Zanubrutinib demonstrates superior progression-free survival (PFS) compared with ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL): final analysis of ALPINE randomized phase 3 study

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ABSTRACT

Objectives: Ibrutinib, a first-generation Bruton tyrosine kinase (BTK) inhibitor, has become standard therapy for CLL/SLL, but its well-described off-target effects can limit use. In the randomized phase 3 ALPINE study (NCT03734016), zanubrutinib, a next-generation BTK inhibitor with improved BTK occupancy and greater kinase selectivity, was compared head-to-head with ibrutinib as treatment for R/R CLL/SLL and demonstrated a superior overall response rate (ORR) at the predefined interim response analysis. Here we report findings from the predefined final PFS analysis of the ALPINE trial.

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, geographic 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 were 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%, respectively; male, 65.1% vs 71.4%; unmutated *IGHV*, 73.1% vs 73.5%; del[17p], 13.8% vs 15.4%; *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 number of prior lines of therapy was 1. With a median follow-up of 29.6 months (data cutoff: August 8, 2022), PFS assessed by independent review committee (PFS_{IRC}) was superior with zanubrutinib vs ibrutinib in the intention-to-treat population (24-month PFS rate, 79.5% vs 67.3%; hazard ratio [HR], 0.65; 95% CI, 0.49-0.86; 2-sided *P*=.0024). Identical statistical values were reported when assessed by investigator. Median PFS_{IRC} was 35.0 months (95% CI, 33.2-44.3 months) in ibrutinib-treated patients but was not reached in zanubrutinib-treated patients. In a predefined subgroup of patients with del(17p)/*TP53* mutation, longer PFS_{IRC} was demonstrated with zanubrutinib vs ibrutinib (24-month PFS rate, 77.6% vs 55.7%; HR, 0.52; 95% CI, 0.30-0.88; nominal *P*=.0134). PFS, whether by IRC or investigator assessment, consistently favored zanubrutinib in other major predefined subgroups, including *IGHV* mutation status. Additionally, ORR_{IRC} was higher with zanubrutinib vs ibrutinib (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 rate of treatment discontinuation was lower with zanubrutinib (26.3%) vs ibrutinib (41.2%), and discontinuation was mainly due to adverse events (AEs) (16.2% vs 22.8%) or progressive disease (7.3% vs 12.9%); the rate of discontinuation 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 interruption (50.0% vs 56.8%), and dose reduction (12.3% vs 17.0%) were also lower with zanubrutinib vs ibrutinib. The rate of atrial fibrillation/flutter was lower with zanubrutinib vs ibrutinib (5.2% vs 13.3%); rates of other AEs of special interest were similar between treatment arms. No grade 5 AEs due to cardiac disorders occurred with zanubrutinib vs 6 (1.9%) with ibrutinib. Overall, 48 patients (14.7%) treated with zanubrutinib and 60 (18.5%) treated with ibrutinib died (OS HR, 0.76; 95% CI, 0.51-1.11).

Conclusion: ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTK inhibitors, and with this updated final analysis, zanubrutinib has proven superiority to ibrutinib for 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 deaths. These data suggest that zanubrutinib is more efficacious and better tolerated than ibrutinib as treatment for patients with R/R CLL/SLL.