Characterization of the Safety/Tolerability Profile of Zanubrutinib and Comparison With the Profile of Ibrutinib in Patients With B-Cell Malignancies: Post Hoc Analysis of a Large Clinical Trial Safety Database

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BACKGROUND

- Bruton tyrosine kinase inhibitors (BTKis) have revolutionized treatment of B-cell malignancies^{1,2}
- Use of the first-generation BTKi ibrutinib may be limited by toxicities including cardiovascular and gastrointestinal side effects and rash attributed to off-target kinase inhibition³⁻⁶
- Zanubrutinib is a potent and selective next-generation BTKi that has been designed to improve tolerability by maximizing BTK occupancy and minimizing off-target effects⁷
- In a previous analysis of pooled data of 779 patients from 6 clinical trials, zanubrutinib was generally well tolerated and showed a consistent safety profile⁸
- Here we present an updated pooled analysis that characterizes the overall safety/tolerability profile of zanubrutinib in 1550 patients from 10 clinical studies, including 2 that compared zanubrutinib head-to-head with ibrutinib

METHODS

• Clinical trials (N=10) of zanubrutinib monotherapy included in these post hoc safety analyses are shown in Table 1

- Patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL), mantle cell lymphoma, marginal zone lymphoma, Waldenström macroglobulinemia, follicular lymphoma, and other B-cell malignancies were included
- ASPEN (cohort 1) and ALPINE compared zanubrutinib head-to-head with ibrutinib

Table 1. Clinical Trials Included in the Pooled Analysis

Clinical trial	NCT number	Phase	Disease state	Zanubrutinib dose	Location	No. of patients treated with zanubrutinib (N=1550)
BGB-3111-1002	03189524	1	B-cell malignancies	160 mg BID 320 mg QD	China	44
BGB-3111-205	03206918	2	R/R CLL/SLL	160 mg BID	China	91
BGB-3111-206	03206970	2	R/R mantle cell lymphoma	160 mg BID	China	86
BGB-3111-210	03332173	2	Waldenström macroglobulinemia	160 mg BID	China	44
BGB-3111-AU-003	02343120	1/2	B-cell malignancies	160 mg BID 40 mg QD 80 mg QD 160 mg QD 320 mg QD	Global	373ª
BGB-3111-214	03846427	2	Marginal zone lymphoma	160 mg BID	Global	68
BGB-3111-302 (ASPEN) ^b	03053440	3	Waldenström macroglobulinemia	160 mg BID	Global	129
BGB-3111-304 (SEQUOIA)	03336333	3	TN CLL/SLL	160 mg BID	Global	391
BGB-3111-305 (ALPINE) ^b	03734016	3	R/R CLL/SLL	160 mg BID	Global	324
BGB-3111-LTE1	04170283	3	B-cell malignancies	160 mg BID	Global	337°

- Treatment-emergent adverse events (TEAEs) were summarized using MedDRA preferred terms
- Adverse events of special interest (AESIs) were defined using grouped terms

QD). $^{
m c}$ The 337 patients in this long-term extension study previously participated in 1 of the other studies and were counted in the parent studies

- AESIs included anemia, atrial fibrillation/flutter, hemorrhage, hypertension, infections, neutropenia, second primary malignancies, and thrombocytopenia
- Incidence rates of TEAEs, exposure-adjusted incidence rates (EAIRs), and prevalence of AESIs over time were assessed

RESULTS

Patients and Exposure

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Age, median (range), years Sex, n (%) Male Female Race, n (%)	All zanubrutinib (N=1550) 67.0 (20-95) 1027 (66.3) 523 (33.7)	Zanubrutinib (n=425) 68.0 (35-90)	Ibrutinib (N=422)
Sex, n (%) Male Female	1027 (66.3)	68.0 (35-90)	
Male Female			68.0 (35-90)
Female			
	523 (337)	280 (65.9)	295 (69.9)
Race, n (%)	020 (00)	145 (34.1)	127 (30.1)
Asian	424 (27.4)	49 (11.5)	44 (10.4)
White	1032 (66.6)	348 (81.9)	357 (84.6)
Other	51 (3.3)	11 (2.6)	4 (0.9)
Not reported or missing	43 (2.8)	17 (4.0)	17 (4.0)
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 ^b	26 (1.7)	0	0
Prior treatment status, n (%)			
Treatment naive	482 (31.1)	19 (4.5)°	18 (4.3) ^c
Relapsed/refractory	1068 (68.9)	406 (95.5)	404 (95.7)
No. of prior lines of therapy			
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)

• EAIRs in units of persons per 100 person-months were calculated as follows: (Number of patients who experienced a TEAE of interest/total treatment exposure time in months for all patients) × 100

• An EAIR of 0.5 persons per 100 person-months indicates that if 1000 patients were each treated for a month, 5 would be estimated to experience the TEAE of interest

• Data from 1550 patients treated with zanubrutinib and 422 patients treated with ibrutinib were included (**Table 2**)

nographics and Baseline Disease Characteristics

than with ibrutinib (0.2% vs 1.7%) in the head-to-head trial populations

Table 3. Exposure, Dose Adjustments, and Deaths

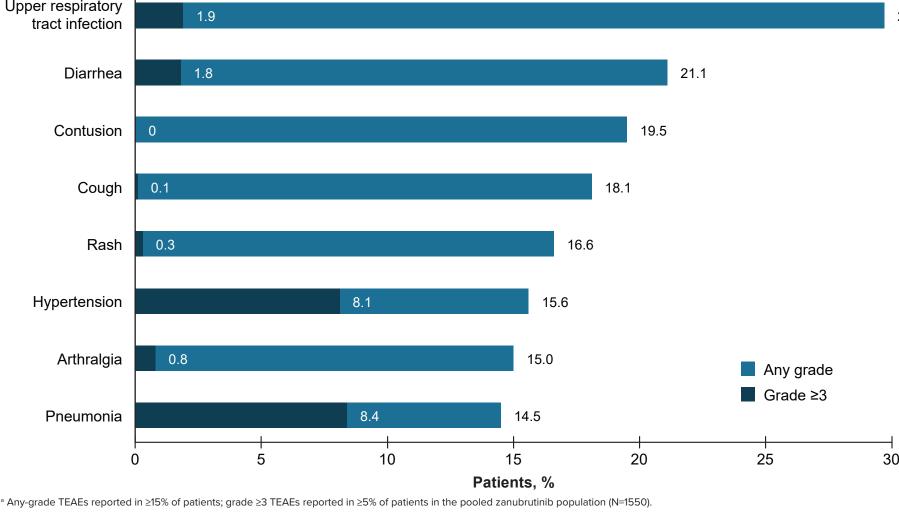
		ASPEN/A	
	All zanubrutinib (N=1550)	Zanubrutinib (n=425)	lbrutinib (N=422)
Duration of treatment, median (range), months	34.4 (0.1-90.0)	32.6 (0.4-68.7)	25.7 (0.1-59.3)
<12 months, n (%)	280 (18.1)	41 (9.6)	78 (18.5)
12 to <24 months, n (%)	235 (15.2)	96 (22.6)	106 (25.1)
24 to <36 months, n (%)	338 (21.8)	163 (38.4)	131 (31.0)
≥36 months, n (%)	697 (45.0)	125 (29.4)	107 (25.4)
Patients with ≥1 TEAE leading to, n (%)			
Dose reduction	156 (10.1)	59 (13.9)	81 (19.2)
Dose interruption	791 (51.0)	230 (54.1)	249 (59.0)
Treatment discontinuation	211 (13.6)	60 (14.1)	93 (22.0)
Treatment discontinuation due to cardiac TEAE	16 (1.0)	2 (0.5)	18 (4.3)
Deaths, n (%)			
Any TEAE	113 (7.3)	37 (8.7)	43 (10.2)
Cardiac TEAE	12 (0.8)	1 (0.2)	7 (1.7)

^a Head-to-head randomized trials of zanubrutinib vs ibrutinib

Safety and Tolerability of Zanubrutinib

- The most common nonhematologic TEAEs in patients who received - No grade \geq 3 TEAEs occurred in >10% of patients; the most common
- The only serious AE in \geq 5% of patients in the pooled zanubrutinib population was pneumonia (8.2%)

Figure 1. Most Common Nonhematologic TEAEs With Zanubrutinib^a Upper respiratory

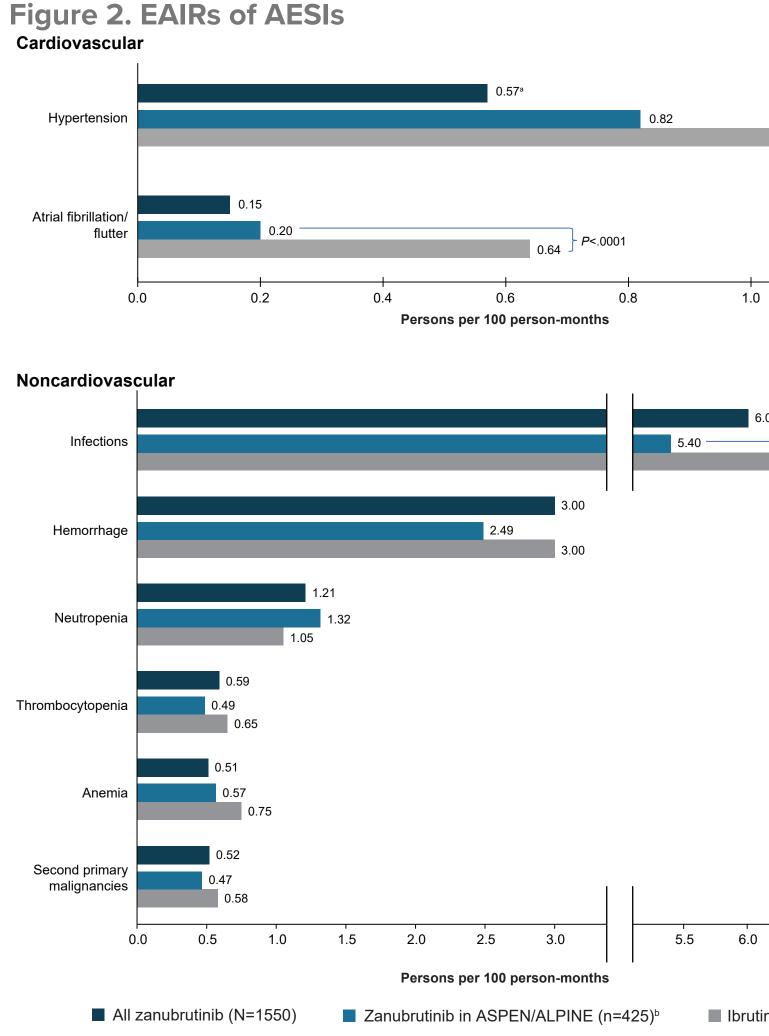


AESIs

- EAIRs of AESIs, including infections, with zanubrutinib were numerically lower than with ibrutinib in head-to-head comparisons of the ASPEN/ ALPINE study populations, except for neutropenia (Figure 2)
- EAIRs of atrial fibrillation and infections were significantly lower with zanubrutinib vs ibrutinib (*P*<.0001 and *P*=.0098, respectively)
- were low (pooled EAIR < 0.5 persons per 100 person-months) and consistent across studies
- The prevalence of AESIs tended to remain constant or decrease over time with zanubrutinib (**Figure 3**)
- In head-to-head comparisons of the ASPEN/ALPINE study populations, hypertension tended to increase over time with ibrutinib, whereas it remained relatively stable with zanubrutinib
- The prevalence of atrial fibrillation with zanubrutinib remained lower than with ibrutinib over time

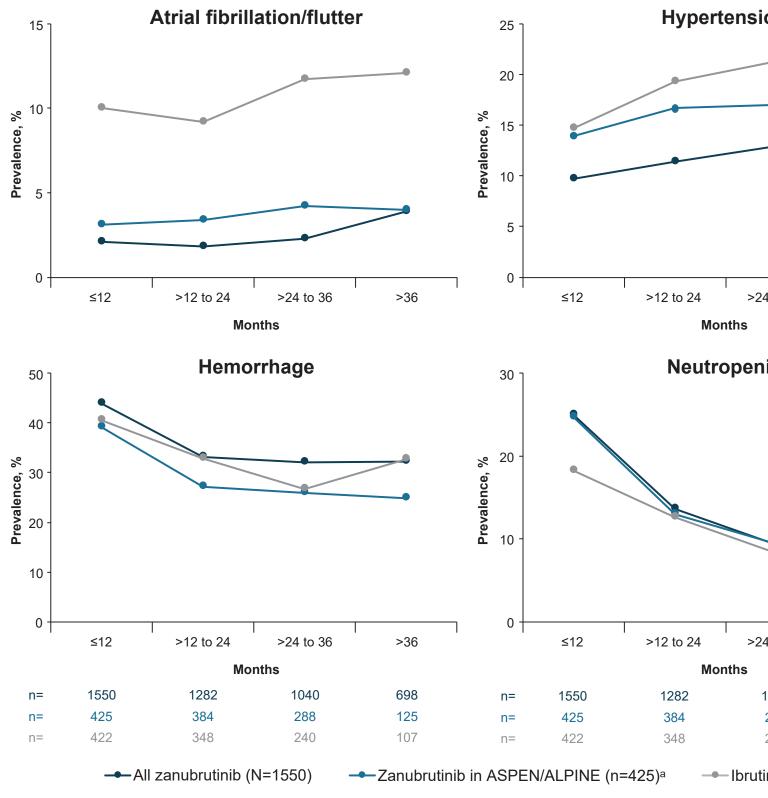
zanubrutinib were upper respiratory tract infection and diarrhea (Figure 1) grade \geq 3 TEAEs were pneumonia (8.4%) and hypertension (8.1%) • Serious AEs occurred in 49.2% of patients who received zanubrutinib

- With the exception of ALPINE, EAIRs for hypertension with zanubrutinib



^a The EAIR for hypertension is 0.48 persons per 100 person-months in the subset of patients (n=1226) that excluded patients from ALPINE.^b Zanubrutinib was compa the phase 3 ASPEN (cohort 1) and ALPINE tria

Figure 3. Prevalence of Selected AESIs Over Time



^a Zanubrutinib was compared head-to-head with ibrutinib in the phase 3 ASPEN (cohort 1) and ALPINE trials.

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	CONCLUSIONS
1.08	 These pooled safety analyses showed that zanubrutinib is well tolerated in patients with B-cell malignancies, with TEAEs (upper respiratory tract infection, diarrhea, contusion) that were generally mild to moderate in severity
	 When comparing zanubrutinib vs ibrutinib in pooled head-to-head studies, rates of TEAEs or cardiac TEAEs leading to discontinuation were lower with zanubrutinib
01 6.64 P=.0098	 In pooled head-to-head comparisons, rates of death due to cardiac events were lower with zanubrutinib than ibrutinib (0.2% vs 1.7%), which is comparable to findings in the phase 3 ALPINE study⁹
	 EAIRs for AESIs, especially for hypertension and atrial fibrillation/flutter, were lower with zanubrutinib than ibrutinib in head-to-head comparisons
	 In this pooled analysis, the EAIR for hypertension was largely influenced by data from ALPINE, which was an outlier from the rates observed in other studies of zanubrutinib^{9,10}
	 Although hypertension rates were higher in ALPINE, cardiac events (eg, atrial fibrillation/flutter) were low and consistent with other zanubrutinib studies
6.5 7.0	 The prevalence of AESIs tended to decrease over time, without the emergence of new safety signals
hib (N=422) ^b ared head-to-head with ibrutinib in	 Due to the continuous dosing of BTKis in most B-cell malignancies, long-term tolerability and low treatment discontinuation rates with BTKis are important
on	 These analyses support zanubrutinib as an appropriate long-term treatment option for patients with B-cell malignancies
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