Extended follow-up of ALPINE randomized phase 3 study confirms sustained superior progression-free survival of zanubrutinib versus ibrutinib for treatment of relapsed/refractory chronic lymphocytic leukemia and small lymphocytic lymphoma (R/R CLL/SLL)

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ABSTRACT

Introduction: In the randomized, phase 3 ALPINE study (NCT03734016), zanubrutinib demonstrated superior progression-free survival (PFS) and overall response rate (ORR) over ibrutinib in patients with R/R CLL/SLL (Brown et al. *NEJM*; 2022). Here, we report updated results after more than 3 years of follow-up.

Patients and Methods*:* Patients with R/R CLL/SLL, ≥1 prior therapy, and measurable disease were randomized 1:1 to receive zanubrutinib or ibrutinib. Efficacy was evaluated by the investigator based on 2008 iwCLL criteria; sensitivity analyses were conducted to confirm PFS results. Updated safety analyses were performed. All reported *P*-values are descriptive.

Results*:* As of 15-September-2023, 652 patients received zanubrutinib (n=327) or ibrutinib (n=325); 194 (59%) remain on zanubrutinib and 152 (47%) on ibrutinib. 130 zanubrutinib-treated and 172 ibrutinib-treated patients discontinued treatment, most commonly due to AE (n=69, zanubrutinib; n=88, ibrutinib) or disease progression (n=51, zanubrutinib; n=62, ibrutinib). At a median study follow-up of 39.0 months, PFS benefit of zanubrutinib was sustained over ibrutinib (HR: 0.68 [95% CI, 0.53-0.86]; *P*=.0011); 36-month PFS rates were 64.9% with zanubrutinib and 54.8% with ibrutinib. PFS benefits with zanubrutinib were observed in the del(17p)/*TP53* subgroup (HR: 0.52 [95% CI, 0.33-0.83]; *P*=.0047); 36-month PFS rates were 58.6% and 41.3%, respectively. The zanubrutinib PFS benefit was confirmed in a sensitivity analysis that included only progression and death events occurring on active treatment (HR: 0.69 [95% CI, 0.50-0.95]; *P*=.0206). ORR was 85.6% and 74.8% (*P*=.0006), CR/CRi rates were 10.7% and 7.1%, and 90.2% and 82.8% achieved PR-L or better with zanubrutinib and ibrutinib, respectively. 64 (19.6%) patients treated with zanubrutinib and 78 (24.0%) with ibrutinib had died (OS HR: 0.75 [95% CI, 0.54-1.05]); median OS was not reached.
The most common any-grade AE with zanubrutinib and ibrutinib was COVID-19 (39.2% vs 27.2%). The most common grade ≥3 AE was neutropenia (both 17.3%). Overall cardiac events remained lower with zanubrutinib, including atrial fibrillation/flutter (6.8% vs 16.4%; *P*<.0001). No fatal cardiac events occurred with zanubrutinib, while 6 (1.9%) occurred with ibrutinib.

Conclusions: ALPINE was the first head-to-head comparison of BTK inhibitors to demonstrate PFS superiority. At median follow-up of 39 months, durable PFS benefits with zanubrutinib were observed across major subgroups, including multiple sensitivity analyses. Safety/tolerability profiles were consistent with previous reports; cardiac safety profile remained favorable for zanubrutinib, with no new safety signals emerging with longer follow-up. These results reconfirm zanubrutinib improved efficacy over ibrutinib and a more favorable safety profile in patients with R/R CLL/SLL.