First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

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Abstract Content: Treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) has been transformed with 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 next-generation BTK inhibitor designed to maximize BTK occupancy and minimize off-target inhibition. It was hypothesized that the increased specificity of zanubrutinib may minimize toxicities related to ibrutinib off-target inhibition and that more complete and sustained BTK occupancy may improve efficacy outcomes. Activity and tolerability of zanubrutinib in patients with CLL/SLL has been demonstrated in early phase trials. ALPINE (BGB-3111-305; NCT03734016) is a global, randomized, phase 3 study comparing zanubrutinib vs ibrutinib in patients 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 patients were enrolled.

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 years vs ≥65 years), geographic region, refractory status, and del17p/TP53 mutation status. The primary end point was overall response rate (ORR) as determined by investigators using the 2008 International Workshop on CLL guidelines and the Lugano criteria for CLL/SLL. Sample size was calculated to provide 90% power to demonstrate non-inferiority of zanubrutinib to ibrutinib as determined by investigators using the 2008 International Workshop on CLL guidelines and the Lugano criteria for CLL/SLL. Here we present the results of a pre-planned interim analysis scheduled approximately 12 mo after the first 415 out of 652 patients were enrolled.

Between 5 Nov 2018 and 20 Dec 2019, 415 patients were randomized. Treatment groups were well balanced for demographic and disease characteristics: age ≥65 years 62.3% vs 61.5%, male 68.6% vs 75%, >3 prior lines of therapy 7.3% 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 \( P = .0006 \) compared with a pre-specified alpha of .0099 for interim analysis). ORR was higher in patients 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%) 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 \( P = .0014 \), compared with a pre-specified alpha of .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%).

In this interim analysis of a randomized, phase 3 ALPINE study in patients 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 support that more selective BTK inhibition, with more complete and sustained BTK occupancy, results in improved efficacy and safety outcomes.