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ORIGINAL RESEARCH

Real-World Outcomes Among Medicare Beneficiaries Treated with Bruton Tyrosine Kinase Inhibitors for Treatment-Naïve CLL

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ABSTRACT

***Introduction*:** There is a dearth of head-to-head studies comparing covalent Bruton tyrosine kinase (cBTK) inhibitors in adults with chronic lymphocytic leukemia (CLL). Real-world evidence may complement clinical trial data by assessing relative effectiveness in routine practice. This retrospective observational study used a de-identified Medicare Fee-For-Service database to compare real-world outcomes associated with first-line cBTKi monotherapies in older adults with CLL.

***Methods*:** Patients aged ≥ 65 years with CLL initiating first-line ibrutinib, acalabrutinib, or zanubrutinib monotherapy between January 1, 2020 and September 30, 2025 were included. Real-world time to treatment discontinuation (rwTTD), time to next treatment (rwTTNT), and overall survival (rwOS) were evaluated using Kaplan–Meier analyses and Cox proportional hazards models. Subgroup analyses were performed by age group.

***Results*:** Among 10,523 patients included, 3006 (28.6%) received zanubrutinib (median follow-up 15.8 months), 4309 (40.9%) received acalabrutinib (20.7 months), and 3208 (30.5%) received ibrutinib (34.9 months). Median rwTTD was not reached (NR) for zanubrutinib, compared with 24 months for acalabrutinib and 14 months for ibrutinib. Median rwTTNT was NR for zanubrutinib, 40 months for acalabrutinib, and 20 months for ibrutinib. After adjustments for age, sex, race, CCI, and year of index, zanubrutinib had significantly longer rwTTD (hazard ratio [HR] 0.57 [95% CI 0.51–0.61]), rwTTNT (HR 0.63 [0.55–0.71]), and rwOS (HR 0.64 [0.54–0.77]) compared to ibrutinib. Zanubrutinib also had significantly improved rwTTD (HR 0.86 [0.78–0.94]), rwTTNT (HR 0.87 [0.78–0.96]), and rwOS (HR 0.77 [0.66–0.88])

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compared to acalabrutinib. Similar patterns were observed when stratified by age group over 65.
Conclusions: These findings demonstrate that zanubrutinib is associated with improved real-world outcomes compared with other cBTK inhibitors.

Keywords: Chronic lymphocytic leukemia; BTK inhibitor; Acalabrutinib; Ibrutinib; Zanubrutinib; Real-world outcomes

Key Summary Points
Why carry out this study?
Acalabrutinib and zanubrutinib are NCCN-guideline preferred regimens for the treatment of chronic lymphocytic leukemia (CLL) in the USA; however, data on the real-world effectiveness of acalabrutinib versus zanubrutinib remains limited.
In real-world first-line treatment of CLL among patients aged ≥ 65 years, we hypothesized that zanubrutinib is associated with longer treatment duration and improved clinical outcomes compared with acalabrutinib, and patterns persist despite age group.
What was learned from the study?
In this large real-world observational study, zanubrutinib had significantly longer real-world time to discontinuation, real-world time to next treatment, and real-world overall survival versus ibrutinib or acalabrutinib among patients aged 65 or older in first-line CLL.
Similar patterns in treatment and survival outcomes were observed when stratified by age group (65–74, 75–84, and ≥ 85 years).
These real-world findings provide valuable insights into the treatment duration of zanubrutinib versus acalabrutinib or ibrutinib in a large, observational study with long-term follow-up, helping to inform frontline BTK inhibitor treatment decisions in clinical practice.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) is the most common type of leukemia or lymphoma among adults in the USA, accounting for approximately 25–35% of all new leukemia or lymphoma diagnoses [1]. CLL primarily affects older adults, with a median age at diagnosis of about 70 years [2, 3]. In 2014, the first-generation covalent Bruton tyrosine kinase (cBTK) inhibitor, ibrutinib, received US Food and Drug Administration (FDA) approval for the treatment of CLL [4]. Although ibrutinib remains an effective therapeutic for CLL, its role in recent treatment guidelines has diminished because of off-target toxicities including cardiotoxicity, atrial fibrillation/flutter, hypertension, and bleeding risks, which contribute to high discontinuation rates, reported as high as 30% in 3.5 years [5–10].

Over the past decade, the CLL treatment landscape has evolved significantly with the introduction of more selective cBTK inhibitors that demonstrate superior efficacy and improved tolerability compared with chemoimmunotherapy (CIT) regimens. As a result, real-world clinical practice has increasingly positioned second-generation cBTK inhibitors, acalabrutinib and zanubrutinib, as preferred regimens for first-line (1L) and subsequent therapy for the treatment of symptomatic CLL/SLL according to the National Comprehensive Cancer Network® (NCCN®; Version 1.2026). Acalabrutinib was granted approval by the US FDA in 2019 for adults with CLL after demonstrating clinical benefit comparable to CITs [11, 12]. In ELEVATE-RR, acalabrutinib was found to have similar efficacy to ibrutinib but was associated with fewer side effects [13]. Zanubrutinib was granted US FDA approval in 2023, supported by pivotal clinical trials demonstrating improved progression-free survival (PFS) and overall response rates (ORR) compared with ibrutinib and CIT in relapsed or refractory (R/R) and treatment-naïve (TN) CLL [14, 15]. Mechanistically, zanubrutinib provides greater BTK selectivity and occupancy than ibrutinib or acalabrutinib [16, 17]. In the SEQUOIA trial, differences in treatment response did not differ by sex or ECOG performance status [18].

In addition, an unanchored matching-adjusted indirect comparison using individual patient-level data from ALPINE, the pivotal zanubrutinib trial, and aggregate data from ASCEND, the pivotal acalabrutinib study, demonstrated that zanubrutinib significantly reduced the risk of progression or death in R/R CLL relative to acalabrutinib [19].

Although clinical trials have shown superior benefits of zanubrutinib compared with ibrutinib, and non-inferiority of acalabrutinib compared with ibrutinib in R/R CLL, there are no head-to-head comparative trials between cBTK inhibitors in TN CLL [13, 20]. Real-world evidence can be used to assess comparative effectiveness of cBTK inhibitors in 1L CLL and understand how these therapies perform in routine practice. Previous real-world studies are often limited by short follow-up periods, small sample sizes, or derivation from a single institution practice. Therefore, this study utilized Medicare, the largest payer for patients aged 65 years and older in the USA, to examine real-world treatment characteristics and outcomes in a large, nationally representative CLL population.

METHODS

Data Source and Study Design

This retrospective observational cohort study used the 100% de-identified Medicare FFS database. Medicare is a federal health insurance program for those aged 65 and older, certain people under 65 with disabilities, and people of any age with end-stage renal disease. Medicare covers about 96% of all US citizens aged 65 and older [21]. Medicare Fee-For-Service Data, which composes about half of the total enrolled Medicare beneficiaries, include claims for inpatient, skilled care nursing facility, and hospice care (Part A) as well as outpatient care (Part B) and prescription drugs (Part D) [22]. Eligible patients were identified as patients aged ≥ 65 years with CLL who initiated cBTK inhibitor monotherapy at 1L. The index was defined as the start date of the treatment initiation with 1L cBTK inhibitor monotherapy. The baseline period was defined as the 12-month period prior to the index date, unless otherwise specified. The follow-up period was defined as the time from the index date to the end of record (date of death, end of enrollment, or data cutoff). Data cutoff was December 31, 2025.

Study Population

Eligible patients had ≥ 2 Medicare Part A, B, or C medical claims with diagnostic codes (International Classification of Disease, 10th Revision [ICD-10]) for CLL as a primary diagnosis on separate dates ≥ 14 days apart on or after 2010; received 1L zanubrutinib, acalabrutinib, or ibrutinib between January 1, 2020 and September 30, 2025; and had continuous enrollment in Medicare Part A, B, and D during the baseline period. Patients were excluded if they received any other CLL treatment before index, including combination or concurrent therapy with other agents, or had clinical trial participation during the study period (Fig. 1).

Patients were classified as receiving 1L cBTK inhibitor monotherapy if no additional therapy was initiated within 90 days of the index date. Any additional CLL regimens received more than 90 days from the index date are considered second-line (2L) treatment, with the exception of re-initiation of the same cBTK inhibitor, which is classified as 1L treatment if it occurs within 180 days after the end of the prior cBTK inhibitor supply does not advance to 2L.

Study Outcomes and Covariates

Baseline demographic and clinical characteristics included age at the index date (continuous and categorical), race/ethnicity, sex, region, socioeconomic status (dual Medicare and Medicaid eligibility, low income subsidy), rural–urban community area (RUCA; urban, rural; defined by the US Census Bureau based on geographical zones), year of index date, time from initial diagnosis to index date, Charlson Comorbidity Index (CCI, excluding any B cell malignancies: 0, 1–2, 3–4, ≥ 5), and other comorbidities of interest. Baseline demographic and clinical characteristics were summarized descriptively.

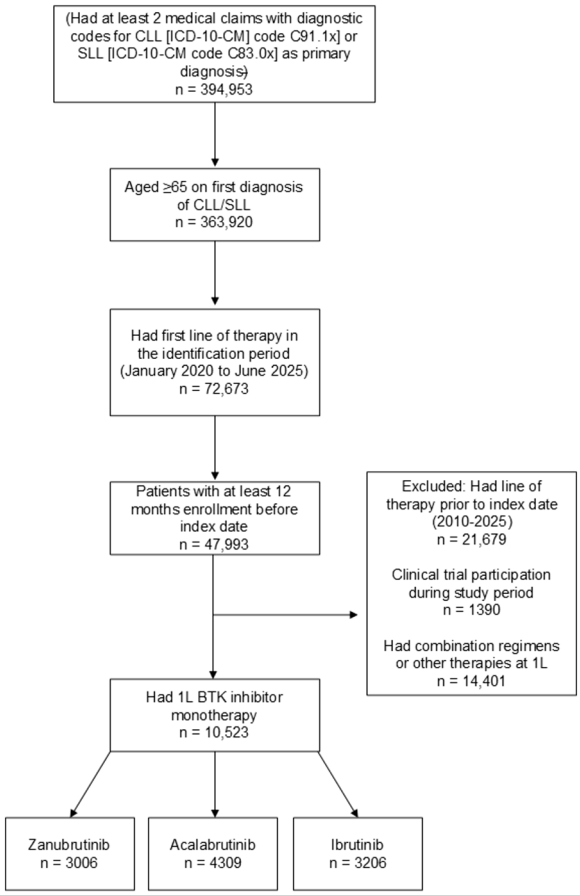

Fig. 1 Flowchart of inclusion and exclusion for patient cohort. *CLL* chronic lymphocytic leukemia, *SLL* small lymphocytic lymphoma, *BTK* Bruton tyrosine kinase

Sex was defined based on beneficiary's biological sex at birth, sourced from the CMS enrollment database. "Other" racial category is used by the Social Security Administration's Master Beneficiary Record to identify individuals of races other than White, Black, Asian/Pacific Islander, or American Indian/Alaska Native and when an individual does not fall into these specific, mutually exclusive categories.

Real-world time to treatment discontinuation (rwTTD) was defined as the time from index date to the earliest treatment discontinuation (i.e., last prescription fill date and supply), death, or censored at the last confirmed activity (end of enrollment or end of study). Discontinuation was defined as having a subsequent systemic therapy after the current line of therapy (LOT), having a gap of >180 days with no systemic therapy after the last drug episode of the current LOT, or having a date of death. A gap of >180 days was selected to help distinguish temporary treatment interruptions (e.g., due to surgery, travel, or other non-disease-related reasons) from true treatment discontinuation followed by re-initiation upon disease progression. Given the treatments of interest were oral therapies and this was an older patient population, this threshold was intentionally chosen to be conservative, with 180 days representing a relatively liberal interval to minimize the risk of misclassifying short-term treatment holds as discontinuation. Patients were censored at the end of the current LOT if they did not have treatment discontinuation. Real-world time to next treatment (rwTTNT) was defined as the time from index date to the earliest of either the start of the next LOT, death, or censoring at the last confirmed activity. Real-world overall survival (rwOS) was defined as the time from the index date to the date of death or censoring on the last confirmed activity.

Statistical Analysis

Descriptive statistics were used to summarize baseline and clinical characteristics including median, range, and interquartile range (IQR) for continuous variables, and relative frequency and percentage for categorical variables. Patient characteristics were reported for the overall 1L cBTK inhibitor population and by each index therapy.

The Kaplan–Meier method was used to generate survival curves for rwTTD, rwTTNT, and rwOS. Median time to event and survival and treatment probabilities with corresponding 95% CIs were calculated at 12 and 24 months after the index date by treatment group. Kaplan–Meier curves were truncated when patient counts were ≤10. Unadjusted and multivariate Cox proportional hazard models were used to estimate HRs and corresponding 95% CIs for treatment comparisons (zanubrutinib versus ibrutinib or acalabrutinib). Adjusted covariates included categorical age (65–74, 75–84, and ≥85), sex, race/ethnicity (non-Hispanic White versus other), CCI score (0, 1–2,

3–4, ≥5), and year of index. Stratified analyses were also performed by categorical age group. A *P* value less than 0.05 was the cutoff for statistical significance.

Ethical Approval

No institutional review board/independent ethics committee review was required for this secondary analysis of de-identified existing data. All work performed by ADVI Health was subject to their respective requirements for access. The data used in this study are derived from Medicare claims files maintained by the Centers for Medicare & Medicaid Services (CMS). ADVI Health has a Data Use Agreement (DUA) agreement and access to these claims through a CMS Virtual Research Data Center (VRDC) license. Data are not publicly available because of federal restrictions protecting beneficiary privacy. Qualified researchers interested in accessing these data must apply directly to CMS through the Research Data Assistance Center (ResDAC).

All data presented are aggregated in accordance with CMS privacy standards. All source data were de-identified by CMS. Individual patient consent was not required, as the data were anonymized and reported in aggregated.

RESULTS

Patient Characteristics

A total of 10,523 patients with CLL who received 1L cBTK inhibitor monotherapy were included; 3006 (28.6%) received zanubrutinib, 4309 (40.9%) received acalabrutinib, and 3208 (30.5%) patients received ibrutinib. Baseline demographics and clinical characteristics are summarized in Table 1. Overall, 58.3% of patients were male, and most were non-Hispanic White (89.5%), followed by Black (3.2%) and Hispanic (2.3%). The median age at index date was 77 years (IQR 72, 82). Most patients resided in urban areas (78.0%), and 34.9% of patients lived in the Southern regions and 22.0% of patients lived in the Northeastern regions of the USA. Demographics were broadly similar. However, patients treated with ibrutinib were younger (median age 76 versus 77 and 77 for zanubrutinib and acalabrutinib, respectively; $P<0.001$) and more likely to have dual eligibility status (11.1% ibrutinib versus 8.9% acalabrutinib versus 7.2% zanubrutinib).

Patients had a median CCI score of 4.0, with 38.8% of patients having a CCI score ≥5. Patients treated with zanubrutinib had numerically higher comorbidity burden (CCI≥5: 41.1% versus 38.0% other cBTK inhibitors). In contrast, patients treated with ibrutinib had lower median CCI scores (3.0 versus 4.0 other cBTK inhibitors). Among other comorbidities of interest, the most common at baseline were hypertension (64.7%), diabetes (27.2%), coronary artery disease (24.3%), and atrial fibrillation (15.5%). Baseline atrial fibrillation was less prevalent among patients with ibrutinib (11.6% versus 17.2% for acalabrutinib versus 17.1% for zanubrutinib).

The median time from diagnosis to index date was 30.2 months (range 0.0, 69.4). Overall median follow-up was 20.5 months (IQR 9.4, 38.8). The median follow-up for patients treated with zanubrutinib, acalabrutinib, and ibrutinib was 15.8 (IQR 8.7, 23.3), 20.7 (IQR 8.5, 40.5), and 34.9 (IQR 14.3, 53.1) months, respectively. At the end of the data cutoff (December 31, 2025), 7451 (70.8%) of all patients remained on treatment; 2589 (86.1%) receiving zanubrutinib, 3068 (71.2%) receiving acalabrutinib, and 1794 (55.9%) receiving ibrutinib.

Real-World Time to Discontinuation and Next Treatment

The median rwTTD was not reached (NR) for zanubrutinib, 24 months (95% CI 22–25) for acalabrutinib, and 14 months (95% CI 13–15) for ibrutinib (Fig. 2). Zanubrutinib-treated patients had a higher probability of remaining on treatment at 12 months (72.3% [95% CI 70.5–73.9]) and at 24 months (63.2% [95% CI 61.0–65.4]), followed by those treated with acalabrutinib (62.6% [95% CI 61.0–64.1] and 48.9% [95% CI 47.1–50.6]) and ibrutinib (52.9% [95% CI 51.1–4.7] and 35.1% [95% CI 33.4–36.9]) (Table 2). Similarly, in both unadjusted and adjusted analyses, patients treated

Table 1 Baseline demographic and clinical characteristics

Characteristics	Regimen at first LOT			Total ($N = 10,523$)
	Acalabrutinib ($n = 4309$, 40.9%)	Ibrutinib ($n = 3208$, 30.5%)	Zanubrutinib ($n = 3006$, 28.6%)	
Median age (IQR) at index date	77 (72, 83)	76 (71, 82)	77 (72, 82)	77 (72, 82)
Age group (years), *n* (%)				
65–69	606 (14.1)	518 (16.1)	451 (15.0)	1575 (15.0)
70–74	1005 (23.3)	831 (25.9)	702 (23.4)	2538 (24.1)
75–79	992 (23.0)	792 (24.7)	706 (23.5)	2490 (23.7)
80–84	880 (20.4)	568 (17.7)	629 (20.9)	2077 (19.7)
≥ 85	826 (19.2)	499 (15.6)	518 (17.2)	1843 (17.5)
Sex, *n* (%)				
Female	1771 (41.1)	1379 (43.0)	1240 (41.3)	4390 (41.7)
Male	2358 (58.9)	1829 (57.0)	1766 (58.7)	6133 (58.3)
Race (RTI race code), *n* (%)				
Non-Hispanic White	3847 (89.3)	2863 (89.3)	2691 (89.5)	9401 (89.5)
Hispanic	90 (2.1)	72 (2.2)	68 (2.3)	230 (2.3)
Black	166 (3.8)	148 (4.6)	96 (3.2)	410 (3.2)
Asian/Pacific Islander	51 (1.2)	36 (1.1)	39 (1.3)	126 (1.2)
Other	27 (0.6)	18 (0.6)	20 (0.7)	65 (0.7)
Unknown	128 (3.0)	71 (2.2)	92 (3.0)	291 (2.8)
Geographical location, *n* (%)				
Northeast	1032 (23.9)	599 (18.7)	687 (22.9)	2318 (22.0)
South	1464 (34.0)	1200 (37.4)	1008 (33.5)	3672 (34.9)
West	841 (19.5)	635 (19.8)	608 (20.2)	2084 (19.8)
Midwest/Unknown	972 (22.6)	774 (24.1)	703 (23.4)	2449 (23.3)
Socioeconomic status, *n* (%)				
Dual eligibility	384 (8.9)	357 (11.1)	216 (7.2)	957 (9.1)
Low income subsidy	436 (10.1)	413 (12.9)	249 (8.3)	1098 (10.4)
Rural–urban community area, *n* (%)				
Urban	3425 (79.5)	2392 (74.6)	2386 (79.4)	8203 (78.0)
Rural	884 (20.5)	816 (25.4)	620 (20.6)	2320 (22.0)
Median CCI	4.0	3.0	4.0	4.0

Table 1 continued

Characteristics	Regimen at first LOT			Total (N = 10,523)
	Acalabrutinib (n = 4309, 40.9%)	Ibrutinib (n = 3208, 30.5%)	Zanubrutinib (n = 3006, 28.6%)	
CCI score, *n* (%)				
None (0)	416 (9.7)	322 (10.0)	277 (9.2)	1015 (9.6)
Mild (1–2)	1050 (24.4)	810 (25.2)	680 (22.6)	2540 (24.1)
Moderate (3–4)	1203 (27.9)	865 (27.0)	813 (27.1)	2881 (27.4)
Severe (≥ 5)	1640 (38.0)	1211 (37.8)	1236 (41.1)	4087 (38.8)
Comorbidities of interest, *n* (%)				
Atrial fibrillation	743 (17.2)	371 (11.6)	514 (17.1)	1628 (15.5)
Arrhythmia	343 (8.0)	182 (5.7)	250 (8.3)	775 (7.4)
Cerebrovascular disease	56 (1.3)	37 (1.1)	41 (1.4)	134 (1.3)
Hypertension	2758 (64.0)	2106 (65.6)	1943 (64.6)	6807 (64.7)
Coronary artery disease (including MI)	1098 (25.5)	690 (21.5)	770 (25.6)	2558 (24.3)
Diabetes	1155 (26.8)	905 (28.2)	808 (26.9)	2868 (27.2)
Neutropenia	100 (2.3)	59 (1.8)	83 (2.8)	242 (2.3)
Headache	18 (0.4)	11 (0.3)	18 (0.6)	47 (0.4)
Migraine	51 (1.2)	38 (1.2)	50 (1.7)	139 (1.3)
Hepatic disease	181 (4.2)	112 (3.5)	164 (5.5)	457 (4.3)
GI bleeding	85 (2.0)	70 (2.2)	69 (2.3)	224 (2.1)
Time (months) from initial diagnosis to first LOT				
Median (range)	33 (0.0, 186.0)	28.9 (0.0, 179.5)	27.6 (0.0, 184.7)	30.2 (0.0, 186.0)
Median follow-up time, months (range)	20.7 (0.0, 69.2)	34.9 (0.0, 69.4)	15.8 (0.1, 61.2)	20.5 (0.0, 69.4)
Year of index events, *n* (%)‡				
2020	>460 (>10.0)	1282 (40.0)	<11 (< 1.0)	1748 (16.6)
2021	>885 (>20.0)	876 (27.3)	>35 (<2.0)	1801 (17.1)
2022	875 (20.3)	549 (17.1)	183 (6.1)	1607 (15.3)
2023	580 (13.5)	196 (6.1)	806 (26.8)	1582 (15.0)
2024	779 (18.1)	202 (6.3)	1393 (46.3)	2374 (22.6)
2025 (through September 2025)	723 (16.8)	103 (3.2)	585 (19.5)	1411 (13.4)

CCI Charlson Comorbidity Index, *GI* gastrointestinal, *LOT* line of therapy, *MI* myocardial infarction, *RTI* Research Triangle Institute

‡Cells are blinded due to data use agreement with CMS

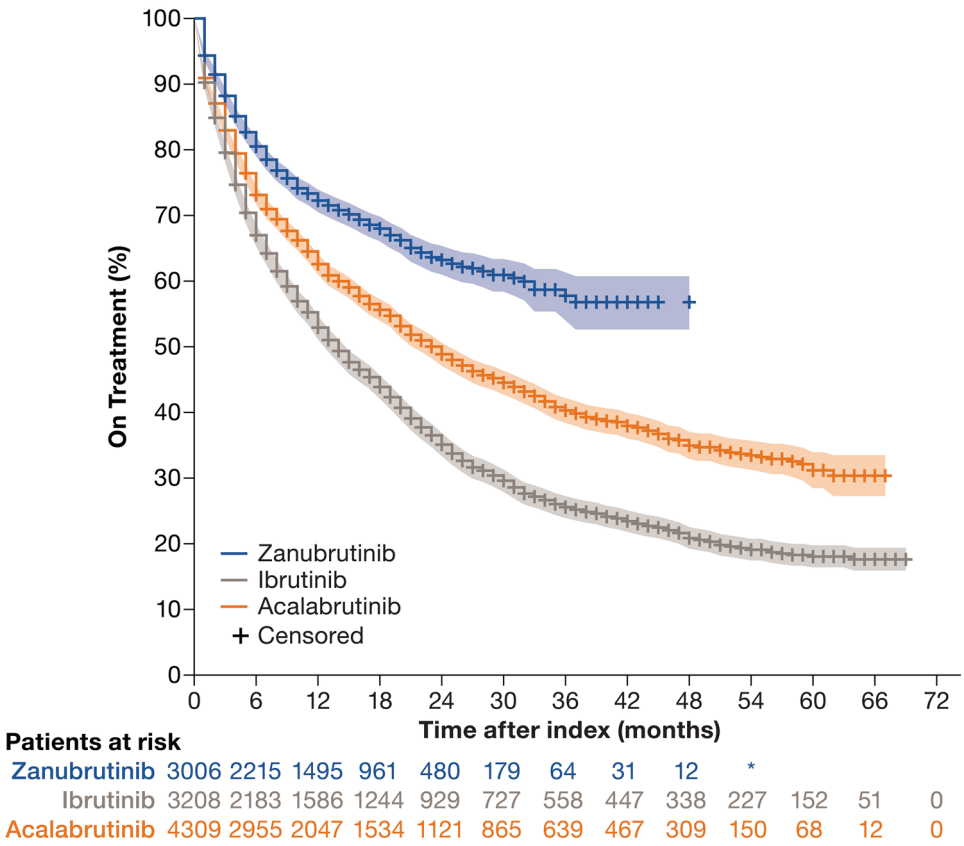

Fig. 2 Real-world time to discontinuation by cBTK inhibitor

Table 2 Real-world time to discontinuation analysis of ibrutinib or acalabrutinib as reference versus zanubrutinib using Cox proportional hazards regression

Outcome	Zanubrutinib	Ibrutinib[†]	Acalabrutinib[†]
12-month rwTTD, % (95% CI)	72.3 (70.5, 73.9)	52.9 (51.1, 54.7)	62.6 (61.0, 64.1)
24-month rwTTD, % (95% CI)	63.2 (61.0, 65.4)	35.1 (33.4, 36.9)	48.9 (47.1, 50.6)
Unadjusted HR (95% CI)	–	0.48 (0.44, 0.51)	0.66 (0.61, 0.72)
P value (unadjusted)	–	< .0001	< .0001
Adjusted HR (95% CI)[‡]	–	0.57 (0.51, 0.64)	0.86 (0.78, 0.94)
P value (adjusted)	–	< .0001	.0007

aHR adjusted hazard ratio, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *HR* hazard ratio, *rwTTD* real-world time to discontinuation

[†]Denotes reference group versus zanubrutinib

[‡]Adjusted covariates included age (65–74, 75–84, and ≥ 85), sex, race/ethnicity (non-Hispanic White versus other), CCI score (0, 1–2, 3–4, ≥ 5), and year of index

with zanubrutinib had significantly longer rwTTD, compared to those treated with acalabrutinib (unadjusted HR [uHR] 0.66 [95% CI 0.61–0.72], $P<0.0001$; adjusted HR [aHR] 0.86 [95% CI 0.78–0.94], $P=0.0007$) or ibrutinib (uHR 0.48 [95% CI 0.44–0.51], $P<0.0001$; aHR 0.57 [95% CI 0.51–0.64], $P<0.0001$).

The median rwTTNT was NR (95% CI 45–NR) in patients treated with zanubrutinib (Fig. 3). For patients treated with acalabrutinib and ibrutinib, the median rwTTNT was 40 months (95% CI 38–42) and 30 months (95% CI 29–32), respectively. At 12 and 24 months, the probability of not advancing to the next treatment or death was higher for patients treated with zanubrutinib (82.3% [95% CI 80.8–83.7] and 71.3% [95% CI 69.1–73.4]), followed by those treated with acalabrutinib (78.4% [95% CI 77.0–79.6] and 66.7% [95% CI 65.1–68.3]), and those treated with ibrutinib (73.8% [95% CI 72.2–75.3] and 56.4% [95% CI 54.6–58.1]) (Table 3). In both unadjusted and adjusted analyses, patients treated with zanubrutinib had significantly longer rwTTNT compared with patients treated with acalabrutinib (uHR 0.80 [95% CI 0.73–0.88], $P<0.0001$; aHR 0.87 [95% CI 0.78–0.96], $P=0.008$) or ibrutinib (uHR 0.61 [95% CI 0.56–0.67], $P<0.0001$; aHR 0.62 [95% CI 0.55–0.71], $P<0.0001$).

Upon stratification by age group, similar patterns in treatment discontinuation and transition to next therapy were observed between treatment groups (Supplementary Figs. 1–2, Supplementary Tables 1–2). In both unadjusted and adjusted analyses, patients treated with zanubrutinib had statistically significantly longer rwTTD and rwTTNT, compared with patients treated with ibrutinib across all age groups. Patients treated with zanubrutinib had statistically significantly longer rwTTD and rwTTNT than those treated with acalabrutinib in the 65–74- and 75–84-year age groups.

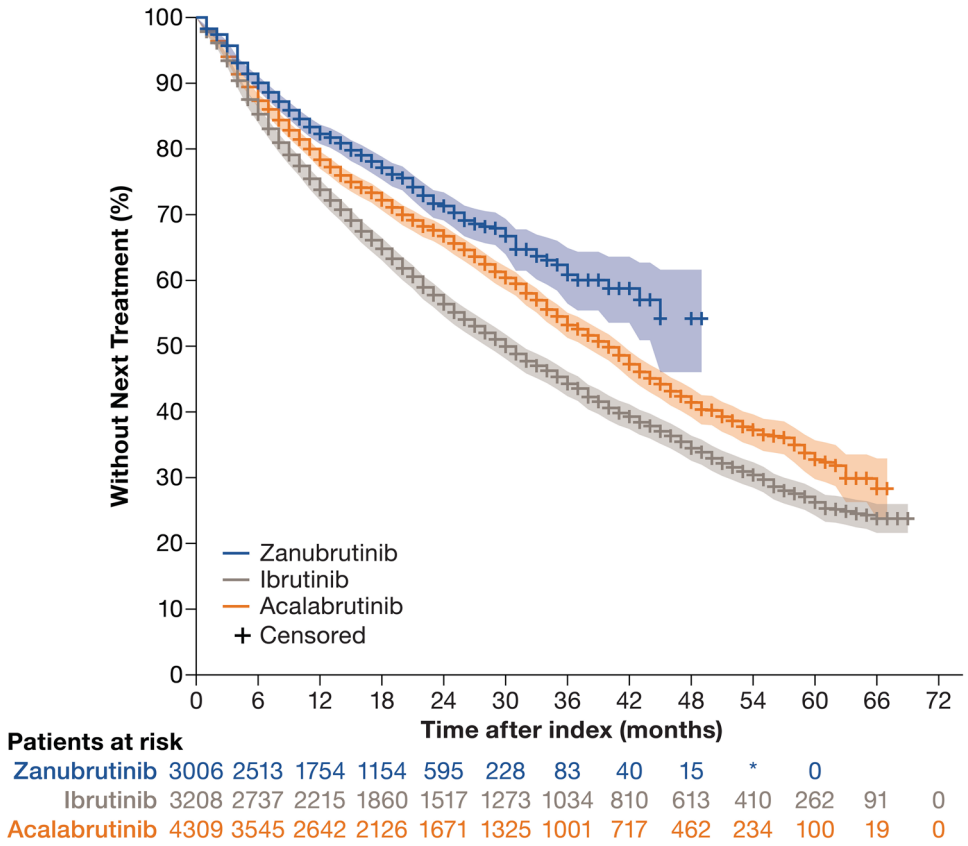

Fig. 3 Real-world time to next treatment by cBTK inhibitor

Table 3 Real-world time to next treatment analysis of ibrutinib or acalabrutinib as reference versus zanubrutinib using Cox proportional hazards regression

Outcome	Zanubrutinib	Ibrutinib[†]	Acalabrutinib[†]
12-month rwTTNT, % (95% CI)	82.3 (80.8, 83.7)	73.8 (72.2, 75.3)	78.4 (77.0, 79.6)
24-month rwTTNT, % (95% CI)	71.3 (69.1, 73.4)	56.4 (54.6, 58.1)	66.7 (65.1, 68.3)
Unadjusted HR (95% CI)	–	0.61 (0.56, 0.67)	0.80 (0.73, 0.88)
P value (unadjusted)	–	< .0001	< .0001
Adjusted HR (95% CI)[‡]	–	0.63 (0.55, 0.71)	0.87 (0.78, 0.96)
P value (adjusted)	–	< .0001	.008

aHR adjusted hazard ratio, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *HR* hazard ratio, *rwTTNT* real-world time to next treatment

[†]Denotes reference group versus zanubrutinib

[‡]Adjusted covariates included age (65–74, 75–84, and ≥ 85), sex, race/ethnicity (non-Hispanic White versus other), CCI score (0, 1–2, 3–4, ≥ 5), and year of index

Real-World Overall Survival

The median rwOS was NR for any group (Fig. 4). At 12 and 24 months, zanubrutinib-treated patients had higher probability of survival (90.8% [95% CI 89.7–91.9] and 85.9% [95% CI 84.2–87.4]) compared with those treated with acalabrutinib (86.9% [95% CI 85.8–87.9] and 79.7% [95% CI 78.3–81.0]) and ibrutinib (84.8% [95% CI 83.5–86.0] and 75.4% [95% CI 73.8–76.9]) (Table 4). In the unadjusted model, zanubrutinib was associated with 33% and 45% lower risk of death compared with acalabrutinib (uHR 0.67; 95% CI 0.59–0.76; $P < 0.0001$) and ibrutinib (uHR 0.55; 95% CI 0.49–0.63; $P < 0.0001$), respectively. After adjusting for age, sex, race/ethnicity, CCI score, and year of index, zanubrutinib was associated with significantly longer OS compared with acalabrutinib (aHR 0.76; 95% CI 0.66–0.88; $P = 0.0002$) and ibrutinib (aHR 0.64; 95% CI 0.54–0.77; $P < 0.0001$).

Trends in rwOS between cBTK inhibitors had similar patterns when stratified by age group (Supplementary Fig. 3). Patients treated with zanubrutinib had 33–44% lower risk of death, compared with patients treated with ibrutinib across age groups, after adjustment. Patients treated with zanubrutinib also had 45% and 27% lower risk of death than those treated with acalabrutinib in age groups 65–74 (aHR 0.55, 95% CI 0.38–0.81, $P = 0.002$) and 75–84 (aHR 0.73, 95% CI 0.59–0.91, $P = 0.005$), but not in age group ≥ 85 (aHR 0.91, 95% CI 0.73–1.12; $P = 0.35$) (Supplementary Table 3).

DISCUSSION

Continuous cBTK inhibitor therapies have been a standard of care for 1L CLL in the USA (NCCN guideline, Version 3.2025; updated April 2025) and are the most commonly used 1L treatment among patients aged ≥ 65 years [23, 24]. Randomized clinical trials have demonstrated superior clinical benefit with zanubrutinib compared with ibrutinib in patients with R/R CLL, while acalabrutinib has shown noninferior clinical benefit compared with ibrutinib [13, 15, 20]. However, no head-to-head randomized clinical trials have compared cBTK inhibitors in 1L CLL, highlighting the utility for real-world evidence

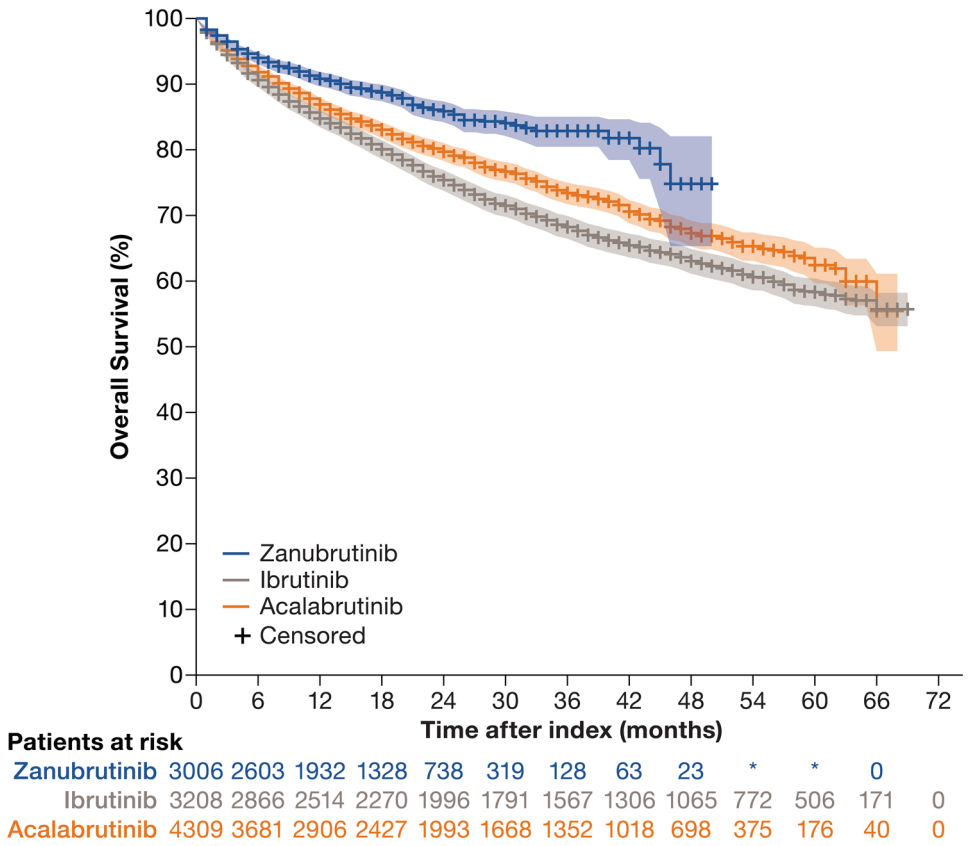

Fig. 4 Real-world overall survival by cBTK Inhibitor

Table 4 Real-world overall survival analysis of ibrutinib or acalabrutinib as reference versus zanubrutinib using Cox proportional hazards regression

Outcome	Zanubrutinib	Ibrutinib[†]	Acalabrutinib[†]
12-month rwOS, % (95% CI)	90.8 (89.7, 91.9)	84.8 (83.5, 86.0)	86.9 (85.8, 87.9)
24-month rwOS, % (95% CI)	85.9 (84.2, 87.4)	75.4 (73.8, 76.9)	79.7 (78.3, 81.0)
Unadjusted HR (95% CI)	–	0.55 (0.49, 0.62)	0.67 (0.59, 0.76)
P value (unadjusted)	–	< .0001	< .0001
Adjusted HR (95% CI) [‡]	–	0.64 (0.54, 0.77)	0.76 (0.66, 0.88)
P value (adjusted)	–	< .0001	.0002

aHR adjusted hazard ratio, *CCI* Charlson Comorbidity Index, *CI* confidence interval, *HR* hazard ratio, *rwOS* real world overall survival

[†]Denotes reference group versus zanubrutinib

[‡]Adjusted covariates included age (65–74, 75–84, and ≥ 85), sex, race/ethnicity (non-Hispanic White versus other), CCI score (0, 1–2, 3–4, ≥ 5), and year of index

to assess their comparative effectiveness. To our knowledge, this study represents the largest real-world comparison of 1L cBTK inhibitor monotherapy among patients aged ≥ 65 years with CLL in the USA. The findings demonstrate that patients treated with zanubrutinib had a higher probability of survival and lower discontinuation rates compared with those treated with acalabrutinib or ibrutinib. Additionally, zanubrutinib-treated patients remained on 1L therapy longer, with consistent treatment patterns observed across age groups.

Our findings are also consistent with the ALPINE trial in R/R CLL and previous real-world evidence in patients with CLL undergoing 1L treatment [19, 25, 26]. For example, in a large cohort study using an open claims database, patients treated with zanubrutinib had a longer median TTD and the lowest overall discontinuation rate compared with those treated with acalabrutinib or ibrutinib, including among patients aged 65 years and older [25]. Another real-world study based on electronic health records (EHR) from the US Flatiron database suggested that patients treated with zanubrutinib had significantly lower risk of rwTTD and rwTTNT compared to patients treated with ibrutinib [26]. In addition, the study suggested a trend in improved outcomes among patients treated with zanubrutinib compared with those treated with acalabrutinib [26]. A matched analysis using EHR data suggested patients treated with zanubrutinib had significantly lower risks of rwTTD and rwTTNT compared with patients treated with ibrutinib [27]. Similarly, a retrospective study of 505 patients with CLL/SLL treated at an academic health system demonstrated that zanubrutinib was associated with a significantly longer TTD than acalabrutinib (median 30.1 versus 14.0 months; HR 0.41; 95% CI 0.34–0.51), as well as higher probability of staying on treatment at 12 months (74% of zanubrutinib-treated patients versus 55% of acalabrutinib-treated patients) [28].

Although reasons for discontinuation were not captured in this study, evidence from clinical trials and real-world studies suggests that discontinuation due to toxicity may be more common among patients treated with acalabrutinib or ibrutinib. A head-to-head comparative study between ibrutinib and zanubrutinib demonstrated that zanubrutinib was associated with fewer adverse events leading to discontinuation compared with ibrutinib (15% versus 22%) and fewer cardiac adverse events [20]. Real-world evidence supports that both zanubrutinib and acalabrutinib had lower discontinuation rates than ibrutinib. A retrospective study comparing ibrutinib with zanubrutinib found that zanubrutinib was associated with lower overall discontinuation rates, including discontinuation due to adverse events [29]. Similarly, in a head-to-head comparative study, acalabrutinib-treated patients had a lower adverse event-related discontinuation rate than those treated with ibrutinib (14.7% versus 21.3%) [13]. A multicenter retrospective registry of 616 ibrutinib-treated patients also observed a median rwTTD of 7 months, with intolerance as the most common reason for discontinuation [30]. In addition, a retrospective cohort study using TriNetX global health networks found that zanubrutinib was associated with lower rates of certain adverse events, including fatal hemorrhage, infections, cytopenia, and cardiotoxicity, compared to acalabrutinib [31]. In contrast, a retrospective analysis of Veterans Health Administration structured EHR reported numerically higher rwOS for ibrutinib relative to second-generation BTK inhibitors (HR 1.32; 95% CI 1.00–1.74; $P = 0.05$) [32]. However, the study categorized treatment groups only based on the use of cBTK inhibitors within the first month. Patients who experienced intolerance to ibrutinib after the first month of treatment and subsequently changed to second-generation BTK inhibitors as a result of toxicity or other reasons may have been misclassified as remaining in the ibrutinib cohort [33]. Nevertheless, findings from adequate and well-controlled randomized clinical trials have established that zanubrutinib offers superior PFS and OS benefits relative to ibrutinib, while acalabrutinib demonstrates comparable efficacy [13, 20].

Despite prior efforts to evaluate comparative effectiveness, earlier studies have been limited by small sample sizes, single institution datasets, and short follow-up periods, which have hindered robust statistical comparisons. In contrast, this real-world analysis provides a

comprehensive assessment of a large cohort of patients with CLL/SLL treated with cBTK inhibitors in the USA in a contemporary period. The closed claims nature of the dataset allows for relatively complete documentation of treatments, comorbidities, and mortality, and most patients remain enrolled in some form of Medicare coverage for multiple years [34]. In addition, the large sample size and longer follow-up period (until the end of 2025) provided sufficient statistical power for the analysis overall and by age group. However, several limitations should be acknowledged. Important clinical characteristics and molecular disease features (e.g., IGHV, del(17)p, and *TP53* status) are not available as a result of the nature of claims databases and thus cannot be accounted for. Although the study population had similar distribution of sex and race/ethnicity as the general population of patients with CLL in the USA [35], only patients aged 65 or older were included in this study. The generalizability of the results to patients aged under 65 may be limited. For the adjusted analysis, race and ethnicity were not comprehensively investigated because of the small sample size in other racial/ethnic categories, and the need to maintain statistically stable sample size in the analysis. The coding structure used by the Social Security Administration's Master Beneficiary Record results in less accurate categorization for minority populations. Similarly, sex-specific analyses were not included given the primary objective was to evaluate outcomes between cBTK inhibitors in the population of patients aged 65 or older with CLL/SLL under routine clinical practice in the USA. Subgroup analysis from previous clinical trial did not show different treatment effect based on sex [18]. Sex was also relatively balanced across treatment in this study. Future studies are warranted to explore the impact of race, ethnicity, and sex on treatment effects in CLL.

Treatment choices may also reflect factors such as physician judgement, fragility, and patient preference, which are not directly observable in claims data. In addition, other outcomes such as treatment response, disease progression, or reasons for treatment discontinuation were not available. This study includes only Medicare FFS beneficiaries, who may differ from patients enrolled in Medicare Advantage plans or younger, commercially insured populations. Some patients may have been censored as a result of loss of Part D coverage. Similarly, the Medicare FFS database captures US citizens aged 65 years and older and would not be generalizable to patients outside the USA. The follow-up time for zanubrutinib-treated patients, although longer than previous studies, was shorter than acalabrutinib and ibrutinib-treated patients. In addition, the estimated 24 months landmark probabilities may be immature for zanubrutinib- and acalabrutinib-treated patients since the median follow-up durations were shorter than 24 months. The differences in overall follow-up time between cohorts and limited follow-up time may influence the interpretation of the findings beyond the 12-month landmark. To address this, we present landmark analyses at 12 months, with sufficient sample size followed up in each treatment group, to facilitate a more balanced comparison. We also included year of index date in the adjusted analysis. Future studies are needed to further evaluate long-term outcomes with longer follow-up duration in different patient populations including sex and race/ethnicity.

CONCLUSION

This large real-world analysis of patients aged 65 years and older with CLL provides consistent and reproducible evidence that zanubrutinib demonstrated longer treatment duration, lower discontinuation rates, and better OS outcomes compared with acalabrutinib and ibrutinib. These findings, which mirror patterns observed across multiple real-world datasets, suggest that improved tolerability may contribute to the greater durability of zanubrutinib treatment in routine clinical practice. While the absence of certain clinical variables and the inherent constraints of claims data limit causal inference, the strength of the observed associations across age groups and extended follow-up support these results. Together, these data reinforce that zanubrutinib may represent a comparatively superior treatment option for older adults with CLL and

highlights the need for additional studies evaluating FDA approved BTK inhibitors to further clarify differences in real-world effectiveness and safety.

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Data Availability. The data used in this study are derived from Medicare claims which were obtained from CMS and cannot be made publicly available by the authors. The data that supports the finding of this study are available from ADVI Health. Restrictions apply to the availability of these data, which were used under license for this study.

Declarations

Conflict of Interest. Gregory A. Maglinte, Xiaoliang Wang, Qianhong Fu, Erlene K. Seymour, Rhys Williams, and Derrick van Beuge are BeOne Medicines, Ltd employees and shareholders. Gregory A. Maglinte is a shareholder of Amgen, Gilead, and CRISPR Therapeutics. Xiaoliang Wang and Erlene K. Seymour are shareholders of Roche. Qianhong Fu is a shareholder of AbbVie. Derrick van Beuge is a shareholder of Pfizer, GSK, and Nurix. Mazyar Shadman is a shareholder of Koi Biotherapeutics. Daniel A. Ermann has received honoraria from BeOne Medicines, Ltd; consulting fees from BeOne Medicines, Ltd and ADC Therapeutics; participation in Speaker's Bureau for Incyte and AstraZeneca. Deborah M. Stephens has received consulting fees from AbbVie, AstraZeneca, BeOne Medicines, Ltd, Genentech, J&J, Eli Lilly, Pfizer, and Pharmacyclics; research funding from AbbVie, BeOne Medicines, Ltd, and Genentech. Ryan Jacobs has received honoraria from SecuraBio; consulting fees from AbbVie, AstraZeneca, Genentech, BeOne Medicines, Ltd, Genmab, and Eli Lilly; participation in Speaker's Bureau for AbbVie, Adaptive, BeOne Medicines, Ltd, and AstraZeneca; and had travel accommodation by AbbVie, Adaptive, BeOne Medicines, Ltd, and AstraZeneca. Irene Varghese, Heidi De Souza, and Caitlin Sheetz are ADVI Health employees and shareholders.

Ethical Approval. No institutional review board/independent ethics committee review was required for this secondary analysis of de-identified existing data. All work performed by ADVI Health was subject to their respective requirements for access. The data used in this study are derived from Medicare claims files maintained by the Centers for Medicare & Medicaid Services (CMS). ADVI Health has a Data Use Agreement (DUA) agreement and access to these claims through a CMS Virtual Research Data Center (VRDC) license. Data are not publicly available because of federal restrictions protecting beneficiary privacy. Qualified researchers interested in accessing these data must apply directly to CMS through the Research Data Assistance Center (ResDAC). All data presented are aggregated in accordance with CMS privacy standards. All source data were de-identified by CMS. Individual patient consent was not required, as the data were anonymized and reported in aggregated.

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