Mediterranean Journal of Hematology and Infectious Diseases

Review Articles

Evolving Paradigms in the Management of Primary Immune Thrombocytopenia in Adults: From Corticosteroids to Targeted Therapies

Massimo Martino[1], Laura Giordano[1], Maria Bruna Greve[1], Violetta Marafioti[1] and Caterina Alati[1].

[1] Department of Hemato-Oncology and Radiotherapy, Hematology and Stem Cell Transplantation and Cellular Therapies Unit (CTMO), Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", Reggio Calabria, Italy.

Competing interests: The authors declare no competing interest.

Abstract. Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by isolated thrombocytopenia (platelet count <100 × 10⁹/L) in the absence of another explanatory cause. Bleeding risk has traditionally anchored clinical management, yet patient-reported data show that fatigue and impaired quality of life represent an equally prominent burden of the disease and are increasingly proposed as a practical, patient-centered axis for personalizing treatment rather than as a secondary consideration. For decades, treatment relied on corticosteroids as first-line therapy, followed by a limited range of second-line options including thrombopoietin receptor agonists (TPO-RAs), rituximab, splenectomy, and, more recently, fostamatinib. Growing understanding of the immune mechanisms underlying both accelerated platelet destruction and impaired platelet production has expanded the therapeutic landscape to include mechanism-directed agents targeting Bruton tyrosine kinase, BAFF-receptor-dependent B-cell biology, the neonatal Fc receptor, and plasma-cell compartments, together with emerging clinical interest in combining agents that act on complementary mechanistic nodes. This narrative review focuses on primary ITP in adults and examines how fatigue and other patient-reported symptoms, alongside platelet counts, can inform personalized selection among established and emerging targeted therapies. Particular attention is given to distinguishing approved therapies from investigational agents by region and date, interpreting heterogeneous trial endpoints with appropriate caution, and integrating disease features, safety considerations, and patient preferences into treatment selection. Although recent phase II and III studies support the biological and clinical promise of several targeted agents, the optimal sequencing and combination of these therapies remain to be defined.

Keywords: Immune thrombocytopenia; Thrombopoietin receptor agonist; Bruton tyrosine kinase inhibitor; FcRn antagonist; BAFF receptor; Fatigue; Quality of life.

Citation: Martino M., Giordano L., Greve M.B., Marafioti V., Alati C. Evolving paradigms in the management of primary immune thrombocytopenia in adults: from corticosteroids to targeted therapies. Mediterr J Hematol Infect Dis 2026, 18(1): e2026067, http://dx.doi.org/10.4084/MJHID.2026.067

Published: September 01, 2026 **Received: June 29, 2026** **Accepted: August 04, 2026**

Correspondence to: Laura Giordano. Hematology and Stem Cell Transplantation and Cellular Therapies Unit (CTMO), Department of Hemato-Oncology and Radiotherapy, Grande Ospedale Metropolitano "Bianchi-Melacrino-Morelli", 89133 Reggio Calabria, Italy. E-mail: giordanolau@gmail.com

Literature Search and Scope. This narrative review primarily examines primary immune thrombocytopenia (ITP) in adults. To identify relevant literature, we searched PubMed/MEDLINE and major hematology congress proceedings for studies published between January 2000 and April 2026, with the final search conducted on April 30, 2026. Search terms included combinations of immune thrombocytopenia, primary ITP, adult ITP, corticosteroids, rituximab, splenectomy, thrombopoietin receptor agonists, fostamatinib, rilzabrutinib, ianalumab, efgartigimod, mezagitamab, combination therapy, fatigue, and quality of life.

We reviewed articles published in English and prioritized international guidelines, consensus documents, pivotal randomized trials, major prospective cohort studies, and full peer-reviewed publications. Conference abstracts were included only when deemed clinically significant and when full peer-reviewed publications were not available at the time of manuscript revision. This is not a systematic review or meta-analysis; the selection of studies was guided by clinical relevance, methodological rigor, and the goal of summarizing the evolution of adult primary ITP management, with particular emphasis on how fatigue and quality-of-life data can inform individualized treatment selection.

Introduction. Immune thrombocytopenia (ITP) is an acquired autoimmune disorder defined by isolated thrombocytopenia, a platelet count below 100×10^9/L, in the absence of an identifiable secondary cause.[1] As a diagnosis of exclusion, ITP encompasses a clinically heterogeneous population: approximately 80% of cases are primary, while the remainder are secondary to an underlying condition such as systemic lupus erythematosus, antiphospholipid syndrome, common variable immunodeficiency, chronic lymphocytic leukemia, Evans syndrome, viral infection (HIV, hepatitis C), Helicobacter pylori infection, or recent vaccination.[2] The annual incidence of ITP in adults is estimated at 2–3.9 per 100,000 person-years, rising sharply after age 60, particularly among men, with a second, smaller peak in early childhood.[3]

Although ITP was historically regarded primarily as a bleeding disorder, patient-reported data indicate that its clinical impact extends beyond hemorrhagic risk to fatigue, daily functioning, and psychosocial well-being — and that fatigue, in particular, is rated by patients as at least as burdensome as bleeding itself. Management traditionally relied on a limited set of immunosuppressive and splenectomy-based strategies, each constrained by toxicity, invasiveness, or limited durability. In the past two decades, advances in understanding the immune pathways responsible for both accelerated platelet destruction and impaired platelet production have driven the development of a broader range of mechanism-targeted agents.[4] Rather than treating symptom burden as an afterthought to platelet-count endpoints, this review uses fatigue and other patient-reported symptoms as a recurring, explicit thread: for each established and emerging therapy discussed below, we summarize what is (and is not yet) known about its effect on fatigue and quality of life, and we use this information, together with disease and patient characteristics, to build a practical framework for personalized treatment selection. We also address the emerging clinical discussion around combining agents that act on complementary mechanistic nodes, a strategy conceptually distinct from the sequential, single-agent approach that has dominated ITP management to date.

Pathophysiology. The cardinal pathophysiologic event in ITP is a breakdown of immune tolerance to platelet and megakaryocyte surface antigens, most notably glycoprotein (GP) IIb-IIIa and GPIb-IX-V.[4] Loss of tolerance triggers two complementary, frequently coexisting disease mechanisms (**Figure 1**). First, autoreactive B cells — supported by CD4+ T-cell help — produce antiplatelet IgG autoantibodies that opsonize circulating platelets, which are then cleared via Fcγ-receptor–mediated phagocytosis by macrophages in the spleen and liver; complement activation provides an additional, antibody-dependent route to platelet clearance, and the spleen functions both as a principal site of platelet destruction and as a source of pathogenic antibody production.[5] This humoral mechanism was demonstrated as early as 1951, when Harrington and colleagues showed that infusion of plasma from patients with ITP induced transient thrombocytopenia in healthy volunteers, establishing the disease's antibody-mediated basis.[5]

Second, and increasingly recognized as clinically important, antiplatelet and anti-megakaryocyte immune responses, together with cytotoxic T-cell-mediated effects, can impair megakaryocyte maturation, proplatelet formation, and survival — processes consistent with megakaryocyte apoptosis demonstrated in ITP.[6] The result is an inadequate compensatory increase in platelet production despite peripheral thrombocytopenia, a defect incompletely corrected by endogenous thrombopoietin.[4,6] The coexistence of accelerated peripheral clearance and impaired marrow output helps explain why therapies targeting a single mechanistic node — corticosteroids broadly suppressing immune activity, rituximab depleting CD20+ B cells, splenectomy removing the principal site of antibody production and platelet destruction, or TPO-RAs stimulating megakaryopoiesis — often produce only partial or transient benefit, underscoring the rationale both for mechanistically novel agents and, as discussed later, for combining agents that address complementary nodes (**Figure 1**).[7,8]

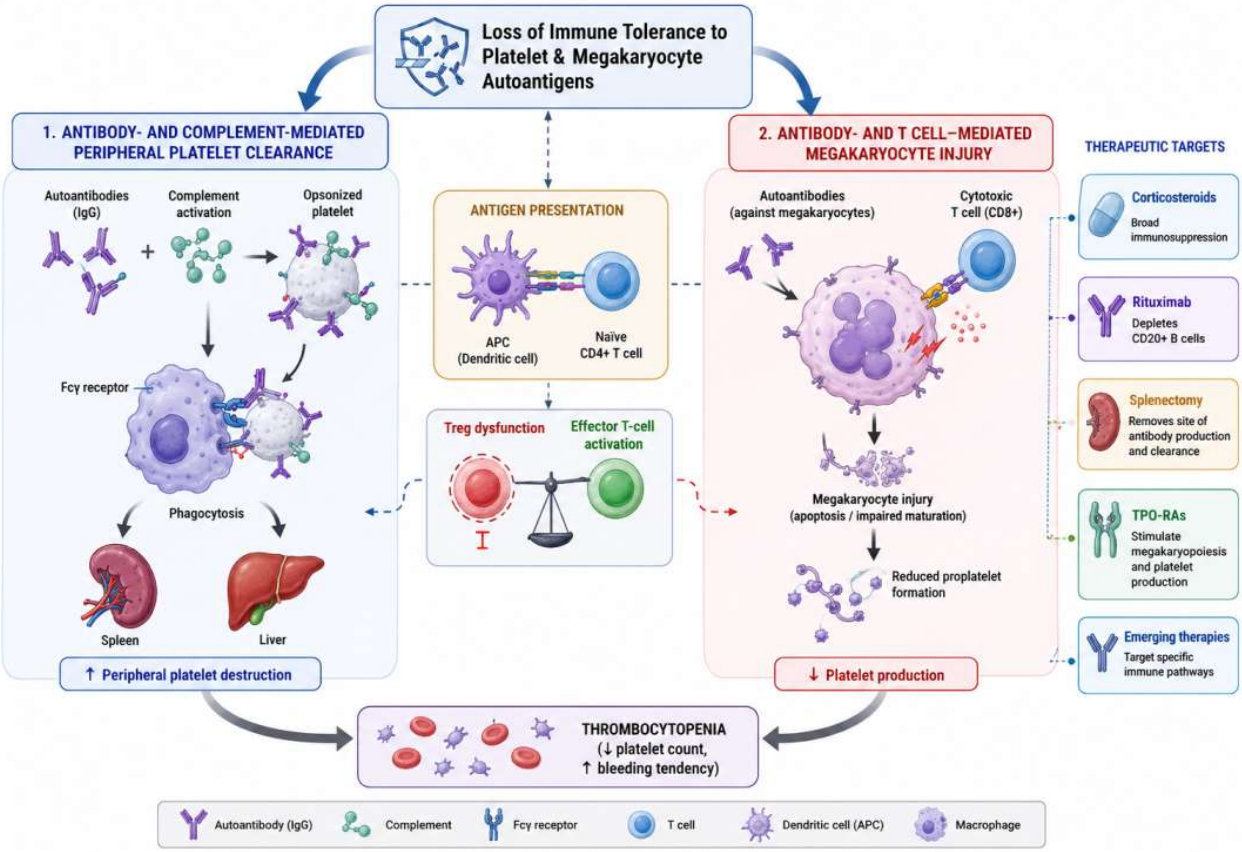

Figure 1. Pathophysiologic mechanisms of immune thrombocytopenia. Loss of immune tolerance to platelet and megakaryocyte autoantigens activates two parallel, frequently coexisting pathways: antibody- and complement-mediated peripheral platelet clearance via splenic/hepatic macrophage phagocytosis, and antibody- and T-cell-mediated megakaryocyte injury leading to impaired, inadequate compensatory platelet production. Both pathways converge on clinically significant thrombocytopenia. Adapted conceptually from data in references.[4-6]

Clinical Burden of Disease. Bleeding manifestations in ITP are heterogeneous, ranging from asymptomatic thrombocytopenia to mucocutaneous bleeding (petechiae, purpura, epistaxis, gingival bleeding, menorrhagia) and, rarely, life-threatening hemorrhage.[1,2] The large international ITP World Impact Survey (I-WISH), which surveyed more than 1,500 patients across 13 countries, demonstrated that the disease burden of ITP extends well beyond bleeding.[9,10] A majority of patients reported that ITP affected their energy levels, capacity for exercise, ability to perform daily tasks, work or study, concentration, hobbies, and social and sexual functioning at least some of the time, with a substantial minority reporting impact "all the time." Fatigue emerged as both the most prevalent and most severely rated symptom, reported as severe by approximately half of patients, exceeding even classic hemorrhagic manifestations such as bruising and petechiae in perceived severity.[10] This finding is the empirical basis for treating fatigue, alongside bleeding risk, as a primary organizing principle for treatment selection throughout this review, rather than as a secondary descriptor of disease impact.

The mechanisms underlying ITP-related fatigue are multifactorial, involving chronic low-grade inflammation, anxiety from fluctuating platelet counts, depression, comorbidities such as hypothyroidism, iron-deficiency anemia from chronic bleeding, sleep disturbances, psychosocial stressors, activity restriction, and adverse effects of therapy, particularly corticosteroids.[10] In patient surveys, increasing energy levels ranked among the top three treatment goals for 41% of respondents and was the most important goal for 20%, second only to achieving healthy blood counts.[9] These findings led to the development of disease-specific patient-reported outcome instruments, such as the ITP Life Quality Index (ILQI), which assesses the impact of ITP on daily functioning, work, relationships, and energy over the preceding month, independent of bleeding symptoms.[11] Fatigue and quality-of-life measures, including the ITP Patient Assessment Questionnaire (ITP-PAQ) and PROMIS-Fatigue, are increasingly incorporated as secondary or exploratory endpoints in pivotal trials of emerging therapies, reflecting a shift toward more comprehensive, patient-centered outcome assessment; as detailed below, however, this incorporation remains inconsistent across agents, which is itself a limitation of the current evidence base.

Conventional Treatment Paradigm. The principal treatment goal in adult primary ITP is not normalization of the platelet count, but the achievement and

maintenance of a safe hemostatic platelet level, generally above 20-30 × 10⁹/L, sufficient to prevent clinically relevant bleeding while minimizing treatment-related toxicity and preserving quality of life.[12] Treatment decisions should be individualized, balancing bleeding risk against the potential adverse effects of therapy: platelet counts above 20-30 × 10⁹/L are often adequate absent bleeding or additional hemorrhagic risk factors and counts exceeding 50 × 10⁹/L frequently allow safe observation. Platelet count alone, however, should never be the sole determinant of treatment. Active bleeding, planned invasive procedures, concomitant anticoagulant or antiplatelet medications, pregnancy, advanced age or frailty, trauma risk, and relevant comorbidities should all be considered.[7,12]

First-line therapy for adults with newly diagnosed ITP requiring treatment continues to consist of a short course (≤6 weeks) of corticosteroids, most commonly prednisone (0.5-2.0 mg/kg/day) or high-dose dexamethasone (40 mg/day for 4 consecutive days).[12] A meta-analysis comparing these regimens demonstrated a significantly higher early response rate with dexamethasone at 7 days (73.2% vs 55.8%), although response rates converged by one month (73.6% vs 76.6%), supporting dexamethasone when a rapid platelet increase is clinically desirable.[13] Corticosteroid-based therapy induces an initial response in approximately 80-90% of patients, but durable remission is uncommon, with 10-year relapse-free survival of only about 13%.[14,15] In a large patient-reported survey, 98% of corticosteroid-treated patients experienced at least one adverse event, more than half reported severe treatment-related burden, and over one-third required dose reduction or discontinuation because of toxicity.[16] Current ASH guidelines therefore strongly recommend limiting corticosteroid treatment to no more than six weeks.[12] Intravenous immunoglobulin (IVIG) may be added when a more rapid platelet increase is required, such as with significant bleeding or before urgent surgery.

For patients with persistent or relapsed thrombocytopenia after first-line therapy, established second-line options include TPO-RAs, rituximab, splenectomy, and fostamatinib.[7,12] Selection depends on disease duration, bleeding risk, patient preferences, comorbidities, treatment goals, and the balance between durable remission and avoiding prolonged medical therapy or surgery. The 2019 ASH guideline emphasizes shared decision-making incorporating disease duration (3-12 months versus >12 months) together with patient priorities such as avoiding surgery, avoiding long-term medication, or maximizing the likelihood of durable remission.[12]

Rituximab, an anti-CD20 monoclonal antibody, provides a time-limited B-cell-directed strategy by reducing autoantibody production. Overall response rates approach 60%, although durability is limited, with response declining to approximately 40% at one year and 20% at five years.[17,18] Treatment may impair vaccine responsiveness for several months, delay immune reconstitution, increase infection susceptibility, and occasionally cause hypogammaglobulinemia or infusion-related reactions.

Splenectomy remains the treatment historically associated with the highest rate of durable remission, achieving complete responses in approximately 70% of appropriately selected patients, by eliminating both the principal site of antibody-mediated platelet destruction and a major source of autoantibody production. Younger patients and those with predominant splenic platelet sequestration may respond better, although predictive markers remain insufficiently validated. Splenectomy is irreversible and carries lifelong risks of overwhelming post-splenectomy infection and thromboembolic complications; contemporary guidelines generally recommend postponing it for at least 12 months after diagnosis whenever feasible.[19-21]

TPO-RAs stimulate megakaryopoiesis by activating the thrombopoietin receptor and are the most commonly used second-line treatment in clinical practice. Available agents include romiplostim (weekly subcutaneous injection), eltrombopag (oral once daily, with dietary restrictions due to interactions with polyvalent cations), and avatrombopag (oral once daily, without dietary limitations).[22-26] These agents frequently induce platelet responses within 1-2 weeks, with durable response rates ranging from approximately 50% to 90%; lack of response to one TPO-RA does not preclude response to another. Treatment usually needs to be continued long term, and thrombotic risk, hepatotoxicity (particularly with eltrombopag), route and frequency of administration, adherence, and cost should all be considered. Although TPO-RAs are not curative for most patients, approximately one-third of treated individuals achieve sustained treatment-free remission after discontinuation.[12,22-26]

Fostamatinib, an oral spleen tyrosine kinase (SYK) inhibitor, targets a different pathogenic mechanism by inhibiting Fcγ receptor-mediated macrophage phagocytosis of antibody-coated platelets, and may be particularly valuable when immune-mediated platelet clearance predominates or when TPO-RAs are unsuitable because of thrombotic concerns or prior treatment failure. In two phase III randomized studies, the prespecified primary endpoint — stable response — was achieved by 18% of fostamatinib-treated patients versus 2% with placebo; the overall (any) response rate, a secondary measure, was 43% versus 14% with placebo. Real-world and expanded-access studies have reported response rates approaching 78% when the drug is used earlier as second-line therapy. The most frequent adverse effects include diarrhea, hypertension, nausea, and elevated liver transaminases.[27,28]

Table 1. Established second-line therapies for primary immune thrombocytopenia in adults. Fostamatinib figures corrected to reflect the phase III prespecified primary endpoint (stable response) and the secondary overall-response comparison.

Therapy	Mechanism of action	Administration	Overall response	Typical time to response	Main limitations / adverse effects
Rituximab	Anti-CD20 monoclonal antibody causing B-cell depletion and reduced autoantibody production	Intravenous infusion (375 mg/m² weekly × 4, or fixed-dose regimens)	~60% overall response; ~40% maintain response at 12 months; ~20% at 5 years	Median ~6 weeks	Variable durability; infusion reactions; infections; hypogammaglobulinemia; impaired vaccine response for 6–12 months
Splenectomy	Removes the principal site of antibody-mediated platelet destruction and a major source of autoantibody production	Laparoscopic surgical procedure	~70% complete response, the highest long-term remission rate	Usually within days	Irreversible; lifelong risk of overwhelming infection and thrombosis; generally deferred until ≥12 months after diagnosis
TPO-RAs (romiplostim, eltrombopag, avatrombopag)	Stimulate megakaryopoiesis through thrombopoietin receptor agonism	Romiplostim: weekly subcutaneous injection; eltrombopag and avatrombopag: oral once daily	Durable platelet response in approximately 50–90% of patients	1–2 weeks	Long-term treatment often required; thrombotic risk; agent-specific limitations (dietary restrictions/transaminitis with eltrombopag; weekly injections with romiplostim); not curative for most patients
Fostamatinib	Oral spleen tyrosine kinase (SYK) inhibitor blocking Fcγ receptor-mediated macrophage phagocytosis	Oral, twice daily	Primary (stable response) endpoint: 18% vs 2% with placebo; overall response 43% vs 14% with placebo; up to 78% when used earlier as second-line therapy (expanded-access data)	Within several weeks	Diarrhea, hypertension, nausea, elevated liver transaminases

Anti-D immunoglobulin currently has only a limited role in adult ITP because of safety concerns, particularly severe intravascular hemolysis, and its limited availability and use in many countries, especially in Europe.

Emerging Targeted Therapies. Mechanistic dissection of the multiple, parallel pathways driving ITP (**Figure 1**) has identified several new druggable targets, giving rise to a cohort of agents that — together with TPO-RAs and fostamatinib — have transformed ITP from a disease managed almost exclusively with steroids, splenectomy, and broadly immunosuppressive salvage regimens into one addressed by an expanding repertoire of mechanism-specific therapies (**Table 2**). [7] Consistent with the fatigue-centered framework introduced above, each agent is discussed below not only for its effect on platelet counts but, wherever data exist, for its effect on fatigue and quality of life; where such data are not yet available, this is noted explicitly as a gap for future trials. **Table 2** has been expanded with a dedicated quality-of-life/fatigue column to support this comparison at a glance.

Bruton tyrosine kinase inhibition. Bruton tyrosine kinase (BTK) is a signaling node downstream of the B-cell receptor and Fcγ/Fcε receptors; its inhibition may reduce autoreactive B-cell signaling and autoantibody production, block Fcγ-receptor–mediated macrophage phagocytosis of opsonized platelets, and inhibit IgE-mediated mast-cell/basophil degranulation, without affecting T-cell function.[8] Rilzabrutinib is a reversible, highly selective BTK inhibitor that, unlike the first-generation agent ibrutinib (which inhibits 21 kinases by >90% and impairs collagen-induced platelet aggregation), inhibits only 6 kinases to a comparable degree and does not impair platelet aggregation in healthy volunteers or in patients with ITP[29,30] — a pharmacologically important distinction for an agent intended to raise platelet counts.

In the international, double-blind, placebo-controlled phase III LUNA 3 trial, 202 patients with persistent or chronic primary ITP were randomized to rilzabrutinib 400 mg twice daily or placebo, each with or without background corticosteroid/TPO-RA.[31] The prespecified primary endpoint — durable platelet response — was met, with a markedly shorter median time to platelet response (36 days vs not reached with placebo; P<.0001) and a substantially lower requirement for rescue therapy (33% vs 58% of patients; P=.0007) as key secondary findings. Notably for the fatigue-centered aim of this review, physical fatigue measured by ITP-PAQ improved progressively from week 2 onward and was sustained through week 25, contrasting with a worsening trend in the placebo arm — one of the more direct demonstrations to date that a targeted, mechanism-specific agent can improve fatigue independent of, and

Table 2. Characteristics and key findings of pivotal clinical trials evaluating emerging targeted therapies for primary immune thrombocytopenia, now including a dedicated quality-of-life/fatigue column and a corrected description of the ADVANCE SC results. Abbreviations: R=randomized; DB=double-blind; PC=placebo-controlled; OL=open-label; CS=corticosteroids; TPO-RA=thrombopoietin receptor agonist; ORR=overall response rate; CR=complete response; TTR=time to response; NR=not reported.

Therapy	Study (design)	Population	Primary endpoint / response definition	Key efficacy results	QoL / Fatigue outcome	Safety	Ref.
Rilzabrutinib	LUNA3 (Ph III, R, DB, PC)	202 persistent/chronic ITP; previously treated; stable CS±TPO-RA	Durable response: PLT ≥50×10⁹/L for ≥8/12 final weeks without rescue	Platelets ↑ from week 2; median TTR 36 d; rescue 33% vs 58%	ITP-PAQ physical fatigue improved from wk 2, sustained to wk 25 (placebo worsened)	Mainly grade 1–2 GI AEs; few grade ≥3 TRAEs	31,32
Ianalumab + eltrombopag	VAYHIT2 (Ph III, R, DB, PC)	Failed first-line corticosteroids	Time to treatment failure; stable response ≥50×10⁹/L in ≥75% of assessments (wk19–25)	HR 0.55/0.58; ORR 73.5% vs 48%; CR 55.1% vs 26%; fewer bleeding events	PROMIS-Fatigue improved more than with eltrombopag alone	Neutropenia; infusion reactions	34
Ianalumab	VAYHIT3 (Ph II, OL)	≥2 prior lines; prior CS and TPO-RA	Confirmed response: ≥50×10⁹/L at 2 visits ≥7 d apart	ORR 44%; median TTR 1.3 mo; CR in 90% of stable responders	Not reported — identified gap	Predominantly low-grade AEs	35
Efgartigimod IV	ADVANCE IV (Ph III, R, DB, PC)	131 previously treated persistent/chronic ITP	Sustained response: ≥50×10⁹/L for ≥4/6 final weeks	Week-1 response 38.4% vs 11.1%; >60% IgG reduction; reduced bleeding	Not reported in comparable granularity — identified gap	Mostly mild–moderate AEs	37
Efgartigimod PH20 SC	ADVANCE SC (Ph III, R, DB, PC)	Previously treated ITP	Sustained platelet response (as ADVANCE IV)	Primary endpoint **not met**: 13.7% vs 16.2% placebo (P=0.51); efficacy not confirmed	Not applicable — efficacy endpoint not met	Acceptable safety profile of SC formulation	38
Mezagitamab	Phase II (R, DB, PC)	Persistent/chronic ITP; ~4 prior therapies	Safety (primary); platelet response (secondary)	Dose-dependent durable responses; bleeding AEs 17.9% vs 46.2%	Not assessed — identified gap	AE frequency similar to placebo	39

in parallel with, platelet response.[32] The safety profile was notable chiefly for low-grade gastrointestinal effects (diarrhea, nausea) and a low rate of severe treatment-related events.

Anti-BAFF-receptor blockade. Ianalumab is a monoclonal antibody with a dual mechanism: it blocks B-cell activating factor receptor (BAFF-R) signaling, modulating the activation, differentiation, and survival of autoreactive BAFF-R-expressing B-cell populations, while simultaneously enhancing antibody-dependent cellular cytotoxicity (ADCC)-mediated B-cell depletion through natural killer cells.[33] Although modulation of autoreactive B-cell responses may ultimately reduce the generation of antibody-secreting cells, BAFF-R blockade should not be considered a direct long-lived plasma-cell-depleting strategy comparable to anti-CD38 therapy, as any effect on plasma-cell compartments is likely indirect.[33] Ianalumab has been evaluated at three points in the treatment pathway, and notably is the only agent in this review already studied in formal combination with a production-stimulating agent, making it a useful proof-of-concept case for the combination-therapy discussion below.

In VAYHIT2, a phase III trial in patients with an insufficient response to first-line corticosteroids, ianalumab (3 or 9 mg/kg every 4 weeks for 4 doses) combined with eltrombopag significantly prolonged median time to treatment failure compared with eltrombopag plus placebo (13.0 months with the 9-mg/kg dose, not reached with the 3-mg/kg dose, versus 4.7 months with placebo; hazard ratios 0.55 and 0.58, respectively), and produced higher response (73.5% vs 48.0%) and complete response (55.1% vs 26.0%) rates at 6 months. Fatigue, assessed with PROMIS-Fatigue as a secondary endpoint, improved more with combination therapy than with eltrombopag alone, alongside fewer bleeding events; neutropenia (more frequent at the higher dose) and infusion-related reactions were the principal toxicities.[34]

In VAYHIT3, a phase II study of ianalumab monotherapy in heavily pretreated primary ITP (≥2 prior lines, including failure of both a corticosteroid and a TPO-RA), 44% of patients achieved a confirmed response by week 25, with a rapid median time to response of 1.3 months and complete response in 90% of stable responders — notable given how difficult durable, treatment-free responses are to achieve in this population. Fatigue and quality-of-life outcomes were not reported for this cohort, which we flag as a specific gap given the heavily pretreated, high-symptom-burden population studied.[35] VAYHIT1, a phase III trial combining ianalumab with first-line corticosteroids in newly diagnosed ITP, is ongoing; its design reportedly includes patient-reported fatigue endpoints, which will help determine whether earlier intervention with this mechanism can alter both platelet and symptom trajectories.[36]

FcRn antagonism. Efgartigimod competitively blocks the neonatal Fc receptor (FcRn), which normally recycles IgG and protects it from lysosomal degradation. FcRn blockade accelerates clearance of pathogenic IgG autoantibodies, including antiplatelet and antimegakaryocyte antibodies, thereby reducing pathogenic IgG levels without directly suppressing cellular immunity.[37] Regulatory status for this class varies substantially by region and should be verified against the current local label at the time of prescribing: as of this writing, intravenous efgartigimod is approved for chronic ITP in Japan, but is not approved for ITP by regulators in the United States or the European Union, where its approved indications lie in other autoantibody-mediated diseases. This distinction is important because it is easy to conflate approval in one indication or region with approval for ITP more broadly.

In the phase III ADVANCE IV trial, 131 adults with persistent or chronic primary ITP who had received at least one prior therapy were randomized to intravenous efgartigimod (10 mg/kg) or placebo on a response-adapted weekly/biweekly schedule.[37] Efgartigimod produced a rapid reduction in total IgG levels (>60% from baseline within 4 weeks), accompanied by platelet count increases during treatment; by week 1, 38.4% of efgartigimod-treated patients achieved a platelet count ≥30 × 10^9/L compared with 11.1% of placebo-treated patients, and most patients who transitioned from weekly to every-other-week dosing maintained their platelet response, supporting a flexible, response-guided dosing strategy. Fatigue and quality-of-life data from ADVANCE IV have not, to our knowledge, been reported in comparable granularity to the BTK- and BAFF-R-directed programs above, which limits direct comparison on this dimension.[37]

The subcutaneous formulation (efgartigimod PH20) was subsequently evaluated in the phase III ADVANCE SC trial. This point requires correction relative to how the trial has sometimes been characterized: ADVANCE SC did not demonstrate superiority over placebo on its primary or secondary efficacy endpoints. The primary endpoint (sustained platelet response) was achieved by 13.7% of patients receiving efgartigimod PH20 SC versus 16.2% receiving placebo (P=0.51). The trial can reasonably be described as demonstrating an acceptable safety profile for the subcutaneous formulation, but its results should not be presented as confirming clinical efficacy comparable to intravenous efgartigimod, and we have revised our description of this trial accordingly throughout the manuscript and in **Table 2**.[38]

Anti-CD38 depletion. Mezagitamab is a monoclonal antibody against CD38 that selectively depletes CD38-high long-lived plasma cells and other CD38-expressing immune cells implicated in pathogenic autoantibody production, a mechanism with established precedent in plasma-cell-driven diseases such as multiple myeloma. In a phase II, dose-ranging, placebo-controlled study in primary ITP, all three mezagitamab doses tested (100, 300, and 600 mg) produced rapid, dose-related, and durable increases in platelet count relative to placebo, sustained through 16 weeks of follow-up after completion of dosing, and were associated with numerically fewer bleeding adverse events (17.9% with combined mezagitamab vs 46.2% with placebo). This phase II study was designed with safety as its primary endpoint and platelet response as a secondary measure; fatigue/quality-of-life outcomes were not among the endpoints assessed, another gap relevant to the personalization framework proposed here.[39] These findings support continued clinical development of CD38-directed therapy in ITP, ideally with patient-reported outcomes incorporated from an earlier stage of development.

Combination Therapies: Concurrently Targeting Platelet Production and Destruction. The therapies discussed above have, with one partial exception (ianalumab plus eltrombopag in VAYHIT2), been developed and reported as isolated, sequential options: a patient fails one mechanism and moves to the next. This sequential framing leaves an increasingly recognized gap, because the two-pathway model of ITP pathophysiology described above (**Figure 1**) predicts that concurrently combining an agent that stimulates platelet production (a TPO-RA) with an agent that blocks immune-mediated destruction (rituximab, a BTK inhibitor, an FcRn antagonist, or a BAFF-R- or CD38-directed antibody) could, in principle, produce more complete and durable disease control than either mechanism alone, particularly in patients with both a demonstrable production defect and ongoing antibody-mediated clearance.

The clearest current clinical evidence for this concept comes from VAYHIT2, in which ianalumab (destruction/production-of-autoantibody-directed) added to eltrombopag (production-directed) prolonged time to treatment failure and improved response rates compared with eltrombopag alone, providing proof of concept that concurrent, complementary-mechanism combinations can outperform a single-mechanism approach in at least one controlled setting.[34] Outside formal trials, combination use is already common in practice in an empirical, largely undocumented form — for example, TPO-RA continuation during or after rituximab, or background corticosteroid/TPO-RA use in patients enrolled in trials of newer agents such as rilzabrutinib — but this experience has rarely been analyzed as a combination strategy in its own right.[31,40]

The rationale for combination therapy must be weighed against its risks. Agents that stimulate production (TPO-RAs) carry a thrombotic signal, while agents that block destruction through B-cell or plasma-cell depletion (rituximab, ianalumab, mezagitamab) carry infection and hypogammaglobulinemia risk; combining agents from these two families could plausibly compound rather than merely add these toxicities, and prospective, adequately powered safety data for most combinations beyond ianalumab-eltrombopag are not yet available. Practical barriers — cost, regulatory approval of combination regimens, and the absence of validated biomarkers to identify which patients have both a production defect and ongoing destructive autoimmunity — further constrain current use.[7,8,40] At present, the clinical perspective on combination therapy in ITP is therefore best described as an emerging, biologically well-motivated strategy supported by one positive controlled trial, rather than a validated standard of care; dedicated head-to-head and combination trials, with prespecified safety monitoring and patient-reported outcomes, represent a priority for the field.[40]

Toward Individualized, Patient-Centered Treatment Selection. The expanding therapeutic armamentarium in adult primary ITP has shifted the clinical challenge from selecting among a limited number of drugs to rational sequencing — and, potentially, combination — among mechanistically distinct therapies. The 2019 ASH guidelines laid the foundation for patient-centered treatment selection by incorporating not only disease duration but also patient preferences — such as the desire for durable remission, avoidance of chronic medication, or avoidance of splenectomy — into therapeutic decision-making.[12] The growing availability of novel targeted therapies, together with the fatigue and quality-of-life data reviewed above, has further expanded this framework.

In current clinical practice, treatment decisions extend beyond disease duration alone and should integrate multiple patient- and disease-related factors. The urgency of platelet recovery and the bleeding phenotype remain key considerations: when a rapid platelet increase is required — clinically relevant mucosal bleeding, profound thrombocytopenia, or preparation for an urgent invasive procedure — corticosteroids, with or without IVIG, remain the cornerstone of initial management, while TPO-RAs may also be appropriate when a platelet increase is needed within approximately 1–2 weeks. In chronic disease, priorities often shift toward minimizing cumulative corticosteroid exposure, improving quality of life, and achieving more durable disease control.[12,40]

Patient comorbidities further influence therapeutic choice. Thrombotic risk should be carefully considered when selecting TPO-RAs or splenectomy for older individuals or patients with cardiovascular disease, previous thrombosis, prolonged immobility, or other prothrombotic conditions. Conversely, in patients with hypogammaglobulinemia, chronic viral infection, substantial infection risk, or a need to preserve vaccine responsiveness, B-cell-directed therapies may be less attractive. Frailty, hepatic dysfunction, gastrointestinal vulnerability, and concomitant medications should likewise be incorporated into individualized decision-making.[12,41]

Previous treatment exposure is equally important: failure of one therapeutic class does not preclude response to another with a different mechanism and switching between thrombopoietic and immune-targeted strategies is frequently appropriate. Following corticosteroid failure, TPO-RAs are commonly used because of their established efficacy and extensive clinical experience, whereas rituximab may be considered when a finite immune-directed strategy is desired, and fostamatinib represents an alternative non-thrombopoietic approach. Emerging targeted therapies further expand options for patients refractory to or intolerant of established second-line agents.[33,40] Treatment sequencing should be guided by mechanistic differences without oversimplified biological assumptions: BAFF-R blockade primarily modulates BAFF-R-expressing B-cell populations rather than directly depleting long-lived plasma cells and should not be considered biologically equivalent to plasma-cell-directed therapies.[33]

Patient preference remains fundamental. Some individuals prioritize avoiding indefinite pharmacological therapy and may favor rituximab or, in carefully selected cases, splenectomy, whereas others prefer to avoid surgery despite the need for long-term medical treatment. Shared decision-making should explicitly balance durability of response, reversibility, convenience, toxicity, uncertainty, and lifestyle priorities.

Table 3. Practical, non-exhaustive summary matching common patient phenotypes to potentially appropriate therapies. This table is a heuristic aid to individualized discussion and does not represent a validated treatment algorithm.

Patient phenotype	Potentially appropriate therapies and rationale	Key caveats
Severe baseline fatigue / QoL impairment, without urgent bleeding	Agents with reported fatigue benefit: rilzabrutinib (ITP-PAQ improvement in LUNA3); ianalumab + eltrombopag (PROMIS-Fatigue improvement in VAYHIT2)	Fatigue data are not yet available for most other agents (Table 2); absence of data is not evidence of absence of benefit
High thrombotic risk (prior VTE/ATE, cardiovascular disease, prolonged immobility)	Non-thrombopoietic mechanisms preferred: rituximab, fostamatinib, BAFF-R/FcRn/CD38-directed agents where available; TPO-RAs used cautiously if at all	Thrombotic risk with TPO-RAs is agent- and dose-dependent; specialist input advised
Urgent hemostasis required (active bleeding, pre-procedure)	Corticosteroids ± IVIG for immediate effect; TPO-RA if 1–2 weeks is an acceptable timeframe	Targeted agents in this review are not positioned for urgent rescue; onset of action is generally too slow
Substantial infection risk / need to preserve vaccine response	TPO-RAs or fostamatinib preferred over B-cell- or plasma-cell-depleting agents (rituximab, ianalumab, mezagitamab)	Individualize against infection history and vaccination schedule
Strong preference to avoid indefinite medication / desire for durable remission	Rituximab (time-limited course) or splenectomy in carefully selected patients	Splenectomy is irreversible; regional guideline preferences and surgical risk must be discussed
Failure of ≥2 prior lines including a TPO-RA and an immune-directed agent	Investigational mechanism-based agents (BTK, BAFF-R, FcRn, CD38) as available through trials or approved regional indications; combination strategies under active investigation	Regulatory availability varies markedly by country and date; verify current local label (Figure 2)

Special clinical scenarios — pregnancy, anticoagulant therapy, secondary ITP, advanced age, frailty, and concomitant autoimmune disease — require further individualized management, as evidence supporting several newer targeted agents remains limited in these populations.[12,40] Finally, and central to the framework proposed in this review, patient-reported outcomes — fatigue and health-related quality of life — are increasingly incorporated as secondary or exploratory outcomes in clinical trials using validated instruments such as the ITP-PAQ, PROMIS-Fatigue, and ILQI.[9,11] Although platelet response remains the primary efficacy endpoint in most registration studies, and quality-of-life measures are not, at present, routinely used as co-primary endpoints, these complementary measures provide valuable information on the overall patient experience and should be weighted explicitly — not treated as an afterthought — in treatment selection.

Matching patient phenotypes to therapy: a practical summary. **Table 3** summarizes, at a practical level, how the disease- and patient-related factors discussed above — including fatigue burden — map onto the therapies with the most relevant supporting data. This summary is intended as a starting point for individualized discussion, not as a validated algorithm or a ranking of efficacy; regulatory availability must always be confirmed locally before an agent is considered (see **Figure 2**).

Future Directions and Unmet Needs. Several unmet needs must be addressed before mechanism-directed therapy can be optimally integrated into routine ITP care. First, comparative evidence remains limited, as most recent studies have used placebo-controlled designs in heterogeneous patient populations with differences in baseline therapies, rescue policies, follow-up duration, and endpoint definitions, making cross-trial comparisons and treatment sequencing difficult; such comparisons, where made in this review, should be interpreted with this caution in mind. Head-to-head trials comparing novel agents with one another and with established second-line therapies — and dedicated combination trials building on the VAYHIT2 proof of concept — are needed to better inform clinical decision-making. Second, validated biomarkers capable of identifying the predominant pathogenic mechanism in individual patients — antibody-mediated platelet clearance, T-cell-mediated megakaryocyte injury, impaired thrombopoiesis, or broader immune dysregulation — are not yet available for routine clinical use; their development could enable mechanism-matched first-line therapy, and identification of patients most likely to benefit from combination approaches. Third, longer-term data are required on infection risk, immune effects, durability of remission, retreatment strategies, and cost-effectiveness, particularly for B-cell- and plasma-cell-directed therapies used repeatedly, chronically, or in combination. Fourth, fatigue and quality-of-life outcomes should be measured consistently, using comparable instruments, across all future trials of emerging agents — a gap identified repeatedly in this review — to allow the kind of symptom-informed comparison this review has attempted to construct from incomplete data. Finally, real-world implementation will depend on long-term safety, accessibility, and cost relative to established treatments, and dedicated studies

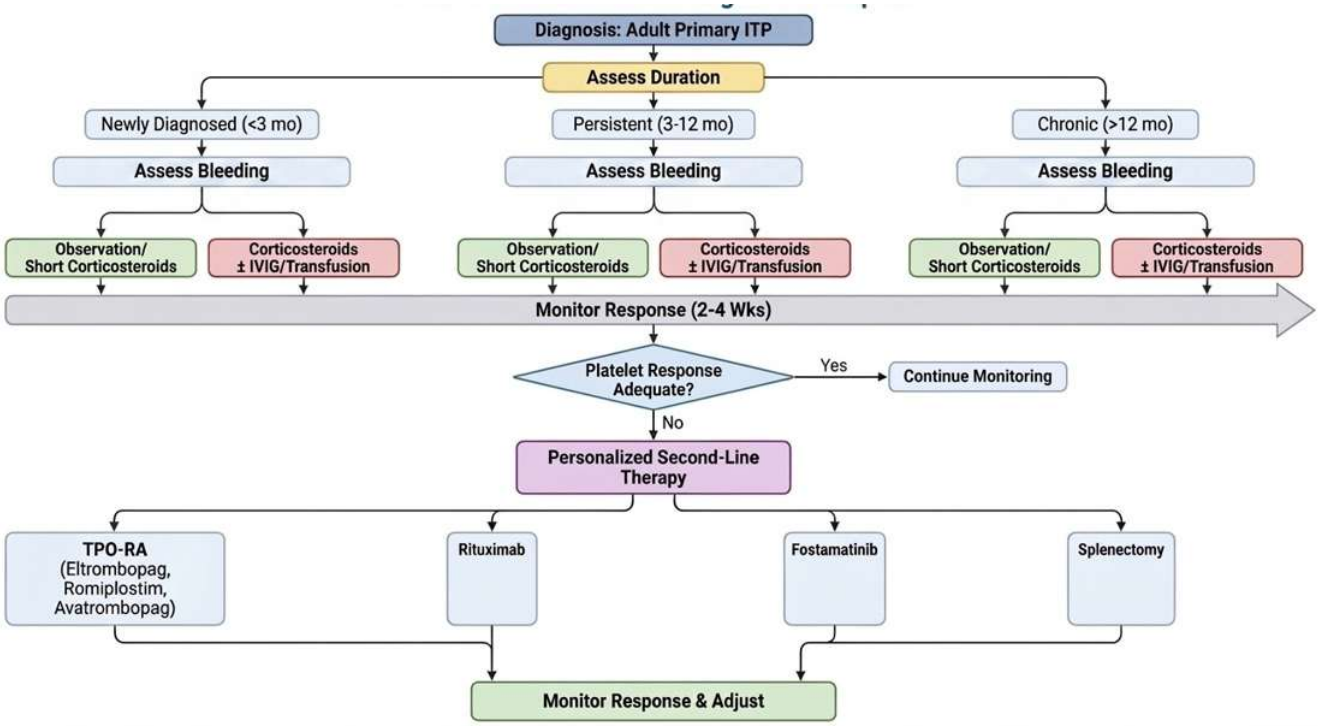

Figure 2. Evolving Paradigms in the Management of Primary Immune Thrombocytopenia in Adults. This flow chart represents a conceptual framework for individualized treatment discussion in adult primary immune thrombocytopenia and does not constitute a validated evidence-based sequential treatment algorithm. Therapeutic selection should be individualized according to disease duration, bleeding phenotype, previous treatments, comorbidities, regulatory availability, route of administration, and patient preferences.

in underrepresented populations — pediatric patients, pregnant women, individuals with secondary ITP, and older multimorbid adults — are needed to extend the applicability of these therapies beyond the adult trial populations studied to date.[42]

Conclusions. Over the past two decades, the management of immune thrombocytopenia has evolved from a predominantly empirical sequence of corticosteroids, splenectomy, and broad immunosuppressive approaches toward an expanding therapeutic landscape that includes TPO-RAs, SYK and BTK inhibitors, anti-BAFF-R and FcRn-targeted agents, and CD38-directed therapies, with early evidence supporting combinations of complementary mechanisms. This evolution has been accompanied by increasing recognition that the burden of ITP extends beyond bleeding to include fatigue and impaired quality of life, which are increasingly incorporated as secondary or exploratory patient-reported outcomes in contemporary clinical trials, although inconsistently across agents. As mechanistically diverse therapies continue to emerge, the major challenge for clinicians will be to integrate disease characteristics, comorbidities, safety considerations, regulatory availability, and patient preferences into individualized treatment decisions. Although mechanism-directed therapy is becoming increasingly important in ITP management, biomarker-guided treatment selection has not yet been established for routine clinical practice, and the optimal sequencing and combination of newer agents remain to be defined.

Author contributions. MM: conceptualization, literature review, writing original draft preparation, supervision, and critical revision of the manuscript. LG, MBG, VM, and CA: literature review, data collection, and manuscript revision. All authors read and approved the final version of the manuscript.

References:

1. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-2393. https://doi.org/10.1182/blood-2008-07-162503 PMid:19005182 PMCid:PMC10806291
2. Cuker A, Cines DB. Immune thrombocytopenia. Hematology Am Soc Hematol Educ Program. 2010;2010:377-84. https://doi.org/10.1182/asheducation-2010.1.377 https://doi.org/10.1182/asheducation.V2010.1.377.3643150 PMid:21239822
3. Moulis G, Palmaro A, Montastruc JL, Godeau B, Lapeyre-Mestre M, Sailler L. Epidemiology of incident immune thrombocytopenia: a nationwide population-based study in France. Blood. 2014 Nov 20;124(22):3308-15. https://doi.org/10.1182/blood-2014-05-578336 PMid:25305203
4. Provan D, Semple JW. Recent advances in the mechanisms and treatment of immune thrombocytopenia. EBioMedicine. 2022;76:103820. https://doi.org/10.1016/j.ebiom.2022.103820 PMid:35074629 PMCid:PMC8792416

5. HARRINGTON WJ, MINNICH V, HOLLINGSWORTH JW, MOORE CV. Demonstration of a thrombocytopenic factor in the blood of patients with thrombocytopenic purpura. J Lab Clin Med. 1951 Jul;38(1):1-10.
6. Vrbensky JR, Nazy I, Toltl LJ, et al. Megakaryocyte apoptosis in immune thrombocytopenia. Platelets. 2018;29(7):729-732. https://doi.org/10.1080/09537104.2018.1475637 PMid:29787328
7. Audia S, Bonnotte B. Emerging Therapies in Immune Thrombocytopenia. J Clin Med. 2021 Mar 2;10(5):1004. https://doi.org/10.3390/jcm10051004 PMid:33801294 PMCid:PMC7958340
8. Provan D, Semple JW. Recent advances in the mechanisms and treatment of immune thrombocytopenia. EBioMedicine. 2022 Feb;76:103820. https://doi.org/10.1016/j.ebiom.2022.103820 PMid:35074629 PMCid:PMC8792416
9. Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, Ghanima W, Arnold DM, Tomiyama Y, Santoro C, Michel M, Laborde S, Lovrencic B, Hou M, Bailey T, Taylor-Stokes G, Haenig J, Bussel JB. Immune thrombocytopenia (ITP) World Impact Survey (I-WISh): Impact of ITP on health-related quality of life. Am J Hematol. 2021 Feb 1;96(2):199-207. https://doi.org/10.1002/ajh.26036 PMid:33107998 PMCid:PMC7898815
10. Cooper N, Kruse A, Kruse C, Watson S, Morgan M, Provan D, Ghanima W, Arnold DM, Tomiyama Y, Santoro C, Michel M, Laborde S, Lovrencic B, Hou M, Bailey T, Taylor-Stokes G, Haenig J, Bussel JB. Immune thrombocytopenia (ITP) World Impact Survey (iWISh): Patient and physician perceptions of diagnosis, signs and symptoms, and treatment. Am J Hematol. 2021 Feb 1;96(2):188-198. https://doi.org/10.1002/ajh.26045 PMid:33170956 PMCid:PMC7898610
11. Viana R, D'Alessio D, Grant L, Cooper N, Arnold D, Morgan M, Provan D, Cuker A, Hill QA, Tomiyama Y, Ghanima W. Psychometric Evaluation of ITP Life Quality Index (ILQI) in a Global Survey of Patients with Immune Thrombocytopenia. Adv Ther. 2021 Dec;38(12):5791-5808. https://doi.org/10.1007/s12325-021-01934-0 PMid:34704193 PMCid:PMC8572218
12. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829-3866. Blood Adv. 2020 Jan 28;4(2):252. https://doi.org/10.1182/bloodadvances.2019001380 PMid:31945156 PMCid:PMC6988391
13. Mithoowani S, Gregory-Miller K, Goy J, et al. High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis. Lancet Haematol. 2016;3:e489-e496. https://doi.org/10.1016/S2352-3026(16)30109-0 PMid:27658982
14. Sailer T, Lechner K, Panzer S, Kyrle PA, Pabinger I. The course of severe autoimmune thrombocytopenia in patients not undergoing splenectomy. Haematologica. 2006 Aug;91(8):1041-5. PMID: 16885043.
15. Pamuk GE, Pamuk ON, Başlar Z, Ongoren S, Soysal T, Ferhanoglu B, Aydin Y, Ulku B, Aktuglu G, Akman N. Overview of 321 patients with idiopathic thrombocytopenic purpura. Retrospective analysis of the clinical features and response to therapy. Ann Hematol. 2002 Aug;81(8):436-40. https://doi.org/10.1007/s00277-002-0488-x PMid:12224000
16. Brown TM, Horblyuk RV, Grotzinger KM, Matzdorff AC, Pashos CL. Patient-reported treatment burden of chronic immune thrombocytopenia therapies. BMC Blood Disord. 2012 Mar 22;12:2. https://doi.org/10.1186/1471-2326-12-2 PMid:22436142 PMCid:PMC3350461
17. Arnold DM, Dentali F, Crowther MA, Meyer RM, Cook RJ, Sigouin C, Fraser GA, Lim W, Kelton JG. Systematic review: efficacy and safety of rituximab for adults with idiopathic thrombocytopenic purpura. Ann Intern Med. 2007 Jan 2;146(1):25-33. https://doi.org/10.7326/0003-4819-146-1-200701020-00006 PMid:17200219
18. Tjønnfjord E, Holme PA, Darne B, Khelif A, Waage A, Michel M, Ben Romdhan N, Ghanima W. Long-term outcomes of patients treated with rituximab as second-line treatment for adult immune thrombocytopenia - Follow-up of the RITP study. Br J Haematol. 2020 Nov;191(3):460-465. https://doi.org/10.1111/bjh.16672 PMid:32342497
19. Kojouri K, Vesely SK, Terrell DR, George JN. Splenectomy for adult patients with idiopathic thrombocytopenic purpura: a systematic review to assess long-term platelet count responses, prediction of response, and surgical complications. Blood. 2004 Nov 1;104(9):2623-34. https://doi.org/10.1182/blood-2004-03-1168 PMid:15217831
20. Tastaldi L, Krpata DM, Prabhu AS, Petro CC, Haskins IN, Perez AJ, Alkhatib H, Colturato I, Tu C, Lichtin A, Rosen MJ, Rosenblatt S. Laparoscopic splenectomy for immune thrombocytopenia (ITP): long-term outcomes of a modern cohort. Surg Endosc. 2019 Feb;33(2):475-485. https://doi.org/10.1007/s00464-018-6321-y PMid:29987573
21. Crary SE, Buchanan GR. Vascular complications after splenectomy for hematologic disorders. Blood. 2009 Oct 1;114(14):2861-8. https://doi.org/10.1182/blood-2009-04-210112 PMid:19636061 PMCid:PMC2756197
22. Al-Samkari H, Kuter DJ. Optimal use of thrombopoietin receptor agonists in immune thrombocytopenia. Br J Haematol. 2022;197:359-369. https://doi.org/10.1182/hematology.2022000374 PMid:36485134 PMCid:PMC9821429
23. Romiplostim. Prescribing information. Thousand Oaks, CA: Amgen Inc.
24. Eltrombopag. Prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation.
25. Avatrombopag. Prescribing information. Stockholm, Sweden: Sobi Inc.
26. Ghanima W, Cooper N, Rodeghiero F, Godeau B, Bussel JB. Thrombopoietin receptor agonists: ten years later. Haematologica. 2019 Jun;104(6):1112-1123. https://doi.org/10.3324/haematol.2018.212845 PMid:31073079 PMCid:PMC6545830
27. Bussel J, Arnold DM, Grossbard E, Mayer J, Trelinski J, Homenda W, Hellmann A, Windyga J, Sivcheva L, Khalafallah AA, Zaja F, Cooper N, Markovtsov V, Zayed H, Duliege AM. Fostamatinib for the treatment of adult persistent and chronic immune thrombocytopenia: Results of two phase 3, randomized, placebo-controlled trials. Am J Hematol. 2018 Jul;93(7):921-930. https://doi.org/10.1002/ajh.25125 PMid:29696684 PMCid:PMC6055608
28. Boccia R, Cooper N, Ghanima W, Boxer MA, Hill QA, Sholzberg M, Tarantino MD, Todd LK, Tong S, Bussel JB; FIT Clinical Trial Investigators. Fostamatinib is an effective second-line therapy in patients with immune thrombocytopenia. Br J Haematol. 2020 Sep;190(6):933-938. https://doi.org/10.1111/bjh.16959 PMid:33439486 PMCid:PMC7540289
29. Kuter DJ, Efraim M, Mayer J, Trneny M, McDonald V, Bird R, Regenbogen T, Garg M, Kaplan Z, Tzvetkov N, Choi PY, Jansen AJG, Kostal M, Baker R, Gumulec J, Lee EJ, Cunningham I, Goncalves I, Warner M, Boccia R, Gernsheimer T, Ghanima W, Bandman O, Burns R, Neale A, Thomas D, Arora P, Zheng B, Cooper N. Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia. N Engl J Med. 2022 Apr 14;386(15):1421-1431. https://doi.org/10.1056/NEJMoa2110297 PMid:35417637
30. Langrish CL, Bradshaw JM, Francesco MR, Owens TD, Xing Y, Shu J, LaStant J, Bisconte A, Outerbridge C, White SD, Hill RJ, Brameld KA, Goldstein DM, Nunn PA. Preclinical Efficacy and Anti-Inflammatory Mechanisms of Action of the Bruton Tyrosine Kinase Inhibitor Rilzabrutinib for Immune-Mediated Disease. J Immunol. 2021 Apr 1;206(7):1454-1468. https://doi.org/10.4049/jimmunol.2001130 PMid:33674445 PMCid:PMC7980532
31. Kuter DJ, Bussel JB, Ghanima W, Cooper N, Gernsheimer T, Lambert MP, Liebman HA, Tarantino MD, Lee M, Guo H, Daak A. Rilzabrutinib versus placebo in adults and adolescents with persistent or chronic immune thrombocytopenia: LUNA 3 phase III study. Ther Adv Hematol. 2023 Oct 18;14:20406207231205431. https://doi.org/10.1177/20406207231205431 PMid:37869360 PMCid:PMC10585997
32. Kuter DJ, Ghanima W, Cooper N, et al. Safety and efficacy of rilzabrutinib vs placebo in adults with immune thrombocytopenia: the phase 3 LUNA3 study. Blood. 2025;145(24):2914-2926. https://doi.org/10.1182/blood.2024027336 PMid:40090011 PMCid:PMC12824683
33. Min YN, Wang CY, Li XX, et al. Participation of B-cell-activating factor receptors in the pathogenesis of immune thrombocytopenia. J Thromb Haemost. 2016;14(3):559-571. https://doi.org/10.1111/jth.13246 PMid:26749059
34. Cuker A, Stauch T, Cooper N, et al. Ianalumab plus Eltrombopag in Immune Thrombocytopenia. N Engl J Med. 2026;394(15):1503-1513.

https://doi.org/10.1056/NEJMoa2515168
PMid:41363800
35. Choi P, et al. Ianalumab monotherapy in primary immune thrombocytopenia following ≥2 prior lines of therapy (VAYHIT3/PAYHIT3): a phase 2 study. Presented at: American Society of Hematology Annual Meeting; 2025. Abstract 844. https://doi.org/10.1182/blood-2025-844
36. Cooper N, Cuker A, Michel M, Wong R, Ghanima W, Zaja F, Barcellini W, Zhang F, Lawniczek T, Weill M, Al-Samkari H. PB2636: VAYHIT1: A multicenter, randomized, double-blind, phase III trial of ianalumab versus placebo in addition to first-line corticosteroids in patients with primary immune thrombocytopenia (ITP). Hemasphere. 2023 Aug 8;7(Suppl):e29155a4. https://doi.org/10.1097/01.HS9.0000977232.29155.a4
PMCid:PMC10429351
37. Broome CM, McDonald V, Miyakawa Y, 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. Lancet. 2023;402(10413):1648-1659. https://doi.org/10.1016/S0140-6736(23)01460-5
PMid:37778358
38. Cooper N, Broome CM, Miyakawa Y, et al. Efficacy and Safety of Subcutaneous Efgartigimod PH20 in Adults With Primary Immune Thrombocytopenia (ADVANCE SC): A Multicenter, Randomized, Double-Blinded, Placebo-Controlled, Phase 3 Trial. Am J Hematol. 2026;101(7):1494-1506. https://doi.org/10.1002/ajh.70303
PMid:41943179
39. Kuter DJ, Miura K, Patriarca A, et al. A Phase 2 Randomized Trial of Mezagitamab in Primary Immune Thrombocytopenia. N Engl J Med. 2026;394(14):1388-1398. https://doi.org/10.1056/NEJMoa2513120
PMid:41950473
40. Ghanima W, Cuker A, Michel M. Insights on treatment of adult ITP: algorithm for management and role of multimodal therapy. Hematology Am Soc Hematol Educ Program. 2024;2024(1):678-684. https://doi.org/10.1182/hematology.2024000594
PMid:39643995 PMCid:PMC11665734
41. Gafter-Gvili A. Current approaches for the diagnosis and management of immune thrombocytopenia. Eur J Intern Med. 2023;108:18-24. https://doi.org/10.1016/j.ejim.2022.11.022
PMid:36424271
42. Neunert CE, Arnold DM, Grace RF, Kuhne T, McCrae KR, Terrell DR. The 2022 review of the 2019 American Society of Hematology guidelines on immune thrombocytopenia. Blood Adv. 2024;8(13):3578-3582. https://doi.org/10.1182/bloodadvances.2023012541
PMid:38608258 PMCid:PMC11319830