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EXPERTS KNOWLEDGE SHARE

PRACTICAL CONSIDERATIONS AROUND THE USE OF THROMBOPOIETIN-RECEPTOR ANTAGONISTS (TPO-RAs) IN IMMUNE THROMBOCYTOPENIA (ITP)

Dr. Hillary Maitland, Dr. Michael Tarantino, and Dr. Vickie McDonald

Friday December 11th, 2020

EXPERTS KNOWLEDGE SHARE

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THE OBJECTIVE OF THIS MEETING IS TO DISCUSS PRACTICAL CONSIDERATIONS AROUND THE USE OF TPO-RAs IN ITP

YOUR OPPORTUNITY TO **DISCUSS AND SHARE LEARNINGS** ON A CHALLENGING TOPIC WITHIN THE AREA OF ITP

A CHANCE TO HEAR THE **VIEWS OF EXPERTS** AND ALLOW THEM TO ANSWER THE QUESTIONS THAT ARE IMPORTANT TO YOU

REVIEW AND DISCUSS **PATIENT CASE STUDIES**, USING THE QUESTIONS THAT YOU HAVE SENT IN ADVANCE OF THIS EVENT

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

EXPERTS KNOWLEDGE SHARE EDUCATIONAL OBJECTIVES

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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

INTRODUCING THE SCIENTIFIC COMMITTEE

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Hillary Maitland

University of Virginia, Charlottesville, VA, USA

Michael Tarantino

University of Illinois College of Medicine-Peoria, IL, USA

Vickie McDonald

Royal London Hospital, London, United Kingdom

DISCLAIMER

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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

EXTENDING THE REACH FOR THOSE NOT ABLE TO ATTEND TODAY

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Newsletter

e-learning

Newsletter #1:
Summarising video and slides from EKS

Newsletter #2:
Link to e-learning:

- Videos, Slides and Supporting reading material
- Assessment test to obtain continuing medical education (CME) credit

EXPERTS KNOWLEDGE SHARE AGENDA

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PRACTICAL CONSIDERATIONS AROUND THE USE OF TPO-RAs IN ITP

Time	Topic	Facilitator
5 minutes	Welcome and introductions	Iain Murdoch and Kim Grootscholten (COR2ED)
5 minutes	Overview and scene setting	Hillary Maitland
15 minutes	Initiation of treatment for ITP	Hillary Maitland
15 minutes	Monitoring safety and efficacy	Michael Tarantino
15 minutes	Long-term remission, tapering and adjusting treatment	Vickie McDonald
5 minutes	Lead-in to breakout sessions	Iain Murdoch (COR2ED)
25 minutes	Three breakout sessions Groups discussing questions and case studies and sharing experience	All
5 minutes	Closing remarks	Michael Tarantino and Iain Murdoch (COR2ED)

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

INITIATION OF TREATMENT FOR ITP

Dr. Hillary Maitland, MD
University of Virginia, Charlottesville, VA, USA

DISCLOSURES

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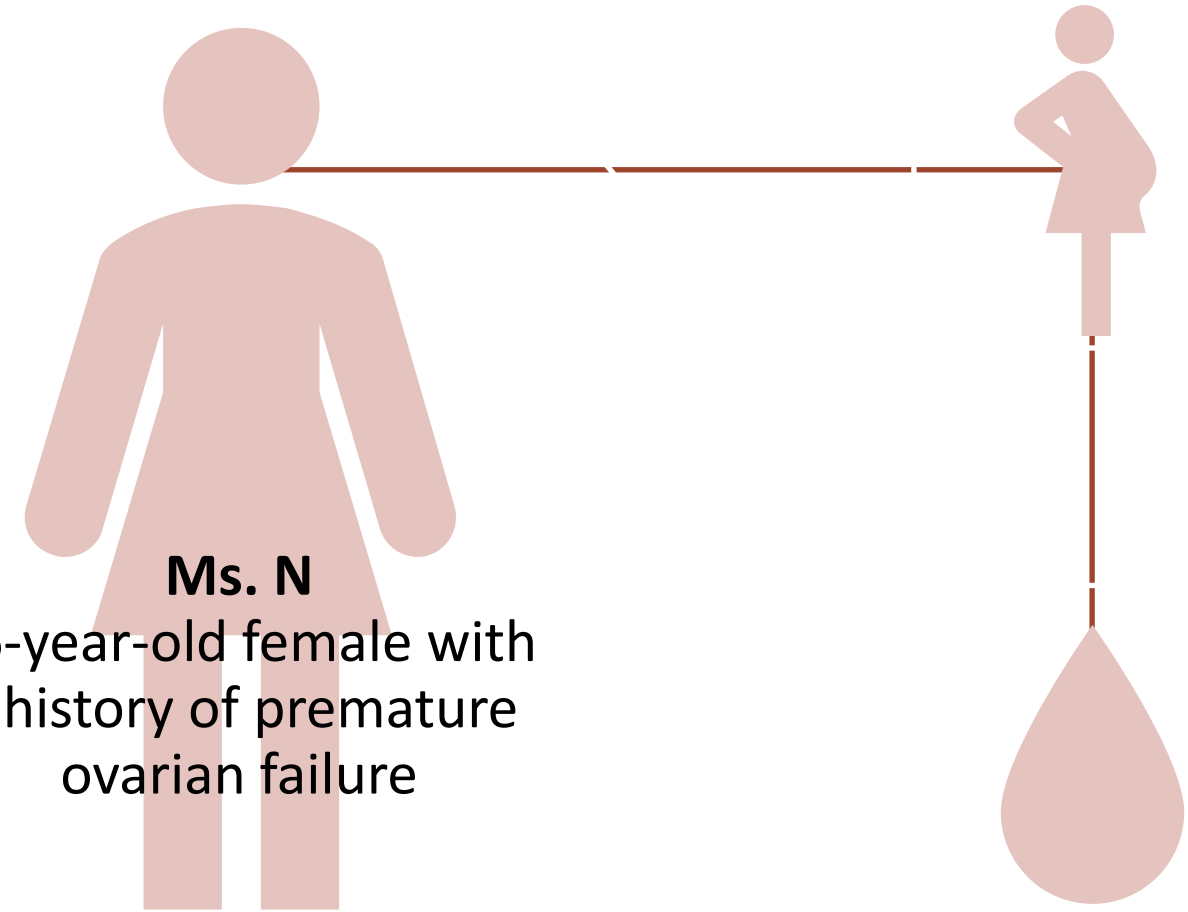
- Grants/honoraria from Dova and Sanofi

CASE



Ms. N
36-year-old female with a history of premature ovarian failure

She underwent in vitro fertilization (IVF) with a donor egg and delivered her daughter in January

In May she developed gingival bleeding and easy bruising and was found to have a platelet count of 8k

IVF, in vitro fertilisation

INITIAL TREATMENT OF ITP

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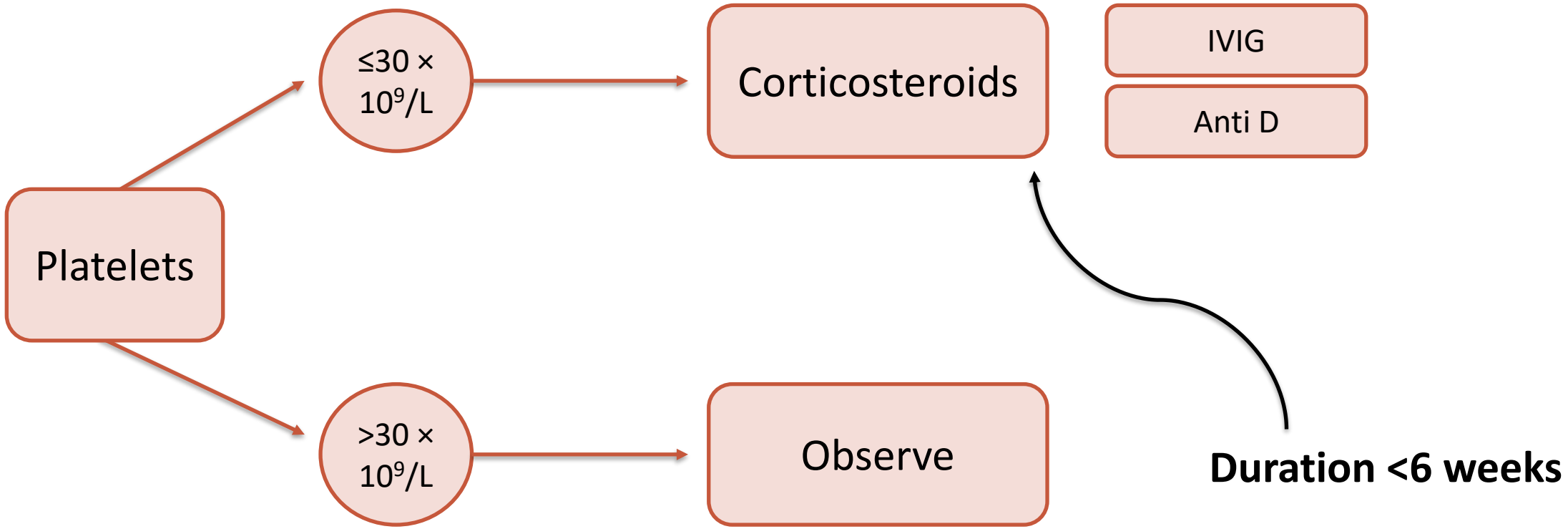
ASH GUIDELINES



Anti-D, anti-rhesus-D immunoglobulin; ASH, American Society of Hematology; ITP, immune thrombocytopenia; IVIG, intravenous immunoglobulin

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

DEXAMETHASONE OR PREDNISONE?

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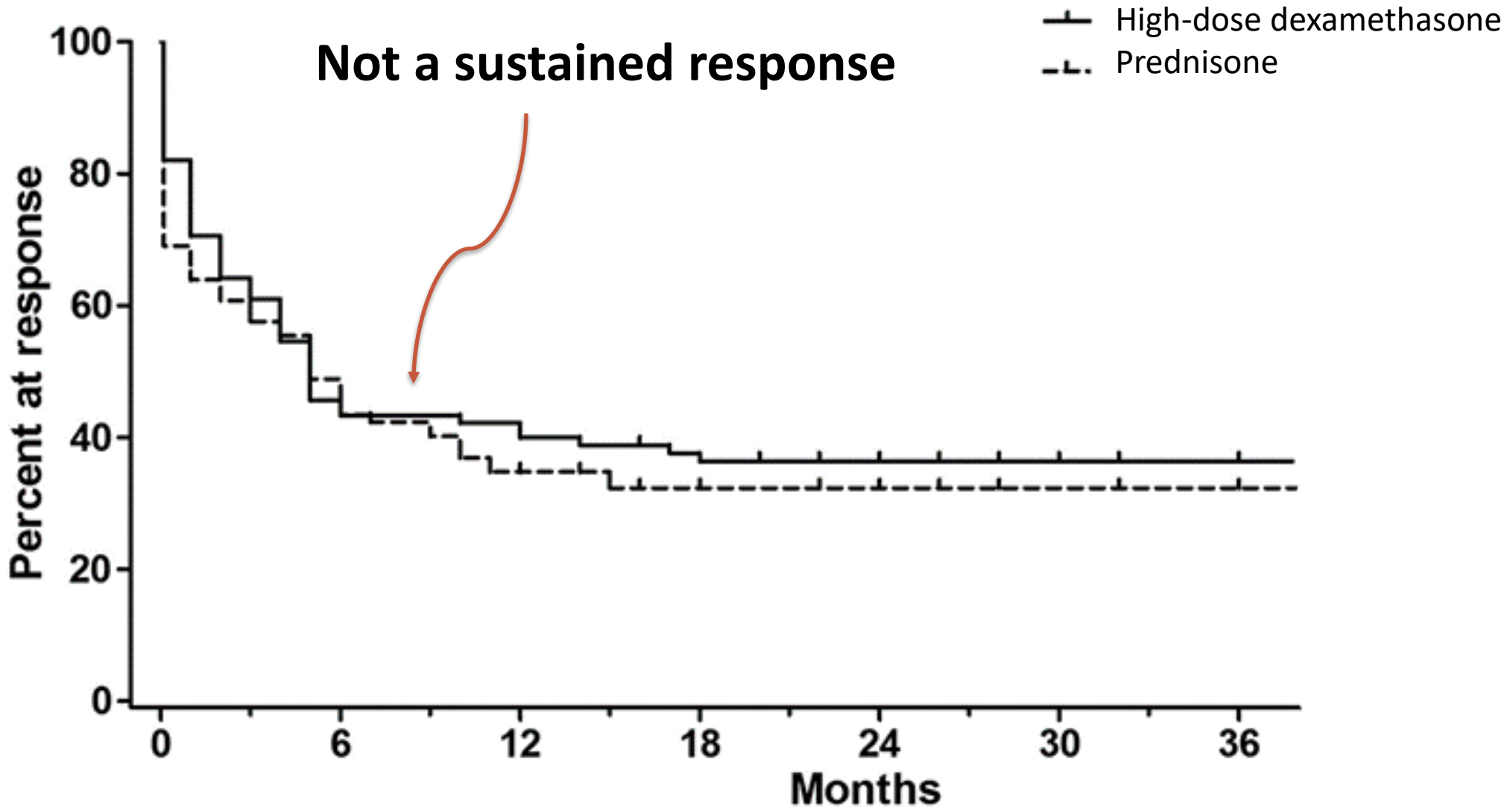
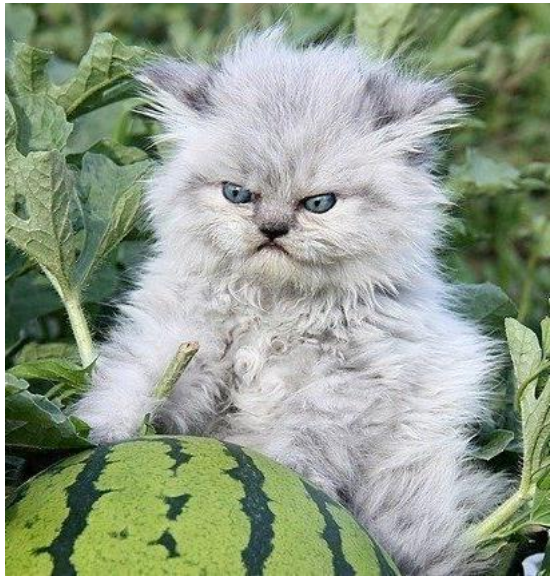


Wei Y, et al. Blood. 2016;127:296-302

CASE

- Ms. N gets dexamethasone 40 mg daily for 4 days
- Her platelet count normalises
- One month later platelet count is 23k



SECOND-LINE THERAPY

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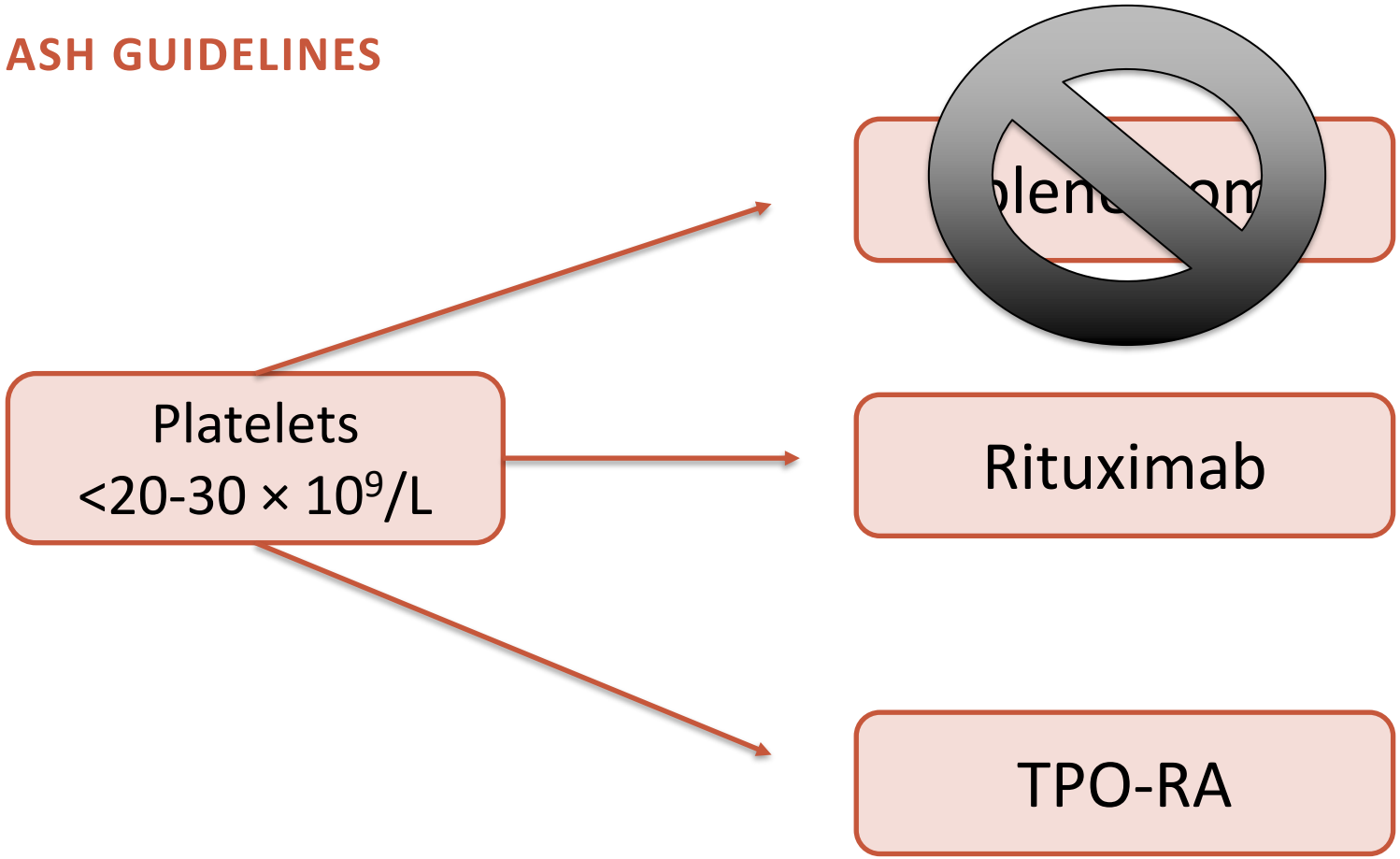

No splenectomy until 1 year out

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

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

RITUXIMAB

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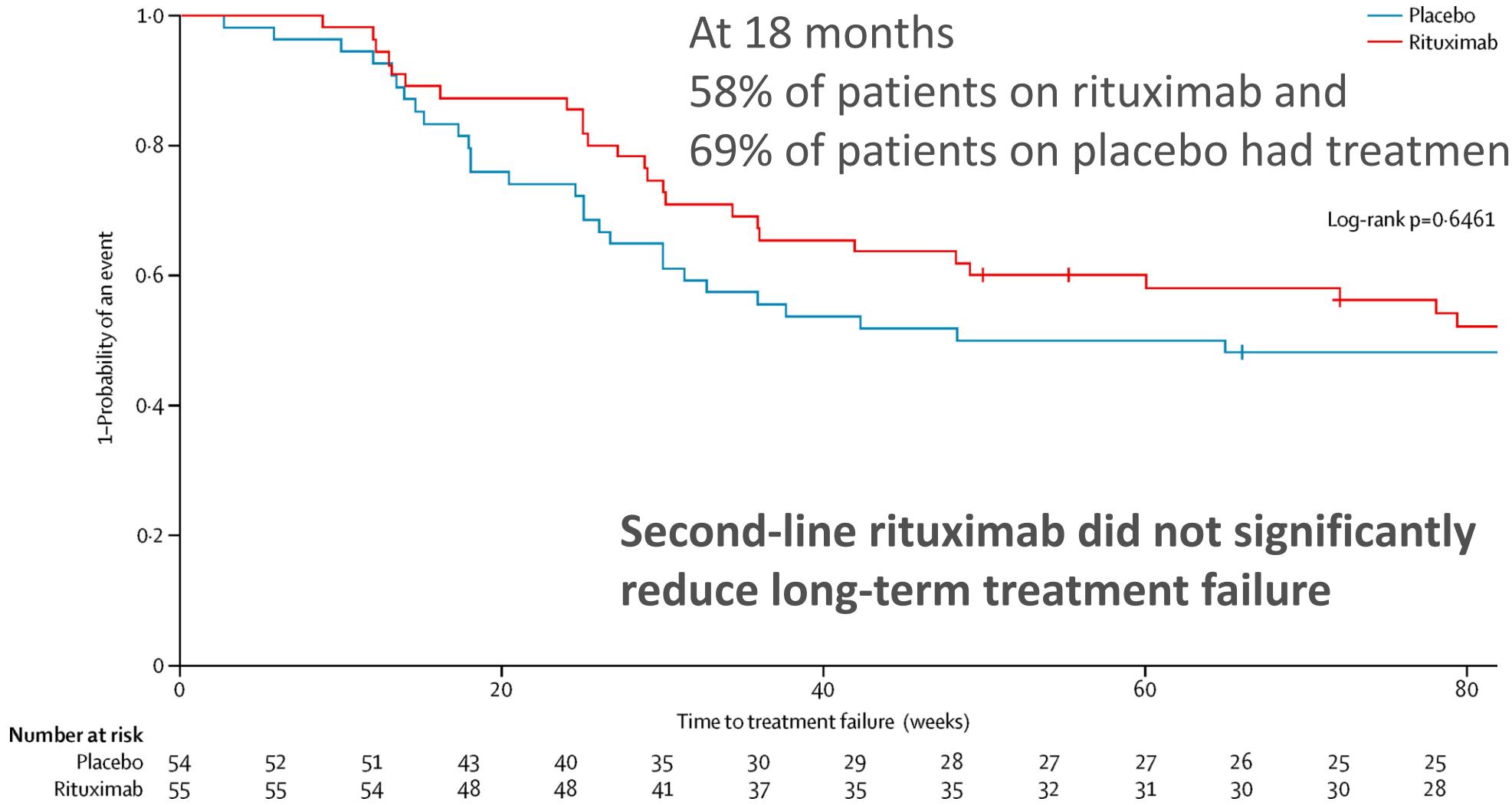

At 18 months
58% of patients on rituximab and
69% of patients on placebo had treatment failure

Second-line rituximab did not significantly reduce long-term treatment failure

Ghanima W, et al. Lancet. 2015;385:1653-61

SECOND-LINE THERAPY

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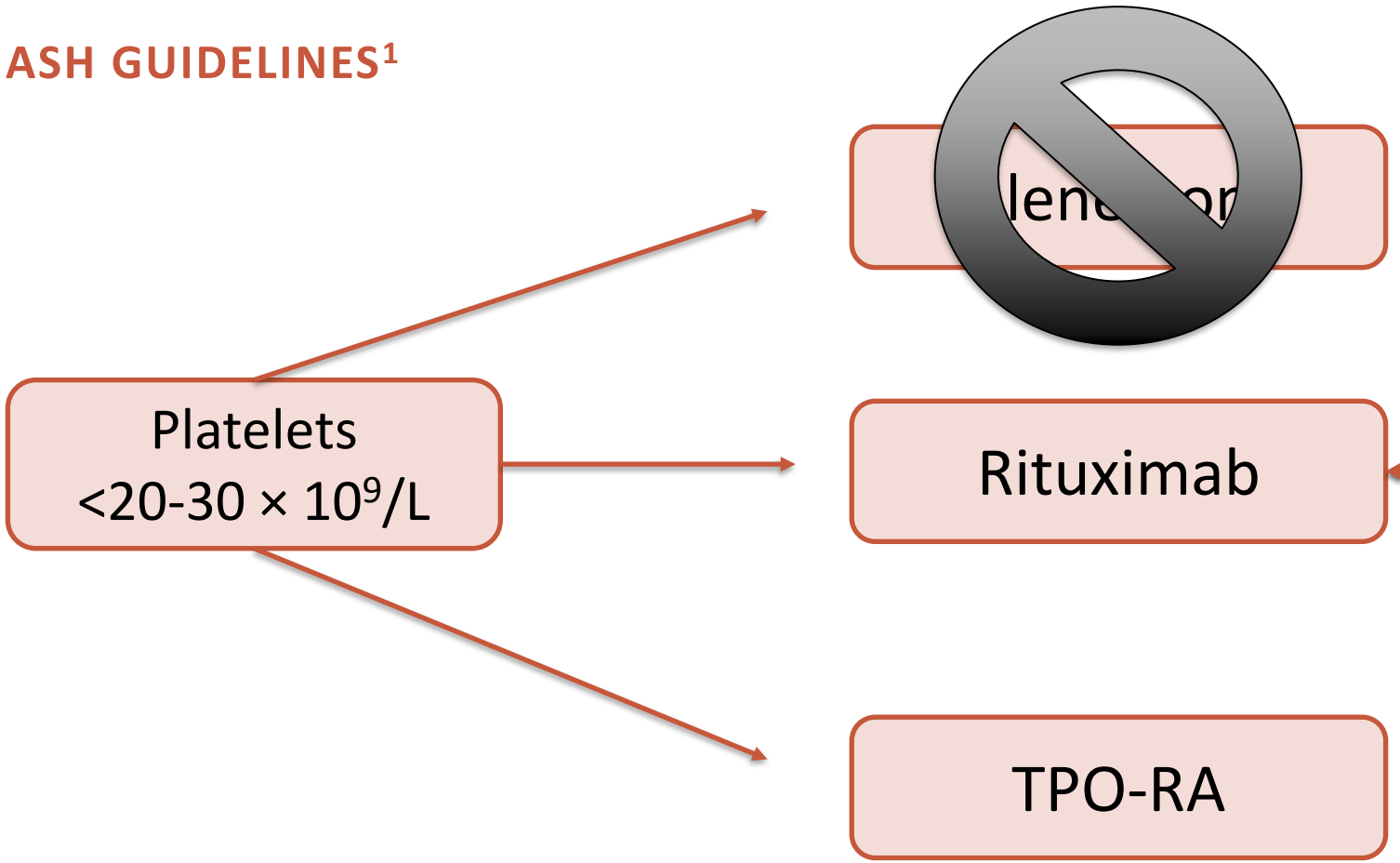
ASH GUIDELINES[1]



Appropriate for patients who want to avoid long-term medication, high risk of relapse[2]

Most beneficial in women <40 years old[3]

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

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

CASE

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- Ms. N decides to start rituximab
- During her first infusion she develops itching and tachycardia, so the infusion is stopped
- Platelets are now 19k

SECOND-LINE THERAPY

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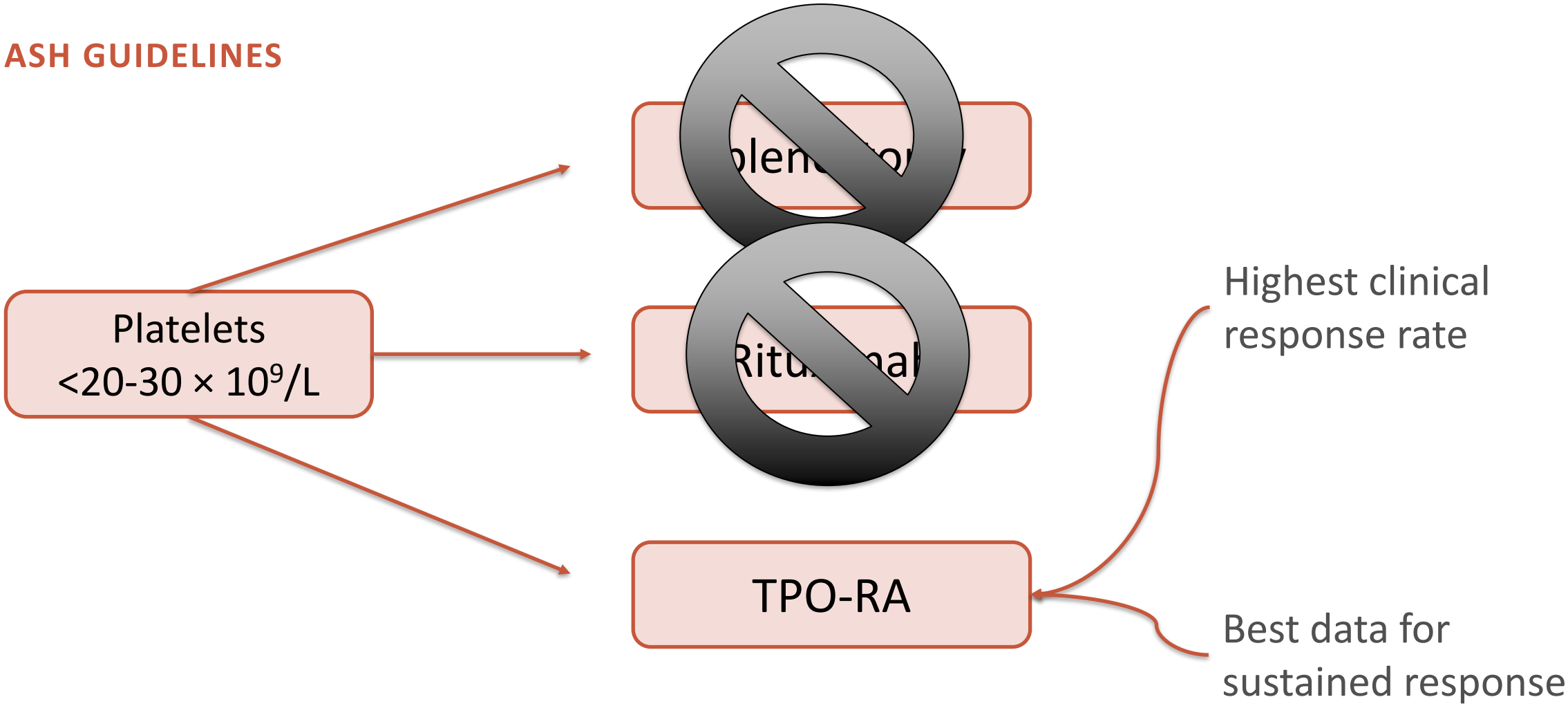
ASH GUIDELINES



TPO-RA, thrombopoietin receptor agonist

1. Neunert C, et al. Blood Adv. 2019;3:3829-66; 2. Cooper N and Ghanima W. N Engl J Med. 2019;381:945-55

THROMBOPOIETIN RECEPTOR AGONISTS

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	Romiplostim	Eltrombopag	Avatrombopag
Dosing			
Starting dose	1 µg/kg/week (label) 3 µg/kg/week (realistic) 5 µg/kg/week (severe)	50 mg daily 25 mg daily (Asian patients)	20 mg daily
Min/max dose	10 µg/kg/week 1 µg/kg/week	75 mg/day (150 mg approved for AA) 12.5 mg/day	40 mg/day 20 mg/week
Route	Subcutaneously once weekly	Oral, daily	Oral, daily
Administration considerations	Can patient self-administer injections Increased monitoring Cost (+/-)	Timing in relation to food containing calcium	Taken with any food
Safety considerations	Well tolerated, low AEs Increased platelet variability	Well tolerated, low AEs Hepatotoxicity Less bleeding events	Well tolerated, low AEs Headache Newer drug

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

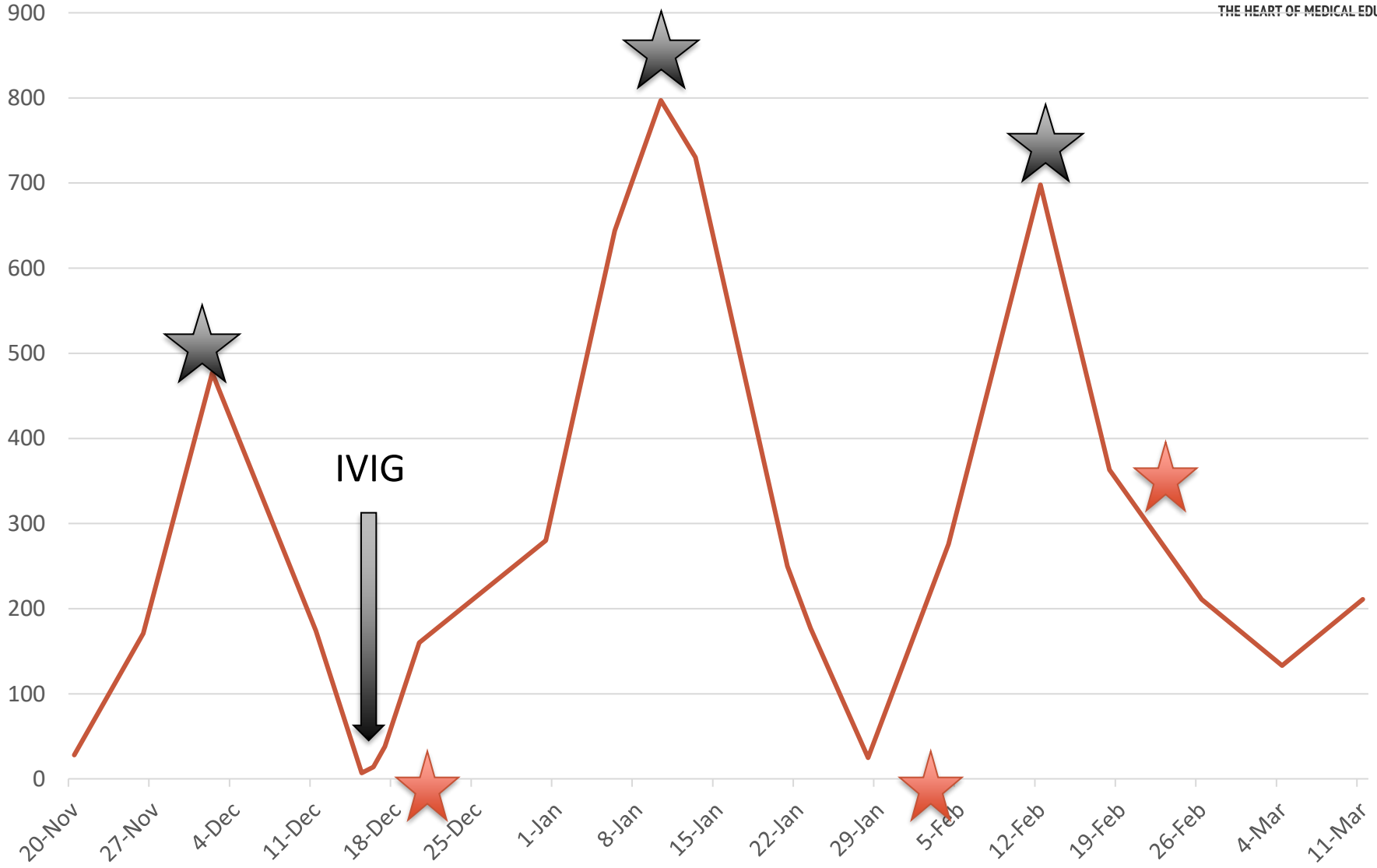
Forsythe A, et al. J Comp Eff Res. 2020;9:447-57; Al-Samkari H and Kuter DJ. Ther Adv Hematol. 2019;10:2040620719841735. Nplate (romiplostim) Prescribing Information. Promacta (eltrombopag) Prescribing Information. Doptelet (avatrombopag) Prescribing Information.

We start Ms. N on avatrombopag 20 mg daily

CASE

Hold

Restart at reduced dose



IVIG, intravenous immunoglobulin

SUMMARY
THROMBOPOIETIN RECEPTOR AGONISTS

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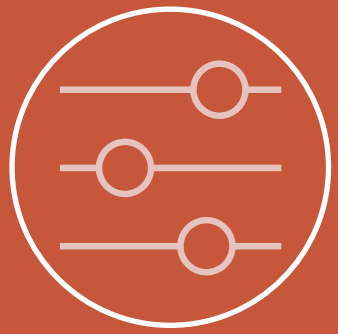
Try to limit steroid exposure to <6 weeks



Choice of second-line treatment is based on patient preference

TPO-RAs have similar efficacy and safety profiles

TPO-RA, thrombopoietin receptor agonist

MONITORING SAFETY AND EFFICACY OF TPO-RAs

Michael Tarantino, MD
CEO, CMO and President
Bleeding and Clotting Disorders Institute
Professor of Pediatrics and Medicine
University of Illinois College of Medicine-Peoria, IL, USA

DISCLOSURES

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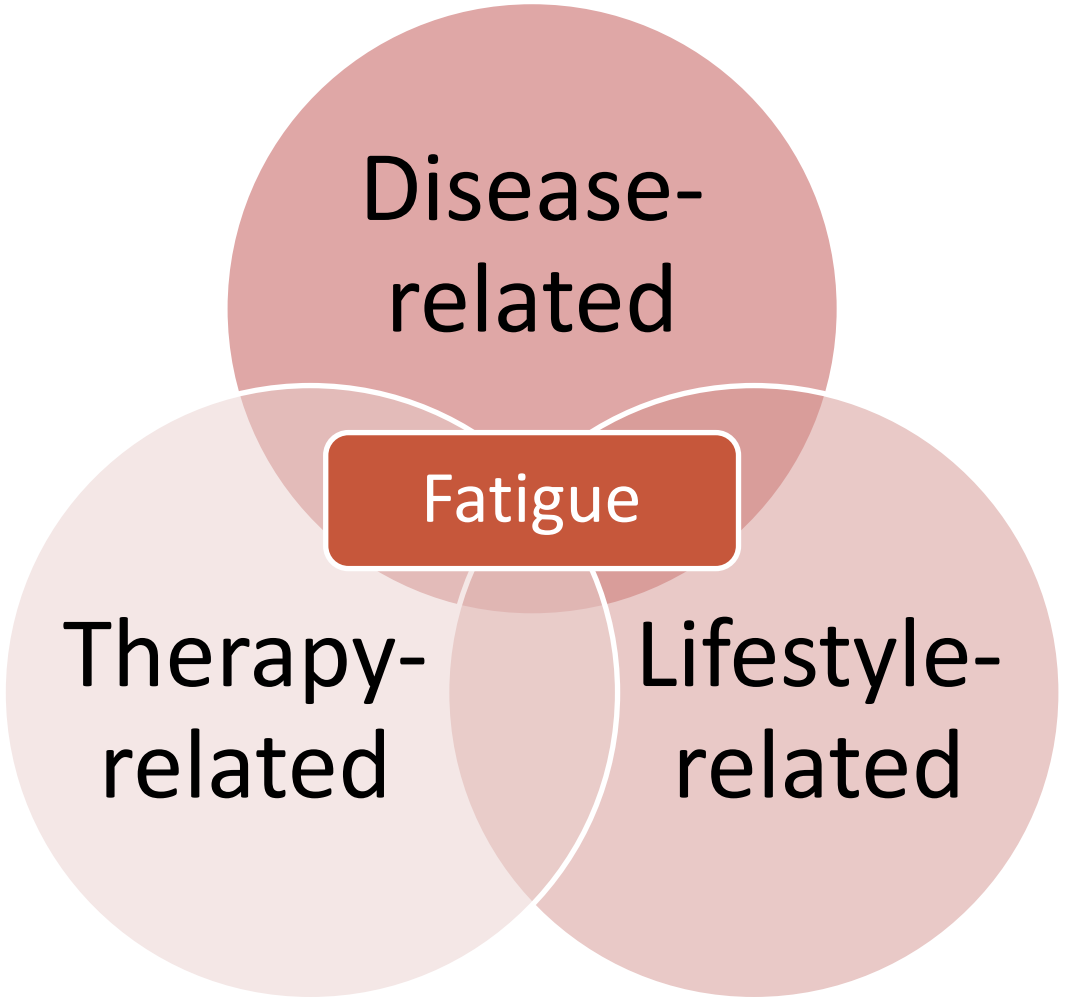
- Honoraria/Grants from Amgen, Biogen, BioMarin, Genentech, Grifols, Hemabiologics, Novartis, NovoNordisk, Octapharma, Pfizer, Principia, Rigel, Spark Therapeutics, Sobi and Takeda

CLINICAL CONSEQUENCES OF ITP

MORBIDITY



TPO-RAs: THE MANY DEFINITIONS OF RESPONSE

MONITORING OBJECTIVES

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Quantitative

- Platelet count
  - Rate of response (durable, overall, any)
  - Height of response (median, mean platelet counts)
  - Time to response
  - Durability of response (% of time [weeks] with response)
  - Odds of response (compared with placebo or SOC)

Qualitative

- Bleeding prevention or cessation
  - Determining the hemostatic range for platelet count
    - In clinical trials, 50-200 × 10^9/L
    - Real world: tailored to individual patient
- Discontinuation of concomitant medications
- Fatigue and other QoL improvement

QoL, quality of life; SOC, standard of care; TPO-RA, thrombopoietin receptor agonist

ASSESSING RESPONSE TO ITP TREATMENTS

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Quality of response

- CR: platelet count ≥100 × 10^9/L and absence of bleeding
- R: platelet count ≥30 × 10^9/L and at least 2-fold increase the baseline count and absence of bleeding
- NR: platelet count <30 × 10^9/L or less than 2-fold increase of baseline platelet count or bleeding

Duration of response

- Measured from the achievement of CR or R to loss of CR or R

Corticosteroid dependence

- The need for ongoing or repeated doses administration of corticosteroids for at least 2 months to maintain a platelet count at or above 30 × 10^9/L and/or to avoid bleeding (patients with corticosteroid dependence are considered non-responders)

CR, complete response; ITP, immune thrombocytopenia; NR, no response; R, response

Adapted from: Rodriguero F, et al. Blood. 2009;113:2386-93

EVALUATION OF BLEEDING EVENTS DURING LONG-TERM USE OF ROMIPLOSTIM IN PATIENTS WITH CHRONIC ITP

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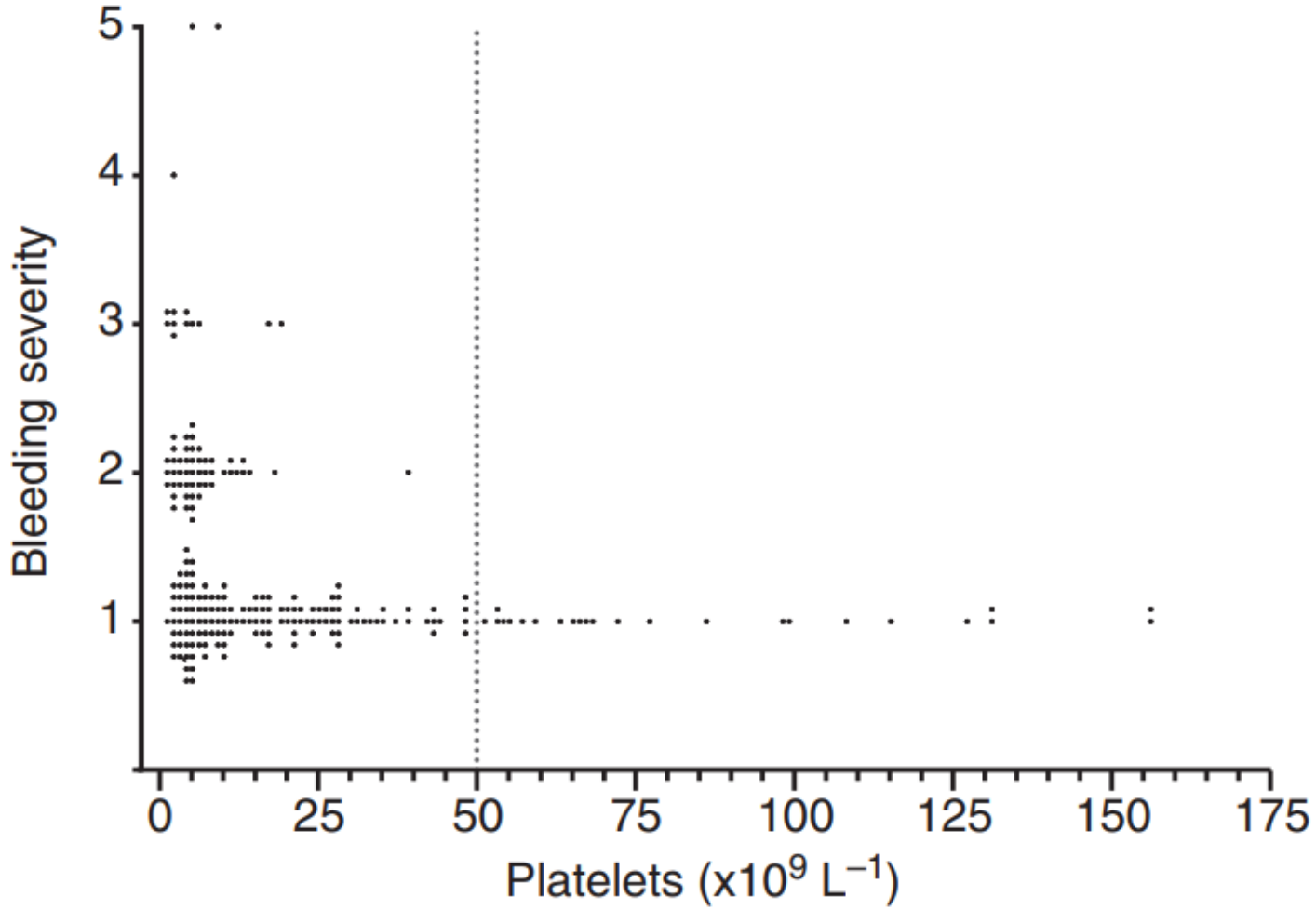

ITP, immune thrombocytopenia

Gernsheimer TB, et al. J Thromb Haemost. 2010;8:1372-82

ADMINISTRATION AND DOSING OF THE TPO-RAS

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Name	Maker	Molecule	Route of administration	Approved starting dose
Romiplostim	Amgen	Peptibody	Subcutaneous	1 mcg/kg
Eltrombopag	Novartis	Small molecule	Oral	50 mg/day*
Avatrombopag	Sobi/Dova	Small molecule	Oral	20 mg/day

**starting dose for patients of Asian ancestry and children 1 to <6 years of age is 25 mg/day*

TPO-RA, thrombopoietin receptor agonist
Adapted from: Tarantino, MD, Chalmers S. Therapeutic Thrombopoietin Mimetics. In: Platelets in Thrombotic and Nonthrombotic Disorders: Pathophysiology, Pharmacology and Therapeutics. 2nd Edition. Cambridge University Press. Gresele P, et al, eds. 2016, pp 1417-29

PRIMARY OUTCOME IN PIVOTAL TRIALS OF TPO-RAs

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Agent	Platelet response metric
Romiplostim[1]	**Durable Response:** platelet count ≥50 × 10^9/L during 6 or more of the last 8 weeks of treatment
Eltrombopag[2]	**Odds of response** to eltrombopag versus placebo
Avatrombopag[3]	**Cumulative number of weeks of platelet response** (platelet count ≥50 × 10^9/L) without rescue therapy for bleeding

TPO-RA, thrombopoietin receptor agonist

1. Kuter KJ, et al. Lancet. 2008;371:395-403; 2. Cheng G, et al. Lancet. 2011;377:379-402; 3. Jurczak W, et al. Br J Haematol. 2018;183:479-90

ADDITIONAL EFFICACY METRICS FOR TPO-RAs FOR CHRONIC ITP

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Drug	Dose	Response rate		Selected toxicities
		Rate	Time to	
Rituximab[1]	375 mg/m^2 IV weekly × 4	60% overall 40% CR 20-25% at 5 years	1-8 weeks	Infusion reactions, serum sickness, HBV reactivation, PML (rare)
Romiplostim[1]	**1-10 µg/kg SC weekly**	**80% overall 40-50% persistent**	**1-4 weeks**	**Reticulin fibrosis, rebound thrombocytopenia, thrombosis**
Eltrombopag[1]	**25-75 mg PO daily**	**80% overall 40-50% persistent**	**1-2 weeks**	**Reticulin fibrosis, rebound thrombocytopenia, thrombosis, hepatotoxicity**
Avatrombopag[2]	**20 mg PO weekly – 40 mg PO daily**	**66% overall (day 8) 34% durable**	**1-2 weeks**	**HA, URI, thrombosis (class effect), rebound thrombocytopenia**
Fostamatinib[3]	100-300 mg PO daily	44% overall 17% durable	2 weeks	HTN, transaminitis, hyperbilirubinemia, neutropenia

CR, complete response; HA, headache; HBV, hepatitis B virus; HTN, hypertension; ITP, immune thrombocytopenia; IV, intravenous; PML, progressive multifocal leukoencephalopathy; PO, orally; SC, subcutaneous; TPO-RA, thrombopoietin receptor agonist; URI, upper respiratory infection

1. Adapted from: Cuker A and Neunert CE. Blood. 2016;128:1547-54; 2. Jurczak W, et al. Br J Haematol. 2018;183:479-90; 3. Bussel JB, et al. Am J Hematol. 2019;94:546-53

APPROXIMATE TIME TO RESPONSE FOR SECOND-LINE ITP TREATMENTS

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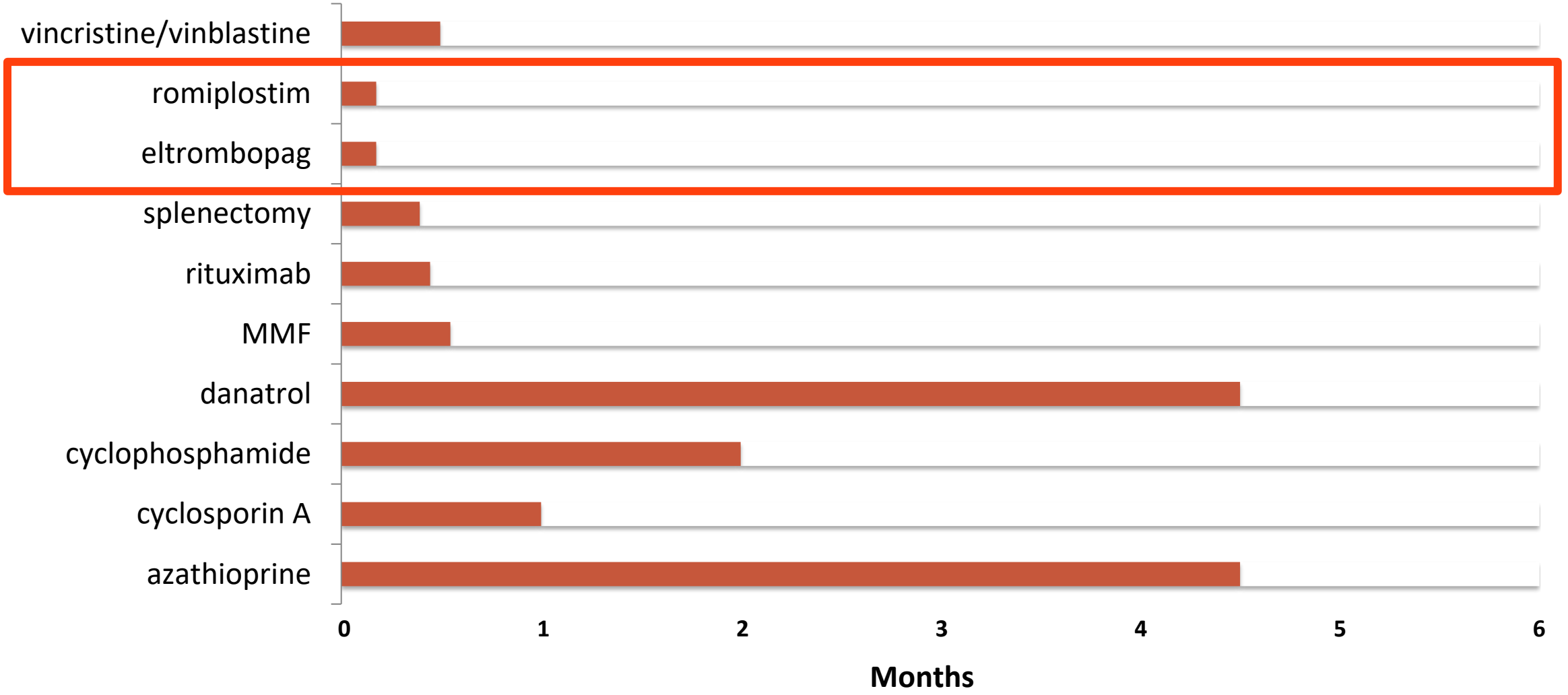

ITP, immune thrombocytopenia; MMF, mycophenolate mofetil

Provan D, et al. Blood. 2010;115:168-86

DOSE ADJUSTMENT ALGORITHMS FOR TPO-RAs
ROMIPLOSTIM

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- The starting dose: 1 µg/kg
- Target 50-200 × 10^9/L:
  - If platelet count 10 × 10^9/L or less: increase dose by 2 µg/kg every week
  - If platelet count 11-50 × 10^9 increase by 2 µg/kg every 2 weeks
  - If platelet count >50 × 10^9/L, the maintenance algorithm was used:
    - increased by 1 µg/kg every week if 10 × 10^9/L or less
    - increased by 1 µg/kg after 2 weeks if 11 to 50 × 10^9/L
    - reduced by 1 µg/kg after 2 consecutive weeks at 201 to 400 × 10^9/L
    - withheld if >400 × 10^9/L and subsequent doses reduced by 1 µg/kg and given after count was less than 200 × 10^9/L
- The maximum allowed dose was 15 µg/kg

TPO-RA, thrombopoietin receptor agonist

Kuter KJ, et al. Lancet. 2008;371:395-403

PIVOTAL STUDY PROTOCOL: AVATROMBOPAG

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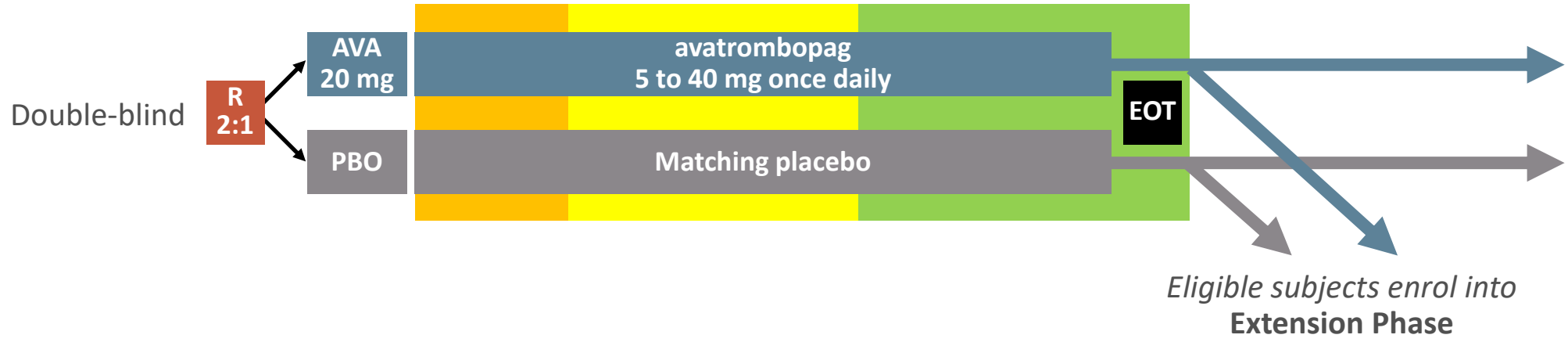
Core study design

PRE-RANDOMISATION	CORE STUDY					
Screening period	Baseline/ randomis-ation	Titration	ITP concomitant medication reduction	Maintenance	Dose tapering	Follow-up
Days -14 to -1	Day 1	Days 5 ± 1-28	Weeks 6 to 16	Weeks 18 to 26	Weeks 27 to 30	Weeks 31 to 34



AVA, avatrombopag; EOT, end of treatment; ITP, immune thrombocytopenia; PBO, placebo; R, randomisation

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

EFFICACY AND SAFETY OF TPO-RAs

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Consideration	Romiplostim[1-5]	Eltrombopag[6-8]	Avatrombopag[9,10]
Efficacy			
Onset of action	1-4 weeks	1-2 weeks	1-2 weeks
Rate of response	79-88%	70-81%	66% (day 8)
Remission potential	32% adult 23% children	10%	NE
Experience around surgery	+	+	+
Safety			
Dietary restrictions	-	+	-
Drug interactions	-	+*	+**
Thromboembolism	7%	6%	7%
Hepatobiliary effect	-	12%	-
Reticulin fibrosis/accumulation	3.7%	<10%	-
Rebound thrombocytopenia	7%	11%	NR
Neutralising antibodies	0.4%	-	-

** Competitively binds to transporter proteins, chelates polyvalent cations*

*** Binds OAT3, BRCP, competes for Pgp*

NE, not evaluated; NR, not reported;

1. Kuter DJ, et al. Br J Haematol. 2013;161:411-23; 2. Cines DB, et al. Int J Hematol 2015;102:259-70; 3. Nplate (romiplostim) Prescribing Information; 4. Newland A, et al. Br J Haematol. 2016;172:262-73; 5. Tarantino MD, et al. Haematologica. 2019;104:2283-2291; 6. Bussel JB, et al. Lancet 2009;373: 641-8; 7. Wong RSM, et al. Blood. 2017;130:2527-36; 8. Promacta (eltrombopag) Prescribing Information; 9. Piatek CI, et al. 62nd Annual Meeting of the Am Soc Hematol. abstract 844; 10. Doptelet (avatrombopag) Prescribing Information.

MONITORING TPO-RA BASED ON GOALS OF TREATMENT

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Goal	Means
Bleeding	At what platelet count is bleeding resolved?
Fatigue	At what platelet count is fatigue mitigated or resolved?
Discontinuation of concomitant medication	Does treatment allow reduction or discontinuation of concomitant medication?
Successful surgery	Does treatment reliably achieve hemostatic platelet count for surgery?
Liberation of activity	What platelet count will allow safe participation?

TPO-RA, thrombopoietin receptor agonist

TPO-RAs
MONITORING FOR SAFETY

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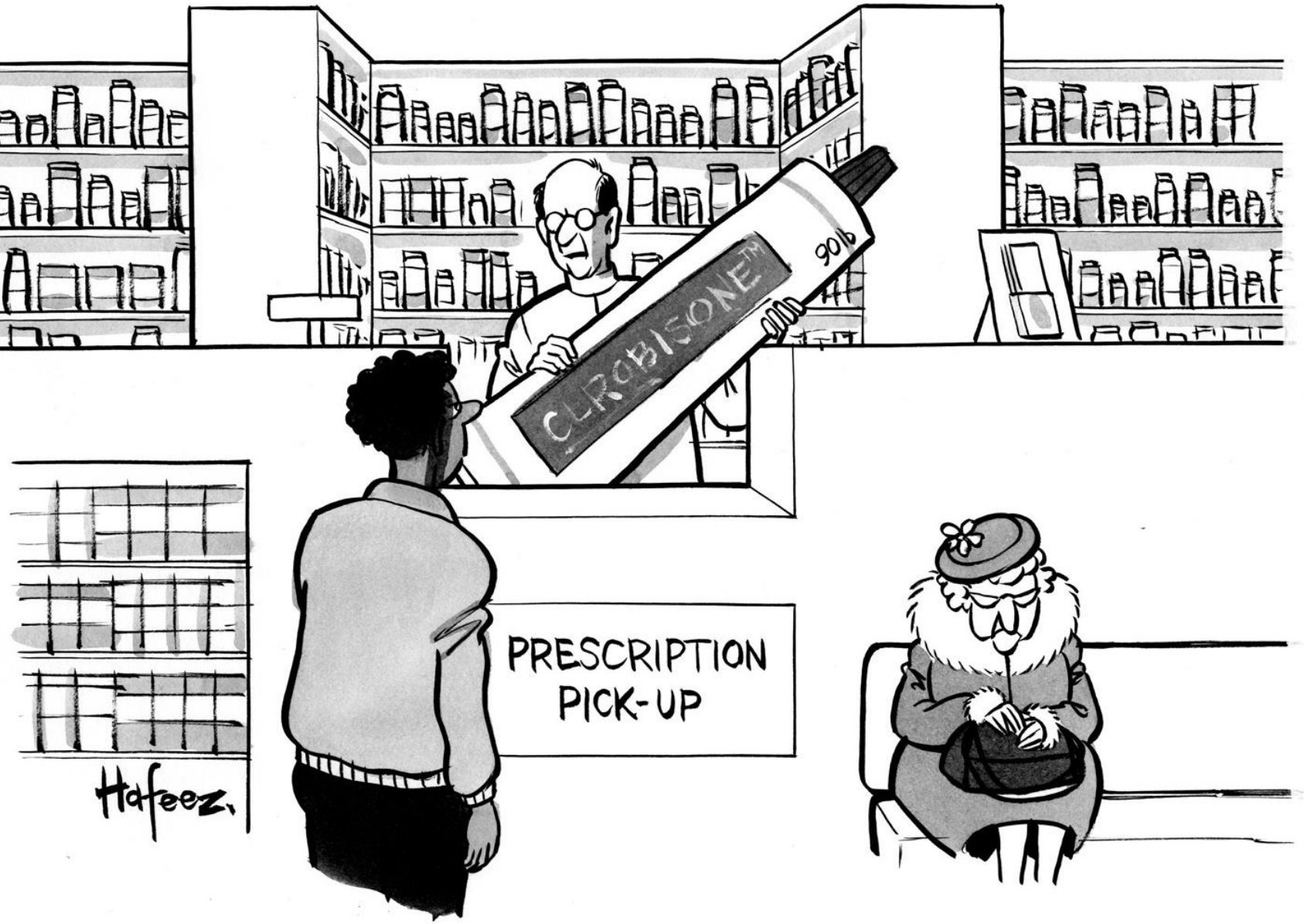
Adverse Event	Trigger	Cause	Action
Thrombocytosis	Platelet count	Drug sensitivity	Dose adjustment
Thrombocytopenia	Platelet count	Drug insensitivity	Dose adjust
		Reticulin/Collagen fibrosis	Bone marrow examination Discontinue TPO-RA
		Anti-drug antibody	Specific assay Discontinue drug
		Poor adherence	Improve adherence
VTE, arterial thrombosis	Related signs/symptoms	Appropriate imaging	Discontinue drug
Hepatitis	Screening HFP	Unknown	Decrease dose or discontinue
Cataract	Visual field change Surveillance ocular examination	Unknown	Discontinue if TEAE

HFP, hepatic function panel; TPO-RA, thrombopoietin receptor agonist; TEAE, treatment-emergent adverse event; VTE, venous thromboembolism



"Rub this on everything."

LONG-TERM REMISSION, TAPERING AND ADJUSTING TREATMENT WITH TPO-RAs

Dr. Vickie McDonald, MD
Royal London Hospital, London, United Kingdom

DISCLOSURES

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- Honoraria/Grants from Amgen, Bayer, Grifols, Novartis, Rigel and Sobi

OUTLINE

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- How are TPO-RAs dosed?
- What are the goals of therapy in ITP?
  Does that alter how we approach TPO-RA therapy?
- Is there data to support long-term remission of ITP after TPO-RA therapy?
- Tapering of TPO-RAs

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

SEQUENCING TREATMENT:
WHEN TO USE A TPO-RA?

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Newly diagnosed	Persistent	Chronic

• 0-3 months
• Manage bleeding
• Steroids / intravenous immunoglobulin (IVIG)
• Average course prednisolone ~10 weeks
• If low counts / fall on weaning: early 2nd line treatment
	• 3-12 months
	• Avoid long term steroids
	• 2nd line (consider comorbidities):
	  • TPO-RA
	  • Rituximab
	  • Mycophenolate mofetil (MMF)
	  • Other agents…
		• 12 months+
		• Agent choice determined by comorbidities / patient preference:
		  • TPO-RA
		  • Rituximab
		  • MMF
		  • Other agents…

IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; TPO-RA, thrombopoietin receptor agonist

1. Neunert C, et al. Blood Adv. 2019;3:3829-66; 2. Provan D, et al. Blood Adv. 2019;3:3780-817

IDENTICAL FREQUENCIES OF PLATELET RESPONSE: ITP ≤1 YEAR VS >1 YEAR

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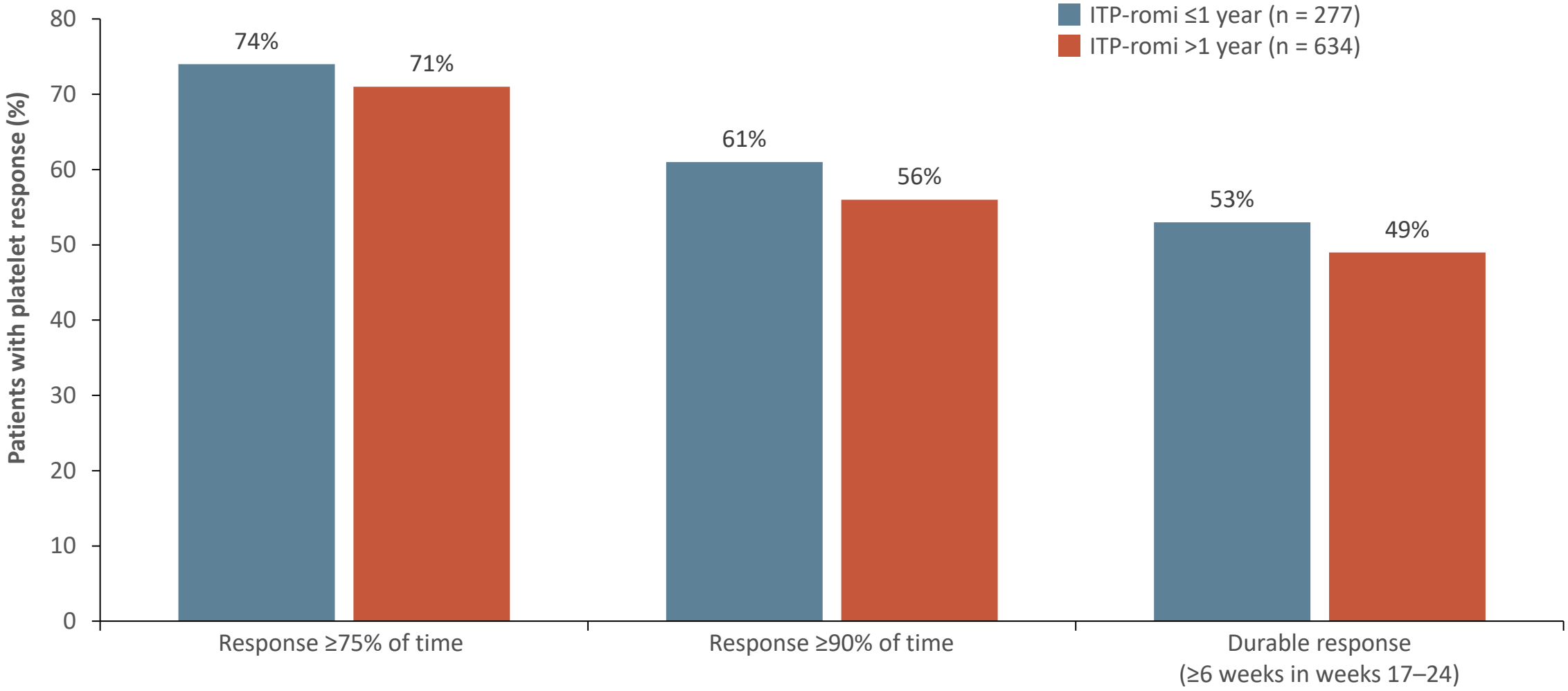

ITP-romi, patients with immune thrombocytopenia treated with romiplostim
Kuter DJ, et al. Br J Haematol. 2019;185:503-13

DOSE ADJUSTMENT 'BY THE BOOK': ROMIPLOSTIM AND ELTROMBOPAG

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Romiplostim[1]

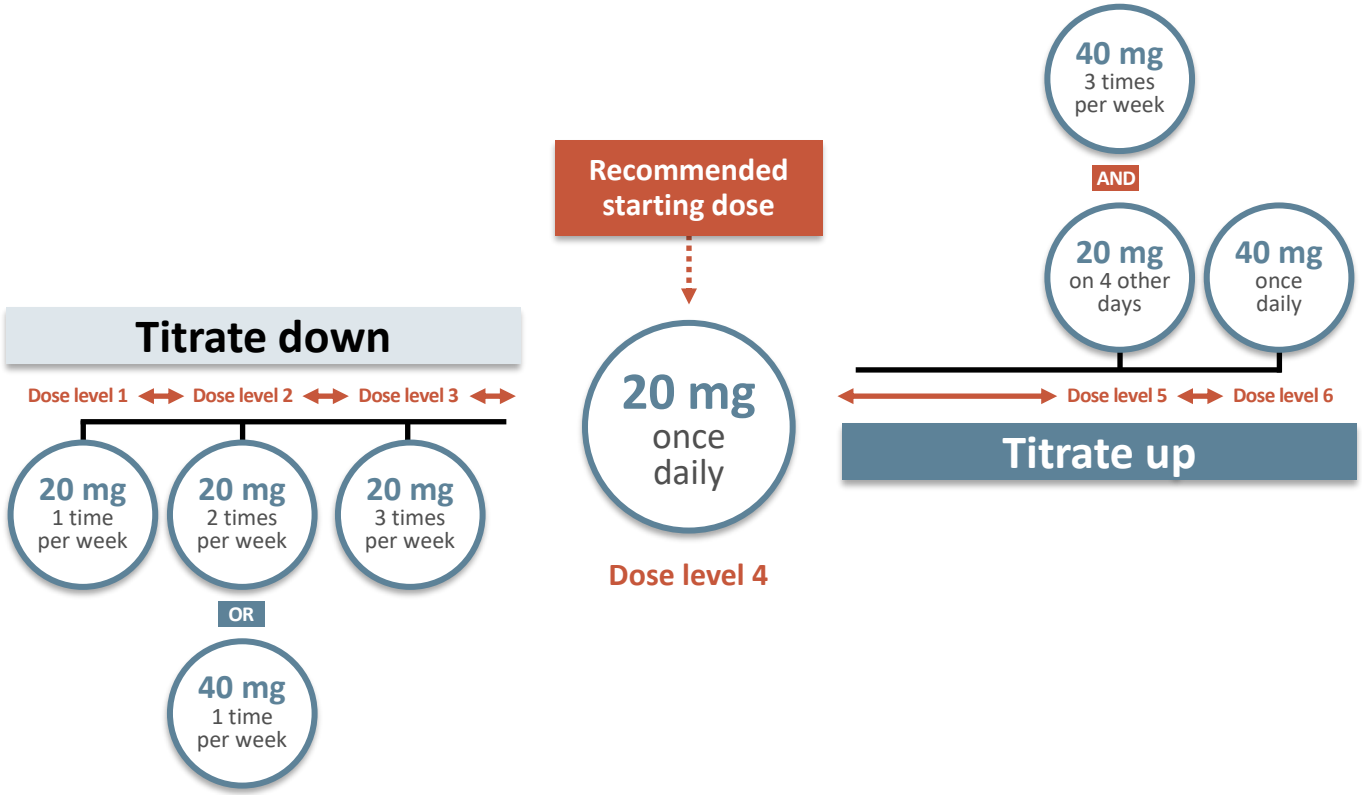
- Starting dose 1 µg/kg once weekly
- Platelets <50 × 10^9/L: increase by 1 µg/kg
- Platelets >150: decrease by 1 µg/kg
- Platelets >250: suspend; restart when platelets <150 at dose reduced by 1 µg/kg

Eltrombopag[2]

- Starting dose 50 mg once daily
  - 25 mg for Asian patients
- Platelets <50 after at least 2 weeks of therapy: increase dose by 25 mg to max 75 mg
- Platelets >150 to ≤250: decrease daily dose by 25mg – wait 2 weeks to assess effect
- Platelets >250: stop, once platelets ≤100 restart at daily dose reduced by 25 mg

1. Nplate (romiplostim) summary of product characteristics 2013; 2. Revolade (eltrombopag) summary of product characteristics 2015

DOSE ADJUSTMENT 'BY THE BOOK' AVATROMBOPAG



Avatrombopag starting dose 20 mg

- *40 mg once daily for patients on moderate or strong dual inducers of CYP2C9 and CYP3A4

CYP, cytochrome P

Doptelet (avatrombopag) Prescribing Information.

GOALS OF THERAPY IN ITP: WHAT TO TARGET WHEN DECIDING DRUG DOSES

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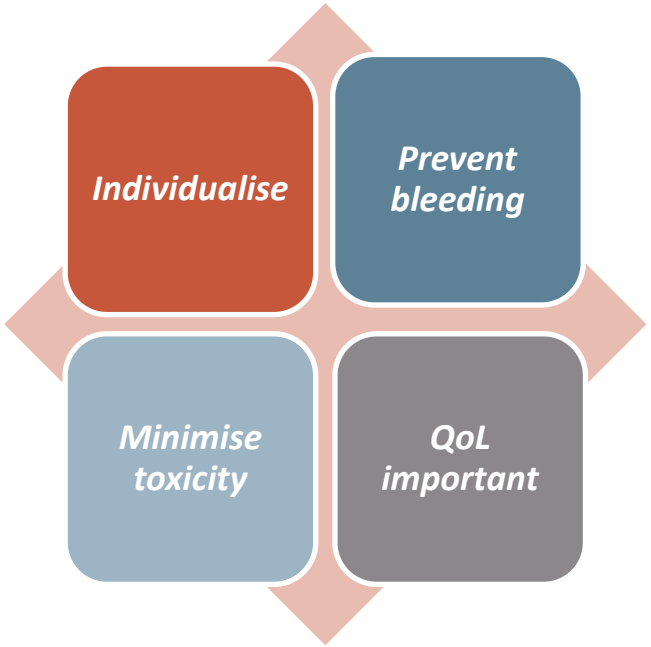

Moved from
"The platelet count is key"
to
"Platelets plus symptoms (and minimising toxicity) are key"

- Patients need a **safe** platelet count, not a normal platelet count:
  - Platelets **<10 × 10^9/L** usually need treatment
  - Platelets **>30 × 10^9/L** can usually be managed by observation
  - Platelets **10 to 30 × 10^9/L**, more likely to treat if:
    - High bleed risk, prior bleeding, active bleeding
    - Age
    - Symptoms
    - Lifestyle, occupation and risks
    - Co-morbidities/ concurrent medication: anticoagulation
- Increased move to **individualised therapy** where possible

ITP, immune thrombocytopenia; QoL, quality of life

1. Provan D, et al. Blood Adv. 2019;3:3780-817; 2. Neunert C, et al. Blood Adv. 2019;3:3829-66; 3. Matzdorff A, et al. Oncol Res Treat. 2018;41 suppl 5:1-30

TPO-RAs CAN INDUCE A LONG-LASTING IMMUNOLOGICAL RESPONSE

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- Increased or improved T-regulatory cell activity[1]
- Increased B-regulatory cell activity[2]
- Increased TGF-beta (mediates the increased T- and B-regulatory cell activity)[3]
- Change in Fc receptors: reversal of Fc receptor balance towards FcRIIb (inhibitory)[4]
- Reduces antiplatelet antibody levels in mice with ITP[5]

FcRIIb, Fc receptor IIb; ITP, immune thrombocytopenia; TGF, transforming growth factor; TPO-RA, thrombopoietin receptor agonist

1. Bao W, et al. Blood. 2010;116:4639-45; 2. Li X, et al. Blood. 2012;120:3318-25; 3. Wan YY and Flavell RA. Immunol Rev. 2007;220:199-213; 4. Liu X-G, at al. Blood. 2016;128:852-61; 5. Kapur R, et al. Platelets. 2020;31:399-402

TREATMENT-FREE "REMISSION" IN ITP
TERMINOLOGY

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- Treatment-free remission vs thrombocytopenia-free remission
  - Significance of terminology
  - Complete response (CR): platelets ≥100 x 10^9/L
  - (Partial) response: platelets ≥30 x 10^9/L and two-fold increase from baseline
- Treatment-free remission
  - No longer requiring active therapy, considered low risk for bleeding
- What threshold?
  - Platelets >50 x 10^9/L
  - Platelets >30 x 10^9/L
- For how long?
- Mazzucconi et al (2017)[1]
  - "Durable response": response or CR lasting ≥4 weeks with a stable dose of TPO-RA
  - "Sustained response": platelet count ≥30 × 10^9/L after > 4 weeks since TPO-RA discontinuation, in the absence of concomitant treatments

CR, complete response; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist

1. Mazzucconi MG, et al. Eur J Haematol. 2017;98:242-9

UK ADULT ITP REGISTRY DATA

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Adults treated with romiplostim (N = 118)	
Year of romiplostim initiation, n (%)	
2009	1 (1)
2010	5 (4)
2011 (NICE recommendation)	29 (25)
2012	26 (22)
2013	31 (26)
2014	26 (22)
Duration of romiplostim administration, months	
Mean (SE)	5.7 (0.9)
Median (IQR)	1.4 (0.2-6.5)
Median (IQR) maximum weekly dose of romiplostim, mcg/kg	3.0 (2.0-6.0)
≥ 6 months of follow-up after last romiplostim dose, n (%)	84 (71)
Did not have romiplostim for > 6 months after receiving the last dose, n (%)	45 (38)

Time from romiplostim initiation to the last dose for those who discontinued, n (%)	
N	**84**
<1 month	37 (44)
1 to <3 months	8 (10)
3 to <6 months	10 (12)
6 to <12 months	10 (12)
>12 months	19 (23)

IQR, interquartile range; ITP, immune thrombocytopenia; NICE, National Institute for Health and Care Excellence; SE, standard error

Doobaree IU, et al. Eur J Haematol. 2019;102:416-23

SUSTAINED RESPONSES TO TPO-RA OFF TREATMENT[1]

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Study	TPO-RA	Patients, n	Patients who discontinued TPO-RA, n (% of all patients)	Patients with off-treatment responses, n (% of all patients)	Median follow-up, months
Leven et al, 2012	E	15	5 (33)	5 (33)	6+
Mahevas et al. 2014	E, R	54	20 (37)	8 (15)	13.5
Cervinek et al. 2015		46	11 (24)	11 (24)	33
Gonzalez-Lopez et al. 2015	E	12	12 (100)	12 (100)	7
Newland et al. 2016	R	4	3 (75)	3 (75)	29.5
Marshall et al. 2016	R	43	12 (28)	12 (28)	20
Bussel et al. 2016	R	302	10 (3)	9 (3)	6+
Carpenedo et al. 2015	R	27	13 (48)	13 (48)	26
Mazzucconi et al. 2017[2]	E,R	39	7 (18)	7 (18)	19.4

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

1. Modified from: Zaja F, et al. Blood Rev. 2020;41:100647; 2. Mazzucconi MG, et al. Eur J Haematol. 2017;98:242-9

POSSIBLE CRITERIA TO BE CONSIDERED AS PARAMETERS OF TPO-RA TAPERING AND DISCONTINUATION

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- Response status
  - Patients with a CR and treated with lower doses of a TPO-RA for ≥ 6 months
  - *? CR or lower platelet count acceptable
- ITP duration
- Age of patient
  - ? predictive
- Number of lines of previous treatment
  - ? better if low

- Response status
  - Patients requiring high-dose TPO-RA
  - Platelets < 50 x 10^9/L
- ITP that was previously hard to manage
- Duration
  - TPO-RA < 6/12 months
- High risk of bleeding if treatment stopped
- Concurrent medication
  - Antiplatelets or anticoagulants
- Significant comorbidities, risk of recurrent infection

CR, complete response; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist

Bradbury C, et al. HemaSphere. 2(Suppl 1):PF668. Cooper N, et al. HemaSphere. 2(Suppl 1):PF670. Thachil J, et al. Br J Haematol. 2018;180:591–4.
Zaja F, et al. Blood Rev. 2020;41:100647

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Five characteristics significantly impacted ratings

Characteristics included in patient scenarios	p-value
Platelet count (normal/above normal [>150 x 10^9/L]), adequate [50-150 x 10^9/L], responding but still low [30-50 x 10^9/L])	<0.001
History of bleeding (none, minor, major)	0.001
Intensification of treatment (between 3 and 6 months ago, none in the past 6 months)	<0.001
Trauma risk (low, high)	<0.001
Use of anticoagulants or platelet inhibitors (no, yes)	<0.001
Duration of ITP (persistent, chronic)	0.427
Months on TPO-RA monotherapy (≤12, >12 months)	0.964
Platelet response to TPO-RA (early, not early)	0.881

ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist
Cuker A, et al. Blood. 2020;136(Suppl 1):6-8

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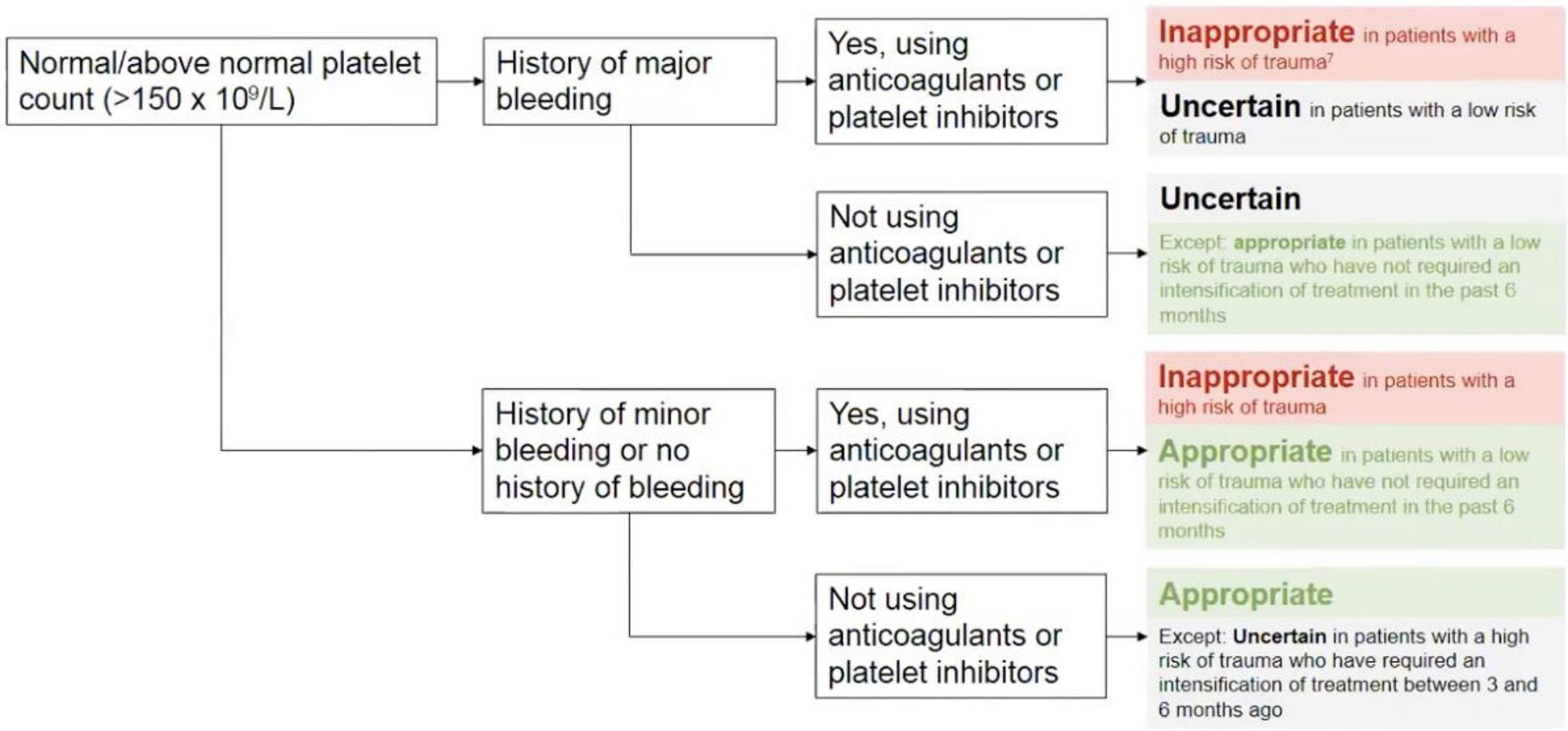
Consensus about when to taper TPO-RAs



TPO-RA, thrombopoietin receptor agonist
Cuker A, et al. Blood. 2020;136(Suppl 1):6-8

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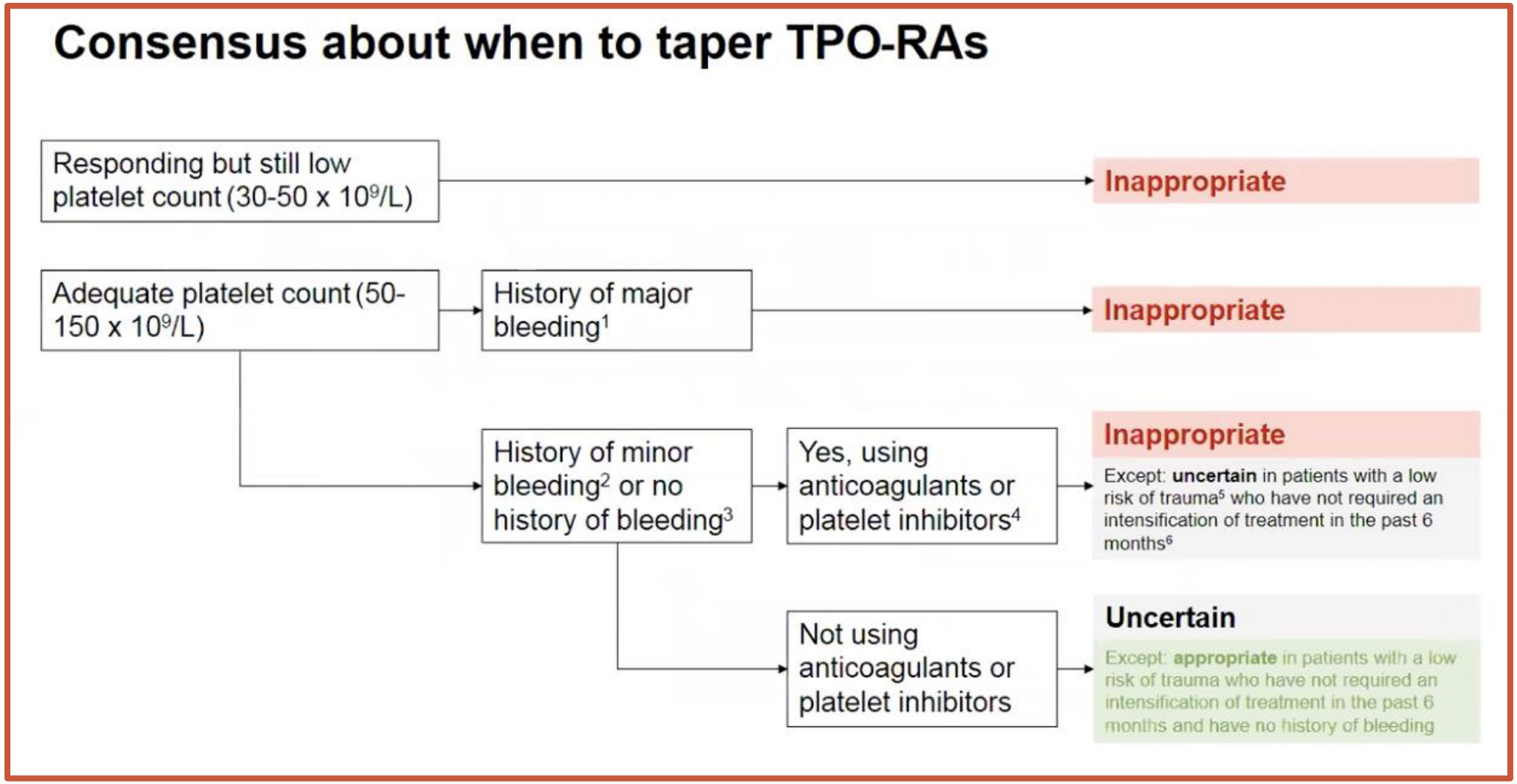


TPO-RA, thrombopoietin receptor agonist
Cuker A, et al. Blood. 2020;136(Suppl 1):6-8

HOW TO TAPER:
NO INTERNATIONAL CONSENSUS

EXPERT OPINION

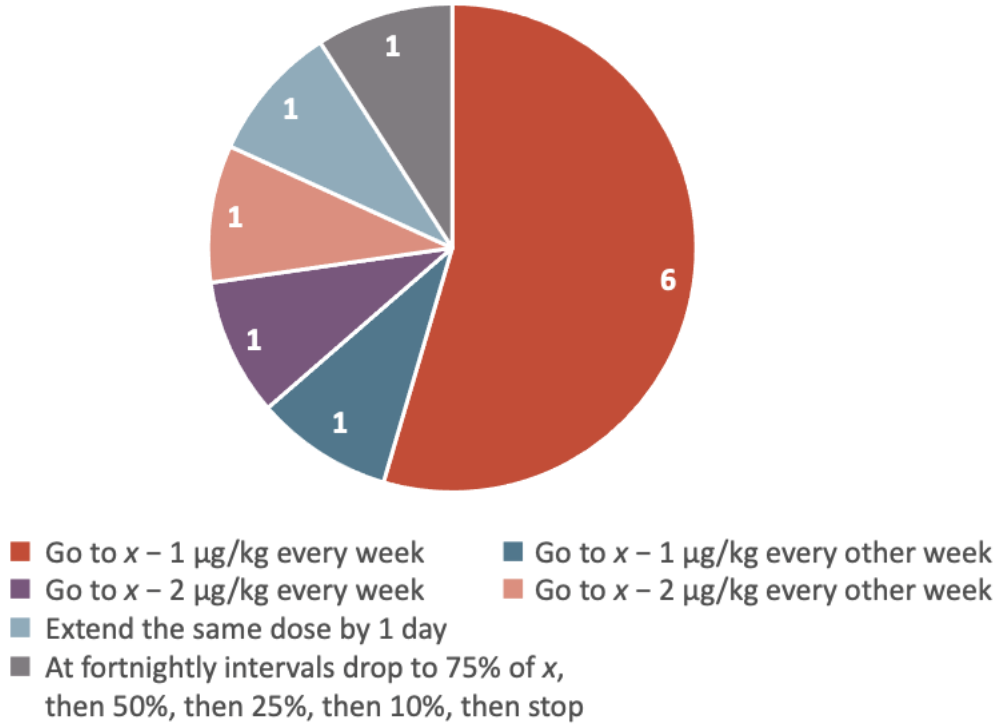
Tapering
Dose reduction by 25 mg every 2 weeks, to a minimum dose of 25 mg every 4 days, before interrupting treatment

Period of tapering and discontinuation (week 25–week 32)

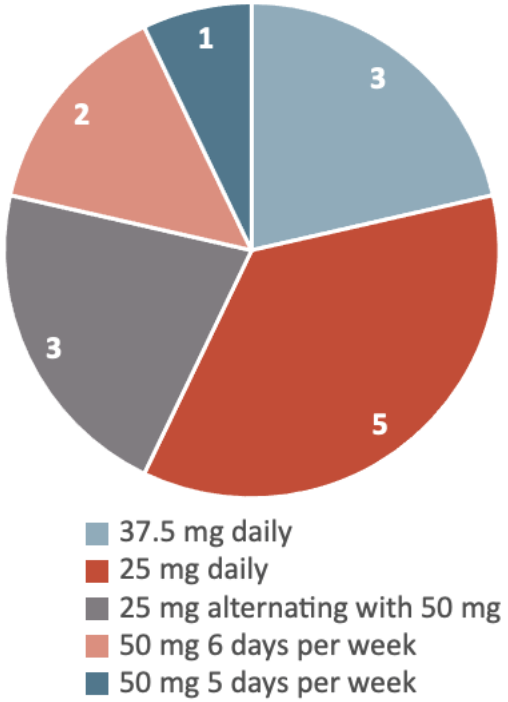
Period of observation (week 33–week 52)

DOSE REDUCTION: HOW QUICKLY?

romiplostim (considering a dose of *x* µg/kg every week before tapering)



eltrombopag (considering a dose of 50 mg every day before tapering)



Cooper N, et al. EHA 2019; abstract PB2251; Zaja F, et al. Blood Rev. 2020;41:100647

HOW DO WE MONITOR TAPERING AND DEFINE FAILURE?

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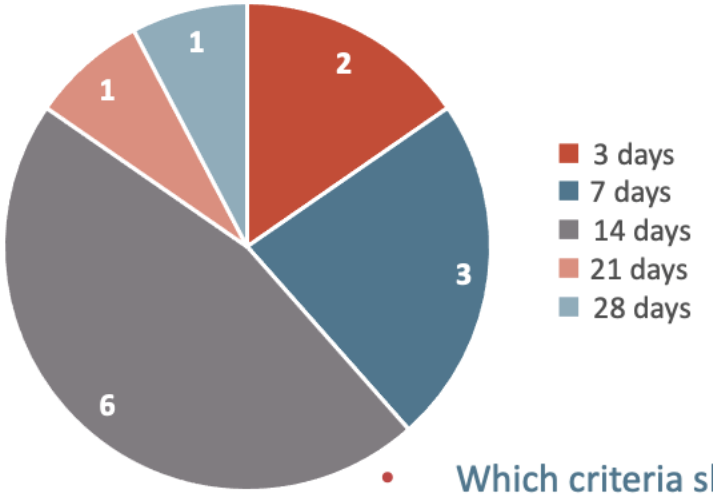
EXPERT OPINION

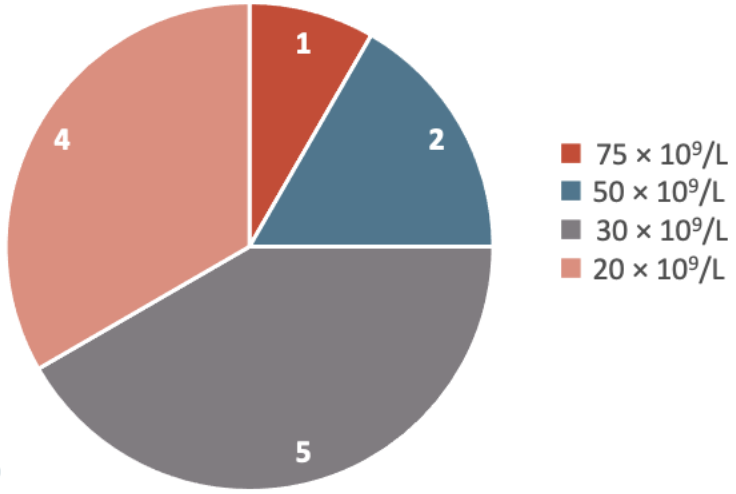
MONITOR: HOW CLOSELY?

Time to platelet-count monitoring after initiating TPO-RA dose reduction



TAPER FAILURE?

If you are tapering off TPO-RA, below which platelet count would you reinstitute treatment or stop tapering or add another treatment?



- Which criteria should we use?
  - Platelet count: 50 vs 30 vs 20 × 10^9/L
  - Bleeding
  - QoL
- Trial data needed: TAPER[1]

NO EVIDENCE

QoL, quality of life; TPO-RA, thrombopoietin receptor agonist

1. Cooper N, et al. EHA 2019; abstract PB2251; 2. Zaja F, et al. Blood Rev. 2020;41:100647

SUMMARY

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TPO-RAs are **increasingly being used second line** in the treatment of ITP

Treatment should be **tailored to the patient's platelet count**, but wider **symptoms** should also be taken into consideration

Lowest dose that achieves a safe platelet count, with improvement in QoL should be used

There is an increasing body of evidence showing that TPO-RAs can lead to **durable responses off treatment** – and induce long-lasting immunological responses in some patients

At present there are **no clear indicators for which patients are likely to achieve durable responses** off treatment

Tapering is an **'evidence-free zone'** and requires more studies

ITP, immune thrombocytopenia; QoL, quality of life; TPO-RA, thrombopoietin receptor agonist

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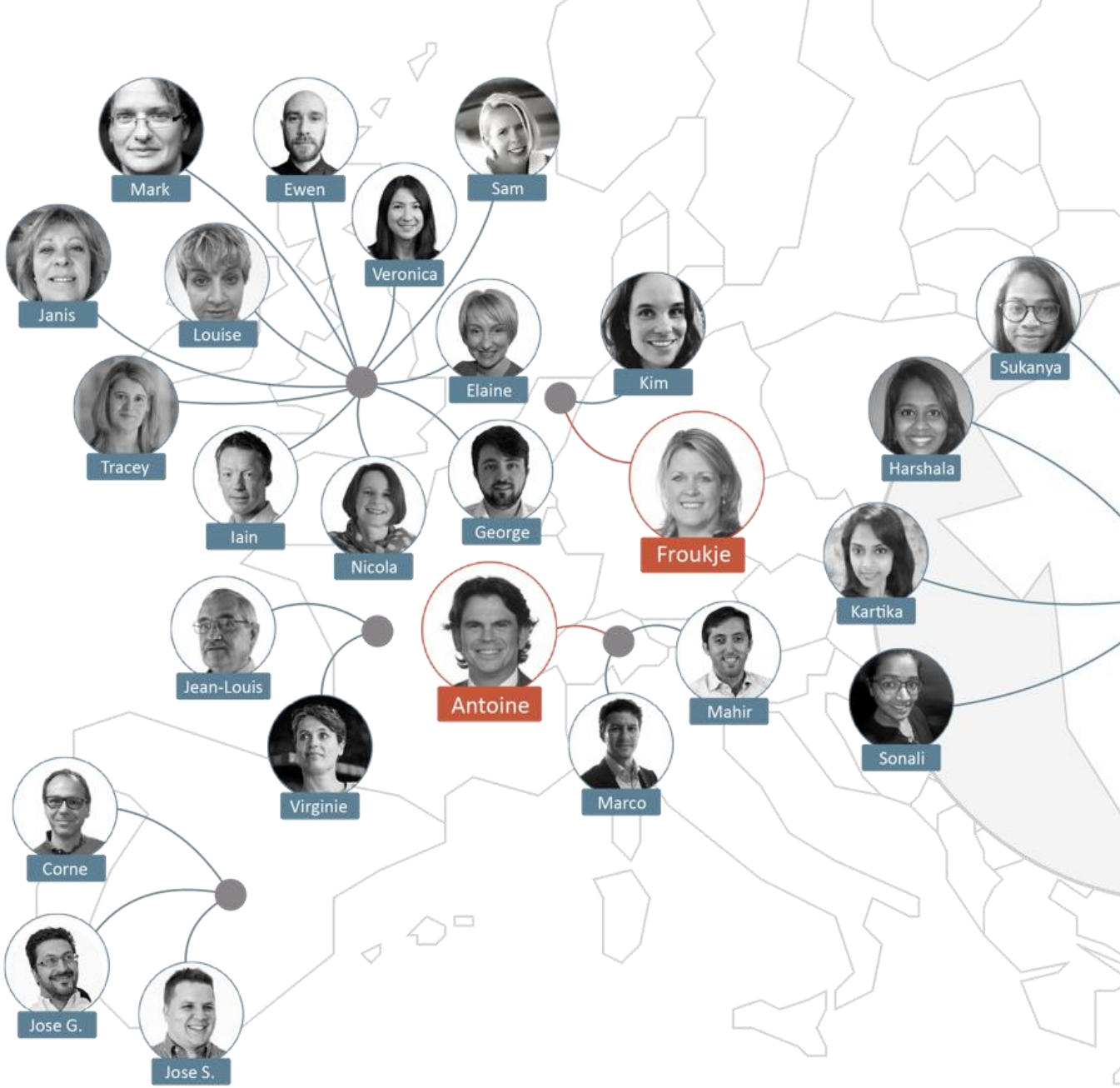

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