Zanubrutinib demonstrates superior progression-free survival versus ibrutinib for relapsed/refractory CLL/SLL: ALPINE final analysis

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Introduction: Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) is often characterized by consecutive relapses and renewed need for therapy. First-generation Bruton tyrosine kinase inhibitor (BTKi) ibrutinib is standard of care but has off-target side effects that can limit use. Zanubrutinib, a next-generation BTKi, provides improved BTK occupancy across disease-relevant tissues with greater kinase selectivity. In predefined interim response analyses of ALPINE, a randomized phase 3 study comparing zanubrutinib with ibrutinib (NCT03734016), zanubrutinib demonstrated superior overall response rate (ORR) in patients with relapsed/refractory CLL/SLL. Here, the progression-free survival (PFS) final analysis is reported.

Methods: Patients with relapsed/refractory CLL/SLL who had received ≥1 prior therapy and had measurable disease (N=652) were randomized 1:1 to receive zanubrutinib (n=327) or ibrutinib (n=325) until disease progression or unacceptable toxicity. 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.

Results: As of August 8, 2022 (median follow-up: 29.6 months), zanubrutinib PFS by independent review committee (PFS_{IRC}) was superior to ibrutinib in the intent-to-treat population (HR: 0.65 [95% CI, 0.49-0.86]; 2-sided *P*=.0024); statistical values were identical by investigator assessment. In a predefined subgroup of patients with del(17p)/*TP53* mutation, longer PFS_{IRC} was demonstrated with zanubrutinib than ibrutinib. PFS consistently favored zanubrutinib across other major predefined subgroups, including *IGHV* status, regardless of IRC or investigator assessment. Rates of treatment discontinuation, overall (26.3% versus 41.2%) and due to cardiac disorders (0.3% versus 4.3%), were lower with zanubrutinib versus ibrutinib, respectively. Grade ≥3 adverse events (AEs), serious AEs, dose interruption, and dose reduction were also lower with zanubrutinib compared with ibrutinib. Rate of atrial fibrillation/flutter was lower with zanubrutinib compared with ibrutinib (5.2% versus 13.3%); rates of other AEs of special interest were similar between treatments. No grade 5 AEs due to cardiac disorders with zanubrutinib versus 6 (1.9%) with ibrutinib were observed. Overall, 48 (14.7%) and 60 (18.5%) patients treated with zanubrutinib or ibrutinib, respectively, died (OS HR: 0.76 [95% CI, 0.51-1.11]).

Conclusions: ALPINE is the first study to demonstrate PFS superiority in a head-to-head comparison of BTKi in patients with relapsed/refractory CLL/SLL. With these data, coupled with results from the pre-defined interim analyses, zanubrutinib has now proven superiority to ibrutinib in both PFS and ORR endpoints.