Efficacy of continuous zanubrutinib vs fixed-duration venetoclax in combination with obinutuzumab in treatment-naive chronic lymphocytic leukemia (CLL): a matching-adjusted indirect comparison (MAIC)

Authors: Talha Munir,[1] Keri Yang,[2] Leyla Mohseninejad,[3] Sheng Xu,[4] Pal Rakonczai,[5] Balazs Dobi,[5] Rhys Williams,[2] Nicolas Martinez-Calle[6]

Affiliations: [1]Leeds Teaching Hospitals NHS Trust, Leeds, UK; [2]BeOne Medicines Ltd, San Carlos, CA, USA; [3]BeOne Medicines Ltd, Schiphol, the Netherlands; [4]BeOne Medicines Ltd, Shanghai, China; [5]Evidera, London, UK; [6]Nottingham University Hospitals NHS Trust, Nottingham, UK

ABSTRACT

Introduction: Efficacy of continuous zanubrutinib was evaluated in SEQUOIA (NCT03336333), while combination of fixed-duration venetoclax + obinutuzumab (VenO) was evaluated in CLL14 (NCT02242942). In the absence of head-to-head trials comparing zanubrutinib and VenO, an unanchored MAIC was conducted between zanubrutinib (SEQUOIA) and VenO (CLL14).

Methods: An unanchored MAIC was conducted using study data with similar median follow-up (SEQUOIA, 62.67 months; CLL14, 65.4 months). Individual patient data (IPD) for zanubrutinib from SEQUOIA were reweighted to match key population characteristics of VenO patients in CLL14, given the lack of common control arms between SEQUOIA and CLL14. Matching adjustments for age, sex, ECOG performance status, CLL/SLL proportion, disease stage, IGHV mutation status, beta-2 microglobulin, creatinine clearance, B symptoms, and time from diagnosis were considered based on data availability and magnitude of imbalance between populations. To mitigate potential bias from COVID-19 pandemic that overlapped in timing with SEQUOIA but not CLL14, additional analysis was conducted censoring for COVID-19–related deaths. Subgroup analysis was conducted for IGHV mutation status. Pseudo-IPD for VenO were reconstructed from digitized Kaplan-Meier curves of progression-free survival per investigator (PFS-INV) and overall survival (OS). Sensitivity analyses were conducted in model scenarios with different matching variables.

Results: After applying matching adjustment to align with population characteristics of VenO patients in CLL14 (N=216), effective sample size (ESS) for zanubrutinib in SEQUOIA was 163. Zanubrutinib had longer PFS ($HR_{PFS\text{-}INV}$=0.66 [95% CI, 0.44-0.97], p=0.0351) and a trend for extended OS (HR_{OS}=0.89 [95% CI, 0.55-1.46], p=0.6468). Results remained consistent after COVID-19 adjustment ($HR_{PFS\text{-}INV}$=0.58 [95% CI, 0.38-0.88], p=0.0095; HR_{OS}=0.74 [95% CI, 0.43-1.25], p=0.2587), suggesting potential treatment benefit favoring zanubrutinib for PFS-INV and OS. Efficacy was compared in the IGHV unmutated subgroup. After matching (SEQUOIA ESS=93; CLL14 N=121), $HR_{PFS\text{-}INV}$ was 0.63 (95% CI, 0.39-1.03, p=0.0652) and 0.61 (95% CI, 0.37-0.99, p=0.0475) for base and COVID-19 adjusted scenarios, respectively. Sensitivity analyses using different matching factors showed consistent results.

Conclusions: This unanchored MAIC investigated the relative efficacy of zanubrutinib vs VenO, suggesting zanubrutinib had longer PFS and a trend for extended OS. Results should be interpreted considering MAIC model assumptions and limitations. Further studies are needed to confirm these findings.