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Real-world safety and effectiveness of zanubrutinib vs ibrutinib in CLL: the CLL-ZANU2024 Italian cohort

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Key Points

- In a large real-world Italian cohort, zanubrutinib showed significantly lower treatment discontinuation rates compared with ibrutinib.
- Zanubrutinib-treated patients experienced fewer off-target AEs supporting its preferential use than Ibrutinib in CLL with comorbidities.

Bruton tyrosine kinase inhibitors (BTKis) have dramatically changed the therapeutic landscape of chronic lymphocytic leukemia (CLL), with ibrutinib, first-in-class, demonstrating durable efficacy even in high-risk patients. However, off-target adverse events (AEs) have raised concerns, prompting the development of more selective second-generation BTKis, such as zanubrutinib, designed to improve tolerability while maintaining efficacy. Despite encouraging results from clinical trials, real-world data comparing zanubrutinib with ibrutinib remain limited. In this multicenter, retrospective study, we analyzed 934 patients with CLL treated outside clinical trials, including 393 receiving zanubrutinib and 541 receiving ibrutinib. We evaluated time to treatment discontinuation (TTD) and time to next treatment or death (TTNTD) in both the overall cohort and a propensity score–matched population. Patients who were treated with zanubrutinib experienced lower 12-month discontinuation rates (overall: 12.6% vs 21.4%; matched: 12.4% vs 20.2%) and higher 12-month TTNTD rates (overall: 91.9% vs 83.0%; matched: 93.2% vs 83.4%). Multivariable analyses confirmed zanubrutinib as an independent predictor of longer TTD and TTNTD, whereas high-risk features, including age, relapsed/refractory disease, Binet stage C, *TP53* disruption, Eastern Cooperative Oncology Group 2 to 3, and congestive heart failure, were consistently associated with poorer outcomes. AEs leading to discontinuation, particularly atrial fibrillation, bleeding, and infections, were less frequent with zanubrutinib, reflecting its favorable safety profile. These findings provide real-world evidence that zanubrutinib offers more durable disease control and improved persistence compared with ibrutinib, reinforcing its clinical value as a preferred second-generation BTKi. Nevertheless, the relatively short follow-up for zanubrutinib warrants cautious interpretation of long-term outcomes, and underscores the need for ongoing observation to fully characterize its durability and safety.

Introduction

Bruton tyrosine kinase inhibitors (BTKis) have significantly improved outcomes of patients with chronic lymphocytic leukemia (CLL) and small lymphocytic leukemia (SLL).[1] Ibrutinib, the first-in-class BTKi to receive regulatory approval, represented a major advance in the treatment landscape of CLL/SLL.[2] Its efficacy has been demonstrated in seminal studies both as monotherapy and in combination with anti-CD20 monoclonal antibodies, in treatment-naïve (TN) and relapsed/refractory (R/R) settings.[2-9] Notably, ibrutinib has shown durable efficacy even in patients with high-risk cytogenetic abnormalities, such as del17p and TP53 mutations, subgroups typically resistant to conventional chemoimmunotherapy.[10,11] However, long-term follow-up data from major clinical trials and real-world cohorts have consistently reported high rates of treatment discontinuation, primarily due to off-target toxicities.[9]

Second-generation BTKis have been developed with greater selectivity for BTK, aiming to reduce off-target adverse events (AEs).[12] Among these, zanubrutinib, which is a highly selective BTKi, was approved by the European Medicines Agency in November 2022 for the treatment of CLL,[13] and subsequently received reimbursement approval by the Agenzia Italiana del Farmaco in October 2023 for use as monotherapy.[14] These approvals were based on the results of 2 pivotal phase 3 trials: SEQUOIA (NCT03336333)[15] and ALPINE (NCT03734016).[16] In addition to ibrutinib and zanubrutinib, acalabrutinib is also an approved BTKi for CLL/SLL.[17,18]

The SEQUOIA trial evaluated zanubrutinib in patients with CLL/SLL who were TN. After a median follow-up of 61.2 months, zanubrutinib demonstrated a significant improvement in progression-free survival (PFS) compared with chemoimmunotherapy (median PFS not reached vs 44.1 months), irrespective of immunoglobulin heavy chain variable (*IGHV*) mutational status. Similarly, favorable outcome was observed in the cohort of patients with del(17p), with both median PFS and overall survival not reached.[15]

The ALPINE trial, a randomized phase 3 study in R/R CLL/SLL, compared zanubrutinib with ibrutinib. Zanubrutinib showed a

Table 1. Baseline characteristics of the patients with CLL treated with zanubrutinib or ibrutinib

	Zanubrutinib (N = 393)	Ibrutinib (N = 541)	*P* value	SMD
Median age (range), y	76 (44-94)	70 (37-88)	**<.001**	0.53
Sex, n (%)				
Male	237 (60.3)	353 (65)		
Female	156 (39.7)	188 (35)	.122	0.10
Line of therapy, n (%)				
TN	239 (60.7)	221 (41)		
R/R	154 (39.3)	320 (59)	**<.001**	−0.41
Binet stage, n (%)				
A	41 (10.4)	65 (12)		
B	151 (38.4)	237 (44)		
C	201 (51.1)	239 (44)	.109	0.13
IGHV mutational status, n (%)				
Mutated	103 (26.2)	181 (33)		
Germ line	242 (61.6)	360 (67)		
Unknown	48 (12.2)	–	.26	0.08
TP53 disruption, n (%)*				
Absent	254 (72.5)	269 (49.7)	**<.001**	−0.32
Present	98 (18.3)	206 (38.1)		
Unknown	36 (9.2)	66 (12.2)		
ECOG-PS, n (%)				
0-1	290 (74)	399 (74)		
2-3	103 (26)	142 (26)	1	0.001
Cardiovascular risk factor, n (%)				
Hypertension	155 (39.4)	213 (39)	.98	0.001
Atrial fibrillation	51 (13)	70 (13)	.98	0.001
Hypercholesterolemia	60 (15.3)	83 (15.3)	.97	−0.002
Congestive heart failure	24 (6.1)	33 (6)	.99	0.06
Peripheral arterial disease	12 (3.1)	17 (3)	.93	0.03
Cerebrovascular disease	13 (3.3)	18 (3.1)	.98	0.03
Diabetes	67 (17)	92 (17.1)	.98	0.001
Myocardial infarction	48 (12.2)	66 (12)	.98	0.0004

Boldface values indicate statistically significant results.
SMD, standardized mean difference.
*TP53 disruption was determined by the documentation of 17p deletion and/or TP53 mutation by fluorescence in situ hybridization and sequencing, respectively; present, del17p positive and/or TP53 mutated; absent, del17p negative and TP53 negative.

higher overall response rate (85.6% vs 75.4%) and superior PFS, with a 32% relative reduction in the risk of progression or death. In high-risk patients harboring del(17p) and/or TP53 mutations, zanubrutinib was associated with a 49% improvement in PFS compared with ibrutinib.[16] Both trials reported a favorable safety profile for zanubrutinib, including lower rates of treatment discontinuation due to AEs compared with control arms.[15,16]

Despite these results, real-world evidence on the use of zanubrutinib outside of clinical trials remains limited, particularly in comparison with first-generation BTKis, such as ibrutinib.[19-21]

To address this gap, we conducted a retrospective, multicenter analysis of patients with CLL treated with zanubrutinib in routine clinical practice. Additionally, we performed a comparative evaluation of outcomes in patients treated with zanubrutinib vs ibrutinib, focusing on time to treatment discontinuation (TTD) and time to next treatment or death (TTNTD), both in the overall cohort and in a propensity score–matched population.

Materials and methods

Patients

We retrospectively analyzed CLL databases from 52 Italian centers, including all consecutive patients with TN or R/R CLL who received zanubrutinib or ibrutinib outside of a clinical trial. Data sets contained comprehensive clinical and laboratory information, including age, sex, date of diagnosis, Rai and Binet stage, laboratory parameters, biological markers (interphase fluorescence in situ hybridization analyses for the short arm of chromosome 17 -del(17p)-, mutational status of the *IGHV*, and *TP53* mutations),

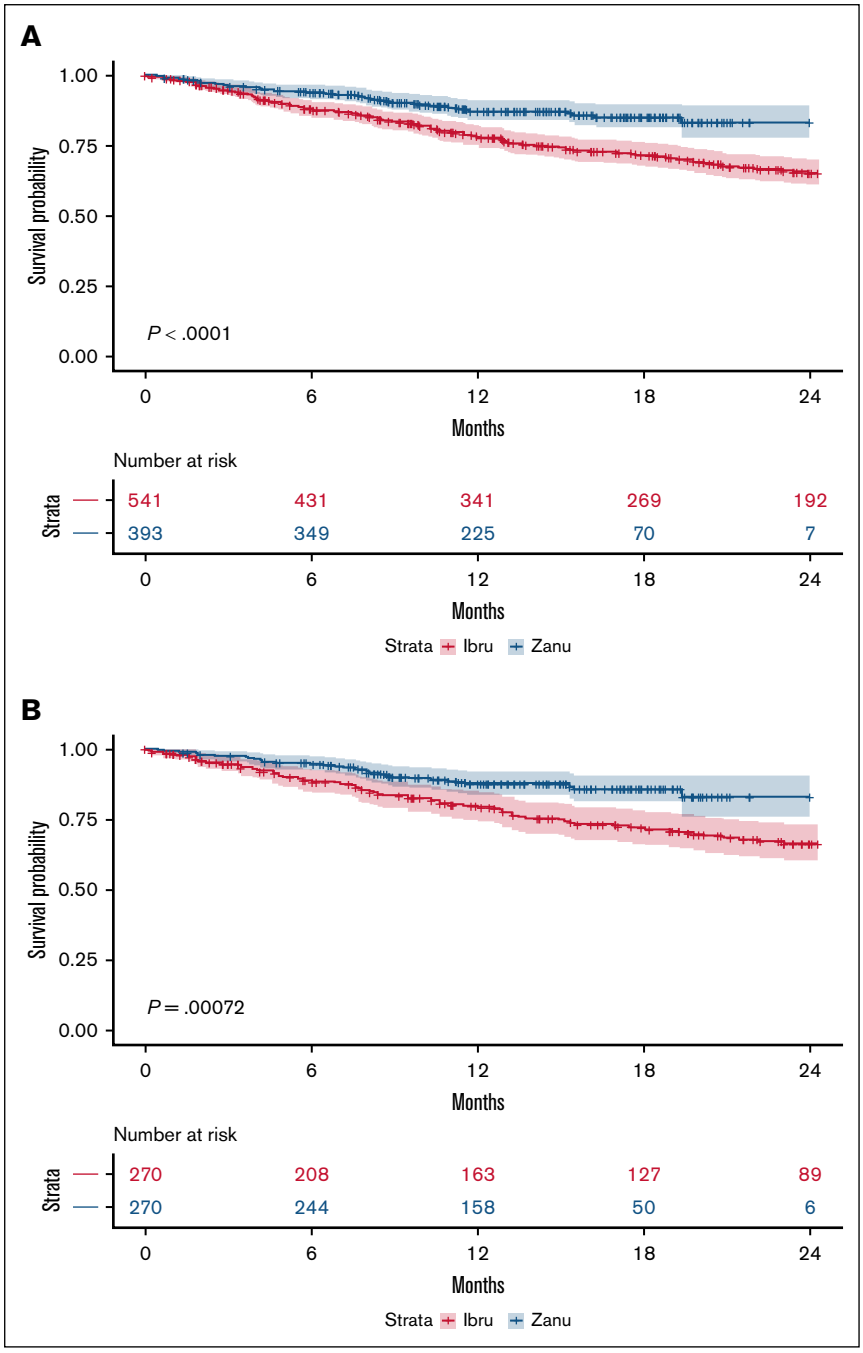

Figure 1. Kaplan-Meier curves of TTD for all 934 patients with CLL treated with zanubrutinib or ibrutinib. (A) Kaplan-Meier curve of TTD according to treatment arm in the original cohorts. (B) Kaplan-Meier curve of TTD according to treatment arm in the propensity score–matched cohorts.

Eastern Cooperative Oncology Group-performance status (ECOG-PS), comorbidities, treatment history, and date of last follow-up or death. All data were abstracted from clinical records at the time of treatment initiation and updated prospectively. The assessment of *IGHV* status and *TP53* abnormalities (including deletion and/or mutation) was performed locally in certified laboratories adhering to European Research Initiative on CLL, as previously described.[22,23] Treatment-emergent AEs were collected and graded according to the Common Terminology Criteria for Adverse Events, version 5.0.

This research is part of the CLL-ZANU2024 study, an Italian, observational, multicenter, longitudinal secondary data analysis evaluating the safety and effectiveness of zanubrutinib in the real-world post-marketing setting. This observational comparative study used registry data, with retrospective data collection for ibrutinib (from June 2013 to June 2019; these data have been partially published[22-32]) and ambispective (retrospective/prospective) data collection for zanubrutinib (from October 2023 onward).

Table 2. Univariate and multivariate analyses for TTD

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age*	1.01 (0.99-1.02)	.280	1.01 (0.99-1.03)	.250
Sex				
Male vs female	0.96 (0.72-1.28)	.771	0.92 (0.66-1.26)	.596
Therapy				
Zanubrutinib vs ibrutinib	0.49 (0.36-0.69)	**.000**	0.45 (0.31-0.65)	**.000**
Line of therapy				
R/R vs TN	1.56 (1.17-2.07)	**.002**	1.33 (0.98-1.81)	.071
Binet stage				
B vs A	1.41 (0.82-2.41)	.215	1.31 (0.76-2.28)	.334
C vs A	1.85 (1.1-3.13)	.022	1.85 (1.08-3.16)	**.024**
IGHV mutational status				
Germ line vs mutated	1.04 (0.77-1.4)	.816	–	
TP53 disruption†				
Present vs absent	1.67 (1.24-2.24)	**.001**	1.57 (1.16-2.12)	**.003**
ECOG-PS				
2-3 vs 0-1	1.56 (1.17-2.08)	**.003**	1.52 (1.11-2.07)	**.009**
Cardiovascular risk factor				
Hypertension	1.19 (0.9-1.57)	.214	–	
Atrial fibrillation	1.03 (0.68-1.56)	.884	–	
Hypercholesterolemia	0.93 (0.62-1.38)	.717	–	
Congestive heart failure	1.82 (1.16-2.87)	**.009**	1.7 (1.06-2.72)	**.028**
Peripheral arterial disease	0.86 (0.38-1.93)	.710	–	
Cerebrovascular disease	0.91 (0.41-2.06)	.828	–	
Diabetes	0.91 (0.62-1.33)	.629	–	
Myocardial infarction	0.89 (0.57-1.37)	.582	–	

Boldface values indicate statistically significant results.
*The effect corresponds to 1 year of increase in age.
†TP53 disruption was determined by the documentation of 17p deletion and/or TP53 mutation by fluorescence in situ hybridization and sequencing, respectively; present, del17p positive and/or TP53 mutated; absent, del17p negative and TP53 negative.

Statistical analysis

Continuous variables were summarized by medians and ranges, whereas categorical variables were reported as absolute frequencies and percentages, as appropriate.

The main end point was TTD, defined as the interval from treatment initiation to permanent discontinuation. Treatment discontinuation was defined as the permanent cessation of the BTKi for any reason, including AEs, disease progression, transformation to Richter syndrome, patient decision, or death. A discontinuation event required a treatment gap of >30 consecutive days without BTKi reinitiation. Temporary interruptions of treatment (eg, for intercurrent illness, planned procedures, or toxicity) lasting ≤30 days were not classified as discontinuation. Dose reductions or physician-directed treatment holds were considered treatment modifications rather than discontinuations, provided that therapy was resumed within 30 days. Discontinuation events were not centrally adjudicated; however, participating centers applied standardized criteria aligned with real-world clinical practice and International Workshop on Chronic Lymphocytic Leukemia recommendations. All AEs resulting in definitive treatment discontinuation were classified as grade >3 and irreversible.

TTNTD was defined as the time from treatment initiation to the earlier of 2 events: the start of a subsequent therapy or death. Patients not receiving a new line of therapy were censored at their last known clinical activity. All subsequent therapies were given according to International Workshop on Chronic Lymphocytic Leukemia criteria.[33] Reasons for treatment discontinuation were documented from clinical charts for a subset of patients.

Follow-up was truncated at 24 months to minimize differences in observation time between treatment groups, as patients treated with ibrutinib had longer follow-up periods than those treated with zanubrutinib. Patients lost to follow-up were not excluded, but treated as censored observations in the survival analysis.

Univariable Cox regression models were used to assess the association between covariates and TTD or TTNTD. Covariates included treatment type (zanubrutinib vs ibrutinib), age, gender, Binet stage, *IGHV* mutational status, *TP53* disruption [del(17p) and/or *TP53* mutation], line of therapy, β2-microglobulin, lactate dehydrogenase, ECOG-PS, and cardiovascular risk factors.

To reduce treatment-selection bias (or confounding by indication), a propensity score model was developed using multivariable

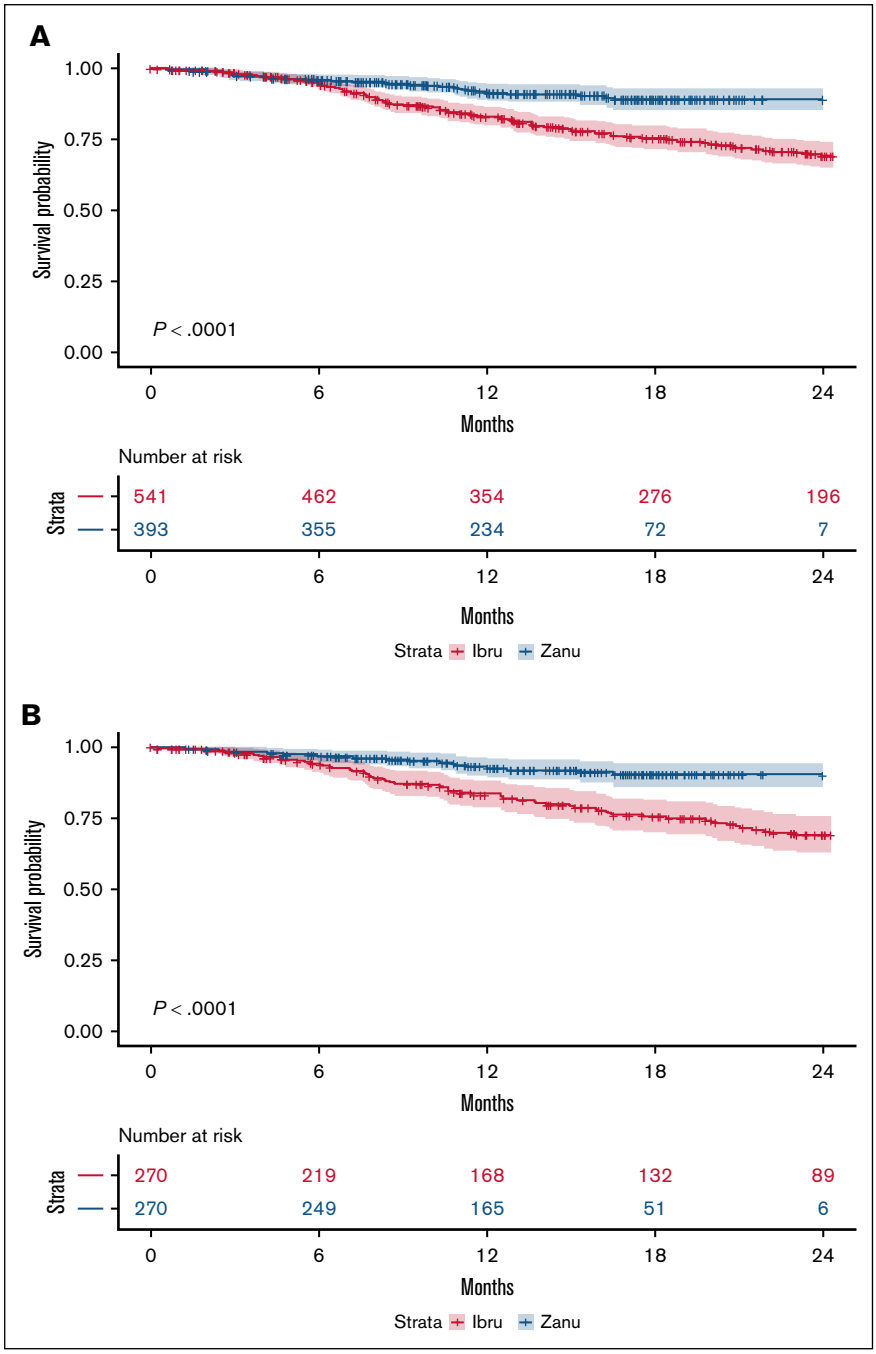

Figure 2. Kaplan-Meier curves of TTNTD for all 934 patients with CLL treated with zanubrutinib or ibrutinib. (A) Kaplan-Meier curve of TTNTD according to treatment arm in the original cohorts. (B) Kaplan-Meier curve of TTNTD according to treatment arm in the propensity score–matched cohorts.

logistic regression, incorporating covariates with a standardized mean difference ≥0.1 between treatment groups. This method is considered more robust than relying on *P* value thresholds, which can be overly sensitive to sample size. The model also included an interaction term between age and the number of previous lines of therapy. The dependent variable was the treatment received (zanubrutinib vs ibrutinib), and the resulting predicted probabilities were used as propensity scores. Matching was performed using a caliper width of 0.02 standard deviations of the logit of the propensity score, in a 1:1 ratio (1 ibrutinib-treated control for each zanubrutinib-treated patient). No weighting was applied as matching was 1-to-1; all patients in the matched cohort received a weight of 1.

Univariable and multivariable Cox regression models were fitted on the matched cohort to identify factors associated with TTD and TTNTD. In all multivariable models, we always forced age and sex. Variables significantly associated with the outcomes on univariable analyses were included in multivariable models. Hazard ratios (HRs), 95% confidence intervals (CIs), and *P*-values were

Table 3. Univariate and multivariate analyses for TTNTD

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age*	1.01 (0.99-1.02)	.364	1.01 (0.99-1.03)	.189
Sex				
Male vs female	0.96 (0.7-1.33)	.806	0.89 (0.62-1.27)	.509
Therapy				
Zanubrutinib vs ibrutinib	0.42 (0.29-0.62)	**.000**	0.35 (0.22-0.56)	**.000**
Line of therapy				
R/R vs TN	1.76 (1.28-2.43)	**.001**	1.46 (1.03-2.06)	**.033**
Binet stage				
B vs A	1.33 (0.73-2.43)	.347	1.28 (0.69-2.38)	.426
C vs A	1.91 (1.07-3.42)	**.029**	2.03 (1.12-3.66)	**.019**
IGHV mutational status				
Germ line vs mutated	1 (0.72-1.4)	.985	–	
TP53 disruption†				
Present vs absent	1.87 (1.35-2.59)	**.000**	1.75 (1.25-2.44)	**.001**
ECOG-PS				
2-3 vs 0-1	1.39 (1-1.93)	.047	1.35 (0.95-1.92)	.094
Cardiovascular risk factor				
Hypertension	1.19 (0.87-1.61)	.282	–	
Atrial fibrillation	1.03 (0.65-1.63)	.892	–	
Hypercholesterolemia	0.95 (0.61-1.48)	.824	–	
Congestive heart failure	2.14 (1.34-3.42)	.001	1.91 (1.17-3.11)	**.009**
Peripheral arterial disease	0.87 (0.36-2.11)	.750	–	
Cerebrovascular disease	1.16 (0.51-2.63)	.717	–	
Diabetes	0.92 (0.6-1.41)	.704	–	
Myocardial infarction	0.74 (0.44-1.25)	.260	–	

Boldface values indicate statistically significant results.
*The effect corresponds to 1 year of increase in age.
†TP53 disruption was determined by the documentation of 17p deletion and/or TP53 mutation by fluorescence in situ hybridization and sequencing, respectively; present, del17p positive and/or TP53 mutated; absent, del17p negative and TP53 negative.

reported for all Cox models. All statistical analyses were performed using R version 4.5.0 (Copyright [C] 2025 The R Foundation for Statistical Computing: package survival, survminer, TableOne, cobalt, MatchIt). Additional analyses were conducted using IBM SPSS Statistics, version 29.

All participating centers obtained ethics approval, and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent has been obtained from all patients.

Results

Study population and baseline characteristics

A total of 934 patients with CLL who initiated treatment with either zanubrutinib or ibrutinib met the inclusion criteria and were included in this analysis. Of these, 541 (57.9%) received ibrutinib, and 393 (42.1%) received zanubrutinib (Table 1). The median age was 76 years (range, 44-94) in patients of the zanubrutinib cohort, and 70 years (range, 37-88) in those of the ibrutinib cohort (Table 1). The 2 cohorts were generally balanced in terms of sex, *IGHV* mutational status, ECOG-PS, and cardiovascular risk factors. Beyond age, they also differed as for line of therapy, Binet stage, and *TP53* disruption status. Specifically, the ibrutinib group had higher rates of patients who were R/R (59% vs 39.3%) and of *TP53* disruption (38.1% vs 18.3%) than the zanubrutinib group.

TTD

Over a median follow-up of 13 months for the zanubrutinib cohort and 18 months for the ibrutinib cohort, the median TTD was not reached in both groups (Figure 1A). At 12 months, the discontinuation rate was significantly lower for zanubrutinib (12.6%) than for ibrutinib (21.4%; $P < .001$; Figure 1A).

On univariable analysis, the following variables were significantly associated with shorter TTD: >1 previous line of therapy (HR, 1.56; 95% CI, 1.17-2.07; $P = .002$), Binet stage C (HR, 1.85; 95% CI, 1.10-3.13; $P = .02$), *TP53* disruption (HR, 1.67; 95% CI, 1.24-2.24; $P = .001$), ECOG-PS 2 to 3 (HR, 1.56; 95% CI, 1.17-2.08; $P = .003$), and congestive heart failure (HR, 1.82; 95% CI, 1.16-2.87; $P = .009$; Table 2).

Table 4. Reasons for zanubrutinib or ibrutinib discontinuation in patients with CLL

	Zanubrutinib	Ibrutinib
Total patients, N	393	541
Patients who discontinued treatment, n (%)	49 (12.5)	155 (28.6)
Median follow-up, mo	13	18
Reasons for discontinuation		
Toxic effect of therapy	14 (3.6)	71 (13.1)
Arthralgia/myalgia/arthritis	0	21 (3.9)
Atrial fibrillation	1 (0.3)	11 (2.0)
Bleeding episodes	5 (1.3)	16 (2.9)
Rash	1 (0.3)	11 (2.0)
Infection	6 (1.6)	4 (07)
Diarrhea	0	8 (1.5)
Hepatitis B virus reactivation	1 (0.3)	0
Disease progression		
CLL	16 (4.1)	63 (11.6)
Richter syndrome	1 (0.3)	24 (4.4)
Second neoplasia	3 (0.8)	4 (0.7)
Patient request	1 (0.3)	0
Other	1 (0.3)	1 (0.2)
Non-CLL–related death	6 (1.5)	4 (0.7)
Death from unknown causes	7 (1.8)	12 (2.2)

On multivariable analysis, treatment with zanubrutinib was independently associated with significantly longer TTD (HR, 0.45; 95% CI, 0.31-0.65; $P < .001$; Table 2). In the same model, Binet stage C (HR, 1.85; 95% CI, 1.08-3.16; $P = .02$), *TP53* disruption (HR, 1.57; 95% CI, 1.16-2.12; $P = .003$), ECOG-PS 2 to 3 (HR, 1.52; 95% CI, 1.11-2.07; $P = .009$), and congestive heart failure (HR, 1.70; 95% CI, 1.06-2.72; $P = .028$) were independently associated with shorter TTD.

TTNTD

The median TTNTD was not reached in either cohort (Figure 2A). At 12 months, TTNTD estimates were significantly improved in the zanubrutinib cohort (91.9%) compared with the ibrutinib cohort (83.0%; $P < .001$; Figure 2A). Univariable analysis identified the following variables as significantly associated with shorter TTNTD: >1 previous line of therapy (HR, 1.76; 95% CI, 1.28-2.43; $P = .001$), Binet stage C (HR, 1.91; 95% CI, 1.07-3.42; $P = .029$), *TP53* disruption (HR, 1.87; 95% CI, 1.35-2.59; $P < .001$), ECOG-PS 2 to 3 (HR, 1.39; 95% CI, 1.00-1.93; $P = .047$), and congestive heart failure (HR, 2.14; 95% CI, 1.34-3.42; $P = .001$; Table 3). Conversely, zanubrutinib treatment was significantly associated with a reduced risk of TTNTD (HR, 0.42; 95% CI, 0.29-062; $P < .001$). In multivariable analysis, >1 previous line of therapy (HR, 1.46; 95% CI, 1.03-2.06; $P = .033$), Binet stage C (HR, 2.03; 95% CI, 1.12-3.66; $P = .019$), *TP53* disruption (HR, 1.75; 95% CI, 1.25-2.44; $P = .001$), and congestive heart failure (HR, 1.91; 95% CI, 1.17-3.11; $P = .009$) were independently associated with lower TTNTD, whereas zanubrutinib therapy was associated with a significantly improved TTNTD (HR, 0.35; 95% CI, 0.22-0.56; $P < .001$; Table 3).

Table 5. Baseline characteristics of the patients with CLL treated with zanubrutinib or ibrutinib after propensity score matching

	Zanubrutinib (N = 270)	Ibrutinib (N = 270)	SMD
Mean age (SD), y	72.1 (9.81)	71.2 (9.16)	0.095
Sex, n (%)			
Male	173 (64.1)	168 (62.2)	
Female	97 (35.9)	102 (37.8)	−0.018
Line of therapy, n (%)			
1L	146 (54.1)	145 (53.7)	
2L+	124 (45.9)	125 (46.3)	−0.0037
Binet stage, n (%)			
A	30 (10.4)	37 (12)	−0.0259
B	106 (38.4)	113 (44)	−0.0259
C	134 (51.1)	120 (44)	0.0519
IGHV mutational status, n (%)			
Mutated	80 (29.6)	88 (32.6)	
Germ line	190 (70.4)	182 (67.4)	0.0296
TP53 disruption, n (%)*			
Absent	183 (67.8)	183 (67.8)	
Present	87 (32.2)	87 (32.2)	0.0000
ECOG-PS, n (%)			
0-1	212 (78.5)	197 (73)	
2-3	58 (21.5)	73 (27)	−0.0556
Cardiovascular risk factor, n (%)			
Hypertension	106 (39.3)	109 (40.4)	−0.0111
Atrial fibrillation	35 (13)	35 (13)	0.0000
Hypercholesterolemia	36 (13.3)	47 (17.4)	−0.0407
Congestive heart failure	13 (4.8)	17 (6.3)	−0.015
Peripheral arterial disease	10 (3.7)	10 (3.7)	0.00001
Cerebrovascular disease	8 (3)	9 (3.3)	−0.0037
Diabetes	40 (14.8)	46 (17)	−0.0222
Myocardial infarction	34 (12.6)	33 (12.2)	0.0037

*TP53 disruption was determined by the documentation of 17p deletion and/or TP53 mutation by FISH and sequencing, respectively; present=del17p positive and/or TP53 mutated; absent=del17p negative and TP53 negative. 1L, first line; 2L+, 2 or more prior lines of therapy; SMD, standardized mean difference.

Reasons for discontinuation

Overall, 12.5% of patients (n = 49) in the zanubrutinib cohort and 28.6% of patients (n = 155) in the ibrutinib cohort discontinued treatment during the study period (Table 4).

In both cohorts, toxicity (14/49 patients [28.6%] for zanubrutinib; 71/155 patients [46.3%] for ibrutinib) and disease progression (17/49 patients [34.7%] for zanubrutinib; 63/155 patients [41%] for ibrutinib) were the most frequently reported reasons for discontinuation. Discontinuation due to disease progression was more common in the ibrutinib group (Table 4). Supplemental Table 1 reports the most common grade 3 to 4 treatment-emergent AEs observed in both cohorts. The incidence of AEs was generally comparable between the 2 treatment groups.

Table 6. Univariate and multivariate analyses for TTD after propensity score matching

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age*	1.03 (1.01-1.06)	**.008**	1.02 (1-1.05)	**.028**
Sex				
Male vs female	0.98 (0.65-1.48)	.942	0.99 (0.65-1.51)	.947
Therapy				
Zanubrutinib vs ibrutinib	0.49 (0.33-0.74)	**.001**	0.51 (0.35-0.76)	**.001**
Line of therapy				
2L+ vs 1L	1.51 (1.03-2.22)	**.035**	1.44 (0.96-2.15)	.079
Binet stage				
B vs A	1.27 (0.64-2.52)	.499		
C vs A	1.69 (0.87-3.28)	.121		
IGHV mutational status				
Germ line vs mutated	1.22 (0.79-1.89)	.362		
TP53 disruption†				
Present vs absent	1.44 (0.98-2.11)	.063		
ECOG-PS				
2-3 vs 0-1	2.05 (1.39-3.04)	**.000**	1.74 (1.15-2.63)	**.009**
Cardiovascular risk factor				
Hypertension	1.38 (0.94-2.03)	.100	–	
Atrial fibrillation	1.19 (0.69-2.06)	.523	–	
Hypercholesterolemia	0.76 (0.4-1.42)	.383	–	
Congestive heart failure	3.4 (1.96-5.88)	**.000**	2.46 (1.3-4.64)	**.006**
Peripheral arterial disease	1.24 (0.47-3.23)	.666	–	
Cerebrovascular disease	1.43 (0.49-4.13)	.514	–	
Diabetes	1.02 (0.6-1.72)	.947	–	
Myocardial infarction	1.07 (0.62-1.85)	.800	–	

Boldface values indicate statistically significant results.
1L, first line; 2L+, 2 or more prior lines of therapy.
*The effect corresponds to 1 year of increase in age.
†TP53 disruption was determined by the documentation of 17p deletion and/or TP53 mutation by fluorescence in situ hybridization and sequencing, respectively; present, del17p positive and/or TP53 mutated; absent, del17p negative and TP53 negative.

However, arthralgia, diarrhea, and atrial fibrillation occurred significantly more frequently in patients receiving ibrutinib than in those treated with zanubrutinib.

Propensity score–matching analysis

After 1:1 propensity score matching, 2 well-balanced cohorts of 270 patients each were selected (Table 5). With a median follow-up of 13 months for zanubrutinib and 16 months for ibrutinib, the 12-month discontinuation rate was significantly lower in the zanubrutinib group (12.4%) than in the ibrutinib group (20.2%; $P < .001$; Figure 1B).

On univariable analysis, age (HR, 1.03; 95% CI, 1.01-1.06; $P = .008$), >1 previous line of therapy (HR, 1.51; 95% CI, 1.03-2.22; $P = .035$), ECOG-PS 2 to 3 (HR, 2.0; 95% CI, 1.39-3.04; $P < .001$), and congestive heart failure (HR, 2.46; 95% CI, 1.30-4.64; $P = .006$) were independently associated with an increased risk of discontinuing therapy. Conversely, zanubrutinib treatment was significantly associated with a reduced risk of discontinuation (HR, 0.49; 95% CI, 0.33-0.74; $P < .001$; Table 6).

On multivariable analysis, age (HR, 1.02; 95% CI, 1.01-1.05; $P = .028$), ECOG-PS 2 to 3 (HR, 1.74; 95% CI, 1.15-2.63; $P = .009$), and congestive heart failure (HR, 2.46; 95% CI, 1.30-4.64; $P = .006$) were independently associated with an increased risk of discontinuing therapy. Conversely, zanubrutinib treatment was significantly associated with a reduced risk of discontinuation (HR, 0.51; 95% CI, 0.35-0.76; $P = .001$; Table 6).

As for TTNTD, the 12-month estimates were again improved for the zanubrutinib (93.2%) vs the ibrutinib (83.4%) cohorts ($P < .001$; Figure 2B).

In univariable analysis, age (HR, 1.03; 95% CI, 1.01-1.06; $P = .039$), >1 previous line of therapy (HR, 1.78; 95% CI, 1.12-2.82; $P = .015$), TP53 disruption (HR, 1.63; 95% CI, 1.06-2.51; $P = .026$), ECOG PS (HR, 1.74; 95% CI, 1.12-2.70; $P = .014$), and congestive heart failure (HR, 3.53; 95% CI, 1.97-6.33; $P < .001$) were independently associated with inferior TTNTD, whereas zanubrutinib therapy was independently associated with significantly improved TTNTD (HR, 0.37; 95% CI, 0.22-0.60; $P < .001$; Table 7).

Table 7. Univariate and multivariate analyses for TTNTD after propensity score matching

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age*	1.03 (1-1.06)	**.039**	1.03 (1.01-1.05)	**.019**
Sex				
Male vs female	0.86 (0.53-1.38)	.528	0.82 (0.5-1.34)	.421
Therapy				
Zanubrutinib vs ibrutinib	0.37 (0.22-0.6)	**.000**	0.36 (0.22-0.59)	**.000**
Line of therapy				
2L+ vs 1L	1.78 (1.12-2.82)	**.015**	1.89 (1.14-3.13)	**.014**
Binet stage				
B vs A	1.32 (0.58-3.01)	.511	–	
C vs A	2.13 (0.96-4.69)	.062		
IGHV mutational status				
Germ line vs mutated	1.3 (0.8-2.12)	.294	–	
TP53 disruption†				
Present vs absent	1.63 (1.06-2.51)	**.026**	1.95 (1.23-3.08)	**.004**
ECOG-PS				
2-3 vs 0-1	1.74 (1.12-2.7)	**.014**	1.48 (0.94-2.31)	.090
Cardiovascular risk factor				
Hypertension	1.34 (0.89-2.03)	.165	–	
Atrial fibrillation	1.33 (0.74-2.4)	.341	–	
Hypercholesterolemia	0.73 (0.36-1.48)	.381	–	
Congestive heart failure	3.53 (1.97-6.33)	.000	2.36 (1.24-4.47)	**.009**
Peripheral arterial disease	1.55 (0.59-4.07)	.377	–	
Cerebrovascular disease	1.43 (0.41-4.94)	.574	–	
Diabetes	1.18 (0.67-2.08)	.579	–	
Myocardial infarction	0.94 (0.49-1.82)	.857	–	

Boldface values indicate statistically significant results.
1L, first line; 2L+, 2 or more prior lines of therapy.
*The effect corresponds to 1 year of increase in age.
†TP53 disruption was determined by the documentation of 17p deletion and/or TP53 mutation by fluorescence in situ hybridization and sequencing, respectively; present, del17p positive and/or TP53 mutated; absent, del17p negative and TP53 negative.

In multivariable analysis, age (HR, 1.03; 95% CI, 1.01-1.05; $P = .019$), >1 previous line of therapy (HR, 1.89; 95% CI, 1.14-3.13; $P = .014$), TP53 disruption (HR, 1.95; 95% CI, 1.23-3.08; $P = .004$), and congestive heart failure (HR, 2.36; 95% CI, 1.24-4.47; $P = .009$) were independently associated with inferior TTNTD, whereas zanubrutinib therapy was independently associated with significantly improved TTNTD (HR, 0.36; 95% CI, 0.22-0.59; $P < .001$; Table 7).

Discussion

In this large, multicenter, real-world study, we compared outcomes in patients with CLL treated with zanubrutinib or ibrutinib outside of clinical trials. Zanubrutinib was associated with significantly improved treatment persistence and disease control, as reflected by longer TTD and TTNTD, in both the overall and propensity score–matched populations, underscoring their clinical relevance in routine practice.

A key finding was the significantly lower 12-month treatment discontinuation rate with zanubrutinib (12.6%) compared with ibrutinib (21.4%), primarily attributable to its favorable safety profile and fewer instances of disease progression. This difference remained significant after adjustment for clinical covariates and in the matched cohort (12.4% vs 20.2%, $P < .001$). Patients treated with zanubrutinib experienced fewer interruptions due to off-target effects such as atrial fibrillation, bleeding, arthralgia, and diarrhea.

In contrast, real-world studies consistently report high discontinuation rates for ibrutinib: 41% in a US multicenter cohort (median TTD 7 months),[34] ~33.5% (range 14.5%-43%) across multiple real-life studies,[35] and similar observations in French[36] and UK/Ireland cohorts,[37] closely mirroring the discontinuation rate reported in registration trials (32%).[35] Nevertheless, comparisons of discontinuation rates between clinical trials and real-world data do not account for differences in exposure time and median follow-up.

Zanubrutinib was also associated with improved 12-month TTNTD estimates compared with ibrutinib (91.9% vs 83.0%, $P < .001$ in the overall population; 93.2% vs 83.4%, $P < .001$ in the matched analysis), indicating more durable disease control. Multivariable analyses identified, R/R disease, Binet stage C, *TP53* disruption,

and congestive heart failure as negative prognostic factors for TTNTD, whereas zanubrutinib remained independently associated with improved outcomes. These benefits were observed in both first-line and R/R settings, although the shorter follow-up in the zanubrutinib cohort warrants cautious interpretation.

Given the higher prevalence of unfavorable features in the ibrutinib group, propensity score matching was used to mitigate imbalance. Although residual confounding cannot be excluded, age and congestive heart failure resulted in consistently poorer TTD and TTNTD, and zanubrutinib retained its favorable association across all models. ECOG-PS 2 to 3 negatively affected TTD, whereas *TP53* disruption and R/R disease affected TTNTD. Notably, in the ibrutinib setting, *TP53* disruption influenced outcomes primarily when mutation and 17p deletion co-occurred;[24,38] whether this applies to second-generation BTKis warrants further study. Other biomarkers, including CD49d expression, unavailable in our cohort but prognostically relevant for ibrutinib and acalabrutinib,[39-41] could also be explored for patients who were treated with zanubrutinib.

Two smaller Chinese retrospective studies reported favorable outcomes with zanubrutinib, but lacked comparators and had limited follow-up.[20,21]

A recent US abstract by Hou et al[19] described >3000 patients treated with ibrutinib, acalabrutinib, or zanubrutinib, and showed that zanubrutinib had the most favorable cardiovascular safety profile, and highest 6- and 12-month treatment persistence. Median TTNTD was not reached for zanubrutinib, compared with 30.2 and 35.8 months for ibrutinib and acalabrutinib, respectively, consistent with our findings.

Complementary real-world evidence from the Flatiron Health database compared acalabrutinib and ibrutinib.[42] Acalabrutinib showed longer therapy duration, primarily due to improved tolerability, in line with the ELEVATE-RR trial.

Direct comparisons between acalabrutinib and zanubrutinib remain lacking, but early observational data suggest potential advantages for zanubrutinib in cardiovascular safety and treatment continuity. Overall, real-world data, including ours, support the clinical transition toward second-generation BTKis, particularly for patients at high risk of treatment-related toxicity.

Several limitations of our study should be acknowledged. The follow-up for the zanubrutinib cohort was necessarily shorter due to later regulatory approval, potentially limiting long-term outcome assessment, although early divergence of survival curves supports robustness. Given the retrospective nature of data collection, reliable grading of AEs according to Common Terminology Criteria for Adverse Events was feasible mainly for laboratory-based parameters, whereas subjective or clinically reported events may have been underestimated. Treatment allocation was nonrandomized, and may have been influenced by physician or institutional preferences. Temporal differences existed between cohorts (ibrutinib, June 2013–June 2019; zanubrutinib, October 2023 onward), potentially introducing residual confounding related to the treatment era. To reduce bias from unequal observation periods, follow-up was truncated at 24 months. Although this harmonization mitigates differences, residual effects cannot be entirely excluded. Despite these limitations, propensity score matching, multivariable adjustment, and the multicenter design strengthen the generalizability of our findings.

In conclusion, this study provides the first real-world comparative effectiveness analysis of zanubrutinib vs ibrutinib in CLL, confirming superior tolerability and treatment durability of zanubrutinib. Patients treated with zanubrutinib experienced fewer off-target AEs, particularly atrial fibrillation, diarrhea, and arthralgia, supporting its preferential use in patients with CLL with comorbidities or a higher risk of treatment-related toxicity. When contextualized with emerging real-world data, including acalabrutinib, our findings reinforce the clinical transition toward second-generation BTKis in routine practice, zanubrutinib appears particularly well suited for patients with a high comorbidity burden or increased risk of AEs. Direct head-to-head comparisons with acalabrutinib will be critical to further refine BTKi selection and optimize outcomes.

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Authorship

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