

First Interim Analysis Results of ALPINE Phase 3 Study of Zanubrutinib vs Ibrutinib in R/R Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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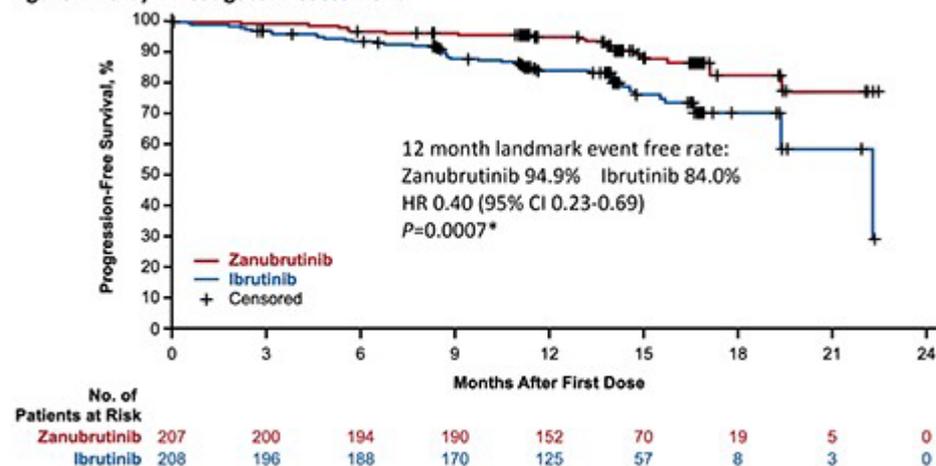
Background: Treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has been transformed with the advent of effective inhibitors of B-cell receptor signaling, such as Bruton tyrosine kinase (BTK) inhibitors. The first-generation BTK inhibitor ibrutinib is a standard of care in CLL/SLL. Zanubrutinib is an irreversible, potent, next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition of TEC and EGFR family kinases. Activity and tolerability of zanubrutinib in patients (pts) with CLL/SLL has been demonstrated in early phase trials. ALPINE (BGB-3111-305; NCT03734016) is a global, randomized, phase 3 study of zanubrutinib vs ibrutinib in pts with relapsed/refractory (R/R) CLL/SLL. Here we present the results of a pre-planned interim analysis scheduled approximately 12 mo after the first 415 out of 652 pts were enrolled.

Methods: Patients with R/R CLL/SLL were randomly assigned 1:1 to receive zanubrutinib 160 mg twice daily or ibrutinib 420 mg once daily until disease progression. Randomization was stratified by age (<65 yrs vs ≥65 yrs), geographic region, refractory status, and del17p/TP53 mutation status. The primary endpoint was overall response rate (ORR) as determined by investigators using the 2008 iwCLL guidelines for CLL and the Lugano criteria for SLL. Sample size was calculated to provide 90% power to demonstrate non-inferiority of zanubrutinib to ibrutinib response ratio at the non-inferiority margin of 0.8558. A hierarchical testing approach was implemented to test the superiority of zanubrutinib over ibrutinib in ORR if non-inferiority was demonstrated.

Results: Between 5 Nov 2018 and 20 Dec 2019, 415 pts were randomized. Treatment groups were well balanced for demographic and disease characteristics: age ≥ 65 yrs 62.3% vs 61.5%, male 68.6% vs 75%, >3 prior lines of therapy 7.2% vs 10.1%, del17p 11.6% vs 12.5%, TP53 mutated without del17p 8.2% vs 5.8%, in zanubrutinib and ibrutinib arms, respectively. At a median follow-up of 15 mo, ORR was significantly higher with zanubrutinib vs ibrutinib (78.3% vs 62.5%, 2-sided $P=0.0006$ compared with pre-specified alpha of 0.0099 for interim analysis). ORR was higher in pts with del11q (83.6% vs 69.1%) and del17p (83.3% vs 53.8%) with zanubrutinib, as were overall 12-mo progression-free survival (PFS) (94.9% vs 84.0%; **Figure**) and overall survival rates (97.0% vs 92.7%). The rate of atrial fibrillation/flutter, a pre-specified safety endpoint, was significantly lower with zanubrutinib vs ibrutinib (2.5% vs 10.1%, 2-sided $P=0.0014$, compared with pre-specified alpha of 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 zanubrutinib. Rate of neutropenia was higher with zanubrutinib (28.4% vs 21.7%), while grade ≥ 3 infections were lower with zanubrutinib (12.7% vs 17.9%).

Conclusions: In this interim analysis of a randomized, phase 3 ALPINE study in pts with R/R CLL/SLL, zanubrutinib was shown to have a superior response rate, an improved PFS, and a lower rate of atrial fibrillation/flutter compared with ibrutinib. These data confirm that more selective BTK inhibition, with more complete and sustained BTK occupancy, results in improved efficacy and safety outcomes.

Figure. PFS by Investigator Assessment



*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.