Cost-utility analysis of idelalisib in combination with rituximab in relapsed or refractory chronic lymphocytic leukaemia

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Abstract
Objective: To evaluate the incremental cost-utility ratio (ICUR) of idelalisib in combination with rituximab (IR) versus rituximab monotherapy (R) in the treatment of patients with relapsed or refractory (R/R) chronic lymphocytic leukaemia (CLL), from the Spanish National Health System (NHS) perspective.

Methods: A partitioned survival Markov model for a lifetime horizon (30 years) was developed to estimate costs (€, 2016) and quality-adjusted life years (QALY) with IR and R. Initial cohort included patients with CLL receiving a second or subsequent line (2L) of treatment with IR or R. Survival data were based on CLL clinical trial. Drug, administration, monitoring, adverse events and clinical management of CLL costs were included in the model. Costs and outcomes were discounted using a 3% annually. Deterministic and probabilistic sensitivity analyses (PSA) were performed.

Results: Compared to R, 2L IR treatment resulted in QALY gain of 3.147 (4.965 versus 1.818). Total costs were €118 254 for IR versus €23 874 for R. ICUR was €29 990/QALY gained with IR versus R. In the PSA, IR was cost-effective in 78% of iterations using a threshold of €45 000/QALY.

Conclusion: IR can be considered a cost-effective treatment compared to R, in the treatment of R/R CLL patients for the Spanish NHS.

KEYWORDS
chronic lymphocytic leukaemia, cost-effectiveness, cost-utility, idelalisib, rituximab

1 | INTRODUCTION

Chronic lymphocytic leukaemia (CLL) is a disease characterised by the proliferation and accumulation of immunoincompetent lymphocytes of small size, mature appearance and B-monoclonal phenotype. It is the most common form of adult leukaemia in Western countries with an estimated incidence of 4.2:100 000/year. The incidence increases to >30:100 000/year at an age of >80 years. The median age at diagnosis is 72 years. Approximately, 10% of the CLL patients are reported to be younger than 55 years.1

Many CLL patients relapse but remain asymptomatic and can be followed up without therapy for a long period of time. Therefore, treatment should only be initiated in patients with symptomatic active disease.1 Despite high response rates, CLL remains incurable. Patients...
usually alternate between response and relapse periods, with the responses becoming less frequent and durable over time, and relapses becoming more frequent, especially after a second relapse.2

Until recently, the treatment options for relapsed or refractory CLL were limited and included either retreatment with a prior regimen (fludarabine or chlorambucil combinations with rituximab) or agents such as ofatumumab, bendamustine, rituximab alone or combinations.3

Idelalisib (Zydelig®) is a small oral molecule, that is a potent and selective inhibitor of phosphatidylinositol 3-kinase p110δ (PI3Kδ), which is expressed in B-cell malignancies and is central to multiple signaling pathways that drive proliferation, survival, homing and retention of malignant cells in lymphoid tissues and bone marrow. By inhibiting PI3K delta kinases, idelalisib induces apoptosis and inhibits proliferation in primary patient-derived tumour samples and in cell lines derived from malignant B cells.4 Idelalisib is indicated in combination with an anti-CD20 monoclonal antibody (rituximab or ofatumumab) for the treatment of adult patients with CLL who have received at least one prior therapy, or as first-line treatment in the presence of 17p deletion or TP53 mutation in patients who are not eligible for any other therapies.5,6 The regimen has demonstrated an acceptable benefit-risk ratio being an optimal treatment in older patients or for patients with several comorbidities, which frequently make them non-eligible for standard chemoimmunotherapy.5

New oral targeted therapies have shown relevant efficacy improvements over the treatments frequently used for CLL; however, their current pricing is expected to have a substantial impact on the cumulative cost of CLL patients care.7,8

The objective of this study was to evaluate the cost-utility of treatment with idelalisib in combination with rituximab versus rituximab as monotherapy in adults with CLL previously treated (who have received at least one prior therapy), from the perspective of the Spanish National Health System (NHS). Rituximab monotherapy was the selected comparator for this analysis, in alignment with the idelalisib pivotal trial. In that trial, due to the inclusion criteria of grade ≥3 neutropenia or thrombocytopenia due to prior myelotoxicity, or estimated creatinine clearance <60 mL/min or CIRS score >6, the patients were unable to receive cytotoxic therapy, therefore the control arm received rituximab monotherapy.5

2 MATERIAL AND METHODS

2.1 Model structure

A partitioned survival model of area under the curve (AUC) designed with three mutually exclusive health states based on survival status (alive/dead), and the status of those who are alive by disease progression (preprogression, postprogression) was developed (Figure 1). This approach has been used in numerous health technology assessments of interventions in late-stage cancer, including relevant appraisals reviewed by the National Institute for Health and Care Excellence.

The model begins with 100% of individuals in the preprogression state. During any given model cycle, patients can be dead; alive in the preprogression state; or alive in the postprogression state. Those in the latter state remain there until death. Separate parametric survival functions were used to directly estimate the proportion of the cohort who were dead and alive in the preprogression state, with the proportion of patients in the postprogression state being the difference between these two states. Rituximab as a baseline therapy for the purpose of the parametric function fitting was used, and the Weibull function provided the most plausible long-term survival estimates and therefore was implemented as the base-case distribution.

To accurately capture the treatment costs, and to best quantify the average number of cycles of therapy received, a cycle length of one week was used, with costs and benefits accrued over a lifetime horizon (30 years, given the mean age at diagnosis).

The model design and structure, disease stages, population, adverse event (AE) management, disease management and resource consumption were validated by three experts in the haematology field, to ensure that this analysis is representative of the Spanish setting.
2.2 | Population

The cohort of CLL patients had specific anthropometric characteristics, with a mean body surface area of 1.80 m² which is representative of the Spanish population. The mean age of patients at diagnosis was set at 70 years, being 58.8% male patients.

2.3 | Clinical data

In the comparison performed, data were obtained directly from the pivotal clinical trial comparing the efficacy and safety of the combination of idelalisib and rituximab versus rituximab alone.

In line with the approach commonly used in advanced stage oncology models, it was assumed that all treatment-related AEs occur during the first cycle. The AEs included in the model represent the grade 3 and 4 AEs most commonly observed in clinical trials in CLL (anaemia, diarrhoea, infection, leucopenia, pneumonia, neutropenia, febrile neutropenia and thrombocytopenia). The frequencies for AE in the model were derived from the idelalisib trial, excepting leucopenia and its proportion that was assumed to be equivalent to that seen with bendamustina monotherapy. Serious infections have been observed with idelalisib in experimental studies involving patient groups for whom it is not licensed, or in unlicensed combinations with other medicines. As this analysis is based on 116 trial (pivotal trial for current indication), this new safety issue was not included. Table 1 presents the frequency of each AE in IR arm and in R arm.

2.4 | Mortality

Five- and 10-year relative survival estimates were 80.2-82.4 and 59.5%-64.7%, respectively. For this reason, competitive mortality from non-CLL causes would have a very secondary effect on the target population, so no correction was made to adjust all-cause mortality by age and gender.

2.5 | Resource use and disease management

The analysis was performed from a Spanish NHS perspective; therefore, only direct medical costs (drugs, administration, monitoring and AE and disease management) were included.

The simulation starts with all patients receiving treatment with idelalisib in combination with rituximab or with rituximab monotherapy. Table 1 shows posologies and duration for the different treatment options considered in the model.

2.5.1 | Treatment administration

In the present model, administration of intravenous immunotherapy requires qualified professionals. Therefore, it is assumed for each administration, a day visit to a hospital haematology clinic is required. For the administration of oral medication, self-administration by the patient is assumed, without additional consumption of healthcare resources.

2.5.2 | Treatment monitoring

Prior to the administration of the therapy, certain laboratory tests or premedication administration is generally needed to ensure the patient is fit to receive treatment. The expert panel considered that the consumption of healthcare resources prior to drug administration should be equivalent for both treatment options (conservative approach) (Table 1).

2.5.3 | Disease management

In addition to the medical visits required for the administration and monitoring of medication, and management of therapy-related toxicity, the model assumed that CLL management also entails non-medication-related medical visits and hospital admissions, which have been included in the model as aggregated costs (Table 1).

Table 1 further details the expert panel's estimated resource consumption for each disease stage (preprogression and postprogression).

2.6 | Utilities and disutilities

To estimate the quality-adjusted life years (QALY), different utility values were considered depending on the health status of patients. The term "utility" refers to the quality perceived by patients based on their health status and receives a value between 1 (perfect health) and 0 (state of health equivalent to death).

Quality of life data were obtained from a population in England and Scotland, using the standard gamble method. Utilities applied for patients in the preprogression state were 0.91, in cases of complete response to treatment, 0.84 for partial response to treatment, 0.78 for patients without changes (perfect health in newly diagnosed patients) and 0.71 for patients on treatment. For patients in the post-progression disease state, the assigned utility was 0.68.

The present analysis, in addition to the utilities in function of the patients' health status, applies a decrease in utility (disutility) to the appearance of any AE. In the absence of specific disutility values in CLL patients, it was considered that the disutility values by the appearance of an AE are not determined by the underlying pathology and are independent of the type of cancer or the treatment received. The disutilities due to AE used in the analysis were obtained from scientific literature. Despite the wide range of articles used to obtain the information, some assumptions had to be made based on expert opinion (Table 1).

2.7 | Costs

According to the perspective of the study, only direct healthcare costs were included. All costs were obtained from Spanish sources and are reported in euros for the year 2016.
TABLE 1  Model inputs

|                                | Idelalisib + Rituximab (I+R) | Rituximab (R) | Reference |
|--------------------------------|-----------------------------|---------------|-----------|
| **Treatment pattern, duration and cost of therapies** |                             |               |           |
| Dose for a body surface area (BSA) of 1.80 m² | I: 150 mg b.i.d. orally | R: 375 mg/m² BSA infusion on day 1 for first cycle | 5 |
|                                | R: 500 mg/m² BSA infusion on day 1 for subsequent cycles | R: 500 mg/m² BSA infusion on day 1 for subsequent cycles |   |
| Treatment duration             | I: Until disease progression or unacceptable toxicity | R: 8 cycles maximum | 5 |
| Trade name                     | I: Zydelig®, 60 tablets, 150 mg | R: Mabthera®, 1 vial, 500 mg | 16 |
| Ex-factory price with mandatory deduction (RDB/2010) (£, 2016) | I: 3885.00 | R: 1049.35 |   |
|                                |                             |               |           |
|                                |                             |               |           |
| **Frequency of adverse events grades 3 and 4 (%)** |                             |               |           |
| Anaemia                        | 5.00                        | 14.00         | 5         |
| Diarrhoea                      | 13.00                       | 0.00          |           |
| Infection                      | 4.00                        | 3.00          |           |
| Leucopenia                     | 18.00                       | 18.00         | Assumption12 |
| Pneumonia                      | 6.00                        | 8.00          | 5         |
| Neutropenia                    | 3.00                        | 1.00          |           |
| Febrile neutropenia            | 5.00                        | 6.00          |           |
| Thrombocytopenia               | 10.00                       | 16.00         |           |
|                                |                             |               |           |
| **Disutility**                 |                             |               |           |
| Anaemia                        | −0.09                       | 584.87        | 15        |
| Diarrhoea                      | −0.09                       | 1041.81       | Expert Panel |
| Infection                      | −0.05                       | 4062.68       | Expert Panel |
| Leucopenia                     | −0.05                       | 1404.62       | 28        |
| Pneumonia                      | −0.20                       | 4018.89       | Expert Panel |
| Neutropenia                    | −0.09                       | 719.05        | 28        |
| Febrile neutropenia            | −0.09                       | 3586.40       | Expert Panel |
| Thrombocytopenia               | −0.09                       | 512.18        | Assumed same as Leucopenia and Neutropenia |
|                                |                             |               |           |
| **Annual number**              |                             |               |           |
| Visits                         |                             |               |           |
| Haematologist                  | 12                          | 50            | Expert Panel |
| Haematologist day hospital     | 18                          | 50            | Expert Panel |
| Procedures                     |                             |               |           |
| Blood count and biochemistry   | 12                          | 50            | Expert Panel |
| Blood count and biochemistry   | 18                          | 50            | Expert Panel |
| Immunophenotype and/or FISH    | 2                           | 50            | Expert Panel |
| Abdominal computed tomography scan | 2                         | 10            | Expert Panel |

(Continues)
Drug costs were obtained from the Spanish General Council of Official Pharmaceutical Colleges catalogue. Ex-factory prices were adjusted with mandatory deduction (Table 1). Posologies were derived from the authorised summaries of products characteristics, which were validated by the expert panel as representative of usual care. All patients alive and in the progression-free state received treatment. As such, the implicit relative dose intensity (RDI) for these therapies would be 100%. However, real-world data from Furman study showed that the weighted average dose used corresponded to a lower RDI. For that reason, cost per cycle for any of the treatment options considered in the analysis was estimated based on 93.25% of RDI (data on file).
The cost of intravenous administration was also taken from a Spanish database. Table 1 shows the unitary costs of the different health resources considered for both the management of the disease and AE. All unitary costs and managing costs of AE (grade 3/4) (Table 1) were obtained from a database of national health costs. Costs were expressed in euros for the year 2016.

### 2.8 | Sensitivity analysis

Deterministic and probabilistic sensitivity analyses (PSA) were performed to test the robustness of the model and to determine the impact of uncertainty on the incremental cost-utility ratio (ICUR). For the deterministic sensitivity analyses, the following parameters were varied: time horizon (5 and 10 years horizon), discount rate (0% and 5%), drug cost (−25% and −45%), parametric curve for overall survival (OS) extrapolation (exponential distribution), progression-free survival (PFS) curve using log-logistic distribution (it was the second best-fitting model) and not considering disutility values.

Probabilistic analyses by Monte Carlo simulation were performed. The value of each key model parameter would vary within a specific probability distribution assigned to each parameter. This process was repeated 1000 times to provide a distribution of the model results.

### 3 | RESULTS

The results are presented as cost differences, life-years gained (LYG) and QALY gained per patient treated with idelalisib plus rituximab.
versus rituximab. The primary study outcome is the ICER and ICUR, considering the cost per LYG and cost per QALY gained with the most effective regimen.

Over a lifetime horizon, idelalisib in combination with rituximab yielded approximately 2.7 times the efficacy of rituximab monotherapy (IR: 9.998 LYG and 4.965 QALY; R: 3.592 LYG and 1.818 QALY). In terms of total expenditure, idelalisib in combination with rituximab costs €118 254 per patient versus €23 874 per patient with rituximab. This resulted in an incremental cost-effectiveness ratio (ICER) of €14 733/LYG and an ICUR of €29 990/QALY gained with idelalisib plus rituximab compared to rituximab monotherapy (Table 2).

According to the deterministic sensitivity analysis (Figure 2), the parameters having most influence on the results were the time horizon (shorter time horizon, higher ICUR) and the distribution that adjusts the PFS data (considering a PFS based on log-logistic distribution, the second best-fitting model, higher ICUR).

As an average of the 1000 iterations performed on the probabilistic sensitivity analysis, an ICUR of €34 436 per additional QALY was obtained. Figure 3 shows the cost-effectiveness plane of idelalisib in combination with rituximab when compared to rituximab alone. Almost all of the results are found in the first quadrant; most simulations of the combination of idelalisib plus rituximab were more effective and associated with higher cost than treatment with rituximab monotherapy. The remaining simulations were associated with lower effectiveness and higher costs, so they were considered as dominated. It was also found that the likelihood of idelalisib plus rituximab being a cost-effective strategy compared with rituximab monotherapy was 78%, given a frequently referenced threshold of €45 000 per QALY gained in Spain (Figure 4).

4 | DISCUSSION

The present study is the first cost-utility analysis of idelalisib in relapsed or refractory CLL patients, which is conducted from the perspective of the Spanish NHS. The results show that the cost per additional QALY gained with idelalisib in combination with rituximab
compared to rituximab monotherapy remains below €45 000 per QALY, a threshold frequently used as reference value in economic evaluations performed in Spain. Considering this willingness-to-pay threshold, the combination of idelalisib and rituximab is cost-effective in 78% of simulations. The results of the study are in line with those from other economic analyses in other settings previously published, which have evaluated the cost-effectiveness or cost-utility of adding rituximab to idelalisib versus rituximab for the treatment of CLL in Europe. In this sense, ICUR obtained in other countries was similar to those obtained in our analysis, such as £26 403 per additional QALY in England and Wales, £32 180/QALY in Scotland, €30 480/QALY in France and €32 702/QALY in Portugal.

The present model has several strengths. Primarily, clinical effectiveness was taken from a multicentre, randomised, double-blind, phase 3 study that assessed the efficacy and safety of idelalisib in combination with rituximab versus rituximab plus placebo. Although the use of rituximab monotherapy is not the gold standard for the treatment of CLL patients, in this case it can be considered as an appropriate comparator because patients have baseline conditions that render them ineligible for chemotherapy (grade ≥3 neutropenia or thrombocytopenia due to prior myelotoxicity, estimated creatinine clearance <60 mL/min or CIRS score >6).

Additionally, a partitioned survival model was used to simulate the disease progression and the impact of idelalisib plus rituximab or rituximab monotherapy in CLL patients. Partitioned survival models represent a more straightforward option than Markov modelling when patient-level data are available, as is shown in this analysis. Selection of parametric survival distributions is required for modelling PFS and OS data from Kaplan-Meier curves. Although the best-fitting curves were chosen for the base-case analysis, in some cases the extrapolated data could not represent real practice. The sensitivity analysis performed using an alternative function for PFS did not show relevant influence on the ICUR results, but was associated with variations of ICUR when a log-logistic function was used for OS, due to a potential overestimation of PFS in the tails.

Conversely, our study has some limitations. First, the parameters used in the modelling have been extracted from different sources. However, all of the variables are based on official sources or in publications with a high level of clinical evidence and have been validated by three expert haemat-oncologists. The potentially associated uncertainty in some of the parameters was tested by a probabilistic sensitivity analysis.

Second, due to a lack of utility data availability in the Spanish population, utilities are taken from a study that evaluated this information in patients with CLL in the UK, such as has been done in other CLL Spanish economic evaluations. In this sense, there is published evidence suggesting that utility values for different health states in six European countries (Finland, Germany, the Netherlands, Spain, Sweden and the UK) could be described by a common model; therefore, no relevant influence is expected to be associated with the use of utilities from UK population, instead of specific values for Spanish patients. The model includes disutilities in order to capture the impact of the drug safety profile on patient's quality of life. In line with the approach commonly used in late-stage oncology models, it was assumed that all treatment-related AEs occur in the first model cycle. Despite the potential interest for modelling late onset events in the idelalisib plus rituximab arm, particularly pneumonitis and diarrhoea, the required information on these events was not reported in the pivotal trial. Moreover, the absolute rate over the randomised follow-up period included in the clinical study report was low, so to avoid unnecessary complexity, it was decided to exclude these events from the model.

The sensitivity analysis results did not reveal any important variations in the estimated incremental ratio.

Within the present model, the progression health state is intended to reflect third and later lines of therapy. Due to the existing uncertainty related to the costs of additional lines of therapy, no one-off cost was applied to patients entering the progressed state.

Finally, the drug acquisition costs were calculated assuming that treatment duration is equivalent to the median PFS. This assumption is frequently employed in economic evaluations of oncohaematology drugs, but it is a conservative approach, as treatment duration is usually shorter than median PFS. It is likely, therefore, that a lower ICUR would result if mean treatment duration was applied.

Despite the limitations described above, the results of the sensitivity analysis confirm that the uncertainty associated with the parameters used in the modelling did not represent a significant deviation from the results obtained in the base case. In summary, our analysis shows that idelalisib in combination with rituximab increases the survival of CLL adult patients previously treated (who have received at least one prior therapy), compared to rituximab monotherapy, and can therefore be a cost-effective approach from the perspective of the Spanish NHS.

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