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

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 six 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 (TEAE) of special interest (AESI). 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 six studies examined in a prior pooled analysis[1] with data from four additional studies (*Online Supplementary Table S1*). A comparative analysis of zanubrutinib *versus* ibrutinib was also conducted using data from two of these ten studies - the randomized phase III 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=1,550) 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) (*clinicaltrials gov. Identifiers: NCT03189524, NCT03206918, NCT03206970, NCT03332173, NCT03846427, NCT02343120, NCT03053440, NCT03336333, NCT03734016, NCT04170283*).

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 *versus* 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 *versus* 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%).

TEAE 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, TEAE leading to treatment discontinuation were less common with zanubrutinib *versus* ibrutinib (14.1% *vs*. 22.0%). Infections were the most common TEAE 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 disorder (MedDRA system organ class) TEAE 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 TEAE 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 TEAE leading to death (total pooled zanubrutinib, 3.7%; ASPEN/ALPINE zanubrutinib, 5.2%; ASPEN/ALPINE ibrutinib, 6.2%). Cardiac disorder TEAE leading to death occurred in seven patients (1.7%) treated with ibrutinib *versus* one 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 TEAE (*Online Supplementary Table S2*). TEAE 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%) non-hematologic TEAE reported are shown in Figure 1A. No grade ≥3 non-hematologic TEAE were reported in ≥10% of patients; the most common were pneumonia (8.4%; treatment-related, 4.1%) and hypertension (8.1%; treatment-re-

Table 1. Demographics and baseline characteristics.

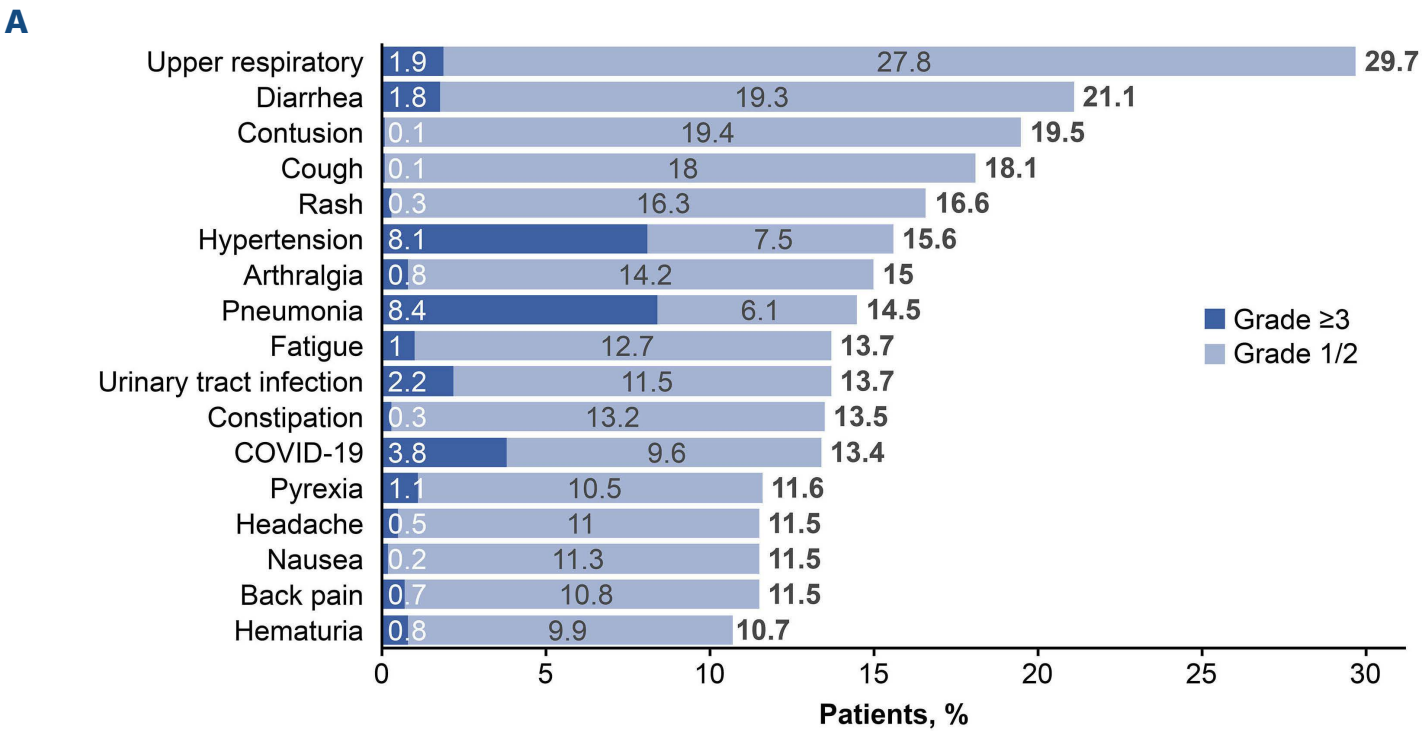
Characteristics		Comparative analysis	
	All zanubrutinib, N=1,550	Zanubrutinib, N=425[a]	Ibrutinib, N=422[b]
Age in years, median (range)	67.0 (20-95)	68.0 (35-90)	68.0 (35-90)
<65, N (%)	600 (38.7)	160 (37.6)	148 (35.1)
≥65 to <75, N (%)	615 (39.7)	155 (36.5)	181 (42.9)
≥75, N (%)	335 (21.6)	110 (25.9)	93 (22.0)
Sex, N (%)			
Male	1,027 (66.3)	280 (65.9)	295 (69.9)
Female	523 (33.7)	145 (34.1)	127 (30.1)
Race, N (%)			
White	1,032 (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	1,068 (68.9)	406 (95.5)	404 (95.7)
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 UK; 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=1,477; 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.

lated, 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 AESI ("opportunistic infections" included preferred terms under the narrow standardized MedDRA query "opportunistic infections"; for all other AESI preferred terms, see Tam *et al.*[1]). In order to account for differing treatment exposures across the trials, exposure-adjusted incidence rates (EAIR) of these AESI 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 AESI in the total pooled zanubrutinib population, even after adjusting for dose exposure (Figure 1B). Despite a longer median treatment duration, the EAIR of the cardiovascular AESI 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. 1;



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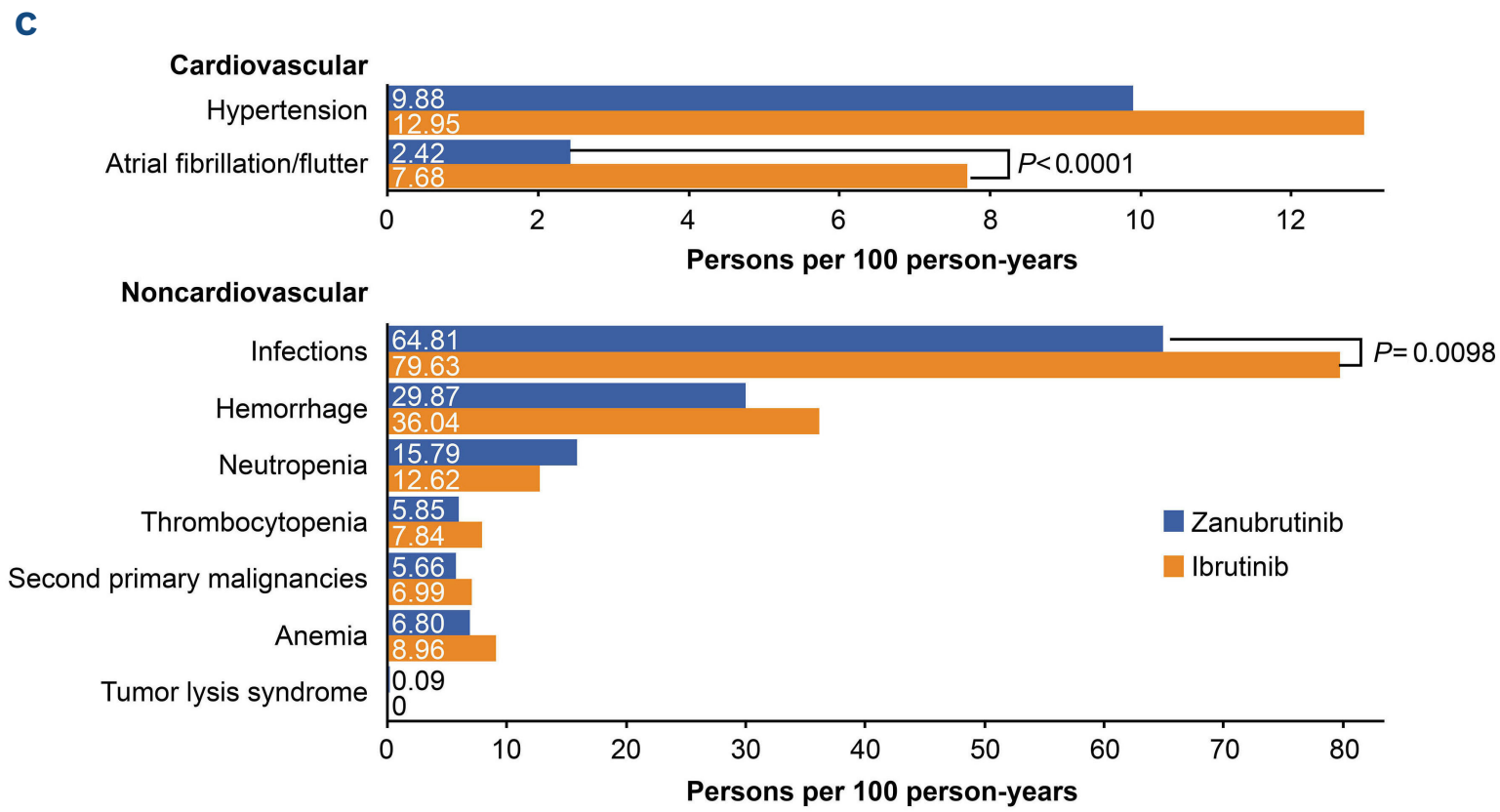
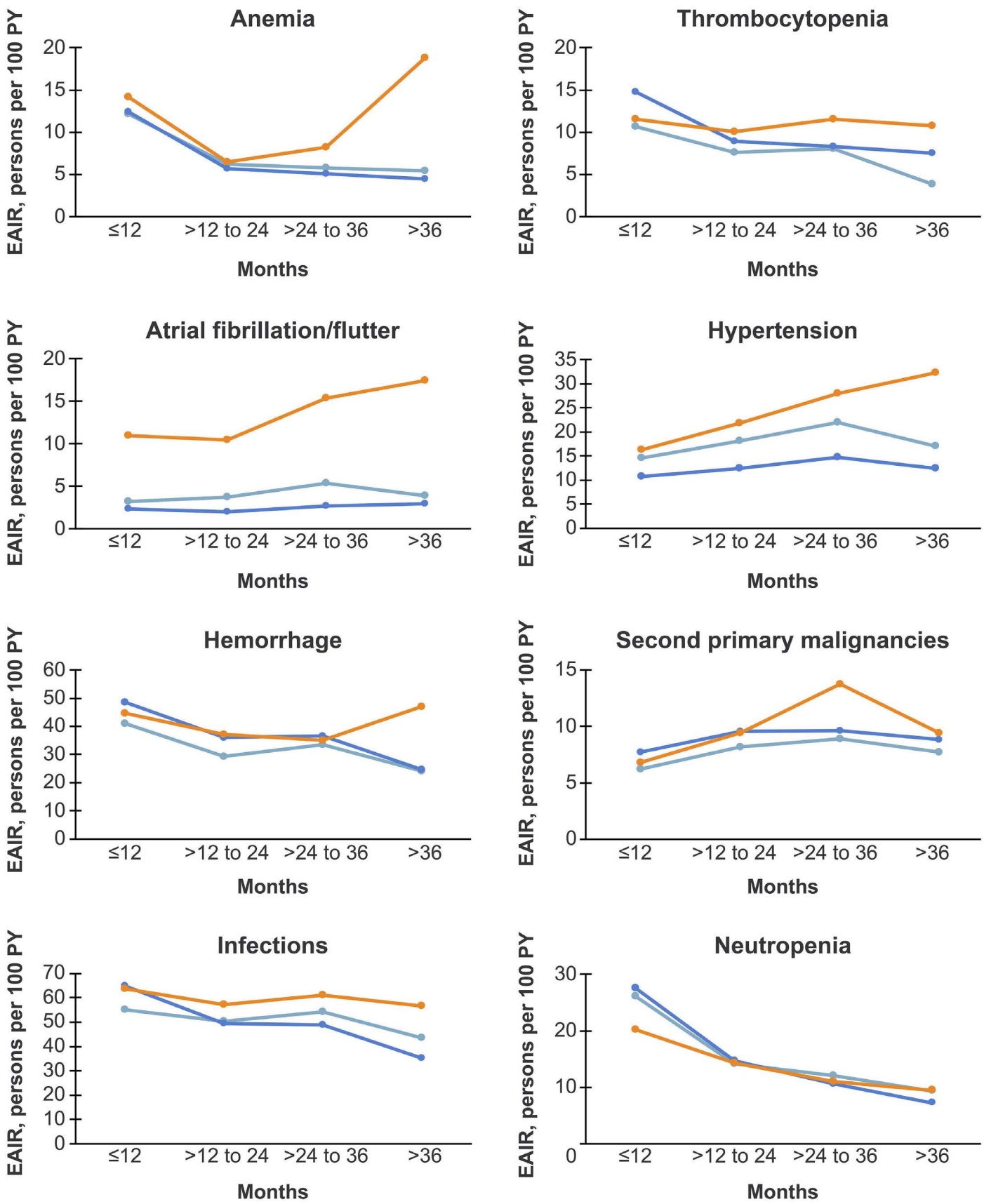


Figure 1. Incidence of any-grade non-hematologic treatment-emergent adverse events and exposure-adjusted incidence rates of adverse events of special interest. (A) Treatment-emergent adverse events (TEAE) reported in ≥10% or grade ≥3 TEAE in ≥5% of patients treated with zanubrutinib (N=1,550) are shown. TEAE were defined as adverse event (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 AE of special interest (AESI) shown are grouped terms. The preferred terms for the TEAE 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." Exposure-adjusted incidence rates (EAIR) were calculated as the number of patients who experienced a specific AESI divided by the total exposure time (i.e., 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=1,550). 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 EAIR 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 χ^2 test was reported. All statistical tests were two-sided, with $P<0.05$ considered significant; no adjustments for multiple comparisons were made. COVID-19: coronavirus disease 2019.

Importantly, across all ten trials, no zanubrutinib-treated patients discontinued due to hypertension.

In the comparative analysis, all EAIR of AESI, except for neutropenia, were numerically lower in patients treated with zanubrutinib *versus* 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*=0.0098) with zanubrutinib, even after excluding COVID-19-related infection terms (54.48 *vs*. 69.96 persons per 100 PY; *P*=0.0029). The EAIR for afib/flutter was also significantly lower with zanubrutinib *versus* ibrutinib (*P*<0.0001). The hypertension EAIR was also reduced in patients receiving zanubrutinib *versus* ibrutinib (*P*=0.0610). AESI EAIR 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 EAIR over time were numerically lower with zanubrutinib *versus* 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 EAIR 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



No. at risk (person-years at risk)

All zanubrutinib (N=1,550)	1,550 (1,399.9)	1,282 (1,179.0)	1,040 (912.0)	698 (913.8)	1,550 (1,399.9)	1,282 (1,179.0)	1,040 (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)

Figure 2. Exposure-adjusted incidence rates of select adverse events of special interest over time. Adverse events of special interest (AESI) are grouped terms as defined in the legend for Figure 1. Exposure-adjusted incidence rates (EAIR) 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 (PY). Data are shown for the total pooled zanubrutinib population (N=1,550) 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).

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 (e.g., anticoagulants, antiplatelet agents) that can further increase the bleeding risk associated with BTKi. Finally, although hypertension in patients receiving ibrutinib has been associated with increased incidence of major cardiovascular AE,[7] the incidence of cardiac disorder TEAE 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 (e.g., 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 TEAE, 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.

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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.

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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/.

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