Cost-Effectiveness of Ibrutinib Compared With Obinutuzumab With Chlorambucil in Untreated Chronic Lymphocytic Leukemia Patients With Comorbidities in the United Kingdom

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Abstract

A Markov model was used to assess the cost-effectiveness of ibrutinib compared with obinituzumab in combination with chlorambucil for untreated patients in the United Kingdom. The results showed ibrutinib not to be cost-effective. However, additional analyses showed ibrutinib to be significantly cost-effective compared with the current mode of care in which ibrutinib is administered as the second-line treatment.

Background: Ibrutinib shows superiority over obinutuzumab with chlorambucil (G-Clb) in untreated patients with chronic lymphocytic leukemia with comorbidities who cannot tolerate fludarabine-based therapy. However, ibrutinib is relatively more expensive than G-Clb. In this study we evaluated the cost-effectiveness of ibrutinib compared with G-Clb from the United Kingdom (UK) health care perspective. **Materials and Methods:** A 3-state semi-Markov model was parameterized to estimate the lifetime costs and benefits associated with ibrutinib compared with G-Clb as first-line treatment. Idelalisib with rituximab was considered as second-line treatment. Unit costs were derived from standard sources, (dis)utilities from UK elicitation studies, progression-free survival, progression, and death from clinical trials, and postprogression survival and background mortality from published sources. Additional analyses included threshold analyses with ibrutinib and idelalisib at various discount rates, and scenario analysis with ibrutinib as second-line treatment after G-Clb. **Results:** An average gain of 1.49 quality-adjusted life-years (QALYs) was estimated for ibrutinib compared with G-Clb at an average additional cost of £112,835 per patient. To be cost-effective as per the UK thresholds, ibrutinib needs to be discounted at 30%, 40%, and 50% if idelalisib is discounted at 0%, 25%, and 50% respectively. The incremental cost-effectiveness ratio was £75,648 and £−143,279 per QALY gained for the base-case and scenario analyses, respectively. Sensitivity analyses showed the robustness of the results. **Conclusion:** As per base-case analyses, an adequate discount on ibrutinib is required to make it cost-effective as per the UK thresholds. The scenario analysis substantiates ibrutinib's cost-savings for the UK National Health Services and advocates patient's access to ibrutinib in the UK.

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Introduction

Chronic lymphocytic leukemia (CLL)[1] is the most common adult leukemia, affecting 6.9 per 100,000 population.[2] Every year, 3515 new cases and 1033 deaths of CLL are reported in the United Kingdom (UK).[2] The incidence of CLL increases with age, and men are twice as likely to be affected. The incidence rate rises sharply around 45-49 years, with the highest rates in 85-89 years for men and in 90 years and older for women.[2] Compared with the general population, the 10-year relative survival is 59%-63% in patients younger than 70 years and 22%-42% in patients older than 70 years.[3-5] The median survival has been reported to be more than 10 years in the earliest stage of CLL and around 6.5 years in the most advanced stage.[6]

Ibrutinib (IB)[7] is a first-in-class targeted agent permanently binding and inhibiting Bruton tyrosine kinase (BTK)[8] activity, which is critical to the growth and survival of B-cells, a type of

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immune system cell affected in 85% of non-Hodgkin lymphoma,[9] the most common cancer of the lymphatic system. By preventing BTK from functioning, IB kills the malignant B-cells but leaves the healthy T-cells in the immune system largely unaffected, unlike many current therapies. This enables a patient to remain healthier during the treatment, increasing their chances for long-term survival.[10] Additionally, IB is an orally administered monotherapy and does not need intravenous monoclonal antibody administration. It has been approved in the United States by US Food and Drug Administration (FDA)[11] and in Europe by the European Commission[11,12] for relapsed/refractory CLL and also for untreated 17p deletion or TP53 mutation (del17p/mutTP53),[13] which are difficult to treat.

Ibrutinib showed positive results in phase 1b/2 trial in an untreated CLL population; only 1 of 31 patients experienced disease progression, and all but 5 patients (84%) continued IB treatment at a median follow-up of 22 months.[14] The US Food and Drug Administration (FDA) and European Commission approved IB for first-line-treatment in CLL in March 2016[7] and May 2016,[15] respectively, on the basis of the results from the multicenter RESONATE-2[16] clinical trial.

The choice of treatment for CLL depends on the level of fitness and cytogenetic risk factors.[6] IB and chlorambucil (Clb) in combination with CD-20 antibody (obinutuzumab or ofatumumab) is recommended by the European Society of Medical Oncology (ESMO) for untreated CLL patients without del17p/mutTP53 and not fit for fludarabine-based chemoimmunotherapy.[6] Ofatumumab is no longer available through the Cancer Drugs Fund in the UK,[17] and therefore, G-Clb (obinutuzumab in combination with Clb) is an appropriate comparator for IB in the UK. G-Clb has also been reported to be more clinically effective compared with other available treatments. A meta-analyses including different commercially available treatments for unfit CLL patients showed G-Clb to have superior efficacy.[18] Apart from this, it has also been reported to be the most cost-effective treatment compared with several different treatments in the UK.[19]

Ibrutinib is recommended presently by the National Institute for Health and Care Excellence (NICE) as second-line treatment,[17] however, not as first-line treatment for patients with CLL in the UK. A matching adjusted indirect comparison (MAIC) study,[20] which controls for the cross-trial differences in the study population in the absence of a head-to-head trial, thereby yielding more reliable estimates of treatment efficacy, showed IB to have better survival outcomes compared with G-Clb.[21]

Ibrutinib is comparatively more expensive than G-Clb because IB costs £51.10 per tablet and the recommended dose comprises 3 tablets every day. Therefore, the treatment would amount to £55,954 annually, and the patient would continue taking the medication until progression. However, obinutuzumab is administered over a period of 6 months and costs £26,496. However, the total cost over a lifetime associated with each treatment would depend on the life-years (LYs) lived as well as other costs, like adverse event costs and maintenance costs associated with each treatment. Additionally, the quality-adjusted LYs (QALYs) will differ for the treatments depending on the LYs and utility of each treatment, thereby affecting the incremental cost-effectiveness (CE) ratio (ICER)[22] of IB compared with G-Clb.

As per our knowledge, a CE study of IB compared with G-Clb has not been conducted in untreated patients with CLL in the UK to show the value of the use of IB within the UK National Health Services (NHS) with respect to the commonly referenced UK willingness-to-pay (WTP) thresholds. The aim of this study was, therefore, to assess whether IB is cost-effective compared with G-Clb for first-line treatment of patients with CLL in the UK.

Materials and Methods

Analytical Framework

Cost-effectiveness analysis of IB compared with G-Clb was performed using an ICER[22] computed with the incremental difference in treatment costs of IB versus G-Clb constituting the numerator and the gains in QALYs as the denominator.

Performing CE analyses requires modeling to combine costs and effects data from multiple sources and to extrapolate the costs and effects over time because of the limited follow-up time possible in a clinical trial. The modeling process involves creating a model structure involving different health states observed in clinical practice, assigning transition probabilities to each health state for the different cycles, and assigning input parameters like costs and utility values to each health state in the context of the health care system and the study population under consideration.

Cost-effectiveness models calculate the incremental cost per unit of benefit gained. The benefit gained is typically reported in QALYs, which combines the quantity as well as quality of life lived,[22] and is computed by multiplying the years lived in a health state with the utility of that health state. Finally, sensitivity analyses are performed to assess the effect of the assumptions and uncertainty across input parameters of the model.

Target Population

The target population comprised a subpopulation from the open-label phase III trial of G-Clb (CLL11 study [NCT01010061]) in 18 years or older untreated CLL patients. The median age of the patients was 74 years and median Cumulative Illness Rating Scale (CIRS) score was 8 and ranged from 1 to 20 (CIRS scale scores range from 0 to 56; higher scores indicate worse health status).[6] The coexisting conditions were hypertension (71%), endocrine or metabolic (53%), cardiac (50%), musculoskeletal (45%), renal (44%), vascular (38%), respiratory (36%), eye, ear, throat, or larynx (36%), genitourinary (35%), upper gastrointestinal (34%), lower gastrointestinal (21%), neurologic (19%), hepatic or biliary (16%), and psychiatric (16%). The median creatinine clearance was 61.4 mL/min, and the percentage of patients with Binet stage A, B, and C were 23%, 41%, and 36%, respectively.

Treatment Strategies

The first treatment strategy relevant for the current CE analyses is IB, which is approved by the European Commission for untreated patients with CLL.[15] The RESONATE-2 trial (NCT01722487)[23] reported the safety and efficacy of IB versus Clb in untreated patients with CLL. Patients (n = 269) were randomized in a 1:1 fashion to receive IB (420 mg once daily) until disease progression or development of an unacceptable level of toxicity, or Clb. Only the IB arm (n = 136) of RESONATE-2 is applicable for this CE study.

The second treatment strategy is G-Clb, which is the comparator for IB for the current CE analysis. The CLL11 trial

(NCT01010061)[24] reported the safety and efficacy of G-Clb versus Clb in untreated CLL patients with comorbidities. Patients (n = 781) were randomized in a 1:2:2 fashion to receive Clb, G-Clb, or rituximab in combination with Clb in six 28-day cycles. Only the G-Clb arm (n = 241) is applicable for the current CE analyses. The administration of G-Clb was as follows: Clb was administered orally at a dose of 0.5 mg/kg body weight on days 1 and 15 of each cycle, and obinutuzumab was administered intravenously at a dose of 1000 mg on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6. The first infusion was administered over a period of 2 days.[24]

Markov Model Structure

An adapted version of the 3-state Markov model[25] used by Becker et al[19] for untreated CLL patients is used in this CE study. The model is depicted in Figure 1, and consists of 3 mutually exclusive health states: progression-free survival (PFS), progression, and death.

The PFS health state consists of "with treatment" and "without treatment" health substates imitating the treatment schedule of G-Clb, which is administered only during the first 6 months of treatment. The 2 health substates accounted more accurately for the difference in treatment costs as well as patients' quality of life. Only the "with treatment" health substate is applicable in case of IB, because the treatment continues until progression or death.

The progression health state comprises idelalisib[26] in combination with rituximab (IR) and best supportive care (BSC) health substates to mimic the intervention strategy of IR.[27] IR is used as the second-line treatment in this CE study considering the level of fitness and cytogenic risk factors of the study population. It is recommended only for patients relapsing during the first 2 years after starting the first-line treatment.[27] Therefore, the patients progressed to the IR state if they moved to progression within 24 months, or else they moved to the BSC state. The patients in BSC state received treatments for symptom management.

A semi-Markov model was used to estimate the time spent in each health state (ie, the transition probabilities depend on the model cycle), thereby reflecting the clinical trial data more accurately. The model cycle was 4 weeks, which was in line with the treatment administration schedule of the comparator. Next, costs and health effects were assigned to each health state. A half-cycle correction[25] was used to adjust for the distribution of costs and benefits accrued throughout the cycle. The analyses were performed using a lifetime horizon to fully capture the costs and effects associated with IB compared with G-Clb as envisaged by NICE and the International Society of Pharmacoeconomics and Outcomes Research modeling good research practices task force.[28] The analyses were performed using R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Effectiveness

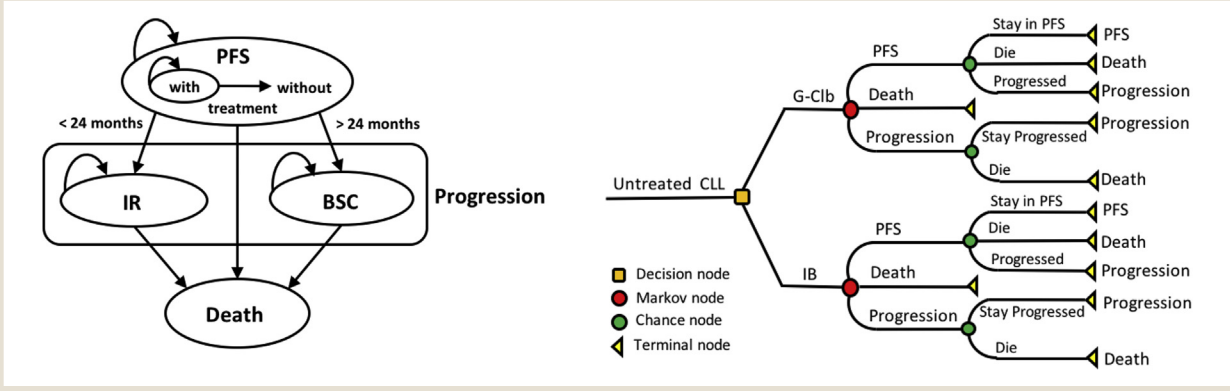
In the absence of randomized controlled trials directly comparing the treatment with the comparator(s), indirect treatment comparison is performed to estimate the relative treatment effect of the treatment with respect to the intended comparator(s). However, unadjusted treatment comparisons of treatment arms from different trials are prone to bias because of heterogeneity in patient populations across trials, because this heterogeneity can include factors that can influence the relative treatment effect. It is therefore important to control for this heterogeneity in the patient populations while performing an indirect treatment comparison.

Matching-adjusted indirect comparison[20] uses individual patient data (IPD) from trials of one treatment to match baseline summary statistics reported from trials of another treatment. The treatment effects thus obtained are better estimates of the real benefits accruing because of the treatment.

Transition Probabilities

Transition probabilities determine how patients move between the different health states in the Markov model. The overall survival (OS) and PFS Kaplan–Meier (KM) curves of G-Clb from the CLL11 study[24] were digitized using Engauge Digitizer software (version 10.1, available at http://markummitchell.github.io/engauge-digitizer). An approximation of IPD was reconstructed on the basis of the algorithm of Guyot et al[29] using the digitized KM survival curves and information regarding the number of patients at risk at several follow-up times.

Figure 1 Markov Model Influence Diagram (Left) and Decision Tree (Right)



Abbreviations: BSC = best supportive care; CLL = chronic lymphocytic leukemia; G-Clb = obinutuzumab with chlorambucil; IB = ibrutinib; IR = idelalisib with rituximab; PFS = progression-free survival.

The PFS is defined as the time until progression or death and OS as the time from the progression-free state or progression state until death. The IPD was used to parametrize the OS and PFS to enable the extrapolation of survival beyond the reported follow-up period of the clinical trial.[30] The choice of the parametric function was informed using the Akaike information criterion (AIC) and log-likelihood of parametric fits using exponential, log-logistic, log-normal, Gompertz and Weibull distributions. Smaller values of negative of the log-likelihood and AIC indicate better model fits. The final choice of the parametric function was also guided by graphical analysis and knowledge of the expected extrapolation of the survival curves.

Van Sanden et al[21] conducted MAIC of IB versus G-Clb using IPD of the RESONATE-2[23] study and the baseline summary statistics published from the CLL11[24] study to adjust for variation in the study populations in several key potential treatment effect modifiers. The estimates of the relative efficacy of IB versus G-Clb are provided in the form of hazard ratios (HRs)[31] for PFS as well as OS. These HR estimates were combined with the PFS and OS of G-Clb to derive the PFS and OS associated with IB. It was assumed that subsequent treatments did not affect OS captured in the respective clinical trials, because such treatments have diminishing returns for prolonging OS and also because of a lack of data to inform an alternative assumption for postprogression survival.

Age-specific postprogression survival was obtained using standard sources[32] to inform probability of dying after progression. Age-specific background mortality probabilities obtained from the World Health Organization Mortality database[33] were added as competing risks for transitioning to the death state from PFS or progression state. This ensured that the probability of dying at a certain age in the model remained equal to or more than the background mortality for that age. The age distribution in the CLL11[24] study (60% male and 40% female participants) was used to obtain the weighted postprogression survival and general mortality probabilities for various age groups.

Utilities

One method to assess the burden related to a disease is the elicitation of utility scores. Utility scores reflect the value of the health-related quality of life (HRQL) of a health state. HRQL utility is typically summarized as a single score, and ranges from 1 (full health) to 0 (dead) and below (negative scores are possible for worse than dead states). One way to elicit utility scores is through administration of generic preference-based patient reported outcomes measures, such as the EuroQoL 5 dimensions,[34] which is commonly used in clinical trials to assess HRQL outcomes in 5 domains of functioning, and can be completed by the patient independently.

Utility elicitation from the trial population are most reliable. However, where such assessment might not be possible or suitable (such as in the case of postprogression), alternative methods are used. One commonly used method is valuation of health state descriptions using vignettes by the general public by using time trade-off (TTO) methodology. This methodology was used by Kosmas et al[35] to elicit UK societal utility values for the different health states associated with CLL. "PFS without therapy" was reported to be the least burdensome, whereas "relapsed lines of treatment" was the most burdensome to HRQL. Disutilities because of adverse events were sourced from Tolley et al,[36] which also used TTO methodology to elicit preferences because of adverse events associated with CLL treatment in the UK. CLL treatment-related (dis) utilities were also sourced from Beusterien et al,[37] which provided patient-perceived disutilities using standard gamble methodology for the UK population.

Costs

Only direct medical costs have been considered as per NICE guidelines.[38] Therefore, costs related to medical management required during treatment and follow-up, treatment of adverse events, and end-of-life costs have been included. Costs were assigned to each unit of resource to estimate the total costs. Unit cost information was obtained from published literature and NHS reference costs.[39] Drug costs were derived from the British National Formulary.[40] The costs for entire vials were applied assuming no vial reuse. The supportive costs needed by patients for staying in PFS and progression states were assigned according to the distribution of patients' response to the drug during the respective clinical trials.

Adverse events affect costs associated with a treatment as well as HRQL of patients receiving treatment. Grade 3 and 4 adverse events, often categorized as serious adverse events, from the RESONATE-2[23] and CLL11[24] studies were included in modeling of the costs and disutilities as shown in Table 1. The most frequent serious (Grade ≥3) adverse events associated with IB treatment were neutropenia (10%), anemia (6%), hypertension (4%), pneumonia (4%), and diarrhea (4%), whereas those associated with G-Clb treatment were neutropenia (35%), infusion-related reactions

Table 1 Adverse Event Probabilities

Adverse Event	Probability (%) of Grade 3 or Higher	
	IB	G-Clb
Neutropenia	10	35
Anemia	6	5
Hypertension	4	–
Pneumonia	4	3
Diarrhea	4	–
Maculopapular Rash	3	–
Decreased Platelet Count	3	–
Abdominal Pain	3	–
Hyponatremia	3	–
Thrombocytopenia	2	11
Febrile Neutropenia	2	2
Upper Respiratory Tract Infection	2	–
Pleural Effusion	2	–
Cellulitis	2	–
Fatigue	1	–
Syncope	1	–
Basal Cell Carcinoma	4	–
Leukopenia	–	5
Infections	–	11
Infusion-Related Reactions	–	21

Abbreviations: IB = ibrutinib; G-Clb = obinutuzumab with chlorambucil.

Table 2 Markov Model Input Parameters

Attribute	Value	Distribution	Unit
Time Horizon	35	NA	Years (lifetime)
Average Age of Cohort at Baseline	74	NA	Years
Mean Body Surface Area	1.85 ± 0.46	Normal	m^2
Transition Probabilities	**Treatment**	**Distribution**	**Parameter (SE)**
PFS	G-Clb[24]	Weibull	Shape: 1.83 (0.17)
			Scale: 33.22 (2.24)
OS	G-Clb[24]	Exponential	Rate: 0.004 (0.00089)
PFS Hazard Ratio (log)	IB versus G-Clb[21]	Normal	−1.42 (0.44)
OS Hazard Ratio (log)	IB versus G-Clb[21]	Normal	−1.56 (0.86)
Utilities	**Mean ± SD**	**Distribution**	**Source**
PFS		β	
Oral Treatment	0.71 ± 0.20		35
I.V. Treatment	0.67 ± 0.22		35
I.V. Treatment With More Hospital Visits	0.55 ± 0.26		35
After Treatment	0.82 ± 0.17		35
Utilities	**Mean ± SD**	**Distribution**	**Source**
Progression		β	
After First-Line Treatment	0.66 ± 0.22		35
Relapsed Treatment Lines	0.42 ± 0.25		35
Adverse Events		β	
IB Disutility	−0.07 ± 0.02		36,58
G-Clb Disutility	−0.15 ± 0.04		36,58
IR Disutility	−0.08 ± 0.02		36,58
Costs, £	**Mean (SE)**	**Distribution**	**Source**
Drug costs		Not varied	
Ibrutinib (140 mg)	51.10		40
Idelalisib (150 mg)	51.91		40
Rituximab (100 mg)	173.64		40
Obinutuzumab (1000 mg)	3312		40
Chlorambucil (2mg)	1.62		40
Administrative costs		Lognormal	
Oral drug pharmacy per week	5.58 (1.40)		19
Oral drug administration per week	136 (34)		19
I.V. drug pharmacy per week	16.75 (4.19)		19
I.V. drug first administration	514 (128)		19
I.V. drug subsequent administration	343 (85.75)		19
Supportive Care Costs Per Month		Lognormal	
PFS: IB	19.83 (4.96)		23,58
PFS: G-Clb	38.05 (9.51)		24,58
Progressed	250 (62.50)		58
Adverse Event Costs (One Time)		Lognormal	
IB	1581.84 (395.46)		23,58
G-Clb	3042 (760.50)		24,58
IR	2877.73 (719.43)		58,59
End of Life Costs (One Time)	7360 (1840)	Lognormal	58

Abbreviations: G-Clb = obinutuzumab with chlorambucil; IB = ibrutinib; IR = idelalisib with rituximab; OS = overall survival; PFS = progression-free survival; SE = standard error.

(21%), infections (11%), thrombocytopenia (11%), leukopenia (5%), and anemia (5%). Costs of adverse events were accounted separately for each comparator as a 1-time cost computed by multiplying the rate of the event for that comparator by the average cost for that event. Table 2 lists the various input parameters for the Markov model.[19,23,24,35,36,40,58,59]

Analyses

Base Case and Threshold Analyses. The utility values and specific costs were inserted into the model to estimate the incremental costs, LYs, and QALYs. Future costs and effects were discounted[41] at an annual rate of 3.5%, as recommended by the UK Treasury.[38] The incremental costs per LY gained and QALY gained were calculated as the incremental costs of IB compared with G-Clb divided by the LYs and QALYs gained for IB compared with G-Clb, respectively.

Idelalisib[26] is available in the UK through a special patient access scheme,[17,27] whereby the drug is available through a confidential discount agreement with the manufacturer. IB as second-line treatment for CLL is also available under such an agreement.[17] Threshold analyses[42] were performed with discount rates on drug prices of idelalisib and IB to decrease the incremental costs per QALY gained to meet the commonly referenced UK WTP thresholds.[43] Several discounts on drug prices of idelalisib were considered and subsequently, appropriate discounts on drug prices of IB were determined.

Sensitivity Analyses. The NICE recommends sensitivity analyses to aid decision-makers in assessing the uncertainty in several factors that can potentially influence the estimated CE because of lack of long-term data on efficacy and safety, lack of credible data on costs and utilities, apart from other factors like variability in the underlying data, choice of economic model, and validity of the results for the intended population.[43] Sensitivity analyses aim to address the uncertainties because of these factors.

Deterministic sensitivity analysis involves varying 1 (univariate) or more (multivariate) variables simultaneously and obtaining the results for various scenarios.[44] However, the use of this type of sensitivity analysis is limited for decision-making purposes, because it does not reveal the likelihood of the occurrence of each possible scenario. To show the possibility of a technology being cost-effective at a certain WTP threshold, a probabilistic sensitivity analysis (PSA) is required in which distributions of the variables being modeled can be set. PSA also informs regarding the robustness of the models. However, a PSA does not have the ability to reduce uncertainty regarding the analytical method being used.[45]

To account for uncertainty in parameter estimates of costs, utility, and transition probabilities, deterministic sensitivity analyses were conducted by systematically varying the input parameters over a range of plausible scenarios to assess their effect on the estimated outcomes. Drug costs were directly sourced from British National Formulary,[40] and therefore not varied in the sensitivity analyses, because they were not subject to sampling uncertainty.[19] Unless known otherwise, the base case parameter values were varied by 25% to assess the sensitivity of the results to changes in the input parameters.

Probabilistic sensitivity analyses were performed using the variability around base case estimates of the model input parameters. The costs and utilities were varied using lognormal and β distributions, respectively. The mean body surface area and the logarithm of HRs were assumed to follow a normal distribution. Several parameters such as HRs were jointly sampled using Cholesky decomposition to ensure correlation between the parameters during the sampling process. The input parameters were simultaneously varied for 10,000 runs. The PSA results are presented on the CE plane, whereas the incremental effects and costs are depicted on the horizontal and vertical axes respectively, and as a CE acceptability curve (CEAC) depicting the probability that IB or G-Clb is cost-effective at various WTP thresholds.

Scenario Analysis. For G-Clb as comparator of IB for first-line treatment, an assumption was made that IB did not exist either as the first-line or second-line treatment.[43] For the IB arm, if the patients did not respond to IB as the first-line treatment, IB as the second-line treatment is not appropriate.[43] Therefore, for the base case analyses, IR was considered as the second-line treatment for the IB as well as G-Clb arms as per the second-line treatment options recommended for CLL patients in the UK.

Patients who receive G-Clb as the first-line treatment are likely to receive IB as the second-line treatment because these are approved as the first-[46] and second-lines[17] of treatment in the UK. A scenario analysis was performed to analyze the CE of this alternate treatment strategy in the G-Clb comparator arm.

Results

Kaplan–Meier Survival Probabilities

Parametric survival analysis was used to project the KM OS and PFS curves beyond the end of the clinical trial data. The parametric fitting of the OS and PFS KM curves of G-Clb was performed with exponential, log-logistic, log-normal, Weibull, and Gompertz probability distributions. On the basis of the visual fit and goodness of fit criteria (log-likelihood and AIC), exponential and Weibull distributions were chosen for PFS and OS, respectively. The HR estimates obtained from MAIC study by Van Sanden et al[21] were combined with the PFS and OS of G-Clb to obtain the PFS and OS associated with IB. Figure 2 shows the resulting survival probabilities for G-Clb and IB.

Analyses

Base-Case and Threshold Analyses. As depicted in Table 3, IB demonstrated LY gain of 1.35 compared with G-Clb, which could be attributed to more time being spent in the PFS health state. Incremental QALY gains of 1.49 were smaller after accounting for HRQL. IB treatment strategy was associated with an increased incremental cost of £112,835. This difference was driven by the drug acquisition costs of IB and idelalisib.

Incremental cost of IB compared with G-Clb per LY and per QALY gained was £83,435 and £75,648 respectively. The ICER is above the commonly referenced UK thresholds of £20,000 to £30,000 per QALY gained for assessing CE of (new) treatments by NICE, and is also above the referenced threshold of £50,000 per QALY gained for assessing end-of-life treatment(s).[47] Three conditions need to be satisfied for end-of-life treatments, namely small patient population, prognosis <24 months, and life-extension (>3 months), which is not likely to be met for IB as a first-line treatment.

Sensitivity Analyses. The left of Figure 3 shows the scatter plot on the CE plane. Each point in the scatter plot indicates the incremental costs and gained QALYs for 1 of the 10,000 runs of the PSA, and indicates the location of ICERs for that run. The ICERs are located either in the northeast quadrant (IB leads to more

Table 3 Base Case and Threshold Analyses

	Base Case			0% ID + 30% IB			25% ID + 40% IB			50% ID + 50% IB		
Outcome	**G-Clb**	**IB**	**Incremental**	**G-Clb**	**IB**	**Incremental**	**G-Clb**	**IB**	**Incremental**	**G-Clb**	**IB**	**Incremental**
Years in PFS	2.33	4.78	2.45	2.33	4.78	2.45	2.33	4.78	2.45	2.33	4.78	2.45
Years in Progressed	9.00	7.90	−1.10	9.00	7.90	−1.10	9.00	7.90	−1.10	9.00	7.90	−1.10
Total LYs	11.33	12.68	1.35	11.33	12.68	1.35	11.33	12.68	1.35	11.33	12.68	1.35
QALYs in PFS	1.82	3.39	1.57	1.82	3.39	1.57	1.82	3.39	1.57	1.82	3.39	1.57
QALYs in Progressed	5.02	4.93	−0.09	5.02	4.93	−0.09	5.02	4.93	−0.09	5.02	4.93	−0.09
Total QALYs	6.83	8.32	1.49	6.83	8.32	1.49	6.83	8.32	1.49	6.83	8.32	1.49
Costs in PFS, £												
Drug acquisition costs	26,425	246,256	219,831	26,425	172,379	145,954	26,425	147,754	121,328	26,425	123,128	96,703
Administration costs	5020	1281	−3740	5020	1281	−3740	5020	1281	−3740	5020	1281	−3740
Supportive care costs	1022	1138	116	1022	1138	116	1022	1138	116	1022	1138	116
Adverse event costs	3039	1582	−1458	3039	1582	−1458	3039	1582	−1458	3039	1582	−1457
Costs in progressed	172,647	70,732	−101,915	172,647	70,732	−101,915	139,174	60,562	−78,612	105,701	50,392	−55,309
Total costs	208,154	320,988	112,835	208,154	247,111	38,958	174,680	212,315	37,635	141,207	177,520	36,313
Incremental costs/LY gained			83,435			28,858			27,878			26,899
Incremental costs/QALY gained			75,648			26,146			25,258			24,371

Abbreviations: G-Clb = obinutuzumab with chlorambucil; IB = ibrutinib; ID = idelalisib; LY = life-year; PFS = progression-free survival; QALY = quality-adjusted life-year.

Table 4 Scenario Analysis

Outcome	G-Clb With IB	IB With IR	Incremental
Years in PFS	2.33	4.78	2.45
Years in Progressed	9.00	7.90	−1.10
Total LYs	11.33	12.68	1.35
QALYs in PFS	1.82	3.39	1.57
QALYs in Progressed	5.02	4.93	−0.09
Total QALYs	6.83	8.32	1.49
Costs in PFS, £			
Drug Acquisition Costs	26,425	246,256	219,831
Administration Costs	5020	1281	−3740
Supportive Care Costs	1022	1138	116
Adverse Event Costs	3039	1582	−1458
Costs in Progressed	499,192	70,732	−428,460
Total Costs	534,699	320,988	−213,711
Incremental Costs/LY Gained			−158,028
Incremental Costs/QALY Gained			−143,279

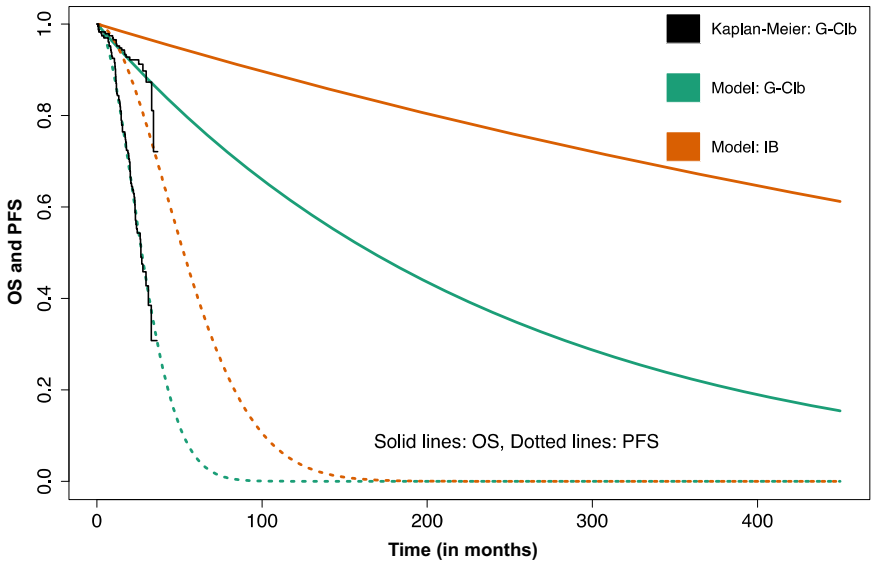
Abbreviations: G-Clb = obinutuzumab with chlorambucil; IB = ibrutinib; IR = idelalisib with rituximab; LY = life-year; PFS = progression-free survival; QALY = quality-adjusted life-year.

QALYs but also costs more than G-Clb) or the northwest quadrant (IB leads to lower QALYs and also costs more than G-Clb) of the CE plane with most of the ICERs being located in the northeast quadrant.

The CEAC on the right of Figure 3 depicts the probability of IB being cost-effective compared with G-Clb. IB has a >50% probability of being more cost-effective than G-Clb at WTP thresholds higher than £100,000 per QALY. The probability of IB being more cost-effective compared with G-Clb levels off at 76% with increasing WTP thresholds indicating that there are some ICERs located in the northwest quadrant of the CE plane.

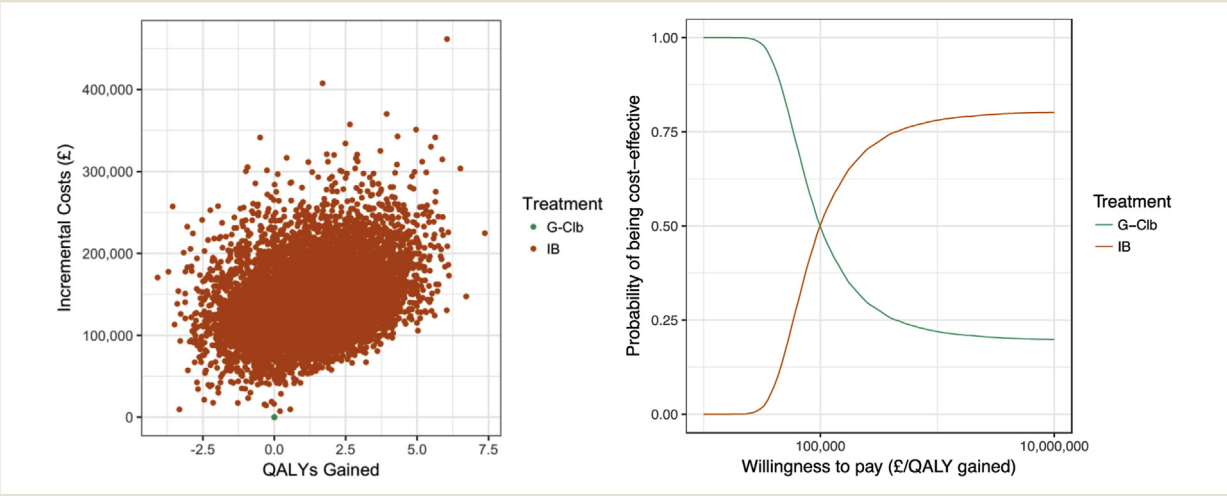
Scenario Analysis. Patients receiving G-Clb as the first-line treatment are likely to receive IB as the second-line treatment because these are the approved as the first-[46] and second-lines[17] of treatment in the UK. A scenario analysis was performed to analyze the CE of this alternate treatment strategy in the G-Clb comparator arm.

Figure 2 OS and PFS Probabilities of G-Clb and IB



Abbreviations: G-Clb = obinutuzumab with chlorambucil; IB = ibrutinib; OS = overall survival; PFS = progression-free survival.

Figure 3 Scatter Plot in CE Plane (Left) and Cost Effectiveness Acceptability Curve (Right)



Abbreviations: CE = cost effectiveness; G-Clb = obinutuzumab with chlorambucil; IB = ibrutinib; QALY = quality-adjusted life-year.

Ibrutinib proved to be cost-effective compared with G-Clb. The total cost in the progression health state for G-Clb and IB arm was £499,192 and £70,732 respectively (Table 4), and the drug acquisition cost was found to be the main driver for the costs. Because of the high costs in the progression health state accruing because of IB as the second-line treatment, the overall costs of the G-Clb arm were considerably higher compared with the IB arm, namely £534,699 and £320,988, respectively. The incremental cost per QALY gained for IB compared with G-Clb was £−78,327 because G-Clb treatment cost more for a lower gain in QALYs.

Discussion

The treatment options for untreated CLL patients with comorbidities and ineligible for fludarabine-based chemoimmunotherapy are Clb with CD-20 antibody (obinutuzumab/ofatumumab), or IB.[6] Although G-Clb is approved within the UK NHS for treating such patients, IB is still not approved. There is no clinical trial directly comparing IB with G-Clb. IB and G-Clb were both reported to be superior to Clb in the RESONATE-2[23] and CLL11[24] clinical trials, respectively. A recent study estimated relative efficacy of IB compared with G-Clb using MAIC methodology[21] and IB was reported to be superior to G-Clb.

However, IB is considerably more expensive compared with G-Clb as is usually the case with novel cancer drugs.[48] The superiority of IB in terms of its benefits to the patients with respect to (QA)LYs gained and the incremental costs per (QA)LY need to be justified to NICE for recommending it in the UK NHS. To our knowledge, such evidence is presently lacking. Therefore, we sought to study the CE of IB compared with G-Clb for untreated CLL patients with comorbidities from the UK health care perspective. We used the Markov model for estimating the CE, which is advocated by NICE in the UK.[43]

In the base case analyses, IB was found not to be cost-effective compared with G-Clb when referencing the commonly used UK WTP thresholds of £20,000 to £30,000 per QALY gained. Threshold analyses were performed to assess the price discounts needed for IB and idelalisib to decrease the incremental costs per QALY gained. The results indicated that for a 0%, 25%, and 50% discount on idelalisib, IB needs to be discounted by 30%, 40%, and 50% to bring the incremental costs under the commonly referenced WTP threshold in the UK.

Deterministic and probabilistic sensitivity analyses were conducted to analyze the effect of uncertainties in the Markov model input parameters on the model outcomes. The deterministic analyses were limited to 1-way sensitivity analyses (ie, only a single parameter was varied at a time). The incremental costs, LYs gained, and incremental costs per LY gained were highly sensitive to the variation in the HRs of IB versus G-Clb, and the parameters of the probability distributions fitted to the PFS and OS survival curves of G-Clb. The QALYs gained and incremental costs per QALY gained were highly sensitive to utilities of the various health (sub-) states, and were most sensitive to the oral treatment utility in the PFS state. The effect of joint uncertainty in the model parameters was studied by the probabilistic sensitivity analyses. The resulting CEAC showed that IB has a >50% probability of being more cost-effective than G-Clb at WTP thresholds higher than £100,000 per QALY gained.

As per the scenario analysis results, IB proved to be cost-effective compared with G-Clb. This is because the patients in the G-Clb arm move to progression faster than those in the IB arm, after which IB was administered as a second-line treatment, thereby, increasing the costs in the progression state. The total cost in the progression health state for the G-Clb and IB arm was £499,192 and £70,732, respectively, and the drug acquisition cost was found to be the main driver for the costs.

Because of the high costs in the progression health state accruing because of IB as the second-line treatment, the total costs of the G-Clb arm were considerably larger compared with the IB arm, namely £534,699 and £320,988, respectively. The patients in the

IB arm also received IR, subject to progressing within 24 months, which is also an expensive treatment. However, relatively fewer people in the IB arm were administered this treatment because of the patients staying in the PFS health state for a longer time.

This suggests that administering IB as a first-line treatment is a plausible cost-saving strategy for the UK NHS. The cost savings are likely to further increase with discounts on the drug prices of IB. As per the analyses from this study, the current standard of care, G-Clb followed by IB, appears to be not only a suboptimal utilization of the NHS resources, but also leads to a considerable undermining of the LYs and QALYs of the patients.

The study results were compared with other CE studies including either IB or G-Clb as first-line treatments. Becker et al[19] reported 2.67 years and cost of £30,609 in the PFS health state for the G-Clb arm, whereas in our study, the respective estimates were 2.33 years and £35,506. These differences can be attributed to the methodological differences between the studies, for example, parametrization of survival curves might lead to a difference in the estimates.[42] However, these differences are unlikely to affect the study results, as per the robustness of the estimates evaluated in the sensitivity analyses.

In our knowledge, this is the first CE study of IB for untreated CLL patients with comorbidities in the UK, and has generated evidence to inform policymakers regarding the benefits of IB to support them in the negotiation agreements and reimbursement decisions for the UK NHS. The most important finding of the study is the recommendation to include IB as a first-line treatment, which would result in significant cost savings for the UK NHS. The study findings show a mean saving of £213,711 per patient over lifetime apart from the mean LYs and QALYs gained of 1.35 and 1.49 per patient, respectively.

The threshold analyses performed with the various discount rates should further assist the policymakers in negotiating prices with the drug manufacturer. Because the proposal to include IB as a first-line treatment is a cost-saving strategy, the budget-impact analyses[49] for IB as a first-line treatment is likely to be favorable compared with G-Clb followed by IB as the second-line treatment, which is the current standard of care.[17] The price of IB can be expected to reduce in the future because of economies of scale[50] and the expiry of exclusivity for drug patent,[51] and therefore, the effect on the budget would be further minimized.

The trend toward treating CLL as per disease classification should enable the treatment(s) to become more cost-effective for patient access. The current therapeutic strategy is guided by the prognostic subgroups classified according to cytogenetic risk factors and gene mutations.[13] Recent developments, such as identification of the proportion of the abnormal clone is gaining importance[13] enabling further stratification of the prognostic subgroups. These contemporary strategies would guide delivery of treatment(s) as per prognostic efficacy, and enable administration of expensive treatments such as IB to patients who are more likely to (completely) respond to the treatment, thereby, making IB (more) cost-effective for specific categories of patients.

The strength of the study is the use of HRs which were sourced from a MAIC study conducted by Van Sanden et al,[21] which matched the patient baseline characteristics of the CLL11 study population with that of RESONATE-2 before the estimation of treatment efficacy. This mitigates the issue of lack of a clinical trial directly comparing IB with G-Clb.

Our study has several limitations. First, the survival curves from RESONATE-2 and CLL11 studies are limited to follow-up of 24 and 36 months, respectively. Therefore, there are uncertainties regarding the time to progression. Second, the median PFS and OS were not reached in the RESONATE-2 study, and median OS was not reached in the CLL11 study. Apart from this, postprogression survival was obtained from standard sources[32] because of lack of IPD from the clinical trials or observational studies. This might bias the postprogression survival estimates. These issues have adverse implications for the extrapolation of survival curves, and thereby the transition probabilities might be over- or underestimated.

We used a single HR to estimate PFS and OS of IB, which assumes a constant treatment HR for all patient age groups, whereas in real life, the HRs for younger age groups are likely to be different than those for the older age groups. There were not many relatively younger people in our study population because the median age was 73 years.[21] Also, the background characteristics of the respective study populations were matched in both of the arms using the MAIC[21] methodology, therefore, the constant HR is likely to similarly affect the LYs in both of the arms.

We acknowledge that in the real world scenario, the patients might not show similar gains in (QA)LYs because of several background factors such as patient characteristics, and health care system delivery mechanisms, like mitigation of adverse events followed by reinitiation of treatment, etc. Because the clinical trials use rigorous inclusion criteria, this might lead to optimistic clinical study outcomes. This would imply that the total cost and (QA)LYs obtained in our study might be overestimated.

The utility estimates were obtained from the utility elicitation studies because trial-based utility estimates were not available. Such utility elicitation studies used TTO and standard-gamble methods to elicit utilities using vignettes. Vignettes encompass health descriptions and are prone to being interpreted differently by people, and therefore the obtained utility estimates might not be precise. Nevertheless, the obtained utilities seemed comparable with those used in other studies for similar health states.[52,53] We have conducted deterministic and probabilistic sensitivity analyses to study the influence of these uncertainties, and the results show the obtained estimates to be sound.

The RESONATE-2 study has been recently completed whereas the CLL11 clinical trial is still ongoing. Upon availability of matured survival data with longer follow-up, additional analyses are envisaged to obtain more accurate and robust estimates of the CE. Additionally, as additional observational study data from these treatments become available, it would be imperative to confirm whether the obtained study estimates would be transferable to the real world patient population.[54] We also envisage a head-to-head trial of IB versus G-Clb to mitigate the issues related to the MAIC estimates.

New clinical trials have been initiated of IB in combination with G-Clb, as well as other combinations.[55] A search on the clinicaltrials.gov Web site yielded 16 ongoing studies with IB as combination therapy in untreated CLL patients.[56] It is recommended to include these treatment strategies as comparators with the IB treatment strategy to obtain a holistic understanding of the

CE of the various treatments available for untreated CLL patients. The average age of the CLL community is 72 years, and many people suffer with comorbidities and are less fit and need access to tolerable treatments that are effective.[57] However, relatively fewer studies are conducted in this age group. Therefore, dedicated trials for this patient population are recommended.

Conclusion

Ibrutinib as a first-line treatment appears to be a cost-saving strategy compared with G-Clb with IB as a second-line treatment. IB is likely to be cost-effective compared with G-Clb when available at the prescribed discount rates. Results of this study can be used to inform the NICE recommendations regarding treatment strategies for CLL patients with comorbidities, and further support negotiation agreements and reimbursement decisions in the UK. A direct comparison of IB with G-Clb from the results of a head-to-head trial of IB versus G-Clb is envisaged to corroborate the currently available evidence.

Clinical Practice Points

- Ibrutinib is approved by the FDA and European Medicines Agency (EMA) for patients with treated CLL and was also recently approved by the FDA as well as the EMA for untreated CLL patients on the basis of the results of the RESONATE-2 clinical trial.
- Ibrutinib and Clb in combination with CD-20 antibody (obinutuzumab or ofatumumab) are recommended by the ESMO for untreated CLL patients who are not fit for fludarabine-based chemoimmunotherapy.
- However, it has still not been included by the NICE for this group of CLL patients in the UK because the CE of IB needs to be shown with respect to the current standard of care.
- We sought to compare the treatment benefits (QALYs gained) and CE of IB compared with G-Clb.
- Ibrutinib showed an incremental gain in LY and QALY of 1.35 years and 1.49, respectively, over G-Clb.
- The incremental cost per LY and QALY gained was found to be £83,435 and £75,648, respectively.
- However, a comparison of the current treatment strategy compared with IB administered as first-line-treatment showed IB to be a cost-saving strategy with savings of £158,028 and £143,279 per LY and QALY, respectively.
- This finding is likely to not only facilitate accessibility of superior treatment for untreated CLL but also lead to significant cost savings for the UK National Health Services.

Disclosure

The authors have stated that they have no conflicts of interest.

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