

Case #8—Immune Thrombocytopenic Purpura: New Opportunities for Management

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Disclosures for Roberto Stasi, MD, PhD

Consultant / Speaker's Bureau: Amgen,
GSK

Case Report

- A 35-year-old lab technician presents with a history of mild nose bleeds and easy bruising for 10 days. She has been healthy with no previous history of bleeding.
- Physical exam:
 - Petechiae on both lower legs and several ecchymotic areas on both arms. There are no petechiae seen in the conjunctivae or mouth.
 - No hepatosplenomegaly or adenopathy.
- Evaluation:
 - WBC: 4800/ μ L
 - Hgb: 11.8 g/dL
 - Platelet ct: 9000/ μ L
 - Peripheral blood film: Normal except for \downarrow platelets
 - Chemistry profile: WNL

Case Report

- A 35-year-old lab technician presents with a history of mild nose bleeds and epistaxis for the past 10 days. She has been healthy and has no history of bleeding.
- Physical examination:
 - Petechiae and purpura in mucocutaneous areas
 - No other abnormalities
- Evaluation:
 - WBC: 10,000/mm³
 - Hgb: 12.5 g/dL
 - Platelets: 50,000/μL
 - Peripheral smear: Normal except for ↓ platelets
 - Chemistry profile: WNL

Most likely diagnosis:
ITP
No need for BM

Clinical Course – Part 1

- She was treated with prednisone 60 mg/day (1 mg/kg).
- One week later plt count 20,000/ μ L. PDN is tapered.
- Plt count \downarrow 20,000/ μ L when PDN reaches 20 mg/d.
- After 3 months of PDN treatment at 20mg/d, the patient reports weight gain, facial and mood changes.
- Hb 12.0 g/dL, WBC 12,500/ μ L with 88% PMNs, Plt count 15,000/ μ L. Her blood is Rh negative.
- There are a few petechiae on her ankles and bruises on her arms and legs but no evidence of mucosal bleeding.

Options to Consider

- **Observe off of therapy since the patient has had no serious bleeding**
- **Intravenous immune globulin (IVIg) 1 gm/kg over two consecutive days, repeated as needed to maintain a platelet count $>30,000/\mu\text{L}$**
- **Rituximab 375 mg/m² IV infusion weekly x 4**
- **Azathioprine 2 mg/kg/d PO for 3-4 months**
- **Laparoscopic splenectomy**

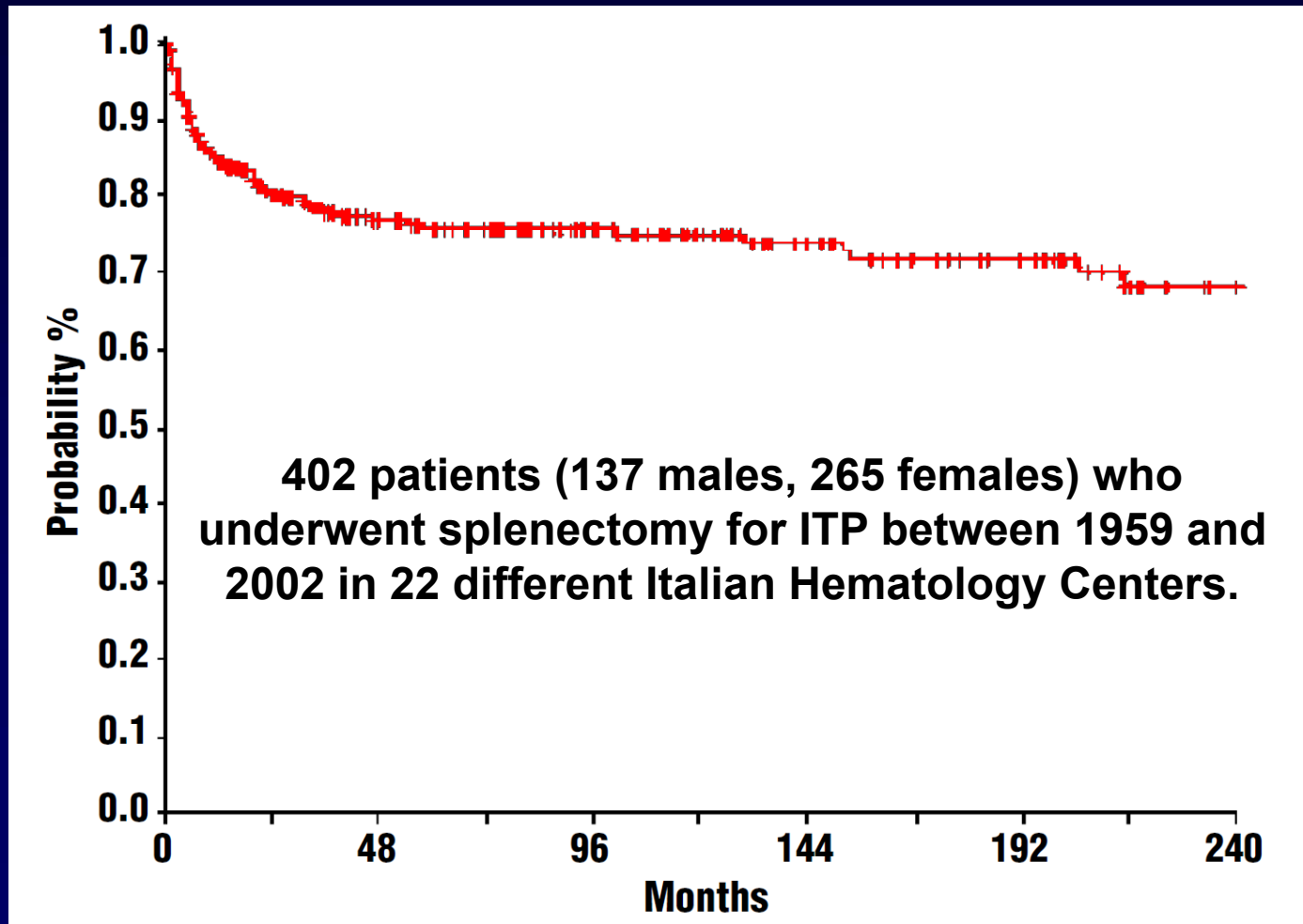
Patient's Choice

- Observe off of therapy since the patient has had no serious bleeding
- Intravenous immune globulin (IVIg) 1 gm/kg over two consecutive days, repeated as needed to maintain a platelet count $>30,000/\mu\text{L}$
- Rituximab 375 mg/m² IV infusion weekly x 4
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- Laparoscopic splenectomy

Splenectomy Long-Term Outcome: 2623 Adults with Follow-Up for 1 to 153 Months

- **Sustained** response rate:
 - At 9 months 66%
 - At 5 years 64%
- **Relapse** rate 15%
 - TTR 33 months
- **Mortality** rate:
 - Laparoscopic splenectomy 0.2%
 - Open splenectomy 1%
- **Sepsis** 0.7/1000 py
- **Thrombosis** 1/1000 py
- **Other morbidities** 9.6% to 12.9%

Splenectomy Long-Term Outcome: 2623 Adults with Follow-Up for 1 to 153 Months



Laparoscopic Splenectomy

- **Accessory spleens are identified at a rate similar to open splenectomy**
- **Low recurrence rates, similar to open splenectomy**
- **Complication rates higher than with open splenectomy**
- **Mean length of hospital stay shorter with laparoscopy (3 days vs 10 days)**
- **Deaths caused by laproscopic splenectomy: 0.2% (3/1301)**

Kojouri K, et al. *Blood*. 2004;104(9):2623-2634.

Sampath S, et al. *Am J Surg*. 2007;193(5):580-584.

Other Options

- **Observe off of therapy – 5% to 10% spontaneous remissions**
- **IVIg – Response rates ~80%, mostly transient, ~40% can avoid splenectomy**
- **Rituximab – response rates ~50%, long term responses 15%**
- **Azathioprine 2 mg/kg/d PO for 3-4 months – Response rates ~30%, usually taking several weeks to occur**
- **Laparoscopic splenectomy**

Clinical Course – Part 2

- Uncomplicated laparoscopic splenectomy
- Initial postoperative spike platelets to 220,000/ μ L
- The count rapidly drops back to 15,000/ μ L a few days later
- The patient continues to have occasional episodes of epistaxis (nosebleeds) as well as persistent bruising. No gingival bleeding. Menstrual bleeding slightly heavier than usual but ends after 5 days.

What Would You Recommend At This Time?

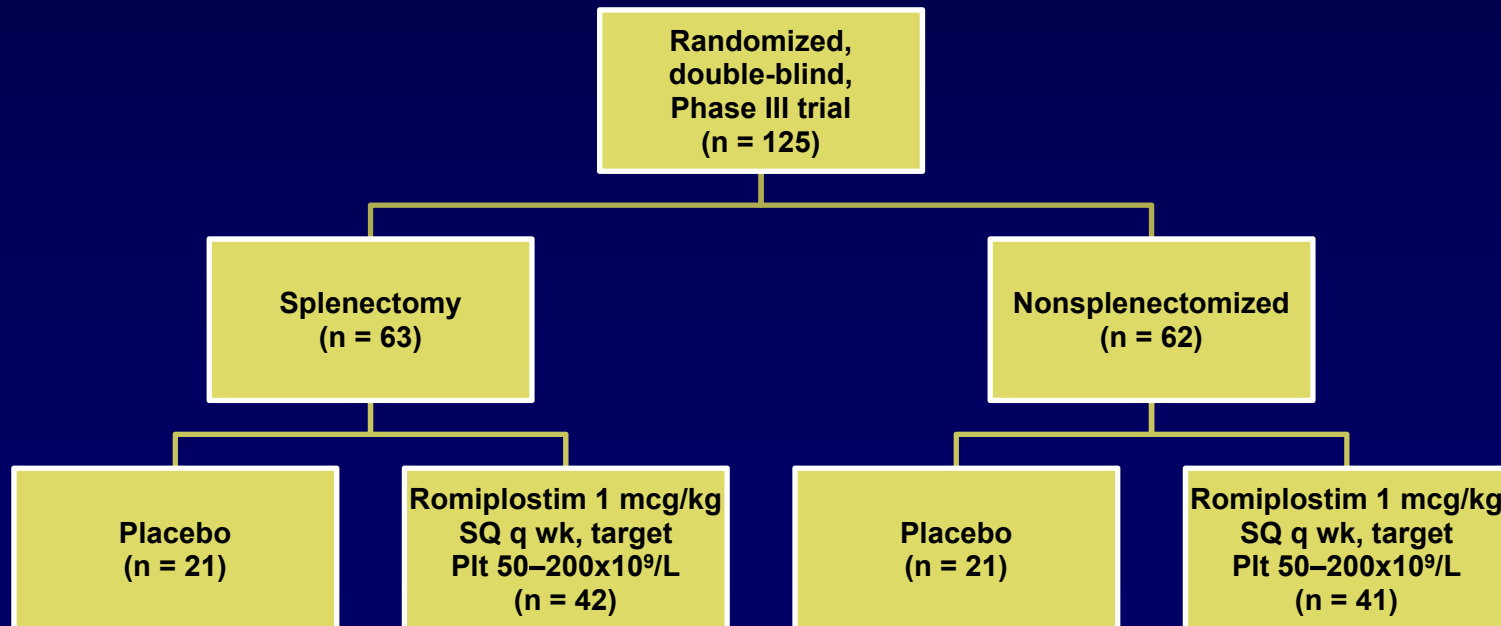
- **Observe off therapy since the patient has no serious bleeding**
- **Dexamethasone 40 mg/d for 4 days every 28 days**
- **IVIg 1 gm/kg**
- **Romiplostim once a week SC**
- **Rituximab 375 mg/m² IV infusion weekly x 4**
- **Azathioprine 2 mg/kg/d PO for 3-4 months**
- **Eltrombopag, an oral thrombopoietin receptor agonist**

My Choice

- Observe off therapy since the patient has no serious bleeding
- Dexamethasone 40 mg/d for 4 days every 28 days
- IVIG 1 gm/kg
- **Romiplostim once a week SC**
- Rituximab 375 mg/m² IV infusion weekly x 4
- Azathioprine 2 mg/kg/d PO for 3-4 months
- Eltrombopag, an oral thrombopoietin receptor agonist

Romiplostim in Chronic ITP Phase III Study

- Weekly, SC romiplostim in slowly escalating doses (1 µg/kg up to 15 µg/kg) for 24 weeks
- Dose adjusted to achieve a platelet count of 50,000-200,000
- Inclusion criteria: Age ≥18; ITP with platelet count <30,000
- Other treatments were discontinued at least 4 weeks before entry



Definition of Platelet Response

Durable

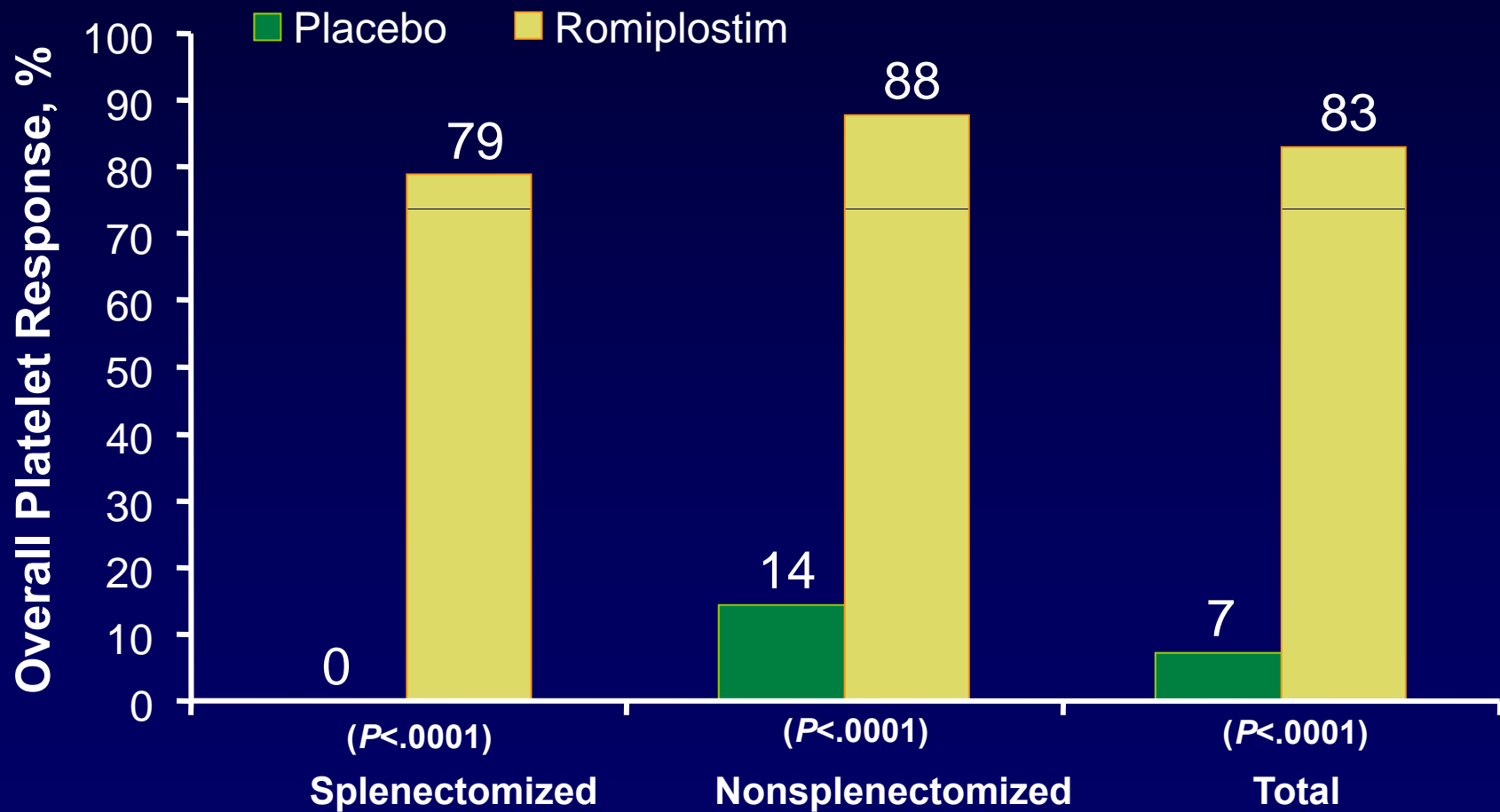
Platelets $\geq 50,000/\mu\text{L}$ for **at least 6 of the last 8 weeks** of treatment

Transient

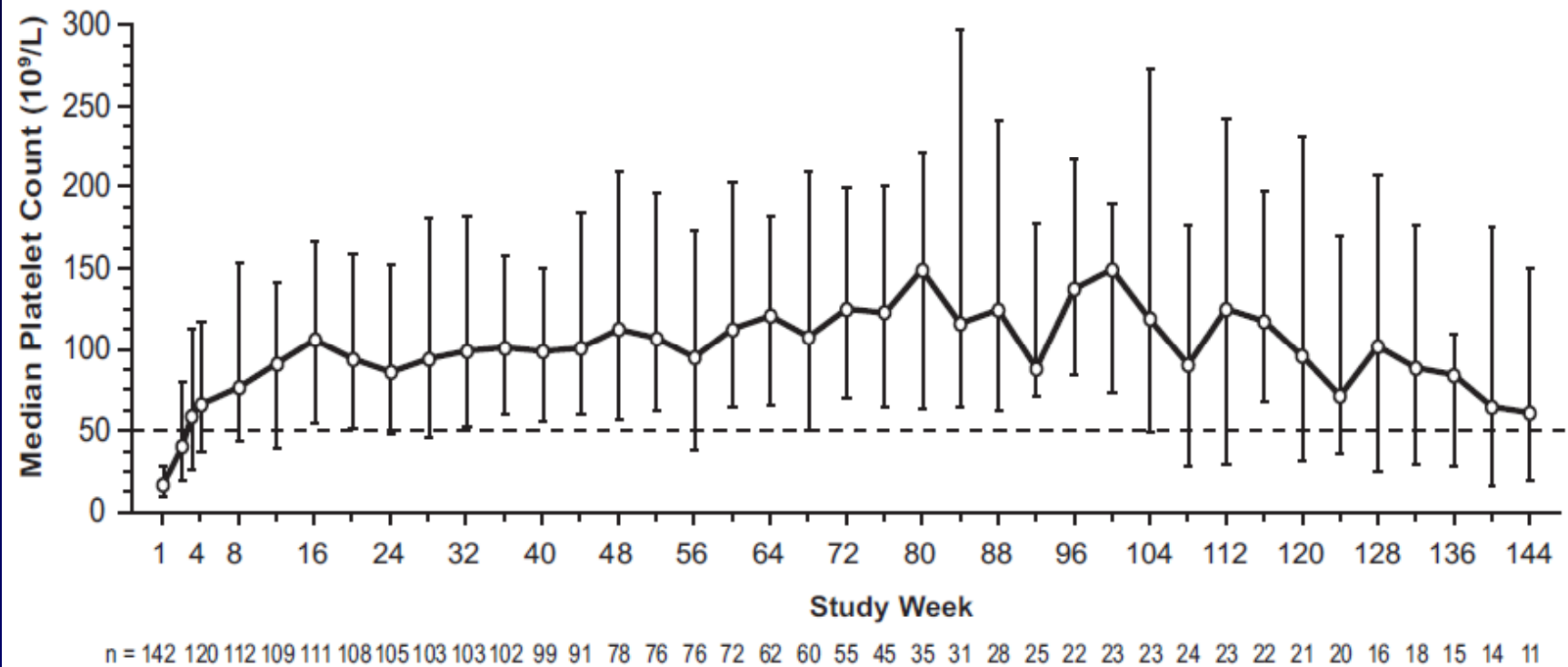
Four or more weekly platelet responses (Platelets $\geq 50,000/\mu\text{L}$) at any time during the study



Phase III: Overall Platelet Response

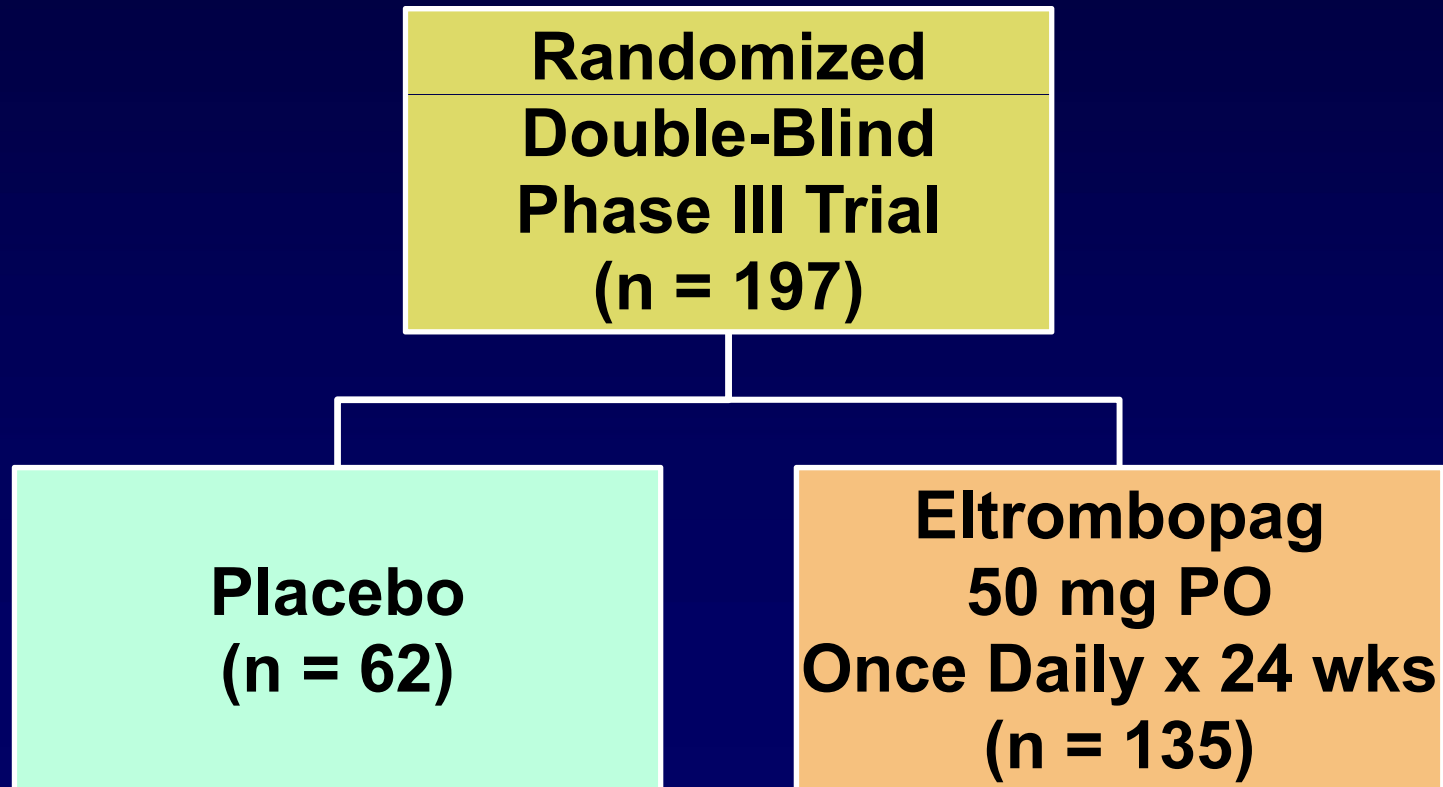


Long-Term Treatment



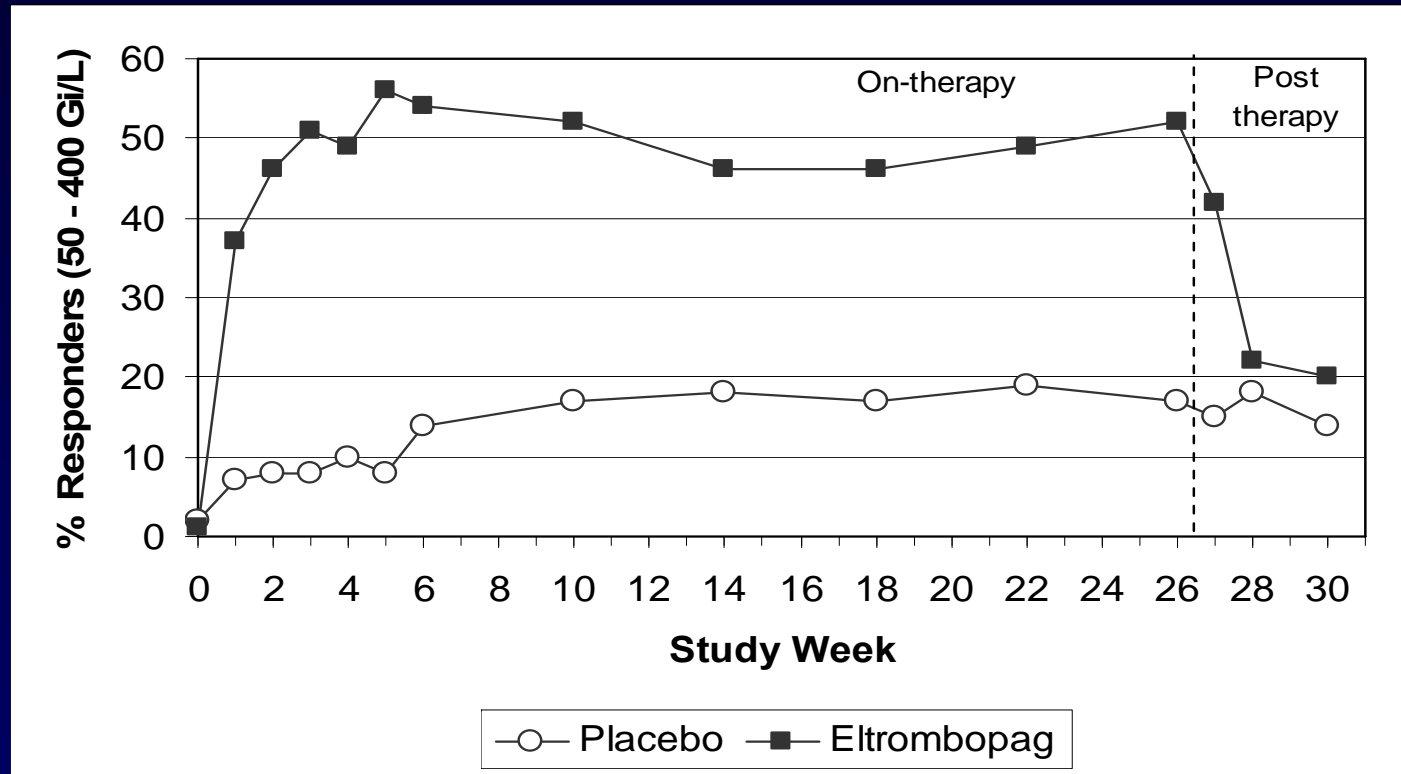
Eltrombopag in ITP: Phase III, Double-Blind, Placebo-Controlled Study (RAISE)

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



RAISE: Odds of Platelet Response

OR (99% CI) = 8.2 (3.59, 18.73) $P < .001^1$



No differences in response to E-PAG relative to placebo, regardless of splenectomy, concomitant ITP medication or baseline platelet counts (≤ 15 Gi/L)

¹ Based on repeated measures model for binary data adjusted for randomisation stratification variables. GEE used to estimate regression model parameters, exchangeable working correlation structure

Cheng G, et al. *Blood* 2008;112: Abstract 400. Stasi R, et al. *Haematologica* 2009; 94(Suppl 2): Abstract 0231.

Definition of Platelet Response: *Post Hoc Analysis*

Durable

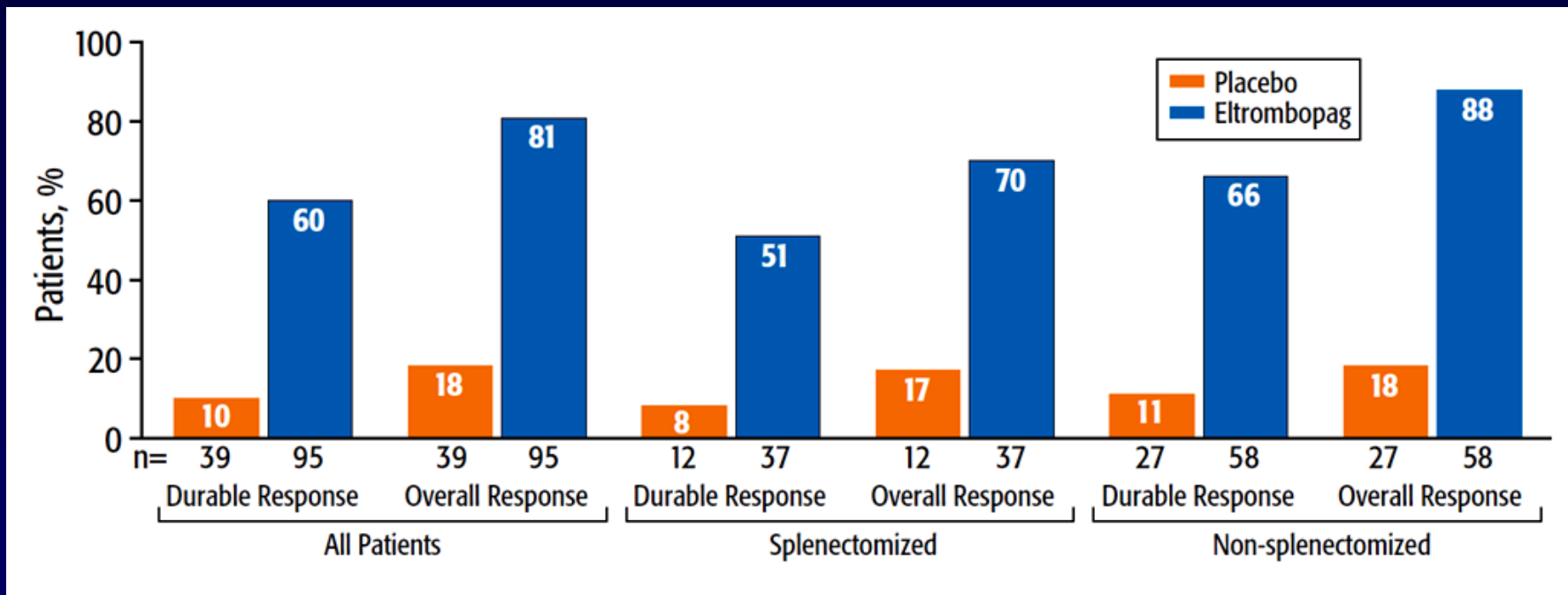
Platelets $\geq 50,000/\mu\text{L}$ for **at least 6 of the last 8 weeks** of treatment

Transient

Four or more weekly platelet responses (Platelet $\geq 50,000/\mu\text{L}$) at any time during the study

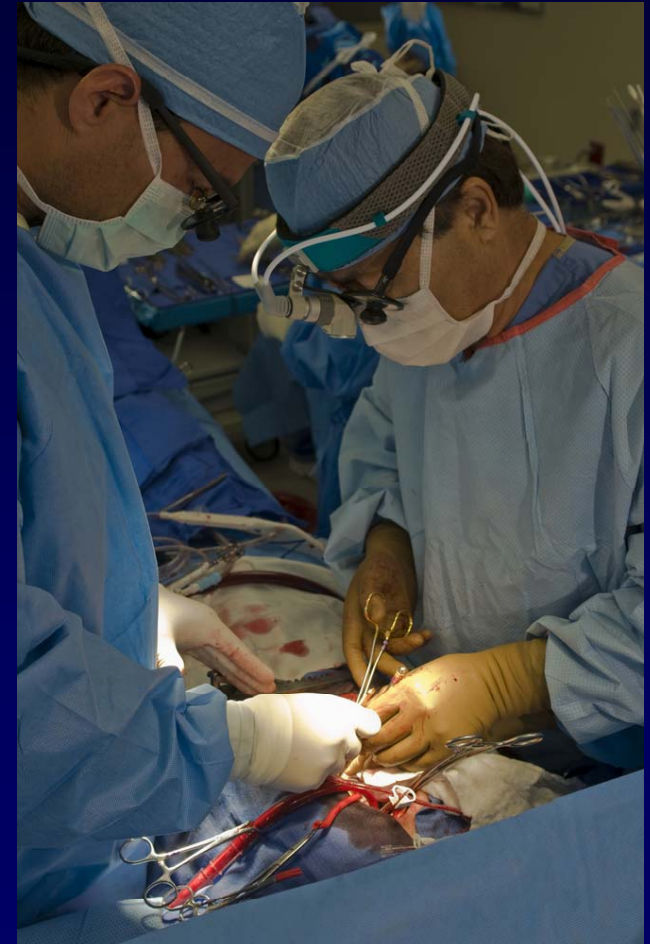


Overall and Complete Platelet Response: *Post Hoc Analysis*



TPO-R Agonists: Short-Term Use

- Well-defined goals
- To cover hemostatic challenges
- Predictable timing
- Avoids:
 - Blood products
 - Immunosuppression
 - Steroids
- Elective surgery, dentistry, high risk procedures/activities



TPO-R Agonists: Long-Term Use

- Goals are different
- Target platelet count variable

Young vs old patient
Healthy vs comorbid disease
What is safe platelet count?

- Individualized dosing



Potential Adverse Consequence of Thrombopoietic Growth Factors

- **Thrombocytosis**
- **Thrombosis**
- **Stimulation of tumor growth**
- **Stimulation of leukemia cell growth**
- **Interactions with other cytokines**
- **Autoantibody formation**
- **Stem cell depletion**
- **Reduction in threshold for platelet activation**
- **Rebound worsening of thrombocytopenia**
- **Increased bone marrow reticulin**

Thromboembolic Events

- In double-blind, placebo-controlled studies, no statistically significantly increased risk of TEE with both agents
- No correlation between platelet count increases and TEEs
- TEE in long-term studies:
 - Romiplostim 4.9%¹
 - Eltrombopag 4%²

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

2. Bussel JB, et al. *Blood*. 2009;114; Abstract 2423.

Bone Marrow Reticulin

- TPO-R agonist-naïve ITP patients: ~ 2/3 have ↑ BM reticulin
- ITP: Not known to progress to myeloproliferative disorders with clonal malignant proliferation (eg, CIMF)
- Reversible reticulin increase observed in some ITP patients treated with romiplostim & eltrombopag—no signs of myeloproliferative disorder with clonal malignant proliferation

Thrombopoietic Agents in ITP: Conclusions

- **No homology with endogenous TPO**
- **Proven efficacy in short and medium term for the treatment of ITP**
- **Work well both prior to and after splenectomy**
- **Increase plt count, reduce bleeding, improve QOL**
- **Favorable benefit/risk profile in published studies**
- **Unknown long-term side effects**