***Title (Italian):*** ZANUBRUTINIB DIMOSTRA UNA SOPRAVVIVENZA LIBERA DA PROGRESSIONE SUPERIORE RISPETTO A IBRUTINIB NEL TRATTAMENTO DELLA LEUCEMIA LINFATICA CRONICA E DEL LINFOMA A PICCOLI LINFOCITI RECIDIVATI/ REFRATTARI: ANALISI FINALE DELLO STUDIO ALPINE DI FASE 3

***Title (English):*** ZANUBRUTINIB (ZANU) DEMONSTRATES SUPERIOR PROGRESSION-FREE SURVIVAL (PFS) VS IBRUTINIB (IBR) FOR TREATMENT OF RELAPSED/ REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA (R/R CLL/SLL): FINAL ANALYSIS OF PHASE 3 ALPINE STUDY

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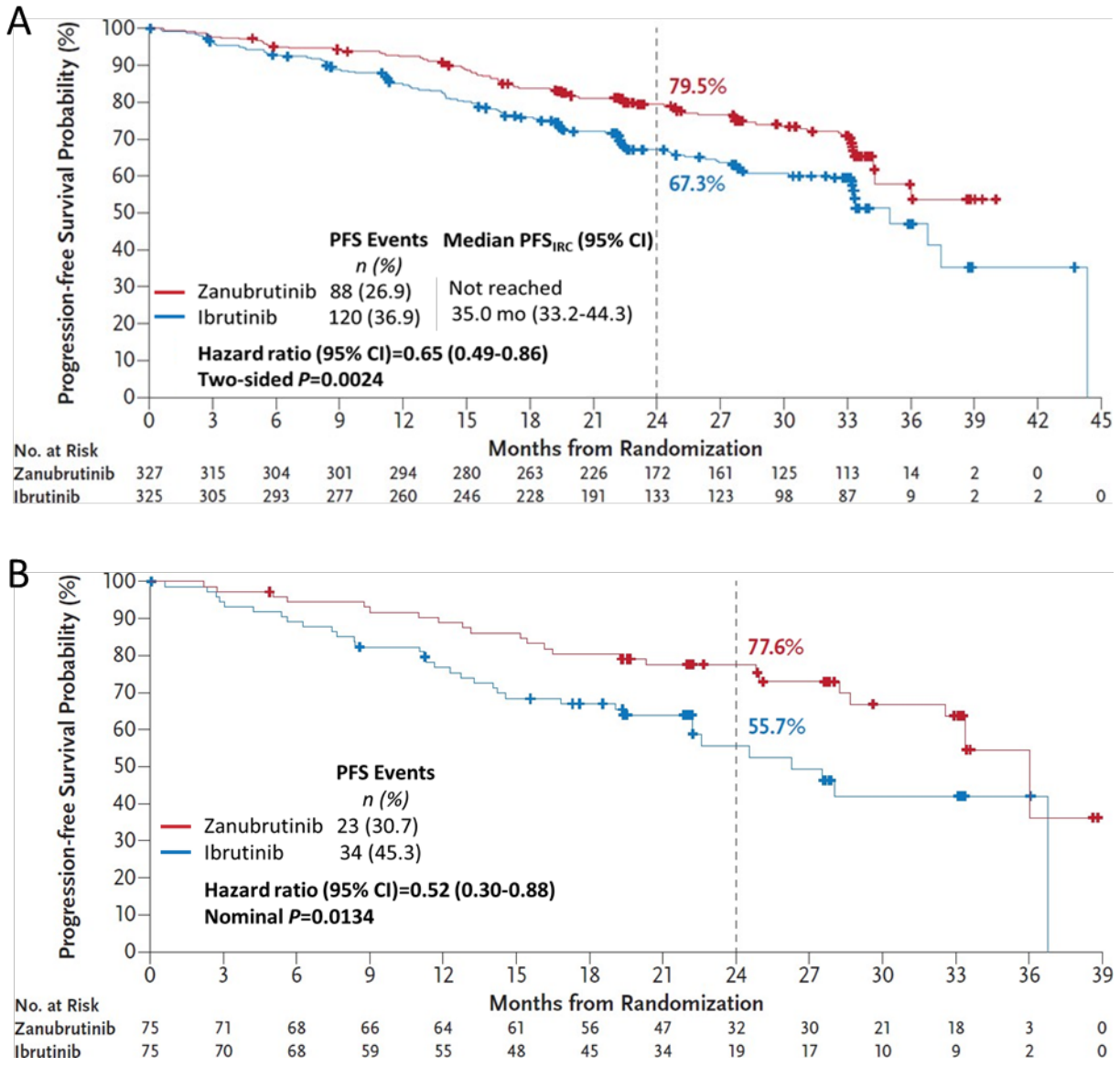
**Introduction:** ZANU is a next-generation Bruton tyrosine kinase inhibitor (BTKi) that has improved BTK occupancy across disease-relevant tissues with greater kinase selectivity compared with the first-generation BTKi IBR. In the phase 3 ALPINE study (NCT03734016), ZANU was superior to standard therapy, IBR, in the treatment of R/R CLL/SLL in the predefined interim analysis of the primary endpoint, overall response rate (ORR) assessed by both independent review committee (IRC) and investigator. Here, data from the predefined final analysis of the key secondary efficacy endpoint of PFS are reported.

**Methods:** Patients (pts) with R/R CLL/SLL who received ≥1 prior therapy and had measurable disease were randomized 1:1 to receive ZANU (n=327) or IBR (n=325) until disease progression or unacceptable toxicity. As results for the primary endpoint of ORR were superior with ZANU, the key secondary efficacy endpoint, PFS, was examined using hierarchical testing after 205 PFS events were reached. If ZANU noninferiority was shown, superiority of ZANU over IBR could be tested and supported at a 2-sided *P* value of <.04996. Other endpoints included overall survival (OS) and safety.

**Results:** At the data cutoff (August 8, 2022; median follow-up, 29.6 mo), PFS per IRC with ZANU was superior to that with IBR in the intention-to-treat population (hazard ratio [HR], 0.65; *P*=.0024) (**Figure 1a**). Across major predefined subgroups, PFS by IRC and investigator consistently favored ZANU over IBR, including in pts with del(17p)/*TP53* mutation (**Figure 1b**). Rates of overall treatment discontinuation (26% vs 41%) and discontinuation due to cardiac disorders (0.3% vs 4.3%), grade ≥3 AEs (67% vs 70%), serious AEs (42% vs 50%), atrial fibrillation/flutter (5% vs 13%), dose interruption (50% vs 57%), dose reduction (12% vs 17%), and death (15% vs 19%) were all lower with ZANU vs IBR. No grade 5 AEs due to cardiac disorders were observed with ZANU vs 6 (1.9%) with IBR. The HR for OS with ZANU vs IBR was 0.76 (95% CI, 0.51-1.11).

**Conclusions:** ALPINE is the first study to show PFS superiority with ZANU in a head-to-head comparison of BTKis in pts with R/R CLL/SLL. With these data and the results from the predefined interim analysis, ZANU has shown superior ORR and PFS and a favorable safety profile vs IBR for treatment of R/R CLL/SLL.

**Figure 1. IRC-Assessed Progression-Free Survival in (A) the Intention-to-Treat Population and (B) Pts With del17p/*TP53* Mutation.**




IRC, independent review committee; PFS, progression-free survival.