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Zanubrutinib vs FCR in Treatment-Naive Patients With Chronic Lymphocytic Leukemia: A Matching-Adjusted Indirect Comparison

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INTRODUCTION

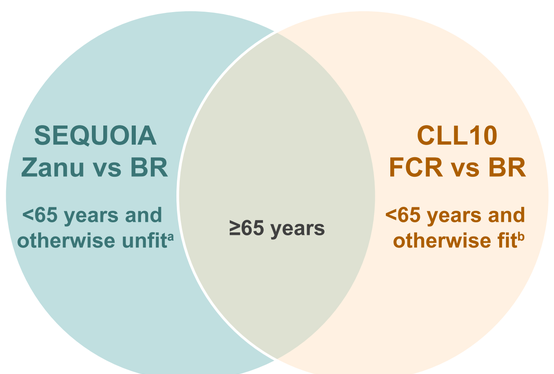
- Fludarabine, cyclophosphamide, and rituximab combination therapy (FCR) is the standard first-line treatment for fit (physically active, no major health problems, and normal renal function) treatment-naive patients with chronic lymphocytic leukemia (CLL)
  - Associated hematotoxicity and infections necessitate more efficacious, safer treatments
- Zanubrutinib, a highly specific, potent, small-molecule Bruton tyrosine kinase inhibitor, is approved for treatment-naive patients with CLL[2]
  - Comparative efficacy vs FCR has not been investigated in the fit patient population
- Indirect treatment comparisons (ITCs) can provide comparative estimates of reported treatment effects among patients with CLL
- The objective of this analysis was to determine the relative treatment effects of zanubrutinib vs FCR among treatment-naive patients with CLL who are considered fit for treatment with FCR

METHODS

Data Sources

- FCR was compared with bendamustine + rituximab (BR) in the phase 3, open-label CLL10 trial (NCT00769522) as a front-line therapy for patients (≥18 years) with FCR-fit CLL[3]
- Zanubrutinib was compared with BR in SEQUOIA (NCT03336333), which was also a phase 3, open-label trial investigating patients (≥18 years) with CLL considered unfit for FCR[4]
  - Patients considered unfit for FCR were those aged ≥65 years or ≥18 years with a Cumulative Illness Rating Scale (CIRS) score >6, creatinine clearance <70 mL/min, or history of serious or frequent infections
- Both studies included patients aged ≥65 years without impaired fitness in terms of CIRS, creatinine clearance, and previous serious infection (**Figure 1**)

Figure 1. Overlap Between SEQUOIA and CLL10 Patient Populations



[a] FCR ineligible, defined as 18–64 years + CIRS >6 or creatinine clearance <70 mL/min or history of previous serious infection or multiple infections in the past 2 years. [b] Low comorbidity burden as defined by a CIRS score up to 6, and normal creatinine clearance of at least 70 mL/min, and ECOG performance status of 0–2.
BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; FCR, fludarabine + cyclophosphamide + rituximab combination therapy; HR, hazard ratio; Zanu, zanubrutinib.

Statistical Analysis

- An anchored matching-adjusted indirect comparison (MAIC) was conducted, comparing zanubrutinib with FCR, using the BR arms as a common comparator[5]
  - Propensity score matching using patient-level data from SEQUOIA adjusted for the differences in relevant patient characteristics
- Independent review committee assessed progression-free survival (PFS) was compared using the matched patient populations
  - Matching variables were selected based on a literature review of subgroup analyses in randomized trials and clinical expert opinion
  - Patient characteristics identified solely as prognostic factors did not need to be included because randomization is preserved in anchored ITCs
- The core model included:
  - Immunoglobulin heavy-chain gene (IGHV) mutation, 11q deletion, β2-microglobulin, Binet stage, and age
  - Geographic region, sex, creatinine clearance, CIRS score, Eastern Cooperative Oncology Group performance status (ECOG PS), and previous infections underwent sensitivity analyses
- The Bucher methodology was used to estimate reweighted relative treatment effects of zanubrutinib vs FCR
- To account for the impact of COVID-19, a sensitivity analysis was conducted by censoring PFS at the last assessment if there was a COVID-19 death
  - Censoring rules in CLL10 remained unchanged, as COVID-19 was not present during this trial

RESULTS

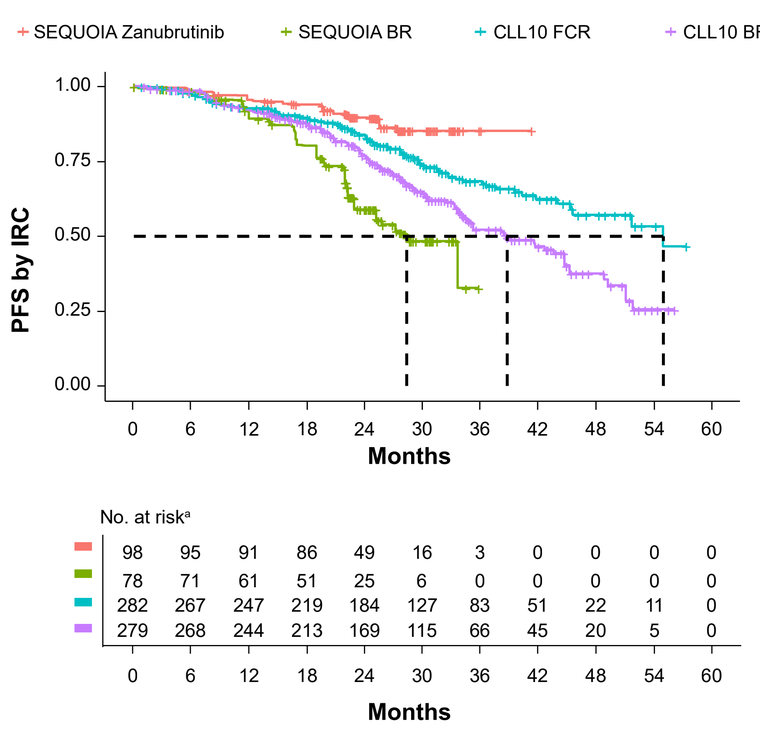
- Baseline characteristics that were included in the propensity score adjustment were balanced between the 2 trials after matching (**Table 1**)
- In the base-case model, zanubrutinib demonstrated significantly improved PFS over FCR (hazard ratio [HR], 0.41; 95% CI, 0.20-0.81; *P*=.01; effective sample size [ESS]=174) (**Figure 2**, **Table 2**)
- Results from the MAIC are reported in **Table 2**, with unadjusted comparisons presented for informative purposes only

Table 1. Baseline Patient Characteristics Before and After Matching Adjustment (Base Case)[a]

Matched variables, %	SEQUOIA unweighted (before matching) n=479[b]	SEQUOIA weighted (after matching) n (ESS)=174	CLL10 n=561
Age >65 years	76.4	34.6	34.6
IGHV mutation	52.5	61.5	61.5
Cytogenetic mutation, 11q deletion	18.6	23.4	23.4
β2-microglobulin >3.5 mg/L	57.5	34.5	34.5
CLL staging by Binet (stage A or B vs C)	70.8	60.1	60.1
Region, Europe	72.2	65.8	100
Male sex	62.2	62.4	72.7
CIRS >6	26.4	46.1	0
Creatinine clearance ≥70 mL/min	51.4	66.9	100
ECOG PS			
0	44.1	37.7	64.1
1	48.6	55.5	34.7
2	7.3	6.8	1.2
Previous infections[c]	9.0	15.0	0
B symptoms	55.1	67.2	40.8

[a] White row variables were included in the base case model; Grey row variables were not included in the base case model; therefore, the distribution of patients differed between SEQUOIA and CLL10. [b] The analysis included only patients with nonmissing baseline characteristics selected for matching. Note that SEQUOIA patients were not excluded from the analyses based on the CLL10 patient selection criteria because the CLL10 and SEQUOIA eligibility criteria were similar for the base-case MAIC. [c] "Previous serious infection" is defined as infection requiring hospitalization, parenteral antibiotic therapy, or both. "Multiple infections" is defined as ≥3 infections requiring, at a minimum, oral antibiotic therapy.
CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; FCR, fludarabine + cyclophosphamide + rituximab combination therapy; IGHV, immunoglobulin heavy-chain variable; MAIC, matching-adjusted indirect comparison.

Figure 2. Kaplan-Meier Plot for PFS in Reweighted SEQUOIA and CLL10 Patients (Base Case)



[a] The number at risk in the SEQUOIA arms was calculated by the sum of the weight of the patients at risk, in which the sum of weight has been normalized to ESS. The calculation of ESS is nonlinear, so the sum of the ESS across SEQUOIA arms in the "number at risk" table differs from the ESS presented in the baseline characteristics table.
BR, bendamustine + rituximab; CLL, chronic lymphocytic leukemia; ESS, effective sample size; FCR, fludarabine + cyclophosphamide + rituximab combination therapy; IRC, independent review committee; PFS, progression-free survival.

CONCLUSIONS

- In this MAIC of phase 3 trials, zanubrutinib offers clinically meaningful benefits in PFS over FCR in fit treatment-naive patients with CLL

- The COVID-adjusted analysis confirmed that zanubrutinib was associated with a favorable PFS in the COVID-19–adjusted analysis (**Table 2**, Model 2, HR, 0.33; 95% CI, 0.16-0.69)
- Sensitivity analyses adjusting for additional patient characteristics showed generally consistent results (**Table 2**)
  - Differences for PFS remained significant when adding geographic region (HR, 0.43; 95% CI, 0.21-0.90; *P*=.03), sex (HR, 0.44; 95% CI, 0.22-0.89; *P*=.02), ECOG PS (HR, 0.30; 95% CI, 0.14-0.64; *P*<.01), and previous infections (HR, 0.45; 95% CI, 0.22-0.93; *P*=.03) to the base-case model
  - When incorporating CIRS, there was only numerically favorable PFS with zanubrutinib due to the expanded model's low ESS (HR, 0.45; 95% CI, 0.16-1.24; *P*=.12)
  - Adding creatinine clearance to the base-case model yielded similar results (HR, 0.52; 95% CI, 0.24-1.13; *P*=.10)
  - ESS ranged from 64.1-174.1 across analyses, indicating uncertainty of some of the analyses due to different patient selection criteria of both trials
- MAICs further rely on availability of relevant patient characteristics. ZAP-70 methylation and *TP53* mutation were not reported in CLL10 and were not accounted for in the propensity score model

Table 2. Sensitivity Analyses Results Compared With Base-Case

Model	Variables in model	SEQUOIA ESS	PFS HR[a] (95% CI)
#	**Unadjusted comparison**	–	0.69 (0.43-1.12)
1	**Base case** Age IGHV mutation Cytogenetic mutation β2-microglobulin CLL staging by Binet	174.1	0.41 (0.20-0.81)
2	**Base case (COVID-19 adjusted)[b]**	174.1	0.33 (0.16-0.69)
3	**Base case** + geographic region	100.4	0.43 (0.21-0.90)
4	**Base case** + sex	163.7	0.44 (0.22-0.89)
5	**Base case** + CIRS	64.1	0.45 (0.16-1.24)
6	**Base case** + creatinine clearance	122.5	0.52 (0.24-1.13)
7	**Base case** + ECOG PS	137.6	0.30 (0.14-0.64)
8	**Base case** + previous infections[c]	140.9	0.45 (0.22-0.93)

[a] The HR was estimated based on the Bucher methodology for indirect comparisons, which uses the HRs from CLL10 and SEQUOIA. The HR in SEQUOIA was reweighted in models 1 to 8 and adjusted for factors used to stratify the randomization – age (<65 years vs ≥65 years), Binet stage (C vs A or B), and IGHV mutational status (mutated vs unmutated). [b] Model 2 included the same matching variables as Model 1; patients with a COVID-19– related death were censored at the last assessment. [c] "Previous serious infection" is defined as infection requiring hospitalization, parenteral antibiotic therapy, or both. "Multiple infections" is defined as ≥3 infections requiring, at a minimum, oral antibiotic therapy.
CIRS, Cumulative Illness Rating Scale; CLL, chronic lymphocytic leukemia; ECOG PS, Eastern Cooperative Oncology Group performance status; ESS, effective sample size; HR, hazard ratio; IGHV, immunoglobulin heavy-chain variable; PFS, progression-free survival.

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DISCLOSURES

TM: Honoraria: Janssen, AbbVie, Gilead, Alexion, Novartis, Roche; Consulting role: MorphoSys, Sunesis; **LM:** Employment: BeiGene; **SX:** Employment: BeiGene; Equity Holder: BeiGene; **MJ, WB:** Research funding: BeiGene; **KY:** Employment: BeiGene; Leadership: BeiGene; Stock or other ownership: BeiGene; Research funding: BeiGene; Travel, accommodations, and expenses: BeiGene.

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