Real-World Comparative Effectiveness of First-Line Bruton Tyrosine Kinase Inhibitors in Patients with Chronic Lymphocytic Leukemia

Ryan Jacobs,[1] Xiaoliang Wang,[2] Qianhong Fu,[2] Dong Yuan,[2] Derrick van Beuge,[2] Gregory A. Maglinte,[2] Erlene K. Seymour,[2] Mazyar Shadman[3]

[1]Atrium Health Levine Cancer Institute, Charlotte, NC, USA; [2]BeOne Medicines Ltd., San Carlos, CA, USA; [3]Fred Hutchinson Cancer Center, Seattle, WA, USA

CONCLUSIONS

- In this retrospective observational real-world study, patients with chronic lymphocytic leukemia (CLL) receiving first-line (1L) Bruton tyrosine kinase (BTK) inhibitor monotherapy with zanubrutinib had significantly prolonged real-world time to next treatment (rwTTNT), real-world time to treatment discontinuation (rwTTD), and real-world overall survival (rwOS) compared with those receiving ibrutinib
- Further analyses should be performed at longer follow-up to confirm and expand findings

INTRODUCTION

- Next-generation BTK inhibitor monotherapy is a preferred 1L treatment option for patients with CLL[1]

Aim

- In the absence of head-to-head trial comparisons, we evaluated real-world clinical outcomes for 1L BTK inhibitor monotherapy in patients with CLL in a large US population

METHODS

Data Source and Study Design

- This retrospective observational study utilized the US nationwide Flatiron Health electronic health record-derived database comprising patient-level de-identified data from approximately 800 academic and community cancer clinics across the US

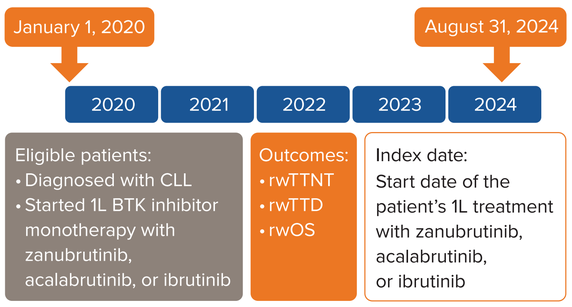
Study Population

- Patients were eligible if they were diagnosed with CLL and started 1L BTK inhibitor monotherapy with zanubrutinib, acalabrutinib, or ibrutinib between January 1, 2020 and August 31, 2024 (**Figure 1**)

Study Outcomes

- Outcomes included:
  - rwTTNT, defined as the time from the index date to the date of next treatment initiation or death, with censoring at last confirmed activity
  - rwTTD, defined as the time from the index date to the date of treatment discontinuation or death, with censoring at last drug episode
  - rwOS, defined as the time from the index date until death, with censoring at last confirmed activity

Figure 1. Study Design



Statistical Analyses

- Kaplan–Meier methods were used to generate time-to-event curves from which medians for rwTTNT, rwTTD, and rwOS, and landmark probabilities for survival and not advancing to the next line of therapy, survival and not discontinuing treatment, and OS were estimated
- Hazard ratios (HRs), 95% confidence intervals (CIs), and *P*-values were estimated using Cox proportional hazard models, adjusted for age, sex, race/ethnicity, practice type, Eastern Cooperative Oncology Group (ECOG) performance status, immunoglobulin heavy-chain variable (IGHV) mutation status, and del17p/*TP53* mutation status

RESULTS

Patients

- A total of 2515 patients with CLL received 1L therapy with zanubrutinib (n=310), acalabrutinib (n=1111), or ibrutinib (n=1094) and were included in this analysis
- The majority of patients were White, male, and came from community oncology settings (**Table**)

Table. Patient Characteristics and Baseline Demographics

	Zanubrutinib (n=310)	Acalabrutinib (n=1111)	Ibrutinib (n=1094)
Median (range) age, years			
At diagnosis	69.0 (33.0-84.0)	69.0 (32.0-84.0)	67.5 (28.0-84.0)
At index date[a]	73.0 (34.0-84.0)	74.0 (34.0-84.0)	72.0 (32.0-84.0)
Median (range) time from diagnosis to index date,[a] months	26.5 (0.0-261.9)	31.9 (0.1-470.1)	34.1 (0.0-480.0)
Sex, n (%)			
Male	199 (64.2)	672 (60.5)	624 (57.0)
Female	111 (35.8)	439 (39.5)	470 (43.0)
Race and ethnicity, n (%)			
White	230 (74.2)	825 (74.3)	773 (70.7)
Black	28 (9.0)	77 (6.9)	105 (9.6)
Asian	<5 (1.6)	10 (0.9)	8 (0.7)
Hispanic or Latino	<5 (1.6)	29 (2.6)	40 (3.7)
Other	12 (3.9)	70 (6.3)	77 (7.0)
Unknown	34 (11.0)	100 (9.0)	91 (8.3)
Practice type, n (%)			
Community	234 (75.5)	846 (76.2)	941 (86.0)
Academic	76 (24.5)	265 (23.9)	153 (14.0)
ECOG performance status, n (%)			
0	125 (40.3)	405 (36.5)	447 (40.9)
1	84 (27.1)	309 (27.8)	291 (26.6)
2-4	29 (9.4)	97 (8.7)	84 (7.7)
Unknown	72 (23.2)	300 (27.0)	272 (24.9)
Rai stage at diagnosis, n (%)			
0	75 (24.2)	327 (29.4)	315 (28.8)
I	50 (16.1)	151 (13.6)	158 (14.4)
II	17 (5.5)	74 (6.7)	68 (6.2)
III	13 (4.2)	47 (4.2)	63 (5.8)
IV	15 (4.8)	68 (6.1)	68 (6.2)
Not documented	140 (45.2)	444 (40.0)	422 (38.6)
Del17p/*TP53* status at diagnosis, n (%)			
Del17p or *TP53*-positive	49 (15.8)	137 (12.3)	119 (10.9)
Del17p and *TP53*-negative	225 (72.6)	836 (75.3)	793 (72.5)
Not tested	36 (11.6)	138 (12.4)	182 (16.6)
IGHV status at diagnosis, n (%)			
Unmutated	65 (21.0)	191 (17.2)	186 (17.0)
Mutated	33 (10.7)	114 (10.3)	88 (8.0)
Results unknown[b]	10 (3.2)	36 (3.2)	27 (2.5)
Not tested	202 (65.2)	770 (69.3)	793 (72.5)
Del11q status at diagnosis, n (%)			
Positive	33 (10.7)	116 (10.4)	116 (10.6)
Negative	168 (54.2)	571 (51.4)	520 (47.5)
Not tested	109 (35.2)	424 (38.2)	458 (41.9)

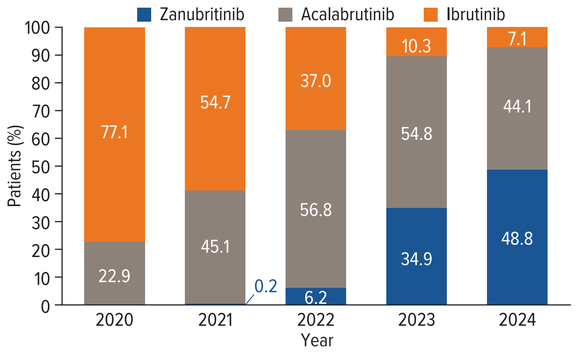
Percentages may not total 100 because of rounding.
[a]The index date is the start date of the patient's 1L treatment with zanubrutinib, acalabrutinib, or ibrutinib.
[b]"Results unknown" was defined as unsuccessful, indeterminate, unknown, or not documented.

- At diagnosis, more patients receiving zanubrutinib had a del17p/*TP53* mutation, compared with those receiving acalabrutinib or ibrutinib (15.8% vs 12.3% and 10.9%, respectively)
- More patients receiving zanubrutinib than acalabrutinib or ibrutinib had unmutated IGHV at diagnosis (21.0%, 17.2%, and 17.0%, respectively)

Treatment Patterns

- The median (range) duration of follow-up from the index date to last confirmed activity was 12.3 (0.0-37.1) months for zanubrutinib, 23.1 (0.2-57.9) months for acalabrutinib, and 33.3 (0.0-57.9) months for ibrutinib
  - 1L use of ibrutinib decreased over time (**Figure 2**)
  - Zanubrutinib was the most commonly used 1L BTK inhibitor monotherapy in 2024

Figure 2. Use of BTK Inhibitor Monotherapy for the 1L Treatment of CLL from 2020 to 2024



Treatment Outcomes

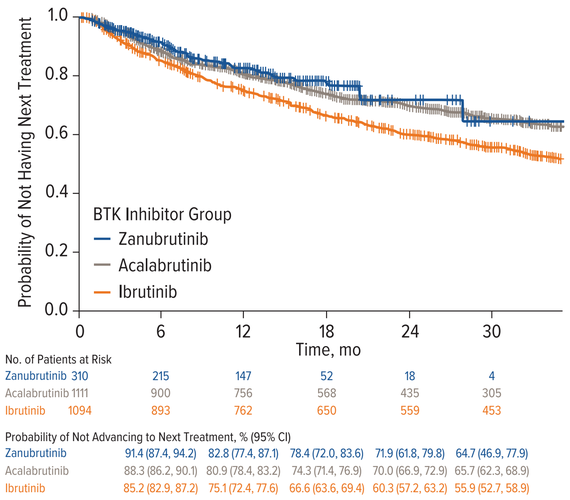
- Median rwTTNT was not reached (NR) for zanubrutinib and acalabrutinib and was 38.2 (95% CI, 33.2, 42.3) months for ibrutinib (**Figure 3A**)
  - Based on Kaplan–Meier estimates, patients receiving zanubrutinib had a numerically higher probability of survival and not advancing to the next line of therapy at 6, 12, and 18 months than those receiving acalabrutinib or ibrutinib
  - Patients receiving zanubrutinib had a statistically significantly lower risk of advancing to the next line of therapy or death than those receiving ibrutinib (adjusted HR, 0.59; 95% CI, 0.44, 0.79; *P*=.0004) and a numerically lower risk than those receiving acalabrutinib (adjusted HR, 0.86; 95% CI, 0.64, 1.16; *P*=.3237)
- Median rwTTD was NR for zanubrutinib versus 43.7 (95% CI, 34.4, NR) months for acalabrutinib and 21.9 (95% CI, 18.3, 25.7) months for ibrutinib (**Figure 3B**)
  - Based on Kaplan–Meier estimates, patients receiving zanubrutinib had a numerically higher probability of survival and not discontinuing treatment at 6, 12, and 18 months than those receiving acalabrutinib or ibrutinib
  - Patients receiving zanubrutinib had a statistically significantly lower risk of treatment discontinuation or death than those receiving ibrutinib (adjusted HR, 0.56; 95% CI, 0.44, 0.72; *P*<.0001) and a numerically lower risk than those receiving acalabrutinib (adjusted HR, 0.89; 95% CI, 0.69, 1.15; *P*=.3827)
- Median rwOS was NR for patients receiving any of the treatments (**Figure 3C**)
  - Based on Kaplan–Meier estimates, patients receiving zanubrutinib had a numerically higher probability of survival at 12 and 18 months than those receiving acalabrutinib or ibrutinib
  - Patients receiving zanubrutinib had statistically significantly improved rwOS compared with those receiving ibrutinib (adjusted HR, 0.46; 95% CI, 0.28, 0.76; *P*=.0024) and numerically improved rwOS compared with those receiving acalabrutinib (adjusted HR, 0.80; 95% CI, 0.49, 1.33; *P*=.3931)

LIMITATIONS

- This study is subject to the inherent limitations of a retrospective observational real-world database study
- The shorter duration of follow-up for zanubrutinib versus ibrutinib and acalabrutinib is also a limitation of this study

Figure 3. Kaplan–Meier Curves of (A) rwTTNT, (B) rwTTD, and (C) rwOS

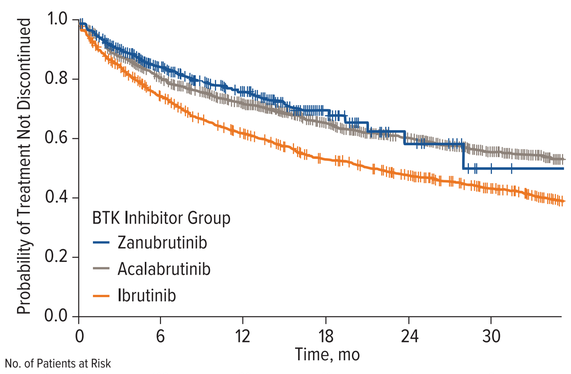
A. rwTTNT



No. of Patients at Risk						
Zanubrutinib	310	215	147	52	18	4
Acalabrutinib	1111	900	756	568	435	305
Ibrutinib	1094	893	762	650	559	453

Probability of Not Advancing to Next Treatment, % (95% CI)					
Zanubrutinib	91.4 (87.4, 94.2)	82.8 (77.4, 87.1)	78.4 (72.0, 83.6)	71.9 (61.8, 79.8)	64.7 (46.9, 77.9)
Acalabrutinib	88.3 (86.2, 90.1)	80.9 (78.4, 83.2)	74.3 (71.4, 76.9)	70.0 (66.9, 72.9)	65.7 (62.3, 68.9)
Ibrutinib	85.2 (82.9, 87.2)	75.1 (72.4, 77.6)	66.6 (63.6, 69.4)	60.3 (57.2, 63.2)	55.9 (52.7, 58.9)

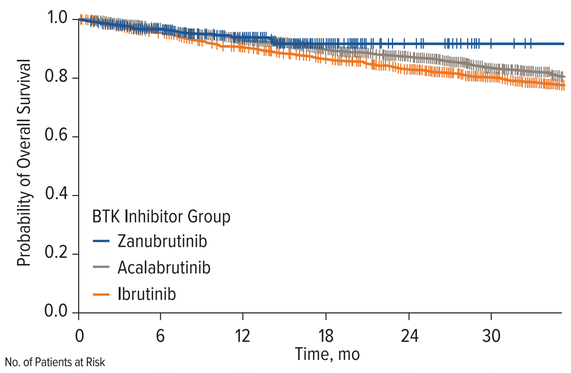
B. rwTTD



No. of Patients at Risk						
Zanubrutinib	310	193	128	40	14	3
Acalabrutinib	1111	814	663	491	375	261
Ibrutinib	1094	776	626	519	442	352

Probability of Not Discontinuing Treatment, % (95% CI)					
Zanubrutinib	84.7 (79.9, 88.5)	76.2 (70.3, 81.2)	69.9 (62.8, 75.9)	58.6 (45.6, 69.6)	50.3 (31.0, 66.8)
Acalabrutinib	80.6 (78.0, 82.8)	72.1 (69.3, 74.8)	65.6 (62.5, 68.5)	60.6 (57.3, 63.7)	54.0 (52.5, 59.4)
Ibrutinib	74.6 (71.9, 77.1)	62.0 (59.0, 64.9)	53.4 (50.3, 56.4)	48.1 (45.0, 51.1)	43.7 (40.6, 46.8)

C. rwOS



No. of Patients at Risk						
Zanubrutinib	310	227	163	61	20	5
Acalabrutinib	1111	987	869	687	539	378
Ibrutinib	1094	999	916	840	757	631

Probability of Overall Survival, % (95% CI)					
Zanubrutinib	96.5 (93.6, 98.1)	94.0 (90.2, 96.4)	91.8 (87.0, 94.9)	91.8 (87.0, 94.9)	91.8 (87.0, 94.9)
Acalabrutinib	97.1 (95.9, 98.0)	93.1 (91.4, 94.5)	89.8 (87.6, 91.5)	87.5 (85.1, 89.5)	83.5 (80.6, 86.0)
Ibrutinib	95.3 (93.9, 96.4)	90.5 (88.5, 92.1)	86.5 (84.3, 88.5)	83.1 (80.7, 85.3)	80.4 (77.8, 82.8)

Mo, month.

REFERENCE

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma V.3.2025. © National Comprehensive Cancer Network, Inc. 2025. All rights reserved. Accessed May 19, 2025. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.

DISCLOSURES

RJ: Research funding: AbbVie, AstraZeneca, BeOne Medicines, Lilly, Pharmacyclics, Regeneron; Consulting fees: AbbVie, AstraZeneca, BeOne Medicines, Galapagos, Genentech, Genmab, SecuraBio; Payment or honoraria for lectures, presentations, speakers bureaus, abstract writing or educational events: AbbVie, Adaptive, AstraZeneca, BeOne Medicines; **XW**, **QF**, **DY**, **DvB**, **GAM**, **EKS**: Employment by BeOne Medicines and may hold stock or other ownership; **MS**: Research funding: AbbVie, AstraZeneca, BeOne Medicines, Genentech, Genmab, Morphosys/Incyte, Mustang Bio, Vincerx; Consulting or advisory role: AbbVie, AstraZeneca, BeOne Medicines, Bristol Myers Squibb, Eli Lilly, Fate Therapeutics, Genentech, Genmab, Janssen, Kite Pharma, Merck, Morphosys/Incyte, Nurix; Stock or other ownership: Koi Biotherapeutics; Employment: Bristol Myers Squibb.

ACKNOWLEDGMENTS

The authors thank the patients and their families, investigators, co-investigators, and the study teams at each of the participating centers. This study was sponsored by BeOne Medicines Ltd. Medical writing support and editorial assistance was provided by Gillian Keating, MBChB, of AMICULUM, and supported by BeOne Medicines Ltd.

CORRESPONDENCE: Ryan Jacobs, Ryan.Jacobs@atriumhealth.org

Presented at 18th ICML, 2025; June 17-21; Lugano, Switzerland
Data originally presented at the EHA 2025 Congress; June 12-15; Milan, Italy