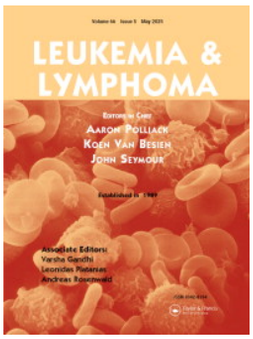

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ORIGINAL ARTICLE

Real-world outcomes after discontinuation of covalent BTK inhibitor-based therapy in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma

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ABSTRACT

This study described real-world treatment patterns and outcomes among patients with CLL/SLL in the post-cBTKi setting. Included were patients who received at least one cBTKi and subsequent line of therapy (LOT) within the Flatiron Health nationwide electronic health record-derived de-identified database (FHD; *N* = 1,479) and Optum's de-identified Clinformatics® Data Mart Database (CDM; *N* = 1,020). Frequently observed post-cBTKi treatments in both databases included cBTKi monotherapy (23–30%), anti-CD20 mab monotherapy (~10%), BCL2i monotherapy (~9%), BCL2i + anti-CD20 mab (~9%), cBTKi + BCL2i (~3%), and cBTKi + anti-CD20 mab (5–7%). From start of immediate LOT following cBTKi discontinuation, median time-to-treatment-discontinuation ranged across databases between 6 and 9 months; median time-to-next-treatment and median overall survival ranged between 18–23 months and 36–57 months, respectively. Observed heterogeneity in treatment patterns and outcomes in two cohorts of patients with CLL/SLL suggests lack of clarity in clinical evidence for treatment choice, and there remains a need for treatment options that deliver improved outcomes in the post-cBTKi setting.

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CLL/SLL; targeted; BTKi; post-cBTKi; real-world; outcomes

Introduction

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are clonal B-cell diseases (hereafter, simply CLL) characterized by the proliferation and accumulation of morphologically mature but immunologically dysfunctional B-cell lymphocytes [1,2]. Prior to 2014, CLL was mostly treated using chemotherapy in combination with anti-CD20 monoclonal antibody (anti-CD20 mab) therapy (collectively otherwise known as chemoimmunotherapy). Since then, the introduction of several novel classes of targeted small molecules have dramatically changed the CLL treatment landscape. These include covalent Bruton tyrosine kinase inhibitors (cBTKi), B-cell lymphoma 2 inhibitors (BCL2i), chimeric antigen receptor T-cell (CAR-T) therapies, and phosphoinositide 3-kinase inhibitors (PI3Ki). The current treatment guidelines for CLL in the first-line include cBTKi (acalabrutinib, zanubrutinib) as monotherapy or in combination with BCL2i (venetoclax) or anti-CD20 mab (obinutuzumab), and BCL2i (venetoclax) in combination with obinutuzumab [3–6]. Guideline-recommended second- or third-line treatment options, including those for use after discontinuation of cBTKi (post-cBTKi setting), consist of cBTKi-based, BCL2i-based, or non-covalent BTKi (ncBTKi; pirtobrutinib) treatment regimens either alone or in combination. Recommended treatments in subsequent lines may include PI3Ki-based (idelalisib or duvelisib), chemotherapy, or CAR-T cell therapy (lisocabtagene maraleucel) regimens [3,6–8]. However, the selection of treatment regimen will, in part, depend on the regimen received in prior line of therapy (LOT), quality of response, tolerability, in addition to patient and clinical characteristics.

Despite the range of available treatments across LOT, the optimal treatment sequencing remains

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unknown. Published prospective clinical trial evidence in the post-cBTKi setting is limited, and when available, the number of patients treated is small in relevant clinical trials, complete remission rates are low, and/or survival outcomes remain limited [9–11]. There are also a limited number of studies investigating real-world patient outcomes in the post-cBTKi setting [12–16]. This study was designed to describe real-world patient characteristics, treatment patterns, and time-to-event (TTE) outcomes associated with subsequent treatment after discontinuation of initial cBTKi among patients with CLL in the U.S.

Methods

Study design, data sources & eligibility criteria

This descriptive, retrospective observational study included patients with CLL from two de-identified real-world databases: the nationwide Flatiron Health electronic health record-derived database (FHD) and the nationwide Optum's de-identified Clinformatics® Data Mart Database (CDM) (Figure 1). The index date was defined as the start of the subsequent LOT following the discontinuation of initial cBTKi-based therapy. Note that the initial cBTKi-based treatment is not restricted to first-line only, so patients could have received treatments prior to their initial cBTKi-based therapy.

Flatiron health enhanced datamart (FHD)

Flatiron Health is a U.S. nationwide longitudinal database, comprising de-identified patient-level structured (e.g. laboratory values, prescribed drugs) and unstructured data (e.g. physician's notes, biomarker reports), curated *via* technology-enabled abstraction. The FHD database includes patient demographics, treatment, and clinical outcomes from a diverse pool of data [17]. During the study period, the de-identified data originated from approximately 280 cancer clinics in the U.S. (~800 unique sites of care) [18,19].

Patients with CLL were selected from the FHD CLL database from 01 Jan 2011 with data available through 30 Nov 2023. Patient selection was based on the following criteria: aged ≥18 years diagnosed with CLL (ICD-9: 204.1x or ICD-10: C91.1x, C83.0x); physician documentation of CLL; evidence in unstructured documents of having been treated specifically for CLL; received at least one cBTKi-based treatment in any LOT (ibrutinib, acalabrutinib, or zanubrutinib); and received at least one additional oncologist-defined, rule-based LOT immediately after the initial cBTKi. Patients with evidence of unknown prior treatment history and unknown LOTs were excluded. All available data in the FHD were used.

Optum clinformatics data mart (CDM)

Optum's de-identified Clinformatics® Data Mart Database (CDM or Clinformatics®) is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. Clinformatics® utilizes medical and pharmacy claims to derive patient-level enrollment information, health care costs, and resource utilization information. The population is geographically diverse, spanning all 50 states and is statistically de-identified under the Expert Determination method consistent with HIPAA and managed according to Optum® customer data use agreements. CDM administrative claims submitted for payment by providers and pharmacies are verified, adjudicated and de-identified prior to inclusion (Optum Inc.; www.optum.com/). Unlike FHD, LOTs are not readily available in CDM; however, similar LOT rules were implemented to characterize LOTs for the purpose of this study (e.g. defined generally to include antineoplastic drugs documented within a 28 day window of each other, to escalate LOT with gaps in therapy of 120 days/365 days [oral drugs]/180 days [rituximab] or addition of a new drug to the regimen outside of the 28 day window, to end upon last confirmed activity/death/start of a next LOT).

Patients with CLL were selected from the full CDM dataset from 01 Jan 2011 with data available through 30 Jun 2023. Patient selection was based on the following criteria: aged ≥18 years; diagnosed with CLL (ICD-9: 204.1x or ICD-10: C91.1x, C83.0x); two CLL diagnoses codes 30 days apart; 90-day pre-diagnosis medical continuous enrollment; received at least one cBTKi-based treatment in any LOT (ibrutinib, acalabrutinib, or zanubrutinib); received at least one additional LOT immediately after the initial cBTKi. Patients with CLL diagnosis codes within 180 days prior to identified CLL diagnosis or who received cBTKi prior to CLL diagnosis were excluded. Additionally, patients without continuous enrollment (except with allowable 60-day gap) after post-cBTKi initiation were excluded from the study.

Real-world outcomes

Real-world TTE outcomes included time-to-treatment-discontinuation or death (TTD), time-to-next-treatment or death (TTNT), and overall survival (OS). TTD was defined as the earliest of the time from index date to the episode end date of either post-cBTKi regimen if the patient initiated a subsequent LOT, or if the episode end date was >90 days before the end of database among those who did not initiate a subsequent LOT, or death. TTNT was defined as the earliest of the time from index date to the start date of a subsequent

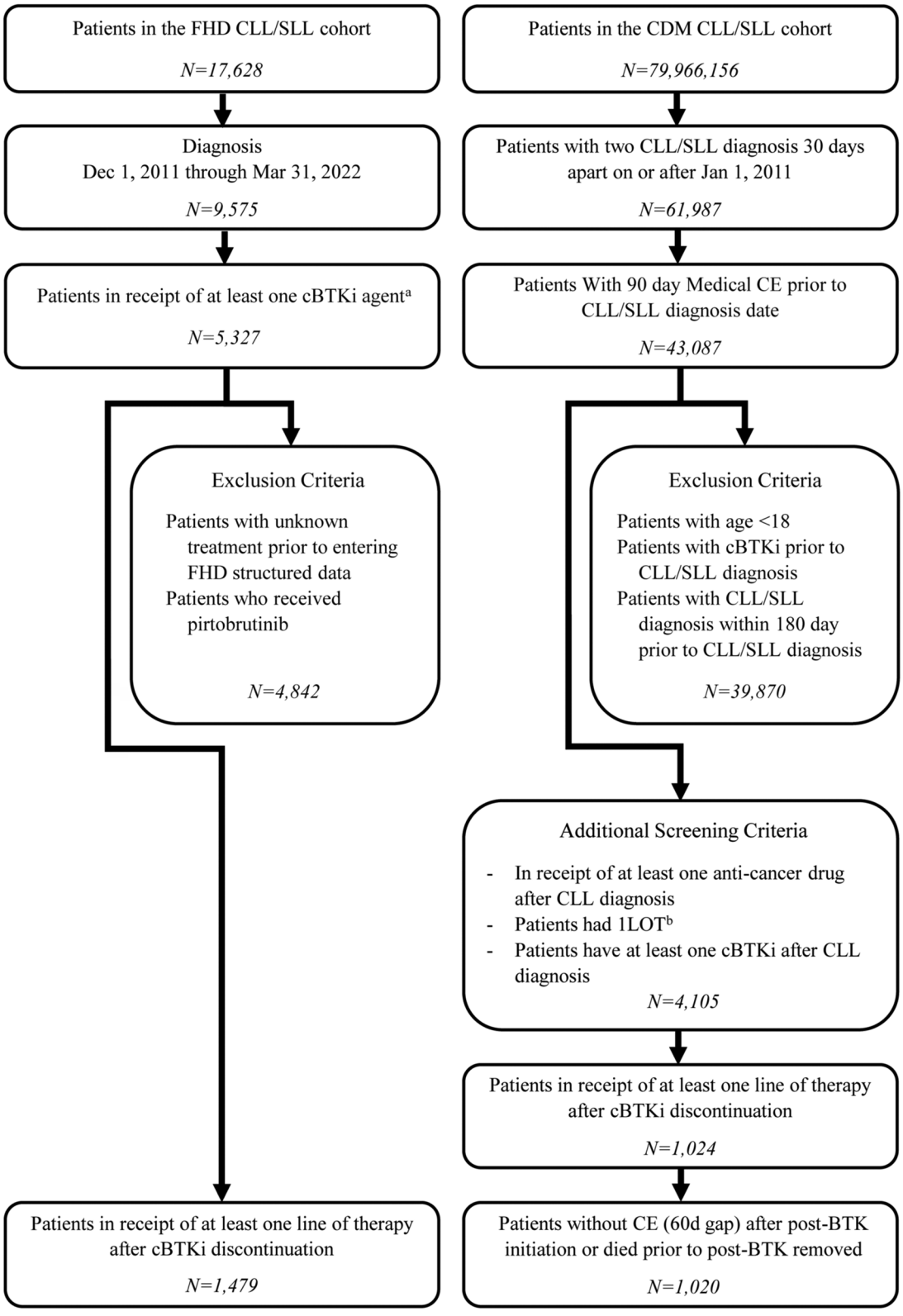

Figure 1. CONSORT diagram of study population selection in Flatiron Health Database and Clinformatics® Data Mart datasets.
[a]ibrutinib, zanubrutinib or acalabrutinib on or after the first observation of eligible ICD.
[b]Restricted to drugs within CE (60d gap) after CLL/SLL diagnosis.
Abbreviations: CLL/SLL: Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma, CDM: Clinformatics® DataMart, FHD: Flatiron Health Database, CE: Continuous Enrollment, cBTKi: covalent Bruton Tyrosine Kinase inhibitor, LOT: Line of Therapy, N: total patient number.

LOT or death. OS was measured from the index date until death from any cause. Patients without events were censored at the last observation in the database.

Statistical analyses

Descriptive statistics were used to evaluate clinical and demographic characteristics for the FHD and CDM post-cBTKi cohorts, respectively. Treatment patterns were described using Sankey plots showing treatment received in the line prior to receiving initial cBTKi line (pre-cBTKi), treatment received in the initial cBTKi line (initial cBTKi), and subsequent treatment received after initial cBTKi line (post-cBTKi). Descriptive TTE analyses were conducted using the Kaplan-Meier method and median (95% CI) values were reported in the overall post-cBTKi cohort as well as by LOT in which post-cBTKi treatment was received.

Results

A total of $N = 1479$ and $N = 1020$ patients from FHD and CDM, respectively, were included in the study (Figure 1), indicating that 27.8% (FHD) and 24.8% (CDM) of patients who had received a cBTKi treatment were then treated in the post-cBTKi setting. The overall median (IQR, interquartile range) follow-up time from index date to end of database or death was 17.1 months (6.9, 33.6) in the FHD cohort and 15.0 months (6.4, 29.1) in the CDM cohort. Extended patient demographic and clinical characteristics for each cohort are listed in Table 1. The overall median duration of treatment with initial cBTKi ranged between 5–8.5 months, which varied slightly depending on the sequence of treatments received (initial cBTKi to post-cBTKi) across both databases. The overall median duration of gap between the discontinuation of initial cBTKi and the initiation of subsequent post-cBTKi treatment was <1 month, which increased up to 17–20 months among those who received the same cBTKi treatment in both lines across patients in both databases (refer to Supplementary Table 1 for more details).

Treatment patterns

Treatments received in the pre-cBTKi line and the initial cBTKi line (Table 1; >5% frequencies listed) for FHD and CDM cohorts are summarized in their respective Sankey plots (Figure 2). In the post-cBTKi setting, 45.2% ($n = 668/1479$; FHD) and 40.1% ($n = 409/1020$; CDM) of patients received any cBTKi-based treatment (excluding combinations with BCL2i), 19.3% (285/1479; FHD) and 19.1% (195/1020; CDM) of patients received any BCL2i-based treatment (excluding combinations with cBTKi), and 4.5% (66/1479; FHD) and 3.4% (35/1020; CDM) of patients received cBTKi in combination with BCL2i with or without any other treatment.

Among these patients who received cBTKi-based treatment in the post-cBTKi line, 82.4% ($n = 605/734$; FHD) and 83.8% ($n = 378/451$; CDM) received ibrutinib-based therapy, with most being monotherapy (72.6% [$n = 533/734$; FHD] and 75.4% [$n = 340/451$; CDM]) as their initial cBTKi-based line of treatment. Among the patients who received ibrutinib-based treatment as their initial cBTKi therapy, 48.6% ($n = 294/605$; FHD) and 38.9% ($n = 147/378$; CDM) patients received acalabrutinib-based therapy and 8.9% ($n = 54/605$; FHD) and 7.7% ($n = 29/378$; CDM) patients received zanubrutinib-based therapy in the post-cBTKi line of treatment.

Additionally, BCL2i-based treatments (23.7% [$n = 351/1479$; FHD] and 22.5% [$n = 230/1020$; CDM]) with venetoclax monotherapy (9.4% [FHD], 8.9% [CDM]) or in combination with anti-CD20 mab (rituximab; 2.0% [FHD], 4.5% [CDM]) or obinutuzumab; 4.3% [FHD], 5.1% [CDM]) were observed in the post-cBTKi setting. Other post-cBTKi regimens included anti-CD20 mab monotherapy such as rituximab (3.1% [FHD], 6.2% [CDM]), obinutuzumab (4.4% [FHD], 4.2% [CDM]), or anti-CD20 mab with chemotherapy (rituximab + bendamustine; 3.0% [FHD], 5.3% [CDM]). Less common regimens observed included chlorambucil (0.7% [FHD], 1.4% [CDM]), chlorambucil + obinutuzumab (0.7% [FHD], 1.2% [CDM]), bendamustine (0.5% [FHD], 0.7% [CDM]) or combinations with PI3Ki such as idelalisib (idelalisib + rituximab; 1.5% [FHD], 1.3% [CDM]) or duvelisib (duvelisib + rituximab; 0.0% [FHD], 0.1% [CDM].

Real-world outcomes

In the overall post-cBTKi population, median (95% CI) TTD was 7.5 (6.6–8.9) months in FHD and 8.3 (7.0–9.3) months in CDM (Figure 3). The median TTD in the second-line setting was 9.2 (7.6–11.3) months and 8.7 months (7.2–10.0) in FHD and CDM, respectively. The median TTD was 6.0 (5.0–7.2; FHD) months and 7.5 (5.6–10.6; CDM) months in third-line and 6.2 (4.5–8.9; FHD) and 6.7 (3.8–10.8; CDM) months in the fourth and later lines of therapy (Figures 4 and 5).

The overall median (95% CI) TTNT was 22.9 (19.2–26.5) months in FHD and 17.6 (15.2–20.0) months in CDM (Figure 3). Among patients who received post-cBTKi treatment in the second-line setting, the median TTNT was 30.5 (25.2–36.5) months and 20.4 (17.2–26.2) months in FHD and CDM, respectively. The

Table 1. Patient demographic and clinical characteristics for Flatiron Health Database and Clinformatics® Data Mart.

	Overall post-cBTKi	
Patient baseline characteristics at index	FHD $N=1479$	CDM $N=1020$
Age, median (range), years[a]	72 (65,79)	72 (66,78.5)
Sex, n (%)		
Male	938 (63.4)	642 (62.9)
Female	541 (36.6)	376 (36.9)
Race, n (%)		
White	1106 (74.8)	786 (79.3)
Black/African American	144 (9.7)	112 (11.3)
Other[b]	229 (15.5)	93 (9.4)
Year of initiation of post-cBTKi treatment, n (%)		
2014–2019	414 (28.0)	367 (36.0)
2020	277 (18.7)	172 (16.9)
2021	255 (17.2)	200 (19.6)
2022	283 (19.1)	196 (19.2)
2023	250 (16.9)	85 (8.3)
Most common initial cBTKi regimens, n (%)[c]		
Ibrutinib monotherapy	1131 (76.5)	767 (75.2)
Ibrutinib-based combination therapy	127 (8.6)	90 (8.8)
Acalabrutinib monotherapy	166 (11.2)	120 (11.8)
LOT in which post-cBTKi treatment received, n (%)		
2	925 (62.5)	683 (67)
3	394 (26.6)	252 (24.7)
4+	160 (10.8)	85 (8.3)
Practice setting, n (%)		
Academic	255 (17.2)	N/A
Community	1172 (79.2)	N/A
Disease subtype n (%)		
CLL	1163 (78.6)	N/A
CLL/SLL	207 (14.0)	N/A
SLL	109 (7.4)	N/A
ECOG PS, n (%)		
0	533 (36.0)	N/A
1	476 (32.2)	N/A
2+	175 (11.8)	N/A
Missing/unknown	295 (19.9)	
Rai stage, n (%)		
0	328 (22.2)	N/A
I	220 (14.9)	N/A
II	119 (8.0)	N/A
III	107 (7.2)	N/A
IV	167 (11.3)	N/A
Not documented	538 (36.4)	N/A
Deletion 11q, n (%)[d]		
No	1013 (68.5)	N/A
Yes	277 (18.7)	N/A
Missing/unknown	189 (12.8)	N/A
Deletion 13q, n (%)[d]		
No	710 (48.0)	N/A
Yes	587 (39.7)	N/A
Missing/unknown	182 (12.3)	N/A
Deletion 17p, n (%)[d]		
No	1032 (69.8)	N/A
Yes	263 (17.8)	N/A
Missing/unknown	184 (12.4)	N/A
Trisomy 12, n (%)[d]		
No	931 (62.9)	N/A
Yes	345 (23.3)	N/A
Missing/unknown	203 (13.7)	N/A
IgHV, n (%)		
Mutated	229 (15.5)	N/A
Unmutated	486 (32.9)	N/A
Missing/unknown[e]	764 (51.7)	N/A

[a]Patients with a BirthYear of 1938 or earlier may have an adjusted BirthYear in FHD datasets due to patient de-identification requirements.
[b]Other includes; 19 (1.3%) Asian, 3 (0.2%) Hispanic/Latino, 76 (5.1%) Other, 131 (8.9%) Missing/Unknown, patients in the FHD cohort, and 22 (2.2%) Asian, 63 (6.4%) Hispanic/Latino, 8 (0.8%) Missing/Unknown patients in the CDM cohort.
[c]Most common initial cBTKi regimens were those greater than 5% frequency.
[d]Biomarker data not restricted to 'at Index' timepoint.
[e]Includes all patients that were unknown/undocumented and unsuccessful/indeterminate.
cBTKi; covalent Bruton tyrosine kinase inhibitor, CDM; Clinformatics® Data Mart database, ECOG PS; Eastern Cooperative Oncology Group Performance Status, FHD; Flatiron Health Database, N/A: Not applicable.

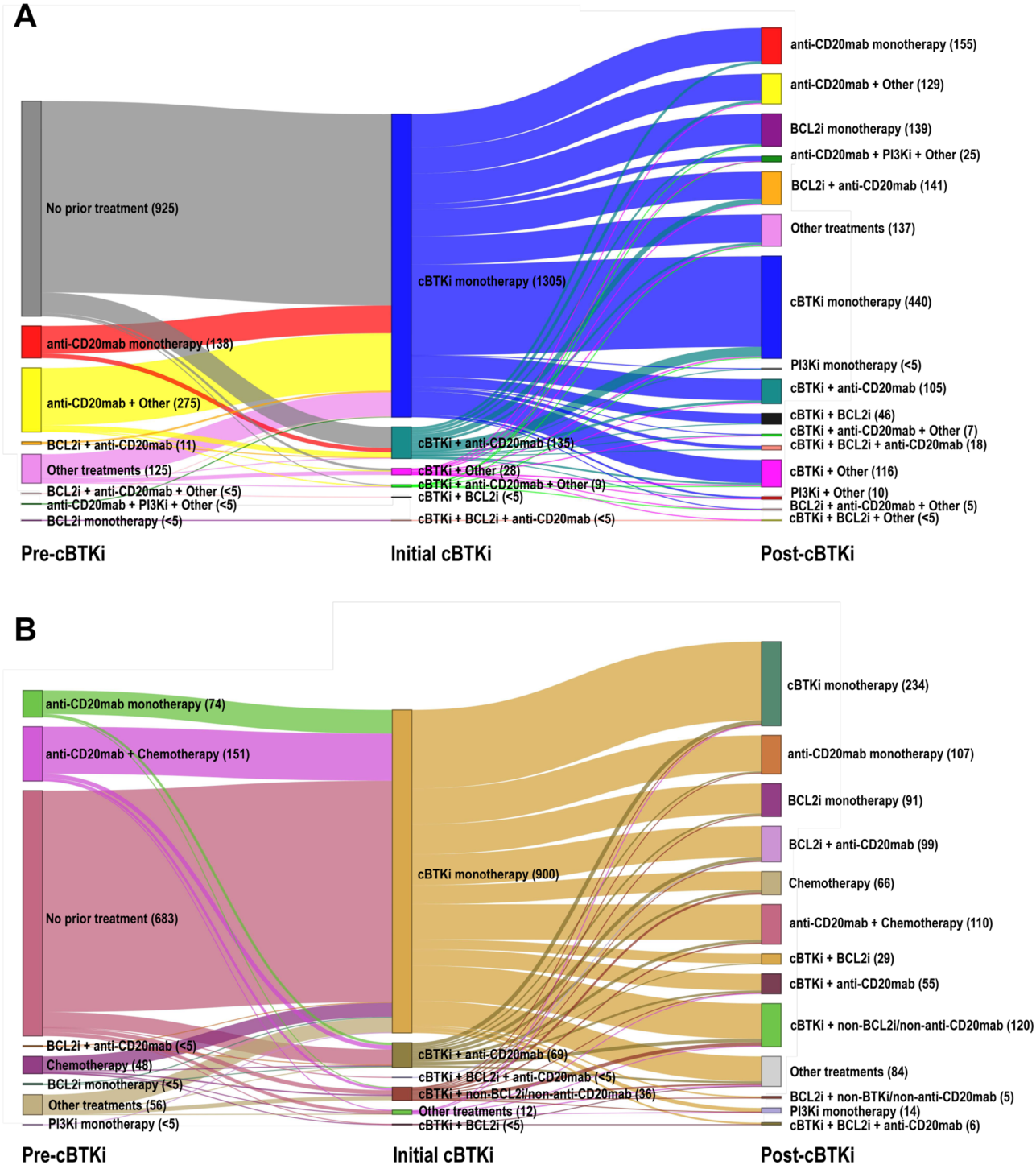

Figure 2. Sankey plots of therapies received by patients in the (A) Flatiron Health Database and (B) Clinformatics® Data Mart.
Anti-CD20 mab; Anti-CD20 antibody, BCL2i; B-cell lymphoma 2 inhibitors, cBTKi; covalent Bruton Tyrosine Kinase inhibitor.

median TTNT was 17.0 (12.5–20.9; FHD) months and 16.1 (13.0–19.1; CDM) months in third-line and 11.6 (9.0–14.2; FHD) months and 10.8 (6.7–15.1; CDM) months in the fourth and later lines of therapy (Figures 4 and 5).

The overall median (95% CI) OS was 57.2 (50.1–68.6) months in FHD and 36.1 (33.4–42.0) months in CDM (Figure 3). Median OS in the second-line setting was 69.2 (64.6–NR) months and 42.0 (36.1–45.3) months in FHD and CDM, respectively. Median OS was 42.2 (30.8–55.0; FHD) months and 32.2 (25.7–35.6; CDM) months in the third-line and 35.2 (25.3–55.5; FHD) months and 16.9 (12.8–43.9; CDM) months in the fourth and later lines of therapy (Figures 4 and 5).

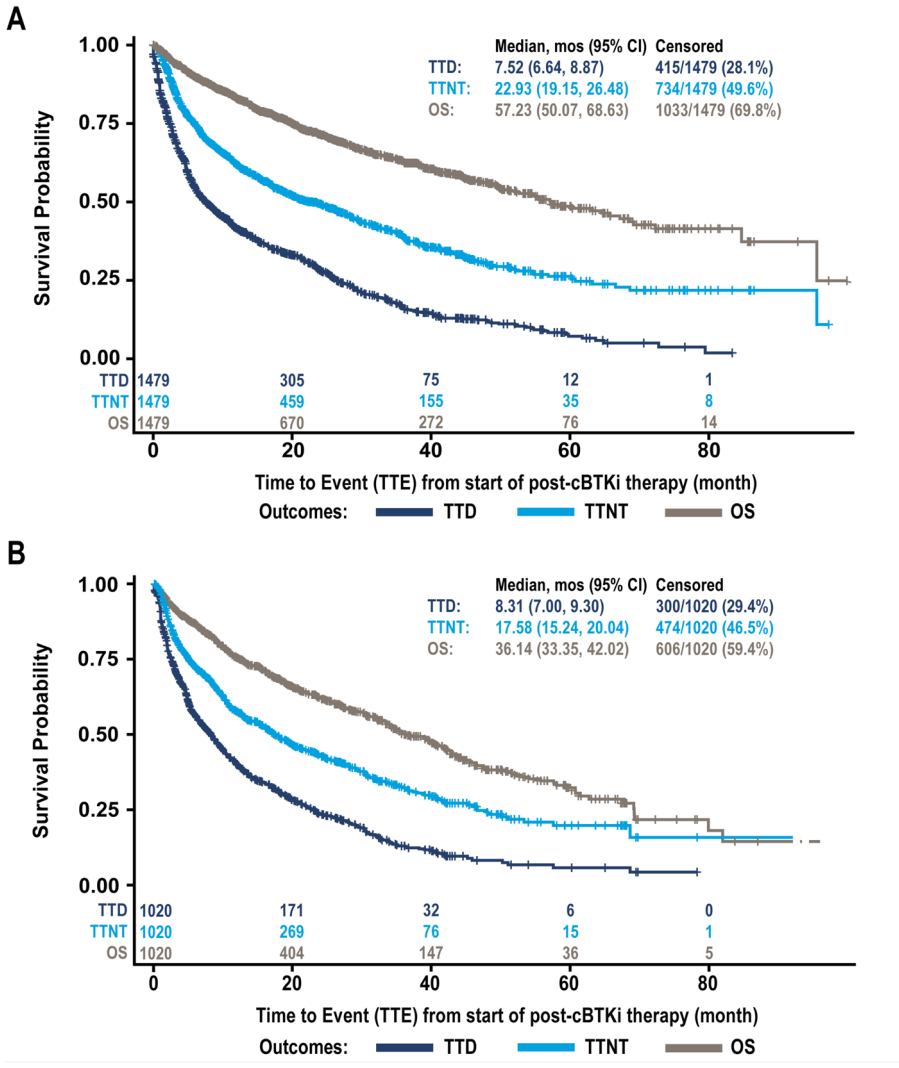

Figure 3. Clinical outcomes from start of post-cBTKi therapy. Panel A: Flatiron Health Database ($n = 1479$); panel B: Clinformatics® Data Mart ($n = 1020$).
95% CI, Confidence Interval; mos; Months, TTD; Time-to-discontinuation or death, TTNT; Time-to-next-treatment or death, OS; overall survival.

Discussion

This real-world study provides clinical evidence describing treatment options after discontinuation of cBTKi-based treatment in patients with CLL in the US. The results demonstrated heterogeneity in treatment patterns in two different cohorts of patients with CLL. Findings from both datasets suggest a lack of clarity in clinical evidence for treatment choice in the post-cBTKi setting.

Notably, cBTKi therapy was frequently observed in the LOT immediately following the initial cBTKi treatment. Interestingly, the median durations of gap between the discontinuation of initial cBTKi and the initiation of subsequent cBTKi (in the post-cBTKi setting; Supplementary Table 1) were 17–20 months when same cBTKi was used in both lines and <1 month when a different cBTKi was used in both lines across both the databases. Since the reason for discontinuation is unavailable in these datasets, it is unknown if patients who were re-treated possibly had disease response with/without intolerance or progression on initial cBTKi before initiating retreatment. Previous studies have shown similar observations but with a relatively lower frequency of utilization of cBTKi-based treatment in the post-cBTKi setting [15]. To the best of our knowledge, however, there are no published clinical trials that demonstrate benefit associated with rechallenging patients with cBTKi in the post-cBTKi setting after having disease progression on initial cBTKi-based treatment. The development of resistance mechanisms (such as C481 mutations) to initial cBTKi-based therapy may preclude the use of another cBTKi, suggesting a potential role for ncBTKi agents in

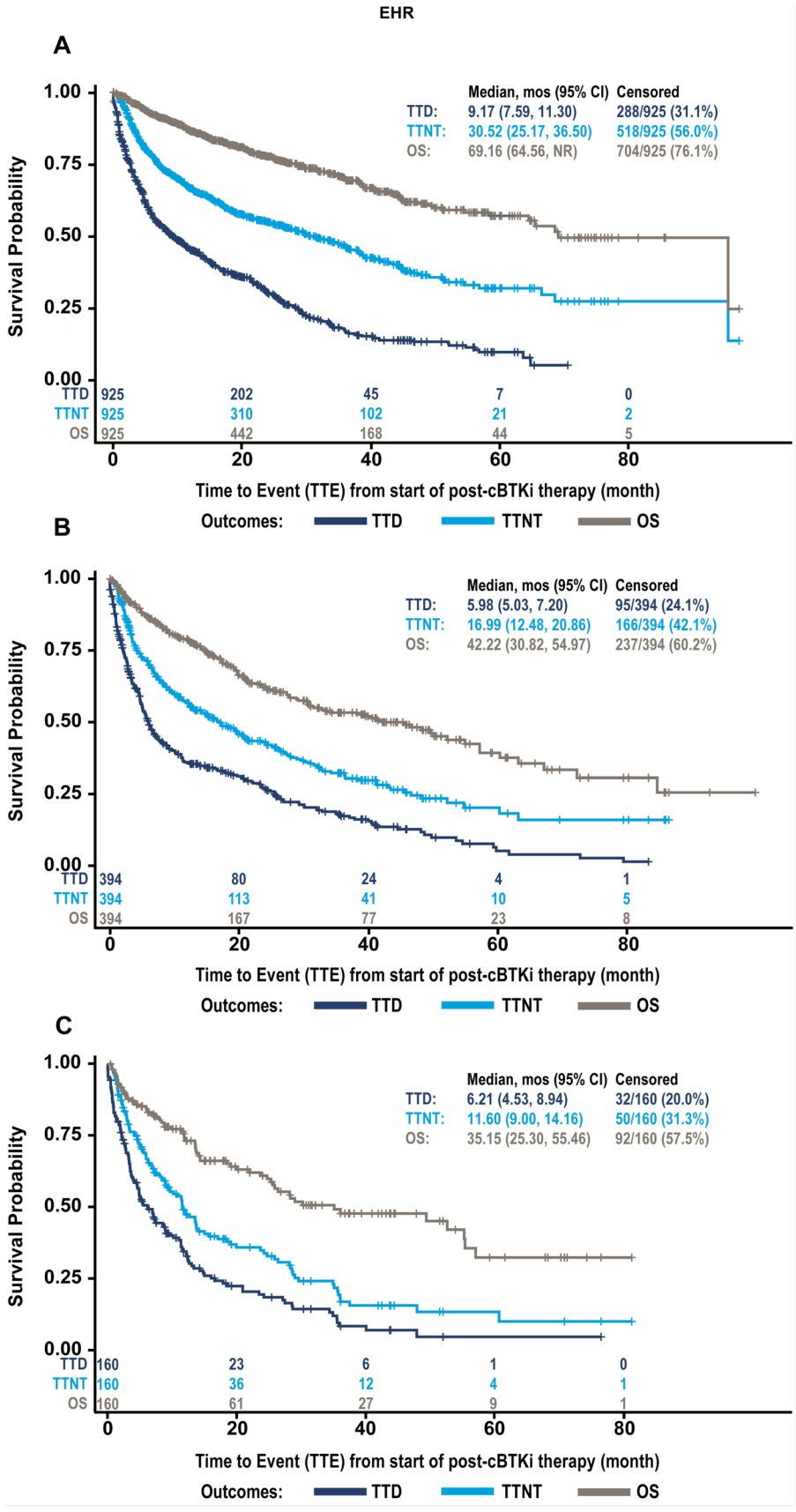

Figure 4. Clinical outcomes from start of post-cBTKi therapy in the Flatiron Health Database cohort by line of post-cBTKi treatment. Panel A: second-line; panel B: third-line; panel C: fourth-line or more.
95% CI, Confidence Interval; mos; Months, TTD; Time-to-discontinuation or death, TTNT; Time-to-next-treatment or death, OS; overall survival.

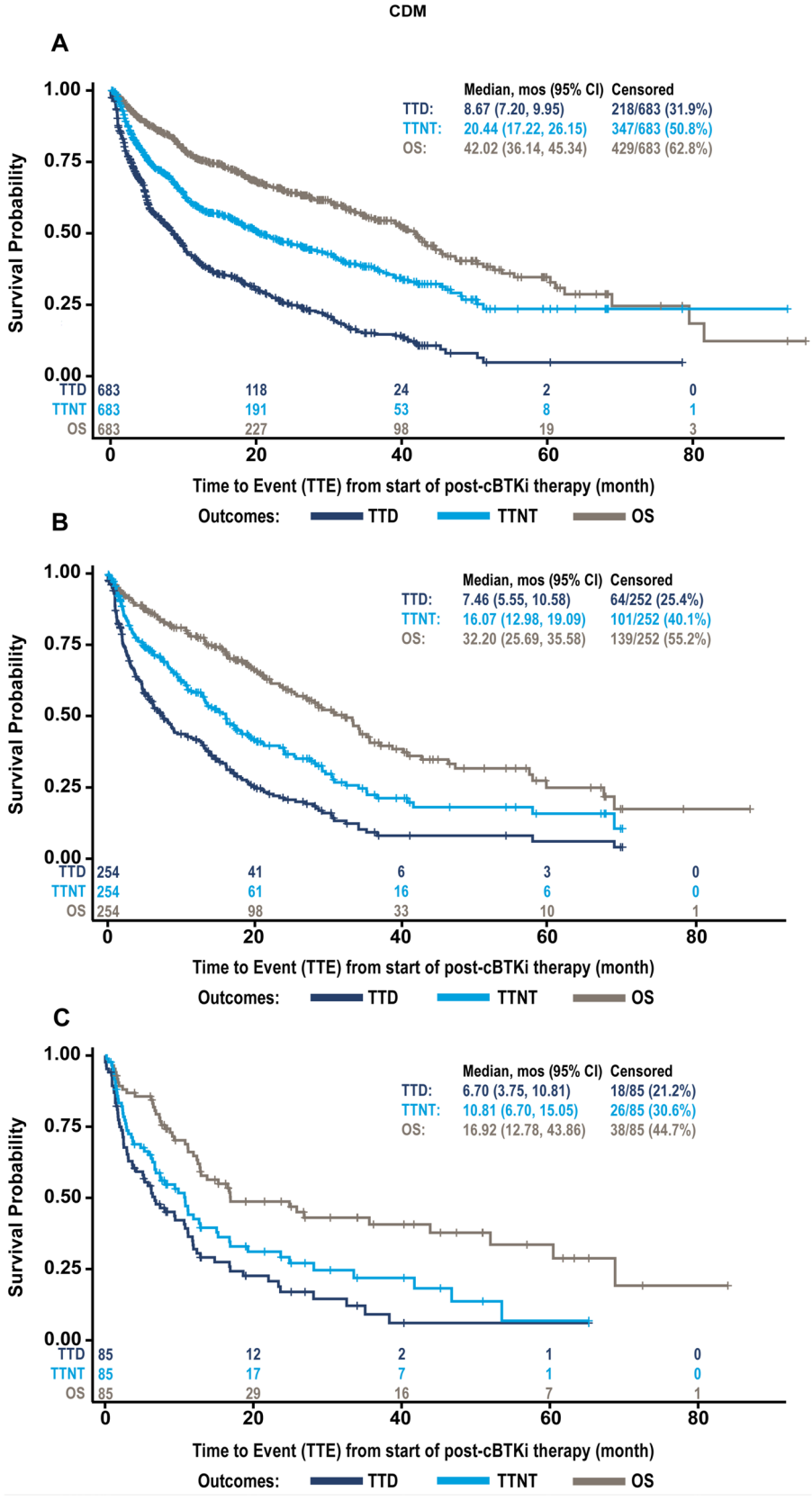

Figure 5. Clinical outcomes from start of post-cBTKi therapy for Clinformatics® Data Mart cohort by line of post-cBTKi treatment. Panel A: second-line; panel B: third-line; panel C: fourth-line or more.

95% CI, Confidence Interval; mos; Months, TTD; Time-to-discontinuation or death, TTNT; Time-to-next-treatment or death, OS; overall survival.

this setting [20], if providers and patients prefer to continue treatment with oral anticancer agents targeting the BTK pathway. While there is published literature demonstrating patients' preference for oral treatment (versus intravenous infusion every four weeks) among other attributes of treatments in patients with CLL [21–24], the reason for re-challenge with cBTKi therapy is not recorded in this dataset. The short duration of gap between the use of a different cBTKi in both lines observed in this study (Supplementary Table 1) could be considered indicative of intolerance to initial cBTKi. However, due to lack of reasons for discontinuation, this dataset is unable to make a concrete distinction between intolerance and progression, and questions remain regarding the choice to re-treat with cBTKi-based treatments in the post-cBTKi setting. This concept of rechallenging is an emerging area of exploration and should be investigated further.

Patients who did not receive treatment with prior BCL2i-based regimens could be eligible to receive BCL2i-based treatment in the post-cBTKi setting. However, the availability of clinical evidence supporting its use in similar setting is limited to two studies with a small number of patients. Jones et al. [9] reported an objective response rate of 65% along with a median PFS of about 25 months among heavily pretreated patients who received venetoclax monotherapy following progression on ibrutinib [9]. Kater et al. [10] reported an overall response rate of 64% along with a median PFS of about 23 months among patients who received venetoclax monotherapy following prior exposure to B-cell receptor inhibitors (BCRi)-based treatments. Additionally, while the MURANO Phase 3 trial evaluated venetoclax + rituximab and demonstrated improved outcomes versus bendamustine + rituximab in patients with relapsed or refractory CLL, the applicability of this evidence to the post-cBTKi setting is extremely limited as only ~3% (5/194) of patients with prior exposure to BCRi were included in the trial [11]. In the current study, while over 60% of patients initiated their post-cBTKi treatment in the year 2020 or later, ~25% of patients overall received BCL2i-based treatments in this setting including combinations with cBTKi, with venetoclax monotherapy being the most frequent of these in both databases. A recent retrospective study by Ghosh et al. [25] reported use of BCL2i-based treatments by 14% of patients in second LOT (8.9% venetoclax monotherapy) after receiving first line cBTKi-based treatment using data from the CLL Collaborative Study of Real-World Evidence (CORE). Similarly, several other retrospective studies have reported between 14.3 and 25.6% use of venetoclax monotherapy or venetoclax-based combination treatments in the second LOT following cBTKi-based treatment [15,26]. Mato et al. [15] additionally reported about 7.5% patients who received venetoclax in combination with cBTKi with/without other agents in the post-cBTKi setting. Therefore, the observed real-world utilization of venetoclax-based regimens in this setting is not necessarily surprising, and it is likely due to multiple reasons such as limited venetoclax availability earlier in the study period, applicability of evidence demonstrating its use in the post-cBTKi setting, and potential challenges related to TLS monitoring.

The median TTD of post-cBTKi treatments ranged between 6–9 months in both databases across various LOTs, and the median TTNT ranged from 18–23 months overall and appeared to be lower as LOT advanced. The magnitude of difference observed between TTD and TTNT may be due to gaps between LOT and require further investigation in future studies. With the current data limitations, it is unknown whether this difference is due to fixed duration of treatment or intolerance. Mato et al. [15] using the ConcertAI RWD360 database reported median duration of treatment of only 4.1 (3.7–4.6) months in patients with CLL who received post-cBTKi treatment after discontinuation of initial cBTKi-based therapy. While not directly comparable to TTNT as measured and observed in this study, Mato et al. [15] also reported a median of 9.5 (8.8–10.4) months as the time from discontinuation of initial cBTKi-based treatment to the discontinuation of the post-cBTKi line of treatment or death, thus indicating a somewhat similar discrepancy in TTD and TTNT as in the current study. The duration of treatment in post-cBTKi line after receiving prior cBTKi and BCL2i was reported in 39% patients (228/581) with a median TTD of 5.5 (3.5–6.9) months while the median TTNT was reported as 5.6 (4.3–6.0) months. This consistency in TTD and TTNT in patients with previous venetoclax exposure in the Mato et al. study suggests that fixed duration treatments may be contributing to the difference in TTD and TTNT in this study; however, it cannot be assessed with certainty given the lack of data on reasons for discontinuation. Similarly, in a small retrospective study of 47 patients with CLL, majority of whom received BCL2i-based treatment in the post-cBTKi setting, median PFS of 25.9 (9.2–42.2) months was reported for venetoclax + rituximab (VenR) and 10.5 (1.1–28.9) months was reported for venetoclax monotherapy [27]. Overall, the TTD and TTNT outcomes associated with heterogenous post-cBTKi treatments observed in this study are generally similar to those reported in a few smaller studies in the literature.

OS demonstrated wider ranges in the two databases (median of 36 months in CDM and 57 months in FHD); the confidence intervals are largely overlapping, and the differences should not be over interpreted due to the varying approaches each dataset uses to obtain death dates. These data are consistent with limited published literature available in the post-cBTKi setting. Lew et al. [27] reported post-cBTKi median OS of 46.1 (21.9–NE) months for VenR and 30.5 (1.1–NE) months for venetoclax monotherapy in patients with CLL. In 62 patients with CLL who received venetoclax monotherapy in the post-cBTKi setting, Eyre et al. [28] reported median OS of approximately 21 months. Overall, these observations raise additional questions about outcomes associated with specific treatment regimens in the post-cBTKi setting, which should be evaluated in future research using comparative effectiveness methods that comprehensively adjust for key clinical and sociodemographic characteristics of this patient population.

Additionally, newer data demonstrate the efficacy of ncBTKi and CAR-T treatments in the post-cBTKi setting, with several ongoing trials showing promise for improved patient outcomes (BRUIN; NCT03740529 and BRUIN CLL321; NCT04666038 [pirtobrutinib] [29,30], BELLWAVE-001; NCT03162536 [nemtabrutinib], TRANSCEND CLL 004; NCT03331198 [lisocabtagene maraleucel]). In the first randomized Phase 3 study conducted exclusively in patients who all received prior cBTKi treatment, the ncBTKi pirtobrutinib demonstrated an efficacy benefit with significant improvement in PFS versus investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab along with a more favorable safety profile. Moreover, in this study TTNT was meaningfully improved with pirtobrutinib, as patients were able to delay subsequent treatment or death for a median of nearly 2 years (2.5 years in venetoclax-naïve patients) [29].

More recently, a retrospective analysis of heavily pretreated patients with CLL who received ncBTKi, reported a high ORR (72%) to venetoclax treatment following ncBTKi discontinuation. The median PFS of patients with CLL was 15 months for any treatment following ncBTKi discontinuation and 23 months when venetoclax was the immediate treatment following ncBTKi discontinuation [31]. There is a growing interest in understanding optimal sequencing of treatments given the availability of various novel treatments and/or combination-regimens. A recent contemporary research study in U.S. patients with CLL highlighted the heterogeneity observed in real-world treatment sequences and the lack of use of targeted agents in the first two lines of therapy while concluding uncertainty in identifying an optimal sequence amongst various sequences compared [32].

The strength of this study includes the utilization of two very different, large real-world databases with source data coming from electronic health records and administrative claims. These report consistent characteristics, treatment patterns, and associated outcomes in the post-cBTKi setting in patients with CLL. These real-world data should be interpreted in the context of their limitations. They are collected as a part of routine clinical practice and not for research purposes; the outcomes therefore should not be compared to that observed in clinical trials without appropriate balance or weighting applied to the cohorts being studied. The generalizability of findings is limited beyond the US given the potential differences in healthcare system, practice patterns, and access to treatments. Additionally, lack of cause of death and reasons for discontinuation and/or progression status limits the interpretation of some of the treatment patterns described in this study, particularly the high cBTKi use in the post-cBTKi setting.

Conclusion

Observed heterogeneity in treatment patterns together with the observed survival outcomes in two different real-world cohorts of patients with CLL suggests lack of clarity in clinical evidence in the post-cBTKi setting. This could suggest that clinical decision-making in the real-world is complex and may be based on individual patient characteristics, preferences, and other contextual factors rather than available clinical evidence alone. Additionally, there remains a need for treatment options in this setting that can deliver improved outcomes and help clarify the optimal treatment sequencing strategy. As more treatment options become available in the post-cBTKi setting, future studies should be conducted to evaluate their impact on the heterogeneity observed in this study.

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Authors' contributions

NJ, NRB and KBW were responsible for the conceptualization and design of the work. MK contributed to the design, NJ, KBW, MK, YC, TS, TE, and PA contributed to the analysis of data and KP was responsible for data acquisition. All authors were involved in the interpretation and critical revision of the work and contributed substantially to the final manuscript. All authors have approved the final version for submission.

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Data availability statement

Flatiron Health Data Availability Statement: The data that support the findings of this study were originated by and are the property of Flatiron Health, Inc., which has restrictions prohibiting the authors from making the data set publicly available. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to PublicationsDataAccess@flatiron.com.

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