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ADIS DRUG EVALUATION

Venetoclax: A Review in Previously Untreated Chronic Lymphocytic Leukaemia

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Abstract

Venetoclax (Venclexta®; Venclyxto®) is a first-in-class, oral, selective inhibitor of B cell lymphoma 2 (BCL2). In several countries, including the USA and those of the EU, venetoclax is indicated in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphocytic leukaemia (CLL). Approval was based on the results of the phase III CLL14 trial in patients with previously untreated CLL and co-existing conditions. In this study, fixed-duration (12 months) targeted treatment with venetoclax + obinutuzumab resulted in significantly longer progression-free survival (PFS; primary endpoint) relative to fixed-duration chemoimmunotherapy with chlorambucil + obinutuzumab. Venetoclax + obinutuzumab was also associated with significantly higher rates of undetectable minimal residual disease (MRD), complete response and overall response than chlorambucil + obinutuzumab. Improvements in clinical outcomes with venetoclax + obinutuzumab were maintained during long-term follow-up, when all patients had been off treatment for ≥ 2 years. No significant between-group difference was observed in overall survival (OS). Venetoclax had an acceptable tolerability profile. Notable adverse events such as grade 3 or 4 neutropenia can be managed with supportive therapy and venetoclax dose modifications. In conclusion, fixed-duration venetoclax + obinutuzumab represents an important chemotherapy-free first-line treatment option for patients with CLL, particularly those who are not fit enough to receive intensive chemoimmunotherapy.

Venetoclax: clinical considerations in previously untreated CLL

First-in-class, oral, selective inhibitor of the anti-apoptotic protein BCL2

Fixed-duration (12 months) venetoclax + obinutuzumab is more effective than chlorambucil + obinutuzumab in prolonging PFS and inducing undetectable MRD

No significant between-group difference in OS

Acceptable tolerability profile

Enhanced material for this Adis Drug Evaluation can be found at https://doi.org/10.6084/m9.figshare.13146479.

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1 Introduction

Chronic lymphocytic leukaemia (CLL), a B cell malignancy that occurs mainly in older age [1], is the most common type of adult leukaemia in the Western world [1–3]. CLL is characterized by the progressive proliferation and accumulation of B cells in the blood, bone marrow, lymph nodes and spleen [3–5]. The clinical course of the disease is heterogeneous [1, 6], ranging from slow-growing, indolent forms to aggressive, life-threatening forms [6]. CLL is not treated until patients develop symptomatic/active disease, as evidence suggests that treating patients with early-stage disease does not result in a survival benefit [3, 7]. Treatment decisions are guided by several prognostic and predictive markers, including age, presence and level of comorbidities, *TP53* mutation and/or deletion status, and immunoglobulin heavy-chain variable region (*IGHV*) mutational status [6].

Chemoimmunotherapy has long been considered the gold standard for first-line treatment of CLL [5, 6]. However, more recently, several new pharmacological targets have been identified [1, 6]. One such target is B cell lymphoma 2 (BCL2), an anti-apoptotic (i.e. pro-survival) protein [8, 9]. Apoptosis is regulated by interactions between three groups of BCL2 family members: anti-apoptotic proteins, pro-apoptotic effectors, and pro-apoptotic initiators/sensitizers.

As BCL2 is overexpressed in CLL cells, BCL2 inhibition represents a rational and novel therapeutic approach for the treatment of CLL [8, 9].

Venetoclax (Venclexta®; Venclyxto®) is a first-in-class, oral, selective BCL2 inhibitor. Venetoclax, in combination with obinutuzumab, is approved in several countries, including the USA [10] and those of the EU [11], for the treatment of adult patients with previously untreated CLL [or small lymphocytic leukaemia (SLL) [10]; CLL and SLL are different manifestations of the same disease [4]]. The pharmacological properties of venetoclax have been reviewed in detail previously [12] and are summarized in Table 1. This review focuses on the clinical use of venetoclax in patients with previously untreated CLL. Discussion of the use of venetoclax in relapsed/refractory CLL is beyond the scope of this review.

2 Therapeutic Efficacy of Venetoclax

The efficacy of venetoclax + obinutuzumab versus chlorambucil + obinutuzumab in patients with previously untreated CLL was evaluated in the randomized, open-label, multicentre, phase III CLL14 trial [13]. The venetoclax dosage evaluated in this trial [400 mg/day; approved dosage (Sect. 4)] was established in an earlier phase Ib dose-finding study [14], which is not discussed further.

Eligible participants in CLL14 were aged ≥ 18 years with documented previously untreated CLL that required treatment [i.e. Binet stage C (low haemoglobin or platelet count from bone marrow infiltration of CLL cells) or symptomatic disease] [13]. All patients had co-existing conditions, with a total score of > 6 on the Cumulative Illness Rating Scale (CIRS; scores range from 0 to 56, with higher scores indicating more impaired function of organ systems) or a creatinine clearance (CL_{CR}) of < 70 mL/min. Patients with a *TP53*

Table 1 Overview of key pharmacological properties of venetoclax

Pharmacodynamic properties	
Potent, selective BCL2 inhibitor [14, 32]; > 1000-fold greater affinity for BCL2 (Ki < 0.010 nmol/L) than for BCL-X_L (Ki 48 nmol/L) or BCL-W (Ki 245 nmol/L); no measurable binding to MCL-1 (Ki > 444 nmol/L) [32]; acts independently of *TP53* [14]	
Binds directly to BH3-binding groove of BCL2; displaces BH3 motif-containing pro-apoptotic proteins to initiate mitochondrial outer membrane permeabilization, caspase activation and restoration of tumour cell apoptosis [10, 11, 32–36]	
Induces rapid apoptosis of tumour cells (including CLL cells); platelet sparing due to lack of activity against BCL-X_L [32, 36, 37]	
Inhibition of BCL2 restores intrinsic apoptotic pathway via activation of pro-apoptotic proteins (↓ tumour burden) [32, 36, 37]	
Demonstrates cytotoxic anti-tumour activity against various cell lines in vitro and against xenografts in vivo for a variety of haematological malignancies [32–37] (including CLL); does not induce severe thrombocytopenia [32, 36, 37]	
Sensitivity to VEN correlates with ↑ BCL2 expression [32, 35, 38]; ↑ BCL2 status [i.e. *BCL2* gains, *BCL2* amplifications or the t(14;18) translocation, which causes deregulated BCL2 expression] [32, 39] and ↑ BCL2/MCL-1 ratios [38] are potentially predictive of sensitivity	
Time-restricted exposure to VEN in combination with a second drug (i.e. antibody) is likely to ↓ risk of acquired resistance to VEN [40]	
No clinically relevant effect on QTc interval at supratherapeutic doses (≤ 1200 mg once daily); no relationship between VEN exposure and QTc interval changes [10, 11, 41]	
Pharmacokinetic properties	
C_{max} reached after 5–8 h (fed state); steady-state exposure ↑ dose-proportionally across dose range of 150–800 mg [10, 11]; VEN exposure ↑ ≈ 3.4-fold when administered with low-fat meal and ↑ 5.1- to 5.3-fold when administered with high-fat meal (Sect. 4) [10, 11, 42]	
Highly bound to plasma proteins (< 0.01% unbound); apparent Vd 256–321 L [10, 11]; crosses BBB and penetrates into CSF [43]	
Primarily metabolized by CYP3A4; major metabolite (M27) is ≥ 58-fold less potent than parent drug in inhibiting BCL2 [10, 11]	
> 99.9% of radiolabelled dose eliminated in faeces (20.8% as unchanged drug) and < 0.1% in urine; terminal elimination half-life ≈ 26 h [10, 11]	
Special populations[a]	No clinically relevant differences in VEN pharmacokinetics based on age, sex, race or bodyweight [10, 11, 44]
	No clinically relevant effects on VEN pharmacokinetics in pts with mild or moderate hepatic [10, 11, 45] or renal [10, 11] impairment; VEN exposure ↑ 2.7-fold in pts with severe hepatic impairment (VEN dosage ↓ is recommended) [10, 11]
Drug interactions[a]	Weak inhibitor of CYP2C8, CYP2C9 and UGT1A1 but not predicted to cause clinically relevant inhibition; weak inhibitor of OATP1B1 [10, 11]
	Inhibitor and substrate of P-gp and BCRP; coadministration of VEN with P-gp and BCRP inhibitors should be avoided; if concomitant use is necessary, VEN dosage ↓ is recommended; P-gp and BCRP substrates with narrow therapeutic indices should be administered ≥ 6 h prior to VEN [10, 11]
	VEN ↑ systemic exposure to warfarin [46]; INR monitoring is recommended when these drugs are coadministered [10, 11]
	VEN exposure may ↑ or ↓ when coadministered with CYP3A4 inducers or inhibitors; strong CYP3A4 inhibitors are contraindicated when starting VEN therapy and during dose-titration period; if coadministration with strong or moderate CYP3A4 inhibitors is necessary, VEN steady-state dosage ↓ is recommended [10, 11]
	Foods containing CYP3A inhibitors (e.g. grapefruit products, Seville oranges, starfruit) should be avoided during treatment with VEN, as should strong or moderate CYP3A4 inducers [10, 11]

↓ decrease(s), ↑ increase(d), *BBB* blood-brain barrier, *BCL2* B cell lymphoma 2, *BCL-W* BCL2-like 2, *BCL-X_L* BCL2-like 1, *BH3* BCL2 homology domain, *CLL* chronic lymphocytic leukaemia, *C_{max}* maximum plasma concentration, *CSF* cerebrospinal fluid, *INR* international normalized ratio, *Ki* inhibitor constant, *MCL-1* myeloid cell leukaemia sequence 1, *pts* patients, *Vd* volume of distribution, *VEN* venetoclax

[a]Consult local prescribing information for further detailed information

deletion or mutation could be enrolled at the investigator's discretion [13].

Patients were randomized to receive venetoclax + obinutuzumab ($n = 216$) or chlorambucil + obinutuzumab ($n = 216$), with randomization stratified according to geographic region and Binet stage [13]. Treatment consisted of 12 cycles, each lasting 28 days. In both groups, intravenous obinutuzumab was administered for six cycles, starting with 100 mg on day 1 and 900 mg on day 2 (or 1000 mg on day 1), 1000 mg on day 8 and 1000 mg on day 15 of cycle 1, followed by 1000 mg on day 1 of cycles 2–6. Patients in the venetoclax + obinutuzumab group received oral venetoclax starting on day 22 of cycle 1 using a dose titration regimen over 5 weeks (20 mg/day incremented weekly to 50, 100, 200 and then 400 mg/day) and thereafter 400 mg/day until completion of cycle 12. Patients in the chlorambucil + obinutuzumab group received oral chlorambucil 0.5 mg/kg on days 1 and 15 of each cycle until completion of 12 cycles. The median duration of treatment was 11.1 and 10.8 months in the venetoclax + obinutuzumab and chlorambucil + obinutuzumab groups [13].

Baseline demographics and disease characteristics were well balanced between the two treatment groups [13]. The median age of patients was 72 years (≈ 35% were aged ≥ 75 years) and the median time since CLL diagnosis was ≈ 30 months. The median total CIRS score was 8 and the median CL_{CR} was 66.4 mL/min. Sixty percent of patients harboured an unmutated *IGHV* gene and 14% had a *TP53* deletion, mutation or both. The majority of patients (88%) had an Eastern Cooperative Oncology Group (ECOG) performance status of < 2. The primary endpoint was investigator-assessed progression-free survival (PFS), defined as the time from randomization to the first occurrence of progression, relapse or death from any cause. A preplanned interim analysis was conducted when 110 of 170 events had occurred; at this timepoint, the independent data and safety monitoring committee recommended conducting the primary analysis of the primary and secondary endpoints. Testing of key secondary endpoints was performed using a prespecified hierarchical procedure [13].

At the time of the primary analysis (median follow-up 28.1 months; data cut-off date 17 August 2018 [11]), venetoclax + obinutuzumab significantly prolonged investigator-assessed PFS relative to chlorambucil + obinutuzumab, reducing the risk of progression or death by 65% (Table 2) [13]. Similar results were seen with regard to PFS as assessed by an independent review committee (Table 2). Venetoclax + obinutuzumab also prolonged investigator-assessed PFS in all prespecified subgroup analyses [hazard ratios (HRs) ranged from 0.11 to 0.93], including those based on sex, age (< 75 or ≥ 75 years), Binet stage at screening (A, B or C), cytogenetic profile [del(17p), del(11q), trisomy 12, no abnormalities or del(13q)], *TP53* deletion and/or mutation status (present or absent) and *IGHV* mutation status (mutated or unmutated) [13].

For key secondary endpoints, the rates of minimal residual disease (MRD) negativity, complete response and overall response were significantly higher with venetoclax + obinutuzumab than with chlorambucil + obinutuzumab (Table 2) [13]. MRD negativity was more sustainable with venetoclax + obinutuzumab than with chlorambucil + obinutuzumab. Among patients with undetectable MRD in peripheral blood at the end of treatment, there were 34 (21%) re-detection events in the venetoclax + obinutuzumab group and 55 (72%) in the chlorambucil + obinutuzumab group [15]. The median time to re-detection of MRD was 17.7 months with venetoclax + obinutuzumab versus 7.5 months with chlorambucil + obinutuzumab (HR 0.192; 95% CI 0.124–0.296). MRD negativity was correlated with improved PFS, regardless of clinical response status at the end of treatment [15]. Median overall survival (OS; key secondary endpoint) was not reached in either treatment group (Table 2) [13]. Estimated OS rates at 24 months are shown in Table 2 [13]. Venetoclax + obinutuzumab was superior to chlorambucil + obinutuzumab for other secondary time-to-event endpoints, including time to next anti-leukaemic treatment (HR 0.60; 95% CI 0.37–0.97), duration of response (HR 0.31; 95% CI 0.20–0.50) and event-free survival (HR 0.36; 95% CI 0.24–0.54) [13].

With regard to patient-reported outcomes, venetoclax + obinutuzumab was associated with clinically meaningful improvement on the European Organisation for Research and Treatment of Cancer Quality of Life (QoL) Questionnaire-Core 30 (EORTC QLQ-C30) Global Health Status/QoL scale at cycle 3, while a less pronounced and consistent improvement was observed with chlorambucil + obinutuzumab at cycle 8 [16]. Venetoclax + obinutuzumab was also associated with earlier improvements than chlorambucil + obinutuzumab in fatigue (cycle 3 vs cycle 6). Neither treatment was associated with clinically meaningful improvement or deterioration in physical functioning and role functioning (assessed using the EORTC QLQ-C30) or symptom burden and interference (assessed using the M.D. Anderson Symptom Inventory) [16].

2.1 Updated Analysis

Improvements in clinical outcomes with venetoclax + obinutuzumab relative to chlorambucil + obinutuzumab were maintained over the longer term [17]. At the time of the updated analysis (median follow-up 39.6 months; data cut-off date 23 August 2019), when all patients had been off treatment for ≥ 2 years, PFS was sustained in the venetoclax + obinutuzumab group, with a 69% reduction in the risk of progression or death relative to the chlorambucil + obinutuzumab group (Table 2). There were 42 (19%) PFS

Table 2 Efficacy of venetoclax plus obinutuzumab in patients with previously untreated chronic lymphocytic leukaemia in the phase III CLL14 trial

Endpoint (ITT population)	VEN + OBI ($n = 216$)	CLB + OBI ($n = 216$)	HR or OR[a] (95% CI)
Primary analysis (median FU 28.1 mo) [11, 13]			
Investigator-assessed PFS			
Median PFS[b] (mo)	NR	NR	0.35 (0.23–0.53)*
12-mo PFS (% pts)	95	92	
24-mo PFS (% pts)	88	64	
IRC-assessed PFS			
Median PFS (mo)	NR	NR	0.33 (0.22–0.51)*
12-mo PFS (% pts)	95	91	
24-mo PFS (% pts)	89	64	
No MRD[c] in bone marrow[d,e] (% pts)	57	17	6.4 (4.1–10.0)*
CR[d,e] (% pts)	50	23	3.3 (2.2–5.1)*
No MRD[c] in peripheral blood[d,e] (% pts)	76	35	5.7 (3.7–8.6)*
CR + no MRD[c] in bone marrow[d,e] (% pts)	34	11	4.3 (2.6–7.2)*
CR + no MRD[c] in peripheral blood[d,e] (% pts)	42	14	4.3 (2.7–6.9)*
Overall response rate[d,e] (% pts)	85	71	2.3 (1.4–3.6)*
Median OS[d] (mo)	NR	NR	1.24 (0.64–2.40)
24-mo OS (% pts)	92	93	
Updated analysis (median FU 39.6 mo) [17]			
Investigator-assessed PFS			
Median PFS (mo)	NR	35.6	0.31 (0.22–0.44)*
36-mo PFS (% pts)	82	50	
No MRD[c] in peripheral blood[f] (% pts)	47	7	
Median OS (mo)	NR	NR	1.03 (0.60–1.75)

CLB chlorambucil, *CR* complete response, *FU* follow-up, *HR* hazard ratio, *IRC* independent review committee, *ITT* intention-to-treat, *mo* month/s, *MRD* minimal residual disease, *NR* not reached, *OBI* obinutuzumab, *OR* odds ratio, *OS* overall survival, *PFS* progression-free survival, *pts* patients, *VEN* venetoclax

*$p < 0.001$ vs CLB + OBI

[a]HR for PFS and OS; OR for all other endpoints

[b]Primary endpoint

[c]Cut-off was 10^{-4} (< 1 CLL cell in 10,000 leukocytes)

[d]Hierarchically-tested key secondary endpoint (listed in hierarchical order)

[e]Assessed 3 mo after treatment completion

[f]Assessed 18 mo after treatment completion

events in the venetoclax + obinutuzumab group, 21 of which were disease progressions, and 113 (52%) PFS events in the chlorambucil + obinutuzumab group, 102 of which were disease progressions. Nine (4%) patients in the venetoclax + obinutuzumab group and 44 (20%) patients in the chlorambucil + obinutuzumab group received second-line therapy after disease progression. The PFS benefit with venetoclax + obinutuzumab was seen across all clinical and biological risk groups, including patients with or without *TP53* mutations and in either mutated or unmutated *IGHV* subgroups [17].

At 18 months after treatment completion, almost half of patients in the venetoclax + obinutuzumab group still had undetectable MRD, compared with 7% of patients in the chlorambucil + obinutuzumab group (Table 2) [17]. In a landmark analysis from last treatment exposure (i.e. after 12 cycles), patients with undetectable MRD at the end of either treatment regimen had longer PFS than patients with low MRD ($\geq 10^{-4}$ and $< 10^{-2}$) or high MRD ($\geq 10^{-2}$). At the time of data cut-off, there was no difference in OS between treatment groups (Table 2). Undetectable MRD was associated with longer OS in a post hoc analysis. The median time to MRD conversion (i.e. an increase from undetectable to detectable MRD) was not reached in the venetoclax + obinutuzumab group and was 6 months in the chlorambucil + obinutuzumab group [17].

3 Tolerability of Venetoclax

Venetoclax had an acceptable tolerability profile in patients with previously untreated CLL participating in the CLL14 trial discussed in Sect. 2. No new safety signals were identified with venetoclax + obinutuzumab or chlorambucil + obinutuzumab [13]. The adverse events (AEs) of any grade that occurred most frequently (≥ 15% incidence) with venetoclax + obinutuzumab were neutropenia (58 vs 57% with chlorambucil + obinutuzumab), infusion-related reactions (45 vs 51%), diarrhoea (28 vs 15%), thrombocytopenia (24 vs 23%), pyrexia (23 vs 15%), nausea (19 vs 22%), anaemia (17 vs 19%), cough (16 vs 12%) and fatigue (15 vs 14%). The most common grade 3 or 4 AEs were neutropenia (53 vs 48%), infections and infestations (18 vs 15%) and thrombocytopenia (14 vs 15%). Serious AEs occurred in 49% of venetoclax + obinutuzumab recipients and 42% of chlorambucil + obinutuzumab recipients; the most common serious AEs were febrile neutropenia (5 vs 4%) and pneumonia (5 vs 4%) [13]. AEs led to treatment discontinuation, dose reduction and dose interruption in 16, 21 and 74% of venetoclax + obinutuzumab recipients, respectively [10, 11]. Fatal AEs (in the absence of disease progression and with onset within 28 days of the last study treatment) occurred in 2% of patients, most commonly from infection [10]. Secondary primary malignancies occurred in 14% of venetoclax + obinutuzumab recipients and 10% of chlorambucil + obinutuzumab recipients; the most common of these were squamous cell skin carcinoma (3 vs 4%) and basal cell carcinoma (3 vs 3%) [13].

Neutropenia is an identified risk with venetoclax treatment [11]. In CLL14, neutropenia led to dose interruption in 41%, dose reduction in 13% and treatment discontinuation in 2% of venetoclax recipients [10, 11]. The median duration of grade 3 or 4 neutropenia was 22 days [11]. Grade ≥ 3 infections and serious infections each occurred in 19% of venetoclax recipients. The incidence of fatal infections was 2% during treatment with venetoclax and 2% following discontinuation of venetoclax [11]. Complete blood counts should be performed throughout the treatment period, and patients should be closely monitored for signs and symptoms of infection [10, 11]. Local prescribing information should be consulted for further details regarding the management of grade 3 or 4 neutropenia with infection or fever, grade 3 or 4 non-haematological toxicities, or grade 4 haematological toxicities except lymphopenia, including supportive treatment (e.g. antimicrobials, growth factors) and venetoclax dose modifications.

3.1 Tumour Lysis Syndrome

Tumour lysis syndrome (TLS) is a rare but potentially life-threatening event in patients with CLL [18]. It is an important identified risk when initiating treatment with anti-CLL agents (including venetoclax) due to the rapid reduction in tumour [10, 11]. The risk of TLS is a continuum based on multiple factors, including tumour burden. Patients with high tumour burden (defined in CLL14 as any measurable lymph node with the largest diameter ≥ 10 cm or the presence of both absolute lymphocyte count ≥ 25×10^9/L and any measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm [13]) or reduced renal function (i.e. CL_{CR} < 80 mL/min) have an increased risk of TLS. There have been reports of TLS, including fatal events, in patients with high tumour burden receiving venetoclax [10, 11].

In CLL14, there were few TLS events in patients receiving venetoclax + obinutuzumab [13]. TLS occurred in three venetoclax + obinutuzumab recipients and five chlorambucil + obinutuzumab recipients [13, 18]. However, none of these events met the Howard criteria for clinical TLS (i.e. the presence of specific electrolyte changes and clinical manifestations) [13]. All three TLS events in the venetoclax + obinutuzumab group occurred prior to the first dose of venetoclax, were associated with obinutuzumab [18], resolved, and did not result in withdrawal from the study [10, 11]. All patients had received TLS prophylaxis with allopurinol [18]. Aside from these AEs, 12 venetoclax + obinutuzumab recipients experienced laboratory abnormalities consistent with Howard criteria during cycles 1 and 2 (i.e. hypocalcaemia, hyperphosphataemia, hyperkalaemia and hyperuricaemia). However, most of these abnormalities were not considered to be clinically significant [18].

Prior to the initiation of venetoclax, tumour burden assessments, including radiographic examination (e.g. CT scan), must be performed and blood chemistries (e.g. calcium, creatinine, phosphorus, potassium and uric acid) should be assessed and pre-existing abnormalities corrected [10, 11]. TLS prophylaxis should be followed and, depending on risk, may include adequate hydration, use of anti-hyperuricaemic agents, monitoring of blood chemistries, dose modifications and/or hospitalization [10, 11]. Local prescribing information should be consulted for further details.

4 Dosage and Administration of Venetoclax

In the USA [10] and the EU [11], oral venetoclax is indicated in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL (or SLL [10]). The starting dosage of venetoclax is 20 mg once daily for 1 week, with the dosage gradually increased in weekly increments to 50, 100, 200 and then 400 mg once daily over a 5-week period [10, 11]; this dose-titration schedule is designed to gradually reduce tumour burden and decrease the risk of TLS (Sect. 3.1). Venetoclax should be administered with water and a meal at approximately the same time each day. Obinutuzumab (intravenous infusion) should be started at 100 mg on day 1 of cycle 1, followed by 900 mg on day 1

or 2 of cycle 1, then 1000 mg on days 8 and 15 of cycle 1 and on day 1 of each subsequent 28-day cycle, for a total of six cycles. The 5-week venetoclax dose-titration schedule should be started on day 22 of cycle 1. After completion of dose titration on day 28 of cycle 2, the recommended dosage of venetoclax is 400 mg once daily from day 1 of cycle 3 until the last day of cycle 12 [10, 11]. Consult local prescribing information for detailed information regarding contraindications, warnings and precautions, drug interactions and use in special populations.

5 Place of Venetoclax in the Management of Previously Untreated CLL

Patients with CLL have been treated with chemoimmunotherapy for many years, with the combination of fludarabine, cyclophosphamide and rituximab (FCR) becoming the standard of care for young, fit patients in good physical condition [3, 5, 6]. However, FCR regimens are poorly tolerated by elderly, unfit patients with comorbid conditions [5, 19]. Therefore, chlorambucil has long been used as the standard of care in these patients, with the addition of anti-CD20 monoclonal antibodies (e.g. rituximab, obinutuzumab) resulting in improved outcomes [5].

With the recent advent of novel targeted agents such as the phosphoinositide-3 kinase inhibitor idelalisib, the Bruton's tyrosine kinase (BTK) inhibitors ibrutinib and acalabrutinib, and the BCL2 inhibitor venetoclax [5, 20], the CLL treatment landscape is shifting away from chemoimmunotherapy [6]. Current iwCLL [7], ESMO [2] and NCCN [4] guidelines for CLL recommend an individualized treatment approach, with the choice of first-line therapy based on factors such as disease stage, patient age, comorbidities, ECOG performance status, functional activity, presence or absence of mutations, and properties of the drug (e.g. potential toxicities, route of administration) [2, 4, 7]. According to the NCCN, the preferred regimens for the first-line treatment of CLL in frail patients with significant comorbidities are venetoclax + obinutuzumab, ibrutinib, and acalabrutinib + obinutuzumab (all category 1) [4].

The approval of venetoclax in combination with obinutuzumab for the treatment of adult patients with previously untreated CLL was based on data from the CLL14 trial, which enrolled patients with co-existing conditions (Sect. 2). Given that most patients with CLL are elderly and have multiple comorbidities, the CLL14 trial population (median age 72 years and median CIRS score of 8) was representative of the general CLL population [13]. In this trial, venetoclax + obinutuzumab significantly prolonged PFS relative to chlorambucil + obinutuzumab, reducing the risk of progression or death by 65% (Sect. 2). Results of an updated analysis 2 years after treatment cessation were generally consistent with those of the primary analysis (Sect. 2.1).

MRD status is important for deep and durable responses in patients with CLL [21]. In CLL14, venetoclax + obinutuzumab was associated with significantly higher rates of undetectable MRD than chlorambucil + obinutuzumab (Sect. 2). MRD negativity occurred early in the venetoclax + obinutuzumab group and was sustained after completion of treatment, while there was a rapid increase in MRD in the chlorambucil + obinutuzumab group [13]. The level of MRD at the end of treatment was prognostic for PFS (Sect. 2), confirming that achievement of undetectable MRD is an important predictor of treatment efficacy in patients with CLL [1, 4]. Indeed, MRD testing now plays a crucial role in clinical trial design [20], with most trials using MRD status as a secondary or exploratory endpoint [21]. The continued incorporation of MRD status as an efficacy endpoint in clinical trials will help to further define its potential role in guiding therapeutic decision making [22].

There were no differences in OS between venetoclax + obinutuzumab and chlorambucil + obinutuzumab after a median of 39.6 months' follow-up (Sect. 2.1). It has been suggested that the availability of effective salvage therapies can make the ability to show OS differences within individual trials difficult [23].

Venetoclax had an acceptable tolerability profile in patients with previously untreated CLL and co-existing conditions (Sect. 3). No new safety signals were identified with venetoclax + obinutuzumab or chlorambucil + obinutuzumab in CLL14. Although grade 3 or 4 neutropenia was common, this AE appears to be manageable with supportive treatment (e.g. growth factors) and venetoclax dose modifications. TLS is a well-recognized and potentially life-threatening AE associated with venetoclax (Sect. 3.1). However, the risk of TLS can be mitigated by the use of prophylactic measures and blood chemistry monitoring (Sect. 3.1), and by slowly ramping up the dosage of venetoclax when treatment is initiated (Sect. 4). In CLL14, the incidence of TLS with venetoclax + obinutuzumab was low, highlighting the value of the recommended safety measures [13].

To date, no studies have directly compared venetoclax + obinutuzumab with other regimens containing novel targeted agents (e.g. BTK inhibitors) in patients with previously untreated CLL. Network meta-analyses, systematic reviews and indirect treatment comparisons have demonstrated some apparent differences in efficacy between venetoclax + obinutuzumab and other frontline regimens for previously untreated CLL (e.g. FCR, bendamustine + rituximab, chlorambucil ± rituximab or obinutuzumab, ibrutinib ± rituximab or obinutuzumab, acalabrutinib ± obinutuzumab) [24–29]. With regard to PFS, novel combination therapy regimens appeared to be more effective than standard chemoimmunotherapy regimens [24–28]. However, results of these comparisons should be interpreted with caution due to their indirect nature. Well-designed head-to-head trials comparing these various regimens would be of interest.

Despite the need for a dose ramp-up schedule, and some patients (i.e. those at high risk of TLS) requiring hospital admission for the initiation of treatment [22], venetoclax may offer some advantages over other targeted therapies. The achievement of undetectable MRD induces deep and durable remissions, allowing for fixed-duration therapy [1, 3]. Unlike other targeted agents such as BTK inhibitors, which are administered continuously until disease progression or unacceptable toxicity, venetoclax + obinutuzumab therapy is time-limited to 12 months [19]. Fixed-duration therapy may be more desirable and/or appropriate than treat-to-progression therapy for some patients, and may also translate into QoL improvements and cost savings [1, 19].

Novel targeted therapies such as those for CLL are associated with high acquisition costs, placing a substantial economic burden on healthcare systems [30]. From a US payer perspective, time-limited venetoclax + obinutuzumab was cost effective compared with several ibrutinib-based treat-to-progression regimens [31]. In a budget impact analysis, the introduction of fixed-duration venetoclax + obinutuzumab to a US health plan resulted in substantial cost savings compared with chemoimmunotherapies (e.g. FCR, bendamustine + rituximab, chlorambucil + obinutuzumab) and continuously administered ibrutinib-based regimens [30].

In conclusion, venetoclax + obinutuzumab was more effective than chlorambucil + obinutuzumab in prolonging PFS and inducing MRD negativity in patients with previously untreated CLL and co-existing conditions. Venetoclax had an acceptable tolerability profile in this patient population. Therefore, fixed-duration venetoclax + obinutuzumab represents an important chemotherapy-free first-line treatment option for patients with CLL, particularly those who are not fit enough to receive intensive chemoimmunotherapy.

Data Selection Venetoclax: 226 records identified	
Duplicates removed	32
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	147
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	1
Cited efficacy/tolerability articles	8
Cited articles not efficacy/tolerability	38
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were venetoclax, Venclexta, Venclyxto, obinutuzumab, Gazyva, chronic lymphocytic leukaemia, CLL. Records were limited to those in English language. Searches last updated 26 October 2020	

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