INDIRECT COMPARISON OF ZANUBRUTINIB VS ACALABRUTINIB AND IBRUTINIB EFFICACY IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA

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Background: In treatment-naive (TN) chronic lymphocytic leukemia (CLL)**,** zanubrutinib (SEQUOIA [NCT03336333]), acalabrutinib (ELEVATE-TN; [NCT02475681]), and ibrutinib (RESONATE-2; [NCT01722487]) were evaluated in separate trials. This study compared zanubrutinib vs acalabrutinib and zanubrutinib vs ibrutinib via indirect naive comparison analysis.

Methods: The zanubrutinib vs acalabrutinib comparison comprised zanubrutinib-treated patients without del(17p) and/or *TP53* mutation (mut) from arm A of SEQUOIA (n=215; median follow-up, 72.8 months) and acalabrutinib monotherapy-treated patients from ELEVATE-TN, (n=156; median follow-up, 74.5 months). SEQUOIA arm A and RESONATE-2 enrolled patients without del(17p), but patients could have *TP53*mut. The zanubrutinib vs ibrutinib comparison comprised zanubrutinib-treated patients from SEQUOIA arm A (n=241; median follow-up, 72.8 months) and ibrutinib-treated patients from RESONATE-2 (n=136; median follow-up, 82.7 months); the proportion of patients with *TP53*mut were comparable for zanubrutinib vs ibrutinib. For the zanubrutinib vs ibrutinib analysis, COVID-19–adjusted progression-free survival (PFS) and overall survival (OS) were used from SEQUOIA due to impact of the COVID-19 pandemic on SEQUOIA. Pseudo-individual patient data for patients treated with acalabrutinib and ibrutinib were reconstructed from digitized Kaplan-Meier (KM) curves of PFS per investigator assessment, and OS. Hazard ratios (HRs) and 95% CIs were estimated using a Cox proportional hazards model, and landmark rates and rate differences were estimated using the KM method; 95% CIs for rate differences were calculated using a Wald-type statistic.

Results: Baseline clinical characteristics between groups were relatively well balanced for each comparison. PFS and OS rates are shown (**Table**). The HRs for zanubrutinib vs acalabrutinib for PFS and OS were 0.76 (95% CI, 0.52-1.11; *P*=.1553) and 0.66 (95% CI, 0.41-1.06; *P*=.0836), respectively. For zanubrutinib vs ibrutinib, these were 0.65 (95% CI, 0.44-0.97; *P*=.0330) for PFS and 0.60 (95% CI, 0.36-1.01; *P*=.0532) for OS. At the 72-month landmark, the rate difference in PFS between zanubrutinib vs acalabrutinib was 9.9% (95% CI, 3.0%-16.9%); for OS, the rate difference was 8.8% (95% CI, 2.0%-15.5%). For zanubrutinib vs ibrutinib, the rate difference was 15.3% (95% CI, 8.3%-22.2%) for PFS and 9.9% (95% CI, 3.0%-16.7%) for OS.

Summary/Conclusion: In this indirect naive comparison analysis of patients with TN CLL, zanubrutinib demonstrated higher PFS and OS than ibrutinib, and higher PFS and OS than acalabrutinib at 72 months. The analysis included a large population with comparable risk features and similar median follow-up across SEQUOIA, ELEVATE-TN, and RESONATE-2, though remaining differences in patient characteristics should be considered when interpreting these results.

Table: PFS and OS rates

Time (months)	SEQUOIA vs ELEVATE-TN				SEQUOIA vs RESONATE-2[a]			
	PFS, %		OS, %		PFS, %		OS, %	
	Zanu w/o del(17p) and/or *TP53*mut n=215	Acala w/o del(17p) and/or *TP53*mut n=156	Zanu w/o del(17p) and/or *TP53*mut n=215	Acala w/o del(17p) and/or *TP53*mut n=156	Zanu n=241	Ibru n=136	Zanu n=241	Ibru n=136
12	95.8	94	98.6	98	95.8	95	98.3	98
24	90.6	90	95.7	95	90.7	88	96.2	95
36	85.8	83	92.4	93	87.1	82	94.0	88
48	83.4	80	90.4	88	85.3	77	92.7	86
60	78.0	73	87.0	84	80.3	72	89.4	83
72	74.0	64	85.0	76	76.5	61	87.6	78

[a]Includes *TP53*mut

Abbreviations: acala, acalabrutinib; ibru, ibrutinib; mut, mutated; OS, overall survival; PFS, progression-free survival; w/o, without; zanu, zanubrutinib.