Risk of hypertension in patients with CLL/SLL who participated in ALPINE: a post hoc analysis

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Background: Bruton tyrosine kinase (BTK) inhibitors are an important therapeutic option for patients with CLL/SLL. The first-generation BTK inhibitor, ibrutinib (ibru), is associated with an increased risk of hypertension. Zanubrutinib (zanu) is a next-generation BTK inhibitor designed to maximize BTK occupancy and minimize toxicity with fewer off-target effects. This analysis evaluated the risk of developing hypertension based on initiation of antihypertensives (anti-HTN) in ALPINE (NCT03734016).

Methods: Anti-HTN use in the zanu (n=324) and ibru (n=324) treatment arms was assessed. The definition of anti-HTN was based on Standardized Drug Grouping; concomitant anti-HTN were adjudicated by an independent hypertension specialist blinded to BTK inhibitor assignment. Time to initiating new anti-HTN and time to adding a new class of anti-HTN were assessed using the Kaplan-Meier method. Comparisons of time-to-onset endpoints were analyzed based on the log-rank test.

Results: At baseline, patient characteristics were generally balanced between zanu and ibru arms (median age, 66.7 vs 67.1 y; male, 65.1% vs 71.4%; history of hypertension, 50.9% vs 50.0%; type 2 diabetes mellitus, 10.1% vs 8.9%). Among patients not on anti-HTN at baseline, 20.7% (n=35/169) of zanu- and 28.7% (n=51/178) of ibru-treated patients initiated anti-HTN during the study. Among all patients, fewer patients in the zanu arm initiated new anti-HTN (28.4% [n=92/324] vs 32.4% [n=105/324]) and the anti-HTN were initiated later (hazard ratio [HR], 0.77; *P*-value=.071). Additionally, statistically fewer patients in the zanu arm compared with the ibru arm started anti-HTN in a new class (24.1% [n=78/324] vs 29.3% [n=95/324]) and the anti-HTN were started later (HR, 0.72; *P*-value=.034). The event rates for initiation of new anti-HTN or a new class of anti-HTN were consistently lower in the zanu vs ibru arm at each timepoint (**Table**).

Conclusions: In ALPINE, initiation of new anti-HTN or a new class of anti-HTN occurred less frequently in the zanu arm vs the ibru arm in patients with CLL/SLL. Adoption of anti-HTN occurred sooner with ibru than zanu. These findings should be considered when initiating BTK inhibitor therapy in patients with CLL/SLL who have an elevated cardiovascular risk.

	Initiation of new anti-HTN				Initiation of new class of anti-HTN			
	Zanubrutinib		Ibrutinib		Zanubrutinib		Ibrutinib	
	No. at risk	Cumulative event rate, %	No. at risk	Cumulative event rate, %	No. at risk	Cumulative event rate, %	No. at risk	Cumulative event rate, %
3 mo	289	8.4	271	11.0	295	6.5	277	9.1
6 mo	268	12.9	238	19.0	276	10.4	246	16.4
12 mo	238	19.5	208	24.6	252	14.7	216	22.0
18 mo	214	23.7	169	30.7	225	19.5	179	27.0
24 mo	149	28.0	115	33.8	157	23.5	127	29.2
30 mo	106	29.2	76	36.5	109	25.4	84	33.0