Role of Thrombopoietin Receptor Agonists in Chronic and Refractory ITP

Gregory Cheng

Mechanism of ITP

- Traditionally immune thrombocytopenia (ITP) is thought to be a disease characterised by accelerated destruction of platelets by anti-platelet antibodies

Mechanism of ITP

- Treatment is therefore primarily directed at reducing destruction of antibody-coated platelets

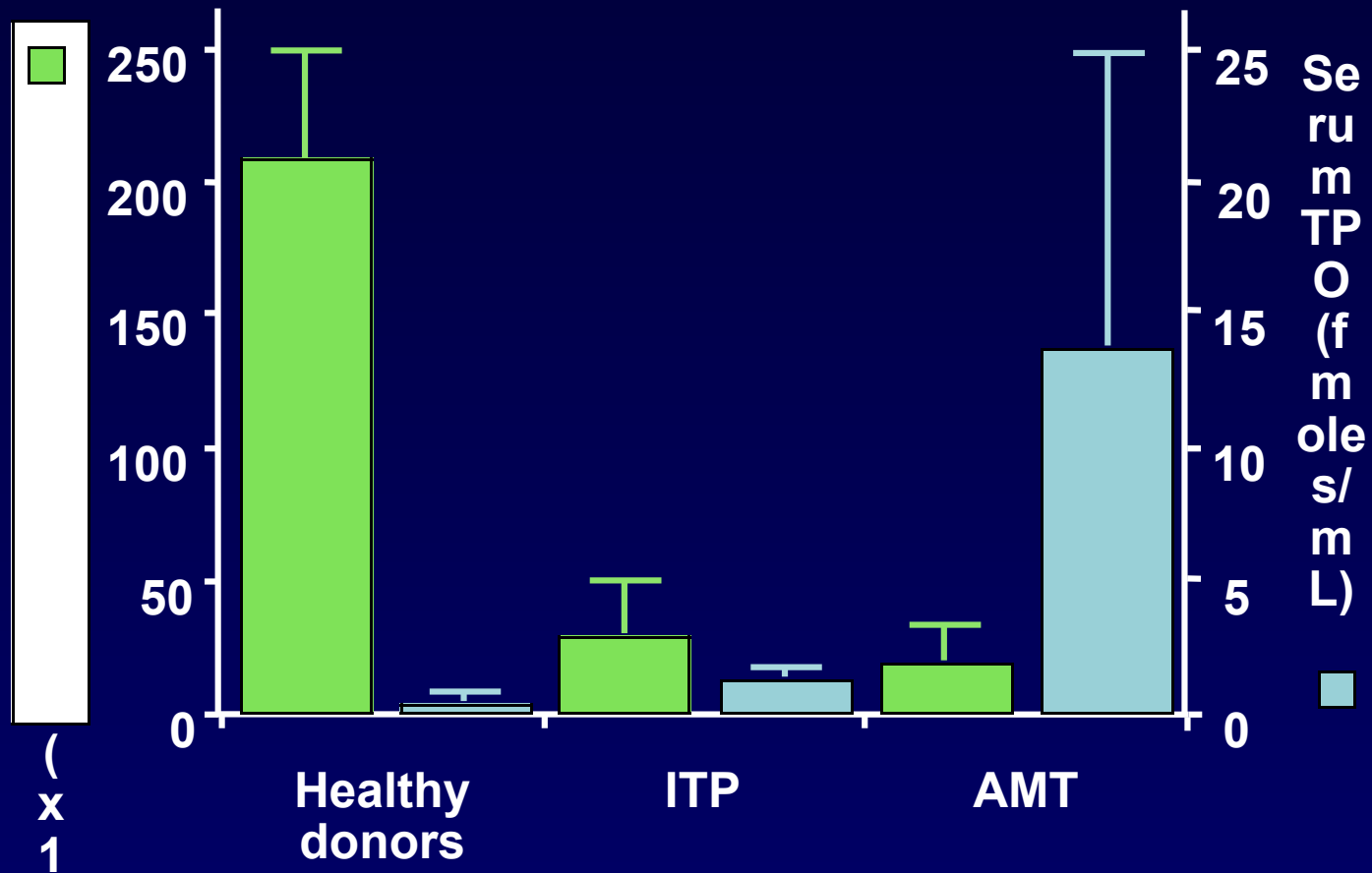
Economic Crisis

- Cut Budget
- Cut Jobs / Social benefits

Platelets Crisis

- Cut out the Spleen (Splenectomy)

Thrombopoietin (TPO) levels in ITP



- TPO levels are inappropriately low (near normal) in thrombocytopenic ITP patients

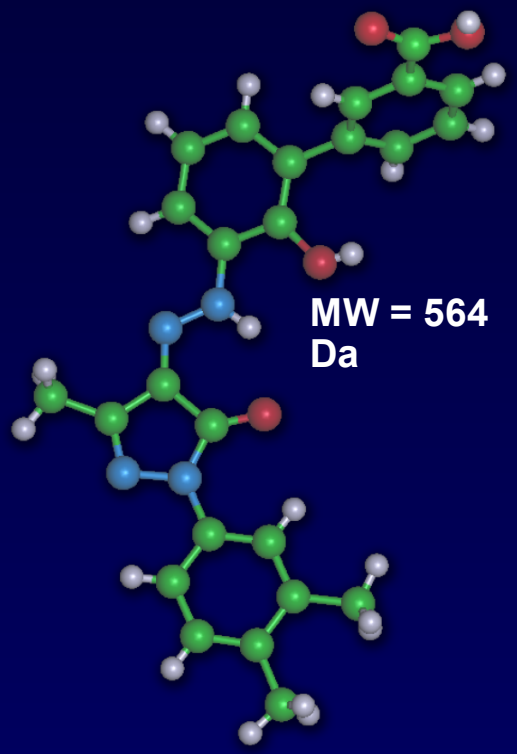
AMT=amegakaryocytic thrombocytopenia

Mukai HY, et al. Thromb Haemost 1996;76:675–78

Thrombopoietic Factors in ITP: Thrombopoietin Receptor (TPOr)-Targeted Therapy

- Stimulation of platelet production by TPO mimetics may be especially useful in patients not responsive to currently available treatment

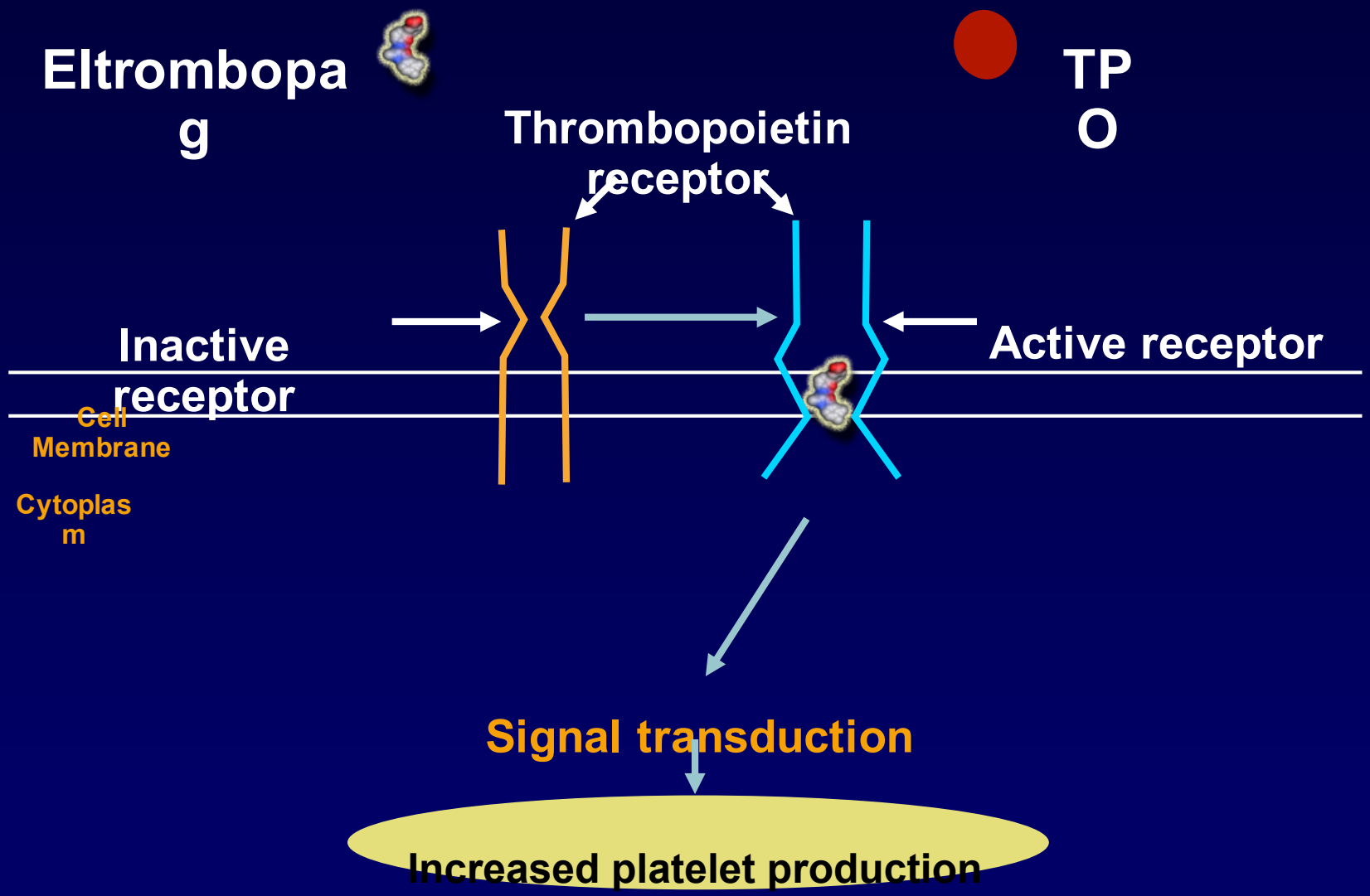
Eltrombopag (Revolade)



- Small molecule, non-peptide thrombopoietin receptor (TPO-R) agonist
- Dose-dependent increases in normally functioning platelets
- Does not prime platelet activation

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):4739–41,
Garnock-Jones KP, et al. Drugs 2009;69(5):567–76

TPO-R agonists: mechanism of action



Studies with Eltrombopag in Chronic ITP

- **Phase II/III:** Double-blind, placebo-controlled trials
  - **773A*:** placebo or 30, 50, 75mg daily for 6 weeks[1]
  - **773B:** placebo or 50mg daily for 6 weeks[2]
- **Phase II:** REPEAT – three cycles of 6 weeks each of active, open-label treatment[3]
- **Phase III:** RAISE – double-blind, placebo-controlled trial for 6 months of variable doses of eltrombopag vs placebo in patients with or without splenectomy[4]
- **Extension Study:** EXTEND (ongoing) open label safety and efficacy study of long-term daily treatment of subjects from Phase II–III[5]
- **Phase IV:** (ongoing) open-label safety study to evaluate the long-term effect of eltrombopag on bone marrow reticulin and/or collagen fibers[6]

1. Bussel JB, et al. N Engl J Med 2007;357:2237–47,
2. Bussel JB, et al. Lancet 2009;373:641–8,
3. Bussel JB, et al. Blood 2008;112:abstract 3431,
4. Cheng G, et al. Lancet 2011;377:393–402.(Erratum; 377: 382),
5. Saleh M, et al. Blood 2009;114: Abstract 682,
6. www.clinicaltrials.gov NCT01098487

*Supportive dose-finding studies – includes dose/schedule not licensed as per the SmPC

Phase III Eltrombopag treatment of chronic ITP

Phase III (Part B)
6 weeks
2:1 randomisation

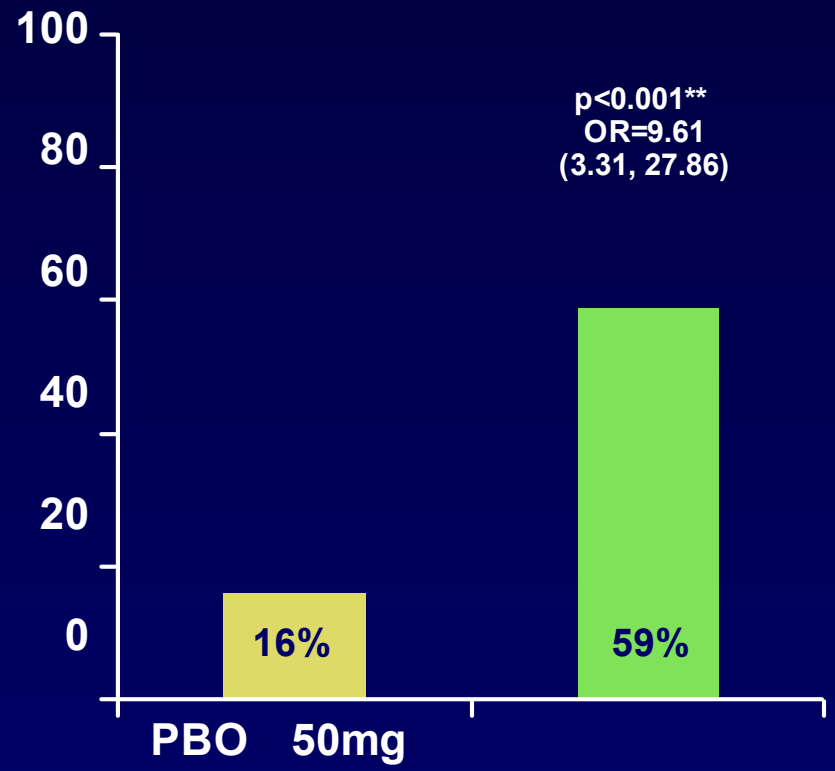
SoC + placebo (n=38)

vs

SoC + 50mg eltrombopag (n=76)

N=114

TRA100773 B



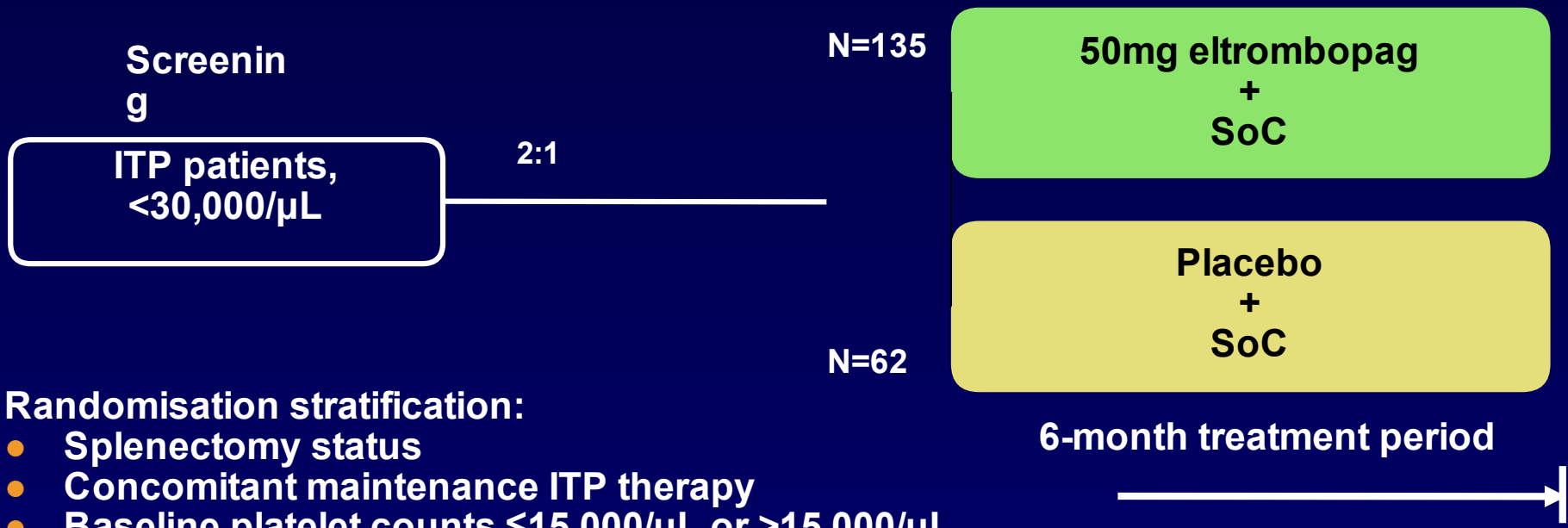
SoC=standard of care
**2-sided p value; odds ratio (OR) eltrombopag / placebo

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



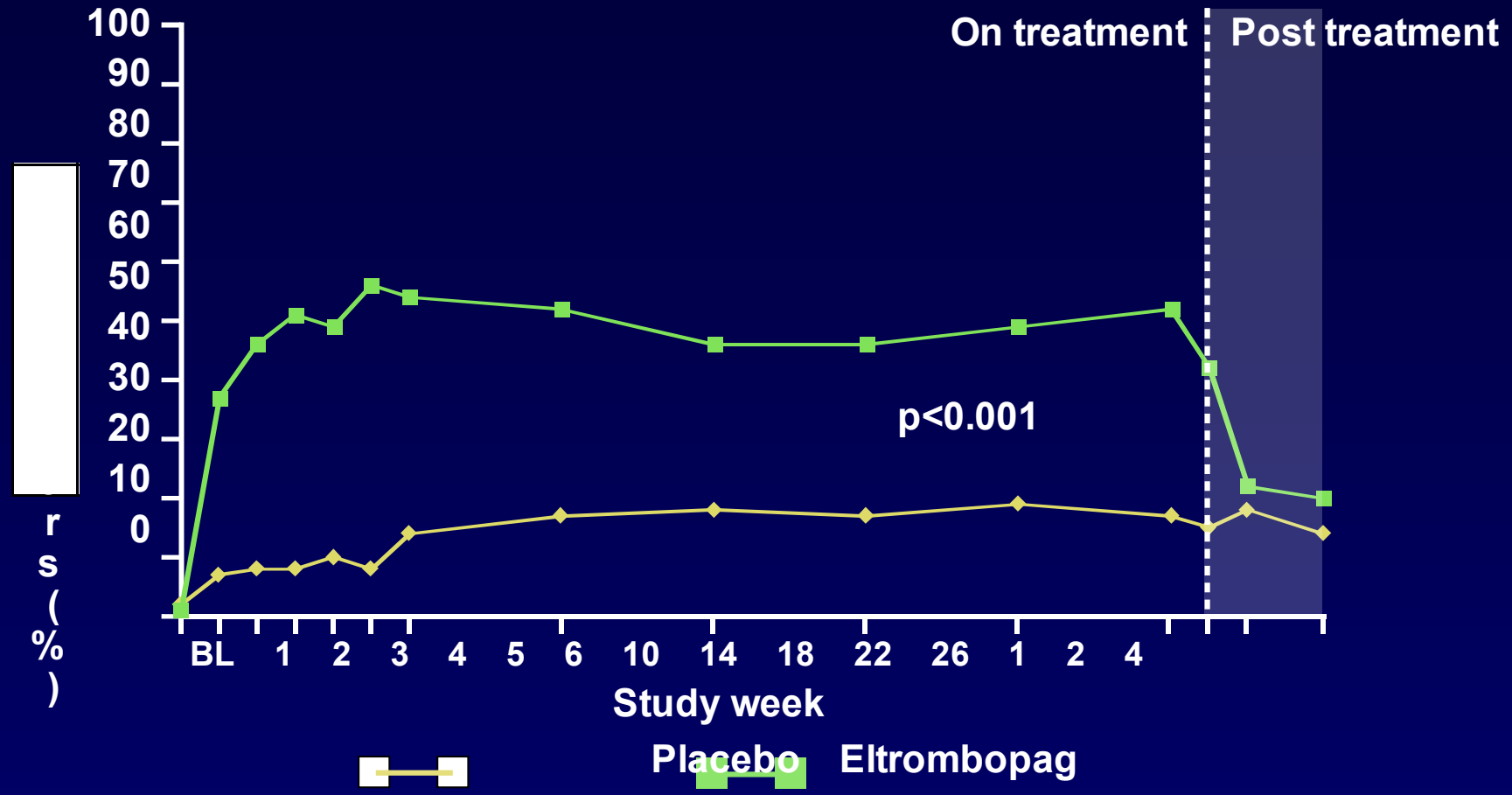
Randomisation stratification:

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

SoC=standard of care

Cheng G, et al. Lancet 2011;377:393–402.(Erratum; 377: 382)

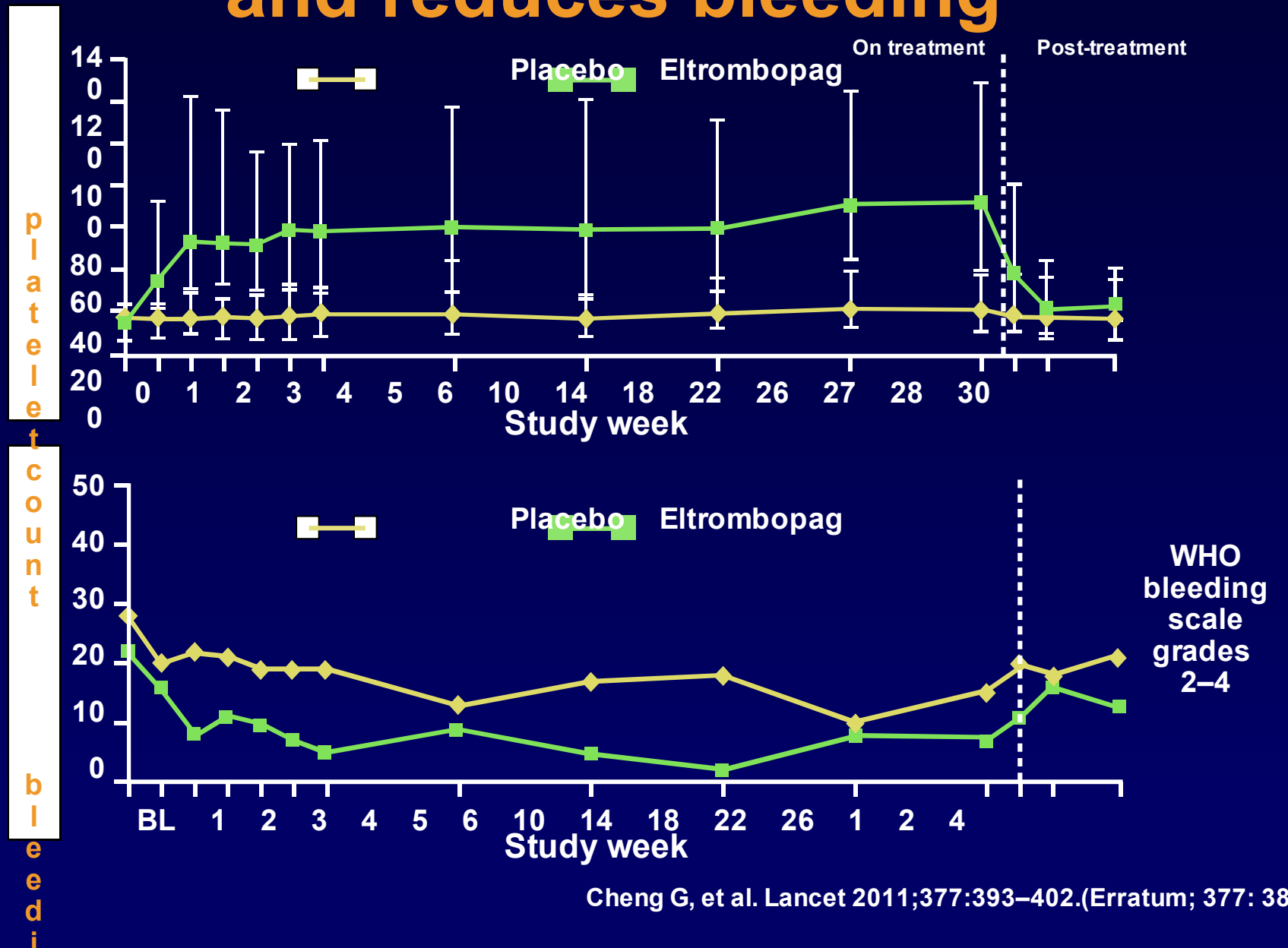
Proportion of patients responding to eltrombopag vs placebo



Patients in the eltrombopag group were 8 times more likely to respond compared with those in the placebo group *[primary endpoint: odds ratio [99% confidence interval 8.2 [3.59, 18.73]; p<0.001]*

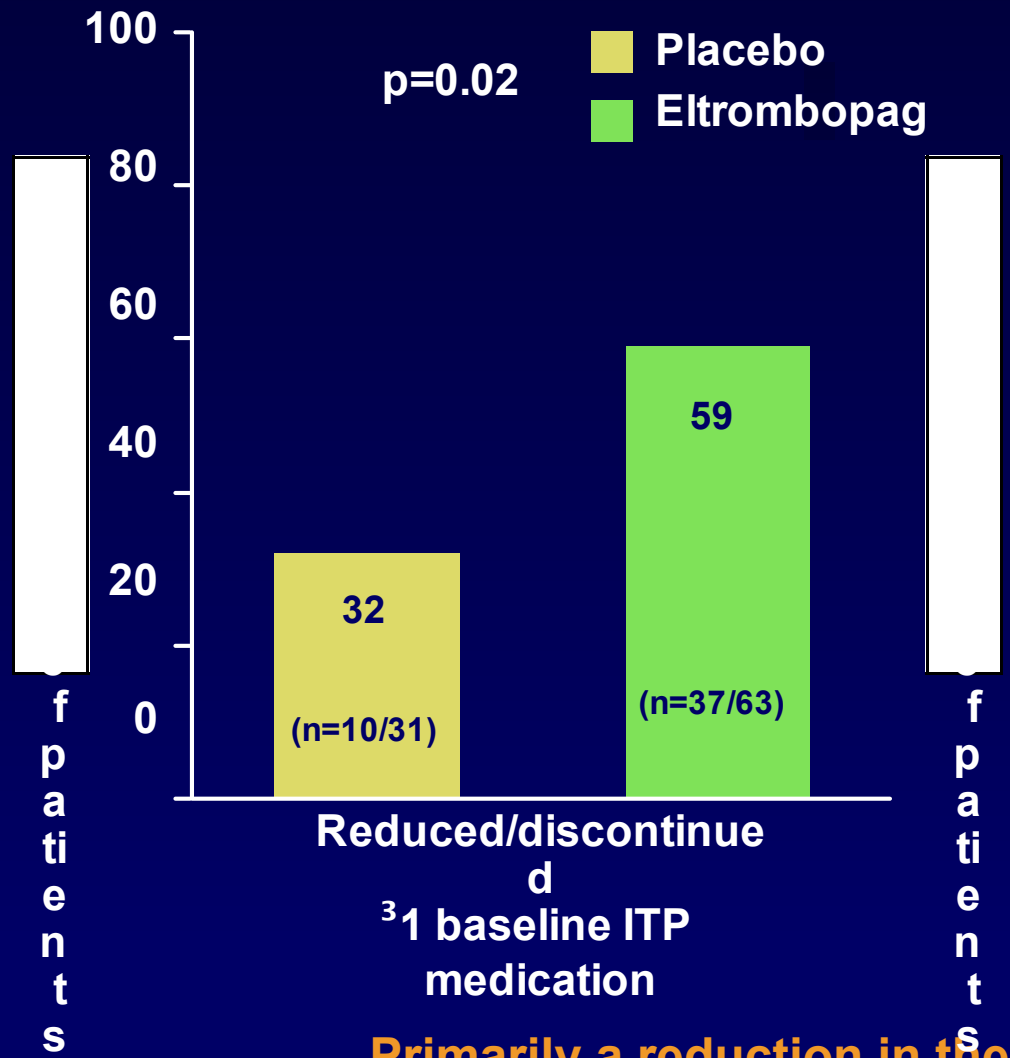
Cheng G, et al. Lancet 2011;377:393–402.(Erratum; 377: 382)

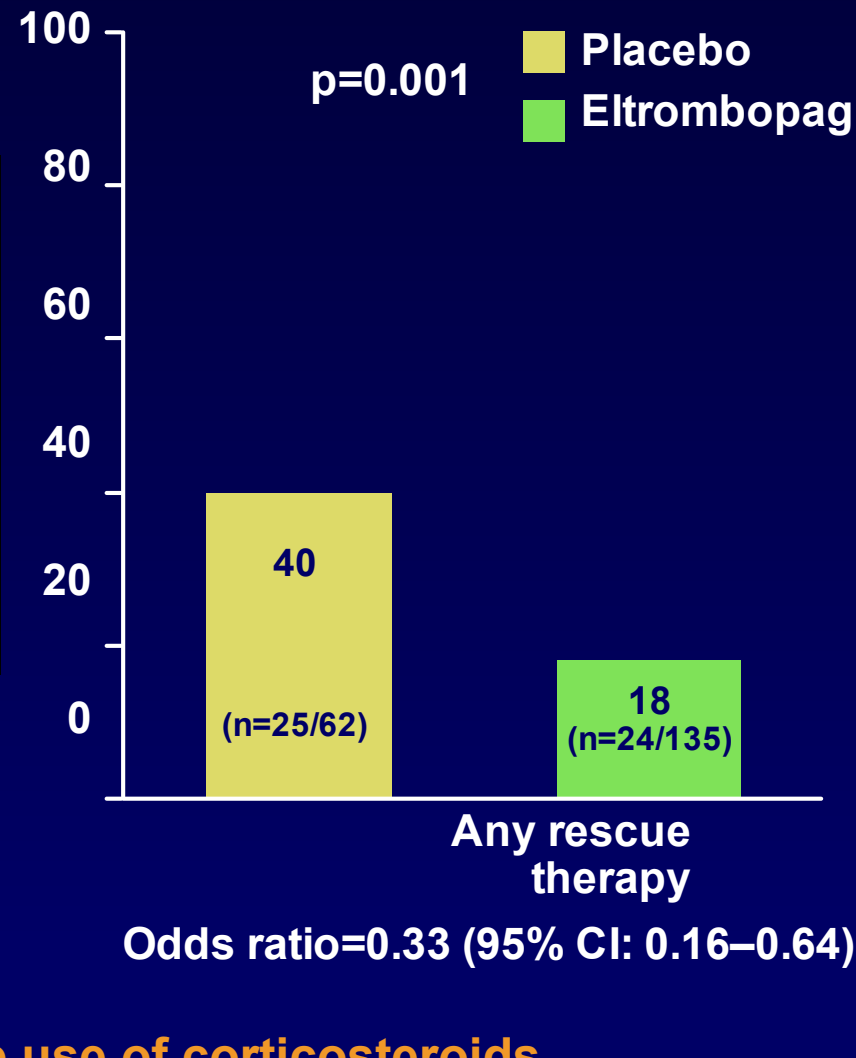
Eltrombopag increases platelet counts and reduces bleeding



Cheng G, et al. Lancet 2011;377:393–402.(Erratum; 377: 382)

Reduction in concomitant ITP therapy and rescue medication



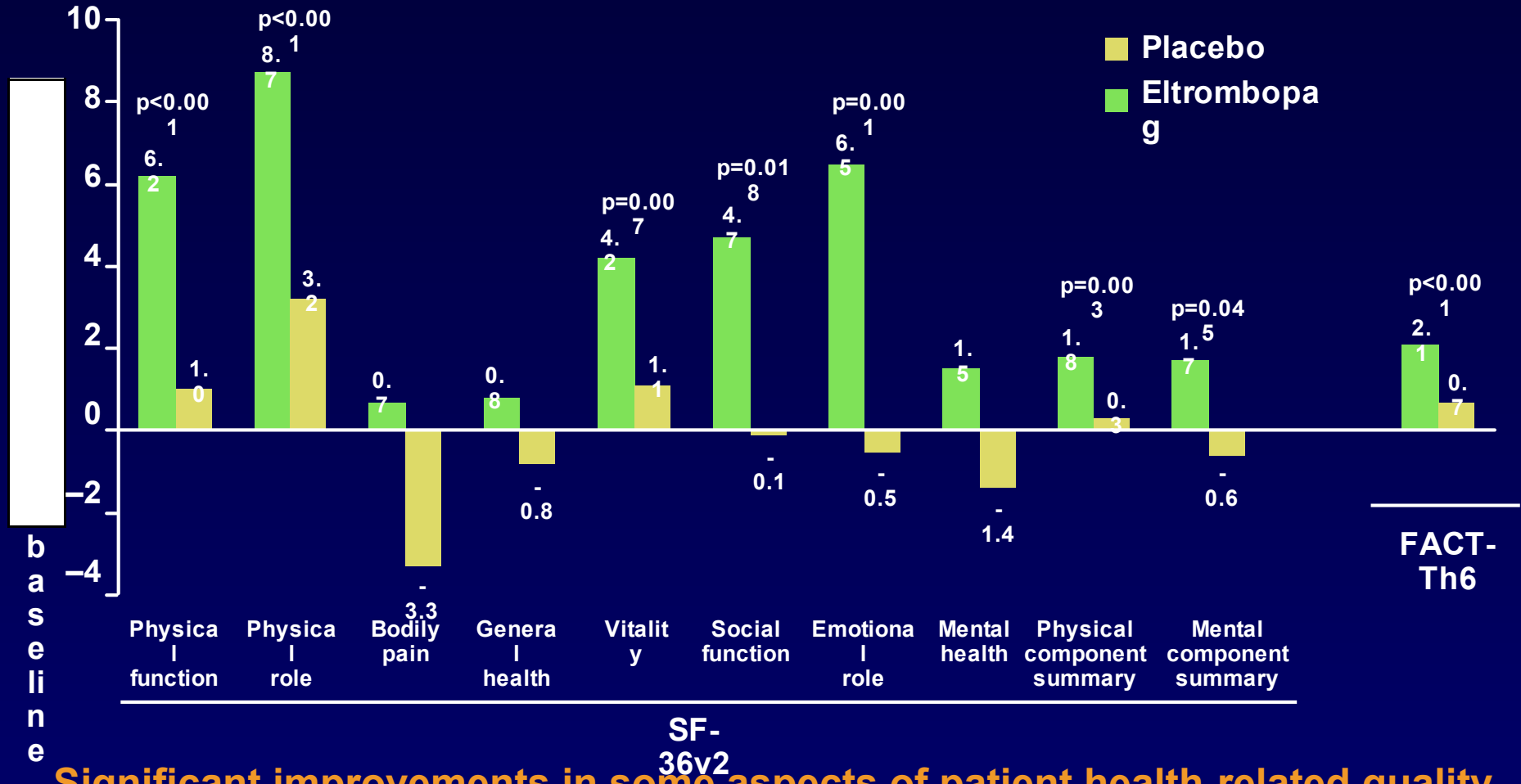


Odds ratio=0.33 (95% CI: 0.16–0.64)

Primarily a reduction in the use of corticosteroids

Cheng G, et al. Lancet 2011;377:393–402.(Erratum; 377: 382)

Mean change in SF-36v2 and FACT-Th6 scores

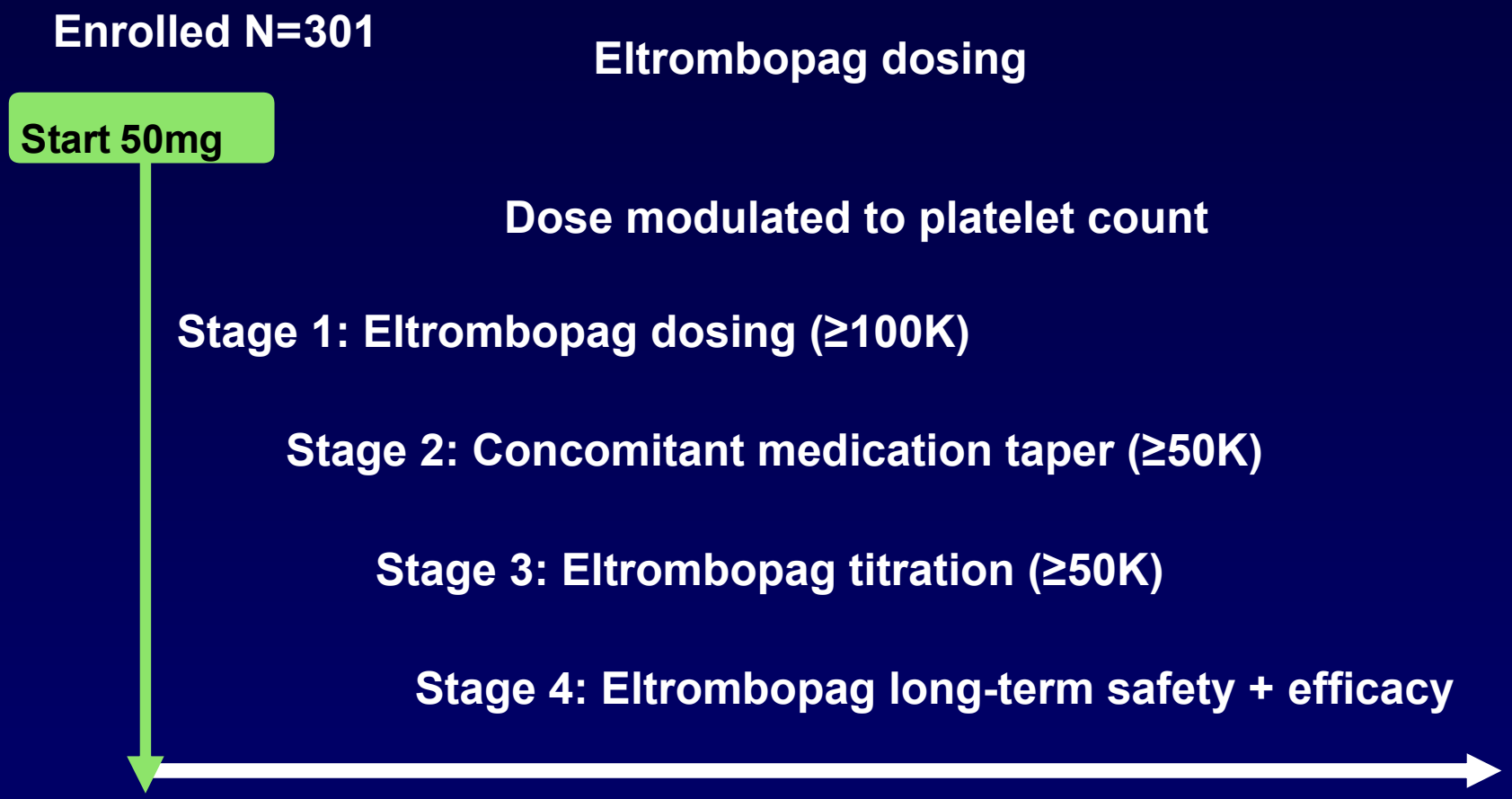


Significant improvements in some aspects of patient health-related quality of life: vitality (SF-36v2), less fatigue (FACIT) and the 6 items of FACT-Th6

Cheng G, et al. Lancet 2011;377:393–402.(Erratum; 377: 382)

EXTEND: open-label extension study

Chronic ITP patients previously enrolled in eltrombopag studies



EXTEND study: efficacy

- 88% (264/301) of patients achieved a response, i.e. platelet count ≥50,000/μL
  - Response was similar irrespective of baseline platelet count, use of ITP medications and splenectomy status

Saleh M, et al. Blood 2011;118(24):Abstract 3269

Hepatobiliary laboratory abnormalities (HBLA) across eltrombopag ITP trials

HBLA type	773A + 773B (all doses) N=164	RAISE N=135	EXTEND N=299
Patients, n(%)	16 (10)	17 (13)	24 (8)
Median days to onset (range)			
Any HBLA	15 (1*–36)	29 (1–130)	105 (1–482)
ALT ≥3x ULN	8 (1–36)	37 (16–113)	227 (47–351)
AST ≥3x ULN	29 (15–29)	27 (16–130)	195 (47–482)
Bilirubin >1.5x ULN	8 (1–21)	28 (1–128)	105 (1–351)
AP >1.5x ULN	1 (1–33)	2 (1)	24 (1–308)

*A lower range of 1 indicates that patient had an enzyme value over the ULN at baseline

- The incidence of HBLAs meeting drug-induced liver injury screening criteria was low
- No pattern observed in median time to onset
- Most HBLAs were mild, reversible and without associated symptoms of impaired liver function

ALT=alanine aminotransferase, AP=alkaline phosphatase, AST=aspartate aminotransferase

Maddrey W, et al. Blood 2009;114: Abstract 2410 (post-hoc data)

Incidence of thromboembolic events (TEEs) across eltrombopag ITP trials

- 23 (5.1%) of 448 patients treated with eltrombopag experienced 30 TEEs
  - 5 patients experienced >1 TEE

Event	n
Deep vein thrombosis	12
Pulmonary embolism	6
Myocardial infarction	5
Ischemic stroke	5
Transient ischemic attack	1
Prolonged reversible ischemic neurologic deficit	1

- 2 deaths (unrelated to TEE)
- No association observed with elevated platelet counts

Incidence of TEEs in ITP

	Patients with ITP	Patients without ITP
US Claims Database1	6.9% (197/2873)	3.4% (4027/116,933)
UK General Practice Research Database2	6.1% (65/1070)	4.6% (197/4280)

- Limited epidemiologic data
- Incidence of TEEs seems to be higher in patients with ITP compared with patients without ITP

1. Bennett I, et al. Haematologica 2008;93(s1):125 (Abstract 0307)
2. Sarpatwari A, et al. Haematologica 2010;95:1167–75

TEE risk factors

- All patients experiencing a TEE had ≥1 risk factor for TEE
  - Hospitalisation without prophylactic anticoagulation, smoking, hypertension, oral contraceptive use, surgery for abdominal-pelvic malignancy, family history etc
- 15 patients with TEEs underwent genetic testing
  - 2/15 heterozygous for factor V Leiden mutation
- Median time to onset 229 days, range 1–981 days
- No relation with platelet counts

Bussel J, et al. Blood 2010;116(21):Abstract70 (post-hoc data)

EXTEND study: bone marrow biopsies

- Over 180 on-treatment bone marrow biopsies performed in patients treated for >1 year

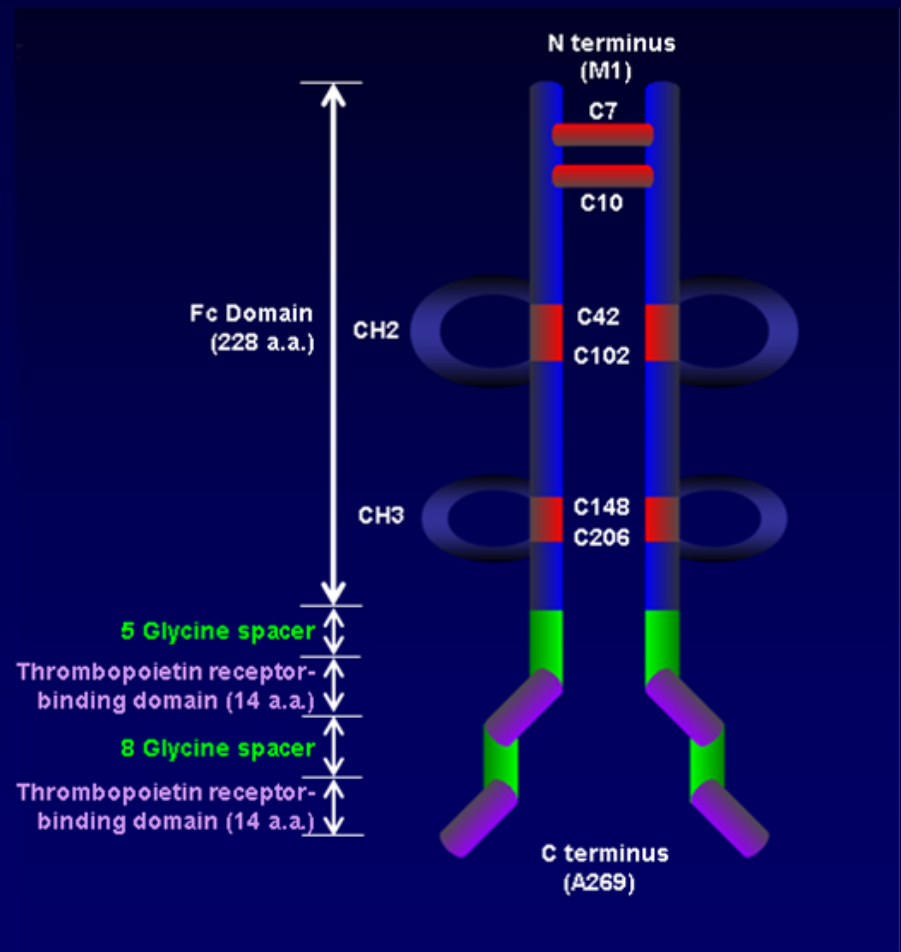
- 12 patients (8%) had reticulin grade MF-2 (no MF-3)
  - None had clinically relevant abnormalities in WBC or peripheral blood smear

  39 Serial Biopsies showed no progression to MF grade 3(one case of MF-1 to MF-2)
  2 experienced a decrease in reticulin grade (MF-2 to MF-0 and MF-1 to MF-0)

1. Saleh M, et al. Blood 2011;118(24):Abstract 3269,

Romiplostim(N-Plate)

- Fusion protein of Fc and TPO mimetic peptides
- No sequence homology with endogenous TPO
- Administered as weekly subcutaneous injections
  - Titrations between 1–10 µg/kg (adjustable based on platelet count)



Bussel JB, et al. N Engl J Med 2006;355:1672–81

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.

Romiplostim (N-Plate)

Study ID-	Patients Design (n)	duration (weeks)	dose(µg/kk BW)	Results
NCT0011147 Phase 1	24	6	0.2, 0.5, 1.0, 3.0, 6.0, 10.0	7/12 3-10ug/kg responded
NCT0011147 Phase2	21	6	1 .0, 3.0, 6.0 once weekly	0/16 1-3 ug/kg responded
NCT00102323 Splenectomised	63	24	1.0 – 15.0 once weekly	79 vs 0% response
NCT00102336 Non-splenectomised	62	24	1.0 – 15.0 once weekly	88 vs 14% response
NCT00415592 vs SOC	234	52	3.0 – 15.0 once weekly	10 vs 30% failure
NCT00515203 Pediatric	22	12	1.0 – 5.0 once weekly	88% response

N Engl J Med 2006;355(16):1672-81.
Lancet 2008;371(9610):395-403.

N Engl J Med 2010;363(20):1889-99.
Blood 2011;118(1):28-36.

Summary of TPOr agonist

	• Eltrombopag (Revolade)	• Romiplostinm (N-Plate)
Structure	Non-peptide	peptide body
Route of Administration	Oral daily	sc weekly
Onset of action	1 week Peak 2 weeks	1 to 2 weeks peak 2 to 4 weeks
Efficacy	60-80%	60-80%
Reduction of Concomitant ITP medication	40-60%	40-60%
Reduction of bleeding	65-80%	60-80%

Summary of TPOr agonist

	• Eltrombopag (Revolade)	Romiplostim (N-Plate)
Thrombocytosis	Reversible	Reversible
Thrombosis	5.1%	5%
platelet activation	No	No
Autoantibody formation	No	No ANTI-TPO ANTIBODIES
	1 ANTI-ROMIPLOSTIM ANTIBODY	
Marrow fibrosis	180 bx	no progression
	12 fibrosis	
Rebound thrombocytopenia	No	No

Lancet Vol 371, Feb 2008 p 395-401,
Lancet 373 Feb 2009, p641-648
Lancet Vol 377, Jan 2011 p 393-402
NEJM Vol 357, @007 p2237-47
Blood Vol 113, 2009, p 2161-2171

R-FAEL NADAL

N-OVAK DJOKOVIC

Role of TPO-R agonists

- The most obvious patients would be chronic ITP splenectomised patients who are refractory to current treatments or those in whom splenectomy is contraindicated.

ASH guidelines: second-line treatment

ASH 2011 guidelines1

Recommendation:

- Splenectomy if failed corticosteroids (1B)
- TPO-R agonists following relapse after splenectomy OR if splenectomy contraindicated and failed ≥1 other therapy (1B)

Suggestion:

- Eltrombopag and romiplostim for patients who have failed one therapy e.g. corticosteroids or IVIg and have not had a splenectomy (2C)*

*Licensed for second-line use where there is a contraindication for splenectomy (EMA)
This slide contains information about drugs that may not be licensed for certain indications as listed

1Neunert C, et al. Blood 2011;117:4190–207

LESS 30 x 10_9/lts

ITP

Steroids/Dexamethasone

Fail

Splenectomy

Fail

Refused

Contraindicated

TPOr Agonist

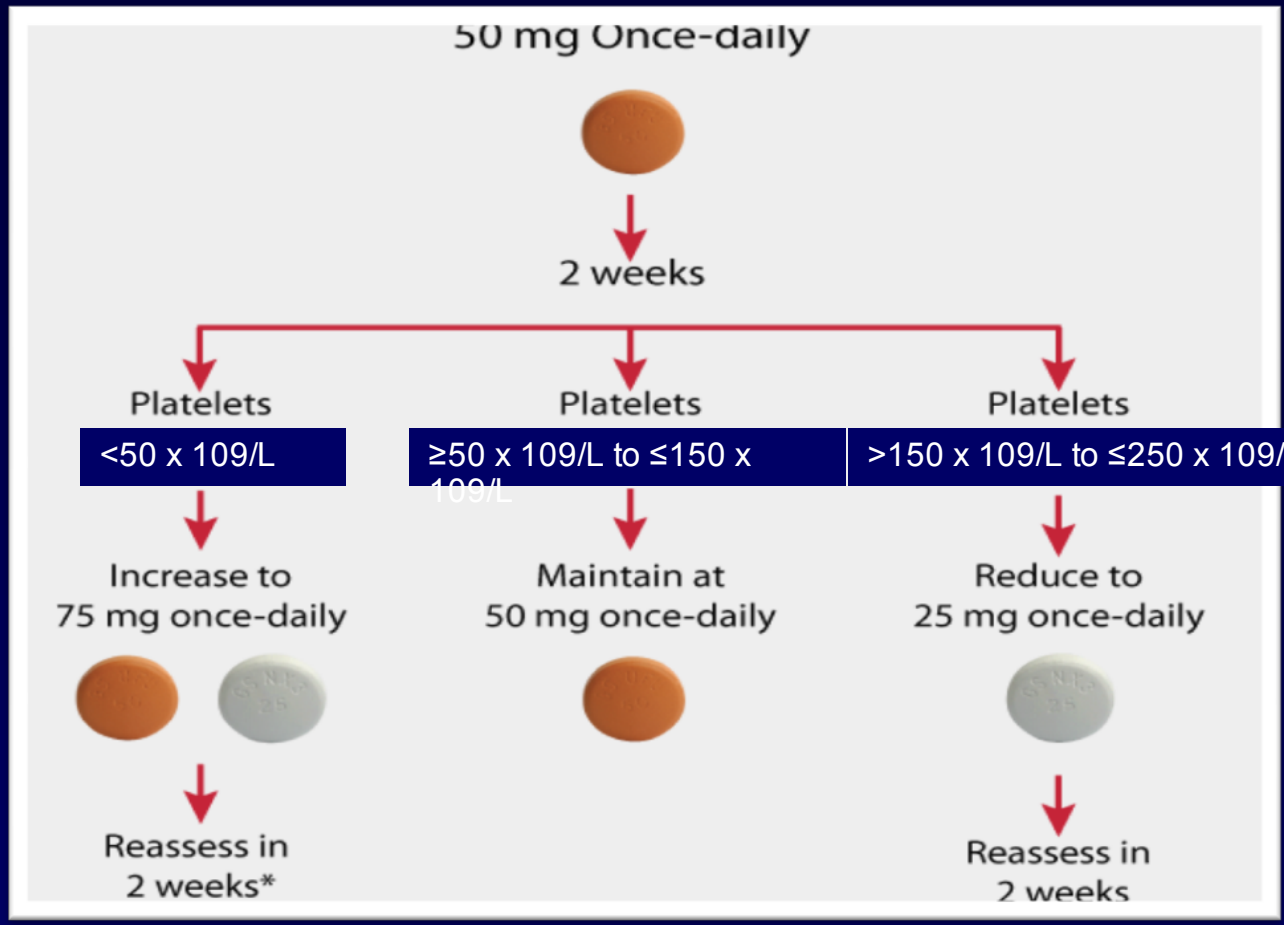
Use of TPO-R agonists in ITP: questions…

- What dose should we start at and how quickly should we increase?
- Will different TPO-R agonists work in different patients?
- Are there additive effects/synergy with other treatments?
- Will TPO-R agonists be given indefinitely: will some patients go in to remission?
- What will be the long term toxicity of continuous treatment?

Eltrombopag

- Once daily oral dose: 50mg
  - Adjusted between 25mg and 75mg as needed
  - AUC 70% to 80% higher in East Asian patients
  - Administered 4 hours before or after any calcium containing products or mineral supplements containing polyvalent cations

Revolade®: dose adjustments



- After initializing treatment with Revolade®, or after a dose alteration, no further changes to the dose should be made for at least 2 weeks

EMA. Revolade Summary of Product Characteristics. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-

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EXTEND

- 13 subjects –prolonged response off eltrombopag
- Median-54.9 weeks
- Median time since diagnosis of ITP- 25.8 months(range 9-73 months)
- Median time oneltrombopag-258 days(14-1107)
- 5 patients had splenectomy

EHA London 2012. poster 796

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Elevated Liver Enzymes
Long remission
Thromboembolism
Rebound thrombocytopenia
Opthamological
Myelofibrosis
Budget
Obstetrics
Pediatrics
Autoantibodies
Growing applications