FIRST INTERIM ANALYSIS OF ALPINE STUDY: RESULTS OF A PHASE 3 RANDOMIZED STUDY OF ZANUBRUTINIB (ZANU) VS IBRUTINIB (IBRU) IN PATIENTS WITH RELAPSED/REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA (CLL/SLL)

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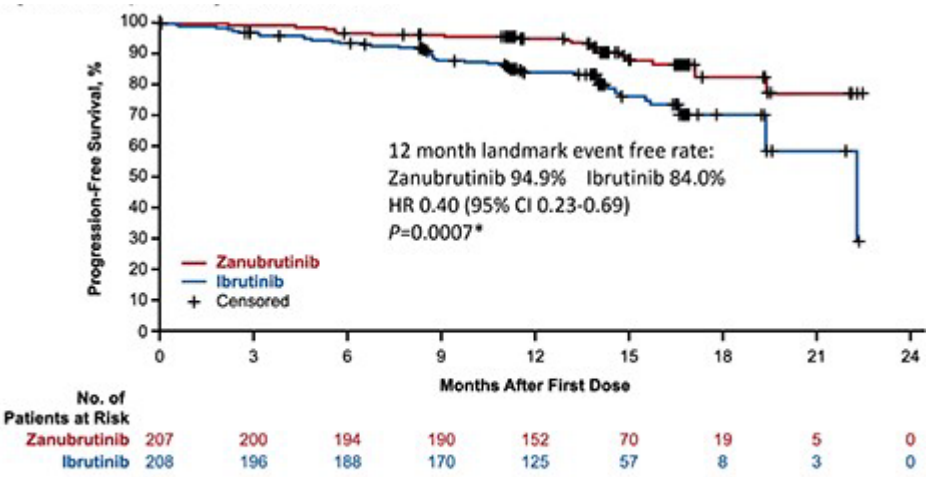
ABSTRACT

Treatment of CLL/SLL has been transformed with Bruton tyrosine kinase inhibitors (BTKi) such as ibru. Zanu is a next-generation BTKi designed to maximize BTK occupancy and minimize off-target kinase inhibition, which may improve efficacy and safety outcomes. ALPINE (BGB-3111-305; NCT03734016) is a global, randomized, phase 3 study of zanu vs ibru in patients (pts) with R/R CLL/SLL. Presented here are results of a preplanned interim analysis that occurred ~12 mo after enrollment of the first 415 pts (of 652 total pts). Pts with R/R CLL/SLL were randomized 1:1 to receive zanu 160 mg twice daily or ibru 420 mg once daily until disease progression. Randomization was stratified by age (<65 y vs ≥65 y), geographic region, refractory status, and del(17p)/*TP53* mutation status. The primary endpoint was overall response rate (ORR) by investigator assessment per 2008 IWCLL guidelines or Lugano criteria (SLL), to evaluate noninferiority of zanu to ibru response ratio at a noninferiority margin of 0.8558. If noninferiority was demonstrated, a hierarchical testing approach was used to test superiority of zanu vs ibru in ORR. From 5Nov2018 and 20Dec2019, 415 pts were randomized. Treatment groups were balanced for baseline characteristics (zanu vs ibru): age ≥65 y 62.3% vs 61.5%; male 68.6% vs 75%; >3 prior therapy lines 7.2% vs 10.1%; del(17p) 11.6% vs 12.5%; *TP53* mutated without del(17p) 8.2% vs 5.8%. At a median follow-up of 15 mo, ORR was significantly higher with zanu vs ibru (78.3% vs 62.5%, 2-sided *P*=0.0006 compared with prespecified α=0.0099 for interim analysis). ORR was higher in pts with del(11q) (83.6% vs 69.1%) and del(17p) (83.3% vs 53.8%) with zanu, as were overall 12-mo progression-free survival (PFS; 94.9% vs 84.0%; figure) and overall survival (97.0% vs 92.7%). The rate of atrial fibrillation/flutter (AF) was significantly lower with zanu vs ibru (2.5% vs 10.1%, 2-sided *P*=0.0014, compared with prespecified α=0.0099 for interim analysis). Rates of major bleeding (2.9% vs 3.9%), and adverse events leading to discontinuation (7.8% vs 13.0%) or death (3.9% vs 5.8%) were also lower with zanu. The rate of neutropenia was higher with zanu (28.4% vs 21.7%), while grade ≥3 infections were lower with zanu (12.7% vs 17.9%). In this interim analysis, zanu had a superior response rate, improved PFS, and a lower rate of AF compared with ibru. These data suggest that more selective BTK inhibition, with more complete, sustained BTK occupancy, improved efficacy and safety outcomes.

Figure. PFS by Investigator Assessment



No. of Patients at Risk									
Zanubrutinib	207	200	194	190	152	70	19	5	0
Ibrutinib	208	196	188	170	125	57	8	3	0

*Not a prespecified analysis; formal analysis of PFS will be based on all patients when the target number of events are reached.
Median PFS follow-up was 14.0 months for both zanubrutinib and ibrutinib arms by reverse KM method.