

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 leukaemia/small lymphocytic lymphoma (CLL/SLL)

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ABSTRACT

Aim: 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 vs ibrutinib in patients with R/R

CLL/SLL; presented here is a preplanned interim analysis conducted ~12 months after 415 patients enrolled between 5Nov2018–20Dec2019.

Method: Patients were randomized 1:1 to zanubrutinib (160 mg twice daily) or ibrutinib (420 mg once daily), stratified by age (<65 years vs ≥65 years), geographic region, refractory status, and del(17p)/*TP53* mutation. 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 vs ibrutinib in ORR was tested.

Results: Baseline characteristics (zanubrutinib vs ibrutinib): age ≥65 years: 62.3% vs 61.5%; male: 68.6% vs 75%; >3 prior therapies: 7.2% vs 10.1%; del(17p): 11.6% vs 12.5%; *TP53* mutation without del(17p): 8.2% vs 5.8%. With median follow-up of 15 months, ORR was 78.3% vs 62.5% for zanubrutinib vs ibrutinib (2-sided $P=.0006$, prespecified $\alpha=0.0099$). ORR was higher for zanubrutinib vs ibrutinib in patients with del(11q) (83.6% vs 69.1%) and del(17p) (83.3% vs 53.8%); zanubrutinib had higher overall 12-months 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 vs ibrutinib (2.5% vs 10.1%, 2-sided $P=.0014$, prespecified $\alpha=0.0099$). 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.

Conclusion: This interim analysis showed zanubrutinib had a superior ORR, improved PFS, and lower AF rate compared with ibrutinib.