Retrospective Analysis of Real-World Outcomes of Chronic/Small Lymphocytic Leukemia (CLL/SLL) Patients Treated With First-Line Ibrutinib Versus Chemoimmunotherapy (CIT)

Tao Ran[1], Jinghua He[1], Linda Wu[2], Sumeet Panjabi[1], Xiaoxiao Lu[2]

[1]Janssen Scientific Affairs, LLC, Titusville, NJ, USA; [2]Janssen Scientific Affairs, LLC, Horsham, PA, USA

BACKGROUND

- Chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) is a malignancy in which the bone marrow produces excessive amounts of abnormal lymphocytes[1].
- CLL is a progressive disease, with some patients progressing faster, known as high risk patients, characterized by cytogenetic abnormalities[2] (e.g., chromosomal 17p or 11q deletion, or unmutated IGHV).
- The National Comprehensive Cancer Network's recommended treatments for CLL/SLL include targeted therapies (e.g. ibrutinib) and chemoimmunotherapy (CIT) - such as fludarabine-cyclophosphamide-rituximab (FCR), and bendamustine-rituximab (BR).
- Ibrutinib is an oral, once daily Bruton's tyrosine kinase inhibitor (BTKi) approved for the treatment of adults with CLL/ SLL[3].
- Ibrutinib is the only targeted treatment that has demonstrated progression-free survival and overall survival in multiple phase 3 trials across age, fitness, and high-risk markers for CLL/SLL.

OBJECTIVES

- To describe testing trends (cytogenetic/FISH and IGHV) among 1L CLL patients
- To describe the demographic and clinical characteristics of CLL/SLL patients treated with first-line (1L) ibrutinib or chemoimmunotherapy (CIT)
- To compare time to next treatment (TTNT) between 1L ibrutinib and CIT, including high-risk and IGHV-untested subgroups

METHODS

Data source

The study utilized the Flatiron CLL Core Registry database in the United States (US). The dataset consists of de-identified electronic health records enabling a longitudinal data view of cancer patients with resolution at the disease and treatment level. Flatiron extracts and processes both structured and unstructured real-world clinical data collected from the electronic health records (EHRs) used by cancer care providers across the US.

Study design

- For testing trend, 1L patients who had genetic testing records in Flatiron data in four periods (January 2007-July 2014, August 2014-August 2016, September 2016-July 2017, and August 2017-September 2021) were identified.
- A retrospective cohort study was conducted for the comparison of 1L ibrutinib and CIT comparison.
- Included patients had diagnosis of CLL/SLL, with 1L ibrutinib or CIT initiated between 03/04/2016 09/31/2021 (index date defined as the date of 1L treatment initiation)
- Excluded patients with missing date of first systemic therapy for CLL; patients with line 0; patients whose first date of systemic therapy for CLL is >30 before 1L start date; patients who started 1L before the diagnosis of CLL.
- Monotherapy was defined as the absence of other antineoplastic agents within 28 days of initiation of ibrutinib

The follow-up period was defined as the period from the index date to the earliest of initiation of second-line (2L) therapy or patients' last clinical activity, or death

- Two subgroup analyses were performed in addition to the overall patients:
  - Patients with observed high-risk cytogenetic markers (deletion 17p, 11q or unmutated IGHV)
  - Patients without IGHV testing results

Outcomes

- TTNT was defined as the interval from the initiation of 1L to the initiation of 2L. Patients were censored when last activity or death was observed

Statistical analyses

- Baseline characteristics were reported using means, standard deviations (SDs), and medians for continuous variables, and frequencies and proportions for categorical variables.
- Baseline characteristics were summarized by using standard mean difference between the ibrutinib and CIT cohorts.
- Kaplan-Meier (KM) analysis was used to evaluate TTNT from 1L initiation.
- TTNT was compared between the 1L users of ibrutinib mono vs. CIT by using COX proportional hazard model.
- Missing baseline covariates were imputed by using the multiple imputation (MI).
- Baseline differences were adjusted by using propensity score-based inverse probability of treatment weighting (IPTW). Baseline covariate balance after weighting was examined using standardized mean differences (SMD) with absolute SMD values < 0.1 indicative of good balance.

B-CELL MALIGNANCIES

RESULTS

Genetic testing

- Out of 1L CLL patients who had the testing records, the rate of genetic testing increased from 2007 to 2019 especially after adding ibrutinib to 1L CLL with del17p treatment in NCCN guidelines v4.2014 (from 52.3% in 2007-2014 to 74.3% in 2017-2021), although a smaller proportion was tested for IGHV (from 13.1% in 2007-2014 to 37.7% in 2017-2021).

Ibrutinib and CIT comparison

- A total of 3,064 CLL/SLL patients were included in the current study after applying the inclusion and exclusion criteria:
  - 1,882 patients (61.4%; mean [SD] age 71 [9.4] years)
  - 1,182 (38.6%; mean [SD] age 68 [9.9] years)
- Patient characteristics before multiple imputation and IPTW are summarized in **Table 1**.

FIGURE 1: Testing Trend

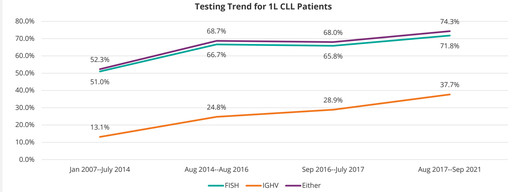


TABLE 1. Baseline demographics and clinical characteristics before multiple imputation and weighting

	Ibrutinib		CIT		Standardized Mean Difference
All patients, n	**1,882**		**1,182**		
Age groups (years), n (%)					
0 to <65	417	22.2%	431	36.4%	31.8%
65 to <70	273	14.4%	217	18.4%	10.4%
70 to <75	389	20.7%	208	17.6%	7.8%
75 to <80	316	16.8%	150	12.7%	11.6%
>=80	487	25.9%	176	14.9%	27.5%
Gender, n (%)					
Female	1,151	61.2%	788	66.7%	11.5%
Male	731	38.8%	394	33.3%	11.5%
Race (n, %)					
White	1,384	73.5%	863	73.0%	1.2%
Black or African American	158	8.4%	107	9.0%	2.3%
Asian	19	1.0%	8	0.7%	3.6%
Other	161	8.6%	111	9.4%	2.9%
Unknown/missing	160	8.5%	93	7.9%	2.3%
Year of index date, n (%)					
2016	229	12.2%	266	22.5%	27.6%
2017	330	17.5%	347	29.4%	28.2%
2018	370	19.7%	321	27.2%	17.8%
2019	522	27.7%	147	12.4%	38.9%
2020	334	17.7%	78	6.6%	34.6%
January-August 2021	97	5.2%	23	1.9%	17.4%
Time from initial diagnosis to index date, days, mean (SD)	1,402	1809.1	1,085	1413.9	19.5%
Time from initial diagnosis to index date, n (%)					
≤1 year	675	36%	503	43%	13.7%
≥1 year	1,207	64%	679	57%	13.7%
Rai Stage (n, %)					
Stage 0	558	29.6%	265	22.4%	16.5%
Stage I	261	13.9%	182	15.4%	4.3%
Stage II	106	5.6%	82	7.0%	5.4%
Stage III	107	5.7%	75	6.3%	2.8%
Stage IV	134	7.1%	137	11.6%	15.4%
Unknown/not documented	716	38.1%	441	37.3%	1.5%
ECOG PS (n, %)					
0	749	39.8%	497	42.0%	4.6%
1	529	28.1%	363	30.7%	5.7%
2	139	7.4%	57	4.8%	10.7%
3	32	1.7%	8	0.7%	9.5%
4	3	0.2%	2	0.2%	0.2%
Unknown/missing	430	22.8%	255	21.6%	3.1%
Disease type (n, %)					
CLL	1,548	82.2%	884	74.8%	18.3%
CLL/SLL	205	10.9%	160	13.5%	8.1%
SLL	129	6.9%	138	11.7%	16.7%
Follow-up time (months), mean, median	26	23.3	33	30.4	
CCI score (mean, SD)	2.4	1.3	2.4	1.2	0.9%
Cytogenetic risk of del 17p, del 11q, or unmutated IGHV (n, %)					
Presence (any of the three)	819	43.5%	402	34.0%	19.6%
Absence (none of the three)	209	11.1%	182	15.4%	12.7%
Unknown/untested	854	45.4%	598	50.6%	10.5%

Abbreviations: CCI: Charlson Comorbidity Index; CIT, chemoimmunotherapy; CLL: chronic lymphocytic leukemia; ECOG: Eastern Cooperative Oncology Group Performance Status; SD: standard deviation; SLL: small lymphocytic lymphoma.

- Compared to CIT users, CLL patients treated by ibrutinib were slightly older and more likely to have high-risk cytogenetic markers (43.5% vs. 34.0%), especially those with del17p (15% vs 4%).
- The rate of unknown IGHV mutation status is approximately 50% in the included CLL/SLL cohort.
- After IPTW, the imputed baseline characteristics were well balanced between the two comparison groups with all Standardized mean differences < 10%

- **Table 2 and Figure 2** summarized comparative analysis results of 1L ibrutinib vs. CIT regarding TTNT after IPTW
  - Ibrutinib is associated with a significantly 51% lower risk of initiating 2L treatment than CIT in the overall patients (HR = 0.49). Similar results were found in the subgroups of patients without IGHV testing.
  - For high-risk group, ibrutinib is associated with 60% lower risk of initiating 2L treatment than CIT in the overall patients (HR = 0.40).

TABLE 2. Time to next treatment in patients receiving 1L ibrutinib monotherapy versus CIT

	Median TTNT (months)		Hazard Ratio		
	Ibrutinib	CIT	Ibrutinib vs. CIT	95% CI	p-value
Overall population (n=3064)	Not reached	39.6	0.49	0.44-0.54	<0.001
High-risk* subgroup (n=1221)	Not reached	32.1	0.40	0.34-0.47	<0.001
Untested IGHV subgroup (n=1806)	Not reached	44.9	0.51	0.44-0.58	<0.001

Abbreviations: CI, confidence interval; CIT, chemoimmunotherapy; HR, hazard ratio; TTNT, time to next treatment.
*High-risk: presence of ≥1 of the following: deletion 17p, deletion 11q, IGHV unmutated.

FIGURE 2: Weighted Kaplan-Meier curves for TTNT comparison

FIGURE 2.1

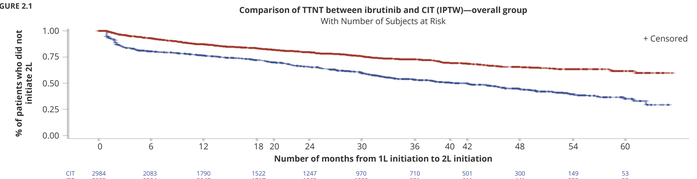


FIGURE 2.2

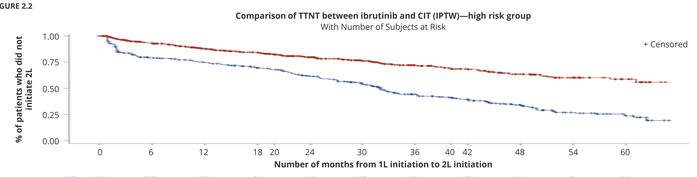
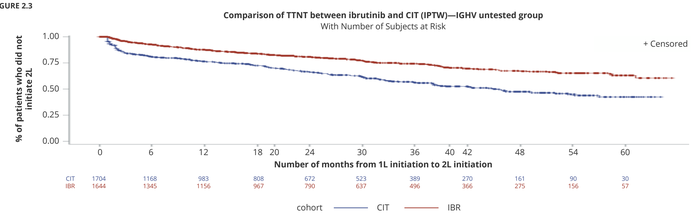


FIGURE 2.3



LIMITATIONS

- The Flatiron database does not capture treatments and healthcare services received outside of the network.
- The "missing at random" assumption for multiple imputation cannot be validated.
- Although a propensity score method was used to adjust for baseline confounders, residual confounding due to unobserved confounders may remain. The current findings should be interpreted as the association instead of causality.

CONCLUSIONS

- First-line treatment of ibrutinib monotherapy in CLL/SLL patients was associated with a statistically significantly lower risk of initiating subsequent treatment compared with CIT
- Similar findings were observed in the high-risk and IGHV-untested subgroups
- Genetic risk testing rate increased among CLL patients over time, although IGHV testing remains suboptimal. Improvement of testing rate is warranted in order to optimize clinical and economic outcomes, especially in the novel agent era

ACKNOWLEDGMENTS

Supported by Janssen Scientific Affairs, LLC.

Scan the QR code

https://www.congresshub.com/Oncology/SOHO2022/Ibrutinib/Lu-Persistence

The QR code is intended to provide scientific information for individual reference, and the information should not be altered or reproduced in any way.

REFERENCES:

1. Zelenetz AD, et al. *J Natl Compr Canc Netw.* 2015;13(3):326-362. 2. Döhner H, Stilgenbauer S, Benner A, et al. Genomic aberrations and survival in chronic lymphocytic leukemia. *N Engl J Med.* 2000;343(26):1910-6. 3. IMBRUVICA (ibrutinib) Full Prescribing Information. Pharmacyclics, LLC, Janssen Biotech, Inc. May 2022.

Presented at the 10th Society of Hematologic Oncology (SOHO) Annual Meeting, September 28-October 1, 2022, Houston, TX, USA