Zanubrutinib Demonstrated Superior Progression-Free Survival vs Ibrutinib for Treatment of Relapsed/Refractory Chronic Lymphocytic Leukemia and Small Lymphocytic Lymphoma: Final Analysis of Phase 3 ALPINE Study

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Introduction: Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are usually characterized by consecutive relapses, and response to therapy ultimately dictates survival. While ibrutinib, a first-generation Bruton tyrosine kinase inhibitor (BTKi), has become standard therapy, it has well-described off-target effects that can limit use. Compared with ibrutinib, zanubrutinib, a next-generation BTKi, provides improved BTK occupancy across disease-relevant tissues with greater kinase selectivity. In a randomized phase 3 study (ALPINE; NCT03734016), zanubrutinib was compared head to head with ibrutinib as treatment for relapsed/refractory (R/R) CLL/SLL. At predefined interim response analyses, zanubrutinib demonstrated a superior overall response rate (ORR) assessed by both

independent review committee (IRC) and investigator; data from the predefined final progression-free survival (PFS) analysis are reported here.

Materials and methods: Patients with R/R CLL/SLL who had received ≥1 prior therapy and had measurable disease were randomized 1:1 to receive zanubrutinib or ibrutinib until disease progression or unacceptable toxicity. Stratification was based on age, refractory status, geographical region, and del(17p)/*TP53* mutation status. As the primary endpoint of ORR was superior with zanubrutinib, the key secondary efficacy endpoint of PFS was tested for noninferiority under hierarchical testing when 205 PFS events had been observed. If PFS noninferiority between zanubrutinib and ibrutinib was demonstrated, superiority of zanubrutinib vs ibrutinib could be tested and claimed if the 2-sided *P* value was <.04996. Other endpoints included overall survival (OS), ORR including partial response with lymphocytosis (PR-L) or better, and safety parameters including atrial fibrillation/flutter.

Results: Patients (N=652) from 15 countries were randomized to receive zanubrutinib (n=327) or ibrutinib (n=325). Demographic and disease characteristics were balanced between zanubrutinib and ibrutinib arms (age ≥65 years [61.5 vs 61.5%]; male [65.1 vs 71.4%]; unmutated IGHV [73.1 vs 73.5%]; del(17p) [13.8 vs 15.4%]; and *TP53* mutated without del(17p) [9.2 vs 7.7%]). Across the study population, median age was 67 and 68 years, respectively; in both arms, median prior lines of therapy was 1.

With a median follow-up of 29.6 months (data cutoff, 8 August 2022), zanubrutinib PFS, assessed by IRC (PFS_{IRC}), was superior to that of ibrutinib in the intention-to-treat population (hazard ratio [HR]: 0.65 [95% CI, 0.49-0.86]; 2-sided *P*=.0024; 24-month PFS: 79.5 vs 67.3%, respectively). Identical statistical values were reported when assessed by investigator. Median PFS_{IRC} was 35.0 months (95% CI, 33.2-44.3) for ibrutinib-treated patients but not reached for zanubrutinib-treated patients. In a predefined subgroup of patients with del(17p)/*TP53* mutation, longer PFS_{IRC} was demonstrated with zanubrutinib than ibrutinib (HR: 0.52 [95% CI, 0.30-0.88]; nominal *P*=.0134; 24-month PFS: 77.6 vs 55.7%, respectively). PFS, regardless of IRC or investigator assessment, consistently favored zanubrutinib across other major predefined subgroups, including IGHV status. Compared with ibrutinib, zanubrutinib had a higher ORR_{IRC} (86.2 vs 75.7%, nominal 2-sided *P*=.0007), with a rate of PR-L or better of 91.7 vs 83.1% (nominal 2-sided *P*=.001).

The treatment discontinuation rate was lower with zanubrutinib (26.3%) vs ibrutinib (41.2%), with most discontinuations due to AEs (16.2 vs 22.8%) or progressive disease (7.3 vs 12.9%); the discontinuation rate due to cardiac disorders was 0.3 vs 4.3%. Rates of grade ≥3 AEs (67.3 vs 70.4%), serious AEs (42.0 vs 50.0%), dose interruptions (50.0 vs 56.8%), and dose reductions (12.3 vs 17.0%) were also lower with zanubrutinib vs ibrutinib. The rate of atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2 vs 13.3%); rates of other AEs of special interest were similar between treatments. There were no grade 5 AEs due to cardiac disorders with zanubrutinib vs 6 (1.9%) with ibrutinib. Overall, 48 (14.7%) patients treated with zanubrutinib and 60 (18.5%) treated with ibrutinib died (OS HR: 0.76 [95% CI, 0.51-1.11]).

Conclusions: As ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTKis, zanubrutinib has now proven superiority to ibrutinib in both ORR and PFS in patients with R/R CLL/SLL. Efficacy benefits with zanubrutinib were observed across all major subgroups, including patients with high-risk disease. Zanubrutinib had a favorable safety profile compared with ibrutinib, with a lower rate of treatment discontinuation and fewer cardiac disorder events, including fewer cardiac

events leading to death. These data suggest that zanubrutinib is more efficacious and better tolerated than ibrutinib as treatment for R/R CLL/SLL.