haematologica
Journal of the Ferrata Storti Foundation

Characterization of zanubrutinib safety and tolerability profile and comparison with ibrutinib safety profile in patients with B-cell malignancies: *post hoc* analysis of a large clinical trial safety database

by Jennifer R. Brown, Paolo Ghia, Wojciech Jurczak, Brad S. Kahl, Nicole Lamanna, Tadeusz Robak, Mazyar Shadman, Constantine S. Tam, Lugui Qiu, Jason Paik, Tommi Salmi, Liping Wang, Jun Zhang, Meng Zhang, Aileen Cohen, Han Ma, and Alessandra Tedeschi

Received: September 5, 2023.
Accepted: February 14, 2024.

Citation: Jennifer R. Brown, Paolo Ghia, Wojciech Jurczak, Brad S. Kahl, Nicole Lamanna, Tadeusz Robak, Mazyar Shadman, Constantine S. Tam, Lugui Qiu, Jason Paik, Tommi Salmi, Liping Wang, Jun Zhang, Meng Zhang, Aileen Cohen, Han Ma, and Alessandra Tedeschi. Characterization of zanubrutinib safety and tolerability profile and comparison with ibrutinib safety profile in patients with B-cell malignancies: post hoc analysis of a large clinical trial safety database.
Haematologica. 2024 Feb 29. doi: 10.3324/haematol.2023.283846 [Epub ahead of print]

Title

Characterization of zanubrutinib safety and tolerability profile and comparison with ibrutinib safety profile in patients with B-cell malignancies: post hoc analysis of a large clinical trial safety database

Authors

Jennifer R. Brown,[1] Paolo Ghia,[2] Wojciech Jurczak,[3] Brad S. Kahl,[4] Nicole Lamanna,[5] Tadeusz Robak,[6] Mazyar Shadman,[7] Constantine S. Tam,[8] Lugui Qiu,[9] Jason Paik,[10] Tommi Salmi,[11] Liping Wang,[12] Jun Zhang,[10] Meng Zhang,[10,a] Aileen Cohen,[10] Han Ma,[10] Alessandra Tedeschi[13]

Affiliations

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[2]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy
[3]Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland
[4]Siteman Cancer Center, Washington University School of Medicine, St Louis, MO, USA
[5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA
[6]Medical University of Łódź, Łódź, Poland
[7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA
[8]Alfred Hospital and Monash University, Melbourne, VIC, Australia
[9]State Key Laboratory of Experimental Hematology, National Clinical Medical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China
[10]BeiGene USA, Inc, San Mateo, CA, USA
[11]BeiGene International GmbH, Basel, Switzerland
[12]BeiGene (Shanghai) Co, Ltd, Shanghai, China
[13]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

[a]Affiliation at the time the analysis was conducted

Authors' contributions

JRB, PG, WJ, BSK, NL, TR, MS, CST, LQ, and AT enrolled patients, performed research, and contributed to data collection, analysis, and interpretation. JP, TS, LW, MZ, AC, and HM contributed to this study's conceptualization and design, data curation, formal analysis, data interpretation, methodology, and validation. All authors contributed to the writing, review, editing, and final approval of this manuscript.

Running title (39/50 characters)

Pooled safety analysis of zanubrutinib

Corresponding author

Jennifer R. Brown, MD, PhD
Department of Medical Oncology, Dana-Farber Cancer Institute
Boston, MA, USA
Email: Jennifer_Brown@dfci.harvard.edu

Data-sharing statement
BeiGene voluntarily shares anonymous data on completed studies responsibly and provides qualified scientific and medical researchers access to anonymous data and supporting clinical trial documentation for clinical trials in dossiers for medicines and indications after submission and approval in the United States, China, and Europe. Clinical trials supporting subsequent local approvals, new indications, or combination products are eligible for sharing once corresponding regulatory approvals are achieved. BeiGene shares data only when permitted by applicable data privacy and security laws and regulations. In addition, data can only be shared when it is feasible to do so without compromising the privacy of study participants. Qualified researchers may submit data requests/research proposals for BeiGene review and consideration through BeiGene's Clinical Trial Webpage at https://www.beigene.com/our-science-and-medicines/our-clinical-trials/.

Word counts
Text: 1499/1500
Number of tables and figures: 3/3
References: 15/15
Supplement: Yes; figures/tables: 3/3

Trial registration
ClinicalTrials.gov identifiers: NCT03189524, NCT03206918, NCT03206970, NCT03332173, NCT03846427, NCT02343120, NCT03053440, NCT03336333, NCT03734016, NCT04170283

Acknowledgments
The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers for the clinical trials included in this analysis. This analysis was sponsored by BeiGene Co, Ltd. Medical writing and editorial assistance were provided by Jenna M. Gaska, PhD, of Nucleus Global, an Inizio Company, and supported by BeiGene.

Funding statement
This work was supported by funding from BeiGene USA, Inc. Data analyses were performed by biostatisticians at BeiGene USA, Inc, and BeiGene (Beijing) China.

Authors' disclosures
JRB: Consultancy: Abbvie, Acerta/Astra-Zeneca, Alloplex Biotherapeutics, BeiGene, Galapagos NV, Genentech/Roche, Grifols Worldwide Operations, InnoCare Pharma Inc, iOnctura, Kite, Loxo/Lilly, Merck, Numab Therapeutics, Pfizer, Pharmacyclics; Research funding: BeiGene, Gilead, iOnctura, Loxo/Lilly, MEI Pharma, TG Therapeutics. **PG:** Honoraria: AbbVie, ArQule/MSD, AstraZeneca, BeiGene, Celgene/Juno/Bristol Myers Squibb, Janssen, Lilly/Loxo, MEI Pharma, Roche, Sanofi; Research funding: AbbVie, AstraZeneca, Janssen, Sunesis. **WJ:** Consultancy: Janssen, AstraZeneca, MEI Pharma, Lilly, Takeda, Roche, AbbVie, BeiGene; Research funding: AbbVie, Bayer, BeiGene, Celgene, Janssen, Roche, Takeda, TG Therapeutics, AstraZeneca, MEI Pharma, Lilly. **BSK:** Research funding: BeiGene to

Washington University School of Medicine (St Louis, MO, USA); Consulting fees: AbbVie, AstraZeneca, BeiGene, Janssen, Pharmacyclics. **NL:** Consultancy: AbbVie, AstraZeneca, BeiGene, Lilly/Loxo, Genentech, Janssen, Pharmacyclics; Research funding: AbbVie, AstraZeneca, BeiGene, Lilly/Loxo, Genentech, Octapharma, Oncternal, MingSight, TG Therapeutics. **TR:** Research funding: BeiGene, Octapharma, AstraZeneca, Janssen, Regeneron, GSK; Honoraria: AstraZeneca, BeiGene, Janssen, AbbVie, Octapharma, Regeneron, GSK; Travel, accommodations, expenses: AstraZeneca. **MS:** Consultancy: AbbVie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, BeiGene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate Therapeutics, MEI Pharma, Atara Biotherapeutic; Research funding: Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, Morphosys/Incyte, Vincerx. **CST:** Research funding: Janssen, AbbVie, BeiGene; Honoraria: Janssen, AbbVie, BeiGene, Loxo, AstraZeneca. **LQ:** Janssen, AstraZeneca, Takeda, Roche, AbbVie, BeiGene. **TS:** Employment: BeiGene Switzerland GmbH; Equity holder: BeiGene Ltd. **MZ, JP, LW, JZ, HM:** Employment: BeiGene. **AC:** Employment: BeiGene; Equity holder: BeiGene; Travel, accommodations, expenses: BeiGene. **AT:** Consultancy: BeiGene, AstraZeneca, AbbVie, Janssen; Honoraria: BeiGene, AstraZeneca, AbbVie, Janssen; Speakers bureau: BeiGene, AstraZeneca, AbbVie, Janssen; Travel, accommodations, expenses: BeiGene, AstraZeneca, AbbVie, Janssen.

Zanubrutinib is a next-generation Bruton tyrosine kinase inhibitor (BTKi) designed to minimize off-target effects associated with toxicities that have limited long-term treatment with ibrutinib, a first-generation BTKi. A previous pooled safety analysis of zanubrutinib monotherapy using data from 6 clinical trials (N=779) found that treatment was generally well tolerated,[1] with infections, hemorrhage, and neutropenia the most commonly reported categories of treatment-emergent adverse events (TEAEs) of special interest (AESIs). Rates of cardiovascular toxicities with zanubrutinib, including atrial fibrillation (afib)/flutter and hypertension, were considerably lower than those observed previously with ibrutinib. Here, we expanded on these findings and combined updated data from 6 studies examined in a prior pooled analysis[1] with data from 4 additional studies (**Online Supplementary Table S1**). A comparative analysis of zanubrutinib vs ibrutinib was also conducted using data from 2 of these 10 studies—the randomized phase 3 trials ALPINE (relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma[2,3]) and ASPEN cohort 1 (Waldenström macroglobulinemia[4]). The findings for the pooled zanubrutinib population (N=1550) were consistent with those of the prior analysis, and the comparative analysis demonstrated the favorable safety profile of zanubrutinib 160 mg twice daily (n=425) compared with ibrutinib 420 mg once daily (n=422).

Studies were approved by the independent ethics committees/institutional review boards at each participating institution and conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided written informed consent. The median age of the pooled zanubrutinib population was 66.2 years, and the majority of patients were male (66.3%) (**Table 1**). Most patients had chronic lymphocytic leukemia/small lymphocytic lymphoma (60.5%), and approximately two-thirds had relapsed/refractory disease (68.9%). In the comparative analysis using data from ALPINE[3] and ASPEN (cohort 1),[5] baseline characteristics were generally similar between zanubrutinib- and ibrutinib-treated patients.

In the total pooled zanubrutinib population, 45.0% of patients received zanubrutinib for ≥36 months (median, 34.4 months [range, 0.1-90.0 months]), and 56.5% of patients remained on zanubrutinib as of the data cutoff. In the comparative analysis, median treatment duration was 32.6 months (range, 0.4-68.7 months) for zanubrutinib vs 25.7 months (range, 0.1-59.3 months) for ibrutinib. Relative dose intensity was comparable between treatments, but a greater percentage of patients were on zanubrutinib vs ibrutinib treatment for ≥36 months (29.4% vs 25.4%; median time to discontinuation by Kaplan-Meier estimate, 63.3 vs 42.2 months). In the comparative analysis, zanubrutinib-treated patients were more likely to still be on treatment at data cutoff than those treated with ibrutinib (69.9% vs 45.0%).

TEAEs leading to treatment discontinuation were reported in 13.6% of patients in the total pooled zanubrutinib population (**Online Supplementary Table S2**). In the comparative analysis, TEAEs leading to treatment discontinuation were less common with zanubrutinib vs ibrutinib (14.1% vs 22.0%). Infections were the most common TEAEs leading to treatment discontinuation in the pooled zanubrutinib and comparative analysis populations (total zanubrutinib, 4.5%; ASPEN/ALPINE zanubrutinib, 5.4%; ASPEN/ALPINE ibrutinib, 6.6%). In the comparative analysis, ibrutinib-treated patients were more likely than zanubrutinib-treated patients to experience cardiac disorders (MedDRA system organ class) TEAEs that led to

discontinuation (4.3% [n=18; most common, afib, n=7] vs 0.5% [n=2; cardiomegaly and ventricular extrasystoles, each n=1]).

Deaths attributed to TEAEs occurred in 7.3% of patients in the total pooled zanubrutinib population and 8.7% and 10.2% of patients treated with zanubrutinib and ibrutinib, respectively, in the comparative analysis (**Online Supplementary Table S2**). Infections were the most common TEAEs leading to death (total pooled zanubrutinib, 3.7%; ASPEN/ALPINE zanubrutinib, 5.2%; ASPEN/ALPINE ibrutinib, 6.2%). Cardiac disorder-TEAEs leading to death occurred in 7 patients (1.7%) treated with ibrutinib vs 1 patient (0.2%) treated with zanubrutinib (see footnotes to **Online Supplementary Table S2**).

In this pooled analysis, 97.9% of patients who received zanubrutinib monotherapy had ≥1 TEAE (grade ≥3, 66.9%), and 49.2% had serious TEAEs (**Online Supplementary Table S2**). TEAEs considered treatment related by the investigator were reported in 79.4% of patients (grade ≥3, 35.7%). The most common (any grade in ≥10% of patients; grade ≥3 in ≥5%) nonhematologic TEAEs reported are shown in **Figure 1A**. No grade ≥3 nonhematologic TEAEs were reported in ≥10% of patients; the most common were pneumonia (8.4%; treatment related, 4.1%) and hypertension (8.1%; treatment related, 3.4%). Pneumonia (8.2%) was the only serious TEAE in ≥5% of patients. In summary, these findings were consistent with those for the prior pooled safety analysis,[1] even with a median treatment duration ≈9 months longer.

Select TEAE preferred terms were grouped as AESIs ("opportunistic infections" included preferred terms under the narrow standardized MedDRA query "opportunistic infections"; for all other AESI preferred terms, see Tam et al[1]). To account for differing treatment exposures across the trials, exposure-adjusted incidence rates (EAIRs) of these AESIs were determined for the total pooled zanubrutinib population (**Figure 1B;** see legend for EAIR calculation and assumption) and comparative analysis populations (**Figure 1C**).

Infections, hemorrhage, and neutropenia were the most frequently reported AESIs in the total pooled zanubrutinib population, even after adjusting for dose exposure (**Figure 1B**). Despite a longer median treatment duration, the EAIRs of the cardiovascular AESIs were comparable to those of the earlier analysis (hypertension, 6.81 in the present analysis vs 6.87 persons per 100 person-years [PY] in Tam et al[1]; afib/flutter, 1.74 vs 1.45 persons per 100 PY, respectively). ALPINE had a greater hypertension EAIR than SEQUOIA and ASPEN; exclusion of data from ALPINE decreased the hypertension EAIR to 5.73 persons per 100 PY. In ALPINE, the hypertension rate was similar between the zanubrutinib and ibrutinib arms; however, the incidence of cardiac disorders such as afib/flutter was higher in the ibrutinib arm,[3] whereas incidence in the zanubrutinib arm remained low and comparable to that observed in SEQUOIA and ASPEN. Importantly, across all 10 trials, no zanubrutinib-treated patients discontinued due to hypertension.

In the comparative analysis, all EAIRs of AESIs, except for neutropenia, were numerically lower in patients treated with zanubrutinib vs ibrutinib (**Figure 1C**). Although the neutropenia EAIR was slightly higher with zanubrutinib, the infection EAIR was significantly lower (64.81 vs 79.63 persons per 100 PY; *P*=.0098) with zanubrutinib, even after excluding COVID-19–related infection terms (54.48 vs 69.96 persons per 100 PY; *P*=.0029). The EAIR for afib/flutter was

also significantly lower with zanubrutinib vs ibrutinib (*P*<.0001). The hypertension EAIR was also reduced in patients receiving zanubrutinib vs ibrutinib (*P*=.0610).

AESI EAIRs analyzed over time were relatively constant or decreased with zanubrutinib (**Figure 2;** time to first event data, **Online Supplementary Figure S1**). In the comparative analysis, AESI EAIRs over time were numerically lower with zanubrutinib vs ibrutinib, except for neutropenia, which was higher in the first 12 months of treatment and is considered an on-target effect of BTK inhibition.[6] However, this was not accompanied by an elevated infection EAIR nor was neutropenia a substantial cause of discontinuation (7.1% [3/42]). Increases of >10 persons per 100 PY in the EAIRs for anemia and hemorrhage were observed with ibrutinib between the >24-month exposure intervals. In contrast, the greatest increase between consecutive intervals with zanubrutinib was 4.1 persons per 100 PY (hemorrhage).

At all treatment intervals evaluated, the EAIR for afib/flutter was 6.7 to 13.6 persons per 100 PY higher with ibrutinib than with zanubrutinib. In the present analysis, the afib/flutter EAIR was relatively constant in the first 2 years of ibrutinib exposure but steadily increased with each subsequent year of treatment. In contrast, the EAIR in patients who received zanubrutinib was much lower at all intervals, with only slight increases observed after 2 to 3 years of exposure. This relatively stable incidence of afib/flutter with zanubrutinib, despite extended exposure, is important for long-term treatment. Additionally, a lower incidence of afib may minimize the need for supportive care (eg, anticoagulants, antiplatelet agents) that can further increase the bleeding risk associated with BTKis. Finally, although hypertension in patients receiving ibrutinib has been associated with increased incidence of major cardiovascular AEs,[7] the incidence of cardiac disorder TEAEs was comparable for zanubrutinib across ALPINE, ASPEN, and SEQUOIA despite the higher hypertension EAIR observed in ALPINE.

Due to the continuous dosing of BTKi in most B-cell malignancies, low treatment discontinuation rates and long-term tolerability are key considerations, particularly in patients with B-cell malignancies such as chronic lymphocytic leukemia/small lymphocytic lymphoma who tend to be aged >65 years and have other (eg, cardiovascular) comorbidities.[8,9] The first-in-class BTKi ibrutinib has drastically improved treatment of numerous B-cell malignancies, but cardiac arrhythmias and their associated outcomes are a frequently cited concern[10-12] and are possibly due to off-target inhibition of kinases such as TEC and CSK.[13,14] Such toxicities can limit the duration and, consequently, the benefit[15] of treatment. Zanubrutinib was designed with greater selectivity to minimize off-target effects. In this analysis, zanubrutinib remained well tolerated, consistent with the previous analysis,[1] with no emergence of new safety signals, even at a median treatment duration of approximately 3 years. In the comparative analysis, zanubrutinib exhibited a more favorable safety profile than ibrutinib, as demonstrated by the longer median treatment duration and lower frequency of TEAEs, including cardiac disorders, that led to treatment discontinuation or death. These analyses support zanubrutinib as an appropriate long-term treatment option for patients with B-cell malignancies.

References

1. Tam CS, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. Blood Adv. 2022;6(4):1296-1308.
2. 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. J Clin Oncol. 2023;41(5):1035-1045.
3. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023;388(4):319-332.
4. Tam CS, Garcia-Sanz R, Opat S, et al. ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia. J Clin Oncol. 2022;40(s16):7521.
5. 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. 2020;136(18):2038-2050.
6. Honda F, Kano H, Kanegane H, et al. The kinase Btk negatively regulates the production of reactive oxygen species and stimulation-induced apoptosis in human neutrophils. Nat Immunol. 2012;13(4):369-378.
7. Estupiñán HY, Berglof A, Zain R, et al. Comparative analysis of BTK inhibitors and mechanisms underlying adverse effects. Front Cell Dev Biol. 2021;9:630942.
8. Thandra KC, Barsouk A, Saginala K, et al. Epidemiology of non-Hodgkin's lymphoma. Med Sci (Basel). 2021;9(1):5.
9. Hester LL, Park SI, Wood WA, et al. Cause-specific mortality among Medicare beneficiaries with newly diagnosed non-Hodgkin lymphoma subtypes. Cancer. 2019;125(7):1101-1112.
10. Coutre SE, Byrd JC, Hillmen P, et al. Long-term safety of single-agent ibrutinib in patients with chronic lymphocytic leukemia in 3 pivotal studies. Blood Adv. 2019;3(12):1799-1807.
11. Gordon MJ, Jones JE, George B, et al. Long-term outcomes in patients with chronic lymphocytic leukemia treated with ibrutinib: focus on hypertension and cardiovascular toxicity. Cancer. 2023;129(14):2192-2200.
12. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. Haematologica. 2017;102(10):1796-1805.
13. Fleming MR, Xiao L, Jackson KD, et al. Vascular impact of cancer therapies: the case of BTK (Bruton tyrosine kinase) inhibitors. Circ Res. 2021;128(12):1973-1987.
14. McMullen JR, Boey EJ, Ooi JY, et al. Ibrutinib increases the risk of atrial fibrillation, potentially through inhibition of cardiac PI3K-Akt signaling. Blood. 2014;124(25):3829-3830.
15. Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. Blood. 2017;129(19):2612-2615.

Table 1. Demographics and baseline characteristics

	All zanubrutinib (N=1550)	Comparative analysis	
		Zanubrutinib (n=425)[a]	Ibrutinib (n=422)[b]
Age, median (range), years	67.0 (20-95)	68.0 (35-90)	68.0 (35-90)
<65 years, n (%)	600 (38.7)	160 (37.6)	148 (35.1)
≥65 to <75 years, n (%)	615 (39.7)	155 (36.5)	181 (42.9)
≥75 years, n (%)	335 (21.6)	110 (25.9)	93 (22.0)
Sex, n (%)			
Male	1027 (66.3)	280 (65.9)	295 (69.9)
Female	523 (33.7)	145 (34.1)	127 (30.1)
Race, n (%)			
White	1032 (66.6)	348 (81.9)	357 (84.6)
Asian	424 (27.4)	49 (11.5)	44 (10.4)
Other	51 (3.3)	11 (2.6)	4 (0.9)
Not reported or missing	43 (2.8)	17 (4.0)	17 (4.0)
Geographic region, n (%)[c]			
Europe	551 (35.5)	259 (60.9)	250 (59.2)
Australia/New Zealand	414 (26.7)	60 (14.1)	60 (14.2)
Asia	406 (26.2)	45 (10.6)	43 (10.2)
North America	179 (11.5)	61 (14.4)	69 (16.4)
ECOG performance status, n (%)			
0	692 (44.6)	174 (40.9)	164 (38.9)
1	763 (49.2)	239 (56.2)	238 (56.4)
2	95 (6.1)	12 (2.8)	20 (4.7)
Diagnosis, n (%)			
CLL/SLL	938 (60.5)	324 (76.2)	324 (76.8)
Mantle cell lymphoma	140 (9.0)	0	0
Waldenström macroglobulinemia	249 (16.1)	101 (23.8)	98 (23.2)
Marginal zone lymphoma	93 (6.0)	0	0
Follicular lymphoma	59 (3.8)	0	0
Diffuse large B-cell lymphoma	45 (2.9)	0	0
Other[d]	26 (1.7)	0	0
Prior treatment status, n (%)			
Treatment naive	482 (31.1)	19 (4.5)[e]	18 (4.3)[e]
Relapsed/refractory	1068 (68.9)	406 (95.5)	404 (95.7)
No. of prior lines of therapy, n (%)			
0	482 (31.1)	19 (4.5)[e]	18 (4.3)[e]
1	496 (32.0)	237 (55.8)	231 (54.7)
2	275 (17.7)	99 (23.3)	86 (20.4)
≥3	297 (19.2)	70 (16.5)	87 (20.6)

Medical history, n (%)[f]			
History of cardiac disorders[g]	368 (24.9)	117 (28.6)	116 (28.2)
History of atrial fibrillation and flutter[h]	101 (6.8)	29 (7.1)	26 (6.3)
History of hypertension[h]	651 (44.1)	198 (48.4)	201 (48.9)
History of skin cancer[h]	20 (1.4)	1 (0.2)	2 (0.5)
Concomitant medications, n (%)[i]			
Antithrombotic agents[j]	413 (26.6)	126 (29.6)	138 (32.7)

CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; ECOG, Eastern Cooperative Oncology Group. [a] Includes patients with Waldenström macroglobulinemia from ASPEN cohort 1 (n=101) and patients with CLL/SLL from ALPINE (n=324). [b] Includes patients with Waldenström macroglobulinemia from ASPEN cohort 1 (n=98) and patients with CLL/SLL from ALPINE (n=324). [c] Location of study site enrollment. Asia includes China (Mainland and Taiwan) and South Korea; Europe includes Austria, Belgium, Belarus, Bulgaria, Czech Republic, France, Germany, Greece, Italy, the Netherlands, the Russian Federation, Poland, Spain, Sweden, Turkey, and the United Kingdom; and North America includes the United States and Canada. [d] Includes patients with Richter transformation (n=13), hairy cell leukemia (n=11), B-lineage lymphoma (n=1), and indolent lymphoma (n=1). [e] Patients with Waldenström macroglobulinemia from ASPEN cohort 1. [f] Percentages are expressed using the number of patients with available medical history (all zanubrutinib, n=1477; ASPEN/ALPINE zanubrutinib, n=409; ASPEN/ALPINE ibrutinib, n=411). [g] System organ class. [h] Individual preferred term. [i] Concomitant medications are defined as medications that started before the first dose of study treatment and were continuing at the time of the first dose of study treatment or started on or after the date of the first dose of zanubrutinib treatment up to the last zanubrutinib dose date + 30 days or initiation of a new anticancer therapy. Patients with >1 medication within a class level and preferred name were counted only once within that class level and preferred name. Medication class was designated per the Anatomical Therapeutic Chemical classification system. [j] Excluding acetylsalicylic acid.

Figure Legends

Figure 1. Incidence of any-grade nonhematologic TEAEs and EAIRS of AESIs. (A) TEAEs reported in ≥10% or grade ≥3 TEAEs in ≥5% of patients treated with zanubrutinib (N=1550) are shown. TEAEs were defined as AE preferred terms with an onset date or worsening in severity from baseline (prior to treatment) at or after the first dose of zanubrutinib and up to the last zanubrutinib dose date + 30 days or initiation of new anticancer therapy, whichever occurred first. Worsening of an event to grade 5 beyond the last zanubrutinib dose date + 30 days and prior to initiation of new anticancer therapy was also considered treatment emergent. (B-C) The AESIs shown are grouped terms. The preferred terms for the TEAEs included in each AESI category are as previously published,[1] except for "opportunistic infections," which included preferred terms under the narrow standardized MedDRA query "opportunistic infections." EAIRs were calculated as the number of patients who experienced a specific AESI divided by the total exposure time (ie, the first dose date to the first event date or to the treatment-emergent period end date if there was no event) in years for all patients and then multiplied by 100 to express as persons per 100 person-years. Of note, EAIR assumes that the risk of an event occurring is constant over time and serves as an additional means for evaluating safety events. In (B), data are shown for the total pooled zanubrutinib population (N=1550). In (C), data are shown for the comparative analysis of patients treated with zanubrutinib (n=425) or ibrutinib (n=422) as part of the randomized studies ASPEN (cohort 1) or ALPINE. The Poisson regression model was used to compare EAIRs between treatment groups, with the number of patients who experienced events as the dependent variable and log(exposure time) as the offset. The *P* value based on chi-square test was reported. All statistical tests were 2-sided, with $P<.05$ considered significant; no adjustments for multiple comparisons were made.
AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; EAIR, exposure-adjusted incidence rate; TEAE, treatment-emergent adverse event.

Figure 2. EAIRs of select AESIs over time. AESIs are grouped terms as defined in the legend for Figure 1. EAIRs at each time interval were calculated as the number of patients who experienced a specific AESI during that time interval divided by the total exposure time in years at the corresponding time interval. This value was then multiplied by 100 to express as persons per 100 person-years. Data are shown for the total pooled zanubrutinib population (N=1550) and the comparative analysis patient populations (patients treated with zanubrutinib [n=425] or ibrutinib [n=422] as part of the randomized studies ASPEN cohort 1 or ALPINE; each treatment group is labeled as ASPEN/ALPINE).
AESI, adverse event of special interest; EAIR, exposure-adjusted incidence rate; PY, person-years.

Figure 1.

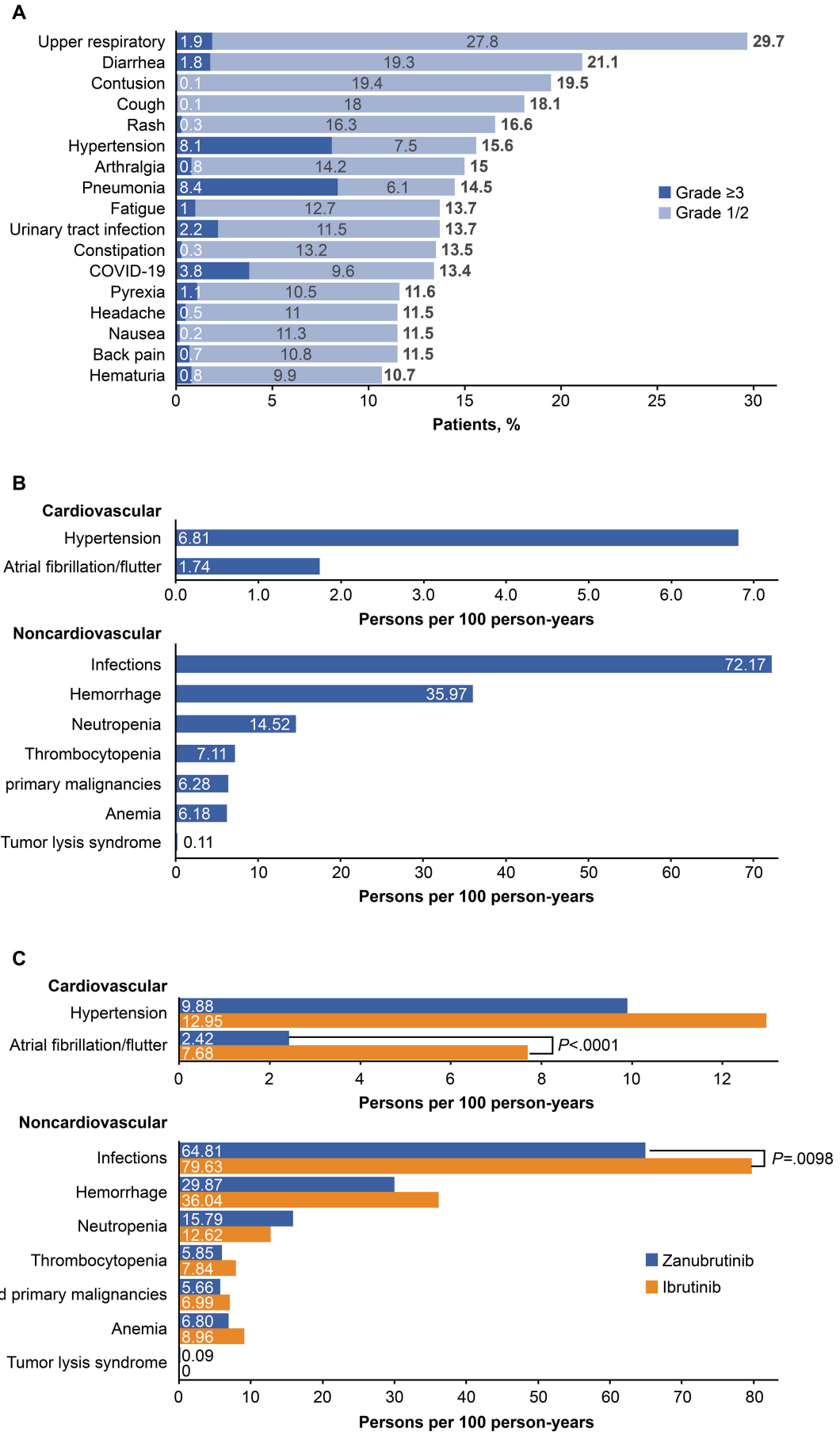
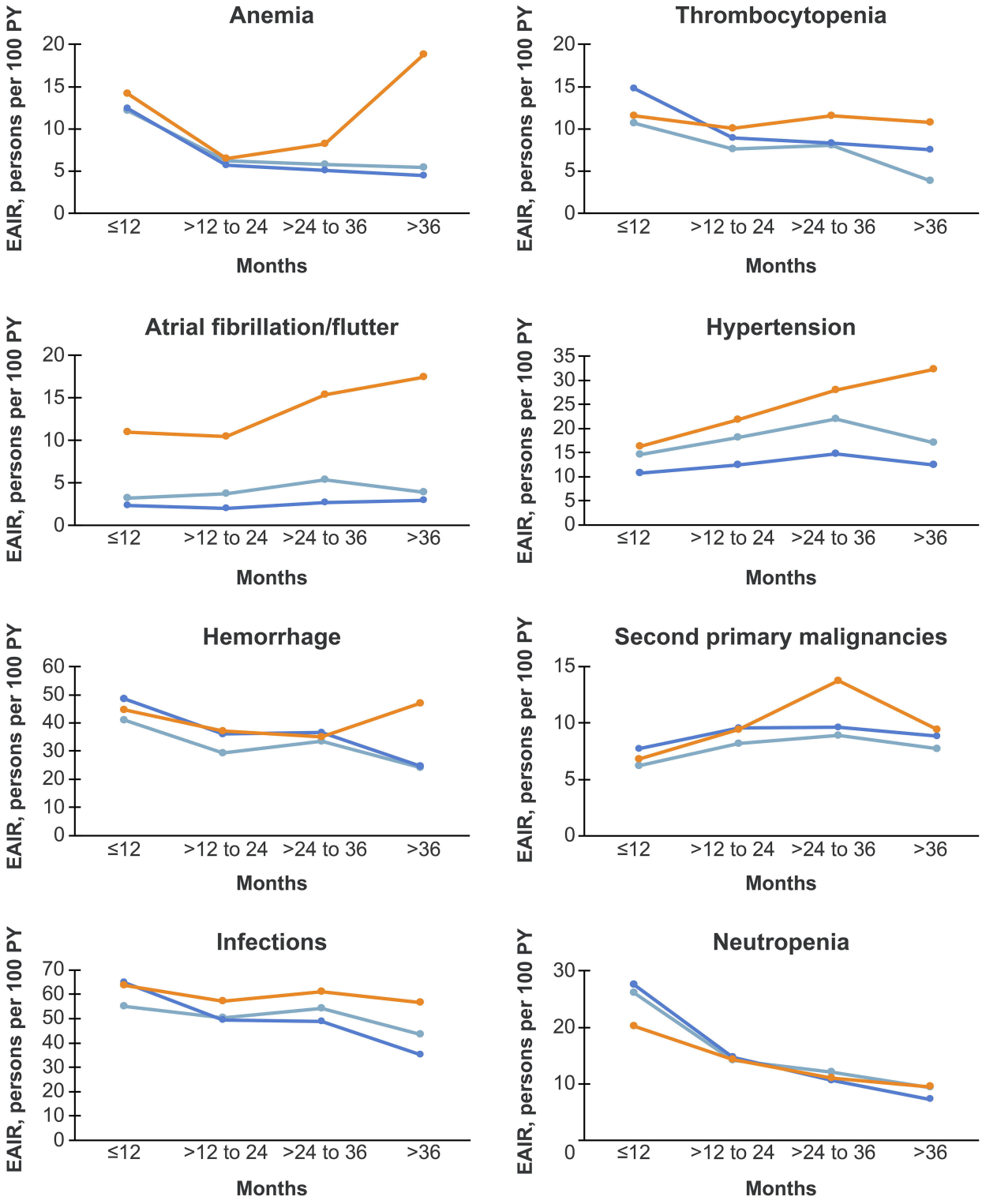

A
Upper respiratory 1.9 27.8 29.7
Diarrhea 1.8 19.3 21.1
Contusion 0.1 19.4 19.5
Cough 0.1 18 18.1
Rash 0.3 16.3 16.6
Hypertension 8.1 7.5 15.6
Arthralgia 0.8 14.2 15
Pneumonia 8.4 6.1 14.5
Fatigue 1 12.7 13.7
Urinary tract infection 2.2 11.5 13.7
Constipation 0.3 13.2 13.5
COVID-19 3.8 9.6 13.4
Pyrexia 1.1 10.5 11.6
Headache 0.5 11 11.5
Nausea 0.2 11.3 11.5
Back pain 0.7 10.8 11.5
Hematuria 0.8 9.9 10.7
Grade ≥3
Grade 1/2
0 5 10 15 20 25 30
Patients, %
B
Cardiovascular
Hypertension 6.81
Atrial fibrillation/flutter 1.74
0.0 1.0 2.0 3.0 4.0 5.0 6.0 7.0
Persons per 100 person-years
Noncardiovascular
Infections 72.17
Hemorrhage 35.97
Neutropenia 14.52
Thrombocytopenia 7.11
Second primary malignancies 6.28
Anemia 6.18
Tumor lysis syndrome 0.11
0 10 20 30 40 50 60 70
Persons per 100 person-years
C
Cardiovascular
Hypertension 9.88 12.95
Atrial fibrillation/flutter 2.42 7.68 P<.0001
0 2 4 6 8 10 12
Persons per 100 person-years
Noncardiovascular
Infections 64.81 79.63 P=.0098
Hemorrhage 29.87 36.04
Neutropenia 15.79 12.62
Thrombocytopenia 5.85 7.84
Second primary malignancies 5.66 6.99
Anemia 6.80 8.96
Tumor lysis syndrome 0.09 0
Zanubrutinib
Ibrutinib
0 10 20 30 40 50 60 70 80
Persons per 100 person-years

Figure 2.



No. at risk (person-years at risk)

All zanubrutinib (N=1550)	1550 (1399.9)	1282 (1179.0)	1040 (912.0)	698 (913.8)		1550 (1399.9)	1282 (1179.0)	1040 (912.0)	698 (913.8)
Zanubrutinib in ASPEN/ALPINE (n=425)	425 (403.0)	384 (353.1)	288 (223.9)	125 (129.1)		425 (403.0)	384 (353.1)	288 (223.9)	125 (129.1)
Ibrutinib in ASPEN/ALPINE (n=422)	422 (381.8)	348 (306.8)	240 (182.1)	107 (74.4)		422 (381.8)	348 (306.8)	240 (182.1)	107 (74.4)

SUPPLEMENTARY INFORMATION

Title

Characterization of zanubrutinib safety and tolerability profile and comparison with ibrutinib safety profile in patients with B-cell malignancies: post hoc analysis of a large clinical trial safety database

Authors

Jennifer R. Brown,[1] Paolo Ghia,[2] Wojciech Jurczak,[3] Brad S. Kahl,[4] Nicole Lamanna,[5] Tadeusz Robak,[6] Mazyar Shadman,[7] Constantine S. Tam,[8] Lugui Qiu,[9] Jason Paik,[10] Tommi Salmi,[11] Liping Wang,[12] Jun Zhang,[10] Meng Zhang,[10,a] Aileen Cohen,[10] Han Ma,[10] Alessandra Tedeschi[13]

Affiliations

[1]Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, MA, USA
[2]Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy
[3]Maria Skłodowska-Curie National Research Institute of Oncology, Kraków, Poland
[4]Siteman Cancer Center, Washington University School of Medicine, St Louis, MO, USA
[5]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY, USA
[6]Medical University of Łódź, Łódź, Poland
[7]Fred Hutchinson Cancer Center, Seattle, WA, USA
[8]Alfred Hospital and Monash University, Melbourne, VIC, Australia
[9]State Key Laboratory of Experimental Hematology, National Clinical Medical Research Center for Blood Diseases, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Tianjin, China
[10]BeiGene USA, Inc, San Mateo, CA, USA
[11]BeiGene International GmbH, Basel, Switzerland
[12]BeiGene (Shanghai) Co, Ltd, Shanghai, China
[13]ASST Grande Ospedale Metropolitano Niguarda, Milan, Italy

[a]Affiliation at the time the analysis was conducted

Online Supplementary Table S1. Clinical trial patients included in the analysis

Clinical trial	NCT number	Phase	Disease state	Study drug[a]	Dose	Patients, n	Location	Data cutoff
BGB-3111-1002[1,b]	03189524	1	R/R B-cell malignancies (CLL/SLL, MCL, WM, FL, MZL)	Zanubrutinib	160 mg BID 320 mg QD	34 10	China	Aug 30, 2020
BGB-3111-205[2,b]	03206918	2	R/R CLL/SLL	Zanubrutinib	160 mg BID	91	China	Sep 11, 2020
BGB-3111-206[3-5,b]	03206970	2	R/R MCL	Zanubrutinib	160 mg BID	86	China	Sep 8, 2020
BGB-3111-210[6,b]	03332173	2	WM	Zanubrutinib	160 mg BID	44	China	Jan 11, 2021
BGB-3111-214	03846427	2	MZL	Zanubrutinib	160 mg BID	68	Global	May 4, 2022
BGB-3111-AU-003[7-11,b]	02343120	1/2	B-cell malignancies (CLL/SLL, WM, MCL, MZL, FL, DLBCL, RT, HCL)	Zanubrutinib	160 mg BID 320 mg QD	278 95	Global	Mar 31, 2021
BGB-3111-302 (ASPEN)[12,13,b]	03053440	3	WM	Zanubrutinib Ibrutinib	160 mg BID 420 mg QD	129[c] 98	Global	Jun 21, 2022
BGB-3111-304 (SEQUOIA)[14,15]	03336333	3	TN CLL/SLL	Zanubrutinib	160 mg BID	391	Global	Mar 7, 2022
BGB-3111-305 (ALPINE)[16,17]	03734016	3	R/R CLL/SLL	Zanubrutinib Ibrutinib	160 mg BID 420 mg QD	324 324	Global	Aug 8, 2022
BGB-3111-LTE1[d]	04170283	3	B-cell malignancies (enrolled in a BeiGene parent study)	Zanubrutinib	160 mg BID	337	Global	Oct 17, 2022

BID, twice daily; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; HCL, hairy cell leukemia; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; QD, once daily; R/R, relapsed/refractory; RT, Richter transformation; TN, treatment naive; WM, Waldenström macroglobulinemia.
[a] Summary information shown only for patients who received zanubrutinib or ibrutinib monotherapy. [b] Data from an earlier data cutoff were included in the previous pooled safety analysis.[18]
[c] For the comparative analysis, only data from the 101 patients treated with zanubrutinib as part of cohort 1 were included. [d] The 337 patients in this long-term extension study previously participated in one of the other studies and were counted in the parent studies.

Online Supplementary Table S2. Summary of TEAEs and AESIs

Patients, n (%)	All zanubrutinib (N=1550)	Comparative analysis (ASPEN cohort 1 and ALPINE)	
		Zanubrutinib (n=425)	Ibrutinib (n=422)
Patients with ≥1 TEAE			
Any grade	1518 (97.9)	419 (98.6)	419 (99.3)
Grade ≥3	1037 (66.9)	295 (69.4)	300 (71.1)
Serious	763 (49.2)	196 (46.1)	212 (50.2)
Cardiac disorders[a]	83 (5.4)	19 (4.5)	39 (9.2)
Leading to treatment discontinuation[b]	211 (13.6)	60 (14.1)	93 (22.0)
Infections and infestations	70 (4.5)	23 (5.4)	28 (6.6)
Neoplasms[c]	48 (3.1)	11 (2.6)	9 (2.1)
Cardiac disorders[d]	16 (1.0)	2 (0.5)	18 (4.3)
Leading to dose modification	811 (52.3)	237 (55.8)	258 (61.1)
Dose reduction	156 (10.1)	59 (13.9)	81 (19.2)
Dose interruption	791 (51.0)	230 (54.1)	249 (59.0)
Leading to death[e]	113 (7.3)	37 (8.7)	43 (10.2)
Infections and infestations[f]	57 (3.7)	22 (5.2)	26 (6.2)
Cardiac disorders[g]	12 (0.8)	1 (0.2)	7 (1.7)
Patients with ≥1 treatment-related TEAE			
Any grade	1231 (79.4)	327 (76.9)	355 (84.1)
Grade ≥3	553 (35.7)	160 (37.6)	187 (44.3)
Serious	266 (17.2)	60 (14.1)	85 (20.1)
Leading to treatment discontinuation	77 (5.0)	19 (4.5)	43 (10.2)
Leading to death	24 (1.5)	8 (1.9)	8 (1.9)
Patients with ≥1 AESI			
Any grade	1404 (90.6)	387 (91.1)	387 (91.7)
Grade ≥3	847 (54.6)	249 (58.6)	240 (56.9)
Serious	567 (36.6)	155 (36.5)	151 (35.8)
Leading to treatment discontinuation	138 (8.9)	42 (9.9)	52 (12.3)
Infections	70 (4.5)	23 (5.4)	28 (6.6)
Opportunistic infections	5 (0.3)	2 (0.5)	1 (0.2)
Second primary malignancies	44 (2.8)	10 (2.4)	8 (1.9)
Skin cancers	3 (0.2)	1 (0.2)	1 (0.2)
Hemorrhage	19 (1.2)	5 (1.2)	7 (1.7)
Major hemorrhage	16 (1.0)	3 (0.7)	5 (1.2)
Thrombocytopenia	4 (0.3)	1 (0.2)	1 (0.2)
Neutropenia	3 (0.2)	3 (0.7)	0
Anemia	2 (0.1)	0	2 (0.5)
Atrial fibrillation and flutter	2 (0.1)	0	7 (1.7)
Hypertension	0	0	1 (0.2)
Leading to dose modification	615 (39.7)	186 (43.8)	205 (48.6)
Dose reduction	103 (6.6)	39 (9.2)	47 (11.1)
Dose interruption	595 (38.4)	180 (42.4)	200 (47.4)
Leading to death	79 (5.1)	30 (7.1)	28 (6.6)
Infections	57 (3.7)	22 (5.2)	26 (6.2)
Opportunistic infections	4 (0.3)	2 (0.5)	0
Second primary malignancies	14 (0.9)	4 (0.9)	0
Skin cancers	2 (0.1)	1 (0.2)	0

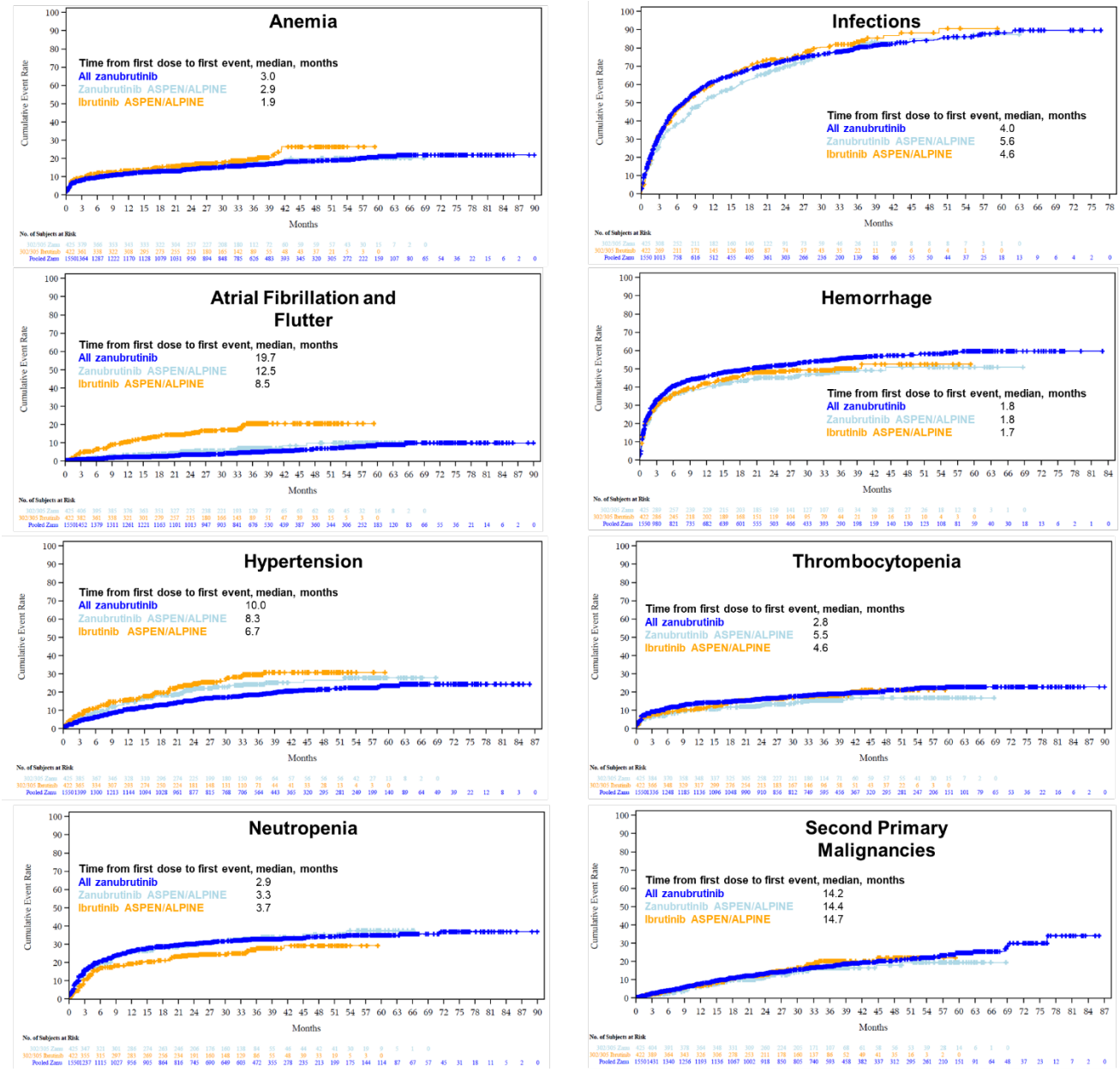
Hemorrhage	6 (0.4)	4 (0.9)	2 (0.5)
Major hemorrhage	6 (0.4)	4 (0.9)	2 (0.5)
Hypertension	1 (0.1)	0	0
Hypertensive heart disease[h]	1 (0.1)	0	0
Tumor lysis syndrome	1 (0.1)	0	0
Patients with ≥1 treatment-related AESI			
Any grade	1038 (67.0)	271 (63.8)	288 (68.2)
Grade ≥3	486 (31.4)	141 (33.2)	159 (37.7)
Serious	228 (14.7)	50 (11.8)	72 (17.1)
Leading to treatment discontinuation	49 (3.2)	11 (2.6)	21 (5.0)
Leading to death	20 (1.3)	7 (1.6)	6 (1.4)

AE, adverse event; AESI, adverse event of special interest; COVID-19, coronavirus disease 2019; TEAE, treatment-emergent adverse event.

TEAEs were defined as AEs with an onset date or worsening in severity from baseline (prior to treatment) at or after the first dose of zanubrutinib and up to the last zanubrutinib dose date + 30 days or initiation of new anticancer therapy, whichever occurred first. Worsening of an event to grade 5 beyond the last zanubrutinib dose date + 30 days and prior to initiation of new anticancer therapy was also considered treatment emergent. AESIs are grouped terms; the preferred terms for the TEAEs included in each AESI category are as previously published,[18] except for "opportunistic infections," which included preferred terms under the narrow standardized MedDRA query "opportunistic infections." AESIs that did not lead to discontinuation or death in any of the analysis populations are not shown. Major hemorrhage, opportunistic infections, and skin cancers are subsets of preferred terms included in their parent term (hemorrhage, infections, and second primary malignancies, respectively).

[a] System organ class of TEAEs. The most common TEAE in each of the 3 populations was atrial fibrillation (total zanubrutinib population, n=21; ASPEN/ALPINE zanubrutinib population, n=3 [cardiac failure was also reported in n=3]; ASPEN/ALPINE ibrutinib population, n=13). [b] The system organ classes of TEAEs that led to discontinuation in ≥1.5% of patients in any of the 3 populations are shown. [c] Benign, malignant, and unspecified (includes cysts and polyps).[d] Cardiac disorder (system organ class) TEAEs leading to discontinuation in the total zanubrutinib population (N=1550) were atrial fibrillation (n=2), cardiac arrest (n=2), cardiac failure (n=2), acute myocardial infarction, cardiac failure congestive, cardiomegaly, cardiopulmonary failure, myocardial infarction, pericardial effusion, pulseless electrical activity, tachycardia, ventricular arrhythmia, and ventricular extrasystoles (each n=1); in the ASPEN/ALPINE zanubrutinib population, cardiac disorder TEAEs leading to discontinuation were cardiomegaly and ventricular extrasystoles (each n=1), and in the ASPEN/ALPINE ibrutinib population, they were atrial fibrillation (n=7), cardiac arrest (n=2), cardiac failure (n=2), acute myocardial infarction, myocardial infarction, cardiac failure acute, congestive cardiomyopathy, palpitations, pericardial hemorrhage, and ventricular fibrillation (each n=1). [e] The system organ classes of TEAEs that led to death in ≥1.5% of patients in any of the 3 populations are shown. [f] COVID-19 (including COVID-19 and COVID-19 pneumonia) was the leading cause of death related to infection (total zanubrutinib population, n=26; ASPEN/ALPINE zanubrutinib population, n=13; ASPEN/ALPINE ibrutinib population, n=15). [g] Cardiac disorder (system organ class) TEAEs leading to death in the total zanubrutinib population (N=1550) were acute myocardial infarction (n=2), cardiac arrest (n=2), cardiac failure (n=2), cardiac failure congestive (n=2), cardiogenic shock, cardiomegaly, cardiopulmonary failure, hypertensive heart disease, myocardial infarction, and pulseless electrical activity (each n=1). In the ASPEN/ALPINE zanubrutinib population, the cardiac disorder TEAE leading to death was cardiomegaly (n=1); in the ASPEN/ALPINE ibrutinib population, cardiac disorder TEAEs leading to death were cardiac arrest (n=2), myocardial infarction (n=2), cardiac failure acute (n=2), and congestive cardiomyopathy (n=1). [h] Hypertensive heart disease occurred in a patient with baseline hypertension and diabetes mellitus and concurrent COVID-19. No treatment-emergent worsening of hypertension was reported. Autopsy showed congestive heart failure and hypertensive heart disease. The investigator considered the hypertensive heart disease unrelated to zanubrutinib treatment.

Online Supplementary Figure S1.



Kaplan-Meier curves of time to first event for AESIs. AESIs are grouped terms; the preferred terms for the TEAEs included in each AESI category are as previously published.[18] Data are shown for the pooled population of patients who received zanubrutinib (N=1550) and for the comparative analysis (patients treated with zanubrutinib [n=425] or ibrutinib [n=422] as part of the randomized studies ASPEN cohort 1 and ALPINE). Median time from first dose to first event for the 3 AESI sub-categories not shown are as follows: opportunistic infections (sub-category of "infections"): pooled zanubrutinib, 6.4 months; zanubrutinib in ASPEN/ALPINE, 11.1 months; ibrutinib in ASPEN/ALPINE, 11.9 months; skin cancers (sub-category of "second primary malignancies"): pooled zanubrutinib, 13.1 months; zanubrutinib in ASPEN/ALPINE, 14.8 months; ibrutinib in ASPEN/ALPINE, 13.4 months; major hemorrhage (sub-category of

“hemorrhage”): pooled zanubrutinib, 11.3 months; zanubrutinib in ASPEN/ALPINE, 11.6 months; ibrutinib in ASPEN/ALPINE, 9.4 months. For the AESI tumor lysis syndrome (Kaplan-Meier curve not shown), an event was reported in ≤5 patients. The median time from first dose to first event was 4.9 months in the pooled zanubrutinib population and 0.2 months in the ASPEN/ALPINE zanubrutinib population. No tumor lysis syndrome events were reported in the ASPEN/ALPINE ibrutinib population.
AESI, adverse event of special interest; TEAE, treatment-emergent adverse event.

References

1. Song Y, Sun M, Qi J, et al. A two-part, single-arm, multicentre, phase I study of zanubrutinib, a selective Bruton tyrosine kinase inhibitor, in Chinese patients with relapsed/refractory B-cell malignancies. Br J Haematol. 2022;198(1):62-72.
2. Xu W, Yang S, Zhou K, et al. Treatment of relapsed/refractory chronic lymphocytic leukemia/small lymphocytic lymphoma with the BTK inhibitor zanubrutinib: phase 2, single-arm, multicenter study. J Hematol Oncol. 2020;13(1):48.
3. 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. Clin Cancer Res. 2020;26(16):4216-4224.
4. Song Y, Zhou K, Zou D, et al. Zanubrutinib in relapsed/refractory mantle cell lymphoma: Long-term efficacy and safety results from a phase 2 study. Blood. 2022;139(21):3148-3158.
5. Song Y, Zhou K, Zou D, et al. Safety and activity of the investigational Bruton tyrosine kinase inhibitor zanubrutinib (BGB-3111) in patients with mantle cell lymphoma from a phase 2 trial. Blood. 2018;132(suppl 1):148.
6. An G, Zhou D, Cheng S, et al. A phase II trial of the Bruton tyrosine-kinase inhibitor zanubrutinib (BGB-3111) in patients with relapsed/refractory Waldenstrom macroglobulinemia. Clin Cancer Res. 2021;27(20):5492-5501.
7. Cull G, Burger JA, Opat S, et al. Zanubrutinib for treatment-naive and relapsed/refractory chronic lymphocytic leukaemia: long-term follow-up of the phase I/II AU-003 study. Br J Haematol. 2022;196(5):1209-1218.
8. Tam CS, Opat S, Simpson D, et al. Zanubrutinib for the treatment of relapsed or refractory mantle cell lymphoma. Blood Adv. 2021;5(12):2577-2585.
9. Tam CS, Trotman J, Opat S, et al. Phase 1 study of the selective BTK inhibitor zanubrutinib in B-cell malignancies and safety and efficacy evaluation in CLL. Blood. 2019;134(11):851-859.
10. Trotman J, Opat S, Gottlieb D, et al. Zanubrutinib for the treatment of patients with Waldenstrom macroglobulinemia: 3 years of follow-up. Blood. 2020;136(18):2027-2037.
11. Phillips T, Chan H, Tam CS, et al. Zanubrutinib monotherapy in relapsed/refractory indolent non-Hodgkin lymphoma. Blood Adv. 2022;6(11):3472-3479.
12. Tam CS, Garcia-Sanz R, Opat S, et al. ASPEN: Long-term follow-up results of a phase 3 randomized trial of zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia. J Clin Oncol. 2022;40(s16): abstract 7521.
13. 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. 2020;136(18):2038-2050.
14. Tam CS, Robak T, Ghia P, et al. Zanubrutinib monotherapy for patients with treatment naive chronic lymphocytic leukemia and 17p deletion. Haematologica. 2020;106(9):2354-2363.
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. Lancet Oncol. 2022;23(8):1031-1043.
16. 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. J Clin Oncol. 2023;41(5):1035-1045.
17. Brown JR, Eichhorst B, Hillmen P, et al. Zanubrutinib or ibrutinib in relapsed or refractory chronic lymphocytic leukemia. N Engl J Med. 2023;388(4):319-332.
18. Tam CS, Dimopoulos M, Garcia-Sanz R, et al. Pooled safety analysis of zanubrutinib monotherapy in patients with B-cell malignancies. Blood Adv. 2022;6(4):1296-1308.