

## A Network Meta-Analysis (NMA) of Efficacy of Zanubrutinib versus Fixed-Duration Acalabrutinib Plus Venetoclax in Treatment-naïve (TN) Chronic Lymphocytic Leukemia (CLL)

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**Background:** While the efficacy of zanubrutinib (ZANU) has been evaluated in the phase 3 SEQUOIA trial (NCT03336333), and the combination regimen of fixed duration acalabrutinib plus venetoclax (AV) has been reported in recent interim analysis of the phase 3 AMPLIFY trial (NCT03836261), the efficacy of these oral regimens has not been directly compared in head-to-head trials. Thus, a NMA was conducted to estimate the relative efficacy in low-risk TN CLL patients.

**Methods:** A systematic literature review was conducted to identify phase 3 randomized controlled trials including low-risk CLL patients to be included in the NMA. Low-risk populations were defined based on the pre-specified trial definitions, including patients without del(17p) or *TP53* mutations. Bendamustine plus rituximab (BR) and fludarabine plus cyclophosphamide and rituximab (FCR)/BR were assumed to be treated as common control arms in the network. Bayesian NMA framework was used to estimate hazard ratios (HRs) with 95% credible intervals (CrIs). Outcomes analyzed included progression-free survival (PFS) in low-risk patients and subgroup analysis by IGHV mutation status. Given the timing of the included trials in relation to the COVID-19 pandemic, PFS data were analyzed with and without adjustment for COVID-19 related deaths.

**Results:** The NMA demonstrated a favorable PFS of ZANU over AV, HR<sub>PFS</sub> (95% CrI) = 0.41 (0.25, 0.67; Table). The 36-month PFS rate for ZANU was 85.6% versus 76.5% for AV. Results were consistent with COVID-19 adjustment, HR<sub>PFS</sub> = 0.28 (0.16, 0.49). Subgroup analysis examining IGHV mutation status demonstrated that the HR<sub>PFS</sub> (95% CrI) of ZANU versus AV in low-risk IGHV unmutated and mutated patients were 0.30 (0.16, 0.57) and 0.49 (0.21, 1.13), respectively.

**Conclusions:** This NMA found a statistically significant improvement in PFS for ZANU over AV for patients with low-risk TN CLL. The observed efficacy differences should be interpreted under the limitation and assumptions of NMA, with further analysis upon trial data maturation.

**Table**

Outcomes	SEQUOIA ZANU	SEQUOIA BR	AMPLIFY AV*	AMPLIFY FCR/BR*	ZANU vs AV
PFS Rate (months)					
12	96.0%	91.3%	95%	88%	
24	90.8%	78.8%	88%	79%	
36	85.6%	58.1%	77%	67%	
48	79.7%	46.4%	64%	49%	
PFS HR (Scenario)					
Base case					0.41 (0.25, 0.67)
COVID-19 adjustment					0.28 (0.16, 0.49)
IGHV unmutated					0.30 (0.16, 0.57)
IGHV mutated					0.49 (0.21, 1.13)

\*Estimates are calculated from digitalized KM curve