

Rate of Cardiac Disorders in Patients With B-Cell Malignancies Who Undergo Treatment With Zanubrutinib

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INTRODUCTION

- Treatment of B-cell malignancies has been improved by effective inhibitors of B-cell receptor signaling, such as the first-generation Bruton tyrosine kinase (BTK) inhibitor, ibrutinib¹
- Although ibrutinib has demonstrated efficacy, it has been associated with an increased risk of cardiovascular toxicities such as atrial fibrillation/flutter (Afib)^{2,5} and ventricular arrhythmias (VAs)⁶
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition-related toxicities⁷
- Zanubrutinib has been generally well tolerated, with an established efficacy in clinical trials in patients with B-cell malignancies⁸⁻¹³
- Here, we report the occurrence of Afib and symptomatic idiopathic VA (IVA; VA without history of myocardial infarction/left ventricular ejection fraction <50%/severe active infections)¹⁴ in the 2 head-to-head trials of zanubrutinib vs ibrutinib, ASPEN⁸ (NCT03053440) and ALPINE¹³ (NCT03734016), and a larger pooled analysis of zanubrutinib studies

METHODS

- Safety data reported by investigators from clinical studies of zanubrutinib were pooled and descriptively analyzed
 - Event rates and exposure-adjusted incidence rates (EAIRs) of Afib and IVA with zanubrutinib vs ibrutinib were calculated in a post hoc analysis of the phase 3 clinical studies ASPEN⁸ (cohort 1) and ALPINE¹³ and in a pooled analysis of 10 clinical studies of zanubrutinib in patients with B-cell malignancies (**Table 1**)
 - The primary analysis was to compare EAIR between ibrutinib and zanubrutinib, with *P* values of the comparison calculated based on asymptotic normal distribution
- Medical history of Afib and cardiovascular disorders (ie, VA or hypertension [HTN]) was assessed at the time of enrollment and before treatment with zanubrutinib or ibrutinib using Medical Dictionary for Regulatory Activities (MedDRA) v24.0
- Afib included atrial fibrillation and atrial flutter events; VA included any event in standardized MedDRA queries (SMQs) of ventricular tachyarrhythmias (narrow) and MedDRA high-level term of VA and cardiac arrest; cases were adjudicated to include IVA
- Afib and VA events that occurred during treatment were graded by Common Terminology Criteria for Adverse Events (CTCAE; v5.0 in the LTE1 study and v4.03 in all other studies); symptomatic VAs were grade ≥2 VA events per CTCAE

Table 1. Clinical Studies Included in Pooled Analysis of Zanubrutinib in B-Cell Malignancies

Clinical study	Disease state	NCT number	Location	No. of patients treated with zanubrutinib (N=1550)
BGB-3111-1002	B-cell malignancies	03189524	China	44
BGB-3111-205	R/R CLL/SLL	03206918	China	91
BGB-3111-206	R/R MCL	03206970	China	86
BGB-3111-210	WM	03332173	China	44
BGB-3111-AU-003	B-cell malignancies	02343120	International	373
BGB-3111-214	MZL	03846427	International	68
BGB-3111-LTE1*	B-cell malignancies	04170283	International	337
BGB-3111-302 (ASPEN)	WM	03053440	International	129
BGB-3111-304 (SEQUOIA)	TN CLL/SLL	03336333	International	391
BGB-3111-305 (ALPINE)	R/R CLL/SLL	03734016	International	324

*Subjects enrolled in LTE were counted in parental studies. CLL, chronic lymphocytic leukemia; LTE, long-term extension; MCL, mantle cell lymphoma; MZL, marginal zone lymphoma; NCT, national clinical trial; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment naïve; WM, Waldenström macroglobulinemia.

RESULTS

- In the pooled analyses, 1550 patients received zanubrutinib as monotherapy for the treatment of B-cell malignancies, with the largest subgroup being CLL/SLL (61%; 938/1550 patients)
 - Median age was 67 years, with 61% of patients aged ≥65 years
 - Most patients were male (66%), White (67%), and had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (44.5% and 49.4%, respectively)

Medical History of Cardiac Disorders

- The medical histories of Afib and HTN were comparable between patients who received zanubrutinib and ibrutinib in the 2 head-to-head studies (**Table 2**)
 - The medical history of VA in the pooled populations was numerically higher for zanubrutinib (0.9%; 14/1550) vs ibrutinib (0.2% [1/422]; **Table 2**)

RESULTS (cont.)

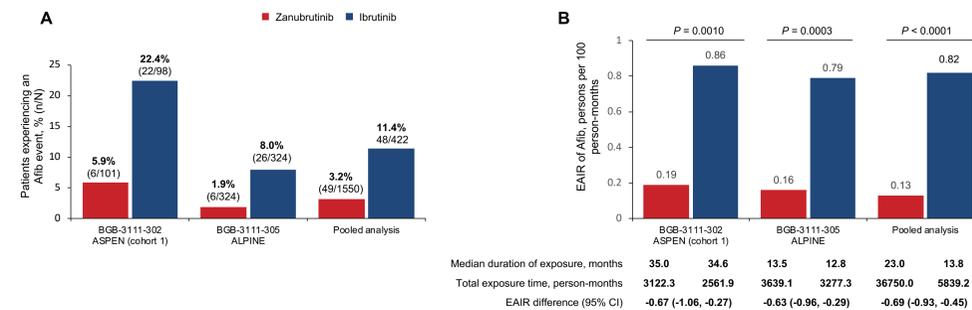
Table 2. Medical History of Cardiovascular Disorders

Medical history of cardiovascular disorders, n (%)	BGB-3111-302 ASPEN cohort 1 WM		BGB-3111-305 ALPINE R/R CLL/SLL		Pooled analysis B-cell malignancies	
	Zanubrutinib (n=101)	Ibrutinib (n=98)	Zanubrutinib (n=324)	Ibrutinib (n=324)	Zanubrutinib (N=1550)	Ibrutinib (N=422)
Any cardiac disorders	26 (25.7)	24 (24.5)	90 (27.8)	92 (28.4)	366 (23.6)	116 (27.5)
Afib	10 (9.9)	8 (8.2)	19 (5.9)	18 (5.6)	101 (6.5)	26 (6.2)
VA	1 (1.0)	0	2 (0.6)	1 (0.3)	14 (0.9)	1 (0.2)
HTN	40 (39.2)	44 (44.4)	160 (48.9)	156 (48.0)	650 (41.9)	200 (47.1)

Analysis of Atrial Fibrillation

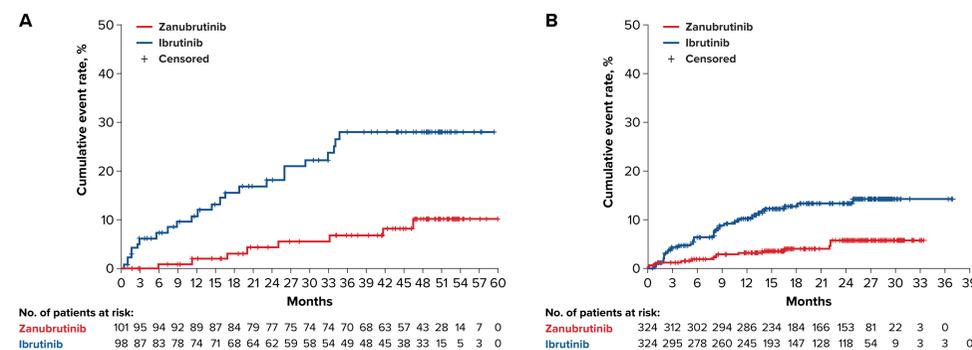
- Despite the similar proportion of patients with a medical history of Afib in the zanubrutinib arm compared with the ibrutinib arm in ASPEN (cohort 1) or ALPINE, respectively (**Table 2**), the rate of treatment-emergent Afib events was approximately 4-fold lower with zanubrutinib than ibrutinib (**Figure 1A**)
 - In cohort 1 of ASPEN, the rate of Afib events was lower with zanubrutinib (5.9%; 6/101) than ibrutinib (22.4%; 22/98)
 - In ALPINE, Afib rates during the study were lower with zanubrutinib (1.9%; 6/324) compared with ibrutinib (8.0%; 26/324)
- The EAIR of Afib was significantly lower with zanubrutinib than ibrutinib in both studies (*P* < 0.05); zanubrutinib Afib EAIRs in the pooled analysis were comparable to those observed in ASPEN and ALPINE (**Figure 1B**)
- The time to Afib event with ibrutinib vs zanubrutinib in both ASPEN and ALPINE studies are presented in **Figure 2**

Figure 1. (A) Event Rate and (B) EAIR of Afib in Clinical Studies With Zanubrutinib



EAIR of Afib was a prespecified analysis; differences between treatment duration were compensated for by calculation of EAIR.¹⁵ N, number of patients treated.

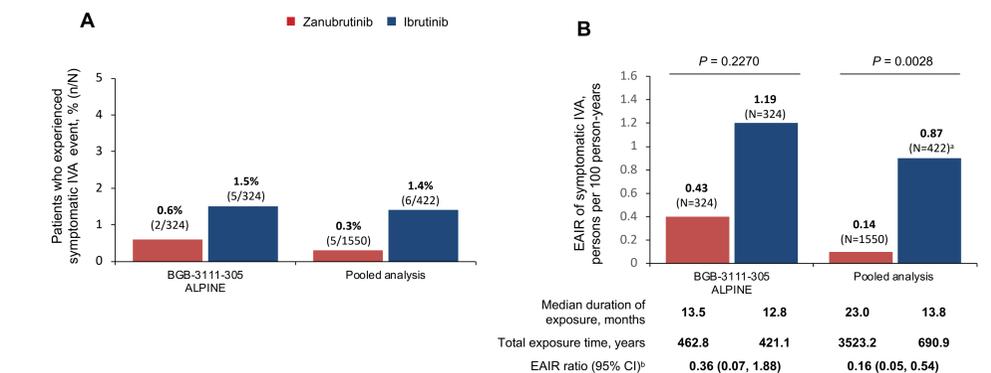
Figure 2. Time to Afib in Patients Treated With Zanubrutinib vs Ibrutinib in (A) ASPEN Cohort 1 and (B) ALPINE Studies



Analysis of Ventricular Arrhythmias

- Symptomatic IVA was reported in 0.3% (5/1550) of patients treated with zanubrutinib vs 1.4% (6/422) with ibrutinib (**Figure 3A**)
 - In the ALPINE study, 0.6% (2/324) vs 1.5% (5/324) of patients reported adverse events (AEs) of symptomatic IVA with zanubrutinib vs ibrutinib, respectively
 - No events of symptomatic IVA were reported in the zanubrutinib arm of the ASPEN study; 1 event was observed in the ibrutinib arm
- The EAIR of symptomatic IVA was lower with zanubrutinib (0.43 per 100 person-years) vs ibrutinib (1.19 per 100 person-years) in the ALPINE study (*P* = 0.2270) and in the pooled analysis for zanubrutinib (0.14 per 100 person-years) vs ibrutinib (0.87 per 100 person-years; *P* = 0.0028; **Figure 3B**)
- Across the pooled populations, symptomatic IVA led to discontinuation in 0.06% (1/1550) of patients treated with zanubrutinib and 0.5% (2/422) of patients treated with ibrutinib
 - No deaths due to symptomatic IVA occurred with zanubrutinib, and 1 death occurred with ibrutinib

Figure 3. (A) Event Rate and (B) EAIR of IVA in Clinical Studies With Zanubrutinib



Patients with structural heart diseases at baseline or at the time of VA occurrence were excluded from the IVA analysis. Patients with active infection such as COVID-19 without evidence of arrhythmia were excluded. Symptomatic IVA are grade 2 or higher VA events. *Pooled analysis of the ibrutinib arms in ASPEN cohort 1 and ALPINE studies. †Based on the asymptotic distributions of the EAIR, assuming that EAIRs of the 2 groups are independent and identically distributed and that time to first event follows exponential distribution of constant hazard. N, number of patients.

CONCLUSIONS

- The EAIRs of Afib in the ASPEN cohort 1 (*P* = 0.0010) and ALPINE (*P* = 0.0003) studies were significantly lower for zanubrutinib than ibrutinib, and consistent with the rates in the pooled analysis of patients with B-cell malignancies treated with zanubrutinib
- EAIR of symptomatic IVA was significantly lower with zanubrutinib than ibrutinib in the pooled populations (*P* = 0.0028) and numerically lower in the ALPINE study (*P* = 0.2270)
 - The EAIR of symptomatic IVA with zanubrutinib in ALPINE was low (0.4 per 100 person-years), but the EAIR with ibrutinib was consistent with that of previous reports (1.2 per 100 person-years)^{14,16}
- The data from the 2 head-to-head studies comparing zanubrutinib with ibrutinib in patients with CLL or WM, as well as pooled data presented here, demonstrate that the rates of Afib and symptomatic IVA with zanubrutinib are overall low and occur less frequently compared with those of ibrutinib
- Our findings confirm that zanubrutinib has a favorable cardiac safety profile and support the use of zanubrutinib as a treatment option for patients with B-cell malignancies

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DISCLOSURES

MZ, AC, LC, HM, NW, SA, JZ: employment and stock ownership with BeiGene. CST: honoraria from Janssen, AbbVie, BeiGene, Loxo Oncology, Novartis; research funding from Janssen, AbbVie, BeiGene.

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