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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ABSTRACT

Introduction: 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_{PFS} (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_{PFS}= 0.28 (0.16, 0.49). Subgroup analysis examining IGHV mutation status demonstrated that the HR_{PFS} (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