

## **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): Results From Final Analysis of ALPINE Randomized Phase 3 Study**

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**Introduction:** CLL/SLL is 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 R/R CLL/SLL. At predefined response analyses, zanubrutinib demonstrated superior overall response rate (ORR); data from the predefined final PFS analysis are reported here.

**Methods:** Patients (pts) with R/R CLL/SLL who had received  $\geq 1$  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 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 PR with lymphocytosis (PR-L) or better, and safety parameters including atrial fibrillation/flutter.

**Results:** Pts (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  $\geq 65$  yrs [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%]; TP53 mutated without del(17p) [9.2 vs 7.7%]). Across the study population, median age was 67 and 68 yrs, respectively; in both arms, median prior lines of therapy was 1.

With a median follow-up of 29.6 mo (data cutoff, 8 Aug 2022), zanubrutinib PFS, assessed by independent review committee (PFS<sub>IRC</sub>), was superior to ibrutinib in the ITT population (HR: 0.65 [95% CI, 0.49-0.86]; 2-sided *P*=.0024 [Fig 1]); identical statistical values were reported when assessed by investigator (INV). Median PFS<sub>IRC</sub> was 35.0 mo (95% CI, 33.2-44.3) for ibrutinib-treated pts but not reached for zanubrutinib-treated pts. In a predefined subgroup of pts with del(17p)/TP53 mutation, longer PFS<sub>IRC</sub> was demonstrated with zanubrutinib than ibrutinib (Fig 2). PFS, regardless of IRC or INV assessment, consistently favored zanubrutinib across other major predefined subgroups, including IGHV

status. Compared with ibrutinib, zanubrutinib had a higher ORR<sub>IRC</sub> (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  $P=.001$ ).

Treatment discontinuation rate was lower with zanubrutinib (26.3%) vs ibrutinib (41.2%) with most due to AEs (16.2 vs 22.8%) or progressive disease (7.3 vs 12.9%); discontinuation rates due to cardiac disorders were 0.3% vs 4.3%. Rates of grade  $\geq 3$  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. 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%) pts treated with zanubrutinib and 60 (18.5%) treated with ibrutinib had 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 BTK inhibitors, zanubrutinib has now proven superiority to ibrutinib in both ORR and PFS in pts with R/R CLL/SLL. Efficacy benefits with zanubrutinib were observed across all major subgroups, including high-risk pts. 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 zanubrutinib is more efficacious and better tolerated than ibrutinib as treatment for R/R CLL/SLL.

Figure 1. IRC-Assessed Progression-Free Survival (ITT Population)

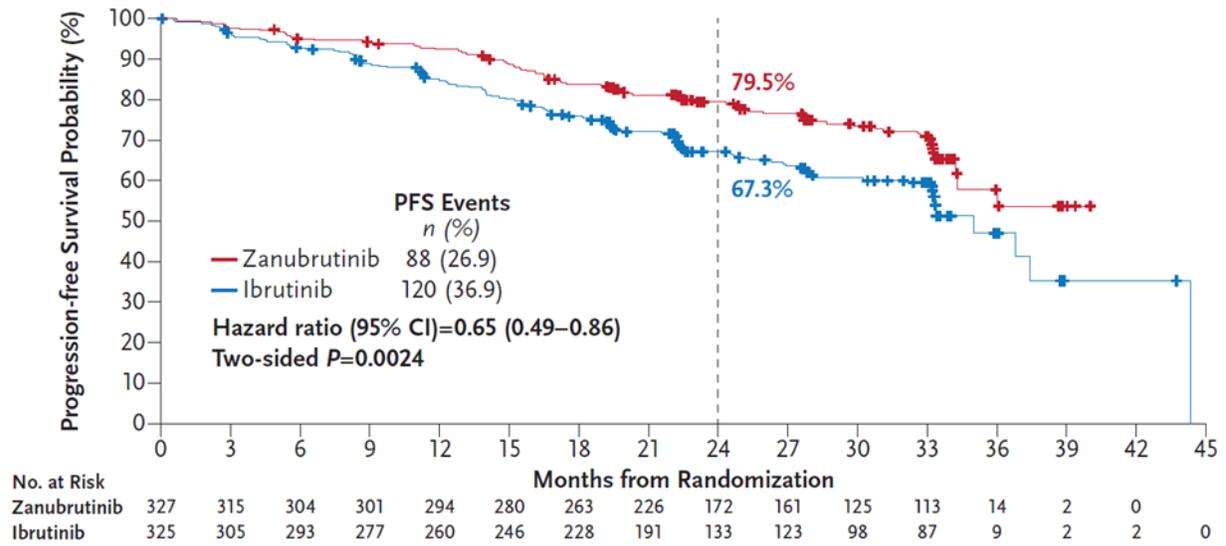


Figure 2. IRC-Assessed Progression-Free Survival in Patients With del(17p)/TP53 Mutation

