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Cost-effectiveness of First-line Chronic Lymphocytic Leukemia Treatments When Full-dose Fludarabine Is Unsuitable

Erkki Soini, MSc (health econ)[1]; Anne Hautala, MSc (pharm)[2,*]; Eira Poikonen, MD, PhD[3]; Ursula Becker, MSc[4]; Mira Kyttälä, PhD[2,**]; and Janne Martikainen, PhD, Adjunct Professor[1]

[1]ESiOR Oy, Kuopio, Finland; [2]Roche Oy, Espoo, Finland; [3]Department of Hematology, Helsinki University Hospital Comprehensive Cancer Center, and University of Helsinki, Helsinki, Finland; and [4]F. Hoffmann–La Roche Ltd, Pharmaceuticals Division, Basel, Switzerland

ABSTRACT

Purpose: The cost-effectiveness of first-line chronic lymphocytic leukemia treatments was assessed among patients unsuitable for full doses of fludarabine.

Methods: The study's key outcome was the lifetime incremental cost-effectiveness ratio (ICER) (euro/quality-adjusted life-year [QALY] gained) with an annual 3% discounting. A probabilistic Markov model with 3 health states (progression-free, progression, and death) was developed. Survival time was modeled based on age-matched clinical data by using appropriate survival distributions. Each health state was assigned an EuroQoL-5D-3L quality-of-life estimate and Finnish payer costs according to treatment received, and Binet stage of disease; severe adverse events and treatment inconvenience were also included. Six approaches considered the risk and value of key outcomes: cost-effectiveness efficiency frontiers; Bayesian treatment ranking (BTR) rated the lowest ICERs and best QALY gains; the cost-effectiveness acceptability frontier demonstrated optimal treatment; expected value of perfect information; and the cost–benefit assessment (CBA), a type of clinical value analysis, increased the clinical interpretation and appeal of modeled outcomes by including both relative and absolute (impact investment [benefit obtained with a fixed limited budget]) benefit assessments.

Findings: The ICERs compared with chlorambucil varied from €29,334 with obinutuzumab + chlorambucil to €82,159 with ofatumumab + chlorambucil. Based on the BTR of ICERs versus chlorambucil, obinutuzumab + chlorambucil was the most cost-effective with 93% probability; rituximab + chlorambucil was the second most cost-effective (73%); and rituximab + bendamustine was the third most cost-effective (65%). The ICERs of obinutuzumab + chlorambucil were €20,038, €11,556, and €15,586 compared with rituximab + chlorambucil, rituximab + bendamustine, and ofatumumab + chlorambucil. Obinutuzumab + chlorambucil was the most cost-effective treatment, with 54% and 99% probability at €30,000 and €50,000/QALY gained, respectively. The corresponding expected values of perfect information were €1438 and €44 per patient. Based on the BTR of QALYs gained, obinutuzumab + chlorambucil was the most effective, with 100% probability; rituximab + chlorambucil was the second most effective (56%); and rituximab + bendamustine was the third most effective treatment (81%). Results were robust in sensitivity analyses. For obinutuzumab + chlorambucil, the CBA demonstrated the best clinical value–to–cost-effectiveness relation and the longest time progression-free with a limited budget.

Implications: The mean results were sensitive to large changes in time horizon, indirect comparison hazard ratios, survival distributions, and discounting; however, obinutuzumab + chlorambucil provided considerable effectiveness and best value for money among chronic lymphocytic leukemia patients unsuitable to

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*Mrs. Hautala is currently an employee of Farenta Oy, Espoo, Finland.

**Dr. Kyttälä is currently an employee of Roche Pharma AG, Grenzach-Wyhlen, Germany.

receive full doses of fludarabine. In this case, CBA concurred with the key outcome of the study. However, the CBA cannot fully substitute the key outcome, and further cost-effectiveness studies with different cancer types are needed to assess the validity of a limited CBA. (*Clin Ther*. 2016;38:889–904) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: bendamustine, chronic lymphocytic leukemia, economic evaluation, obinutuzumab, ofatumumab, rituximab.

INTRODUCTION

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia, accounting for 25% to 40% of all leukemias.[1,2] The annual incidence of CLL is 2 to 6 per 100,000 population,[1,3] with a preponderance of male subjects over female subjects. CLL is more common in elderly people, with almost one half of the newly diagnosed CLL patients being at least 75 years of age. CLL causes significant humanistic[4–10] and economic[9,11,12] burdens.

Immunochemotherapy with rituximab + fludarabine + cyclophosphamide (RFC) has been the standard first-line treatment for patients with CLL who require and can tolerate intense chemotherapy. However, older patients with comorbidities are often ineligible for RFC.[13] For these patients, chlorambucil monotherapy (Clb) is often used, even though it rarely induces complete responses.[14–16] Currently, combination regimens, including obinutuzumab + chlorambucil (GClb), ofatumumab + chlorambucil (OClb), rituximab + bendamustine (RB), and rituximab + chlorambucil (RClb), are considered because of their efficacy and limited toxicity.

The present study is the first to estimate the cost-effectiveness of all relevant treatments among patients with CLL unsuitable for full-dose fludarabine and, thus, RFC therapy to the best of our knowledge. It is also probably the first to elaborate on the results of a full health economic assessment involving 6 different methods: cost-effectiveness efficiency frontiers; Bayesian treatment ranking (BTR); cost-effectiveness acceptability frontier (CEAF); expected value of perfect information per patient (EVPI); limited cost–benefit assessment (CBA), which is a clinical value analysis; and impact investment analysis (IIA) based on the CBA.

MATERIALS AND METHODS

A decision-analytic modeling approach was used to conduct the cost-effectiveness analysis (CEA) presented here. This CEA meets the Finnish requirements for health economic evaluations,[17] which concurs with most European guidelines.[18–27]

Clb, GClb, OClb, RB, and RClb were compared by using a probabilistic, long-term, Markov transition model (Figure 1) with 3 mutually exclusive key health states in patients with CLL who were unsuitable for RFC. A 1-week model cycle length with life-table method of half-cycle correction[28,29] was applied.

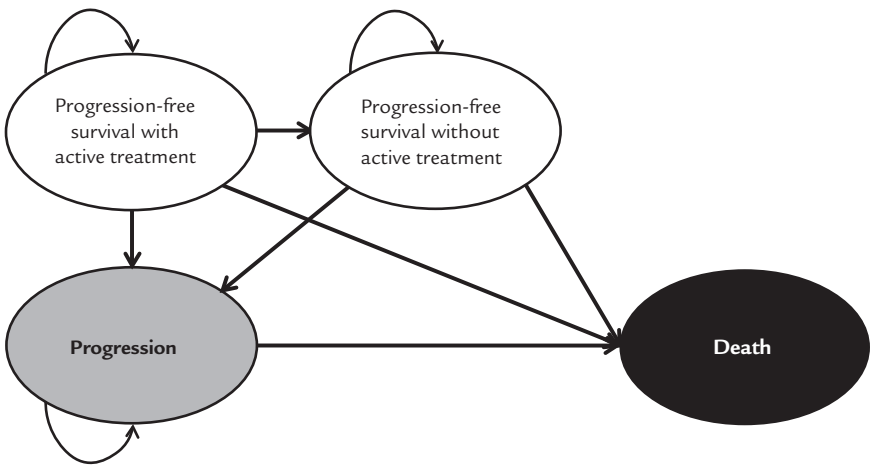

Figure 1. Simplified presentation of the Markov model.

Modeled Cohort

This CEA included a cohort of adult CLL patients with comorbidities or physical decline. The cohort's characteristics were based on Finnish-specific features and the CLL11 trial[15] assessing Clb, GClb, and RClb in previously untreated patients with CLL. Fifty percent of the Finnish cohort members were male (60% in CLL11). The proportion of cohort members with Binet stages A, B, and C were 22%, 42%, and 36%, respectively, in CLL11. The mean age, weight, and height were 71.7 years, 73.7 kg, and 166.7 cm in CLL11. The mean estimated body surface area was 1.8 m^2.[30]

Progression-free Survival

The CEA was based on individual patient data from CLL11 (An Open-label, Multi-center, Three Arm Randomized Study to Investigate the Safety and Efficacy on Progression-free Survival of RO5072759 + Chlorambucil (GClb) Compared to Rituximab + Chlorambucil (RClb) or Chlorambucil (Clb) Alone in Previously Untreated CLL Patients With Comorbidities), including progression-free survival (PFS) for Clb, GClb, and RClb (March 3, 2014 data cut[16]), and aggregated PFS from Knauf et al,[14,31] COMPLEMENT 1 (Ofatumumab + Chlorambucil vs Chlorambucil Monotherapy in Previously Untreated Patients With Chronic Lymphocytic Leukemia)[32] for OClb, and CLL10 (Phase III Trial of Combined Immunochemotherapy With Fludarabine, Cyclophosphamide and Rituximab (FCR) Versus Bendamustine and Rituximab (BR) in Patients With Previously Untreated Chronic Lymphocytic Leukaemia)[33] for RB. The CLL11 trial program had 2 stages for GClb and RClb, with stage 1 being a subgroup of stage 2. The stage 2 individual patient data from CLL11 were used for GClb and RClb. For Clb, only the stage 1 individual patient data were available. The baseline characteristics of patients in the key trials are reported in Supplemental Table I (as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005). The key differences were as follows: the CLL11 patients were older, had more comorbidities, and had worse creatinine clearance compared with the COMPLEMENT 1 or CLL10 patients. Unlike the CLL11 and COMPLEMENT 1 patients, the CLL10 patients had a low Cumulative Illness Rating Scale, and the patients were basically suitable for fludarabine treatment. The dosing regimens of the trials are reported in the Costs section of this article.

All simulated cohort members started the model in the PFS health state, on treatment, and could progress, die, or discontinue treatment based on the actual treatment duration in line with the CLL11 results. Because the maximum treatment duration was 6 cycles in CLL11, parametric survival functions were not used for treatment duration, but the actual proportions of patients on treatment from CLL11 were used.

Weibull's parametric survival distribution was selected to model the CLL11 PFS based on statistical tests, the Akaike information criterion, visualization, and expected PFS times from longer term clinical studies. The following parameter values (SEs) were used: Clb intercept, 2.591 (0.065); Clb scale, 0.636 (0.049); GClb intercept 3.628 (0.057); GClb scale, 0.635 (0.046); RClb intercept, 3.070 (0.036); and RClb scale, 0.560 (0.029). Cholesky decomposition was applied to include the correlation of survival model parameters.[34]

For the comparison versus OClb and RB, a Bayesian meta-analysis[35] with age adjustment was available. The hazard ratios (HRs) were converted into logarithmic HRs to inform probabilistic sensitivity analysis distributions, and they were used to adjust the PFS estimates of RB and OClb: GClb versus RB, HR of 0.412 (lnHR, –0.937; SD, 0.314); GClb versus OClb, HR of 0.295 (lnHR, –1.241; SD, 0.203).

The probability of death during PFS was the maximum of death rate in CLL11 and the Finnish age- and gender-specific mortality in 2013.[36,37] Survival curves are depicted in Figure 2.

Postprogression Survival

After progression, the proportion of cohort members with Binet stages A, B, and C were 14.5%, 47.2%, and 37.8%, respectively.[38] Postprogression survival (PPS), the transition from progressive disease to death, was modeled based on the CLL5 (Fludarabine Versus Chlorambucil in First Line Therapy of Elderly Patients (More Than 65 Years) With Advanced Chronic Lymphocytic Leukemia) trial (January 14, 2013, data-cut) due to immaturity of overall survival and crossover in CLL11. Applicability was ascertained by taking into account the age of patients at the time of disease progression by using an exponential parametric survival model with age as a covariate (SE): intercept, 6.492 (1.920); age, –0.035

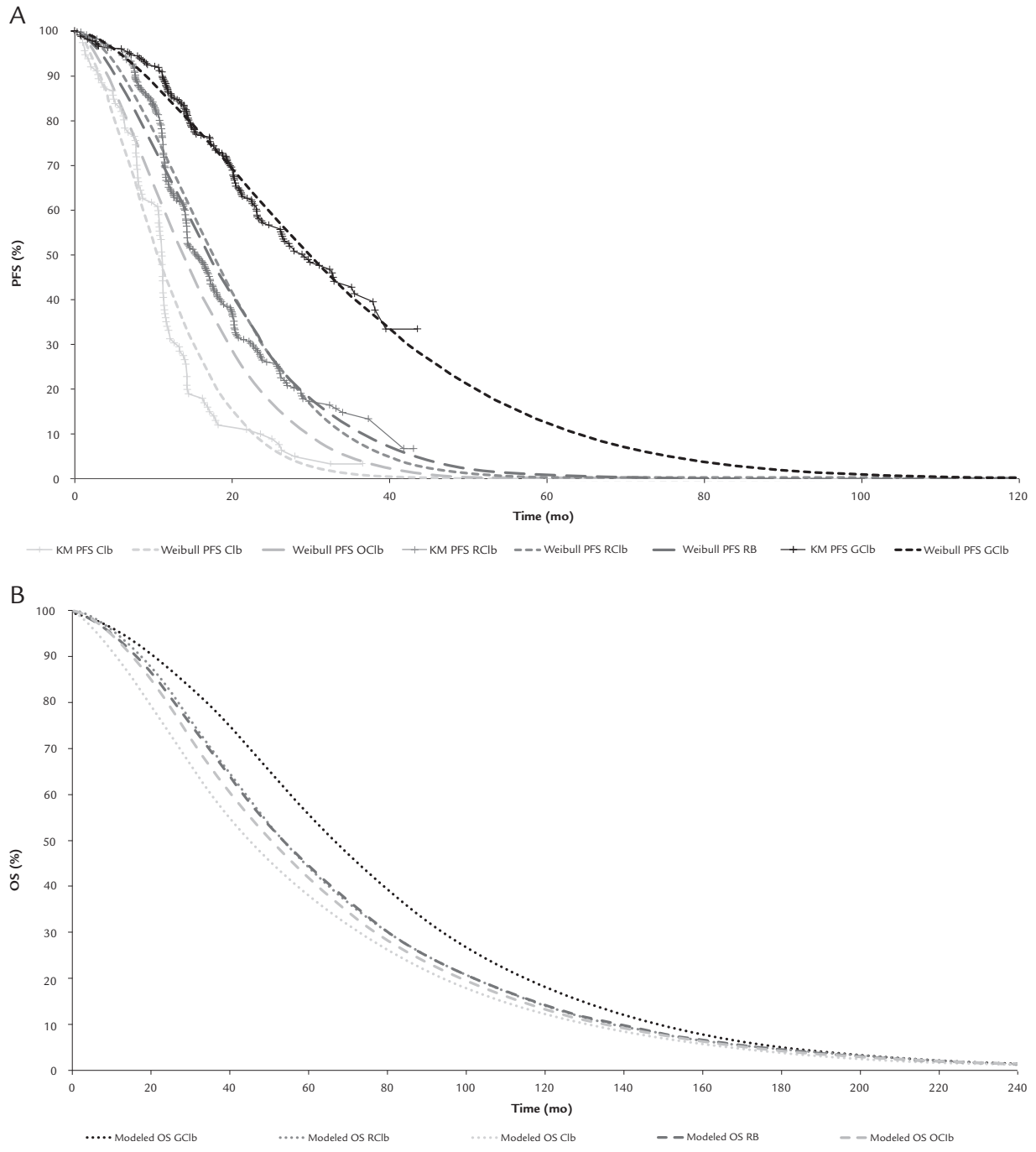

Figure 2. (A) Ten-year progression-free survival (PFS) and (B) 20-year overall survival (OS) related to treatments. Clb = chlorambucil alone; GClb = obinutuzumab + chlorambucil; KM = observed Kaplan-Meier; OClb = ofatumumab + chlorambucil; RB = rituximab + bendamustine; RClb = rituximab + chlorambucil.

(0.027). The exponential model was selected based on the Akaike information criterion, visual inspection, and expected overall survival from longer term clinical studies and Finnish data.[39] Cholesky decomposition[34] was applied for PPS.

Costs

Direct health state–specific costs were applied based on the treatments and Binet stages (Table I). Costs consisted of drug acquisition, drug administration, monitoring, follow-up, progression/relapse resources, postprogression treatment, and treatment of serious adverse events (SAEs). Indirect costs and losses such as absenteeism, presenteeism, caregiver and time costs, and disutilities due to informal care were ignored according to the Finnish guidance[17] and CLL11 mean patient age exceeding the Finnish retirement age.

Drugs

The actual treatment duration and dosing from the trials were used without vial sharing. Furthermore, a distinction was made between the first and consecutive drug administrations and is shown in Table I, which also reports the dosing regimens from the trials. The first dose of obinutuzumab may be given on 1 day or split over 2 consecutive days. Not benefiting obinutuzumab in terms of administration costs, 1 vial split to 100 mg day 1 and 900 mg day 2, and consequent higher drug administration cost was assumed (ie the 1000 mg vial may be given in day 1 and lower drug administration may be used). Up-to-date costs [40,41] were used together with the cost correction for administration time needed in order not to underestimate the administration cost of intravenous drugs (see [42]).

Individual patient drug utilization data were available for Clb, GClb, and RClb. For OClb, the estimated treatment duration was, on average, 6.4 cycles of a planned 12 cycles (ie, 53.3%)[32] with 100% assumed dose intensity. For RB, the mean number of treatment cycles was 5.41 of a planned 6.00.[33] The mean dose was estimated to be 96.84% (ie, 90.0% * 31.6% + 100% * 68.4% based on Eichhorst et al[33]). Postprogression cancer drugs were based on CLL5 (6.5 months of Clb 0.5 mg/kg[38] together with administration/monitoring costs).

Adverse Events

Grade 3 to 5 SAEs observed in CLL11 individual patient data, COMPLEMENT 1,[32] and CLL10[33] were included based on their potential association with CLL treatment. For OClb and RB, a maximum 1 SAE/preferred term was included,[32,33] whereas for Clb, GClb, and RClb, multiple SAEs/preferred term or patient was possible. This inconsistency resulting from the publications benefited OClb and RB compared with Clb, GClb, or RClb. All expected SAE costs (Supplemental Table II [as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005]) were applied in the first model cycle. A sensitivity analysis (Supplemental Appendix I [as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005]) incorporated AEs based on the CLL11 publication.[15]

Binet and End-stage

The resources were partitioned based on Binet stages. Based on the Finnish experience, the following annual resources were fixed for all: 1 primary care visit (€116.18), 1 specialist visit (€309.04), and a comprehensive blood test.[40,41] In addition, the following factors were considered annually: Binet stage A, 2.67 primary care calls (€27.46/call) and 4.80 calls if progressed; Binet stage B, 3.00 primary care calls (4.80 calls and 1 specialist visit if progressed); and Binet stage C, 4.80 primary care calls and 1 specialist visit. One blood cell count + neutrophil assessment per visit were included.

Based on the Finnish experience, end-stage treatment consisted of pneumonia in 40% of patients (€7827.49 per hospitalization[40,41]); autoimmune hemolytic anemia or immune thrombocytopenia in 5% of patients[13] (10-day hospital stay for autoimmune hemolytic anemia/immune thrombocytopenia, €6205.06[40,41]); and 1 primary care call per week for the last 2 months (included as an expected cost during the PPS).

Quality-adjusted Survival

Patient utility was based on a recent UK utility elicitation study with validated health states and EuroQoL-5D-3L (EQ-5D-3L) dimensions.[10] The impact of on/off treatment on quality of life (QoL) was accounted for. The UK utility values based on elicitation were adjusted to take into account the representative EQ-5D-3L tool-based generic QoL of 65- to 74-year-old Finns together with their symptoms/comorbidities (adjusting factor 0.776/0.820 based on the EQ-5D-3L QoL of 65- to 74-year-old Finns per utility with PFS off- treatment [43]/[10],

Table I. Treatment-related resources and costs.

Treatment Drug, mg	Drug (€)/Cycle 1st	Drug (€)/Cycle 2nd	Administration Time	Administration €/Cycle 1st†	Administration €/Cycle 2nd†	Other Medications/Cycle 1st	Other Medications/Cycle 1st, €	Other Medications/Cycle 2nd	Other Medications/Cycle 2nd, €
Clb* po (0.5/kg × 2)	119.59	119.59	Not needed	0	0	Not needed			
GClb*	11,614.96	3951.38		1530.17	364.17	Day 1, Day 2: Drugs 1	66.61	Drugs 2	0.39
Obinutuzumab IV (cycle 1, 3000 for 4 d; later, 1000 for 1 day)	11,495.37	3831.79	Cycle 1, 4 h, 4 days Later, 3.25 h	1530.17	364.17				
Chlorambucil po (0.5/kg × 2)	119.59	119.59	Not needed	0	0				
OClb*	3018.68	2372.90		826.34	382.54	Drugs 1	33.31	Drugs 1	33.31
Ofatumumab IV (cycle 1, 1300 for 2 d; later, 1000 for 1 d)	2798.38	2152.60	Cycle 1, 6 h Day 1, 4.5 h Day 8 Later, 4 h	826.34	382.54				
Chlorambucil po (10/m^2 × 7)	220.30	220.30	Not needed	0	0				
RB*	3199.66	4077.18		1098.63	654.84	Drugs 3	0.48	Drugs 3	0.48
Rituximab IV (cycle 1, 375/m^2 for 2 d; later, 500/m^2 for 1 d)	2047.54	2925.05	Cycle 1, 4 h Day 1, 4 h Day 2 Later, 1.5 h	765.09	321.29				
Bendamustine IV (90/m^2 × 2, 2 d/cycle)	1152.13	1152.13	Cycle 1: +1 h Day 2, 1 h Day 3 Later: +1 h Day 1, 1 h Day 2	333.54	333.54				
RClb*	2167.13	3044.64		765.09	321.29	Drugs 2	0.39	Drugs 2	0.39
Rituximab IV (cycle 1, 375/m^2 for 2 d; later, 500/m^2 for 1 d)	2047.54	2925.05	Cycle 1, 4h Day 1, 4h Day 2. Later, 1.5h	765.09	321.29				
Chlorambucil po (0.5/kg × 2)	119.59	119.59	Not needed	0	0				

Clb = chlorambucil alone; GClb = obinutuzumab + chlorambucil; OClb = ofatumumab + chlorambucil; RB = rituximab + bendamustine; RClb = rituximab + chlorambucil; po = orally;

*In addition, cycle 1 monitoring included the following: 1 specialist visit (€309.04/visit[40]; index, 1.056198[41]); 3 blood cell counts + neutrophils; 1 creatinine measurement; and assessment of alanine transaminase, alkaline phosphatase, C-reactive protein, potassium, sodium, urate, and l-day enzyme levels (tests total €18.69/cycle); that is, total of €327.73/first cycle. Later monitoring/cycle included the following: 0.25 specialist clinician visit; 0.75 specialist clinician call (€27.46/call[40,41]); and 3 blood cell count + neutrophils (tests total €7.60/cycle); that is, a total of €105.46/cycle when on treatment.

†To avoid the underestimation of the intravenous drug administration costs,[42] the administration cost was approximated by using specialist health care visit/administration (1 hour of time included) and additional time counted with nurse's employment cost (€24.50/hour[40,41]). Drugs 1 included corticosteroid prednisolon 100 mg IV, the antihistamine cetirizine 10 mg, and paracetamol PanadolR 1 g po. Drugs 2 included cetirizine 10 mg and paracetamol 1 g po. Drugs 3 included cetirizine 10 mg, paracetamol 1 g, and antiemetic metoclopramide 10 mg po. Drug costs were taken from the Finnish Medicines Tariff 9/2014.

which was used as an adjusting multiplier for the utility values based on the elicitation[10]). Expected PPS and the adjusting factor were taken into account in the postprogression QoL estimate.

The mean (SD) QoL values were as follows: 0.672 (0.189) PFS with nonintravenous treatment, 0.634 (0.208) PFS with intravenous treatment, 0.520 (0.246) PFS with increased hospital visits, 0.776 (0.181) PFS off-treatment (mean equivalent to the EQ-5D-3L QoL of 65- to 74-year-old Finns[43]), and 0.563 for PPS. Treatment inconvenience was assumed to last the longest between 2 planned treatment administrations (eg, GClb 4 weeks). The disutility due to increased hospital visits affected only GClb, although administration of RB and RClb can also be associated with multiple visits.

Time Horizon

Health outcomes should be modeled over the remaining lifetime of the patients[34] if a mortality difference is expected. With the base-case settings, 1.7% of the GClb cohort was predicted to be alive within 20 years, and thus a 20-year time horizon was used. Adhering to the Finnish guidelines,[17] all outcomes were discounted with 3% per year.

Distributions

The second-order Monte Carlo simulation with 2000 simulations was conducted by using Visual Basic for Applications for Microsoft Excel 2013 (Microsoft Corporation, Redmond, Washington) and was used to jointly take into account variation in the outcomes due to potential sampling uncertainty related to the model parameters. β-Distributions were used for QoL values, multivariate normal distributions for parametric PFS and PPS based on individual patient data, and log-normal distributions for SAE amounts, costs, and PFS HRs. In case of unknown SE, ±20% of mean value was used.

Outcomes

The primary outcome of the analysis was cost-utility measured as the incremental cost-effectiveness ratio (ICER), which is the ratio of the cost and quality-adjusted life-year (QALY) difference between 2 interventions. The ICERs were determined versus the most affordable and the most efficient option. The efficient nondominant options were also depicted as the cost-effectiveness efficiency frontier.[44] Bayesian treatment ranking (BTR) was used to incorporate risk assessment to the ranking of the lowest ICERs (best relative value with euro), best quality-adjusted survivals (highest QALY gains), and impact investing.

The secondary outcomes included incremental cost per life-year gained, uncertainty assessment in terms of the cost-effectiveness acceptability frontier (CEAF), and expected value of perfect information per patient (EVPI). The CEAF illustrates the optimal treatments with the highest expected monetary net benefit (pay-off) as a function of willingness-to-pay (euro/QALY gained). The EVPI demonstrates the maximum monetary value of total parameter uncertainty that can be resolved by acquiring perfect evidence for the included model parameters or alternatively the expected net monetary consequences related to a "wrong" resource allocation decision.[45–47] In Finland, the interpretation of cost-effectiveness is complicated because the decision-maker's willingness-to-pay is not publicly announced,[48] and, thus, the CEAF and EVPI complement the primary outcomes. Based on our experience, the maximum willingness-to-pay for CLL would be approximately €50,000/QALY gained, and values less than €30,000/QALY (€20,000/QALY) gained are likely to indicate good (very good) cost-effectiveness, respectively. These findings are in line with similar UK thresholds.[27]

Because ICER and CEAF are sensitive to the number of comparators included (and EVPI may be also), results excluding Clb were also reported.[49] Clb may not be a relevant first-line treatment, and Clb results were based on stage 1 in CLL11.

To increase the clinical appeal and interpretation of CEA findings, the modeled primary and secondary results were used to develop tertiary results to complement them. The tertiary analysis approach was a CBA type (a form of clinical value analysis that could be labeled as drug cost–benefit approach), which essentially analyzes results during PFS and can include less extrapolation uncertainty in its limited perspective. Main CBAs were performed in terms of cost per QALY or PFS year gained during PFS (relative benefit assessment) and the length of benefit obtained with a fixed limited drug or PFS budget (absolute benefit assessment, impact investment) of €20,000 per patient. The impact investment analysis (IIA) incorporates an explicit willingness-to-invest value (ie, here assumed to be €20,000/patient) and thus illustrates the mean outcome in terms of a single unit (ie, time in years).

RESULTS

The ICERs (euro/QALY gained) compared with the most affordable treatment (Clb) were as follows: GClb, €29,334; RClb, €43,958; RB, €59,316; and OClb, €82,159. At the willingness-to-pay threshold of €30,000/QALY gained threshold, only GClb was cost-effective compared with Clb. The ICERs for the most efficient option (GClb) compared with other combination treatments were below the most acceptable willingness-to-pay threshold (€11,556–€20,038) (Table II).

Table II. Probabilistic base-case results: incremental cost-effectiveness ratios (ICER) and quality-adjusted life years (QALYs), life-years gained (LYG), and payer costs with their 95% credibility intervals (CrI; 2.5%–97.5% percentiles [2000 iterations]).

Primary Outcome	Cost-Utility Analysis: ICER, €/QALY Gained			Cost-Effectiveness Analysis: ICER, €/LYG		
Treatment	Versus Clb	Versus RClb	GClb Versus	Versus Clb	Versus RClb	GClb Versus
GClb	29,334	20,038	–	24,474	18,035	–
RClb	43,958	RClb versus	20,038	32,896	RClb versus	18,035
RB	59,316	Dominated	11,556	45,238	Dominated	10,210
OClb	82,159	639	15,586	53,278	580	14,051
Clb	–	43,958	29,334	–	32,896	24,474
Total	QALYs		LYGs		Costs, €	
Treatment	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
GClb	3.75	3.35–4.18	5.75	5.11–6.45	42,467	39,001–46,876
RClb	3.11	2.73–3.51	5.05	4.38–5.73	29,810	26,221–34,577
RB	3.10	2.60–3.68	5.02	4.25–5.82	34,972	31,444–39,571
OClb	2.93	2.48–3.38	4.84	4.12–5.54	29,690	25,950–34,544
Clb*	2.71	2.33–3.11	4.51	3.85–5.18	12,159	8657–17,066
PF	QALYs		LYGs		Costs €	
Treatment	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
GClb	2.03	1.80–2.29	2.71	2.42–3.02	34672	33,381–36,231
RClb	1.16	1.06–1.25	1.57	1.46–1.68	21031	20,207–22,014
RB	1.16	0.74–1.74	1.57	1.02–2.33	26160	24,937–27,497
OClb	0.92	0.67–1.22	1.28	0.96–1.67	20604	19,512–22,016
Clb*	0.73	0.64–0.83	0.99	0.87–1.12	3055	2591–3594
PP	QALYs		LYGs		Costs (€)	
Treatment	Mean	95% CrI	Mean	95% CrI	Mean	95% CrI
GClb	1.71	1.35–2.10	3.04	2.41–3.70	7796	4721–11,896
RClb	1.96	1.58–2.34	3.48	2.83–4.15	8779	5364–13,643
RB	1.94	1.55–2.36	3.45	2.76–4.15	8812	5475–13,316
OClb	2.01	1.62–2.41	3.56	2.90–4.27	9086	5563–13,793
Clb*	1.98	1.61–2.37	3.52	2.87–4.19	9104	5674–14,045

Clb = chlorambucil alone; Dominated = more costly and less effective than its comparator; GClb = obinutuzumab + chlorambucil; OClb = ofatumumab + chlorambucil; PF = progression-free health state; PP = progressive disease health state. RB = rituximab + bendamustine; RClb = rituximab + chlorambucil.
*Based on CLL11 stage 1, others based on CLL11 stage 2.

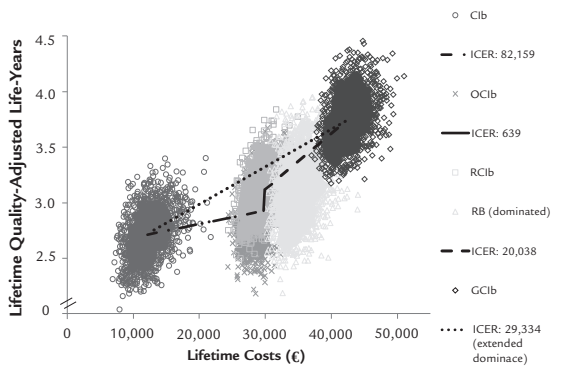

Figure 3. Cost-effectiveness plane with expected (discounted) lifetime costs, quality-adjusted life-years, and cost-effectiveness efficiency frontier (CEEF) (incremental cost-effectiveness ratio [ICER] = euro/quality-adjusted life-year gained). Clb = chlorambucil alone; GClb = obinutuzumab + chlorambucil; OClb = ofatumumab + chlorambucil; RB = rituximab + bendamustine; RClb = rituximab + chlorambucil.

According to the cost-effectiveness efficiency frontier (Figure 3, Table II), RClb, RB, and OClb were extendedly dominated by GClb and Clb. The ICERs for OClb versus Clb, and RB versus Clb, were €82,159 and €59,316, respectively, which may not be cost-effective.

Based on the conditional BTR of smallest ICER versus Clb (ie, the highest value for money), GClb was the most cost-effective (ie, efficient) treatment, with 92.9% probability; RB had 3.7% probability. The second most cost-effective treatments were RClb and RB, with probabilities of 72.8% and 21.7%, respectively. The third most cost-effective treatments were RB and OClb, with 65.2% and 34.8% probabilities. Consequently, GClb was the first best option, with only 7.1% risk of wrong allocation, RClb was second best option with 27.2% risk, and RB was third best option with 34.8% risk.

Secondary Outcomes

The average discounted survival ranged from 4.51 (Clb) to 5.75 (GClb) years (Table II). The discounted quality-adjusted survival ranged from 2.71 (Clb) to 3.75 (GClb) QALYs (Supplemental Figure 1), whereas the respective lifetime costs ranged from €12,159 to €42,467 (Supplemental Figure 2) (both as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005).

Based on the QALY and life-year differences, GClb was considerably more effective compared with the other treatments based on the 2.5% to 97.5% percentiles. Based on the BTR of greatest expected quality-adjusted survival (QALYs gained), GClb was the most effective, with 99.9% probability; RB had a probability of 0.1%. The second most effective treatments were RClb and RB, with 56.2% and 41.5% probabilities, respectively. The third most effective treatments were RB and OClb, with 81.1% and 18.9% probabilities. The fourth most effective rank was OClb, with 98.7% probability. Consequently, GClb is the first most effective option with only a 0.1% risk of wrong inference; RClb is the second most effective option, with a 43.8% risk; RB is third, with an 18.9% risk; and OClb is the fourth most effective option, with only 1.3% risk.

Costs for treatment acquisition (5%–64%), treatment administration/monitoring (10%–14%), and progression (18%–75%) were the biggest cost drivers for total costs (Supplemental Figure 2 [as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005]).

The ICERs compared with stage 1 Clb were as follows: GClb, €24,474/life-year gained; RClb, €32,896/life-year gained; RB, €45,238/life-year gained; and OClb, €53,278/life-year gained. The ICER of GClb versus RClb was €18,035/life-year gained, demonstrating the extended dominance of GClb and Clb over other treatments.

Sensitivity Analyses for Primary and Secondary Outcomes

Multinomial cost-effectiveness acceptability curves were drawn (Supplemental Figure 3 [as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005). In summary, Clb and GClb constituted the CEAF (Figure 4**A**). At €30,000 and €50,000/QALY gained, GClb had 54% and 99% probability for cost-effectiveness, respectively. The respective mean EVPIs were €1438 (2.5%–97.5% percentile, €0–€7379) and €44/patient, indicating low to moderate value of additional research to support decision-making or opportunity loss for a wrong

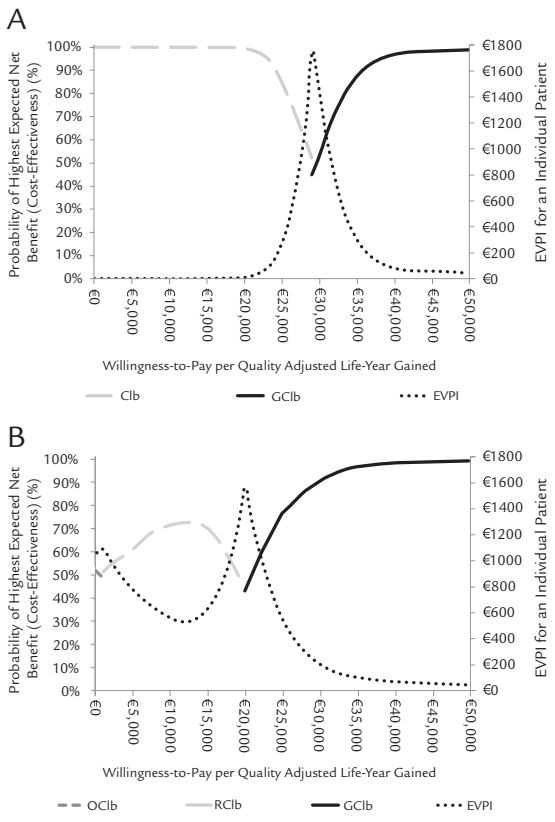

Figure 4. Cost-effectiveness acceptability frontiers (CEAF) and expected value of perfect information (EVPI) for comparison (A) including and (B) excluding Clb. Rituximab + bendamustine was never on CEAF (see also Supplemental Figure 3, as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005). Clb = chlorambucil alone; GClb = obinutuzumab + chlorambucil; OClb = ofatumumab + chlorambucil; RClb = rituximab+chlorambucil.

decision. The maximum mean EVPI was €1739 per patient (€0–€8182).

Combination Treatment Comparison

OClb, RClb, and GClb constituted the CEAF in the comparison excluding Clb (Figure 4B). At €30,000 and €50,000/QALY gained, GClb had 90% and 99% probability for cost-effectiveness, respectively. The respective mean EVPIs were €204 (€0–€2797) and €42/patient, indicating very low value of additional research or loss for a wrong decision. The maximum mean EVPI was €1562/patient (€0–€7827).

Scenario Analyses

The relative base-case results were robust for various changes in method, population characteristic, efficacy, QoL, and cost inputs (Supplemental Appendix I [as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005]). Scenario analyses produced lower mean ICERs for GClb (difference in ICER, –2340), RClb (–913), and RB (–306), and a higher mean ICER for OClb (5466) compared with the deterministic base-case scenario.

Tertiary Outcomes

The tertiary objective was to elaborate on the primary and secondary outcomes by using CBA. Generally, CBA cannot fully substitute the primary outcomes of standard CEA, if CBA ignores all other than drug costs, differences in quality of life, differences in AEs, differences other than selected survival parameters (eg, overall survival or PFS depending on the selected approach), and concordance between costs and benefits (ie., costs and survivals are gained from different timelines). Consequently, compared with conventional standard CEA, CBA may result in a high level of ignorance.

Based on the CBA (Supplemental Appendix II [as shown in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005]), GClb had the highest relative clinical value, only a low risk for a high cost–benefit ratio, best clinical value–cost-effectiveness relation, had the best impact on investment, and made the best value out of budget. In general, the CBA results concurred with the key outcomes, and the conclusions were similar.

DISCUSSION

This study illustrated the cost-effectiveness of first-line CLL treatments when RFC is unsuitable. The ICERs compared with Clb treatment (primary outcomes) were between €29,334 and €82,159/QALY gained, and GClb demonstrated the best value for money option and OClb demonstrated the worst. When ranked, GClb had the highest probabilities of lowest ICER versus Clb (the first best payoff) and highest QALY gain (the first best effectiveness). In addition,

the potential cost-effectiveness was projected to be achievable with low to moderate willingness-to-pay thresholds when selecting GClb (ie, best overall value with reasonable willingness-to-pay thresholds). Furthermore, the value of conducting additional research to support decision-making or loss from making a wrong decision was low to moderate, and relative results were robust based on the 26 different scenario analyses. Finally, the developed CBA demonstrated the best relative clinical value, the lowest risk for high cost–benefit ratio, the best clinical value–cost-effectiveness relation, and the most value gained with the limited budget (highest impact on investment) for GClb. Both drug and PFS costs seemed to follow the clinical value of drug, but the trend decreased as a function of costs, meaning that more efficient drugs also had a lower cost–benefit ratio; this scenario was also observed in the key outcomes. Generally, the CBA results and key outcomes concurred, but additional CEAs with different cancer types are needed to assess the validity of CBA due to its inherent limitations.

CBA is a clinical value assessment method that can increase the clinical interpretation and appeal of results; however, it cannot fully substitute the primary outcomes of standard cost-effectiveness analysis. CBA may ignore differences in a number of cost categories (eg, treatment administration, monitoring, AEs, end-stage treatment). Depending on the benefit side, it may also ignore the impact of QoL, AEs, and various types of survival parameters. If CBA is performed without further consideration, costs and benefits may be assessed from different timelines, and discounting can be ignored. Thus, CBA can easily result in investment biases and partial optimization of limited budgets. CBA as such should probably not be used as the primary method of analysis without acknowledging its limitations and their potential consequences, and its results should be interpreted with caution. In the present study, the objective of using CBA was only to elaborate and complement the primary and secondary outcomes.

The CBA provided new insights in the present study. All the primary, secondary, and tertiary findings were based on a decision-analytic modeling approach capable of synthesizing all the known evidence. With direct data elicitation methods or analysis of publications alone (eg, without handling of local age- and gender-specific mortality or without assessing the mean survival rates), CBA, as with any piggy-back assessment, may lack agreement between the benefits and costs and may not concur with solid standard modeled CEA results. Mean (not median) survival is the expected value of distribution; costs are usually means,[50] and with means, arithmetic calculations are feasible. As was performed in the present study, dose–response should be accounted for in the CBA. Consequently, CBA can offer new insights, although it is not a simple procedure; comprehensive methods and data are needed to conduct a valid CBA.

As observed before, treatment tolerability has an important role when the treatment response is not age related.[51] Since the early 1990s, the first and relapsed/refractory line cost-effectiveness of CLL treatments have been modeled,[52–57] and rituximab and bendamustine alone or as combinations with other treatments have been found to provide reasonable value for money. In this analysis, the ICER for RB versus Clb was €59,316/QALY gained, a result that was potentially not cost-effective.

Generally, health economic modeling results in the simplification of a more complex reality. The key sources of uncertainty in this study were model structure, parameter values (imprecision of parameters), and patient variability. We discuss these uncertainties in detail. First, the cost-effectiveness model had 3 key health states in which PFS was divided into on-and-off treatment, whereas other important factors such as Binet staging and treatment inconvenience were taken into account. However, the transition probabilities derived considered these health states as unique because of a lack of data.

In a previous study,[53] concerns were raised that a 3-state Markov model structure was too simplistic for CLL, which also applies for any simple data-based analysis. Alternative modeling approaches (eg, AUC modeling, in which overall survival is estimated on the basis of PFS by using PFS as a surrogate end point for overall survival and including a response for PFS health state) are available. However, long-term data on PFS and overall survival relationship, sample sizes, and potential interaction information between treatment and response were too sparse for the AUC or PFS responder status modeling. Most importantly, the selected approach unlikely benefits the most cost-effective treatment (GClb) because the PFS Kaplan-Meier curves of GClb patients in CLL11 lay

consistently above the RClb and Clb curves regardless of response class.

Second, a median PFS was reached in all 3 treatment arms in the latest CLL11 data-cut. However, there was still censoring and uncertainty about the best-fitting function and its tail for PFS, in particular for the GClb arm. The Weibull distribution was selected because it provided a good fit, had reasonable tail shape, resulted in conservative estimates, and enabled comparability with many other earlier CEAs. A limitation of the meta-analysis used for OClb and RB PFS estimation was the small number of trials found in the evidence network. To indirectly incorporate evidence via HR, the proportional hazards assumption should hold. This was checked by using standard techniques, which held reasonably in the CLL11 data. The relative results of this analysis were also agreeable with another recent meta-analysis.[58] However, the absolute results of this analysis were more conservative, potentially indicating that the effects and clinical value were not overestimated in the CEA or CBA. Furthermore, the scenarios with upper or lower 95% CI HR thresholds for the OClb and RB PFS confirmed that the cost-effectiveness of GClb is not volatile to indirect data.

CLL11 data were not sufficiently mature to model PPS. Because it was unknown in CLL11 whether PPS depends on first-line treatment received, the same modeling approach for PPS was applied to all treatment arms. In the CLL5 trial, the effect of the first-line treatment was not statistically significant for the prediction of PPS. However, GClb patients will probably survive beyond the modeled overall survival in this CEA, given the recent overall survival data.[16] This result could further improve the cost-effectiveness of GClb.

CLL5 used the earlier progression definition,[59] whereas CLL11 used the updated progression definition.[60] The latter may be more sensitive because imaging techniques gained a higher weight, and cytopenia was added. However, the progression assessment in the CLL5 and CLL8 trials was rigorously conducted.

The QoL variables applied were not provided directly by the patients but were sourced through the utility elicitation study. Lack of accuracy risk in the vignettes was reduced by a staged approach with input from literature, patients, and health care professionals and by using the EQ-5D-3L dimensions. The interviewees were younger than the CLL11 patients, and thus all QoL values were anchored to Finland to capture the impact of comorbidities, age, and Finnish preferences. When the general Finnish population values[43] and previous cancer QoL studies[5–8,61,62] were reviewed, there was no obvious discrepancy with the anchored QoL values.

None of the earlier CEAs included consideration of Binet stages, although they do have an impact on the treatment decisions.[13] Follow-up resource use was based on Finnish clinical practice, in line with recommendations, and specified for different Binet stages. These resource estimates were lower than recent study results, including a Danish study[12] and a German study using Elixhauser comorbidity scores and generalized estimating equations.[11] However, sensitivity analysis showed that these Finnish results could be generalized to a wider landscape, namely UK QoL and German resource use were used in sensitivity analysis scenarios and results were robust. The generalizability may also be good in countries with similar cost structures (most probably Nordic and maybe other European Union countries). The biggest cost drivers were drug or progression related, and those 2 seemed to have a tradeoff. If relative costs related to progression were high, drug costs and QALYs gained were low, and vice versa.

Third, Finnish experience and CLL11 individual patient data were used to define cohort characteristics, and patients were elderly when they entered PPS. The trial populations of CLL11 and CLL5 resembled each other, and their Binet staging was incorporated into the analysis. However, individual patient data were not available for OClb or RB. Age was adjusted in the network meta-analysis, but a risk of residual confounding due to the 17p deletion status and Binet stages remained. Patients included in the COMPLEMENT 1 study[32] were similar to CLL11 patients, with minor differences (they were younger and were more frequently at Binet stage A). In addition, when cumulative chlorambucil doses were compared, the dose in CLL11 was at the lower end (with circa 400 to 440 mg) compared with Knauf et al[14] (with circa 560 mg) or CLL5 (with circa 490 mg).

Thus far, there has been no publication of studies regarding the effects and cost-effectiveness of the changes in the CLL guidelines or response/progression criteria, optimal chlorambucil regimen, or sequential modeling of CLL (eg, Soini et al[46,47]). Studies regarding the importance of defining disease staging and clinical end points[63], CBA and CEA relations, unconfounded PPS

survival[38,64] and societal willingness-to-pay[65] are also needed. From the conventional perspective of extra-welfarism (ie, maximize health benefits), and lacking data for per-patient incremental cost-effectiveness, these results indicate that GClb should be selected for the modeled patients, and the risk of making wrong decisions is minor in terms of efficiency and effectiveness. However, if the budget is not sufficient for all patients who need GClb, then an explicit target for PFS (and PFS QALYs) that is thought to be societally "enough PFS" for these patients should be set in a political decision-making process and the treatment mix optimized conditional on process.

CONCLUSIONS

With €30,000/QALY gained or higher thresholds, GClb was clearly the most cost-effective CLL treatment when RFC was unsuitable. In general, GClb provided the best value for money option in terms of relative and absolute outcomes. The low to moderate value of additional research or loss from a wrong decision was assessed.

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Mr. Soini and Mrs. Hautala were responsible for study management; Mr. Soini provided study analysis and manuscript drafting and Dr., Adjunct Prof. Martikainen, Drs. Poikonen and Kyttälä, and Mrs. Hautala and Becker performed critical manuscript revisions. All authors were responsible for concept/design and study/analysis plans, as well as data assembly, and all authors gave final approval for the version to be published.

CONFLICTS OF INTEREST

Mr. Soini and Dr., Adjunct Prof. Martikainen are founding partners, employees, and board members of ESiOR Oy. ESiOR Oy conducts studies, statistical analysis, consultancy, education, reporting, and health economic evaluations for several pharmaceutical, food industry, diagnostics and device companies, hospitals, consultancies, and academic institutions. Mrs. Hautala was an employee of Roche Oy at the time of the study. Dr. Poikonen declares consultation fees (Roche), lecture fees (Novartis, Celgene, Baxter, and Glaxo-Smith-Kline), and meeting participation support (Novartis). Mrs. Becker is employed by F. Hoffmann–La Roche Ltd. Dr. Kyttälä was an employee of Roche Oy at the time of study. All authorship decisions were made on the basis of scientific consideration. The authors have indicated that they have no other conflicts of interest regarding the content of this article.

The study sponsor participated in the study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

SUPPLEMENTARY MATERIAL

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.clinthera.2016.02.005.

REFERENCES

1. Ghia P, Ferreri AM, Caligaris-Cappio F. Chronic lymphocytic leukemia. *Crit Rev Oncol Hematol*. 2007;64:234–246.
2. Watson L, Wyld P, Catovsky D. Disease burden of chronic lymphocytic leukaemia within the European Union. *Eur J Haematol*. 2008;81:253–258.
3. Eichhorst B, Dreyling M, Robak T, Montserrat E, Hallek M, on behalf of the ESMO Guidelines Working Group. Chronic lymphocytic leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2011;22(suppl 6):vi50–54.
4. Holzner B, Kemmler G, Kopp M, et al. Quality of life of patients with chronic lymphocytic leukemia: results of a longitudinal investigation over 1 yr. *Eur J Haematol*. 2004;72:381–389.
5. Eichhorst BF, Busch R, Obwandner T, et al. Health-related quality of life in younger patients with chronic lymphocytic leukemia treated with fludarabine plus cyclophosphamide or fludarabine alone for first-line therapy: a study by the German CLL Study Group. *J Clin Oncol*. 2007;25:1722–1731.
6. Shanafelt TD, Bowen D, Venkat C, et al. Quality of life in chronic lymphocytic leukemia: an international survey of 1482 patients. *Br J Haematol*. 2007;139:255–264.

7. Beusterien KM, Davies J, Leach M, et al. Population preference values for treatment outcomes in chronic lymphocytic leukaemia: a cross-sectional utility study. *Health Qual Life Outcomes*. 2010;8:50.
8. Tolley K, Goad C, Yi Y, et al. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ*. 2013;14:749–759.
9. Skrepnek GH, Tate WR, Baker AF. Clinical and economic burden of Richter syndrome in inpatient cases of chronic lymphocytic leukemia within the United States, 2001–2010. *Leuk Lymphoma*. 2014;55:834–840.
10. Kosmas CE, Shingler SL, Samanta K, et al. Health state utilities for chronic lymphocytic leukemia: importance of prolonging progression free survival. *Leuk Lymphoma*. 2015;56:1320–1326.
11. Blankart CR, Koch T, Linder R, et al. Cost of illness and economic burden of chronic lymphocytic leukemia. *Orphanet J Rare Dis*. 2013;8:32.
12. Holtzer-Goor KM, Bouwmans-Frijters CA, Schaafsma MR, et al. Real-world costs of chronic lymphocytic leukaemia in the Netherlands. *Leuk Res*. 2014;38:84–90.
13. Ghielmini M, Vitolo U, Kimby E, et al. ESMO guidelines consensus conference on malignant lymphoma 2011 part 1: diffuse large B-cell lymphoma (DLBCL), follicular lymphoma (FL) and chronic lymphocytic leukemia (CLL). *Ann Oncol*. 2013;24:561–576.
14. Knauf WU, Lissichkov T, Aldaoud A, et al. Phase III randomized study of bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukemia. *J Clin Oncol*. 2009;27:4378–4384.
15. Goede V, Fischer K, Busch R, et al. Obinutuzumab plus chlorambucil in patients with cll and coexisting conditions. *N Engl J Med*. 2014;370:1101–1110.
16. Goede V, Fischer K, Engelke A, et al. Obinutuzumab as frontline treatment of chronic lymphocytic leukemia: updated results of the CLL11 study. *Leukemia*. 2015;29:1602–1604.
17. Lääkkeiden hintalautakunta. Terveystaloudellisen selvityksen laatiminen lääkevalmisteen korvattavuus- ja tukkuhintahakemukseen. Lääkkeiden hintalautakunta; 2015.
18. Baltic Guideline for Economic Evaluation of Pharmaceuticals (Pharmacoeconomic Analysis). 2002.
19. Department of Economics and Public Health Assessment. Choices in Methods for Economic Evaluation. Saint-Denis: Haute Autorité de santé; 2012.
20. College voor zorgverzekeringen. Guidelines for pharmacoeconomic research, updated version. Diemen: College voor zorgverzekeringen; 2006.
21. IPF Institut für Pharmaökonomische Forschung. Guidelines on Health Economic Evaluation. Vienna: IPF Institut für Pharmaökonomische Forschung; 2006.
22. Scottish Medicines Consortium. Guidance to Manufacturers for Completion of New Product Assessment Form (NPAF). Scottish Medicines Consortium; 2007.
23. Health Information and Quality Authority. Guidelines for the Economic Evaluation of Health Technologies in Ireland. Health Information and Quality Authority; 2010.
24. López-Bastida J, Oliva J, Antoñanzas F, et al. Spanish recommendations on economic evaluation of health technologies. *Eur J Health Econ*. 2010;11:513–520.
25. Belgian Health Care Knowledge Centre. Belgian guidelines for economic evaluations and budget impact analyses. Second edition. Belgian Health Care Knowledge Centre; 2012.
26. Norwegian Medicines Agency (Statens legemiddelverk). Guidelines on how to conduct pharmacoeconomic analyses. Norwegian Medicines Agency; 2012.
27. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. National Institute for Health and Care Excellence; 2013.
28. Naimark DM, Kabboul NN, Krahn MD. The half-cycle correction revisited: redemption of a kludge. *Med Decis Making*. 2013;33:961–970.
29. Barendregt JJ. The life table method of half cycle correction: getting it right. *Med Decis Making*. 2014;34:283–285.
30. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098.
31. Knauf WU, Lissitchkov T, Aldaoud A, et al. Bendamustine compared with chlorambucil in previously untreated patients with chronic lymphocytic leukaemia: updated results of a randomized phase III trial. *Br J Haematol*. 2012;159:67–77.
32. Hillmen P, Robak T, Janssens A, et al. Chlorambucil plus ofatumumab versus chlorambucil alone in previously untreated patients with chronic lymphocytic leukaemia (COMPLEMENT 1): a randomised, multicentre, open-label phase 3 trial. *Lancet*. 2015;385:1873–1883.
33. Eichhorst B, Fink AM, Busch R, et al. Chemoimmunotherapy With Fludarabine (F), Cyclophosphamide (C), and Rituximab (R) (FCR) Versus Bendamustine and Rituximab (BR) In Previously Untreated and Physically Fit Patients (pts) With Advanced Chronic Lymphocytic Leukemia (CLL): Results Of a Planned Interim Analysis Of The CLL10 Trial, An International, Randomized Study Of The German CLL Study Group (GCLLSG). Blood 2013; 122: Proc ASH 2013. Abstract 526.
34. Briggs A, Claxton C, Sculpher M. Decision Modelling for Health Economic Evaluation. Oxford University Press; 2008.
35. Waterboer T, Moreno S, Shang A, et al. Indirect Treatment Comparisons of Obinutuzumab (GA101)

Plus Chlorambucil (Clb) Versus Bendamustine and Versus Ofatumumab Plus Clb in Patients with Chronic Lymphocytic Leukemia. International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 19th Annual International Meeting, 31 May–4 June 2014, Montreal, QC, Canada.
36. Suomen virallinen tilasto (SVT): Kuolleet [Deads]. Helsinki: Tilastokeskus; 2014.
37. Suomen virallinen tilasto (SVT): Väestörakenne [Population structure]. Helsinki: Tilastokeskus; 2014.
38. Eichhorst BF, Busch R, Stilgenbauer S, et al. First-line therapy with fludarabine compared with chlorambucil does not result in a major benefit for elderly patients with advanced chronic lymphocytic leukemia. *Blood*. 2009;114:3382–3391.
39. NORDCAN. Suomi – Leukemia. Association of the Nordic Cancer Registries; 2013.
40. Kapiainen S, Väisänen A, Haula T. Terveyden- ja sosiaalihuollon yksikkökustannukset Suomessa vuonna 2011. Tampere: Terveyden ja hyvinvoinnin laitos; 2014.
41. Suomen virallinen tilasto (SVT): Julkisten menojen hintaindeksi [Price index for public expenditures]. Helsinki: Tilastokeskus; 2014.
42. Soini E, Leussu M, Hallinen T. Administration costs of intravenous biologic drugs for rheumatoid arthritis. *Springerplus*. 2013;2:531.
43. Saarni SI, Härkänen T, Sintonen H, et al. The impact of 29 chronic conditions on health-related quality of life: a general population survey in Finland using 15D and EQ-5D. *Qual Life Res*. 2006;15:1403–1414.
44. Stollenwerk B, Lhachimi SK, Briggs A, et al. Communicating the parameter uncertainty in the IQWiG efficiency frontier to the decision-makers. *Health Econ*. 2015;24:481–490.
45. Barton GR, Briggs AH, Fenwick EA. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Value Health*. 2008;11:886–897.
46. Soini EJ, Martikainen JA, Nousiainen T. Treatment of follicular non-Hodgkin's lymphoma with or without rituximab: cost-effectiveness and value of information based on a 5-year follow-up. *Ann Oncol*. 2011;22:1189–1197.
47. Soini EJ, Martikainen JA, Vihervaara V, et al. Economic evaluation of sequential treatments for follicular non-Hodgkin lymphoma. *Clin Ther*. 2012;34:915–925.
48. Soini EJ, Hallinen T, Sokka AL, Saarinen K. Cost-utility of first-line actinic keratosis treatments in Finland. *Adv Ther*. 2015;32:455–476.
49. Barton P. What happens to value of information measures as the number of decision options increases? *Health Econ*. 2011;20:853–863.
50. Soini EJ. Cost-utility and expected value of perfect information related to trabectedin in the treatment of metastatic soft-tissue sarcoma: the publicly funded comments explored. *Ann Oncol*. 2011;22:1465–1466.
51. Danese MD, Griffiths RI, Gleeson M, et al. An observational study of outcomes after initial infused therapy in Medicare patients diagnosed with chronic lymphocytic leukemia. *Blood*. 2011;117:3505–3513.
52. Weeks JC, Tierney MR, Weinstein MC. Cost effectiveness of prophylactic intravenous immune globulin in chronic lymphocytic leukemia. *N Engl J Med*. 1991;325:81–86.
53. Main C, Pitt M, Moxham T, Stein K. The clinical effectiveness and cost-effectiveness of rituximab for the first-line treatment of chronic lymphocytic leukaemia: an evidence review of the submission from Roche. *Health Technol Assess*. 2010;14(Suppl 2):27–32.
54. Casado LF, García Marco JA, et al. Economic evaluation of rituximab added to fludarabine plus cyclophosphamide versus fludarabine plus cyclophosphamide for the treatment of chronic lymphocytic leukemia [Article in Spanish]. *Gac Sanit*. 2011;25:274–281.
55. Hornberger J, Reyes C, Shewade A, et al. Cost-effectiveness of adding rituximab to fludarabine and cyclophosphamide for the treatment of previously untreated chronic lymphocytic leukemia. *Leuk Lymphoma*. 2012;53:225–234.
56. Woods B, Hawkins N, Dunlop W, et al. Bendamustine versus chlorambucil for the first-line treatment of chronic lymphocytic leukemia in England and Wales: a cost-utility analysis. *Value Health*. 2012;15:759–770.
57. Adena M, Houltram J, Mulligan SP, et al. Modelling the cost effectiveness of rituximab in chronic lymphocytic leukaemia in first-line therapy and following relapse. *Pharmacoeconomics*. 2014;32:193–207.
58. Ladyzynski P, Molik M, Foltynski P. A network meta-analysis of progression free survival and overall survival in first-line treatment of chronic lymphocytic leukemia. *Cancer Treat Rev*. 2015;41:77–93.
59. Cheson BD, Bennett JM, Grever M, et al. National Cancer Institute-sponsored working group guidelines for chronic lymphocytic leukemia: revised guidelines for diagnosis and treatment. *Blood*. 1996;87:4990–4997.
60. Hallek M, Cheson BD, Catovsky D, et al. Guidelines for the diagnosis and treatment of chronic lymphocytic leukemia: a report from the International Workshop on Chronic Lymphocytic Leukemia updating the National Cancer Institute-Working Group 1996 guidelines. *Blood*. 2008;111:5446–5456.
61. Else M, Smith AG, Cocks K, et al. Patients' experience of chronic lymphocytic leukaemia: baseline health-related quality of life results from the LRF CLL4 trial. *Br J Haematol*. 2008;143:690–697.
62. Färkkilä N, Sintonen H, Saarto T, et al. Health-related quality of life

in colorectal cancer. *Colorectal Dis*. 2013;15:e215–222.
63. Cheson BD, Byrd JC, Rai KR, et al. Novel targeted agents and the need to refine clinical end points in chronic lymphocytic leukemia. *J Clin Oncol*. 2012;30:2820–2822.
64. Hallek M, Fischer K, Fingerle-Rowson G, et al. Addition of rituximab to fludarabine and cyclophosphamide in patients with chronic lymphocytic leukaemia: a randomised, open-label, phase 3 trial. *Lancet*. 2010;376:1164–1174.
65. Soini EJ, Kukkonen J, Myllykangas M, Ryynänen OP. Contingent valuation of eight new treatments: what is the clinician's and politician's willingness to pay? *Open Complementary Med J*. 2012;4:1–11.

Address correspondence to: CEO Erkki Soini, MSc (health econ), ESiOR Ltd, Tulliportinkatu 2 LT4, 70100 Kuopio, Finland. E-mail: erkki.soini@esior.fi

SUPPLEMENTARY MATERIALS

A: Patient Characteristics in Clinical Trials

Table A1

Supplemental Table A1. Baseline patient characteristics between relevant trials

Used	Pre-progression				Post-progression
Characteristic / Trial	*CLL11 [15] Stage 2*[*]	*CLL11 [15] Stage 1 (Clb)*	*COMPLEMENT 1*[†] *[32]*	*CLL10*[‡] *[33]*	*CLL5 [38]*
Patients included	663	118	447	564	193
Enrolment time	4/2010-7/2012		12/2008-5/2011	10/2008-6/2011	7/1999-9/2004
Age, mean years	72[§]	71[§]	na	na	71[§]
Age, median (range) years	74 (39-90)	72 (43-87)	69 (35-92)	62 (33-82)	70 (65-79)
Age ≥65 years	na	na	69%	na	100%
Age ≥70 years	na	na	49%	na	100%
Men	na	na	63%	na	64%
No comorbidity	na	na	13%	na	34%
Comorbidities ≥1	na	na	87%	na	34%
Comorbidities ≥2	na	na	72%	na	33%
Comorbidities ≥3	82%[‖]		na	na	na
Cardiac comorbidity	51%	53%	21%	na	na
Hypertension comorbidity	68%	75%	na	na	na
Vascular comorbidity	32%	29%	55%	na	na
Respiratory comorbidity	37%	36%	25%	na	na
Eye, ear, throat or larynx comorbidity	41%	45%	na	na	na
Upper gastrointestinal comorbidity	31%	33%	na	na	na
Lower gastrointestinal comorbidity	19%	21%	na	na	na
Gastrointestinal comorbidity	na	na	25%	na	na
Hepatic or biliary comorbidity	18%	18%	na	na	na
Renal comorbidity	43%	38%	na	na	na
Genitourinary comorbidity	34%	37%	na	na	na
Musculoskeletal comorbidity	43%	38%	29%	na	na
Metabolic comorbidity	na	na	36%	na	na
Endocrine or metabolic comorbidity	52%	54%	na	na	na
Neurologic comorbidity	22%	28%	na	na	na
Psychiatric comorbidity	16%	9%	na	na	na
Eastern Cooperative Oncology Group (ECOG) performance status 0	na	na	38%	na	44%
ECOG performance status 1	na	na	54%	na	50%
ECOG performance status 2	na	na	8%	na	6%
ECOG performance status ≥3	na	na	0%	na	0%
Binet A	22%	20%	33%	22%	15%
Binet B	42%	42%	36%	38%	47%
Binet C	36%	37%	31%	40%	38%

(continued)

Supplemental Table A1. (continued).

Used	Pre-progression				Post-progression
Characteristic / Trial	*CLL11 [15] Stage 2*[*]	*CLL11 [15] Stage 1 (Clb)*	*COMPLEMENT 1*[†] *[32]*	*CLL10*[‡] *[33]*	*CLL5 [38]*
Creatinine clearance (CC) mL/min, median	63	62	na	na	na
CC <70mL/min	64%[§]	61%[§]	48%	0%	62%[§]
CC ≥70mL/min	36%[§]	39%[§]	52%	100%	38%[§]
6q deletion	na	na	54% no 17p/11q deletion	na	na
12q deletion	na	na		na	21%
13q deletion	49%[§]	59%[§]		na	na
11q deletion	17%[§]	15%[§]	15% no 17p deletion	na	14%
17p deletion	7%	10%	6%	0%	6%
Trisomy 12	20%[§]	19%[§]	cut-off 20%	na	na
Cumulative Ilness Rating Scale for Geriatrics (CIRS-G), median (range)	8 (0-22)	8 (0-18)	9 (4-21)	2 (0-6)	na
CIRS lower category, ≤6	24%[§]	22%[§]	na	100%	na
CIRS higher category, >6	76%[§]	78%[§]	na	0%	na
Immunoglobulin heavy chain (IGHV or IGVH) unmutated	61%	58%	56%	61%	63%
F unsuitable based on clinical facts	100%[¶]	100%[¶]	na	0%[¶]	na
F unsuitable based on age	na	na	39%	0%[¶]	na
F unsuitable based on comorbidities	na	na	19%	0%[¶]	na
F unsuitable based on age and comorbidities	na	na	14%	0%[¶]	na
F unsuitable based on age, comorbidities, patient preference or medical decision	na	na	100%	0%[¶]	na
Previous anticancer treatment received	0%[¶]	0%[¶]	0%[¶]	0%[¶]	0%[¶]

[*]Obinutuzumab+chlorambucil and rituximab+chlorambucil.
[†]Ofatumumab+chlorambucil.
[‡]Rituximab+bendamustine.
[§]Estimated from individual patient data (IPD on file) results.
[‖]Based on all patients included to the CLL11 trial.
[¶]Logical assumption based on the inclusion criteria or treatments received.
na = not available.
F = fludarabine.

B. Treatment Costs of Adverse Events

Table B1

Supplemental Table B1. Additional resources and costs associated with treatment-related severe adverse events (SAE) included to the cost-effectiveness model based on the Finnish practice

Adverse event	Specialized care		Tests & imaging		Medications & infusions		Total
Type, severity grade	*Res.*	*(€)*	*Res.*	*(€)*	*Res.*	*(€)*	*(€)*
Anemia / hemolytic anemia, 3-4	Visit	309.04			Blood red cells 2 units	414.04	723.08
CNS / intracranial hemorrhage, 5	Stay	2635.53					2635.53
Dermatitis allergic / atopic, 3					Corticosteroid cream	7.71	7.71
Diarrhea, 3	Call	27.46	Electrolytes, kidney function	4.12			31.58
Gout, 3	Visit	309.04			Allopurinol, paracetamol 1g	13.55	322.59
Hepatic enzyme increased, 3-4	Call	27.46	AST, ALT, ALP, PTT, INR	10.03			37.50
Hyperuricaemia, 4	Stay	1653.48			Allonopurinol, paracetamol 1g, i.v. NaCl 1000 ml	121.55	1775.03
Infection, 3	Visit	309.04					309.04
IRC: Bronchospasm / dyspnea / larynx spasm / stridor / wheezing, 3-4	+1h time	24.50			Methylpredni-solone 125 mg, adrenalin	12.17	36.67
IRC: Chills / headache / pyrexia, 3					Paracetamol 1g	6.71	6.71
IRC: Hepatotoxicity, 4	Delay	309.04					309.04
IRC: Hypotension, 4	+1h time	24.50			i.v. NaCl 1000 ml	108.00	132.50
IRC: Nausea / vomiting, 3					Metoclopramide 10 mg	9.22	9.22
IRC: Tachycardia, 3					Bisoprolol	8.61	8.61
IRC: Thrombocytopenia, 3	Visit	309.04	Full blood count	2.53			311.58
IRC: Urticaria, 3					Cetirizine 10 mg	9.55	9.55
Leukopenia, 3-4	Call	27.46	Full blood count	2.53			30.00
Mucosal inflammation, 3	Visit	309.04			Amphotericin B	39.16	348.20
Neutropenia / granulocytopenia, 3	Visit	309.04			GCSF	318.06	627.10
Neutropenia / granulocytopenia, 4	Stay	1653.48			i.v. antibiotic, GCSF	449.41	2102.89

(continued)

Supplemental Table B1. (continued).

Adverse event	Specialized care		Tests & imaging		Medications & infusions		Total
Neutropenic sepsis, 4	Stay	6556.25			i.v. antibiotic, GCSF	449.41	7005.66
Pancytopenia, 3	Call	27.46	Full blood count	2.53			30.00
Pancytopenia, 4	Stay	1653.48			GCSF, trombocytes 4-8, blood red cells 1-2	1843.13	3596.61
Platelet count decreased, 3	Call	27.46	Full blood count	2.53			30.00
Pneumocystis jirovecii pneumonia, 3	Stay	2330.92			i.v. antibiotic, corticosteroid	147.32	2478.24
Pneumonia, 3-4	Stay	2330.92			i.v. antibiotic	131.35	2462.27
Pneumonitis, 3	Visit	309.04	Thorax x-ray	35.91			344.95
Pyrexia, 3	Visit	309.04			Paracetamol 1g	6.71	315.17
Rash maculo-papular / pruritic, 3	Visit	309.04			Cetirizine 10 mg, steroid cream	17.26	326.30
Renal impairment, 3	Call	27.46	Creatinine	2.53			30.00
Renal failure, 3	Visit	309.04					309.04
Renal failure, 4	Stay	3028.54					3028.54
Sepsis, 3-4	Stay	6556.25			i.v. antibiotic	131.35	6687.60
Thrombocytopenia, 3	Visit	309.04	Full blood count	2.53			311.58
Thrombocytopenia, 4	Stay	1653.48			Platelet transfusion 4-8 units	1211.03	2 864.51
Varicella, 3	2 visits	618.08					618.09

Res. = resource. CNS = central nervous system. IRC = infusion-related complication. GCSF = granulocyte-colony stimulating factor. AST = aspartate aminotransferase. ALT = alanine aminotransferase. ALP = alkaline phosphatase. PTT = partial thromboplastin time. INR = international normalized ratio.

C: Scenario-Type Sensitivity Analyses

The following sensitivity analyses were implemented using the deterministic (mean value) modeling method.

Methods

- Deterministic: base case results using deterministic modeling.
- Undiscounted: No discounting of results was done.
- 10 year horizon: Time horizon was limited to 10 years in the modeling.
- 5 year horizon: Time horizon was limited to 5 years in the modeling.
- 3.5 year horizon: Time horizon was limited to 3.5 years (within CLL11 trial setting, basically no extrapolation) in the modeling.

Population

- CLL11 cohort: All modeled population characteristics from CLL11 trial.
- Fit cohort: Modeled population characteristics from CLL8 trial [64] (sc. fit population: mean age

60 years, Binet stages 5%, 64% and 31% for A, B and C, respectively) and also PPS (exponential distribution's parameter values (standard errors): intercept 5.427 (0.533) and age -0.021 (0.008) 31st October 2011 data cut)) was applied to test the sensitivity of the results to cohort characteristics ("generalizability" to a wider population).

Efficacy

- Exponential PFS: PFS modeled based on exponential survival distribution.
- LogLogistic PFS: PFS modeled based on LogLogistic survival distribution.
- LogNormal PFS: PFS modeled based on LogNormal survival distribution.
- Gamma PFS: PFS modeled based on Gamma survival distribution.
- Gompertz PFS: PFS modeled based on Gompertz survival distribution.
- KM PFS: Kaplan-Meier estimates with a parametric tail were used for the extrapolation.
- 95%CI HL PFS HR: PFS adjustment GClb vs. using the indirect comparators set to the 95% CI higher threshold of HR (OClb 0.43, RB 0.72).
- 95%CI LL PFS HR: PFS adjustment GClb vs. using the indirect comparators set to the 95% CI lower threshold of HR (OClb 0.19, RB 0.21).
- $\lambda = 0.80$: 20% lower failure probability assumed for PPS.
- $\lambda = 1.20$: 20% higher failure probability assumed for PPS.

Quality of Life

- No IV disutility: QoL on intravenous treatment assumed to be the same as QoL on per os treatment.
- No visit disutility: No disutility due to increased hospital visits assumed.
- Higher PPS QoL: PPS QoL assumed to be similar to QoL on per oral treatment.
- Foreign QoL: QoL values were not anchored to Finland.

Costs and Resource Use

- Label doses: Drugs were used according to their label.
- Vial sharing & non-fit RB dose: Drugs left in vials can be shared and, for non-fit, the bendamustine dose may be 50-75mg/m^2 (on average, 60mg/m^2 was used for bendamustine).
- No additional administration visit: No additional visit may be needed for the drug administration and only nurse/bed time was taken into account (cycle 1/later cycles: GClb €392.00/79.63, OClb €257.25/98.00, RB €245.00/85.75, RClb €196.00/36.75, respectively).
- CLL11 AEs based on the publication [15].
- Hospital perspective: estimated patient co-payments and costs for reimbursed treatments (Clb) excluded.
- Foreign resources: Resource use not related to drugs was based on a German study [11].

Results

Table C1.

D. Modeled Quality-Adjusted Survivals

Figure D1.

E. Cost Drivers by Treatment

Figure E1.

Supplemental Table C1. Sensitivity analyses results (deterministic analysis, 20 year time horizon, and 3% discounting per annum if not otherwise stated) demonstrated the robustness of relative base case results

Methods												
Determ-inistic	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	29497	44433	59176	81663
	Costs (€)	42101	29595	34697	29401	11797	GClb vs.	-	19953	11562	15644
Undisc-ounted	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	4.171	3.448	3.434	3.245	3.001	vs. Clb	26191	40200	53242	72807
	Costs (€)	43674	30994	36087	30747	13046	GClb vs.	-	17539	10299	13956
10- year horizon	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	3.474	2.901	2.888	2.725	2.525	vs. Clb	31574	46984	62781	87522
	Costs (€)	40916	28648	33751	28493	10956	GClb vs.	-	21436	12232	16597
5- year horizon	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	2.655	2.288	2.274	2.146	1.996	vs. Clb	44091	59277	80523	115612
	Costs (€)	37669	25932	31041	25926	8612	GClb vs.	-	31996	17420	23059
3.5- year horizon	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	2.113	1.885	1.870	1.769	1.655	vs. Clb	63072	74195	103295	151050
	Costs (€)	36016	24193	29335	24276	7103	GClb vs.	-	51839	27474	34057
Population *CLL11 cohort*	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	29510	44435	59180	81659
	Costs (€)	42035	29520	34624	29325	11721	GClb vs.	-	19971	11577	15660
Fit cohort	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	4.046	3.434	3.417	3.249	3.022	vs. Clb	29530	43338	58013	77821
	Costs (€)	43538	31131	36220	30947	13295	GClb vs.	-	20253	11635	15792
Efficacy *Expon-ential PFS*	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	4.185	3.229	3.092	2.846	2.728	vs. Clb	20591	34292	60256	147874
	Costs (€)	41779	28943	33674	29231	11771	GClb vs.	-	13419	7410	9369
Log-Logistic PFS	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	4.112	3.183	3.141	2.944	2.777	vs. Clb	22491	43940	63158	105767
	Costs (€)	41753	29573	34679	29398	11737	GClb vs.	-	13116	7283	10582
Log-Normal PFS	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	4.361	3.201	3.172	2.935	2.763	vs. Clb	18625	40617	55861	102168
	Costs (€)	41555	29598	34667	29415	11781	GClb vs.	-	10308	5793	8514
Gamma PFS	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
	QALYs	3.719	3.144	3.099	2.929	2.718	vs. Clb	30284	41837	60087	83287
	Costs (€)	42110	29611	34698	29401	11805	GClb vs.	-	21734	11961	16099

(continued)

Supplemental Table C1. (continued)

	Gompertz PFS	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.606	3.097	3.079	2.912	2.708	vs. Clb	33789	45762	61377	86553
		Costs (€)	42154	29597	34570	29410	11805	GClb vs.	-	24650	14383	18341
	KM PFS	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	5.875	3.602	3.610	3.153	3.032	vs. Clb	10444	30675	39194	144680
		Costs (€)	41757	29534	34711	29536	12066	GClb vs.	-	5376	3110	4489
	95%CI LL PFS HR	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	3.456	3.114	2.714	vs. Clb	29497	44433	30628	43785
		Costs (€)	42101	29595	34525	29305	11797	GClb vs.	-	19953	26557	20393
	95%CI LL PFS HR	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	2.809	2.763	2.714	vs. Clb	29497	44433	241074	365305
		Costs (€)	42101	29595	34503	29439	11797	GClb vs.	-	19953	8143	12933
	$\lambda = 0.8$	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	4.084	3.508	3.491	3.333	3.113	vs. Clb	30937	44951	60450	80032
		Costs (€)	43620	31338	36424	31188	13563	GClb vs.	-	21318	12126	16546
	$\lambda = 1.2$	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.492	2.829	2.818	2.637	2.425	vs. Clb	28567	44087	58319	82929
		Costs (€)	40994	28328	33442	28103	10514	GClb vs.	-	19107	11208	15079
Quality of life	*No IVdisutility*	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.754	3.131	3.117	2.949	2.714	vs. Clb	29152	42699	56862	75163
		Costs (€)	42101	29595	34697	29401	11797	GClb vs.	-	20084	11627	15770
	No visit disutility	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.753	3.115	3.101	2.930	2.714	vs. Clb	29169	44433	59176	81663
		Costs (€)	42101	29595	34697	29401	11797	GClb vs.	-	19591	11356	15424
	Higher PPS QoL	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	4.073	3.493	3.476	3.318	3.097	vs. Clb	31063	44957	60449	79971
		Costs (€)	42101	29595	34697	29401	11797	GClb vs.	-	21574	12407	16811
	Foreign QoL	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.955	3.292	3.278	3.097	2.869	vs. Clb	27915	42043	55995	77257
		Costs (€)	42101	29595	34697	29401	11797	GClb vs.	-	18884	10942	14806
Resource use	*Label drug doses*	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	29540	44481	62641	81653
		Costs (€)	42147	29616	36040	29401	11799	GClb vs.	-	19992	9536	15701

(continued)

Supplemental Table C1. (continued)

	Vial sharing, low RB	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	29497	41302	57580	81663
		Costs (€)	42101	28341	34080	29401	11797	GClb vs.	-	21953	12526	15644
	Hospital perspective	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	29515	44246	60597	77729
		Costs (€)	41086	28487	34214	27520	10763	GClb vs.	-	20102	10732	16712
	No additional visit	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	26757	39766	50557	71807
		Costs (€)	39286	27725	31362	27276	11797	GClb vs.	-	18444	12374	14794
	CLL11 AEs from [15]	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	29343	44332	59637	82490
		Costs (€)	41476	29376	34697	29401	11618	GClb vs.	-	19764	11036	15230
	Foreign resources	*Outcome*	*GClb*	*RClb*	*RB*	*OClb*	*Clb*	*ICER*	*GClb*	*RClb*	*RB*	*OClb*
		QALYs	3.742	3.115	3.101	2.930	2.714	vs. Clb	31474	46006	60854	82983
		Costs (€)	43452	29545	34666	29005	11116	GClb vs.	-	22188	13720	17796
Average	*All sensitivity analyses*	Outcome	GClb	RClb	RB	OClb	Clb	ICER	GClb	RClb	RB	OClb
		QALYs	3.809	3.109	3.090	2.905	2.704	vs. Clb	27238	43553	58882	86912
		Costs (€)	41634	29155	34278	29006	11527	GClb vs.	-	17812	10232	13966

QALY = quality-adjusted life year. Clb = chlorambucil alone. OClb = ofatumumab + chlorambucil. RClb = rituximab + chlorambucil. RB = rituximab + bendamustine. GClb = obinutuzumab + chlorambucil. ICER = cost (€) per QALY gained.

F. Multinomial Cost-Effectiveness Acceptability Curves

Figure F1.

G. Clinical Value Analysis (CVA)

Cost-Benefit Analysis (CBA, a type of CVA – also called as Drug Cost-Benefit Analysis, DCBA) was developed based on the decision analytical modelling results. For some parts, CBA can be more clinically appealing and easier to understand in practice than incremental cost-utility analysis. However, CBA has few inherent limitations which were shortly discussed in the main article.

The CBA with drug costs only included mean drug costs based on the actual first-line drugs consumed (wastage assumed) and ignored other (e.g. administration, monitoring, adverse event, end-stage) costs – the perspective of analysis was limited to oncologic drug payer perspective. PFS payer perspective results were reported as sensitivity analysis and included all mean PFS time direct costs. The clinical outcomes of CBA were also modelled as means.

Here, as examples, following tertiary outcomes were reported in terms of CBA:

- Relative benefit assessment based on PFS years gained (includes the potential "trial value" of drug during PFS) and PFS QALYs gained (includes the potential "full value" of drug)
- Absolute benefit assessment (investment impact assessment, IIA) based on QALYs, and PFS and OS years gained with limited assumed drug budget of €20,000/patient.

Results

As was observed based on the Table G1 and Figure G1, CBA results concurred well with the key

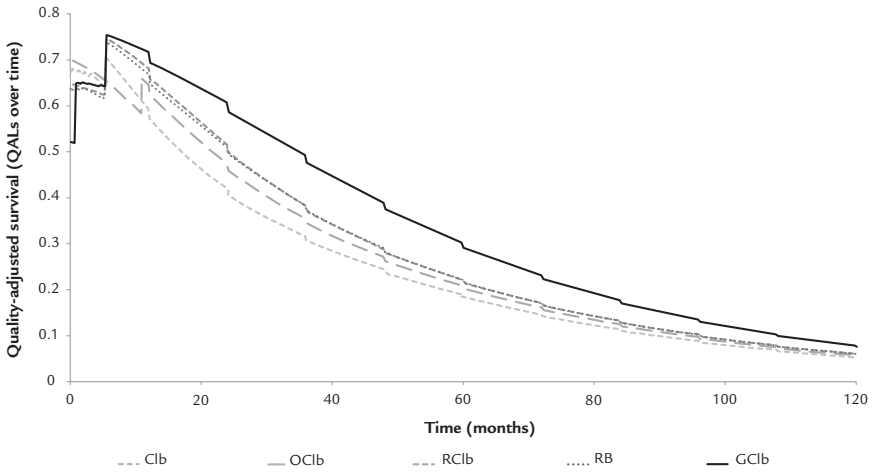

Figure D1. Discounted 10-year quality-adjusted survivals.
Detailed legend: QALY = quality-adjusted life year. Clb = chlorambucil alone. OClb = ofatumumab + chlorambucil. RClb = rituximab + chlorambucil. RB = rituximab + bendamustine. GClb = obinutuzumab + chlorambucil.

cost-utility analysis results reported in the main article. The results indicated the best relative clinical value and most efficient use of limited budget for GClb.

Due to assumption of no survival benefits after progression, lifetime CBA and key results concurred less well with each other (Figure G2).

When these results (Table G1, Figure G1 and G2) were interpreted, caution was needed: the comparator for cost per benefit in average (i.e. not incremental) analysis was basically instant death [65]. Thus, the incremental relative benefit vs. Clb was plotted to the Figures G1–3 to demonstrate what was lost if the most

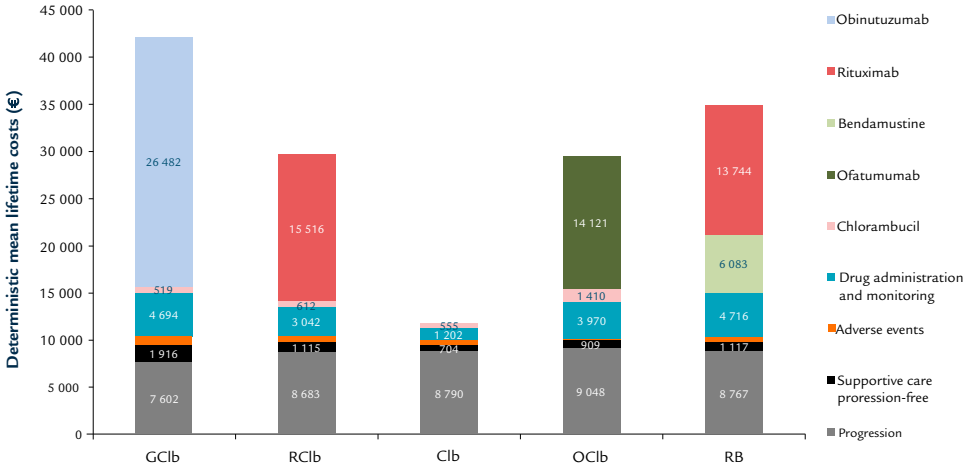

Figure E1. Cost drivers by treatment, 3% per annum discounted deterministic lifetime mean values.
Detailed legend: Drug name refers to drug acquisition cost. GClb = obinutuzumab + chlorambucil. RClb = rituximab + chlorambucil. Clb = chlorambucil alone. OClb = ofatumumab + chlorambucil. RB = rituximab + bendamustine.

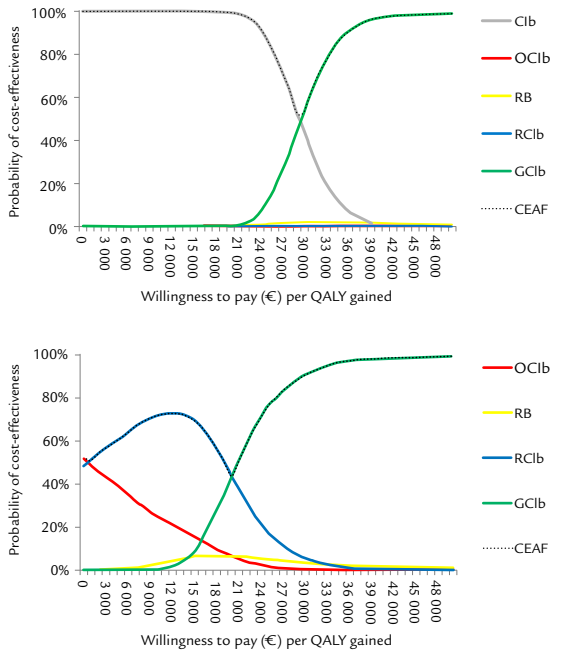

Figure F1. Multinomial cost-effectiveness acceptability curves (mCEAC) and cost-effectiveness acceptability frontier (CEAF) for comparison either including (higher part) or excluding (lower part) chlorambucil alone (Clb). In the comparison including (excluding) Clb, GClb was optimal and potentially cost-effective treatment with over 50% probability for cost-effectiveness with the threshold exceeding 29,558 (20,803) per QALY gained, respectively. Detailed legend: QALY = quality-adjusted life year. OClb = ofatumumab + chlorambucil. RB = rituximab + bendamustine. RClb = rituximab + chlorambucil. GClb = obinutuzumab + chlorambucil. RB was newer on the CEAF.

effective treatment was not selected and the cheapest or less effective option was taken. In this case, GClb was the most beneficial treatment and the loss of not choosing it was the biggest. In addition, the cost-benefit ratio of GClb during progression-free time was the lowest, meaning that every euro with GClb produced the biggest effect. GClb resulted to best relative clinical value–cost-effectiveness relation.

In order to assess the joint uncertainty around the results, relative benefit – cost-effectiveness planes were shown below (Figure G3) based on the probabilistic analysis.

Based on the Figure G3, RB and OClb had high risk for higher costs per benefit when the results in comparison to Clb were poor or negative. GClb and RClb seemed to have low risk for higher costs per benefit. In patient level analysis, this observation could be used as a tool for indicating poorer cost per benefit ratio through the incremental benefit and multivariate methods.

Based on the probabilistic results of PFS costs and relative incremental PFS years in comparison to Clb, GClb resulted to the highest relative PFS in comparison to Clb with 99.9% probability based on Bayesian Treatment Ranking (BTR). RClb resulted to second highest relative PFS with 51.7% probability. RB resulted to third highest relative PFS with 78.6% probability.

Based on the probabilistic results of PFS costs and relative incremental PFS QALYs in comparison to Clb, GClb resulted to the highest relative PFS QALYs in comparison to Clb with 99.9% probability based on the BTR. RClb resulted to second highest relative PFS QALYs with 51.4% probability. RB resulted to third highest relative PFS QALYs with 80.5% probability.

Finally, PFS and QALY benefits gained with fixed limited drug and PFS cost budget of €20,000 were estimated (Table G1, Figure G4) in IIA. Based on these, obinutuzumab+chlorambucil resulted to longest benefits and made the best value of limited budgets. On the other hand, RB seemed to make the worst use of budgets (i.e. RB had the highest cost per benefit gained and lowest times with the fixed budget).

Based on the probabilistic results of PFS costs and PFS years, GClb resulted to the highest health impact on €20 000/patient investment (mean 1.561 PFS years, 2.5-97.5% percentiles 1.391–1.747) with 66.5% probability based on the BTR. RClb was second best (1.494 PFS years, 1.388–1.611) with 81.9% probability. OClb was third best (1.239 PFS years, 0.938–1.592) with 57.7% probability. RB was fourth best (1.196 PFS years, 0.806–1.745). The BTR probabilities were similar for the PFS cost per PFS years.

Based on the probabilistic results of PFS costs and PFS QALYs, GClb resulted to the highest health impact on €20 000/patient investment (mean 1.173 PFS QALYs, 2.5-97.5% percentiles 1.032–1.322)

Table G1. CVA base for the CBA (relevant with *italics*), all with 3%/year discounting.

Relative benefit vs Clb (clinical value)	GClb	RClb	RB	OClb
QALYs PFS	*177.1 %*	*58.1 %*	*58.7 %*	*26.2 %*
QALYs lifetime	*37.8 %*	*14.8 %*	*14.3 %*	*7.9 %*
PFS years	*172.1 %*	*58.3 %*	*58.7 %*	*29.2 %*
OS years	*27.2 %*	*11.9 %*	*11.2 %*	*7.3 %*
Drug cost (, oncological drug cost) per	**GClb**	**RClb**	**RB**	**OClb**
QALY PFS	*13 322*	*13 948*	*17 083*	*16 819*
QALY OS	7 216	5 178	6 393	5 301
PFS year	*10 017*	*10 283*	*12 616*	*12 136*
OS year	4 704	3 196	3 952	3 207
PFS costs (, payer costs) per	**GClb**	**RClb**	**RB**	**OClb**
QALY PFS	*17 021*	*18 087*	*22 483*	*22 207*
QALY OS	9 220	6 714	8 414	6 999
PFS year	*12 799*	*13 334*	*16 605*	*16 024*
OS year	6 010	4 144	5 201	4 235
Lifetime costs (, payer costs) per	**GClb**	**RClb**	**RB**	**OClb**
QALY	11 252	9 501	11 188	10 035
OS year	7 334	5 865	6 915	6 072
PFS years with 20,000 budget	**GClb**	**RClb**	**RB**	**OClb**
Drug costs	1.997	1.945	1.585	1.648
PFS costs	*1.563*	*1.500*	*1.204*	*1.248*
PFS QALYs with 20,000 burget	**GClb**	**RClb**	**RB**	**OClb**
Drug costs	1.501	1.434	1.171	1.189
PFS costs	*1.175*	*1.106*	*0.890*	*0.901*

Detailed legend: QALY = quality-adjusted life year. PFS = progression-free survival. OS = overall survival. GClb = obinutuzumab + chlorambucil. RClb = rituximab + chlorambucil. RB = rituximab + bendamustine. OClb = ofatumumab + chlorambucil.

with 74.5% probability based on the BTR. RClb was second best (1.101 PFS QALYs, 1.008–1.198) with 81.7% probability. OClb was third best (0.893 PFS QALYs, 0.659–1.169) with 54.0% probability. RB was fourth best (0.882 PFS QALYs, 0.584–1.299). The BTR probabilities were similar for the PFS cost per PFS QALYs.

In conclusion, the CBA demonstrated highest payoff for obinutuzumab+chlorambucil, when assessing only its drug costs or PFS costs. Generally, the both cost types seemed to follow the clinical value (mean PFS) of drug in this case, but the trend decreased as the function of costs meaning that more efficient drugs such as GClb had also lower cost-benefit ratio and higher health impact based on the investment. This may be a result of decreasing marginal benefit (an assumption in health economics) and price competition to be studied elsewhere.

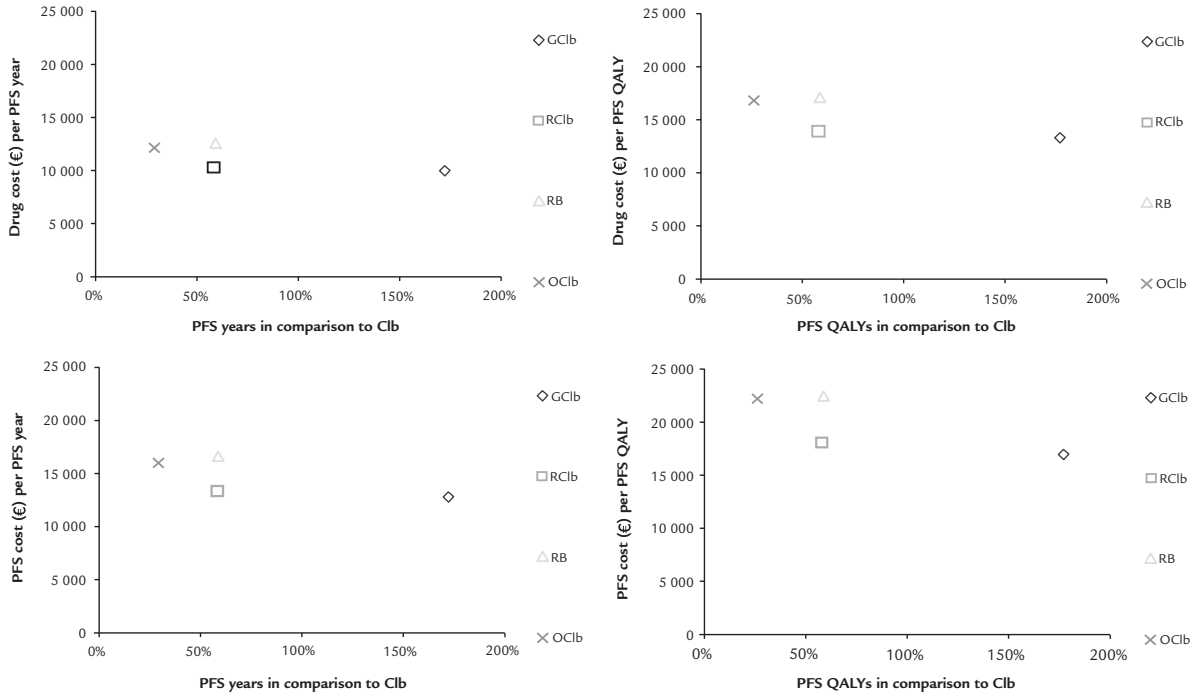

Figure G1. DCBA results based on PFS years or PFS QALYs and first-line oncological drug or PFS costs.

Detailed legend: PFS = progression-free survival. QALY = quality-adjusted life year. GClb = obinutuzumab + chlorambucil. RClb = rituximab + chlorambucil. RB = rituximab + bendamustine. OClb = ofatumumab + chlorambucil.

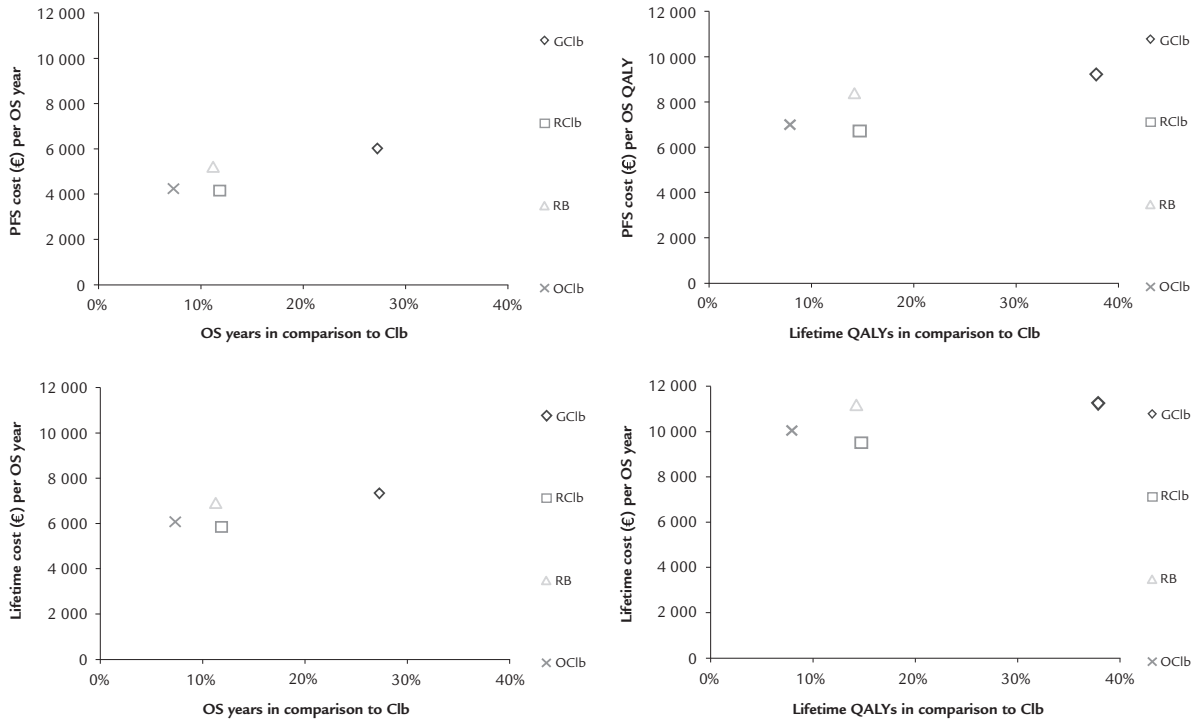

Figure G2. DCBA results based on OS years or QALYs and PFS or lifetime costs.

Detailed legend: PFS = progression-free survival. QALY = quality-adjusted life year. GClb = obinutuzumab + chlorambucil. RClb = rituximab + chlorambucil. RB = rituximab + bendamustine. OClb = ofatumumab + chlorambucil.

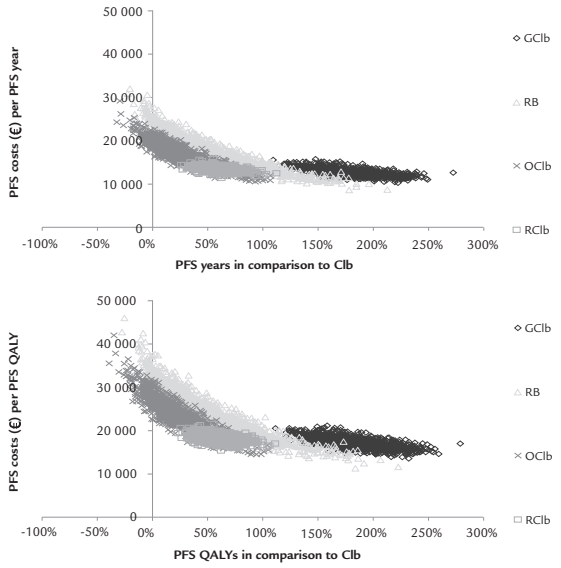

Figure G3. Planes for PFS costs and PFS years, and PFS costs and PFS QALYs scenarios.

Detailed legend: PFS = progression-free survival. QALY = quality-adjusted life year. GClb = obinutuzumab + chlorambucil. RClb = rituximab + chlorambucil. RB = rituximab + bendamustine. OClb = ofatumumab + chlorambucil.

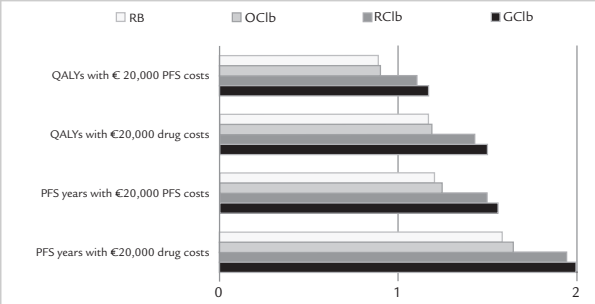

Figure G4. IIA: PFS and QALY benefits gained with fixed limited oncological drug or PFS cost budget of 20,000/patient.

Detailed legend: IIA = impact investment analysis. PFS = progression-free survival. QALY = quality-adjusted life year. GClb = obinutuzumab + chlorambucil. RClb = rituximab + chlorambucil. RB = rituximab + bendamustine. OClb = ofatumumab + chlorambucil.