QUANTITATIVE PLATELET DISORDERS

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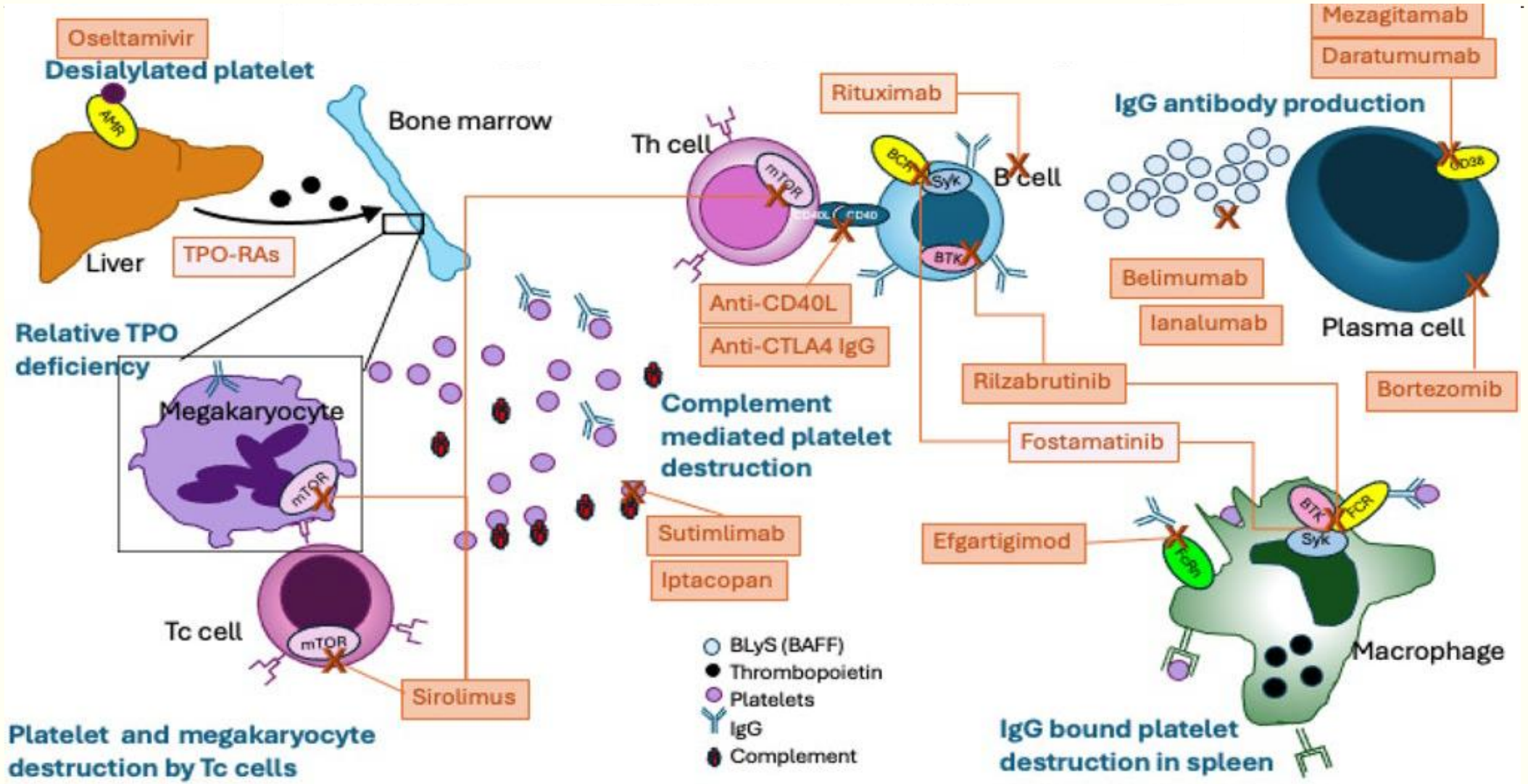
Objectives

- Novel approaches to ITP treatment
- Demystifying HIT
- New strategies in TTP

NOVEL APPROACHES TO ITP TREATMENT

ITP Biology with Regard to Therapeutics



New data on the burden of ITP

Outcomes

During average follow-up (2.3 vs 2.6 years), compared with matched population, the ITP cohort had a higher rate of:

- **Bleed-related hospitalization** (aRR 4.2 [95% CI 3.5–4.9])
- **Venous TE** (aRR 1.7 [95% CI 1.4–2.1])
- **CNS arterial TEs** (aRR 1.2 [95% CI 1.0–1.5])
- **Non-CNS arterial TEs** (aRR 1.5 [95% CI 1.1–1.9])
- **Malignancies** (RR 1.6 [95% CI 1.3–2.1])
- **Autoimmune conditions** (RR 4.0 [95% CI 2.3–7.1])
- **Infections** (RR 3.1 [95% CI 2.6–3.8])
- **New onset cognitive impairment/dementia** (RR 1.7 [95% CI 1.3–2.2])
- **Death**: 21% ITP vs 10% matched population. HR for death 1.5 (95% CI 1.2–1.7) after adjusting for potential confounders

Fatigue	Venous thromboses	Heavy menstrual bleeding
Unmet medical need	**Unmet medical need**	**Unmet medical need**
• Fatigue **affects HRQoL** and has significant **socioeconomic consequences**[1] • Fatigue affects 22–45% of patients with ITP[2] • Causes not fully understood[1]	• Adults with ITP have **greater risk of TE** vs general population[4] • Estimated VT incidence in ITP population: **0.41–0.67 per 100 person-years**[5]	• ITP may cause **HMB**, which can **impact QoL**[6] • Estimated **prevalence of HMB** in patients with ITP is 6–55% at **diagnosis** and 17–79% **during disease**[6] • **HMB may cause iron deficiency or IDA**[6]
Management[3]	**Management**	**Management**

• **Support** from ITP patient groups
• **Psychosocial support** includes:
  • Regular **exercise**
  • **Healthy eating**
  • **Reducing stress**
  • Balancing **home-work-life**
  • Talking to **family/friends**
	• **No standard treatment guidelines**[5]
	• **Treatments** include:[4]
	  • **Antithrombotics** e.g. warfarin, LMWH, DOAC
	  • **Anticoagulants + antiplatelet**
		• **Limited options that do not permanently impair fertility:**
		  • Antifibrinolytics ± hormonal therapy
		• **Options that permanently impair fertility:**
		  • Endometrial ablation; hysterectomy[6]
		• **Iron supplementation** for iron deficiency/IDA[7]

New data on first-line treatments for ITP

Treatment (N)	Study information	Outcomes
8 RCTs with participants ≥16 years receiving **dexamethasone** (n=427) and **prednisolone** (n=404)	• Systematic review and meta-analysis • Search of RCTs comparing dexamethasone 40 mg/d for 4 days per cycle to prednisolone 0.5–2.0 mg/kg/d for 4 weeks	• **Dexamethasone yielded higher IR rates vs prednisolone** (RR 1.21, 95% CI 1.09–1.34; I^2=52%, n=5 studies) • **No improvement in ER, DR and PR** • **No significant difference in IR, DR or PR observed between 1–2 vs 3 cycles of dexamethasone** • **Higher frequency of AEs in dexamethasone vs prednisolone arm** (n=141 vs n=71 events) • **n=20 grade ≥3 AEs** (dexamethasone n=7; prednisolone n=13) • **Dexamethasone was discontinued** in n=4 patients; **prednisolone was discontinued** in n=5 patients

New data on approved TPO-RAs for ITP (1)

Treatment (N)	Study information	Outcomes
Eltrombopag (N=103)[1]	• Retrospective study in China[1] • Children with primary ITP with ≥12 weeks of eltrombopag treatment and follow-up, receiving study drug between January 2020 and December 2022[1]	• **OR rate*: 67%; CR rate: 55.3%; R rate: 11.7%; DR rate†: 56.3%; TFR rate‡: 60.0%; relapse rate§:** 36.2%; **NR rate‖:** 33.0%[1] • **DR and TFR rate were significantly higher in patients with newly diagnosed vs persistent/chronic ITP:** DR, 68.8% vs 45.5% (p=0.017); TFR, 76.7% vs 35% (p=0.003)[1] • **Relapse rate significantly higher in patients with persistent/chronic vs newly diagnosed ITP:** 57.6% vs 16.7% (p=0.000)[1] • **AEs in n=14 patients; no SAEs reported; no AEs led to treatment discontinuation[1]** • **Patients aged 2–6 months (n=5): CR, DR and TFR rates 100%; no patients relapsed; AEs in n=3 patients[1]**
Eltrombopag (n=78) vs SOC¶ (n=40)[2]	• Prospective PINES trial in the USA (phase III)[2] • Children aged 1–<18 years with ITP <3 months and PC <30 x 10^9/L followed for 1 year[2] • Data collected May 2019 to January 2024[2]	• Primary outcome: **platelet response** achieved by 63% in eltrombopag arm vs 35% in SOC arm (n=108; p=0.0054)[2]** • **Rescue therapy** received by 18% vs 38% in eltrombopag arm vs SOC arm (n=117; p=0.02)[2] • **Composite endpoint*** at 12 weeks** achieved by 66% vs 44% in eltrombopag vs SOC arms (n=117; p=0.03)[2] • **Grade ≥3 AEs at 12 weeks:** Eltrombopag, n=9 AEs and n=6 SAEs; SOC, n=3 AEs and n=3 SAEs[2]

*Total of patients who have achieved CR and R; †PC ≥30 x 10^9/L and at least doubling of the baseline count at 6 months; ‡PC ≥50 x 10^9/L and the maintenance time ≥6 months after discontinuation of eltrombopag and its accompanying treatment; §patients need rescue treatment including the infusion of platelet and IVIG infusion, and using glucocorticoid either during or after discontinuation of eltrombopag treatment; ‖PC <30 x 10^9/L, or less than a twofold increase in the baseline count, or bleeding events when the patient had received an appropriate dose of eltrombopag for 8 weeks. ¶Investigators choice of one of three standard therapies (prednisone, IVIG or anti-D); **≥3 of 4 PCs >50 x10^9/L during weeks 6–12 without rescue treatment; ***PC ≥30 x 10^9/L and two-fold increase and no bleeding. AE, adverse event; CR, complete R; DR, durable R; ITP, immune thrombocytopenia; NR, no R; OR, overall R; PC, platelet count; PR, persistent R; R, response; SAE, serious AE; SOC, standard of care; TFR, treatment-free remission.

1. Yang L, et al. *Ann Hematol*. 2024;103:2721–7; 2. Shimano KA, et al. Presented at: 66th ASH Annual Meeting and Exposition, 7–10 December 2024, San Diego, CA, USA. Abstr 709.

New data on approved TPO-RAs for ITP (3)

Treatment (N)	Study information	Outcomes
Avatrombopag (N=190 safety; n=18 effectiveness)[1]	• ADOPT study (phase IV)[1] • Adult patients ≥18 years with primary ITP in Europe[1] • Data cutoff 2 May 2024[1]	• **Primary outcome: Cumulative number of weeks with PC ≥30 x 10^9/L**: mean (SD) 45.9 (10.8) weeks; median (min, max) 50.4 (5.9, 51.4) weeks[1] • **Cumulative number of weeks with PC ≥50 x 10^9/L**: mean (SD) 43.5 (12.7) weeks; median (min, max) 47.2 (0.0, 51.4) weeks[1] • **PC ≥30 x 10^9/L and PC ≥50 x 10^9/L for ≥8 consecutive weeks:** n=17[1] • **All AEs / SAEs:** n=29 patients / n=15 patients (n=2 discontinued treatment)[1] • **TRAEs:** n=10 patients • **Improvement in HRQoL associated with treatment:** Mean change in FACIT-F score at month 12 of -4.0[1]
Avatrombopag (N=72)[2]	• REAL-AVA 2.0 retrospective chart review study[2] • Adult patients with primary persistent (n=21) or chronic ITP (n=51) in the USA who initiated treatment with avatrombopag between July 2019 and June 2024[2] • Data cutoff 11 October 2024[2]	• **Primary outcome: 90% of patients achieved or maintained a PC ≥30 x 10^9/L** (median time to response 9.0 days) **or ≥50 x 10^9/L** (median time to response 13.0[2] days)**; 85% achieved or maintained a PC ≥100 x 10^9/L** (median time to response 21.0 days) [2] • **Mean duration of response** for all patients was >1 year at each PC threshold[2] • **Mean (SD) durability of response** for all patients was 90% (17%) at PC ≥30 x 10^9/L, 85% (22%) PC at ≥50 x 10^9/L and 71% (29%) at PC ≥100 x 10^9/L[2] • 79% of patients on concomitant steroids at study initiation (n=15/19) discontinued their use after avatrombopag initiation; n=2/3 patients receiving concomitant immunosuppressants discontinued their use after avatrombopag initiation[2]

Switching from Eltrombopag/Romiplostim to Avatrombopag

New data on approved TPO-RAs for ITP (2)

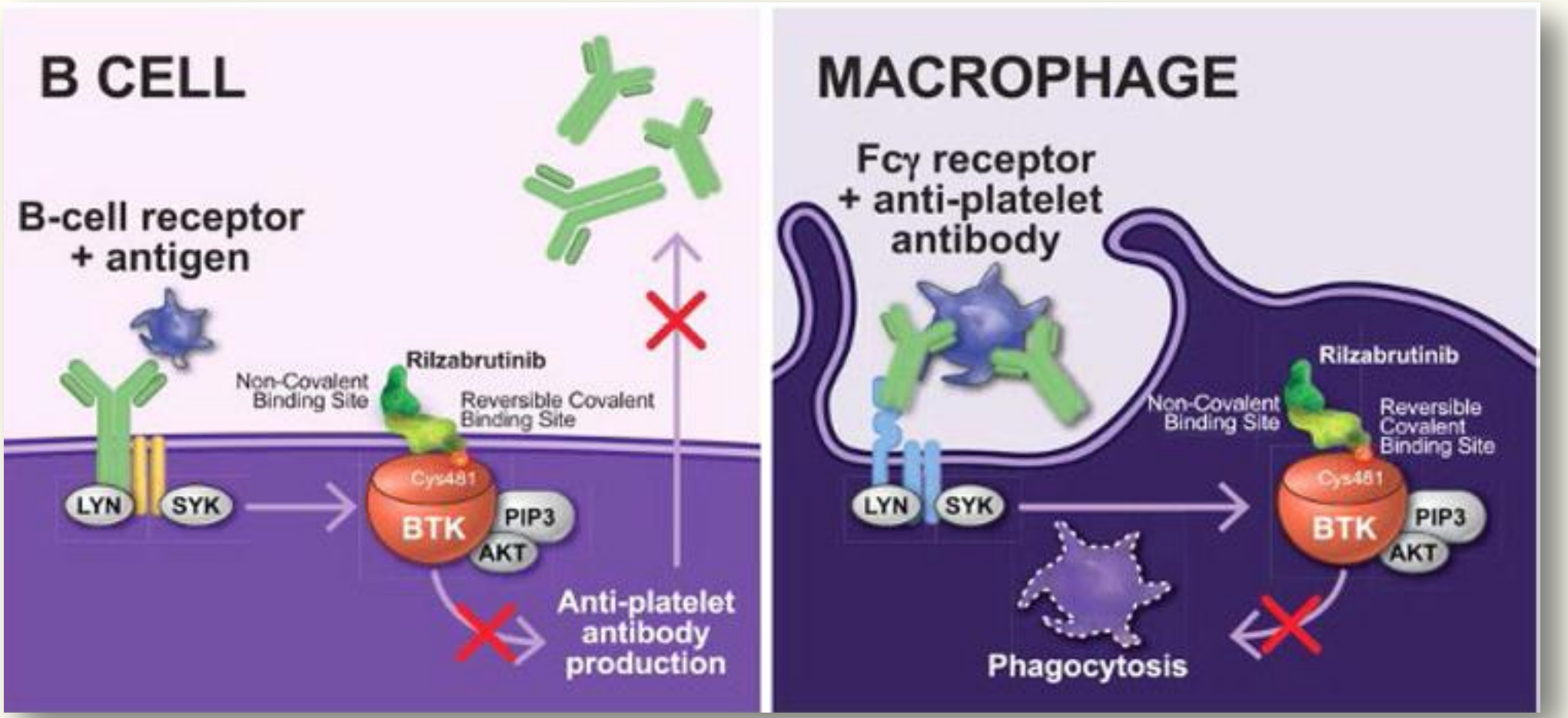
Treatment (N)	Study information	Outcomes
Switch from eltrombopag or romiplostim to **avatrombopag** (N=60; n=38 switched from eltrombopag and n=22 switched from romiplostim)[1,2]	• Prospective study in the USA (phase IV)[1,2] • Patients receiving prior TPO-RA for ≥90 days with any PC response[1,2] • Patients switched due to ineffectiveness (28%), convenience (63%) and AEs (13%)[1,2]	• **TEAEs in 25% (n=15/60); serious TEAE in 10% (n=6/60)**[1] • **PCs improved or maintained** at 90 days[1] • **Significant improvement in satisfaction (TSQM domain score mean difference from baseline to day 90/EOS):** for effectiveness, convenience and global satisfaction (all p<0.001); for side effects (p=0.01)[1] • **Post hoc analysis (n=55):** Median TSQM scores increased for convenience, effectiveness and global satisfaction for eltrombopag switchers, and for convenience and global satisfaction for romiplostim switchers at Day 90 regardless of baseline dose[2]

Novel non-TPO-RA agents

Sovleplenib	Rilzabrutinib	Avatrombopag (paediatric use)	Mezagitamab
SYK inhibitor[22]	BTK inhibitor[23]	TPO-RA[25]	CD38 inhibitor[21]

ESLIM-01[22]	LUNA 2[23,24]	AVA-PED-301[25]	NCT04278924[21,26]
Phase III	Phase II	Phase III	Phase II
Randomized 2:1 sovleplenib (n=126) vs placebo (n=62) 300 mg QD	Rilzabrutinib (N=71) 400 mg BID	Randomized 3:1 avatrombopag (n=54) vs placebo (n=21) 10 or 20 mg QD (age dependent)	Randomized mezagitamab (n=28) vs placebo (n=13) 100, 300 or 600 mg QW
DRR: 48% vs 0% (p<0.0001)* **ORR** (all p<0.0001) • **≥1 PC ≥50 x 10^9/L:** 71% vs 16%† • **Two consecutive PCs ≥30 x 10^9/L and double from BL:** 73% vs 6% • **PC ≥30 x 10^9/L and increased ≥20 x 10^9/L from BL:** 75% vs 22%‡	**Pooled outcomes**[23] • **Durable response:** 28%§ • **Overall response:** 41%‖ • **Complete response:** 35%¶ **Long-term outcomes**[24] • n=8/17 discontinued ≥1 or↓ concomitant ITP therapy • Visits reaching median PC of ≥50 x 10^9/L: 90%	• **DPR:** 27.8% vs 0% of patients (p=0.0077)** • **PR:** 81.5% vs 0% of patients (p<0.0001)*† • **PC ≥50 x 10^9/L:** 48.9% vs 1.2% of weeks (p<0.0001)*‡ • **PC ≥50 and ≤150 x 10^9/L:** 29.2% vs 1.2% of weeks (p<0.0001)*‡	**Mezagitamab 100/300/600 mg vs placebo** • **PR:** 66.7/62.5/90.9% vs 23.1%*§ • **Complete PR:** 55.6/50.0/81.8% vs 0%*‖ • **Clinically meaningful PR:** 66.7/75.0/90.9% vs 30.8%*¶ • **Haemostatic PR:** 40.0/25.0/100% vs 0%***
TEAEs: 99% vs 85% **Grade 3/4 TEAEs: 25% vs 24%** **Most common TEAEs:** URTI, COVID-19, ↑ blood LDH **GI toxicities**: Nausea 1.6% vs 3.2%; vomiting 1.6% vs 1.6%; diarrhoea 1.6% vs 0% **Thromboembolic events:** 0%	**All AEs:** 86%[23] (LT data: 81%)[24] **TRAEs:** 61%[23] (LT data: 41%)[24] **Grade ≥3 AEs:** 17% (all TRAEs grade 1/2)[23] **Most common TRAEs:** Diarrhoea; nausea; headache; fatigue; vomiting[23] **Thromboembolic events:** 0%[23,24]	**TEAEs:** 92.6% vs 76.2% **TRAEs:** 13.0% vs 4.8% **Most common TEAEs:** Petechiae; epistaxis; bruising; headache **Thromboembolic events:** 0%	**TEAEs:** 67.9% vs 69.2% **TRAEs:** 32.1% vs 38.5% **Grade ≥3 TEAEs:** 17.9% vs 23.1%

Rilzabrutinib

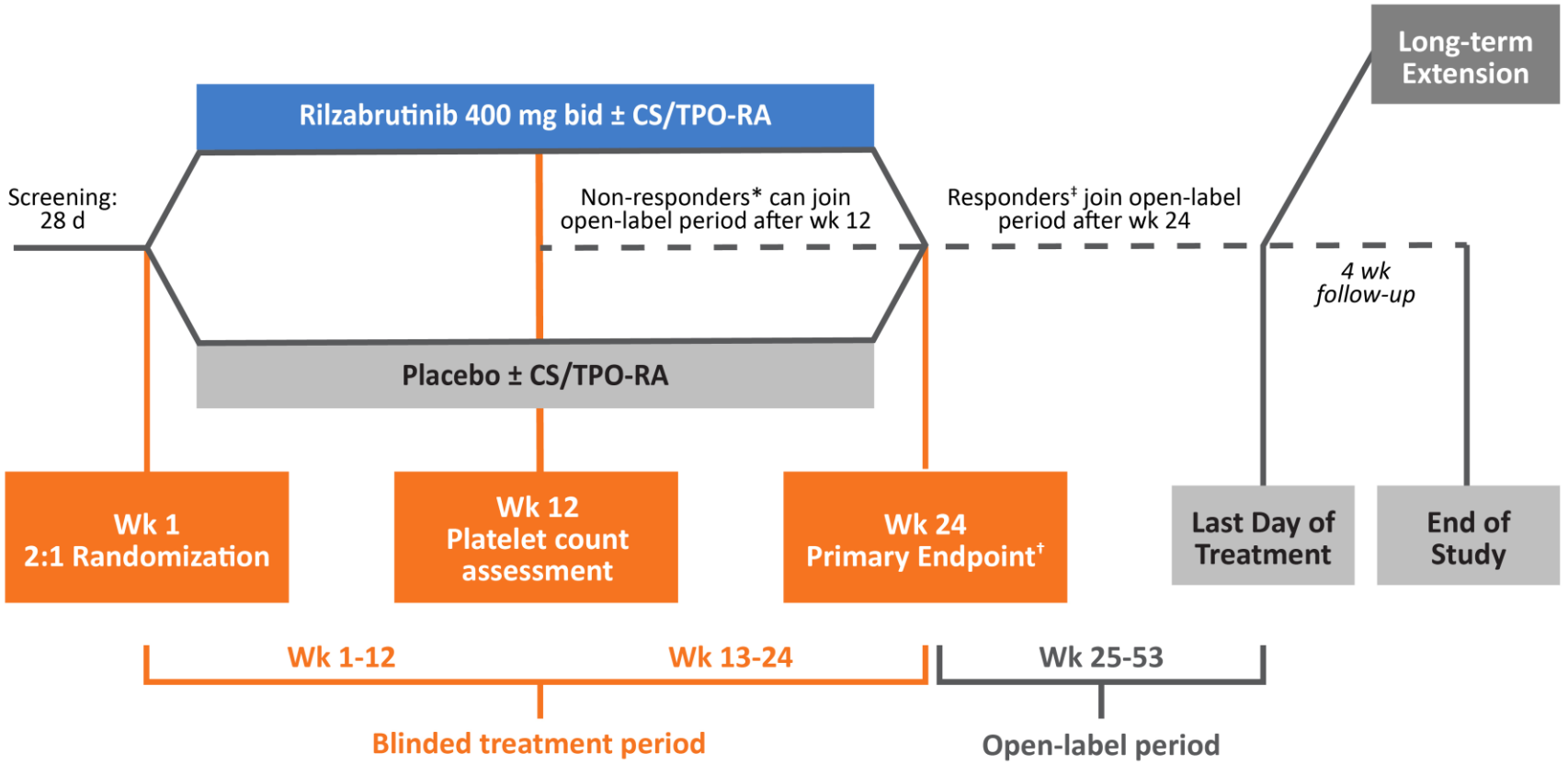


LUNA 3

Figure. LUNA3 Phase III Study Design

Primary ITP Patients

- Persistent or chronic
- n=194 adults aged ≥18 y with primary ITP >3 mo
- n=30 adolescents aged 12-17 y with primary ITP >6 mo



*Non-responder: platelet counts <30×10^9/L or <20×10^9/L above baseline on two consecutive visits.
†Primary endpoint: platelet counts ≥50×10^9/L for ≥8 of the last 12 wk of the 24-wk blinded treatment period without rescue medication.
‡Responder: platelet counts ≥50×10^9/L or ≥30×10^9/L and at least doubled from baseline at ≥50% of visits without rescue therapy during the last 8 wk of the open-label period.

LUNA 3

Outcomes
• **Primary outcome: Durable response* at week 25 was met** (23% difference between rilza vs placebo (95% CI 16–30%; p<0.0001))[1] • **Duration of PR†:** significantly longer all patients and responders receiving rilza vs placebo (p<0.0001 for both)[1] • **Significantly less rescue therapy use** associated with rilzabrutinib vs placebo (p=0.0007)[1] • **Similar proportion of AEs and SAEs**[1]
• **Significant improvement in physical fatigue** from baseline to week 13 (p=0.0114) and week 25 (p=0.0003) with rilza vs placebo (assessed by LS mean change)[2] • **Improvements in multiple measures of ITP-specific HRQoL at week 25** observed with rilza vs placebo (symptoms, bother-physical health, activity, psychological health, social activity and overall HRQoL)[2]

Tapering TPO-RA

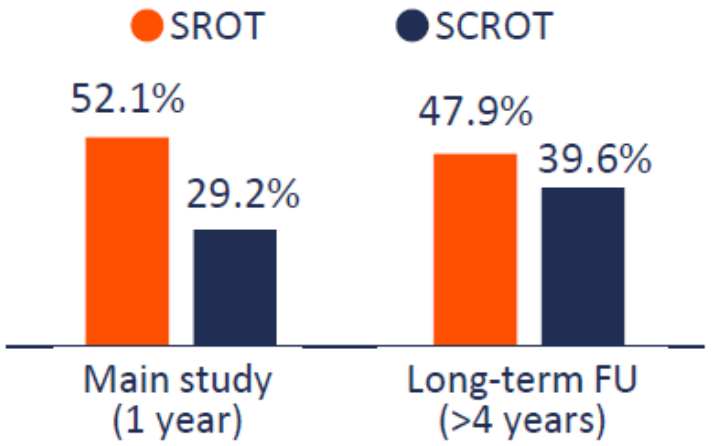
Treatment (N)	Study information	Outcomes
TPO-RA (N=48)[1]	• Open prospective, multicentre trial in France[1] • Adult patients with persistent/chronic primary ITP who achieved CR* for >3 months on a TPO-RA[1] • Enrolment between September 2017 and February 2020[1]	• **Achieved SROT† at 12 months:** n=25/48[1] • Followed-up for a median of 5 years (range 4–6.3 years)[1] • **Achieved SROT† and SCROT‡ at the end of follow-up:** 47.9% (n=23/48) and 39.6% (n=19/48), respectively, in the ITT group[1] • **Relapsed during extended follow-up:** n=2 (no bleeds)[1]
Romiplostim for 1 year, followed by tapering and follow-up for ≤1 year (N=39)	• Prospective STIP trial in the Netherlands to determine rate of SROT§[2] • Adults with persistent/chronic ITP (77% with chronic ITP; 41% received ≥2 prior treatment lines)[2]	• **Primary outcome: SROT at 1 year after tapering (n=25):** 23.6%[2] • **Patients with SROT had higher PCs and received lower doses of romiplostim**[2] • **Median time to relapse** 58 days[2] • **Only mild bleeding reported during/after tapering** in 41.2% (n=7/17) in patients who relapsed[2]

STOP & GO :
RFS after discontinuing TPO-RA in chronic ITP

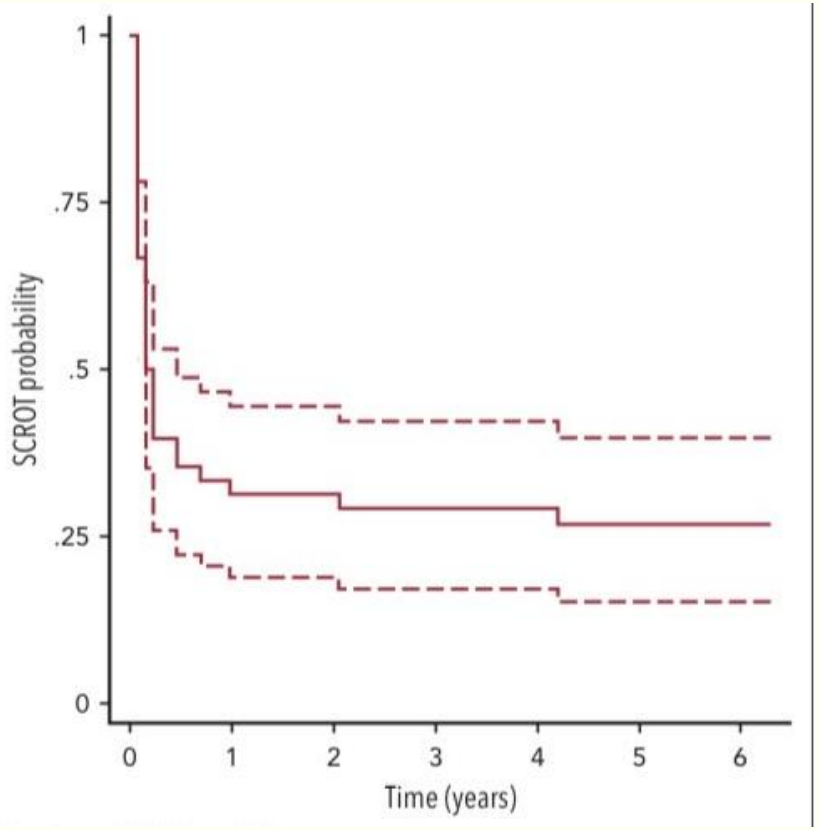
- **Prospective, multicenter study**
- **French ITP reference center network**
- **Persistent or chronic ITP & had achieved a platelet count >100 × 10_9/L for at least 2 months on**
- **Either eltrombopag or romiplostim. After**

Long-term follow-up of the STOPAGO study in persistent/chronic primary ITP (N=48)[18]

Clinical response after TPO-RA discontinuation



~50% of patients maintained SROT for >4 years after TPO-RA discontinuation

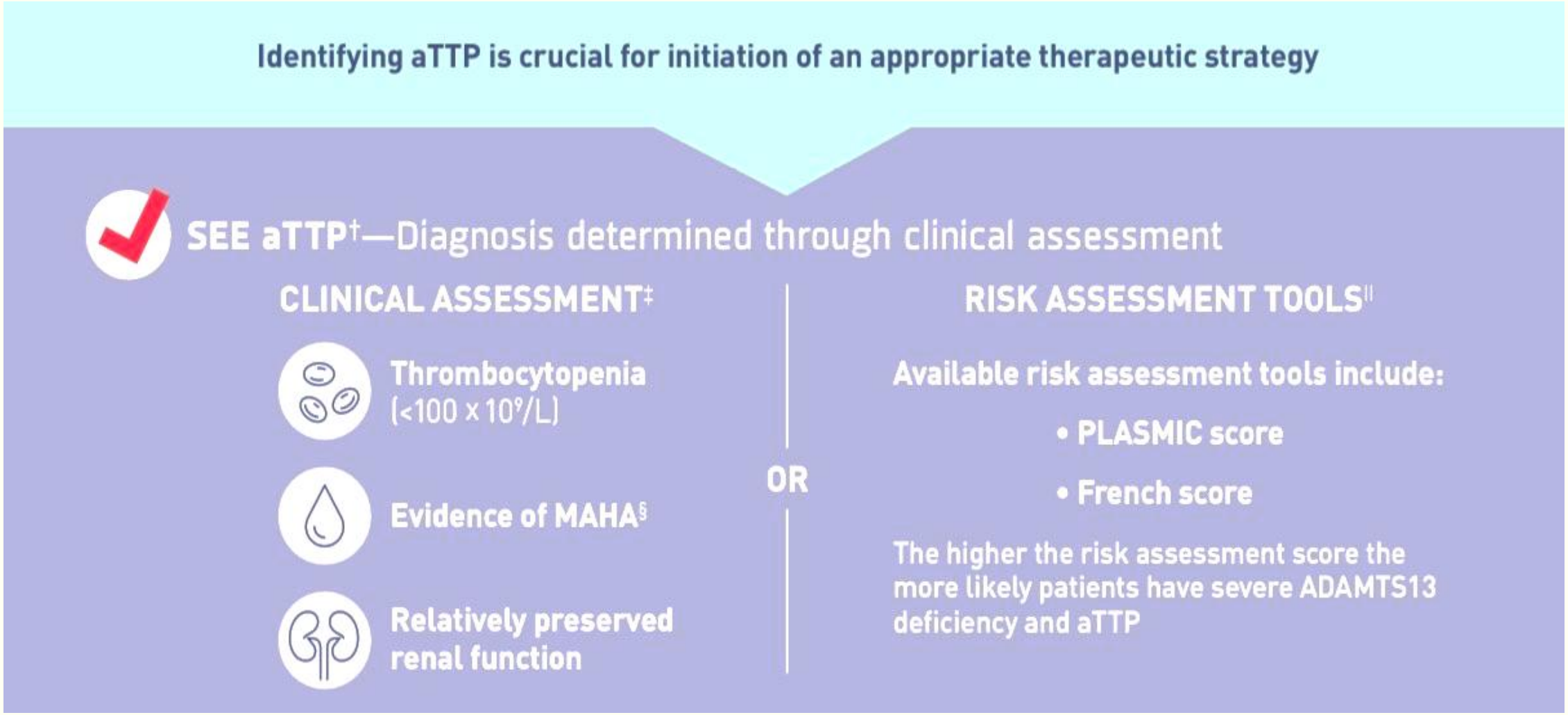


NEW STRATEGY IN TTP

Table 3 Etiology-based subclassifications and clinical diagnoses of TMA

Etiology-based subclassification	Etiology	Underlying cause	Clinical diagnosis	Important clinical findings
ADAMTS13-deficient TMA	Severe decrease in ADAMTS13 activity	*ADAMTS13* gene abnormality	Congenital TTP (Upshaw-Schulman syndrome)	*ADAMTS13* gene abnormality
		Anti-ADAMTS13 autoantibodies	Immune-mediated TTP	Severe decrease in ADAMTS13 activity and the presence of anti-ADAMTS13 autoantibodies
Infection-induced TMA	Infection	STEC (e.g., *Escherichia coli* O157)	STEC-HUS	STEC infection established by blood or stool culture
		Neuraminidase-secreting *Streptococcus pneumoniae*	Pneumococcal-associated HUS	Proven pneumococcal infection
Complement-mediated TMA	Complement abnormality	Hereditary complement abnormalities (e.g., factors B, H, and I; C3; and membrane cofactor protein)	Atypical HUS	Genetic complement factor abnormalities; Low C3 and normal C4 levels (not necessarily observed in all patients with atypical HUS)
		Anti-factor H antibodies		Proven presence of anti-factor H antibodies
Coagulation-mediated TMA	Coagulation abnormality	Mutations in diacylglycerol kinase ε and thrombomodulin genes	Atypical HUS (possibly)	Proven genetic mutations
Secondary TMA	Unknown	Autoimmune diseases	Connective tissue disease–associated TMA, etc	SLE, scleroderma, or other connective tissue disorders
		Hematopoietic stem cell transplant	Hematopoietic stem cell transplantation–associated TMA	Unresponsive to platelet transfusion Hemolysis (accompanied with, e.g., low haptoglobin levels)
		Organ transplant (e.g., kidney, liver)	Post–organ transplant TMA	Thrombocytopenia of unknown etiology and hemolysis (accompanied with, e.g., low haptoglobin levels)
		Malignant tumors	Tumor-associated TMA	Frequently diagnosed in patients with malignant lymphomas, stomach cancer, and pancreatic cancer
		Pregnancy	Pregnancy-associated TMA, HELLP syndrome	HELLP syndrome typically develops at ≥ 30 weeks of gestation in combination with hypertension
		Drugs (e.g., mitomycin)	Drug-induced TMA	Medication prescription
Other TMAs	Unknown	Other	TTP-like disorders or similar	Classic TTP pentad

Thrombotic Thrombocytopenic Purpura



Risk Assessment Tools

Parameters	French score	PLASMIC score
Platelet count	$<30\times10^9$/L (+1)	$<30\times10^9$/L (+1)
Serum creatinine	<2.26 mg/dL (+1)	<2.0 mg/dL (+1)
Hemolysis		+1
Indirect bilirubin > 2 mg/dL or reticulocyte count > 2.5% or undetectable haptoglobin		
No active malignancy in previous year		+1
No history of solid organ or stem cell transplantation		+1
PT-INR < 1.5		+1
MCV < 90 fL		+1
Likelihood of severe decrease in ADAMTS13 activity (< 10%)	0: 2%	0–4: 0–4%
	1: 70%	5: 5–24%
	2: 94%	6–7: 62–82%

The French and PLASMIC scores range from 0–2 to 0–7, respectively

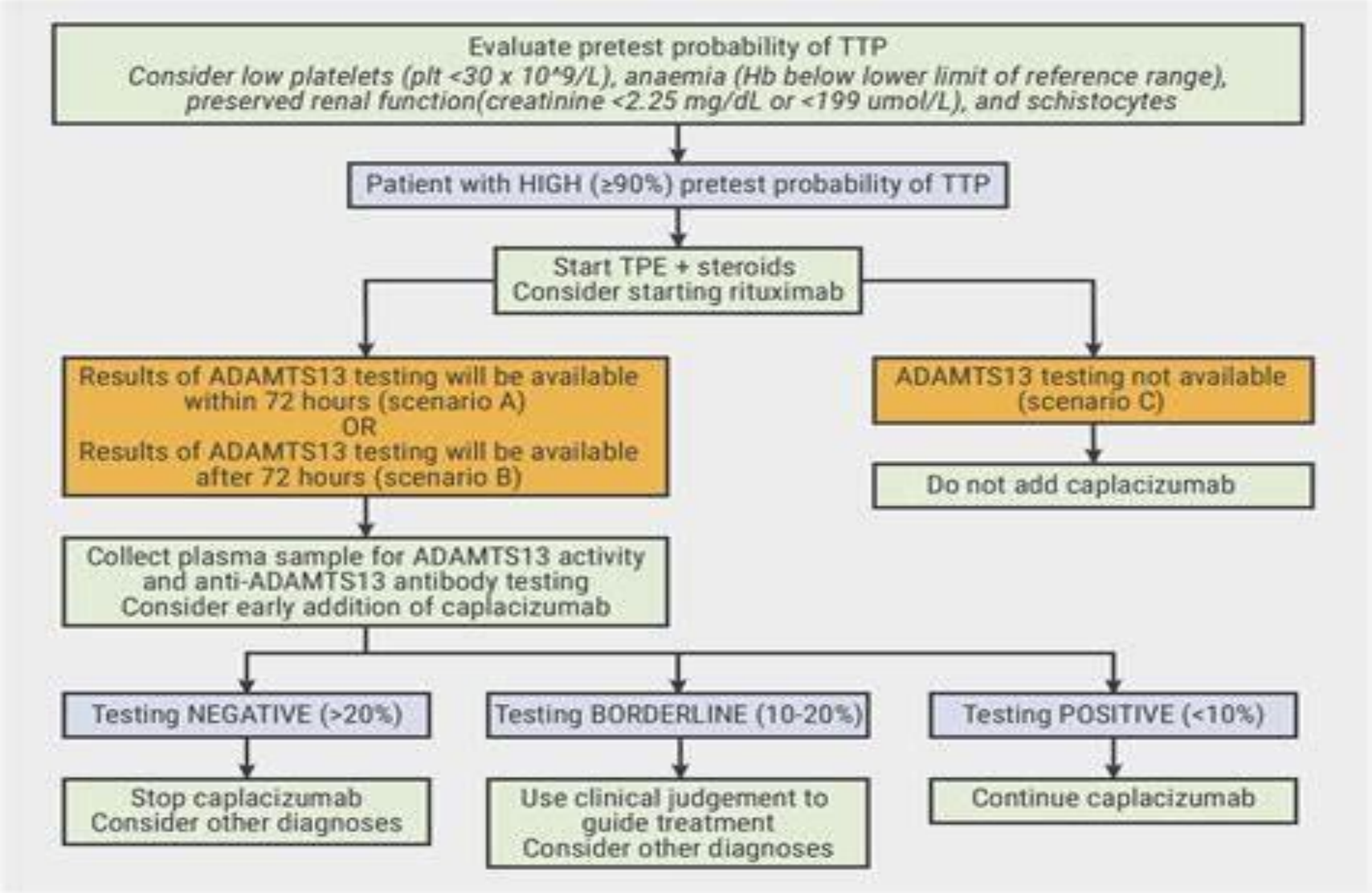
These two scoring systems are used in patients suspected of having thrombotic microangiopathy. This table was adapted from reference [23]

PT-INR prothrombin time-international normalized ratio; *MCV* mean corpuscular volume; *ADAMTS13* a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13

TTP Burden **REVOLUTIONIZED**

- TTP was formerly associated with a poor prognosis, with a mortality rate > 90% in untreated patients
- Survival rate to approximately 80%
- High levels of serum creatinine and ADAMTS13 inhibitor titers of ≥2 BU/mL are poor prognostic factors in patients with ADAMTS13 activities < 10%
- Cardiovascular death

Algorithmic Approach

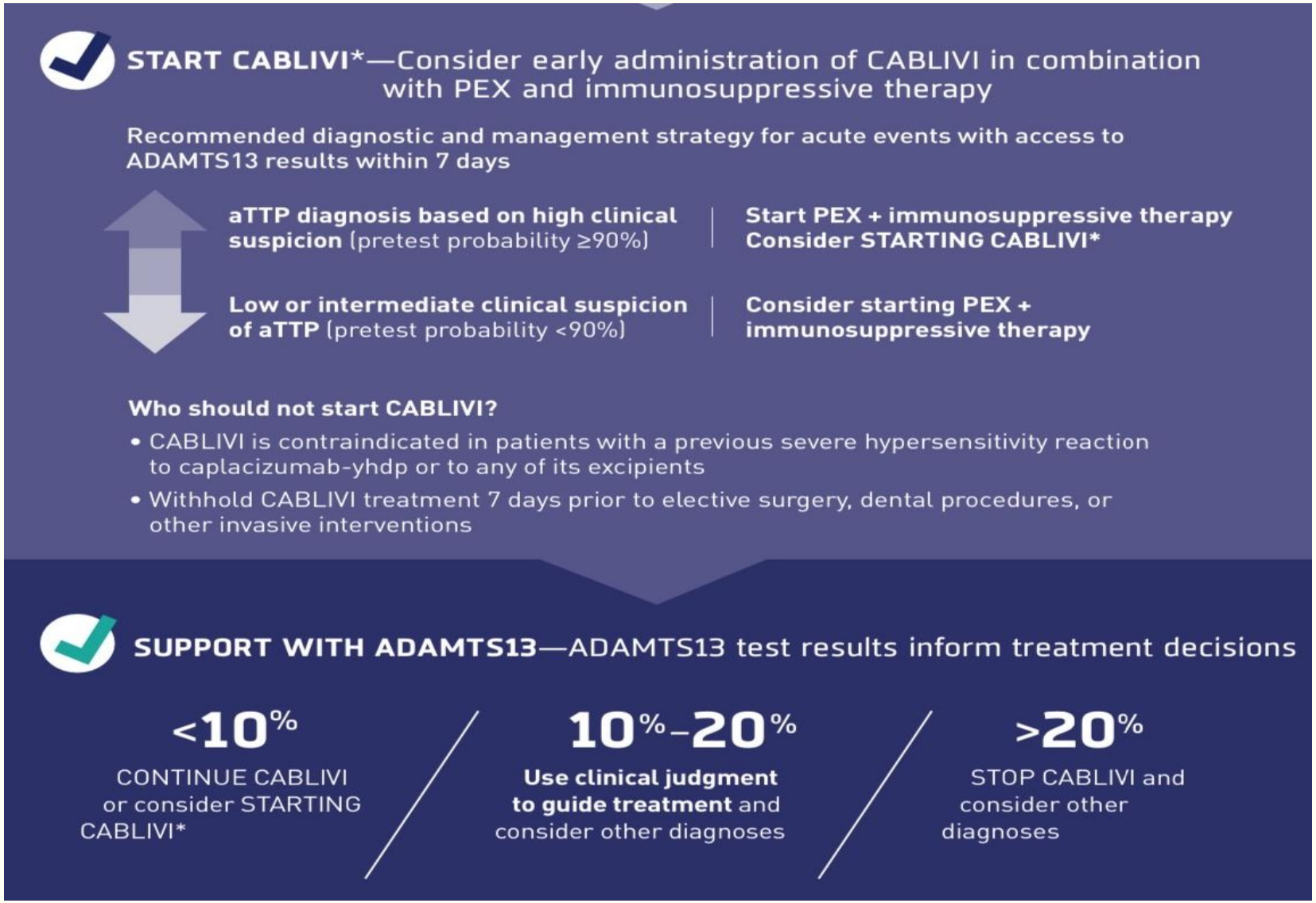


Treatment

- Plasma exchange is the only historically accepted treatment modality for iTTP
- The FFP volume is 1.0–1.5times the patient's circulating plasma volume
- ADAMTS13 supplementation
- Removal of ADAMTS13 inhibitors
- Elimination of UL-VWFMs unsusceptible to proteolytic cleavage
- Corticosteroids are expected to suppress autoantibody production.
- Caplacizumab significantly reduced the time to platelet count normalization when administered concomitantly with plasma exchange and corticosteroid therapy.

Caplacizumab

ISTH GUIDELINES RECOMMEND CABLIVI*



Caplacizumab therapy

✓Caplacizumab 10 mg first day, intravenously

✓15 min before the start of plasma exchange

✓Second dose 10 mg subcutaneously after the end of the plasma exchange

- 10 mg subcutaneously after each daily plasma exchange
- Once-daily 10-mg doses subcutaneously for 30 days

- If ADAMTS13 activity remains < 10% after the 30 days, caplacizumab may be continued for an additional 28 days

- Should be discontinued immediately if ADAMTS13 activity ≥10% and TTP is ruled out

DEMYSTIFYING HIT

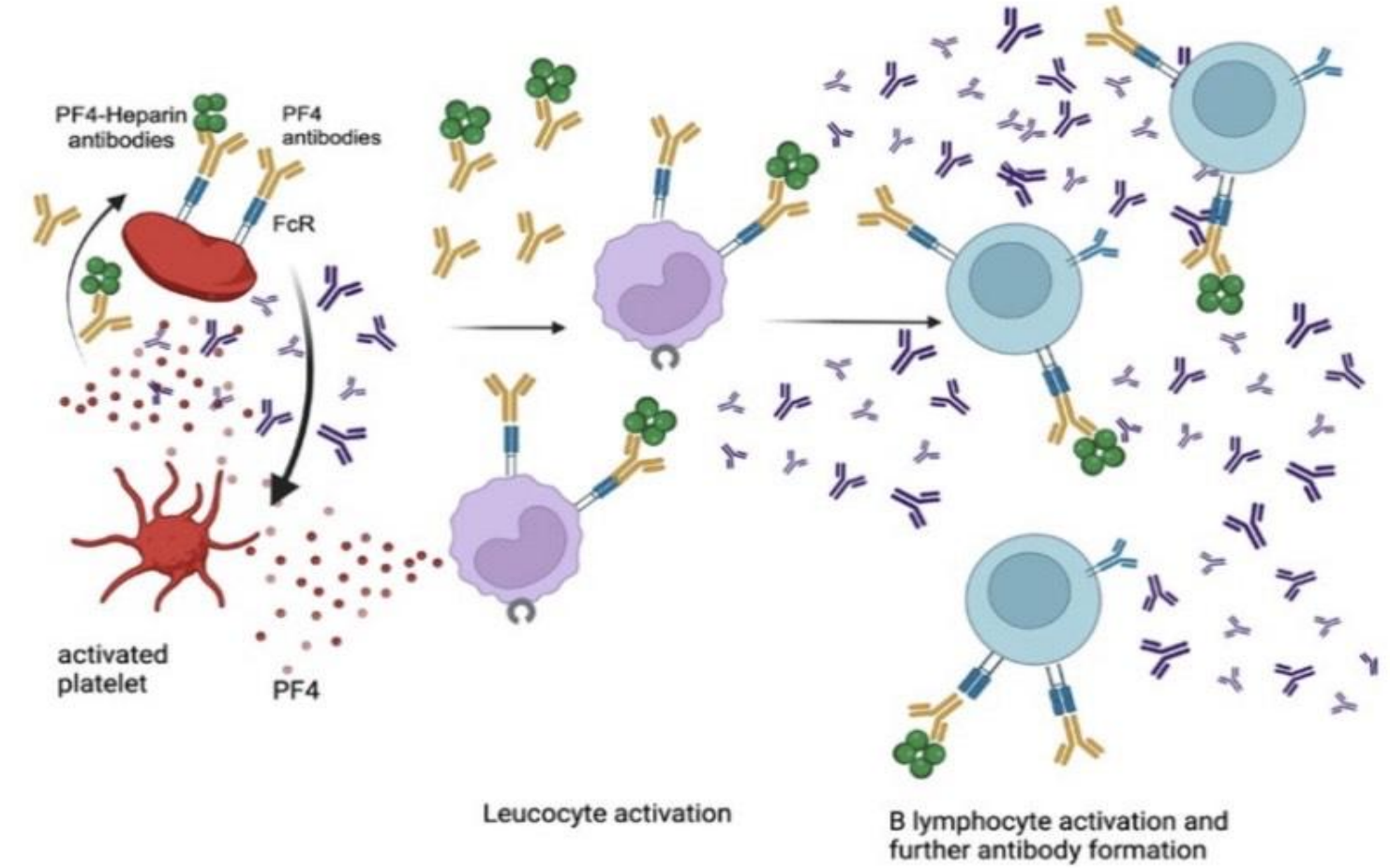
Anti-PF4 Antibodies

- Type 1: nonpathogenic, non-platelet activating
- Type 2: heparin dependent, platelet activating

  cHIT
- Type 3: heparin independent, platelet activating

  aHIT .VITT

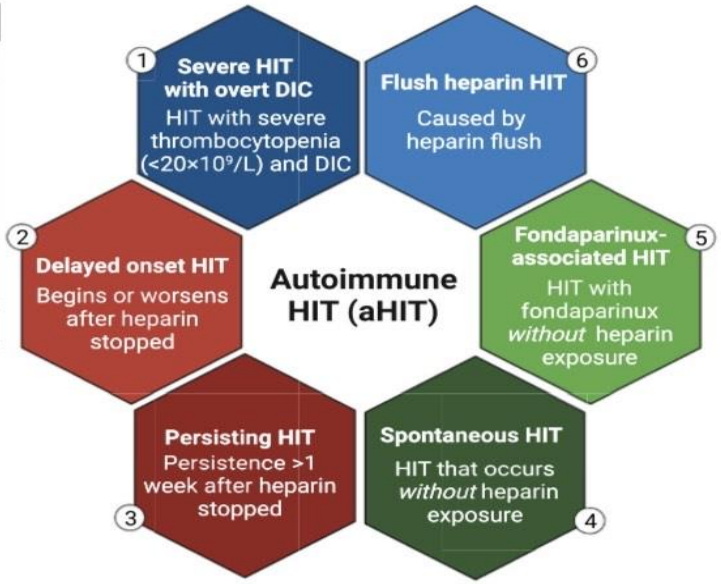
HIT Mechanism



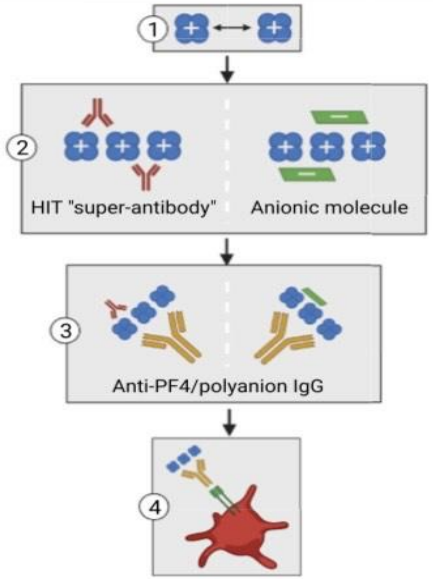
Autoimmune HIT (aHIT)

What is autoimmune HIT?

- Rarely, the clinical manifestations of HIT can develop via **heparin-independent platelet activation**.
- Autoimmune HIT (aHIT) refers to any HIT-related platelet count fall that begins or persists in the absence of heparin.[70,71]
- Six subtypes of aHIT have been described.
- Notably, spontaneous HIT has been reported to occur most commonly after knee replacement or infection.[71]



Pathophysiology



(1) Positively charged PF4 tetramers repel one another. (2) In aHIT, a non-heparin molecule overcomes this electrostatic repulsion, bringing individual PF4 tetramers together to form large multimolecular PF4 complexes. The exact non-heparin molecule able to perform this action is debated and may vary based on aHIT subtype, but proposed examples include HIT "super-antibodies" that bridge two PF4 tetramers and/or highly anionic molecules which could include chondroitin sulfate (released from joint cartilage in joint surgery), polyphosphate, and/or nucleotides such as DNA and RNA.[70,71] (3) The PF4 complexes then serve as antigens bound by anti-PF4/polyanion IgG, which (4) trigger activation of platelets and other cell types.

Principles of diagnosis & management of aHIT syndromes are ***the same as classical HIT,*** with some unique considerations:

When to suspect?

- Thrombosis *and*
- Thrombocytopenia

that is otherwise unexplained *even in the absence of heparin exposure*

Diagnosis

- Immunoassay +
- Functional assay +

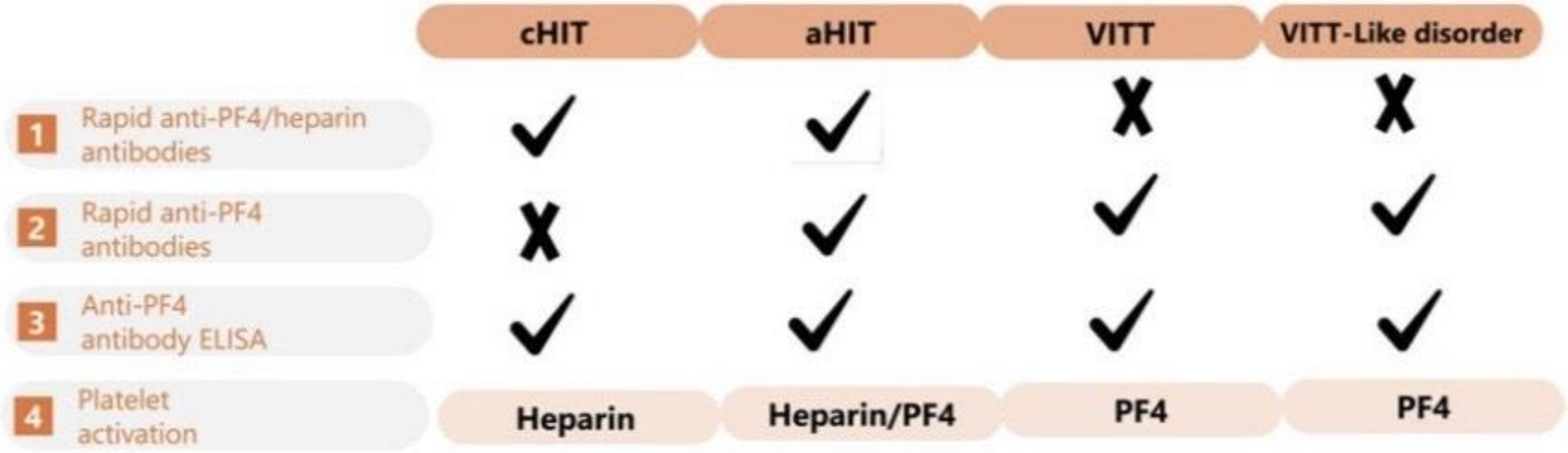
Functional assay may show platelet activation in the absence of heparin, but a non-heparin control is not performed in all laboratories.

Management

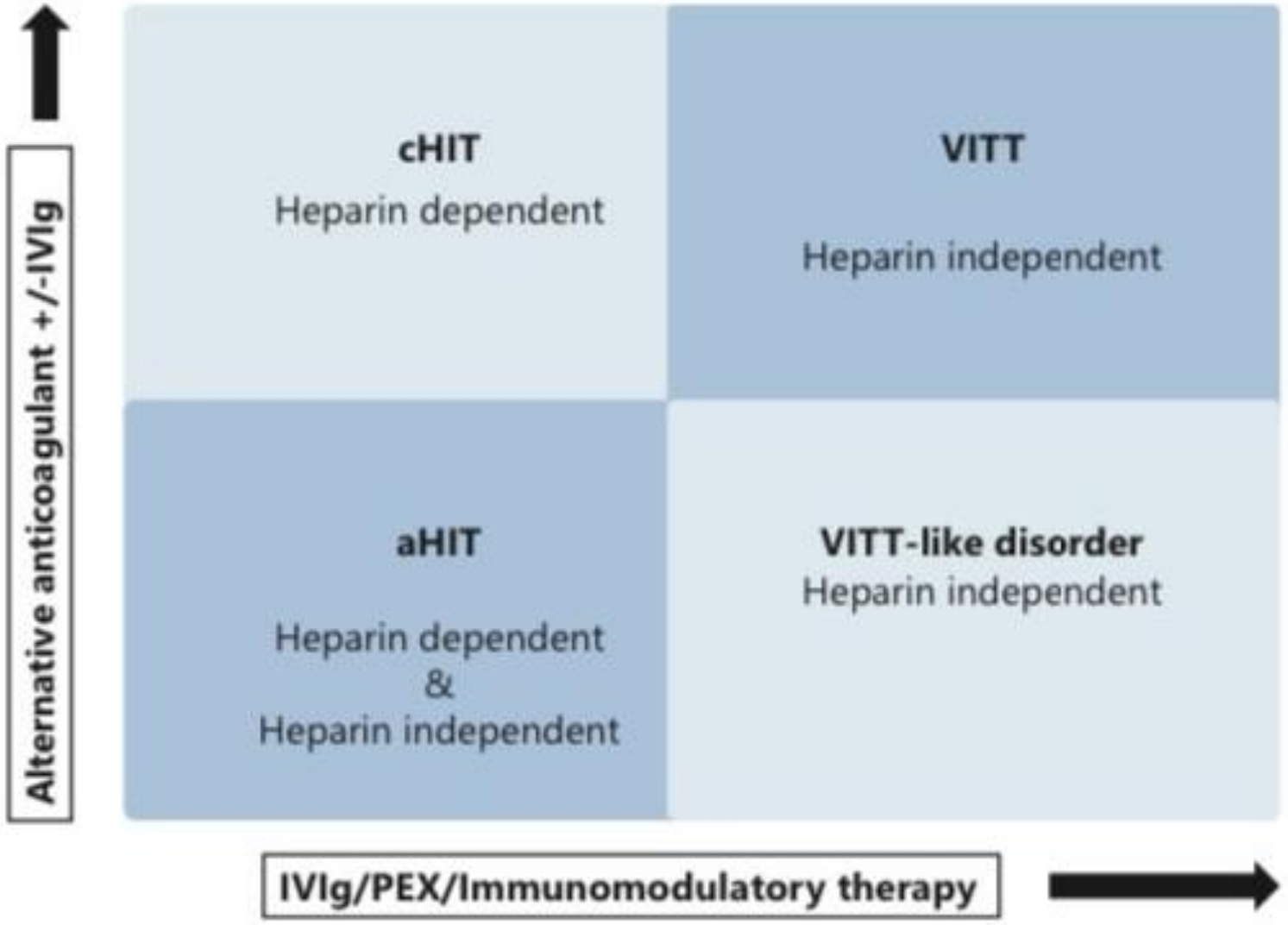
- Avoid heparin
- Use non-heparin anticoagulation

Experts recommend consideration of high-dose IVIg in severe cases.[70,71]

Diagnostic antibodies



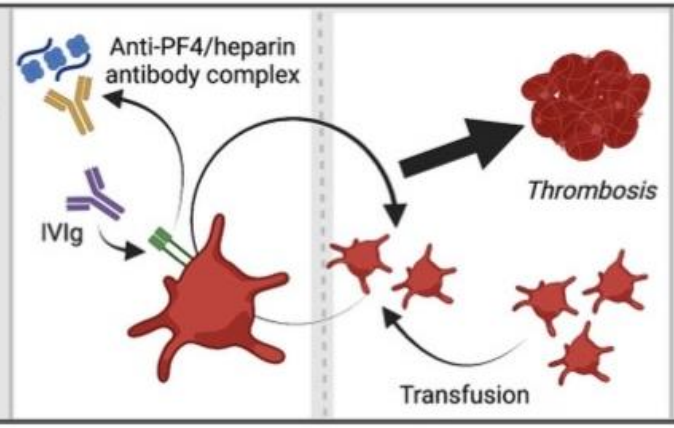
Mechanism & Therapeutic approach



Additional treatment considerations

Intravenous immunoglobulin (IVIg)

- Hypothesized to competitively inhibit binding of anti-PF4/heparin antibody to platelet FcR.[62]
- Can be considered in cases of **severe and/or refractory thrombosis or thrombocytopenia**.



STOP Platelet transfusion?

- Routine use **NOT** recommended due to concern it may "fuel the fire" and increase thrombotic risk, particularly arterial
- Can be considered in patients with active bleeding or prior to urgent procedures.[51,5]