Real-World Pharmacovigilance Assessment of Hematologic Safety Signals Among BTK Inhibitors: Insights from the FDA Adverse Event Reporting System

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INTRODUCTION

- The advent of Bruton's tyrosine kinase (BTK) inhibitors has markedly reshaped the treatment landscape of B-cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL).
- Pirtobrutinib, a novel non-covalent BTK inhibitor approved by the FDA in 2023, may be associated with a distinct safety profile relative to covalent BTK inhibitors.
- This study evaluates and compares hematologic adverse event reporting patterns among four BTK inhibitors using post-marketing surveillance data.

AIM

To compare hematologic adverse-event reporting signals among four BTK inhibitors using real-world FDA Adverse Event Reporting System (FAERS) pharmaco vigilance data.

METHODS

- A disproportionality analysis was conducted using the FAERS database **from 2023 to 2026**, including reports associated with ibrutinib, acalabrutinib, zanubrutinib, and pirtobrutinib.
- Hematologic adverse events were identified using MedDRA Preferred Terms (PTs) selected from the Blood and lymphatic system disorders System Organ Class, and were grouped into three categories: **cytopenias**, **bone marrow failure disorders**, and **hemorrhagic events**. These groupings were defined ad hoc for this analysis and do not correspond to official MedDRA Standardised MedDRA Queries (SMQs) or High Level Group Terms (HLGTs)
- Signal detection was using the reporting odds ratio **(ROR)** and proportional reporting ratio **(PRR).**
- A signal was defined as **≥3 reports**, an **ROR >1** with **a lower 95% confidence interval >1** and **a PRR ≥2**.

REFERENCES

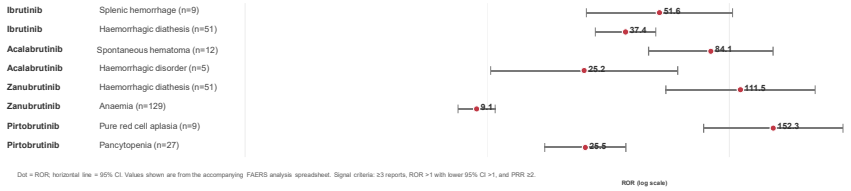
U.S Food and Drug Administration. FDA Adverse Event Reporting System (FAERS) Public Dashboard. Accessed April 25, 2026.

RESULTS

- The analysis included **17,924** ibrutinib-, **7,768** acalabrutinib-, **2,852** zanubrutinib-, and **622** pirtobrutinib-associated reports.
- Among cytopenic events, anemia and pancytopenia generated signals across all four agents. **Ibrutinib** and **zanubrutinib** demonstrated **signals across most cytopenic** categories, whereas **acalabrutinib** and **pirtobrutinib** showed **fewer** cytopenia-related signals.
- Among bone marrow failure disorders, **pure red cell aplasia generated signals across all four** agents, with **pirtobrutinib** showing **a strong signal** based on 9 reports (ROR 152.12; 95% CI, 78.54–295.51; PRR 150.12). In contrast, **aplastic anemia generated a signal only for acalabrutinib** (ROR 11.06; 95% CI, 6.40–19.12; PRR 11.04).
- Among hemorrhagic events**, ibrutinib displayed the broadest** signal profile, with the **strongest signal observed for splenic hemorrhage** (ROR 51.60; 95% CI, 25.74–103.43; PRR 51.57). Acalabrutinib and zanubrutinib exhibited selective hemorrhagic signals, whereas pirtobrutinib bleeding events were each derived from single case reports, limiting their clinical interpretability.

Selected strongest hematologic reporting signals

Top two ROR signals per BTK inhibitor among the predefined hematologic events



Dot = ROR; horizontal line = 95% CI. Values shown are from the accompanying FAERS analysis spreadsheet. Signal criteria: ≥3 reports, ROR >1 with lower 95% CI >1, and PRR ≥2.

Hematologic event	Ibrutinib	Acalabrutinib	Zanubrutinib	Pirtobrutinib
Cytopenias				
Anemia	SIGNAL	SIGNAL	SIGNAL	SIGNAL
Thrombocytopenia	SIGNAL	SIGNAL	SIGNAL	NO SIGNAL
Neutropenia	SIGNAL	NO SIGNAL	SIGNAL	SIGNAL
Febrile neutropenia	SIGNAL	NO SIGNAL	SIGNAL	NO SIGNAL
Leukopenia	SIGNAL	NO SIGNAL	SIGNAL	NO EVENTS
Pancytopenia	SIGNAL	SIGNAL	SIGNAL	SIGNAL
Cytopenia	SIGNAL	SIGNAL	SIGNAL	NO SIGNAL
Agranulocytosis	SIGNAL	NO SIGNAL	NO SIGNAL	NO SIGNAL
Bone marrow failure disorders				
Aplastic anemia	NO SIGNAL	SIGNAL	NO EVENTS	NO EVENTS
Pure red cell aplasia	SIGNAL	SIGNAL	SIGNAL	SIGNAL
Hemorrhagic events				
Splenic hemorrhage	SIGNAL	NO EVENTS	NO SIGNAL	NO EVENTS
Haemorrhagic disorder	SIGNAL	SIGNAL	NO EVENTS	NO EVENTS
Haemorrhagic diathesis	SIGNAL	SIGNAL	SIGNAL	NO EVENTS
Spontaneous hematoma	SIGNAL	SIGNAL	NO EVENTS	NO SIGNAL

CONCLUSIONS

- BTK inhibitors showed heterogeneous reporting signal profiles.
- Ibrutinib exhibited the broadest signal distribution, whereas pirtobrutinib demonstrated fewer signals.
- Selected findings, including the pure red cell aplasia signal observed with pirtobrutinib, warrant further evaluation in larger datasets and prospective studies.
- These results should be interpreted cautiously given the inherent limitations of spontaneous reporting systems.