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

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SUPPLEMENTARY INFORMATION

Title

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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

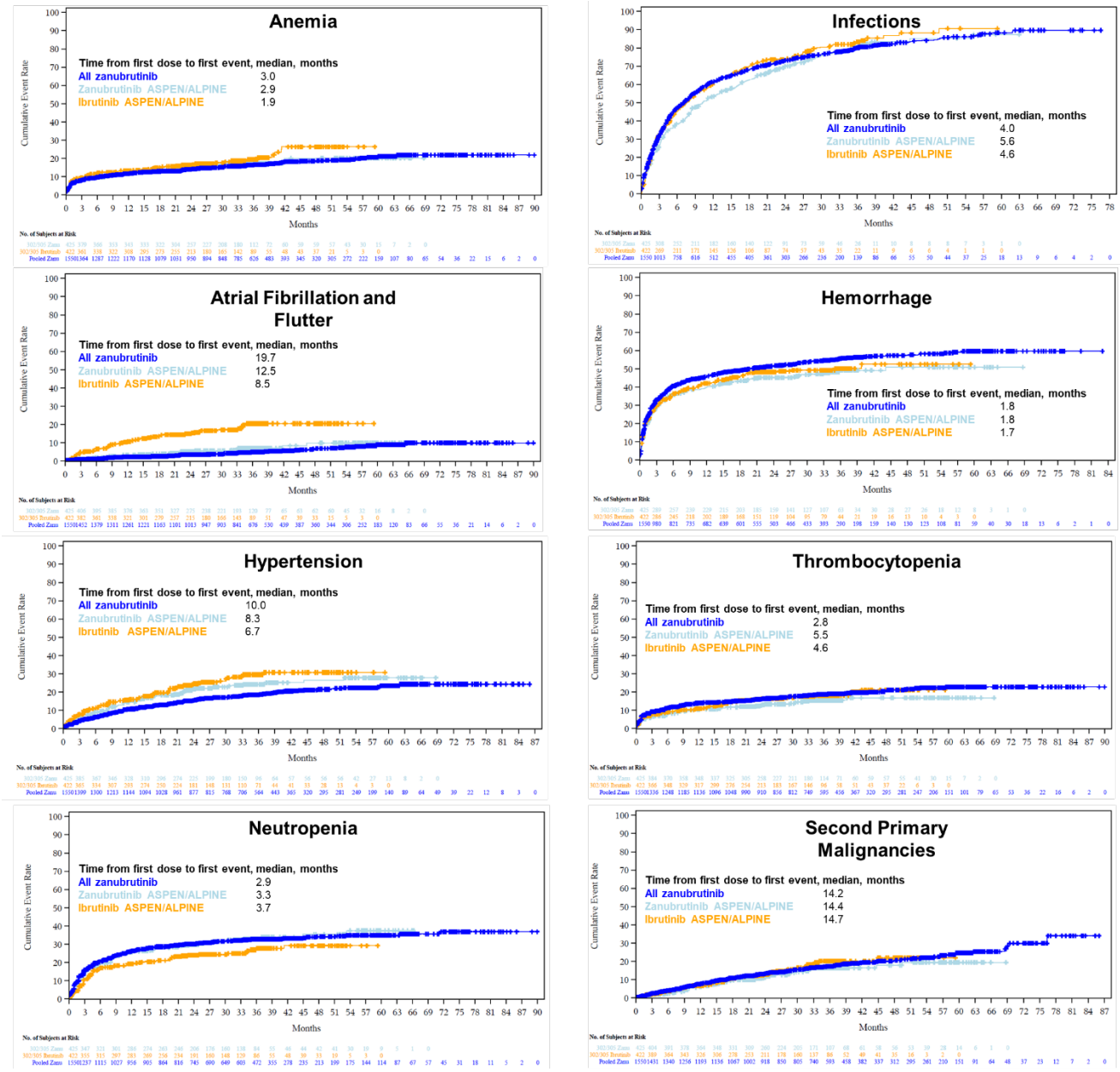
Hemorrhage	6 (0.4)	4 (0.9)	2 (0.5)
Major hemorrhage	6 (0.4)	4 (0.9)	2 (0.5)
Hypertension	1 (0.1)	0	0
Hypertensive heart disease[h]	1 (0.1)	0	0
Tumor lysis syndrome	1 (0.1)	0	0
Patients with ≥1 treatment-related AESI			
Any grade	1038 (67.0)	271 (63.8)	288 (68.2)
Grade ≥3	486 (31.4)	141 (33.2)	159 (37.7)
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.

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