SUPPLEMENTARY MATERIAL

Zanubrutinib versus fludarabine, cyclophosphamide, and rituximab in fit, treatment-naïve patients with chronic lymphocytic leukemia: a matching-adjusted indirect comparison

Supplementary tables

Table S1. Overview of the evidence for the analyses

	SEQUOIA (cohort 1)		CLL10	
Treatment	**Zanubrutinib**	**BR**	**FCR**	**BR**
Clinical trial registry	NCT03336333		NCT00769522	
Trial sponsor	BeOne Medicines Ltd		Roche Pharma AG, Mundipharma, German Federal Ministry of Education and Research	
Trial design	Open-label, phase 3 RCT		Open-label, phase 3 RCT	
Treatment	Zanubrutinib 160 mg twice per day	B: 90 mg/m² per day R: 375 mg/m²; 500 mg/m²	F: 25 mg/m² per day C: 250 mg/m² per day R: 375 mg/m²; 500 mg/m²	B: 90 mg/m² per day R: 375 mg/m²; 500 mg/m²
Recruitment period	October 31, 2017, to July 22, 2019		October 2, 2008, to July 11, 2011	
Region	14 countries, multiple continents		5 European countries	
Sample size	241	238	282	279
Patient eligibility criteria				
Population	FCR unsuitable Aged ≥65 years, or 18-64 years *and* CIRS >6 *or* creatinine clearance		Fit Low comorbidity burden as defined by a CIRS score up to and including 6 *and*	

	SEQUOIA (cohort 1)		CLL10	
Treatment	**Zanubrutinib**	**BR**	**FCR**	**BR**
	<70 mL/min *or* history of previous serious infection *or* multiple infections in the past 2 years[a]		normal creatinine clearance of at least 70 mL/min *and* ECOG-PS 0-2	
Age	Aged ≥18 years[b]		Aged ≥18 years[c]	
ECOG PS	0-2		0-2	
CIRS	Any[b]		≤6	
Creatinine clearance	≥30 mL/min[b]		≥70 mL/min	
Del(17p)	Not eligible		Not eligible	
Richter transformation	Not eligible		Not eligible	

[a]Previous serious infection is defined as infection requiring hospitalization, parenteral antibiotic therapy, or both. [b]Conditional on fit/unfit criteria in the SEQUOIA trial. [c]Derived from ClinicalTrials.gov. BR, bendamustine+rituximab combination therapy; CIRS, Cumulative Illness Rating Scale; del(17p), deletion 17p; FCR, fludarabine+cyclophosphamide+rituximab combination therapy; ECOG PS, Eastern Cooperative Oncology Group performance status; RCT, randomized controlled trial.

Table S2. Selection of matching variables

Characteristic	Factor type	PS model	Covariate coding for analyses
IGHV mutation	EM	*1 (base case)*	Mutated yes/no
Cytogenetic mutations	EM	*1 (base case)*	Del(11q) yes/no
β2-microglobulin	EM	*1 (base case)*	>3.5 mg/L
CLL staging by Binet	EM	*1 (base case)*	A vs C; B vs C
Age	Defines (un-)fit and potential treatment EM	*1 (base case)*	≤65 years
Geographic region	Potential treatment EM	2	Europe yes/no (CLL10 was in Europe)
Sex	Potential treatment EM	3	Males yes/no
CIRS score	Defines (un-)fit and PF	4	>6 vs ≤6[a]
Creatinine clearance	Defines (un-)fit and PF	5	≥70 mL/min
ECOG PS	Defines fit in CLL10 and PF	6	0 vs 1+2
Previous serious infections[b]	Defines (un-)fit	7	Yes/no
ZAP-70 methylation	EM	NA (NR in CLL10)	NA
Complex karyotype	Potential treatment EM	NA (NR in CLL10)	NA
Any cytopenia	Potential treatment EM	NA (NR in CLL10)	NA
Bulky disease	Potential treatment effect modifier	NA (NR in CLL10)	NA

[a]Available in SEQUOIA IPD only as a dichotomized covariate. [b]Previous serious infection is defined as infection requiring hospitalization, parenteral antibiotic therapy, or both. CIRS, Cumulative Illness Rating Scale; del(11q), deletion of the long arm of chromosome 11; ECOG PS, Eastern Cooperative Oncology Group performance status; EM, effect modifier; IGHV, immunoglobulin heavy chain variable region; NR, not reported; NA, not applicable; PF, prognostic factor; PS, propensity score; ZAP-70, zeta-associated protein kinase 70.

Table S3. Patient characteristics missing in one of the trials

	SEQUOIA		CLL10	
Treatment arm	**Zanubrutinib (N=241)**	**BR (N=238)**	**FCR (N=282)**	**BR (N=279)**
Race			NR	NR
White	221 (92%)	206 (87%)		
Black	4 (2%)	4 (2%)		
Asian/Pacific islander	5 (2%)	9 (4%)		
Not reported/unknown	11 (5%)	22 (9%)		
Rai stage	NR	NR		
0			7/221 (3%)	11/224 (5%)
I			29/221 (13%)	32/224 (14%)
II			86/221 (39%)	84/224 (37%)
III			44/221 (20%)	34/224 (15%)
IV			55/221 (25%)	65/224 (29%)
***TP53* mutation**	15/232 (6%)	13/223 (6%)	NR	NR
Bulky disease ≥5 cm	69 (29%)	73 (31%)	NR	NR
Cytopenia at baseline	102 (42%)	109 (46%)	NR	NR

BR, bendamustine+rituximab combination therapy; FCR, fludarabine+cyclophosphamide+rituximab combination therapy; NR, not reported; *TP53*, tumor protein p53 gene.

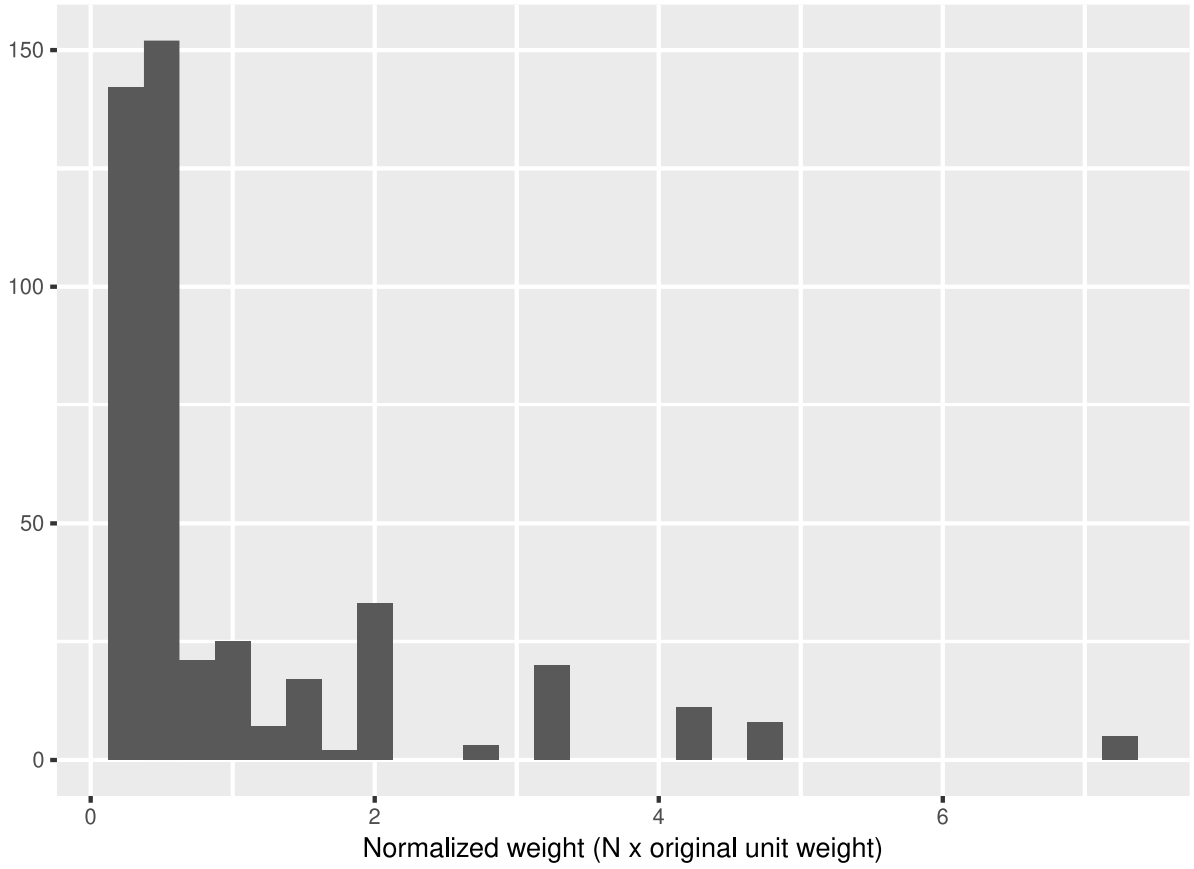
Table S4. Safety data in SEQUOIA and CLL 10

	SEQUOIA		CLL10	
	Zanubrutinib (N=240)	**BR (N=227)**	**FCR (N=279)**	**BR (N=278)**
Patients with AEs of any grade	224 (93%)	218 (96%)	272 (98%)	256 (92%)
Patients with grade 3-5 AEs	126 (53%)	181 (80%)	261 (94%)	234 (84%)
Discontinuation due to AEs	20 (8%)	31 (14%)	64 (23%)	37 (13%)
Neutropenia (grade 3-5)	27 (11%)	116 (51%)	235 (84%)	164 (59%)
Infections (grade 3-5)	39 (16%)	43 (19%)	111 (40%)	74 (27%)

AE, adverse event; BR, bendamustine+rituximab combination therapy; FCR, fludarabine+cyclophosphamide+rituximab combination therapy.

Supplementary figure

Figure S1. Distribution of weights (base-case analysis)



Supplementary appendices

Appendix A. Selection of matching variables

Appendix B. Distribution of weights: base-case analysis

Appendix A. Selection of matching variables

Baseline factors were highlighted as effect modifiers if a statistically significant difference in the treatment effect across different factor levels was detected in at least one of the studies (ELEVATE-TN [1], CLL14 [2], ALLIANCE [3], RESONATE-2 [4], and SEQUOIA [5]) in a subgroup analysis. If the numerical difference in treatment effects across different factor levels was remarkable but not statistically significant, the variables were noted as potential treatment-effect modifiers in order to differentiate them from other factors showing no signal of effect modification.

Appendix B. Distribution of weights: base-case analysis

The weights are first rescaled relative to the unit weights of the original individual patient data (IPD) dataset based on sample size (N), which facilitates the interpretation of the distribution of weights:

Rescaled weights: $\widetilde{w_i} = \frac{w_i N}{\sum_i^N w_i}$

Patients with rescaled weights greater than 1 provided more information when matched to the target population than they did in the SEQUOIA population, and vice versa for patients with weights less than 1.

Note that the characteristics of patients in CLL10 were pooled across the treatment arms before matching.

References

1. Sharman JP, Egyed M, Jurczak W *et al*. Efficacy and safety in a 4-year follow-up of the ELEVATE-TN study comparing acalabrutinib with or without obinutuzumab versus obinutuzumab plus chlorambucil in treatment-naïve chronic lymphocytic leukemia. *Leukemia* 36(4), 1171–1175 (2022)
2. Al-Sawaf O, Zhang C, Tandon M *et al*. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol.* 21(9), 1188–1200 (2020)
3. Woyach JA, Ruppert AS, Heerema NA *et al*. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N. Engl. J. Med.* 379(26), 2517–2528 (2018)
4. Burger JA, Tedeschi A, Barr PM *et al*. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N. Engl. J. Med.* 373(25), 2425–2437 (2015)
5. Tam CS, Brown JR, Kahl BS *et al*. Zanubrutinib versus bendamustine and rituximab in untreated chronic lymphocytic leukaemia and small lymphocytic lymphoma (SEQUOIA): a randomised, controlled, phase 3 trial. *Lancet Oncol.* 23(8), 1031–1043 (2022)