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REVIEW

Real-world evidence on venetoclax in chronic lymphocytic leukemia: The Italian experience

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Abstract

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the western world. In Italy, venetoclax was approved for use in patients with CLL as monotherapy in 2017 and in combinations in 2019. As a result of this delayed approval, there are relatively few real-world studies from Italian clinical practice and much of the data are in heavily pretreated patients. We have collected the available studies in Italian routine practice. Three studies confirm the effectiveness and tolerability of this agent in patients with relapsed/refractory CLL and high-risk disease characteristics, many of whom had received prior B-cell receptor signaling treatment. Addition of rituximab to venetoclax produced more complete responses in patients with relapsed/refractory CLL, while higher disease burden and progression while receiving a prior Bruton's tyrosine kinase inhibitor were both associated with poorer outcomes in patients treated with venetoclax. Venetoclax was well-tolerated with low discontinuation rates. No studies of venetoclax plus obinutuzumab for the first-line treatment of patients with CLL were available due to the short time since approval in Italy. Several cohorts addressed the impact of COVID-19 on patient management and outcomes, suggesting that treated patients and those in clinical observation had similar rates of COVID-19-related hospital admission, intensive care unit admission, and mortality. Overall, the responses and tolerance to venetoclax observed in the Italian real-world setting confirm the tolerability and effectiveness of venetoclax regimens in high-risk patients.

KEYWORDS
B-cell, Bcl-2, chronic, Italy, leukemia, lymphocytic, real-world evidence, venetoclax

1 | INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common form of adult leukemia in the western world.[1] The incidence in Italy ranges between 5.0 and 5.5 per 100,000 in males, and 3.5 and 4.0 per 100,000 in females.[2] The clinical course of CLL is highly variable and risk stratification plays an important role in guiding treatment decisions. Unmutated IGHV and *TP53* aberrations, including both mutations and/or del(17p), are associated with increased genomic instability, poorer responses to chemoimmunotherapy (CIT), and

shorter overall survival (OS).[3,4] The CLL International Prognostic Index (CLL-IPI)[5] predicts progression-fee survival (PFS) and OS in patients receiving CIT as first-line treatment.[6] However, the CLL-IPI does not perform as well with targeted therapies, where the presence of *TP53* mutations or del(17p) have a less relevant impact.[7] Additional parameters, including tumor burden, cytopenias, and prior treatments, showed prognostic value in patients treated with targeted therapies.[8–12] CLL is an incurable condition and physicians need to identify the optimal treatment strategy for each patient to improve PFS and OS, and maintain good quality of life.

In Italy, approval of venetoclax for use in patients with CLL came later than in other European countries, both as monotherapy (August 2017) and in combination (December 2019). As a result, there are relatively few real-world studies from Italian clinical practice and much of the real-world experience involves heavily pretreated patients. We have collected the available studies in Italian routine practice and discuss them in the context of patient management.

1.1 | Recent progress in CLL therapy

Until recently, time-limited CIT with fludarabine, cyclophosphamide, and rituximab (FCR) was the standard of care for young, fit patients with CLL requiring treatment[13,14]; however, such an intensive combination is often associated with myelosuppression, infections, and can increase the long-term risk of myeloid disorders, including myelodysplastic syndrome and acute myeloid leukemia.[15,16] The use of FCR is now mainly limited to the first-line treatment of fit patients with favorable biologic factors (mutated IGHV, no 17p- or 11q-), where long-term benefits have been obtained with this combination.[17] CLL treatment has evolved with the approval of novel agents targeting either B-cell receptor signaling (BCRi) through Bruton's tyrosine kinase inhibitors (BTKis; ibrutinib, acalabrutinib) or phosphoinositide 3-kinase delta inhibitors (idelalisib), or by antagonizing the anti-apoptotic B-cell lymphoma 2 protein (BCL2) using venetoclax.[18] These molecules are better tolerated than CIT.

Unlike CIT, BCRi therapy is administered until progression or unacceptable toxicity occurs,[19] and interruption or discontinuation of BCRi therapy in patients with progressive disease can be associated with disease flares and relapse.[20] These agents effectively suppress the proliferation of CLL cells, but they are usually less effective in achieving complete responses and responses with undetectable minimal residual disease (uMRD).[21] Venetoclax plus rituximab can be administered as a time-limited therapy as it produces high rates of deep responses that are durable after treatment discontinuation.[22–24] This is an important treatment result, as uMRD was shown to be an independent prognostic marker of PFS and OS in patients receiving CIT for CLL.[25]

Moreover, time-limited therapy provides a substantial benefit for patients and their caregivers in terms of improved quality of life associated with the reduced time of treatment, hospital visits, and management of side effects. In addition, limiting treatment duration may potentially improve adherence, and reduced selective pressure and clonal evolution.

Budget models of time-limited CLL therapy with first-line venetoclax plus obinutuzumab suggest that it is cost-effective.[26–28] The ongoing CLL17 trial (NCT04608318) is comparing continuous monotherapy with ibrutinib versus time-limited treatment comprising either venetoclax plus obinutuzumab or venetoclax plus ibrutinib in the first-line CLL setting.

1.2 | Venetoclax

Several characteristics make BCL2 an important target in the treatment of CLL.[29] BCL2 is highly expressed in CLL, and CLL cells are dependent on BCL2 for survival.[30] Venetoclax is a BCL2-selective, orally bioavailable BH3 mimetic that bypasses p53 and disrupts the anti-apoptotic function of BCL2.[31] BCR is increase the dependence of CLL cells on BCL2,[32,33] providing a rationale for combination therapy.

In the US, venetoclax is indicated for the treatment of adult patients with CLL or small lymphocytic lymphoma.[34] In Europe since December 2016, venetoclax has been approved in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL, and in combination with rituximab for the treatment of adult patients with CLL who have received at least one prior therapy. Venetoclax monotherapy is indicated for the treatment of CLL in adult patients with a del(17p) or *TP53* mutation who are unsuitable for or have failed a BCRi, or in adult patients without a del(17p) or *TP53* mutation who have failed both CIT and a BCRi.[35] In Italy, venetoclax has been eligible for reimbursement by the Health Care System for CLL as monotherapy since August 2017,[36] in combination with rituximab in pretreated patients since December 2019,[37] and in combination with obinutuzumab in the first line since May 2022.[38]

Venetoclax was granted approval for treating CLL with *TP53* aberrations based on the results of the phase 2, open-label, single-arm M13-982 study, which enrolled 158 patients with relapsed/refractory (R/R) CLL and confirmed del(17p).[39] Approval for use in combination with rituximab was based on the results from the phase 3, randomized MURANO study in patients with R/R CLL,[40] which compared the venetoclax plus rituximab combination versus the bendamustine plus rituximab combination. This study demonstrated that a time-limited chemotherapy-free regimen with venetoclax and rituximab was more effective than CIT in patients with R/R CLL, including those with high-risk disease. At the end of combination treatment (9 months), venetoclax plus rituximab had resulted in uMRD in peripheral blood in 62.4% of patients versus 13.3% with bendamustine plus rituximab. Five-year follow-up of patients from the MURANO study showed that responses with venetoclax plus rituximab were durable, with sustained benefits in terms of PFS and OS.[41]

In the first-line setting, the CLL14 trial demonstrated that the 1-year, fixed-duration therapy with venetoclax plus obinutuzumab provided longer PFS than chlorambucil plus obinutuzumab in unfit patients with CLL.[42] The results of this study led to the approval of this combination for first-line treatment of CLL.[34] After extended follow-up of median 52.4 months, a significant PFS improvement was maintained in the venetoclax–obinutuzumab arm compared with the chlorambucil–

obinutuzumab arm (median not reached vs. 36.4 months; hazard ratio 0.33; 95% confidence interval: 0.25–0.45; $p < 0.0001$).[43]

1.3 | Real-world evidence in CLL

Randomized controlled trials are necessary to establish *efficacy*, but they focus on selected and homogeneous populations and usually report limited outcome data.[44] Sources of real-world evidence (RWE) include administrative healthcare databases, patient registries, medical records, as well as case reports. RWE studies provide data in unselected patients, and the results of these studies provide useful information in underrepresented patient populations, address important clinical issues, and provide feedback on the implementation of data from controlled trials.[45, 46] Real-world studies investigate long-term safety and the impact of adverse events (AEs) on dose reductions and treatment discontinuations,[47] and provide important information on healthcare system costs.[48] Moreover, these studies are used to assess prognostic testing and treatment patterns,[49] and to collect data on specific CLL patient populations.[50] Other important information that can be obtained from RWE studies includes comparing real-world response rates to those described in clinical trials,[51] assessing the effectiveness of treatments in heavily pretreated high-risk patients with CLL,[52] or in different age groups,[53] evaluating the sequencing of targeted therapies in CLL,[54,55] as well as defining the impact of specific AEs.[56]

Regarding venetoclax for CLL, Eyre et al.[53] assessed the effectiveness of venetoclax according to age in a retrospective cohort of 342 patients with R/R CLL in the US and UK real-world setting, reporting equivalent efficacy and safety among patients ≥75 and < 75 years of age. This finding confirmed aggregated safety data from three early-phase trials showing similar toxicity profiles in these age groups.[57] Further analysis of this cohort by Roeker et al.[56] assessed the rates of selected AEs in 297 patients, confirming the low tumor lysis syndrome (TLS) rates observed in clinical trials after the introduction of a ramp-up dosing schedule and TLS prophylaxis.[58,59] Mato et al.[51] assessed discontinuation rates in a retrospective real-world cohort of 141 patients with R/R CLL treated with venetoclax, reporting after a median 7 months of follow-up that 39 (28%) patients discontinued, mostly because of progression (21/39; 53.8%), whereas relatively few discontinued due to toxicity (8/39; 20.5%), confirming the clinical trial results.[58]

Recently, Thompson et al.[60] conducted an international retrospective study investigated the feasibility of venetoclax re-treatment in 46 patients with CLL who had initially responded to time-limited venetoclax-based regimens (64.2% had uMRD). The most frequent reasons for stopping treatment had been completing planned treatment (39.1%) or discontinuation due to toxicity (21.7%). Most patients were re-treated because of disease progression and re-treatment was started after a median 16-month interval. The observed overall response rate (ORR) on re-treatment was 79.5%.

The limitations of real-world studies in general include missing data and the intrinsic bias associated with retrospective data collection.[44] It is also important to note that the results of real-world studies may differ between countries due to the different time of drug approval and local guidelines for treatment approaches. For this reason, we reviewed clinical insights on venetoclax for CLL in the Italian context.

2 | METHODS

We searched Embase and PubMed databases with the terms: "chronic lymphocytic leukemia" [title/abstract] AND "venetoclax" (title/abstract) AND "Italy." We then hand-sorted the results to identify real-world studies. We searched the reference lists of identified reports, as well as published congress proceedings for additional studies (Figure 1).

3 | REAL-WORLD EVIDENCE ON VENETOCLAX IN CLL IN ITALY

The real-world experience with venetoclax developed in Italy has been described in three studies that confirm the effectiveness and tolerability of this agent in patients with R/R CLL and high-risk disease characteristics, many of whom had received prior BCRi treatment. The combination of venetoclax with obinutuzumab for the first-line treatment of patients with CLL has only recently been approved in Italy; we did not identify any real-world studies in this patient setting.

3.1 | Effectiveness of venetoclax

An ongoing retrospective/prospective cohort study (NCT04282811) conducted by Scarfò et al.[61] on behalf of the Italian Adult Hematological Diseases Group (GIMEMA) is assessing the outcomes of 124 Italian patients with R/R CLL treated with venetoclax-based regimens outside of clinical trials (Table 1). The planned follow-up of this study is 48 months from start of venetoclax treatment, and quality of life will be assessed in the prospective cohort.

Preliminary results show that del(17p) or *TP53* mutations were present in 32% of patients, and 77% had unmutated IGHV. Most patients (57%) received venetoclax monotherapy, whereas 40% received venetoclax plus rituximab. Venetoclax-based regimens provided responses in 85% of patients (Table 1). Compared with patients who had received the combination, patients who had received venetoclax monotherapy had a higher number of prior treatments (median three treatment lines vs. one), including ibrutinib (66% vs. 27%) and/or idelalisib plus rituximab (29% vs. 4%), and a higher proportion had elevated lactate dehydrogenase at baseline (64% vs. 38%).

Complete responses were significantly more frequent in patients receiving venetoclax plus rituximab compared with venetoclax monotherapy (57% vs. 30%, $p = 0.011$); however, the ORR

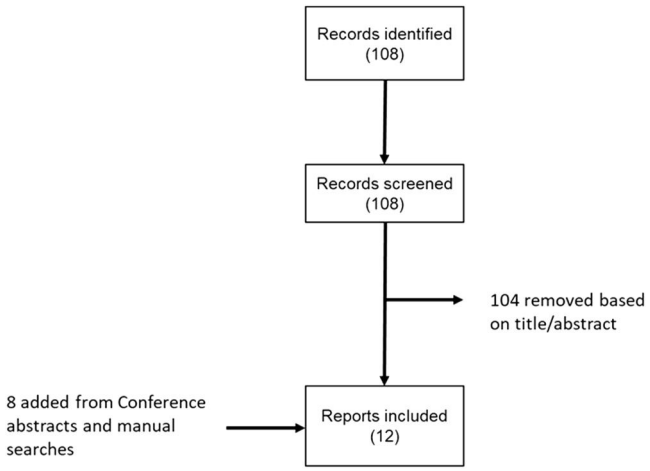

FIGURE 1 Records identified and included.[61–72]

was not significantly different between these groups (83% vs. 88%). Median (range) time to best response was 3.9 (0.6–30.5) months. Patients previously exposed to ibrutinib showed shorter 12-month PFS compared with ibrutinib-naïve patients (75% vs. 89%, $p = 0.005$).

In another Italian real-world study, Morelli et al.[62] conducted a retrospective analysis of the safety and efficacy of venetoclax monotherapy in 38 patients (median age 66 years, median follow-up 20 months). Two-thirds of these patients had high-risk genotypes; one-third had a high comorbidity burden (Cumulative Illness Rating Scale [CIRS] >6); two-thirds had received more than two treatments before venetoclax. After 12 months, PFS and OS were 62% and 63%, respectively. The ORR was 75%, of which 25% were complete responses. Responses were comparable between patients with high-risk and standard-risk disease; however, outcomes were more

TABLE 1 Outcomes with venetoclax in previously treated patients with CLL in the Italian real-world setting.

Characteristic	Innocenti et al. 2019[63] venetoclax	Morelli et al. 2020[62] venetoclax	Scarfo et al. 2021[61] venetoclax + rituximab
Patients, *n*	76	38	124
Median age, years	-	66	70 (range 44–91)
Number of prior therapies	Median 4	68% with >2	Median 2 (range 1–8)
Prior BCRi, *n* (%)			
Any	76 (100%)	30 (79%)	71 (57%)
1 BCRi	52 (68%)	25 (66%)	-
2 BCRi	24 (32%)	5 (13%)	-
Median follow-up, months	-	20	13.7 (range 0–41.9)
ORR	66%	75%	85% (95% CI 76–91)
12-month PFS			82% (95% CI 74–90)
venetoclax	64%	62%	30%
venetoclax + rituximab	-	-	57%
12-month OS			83% (95% CI 76–91)
venetoclax	78%	63%	83%
venetoclax + rituximab	-	-	88%
CLL risk characteristics			
17p-/TP53 disruption	–	–	40 (32%)
17p-/TP53 disruption/11q-	–	65%	–
Unmutated IGHV	–	85%	96 (77%)
Hematological toxicity			
Total (any grade)	–	–	99 (80%)
Grade1–2	–	–	25 (20%)
Grade3–4	–	–	74 (60%)
Requiring dose reduction	–	5 (6.6%)	–
Discontinuation for any AE	19 (25%)		7 (5.6%)
Tumor lysis syndrome	–	None	2 (1.6%)

favorable in patients who had received only one previous BCRi treatment.

Innocenti et al.[63] carried out a multicenter retrospective analysis evaluating PFS and OS in 76 patients who received venetoclax monotherapy after one ($n = 52$) or two ($n = 24$) lines of treatment with a BCRi (median four lines of previous therapy before initiating venetoclax). The reason for discontinuing prior BCRi influenced the rate of responses with subsequent venetoclax treatment. Patients who discontinued prior treatment with BTKi because of AEs had a significantly higher ORR with venetoclax compared with those who had discontinued due to disease progression (91% vs. 49%, $p = 0.03$); 12-month PFS and OS were also significantly better in patients who discontinued due to AEs (PFS 84% vs. 45%, $p = 0.003$; OS 93% vs. 62%, $p = 0.028$). Patients who received venetoclax after two prior BCRi had the lowest 12-month PFS rates.

3.2 | Safety

In the study by Scarfò et al.,[61] venetoclax-based regimens were well tolerated, with the most frequent AE of any grade being neutropenia, which occurred in 80% of patients and was grade 3–4 in 62% of cases. Of 113 AEs of any grade, 52 were grade 3, and 28 were grade 4. Seven patients discontinued venetoclax due to AEs, and 11 patients due to disease progression, including three cases of Richter's transformations. The median time to discontinuation was 4.1 months (range: 0.4–10.8). During the dose-escalation phase, one patient experienced clinical TLS that resolved without sequelae, while two had laboratory TLS.

In the study by Morelli et al.,[62] hematological toxicity requiring a dose reduction had occurred in 5 of 38 patients at a median follow-up of 20 months. There were no reported instances of extra-hematological toxicities and no instances of TLS during the dose-escalation phase.

3.3 | Patient profile: The evolving concept of fitness

The mean age at diagnosis of CLL is 72 years [1]; therefore, patient fitness may influence the ability to tolerate the full-dose treatment required for optimal outcomes. Comorbidities and advanced age can present a challenge to treating CLL with a chemotherapy-containing regimen such as CIT. Older adults may tolerate combinations with less intense chemotherapy components better[73]; however, these combinations may be less effective in the long term. Regarding targeted therapy, the role of patient fitness in treatment decisions is evolving.[74] BTKi and BCL2i, while not devoid of adverse effects, are better tolerated than chemotherapy-containing regimens. In addition, targeted agents are more effective than CIT,[40,42,75,76] and also for treating unfit patients.[42] In a retrospective cohort of 158 patients treated with venetoclax monotherapy at 14 Italian centers, Frustaci et al.[64] analyzed the influence of age (<65 years vs. ≥65 years) and fitness on patient management and outcomes. Fitness was defined in terms of CIRS score (≤6 vs. >6), presence of major comorbidities, Eastern Cooperative Oncology Group performance status (ECOG PS; 0–1 vs. >1), renal function (creatinine clearance <30 mL/min vs. ≥30 mL/min), Charlson Comorbidity Index (<2 vs. ≥2), the presence of baseline neutropenia, and concomitant medications. Outcomes included treatment discontinuation due to toxicity, permanent dose reductions, PFS, and OS.

None of the baseline parameters considered had an influence on TLS development or treatment management. Performance status (ECOG PS > 1), was the only pretreatment factor significantly associated with survival while on venetoclax at univariate analysis, confirming its independent role only on event-free survival (EFS) and OS. Although permanent discontinuation due to toxicity was detrimental for all survival outcomes, neither permanent dose reduction nor venetoclax interruption >7 days led to worse PFS, EFS, or OS. Age and comorbidities were not predictive factors, and the number and types of concomitant medications did not influence treatment outcomes. In multivariate analysis, ECOG PS was the only fitness-related factor that independently influenced outcomes. Thus, none of the parameters that traditionally influence treatment choices appeared to influence outcomes with venetoclax.

3.4 | Impact of COVID-19 on patients with CLL

The COVID-19 pandemic has created enormous challenges for healthcare professionals, especially in the management of patients with hematological disorders associated with immunodeficiency.[77] Multiple immune defects are present in CLL patients and are associated with an increased risk of infections,[78] and a reduced response to vaccines.[79] The two largest studies that have evaluated the clinical impact of COVID-19 on patients with CLL analyzed the outcomes of nearly 400 patients.[65,80] Most of the treated patients were receiving BCRi (105/388) at the time of COVID-19, and 26/388 patients were on venetoclax-based regimens. In the study by Mato et al.,[80] previously treated patients and those in clinical observation had similar COVID-19-related hospital admission rates (89% vs. 90%), intensive care unit admission (35% vs. 36%), and mortality rates (37% vs. 32%).

Molica et al.[66] conducted a survey in five regions in South-Central Italy (Calabria, Campania, Puglia, Sicily, and Umbria) to define the clinical management and the prevalence/severity of COVID-19 among 124 patients with R/R CLL treated with the standard venetoclax plus rituximab regimen between February 1 and 31 December 2020. Adherence to the treatment regimen was reported in 71% of patients, with 29% of patients receiving modified regimens mainly because of grade 3 neutropenia. Modifications consisted of transient interruption of venetoclax (22%), dose reduction (48%), or delay of rituximab infusion (30%). Only two physicians (8.3%) reported modifying treatment due to the concern over infection risk. COVID-19 did cause changes to the monitoring strategy for patients with CLL who were receiving a treatment that required clinical visits, included testing before starting the ramp-up with venetoclax and before each rituximab infusion; however,

testing for SARS-CoV-2 allowed CLL therapy to continue without interruption. Two patients developed symptomatic COVID-19 infections (1.6%) requiring intensive care unit admission and oxygen therapy; one died.

Cuneo et al.[67] assessed the prevalence of SARS-CoV-2 infection during the first wave of the COVID-19 pandemic in a cohort of 9330 patients with CLL across 33 Italian centers, finding 47 infections (0.5%) as of 15 April 2020. This was higher than the national prevalence of 0.27%, but the difference was attributed to selection bias for testing. Data from this study revealed the impact of COVID-19 on patient management and treatment choices during that period, suggesting that reduced access to laboratory services during the early phase of the pandemic had hampered COVID-19 diagnosis, prognosis, and monitoring. This informed strategies for providing the best therapy while protecting patients and medical personnel.

A large tertiary hospital in Lombardy, Italy, reported their strategy for successfully navigating the early phase of the pandemic.[68] Measures included deferral of non-urgent outpatient visits, a shift to telemedicine contacts where possible, and home delivery of hospital-distributed drugs to ensure continuity of care for hematology patients.

Reda et al.[69] reported their experience in Lombardy, Italy during the first wave of the COVID-19 pandemic with SARS-CoV-2 infection prevalence and outcomes among 2902 patients with CLL, of whom 337 (12%) were receiving treatment (278 with ibrutinib, 50 with venetoclax, and 9 with idelalisib). Confirmed COVID-19 infections were reported in 23 patients (0.8%). Of these, seven were treatment-naïve, eight were previously treated but off therapy, and eight were receiving targeted therapy (four with ibrutinib, three with venetoclax, and one with idelalisib). One death occurred in a heavily treated comorbid patient receiving ibrutinib.

3.5 | Other real-world cases in CLL

Several real-world case reports have been described that demonstrated the efficacy of venetoclax in CLL and concomitant diseases.

3.5.1 | Central nervous system involvement

Central nervous system (CNS) involvement is rare in CLL, occurring in <1% of patients, and most reported CNS symptoms have other etiologies [81]; however, Reda et al.[70] described a heavily pretreated CLL patient with CNS involvement characterized by atypical lymphocytes in the cerebrospinal fluid (CSF), periventricular lesions, and meningeal involvement at L4–L5. The authors demonstrated that venetoclax crosses the blood–brain barrier and penetrates CSF. The patient responded after 1 month to treatment with oral venetoclax plus intrathecal chemotherapy with cytarabine plus methotrexate. Therapeutic concentrations of venetoclax were detected in CSF during treatment, with peak and trough concentrations of 2.8 and 1.5 ng/mL, respectively. Suggesting that venetoclax may be effective in CLL cases with CNS involvement.

3.5.2 | Acquired von Willebrand syndrome

Acquired von Willebrand syndrome is a rare condition that has been observed in patients with autoimmune or neoplastic disorders, including CLL.[82] Innocenti et al.[71] described a heavily pretreated patient with CLL with no medical or family history of bleeding disorders who developed acquired von Willebrand syndrome. The patient achieved a complete (uMRD) response with venetoclax that was associated with normalization of coagulation parameters.

3.5.3 | Polyneuropathy with anti-MAG antibodies

Briani et al.[72] recently reported that venetoclax plus rituximab was active in a patient with wild-type MYD88 polyneuropathy and antibodies to myelin-associated glycoprotein (MAG). A 62-year-old woman with CLL and monoclonal IgM/K protein had experienced anti-MAG antibody neuropathy for several years. Anti-MAG antibody neuropathy is the most common IgM paraproteinemic neuropathy, and is characterized by sensory ataxic gait and upper limbs tremor, with motor involvement occurring late in the disease course.[72] After 12 months of treatment, IgM levels decreased, paraprotein became undetectable and the anti-MAG antibody titer decreased. The patient regained the ability to walk independently.

3.5.4 | Experience addressing hematological complications of CLL in the Italian setting

Other autoimmune conditions associated with CLL include autoimmune hemolytic anemia,[83] and autoimmune cytopenias (AICs).[84] In Italy, Vitale et al.[85] assessed the incidence and management of pre-existing and treatment-emergent AICs during therapy with targeted drugs in a large retrospective series of patients with CLL (n = 100 treated with venetoclax; median age 70 years [range: 44–84]; median number of previous treatments two [range: 0–8]). Venetoclax was administered as monotherapy in 88% and in association with an anti-CD20 agent in the rest, most patients were heavily pretreated. After a median follow-up of 14 months (range: 1–70 months) in the venetoclax group, the ORR was 78%, with a partial response rate of 67% and a complete response rate of 11%. Consistent with previous reports,[86] most treatment-emergent AICs occurred in patients with high-risk disease characteristics. Treatment-emergent AICs occurred in about 7% of patients who received venetoclax, a rate higher than that observed in patients treated with other CLL-targeted therapies (7% vs. 1%; $p \leq 0.001$), likely due to patient characteristics. The results suggest that targeted treatments may not increase the risk of AIC.[87]

4 | CONCLUSIONS

In Italy, venetoclax was approved for CLL as monotherapy in August 2017, and initially was used primarily in heavily pretreated patients. Therefore, the early real-world experience that we report focuses on venetoclax monotherapy in heavily pretreated patients, mainly those previously treated with BCRi. The combination with rituximab was reimbursed by the Italian health system from 2019, resulting in its positioning as second-line treatment; moreover, the introduction of this combination just before the start of the COVID-19 pandemic may have resulted in its underutilization due to concern over the use of B cell depleting agents. Overall, the responses and tolerance to venetoclax observed in the Italian real-world setting confirm the tolerability and effectiveness of venetoclax regimens in high-risk patients.[40,88]

In line with the results of controlled clinical trials,[89] the real-world data reported by Scarfò et al.[61] showed more complete responses among patients with R/R CLL who had received the venetoclax plus rituximab combination, compared with venetoclax monotherapy, although patients receiving venetoclax monotherapy were more heavily pretreated and had more high-risk features. As observed in previously published studies,[55,90] the Italian real-world study by Innocenti et al.[63] revealed that higher disease burden and progression with a prior BTKi were associated with poorer outcomes in patients treated with venetoclax.

Venetoclax was well tolerated with low discontinuation rates. Among factors such as age and components of fitness, only ECOG-PS had a significant impact on the outcomes of patients treated with venetoclax.

The low incidence of TLS during the dose-escalation phase of the reviewed studies suggests that, despite the lack of patient selection and close monitoring associated with clinical trials, TLS prophylaxis measures and monitoring appear to be effective also in routine practice.

The available RWE on first-line treatment with venetoclax in Italy is very limited due to the short time since approval; however, our findings suggest that venetoclax is effective when used early in the treatment algorithm for R/R CLL.

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CONFLICT OF INTEREST STATEMENT

Paola Finsinger, Morena Caira, Emilia Iannella, Silvia Schifano, and Benedetta Neri are AbbVie employees and may own AbbVie stocks/options. Luca Laurenti has received honoraria from Janssen, Abbvie, AstraZeneca, Beigene. Research funding from AbbVie, Roche. Lydia Scarfò received honoraria for advisory boards (AbbVie, AstraZeneca, BeiGene, and Janssen), for speaker bureau (Octapharma) and travel grants (Beigene and Janssen). Anna Maria Frustaci received honoraria for advisory boards (AbbVie, AstraZeneca, Beigene, and Janssen) and travel grants (BeiGene, Janssen, and AbbVie). Alessandro Sanna received honoraria for AbbVie, AstraZeneca, Janssen, Takeda. Stefano Molica received honoraria for advisory boards (AbbVie, AstraZeneca, and Janssen) and consulting (AbbVie, AstraZeneca, and Janssen). Francesca Romana Mauro received honoraria for speakers' bureaus, (AbbVie, AstraZeneca, and Janssen) and support for attending meetings (AbbVie and Janssen).

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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PEER REVIEW

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