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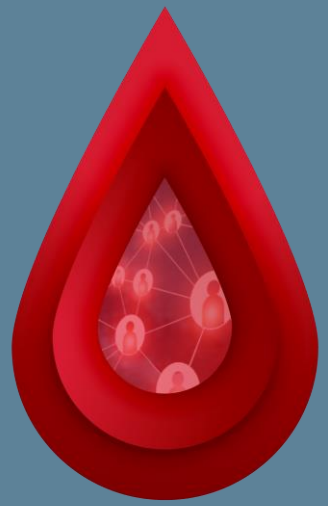

PRACTICAL CONSIDERATIONS AROUND THE USE OF TPO-RAs IN ITP

AN INDEPENDENT, CME-ACCREDITED SYMPOSIUM

20 July 2021

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist

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- The programme is therefore independent; the content is not influenced by Sobi and is the sole responsibility of the experts

- **Please note:** The views expressed within this presentation are the personal opinions of the experts. They do not necessarily represent the views of the experts' academic institutions or the rest of the faculty

TODAY'S FACULTY

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Hillary Maitland

University of Virginia, Charlottesville, VA, USA

Hanny Al-Samkari

Massachusetts General Hospital & Harvard Medical School, Boston MA, USA

Waleed Ghanima

Østfold Hospital & University of Oslo, Norway

EDUCATIONAL OBJECTIVES

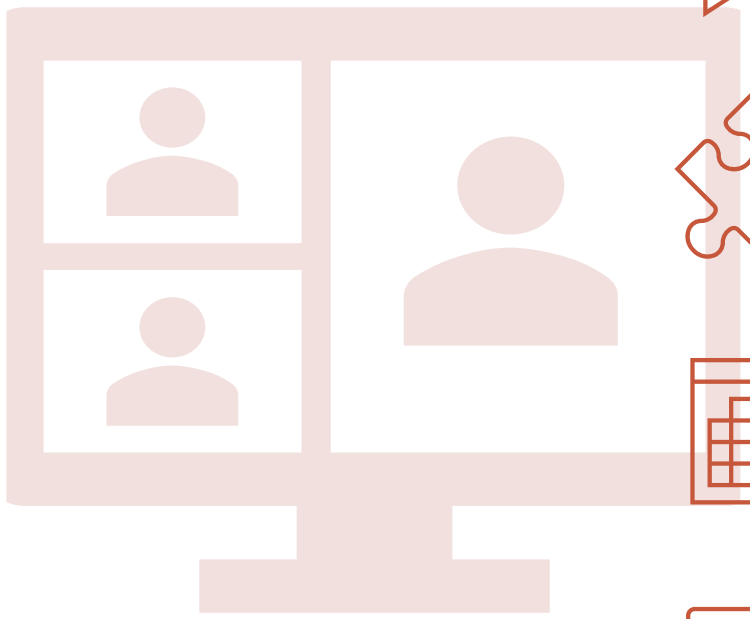
Understand the role of TPO-RAs in the treatment of chronic ITP in adults

Review all practical considerations, including:

- When to start treatment
- Administration
- Safety
- Efficacy and how to monitor it
- Adjusting treatment
- Long-term remission and tapering

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist

TODAY'S PROGRAMME



Initiation of treatment for ITP

Hillary Maitland

Practical considerations around choosing a TPO-RA

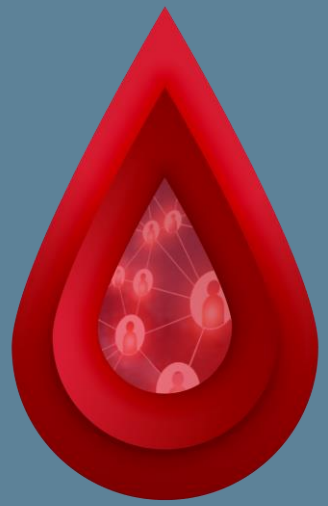
Hanny Al-Samkari

Long-term use of a TPO-RA: safety and disease remission

Waleed Ghanima

Q&A

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist



INITIATION OF TREATMENT FOR ITP

Hillary Maitland, MD

University of Virginia, Charlottesville, VA, USA

ITP, immune thrombocytopenia

DISCLOSURES

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- Grants/honoraria from Sanofi and Sobi

CASE

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- Ms. L is a 39-year-old female without significant past medical history who presents to the emergency department with **nose and gingival bleeding**
- She reports that the **bruising** started 4-5 days prior
- Then she began to have **nose bleeds and gum bleeding**
- She has never had similar symptoms in the past

CASE

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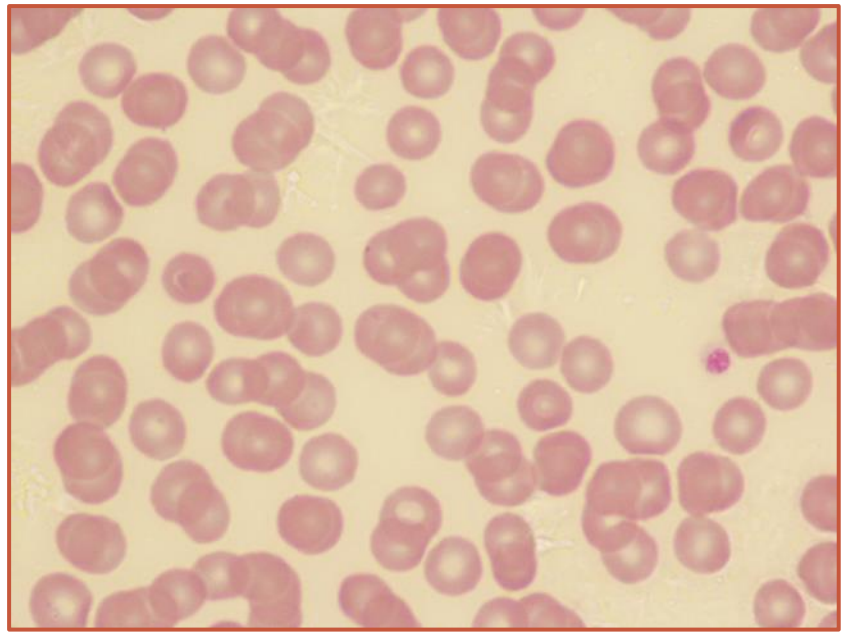
WBC count, × 10^9/L	5.6
Haemoglobin, g/dL	12.4
Platelet count, × 10^9/L	26



WBC, white blood cell count

CASE

- Ms. L is a 39-year-old female without significant past medical history who presents to the emergency department with **nose and gingival bleeding**
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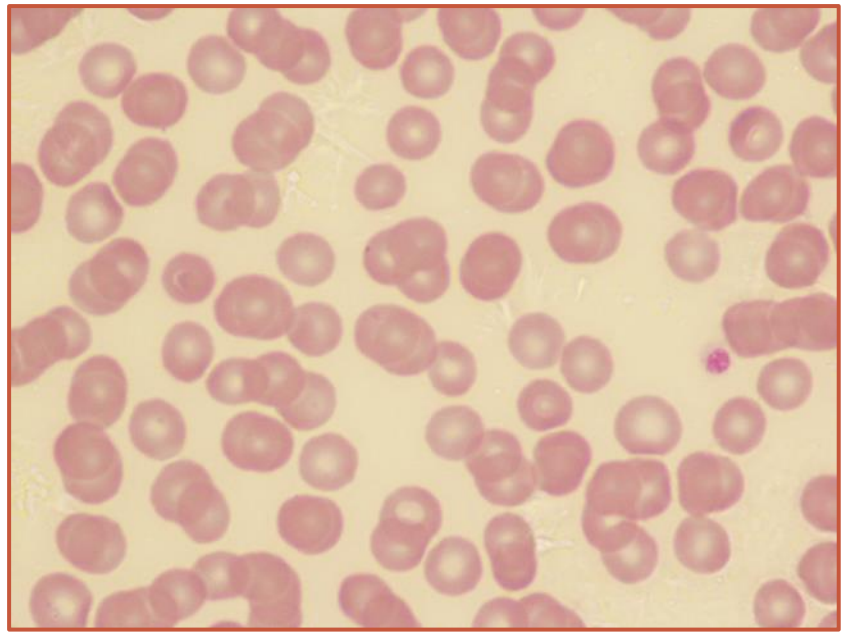
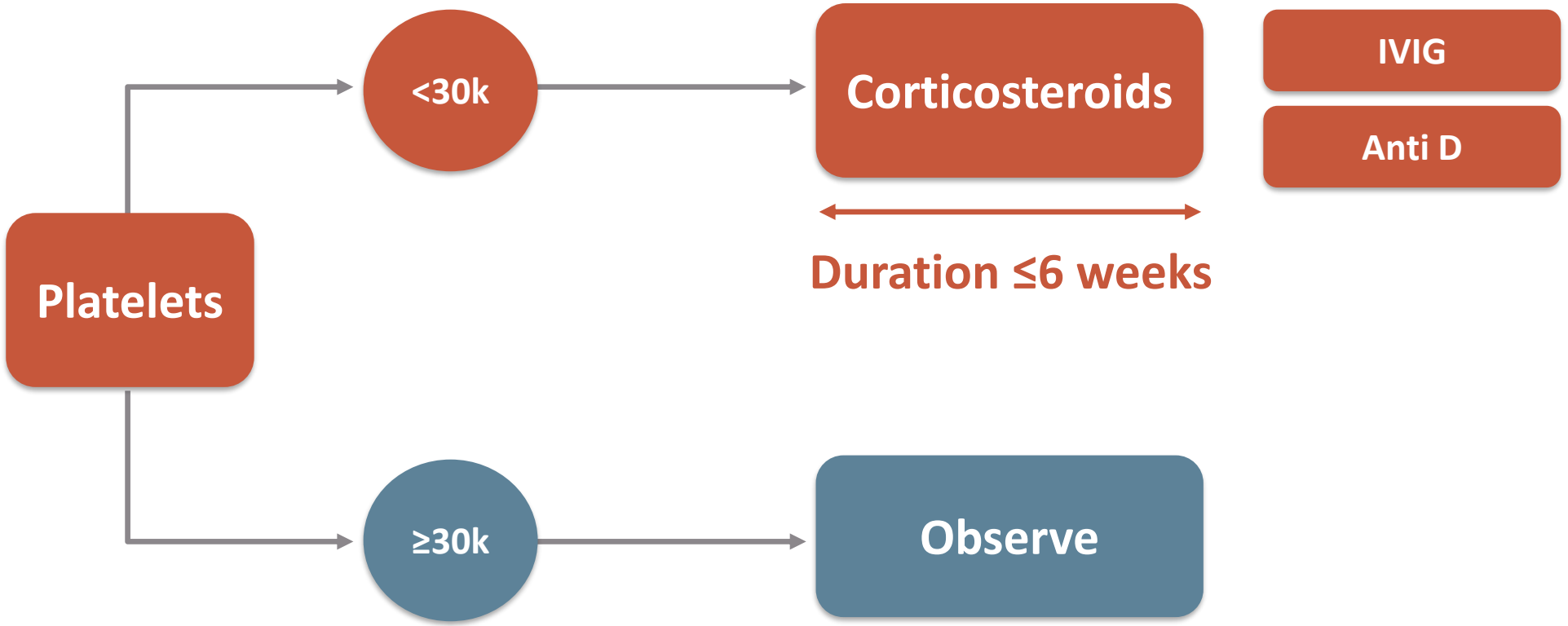
WBC count, × 10^9/L	5.6
Haemoglobin, g/dL	12.4
Platelet count, × 10^9/L	26
TSH	normal limits
Hepatitis B/C, HIV	negative



HIV, human immunodeficiency virus; TSH, thyroid-stimulating hormone; WBC, white blood cell count

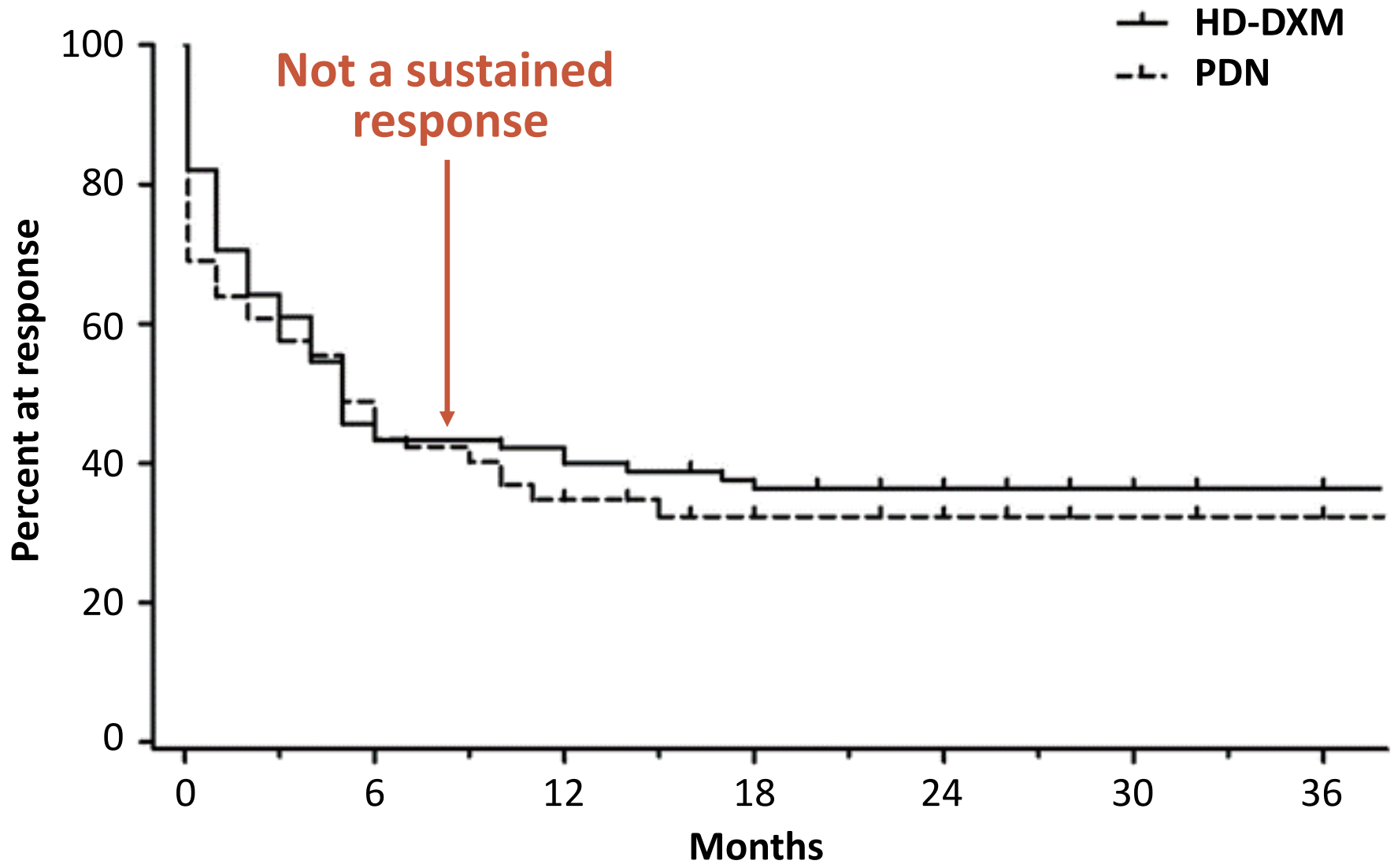
INITIAL TREATMENT OF ITP



Anti D, anti-D immunoglobulin; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin

Neunert C, et al. Blood Adv. 2019;3(23):3829-66

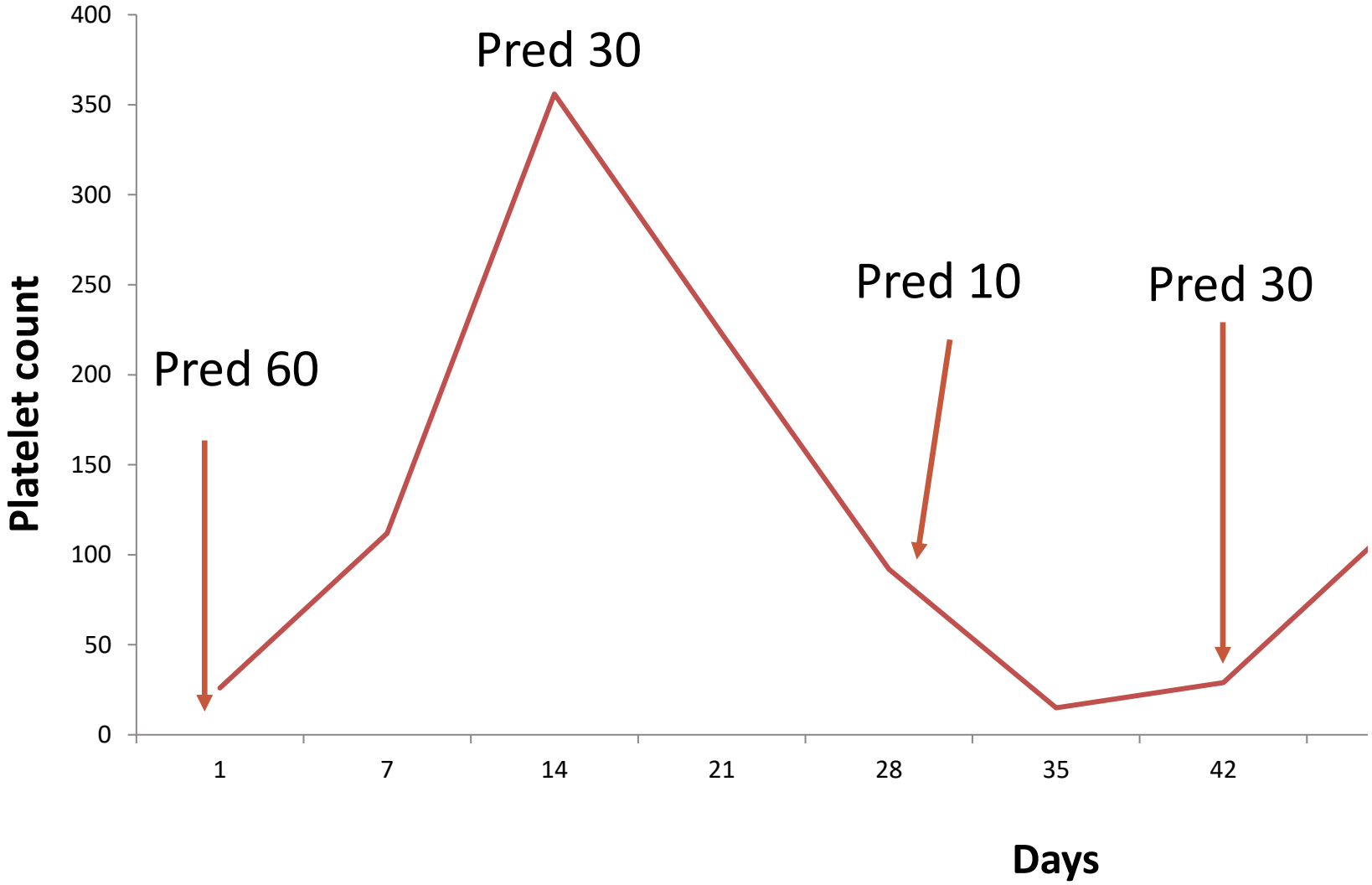
DEXAMETHASONE OR PREDNISONE?



HD-DXM, high-dose dexamethasone; PDN, prednisone

Wei Y, et al. Blood. 2016;127(3):296-302

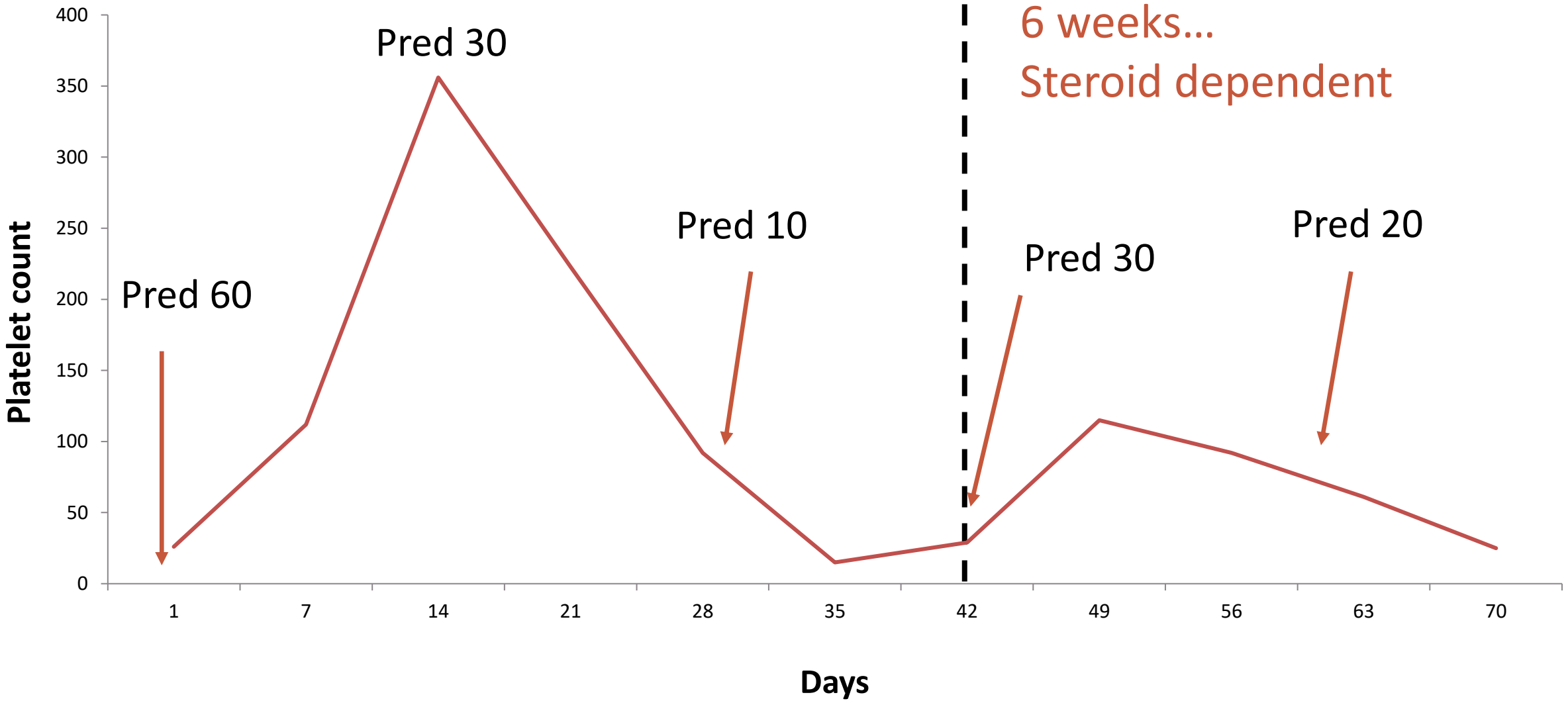
CASE



- Start 1 mg/kg prednisone
- Platelets normalise so we start a slow taper

Pred, prednisone

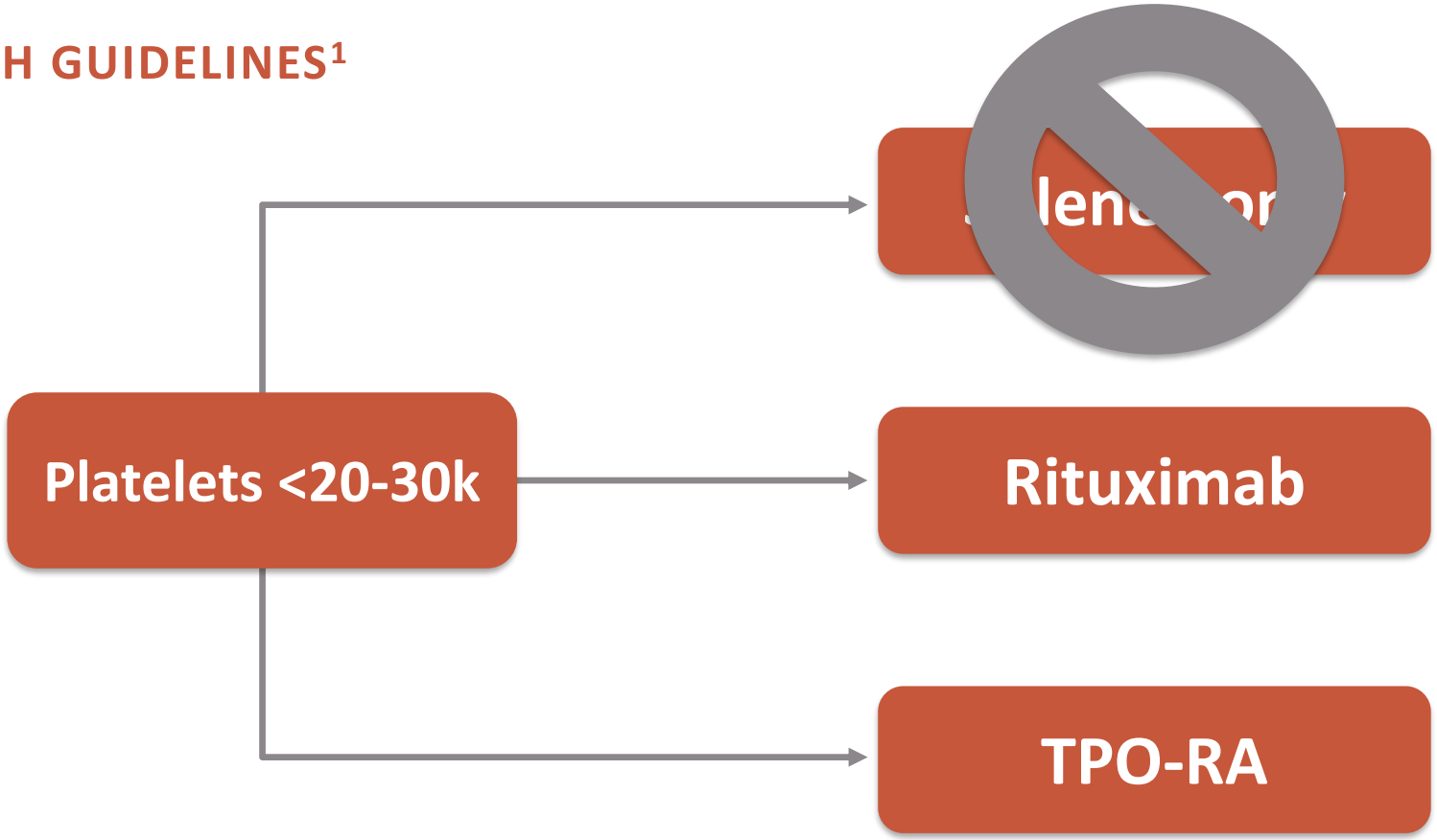
CASE



Pred, prednisone

SECOND-LINE THERAPY

ASH GUIDELINES[1]



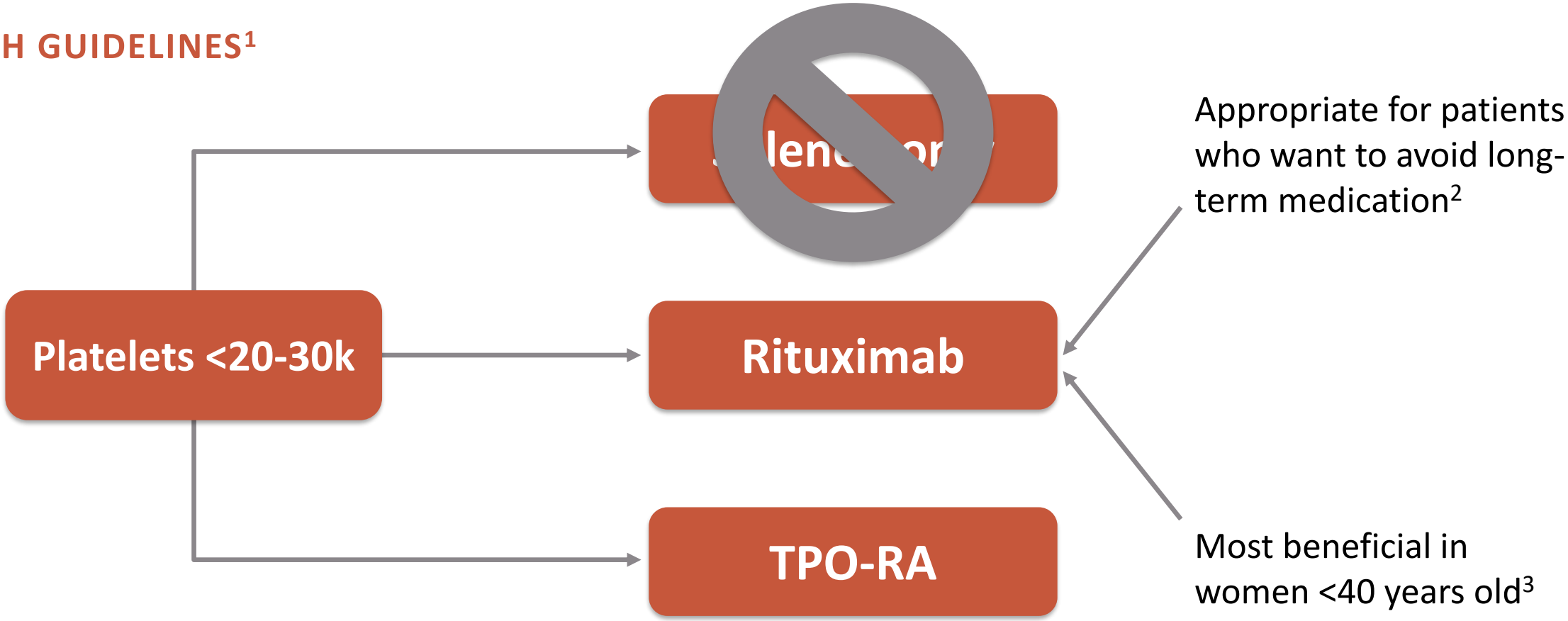
No splenectomy until at least 1 year out

ASH, American Society of Hematology; TPO-RA, thrombopoietin receptor agonist

1. Neunert C, et al. Blood Adv. 2019;3(23):3829-66

SECOND-LINE THERAPY

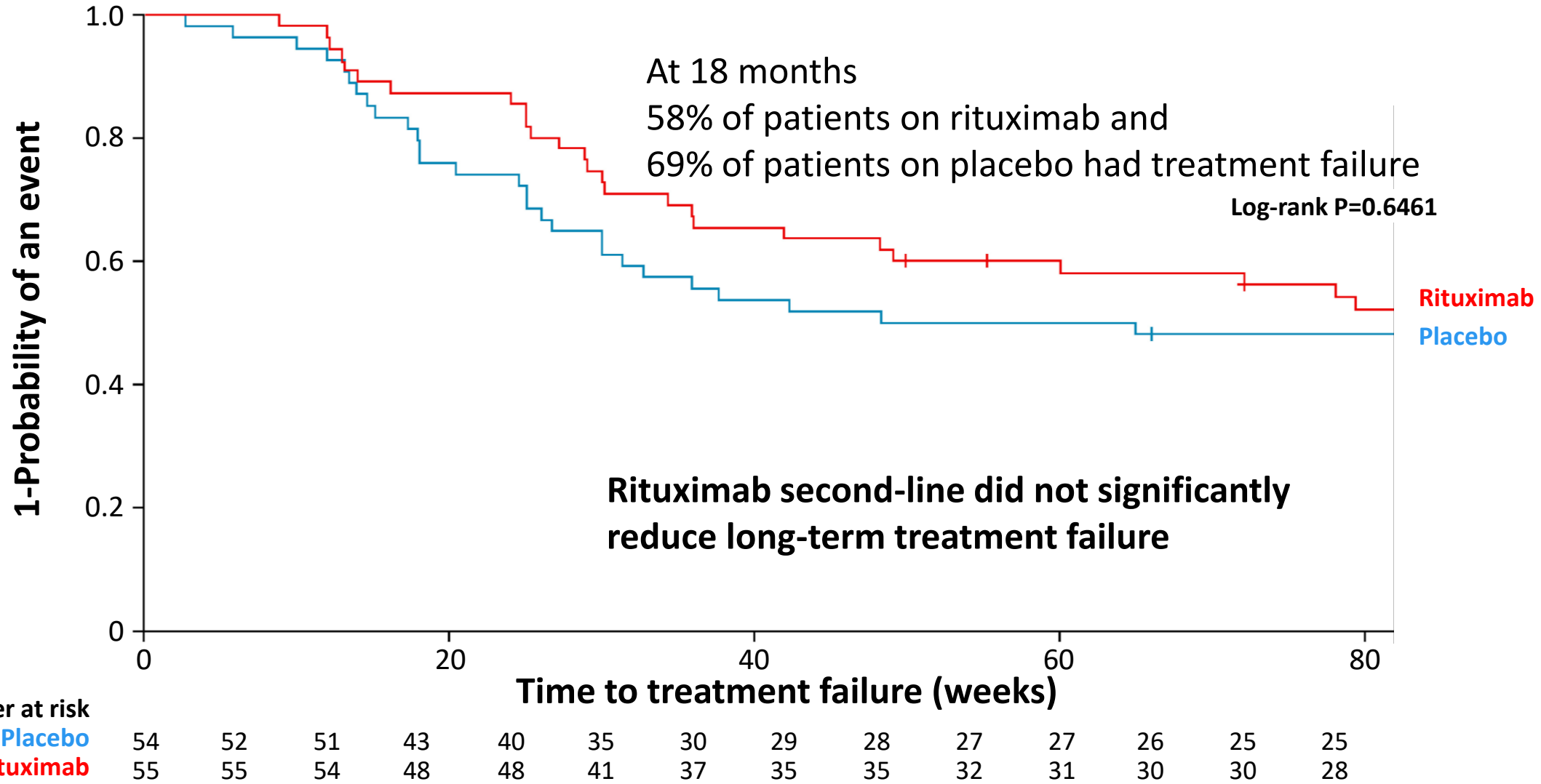
ASH GUIDELINES[1]



ASH, American Society of Hematology; TPO-RA, thrombopoietin receptor agonist

1. Neunert C, et al. Blood Adv. 2019;3(23):3829-66; 2. Ghanima W, et al. Lancet. 2015;385:1653-61; 3. Marangon M, et al. Eur J Haematol. 2017;98:371-77

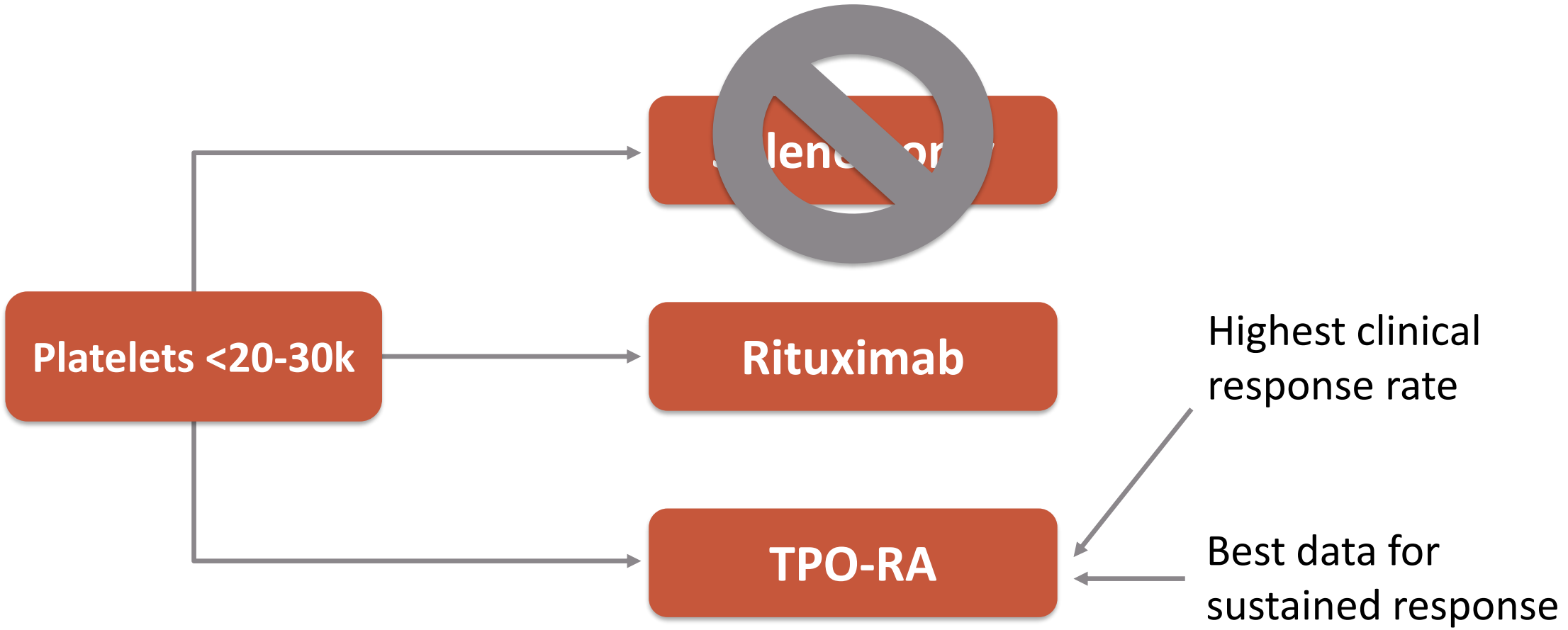
RITUXIMAB



Number at risk														
Placebo	54	52	51	43	40	35	30	29	28	27	27	26	25	25
Rituximab	55	55	54	48	48	41	37	35	35	32	31	30	30	28

Ghanima W, et al. Lancet. 2015;385.9978:1653-61

SECOND-LINE THERAPY



TPO-RA, thrombopoietin receptor agonist

Neunert C, et al. Blood Adv. 2019;3(23):3829-66; Marangon M, et al. Eur J Haematol. 2017;98:371-77; Cooper N, et al. N Engl J Med. 2019;381:945-55

THROMBOPOIETIN RECEPTOR AGONISTS

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	Pro	Con
Romiplostim	Cost (+/-) ↑ Monitoring	Subcutaneous injection Platelet variability
Eltrombopag	Oral ↓ Bleeding	Food restriction Hepatotoxicity
Avatrombopag	Oral No food-type restriction	Headache Newer drug

Forsythe A, et al. J Comp Eff Res. 2020;9(7):447-57

THROMBOPOIETIN RECEPTOR AGONISTS

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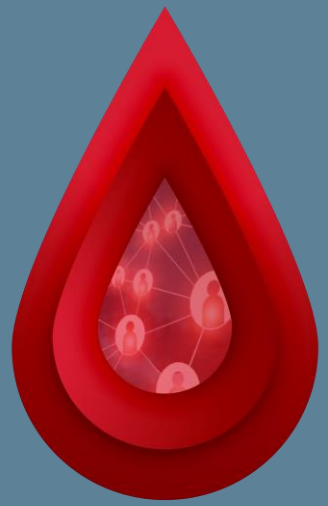
	Starting Dose	Titration	Max/Min dose
Romiplostim	1 µg/kg/week (label) 3 µg/kg/week (realistic) 5 µg/kg/week (severe)	Adjust 1 µg/kg weekly	10 µg/kg/week 1 µg/kg/week
Eltrombopag	50 mg daily 25 mg daily (Asian patients)	Assess CBC weekly and LFTs every 2 weeks, adjust by 25 mg Consider intermittent dosing	75 mg/day (150 mg approved for AA) 12.5 mg/day
Avatrombopag	20 mg daily	Assess CBC weekly, adjust by 20 mg	40 mg/day 20 mg/week

AA, aplastic anaemia; CBC, complete blood count; LFT, liver function test

Al-Samkari H, et al. Ther Adv Hematol. 2019;10:2040620719841735; Nplate (romiplostim) prescribing information; Promacta (eltrombopag) prescribing information; Doptelet (avatrombopag) prescribing information



PRACTICAL CONSIDERATIONS AROUND CHOOSING A TPO-RA

Hanny Al-Samkari, MD

Massachusetts General Hospital & Harvard Medical School, Boston, MA, USA

TPO-RA, thrombopoietin receptor agonist

DISCLOSURES

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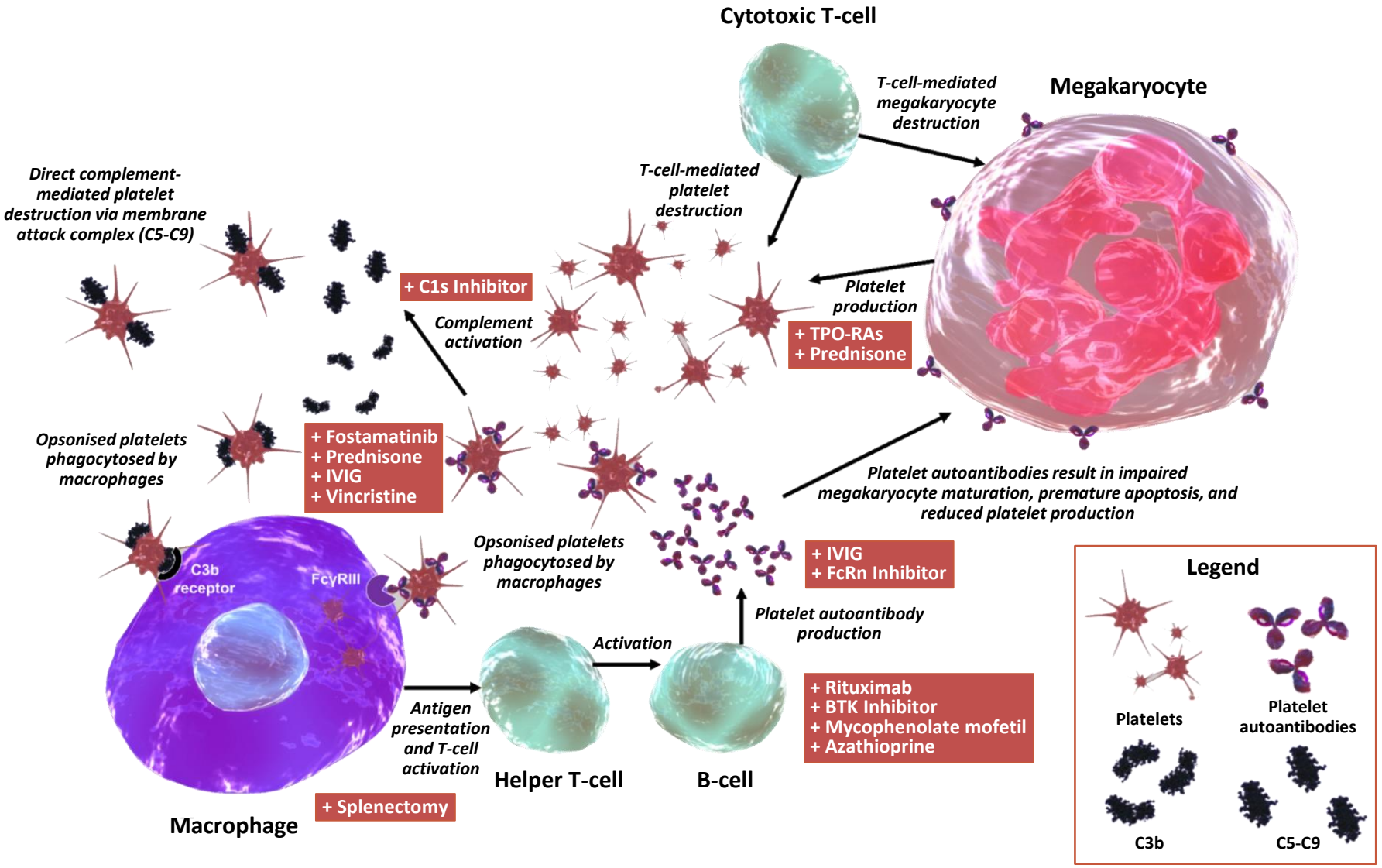
- Grants/honoraria from Agios, Amgen, Argenx, Dova, Rigel, Novartis and Sobi

MECHANISM OF ACTION OF ITP THERAPIES



BTK, Bruton tyrosine kinase; FcRn, neonatal Fc receptor; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist

Al-Samkari H, et al. Semin Thromb Hemost. 2020;46(3):275-88

THE THROMBOPOIETIN RECEPTOR AGONISTS (TPO-RA)

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	Romiplostim	Eltrombopag	Avatrombopag	Lusutrombopag
Molecular structure	**Peptide**	Small molecule	Small molecule	Small molecule
TPO receptor site of action	**Extracellular domain**	Transmembrane domain	Transmembrane domain	Transmembrane domain
Route of administration	**Subcutaneous**	Oral	Oral	Oral
Dosing frequency[a]	**Weekly**	Daily	Daily	Daily
Relevant food interactions	N/A	**Yes**	No	No
Current indications	• ITP (adults and children)	• ITP (adults and children) • Hepatitis C-associated thrombocytopenia • Severe aplastic anaemia	• ITP (adults) • Periprocedural thrombocytopenia in CLD patients	• **Periprocedural thrombocytopenia in CLD patients**

[a]Per drug label

CLD, chronic liver disease; N/A, not applicable; TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist

Cheloff AZ, et al. J Blood Med. 2019;10:313-21

RANDOMISED TRIALS EVALUATING TPO-RAs IN ADULT ITP

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Study	Treatment (N)	Location	Study population	Major results (compared with placebo/standard of care)
Bussel	Eltrombopag N=76 Placebo N=38	Worldwide (63 sites)	ITP for ≥6 months; plt <30 × 10^9/L 36% splenectomised	Significantly higher rate of platelet response[a] Significantly less bleeding
Cheng	Eltrombopag N=135 Placebo N=62	Worldwide (75 sites)	ITP for ≥6 months; plt <30 × 10^9/L 39% splenectomised	Significantly higher rate of platelet response[a] Reduced use of concomitant ITP medications Reduced need for rescue therapy
Tomiyama	Eltrombopag N=15 Placebo N=8	Japan	ITP for ≥6 months; plt <30 × 10^9/L 70% splenectomised	Significantly higher rate of platelet response[a] Significantly less bleeding Lower doses of eltrombopag effective in Japanese patients
Yang	Eltrombopag N=104 Placebo N=51	China	ITP for ≥12 months; plt <30 × 10^9/L 16% splenectomised	Significantly higher rate of platelet response[a]
Kuter	Romiplostim N=83 Placebo N=42 (2 parallel studies)	US and Europe	ITP for ≥12 months; plt <30 × 10^9/L 50% splenectomised	Significantly higher rate of platelet response[a] Reduced use of concomitant ITP medications
Kuter	Romiplostim N=157 Standard of care N=77	North America, Europe and Australia	ITP for ≥12 months; plt <50 × 10^9/L 0% splenectomised	Significantly higher rate of platelet response[a] Reduced use of concomitant ITP medications Lower rate of treatment failure Lower rate of splenectomy Significantly less bleeding and transfusions Significantly improved quality of life
Shirasugi	Romiplostim N=22 Placebo N=12	Japan	ITP for ≥6 months; plt ≤30 × 10^9/L 44% splenectomised	Significantly higher rate of platelet response[a] Reduced need for rescue therapy
Jurczak	Avatrombopag N=32 Placebo N=17	Europe, Asia, Africa and Australia	ITP for ≥12 months; plt <30 × 10^9/L 33% splenectomised	Significantly higher cumulative weeks of platelet response[a] Reduced use of concomitant ITP medications (not significant; small number of patients)

[a] Platelet response defined as a platelet count ≥50 × 10^9/L at a given assessment on treatment with TPO-RA or placebo

ITP, immune thrombocytopenia; Plt, platelets; TPO-RA, thrombopoietin receptor agonist

Al-Samkari H, et al. Ther Adv Hematol. 2019;10:2040620719841735

CONSIDERATIONS FOR USE OF TPO-RA IN ITP

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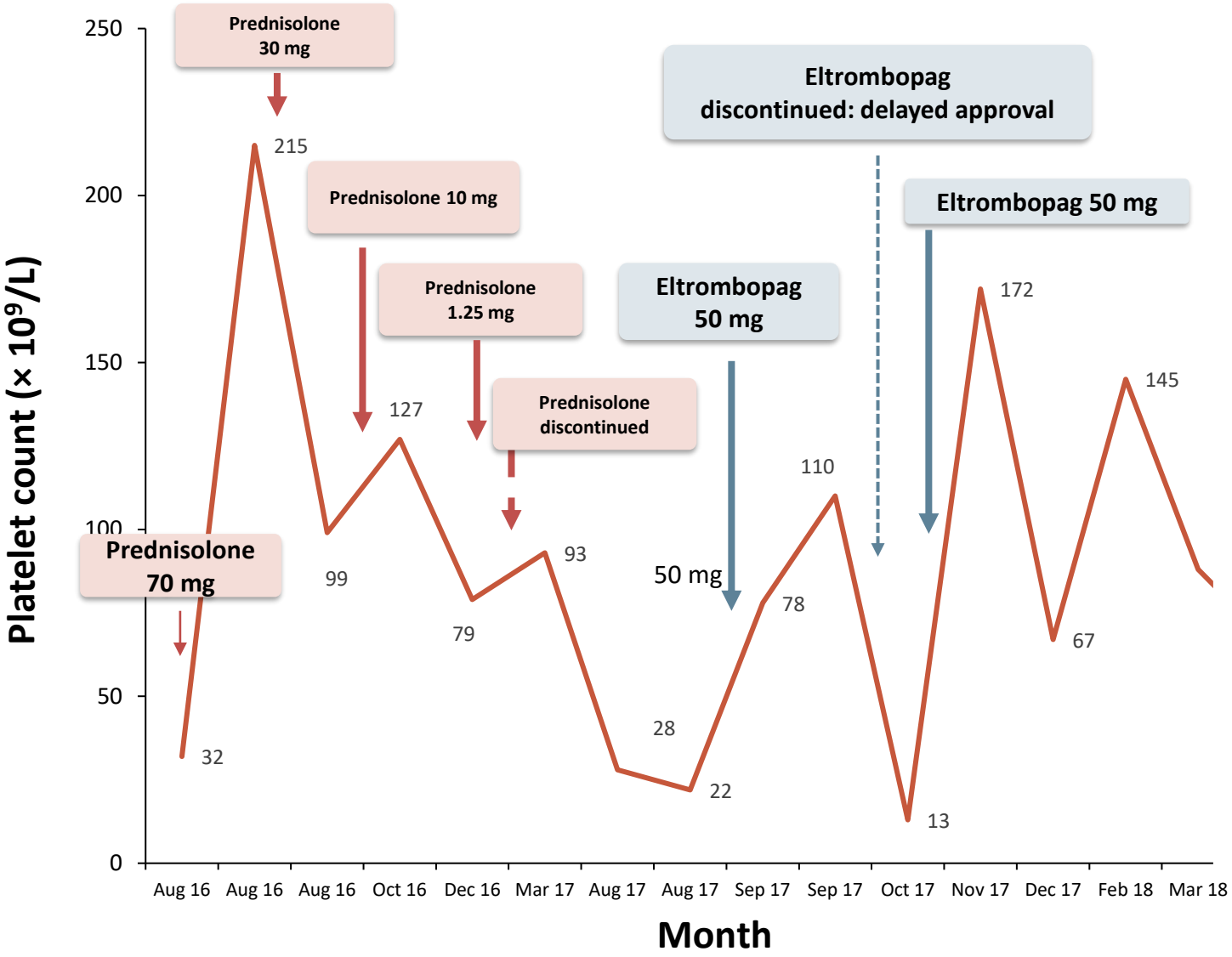
- **May be used after any disease duration** but typically at least second line
- Response rates and AE profiles **similar in ITP <1 year and ITP >1 year**
- Decision primarily **TPO-RA vs. immunosuppressant**
  - TPO-RAs have higher response rates
  - TPO-RAs may have higher thrombotic risk
  - Immunosuppressants increase infection risks (which can cause an ITP exacerbation)
- **Administration**
  - Daily oral
  - Weekly subcutaneous
  - 2 to 4 infusions of rituximab
- Avoid eltrombopag in patients with **liver disease** (hepatotoxicity, portal vein thrombosis)

AE, adverse event; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
Al-Samkari H, et al. Ther Adv Hematol. 2019;10:2040620719841735

CASE, CONTINUED

Platelet count after remission



- Patient treated with rituximab initially, with effect
- However, relapse occurred 11 months later
- Eltrombopag was selected as the next treatment option
  - After initial retreatment with prednisone (current guidelines recommend against retreating with steroids)

ROMIPLOSTIM AND ELTROMBOPAG DOSING IN ITP

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Romiplostim

- **Label says start 1 µg/kg/week, increase by 1 µg/kg/week**
  - In my experience, this is too low, too slow for most patients
- **What I do in clinical practice:**
  - I start at 3 µg/kg/week (5 µg if severely thrombocytopenic) and do not hesitate to titrate by ≥2 µg/kg/week
  - I start at 10 µg/kg/week for clinical emergency
  - I *do not hold doses for thrombocytosis* unless Plt > 1 million; leads to less volatility

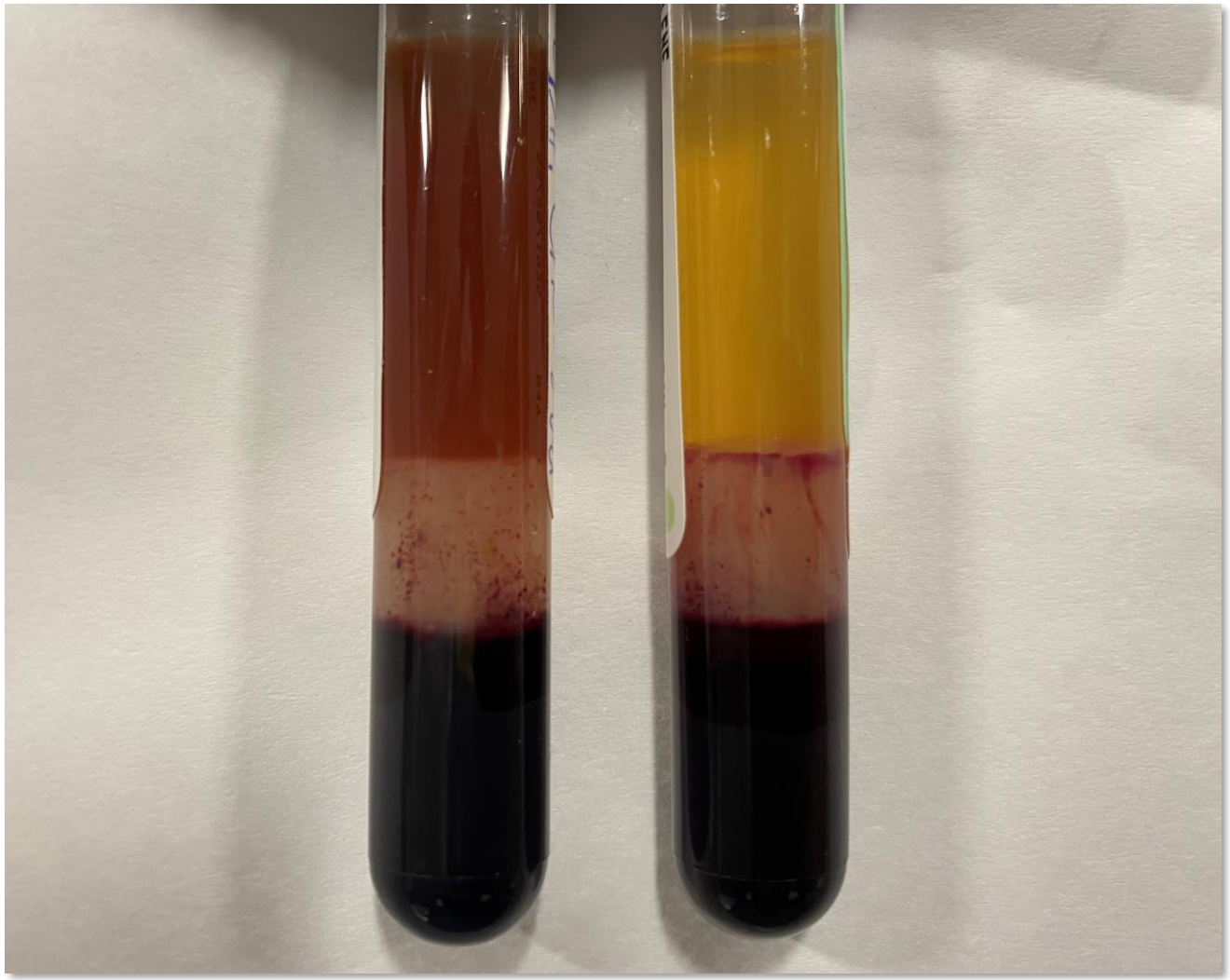
Eltrombopag

- Start 50 mg/day in all except East Asian descent, CLD, children 1-5 years who get 25 mg/day
- Technically 75 mg/day is max ITP dose, but in my experience, you can go higher (though scant evidence)
- Beware of plasma, skin, sclera changes with high dose; can interfere with bilirubin measurement
- Must monitor LFTs; consider iron chelation

CLD, chronic liver disease; ITP, immune thrombocytopenia; LFT, liver function test; Plt, platelets

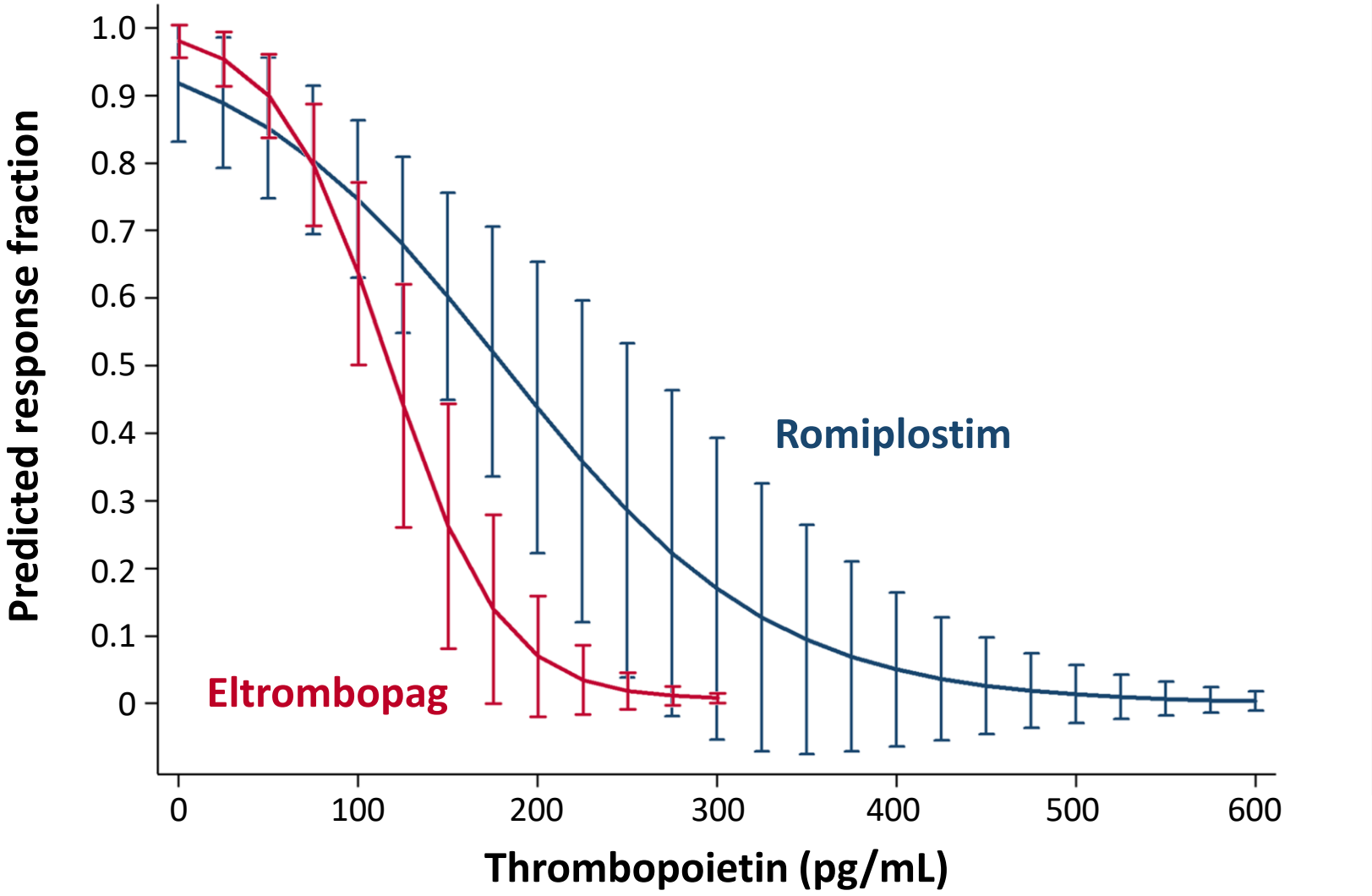
Al-Samkari H, et al. Ther Adv Hematol. 2019;10:2040620719841735; Nplate (romiplostim) prescribing information; Promacta (eltrombopag) prescribing information

REDDISH-BROWN DISCOLOURATION FROM ELTROMBOPAG



Al-Samkari H, et al. Acta Haematol. 2021;144(2):227-28

ENDOGENOUS TPO LEVEL MAY BE HELPFUL IN PREDICTING RESPONSE



TPO, thrombopoietin

Al-Samkari H, et al. Am J Hematol. 2018 ;93(12):1501-8

AVATROMBOPAG DOSING IN ITP

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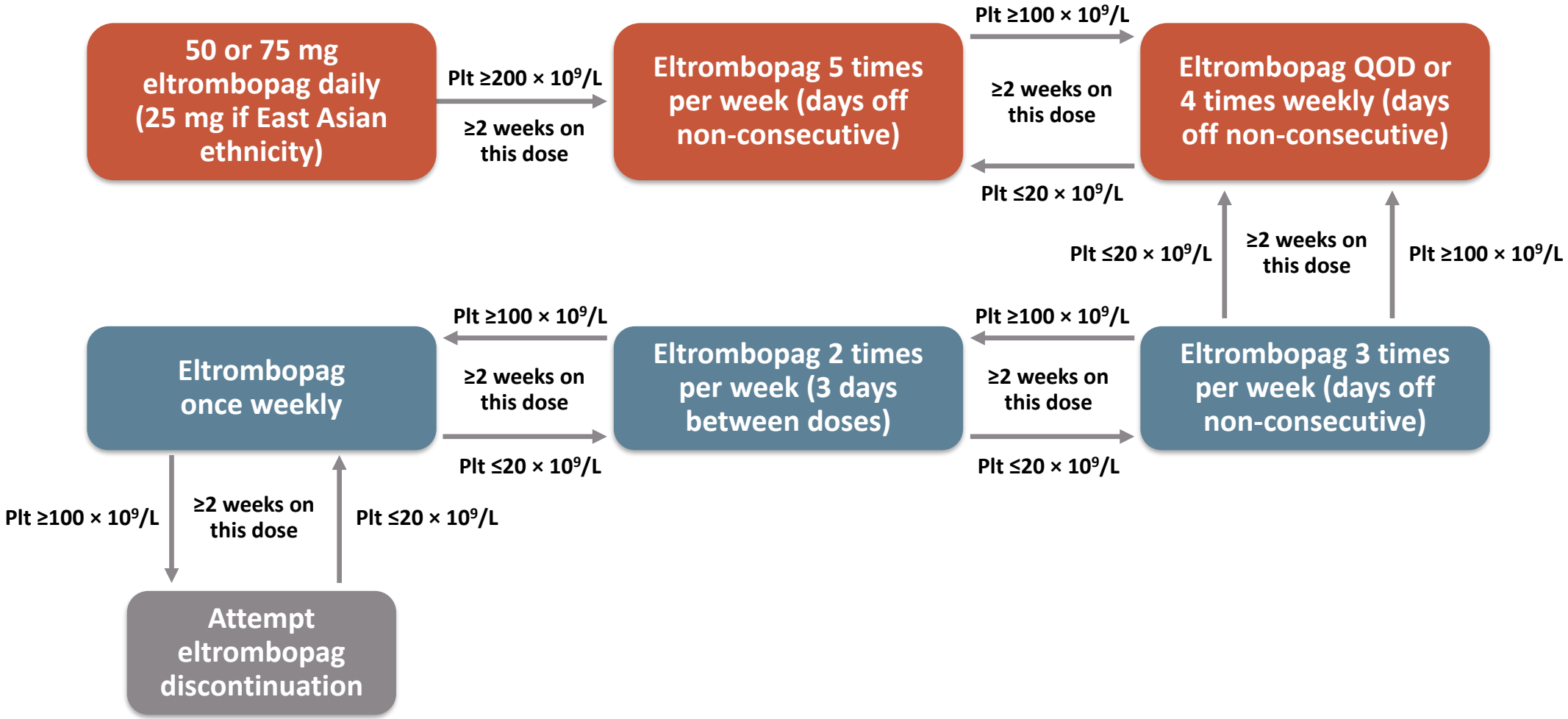
Avatrombopag dose levels for titration in patients with chronic ITP

Dose	Dose Level
40 mg once daily	6
40 mg three times a week *AND* 20 mg on the four remaining days of each week	5
20 mg once daily*	4
20 mg three times a week	3
20 mg twice a week *OR* 40 mg once weekly	2
20 mg once weekly	1

* Initial dose regimen for all patients *except* those taking moderate or strong dual inducers or moderate or strong dual inhibitors of CYP2C9 or CYP3A4

ITP, immune thrombocytopenia
Doptelet (avatrombopag) prescribing information

ALTERNATIVE INTERMITTENT ELTROMBOPAG DOSING IN ITP



ITP, immune thrombocytopenia; Plt, platelets; QOD, every other day

Al-Samkari H, et al. Br J Clin Pharmacol. 2018;84(11):2673-7

ORAL TPO-RAs: ABSORPTION DIFFERENCES

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- **Eltrombopag** absorption severely impacted by consumption of fat or polyvalent cations (i.e. $Ca2^{+}$, $Mg2^{+}$, etc)
  - Reduces absorption of eltrombopag by >50%
  - Essentially requires a **4-hour fasted window around administration** (or 6 hours if 50 mg $Ca2^{+}$ is consumed, present in a single serving of many dairy, grain, and vegetable products)

- **Avatrombopag** is taken **with food**, absorption is optimised when taken with food

- Given that patients frequently take TPO-RAs for years, this is **not a trivial issue** and initial dietary compliance not infrequently gives way over time

TPO-RA, thrombopoietin receptor agonist

Cheloff AZ, et al. J Blood Med. 2019;10:313-21; Al-Samkari H, et al. Ther Adv Hematol. 2019;10:2040620719841735; Williams DD, et al. Clin Ther. 2009;31:764-76

SWITCHING BETWEEN ROMIPLOSTIM AND ELTROMBOPAG

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Publications reporting outcomes in patients with ITP who switched their TPO-RA therapy

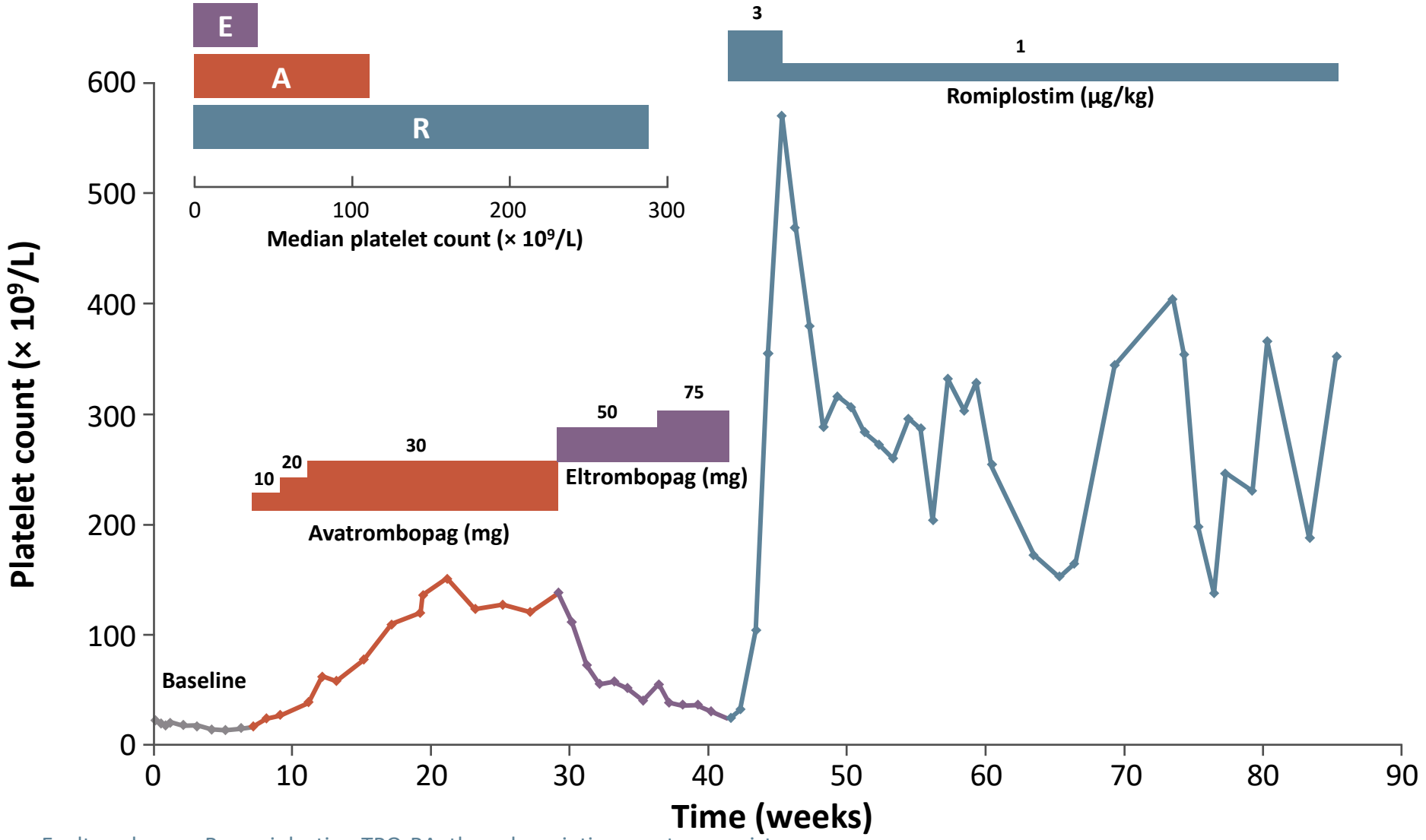
Study	Number of patients			Response rate after switching (%)		
	Romiplostim →eltrombopag	Eltrombopag →romiplostim	Total	Romiplostim →eltrombopag	Eltrombopag →romiplostim	Total
Gonzalez et al.	17	4	21	77	75	76
Lakhwani et al.	17	9	26	94	78	88
Cantoni et al.	59	47	106	–	–	65
Depre et al.	8	28	36	63	71	69
Gonzalez-Porras et al.	51	–	51	80	–	80
Mazza et al.	7	2	9	57	100	67
Mori et al.	–	1	1	–	100	100
Kuter et al.	44	42	86	–	–	–
Sartori et al.	1	–	1	100	–	100
Scaramucci et al.	1	2	3	100	50	67
Khellaf et al.	35	11	46	66	80	70
Meyer et al.	–	2	2	–	100	100
Nakazato et al.	–	1	1	–	100	100
Piccin et al.	–	1	1	–	100	100
Polverelli et al.	1	1	2	100	100	100
D'Arena et al.	2	–	2	100	–	100
Aoki et al.	–	1	1	–	100	100
Tsukamoto et al.	–	6	6	–	100	100
Total	**243**	**158**	**401**	**76 (107/140)***	**80 (55/69)***	**78 (162/209)***

* Overall response rates were not specified Kuter et al. and available only as a combined percentage in Cantoni et. al. These values were not included in the total calculation

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist

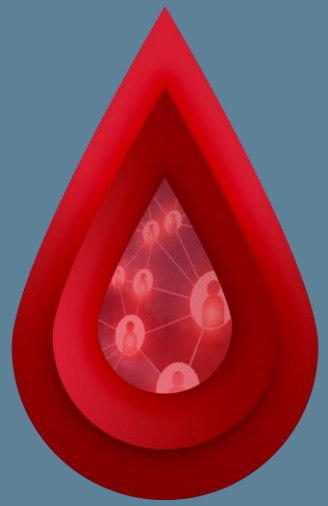
Gonzalez-Porras JR, et al. Ther Adv Hematol. 2019;10:2040620719837906

64-YEAR-OLD WOMAN TREATED SEQUENTIALLY WITH 3 TPO-RAs



A, avatrombopag; E, eltrombopag; R, romiplostim; TPO-RA, thrombopoietin receptor agonist

Al-Samkari H, et al. Br J Haematol. 2018;183(2):168



LONG-TERM USE OF A TPO-RA: SAFETY AND DISEASE REMISSION

Waleed Ghanima, MD, PhD
Østfold Hospital and University of Oslo, Norway

TPO-RA, thrombopoietin receptor agonist

DISCLOSURES

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- Grants from Bayer, Pfizer/BMS
- Ad board/honoraria from Amgen, MSD, Novartis, Bayer, Pfizer, Principia, Sanofi and Sobi, UCB

WHAT SIDE EFFECTS MAY WE EXPECT IN PATIENTS ON TPO-RA?

TPO-RA, thrombopoietin receptor agonist

GENERAL SIDE EFFECTS

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- Reported in >5% of patients[1-5]
  - Headache (8-37%)
  - Upper respiratory tract infection/nasopharyngitis (7-19%)
  - GI symptoms
  - Arthralgia
  - Myalgia

- These adverse events were also reported in placebo arms

- Difference in time-adjusted rates

GI, gastrointestinal

1. Bussel J, et al. N Engl J Med. 2006;355:1672-81; 2. Kuter D, et al. Lancet. 2008;371:395-403; 3. Bussel J, et al. Lancet. 2009;377:641-8;
4. Cheng G, et al. Lancet. 2011;377:393-402; 5. Jurczak W, et al. Br J Haematol. 2018;183:479-90

META-ANALYSIS: AE PROFILES ARE SIMILAR BETWEEN TPO-RAs AND CONTROL REGIMENS

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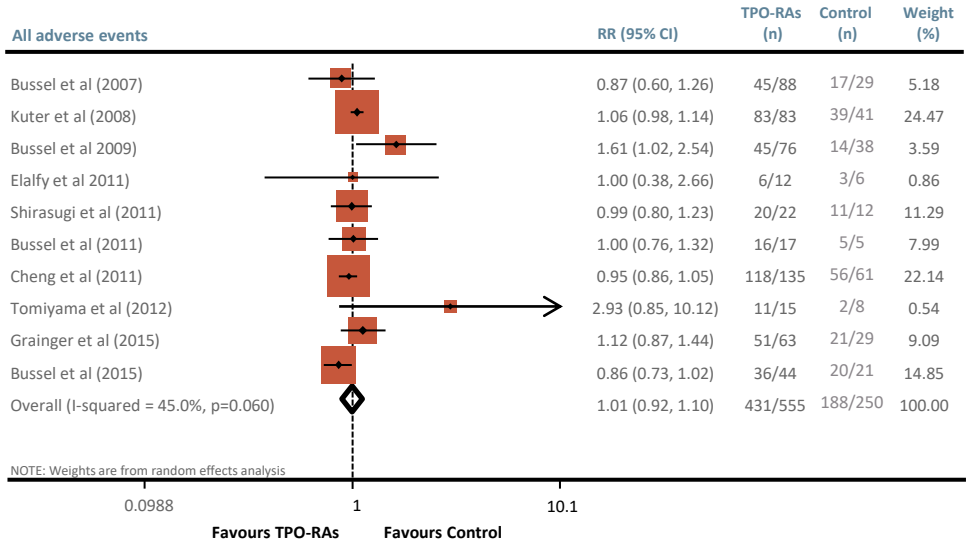
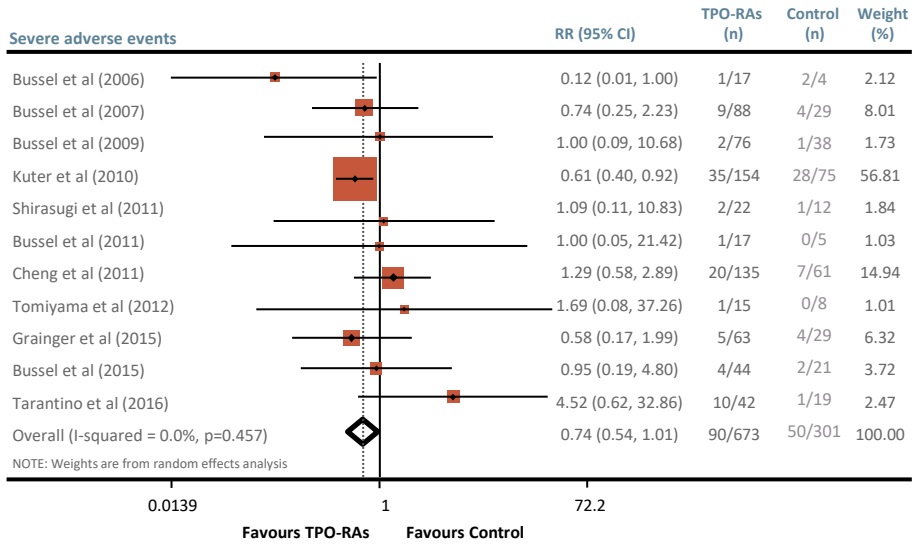
Adverse events

AEs were similar between the TPO-RA and control regimens
(RR: 1.01, 95% CI: 0.92-1.10, p=0.913)



Severe adverse events

The rates of severe AEs tended to be lower in the TPO-RA groups than in the control groups
(RR: 0.74, 95% CI: 0.54-1.01, p=0.054)



AE, adverse event; CI, confidence interval; RR, risk ratio; TPO-RA, thrombopoietin receptor agonist
Wang L, et al. Sci Rep. 2016;6:39003

MORE SERIOUS SIDE EFFECTS OCCASIONALLY ENCOUNTERED IN PATIENTS TREATED WITH TPO-RAs

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- Transaminitis (eltrombopag)
- Bone marrow fibrosis
- Thromboembolism

TPO-RA, thrombopoietin receptor agonist

TRANSAMINITIS

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- Transaminitis occurs in up to 10%, especially on eltrombopag[1-4]
- Mostly asymptomatic and reversible with dose interruption, reduction or discontinuation[1,3,5]
- Occurs more in the first year, which justifies regular monitoring of liver enzymes[2]
- Transaminitis does not seem to be a problem with avatrombopag[6]

1. Saleh M, et al. Blood. 2013;121:537-45; 2. Wong R, et al. Blood. 2017;130:2527-36; 3. PROMACTA (eltrombopag) prescribing information; 4. Ghanima W, et al. Haematologica. 2019;104:1112-23. 5. Grainger J, et al. Lancet. 2015;386:1649-58; 6. Jurczak W, et al. Br J Haematol. 2018;183(3):479-90

IN PATIENTS WITH ITP RECEIVING ROMIPLOSTIM, BONE MARROW CHANGES WERE OBSERVED IN A SMALL PROPORTION OF PATIENTS

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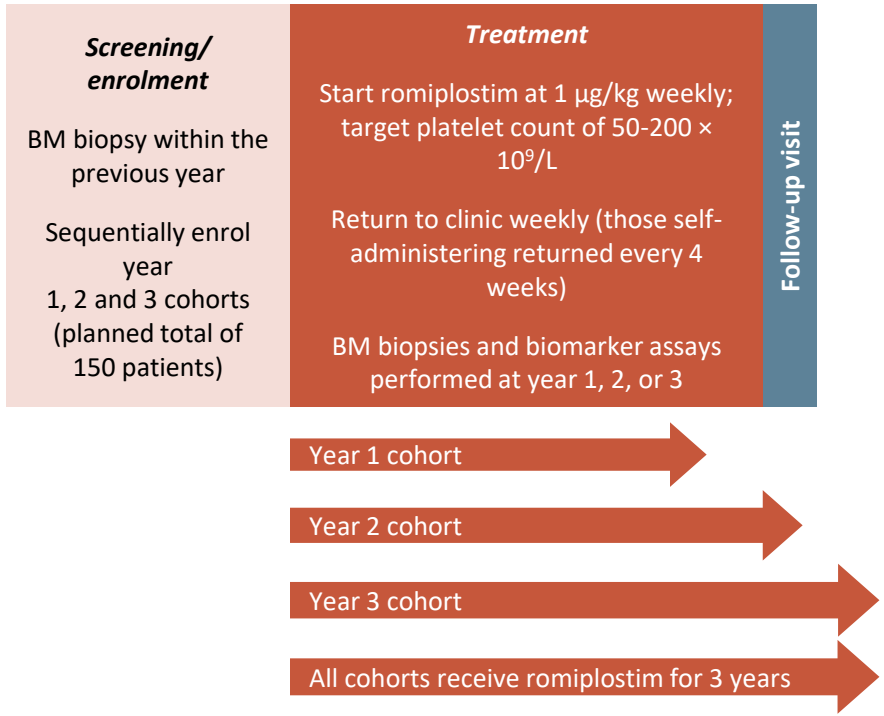
Phase 4, prospective, open-label, multicenter study evaluating changes in bone marrow reticulin and collagen in 169 patients with ITP receiving romiplostim.



Number of patients with reticulin or collagen present in BM biopsies

By Cohort	Cohort 1 (n=50)	Cohort 2 (n=50)	Cohort 3 (n=69)	Total (N=169)
Bone marrow biopsies after receiving romiplostim	39	40	58	137
Biopsies evaluable for collagen (trichrome stain)	35	39	58	132
Positive for collagen	0	0	2 (3.4%)	2 (1.5%)
Patients with biopsies evaluable for reticulin (silver stain)	34	39	58	131
Increase in reticulin by ≥2 grades excluding collagen	0	2 (5.1%)	5 (8.6%)	7 (5.3%)
By exposure at time of biopsy	**1 year**	**2 years**	**3 years**	**Total**
Biopsies evaluable for collagen (trichrome stain)	42	38	52	132
Positive for collagen	1 (2.4%)	0	1 (1.9%)	2 (1.5%)
Patients with biopsies evaluable for reticulin (silver stain)	41	38	52	131
Increase in reticulin by ≥2 grades excluding collagen	2 (4.9%)	1 (2.6%)	4 (7.7%)	7 (5.3%)

BM, bone marrow; ITP, immune thrombocytopenia

Janssens A, et al. Ann Hematol. 2016;95:1077-87

EFFECTS OF ELTROMBOPAG ON BM RETICULIN FORMATION

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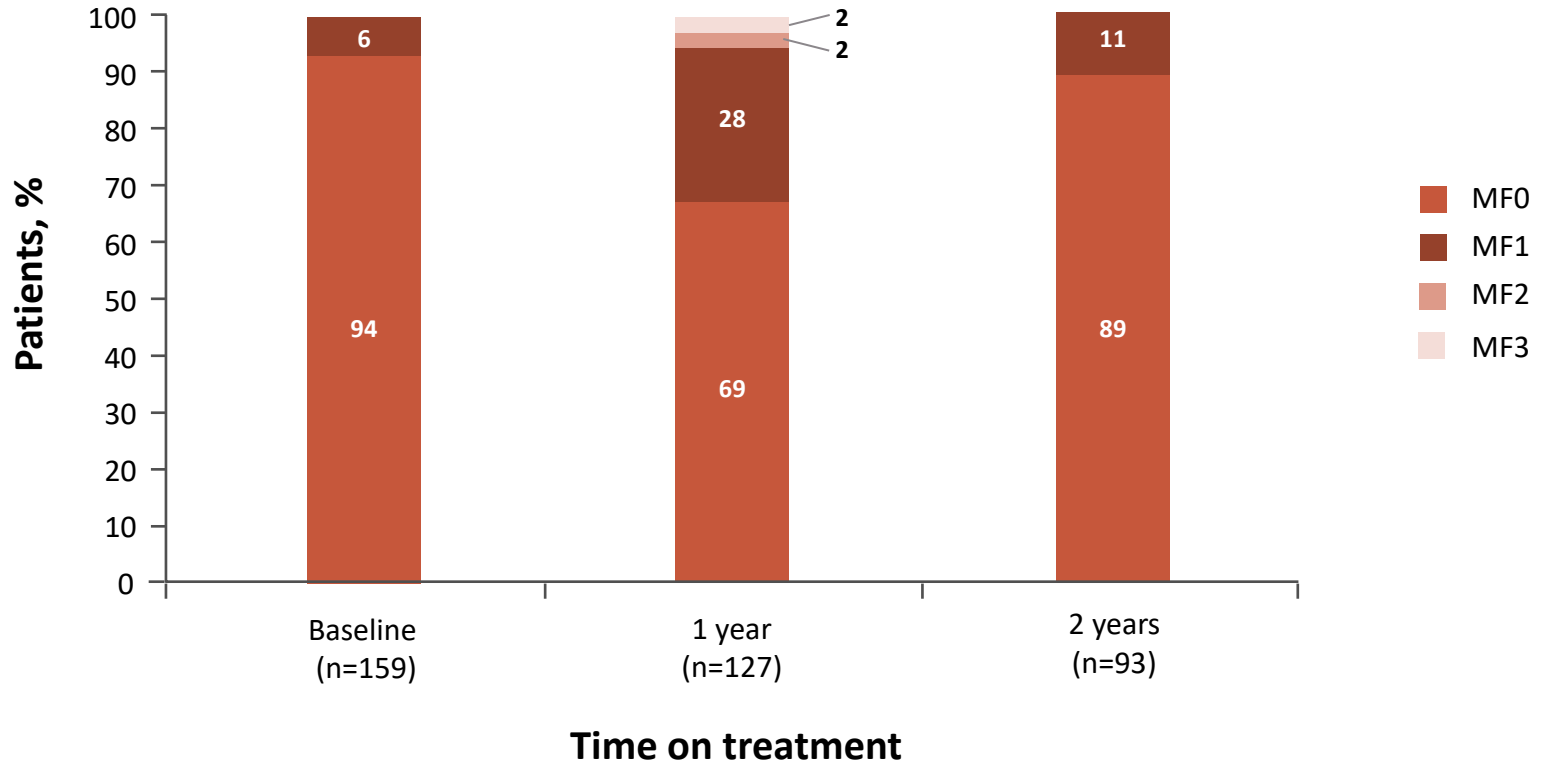
Reticulin level at baseline and the 1- and 2-year assessments



BM, bone marrow; ITP, immune thrombocytopenia

Brynes RK, et al. Acta Haematol. 2017;137(2):66-72

BONE MARROW FIBROSIS

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- Most patients' **grade of fibrosis did not change or only slightly increased** (MF-1 or Bauermeister <2) during treatment[1]
- **Moderate increase in reticulin fibrosis** (≥2 grades or ≥MF-2) occurred in <10% of patients[2-4]
- In the majority of patients both reticulin and collagen fibrosis **regressed after discontinuation** of TPO-RA[1,3]
- Usually, **no change** in number or morphology of **peripheral blood cells** is seen[1,3,5,6]

- There is **no consensus on whether/how to monitor** bone marrow fibrosis
  - No need for regular bone marrow biopsies
  - If biopsy is done: MF-3 → discontinue; MF-2 continue + repeat biopsy

MF, myelofibrosis

1. Ghanima W, et al. Haematologica. 2014;99:937-44; 2. Wong R, et al. Blood. 2017;130:2527-36; 3. Brynes R, et al. Acta Haematol. 2017;137:66-72; 4. Jansens A, et al. Ann Hematol. 2016;95:1077-87; 5. Kim Y, et al. Blood Res. 2015;50:19-25; 6. Boiocchi L, et al. Mod Pathol. 2012;25:65-74

VTE AND AT EVENTS IN ROMIPLOSTIM STUDIES

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Study	Duration of follow-up (weeks)	TPO arm n/N (%)	Comparison arm n/N (%)	Remarks
Phase 2 and 3 studies				
Bussel et al. 2006[1]	6	0/41 (0.0%)	1/4 (25%)	1 DVT
Kuter et al. 2008[2]	24	2/83 (2.4%)	1/42 (2.4%)	1 VTE in each arm
Kuter et al. 2010[3]	52*	6/154 (3.9%)	2/75 (2.7%)	11 events in 6 patients on romiplostim and 2 in SOC (P=0.07)
Long-term follow-up studies				
Kuter et al. 2013[4]	110#	19/291 (6.5%)		16 ATE (0.04/100 p.w.) 9 VTE (0.03/100 p.w.)
Steurer et al. 2016[5]	102**	7/340 (2.0%)		10 thrombotic events

* 52-week long study and follow-up period of 6 months for patients who did not enter another romiplostim study;
# Mean duration of treatment
** Duration of exposure

AT(E), arterial thromboembolism; DVT, deep vein thrombosis; p.w., patient-weeks; SOC, standard of care; TPO, thrombopoietin; VTE, venous thromboembolism

1. Bussel J, et al. N Engl J Med. 2006;355:1672-81; 2. Kuter D, et al. Lancet. 2008;371:395-403; 3. Kuter D, et al. N Engl J Med. 2010;363:1889-99; 4. Kuter D, et al. Br J Haematol. 2013;161:411-23; 5. Steurer M, et al. Eur J Haematol. 2017;98:112-20

VTE AND AT EVENTS IN ELTROMBOPAG STUDIES

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Study	Duration of follow-up (weeks)	TPO-RA arm n/N (%)	Comparison arm n/N (%)	Remarks
Phase 2 and 3 studies				
Bussel et al. 2007[1]	6	0/88 (0.0%)	0/29 (0.0%)	
Bussel et al. 2009[2]	6	0/76 (0.0%)	0/38 (0.0%)	
Cheng et al. 2011[3]	26	3/135 (2.2%)	0/62 (0.0%)	3 VTE
Long-term follow-up studies				
Bussel et al. 2013[4]	–	0/65 (0.0%)		
Wong et al. 2017[5]	123*	19/302 (6.3%)		24 events; 10 VTE (2.69/100 patient years)

* Median duration

AT, arterial thromboembolism; TPO-RA, thrombopoietin receotor antagonist; VTE, venous thromboembolism

1. Bussel J, et al. N Engl J Med. 2007;357:2237-47; 2. Bussel J, et al. Lancet. 2009;373:641-8; 3. Cheng G, et al. Lancet. 2011;377:393-402;
4. Bussel J, et al. Br J Haematol. 2013;160:538-46; 5. Wong RSM, et al. Blood. 2017; 130(23):2527-36

VTE AND AT EVENTS IN THE AVATROMBOPAG STUDY

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Study	Study duration (weeks)	TPO arm n/N (%)	Comparison arm n/N (%)	Remarks
Phase 3 core study				
Jurczak et al. 2018[1]	26	3/32 (10%)	0/17 (0.0%)	DVT (day 8), asymptomatic PE (day 154); cerebrovascular event (day 89)
Phase 3 extension study				
Jurczak et al. 2018[1]	104	1/39		Jugular vein thrombosis (day 335)

Of the 4 patients, 3 had multiple risk factors for thromboembolic disease, with the reported events associated with platelet counts from 39-271 × 10^9/L and doses of avatrombopag from 10 to 40 mg.

AT, arterial thromboembolism; DVT, deep vein thrombosis; PE, pulmonary embolism; TPO, thrombopoietin; VTE, venous thromboembolism

1. Jurczak W, et al. Br J Haematol. 2018;183:479-90

THROMBOEMBOLISM

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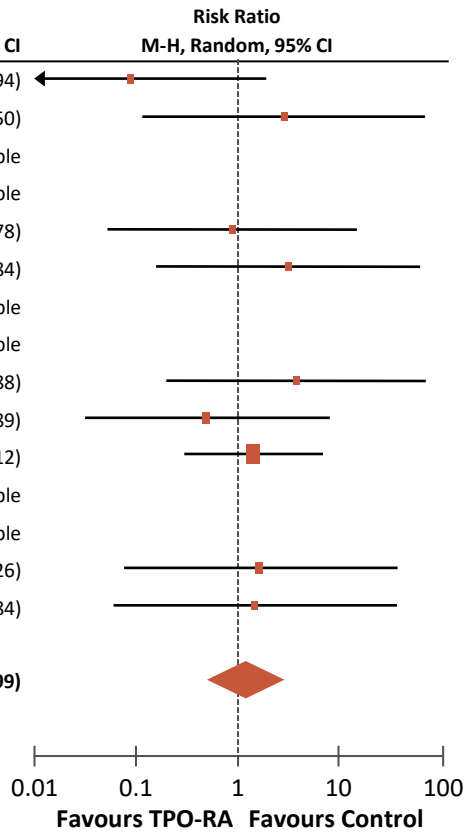
Thrombotic events in RCTs

Study or Subgroup	TPO-RA Events	TPO-RA Total	Control Arm Events	Control Arm Total	Weight	Risk Ratio M-H, Random, 95% CI
Bussel 2006	0	17	1	4	8.3%	0.09 (0.00-1.94)
Bussel 2007	1	30	0	29	7.7%	2.90 (0.12-68.50)
Bussel 2009	0	76	0	38		Not estimable
Bussel 2011	0	17	0	5		Not estimable
Bussel 2014	4	59	0	5	9.8%	0.90 (0.05-14.78)
Cheng 2011	3	135	0	62	8.8%	3.24 (0.17-61.84)
Elalfy 2011	0	12	0	6		Not estimable
Grainger 2015	0	63	0	29		Not estimable
Jurczak 2018	3	32	0	17	9.1%	3.82 (0.21-69.88)
Kuter 2008	1	83	1	42	10.1%	0.51 (0.03-7.89)
Kuter 2010	6	157	2	77	30.8%	1.47 (0.30-7.12)
Shirasugi 2011	0	22	0	12		Not estimable
Tarantino 2016	0	42	0	20		Not estimable
Tomiyama 2012	1	15	0	8	8.0%	1.69 (0.08-37.26)
Yang 2017	1	104	0	51	7.6%	1.49 (0.06-35.84)
Total (95% CI)		**864**		**405**	**100.0%**	**1.25 (0.52-2.99)**
Total events	**20**		**4**			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.63$, df = 8 (p=0.80); $I^2 = 0\%$

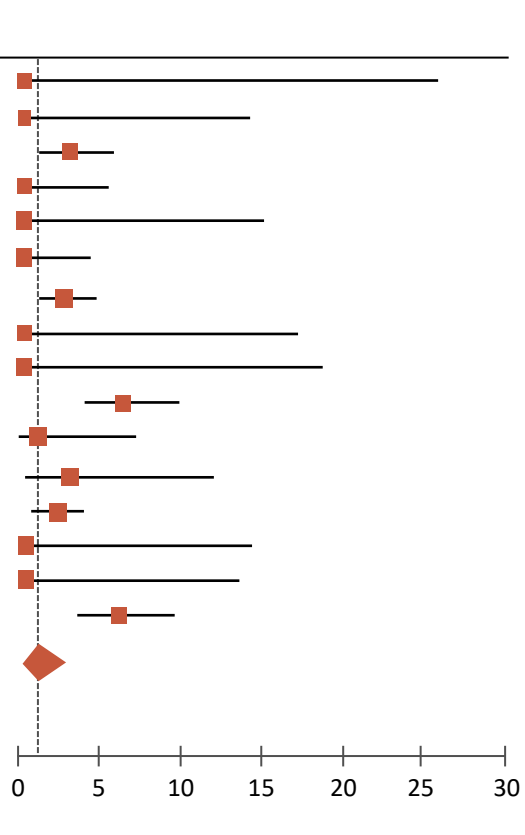
Test for overall effect Z = 0.50 (p=0.62)



Thrombotic events in cohort studies

Study ID	N of events/ N of patients	Rate (%) (95% CI)
Almaguer 2014	0/12	0.0 (0.0-26.5)
Bussel 2006 phase 1	0/24	0.0 (0.0-14.2)
Bussel 2009	5/142	3.5 (1.2-8.0)
Bussel 2013	0/66	0.0 (0.0-5.4)
Bussel 2015 cohort	0/22	0.0 (0.0-15.4)
Grainger 2015 ext	0/79	0.0 (0.0-4.6)
Janssens 2015	11/407	2.7 (1.4-4.8)
Katsutani 2013	0/19	0.0 (0.0-17.6)
Kim 2015	0/18	0.0 (0.0-18.5)
Kuter 2013	19/291	6.5 (4.0-10.0)
Newland 2016	1/75	1.3 (0.0-7.2)
Shirasugi 2012	1/44	2.3 (0.1-12.0)
Steurer 2017	7/340	2.1 (0.8-4.2)
Tomiyama 2012 ext	0/23	0.0 (0.0-14.8)
Triphati 2014	0/25	0.0 (0.0-13.7)
Wong 2017	19/302	6.3 (3.8-9.7)
Overall		**1.4 (0.5-2.7)**

Heterogeneity: p=0.008); $I^2 = 46.1\%$



Incidence of arterial or venous thrombosis in patients treated with TPO-RA was 2.42%; RR 1.47 (95% CI, 0.61-3.53)

CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel statistic; RCT, randomised clinical trial; RR, risk ratio; TPO-RA, thrombopoietin receptor agonist

Birocchi, S et al. Platelets. 2021;32(2):216-226

THROMBOEMBOLISM

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It seems that TPO-RAs increase the risk of VTE

Thrombosis during use of TPO-RAs is not related to:

- Type and dose of TPO-RA
- Duration of treatment
- Platelet count

Individual risk profile should be considered when initiating treatment with TPO-RA

- Previous thromboembolism, splenectomy, presence of antiphospholipid antibodies and concomitant medications like oestroprogestinic preparations, and corticosteroids

TPO-RA, thrombopoietin receptor agonist; VTE, venous thromboembolism
Rodeghiero F, et al. Am J Hematol. 2016;91:39-45

DOES THE PATIENT NEED TO CONTINUE ON TPO-RA INDEFINITELY?

TPO-RA, thrombopoietin receptor agonist

REMISSION AND PLATELET RESPONSES WITH ROMIPLOSTIM IN PRIMARY ITP: A PHASE 2 STUDY

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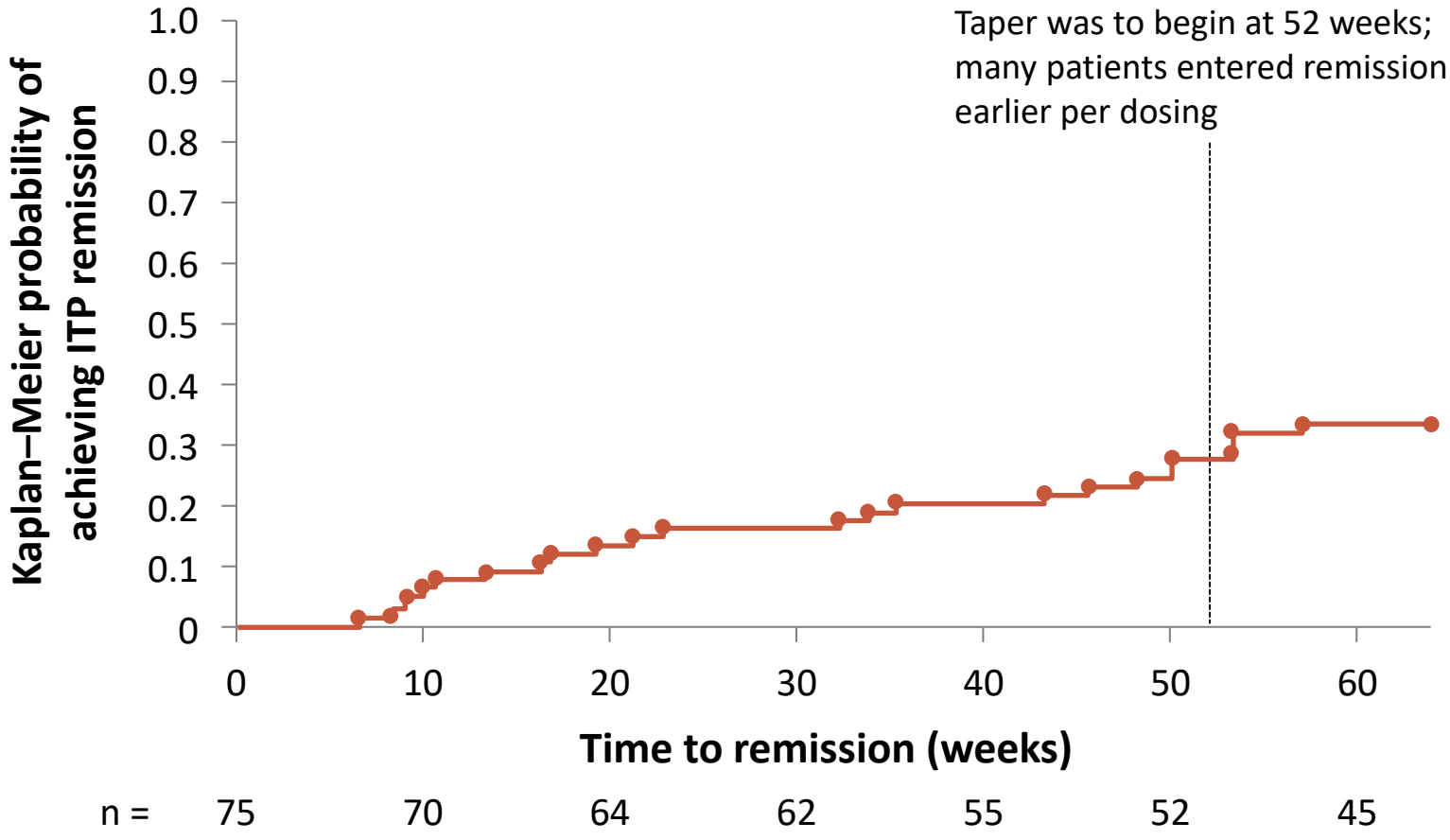
- N=75
- **Response** achieved in 70 patients (93%)
- **Remission** observed in 24 patients (32%)



No significant predictors of remission identified

ITP, immune thrombocytopenia

Newland A, et al. Br J Haematol. 2016;172:262-73

PHASE 2 STUDY ON 2ND-LINE ELTROMBOPAG IN ADULTS WITH PRIMARY ITP, AIMING TO ACHIEVE SUSTAINED REMISSION OFF TREATMENT

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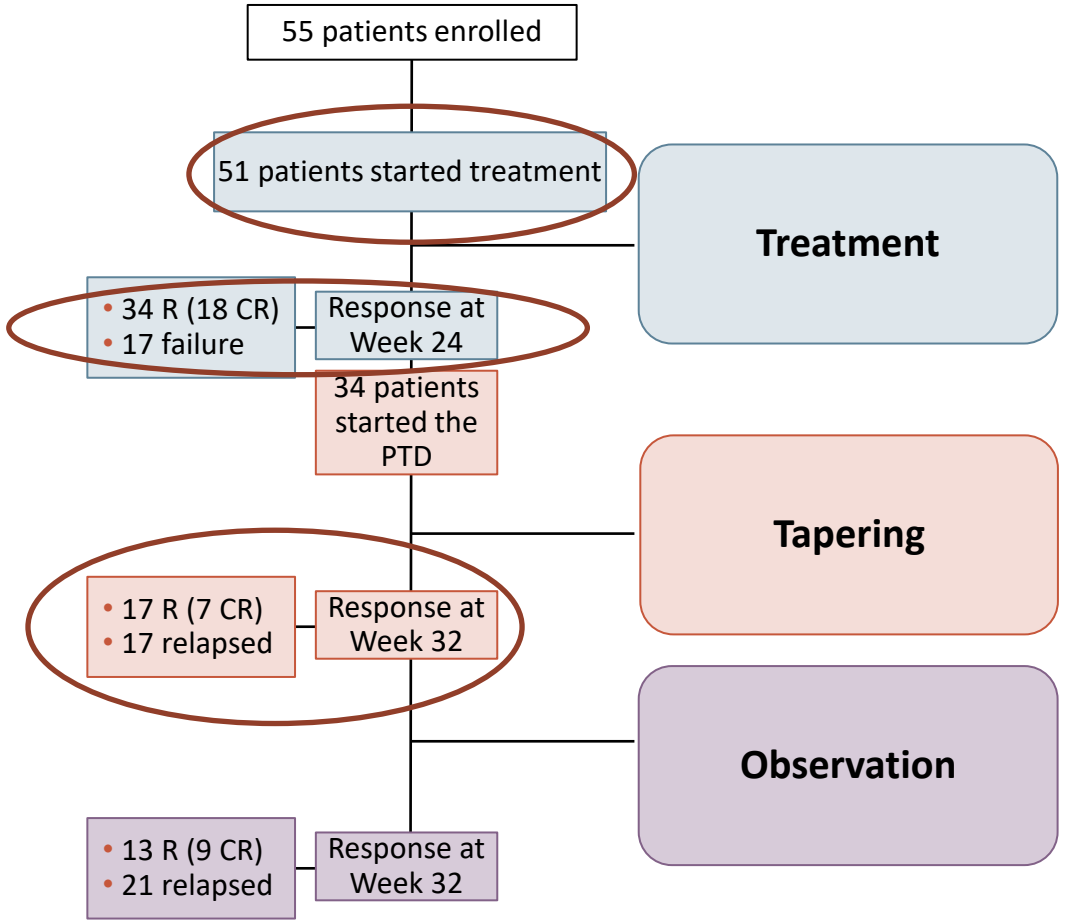

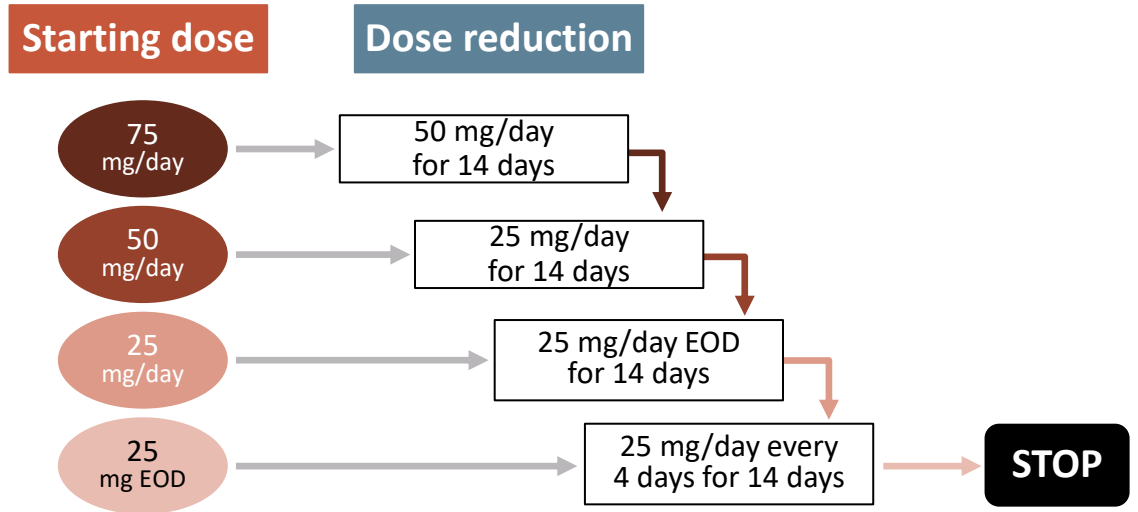

Primary end-point: sustained remission off-treatment

(proportion of responders that were able to taper and discontinue eltrombopag maintaining the response for 6 months)

AE, adverse event; CR, complete response; EOD, every other day; ITP, immune thrombocytopenia; PO, period of observation; SAE, serious AE; wk, week

Lucchini E, et al. Br J Haematol. Published online Feb 22, 2021. doi: 10.1111/bjh.17334

SUSTAINED REMISSION OFF-TREATMENT WAS ACHIEVED IN 25%

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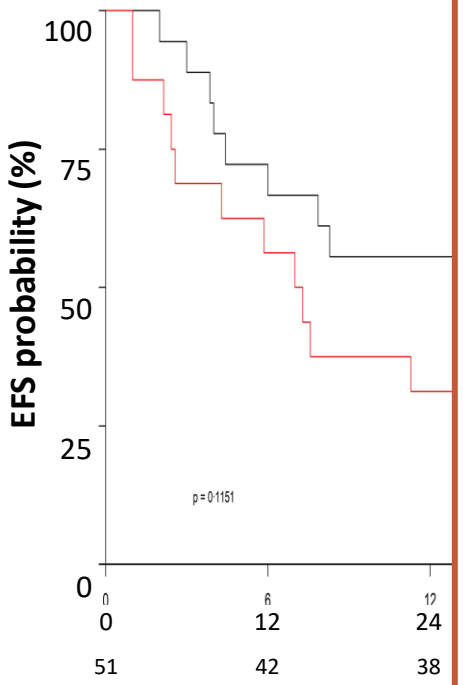
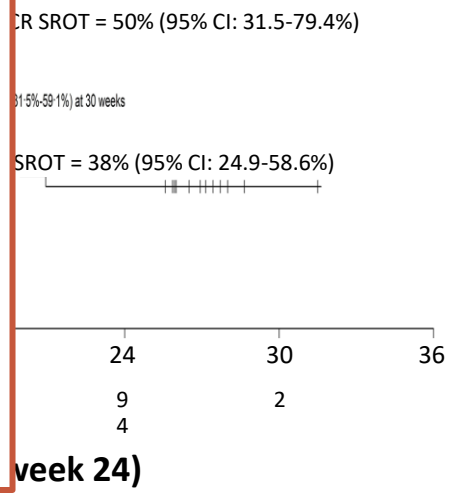


- No association between baseline TPO level and response at week 24 or the achievement of SROT was observed!
- No mark



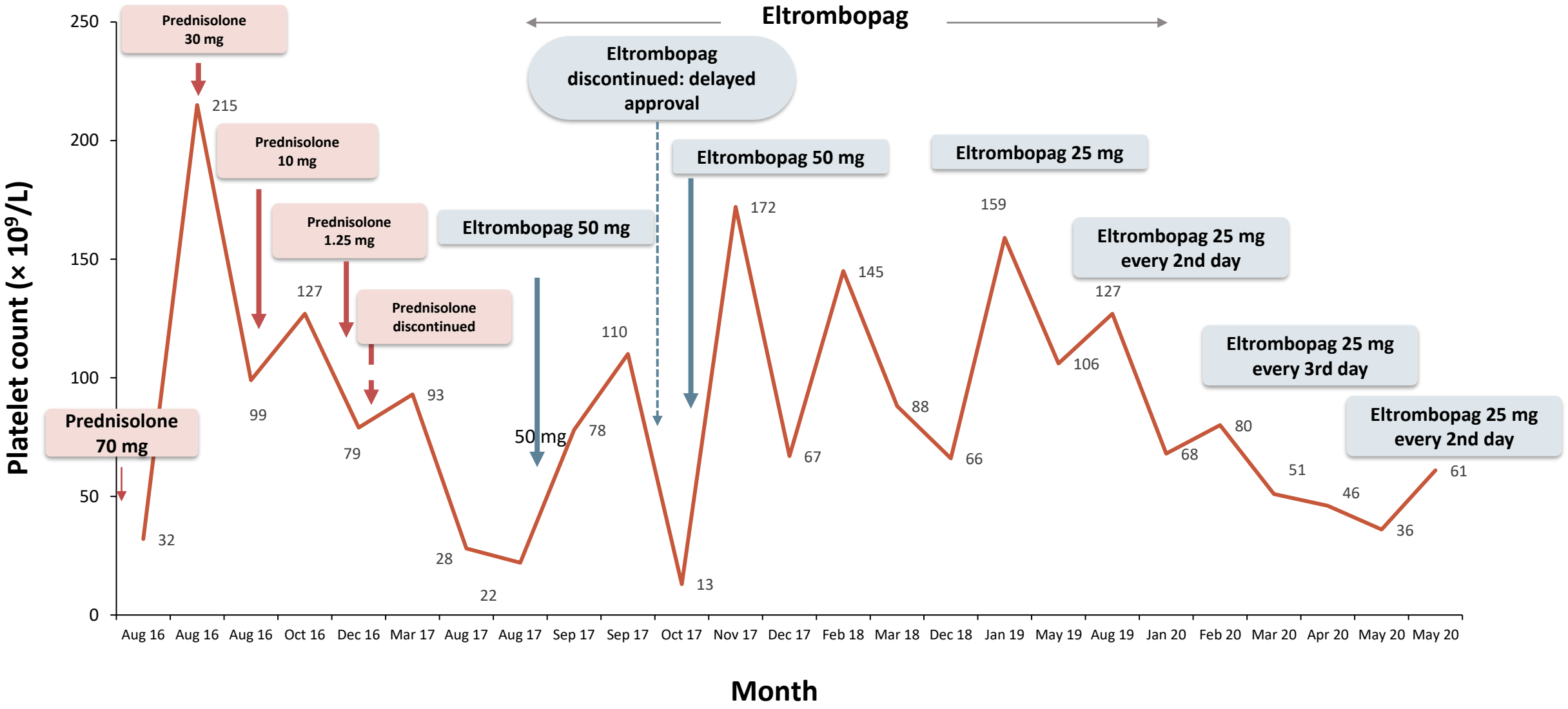
Event-free survival of all 51 evaluable
The majority of patients relapsed during PTD (week 25-32)

e-free survival in patients who started tapering and discontinuation and continued in the period of observation

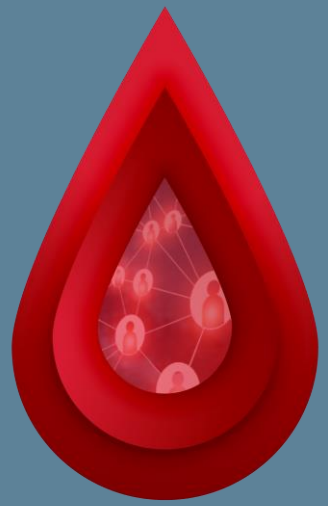
CI, confidence interval; CR, complete response; EFS, event-free survival; RFS, relapse-free survival; SROT, sustained remission off-treatment

Lucchini E, et al. Br J Haematol. Published online Feb 22, 2021. doi: 10.1111/bjh.17334

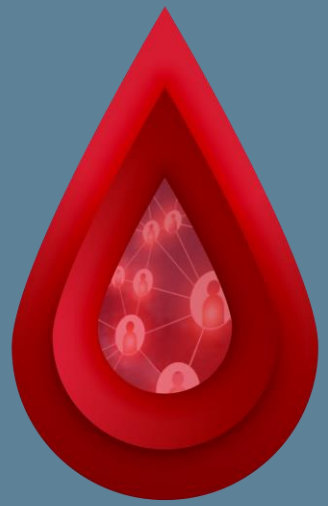
CASE



Slide courtesy of Waleed Ghanima



QUESTIONS AND CONCLUSIONS



THANK YOU

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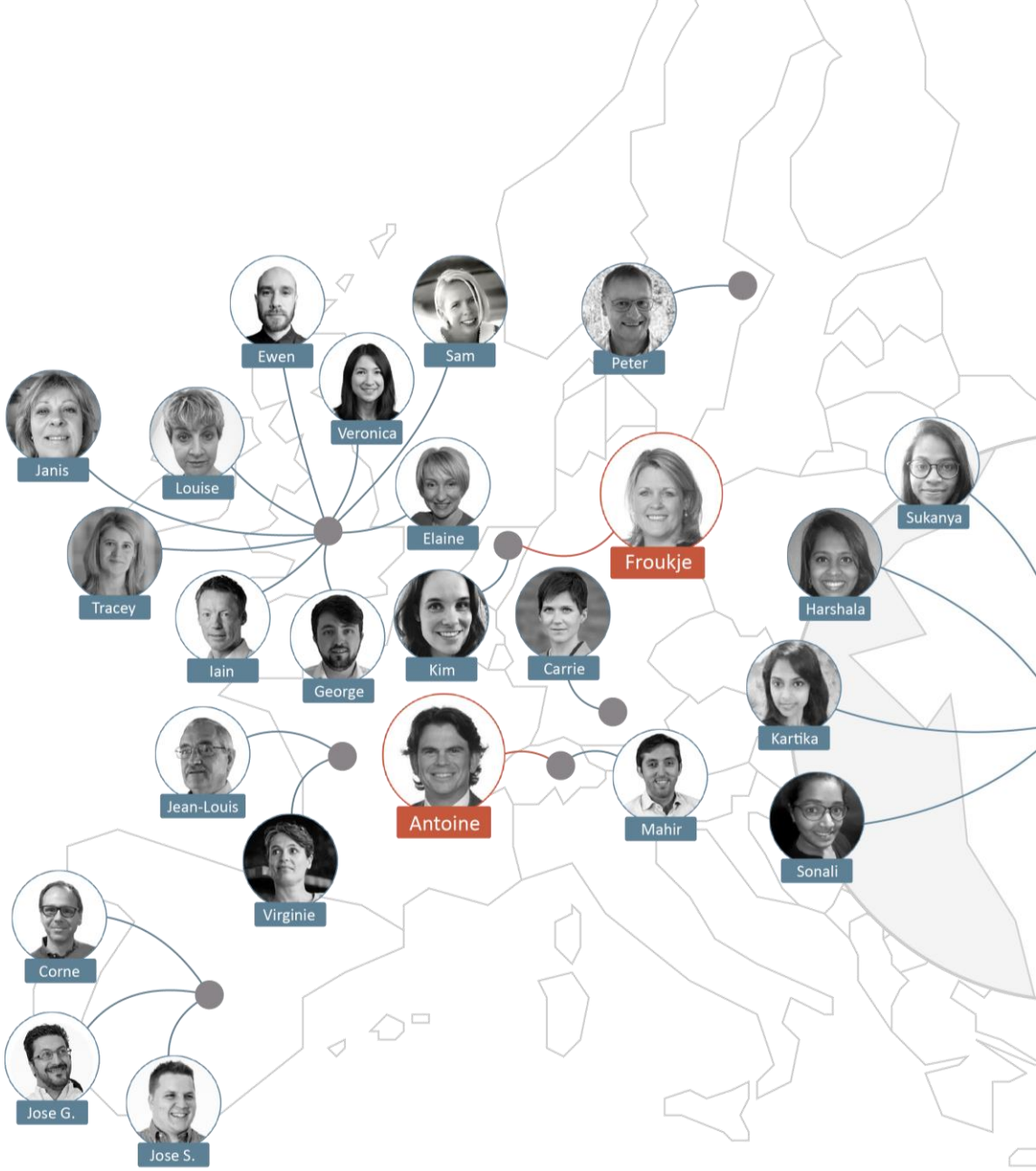

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