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

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Background: The efficacy of continuous zanubrutinib (zanu) has been evaluated in the SEQUOIA study (NCT03336333) in TN CLL/SLL, while the combination of fixed-duration venetoclax + obinutuzumab (VenO) has been evaluated in CLL14 (NCT02242942). In the absence of head-to-head clinical trials comparing zanu and VenO, an unanchored MAIC was conducted between zanu (SEQUOIA) and VenO (CLL14).

Methods: The unanchored MAIC was conducted using study data with similar median follow-up periods (SEQUOIA, 62.67 months; CLL14, 65.4 months). Individual patient data (IPD) of zanu patients in SEQUOIA were reweighted to match the key population characteristics of VenO patients in CLL14 to perform an unanchored MAIC, given the lack of common control arms between SEQUOIA and CLL14. Matching adjustments for age, sex, ECOG performance status, CLL/SLL patient 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 the COVID-19 pandemic that overlapped in timing with SEQUOIA and not CLL14, additional analysis was conducted censoring for COVID-19 related deaths. Subgroup analysis was also 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 of different matching variables.

Results: After applying the matching adjustment to align with the population characteristics of the VenO patients in CLL14 (N=216), the effective sample size (ESS) for zanu in SEQUOIA was 163. Zanu 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 were consistent after adjustment for COVID-19, $HR_{PFS\text{-}INV}$=0.58 (95% CI: 0.38-0.88, p=0.0095) and HR_{OS}=0.74 (95% CI: 0.43-1.25, p=0.2587), suggesting potential treatment benefit favoring zanu in terms of PFS-INV and OS, respectively. The efficacy of zanu vs VenO was also 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 the base and COVID-19 adjusted scenarios, respectively. Sensitivity analyses exploring the impact of using different sets of matching factors showed consistent results.

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