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First-Line Ibrutinib Treatment Is Associated With Longer Time to Next Treatment in a Real-World US Veteran Population

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OBJECTIVE

To evaluate time to next treatment (TTNT) among US veterans diagnosed with chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), who initiated first-line (1L) single-agent ibrutinib vs 1L chemoimmunotherapy (CIT), and 1L ibrutinib vs ibrutinib in second-line/third-line (2L+).

BACKGROUND

- CLL and SLL account for ~7% of newly diagnosed non-Hodgkin's lymphoma (NHL) cases.[1]
- In 2019, an estimated 20,720 people will be diagnosed with CLL in the United States, accounting for 1.2% of all new cancer cases.[2]
- The incidence of CLL is 2 times higher in men, and ~70% of patients are ≥65 years of age at time of diagnosis.[3] Additionally, positive family history of CLL, European ancestry, and exposure to chemicals such as Agent Orange and pesticides are considered risk factors of CLL.[4] Considering these risk factors, veterans have a higher risk for CLL as related to exposure to Agent Orange/other herbicides during military service.[5]
- The National Comprehensive Cancer Network (NCCN)-recommended treatments for CLL/SLL include targeted therapies such as ibrutinib and intravenous CD20 monoclonal antibody-based chemoimmunotherapy (CIT), such as fludarabine, cyclophosphamide, rituximab (FCR) and bendamustine plus rituximab (BR).[6]
- Ibrutinib, an oral inhibitor of Bruton's tyrosine kinase, was initially approved by the US Food and Drug Administration in February 2014 for the treatment of CLL after receiving ≥1 prior therapy and subsequently approved on July 28,2014 as 1L treatment for patients with del (17p) and on March 04, 2016 as 1L treatment for all CLL patients. Ibrutinib is now the only preferred regimen (NCCN Category 1) for 1L CLL treatment regardless of age, fitness, or comorbidities. [6]
- Previous real-world studies demonstrated that 1L ibrutinib treatment is associated with a significantly longer TTNT as well as lower HRU and net total cost reduction than 1LCIT in CLL patients.[7,8]
- However, limited evidence is available on the outcomes in US veterans with CLL/SLL initiating ibrutinib.

MATERIALS AND METHODS

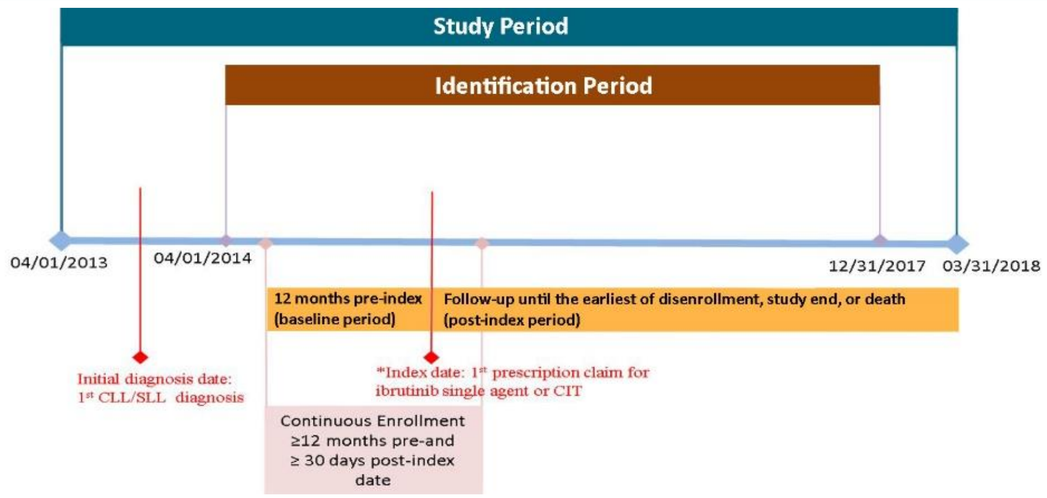
Data Source

- The Veterans Health Administration (VHA) database population was assessed for the period of 04/01/2013 through 03/31/2018.
- The VHA is the largest integrated health care system in the United States, providing care at 1,250 facilities, including 172 VA medical centers and 1,069 outpatient sites of care of varying complexity to over ~9 million veterans across the country.[9]

Study Design

A retrospective study design was used (**Figure 1**).

Figure 1. Study Design

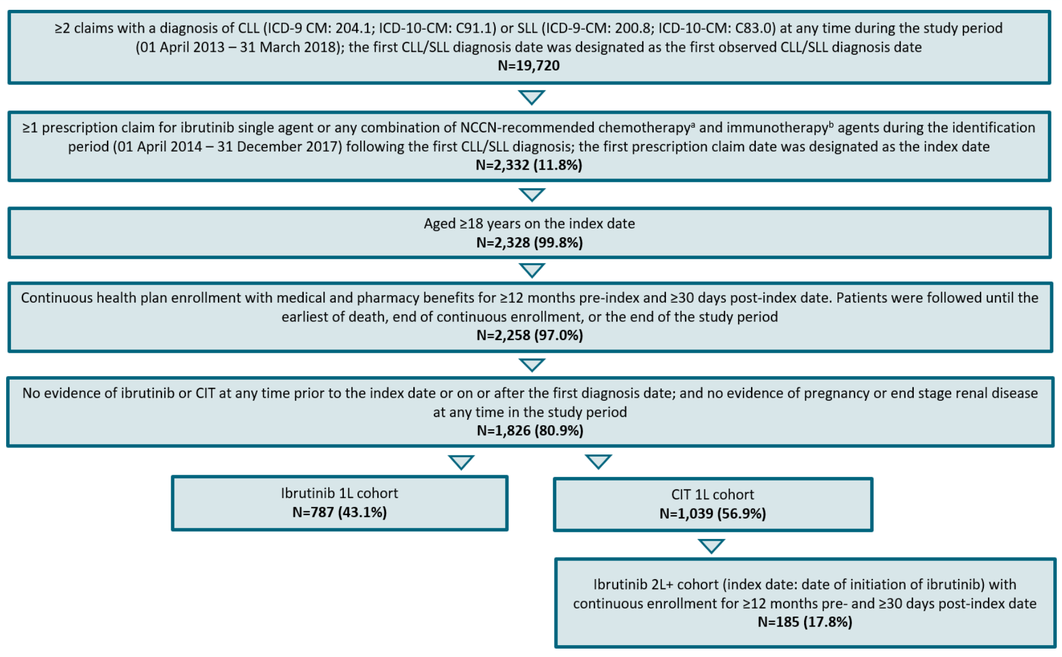


CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma
** Only the patients who were prescribed ibrutinib single agent were considered and those who might have received CD20 agents together with the ibrutinib were excluded. The index date for the 2L+ ibrutinib cohort was defined by the date of initiation of ibrutinib in the 2L or 3L. Ending the identification period three months prior to the end of the data availability is intentional, to exclude patients with limited follow-up*

Study Population

Inclusion and exclusion criteria are detailed in **Figure 2**.

Figure 2. Selection Criteria



1L: first-line therapy; 2L: second-line therapy; CIT: chemoimmunotherapy; CLL: chronic lymphocytic leukemia; SLL: small lymphocytic lymphoma; ICD-9/10-CM: International Classification of Diseases, Ninth/Tenth Revision Clinical Modification code; NCCN: National Comprehensive Cancer Network; SLL: small lymphocytic lymphoma; [a]Chemotherapy agents included bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, fludarabine, lenalidomide, oxaliplatin, pentostatin, vincristine, and cladribine; [b]Immunotherapy agents included alemtuzumab, obinutuzumab, ofatumumab, and rituximab

- Based on the 1L treatment received, patients were assigned into the ibrutinib 1L cohort (ibrutinib single-agent) or the CIT 1L cohort (CIT regimen; agents prescribed within 30 days of the index date constituted the index regimen).
- In the CIT 1L cohort, the subgroup of patients treated with a single ibrutinib agent in the 2L/3L were identified and included in the ibrutinib 2L+ cohort.
- Comparisons were performed between the following cohorts: Ibrutinib 1L vs CIT 1L, and ibrutinib 1L vs ibrutinib 2L+

Study Measures

Outcomes

TTNT was defined as the period from the index date to the initiation of next-line treatment. Patients without evidence of next-line treatment or lost to follow-up were censored. The 1L therapy included agents prescribed within 30 days of the index date through the earliest of:

- addition or subtraction of any agent to the index regimen;
- initiation of a non-index regimen;
- resumption of index regimen after >90-day gap; or
- death/end of continuous health plan enrollment/study end.

Baseline Variables

- Demographic characteristics including age, sex, and race as of the index date were measured, and index year was reported.
- The following clinical characteristics in the 12-month baseline (pre-index) period were examined:
  - Quan-Charlson Comorbidity Index (Q-CCI) score;
  - Clinical conditions of interest: abdominal pain, anemia, autoimmune hemolytic anemia, enlarged lymph nodes, fatigue/weakness, fever, lymphocytosis, thrombocytopenia, weight loss, atrial fibrillation, and major bleeding; and
  - Baseline medications: antiplatelet drugs, anticoagulants, proton pump inhibitors, dexamethasone, prednisone, methylprednisolone, and antidepressants.

Statistical Analyses

- Descriptive statistics were provided for all variables including demographic and clinical characteristics for all study cohorts.
- Chi-square and Student t-tests were used to evaluate the statistical significance for categorical and continuous variables, respectively.
- Propensity Score Matching (PSM)
  - Patients in ibrutinib 1L cohort were matched 1:1 to those in the CIT 1L and ibrutinib 2L+ cohorts, using nearest neighbor matching with a caliper width of 0.2 of the standard deviation of the logit of the propensity score.
  - Covariates used in propensity score calculation included demographics, index year, and clinical characteristics.
  - Adequacy of the matching procedure was assessed using the standardized difference (STD); STD<10% is considered well balanced.[10]
- Kaplan Meier (KM) curves and Cox proportional hazards models were used to evaluate and compare TTNT in the propensity score matched cohorts.
- Covariates adjusted in the Cox model for ibrutinib 1L vs CIT 1L included baseline inpatient length of stay (LOS) and baseline all-cause total costs. Covariates adjusted in the Cox model for ibrutinib 1L vs ibrutinib 2L+ included baseline demographic and clinical characteristics (age, race, index year, anemia, autoimmune hemolytic anemia, atrial fibrillation, dexamethasone), number of inpatient visits PPPM, number of outpatient visits PPPM, inpatient LOS, and baseline all-cause inpatient, outpatient, and total costs. Covariates were chosen based on literature for potential confounders along with covariates that were not balanced after PSM.

RESULTS

- After applying the sample selection criteria, there were a total of 787 patients in the ibrutinib 1L cohort and 1,039 patients in the CIT 1L cohort. Of those CIT 1L patients, 597 initiated BR (57.5%), 150 initiated FCR (14.4%), and 94 initiated chlorambucil + obinutuzumab (9.0%).
- Additionally, among the ibrutinib 1L patients, 146 (18.6%) had evidence of 2L, of whom 92 (63.0%) restarted ibrutinib as a 2L regimen. In contrast, among the CIT 1L patients, 409 (39.4%) had evidence of next line, of whom 185 (45.2%) had ibrutinib as a 2L/3L regimen.

Baseline Characteristics

Before PSM

- Compared to patients in the CIT 1L cohort, those in the ibrutinib 1L cohort:
  - were significantly older and had higher proportion of male and Caucasian patients;
  - had significantly lower mean Q-CCI score, and lower percentage of patients with anemia, enlarged lymph nodes, fatigue/weakness, fever, and lymphocytosis; and
  - had significantly lower percentage of patients with baseline medications including anticoagulant agents, dexamethasone, prednisone, and methylprednisone.
- A similar trend was observed when demographic and clinical characteristics between the ibrutinib 1L and the ibrutinib 2L+ cohort s were compared.

Table 1. Comparison of Baseline Demographic and Clinical Characteristics After PSM for the Ibrutinib 1L vs CIT 1L and Ibrutinib 2L+ Cohorts

	Ibrutinib 1L Cohort (N=614)		CIT 1L Cohort (N=614)		STD	Ibrutinib 1L Cohort (N=149)		Ibrutinib 2L+ Cohort (N=149)		STD
	N/ Mean	%/ SD	N/ Mean	%/ SD		N/ Mean	%/ SD	N/ Mean	%/ SD	
Demographics										
Age (in years)	71.8	10.4	71.3	10.6	5.1	73.9	12.2	70.5	9.9	30.4
< 60	38	6.19%	45	7.33%	4.5	NA	NA	13	8.7%	13.1
60-64	50	8.14%	52	8.47%	1.2	NA	NA	14	9.4%	12.6
65-69	197	32.08%	201	32.74%	1.4	44	29.5%	46	30.9%	2.9
70-74	159	25.90%	151	24.59%	3.0	32	21.5%	42	28.2%	15.5
75-79	82	13.36%	79	12.87%	1.4	17	11.4%	13	8.7%	8.9
≥80	88	14.33%	86	14.01%	0.9	39	26.2%	21	14.1%	30.4
Sex										
Male	610	99.35%	607	98.86%	5.2	148	99.3%	147	98.7%	6.7
Race										
Caucasian	488	79.48%	482	78.50%	2.4	120	80.5%	113	75.8%	11.4
African American	82	13.36%	90	14.66%	3.8	19	12.8%	26	17.4%	13.1
Other or Unknown	44	7.17%	42	6.84%	1.3			NA		
Index Year										
2014	86	14.01%	97	15.80%	5.0	17	11.4%	NA	NA	16.4
2015	130	21.17%	131	21.34%	0.4	24	16.1%	29	19.5%	8.8
2016	194	31.60%	195	31.76%	0.3	51	34.2%	54	36.2%	4.2
2017	204	33.22%	191	31.11%	4.5	57	38.3%	56	37.6%	1.4
Clinical Characteristics										
Quan Charlson Comorbidity Index Score	3.5	2.0	3.7	2.1	8.3	3.8	2.2	3.8	2.2	0.1
Clinical Conditions of Interest										
Abdominal pain	45	7.33%	42	6.84%	1.9	13	8.7%		NA	
Anemia	158	25.73%	165	26.87%	2.6	40	26.8%	56	37.6%	23.1
Autoimmune hemolytic anemia	12	1.95%	14	2.28%	2.3			NA		
Enlarged lymph nodes	112	18.24%	105	17.10%	3.0	32	21.5%	28	18.8%	6.7
Fatigue/weakness	49	7.98%	45	7.33%	2.4	22	14.8%	20	13.4%	3.8
Fever	12	1.95%	16	2.61%	4.4			NA		
Lymphocytosis	19	3.09%	19	3.09%	0.0			NA		
Thrombocytopenia	82	13.36%	89	14.50%	3.3	25	16.8%	26	17.4%	1.8
Weight loss	40	6.51%	43	7.00%	1.9	16	10.7%	14	9.4%	4.4
Atrial fibrillation	49	7.98%	52	8.47%	1.8	17	11.4%		NA	
Major bleeding	26	4.23%	24	3.91%	1.6			NA		
Baseline Medications										
Antiplatelet drugs	141	22.96%	140	22.80%	0.4	27	18.1%	29	19.5%	3.4
Anticoagulant agents	52	8.47%	60	9.77%	4.5	18	12.1%	19	12.8%	2.0
Dexamethasone	20	3.26%	26	4.23%	5.1	18	12.1%	30	20.1%	22.0
Prednisone	83	13.52%	87	14.17%	1.9	34	22.8%	36	24.2%	3.2
Methylprednisolone	19	3.09%	16	2.61%	2.9	NA	NA	12	8.1%	5.1
Proton pump inhibitors	217	35.34%	208	33.88%	3.1	61	40.9%	59	39.6%	2.7
Antidepressants	30	4.89%	29	4.72%	0.8			NA		

1L: first-line therapy; CIT: chemoimmunotherapy; PSM: propensity score matching; SD: standard deviation; STD: standardized difference
*Demographic and clinical characteristics with a prevalence of ≤11 were denoted as NA to preserve patient confidentiality. *Variables used in the propensity score calculation included age (mean and <60, 60-64, 65-69, 70-74, 75-79, and ≥80 years), sex (male), race (Caucasian, African American, other or unknown), index year, baseline clinical conditions of interest and baseline medications*

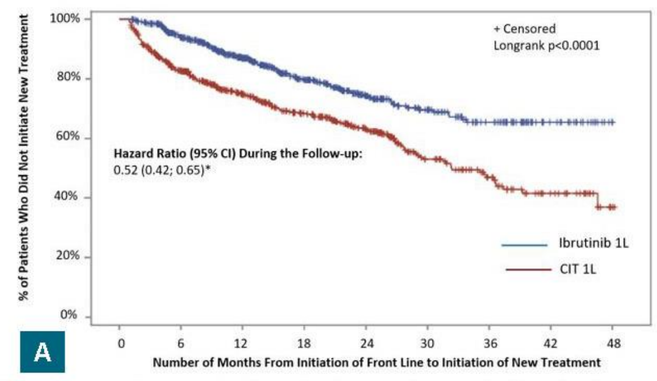
After PSM

- A total of 614 patients were included in each of the matched ibrutinib 1L vs CIT 1L cohorts, and were well-balanced with respect to all demographic and clinical characteristics examined. Additionally, 149 patients were included in each of the ibrutinib 1L and ibrutinib 2L+ cohorts, the cohorts were well-balanced in general with a few remaining differences in baseline characteristics due to limited sample size **(Table 1)**.
- The mean length of follow-up period was 19.8 months (standard deviation [SD]: 12.0 months; median: 17.6 months) in the ibrutinib 1L cohort and 21.5 months (SD: 12.8 months; median: 20.2 months) in the CIT 1L cohort.
- The duration of 1L therapy (active treatment period + no treatment period before starting 2L) was 17.4 months (SD: 11.6 months; median: 14.4 months) in the ibrutinib 1L cohort and 15.9 months (SD: 12.1 months; median: 13.0 months) in the CIT 1L cohort.
- Additionally, in the ibrutinib 1L vs ibrutinib 2L+ cohorts, the mean length of follow-up period was 16.7 months (SD: 11.5 months; median: 13.1 months) and 16.9 months (SD: 10.5 months; median: 14.8 months), respectively.
- Similarly, in the ibrutinib 1L vs ibrutinib 2L+ comparison, the duration of 1L therapy was 15.9 months (SD: 11.9 months; median: 12.9 months) in ibrutinib 1L cohort and the duration on 2L/3L therapy was 13.7 months (SD: 10.1 months; median: 11.6 months) in ibrutinib 2L+ cohort.

Time to Next Treatment

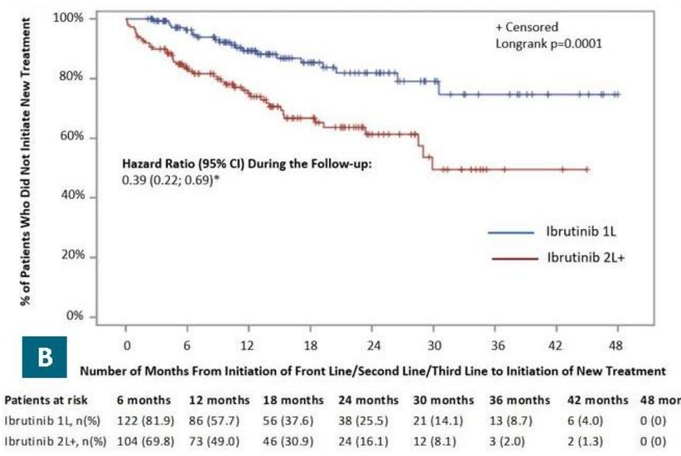
- KM analysis of TTNT revealed that, at 30 months and 48 months post-index, 69.6% and 65.4% of ibrutinib 1L patients did not require subsequent treatment, compared to 53.0% and 36.9% among CIT 1L patients, respectively (log-rank *P*<0.0001; **Figure 3A).** Median TTNT was not reached in the ibrutinib 1L cohort during the available follow-up period.
- At 30 months post-index, 79.1% of ibrutinib 1L patients did not require subsequent treatment vs 49.5% among ibrutinib 2L+ patients. Similar percentages were observed at 48 months (log-rank *P*=0.0001; **Figure 3B**).
- During the follow-up period, the hazard of initiating a new treatment was also lower for patients treated with ibrutinib 1L vs CIT 1L **(**48% lower; **Figure 3A)** or ibrutinib 2L+ **(**61% lower; **Figure 3B).**

Figures 3A-B. Comparison of TTNT for (A) Ibrutinib 1L vs CIT 1L Cohort and (B) Ibrutinib 1L vs Ibrutinib 2L+ Cohort



A

Patients at risk	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Ibrutinib 1L, n(%)	510 (83.1)	361 (58.8)	247 (40.2)	156 (25.4)	99 (16.1)	63 (10.3)	24 (3.9)	1 (0.2)
CIT 1L, n(%)	453 (73.8)	322 (52.4)	237 (38.6)	161 (26.2)	82 (13.4)	51 (8.3)	23 (3.7)	2 (0.3)



B

Patients at risk	6 months	12 months	18 months	24 months	30 months	36 months	42 months	48 months
Ibrutinib 1L, n(%)	122 (81.9)	86 (57.7)	56 (37.6)	38 (25.5)	21 (14.1)	13 (8.7)	6 (4.0)	0 (0)
Ibrutinib 2L+, n(%)	104 (69.8)	73 (49.0)	46 (30.9)	24 (16.1)	12 (8.1)	3 (2.0)	2 (1.3)	0 (0)

1L: first-line therapy; 2L: second-line therapy; CIT: chemoimmunotherapy; CI: confidence interval; TTNT: time to next treatment.

**Indicates p-value<0.05.*

**Hazard ratios were calculated using Cox proportional hazards regression models in the propensity score-matched cohorts.*

DISCUSSION

- The results of this study showed that initiating treatment with ibrutinib single agent in the 1L resulted in a significantly longer TTNT as compared to IL CIT treatment among newly-diagnosed CLL/SLL patients.
- Additionally, the results demonstrated that early treatment with ibrutinib was associated with a longer TTNT.
- Consistent with the sustainable high rates of progression-free survival (PFS) observed among ibrutinib patients during a long-term follow-up in clinical trials[11,12,13], we observed that approximately three-fourths of the patients initiated on ibrutinib single agent in 1L did not initiate a new treatment after 48 months of follow-up.
- Due to the nature of administrative claims-based study, findings are subject to potential miscoding or diagnoses entered for administrative processing rather than clinical completeness.
- Additionally, it is important to note that del(17p)/TP53 mutation information is not available in VHA claims. The differences in outcomes between the subgroup of ibrutinib vs CIT patients with the del(17p)/TP53 mutation would likely be even more prominent than the results presented in this study.
- Generalizability of the findings may be limited to male patients who served in the active military service, as the current analysis was conducted using the VHA data population.

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