# Rethinking the feasibility and safety of venetoclax-obinutuzumab in chronic lymphocytic leukemia: non-traditional factors may play a role in clinical practice

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## Abstract

The concept of fitness to receive treatment with novel agents in chronic lymphocytic leukemia (CLL) remains debated. Comorbidities and treatment-related logistics are increasingly recognized as key factors in treatment feasibility. Venetoclax-obinutuzumab (VO) has demonstrated efficacy in both fit and unfit patients in clinical trials, yet real-world data remain limited. This retrospective, multicenter study analyzed disease- and patient-related factors affecting VO management and outcomes in 271 patients. Fitness was assessed using comorbidity indices (CLL-CI, CIRS, CCI), Eastern Cooperative Oncology Group performance status, and caregiver need. Adverse events (AE) and treatment modifications were evaluated across four treatment phases. The median age of the patients was 66 years (19% ≥75 years old); 83% had comorbidities, 34% required polypharmacy, and 10% needed caregiver support. Overall, 96% completed debulking, 89% the full regimen, while 11% discontinued due to toxicity (Tox-DTD). Grade ≥3 AE occurred in 55%, tumor lysis syndrome in 6%, severe infusion-related reactions in 5%. Overall, 3.3% of the patients died during treatment. Unfit patients did not show a significantly higher risk of treatment modifications due to AE. Dose adjustments were more frequent during debulking. None of the validated fitness scores predicted treatment feasibility or Tox-DTD. Global feasibility was impacted by age ($P$=0.002), prior malignancies ($P$=0.003), prolonged steroid pre-treatment ($P$<0.001), and baseline thrombocytopenia ($P$=0.013). Tox-DTD correlated with caregiver need ($P$=0.029), endocrine comorbidities ($P$=0.025), prior malignancies ($P$=0.002), hypogammaglobulinemia ($P$=0.003), high lymphocyte count ($P$=0.034), and prolonged steroid pre-treatment ($P$=0.006). In conclusion, this study confirms the feasibility of VO treatment in CLL clinical practice, highlighting the role of traditionally overlooked factors that ultimately do have an impact.

## Introduction

The chronic lymphocytic leukemia (CLL) treatment landscape has changed radically in the last years with an increasing number of trials focusing on elderly or unfit patients, typically poorly represented in previous studies.[1]
The venetoclax-obinutuzumab (VO) regimen was approved for treatment-naïve disease based on the results of the pivotal CLL14 trial addressed at patients with coexisting conditions, with a median age of 72 years and median Cumulative Illness Rating Scale (CIRS) score of 8.[2-6] The efficacy of the combination was further confirmed even in the fit population enrolled in the CLL13 trial.[7,8] According to the recent European Society of Medical Oncology (ESMO) guidelines, time-limited venetoclax-based combinations are preferred over continuous treatment with Bruton tyrosine kinase (BTK) inhibitors when there is equal evidence for different treatment options.[9] Hence, such combinations are strongly recommended with a high level of evidence for both young and elderly patients.
Differently from common practice, in clinical trials patients are selected based on prespecified inclusion and exclusion criteria; furthermore, to maintain good patient retention, treatment management is standardized. The VO schedule has several limitations in clinical practice including the need for multiple hospital accesses for administration of the monoclonal antibody and venetoclax ramp-up. Moreover, obinutuzumab, administered as a lead-in drug in patients often presenting with high disease burden, may lead to infusion-related reactions (IRR) or tumor lysis syndrome (TLS).[10] Finally, patients in clinical practice often have comorbidities that can affect treatment feasibility.
Although there is a general consensus on considering fitness as one of the key factors influencing treatment choices,[11,12] no reliable tool currently exists to categorize patients' fitness in CLL, even more so after the introduction of targeted agents.
To our knowledge, limited published data on the VO combination in the real-world setting are available in the literature.[13,14] With the aim of evaluating the reproducibility of VO data in clinical practice, and of identifying patients' and disease characteristics that may impair treatment administration and outcomes, we conducted a retrospective multicenter study on patients receiving VO during the first year after its approval in Italy.

## Methods

The population of this study included consecutive patients treated with VO outside clinical trials in 55 Italian centers from May 2022 to July 2023 (first year of VO approval in Italy).

The study was approved by the institutional-review board of each participating institution in accordance with the Declaration of Helsinki. All patients signed informed consent. All participant centers reported the total number of consecutive patients treated outside of clinical trials in their institution, the type of treatment administered and the key reasons driving the choice of treatment. All patients who received at least one dose of either venetoclax or obinutuzumab were considered. Data were collected from medical records of each participating center through a database, they were reviewed to determine patients' and disease characteristics at the time of treatment initiation, and are listed in *Online Supplementary Table S1*. The data cut-off for the whole population was set at September 2024 to allow all patients to complete the whole VO treatment program and for the response evaluation to be performed. Comorbidities were evaluated at the time of VO initiation and the CLL Comorbidity Index (CLL-CI),[15] Charlson Comorbidity Index (CCI)[16] and CIRS[17] score were calculated. As in other studies, medical conditions that were deemed to be complications of CLL (e.g., anemia, thrombocytopenia, and splenomegaly) were not included as part of the total comorbidity scores. Patients were considered as having a high comorbidity burden if they had a total CIRS score >6, CCI >2, or CLL-CI ≥2. Patients were also assessed for the presence of CIRS3+, defined as a severe impairment (score 3 or 4) in any single organ system. Data on concomitant medications, CYP3A4 inhibitors or inducers, P-glycoprotein inhibitors, anticoagulants, antiplatelets and polypharmacy (>3 concomitant drugs other than CLL-directed therapy or prophylactic treatment) were recorded. Among the anamnestic data, we evaluated the need for a caregiver, defined as the presence of a person who assists with activities of daily living or instrumental activities of daily living, and whose role is essential for maintaining the patient's quality of life and well-being.

The primary outcome of the study was to describe the rate and impact of patients' baseline characteristics, including patients' fitness (defined as comorbidities, Eastern Cooperative Oncology Group performance status, CIRS score, CIRS3+, CCI, CLL-CI), need for a caregiver, and disease characteristics on definitive treatment discontinuation due to toxicity (Tox-DTD). Secondary outcomes includedreasons for VO choice over continuous BTK inhibitors, schedule modifications, rate and impact of baseline features on treatment feasibility (Tox-DTD, permanent dose reductions, administration of <9 planned obinutuzumab infusions), temporary interruptions and dose reductions, and severe (grade ≥3) adverse events (AE) according to CTCAE 5.0. Efficacy was also evaluated in terms of overall response rate, complete remission rate, progression-free survival and overall survival. Finally, patients were classified as CLL13-like and CLL14-like according to inclusion criteria of these trials to assess any difference between fit and unfit patients.

To assess variations in safety and feasibility during treatment, we identified four time periods: (i) the debulking phase: first 56 days, cycles 1 and 2 (obinutuzumab and venetoclax ramp-up); (ii) the combination phase: 112 days from cycle 3 to cycle 6 (administration of venetoclax and obinutuzumab at target dose); (iii) the maintenance phase: 168 days from cycle 7 to end of treatment (venetoclax monotherapy); and (iv) the post-treatment phase: from end of treatment to the end of follow-up.

Categorical variables were analyzed using $\chi^2$ or Fisher exact tests, and continuous variables with Mann-Whitney or Wilcoxon signed-rank tests. Incidence rates for AE were calculated and compared using Poisson regression. Logistic regression models were employed for categorical variables in both univariable and multivariable analyses. Survival and time-to-event outcomes were analyzed using the Kaplan-Meier method and Cox proportional hazards models. Multivariable regression models were constructed by including all clinically significant characteristics associated with a *P* value <0.1 in univariable analysis. A backward iterative elimination process was applied to remove the least significant variables, retaining only those with a *P* value <0.05 in the final model. Given the retrospective nature of the data, all analyses were exploratory, and no adjustments for a type I error were made. A *P* value <0.05 was considered statistically significant, except during the covariate selection process described above. Missing data were handled using multiple imputation by chained equations. All statistical analyses were conducted using R version 4.3.1.

# Results

## Patients' and disease characteristics

During the study period, 939 patients with active CLL, as defined by International Working Group CLL criteria (iwCLL),[18] were treated. Of these, 271 received at least one dose of any VO study drug, representing our study population. The decision to use VO was driven primarily by: disease biology (46%), clinicians' preference for fixed-duration therapy (33%), comorbidities contraindicating BTK inhibitors (14%) and patients' choice (7%). The median follow-up in the study was 17.3 months (interquartile region [IQR], 12-19.97). The baseline patients' and disease characteristics of the 271 subjects treated with VO, stratified according to CLL13- and CLL14-like populations, are summarized in Table 1. The median age at VO initiation was 66 years (range, 34-89). Fifty-one patients (19%) were older than 75 years. At least one comorbidity was recorded in 226 patients (83%), with the most frequentl being hypertension (39%), cardiac (22.5%) and vascular disease (20%). Details on comorbidities are reported in *Online Supplementary Table S2*. The median CIRS score was 4 (IQR, 2-6; maximum 14), with 56 (21%) patients scoring >6 and 48 (18%) having CIRS3+. The

**Table 1.** Baseline characteristics of the study population, stratified by treatment groups (CLL13-like *vs.* CLL14-like).

| Characteristics | Total N=271 | CLL13-like N=138 (50.9%) | CLL14-like N=133 (49.1%) | *P* |
|---|---|---|---|---|
| Male sex, N (%) | 179 (66.1) | 99 (71.7) | 80 (60.2) | 0.059 |
| Age, years, median (IQR) | 65.8 (58.0-73.4) | 59.9 (54.5-66.4) | 72.7 (64.0-76.4) | <0.001 |
| Need for a caregiver, N (%) | 28 (10.3) | 4 (2.9) | 24 (18.0) | <0.001 |
| ECOG-PS ≥2, N (%) | 17 (6.3) | 2 (1.4) | 15 (11.3) | 0.002 |
| CIRS, median (IQR) | 4.0 (2.0-6.0) | 2.0 (0.2-4.0) | 5.0 (3.0-9.0) | <0.001 |
| CIRS3+, N (%) | 48 (17.7) | 10 (7.2) | 38 (28.6) | <0.001 |
| CIRS>6 and CIRS3+, N (%) | 33 (12.2) | 0 | 33 (24.8) | <0.001 |
| CCI, median (IQR) | 4.0 (3.0-5.0) | 3.0 (2.0-4.0) | 5.0 (3.0-6.0) | <0.001 |
| CLL-CI risk category, N (%)<br>low<br>intermediate<br>high | <br>178 (65.7)<br>63 (23.2)<br>30 (11.1) | <br>103 (74.6)<br>29 (21.0)<br>6 (4.3) | <br>5 (56.4)<br>34 (25.6)<br>24 (18.0) | <0.001 |
| Nephropathy, N (%) | 15 (5.5) | 0 (0.0) | 15 (11.3) | <0.001 |
| Upper GI disorders, N (%) | 25 (9.2) | 4 (2.9) | 21 (15.8) | 0.001 |
| Endocrine disorders, N (%) | 47 (17.3) | 16 (11.6) | 31 (23.3) | 0.017 |
| Vascular disorders, N (%) | 53 (19.6) | 21 (15.2) | 32 (24.1) | 0.093 |
| Cardiac comorbidities, N (%) | 61 (22.5) | 17 (12.3) | 44 (33.1) | <0.001 |
| Hypertension, N (%) | 107 (39.5) | 38 (27.5) | 69 (51.9) | <0.001 |
| N of concomitant medications, N (%) | 1.0 (0.0-3.0) | 1.0 (0.0-2.0) | 3.0 (1.0-5.0) | <0.001 |
| Polypharmacy, N (%) | 91 (33.6) | 23 (16.7) | 68 (51.1) | <0.001 |
| Venetoclax-drug interaction, N (%) | 31 (11.4) | 6 (4.3) | 25 (18.8) | <0.001 |
| Proton pump inhibitors, N (%) | 60 (22.1) | 17 (12.3) | 43 (32.3) | <0.001 |
| Anticoagulant, N (%) | 26 (9.6) | 7 (5.1) | 19 (14.3) | 0.018 |
| Antiplatelet agents, N (%) | 38 (14.0) | 7 (5.1) | 31 (23.3) | <0.001 |
| Creatinine clearance, mL/min, median (IQR) | 78.0 (62.0-91.7) | 90.0 (81.0-98.8) | 62.0 (52.0-68.0) | <0.001 |
| U-IGHV, N (%)<br>NA, N (%) | 130 (48.0)<br>17 (6.3) | 74 (53.6)<br>9 (6.5) | 56 (42.1)<br>8 (6.0) | 0.133 |
| Döhner FISH, N=243, N (%)<br>13q deletion<br>negative<br>trisomy 12<br>11q deletion<br>17p deletion | <br>83 (34.2)<br>82 (33.7)<br>46 (18.9)<br>24 (9.9)<br>8 (3.3) | <br>38 (30.4)<br>49 (39.2)<br>19 (15.2)<br>14 (11.2)<br>5 (4.0) | <br>45 (38.1)<br>33 (27.9)<br>27 (22.9)<br>10 (8.5)<br>3 (2.5) | 0.194 |
| *TP53* mutations, N (%) | 5 (1.8) | 2 (1.4) | 3 (2.3) | 0.946 |
| del(17p) and/or *TP53* mutations, N (%) | 10 (3.7) | 5 (3.7) | 5 (3.8) | 0.952 |
| Complex karyotype, N=97*, N (%) | 7 (7.2) | 5 (10.9) | 2 (3.9) | 0.354 |
| Rai stage at venetoclax start, N (%)<br>0-II<br>III-IV | <br>121 (44.6)<br>150 (55.4) | <br>69 (50.0)<br>69 (50.0 | <br>52 (39.1)<br>81 (60.9) | 0.071 |
| Hemoglobin, g/dL, median (IQR) | 11.8 (10.0-13.2) | 12.1 (10.1-13.5) | 11.3 (9.9-12.8) | 0.022 |
| ANC, $10^9$/L, median (IQR) | 4.1 (2.76-6.38) | 4.3 (2.93-6.75) | 3.89 (2.59-5.9) | 0.079 |
| ALC, $10^9$/L, median (IQR) | 47.58 (17.85-10.80) | 55.0 (17.0-10.84) | 41.3 (19.0-10.6) | 0.528 |
| Platelets, $10^9$/L, median (IQR) | 145 (96-198) | 151 (104-194) | 140 (95-207) | 0.875 |
| TLS risk, N (%)<br>low<br>medium<br>high | <br>45 (16.6)<br>164 (60.5)<br>62 (22.9) | <br>23 (16.7)<br>87 (63.0)<br>28 (20.3) | <br>22 (16.5)<br>77 (57.9)<br>34 (25.6) | 0.571 |
| Lymph node >5 cm, N (%) | 91 (33.6) | 42 (30.4) | 49(36.8) | 0.323 |
| Lymph node >10 cm, N (%) | 19 (7.0) | 11 (8.0) | 8 (6.0) | 0.695 |
| Splenic bulky disease, N (%) | 62 (22.9) | 34 (24.6) | 28 (21.1) | 0.577 |
| IgG, mg/dL, median (IQR) | 720 (501-925) | 742 (544-932) | 690 (487-924) | 0.283 |

Continued on following page.

Data for categorical variables are presented as numbers and percentages, those for continuous variables as medians with interquartile ranges. *Complex karyotype defined as ≥3 abnormalities. IQR: interquartile range; CIRS, Cumulative Illness Rating Scale; CCI: Charlson Comorbidity Index; CLL-CI: CLL Comorbidity Index; GI: gastrointestinal; U-IGHV: unmutated immunoglobulin heavy chain variable region; NA: not available; Döhner FISH: fluorescence *in situ* hybridization classification by Döhner *et al.*; ANC: absolute neutrophil count; ALC: absolute lymphocyte count; TLS: tumor lysis syndrome; Polypharmacy: >3 concurrent medications; IgG: immunoglobulin G.

organ system mainly involved by CIRS3+ was the cardiac one (24/48 cases, 50%), with a history of ischemic cardiomyopathy and cardiac failure representing the most common reasons for severe impairment. The median CCI was 4 (IQR, 3-5; maximum 13). According to the CLL-CI, 30 (11%) patients were classified as high risk. Seventeen (6%) patients had an Eastern Cooperative Oncology Group performance status score ≥2, and 28 (10%) required caregiver support for treatment. The median creatinine clearance was 77 mL/min (IQR, 62-91; minimum 23).

A total of 183 patients (67.5%) were on concomitant systemic medications, with polypharmacy in 91 (34%). Fourteen (5%) were receiving drugs that interfere strongly with venetoclax, 26 (10%) were on anticoagulants (mainly direct oral anticoagulants), and 38 (14%) were taking antiplatelet agents. At the time of VO initiation, 14 patients (5%) were receiving steroids for reasons other than CLL or immune cytopenia-directed therapy.

Regarding disease characteristics, 150 (55%) were in Rai stage III-IV. The largest lymph node was >5 cm in 91 cases (34%) and >10 cm in 19 (7%); 62 (23%) had bulky splenic disease (spleen enlarged ≥6 cm below the left costal margin). The risk of TLS was high in 62 patients (23%).

Overall, 130 patients (48%) had unmutated IGHV. Subset stereotypy was evaluated in 105 patients, with three identified as having subset #2. A total of ten patients (3.7%) carried del(17p)/*TP53* aberrations.

When stratifying patients according to VO clinical trial inclusion criteria, 138 (51%) exhibited CLL13-like characteristics, and 133 (49%) CLL14-like. While patients' fitness, age, concomitant medications and need for a caregiver were significantly different between the two groups, biological and clinical disease characteristics were comparable (Table 1).

Of the 271 patients starting VO, 259 (96%) completed the debulking phase, 253 (93%) the combination phase and 242 (89%) the full treatment schedule. Overall, 29 (11%) patients definitively discontinued treatment, of whom nine (3%) died. An additional five (1.8%) patients died after the end of treatmemt. The patients' disposition in the trial is reported in Figure 1.

## Adverse event mitigation strategies

In accordance with the indication in the Summary of Product Characteristics for obinutuzumab, all patients received steroids for prophylaxis of IRR: methylprednisolone in 211 patients (78%) and dexamethasone in 60 (22%). The median prednisone-equivalent steroid dose was 1.39 mg/kg (IQR, 1.12-1.66; range, 0.29-3.33). With the aim of minimizing IRR, physicians decided to either postpone obinutuzumab infusion after completing venetoclax ramp-up (17 patients, 6.3%) or prolong steroid pre-treatment before the first obinutuzumab infusion (128 patients, 47%). The median pre-treatment dose of steroid (mainly prednisone) was 0.55 mg/kg (IQR, 0.35-0.79) and the pre-treatment steroid was given for a median of 7 days (IQR, 5-9); in 66 cases (24%)

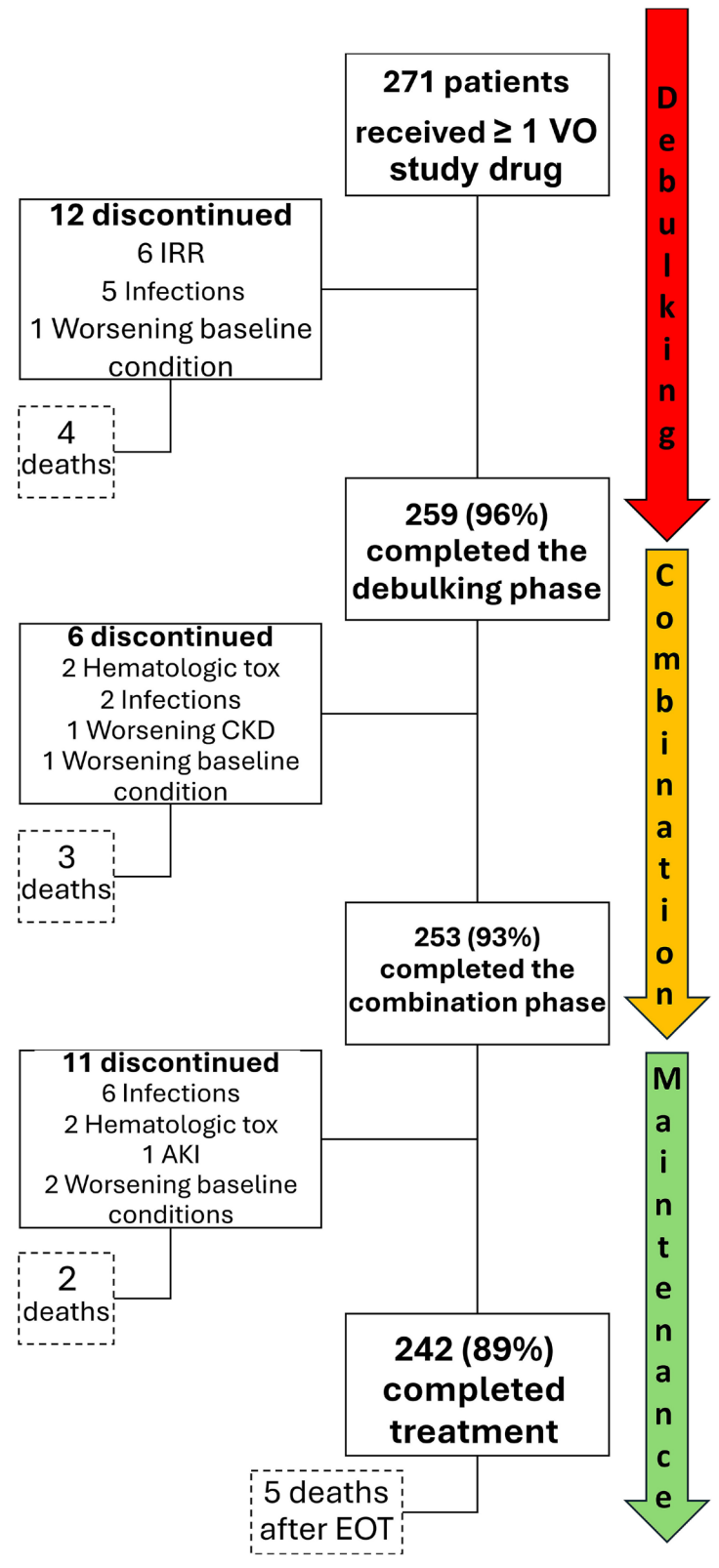



**Figure 1. Patients' disposition throughout the phases of treatment with venetoclax-obinutuzumab.** VO: venetoclax-obinutuzumab; IRR: infusion-related reaction; tox: toxicities; CKD: chronic kidney disease; AKI: acute kidney injury; EOT: end of treatment.

steroids were administered for more than 6 days.
All but seven patients (97.4%) received TLS prophylaxis, overlapping in some cases, with allopurinol/febuxostat (250, 92%), intravenous hydration (229, 84.5%) and rasburicase (104, 38%). A total of 27 patients (10%) were hospitalized for treatment initiation, including nine (33%) because of a high risk of TLS. Six of these 27 received venetoclax first. None of the patients undergoing obinutuzumab lead-in were subsequently hospitalized for venetoclax ramp-up.
Overall, 268 patients (99%) received antimicrobial prophylaxis to prevent herpes simplex virus or varicella-zoster virus reactivation (217 patients, 80%) and *Pneumocystis jirovecii* pneumonia (PJP) (261 patients, 96%). Hepatitis B status was assessed before treatment in all patients: 38 had occult hepatitis B infection and three were positive for HBsAg or HBV-DNA. All cases of occult hepatitis B infection and HBsAg/HBV-DNA positivity were treated with lamivudine or entecavir, as appropriate.

### Safety and adverse events

Overall, 148 patients (55%) experienced at least one grade ≥3 AE, with a total of 310 events and an overall exposure-adjusted AE incidence rate of 6.54/100 patient-months (95% confidence interval [95% CI]: 5.83-7.30). Of these, 35 patients (12.9%) were hospitalized due to AE with a median time of hospitalizazion of 8 days (range, 3-41 days). The main reason for hospitalization was pneumonia requiring intravenous antibiotic therapy. Nine (3.3%) patients died during treatment, seven due to infections (3 coronavirus disease 2019 [COVID-19] pneumonia; 1 *Acinetobacter spp*. sepsis, 1 *Aspergillus spp*. pneumonia, 1 PJP, 1 radiologically documented pneumonia), two due to worsening of baseline conditions. After the end of treatment, five (1.8%) additional deaths were observed: one due to COVID-19 pneumonia, two cases of radiologically documented pneumonia, one myocardial infarction and one of unknown cause. Most common grade ≥3 AE were neutropenia (32%), thrombocytopenia (16%) and infections (13%) (Table 2). The rate of severe AE was significantly higher during the debulking phase (1.08 events/100 patient-days) and decreased progressively in subsequent phases and after the end of treatment (Figure 2). Although in univariable analysis the CLL-14-like population, compared to the CLL-13 like population, had a higher risk of developing grade ≥3 AE and hematologic toxicity during the whole treatment (odds ratio [OR]=1.80, 95% CI: 1.11-2.93, *P*=0.017, and OR=1.77, 95% CI: 1.08-2.92, *P*=0.025), and neutropenia specifically during the debulking phase (OR=1.87, 95% CI: 1.10-3.20, *P*=0.021), these factors were not retained at multivariable analysis (Table 2).
TLS occurred in 16 patients (6%), including six clinical forms: 12 after the first obinutuzumab infusion and four while on venetoclax ramp-up. All cases of clinical TLS were related

**Table 2.** Grade ≥3 adverse events during treatment with venetoclax-obinutuzumab.

| Adverse events | Total, N (%) | CLL13-like group, N (%) | CLL14-like group, N (%) | *P* |
|---|---|---|---|---|
| Any AE ≥3 | 145 (53.5) | 64 (46.4) | 81 (60.9) | 0.023 |
| Hematologic | 100 (36.9) | 42 (30.4) | 58 (43.6) | 0.034 |
| Anemia | 5 (1.8) | 4 (2.9) | 1 (0.8) | 0.389 |
| Neutropenia | 87 (32.1) | 41 (29.7) | 46 (34.6) | 0.466 |
| Febrile neutropenia | 5 (1.8) | 2 (1.4) | 3 (2.3) | 0.967 |
| Thrombocytopenia | 43 (15.9) | 17 (12.3) | 26 (19.5) | 0.144 |
| Infections<br>COVID pneumonia<br>Non-COVID pneumonia<br>Sepsis/septic shock<br>Opportunistic | 36 (13.3)<br>16 (5.9)<br>12 (4.4)<br>9 (3.3)<br>6 (2.2) | 17 (12.3)<br>5 (3.6)<br>5 (3.6)<br>4 (2.9)<br>1 (0.7) | 19 (14.3)<br>11 (8.3)<br>7 (5.2)<br>5 (3.8)<br>5 (3.8) | 0.766 |
| Tumor lysis syndrome<br>Clinical<br>Laboratory | 16 (5.9)<br>6 (2.2)<br>10 (3.7) | 7 (5.1)<br>2 (1.4)<br>5 (3.6) | 9 (6.8)<br>4 (3.0)<br>5 (3.8) | 0.738 |
| IRR | 13 (4.8) | 7 (5.1) | 6 (4.5) | 1.000 |
| Cardiovascular* | 5 (1.8) | 2 (1.4) | 3 (2.3) | 0.967 |
| Lower GI** | 7 (2.6) | 2 (1.4) | 5 (3.8) | 0.415 |
| Other toxicities*** | 8 (3.0) | 3 (2.2) | 5 (3.8) | 0.680 |

*Cardiovascular: 2 pulmonary embolisms after the first obinutuzumab infusion, 2 acute coronary syndromes, 1 hypertension. **Lower gastrointestinal: 6 diarrhea, 1 intestinal volvulus. ***Other: 2 liver toxicity, 3 hyponatremia, 1 acute kidney injury, 1 osteoporosis fracture, 1 psychiatric illness. AE: adverse events; COVID: coronavirus disease 2019; IRR: infusion-related reaction; GI: gastrointestinal.

to obinutuzumab.

IRR of any grade occurred in 100 patients (37%), and in 13 (5%) patients were of grade ≥3. No IRR were noted in patients receiving venetoclax lead-in (Fisher exact test, *P*=0.003).

Any grade infection was observed in 82 patients (30%), being severe in 36 (13%). COVID-19 was the most reported infection, occurring in 31/82 (38%) with 52% of cases being grade 3-5. Sepsis or septic shock occurred in nine patients (11%). Six opportunistic infections were recorded: three cases of PJP (2 on cotrimoxazole prophylaxis), one cytomegalovirus reactivation, and two cases of aspergillosis. Two patients had reactivation of hepatitis B virus, one while on lamivudine, and the other one without evidence of occult hepatitis B infection.

Baseline factors influencing AE in the whole population in univariable analysis are summarized in *Online Supplementary Table S3*.

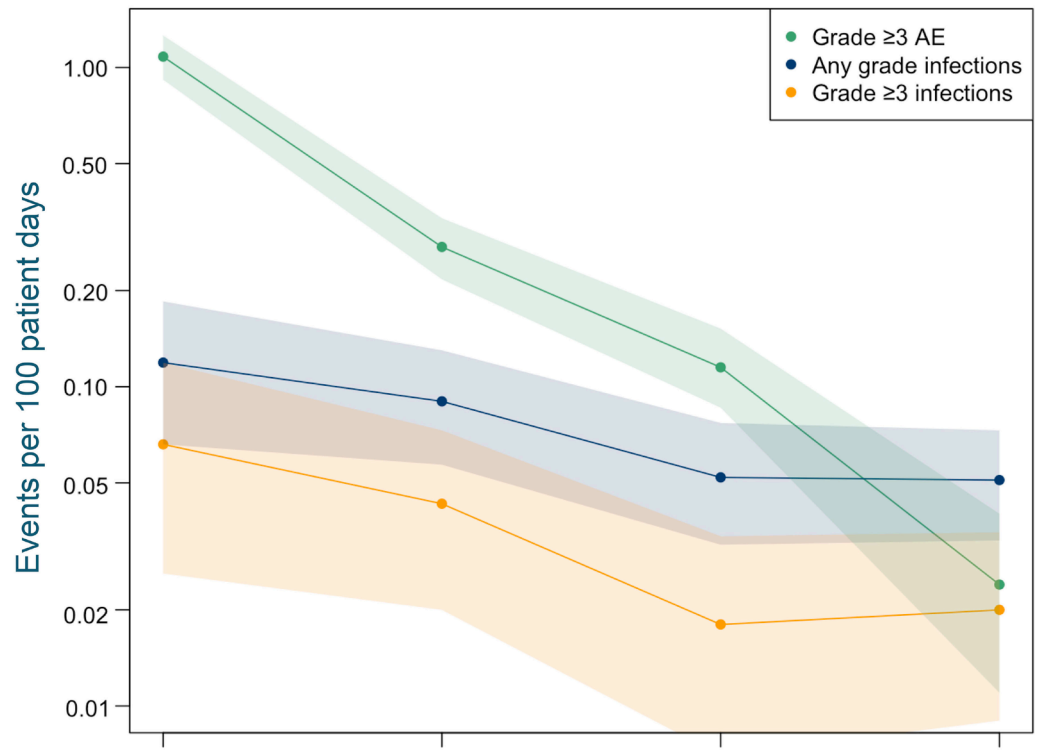
Results from multivariate analysis are shown in Table 3. According to patients' clinical and disease characteristics, neither age nor patients' fitness played a role in the development of severe AE. Instead, younger patients and those with major comorbidities more frequently had IRR (*P*=0.001 and *P*=0.004, respectively). High comorbidity burden and the need for a caregiver were significantly associated with an increased infection risk (*P*=0.019 and *P*=0.032, respectively). Treatment-emergent hematologic toxicity was associated with baseline anemia (*P*=0.006) and neutropenia (*P*=0.002). Tumor lysis syndrome risk was increased in patients with bulky adenopathies (*P*=0.001) or splenomegaly (*P*=0.015) and high CLL-CI (*P*=0.030). None of the biological baseline characteristics, including the presence of 11q deletion or trisomy 12, commonly associated with bulky disease had an impact on TLS development.

The administration of a weight-adjusted steroid dose >1.5 mg of prednisone or equivalent as obinutuzumab premedication significantly reduced the risk of IRR. While prolonged steroid pretreatment did not reduce the IRR risk, its use translated into a higher incidence of severe AE (*P*=0.042), hematologic toxicity (*P*=0.049) and infections (*P*=0.007).

## Feasibility and treatment modifications and discontinuations

The treatment schedule was modified *a priori* in 27 patients (10%): 17 started with venetoclax lead-in and ten omitted the obinutuzumab infusions on days 8 and 15 for logistic reasons.

Overall, dose adjustments due to AE occurred in 143 patients (53%). This proportion was higher during the debulking




| Summary table IR (95%CI) | Debulking | Combination | Maintenance | Post-Treatment | *P* |
|---|---|---|---|---|---|
| Grade ≥3 AE | 1.08 (0.92–1.26) | 0.27 (0.22–0.34) | 0.12 (0.09–0.15) | 0.015 (0.005–0.03) | <0.001 |
| Any-Grade Infections | 0.12 (0.07–0.185) | 0.09 (0.06–0.13) | 0.05 (0.03–0.08) | 0.05 (0.03–0.07) | 0.001 |
| Grade ≥3 Infections | 0.07 (0.03–0.12) | 0.04 (0.02–0.07) | 0.018 (0.007–0.03) | 0.02 (0.009–0.03) | 0.002 |

**Figure 2. Exposure-adjusted incidence rates of adverse events and infections.** The figure illustrates the incidence rates of adverse events per 100 patient-days across the four treatment phases: Debulking, Combination, Maintenance, and Post-Treatment. The three lines represent the incidence rates for all grade ≥3 adverse events, any-grade infections, and grade ≥3 infections, with shaded areas indicating 95% confidence intervals. Corresponding incidence rate values and 95% confidence intervals are summarized in the table below, along with the overall *P* value for trend to assess statistical significance over time. AE: adverse event; IR: incidence rate; 95% CI: 95% confidence interval.

phase (81/271 patients, 30%) and progressively decreased in the combination (60/259 patients, 23%) and maintenance (39/242 patients, 16%) phases.

Centers treating a higher number of patients were associated with increased feasibility of the debulking phase (OR=0.89 per each additional patient treated, 95% CI: 0.83-0.95, *P*=0.001). Baseline factors associated with treatment modifications and feasibility during the debulking phase in multivariable and univariable analyses are shown in *Online Supplementary Table S4.*

Overall, 90 (33%) patients required permanent treatment modifications. In 48 patients (18%), at least one obinutuzumab infusion was omitted, with a median number of six infusions delivered (IQR, 2-8). The dose of venetoclax was reduced in 51 patients (19%), permanently in 33 (12%), and temporarily discontinued in 74 patients (27%) with a median treatment interruption of 9.5 days (IQR, 5-20).

Tox-DTD occurred in 29 patients (11%) due to infections (7 COVID-19, 6 non-COVID), IRR (6 patients), acute kidney injury or worsening chronic kidney disease (2 patients), prolonged hematologic toxicity (4 patients), and worsening of baseline comorbid conditions (4 patients). Twelve (41%) of the cases of Tox-DTD occurred during the debulking phase, the majority after the first obinutuzumab infusion.

**Table 3.** Multivariable logistic regression models for selected adverse events.

| Baseline condition | Any AE ≥3 OR (95% CI) | TLS OR (95% CI) | IRR OR (95% CI) | Hematologic toxicity OR (95% CI) | Infections OR (95% CI) |
|---|---|---|---|---|---|
| Age >65 years | - | - | 0.34 (0.19-0.62) *P*<0.001 | - | - |
| Need for a caregiver | - | - | - | - | 2.85 (1.05-7.29) *P*=0.032 |
| ECOG-PS | - | - | - | - | - |
| CCI | - | - | - | - | - |
| CLL-CI risk: high | - | 4.21 (1.08-15.39) *P*=0.030 | - | - | - |
| CIRS >6 | - | - | - | - | 2.62 (1.15-5.83) *P*=0.019) |
| CIRS3+ | - | - | 2.99 (1.43-6.40) *P*=0.004 | - | - |
| Upper GI comorbidity | - | - | - | 2.63 (1.07-6.80) *P*=0.038 | - |
| Endocrine comorbidty | 2.11 (1.06-4.35) *P*=0.036 | - | - | 2.00 (1.00-4.02) *P*=0.048 | - |
| Steroid premedication dose | - | - | 0.36 (0.18-0.68) *P*=0.002 | - | - |
| N of days of steroids before obinutuzumab | 1.05 (1.01-1.10) *P*=0.042 | - | - | 1.02 (1.00-1.05) *P*=0.045 | 1.02 (1.01-1.04) *P*=0.007) |
| Hemoglobin concentration | 0.79 (0.70-0.90) *P*<0.001 | - | - | 0.83 (0.73-0.96) *P*=0.006 | - |
| Absolute neutrophil count | - | - | - | 0.85 (0.76-0.94) *P*=0.002 | - |
| IgG <500 mg/dL | 1.98 (1.09-3.67) *P*=0.026 | - | - | - | - |
| Lymph node >10 cm | - | 8.08 (2.12-29.03) *P*=0.001 | - | - | - |
| Bulky spleen | - | 4.28 (1.32-14.27) *P*=0.015 | - | - | - |

This table presents adjusted odds ratios with 95% confidence intervals and *P* values for associations between baseline conditions and adverse events (all adverse events graded ≥3, tumor lysis syndrome, any grade infusion-related reactions, grade ≥3 hematologic toxicities, grade ≥3 infections). Hyphens indicate variables not included in the model due to lack of significance at baseline or removal through backward elimination. OR: odds ratio; 95% CI: 95% confidence interval; AE: adverse events; TLS: tumor lysis syndrome; IRR: infusion-related reactions; ECOG-PS: Eastern Cooperative Oncology Group performance status; CCI: Charlson Comorbidity Index; CLL-CI: Chronic Lymphocytic Leukemia Comorbidity Index; CIRS: Cumulative Illness Rating Scale; GI: gastrointestinal comorbidities; IgG: immunoglobulin G.

The debulking phase was prolonged in 45 patients (16.6%), with a median completion time of 64 days (IQR, 63-70, maximum 130). In 17/45 (37.7%) cases the start of venetoclax was delayed after the obinutuzumab infusion, and 27 had a prolonged venetoclax ramp-up. A total of 13 patients never reached the full venetoclax dose because of AE (median dose reached: 200 mg; range, 50-300 mg).

Univariable models for baseline factors associated with treatment modifications are presented in *Online Supplementary Table S5*. Patients with CLL14-like characteristics did not show a significantly increased risk of treatment modifications for AE, presenting only a moderately increased risk of temporary venetoclax discontinuation (OR=1.78, 1.04-3.08, *P*=0.037).

In multivariable models, baseline factors affecting Tox-DTD were need for a caregiver (*P*=0.029), endocrine comorbidity (*P*=0.025), history of other malignancy (*P*=0.002), hypogammaglobulinemia (*P*=0.003), lymphocyte count >25 x$10^9$/L (P=0.034) and steroid pre-treatment >6 days (*P*=0.006). Global feasibility was instead affected by age (*P*=0.002), history of other malignancy (*P*=0.003), steroid pre-treatment >6 days (*P*<0.001) and baseline thrombocytopenia (*P*=0.013). The administration of rasburicase was associated with a lower incidence of permanent reduction of venetoclax dose (*P*=0.044) and temporary interruption (*P*=0.026). The only patients' fitness characteristic significant for treatment changes was high comorbidity burden, which had an impact on temporary interruption of venetoclax (*P*=0.041). Factors

**Table 4.** Multivariable logistic regression models for treatment modifications.

| Baseline condition | Venetoclax PDR OR (95% CI) | Venetoclax TI OR (95% CI) | Tox-DTD OR (95% CI) | Obinutuzumab omission OR (95% CI) | Global feasibility OR (95% CI) |
|---|---|---|---|---|---|
| Age | - | - | - | - | 1.05 (1.02-1.08) *P*=0.002 |
| Need for a caregiver | - | 2.70 (1.08-6.74) *P*=0.032 | 3.49 (1.09-10.55) *P*=0.029 | - | - |
| ECOG-PS | - | - | - | - | - |
| CCI | - | - | - | - | - |
| CLL-CI | - | - | - | - | - |
| CIRS>6 | - | 2.04 (1.02-4.02) *P*=0.041 | - | - | - |
| CIRS3+ | - | - | - | - | - |
| Endocrine comorbidity | - | - | 2.87 (1.12-7.15) *P*=0.025 | - | - |
| Cancer | - | - | 5.40 (1.75-15.95) *P*=0.002 | - | 4.19 (1.64-11.40) *P*=0.003 |
| Venetoclax-drug interaction | 2.45 (0.93-5.95) *P*=0.05) | - | - | - | - |
| Hb concentration | - | 0.86 (0.74-0.99) *P*=0.039 | - | - | - |
| ALC >25x$10^9$/L | - | - | 4.04 (1.27-18.23) *P*=0.034 | - | - |
| PLT <100x$10^9$/L | - | - | - | 2.07 (1.02-4.36) *P*=0.041 | 2.14 (1.17-3.92) *P*=0.013 |
| IgG <500 mg/dL | - | 2.71 (1.43-5.14) *P*=0.002 | 2.74 (1.09-6.84) *P*=0.030 | 2.19 (1.08-4.36) *P*=0.027) | - |
| Steroid days >6 | - | - | 3.40 (1.42-8.26) *P*=0.006 | 3.48 (1.75-6.95) *P*<0.001) | 3.29 (1.76-6.23) *P*<0.001 |
| Rasburicase | 0.41 (0.16-0.93) *P*=0.044 | 0.48 (0.25-0.90) *P*=0.026 | - | - | - |

The table presents adjusted odds ratios with 95% confidence intervals and *P* values from multivariable logistic regression models assessing factors associated with venetoclax dose modifications (permanent dose reduction, temporary interruption, toxicity-driven discontinuation, obinutuzumab omission, and global feasibility). PDR: permanent dose reduction; OR: odds ratio; 95% CI: 95% confidence interval; TI: temporary interruption; Tox-DTD: toxicity-driven discontinuation; ECOG-PS: Eastern Cooperative Oncology Group performance status; CCI: Charlson Comorbidity Index; CLL-CI: Chronic Lymphocytic Leukemia Comorbidity Index; CIRS: Cumulative Illness Rating Scale; Hb: hemoglobin; ALC: absolute lymphocyte count; PLT: platelets; IgG: Immunoglobulin G.

impacting each treatment modification are summarized in Table 4.

### Efficacy outcomes

The overall response rate according to iwCLL 2018 criteria was 98% including 198 (72%) partial responses and 70 (26%) complete responses. Among those classified as partial responses, 138 (51%) were considered in clinical complete response (bone marrow evaluation not performed).

Overall, four patients progressed (1.5%). One patient progressed 16 months after full VO treatment completion having achieved a complete response. The remaining three progressions were observed at 1, 3 and 14 months after treatment cessation among patients receiving only obinutuzumab and then definitively discontinuing treatment because of toxicity.

Of nine deaths occurring while on active treatment, none was related to disease progression.

At 24 months, progression-free survival was 91.9% (95% CI: 88.0-96.1%) and the overall survival was 93.5% (95% CI: 90.0-97.3%). Factors associated with overall survival are summarized in Table 5.

Patients with CLL14-like characteristics had a higher risk of shorter overall survival with a hazard ratio of 6.56 (95% CI: 1.47-29.35, *P*=0.014).

## Discussion

According to recent ESMO guidelines,[9] fitness status has emerged as a pivotal factor in guiding treatment decisions. However, neither a clear definition nor specific tools have been established to categorize patients effectively. Unlike in the chemoimmunotherapy era, the concept of fitness now encompasses a broader spectrum of patients well-being, including physical, cognitive, and psychological functioning, functional and nutritional status, and social support, extending beyond the traditional assessment of comorbidities.[11]

The aim of our study was to investigate the fitness and logistical characteristics influencing patients' outcomes in a real-world setting of patients treated with VO, focusing on aspects that are not typically captured in clinical trials. Our results confirm the feasibility of VO treatment in an unselected population, with toxicity-driven discontinuation rates comparable to those observed in controlled clinical trials, both in our fit (Tox-DTD 9% *vs*. 5.7% in the CLL13 trial)[7] and comorbid group (Tox-DTD 12% *vs*. 16% in the CLL14 trial).[2] However, while the rate of deaths during treatment remained relatively low, it was slightly higher in the unfit population (0.7% and 6% in fit and unfit patients, respectively) than in clinical trials (0.4% and 2.4% in fit and unfit patients, respectively).[2,7] Notably, half of the deaths in our unfit population were related to COVID-19, which, unlike in the CLL13 trial,[19] did not affect CLL14 patients during the treatment period, highlighting the pandemic's impact on more recent real-world and trial data.

To provide a comprehensive overview of the VO schedule, we decided to analyze each treatment phase individually. The debulking phase likely represents the most critical challenge in the VO schedule, given the heightened risk of AE, particularly TLS and IRR, which arise precisely when patients exhibit the greatest disease burden. Our data confirm this critical issue. Indeed, the majority of cases of

**Table 5.** Univariable and multivariable Cox regression models for overall survival.

| Baseline factor | Univariable HR (95% CI) | *P* | Multivariable HR (95% CI) | *P* |
|---|---|---|---|---|
| Age | 1.09 (1.03-1.16) | 0.005 | - | - |
| Need for a caregiver | 5.00 (1.67-14.95) | 0.004 | - | - |
| ECOG-PS | 2.26 (1.42-3.59) | 0.001 | - | - |
| ECOG-PS ≥2 | 4.91 (1.36-17.79) | 0.015 | - | - |
| CIRS | 1.30 (1.13-1.51) | <0.001 | - | - |
| CIRS >6 | 7.46 (2.50-22.28) | <0.001 | 5.71 (1.86-17.53) | 0.002 |
| Endocrine comorbidity | 3.80 (1.32-10.95) | 0.013 | - | - |
| Nephropathy | 7.97 (2.50-25.42) | <0.001 | - | - |
| Creatinine clearance | 0.96 (0.94-0.99) | 0.006 | 0.97 (0.95-1.00) | 0.045 |
| Venetoclax-drug interaction | 3.35 (1.05-10.73) | 0.042 | - | - |
| Polypharmacy | 3.65 (1.22-10.90) | 0.020 | - | - |
| N of concomitant medications | 1.22 (1.06-1.41) | 0.005 | - | - |

HR: hazard ratio; 95% CI: 95% confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CIRS: Cumulative Illness Rating Scale; Polypharmacy: >3 concurrent medications.

Tox-DTD (41%) occurred during the debulking phase and this is emphasized even more by the impaired debulking phase feasibility in VO less experienced centers.

Furthermore, many physicians adopted strategies to mitigate adverse events (i.e., venetoclax lead-in in 6.3%, steroid pre-treatment in 47%) based on evidence that prolonged steroid premedication may reduce obinutuzumab-related IRR[20] and that the incidence of severe rituximab-related IRR was low in trials with venetoclax lead-in.[21,22]

It is important to emphasize that prolonged steroid pre-treatment, while not lowering the rate of IRR, was independently associated with increased infections, ultimately leading to permanent discontinuations. The use of corticosteroids over the days before treatment initiation is generally contraindicated in clinical trials because of the potential confounding effect on disease response. On the other hand, our data demonstrate that this strategy is actually more commonly employed than expected, being used in nearly half of the patients. It is therefore important to emphasize that, also in clinical practice, steroid use should adhere strictly to the drug's label, which does not support an expanded use beyond what is indicated for premedication purposes. Conversely tailoring standard steroid premedication on a weight-adjusted dosage may be beneficial, as in our population a prednisone or equivalent dose lower than 1.5 mg/kg was associated with an increased risk of IRR.

Among AE mitigation strategies, venetoclax administered as a lead-in drug, before the monoclonal antibody (similarly to the MURANO schedule) was shown to be an effective option to avoid IRR while not affecting patients' outcome.

Of note, a greater incidence of IRR was observed in younger patients in our series, which may be attributed to a possible greater disease burden at the start of treatment compared to that in the older cohort. This increased rate aligns with the findings of a recent comparison between the CLL13 and CLL14 trials, reported by Al-Sawaf *et al.*[23]

When considering additional premedication measures, clinicians primarily rely on TLS risk assessment. Notably, splenomegaly is not included in the standard TLS risk scoring system.[24] However, in our experience, alongside adenopathies, bulky splenomegaly, arguably more so than lymphocytosis, played a significant role in TLS development and should therefore be incorporated into patient assessments prior to VO initiation.

As previously reported regarding the use of targeted agents in real-world settings,[25,26] our data underscore that with the fixed-duration VO combination, traditional fitness definitions, as historically conceived, may not apply completely. Age still remains a critical factor independently influencing overall treatment feasibility. Importantly, our findings highlight the need to account for logistical challenges (e.g., the absence of a caregiver) when making treatment decisions, given the increased risk of discontinuation observed in this specific category of patients. In addition, patients with a history of other malignancies, even if under control, were more prone to definitive discontinuations due to AE and overall treatment modifications.

To our knowledge, this is the first study validating the CLL-CI score in the context of VO treatment.[15] Although none of the commonly used comorbidity scores in CLL demonstrated an independent effect on treatment feasibility, upper gastrointestinal and endocrine comorbidities, both included in the CLL-CI, specifically impacted TLS, serious AE, hematologic toxicity and Tox-DTD. The association between CLL and infections[27] is well-known. In our experience, patients with CIRS >6 had a heightened risk of major infections, the leading cause of mortality in this population.

For this reason, particular attention should be given to the risk of infections in patients with multiple comorbidities. Proactive measures may be warranted, including administration of vaccines prior to initation of the monoclonal antibody, eventual immunoglobulin replacement therapy, patient's and caregiver education to facilitate early recognition of infections and restriction of steroid use to the first cycle only, provided there is no IRR, in accordance with the obinutuzumab label.

According to the latest ESMO guidelines,[9] the combination of ibrutinib and venetoclax emerges as a fully oral, fixed-duration therapeutic alternative suitable for fit patients, as supported by the CAPTIVATE trial.[28,29] In contrast, in the elderly a careful evaluation is warranted based on the unexpected high mortality rate seen in the GLOW trial. No comparison can be made in this setting with our population, as the impact of ibrutinib plus venetoclax in clinical practice has not been assessed yet. Given this limitation and despite being administered in an unselected population, in our experience we did not encounter a significantly higher discontinuation rate with VO than in the ibrutinib-venetoclax trials (12% *vs*. 10% in unfit patients and 9% *vs*. 5% in fitter ones, respectively). This was observed despite the regimen being in its first year of use, with limited clinical experience. Furthermore, it is important to highlight that, despite 22% of patients in our population having a history of severe cardiovascular comorbidities, only five patients (1.8%) developed a severe cardiac AE. While this finding reinforces the notion that VO therapy can serve as a viable therapeutic option for patients with a baseline history of cardiac conditions, it should be noted that in our series patients with a history of severe cardiac comorbidity (50% of those with CIRS3+) had a higher rate of IRR. Although no direct associations between cardiopathy and the development of IRR have been clearly described in literature, we can speculate that patients with pre-existing heart disease may be more prone to hypotensive or arrhythmic events within the IRR context, due to inflammatory stress or cytokine release during infusion.

Finally the high remission rate (98%) observed in this series reflects the favorable tolerability of the VO scheme as evidenced by the fact that the great majority of patients completed all 12 planned cycles.

In conclusion, this study provides several insights into VO treatment, particularly by evaluating factors typically overlooked in clinical trials. On the other hand, there is still an unmet clinical need for a comprehensive assessment tool capable of effectively stratifying patients at higher risk of impaired treatment feasibility across different therapies, and thus supporting clinicians in therapeutic decision-making.

**Disclosures**

*AMF has received honoraria for participation in advisory boards and has received sponsorships for congresses from Janssen, BeiGene, AbbVie and AstraZeneca. ATe has received honoraria for participation in advisory boards from Janssen, BeiGene, AbbVie, Lilly and AstraZeneca and has participated in speaker bureaus for BeiGene, Abbie and Johnson & Johnson. IF has received honoraria from AbbVie, Beigene and Janssen and research funding from AbbVie, Beigene and Eli-Lilly. GL has acted as a consultant for Janssen, Gilead, Roche, AstraZeneca and Lilly; participated in speaker bureaus for Janssen, Gilead, Roche, AbbVie, Astrazeneca, Beone, GSK and Lilly; and participated in advisory boards for Janssen, Gilead, Roche, AbbVie, AstraZeneca, Beone, GSK and Lilly. RM has participated in advisory boards for AbbVie, AstraZeneca and Beigene and has received travel grants or speaker's fees from AbbVie, AstraZeneca, Beigene and Johnson & Johnson. MV has participated in advisory boards for or received speaker's honoraria from AbbVie, AstraZeneca and Beigene. EB has received travel grants or speaker's fees fees from AstraZeneca, Amgen, Beigene, Mayo Clinic and Kyowa Kirin. MM has participated in an advisory board for Eli Lilly.*

**Contributions**

*AMF, AGa and ATe conceived the work that led to the submission. AMF, AGa, MLuci, LA, JO, AS, CBa, FP, LS, BC, IF, AFi, PS, GL, CS, AVi, MCe, FRM, MP, MCo, VI, RM, MMo, FR, MT, AA, EB, CBo, EC, AFe, MG, RG, AGi, MB, EL, LM, MMu, MV, FV, FC, MMe, LN, MCP, AAR, VR, GT, AVa, MCa, AGo, LC, MLuce, MD, ATo, AZ, RM, CP, LL and ATe designed the work that led to the submission, acquired data and played an important role in interpreting the results. AGa, AMF, ATe, MD and AZ drafted the manuscript; AMF, AGa, MLuci, LA, JO, AS, CBa, FP, LS, BC, IF, AFi, PS, GL, CS, AVi, MCe, FRM, MP, MCo, VI, RM, MMo, FR, MT, AA, EB, CBo, EC, AF, MG, RG, AGi, MB, EL, LM, MMu, MV, FV, FC, MMe, LN, MCP, AAR, VR, GT, AVa, MCa, AGo, LC, MLuce, MD, ATo, AZ, RM, CP, LL and ATe revised the manuscript. AMF, AGa, MLuci, LA, JO, AS, ClaB, FP, LS, BC, IF, AFe, PS, GL, CS, AVi, MC, FRM, MP, MC, VI, RM, MMo, FR, MT, AA, EB, CBo, EC, AF, MG, RG, AGi, MB, EL, LM, MMu, MV, FV, FC, MMe, LN, MCP, AAR, VR, GT, AVa, MC, AGo, LC, MLuce, MD, ATo, AZ, RM, CP, LL and ATe approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*

**Data-sharing statement**

*For data sharing and any further information, please contact annamaria.frustaci@ospedaleniguarda.it or a.galitzia@gmail.com*

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