BMJ Open

Real-world Safety Profile of Zanubrutinib: a Disproportionality Analysis based on the FAERS Database

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-084991
Article Type:	Original research
Date Submitted by the Author:	06-Feb-2024
Complete List of Authors:	Wang, Jiangfeng; Ipharmacare Ltd, Department of Pharmaceutical Services Zheng, Xiaochun; Zhejiang Provincial People's Hospital, Pharmacy Lin, Jingyang; Hangzhou Medical College, Department of Cardiovascular Medicine Huang, Jinlong; Hangzhou Normal University; Hangzhou Medical College, Department of Pharmacy Zhang, Miaomiao; Hangzhou Normal University; Hangzhou Medical College, Department of Pharmacy Huang, Ping; Hangzhou Medical College, Department of Pharmacy Yang, Xiuli; Hangzhou Medical College, Department of Pharmacy
Keywords:	Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Real-world Safety Profile of Zanubrutinib: a Disproportionality Analysis based on the FAERS Database

Jiangfeng Wang, MM,[1] Xiaochun Zheng, MM,[2] Jingyang Lin, MM,[3] Jinlong Huang, BSc,[4,2] Miaomiao Zhang, BSc,[4,2] Ping Huang, MD,[2*] Xiuli Yang, MM,[2*]

[1]Department of Pharmaceutical Services, Ipharmacare Ltd., Hangzhou, Zhejiang, China

[2]Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital(Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, China;

[3]Heart Center, Department of Cardiovascular Medicine, Zhejiang Provincial People's Hospital （Affiliated People's Hospital, Hangzhou Medical College） ,Hangzhou, Zhejiang, China 310014;

[4]School of Pharmacy, Hangzhou Normal University, Hangzhou, Zhejiang, China;

Corresponding Author: Ping Huang, MD, Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital(Affiliated People's Hospital), Hangzhou Medical College, 158 Shangtang Rd, Gongsu District, Hangzhou, Zhejiang310014, China (Email: huangpwly@sina.com); Xiuli Yang, MM, Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital(Affiliated People's Hospital), Hangzhou Medical College, 158 Shangtang Rd, Gongsu District, Hangzhou, Zhejiang310014, China (Email: xiuli8245@163.com)

Abstract

Objective: Zanubrutinib is a second-generation BTK inhibitor that has been approved for the treatment of several B-cell malignancies. The aim of this study was to evaluate adverse events (AEs) associated with zanubrutinib based on real-world data.

Design: A disproportionality analysis was performed to identify the potential zanubrutinib-related AEs.

Setting: The Food and Drug Administration Adverse Event Reporting System (FAERS) database from the fourth quarter of 2019 to the third quarter of 2023.

Main outcome measures: The results of the disproportionality analyses were

presented as reported odds ratios (ROR). When the lower limit of the 95% confidence interval (CI) for the ROR is greater than 1 and the number of AE reports is ≥ 3, it indicates that the preferred term (PT) may be a positive AE signal.

Results: A total of 846 AE reports with zanubrutinib as the primary suspect (PS) drug were obtained, with 2,826 AEs. A total of 74 positive PT signals were detected across 18 system organ classes (SOCs). The most significant signal for SOC was "Blood and lymphatic system disorders" (ROR = 2.8, 95% CI 2.3-3.3), while the most significant signal for PT was "Haemorrhage subcutaneous" (ROR = 190.8, 95% CI 128.0-284.5). Thirteen unexpected off-label AEs were also observed, such as abnormal hair texture, skin discolouration, hypernatraemia, pericardial effusion, and hypersomnia. The median time to onset of AEs associated with zanubrutinib was 51 days (interquartile range 13-192 days) and was consistent with the early failure model. Compared to zanubrutinib monotherapy, the combination of zanubrutinib and rituximab was associated with an increased risk of certain AEs, such as myelosuppression, pneumonia, leukopenia, decreased platelet counts, abdominal pain, anaemia, pancytopenia, and respiratory failure.

Conclusions: The results of the analysis provided valuable insights into the safety profile of zanubrutinib-treated patients, which was helpful for clinical monitoring and identifying potential AEs related to zanubrutinib.

Strengths and limitations of this study

- The present study evaluated potential AEs related to Zanubrutinib based on the Food and Drug Administration Adverse Event Reporting System (FAERS).
- Thirteen new AEs were found, such as abnormal hair texture, skin discolouration, hypernatraemia, pericardial effusion, and hypersomnia.
- Zanubrutinib-related AEs are more likely to occur during the early period after the initial dose and gradually decrease over time.
- The FAERS database is a voluntary reporting system that may have some limitations, such as incomplete information and awareness bias.

1. Induction

Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase that is a member of the Tec (tyrosine kinase expressed in hepatocellular carcinoma) kinase family.[1,2] BTK is mainly expressed in B lymphocytes, myeloid cells, and platelets.[3] BTK is a vital signalling molecule in B-cell receptor (BCR) pathway and plays a crucial role in B-cell differentiation, proliferation, and survival.[2] The treatment of B-cell malignancies has been greatly improved by the development of the inhibition of Bruton's tyrosine kinase. Since the approval of the first BTK inhibitor, ibrutinib, by the US Food and Drug Administration (FDA) in 2013, a variety of BTK inhibitors have been used clinically to treat patients with B-cell malignancies over the past decade and have demonstrated significant efficacy.[4-9]

Zanubrutinib is a selective second-generation oral BTK inhibitor that covalently and irreversibly binds to Cys-481 in the BTK ATP binding site.[10] By optimizing the molecular structure, zanubrutinib improves BTK target selectivity and minimizes off-target binding, resulting in more precise and sustained BTK inhibition.[10,11] Zanubrutinib was first approved by the FDA in November 2019 to treat patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL). [10] The approval was based on the results of two studies: phase 1/2 study BGB-3111-AU-003 (NCT02343120) and phase 2 study BGB-3111-206 (NCT0320697). The trial NCT02343120 recruited 32 patients who had previously received treatment for MCL. The study achieved an overall response rate (ORR) of 84%, with a complete response rate (CRR) of 29.7%.[12] In the phase II trial, 72 of 86 patients (84%) achieved an objective response (OR), with 59 (68.6%) of them achieving a complete response (CR). [13] The median duration of response (DOR) and progression-free survival (PFS) were 19.5 and 22.1 months, respectively. Zanubrutinib was approved by the FDA in August 2021 for the treatment of Waldenström macroglobulinemia (WM) and in September 2021 for marginal zone lymphoma (MZL).[11] In January 2023, zanubrutinib was granted FDA approval for the treatment of chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) based on the results of the ALPINE and SEQUOIA trials. The ALPINE study, an open-label, multicentre, randomized, phase III clinical trial evaluating the efficacy and safety of zanubrutinib versus ibrutinib in 652 patients with R/R CLL/SLL, showed that zanubrutinib was superior to ibrutinib in terms of ORR and PFS. [14] The SEQUOIA study, which randomized patients with previously untreated CLL/SLL to zanubrutinib

or bendamustine plus rituximab, showed a significant improvement in progression-free survival with zanubrutinib compared to bendamustine-rituximab.[15]

Although BTK inhibitors have shown impressive efficacy and activity, they still require careful attention to safety and monitoring for some unique toxic reactions.[16] Pooled data from six zanubrutinib monotherapy trials involving 779 patients showed that 98% of patients experienced at least one adverse event (AE).[17] The most common non-hematologic AEs were upper respiratory tract infection, rash, bruising, musculoskeletal pain, diarrhoea, cough and pneumonia, urinary tract infection, fatigue, hematuria, constipation, headache, pyrexia, hypertension, and nausea. However, clinical trials are conducted under strict limitations, and AEs of zanubrutinib observed in clinical trials may not fully reflect all AEs observed in clinical practice. Therefore, a comprehensive assessment of the post-marketing safety of zanubrutinib based on real-world data is needed.

The FDA Adverse Event Reporting System (FAERS) is a free database of spontaneous AE reports submitted by manufacturers, healthcare professionals, individual patients and others. FAERS is widely used in signal mining studies of AEs, which can effectively monitor and evaluate the post-marketing safety of drugs.[18] In the present study, we used data mining of FAERS to retrospectively identify and investigate the signals of zanubrutinib-associated ADRs.

2. Methods

2.1. Data Sources and Cleaning

This disproportionality analysis was performed to analyze zanubrutinib-related AEs using data from the FAERS database. Data ranging from the fourth quarter of 2019 (when zanubrutinib was approved by the FDA) to the third quarter of 2023 were selected for analysis. FAERS data is composed of seven datasets: demographic and administrative information (DEMO), drug information (DRUG), adverse event information (REAC), drug therapy start dates and end dates (THER), indications for the reported drugs (INDI), patient outcomes information (OUCT), and reported sources (RPSR). PRIMARYID linked the same AE report across different datasets. Data units from different seasons were combined using R software. Prior to statistical analysis, we performed deduplication based on the following standards: if the PRIMARYIDs were identical, the most recent FDA_DT was chosen, if both the PRIMARYIDs and FDA_DTs were identical, the lower PRIMARYIDs were deleted.[19]

2.2. Adverse Event Identification and Mining

Various drug names including "zanubrutinib", "BGB 3111" and "Brukinsa" were used in the search for zanubrutinib. In the FAERS database, there are four codes for the role of drugs in reported adverse events: Primary Suspect (PS), Secondary Suspect (SS), Concomitant (C), and Interacting (I). Only reports that document zanubrutinib as the role code of PS were selected for analysis to improve accuracy. AE reports in the FAERS database are coded using Preferred Terms (PTs) from the Medical Dictionary for Regulatory Activities (MedDRA). For the present analysis, the PTs and System Organ Classes (SOC) were categorized according to MedDRA version 26.1. The European Union Drug Regulating Authorities Pharmacovigilance of Important Medical

Events (IME) was utilized to evaluate serious adverse events. Additionally, clinical characteristics such as gender, age, outcomes of AEs, country of report, and reporter occupation were gathered.

A disproportionality signal occurs when the reported incidences of AEs for a targeted drug are higher than those in the background data. Reporting odds ratios (ROR) were used in our analysis to identify potential signals that may indicate an increased risk of drug-associated AEs for zanubrutinib. The ROR was calculated using a two-by-two contingency table that contrasted the reported event counts for the target medication with those of other background drugs.[20] The calculation formula of ROR is shown in Supplementary Table S1. The magnitude of the ROR value represents the strength of the association between the reported drug and specific AE. The signal of PT was considered positive if the lower limit of the 95% confidence interval (CI) for ROR was greater than 1 and the number of AE reports was ≥ 3.[20] PTs related to the progression of disease, medication errors, and surgical operations were excluded.

2.3. Time-to-onset analysis

The time-to-onset of AEs was calculated by subtracting the zanubrutinib initiation date (START_DT) from the AE onset date (EVENT_DT). AE reports with incomplete dates, no dates, and incorrectly formatted dates were excluded. The time-to-onset was described using the Weibull shape parameter test and the proportion of events by time. The Weibull distribution is a continuous probability distribution that is described by a scale parameter (α) and a shape parameter (β). The time-to-onset analysis predicted the risk of AEs over time-based on the shape parameter. The predicted results were

classified into three categories: “early failure”, “random failure”, or “wear-out failure”. If both the shape parameter and its 95% CI were less than 1, the risk of AE is estimated to decrease over time, which is referred to as early failure. If the shape parameter is equal to or close to 1 and its 95% CI encompasses 1, the risk of AE is considered not to change over time, which is referred to as ' random failure '. If both the shape parameter and its 95% CI were above 1, the risk of AE is predicted to increase gradually, which is referred to as ' wear-out failure'.[21]

2.4. Drug combination analysis

The safety of zanubrutinib in combination with other drugs was also investigated. First, the drugs used in combination were retrieved from all reports that included zanubrutinib (PS, SS, I, and C) and ranked according to the number of cases of combination. Preliminary results showed that the drug with the highest number of combinations with zanubrutinib was rituximab. Further disproportionality analyses were then performed on the drugs with the highest number of combination cases. In the disproportionality analyses for combination therapy, target drug cases were defined as zanubrutinib (PS) + rituximab (any role code) or rituximab (PS) + zanubrutinib (any role code), and background data were defined as zanubrutinib (PS) without rituximab. When the ROR signal was positive and p-value < 0.05 (chi-squared test), this indicated that the combination therapy was more likely to cause a specific AE than zanubrutinib monotherapy.[22]

R software version 4.3.2 was used for all data cleaning, mining, statistical analyses, and graphs.

3. Result

3.1. Population Characteristics

A total of 7,575,864 AE reports were recorded in the FAERS database between October 2019 and September 2023 (Supplementary Figure S1). After removing duplicates, there were 846 AE reports associated with zanubrutinib as the PS, documenting a total of 2,826 zanubrutinib-related AEs. Patient characteristics are summarized in Table 1. In the included cases, hospitalization - initial or prolonged was the most common severe outcome, accounting for 25.7% (218/848). AEs with zanubrutinib resulted in 64 deaths (7.5%). Approximately 60% of the reports were submitted by healthcare professionals, such as physicians (33.0%), pharmacists (11.2%), and other healthcare professionals (14.4%). The majority of AEs were reported from the United States (61.7%), followed by China (16.6%).

A total of 166 AEs were reported in the FAERS for the combination of zanubrutinib and rituximab, with either zanubrutinib or rituximab as the PS. The most frequent severe outcome of adverse events remained the hospitalization - initial or prolonged. The majority of the reports (62.0%) originated from China.

3.2. Signal of System Organ Classifications

AEs induced by zanubrutinib were found in 26 different organ systems (Figure 1). Among them, six significant SOCs were identified, including “Blood and lymphatic system disorders”, “Skin and subcutaneous tissue disorders”, “infections and infestations”, “Investigations”, “Injury, poisoning and procedural complications”, and “Cardiac disorders”.

3.3. Signal of preferred terms

A total of 74 positive PT signals belonging to 18 SOCs were detected in our analysis. Several positive signals that may be associated with lymphoma complications, such as "blood lactate dehydrogenase increased", "splenomegaly", "blood immunoglobulin M increased", and "lymphadenopathy" were not taken into account. The top 25 AEs with the highest ROR for zanubrutinib are displayed in Figure 2, and the full list of positive PT signals based on the SOCs is listed in Supplementary Table S2. The strongest AE signal was the PT of "Haemorrhage subcutaneous" (ROR = 190.8, 95%CI 128.0-284.5), followed by "Penile haemorrhage" (ROR = 112.6, 95%CI 35.9-352.6). Most of the positive signals were reported in previous clinical studies or listed on the label for zanubrutinib. Nevertheless, thirteen positive signals, such as skin discolouration, abnormal hair texture, hypernatremia, pericardial effusion, and hypersomnia, were not mentioned on the label.

In addition, 20 of the 74 positive PT signals were considered serious AEs according to the IME list (Supplementary Figure S2). The largest number of cases occurred in myelosuppression, with 39 reported cases.

3.4. Results for the time-to-onset analysis

After excluding reports with incomplete dates, a total of 223 reports were included in the time-to-onset analysis, with a median onset time of 51 days (interquartile range [IQR] 13-192). Out of the 223 reports, 91 (40.8%) occurred during the first month of zanubrutinib treatment, and a total of 164 (73.5%) occurred within six months of the initial dose (Figure 3). A scale parameter of 123.7 (95% CI 95.0-152.4) and a shape

parameter of 0.60 (95% CI 0.54-0.66) were obtained when fitting the time-to-onset to the Weibull distribution. It indicated that the risk of AEs associated with zanubrutinib should be referred to as 'early failure', and that the likelihood of experiencing AEs decreases over time.

3.5. Results for the combination analysis

The five most commonly combined drugs with zanubrutinib in all reports from Q4 2019 through Q3 2023 in the FAERS database were rituximab (n = 373), cyclophosphamide (n = 231), prednisone (n = 216), obinutuzumab (n = 205), and vincristine (n = 114). A disproportionality analysis was conducted to investigate the impact of co-administering rituximab on the safety profile of zanubrutinib. The results showed that 10 AEs (Figure 4), such as myelosuppression, pneumonia, leukopenia, and platelet count decreased, may be more likely to occur in patients treated with rituximab + zanubrutinib than in patients treated with zanubrutinib alone.

4. Discussion

BTK inhibitors have demonstrated superior clinical efficacy and tolerability in patients with B-cell malignancies in comparison to standard chemotherapy and immunotherapy regimens. [23] The AEs related to BTK inhibitors were mostly classified as grade 1-2, with a low frequency of grade ≥ 3 AEs.[24] The rate of treatment termination due to AEs was relatively low. The first-generation BTK inhibitor ibrutinib displayed significant off-target effects. It inhibited other kinases non-specifically and bound to other signalling channel proteins, leading to a range of adverse effects. In contrast, zanubrutinib was a next-generation BTK inhibitor that had improved specificity and

off-target effects, resulting in a lower incidence of treatment-related adverse events.[8,9] Nonetheless, patients treated with zanubrutinib may experience unique AEs that require close monitoring to ensure optimal efficacy.

A comprehensive disproportionality analysis of the safety profile of zanubrutinib was conducted based on post-marketing data from the FAERS database. In the almost four years since zanubrutinib was marketed, the FAERS database has documented 846 AE reports where zanubrutinib was the primary suspect. A total of 74 positive PT signals were identified, which were involved in 18 of the SOCs.

The disproportionality analysis revealed that the AEs with the most significant signal at the SOC levels were related to 'blood and lymphatic system disorders'. Hematologic toxicity, including neutropenia, thrombocytopenia, and anaemia, was one of the most common adverse events (AEs) associated with zanubrutinib. Neutropenia was one of the few adverse events that occurred more frequently with zanubrutinib than with ibrutinib (29% vs. 13%; hazard ratio, 2.18; 95% CI, 1.15 to 4.12).[9] The various complex mechanisms of immune dysregulation resulting from B lymphocytoma may contribute to the hematologic toxicity.[23] Severe hematologic toxicity may lead to dose adjustment or discontinuation of zanubrutinib therapy.[8,9] The most common cause of zanubrutinib dose reductions is neutropenia.[17] Jiang et al.[25] developed an XGBoost model to predict the severe haematological toxicity of BTK inhibitors. The XGBoost model was constructed based on ten parameters: leukocytes, neutrophils, erythrocytes, platelets, fibrinogen, total albumin, aspartate aminotransferase, lactate dehydrogenase, gender, and the type of BTK inhibitor. Among them, lactate dehydrogenase, neutrophils,

BTK inhibitor (ibrutinib), and gender (female) were positively correlated with the outcome, while other factors were negatively correlated with the outcome. The XGBoost model is available online for clinical use.

Of the 74 positive PT signals we obtained, up to 18 were associated with haemorrhages, such as eye haemorrhage, haematemesis, subdural hematoma, haemarthrosis, haemorrhage intracr, haematuriaanial, penile haemorrhage, ecchymosis, and skin haemorrhage. Bleeding was a frequently observed AE in patients treated with zanubrutinib, and the majority of these AEs were mild (grade ≤ 2).[8,17] Clinical studies have shown that bleeding events of any grade occurred in 4.4%-66.0% of patients treated with zanubrutinib, with major bleeding occurring in 0.3%-3.5%. [8,9,17,26] Bleeding was more likely to occur in patients ≥ 75 years. [17] Patients who suffered a bleeding event of ≥ grade 3 needed to discontinue zanubrutinib permanently unless the risk of rebleeding was deemed acceptable.[23] Studies have shown an increased risk of bleeding when BTK inhibitors are combined with anticoagulants or antiplatelet agents.[23]

Studies on the pathophysiology of zanubrutinib-associated bleeding are limited. Currently, the mechanisms of haemorrhage associated with BTK inhibitors are mainly explored based on ibrutinib.[3,27] It has been suggested that the risk of bleeding associated with BTK inhibitors may be due to both on- and off-target effects. BTK and TEC interfered with collagen-induced platelet activation by regulating the platelet transmembrane receptors, including the platelet glycoprotein VI (GPVI) and the C-type lectin-like receptor 2 (CLEC-2). GPVI is the main signalling receptor for collagen. The

binding of collagen to GPVI triggers the platelet activation cascade.[28] CLEC-2 activates signal transduction via tyrosine phosphorylation of a single YXXL motif in its cytoplasmic tail, which triggers the platelet activation cascade.[29] BTK inhibitors irreversibly inhibit the BTK and TEC leading to the inhibition of GPVI- and CLEC-2-mediated platelet activation.[3,27] In addition to GPVI and CLEC-2 signalling, inhibition of the GPIb and αIIbβ3-integrin pathways may also contribute to bleeding caused by BTK inhibitors.[3,16]

Patients treated with zanubrutinib were at high risk of infection due to immunosuppression. The infectious event with the most cases reported in the FAERS database was urinary tract infection (n = 19; ROR 2.4; 95% CI 1.6 to 3.8). Opportunistic infections, including fungal pneumonia (ROR=23.7, 95% CI 10.6-53.0), cryptococcal meningitis (ROR=40.1, 95% CI 12.9-124.9), and pneumocystis carinii pneumonia (ROR=15.5, 95% CI 1.8-17.2), were detected. The pooled safety analysis revealed that infections had the highest incidence of AEs, with a 76% occurrence rate.[17] Additionally, serious infections were reported in 27% of cases. The ALPINE trial showed that infectious events were the most common AEs leading to discontinuation.[8] The mechanism of increased susceptibility to infection is complex, primarily involving the effect of BTK inhibitors on the immune system.[26] BTK played a crucial role in detecting a broad spectrum of microbes via various Toll-like receptors.[30] BTK inhibitors may interfere with the sensing of pathogens. In addition, neutrophils are a crucial component of the human immune system, serving as a key defender against pathogenic pathogens. However, neutropenia is a common AE experienced by patients receiving zanubrutinib.

Unexpected and significant PT signals such as abnormal hair texture, skin discolouration, hypernatremia, pericardial effusion, hypersomnia, intestinal perforation, and blood iron decrease were detected in our analysis. All of the unexpected and novel AEs need to be further confirmed in future studies and require vigilance in clinical practice. Hair changes were thought to be one of the skin toxicities of ibrutinib, but have not been reported in zanubrutinib-treated patients. A meta-analysis of 32 clinical trials evaluated the dermatologic toxicity of ibrutinib.[31] Among the 32 clinical trials included, two of the phase II clinical studies for the treatment of CLL/SLL reported hair changes associated with ibrutinib (7.9%; 95% CI, 0.0-21.3%). A pharmacovigilance analysis of ibrutinib and acalabrutinib using the FAERS database identified 84 cases of ibrutinib-associated hair changes by December 2021 (ROR = 108.7, 95% CL 85.0-139.1).[32] However, no positive signal was found for acalabrutinib. The proteins in the keratinocytes of the hair contained an abundance of sulfur-containing amino acids that formed disulfide bonds, which were important for the tensile strength and structural integrity of the hair.[33] The covalent binding of the BTK inhibitors to cysteine residues in the BTK active site disrupted the disulfide bond between cysteine residues, which may lead to hair changes.[34] Skin discolouration, another unexpected dermatologic toxicity that we detected, manifested primarily as abnormal skin pigmentation. However, it was not detected in either ibrutinib or acalabrutinib.[31,32,34]

Our analysis revealed that the median time to onset of all adverse events (AEs) associated with zanubrutinib was 51 days (IQR 13-192), with 73.5% of cases occurring within 6 months of exposure to the drug. This onset time appears to be shorter than that

of most AEs reported in clinical studies. Clinical studies have shown that bleeding events, infectious events, neutropenia, thrombocytopenia, anemia, and atrial fibrillation had a median time to onset of 52 days (IQR 15-167), 89 days (IQR 29-199), 86 days (IQR 45-339), 84 days (IQR 28-343), 102 days (IQR 64-109), and 183 days (IQR 36-622), respectively.[17,35]

As the combination regimens of zanubrutinib are gaining clinical interest, we conducted a further search in the FAERS database for adverse events (AEs) associated with these combinations.[36-39] According to our analysis, rituximab was the most frequently used agent in combination with zanubrutinib, with a total of 373 reports. Out of these cases, 166 were identified as the PS for either zanubrutinib or rituximab. AEs that occur at higher risk in patients treated with zanubrutinib plus rituximab include myelosuppression, pneumonia, leukopenia, decreased platelet count, abdominal pain, anaemia, pancytopenia, respiratory failure, pneumonitis, and elevated blood lactate dehydrogenase. This is similar to the results of a phase Ⅱ clinical study, which demonstrated that the combination of zanubrutinib and rituximab resulted in AEs with an incidence of ≥10%, including leukopenia, neutropenia, anaemia, upper respiratory tract infection, elevated liver enzymes, hematuria, pneumonitis, decreased platelet count, and purpura.[37]

Our study existed several limitations that were inherent to data mining research with the FAERS database. First of all, The FAERS is a self-reporting database that inevitably contains omissions, incomplete information, arbitrary reporting, misreporting, and misinterpreted relationships, which can lead to potentially biased results in

disproportionality analyses. Secondly, the disproportionality analysis only revealed a statistical correlation, rather than a clear causal association between the target drug and the specific AEs. Therefore, further causal evaluation is required, which may include reviewing drug labels, literature reports, expert opinions, or conducting well-designed clinical trials. However, signals identified through big data analytics from post-marketing drug surveillance remain clinically significant in suggesting potential drug risk.

5. Conclusion

The safety profile of zanubrutinib was analysed in the real world, revealing a strong association with haematological toxicity, bleeding, infection, and other adverse events. These findings were consistent with the label and confirmed the reliability of this study. The analysis showed that zanubrutinib may be susceptible to AEs not listed on the label, such as abnormal hair texture, skin discolouration, hypernatraemia, pericardial effusion, and hypersomnia. The time-of-event analysis showed that zanubrutinib-related AEs were characterised by an early failure profile, indicating that the risk of zanubrutinib-related AEs was higher in the early stage of treatment, with a decreasing risk over time. Furthermore, it has been demonstrated that the combination of zanubrutinib and rituximab increases the risk of several AEs, such as myelosuppression, pneumonia, leukopenia, decreased platelet counts, abdominal pain, anaemia, pancytopenia and respiratory failure compared to zanubrutinib alone. Our study provides important evidence for the clinical safety of zanubrutinib.

Authors' contributions

Contributors JW and XY conceived and designed the study. XZ, JL, JH and MZ performed the data extraction and data analyses. JW drafted the manuscript. PH and XY revised the manuscript. JW is the guarantor of the manuscript and accepts full responsibility for the work. All authors have read and approved the version of the manuscript submitted for publication.

Competing interests

All authors declare that they have no competing interests.

Funding

This study was supported by the Research Program for Medicine and Health Science and Technology of Zhejiang Province (2022KY585, 2024KY761), Zhejiang Pharmaceutical Association Foundation Project (2020zyy22), Zhejiang Medical Doctors Association Foundation Project（YS2022-3-009）. Role of the funder: The funders had no role in the study, including collection, analysis, and interpretation of the data, writing of the manuscript, and the decision to submit the manuscript for publication.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics approval

Patient information in the FAERS database is anonymized. Therefore, ethical approval according to the Declaration of Helsinki is not required.

Data sharing statement

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Acknowledgements

Not applicable.

Reference

1. Burger JA. Bruton Tyrosine Kinase Inhibitors: Present and Future. *Cancer journal.* Nov/Dec 2019;25(6):386-393.

2. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Molecular cancer.* Feb 19 2018;17(1):57.
3. von Hundelshausen P, Siess W. Bleeding by Bruton Tyrosine Kinase-Inhibitors: Dependency on Drug Type and Disease. *Cancers.* Mar 4 2021;13(5).
4. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *American journal of hematology.* Dec 2019;94(12):1353-1363.
5. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet.* Mar 6 2021;397(10277):892-901.
6. Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. *Haematologica.* Sep 1 2021;106(9):2364-2373.
7. Sekiguchi N, Rai S, Munakata W, et al. A multicenter, open-label, phase II study of tirabrutinib (ONO/GS-4059) in patients with Waldenstrom's macroglobulinemia. *Cancer science.* Sep 2020;111(9):3327-3337.
8. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Feb 10 2023;41(5):1035-1045.
9. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. *Blood.* Oct 29 2020;136(18):2038-2050.
10. Syed YY. Zanubrutinib: First Approval. *Drugs.* Jan 2020;80(1):91-97.
11. Tam CS, Munoz JL, Seymour JF, Opat S. Zanubrutinib: past, present, and future. *Blood cancer journal.* Sep 11 2023;13(1):141.
12. Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. *Blood advances.* Jun 22 2021;5(12):2577-2585.
13. Song Y, Zhou K, Zou D, et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Aug 15 2020;26(16):4216-4224.
14. Wolska-Washer A, Robak T. Zanubrutinib for the treatment of lymphoid malignancies: Current status and future directions. *Frontiers in oncology.* 2023;13:1130595.
15. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *The Lancet. Oncology.* Aug 2022;23(8):1031-1043.
16. Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematology. American Society of Hematology. Education Program.* Dec 4

2020;2020(1):336-345.

17. Tam CS, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood advances.* Feb 22 2022;6(4):1296-1308.

18. Beninger P, Murray M. Review of FDA Amendments Act Section 921 Experience in Posting Data-mining Results from the FAERS Database. *Clinical therapeutics.* Feb 2021;43(2):380-395.

19. Shu Y, He X, Liu Y, Wu P, Zhang Q. A Real-World Disproportionality Analysis of Olaparib: Data Mining of the Public Version of FDA Adverse Event Reporting System. *Clinical epidemiology.* 2022;14:789-802.

20. Liu P, He M, Xu X, He Y, Yao W, Liu B. Real-world safety of Lacosamide: A pharmacovigilance study based on spontaneous reports in the FDA adverse event reporting system. *Seizure.* Aug 2023;110:203-211.

21. Mazhar F, Battini V, Gringeri M, et al. The impact of anti-TNFalpha agents on weight-related changes: new insights from a real-world pharmacovigilance study using the FDA adverse event reporting system (FAERS) database. *Expert opinion on biological therapy.* Sep 2021;21(9):1281-1290.

22. Li Z, Zou W, Yuan J, Zhong Y, Fu Z. Gender differences in adverse events related to Osimertinib: a real-world pharmacovigilance analysis of FDA adverse event reporting system. *Expert opinion on drug safety.* Jul 31 2023:1-8.

23. Song Y, Wu SJ, Shen Z, et al. Chinese expert consensus on Bruton tyrosine kinase inhibitors in the treatment of B-cell malignancies. *Experimental hematology & oncology.* Oct 16 2023;12(1):92.

24. O'Brien SM, Brown JR, Byrd JC, et al. Monitoring and Managing BTK Inhibitor Treatment-Related Adverse Events in Clinical Practice. *Frontiers in oncology.* 2021;11:720704.

25. Jiang D, Song Z, Liu P, Wang Z, Zhao R. A prediction model for severe hematological toxicity of BTK inhibitors. *Annals of hematology.* Oct 2023;102(10):2765-2777.

26. Estupiñán HY, Berglöf A, Zain R, Smith CIE. Comparative Analysis of BTK Inhibitors and Mechanisms Underlying Adverse Effects. (2296-634X (Print)).

27. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. *Journal of thrombosis and haemostasis : JTH.* May 2017;15(5):835-847.

28. Rayes J, Watson SP, Nieswandt B. Functional significance of the platelet immune receptors GPVI and CLEC-2. *The Journal of clinical investigation.* Jan 2 2019;129(1):12-23.

29. May F, Hagedorn I, Pleines I, et al. CLEC-2 is an essential platelet-activating receptor in hemostasis and thrombosis. *Blood.* Oct 15 2009;114(16):3464-3472.

30. Weber ANR, Bittner Z, Liu X, Dang TM, Radsak MP, Brunner C. Bruton's Tyrosine Kinase: An Emerging Key Player in Innate Immunity. *Frontiers in immunology.* 2017;8:1454.

31. Nocco S, Andriano TM, Bose A, et al. Ibrutinib-associated dermatologic

toxicities: A systematic review and meta-analysis. *Critical reviews in oncology/hematology.* Jun 2022;174:103696.

32. Wan Q, Li Q, Lai X, Xu T, Hu J, Peng H. Data mining and safety analysis of BTK inhibitors: A pharmacovigilance investigation based on the FAERS database. *Frontiers in pharmacology.* 2022;13:995522.
33. de Sa Dias TC, Baby AR, Kaneko TM, Robles Velasco MV. Relaxing/straightening of Afro-ethnic hair: historical overview. *Journal of cosmetic dermatology.* Mar 2007;6(1):2-5.
34. Bitar C, Farooqui MZ, Valdez J, et al. Hair and Nail Changes During Long-term Therapy With Ibrutinib for Chronic Lymphocytic Leukemia. *JAMA dermatology.* Jun 1 2016;152(6):698-701.
35. Opat S, Tedeschi A, Hu B, et al. Safety and efficacy of zanubrutinib in relapsed/refractory marginal zone lymphoma: final analysis of the MAGNOLIA study. *Blood advances.* Nov 28 2023;7(22):6801-6811.
36. Soumerai JD, Mato AR, Dogan A, et al. Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase 2 trial. *The Lancet. Haematology.* Dec 2021;8(12):e879-e890.
37. Zhang Q, Tao R, Li Z, et al. A phase II study of Zanubrutinib in combination with rituximab in patients with relapsed/refractory aggressive and indolent B-cell lymphoma. *Leukemia & lymphoma.* Oct 2022;63(10):2503-2506.
38. Allan JN, Helbig D, Mulvey E, et al. Zanubrutinib and Venetoclax As Initial Therapy for CLL/SLL with Obinutuzumab Triplet Consolidation in Patients with Minimal Residual Disease Positivity (BruVenG). *Blood.* 2023/11/02/ 2023;142:3285.
39. Geng H, Jia S, Zhang Y, et al. Efficacy and safety of zanubrutinib plus R-CHOP in treatment of non-GCB DLBCL with extranodal involvement. *Frontiers in immunology.* 2023;14:1219167.

Figure titles and legends

Figure 1. Forest plot of the AEs for zanubrutinib at the System Organ Class Level. SOC, system organ class; CI, confidence interval.

Figure 2. Forest plot of the top 25 AE risk signals for zanubrutinib. PT, preferred term; ROR, reported odds ratio; CI, confidence interval.

Figure 3. Time to onset of zanubrutinib-related AEs.

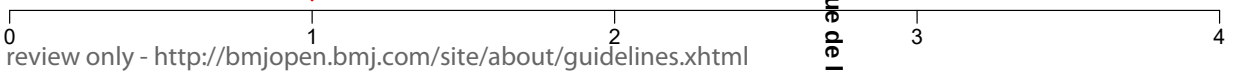
Figure 4. Volcano plots of the difference in PT signals between zanubrutinib+rituximab and Zanubrutinib alone. ROR, reported odds ratio.

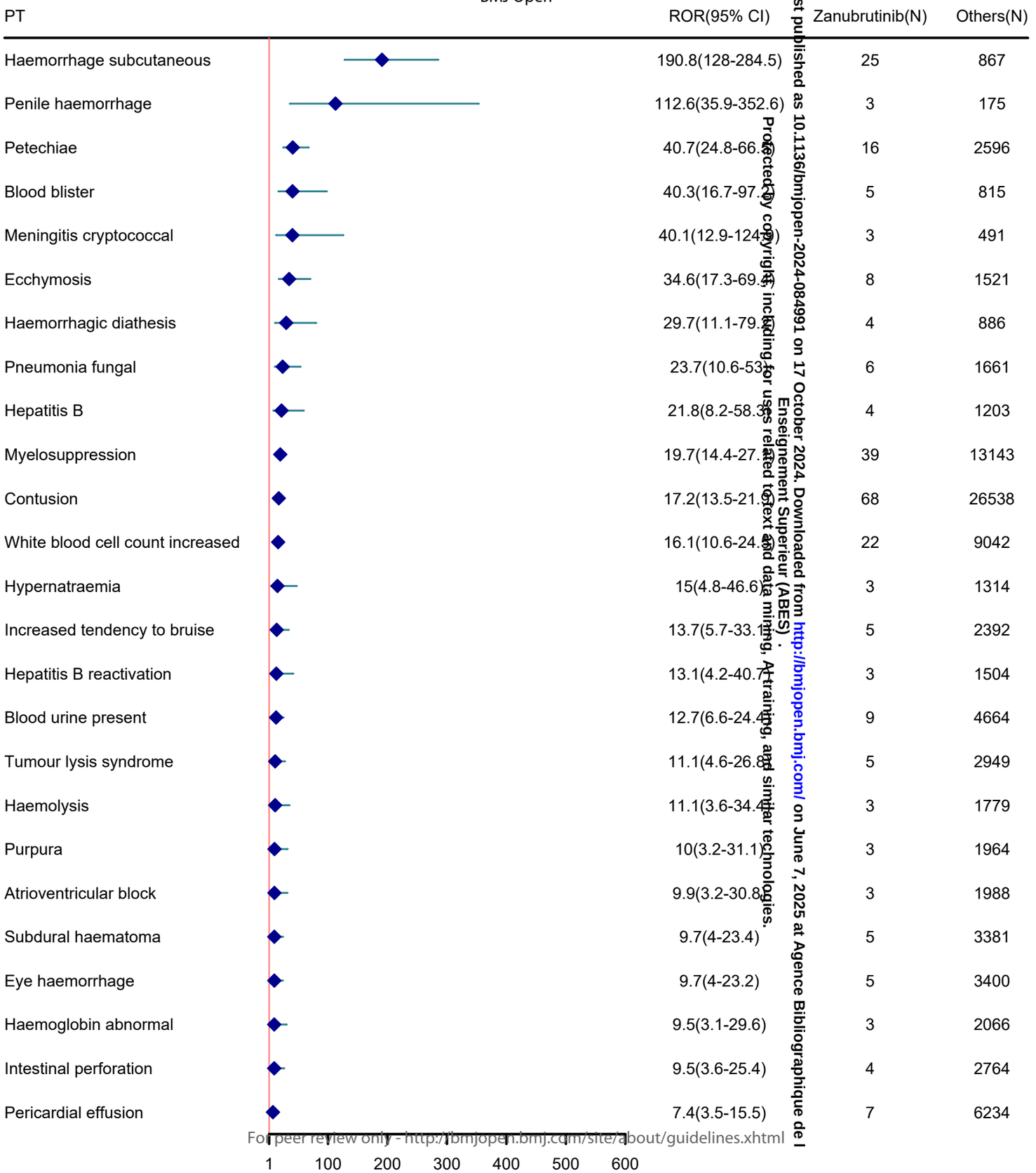
Table titles and legends

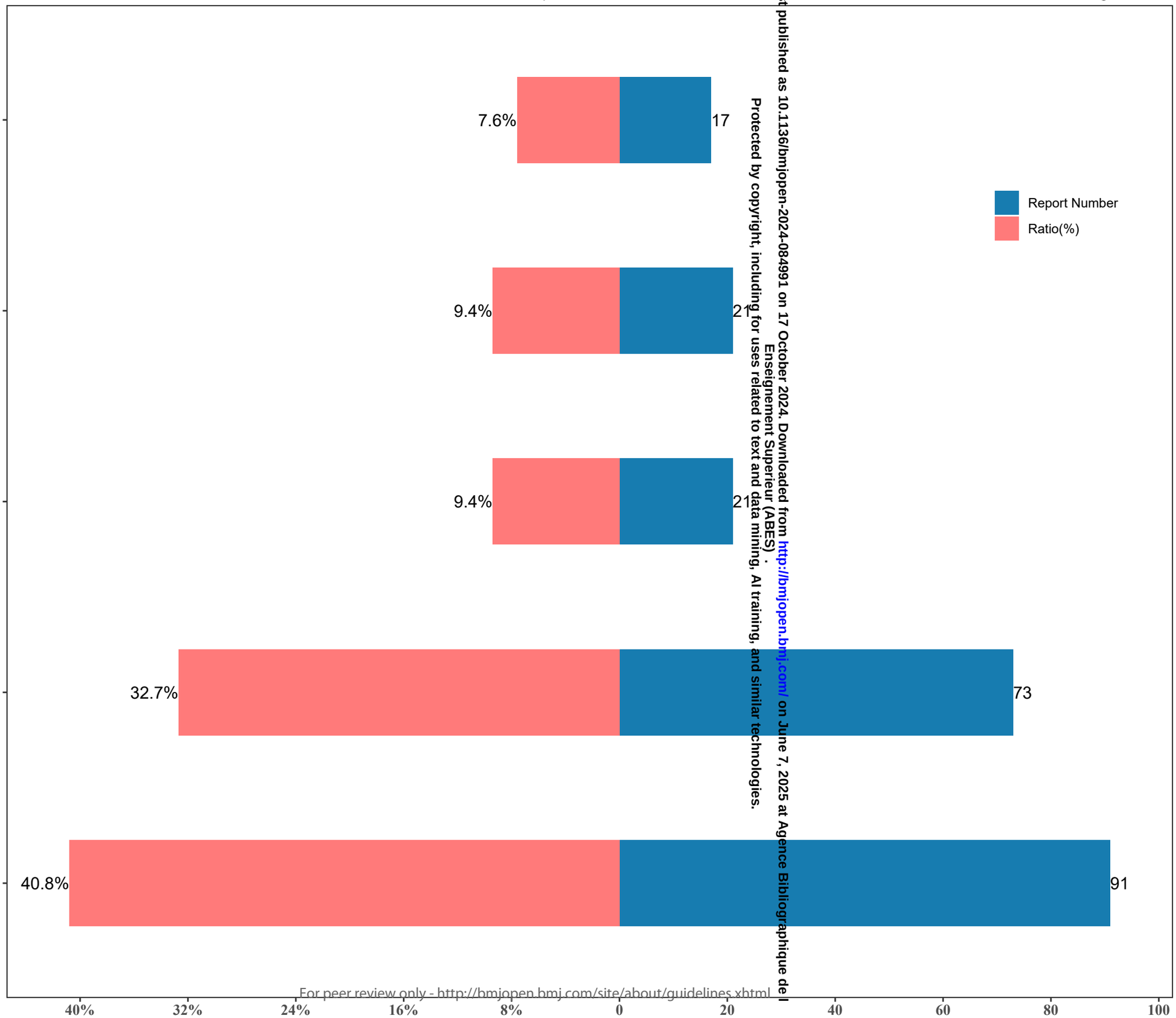
Table 1. Characteristics of reports associated with Zanubrutinib

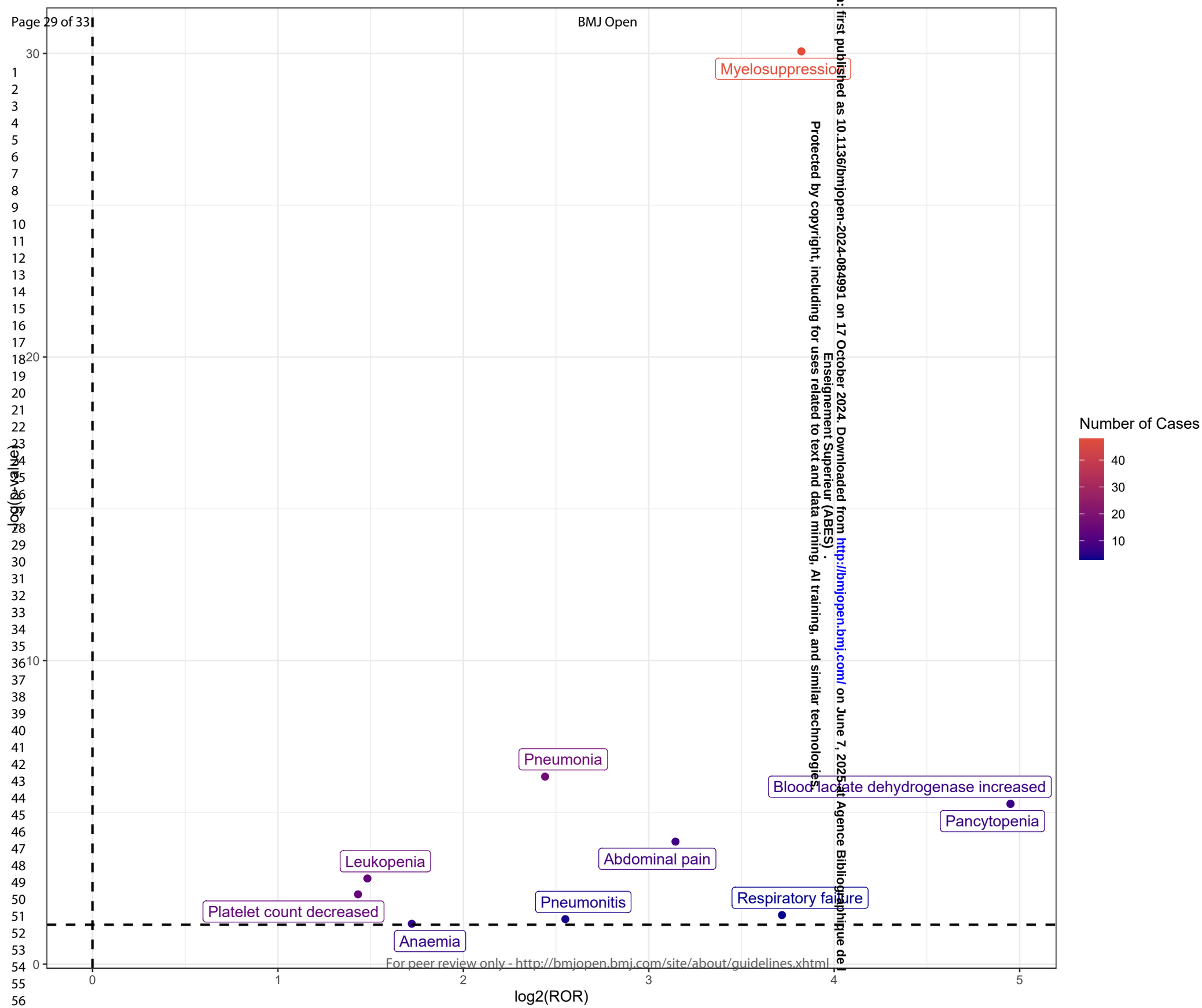
	Zanubrutinib n（%）	Zanubrutinib+ Rituximab n（%）
Number of reports	848	166
Number of adverse events	2826	603
Sex		
Female	8 (0.9%)	30 (18.1%)
Male	19 (2.2%)	49 (29.5%)
Missing	821 (96.8%)	87 (52.4%)
Age(years)		
≥86	3 (0.4%)	1 (0.6%)
65～85	14 (1.7%)	27 (16.3%)
18～64	4 (0.5%)	35 (21.1%)
Missing	827 (97.5%)	103 (62.0%)
Outcomes		
Death	64 (7.5%)	8(4.8%)
Life-threatening	15 (1.8%)	3(1.8%)
Hospitalization	218 (25.7%)	25(15.1%)
Disability	7 (0.8%)	2(1.2%)
Congenital Anomaly	1 (0.1%)	0
Required intervention	2 (0.2%)	0
Other Serious	176 (20.8%)	96(57.8%)
Missing	365 (43.0%)	32(19.3%)
Reporter's Occupation		
Consumer	342 (40.3%)	8 (4.8%)
Health professional	122 (14.4%)	64 (38.6%)
Physician	280 (33.0%)	84 (50.6%)
Pharmacist	95 (11.2%)	9 (5.4%)
Missing	9 (1.1%)	1 (0.6%)
Reporter Countries		
USA	523 (61.7%)	15 (9.0%)
China	141 (16.6%)	103 (62.0%)
Australia	52 (6.1%)	36 (21.7%)
Canada	29 (3.4%)	1 (0.6%)
Others	103 (12.2%)	11(6.7%)

SOC	N	ROR(95% CI)
Injury, poisoning and procedural complications	471	1.46(1.32-1.61)
General disorders and administration site conditions	390	0.74(0.67-0.83)
Investigations	244	1.51(1.32-1.72)
Infections and infestations	240	1.57(1.38-1.79)
Skin and subcutaneous tissue disorders	238	1.61(1.41-1.84)
Gastrointestinal disorders	222	1.01(0.88-1.16)
Nervous system disorders	143	0.68(0.57-0.8)
Respiratory, thoracic and mediastinal disorders	130	1.02(0.86-1.22)
Blood and lymphatic system disorders	129	2.78(2.33-3.32)
Musculoskeletal and connective tissue disorders	128	0.87(0.73-1.04)
Cardiac disorders	72	1.3(1.03-1.65)
Vascular disorders	60	1.15(0.89-1.48)
Renal and urinary disorders	53	0.97(0.74-1.28)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	51	0.41(0.31-0.54)
Psychiatric disorders	49	0.3(0.23-0.4)
Surgical and medical procedures	49	1.22(0.92-1.62)
Metabolism and nutrition disorders	47	0.87(0.65-1.16)
Eye disorders	34	0.63(0.45-0.88)
Hepatobiliary disorders	20	0.88(0.57-1.36)
Ear and labyrinth disorders	15	1.3(0.78-2.16)
Immune system disorders	13	0.4(0.23-0.69)
Product issues	10	0.19(0.1-0.36)
Reproductive system and breast disorders	9	0.51(0.26-0.98)
Social circumstances	4	0.3(0.11-0.79)
Congenital, familial and genetic disorders	3	0.39(0.13-1.21)
Endocrine disorders	2	0.27(0.07-1.09)









Supplementary

Table S1. Formulas and signal detection criteria for ROR.

Formula	Signal standard
ROR = (ad/bc)	**· lower limit of ROR 95%CI > 1;** **· a ≥3**
ROR 95%CI = $e^{\ln(ROR) \pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}$	

a: number of specific adverse events to the target drug; b: number of other adverse events to the target drug; c: number of specific adverse events to background drugs; d: number of other adverse events to the background drug;

ROR: reporting odds ratio, CI: confidence interval

Table S2. All positive Preferred Terms associated with Zanubrutinib.

soc	PT	n	ROR(95%CI)
Blood and lymphatic system disorders	Myelosuppression	39	19.7(14.4-27.1)
	Febrile neutropenia	14	4.4(2.6-7.4)
	Neutropenia	13	1.8(1-3)
	Increased tendency to bruise	5	13.7(5.7-33.1)
	Haemorrhagic diathesis	4	29.7(11.1-79.2)
	Cytopenia	4	5.2(1.9-13.8)
	Haemolysis*	3	11.1(3.6-34.4)
Cardiac disorders	Atrial fibrillation	21	4.9(3.2-7.6)
	Pericardial effusion*	7	7.4(3.5-15.5)
	Atrioventricular block	3	9.9(3.2-30.8)
	Ventricular tachycardia	3	5(1.6-15.5)
Ear and labyrinth disorders	Ear discomfort*	3	6.9(2.2-21.5)
Eye disorders	Eye haemorrhage	5	9.7(4-23.2)
Gastrointestinal disorders	Dysphagia	14	4(2.4-6.8)
	Dyspepsia*	8	2.1(1-4.2)
	Intestinal perforation*	4	9.5(3.6-25.4)
	Faeces discoloured	3	3.8(1.2-11.7)
	Haematemesis	3	3.3(1.1-10.2)
	Tooth disorder*	3	3.2(1-10.1)
General disorders and administration site conditions	Fatigue	50	1.4(1-1.8)
	Asthenia	30	2(1.4-2.9)
	Peripheral swelling	18	2(1.3-3.2)
	Oedema peripheral	12	3.4(1.9-5.9)
	Oedema	5	2.6(1.1-6.3)
	Mass*	3	4.9(1.6-15.2)
Hepatobiliary disorders	Hepatic function abnormal	5	3.2(1.3-7.6)
Infections and infestations	Urinary tract infection	19	2.4(1.6-3.8)
	Infection	15	2.2(1.3-3.6)
	Cellulitis	10	4.8(2.6-8.9)
	Sepsis	9	2(1-3.8)
	Pneumonia fungal	6	23.7(10.6-53)
	Hepatitis B	4	21.8(8.2-58.3)
	Meningitis cryptococcal	3	40.1(12.9-124.9)
	Hepatitis b reactivation	3	13.1(4.2-40.7)
	Pneumocystis jirovecii pneumonia	3	5.5(1.8-17.2)
	Skin infection	3	5.4(1.7-16.8)
Injury, poisoning and procedural complications	Contusion	68	17.2(13.5-21.9)
	Subdural haematoma	5	9.7(4-23.4)
Investigations	Platelet count decreased	29	5.7(4-8.3)
	White blood cell count decreased	24	4.4(2.9-6.6)

	White blood cell count increased	22	16.1(10.6-24.5)
	Haemoglobin decreased	14	3.4(2-5.8)
	Blood urine present	9	12.7(6.6-24.4)
	Blood creatinine increased	8	3(1.5-6.1)
	Red blood cell count decreased	6	4.4(2-9.7)
	Haemoglobin abnormal	3	9.5(3.1-29.6)
	Blood iron decreased*	3	4.7(1.5-14.7)
Metabolism and nutrition disorders	Tumour lysis syndrome	5	11.1(4.6-26.8)
	Hypernatraemia*	3	15(4.8-46.6)
	Increased appetite*	3	4.7(1.5-14.7)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	4	2.8(1.1-7.6)
	Haemarthrosis	3	4.7(1.5-14.7)
Nervous system disorders	Hypersomnia*	4	3.3(1.2-8.8)
	Haemorrhage intracranial	3	6.3(2-19.6)
Renal and urinary disorders	Haematuria	8	5.9(3-11.9)
	Dysuria	5	3.5(1.4-8.3)
Reproductive system and breast disorders	Penile haemorrhage	3	112.6(35.9-352.6)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	14	6.2(3.7-10.5)
	Epistaxis	8	2.7(1.3-5.4)
	Sinus disorder	4	4.4(1.6-11.7)
Skin and subcutaneous tissue disorders	Rash	48	2.4(1.8-3.2)
	Haemorrhage subcutaneous	25	190.8(128-284.5)
	Petechiae	16	40.7(24.8-66.5)
	Skin discolouration*	10	5.1(2.7-9.5)
	Rash macular	9	5.8(3-11.2)
	Ecchymosis	8	34.6(17.3-69.4)
	Night sweats	6	4.5(2-10)
	Rash pruritic	6	2.8(1.2-6.2)
	Blood blister	5	40.3(16.7-97.2)
	Skin lesion	4	3.1(1.2-8.4)
	Purpura	3	10(3.2-31.1)
	Hair texture abnormal*	3	4.9(1.6-15.2)
	Skin haemorrhage	3	4.6(1.5-14.3)
Vascular disorders	Haemorrhage	18	4.4(2.7-6.9)

* unexpected adverse event

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval.

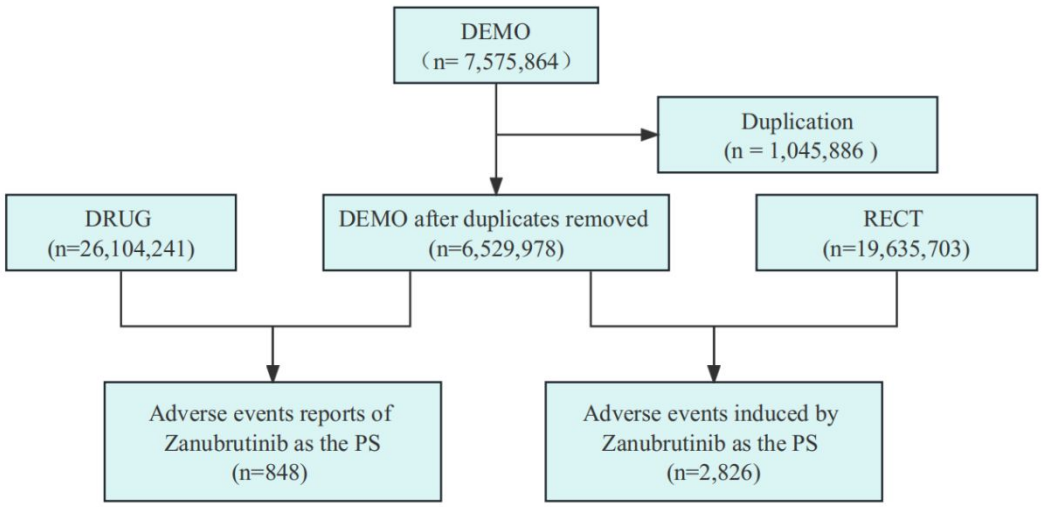


Figure S1. The flow diagram of screening zanubrutinib-related AEs from the FAERS database. DEMO, demographic and administrative information; DRUG, drug information; REAC, adverse event information; PT, preferred term.

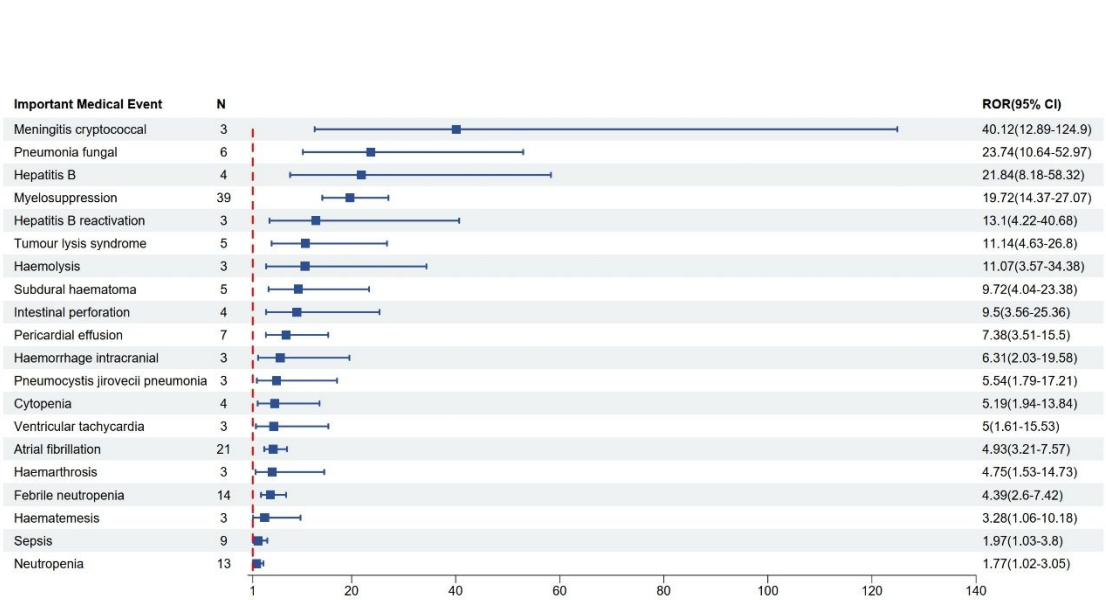


Figure S2. Forest plot of the important medical event signals for zanubrutinib. ROR, reported odds ratio; CI, confidence interval.

.

BMJ Open

Real-world Safety Profile of Zanubrutinib: a Disproportionality Analysis based on the FAERS Database

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-084991.R1
Article Type:	Original research
Date Submitted by the Author:	05-Sep-2024
Complete List of Authors:	Wang, Jiangfeng; Ipharmacare Ltd, Department of Pharmaceutical Services Zheng, Xiaochun; Zhejiang Provincial People's Hospital, Pharmacy Lin, Jingyang; Hangzhou Medical College, Department of Cardiovascular Medicine Huang, Jinlong; Hangzhou Normal University; Hangzhou Medical College, Department of Pharmacy Zhang, Miaomiao; Hangzhou Normal University; Hangzhou Medical College, Department of Pharmacy Huang, Ping; Hangzhou Medical College, Department of Pharmacy Yang, Xiuli; Hangzhou Medical College, Department of Pharmacy
Primary Subject Heading:	Medical management
Secondary Subject Heading:	Medical management, Health services research
Keywords:	Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, Health & safety < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Real-world Safety Profile of Zanubrutinib: a Disproportionality Analysis based on the FAERS Database

Jiangfeng Wang, MM,[1] Xiaochun Zheng, MM,[2] Jingyang Lin, MM,[3] Jinlong Huang, BSc,[4,2] Miaomiao Zhang, BSc,[4,2] Ping Huang, MD,[2*] Xiuli Yang, MM,[2*]

[1]Department of Pharmaceutical Services, Ipharmacare Ltd., Hangzhou, Zhejiang, China

[2]Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital(Affiliated People's Hospital), Hangzhou Medical College, Hangzhou, Zhejiang, China;

[3]Heart Center, Department of Cardiovascular Medicine, Zhejiang Provincial People's Hospital （Affiliated People's Hospital, Hangzhou Medical College） ,Hangzhou, Zhejiang, China 310014;

[4]School of Pharmacy, Hangzhou Normal University, Hangzhou, Zhejiang, China;

Corresponding Author: Ping Huang, MD, Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital(Affiliated People's Hospital), Hangzhou Medical College, 158 Shangtang Rd, Gongsu District, Hangzhou, Zhejiang310014, China (Email: huangpwly@sina.com); Xiuli Yang, MM, Center for Clinical Pharmacy, Cancer Center, Department of Pharmacy, Zhejiang Provincial People's Hospital(Affiliated People's Hospital), Hangzhou Medical College, 158 Shangtang Rd, Gongsu District, Hangzhou, Zhejiang310014, China (Email: xiuli8245@163.com)

Abstract

Objective: Zanubrutinib is a second-generation BTK inhibitor that has been approved for the treatment of several B-cell malignancies. The aim of this study was to evaluate adverse events (AEs) associated with zanubrutinib based on real-world data.

Design: A disproportionality analysis was performed to identify the potential zanubrutinib-related AEs.

Setting: The Food and Drug Administration Adverse Event Reporting System (FAERS) database from the fourth quarter of 2019 to the third quarter of 2023.

Main outcome measures: The results of the disproportionality analyses were

presented as reported odds ratios (ROR). When the lower limit of the 95% confidence interval (CI) for the ROR is greater than 1 and the number of AE reports is ≥ 3, it indicates that the preferred term (PT) may be a positive AE signal.

Results: A total of 846 AE reports with zanubrutinib as the primary suspect (PS) drug were obtained, with 2,826 AEs. A total of 74 positive PT signals were detected across 18 system organ classes (SOCs). The most significant signal for SOC was "Blood and lymphatic system disorders" (ROR = 2.8, 95% CI 2.3-3.3), while the most significant signal for PT was "Haemorrhage subcutaneous" (ROR = 190.8, 95% CI 128.0-284.5). Thirteen unexpected off-label AEs were also observed, such as abnormal hair texture, skin discolouration, hypernatraemia, pericardial effusion, and hypersomnia. The median time to onset of AEs associated with zanubrutinib was 51 days (interquartile range 13-192 days) and was consistent with the early failure model. In comparison to zanubrutinib monotherapy, the combination of zanubrutinib and rituximab therapy was linked to a higher risk of specific AEs, including myelosuppression, pneumonia, leukopenia, thrombocytopenia, abdominal pain, anaemia, pancytopenia, and respiratory failure. Furthermore, the combination of zanubrutinib and chemotherapy increased the risk of several severe AEs, such as cardiac arrest, elevated blood lactate dehydrogenase levels, and pancytopenia.

Conclusions: The results of the analysis provided valuable insights into the safety profile of zanubrutinib-treated patients, which was helpful for clinical monitoring and identifying potential AEs related to zanubrutinib.

Strengths and limitations of this study

- The present study employs a disproportionality analysis to identify potential adverse events (AEs) associated with Zanubrutinib, utilizing the Food and Drug Administration Adverse Event Reporting System (FAERS).
- Reported odds ratios (RORs) and their corresponding 95% confidence intervals (CIs) were employed to identify the potential signals.
- The FAERS database is a self-reporting system that may have some limitations, such as incomplete information and awareness bias.
- The disproportionality analysis indicated a statistical correlation, but did not establish a definitive causal relationship between the target drug and the specific AEs.

1. Induction

Bruton's tyrosine kinase (BTK) is a non-receptor tyrosine kinase that is a member of the Tec (tyrosine kinase expressed in hepatocellular carcinoma) kinase family.[1,2] BTK is mainly expressed in B lymphocytes, myeloid cells, and platelets.[3] BTK is a vital signalling molecule in B-cell receptor (BCR) pathway and plays a crucial role in B-cell differentiation, proliferation, and survival.[2] The treatment of B-cell malignancies has been greatly improved by the development of the inhibition of Bruton's tyrosine kinase. Since the approval of the first BTK inhibitor, ibrutinib, by the US Food and Drug Administration (FDA) in 2013, a variety of BTK inhibitors have been used clinically to treat patients with B-cell malignancies over the past decade and have demonstrated

significant efficacy.[4-9]

Zanubrutinib is a selective second-generation oral BTK inhibitor that covalently and irreversibly binds to Cys-481 in the BTK ATP binding site.[10] By optimizing the molecular structure, zanubrutinib improves BTK target selectivity and minimizes off-target binding, resulting in more precise and sustained BTK inhibition.[10,11] Zanubrutinib was first approved by the FDA in November 2019 to treat patients with relapsed/refractory (R/R) mantle cell lymphoma (MCL). [10] The approval was based on the results of two studies: phase 1/2 study BGB-3111-AU-003 (NCT02343120) and phase 2 study BGB-3111-206 (NCT0320697). The trial NCT02343120 recruited 32 patients who had previously received treatment for MCL. The study achieved an overall response rate (ORR) of 84%, with a complete response rate (CRR) of 29.7%.[12] In the phase II trial, 72 of 86 patients (84%) achieved an objective response (OR), with 59 (68.6%) of them achieving a complete response (CR). [13] The median duration of response (DOR) and progression-free survival (PFS) were 19.5 and 22.1 months, respectively. Zanubrutinib was approved by the FDA in August 2021 for the treatment of Waldenström's macroglobulinemia (WM) and in September 2021 for marginal zone lymphoma (MZL).[11] In January 2023, zanubrutinib was granted FDA approval for the treatment of chronic lymphocytic leukaemia (CLL) and small lymphocytic lymphoma (SLL) based on the results of the ALPINE and SEQUOIA trials. The ALPINE study, an open-label, multicentre, randomized, phase III clinical trial evaluating the efficacy and safety of zanubrutinib versus ibrutinib in 652 patients with R/R CLL/SLL, showed that zanubrutinib was superior to ibrutinib in terms of ORR and PFS. [14] The SEQUOIA

study, which randomized patients with previously untreated CLL/SLL to zanubrutinib or bendamustine plus rituximab, showed a significant improvement in progression-free survival with zanubrutinib compared to bendamustine-rituximab.[15]

Although BTK inhibitors have shown impressive efficacy and activity, they still require careful attention to safety and monitoring for some unique toxic reactions.[16] Pooled data from six zanubrutinib monotherapy trials involving 779 patients showed that 98% of patients experienced at least one adverse event (AE).[17] The most common non-hematologic AEs were upper respiratory tract infection, rash, bruising, musculoskeletal pain, diarrhoea, cough and pneumonia, urinary tract infection, fatigue, hematuria, constipation, headache, pyrexia, hypertension, and nausea. However, clinical trials are conducted under strict limitations, and AEs of zanubrutinib observed in clinical trials may not fully reflect all AEs observed in clinical practice. Therefore, a comprehensive assessment of the post-marketing safety of zanubrutinib based on real-world data is needed.

The FDA Adverse Event Reporting System (FAERS) is a free database of spontaneous AE reports submitted by manufacturers, healthcare professionals, individual patients and others. FAERS is widely used in signal mining studies of AEs, which can effectively monitor and evaluate the post-marketing safety of drugs.[18] In the present study, we used data mining of FAERS to retrospectively identify and investigate the signals of zanubrutinib-associated ADRs.

2. Methods

2.1. Patient and public involvement

Patients and the public were not involved in our study.

2.2. Data Sources and Cleaning

This disproportionality analysis was performed to analyze zanubrutinib-related AEs using data from the FAERS database. Data ranging from the fourth quarter of 2019 (when zanubrutinib was approved by the FDA) to the third quarter of 2023 were selected for analysis. FAERS data is composed of seven datasets: demographic and administrative information (DEMO), drug information (DRUG), adverse event information (REAC), drug therapy start dates and end dates (THER), indications for the reported drugs (INDI), patient outcomes information (OUCT), and reported sources (RPSR). PRIMARYID linked the same AE report across different datasets. Data units from different seasons were combined using R software. Prior to statistical analysis, we performed deduplication based on the following standards: if the PRIMARYIDs were identical, the most recent FDA_DT was chosen, if both the PRIMARYIDs and FDA_DTs were identical, the lower PRIMARYIDs were deleted.[19]

2.3. Adverse Event Identification and Mining

Various drug names including "zanubrutinib", "BGB 3111" and "Brukinsa" were used in the search for zanubrutinib. In the FAERS database, there are four codes for the role of drugs in reported AEs: Primary Suspect (PS), Secondary Suspect (SS), Concomitant (C), and Interacting (I). Only reports that document zanubrutinib as the role code of PS were selected for analysis to improve accuracy. AE reports in the FAERS database are coded using Preferred Terms (PTs) from the Medical Dictionary for Regulatory

Activities (MedDRA). For the present analysis, the PTs and System Organ Classes (SOC) were categorized according to MedDRA version 26.1. The European Union Drug Regulating Authorities Pharmacovigilance of Important Medical Events (IME) was utilized to evaluate serious adverse events. Additionally, clinical characteristics such as gender, age, outcomes of AEs, country of report, and reporter occupation were gathered.

A disproportionality signal occurs when the reported incidences of AEs for a targeted drug are higher than those in the background data. Reporting odds ratios (ROR) were used in our analysis to identify potential signals that may indicate an increased risk of drug-associated AEs for zanubrutinib. The ROR was calculated using a two-by-two contingency table that contrasted the reported event counts for the target medication with those of other background drugs.[20] The calculation formula of ROR is shown in Supplementary Table S1. The magnitude of the ROR value represents the strength of the association between the reported drug and specific AE. The signal of PT was considered positive if the lower limit of the 95% confidence interval (CI) for ROR was greater than 1 and the number of AE reports was ≥ 3.[20] PTs related to the progression of disease, medication errors, and surgical operations were excluded.

2.4. Subgroup analysis

Subgroup analyses were conducted to investigate the correlation between zanubrutinib and AEs within defined subgroups, classified according to indication and geographical region. The currently approved indications for zanubrutinib included MCL, CLL/SLL, WM, MZL, and follicular lymphoma (FL). Owing to the limited number of cases of

MZL and FL in our dataset, the subgroup analysis by indication was primarily focused on MCL, CLL/SLL, and WM. With regard to regional subgroups, distinct analyses were performed for the United States and China, as these two countries constituted the largest number of cases in our dataset.

2.5. Time-to-onset analysis

The time-to-onset of AEs was calculated by subtracting the zanubrutinib initiation date (START_DT) from the AE onset date (EVENT_DT). AE reports with incomplete dates, no dates, and incorrectly formatted dates were excluded. The time-to-onset was described using the Weibull shape parameter test and the proportion of events by time. The Weibull distribution is a continuous probability distribution that is described by a scale parameter (α) and a shape parameter (β). The time-to-onset analysis predicted the risk of AEs over time-based on the shape parameter. The predicted results were classified into three categories: early failure", "random failure", or "wear-out failure". If both the shape parameter and its 95% CI were less than 1, the risk of AE is estimated to decrease over time, which is referred to as early failure. If the shape parameter is equal to or close to 1 and its 95% CI encompasses 1, the risk of AE is considered not to change over time, which is referred to as "random failure". If both the shape parameter and its 95% CI were above 1, the risk of AE is predicted to increase gradually, which is referred to as "wear-out failure".[21]

2.6. Drug combination analysis

The safety of zanubrutinib in combination with other drugs was also investigated. First, the drugs used in combination were retrieved from all reports that included zanubrutinib

(PS, SS, I, and C) and ranked according to the number of cases of combination. Preliminary results showed that the drug with the highest number of combinations with zanubrutinib was rituximab. Further disproportionality analyses were then performed on the drugs with the highest number of combination cases. In the disproportionality analyses for combination therapy, target drug cases were defined as zanubrutinib (PS) + rituximab (any role code) or rituximab (PS) + zanubrutinib (any role code), and background data were defined as zanubrutinib (PS) without rituximab. When the ROR signal was positive and p-value < 0.05 (chi-squared test), this indicated that the combination therapy was more likely to cause a specific AE than zanubrutinib monotherapy.[22] The second most common drug combined with zanubrutinib was cyclophosphamide. Therefore, a further analysis was performed to explore the risk of AEs associated with the combination of zanubrutinib and chemotherapy.

R software version 4.3.2 was used for all data cleaning, mining, statistical analyses, and graphs.

3. Result

3.1. Population Characteristics

A total of 7,575,864 AE reports were recorded in the FAERS database between October 2019 and September 2023 (Supplementary Figure S1). After removing duplicates, there were 846 AE reports associated with zanubrutinib as the PS, documenting a total of 2,826 zanubrutinib-related AEs. Patient characteristics are summarized in Table 1. In the included cases, hospitalization - initial or prolonged was the most common severe outcome, accounting for 25.7% (218/848). AEs with zanubrutinib resulted in 64 deaths

(7.5%). Approximately 60% of the reports were submitted by healthcare professionals, such as physicians (33.0%), pharmacists (11.2%), and other healthcare professionals (14.4%). The majority of AEs were reported from the United States (61.7%), followed by China (16.6%).

A total of 166 cases were reported in the FAERS for the combination of zanubrutinib and rituximab, with either zanubrutinib or rituximab as the PS. The most frequent severe outcome of adverse events remained the hospitalization - initial or prolonged. The majority of the reports (62.0%) originated from China. Additionally, there were 78 reports associated with the combination of zanubrutinib and chemotherapy.

3.2. Signal of System Organ Classifications

AEs induced by zanubrutinib were found in 26 different organ systems (Figure 1). Among them, six significant SOCs were identified, including “Blood and lymphatic system disorders”, “Skin and subcutaneous tissue disorders”, “infections and infestations”, “Investigations”, “Injury, poisoning and procedural complications”, and “Cardiac disorders”.

3.3. Signal of preferred terms

A total of 74 positive PT signals belonging to 18 SOCs were detected in our analysis. Several positive signals that may be associated with lymphoma complications, such as “blood lactate dehydrogenase increased”, “splenomegaly”, “blood immunoglobulin M increased”, and “lymphadenopathy” were not taken into account. The top 25 AEs with the highest ROR for zanubrutinib are displayed in Figure 2, and the full list of positive PT signals based on the SOCs is listed in Supplementary Table S2. The

strongest AE signal was the PT of "Haemorrhage subcutaneous" (ROR = 190.8, 95% CI 128.0-284.5), followed by "Penile haemorrhage" (ROR = 112.6, 95% CI 35.9-352.6). Most of the positive signals were reported in previous clinical studies or listed on the label for zanubrutinib. Nevertheless, thirteen positive signals, such as skin discolouration, abnormal hair texture, hypernatremia, pericardial effusion, and hypersomnia, were not mentioned on the label.

In addition, 20 of the 74 positive PT signals were considered serious AEs according to the IME list (Supplementary Figure S2). The largest number of cases occurred in myelosuppression, with 39 reported cases.

3.4. Results for Subgroup Analysis

The results of the indication-based subgroup disproportionate analysis are presented in Supplementary Table S3. Across the MCL, CLL/SLL, and WM subgroups, the ROR for the AE of "haemorrhage subcutaneous" was found to be consistently the highest, with values of 32.2 (95% CI 9.4-110.3), 41.3 (95% CI 19.0-89.6), and 46.6 (95% CI 12.3-175.9), respectively. The most frequently reported AE in the MCL subgroup was dyspnea, with 11 cases, in the CLL/SLL subgroup was a contusion, with 21 cases, and in the WM subgroup was rash, with 18 cases.

In the subgroup analysis of the United States population, a total of 68 Preferred Terms (PTs) exhibited positive signals (Supplementary Table S4). Notably, "Haemorrhage subcutaneous" demonstrated the strongest signal with an ROR of 601.7 (95% CI 369.4-980.3). This was followed by "Penile haemorrhage" (ROR = 176.1, 95% CI 55.7-556.1) and "Petechiae" (ROR = 87.7, 95% CI 53.4-143.9).

In the Chinese population, the highest signal PT was “haemolysis” (ROR=44.8, 95% CI 13.8-145.0), followed by “hepatitis B” (ROR=40.0, 95% CI 12.4-129.1) and “tumour lysis syndrome” (ROR=31.3, 95% CI 9.8-100.3).

3.5. Results for the time-to-onset analysis

After excluding reports with incomplete dates, a total of 223 reports were included in the time-to-onset analysis, with a median onset time of 51 days (interquartile range [IQR] 13-192). Out of the 223 reports, 91 (40.8%) occurred during the first month of zanubrutinib treatment, and a total of 164 (73.5%) occurred within six months of the initial dose (Figure 3). A scale parameter of 123.7 (95% CI 95.0-152.4) and a shape parameter of 0.60 (95% CI 0.54-0.66) were obtained when fitting the time-to-onset to the Weibull distribution. It indicated that the risk of AEs associated with zanubrutinib should be referred to as 'early failure', and that the likelihood of experiencing AEs decreases over time.

3.6. Results for the combination analysis

The five most commonly combined drugs with zanubrutinib in all reports from Q4 2019 through Q3 2023 in the FAERS database were rituximab (n = 373), cyclophosphamide (n = 231), prednisone (n = 216), obinutuzumab (n = 205), and vincristine (n = 114). A disproportionality analysis was conducted to investigate the impact of co-administering rituximab on the safety profile of zanubrutinib. The results showed that 10 AEs (Figure 4), such as myelosuppression, pneumonia, leukopenia, and platelet count decreased, may be more likely to occur in patients treated with rituximab + zanubrutinib than in patients treated with zanubrutinib alone. Furthermore, the analysis of zanubrutinib

combined with chemotherapy revealed that nine AEs, such as cardiac arrest, increased blood lactate dehydrogenase levels, and pancytopenia, were at a higher risk of occurrence in the patient group receiving chemotherapy plus zanubrutinib than in those on zanubrutinib monotherapy.

4. Discussion

BTK inhibitors have demonstrated superior clinical efficacy and tolerability in patients with B-cell malignancies in comparison to standard chemotherapy and immunotherapy regimens. [23] The AEs related to BTK inhibitors were mostly classified as grade 1-2, with a low frequency of grade ≥ 3 AEs.[24] The rate of treatment termination due to AEs was relatively low. The first-generation BTK inhibitor ibrutinib displayed significant off-target effects. It inhibited other kinases non-specifically and bound to other signalling channel proteins, leading to a range of AEs. In contrast, zanubrutinib was a next-generation BTK inhibitor that had improved specificity and off-target effects, resulting in a lower incidence of treatment-related AEs.[8,9] Nonetheless, patients treated with zanubrutinib may experience unique AEs that require close monitoring to ensure optimal efficacy.

A comprehensive disproportionality analysis of the safety profile of zanubrutinib was conducted based on post-marketing data from the FAERS database. In the almost four years since zanubrutinib was marketed, the FAERS database has documented 846 AE reports where zanubrutinib was the primary suspect. A total of 74 positive PT signals were identified, which were involved in 18 of the SOCs.

The disproportionality analysis revealed that the AEs with the most significant signal

at the SOC levels were related to 'blood and lymphatic system disorders'. Hematologic toxicity, including neutropenia, thrombocytopenia, and anaemia, was one of the most common AEs associated with zanubrutinib. Neutropenia was one of the few AEs that occurred more frequently with zanubrutinib than with ibrutinib (29% vs. 13%; hazard ratio, 2.18; 95% CI, 1.15 to 4.12).[9] The various complex mechanisms of immune dysregulation resulting from B lymphocytoma may contribute to the hematologic toxicity.[23] Severe hematologic toxicity may lead to dose adjustment or discontinuation of zanubrutinib therapy.[8,9] The most common cause of zanubrutinib dose reductions is neutropenia.[17] Jiang et al.[25] developed an XGBoost model to predict the severe haematological toxicity of BTK inhibitors. The XGBoost model was constructed based on ten parameters: leukocytes, neutrophils, erythrocytes, platelets, fibrinogen, total albumin, aspartate aminotransferase, lactate dehydrogenase, gender, and the type of BTK inhibitor. Among them, lactate dehydrogenase, neutrophils, BTK inhibitor (ibrutinib), and gender (female) were positively correlated with the outcome, while other factors were negatively correlated with the outcome. The XGBoost model is available online for clinical use.

Of the 74 positive PT signals we obtained, up to 18 were associated with haemorrhages, such as eye haemorrhage, haematemesis, subdural hematoma, haemarthrosis, haemorrhage intracr, haematuriaanial, penile haemorrhage, ecchymosis, and skin haemorrhage. Bleeding was a frequently observed AE in patients treated with zanubrutinib, and the majority of these AEs were mild (grade ≤ 2).[8,17] Clinical studies have shown that bleeding events of any grade occurred in 4.4%-66.0% of patients

treated with zanubrutinib, with major bleeding occurring in 0.3%-3.5%. [8,9,17,26] Bleeding was more likely to occur in patients ≥ 75 years. [17] Patients who suffered a bleeding event of ≥ grade 3 needed to discontinue zanubrutinib permanently unless the risk of rebleeding was deemed acceptable.[23] Studies have shown an increased risk of bleeding when BTK inhibitors are combined with anticoagulants or antiplatelet agents.[23]

Studies on the pathophysiology of zanubrutinib-associated bleeding are limited. Currently, the mechanisms of haemorrhage associated with BTK inhibitors are mainly explored based on ibrutinib.[3,27] It has been suggested that the risk of bleeding associated with BTK inhibitors may be due to both on- and off-target effects. BTK and TEC interfered with collagen-induced platelet activation by regulating the platelet transmembrane receptors, including the platelet glycoprotein VI (GPVI) and the C-type lectin-like receptor 2 (CLEC-2). GPVI is the main signalling receptor for collagen. The binding of collagen to GPVI triggers the platelet activation cascade.[28] CLEC-2 activates signal transduction via tyrosine phosphorylation of a single YXXL motif in its cytoplasmic tail, which triggers the platelet activation cascade.[29] BTK inhibitors irreversibly inhibit the BTK and TEC leading to the inhibition of GPVI- and CLEC-2-mediated platelet activation.[3,27] In addition to GPVI and CLEC-2 signalling, inhibition of the GPIb and αIIbβ3-integrin pathways may also contribute to bleeding caused by BTK inhibitors.[3,16]

Patients treated with zanubrutinib were at high risk of infection due to immunosuppression. The infectious event with the most cases reported in the FAERS

database was urinary tract infection (n = 19; ROR 2.4; 95% CI 1.6 to 3.8). Opportunistic infections, including fungal pneumonia (ROR=23.7, 95% CI 10.6-53.0), cryptococcal meningitis (ROR=40.1, 95% CI 12.9-124.9), and pneumocystis carinii pneumonia (ROR=15.5, 95% CI 1.8-17.2), were detected. The pooled safety analysis revealed that infections had the highest incidence of AEs, with a 76% occurrence rate.[17] Additionally, serious infections were reported in 27% of cases. The ALPINE trial showed that infectious events were the most common AEs leading to discontinuation.[8] The mechanism of increased susceptibility to infection is complex, primarily involving the effect of BTK inhibitors on the immune system.[26] BTK played a crucial role in detecting a broad spectrum of microbes via various Toll-like receptors.[30] BTK inhibitors may interfere with the sensing of pathogens. In addition, neutrophils are a crucial component of the human immune system, serving as a key defender against pathogenic pathogens. However, neutropenia is a common AE experienced by patients receiving zanubrutinib. Unexpected and significant PT signals such as abnormal hair texture, skin discolouration, hypernatremia, pericardial effusion, hypersomnia, intestinal perforation, and blood iron decrease were detected in our analysis. All of the unexpected and novel AEs need to be further confirmed in future studies and require vigilance in clinical practice. Hair changes were thought to be one of the skin toxicities of ibrutinib, but have not been reported in zanubrutinib-treated patients. A meta-analysis of 32 clinical trials evaluated the dermatologic toxicity of ibrutinib.[31] Among the 32 clinical trials included, two of the phase II clinical studies for the treatment of CLL/SLL reported hair changes associated with ibrutinib (7.9%; 95% CI, 0.0-21.3%). A pharmacovigilance

analysis of ibrutinib and acalabrutinib using the FAERS database identified 84 cases of ibrutinib-associated hair changes by December 2021 (ROR = 108.7, 95% CL 85.0-139.1).[32] However, no positive signal was found for acalabrutinib. The proteins in the keratinocytes of the hair contained an abundance of sulfur-containing amino acids that formed disulfide bonds, which were important for the tensile strength and structural integrity of the hair.[33] The covalent binding of the BTK inhibitors to cysteine residues in the BTK active site disrupted the disulfide bond between cysteine residues, which may lead to hair changes.[34] Skin discolouration, another unexpected dermatologic toxicity that we detected, manifested primarily as abnormal skin pigmentation. However, it was not detected in either ibrutinib or acalabrutinib.[31,32,34]

Our analysis revealed that the median time to onset of all AEs associated with zanubrutinib was 51 days (IQR 13-192), with 73.5% of cases occurring within 6 months of exposure to the drug. This onset time appears to be shorter than that of most AEs reported in clinical studies. Clinical studies have shown that bleeding events, infectious events, neutropenia, thrombocytopenia, anemia, and atrial fibrillation had a median time to onset of 52 days (IQR 15-167), 89 days (IQR 29-199), 86 days (IQR 45-339), 84 days (IQR 28-343), 102 days (IQR 64-109), and 183 days (IQR 36-622), respectively.[17,35]

As the combination regimens of zanubrutinib are gaining clinical interest, we conducted a further search in the FAERS database for AEs associated with these combinations.[36-39] According to our analysis, rituximab was the most frequently used agent in combination with zanubrutinib, with a total of 373 reports. Out of these cases, 166 were

identified as the PS for either zanubrutinib or rituximab. AEs that occur at higher risk in patients treated with zanubrutinib plus rituximab include myelosuppression, pneumonia, leukopenia, decreased platelet count, abdominal pain, anaemia, pancytopenia, respiratory failure, pneumonitis, and elevated blood lactate dehydrogenase. This is similar to the results of a phase Ⅱ clinical study, which demonstrated that the combination of zanubrutinib and rituximab resulted in AEs with an incidence of ≥10%, including leukopenia, neutropenia, anaemia, upper respiratory tract infection, elevated liver enzymes, hematuria, pneumonitis, decreased platelet count, and purpura.[37] In the analysis of Zanubrutinib combined with chemotherapy, the highest risk was identified for cardiac toxicity, specifically the risk of cardiac arrest. This may be related to the significant cardiotoxicity of certain chemotherapeutic agents used in combination, such as cyclophosphamide, epirubicin, and pirarubicin.

Our study existed several limitations that were inherent to data mining research with the FAERS database. First of all, The FAERS is a self-reporting database that inevitably contains omissions, incomplete information, arbitrary reporting, misreporting, and misinterpreted relationships, which can lead to potentially biased results in disproportionality analyses. Secondly, the analysis did not account for potential confounding factors such as drug interactions and patient comorbidities, which could significantly influence the occurrence of AEs. Thirdly, the disproportionality analysis only revealed a statistical correlation, rather than a clear causal association between the target drug and the specific AEs. Therefore, further causal evaluation is required, which may include reviewing drug labels, literature reports, expert opinions, or conducting

well-designed clinical trials. However, signals identified through big data analytics from post-marketing drug surveillance remain clinically significant in suggesting potential drug risk.

5. Conclusion

The safety profile of zanubrutinib was analysed in the real world, revealing a strong association with haematological toxicity, bleeding, infection, and other AEs. These findings were consistent with the label and confirmed the reliability of this study. The analysis showed that zanubrutinib may be susceptible to AEs not listed on the label, such as abnormal hair texture, skin discolouration, hypernatraemia, pericardial effusion, and hypersomnia. The time-of-event analysis showed that zanubrutinib-related AEs were characterised by an early failure profile, indicating that the risk of zanubrutinib-related AEs was higher in the early stage of treatment, with a decreasing risk over time. Furthermore, our study elucidates the increased risk of several AEs associated with the combination of zanubrutinib and rituximab, including myelosuppression, pneumonia, leukopenia, thrombocytopenia, abdominal pain, anaemia, pancytopenia, and respiratory failure, compared to zanubrutinib monotherapy. Similarly, the combination of zanubrutinib with chemotherapy elevates the risk of nine AEs, such as cardiac arrest, elevated blood lactate dehydrogenase levels, and pancytopenia. Our study provides important evidence for the clinical safety of zanubrutinib.

Authors' contributions

Contributors JW and XY conceived and designed the study. XZ, JL, JH and MZ performed the data extraction and data analyses. JW drafted the manuscript. PH and

XY revised the manuscript. JW is the guarantor of the manuscript and accepts full responsibility for the work. All authors have read and approved the version of the manuscript submitted for publication.

Competing interests

All authors declare that they have no competing interests.

Funding

This study was supported by the Research Program for Medicine and Health Science and Technology of Zhejiang Province (2022KY585, 2024KY761), Zhejiang Pharmaceutical Association Foundation Project (2020zyy22), Zhejiang Medical Doctors Association Foundation Project（YS2022-3-009）. Role of the funder: The funders had no role in the study, including collection, analysis, and interpretation of the data, writing of the manuscript, and the decision to submit the manuscript for publication.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Ethics approval

Patient information in the FAERS database is anonymized. Therefore, ethical approval according to the Declaration of Helsinki is not required.

Data sharing statement

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Acknowledgements

Not applicable.

Reference

1. Burger JA. Bruton Tyrosine Kinase Inhibitors: Present and Future. *Cancer journal.* Nov/Dec 2019;25(6):386-393.
2. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Molecular cancer.* Feb 19 2018;17(1):57.
3. von Hundelshausen P, Siess W. Bleeding by Bruton Tyrosine Kinase-Inhibitors:

Dependency on Drug Type and Disease. *Cancers.* Mar 4 2021;13(5).
4. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: Up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *American journal of hematology.* Dec 2019;94(12):1353-1363.
5. Mato AR, Shah NN, Jurczak W, et al. Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. *Lancet.* Mar 6 2021;397(10277):892-901.
6. Rogers KA, Thompson PA, Allan JN, et al. Phase II study of acalabrutinib in ibrutinib-intolerant patients with relapsed/refractory chronic lymphocytic leukemia. *Haematologica.* Sep 1 2021;106(9):2364-2373.
7. Sekiguchi N, Rai S, Munakata W, et al. A multicenter, open-label, phase II study of tirabrutinib (ONO/GS-4059) in patients with Waldenstrom's macroglobulinemia. *Cancer science.* Sep 2020;111(9):3327-3337.
8. Hillmen P, Eichhorst B, Brown JR, et al. Zanubrutinib Versus Ibrutinib in Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Interim Analysis of a Randomized Phase III Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Feb 10 2023;41(5):1035-1045.
9. Tam CS, Opat S, D'Sa S, et al. A randomized phase 3 trial of zanubrutinib vs ibrutinib in symptomatic Waldenstrom macroglobulinemia: the ASPEN study. *Blood.* Oct 29 2020;136(18):2038-2050.
10. Syed YY. Zanubrutinib: First Approval. *Drugs.* Jan 2020;80(1):91-97.
11. Tam CS, Munoz JL, Seymour JF, Opat S. Zanubrutinib: past, present, and future. *Blood cancer journal.* Sep 11 2023;13(1):141.
12. Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. *Blood advances.* Jun 22 2021;5(12):2577-2585.
13. Song Y, Zhou K, Zou D, et al. Treatment of Patients with Relapsed or Refractory Mantle-Cell Lymphoma with Zanubrutinib, a Selective Inhibitor of Bruton's Tyrosine Kinase. *Clinical cancer research : an official journal of the American Association for Cancer Research.* Aug 15 2020;26(16):4216-4224.
14. Wolska-Washer A, Robak T. Zanubrutinib for the treatment of lymphoid malignancies: Current status and future directions. *Frontiers in oncology.* 2023;13:1130595.
15. Tam CS, Brown JR, Kahl BS, et al. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *The Lancet. Oncology.* Aug 2022;23(8):1031-1043.
16. Lipsky A, Lamanna N. Managing toxicities of Bruton tyrosine kinase inhibitors. *Hematology. American Society of Hematology. Education Program.* Dec 4 2020;2020(1):336-345.
17. Tam CS, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. *Blood advances.*

Feb 22 2022;6(4):1296-1308.

18. Beninger P, Murray M. Review of FDA Amendments Act Section 921 Experience in Posting Data-mining Results from the FAERS Database. *Clinical therapeutics*. Feb 2021;43(2):380-395.

19. Shu Y, He X, Liu Y, Wu P, Zhang Q. A Real-World Disproportionality Analysis of Olaparib: Data Mining of the Public Version of FDA Adverse Event Reporting System. *Clinical epidemiology*. 2022;14:789-802.

20. Liu P, He M, Xu X, He Y, Yao W, Liu B. Real-world safety of Lacosamide: A pharmacovigilance study based on spontaneous reports in the FDA adverse event reporting system. *Seizure*. Aug 2023;110:203-211.

21. Mazhar F, Battini V, Gringeri M, et al. The impact of anti-TNFalpha agents on weight-related changes: new insights from a real-world pharmacovigilance study using the FDA adverse event reporting system (FAERS) database. *Expert opinion on biological therapy*. Sep 2021;21(9):1281-1290.

22. Li Z, Zou W, Yuan J, Zhong Y, Fu Z. Gender differences in adverse events related to Osimertinib: a real-world pharmacovigilance analysis of FDA adverse event reporting system. *Expert opinion on drug safety*. Jul 31 2023:1-8.

23. Song Y, Wu SJ, Shen Z, et al. Chinese expert consensus on Bruton tyrosine kinase inhibitors in the treatment of B-cell malignancies. *Experimental hematology & oncology*. Oct 16 2023;12(1):92.

24. O'Brien SM, Brown JR, Byrd JC, et al. Monitoring and Managing BTK Inhibitor Treatment-Related Adverse Events in Clinical Practice. *Frontiers in oncology*. 2021;11:720704.

25. Jiang D, Song Z, Liu P, Wang Z, Zhao R. A prediction model for severe hematological toxicity of BTK inhibitors. *Annals of hematology*. Oct 2023;102(10):2765-2777.

26. Estupiñán HY, Berglöf A, Zain R, Smith CIE. Comparative Analysis of BTK Inhibitors and Mechanisms Underlying Adverse Effects. (2296-634X (Print)).

27. Shatzel JJ, Olson SR, Tao DL, McCarty OJT, Danilov AV, DeLoughery TG. Ibrutinib-associated bleeding: pathogenesis, management and risk reduction strategies. *Journal of thrombosis and haemostasis : JTH*. May 2017;15(5):835-847.

28. Rayes J, Watson SP, Nieswandt B. Functional significance of the platelet immune receptors GPVI and CLEC-2. *The Journal of clinical investigation*. Jan 2 2019;129(1):12-23.

29. May F, Hagedorn I, Pleines I, et al. CLEC-2 is an essential platelet-activating receptor in hemostasis and thrombosis. *Blood*. Oct 15 2009;114(16):3464-3472.

30. Weber ANR, Bittner Z, Liu X, Dang TM, Radsak MP, Brunner C. Bruton's Tyrosine Kinase: An Emerging Key Player in Innate Immunity. *Frontiers in immunology*. 2017;8:1454.

31. Nocco S, Andriano TM, Bose A, et al. Ibrutinib-associated dermatologic toxicities: A systematic review and meta-analysis. *Critical reviews in oncology/hematology*. Jun 2022;174:103696.

32. Wan Q, Li Q, Lai X, Xu T, Hu J, Peng H. Data mining and safety analysis of

BTK inhibitors: A pharmacovigilance investigation based on the FAERS database. *Frontiers in pharmacology.* 2022;13:995522.

33. de Sa Dias TC, Baby AR, Kaneko TM, Robles Velasco MV. Relaxing/straightening of Afro-ethnic hair: historical overview. *Journal of cosmetic dermatology.* Mar 2007;6(1):2-5.
34. Bitar C, Farooqui MZ, Valdez J, et al. Hair and Nail Changes During Long-term Therapy With Ibrutinib for Chronic Lymphocytic Leukemia. *JAMA dermatology.* Jun 1 2016;152(6):698-701.
35. Opat S, Tedeschi A, Hu B, et al. Safety and efficacy of zanubrutinib in relapsed/refractory marginal zone lymphoma: final analysis of the MAGNOLIA study. *Blood advances.* Nov 28 2023;7(22):6801-6811.
36. Soumerai JD, Mato AR, Dogan A, et al. Zanubrutinib, obinutuzumab, and venetoclax with minimal residual disease-driven discontinuation in previously untreated patients with chronic lymphocytic leukaemia or small lymphocytic lymphoma: a multicentre, single-arm, phase 2 trial. *The Lancet. Haematology.* Dec 2021;8(12):e879-e890.
37. Zhang Q, Tao R, Li Z, et al. A phase II study of Zanubrutinib in combination with rituximab in patients with relapsed/refractory aggressive and indolent B-cell lymphoma. *Leukemia & lymphoma.* Oct 2022;63(10):2503-2506.
38. Allan JN, Helbig D, Mulvey E, et al. Zanubrutinib and Venetoclax As Initial Therapy for CLL/SLL with Obinutuzumab Triplet Consolidation in Patients with Minimal Residual Disease Positivity (BruVenG). *Blood.* 2023/11/02/ 2023;142:3285.
39. Geng H, Jia S, Zhang Y, et al. Efficacy and safety of zanubrutinib plus R-CHOP in treatment of non-GCB DLBCL with extranodal involvement. *Frontiers in immunology.* 2023;14:1219167.

Figure titles and legends

Figure 1. Forest plot of the AEs for zanubrutinib at the System Organ Class Level. SOC, system organ class; CI, confidence interval.

Figure 2. Forest plot of the top 25 AE risk signals for zanubrutinib. PT, preferred term; ROR, reported odds ratio; CI, confidence interval.

Figure 3. Time to onset of zanubrutinib-related AEs.

Figure 4. Volcano plots of the difference in PT signals for the combination analysis. A: Zanubrutinib+Rituximab VS. Zanubrutinib alone. B: Zanubrutinib+ Chemotherapy VS. Zanubrutinib alone. ROR, reported odds ratio; PT, preferred term.

Table titles and legends

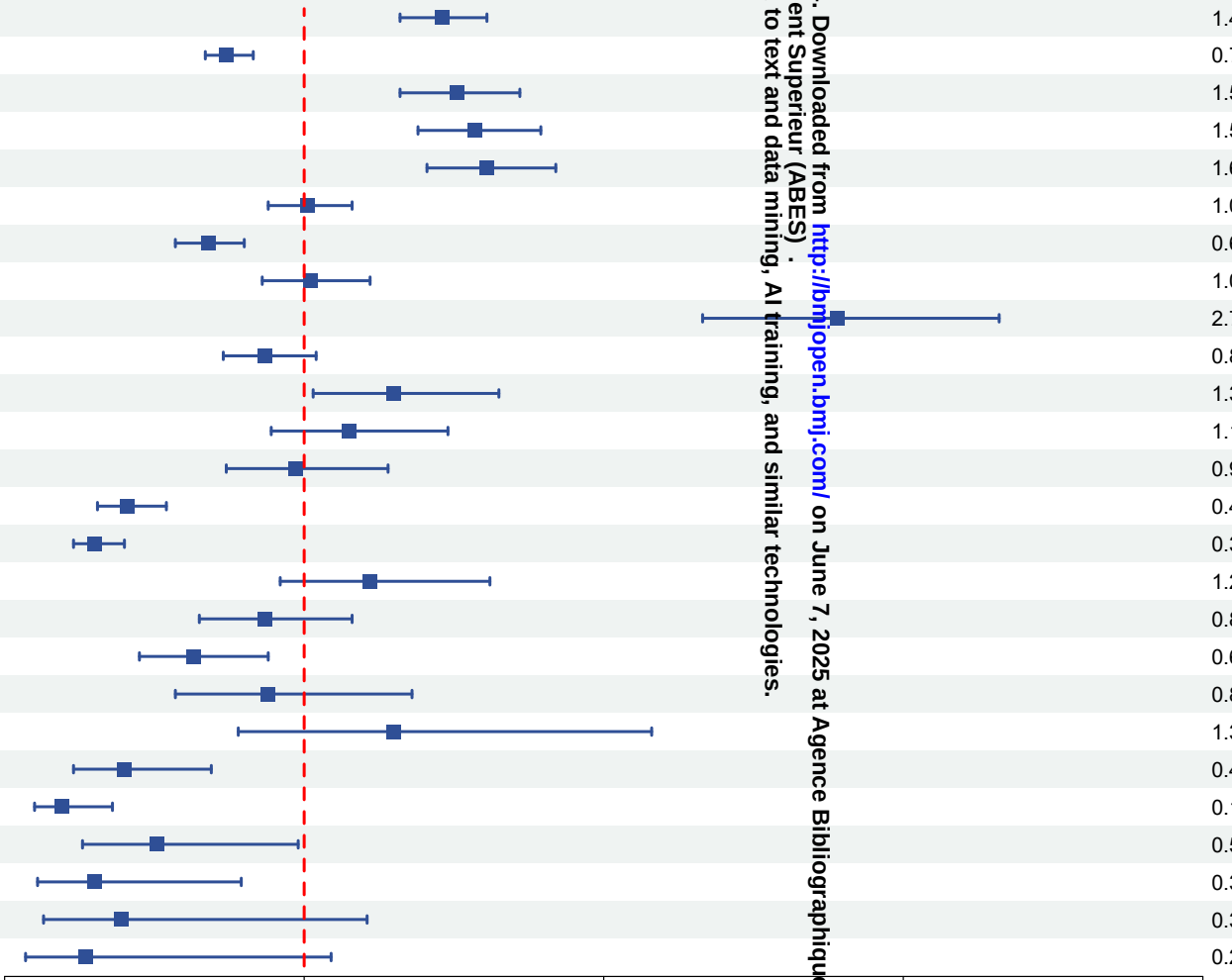
Table 1. Characteristics of reports associated with Zanubrutinib

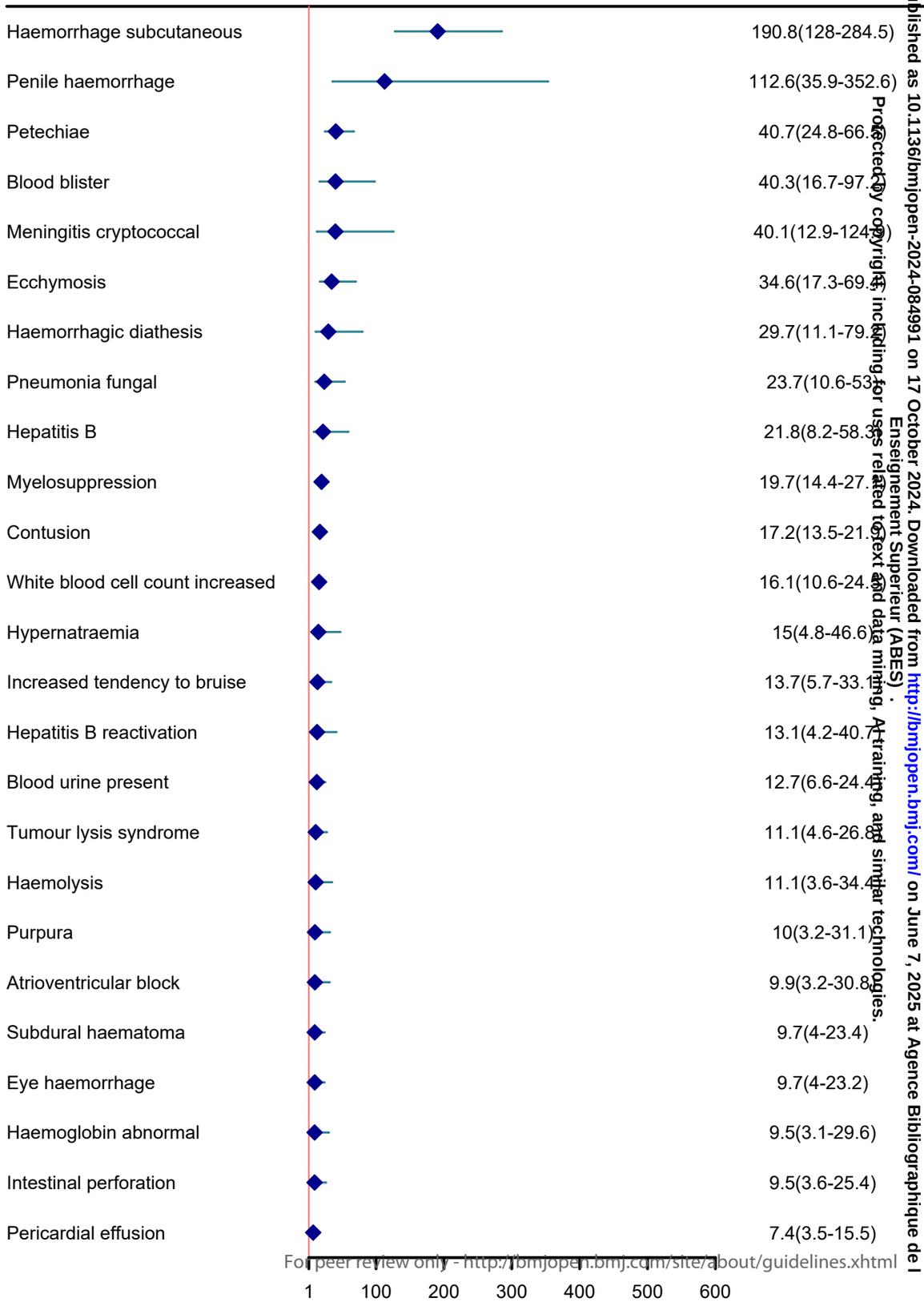
	Zanubrutinib n（%）	Zanubrutinib+ Rituximab n（%）	Zanubrutinib+ Chemotherapy n（%）
Number of reports	848	166	78
Number of adverse events	2826	603	228
Sex			
Female	8 (0.9%)	30 (18.1%)	5 (6.4%)
Male	19 (2.2%)	49 (29.5%)	14 (17.9%)
Missing	821 (96.8%)	87 (52.4%)	59 (75.6%)
Age(years)			
≥86	3 (0.4%)	1 (0.6%)	0
65～85	14 (1.7%)	27 (16.3%)	5 (6.4%)
18～64	4 (0.5%)	35 (21.1%)	13 (16.7%)
Missing	827 (97.5%)	103 (62.0%)	60 (76.9%)
Outcomes			
Death	64 (7.5%)	8(4.8%)	9 (11.5%)
Life-threatening	15 (1.8%)	3(1.8%)	3 (3.8%)
Hospitalization	218 (25.7%)	25(15.1%)	19(24.4%)
Disability	7 (0.8%)	2(1.2%)	2 (2.6%)
Congenital Anomaly	1 (0.1%)	0	0
Required intervention	2 (0.2%)	0	0

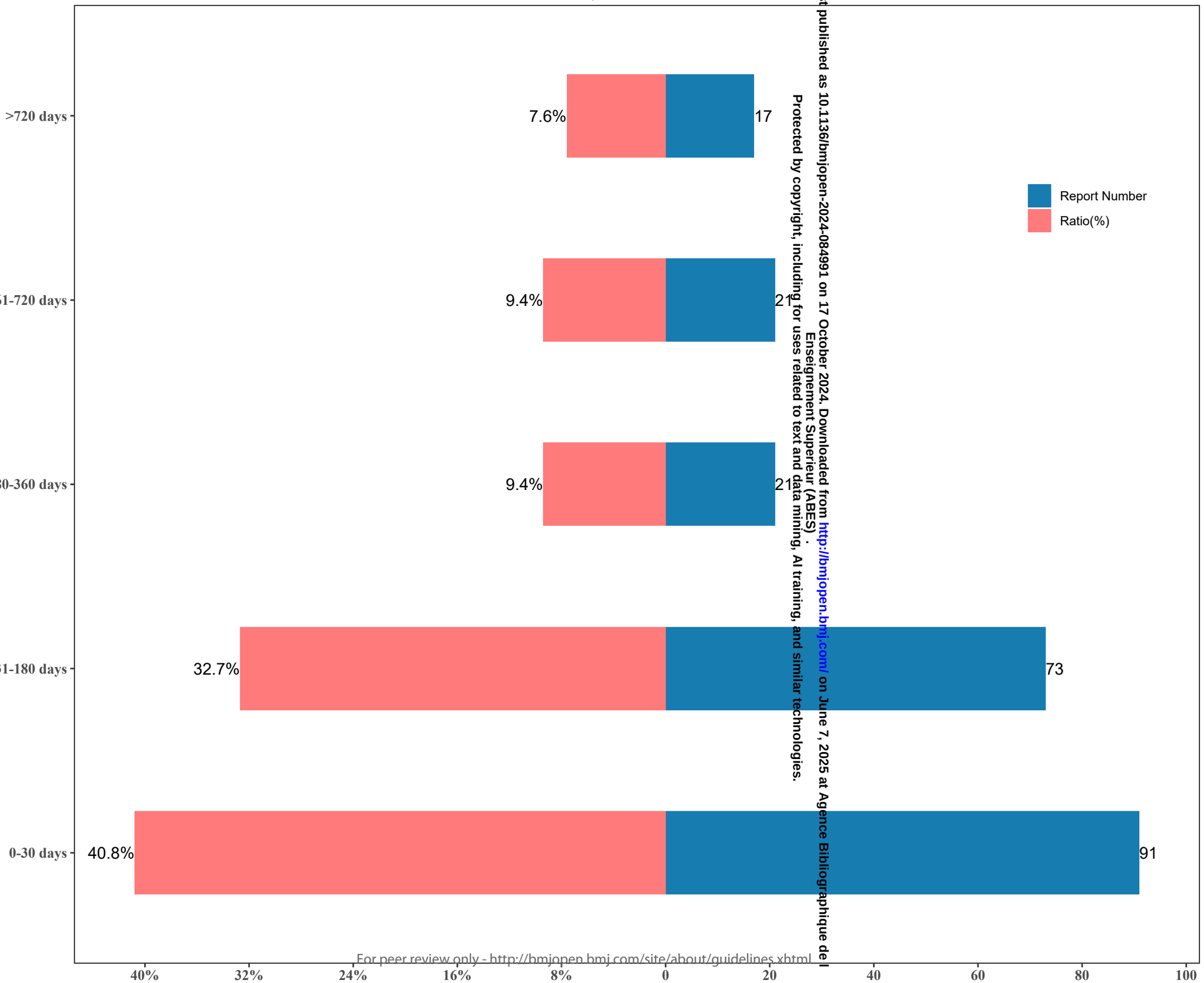
Other Serious	176 (20.8%)	96(57.8%)	19(24.4%)
Missing	365 (43.0%)	32(19.3%)	26 (27.7%)
Reporter's Occupation			
Consumer	342 (40.3%)	8 (4.8%)	7 (9.0%)
Health professional	122 (14.4%)	64 (38.6%)	46 (59.0%)
Physician	280 (33.0%)	84 (50.6%)	15 (19.2%)
Pharmacist	95 (11.2%)	9 (5.4%)	8 (10.3%)
Missing	9 (1.1%)	1 (0.6%)	2 (2.6%)
Reporter Countries			
USA	523 (61.7%)	15 (9.0%)	8 (10.3%)
China	141 (16.6%)	103 (62.0%)	42 (53.8%)
Australia	52 (6.1%)	36 (21.7%)	17 (21.8%)
Canada	29 (3.4%)	1 (0.6%)	0
Others	103 (12.2%)	11(6.7%)	11 (14.1%)

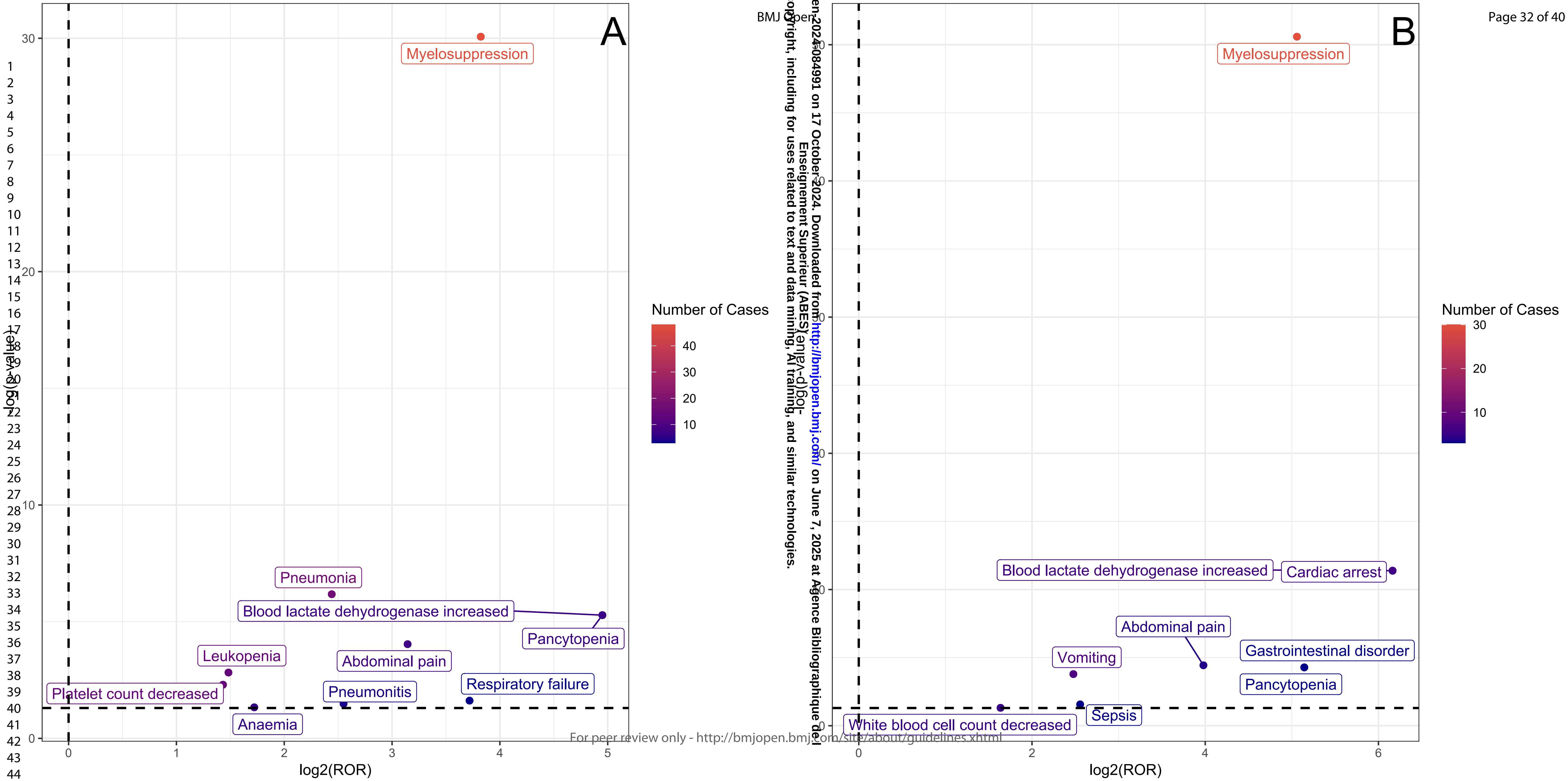
612

	SOC	N	ROR(95% CI)
1	**Injury, poisoning and procedural complications**	471	1.46(1.32-1.61)
2	General disorders and administration site conditions	390	0.74(0.67-0.83)
3	**Investigations**	244	1.51(1.32-1.72)
4	**Infections and infestations**	240	1.57(1.38-1.79)
5	**Skin and subcutaneous tissue disorders**	238	1.61(1.41-1.84)
6	Gastrointestinal disorders	222	1.01(0.88-1.16)
7	Nervous system disorders	143	0.68(0.57-0.8)
8	Respiratory, thoracic and mediastinal disorders	130	1.02(0.86-1.22)
9	**Blood and lymphatic system disorders**	129	2.78(2.33-3.32)
10	Musculoskeletal and connective tissue disorders	128	0.87(0.73-1.04)
11	**Cardiac disorders**	72	1.3(1.03-1.65)
12	Vascular disorders	60	1.15(0.89-1.48)
13	Renal and urinary disorders	53	0.97(0.74-1.28)
14	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	51	0.41(0.31-0.54)
15	Psychiatric disorders	49	0.3(0.23-0.4)
16	Surgical and medical procedures	49	1.22(0.92-1.62)
17	Metabolism and nutrition disorders	47	0.87(0.65-1.16)
18	Eye disorders	34	0.63(0.45-0.88)
19	Hepatobiliary disorders	20	0.88(0.57-1.36)
20	Ear and labyrinth disorders	15	1.3(0.78-2.16)
21	Immune system disorders	13	0.4(0.23-0.69)
22	Product issues	10	0.19(0.1-0.36)
23	Reproductive system and breast disorders	9	0.51(0.26-0.98)
24	Social circumstances	4	0.3(0.11-0.79)
25	Congenital, familial and genetic disorders	3	0.39(0.13-1.21)
26	Endocrine disorders	2	0.27(0.07-1.09)









Supplementary

Table S1. Formulas and signal detection criteria for ROR.

Formula	Signal standard
ROR = (ad/bc)	**· Lower limit of ROR95%CI>1;** **· a≥3**
$\mathbf{ROR95\%CI = e^{\ln(ROR)\pm 1.96\sqrt{(\frac{1}{a}+\frac{1}{b}+\frac{1}{c}+\frac{1}{d})}}}$	

a: number of specific adverse events to the target drug; b: number of other adverse events to the target drug; c: number of specific adverse events to background drugs; d: number of other adverse events to the background drug;

ROR: reporting odds ratio, CI: confidence interval

Table S2. All positive Preferred Terms associated with Zanubrutinib.

soc	PT	n	ROR (95%CI)
Blood and lymphatic system disorders	Myelosuppression	39	19.7 (14.4-27.1)
	Febrile neutropenia	14	4.4 (2.6-7.4)
	Neutropenia	13	1.8 (1-3)
	Increased tendency to bruise	5	13.7 (5.7-33.1)
	Haemorrhagic diathesis	4	29.7 (11.1-79.2)
	Cytopenia	4	5.2 (1.9-13.8)
	Haemolysis*	3	11.1 (3.6-34.4)
Cardiac disorders	Atrial fibrillation	21	4.9 (3.2-7.6)
	Pericardial effusion*	7	7.4 (3.5-15.5)
	Atrioventricular block	3	9.9 (3.2-30.8)
	Ventricular tachycardia	3	5 (1.6-15.5)
Ear and labyrinth disorders	Ear discomfort*	3	6.9 (2.2-21.5)
Eye disorders	Eye haemorrhage	5	9.7 (4-23.2)
Gastrointestinal disorders	Dysphagia	14	4 (2.4-6.8)
	Dyspepsia*	8	2.1 (1-4.2)
	Intestinal perforation*	4	9.5 (3.6-25.4)
	Faeces discoloured	3	3.8 (1.2-11.7)
	Haematemesis	3	3.3 (1.1-10.2)
	Tooth disorder*	3	3.2 (1-10.1)
General disorders and administration site conditions	Fatigue	50	1.4 (1-1.8)
	Asthenia	30	2 (1.4-2.9)
	Peripheral swelling	18	2 (1.3-3.2)
	Oedema peripheral	12	3.4 (1.9-5.9)
	Oedema	5	2.6 (1.1-6.3)
	Mass*	3	4.9 (1.6-15.2)
Hepatobiliary disorders	Hepatic function abnormal	5	3.2 (1.3-7.6)
Infections and infestations	Urinary tract infection	19	2.4 (1.6-3.8)
	Infection	15	2.2 (1.3-3.6)
	Cellulitis	10	4.8 (2.6-8.9)
	Sepsis	9	2 (1-3.8)
	Pneumonia fungal	6	23.7 (10.6-53)
	Hepatitis B	4	21.8 (8.2-58.3)
	Meningitis cryptococcal	3	40.1 (12.9-124.9)
	Hepatitis b reactivation	3	13.1 (4.2-40.7)
	Pneumocystis jirovecii pneumonia	3	5.5 (1.8-17.2)
	Skin infection	3	5.4 (1.7-16.8)
Injury, poisoning and procedural complications	Contusion	68	17.2 (13.5-21.9)
	Subdural haematoma	5	9.7 (4-23.4)
Investigations	Platelet count decreased	29	5.7 (4-8.3)
	White blood cell count decreased	24	4.4 (2.9-6.6)

	White blood cell count increased	22	16.1 (10.6-24.5)
	Haemoglobin decreased	14	3.4 (2-5.8)
	Blood urine present	9	12.7 (6.6-24.4)
	Blood creatinine increased	8	3 (1.5-6.1)
	Red blood cell count decreased	6	4.4 (2-9.7)
	Haemoglobin abnormal	3	9.5 (3.1-29.6)
	Blood iron decreased*	3	4.7 (1.5-14.7)
Metabolism and nutrition disorders	Tumour lysis syndrome	5	11.1 (4.6-26.8)
	Hypernatraemia*	3	15 (4.8-46.6)
	Increased appetite*	3	4.7 (1.5-14.7)
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	4	2.8 (1.1-7.6)
	Haemarthrosis	3	4.7 (1.5-14.7)
Nervous system disorders	Hypersomnia*	4	3.3 (1.2-8.8)
	Haemorrhage intracranial	3	6.3 (2-19.6)
Renal and urinary disorders	Haematuria	8	5.9 (3-11.9)
	Dysuria	5	3.5 (1.4-8.3)
Reproductive system and breast disorders	Penile haemorrhage	3	112.6 (35.9-352.6)
Respiratory, thoracic and mediastinal disorders	Pleural effusion	14	6.2 (3.7-10.5)
	Epistaxis	8	2.7 (1.3-5.4)
	Sinus disorder	4	4.4 (1.6-11.7)
Skin and subcutaneous tissue disorders	Rash	48	2.4 (1.8-3.2)
	Haemorrhage subcutaneous	25	190.8 (128-284.5)
	Petechiae	16	40.7 (24.8-66.5)
	Skin discolouration*	10	5.1 (2.7-9.5)
	Rash macular	9	5.8 (3-11.2)
	Ecchymosis	8	34.6 (17.3-69.4)
	Night sweats	6	4.5 (2-10)
	Rash pruritic	6	2.8 (1.2-6.2)
	Blood blister	5	40.3 (16.7-97.2)
	Skin lesion	4	3.1 (1.2-8.4)
	Purpura	3	10 (3.2-31.1)
	Hair texture abnormal*	3	4.9 (1.6-15.2)
	Skin haemorrhage	3	4.6 (1.5-14.3)
Vascular disorders	Haemorrhage	18	4.4 (2.7-6.9)

* unexpected adverse event

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval.

Table S3. Subgroup Disproportionality Analysis by Indications

PT	n	ROR (95%CI)
Mantle cell lymphoma		
Haemorrhage subcutaneous	4	32.2 (9.4-110.3)
Chest pain	5	7.6 (3.0-19.5)
White blood cell count increased	4	7.0 (2.5-20.0)
Myelosuppression	6	5.1 (2.2-11.9)
Contusion	8	4.8 (2.3-9.9)
Pain	6	4.2 (1.8-9.6)
Dizziness	7	4.1 (1.9-8.9)
Oedema peripheral	3	3.7 (1.1-11.8)
Dyspnoea	11	3.6 (2.0-6.7)
Peripheral swelling	5	3.5 (1.4-8.6)
Platelet count decreased	10	3.2 (1.7-6.0)
Asthenia	7	2.7 (1.3-5.9)
Nausea	7	2.7 (1.2-5.7)
Rash	11	2.6 (1.4-4.8)
Chronic lymphocytic leukemia or small lymphocytic lymphoma		
Haemorrhage subcutaneous	8	41.3 (19.0-89.6)
Atrioventricular block	3	26.7 (7.9-90.4)
Skin infection	3	6.9 (2.2-21.8)
Haematochezia	3	6.0 (1.9-19.1)
Blood creatinine increased	5	6.0 (2.4-14.6)
Petechiae	4	4.0 (1.5-10.8)
Erythema	6	3.7 (1.6-8.3)
Rash pruritic	3	3.5 (1.1-11.1)
Pericardial effusion	3	3.5 (1.1-10.8)
Contusion	21	3.4 (2.2-5.3)
Visual impairment	3	3.4 (1.1-10.5)
Skin discolouration	3	3.2 (1.0-9.9)
Anxiety	5	3.1 (1.3-7.6)
Dehydration	6	3.1 (1.4-6.9)
Cardiac failure	4	3.0 (1.1-8.1)
White blood cell count increased	13	2.9 (1.7-5.1)
Abdominal discomfort	5	2.9 (1.2-7.0)
Waldenström's macroglobulinemia		
Haemorrhage subcutaneous	8	46.6 (12.3-175.9)
Drug-induced liver injury	3	10.4 (2.5-43.6)
Petechiae	8	8.7 (3.7-20.5)
Vertigo	3	8.7 (2.2-34.8)
Eye haemorrhage	4	7.7 (2.4-25.1)
Blood urine present	4	6.3 (2.0-19.9)
Blood blister	4	5.8 (1.9-18.0)

Sinus disorder	3	5.8 (1.6-21.4)
Depressed mood	3	5.2 (1.4-19.0)
Gait inability	3	4.7 (1.3-17.0)
Cellulitis	4	4.3 (1.5-13.0)
Gastroesophageal reflux disease	4	4.3 (1.5-13.0)
Musculoskeletal stiffness	3	4.3 (1.2-15.4)
Night sweats	3	3.7 (1.1-13.0)
Erythema	5	3.6 (1.4-9.5)
Rash	18	3.4 (2.0-5.6)
Abdominal discomfort	4	3.3 (1.1-9.7)
Contusion	25	3.0 (1.9-4.6)
Pruritus	7	2.8 (1.3-6.3)

Table S4. Subgroup Disproportionality Analysis Results in the United States and China

PT	n	ROR (95%CI)
United States		
Haemorrhage subcutaneous	18	601.7 (369.4-980.3)
Penile haemorrhage	3	176.1 (55.7-556.1)
Petechiae	16	87.7 (53.4-143.9)
Ecchymosis	6	62.3 (27.8-139.4)
Haemorrhagic diathesis	4	51.1 (19.1-136.8)
Hypernatraemia	3	44.8 (14.4-139.8)
Blood blister	5	44.8 (18.6-108.1)
Pneumonia fungal	3	30.1 (9.7-93.8)
Procedural haemorrhage	3	22.7 (7.3-70.5)
Contusion	67	21.6 (17.0-27.6)
Blood urine present	9	16.5 (8.6-31.9)
White blood cell count increased	13	15.8 (9.2-27.3)
Eye haemorrhage	5	15.2 (6.3-36.7)
Increased tendency to bruise	5	13.5 (5.6-32.6)
Subdural haematoma	3	10.7 (3.5-33.3)
Ear discomfort	3	8.4 (2.7-26.0)
Haematuria	6	8.3 (3.7-18.4)

Cardiac operation	3	8.2 (2.7-25.5)
Skin infection	3	8.1 (2.6-25.3)
Platelet count decreased	22	7.2 (4.7-10.9)
Mass	3	7.1 (2.3-22.0)
Blood iron decreased	3	6.6 (2.1-20.5)
Pericardial effusion	3	6.0 (1.9-18.5)
Musculoskeletal pain	4	5.9 (2.2-15.7)
Rash macular	9	5.7 (3.0-11.1)
Faeces discoloured	3	5.6 (1.8-17.4)
Night sweats	5	5.4 (2.3-13.1)
Increased appetite	3	5.4 (1.7-16.8)
Haemorrhage	16	5.3 (3.3-8.7)
Dysphagia	12	5.1 (2.9-9.0)
Oedema	5	5.0 (2.1-12.0)
Skin haemorrhage	3	5.0 (1.6-15.5)
Skin discolouration	9	4.9 (2.6-9.4)
Red blood cell count decreased	5	4.7 (2.0-11.3)
Pleural effusion	5	4.7 (2.0-11.3)
Atrial fibrillation	14	4.7 (2.8-7.9)
Sinus disorder	4	4.6 (1.7-12.2)
Haemoglobin decreased	11	4.5 (2.5-8.1)
Skin lesion	3	4.5 (1.4-13.9)
Joint injury	3	4.2 (1.4-13.2)
Oedema peripheral	7	4.1 (1.9-8.6)
Tooth disorder	3	4.0 (1.3-12.3)
Hair texture abnormal	3	3.9 (1.3-12.1)
Cellulitis	5	3.7 (1.5-8.9)
White blood cell count decreased	15	3.7 (2.2-6.1)
Hypersomnia	4	3.7 (1.4-9.8)
Localised infection	3	3.5 (1.1-10.8)
Depressed mood	5	3.4 (1.4-8.2)
Rectal haemorrhage	3	3.4 (1.1-10.6)
Dysuria	3	3.3 (1.1-10.2)
Blood creatinine increased	5	3.3 (1.4-7.8)
Neck pain	5	3.1 (1.3-7.4)
Productive cough	4	3.1 (1.2-8.2)
Rash pruritic	5	2.9 (1.2-6.9)
Stomatitis	5	2.7 (1.1-6.5)
Infection	11	2.7 (1.5-4.9)
Dyspepsia	8	2.6 (1.3-5.2)
Urinary tract infection	15	2.5 (1.5-4.2)
Neutropenia	9	2.4 (1.3-4.7)

Rash	40	2.4 (1.7-3.3)
Myalgia	10	2.4 (1.3-4.4)
Asthenia	24	2.4 (1.6-3.5)
Abdominal distension	7	2.3 (1.1-4.9)
Dehydration	8	2.2 (1.1-4.4)
Hypertension	11	2.1 (1.2-3.8)
Peripheral swelling	13	1.9 (1.1-3.3)
Fatigue	49	1.7 (1.3-2.3)
Cough	16	1.7 (1.01-2.7)
China		
Haemolysis	3	44.8 (13.8-145.0)
Hepatitis B	3	40.0 (12.4-129.1)
Tumour lysis syndrome	3	31.3 (9.8-100.3)
Haemorrhage subcutaneous	6	22.3 (9.8-50.6)
White blood cell count increased	8	19.9 (9.8-40.6)
Pericardial effusion	3	9.3 (3.0-29.1)
Peripheral swelling	3	7.9 (2.5-24.9)
Pleural effusion	5	7.5 (3.1-18.2)
Febrile neutropenia	3	6.4 (2.1-20.1)
Covid-19	3	6.0 (1.9-18.9)
Sepsis	3	5.4 (1.7-17.0)
Oedema peripheral	4	5.1 (1.9-13.7)
Interstitial lung disease	3	4.5 (1.4-14.0)
Myelosuppression	39	3.4 (2.5-4.8)

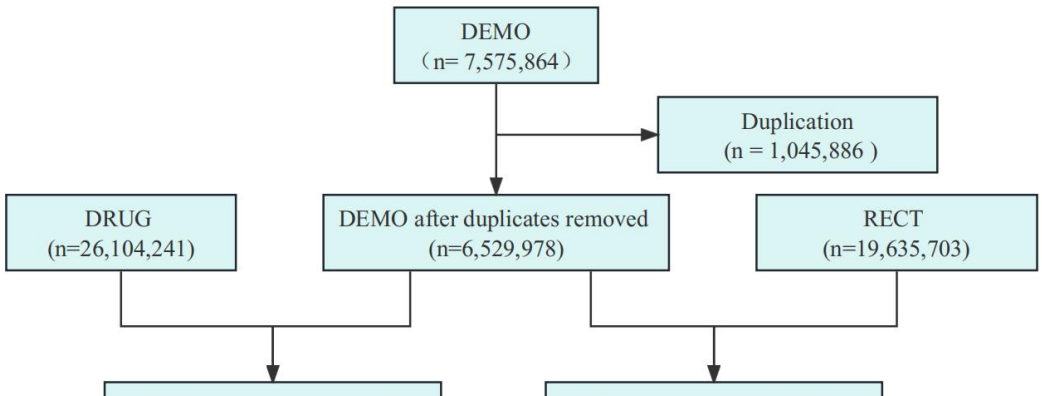


Figure S1. The flow diagram of screening zanubrutinib-related AEs from the FAERS database. DEMO, demographic and administrative information; DRUG, drug information; REAC, adverse event information; PT, preferred term.

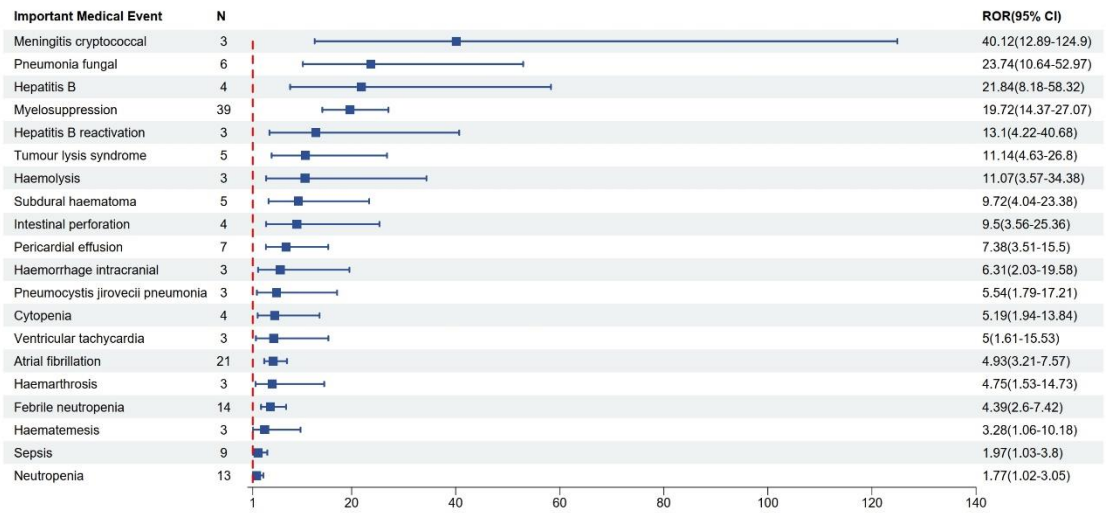


Figure S2. Forest plot of the important medical event signals for zanubrutinib. ROR, reported odds ratio; CI, confidence interval.

.