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Efficacy and Safety of Bruton Tyrosine Kinase Inhibitors in Primary Immune Thrombocytopenia: A Systematic Review and Meta-Analysis

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INTRODUCTION

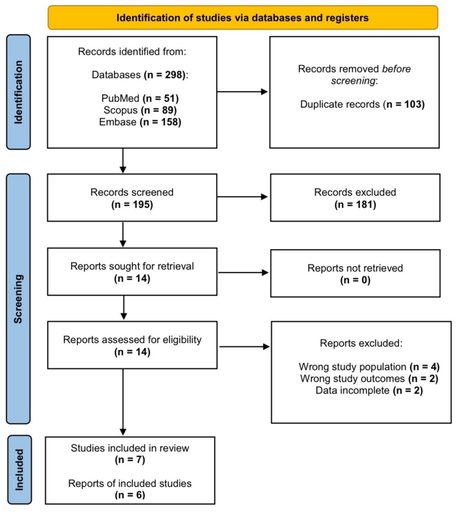
- Immune thrombocytopenia (ITP), an acquired autoimmune disorder is managed primarily by corticosteroids.
- However, up to one-third develop persistent or chronic disease requiring second-line therapies such as thrombopoietin receptor agonists (TPO-RAs), rituximab, or splenectomy, yet treatment refractoriness, relapse, and cumulative toxicity remain significant challenges in long-term management.
- B-cell activation and Fcγ receptor–mediated phagocytosis play central roles in the pathogenesis of ITP. Bruton tyrosine kinase (BTK) is a critical signalling molecule in B-cell receptor and FcγR pathways, mediating autoantibody production and platelet clearance.
- Inhibition of BTK offers a novel, mechanism-directed therapeutic approach that may overcome the limitations of existing immunosuppressive or thrombopoietic agents.
- Rilzabrutinib, an oral, reversible covalent BTK inhibitor, demonstrated promising activity in early-phase ITP trials, achieving platelet responses in approximately 30–40% of patients with a favourable safety profile.
- Zanubrutinib and orelabrutinib, next-generation irreversible BTK inhibitors with improved selectivity, have recently been evaluated in smaller phase II trials and early clinical programs. Despite encouraging data, evidence remains fragmented across heterogeneous studies with varying sample sizes and designs.

AIM

We aimed to assess the pooled efficacy and safety of BTK inhibitors, rilzabrutinib, zanubrutinib, and orelabrutinib in primary ITP among adults and adolescents.

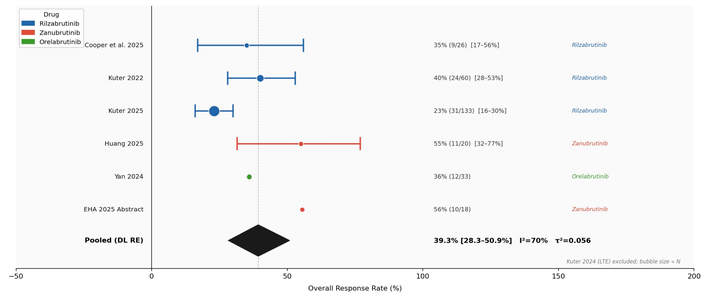
METHODOLOGY

- Systematic review and meta-analysis per PRISMA 2020. Proportions were pooled using a DerSimonian–Laird random-effects model with Freeman-Tukey double arcsine transformation. Heterogeneity was assessed with I^2 and Cochran's Q.
- **SETTING**: PubMed/MEDLINE, Embase, Scopus, ClinicalTrials.gov, and ASH/EHA conference abstracts (2020–2025), searched from inception to October 2025.
- **PARTICIPANTS**: Adults and adolescents with primary ITP enrolled in randomised controlled trials, prospective single-arm studies, or observational series with ≥10 participants.
- **INTERVENTIONS**: Rilzabrutinib (400 mg twice daily), zanubrutinib (80 mg once daily or 160 mg twice daily), or orelabrutinib (30–50 mg once daily), each administered orally.
- **PRIMARY OUTCOME MEASURES**: Pooled overall response rate (ORR; platelet count ≥30 or ≥50 $\times 10^9$/L without rescue therapy).
- **SECONDARY OUTCOME MEASURES**: complete response rate, pooled grade ≥3 adverse event rate, and drug-class subgroup ORRs.



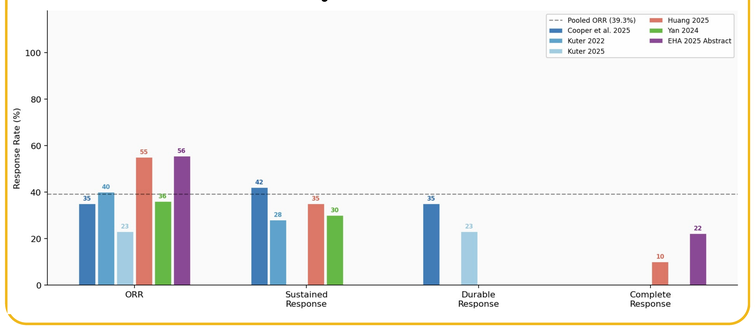
RESULTS

Forest Plot: Overall Response Rate (ORR)

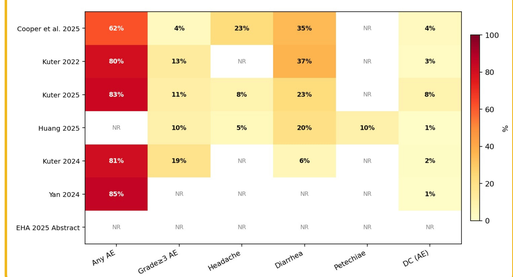


- Seven studies (N=306 enrolled) were identified; six (N=290) were pooled after excluding one long-term extension cohort for patient overlap.
- Pooled ORR was 39.3% (95% CI 28.3–50.9%; I^2=70.3%; τ^2=0.056).
- Drug-specific ORRs were: rilzabrutinib 32.1% (95% CI 20.5–44.9%; k=3; I^2=69%), zanubrutinib 56.4% (95% CI 40.7–71.4%; k=2; I^2=0%), and orelabrutinib 36.0% (k=1).
- RCTs yielded a lower pooled ORR (31.0%) compared with non-randomised studies (44.7%), consistent with selection bias in single-arm designs.
- Pooled grade ≥3 adverse event rate was 11.2% (95% CI 7.6–15.5%; I^2=0%; k=4), with the most common events being diarrhoea and nausea, predominantly grade 1–2.
- No treatment-related deaths were recorded in any study.

Efficacy outcomes



Adverse event profile heat map



CONCLUSIONS

- BTK inhibitors demonstrate clinically meaningful platelet responses with a homogeneous and manageable safety profile across drug classes. Significant between-study heterogeneity warrants cautious interpretation.
- The August 2025 FDA approval of rilzabrutinib (Wayrilz) as the first BTK inhibitor for ITP validates this therapeutic class; however, head-to-head comparative data and long-term durability evidence remain outstanding clinical priorities.

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