



Real-World Characteristics and Outcome of Patients Treated With Single-Agent Ibrutinib for Chronic Lymphocytic Leukemia in Spain (IBRORS-LLC Study)

Pau Abrisqueta,¹ Javier Loscertales,² Maria José Terol,³ Ángel Ramírez Payer,⁴ Macarena Ortiz,⁵ Inmaculada Pérez,⁶ Carolina Cuellar-García,⁷ Margarita Fernández de la Mata,⁸ Alicia Rodríguez,⁹ Ana Lario,¹⁰ Julio Delgado,¹¹ Ana Godoy,¹² José M^a Arguiñano Pérez,¹³ M^a José Berrueto,¹⁴ Ana Oliveira,¹⁵ José-Ángel Hernández-Rivas,¹⁶ Maria Dolores García Malo,¹⁷ Ángeles Medina,¹⁸ Paloma García Martín,¹⁹ Santiago Osorio,²⁰ Patricia Baltasar,²¹ Miguel Fernández-Zarzoso,²² Fernando Marco,²³ M^a Jesús Vidal Manceñido,²⁴ Alicia Smucler Simonovich,²⁵ Montserrat López Rubio,²⁶ Isidro Jarque,²⁷ Alexia Suarez,²⁸ Rubén Fernández Álvarez,²⁹ Aima Lancharro Anchel,³⁰ Eduardo Ríos,³¹ María del Carmen Losada Castillo,³² Ernesto Pérez Persona,³³ Ricardo García Muñoz,³⁴ Rafael Ramos,³⁵ Lucrecia Yáñez,³⁶ José Luis Bello,³⁷ Cristina Lorient,³⁸ Daniel Acha,³⁸ Miguel Villanueva³⁸

Abbreviations: AE, adverse event; BR, bendamustine plus rituximab; Clb, chlorambucil; CLL, chronic lymphocytic leukemia; CI, confidence interval; CIT, chemoimmunotherapy; CR, complete response; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; FCR, fludarabine, cyclophosphamide, and rituximab; HR, hazard ratio; IgA, immunoglobulin A; IGHV, immunoglobulin heavy chain; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for adverse events; NR, not reached; OR, Odds ratio; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR-L, partial remission with lymphocytosis; R/R, relapsed/refractory; TN, treatment naïve.

¹Hospital Universitario Vall d'Hebron, Barcelona, Spain

²Hospital Universitario La Princesa, IIS-IP, Madrid, Spain

³Hospital Clínico Universitario de Valencia, Valencia, Spain

⁴Hospital Universitario Central de Asturias, Oviedo, Spain

⁵Hospital Regional Universitario de Málaga, Málaga, Spain

⁶Hospital Virgen de la Victoria, Málaga, Spain

⁷Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

⁸Hospital Universitario Reina Sofía, Córdoba, Spain

⁹Hospital Universitario Virgen Macarena, Sevilla, Spain

¹⁰Hospital Universitario Ramón y Cajal, Madrid, Spain

¹¹Hospital Clinic i Provincial, Barcelona, Spain

¹²Hospital Universitario Miguel Servet, Zaragoza, Spain

¹³Complejo Hospitalario de Navarra, Pamplona, Spain

¹⁴Hospital Universitario de Jerez, Cádiz, Spain

¹⁵ICO L'Hospitalet, L'Hospitalet de Llobregat, Spain

¹⁶Hospital Universitario Infanta Leonor, Madrid, Spain

¹⁷Hospital General Universitario Morales Meseguer, Murcia, Spain

¹⁸Hospital Costa del Sol, Málaga, Spain

¹⁹Hospital Universitario Virgen de las Nieves, Granada, Spain

²⁰Hospital General Universitario Gregorio Marañón, Madrid, Spain

²¹Hospital Universitario La Paz, Madrid, Spain

²²Hospital Universitario Dr. Peset, Valencia, Spain

²³Hospital Universitario de Basurto, Bilbao, Bizkaia, Spain

²⁴Hospital Universitario de León, León, Spain

²⁵Hospital Universitario El Bierzo, Ponferrada, León, Spain

²⁶Hospital Universitario Príncipe de Asturias, Alcalá De Henares, Madrid, Spain

²⁷Hospital Universitario La Fe, Valencia, Spain

²⁸Hospital Universitario de Gran Canaria Doctor Negrín, Las Palmas, Spain

²⁹Hospital de Cabueñes, Gijón, Spain

³⁰Hospital General Universitario de Castellón, Castellón, Spain

³¹Hospital Universitario Virgen de Valme, Sevilla, Spain

³²Hospital Universitario Insular de Gran Canarias, Las Palmas de Gran Canaria, Las Palmas, Spain

³³Hospital Txagorritxu, Vitoria-Gasteiz, Spain

³⁴Hospital San Pedro, Logroño, Spain

³⁵Hospital Universitario de Badajoz, Badajoz, Spain

³⁶Hospital Universitario Marqués de Valdecilla, Santander, Spain

³⁷Hospital Clínico Universitario de Santiago-CHUS, Santiago de Compostela, A Coruña, Spain

³⁸Medical Department-Hematology Janssen-Cilag, S.A., Madrid, Spain

Submitted: May 21, 2021; Revised: Jul 16, 2021; Accepted: Jul 19, 2021; Epub: 3 August 2021

Address for correspondence: Pau Abrisqueta, MD, PhD. Department of Hematology, Hospital Universitario Vall d'Hebron, Passeig de la Vall d'Hebron, 119-129, 08035 Barcelona, Spain.

E-mail contact: pabrisqueta@vhebron.net

Abstract

Ibrutinib demonstrated robust efficacy, regardless of high-risk features, in previously untreated or relapsed/refractory chronic lymphocytic leukemia (CLL). The IBRORS-CLL study supports the effectiveness and the manageable safety profile of single-agent ibrutinib, which was not adversely affected by high-risk characteristics in real-world CLL patients in Spain. We also found a high molecular testing rate of del(17p)/TP53 mutation and IGHV mutation status.

Background: Ibrutinib demonstrated remarkable efficacy and favorable tolerability in patients with untreated or relapsed/refractory (R/R) chronic lymphocytic leukemia (CLL), including those with high-risk genetic alterations. The IBRORS-CLL study assessed the characteristics, clinical management and outcome of CLL patients receiving ibrutinib in routine clinical practice in Spain. **Patients:** Observational, retrospective, multicenter study in CLL patients who started single-agent ibrutinib as first-line treatment or at first or second relapse between January 2016 and January 2019. **Results:** A total of 269 patients were included (median age: 70.9 years; cardiovascular comorbidity: 55.4%, including hypertension [47.6%] and atrial fibrillation [AF] [7.1%]). Overall, 96.7% and 69% of patients underwent molecular testing for del(17p)/TP53 mutation and IGHV mutation status. High-risk genetic features included unmutated IGHV (79%) and del(17p)/TP53 mutation (first-line: 66.3%; second-line: 23.1%). Overall, 84 (31.2%) patients received ibrutinib as first-line treatment, and it was used as second- and third-line therapy in 121 (45.0%) and 64 (23.8%) patients. The median progression-free survival and overall survival were not reached irrespective of del(17p)/TP53, or unmutated IGHV. Common grade ≥ 3 adverse events were infections (12.2%) and bleeding (3%). Grade ≥ 3 AF occurred in 1.5% of patients. **Conclusion:** This real-world study shows that single-agent ibrutinib is an effective therapy for CLL, regardless of age and high-risk molecular features, consistent with clinical trials. Additionally, single-agent ibrutinib was well tolerated, with a low rate of cardiovascular events. This study also emphasized a high molecular testing rate of del(17p)/TP53 mutation and IGHV mutation status in clinical practice according to guideline recommendations.

Clinical Lymphoma, Myeloma and Leukemia, Vol. 21, No. 12, e985–e999 © 2021 The Author(s). Published by Elsevier Inc.

This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Keywords: Chronic lymphocytic leukemia (CLL), Effectiveness, First-line, Ibrutinib, Real-world, Relapsed/refractory (R/R)

Introduction

Chronic lymphocytic leukemia (CLL) is characterized by a marked immune dysfunction¹ and a heterogeneous clinical outcome mainly determined by the patients' clinical features, cytogenetic alterations and gene mutations.^{2,3} Deletions in chromosome 17p [del(17p)] and mutation in TP53 gene, deletion of 11q [del(11q)], and unmutated immunoglobulin heavy chain variable (IGHV) region gene status is associated with poor response and outcome to chemoimmunotherapy (CIT).⁴⁻⁹ Testing of these alterations is therefore of paramount importance for guiding treatment decisions in routine clinical practice in CLL.¹⁰⁻¹² Additional analysis as complex karyotype (i.e., ≥ 3 chromosomal abnormalities), that have an adverse prognostic significance, are still considered investigational.^{10,11,13}

Ibrutinib is a first-in-class, oral once-daily, covalent inhibitor of Bruton's tyrosine kinase (BTK), which has demonstrated higher efficacy and favorable tolerability profile compared to the most effective CIT regimens in both relapsed/refractory (R/R)^{14,15} and treatment-naïve (TN)¹⁶⁻¹⁹ patients. Therefore, the efficacy and safety seen in clinical trials support the use of ibrutinib for all CLL patient profiles which require treatment.

The benefit demonstrated with ibrutinib in clinical trials has also been observed in the real-world setting.²⁰⁻³¹ However, most real-world evidence came from studies in R/R CLL,^{20,25-27,30,31} including reports where ibrutinib was used in compassionate use programs^{24,27,30,31} and from single-site experience.^{22,26} Additionally, real-world data from different healthcare systems across countries may

be heterogeneous due to divergences in clinical practice, and nationwide experiences are of particular interest.

This real-world study aimed to explore the clinical, genetic, and molecular characteristics of CLL patients receiving single-agent ibrutinib in earlier lines of therapy in Spain. We also assessed the effectiveness of ibrutinib in terms of response and clinical outcome and the safety and tolerability profile of this agent when used under routine clinical practice conditions.

Patients and Methods

Study Design and Patients

The IBRORS-LLC was a multicenter, retrospective, observational study to explore the characteristics and clinical outcome of patients treated with single-agent ibrutinib in earlier therapy lines in the real-world setting in Spain.

The study included patients aged ≥ 18 years diagnosed with CLL requiring treatment who started single-agent ibrutinib as first-line treatment or at first or second relapse from January 2016 (start of ibrutinib commercialization in Spain) to January 2019 (at least 6 months before study entry) under routine clinical practice conditions. Patients were excluded if they had participated in an interventional study while receiving ibrutinib.

The primary study endpoint was the demographic, clinical, genetic and molecular characterization of patients at diagnosis and ibrutinib treatment initiation. For this purpose, a retrospective chart review was performed to collect data on comorbidities, concomitant therapies, disease characteristics such as the stage of

the disease, common chromosomal aberrations, namely del(13q), trisomy 12, del(11q), and del(17p), and molecular alterations including del(17p)/TP53 mutation, IGHV mutation status and complex karyotype. Secondary endpoints included overall response rate (ORR), OS, PFS, time to response, time to subsequent CLL therapy, and immune reconstitution based on immunoglobulin A (IgA) levels and CD4/CD8 ratio. Single-agent ibrutinib safety profile and management (dose reduction and interruption, discontinuation), and post-ibrutinib therapy for CLL were also assessed.

Independent ethics committees approved the study, which was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines and applicable regulatory requirements. Written informed consent was obtained from all patients before their inclusion in the study, except for those deceased at the time of study initiation, in which case the requirement for informed consent was waived for retrospective collection of data from medical charts. Centralized monitoring (remote evaluation of the study data) was carried out to ensure study data quality.

Statistical Analysis

A descriptive statistical analysis was performed to describe the demographic, clinical, genetic and molecular characteristics of patients receiving single-agent ibrutinib. The analysis focused on the overall population (ibrutinib administered at any treatment line) and in the first- and second-line setting.

Measures of central tendency and dispersion (mean $\pm$ standard deviation, median and interquartile range [IQR]) were used to describe quantitative variables and counts and percentages were applied to report qualitative variables. Comparisons between categorical variables were performed using the Chi-squared or the Fischer exact test, and continuous variables were compared using the Mann-Whitney U test or the Kruskal-Wallis test.

The ORR was defined as the proportion of patients achieving a complete response (CR), nonconfirmed CR, partial response (PR), and partial remission with lymphocytosis (PR-L). The best response to treatment was defined based on the clinical description and biochemistry¹⁰ as bone marrow biopsy and computed tomography (CT) scan are not mandatory in clinical practice to evaluate response. OS was calculated from ibrutinib treatment initiation to death from any cause. PFS was calculated from ibrutinib treatment initiation to disease progression or death from any cause. Time to subsequent CLL therapy was measured from treatment initiation to the administration of a new CLL therapy or death, whichever was first. Time-to-event variables were estimated by using the Kaplan-Meier method, and groups were compared with the Log-rank test.

Post-hoc analyses were conducted to assess ORR and the outcome in terms of PFS and OS according to age (≤ 65 years vs. > 65 years) and cardiovascular comorbidities (hypertension, diabetes mellitus [DM], atrial fibrillation [AF], other arrhythmias, and/or stroke). Additionally, the impact of del(11q), del(17p)/TP53 mutation, IGHV mutational status, and complex karyotype on the response, PFS and OS, was also assessed.

A multivariate COX regression analysis of potential factors associated with PFS was carried out. Variables with statistical significance $P < .2$ in the univariate analysis were included in a multivariate model using a stepwise selection method. Hazard ratio (HR)

and 95% confidence intervals (CI) were calculated. The covariates assessed as potential independent factors for PFS in the univariate analysis included age, disease stage (based on Rai and Binet), $\beta 2$ -microglobulin level, and cytogenetic and molecular alterations at diagnosis (trisomy 12, del(11q), del(17p)/TP53 mutation, IGHV mutation status, and complex karyotype).

Adverse events (AEs) occurring during single-agent ibrutinib treatment (regardless of attribution) were described and graded according to the National Cancer Institute Common Terminology Criteria for AEs (NCI-CTCAE) version 4.0.

Statistical analyses were performed using the Statistical Package for the Social Sciences version 18.0, with a significance level of 0.05.

Results

Patient Characteristics

Between December 2018 and August 2019, 286 patients were enrolled in the study at 37 Spanish hospitals. Seventeen patients were excluded due to non-compliance with eligibility criteria. Thus, 269 patients were included in the study and evaluable for effectiveness and safety analyses.

Overall, 84 (31.2%) patients received single-agent ibrutinib as first-line treatment for CLL, and it was used as second- and third-line therapy in 121 (45.0%) patients and 64 (23.8%) patients, respectively.

Table 1 shows the baseline demographic, clinical, and genetic characteristics of the overall population and according to the line in which ibrutinib was received. The median age of patients at treatment initiation was 70.9 years, with 46.8% of patients being older than 65 years. Most patients had an ECOG performance status of 0 to 1 (94.9%). Overall, 50.8% of patients presented Rai Binet stage B/C. The most common comorbidity before ibrutinib treatment initiation was cardiovascular disease, most commonly arterial hypertension (47.6%), dyslipidemia (26.8%), DM (19%), and AF (7.1%). Accordingly, concomitant treatment mainly included antihypertensives (41.6%), antiplatelet (11.5%), and anticoagulant therapy (7.8%). Overall, 10 (3.7%) and 6 (2.2%) patients were receiving vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs) (apixaban), respectively, at ibrutinib treatment initiation (Table 1).

Del(11q) and del(13q) were detected in 17.7% (45/254) and in 38.1% (98/257) of patients, respectively. Trisomy 12 was reported in 16.5% (43/261) of patients. The presence of del(17p)/TP53 mutation was evaluated in most patients (96.7%; 260/269), and IGHV mutation status was assessed in 69% (186/269) of patients at diagnosis. Del(17p)/TP53 mutation was detected in 66.3% (55/83) and 23.1% (27/117) of patients who received ibrutinib in the first- and the second-line setting, respectively. Unmutated IGHV was reported in 79% (147/186) of patients. Complex karyotype was present in 7.9% (18/227) of patients. (Table 1).

Preibrutinib Therapy for CLL

The CLL therapies used as first- and second-line treatment before ibrutinib treatment initiation are described in Table 2. A total of 185 patients had previously received CLL treatment, with 121 and 64 patients receiving one and two previous lines of therapy, respectively. Overall, 144 (77.8%) patients receiving ibrutinib in the R/R setting

Table 1 Demographic, Clinical, and Genetic Characteristics of Patients Receiving Single-Agent Ibrutinib in the Overall Population and in the First- and the Second-Line Setting

Variable	First Line (N = 84)	Second Line (N = 121)	Overall Population (N = 269)
Median age (range), years ^a	71.3 (63-77)	70.1 (62.2-78.5)	70.9 (63.1-77.4)
> 65 y, n (%)	50 (59.5)	53 (43.8)	126 (46.8)
Gender, male, n (%)	52 (61.9)	84 (69.4)	178 (66.2)
ECOG performance status, n (%)			
0	44/70 (62.9)	78/110 (70.9)	158/234 (67.5)
1	25/70 (35.7)	25/110 (22.7)	64/234 (27.4)
2	1/70 (1.4)	7/110 (6.4)	10/234 (4.3)
4	0 (0.0)	0 (0.0)	2/234 (0.9)
Comorbidities, n (%) ^b			
Cardiovascular risk factors			
Hypertension	46 (54.8)	50 (41.3)	128 (47.6)
Diabetes mellitus	17 (20.2)	24 (19.8)	51 (19.0)
Cardiovascular disorders			
Dyslipidemia	27 (32.1)	31 (25.6)	72 (26.8)
Atrial fibrillation	6 (7.1)	6 (5.0)	19 (7.1)
Ischemic heart disease	4 (4.8)	7 (5.8)	13 (4.8)
Stroke	1 (1.2)	4 (3.3)	7 (2.6)
Heart failure	2 (2.4)	2 (1.7)	6 (2.2)
Other arrhythmias	2 (1.7)	2 (1.7)	4 (1.5)
Other comorbidities			
Respiratory disease	17 (20.2)	22 (18.2)	51 (19.0)
Gastrointestinal disease	15 (17.9)	15 (12.4)	43 (16.0)
Concomitant treatment, n (%) ^d			
Antihypertensives	42 (50.0)	42 (34.7)	112 (41.6)
Anticoagulants	8 (9.5)	6 (5.0)	21 (7.8)
VKAs	4 (4.7)	5 (4.1)	10 (3.7)
DOACs	1 (1.2)	1 (1.2)	6 (2.2)
LMWH	3 (3.6)	0 (0.0)	5 (1.9)
Antiplatelets	10 (11.9)	14 (11.6)	31 (11.5)
Antibiotic/antiviral/antifungal therapy, n (%)	8 (9.5)	26 (21.5)	55 (20.4)
Rai-Binet stage, n (%)			
Rai stage 0 - Binet stage A	36/83 (43.4)	64/118 (54.2)	128/260 (49.2)
Rai stage I or II - Binet stage B	29/83 (34.9)	39/118 (33.1)	90/260 (34.6)
Rai stage III or IV - Binet stage C	18/83 (21.7)	15/118 (12.7)	42/260 (16.2)
Laboratory parameters ^c			
Median β 2-microglobulin level (range), mg/L	3.8 (2.5-5.5)	3.3 (2.4-4.6)	3.3 (2.4-4.6)
Median hemoglobin (range), g/dL	13.3 (12.0-14.6)	13.3 (11.6-14.6)	13.4 (11.9-14.6)
Median platelets (range), $\times 10^3/\mu\text{L}$	175.5 (139.3-226.3)	155.0 (112.5-208.0)	164.0 (117.0-214.0)
Creatinine (mg/dL)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	0.9 (0.8-1.1)
Genomic aberrations, n (%) ^c			
Del(11q) deletion	11/80 (13.8)	22/114 (19.3)	45/254 (17.7)
Del(17p)/TP53 mutation	55/83 (66.3)	27/117 (23.1)	95/260 (36.5)
IGHV, n (%)			
Unmutated	45/58 (77.6)	63/82 (76.8)	147/186 (79.0)
Mutated	13/58 (22.4)	19/82 (23.2)	39/186 (21.0)

(continued on next page)

Table 1 (continued)

Variable	First Line (N = 84)	Second Line (N = 121)	Overall Population (N = 269)
Complex karyotype, n (%) ^d	4/67 (6.0)	13/102 (12.7)	18/227 (7.9)
Molecular high-risk, n (%) ^e	74 (88.1)	80 (66.1)	199 (74.0)

DOACs: direct oral anticoagulants; ECOG: Eastern Cooperative Group; IGHV = immunoglobulin heavy variable chain; LMWH = low-molecular-weight heparin; VKA = vitamin K antagonists;

^a Age at treatment initiation;

^b At ibrutinib treatment initiation;

^c At diagnosis;

^d Complex karyotype: ≥ 3 chromosomal abnormalities;

^e Unmutated IGHV, del(17p)/TP53 disruption, or complex karyotype.

Table 2 Prior Therapy for CLL in the First- and the Second-Line Setting

Treatment	First Line N (%) (N = 185)	Second Line N (%) (N = 64)
Chemoimmunotherapy^a	144 (77.8)	48 (75.0)
FCR	75 (40.5)	6 (9.3)
BR	29 (15.7)	28 (43.8)
Clb-R	16 (8.6)	6 (9.3)
R	8 (4.3)	2 (3.1)
R-CHOP	7 (3.8)	—
G-Clb	5 (2.7)	0 (0.0)
G-benda	2 (1.1)	4 (6.25)
R-FCM	2 (1.1)	0 (0.0)
R-CVP	2 (1.1)	0 (0.0)
Chemotherapy^b	38 (20.5)	11 (17.2)
Clb	18 (9.7)	2 (3.1)
FC	11 (5.9)	2 (3.1)
Bendamustine	8 (4.3)	2 (3.1)
Fludarabine	3 (1.6)	0 (0.0)
Targeted agents	4 (2.2)	3 (4.7)
Idelalisib-R	4 (2.2)	1 (1.5)
Idelalisib	0 (0.0)	2 (3.1)
Other therapies^c	8 (4.3)	4 (6.3)

Benda = bendamustine; BR = bendamustine plus rituximab; CHOP = cyclophosphamide, doxorubicin, vincristine, and prednisolone; Clb = chlorambucil; FC = fludarabine-cyclophosphamide; CVP = cyclophosphamide, vincristine, and prednisone; FCM = fludarabine, cyclophosphamide, and mitoxantrone; G = obinutuzumab; R = rituximab

^a Chemoimmunotherapy regimens used in >1 patient each;

^b Chemotherapy regimens used in >1 patient each;

^c Other therapies used in one patient each

had previously received CIT as first-line treatment, most commonly FCR (40.5%) and BR (15.7%). Forty-eight (75%) patients receiving ibrutinib as third-line treatment had been treated with CIT in the second line, most frequently BR (43.8%). Idelalisib was used in 4 and 3 patients in the first- and the second-line setting, respectively.

Ibrutinib Treatment

Patients initiated treatment with single-agent ibrutinib between June 2016 and January 2019. The median time from diagnosis to

ibrutinib treatment initiation was 21 (IQR: 3.4-48.6) months. The median duration of ibrutinib treatment was 18.4 (IQR: 12.5-26.6) months (up to 40 months). At data cut-off, 220 (82.8%) patients remained on ibrutinib treatment while 49 (18.2%) patients had discontinued ibrutinib. The main reasons for treatment discontinuation were disease progression (16/269; 5.9%) and AEs (16/269; 5.9%). Four (4.8%) and 6 (4.9%) patients discontinued ibrutinib treatment due to AEs in the first- and second-line settings. Discontinuation due to disease progression occurred in 6 (7.1%) first-line patients and in 9 (7.4%) patients receiving ibrutinib in the second-line setting (Table 3). The proportion of patients discontinuing treatment due to disease progression (≤ 65 years: 30.0%; >65 years: 34.5%) and AEs (≤ 65 years: 30.0%; >65 years: 34.5%) was not significantly different between patients aged ≤ 65 years and patients older than 65 years ($P = .811$).

Out the 16 patients who discontinued ibrutinib treatment due to disease progression (first-line: $n=6$; second-line: $n=9$), 9 (56.3%) patients harbored del(17p)/TP53 mutation (first-line: $n = 5$; second-line: $n = 4$), 2 (13.3%) patients had del(11q) (second-line: $n = 2$), and 7 (77.8%) patients carried unmutated IGHV (first-line: $n = 3$; second-line: $n = 3$).

Dose reduction was required in 53 (19.7%) patients, and of these, only 7 patients (13.2%) needed a further dose reduction. The occurrence of AEs was the reason for dose reduction in 31 (11.5%; 31/269) patients. Overall, 13 (4.8%) and 18 (6.7%) patients required dose reductions due to hematological and non-hematological AEs, respectively. Eight (9.5%) and 14 (11.6%) patients required dose reductions due to AEs during first- and second-line ibrutinib treatment, respectively ($P = .819$) (Table 3). Ibrutinib dose was increased to 420 mg in 25 (47.2%) patients in whom dose reductions had previously been necessary ($n = 53$). Ibrutinib was temporarily interrupted in 107 (39.8%) patients, with 66 (61.7%) patients requiring one treatment interruption only. Of the treatment interruptions ($n = 168$), 25% (42/168) were due to major and/or minor surgical procedures. Temporary interruption of first- and second-line ibrutinib occurred in 27 (32.1%) and 52 (42.9%) patients, respectively. We observed a trend toward a higher rate of treatment interruptions due to AEs in the second line (21.5%) compared with the frontline setting (10.7%) ($P = .058$) (Table 3). Median time to treatment re-initiation after temporary interruption was 11 (6.2-21.3) days. Single-agent ibrutinib treatment was reintroduced at the standard dose of 420 mg in

Table 3 Ibrutinib Treatment Modification and Discontinuation

Treatment modification	First Line N (%) (N = 84)	Second Line N (%) (N = 121)	Overall Population N (%) (N = 269)
Dose reduction	17 (20.2)	22 (18.2)	53 (19.7)
Patients with at least one dose reduction due to toxicity ^a	8 (9.5)	14 (11.6)	31 (11.5)
Total number of dose reductions	18	24	60
Dose reductions due to toxicity ^b	8 (44.4)	16 (66.7)	34 (56.7)
Hematological toxicity	4 (22.2)	7 (29.2)	16 (26.7)
Non-hematological toxicity	4 (22.2)	9 (37.5)	18 (30.0)
Dose increase after reduction ^b	7 (38.9)	12 (50.0)	33 (55.0)
Temporal treatment interruption	27 (32.1)	52 (43.0)	107 (39.8)
Patients with at least one interruption due to toxicity ^a	9 (10.7)	26 (21.5)	31 (11.5)
Total number of treatment interruptions	39	87	168
Treatment interruptions due to toxicity ^c	11 (28.2)	38 (43.7)	63 (37.5)
Hematological toxicity	10 (25.6)	13 (14.9)	19 (11.3)
Non-hematological toxicity	2 (5.1)	25 (28.7)	46 (27.4)
Treatment discontinuation	15 (17.8)	21 (17.3)	49 (18.2)
Reasons for treatment discontinuation ^a			
Disease progression	6 (7.1)	9 (7.4)	16 (5.9)
Adverse events	4 (4.8) ^d	6 (4.9) ^e	16 (5.9)
Death	1 (1.2)	2 (1.7)	6 (2.2)
Patient decision	0 (0.0)	1 (0.8)	1 (0.4)
Other reasons	4 (4.8)	3 (2.5)	10 (3.7)

^a Percentages calculated over the total number of patients receiving ibrutinib in the overall population (n = 269), in the first line (n = 84) and the second-line setting (n = 121);

^b Percentages calculated over total number of dose reductions;

^c Percentages calculated over total number of interruptions;

^d Pancytopenia (n = 1), infection (UTI) (n = 1), esophagitis (n = 1), and ischemic cerebrovascular accident (n = 1);

^e gastrointestinal bleeding (n = 2), pneumonia (n = 1), infection (n = 1), and pleural effusion (n = 1).

84 (78.5%) patients whose treatment was temporarily interrupted (n = 107).

Response to Treatment and Outcome

ORR with single-agent ibrutinib was 79.2% (95% CI: 73.7%-83.8%) (CR: 14.1%). ORR was 79.8% (CR: 16.7%) in the first line and 76.9% (CR: 13.2%) in the second line (Table 4).

With a median (range) follow-up of 19.2 (12.8-26.9) months (up to 40 months), the median PFS was not reached (Figure 1A) in either the first-line or second-line (Supplementary Figure 1), and estimated PFS rate at 24 months was 84.7% (95% CI: 79.2%-90.1%). Similarly, median OS was not reached (Figure 1B), irrespective of the line in which ibrutinib was used (Supplementary Figure 1). At the time of analysis, 30 patients had died. Eleven (4.1%) patients died due to disease progression, and second neoplasia was the reason for death in two patients. Median time to subsequent CLL treatment was not reached.

The age of patients at ibrutinib treatment (≤ 65 vs. > 65 years) did not have a significant impact either on PFS ($p = 0.285$) or OS ($P = .055$), and the median PFS and OS were not reached, irrespective of the age of patients. Similarly, ORR was comparable between patients

aged ≤ 65 years (95.9%) and patients older than 65 years (94.1%) ($P = .538$) (Supplementary Table 1).

Median PFS and OS were not reached regardless of whether patients had any cardiovascular disorder (hypertension, DM, AF, other arrhythmias, and/or stroke) before ibrutinib treatment initiation (n = 149) (Supplementary Table 2). ORR was not affected either by the presence of any cardiovascular disorder (affecting > 5 patients) (Supplementary Table 3).

Subgroup analyses regarding high-risk genetic factors showed that overall response was not affected by either del(17p)/TP53 mutation ($P = .816$) or unmutated IGHV ($P = .205$). Similarly, the presence of del(11q) did not unfavorably affect treatment response ($P = .298$) (Supplementary Table 4). The presence of complex karyotype (n = 18) did not impact response to treatment either ($P = .308$) (Data not shown).

Median PFS was not reached with single-agent ibrutinib, irrespective of the presence of del(17p)/TP53 mutation ($p = 0.439$), del(11q) ($P = .826$), or unmutated IGHV ($P = .282$). Similarly, none of these genetic alterations adversely affected OS, which was not reached in all subgroups (Figure 2). Median PFS for patients without complex karyotype (n = 209) was not reached (95% CI: not reached [NR]-NR), while it was 28 months (95% CI: 17.4-

Table 4 Summary of Response to Single-Agent Ibrutinib in the Overall Population and the First- and the Second-Line Setting

Variable	First-Line N (%) (N = 84)	Second-Line N (%) (N = 121)	Overall Population N (%) (N = 269)
Response			
CR	14 (16.7)	16 (13.2)	38 (14.1)
PR	27 (32.1)	30 (24.8)	85 (31.6)
PR+ lymphocytosis	12 (14.3)	17 (14.0)	33 (12.3)
SD	1 (1.2)	3 (2.5)	5 (1.9)
PD	0 (0.0)	4 (3.3)	4 (1.5)
Refractoriness	0 (0.0)	2 (1.7)	2 (0.7)
Not evaluated	13 (15.5)	17 (14.0)	40 (14.9)
Death	3 (3.6) ^a	2 (1.7) ^b	5 (1.9) ^c
Non-confirmed CR ^d	14 (16.7)	30 (24.8)	57 (21.2)
ORR^e	79.8	76.9	79.2
95% CI	69.6-87.8	68.3-84.0	73.7-83.8

CI = confidence interval; CR = complete response; ORR = overall response rate; PD = progressive disease; PR = partial response; SD = stable disease.

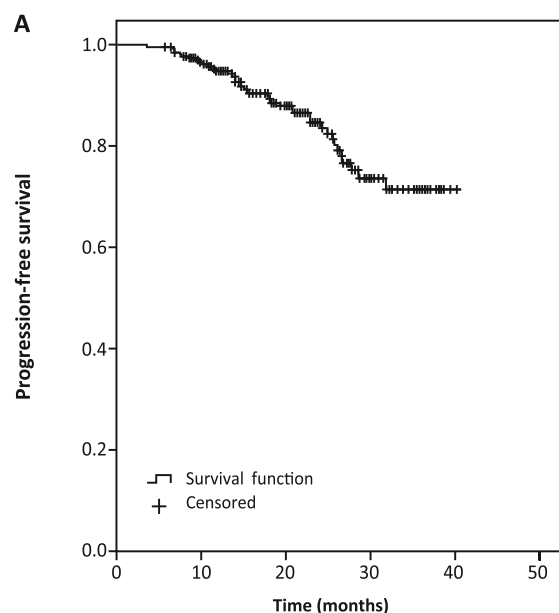
^a Due to disease progression in one patient

^b Due to disease progression in patients

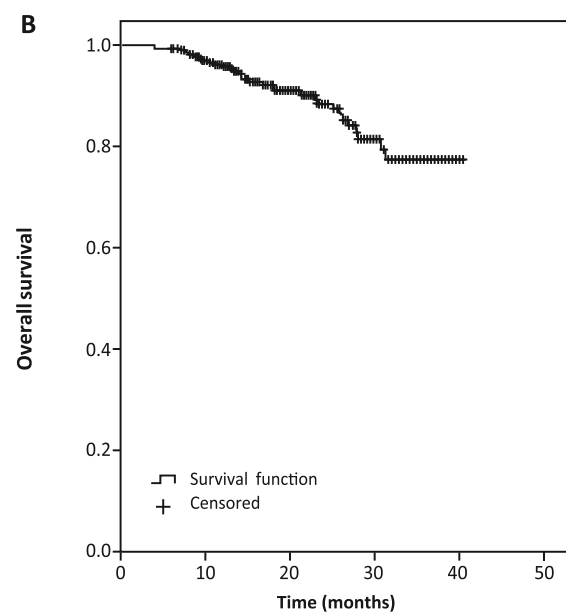
^c Due to disease progression in 4 patients

^d Not confirmed by bone marrow biopsy or imaging (CT)

^e Including CR, non-confirmed CR, PR, and PR + lymphocytosis.

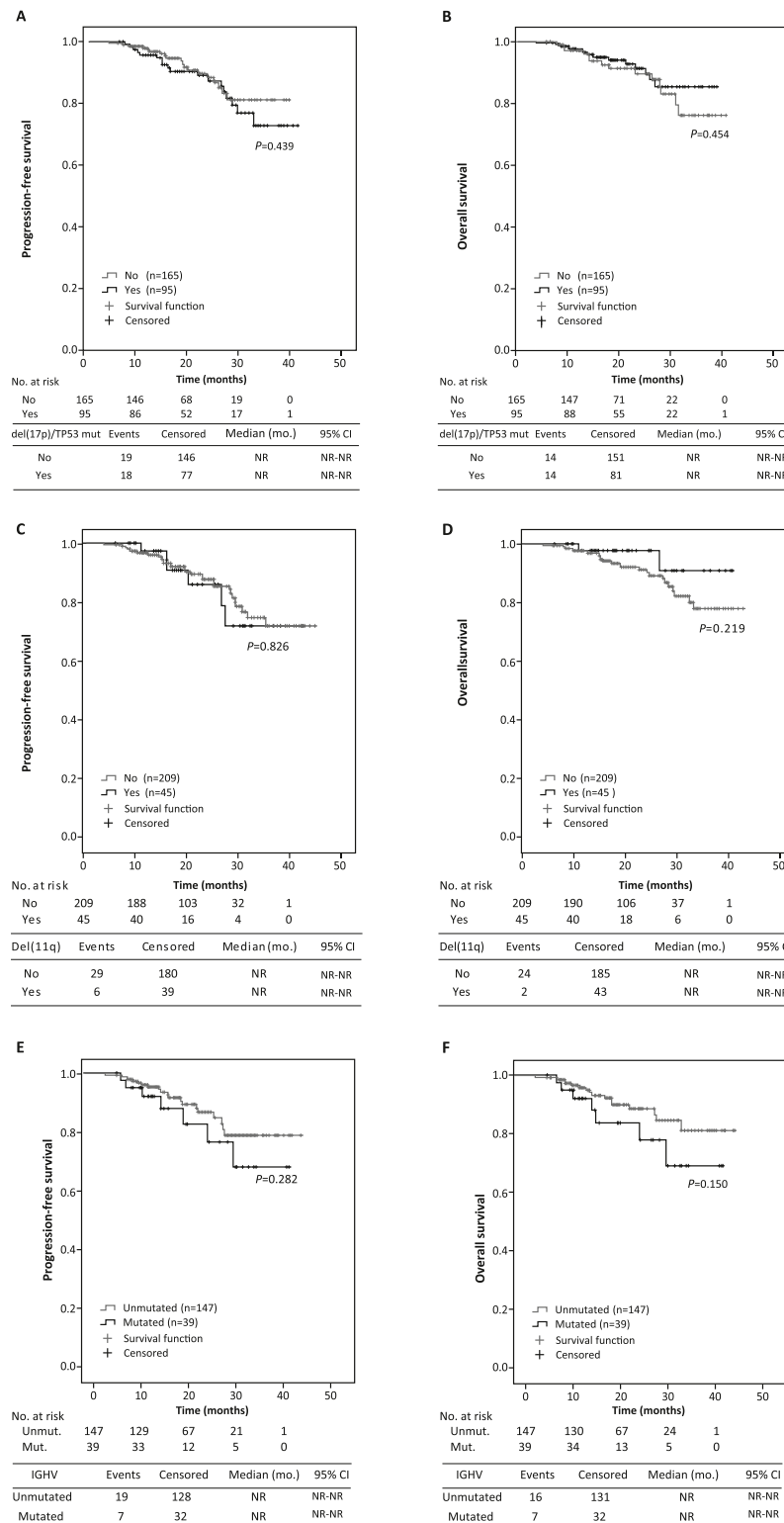
Figure 1 Kaplan-Meier curves for progression-free survival (A) and overall survival (B) with single-agent ibrutinib. CI = confidence interval, NR = not reached. Patients were censored at the date of the last available follow up if still alive or without disease progression at the time of the analysis.


No. at risk	269	240	125	37	1	0
Events	39	230	NR	95% CI		



No. at risk	269	243	131	45	1	0
Events	30	239	NR	95% CI		

Figure 2 Kaplan-Meier curves for progression-free survival according to the presence/absence of del(17p)/TP53 mutation (A) and del(11q) (C), and IGHV mutation status (E). Kaplan-Meier curves for overall survival according to the presence/absence of del(17p)/TP53 mutation (B) and del(11q) (D), and IGHV mutation status (F). CI = confidence interval, NR = not reached. Patients were censored at the date of the last available follow up if still alive or without disease progression at the time of the analysis.



40.0) for patients with a complex karyotype ($n = 18$), with no significant differences between these subgroups ($P = .174$). The presence of complex karyotype did not have an adverse impact on OS either (NR [95% CI: NR-NR] vs. 31.3 [95% CI: 30.4-32.2], $P = .127$).

Univariate COX regression analysis showed that none of the covariates assessed were significantly associated with PFS, regardless of the line in which ibrutinib was used. None of the variables achieving a statistical significance $P < .2$ in the univariate analysis were identified as independent factors adversely affecting PFS with single-agent ibrutinib in the multivariate analysis (Supplementary Table 5).

Among patients who experienced disease progression on ibrutinib treatment ($n = 19$), 11 (57.9%) patients carried del(17p)/TP53 mutation, 4 (23.5%) patients had del(11q), and 3 (27.3%) patients harbored unmutated IGHV. A multivariate logistic regression analysis was performed to assess potential factors associated with disease progression, in which age, line of therapy, and cytogenetic characteristics (del(11q), del(17p)/TP53 mutation, and IGHV mutation status) were assessed. The multivariate analysis identified del(17p)/TP53 mutation as the only independent factor associated with disease progression (OR: 2.570, 95% CI: 0.995-6.635; $P = .05$), which was associated with a higher risk of disease progression (data not shown).

Immune Reconstitution

Mean IgA levels increased from 133.0 ± 285 mg/dL at ibrutinib treatment initiation ($n = 212$) to 143.0 ± 230.7 mg/dL at the end of treatment ($n = 178$). When paired analysis was performed ($n = 165$), we found that mean IgA levels significantly increased from the initiation of single-agent ibrutinib to the end of treatment (124.1 vs. 146.6 mg/dL, respectively; $P < .001$). The mean CD4/CD8 ratio was 1.6 at ibrutinib treatment initiation ($n = 80$), and 1.4 at the end of treatment ($n = 42$). Overall, 37 patients had available data for paired analysis, showing that the CD4/CD8 ratio did not change from ibrutinib treatment initiation to the end of treatment (1.3 vs. 1.2 respectively; $p = 0.100$).

Postibrutinib Treatment for R/R CLL

Sixteen (5.9%) patients received a further line of therapy for CLL after ibrutinib treatment discontinuation. The therapies (CIT, chemotherapy, and targeted agents) used after discontinuation of first- and second-line ibrutinib treatment are described in Supplementary Table 6.

Safety

A total of 188 (69.9%) patients experienced at least one AE during ibrutinib treatment. The most frequent AEs (any grade) (reported in $>10\%$) were infections (28.3%), bleeding (20.8%), diarrhea (14.9%), and arthralgia/myalgia (11.2%). AF and other arrhythmias of any grade occurred in 8 (3%) and 7 (2.6%) patients, respectively. Hypertension occurred in 11 (4.1%) patients. Overall, 83 (30.9%) patients experienced at least one grade 3 or higher AE, with infections (12.2%), neutropenia (7.0%), and bleeding (3.0%) being the most common (reported in $\geq 3\%$) (Table 5).

Overall, 67.9% (57/84) and 71.9% (87/121) of patients experienced at least one AE during first- and second-line ibrutinib treatment, respectively. The most common grade 3-4 AEs (reported in $>2\%$) were infections (first-line: 7.2%; second-line: 11.6%), and bleeding (first-line: 2.4%; second-line: 2.5%). Grade ≥ 3 AF was reported in one patient (1.2%) and 2 patients (1.7%) during first- and second-line ibrutinib, respectively. None of the patients experienced other arrhythmias of grade ≥ 3 . Grade ≥ 3 hypertension occurred in one patient receiving second-line ibrutinib (Table 5). Richter transformation was not reported in any patient.

Of the 149 (55.4%) patients with baseline cardiovascular comorbidity (hypertension, DM, AF, other arrhythmias, and/or stroke), 6 (4%) patients developed AF (any grade) during ibrutinib treatment. The incidence of new-onset AF during ibrutinib treatment was not significantly associated with the presence of cardiovascular comorbidity at treatment initiation ($p = 0.305$) (data not shown).

Overall, 56 (20.8%) patients experienced bleeding during ibrutinib therapy, mainly minor bleeding (grade 1 or 2) (17.5%). Major bleeding (grade ≥ 3) was reported in 7 (2.6%) patients. Minor bleeding occurred before major bleeding in 2 patients. The use of anticoagulants and/or antiplatelets was associated neither with the occurrence of bleeding ($P = .137$) nor with the type of bleeding ($P = .579$) (Supplementary Table 7). Overall, 66 patients were receiving anticoagulant and/or antiplatelet therapy during ibrutinib treatment, with 39 (14.5%) patients being treated with DOACs (apixaban: $n = 17$; dabigatran: $n = 3$; edoxaban: $n = 2$; rivaroxaban: $n = 2$). Three patients who were receiving VKAs ($n = 1$) and DOACs ($n = 2$) experienced major bleeding. Of these, one patient was treated with acenocoumarol, and one patient was given dabigatran while receiving first- and second-line ibrutinib treatment, respectively.

A total of 167 infections (any grade) (infections: $n = 131$; respiratory infections; $n = 36$) occurred in 93 (34.6%) patients. Of the 131 infections detected, 98 (77.2%) were bacterial infections, mainly pneumonia (32.3%) and infections affecting the urinary tract (12.6%). Overall, 20.5% of infections reported were viral infections, most commonly influenza (6.2%) and herpes zoster (3.9%). Seven fungal infections were reported (noninvasive candidiasis: $n = 5$; invasive aspergillosis (IA): $n = 1$; mucormycosis: $n = 1$). Two (0.7%) patients experienced opportunistic infections (IA and mucormycosis), both reported in patients in the R/R setting. An opportunistic infection (IA) was reported in one patient receiving second-line ibrutinib who had been previously treated with high-dose corticosteroids and alemtuzumab (Supplementary Table 8). Of note, the occurrence of infections was not significantly associated with the evolution of IgA levels from ibrutinib treatment initiation to treatment end (decrease, maintenance, increase) ($P = 0.301$) (Data not shown).

Grade ≥ 3 infections (any type of infection, including lower and upper respiratory tract infection) were reported in 37 (13.8%) patients (first-line: 8 [9.5%]; second-line: 15 [12.4%]; third-line: 14 [21.9%]). Of these, 14 (37.8%) patients carried del(17p)/TP53 mutation, 7 (19.4%) patients had del(11q), and 4 (17.4%) patients had unmutated IGHV. A multivariate logistic regression analysis where the treatment line and the abovementioned genetic characteristics were assessed showed that the line in which ibrutinib was

Table 5 Summary of Adverse Events Reported During Single-Agent Ibrutinib Treatment

Adverse events	First Line N (%) (N = 84)	Second Line N (%) (N = 121)	Overall Population N (%) (N = 269)
Any grade^a	57 (67.9)	87 (71.9)	188 (69.9)
Infections			
Infections	19 (22.6)	35 (28.9)	76 (28.3)
Respiratory infections ^b	6 (7.1)	12 (9.9)	22 (8.2)
Other non-hematological toxicities			
Bleeding	14 (16.7)	27 (22.3)	56 (20.8)
Diarrhea	11 (13.1)	21 (17.4)	40 (14.9)
Arthralgia/myalgia	11 (13.1)	12 (9.9)	30 (11.2)
Lymphocytosis	5 (6.0)	14 (11.6)	23 (8.6)
Arterial hypertension	3 (3.6)	5 (4.1)	11 (4.1)
Constitutional syndrome	5 (6.0)	5 (4.1)	11 (4.1)
Nausea/vomiting	4 (4.8)	4 (3.3)	9 (3.3)
Cramping	0 (0.0)	4 (3.3)	8 (3.0)
Atrial fibrillation	1 (1.2)	4 (3.3)	8 (3.0)
Fever	0 (0.0)	4 (3.3)	8 (3.0)
Hematological toxicities			
Neutropenia	1 (1.2)	14 (11.6)	23 (8.6)
Thrombocytopenia	1 (1.2)	3 (2.5)	8 (3.0)
Anemia	4 (4.8)	1 (0.8)	7 (2.6)
Grade 3-4^c	19 (22.6)	36 (29.8)	81 (30.1)
Non-hematological toxicities			
Infections	6 (7.2)	14 (11.6)	33 (12.2)
Bleeding	2 (2.4)	3 (2.5)	8 (3.0)
Lymphocytosis	2 (2.4)	5 (4.1)	7 (2.6)
Atrial fibrillation	1 (1.2)	2 (1.7)	4 (1.5)
Arthralgia/myalgia	1 (1.2)	1 (0.8)	3 (1.1)
Hematological toxicities			
Neutropenia	1 (1.2)	11 (9.1)	19 (7.0)
Thrombocytopenia	0 (0.0)	0 (0.0)	3 (1.1)
Anemia	1 (1.2)	0 (0.0)	2 (0.8)
Grade 5			
Bleeding	0 (0.0)	1 (0.8)	1 (0.4)
Atrial fibrillation	0 (0.0)	0 (0.0)	1 (0.4) ^d
Hepatotoxicity	1 (1.2)	0 (0.0)	1 (0.4)
Hemorrhagic cerebrovascular accident	0 (0.0)	0 (0.0)	1 (0.4) ^e

In order to assess toxicity per patient, maximum grade for each toxicity recorded during ibrutinib treatment was considered for evaluation.

^a Most common adverse events (AEs) of any grade detected in $\geq 3\%$ of patients each

^b At least one respiratory infection including upper respiratory tract infection or lower respiratory tract infection, including pneumonia

^c Most common grade 3-4 AEs detected in more than 2 patients each.

^d One patient died due to atrial fibrillation during third-line ibrutinib treatment

^e One patient died due to a hemorrhagic cerebrovascular accident during third-line ibrutinib treatment.

used was the only factor independently associated with the occurrence of grade ≥ 3 infections. Patients receiving ibrutinib as third-line therapy were more likely to develop grade ≥ 3 infections (vs. TN patients; OR: 2.660 [95% CI: 1.040-6.804], $P = .041$).

The incidence of the most common AEs reported during ibrutinib treatment, including infections, bleeding, and arthralgia/myalgia, was similar between patients aged ≤ 65 years and those patients older than 65 years (Supplementary Table 9).

Four (1.5%) patients died due to AEs during ibrutinib treatment (Table 5).

Discussion

This real-world study aimed to assess the characteristics and clinical management and outcomes of patients receiving single-agent ibrutinib under routine clinical practice conditions in Spain. CLL patients included in our study had high-risk genetic features and significant baseline comorbidities, mainly cardiovascular disease. We found that ibrutinib administered in earlier therapy lines achieved a high response and a favorable clinical outcome in real-life patients, which was not adversely affected by age or high-risk genetic features.

The study population was representative of the general population encountered in clinical practice, including a heterogeneous patient profile due to age, comorbidities, concomitant therapies and genetic characteristics of the disease. Our series included a significant proportion of patients with at least one high-risk genetic alteration, including del(17p)/TP53 mutation, unmutated IGHV and/or complex karyotype (74%). Notably, the high frequency of del(17p)/TP53 mutation in the previously-untreated CLL population in this study (66%) is higher than that seen in the TN population²⁵. It reflects the approval of ibrutinib for this subgroup of patients in Spain when the study patients initiated ibrutinib (January 2016). Of particular interest, the observed high rate of molecular determination of del(17p)/TP53 mutation (97%) and IGHV mutation status (69%) is unprecedented compared to other real-world studies.^{32,33} It reflects a high level of compliance with guideline recommendations on molecular testing of these alterations before CLL treatment initiation,¹⁰ and occurred as a result of effective collaboration between academic institutions and pharmaceutical company: the RED53 Spanish network.³⁴

This real-world study supports the benefit demonstrated with ibrutinib in randomized clinical trials, despite including a high-risk population with poor prognostic clinical and genetic features. Single-agent ibrutinib achieved a high ORR of 79.2%, which is within the range of the ORR reported in prior real-world studies (71%-89%), mainly derived from R/R patients who had generally been more heavily pretreated.^{20,21,30,31} Real-world data on PFS and OS with ibrutinib is also heterogeneous, mainly due to the differences in patient characteristics, prior therapies, and median duration of exposure to ibrutinib and follow up. The median PFS and OS were not reached with single-agent ibrutinib in line with clinical trials³⁵ and prior real-world studies evaluating ibrutinib in compassionate programs in R/R CLL^{27,30} and in the frontline setting.²⁵

The PFS and OS benefit for single-agent ibrutinib was observed across all patient subgroups defined by patient clinical and genomic risk factors. Of note, ibrutinib enabled a favorable outcome regardless of high-risk genomic features. Thus, we found that the presence of del(17p)/TP53 mutation, unmutated IGHV, and complex karyotype did not adversely impact outcome, and with a median follow-up of 19.2 months (up to 40 months), median PFS and OS were not reached in patients with or without these genetic alterations. Multivariate COX regression analysis revealed that none of these genetic alterations have a significant prognostic value in

line with findings reported in a pooled analysis of the RESONATE 2, the RESONATE, and the HELIOS studies.³⁶ A long-term follow-up analysis of the RESONATE-2 and iLLUMINATE studies has recently reported similar PFS with ibrutinib in patients with or without high-risk genomic features, including del(17p)/TP53 mutation.³⁷ The sustained clinical benefit obtained with ibrutinib regardless of risk status has also been shown in the real-world setting.³⁸ Accordingly, the long-term real-world results of the Swedish compassionate use cohort showed that del(17p)/TP53 mutation did not adversely impact survival in line with our results.²⁹

The median PFS and OS were not achieved, regardless of age, with no significant differences between patients aged ≤ 65 and older than 65 years. Similar PFS and OS outcomes have also been reported across all age cohorts in the real-world setting²⁵. The benefit observed in elderly patients is of particular interest, given that this subgroup makes up most of the general population with CLL. Cardiovascular comorbidity at ibrutinib treatment initiation, including hypertension and AF, did not affect median PFS or OS unfavourably either, a finding which was also observed in the clinical trial setting³⁹ and is especially relevant considering the high frequency of cardiovascular disease in CLL patients.

CLL is characterized by substantial immune dysfunction, which increases the incidence of infections.^{1,40} Ibrutinib has been shown to confer significant improvement on immunological parameters,^{41,42} and the increase in IgA levels during ibrutinib treatment has been associated with a reduction of infection rate.^{42,43} We found that mean IgA levels significantly increased from the initiation of ibrutinib to the end of treatment, a finding which is consistent with the significant rise in IgA levels observed in clinical trials.^{41,42} T-cell dysfunction in CLL is characterized by abnormalities in the proportion of CD4 and CD8 T cells, including the inverted CD4/CD8 ratio (< 1), which has been associated with poor outcomes.⁴⁴ We found that the mean CD4/CD8 ratio remained unchanged with ibrutinib therapy in line with prior evidence.⁴⁵ However, the determination of CD4/CD8 is not routinely performed, and therefore, the low sample population available for comparison does not allow us to draw conclusions.

The safety data show that single-agent ibrutinib had a manageable safety profile, with no new or unexpected safety issues identified in our series. The type of toxicities reported was similar for TN and R/R patients, although the frequency of toxicities of any grade differed, with a slightly lower frequency in the frontline setting as previously reported.³⁵ It is noteworthy that ibrutinib was well tolerated regardless of age, with a similar incidence of the most common toxicities, including infections and bleeding, between patients aged ≤ 65 and older than 65 years, a finding that was previously seen in the real world.³¹

Infections occurred at a higher rate among patients receiving second-line ibrutinib than first-line patients (11.6% vs 7.2%), a trend previously reported in clinical trials.^{35,42} Accordingly, the line in which ibrutinib is used was identified as an independent factor associated with the occurrence of grade ≥ 3 infections, with patients receiving ibrutinib in the third line being at a higher risk of grade ≥ 3 infection. Interestingly, opportunistic infections in TN patients were not observed and only occurred in 2 R/R patients who had been previously treated with immunosuppressor agents (corti-

costeroids, alemtuzumab). The trend toward a higher incidence of infections in the R/R setting could, therefore, suggests the potential contribution of a cumulative immunosuppressive effect of prior therapy to the risk of infection as previously suggested.⁴⁶ The increase in IgA levels in ibrutinib-treated patients has been linked with a lower risk of infections.^{42,43} However, the increase in IgA levels observed in our series was not associated with a decrease in the occurrence of infections, although this analysis was limited by the small sample population available for comparison.

Despite being a population with a significant cardiovascular burden, it is noteworthy that the incidence of new-onset cardiovascular events was low in our series. The frequency of hypertension of any grade (4.1%) is consistent with that seen in clinical trials⁴⁷ and slightly lower than that recently described in real-world reports, including TN and R/R patients, which identified 6.8%²¹ and 5.2%²² patients with any grade hypertension. A low rate of new-onset AF was observed in our series (3%), which seems to be lower than that previously reported in real-world studies evaluating ibrutinib (6.5%-16%),^{21,25,27,30,31} but it is in line with the frequency observed in the clinical trial setting.⁴⁷

The presence of comorbidities that increase cardiovascular risk, such as hypertension, has not been identified as a significant risk factor for developing AF during ibrutinib treatment in clinical trials.³⁹ Similarly, this real-world study showed that the occurrence of new-onset AF was not significantly associated with cardiovascular comorbidity at treatment initiation.

The incidence of grade ≥ 3 bleeding (3%) was comparable to that observed in a real-world cohort, including TN and R/R patients (2.9%)²¹. Notably, the occurrence of grade 3-4 bleeding was similar between TN and R/R patients (2.4% and 2.5%) as previously seen in the clinical trial setting.⁴⁸ Major bleeding occurred in 2.6% of patients, comparable to the incidence reported in real-world patients.^{24,25,27,30,31} Interestingly, this real-world analysis shows that the occurrence of major bleeding was not related to the use of anticoagulant and/or antiplatelet therapy in line with clinical trial data.⁴⁹ Of note, only two patients who were concomitantly treated with anticoagulants and/or antiplatelets experienced major bleeding while receiving acenocoumarol and dabigatran, respectively. Indeed, anticoagulated patients receiving DOACs were mostly treated with apixaban in line with consensus recommendations⁵⁰. Therefore, our findings may suggest high compliance with recommendations regarding the use of concomitant anticoagulants and/or antiplatelets with ibrutinib.⁵⁰

The overall rate of ibrutinib discontinuation (18%) is within the range of the discontinuation rate reported in the real-world setting (14%-49%)^{20,24,25,30,31,51} where heterogeneous rates observed may mainly be explained by the differences mentioned above between real-world studies and potential divergences in the management of ibrutinib in routine clinical practice. It is noteworthy that only 6% of patients discontinued ibrutinib due to AEs, which is even lower than the rate of discontinuation previously reported in compassionate use programs.^{29,31} The low rate of discontinuation may suggest a minimal impact of toxicity in the continuation of treatment in routine clinical practice and likely reflect careful monitoring of ibrutinib toxicity. Additionally, a low treatment discontinuation rate due to PD (6%) was also reported in our series. Contrary to

findings from clinical trials and multiple real-world studies, which revealed toxicity as the most common reason for ibrutinib discontinuation,^{21,25,30} we found a similar rate of discontinuation due to PD and toxicity, a finding which has also been recently reported in real-world R/R patients.²⁷

Some study limitations should be acknowledged when interpreting study data. The main limitation arises from the retrospective nature of this study, which uses information recorded for non-research purposes in the medical chart. Additionally, single-agent ibrutinib was prescribed under clinical practice conditions, which led to the unbalanced number of patients in the groups defined by the line of therapy. Nevertheless, the comparisons made between these groups are merely descriptive. Additionally, this study was not powered for post hoc analysis. Despite the limitations, to the best of our knowledge, this is the most extensive study offering real-world data on the clinical and genetic characteristics of patients receiving ibrutinib, therefore providing interesting data on prescription patterns of this targeted agent in Spain. Of particular interest, this study describes the most extensive real-world experience on patients with del(17p)/TP53 mutation and unmutated IGHV given the high rate of testing of these high-risk molecular features in the clinical practice in Spain.

Conclusion

This real-world study shows that single-agent ibrutinib is an effective treatment option in TN and R/R patients, regardless of age and high-risk genetic features, in line with clinical trials. Additionally, the unprecedented rate of testing of del(17p)/TP53 and IGHV mutation status in the real-world setting reflects high compliance with guideline recommendations regarding molecular testing of these alterations before treatment initiation. This study also supports that single-agent ibrutinib has a manageable safety and tolerability profile, with no unexpected safety issues and a low discontinuation rate due to toxicity. Notably, despite a high cardiovascular burden, the incidence of new-onset cardiovascular events was low and did not lead to interruption or discontinuation of ibrutinib treatment.

Clinical Practice Points

- The robust efficacy of ibrutinib has been demonstrated regardless of high-risk genetic features in chronic lymphocytic leukemia (CLL), including del(17p)/TP53 mutation, and unmutated IGHV.
- The IBRORS-LLC study has shown that single-agent ibrutinib, when administered in early therapy lines, achieves a high response and a favorable clinical outcome, in terms of progression-free survival (PFS) and overall survival (OS), in real-world CLL patients in Spain.
- This study also supports the effectiveness of single-agent ibrutinib, regardless of age and high-risk molecular features, in line with clinical trials. The PFS and OS benefit was observed across all patient subgroups defined by clinical and molecular risk factors.
- A high rate of molecular determination of del(17p)/TP53 mutation and IGHV mutation status has been identified in this real-world study, which might reflect high compliance

with guideline recommendations on molecular testing of these genetic alterations before CLL treatment initiation.

- A significant increase of IgA levels during ibrutinib treatment was observed in our series, in line with clinical trials, although it does not seem to be associated with a decrease in the occurrence of infections.
- The safety results from the IBRORS-LLC study are consistent with the known safety profile of ibrutinib in CLL patients from clinical trials. A low rate of ibrutinib treatment discontinuation due to toxicity was observed in real-world patients. Additionally, a low incidence of cardiovascular events was reported, which did not lead to treatment discontinuation.
- This study describes the most extensive study providing real-world data on the clinical and genetic characteristics of CLL patients receiving single-agent ibrutinib in early therapy lines, therefore providing valuable data on prescription patterns of this targeted agent in Spain.

Acknowledgments

The authors would like to thank the IBRORS-CLL study investigators: Ana Saus Carreres, Ana Isabel Teruel Casasús, Blanca Ferrer Lores, María Concepción Ruiz Nuño, Gloria Moreno Carrasco, Myriam Revelles Peñas, Carol Moreno Atanasio, Anna Bosch Vilaseca, Silvana Saavedra Gerosa, Vanesa Martín Palanco, Javier López Jiménez, Juan Gonzalo Correa Saldarriaga, Gonzalo Caballero Navarro, Araceli Rubio Martínez, Alejandro García Ortego, Sergio Felipe Pinzón Mariño, Piva Sánchez Antón, Elena Pérez Ceballos, Marta Ruiz Mercado, María Esperanza Moreno Beltrán, Isabel María García Cabrera, Gabriela Rodríguez Macías, Mariana Bastos Oreiro, Mónica Ballesteros Andrés, Miguel Ángel Canales Albendea, Eva María Donato Martín, Silvia María Fernández Ferrero, Susana Valenciano Martínez, Samuel Romero Domínguez, Rafael Andreu Lapiedra, Ana Isabel Vicente Sánchez, Mario Arnao Herraiz, Hugo Luzardo Henríquez, Luisa Guerra Domínguez, Sara Sánchez Matías, Esther González García, Carolina Cañigral Ortiz, Juana María Clavel Pia, Raimundo García Boyero, Adriana Gascón Bug, Luis Serrano Picazo, Guillermo Cañigral Ferrando, María Dolores Linares Latorre, Laida Cuevas Palomares, Ana Santamaría López, Itziar Oizartabal Ormategi, María del Pilar Anaya Aznar, Juan Camilo Restrepo Correa, Elena Hernández Sánchez, Nicolás Antonio Díaz Varela. We also thank the patients who consented to participate in this study. The authors would like to acknowledge Janssen-Cilag S.A for sponsoring the study. Medical writing and editorial support were provided by Cristina Vidal and Antonio Torres-Ruiz from Dynamic Science S.L. (Spain), and was funded by Janssen-Cilag S.A.

Author Contributions: Pau Abrisqueta and Javier Loscertales: design, acquisition of data, data analysis and interpretation, manuscript preparation and review. María José Terol, Ángel Ramírez Payer, Macarena Ortiz, Inmaculada Pérez, Carolina Cuellar-García, Margarita Fernández de la Mata, Alicia Rodríguez, Ana Lario, Julio Delgado, Ana Godoy, José M^a Arguñano Pérez, M^a José Berrueto, Ana Oliveira, José-Ángel Hernández-Rivas, María Dolores García Malo, Ángeles Medina, Paloma García Martín, Santiago Osorio, Patricia Baltasar, Miguel Fernández-Zarzoso, Fernando Marco, M^a Jesús Vidal Manceñido, Alicia Smucler Simonovich, Montser-

rat López Rubio, Isidro Jarque, Alexia Suarez, Rubén Fernández Álvarez, Aima Lancharro Anchel, Eduardo Ríos, María del Carmen Losada Castillo, Ernesto Pérez Persona, Ricardo García Muñoz, Rafael Ramos, Lucrecia Yáñez, and José Luis Bello: acquisition of data, data analysis and interpretation, manuscript preparation and review. Cristina Lorient, Daniel Acha and Miguel Villanueva: design, data analysis and interpretation, and manuscript preparation and review. All authors read and approved the final version of the manuscript.

Disclosure

P. Abrisqueta has received honoraria for scientific advice from Janssen, Astrazeneca, Roche, Celgene, Abbvie, has participated in medical meetings sponsored by Janssen, Astrazeneca, Roche, Celgene, Abbvie, and Gilead, and has received speaker and consultancy/advisory board honoraria from Janssen, Astrazeneca, Roche, Celgene, Abbvie, and Gilead. **J. Loscertales** has served in an advisory board role from Janssen, Abbvie, Astrazeneca, and Beigene, has received speaker honoraria from Janssen, Gilead, and Roche, and has received attendance fees and travel expenses from Janssen. **M.J. Terol** has received honoraria for advisory board from Roche, Gilead, Janssen, Takeda, and Abbvie, has received grant funding from Gilead, Janssen, and has received travel expenses from Roche, Gilead, Janssen, Takeda, and Abbvie. **A. Ramírez Payer** has served in an advisory board role for BMS/Celgene, Janssen, Novartis, EusaPharma, Abbvie, Roche, Takeda, Pfizer, AstraZeneca, Incyte and GSK, and has received speaker bureau fees from Abbvie, BMS/Celgene, Janssen, EusaPharma, Roche, Novartis, and Takeda. **M. Ortiz** has served on the advisory role for Janssen and Roche and has received speaker honoraria for Janssen, AbbVie and Roche. **M. Fernández de la Mata** has received research support from Janssen and Gilead, has received speaker bureau honoraria from Janssen, has served in an advisory board role for Janssen, Roche, Abbvie, Celgene, Amgen, and GSK, and has received honoraria from Janssen, Roche, Gilead, Abbvie, Celgene, Amgen, and GSK. **A. Rodríguez** has received honoraria for advisory board from Janssen and has received honoraria as speaker in scientific meetings from Janssen, AstraZeneca and Abbvie. **J. Delgado** has received honoraria from Janssen, BMS-Celgene, Abbvie, Amgen, and Roche. **A. Godoy** has received honoraria as speaker in scientific meetings from Bristol-Miers and Janssen. **J.M. Arguñano Pérez** has received honoraria from Janssen, BMS-Celgene, Abbvie, Amgen, and Roche. **M. J. Berrueto** has received honoraria as speaker in scientific meetings from Janssen and Abbvie. **A. Oliveira** has received honoraria for scientific advice from Abbvie, Alexion, Janssen and Roche, has received honoraria for participation in medical meetings from Abbvie, Alexion, Janssen and Roche, has received research funding from Janssen, and has received honoraria for scientific advice and as speaker in meetings from Abbvie, Alexion, Janssen y Roche. **J.A. Hernández-Rivas** has received honoraria for consultancy from Janssen, Roche, Abbvie, AstraZeneca, Beigene, Gilead, BMS-Celgene, Lilly, Amgen, Takeda, Jazz Pharmaceuticals, and Rovi. **A. Medina** has served in an advisory board for Janssen, Abbvie and AstraZeneca. **P. García Martín** has received speaker honoraria from Roche, Janssen and Abbvie. **S. Osorio** has received honoraria for advisory board and as speaker in scientific meeting from Roche,

Abbvie, and Janssen. **P. Baltasar** has received honoraria for scientific advice, speaker in meetings, and attendance to meetings sponsored by Roche, Janssen, and Abbvie. **M. Fernández-Zarzoso** has received research support from Sanofi, has served on the advisory board for Janssen, Roche, Takeda, and Sanofi, has received speaker bureau honoraria from Janssen, Takeda, Sanofi and Roche, and has received honoraria from Janssen, Takeda, Sanofi, and Roche. **F. Marco** has received speaker bureau fees from Janssen and AbbVie. **M. J. Vidal Manceñido** has received honoraria for advisory role from Janssen and Roche, and has received speaker bureau fees from Janssen, Abbvie, Roche and Takeda. **I. Jarque** has received consultancy fees and/or has supported speaker bureaus for Abbvie, Alexion, Amgen, AstraZeneca, BMS, Celgene, CellTrion, Grifols, Janssen, MSD, Novartis, Pfizer, Roche, Servier, Shionogi, Shire and Takeda. **A. Suárez** has received honoraria for advisory board from Janssen, Amgen, BMS Celgene, Abbvie, and Sanofi. **E. Ríos** has received honoraria as speaker from Abbvie, Servier, Janssen and Takeda, has received honoraria for participation in scientific conferences/meetings from Takeda and Roche, and has served in an advisory board role for Servier, Takeda and Gilead. **M. C. Losada Castillo** has served in an advisory board role for Roche, Janssen, Celgene, Amgen and Abbvie, and has received honoraria as speaker from Abbvie, Takeda, Roche, Janssen, and Astra Zeneca. **E. Pérez Persona** has served in an advisory board role for BMS/Celgene, Amgen, Janssen and GSK, and has received speaker bureau fees from BMS, Amgen, Janssen, AstraZeneca and AbbVie. **R. Ramos** has received attendance fees and travel expenses from Janssen and Celgene, has received honoraria for participation in clinical trials from Janssen, and has received honoraria for participation in conferences and workshops from Celgene. **L. Yañez** has served in the advisory board for Janssen, AstraZeneca, BeiGene, Roche and Abbvie, and has received honoraria from Janssen, Astra Zeneca, Roche, and Abbvie. **J. L. Bello** has participated as a principal investigator in clinical trial supported by Roche. **C. Loriente, D. Acha, and M. Villanueva** are Janssen Cilag employees (Medical Department-Hematology). **I. Pérez, C. Cuellar-García, A. Lario, M. D. García Malo, A. Smucler Simonovich, M. López Rubio, R. Fernández Álvarez, A. Lancharro Anchel, R. García Muñoz** have no conflict of interest to disclose.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.clml.2021.07.022](https://doi.org/10.1016/j.clml.2021.07.022).

References

- Forconi F, Moss P. Perturbation of the normal immune system in patients with CLL. *Blood*. 2015;126:573–581. doi:[10.1182/blood-2015-03-567388](https://doi.org/10.1182/blood-2015-03-567388).
- Gaidano G, Rossi D. The mutational landscape of chronic lymphocytic leukemia and its impact on prognosis and treatment. *Hematology Am Soc Hematol Educ Program*. 2017;2017:329–337. doi:[10.1182/asheducation-2017.1.329](https://doi.org/10.1182/asheducation-2017.1.329).
- Nadeu F, Clot G, Delgado J, et al. Clinical impact of the subclonal architecture and mutational complexity in chronic lymphocytic leukemia. *Leukemia*. 2018;32:645–653. doi:[10.1038/leu.2017.291](https://doi.org/10.1038/leu.2017.291).
- Eichhorst B, Fink AM, Bahlo J, et al. First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. *Lancet Oncol*. 2016;17:928–942. doi:[10.1016/S1470-2045\(16\)30051-1](https://doi.org/10.1016/S1470-2045(16)30051-1).
- Fischer K, Cramer P, Busch R, et al. Bendamustine combined with rituximab in patients with relapsed and/or refractory chronic lymphocytic leukemia: a multicenter phase II trial of the German chronic lymphocytic leukemia study group. *J Clin Oncol*. 2011;29:3559–3566. doi:[10.1200/JCO.2010.33.8061](https://doi.org/10.1200/JCO.2010.33.8061).
- Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376:1164–1174. doi:[10.1016/S0140-6736\(10\)61381-5](https://doi.org/10.1016/S0140-6736(10)61381-5).
- Robak T, Dmoszynska A, Solal-Celigny P, et al. Rituximab plus fludarabine and cyclophosphamide prolongs progression-free survival compared with fludarabine and cyclophosphamide alone in previously treated chronic lymphocytic leukemia. *J Clin Oncol*. 2010;28:1756–1765. doi:[10.1200/JCO.2009.26.4556](https://doi.org/10.1200/JCO.2009.26.4556).
- Stügelbauer S, Schnaiter A, Paschka P, et al. Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial. *Blood*. 2014;123:3247–3254. doi:[10.1182/blood-2014-01-546150](https://doi.org/10.1182/blood-2014-01-546150).
- Tam CS, O'Brien S, Plunkett W, et al. Long-term results of first salvage treatment in CLL patients treated initially with FCR (fludarabine, cyclophosphamide, rituximab). *Blood*. 2014;124:3059–3064. doi:[10.1182/blood-2014-06-583765](https://doi.org/10.1182/blood-2014-06-583765).
- Hallek M, Cheson BD, Catovsky D, et al. iwCLL guidelines for diagnosis, indications for treatment, response assessment, and supportive management of CLL. *Blood*. 2018;131:2745–2760. doi:[10.1182/blood-2017-09-806398](https://doi.org/10.1182/blood-2017-09-806398).
- Medina A, RA Hernández JA, Loscertales J, et al. *On behalf of Grupo Español de Leucemia Linfocítica Crónica (GELLC)*. Guía nacional de leucemia linfática crónica y linfoma linfocítico; 2020 Available from : www.sehh.es/recursos-Guia-Clinica-LLC-abril-2020. 21 - April - 2020.
- Rossi D, Gerber B, Stussi G. Predictive and prognostic biomarkers in the era of new targeted therapies for chronic lymphocytic leukemia. *Leuk Lymphoma*. 2017;58:1548–1560. doi:[10.1080/10428194.2016.1250264](https://doi.org/10.1080/10428194.2016.1250264).
- Bosch F, Dalla-Favera R. Chronic lymphocytic leukaemia: from genetics to treatment. *Nat Rev Clin Oncol*. 2019;16:684–701. doi:[10.1038/s41571-019-0239-8](https://doi.org/10.1038/s41571-019-0239-8).
- Fraser G, Cramer P, Demirkan F, et al. Updated results from the phase 3 HELIOS study of ibrutinib, bendamustine, and rituximab in relapsed chronic lymphocytic leukemia/small lymphocytic lymphoma. *Leukemia*. 2019;33:969–980. doi:[10.1038/s41375-018-0276-9](https://doi.org/10.1038/s41375-018-0276-9).
- 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;94:1353–1363. doi:[10.1002/ajh.25638](https://doi.org/10.1002/ajh.25638).
- Burger JA, Tedeschi A, Barr PM, et al. Ibrutinib as initial therapy for patients with chronic lymphocytic leukemia. *N Engl J Med*. 2015;373:2425–2437. doi:[10.1056/NEJMoa1509388](https://doi.org/10.1056/NEJMoa1509388).
- Moreno C, Greil R, Demirkan F, et al. Ibrutinib plus obinutuzumab versus chlorambucil plus obinutuzumab in first-line treatment of chronic lymphocytic leukaemia (iLLUMINATE): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2019;20:43–56. doi:[10.1016/S1470-2045\(18\)30788-5](https://doi.org/10.1016/S1470-2045(18)30788-5).
- Shanafelt TD, Wang XV, Kay NE, et al. Ibrutinib-rituximab or chemoimmunotherapy for chronic lymphocytic leukemia. *N Engl J Med*. 2019;381:432–443. doi:[10.1056/NEJMoa1817073](https://doi.org/10.1056/NEJMoa1817073).
- Woyach JA, Ruppert AS, Heerema NA, et al. Ibrutinib regimens versus chemoimmunotherapy in older patients with untreated CLL. *N Engl J Med*. 2018;379:2517–2528. doi:[10.1056/NEJMoa1812836](https://doi.org/10.1056/NEJMoa1812836).
- Ibrutinib for relapsed/refractory chronic lymphocytic leukemia: a UK and Ireland analysis of outcomes in 315 patients. *Haematologica*. 2016;101:1563–1572. doi:[10.3324/haematol.2016.147900](https://doi.org/10.3324/haematol.2016.147900).
- Aarup K, Rotbain EC, Enggaard L, et al. Real-world outcomes for 205 patients with chronic lymphocytic leukemia treated with ibrutinib. *Eur J Haematol*. 2020. doi:[10.1111/ejh.13499](https://doi.org/10.1111/ejh.13499).
- Dimou M, Iliakis T, Pardalis V, et al. Safety and efficacy analysis of long-term follow up real-world data with ibrutinib monotherapy in 58 patients with CLL treated in a single-center in Greece. *Leuk Lymphoma*. 2019;60:2939–2945. doi:[10.1080/10428194.2019.1620944](https://doi.org/10.1080/10428194.2019.1620944).
- Hansson L, Askild A, Diels J, et al. Ibrutinib versus previous standard of care: an adjusted comparison in patients with relapsed/refractory chronic lymphocytic leukaemia. *Ann Hematol*. 2017;96:1681–1691. doi:[10.1007/s00277-017-3061-3](https://doi.org/10.1007/s00277-017-3061-3).
- Iskierka-Jazdzewska E, Hus M, Giannopoulos K, et al. Efficacy and toxicity of compassionate ibrutinib use in relapsed/refractory chronic lymphocytic leukemia in Poland: analysis of the Polish Adult Leukemia Group (PALG). *Leuk Lymphoma*. 2017;58:2485–2488. doi:[10.1080/10428194.2017.1292353](https://doi.org/10.1080/10428194.2017.1292353).
- Mato AR, Roeker LE, Allan JN, et al. Outcomes of front-line ibrutinib treated CLL patients excluded from landmark clinical trial. *Am J Hematol*. 2018;93:1394–1401. doi:[10.1002/ajh.25261](https://doi.org/10.1002/ajh.25261).
- 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.S20286](https://doi.org/10.2147/JBM.S20286).
- Pula B, Iskierka-Jazdzewska E, Dlugosz-Danecka M, et al. Long-term efficacy of ibrutinib in relapsed or refractory chronic lymphocytic leukemia: results of the polish adult leukemia study group observational study. *Anticancer Res*. 2020;40:4059–4066. doi:[10.21873/anticancer.14403](https://doi.org/10.21873/anticancer.14403).
- Salles G, Bachy E, Smolej L, et al. Single-agent ibrutinib in RESONATE-2 and RESONATE versus treatments in the real-world PHEDRA databases for patients with chronic lymphocytic leukemia. *Ann Hematol*. 2019;98:2749–2760. doi:[10.1007/s00277-019-03830-8](https://doi.org/10.1007/s00277-019-03830-8).
- Wingqvist M, Andersson PO, Askild A, et al. Long-term real-world results of ibrutinib therapy in patients with relapsed or refractory chronic lymphocytic leukemia: 30-month follow up of the Swedish compassionate use cohort. *Haematologica*. 2019;104:e208–ee10. doi:[10.3324/haematol.2018.198820](https://doi.org/10.3324/haematol.2018.198820).

30. Winqvist M, Askild A, Andersson PO, et al. Real-world results of ibrutinib in patients with relapsed or refractory chronic lymphocytic leukemia: data from 95 consecutive patients treated in a compassionate use program. A study from the Swedish Chronic Lymphocytic Leukemia Group. *Haematologica*. 2016;101:1573–1580. doi:10.3324/haematol.2016.144576.
31. Ysebaert L, Aurran-Schleinitz T, Dartigeas C, et al. Real-world results of ibrutinib in relapsed/refractory CLL in France: Early results on a large series of 428 patients. *Am J Hematol*. 2017;92:E166–E1E8. doi:10.1002/ajh.24773.
32. Islam P, Mato AR. Real-World Evidence for Chronic Lymphocytic Leukemia in the Era of Targeted Therapies. *Cancer J*. 2019;25:442–448. doi:10.1097/PPO.0000000000000407.
33. Mato AR, Barrientos JC, Ghosh N, et al. Prognostic Testing and Treatment Patterns in Chronic Lymphocytic Leukemia in the Era of Novel Targeted Therapies: Results From the informCLL Registry. *Clin Lymphoma Myeloma Leuk*. 2020;20:174–183 e3. doi:10.1016/j.clml.2019.10.009.
34. Bosch F, Navarro B, Crespo M, et al. Building a network of TP53 and IGHV testing reference centers across Spain: the Red53 initiative. *Ann Hematol*. 2021. doi:10.1007/s00277-020-04331-9.
35. O'Brien SM, Byrd JC, Hillmen P, et al. Outcomes with ibrutinib by line of therapy and post-ibrutinib discontinuation in patients with chronic lymphocytic leukemia: Phase 3 analysis. *Am J Hematol*. 2019;94:554–562. doi:10.1002/ajh.25436.
36. Kipps TJ, Fraser G, Coutre SE, et al. Long-Term Studies Assessing Outcomes of Ibrutinib Therapy in Patients With Del(11q) Chronic Lymphocytic Leukemia. *Clin Lymphoma Myeloma Leuk*. 2019;19:715–722 e6. doi:10.1016/j.clml.2019.07.004.
37. Burger JA, Robak T, Demirkan F, et al. *American Society of Hematology Annual Meeting*. Outcomes of first-line ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and high-risk genomic features with up to 6.5 years follow-up: integrated analysis of two phase 3 studies (RESONATE-2 and iLLUMINATE). Abstract #2220; 2020.
38. Huang Q, DKL, Harshaw Q, Bhagnani T, Leslie LA. Clinical outcomes among real-world patients with chronic lymphocytic leukemia (CLL) initiating first-line ibrutinib or chemoimmunotherapy (CIT) stratified by risk status: results from a US retrospective chart review study. *Blood*. 2020;136(Supplement 1):16–18.
39. Brown JR, Moslehi J, O'Brien S, et al. Characterization of atrial fibrillation adverse events reported in ibrutinib randomized controlled registration trials. *Haematologica*. 2017;102:1796–1805. doi:10.3324/haematol.2017.171041.
40. Williams AM, Baran AM, Meacham PJ, et al. Analysis of the risk of infection in patients with chronic lymphocytic leukemia in the era of novel therapies. *Leuk Lymphoma*. 2018;59:625–632. doi:10.1080/10428194.2017.1347931.
41. Barrientos JC, O'Brien S, Brown JR, et al. Improvement in parameters of hematologic and immunologic function and patient well-being in the phase III RESONATE study of ibrutinib versus ofatumumab in patients with previously treated chronic lymphocytic leukemia/small lymphocytic lymphoma. *Clin Lymphoma Myeloma Leuk*. 2018;18:803–813 e7. doi:10.1016/j.clml.2018.08.007.
42. Sun C, Tian X, Lee YS, et al. Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib. *Blood*. 2015;126:2213–2219. doi:10.1182/blood-2015-04-639203.
43. Cassin R, Visentin A, Giannarelli D, et al. Increase of immunoglobulin A during ibrutinib therapy reduces infection rate in chronic lymphocytic leukemia patients. *Hematol Oncol*. 2020. doi:10.1002/hon.2814.
44. Nunes C, Wong R, Mason M, Fegan C, Man S, Pepper C. Expansion of a CD8(+)PD-1(+) replicative senescence phenotype in early stage CLL patients is associated with inverted CD4:CD8 ratios and disease progression. *Clin Cancer Res*. 2012;18:678–687. doi:10.1158/1078-0432.CCR-11-2630.
45. Niemann CU, Herman SE, Maric I, et al. Disruption of in vivo Chronic Lymphocytic Leukemia Tumor-Microenvironment Interactions by Ibrutinib—Findings from an Investigator-Initiated Phase II Study. *Clin Cancer Res*. 2016;22:1572–1582. doi:10.1158/1078-0432.CCR-15-1965.
46. Rogers KA, Mousa L, Zhao Q, et al. Incidence of opportunistic infections during ibrutinib treatment for B-cell malignancies. *Leukemia*. 2019;33:2527–2530. doi:10.1038/s41375-019-0481-1.
47. O'Brien S, Hillmen P, Coutre S, et al. Safety analysis of four randomized controlled studies of ibrutinib in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma or mantle cell lymphoma. *Clin Lymphoma Myeloma Leuk*. 2018;18:648–657 e15. doi:10.1016/j.clml.2018.06.016.
48. Byrd JC, Furman RR, Coutre SE, et al. Ibrutinib treatment for first-line and relapsed/refractory chronic lymphocytic leukemia: final analysis of the pivotal phase Ib/II PCYC-1102 Study. *Clin Cancer Res*. 2020;26:3918–3927. doi:10.1158/1078-0432.CCR-19-2856.
49. Jones JA, Hillmen P, Coutre S, et al. Use of anticoagulants and antiplatelet in patients with chronic lymphocytic leukaemia treated with single-agent ibrutinib. *Br J Haematol*. 2017;178:286–291. doi:10.1111/bjh.14660.
50. López-Fernández T, CM, Farmakis D, García-Sanz R, et al. Ibrutinib-associated atrial fibrillation: a practical approach. *Ann Hematol Oncol*. 2018;5.
51. 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;103:874–879. doi:10.3324/haematol.2017.182907.