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

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Disclosure information

Han Ma, MD, PhD

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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]
- Ibrutinib treatment has been associated with an increased risk of cardiovascular toxicities such as atrial fibrillation or atrial flutter (Afib)[2-5] and ventricular arrhythmia (VA)[6]
- Zanubrutinib is…
  - An irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition-related toxicities[7]
  - Generally well tolerated, with an established efficacy in clinical trials in patients with B-cell malignancies[8-13]

We report the occurrence of Afib, symptomatic IVA, and hypertension (HTN) in the 2 head-to-head trials of zanubrutinib vs ibrutinib, ASPEN[8] (NCT03053440) and ALPINE[13] (NCT03734016), and a pooled analysis of 8 additional zanubrutinib studies

BTK, Bruton tyrosine kinase.

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.

Methods

- Safety data from clinical studies of zanubrutinib were pooled and descriptively analyzed
- Primary analysis: compare exposure-adjusted incidence rate (EAIR) of Afib and IVA between ibrutinib and zanubrutinib in a post hoc analysis of ASPEN[1] (cohort 1) and ALPINE[2] and in a pooled analysis of 10 clinical studies
  - *P*-values of the comparison calculated based on asymptotic normal distribution

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-033	B-cell malignancies	02343120	International	373
BGB-3111-214	MZL	03846427	International	68
BGB-3111-LTE1[a]	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

[a]Subjects enrolled in LTE were counted in parental studies.

Afib, atrial fibrillation or atrial flutter; CLL, chronic lymphocytic leukemia; EAIR, exposure-adjusted incidence rates; IVA, idiopathic ventricular arrhythmia; 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.

1. Tam C et al. *Blood.* 2020;136(18):2038-2050; 2. Hillmen P, et al. *J Clin Oncol*. 2023;41(5):1035-1045.

Methods

- Exposure-adjusted incidence rate (EAIR) reflects the incidence of AEs, adjusting for exposure time, and describes number of patients who experienced the event per 100 patients-months of follow-up
- 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
- Symptomatic VAs were Grade ≥2 VA events per CTCAE[a]

Afib	VA	IVA	HTN
Atrial fibrillation or atrial flutter events	Any event in SMQs of ventricular tachyarrhythmias (narrow) and MedDRA HLT of ventricular arrhythmias and cardiac arrest	VA without history of myocardial infarction/left ventricular ejection fraction <50% or concurrent severe active infections[1]	Any event coded to HTN (SMQ narrow)

[a]CTCAE v5.0 was used in the LTE1 study and v4.03 was used in all other studies.
CTCAE, Common Terminology Criteria for AEs; HLT, high-level term; HTN, hypertension; IVA, idiopathic ventricular arrhythmia; MedDRA, Medical Dictionary for Regulatory Activities; SMQs, standardized MedDRA queries; TEAE, treatment-emergent adverse event; VA, ventricular arrhythmia.
1. Bhat A et al. *Blood*. 2022;140 (20):2142–2145.

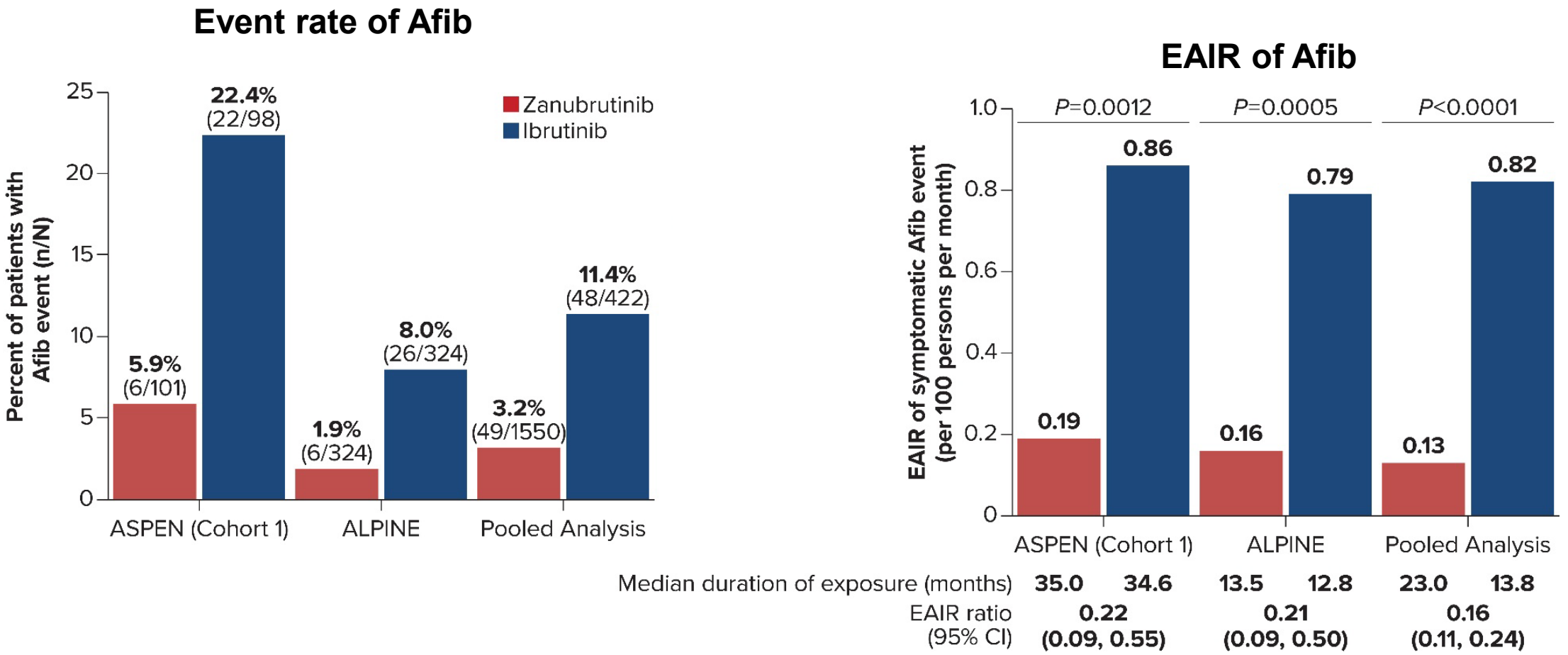
Patient Disposition and Medical History of Cardiovascular Disorders

- Overall, 1550 patients received zanubrutinib as monotherapy for the treatment of B-cell malignancies, with the largest subgroup being CLL/SLL, constituting 61% of patients
  - Median age was 67 years, with 61% of patients aged ≥65 years old
  - 66% of patients were male, 67% were white, and 93.9% had a baseline ECOG PS of 0 or 1

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)	166 (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)

Afib, atrial fibrillation or atrial flutter; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; HTN, hypertension; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; VA, ventricular arrhythmia; WM, Waldenström macroglobulinemia.

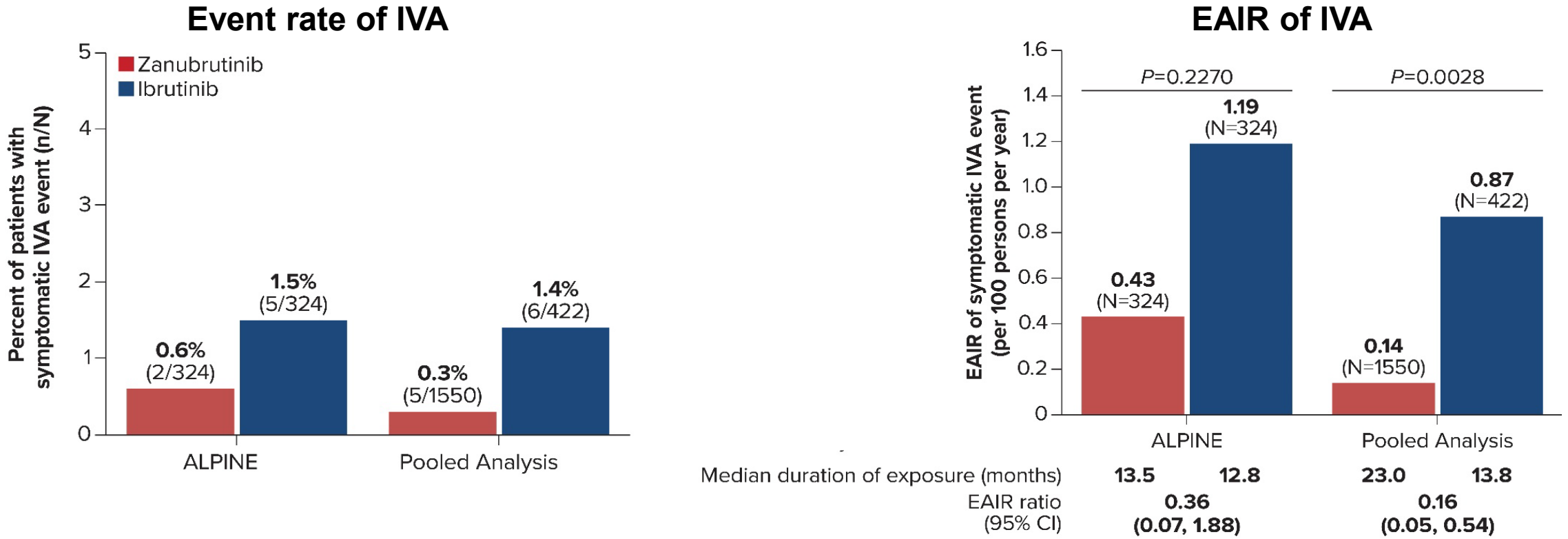
Atrial Fibrillation/Flutter (Afib) Occurred Less Frequently in Patients Treated with Zanubrutinib



Frequency of Afib was a predefined endpoint for the in the ALPINE study. EAIR analysis was ad hoc for all other studies.[1]
CI, confidence interval; EAIR, exposure-adjusted incidence rates.

1. Ganatra S, et al. *JACC Clin Electrophysiol.* 2018;4(12):1491-1500.

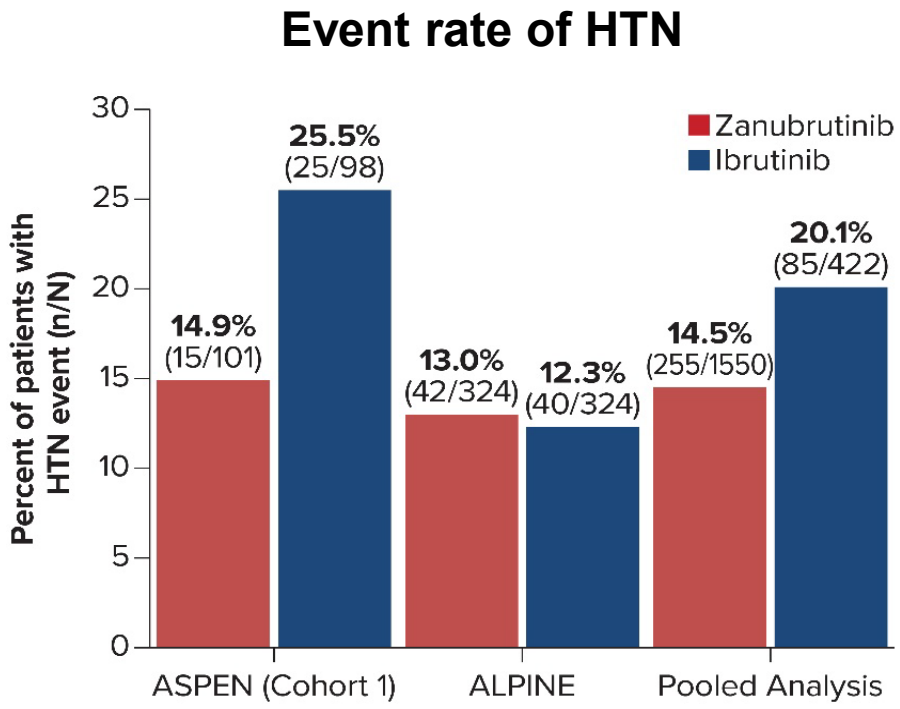
Symptomatic IVA Occurred Less Frequently in Patients Treated with Zanubrutinib[a]

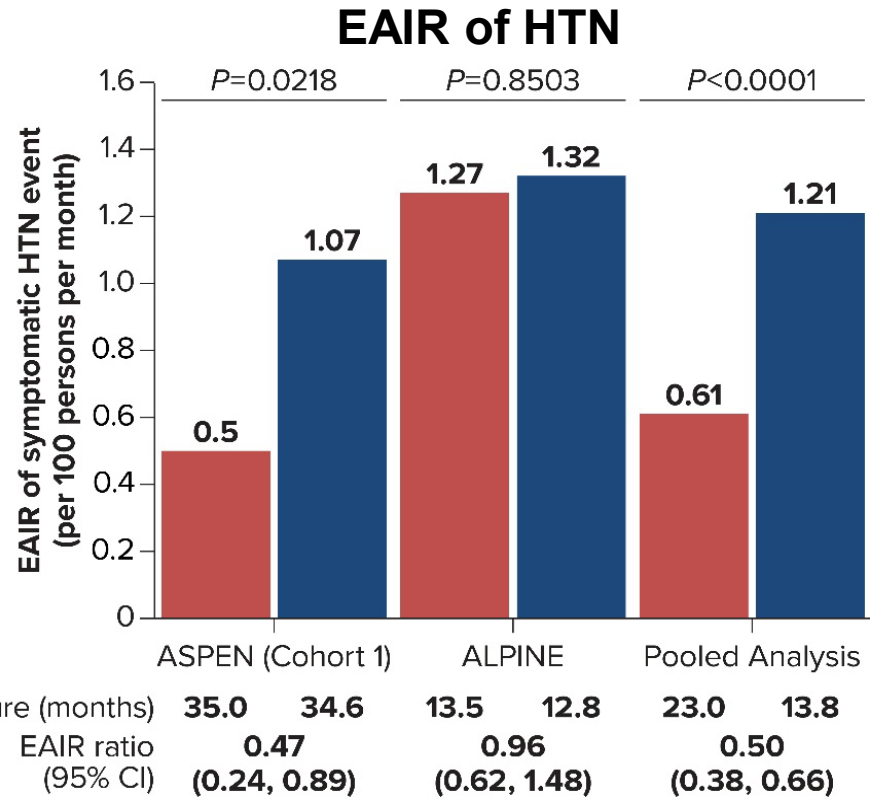


- No events of symptomatic IVA were reported in the zanubrutinib arm of the ASPEN study and 1 event was observed in the ibrutinib arm
- Across the pooled populations, symptomatic IVA led to discontinuation in 0.06%, or 1/1550 patients treated with zanubrutinib and 0.5%, or 2/422 patients treated with ibrutinib
  - No deaths due to symptomatic IVA occurred with zanubrutinib, and 1 death occurred with ibrutinib

CI, confidence interval; EAIR, exposure-adjusted incidence rates; IVA, idiopathic ventricular arrhythmia.

Rates of HTN were Generally Lower with Zanubrutinib, Except in the ALPINE Study[1]





Median duration of exposure (months)	35.0	34.6	13.5	12.8	23.0	13.8
EAIR ratio (95% CI)	0.47 (0.24, 0.89)		0.96 (0.62, 1.48)		0.50 (0.38, 0.66)	

- Despite the similar HTN rates in the ALPINE study, incidence of cardiac events were lower with zanubrutinib compared with ibrutinib, and there were no discontinuations due to cardiac events with zanubrutinib

CI, confidence interval; EAIR, exposure-adjusted incidence rates; HTN, hypertension.

1. Hillmen P, et al. *J Clin Oncol.* 2023;41(5):1035-1045.

ALPINE was an Outlier for HTN

- ASPEN shows a clear 2-fold reduction in EAIR of HTN with zanubrutinib vs ibrutinib

Source	Indication	N (Zanubrutinib/ Ibrutinib or BR)	EAIR Zanubrutinib	EAIR Ibrutinib
ASPEN	WM	101/98	0.45	0.89
ALPINE	R/R CLL/SLL	324/324	1.04	1.17
SEQUOIA	TN CLL/SLL	240/227	0.54	N/A (BR=0.81)
All R/R CLL	R/R CLL/SLL	525	0.76	N/A
All Pooled	All B-cell	1550	0.61	N/A

BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; EAIR, exposure-adjusted incidence rate; HTN, hypertension; R/R, relapsed/refractory; SLL, small lymphocytic lymphoma; TN, treatment-naive; WM, Waldenström macroglobulinemia.

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 safety populations
- EAIR of symptomatic IVA was significantly lower with zanubrutinib than ibrutinib in the pooled populations (P = 0.0028)
  - 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), and the EAIR with ibrutinib was consistent with that of previous reports (1.2 per 100 person-years)[1,2]
- Compared with ibrutinib, HTN rates were lower with zanubrutinib except in the ALPINE study
- Discontinuation due to cardiac events was lower with zanubrutinib compared with ibrutinib; symptomatic IVA led to fewer discontinuations with zanubrutinib vs ibrutinib in the pooled population, and there were no discontinuations due to cardiac events with zanubrutinib in the ALPINE study
- Our findings support the use of zanubrutinib as a treatment option with low cardiac toxicity for patients with B-cell malignancies

1. Bhat A et al. *Blood*. 2022;140 (20):2142–2145; 2. Lampson B, et al. *Blood.* 2017;129(18):2581-2584.

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