Comparative Effectiveness of Ibrutinib Flexible Dosing Treatment Strategies on Time to Next Treatment in a Largely Community-Based Claims Database: A Target Trial Emulation Study

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INTRODUCTION

- Ibrutinib, a once-daily Bruton tyrosine kinase inhibitor (BTKi),[1] is recommended as first-line (1L) treatment for patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL)
- Dosing flexibility with ibrutinib helps prevent recurrence or worsening of adverse events while maintaining treatment efficacy[2,3]
  - In the RESONATE-2 clinical trial, patients with CLL/SLL initiating 1L single-agent ibrutinib had comparable progression-free survival and overall survival regardless of dose adjustment (DA); furthermore, DA helped prevent recurrence or worsening of adverse events[3]
  - In a descriptive real-world analysis of patients treated in the 1L setting with or without an ibrutinib DA, no differences in time to next treatment (TTNT) were observed, and patients with DAs had higher adherence than those without DAs[4]
- Formal statistical approaches that mimic a clinical trial in the real-world setting are needed to compare clinical outcomes between patients with or without ibrutinib DAs

OBJECTIVE

- To compare the real-world effectiveness in terms of TTNT as a proxy for disease progression for DA and standard dose treatment strategies in patients with CLL/SLL treated with 1L single-agent ibrutinib, overall and among a subgroup of patients with high cardiovascular (CV) risk

METHODS

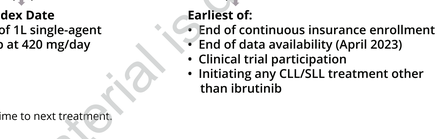
Data source

- This study used the Komodo Healthcare Map payer-complete claims dataset
- Komodo is a claims-based database derived from >150 private insurers in the United States and covers >160 million individuals, with the majority of patients being cared for in community practices

Study design

- In this retrospective observational study, patients with CLL/SLL who initiated 1L single-agent ibrutinib treatment at 420 mg/day were identified from the Komodo database between March 2016 (month of ibrutinib US Food and Drug Administration [FDA] approval for 1L CLL/SLL) and April 2023 (**Figure 1**)
- To preserve the features of randomized clinical trials in the analysis of observational data and to avoid immortal time bias, a target trial emulation (TTE) approach was implemented[5] with 2 treatment strategies:
  - (1) DA strategy: Single-agent ibrutinib treatment at 420 mg/day for 3 to 12 months, followed by DA to any dose below 420 mg/day until the initiation of next treatment or ibrutinib treatment discontinuation
    - Alternative duration of treatment at 420 mg/day before DA: 3 to 6 months; 3 to 9 months
  - (2) Standard dose strategy: Sustained ibrutinib treatment at 420 mg/day for >12 months until the initiation of next treatment or ibrutinib treatment discontinuation
- A successful TTE involves a 2-step process described in **Figure 2**

FIGURE 2: Target trial emulation method



Study population

- Analyses were conducted among all patients with CLL/SLL who initiated single-agent ibrutinib treatment at 420 mg/day, including a subgroup of patients with high CV risk
  - High CV risk subgroup was defined as having ≥1 pre-existing CV comorbidity or being in the "high-risk" category for CHA_2DS_2-VASc (congestive heart failure, hypertension, age, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age, sex category) risk score (≥3 for women; ≥2 for men)

Study outcome measures

- TTNT, used as a surrogate measure for disease progression, was defined as the time from index date to the initiation of next line of therapy
  - For patients treated with 1L single-agent ibrutinib, initiation of an alternative BTKi (i.e., acalabrutinib or zanubrutinib) any time post-index may have indicated a switch due to tolerability rather than progression; therefore, these patients were censored at the time of "in-class" switch
  - In addition, add-on of an anti-CD20 antibody or venetoclax to ibrutinib within 6 months post-index may not have indicated overt disease progression but rather late initiation of a second anticancer agent as a 1L combination treatment strategy; therefore, these patients were censored at time of anti-CD20 or venetoclax add-on

Statistical analysis

- Inverse probability of censoring weights (IPCW) was used to account for time-varying clinical diagnoses related to ibrutinib DA or discontinuation
- TTNT hazard ratio (HR; robust 95% CIs) was estimated using an IPCW-weighted pooled logistic regression model
- Evaluations of alternative lead-in periods with ibrutinib standard dosing (3-6 and 3-9 months) and of a subgroup of patients with high CV risk were also conducted

FIGURE 1: Study design

1L, first-line; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; TTNT, time to next treatment.

B-cell Malignancies

RESULTS

- 3342 adults initiated 1L single-agent ibrutinib at 420 mg/day (**Figure 3; Supplementary Table 1**)
- Mean (SD) age was 67.5 (10.6) years, 62% were men, and mean (SD) Quan-Charlson Comorbidity Index (Quan-CCI) score was 3.0 (1.5)
- 2640 (79%) had high CV risk

Ibrutinib dosing patterns

- Among 3342 patients in the overall study population, 608 (18%) had a DA any time post-index over a median (interquartile range) follow-up duration of 19.6 (7.5-35.0) months (**Table 1**)
  - Of 608 patients who had a DA, 281 patients (46%) had DAs occur between 3- and 12-months post-index
- In the high CV risk subgroup, ibrutinib dosing patterns post-index were similar to those of the overall study cohort

Time to initiation of next treatment

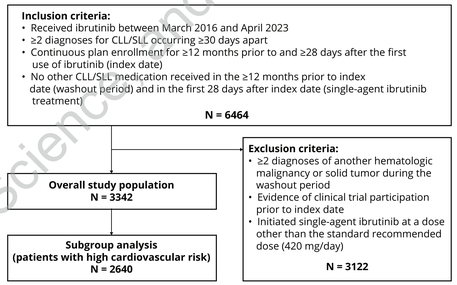
- Next treatment was initiated by 463 of 3342 patients (14%)
- The ibrutinib DA strategy (treatment at 420 mg/day for 3-12 months followed by DA) was not associated with increased risk of initiating next treatment when compared with standard dose strategy (sustained treatment at 420 mg/day for >12 months) (**Figure 4**)

FIGURE 4: Kaplan-Meier survival curves of TTNT comparing the ibrutinib DA strategy to the standard dose strategy in the overall cohort

1L, first-line; DA, dose adjustment; HR, hazard ratio; TTNT, time to next treatment.
[a]Adjusted HR was approximated using odds ratio obtained from a weighted pooled logistic regression model.[6]
[b]Attrition due to artificial censoring that occurred immediately 12 months post-index. Selection bias due to artificial censoring has been corrected using inverse probability of censoring weights in the predicted Kaplan-Meier curves.

- Ibrutinib DA strategy was not associated with increased risk of initiating next treatment when considering alternative durations of treatment with ibrutinib at 420 mg/day prior to DA (3-6 months or 3-9 months) (**Table 2**)
- In the subgroup of patients with high CV risk, results were consistent with the overall study cohort

FIGURE 3: Patient flow chart



CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma.

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

	All patients N = 3342	Patients with high CV risk N = 2640
Had DA anytime post-index, n (%)	**608 (18)**	**476 (18)**
Dose at first DA, n (%)		
70 mg, n/N (%)	4/608 (1)	4 /476 (1)
140 mg	85 (14)	68 (14)
280 mg	519 (84)	404 (84)
Time to first DA from index date, n (%)		
≤1 month, n/N (%)	36/608 (6)	30/476 (6)
≤2 months	96 (16)	73 (15)
≤3 months	159 (26)	127 (27)
≤6 months	300 (49)	246 (52)
≤9 months	377 (62)	308 (65)
≤12 months	440 (72)	351 (74)

1L, first-line; CLL, chronic lymphocytic leukemia; CV, cardiovascular; DA, dose adjustment; SLL, small lymphocytic lymphoma.

TABLE 2: Alternative DA strategies and subgroup analysis

	All patients N = 3342		Patients with high CV risk N = 2640	
Duration of treatment with ibrutinib 420 mg/day prior to DA	**Adjusted HR[a] for DA strategy (95% CI)**	***P* value**	**Adjusted HR[a] for DA strategy (95% CI)**	***P* value**
Primary scenario				
3-12 months	0.95 (0.80-1.14)	0.61	0.93 (0.76-1.13)	0.47
Alternative scenarios				
3-6 months	0.95 (0.76-1.18)	0.64	0.94 (0.74-1.19)	0.59
3-9 months	0.99 (0.82-1.21)	0.96	0.99 (0.79-1.22)	0.89

CV, cardiovascular; DA, dose adjustment; HR, hazard ratio.
[a]Adjusted HR was approximated using odds ratio obtained from a weighted pooled logistic regression model.[6]

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Originally presented at American Society of Hematology (ASH) Meeting and Exposition, December 9-12, 2023, San Diego, CA, USA.
Poster presented at the European Hematology Association (EHA) Hybrid Congress; June 13-16, 2024; Madrid, Spain

LIMITATIONS

- The reasons for ibrutinib DA or discontinuation cannot be ascertained given the administrative nature of the data collected in the Komodo database
- This study used a washout period of 12 months. While a 12-month washout period is common in real-world studies, it may have resulted in the inclusion of patients with CLL/SLL therapy prior to the 12-month period
- Claims data may contain coding errors and omissions. As a result, 2 diagnoses were required to reduce the chance of misclassification of patients with CLL/SLL
- The Komodo database only captures healthcare data from the insured US population who may be systematically different from uninsured and underserved populations. Therefore, our results may not be directly generalizable to the entire US population
- Due to the observational nature of our analyses, unmeasured confounding may remain. However, cloning and IPCW, adjusting for a comprehensive list of factors, were employed to minimize confounding effect

CONCLUSIONS

- In this large, real-world study involving patients with CLL/SLL initiating 1L single-agent ibrutinib at 420 mg/day, a relatively small proportion of patients required a subsequent DA (18% over a median follow-up duration of 19.6 months)
- Ibrutinib DA within 3 to 12 months post-index was not associated with an increased risk of initiating next treatment when compared with continuous standard dose treatment (adjusted HR 0.95 [95% CI, 0.80-1.14])
  - Findings were consistent with alternative DA strategies and among a subgroup of patients with high CV risk
- These results suggest that employing a flexible dosing approach with ibrutinib may be an effective management strategy in achieving an optimal balance between clinical therapeutic effectiveness and safety for patients with CLL/SLL in 1L setting

ACKNOWLEDGMENTS
This study was sponsored by Janssen Scientific Affairs, LLC. Editorial support was provided by Agnieszka Looney, PhD, of ApotheCom, and funded by Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC, a Johnson & Johnson company.

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SUPPLEMENTAL METHODS

SUPPLEMENTAL TABLE 1: Baseline demographics and clinical characteristics

	All patients N = 3342	Patients with high CV risk N = 2640
Age, mean ± SD	67.50 ± 10.58	69.44 ± 10.33
Men, n (%)	2084 (62)	1647 (62)
US Region, n (%)		
Northeast	845 (25)	684 (26)
Midwest	829 (25)	653 (25)
South	1021 (31)	814 (31)
West	521 (16)	390 (15)
Puerto Rico	7 (<1)	6 (<1)
Unknown	119 (4)	93 (4)
Q-CCI, mean ± SD	2.96 ± 1.52	3.11 ± 1.58
Pre-existing CV comorbidities, n (%)		
CHA_2DS_2-VASc Score, mean ± SD	2.30 ± 1.73	2.72 ± 1.68
Atrial fibrillation	254 (8)	254 (10)
Hypertension	1904 (57)	1904 (72)

CV, cardiovascular; Q-CCI, Quan-Charlson Comorbidity Index.