

## ZANUBRUTINIB VS IBRUTINIB IN TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): IMPLICATIONS FOR INTERPRETING FIXED-DURATION TREATMENT OUTCOMES FROM CLL17

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### **Background:**

In the phase 3 CLL17 trial (NCT04608318), fixed-duration (FD) venetoclax + obinutuzumab (V+O) and FD venetoclax + ibrutinib (V+I) demonstrated noninferiority to continuous ibrutinib in patients with treatment naive (TN) CLL. However, as ibrutinib is a first generation Bruton tyrosine kinase inhibitor (BTKi), the extent to which these findings can be extrapolated to newer BTKis, such as zanubrutinib, remains uncertain. In the phase 3 SEQUOIA study (NCT03336333), continuous zanubrutinib (arm A) demonstrated superior progression free survival (PFS) compared with bendamustine + rituximab (arm B) in patients with TN CLL without del(17p), while PFS outcomes in zanubrutinib treated patients with del(17p) (arm C) were comparable to those observed in patients without del(17p).

### **Aims:**

To compare the efficacy of continuous zanubrutinib with treatments evaluated in the CLL17 study and assess whether conclusions for ibrutinib are generalizable to zanubrutinib.

### **Methods:**

In the absence of head-to-head trials, unanchored matching-adjusted indirect comparisons (MAICs) were conducted using individual patient data from SEQUOIA arms A+C (median follow-up, 58.0 months) and published aggregate data from CLL17 (median follow-up, 34.2 months). Feasibility assessment confirmed alignment in study design and eligibility criteria. However, owing to the limited follow-up for FD regimens in CLL17 and the absence of COVID-19-adjusted overall survival (OS) data, continuous ibrutinib was the only methodologically feasible comparator. Zanubrutinib-treated patients were reweighted to match the CLL17 ibrutinib intent-to-treat population based on age, sex, Binet stage, ECOG performance status, presence of bulky disease, cancer type, and genomic risk factors. Alternative matching factor sets were tested in sensitivity analysis. Investigator-assessed PFS (PFS-INV) and OS were evaluated. As no COVID-

19–related deaths were reported in the CLL17 ibrutinib arm, COVID-19–adjusted analyses were performed for SEQUOIA to improve comparability.

**Results:**

After weighting, baseline characteristics were balanced, with an effective sample size of 91 for zanubrutinib. COVID-19–adjusted PFS-INV significantly favored zanubrutinib vs ibrutinib after matching (hazard ratio, 0.23; 95% CI, 0.12-0.42) (**Table**). COVID-19–adjusted analyses for OS numerically favored zanubrutinib. Several sensitivity analyses using alternative matching variables yielded consistent results.

**Summary/Conclusion:**

This MAIC demonstrates substantially improved PFS and numerically favorable OS with zanubrutinib compared with ibrutinib in TN CLL. These findings suggest that efficacy observed with ibrutinib in CLL17 may not be representative of the whole BTKi class. Therefore, any conclusions supporting broad use of FD regimens should not be extrapolated beyond the specific comparator studied, given differences in efficacy across continuous BTKis. Real-world data or indirect comparisons using similar follow-up duration for FD treatments vs continuous zanubrutinib are warranted to define the optimal frontline approach for patients with CLL.

**Table. COVID-19–Adjusted Comparative Efficacy of Zanubrutinib (SEQUOIA) vs Ibrutinib (CLL17)**

<b>Outcomes</b>	<b>Naive HR (95% CI)</b>	<b>MAIC-weighted HR (95% CI)</b>
<b>PFS-INV</b>	0.44 (0.30-0.64)	0.23 (0.12-0.42)
<b>OS</b>	1.17 (0.61-2.25)	0.70 (0.29-1.73)

**Abbreviations:** HR, hazard ratio; MAIC, matching-adjusted indirect comparison; OS, overall survival; PFS-INV, investigator-assessed progression-free survival.