

## Case #7 Idiopathic Thrombocytopenic Purpura: New Therapeutic Options for an Old Disease

Drew Provan, MD  
Barts & The London School of Medicine  
London, UK



## Does She Have Idiopathic Thrombocytopenic Purpura (ITP)?

- Likely
- Typical presentation
- Sounds like ITP (history, signs)
- Remains diagnosis of exclusion

## ITP (Immune Not Idiopathic)

- “Minor” disorder for most
- But unpredictable
- Morbidity & mortality



Portielje JE, et al. *Blood* 2001;97:2549-2554.

## Does She Need Treatment?

- Platelets 9000/ $\mu$ L + wet purpura
- Yes
- Good response to corticosteroids
  - Responses in 2/3
  - Sustained in 10% to 30% cases

George JN, et al. *N Engl J Med*. 1994;331(18):1207-1211.

## First-Line Options

- Corticosteroids
- IVIg
- Anti-D (not Europe)

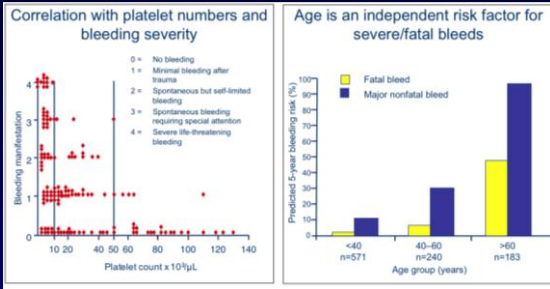
Cines DB, et al. *N Engl J Med*. 2002;346(13):995-1008.

## What Next?

- Platelets 15,000/ $\mu$ L, no bleeding
- Observe & rescue as needed
- Mycophenolate > azathioprine
- Rituximab (low dose)
- Splenectomy popularity declining?
  - Response: 70%
  - Relapse: 15% to 25%
- Or try new strategy -  $\uparrow$  marrow production of platelets

Provan D, et al. *Haematologica*. 2007;92(12):1695-1698. Zaja F, et al. *Haematologica*. 2008;93(6):930-933.

## Is She Low Risk Or High Risk Overall?



Lacey JV, et al. *Semin Thromb Hemost.* 1977;3(3):160-174. Cohen YC, et al. *Arch Intern Med.* 2000;160(11):1630-1638.

## Recommend

Platelets 9 → Pred → 120 then drop to 15

Watch-and-wait

BUT If platelets <10  
 + bleeds → IVIg  
 No bleed → low-dose rituximab or MMF

What next?

Watch-and-wait

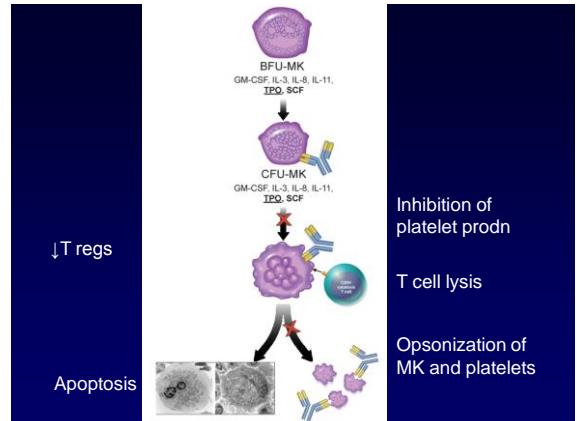
BUT If platelets <10  
 + bleeds → IVIg then TRA  
 No bleed → TRA

After failed splenectomy

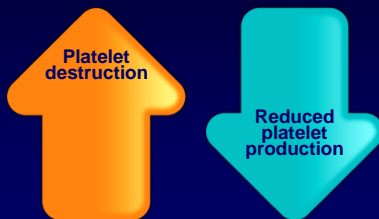
What next?

## “Traditional” Treatments

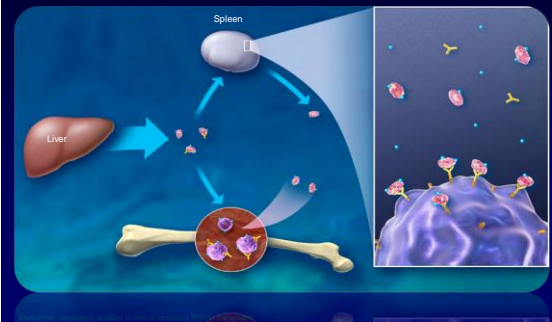
- Reduce platelet destruction
- Toxicities
- Most not approved for ITP
- But ITP is not simply platelet destruction



## ITP Is More Complex Than We Thought...



## New Concept: Accelerated Platelet Destruction and Suboptimal Platelet Production



## Novel Agents

### TPO-mimetics

1st generation

rhTPO & rhMGDF

2nd generation

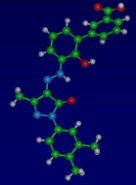
Romiplostim  
Eltrombopag  
AKR501  
TPO minibodies

### Others

Anti-Fc antibodies  
Anti-complement

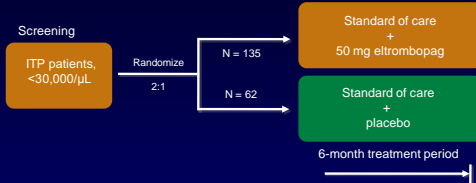
## Eltrombopag

- Small molecule TPO-R agonist (mw = 442)
- Targets the transmembrane domain
- Stimulates megakaryocyte proliferation and differentiation
- Orally bioavailable
- Does not prime platelets for activation
- Not immunogenic



Kuter DJ. *Blood*. 2007;109(11):4607-4616.

## Phase III: RAISE Study Design

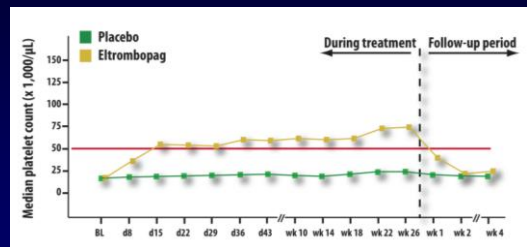


Primary endpoint: Response rate

- Randomized, double-blind, placebo-controlled, 6 months
- Stratified: Splenectomy status, concomitant ITP therapy, platelet count  $\leq 15,000/\mu\text{L}$
- Eltrombopag dose adjustments were allowed (between 25 mg – 75 mg)
- Reduction of concomitant medication and use of rescue treatments allowed

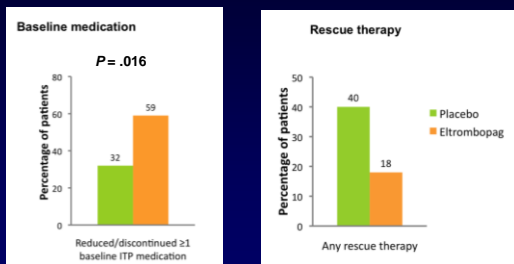
Stasi R, et al. *Haematologica*. 2009;94(Suppl 2): Abstract 0231

## Phase III—RAISE Study



Bussel JB, et al. *Haematologica*. 2009;94(Suppl.2): Abstract 1058.

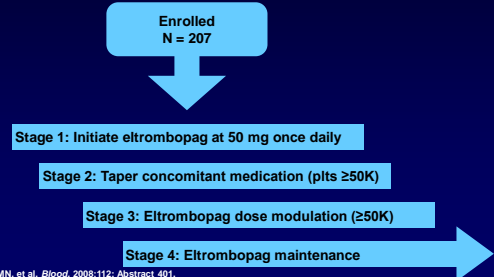
## Baseline ITP Medication and Use of Rescue



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

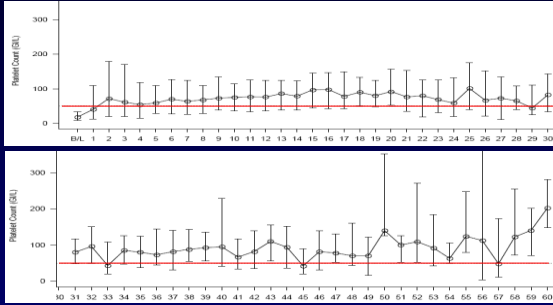
## EXTEND: Ongoing, Open-Label, Long-Term, Phase III, Extension Study

Patients with chronic ITP previously enrolled in eltrombopag studies



Saleh MN, et al. *Blood*. 2008;112: Abstract 401.

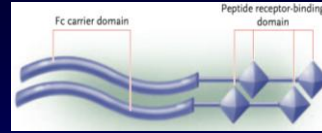
## EXTEND: Durable Platelet Count Elevation



35% of subjects had a response for  $\geq 10$  weeks

Bussell JB, et al. *Blood*. 2008;112: Abstract 3423.

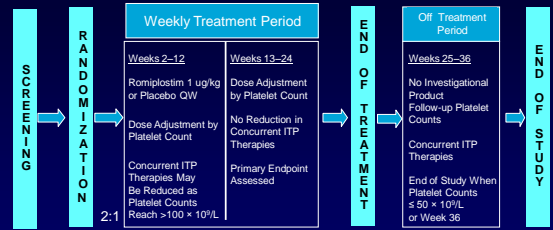
## Romiplostim



- Novel thrombopoiesis-stimulating peptibody
- Structurally unrelated to thrombopoietin
- Dipeptide linked to Fc fragment of IgG ( $\uparrow$  half-life)
- Targets thrombopoietin receptor — 4 Mpl binding sites
- Weekly subcutaneous injection

## Romiplostim Phase III: Study Design

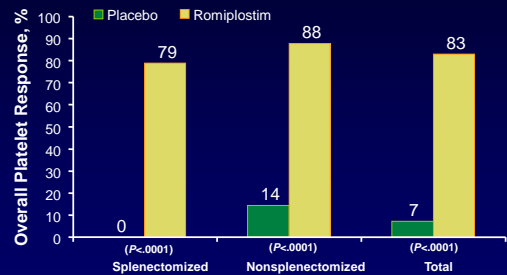
Primary endpoint: durable platelet response



20030105: A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of Romiplostim Treatment of Thrombocytopenic Patients With Immune Thrombocytopenic Purpura (ITP) Refractory to Splenectomy  
 20030212: A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of Romiplostim Treatment of Thrombocytopenic Patients With Immune Thrombocytopenic Purpura (ITP) Prior to Splenectomy

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

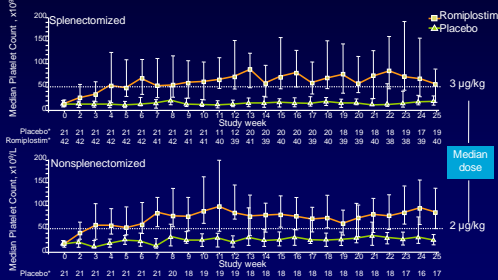
## Phase III: Overall Platelet Response



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

## Phase III: Weekly Platelet Response

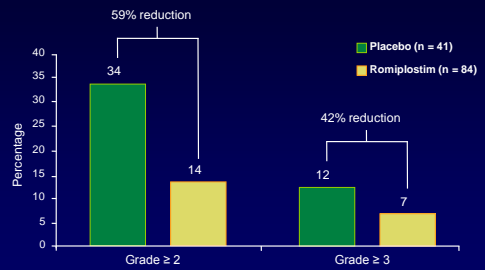
Weekly median platelet response (Platelet ct  $\leq 50 \times 10^9/L$ )



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

\*Number available for measurement

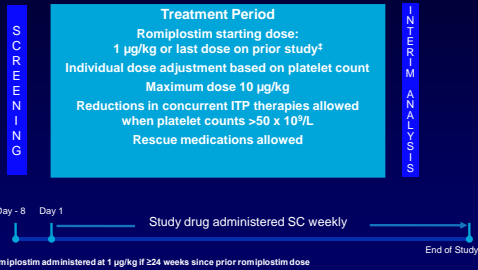
## Bleeding Events



Severity grades according to MedDRA 9.0 definition

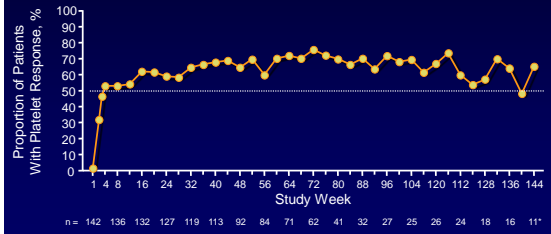
Lyons R, et al. *Blood*. 2007;110: Abstract 1300.

## Long-Term Open-Label Extension Study



Terebelo HR, et al. Presented at: Annual Chicago Supportive Oncology Conference 2008; October 15-18, 2008; Chicago, Illinois. Poster. Bussell JB, et al. *Blood*. 2009;113(10):2161-2171.

## Long-Term Platelet Response



Terebelo HR, et al. Presented at: Annual Chicago Supportive Oncology Conference 2008; October 15-18, 2008; Chicago, Illinois. Poster. Bussell JB, et al. *Blood*. 2009;113(10):2161-2171.

## 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 Safety Issues

- Thrombocytosis
- Platelet activation & thrombosis
- Stimulation of tumor/leukemia growth
- Autoantibody stimulation
- Rebound (worsening) of thrombocytopenia
- Increased bone marrow reticulin/collagen
- Cataract (eltrombopag)
- Liver function (eltrombopag)

## 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

Kuter DJ, et al. *Lancet*. 2008;371(9610):395-403. Muftic G, et al. *Blood*. 2006;108: Abstract 3982. Kuter DJ, et al. *Brit J Haematol*. 2007;139(3):351-362.

## Summary

- Current ITP management unsatisfactory
  - Lack of evidence base
  - Toxicities
  - Confusing terminology
- New terminology
- New treatments: TPO-R agonists
- International guidelines