Farmacia HOSPITALARIA

Órgano oficial de expresión científica de la Sociedad Española de Farmacia Hospitalaria

Cost–utility analysis of venetoclax in combination with obinutuzumab as first-line treatment of chronic lymphocytic leukaemia in Spain

Análisis coste-utilidad de venetoclax en combinación con obinutuzumab como tratamiento de primera línea de la leucemia linfocítica crónica en España

Estela Moreno-Martínez[1], Javier de la Serna-Torroba[2], Vicente Escudero-Vilaplana[3], José Ángel Hernández-Rivas[4], Marina Sánchez-Cuervo[5], Raquel Sánchez-Hernández[6]

[1]Servicio de Farmacia, Hospital de la Santa Creu i Sant Pau, Barcelona. Spain. [2]Servicio de Hematología, Hospital Universitario 12 de Octubre, Madrid. Spain. [3]Servicio de Farmacia, Hospital Universitario Gregorio Marañón, Madrid. Spain. [4]Servicio de Hematología, Hospital Universitario Infanta Leonor, Madrid. Spain. [5]Servicio de Farmacia, Hospital Universitario Ramón y Cajal, Madrid. Spain. [6]AbbVie Spain S. L. U., Madrid. Spain.

Author of correspondence
Raquel Sánchez Hernández
Market Access Value Proposition
Manager Hematooncología
Avda. Burgos, 91
28050 Madrid. Spain.

Email:
raquel.sanchezhernandez@abbvie.com

How to cite this paper
Moreno-Martínez E, De la Serna-Torroba J, Escudero-Vilaplana V, Hernández-Rivas JA, Sánchez-Cuervo M, Sánchez-Hernández R.
Cost-utility analysis of venetoclax in combination with obinutuzumab as first-line treatment of chronic lymphocytic leukaemia in Spain.
Farm Hosp. 2022;46(3):121-32.

Abstract

Objective: Venetoclax in combination with obinutuzumab has significantly improved efficacy versus immunochemotherapy (progression-free survival) in patients with chronic lymphocytic leukaemia who have not received prior treatment. The objective of this study was to evaluate its efficiency in Spain using a cost-utility analysis.

Method: Using a partitioned-survival analysis model adapted to the Spanish context and based on three health states (progression-free survival, survival after progression, and death), a simulation of the evolution of patients who were candidates for initiating first-line treatment was conducted for a lifetime time horizon. Venetoclax in combination with obinutuzumab was compared to the most commonly used therapeutic options for these patients at the time of study design: chlorambucil in combination with obinutuzumab, ibrutinib, fludarabine in combination with cyclophosphamide and rituximab, and bendamustine in combination with rituximab. In order to estimate survival curves, efficacy data were derived from the CLL14 trial and a network meta-analysis. The

Resumen

Objetivo: Venetoclax en combinación con obinutuzumab ha mostrado frente a la inmunoquimioterapia mejoras significativas en términos de eficacia (supervivencia libre de progresión) en pacientes con leucemia linfocítica crónica que no han recibido tratamiento previo. El objetivo de este estudio fue evaluar su eficiencia en España a partir de un análisis de coste-utilidad.

Método: A partir de un modelo de análisis de la supervivencia adaptado al contexto español y basado en tres estados de salud (supervivencia libre de progresión, supervivencia tras progresión y muerte), se llevó a cabo una simulación de la evolución de los pacientes candidatos a iniciar una primera línea de tratamiento para un horizonte temporal de toda la vida. Venetoclax en combinación con obinutuzumab se comparó frente a las opciones terapéuticas más utilizadas para estos pacientes en el momento del diseño del estudio: clorambucilo en combinación con obinutuzumab, ibrutinib, fludarabina en combinación con ciclofosfamida y rituximab, y bendamustina en combinación con rituximab. Los datos de eficacia para estimar las curvas de supervivencia fueron derivados del estudio CLL14 y

analysis was conducted from the perspective of the Spanish National Healthcare System and included direct healthcare costs (i.e. pharmacological costs and their administration), and those associated with the management of the disease and adverse events. The resource use was validated by an expert group. Quality of life data were used to estimate the quality-adjusted life years obtained for each alternative. A threshold of €25,000/quality-adjusted life years was used. The robustness of the model was evaluated using deterministic and probabilistic sensitivity analyses.

Results: Venetoclax in combination with obinutuzumab was shown to be a dominant alternative compared to the rest of the treatment alternatives, with a lower cost per patient (€−67,869 compared to chlorambucil in combination with obinutuzumab, €−375,952 compared to ibrutinib, €−61,996 compared to fludarabine in combination with cyclophosphamide and rituximab, and €−77,398 compared to bendamustine in combination with rituximab). It also had a greater gain in quality-adjusted life years (0.551 quality-adjusted life years gained compared to chlorambucil in combination with obinutuzumab and ibrutinib, 1.639 quality-adjusted life years gained compared to fludarabine in combination with cyclophosphamide and rituximab, and 1.186 quality-adjusted life years gained compared to bendamustine in combination with rituximab). Between 68% and 85% of the simulations performed in the sensitivity analysis showed that venetoclax in combination with obinutuzumab had lower costs and more quality-adjusted life years gained.

Conclusions: Venetoclax in combination with obinutuzumab is an efficient and dominant alternative for treating previously untreated patients with chronic lymphocytic leukaemia compared to the available alternatives and from the perspective of the Spanish National Health System.

de un metaanálisis en red. El análisis consideró la perspectiva del Sistema Nacional de Salud incluyendo los costes sanitarios directos, en concreto los farmacológicos y su administración, y los asociados al manejo de la enfermedad y acontecimientos adversos. El uso de recursos fue validado por un grupo de expertos. Se emplearon datos de calidad de vida para estimar los años de vida ajustados por calidad obtenidos para cada alternativa. Se consideró un umbral de 25.000 €/años de vida ajustados por calidad. La robustez del modelo se evaluó mediante análisis de sensibilidad deterministicos y probabilísticos.

Resultados: Venetoclax en combinación con obinutuzumab se mostró como una alternativa dominante frente al resto de alternativas de tratamiento, con un menor coste por paciente (−67.869 € frente a clorambucilo en combinación con obinutuzumab, −375.952 € frente a ibrutinib, −61.996 € frente a fludarabina en combinación con ciclofosfamida y rituximab, y −77.398 € frente a bendamustina en combinación con rituximab) y una mayor ganancia en años de vida ajustados por calidad (0,551 años de vida ajustados por calidad ganados frente a clorambucilo en combinación con obinutuzumab e ibrutinib, 1,639 años de vida ajustados por calidad ganados frente a fludarabina en combinación con ciclofosfamida y rituximab, y 1,186 años de vida ajustados por calidad ganados frente a bendamustina en combinación con rituximab). Entre el 68% y el 85% de las simulaciones realizadas en el análisis de sensibilidad mostraban a venetoclax en combinación con obinutuzumab con un menor coste y un mayor número de años de vida ajustados por calidad ganados.

Conclusiones: Venetoclax en combinación con obinutuzumab se muestra como una alternativa eficiente y dominante como tratamiento de pacientes con leucemia linfocítica crónica no tratados previamente frente a las alternativas disponibles y desde la perspectiva del Sistema Nacional de Salud.

Introduction

Chronic lymphocytic leukaemia (CLL) is a lymphoproliferative disorder characterized by the expansion of mature-appearing CD5+ B cells in the peripheral blood, secondary lymphoid tissues, and bone marrow[1]. CLL is the most common form of leukaemia in adults in Western countries, with an estimated incidence of 4 to 5 cases per 100,000 population-years and a particularly significant prevalence in areas in which the population is older[2]. More than half of these patients have age-related comorbidities, such as hypertension, diabetes, osteoarthritis, or cardiorespiratory involvement[3]. The treatment decision is based on the presence or absence of adverse prognostic factors (deletion [17p], deletion [11q], *TP53* mutation, *IGHV* mutational status) and on the functional status of the patient[2].

In recent years, significant advances have been made in understanding the pathophysiology of CLL, and substantial progress has been made in the clinical management of the disease due to the identification of poor prognostic genetic variables, particularly those associated with chemoresistance and progression to highly aggressive forms of CLL[4,5]. Currently, chemoimmunotherapy is being displaced by biologic therapies, such as B-lymphocyte receptor inhibitors and BCL-2 inhibitors[6,7].

Overexpression of BCL-2 contributes to the evasion of apoptosis, making tumour cells highly dependent on BCL-2 for their survival[8]. High expression of BCL-2 is observed uniformly across all CLL subtypes[9]. Venetoclax, the first selective BCL-2 inhibitor, restores the ability of tumour cells to initiate the process of apoptosis and, administered together with obinutuzumab, has a complementary and synergistic mechanism of action that provides high efficacy rates and profound responses, with a fixed duration of 1 year of treatment[5,10]. In the CLL14 trial, 2-year progression-free survival (PFS) was 88.2% (95% confidence interval [CI]: 83.7%-92.6%) in patients treated with venetoclax in combination with obinutuzumab (VenO) vs 64.1% (95% CI: 83.7%-92.6%) in the control group treated with chlorambucil in combination with obinutuzumab (ClbO)[5]. After a median follow-up of 28.1 months, these results showed a slow-down in the risk of progression or death with VenO (hazard ratio [HR] = 0.35; 95% CI: 0.23-0.53; P < 0.001). At data cutoff, the results of overall survival (OS) were immature, with the median not having been reached in either group (less than 10% of events in each arm)[5]. These results were confirmed at the subsequent cutoff time, after a median follow-up of 39.6 months, where PFS was 81.9% in the VenO arm and

49.5% in the ClbO arm. These results showed a slow-down in the risk of progression or death with VenO (HR = 0.31; 95% CI: 0.22-0.44; P < 0.001)[11].

The aim of this study was to conduct a cost-utility analysis to determine whether VenO, which is a therapy indicated for previously untreated patients with CLL, would be an efficient intervention within the Spanish National Health System (NHS) compared to the therapeutic alternatives available in Spain.

Methods

Study participants and comparators

The characteristics of the study population were matched to those of the patients included in the CLL14 Phase 3 clinical trial[5] (i.e., patients with CLL who had not received prior treatment, 33% female, and a median age of 71.1 years).

At the time of study design, VenO was also compared to the most commonly used first-line alternative treatments in CLL patients: ClbO, fludarabine in combination with cyclophosphamide and rituximab (FCR), bendamustine in combination with rituximab (BR), and ibrutinib.

Type of analysis

It was estimated the mean cost and effectiveness per patient associated with each therapeutic alternative and calculated the incremental cost-utility ratio of VenO vs the other comparators to determine the additional cost of VenO to obtain 1 quality-adjusted life year (QALY).

The analysis was conducted from the perspective of the Spanish NHS, and included direct health care costs (updated to 2020 euros using the historical year-on-year consumer price index). The time horizon was extended to the patient's lifetime. An annual discount rate of 3% was applied to costs and clinical results[12]. The cost-effectiveness threshold was considered to be €25,000/QALY[13].

The adaptation to the Spanish context was facilitated after consultation with an expert group selected based on their experience and knowledge of clinical practice. (i.e. the co-authors of the present study). After completing individual questionnaires, a base case was proposed for validation.

Cost-utility analysis of venetoclax in combination with obinutuzumab as first-line treatment of chronic lymphocytic leukaemia in Spain

Farmacia Hospitalaria 2022
I Vol. 46 I Nº 3 I 121 - 132 I **123**

Figure 1. *Simplified outline of the model.*
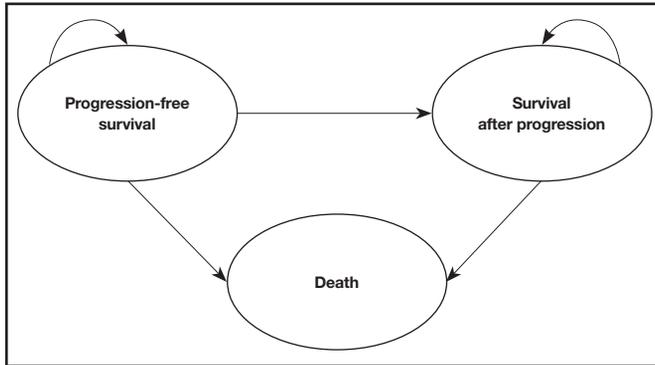
Structure of the model

A partitioned survival model[14,15] was adapted to the Spanish setting. A model previously presented at the National Institute for Health and Clinical Excellence (NICE), and that simulated the evolution of patients with CLL who have not received previous treatment across different clinical situations (health states). Figure 1 shows a simplified schematic of the model, with three mutually exclusive health states: progression-free state, state after progression, and death. The proportion of patients who were alive for each cycle of the model (28-day cycles) was estimated from the area under the OS curve, and the proportion of patients who were alive free of progression was estimated from the area under the PFS curve. The proportion of patients who were alive after progression was estimated by the difference between the OS and PFS curves. The OS and PFS curves were estimated using parametric curves based on clinical evidence. To obtain the best estimate of the pharmacological cost, the model considered time-on-treatment information to measure discontinuation, which can occur due to adverse events (AEs) or disease progression. It should be noted that treatments with VenO, ClbO, FCR, and BR have a fixed duration, whereas the duration of treatment with ibrutinib is indefinite until disease progression or unacceptable toxicity. After discontinuation, patients were assumed to be able to receive subsequent treatments.

Clinical data

The efficacy data used in the VenO and ClbO model were derived from the CLL14 trial[5]. Because the study follow-up period was shorter than

the horizon used in the economic studies (i.e. the recommended horizon being the patient's lifetime), the PFS, OS, and time-on-treatment curves had to be extrapolated using parametric distribution functions fitted to Kaplan-Meier (KM) curves. A goodness-of-fit criteria was followed in order to decide which parametric distribution was the best fit. This criteria described how well a given distribution fits a set of observations (KM curves). Specifically, the Akaike and Bayesian information criteria[15] were followed (Appendix 1). The parameterized curves were adjusted according to the overall mortality of the Spanish population[16], thus preventing the survival curves estimated in the model from being above the survival of the general population.

In the absence of direct evidence on ibrutinib, FCR, and BR as comparators compared to VenO, the parametric curves were estimated using HRs vs VenO (reference treatment). These were obtained from a Bayesian fixed-effect network meta-analysis[17]. This approach allowed an indirect comparison of VenO vs ibrutinib, FCR, or BR. To derive the PFS curve for ibrutinib, FCR and BR, it was assumed the corresponding HRs relative to VenO derived from the network meta-analysis. A log-logistic distribution for the PFS curve for VenO and ClbO was used (Figure 2A).

Regarding OS, it was assumed that there were no differences between VenO and ClbO based on the results of the CLL14 trial and corroborated by expert opinion. Thus, an exponential distribution was assumed for the purposes of extrapolation. To derive the OS curve for ibrutinib, FCR and BR, it was used the HRs relative to VenO derived from network meta-analyses (Figure 2B).

The analysis used time-on-treatment information to measure discontinuation. VenO, ClbO, FCR, and BR treatments have a fixed time duration (12 cycles for VenO and ClbO, 6 cycles for FCR and BR), whereas the duration of treatment with ibrutinib is considered to be indefinite until disease progression or unacceptable toxicity (a median of 60 months was assumed based on longer-term follow-up in the RESONATE-2 study, in which the median PFS was not reached[4]). After discontinuation, it was assumed that patients were able to receive subsequent treatments. For this purpose, a log-logistic distribution was assumed for VenO and ClbO, whereas the PFS curve was assumed for ibrutinib, FCR, and BR.

Quality of life

For the estimation of QALYs, different utility values were assumed depending on the health status of the patients. The utility values were used to represent the quality of life associated with a particular health status on a scale from 0 (death) to 1 (perfect health). Specifically, a utility of 0.80 was used for PFS health status (NICE TA174) and 0.68 for survival-after-progression status[18,19]. To represent the loss of utility (disutility) associated with increasing

Figure 2. *Survival curves and time to need for next treatment.*

BR: bendamustine in combination with rituximab; ClbO: chlorambucil in combination with obinutuzumab; FCR: fludarabine in combination with cyclophosphamide and rituximab; Ibr: ibrutinib; OS: overall survival; PFS: progression-free survival; VenO: venetoclax in combination with obinutuzumab.
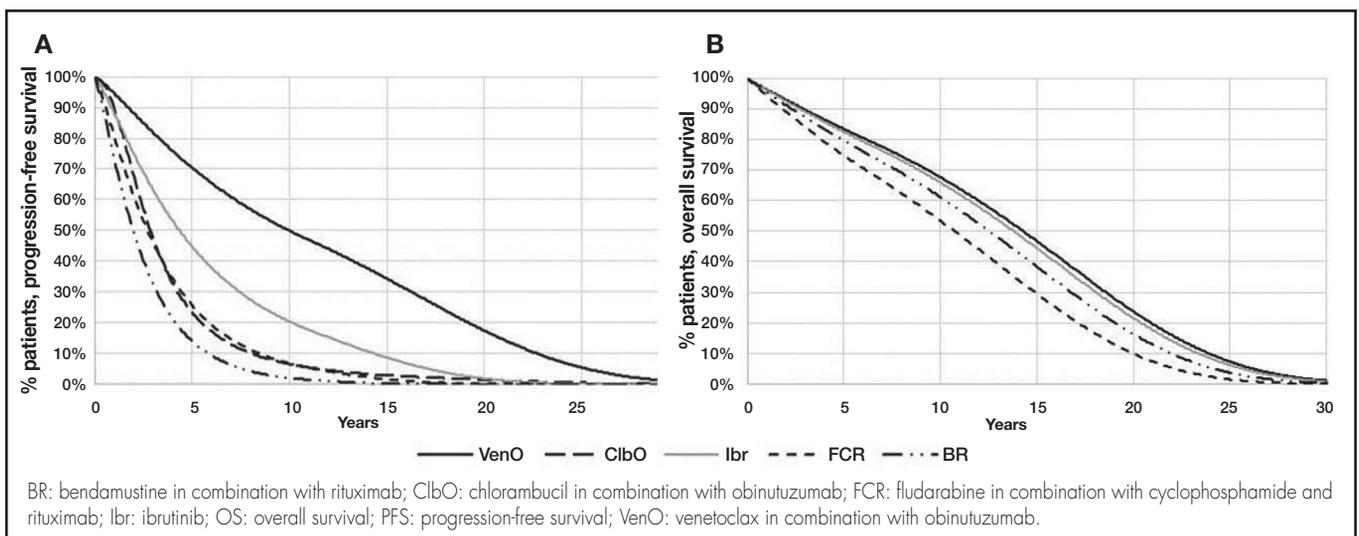
Table 1. Resource use and costs of analysis

Pharmacological cost				
			Treatment after progression	
Treatment	**Cost[21]**	**Comment**	**Base case**	**Sensitivity analysis**
VenO[5]	€101,975	Cost, 12 treatment cycles	50% Ibr, 50% VenR	90% Ibr, 10% VenR
Venetoclax	€70,215	12 treatment cycles		
Obinutuzumab	€31,760	6 treatment cycles		
Ibrutinib[4,22]	€400,473	Cost until progression (assuming 60 months following RESONATE-2[4])	100% Ven	100% VenR
FCR[23]	€10,323	Cost, 6 treatment cycles	50% Ibr, 50% VenR	–
BR[23]	€12,499	Cost, 6 treatment cycles	50% Ibr, 50% VenR	25% Ibr, 75% VenR
ClbO[5]	€31,778	Cost, 12 treatment cycles	50% Ibr, 50% VenR	25% Ibr, 75% VenR
Treatment duration after progression (mo)			Ibr: 41.0[22]; VenR: 24.4[24]; Ven: 16.0[25]	

Cost by administration route[26]			
Intravenous administration	€240.43	**Subcutaneous administration (first)**	€30.13

Cost, disutility, and percentage of patients with adverse events							
Adverse event*	**Cost[26]**	**Disutility and duration**	**VenO[5]**	**ClbO[5]**	**Ibrutinib[27]**	**FCR[28]**	**BR[23]**
Weakness	€592.61	−0.115[29,30] (35.3 days)[29]	2.80%	0.50%	–	–	–
Diarrhoea	€454.65	−0.08[19,31] (3.5 days)[32]	3.80%	0.50%	4.00%	–	7.00%
Dyspnoea	€178.52	−0.103[29,30] (12.7 days)[29]	2.40%	0.50%	–	–	–
Febrile neutropenia	€2,749.45	−0.15[30,32] (3.5 days)[32]	5.20%	3.70%	1.00%	–	–
Infusion reactions	€892.10	−0.2[32] (3.5 days)[32]	9.00%	10.30%	–	–	–
Leukopenia	€1,628.28	−0.09** (14.0 days)[29]	2.40%	4.70%	–	24.00%	48.00%
Neutropenia	€1,697.72	−0.09[32,33] (3.5 days)[32]	52.80%	47.70%	12.00%	34.00%	59.00%
Pneumonia	€4,460.89	−0.195[34] (18.2 days)[35]	5.70%	4.20%	–	–	9.00%
Sepsis	€6,866.85	−0.195[34] (7.0 days)[35]	4.20%	1.40%	–	–	1.00%
Thrombocytopenia	€942.87	−0.108[34] (23.2 days)[35]	13.70%	15.00%	–	7.00%	14.00%

Costs associated with disease management			
		HEALTH STATE (annual units)	
Health resources	**Unit cost[26]**	**Without progression**	**After progression**
Complete blood count	€4.75	8	10
Lactate dehydrogenase test	€5.66	7	8
Chest X-ray	€38.20	1	1
Bone marrow study	€357.55	0	1
Haematologist visit	€86.76	8	10
Other specialist visits	€86.76	1	3
Blood transfusion	€428.29	0	1
Computed axial tomography (CAT) scan	€162.66	2	2
Biochemistry	€1.69	8	9
Liver function tests	€17.51	7	7
Blood immunoglobulin test	€11.93	2	3
Total annual cost		**€1,382**	**€2,544**
Costs of terminal care at end-of-life[6]	€3,874.01	(applied in the cycle before death)	

*Considered to be serious adverse events (neutropenia, febrile neutropenia, pneumonia, sepsis, and thrombocytopenia) and grade 3-4 with at least 2% difference between VenO and ClbO identified in the CLL14 study. Assumed to occur in the first cycle of the model.

**Assumed neutropenia.

BR: bendamustine in combination with rituximab; ClbO: chlorambucil in combination with obinutuzumab; FCR: fludarabine in combination with cyclophosphamide and rituximab; Ibr: ibrutinib; Ven: venetoclax; VenO: venetoclax in combination with obinutuzumab; VenR: venetoclax in combination rituximab.

Cost-utility analysis of venetoclax in combination with obinutuzumab as first-line treatment of chronic lymphocytic leukaemia in Spain

Farmacia Hospitalaria 2022
I Vol. 46 I N° 3 I 121 - 132 I 125

patient age, the defined utilities were adjusted by the utility according to the age of the general Spanish population derived from the Spanish National Health Survey (available from the Spanish National Institute of Statistics for 2011/12)[20]. The model also addressed disutility due to treatment-associated AEs. It was assumed that AEs, as well as their effects on quality of life and economic effects, occur in the first cycle of the analysis.

Resource use and costs

The analysis addressed the direct healthcare costs associated with the management of CLL (Table 1). The pharmacological cost, including treatments after progression, was calculated based on the laboratory selling price[21]. The use of resources and assumptions made were validated by clinical expert opinion.

Sensitivity analysis

Several sensitivity analyses were performed to assess the uncertainty of the variables used in the model and to determine the robustness of the base case results.

Firstly, results were obtained by varying the base case discount rate (0% and 5%).

Given the differences in resource use in patient management indicated by the clinical experts, the annual cost of patient management in both the progression-free state and after progression was varied by ±20%. Discrepancies were also noted regarding the distribution of subsequent treatments after disease progression for each alternative treatment, except in the case of FCR, where it remained the same (Table 1).

A probabilistic sensitivity analysis was also performed by simultaneously modifying the model parameters according to an established distribution (Appendix 2). Specifically, 1000 simulations were performed using the Monte-Carlo method[36].

Results

The base case results showed that the costs per patient were lower and the gains in QALYs were greater with VenO than with other treatment alternatives (Table 2). In terms of economic assessment, VenO was the dominant alternative.

The lower cost of VenO vs ClbO, FCR, and BR was mainly due to a lower pharmacological cost of the subsequent treatments administered after

progression. The lower cost of VenO vs ibrutinib as a comparator was mainly due to the shorter duration of time on treatment with VenO.

The sensitivity analyses supported these results. Table 3 shows the results of the deterministic sensitivity analyses. The probabilistic sensitivity analysis showed that 68% to 85% of the simulations performed identified VenO as the dominant alternative, with lower costs and more QALYs gained (Figure 3).

Discussion

This study assessed the efficiency of VenO in the Spanish setting as a treatment for CLL in previously untreated patients against comparators that are commonly used in clinical practice and are indicated for such pathology. The results of this analysis were presented at the LXII National Congress of the Spanish Society of Haematology and Chemotherapy (SEHH) and at the XXXVI National Congress of the Spanish Society of Thrombosis and Haemostasis (SETH)[37].

The modelled population was based on the CLL14 trial population, which included patients with unfavourable cytogenetic prognosis (including patients with 17p deletion and TP53 mutation). It is noteworthy that these patients were not excluded from the baseline study population, what can make the study population more representative of the real clinical practice. The pivotal ibrutinib trial, RESONATE-2[4], excluded patients with 17p deletion, which was thus a methodological limitation of the study design.

In the present study, VenO was considered to be the dominant alternative to all comparators because of the increased number of QALYs obtained and lower cost per patient. These results are mainly due to VenO achieving greater PFS due to its increased effectiveness and its lower pharmacological costs. The cost of using VenO was substantially lower than that of ibrutinib because VenO has a fixed treatment duration of 1 year, whereas ibrutinib has an indefinite treatment duration until disease progression or unacceptable toxicity (a median treatment duration of 60 months was assumed based on the RESONATE-2[4] study, in which the median PFS was not reached). This is also particularly relevant from a budgetary point of view because, in addition to being efficient, the VenO combination can generate savings in pharmaceutical expenditures (the pharmacological cost of treatment per patient is €101,975 with VenO compared to €400,473 with ibrutinib)[38], while providing budgetary predictability due to the fixed duration of treatment. Compared to the other comparators, VenO has lower treatment costs after disease progression. This lower cost is due to the high

Table 2. Base case results

	VenO	ClbO	Ibr	FCR	BR
Total cost per patient	**€162,897**	**€237,587**	**€538,849**	**€232,574**	**€248,208**
Associated with treatment	€95,884	€32,501	€426,031	€12,078	€16,662
Associated with patient follow-up	€17,973	€24,414	€21,759	€19,272	€23,100
Associated with subsequent treatments	€43,079	€175,218	€88,140	€197,313	€203,274
Other costs*	€5,960	€5,455	€2,919	€3,912	€5,172
QALYs	**7.614**	**7.063**	**7.103**	**5.975**	**6.428**
Incremental cost	*Reference*	*€−74,690*	*€−375,952*	*€−69,677*	*€−85,311*
Incremental QALYs	*Reference*	*0.551*	*0.511*	*1.639*	*1.186*
ICER		€−135.554/AVAC VenO DOMINANT	€−735.718/AVAC VenO DOMINANT	€−42.512/AVAC VenO DOMINANT	€−71.932/AVAC VenO DOMINANT

*Adverse events, end-of-life cost, tumour lysis syndrome prophylaxis.
BR: bendamustine in combination with rituximab; ClbO: chlorambucil in combination with obinutuzumab; FCR: fludarabine in combination with cyclophosphamide and rituximab; Ibr: ibrutinib; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenO: venetoclax in combination with obinutuzumab.

Table 3. Results of the deterministic sensitivity analysis

	Incremental cost	Incremental QALY	ICER	
VenO vs		**Discount rate, 0%**		
ClbO	€ −105,645	0.723	€ −146,131	Dominant
FCR	€ −75,703	2.282	€ −33,177	Dominant
BR	€ −86,975	1.613	€ −53,908	Dominant
Ibr	€ −436,534	0.706	€ −617,890	Dominant
VenO vs		**Discount rate, 5%**		
ClbO	€ −59,368	0.468	€ −126,772	Dominant
FCR	€ −63,835	1.345	€ −47,458	Dominant
BR	€ −81,565	0.989	€ −82,474	Dominant
Ibr	€ −342,614	0.421	€ −814,349	Dominant
VenO vs		**Cost of patient management free of progression, (−20%)**		
ClbO	€ −76,223	0.551	€ −138,259	Dominant
FCR	€ −71,259	1.639	€ −43,475	Dominant
BR	€ −87,151	1.186	€ −73,460	Dominant
Ibr	€ −377,024	0.511	€ −738,164	Dominant
VenO vs		**Cost of patient management free of progression, (+20%)**		
ClbO	€ −73,158	0.551	€ −132,700	Dominant
FCR	€ −68,096	1.639	€ −41,545	Dominant
BR	€ −83,471	1.186	€ −70,358	Dominant
Ibr	€ −374,881	0.511	€ −733,968	Dominant
VenO vs		**Cost of patient management after progression, (−20%)**		
ClbO	€ −71,870	0.551	€ −130,363	Dominant
FCR	€ −67,836	1.639	€ −41,387	Dominant
BR	€ −82,446	1.186	€ −69,494	Dominant
Ibr	€ −374,123	0.511	€ −732,486	Dominant
VenO vs		**Cost of patient management after progression, (+20%)**		
ClbO	€ −77,511	0.551	€ −140,596	Dominant
FCR	€ −71,519	1.639	€ −43,634	Dominant
BR	€ −88,177	1.186	€ −74,324	Dominant
Ibr	€ −377,781	0.511	€ −739,646	Dominant
VenO vs		**Cost of patient management free of progression and after progression, (−20%)**		
ClbO	€ −73,402	0.551	€ −133,143	Dominant
FCR	€ −69,418	1.639	€ −42,352	Dominant
BR	€ −84,286	1.186	€ −71,045	Dominant
Ibr	€ −375,195	0.511	€ −734,583	Dominant
VenO vs		**Cost of patient management free of progression and after progression, (+20%)**		
ClbO	€ −75,979	0.551	€ −137,816	Dominant
FCR	€ −69,937	1.639	€ −42,669	Dominant
BR	€ −86,337	1.186	€ −72,773	Dominant
Ibr	€ −376,709	0.511	€ −737,549	Dominant
VenO vs		**Distribution of subsequent treatments after progression, (Table 1)**		
ClbO	€ −58,233	0.551	€ −105,628	Dominant
FCR	€ −73,357	1.639	€ −44,755	Dominant
BR	€ −65,630	1.186	€ −55,319	Dominant
Ibr	€ −434,373	0.511	€ −850,446	Dominant

BR: bendamustine in combination with rituximab; ClbO: chlorambucil in combination with obinutuzumab; FCR: fludarabine in combination with cyclophosphamide and rituximab; Ibr: ibrutinib; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; VenO: venetoclax in combination with obinutuzumab.

Cost-utility analysis of venetoclax in combination with obinutuzumab as first-line treatment of chronic lymphocytic leukaemia in Spain

Farmacia Hospitalaria 2022
Ι Vol. 46 Ι N° 3 Ι 121 - 132 Ι **127**

Figure 3. *Probabilistic sensitivity analysis.*

BR: bendamustine in combination with rituximab; ClbO: chlorambucil in combination with obinutuzumab; FCR: fludarabine in combination with cyclophosphamide and rituximab; Ibr: ibrutinib; QALY: quality-adjusted life year; VenO: venetoclax in combination with obinutuzumab.
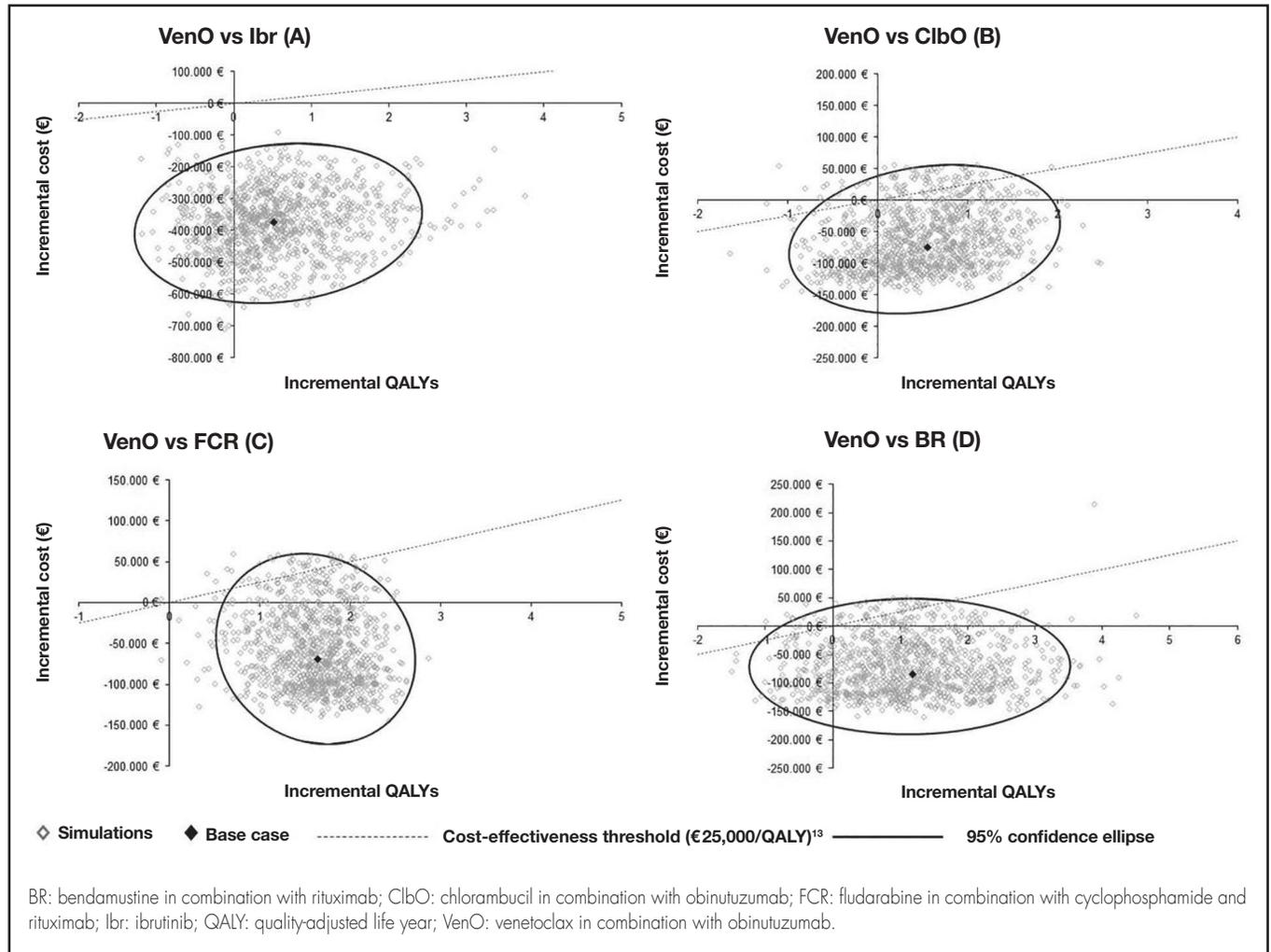
rates of deep response achieved with VenO. Deep response is understood as the achievement of complete remission and undetectable minimal residual disease, which avoids or delays the initiation of a second line of treatment[11]. Costs related to patient follow-up are also lower with VenO than with the other alternatives because the patient remains longer in progression-free and treatment-free states.

Several cost-effectiveness studies on CLL in previously untreated patients have been conducted in other countries, but most of these studies were conducted prior to the approval of VenO and none have used this therapy as a comparator.

Soini *et al.* (2016) studied the cost-effectiveness of first-line treatments for CLL in patients ineligible for full-dose fludarabine[39]. The most cost-effective treatment was ClbO vs the other alternatives studied, such as chlorambucil in combination with ofatumumab, chlorambucil in combination with rituximab, and BR.

Furthermore, after the approval of ibrutinib, several studies conducted in other countries conducted economic analyses on its efficiency as first-line treatment for CLL[40-42]. Although the results of these studies are not directly applicable to Spain, all of them seem to agree that ibrutinib offers reasonable results in terms of PFS and QALYs, but it is not considered to be cost-effective.

Due to the type of analysis, the present study is limited by the need to extrapolate survival data to a longer-term horizon than the trial follow-up period. However, the extrapolation was based on the distributions with the best goodness-of-fit to the KM curves in the CLL study[14]. It would be relevant

to perform additional analyses when longer-term CLL14 study follow-up data are obtained or to conduct real-world evidence studies.

On the other hand, in the absence of direct evidence related to the other comparators, except for ClbO[5], an indirect comparison was performed by means of a network meta-analysis. This type of analysis is not free of limitations, which are mainly at the level of methodological similarity (i.e. heterogeneity between studies). Nevertheless, it is the only possible alternative in order to be able to compare treatments that have not been directly compared in clinical trials. Other limitations are the differences in methodology and the patient selection procedure between the clinical trials chosen for each treatment. To increase the external validity of this type of analysis, all pivotal clinical trials for CLL treatments should include the same type of patients (not excluding those with unfavourable prognosis) and demonstrate efficacy and safety data over the same time horizon. At the time the CLL14 study was designed, ClbO was the standard treatment for this type of patient, although currently ibrutinib is considered to be the standard treatment for previously untreated CLL patients with the 17p deletion or *TP53* mutation.

In conclusion, this study shows that VenO is emerging as an efficient and dominant alternative for the treatment of CLL in previously untreated patients in Spain. According to our analysis, the introduction of VenO in the Spanish NHS could reduce treatment costs, costs associated with patient follow-up, and the costs of subsequent treatments after progression, as well as improve the life expectancy and quality of life of Spanish patients with CLL.

Funding

Acknowledgments

Conflicts of interest

Estela Moreno Martínez has received honoraria for her participation in training activities, lectures, and expert panels from AbbVie, Amgen, Astellas, Astrazeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Fresenius Kabi, Incyte Biosciences Iberia, Ipsen, Janssen, Merck SL, Merck Sharp & Dohme, Novartis, Pierre Fabre, Roche, Sanofi and Tesaro.

Javier de la Serna Torroba has received honoraria for his participation in training activities, lectures, and expert panels from AbbVie, AstraZeneca, Beigene Gilead, Janssen and Roche.

Vicente Escudero Vilaplana has conducted training support activities or received fees for lectures or consulting services from AbbVie, Astellas, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis and Pfizer.

José Ángel Hernández Rivas has been a consultant and lecturer for Janssen, AbbVie, Gilead, Roche, BMS-Celgene, Takeda, AstraZeneca and Beigene.

Marina Sánchez Cuervo has participated in consultancies for AbbVie.

Raquel Sánchez Hernández is an employee of AbbVie and may own AbbVie stock.

Presentation at Congresses

LXII Congreso Nacional de la Sociedad Española de Hematología y Hemoterapia and XXXVI Congreso Nacional de la Sociedad Española de Trombosis y Hemostasia. Virtual; October 26-30, 2020.

Contribution to the scientific literature

This is the first cost-utility study to assess the potential efficiency of including venetoclax in combination with obinutuzumab in the pharmaceutical provision of the Spanish National Health System as an alternative for the treatment of chronic lymphocytic leukaemia in previously untreated patients in Spain.

Annex 1

Parametric distributions assessed to extrapolate the PFS and OS curves for VenO and ClbO, and the Akaike (AIC) and Bayesian (BIC) information criteria

Distribución	PLS				OS	
	AIC		BIC		AIC	BIC
	VenO	ClbO	VenO	ClbO	VenO and ClbO	
Exponential	779.68	1,796.62	786.39	1,803.32	1,023.74	1,035.88
Weibull	780.45	1,766.70	790.52	1,776.74	1,025.50	1,041.68
Gompertz	778.49	1,773.38	788.56	1,783.42	1,024.99	1,041.17
Log-logistic	781.14	1,759.73	791.21	1,769.77	1,024.82	1,041.00
Log-normal	783.00	1,761.13	793.07	1,771.17	1,022.97	1,039.15
Gamma	780.61	1,763.38	790.68	1,773.43	1,025.41	1,041.59
Generalized gamma	782.08	1,763.03	795.50	1,776.42	1,024.40	1,044.62

AIC: Akaike information criteria; BIC: Bayesian information criteria; ClbO: chlorambucil in combination with obinutuzumab; OS: overall survival; PFS: progression-free survival; VenO: venetoclax in combination with obinutuzumab.

Annex 2

Probabilistic sensitivity analysis: parameters and distributions

Variable	Deterministic value	Standard error	Distribution	Parameter 1	Parameter 2
Characteristics of the population					
Women (%)	33%	0.023	Beta	142.6690	288.3310
Age	71.08	0.390	Normal	71.0787	0.3897
Weight	70.00	0.774	Normal	70.0000	0.7736
Utilities by health state					
Utility status without progression	0.80	0.080	Beta	19.2000	4.8000
Utility status after progression	0.68	0.068	Beta	31.3200	14.7388

Cost-utility analysis of venetoclax in combination with obinutuzumab as first-line treatment of chronic lymphocytic leukaemia in Spain

Farmacia Hospitalaria 2022
❙ Vol. 46 ❙ N° 3 ❙ 121 - 132 ❙ **129**

Annex 2 *(cont.)*

Probabilistic sensitivity analysis: parameters and distributions

Variable	Deterministic value	Standard error	Distribution	Parameter 1	Parameter 2
Resource use by health state					
Without progression: Complete blood count	0.613	0.061	Gamma	100.0000	0.0061
Without progression: Lactate dehydrogenase test	0.537	0.054	Gamma	100.0000	0.0054
Progression free: Chest X-Ray	0.077	0.008	Gamma	100.0000	0.0008
Progression free: Haematologist visit	0.613	0.061	Gamma	100.0000	0.0061
Progression free: Other specialist visits	0.077	0.008	Gamma	100.0000	0.0008
Progression free: Computed axial tomography (CAT) scan	0.153	0.015	Gamma	100.0000	0.0015
Progression free: Biochemistry	0.613	0.061	Gamma	100.0000	0.0061
Progression free: Liver function tests	0.537	0.054	Gamma	100.0000	0.0054
Progression free: Blood immunoglobulin test	0.153	0.015	Gamma	100.0000	0.0015
After progression: Complete blood count	0.767	0.077	Gamma	100.0000	0.0077
After progression: Lactate dehydrogenase assay	0.613	0.061	Gamma	100.0000	0.0061
After progression: Chest X-ray	0.077	0.008	Gamma	100.0000	0.0008
After progression: Bone marrow study	0.077	0.008	Gamma	100.0000	0.0008
After progression: Haematologist visit	0.767	0.077	Gamma	100.0000	0.0077
After progression: Other specialist visits	0.230	0.023	Gamma	100.0000	0.0023
After progression: Blood transfusion	0.077	0.008	Gamma	100.0000	0.0008
After progression: Computed axial tomography (CAT) scan	0.153	0.015	Gamma	100.0000	0.0015
After progression: Biochemistry	0.690	0.069	Gamma	100.0000	0.0069
After progression: Liver function tests	0.537	0.054	Gamma	100.0000	0.0054
After progression: Blood immunoglobulin test	0.230	0.023	Gamma	100.0000	0.0023
Costs					
Complete blood count	€ 4.75	0.475	Gamma	100.0000	0.0475
Lactate dehydrogenase test	€ 5.66	0.566	Gamma	100.0000	0.0566
Chest X-ray	€ 38.20	3.820	Gamma	100.0000	0.3820
Bone marrow study	€ 357.55	35.755	Gamma	100.0000	3.5755
Haematologist visit	€ 86.76	8.676	Gamma	100.0000	0.8676
Other specialist visits	€ 86.76	8.676	Gamma	100.0000	0.8676
Blood transfusion	€ 428.29	42.829	Gamma	100.0000	4.2829
Terminal care at end of life	€ 3,874.01	387.401	Gamma	100.0000	38.7401
Computed axial tomography (CAT) scan	€ 162.66	16.266	Gamma	100.0000	1.6266
Biochemistry	€ 1.69	0.169	Gamma	100.0000	0.0169
Liver function tests	€ 17.51	1.751	Gamma	100.0000	0.1751
Blood immunoglobulin test	€ 11.93	1.193	Gamma	100.0000	0.1193
Cost by administration route					
Intravenous administration	€ 240.43	24.043	Gamma	100.0000	2.4043
Subcutaneous administration	€ 30.13	3.013	Gamma	100.0000	0.3013
Treatment duration after progression					
Ibrutinib (mo)	41.0	4.100	Gamma	100.0000	0.4100
Venetoclax in combination con rituximab (mo)	24.4	2.440	Gamma	100.0000	0.2440
Venetoclax monotherapy (mo)	16.0	1.600	Gamma	100.0000	0.1600

Annex 2 *(cont.)*

Probabilistic sensitivity analysis: parameters and distributions

Variable	Deterministic value	Standard error	Distribution	Parameter 1	Parameter 2
Percentage of patients with adverse events					
VenO: Weakness	2.80%	0.011	Gamma	6.1070	0.0046
VenO: Diarrhoea	3.80%	0.013	Gamma	8.3742	0.0045
VenO: Dyspnoea	2.40%	0.011	Gamma	5.2131	0.0046
VenO: Febrile neutropenia	5.20%	0.015	Gamma	11.6287	0.0045
VenO: Infusion reactions	9.00%	0.020	Gamma	20.9670	0.0043
VenO: Leukopenia	2.40%	0.011	Gamma	5.2131	0.0046
VenO: Neutropenia	52.80%	0.034	Gamma	237.1525	0.0022
VenO: Pneumonia	5.70%	0.016	Gamma	12.8144	0.0044
VenO: Sepsis	4.20%	0.014	Gamma	9.2944	0.0045
VenO: Thrombocytopenia	13.70%	0.024	Gamma	33.6547	0.0041
ClbO: Weakness	0.50%	0.005	Gamma	1.0754	0.0046
ClbO: Diarrhoea	0.50%	0.005	Gamma	1.0754	0.0046
ClbO: Dyspnoea	0.50%	0.005	Gamma	1.0754	0.0046
ClbO: Febrile neutropenia	3.70%	0.013	Gamma	8.2222	0.0045
ClbO: Infusion reactions	10.30%	0.021	Gamma	24.5730	0.0042
ClbO: Leukopenia	4.70%	0.014	Gamma	10.5540	0.0045
ClbO: Neutropenia	47.70%	0.034	Gamma	195.1778	0.0024
ClbO: Pneumonia	4.20%	0.014	Gamma	9.3820	0.0045
ClbO: Sepsis	1.40%	0.008	Gamma	3.0385	0.0046
ClbO: Thrombocytopenia	15.00%	0.024	Gamma	37.7647	0.0040
FCR: Leukopenia	24.00%	0.021	Gamma	127.5789	0.0019
FCR: Neutropenia	34.00%	0.024	Gamma	208.1212	0.0016
FCR: Thrombocytopenia	7.00%	0.013	Gamma	30.4086	0.0023
BR: Diarrhoea	7.00%	0.015	Gamma	21.0000	0.0033
BR: Leukopenia	48.00%	0.030	Gamma	257.5385	0.0019
BR: Neutropenia	59.00%	0.029	Gamma	401.4878	0.0015
BR: Pneumonia	9.00%	0.017	Gamma	27.5934	0.0033
BR: Sepsis	1.00%	0.006	Gamma	2.8182	0.0035
BR: Thrombocytopenia	14.00%	0.021	Gamma	45.4186	0.0031
Ibrutinib: Diarrhoea	4.00%	0.017	Gamma	5.6667	0.0071
Ibrutinib: Febrile neutropenia	1.00%	0.009	Gamma	1.3737	0.0073
Ibrutinib: Neutropenia	12.00%	0.028	Gamma	18.5455	0.0065
Disutilities and duration by adverse event					
Weakness	0.115	0.012	Gamma	100.0000	0.0012
Diarrhoea	0.080	0.005	Gamma	256.0000	0.0003
Dyspnoea	0.103	0.010	Gamma	100.0000	0.0010
Febrile neutropenia	0.150	0.015	Gamma	100.0000	0.0015
Infusion reactions	0.200	0.020	Gamma	100.0000	0.0020
Leukopenia	0.090	0.009	Gamma	100.0000	0.0009
Neutropenia	0.090	0.002	Gamma	3164.0625	0.0000
Pneumonia	0.195	0.004	Gamma	2500.0000	0.0001
Sepsis	0.195	0.004	Gamma	2500.0000	0.0001
Thrombocytopenia	0.108	0.012	Gamma	81.0000	0.0013
Weakness, duration (d)	35.33	3.533	Gamma	100.0000	0.3533
Diarrheal, duration (d)	3.50	0.350	Gamma	100.0000	0.0350
Dyspnoea, duration (d)	12.70	1.270	Gamma	100.0000	0.1270
Febrile neutropenia, duration (d)	3.50	0.350	Gamma	100.0000	0.0350
Infusion reactions, duration (d)	3.50	0.350	Gamma	100.0000	0.0350
Leukopenia, duration (d)	14.00	1.400	Gamma	100.0000	0.1400
Neutropenia, duration (d)	3.50	0.350	Gamma	100.0000	0.0350
Pneumonia, duration (d)	18.21	1.821	Gamma	100.0000	0.1821
Sepsis, duration (d)	7.00	0.700	Gamma	100.0000	0.0700
Thrombocytopenia, duration (d)	23.20	2.320	Gamma	100.0000	0.2320

Cost-utility analysis of venetoclax in combination with obinutuzumab as first-line treatment of chronic lymphocytic leukaemia in Spain

Farmacia Hospitalaria 2022
❙ Vol. 46 ❙ N° 3 ❙ 121 - 132 ❙ **131**

Annex 2 *(cont.)*

Probabilistic sensitivity analysis: parameters and distributions

Variable	Deterministic value	Standard error	Distribution	Parameter 1	Parameter 2
Cost of managing adverse events					
Weakness	€592.61	59.261	Gamma	100.0000	5.9261
Diarrhoea	€454.65	45.465	Gamma	100.0000	4.5465
Dyspnoea	€178.52	17.852	Gamma	100.0000	1.7852
Febrile neutropenia	€2,749.45	274.945	Gamma	100.0000	27.4945
Infusion reactions	€892.10	89.210	Gamma	100.0000	8.9210
Leukopenia	€1,628.28	162.828	Gamma	100.0000	16.2828
Neutropenia	€1,697.72	169.772	Gamma	100.0000	16.9772
Pneumonia	€4,460.89	446.089	Gamma	100.0000	44.6089
Sepsis	€6,866.85	686.685	Gamma	100.0000	68.6685
Thrombocytopenia	€942.87	94.287	Gamma	100.0000	9.4287

BR: bendamustine in combination with rituximab; ClbO: chlorambucil in combination with obinutuzumab; FCR: fludarabine in combination with cyclophosphamide and rituximab; VenO: venetoclax in combination with obinutuzumab.

Bibliography

1. Kipps TJ, Stevenson FK, Wu CJ, Croce CM, Packham G, Wierda WG, *et al.* Chronic lymphocytic leukaemia. Nat Rev Dis Prim. 2017;3(1):16096. DOI: 10.1038/nrdp.2016.96

2. Sociedad Española de Hematología y Hemoterapia (SEHH). Avances en cáncer hematológico [Internet]. 2020 [accessed 10/19/2021]. Available at: https://www.sehh.es/images/stories/recursos/2020/01/publicaciones/docs/02/online/files/basic-html/page4.html

3. Eichhorst B, Robak T, Montserrat E, Ghia P, Hillmen P, Hallek M, *et al.* Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015;26(suppl 5):v78-84. DOI: 10.1093/annonc/mdv303

4. Burger JA, Barr PM, Robak T, Owen C, Ghia P, Tedeschi A, *et al.* Long-term efficacy and safety of first-line ibrutinib treatment for patients with CLL/SLL: 5 years of follow-up from the phase 3 RESONATE-2 study. Leukemia. 2020;30(3):787-98. DOI: 10.1038/s41375-019-0602-x

5. Fischer K, Al-Sawaf O, Bahlo J, Fink AM, Tandon M, Dixon M, *et al.* Venetoclax and Obinutuzumab in Patients with CLL and Coexisting Conditions. N Engl J Med. 2019;380(23):2225-36. DOI: 10.1056/NEJMoa1815281

6. Guías de tratamiento de LLC. Versión diciembre 2021. Grupo Español de Leucemia Linfocítica Crónica (GELLC). Available at: https://www.gellc.es/images/pdf/guias_gellcv1.pdf

7. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Version 2.2022. Available at: https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1478

8. Leverson JD, Sampath D, Souers AJ, Rosenberg SH, Fairbrother WJ, Amiot M, *et al.* Found in Translation: How Preclinical Research Is Guiding the Clinical Development of the BCL2-Selective Inhibitor Venetoclax. Cancer Discov. 2017;7(12):1376-93. DOI: 10.1158/2159-8290.CD-17-0797

9. Del Gaizo Moore V, Brown JR, Certo M, Love TM, Novina CD, Letai A. Chronic lymphocytic leukemia requires BCL2 to sequester prodeath BIM, explaining sensitivity to BCL2 antagonist ABT-737. J Clin Invest. 2007;117(1):112-21. DOI: 10.1172/JCI28281

10. Flinn IW, Gribben JG, Dyer MJS, Wierda W, Maris MB, Furman RR, *et al.* Phase 1b study of venetoclax-obinutuzumab in previously untreated and relapsed/refractory chronic lymphocytic leukemia. Blood. 2019;133(26):2765-75. DOI: 10.1182/blood-2019-01-896290

11. Al-Sawaf O, Lilienweiss E, Bahlo J, Robrecht S, Fink AM, Patz M, *et al.* High efficacy of venetoclax plus obinutuzumab in patients with complex karyotype and chronic lymphocytic leukemia. Blood. 2020;135(11):866-70. DOI: 10.1182/blood.2019003451

12. López Bastida J, Oliva J, Antoñanzas F, García-Altés A, Gisbert R, Mar J, *et al.* Propuesta de guía para la evaluación económica aplicada a las tecnologías sanitarias. Gac Sanit. 2010;24(2):154-70. DOI: 10.1016/j.gaceta.2009.07.011

13. Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. Estimating a cost-effectiveness threshold for the Spanish NHS. Health Econ. 2018;27(4):746-61. DOI: 10.1002/hec.3633

14. Bagust A, Beale S. Survival Analysis and Extrapolation Modeling of Time-to-Event Clinical Trial Data for Economic Evaluation. Med Decis Mak. 2014;34(3):343-51. DOI: 10.1177/0272989X13497998

15. Latimer NR. Response to "Survival Analysis and Extrapolation Modeling of Time-to-Event Clinical Trial Data for Economic Evaluation: An Alternative Approach" by Bagust and Beale. Med Decis Mak. 2014;34(3):279-82. DOI: 10.1177/0272989X13511302

16. Instituto Nacional de Estadística (INE). Tablas de mortalidad por año, sexo, edad y funciones [Internet]. 2020 [accessed 05/05/2020]. Available at: https://www.ine.es/jaxiT3/Tabla.htm?t=27153

17. Sudhapalli P, Piena M, Palaka A, Mato A, Van de Wetering G, Manzoor B, *et al.* Systematic literature review and network meta-analysis comparing therapies for treatment-naive patients with chronic lymphocytic leukemia. Póster presentado de forma virtual en el XXV Congreso de la European Hematology Association, junio-octubre 2020. 2020 [accessed 12/02/2021]. Available at: https://library.ehaweb.org/eha/2020/eha25th/294643/kavita.sail.systematic.literature.review.and.network.meta-analysis.comparing.html

18. Hornberger J, Reyes C, Shewade A, Lerner S, Friedmann M, Han L, *et al.* Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. Leuk Lymphoma. 2012;53(2):225-34. DOI: 10.3109/10428194.2011.605918

19. Beusterien KM, Davies J, Leach M, Meiklejohn D, Grinspan JL, O'Toole A, *et al.* Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. Health Qual Life Outcomes. 2010;8(1):50. DOI: 10.1186/1477-7525-8-50

20. Instituto Nacional de Estadística (INE). Encuesta Nacional de Salud (ENSE) 2011/12 [Internet]. [accessed 05/08/2021]. Available at: https://www.mscbs.gob.es/estadEstudios/estadisticas/encuestaNacional/encuesta2011.htm

21. Consejo General de Colegios Oficiales de Farmacéuticos. Portal Farma. BotPLUS [Internet]. 2020 [accessed 05/28/2020]. Available at: https://botplusweb.portalfarma.com/

22. Byrd JC, Furman RR, Coutre S, Flinn IW, Burger JA, Blum KA, *et al.* Up to 7 Years of Follow-up of Single-Agent Ibrutinib in the Phase 1b/2 PCYC-1102 Trial of First Line and Relapsed/Refractory Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma. Blood. 2018;132(Suppl 1):3133. DOI: 10.1182/blood-2018-99-110847

23. Eichhorst B, Fink AM, Bahlo J, Busch R, Kovacs G, Maurer C, *et al.* First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial. Lancet Oncol. 2016;17(7):928-42. DOI: 10.1016/S1470-2045(16)30051-1

24. Kater AP, Seymour JF, Hillmen P, Eichhorst B, Langerak AW, Owen C, *et al.* Fixed Duration of Venetoclax-Rituximab in Relapsed/Refractory Chronic Lymphocytic Leukemia Eradicates Minimal Residual Disease and Prolongs Survival: Post-Treatment Follow-Up of the MURANO Phase III Study. J Clin Oncol. 2019;37(4):269-77. DOI: 10.1200/JCO.18.01580

25. Davids MS, Hallek M, Wierda W, Roberts AW, Stilgenbauer S, Jones JA, *et al*. Comprehensive Safety Analysis of Venetoclax Monotherapy for Patients with Relapsed/Refractory Chronic Lymphocytic Leukemia. Clin Cancer Res. 2018;24(18):4371-9. DOI: 10.1158/1078-0432.CCR-17-3761

26. Gisbert R, Brosa M. Healthcare cost database eSalud. Barcelona: Oblikue Consulting, SL. Información económica del sector sanitario [Internet]. 2020 [accessed 05/30/2020]. Available at: http://esalud.oblikue.com/

27. Barr PM, Robak T, Owen C, Tedeschi A, Bairey O, Bartlett NL, *et al*. Sustained efficacy and detailed clinical follow-up of first-line ibrutinib treatment in older patients with chronic lymphocytic leukemia: extended phase 3 results from RESONATE-2. Haematologica. 2018;103(9):1502-10. DOI: 10.3324/haematol.2018.192328

28. Hallek M, Fischer K, Fingerle-Rowson G, Fink A, Busch R, Mayer J, *et al*. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. Lancet. 2010;376(9747):1164-74. DOI: 10.1016/S0140-6736(10)61381-5

29. National Institute for Health and Care Excellence. TA306: Pixantrone monotherapy for treating multiply relapsed or refractory aggressive non-Hodgkin's B-cell lymphoma [Internet]. 2014 [accessed 11/09/2021]. Available at: https://www.nice.org.uk/guidance/ta306

30. Lloyd A, Nafees B, Narewska J, Dewilde S, Watkins J. Health state utilities for metastatic breast cancer. Br J Cancer. 2006;95(6):683-90. DOI: 10.1038/sj.bjc.6603326

31. National Institute for Health and Care Excellence. TA216: Bendamustine for the first-line treatment of chronic lymphocytic leukaemia [Internet]. 2011 [accessed 11/09/2021]. Available at: https://www.nice.org.uk/guidance/ta216.

32. National Institute for Health and Care Excellence. TA344: Ofatumumab in combination with chlorambucil or bendamustine for untreated chronic lymphocytic leukaemia [Internet]. 2015 [accessed 11/09/2021]. Available at: https://www.nice.org.uk/guidance/ta344

33. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. Health Qual Life Outcomes. 2008;6(1):84. DOI: 10.1186/1477-7525-6-84

34. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. Eur J Health Econ. 2013;14(5):749-59. DOI: 10.1007/s10198-012-0419-2

35. National Institute for Health and Care Excellence. TA359: Idelalisib for treating chronic lymphocytic leukaemia [Internet]. 2015 [accessed 11/09/2021]. Available at: https://www.nice.org.uk/guidance/ta359/documents/leukaemia-chronic-lymphocytic-previously-treated-idelalisib

36. Briggs AH. Handling Uncertainty in Cost-Effectiveness Models. Pharmacoeconomics. 2000;17(5):479-500. DOI: 10.2165/00019053-200017050-00006

37. Moreno Martínez E, De la Serna Torroba J, Escudero Vilaplana V, Hernández Rivas J, Sánchez Cuervo M, Sánchez Hernández R. Eficiencia de Venetoclax en combinación con obinutuzumab en el tratamiento de pacientes con LLC que no hayan recibido tratamiento previo en España. Haematologica. 2020;(Supl 3):S221.

38. Moreno Martínez E, De la Serna Torroba J, Escudero Vilaplana V, Hernández Rivas J, Sánchez Cuervo M, Sánchez Hernández R. Análisis del impacto presupuestario de venetoclax en combinación con obinutuzumab como tratamiento de pacientes con LLC que no hayan recibido tratamiento previo. Haematologica. 2020; 105(Supl 3):S214.

39. Soini E, Hautala A, Poikonen E, Becker U, Kyttälä M, Martikainen J. Cost-effectiveness of First-line Chronic Lymphocytic Leukemia Treatments When Full-dose Fludarabine Is Unsuitable. Clin Ther. 2016;38(4):889-904.e14. DOI: 10.1016/j.clinthera.2016.02.005

40. Sinha R, Redekop WK. Cost-Effectiveness of Ibrutinib Compared With Obinutuzumab With Chlorambucil in Untreated Chronic Lymphocytic Leukemia Patients With Comorbidities in the United Kingdom. Clin Lymphoma Myeloma Leuk. 2018;18(2):e131-42. DOI: 10.1016/j.clml.2017.12.005

41. Patel KK, Isufi I, Kothari S, Davidoff AJ, Gross CP, Huntington SF. Cost-effectiveness of first-line vs third-line ibrutinib in patients with untreated chronic lymphocytic leukemia. Blood. 2020;136(17):1946-55. DOI: 10.1182/blood.2020004922

42. Barnes JI, Divi V, Begaye A, Wong R, Coutre S, Owens DK, *et al*. Cost-effectiveness of ibrutinib as first-line therapy for chronic lymphocytic leukemia in older adults without deletion 17p. Blood Adv. 2018;2(15):1946-56. DOI: 10.1182/bloodadvances.2017015461