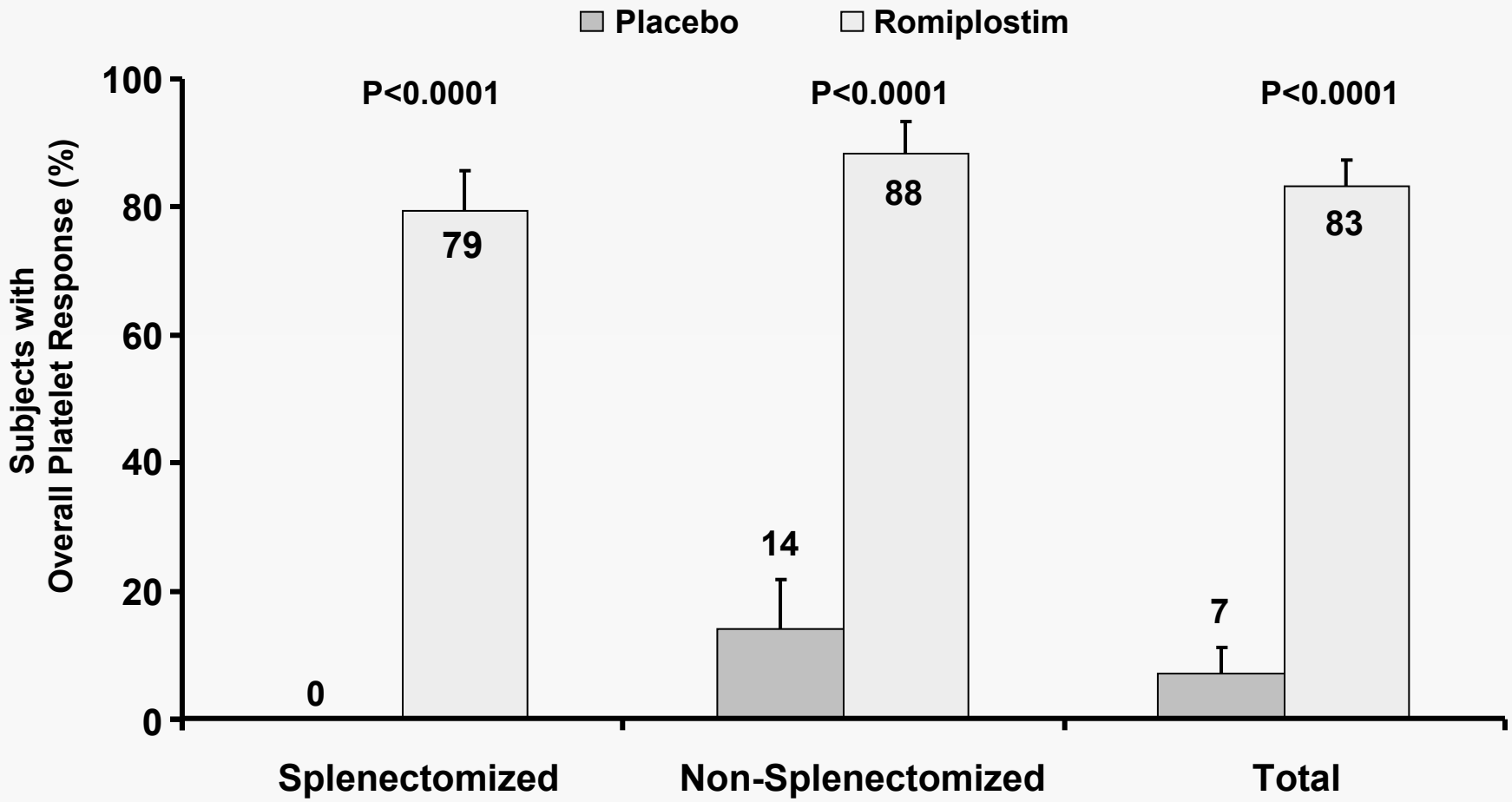
Five most frequently used prior medical therapies: corticosteroids, IVIg, rituximab, anti-D Ig, cyclophosphamide (P3 studies)

Primary Endpoint: Subject Incidence of Durable Platelet Response



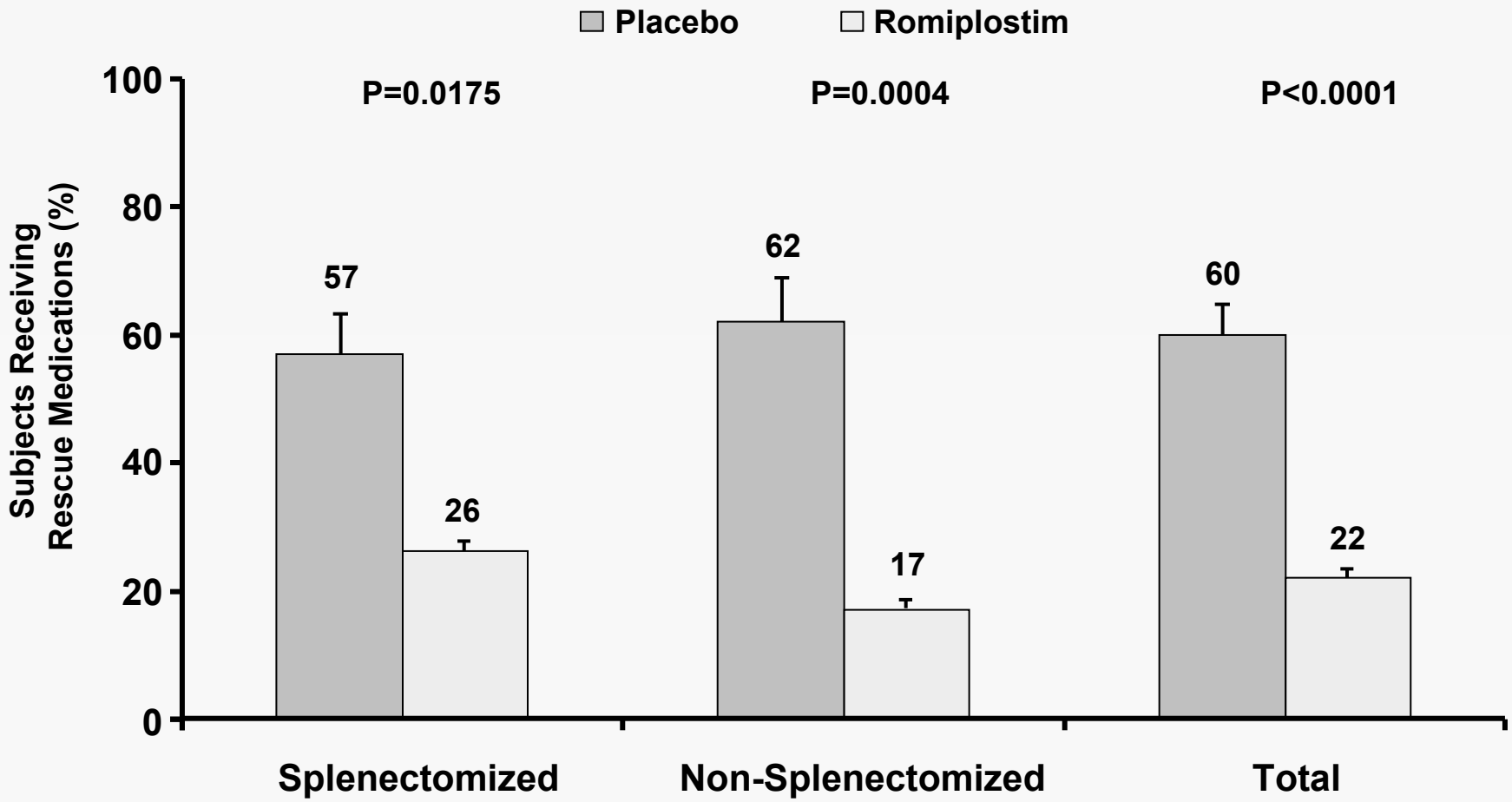
Durable platelet response: ≥6 weekly platelet counts ≥50 x 10^9/L during last 8 weeks of treatment period, in absence of rescue medication. Error bars represent standard error.
Kuter et al., 2008
(P3 studies)

Secondary Endpoint: Subject Incidence of Overall Platelet Response



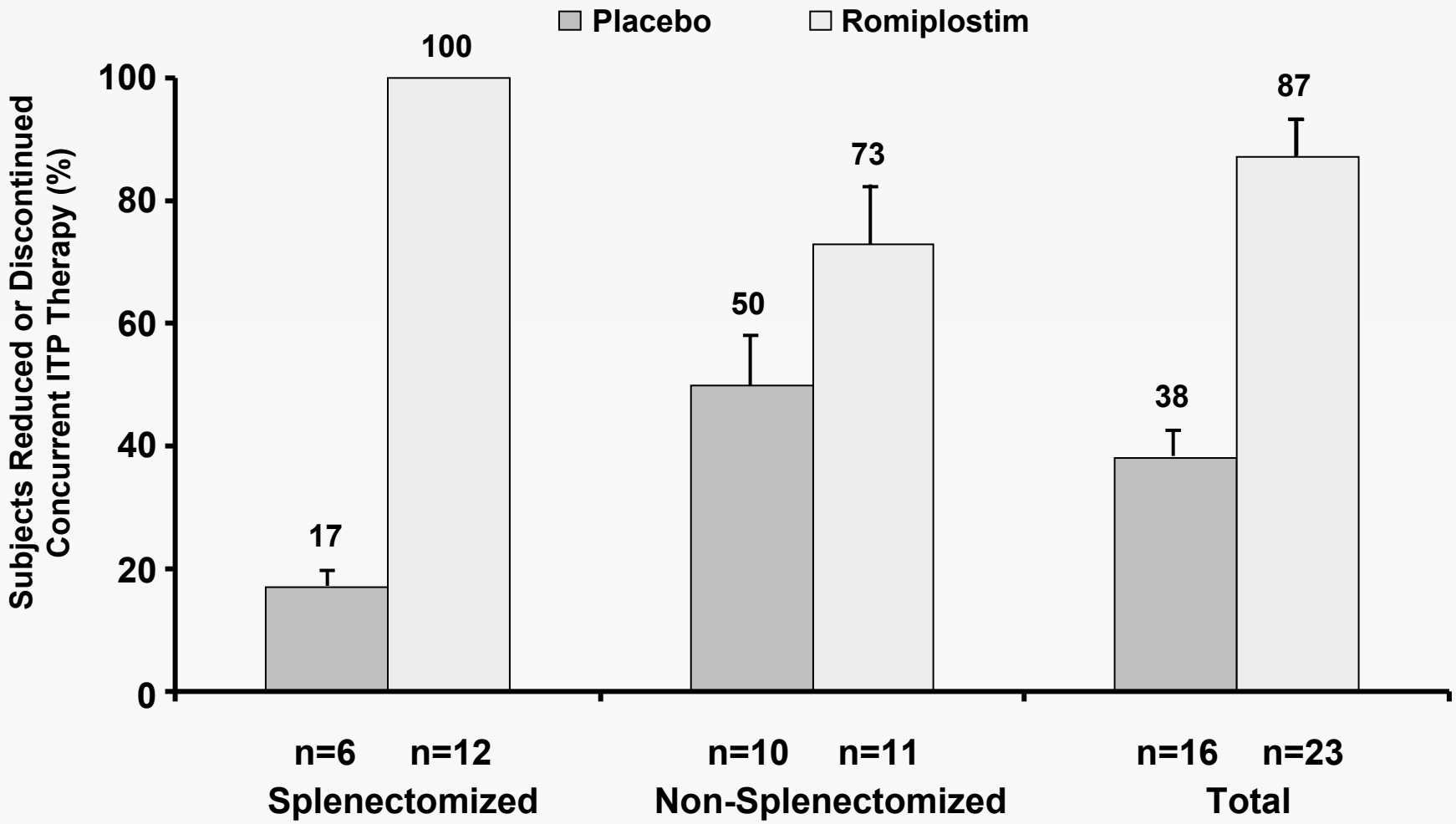
Overall platelet response: ≥4 weekly platelet counts ≥50 x 10^9/L during treatment period, platelet counts excluded within 8 weeks of rescue medication. Error bars represent standard error.
Kuter et al., 2008
(P3 studies)

Secondary Endpoint: Subject Incidence of ITP Rescue Medication Use



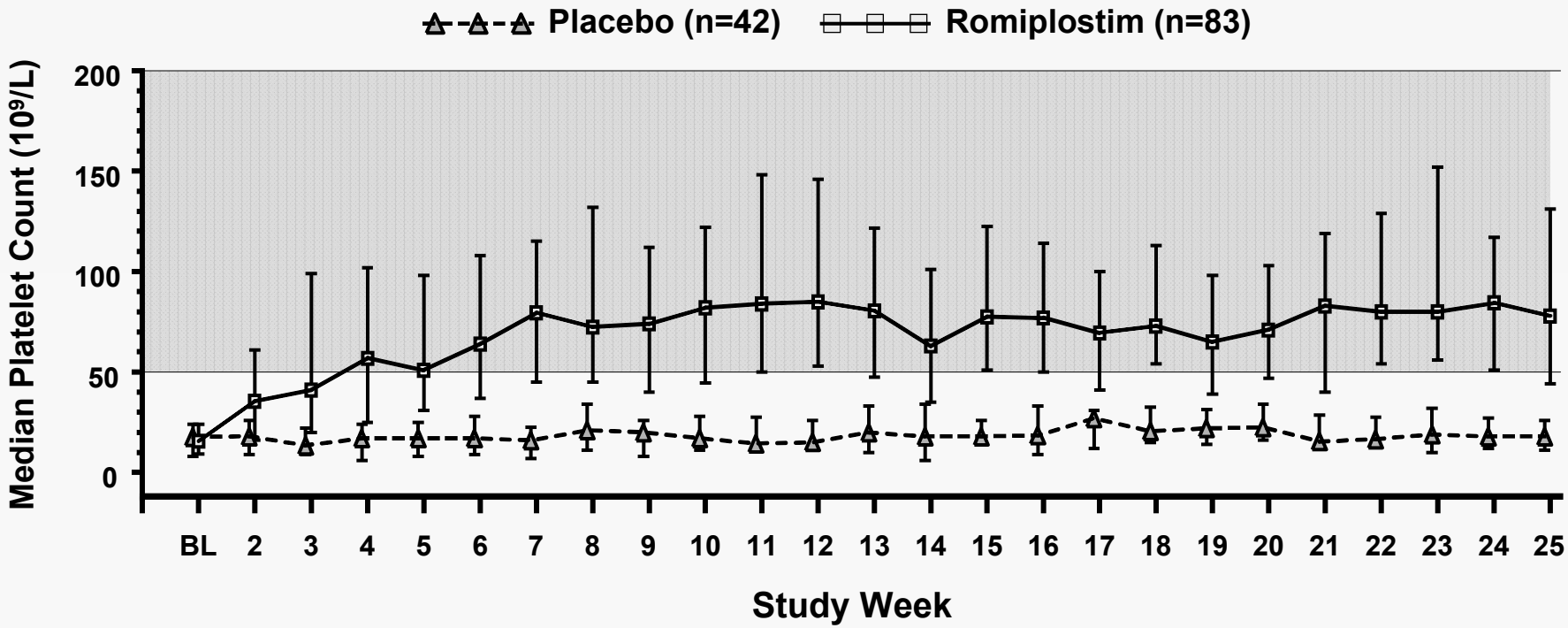
*Any medical intervention administered to increase platelet counts (corticosteroids, IVIg, anti-D Ig, platelet transfusions, cyclosporine). Error bars represent standard error.
(P3 studies)

Secondary Endpoint: Reduction and Discontinuation of Concurrent ITP Therapies



Patients discontinued or reduced by > 25% concurrent ITP therapy. Analysis based on subjects with concurrent ITP medications at baseline. Error bars represent standard error.
(Long term extension study)

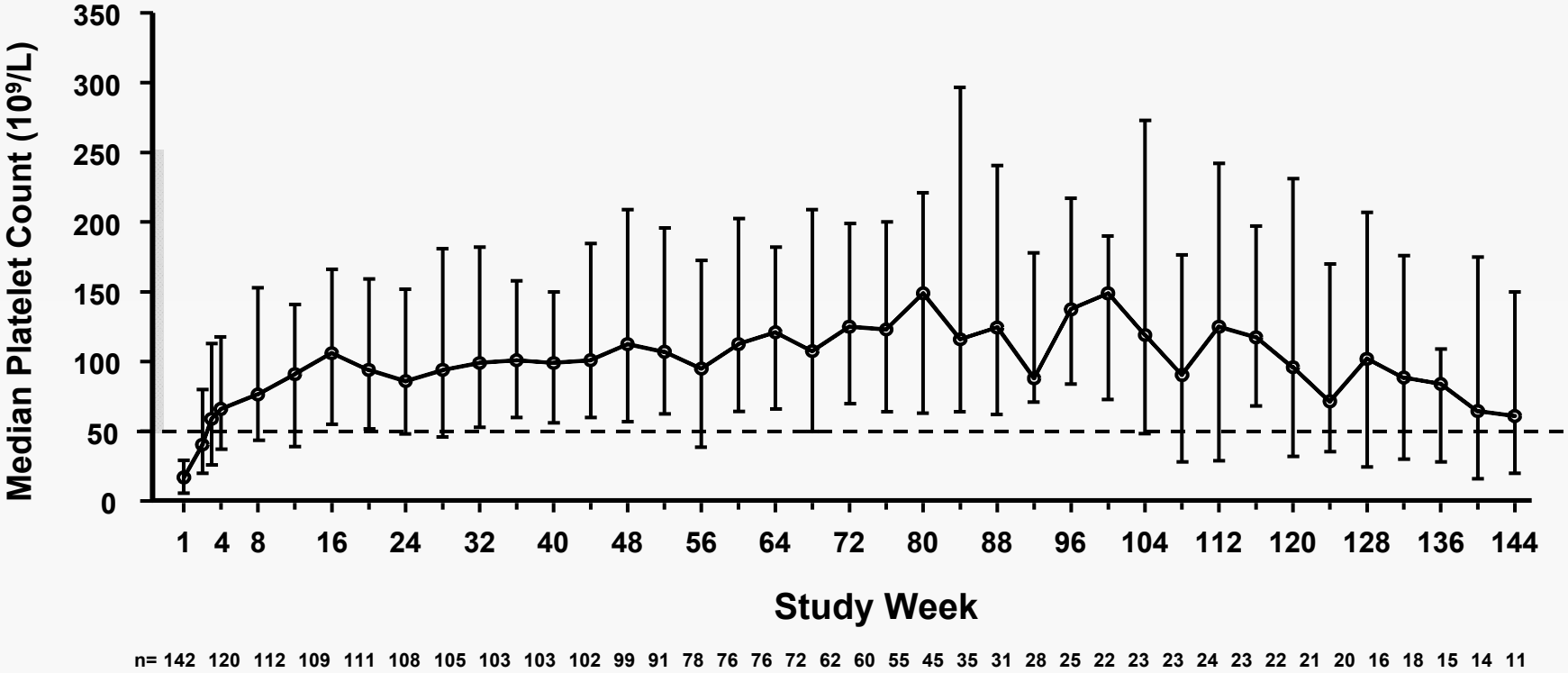
Romiplostim Maintained Median Platelet Counts in an Effective Range



Placebo n=	42	39	33	23	18	19	20	19
Romiplostim n=	83	78	77	71	72	66	67	69

Platelet counts within 8 weeks of rescue medication excluded as per Statistical Analysis Plan.
Error bars represent Q1, Q3.
(P3 studies)

Romiplostim Maintained Median Platelet Counts in Long-term Extension Study



Platelet counts within 8 weeks after receiving any rescue medications were excluded as per Statistical Analysis Plan.
Error bars represent Q1, Q3.
(Long term extension study)

Efficacy Conclusions

- **Romiplostim patients showed significant improvement in platelet count responses compared to placebo**
- **Romiplostim patients used less rescue medication**
- **Romiplostim patients were able to reduce or discontinue concurrent ITP therapies**
- **Majority of patients treated in long-term extension study experienced sustained weekly platelet responses**

Overall Summary of Adverse Events (AEs)

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Subjects with AEs	**39 (95)**	**84 (100)**
All SAEs	**8 (20)**	**14 (17)**
Life-threatening	**1 (2)**	**3 (4)**
Deaths	**3 (7)**	**1 (1)**
Withdrawals due to AE	**1 (2)**	**3 (4)**

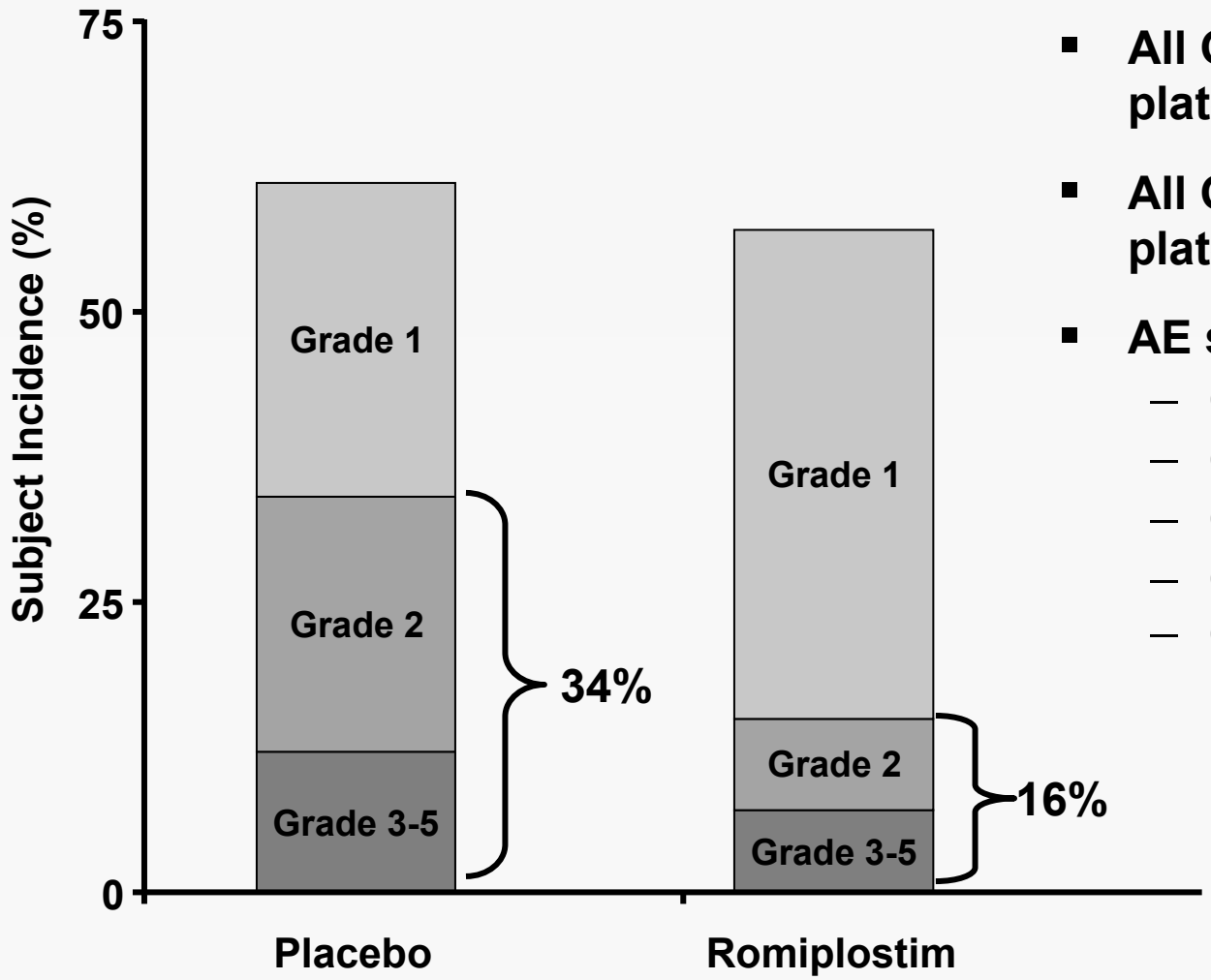
(P3 studies)

AEs with ≥5% Higher Incidence: Majority were Mild or Moderate, Transient, Non-serious

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Epistaxis	10 (24)	27 (32)
Arthralgia	8 (20)	22 (26)
Dizziness	0 (0)	14 (17)
Insomnia	3 (7)	13 (15)
Myalgia	1 (2)	12 (14)
Pain in extremity	2 (5)	11 (13)
Abdominal pain	0 (0)	9 (11)
Shoulder pain	0 (0)	7 (8)
Dyspepsia	0 (0)	6 (7)
Paraesthesia	0 (0)	5 (6)

(P3 studies)

Fewer Subjects With Grade ≥ 2 Bleeding Adverse Events With Romiplostim



- All Grade ≥2 occurred at platelet counts <50 x 10^9/L
- All Grade ≥3 occurred at platelet counts <20 x 10^9/L
- AE scale used
  - Grade 1: mild
  - Grade 2: moderate
  - Grade 3: severe
  - Grade 4: life-threatening
  - Grade 5: fatal

(P3 studies)

Events of Interest

- **Thrombocytopenia after cessation of treatment**
- **Bone marrow reticulin**
- **Neutralizing antibodies**
- **Thromboembolic events**
- **Neoplasms**

Thrombocytopenia After Cessation of Treatment

- **Thrombocytopenia expected after cessation of romiplostim treatment**
- **Phase 1 and 2 studies: AE of severe thrombocytopenia after cessation of treatment in 4/57 subjects (transient)**
- **Thrombocytopenia after cessation of treatment may lead to severe bleeding, particularly in the presence of anti-platelet agents**
  - **One case of fatal intracerebral hemorrhage**

Bone Marrow Reticulin

- **Bone marrow ancillary study (20050123): 10 ITP patients**
- **Spontaneous AE reporting: 10/271 (3.7%) romiplostim-treated ITP patients**
- **Bone marrow expert panel**
  - **Hematologists and hematopathologists (B. Bain, G. Mufti, D. Kuter, R. Hasserjian)**
  - **Reviewed bone marrow samples and reticulin data (study 20050123, 10 spontaneously reported cases)**

Bone Marrow Panel Consensus Statement

- **Potentially insufficient exposure to observe all possible romiplostim effects**
- **Bone marrow effects included hypercellularity, increased reticulin, and megakaryocyte clustering with hyperchromatic nuclei**
- **Patients experiencing these findings tended to be exposed to high doses of drug (>10 µg/kg)**
- **Findings often improved or disappeared after stopping drug**
- **Baseline history may have confounded findings in several patients**
- **No evidence romiplostim causes hematological neoplasms**

Immunogenicity

- **Immunogenicity assays**
  - **Screening assays (Biacore™) detect low and high affinity binding antibodies to romiplostim (400 ng/mL) or TPO (200 ng/mL)**
  - **Cell-based bioassays detect neutralizing antibodies to romiplostim or TPO**
- **Immunogenicity in preclinical studies**
  - **Binding and neutralizing antibodies to MGDF in animal models led to thrombocytopenia**
  - **Binding and neutralizing antibodies to romiplostim in animal models did not cross-react with TPO and did not lead to thrombocytopenia**

Immunogenicity

	Pre-dose Binding Antibodies n (%)	Post-dose Binding Antibodies n (%)	Post-dose Neutralizing Antibodies n (%)
Anti-romiplostim antibodies			
Romiplostim (n=225)	17 (8)	23 (10)	1 (0.4)
Placebo (n=45)	2 (4)	2 (4)	0 (0)
Anti-TPO antibodies			
Romiplostim (n=225)	12 (5)	12 (5)	0 (0)
Placebo (n=45)	2 (4)	4 (9)	0 (0)

(ITP Studies: 20000137, 20010218, 20030105, 20030212, 20030213, 20040209, 20050102)

Thromboembolic Events

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Thromboembolic AEs	1 (2)	2 (2)
Cerebrovascular accident	0 (0)	1 (1)
Peripheral embolism	0 (0)	1 (1)
Pulmonary embolism	1 (2)	0 (0)

ITP Safety Set (n=271): 12 subjects with thromboembolic events: DVT (3), PE (3), Portal vein thrombosis (2), thrombophlebitis (2), thrombosis (2), myocardial infarction (2)

(P3 studies)

Neoplasms

	Placebo (n=41) n (%)	Romiplostim (n=84) n (%)
Neoplasm AEs	**5 (12)**	**2 (2)**
B-cell lymphoma	0 (0)	1 (1)
Basal cell carcinoma	0 (0)	1 (1)
Benign ovarian tumor	1 (2)	0 (0)
Fibroma	1 (2)	0 (0)
Lung neoplasm	1 (2)	0 (0)
Metastases to liver	1 (2)	0 (0)
Multiple myeloma	1 (2)	0 (0)
Uterine leiomyoma	1 (2)	0 (0)

Uterine leiomyoma and benign ovarian tumor in the same subject
(P3 studies)

Individual Cases from Other ITP Studies

- **901002: 63 y/o male**
  - **Enrolled on study 20040209 (01/2006)**
  - **At month 7, AE of splenomegaly**
  - **Bone marrow biopsy (month 8): bone marrow fibrosis**
  - **Baseline biopsy (month -3): del (20q), reticulin +, sclerotic bone, consistent with MDS/MPD**
- **90502: 75 y/o female**
  - **Enrolled on study 20040209 (05/2006)**
  - **At month 6, AE of aplastic anemia, after treatment with azathioprine, steroids, IVIg and rituximab**
  - **Pre-existing macrocytosis**

Study 20030159: Romiplostim in Disease-related Thrombocytopenia in MDS

- **Phase I/II single arm dose escalation study**
- **44 subjects with low/int-1 risk MDS**
- **Platelet response in 54% of patients**
  - **Fewer transfusions and bleeding events**
- **Progression to AML: 2 subjects**
- **Increase in IPSS score: 3 subjects**
- **Transient blast cell increase: 6 subjects**
- **Further clinical studies planned in disease-related and treatment-related thrombocytopenia in MDS**

Safety Conclusions

- **Majority of AEs mild to moderate and transient**
- **Bleeding events grade ≥2 more frequent in placebo (34%) than romiplostim patients (16%)**
- **Thromboembolic and neoplasm events similar for placebo and romiplostim groups**
- **Thrombocytopenia after cessation of treatment and increase of bone marrow reticulin are identified risks of romiplostim in ITP**
- **Risk Management Program**
  - **Risk Minimization Action Plan (RiskMAP)**

Agenda

Background and Introduction	**Joseph Miletich, MD, PhD** **Senior Vice President, Research & Development, Amgen Inc.**
Thrombopoietin (TPO), and Management of Immune Thrombocytopenic Purpura (ITP)	**David Kuter, MD, DPhil** **Professor, Department of Medicine, Harvard Medical School, Director, Clinical Hematology, Massachusetts General Hospital**
Romiplostim in ITP: Efficacy and Risk Assessment	**Dietmar Berger, MD, PhD** **Executive Director Global Clinical Development, Amgen Inc.**
Risk Management Program and Closing Remarks	**Paul Eisenberg, MD, MPH** **Senior Vice President Global Regulatory Affairs & Safety, Amgen Inc.**

Overview of Risk Management Program

- **Safety experience from clinical program**
  - **Identified and potential risks**
- **Proposed Risk Management Program**
  - **Risk assessment (pharmacovigilance, targeted studies)**
  - **Risk minimization (labeling, RiskMAP)**
- **Components of RiskMAP**
  - **Targeted education**
  - **Controlled Distribution Program**
  - **Safety registry**
- **Overall assessment of Benefit:Risk**

Risks Addressed in Risk Management Program

Identified Risks

- **Reoccurrence of thrombocytopenia after cessation of treatment**
- **Increased bone marrow reticulin**

Risks Addressed in Risk Management Program

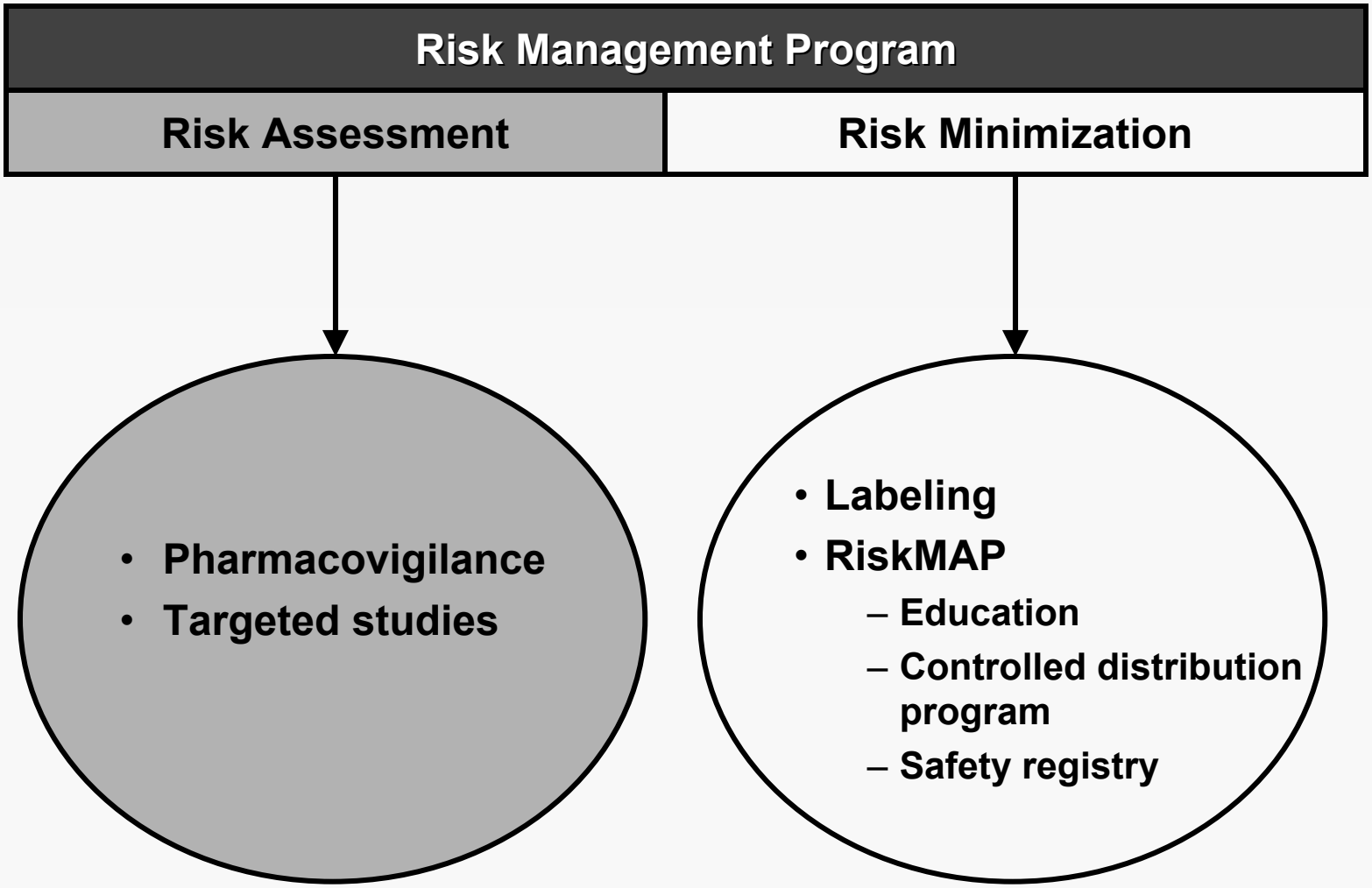
Identified Risks

- **Reoccurrence of thrombocytopenia after cessation of treatment**
- **Increased bone marrow reticulin**

Potential Risks

- **Thrombotic / thromboembolic complications**
- **Neutralizing antibodies that cross react with eTPO**
- **Progression of existing hematopoietic malignancies**
- **Progression of reticulin to irreversible fibrotic state**
- **Use in indications where benefit:risk has not been adequately studied**
- **Medication errors**

Risk Management Program



Risk Assessment: Observational Studies

- **Retrospective epidemiologic study**
  - **Define prevalence of bone marrow reticulin and fibrosis in ITP patients using Danish National Health Registry Database**
  - **Data on 3,000 patients with ITP and over 600 with ITP >6 months from 1996 to 2006**
  - **Extensive bone marrow biopsy data**
- **Prospective study to monitor incidence of increased bone marrow reticulin and bone marrow fibrosis**
  - **Longitudinal assessment of bone marrow reticulin and clinical sequelae in romiplostim treated patients**
  - **All adult patients with ITP in Denmark, Sweden, and Finland between January 1, 2009 and December 31, 2019**

Risk Assessment: Long-term Open Label Prospective Study

- **Longitudinal evaluation of changes in bone marrow morphology in romiplostim-treated ITP subjects (n~200)**
- **Key endpoints**
  - **Increase in bone marrow reticulin and collagen after 24 and 60 months of romiplostim exposure**
  - **Incidence of post-treatment thrombocytopenia**
  - **Incidence of antibody development after 24 and 60 months of romiplostim exposure**
- **Assessment of incidence of hematological malignancies and thromboembolic adverse events**

Risk Minimization: Labeling

Identified Risks	Prescribing Information	
Reoccurrence of thrombocytopenia	✓	Warning
Increased bone marrow reticulin	✓	Max dose 10µg/kg

Risk Minimization: Labeling

Identified Risks	Prescribing Information	
Reoccurrence of thrombocytopenia	✓	Warning
Increased bone marrow reticulin	✓	Max dose 10 µg/kg
Potential Risks		
Off-label use	✓	Indication-ITP only
Neutralizing antibodies	✓	Warning, contact info
Thromboembolic events	✓	Maintain platelet count $\geq 50 \times 10^9$/L and minimize excursions > 200×10^9/L
Progression of reticulin to irreversible fibrotic state	✓	Warning
Progression of existing hematopoietic malignancies	✓	Warning
Medication errors	✓	Administered by HCP

Risk Minimization Action Plan (RiskMAP)

- **Strategic safety program designed to meet specific goals and objectives in minimizing product risks while preserving benefits**
- **Uses tools that**
  - **Are evidence-based**
  - **Allow appropriate product access**
  - **Consider stakeholder input, technology, practice settings**
- **3 categories of tools**
  - **Targeted education and outreach**
  - **Reminder systems**
  - **Controlled distribution**
- **Effectiveness of tools is monitored and periodically reported to FDA**

Guidance for Industry. Development and Use of Risk Minimization Action Plans. U.S. Department of Health and Human Services. FDA. CDER. CBER. March 2005

Overview of Romiplostim RiskMAP

- **Goal**
  - **Appropriate use in ITP**
  - **Assess identified and potential risks associated with use of romiplostim**
- **Objectives**
  - **Patient and physician education on risk profile and appropriate use**
  - **Long term monitoring of identified and potential risks**
  - **Limit off-label use**
- **Proposed RiskMAP based on feedback from stakeholders and FDA**

Proposed Indications and Usage

- **Indicated for treatment of thrombocytopenia in adult patients with chronic ITP**
  - **Who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins**
  - **Who are splenectomized and have an insufficient response to splenectomy**

RiskMAP Tools: Patient Management Program

- **Targeted education and outreach**
  - **Product labeling / Medication Guide**
  - **Provider Education Training Kit**
    - **ASH guidelines**
    - **ITP diagnosis checklist**
- **Reminder systems**
  - **Medication Guide**
  - **Pre-use checklist**
  - **6 month reconfirmation of diagnosis**
- **Controlled Distribution Program**
  - **Patient/physician consent to enter program**
  - **Ships only to physicians for treatment of enrolled ITP patients**
  - **Tracking database/safety registry**

RiskMAP:
Controlled Distribution Program (CDP)

Step 1

Patient **Heme/Onc**

Educates patient
1. **Medication Guide**
2. **Inform on CDP**

Complete and sign program enrollment form

Case manager enters patient into program

RiskMAP Tool: Program Enrollment Questionnaire

Patient demographics and physician attestation to chronic ITP diagnosis

Patient consent for program participation
(Includes sharing of medical and safety data)

Physician information

Patient attestation of Medication Guide review

AMGEN

Program Enrollment Questionnaire

nt Information and Physician Certification of Diagnosis

_____ Patient Initials: _____

ender: ☐M ☐F Weight: _____ kg

m is a thrombopoietin (TPO) mimetic indicated f tre of
ocytopenia in adult patients with chronic immune tic)
mbocytopenic purpura (ITP):

- Who are non-splenectomized and have an in t res nse or are intolerand to corticosteroids and/or immunoglo
- Who are splenectomized and have an insufficient e to splenectomy.

I certify that I am prescribing Romiplos patient atment chronic ITP as described in the prescrib n

Prescriber's signature: _____

2. Physician Inform

Full Name (print): _____

Phone: e-mail: _____

Physi n Sig _____ Date: ___/___/___

3. Co r Pa tion in the Romiplostim Patient Management Program

I consent nta d by the Romiplostim case manager and to the sharing of my medical nt information within the patient management program for Romiplostim a mgen.

Patient signature _____ Date _____

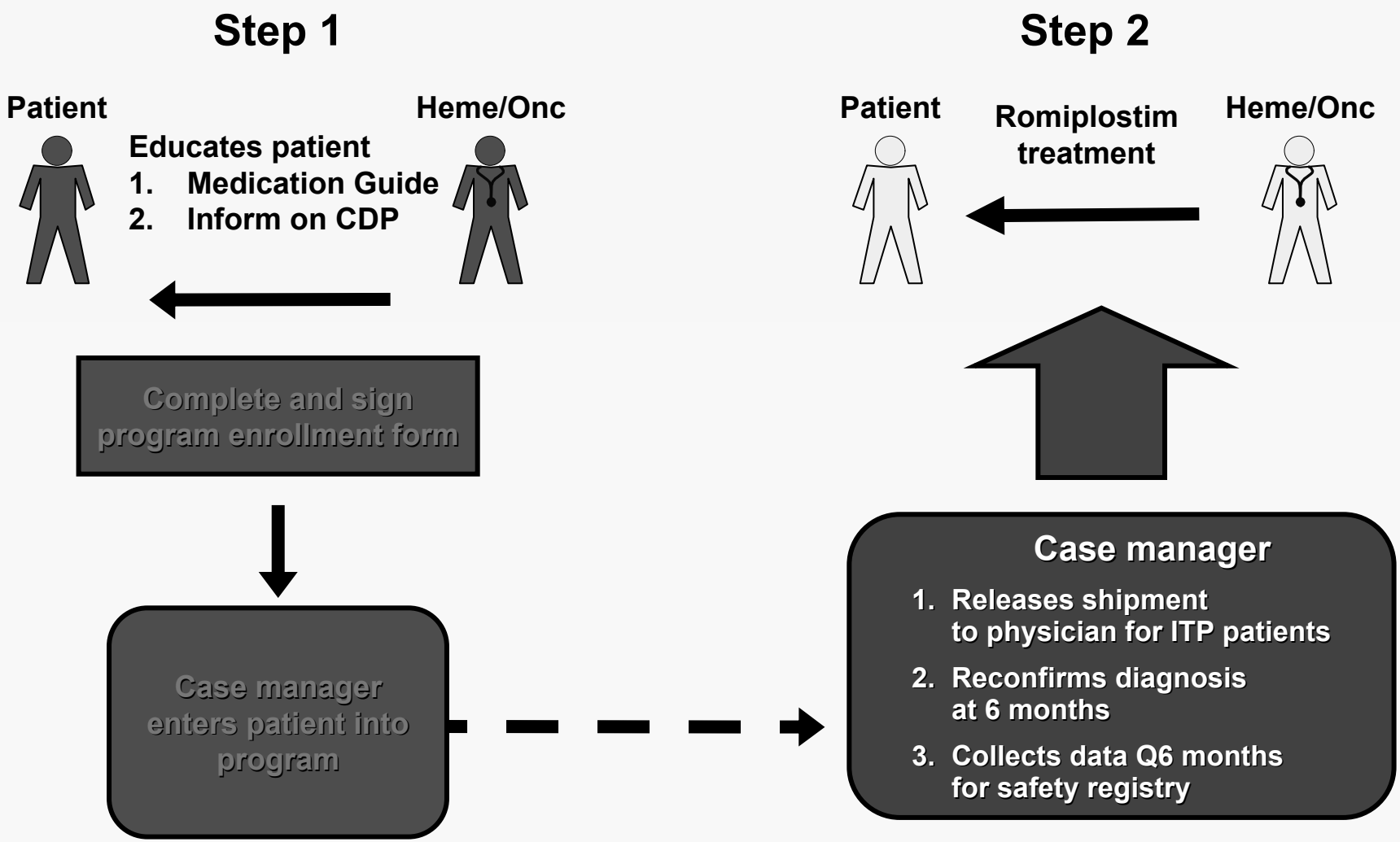
4. Patient Confirmation of Medication Guide Receipt

Prior to receiving my first dose of Romiplostim therapy, my health care provi shared with me the Romiplostim Medication Guide and patient education kit a described the benefits and risks of Romiplostim therapy.

Patient signature _____ Date _____

DRAFT

RiskMAP: Controlled Distribution Program (CDP)



RiskMAP Summary

Identified Risks	RiskMAP Activities		
	Education	Safety Registry	Controlled Distribution
Reoccurrence of thrombocytopenia	✓	✓	
Increased bone marrow reticulin	✓	✓	
Potential Risks			
Off-label use	✓		✓
Neutralizing antibodies	✓	✓	
Thromboembolic events	✓	✓	
Progression of reticulin to irreversible fibrotic state	✓	✓	
Progression of existing hematopoietic malignancies	✓	✓	
Medication errors	✓	✓	

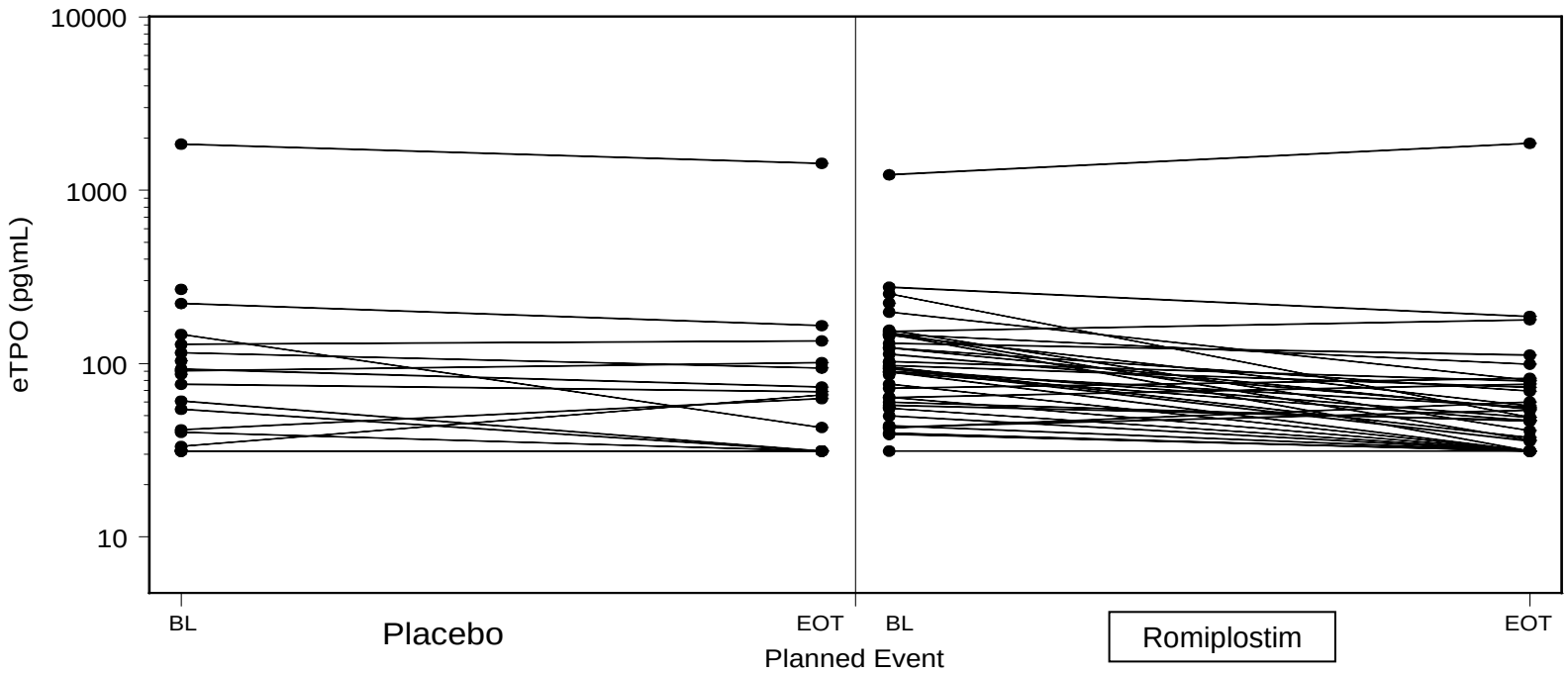
Closing Remarks

- **ITP carries the risk of serious bleeding**
- **Safety and efficacy of current therapies are inadequate and few are approved**
- **Romiplostim is a novel and effective therapy for chronic treatment of ITP with potential to decrease risk of serious bleeding**
- **Amgen has proposed a robust Risk Management Program**
  - **Additional targeted studies**
  - **Comprehensive RiskMAP**

Subjects who Maintained Platelet Counts After Discontinuation of Romiplostim

- **Seven subjects in the pivotal studies (5 non-splenectomized and 2 splenectomized) were able to discontinue romiplostim during the treatment period**
- **All had platelet counts above 50 x 10^9/L at the final week of the treatment period (week 25)**
- **All maintained platelet counts above 50 x 10^9/L until end of study (week 36)**
- **Received no additional Romiplostim treatment or other ITP treatment**

No Changes in TPO levels Before and One Week After a 24-Week Treatment of Romiplostim" Phase 3 study (20030212)



Full analysis set includes all randomized subjects.
Raw eTPO values were plotted on log scale.
Program: /stat/amp2/itp/amp20030212/analysis/final_dev/graphs/g_etpo.sas
Output: g_04_004_002_etpo_log.cgm (Date Generated: 08MAY07:17:05:10) Source Data: etpo.sas7bdat

Rescue Medication Use in Studies 20030105 and 20030212

	Non-splenectomized 20030212		Splenectomized 20030105	
	Placebo (n=21)	Romiplostim (n=41)	Placebo (n=21)	Romiplostim (n=42)
Subjects receiving rescue medications – n (%)	13 (61.9)	7 (17.1)	12 (57.1)	11 (26.2)
Corticosteroids	6 (28.6)	7 (17.1)	8 (38.1)	7 (16.7)
IVIG	7 (33.3)	4 (9.8)	11 (52.4)	7 (16.7)
Anti-D Immunoglobulin	4 (19.0)	2 (4.9)	0 (0.0)	0 (0.0)
Platelet Transfusions	2 (9.5)	0 (0.0)	4 (19.0)	5 (11.9)
Cyclosporin	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)
Rituximab	1 (4.8)	0 (0.0)	0 (0.0)	0 (0.0)
Azathioprine	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)

Source: CSR 20030105 Table 14-4.1.12.2 and CSR 20030212 Table 14-4.1.12.2.

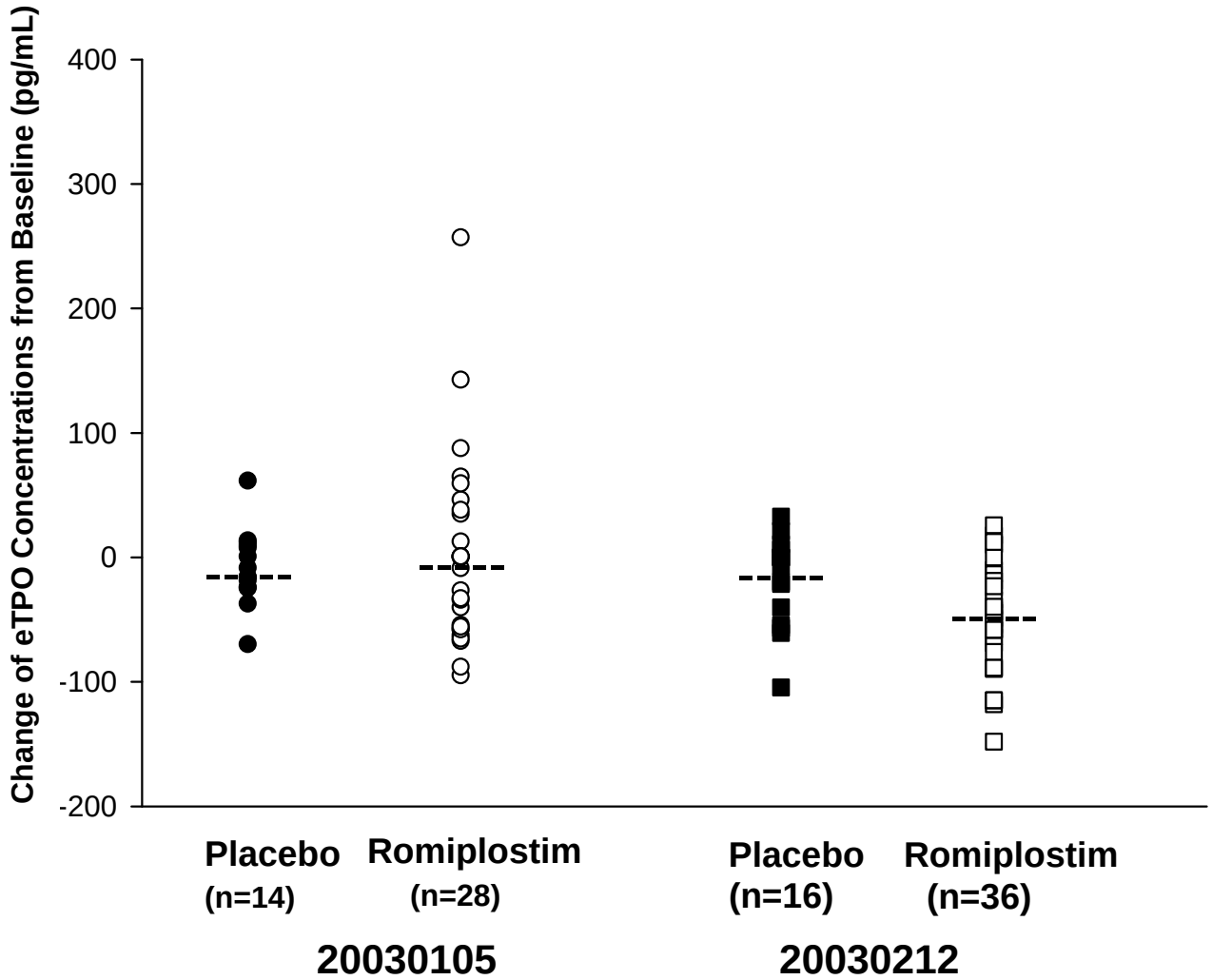
Definition of Rescue Medication

- **Rescue medication is permitted when there is bleeding or wet purpura, or if the investigator feels that the subject is at immediate risk. Rescue medication is defined as any medication that is administered for the intended purpose of raising platelet counts. Recommended rescue medications are IVIG, platelet transfusions, and corticosteroids. An increase in dose or frequency of a concurrent ITP medication is also considered rescue medication**

Indication

- **Nplate is a thrombopoietin (TPO) mimetic indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP):**
  - **Who are non-splenectomized and have an insufficient response or are intolerant to corticosteroids and/or immunoglobulins**
  - **Who are splenectomized and have an insufficient response to splenectomy**

Dose Adjustment

- **Adjust the weekly dose of Nplate by increments of 1 mcg/kg until the patient achieves a platelet count greater than or equal to 50 x 10^9/L. Assess the platelet count weekly until a stable platelet count (greater than or equal to 50 x 10^9/L for at least 4 weeks without dose adjustment) has been achieved and monthly thereafter. Do not exceed a maximum weekly dose of 10 mcg/kg**
- **Use the body weight at initiation of therapy for all dose calculations. Adjust the dose as follows:**
  - **If platelet count is < 50 x 10^9/L, increase the dose by 1 mcg/kg**
  - **If platelet count is > 400 x 10^9/L, do not dose. Assess platelet count weekly. After the platelet count has fallen to < 200 x 10^9/L, resume Nplate at a dose reduced by 1 mcg/kg**
- **Discontinue Nplate if platelet count does not increase after 4 weeks at the highest weekly dose of 10 mcg/kg**

In Phase 3 Studies, Changes in TPO Levels were Similar Between Romiplostim and Placebo Groups