First Interim Analysis of ALPINE Study: Results of a Phase 3 Randomized Study of Zanubrutinib vs Ibrutinib in Patients With Relapsed/Refractory (R/R) Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL)

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Abstract:

Context: CLL/SLL treatment has been transformed with Bruton tyrosine kinase inhibitors (BTKi) such as ibrutinib. Zanubrutinib, a next-generation BTKi, was designed to maximize BTK occupancy and minimize toxicity. ALPINE (NCT03734016) is a global, randomized, phase 3 study of zanubrutinib versus ibrutinib in patients with R/R CLL/SLL; presented here is a pre-planned interim analysis conducted ~12 months after 415 patients enrolled between November 5, 2018, and December 20, 2019.

Design: Patients were randomized 1:1 to zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily) arms; stratification factors were age (<65 years vs ≥65 years), geographic region, refractory status, and del(17)p/*TP53* mutation.

Main outcomes measures: Primary endpoint was investigator-assessed overall response rate (ORR) per 2008 IWCLL guidelines or Lugano criteria; noninferiority of zanubrutinib-to-ibrutinib response ratio was evaluated at noninferiority margin of 0.8558. If noninferiority was demonstrated, superiority of zanubrutinib versus ibrutinib in ORR was tested.

Results: Baseline characteristics (zanubrutinib vs ibrutinib): age ≥65 years: 62.3% versus 61.5%; male sex: 68.6% versus 75%; >3 prior therapies: 7.2% versus 10.1%; del(17)p: 11.6% versus 12.5%; *TP53* mutation without del(17)p: 8.2% versus 5.8%. With median follow-up of 15 months, ORR was 78.3% versus 62.5% for zanubrutinib versus ibrutinib, respectively (2-sided *P*=0.0006, prespecified α=0.0099). ORR was higher for zanubrutinib in patients with del(11)q (83.6% vs 69.1%) and del(17)p (83.3% vs 53.8%); zanubrutinib had higher overall 12-month progression-free survival (PFS; 94.9% vs 84.0%) and overall survival (97.0% vs 92.7%). Significantly fewer patients had atrial fibrillation/flutter (AF) with zanubrutinib versus ibrutinib (2.5% vs 10.1%, 2-sided *P*=0.0014, prespecified α=0.0099). Zanubrutinib had lower rates of major bleeding (2.9% vs 3.9%), adverse events leading to discontinuation (7.8% vs 13.0%), and death (3.9% vs 5.8%). Zanubrutinib had higher neutropenia rate (28.4% vs 21.7%) while grade ≥3 infections (12.7% vs 17.9%) were lower.

Conclusions: In summary, this interim analysis showed zanubrutinib had a superior ORR, improved PFS, and lower AF rate compared with ibrutinib.