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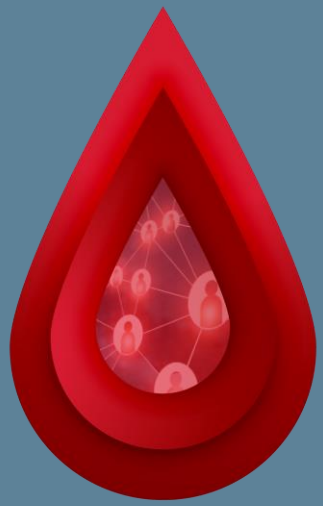

CURRENT PERSPECTIVES ON THE TREATMENT OF PRIMARY CHRONIC ITP IN ADULTS

AN INDEPENDENT, CME-ACCREDITED SYMPOSIUM

14 July 2020

ITP, immune thrombocytopenia

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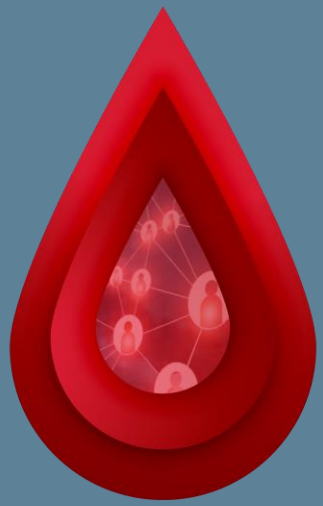

WELCOME AND INTRODUCTION

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Laboratory of Haemostasis and Metabolic Diseases
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DISCLOSURES

- **Research support:** Alexion, Alnylam, Baxalta, Bayer, CSL Behring, Ferring Pharmaceuticals, Novo Nordisk, Octapharma, Rigel Pharmaceuticals, Roche, Sanofi, Shire, Siemens, Sobi, Werfen
- **Stock ownership:** none

EDUCATIONAL OBJECTIVES

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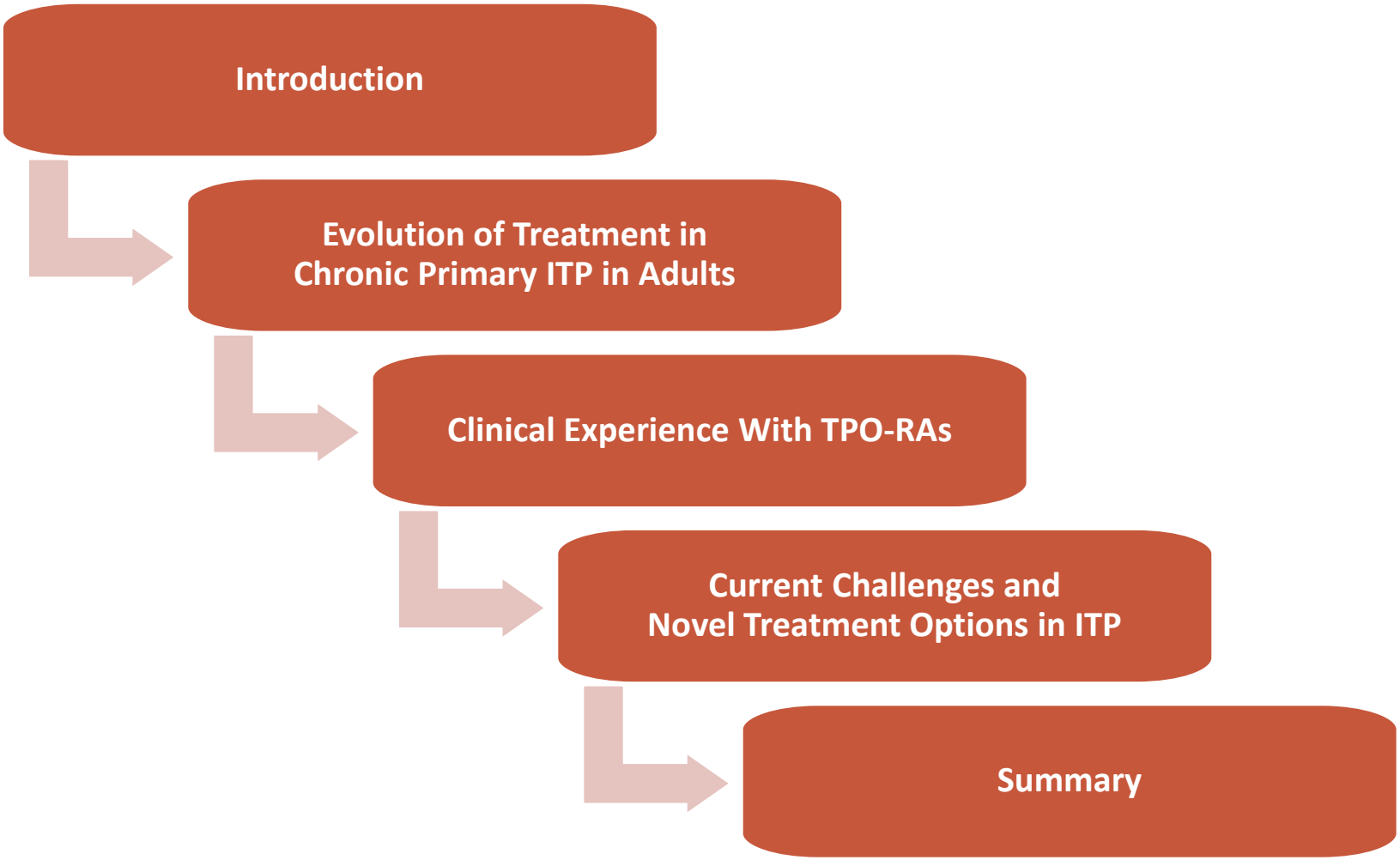
- Review of the **current standard** of care in ITP, detailing its **risk and benefit**
- Explain the **mechanism of action** and **clinical data of potential new and innovative therapeutic options in ITP**
- Comparison of standard of care **today** and **in the future**

PROGRAMME



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

INTRODUCING THE FACULTY

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Chair

Prof Jerzy Windyga, MD, PhD
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Head of the Department of Disorders of Haemostasis and Internal Medicine at the Institute of Haematology and Transfusion Medicine, Warsaw, Poland

Prof David J. Kuter, MD, DPhil
United States

Chief of Hematology at Massachusetts General Hospital, and Professor of Medicine at Harvard Medical School, Boston, USA

Prof Pål Andrè Holme, MD, PhD
Norway

Professor of Haematology and Senior Haematologist at the Oslo University Hospital, Rikshospitalet, and Institute of Clinical Medicine, University of Oslo, Norway

Dr Vickie McDonald, MA, MRCP, FRCPath, PhD
United Kingdom

Consultant Haematologist at the Royal London Hospital, UK; honorary senior lecturer at Queen Mary University of London; and National Chief Investigator for the UK ITP registry

IMMUNE THROMBOCYTOPENIA (ITP)

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Acquired autoimmune disorder characterised by a low platelet count resulting from platelet destruction and impaired platelet production

Incidence 2–5 per 100,000

Isolated primary condition or secondary to other conditions (e.g. concomitant autoimmune disease)

Heterogeneous disorder – variable clinical symptoms (mild to severe bleeds)

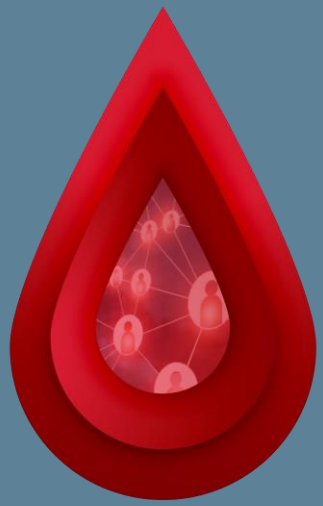
Depré F, et al. PLoS One. 2018;13:e0198184. Neunert C, et al. Blood Adv. 2019;3:3829–66.
Provan D, et al. Blood Adv. 2019;3:3780–817

THE IMPACT OF ITP

- Severe bleeding is reported in 9.5% of adults and 20.2% of children[1]
- Adults with ITP have a 1.3–2.2-fold higher mortality than the general population (due to cardiovascular disease, infection, and bleeding)[2]
- Significant impact on health-related quality of life (HRQoL) (e.g. fatigue is reported in 22–45% of patients with ITP)[1]
- Many patients with ITP may require special attention and long-term treatment[3,4]
- Optimal treatment decisions for each patient remain a challenge in many cases[3,4]

ITP, immune thrombocytopenia

1. Neunert C, et al. Blood Adv. 2019;3:3829–66. 2. Fredriksen H, et al. Br J Haematol. 2014;166:260–7. 3. Depré F, et al. PLoS One. 2018;13:e0198184. 4. Provan D, et al. Blood Adv. 2019;3:3780–817



EVOLUTION OF TREATMENT IN ITP

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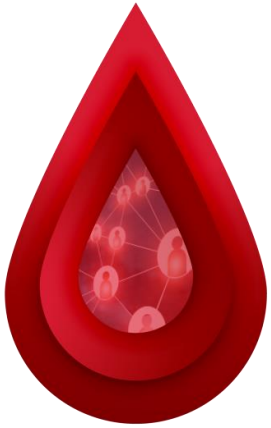
ITP, immune thrombocytopenia



WHAT ARE THE CURRENT TREATMENT OPTIONS FOR CHRONIC ITP IN ADULTS?

ITP, immune thrombocytopenia

DISCLOSURES

- **Consultant:** Bayer, CSL, Novo Nordisk, Octapharma, Pfizer, Shire, Sobi

MANAGEMENT OF NEWLY DIAGNOSED ITP IN ADULTS WHO ARE ASYMPTOMATIC OR HAVE MINOR MUCOCUTANEOUS BLEEDING

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Treatment

Platelet count ≥ 30 x 10^9/L

- Observation

Platelet count < 30 x 10^9/L

- Corticosteroids (without rituximab)
  - Prednisone (0.5–2.0 mg/kg per day) or dexamethasone (40 mg/day for 4 days) as initial therapy
  - Short course (≤ 6 weeks) of prednisone

Admission or outpatient management

Platelet count < 20 x 10^9/L

- Hospital admission (in case of bleeds)

Platelet count ≥ 20 x10^9/L

- Outpatient management

ITP, immune thrombocytopenia

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

ITP TREATMENT OPTIONS

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Clinical situation	Therapeutic option	
Initial treatment of newly diagnosed ITP	Corticosteroids	• dexamethasone • methylprednisolone • prednis(ol)one
	Intravenous immunoglobulin (IVIg)	
	Anti-D (licensed and available for ITP in only a few countries)	
Subsequent treatment	Medical therapies with robust evidence	• rituximab • thrombopoietin receptor agonists (TPO-RAs: eltrombopag, avatrombopag, romiplostim) • fostamatinib
	Medical therapies with less robust evidence	• azathioprine • cyclophosphamide • cyclosporine A • danazol • dapsone • mycophenolate mofetil • TPO-RA switch • vinca alkaloids
	Surgical therapy	• Splenectomy
Treatment after failure of multiple therapies	• Accessory splenectomy • alemtuzumab • Combination of initial and subsequent therapies • Combination chemotherapy • Clinical trials • Haematopoietic stem cell transplantation • Splenectomy, if not already performed • Supportive care	

ITP, immune thrombocytopenia

Provan D, et al. Blood Adv. 2019;3:3780–817

RECOMMENDED ITP TREATMENT GOALS

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Treatment goals should be individualised to the patient and the phase of the disease

Treatment should **prevent severe bleeding episodes**

Treatment should maintain a target platelet count **> 20–30 x 10^9/L**

At least for symptomatic patients, because the risk of major bleeding increases below this level

Treatment should have **minimal toxicity**

Treatment should **optimise HRQoL**

HRQoL, health-related quality of life; ITP, immune thrombocytopenia

Provan D, et al. Blood Adv. 2019;3:3780–817

RECOMMENDED STRATEGY FOR SUBSEQUENT ITP THERAPY

- There are **many medical treatment options** with few adverse events (AEs)[1]
  - Not all therapies are available in all countries
  - Therefore the recommendations should be modified on the basis of available resources and patient preference

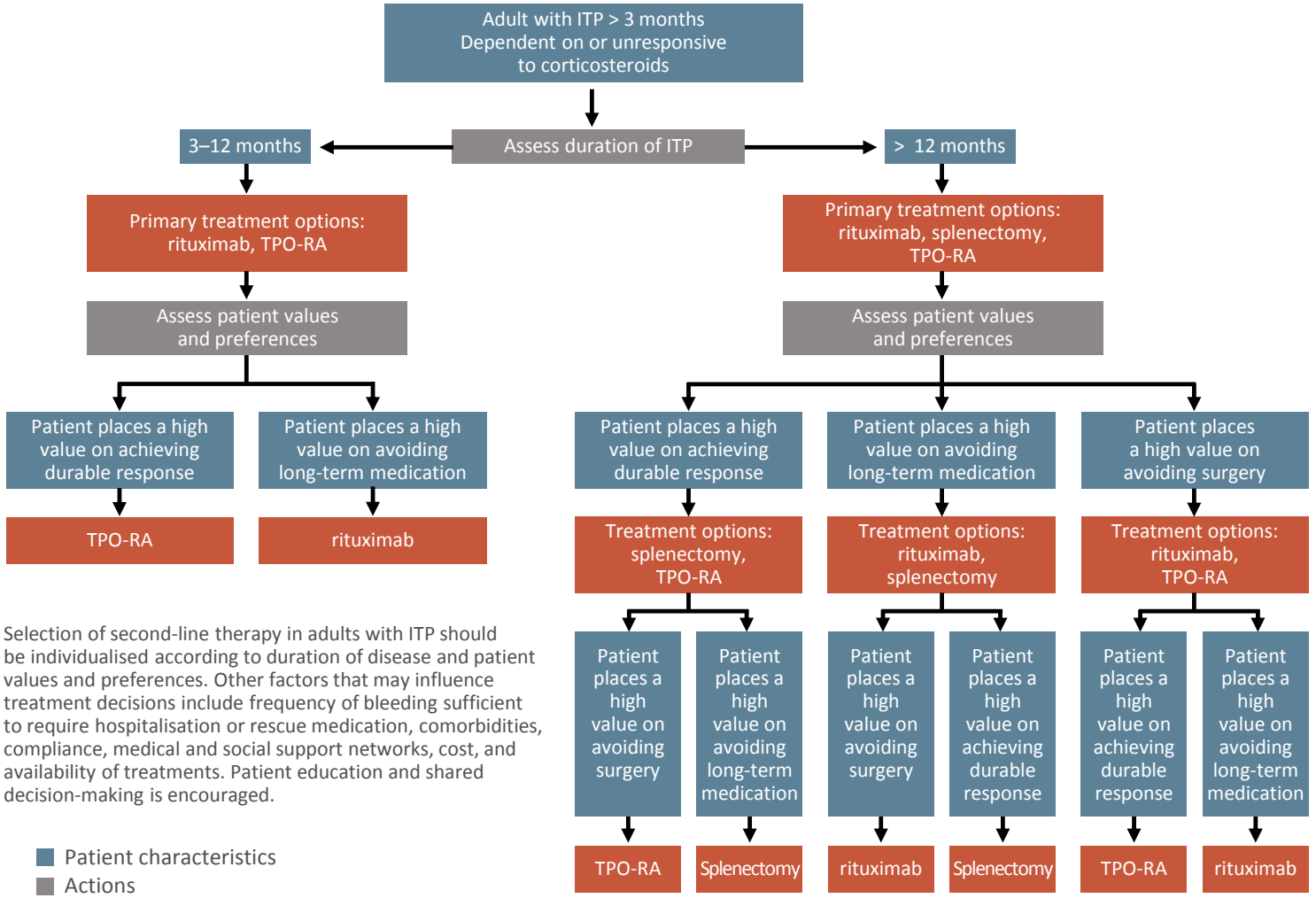
- Some medical options may require **continued treatment**[1]

- Up to 1/3 of patients may **remit** in 1 year and up to 80% may remit in 5 years[2]
  - If possible, splenectomy should be deferred for ≥ 1 year to allow for remission

ITP, immune thrombocytopenia

1. Provan D, et al. Blood Adv. 2019;3:3780–817. 2. Sailer T, et al. Haematologica 2006;91:1041–5

ALGORITHM FOR THE SELECTION OF SECOND-LINE THERAPY IN ADULTS WITH ITP



Selection of second-line therapy in adults with ITP should be individualised according to duration of disease and patient values and preferences. Other factors that may influence treatment decisions include frequency of bleeding sufficient to require hospitalisation or rescue medication, comorbidities, compliance, medical and social support networks, cost, and availability of treatments. Patient education and shared decision-making is encouraged.

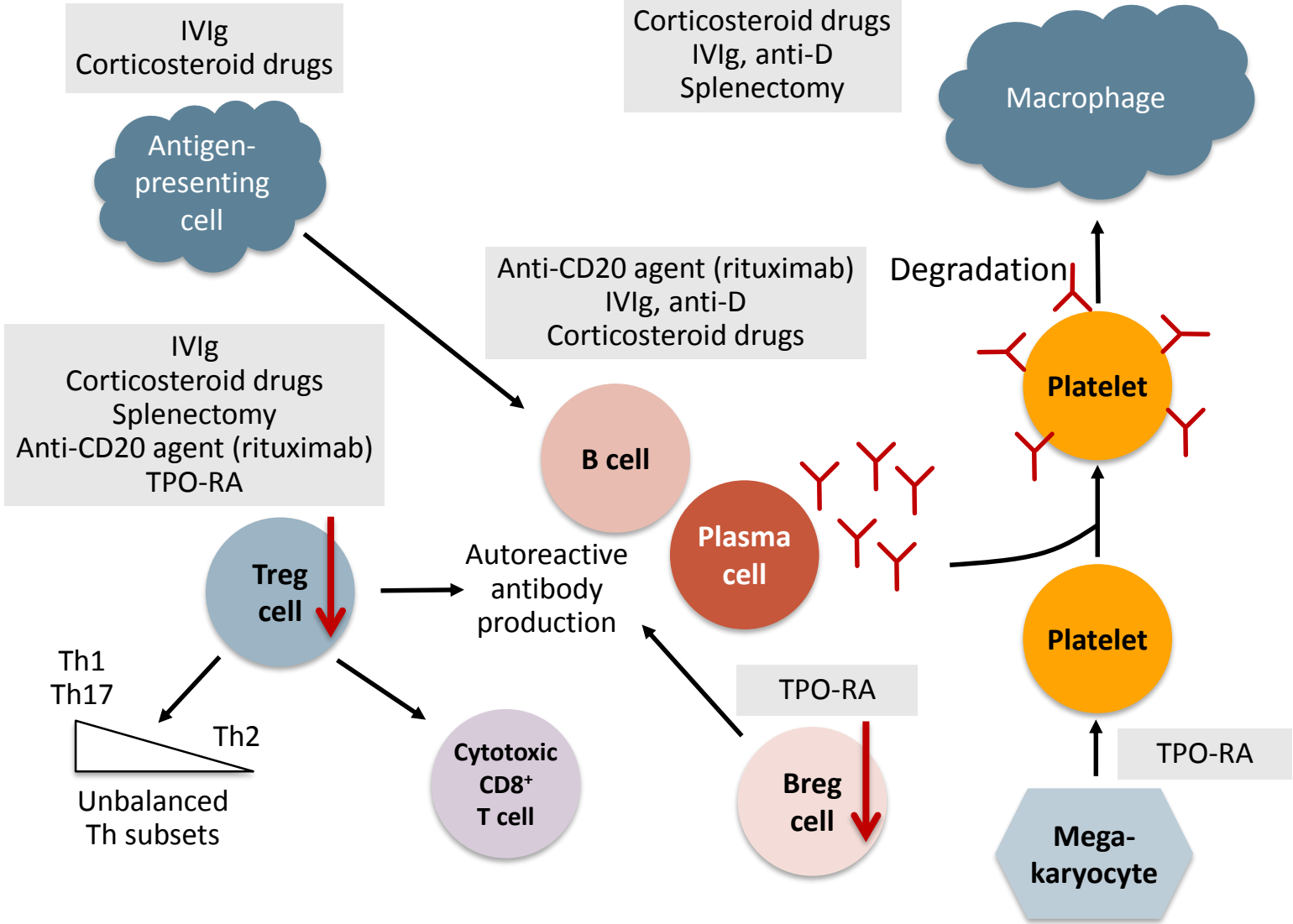
- Patient characteristics
- Actions
- Treatment options

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

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

All recommendations in figure are conditional recommendations

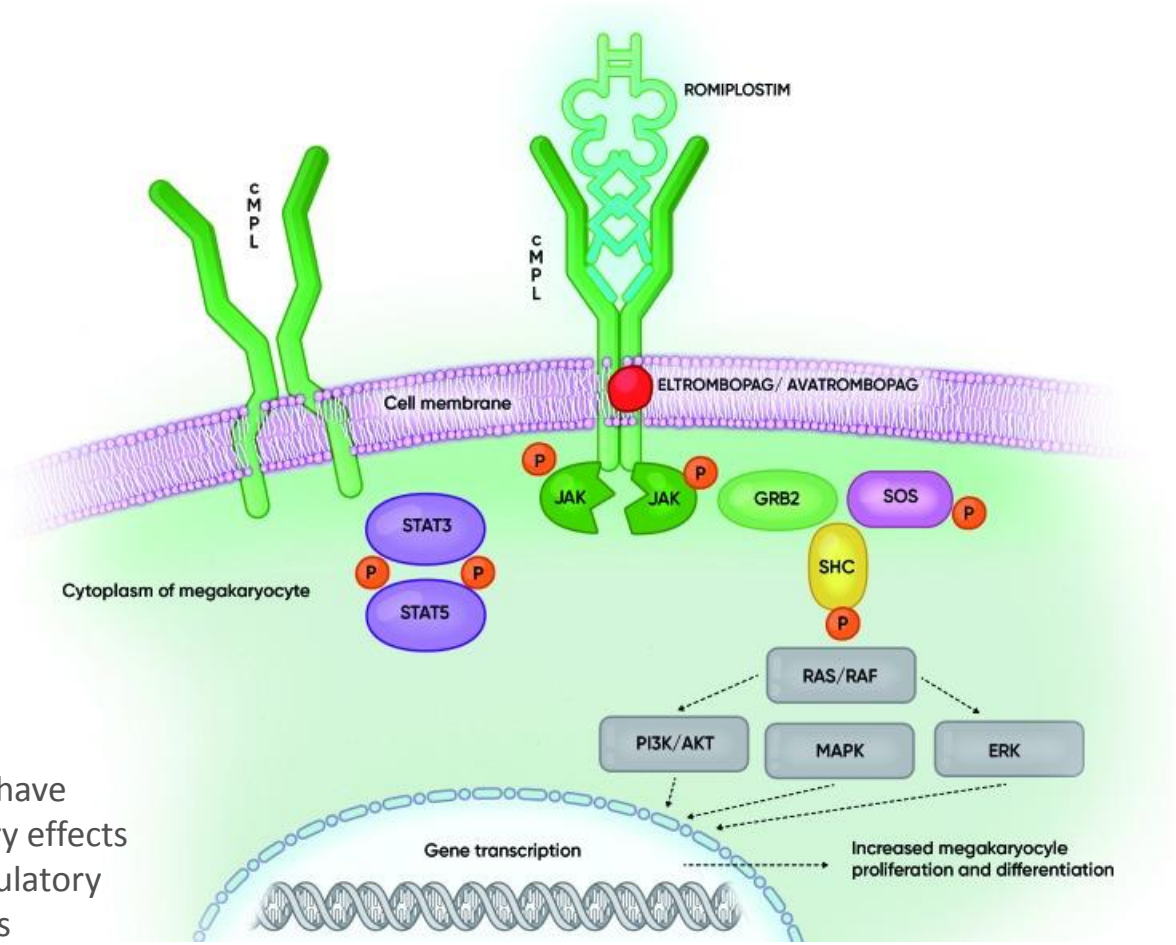
THERAPEUTIC MECHANISMS OF CURRENT ITP TREATMENTS



ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; Th, T helper (cell); TPO-RA, thrombopoietin receptor agonist

Zufferey A, et al. J Clin Med. 2017;6:16

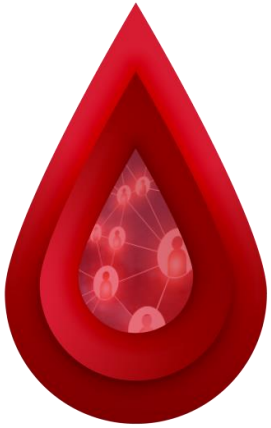
THERAPEUTIC MECHANISMS OF TPO-RAs



TPO-RAs may also have immunomodulatory effects with increased regulatory T- and B-cell effects

AKT, a serine threonine protein kinase; cMPL, thrombopoietin receptor; ERK, extracellular-signal-regulated kinase; GRB2, growth factor receptor-binding protein 2; JAK, Janus kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatid-ylinositol 3-kinase; RAF, rapidly accelerated fibrosarcoma kinase; RAS, rat sarcoma GTPase; SHC, Src homology collagen protein; SOS, son of sevenless; STAT, signal transducer and activator of transcription; TPO-RA, thrombopoietin receptor agonist

Ghanima W, et al. Haematologica. 2019;104:1112–23



WHAT ARE THE KEY SAFETY AND EFFICACY DATA SUPPORTING THESE TREATMENT OPTIONS?

COMPELLING EVIDENCE OF PLATELET RESPONSE WITH TPO-RAs

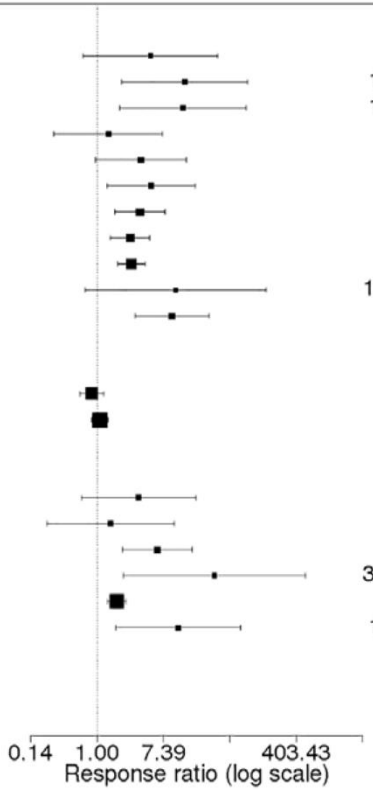
OVERALL PLATELET RESPONSE IN RANDOMISED CONTROLLED TRIALS (RCTs) OF RITUXIMAB OR TPO-RAs

Study	Notes		# Response/Total (%) Treated	Placebo/SOC	Response ratio (95% CI)
Eltrombopag v. Placebo					
Bussel et al (2007)	Non-splenectomized	30 mg	5/15 (33%)	1/15 (7%)	5.00 [0.66 , 37.85]
		50 mg	14/15 (93%)	1/15 (7%)	14.00 [2.10 , 93.45]
		75 mg	15/17 (88%)	1/15 (7%)	13.24 [1.98 , 88.62]
	Splenectomized	30 mg	3/15 (20%)	2/14 (14%)	1.40 [0.27 , 7.18]
		50 mg	8/15 (53%)	2/14 (14%)	3.73 [0.95 , 14.66]
		75 mg	8/11 (73%)	2/14 (14%)	5.09 [1.34 , 19.31]
Bussel et al (2009)	Non-splenectomized and Splenectomized		43/73 (59%)	6/37 (16%)	3.63 [1.70 , 7.74]
			48/73 (66%)	9/37 (24%)	2.70 [1.50 , 4.89]
Cheng et al (2011)	Non-splenectomized and Splenectomized		106/135 (79%)	17/61 (28%)	2.82 [1.86 , 4.26]
Tomiyama et al (2012)	Non-splenectomized and Splenectomized		9/15 (60%)	0/8(0%)***	10.69 [0.70 , 162.90]
Yang et al (2014)	Non-splenectomized and Splenectomized		60/104 (58%)	3/50 (6%)	9.62 [3.17 , 29.16]
Rituximab v. Placebo					
Arnold et al (2012)	Non-splenectomized		20/32 (62%)	19/26 (73%)	0.86 [0.60 , 1.22]
Ghanima et al (2015)	Non-splenectomized		40/55 (73%)	36/54 (67%)	1.09 [0.85 , 1.40]
Romiplostim v. Placebo					
Bussel et al (2006)	Non-splenectomized and Splenectomized	1 µg/kg	7/8 (88%)	1/4 (25%)	3.50 [0.63 , 19.50]
		3 µg/kg	3/8 (38%)	1/4 (25%)	1.50 [0.22 , 10.22]
Kuter et al (2008)*	Non-splenectomized		36/41 (88%)	3/21 (14%)	6.15 [2.14 , 17.63]
	Splenectomized		33/42 (79%)	0/21(0%)***	34.28 [2.20 , 533.41]
Kuter et al (2010)**	Non-splenectomized		127/138 (92%)	26/51 (51%)	1.81 [1.37 , 2.37]
Shirasugi et al (2011)	Non-splenectomized and Splenectomized		21/22 (95%)	1/12 (8%)	11.45 [1.75 , 74.97]

*Reported on two parallel studies

**Romiplostim vs Standard of Care

***Correction factor of +0.5 added to zero cells to calculate response ratio



CI, confidence interval; SOC, standard of care; TPO-RA, thrombopoietin receptor agonist

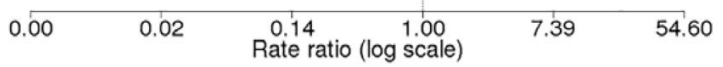
Bylsma LC, et al. Am J Hematol. 2019;94:118–32

REDUCED BLEEDING WITH TPO-RAs

BLEEDING IN RCTs OF RITUXIMAB OR TPO-RAs

Study	Notes		# Bleed/Total (%) Treatment	Placebo/SOC	Rate ratio (95% CI)
Eltrombopag v. Placebo					
Bussel et al (2007)	Non-splenectomized and Splenectomized	30 mg	5/29 (17%)	4/27 (15%)	1.16 [0.35 , 3.89]
		50 mg	2/27 (7%)	4/27 (15%)	0.50 [0.10 , 2.50]
		75 mg	1/26 (4%)	4/27 (15%)	0.26 [0.03 , 2.17]
Bussel et al (2009)	Non-splenectomized and Splenectomized		7/76 (9%)	5/38 (13%)	0.70 [0.24 , 2.06]
			20/51 (39%)	18/30 (60%)	0.65 [0.42 , 1.02]
			46/76 (61%)	30/38 (79%)	0.77 [0.60 , 0.98]
Cheng et al (2011)	Non-splenectomized and Splenectomized		106/135 (79%)	56/60 (93%)	0.84 [0.75 , 0.94]
			44/135 (33%)	32/60 (53%)	0.61 [0.44 , 0.86]
			26/135 (19%)	19/61 (31%)	0.62 [0.37 , 1.03]
			1/135 (1%)	4/61 (7%)	0.11 [0.01 , 0.99]
Rituximab v. Placebo					
Arnold et al (2012)	Non-splenectomized		7/32 (22%)	6/26 (23%)	0.95 [0.36 , 2.48]
Ghanima et al (2015)	Non-splenectomized		19/55 (35%)	21/54 (39%)	0.89 [0.54 , 1.46]
Romiplostim v. Placebo					
Bussel et al (2006)	Non-splenectomized and Splenectomized	1 µg/kg	0/8(0%)**	1/4 (25%)	0.19 [0.01 , 3.75]
		3 µg/kg	0/8(0%)**	1/4 (25%)	0.19 [0.01 , 3.75]
Kuter et al (2008)	Non-splenectomized and Splenectomized		6/84 (7%)	5/41 (12%)	0.59 [0.19 , 1.81]
Kuter et al (2010)*	Non-splenectomized		20/154 (13%)	13/75 (17%)	0.75 [0.39 , 1.42]
			5/154 (3%)	5/75 (7%)	0.49 [0.15 , 1.63]
Shirasugi et al (2011)	Non-splenectomized and Splenectomized		8/22 (36%)	10/12 (83%)	0.44 [0.24 , 0.80]
			1/22 (5%)	1/12 (8%)	0.55 [0.04 , 7.96]

*Romiplostim vs Standard of Care
**Correction factor of +0.5 added to zero cells to calculate response ratio



CI, confidence interval; RCT, randomised controlled trial; SOC, standard of care; TPO-RA, thrombopoietin receptor agonist

Bylsma LC, et al. Am J Hematol. 2019;94:118–32

AVATROMBOPAG SUPERIOR TO PLACEBO

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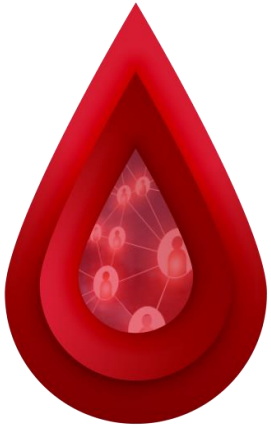
EFFICACY ENDPOINTS, PHASE 3 STUDY

	avatrombopag (n = 32)	placebo (n = 17)	P-value
Median cumulative duration of platelet response, weeks (min., max.)*	12.4 (0, 25)	0.0 (0, 2)	< 0.0001
Platelet count ≥ 50 x 10^9/L at day 8, % (95% CI)	65.6 (49.2–82.1)	0.0	< 0.0001
Any bleeding event†, %	43.8	52.9	NS

*The total number of weeks in which platelet count is ≥ 50 x 10^9/L during the core study in the absence of rescue therapy.
†Lower for avatrombopag when adjusted for the 2.6-fold longer mean exposure time for avatrombopag-treated patients.

CI, confidence interval; NS, not significant; SD, standard deviation
Jurczak W, et al. Br J Haematol. 2018;183:479–90



WHAT ARE THE MAIN UNMET NEEDS IN CHRONIC ITP IN ADULTS?

ITP, immune thrombocytopenia

KEY UNMET NEEDS IN CHRONIC ITP

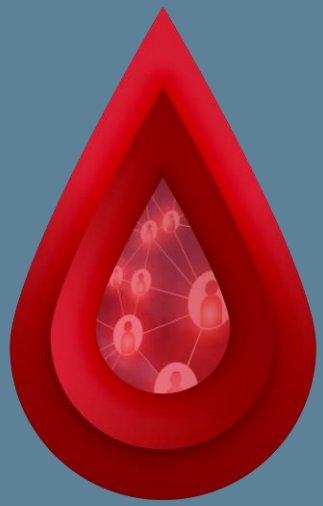
- When to introduce which treatment option
- Access
- Heterogenicity of the disease
- Need for a tailored treatment approach
- Optimal management of platelet fluctuations during treatment
- Risk and minimisation of risk of bleeding and thrombotic events

ITP, immune thrombocytopenia

KEY UNMET NEEDS IN CHRONIC ITP, CONT'D

- No head-to-head RCTs have directly compared subsequent therapy
- More RCTs are needed
- How do we obtain better long-term results using rituximab?
- The mechanisms of failure of TPO-RAs are not well known
- Who will have a durable response after TPO-RA discontinuation?
- What are the long-term effects of TPO-RAs?

ITP, immune thrombocytopenia; RCT, randomised controlled trial; TPO-RA, thrombopoietin receptor agonist



CLINICAL EXPERIENCE WITH TPO-RAs

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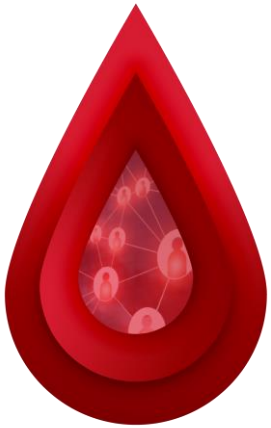
Professor of Medicine, Harvard Medical School

Vickie McDonald, MA, MRCP, FRCPath, PhD

Consultant Haematologist, Royal London Hospital

Honorary Senior Lecturer, Queen Mary University of London

TPO-RA, thrombopoietin receptor agonist



GUIDELINES NOW SUGGEST STARTING TPO-RAs EARLIER IN THE COURSE OF THE DISEASE. WHAT DATA ON EARLY TPO-RA TREATMENT ARE AVAILABLE?

David J. Kuter

TPO-RA, thrombopoietin receptor agonist

DISCLOSURES

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- **Research support:** Agios, Alnylam, Argenx, Bioverativ, Bristol Myers Squibb, Incyte, Principia, Protalix, Rigel, Syntimmune
- **Consulting:** Alnylam, Amgen, Argenx, 3Bios, Bristol Myers Squibb, Dova, Fujifilm, Genzyme, GSK, Kirin, Medimmune, ONO, Pfizer, Principia, Rigel, Shionogi, Syntimmune, UCB
- **Stock ownership:** Rubius
- **Off-label uses:** none

TPO-RAs are as effective in early ITP as in chronic ITP

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

EARLY ITP VS CHRONIC ITP

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Early[1]

- **Newly diagnosed:** 0–3 months
- **Persistent ITP:** > 3–12 months

Chronic

- Before 2009, > 6 months
  - Basis for regulatory approval of romiplostim and eltrombopag
- > 1 year[1]
  - Chronic ITP: > 12 months

- No known pathophysiological difference
  - "Epitope walking"?
- Concept of "chronic" deserves updating

ITP, immune thrombocytopenia

1. Rodeghiero F, et al. Blood. 2009;113:2386–93

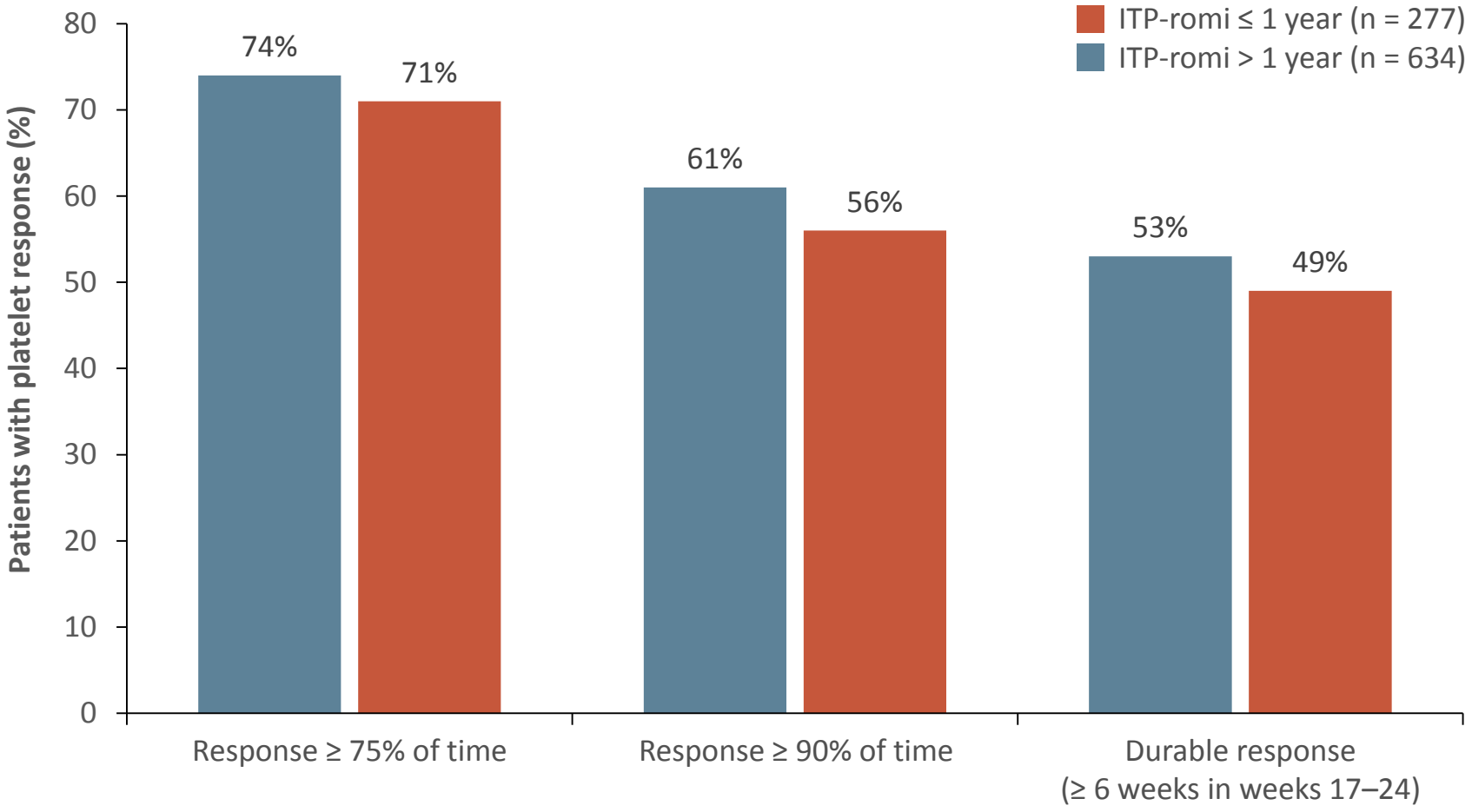
POOLED ANALYSIS OF NINE STUDIES OF ROMIPLOSTIM

	ITP ≤ 1 year			ITP > 1 year (n = 726)
	< 3 months (n = 155)	3–12 months (n = 156)	Total (n = 311)	
Female, n (%)	77 (50)	88 (56)	165 (53)	470 (65)
Age, median (Q1, Q3), years	52 (32, 69)	52 (35, 68)	52 (34, 68)	54 (42, 67)
Baseline platelet count, median (Q1, Q3), × 10^9/L	15 (8, 27)	20 (12, 29)	18 (10, 28)	18 (10, 29)
ITP duration, median (Q1, Q3), months	1.2 (0.7, 2.0)	5.8 (4.2, 8.4)	3.0 (1.2, 5.8)	72 (34, 160)
Prior therapies, n (%)				
≤ 3	104 (67)	98 (63)	202 (65)	251 (35)
> 3	6 (4)	11 (7)	17 (5)	162 (22)
Not collected	45 (29)	47 (30)	92 (30)	313 (43)
Prior splenectomy, n (%)	6 (4)	19 (12)	25 (8)	320 (44)

ITP, immune thrombocytopenia; Q1, quartile 1; Q3, quartile 3

Kuter DJ, et al. Br J Haematol. 2019;185:503–13

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



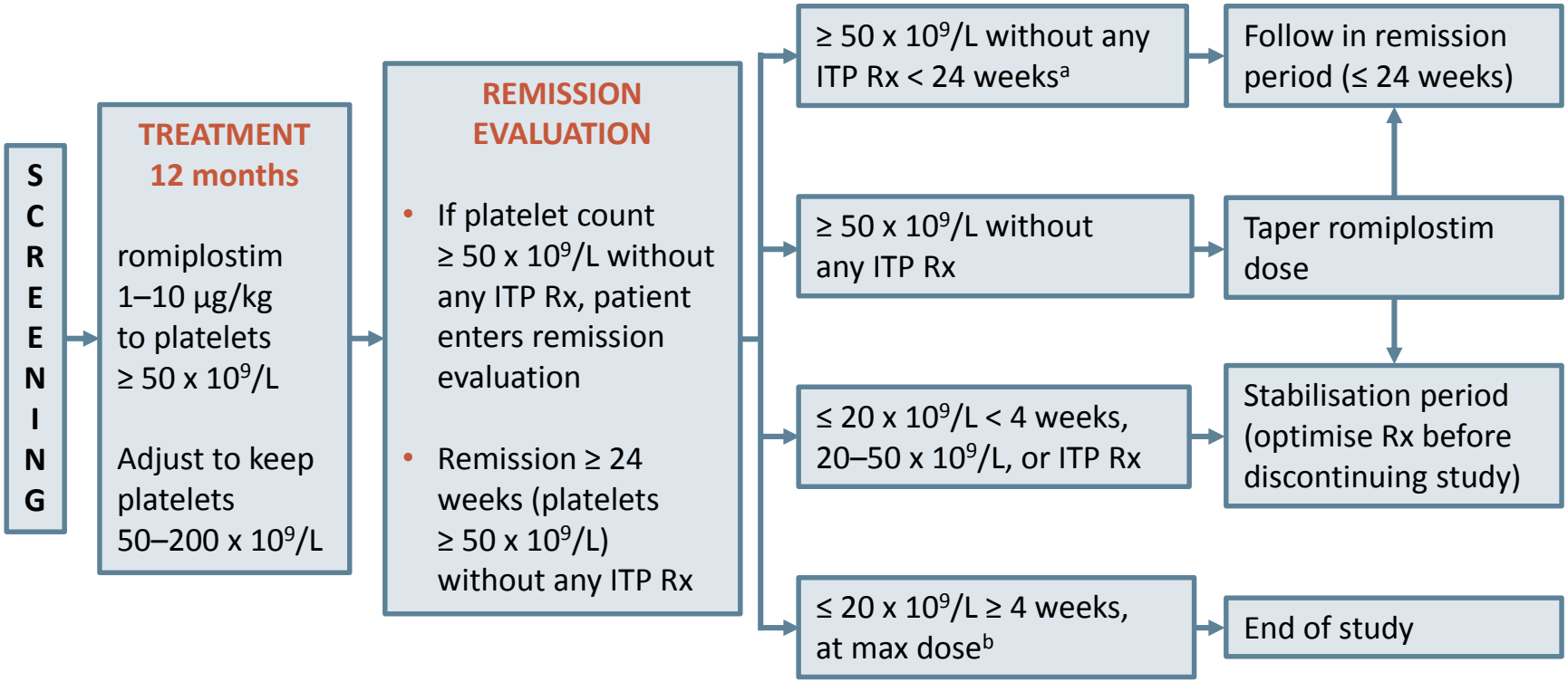
ITP-romi, patients with immune thrombocytopenia treated with romiplostim

Kuter DJ, et al. Br J Haematol. 2019;185:503–13

EARLY ITP: STUDY DESIGN

COR2ED
THE HEART OF MEDICAL EDUCATION

PHASE 2, INTERVENTIONAL, SINGLE-ARM STUDY



[a] For patients meeting these criteria in the treatment period, the 24 weeks would start then.
[b] If these criteria were met in the treatment period, treatment would be discontinued.

ITP, immune thrombocytopenia; Rx, therapy

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

EARLY ITP: RESPONSES

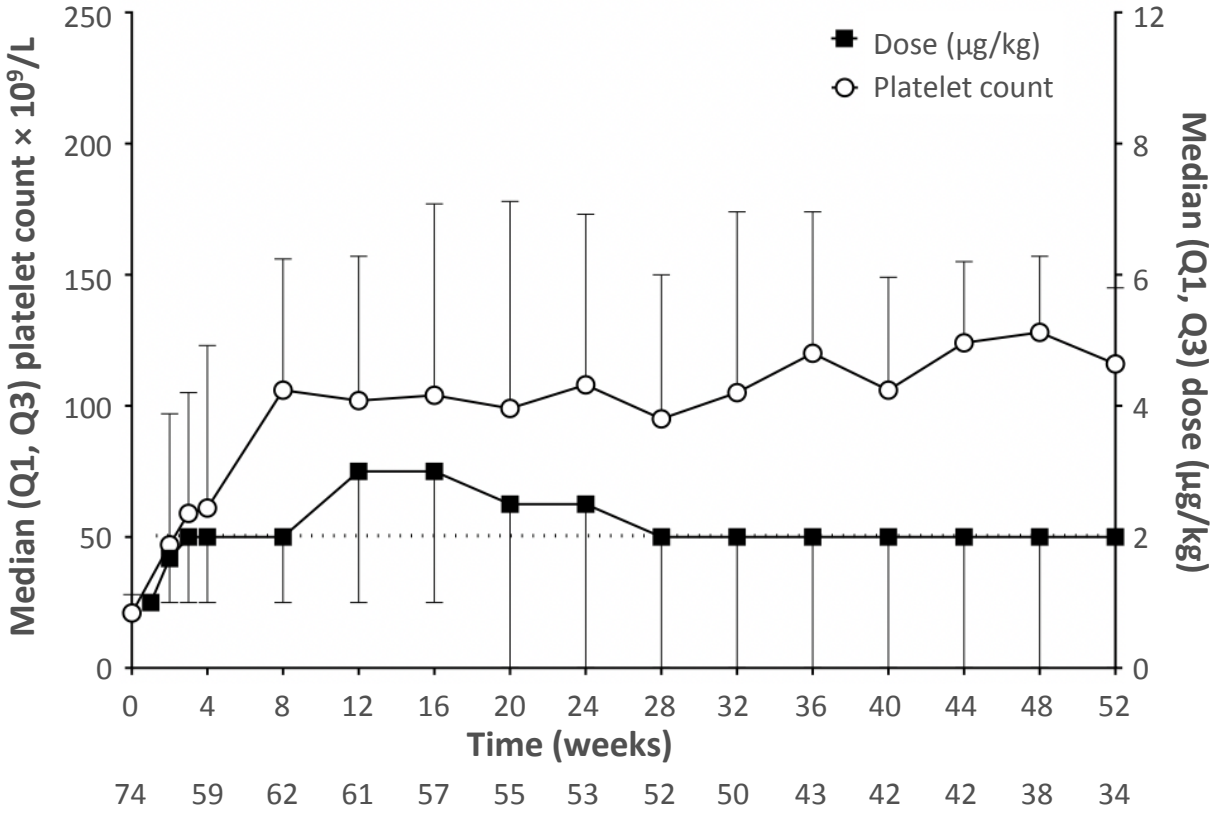
	Romiplostim (n = 75)
Patients with platelet response,[a] n (%)	70 (93)
Time to platelet response, median (95% CI), weeks	2.1 (1.1–3.0)
Patients with ITP remission[b] n (%) 95% CI, %	 24 (32) (22–44)
Time to ITP remission,[b] median (range), weeks	27 (6–57)

[a] Platelet response = median platelet count ≥ 50 x 10^9/L during any month.
[b] Remission = all platelet counts ≥ 50 x 10^9/L for ≥ 6 months without romiplostim or any ITP medication.
31 patients started ITP remission. Patients starting remission were followed for 6 months only.

CI, confidence interval; ITP, immune thrombocytopenia

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

PLATELET COUNTS AND DOSING: ALL PATIENTS



- A platelet count ≥ 50 x 10^9/L was achieved in 25% of patients after 1 week and in 50% after 2 weeks
- Median (Q1, Q3) treatment duration was 51 (18, 52) weeks in a 12-month period; range 0.3–52.4 weeks
- Median (Q1, Q3) average weekly dose was 2.6 (1.6, 3.9) µg/kg; range 0.7–9.0 µg/kg

Q1, quartile 1; Q3, quartile 3

Newland A, et al. Br J Haematol. 2016;172:262–73. Newland A, et al. Blood. 2014;124):2775

GUIDELINES

- In adults with ITP lasting **≥ 3 months** who are corticosteroid-dependent or have no response to corticosteroids, the **ASH guideline** panel suggests[1]
  - Either splenectomy or a TPO-RA
  - Rituximab rather than splenectomy
  - TPO-RA rather than rituximab

- In adults with persistent or chronic ITP **after steroid cessation**, the International Consensus Report[2] recommends **medical therapy** (TPO-RA, rituximab, fostamatinib) for 12–24 months before considering splenectomy

ASH, American Society of Hematology; ITP, immune thrombocytopenia; 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

HOW TO TREAT ITP: SUMMARY

COR2ED
THE HEART OF MEDICAL EDUCATION

Many ITP patients do not need treatment

Initial treatment is prednisone or IVIg

Splenectomy works

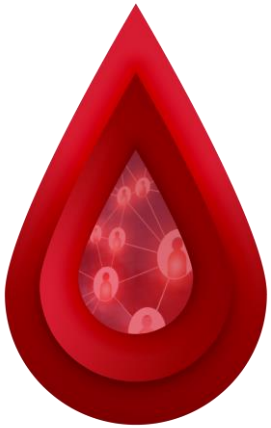
But increased rate of VTE, infection

Not all ITP in adults will become or remain chronic

Give medical therapy a chance before splenectomy

- rituximab occasionally gives a long-term treatment-free response
- TPO-RAs are highly effective
  - Low rate of AEs
  - Improve HRQoL
  - May not need to be “forever”
- fostamatinib may be considered
- Don’t forget danazol, azathioprine, dapsone, MMF, cyclosporine

AE, adverse event; HRQoL, health-related quality of life; ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; TPO-RA, thrombopoietin receptor agonist; VTE, venous thromboembolism



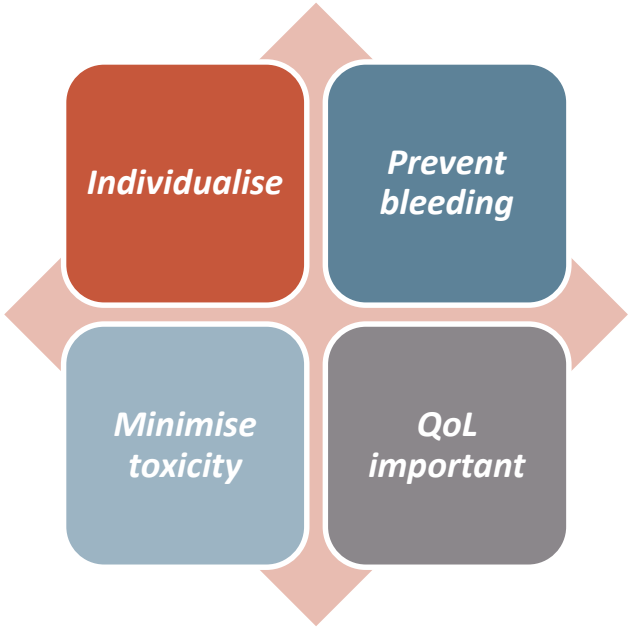
CHANGING TREATMENT PATTERNS IN ITP: WHERE ARE WE NOW?

Vickie McDonald

DISCLOSURES

- **Advisory and speaker work:** AbbVie, Amgen, Bayer, Novartis

GOALS OF THERAPY IN ITP



Phase	Definition	Chance of spontaneous remission	Treatment goal
New diagnosis, acute	Up to 3 months after diagnosis	Common	Stop bleeding Rapid platelet count rise Prevent bleeding Cure?
Persistent	3–12 months after diagnosis	Less common	Stop or prevent bleeding Stabilise platelet count Mindful of AEs from medication Cure?
Chronic	> 12 months from diagnosis	Uncommon	Prevent bleeding Mindful of AEs from medication

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

Optimising treatment

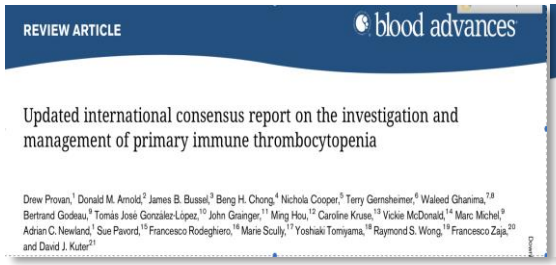
- Minimise steroid use
- Sequence therapy appropriately
- Optimise target platelet count
- Optimise timing of therapy
- Use medication for which there is the largest evidence base
- Use indicators other than platelet count, e.g. QoL and fatigue
- Understand the patient's perspective and anxieties with ITP and its treatment
- Increase patient involvement in the choice of treatment and patient understanding of the impact of ITP on QoL[1, 2, 3]

AE, adverse event; 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

INFLUENCES ON TREATMENT PATTERNS

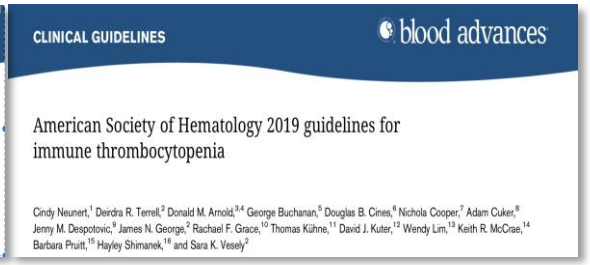
- **Changes in guidance**
  - 1st, 2nd, 3rd line treatment


REVIEW ARTICLE

blood advances

Updated international consensus report on the investigation and management of primary immune thrombocytopenia

Drew Provan,[1] Donald M. Arnold,[2] James B. Bussel,[3] Beng H. Chong,[4] Nichola Cooper,[5] Terry Gernsheimer,[6] Waleed Ghanima,[7,8] Bertrand Godeau,[9] Tomás José González-López,[10] John Grainger,[11] Ming Hou,[12] Caroline Kruse,[13] Vickie McDonald,[14] Marc Michel,[9] Adrian C. Newland,[1] Sue Pavord,[15] Francesco Rodeghiero,[16] Marie Scully,[17] Yoshiaki Tomiyama,[18] Raymond S. Wong,[19] Francesco Zaja,[20] and David J. Kuter[21]

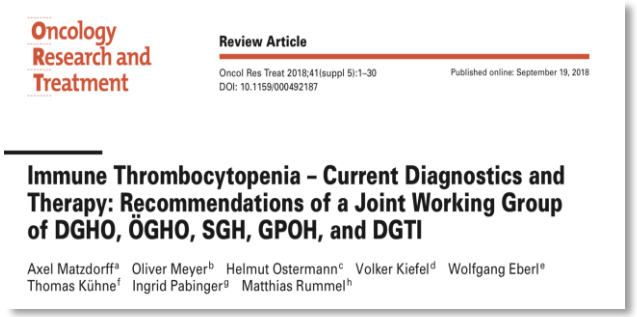

CLINICAL GUIDELINES

blood advances

American Society of Hematology 2019 guidelines for immune thrombocytopenia

Cindy Neunert,[1] Deirdra R. Terrell,[2] Donald M. Arnold,[3,4] George Buchanan,[5] Douglas B. Cines,[6] Nichola Cooper,[7] Adam Cuker,[8] Jenny M. Despotovic,[9] James N. George,[2] Rachael F. Grace,[10] Thomas Kühne,[11] David J. Kuter,[12] Wendy Lim,[13] Keith R. McCrae,[14] Barbara Pruitt,[15] Hayley Shimanek,[16] and Sara K. Vesely[2]

- **Trial data and literature**
  - RCT data


Oncology Research and Treatment

Review Article

Oncol Res Treat 2018;41(suppl 5):1–30
DOI: 10.1159/000492187

Published online: September 19, 2018

Immune Thrombocytopenia – Current Diagnostics and Therapy: Recommendations of a Joint Working Group of DGHO, ÖGHO, SGH, GPOH, and DGTI

Axel Matzdorff[a] Oliver Meyer[b] Helmut Ostermann[c] Volker Kiefel[d] Wolfgang Eberl[e] Thomas Kühne[f] Ingrid Pabinger[g] Matthias Rummel[h]

- **Licensing**
  - Changing definitions of persistent and chronic

- Localised and national **funding arrangements**
  - Links to local and national guidance

CHANGING TREATMENT USE IN THE UK: DATA FROM THE UK (PRIMARY) ITP REGISTRY

- Nationwide registry
- Eligibility criteria
  - > 18 years old
  - Living in UK
  - Platelet count < 100 x 10^9/L
  - No evidence of other cause of thrombocytopenia
- Collects anonymised data
  - Epidemiology
  - Clinical and laboratory features
  - Treatment
- Plus DNA

DEMOGRAPHICS
(DATA ANALYSED 1/9/2019)

Total number of patients: 3,236		
Sex, n (%)		
Female	1,814	56.7
Male	1,375	43.0
Unknown	10	0.3
Median (IQR) age at diagnosis, years		
All	50	31–66
Male	56	36–70
Female	46	28–62
Date of diagnosis, n (%)		
1/12/2008–30/11/2018	1,976	62.9
1998–2008	804	25.6
1988–1998	251	8.0
< 1988	113	3.6

Test	Data entry (%)	Median (IQR)
Full blood count		
Haemoglobin (g/L)	100	135 (127–147)
WBC (x 10^9/L)	100	7.2 (5.5–9.96)
Platelets (x 10^9/L)	100	21 (6–59)
Coagulation screen		
PT (sec)	100	11.7 (10.7–12.9)
APTT (sec)	100	28.5 (25.0–21.5)

APTT, activated partial thromboplastin time; IQR, interquartile range; PT, prothrombin time; WBC, white blood cells

EMERGENCY AND RESCUE THERAPIES

UK ITP REGISTRY (n = 3,236)

	Participants who received therapy (%)		
	1989–1998	1999–2008	2009–2018
prednisolone	70	79.1	82.5
dexamethasone	9.4	8.8	11.6
methylprednisolone	2.4	6.3	4.6
IVIg	42.4	40.3	37.7

SPANISH REGISTRY STUDY[1] (n = 433)

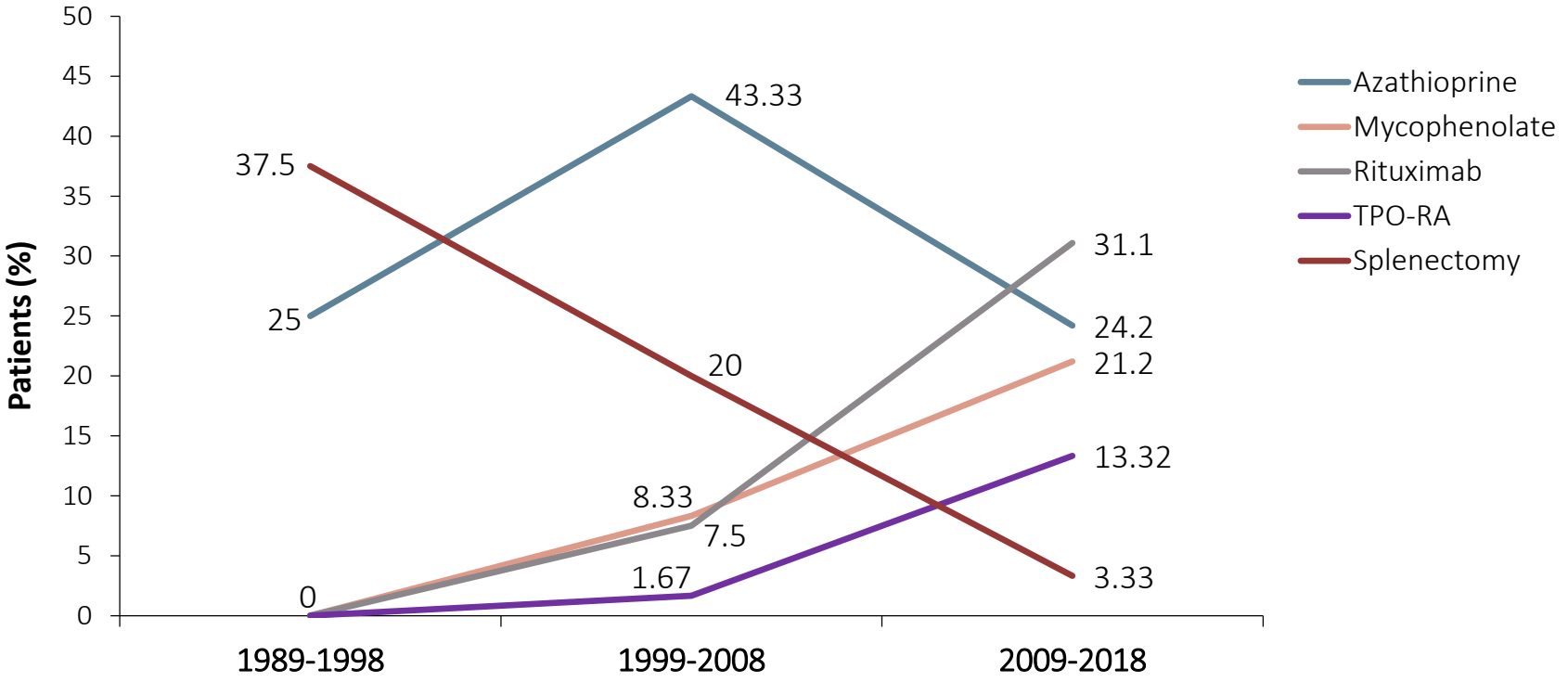
Patterns of corticosteroid use as first-line treatment for primary ITP

	Primary ITP patients, n (%)
Corticosteroid(s) as 1st-line treatment	**324 (74.8)**
Corticosteroid monotherapy	176 (40.6)
Corticosteroid + IVIg (± other therapies)	142 (32.8)
Corticosteroid + other therapies (except IVIg)	6 (1.4)
Type of corticosteroid	
prednisone	282 (65.1)
methylprednisolone	52 (12.0)
dexamethasone	27 (6.2)
deflazacort	5 (1.1)
prednisolone	2 (0.5)

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin

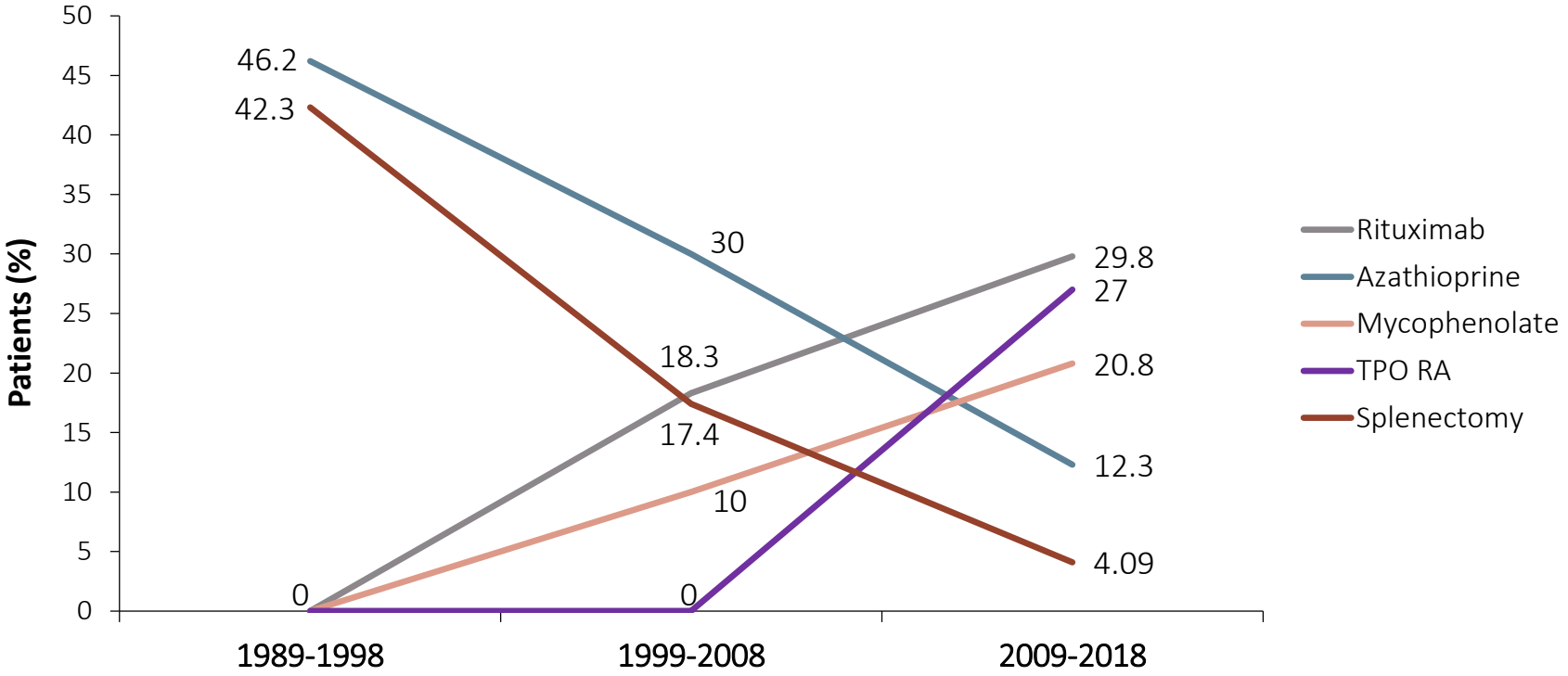
1. Palau J, et al. Hematology. 2017;22:484–92

SECOND-LINE THERAPIES



TPO-RA, thrombopoietin receptor agonist

THIRD-LINE THERAPIES



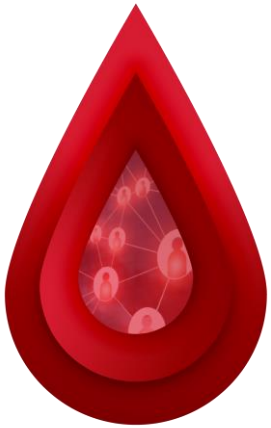
TPO-RA, thrombopoietin receptor agonist

OTHER INTERNATIONAL DATA

	USA[1] (2011–2016)	CARMEN[2]	SPANISH[3]
Patients, n	447	90 (primary ITP)	433 (primary ITP)
Steroids	76% by 1 year from diagnosis	60% (during week of diagnosis)	74.8%
IVIg	–	43% (during week of diagnosis)	5.8%
Other treatments (by 1 year)	rituximab 16% TPO-RA (both) 14% Splenectomy < 4%	rituximab 11 (12%) TPO-RA 15 (17%) Splenectomy 1 (1%) danazol 7 (8%)	Splenectomy 3.5%

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist

1. Cetin K, et al. Blood. 2018;132 suppl 1:497. 2. Moulis G, et al. Am J Hematol. 2017;92:493–500.
3. Palau J, et al. Hematology. 2017;22:484–92

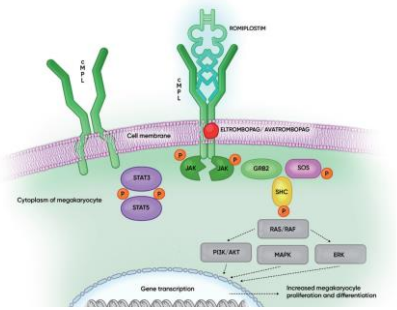


WHAT IS KNOWN ABOUT LONG-TERM REMISSION WITH TPO-RA IN CHRONIC ITP?

Vickie McDonald

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

TPO-RA SUMMARY



	romiplostim	eltrombopag	avatrombopag
Type of molecule	Peptide	Small molecule	Small molecule
TPO receptor site of action	Extracellular	Transmembrane	Transmembrane
Potency	8-10 times increased platelet count at maximum dose compared to eltrombopag	-	3-5 times increased platelet count at maximum dose compared to eltrombopag
Route	Subcutaneously once weekly	Oral, daily	Oral, daily
Administration considerations	Can patient self-administer injections	Timing in relation to food containing calcium	None
Safety and tolerability	Well tolerated, low AEs Reticulin and VTE comparable Antibody development	Well tolerated, low AEs Reticulin and VTE comparable Transaminitis	Well tolerated, low AEs VTE comparable Reticulin has not been studied
Current indications	Chronic ITP (adults and children)	Chronic ITP (adults and children) Hepatitis C-associated thrombocytopenia Severe aplastic anaemia	Periprocedural thrombocytopenia in patients with chronic liver disease Chronic ITP (USA), awaiting regulatory approval in EU

AE, adverse event; ITP, immune thrombocytopenia; TPO, thrombopoietin; VTE, venous thromboembolism

Ghanima W, et al. Haematologica. 2019;104:1112–23. Al-Samkari H and Kuter DJ. Ther Adv Hematol. 2019;10:2040620719841735

TPO-RAs CAN INDUCE A LONG-LASTING IMMUNOLOGICAL RESPONSE

COR2ED
THE HEART OF MEDICAL EDUCATION

- 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, 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

- 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.[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

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

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

SUSTAINED RESPONSES TO TPO-RA OFF TREATMENT[1]

Study	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.	15	5 (33)	5 (33)	6+
Mahevas et al.	54	20 (37)	8 (15)	13.5
Cervinek et al.	46	11 (24)	11 (24)	33
Gonzalez-Lopez et al.	12	12 (100)	12 (100)	7
Newland et al.	4	3 (75)	3 (75)	29.5
Marshall et al.	43	12 (28)	12 (28)	20
Bussel et al.	302	10 (3)	9 (3)	6+
Carpenedo et al.	27	13 (48)	13 (48)	26
Mazzucconi et al.[2]	39	7 (18)	7 (18)	19.4

TPO-RA, thrombopoietin receptor agonist

1. 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

Patients to consider for tapering	Patients to perhaps not consider for tapering
Patients with a CR and treated with lower doses of a TPO-RA for ≥ 6 months *? CR or lower platelet count acceptable	Patients requiring high-dose TPO-RA and platelets < 50 x 10^9/L ITP that was previously hard to manage
ITP duration: not predictive but better if shorter	TPO-RA < 6/12 months
Age of patient: not predictive	High risk of bleeding if treatment stopped
Number of lines of previous treatment: not predictive, but better if low	On concurrent antiplatelets or anticoagulants required to support higher platelet count
	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

HOW TO TAPER:
NO INTERNATIONAL CONSENSUS

EXPERT OPINION

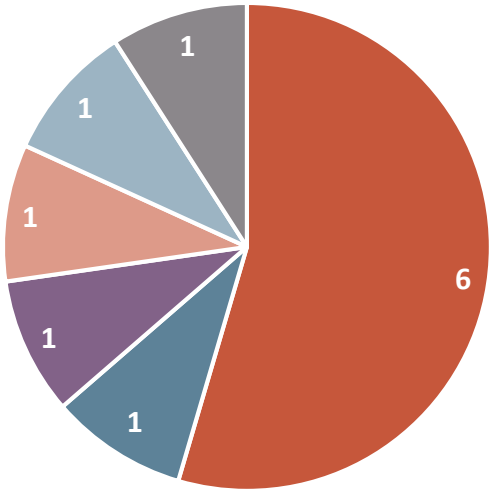
Tapering
Dose reduction by 25 mg every 2 weeks, to a minimum dose of 25 mg every 4 days, before interrupting treatment

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

Period of observation (week 33–week 52)

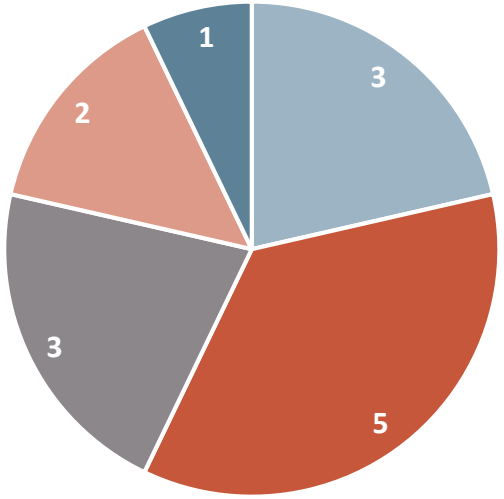
DOSE REDUCTION: HOW QUICKLY?

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



- Go to *x* – 1 µg/kg every week
- Go to *x* – 1 µg/kg every other week
- Go to *x* – 2 µg/kg every week
- Go to *x* – 2 µg/kg every other week
- Extend the same dose by 1 day
- At fortnightly intervals drop to 75% of *x*, then 50%, then 25%, then 10%, then stop

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



- 37.5 mg daily
- 25 mg daily
- 25 mg alternating with 50 mg
- 50 mg 6 days per week
- 50 mg 5 days per week

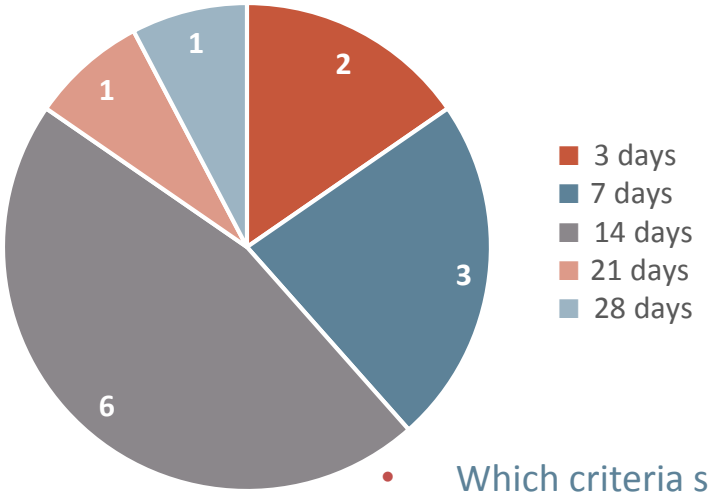
1. Cooper N, et al. EHA 2019; abstract PB2251. 2. Zaja F, et al. Blood Rev. 2020;41:100647

HOW DO WE MONITOR TAPERING AND DEFINE FAILURE?

EXPERT OPINION

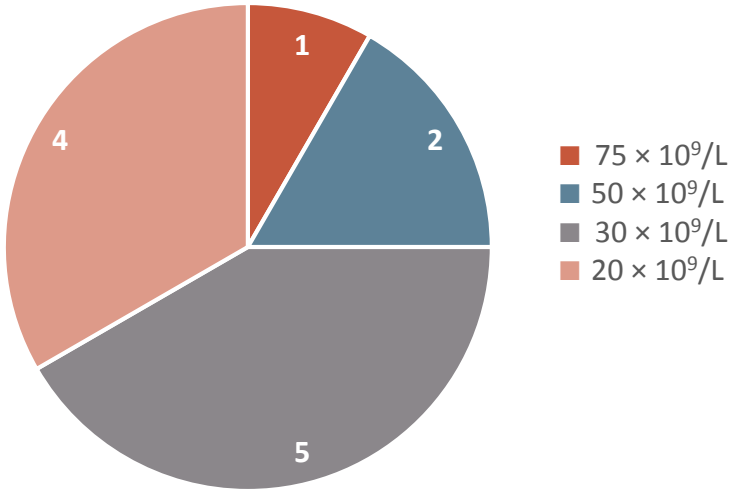
MONITOR: HOW CLOSELY?

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 x 10^9/L
  - Bleeding
  - QoL
- Trial data needed: TAPER[1]

NO EVIDENCE

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

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

ACKNOWLEDGEMENTS

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Dr M Almusawy	Bedford Hospital
Dr M Alobaidi	West Middlesex University Hospital
Dr S Atwal	Kingston Hospital NHS Foundation Trust
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Dr J Chacko	Royal Bournemouth Hospital
Dr O Chapman	Worcestershire Royal Hospital
Dr S Chattree	Sunderland Royal Hospital
Dr L Cooke	The Queen Elizabeth Hospital, King's Lynn NHS Trust
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Dr J Coppell	Royal Devon & Exeter Hospital
Dr J Crowe	Royal United Hospital Bath NHS Trust
Dr R Dang	The James Cook University Hospital
Dr S Davies	Musgrove Park Hospital
Dr C De Lord	Epsom and St Helier University Hospitals NHS Trust
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Dr T Dutt	Royal Liverpool and Broadgreen University Hospital Trust
Dr D Eden	Shrewsbury and Telford Hospital NHS Trust
Dr G Evans	East Kent Hospitals University NHS Foundation Trust
Dr T Everington	Salisbury NHS Trust
Dr R Frewin	Gloucestershire Hospitals NHS Trust
Dr L Fryearson	South Warwickshire Foundation Trust / Warwick Hospital
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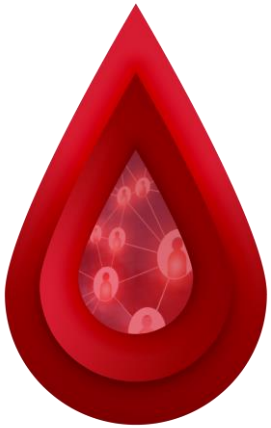
Dr M Garg	Leicester Royal Infirmary
Dr M Goodrick	Betsi Cadwaladr University Health Board, Glan Clwyd Hospital
Dr C Hall	Harrogate and District Hospital
Dr E Heartin	Betsi Cadwaladr University Health Board, Ysbyty Gwynedd
Dr J Hermans	Nottingham University Hospitals NHS Trust / Nottingham City Hospital
Dr V Hervey	South Tyneside NHS Foundation Trust / South Tyneside District Hospital
Dr Q Hill	St James University Hospital (The Leeds Teaching Hospitals NHS Trust)
Dr F Jack	Poole Hospital NHS Foundation Trust
Dr H Jackson	Aneurin Bevan University Health Board, Nevill Hall, Royal Gwent
Dr S Johns	Royal Cornwall Hospital
Dr M Karanth	West Suffolk Hospital
Dr M Kilner	Northumbria Healthcare NHS Foundation Trust
Dr M Kmonicek	North Bristol NHS Trust / South Mead Hosptial
Dr O Kreze	Newham University Hospital
Dr W Lester	Queen Elizabeth Hospital Birmingham
Dr H Lyall	Norfolk and Norwich University Hospital
Dr S Makkuni	Basildon University Hospital
Dr K Mandal	Royal Wolverhampton NHS Trust
Dr S Marshall	Gateshead NHS Foundation Trust / Queen Elizabeth Hospital
Dr G Matthias	Portsmouth Hospitals NHS Trust, Queen Alexandra Hospital
Dr V McDonald	The Royal London Hospital
Dr M Mohan	Colchester General Hospital
Dr T Moorby	Sherwood Forest Hospitals NHS Foundation Trust, King's Mill Hospital
Dr L Munro	Scarborough Hospital, York Teaching Hospital NHS Foundation Trust
Prof M Murphy	Oxford University Hospitals NHS Foundation Trust / The Churchill Hospital
Dr V Murphy	Heartlands Hospital
Dr M Mushkbar	University Hospitals Coventry and Warwickshire NHS Trust
Dr J Neilson	Russells Hall Hospital / The Dudley Group NHS Foundation Trust
Dr E Nga	Airedale NHS Foundation Trust
Dr T Nokes	Plymouth Hospitals NHS Trust, Derriford Hospital
Dr R Oakes	North Cumbria University Hospitals NHS Trust
Dr M Offer	Frimley NHS Trust - previously Heatherwood & Wexhampark Hospitals NHS Foundation Trust
Dr R Rayment	Cardiff and Vale, University Hospital of Wales
Dr C Rinaldi	United Lincolnshire, Pilgrim, Grantham, Lincoln
Dr M Robinson	Cambridge University Hospitals NHS Foundation Trust
Dr S Robinson	Guy's and St Thomas Hospital
Dr L Robinson	County Hospital, Wye Valley NHS Trust (Hereford)
Dr N Sargant	Basingstoke & North Hampshire Hospital; Royal Hampshire County Hospital, Winchester
Prof M Scully	University College London Hospitals
Dr M Sivakumaram	North West Anglia Foundation Trust, Peterborough City Hospital
Dr J Tam	Chesterfield Royal Hospital NHS Foundation Trust
Dr J Thachil	Manchester Royal Infirmary / Manchester University NHS Foundation Trust
Dr M Thanigaikumar	Lewisham & Greenwich NHS Trust
Dr D Turner	Torbay Hospital
Dr B Vadher	Princess Royal University Hospital, King's College Hospital
Dr K Wadehra	Barking, Havering and Redbridge University Hospitals NHS Trust (BHR)
Dr S Watt	Manchester University NHS Foundation Trust / Wythenshawe Hospital
Dr J Wilson	St Richard's Hospital, Worthing Hospital



WHAT IS THE LONG-TERM SAFETY PROFILE OF TPO-RAs?

David J. Kuter

TPO-RA, thrombopoietin receptor agonist

POTENTIAL ADVERSE CONSEQUENCE OF THROMBOPOIETIC GROWTH FACTORS

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THE HEART OF MEDICAL EDUCATION

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

POOLED ANALYSIS: THROMBOTIC EVENTS IN ALL ROMIPLOSTIM STUDIES

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THE HEART OF MEDICAL EDUCATION

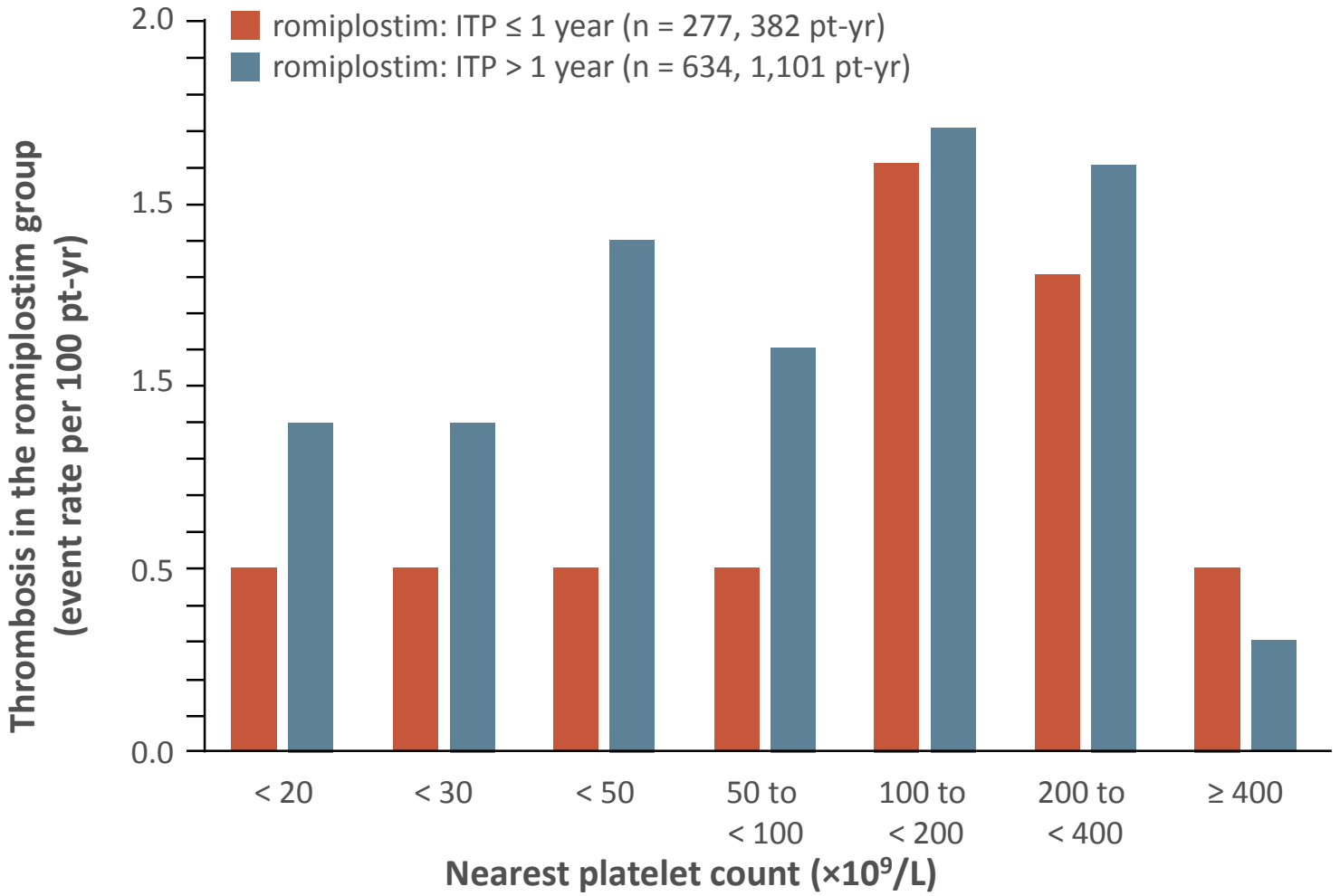
	Romiplostim	Placebo or SOC
	n = 994	n = 138
	1,520 pt-yr	110 pt-yr
Thrombotic or thromboembolic events	83 (8.4%)	6 (4.3%)
	5.5/100 pt-yr CI 4.4–6.8	5.5/100 pt-yr CI 2.0–11.9
Serious thrombotic or thromboembolic events	61 (6.5%)	2 (1.4%)
	4.0/100 pt-yr CI 3.1–5.2	1.8/100 pt-yr CI 0.2–6.6

No relation with platelet count

CI, confidence interval; pt-yr, patient-years; SOC, standard of care

Cines DB, et al. Int J Hematol. 2015;102:259–70

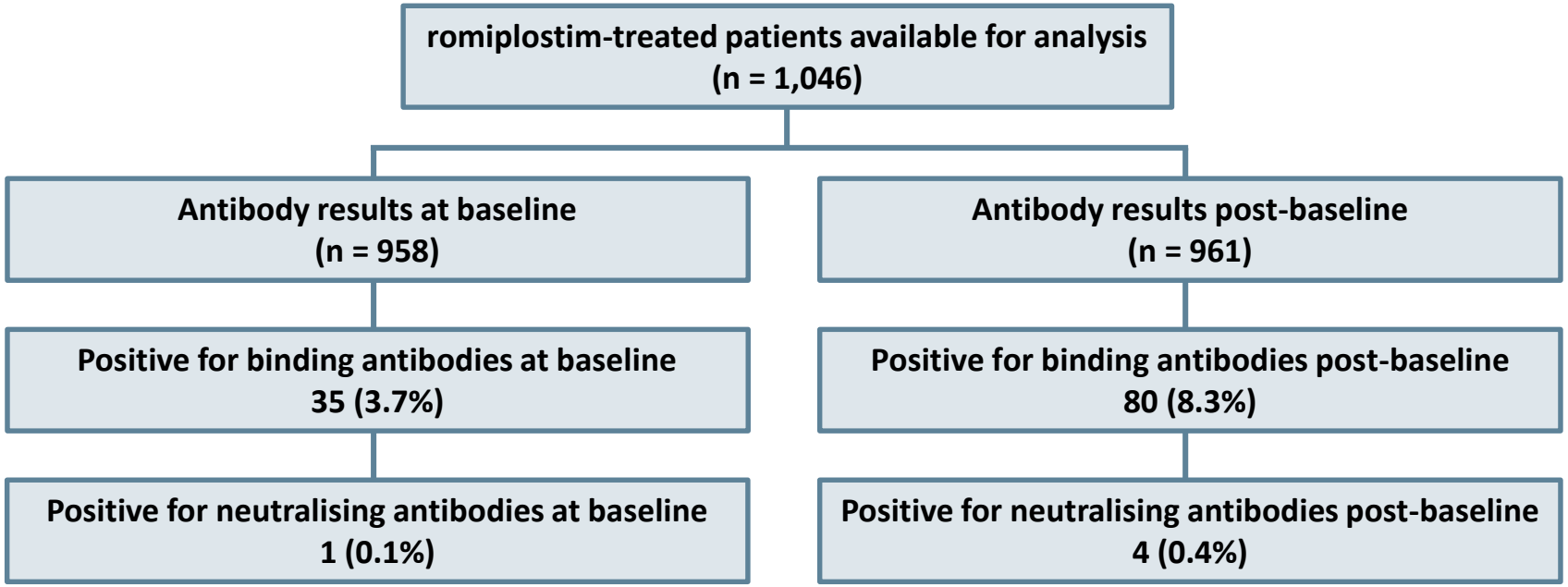
NO RELATION BETWEEN PLATELET COUNT AND THROMBOSIS EVENTS



ITP, immune thrombocytopenia; pt-yr, patient-years

Kuter DJ, et al. Br J Haematol. 2019;185:503–13

ANTIBODIES TO TPO-RA (ROMIPLOSTIM) ARE RARE

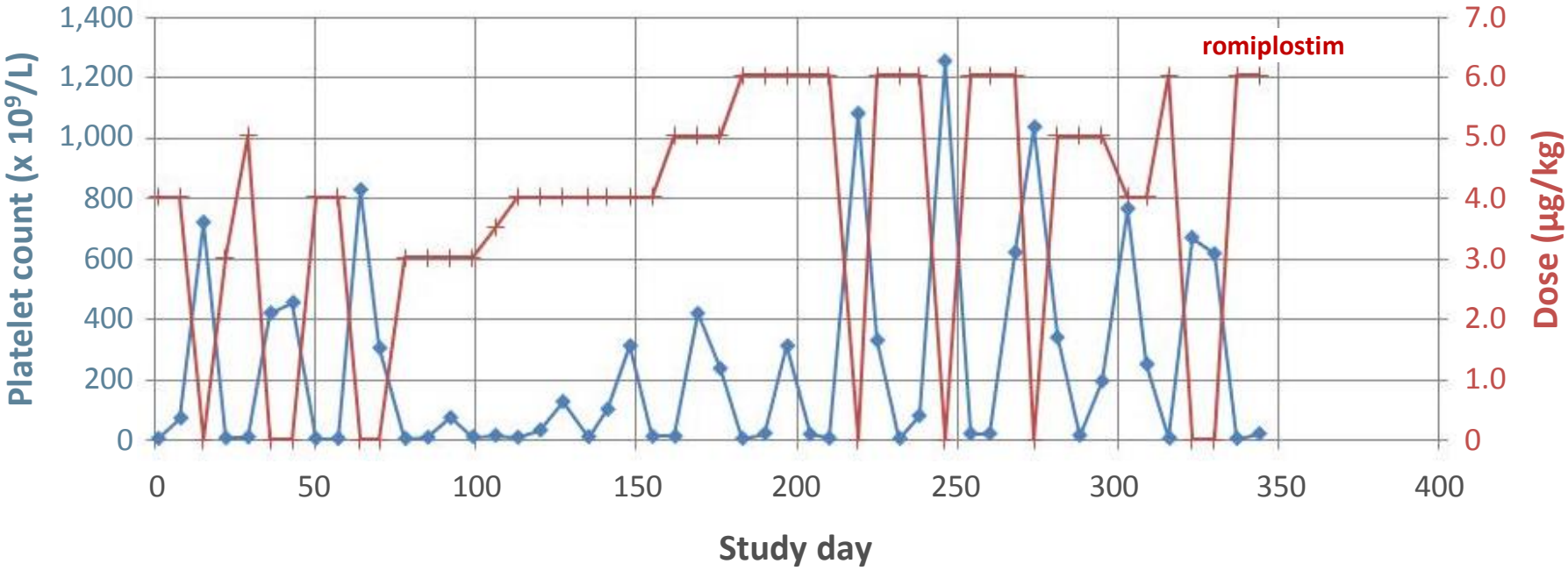


- No TPO-neutralising antibodies
- No effect on platelet count

TPO, thrombopoietin; TPO-RA, thrombopoietin receptor agonist

Mytych DT, et al. Br J Haematol. 2020 Apr 20. doi: 10.1111/bjh.16658

DANGER OF WITHHOLDING A DOSE



Platelet count
Mean (SD) 239 (328)
Median (range) 53 (5–1,257)

Dose
Mean (SD) 4 (2) µg/kg
Median (range) 4 (0–6) µg/kg

SD, standard deviation

BONE MARROW FIBROSIS: PROSPECTIVE TRIALS

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- **NCT00907478:** a prospective study evaluating changes in bone marrow morphology in adult subjects receiving romiplostim for the treatment of thrombocytopenia associated with ITP[1,2]
  - Bone marrow studies at baseline and after 1, 2, and 3 years of treatment
  - Primary endpoint: rate of collagen fibrosis
  - Multiple secondary endpoints: reticulin

- **NCT01098487:** a longitudinal 2-year bone marrow study of eltrombopag in previously treated adults with chronic ITP[3,4]
  - Bone marrow studies at baseline and after 1 and 2 years of treatment

ITP, immune thrombocytopenia

1. Study NCT00907478. Available at http://clinicaltrials.gov. Accessed 12 June 2020. 2. Janssens A, et al. Ann Hematol. 2016;95:1077–87. 3. Study NCT01098487. Available at http://clinicaltrials.gov. Accessed 12 June 2020. 4. Brynes RK, et al. Acta Haematol. 2017;137:66–72

INCIDENCE OF BONE MARROW FIBROSIS IN ITP PATIENTS TREATED WITH ROMIPLOSTIM

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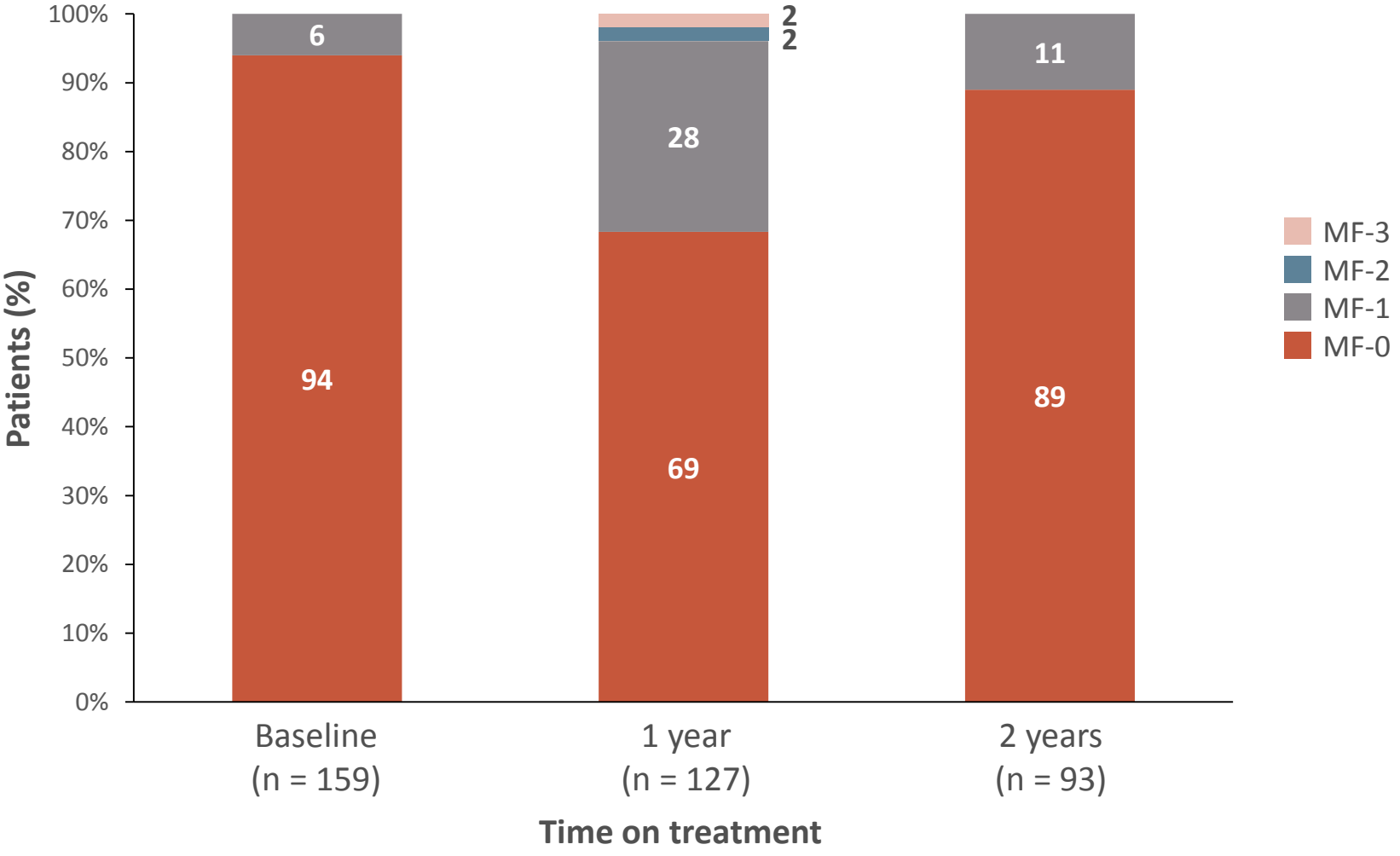
THE HEART OF MEDICAL EDUCATION

	After 1 year (n = 50)	After 2 years (n = 50)	After 3 years (n = 69)	All groups (n = 169)
Evaluable for collagen (trichrome stain), n	42	38	52	132
Positive for collagen, n (%)	**1 (2.4)**	**0**	**1 (1.9)**	**2 (1.5)**
Evaluable for reticulin (silver stain), n	41	38	52	131
Reticulin increase by ≥ 2 grades, n (%)	**2 (4.9)**	**1 (2.6)**	**4 (7.7)**	**7 (5.3)**

ITP, immune thrombocytopenia

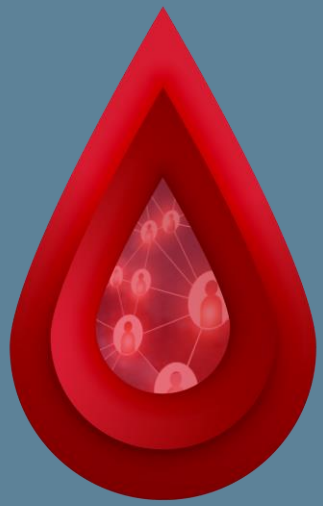
Janssens A, et al. Ann Hematol. 2016;95:1077–87

INCIDENCE OF BONE MARROW FIBROSIS IN ITP PATIENTS TREATED WITH ELTROMBOPAG



ITP, immune thrombocytopenia; MF, marrow fibrosis (European Consensus scale)

Brynes RK, et al. Acta Haematol. 2017;137:66–72



CURRENT CHALLENGES AND NOVEL TREATMENT OPTIONS IN ITP

Jerzy Windyga
David J. Kuter
Vickie McDonald

ITP, immune thrombocytopenia

CASE: MR RUSSO
PART 1

PATIENT FROM A HIGH-RISK CORONAVIRUS AREA PRESENTS WITH ITP

53-year-old man presents with bleeding gums and generalised petechiae

History of episodes of bleeding gums and easy bruising, type 2 diabetes, and rheumatoid arthritis

Platelet count 16 x 10^9/L
Other haematological and biochemical parameters and liver function tests normal

Recently visited family in northern Italy

COVID-19, coronavirus disease 2019; ITP, immune thrombocytopenia

CASE: MR RUSSO
PART 1

PATIENT FROM A HIGH-RISK CORONAVIRUS AREA PRESENTS WITH ITP

How would you treat this patient in the COVID-19 era?

1. Is hospitalisation required?
2. What should be the first-line therapy?
3. Has COVID-19 changed the role of steroids in the treatment of ITP?
4. What can be done to minimize the number of hospital visits?

COVID-19, coronavirus disease 2019; ITP, immune thrombocytopenia

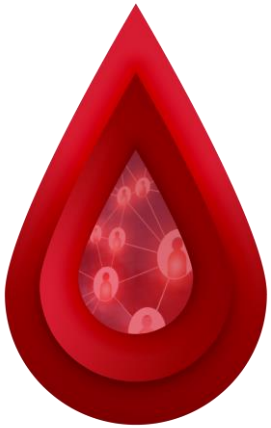
CASE: MR RUSSO
PART 2

PATIENT DEVELOPS REFRACTORY ITP

3 years later, Mr Russo still regularly has bleeding gums, petechiae, and blood in stool, despite treatment with a TPO-RA

What novel treatment options are in the pipeline to treat a patient with refractory, chronic ITP?

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



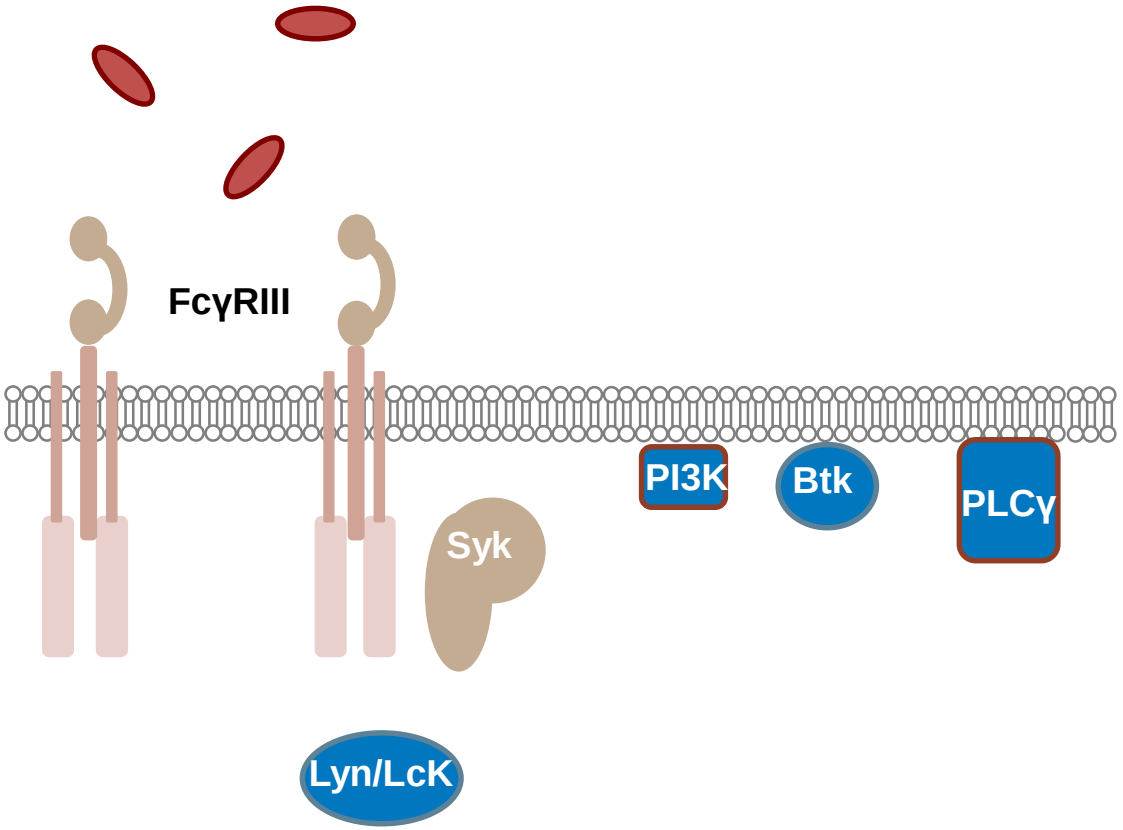
WHAT NOVEL DRUGS ARE IN THE PIPELINE TO TREAT THIS PATIENT?

David J. Kuter

NOVEL THERAPIES FOR ITP

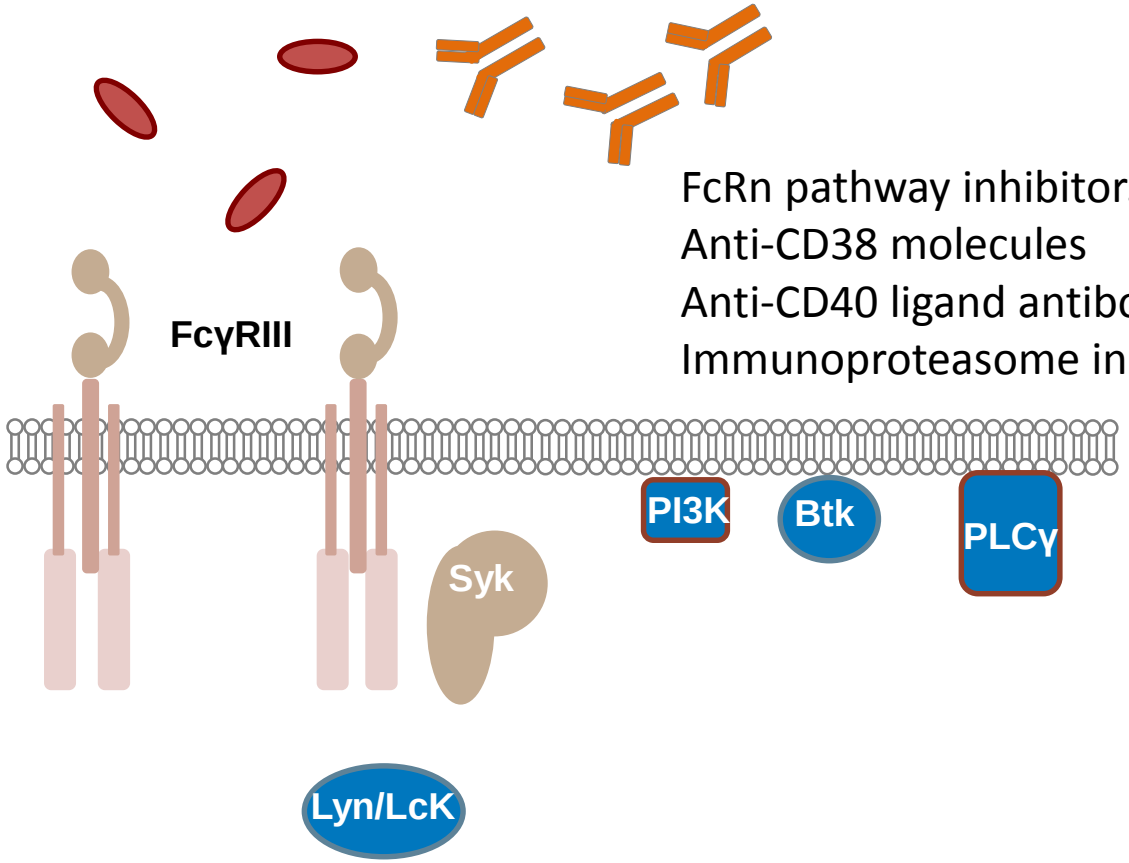
- **FcRn pathway inhibitors**
  - Increase clearance of antiplatelet antibody
- **Anti-CD38 molecules**
  - Inhibit plasma cells
- **Anti-CD40 ligand antibodies**
  - Reduce production of antiplatelet antibody
- **Immunoproteasome inhibitor**
  - Reduces antibody
- **Sialylated IgG**
  - Blocks macrophage FcR
- **Stradomers**
  - Recombinant Fc multimers reduce phagocytosis
- **Bruton kinase inhibitors**
  - Ibrutinib
  - Rilzabrutinib (PRN1008)
- **Syk kinase inhibitors**
  - Fostamatinib
- **Complement inhibitor**
  - Antibody against C1s
- **Recombinant TPO**
  - Use in pregnancy
- **Low-level laser light**
  - Prevents megakaryocyte apoptosis

FcR(n), (neonatal) Fc receptor; ITP, immune thrombocytopenia; Syk, spleen tyrosine kinase; TPO, thrombopoietin



Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

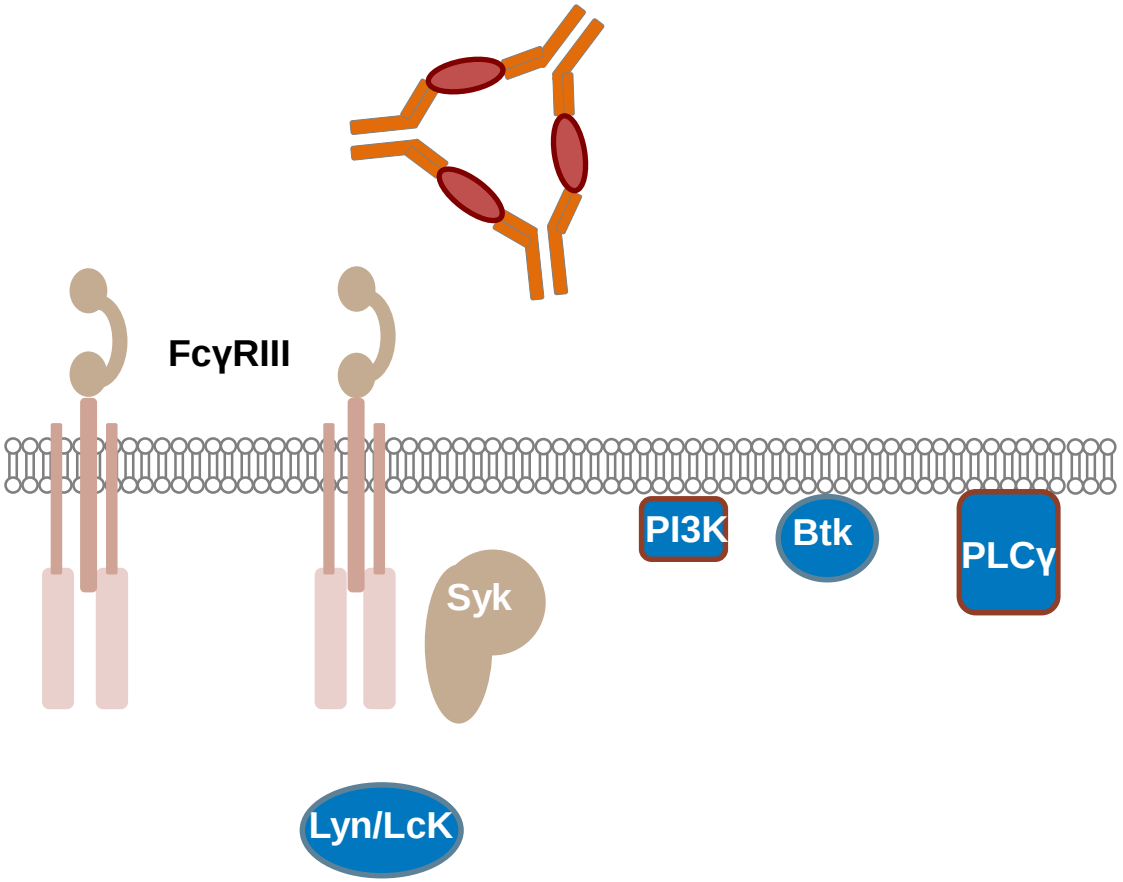
Nimmerjahn F, Ravetch JV. Ann Rev Immunol. 2008;26:513–33



FcRn pathway inhibitors
Anti-CD38 molecules
Anti-CD40 ligand antibodies
Immunoproteasome inhibitor

Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; FcRn, neonatal Fc receptor; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

Nimmerjahn F, Ravetch JV. Ann Rev Immunol. 2008;26:513–33



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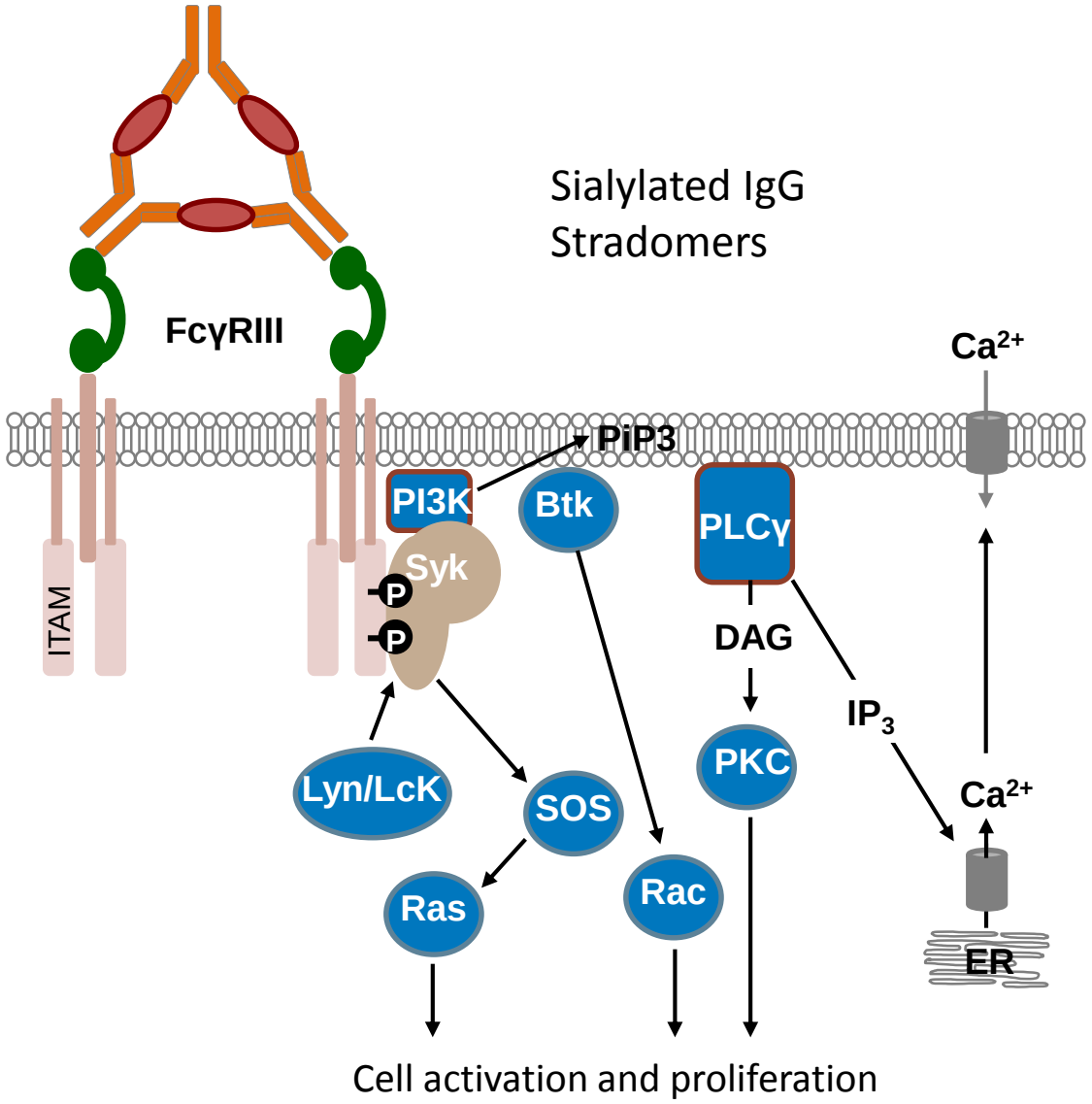
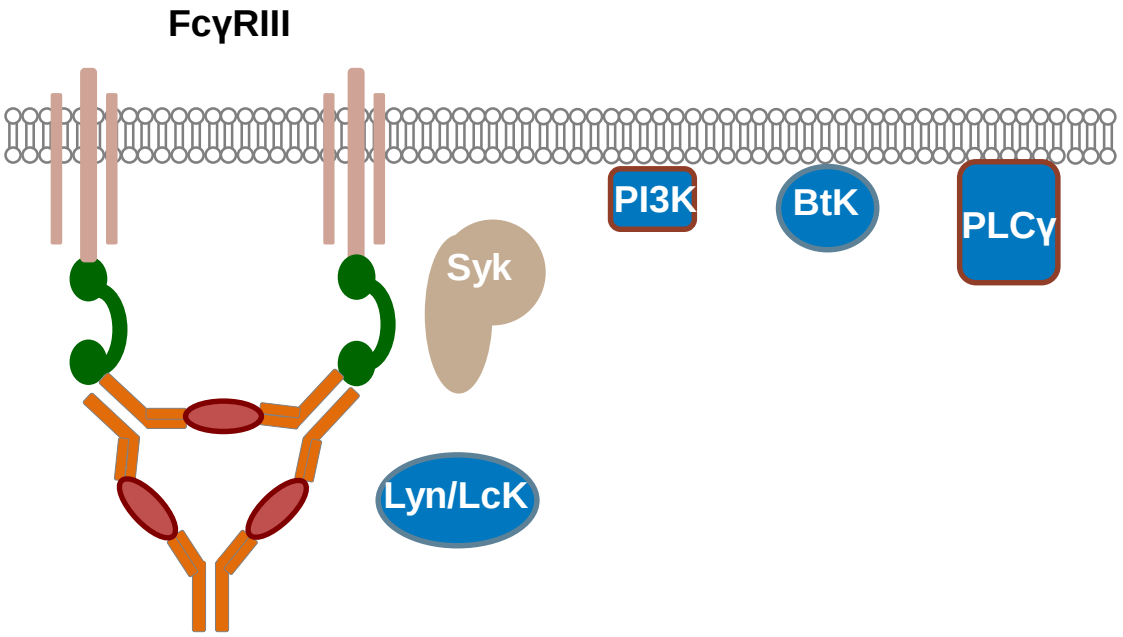


Btk, Bruton tyrosine kinase; ER, endoplasmic reticulum; FcγRIII, Fc gamma receptor III; IP3, inositol trisphosphate; ITAM, immunoreceptor tyrosine-kinase-based activation motifs; PiP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

Nimmerjahn F, Ravetch JV. Ann Rev Immunol. 2008;26:513–33

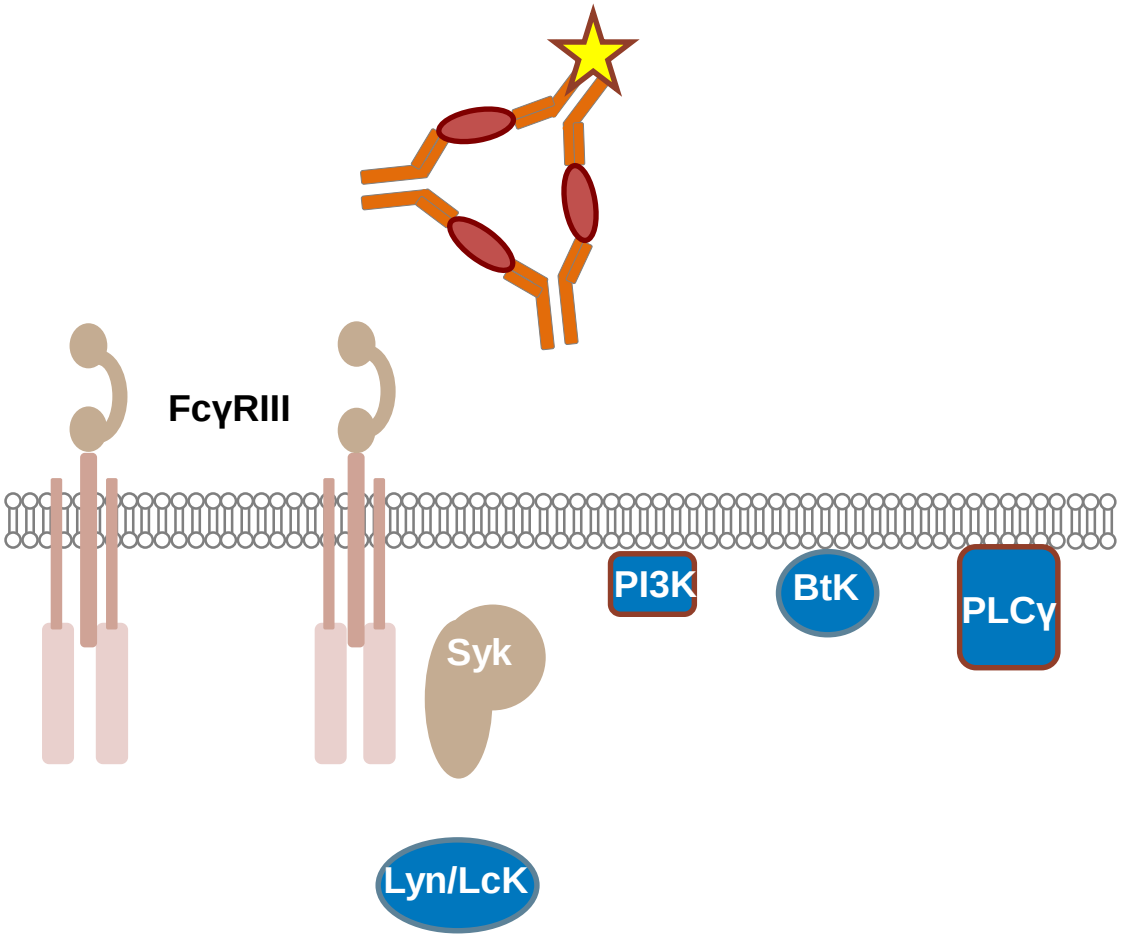
Bruton kinase inhibitor
Syk kinase inhibitors



Complex internalised

Btk, Bruton tyrosine kinase; FcγRIII, Fc gamma receptor III; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C gamma; Syk, spleen tyrosine kinase

Nimmerjahn F, Ravetch JV. Ann Rev Immunol. 2008;26:513–33



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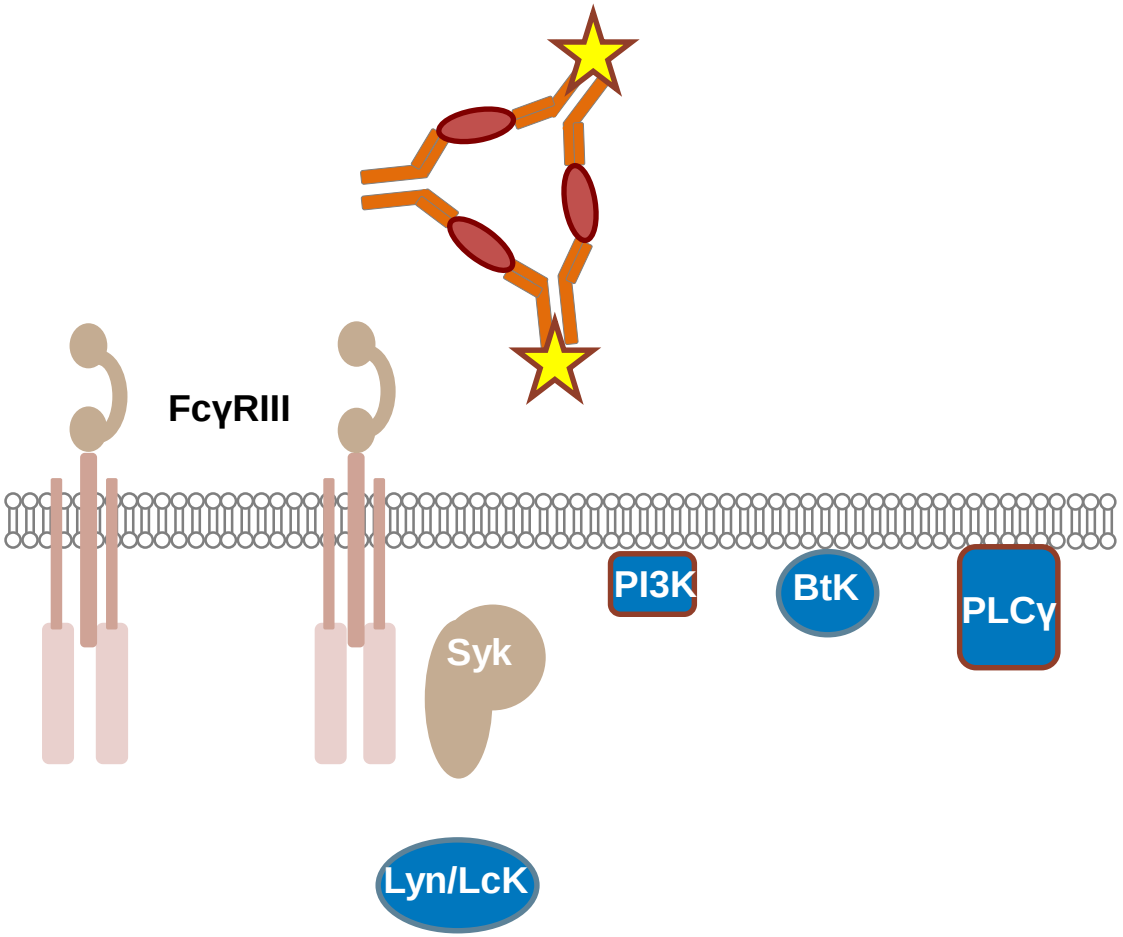

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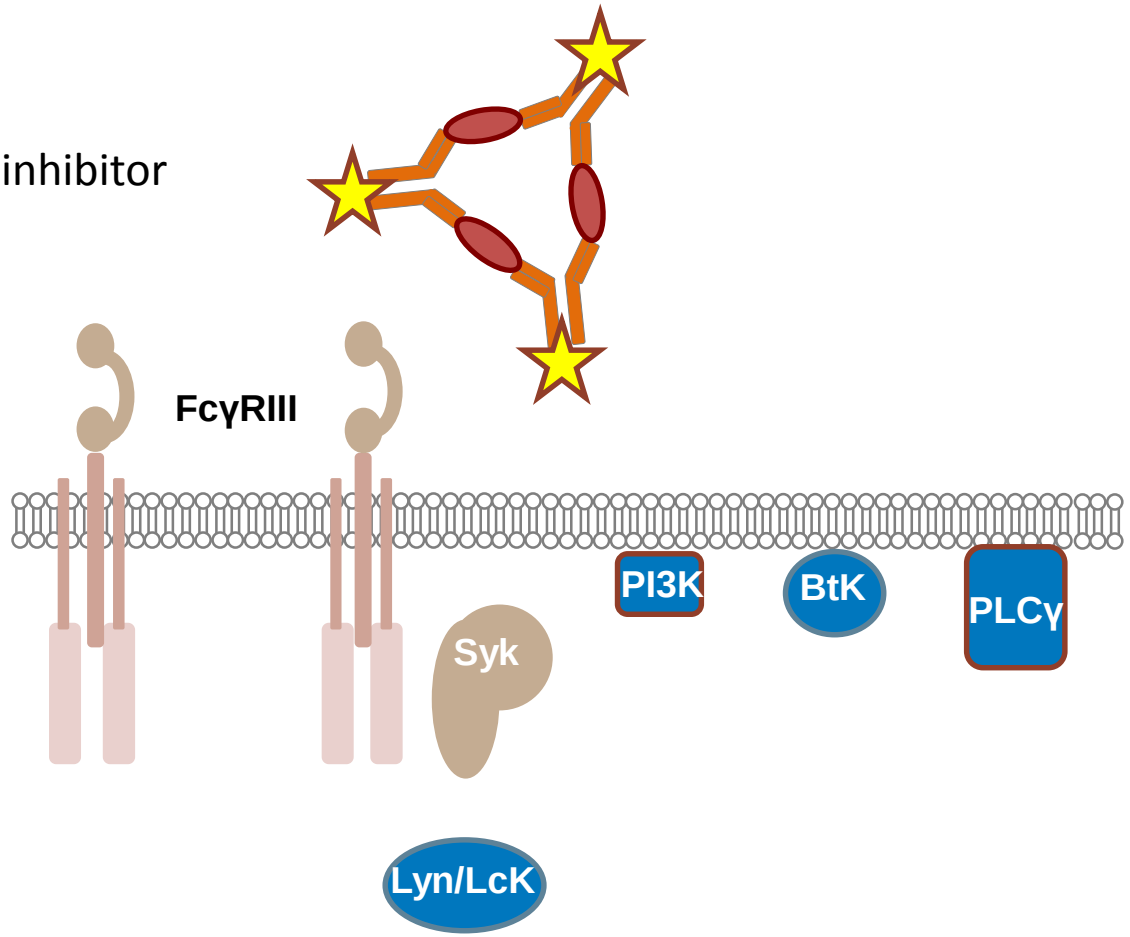
Nimmerjahn F, Ravetch JV. Ann Rev Immunol. 2008;26:513–33

Complement inhibitor



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Nimmerjahn F, Ravetch JV. Ann Rev Immunol. 2008;26:513–33

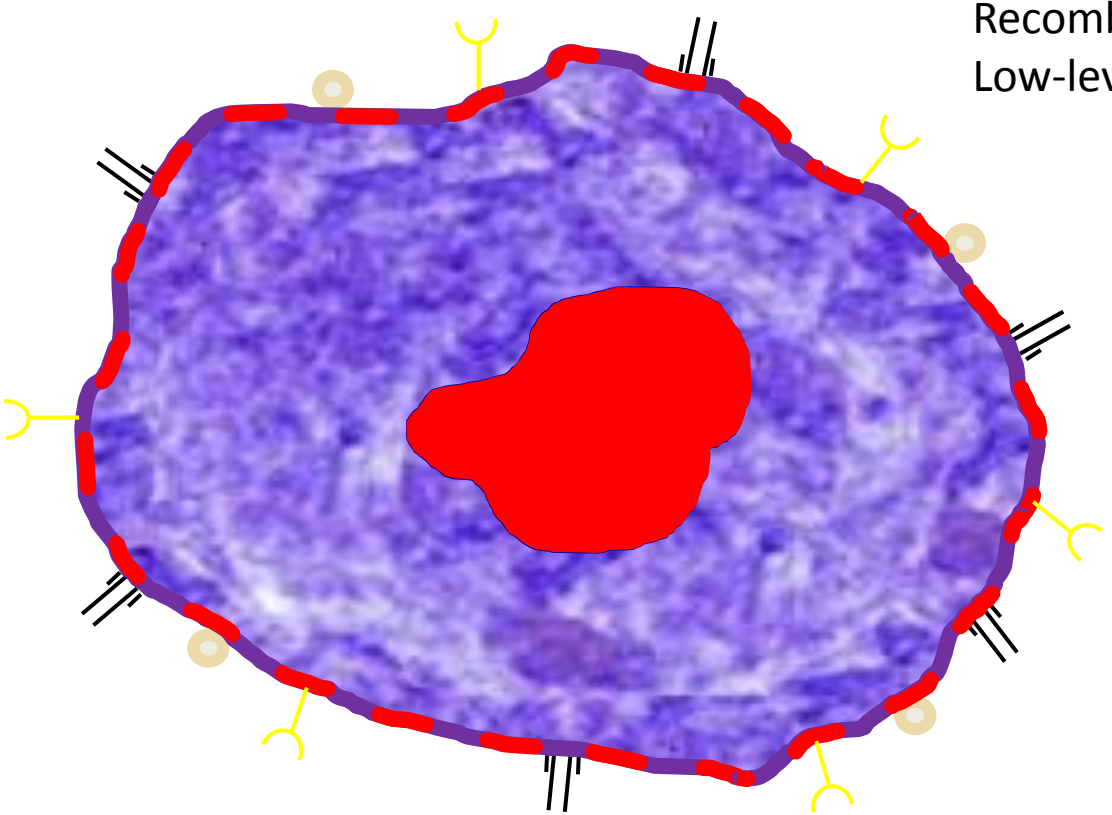
- TPO Receptor

Antiplatelet antibody

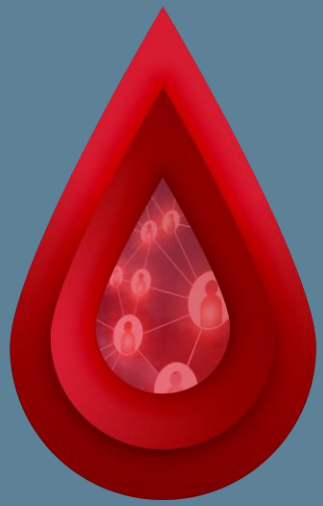
Antiplatelet lymphocyte

1. Antiplatelet antibody attacks megakaryocyte
2. Lymphocyte attacks megakaryocyte
3. Megakaryocyte undergoes apoptosis

Recombinant TPO
Low-level laser light



TPO, thrombopoietin



SUMMARY

SUMMARY

There is a range of medical options for the subsequent treatment of adults with primary ITP, including rituximab and TPO-RAs

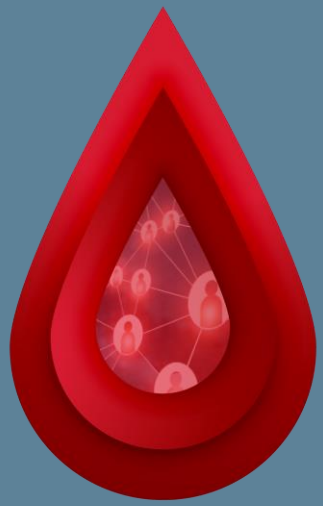
TPO-RAs have shown compelling evidence of platelet response and reduced bleeding; recent data indicate TPO-RAs are as effective in early ITP as chronic ITP

TPO-RAs can induce a long-lasting immunological response, however no consensus currently exists on when and how to taper

Key AEs associated with TPO-RAs include thrombosis, autoantibody formation, rebound worsening of thrombocytopenia and increased bone-marrow reticulin

Unmet needs remain in this disease area, requiring further research and consensus; novel drugs are expected in the years to come

AE, adverse event; ITP, immune thrombocytopenia; TPO-RA, thrombopoietin receptor agonist



APPENDIX

ISTH 2020 ABSTRACTS ON THE TREATMENT OF CHRONIC ITP IN ADULTS

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THE HEART OF MEDICAL EDUCATION

Abstracts are available at abstracts.isth.org

Abstract number	First author	Title
PB1316	J. Agnelli Giacchello	Megakaryocytic Hyperplasia in Bone Marrow Biopsy as a Novel Predictor of Response in Patients with Immune Thrombocytopenia
PB1318	D. Kuter	Phase I/II, Open-Label, Ongoing Study of PRN1008 (Rilzabrutinib), an Oral Bruton Tyrosine Kinase Inhibitor, in Patients with Heavily Pretreated Immune Thrombocytopenia (ITP)
PB1335	I. Altomare	Achieving Clinically Relevant Platelet Count Response Thresholds with Avatrombopag (AVA) in Immune Thrombocytopenia (ITP)
PB1343	J. Yamanouchi	Sustained Remission after Withdrawal of Thrombopoietin Receptor-Agonists in Immune Thrombocytopenia
PB1344	P. Zhao	Risk Stratification for Intracranial Hemorrhage in Adults with Immune Thrombocytopenia: A Retrospective Multicenter Study
PB1345	J. Gebhart	Factors Influencing Bleeding Severity in Adult Patients with Primary Immune Thrombocytopenia
PB1346	M. Stimpson	CD4+ T Cell Expression of IL-10 Compared to IL-17 is Lower in Patients with Immune Thrombocytopenia (ITP) Who Do Not Respond Clinically to High Dose Corticosteroid
PB1349	H. Maitland	Response to Avatrombopag (AVA) in Chronic Immune Thrombocytopenia: Alternative Efficacy Measures
PB1350	N. Gabrail	Pharmacokinetic/Phamacodynamic (PK/PD) Modeling Providing Guidance for Selecting Avatrombopag (AVA) Dose when Switching from Eltrombopag in Chronic Immune Thrombocytopenia (ITP)
PB1357	M. Marcosano	Long Term Complications after Splenectomy in Chronic pITP Patients: A Retrospective Case Control Study
PB1358	W. Ghanima	Fostamatinib as Second-Line Therapy for ITP and in Earlier Stage ITP Patients
PB1360	M.G. Mazzucconi	Randomized Study for the Treatment of Primary Immune Thrombocytopenic Purpura (pITP) in Newly Diagnosed Untreated Adult Patients. Comparison of Standard Dose Prednisone versus High-dose Dexamethasone. Preliminary Results. GIMEMA Protocol ITP0207
PB1363	M.G. Mazzucconi	Response Rate and Response Duration after Discontinuation of Treatment with Thrombopoietin Receptor Agonists (TPO-RAS) in Patients Affected by Primary Immune Thrombocytopenia (pITP): Retrospective Study. Preliminary Results. GIMEMA Protocol ITP0714
PB1378	M. Recht	Corticosteroid Reduction or Discontinuation after Initiation of Avatrombopag Treatment in Patients with Chronic Immune Thrombocytopenia (ITP)

ISTH, International Society on Thrombosis and Haemostasis; ITP, immune thrombocytopenia

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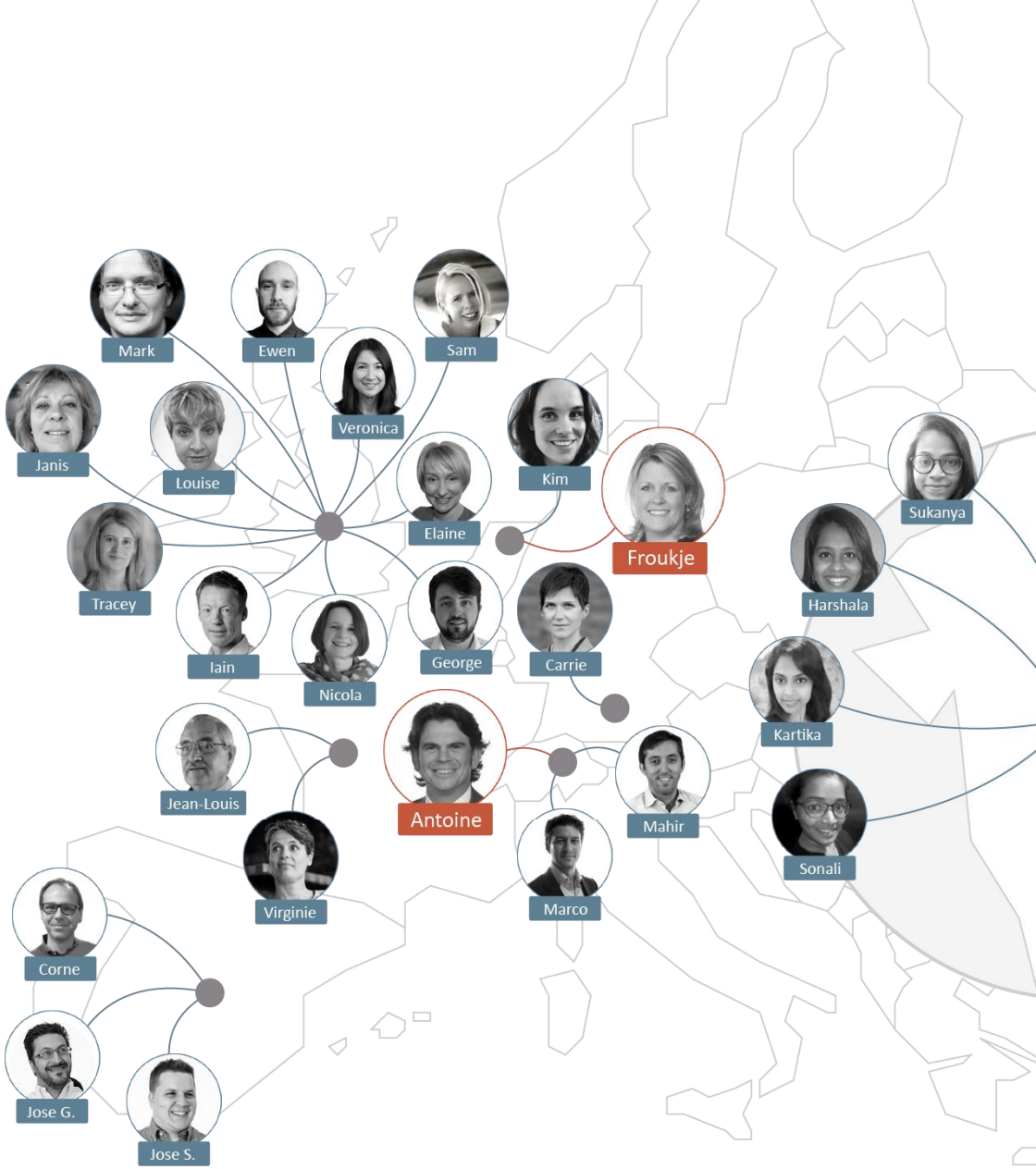

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