Rate of Atrial Fibrillation in Patients With B-Cell Malignancies Who Undergo Treatment With Zanubrutinib

Abstract 1324736

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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 BTK inhibitor, ibrutinib[1]
- 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 (VA)[6]
- Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition-related toxicities[7]
- Zanubrutinib has been generally well tolerated, with an established efficacy in clinical trials in patients with B-cell malignancies[8-13]
- Here, we report the occurrence of Afib and symptomatic idiopathic VA (IVA; defined as a VA occurring in structurally normal hearts in the absence of myocardial scarring and active infections[14]) in the 2 head-to-head trials of zanubrutinib vs ibrutinib, ASPEN[8] (NCT03053440) and ALPINE[13] (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 (EAIR) of Afib and IVA with zanubrutinib vs ibrutinib were calculated in a post hoc analysis of the phase 3 clinical studies ASPEN[8] (cohort 1) and ALPINE[13] 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 (i.e. VA or HTN) was assessed at the time of enrollment and before treatment with zanubrutinib or ibrutinib using MedDRA v24.0
- Afib included atrial fibrillation and atrial flutter events; VA included any event in SMQs of ventricular tachyarrhythmias (narrow) and MedDRA HLT of ventricular arrhythmias and cardiac arrest; cases were adjudicated to include IVA
- Afib and VA events that occurred during treatment were graded by 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

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 men (66%), White (67%), and had an ECOG performance status of 0 or 1 (44.5% and 49.4%, respectively)

Medical History of Cardiac Disorders

- The medical history 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**)

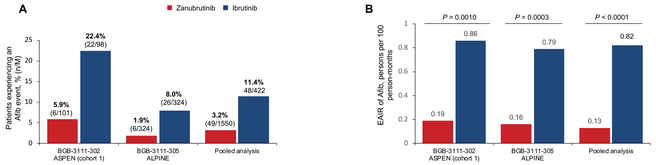
Table 2. Medical History of Cardiovascular Disorders

	BGB-3111-302 ASPEN cohort 1 WM		BGB-3111-305 ALPINE R/R CLL/SLL		Pooled analysis B-cell malignancies	
Medical history of cardiovascular disorders, n (%)	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 EAIR 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**

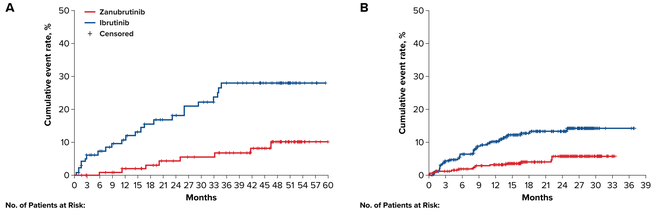
Figure 1. (A) Event Rate and (B) EAIR of Afib in Clinical Studies With Zanubrutinib



	BGB-3111-302 ASPEN (cohort 1)		BGB-3111-305 ALPINE		Pooled analysis	
Median duration of exposure, months	35.0	34.6	13.5	12.8	23.0	13.8
Total exposure time, person-months	3122.3	2561.9	3639.1	3277.3	36750.0	5839.2
EAIR difference (95% CI)	-0.67 (-1.06, -0.27)		-0.63 (-0.96, -0.29)		-0.69 (-0.93, -0.45)	

EAIR of Afib was a prespecified analysis; differences between treatment duration were compensated for by calculation of EAIR.[15]

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

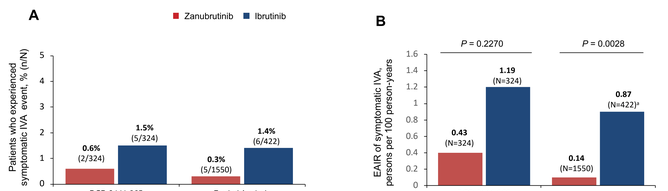


No. of Patients at Risk:																									
Zanubrutinib	101	95	94	92	89	87	84	79	77	75	74	74	70	68	63	57	43	28	14	7	0				
Ibrutinib	98	87	83	78	74	71	68	64	62	59	58	54	49	48	45	38	33	15	5	3	0				
Zanubrutinib	324	312	302	294	286	234	184	166	153	81	22	3	0												
Ibrutinib	324	295	278	260	245	193	147	128	118	54	9	3	3	0											

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 AEs of symptomatic IVA with zanubrutinib vs ibrutinib, respectively
  - No events of symptomatic IVA were reported in the zanubrutinib arm of the ASPEN study; one 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 one death occurred with ibrutinib

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



	BGB-3111-305 ALPINE		Pooled Analysis	
Median duration of exposure, months	13.5	12.8	23.0	13.8
Total exposure time, years	462.8	421.1	3523.2	690.9
EAIR ratio (95% CI)[b]	0.36 (0.07, 1.88)		0.16 (0.05, 0.54)	

[a]Pooled analysis of the ibrutinib arms in ASPEN cohort 1 and ALPINE studies. [b]Based on the asymptotic distributions of the EAIR, assuming that EAIR of the 2 groups are independent and identically distributed and that time to first event follows exponential distribution of constant hazard.
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.

CONCLUSIONS

- The EAIR 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 ibrutinib
- Our findings support the use of zanubrutinib as a treatment option for patients with B-cell malignancies

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ABBREVIATIONS

AE, adverse event; Afib, atrial fibrillation or atrial flutter; BTK, Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CTCAE, Common Terminology Criteria for AEs; EAIR, exposure-adjusted incidence rates; ECOG, Eastern Cooperative Oncology Group; HLT, high-level term; HTN, hypertension; IVA, idiopathic ventricular arrhythmia; M, number of patients treated; MCL, mantle cell lymphoma; MedDRA, Medical Dictionary for Regulatory Activities; MZL, marginal zone lymphoma; N, number of patients; NCI, national clinical trial; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; SMQs, standardized MedDRA queries; TN, treatment naive; VA, ventricular arrhythmia; WM, Waldenström macroglobulinemia.

DISCLOSURES

CST: honoraria from Janssen, AbbVie, BeiGene, Loxo Oncology, Novartis; research funding from Janssen, AbbVie, BeiGene
MZ, AC, LC, HM, NW, SA, JZ: employment and stock ownership with BeiGene
PTS: consulting funding from BeiGene; Executive Committee Member of Cardiac Safety Research Consortium

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ACKNOWLEDGMENTS

The authors wish to thank the study patients, their supporters, and investigators, and clinical research staff at study centers. This study was sponsored by BeiGene. Editorial support was provided by Bio Connections LLC (Chicago, IL), supported by BeiGene USA, Inc.
BeiGene was involved in the study design, compilation of data, and statistical analysis.