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ORIGINAL ARTICLE

Ibrutinib as first line therapy in chronic lymphocytic leukemia patients over 80 years old: A retrospective real-life multicenter Italian cohort

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Abstract

Although chronic lymphocytic leukemia (CLL) predominantly affects the elderly, limited data exists about the outcomes of over 80-year-old patients, usually underrepresented in clinical trials. We conducted a multicenter study enrolling 79 consecutive CLL patients ≥80 years at the time of frontline therapy, all treated with ibrutinib. Nearly 48% of cases exhibited unmutated *IGHV* genes, 32% 17p deletion, and 39.2% *TP53* mutations; 63.3% displayed a cumulative illness rating scale (CIRS) > 6. The overall response rate on ibrutinib, computed in 74/79 patients (5 patients excluded for early withdrawal), was 89.9%. After a median follow-up of 28.9 months, the median progression-free survival (PFS) and overall survival (OS) were 42.5 and 51.8 months, respectively. CIRS>6 and temporary discontinuation of ibrutinib lasting for 7–30 days were the only parameters associated with a significantly shorter PFS and were both relevant in predicting a shorter PFS compared to patients with CIRS≤6 and therapy discontinuation ≤7 days. The most common grade≥3 adverse events were infections (25.5%), neutropenia (10.1%), and anemia (2.5%). Eighteen patients (22.8%) experienced a cardiovascular event, including grade-2 atrial fibrillation (n = 9; 11%), grade-2 hypertension (n = 5; 6%), heart failure (n = 3; 3%), and acute coronary syndrome (n = 1; 1%). Mild bleeding events were observed in 27 patients (34.2%). Ibrutinib was permanently discontinued in 26 patients due to progressive disease (n = 11, including 5 Richter's syndromes),

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secondary malignancies ($n = 6$), infections ($n = 3$), cardiac failure ($n = 3$), severe bleeding ($n = 2$), and sudden death ($n = 1$). In conclusion, our analyses confirmed the overall effectiveness and favorable safety profile of the ibrutinib-single agent therapeutic approach in CLL patients ≥80 years.

KEYWORDS
chronic lymphocytic leukemia, elderly, ibrutinib, therapy

1 | INTRODUCTION

Chronic lymphocytic leukemia (CLL), the most prevalent hematologic neoplasm in Western countries, primarily affects the elderly. Indeed, the majority of patients are over the age of 65 years at diagnosis, and the incidence among those over the age of 80 is estimated to be 30/100,000 per year.[1] After diagnosis, most patients are placed under a "watch and wait" approach, monitoring the disease and initiating specific anti-leukemic therapy upon meeting treatment criteria.[2] At the time of treatment, most elderly patients are frequently affected by multiple chronic comorbidities, leading to decreased performance status and quality of life. These factors potentially limit adherence to therapy, posing a significant challenge for clinicians in their therapeutic decisions.

Ibrutinib, the first-in-class Bruton tyrosine kinase inhibitor (BTKi), dramatically revolutionized the therapeutic landscape of CLL, demonstrating efficacy in both treatment-naïve (TN) and relapsed/refractory (R/R) patients, including those harboring high risk cytogenetic such as 17p deletion or *TP53* mutations. In the pivotal RESONATE-2 phase 3 study, ibrutinib outperformed standard-of-care chemotherapy in terms of efficacy and tolerability in TN patients.[3] Long-term follow-up of the study recently confirmed those relevant results, revealing a 7-year progression-free survival (PFS) of 59% for ibrutinib versus 9% for chlorambucil, with adverse events (AEs) prevalence consistent with previous observations.[4] Although the pivotal study on ibrutinib included a few patients aged over 80 years (range 65–89 years),[3,4] it lacked adequate and specific information on this elderly population. Moreover, the trial did not address the potential impact of comorbidity burden and eventual multiorgan dysfunction on clinical outcomes.

In the present study, we performed a retrospective analysis focused on a cohort of CLL patients ≥80 years old who received front-line treatment with ibrutinib providing evidence of the efficacy and the safety of the BTKi in the real-world clinical practice.

2 | MATERIALS AND METHODS

2.1 | Patients

The present study includes a cohort of 79 treatment-naïve CLL consecutive cases ≥80 years, treated with ibrutinib in 17 Italian centers, separately collected and retrospectively analyzed. Twenty out of 79 cases, previously described in a study published by Reda et al,[5] are here presented with an updated follow-up. The dedicated database contained, along with demographical (age and sex) and clinical data related to CLL (Binet staging, presence of 17p deletion or *TP53* mutations, the mutational *IGHV* gene status), information regarding the patient clinical history and treatment-related adverse events [that is, cumulative illness rating status (CIRS), creatinine clearance, the presence of pre-existing cardiovascular (CV), risk factors, as well as of prior cardiovascular events and concomitant cardioactive therapies]; this data are summarized in Table 1. CLL patients received ibrutinib as first-line therapy between January 2014 and March 2021. The primary endpoints of the study were the survival outcomes of patients in terms of PFS and overall survival (OS). The secondary endpoint included the safety profile. The Institutional Ethics Committee of each of the participating hospitals approved the study, which was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.

2.2 | Immunoglobulin gene mutation and FISH

IGHV mutation analysis and FISH were performed at the reference laboratory of each participating center. The *IGHV* mutation status was tested on tumor DNA collected at diagnosis and was assessed according to ERIC guidelines.[6] Sequences that differed by more than 2% from their corresponding germ-line sequence were considered mutated.[6–8] FISH analysis was performed on nuclei extracted from fresh or frozen peripheral blood mononuclear cells. The probe used for 17p deletion analysis was LSIp53 (Abbott). At least 200 interphase cells were examined. The presence of 17p deletion abnormality was scored when the percentage of nuclei with the abnormality was above each laboratory's internal cut-off defined as the mean plus 3 standard deviations (SD) of the frequency of normal control cells exhibiting the abnormality.[9] Mutation analysis of *TP53* (exons 4–9 or 2–11) was carried out either by direct sequencing of DNA (ABI PRISM 3100 Genetic Analyzer; Applied Biosystems, Foster City, CA) or by next-generation sequencing by MiSeq Illumina or Ion Torrent technologies; in all cases, the cutoff for the variant allele frequency was about 10% as per ERIC recommendations.[10]

2.3 | Statistical analysis

The statistical significance of associations between individual variables and survival was calculated using the log-rank test. Results are expressed as hazard ratios (HRs) and 95% confidence intervals (95% CIs). PFS and OS were computed from the date of treatment start to

TABLE 1 Clinical features of patients treated with ibrutinib in a real-world setting.

Features	*N* of cases (%)
Median age, y (range)	81 (80–87)
Sex	
Male	36 (45.6)
Female	43 (54.4)
CIRS	
0–6	29 (36.7)
>6	50 (63.3)
Median creatinine clearance (mL/min)	45 (25–65)
Binet stage	
A	5 (6.3)
B	37 (46.8)
C	37 (46.8)
17p deletion	
No	54 (68.4)
Yes	25 (31.6)
TP53	
Wild type	48 (61.8)
Mutated	31 (39.2)
IGHV mutational status	
Mutated	42 (51.9)
Unmutated	37 (48.1)
Pre-existent cardiovascular (CV) risk factors	
Hypertension	50 (63.2)
Diabetes	10 (12.6)
Dyslipidemia	8 (10.1)
Obesity	8 (10.1)
Arteriopathy	4 (5)
≥2 CV risk factors	18 (22.7)
Prior cardiovascular events	
Atrial fibrillation	4 (5)
NSTEMI	4 (5)
STEMI	3 (3.8)
Cerebrovascular events	6 (7.5)
Concomitant cardioactive therapies	
At least 1 cardioactive drug	58 (73.4)
>2 cardioactive drugs	24 (30)
Antihypertensive drugs	50 (63.2)
Anticoagulants	4 (5)
Lipid-lowering drugs	13 (16.4)
Antiplatelets drugs	27 (34)

the date of last follow-up or death, as extracted from clinical records, and were analyzed using the Kaplan-Meier method. PFS was measured from the initiation of ibrutinib treatment until death from any cause or progression or last follow-up. OS was measured from the initiation of ibrutinib treatment until death from any cause or last follow-up. p value < 0.05 was considered statistically significant. STATA for Windows v.9 and SPSS Statistics v.21 were used to analyze the data.

3 | RESULTS

3.1 | Patients

Patients' characteristics at the time of ibrutinib initiation are shown in Table 1. The median age of patients was 81 years (range 80–87 years). Overall, 93.6% of patients presented Binet stage B/C. The cohort exhibited a balanced distribution concerning the *IGHV* gene status with 51.9% of mutated CLL and 48.1% of unmutated cases. Nearly 32% of patients (25 cases) harbored 17p deletion, while 39.2% (29 cases) had *TP53* mutated. Among these, 21 cases had both 17p deletion and *TP53* mutations, 4 cases had 17p deletion only, and 8 cases had *TP53* mutation only. Most patients (63.3%) showed a CIRS>6 and a median creatinine clearance of 45 mL/min (range 25–65 mL/min). The most frequent comorbidity at baseline was CV disorder. The most common pre-existent CV risk factors were arterial hypertension (63.2%), followed by diabetes (12.6%), dyslipidemia and obesity (10.1%), and arteriopathy (5%). Fourteen patients had at least 2 CV risk factors. Accordingly, the concomitant treatment mostly included antihypertensive drugs (63.2%), antiplatelet agents (34%), lipid-lowering drugs (16.4%), and anticoagulant therapy (5%). Seventeen patients experienced CV events prior to ibrutinib initiation. In particular, 6 patients (7.5%) had a cerebrovascular event, 4 (5%) experienced atrial fibrillation. Finally, 4 and 3 patients respectively experienced non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI).

3.2 | Response evaluation

Response evaluation was assessed on 74 out of 79 patients (93.7%), with 5 patients (6.3%) being not evaluable due to early withdrawal of ibrutinib. Out of 74 cases, 13 patients (16.5%) achieved a clinical complete remission (CR). However, they did not meet the stringent CR criteria outlined by the IWCLL[2] due to the lack of bone marrow biopsy results. Additionally, 58 (73.4%) had a partial response (PR) or PR with residual lymphocytosis (PR + L), while 3 patients (3.8%) maintained stable disease (SD).

3.3 | Progression-free survival

The median follow-up of the cohort, computed with the inverted censoring method, was 28.9 months (95% CI 20.8–36.0). During this

period, the median PFS was 42.5 months (95% CI 28.1–66.3) (Figure 1). Factors including age, sex, creatinine clearance, Binet stage, *TP53* disruption (i.e., 17p deletion and/or *TP53* mutations), and *IGHV* gene mutational status were not statistically significant in influencing PFS in this patient population (Supplementary Figures S1 and S2). However, patients with CIRS>6 exhibited significantly shorter PFS (median PFS 33.1 months, 95% CI 20.0–49.3 vs. not reached, $P = 0.016$; Figure 2). Furthermore, a notable finding was the extended PFS ($P = 0.03$) observed in the 46 patients who either never discontinued ibrutinib or stopped the drug for less than 7 days (median PFS 51.8 months, 95% CI 49.3–66.3) compared to those with transient treatment interruptions ranging from 7 to 30 days, ($n = 33$; median PFS 32.7 months, 95% CI 20.6–42.5) (Figure 3).

The combined analysis of CIRS and temporary discontinuation of ibrutinib revealed a notable difference in the prognostic significance of CIRS>6 when comparing patients with temporary discontinuation lasting less than 7 days and patients with discontinuation between 7 and 30 days. This distinction was evident in the PFS curves illustrated in Figure 4 ($P = 0.025$), suggesting a potential interaction between these two parameters. Accordingly, utilizing Cox proportional hazard models, CIRS>6 in patients with temporary discontinuation ≤7 days showed an HR for progressive disease of 4.97 (95% CI 1.13–21.96; $P = 0.034$), while no additional prognostic information was provided when CIRS>6 was tested in the context of patients experiencing discontinuation between 7 and 30 days of ibrutinib therapy (HR 1.18, 95% CI 0.37–3.71; $P = 0.78$).

To take into account interactions between CIRS and treatment discontinuation, the combination of these parameters was tested by multivariable analysis (Table 2). All the combinations of CIRS and treatment discontinuation were associated with a significant risk of progression compared to patients with CIRS≤6 and a ≤7 days of treatment discontinuation (HR ranging from 5.12 to 7.96), indicating the relevance of both parameters in predicting PFS in >80 CLL patients under ibrutinib.

3.4 | Overall survival

The median OS was 51.8 months (95% CI 50.1–53.5) (Supplementary Figure S3). Sex, creatinine clearance, Binet stage, *IGHV*, 17p deletion, and *TP53* mutational status, as well as CIRS, did not exert a significant influence on OS. However, a trend toward longer OS ($P = 0.07$) was observed by comparing the 46 patients who did not discontinue or interrupted ibrutinib ≤7 days (67.2 months, 95% CI 43.5–90.9) with the 33 cases who interrupted treatment for 7–30 days (51.8 months, 95% CI 34.4–69.2) (Supplementary Figure S4).

3.5 | Safety

The most common grade ≥3 AEs were infections (25.5%), neutropenia (10.1%), and anemia (2.5%). Eighteen patients (22.8%) experienced a CV event including 9 cases (11%) of atrial fibrillation (AF), 5 hypertension (6%), 3 heart failure (3%), and 1 acute coronary syndrome (1%). All cases of AF and hypertension were of grade 2. Patients with AF received anticoagulant therapy and no thrombotic stroke were recorded. To note, we did not record an increased incidence of AF and hypertension among patients with previous CV events ($P = 0.79$) and with preexisting CV risk factors ($P = 0.68$). Bleeding events were observed in 27 (34.2%) patients and were scored mild (grade 1–2, 24 patients; grade 3, 3 patients). Patients who required anticoagulants or anti-platelet drugs did not experience

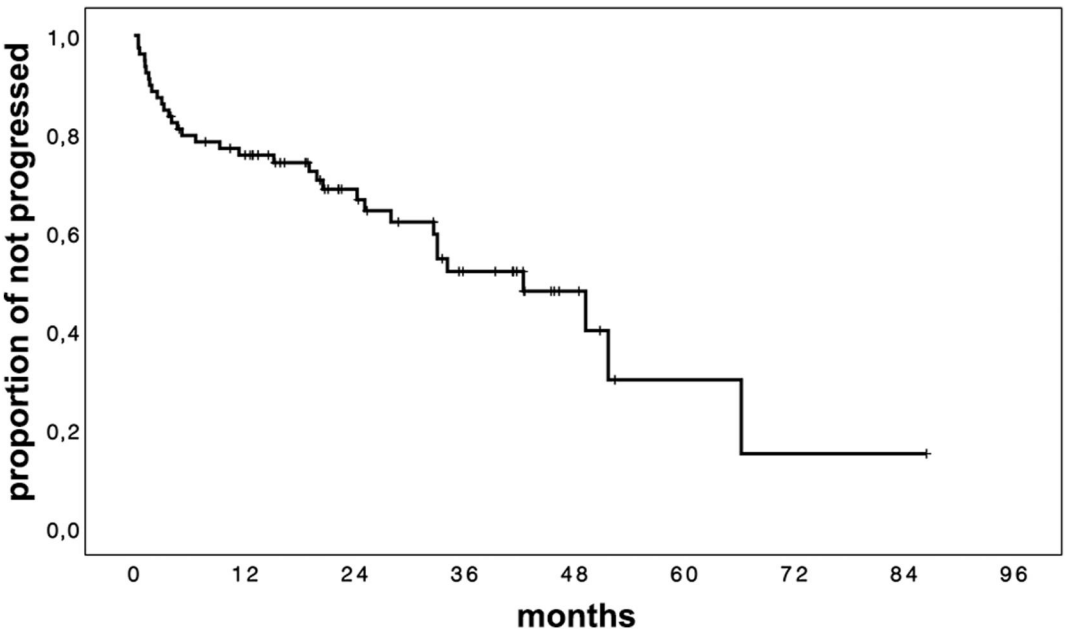

FIGURE 1 Progression-free survival of the entire cohort of elderly CLL patients.

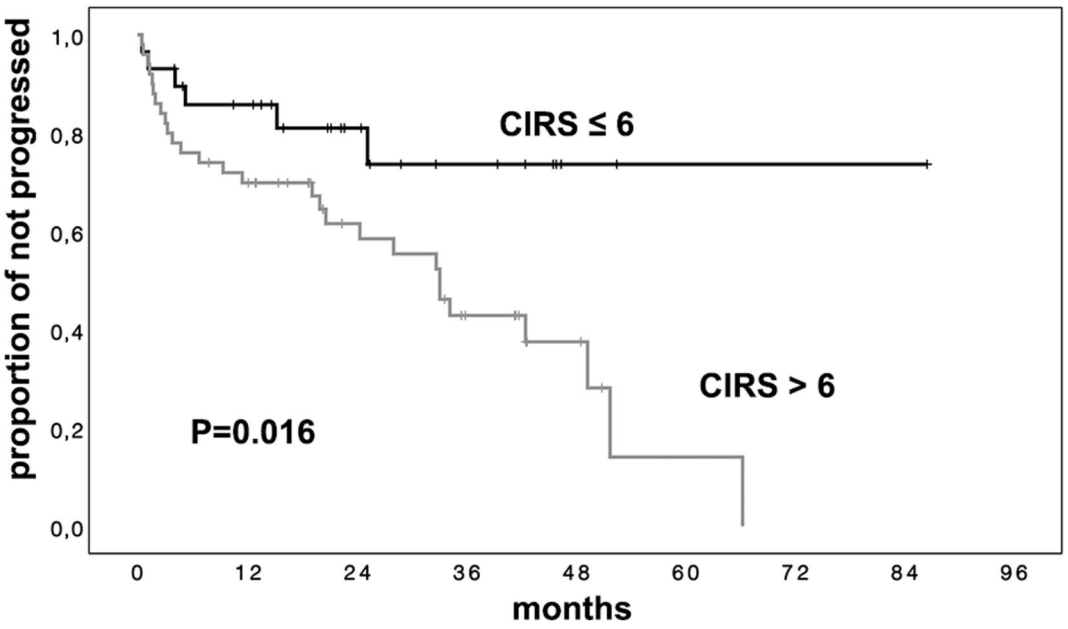

FIGURE 2 Progression-free survival according to CIRS. Cases with CIRS ≤6 (black line) versus cases with CIRS >6 (gray line).

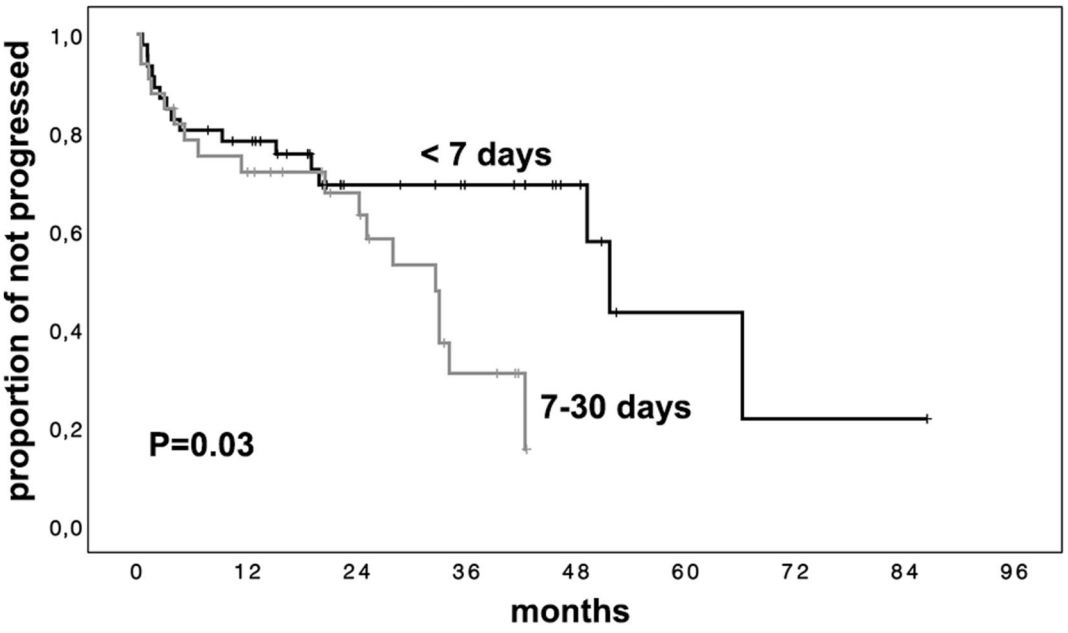

FIGURE 3 Progression-free survival according to treatment discontinuation. Cases who never discontinued ibrutinib or stopped the drug for less than 7 days (black line) versus cases with transient treatment discontinuation between 7 and 30 days (gray line).

a significantly higher rate of hemorrhagic events than those who did not receive anticoagulants. Secondary malignancies were reported in 6 patients (7.8%) and Richter's transformation in 5 (6.3%). Temporary drug withdrawal (lasting 7–30 days) overall occurred in 33/79 patients (41.8%). The reasons for withdrawal included infections in 17 cases (51.5%), CV events in 5 cases (15.1%), hemorrhagic events in 10 cases (30.3%), and hematological toxicity in 1 case (3%). The remaining 46/79 cases who did not discontinue or interrupted ibrutinib ≤7 days are so distributed: 23 cases (50%) did not stop the drug, 3 (6.5%) discontinued for CV events, 3 (6.5%) for infections, 2 (4.3%) for hematological toxicity, 10 (21.7%) for surgeries, 5 (10.8%) for bleeding. Ibrutinib was permanently discontinued in 26 patients (32%) owing to PD (11 cases, with 5 cases developing Richter's syndrome), secondary malignancies (6 cases), infections (3 cases), cardiac failure (3 cases), severe bleeding (2 cases), and sudden death (1 case). A higher rate of cases who permanently discontinued drug for reasons not related to PD was observed in the subset of patients who temporary discontinued treatment for 7–30 days compared to those that discontinued treatment for ≤7 days [9/33 (27%) versus 6/46 (13%); $P = 0.02$].

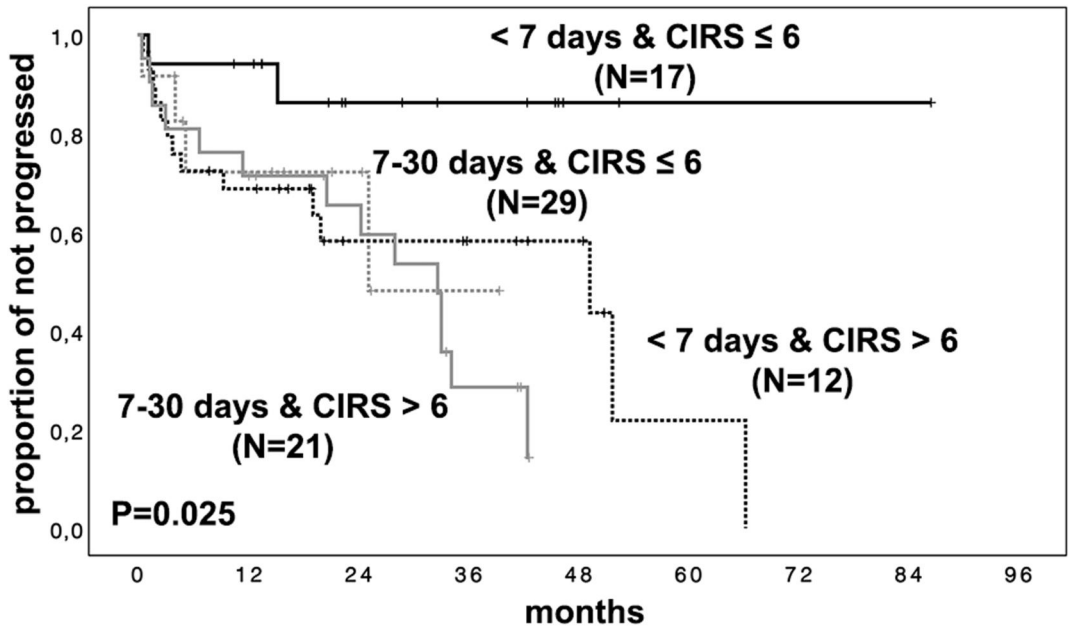

FIGURE 4 Progression-free survival according to CIRS and treatment discontinuation. Cases were split into four groups as follows: (i) black line: cases who never discontinued ibrutinib or stopped the drug for less than 7 days/cases with CIRS ≤6; (ii) gray line: cases who stopped the drug between 7 and 30 days/cases with CIRS >6; (iii) black dotted line: cases who never discontinued ibrutinib or stopped the drug for less than 7 days/cases with CIRS >6; (iv) gray dotted line: cases who stopped the drug between 7 and 30 days/cases with CIRS ≤6.

TABLE 2 Multivariable Cox regression analyses of PFS with interaction according to CIRS and treatment discontinuation.

	Patients	Prog (%)	Multivariable HR (95% CI)[a]	*P* value[b]
CIRS/Treatment interruption				
≤6/≤7 days	17	11.8%	Ref	
≤6/7–30 days	12	33.3%	5.35 (0.95–30.12)	0.0570
>6/≤7 days	29	48.3%	5.12 (1.16–22.60)	0.0310
>6/7–30 days	21	66.7%	7.96 (1.76–35.96)	0.0070

[a]Estimated from the Cox proportional hazard model and adjusted for CIRS and treatment discontinuation.

[b]Evaluated by χ^2.

4 | DISCUSSION

In the last years, the advent of small molecules such as BTK and BCL-2 inhibitors in clinical practice has drastically revolutionized the CLL therapeutic scenario. These new drugs, have significantly improved PFS and OS, even in patients with high-risk cytogenetic profiles, when compared with traditional chemo-immunotherapy.[11,12]

The improved clinical benefit of ibrutinib over chemo-immunotherapy is remarkably evident in "young" elderly patients with a median age of 71 years.[13] However, there is currently a lack of data confirming the PFS/OS benefits in "older" elderly patients, possibly due to their challenges in traveling to tertiary centers for clinical trial participation. Additionally, CLL trials are not sufficiently patient-friendly, worsening the issue. Indeed, although CLL is a typical disease of the elderly, large clinical studies dealing with the efficacy of chemo-immunotherapy included patients with a median age between 58 and 64 years.[14]

More importantly, even though the pivotal RESONATE-2 study encompassed patients up to 80 years of age, it did not provide specific details about this particular elderly subgroup.[3,4] Likewise, real-world evidence investigating the effectiveness and safety of ibrutinib in the elderly, involved patients with a median age ranging from 69 to 75 years.[15–18] A recent Italian retrospective study assessed the effectiveness and safety profile of ibrutinib in a cohort of R/R and TN CLL patients over the age of 80. The analysis revealed that the only factor influencing PFS was the response achievement[5] Importantly, the safety profile observed in this study remained consistent with existing literature data with no unexpected AEs reported.[5]

To our knowledge, this current study is the most extensive real-world analysis investigating outcomes of octogenarian CLL patients receiving ibrutinib as first-line therapy. The CIRS score greater than 6 and the transient discontinuation of ibrutinib (7–30 days), primarily driven by infections and CV events, were the only factors found to harm PFS. In contrast, no difference in PFS was observed based on

the presence of *TP53* deletion and/or mutation. This lack of prognostic significance persisted even when their combined clinical impact was investigated, contradicting recent findings in younger cohorts of CLL patients treated with ibrutinib.[11,12]

Our findings substantiate the association between comorbidities and an unfavorable prognosis in CLL patients.[19–22] Although the number of comorbidities increases linearly with aging,[23] chronological age per se should be avoided as a surrogate parameter to be considered when selecting a treatment. Conversely, CIRS emerges as the leading score to quantify the comorbidities burden and define its impact on CLL patient outcomes both in the chemo-immunotherapy and ibrutinib settings.[20,24,25]

Recently, the importance of geriatric assessment (GA), has been investigated by the HOVON CLL Working Group.[26] In the HOVON139/GiVe trial, in which unfit CLL patients received 12 cycles of fixed-duration Venetoclax plus Obinutuzumab (Ven-O), authors demonstrated that GA allowed to identify patients with increased risk to develop adverse events. Nevertheless, the longitudinal assessment of the GA in this cohort of patients demonstrated that efficacy of the therapeutic regimen allowed to achieve an improvement of GA, and, consequently, of quality of life (QoL). Although in our study we did not investigate the benefit of ibrutinib therapy in terms of QoL, RESONATE-2 trial clearly demonstrated that also the BTK inhibitor positively impact on health status.[27] In conclusion, in the setting of older patients, in which QoL is one of the most important end-points of treatment, target therapies have demonstrated to be effective in disease control and in patients' global health and functioning.[26,27]

We also analyzed the prognostic implications of ibrutinib discontinuation on PFS. The results of our study were consistent with that of previously published studies.[28,29] In particular, Barr et al found that ibrutinib held for more than 1 week throughout the entire treatment duration was linked to a shorter PFS.[28] Notably, our data demonstrated that the subset of patients who temporary discontinued the drug lasting 7–30 days showed a lower PFS then those who discontinued for ≤7 days since they have a higher probability to experience AE eventually leading to permanent discontinuation.

Although our analysis revealed that the safety profile of ibrutinib in this specific patient subset are overall consistent with literature data with no unexpected additional AEs,[30–36] the observation that both CIRS and treatment discontinuation are relevant parameters predicting PFS in >80 CLL patients under ibrutinib (Figure 4 & Table 2), clearly indicates a link between unfavorable CIRS values, AE onset and temporary drug discontinuation.

Finally, despite having a higher burden of comorbidities than younger age patients typically enrolled in registered clinical trials, the rate of CV events observed in our study was substantially comparable to that reported in younger patients.[37,38] In addition, prior CV events or the presence of risk factors for CV events did not appear to increase the onset of AF or hypertension rates. Indeed, the majority of our patients had already experienced such events or harbored risk factors at the time of treatment initiation. Despite the higher rate of cases treated with antiplatelet and/or anticoagulation therapy, the incidence of major bleeding was relatively low (3.7%).

In conclusion, our analyses confirm the overall effectiveness and favorable safety profile of a single-agent ibrutinib therapeutic approach in patients aged over 80 years. A careful evaluation of comorbidities along with the capability of patients to sustain continuative therapy, emerged as the main parameters more accurately predicting patient outcome in this setting.

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AUTHOR CONTRIBUTIONS

Enrica Antonia Martino, Francesca Romana Mauro, Gianluigi Reda, Fortunato Morabito, Valter Gattei, and Massimo Gentile designed the study, analyzed and interpreted data, and wrote the manuscript; Massimo Gentile, Jerry Polesel, and Fortunato Morabito performed statistical analysis; Antonella Zucchetto, Riccardo Bomben, Antonino

Neri performed laboratory tests; Luca Laurenti, Andrea Visentin, Annamaria Frustaci, Ernesto Vigna, Sara Pepe, Gioacchino Catania, Giacomo Loseto, Roberta Murru, Annalisa Chiarenza, Paolo Sportoletti, Maria Ilaria Del Principe, Roberta Laureana, Marta Coscia, Eleonora Ferretti, Sara Galimberti, Alessandra Tedeschi, Davide Rossi and Livio Trentin provided the patients and collected clinical data; and all authors gave final approval for the manuscript.

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CONFLICT OF INTEREST STATEMENT

Nothing to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This study was approved by the ethics committee at all participating hospitals. It adhered to the Declaration of Helsinki and the Good Clinical Practice guidelines.

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PEER REVIEW

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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