Zanubrutinib vs Ibrutinib in Treatment-Naive Chronic Lymphocytic Leukemia: Implications for Interpreting Fixed-Duration Outcomes From CLL17

PS1718

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CONCLUSIONS

- This MAIC demonstrates substantially improved PFS and numerically favorable OS with zanubrutinib from SEQUOIA compared with ibrutinib in patients with TN CLL. These findings suggest that the noninferiority observed with ibrutinib in CLL17 may not represent the BTKi class as a whole
- 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

INTRODUCTION

- Zanubrutinib is a highly effective next-generation Bruton tyrosine kinase inhibitor (BTKi) approved for the treatment of chronic lymphocytic leukemia (CLL)
- 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 treatment-naive (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)[1,2]
- 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 TN CLL[3]
  - However, as ibrutinib is a first generation BTKi, the extent to which these findings can be extrapolated to newer BTKis, such as zanubrutinib, remains uncertain

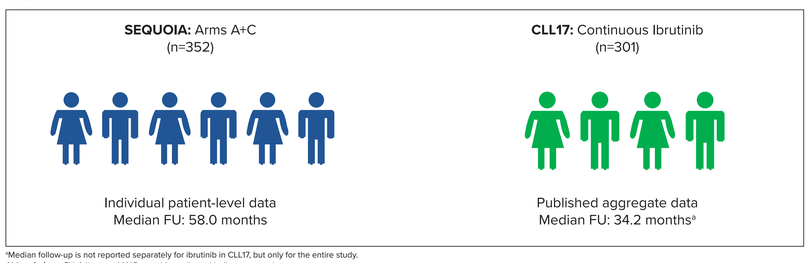
OBJECTIVE

- To compare the efficacy of continuous zanubrutinib with that of continuous ibrutinib evaluated in the CLL17 study and assess whether ibrutinib-based conclusions 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).[4] Due to the lack of common control arms linking SEQUOIA with CLL17, an unanchored MAIC was conducted
- 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 represented the only methodologically feasible comparator
- Data from zanubrutinib-treated patients in SEQUOIA Arms A+C, which included a higher-risk population than CLL17 [especially regarding del(17p) and other genomic risk factors], were reweighted to match the data from 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 (**Figure 1**); alternative matching factor sets were tested in sensitivity analysis
- Investigator-assessed PFS (PFS-INV) and OS were evaluated using weighted Cox proportional hazard regression models; as no COVID-19–related deaths were reported in the CLL17 ibrutinib arm, COVID-19–adjusted analyses were performed in SEQUOIA to improve comparability
- Pseudo-individual patient data for PFS-INV and OS in the ibrutinib arm were reconstructed from the digitized Kaplan-Meier (KM) curves reported in the CLL17 publication using the algorithm by Guyot et al[5]

Figure 1. MAIC Data Availability per Trial



[a]Median follow-up is not reported separately for ibrutinib in CLL17, but only for the entire study.
Abbreviations: FU, follow-up; MAIC, matching-adjusted indirect comparison.

RESULTS

Population Adjustment

- The base-case matching model was successfully fitted with an effective sample size (ESS) of 91 (27.8% of Arms A+C in SEQUOIA) (**Table 1**)
- Adding further variables led to low ESS numbers. Nonetheless, these matching models were explored as part of the sensitivity analysis, and results are presented in the sensitivity analysis section

Table 1. Baseline Characteristics of Zanubrutinib in SEQUOIA (Arms A+C) and Ibrutinib in CLL17

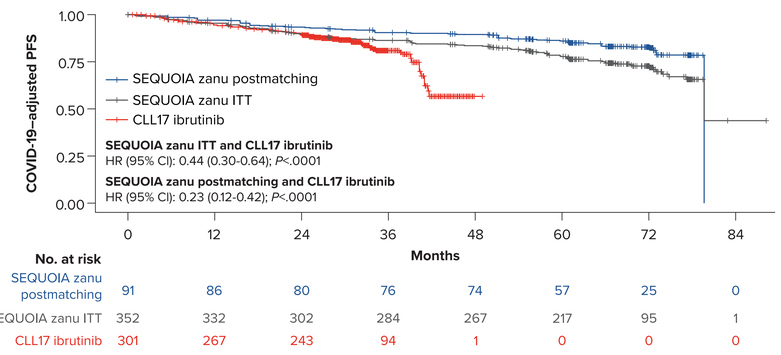
Population characteristics	Included in matching	Ibrutinib in CLL17	Zanubrutinib in SEQUOIA Arms A+C	
		n=301	Prematching, n=327[a]	Postmatching, ESS=91
Age ≥65 years, %	✓	48.5	82.3	48.5
Male, %	✓	65.1	66.1	65.1
ECOG PS 0, %	✓	61.8	44.3	61.8
CLL (vs SLL), %	✓	100.0	93.3	100.0
Binet stage B+C, %	✓	74.8	85.9	74.8
Unmutated IGHV, %	✓	56.8	56.3	56.8
del(17p), %	✓	5.0	31.8	5.0
del(11q), %	✓	21.6	22.0	21.6
TP53 mutation, %	✓	6.3	18.3	6.3
Bulky disease, LD in cm, ≥5, %	✓	27.2	30.3	27.2
Beta2-microglobulin >3.5 mg/L, %	x	69.1	62.3	45.9
Median time from diagnosis, months	x	33.8	28.8	30.4
Median creatinine clearance, mL/min	x	80.1	70.1	77.4
del(13q), %	x	38.5	59.3	67.8

[a]Overall, 327 patients had data on all of the matching factors used to derive the MAIC weights for population adjustment.
Abbreviations: CLL, chronic lymphocytic leukemia; del, deletion; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; IGHV, immunoglobulin heavy-chain variable; LD, longest diameter; MAIC, matching-adjusted indirect comparison; SLL, small lymphocytic lymphoma.

PFS-INV

- Both the naive and population-adjusted comparison of COVID-19–adjusted PFS-INV with zanubrutinib in SEQUOIA (Arms A+C) vs ibrutinib in CLL17 showed a significant treatment benefit in favor of zanubrutinib, with a hazard ratio (HR) of 0.44 (*P*<.0001) and HR of 0.23 (*P*<.0001), respectively (**Figure 2**)
  - At 36 months, the COVID-19–adjusted PFS rate was 90.5% for postmatched zanubrutinib and 80.9% for ibrutinib
- As shown in the comparison of postmatching zanubrutinib vs ibrutinib in CLL17 (**Figure 2**), the PFS-INV KM curves start deviating from the beginning
  - A drop is observed toward the end of the follow-up for both treatments, which is likely due to the diminished number of patients at risk
  - A longer ibrutinib follow-up would be required to make a more informed conclusion

Figure 2. COVID-19–Adjusted PFS-INV



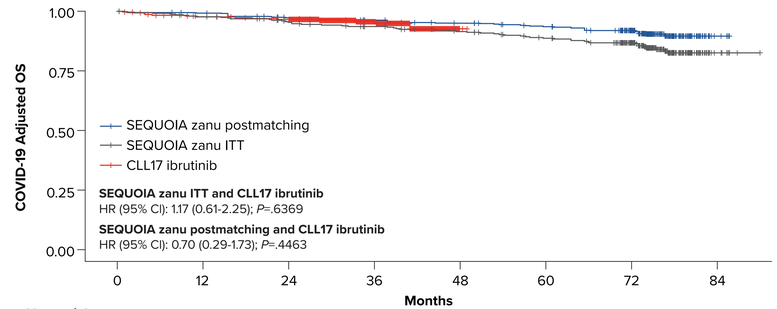
No. at risk								
SEQUOIA zanu postmatching	91	86	80	76	74	57	25	0
SEQUOIA zanu ITT	352	332	302	284	267	217	95	1
CLL17 ibrutinib	301	267	243	94	1	0	0	0

Abbreviations: HR, hazard ratio; ITT, intent to treat; PFS-INV, investigator-assessed progression-free survival.

OS

- The naive comparison of COVID-19–adjusted OS with zanubrutinib in SEQUOIA (Arms A+C) vs ibrutinib in CLL17 with HR of 1.17 (*P*=.6369) indicated that treatment effects were similar, and the population-adjusted estimate HR=0.70 (*P*=.4463) indicated a trend for potential treatment benefit in favor of zanubrutinib vs V+I (**Figure 3**). No statistical significance was observed

Figure 3. COVID-19–Adjusted OS



No. at risk								
SEQUOIA zanu postmatching	91	88	84	79	77	74	54	2
SEQUOIA zanu ITT	352	340	325	312	298	282	226	8
CLL17 ibrutinib	301	284	276	141	2	0	0	0

Abbreviations: HR, hazard ratio; ITT, intent to treat; OS, overall survival.

Sensitivity Analysis

- Several sensitivity analyses using alternative matching variables yielded consistent results:
  - For COVID-19–adjusted PFS-INV, the significant benefit toward zanubrutinib vs ibrutinib was retained for all matching models, including the one that used every commonly available variable (HR, 0.32; *P*=.0266, ESS of 62). Treatment effects ranged between 0.20 and 0.34, depending on the matching model
  - For COVID-19–adjusted OS, the numerical benefit toward zanubrutinib vs ibrutinib was retained for most matching models, including the one that used every commonly available variable (HR, 0.69; *P*=.4940, ESS of 62). Treatment effects ranged between 0.50 and 1.02, depending on the matching model. No statistical significance was observed for any of the matching models

Limitations

- With any MAIC, there is a potential for bias resulting from the strong assumption that cross-trial differences can be entirely explained by variables selected for matching

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