Real-World Comparative Analysis of Treatment Discontinuation with Covalent Bruton Tyrosine Kinase Inhibitors in First-Line Chronic Lymphocytic Leukemia (CLL)

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CONCLUSIONS

- In this real-world study, zanubrutinib demonstrated significantly lower risk of treatment discontinuation and greater treatment persistence than acalabrutinib or ibrutinib in 1L treatment for CLL, especially in patients aged ≥65 years
- While this study provides comparative insights into real-world treatment discontinuation, additional studies with longer follow-up are needed to better understand the reasons for and consequences of treatment discontinuation in 1L CLL

INTRODUCTION

- Covalent Bruton tyrosine kinase inhibitors (cBTKis) are commonly used first-line (1L) therapies approved in the EU and USA for chronic lymphocytic leukemia (CLL)[1,2]
- A previous real-world study using the US Flatiron Health database showed that the risk of death in patients with 1L CLL who received zanubrutinib was significantly lower than in those who received ibrutinib and numerically lower than in those who received acalabrutinib[3]
- Elderly patients (≥65 years) represent nearly 70% of those diagnosed with CLL, but often experience lower treatment rates and poorer outcomes[4,5]
  - Real-world data on treatment patterns with cBTKis remain limited, including in elderly patients

Aim

- This retrospective observational study aimed to evaluate real-world treatment persistence and treatment discontinuation associated with 1L cBTKi use in CLL

METHODS

Data Source and Study Population

- The US IQVIA PharMetrics® closed claims database was used to identify adult patients with ≥2 entries of International Classification of Diseases (ICD) codes for CLL/small lymphocytic leukemia diagnoses (ICD-9-CM, 204.1x, 200.8x; ICD-10-CM, C91.1x, C83.0x) who initiated 1L cBTKi monotherapy (ibrutinib, acalabrutinib, or zanubrutinib) from January 1, 2022, to February 28, 2025
  - The index date was the date of initiation of 1L treatment
- Eligible patients had continuous enrollment in health insurance for ≥3 months before the start of each cBTKi treatment and were followed until the end of the study period or loss to follow-up, whichever occurred first
- Patients who participated in clinical trials (ICD Z00.6) during the study period were excluded

Study Design and Statistical Analysis

- Baseline patient characteristics and outcomes were examined by each cBTKi group
- Outcomes included: treatment discontinuation, defined as the time from index date to regimen end date if there was a subsequent therapy, or a gap of ≥120 days between regimen end date and last activity/enrollment date; and treatment persistence, defined as the probability that a patient continues on treatment
- Real-world time to treatment discontinuation (rwTTD) was analyzed using Kaplan-Meier (KM) estimates
- A multivariable Cox proportional hazards model that adjusted for age, sex, race, ethnicity, payer type, geographic region, and Charlson Comorbidity Index (CCI) was used to estimate the hazard ratio (HR) of treatment discontinuation between zanubrutinib and acalabrutinib or ibrutinib
- A subgroup analysis for these outcomes was conducted in elderly patients aged ≥65 years

RESULTS

Patient Demographics and Baseline Characteristics

- A total of 1850 patients were included (zanubrutinib, n=608; acalabrutinib, n=826; ibrutinib, n=416; **Figure 1**)

Figure 1. Patient Attrition

[a]Diagnosis codes: ICD-9-CM, 204.1x, 200.8x; ICD-10-CM, C91.1x, C83.0x.
CLL, chronic lymphocytic leukemia; ICD, International Classification of Diseases; SLL, small lymphocytic lymphoma.

- Baseline patient demographic and clinical characteristics were generally comparable between cBTKis (**Table 1**), though the median age was higher with zanubrutinib than acalabrutinib or ibrutinib (69.0 vs 68.0 vs 67.0 years; *P*=.0007)
  - A greater proportion of patients who received zanubrutinib were aged ≥65 years than acalabrutinib or ibrutinib (73.9% vs 68.9% vs 65.9%; *P*=.0229)
  - Other baseline differences between cBTKis were race (*P*=.031) and mean CCI (*P*=.013), with patients receiving zanubrutinib having a higher mean CCI (3.6) than those with acalabrutinib (3.5) and ibrutinib (3.1)

Table 1. Baseline Demographics and Clinical Characteristics by cBTKi

	Zanubrutinib monotherapy (n=608)	Acalabrutinib monotherapy (n=826)	Ibrutinib monotherapy (n=416)	*P*-value
Age at index date, years				
Mean (SD)	68.8 (9.0)	68.0 (9.6)	66.3 (9.5)	.0006
Median (IQR)	69.0 (63.0-76.0)	68.0 (62.0-76.0)	67.0 (61.0-73.0)	.0007
Age group at index date, n (%)				.0229
18-55 years	36 (5.9)	63 (7.6)	44 (10.6)	
56-64 years	123 (20.2)	194 (23.5)	98 (23.6)	
≥65 years	449 (73.9)	569 (68.9)	274 (65.9)	
Gender, n (%)				.530
Female	231 (38.0)	290 (35.1)	150 (36.1)	
Male	377 (62.0)	536 (64.9)	266 (63.9)	
Race, n (%)				.031[a]
African American	27 (4.4)	39 (4.7)	37 (8.9)	
Asian	3 (0.5)	5 (0.6)	1 (0.2)	
Caucasian	211 (34.7)	302 (36.6)	151 (36.3)	
Other	28 (4.6)	15 (1.8)	14 (3.4)	
Unspecified/unknown	339 (55.8)	465 (56.3)	213 (51.2)	
Ethnicity, n (%)				.167
Hispanic	11 (1.8)	8 (1.0)	9 (2.2)	
Not Hispanic/other	195 (32.1)	293 (35.5)	155 (37.3)	
Unspecified/unknown	402 (66.1)	525 (63.6)	252 (60.6)	
Payer type, n (%)				.336[b]
Commercial	155 (25.5)	226 (27.4)	117 (28.1)	
Medicaid	43 (7.1)	69 (8.4)	37 (8.9)	
Medicare Advantage	364 (59.9)	444 (53.8)	226 (54.3)	
Self-insured	2 (0.3)	13 (1.6)	4 (1.0)	
Medicare cost	42 (6.9)	72 (8.7)	30 (7.2)	
Unknown/missing	2 (0.3)	2 (0.2)	2 (0.5)	
Geography, n (%)				.575
Northeast	129 (21.2)	153 (18.5)	81 (19.5)	
South	162 (26.6)	214 (25.9)	114 (27.4)	
Midwest	222 (36.5)	310 (37.5)	162 (38.9)	
West	89 (14.6)	137 (16.6)	53 (12.7)	
Unknown/other	6 (1.0)	12 (1.5)	6 (1.4)	
CCI[c]				
Mean (SD)	3.6 (2.5)	3.5 (2.4)	3.1 (1.9)	.013
Median (IQR)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	2.0 (2.0-4.0)	
Index year, n (%)				<.0001
2022	58 (9.5)	300 (36.3)	212 (51.0)	
2023	198 (32.6)	224 (27.1)	99 (23.8)	
2024	304 (50.0)	244 (29.5)	84 (20.2)	
2025	48 (7.9)	58 (7.0)	21 (5.1)	

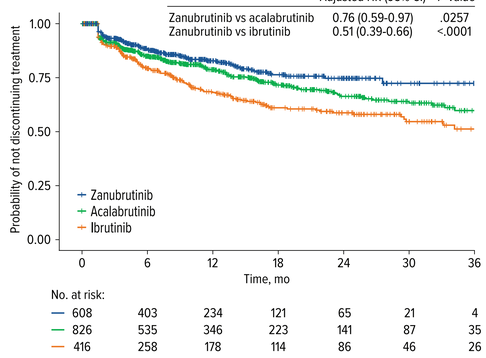
[a]African American, Asian, and Other races were grouped prior to analysis.
[b]The following payer types were combined prior to analysis: Medicare Cost with Medicare Advantage, and self-insured with unknown/missing.
[c]Based on 3 months prior to index month.
cBTKi, covalent Bruton tyrosine kinase inhibitor; CCI, Charlson Comorbidity Index; IQR, interquartile range; SD, standard deviation.

Treatment Discontinuation and Persistence by cBTKi

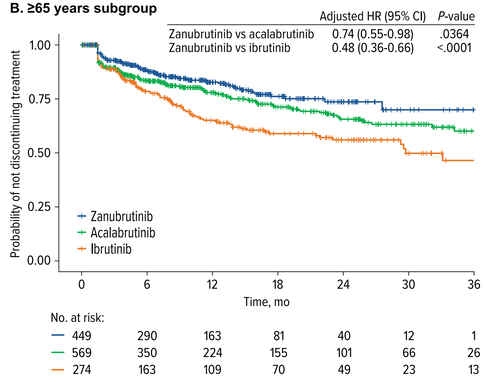
- Median follow-up periods were 12 (interquartile range [IQR], 6-19) months for zanubrutinib, 14 (IQR, 7-25) months for acalabrutinib, and 17 (IQR, 8-28) months for ibrutinib
- Zanubrutinib demonstrated significantly longer rwTTD (**Figure 2A**) and higher treatment persistence at 6, 12, 18, and 24 months than acalabrutinib and ibrutinib (**Table 2**)
  - At 12 months, treatment persistence was highest with zanubrutinib (82.8%; 95% confidence interval [CI], 79.1-85.9), followed by acalabrutinib (78.7%; 95% CI, 75.4-81.7) and ibrutinib (68.1%; 95% CI, 62.8-72.9; *P*<.0001)
  - Similarly, at 24 months, treatment persistence was highest with zanubrutinib (74.7%; 95% CI, 69.3-79.3) versus acalabrutinib (66.3%; 95% CI, 61.6-70.6) or ibrutinib (58.7%; 95% CI, 52.7-64.3; *P*=.0002)
- Similar results were observed in the elderly patient subgroup (**Figure 2B, Table 2**)
  - At 12 months, treatment persistence was highest with zanubrutinib (82.7%; 95% CI, 78.3-86.3), followed by acalabrutinib (78.0%; 95% CI, 73.8-81.6) and ibrutinib (65.1%; 95% CI, 58.3-71.1; *P*<.0001)
  - Similarly, at 24 months, treatment persistence was highest with zanubrutinib (73.6%; 95% CI, 66.7-79.3) versus acalabrutinib (65.6%; 95% CI, 59.8-70.8) or ibrutinib (56.0%; 95% CI, 48.4-63.0; *P*=.0018)

Figure 2. rwTTD with 1L cBTKi

A. Overall population



B. ≥65 years subgroup



1L, first-line; cBTKi, covalent Bruton tyrosine kinase inhibitor; CI, confidence interval; HR, hazard ratio; rwTTD, real-world time to treatment discontinuation.

Table 2. Real-World Treatment Persistence with 1L BTKi

Patient persistency, % (95% CI)	Zanubrutinib monotherapy (n=608)	Acalabrutinib monotherapy (n=826)	Ibrutinib monotherapy (n=416)	*P*-value
All patients				
6 months	88.5 (85.5-90.9)	85.0 (82.2-87.3)	79.2 (74.8-83.0)	.0009
12 months	82.8 (79.1-85.9)	78.7 (75.4-81.7)	68.1 (62.8-72.9)	<.0001
18 months	76.4 (71.4-80.6)	71.6 (67.5-75.2)	61.1 (55.2-66.4)	.0002
24 months	74.7 (69.3-79.3)	66.3 (61.6-70.6)	58.7 (52.7-64.3)	.0002
Age ≥65 years at index date				
6 months	88.5 (85.0-91.2)	83.5 (80.0-86.5)	78.5 (72.8-83.1)	.0027
12 months	82.7 (78.3-86.3)	78.0 (73.8-81.6)	65.1 (58.3-71.1)	<.0001
18 months	76.2 (70.2-81.1)	71.3 (66.3-75.6)	58.9 (51.6-65.5)	.0006
24 months	73.6 (66.7-79.3)	65.6 (59.8-70.8)	56.0 (48.4-63.0)	.0018

1L, first-line; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval.

- Univariate and multivariable Cox regression analyses showed that the risk of treatment discontinuation was significantly lower with zanubrutinib than acalabrutinib or ibrutinib (**Table 3**)
  - Similar results were seen in patients aged ≥65 years

Table 3. Univariate and Multivariable Cox Regression Analyses of Treatment Discontinuation

	Zanubrutinib vs acalabrutinib		Zanubrutinib vs ibrutinib	
	All patients	Patients aged ≥65 years	All patients	Patients aged ≥65 years
Unadjusted HR (95% CI)[a]	0.76 (0.60-0.97)	0.75 (0.56-0.99)	0.54 (0.42-0.70)	0.51 (0.38-0.69)
P-value	.0263	.0439	<.0001	<.0001
Adjusted HR (95% CI)[a]	0.76 (0.59-0.97)	0.74 (0.55-0.98)	0.51 (0.39-0.66)	0.48 (0.36-0.66)
P-value	.0257	.0364	<.0001	<.0001

[a]Unadjusted HRs were estimated using Cox proportional hazards models; adjusted HRs were estimated from multivariable Cox proportional hazards models adjusting for age at index, gender, race, ethnicity, payer type, geography, and CCI.
CCI, Charlson Comorbidity Index; CI, confidence interval; HR, hazard ratio.

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DISCLOSURES

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