Original Study

# Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study

Mazyar Shadman,[1] Beenish S. Manzoor,[2] Kavita Sail,[2] Hande H. Tuncer,[3] John N. Allan,[4] Chaitra Ujjani,[1] Nnadozie Emechebe,[2] Rajesh Kamalakar,[2] Catherine C. Coombs,[5] Lori Leslie,[6] Paul M. Barr,[7] Jennifer R. Brown,[8] Toby A. Eyre,[9] Alexandros Rampotas,[9] Anna Schuh,[9] Nicole Lamanna,[10] Alan Skarbnik,[11] Lindsey E. Roeker,[12] Rajat Bannerji,[13] Barbara Eichhorst,[14] Isabelle Fleury,[15] Matthew S. Davids,[8] Hasan Alhasani,[2] Dingfeng Jiang,[2] Brian T. Hill,[16] Stephen J. Schuster,[17] Danielle M. Brander,[18] Irina Pivneva,[19] Rebecca Burne,[19] Annie Guerin,[19] Anthony R. Mato[12]

## Abstract

**To investigate why patients with CLL stop treatment prematurely, discontinuation patterns were evaluated using electronic medical record data. Among 1364 patients receiving first-line regimens, between 16.3% and 34.5% discontinued, mainly related to adverse events and disease progression. Among 626 patients receiving second-line regimens, 30.1% to 50.0% discontinued, primarily due to adverse events. These findings highlight the continued need for tolerable CLL therapies.**

**Introduction:** This study assessed treatment discontinuation patterns and reasons among chronic lymphocytic leukemia (CLL) patients initiating first-line (1L) and second-line (2L) treatments in real-world settings. **Materials and Methods:** Using deidentified electronic medical records from the CLL Collaborative Study of Real-World Evidence, premature treatment discontinuation was assessed among FCR, BR, BTKi-based, and BCL-2-based regimen cohorts. **Results:** Of 1364 1L patients (initiated in 1997-2021), 190/13.9% received FCR (23.7% discontinued prematurely); 255/18.7% received BR (34.5% discontinued prematurely); 473/34.7% received BTKi-based regimens, of whom 28.1%

*Abbreviation:* 1L, first-line; 2L, second-line; BCL-2, B-cell lymphoma 2; BCRi, B-cell receptor inhibitor; BTKi, Bruton tyrosine kinases inhibitor; BR, bendamustine + rituximab; CIT, chemoimmunotherapy; CLL, chronic lymphocytic leukemia; CORE, CLL Collaborative Study of Real-World Evidence; CT, chemotherapy; ECOG, Eastern cooperative oncology group; FCR, fludarabine + cyclophosphamide + rituximab; IGHV, immunoglobulin heavy chain variable; MRD, minimal residual disease; N, number; SD, standard deviation; VG/VR, venetoclax with obinutuzumab or rituximab.

[1]Fred Hutch Cancer Center and University of Washington, Seattle, WA
[2]AbbVie, Inc., North Chicago, IL
[3]The Cancer Center at Lowell General Hospital, Lowell, MA
[4]Weill Cornell Medicine, New York, NY
[5]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC
[6]John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ
[7]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY
[8]Dana-Farber Cancer Institute, Boston, MA
[9]Churchill Hospital, Oxford University, Oxford, UK
[10]Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY
[11]Novant Health Cancer Institute, Charlotte, NC
[12]CLL Program, Leukemia Service, Division of Hematologic Oncology, Memorial Sloan Kettering Cancer Center, New York, NY
[13]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ
[14]Department of Internal Medicine, Center of Integrated Oncology Köln Bonn, University of Cologne, Cologne, Germany
[15]Hôpital Maisonneuve-Rosemont, Montreal, QC, Canada
[16]Cleveland Clinic, Cleveland, OH
[17]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA
[18]Duke Cancer Institute, Duke University Medical Center, Durham, NC
[19]Analysis Group, Inc., Montreal, QC, Canada

Submitted: Jan 12, 2023; Revised: Mar 14, 2023; Accepted: Mar 20, 2023; Epub: xxx

Address for correspondence: Beenish S. Manzoor, PhD, MPH, Department GMH1, ABV1 – 3NW, 1 North Waukegan Rd., North Chicago, IL, 60064
E-mail contact: beenish.manzoor@abbvie.com



https://doi.org/10.1016/j.clml.2023.03.010



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

discontinued prematurely; and 43/3.2% received venetoclax-based regimens, of whom 16.3% discontinued prematurely (venetoclax monotherapy: 7/0.5%, of whom 42.9% discontinued; VG/VR: 36/2.6%, of whom 11.1% discontinued). The most common reasons for treatment discontinuation were adverse events (FCR: 25/13.2%; BR: 36/14.1%; BTKi-based regimens: 75/15.9%) and disease progression (venetoclax-based: 3/7.0%). Of 626 2L patients, 20/3.2% received FCR (50.0% discontinued); 62/9.9% received BR (35.5% discontinued); 303/48.4% received BTKi-based regimens, of whom 38.0% discontinued; and 73/11.7% received venetoclax-based regimens, of whom 30.1% discontinued (venetoclax monotherapy: 27/4.3%, of whom 29.6% discontinued; VG/VR: 43/6.9%, of whom 27.9% discontinued). The most common reasons for treatment discontinuation were adverse events (FCR: 6/30.0%; BR: 11/17.7%; BTKi-based regimens: 60/19.8%; venetoclax-based: 6/8.2%). **Conclusion:** The findings of this study highlight the continued need for tolerable therapies in CLL, with finite therapy offering a better tolerated option for patients who are newly diagnosed or relapsed/refractory to prior treatments.

*Clinical Lymphoma, Myeloma and Leukemia,* Vol. 000, No.xxx, 1–12 © 2023 The Author(s). Published by Elsevier Inc.

**Keywords:** Targeted agents, Chemotherapy, Adverse events, Chemoimmunotherapy, Disease progression

## Introduction

Treatment options for chronic lymphocytic leukemia (CLL) have expanded considerably following the introduction of several targeted agents that include small molecule inhibitors of B-cell receptor (BCRi) signaling, such as Bruton Tyrosine Kinase inhibitors (BTKis) including ibrutinib, acalabrutinib, zanubrutinib, as well as B-cell lymphoma 2 (BCL-2) signaling (ie, venetoclax).[1-4] Despite clinical efficacy, chemotherapy/chemoimmunotherapy (CT/CIT) is typically associated with poor tolerability and high risk of infections, particularly in patients with comorbidities.[5,6] The emergence of targeted agents now offers clinicians viable chemotherapy-free treatment options for patients, which is particularly relevant for patients who are unfit for CT/CIT regimens (eg, the elderly and patients with multiple comorbidities).[7,8]

Despite advances in the treatment landscape for CLL, patients still discontinue treatment due to a variety of factors.[9] Although targeted agents, compared to CT/CIT, have been generally well-tolerated and effective, their use is not without challenges.[2,4,10-12] For example, there was some evidence that treatment response with targeted agents could occur at a slower rate compared to CIT and with a reduced portion of patients achieving complete remission.[2,13,14] Furthermore, patients receiving targeted agents are typically treated continuously until disease progression or intolerance, the latter of which is an important contributor to treatment discontinuation.[9,11,15,16] Resistance to targeted agent treatments relating to acquired Bruton tyrosine kinase (BTK) and BCL2 mutations has also been demonstrated.[17] However, much of the available evidence to date regarding treatment discontinuation focused on early targeted agents. Results from a long-term follow-up of participants from the multi-center, phase 3 RESONATE trial reported that only a small portion of patients discontinued therapy, often due to disease progression (53 out of 195 patients [27%]) and adverse events (grade ≥3; 23 out of 195 patients [12%]),[18] which further aligns with other assessments from the RESONATE trials.[19-21]

Although prior studies have evaluated treatment discontinuation of targeted agents, they have predominantly been clinical trials or studies involving single centers or restricted geographic areas.[9,15,18-26] The few analyses of patients with CLL who were treated with ibrutinib in clinical practice found that the most common reasons underlying treatment discontinuation included adverse events/intolerance.[9,14,27]

With the recent expansion of targeted therapies in the treatment landscape for CLL, the goal of this study was to help fill the current evidence gap by providing a characterization of the real-world treatment patterns and reasons for treatment discontinuation among patients with CLL who were treated with CT/CIT and available BTKi and BCL-2 targeted agents in the first and second lines of therapy from medical practices in 20 academic centers and community-based practices from several countries.

## Methods

### *Data Source and Study Design*

This study used deidentified electronic medical record data from the CLL Collaborative Study of Real-World Evidence (CORE). CORE is a retrospective, observational international study of patients with CLL in the United States, Canada, Germany, and the United Kingdom from 20 medical practices in academic and/or community-based settings.[28] The CORE data include data on the type of therapy received, including monotherapy and combination therapies, as well as clinician responses regarding disease management.

The present analysis included data collected between June 1, 2018 and June 22, 2021. Adult patients were included if they were diagnosed with CLL, initiated at least one line of therapy for CLL on/after January 1, 2012 (excluding lines of therapy received as part of a clinical trial). The analyses of treatment discontinuation in the first line of therapy included patients who discontinued their treatments in the first line of therapy, while the analyses of treatment discontinuation in the second line of therapy included patients who discontinued their treatments in the second-line of therapy.

### *Study Measures and Analyses*

Treatment discontinuation patterns were characterized among patients treated with CT/CIT and targeted agents across four cohorts: fludarabine + cyclophosphamide + rituximab (FCR),


Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

bendamustine + rituximab (BR), BTKi-based (eg, acalabrutinib, and ibrutinib-based), and BCL-2 (ie, venetoclax-based) regimens. Treatment discontinuation was operationally defined as ending therapy for reason(s) other than the completion of the planned duration of therapy, as recorded in the patient's medical chart. For the reasons of discontinuation that included severe adverse events, the severity was Grade 3, 4, or 5 as recorded in the patient chart.

This study was descriptive; no hypothesis testing was conducted. Mean, median, interquartile range (IQR), and standard deviation (SD) were used to summarize continuous variables; counts, frequencies, and percentages were used to summarize categorical variables. For cumulative incidence plots, Kaplan-Meier estimates are presented. All analyses were performed using SAS version 9.4 and R version 3.4.2.

## Results

### *Treatment Discontinuation in the First Line of Therapy*

A total of 1364 patients received first-line therapy. The most common treatments were BTKi-based and BR regimens; 190 (13.9%) received FCR, 255 (18.7%) received BR, 473 (34.7%) received BTKi-based regimens, and 43 (3.2%) venetoclax-based regimens (venetoclax monotherapy: 7 [0.5%] patients; VG/VR: 36 [2.6%] patients). The remaining 403 (29.5%) patients received a variety of therapies, such as monoclonal antibodies (eg, rituximab), PI3Ki-based regimens (eg, idelalisib), and other CT/CIT (eg, bendamustine, chlorambucil, chlorambucil + obinutuzumab, fludarabine + rituximab, pentostatin + cyclophosphamide + rituximab [PCR], rituximab + cyclophosphamide + vincristine) and were excluded from the analysis.

Of the patients who received first-line therapy with FCR, BR, BTKi-based, and venetoclax-based regimens, the mean age at diagnosis ranged across cohorts from 54.9 to 63.8 years and the majority of patients were male (range: 63.9%-71.6%) (Table 1). Among patients initiating first-line therapy, a higher proportion of those receiving targeted agents tended to have IGHV unmutated status (BTKi-based regimens: 40.8%; venetoclax-based: 39.5%), del(17p)/TP53 abnormality (BTKi-based regimens: 37.2%; venetoclax-based: 34.5%) and at least 1 genetic aberration (BTKi-based regimens: 74.4%; venetoclax-based: 67.4%), such as NOTCH1 (BTKi-based regimens: 16.5%; venetoclax-based: 45.5%). Further information regarding mutated disease is available in Table 1.

Overall, the most common comorbidities at the initiation of the first line of therapy, across all cohorts, were cardiovascular disorders followed by endocrine/metabolic, respiratory, and musculoskeletal disorders. The median (IQR) duration of follow up (ie, the observation period between the initiation of first-line therapy and the earlier of date of last follow up visit, date of referral, or death) was 54.6 (range: 22.1-87.6) months for FCR, 37.3 (range: 17.0-62.5) months for BR, 16.6 (range:6.0-30.9) months for BTKi-based regimens, and 7.4 (range: 4.7-13.1) months for venetoclax-based regimen cohorts (Table 1).

Treatment was discontinued prematurely for 45 (out of 190 patients; 23.7%) patients in the FCR, 88 (out of 255 patients; 34.5%) patients in the BR, 133 (out of 473 patients; 28.1%) patients in the BTKi-based regimen, and 7 (out of 43 patients; 16.3%) patients in the venetoclax-based regimen cohorts (venetoclax monotherapy: 3 out of 7 [42.9%]; VG/VR: 4 out of 36 [11.1%]; Table 2) although median follow-up at the time of analysis was 7.4 months for these patients. The most common reason for premature treatment discontinuation among patients in the FCR (25 out of 190 patients; 13.2%), BR (36 out of 255 patients; 14.1%), and BTKi-based regimen cohorts (75 out of 473 patients; 15.9%) was adverse events, with more than 65% being selected as severe (Grade 3, 4, or 5) adverse events in each cohort. For patients in the FCR and BR cohorts, common adverse events leading to premature treatment discontinuation included hematological abnormalities, such as neutropenia and thrombocytopenia (FCR: 11 out of 190 patients [5.8%]; BR: 11 out of 255 patients [4.3%]). For BR cohort, infusion-related reactions led to premature treatment discontinuation in 7 out of 255 patients (2.7%). For patients in the BTKi-based regimen cohort, adverse events leading to premature treatment discontinuation included: cardiac events (14 out of 473 patients [3.0%]); skin and subcutaneous tissue disorders, such as rash (10 out of 473 patients [2.1%]); musculoskeletal and connective tissue disorders (10 out of 473 patients [2.1%]); and hemorrhage/bleeding (7 out of 473 patients [1.5%]). When looking at the cumulative incidence of discontinuation in the BTKi-based regimen cohort from the start of treatment, 12.8% of patients had discontinued therapy due to an adverse event by 10 months; 19.2% by 20 months, and 23.1% by 30 months (Figure 1). Among patients in the venetoclax-based regimen cohort, the most common reason for premature treatment discontinuation (3 out of 43 patients; 7.0%) was disease progression (Table 2).

### *Treatment Discontinuation in the Second Line of Therapy*

A total of 626 patients received second-line therapy. The most common second-line regimens were BTKi-based regimens, venetoclax-based regimens, BR and FCR; 20 (out of 626 patients; 3.2%) patients received FCR, 62 (out of 626 patients; 9.9%) patients received BR, 303 (out of 626 patients; 48.4%) received BTKi-based regimens, and 73 (out of 626 patients; 11.7%) received venetoclax-based regimens (venetoclax monotherapy: 27 [4.3%] patients; VG/VR: 43 [6.9%] patients; other venetoclax-based combinations: 3 [0.5%] patients). The remaining 168 patients received other regimens (eg, other CT/CIT).

In the second line of therapy, the mean age at 2L initiation ranged from 59.4 to 67.9 years and the majority of patients were male (64.7%-80.0%) (Table 3). The median (SD) duration of follow up from the initiation of second-line therapy (ie, the observation period between the initiation of second-line therapy and the earlier of date of last follow up visit, date of referral, or death) was 70.6 (33.0) months for FCR, 61.5 (32.9) months for BR, 26.1 (19.5) months for BTKi-based regimen, and 5.8 (9.3) months for venetoclax-based regimen cohorts. Consistent with what was observed in first line of therapy, similar trends were seen for del(17p)/TP53 abnormality in BTKi-based and venetoclax-based regimens in second-line; however, a higher proportion of patients initiating a venetoclax-based regimen had an IGHV unmutated status (BTKi-based regimens: 19.6%; venetoclax-based: 30.4%). Further information regarding mutated disease is available in Table 3.



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

**Table 1 Patient Demographics in the First Line of Therapy**

| | FCR N = 190 | BR N = 255 | BTKi[a] N = 473 | Venetoclax[b] N = 43 |
|---|---|---|---|---|
| **Demographics** | | | | |
| Age at diagnosis, (years) | | | | |
| Mean ± SD (Median) | 54.9 ± 9.3 (56) | 62.5 ± 9.2 (63) | 63.8 ± 10.7 (65) | 61.0 ± 12.5 (62) |
| Age at 1L initiation, (years) | | | | |
| Mean ± SD (Median) | 56.9 ± 9.5 (58) | 65.1 ± 9.2 (66) | 67.0 ± 10.4 (68) | 64.0 ± 13.2 (65) |
| Male, N (%) | 136 (71.6%) | 163 (63.9%) | 313 (66.2%) | 29 (67.4%) |
| **Country** | | | | |
| USA | 153 (80.5%) | 236 (92.5%) | 451 (95.3%) | 36 (83.7%) |
| Canada | 18 (9.5%) | 1 (0.4%) | 10 (2.1%) | 0 (0.0%) |
| Germany | 11 (5.8%) | 11 (4.3%) | 11 (2.3%) | 7 (16.3%) |
| UK | 8 (4.2%) | 7 (2.7%) | 1 (0.2%) | 0 (0.0%) |
| **Year of initiation** | | | | |
| <2014 | 90 (47.4%) | 84 (32.9%) | 6 (1.3%) | 0 (0.0%) |
| 2014-2016 | 55 (28.9%) | 101 (39.6%) | 174 (36.8%) | 2 (4.7%) |
| 2017-2019 | 45 (23.7%) | 70 (27.5%) | 276 (58.4%) | 30 (69.8%) |
| 2020-2021 | 0 (0.0%) | 0 (0.0%) | 17 (3.6%) | 11 (25.6%) |
| **Disease stage and performance status at 1L initiation, N (%)** | | | | |
| Rai stage, N (%) | | | | |
| Stage 0 | 5 (2.6%) | 14 (5.5%) | 29 (6.1%) | 0 (0.0%) |
| Stage I or II | 82 (43.2%) | 83 (32.5%) | 173 (36.6%) | 21 (48.8%) |
| Stage III or IV | 77 (40.5%) | 115 (45.1%) | 209 (44.2%) | 14 (32.6%) |
| Not measured or Unknown | 26 (13.7%) | 43 (16.9%) | 62 (13.1%) | 8 (18.6%) |
| ECOG, N (%) | | | | |
| Grade 0-1 | 156 (82.1%) | 186 (72.9%) | 378 (79.9%) | 34 (79.1%) |
| Grade 2-4 | 6 (3.2%) | 21 (8.2%) | 34 (7.2%) | 0 (0.0%) |
| Not measured or Unknown | 28 (14.7%) | 48 (18.8%) | 61 (12.9%) | 9 (20.9%) |
| **IGHV at 1L initiation, N (%)** | | | | |
| Mutated[a] | 37 (19.5%) | 49 (19.2%) | 89 (18.8%) | 6 (14.0%) |
| Unmutated | 54 (28.4%) | 60 (23.5%) | 193 (40.8%) | 17 (39.5%) |
| Testing not performed | 70 (36.8%) | 89 (34.9%) | 124 (26.2%) | 9 (20.9%) |
| Unknown | 29 (15.3%) | 57 (22.4%) | 67 (14.2%) | 11 (25.6%) |
| **Genetic aberrations at 1L initiation, N (%)** | | | | |
| At least one genetic aberration present[c,d] | 109 (57.4%) | 146 (57.3%) | 352 (74.4%) | 29 (67.4%) |
| 6q deletion or MYB mutation | 2 (1.8%) | 6 (4.1%) | 19 (5.4%) | 0 (0.0%) |
| 13q deletion or LAMP1 mutation | 53 (48.6%) | 69 (47.3%) | 143 (40.6%) | 11 (37.9%) |
| 11q deletion or ATM mutation | 38 (34.9%) | 46 (31.5%) | 90 (25.6%) | 4 (13.8%) |
| Trisomy 12 | 26 (23.9%) | 38 (26.0%) | 98 (27.8%) | 8 (27.6%) |
| 17p deletion or TP53 mutation | 13 (11.9%) | 20 (13.7%) | 131 (37.2%) | 10 (34.5%) |
| NOTCH1 | 4 (14.3%) | 0 (0.0%) | 18 (16.5%) | 5 (45.5%) |
| No genetic aberration present | 36 (18.9%) | 52 (20.4%) | 62 (13.1%) | 4 (9.3%) |
| Testing not performed or unknown | 45 (23.7%) | 57 (22.4%) | 59 (12.5%) | 10 (23.3%) |
| **Comorbidities[e], N (%)** | | | | |
| Cardiovascular | 49 (25.8%) | 89 (34.9%) | 194 (41.0%) | 18 (41.9%) |
| Endocrine/metabolic | 27 (14.2%) | 58 (22.7%) | 129 (27.3%) | 6 (14.0%) |
| Musculoskeletal | 15 (7.9%) | 23 (9.0%) | 60 (12.7%) | 7 (16.3%) |
| Psychiatric | 15 (7.9%) | 22 (8.6%) | 54 (11.4%) | 2 (4.7%) |
| Renal | 11 (5.8%) | 38 (14.9%) | 39 (8.2%) | 4 (9.3%) |
| Respiratory | 22 (11.6%) | 33 (12.9%) | 48 (10.1%) | 4 (9.3%) |
| No known comorbidities[f] | 83 (43.7%) | 85 (33.3%) | 137 (29.0%) | 17 (39.5%) |

(*continued on next page*)



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

**Table 1** (*continued*)

| | FCR N = 190 | BR N = 255 | BTKi[a] N = 473 | Venetoclax[b] N = 43 |
|---|---|---|---|---|
| **Duration of follow-up (mo)** | | | | |
| Mean ± SD<br>[$Q_1$; Median; $Q_3$]<br>(min-max) | 60.6 ± 46.5<br>[22.1; 54.6; 87.6]<br>(0.4-216.9) | 43.2 ± 31.9<br>[17.0; 37.3; 62.5]<br>(0.0-142.8) | 19.8 ± 16.2<br>[6.0; 16.6; 30.9]<br>(0.0-74.5) | 9.3 ± 6.7<br>[4.7; 7.4; 13.1]<br>(0.1-25.9) |
| **Treatment duration (mo)** | | | | |
| Mean ± SD<br>[$Q_1$; Median; $Q_3$]<br>(min-max) | 4.8 ± 2.9<br>[3.9; 4.9; 5.7]<br>(0.0-29.1) | 4.8 ± 5.0<br>[3.1; 4.7; 5.4]<br>(0.0-56.3) | 15.8 ± 14.5<br>[4.6; 11.3; 24.2]<br>(0.0-75.0) | 7.4 ± 5.8<br>[3.0; 6.0; 11.3]<br>(0.0-20.3) |

Abbreviations: BCL-2 = B-cell lymphoma 2 signaling; BR = bendamustine + rituximab; BTKi = Bruton tyrosine kinases inhibitor; ECOG = Eastern cooperative oncology group; FCR = fludarabine + cyclophosphamide + rituximab; IGHV = immunoglobulin heavy chain variable; N = number; SD = standard deviation.
[a] BTKi-based regimens included acalabrutinib- and ibrutinib-based treatments.
[b] Venetoclax included BCL-2-based treatments (eg, venetoclax monotherapy).
[c] Calculated out of patients who had a mutation or abnormality detected.
[d] Patients may have had more than one genetic aberration identified (categories are not mutually exclusive).
[e] Patients may have had more than one comorbidity identified (categories are not mutually exclusive).
[f] Includes all patients without any comorbidities selected (category is mutually exclusive).

**Table 2** Treatment Status and Discontinuation Reasons in the First Line of Therapy

| | FCR N = 190 | BR N = 255 | BTKi N = 473 | Venetoclax Monotherapy N = 7 | VG/VR N = 36 |
|---|---|---|---|---|---|
| **Treatment status**[a] | | | | | |
| Still on treatment | 13 (6.8%) | 22 (8.6%) | 316 (66.8%) | 4 (57.1%) | 30 (83.3%) |
| Completed planned duration | 131 (68.9%) | 143 (56.1%) | 18 (3.8%) | 0 (0.0%) | 2 (5.6%) |
| Premature discontinuation of therapy | 45 (23.7%) | 88 (34.5%) | 133 (28.1%) | 3 (42.9%) | 4 (11.1%) |
| **Reason for treatment discontinuation**[b,c] | | | | | |
| Adverse event | 25 (13.2%) | 36 (14.1%) | 75 (15.9%) | 0 (0.0%) | 2 (5.6%) |
| Severe adverse event[d] | 17 (68.0%) | 29 (80.6%) | 49 (65.3%) | 0 (0.0%) | 1 (50.0%) |
| Disease progression | 7 (3.7%) | 8 (3.1%) | 30 (6.3%) | 2 (28.6%) | 1 (2.8%) |
| Watchful waiting due to low or no disease activity | 9 (4.7%) | 32 (12.5%) | 17 (3.6%) | 0 (0.0%) | 1 (2.8%) |

Abbreviations: BTKi = Bruton tyrosine kinases inhibitor; BR = bendamustine + rituximab; FCR = fludarabine + cyclophosphamide + rituximab; N = number; VG/VR = venetoclax with obinutuzumab or rituximab.
[a] Treatment status was unknown for 1 patient receiving FCR, 2 patients receiving BR, and 6 patients receiving BTKi.
[b] Multiple reasons may have been selected; categories are not mutually exclusive.
[c] Other reasons for discontinuation also included: economic reasons, patient preference, non-severe adverse event, disease transformation, patient request, refractory to treatment, terminal illness or death due to CLL, and death unrelated to disease or therapy.
[d] Severe adverse event indicates Grade 3, 4, or 5.

Treatment was discontinued prematurely for 10 (out of 20 patients; 50.0%) patients in the FCR, 22 (out of 62 patients; 35.5%) patients in the BR, 115 (out of 303; 38.0%) patients in the BTKi-based regimen, and 22 (out of 73 patients; 30.1%) in the venetoclax-based regimen cohorts (venetoclax monotherapy: 8 out of 27 [29.6%]; VG/VR: 12 out of 43 [27.9%]; Table 4), although median follow-up at the time of analysis was 5.8 months for these patients. The most common reason for premature treatment discontinuation in all cohorts was adverse events—ie, for FCR (6 out of 20 patients; 30.0%), BR (11 out of 62 patients; 17.7%), BTKi-based regimen (60 out of 303 patients; 19.8%), and venetoclax-based regimen (6 out of 73 patients; 8.2%) cohorts. For patients in the FCR and BR cohorts, the most common adverse events leading to premature treatment discontinuations were hematological abnormalities, such as neutropenia and thrombocytopenia (FCR: 2 out of 20 patients [10.0%]; BR: 5 out of 62 patients [8.1%]). For patients in the BR cohort, another common adverse event leading to premature treatment discontinuation was infections and infestations including pneumonia (2 out of 62 patients [3.2%]). The most common adverse events in the BTKi-based regimen cohort were cardiac events (12 out of 303 patients [4.0%]), skin and subcutaneous tissue disorders, such as rash (6 out of 303 patients [2.0%]), and infections and infestations including pneumonia (4 out of 303 patients [1.3%]). For patients in the venetoclax-based regimen cohort, the most common adverse event was hepatoxicity (2 out of 73 patients [2.7%]). When looking at the cumulative incidence of discontinuation in the BTKi-based regimen cohort from the start of treatment, 13.5% of patients had discontinued therapy due to an adverse event by 10 months, 20.7% by 20 months, and 24.4% by 30 months (Figure 2).



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

**Table 3** Patient Demographics in the Second Line of Therapy

| | FCR | BR | BTKi[a] | Venetoclax[b] |
|---|---|---|---|---|
| | N = 20 | N = 62 | N = 303 | N = 73 |
| **Demographics** | | | | |
| Age at diagnosis, (years) | | | | |
| Mean ± SD (Median) | 53.8 ± 9.6 (54) | 60.1 ± 10.9 (60) | 62.5 ± 9.9 (63) | 62.4 ± 12.5 (63) |
| Age at 2L initiation, (years) | | | | |
| Mean ± SD (Median) | 59.4 ± 7.7 (61) | 65.9 ± 9.6 (65) | 67.9 ± 9.9 (68) | 66.8 ± 12.5 (68) |
| Male, N (%) | 16 (80.0%) | 43 (69.4%) | 196 (64.7%) | 53 (72.6%) |
| **Country** | | | | |
| USA | 18 (90.0%) | 58 (93.5%) | 261 (86.1%) | 68 (93.2%) |
| Germany | 2 (10.0%) | 2 (3.2%) | 2 (0.7%) | 1 (1.4%) |
| UK | 0 (0.0%) | 2 (3.2%) | 33 (10.9%) | 4 (5.5%) |
| Canada | 0 (0.0%) | 0 (0.0%) | 7 (2.3%) | 0 (0.0%) |
| **Year of initiation[c]** | | | | |
| <2014 | 14 (70.0%) | 33 (53.2%) | 6 (2.0%) | 1 (1.4%) |
| 2014-2016 | 4 (20.0%) | 18 (29.0%) | 156 (51.5%) | 3 (4.1%) |
| 2017-2019 | 1 (5.0%) | 10 (16.1%) | 131 (43.2%) | 55 (75.3%) |
| 2020-2021 | 0 (0.0%) | 0 (0.0%) | 6 (2.0%) | 14 (19.2%) |
| **Disease stage and performance status at 2L initiation, N (%)** | | | | |
| Rai stage, N (%) | | | | |
| Stage 0 | 3 (15.0%) | 3 (4.8%) | 16 (5.3%) | 7 (9.6%) |
| Stage I or II | 6 (30.0%) | 22 (35.5%) | 110 (36.3%) | 29 (39.7%) |
| Stage III or IV | 6 (30.0%) | 26 (41.9%) | 135 (44.6%) | 34 (46.6%) |
| Not Measured or unknown | 5 (25.0%) | 11 (17.7%) | 42 (13.9%) | 3 (4.1%) |
| ECOG, N (%) | | | | |
| Grade 0-1 | 15 (75.0%) | 37 (59.7%) | 212 (70.0%) | 49 (67.1%) |
| Grade 2-4 | 0 (0.0%) | 5 (8.1%) | 32 (10.6%) | 11 (15.1%) |
| Not measured or unknown | 5 (25.0%) | 20 (32.3%) | 59 (19.5%) | 13 (17.8%) |
| **IGHV at 2L initiation[d], N (%)** | | | | |
| Mutated[d] | 3 (20.0%) | 2 (4.3%) | 22 (11.3%) | 6 (10.7%) |
| Clan I gene | 1 (33.3%) | 0 (0.0%) | 2 (9.1%) | 1 (16.7%) |
| IGHV4-34 | 0 (0.0%) | 0 (0.0%) | 1 (4.5%) | 0 (0.0%) |
| Unknown | 0 (0.0%) | 0 (0.0%) | 8 (36.4%) | 2 (33.3%) |
| Unmutated | 3 (20.0%) | 6 (12.8%) | 38 (19.6%) | 17 (30.4%) |
| Testing not performed | 6 (40.0%) | 29 (61.7%) | 111 (57.2%) | 28 (50.0%) |
| Unknown | 3 (20.0%) | 10 (21.3%) | 23 (11.9%) | 5 (8.9%) |
| **Genetic aberrations at 2L initiation, N (%)** | | | | |
| At least one genetic aberration present[e,f] | 7 (35.0%) | 27 (43.5%) | 130 (42.9%) | 36 (49.3%) |
| 6q deletion or MYB mutation | 1 (14.3%) | 1 (3.7%) | 5 (3.8%) | 1 (2.8%) |
| 13q deletion or LAMP1 mutation | 4 (57.1%) | 16 (59.3%) | 56 (43.1%) | 20 (55.6%) |
| 11q deletion or ATM mutation | 1 (14.3%) | 10 (37.0%) | 38 (29.2%) | 11 (30.6%) |
| Trisomy 12 | 2 (28.6%) | 8 (29.6%) | 27 (20.8%) | 7 (19.4%) |
| 17p deletion or TP53 mutation | 2 (28.6%) | 8 (29.6%) | 42 (32.3%) | 9 (25.0%) |
| NOTCH1 | 0 (0.0%) | 0 (0.0%) | 4 (10.3%) | 5 (38.5%) |
| No genetic aberration present | 1 (5.0%) | 5 (8.1%) | 46 (15.2%) | 3 (4.1%) |
| Testing not performed or unknown | 12 (60.0%) | 30 (48.4%) | 127 (41.9%) | 34 (46.6%) |
| **Comorbidities[g], N (%)** | | | | |
| Cardiovascular | 3 (15.0%) | 23 (37.1%) | 105 (34.7%) | 34 (46.6%) |
| Endocrine/metabolic | 0 (0.0%) | 11 (17.7%) | 61 (20.1%) | 20 (27.4%) |
| Musculoskeletal | 4 (20.0%) | 6 (9.7%) | 27 (8.9%) | 9 (12.3%) |

(*continued on next page*)



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

**Table 3** (*continued*)

| | FCR N = 20 | BR N = 62 | BTKi[a] N = 303 | Venetoclax[b] N = 73 |
|---|---|---|---|---|
| Psychiatric | 1 (5.0%) | 6 (9.7%) | 27 (8.9%) | 6 (8.2%) |
| Renal | 1 (5.0%) | 8 (12.9%) | 29 (9.6%) | 7 (9.6%) |
| Respiratory | 0 (0.0%) | 9 (14.5%) | 27 (8.9%) | 10 (13.7%) |
| No known comorbidities[h] | 12 (60.0%) | 23 (37.1%) | 98 (32.3%) | 19 (26.0%) |
| **Duration of follow-up (mo)** | | | | |
| Mean ± SD<br>[$Q_1$; Median; $Q_3$]<br>(min-max) | 72.5 ± 33.0<br>[55.7; 70.6; 91.3]<br>(14.3-130.9) | 59.6 ± 32.9<br>[38.5; 61.5; 80.3]<br>(0.0-142.8) | 28.0 ± 19.5<br>[11.5; 26.1; 41.2]<br>(0.0-86.4) | 9.7 ± 9.3<br>[2.5; 5.8; 15.0]<br>(0.0-38.2) |
| **Treatment duration (mo)** | | | | |
| Mean ± SD<br>[$Q_1$; Median; $Q_3$]<br>(min-max) | 4.9 ± 3.6<br>[2.7; 5.2; 6.1]<br>(0.9-17.4) | 3.5 ± 1.8<br>[2.0; 3.8; 5.0]<br>(0.0-6.5) | 21.0 ± 18.8<br>[4.2; 15.6; 35.1]<br>(0.0-83.7) | 8.2 ± 8.8<br>[1.9; 5.2; 11.6]<br>(0.0-38.2) |

Abbreviations: BCL-2 = B-cell lymphoma 2 signaling; BR = bendamustine + rituximab; BTKi = Bruton tyrosine kinases inhibitor; ECOG = Eastern cooperative oncology group; FCR = fludarabine + cyclophosphamide + rituximab; IGHV = immunoglobulin heavy chain variable; N = number; SD = standard deviation.
[a] BTKi-based regimens included acalabrutinib- and ibrutinib-based treatments.
[b] Venetoclax included BCL-2-based treatments (eg, venetoclax monotherapy). The venetoclax cohort includes both patients who received venetoclax monotherapy and those that were treated with VG/VR.
[c] There were 6 patients for whom the date of second-line of therapy initiation was missing.
[d] IGHV testing status at 2L initiation was not collected for data collected during the first round of data collection.
[e] Calculated out of patients who had a mutation or abnormality detected.
[f] Patients may have had more than one genetic aberration identified (categories are not mutually exclusive).
[g] Patients may have had more than one comorbidity identified (categories are not mutually exclusive).
[h] Includes all patients without any comorbidities selected (category is mutually exclusive).

**Table 4** Treatment Status and Discontinuation Reasons in the Second Line of Therapy

| | FCR N = 20 | BR N = 62 | BTKi N = 303 | Venetoclax Monotherapy[a] N = 27 | VG/VR N = 43 |
|---|---|---|---|---|---|
| **Treatment status**[b] | | | | | |
| Still on treatment | 0 (0.0%) | 2 (3.2%) | 171 (56.4%) | 18 (66.7%) | 30 (69.8%) |
| Completed planned duration | 10 (50.0%) | 37 (59.7%) | 14 (4.6%) | 1 (3.7%) | 1 (2.3%) |
| Premature discontinuation of therapy | 10 (50.0%) | 22 (35.5%) | 115 (38.0%) | 8 (29.6%) | 12 (27.9%) |
| **Reason for treatment discontinuation**[c,d] | | | | | |
| Adverse event | 6 (30.0%) | 11 (17.7%) | 60 (19.8%) | 0 (0.0%) | 5 (11.6%) |
| Severe adverse event[e] | 3 (50.0%) | 8 (72.7%) | 37 (61.7%) | 0 (0.0%) | 3 (60.0%) |
| Disease progression | 1 (5.0%) | 3 (4.8%) | 24 (7.9%) | 2 (7.4%) | 3 (7.0%) |
| Watchful waiting due to low or no disease activity | 3 (15.0%) | 6 (9.7%) | 9 (3.0%) | 0 (0.0%) | 3 (7.0%) |

Abbreviations: BTKi = Bruton tyrosine kinases inhibitor; BR = bendamustine + rituximab; FCR = fludarabine + cyclophosphamide + rituximab; N = number; VG/VR = venetoclax with obinutuzumab or rituximab.
[a] Patients who received other venetoclax-based combination therapies have been excluded (ie, 3 patients).
[b] Treatment status was unknown for 1 patient receiving BR and 3 patients receiving BTKi.
[c] Multiple reasons may have been selected; categories are not mutually exclusive.
[d] Other reasons for discontinuation also included: economic reasons, patient preference, non-severe adverse event, disease transformation, patient request, refractory to treatment, terminal illness or death due to CLL, and death unrelated to disease or therapy.
[e] Severe adverse event indicates Grade 3, 4, or 5.

## Discussion

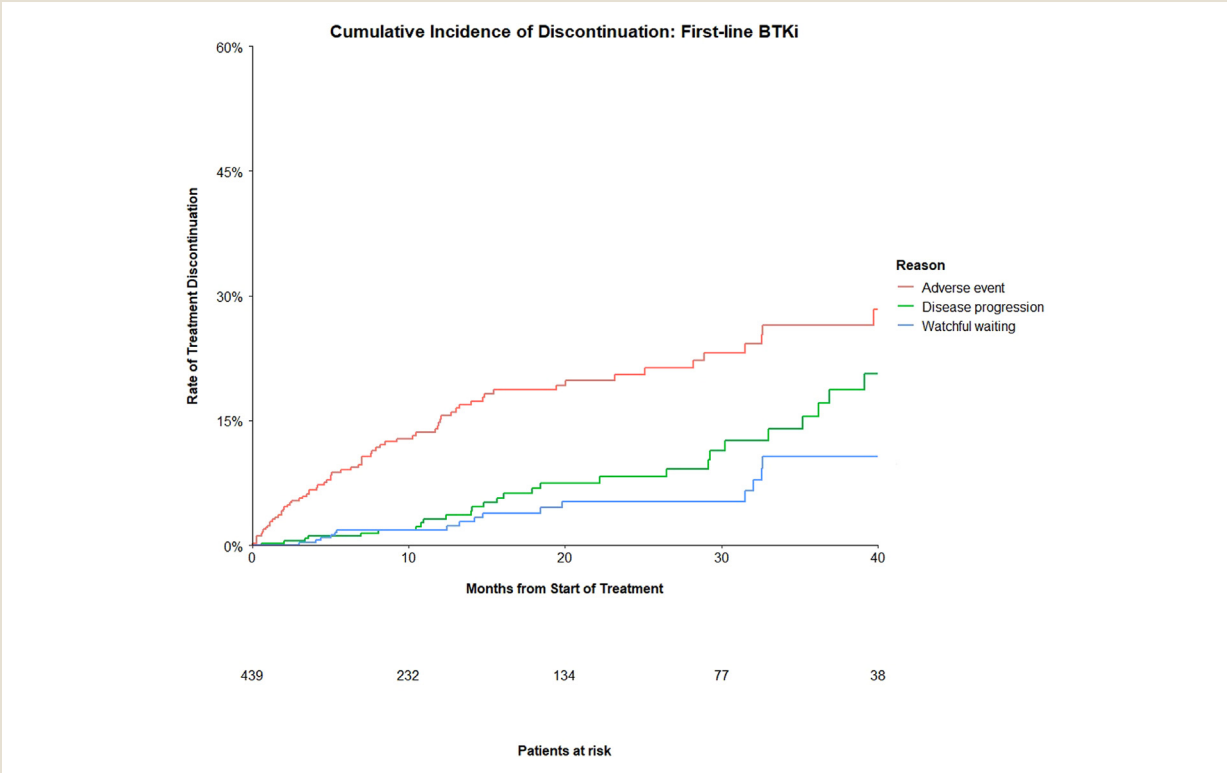
This real-world, multicenter, observational, international study assessed treatment discontinuation patterns in the first and second lines of therapy among patients with CLL. Despite advances in the treatment landscape with respect to tolerability and efficacy, premature treatment discontinuations occurred across all types of therapies analyzed in this study.

Nearly one-third of patients treated with FCR/BR in both the first and second lines of therapy discontinued therapy (23.7-34.5% in the first line of therapy; 35.5%-50.0% in the second line of therapy). The most common reason for premature treatment discontinuations, except for the venetoclax-based regimen cohort in the first line of therapy, was the presence of adverse event(s) with the majority being severe (Grade 3, 4, or 5) adverse events. In the first and second line of therapy, common adverse events were hematological abnormalities among patients in the FCR and BR cohorts. Among patients in the BTKi-based regimen cohort, predominantly comprised of ibrutinib-based regimens, common adverse events were cardiac, skin and subcutaneous tissue disorders in first and second line of therapy and musculoskeletal disorders



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

**Figure 1** Time to treatment discontinuation[1] by reason:[2,3] First-line therapy with BTKi-based Regimens
Abbreviations: BTKi = Bruton tyrosine kinases inhibitor.
Notes:
[1]Kaplan-Meier estimates exclude 34 patients with missing information from the total sample size of 473.
[2]Multiple reasons may have been selected; categories are not mutually exclusive.
[3]Watchful waiting due to low or no disease activity.




in first line only. Among patients in the venetoclax-based regimen cohort in the second line of therapy, hepatoxicity was recorded, whereas infections and infestations were recorded for patients in the BR and BTKi-based regimen cohorts. When analyzing the cumulative incidence of treatment discontinuation over time in the BTKi-based regimen cohort, results demonstrate that discontinuations did not occur exclusively at the treatment onset but continued across time throughout a given line(s) of therapy. Taken together, these findings suggest that there is an unmet clinical need for more tolerable therapies in CLL. Novel agents, based on finite therapy durations, may potentially offer a better tolerated option for newly diagnosed or relapsed/refractory patients or reduce a time period over which the patient is exposed to the risk of adverse events. However, further studies with longer follow-up are warranted to investigate this hypothesis.

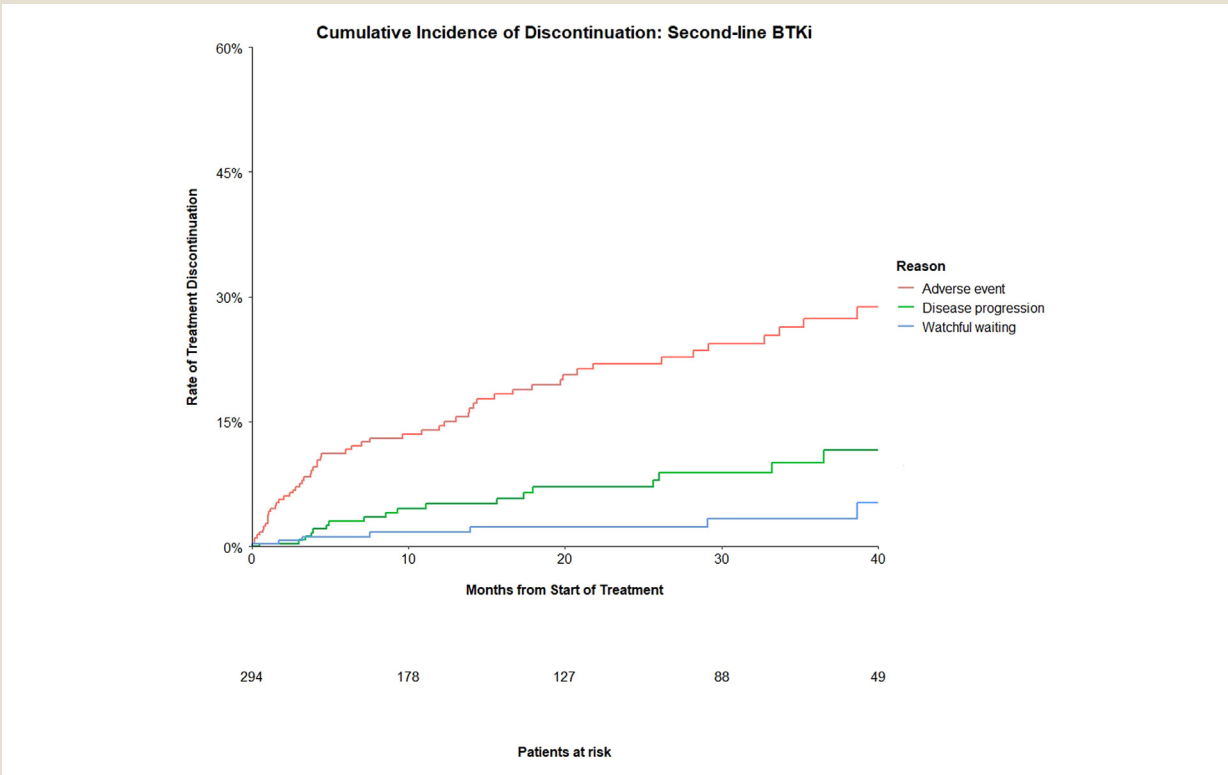
Unlike patients treated with FCR/BR or BTKi-based regimens, for patients in the venetoclax-based regimen cohort, the most common reason for premature treatment discontinuation in the first line of therapy was disease progression (6.9%). In the second line of therapy, in contrast to other regimens where between 18% and 30% patients discontinued therapy due to adverse events, only six patients (8.2%) discontinued venetoclax-based regimens due to adverse events despite baseline cardiac comorbidities and being pretreated. The lowest proportion of patients that discontinued treatment prematurely were of the venetoclax-based regimen cohort, potentially suggesting that venetoclax could be better tolerated than other agents, consistent with literature from clinical trials; however, larger cohorts of patients will be needed to confirm these findings in a broader population.[29-31]

Overall, the proportion of premature discontinuations, and the fact that adverse events represented most commonly reported reasons for discontinuation, together with the types of adverse events leading to discontinuation, were consistent with what has been previously reported in literature. For example, the proportion of patients who discontinued FCR in the first line of therapy in this study (23.7%) aligns with clinical studies[32,33] of premature treatment discontinuations; in one phase 2 study, 23% of patients did not complete the planned number of FCR cycles.[33] Similar to a previously published real-world study[26] and across clinical trials,[32,33] adverse events represented one of the most commonly reported



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

**Figure 2** Time to treatment discontinuation[1] by reason:[2,3] Second-line therapy with BTKi-based regimens
Abbreviations: BTKi = Bruton tyrosine kinases inhibitor.
Notes:
[1]Kaplan-Meier estimates exclude 10 patients with missing information.
[2]Multiple reasons may have been selected; categories are not mutually exclusive.
[3]Watchful waiting due to low or no disease activity.




reasons for treatment discontinuation. Although direct comparisons would be challenging to make due to differences in study design and adverse event assessments[19,24] (eg, the current study only collected information regarding what/how an adverse event was recorded in the patients' chart), this study did find that adverse events were among the most common reasons for premature treatment discontinuation. In addition, the types of adverse events that contributed to premature treatment discontinuation, for both CT/CIT and targeted agents aligned with what has been reported previously in clinical trials[10,19] (eg, CT/CIT: infections [in FCR][33]; BTKi: bleeding [in ibrutinib][33] and atrial fibrillation [in ibrutinib]). Lastly, as treatment discontinuation due to an adverse event in targeted agents (ie, BTKi-based regimens) was observed in first- and second-lines of therapy, these findings further highlight an unmet treatment need in this patient population.

In the evolving era of targeted agents for CLL, clinicians now have a range of options that have the potential to help patients manage their disease, which is particularly relevant in the relapsed/refractory setting.[7] However, despite the array of available targeted therapies, several questions remain unanswered, with the main question focusing on the feasibility of fixed-duration treatment regimens.[11] Targeted therapies have routinely required continuous treatment to disease progression, which presents challenges to patients (eg, intolerance, cost burden) that can result in dose reductions or treatment cessation.[9,11,34] Moreover, patients with advancing age and increasing comorbidities may be especially apt to experience diminished tolerability of long-term treatments; as a result, targeted treatment regimens with fixed duration could potentially be beneficial for patients with CLL.[35] Rather than unplanned, premature treatment discontinuations, the potential benefits associated with well-tolerated fixed-duration regimens, particularly among patients with CLL who are able to reach therapeutic milestones during continuous treatment, may represent a unique therapeutic opportunity.[36] Recently, an analysis of the post-treatment follow-up of the MURANO trial,[37] a phase 3 study that assessed the progression-free survival benefit associated with fixed-duration (24 months) venetoclax + rituximab versus bendamustine-rituximab in patients with relapsed/refractory CLL, found that at a median of approximately 10 months, only 12% (16 out of 130) of patients treated with fixed-duration of venetoclax + rituximab progressed; 70% of patients



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

maintained their achieved level of undetected minimal residual disease (MRD); and among patients who achieved undetected MRD, 98% of patients did not progress.[38]

As treatment options for CLL expand, additional studies are warranted to further evaluate the feasibility and effectiveness of fixed-duration treatment with targeted agents and the impact on treatment discontinuation rates. These studies will require larger and more diverse patient populations to assess the durability of treatment response, as well as quality of life assessments to provide stakeholders with an in-depth understanding of the benefits and risks associated with shifting treatment paradigms.

## Limitations

Although this study offers a recent characterization of treatment discontinuation patterns among different cohorts of patients with CLL across several therapeutic regimens, this study is subject to limitations that are common to retrospective chart review analyses. First, information reported is as recorded in patients' charts and entered by investigators across multiple centers with possible differences in interpretation of clinical data. Second, information regarding the reasons for treatment discontinuation was solely based on reasons recorded in patients' charts. Lastly, the follow-up duration captured in this study was relatively short, particularly for patients who received targeted agents, specifically venetoclax, which may limit the generalizability of treatment discontinuation practices. Future studies with longer follow-up are warranted to further assess treatment discontinuation practices over longer periods. Despite these limitations, our study includes robust, clinician-adjudicated data that has been collected following a rigorous data quality process and provide important insights on real-world discontinuation patterns in CLL.

## Conclusions

Despite the relatively short duration of follow-up, similar premature treatment discontinuation patterns were observed in the first- and second-line settings based on the type of treatment received. Treatment with CT/CIT was commonly discontinued before completion of the planned cycles of therapy. which suggests that these treatment regimens could be difficult to tolerate. In contrast to clinical trials, treat to progression BTKi-based regimens were most often discontinued due to adverse events. The lowest discontinuation rates for venetoclax-based regimens potentially suggests that venetoclax could be better tolerated than other agents. Due to limited information collected and small sample sizes, future studies regarding venetoclax-based regimen discontinuation practices are warranted in a larger patient population. Overall, the results of this study highlight the unmet need for tolerable therapies in CLL, with finite therapy duration specifically offering a better tolerated option for patients who are newly diagnosed and for those who are relapsed or refractory to prior treatments, which would limit continuous exposure to treatment and may prevent treatment discontinuation due to adverse events.

### *Clinical Practice Points*

What is already known about this subject?

- Despite advances in available treatment options, patients with chronic lymphocytic leukemia (CLL) discontinue treatment for a variety of reasons, with toxicity being one of common reasons.
- Outside of clinical trials, there is limited evidence available regarding treatment discontinuation of targeted agents.

What are the new findings?

- Of the 1365 1L patients, 190 (13.9%) received FCR, of whom 23.7% discontinued; 255 (18.7%) received BR, of whom 34.5% discontinued; 481 (35.2%) received BCRi-based regimens, of whom 28.3% discontinued; and 43 (3.1%) received venetoclax-based regimens, of whom 16.3% discontinued.
- The most common reasons for treatment discontinuation within each respective first line cohort were adverse events (FCR: 13.2%; BR: 14.1%; BCRi-based regimens: 15.8%) and disease progression (venetoclax-based regimens: 7.0%).
- Of the 631 2L patients, 20 (3.2%) received FCR, of whom 50.0% discontinued; 62 (9.8%) received BR, of whom 35.5% discontinued; 313 (49.6%) received BCRi-based regimens, of whom 38.0% discontinued; and 73 (11.6%) received venetoclax-based regimens, of whom 30.1% discontinued.
- The most common reason for treatment discontinuation within each respective second-line cohort was adverse events (FCR: 30.0%; BR: 17.7%; BCRi-based regimens: 20.1%; venetoclax-based regimens: 8.2%).

How might it impact on clinical practice in the foreseeable future?

- These results highlight the unmet need for tolerable therapies in CLL, with finite therapy duration specifically offering a better tolerated option for patients who are newly diagnosed or relapsed/refractory to prior treatments, which would limit continuous exposure to treatment and may prevent treatment discontinuation due to adverse events.

## Data Statement

The data analyzed in this study are subject to Health Insurance Portability and Accountability Act privacy restrictions and are not publicly available. Deidentified data could be made available by the corresponding author upon reasonable request.

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. The data will be accessible for 12 months, with possible extensions considered.



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

For more information on the process or to submit a request, visit the following link: https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html.

## Disclosures

MS: Consulting, Advisory Boards, steering committees or data safety monitoring committees: Abbvie, Genentech, AstraZeneca, Sound Biologics, Pharmacyclics, Beigene, Bristol Myers Squibb, Morphosys/Incyte, TG Therapeutics, Innate Pharma, Kite Pharma, Adaptive Biotechnologies, Epizyme, Eli Lilly, Adaptimmune, Mustang Bio, Regeneron, Merck, Fate therapeutics, MEI pharma and Atara Biotherapeutics; Research Funding: Mustang Bio, Celgene, Bristol Myers Squibb, Pharmacyclics, Gilead, Genentech, AbbVie, TG Therapeutics, Beigene, AstraZeneca, Sunesis, Atara Biotherapeutics, Genmab, Morphosys/Incyte. KS, BSM, NE, RK, HA, DJ: employees of AbbVie and may hold stock or stock options. HHT: Consultancy: AbbVie, Astra Zeneca; Advisory Board: Astra Zeneca. JNA: Consultancy and advisory board: AbbVie, ADCT Therapeutics, AstraZeneca/Acerta, Beigene, Epizyme, Genentech, Janssen, Pharmacyclics, TG Therapeutics; Honoraria: Abbvie, AstraZeneca, Beigene, Janssen, Pharmacyclics; Research funding: Genentech, Celgene, Janssen, TG Therapeutics. CU: Honoraria - Genentech, Pharmacyclics, AbbVie, AstraZeneca, loxo, Genentech, Janssen; Research funding, - loxo, Astrazeneca, loxo, adaptive biotechonologies, Pharmacyclics, and AbbVie. CC: Consultancy/Honoraria: AbbVie, Beigene, Genentech, Janssen, MEI Pharma, Mingsight, TG Therapeutics, Octapharma, LOXO/Lilly, AstraZeneca; Speaker Bureau: AbbVie, Beigene, Genentech; Research funding: AbbVie, Loxo Oncology. LL: Speaker Bureau: SeaGen, Celgene/BMS, KitePharma, BeiGene, Pharmacyclics/Janssen/Abbvie, AstraZeneca, Epizyme, Karyopharm, Ely Lilly; Advisory Board and/or Consultancy: Bayer, SeaGen, ADC therapeutics, Abbvie, Janssen, Pharmacyclics, Kite, AstraZeneca, TG Therapeutics, Ely Lilly. LL: Speaker Bureau: Seattle Genetics, Celgene/BMS, KitePharma, BeiGene, Pharmacyclics/Janssen, AstraZeneca, Epizyme, Karyopharm; Advisory Board and/or Consultancy: Bayer, Seattle Genetics, ADC therapeutics, Abbvie, Janssen, Pharmacyclics, Kite, AstraZeneca, TG Therapeutics. PMB: Consultancy for AbbVie, Gilead. JRB: Consultancy: AbbVie, Acerta, AstraZeneca, Beigene, Catapult, Dynamo Therapeutics, Genentech/Roche, Gilead, Juno/Celgene, Kite, Loxo, Novartis, Octapharma, Pfizer, Pharmacyclics, Sunesis, TG Therapeutics, Verastem; Honoraria: Janssen, Teva; Research funding: Gilead, Loxo, Sun, and Verstem; Data safety and monitoring committees: Morphosys, Invectys. TAE: Honoraria: Abbvie, AstraZeneca, Gilead, and Janssen; Advisory Board/Honoraria: Beigene, Incyte, KITE, Loxo Oncology, Roche, and Secura Bio; Education Honorarium: Roche; Research funding: AstraZeneca, Beigene, and Gilead; Travel support: Abbvie, Gilead, and Roche; Trial steering committee: Loxo Oncology. AR: Travel: Gilead. AS: Consultancy: AbbVie, Genentech, Celgene, AstraZeneca, Pharmacyclics; Speaker Bureau: AbbVie, Genentech, Pharmacyclics, Janssen, AstraZeneca, Beigene, Celgene, Verastem, Kite, Gilead, Seattle Genetics, Jazz Pharmaceuticals; Research Funding: Bristol-Myers Squibb. NL: Advisory board member for AbbVie, Celgene, Roche-Genentech, Janssen, Pharmacyclics; Gilead, AstraZeneca; Institutional research funding from AbbVie, Genentech, Gilead, Verastem, Bei-Gene, TG Therapeutics, Acerta. AS: Honoraria: AbbVie, Acerta, AstraZeneca, Gilead, Janssen. LER: Served as a consultant for AbbVie, Ascentage, AstraZeneca, Beigene, Janssen, Loxo Oncology, Pharmacyclics, Pfizer, TG Therapeutics; served as a CME speaker for DAVA, Curio, Medscape, and PeerView; holds minority ownership interest in Abbott Laboratories; received travel support from LOXO oncology; and has received research funding (paid to the institution) from Adaptive Biotechnologies, AstraZeneca, Genentech, AbbVie, Pfizer, Loxo Oncology, Aptose Biosciences, Dren Bio, and Qilu Puget Sound Biotherapeutics. RB: Consultancy: AbbVie, Celgene, Regeneron; Travel: Merck, Regeneron, Pharmacyclics, Gilead; IP rights: Merck. Research Funding: AbbVie, F. Hoffmann-La Roche LTD/Genentech Inc., Regeneron, and Pharmacyclics LLC – an AbbVie Company; Personal Conflict: Sanofi-Pasteur. BE: Research funding, honoraria (consultant or advisory board member), and travel support from AbbVie, Beigene, ARQuele, Celgene, Gilead, Janssen, Mundipharma, Novartis, Roche. IF: Consultant and/or Advisory board: Abbvie, Astrazeneca, Bristol Myers Squibb, Gilead, Janssen, Merck, Novartis, Roche, Seattle Genetics. MSD: Consultancy/Advisory Board: Genentech, Janssen, Astra-Zeneca, AbbVie, TG Therapeutics, Adaptive Biotechnologies, Secura Bio, BeiGene, Takeda, Merck, Eli Lilly, BMS; Research Funding: AbbVie, TG Therapeutics, Genentech, Astra-Zeneca, Surface Oncology. BTH: Advisory boards for Genentech, AbbVie, Pharmacyclics, Gilead. Research funding: Genentech, AbbVie, Pharmacyclics. SJS: Consultant and Institutional Research Funding: Novartis, Pharmacyclics, Celgene; Institutional Research Funding: Gilead, Janssen Research & Development, Merck; Scientific Advisory Committees: Nordic Nanovector; Consultant: Genentech, Acerta. DMB: Advisor/Consultant: AbbVie, Pharmacyclics, Pfizer, TG Therapeutics; Institutional Research Funding: AbbVie, ArQule/Merck, Ascentage, AstraZeneca/Acerta, BeiGene, CATO SMS/Catapult, DTRM, Genentech, Juno/Celgene/BMS, MEI Pharma, NeWave, Pharmacyclics, TG Therapeutics; Other Guidelines/Registry Memberships: NCCN panel member, inform-CLL registry steering committee (Pharmacyclics/AbbVie), CORE, Biosimilars outcomes research panel (Pfizer). IP, RB, AG are employees of Analysis Group, Inc., which has received consultancy fees from AbbVie. ARM: Institutional research funding: Pharmacyclics, Gilead, AbbVie, TG therapeutics, Acerta; Consultant for Pharmacyclics, AbbVie, and Janssen.

Prior presentations: Presented at the 61st Annual Meeting of the American Society of Hematology (ASH) • Dec 7–10, 2019 • Orlando, FL, USA (Data presented has been updated through June 2021).

## Acknowledgments

Editorial assistance was provided by Christine Tam and Loraine Georgy of Analysis Group, Inc. Support for this assistance was funded by AbbVie. Financial support for this study was provided by AbbVie. AbbVie contributed to the design, study conduct, and data interpretation in collaboration with the other authors. All authors contributed to the development of the publication and maintained control over the final content.



Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010

## References


1. Del Poeta G, Postorino M, Pupo L, et al. Venetoclax: Bcl-2 inhibition for the treatment of chronic lymphocytic leukemia. *Drugs Today (Barc)*. 2016;52(4):249–260. doi:10.1358/dot.2016.52.4.2470954.
2. Sanford DS, Wierda WG, Burger JA, Keating MJ, O'Brien SM. Three newly approved drugs for chronic lymphocytic leukemia: incorporating ibrutinib, idelalisib, and obinutuzumab into clinical practice. *Clin Lymphoma Myeloma Leuk*. 2015;15(7):385–391. doi:10.1016/j.clml.2015.02.019.
3. Gentile M, Petrungaro A, Uccello G, et al. Venetoclax for the treatment of chronic lymphocytic leukemia. *Expert Opin Investig Drugs*. 2017;26(11):1307–1316. doi:10.1080/13543784.2017.1386173.
4. Smolewski P, Robak T. Current treatment of refractory/relapsed chronic lymphocytic leukemia: a focus on novel drugs. *Acta Haematologica*. 2021;144(4):365–379.
5. Barrientos JC. Sequencing of chronic lymphocytic leukemia therapies. *Hematology Am Soc Hematol Educ Program*. 2016;2016(1):128–136. doi:10.1182/asheducation-2016.1.128.
6. Goede V, Cramer P, Busch R, et al. Interactions between comorbidity and treatment of chronic lymphocytic leukemia: results of German Chronic Lymphocytic Leukemia Study Group trials. *Haematologica*. 2014;99(6):1095–1100. doi:10.3324/haematol.2013.096792.
7. Brown JR, Hallek MJ, Pagel JM. Chemoimmunotherapy versus targeted treatment in chronic lymphocytic leukemia: when, how long, how much, and in which combination? *Am Soc Clin Oncol Educ Book*. 2016;35:e387–e398. doi:10.14694/EDBK_15901810.1200/EDBK_159018.
8. Patel K, Pagel JM. Current and future treatment strategies in chronic lymphocytic leukemia. *J Hematol Oncol*. 2021;14(1):1–20.
9. Mato AR, Nabhan C, Thompson MC, et al. Toxicities and outcomes of 616 ibrutinib-treated patients in the United States: a real-world analysis. *Haematologica*. 2018;103(5):874–879. doi:10.3324/haematol.2017.182907.
10. Ahn IE, Davids MS. Safety profiles of novel agent therapies in CLL. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):354–357. doi:10.1182/asheducation-2017.1.354.
11. Brander D, Islam P, Barrientos JC. Tailored treatment strategies for chronic lymphocytic leukemia in a rapidly changing era. *Am Soc Clin Oncol Educ Book*. 2019;39:487–498. doi:10.1200/EDBK_238735.
12. Roberts AW, Davids MS, Pagel JM, et al. Targeting BCL2 with venetoclax in relapsed chronic lymphocytic leukemia. *N Engl J Med*. 2016;374(4):311–322. doi:10.1056/NEJMoa1513257.
13. Vitale C, Burger JA. Chronic lymphocytic leukemia therapy: new targeted therapies on the way. *Expert Opin Pharmacother*. 2016;17(8):1077–1089. doi:10.1517/14656566.2016.1168401.
14. Molica S, Matutes E, Tam C, Polliack A. Ibrutinib in the treatment of chronic lymphocytic leukemia: 5 years on. *Hematol Oncol*. 2019;38:129–136. doi:10.1002/hon.2695.
15. Maddocks KJ, Ruppert AS, Lozanski G, et al. Etiology of ibrutinib therapy discontinuation and outcomes in patients with chronic lymphocytic leukemia. *JAMA Oncol*. 2015;1(1):80–87. doi:10.1001/jamaoncol.2014.218.
16. Forum UC. Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. *Haematologica*. 2016;101(12):1563.
17. Fürstenau M, Eichhorst B. Novel agents in chronic lymphocytic leukemia: new combination therapies and strategies to overcome resistance. *Cancers*. 2021;13(6):1336.
18. Byrd JC, Hillmen P, O'Brien S, et al. Long-term follow-up of the RESONATE phase 3 trial of ibrutinib vs ofatumumab. *Blood*. 2019;133(19):2031–2042. doi:10.1182/blood-2018-08-870238.
19. Byrd JC, Brown JR, O'Brien S, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. *N Engl J Med*. 2014;371(3):213–223. doi:10.1056/NEJMoa1400376.
20. Munir T, Brown JR, O'Brien S, et al. Final analysis from RESONATE: up to six years of follow-up on ibrutinib in patients with previously treated chronic lymphocytic leukemia or small lymphocytic lymphoma. *Am J Hematol*. 2019;94(12):1353–1363. doi:10.1002/ajh.25638.
21. Burger JA, Wiestner A. Targeting B cell receptor signalling in cancer: preclinical and clinical advances. *Nat Rev Cancer*. 2018;18(3):148–167. doi:10.1038/nrc.2017.121.
22. Gordon MJ, Churnetski M, Alqahtani H, et al. Comorbidities predict inferior outcomes in chronic lymphocytic leukemia treated with ibrutinib. *Cancer*. 2018;124(15):3192–3200. doi:10.1002/cncr.31554.
23. Jain P, Thompson PA, Keating M, et al. Long-term outcomes for patients with chronic lymphocytic leukemia who discontinue ibrutinib. *Cancer*. 2017;123(12):2268–2273. doi:10.1002/cncr.30596.
24. O'Brien S, Furman RR, Coutre S, et al. Single-agent ibrutinib in treatment-naive and relapsed/refractory chronic lymphocytic leukemia: a 5-year experience. *Blood*. 2018;131(17):1910–1919. doi:10.1182/blood-2017-10-810044.
25. Barr PM, Brown JR, Hillmen P, et al. Impact of ibrutinib dose adherence on therapeutic efficacy in patients with previously treated CLL/SLL. *Blood*. 2017;129(19):2612–2615. doi:10.1182/blood-2016-12-737346.
26. Nuttall E, Tung J, Trounce E, Johnston R, Chevassut T. Real-world experience of ibrutinib therapy in relapsed chronic lymphocytic leukemia: results of a single-center retrospective analysis. *J Blood Med*. 2019;10:199–208. doi:10.2147/JBM.S202286.
27. Hou JZ, Ryan K, Du S, et al. Real-world ibrutinib dose reductions, holds and discontinuations in chronic lymphocytic leukemia. *Future Oncol*. 2021;17(35):4959–4969. doi:10.2217/fon-2021-0964.
28. Mato AR, Yazdy MS, Hill BT, et al. Treatment patterns and outcomes of patients with CLL treated with chemoimmuno-and novel agent-based therapy: a multicenter study. *Blood*. 2018;132:4759.
29. Jones JA, Mato AR, Wierda WG, et al. Venetoclax for chronic lymphocytic leukaemia progressing after ibrutinib: an interim analysis of a multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2018;19(1):65–75. doi:10.1016/S1470-2045(17)30909-9.
30. Coutre S, Choi M, Furman RR, et al. Venetoclax for patients with chronic lymphocytic leukemia who progressed during or after idelalisib therapy. *Blood*. 2018;131(15):1704–1711. doi:10.1182/blood-2017-06-788133.
31. Eyre TA, Roeker LE, Fox CP, et al. The efficacy and safety of venetoclax therapy in elderly patients with relapsed, refractory chronic lymphocytic leukaemia. *Br J Haematol*. 2020;188(6):918–923.
32. Schweighofer CD, Ritgen M, Eichhorst BF, et al. Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission: long-term follow-up of a randomized phase III trial of the German CLL Study Group (GCLLSG). *Br J Haematol*. 2009;144(1):95–98. doi:10.1111/j.1365-2141.2008.07394.x.
33. Short NJ, Keating MJ, Wierda WG, et al. Fludarabine, cyclophosphamide, and multiple-dose rituximab as frontline therapy for chronic lymphocytic leukemia. *Cancer*. 2015;121(21):3869–3876. doi:10.1002/cncr.29605.
34. Shanafelt TD, Borah BJ, Finnes HD, et al. Impact of ibrutinib and idelalisib on the pharmaceutical cost of treating chronic lymphocytic leukemia at the individual and societal levels. *J Oncol Pract*. 2015;11(3):252–258. doi:10.1200/JOP.2014.002469.
35. Ludwig H, Zojer N. Fixed duration vs continuous therapy in multiple myeloma. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):212–222. doi:10.1182/asheducation-2017.1.212.
36. Cuneo A, Foa R. Relapsed/refractory chronic lymphocytic leukemia: chemoimmunotherapy, treatment until progression with mechanism-driven agents or finite-duration therapy? *Mediterr J Hematol Infect Dis*. 2019;11(1). doi:10.4084/MJHID.2019.024.
37. Seymour JF, Kipps TJ, Eichhorst B, et al. Venetoclax-rituximab in relapsed or refractory chronic lymphocytic leukemia. *N Engl J Med*. 2018;378(12):1107–1120. doi:10.1056/NEJMoa1713976.
38. Kater AP, Seymour JF, Hillmen P, et al. Fixed duration of venetoclax-rituximab in relapsed/refractory chronic lymphocytic leukemia eradicates minimal residual disease and prolongs survival: post-treatment follow-up of the MURANO phase III study. *J Clin Oncol*. 2019;37(4):269–277. doi:10.1200/JCO.18.01580.




Please cite this article as: Mazyar Shadman et al, Treatment Discontinuation Patterns for Patients With Chronic Lymphocytic Leukemia in Real-World Settings: Results From a Multi-Center International Study, Clinical Lymphoma, Myeloma and Leukemia, https://doi.org/10.1016/j.clml.2023.03.010