Real-world treatment outcomes in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma who were treated with first-line single-agent ibrutinib or chemoimmunotherapy

Ruibin Wang,[1] Zhijie Ding,[2] Xiaoxiao Lu,[2] Heena Mavani,[2] Jinghua He,[1] Zaina P. Qureshi,[2] Javier Pinilla[3]

[1]Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [2]Janssen Scientific Affairs, LLC, Horsham, PA, USA; [3]Department of Malignant Hematology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

BACKGROUND

- Targeted therapies, including Bruton tyrosine kinase inhibitors (BTKis), have replaced chemoimmunotherapy (CIT) in the guidelines for first-line treatment of chronic lymphocytic leukemia and small lymphocytic lymphoma (CLL/SLL), regardless of patients' clinical or genetic characteristics
- Clinical effectiveness of ibrutinib (IBR)-based therapy, the first-in-class BTKi approved for CLL/SLL, has been established versus CIT across multiple phase 3 trials,[1-3] and confirmed in several real-world studies[4-7]
- The existing real-world evidence has been limited to certain practice settings; therefore, larger, comprehensive studies of community-based sources are needed to evaluate the effectiveness of single-agent IBR or CIT in patients with CLL/SLL

OBJECTIVES

- To describe demographic and clinical characteristics of real-world patients with CLL/SLL who were treated with first-line (1L) single-agent IBR or CIT
- To compare time to next treatment (TTNT) in real-world patients with CLL/SLL treated with 1L single-agent IBR or CIT

METHODS

- This retrospective cohort study examined adult patients with CLL/SLL from the Komodo Health payer-complete dataset who initiated single-agent IBR or CIT as 1L treatment, ie, did not receive any CLL/SLL treatment for ≥ 12 months in the baseline period (**Figure 1**)
  - Komodo Health includes health insurance claims data for over 140 million individuals with commercial, individual, state exchange-purchased, Medicare Advantage, or Medicaid managed-care coverage between January 2015 and October 2022
  - Closed claims in this dataset underwent insurance adjudication
    - 53% of patients with closed claims were from community centers

Identification of Patient Cohorts

- **1L single-agent IBR cohort:** IBR was the first observed medication following a CLL/SLL diagnosis with a washout period of at least 12 months and absence of another antineoplastic agent within 28 days of initiating IBR
- **1L CIT cohort:** CIT was the first observed treatment following a CLL/SLL diagnosis with a washout period of at least 12 months and absence of a targeted therapy (acalabrutinib, duvelisib, ibrutinib, idelalisib, venetoclax, or zanubrutinib) within 28 days of initiating CIT

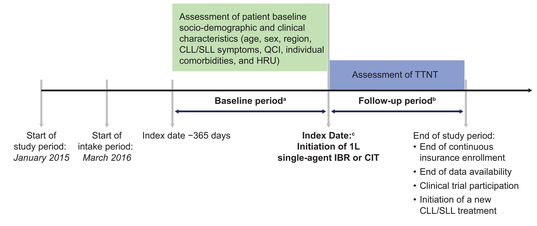
Outcome Definition

- TTNT, used as a proxy for disease progression,[8] was defined as the time from index date to the initiation of next treatment
- Next treatment was defined as one of the following:
  - **In patients who initiated 1L single-agent IBR:** Initiation of a new class add-on or switch that was not part of the 1L regimen and was initiated on or after 29 days from index date or addition of an anti-CD20 antibody or venetoclax after 180 days, with the following exceptions[b]:
    - Initiation of an alternative BTKi (acalabrutinib or zanubrutinib) after index date may have indicated a switch due to tolerability rather than disease progression; therefore, these patients were censored at the time of switch
    - Add-on of an anti-CD20 antibody or venetoclax to IBR within 180 days after index date may not have indicated disease progression, but a delayed initiation of a second anti-cancer agent as a 1L combination treatment strategy; therefore, these patients were censored at time of anti-CD20 or venetoclax add-on
  - **In patients who initiated 1L CIT:** Initiation of a new class add-on or switch that was not part of the 1L regimen or re-initiation of 1L CIT regimen after a treatment gap of at least 120 days

Statistical Analysis

- Demographic and clinical characteristics are reported descriptively
- TTNT was analyzed using weighted Kaplan-Meier estimates and Cox proportional hazard models
  - Propensity score-based inverse probability of treatment weights (IPTW) were created to adjust for potential confounding due to baseline characteristics

Figure 1. Study Design



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

[a]Baseline period was defined as the period from index -365 days to index -1 day, inclusive

[b]Follow-up period was defined as the period from index date to the earliest date of disenrollment from health plan, end of data availability, medical claim indicating participation in a clinical trial, or initiation of a new CLL/SLL treatment

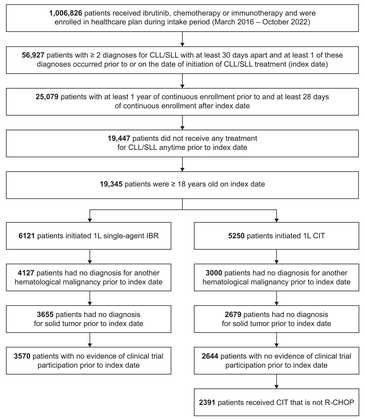
[c]Index date was defined as the date of 1L single agent ibrutinib or CIT initiation

B-CELL MALIGNANCIES

RESULTS

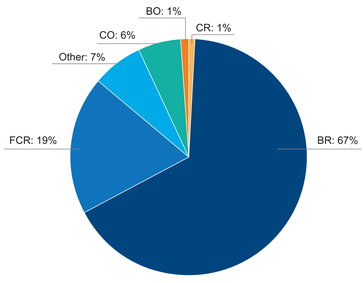
- We identified 5961 eligible patients (IBR, n = 3570; CIT, n = 2391) (**Figure 2**)
  - The most common CIT regimens were bendamustine/rituximab (BR; n = 1599, 67%) and fludarabine/cyclophosphamide/rituximab (FCR; n = 443, 19%) (**Figure 3**)

Figure 2. Patient Attrition



Abbreviations: 1L, first-line; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; IBR, ibrutinib; SLL, small lymphocytic lymphoma; R-CHOP, rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone.

Figure 3. Distribution of 1L CIT Regimens



Abbreviations: 1L, first-line; BO, bendamustine/obinutuzumab; BR, bendamustine/rituximab; CIT, chemoimmunotherapy; CO, chlorambucil/obinutuzumab; CR, chlorambucil/rituximab; FCR, fludarabine/cyclophosphamide/rituximab.

Demographics and Clinical Characteristics

- Before weighting, patients who initiated IBR were, on average, older but had numerically lower mean Quan-Charlson Comorbidity Index (QCI) scores and fewer CLL/SLL-related symptoms during baseline, compared with patients who received 1L CIT (**Table 1**)
- After IPTW weighting, the distributions of baseline characteristics were well balanced between the two cohorts

Table 1. Baseline Demographics and Clinical Characteristics Before and After IPTW Weighting

Characteristics	Number of patients		Percent distribution[a]			
			Unweighted populations		Weighted populations	
	IBR (n = 3570)	CIT (n = 2391)	IBR	CIT	IBR	CIT
Follow-up duration, months, median [IQR]	26 13-44	31 14-52				
Age, years, mean (SD)			68 (11)[b]	64 (10)	67 (11)	67 (11)
Men	2233	1569	63	66	64	64
Geographic region						
Northeast	842	492	24	21	22	23
Midwest	869	676	24	28	26	26
South	1182	768	33	32	32	32
West	580	377	16	16	16	16
PR	7	9	< 1	< 1	< 1	< 1
Unknown	90	69	3	3	3	3
Year of 1L treatment initiation						
2016	499	460	14[b]	19	16	16
2017	684	683	19[b]	29	23	23
2018	649	546	18[b]	23	20	20
2019	639	273	18[b]	11	15	15
2020	494	181	14[b]	8	11	12
2021	433	181	12[b]	8	10	10
2022	172	67	5[b]	3	4	4
Clinical characteristics						
QCI, mean (SD)			2.9 (1.6)[b]	3.1 (1.6)	3.0 (1.6)	3.0 (1.5)
Anemia	1281	1014	36[b]	42	40	39
Leukopenia	49	67	1	3	2	2
Neutropenia	105	142	3[b]	6	4	4
Thrombocytopenia	686	535	19	22	20	21
Pancytopenia	98	138	3[b]	6	4	4
Lymphocytosis	653	473	18	20	19	19
Bleeding	186	150	5	6	6	6
Hepatomegaly	61	68	2	3	2	2
Splenomegaly	651	616	18[b]	26	21	22
Hepatosplenomegaly	89	107	3[b]	5	3	3
Abdominal pain	560	538	16[b]	23	19	19
Autoimmune hemolytic anemia	69	77	2	3	2	2
Chills	18	23	1	1	1	1
Fatigue	955	709	27	30	28	29
Fever	275	229	8	10	9	9
Idiopathic thrombocytopenic purpura	50	33	1	1	2	2
Night sweats	123	100	3	4	4	4
Weight loss	274	263	8[b]	11	9	9
GI disorder	841	662	24	28	26	26
CV-related comorbidities						
CHA_2DS_2-VASc score, mean (SD)			2.3 (1.7)[b]	2.0 (1.7)	2.2 (1.7)	2.2 (1.7)
Cardiovascular disease	935	656	26	27	27	28
Atrial fibrillation	302	198	9	8	9	9
Atrial flutter	27	32	1	1	1	1
Ventricular arrhythmias	1	4	< 1	< 1	< 1	< 1
HRU visits during baseline, mean (SD)						
Outpatient			16.9 (16.6)[b]	19.5 (13.8)	18.8 (22.9)	18.7 (13.4)
Inpatient			0.5 (1.3)[b]	0.8 (1.7)	0.6 (1.5)	0.6 (1.5)
ER			0.4 (1.3)	0.4 (1.1)	0.4 (1.3)	0.4 (1.1)
Non-hospital institution			0.3 (2.6)	0.2 (1.6)	0.2 (2.2)	0.2 (2.2)
Pharmacy			0.01 (0.1)	0.2 (1.6)	0.01 (0.2)	0.01 (0.2)
Home			2.0 (13.5)	1.0 (7.4)	1.6 (10.8)	1.7 (14.1)
Lab			2.6 (4.1)	3.0 (3.6)	2.9 (5.3)	2.8 (3.4)
Ambulance			0.2 (1.8)	0.2 (2.1)	0.2 (1.7)	0.2 (2.1)

Abbreviations: 1L, first-line; CIT, chemoimmunotherapy; CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥ 75, diabetes, stroke, vascular disease, age 65 to 74 and sex category (female); CV, cardiovascular; ER, emergency room; GI, gastrointestinal; HRU, healthcare resource utilization; IBR, ibrutinib; IQR, interquartile range; QCI, Quan-Charlson comorbidity index; SD, standard deviation.

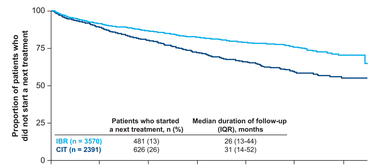
[a]Data are percent distribution of patients unless otherwise stated.

[b]Standardized mean difference IBR vs. CIT > 0.1.

Time to Next Treatment

- Over a median duration of follow-up of 26 months (IBR) and 31 months (CIT), next treatment was initiated in 14% and 26% of patients, respectively (**Figure 4**)
- Treatment with 1L single-agent IBR was associated with a significantly lower risk of initiating next treatment compared with 1L CIT (adjusted hazard ratio = 0.61, $p < 0.001$)
- Findings were consistent across individual CIT regimens, including BR and FCR (**Table 2**)

Figure 4. Weighted Kaplan-Meier Estimates of TTNT Among Patients Treated With 1L Single-Agent IBR Versus 1L CIT



	12 months	24 months	48 months	72 months
IBR				
At risk, n	2366	1530	521	73
Probability of not starting a next treatment,% (95% CI)	92 (91-93)	87 (86-88)	79 (77-81)	70 (66-74)
CIT				
At risk, n	1632	1116	449	36
Probability of not starting a next treatment,% (95% CI)	88 (87-89)	79 (77-81)	63 (61-66)	52 (48-56)

Abbreviations: 1L, first-line; CIT, chemoimmunotherapy; IBR, ibrutinib; IQR, interquartile range.

TABLE 2: Adjusted HR of Initiating Next Treatment: 1L IBR versus 1L CIT

Population	Hazard ratio for IBR (95% CI)	*p*-value
IBR (n = 3570) vs any CIT (n = 2391)	0.61 (0.55-0.69)	<0.001
IBR (n = 3570) vs BR (n = 1599)	0.62 (0.55-0.72)	<0.001
IBR (n = 3570) vs FCR (n = 443)	0.52 (0.35-0.85)	0.001

Abbreviations: 1L, first-line; BR, bendamustine/rituximab; CI, confidence interval; CIT, chemoimmunotherapy; FCR, fludarabine/cyclophosphamide/rituximab; IBR, ibrutinib.

LIMITATIONS

- The outcome variables were subject to potential misclassification as claims data can be prone to coding errors
- Given the observational nature of this study, residual or unmeasured confounding was possible
- Given the small window of data availability, misclassification of the line of treatment during which IBR or CIT was received was possible; therefore, 1L classification was based on having received single-agent IBR or CIT as the first observed regimen
- The Komodo database does not include laboratory data; therefore, we were not able to account for the difference in the distributions of high-risk cytogenetic marker carriers or perform sensitivity analyses in subgroups of patients with different mutation profiles

CONCLUSIONS

In insured patients with CLL/SLL, 1L treatment with single-agent IBR was associated with a significantly lower risk of initiating next treatment compared with 1L CIT, regardless of CIT regimen type. This finding reinforces the effectiveness of 1L IBR for CLL/SLL in a real-world setting

ACKNOWLEDGMENTS

This study was sponsored by Janssen Scientific Affairs, LLC.
Editorial support was provided by Cindi A. Hoover, PhD, of ApotheCom, and funded by Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC

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Presented at the biennial International Workshop on Chronic Lymphocytic Leukemia (XX iwCLL 2023); October 7-9, 2023; Boston, Massachusetts, USA.

This abstract was accepted at the 2023 ASCO Annual Meeting.