



Real-world Clinical Outcomes of First-Line Ibrutinib or Chemoimmunotherapy in Patients with Chronic Lymphocytic Leukemia by Risk Status

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ABSTRACT

Introduction: Certain genetic features in chronic lymphocytic leukemia (CLL) are associated with inferior outcomes after chemoimmunotherapy (CIT). This retrospective study evaluated treatment patterns and clinical outcomes of patients with CLL, stratified into high-risk and non-high-risk groups, who received first-line ibrutinib or CIT therapy.

Methods: High-risk group included confirmed presence of del(17p), del(11q), unmutated *IGHV*, *TP53* mutations, or complex karyotype. Weighted high-risk ibrutinib and CIT groups were compared for treatment effects using inverse probability of treatment weighting. Hazard ratios [95% CI] (HR) for time to next treatment (TTNT) were analyzed using Kaplan–Meier curves.

Results: Bendamustine/rituximab was the most common CIT regimen initiated for high-risk patients. During the available follow-up (median 34–35 months), 74.7% of the weighted high-risk ibrutinib group received only one line of treatment, compared with 47.2% of the weighted high-risk CIT group. The most common second-line treatment was ibrutinib for those in the CIT groups and venetoclax for the ibrutinib groups. The weighted high-risk ibrutinib group had a significantly longer TTNT (median not reached) than the weighted high-risk CIT group (median 34.4 months) and was 54% less likely to start a new treatment (HR 0.5 [0.3–0.6], $P < 0.010$). Among CIT-treated groups, high-risk patients had significantly shorter median TTNT than non-high-risk patients ($P < 0.010$). However, within the ibrutinib-treated groups, the median TTNT was similar between high-risk and non-high-risk patients (HR 2.2 [1.0–5.0]; $P = 0.060$).

Conclusion: This study found that first-line single-agent ibrutinib therapy was associated with significantly longer TTNT than CIT regimens in real-world patients with high-risk CLL. The results support the use of ibrutinib in high-risk patients.

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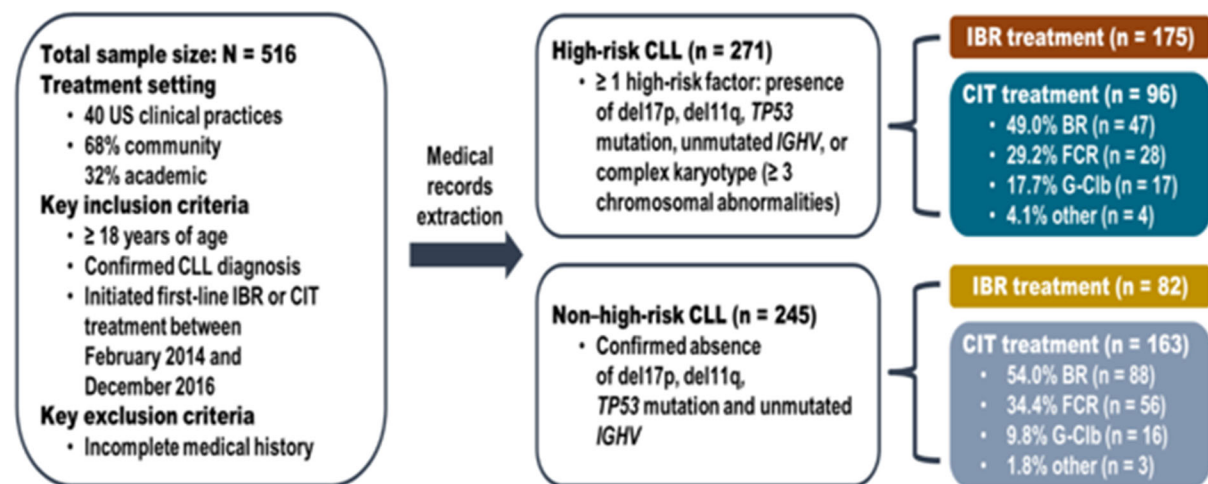
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Real-world Clinical Outcomes of First-Line Ibrutinib or Chemoimmunotherapy in Patients with Chronic Lymphocytic Leukemia by Risk Status

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	Weighted IBR High-Risk (n = 244)	Weighted CIT High-Risk (n = 229)	p Value	IBR High-Risk (n = 175)	IBR Non-High-Risk (n = 82)	p Value	CIT High-Risk (n = 96)	CIT Non-High-Risk (n = 163)	p Value
Median (95% CI) TTNT, months	NR (42.7-NR)	34.4 (32.4-43.1)	< 0.01	NR (47.0-NR)	NR (NR-NR)	0.06	38.8 (33.4-47.1)	52.8 (45.5-NR)	< 0.01
Median (95% CI) follow-up, months	34 (31.8-38.8)	35.1 (33.1-45.1)	0.140	30.7 (27.5-33.0)	29.8 (27.3-30.8)	0.220	42.4 (36.9-45.1)	41.3 (37.7-44.1)	0.533

 This graphical abstract represents the opinions of the authors. For a full list of declarations, including funding and author disclosure statements, please see the full text online. © The authors, CC-BY-NC 2022.

Keywords: Chemoimmunotherapy; Chronic lymphocytic leukemia; Cytogenetics; Ibrutinib; Real-world evidence

Key Summary Points

Why carry out this study?

Patients with high-risk chronic lymphocytic leukemia (CLL), characterized by cytogenetic/molecular abnormalities, are associated with poor prognosis when treated with chemoimmunotherapy; however, it continues to be used in real-world practice.

There is limited real-world evidence on clinical outcomes in high-risk and non-high-risk patients with CLL receiving first-line treatment.

This study describes patient characteristics, treatment patterns, and clinical outcomes among high-risk and non-high-risk patients with CLL receiving first-line chemoimmunotherapy (CIT) or ibrutinib treatment in the real-world setting.

What was learned from the study?

High-risk patients on first-line ibrutinib had a longer time to the next line of therapy than those on first-line chemoimmunotherapy.

Ibrutinib therapy provided sustained clinical benefit regardless of risk status, which is consistent with clinical trial results and supports its use in the first-line setting.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults in the USA and Europe [1–3]. It occurs primarily in older adults at a male-to-female ratio of 1.7:1 [4]. The disease course is highly variable and associated with heterogeneous cytogenetic characteristics. Deletion 13q, the most common chromosomal alteration found in more than 50% of patients with CLL, is associated with favorable prognosis if it is the sole genetic abnormality [5]. Other cytogenetic features, including chromosomal 17p or 11q deletion, *TP53* mutations, unmutated immunoglobulin heavy-chain variable region (*IGHV*), and complex karyotype, are associated with shorter time from diagnosis to treatment initiation and worse prognosis [5–8]. It is reported that, in the treatment-naïve setting, the presence of del(17p), which eliminates the tumor suppressor gene *TP53*, is found in up to 7% of patients, and the del(11q) is found in up to 18% [5]. Unmutated *IGHV* gene, which does not change over time, is present in approximately 50% of patients with CLL, and complex karyotype is present in 14–34% of untreated patients [6, 9]. In addition to poor prognosis, patients with certain genetic features, such as 17p or 11q deletion, *TP53* mutations, and unmutated *IGHV*, have inferior response to chemotherapy and chemoimmunotherapy (CIT) [6, 8–10].

Several targeted agents have been investigated with promising activity in patients with high-risk genetic characteristics, including B cell receptor-targeted small-molecule inhibitors, cyclin-dependent kinase inhibitors, and anti-apoptotic protein B cell lymphoma 2 antagonists [11, 12]. Ibrutinib, a once-daily small-molecule inhibitor of Bruton's tyrosine kinase (BTK), was initially approved in the USA in February 2014 and in Europe in October 2014 for the treatment of relapsed/refractory CLL. Subsequently, ibrutinib was approved for first-line treatment of all CLL in the USA and Europe in 2016. In randomized clinical trials, ibrutinib has demonstrated significant benefits in overall survival and progression-free survival over chemo- and/or immunotherapy in patients

DIGITAL FEATURES

This article is published with digital features, including an infographic, to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.16964926>.

with previously untreated or relapsed/refractory CLL [13–16]. The treatment guidelines recommend single-agent ibrutinib as a Category 1 preferred first-line treatment for treatment-naïve patients without del(17p)/*TP53* mutation and Category 1 preferred treatment for relapsed/refractory patients [17]. Single-agent ibrutinib is also a Category 2A preferred first-line treatment and Category 1 preferred second-line treatment for patients with del(17p)/*TP53* mutation.

There is limited real-world evidence on CLL treatments in patients with different cytogenetic risk features. We conducted a retrospective chart review to analyze treatment patterns and clinical outcomes in patients with CLL who received either ibrutinib or CIT as first-line therapy, stratified into high-risk and non-high-risk groups according to cytogenetic features.

METHODS

Study Design

This was a retrospective, multisite, medical chart review study of treatment patterns and clinical outcomes in patients with CLL, stratified by genetic risk status, who received either ibrutinib or CIT as the first-line treatment. The study was approved by the New England Institutional Review Board, a WIRB Copernicus Group Company (#120190010).

High-risk patients were those with confirmed presence of at least one of the following genetic abnormalities: del(17p), del(11q), unmutated *IGHV*, *TP53* mutations, and complex karyotype (defined as having at least three chromosomal abnormalities) [18]. Non-high-risk patients included those with confirmed absence of all aforementioned abnormalities (excluding complex karyotype). As complex karyotype is not routinely tested in clinical practice, if this information was not available for any patients, they were categorized as non-high risk if they had none of the del(17p), del(11q), unmutated *IGHV*, or *TP53* mutations.

Data were collected from March 2019 to July 2019, after the approval by the New England Institutional Review Board, a WIRB Copernicus

Group Company (#120190010). Oncologists and/or hematologists throughout the USA were identified in a national physician database and invited to participate. Physicians who had treated or managed at least 10 patients with CLL in the past 12 months were randomly sampled from the database to represent different geographic areas and practice settings. These physicians were invited for participation if they were not currently acting as a consultant or clinical investigator for a company involved in marketing or producing of oncology drugs. Participating physicians received honoraria.

Patients with CLL who had been treated by the participating physicians with either ibrutinib or CIT as first-line therapy were identified, and relevant data were extracted to an electronic or paper case report form. The collected data were de-identified and included no protected health information. The extracted data encompassed the period from a patient's diagnosis of CLL through the patient's most recent visit or the end of the data collection period (December 31, 2018), whichever occurred first. If a patient died before December 31, 2018, the patient was censored.

Study Population

The patients included were adults 18 years of age or older, had a confirmed diagnosis of CLL, received first-line treatment for CLL with either single-agent ibrutinib or a CIT regimen consistent with the treatment guidelines at the time [19], and had an index date between February 1, 2014 and December 31, 2016 (the index period). The index date was defined as the initiation of first-line treatment for CLL. The index period was chosen to encompass at least 2 years of data accumulation after the initial US approval of ibrutinib. The CIT regimens were any combinations of an immunotherapy agent among alemtuzumab, obinutuzumab, ofatumumab, and rituximab and one or more chemotherapy agents among bendamustine, chlorambucil, cyclophosphamide, cytarabine, doxorubicin, fludarabine, oxaliplatin, pento-statin, vincristine, and cladribine.

Patients were excluded from the chart review if they were enrolled in a cancer clinical trial after the date of CLL diagnosis or if their medical history was incomplete from diagnosis through the most recent visit (or death). Complete medical history included available CLL diagnosis details, first-line and subsequent treatments, procedures, tests, and follow-up information.

Outcomes and Statistics

The outcomes evaluated were treatment patterns and the time to next treatment (TTNT), summarized using descriptive statistics for each of the following patient groups: (1) high-risk treated with ibrutinib, (2) non-high-risk treated with ibrutinib, (3) high-risk treated with CIT, and (4) non-high-risk treated with CIT.

An assessment was conducted before treatment group comparisons to confirm that a balance could be achieved between the groups for confounders. This balance, termed “equipoise,” is a method frequently used to assess patient similarity and the feasibility of conducting unbiased comparative research between two naturalistic groups [20]. Clinical equipoise was quantified using a preference score, derived from a propensity score, to assess potential overlap of key clinical variables between the ibrutinib and CIT groups. The variables included demographics (age at CLL diagnosis, gender, year of index date, race), clinical characteristics (including family history of CLL, body mass index at diagnosis, Rai stage at diagnosis, comorbidities, Charlson Comorbidity Index score), and cytogenetic/molecular testing status (*TP53* mutation, del(17p), del(11q), unmutated *IGHV*). If more than half of the patients in each group had preference scores between 0.3 and 0.7, the two groups would be considered sufficiently similar for comparative effectiveness research [20]. The equipoise assessment confirmed that comparative analysis was suitable between the high-risk ibrutinib and CIT patient groups. The non-high-risk groups did not reach the acceptable variation between ibrutinib and CIT and were considered not sufficiently similar.

In real-world studies, the treatment chosen for each patient is usually not entirely random, and patient characteristics may be potential confounders in head-to-head comparisons. To minimize the effect of confounders in the comparison between the high-risk ibrutinib and CIT groups, we used inverse probability of treatment weighting (IPTW) [21] to balance key characteristics. First, a logistic regression model was developed to generate a propensity score to reduce the selection bias on the estimates of the treatment effect. Subsequently, the propensity score weight was calculated as the inverse of the propensity score. Each patient was assigned a weighting coefficient, which was the inverse of the propensity score for the ibrutinib group and the inverse of $(1 - \text{propensity score})$ for the CIT group. As a result, the sample size in each weighted treatment group, generated from the IPTW process, was different from the original dataset, even though the same patients contributed to the dataset. Once the IPTW dataset was generated, standardized differences in means (SDM) were used to evaluate the balance in the key characteristics between the weighted high-risk ibrutinib and CIT groups (see Table S1 in the electronic supplementary material for details). When the SDM was less than 10%, a good balance between the groups for a given baseline characteristic was confirmed. *P* values from propensity score-weighted *t* tests were also generated to further evaluate the balance in baseline characteristics.

The outcome TTNT was used as a surrogate for progression-free survival and was defined as the duration from the date of first-line treatment initiation (either CIT or ibrutinib) to the start date of the second-line treatment for CLL. TTNT was compared between the following paired groups: (1) weighted high-risk ibrutinib versus weighted high-risk CIT, (2) high-risk versus non-high-risk ibrutinib, and (3) high-risk versus non-high-risk CIT. The comparisons between high-risk and non-high-risk patients for either treatment did not involve weighted analysis, because high-risk and non-high-risk patients were prescribed the same medication of interest (CIT or ibrutinib).

Patients who did not initiate a second-line treatment by the data cutoff date (December 31,

2018) were censored at the date of their last follow-up visit or date of death, whichever was later. TTNT was evaluated using Kaplan–Meier curves, and median durations with 95% confidence intervals (CIs) are reported. Paired comparisons in TTNT between the previously specified groups were conducted using Cox proportional hazards regression analyses. Log-rank tests were used to assess statistical significance in the comparisons between groups. The Kaplan–Meier curves were truncated at the time point when the number of patients at risk (patients who had not reached second-line treatment) dropped below 10% in either of the compared groups [22]. Median follow-up duration was calculated using the reverse Kaplan–Meier method [23].

RESULTS

Study Patients

Physicians at 40 clinical practices (68% community and 32% academic practices) participated in this study and provided data on 516 patients with CLL, including 271 high-risk patients and 245 non-high-risk patients (see Fig. S1 in the Electronic Supplementary Material for details). Of the high-risk patients, 175 received ibrutinib and 96 received CIT as first-line therapy. Of the non-high-risk patients, 82 received ibrutinib and 163 received CIT. The demographic and baseline characteristics of patients in the unweighted ibrutinib and CIT groups are displayed in Table 1.

On the basis of the equipoise assessment, 50.9% (85 of 167, excluding 8 patients with missing data) of patients in the high-risk ibrutinib group and 52.1% (50 of 96) in the high-risk CIT group had preference scores between 0.3 and 0.7. As more than 50% in each group met this criterion, the two high-risk groups were considered appropriate for IPTW. The non-high-risk ibrutinib and CIT groups had 39% and 38% patients with preference scores between 0.3 and 0.7, respectively. As such, these two groups were not appropriate for comparative analysis.

For the high-risk datasets, applying IPTW produced a weighted high-risk ibrutinib group of 244 and a weighted high-risk CIT group of 229. The demographic and baseline clinical characteristics were well balanced between the weighted high-risk ibrutinib and high-risk CIT groups (Table 1). The mean age was 65.9 years in the weighted high-risk ibrutinib group and 65.4 years in the weighted high-risk CIT group. In the weighted high-risk ibrutinib and CIT groups, 54.0% and 51.2% of the patients, respectively, had Rai stage 3 or 4 CLL. The high-risk cytogenetic features were similarly distributed between the weighted high-risk ibrutinib and CIT groups (Table 2). The most common high-risk feature was del(17p).

Treatment Patterns

The first- and second-line treatment patterns for weighted and non-weighted groups are presented in Table 3. The high-risk ibrutinib group had a median (range) treatment duration of 28.6 (1.0–58.1) months. The weighted high-risk CIT group had a median (range) treatment duration of 5.5 (0.5–38.4) months. Of the CIT regimens initiated for high-risk patients, the most common were bendamustine + rituximab (46.3%), fludarabine + cyclophosphamide + rituximab (26.6%), and chlorambucil + obinutuzumab (23.6%).

During the available follow-up period, 74.7% patients in the weighted high-risk ibrutinib group received only one line of treatment for CLL, compared with 47.2% patients in the high-risk CIT group. Within the CIT group, a larger proportion of non-high-risk patients (69.9%) had only one line of treatment, compared with high-risk patients (45.8%). However, within the ibrutinib group, very few patients required a second-line treatment regardless of risk status (high-risk, 18.3%; non-high-risk, 8.5%).

The documented second-line treatment choices are summarized in Table 3 for weighted and unweighted groups by risk status. The most common second-line treatment was single-agent ibrutinib (81.7%) for the weighted high-risk CIT group and venetoclax monotherapy or in combination with rituximab (62.3%) as the

Table 1 Demographic and baseline characteristics of patients with CLL

Characteristic	Weighted high-risk ibrutinib (N = 244)	Weighted high-risk CIT (N = 229)	P value	High-risk ibrutinib (N = 175)	Non-high-risk ibrutinib (N = 82)	P value	High-risk CIT (N = 96)	Non-high-risk CIT (N = 163)	P value
Age at CLL diagnosis, mean (SD)	65.9 (10.2)	65.4 (11.0)	0.615	66.4 (8.5)	68.7 (7.7)	0.041	65.7 (7.7)	65.7 (8.5)	0.980
Male, n (%)	148 (60.6)	136 (59.5)	0.893	110 (62.9)	45 (54.9)	0.223	60 (62.5)	104 (63.8)	0.834
Race, n (%)									
Caucasian	182 (74.5)	170 (74.3)	0.932	125 (71.4)	61 (74.4)	0.884	74 (77.1)	121 (74.2)	0.737
Black	53 (22.1)	48 (21.1)		43 (24.6)	18 (22.0)		20 (20.8)	36 (22.1)	
Asian	8 (3.4)	10 (4.7)		7 (4.0)	3 (3.7)		2 (2.1)	6 (3.7)	
Hispanic, n (%)	23 (9.7)	15 (6.9)	0.773	15 (8.6)	11 (13.4)	0.486	8 (8.3)	17 (10.4)	0.859
Rai stage, n (%)									
0	42 (17.3)	23 (10.1)	0.261	28 (16.0)	13 (15.9)	0.976	8 (8.3)	24 (14.7)	0.131
I	35 (14.6)	45 (19.9)	0.445	25 (14.3)	16 (19.5)	0.286	11 (11.5)	36 (22.1)	0.032
II	23 (9.5)	35 (15.5)	0.265	21 (12.0)	16 (19.5)	0.110	10 (10.4)	21 (12.9)	0.555
III	52 (21.4)	60 (26.4)	0.429	41 (23.4)	22 (26.8)	0.555	30 (31.3)	43 (26.4)	0.400
IV	79 (32.6)	56 (24.8)	0.237	44 (25.1)	9 (11.0)	0.009	34 (35.4)	32 (19.6)	0.005
ECOG status, n (%)									
0	57 (23.4)	59 (25.8)	0.741	38 (21.7)	14 (17.1)	0.388	23 (24.0)	45 (27.6)	0.519
1	151 (62.1)	148 (64.8)	0.731	95 (54.3)	57 (69.5)	0.021	59 (61.5)	97 (59.5)	0.757
2	34 (14.1)	20 (8.9)	0.186	33 (18.9)	11 (13.4)	0.280	13 (13.5)	17 (10.4)	0.450
3	1 (0.4)	1 (0.5)	0.965	1 (0.6)	0 (0.0)	1.000	1 (1.0)	1 (0.6)	0.704
CCI, mean (SD)	1.0 (1.5)	0.9 (1.8)	0.680	1.0 (1.3)	1.1 (1.1)	0.772	1.0 (1.2)	1.1 (1.2)	0.493
0	106 (43.8)	113 (49.6)	0.203	80 (45.7)	32 (39.0)	0.313	45 (46.9)	69 (42.3)	0.477
1–2	107 (44.0)	84 (37.0)	0.119	72 (41.1)	43 (52.4)	0.090	39 (40.6)	75 (46.0)	0.399
> 2	29 (12.2)	30 (13.4)	0.649	23 (13.1)	7 (8.5)	0.284	12 (12.5)	19 (11.7)	0.840

CCI Charlson Comorbidity Index, CLL chronic lymphocytic leukemia, SD standard deviation, ECOG Eastern Cooperative Oncology Group

second line for the weighted high-risk ibrutinib group.

Time to Next Treatment

Within the index period, the median (95% CI) duration of follow-up was 34.0 (31.8–38.8)

Table 2 Mutation genomic status in high-risk patients who received CIT or ibrutinib

Mutation genomic status	Weighted high-risk ibrutinib (<i>N</i> = 244)	Weighted high-risk CIT (<i>N</i> = 229)	<i>P</i> value
<i>TP53</i> , <i>n</i> (%)			0.968
Mutated	70 (28.7)	65 (28.5)	
Wild type	169 (69.5)	158 (69.2)	
Unknown	4 (1.8)	5 (2.4)	
17p deletion, <i>n</i> (%)			0.857
Yes	134 (54.9)	122 (53.4)	
No	110 (45.1)	106 (46.6)	
Unknown	0 (0.0)	0 (0.0)	
11q deletion, <i>n</i> (%)			0.284
Yes	62 (25.6)	77 (33.9)	
No	181 (74.4)	151 (66.1)	
Unknown	0 (0.0)	0 (0.0)	
<i>IGHV</i> status, <i>n</i> (%)			0.952
Unmutated ($\leq 2\%$)	80 (33.0)	78 (34.3)	
Mutated ($> 2\%$)	154 (63.3)	140 (61.3)	
Unknown	8 (3.6)	9 (4.3)	
Complex karyotype, ^a <i>n</i> (%)			0.744
Yes	11 (4.3)	13 (5.5)	
No	213 (87.2)	202 (88.2)	
Unknown	8 (3.6)	9 (4.3)	

^aComplex karyotype is defined as having at least 3 chromosomal abnormalities including *BIRC3*, *NOTCH1*, *SF3B1*, del13q, trisomy 12, *CD38*, *Zap70*, and *CD49d*

months for the weighted high-risk ibrutinib group and 35.1 (33.1–45.1) months for the weighted high-risk CIT group and were not significantly different (Table 4).

The Kaplan–Meier curves demonstrate that the weighted high-risk ibrutinib group had significantly longer TTNT compared with the weighted high-risk CIT group ($P < 0.010$, Fig. 1a). The median duration of TTNT was not reached in the weighted high-risk ibrutinib group by the end of the study, as fewer than half of the patients had started a new treatment (Table 4). In comparison, the median TTNT in the weighted high-risk CIT group was 34.4 (95% CI 32.4–43.1) months. The weighted high-

risk ibrutinib group was 54% less likely to start a new treatment than the weighted high-risk CIT group (hazard ratio [95% CI] 0.46 [0.3–0.6]).

For ibrutinib-treated patients, the median TTNT was not reached, and the difference between the high-risk and non-high-risk groups was not significantly different (hazard ratio [95% CI] 2.2 [1.0–5.0]; $P = 0.060$) (Fig. 1b, Table 4). Among patients treated with CIT, the high-risk group had significantly shorter median TTNT (median 38.8 months [95% CI 33.4–47.1]) than non-high-risk group (median 52.8 months [95% CI 45.5–not reached]) (Table 4); the hazard ratio for new treatment was 2.4 (95% CI 1.6–3.5) for the high-risk group

Table 3 First- and second-line treatment patterns of high-risk and non-high-risk patients with chronic lymphocytic leukemia

Treatments	Weighted high-risk ibrutinib (N = 244)	Weighted high-risk CIT (N = 229)	P value	High-risk ibrutinib (N = 175)	Non-high-risk ibrutinib (N = 82)	P value	High risk CIT (N = 96)	Non-high-risk CIT (N = 163)	P value
First-line treatment									
Time to initiation, ^a months									
Mean (SD)	11.5 (34.6)	5.5 (16.7)	0.016	11.5 (28.2)	6.5 (12.5)	0.049	6.5 (13.6)	10.3 (23.9)	0.110
Median (range)	1.1 (0.2–167.6)	1.1 (0.1–81.8)	NA	1.0 (0.2–167.6)	0.9 (0.2–55.0)	0.851	0.9 (0–82)	1.0 (0–167)	0.305
Treatment duration, months									
Mean (SD)	29.1 (16.6)	5.5 (3.7)	< 0.001	26.5 (12.8)	29.5 (8.9)	0.034	5.5 (3.6)	5.4 (1.8)	0.756
Median (range)	28.6 (1.0–58.1)	5.5 (0.5–38.4)		26.6 (1.0–58.1)	28.8 (1.4–55.1)	0.168	5.3 (1–38)	5.1 (3–23)	0.760
Treatment discontinuation, ^b n (%)	35 (15.6)	18 (8.0)	0.219	31 (17.7)	9 (11.0)	0.165	18 (8.3)	14 (4.3)	0.179
CIT regimen									
BR	NA	106 (46.3)		NA	NA		47 (49.0)	88 (54.0)	
BO	NA	3 (1.5)		NA	NA		2 (2.1)	0 (0.0)	
CO	NA	54 (23.6)		NA	NA		17 (17.7)	16 (9.8)	
CR	NA	0 (0.0)		NA	NA		0 (0.0)	2 (1.2)	
FCR	NA	61 (26.6)		NA	NA		28 (29.2)	56 (34.4)	
Other	NA	2 (0.87)		NA	NA		2 (2.1)	1 (0.61)	
Second-line treatment									
n (%)	61 (25.3)	120 (52.8)	0.001	32 (18.3)	7 (8.5)	0.042	52 (54.2)	49 (30.1)	0.000
Time to initiation, ^a months									
Mean (SD)	28.2 (18.8)	28.4 (23.8)	0.951	27.9 (11.6)	31.0 (5.8)	0.491	29.2 (17.5)	39.6 (24.7)	0.017

Table 3 continued

Treatments	Weighted high-risk ibrutinib (N = 244)	Weighted high-risk CIT (N = 229)	P value	High-risk ibrutinib (N = 175)	Non-high-risk ibrutinib (N = 82)	P value	High risk CIT (N = 96)	Non-high-risk CIT (N = 163)	P value
Median (range)	30.7 (8.1–48.0)	28.3 (3.2–75.1)	NA	27.9 (8.1–50.0)	33.3 (20.1–35.8)	0.190	28.7 (3–75)	39.4 (3–181)	0.023
Treatment duration, months									
Mean (SD)	6.0 (4.8)	14.3 (18.9)	< 0.001	7.1 (5.4)	7.0 (7.5)	0.975	15.1 (12.5)	11.5 (9.6)	0.112
Median (range)	4.9 (0.9–22.4)	10.6 (0.0–50.4)	NA	5.5 (0.9–22.4)	3.9 (0–18.0)	0.735	11.3 (0–50)	9.0 (0–36)	0.092
Regimen									
Acalabrutinib	1 (1.8)	0 (0.0)		1 (3.1)	0 (0.0)		0 (0.0)	0 (0.0)	
BO	1 (2.6)	0 (0.0)		1 (3.1)	0 (0.0)		0 (0.0)	0 (0.0)	
BR	1 (1.8)	17 (14.1)		1 (3.1)	1 (14.3)		4 (7.7)	3 (6.1)	
CO	0 (0.0)	0 (0.0)		0 (0.0)	2 (28.6)		0 (0.0)	0 (0.0)	
FCR	5 (9.2)	0 (0.0)		2 (6.3)	0 (0.0)		0 (0.0)	1 (2.0)	
Ibrutinib	NA	98 (81.7)		NA	NA		45 (86.5)	41 (83.7)	
Ibrutinib + rituximab	1 (1.8)	0 (0.0)		NA	NA		0 (0.0)	1 (2.0)	
Idelalisib	6 (10.3)	0 (0.0)		2 (6.3)	0 (0.0)		0 (0.0)	0 (0.0)	
Idelalisib + rituximab	6 (10.1)	0 (0.0)		3 (9.4)	0 (0.0)		0 (0.0)	1 (2.0)	
Lenalidomide	0 (0.0)	1 (1.4)		0 (0.0)	0 (0.0)		1 (1.9)	0 (0.0)	
Rituximab	1 (1.8)	0 (0.0)		1 (3.1)	0 (0.0)		0 (0.0)	0 (0.0)	
Venetoclax	23 (37.9)	3 (2.7)		12 (37.5)	2 (28.6)		2 (3.9)	2 (4.1)	
Venetoclax + rituximab	15 (24.4)	0 (0.0)		9 (28.1)	2 (28.6)		0 (0.0)	0 (0.0)	

BO bendamustine, obinutuzumab, BR bendamustine, rituximab, CO chlorambucil, obinutuzumab, CR chlorambucil, rituximab, FCR fludarabine, cyclophosphamide, rituximab, R rituximab, NA not applicable/available

^aThe time to initiation of treatment is defined as the duration from CLL diagnosis to the initiation of the first- or second-line treatment

^bTreatment discontinuation was documented by asking the treating physician: “Was this agent discontinued prior to planned completion?”

Table 4 Median (95% confidence interval) time to next treatment (months) and follow-up duration between groups

Duration	Comparison 1		Comparison 2		Comparison 3		P value ^a	P value
	Weighted high-risk ibrutinib (n = 244)	Weighted high-risk CIT (n = 229)	High-risk ibrutinib (n = 175)	Non-high-risk ibrutinib (n = 82)	High-risk CIT (n = 96)	Non-high-risk CIT (n = 163)		
TTNT	NR (42.7–NR)	34.4 (32.4–43.1)	NR (47.0–NR)	NR (NR–NR)	38.8 (33.4–47.1)	52.8 (45.5–NR) ^b	< 0.010	< 0.010
Follow-up ^c	34.0 (31.8–38.8)	35.1 (33.1–45.1)	30.7 (27.5–33.0)	29.8 (27.3–30.8)	42.4 (36.9–45.1)	41.3 (37.7–44.1)	0.220	0.533

CI confidence interval, NR not reached, TTNT time to next treatment

^alog-rank test

^bThe median time was calculated when ≤ 10% patients remained at risk

^cFollow-up duration refers to the time from index date to the censored date. Calculated using reverse Kaplan–Meier method

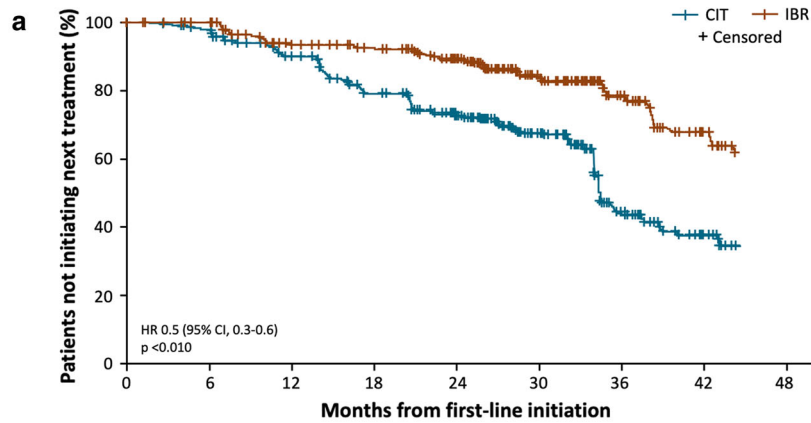
compared with the non-high-risk group ($P < 0.010$) (Fig. 1c).

DISCUSSION

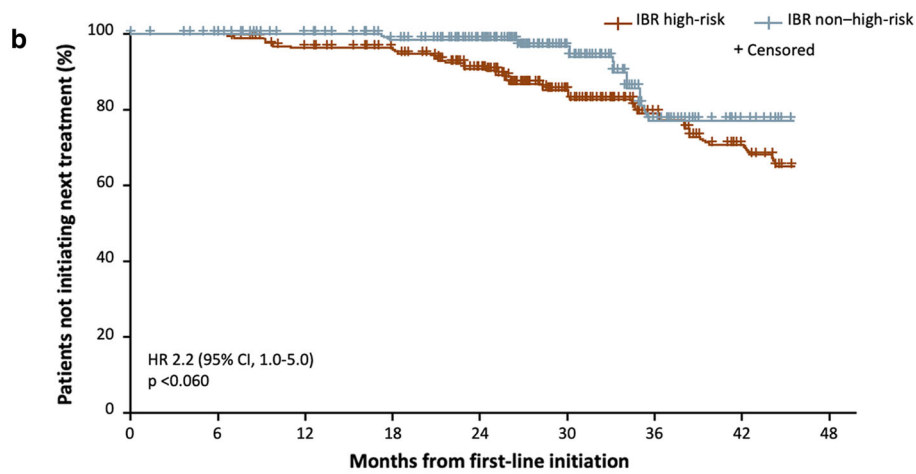
In randomized clinical trials, ibrutinib, as a single-treatment or in combination with a CD20 monoclonal antibody, has shown significant benefits in overall survival and progression-free survival over chemotherapy and/or immunotherapy in patients with previously untreated or relapsed/refractory CLL or small lymphocytic lymphoma [13–16, 24]. Recent studies have confirmed that first-line treatment with ibrutinib results in excellent long-term progression-free survival and overall survival rates in patients with high-risk genomic features, including *TP53* aberrations, unmutated *IGHV*, *BIRC3* mutation, and other mutations associated with poor responses to chemotherapy and/or CIT regimens [25, 26]. The 7-year overall survival rate of patients treated with first-line ibrutinib (median age 71 years), which exceeded 75%, was comparable to those of the age-matched US and UK general populations (see Fig. S2 in the Electronic Supplementary Material) [27, 28].

Previous real-world studies, which did not stratify by risk levels, support the benefits of ibrutinib in CLL, including longer TTNT and lower healthcare resource utilization than first-line CIT regimens [29, 30]. To the best of our knowledge, this study is the largest US real-world study to date that compares the clinical outcomes of first-line ibrutinib and CIT treatments for CLL in patients stratified by risk status. Consistent with the clinical trial results [13, 31, 32], we found that high-risk patients treated with single-agent ibrutinib had significantly longer TTNT and lower likelihood of requiring a second-line treatment than high-risk patients receiving CIT. To date, ibrutinib is the only BTK inhibitor with real-world comparison of clinical outcomes with CIT in patients with high-risk CLL.

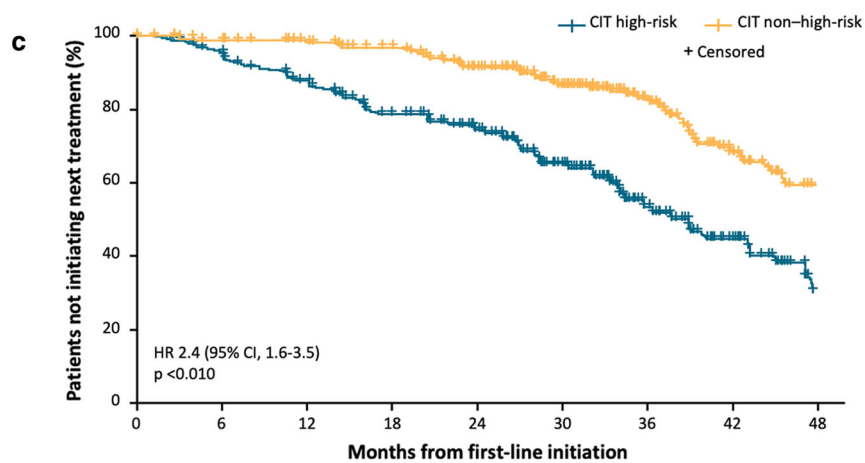
In addition, we compared the outcomes of high-risk and non-high-risk patients within each treatment group. As expected, CIT-treated high-risk patients had significantly shorter



Patients at risk	0	6	12	18	24	30	36	42	48
Weighted IBR high-risk	244	242	222	214	191	129	89	56	32
Weighted CIT high-risk	229	225	207	180	162	138	54	34	12



Patients at risk	0	6	12	18	24	30	36	42	48
IBR high-risk	175	171	156	149	129	75	43	27	17
IBR non-high-risk	82	82	81	78	69	39	19	10	6



Patients at risk	0	6	12	18	24	30	36	42	48
CIT high-risk	96	93	84	76	70	55	34	23	9
CIT non-high-risk	163	162	162	157	144	118	87	54	33

◀ **Fig. 1** Kaplan–Meier analysis of time to next treatment in patients with chronic lymphocytic leukemia. **a** Weighted high-risk ibrutinib versus weighted high-risk CIT. **b** High-risk ibrutinib versus non-high-risk ibrutinib. **c** High-risk CIT versus non-high-risk CIT. CIT chemoimmunotherapy, IBR ibrutinib

TTNT than non-high-risk patients, which highlights the importance of cytogenetic/molecular testing before initiating CIT for all patients with CLL, as recommended by clinical guidelines [17, 33]. Real-world data from the informCLL Prospective Observational Registry suggested that FISH testing was performed in 28% of the patients with CLL/small lymphocytic lymphoma (SLL) in the registry during the period of October 2015–June 2019, and TP53 and IGHV tests were performed in 11% and 12% of the patients, respectively [34]. Among patients receiving ibrutinib, the findings support the use of ibrutinib as first-line treatment for CLL regardless of risk status.

In this retrospective chart review study, the treatment patterns of CLL in the real-world setting reflected the shifting trends in clinical practice from 2014 through 2018. Before 2015, the most common first-line treatments for CLL were chemotherapy agents and rituximab [35–37], as recommended by treatment guidelines at the time [38]. However, the emergence of small-molecule inhibitors (SMIs) led to a shift in treatment guidelines [7, 19], and our findings confirm this shift in clinical practice. Novel agents were preferred for second-line treatment, with the most common choices being ibrutinib after CIT and venetoclax after ibrutinib.

One of the strengths of this study was the collection of extensive information on the treatment pattern and response data by experienced oncologists/hematologists, yielding a substantial sample size. We utilized the IPTW approach to balance potential confounding factors, including demographics, disease stage, and comorbidities, to isolate the treatment effect. We took additional steps to ensure that the datasets were appropriately comparable.

The study is limited by its retrospective design and the availability of medical record data. Potential confounders remain (e.g., tumor

burden, unreported comorbidities, socioeconomic status, clinician preference) despite the efforts to balance the groups. The study only included patients with known risk status, classified by the relevant cytogenetic/molecular testing. Therefore, the generalizability of the results may be limited for patients who do not have complete risk data, as a significant patient population in the real world may not receive all relevant tests [34]. Another limitation of this study is that the non-high-risk ibrutinib and CIT groups were not directly compared, as these groups did not meet the prespecified level of comparability in preference scores and were deemed not appropriate for comparative analysis. In addition, external factors such as cost and access could have influenced clinical decisions such as treatment initiation and discontinuation. In the index period of treatment (2014–2016), the CLL treatment landscape was different from the current clinical practice, which may limit the generalizability of the findings. Finally, only records through December 31, 2018 were extracted, limiting the follow-up information for some patients. As a result of this limited follow-up period for some patients and the difficulties in obtaining death records, we did not evaluate overall survival.

CONCLUSIONS

In this real-world study, first-line treatment with single-agent ibrutinib provided sustained clinical benefits over CIT regimens for the treatment of CLL, as evidenced by significantly longer time to the next treatment, which is consistent with randomized clinical trials. The favorable outcomes of ibrutinib were evident regardless of cytogenetic/molecular risk status, with the majority of patients not requiring second-line treatment. Finally, the findings highlight the importance of risk assessment through cytogenetic/molecular testing before choosing to treat with CIT, as a risk-based approach is recommended by clinical guidelines for high-risk patients.

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Compliance with Ethics Guidelines. The study was approved by the New England Institutional Review Board, a WIRB Copernicus Group Company (#120190010).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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