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Clinical Effectiveness and Safety of Second-Line Therapies for Immune Thrombocytopenia (ITP): A Systematic Literature Review

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KEY FINDINGS & CONCLUSIONS

- Response rates and the likelihood of achieving complete or sustained remission varied widely, reflecting the heterogeneity of patient populations, therapeutic approaches and the considerable diversity in disease monitoring practices and trial designs.
- The review highlights the unmet medical needs in ITP management emphasizing the need for interventions that demonstrate higher efficacy with better safety profile.
- Prioritizing achieving TFR or SRoT, while reducing the risk of bleeding is crucial for enhancing patient outcomes and maintaining both safety and quality of life.
- These goals remain central to ITP management, signifying sustained disease control without the burden of continuous medication or adverse events.

This research was funded by Novartis Pharma AG
Poster presented at ISPOR Europe 2025, held on 9-12 November 2025; Glasgow, Scotland, UK

INTRODUCTION

- Immune-thrombocytopenia (ITP) is an autoimmune disorder characterized by low platelet count and purpura, leading to an increased risk of bleeding with a prevalence of 9–26 cases per 100,000 population.[1]
- Management depends on symptom severity[2] and includes treatments such as corticosteroids, intravenous immunoglobulin (IVIG), anti-D immunoglobulin, thrombopoietin receptor agonists (TPO-RAs), spleen tyrosine kinase inhibitors (SYK), rituximab, and splenectomy.
- Many patients have incomplete responses or relapse, indicating an unmet need. This systematic literature review (SLR) aims to summarize the clinical evidence on the effectiveness and safety of various treatments for primary ITP in adult patients receiving second-line therapy, focusing on studies conducted outside the United States (US)

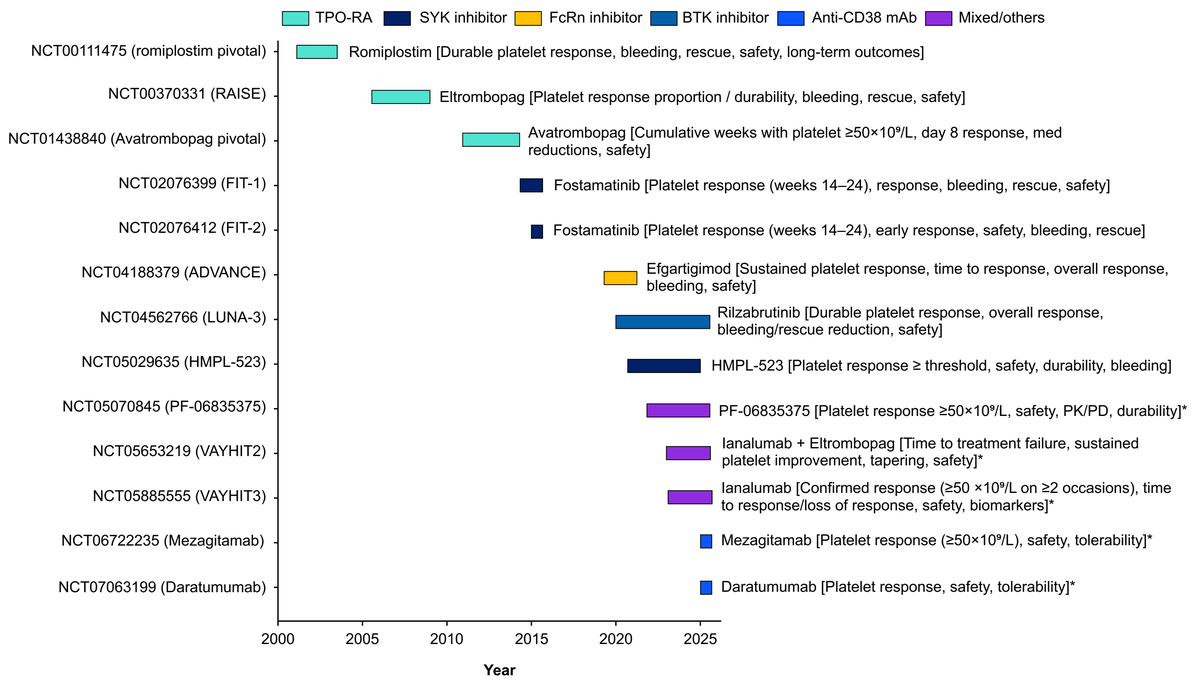
METHODS

- The SLR was conducted in accordance with the Cochrane Handbook, Centre for Reviews and Dissemination (CRD) guidance, and PRISMA guidelines.
- Embase, MEDLINE, PubMed-not-MEDLINE, and the Cochrane Library were searched for studies published from 2007 to June 2024. Grey literature, conference abstracts (2020–2024), clinical trial registries, and HTA reports were also included.
- Two independent reviewers screened titles/abstracts and full texts, with a third resolving disagreements. Data extraction and quality-check were conducted by separate reviewers.
- Randomized controlled trials (RCTs) were assessed with the Cochrane risk of bias tool; other studies used the Newcastle-Ottawa Scale.

RESULTS

- 8,564 citations screened; 45 studies that reported on second-line therapies in adult ITP patients in non-US countries were included [Asia (19), Europe (14), Middle East (6), Global (3), North America (2) and Africa (1); main countries: China (9), France (5), India and Italy (4 each)]. Study types- observational cohorts (30), RCTs (8), single-arm studies (7).
- All studies involved predominantly primary ITP patients (>85%) [(relapsed/refractory ITP (n=9) or refractory ITP (n=8)]. Interventions evaluated included monoclonal antibodies (mABs) (rituximab; n=13), TPO-RA (eltrombopag, romiplostim; n=14), and surgical approaches (n=14), as well as corticosteroids, immunomodulators, and tyrosine kinase inhibitors.
- Median age ranged from 25.0-76.8 years (n=39), with female predominance observed in over 97% of studies (n=40). Prior treatments (n=23): corticosteroids were the most used first-line therapy (n=14, 75%–100%), followed by TPO-RAs (n=4; 2.1%–29.4%) and rituximab (n=6; 2.8%–21%). In 22 studies, patients with prior splenectomy were also included.

Figure 1. Overview of ITP clinical trials landscape



Abbreviations: BAFF-R: B-cell Activating factor receptor; RCT: Randomized controlled trials; TKI: Tyrosine kinase inhibitors; TPO-RA: Thrombopoietin receptor agonists
*Ongoing trials with expected completion beyond 2026

Clinical efficacy

- The evolving landscape of second-line therapies has reshaped treatment strategies by prioritizing durable responses—sustained improvements in platelet counts and reduced bleeding symptoms, even after dose tapering or discontinuation (**Figure 1**) .
- Platelet peaks were observed between 12–48 weeks (33.9–493.1 x10^9/L) and often sustained during later follow-up time-points.
- Definitions for response rates varied across studies included.
- Platelet response, typically defined as a platelet count between 30-100 × 10^9/L, was reported in 20 studies.
- Complete response, commonly characterized by a platelet count of ≥100 × 10^9/L, was documented in 31 studies.
- Overall response rates were mostly defined as achieving either a complete or partial/platelet response and were observed in 19 studies.
- In several studies, over 50% of patients showed no response at the most recent follow-up (f/u).
- There was considerable diversity among clinical trials with respect to endpoints and timing of evaluation, which makes it challenging to compare the effectiveness of different drugs (**Table 1**).

Table 1. Response outcomes reported across included clinical trials

Study/Trial Name	Intervention	Study design	Country	Overall response			Complete response	
				48 wks	52 wks	Last/ other f/u	48 wks	Last/ other f/u
TPO-RAs								
TAPER 2024 NCT03524612	Eltrombopag	Single arm	Multi-country*	-	-	-	✓	-
Lucchini 2021 NCT02402998	Eltrombopag	Single arm	Italy	-	-	-	-	✓
Wang 2024 NCT05369377	Eltrombopag	RCT	China	-	✓	-	-	-
Wang 2012	rhTPO group: rhTPO + danazol	RCT	China	-	-	✓	-	✓
mABs								
RITP trial 2015 NCT00344149	Rituximab	RCT	Multi-country**	-	-	✓	-	✓
Kapoor 2017	Rituximab - Low-dose	Interventional, Single arm	India	-	-	✓	-	✓
HOVON 2010	Rituximab 4 × 375 mg/m² weekly	Single arm	Netherlands	-	-	✓	-	✓
	Rituximab 2 × 750 mg/m² weekly			-	-	✓	-	✓
	Rituximab 2 or 4 × 375 mg/m² weekly			-	-	✓	-	✓
Immunomodulators								
Wang 2012	Danazol	RCT	China	-	-	✓	-	
Feng 2017 NCT01667263	Danazol	RCT	China	✓	-	-	✓	-
	All-trans-retinoic acid + Danazol			✓	-	-	✓	-

Abbreviations: f/u: follow-up; rhTPO: recombinant human thrombopoietin; RCT: Randomized controlled trials; TKI: Tyrosine kinase inhibitors; TPO-RA: Thrombopoietin receptor agonist; wks: weeks
*Austria, Brazil, Chile, France, Greece, Italy, Japan, Mexico, Oman, Russian Federation, Spain, Switzerland, Turkey, UK, US; ** Norway, Tunisia, France

Treatment-free remission (TFR) and Sustained response off treatment (SRoT)

- With a growing emphasis on long-term disease control in ITP, emerging endpoints such as TFR and SRoT are gaining prominence as indicators of durable therapeutic benefit beyond initial platelet response, even in newly diagnosed ITP.
- As per the studies included, achieving TFR or SRoT was possible for only a proportion of ITP patients following second-line treatments, particularly with TPO-RAs and splenectomy (**Table 2**).
- Success rates tend to be higher when treatment was initiated early and in patients who had already achieved a complete response[3].

Table 2. Overview of TFR and SRoT with early line ITP treatments

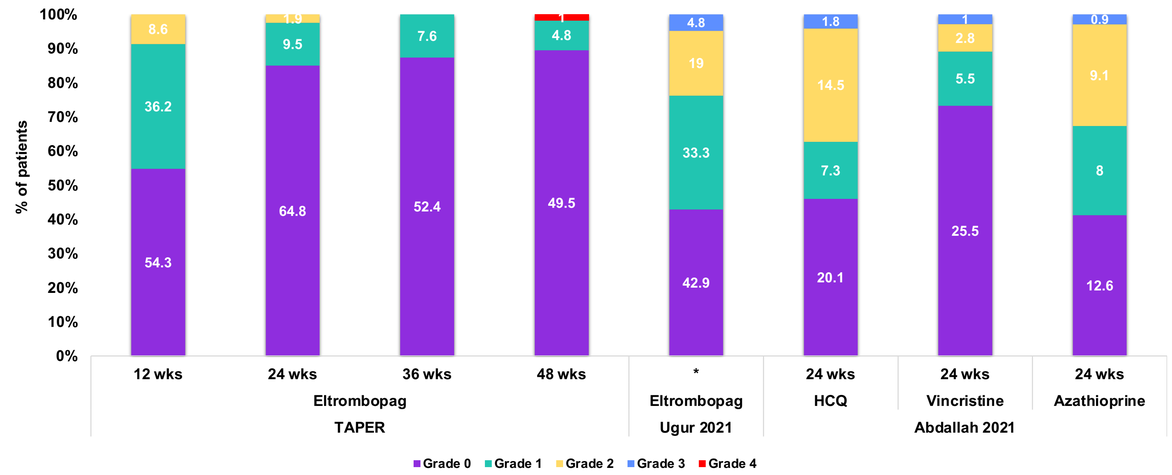
Study/Trial Name	Study design	Study Sample N	Intervention	Sub-group description	Time point (months)	TFR* or SRoT, %
From TPO-RA discontinuation (without receipt of any other ITP treatments or medication) to the date that any treatment for ITP was restarted						
Iino 2020	Observational	77	Eltrombopag, Romiplostim	Newly diagnosed ITP patients who discontinued TPO-RAs after CR	Median f/u: 24 (range: 1-104)	66.4*
Weekly platelet count ≥50 × 10^9/L for 24 consecutive weeks with no ITP treatments						
Newland 2016	Single arm trial	75	Romiplostim	Overall	-	32*
				Newly diagnosed ITP (<3 months); insufficient response to first-line	-	37.8*
				Persistent ITP (≥3- ≥12 months); insufficient response to first-line	-	23.3*
Four step eligibility criteria for SRoT, Step-1: platelet count ≥100 x 10^9/L; Step-2: maintain a stable platelet count (i.e., no counts <70 x 10^9/L) for 2 months; Step-3: Treatment tapered and discontinued, maintain platelets ≥30 x 10^9/L without bleeding events & any rescue therapy; Step-4: Maintain platelets ≥30 x 10^9 /L following discontinuation of eltrombopag, without bleeding or rescue therapy by Month 12						
TAPER 2024	Single arm trial	104	Eltrombopag	Did not respond or had relapsed after initial corticosteroid therapy, with platelet counts <30 x 10^9/L	12	30.5
Discontinuation of treatment with sustained TFR						
iROM-study 2021	Single arm trial	13	Romiplostim	Newly diagnosed ITP (<3 months)	12	66.7*
SROT						
Lucchini 2021	Single arm trial	55	Eltrombopag	Overall	End of observation	25
				Started tapering/discontinuation in CR	6 months	50
				Started tapering/discontinuation not in CR	6 months	25
Overall, successful LS requiring no further medical management was required						
Istl 2018	Observational	141	Laparoscopic splenectomy	Overall	-	78.7*

Abbreviations: CR: Complete response; f/u: follow-up; ITP: Immune thrombocytopenia; LS: Laparoscopic splenectomy; RCT: Randomised controlled trials; SRoT: Sustained response off-treatment; TPO-RA: Thrombopoietin receptor agonists; TFR: Treatment-free remission.
*TFR outcomes reported

Bleeding events

- Five studies reported the occurrence of different grades of bleeding events (**Figure 2**). For instance, eltrombopag treated patients of TAPER trial, grade 1 bleeding events reduced from 36.2% at 12 weeks to 4.8% at 48 weeks[4], while vincristine showed a lower incidence of grade 1-3 bleeding events compared to other treatments like hydroxychloroquine and azathioprine[5].

Figure 2. Grades of bleeding events reported at different time points



Abbreviations: HCQ: Hydroxychloroquine; wks: weeks; WHO bleeding scale: grade 0: no bleeding, grade 1: mild blood loss, grade 2: moderate blood loss, grade 3: gross blood loss, grade 4: debilitating blood loss
*At initiation of eltrombopag.

Safety outcomes

- Safety outcomes were evaluated in 33 studies. The most commonly reported overall adverse events (AEs) encompassed infusion reactions, thrombotic events, liver function abnormalities, increased risk of infections and malignancies, and gastrointestinal complications. Notably, abdominal pain (2.5%- 6.7%), headache (2.1%- 21.9%), and thrombocytopenia (12.5%- 34%) were among the frequently observed complications.
- The incidence of serious AEs across studies spanned between 1.3% to 20%, while treatment-related or emergent AEs occurred in 35% to 84% of participants. Treatment discontinuation due to AEs was reported in 1.4% to 34.3% of cases.

Quality of Life outcomes

- The evidence from the reviewed studies suggested that both eltrombopag and baricitinib were associated with improvements in patient-reported quality of life (QoL) outcomes.
- Across three studies utilizing validated QoL instruments—including FACIT-Fatigue, FACT-Th6, SF-36v2, and ITP-PAQ—patients experienced notable QoL benefits within the initial three months of therapy, with these improvements generally sustained over time[4,6,7].

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Acknowledgements

The authors acknowledge Greeshma (Novartis, Hyderabad) for providing medical writing assistance with this poster.

Disclosures

Isabelle Lundqvist, Kalitsa Filioussi, Meritxell Vendranas, Shaun Walsh, Aditi Kataria, Lovneet Saini are employees of Novartis

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