SYMPOSIUM

Collaboration in chronic ITP:

Improving quality of life and patient outcomes

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Expert panel

Prof. Cindy Neunert (Chair)
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New York, NY, USA

Prof. David Kuter
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Boston, MA, USA

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Hospital Universitario Virgen del Rocío,
Seville, Spain

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Agenda

- **Welcome and introduction**
  Prof. Cindy Neunert
- **Patient voices: The impact of ITP** (20 minutes)
  Prof. Cindy Neunert
- **Patient practicalities: Examining cases of chronic ITP** (20 minutes)
  Dr María Eva Mingot Castellano
- **Patient potentials: Emerging targeted treatments for ITP** (20 minutes)
  Prof. David Kuter
- **Panel discussion – Patient collaboration: Working together to improve outcomes** (20 minutes)
  All faculty
- **Summary and close**
  Prof. Cindy Neunert

Sessions will include interactive audience polling and audience Q&As

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Learning objectives

1. Explain the natural history of chronic ITP and its impact on patients
2. Discuss current and future treatment strategies to improve the HRQoL of patients with chronic ITP
3. Practice shared decision-making and collaboration to optimize outcomes for patients with chronic ITP

Patient voices: The impact of ITP

Prof. Cindy Neunert
Columbia University Irving Medical Center,
New York, NY, USA

Immune thrombocytopenia (ITP)

ITP is an **autoimmune disorder of primary haemostasis**[1]

Prevalence of 9.5 per 100,000 adults[2]

Higher prevalence in women vs men, especially in younger adults, but **more equal in adults >65 years**[2]

~60% of adults with ITP **progress to chronic disease** (>12 months)[3]

Slightly higher overall mortality of adults with ITP vs general population (1.3–2.3 X)[1,4]

ITP is defined by a **platelet count <100 x 10^9/L** with no underlying cause[1]

ITP, immune thrombocytopenia.

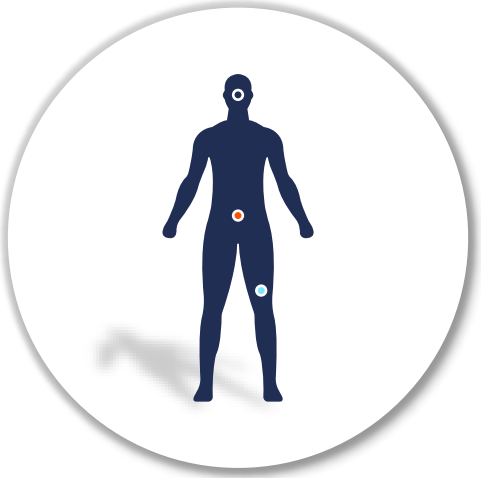
1. Martínez-Carballeira D, et al. *Haematol Rep*. 2024;16:204–19; 2. Lambert MP, Gernsheimer TB. *Blood*. 2017;129:2829–35; 3. Moulis G, et al. *Rev Med Interne*. 2021;42:11–5; 4. Nørgaard M, et al. *Blood*. 2011;117:3514–20.

Increased bleeding tendency is the central clinical symptom of ITP

Symptomatic bleeding affects 60–70% of patients with chronic ITP[1]

Head
Intracranial haemorrhange[2]
Epistaxis[1]
Wet purpura[1]

Abdominal bleeding
Gastrointestinal bleeding[2]
Haematuria[2]
Urogenital bleeding[1]
Increased menstrual bleeding[1]



Skin
Petechiae on legs (less frequently on arms or trunk)[1]

Non-bleeding symptoms:
Fatigue[1]
Cognitive impairment[1,3]

Platelet count does not fully correlate with disease burden[4]

ITP, immune thrombocytopenia.

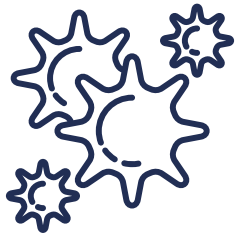
1. Matzdorff A, et al. *Oncol Res Treat*. 2018;41(Suppl. 5):1–30; 2. Moulis G, et al. *Rev Med Interne*. 2021;42:11–15; 3. Kuter DJ, et al. *Br J Haematol*. 2024;205:291–9; 4. Maitland H, et al. *Hematology*. 2024;29:2375177.

Patients with ITP experience significant morbidity and the disease can impact HRQoL

Concern over **risk of bleeding**[1]

Living with **unpredictability** and **a fear of bleeding** impacts QoL[1]

Patients **may have to alter their lifestyle** to reduce bleeding risk, e.g. avoiding contact sports[2]



Patients may experience **social stigmatization** from visible skin manifestations, which can affect self-esteem[2,3,5]

Patients can experience **fatigue** and **cognitive impairment** that can decrease participation in activities and work[3,4]

Heavy menstrual bleeding is common in female patients with ITP and results in high rates of hospitalization[6]

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

1. Kruse C, et al. *Ann Blood*. 2021;6:9; 2. Matzdorff A, et al. *Oncol Res Treat*. 2018;41(Suppl. 5):1–30; 3. Cooper N et al. *Am J Hematol*. 2021;96:199–207;
4. Kuter DJ, et al. *Br J Haematol*. 2024;205:291–9; 5. Hemati Z, Kiani D. *Int J Hematol Oncol Stem Cell Res*. 2016;10:79–84;
6. Doshi BS, et al. Presented at: ISTH 2024, Bangkok, Thailand. 22–26 June 2024. Poster presentation PB0694.

Heavy menstrual bleeding* is one of the most severe symptoms of ITP in female patients

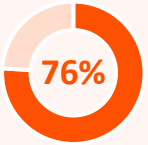
Treatment options can be limited due to the impact on fertility[1]

Therapeutic options that preserve fertility include hormonal therapy and antifibrinolytics[1]

Iron deficiency is common in female patients with ITP and heavy menstrual bleeding[1]

A cross-sectional study of women ≥16 years with primary chronic ITP in The Netherlands (N=37)[1]

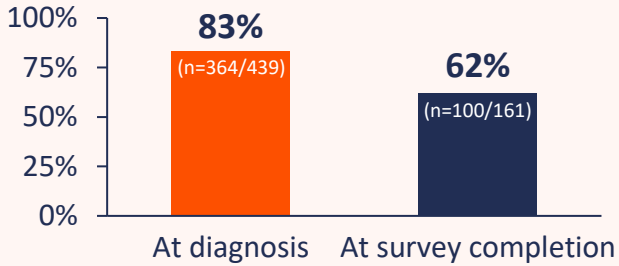
Experienced clinical menstrual problems (now or in the past)



Menstruation affected daily life (MMAS score <100)

No significant link between platelet count and impact of HMB (p=0.30)

In the I-WISh survey, a high proportion of women who experienced HMB rated it as one of their most severe symptoms[2]

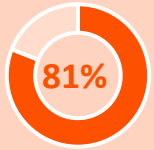


*Defined as menstrual periods with abnormally heavy bleeding and/or prolonged bleeding (lasting more than 7 days).
HMB, heavy menstrual bleeding; ITP, immune thrombocytopenia; I-WISh, ITP world impact survey; MMAS, menorrhagia multi-attribute scale.
1. van Dijk WEM, et al. *Br J Haematol*. 2022;198:754–64; 2. Cooper N, et al. *Am J Haematol*. 2021;98:188–98.

Fatigue is frequently reported as the most debilitating symptom of ITP[1]

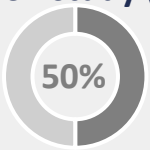
ITP Natural History Study Registry (n=324): patients reflected on fatigue levels over previous week[1]

Reported fatigue

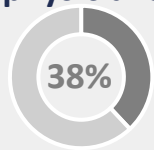


Bothered by fatigue

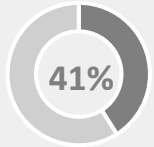
I-WISh study (patients, n=1,507; physicians, n=465):[2]



Patients reported fatigue

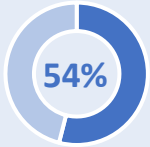


Physicians reported fatigue

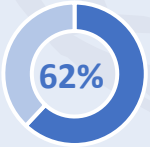


Patients reported increasing their energy levels as a top treatment goal

Observational study of children receiving second-line therapies for ITP: Children (n=54) and adolescents (n=42) with ITP reported a similarly **high level of moderate-to-severe fatigue**[3]



Children



Adolescents

I-WISh, ITP world impact survey; ITP, immune thrombocytopenia.

1. Kruse C, et al. *Ann Blood*. 2021;6:9; 2. Cooper N, et al. *Am J Hematol*. 2021;96:199–207; 3. Grace RF, et al. *Br J Haematol*. 2020;191:98–106.

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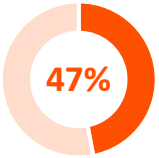
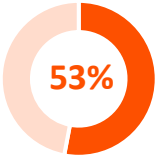
ITP impacts patients' psychological and emotional wellbeing

Data from PDSA patient registry (n=310)
Anxiety over the previous 7 days:[1]

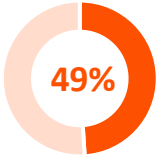


needed help with their anxiety



found it hard to focus on anything due to anxiety

I-WISh survey (n=1,507)[2]



felt ITP negatively impacted their psychological and emotional wellbeing

Issues most affected were:

- Concerns that their **condition would worsen**
- **Unexplained fluctuations** in platelet levels
- The importance of having **stable and safe platelet levels**
- Feeling **anxious/nervous** about **platelet counts**

I-WISh, ITP World Impact Survey; ITP, immune thrombocytopenia; PDSA, Platelet Disorder Support Association.

1. Kruse A, et al. *Blood*. 2019;134(Suppl. 1):2362; 2. Cooper N et al. *Am J Hematol*. 2021;96:199–207.

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Cognitive impairment in patients with ITP has been reported and warrants further investigation

Patients with ITP (N=69) were assessed using CANTAB cognitive testing and MRI scans[1]

50% of patients had at least one impaired cognitive domain

Episodic memory was most affected

Patients with chronic ITP (N=49) were assessed for cognitive impairment using the Cogstate Brief Battery[2]

59% of patients had clinically important cognitive impairment

Impairment was most common for **attention**

Severity of cognitive impairment was **comparable to mild traumatic brain injury**

Further prospective evaluation of cognitive impairment at diagnosis and with treatment is required to consider the potential impact on patients and their overall QoL[2]

ITP, immune thrombocytopenia; MRI, magnetic resonance imaging; QoL, quality of life.

1. Vladescu C, et al. *Blood*. 2022;140:5553–4; 2. Kuter DJ, et al. *Br J Haematol*. 2024;205:291–9.

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The majority of patients with ITP feel their ability to undertake daily tasks is impacted[1]

- Experienced difficulty concentrating[1]
- Burdened by the length of time spent in hospital/at the doctors[2]
- Experienced limitations when travelling[2]

- Reduced or seriously considered reducing working hours[1]
- Productivity at work negatively affected[1]
- Regular activities outside work* affected[1]

*Described as work around the house, shopping, childcare, exercise and studying (score ≥5 on a scale of 1–10 [10 completely prevented productivity]).
ITP, immune thrombocytopenia.
1. Cooper N et al. *Am J Hematol*. 2021;96:199–207; 2. Matzdorff A, et al. *Oncol Res Treat*. 2018;41(Suppl. 5):1–30.

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Numerous PRO measures can be used to assess the impact of ITP on HRQoL

Examples of **general tools** used to measure PROs in patients with ITP

General health status
- SF-36
- EQ-5D

Fatigue/energy levels
- FACIT-F

Worry/concern about bleeding/bruising
- FACT-Th6

Psychological and somatic symptoms
- Hamilton anxiety and expression rating scales
- HARS-IG

These are **generic** PRO tools, which are **not able to identify factors which have the greatest impact on HRQoL specific to ITP**

ITP-specific tools used to measure PROs/QoL

- ITP Life Quality Index
- ITP patient assessment questionnaire
- Kids' ITP tool

These tools can **assess issues related to ITP more precisely**

EQ-5D, EuroQoL 5-dimension; FACIT-F, functional assessment of chronic illness therapy – fatigue; FACT-Th6, Functional Assessment of Cancer Therapy – Thrombocytopenia 6 Item Version; HARS-IG, Hamilton anxiety rating scale interview guide; HRQoL, health-related QoL; ITP, immune thrombocytopenia; PRO, patient-reported outcome; QoL, quality of life; SF-36, short-form health survey.

Maitland H, et al. *Hematology*. 2024;29:2375177.

There are several efficacious treatments for ITP, but various factors should inform treatment decisions

Initial/emergent therapies

- **Corticosteroids**[1]
- IVIg[2]
- Anti-D Ig[2]

Significant toxicity associated with prolonged exposure to corticosteroids[3]

Second line onwards

TPO-RAs
- Eltrombopag[1,2,4]
- Romiplostim[1,2,4]
- Avatrombopag[1,2,4]

Anti-CD20
- Rituximab (*off label*)[1,2,4]

Syk inhibitor
- Fostamatinib[2,4,5]

Splenectomy[1,2,5]

Treatment-related side effects[4]

Patients may be required to remain on treatment long term[6]

There are limited options for patients who are refractory/intolerant to standard therapies[6]

Treatment selection should consider **patient's preferences, beliefs and values**[7]

Shared decision-making results in treatment decisions that are **individualized to the patient** and the phase of disease[7]

CD, cluster of differentiation; Ig, immunoglobulin; ITP, immune thrombocytopenia; IV, intravenous; Syk, spleen tyrosine kinase inhibitor; 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; 3. Cuker A, et al. *eJHaem*. 2023;4:350–7;
4. FDA PI. Available at: www.accessdata.fda.gov/scripts/cder/daf/index.cfm (accessed 12 September 2024); 5. Kim DS. *Blood Res*. 2022;57(Suppl. 1):S112–9;
6. Al-Samkari H. *Am J Hematol*. 2024;99:2178–90; 7. Maitland H, et al. *Haematology*. 2024;29:2375177.

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Patient practicalities: Examining cases of chronic ITP

Dr María Eva Mingot Castellano
Hospital Universitario Virgen del Rocío,
Seville, Spain

Patient case 1: Initial presentation

Sarah

Age: 24 years

Sex: Female

History *No family or personal history of bleeding*

Presentation *Heavy menstrual bleeding (PBAC: 112) and petechiae in the past 4 days*

Impact of symptoms

- *She loves swimming but has felt unable to go recently due to the irregularity of her menstrual bleeding and the appearance of the petechiae*
- *She has felt terrible in recent weeks with constant fatigue and a rapid heartbeat, and has been experiencing a shortness of breath and headaches particularly during exercise*

PBAC, pictorial blood assessment chart.

Patient case 1: Further investigation

Sarah

Age: 24 years **Sex:** Female

Blood tests	*Hb: 9.2 g/dL; MCV: 81 fL; platelets: 1 x 10^9/L; leukocytes: 8 x 10^9/L*
Blood smear	*Evidence of thrombocytopenia*
Clotting tests	*Normal PT, normal aPTT and normal fibrinogen*
Biochemistry	*K^+, Na^+, renal function and LDH normal; ferritin 2 ng/mL*
Immunology	*HIV, HBV and HCV negative*

aPTT, activated patrial thromboplastin time; Hb, haemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PT, prothrombin time.

Patient case 1: First-line therapy

Sarah

Age: 24 years

Sex: Female

Treatment goals:

- *Secure platelet counts*
- *Minimum toxicity*
- *Normalize life*

What would you use as a first-line therapy?

a. Dexamethasone

b. Prednisone

c. IVIg but only to manage major bleeding events

d. Other

IVIg, intravenous immunoglobulin.

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Patient case 1: First-line therapy

Sarah

Age: 24 years **Sex:** Female

First-line treatment ***Four cycles of dexamethasone 40 mg/d for 4 days***

Treatment outcome *Her platelets returned to normal*

Patient case 1: Relapse

Sarah

Age: 24 years **Sex:** Female

- *Sarah presented with **signs of relapse** 5 months after her treatment ended*

Symptoms	*Fatigue and a few petechiae*
Blood tests	*Hb: 12.2 g/dL; MCV: 81 fL; platelets: 8 x 10^9/L; leukocytes: 8 x 10^9/L*
Blood smear	*Evidence of thrombocytopenia*
Clotting tests	*Normal PT, normal aPTT and normal fibrinogen*
Biochemistry	*K^+, Na^+, renal function and LDH normal; ferritin 32 ng/mL*
Immunology	*HIV, HBV and HCV negative* *ANA, proteinogram and immunoglobulins all normal or negative*

ANA, antinuclear antibodies; aPTT, activated patrial thromboplastin time; Hb, haemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PT, prothrombin time.

Patient case 1: Relapse

Sarah

Age: 24 years **Sex:** Female

- *Sarah presented with **signs of relapse** 5 months after her treatment ended*

What treatment would you use to manage her relapse?

a. **Three cycles of dexamethasone**
b. **Prednisone 1 mg/kg/d**
c. **1 cycle of dexamethasone or IVIg followed by TPO-RA initiation**
d. **TPO-RA without rescue treatment**

IVIg, intravenous immunoglobulin; TPO-RA, thrombopoietin receptor agonist.

Patient case 1: Relapse treatment

Sarah

Sarah

Age: 24 years

Sex: Female

First-line treatment and outcome

One cycle of dexamethasone

One week later, her platelet count was 46 x 10^9/L

Second-line treatment and outcome

Avatrombopag 20 mg/day

Her platelets remained stable (85–105 x 10^9/L) during 4 months of treatment

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Patient case 1: Conception and pregnancy

Sarah

Age: 24 years **Sex:** Female

- *At her most recent appointment, Sarah tells you that she and her husband are considering trying for a baby and would like to discuss how to best manage her ITP during conception and pregnancy*

How would you best support this patient in her conception and pregnancy journey?

a. **Discuss the risks and benefits of remaining on avatrombopag during conception and pregnancy**
b. **Suggest she switches to prednisone 20 mg/d, with the dose tapered to the minimum dose necessary**
c. **Suggest she switches to IVIg 1–2 g/kg**
d. **Suggest she stops treatment for ITP during conception and pregnancy with management relying on close observation**
e. **Other**

ITP, immune thrombocytopenia; IVIg, intravenous immunoglobulin.

Patient case 2: Initial presentation

Michael

Age: 72 years **Sex:** Male

Presentation	*Fatigue, frequent nosebleeds and purpura*
Impact of symptoms	• *Michael helps his daughter with childcare for his three young grandchildren, who he collects from school twice a week* • *Recently, he has been feeling too tired to care for his grandchildren, and is bruising more easily during play*
Weight	*88 kg (194 lbs)*
Comorbidities	*Atrial fibrillation, hypertension, type 2 diabetes mellitus*
Current medications	*Apixaban for atrial fibrillation* *Benazepril for hypertension* *Metformin for glucose control*

Patient case 2: Further investigation

Michael

Age: 72 years **Sex:** Male

Blood tests	*Hb: 12.3 g/dL; MCV: 88 fL; platelets: 22 x 10^9/L; leukocytes: 7.2 x 10^9/L*
Blood smear	*Evidence of thrombocytopenia*
Biochemistry	*K^+, Na^+, renal function and LDH normal; ferritin 19 ng/mL*
Immunology	*HIV, HBV and HCV negative*

At this point, how would you manage Michael's anticoagulant therapy?

a. **Maintain anticoagulation with apixaban at full dose because his platelets are >20 x 10^9/L**
b. **Stop anticoagulant therapy because his platelets are <30 x 10^9/L**
c. **Maintain anticoagulation with apixaban at half dose because platelets are 20–50 x 10^9/L**
d. **Discuss the risks and benefits of staying on anticoagulant therapy with Michael**

Hb, haemoglobin; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDH, lactate dehydrogenase; MCV, mean corpuscular volume.

Patient case 2: First-line therapy

Michael

Age: 72 years **Sex:** Male

- *Following review, Michael has discontinued apixaban*

First-line ITP treatment ***Prednisone 60 mg/d***

Treatment outcome *Michael's platelet counts are not stable and fluctuate at his weekly blood tests (30–50 x 10^9/L)*

How long do you recommend Michael continues with prednisone treatment before considering a second-line option?

a. **Up to 4 weeks**
b. **6–8 weeks**
c. **Up to 16 weeks**
d. **Other**

Patient case 2: Halting prednisone

Michael

Age: 72 years **Sex:** Male

- *After **3 weeks of treatment** with prednisone, Michael's **platelets have stabilized***
- *He has been told that his HbA1c is increasing*
- ***You decide to start tapering Michael's prednisone dose**; however, his **platelet count drops** every time the dose is reduced*

What treatment would you consider in the second line?

a. TPO-RA

b. Fostamatinib

c. Rituximab

d. Other

HbA1c, glycated haemoglobin; TPO-RA, thrombopoietin receptor agonists.

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Patient case 2: Long-term therapy

Michael

Age: 72 years **Sex:** Male

- *Michael started treatment with **fostamatinib 100 mg BID***
- *During the first 12 weeks of treatment, his platelet count ranged between 87 and 125 x 10^9/L*
- *Michael's energy levels have improved, and his bruising has started to disappear*
- *He now feels able to resume caring for his grandchildren*
- *Michael is feeling well and is not experiencing diarrhoea or worsening high blood pressure*

BID, twice daily.

Patient case 2: Long-term therapy

Michael

Age: 72 years **Sex:** Male

- *Michael started treatment with **fostamatinib 100 mg BID***
- *During the first 12 weeks of treatment, his platelet count ranged between 87 and 125 x 10^9/L*
- *Michael is feeling well and is not experiencing diarrhoea or worsening high blood pressure*

What do you do next for patients demonstrating clinical response?

a. **Discontinue fostamatinib if at least one platelet count of ≥50 x 10^9/L is recorded during 12 weeks of treatment**
b. **Discontinue fostamatinib if platelet counts of ≥100 x 10^9/L are maintained for at least 6 months without rescue treatment**
c. **Continue long-term treatment unless the patient stops responding or experiences significant toxicity**
d. **Other**

BID, twice daily.

Patient potentials: Emerging targeted treatments for ITP

Prof. David Kuter
Massachusetts General Hospital,
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Novel therapies reducing platelet destruction

Platelet destruction by macrophages in ITP[1]

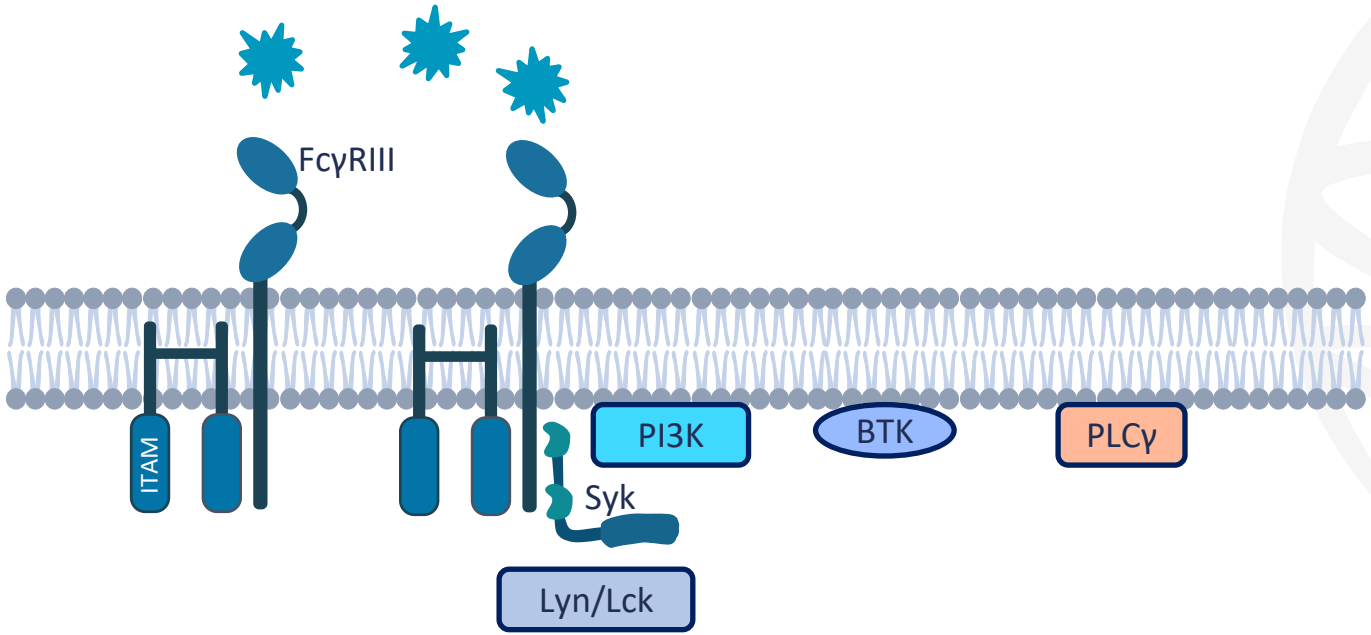

Figure adapted from Nimmerjahn F & Ravetch J. *Ann Rev Immunol.* 2008.
BTK, Bruton's tyrosine kinase; ITAM, immunoreceptor tyrosine-based activation motifs; ITP, immune thrombocytopenia; Lck, lymphocyte-specific protein tyrosine kinase; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C γ; R, receptor; Syk, spleen tyrosine kinase.
1. Kuter DJ. *Br J Haematol*. 2022;196:1311–28; 2. Nimmerjahn F & Ravetch J. *Ann Rev Immunol*. 2008;26:513–33.

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Anti-platelet antibodies appear[1]

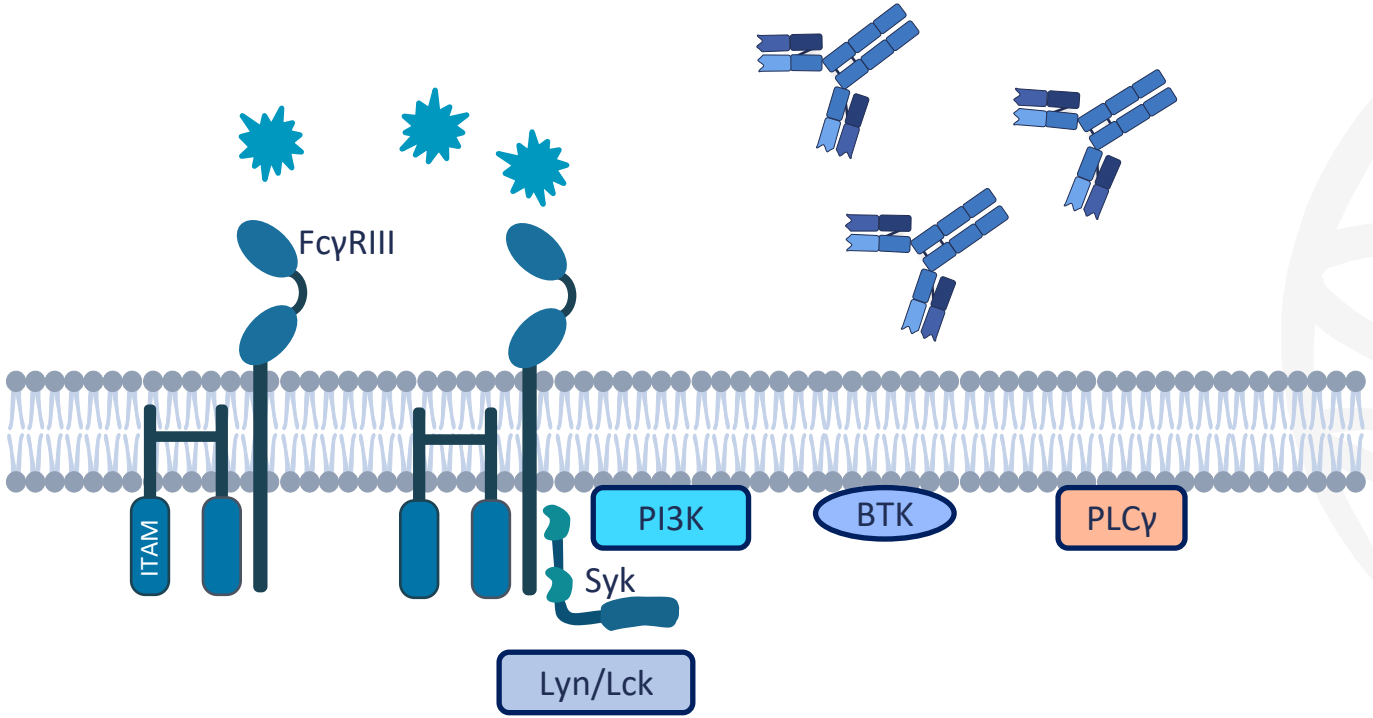


Figure adapted from Kuter DJ. *Br J Haematol*. 2022.
BTK, Bruton's tyrosine kinase; ITAM, immunoreceptor tyrosine-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C γ; R, receptor; Syk, spleen tyrosine kinase.

1. Kuter DJ. *Br J Haematol*. 2022;196:1311–28; 2. Nimmerjahn F & Ravetch J. *Ann Rev Immunol*. 2008;26:513–33.

Reduction of anti-platelet antibody production/survival

Current treatments[1]

Splenectomy

Corticosteroids

Anti-CD20
- Rituximab (*off-label*)

FcRn inhibitors
- IVIg

Investigational agents

Anti-CD38[2]
- Daratumumab
- Mezagitamab (TAK-079)
- CMC313

Anti-CD40
- *IDEC-131*[4]
- *Hu5c8*[4]
- Letolizumab[5]

BAFF receptor inhibitors
- Ianalumab (VAY736)[2]

BAFF/APRIL receptor inhibitor
- Povetacicept[2]

FcRn inhibitors
- Efgartigimod[2]
- *Rozanolixizumab*[3]

IgG proteases[6,7]

Immunoproteasome inhibitors
- Bortezomib[5,8]
- *KZR-616*[9]

Underlined treatments are to be discussed, treatments in italics are no longer in development.

APRIL, A proliferation-inducing ligand; BAFF, B-cell activating factor; CD, cluster of differentiation; FcRn, neonatal Fc receptor; Ig, immunoglobulin; IV, intravenous.

1. Provan D, et al. *Blood Adv*. 2019;3:3780–817; 2. Al-Samkari H. *Am J Hematol*. 2024;99:2178–90; 3. Robak T, et al. *Blood Adv*. 2020;4:4136–46; 4. Patel VL, et al. *Br J Haematol*. 2008:141:545–8; 5. Audia S, Bonnotte B. *J Clin Med*. 2021;10:1004; 6. Johansson BP, et al. *PLOS One*. 2008;3:e1692; 7. Manasson J, et al. Presented at ASH 2024 Annual Meeting and Exposition, San Diego, CA, USA. 7–10 December 2024. Abstract 2562; 8. Clinicaltrials.gov. NCT05599880. Available at: https://clinicaltrials.gov/study/NCT05599880 (accessed 8 November 2024); 9. Clinicaltrials.gov. NCT04039477. Available at: https://clinicaltrials.gov/study/NCT04039477 (accessed 14 November 2024).

CD38

Primitive multi-functional enzyme on the cell surface[1]

Present on plasma cells, B and T cells, NK cells and many others[1]

Enzyme[1]
- NADase activity
- Alters Ca flux in many cells

Receptor[1]
- Activator of B and T cells

Loss of function mutations lead to immune deficiency[1]

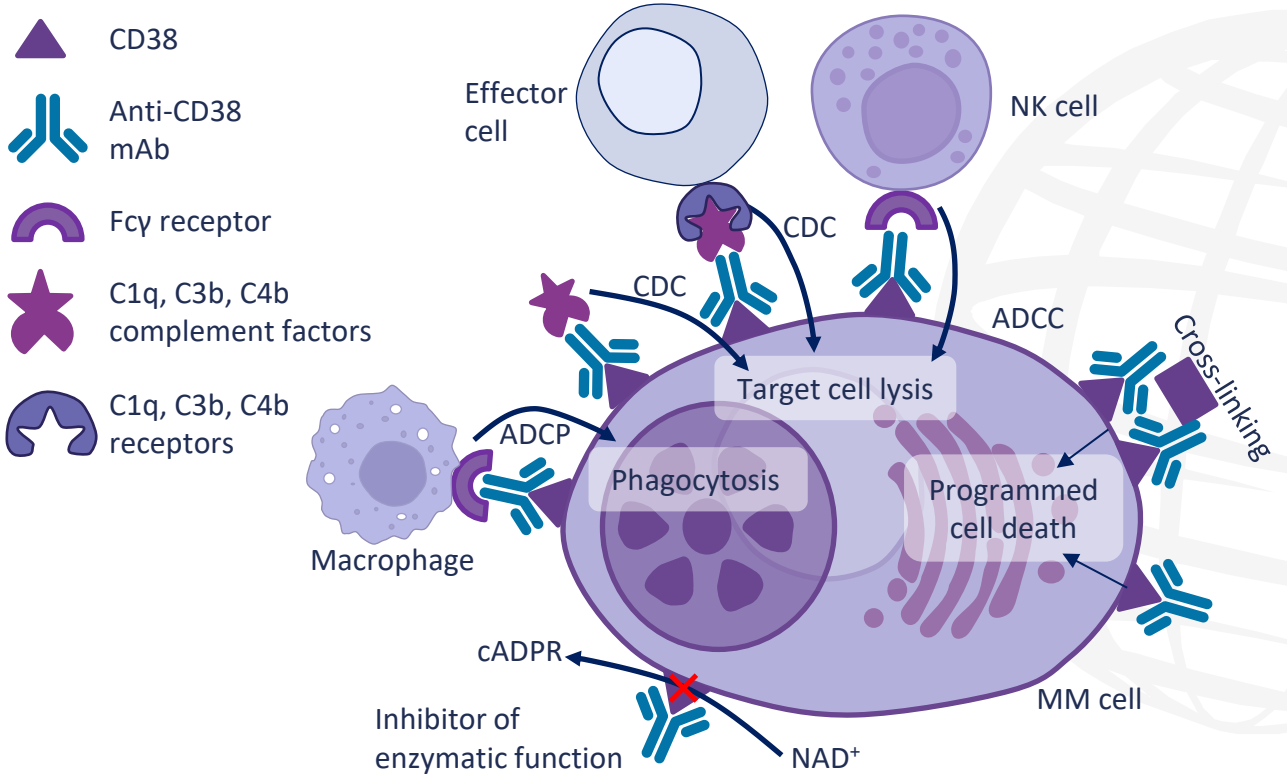
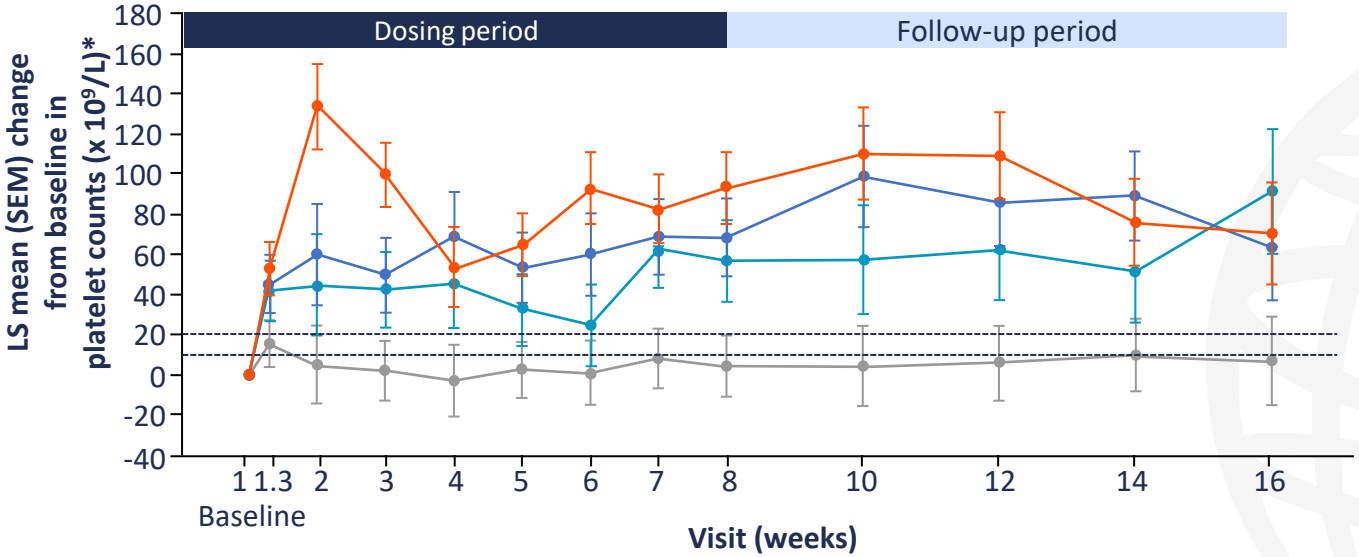


Figure adapted from Morandi F, et al. *Front Immunol*. 2018.
ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; cADPR, cyclic ADP ribose; CD, cluster of differentiation; CDC, complement-dependent cytotoxicity; mAb, monoclonal antibody; MM, multiple myeloma; NAD, nicotinamide adenine dinucleotide; NK, natural killer.
1. Piedra-Quintero ZL, et al. *Front Immunol*. 2020;11:597959; 2. Morandi F, et al. *Front Immunol*. 2018;9:2722.

Mezagitamab (TAK-079)



n												
Placebo combined	12	13	13	13	13	13	13	12	12	12	12	11
TAK-079 100 mg	7	8	8	8	7	6	7	7	5	5	5	5
TAK-079 300 mg	8	8	8	8	8	8	8	8	8	8	8	8
TAK-079 600 mg	10	11	9	10	10	8	9	9	9	9	8	9

Figure reproduced from Kuter DJ et al. ISTH 2024. LB 01.1.
*Mixed-effects model for repeated measures. Dotted horizontal reference lines indicate ≥20 x 10^9/L and ≥10 x 10^9/L change from baseline.
LS, least squares; SEM, standard error of the mean.
Kuter DJ, et al. Presented at: ISTH 2024, Bangkok, Thailand. 22–26 June 2024. Oral presentation LB 01.1.

Mezagitamab (TAK-079)

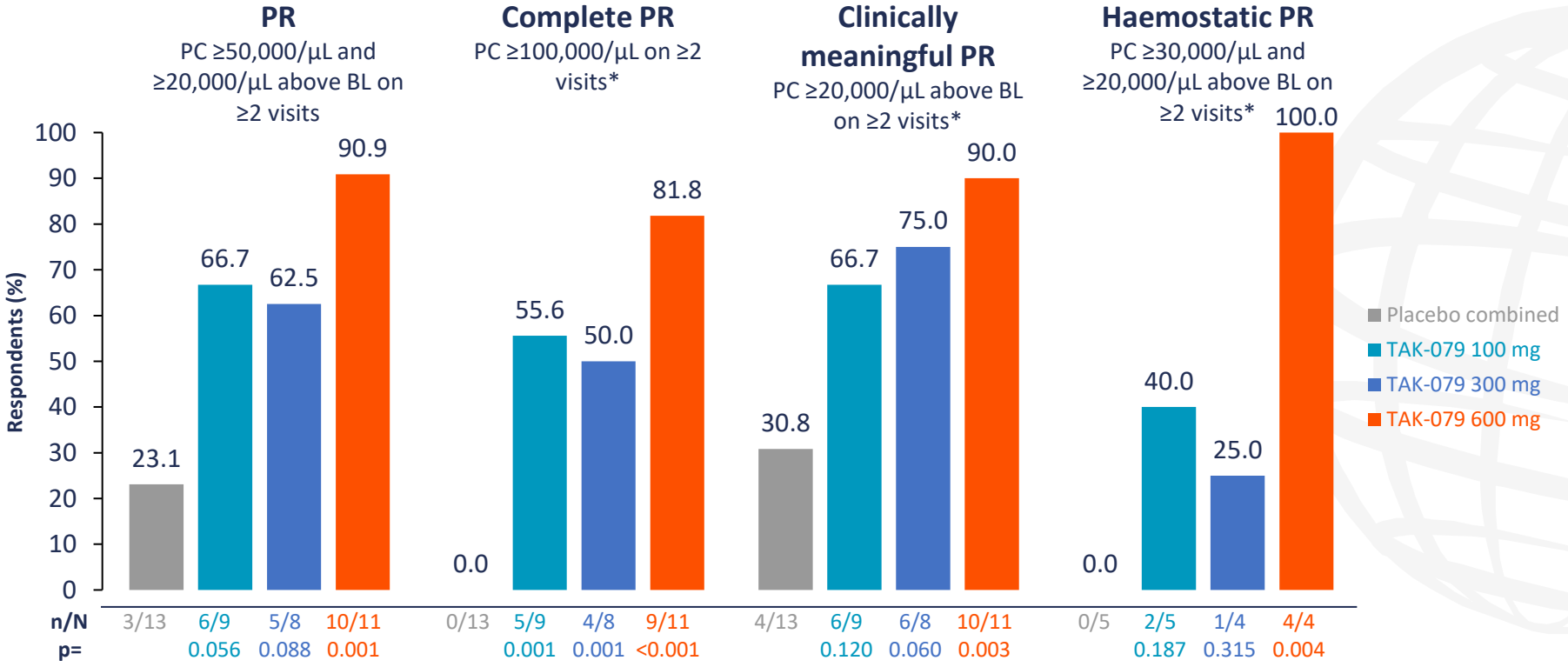


Figure reproduced from Kuter DJ et al. ISTH 2024. LB 01.1.

*Without a dosing period-permitted rescue treatment in the previous 4 weeks and without other previous rescue therapy. For haemostatic PR, the percentages are based on all patients in the full analysis set with BL PC <15,000/µL. BL, baseline; PC, platelet count; PR, platelet response.

Kuter DJ, et al. Presented at: ISTH 2024, Bangkok, Thailand. 22–26 June 2024. Oral presentation LB 01.1.

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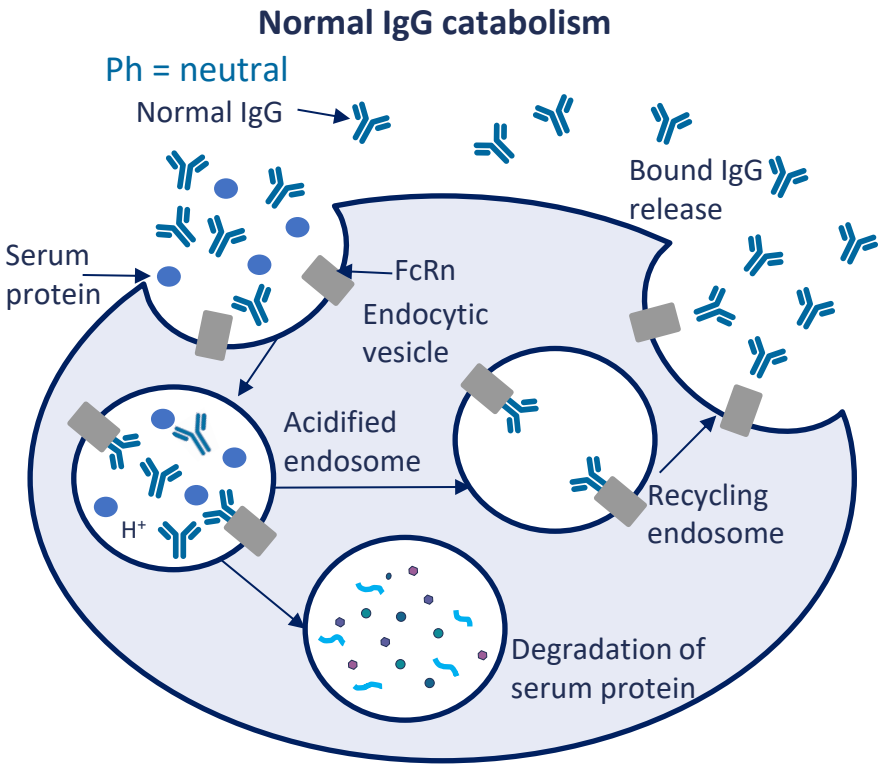
FcRn inhibition reduces IgG half-life



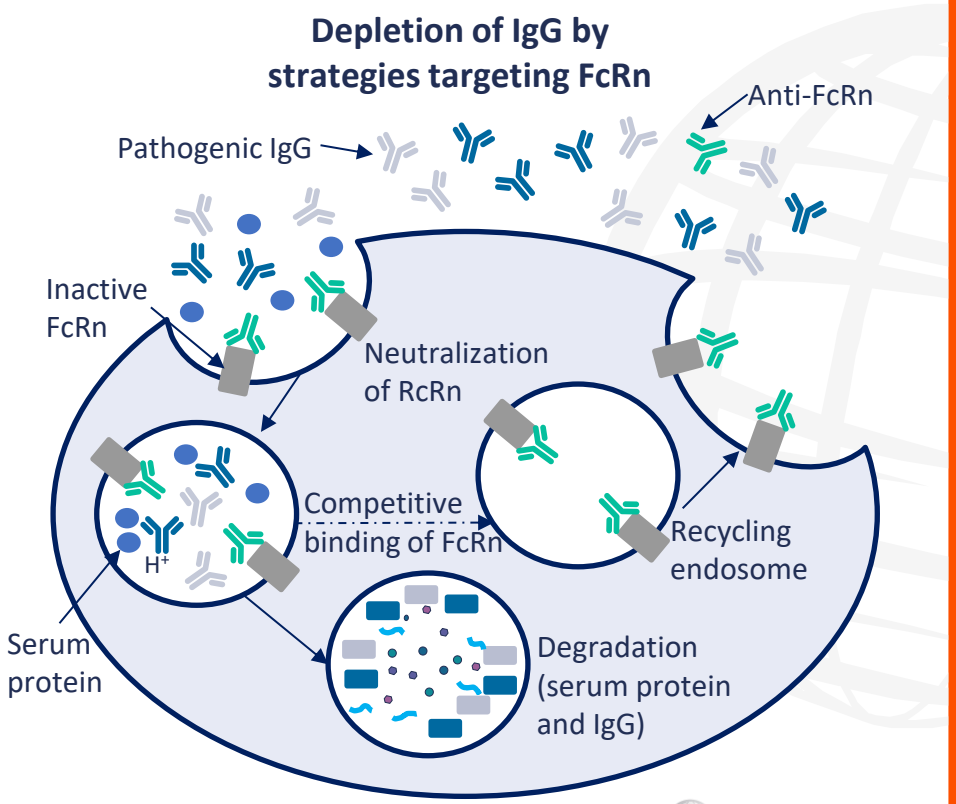


Figure adapted from Kuter DJ. *Br J Haematol*. 2022.
FcRn, neonatal Fc receptor; IgG, immunoglobulin G.
Kuter DJ. *Br J Haematol*. 2022;196:1311–28.

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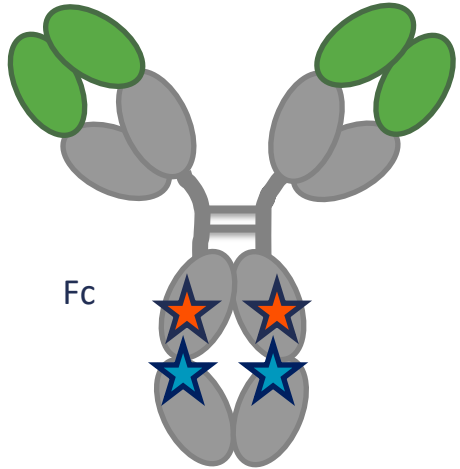
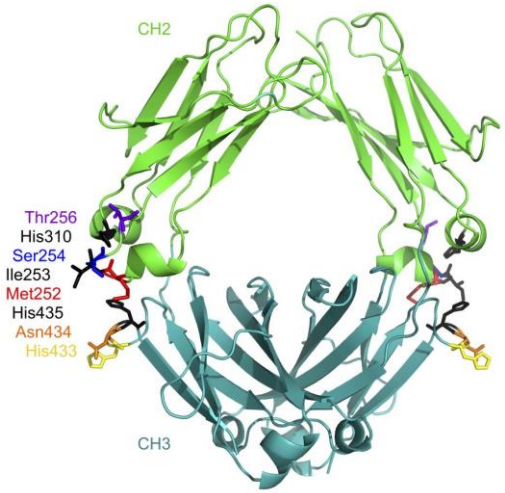
Structure of efgartigimod (ARGX-113)

Abdegs – ‘sticky’ IgG with increased affinity for FcRn and slow ‘off-rate’ at pH 7[1]



Antibody-Fc with
Abdeg technology



Protein ribbon reproduced from Li S. Presented at: The 2nd International Conference on Biological Engineering and Medical Science. DOI: 10.54254/2753-8818/3/20220330.
Abdeg, antibodies that enhance IgG degradation; FcRn, neonatal Fc receptor.
1. Vaccaro C, et al. *Nat Biotech*. 2005;23:1283–8; 2. Ulrichts P, et al. *J Clin Invest*. 2018;128:4372–86.

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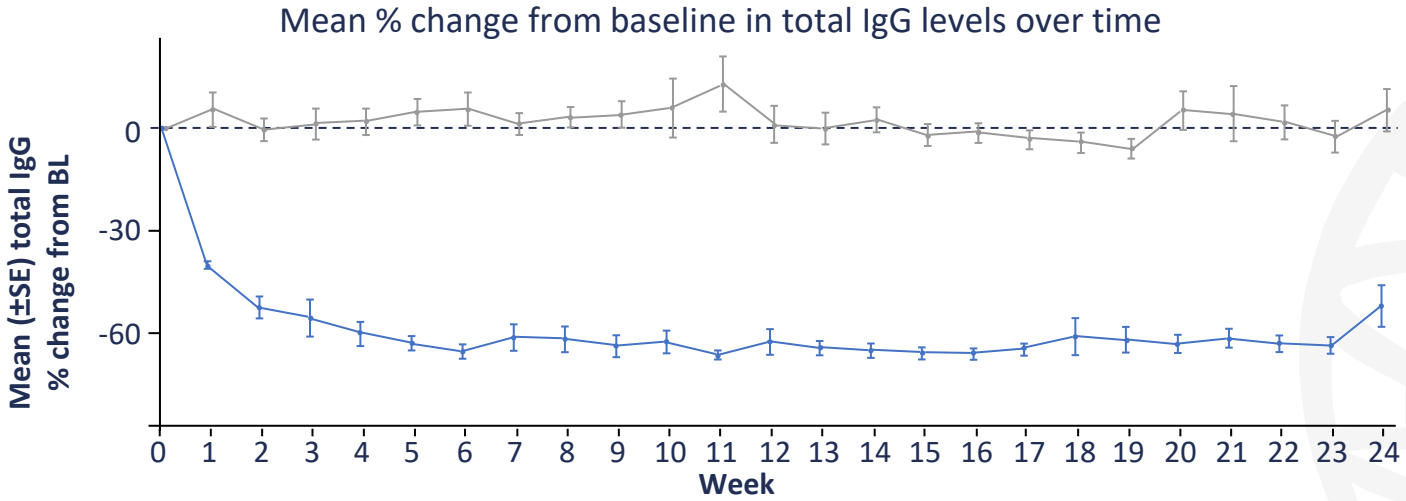
Efgartigimod: ADVANCE IV Study – IgG response



Efgartigimod	80	77	73	74	64	55	59	68	64	60	63	65	57	62	54	62	57	60	56	53	49	53	56	51	58
Placebo	45	42	45	42	36	35	39	38	34	37	34	34	31	26	31	30	29	28	30	28	30	28	31	28	39

Mean IgG levels decreased steadily over the first 4 weeks of treatment, which was sustained across time and aligned with platelet count responses

- After the initial decrease in IgG, mean maximum reductions from baseline remained ≥60% throughout the trial

Reprinted from *The Lancet*, 402, Broome C, et al, Efficacy and safety of the neonatal Fc receptor inhibitor efgartigimod in adults with primary immune thrombocytopenia (ADVANCE IV): a multicentre, randomised, placebo-controlled, phase 3 trial, 1648–59, copyright 2024, with permission from Elsevier.
BL, baseline; IgG, immunoglobulin G; IV, intravenous; SE, standard error.
Broome C, et al. *Lancet*. 2023;402:1648–59.

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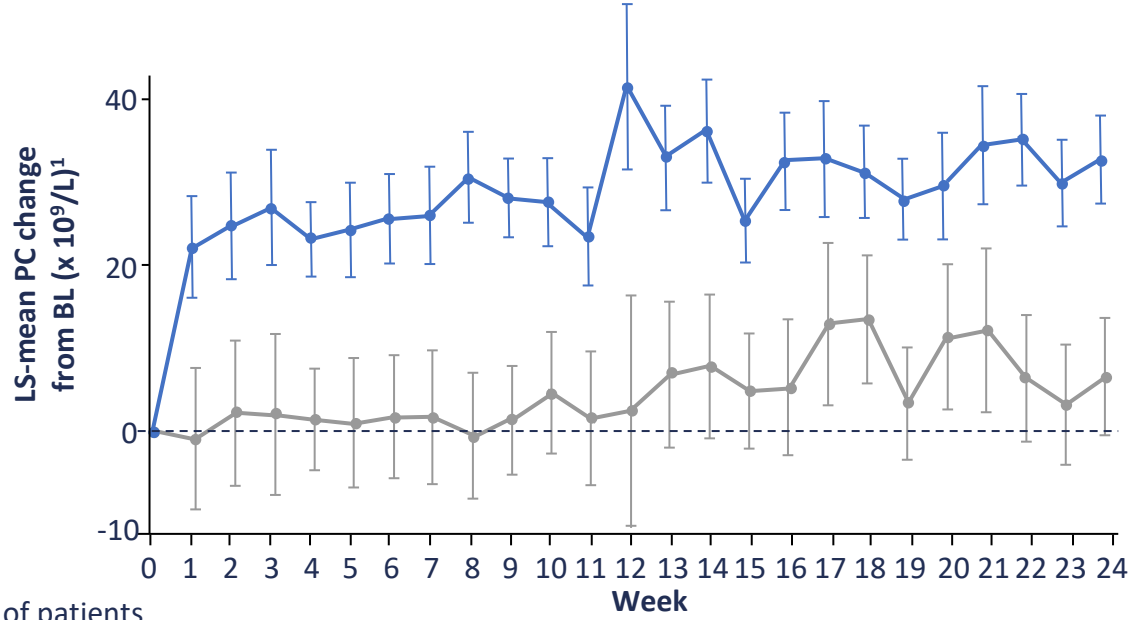
Efgartigimod: ADVANCE IV study – platelet response



Number of patients																								
Efgartigimod	86	86	84	85	83	77	78	77	77	72	75	76	75	76	75	75	73	74	70	68	68	71	72	68	67
Placebo	45	44	45	43	44	42	40	42	40	40	38	40	38	36	38	38	37	37	37	37	38	37	38	37	39

Primary endpoint: Sustained platelet count response* achieved in **22%** (17/78) of efgartigimod patients compared with **5%** (2/40) of placebo patients **(p=0.032)**.[1]

38.4% of efgartigimod treated patients compared with **11.1%** placebo reached a platelet count of ≥30 x 10^9/L platelets at week 1.[2]

The **ADVANCE-SC** (NCT04687072) study **did not meet the primary endpoint** or any prespecified secondary endpoints.[3]

Reprinted from *The Lancet*, 402, Broome C, et al, Efficacy and safety of the neonatal Fc receptor inhibitor efgartigimod in adults with primary immune thrombocytopenia (ADVANCE IV): a multicentre, randomised, placebo-controlled, phase 3 trial, 1648–59, copyright 2024, with permission from Elsevier.

*Platelet count ≥50 x 10^9/L in 4 of 6 visits in weeks 19–24. BL, baseline; IV, intravenous; LS, least squares; PC, platelet count; SC, subcutaneous.

1. Broome C, et al. *Lancet*. 2023;402:1648–59; 2. Broome C, et al. *Blood*. 2023;142;689–91; 3. Al-Samkari H. *Am J Hematol*. 2024;99:2178–90.

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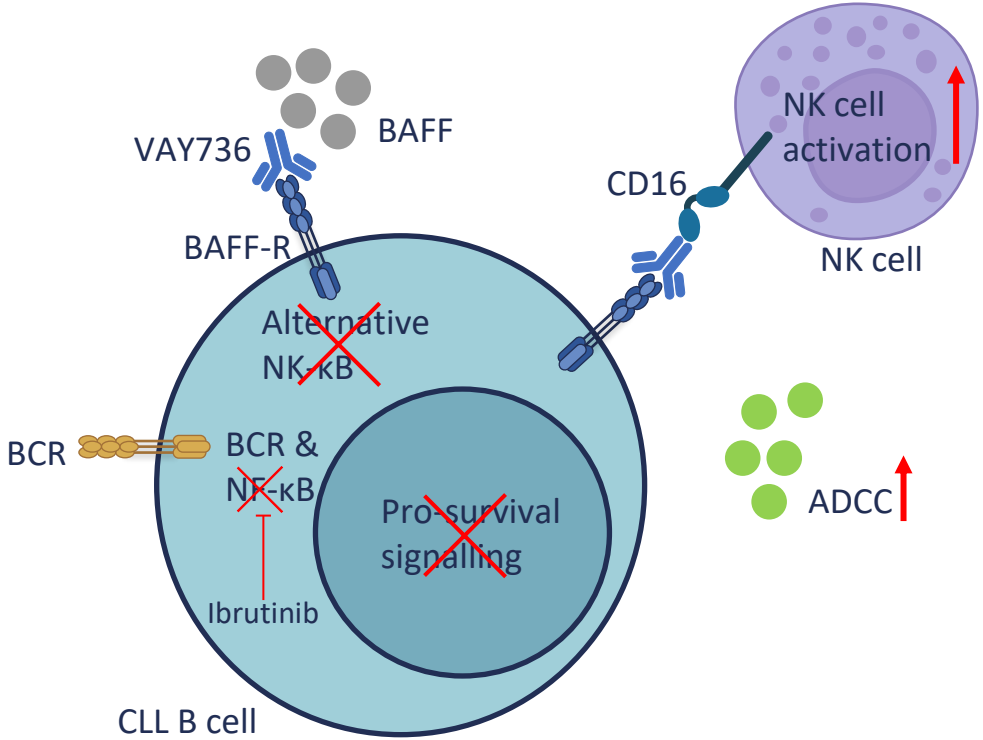
BAFF receptor inhibition – ianalumab (VAY736)



Binds BAFF receptor[1]

↓

Inhibits BAFF receptor[1]

↓

Produces B-cell depletion[1]

Studies are underway in many disease areas, including multiple studies in ITP[1–4]

Figure adapted from McWilliams EM, et al. *Blood Adv*. 2019.

ADCC, antibody-dependent cellular cytotoxicity; BAFF, B-cell activating factor; BAFF-R, BAFF receptor; BCR, B-cell receptor; CD, cluster of differentiation; CLL, chronic lymphocytic leukaemia; ITP, immune thrombocytopenia; NF-κB, nuclear factor kappa B; NK, natural killer.

1. McWilliams EM, et al. *Blood Adv*. 2019;3:447–60; 2. Al-Samkari H. *Am J Hematol*. 2024;99:2178–90; 3. Rebetz J, et al. ASH Annual Meeting and Exposition 2024, San Diego, CA, USA. 7–10 December 2024. Abstract 552; 4. Kuter DJ, et al. ASH Annual Meeting and Exposition 2024, San Diego, CA, USA. 7–10 December 2024. Abstract 710.

IgG cleaving enzymes

IgG-degrading activity common in pathogenic bacteria[1]

IdeS (imlifidase) is a recombinant cysteine protease of *S. pyrogenes* produced in *E. coli*[1]

Cleaves all four human IgG subclasses[1]

IdeS hydrolyzes human IgG at gly236 in the lower hinge region of the IgG heavy chains[1]

Prevents IgG-mediated antibody-dependent cellular cytotoxicity and complement-mediated cytotoxicity[1]

Highly immunogenic one-time use[2]

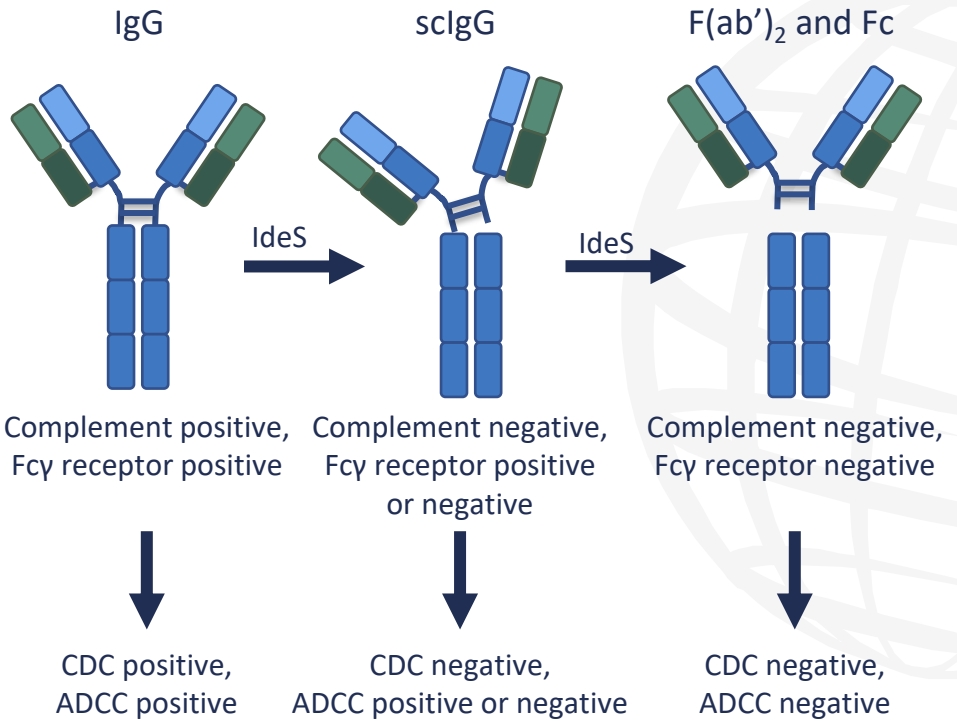


Figure reproduced from Jordan SC, et al. *N Engl J Med*. 2017.
ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; Gly, glycosine; IgG, immunoglobulin G; sc, single cleavage.
1. Jordan SC, et al. *N Engl J Med*. 2017;377:442–53; 2. Huang E, et al. *Am J Transplant*. 2022;22:691–7.

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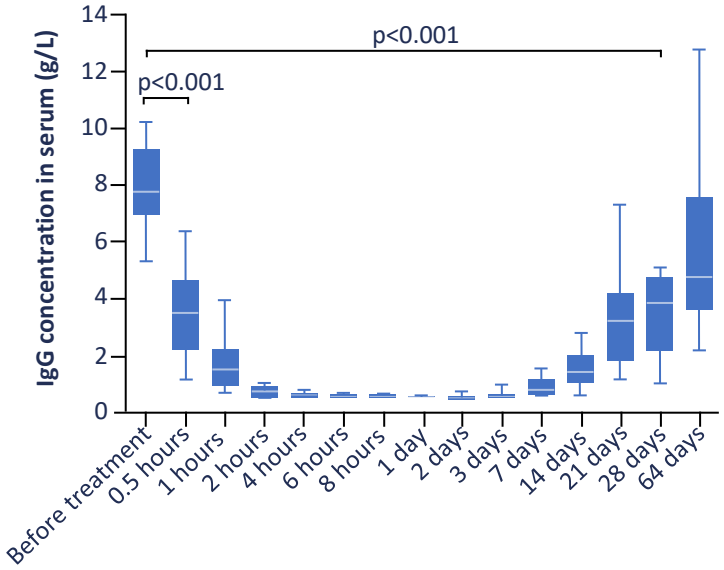
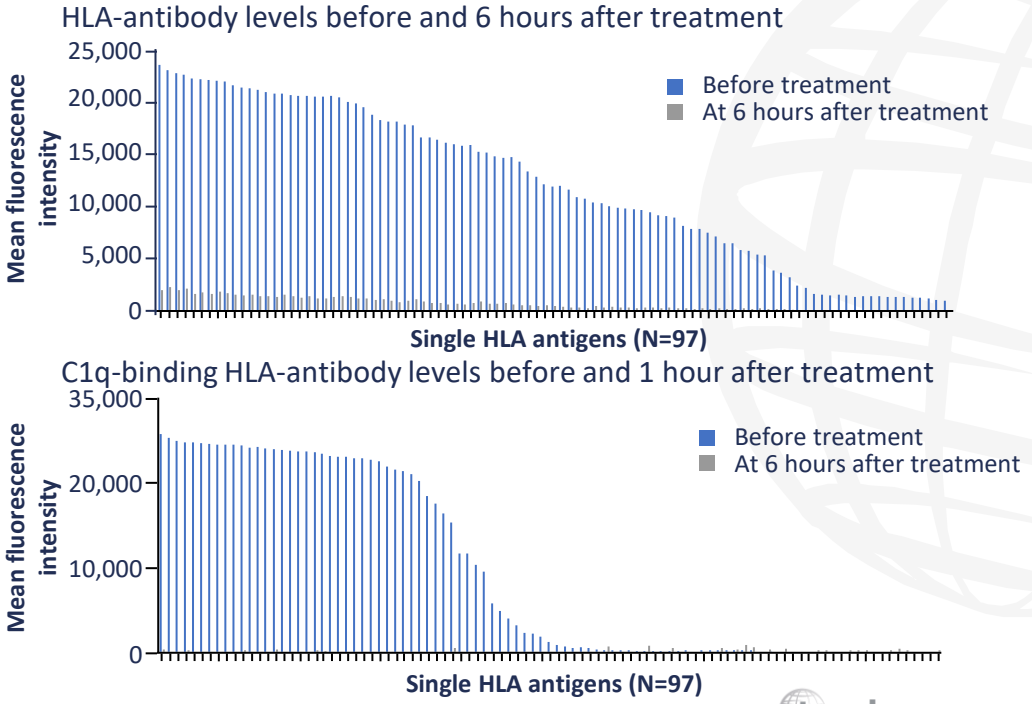
IdeS reduced or eliminated donor-specific antibodies and permitted HLA-incompatible transplantation in 24 of 25 patients





Figures reproduced from Jordan SC, et al. *N Engl J Med*. 2017.
HLA, human leukocyte antigen; IgG, immunoglobulin G.
Jordan SC, et al. *N Engl J Med*. 2017;377:442–53.

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Invisibilizing IgG cleaving enzymes with AI

The promise of machine learning:
The Seismic IMPACT platform is being used to design IgG cleaving enzymes for chronic treatment of autoimmune diseases[1]

Remove B- and T-cell epitopes to make proteins with increased invisibility[1–4]

Elucidate pairwise/higher order residue dependencies to optimize drug properties[1,2]

Remove chemical/manufacturing liabilities[3,4]

Retain/augment enzymatic activity[1,3]

Image taken from Manasson J, et al. ACR Convergence 2024. 0013.
AI, artificial intelligence; IgG, immunoglobulin G.
1. Pellerin A, et al. *J Immunol*. 2023;210(1_Supplement):238.22; 2. Newton AP, et al. *J Immunol*. 2023;210(1_Supplement):85:16;
3. Manasson J, et al. Presented at: ACR Convergence 2024, Washington, D.C., USA. 14–19 November 2024. Poster 0013;
4. Manasson J, et al. ASH Annual Meeting and Exposition 2024, San Diego, CA, USA. 7–10 December 2024. Abstract 2562.

Anti-platelet antibodies bind to platelets producing opsonized platelets and antibody–platelet complexes[1]

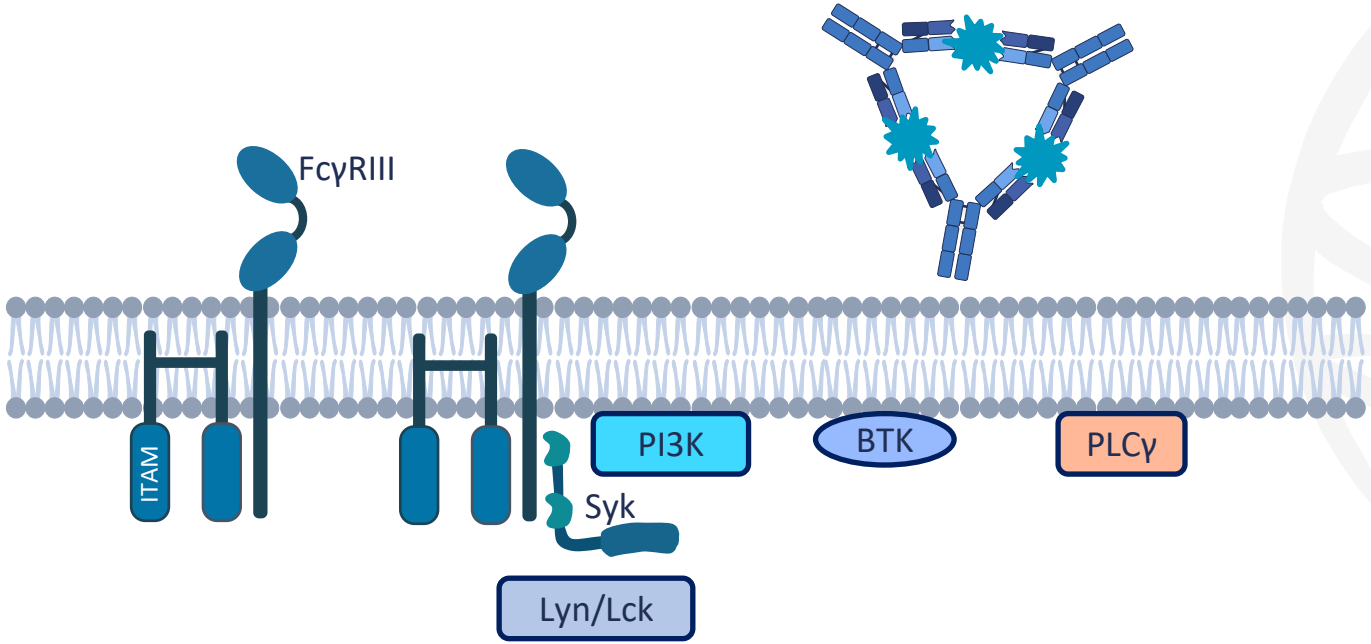

Figure adapted from Nimmerjahn F & Ravetch J. *Ann Rev Immunol*. 2008.
BTK, Bruton's tyrosine kinase; ITAM, immunoreceptor tyrosine-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C γ; R, receptor; Syk, spleen tyrosine kinase.

1. Kuter DJ. *Br J Haematol*. 2022;196:1311–28; 2. Nimmerjahn F & Ravetch J. *Ann Rev Immunol*. 2008;26:513–33.

Antibody–platelet complexes bind to FcRγIII resulting in macrophage activation[1,2]

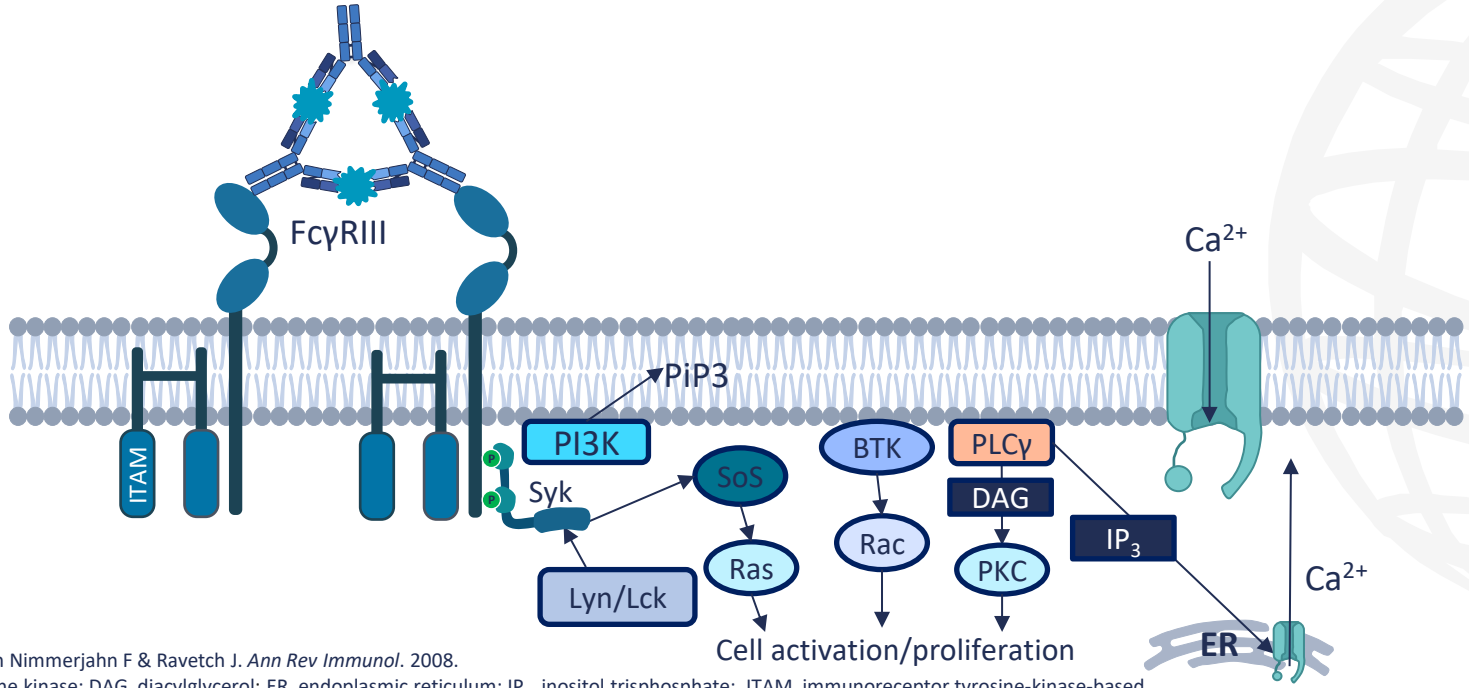

Figure adapted from Nimmerjahn F & Ravetch J. *Ann Rev Immunol*. 2008.

BTK, Bruton's tyrosine kinase; DAG, diacylglycerol; ER, endoplasmic reticulum; IP_3, inositol trisphosphate; ITAM, immunoreceptor tyrosine-kinase-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; PI3K, phosphatidylinositol-3 kinase; PiP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; PLCγ, phospholipase C γ; R, receptor; SoS, son of sevenless; Syk, spleen tyrosine kinase.

1. Kuter DJ, et al. *Br J Haematol*. 2022;196:1311–28; 2. Nimmerjahn F & Ravetch J. *Ann Rev Immunol*. 2008;26:513–33.

Platelets are internalized and destroyed in activated macrophage

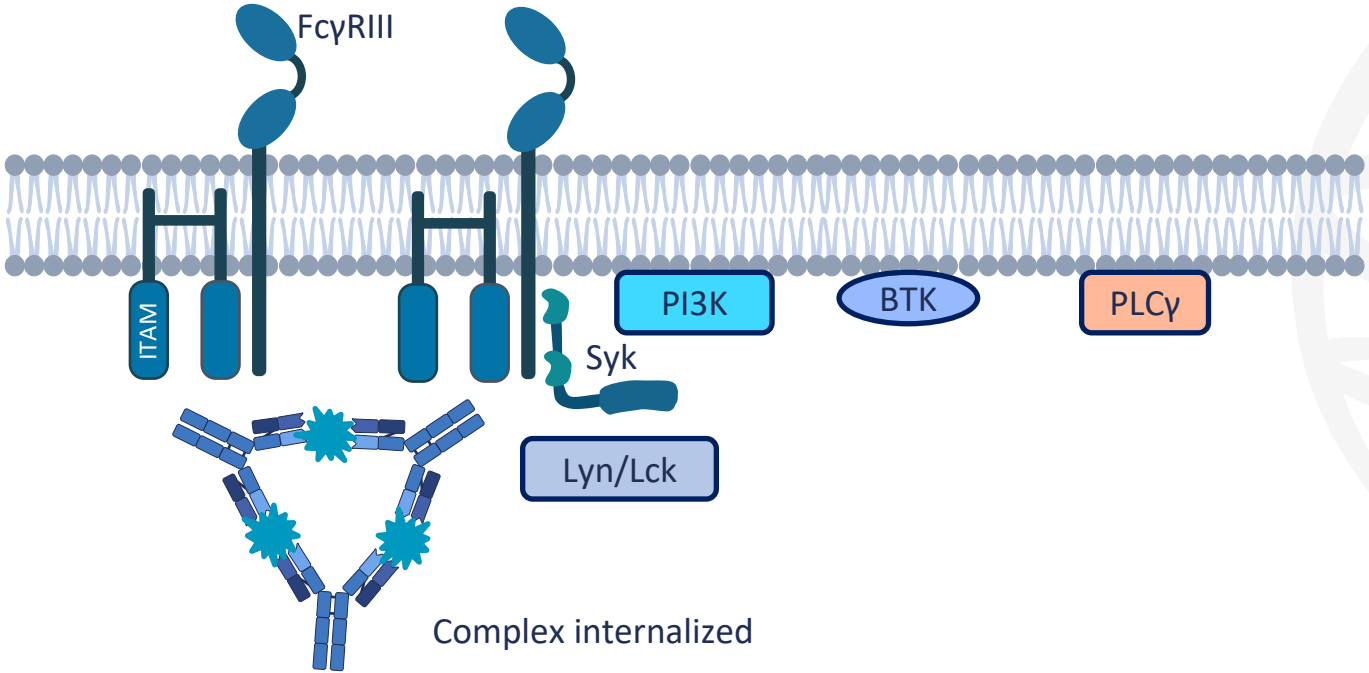

Figure adapted from Kuter DJ. *Br J Haematol*. 2022.
BTK, Bruton's tyrosine kinase; ITAM, immunoreceptor tyrosine-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; PI3K, phosphatidylinositol-3 kinase; PLCγ, phospholipase C γ; R, receptor; Syk, spleen tyrosine kinase.

1. Kuter DJ. *Br J Haematol*. 2022;196:1311–28; 2. Nimmerjahn F & Ravetch J. *Ann Rev Immunol*. 2008;26:513–33.

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Inhibitors of macrophage function

Current treatments[1]

Corticosteroids	Vincristine/ vinblastine (*off-label*)[2,3]	Splenectomy	IVIg	Syk kinase inhibitor
				• Fostamatinib

Investigational agents

Hyper-sialylated IVIg
- M254[4]

BTK inhibitors
- Ibrutinib[5]
- Rilzabrutinib[6]

Recombinant Fc multimers
- *PF-06755347 (GL-2045)*[7]
- *CSL730 (M230)*[8]

Syk kinase inhibitors[6]
- Sovleplenib (HMPL-523)
- Cevidoplenib

Underlined treatments are to be discussed, treatments in italics are no longer in development.
BTK, Bruton's tyrosine kinase; IVIg, intravenous immunoglobulin; syk, spleen tyrosine kinase.

1. Provan D, et al. *Blood Adv*. 2019;3:3780–817; 2. FDA. Vincristine sulfate PI. Available at: https://bit.ly/4f88yhM (accessed 22 November 2024); 3. FDA. Vinblastine PI. Available at: https://bit.ly/3V6u7rX (accessed 22 November 2024); 4. Arroyo S, et al. *Blood*. 2019;134(Suppl. 1):1090; 5. Parish PC, et al. *Ann Hematol*. 2023;102:237–8; 6. Al-Samkari H. *Am J Hematol*. 2024;99:2178–90; 7. Zhang X, et al. *JCI Insight*. 2019;4:e121905; 8. Zuercher AW, et al. *Autoimmunity reviews*. 2019;18:102366.

Targets for inhibitors of macrophage function

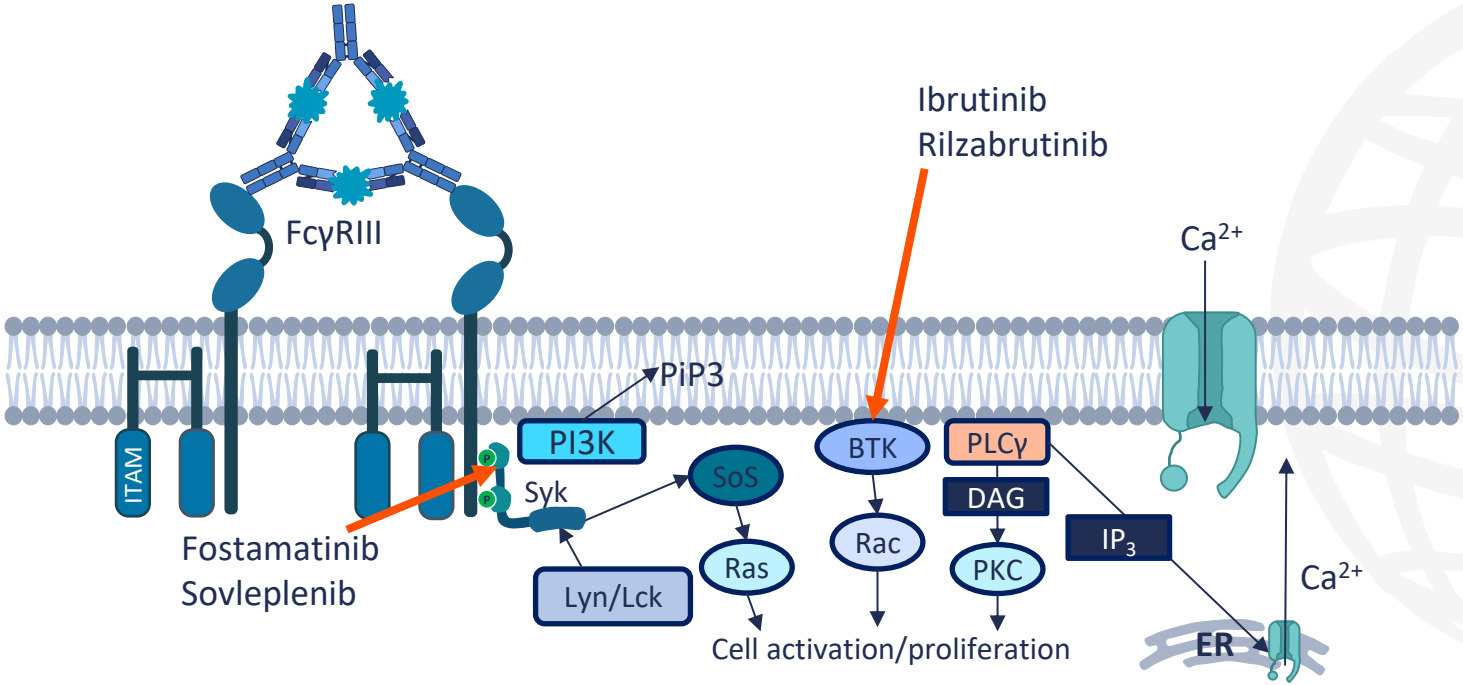
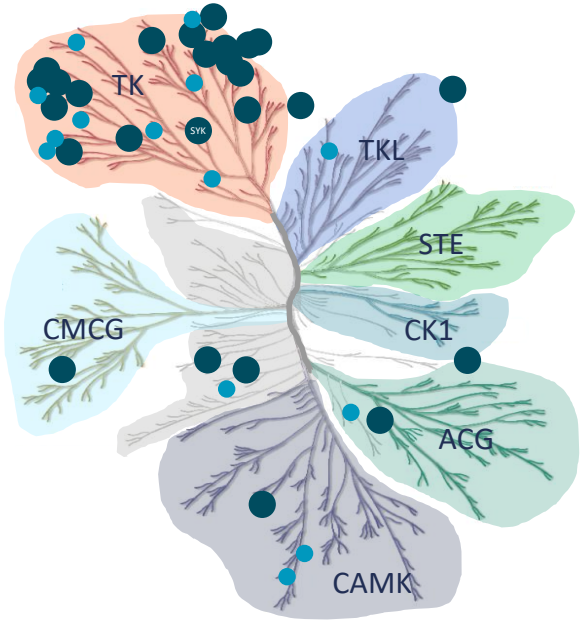


Figure adapted from Kuter DJ. *Br J Haematol*. 2022.

BTK, Bruton's tyrosine kinase; DAG, diacylglycerol; ER, endoplasmic reticulum; IP_3, inositol trisphosphate; ITAM, immunoreceptor tyrosine-kinase-based activation motifs; Lck, lymphocyte-specific protein tyrosine kinase; PI3K, phosphatidylinositol-3 kinase; PiP3, phosphatidylinositol (3,4,5)-trisphosphate; PKC, protein kinase C; PLCγ, phospholipase C γ; R, receptor; SoS, son of sevenless; Syk, spleen tyrosine kinase.

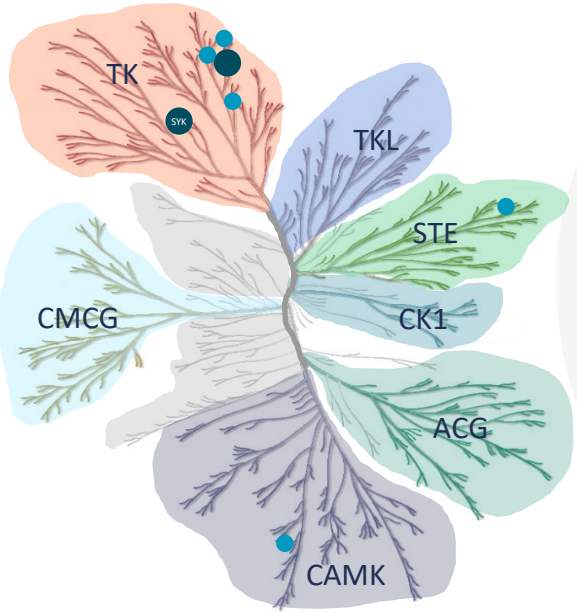
Kuter DJ, et al. *Br J Haematol*. 2022;196:1311–28

Sovleplenib more specific and potent than fostamatinib



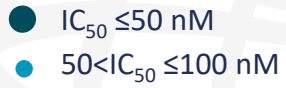
Fostamatinib (R406)[1]

Syk IC_{50}: 50 nM[2]



Sovleplenib (HMPL-523)[2]

Syk IC_{50}: 30 nM[2]



CAMK, calcium/calmodulin-dependent protein kinases; CK1, casein kinase 1; IC_{50}, half-maximal inhibitory concentration; Syk, spleen tyrosine kinase; TK, tyrosine kinase; TKL, tyrosine kinase-like kinases.

1. Rolf MG, et al. *Pharma Res Per*. 2015;3:e00175; 2. Cai Y, et al. *J Pharmacol Exp Ther*. 2024;388:156–70.

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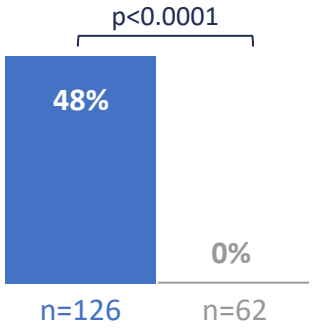
Sovleplenib phase III: Primary endpoints

Primary endpoint

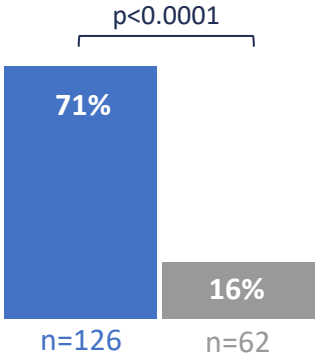
Durable response
(PCs ≥50 x 10^9/L at 4–6 visits during 14–24 weeks)*



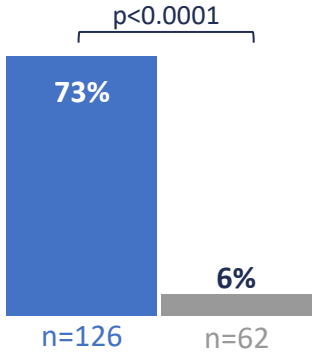
Platelet-related secondary endpoints

Other platelet responses (assessed from 0–24 weeks)

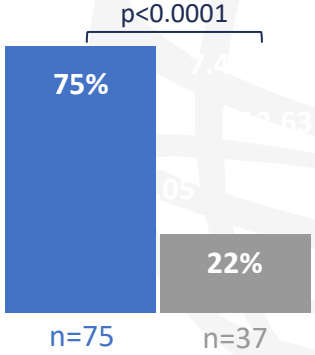
≥1 PC ≥50 x 10^9/L*



Two consecutive PCs ≥30 x 10^9/L and double from BL



PC ≥30 x 10^9/L and increased ≥20 x 10^9/L from BL†



▪ Sovleplenib ▪ Placebo

*Not impacted by rescue treatment; †For patients with a platelet count of <15 x 10^9/L at baseline.
BL, baseline; PC, platelet count.
Hu Y, et al. *Lancet Haematol.* 2024;11:e567–79.

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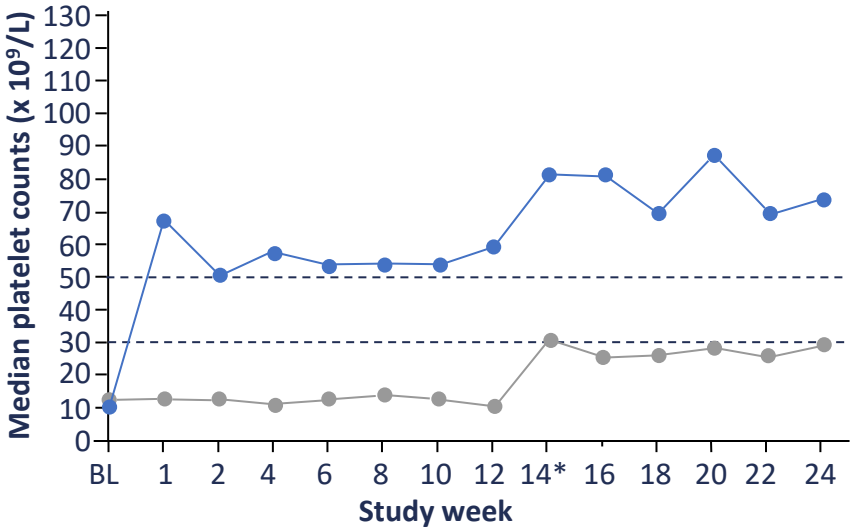
Sovleplenib phase III: Platelet counts



Sovleplenib group	126	41	114	110	109	111	109	105	83	83	84	85	85	84
Placebo group	62	22	54	52	47	50	47	49	8	8	8	8	8	8

Figure reproduced from Hu Y, et al. *Lancet Haematol.* 2024.
*Most of the non-responders ended the double-treatment period at week 12 due to lack of efficacy.
BL, baseline.
Hu Y, et al. *Lancet Haematol.* 2024;11:e567–79.

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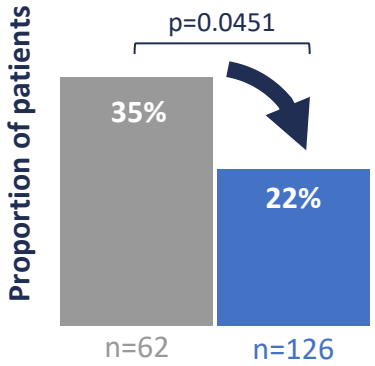
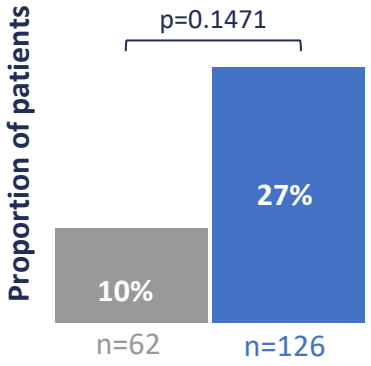
Sovleplenib phase III: Secondary outcomes

Rescue therapy

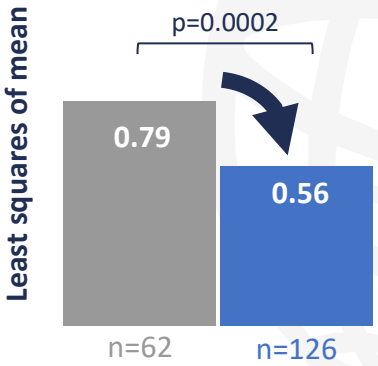


Dose reduction/discontinuation rate of BL concomitant treatments



Two patients discontinued by themselves before the first dose

WHO bleeding score



▪ Sovleplenib ▪ Placebo

Figures reproduced with permission from Yang R, et al. EHA 2024. S316.
BL, baseline; WHO, World Health Organization.
Yang R, et al. Presented at: EHA 2024 Hybrid Congress, Madrid, Spain. 13–16 June 2024. Oral presentation S316.

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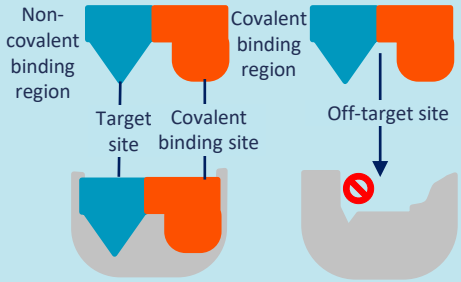
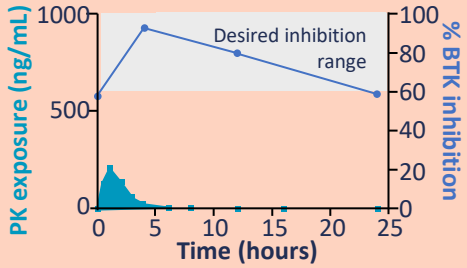
Rilzabrutinib is an oral, reversible, potent BTK inhibitor and does not impact platelet aggregation



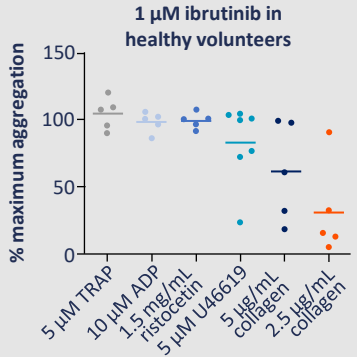
Selective/reversible

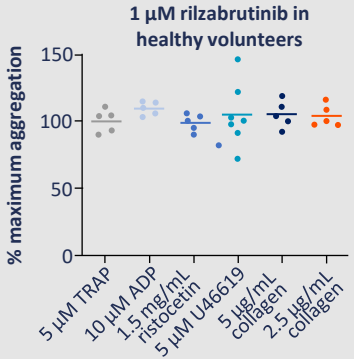
Precise inhibition
No permanent modification of proteins and peptides

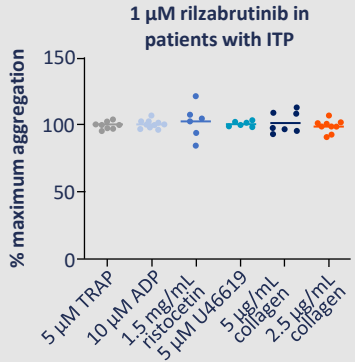


Durable BTK inhibition with low exposure

Potential optimized clinical benefit







No inhibition of platelet aggregation

Potential reduced risk of bleeding

Figures reproduced from Langrish CL, et al. *J Immunol*. 2021 and Kuter DJ, et al. ISTH 2023. OC 65.1.

ADP, adenosine diphosphate; BTK, Bruton's tyrosine kinase; ITP, immune thrombocytopenia; PK, pharmacokinetics TRAP, thrombin receptor activating peptide.

1. Langrish CL, et al. *J Immunol*. 2021;206:1454–68; 2. Kuter DJ, et al. Presented at: ISTH Congress 2023, Montreal, Canada. 24–28 June 2023. Presentation OC 65.1.

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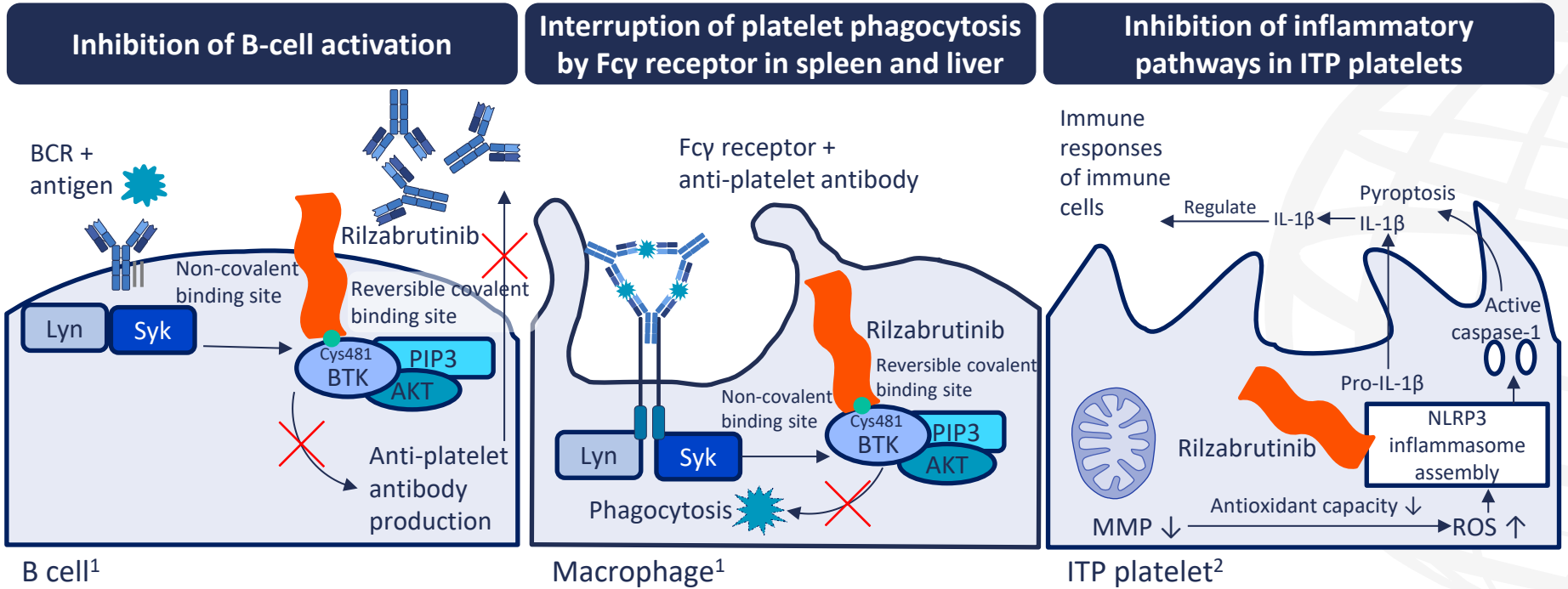
Rilzabrutinib immunological effects



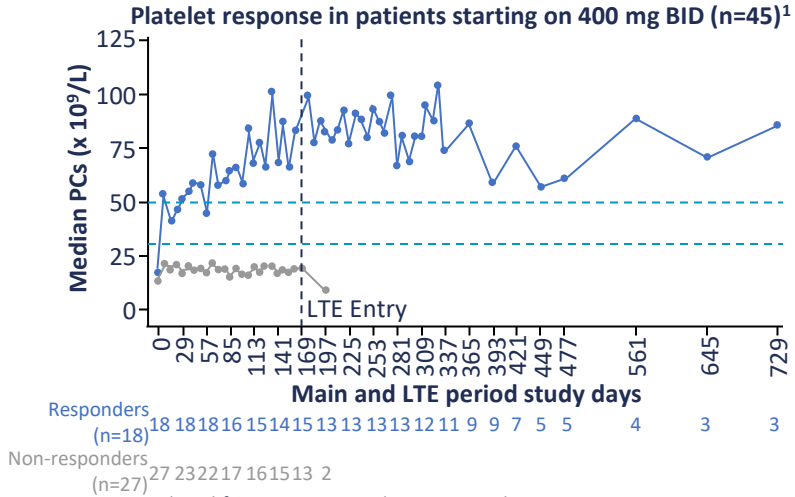
BTK inhibitor impacts different mechanisms that target key aspects of ITP disease pathophysiology[1–4]

Left-hand and centre figures reproduced from Kuter DJ, et al. *Ther Adv Hematol*. 2023. Right-hand figure reproduced from Wang S, et al. *Thromb Res*. 2021.
AKT, protein kinase B; BCR, B cell receptor; BTK, Bruton's tyrosine kinase; IL, interleukin; ITP, immune thrombocytopenia; MMP, matrix metalloproteinases; NLRP3, NOD-like receptor protein; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; ROS, reactive oxygen species; Syk, spleen tyrosine kinase.

1. Kuter DJ, et al. *Ther Adv Hematol*. 2023;14:1–16; 2. Wang S, et al. *Thromb Res*. 2021;199:1–9; 3. Langrish CL, et al. *J Immunol*. 2021;206:1454–68;
4. Daak A, et al. ASH Annual Meeting and Exposition 2024, San Diego, CA, USA. 7–10 December 2024. Abstract 2482.

Rilzabrutinib phase I/II trial in previously treated ITP: Platelet responses with 400 mg BID

- Median treatment duration: 168 days (range: 10–188) for the main treatment period and LTE[1]
- 18 patients (40%) initiating 400 mg BID rilzabrutinib met the primary endpoint: ≥2 consecutive platelet counts ≥50 x 10^9/L and increased ≥20 x 10^9/L without the use of rescue medication in the 4 weeks prior to the latest elevated platelet count[1]
- 16 of these 18 patients showed clinically relevant platelet counts of ≥50 x 10^9/L at any point in the first 8 weeks of the study treatment[1]



Primary efficacy responders PCs (n=18)[1]	Median number of weeks	Duration of response, median % week
≥30 x 10^9/L	20.5	95
≥30 x 10^9/L with ≥20 x 10^9/L above BL	18	86
≥50 x 10^9/L	14	72

Select TRAE (n=60), n (%)[2]	Grade 1	Grade 2	Grade 3/4
Diarrhoea	16 (27)	3 (5)	0
Nausea	16 (27)	2 (3)	0
Fatigue	5 (8)	1 (2)	0

Figure reproduced from Kuter DJ, et al. ASH 2021. Abstr. 14.

BID, twice a day; BL, baseline; ITP, immune thrombocytopenia; LTE, long-term extension; PC, platelet count; TRAE, treatment-related adverse event. 1. Kuter DJ, et al. Presented at: ASH Annual Meeting and Exposition 2021, Atlanta, GA, USA. 11–14 December 2021. Abstract 14; 2. Kuter DJ, et al. *New Engl J Med*. 2022;386:1421–31.

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Pooled Luna 2 data: Overall and durable platelet responses by baseline variables

Patients with fewer prior and earlier lines of ITP therapy had higher responses

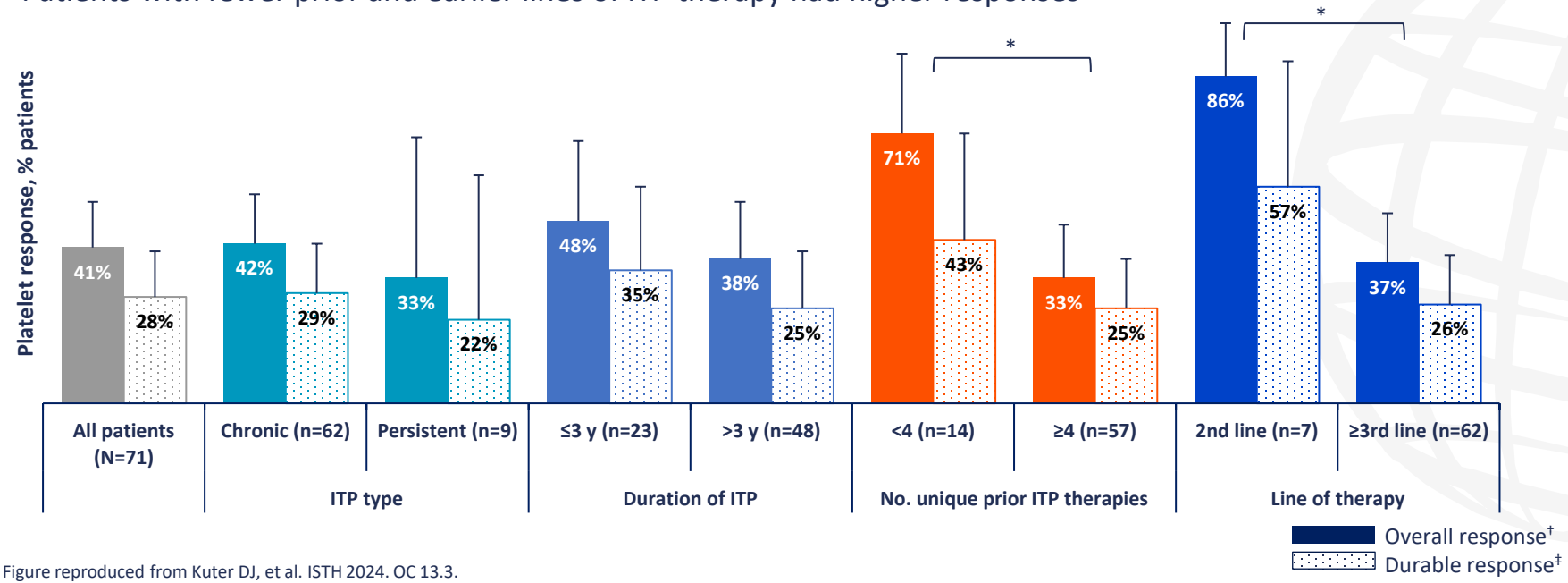

Figure reproduced from Kuter DJ, et al. ISTH 2024. OC 13.3.
Data cut-off for part A was 9 April 2021; part B was 31 January 2023.
*Denotes p≤0.05 based on Fisher-exact method within the subgroup comparison; †Overall platelet response was defined as ≥50 x 10^9/L and increased ≥20 x 10^9/L from baseline; ‡Durable platelet response was ≥8 of the last 12 platelet counts ≥50 x 10^9/L. ITP, immune thrombocytopenia.
Kuter DJ, et al. Presented at: ISTH 2024, Bangkok, Thailand. 22–26 June 2024. Oral presentation OC 13.3.

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Conclusions

ITP pathophysiology is complex and understanding it helps guide development of new treatments[1,2]

ITP is a disorder of reduced platelet production[1]

- Corticosteroids and TPO-RA increase platelet production[3,4]
  - Hetrombopag: the newest TPO-RA

ITP is a disorder of increased platelet destruction[2]

- Reduce antiplatelet antibody: FcRn inhibition,[2] IgG proteases,[5] BAFF receptor inhibitors,[6] anti-CD38 (daratumumab, mezagitamab [TAK-079][6])
- Inhibit complement: sutimlimab, iptacopan[2,6]
- Inhibit phagocytosis
  - Modified IVIg: Sialylated IgG,[7] recombinant FC multimers[8]
  - Syk inhibition: sovleplenib (HMPL-523)[6]
  - BTK inhibition: rilzabrutinib[2,4]

BAFF, B-cell activating factor; BTK, Bruton's tyrosine kinase; CD, cluster of differentiation; FcRN, neonatal Fc receptor; Ig, immunoglobulin; ITP, immune thrombocytopenia; IV, intravenous; Syk, spleen tyrosine kinase; TPO-RA, thrombopoietin receptor agonist.

1. Althaus K, et al. *Hamostaseologie*. 2021;41:275–82; 2. Yan X, et al. *Discov Med*. 2024;1:57; 3. Kuter DJ. *Ann Blood*. 2021;6:7; 4. Tungjitviboonkun S, Bbumrungratanayos N. *Discov Med*. 2024;1:7; 5. Johansson BP, et al. *PLOS One*. 2008;3:e1692; 6. Al-Samkari H. *Am J Hematol*. 2024;99:2178–90; 7. Vattepu R, et al. *Front Immunol*. 2022;13:818736; 8. Ortiz DF, et al. *Sci Transl Med*. 2016;8:365ra158.

Exciting oral ITP presentations at ASH 2024

Eltrombopag (TPO-RA)		
709	Efficacy findings in a phase 3, randomized trial of eltrombopag vs standard first-line treatment for newly diagnosed ITP in children	Monday 9 December
Ianalumab (BAFF receptor inhibitor)		
710	A phase 2 study of ianalumab in patients with primary ITP previously treated with at least two lines of therapy: Interim results from VAYHIT3	Monday 9 December
Rilzabrutinib (BTK inhibitor)		
5	Efficacy and safety of oral BTKi rilzabrutinib in adults with previously treated ITP: A phase 3, placebo-controlled, parallel-group, multicenter study (LUNA 3)	Sunday 8 December
TQB3473 (Syk inhibitor)		
711	Preliminary efficacy and safety results of TQB3473, a novel Syk inhibitor, in adult patients with ITP	Monday 9 December
Terbutaline (β2-adrenergic receptor agonist)		
425	β2-adrenergic receptor agonist terbutaline regulates macrophage polarization via HMGB1 in ITP	Sunday 8 December
MSC-C5b-9 (biomarker)		
712	Updated outcome from biomarker MSC-C5b-9-guided all-trans retinoic acid treatment for resistant/recurrent ITP: A multicenter, randomized, open-label, phase 3 clinical trial	Monday 9 December

BAFF, B-cell activating factor; BTK, Bruton's Tyrosine Kinase; i, inhibitor; ITP, immune thrombocytopenia; Syk, spleen tyrosine kinase; TPO-RA, thrombopoietin receptor agonist.

Panel discussion – Patient collaboration: Working together to improve outcomes

Prof. Cindy Neunert (Chair)
Columbia University,
New York, NY, USA

Prof. David Kuter
Massachusetts General Hospital,
Boston, MA, USA

Dr María Eva Mingot Castellano
Hospital Universitario Virgen del Rocío,
Sevilla, Spain

Shared decision-making should be treated as an ongoing process throughout a patient's ITP journey

HCPs' expertise:
- ITP knowledge
- Treatment options
- Treatment side effects

Patients' expertise:
- Experience of ITP
- Preferences

Patients understand the risks, benefits and consequences of different treatment options, as well as the characteristics and risks of their disease

Patients are empowered to make decisions about the care that is right for them, based on evidence and their preferences, beliefs and values

Shared decision-making can lead to greater decision satisfaction, improved communication and trust between the patient and their HCP, improved adherence to treatment plans and optimal experience of care

HCP, healthcare professional; ITP, immune thrombocytopenia.
Maitland H, et al. *Haematology*. 2024;29:2375177.