Rate of Atrial Fibrillation 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 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, symptomatic idiopathic VA (IVA; defined as VA without history of myocardial infarction/left ventricular ejection fraction <50%/severe active infections[14]), and hypertension (HTN) in the 2 trials comparing zanubrutinib vs ibrutinib (ASPEN[8] and ALPINE[13]), and a pooled analysis of 8 additional 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 (ie, 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. Hypertension included any event coded to hypertension (SMQ narrow)
- 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

*Subjects enrolled in LTE were counted in parental studies.

RESULTS

- Overall, 1550 patients received zanubrutinib as monotherapy for the treatment of B-cell malignancies, with the largest subgroup being CLL/SLL (61%)
  - 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 (93.9%)

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 vs ibrutinib

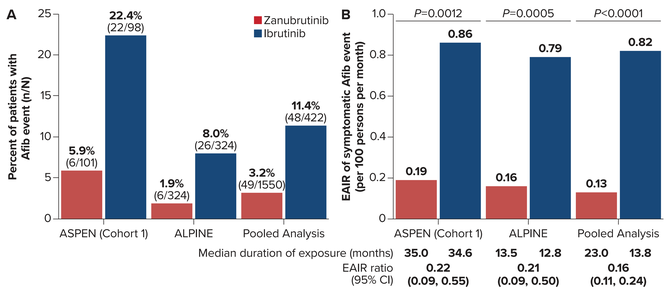
Table 2. Medical History of Cardiovascular Disorders

	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)
Hypertension	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 ASPEN (Cohort 1) or ALPINE, the rate of treatment-emergent Afib events was approximately 4-fold lower with zanubrutinib than ibrutinib (**Figure 1A**)
- The EAIR of Afib was significantly lower with zanubrutinib than ibrutinib in both studies ($P<0.05$); zanubrutinib Afib EAIR in the pooled analysis was comparable with rates observed in ASPEN and ALPINE (**Figure 1B**)

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

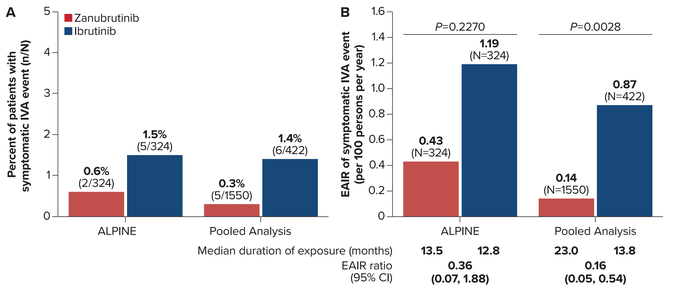


Frequency of Afib was a predefined endpoint for the in in the ALPINE study. EAIR analysis was ad hoc for all other studies.[15]

Analysis of Ventricular Arrhythmias

- Symptomatic IVA rate (**Figure 2A**) and EAIR of symptomatic IVA (**Figure 2B**) were lower with zanubrutinib vs ibrutinib in both the ALPINE study and in the pooled analysis
- 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 2: (A) Event Rate and (B) EAIR of IVA in Clinical Studies With Zanubrutinib*

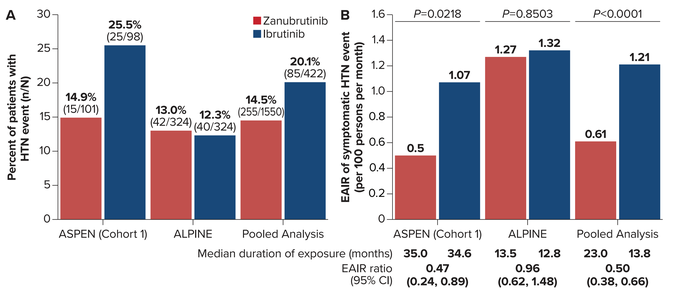


*No events of symptomatic IVA were reported in the zanubrutinib arm of the ASPEN study; one event was observed in the ibrutinib arm. Patients with structural heart diseases at baseline or at the time of VA occurrence were excluded from the IVA analysis. Patients with active infection such as COVID-19 without evidence of arrhythmia were excluded. Symptomatic IVA are grade 2 or higher VA events.

Analysis of Hypertension

- Compared with ibrutinib, the proportion of patients with HTN (**Figure 3A**) and the EAIR of HTN (**Figure 3B**) were lower with zanubrutinib, except in the ALPINE study where these rates were similar
  - Despite the similar HTN rates, incidence of cardiac events and discontinuations due to cardiac events were lower with zanubrutinib compared with ibrutinib[13]

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



CONCLUSIONS

- The EAIR of Afib in the ASPEN cohort 1 and ALPINE 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]
- Compared with ibrutinib, HTN rates were generally lower with zanubrutinib except in the ALPINE study
  - After ~13 months of exposure HTN rates were similar between zanubrutinib and ibrutinib in ALPINE; however, rates of cardiac events, including Afib, discontinuations, and death due to cardiac events remained lower in the patients treated with zanubrutinib
  - While HTN rates between zanubrutinib and ibrutinib in the ASPEN study were similar for the first 12-15 months, with longer follow-up began to differentiate in favor of zanubrutinib
- These data demonstrate that the rates of Afib, symptomatic IVA, and HTN with zanubrutinib are low and generally occur less frequently compared with ibrutinib
- Our findings support the use of zanubrutinib as a treatment option for patients with B-cell malignancies

REFERENCES

1. Coutre S et al. *Blood Adv.* 2019;3(12):1799-1807
2. O'Brien S et al. *Lymphoma Myeloma Leuk.* 2018;18(10):648-657
3. Shanafelt T et al. *Leuk Lymphoma.* 2017;58(7):1630-1639
4. Jain P et al. *J Clin Oncol.* 2022;40(2):202-212
5. Buske C et al. *J Clin Oncol.* 2022;40(1):52-62
6. IMBRUVICA® (ibrutinib) [package insert]. Janssen Biotech, Inc; August 2022.
7. Guo Y et al. *J Med Chem.* 2019;62(17):7923-7940
8. Tam C et al. *Blood.* 2020;136(18):2038-2050
9. Song Y et al. *Blood.* 2022;139(21):3148-3158
10. Tam C et al. *Lancet Oncol.* 2022;23(8):1031-1043
11. Xu W et al. *J Hematol Oncol.* 2020;13(1):48
12. An G et al. *Clin Cancer Res.* 2021;27(20):5492-5501
13. Hillmen P et al. *J Clin Oncol.* 2023;41(5):1035-1045.
14. Bhat SA et al. *Blood.* 2022;140(20):2142-2145
15. Ganatra S et al. *JACC Clin Electrophysiol.* 2018;4(12):1491-1500
16. Lampson B et al. *Blood* 2017;129(18):2581-2584

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; LTE, Long-term expansion; 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.

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