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Original article

# [Translated article] Safety of Bruton kinase inhibitors in chronic lymphocytic leukemia: Real world clinical practice

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ABSTRACT

*Introduction:* Bruton's tyrosine kinase inhibitors (BTKi) have replaced immunochemotherapy in patients with chronic lymphocytic leukemia (CLL). The safety profile, particularly in monotherapy indications under real-world clinical practice conditions, is key to optimizing outcomes.
*Objective:* To describe the safety and tolerability of continuous/indefinite BTKi therapy in patients with CLL treated in the first line and relapse/refractory (R/R) conditions with BTKi monotherapy, within labeled indications, at a tertiary care hospital.
*Methods:* Observational, retrospective, single-centre study including patients with CLL treated with iBTK (2015–2024). Demographic data, previous lines of treatment, dose adjustments and suspensions, and adverse events (AEs) by system and severity were recorded. Proportions were compared using Fisher's exact test. Treatment continuation was analyzed using Kaplan–Meier curves, log-rank tests, and Cox regression.
*Results:* Eighty-three patients (50.6% male) were included, with a mean age at diagnosis of 67.2 years. Forty-eight (58%) received iBTK as first-line therapy and 35 (42%) in R/R. The most commonly used iBTK was ibrutinib (62.5% in first-line and 88.6% in R/R). Median follow-up was 20.8 months. Overall, 28.9% required dose adjustment, with no differences between the two groups ($p = 0.158$). Treatment discontinuation was more frequent in patients with R/R patients (74.3% vs. 39.6%; RR 1.81; 95% CI: 1.23–2.66; $p = 0.002$). AE were the most common reason for treatment discontinuation (15.7%). A total of 161 AEs were recorded, with infectious AE being the most frequent category. Respiratory infections were significantly more common in R/R patients ($p = 0.046$). Patients with prior exposure to immunochemotherapy had an increased risk of treatment discontinuation (HR = 2.15; 95% CI: 1.18–3.89; $p = 0.012$).
*Conclusions:* BTKi showed a manageable safety profile, with infections as the most common toxicity and secondary malignancies occurring at rates comparable to those reported in the literature. Treatment discontinuation was less frequent in the frontline setting, underscoring the influence of clinical context and prior therapies. Despite the limitations of a retrospective, single-centre design, this study provides information applicable to daily practice and highlights the importance of close follow-up to optimize both safety and treatment continuity.
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## Seguridad de los inhibidores de tirosina cinasa de Bruton en la leucemia linfática crónica: práctica en vida real

*Palabras clave:*
Inhibidores de la tirosina cinasa de Bruton
Leucemia linfocítica crónica
Toxicidad
Ibrutinib
Acalabrutinib
Zanubrutinib

RESUMEN

*Introducción:* los inhibidores de la tirosina cinasa de Bruton (iBTK) han desplazado a la inmunoquimioterapia en los pacientes con leucemia linfática crónica (LLC). El perfil de seguridad, sobre todo en las indicaciones de monoterapia en condiciones de práctica clínica real, es clave para optimizar los resultados.
*Objetivo:* describir la seguridad y tolerancia al tratamiento indefinido de los iBTK en pacientes con LLC tratados en primera línea y en recaída/refractariedad (R/R) con un iBTK en monoterapia en sus indicaciones en un hospital terciario.

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*Métodos:* estudio observacional, retrospectivo y unicéntrico, que incluyó pacientes con LLC tratados con iBTK (2015–2024). Se registraron datos demográficos, líneas previas, ajustes y suspensiones de dosis, y eventos adversos (EA) por sistema y gravedad. Las proporciones se compararon con test exacto de Fisher. La continuidad del tratamiento se analizó mediante curvas de Kaplan–Meier, test de log-rank y regresión de Cox.
*Resultados:* se incluyeron 83 pacientes (50,6% varones) con edad media al diagnóstico de 67,2 años. Recibieron iBTK en primera línea 48 pacientes (58%) y 35 (42%) en R/R. El iBTK más empleado fue el ibrutinib (62,5% en primera línea y 88,6% en R/R). La mediana de seguimiento fue de 20,8 meses. El 28,9% requirió ajuste de dosis, sin diferencias entre ambos grupos ($p = 0{,}158$). La discontinuación fue más frecuente en los pacientes en R/R (74,3% vs. 39,6%; RR = 1,81; IC 95%: 1,23-2,66; $p = 0{,}002$). Globalmente, los EA fueron el motivo más habitual de suspensión del tratamiento (15,7%). Se registraron 161 EA, siendo los infecciosos los más frecuentes. Las infecciones respiratorias fueron significativamente más incidentes en R/R ($p = 0{,}046$). Los pacientes con exposición previa a inmunoquimioterapia tuvieron un aumento del riesgo de suspensión del tratamiento (HR = 2,15; IC 95%: 1,18–3,89; $p = 0{,}012$).
*Conclusiones:* los iBTK mostraron un perfil de seguridad manejable, con infecciones como toxicidad más frecuente y segundas neoplasias en tasas comparables a la literatura. La no interrupción del tratamiento fue mayor en primera línea, lo que indica la influencia del contexto clínico y de las terapias previas. Aun con las limitaciones de un diseño retrospectivo y unicéntrico, el estudio aporta información aplicable a la práctica diaria y resalta la importancia de un seguimiento estrecho para optimizar seguridad y continuidad del tratamiento.
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## Introduction

Chronic lymphocytic leukaemia (CLL) is the most common type of leukaemia in adults in Western countries.[1] It occurs more frequently in older patients,[1–3] who often have other comorbidities and have undergone treatment with immunochemotherapy-based regimens.[4] This disease is characterised by marked immune dysfunction. Although CLL is considered an indolent disease, its clinical course is highly heterogeneous owing to variations in patient clinical characteristics, cytogenetic alterations, and genetic mutations.

In this context, Bruton tyrosine kinase inhibitors (iBTK), such as ibrutinib, acalabrutinib and zanubrutinib, have emerged as key therapeutic options, demonstrating superior efficacy and a more favourable tolerability profile than immunochemotherapy regimens in both first-line and refractory or relapsed (R/R) settings.

Clinical studies, including RESONATE[5] and RESONATE-2,[6] as well as real-world studies, have shown that ibrutinib, the first approved iBTK, significantly prolongs progression-free survival and overall survival.[7] Acalabrutinib and zanubrutinib are second-generation inhibitors and offer greater selectivity and a more favourable toxicity profile, thereby addressing some of the limitations of ibrutinib-related adverse events (AEs), such as atrial fibrillation (AF) and bleeding complications.[8]

The primary objective of this study was to describe the safety profile of first- and second-generation iBTKs as monotherapy in patients receiving first-line treatment and in those with R/R CLL at our hospital. We also analysed how the safety and tolerability profile, as well as the need to interrupt treatment, influences outcomes in these patients when iBTKs are used in routine clinical practice.

## Methods

A single-centre, retrospective, cross-sectional observational study was conducted at the Hospital Universitario Miguel Servet (Zaragoza, Spain). Inclusion criteria: patients 18 years or older with a diagnosis of CLL, followed up in the haematology and haemotherapy department, whose iBTKs were dispensed by the hospital pharmacy department.

The following demographic variables were collected: functional status and tumour burden at diagnosis, genetic characteristics, previous treatments, dosage and dosage adjustments, treatment duration, temporary or permanent treatment interruptions and their reasons, as well as AEs and their consequences.

The reasons for dose adjustment were as follows: the onset of AEs, deterioration of renal function, inclusion in a clinical trial, and the presence of drug interactions. The reasons for treatment interruption are as follows: AEs, disease progression, patient decision, transformation to Richter syndrome, unacceptable toxicity, and death from the latter and other causes. Adverse events were categorised by system: infectious, digestive, vascular, cardiac, haematological, dermatological, oncological, central nervous system (CNS), ophthalmological, and general.

Demographic and clinical variables were obtained from electronic medical records. For this purpose, we used the Modulab laboratory information system and the corporate application of the Aragon Health Service, serving as the official sources for laboratory results and clinical data, respectively. Drug data were supplemented by analysing dispensing records in the Farmatools Outpatient Dispensing Module.

The frequency of each event was calculated as the proportion of patients experiencing the event between the initiation of iBTK therapy and the end of the study. Non-parametric statistical tests were employed to analyse categorical variables, and the Fisher Exact Test was used to compare proportions between cohorts. A $P$-value of $<0.05$ was used as the cut-off point for statistical significance. Depending on the nature of the analysis, percentages were expressed as a proportion of either the total number of patients or the total number of events. Treatment continuity was analysed using Kaplan–Meier curves, which were compared using the log-rank test. A univariate Cox regression model was used to estimate the hazard ratio (HR) between cohorts. All statistical analyses were conducted using the Jamovi software package version 2.3.21.

This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Aragón Drug Research Ethics Committee (code EOM24/038) on 10 July, 2024. The committee granted an exemption from the obligation to obtain informed consent for the retrospective collection of data from deceased patients or those who did not attend the hospital during the study period. In accordance with current regulations, all suspected medicine-related ADRs were reported to the Spanish Pharmacovigilance System for Medicines for Human Use.

## Results

The study included 83 patients treated with iBTKs from 1 May, 2015 to 1 June, 2024 (42 [50.6%] male). The mean age at diagnosis was 67.2 years. Regarding prior lines of treatment, 48 patients (58%) received iBTKs as first-line treatment, with 30 (62.5%) receiving ibrutinib, 15 (31.3%) acalabrutinib, and 3 (6.3%) zanubrutinib, while 35 patients (42%) initially received immunochemotherapy before initiating iBTKs, of whom 74.1% had received a single line of therapy (range: 1–4). Of the 35 patients with R/R CLL, 31 (88.6%) received ibrutinib and 4 (11.4%) received acalabrutinib. Table 1 shows the baseline demographic, clinical, and genetic characteristics of the patients stratified by line of treatment.

**Table 1**
Baseline demographic characteristics of patients with chronic lymphocytic leukaemia.

| | First line, *n* % ($n = 48$) | R/R, *n* % ($n = 35$) |
|---|---|---|
| *Sex* | | |
| Male | 24 (50.0) | 18 (51.4) |
| Female | 24 (50.0) | 17 (48.6) |
| *Age, y* | | |
| ≥75 | 24 (50.0) | 21 (60.0) |
| 65–74 | 15 (31.3) | 9 (25.7) |
| ≥18–64 | 9 (18.8) | 5 (14.3) |
| Average age, y (range) | 75 (53–88) | 72 (45–90) |
| *ECOG* | | |
| 0 | 25 (52.1) | 16 (45.7) |
| ≥1 | 23 (47.9) | 19 (54.3) |
| *Rai staging* | | |
| 0 | 1 (2.1) | 1 (2.9) |
| I–II | 25 (52.1) | 12 (34.3) |
| III–IV | 22 (45.8) | 22 (62.8) |
| *Binet staging* | | |
| A | 5 (10.4) | 2 (5.7) |
| B | 24 (50.0) | 10 (28.6) |
| C | 19 (39.6) | 23 (65.7) |
| *Prognostic markers* | | |
| Unmutated IGHV | 35 (72.9) | 25 (71.4) |
| mutTP53 | 14 (29.2) | 8 (22.9) |
| del(11 q) | 11 (22.9) | 11 (31.4) |
| del(17 p) | 6 (12.5) | 6 (17.1) |
| Median time from diagnosis to initiation of iBTKs, mo (range) | 66.1 (0.230–461) | 95.1 (1.17–193) |
| *Previous lines* | | |
| 0 | 48 (100) | – |
| 1 | – | 26 (74.3) |
| 2 | – | 6 (17.1) |
| 4 | – | 3 (8.6) |
| *iBTKs used* | | |
| Ibrutinib | 30 (62.5) | 31 (88.6) |
| Acalabrutinib | 15 (31.3) | 4 (11.4) |
| Zanubrutinib | 3 (6.3) | – |

del(11q), deletion of the long arm of chromosome 11; del(17p), deletion of the short arm of chromosome 17; ECOG, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy chain variable region; CLL, chronic lymphocytic leukaemia; R/R, relapsed or refractory; mutTP53, TP53 gene mutation.

*Reasons for dose adjustment and treatment interruption*

Twenty-four patients (28.9%) required a dose adjustment during a median follow-up period of 20.8 months (interquartile range: 7.3–34.4). Among the patients receiving iBTKs as first-line treatment, 11 patients (22.9%) required a dose adjustment, compared to13 patients (37.1%) in the R/R CLL cohort. No statistically significant differences were observed between the two cohorts ($p = 0.158$).

At the end of the study, patients who had received prior therapy experienced iBTK treatment interruptions more frequently than those treated with iBTKs as first-line treatment (74.3% vs. 39.6%). The analysis showed a risk ratio of 1.81 (95% CI, 1.23–2.66; $p = 0.002$), indicating an 81% higher risk of treatment interruption in the patients who had received prior immunochemotherapy.

Table 2 shows the reasons for treatment interruption. Overall, the most prevalent reasons for this were AEs (15.7%) and death from causes unrelated to treatment or the underlying haematological disease (15.7%). However, disease progression (20%) and unacceptable toxicity (8.6%) were significantly more frequent causes of treatment interruption in the R/R CLL cohort than in the first-line cohort ($p = 0.006$ and $p = 0.039$, respectively).

*Adverse events and safety profile*

During the follow-up period, 64 patients (77.1%) experienced at least one AE of any type. The median time to the first AE was 1.84 months (range, 0–45.12).

**Table 2**
Reasons for treatment interruption of Bruton tyrosine kinase inhibitor treatment in patients with chronic lymphocytic leukaemia.

| | First line, *n* % ($n = 48$) | R/R, *n* % ($n = 35$) | Total *n* % ($n = 83$) | *p* |
|---|---|---|---|---|
| AE | 8 (16.7) | 5 (14.3) | 13 (15.7) | 0.768 |
| Death from other causes | 5 (10.4) | 8 (22.9) | 13 (15.7) | 0.124 |
| Progression | 1 (2.1) | 7 (20.0) | 8 (9.6) | 0.006* |
| Death from CLL-related causes | 3 (6.3) | 2 (5.7) | 5 (6.0) | 1.000 |
| Unacceptable toxicity | 0 (0.0) | 3 (8.6) | 3 (3.6) | 0.039* |
| Richter syndrome | 2 (4.2) | 0 (0.0) | 2 (2.4) | 0.222 |
| Own decision | 0 (0.0) | 1 (2.9) | 1 (1.2) | 0.422 |
| Total | 19 (39.6) | 26 (74.3) | 45 (54.2) | 0.002* |

AE, adverse events; CLL, chronic lymphocytic leukaemia; R/R, refractory or relapsed.
* $p < 0.05$ (Fisher exact test).

The distribution and frequency of AEs were similar between the 2 treatment cohorts. Infectious events of any grade were the most common type of AE, affecting 57.1% of patients with R/R CLL and 45.8% of those receiving first-line treatment ($p = 0.270$). Digestive and vascular AEs were the second most common types of AE, with no significant differences between cohorts. First-line patients experienced CNS-related AEs more frequently (10.4% vs. 0%), showing a non-significant trend ($p = 0.070$).

For grade ≥3 AEs, infectious events also remained the most frequent, with no statistically significant differences between cohorts (45.7% in R/R CLL patients vs. 37.5% in first-line patients; $p = 0.503$). Serious cardiac events were more frequent in first-line patients (10.4% vs. 5.7%), whereas haematological and digestive events were similarly distributed in both cohorts. Oncological AEs, classified as second neoplasms, were identified in 14.3% of R/R CLL patients compared with 6.2% of those receiving first-line treatment ($p = 0.278$).

In total, 10 neoplasms were documented in 8 patients; 3 of these patients had previously received chemotherapy, whereas the 2 patients who developed 2 neoplasms each had no history of chemo treatment. Of the total diagnoses, 6 were solid organ neoplasms and 4 were non-melanoma skin cancers. The median time from the initiation of iBTK therapy to the onset of the first oncological event was 2.9 years.

Table 3 shows the complete distribution of patients affected by AEs of any grade and by grade 3 or higher AEs.

A total of 161 AEs were reported in the analysed cohort, with a similar distribution across thetwo treatment cohorts. Infectious events were the most common type of AE, affecting 48.4% of patients across all grades of AE and 33.5% of patients with AEs greater than grade 3. Within this category, respiratory infections were the most frequent AEs and, as observed for infectious AEs overall, occurred more frequently in R/R patients. These differences were statistically significant, both for infections as a whole (60.0% vs 39.6%; $p = 0.011$) and for respiratory infections (42.9% vs 27.5%; $p = 0.046$).

The remaining AE categories of all grades were distributed evenly across both cohorts. General AEs were reported in 9.9% of patients, with arthralgia and myalgia being the most frequent symptoms (3.7%). Cardiovascular AEs occurred in 7.5% of patients, with AF being the most common AE in first-line patients (5.5% vs 1.4%), although this difference did not reach statistical significance ($p = 0.234$). Similarly, a higher proportion of CNS-related AEs was observed in first-line patients (5.5% vs 0%), showing a trend towards statistical significance ($p = 0.069$).

The distribution of AEs greater than grade 3 was consistent across the two cohorts, with no significant differences observed in most of the analysed categories. Serious infections were more prevalent in R/R patients (41.4% vs. 27.5%), although this difference did not reach statistical significance ($p = 0.067$). The frequency of oncological (3.7%), digestive (2.5%) and vascular (3.7%) complications was low and similar between cohorts.

**Table 3**
Frequency and types of the most common adverse events of any grade and grade ≥3 in CLL patients treated with iBTKs as first-line treatment or in R/R patients.

| Type of AE | First line, *n* (%) (*n* = 48) | R/R, *n* (%) (*n* = 35) | Total, *n* (%) (*n* = 83) | *p* |
|---|---|---|---|---|
| *Any grade* | | | | |
| Infectious | 22 (45.8) | 20 (57.1) | 42 (5.6) | 0.270 |
| Oncological | 3 (6.2) | 5 (14.3) | 8 (9.6) | 0.278 |
| Digestive | 8 (16.7) | 5 (14.3) | 13 (15.7) | 1.000 |
| Vascular | 8 (16.7) | 5 (14.3) | 13 (15.7) | 1.000 |
| General | 6 (12.5) | 5 (14.3) | 11 (13.3) | 1.000 |
| Cardiological | 9 (18.8) | 3 (8.6) | 12 (14.5) | 0.225 |
| Haematological | 4 (8.3) | 3 (8.6) | 7 (8.4) | 1.000 |
| Dermatological | 3 (6.2) | 1 (2.9) | 4 (4.8) | 0.635 |
| Ophthalmological | 0 (0.0) | 1 (2.9) | 1 (1.2) | 0.422 |
| CNS | 5 (10.4) | 0 (0.0) | 5 (6.0) | 0.070 |
| *Grade ≥3* | | | | |
| Infectious | 18 (37.5) | 16 (45.7) | 34 (41.0) | 0.503 |
| Oncological | 3 (6.2) | 5 (14.3) | 8 (9.6) | 0.280 |
| Digestive | 2 (4.2) | 2 (5.7) | 4 (4.8) | 1.000 |
| Vascular | 3 (6.2) | 3 (8.6) | 6 (7.2) | 0.683 |
| General | 0 (0.0) | 2 (5.7) | 2 (2.4) | 0.160 |
| Cardiological | 5 (10.4) | 2 (5.7) | 7 (8.4) | 0.463 |
| Haematological | 3 (6.2) | 3 (8.6) | 6 (7.2) | 0.683 |
| Dermatological | 3 (6.2) | 1 (2.9) | 4 (4.8) | 0.625 |
| Ophthalmological | 0 (0.0) | 0 (0.0) | 0 (0.0) | 1.000 |
| CNS | 2 (4.2) | 0 (0.0) | 2 (2.4) | 0.183 |

AE, adverse event; R/R, refractory or relapsed; CNS, central nervous system.

In the analysis by iBTK type, patients treated with ibrutinib (1st generation, $n = 61$) and with acalabrutinib or zanubrutinib (2nd generation, $n = 23$) experienced similar frequencies of AEs across most analysed of the categories. A total of 161 AEs were reported, with infectious AEs being the most frequent, occurring in 48.4% of patients across all AE grades and in 33.5% with AEs greater than grade 3. Within this category, respiratory infections were the most common AE subtype (34.2% and 22.4%, respectively), with no significant differences between the two cohorts.

Vascular AEs were reported in 8.1% of patients, with bleeding occurring in 1.2% of patients, whereas cardiovascular AEs occurred in 7.5%, with AF being the most common. There were no significant differences between cohorts. Of note, CNS-related AEs were reported more frequently in patients treated with second-generation iBTKs, particularly among all those receiving acalabrutinib (11.8% vs. 0.8%). This difference reached statistical significance ($p = 0.006$).

For AEs grade 3 or higher, infections were the most frequent category (33.5%), predominantly respiratory (22.4%), with no significant differences between the two cohorts.

Tables 4A and 4B show the complete distribution of AEs of any grade and AEs greater than grade 3.

### *Duration and treatment continuity*

The median treatment duration was significantly longer in patients receiving first-line iBTKs (34.7 months, 95% CI, 31.4-NA) than in R/R patients (20.8 months, 95% CI, 11.5–35.0).

Analysis of treatment continuity using Kaplan–Meier curves (see Fig. 1) demonstrated a statistically significant advantage for the first-line cohort (log-rank $p = 0.01$). Treatment continuity was 86.8% in the first-line cohort and 64.0% in R/R patients at 1 year, decreasing to 78.2% and 40.7%, respectively, at 2 years. As illustrated in Table 5, the continuity values are shown for 12, 24, 36, and 60 months.

**Table 4A**
Total number and types of adverse events in patients with chronic lymphocytic leukaemia treated with Bruton tyrosine kinase inhibitors as first-line treatment or for refractory/relapsed disease.

| Type of AE | First line, *n* (%) (*n* = 91) | R/R, *n* (%) (*n* = 70) | Total, *n* (%) (*n* = 161) | *p* |
|---|---|---|---|---|
| *Any grade* | | | | |
| *Infectious* | 36 (39.6) | 42 (60.0) | 78 (48.4) | 0.011* |
| Respiratory infections | 25 (27.5) | 30 (42.9) | 55 (34.2) | 0.046* |
| *Oncological* | 7 (7.7) | 3 (4.3) | 10 (6.2) | 0.516 |
| Solid organ | 4 (4.4) | 2 (2.9) | 6 (3.7) | 0.698 |
| Non-melanoma skin cancer | 3 (3.3) | 1 (1.4) | 4 (2.5) | 0.633 |
| *Digestive* | 8 (8.8) | 5 (7.1) | 13 (8.1) | 0.777 |
| Diarrhoea | 4 (4.4) | 3 (4.3) | 7 (4.3) | 1.000 |
| *Vascular* | 8 (8.8) | 5 (7.1) | 13 (8.1) | 0.777 |
| Bleeding | 1 (1.1) | 1 (1.4) | 2 (1.2) | 1.000 |
| *General* | 9 (9.9) | 7 (10.0) | 16 (9.9) | 1.000 |
| Arthralgia/myalgia | 4 (4.4) | 2 (2.9) | 6 (3.7) | 0.698 |
| *Cardiological* | 9 (9.9) | 3 (4.3) | 12 (7.5) | 0.233 |
| Atrial fibrillation | 5 (5.5) | 1 (1.4) | 6 (3.7) | 0.234 |
| *Haematological* | 5 (5.5) | 3 (4.3) | 8 (5.0) | 1.000 |
| Neutropenia | 2 (2.2) | 2 (2.9) | 4 (2.5) | 1.000 |
| Thrombocytopenia | 3 (3.3) | 1 (1.4) | 4 (2.5) | 0.633 |
| *Dermatological* | 4 (4.4) | 1 (1.4) | 5 (3.1) | 0.389 |
| *Ophthalmological* | 0 (0.0) | 1 (1.4) | 1 (0.6) | 0.435 |
| *CNS* | 5 (5.5) | 0 (0.0) | 5 (3.1) | 0.069 |
| *Grade ≥3* | | | | |
| *Infectious* | 25 (27.5) | 29 (41.4) | 54 (33.5) | 0.067* |
| Respiratory infections | 17 (18.7) | 21 (30.0) | 38 (23.6) | 0.134 |
| *Oncological* | 7 (7.7) | 3 (4.3) | 10 (6.2) | 0.516 |
| Solid organ | 4 (4.4) | 2 (2.8) | 6 (3.7) | 0.698 |
| Non-melanoma skin cancer | 3 (3.3) | 1 (1.4) | 4 (2.5) | 0.633 |
| *Digestive* | 2 (2.2) | 2 (2.9) | 4 (2.5) | 1.000 |
| *Vascular* | 3 (3.3) | 2 (2.9) | 6 (3.7) | 1.000 |
| *General* | 0 (0.0) | 3 (4.3) | 3 (1.9) | 0.080* |
| *Cardiological* | 5 (5.5) | 2 (2.9) | 7 (4.3) | 0.700 |
| Atrial fibrillation | 4 (4.4) | 1 (1.4) | 5 (3.1) | 0.389 |
| *Haematological* | 4 (4.4) | 3 (4.3) | 7 (4.3) | 1.000 |
| Neutropenia | 1 (1.1) | 2 (2.8) | 3 (1.8) | 0.580 |
| Thrombocytopenia | 3 (3.3) | 1 (1.4) | 4 (2.5) | 0.633 |
| *Dermatological* | 4 (4.4) | 1 (1.4) | 5 (3.1) | 0.389 |
| *Ophthalmological* | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA |
| *CNS* | 2 (2.2) | 0 (0.0) | 2 (1.2) | 0.505 |

AE, adverse event; R/R, refractory or relapsed; CNS, central nervous system.
* $p < 0.05$ (Fisher's exact test).

In the univariate Cox regression analysis, treatment in R/R patients was associated with a 2.15-fold higher risk of treatment interruption (HR: 2.15; 95% CI, 1.18–3.89; $p = 0.012$).

## Discussion

Our study provides real-world clinical evidence on the safety profile and treatment continuity of iBTKs in patients with CLL. More than three-quarters of patients experienced at least one AE. Infections were the most common type of AE across all grades and in AEs greater than grade 3. Within this category, respiratory infections were the most common AE subtype and occurred significantly more frequently in R/R patients than in those receiving first-line treatment. This finding is consistent with the results of comparative trials, which also reported that infectious events were among the most common AEs associated with both ibrutinib and second-generation iBTKs.[5,6,9,10] Long-term follow-up shows that infections remain the main toxicity, due to the immunodeficiency intrinsic to CLL and the effects of treatment.[11]

The most common reasons for treatment interruption in the R/R cohort were disease progression and unacceptable toxicity, whereas first-line patients experienced greater treatment continuity. This finding is

**Table 4B**
Total number and type of adverse events in patients with chronic lymphocytic leukaemia treated with first- and second-generation Bruton tyrosine kinase inhibitors.

| Type of AE | 1st generation *n* (%) | 2nd generation *n* (%) | Total, *n* (%) | *p* |
|---|---|---|---|---|
| | (*n* = 128) | (*n* = 33) | (*n* = 161) | |
| *Any grade* | | | | |
| *Infectious* | 65 (51.2) | 13 (38.2) | 78 (48.4) | 0.329 |
| Respiratory infections | 45 (35.4) | 10 (29.4) | 55 (34.2) | 0.683 |
| *Oncological* | 9 (7.1) | 1 (2.9) | 10 (6.2) | 0.689 |
| Solid organ | 6 (4.7) | 0 (0.0) | 6 (3.7) | 0.347 |
| *Non-melanoma skin cancer* | 3 (2.4) | 1 (2.9) | 4 (2.5) | 1.000 |
| *Digestive* | 10 (7.9) | 3 (8.8) | 13 (8.1) | 0.730 |
| Diarrhoea | 6 (4.7) | 1 (2.9) | 7 (4.3) | 1.000 |
| *Vascular* | 10 (7.9) | 3 (8.8) | 13 (8.1) | 0.731 |
| Haemorrhages | 1 (0.8) | 1 (2.9) | 2 (1.2) | 0.369 |
| *General* | 10 (7.9) | 5 (14.7) | 15 (9.3) | 0.194 |
| Arthralgia/myalgia | 3 (2.4) | 3 (8.8) | 6 (3.7) | 0.101 |
| *Cardiological* | 11 (8.7) | 1 (2.9) | 12 (7.5) | 0.462 |
| Atrial fibrillation | 6 (4.7) | 0 (0.0) | 6 (3.7) | 0.347 |
| *Haematological* | 6 (4.7) | 3 (8.8) | 9 (5.6) | 0.391 |
| Neutropenia | 2 (1.6) | 2 (5.9) | 4 (2.5) | 0.186 |
| Thrombocytopenia | 3 (2.4) | 1 (2.9) | 4 (2.5) | 1.000 |
| *Dermatological* | 5 (3.9) | 0 (0.0) | 5 (3.1) | 0.584 |
| *Ophthalmological* | 1 (0.8) | 0 (0.0) | 1 (0.6) | 1.000 |
| *CNS* | 1 (0.8) | 4 (11.8) | 5 (3.1) | 0.006* |
| *Grade ≥3* | | | | |
| *Infectious* | 45 (35.2) | 9 (27.3) | 54 (33.5) | 0.405 |
| Respiratory infections | 29 (22.6) | 7 (21.2) | 36 (22.4) | 1.000 |
| *Oncological* | 9 (7.1) | 1 (2.9) | 10 (6.2) | 0.689 |
| Solid organ | 6 (4.7) | 0 (0.0) | 6 (3.7) | 1.000 |
| Non-melanoma skin cancer | 3 (2.4) | 1 (2.9) | 4 (2.5) | 1.000 |
| *Digestive* | 4 (3.1) | 0 (0.0) | 4 (2.5) | 0 |
| *Vascular* | 4 (3.1) | 2 (6.0) | 6 (3.7) | 0.603 |
| *General* | 3 (2.3) | 0 (0.0) | 3 (1.8) | 1.000 |
| *Cardiological* | 7 (5.5) | 0 (0.0) | 7 (4.3) | 0.346 |
| *Haematological* | 5 (3.9) | 2 (6.0) | 7 (4.3) | 0.633 |
| Neutropenia | 2 (1.6) | 1 (2.9) | 3 (1.8) | 1.000 |
| Thrombocytopenia | 3 (2.3) | 1 (2.9) | 4 (2.5) | 0.499 |
| *Dermatological* | 5 (3.9) | 0 (0.0) | 5 (3.1) | 0.584 |
| *Ophthalmological* | 0 (0.0) | 0 (0.0) | 0 (0.0) | NA |
| *CNS* | 1 (0.8) | 1 (2.9) | 3 (1.8) | 0.369 |

CLL, chronic lymphocytic leukaemia; iBTKs, Bruton tyrosine kinase inhibitors; AE, adverse event; R/R, refractory or relapsed; CNS, central nervous system.
* $p < 0.05$ (Fisher's exact test).

consistent with the results of clinical practice series and comparative trials, which reported that prior exposure was associated with higher rates of treatment interruption due to disease progression or toxicity.[8,12] In addition, the median duration of first-line treatment (34.7 months) is comparable to that reported in international series, suggesting that early use favours greater therapeutic continuity and sustained clinical benefit.[13]

The numerical differences observed in the total number of AEs and in AEs greater than grade 3 between first-line and R/R patients may be explained, at least in part, by the higher burden of prior therapies—primarily immunochemotherapy—in the R/R cohort. Regimens such as FCR, R-bendamustine, or R-chlorambucil can induce persistent immune alterations, including hypogammaglobulinaemia, which can increase the risk of infections and complications in subsequent treatment lines. This effect is well documented and persists in the era of targeted therapies.[14] In real-world ibrutinib cohorts, previously treated patients exhibit higher rates of treatment interruption due to disease progression or toxicity than de novo patients, which is consistent with greater cumulative clinical frailty after previous treatment lines.[15] In our series, treatment discontinuation was more frequent in R/R patients despite similar overall AEs, suggesting that the cumulative impact of prior therapies may reduce patients' tolerance and contribute to therapy interruption.

Cardiovascular and vascular AEs, including bleeding, were infrequent and showed no significant differences between cohorts. The most frequent AE of this type was AF, particularly in patients treated with ibrutinib, with no significant differences between first- and second-generation iBTKs. This finding is consistent with the results of comparative trials such as ELEVATE-RR, in which fewer patients receiving acalabrutinib experienced AF compared with those receiving ibrutinib, as well as with the ALPINE study, in which fewer patients receiving zanubrutinib developed AF.[16]

A notable finding was the higher frequency of CNS-related AEs, specifically headaches, in patients treated with second-generation iBTKs. All of these patients received acalabrutinib, and this difference reached statistical significance. This finding is in line with the results of previous studies, in which headache has been recognised as one of the most common and specific AEs associated with acalabrutinib.[17]

Second-generation iBTKs have shown a more favourable safety profile, resulting in fewer treatment interruptions due to AEs while maintaining comparable efficacy.[8,12,18,19] Thus, their increased use as first-line treatment is a plausible explanation for the trend towards relatively fewer serious AEs in this cohort.

The frequency of second neoplasms (6.2%) was slightly lower than that reported in the literature. In the 6-year update of the RESONATE trial, approximately 11% of patients developed second neoplasms; solid tumours and non-melanoma skin cancer were the most common.[11] Similarly, second neoplasms have been reported during follow-up in first-line clinical trials, such as those by Woyach et al. and Shanafelt et al. This finding suggests that their occurrence may be related to both the prolonged immunosuppression intrinsic to CLL and previous exposure to chemotherapy.[20,21] This hypothesis is supported by the observation that half of our patients with second neoplasms had received immunochemotherapy.

This study has several limitations. Firstly, its retrospective, single-centre design and limited sample size may have led to an underestimation of infrequent events and restricted the generalizability of the results. However, the study provides relevant information on a routine clinical practice setting, where patients exhibit greater clinical heterogeneity and comorbidities than in clinical trials. The strength of this study lies in its detailed characterisation of AEs and evaluation of treatment continuity over an extended follow-up period, thereby providing information applicable to the daily management of CLL in our setting.

Overall, our results confirm that iBTKs demonstrate a manageable safety profile in real-world practice, with infections as the main toxicity and no significant differences between drug generations. Greater treatment continuity in first-line patients than in R/R patients underscores the importance of considering the previous treatment history in therapeutic decision-making and of reinforcing close follow-up to optimise adherence and minimise toxicity.

## Conclusions

In this real-world cohort, iBTKs exhibited a manageable safety profile consistent with that reported in the literature, with a frequency of AEs similar to that reported in pivotal trials and other observational series. Infections were the most frequent AEs, predominantly respiratory, and occurred significantly more frequently in R/R patients than in those receiving first-line treatment. Cardiovascular and vascular AEs were uncommon and showed no significant differences between drug generations, although AF occurred mainly in patients treated with ibrutinib. Tolerance to continuous treatment was higher in the first-line cohort, suggesting that clinical context and prior therapies influence treatment continuity. Greater use of second-generation iBTKs may contribute to a lower frequency of serious AEs, consistent with patterns reported in comparative trials. Despite the methodological limitations of this

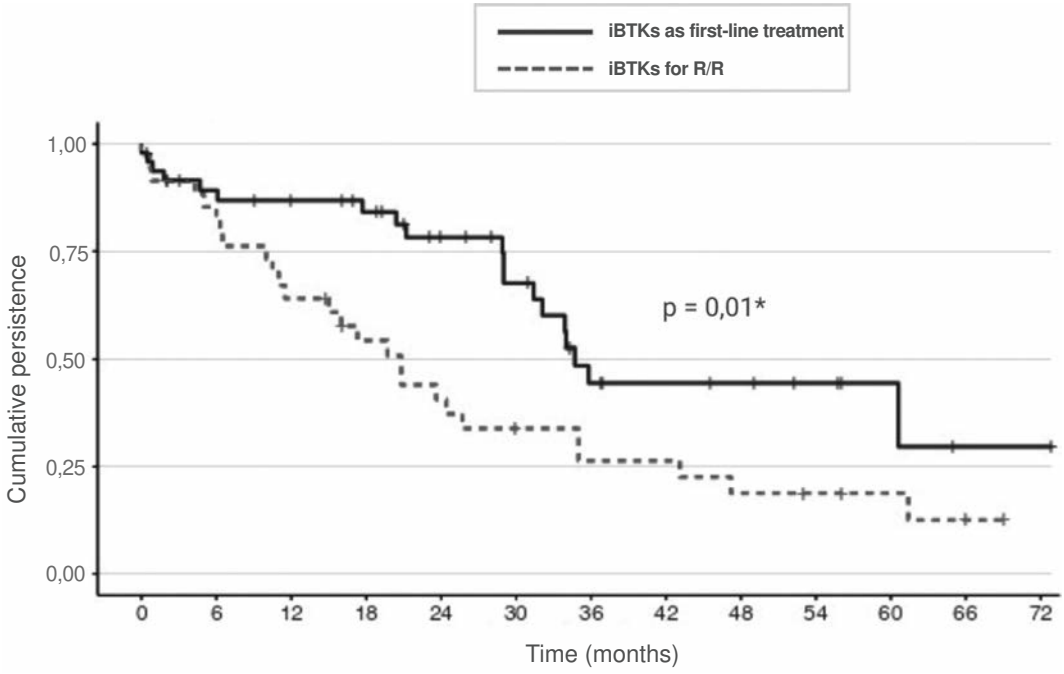


**Figure 1.** Treatment continuity in patients with CLL treated with iBTKs as first-line treatment or for R/R disease. iBTKs, Bruton tyrosine kinase inhibitors; CLL, chronic lymphocytic leukaemia; R/R, refractory or relapsed disease. *$p < 0.05$ (log-rank test).

**Table 5**
Treatment continuity in patients with chronic lymphocytic leukaemia receiving Bruton tyrosine kinase inhibitors as first-line treatment or for refractory/relapsed disease.

| | First line % (95% CI) ($n = 35$) | R/R % (95% CI) ($n = 48$) |
|---|---|---|
| Continuity at 12 months | 86.8 [77.5–97.3] | 64.0 [49.6–82.6] |
| Continuity at 24 months | 78.2 [66.4–92.2] | 40.7 [26.6–62.2] |
| Continuity at 36 months | 44.5 [29.5–67.1] | 26.4 [14.4–48.3] |
| Continuity at 60 months | 44.5 [29.5–67.1] | 18.8 [8.8–40.5] |

CLL, chronic lymphocytic leukaemia; iBTKs, Bruton tyrosine kinase inhibitors; R/R, refractory or relapsed.

study, these findings are applicable to daily clinical practice and support close, multidisciplinary monitoring in order to optimise safety, adherence, and treatment continuity.

## Contribution to the literature

This study compares the safety profiles and treatment continuation rates of 2 generations of Bruton tyrosine kinase inhibitors in patients with chronic lymphocytic leukaemia. It provides real-world clinical evidence that may inform treatment personalisation.

## Ethical responsibilities

All authors have accepted and fulfilled the responsibilities defined by the International Committee of Medical Journal Editors (available at http://www.icmje.org/).

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## CRediT authorship contribution statement

**Rocío Bello-Calvo:** Software, Project administration, Methodology, Formal analysis. **Rita González-Resina:** Writing – original draft, Methodology, Investigation. **Araceli Rubio-Martínez:** Validation, Supervision. **Itziar Larrodé-Leciñena:** Validation, Supervision. **María Pilar Delgado-Beltrán:** Validation, Supervision. **María Reyes Abad-Sazatornil:** Visualization, Validation, Supervision.

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## Conflicts of interest

None declared.

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