Real-World Assessment of Dosing Patterns and Treatment Outcomes in Patients With Chronic Lymphocytic Leukemia who Initiated First-Line Single-Agent Ibrutinib in an Integrated Claims-Based Database

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BACKGROUND

- Bruton tyrosine kinase inhibitors (BTKis) have transformed the treatment landscape of chronic lymphocytic leukemia or small lymphocytic lymphoma (CLL/SLL)
- Ibrutinib (IBR), the first BTKi approved by U.S. Food and Drug Administration CLL/SLL treatment, has demonstrated sustained efficacy in both first-line (1L) and relapsed/refractory patient populations[1]
- The USPI recommended starting dosage of ibrutinib for CLL/SLL is 420 mg once daily. Patients treated with IBR have the option of modifying their dose to manage events occurring during treatment (e.g., adverse events), thus allowing the patient to benefit from continued treatment[1]
- A recent analysis of patients with ≥ 5 years from the RESONATE-2 study showed dose reduction of IBR may have facilitated continued long-term use of IBR treatment and without compromising efficacy[2]
- There are limited real-world studies on dosing patterns and dose adjustment of IBR and its associated outcomes. Therefore, it is important to further understand IBR dosing patterns and investigate the impact of dose modification on outcomes for patients with CLL/SLL treated with IBR in the real-world setting

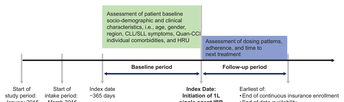
OBJECTIVES

1. To describe real-world dosing patterns among patients with CLL/SLL treated with 1L single-agent IBR
2. To describe treatment outcomes, including measures of adherence and time to next treatment (TTNT), in patients with CLL/SLL treated with 1L single-agent IBR with or without a dose adjustment in the first 6 months
3. To describe real-world dosing patterns and treatment outcomes in a subgroup of patients with high cardiovascular (CV) risk

METHODS

- **Data source:** Komodo Health payer-complete claims dataset
  - Derived from > 150 private insurers in the U.S., recording health insurance claims data from > 140 million individuals with commercial, individual, state exchange-purchased, Medicare Advantage, and Medicaid managed-care insurance coverage between January 2015 and October 2022
  - Closed claims in this dataset have undergone insurance adjudication
  - Provides age and geographic representation of the insured U.S. population including patients from the community practice setting

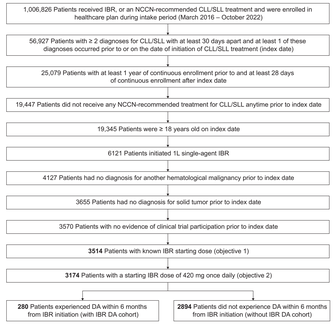
FIGURE 1: Study design



1L, first-line; CLL, chronic lymphocytic leukemia; HRU, healthcare resource utilization; IBR, ibrutinib; Quan-CCI, Quan-Charlson comorbidity index; SLL, small lymphocytic lymphoma

  - **Study period:** January 2015 to October 2022
  - **Intake period:** March 2016 to October 2022
  - **Index date:** date of initiating 1L single-agent IBR
  - **Baseline period:** index date -365 days to index date -1 day, inclusive
  - **Follow-up period:** index date to the earliest date of disenrollment from health plan, initiation of any CLL/SLL treatment other than IBR, end of data availability, or medical claim indicating participation in a clinical trial
- **Inclusion and exclusion criteria (Figure 2):** 3514 adults with CLL/SLL who initiated 1L single-agent IBR in or after March 2016
  - **Definitions of patient cohorts for objective 2:**
    - **With IBR dose adjustment cohort:** 280 patients who initiated IBR at 420 mg/daily and experienced dose adjustment within 6 months from IBR initiation
    - **Without IBR dose adjustment cohort:** 2894 patients who initiated IBR at 420 mg/day and without an IBR dose adjustment within 6 months from IBR initiation
  - **Definition of high CV risk subgroup for objective 3**:
    - Having ≥ 1 pre-existing CV comorbidity or in the "high risk" category for CHA_2DS_2-VASc risk score [≥ 3 for women; ≥ 2 for men]

Figure 2: Study flow chart



1L, first-line; CLL, chronic lymphocytic leukemia; DA, dose adjustment; IBR, ibrutinib; NCCN, National Comprehensive Cancer Network; SLL, small lymphocytic lymphoma

Outcomes:

- **Measures of adherence:**
  - **Proportion of days covered (PDC):** defined as the sum of non-overlapping days of supply, where claims with overlapping days of supply were shifted forward, divided by the line of therapy duration (i.e., number of days between index date and the earliest of initiation of a new CLL/SLL treatment or end of data)
  - **Medication possession ratio (MPR):** defined as the number of days of medication supplied during the regimen, divided by the line of therapy duration and capped at 100%
- **Time to next treatment (TTNT):** used as a proxy for disease progression and defined as the time from index date to the initiation of next line of therapy (LOT), i.e., a new class add-on and/or switch that is not part of the 1L regimen,[3] with the following exceptions:[4]
  - Initiation of an alternative BTKi, i.e., acalabrutinib or zanubrutinib, anytime post-index may have indicated a switch because of tolerability rather than progression. Therefore, patients were censored at the time of BTKi in-class switch
  - Add-on of an anti-CD20 antibody or venetoclax to IBR within 180 days post-index may not have indicated overt disease progression, but rather late initiation of a second anti-cancer agent as a 1L combination treatment strategy. Therefore, patients were censored at time of anti-CD20, or venetoclax add-on within 180 days. Add-on of an anti-CD20 antibody or venetoclax after 180 days were considered as the new LOT

Statistical analysis:

- Descriptive study; no formal statistical comparison was conducted
- Demographic and clinical characteristics:
  - Continuous variables: mean (standard deviation) or median (interquartile range), where appropriate
  - Categorical variables: count (percentage)
- Adherence:
  - Mean PDC and MPR during the line of therapy duration
  - Mean PDC and MPR at 3-, 6-, 9-, and 12-months post-index among patients with sufficient duration of follow-up
- TTNT:
  - Kaplan-Meier estimates
  - Proportions of patients who reached the next LOT by the end of follow-up
  - Proportions of patients who have not initiated next LOT at fixed time points

RESULTS

- **Dosing patterns in patients with CLL/SLL treated with 1L single-agent IBR (Table 1)**
  - Among 3514 patients with CLL/SLL treated with 1L single-agent IBR, majority (90%; n = 3174) of patients started at 420 mg/day; 191 patients (5.4%) started at 280 mg/day; 149 patients (4.6%) started at another dosage
  - At a median follow-up of 20 months, 18% (n = 562/3174) of patients who initiated 1L IBR at 420 mg/day had a dose adjustment below 420 mg/day at any time post-index
    - Among the 18% who had any dose adjustment, 50% (n = 280/562) had a dose adjustment within 6 months post-index
    - Majority (85%; n = 478/562) of patient's first dose adjustments were from 420 mg/day to 280 mg/day
    - 70% (n = 396/562) of patients stayed on the lower dose for the remainder of 1L therapy
    - 12% (n = 68/562) of patients returned to the starting dose of 420 mg/day
    - 13% (n = 74/562) of patients further modified dose after the initial dose adjustment

TABLE 1: Dosing patterns in patients with CLL/SLL treated with 1L single-agent IBR

	All patients (n = 3174)	High CV risk (n = 2334)
Follow-up duration, months, median [Q1, Q3]	19.9 [7.8, 38.2]	19.2 [7.5, 37.9]
Had a DA anytime post-index, n (%)	562 (18)	421 (18)
Dose at first DA, n (%)*		
280 mg	478 (85)	356 (85)
140 mg	80 (14)	61 (14)
70 mg	4 (< 1)	4 (< 1)
Time to first DA from index date, n (%)		
≤ 1 month	38 (7)	29 (7)
≤ 2 months	90 (16)	66 (16)
≤ 3 months	147 (26)	111 (26)
≤ 6 months	280 (50)	216 (51)
≤ 12 months	402 (72)	302 (72)
Dosing patterns following first DA, n (%)*		
Stayed on lower dose	396 (70)	301 (71)
Returning to starting dose	68 (12)	42 (10)
Further dose modified	74 (13)	57 (14)
Other dosing patterns	24 (4)	21 (5)

* Percentages may not add up to 100% due to rounding.

1L, first-line; CLL, chronic lymphocytic leukemia; CV, cardiovascular; DA, dose adjustment; IBR, ibrutinib; Q1, 25th percentile; Q3, 75th percentile; SLL, small lymphocytic lymphoma

- **Baseline demographic and clinical characteristics in patients with CLL/SLL who started 1L single-agent IBR at 420 mg/day with or without a dose adjustment within 6 months post-index (Table 2)**
  - Median duration of follow-up is 20 months and not materially different across the 2 cohorts
  - Mean age is 67 years old; mean Quan-Charlson comorbidity index (QCI) is 2.83
  - At baseline, the distributions of demographic and clinical characteristics are numerically comparable among patients with and without an IBR dose adjustment except for:
    - Men: 55% and 65%
    - Initiated IBR prior to 2019: 58% and 52%
    - High CV risk: 77% and 73%
    - Atrial fibrillation: 13% and 7%
    - Cardiac arrhythmia: 18% and 11%
- **Adherence in patients with CLL/SLL who started 1L single-agent IBR at 420 mg/day with or without a dose adjustment within 6 months post-index (Table 3)**
  - Adherence is descriptively similar in the two cohorts: mean PDC is 0.67 and 0.68, and mean MPR is 0.68 and 0.70 in patients with and without an IBR dose adjustment, respectively
- **Time to next treatment among patients treated with 1L single-agent IBR with or without a dose adjustment within 6 months from index date (Figure 3)**
  - Over a median follow-up duration of approximately 20 months, 87% and 85% did not initiate the next LOT in patients with and without an IBR dose adjustment within 6 months post-index, respectively
  - Unadjusted Kaplan-Meier estimates of TTNT and proportions of patients who did not initiate next LOT are descriptively similar in the 2 cohorts
- **High CV risk subgroup**
  - In the high CV risk subgroup (n = 2619), 2334 (89%) initiated IBR at 420 mg/day. IBR dosing patterns following the starting dose are similar to those of the overall study cohort (**Table 1**)
  - In patients with (n = 216) and without (n = 2118) an IBR dose adjustment within 6 months post-index, mean PDC is 0.66 and 0.67, and mean MPR is 0.67 and 0.68, respectively (**Table 3**).
  - TTNT and proportions of patients who did not initiate next LOT are numerically similar in the two cohorts (**Figure 4**)

TABLE 2: Baseline demographic and clinical characteristics in patients with CLL/SLL who started 1L single-agent IBR at 420 mg/day with or without a DA within 6 months post-index

	All patients (n = 3174)	
	With a DA (n = 280)	Without a DA (n = 2894)
Age, years, mean (SD)	67.6 (11.5)	67.3 (10.5)
Men, n (%)	154 (55.0)	1867 (64.5)
Geographic region, n (%)		
Northeast	68 (24.3)	683 (23.6)
Midwest	69 (24.6)	707 (24.4)
South	92 (32.9)	954 (33.0)
West	46 (16.4)	469 (16.2)
Puerto Rico	0 (0.0)	7 (0.2)
Unknown	5 (1.8)	74 (2.6)
Year of 1L IBR initiation, n (%)		
2016	31 (11.1)	426 (14.7)
2017	66 (23.6)	561 (19.4)
2018	66 (23.6)	508 (17.6)
2019	51 (18.2)	503 (17.4)
2020	29 (10.4)	414 (14.3)
2021	30 (10.7)	338 (11.7)
2022	7 (2.5)	144 (5.0)
Follow-up duration, months, median [Q1, Q3]	21.4 [9.8, 41.2]	19.7 [7.6, 37.9]
QCI score, mean (SD)	2.87 (1.68)	2.82 (1.52)
Pancytopenia, n (%)	13 (4.6)	69 (2.4)
Lymphocytosis, n (%)	41 (14.6)	541 (18.7)
Fever, n (%)	30 (10.7)	215 (7.4)
Baseline CV-related comorbidities		
High CV risk, n (%)	216 (77.1)	2118 (73.2)
CHA_2DS_2-VASc Score, mean (SD)	2.33 (1.74)	2.16 (1.66)
Atrial fibrillation, n (%)	36 (12.9)	206 (7.1)
Cardiac arrhythmias, n (%)	51 (18.2)	318 (11.0)
Cardiovascular disease, n (%)	70 (25.0)	745 (25.7)
Hypertension, %	122 (43.6)	1243 (43.0)

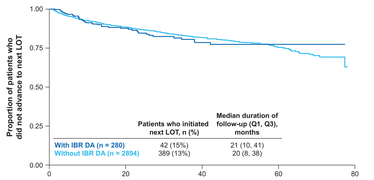
1L, first-line; CLL, chronic lymphocytic leukemia; CV, cardiovascular; DA, dose adjustment; IBR, ibrutinib; Q1, 25th percentile; Q3, 75th percentile; QCI, Quan-Charlson comorbidity index; SD, standard deviation; SLL, small lymphocytic lymphoma

TABLE 3: Adherence in patients with CLL/SLL who started 1L single-agent IBR at 420 mg/day with or without a DA within 6 months post-index

	All patients (n = 3174)		High CV risk (n = 2334)	
	With a DA (n = 280)	Without a DA (n = 2894)	With a DA (n = 216)	Without a DA (n = 2118)
PDC, mean ± SD [median]	0.67 ± 0.30 [0.76]	0.68 ± 0.33 [0.82]	0.66 ± 0.31 [0.76]	0.67 ± 0.33 [0.80]
MPR, mean ± SD [median]	0.68 ± 0.31 [0.78]	0.70 ± 0.33 [0.85]	0.67 ± 0.31 [0.78]	0.68 ± 0.34 [0.82]
≥ 3 months of line of therapy	n = 275	n = 2584	n = 214	n =1889
PDC, mean ± SD [median]	0.89 ± 0.17 [0.98]	0.87 ± 0.22 [0.99]	0.90 ± 0.17 [0.99]	0.86 ± 0.22 [0.99]
MPR, mean ± SD [median]	0.94 ± 0.15 [1.00]	0.90 ± 0.21 [1.00]	0.94 ± 0.14 [1.00]	0.89 ± 0.22 [1.00]
≥ 6 months of line of therapy	n = 244	n = 2294	n = 189	n = 1664
PDC, mean ± SD [median]	0.85 ± 0.19 [0.93]	0.82 ± 0.27 [0.96]	0.86 ± 0.18 [0.94]	0.81 ± 0.28 [0.96]
MPR, mean ± SD [median]	0.89 ± 0.18 [1.00]	0.84 ± 0.27 [1.00]	0.90 ± 0.17 [1.00]	0.83 ± 0.28 [1.00]
≥ 9 months of line of therapy	n = 213	n = 2071	n = 163	n = 1498
PDC, mean ± SD [median]	0.82 ± 0.21 [0.89]	0.78 ± 0.29 [0.94]	0.82 ± 0.21 [0.91]	0.77 ± 0.30 [0.93]
MPR, mean ± SD [median]	0.84 ± 0.21 [0.93]	0.80 ± 0.30 [1.00]	0.85 ± 0.21 [0.94]	0.79 ± 0.31 [1.00]
≥ 12 months of line of therapy	n = 195	n = 1904	n = 152	n = 1373
PDC, mean ± SD [median]	0.78 ± 0.24 [0.87]	0.76 ± 0.31 [0.93]	0.79 ± 0.24 [0.88]	0.74 ± 0.32 [0.92]
MPR, mean ± SD [median]	0.80 ± 0.25 [0.92]	0.78 ± 0.31 [0.99]	0.81 ± 0.25 [0.92]	0.76 ± 0.32 [0.93]

1L, first-line; CLL, chronic lymphocytic leukemia; CV, cardiovascular; DA, dose adjustment; IBR, ibrutinib; MPR, medication possession ratio; PDC, proportion of days covered; SD, standard deviation; SLL, small lymphocytic lymphoma

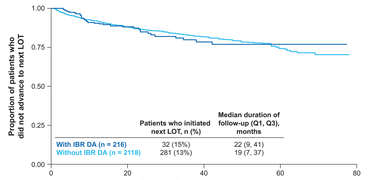
FIGURE 3: Kaplan-Meier survival curves of time to next treatment among patients treated with 1L single-agent IBR with or without dose adjustment within 6 months from index date



	6 months	12 months	24 months	48 months	72 months
With IBR DA (n = 280)					
At risk, n	244	195	129	43	6
Proportion who have not initiated next LOT (95% CI)	97% (95%, 99%)	90% (87%, 94%)	85% (80%, 90%)	77% (71%, 84%)	77% (71%, 84%)
Without IBR DA (n = 2894)					
At risk, n	2294	1904	1236	433	62
Proportion who have not initiated next LOT (95% CI)	95% (94%, 96%)	92% (91%, 93%)	87% (85%, 88%)	80% (77%, 82%)	69% (65%, 74%)

1L, first-line; DA, dose adjustment; IBR, ibrutinib; LOT, line of therapy; Q1, 25th percentile; Q3, 75th percentile

FIGURE 4: Kaplan-Meier survival curves of time to next treatment in the high cardiovascular risk subgroup



	6 months	12 months	24 months	48 months	72 months
With IBR DA (n = 216)					
At risk, n	189	152	99	33	4
Proportion who have not initiated next LOT (95% CI)	98% (96%, 100%)	90% (86%, 95%)	85% (80%, 91%)	77% (70%, 85%)	77% (70%, 85%)
Without IBR DA (n = 2118)					
At risk, n	1664	1373	873	301	42
Proportion who have not initiated next LOT (95% CI)	95% (94%, 96%)	92% (91%, 93%)	86% (85%, 88%)	79% (77%, 82%)	70% (66%, 76%)

1L, first-line; DA, dose adjustment; IBR, ibrutinib; LOT, line of therapy; Q1, 25th percentile; Q3, 75th percentile

LIMITATIONS

- The outcome variable is subject to potential misclassification as claims data can be prone to coding errors
- Given the small window of data availability for this study, misclassification of the line of therapy number during which IBR was received may have occurred. Therefore, patients are referred to as having received single-agent IBR as their first observed regimen (1L)
- As with all claims databases, prescription fills do not account for whether the medication dispensed was taken as prescribed
- Komodo database only captures healthcare data from the insured population who may be systematically different from the uninsured and underserved populations. Therefore, our results may not be directly generalizable to the entire U.S. population

CONCLUSIONS

- In patients with CLL/SLL, including those in the higher CV risk subgroup who initiated 1L single-agent IBR at 420 mg/day, only 18% had a dose adjustment during a median follow-up of 20 months, suggesting that the recommended starting dose was generally well-tolerated in the real-world
- Measures of adherence and probabilities of not initiating the next LOT were numerically comparable in patients with or without a dose adjustment. Similar findings were observed in the subgroup of patients with higher CV risk with or without a dose adjustment
- These real-world findings along with previous clinical trial data[2] suggest that dosing flexibility with IBR may facilitate patients, including those with higher CV risk, to continue to benefit from treatment long-term, and IBR dose adjustments may be an effective management strategy when appropriate in clinical practice

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B-CELL MALIGNANCIES