

First-Line Treatment of Chronic Lymphocytic Leukemia in Italy: Real-World Evidence on Utilization, Outcomes, and Healthcare Costs

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Background: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries, mainly affecting older people. Targeted agents have reshaped first-line (1L) strategies, making real-world evidence important to complement clinical trials.

Objective: To estimate the incidence of Italian patients initiating first-line CLL therapy (2019–2022) and describe demographics/clinical profile, treatment patterns, adherence, outcomes (overall survival [OS], time to next treatment [TTNT]), and healthcare costs from the perspective of the Italian National Health System (NHS).

Methods: A retrospective observational study using administrative healthcare databases (~9 million residents) was conducted on CLL patients starting 1L therapy (index-date) for CLL. Baseline characteristics were assessed in the 12 months pre-index; follow-up was ≥12 months. Drug use, adherence (medication possession ratio), dose adjustments, OS, TTNT, and direct costs were analyzed with descriptive and multivariable methods.

Results: A total of 1479 patients initiated 1L therapy: 63.9% chemotherapy (CHT), 23.2% ibrutinib, 3.2% acalabrutinib, and 9.7% other regimens. CHT remained common, especially among older and more comorbid patients. Ibrutinib showed lower mortality versus CHT (HR 0.663; $p=0.002$) and longer TTNT (median not reached). Dose adjustments were frequent; extended refill intervals did not appear to reduce drug survival. Mean annual cost per patient was €38,573, mainly driven by drug acquisition; ibrutinib users had lower hospitalization and outpatient costs than other 1L groups.

Conclusion: In Italian practice, ibrutinib was the main targeted 1L option and was associated with improved survival and delayed progression versus CHT. Despite higher drug costs, reduced hospital-based resource use suggests favourable overall clinical and economic impact.

Keywords: chronic lymphocytic leukemia, first-line treatment, healthcare costs, ibrutinib, real-world evidence, targeted therapy

Introduction

Chronic lymphocytic leukemia (CLL) is the most common adult leukemia in Western countries, characterized by the clonal proliferation and accumulation of mature B lymphocytes.^{1,2} CLL incidence increases markedly with age, making it a major health burden in the ageing populations.³ The global age-adjusted estimates during the period 2017–2021 reported 4.5 new cases per 100,000 people per year, and a mortality rate of 0.8 per 100,000 people per year.⁴

Epidemiological data in Italy estimated a yearly incidence at 5.0–5.5 cases per 100,000 men and 3.5–4.0 cases per 100,000 women. The prevalence data are vague, as some sources reported 20,000–22,000 cases, and others about approximately 12,000 cases.^{5,6}

Although the exact etiology of CLL is still poorly understood, genetic factors, rather than environmental factors, seem to be the most likely implicated.⁷ The type of genetic alterations behind the pathogenesis of CLL are acquiring increasing interest for their influence on disease clinical management and the development of new therapeutic strategies.⁸

In patients with active disease, systemic therapy is primarily intended to achieve symptomatic relief, induce sustained remission, and extend overall survival (OS). The selection of the initial regimen in patients with symptomatic/advanced CLL is driven by tumor characteristics, therapeutic goals, together with age and patient's preference.^{9–11} Historically, treatment options for CLL have revolved around chemoimmunotherapy-based schedules which, although effective in some patients, are often limited by toxicity and suboptimal long-term disease control, particularly in elderly or comorbid populations.¹²

However, the treatment landscape of CLL has undergone significant evolution in recent years, marked by the regulatory approval of several targeted agents as first-line (1L) therapies. These advances reflect the shift from traditional chemoimmunotherapy to more effective and better-tolerated oral therapies that exploit specific molecular vulnerabilities of the disease.

In line with these global developments, Italy has progressively integrated targeted therapies for CLL into clinical practice through formal regulatory approvals by the Italian Medicines Agency (AIFA). Ibrutinib, the first Bruton's tyrosine kinase inhibitor (BTKi) to become available in Italy, was initially approved for use as second-line (2L) therapy in adult patients with CLL, marking a major milestone in the transition away from chemoimmunotherapy. In October 2019, ibrutinib was officially approved for use as a 1L monotherapy in continuative therapy for adult patients with CLL, marking the introduction of BTKis in the front-line setting.¹³

Subsequently, the combination of venetoclax, a selective BCL-2 inhibitor, with the anti-CD20 monoclonal antibody obinutuzumab received AIFA approval in May 2022 for the 1L treatment of patients with previously untreated CLL who are ineligible for intensive chemoimmunotherapy.¹⁴ In October 2022, zanubrutinib, a next-generation BTKi with improved selectivity and pharmacokinetics, gained 1L approval for patients with CLL unsuitable for chemoimmunotherapy.¹⁵ More recently, in July 2023, acalabrutinib, another second-generation BTKi, was approved for adult patients with CLL harbouring del(17p) or TP53 mutations, further refining the molecularly guided treatment approach in Italy.¹⁶ These successive regulatory decisions have considerably expanded the range of targeted, chemotherapy-free options for Italian clinicians in the management of CLL aligning national treatment strategies with the international treatment standard.

From a clinical and management perspective, continuous BTK inhibitor therapy and fixed-duration venetoclax-based regimens represent two distinct treatment strategies: BTK inhibitors are generally administered until disease progression or unacceptable toxicity, requiring long-term adherence and sustained drug exposure, whereas venetoclax–obinutuzumab is delivered as a time-limited regimen, potentially allowing treatment-free intervals and different patterns of monitoring, persistence, and healthcare costs.^{17–19}

While randomized controlled trials have established the clinical efficacy of these novel agents,^{20,21} there is a growing recognition of the need for real-world evidence (RWE) to understand how these therapies perform in routine clinical practice. This is particularly relevant in the Italian context, where heterogeneity in clinical settings, patient profiles, and access to care may influence therapeutic choices and outcomes.²²

Administrative healthcare databases offer a unique opportunity to assess real-world treatment dynamics and healthcare resource utilization across large, unselected populations. Such data are essential to support informed decision-making by clinicians, regulators, and healthcare stakeholders, especially in an era of rapidly expanding and increasingly personalized therapeutic options for CLL.

The primary objective of this retrospective observational study was to estimate the number of CLL patients who initiated a 1L treatment and to describe their demographic and clinical characteristics, comorbidities and therapeutic pathways in Italian clinical practice. Exploratory objectives included evaluating drug utilization (adherence, time to next

treatment, and dose flexibility), OS, healthcare direct medical costs covered by the Italian National Health System (NHS).

Methods

Study Design and Data Source

An observational retrospective analysis was conducted on data extracted from the administrative flows of Italian healthcare entities, covering 9,325,296 health-assisted inhabitants and with data available from January 2010 to December 2023. For the purposes of the analysis, the following databases were used: beneficiaries' database, for demographic information such as age, sex, and date of death (if applicable); pharmaceutical database for prescription details, including Anatomical Therapeutic Chemical (ATC) code, prescription date, and number of dispensed packages; hospitalization database for admission data, including admission date, primary and secondary diagnoses coded through International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) and Diagnosis Related Group (DRG); outpatient specialist services database for records on laboratory tests, diagnostic procedures, and specialist consultations, including the type and date of each service.

The study was conducted in compliance with the principles of the Declaration of Helsinki and successive updates. In line with Article 110 (Processing of personal data for medical, biomedical or epidemiological research purposes) of the Italian Privacy Code, informed consent was waived, as obtaining it was deemed impossible or required a disproportionate effort. The dataset used consists solely of anonymized data. All the results of the analyses were produced and presented as aggregated summaries. Approval has been obtained from the ethics committees of the participating healthcare entities [authorization of the Ethics Committee “Berica Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza” (protocol number 1627, approval date 28/10/2020); authorization of the Ethics Committee “Foggia Comitato etico interprovinciale Area I” (protocol number 63/CE/20, approval date 3/12/2020); authorization of the Ethics Committee “Frosinone Comitato Etico Lazio 2” (protocol number 0179046/2020, approval date 28/10/2020); authorization of the Ethics Committee “Pedemontana Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza” (protocol number 0036999, approval date 28/04/2021); authorization of the Ethics Committee “Roma 4 Comitato Etico Lazio 1” (protocol number 1079/CE Lazio 1, approval date 23/09/2020); authorization of the Ethics Committee “Roma 5 Comitato Etico Lazio 1” (protocol number 1166/CE Lazio 1, approval date 12/10/2020); authorization of the Ethics Committee “Roma 6 Comitato Etico Lazio 2” (protocol number 0216084/2020, approval date 16/12/2020); authorization of the Ethics Committee “Serenissima Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S. Camillo” (28/07/2020); authorization of the Ethics Committee “Umbria 2 Comitato Etico Regionale Umbria” (protocol number 19414/20/ON, approval date 16/09/2020)].

Study Population and Timeline

From January 2019 to December 2022, adult patients were identified using the following criteria: (i) hospitalization with a main or secondary diagnosis of CLL (ICD-9-CM: 204.1); OR prescription of acalabrutinib (ATC: L01EL02); OR (ii) prescription of obinutuzumab (ATC: L01FA03) AND NOT diagnosis of follicular lymphoma (ICD-9-CM: 202.0); OR (iii) prescription of venetoclax (ATC: L01XX52) AND NOT diagnosis of acute myeloid leukemia (ICD-9-CM: 205.0); OR (iv) prescription of obinutuzumab (ATC: L01FA03) AND prescription of venetoclax (ATC: L01XX52); OR (v) prescription of ibrutinib (ATC: L01EL01) AND NOT diagnosis of Waldenström macroglobulinemia (ICD-9-CM: 273.3) OR dosage ≤ 420 mg; OR (vi) prescription of zanubrutinib (ATC: L01EL03) AND NOT diagnosis of Waldenström macroglobulinemia (ICD-9-CM: 273.3) OR follicular lymphoma (ICD-9-CM: 202.0) OR marginal zone lymphoma (ICD-9-CM: 200.3).

The analysis included patients with CLL who started a 1L treatment from 2019. The index-date was defined as the initiation date of the first treatment for CLL patients, or the start date of the second treatment for those with relapsed or refractory (RR) CLL. The characterization period encompassed all available data preceding the index-date, with a minimum required duration of 36 months, ensuring that each patient had at least three years of medical history prior

to treatment initiation. The follow-up period included all available data after the index-date, with a minimum duration of 12 months, thereby guaranteeing at least one year of observation following the start of therapy.

Drug Utilization and Definition of Treatment Lines

Treatment lines were defined chronologically, beginning in 2019. Patients were classified as 1L if no prior treatments were recorded in the 3–5 years preceding the index-date. Patients progressing to a subsequent therapy after initial treatment were classified as having entered a second or further line of treatment, including those with RR CLL. Combination therapies were defined as different agents initiated within a 60-day window. For those receiving chemotherapy (CHT), the beginning of a new treatment line was identified if a subsequent therapy was administered at least 180 days after the previous CHT administration.

The 1L treatments for CLL included ibrutinib, acalabrutinib, zanubrutinib, venetoclax, obinutuzumab, and rituximab, either as monotherapies or in combination regimens. Among the fixed-duration therapies, the combination of venetoclax with obinutuzumab was also considered a 1L option. In addition to targeted therapies, some patients received aspecific CHT, identified by the ATC code L01 excluding targeted agents, or DRG 410, or procedures 86.07, 99.25, 99.28, 99.29.

For 2L treatments, the same targeted agents were also utilized, either as monotherapy or in combination. These included ibrutinib, venetoclax, obinutuzumab, rituximab, acalabrutinib, and zanubrutinib. Combinations such as venetoclax with obinutuzumab and venetoclax with ibrutinib were included as well. As in 1L, patients could also receive aspecific CHT in 2L setting.

Baseline Characteristics

Demographic variables such as age and sex were recorded at index-date. Clinical characteristics were assessed during the 12 months preceding the index-date, including the Charlson Comorbidity Index (CCI),²³ cardiovascular disease, atrial fibrillation, heart failure, hypertension, diabetes, hypercholesterolemia, and the presence of other cancers (excluding CLL). These comorbidities were identified through hospitalization records, drug prescriptions, and exemption codes.

Outcome Variables

The primary endpoint was to estimate the incidence rate of CLL patients initiating 1L treatment and to describe their therapeutic pathways. Exploratory objectives included analyses of OS, time to next treatment (TTNT), adherence, dose adjustments, and healthcare direct costs.

OS was measured from the index-date to death from any cause. Patients were censored at the date of death or the end of data availability.

TTNT was defined as the duration in months from the index-date to the initiation of a subsequent line of therapy. Patients who did not progress to a 2L of treatment were censored at the date of death or the end of data availability.

The adherence to 1L treatment was measured during the first year of follow-up using the medication possession ratio (MPR), calculated as the ratio of days with medication supply to the total observation period. Based on established thresholds in the literature,²⁴ adherence was categorized as non-adherence (MPR <40%), partial adherence (MPR 40–79%), and adherence (MPR ≥80%). Although the ≥80% cut-off is commonly used to define good adherence, other studies have suggested alternative thresholds depending on disease context, including a 66% cut-off identified as optimal in certain patient populations.²⁵ In this analysis, adherence was evaluated using both the conventional ≥80% threshold and the alternative 66% threshold.

Dose flexibility was assessed by analyzing changes from the index dose of ibrutinib over the first year of treatment. Patients who did not discontinue ibrutinib within the first nine months were further evaluated to determine the frequency and extent of dose adjustment/reductions and any subsequent dose re-escalations. Dose reduction was defined as decreases from 420 mg to 280 mg to 140 mg due to clinical reasons or safety purposes. Dose adjustment refers to minor variations for non-clinical reasons (eg, forgetting to self-administer, delayed package retrieval, etc).

Healthcare Direct Costs

The analysis evaluated healthcare costs in patients with CLL initiating 1L treatment. Direct costs were estimated by calculating the average annual expenditure per patient. Specifically, total healthcare costs were categorized to include expenses related to pharmacological therapies, hospitalizations, and outpatient specialist services.

The cost analysis was conducted from the perspective of the Italian NHS, with all costs reported in euros (€). Drug costs were assessed based on NHS purchase prices. Hospitalization costs were determined using DRG tariffs, which reflect the reimbursement rates from the NHS to healthcare facilities. Costs associated with diagnostic procedures and laboratory tests were estimated according to the regional tariffs.

Statistical Analysis

Continuous variables are given as mean with standard deviation (SD), and categorical variables are reported as numbers and percentages. Comparative analyses between treatment groups were performed to assess differences in baseline characteristics. Two-way analysis of variance (ANOVA) test was used to compare continuous variables across multiple treatment groups. For categorical variables, chi-square test was applied to determine statistically significant differences between groups.

TTNT and OS were analyzed using the Kaplan-Meier method, and survival distributions were compared using the Log rank test. Multivariate analysis was conducted using the Cox proportional hazards model with results expressed as hazard ratios (HRs) and corresponding 95% confidence intervals (95% CIs). The relationship between dosing patterns and clinical outcomes, including treatment discontinuation and mortality, was examined using logistic and Cox regression models.

Cost outliers, defined as values exceeding three SDs from the mean, were excluded. A generalized linear model (GLM) with gamma distribution was applied to evaluate cost differences across treatment groups, adjusting for baseline demographic and clinical characteristics.

According to Opinion 05/2014 on Anonymisation Techniques drafted by the European Commission Article 29 Working Party, analyses involving fewer than 3 patients were not reported, as they could potentially allow re-identification of single individuals. Therefore, results referring directly or indirectly to ≤ 3 patients were reported as NI (not issuable).

A p value <0.05 was considered as statistically significant and all the analyses were performed using STATA SE version 17.0.

Results

Epidemiology Estimates

Figure 1 describes the annual incidence rates of CLL patients starting a 1L treatment from January 2019 to December 2023, expressed per 100,000 people-years and stratified by sex, age classes, and type of 1L therapy. Overall, the estimated annual incidence rate of overall CLL patients starting a 1L treatment was 4.98 per 100,000 person-years, with higher rates in men than in women (6.24/100,000 and 3.78/100,000, respectively). The incidence rate increased markedly with age, peaking at 18.9 per 100,000 person-years in individuals aged 71–80 years. Although multiple therapeutic options are now available in 1L, a significant proportion of patients still received aspecific CHT, which remains a less effective alternative to targeted therapies.

Patient Baseline Characteristics, Comorbidities and Distribution of 1L Treatments

As shown in **Table 1**, among 1,479 patients receiving 1L treatment for CLL, 945 (63.9%) were treated with CHT, 343 (23.2%) received ibrutinib, 144 (9.7%) received other therapies (including various low-count combinations), and 47 (3.2%) received acalabrutinib.

Significant differences were observed across several baseline characteristics. Patients treated with aspecific CHT were significantly older, with a mean age of 73.5 years, compared to the other treatment groups ($p<0.001$). The CCI was higher

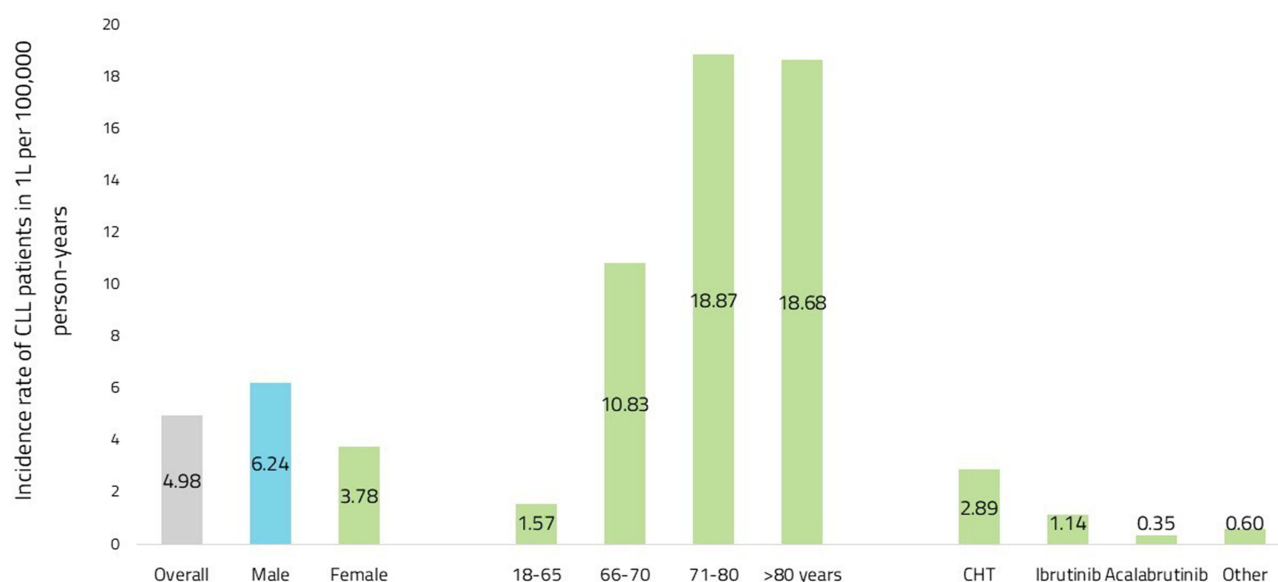


Figure 1 Incidence rates of CLL patients starting a 1L treatment per 100,000 people-years stratified by sex, age classes, and type of 1L therapy.

among patients receiving aspecific CHT or acalabrutinib with respect to those treated with ibrutinib or other therapies ($p=0.024$).

Atrial fibrillation, heart failure, and hypertension were found more frequently among CHT than in the ibrutinib patients. No differences were observed between the different treatment cohorts regarding sex distribution, cardiovascular disease, atrial fibrillation, heart failure, or hypercholesterolemia.

Table 1 Characteristic of Incident CLL Patients in 1L of Treatment, Overall and by Type of 1L Therapy

N	CLL Patients in 1L	Type of 1L Therapy				p*
		Aspecific CHT	Ibrutinib	Other	Acalabrutinib	
	1479	945	343	144	47	
Male, N (%)	905 (61.2%)	581 (61.5%)	202 (58.9%)	90 (62.5%)	32 (68.1%)	0.606
Age, years, mean (SD)	72.5 (11.7)	73.5 (12.1)	72.0 (10.4)	68.8 (11.6)	68.5 (11.5)	<0.001
18-65 years, N (%)	359 (24.3%)	221 (23.4%)	72 (21.0%)	48 (33.3%)	18 (38.3%)	<0.001
66-70 years, N (%)	174 (11.8%)	96 (10.2%)	52 (15.2%)	20 (13.9%)	6 (12.8%)	
71-80 years, N (%)	553 (37.4%)	328 (34.7%)	149 (43.4%)	60 (41.7%)	16 (34.0%)	
>80 years, N (%)	393 (26.6%)	300 (31.7%)	70 (20.4%)	16 (11.1%)	7 (14.9%)	
CCI, mean (SD)	0.9 (1.3)	1.0 (1.4)	0.7 (1.1)	0.7 (1.2)	0.9 (1.1)	0.024
0, N (%)	778 (52.6%)	471 (49.8%)	199 (58.0%)	83 (57.6%)	25 (53.2%)	0.070
1-2, N (%)	566 (38.3%)	380 (40.2%)	121 (35.3%)	50 (34.7%)	15 (31.9%)	
≥3, N (%)	135 (9.1%)	94 (9.9%)	23 (6.7%)	11 (7.6%)	7 (14.9%)	
Cardiovascular disease, N (%)	216 (14.6%)	152 (16.1%)	42 (12.2%)	15 (10.4%)	7 (14.9%)	0.156
Atrial fibrillation, N (%)	88 (5.9%)	76 (8.0%)	7 (2.0%)	NI	NI	<0.001
Heart failure, N (%)	82 (5.5%)	69 (7.3%)	11 (3.2%)	NI	NI	0.001
Hypertension, N (%)	1010 (68.3%)	666 (70.5%)	233 (67.9%)	79 (54.9%)	32 (68.1%)	0.003
Diabetes, N (%)	334 (22.6%)	228 (24.1%)	71 (20.7%)	22 (15.3%)	13 (27.7%)	0.070
Hypercholesterolemia, N (%)	443 (30.0%)	294 (31.1%)	97 (28.3%)	39 (27.1%)	13 (27.7%)	0.627
Other cancer (from hosp.), N (%)	387 (26.2%)	251 (26.6%)	88 (25.7%)	37 (25.7%)	11 (23.4%)	0.955
Cancer (from exempt.), N (%)	675 (45.6%)	379 (40.1%)	170 (49.6%)	96 (66.7%)	30 (63.8%)	<0.001

Note: *Significant differences across treatment groups are highlighted in bold.

Abbreviations: CCI, Charlson Comorbidity Index; CHT, chemotherapy; CLL, chronic lymphocytic leukemia; NI, not issuable; SD, standard deviation; 1L, first-line.

The same variables were then analysed by calendar year during the period 2019–2022 (Table 2). In 2019, among 325 patients who initiated 1L treatment for CLL, 291 (89.5%) received aspecific CHT, and 31 (9.5%) received ibrutinib. In 2020, out of 383 patients, 290 (75.7%) received aspecific CHT, 64 (16.7%) were treated with ibrutinib, and 29 (7.6%) received other therapies. In 2021, of the 396 patients starting treatment, 211 (53.3%) received aspecific CHT, 140 (35.4%) received ibrutinib, and 45 (11.4%) other therapies. In 2022, among 375 patients, 153 (40.8%) were treated with aspecific CHT, 108 (28.8%) received ibrutinib, 67 (17.9%) received other therapies, and 47 (12.5%) received acalabrutinib.

Among ibrutinib-treated CLL patients, the proportion of those with a history of cardiovascular disease was 12.9% in 2019, 20.3% in 2020, 10.0% in 2021, and 10.2% in 2022.

Patterns of Treatment

Regarding treatment choices in 1L and 2L (Table 3), among the 1479 incident CLL patients who started 1L treatment, the most frequently used regimen was CHT, administered to 945 patients (63.9%), followed by ibrutinib in 343 patients (23.2%). Other therapies included acalabrutinib (3.2%) and various regimens grouped as other (9.7%). Of 390 patients who proceeded to additional therapy, the most frequently 2L option was ibrutinib (56.7%).

Concerning treatment sequences (Table 3), of CLL patients previously treated with CHT, 33.5% (317/945) moved to 2L treatment, most commonly ibrutinib (69.7%). Among patients initially treated with ibrutinib, 16.0% (55/343) required a 2L treatment, with CHT being the most frequent subsequent option (74.5%). Patients treated initially with acalabrutinib, or other therapies transitioned to 2L treatment less frequently, with 10.6% and 9.0%, respectively. Mean time to next treatment varied across groups, ranging from 2.7 months for the other groups to 14.4 months for those initially treated with ibrutinib.

Overall Survival and Time to Next Treatment

As depicted in Figure 2A, 34.8% of CLL patients who started a 1L treatment died during the follow-up (2.8 years as mean time of follow-up). Median survival time was 59.5 months. Ibrutinib was associated with a lower risk of death, with a nearly halved mortality with respect to patients who received aspecific CHT as 1L therapy (Figure 2B). Acalabrutinib cohort was excluded from the analysis because of the low number of patients (N=47). The Cox regression model confirmed that 1L ibrutinib therapy resulted in a mortality risk reduced by 34% (HR 0.663; 95% CI: 0.5–0.9, $p=0.002$). Conversely, age >71 years ($p<0.001$), CCI between 1 and 2 ($p=0.001$), and cardiovascular disease ($p=0.001$) were significant predictors of increased mortality risk (Table 4).

As Figure 3A shows, half of patients did not switch treatment after 46 months, and the median TTNT across all groups was 46.1 months. Among those receiving ibrutinib, the median TTNT was not reached during the available follow-up, highlighting its capacity to delay progression or treatment failure (Figure 3B). In the Cox proportional hazards model (Table 5), ibrutinib significantly reduced the likelihood of initiating a subsequent line of therapy compared to aspecific CHT and other targeted combinations, with a HR of 0.268 (95% CI: 0.2–0.4, $p<0.001$).

Adherence

The analysis of real-world adherence focused on patients treated with ibrutinib and acalabrutinib, measuring the MPR over the first 12 months. Using the “conventional” cutoff of $\text{MPR} \geq 80\%$, adherence was achieved in 57% of patients on ibrutinib and 54% of those on acalabrutinib, whereas non-adherence was found in 17% and 33%, respectively (Figure 4A).

Using the alternative cutoff of $\text{MPR} \geq 66\%$ to define adherence, 66.3% patients with ibrutinib resulted to be adherent, compared to 58.1% of acalabrutinib. Besides, patients with low adherence were 34% and 42%, respectively (Figure 4B).

Dose Adjustment

Of the 300 patients who started ibrutinib at the full dose (420 mg/day), 59% experienced a dose adjustment within 12 months of treatment (Figure 5A). Overall, the mean daily dose was 385.4 mg, corresponding to an average -8.5% reduction versus the full dose. In the subgroup of patients who remained on ibrutinib for at least 9 months (N=212),

Table 2 Characteristic of Incident CLL Patients in IL of Treatment, Overall and by Type of IL Therapy at Each Calendar year (2019–2022)

N	2019			2020			
	CLL Patients in IL	Aspecific CHT	Ibrutinib	CLL Patients in IL	Aspecific CHT	Ibrutinib	Other
	325	291	31	383	290	64	29
Male, N (%)	195 (60.0%)	173 (59.5%)	19 (61.3%)	244 (63.7%)	184 (63.4%)	41 (64.1%)	19 (65.5%)
Age, mean (SD)	72.7 (11.9)	73.0 (12.1)	70.1 (9.7)	73.6 (11.3)	73.8 (11.7)	72.6 (9.8)	73.3 (9.8)
18-65, N (%)	79 (24.3%)	70 (24.1%)	9 (29.0%)	77 (20.1%)	58 (20.0%)	13 (20.3%)	6 (20.7%)
66-70, N (%)	36 (11.1%)	29 (10.0%)	6 (19.4%)	39 (10.2%)	31 (10.7%)	4 (6.3%)	4 (13.8%)
71-80, N (%)	121 (37.2%)	107 (36.8%)	13 (41.9%)	160 (41.8%)	114 (39.3%)	33 (51.6%)	13 (44.8%)
>80, N (%)	89 (27.4%)	85 (29.2%)	3 (9.7%)	107 (27.9%)	87 (30.0%)	14 (21.9%)	6 (20.7%)
CCI, mean (SD)	1.0 (1.2)	1.0 (1.3)	0.5 (0.6)	0.9 (1.3)	0.9 (1.4)	0.7 (0.9)	0.9 (1.1)
0, N (%)	148 (45.5%)	131 (45.0%)	17 (54.8%)	195 (50.9%)	149 (51.4%)	33 (51.6%)	13 (44.8%)
1-2, N (%)	147 (45.2%)	131 (45.0%)	14 (45.2%)	154 (40.2%)	115 (39.7%)	27 (42.2%)	12 (41.4%)
≥3, N (%)	30 (9.2%)	29 (10.0%)	0 (0.0%)	34 (8.9%)	26 (9.0%)	4 (6.3%)	4 (13.8%)
Cardiovascular disease, N (%)	50 (15.4%)	45 (15.5%)	4 (12.9%)	58 (15.1%)	41 (14.1%)	13 (20.3%)	4 (13.8%)
Atrial fibrillation, N (%)	24 (7.4%)	24 (8.2%)	0 (0.0%)	22 (5.7%)	20 (6.9%)	NI	0 (0.0%)
Heart failure, N (%)	23 (7.1%)	22 (7.6%)	NI	18 (4.7%)	17 (5.9%)	NI	0 (0.0%)
Hypertension, N (%)	244 (75.1%)	216 (74.2%)	25 (80.6%)	269 (70.2%)	205 (70.7%)	45 (70.3%)	19 (65.5%)
Diabetes, N (%)	64 (19.7%)	59 (20.3%)	4 (12.9%)	116 (30.3%)	92 (31.7%)	19 (29.7%)	5 (17.2%)
Hypercholesterolemia, N (%)	84 (25.8%)	74 (25.4%)	8 (25.8%)	118 (30.8%)	94 (32.4%)	16 (25.0%)	8 (27.6%)
Cancer (from hosp.), N (%)	89 (27.4%)	82 (28.2%)	6 (19.4%)	96 (25.1%)	70 (24.1%)	18 (28.1%)	8 (27.6%)
Cancer (from exmp.), N (%)	106 (32.6%)	94 (32.3%)	10 (32.3%)	155 (40.5%)	115 (39.7%)	26 (40.6%)	14 (48.3%)

N	2021				2022				
	CLL patients in IL	Aspecific CHT	Ibrutinib	Other	CLL patients in IL	Aspecific CHT	Ibrutinib	Other	Acalabrutinib
	396	211	140	45	375	153	108	67	47
Male, N (%)	234 (59.1%)	129 (61.1%)	80 (57.1%)	25 (55.6%)	232 (61.9%)	95 (62.1%)	62 (57.4%)	43 (64.2%)	32 (68.1%)
Age, mean (SD)	72.4 (12.0)	72.7 (13.1)	73.8 (9.0)	66.8 (13.1)	71.4 (11.8)	75.0 (11.2)	69.8 (12.1)	67.9 (10.9)	68.5 (11.5)
18-65, N (%)	94 (23.7%)	61 (28.9%)	17 (12.1%)	16 (35.6%)	109 (29.1%)	32 (20.9%)	33 (30.6%)	26 (38.8%)	18 (38.3%)
66-70, N (%)	52 (13.1%)	20 (9.5%)	24 (17.1%)	8 (17.8%)	47 (12.5%)	16 (10.5%)	18 (16.7%)	7 (10.4%)	6 (12.8%)
71-80, N (%)	138 (34.8%)	56 (26.5%)	66 (47.1%)	16 (35.6%)	134 (35.7%)	51 (33.3%)	37 (34.3%)	30 (44.8%)	16 (34.0%)
>80, N (%)	112 (28.3%)	74 (35.1%)	33 (23.6%)	5 (11.1%)	85 (22.7%)	54 (35.3%)	20 (18.5%)	4 (6.0%)	7 (14.9%)
CCI, mean (SD)	0.7 (1.2)	0.8 (1.3)	0.7 (1.2)	0.4 (0.7)	0.9 (1.4)	1.2 (1.6)	0.8 (1.1)	0.8 (1.4)	0.9 (1.1)
0, N (%)	242 (61.1%)	120 (56.9%)	90 (64.3%)	32 (71.1%)	193 (51.5%)	71 (46.4%)	59 (54.6%)	38 (56.7%)	25 (53.2%)
1-2, N (%)	126 (31.8%)	74 (35.1%)	39 (27.9%)	13 (28.9%)	139 (37.1%)	60 (39.2%)	41 (38.0%)	23 (34.3%)	15 (31.9%)
≥3, N (%)	28 (7.1%)	17 (8.1%)	11 (7.9%)	0 (0.0%)	43 (11.5%)	22 (14.4%)	8 (7.4%)	6 (9.0%)	7 (14.9%)
Cardiovascular disease, N (%)	48 (12.1%)	34 (16.1%)	14 (10.0%)	0 (0.0%)	60 (16.0%)	32 (20.9%)	11 (10.2%)	10 (14.9%)	7 (14.9%)
Atrial fibrillation, N (%)	20 (5.1%)	16 (7.6%)	NI	NI	22 (5.9%)	16 (10.5%)	NI	NI	NI
Heart failure, N (%)	24 (6.1%)	15 (7.1%)	9 (6.4%)	0 (0.0%)	17 (4.5%)	15 (9.8%)	0 (0.0%)	NI	NI
Hypertension, N (%)	259 (65.4%)	137 (64.9%)	99 (70.7%)	23 (51.1%)	238 (63.5%)	108 (70.6%)	64 (59.3%)	34 (50.7%)	32 (68.1%)
Diabetes, N (%)	65 (16.4%)	37 (17.5%)	27 (19.3%)	NI	89 (23.7%)	40 (26.1%)	21 (19.4%)	15 (22.4%)	13 (27.7%)
Hypercholesterolemia, N (%)	115 (29.0%)	60 (28.4%)	44 (31.4%)	11 (24.4%)	126 (33.6%)	66 (43.1%)	29 (26.9%)	18 (26.9%)	13 (27.7%)
Cancer (from hosp.), N (%)	103 (26.0%)	53 (25.1%)	38 (27.1%)	12 (26.7%)	99 (26.4%)	46 (30.1%)	26 (24.1%)	16 (23.9%)	11 (23.4%)
Cancer (from exemp.), N (%)	206 (52.0%)	91 (43.1%)	80 (57.1%)	35 (77.8%)	208 (55.5%)	79 (51.6%)	54 (50.0%)	45 (67.2%)	30 (63.8%)

Abbreviations: CCI, Charlson Comorbidity Index; CHT, chemotherapy; CLL, chronic lymphocytic leukemia; NI, not issuable; SD, standard deviation; IL, first-line.

Table 3 Patterns of Treatment of Incident CLL Patients in 1L Treatment: (A) Treatment Lines in CLL Patients in 1L; (B) Details of Treatment Sequences

A. Treatment lines			
1L (N=1,479)		2L (N=390)	
Treatments	N (%)	Treatments	N (%)
CHT	945 (63.9%)	Ibrutinib	221 (56.7%)
Ibrutinib	343 (23.2%)	Venetoclax	68 (17.4%)
Other	144 (9.7%)	CHT	44 (11.3%)
Acalabrutinib	47 (3.2%)	Acalabrutinib	32 (8.2%)
		Other	25 (6.4%)
B. Treatment sequences			
Treatments (N=1479)	Patients who switched to 2L^o line and TTNT	Treatments in 2L (N=390)	
CHT (N=945)	• N patients with a 2L= 317 (33.5%) • Mean (SD) time to 2L treatment in months = 14.1 (10.9)	Ibrutinib, N=221 (69.7%) Venetoclax, N=59 (18.6%) Acalabrutinib, N=30 (9.5%) Other, N=7 (2.2%)	
Ibrutinib (N=343)	• N patients with a 2L= 55 (16.0%) • Mean (SD) time to 2L treatment in months = 14.4 (10.5)	CHT, N=41 (74.5%) Other, N=9 (16.4%) Venetoclax, N=4 (7.3%) Acalabrutinib, N=NI	
Other (N=144)	• N patients with a 2L= 13 (9.0%) • Mean (SD) time to 2L treatment in months = 2.7 (4.4)	Other, N=9 (69.2%) Venetoclax, N=NI Acalabrutinib, N=NI	
Acalabrutinib (N=47)	• N patients with a 2L= 5 (10.6%) • Mean (SD) time to 2L treatment in months = 10.9 (6.4)	CHT, N=NI Venetoclax, N=NI	

Abbreviations: CHT, chemotherapy; CLL, chronic lymphocytic leukemia; NI, not issuable; 1L, first-line; 2L, second-line.

49.1% (N=104) had a dose adjustment within the first 4.5 months, with a mean daily dose of 336.8 mg (−20% vs full dose). Among these, almost all (>95%) maintained the adjusted dose without any subsequent increase during the following 4.5 months, while <4 patients had a dose re-escalation (Figure 5B).

In patients who initiated ibrutinib as 1L at a starting dose of 420 mg/day and remained on treatment for at least nine months (N=212), 62.7% had a dose adjustment within nine months of follow-up (Figure 6A). The mean daily dose was 381.5 mg (−9.2% vs full dose). In the subgroup with a dose adjustment during the first 4.5 months (N=104; 49.1%), the mean daily dose was 344.6 mg (−18.2% vs full dose). Almost all of these patients (>95%) maintained the reduced dose without subsequent increase over the following 4.5 months, while <4 patients had a re-escalation (Figure 6B). Additionally, 50.9% of patients had at least three treatment cycles with a refill delay of more than seven days beyond the expected refill date within the 9-month follow-up period.

The analysis of refill intervals was used to identify and distinguish between patients whose lower average daily dose reflected a reduction in their dosage (from 420 mg to 280 mg to 140 mg) due to clinically motivated adjustment (ie, a conscious dose downtitration for safety reasons or safety purposes) and those who adjusted their dosage for whose reduced exposure was due to non-clinical reasons (eg, forgetting to self-administer, delayed prescription refill, or late package retrieval, etc).

Furthermore, the collection of extended refill intervals could be used as a proxy to better understand the clinical versus non-clinical drivers of treatment modifications or also dose adjustment among patients who remained on treatment for at least nine months. To assess whether these prolonged intervals compromised treatment persistence or mortality, drug survival was evaluated using Kaplan-Meier curves and Cox proportional hazards models. Specifically, refill

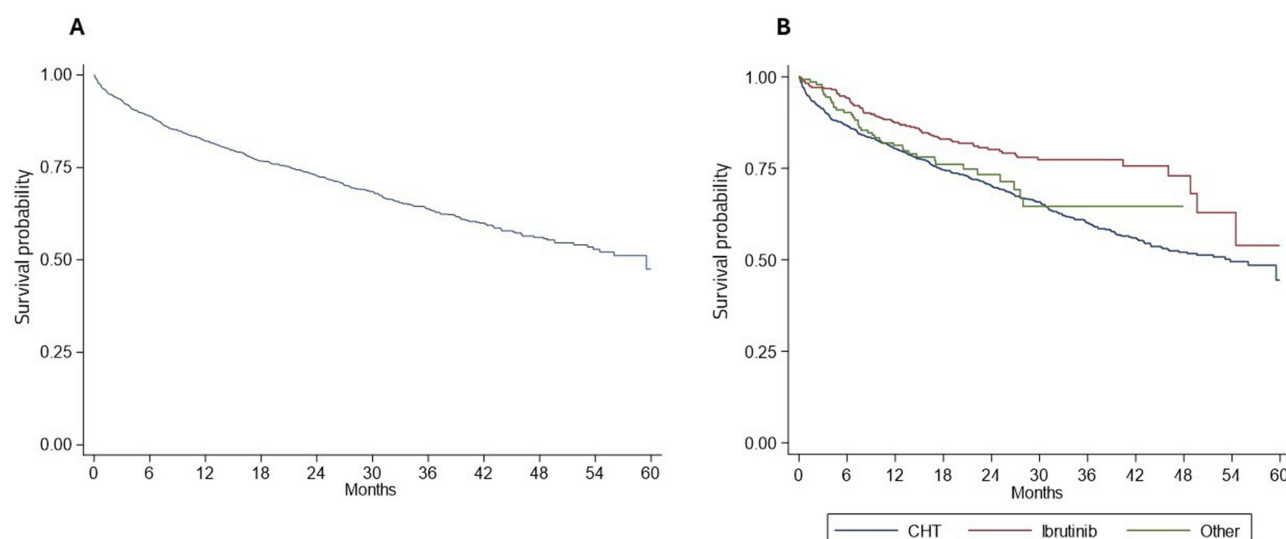


Figure 2 Overall survival among incident CLL patients in 1L treatment, (A) overall, and (B) stratified by treatment.

intervals of at least 37, 40, and 45 days were tested, requiring a minimum of either three prescriptions or, in the final sensitivity analysis, two prescriptions.

In the first Kaplan-Meier analysis, which began nine months after the index date, drug survival in patients with at least three prescriptions spaced 37 days or more apart showed no significant increase in the risk of treatment discontinuation or death (Figure 7A). The Cox regression model yielded a p-value of 0.942, indicating that patients on extended dosing schedules maintained comparable survival probabilities to those on standard regimens (Table S1).

A second analysis tested the impact of extending the refill interval to 40 days. Again, patients with at least three prescriptions with gaps of 40 days or more were included. The survival curve remained consistent (Figure 7B), and the

Table 4 Cox Regression Model for Mortality Predictors

	HR	95% CI	p*
Treatment (Ref.: CHT)			
Ibrutinib	0.663	[0.5; 0.9]	0.002
Other	1.165	[0.8; 1.6]	0.374
Age classes (Ref.: 18–65 years)			
66–70 years	1.467	[1.0; 2.2]	0.066
71–80 years	1.875	[1.4; 2.5]	<0.001
>80 years	4.000	[2.9; 5.4]	<0.001
Sex (Ref.: Female)			
Male	1.015	[0.8; 1.2]	0.875
CCI (Ref.: 0)			
1–2	1.445	[1.2; 1.8]	0.001
≥3	1.340	[1.0; 1.9]	0.079
Cardiovascular disease	1.523	[1.2; 1.9]	0.001
Atrial fibrillation	1.223	[0.9; 1.7]	0.213
Heart failure	1.214	[0.9; 1.7]	0.249
Hypertension	1.198	[0.9; 1.5]	0.144
Diabetes	0.908	[0.7; 1.1]	0.402
Hypercholesterolemia	0.834	[0.7; 1.0]	0.085

Note: *Significant p values are highlighted in bold.

Abbreviations: CCI, Charlson Comorbidity Index; CHT, chemotherapy; CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio.

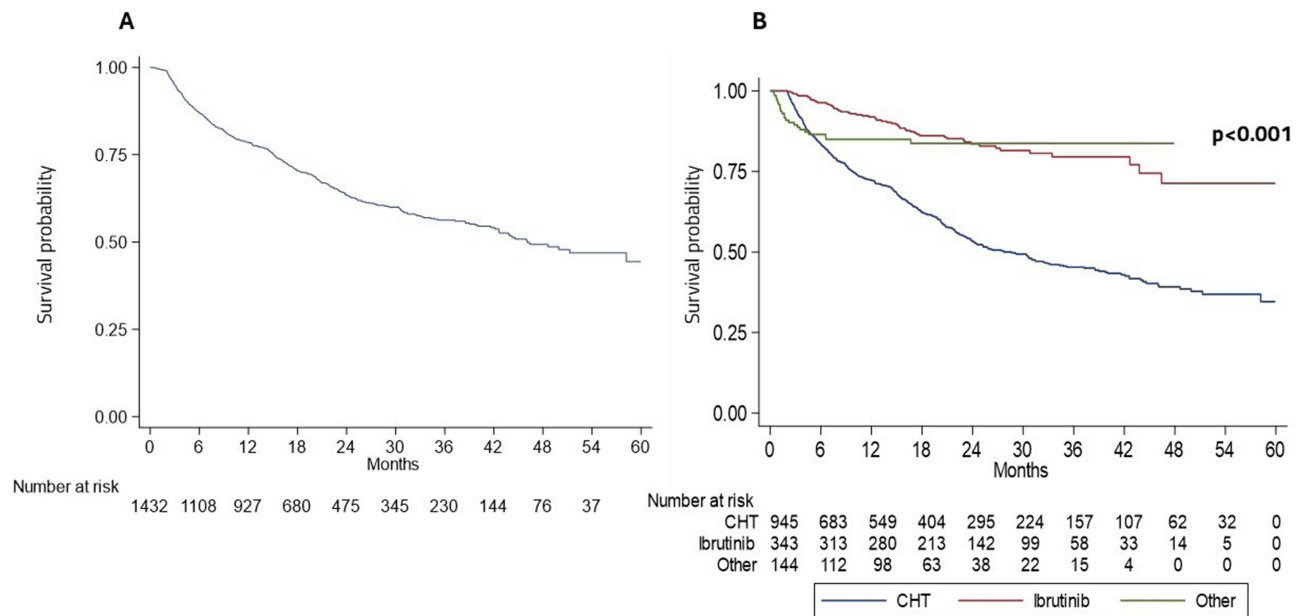


Figure 3 TTNT among incident CLL patients in IL treatment, **(A)** overall, and **(B)** stratified by treatment. Significant p values are highlighted in bold.

Cox model confirmed the lack of statistical association with worse outcomes ($p=0.976$), suggesting that a modest extension of the dosing interval did not impair drug survival (Table S2).

The model then examined refill intervals of at least 45 days using two approaches, one requiring three prescriptions and another requiring two prescriptions. The first 45-day model produced a p-value of 0.577 (Figure 7C), and the second yielded a p-value of 0.709 (Figure 7D), both confirming that extended refill intervals did not significantly influence the likelihood of treatment discontinuation or mortality (Tables S3 and S4).

Table 5 Cox Regression Model for Predictors of Switch

	HR	95% CI	p*
Treatment (Ref.: CHT)			
Ibrutinib	0.268	[0.2; 0.4]	<0.001
Other	0.325	[0.2; 0.5]	<0.001
Age classes (Ref.: 18–65 years)			
66–70 years	1.010	[0.7; 1.4]	0.952
71–80 years	1.155	[0.9; 1.4]	0.215
>80 years	0.786	[0.6; 1.0]	0.098
Sex (Ref.: Female)			
Male	1.114	[0.9; 1.3]	0.256
CCI (Ref.: 0)			
1–2	0.974	[0.8; 1.2]	0.809
≥3	1.064	[0.7; 1.5]	0.742
Cardiovascular disease	1.017	[0.7; 1.4]	0.913
Atrial fibrillation	0.518	[0.3; 0.9]	0.019
Heart failure	0.356	[0.2; 0.7]	0.003
Hypertension	0.939	[0.8; 1.2]	0.555
Diabetes	1.045	[0.8; 1.3]	0.736
Hypercholesterolemia	0.934	[0.7; 1.2]	0.550

Note: *Significant p values are highlighted in bold.

Abbreviations: CCI, Charlson Comorbidity Index; CHT, chemotherapy; CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio.

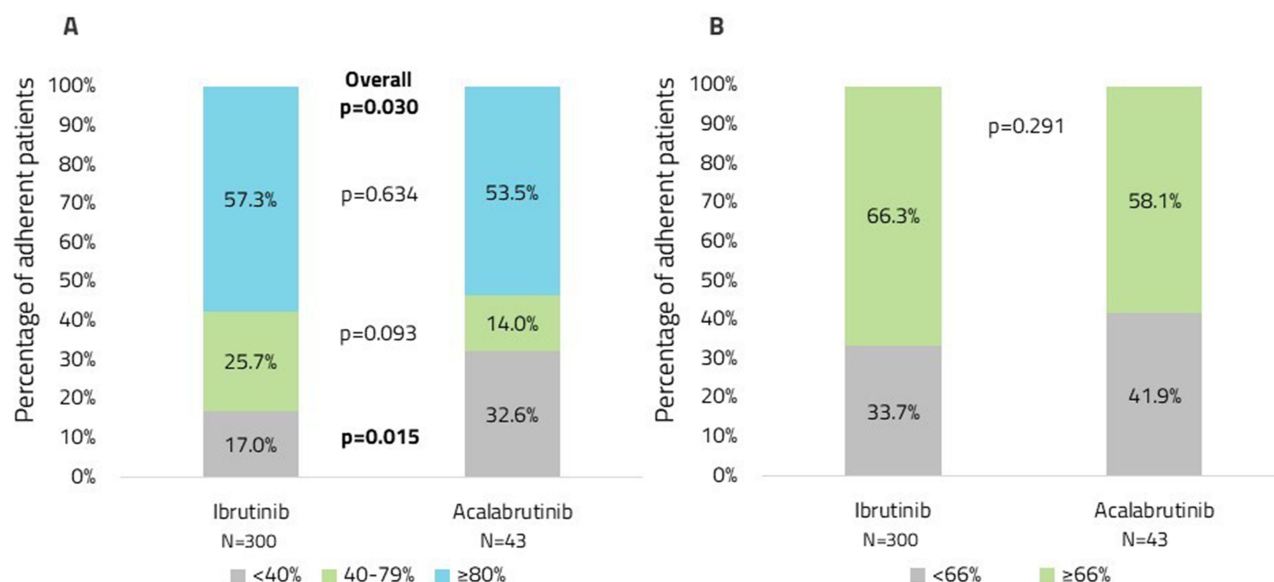


Figure 4 Adherence to IL treatment with ibrutinib or acalabrutinib in incident CLL patients, using adherence cutoffs of (A) MPR ≥80% and (B) MPR ≥66%. Significant p values are highlighted in bold.

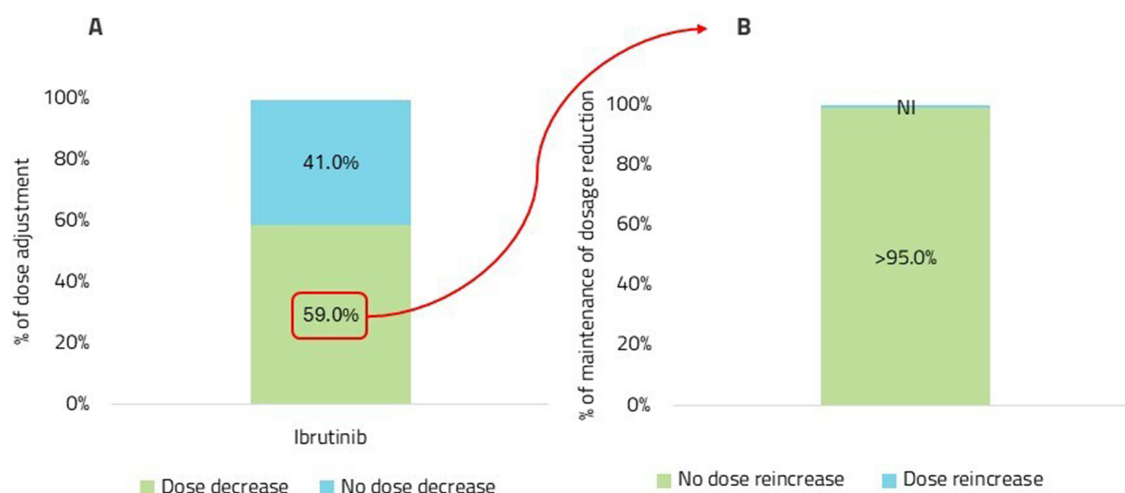


Figure 5 (A) Dose adjustment within 12 months among patients who initiated IL single-agent ibrutinib, and (B) focus on ibrutinib patients with dose decrease.

Cost Analysis

Figure 8 presents a comparative analysis of direct healthcare costs among patients with CLL who initiated 1L. after exclusion of seven outliers. Given the small number of patients treated with acalabrutinib (N=47), their costs were not reported. The mean total cost per patient was €38,573, largely driven by drug prescriptions (€36,979), distantly followed by outpatient services (€1086) and hospitalizations (€507). The comparison across treatment groups highlighted that ibrutinib was associated with significantly lower hospitalization costs than other 1L treatments ($p<0.001$), largely reflecting its oral administration and reduced need for inpatient services. Outpatient costs not related to drug administration were also significantly lower for ibrutinib-treated patients ($p=0.002$). However, drug-related expenditures were higher for ibrutinib, resulting in approximately €21,000 higher costs relative to aspecific CHT. Importantly, these cost differences should be interpreted in light of observed clinical outcomes, since patients treated with ibrutinib experienced

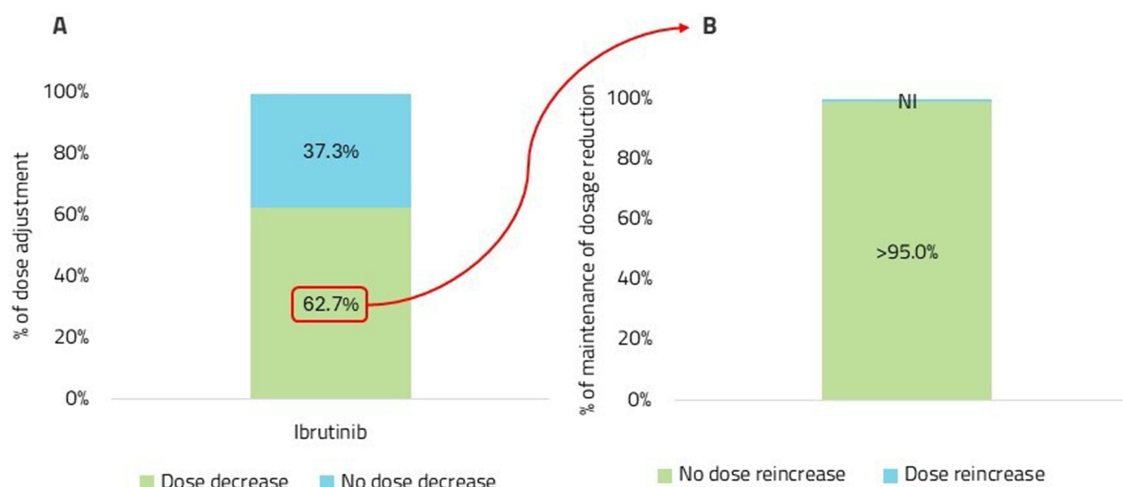


Figure 6 (A) Dose adjustment within 9 months among patients who initiated 1L single-agent ibrutinib, and (B) focus on ibrutinib patients with dose decrease.

nearly half the number of deaths compared with CHT, suggesting that part of the economic difference may be explained by greater treatment effectiveness, as also supported by previously published evidence.

To further explore cost differences, a GLM adjusted for baseline characteristics was applied (Table 6). The GLM confirmed that the €21,000 delta between ibrutinib and CHT referred to total healthcare costs, not solely drug acquisition costs, reinforcing the notion that reduced hospitalization and outpatient expenditures partially offset the higher drug-related expenses, with hospitalization costs decreasing by around 70% of total expenditures. Given the small number of patients treated with acalabrutinib, the costs were not reported in the figure. In this cohort, total costs were 38,573€ per patient, distributed as follows: 36,979€ for drug prescriptions, 507€ for hospitalizations, and 1086€ for outpatient services.

Discussion

This real-world analysis describes the incidence and clinical characteristics of patients with CLL who initiated 1L therapy in Italy, while also quantifying treatment patterns and evaluating therapeutic choices, adherence, clinical outcomes, and healthcare costs, using a large administrative dataset.

The epidemiological data showed that between 2019 and 2023, the annual incidence rate of CLL patients initiating 1L therapy in Italy was 4.98 per 100,000 person-years, with higher rates observed in men and in older age groups, peaking at nearly 19 per 100,000 among individuals aged 71–80 years. These estimates align with previously published national evidence, which suggests a typical incidence range of 2–6 per 100,000 person-years. Men are affected more commonly than women, with a male-to-female ratio of 1.5:1–2:1.⁵

Over the last few years, the introduction of new BTKis, such as acalabrutinib and zanubrutinib, did not substantially alter prescribing patterns, with ibrutinib continuing to be the predominant targeted therapy, together with a still relevant proportion of aspecific CHT-treated patients. This trend likely reflects a combination of clinical familiarity, extensive supporting evidence, and the earlier market access of ibrutinib compared to newer agents.¹⁷ Despite the availability of more effective and better-tolerated targeted therapies, the continued use of CHT, particularly in older or more comorbid populations, suggests a gap between guideline recommendations and real-world practice, possibly influenced by institutional protocols, physician preference, or treatment accessibility.²⁶

Our real-world data suggest that cardiovascular risk did not preclude the use of ibrutinib in normal clinical practice. Across the years 2019 to 2022, the proportion of ibrutinib-treated CLL patients with a history of cardiovascular disease remained notable, ranging from 10.0% to 20.3%.^{27–29} These findings suggest that clinicians continued to prescribe ibrutinib, even in the context of known cardiovascular comorbidities, likely balancing the drug clinical benefits against its cardiovascular risks. This underscores a pragmatic, risk-managed approach rather than outright avoidance within routine clinical settings.

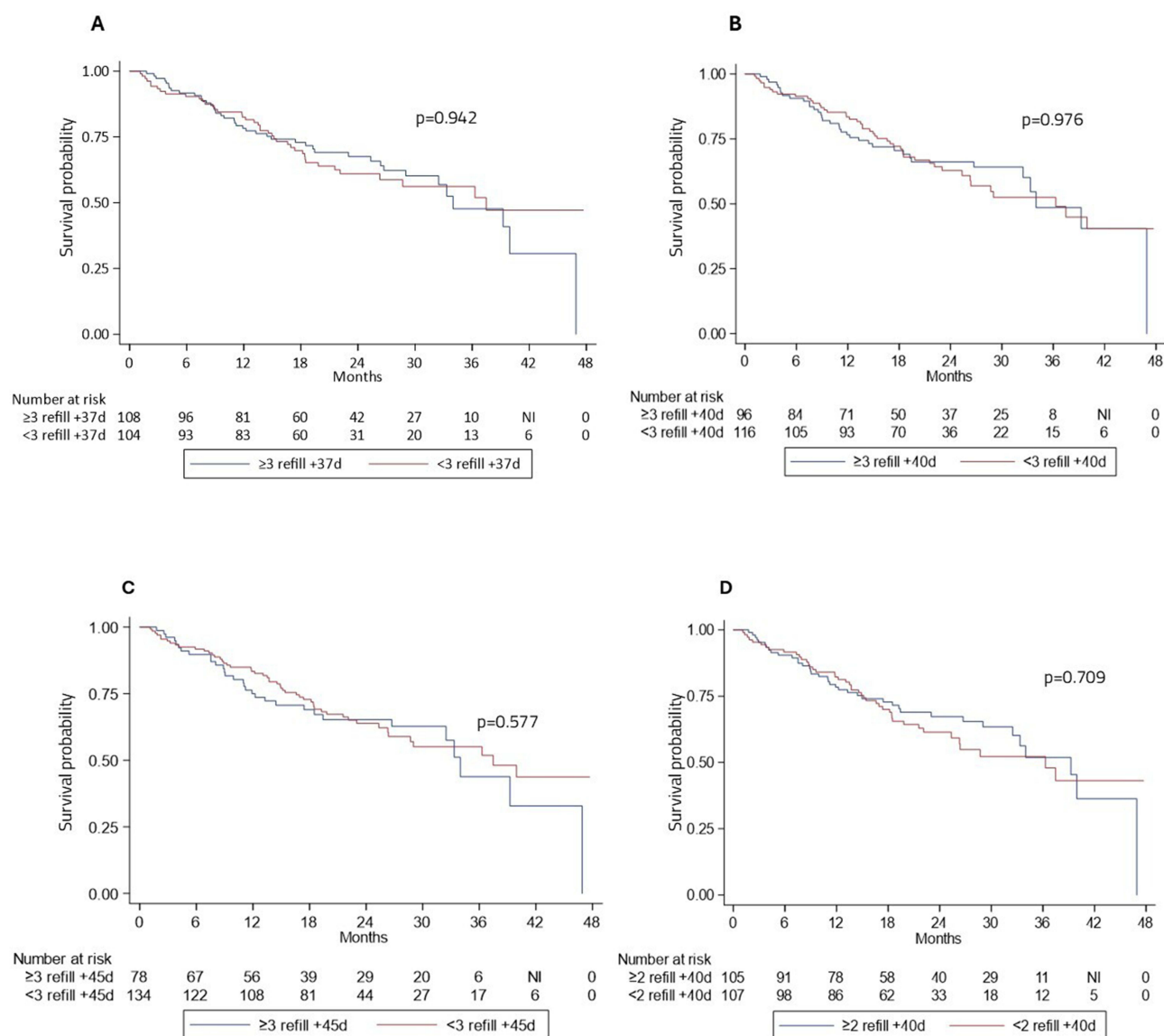


Figure 7 Drug survival analysis with a refill of (A) at least 3 prescriptions in a time interval ≥ 37 days; (B) at least 3 prescriptions in a time interval ≥ 40 days; (C) at least 3 prescriptions in a time interval ≥ 45 days; (D) at least 2 prescriptions in a time interval ≥ 45 days.

The observed treatment patterns indicate that ibrutinib has maintained a central role in the management of CLL, both as a 1L therapy and in subsequent lines. Among 1479 patients initiating 1L treatment, 23.2% received ibrutinib, and this proportion rose to 56.7% among those progressing to 2L therapy. This trend reflects its continued prominence in routine clinical practice, consistent with other real-world analyses. The Italian EVIDENCE study reported that ibrutinib was frequently used across different lines of therapy and resulted to be associated with good persistence and favourable survival outcomes.³⁰ Additionally, a Danish population-based cohort study found that targeted therapies, including ibrutinib, were associated with improved treatment-free and OS compared to chemoimmunotherapy in 2L setting.³¹

The mortality rate of 34.8% over an average follow-up of 2.8 years, with a median survival of 59.5 months, underscores the ongoing clinical burden of CLL, particularly in an older population with comorbidities. Notably, 1L ibrutinib treatment was associated with a substantially lower risk of death compared to aspecific CHT, reducing mortality by 34% in multivariable analysis. These results are consistent with prior real-world and clinical trial data, which have demonstrated improved OS and progression-free survival (PFS) with ibrutinib compared to chemoimmunotherapy regimens.³² The survival benefit observed with ibrutinib supports its role as a preferred frontline therapy, especially

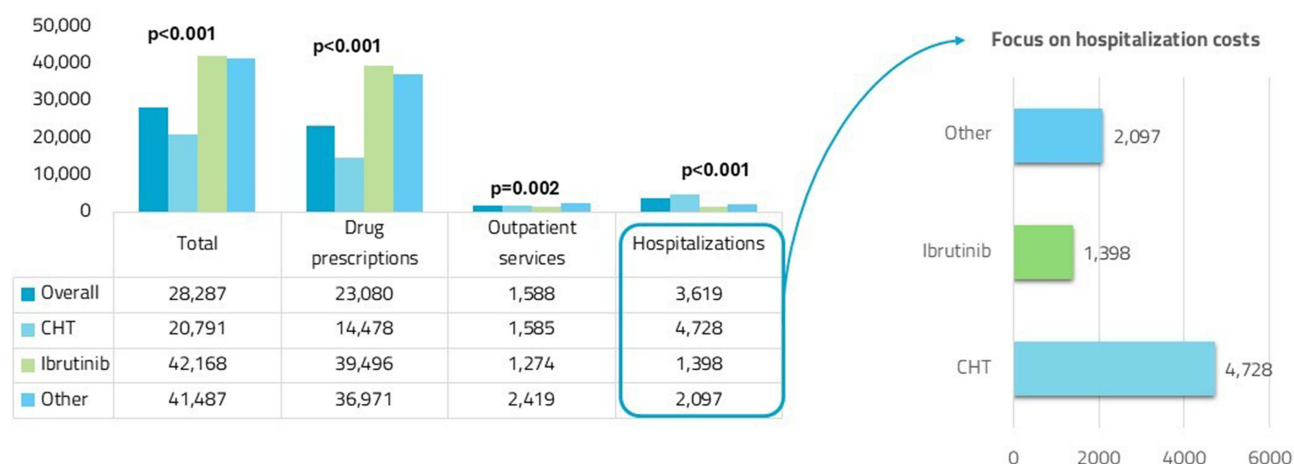


Figure 8 Direct healthcare costs per patient at the first year of follow-up in total CLL population and patients stratified by 1L treatment, and focus on hospitalization costs. Significant p values are highlighted in bold.

for patients unsuitable for intensive CHT. In contrast, older age, higher comorbidity burden, and cardiovascular disease emerged as independent predictors of increased mortality, emphasizing the need for careful risk stratification and individualized treatment planning in this population.

The observed median TTNT of 46.1 months across all patient groups, with half of the patients not requiring a switch in therapy after nearly four years, underscores the durability of 1L treatments in real-world settings. Notably, among patients receiving ibrutinib, the median TTNT was not reached during the available follow-up period, highlighting its capacity to delay disease progression or treatment failure. These data align with the RESONATE-2 trial, which demonstrated sustained PFS benefits with 1L ibrutinib treatment up to 10 year follow-up period.^{18,33} Furthermore, real-

Table 6 Generalized Linear Model (GLM) for Predictors of Healthcare Costs

	Coeff.	95% CI	p*
Treatment (Ref.: CHT)			
Ibrutinib	21,074.6	[17,091.5; 25,057.6]	<0.001
Other	19,651.4	[13,543.2; 25,759.7]	<0.001
Age classes (Ref.: 18–65 years)			
66–70 years	2585.6	[−1829.1; 7000.3]	0.251
71–80 years	2041.0	[−1184.1; 5266]	0.215
≥80 years	−6327.8	[−9636.4; −3019.1]	<0.001
Sex (Ref.: female)			
Male	2041.3	[−106.2; 4188.8]	0.062
CCI (Ref.: 0)			
1–2	280.6	[−2103; 2664.3]	0.818
≥3	9183.8	[3761.6; 14,606.1]	0.001
Cardiovascular disease	−1759.1	[−4724.8; 1206.6]	0.245
Atrial fibrillation	−4363.2	[−7588.9; −1137.5]	0.008
Heart failure	−343.9	[−4505.5; 3817.7]	0.871
Hypertension	−1932.1	[−4909.8; 1045.6]	0.203
Diabetes	1829.2	[−892.5; 4550.9]	0.188
Hypercholesterolemia	−529.2	[−3050.6; 1992.3]	0.681

Note: *Significant p values are highlighted in bold.

Abbreviations: CCI, Charlson Comorbidity Index; CHT, chemotherapy; CI, confidence interval; CLL, chronic lymphocytic leukemia; HR, hazard ratio.

world studies have corroborated these results, indicating that ibrutinib-treated patients experience longer TTNT compared to those receiving other regimens.²⁵

In this analysis, 59% of patients who initiated 1L single-agent ibrutinib at the standard dose of 420 mg/day did not maintain the full prescribed dose over the 12-month period. This finding is consistent with evidence from both clinical trials and real-world settings, where treatment adjustments are frequent, in agreement with data from both clinical trials and real-world settings, where dose modifications are used to manage tolerability. Evidence from the literature indicates that such dose adjustments do not necessarily compromise treatment effectiveness. Akhtar et al demonstrated that patients with CLL who had ibrutinib dose adjustment achieved similar response rates, PFS, and OS compared to those who remained on the full dose.³⁴ The FIRE study also reported no significant difference in PFS between patients who experienced dose adjustments and those who did not.³⁵ In addition, real-world analyses have suggested that dose reductions following serious adverse events may be associated with longer TTNT, in agreement with data indicating that maintaining tolerability through dose modification can enhance treatment durability.³⁶ These findings reinforce the notion that flexible dosing of ibrutinib is an effective strategy for enabling patients to remain on long-term continuous 1L therapy while achieving favourable outcomes.

Across all models tested, Kaplan-Meier survival curves consistently demonstrated that extended refill intervals, used as a real-world proxy for dose reduction, were not associated with poorer drug survival. Specifically, patients who maintained ibrutinib therapy for at least nine months and subsequently received prescriptions spaced by at least 37, 40, or 45 days did not show increased risk of treatment discontinuation or death. These findings suggest that flexible dosing strategies, including lengthened refill periods, do not influence treatment persistence or OS in patients with CLL, supported by evidence in the literature. A UK and Ireland multicenter analysis of 315 patients with relapsed/refractory CLL treated with ibrutinib reported that dose reductions did not significantly affect one-year overall survival, which remained above 90% in both reduced and standard dose groups. However, prolonged treatment interruptions were associated with worse outcomes, highlighting the importance of treatment continuity over strict adherence to standard dosing intensity.³⁷ Taken together, both the results of the present analysis and literature evidence converge on the assumption that dose flexibility in ibrutinib therapy, particularly in the form of extended refill intervals, can be a safe and effective approach. Clinically, this strategy allows for better individualization of treatment while preserving long-term outcomes. From a pharmacoeconomic perspective, it may also reduce healthcare burden without compromising therapeutic benefit.

The comparative analysis of direct healthcare costs among patients with CLL who initiated 1L treatment showed that ibrutinib was associated with significantly lower hospitalization costs compared to other therapies, primarily due to its oral administration, which reduces the need for inpatient services. Other outpatient and administration-related costs were also significantly lower for patients treated with ibrutinib, supporting its favourable healthcare resource profile. Although the drug acquisition cost of ibrutinib is higher, this was offset by reduced hospital-based costs and improved clinical outcomes, as documented by nearly half the mortality rate with respect to CHT. These findings are in line with previous real-world analyses, which demonstrated that patients treated with 1L ibrutinib had significantly lower healthcare resource utilization and total medical costs compared to those receiving chemoimmunotherapy.^{38,39}

The results of the analysis should be interpreted with an awareness of certain inherent limitations associated with the use of administrative healthcare data. Although such databases provide access to large, unselected patient populations in real-world settings, they may lack completeness or precision for specific variables. As these systems are primarily designed to document the financial transactions of reimbursable healthcare services and medications, clinical information must often be extrapolated through indirect proxies like hospital admission codes, exemption codes, or drug prescriptions. Consequently, individuals who were untreated, not hospitalized, or without applicable exemptions may not have been captured. Despite adjustment for available baseline characteristics, residual unmeasured confounding cannot be excluded, particularly confounding by indication, as treatment allocation in routine clinical practice may have been influenced by age, comorbidity burden, frailty, performance status, disease characteristics, physician judgement, and patient preference. In particular, administrative databases do not routinely capture key prognostic and predictive factors guiding treatment selection in CLL, such as IGHV mutational status, TP53 abnormalities/del(17p), disease stage, frailty, performance status, or reasons for treatment selection. Hence, the observed differences in OS and TTNT between CHT

and BTKi-based regimens should be interpreted as associations rather than causal effects. Findings for acalabrutinib should also be considered exploratory because of the limited number of treated patients. Moreover, adverse events such as bleeding complications that might have contributed to treatment interruptions or discontinuation, are not directly captured in administrative databases. Lastly, since the dataset covers roughly 15% of the Italian population, the findings should be interpreted with caution, as their generalizability to the entire national population or to international contexts may be limited.

Conclusions

This real-world analysis provides a comprehensive overview of treatment patterns, clinical outcomes, adherence, dose modifications, and healthcare resource utilization among patients with CLL initiating first-line therapy in Italy. During the study period, ibrutinib was the most frequently prescribed targeted agent, while a substantial proportion of patients, particularly those older or with relevant comorbidities—continued to receive non-specific CHT. In this setting, ibrutinib was associated with longer TTNT and a lower risk of mortality compared with CHT. However, given the observational design and the older and more comorbid profile of patients treated with CHT, these findings should be interpreted as associations rather than causal effects. Findings for acalabrutinib should also be considered exploratory, owing to the limited number of treated patients.

Dose modifications and flexible dosing approaches were common and did not appear to compromise treatment persistence or overall outcomes, reflecting routine clinical management driven by tolerability considerations and individual patient profiles.

From an economic perspective, higher drug acquisition costs for oral targeted therapies were partly offset by lower hospitalization and outpatient expenditures, alongside favourable clinical outcomes. Overall, these findings capture the evolving CLL landscape in Italy and underscore the value of real-world evidence to support clinical decision-making as new options continue to emerge.

Looking ahead, the Italian treatment paradigm is increasingly moving toward chemotherapy-free strategies, with fixed-duration targeted regimens—particularly venetoclax–obinutuzumab—and forthcoming BTKi–venetoclax combinations expected to become front-line standards for most patients, including frail and elderly individuals who historically relied on suboptimal chemoimmunotherapy. This shift aligns national practice with international guidelines and reinforces the role of robust real-world data as a key input for reimbursement and policy decisions. The anticipated reduction in hospital-based services may further strengthen the sustainability of these approaches, positioning targeted therapies as both clinically advantageous and economically sound for the Italian NHS.

Disclosure

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