DP066

Risk of Hypertension in Patients With CLL/SLL Who Participated in the ALPINE Study: A Post Hoc Analysis

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INTRODUCTION

- Ibrutinib, the first-generation BTK inhibitor, is associated with an increased risk of cardiovascular events, including hypertension[1]
- Zanubrutinib is a potent and selective next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target effects[2]
- Results from a pooled safety analysis showed that zanubrutinib is generally well tolerated and has lower rates of hypertension compared with ibrutinib[3]
  - However, in the phase 3 ALPINE study, patients with relapsed/refractory (R/R) CLL/SLL had similar hypertension TEAE rates with zanubrutinib and ibrutinib,[4] which is not consistent with other clinical studies[5,6]
- This post hoc analysis evaluated the risk of developing hypertension with zanubrutinib vs ibrutinib in ALPINE based on initiation of antihypertensive therapy

METHODS

- Time to first event of hypertension and rates of antihypertensive medication use in the zanubrutinib (n=324) and ibrutinib (n=324) arms of ALPINE were assessed (**Figure 1**)
- Concomitant antihypertensive drugs were defined by the WHODrug medicinal information dictionary Standardized Drug Groupings
- Concomitant antihypertensive drugs were adjudicated by an independent hypertension specialist who was blinded to BTK inhibitor assignment
- Time-to-onset endpoints were analyzed using the log-rank test

Figure 1. Study Design

[a] New antihypertensive therapy is defined as any new medications for hypertension taken after the first dose of study drug. [b] New class of antihypertensive is defined as any new medications for hypertension in a new class taken after the first dose of study drug. KM, Kaplan-Meier; SDG, Standardized Drug Grouping; SMQ, Standardized MedDRA Query.

RESULTS

- At baseline, patient characteristics were generally balanced between the zanubrutinib and ibrutinib arms (**Table 1**)

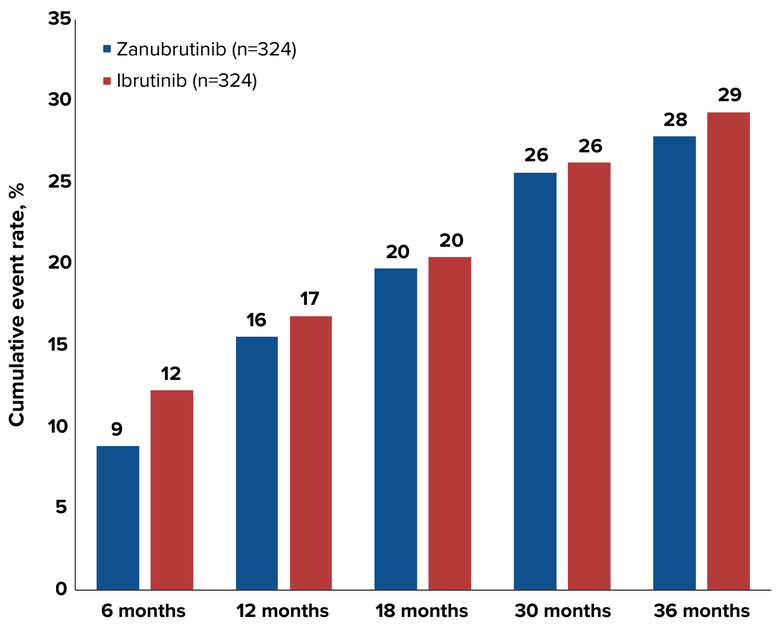
Table 1. Baseline Demographics

Characteristic	Zanubrutinib (n=324)	Ibrutinib (n=324)
Age, median (range), years	67.0 (35-90)	67.5 (35-89)
Male sex, n (%)	212 (65)	231 (71)
Race, n (%)		
White	261 (81)	264 (81)
Asian	45 (14)	44 (14)
BMI, mean (SD), kg/m²	27.2 (4.9)	27.1 (4.6)
Key hematologic parameters, mean (SD)		
Hemoglobin, g/L	121.6 (21.9)	120.5 (20.3)
Neutrophil count, 10^9/L	4.1 (2.5)	4.2 (4.8)
Platelet count, 10^9/L	139.1 (65.5)	132.1 (57.1)
eGFR, mean (SD), mL/min per 1.73 m²	72.8 (17.8)	70.2 (17.8)
Type 2 diabetes mellitus, n (%)	67 (21)	63 (19)
Hyperlipidemia, n (%)	95 (29)	80 (25)
Heart rate, mean (SD), bpm	76.9 (10.7)	76.2 (11.7)
Hypertension SMQ narrow, n (%)	165 (51)	162 (50)
Baseline systolic blood pressure, mean (SD) [range], mmHg	128.9 (16.0) [92-187]	127.3 (15.1) [92-187]
Prior antihypertensive drug use, n (%)	157 (48)	150 (46)

Data cutoff: August 8, 2022.
BMI, body mass index; bpm, beats per minute; eGFR, estimated glomerular filtration rate; SMQ, Standardized MedDRA Query.

- Overall, the rates for time to first event of hypertension were similar in both the zanubrutinib and ibrutinib arms (**Figure 2**)
- Among patients not on an antihypertensive medication at baseline, 21% of zanubrutinib-treated patients and 29% of ibrutinib-treated patients initiated antihypertensive therapy during the study (**Figure 3**)
- Fewer patients in the zanubrutinib arm initiated new antihypertensive therapy (**Figure 3**) and initiation was later compared with the ibrutinib arm (**Figure 4**; hazard ratio [HR], 0.77; *P*=.071)
- Fewer patients in the zanubrutinib arm initiated a new class of antihypertensive drugs (**Figure 3**) and had a statistically significant delay in initiation vs the ibrutinib arm (**Figure 5**; HR, 0.72; *P*<.05)
- The cumulative event rates for initiation of a new antihypertensive drug or a new class of antihypertensive drug were consistently lower with zanubrutinib compared with ibrutinib at each time point (**Figures 4** and **5**)

Figure 2. Cumulative Event Rate of Hypertension Over Time



CONCLUSIONS

- In patients with CLL/SLL from the ALPINE study, initiation of a new antihypertensive drug or a new class of antihypertensive drug occurred less frequently with zanubrutinib vs ibrutinib
- Initiation of antihypertensive therapy occurred sooner with ibrutinib compared with zanubrutinib
- These findings should be considered when initiating BTK inhibitor therapy in patients with CLL/SLL who have an elevated cardiovascular risk

Figure 3. Summary of Antihypertensive Therapy in ALPINE

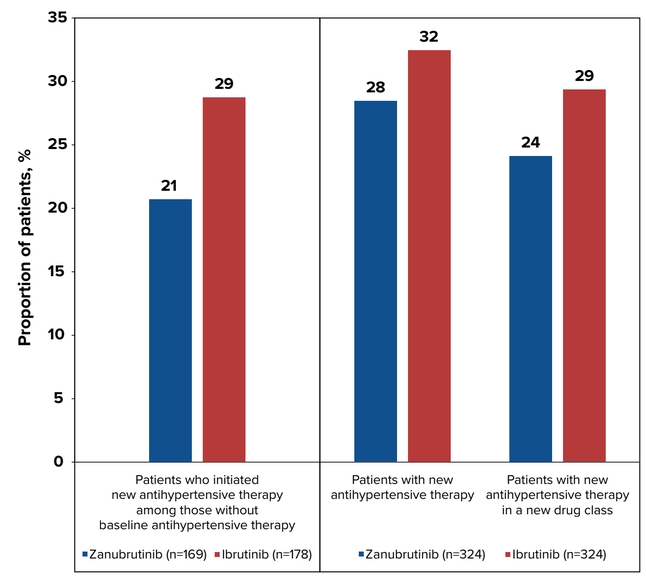
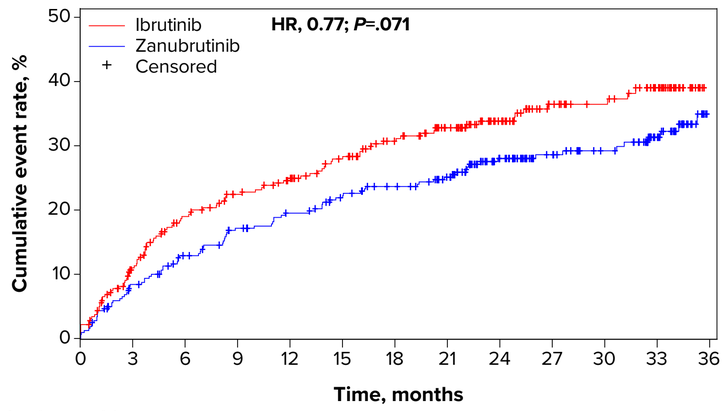


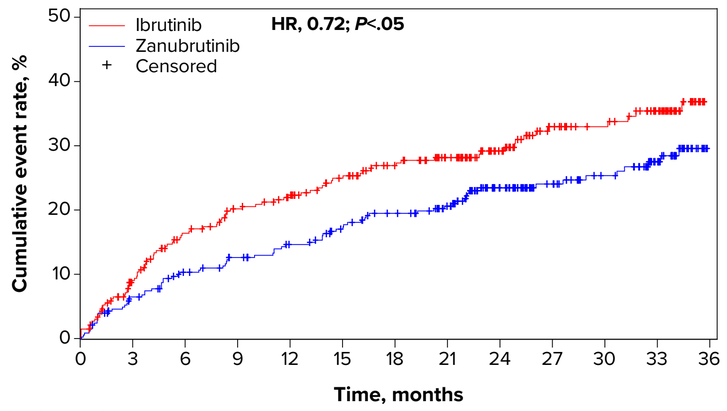
Figure 4. Kaplan-Meier Curve of Time to Initiation of First New Antihypertensive Drug



No. of patients at risk

Ibrutinib	324	271	238	220	208	189	169	150	115	85	76	59	26
Zanubrutinib	324	289	268	250	238	225	214	198	149	120	106	80	33

Figure 5. Kaplan-Meier Curve of Time to Initiation of First Antihypertensive Drug in a New Class



No. of patients at risk

Ibrutinib	324	277	246	227	216	197	179	162	127	94	84	67	28
Zanubrutinib	324	295	276	264	252	238	225	208	157	125	109	83	35

REFERENCES

1. Quartermaine C, et al. *JACC CardioOncol.* 2023;5(5):570-590.
2. Guo Y, et al. *J Med Chem.* 2019;62(17):7923-7940.
3. Tam CS, et al. *Blood Adv.* 2022;6(4):1296-1308.
4. Brown JR, et al. *N Engl J Med.* 2023;388(4):319-332.
5. Tam CS, et al. *Blood.* 2020;136(18):2038-2050.
6. Tam CS, et al. *Lancet Oncol.* 2022;23(8):1031-1043.

DISCLOSURES

AMF: Consulting or advisory role: AbbVie, BeiGene, AstraZeneca, Janssen. Travel, accommodations, expenses: AbbVie, BeiGene. **DR, WA:** Employment, leadership and stock options: BeiGene. **LC, JZ:** Employment and stock options: BeiGene. **WBW:** Consultant: BeiGene.

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