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Economic Evaluation

# Cost-Effectiveness of Venetoclax Plus Obinutuzumab Versus Chlorambucil Plus Obinutuzumab for the First-Line Treatment of Adult Patients With Chronic Lymphocytic Leukemia: An Extended Societal View

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## ABSTRACT

*Objectives:* Efficacy of venetoclax plus obinutuzumab (VenO) compared with chlorambucil plus obinutuzumab (ClbO) for treatment-naïve adult patients with chronic lymphocytic leukemia (CLL) with coexisting medical conditions was investigated in CLL14 (NCT02242942). Our aim was to evaluate the cost-effectiveness of VenO versus ClbO for these patients from a Dutch societal perspective.

*Methods:* A 3-state partitioned survival model was constructed to evaluate the cost-effectiveness of VenO. The outcome of the analysis was the incremental cost-effectiveness ratio (ICER) with effectiveness measured in quality-adjusted life-years (QALYs) gained. Uncertainty was explored through deterministic and probabilistic sensitivity analyses, scenario analyses, and value of information analysis (VOI).

*Results:* The base case resulted in a discounted ICER −49 928 EUR/QALY gained (with incremental negative costs and positive effects). None of the ICERs resulted from deterministic sensitivity and scenario analyses exceeded the chosen willingness-to-pay threshold of 20 000 EUR/QALY, and > 99% of the iterations in the probabilistic sensitivity analysis were cost-effective. VOI analyses showed a maximum expected value of eliminating all model parameter uncertainty of 183 591 EUR.

*Conclusions:* Our study demonstrated VenO being dominant over ClbO in treatment-naïve adult patients with CLL assuming a Dutch societal perspective. We concluded that our results are robust as tested through sensitivity and scenario analyses. Additionally, the VOI analyses confirmed that our current evidence base is strong enough to generate reliable results for our study. Nevertheless, further research based on real-world data or longer follow-up period could further contribute to the robustness of the current study's conclusions.

*Keywords:* chlorambucil plus obinutuzumab, chronic lymphocytic leukemia, cost-effectiveness analysis, cost-utility analysis, economic evaluation, extended social perspective, partitioned survival analysis model, value of information analysis, venetoclax plus obinutuzumab.

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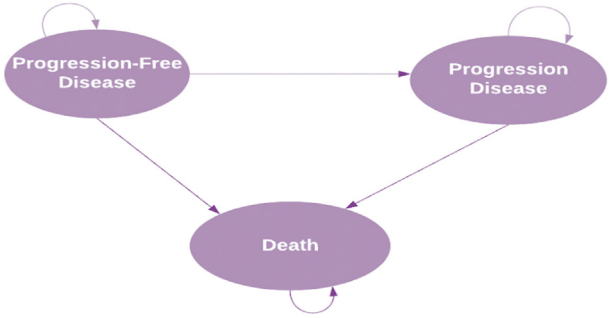
## Introduction

Chronic lymphocytic leukemia (CLL) is one of the most common types of leukemia in adults and especially in the elderly.[1] For those older than 80 years, the annual incidence increases to > 30 per 100 000 person.[1] Although CLL remains incurable,[2,3] the disease can often be successfully managed with chemotherapeutic and immunotherapeutic agents for many years.[2] For elderly or unfit patients with CLL, the European Society for Medical Oncology clinical practice guidelines recommend chlorambucil plus obinutuzumab (ClbO) as the frontline treatment standard.[1] (More details on the frontline treatment standards were also displayed on Appendix Table 2 in Appendix 1 in Supplemental Materials found at https://dx.doi.org/10.1016/j.jval.2022.11.002). In 2014, the European Medicines Agency approved this treatment for treatment-naïve (ie, first-line [1L]) patients with CLL.[4] This approval was based on the results from the CLL11 study (NCT02053610), showing improved progression-free survival (PFS) with ClbO compared with chlorambucil alone.[4]

Despite the substantial improvement in PFS outcomes gained from treating with ClbO, there remains an unmet need for novel chemotherapy-free and fixed-duration 1L therapies with more acceptable and manageable safety profiles and improved clinical outcomes.[5] Consequently, the combination of venetoclax and obinutuzumab (VenO), a first chemotherapy-free, fixed-duration (ie, 12 cycles) combination regimen, was proposed.[5]

Recently, both efficacy and safety of VenO were investigated in the CLL14 study (NCT02242942),[6] a multicenter, randomized, open-label, phase III trial. In comparison with ClbO, VenO demonstrated statistically significant superior PFS (hazard ratio 0.31; $P < .000$) in treatment-naïve patients with CLL with coexisting medical conditions.[7] Although the European Medicines

**Figure 1.** Diagrammatic representation of the partitioned survival analysis model.




Agency issued marketing authorization for VenO in this population in 2020,[8] many European member states base their decision to reimburse novel treatments on a formal health technology assessment. In these assessments, the therapy's cost-effectiveness plays a vital role for the decision-making process. Economic evaluation (EE) studies can provide the necessary information by combining several sources of evidence (ie, on treatment effects and costs).[9,10] Nevertheless, current information on the cost-effectiveness of VenO compared with ClbO are only available from 1 non-European study, 3 conference abstracts, and 2 national assessment reports (one of which is in Dutch).[11-15] Although the conference abstracts reveal only little on the used methodology, most outcomes of the assessment report of the United Kingdom (UK) National Institute for Health and Care Excellence (NICE) are redacted because of commercial or academic confidentiality. This lack of transparency poses a challenge to the evaluation and comparison of these economic models, which heavily limits reproducibility.[16,17] In addition, several methodological choices of the available publications remain unclear and certain aspects were not studied. For instance, none of the EEs fully considered future costs (both medical and nonmedical), although their inclusion is often recommended.[18,19]

Our aim is to add to the existing body evidence by performing and reporting on a comprehensive cost-effectiveness analysis (CEA) comparing VenO with ClbO in treatment-naïve adult patients with CLL. To this end, we adopt a broad, Dutch societal perspective, provide a detailed description of the assumptions made for the model, and make available our economic model following Open Science Practices.[20,21] Consequently, our model and results remain transparent as well as reproducible. This approach facilitates transferability by allowing and simplifying the adaptation of the model to other countries and settings.[22,23] In scenario analyses, we also consider both future medical and nonmedical consumption costs during the life-years gained and possible drug price changes upon their patent expiry rather than assuming a constant price during the whole life cycle of these drugs.[24]

## Methods

To evaluate the cost-effectiveness of VenO compared with ClbO as 1L treatment for adult patients with CLL, we modeled a hypothetical cohort of adult patients with CLL using a partitioned survival analysis in Excel (Microsoft Office for Window, version 16.0.5161.1000).[25] Following the recommendations of the Dutch EE guideline, we adopted a societal perspective entailing not only the direct healthcare costs but also all other relevant societal costs such as travel, informal care, productivity losses, and future medical costs.[18] Additionally, future nonmedical costs were considered in a separate scenario analysis given that the Dutch guideline remains silent their inclusion. The complete Excel model, together with the associated input data and analyses, can be accessed through the Open Science Platform of "Figshare" (Details of our relevant files in Figshare repository can be found in the Appendix 1: Methods – Model Inputs – "Figshare Repository" section, Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002).

### Model Structure

The design of our model structure was based on previously published models, which in turn were informed by the clinical pathway and clinical expert opinion.[11,15] More specifically, the model comprises 3 health states: progression-free (PF), progressed disease (PD), and death.[26] Figure 1 visualizes the model structure and the possible transitions between health states. At any given time, modeled patients could only occupy one of the 3 health states. Patients were initially treated with either treatment option (VenO or ClbO) in the PF state. At the end of each 28-day model cycle, patients remained PF (ie, stayed in PF), progressed (ie, moved to PD), or died (ie, moved to the state of death). Once patients progressed, they received subsequent treatment lines or died. Death was an absorbing health state, and with a chosen lifetime horizon (ie, 29 years), all patients eventually end and remain there. In this way, we also captured long-term effects and costs of the therapies of interest.

### Model Inputs

Given that we did not have access to individual patient-level data (IPD), pseudo-IPD was created from the empirical Kaplan-Meier PFS and overall survival (OS) curves obtained from the CLL14 extended follow-up results.[7] This process followed the method described by Hoyle and Henley.[27]

Short-term pseudo-IPD were then extrapolated to the lifetime horizon. Based on visual assessment of the log-cumulative hazard plots (Appendix Fig. 1A, B in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002), the proportional hazards could not be assumed for PFS or OS. Therefore, we independently fitted a range of standard parametric curves for PFS data. Nevertheless, we found that extrapolating OS independently would yield survival benefits that cannot be justified with the empirical data from the CLL14 trial. Indeed, the trial investigators reported similar OS in both treatment groups with a statistically nonsignificant hazard ratio of 1.03 (95% confidence interval 0.60-1.75, $P = .92$). Consequently, we used dependent model fitting and assumed no difference in OS between both treatments in our base case. This is the most conservative approach and consistent with other studies investigating the same topic.[11,15,28] The choice of parametric distributions used in this study was based on the selection process outlined by Latimer.[29,30] Details of this selection process can be found in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002. Particularly, summary of survival model selection process applied in this study is visualized in Appendix Figures 2-5, and Appendix Tables 6-15 from Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

The model corrected for general Dutch population mortality[31] (ie, extrapolated survival could not exceed this mortality). Additionally, an adjustment for independently fitting PFS and OS in the model was made to ensure extrapolated PFS could not exceed the extrapolated OS.

**Table 1.** Model input parameters and values.

| Type | Parameter name in model | Value | Parameter description | Source |
|---|---|---|---|---|
| Model settings | Discount rare (benefits) | 1.50% | Outcome discount rate | Dutch EE guideline |
| | Discount rare (costs) | 4.00% | Cost discount rate | Dutch EE guideline |
| | Time horizon | 29 years | | N/A |
| Patient characteristics | Starting age (years) | 71 | | CLL14 protocol |
| Efficacy | OS distribution | Exponential | | Selection process outlined by Latimer |
| | PFS distribution | Log-logistic | | Selection process outlined by Latimer |
| Effectiveness – utility | PFS_Oral_trmt | 0.71 | Utility at progression-free state currently receiving therapy administered via oral medication | Blommestein et al (2016)[32] |
| | PFS_IV_trmt | 0.67 | Utility at progression-free state currently receiving therapy administered intravenously | |
| | PFS_After_trmt | 0.82 | Utility at progression-free state currently after receiving 1L therapy treatment | |
| | PD | 0.60 | Utility at progressed state currently receiving subsequent treatments | |
| Effectiveness disutility, AE | du_Anaemia | 0.09 | Disutility due to anemia | Beusterien et al (2010)[34] |
| | du_Feb_neu | 0.15 | Disutility due to febrile neutropenia | ZIN, NICE |
| | du_IRR | 0.20 | Disutility due to infusion related reaction | ZIN, NICE |
| | du_Leu | 0.15 | Disutility due to leukopenia | ZIN, NICE |
| | du_Neutro | 0.09 | Disutility due to neutropenia | ZIN, NICE |
| | du_Neutrophil_count_decreased | 0.09 | Disutility due to Neutrophil count decreased | ZIN, NICE |
| | du_Pneu | 0.20 | Disutility due to pneumonia | Beusterien et al (2010)[34] |
| | du_Sepsis | 0.20 | Disutility due to sepsis | ZIN, NICE |
| | du_Thrombo | 0.11 | Disutility due to thrombocytopenia | Tolley et al (2013)[35] |
| Cost | | | | |
| 1L treatment drugs | Venetoclax 10 mg | 5.64 | Listing price of venetoclax at 10 mg | Medicijnkosten |
| | Venetoclax 50 mg | 28.22 | Listing price of venetoclax at 50 mg | Medicijnkosten |
| | Venetoclax 100 mg | 56.43 | Listing price of venetoclax at 100 mg | Medicijnkosten |
| | Chlorambucil 2 mg | 2.11 | Listing price of chlorambucil at 2 mg | Medicijnkosten |
| | Obinutuzumab 1000 mg/mL | 3713.11 | Listing price of obinutuzumab at 1000 mg/mL | Medicijnkosten |
| Premedication (before 1L treatment) | Paracetamol 325 mg | 0.14 | Listing price of paracetamol at 325 mg | Medicijnkosten |
| | Loratadine 10 mg | 0.43 | Listing price of loratadine at 10 mg | Medicijnkosten |
| | Dexamethasone 0.5 mg | 0.11 | Listing price of Dexamethasone at 0.5 mg | Medicijnkosten |
| Chemotherapy administration | Daycare cost per day | 194 | Chemotherapy administration unit cost of 1 daycare | Holtzer-Goor et al (2014)[33] |
| | Inpatient cost per visit | 441 | Chemotherapy administration unit cost of 1 inpatient visit | Holtzer-Goor et al (2014)[33] |

*continued on next page*

**Table 1.** Continued

| Type | Parameter name in model | Value | Parameter description | Source |
|---|---|---|---|---|
| Routine care and follow-up | Physical exam | 86.53 | Unit cost of physical examination | Dutch manual costing tool |
| | Medical historical exam | 35.69 | Unit cost of medical history examination | Dutch manual costing tool |
| | Genetic analysis | 142.77 | Unit cost of genetic analysis | Dutch manual costing tool |
| | Full blood count test | 2.94 | Unit cost of full blood count test | NICE |
| | Blood test | 5.94 | Unit cost of blood test | NZa (Declaration code: #077121 #070702 #070715) |
| | Hematology visit | 142.77 | Unit cost of hematology visit | Dutch manual costing tool |
| | Bone marrow biopsy | 364.93 | Unit cost of bone marrow biopsy | Holtzer-Goor et al (2014)[33] |
| | CT scan | 156.83 | Unit cost of a computerized tomography scan | Dutch manual costing tool |
| Subsequent treatment distribution after VenO | Ibrutinib | 0.85 | Proportion of progressed patients receiving ibrutinib in VenO treatment arm | ZIN assessment report |
| | VenR | 0.10 | Proportion of progressed patients receiving VenR in VenO treatment arm | ZIN assessment report |
| | ClbR | 0.05 | Proportion of progressed patients receiving ClbR in VenO treatment arm | ZIN assessment report |
| Subsequent treatment distribution after ClbO | Ibrutinib | 0.45 | Proportion of progressed patients receiving ibrutinib in ClbO treatment arm | ZIN assessment report |
| | VenR | 0.50 | Proportion of progressed patients receiving VenR in ClbO treatment arm | ZIN assessment report |
| | ClbR | 0.05 | Proportion of progressed patients receiving ClbR in ClbO treatment arm | ZIN assessment report |
| Subsequent treatment Drug price | Ibrutinib 420 mg | 185.57 | Listing price of ibrutinib at 420 mg | Medicijnkosten |
| | Rituximab 50 mg/mL | 1144.96 | Listing price of Rituximab at 50 mg/mL | Medicijnkosten |
| | Paracetamol 325 mg | 0.14 | Listing price of Paracetamol at 325 mg | Medicijnkosten |
| | Chlorphenamine 4 mg | 8.04 | Listing price of Chlorphenamine at 4 mg | drugs.com |
| | Hydrocortisone 25 mg | 63.22 | Listing price of Hydrocortisone at 25 mg | drugs.com |
| AE management cost | Anemia | 1969.63 | Unit cost of anemia management treatment | Bouwmans et al (2009)[36] |
| | Febrile neutropenia | 3084.45 | Unit cost of febrile neutropenia management treatment | Bouwmans et al (2009)[36] |
| | Infusion related reaction | 754.82 | Unit cost of infusion related reaction management treatment | ZIN and Zindex |
| | Leukopenia | 1489.98 | Unit cost of leukopenia management treatment | ZIN |
| | Neutropenia | 1404.61 | Unit cost of neutropenia management treatment | Bouwmans et al (2009)[36] |
| | Neutrophil count decreased | 1404.61 | Unit cost of neutrophil count decreased management treatment | Assume to be the same as neutropenia |

*continued on next page*

**Table 1.** Continued

| Type | Parameter name in model | Value | Parameter description | Source |
|---|---|---|---|---|
| | Pneumonia | 5904.85 | Unit cost of pneumonia management treatment | Rozenbaum et al (2015)[37] |
| | Sepsis | 7166.90 | Unit cost of sepsis management treatment | Soini et al (2016)[38] |
| | Thrombocytopenia | 3701.52 | Unit cost of thrombocytopenia management treatment | Bouwmans et al (2009)[36] |
| TLS prophylaxis | Rasburicase (price per day) | 4961.67 | Total cost for receiving rasburicase as TLS prevention treatment per day | Medicijnkosten |
| Patient and family costs | Travel costs per visit | 4.68 | Average of transportation costs from patients' homes to hospital | Dutch manual costing |
| | Informal care costs per hour | 15.14 | Average unit cost of informal care per hour | Dutch manual costing |
| Future costs | Future medical costs | Various costs per treatment and age group | Medical-related costs incurred during the life-years gained because of receiving the life-prolonging treatments | Van Baal et al (2011)[39] |
| | End of life costs | Various costs per treatment and age group | Costs incurred at the last year of life | Van Baal et al (2011)[39] |

1L indicates first-line; AE, adverse event; ClbO, chlorambucil plus obinutuzumab; ClbR, chlorambucil plus rituximab; CLL, chronic lymphocytic leukemia; CT, computed tomography; EE, economic evaluation; IRR, infusion related reaction; IV intravenous; N/A, not available; NZa, Nederlandse Zorgautoriteit (Dutch Healthcare Authority); NICE, National Institute for Health and Care Excellence; OS, overall survival; PD, progressed disease; PFS, progression-free survival; TLS, tumor lysis syndrome; VenO, venetoclax plus obinutuzumab; VenR, venetoclax plus rituximab; ZIN, Zorginstituut Nederland.

The study's effect outcomes were represented by quality-adjusted life-years (QALYs) gained. To calculate QALYs, health-state utilities for PD and PF were derived from the literature.[32] Utility scores used in the Dutch and UK assessment reports were explored in scenario analysis. To adhere to the Dutch EE guideline, all effect outcomes were half-cycle corrected (HCC) and discounted with 1.5% to account for the effect of differential timing.[18] All effectiveness parameter values are presented in Table 1.[32-39]

In terms of healthcare costs, we included costs for drugs (acquisition and administration), adverse events (AEs), subsequent treatments, routine care, and follow-up activities, as well as future medical costs. Regarding societal costs, we included costs for travel and informal care. In scenario analyses, we also accounted for the impact of future nonmedical costs. Given that the average age of the modeled population (ie, 71 years) was well above the current Dutch pension age (ie, 66.3 years),[40] we did not include costs of productivity losses.

Drug dosing schedules were based on the planned dose derived from the CLL14 protocol.[41] Details on drug dosing schedules of 1L and subdequent treatmnet drugs can be found in Appendix Tables 1, 4, and 5 from Appendix 1 in Supplemental Matrials found at https://dx.doi.org/10.1016/j.jval.2022.11.002. Prices for drug acquisition (1L and subsequent treatments) were taken from the Dutch official medicine database (ie, Zorginstituut Nederland [ZIN][42]). In scenario analyses, we also accounted for the impact of the so-called patent cliff, meaning that prices of CLL therapies decrease after patent expiration. Particularly, venetoclax, obinutuzumab, and ibrutinib were modeled to go off-patent in May 2030,[43] in November 2024,[44] and in June 2031,[43] respectively. We considered an off-patent price of 59% of the current price, similar to discounts observed on the Dutch market.[24] Administration costs were retrieved from literature.[33,45]

For AEs, we considered their associated disutility and costs. The frequency and types of AEs for both treatment arms were obtained from the CLL14 trial's follow-up results.[7] In reference to other CEA literature,[11,12,15,32] only grade 3 or higher AEs with at least 5% occurrence from either treatment arm were included in the model. The AEs' disutility scores and their associated cost management were based on the literature.[11,15,34-38]

Additionally, we considered costs for tumor lysis syndrome, a principal adverse reaction associated with treatments for patients with CLL,[41] based on frequencies and types reported in CLL14.[46] Both AE management and tumor lysis syndrome prophylaxis were modeled as a one-off cost for all patients in both treatment arms during the first cycle of the model.

Possible subsequent treatments in the PD state were taken from the current Dutch treatment guideline for patients with CLL.[47] Details of these subsequent treatments are displayed in Appendix Table 3 in Appendix 1 in Supplemental Materials founs at https://dx.doi.org/10.1016/j.jval.2022.11.002. Type and frequencies of routine care and follow-up activities were extracted from the CLL14 study protocol.[41] Respective prices were based on the Dutch costing manual[48,49] and the literature.[11,15,33,50]

Assumptions on resource use for travel and informal care were based on the literature[15] and valued with standard unit prices from the Dutch costing manual.[48] Future medical costs were included using the iMTA PAID tool (version 3.0), which is available online (https://imta.shinyapps.io/PAID3code//).[39,51] More information on the nature of these future costs can be found in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

**Table 2.** Deterministic discounted results of the model base case.

| Items | Treatment | |
|---|---|---|
| | VenO | ClbO |
| Disaggregated results (averaged and discounted) | | |
| Costs | | |
| Drug-related costs | 94 923 | 32 450 |
| Routine care costs | 1527 | 1370 |
| Follow-up costs | 3303 | 2354 |
| Subsequent treatment costs | 125 479 | 218 581 |
| TLS prophylaxis costs | 1101 | 987 |
| AE management costs | 2483 | 2229 |
| Travel costs | 227 | 213 |
| Informal care costs | 13 034 | 46 204 |
| Future medical costs | 124 687 | 124 687 |
| Effects | | |
| LYs | 12.13 | 12.13 |
| QALYs | 9.33 | 8.09 |
| Total results (averaged, discounted, and HCC) | | |
| Costs | 366 398 | 428 713 |
| Effects – LYs | 12.09 | 12.09 |
| Effects – QALYs | 9.31 | 8.06 |
| Incremental results (VenO vs ClbO, averaged, discounted, and HCC) | | |
| Incremental costs | – | (62 315.73) |
| Incremental LYs | – | 0.00 |
| Incremental QALYs | – | 1.25 |

AE indicates adverse event; ClbO, chlorambucil plus obinutuzumab; HCC, half-cycle correction; LY, life-year; QALY, quality-adjusted life-year; TLS, tumor lysis syndrome; VenO, venetoclax plus obinutuzumab.

All costs in this study were expressed in Dutch 2020 euros and prices of earlier years were indexed to 2020 with the pertinent consumer price index.[52] Cost outcomes were HCC and discounted with 4.0%, following the Dutch EE guideline.[18] All resource use and cost parameter values are summarized in Table 1.[32-39]

### Statistical Analyses

In the base-case analysis, we calculated the incremental cost-effectiveness ratio (ICER) in QALY gained of VenO compared with ClbO. VenO was considered cost-effective if its associated ICER was below the applicable willingness-to-pay (WTP) threshold of 20 000 euro per QALY gained (estimated using the Burden-of-Disease calculator).[53]

To propagate and analyze uncertainty of the model input parameters and results, we conducted one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). For the former, we varied base-case values of the parameters subjecting to uncertainty (one at a time). For the PSA, we explored the joint parameter uncertainty, by varying these parameters simultaneously across their appropriate distributions by using Monte Carlo simulations with 2000 iterations.

Structural uncertainty was addressed through several scenario analyses by varying efficacy, utility, and cost parameters. The completed scenarios are summarized in Appendix Table 16 in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002. Additionally, we conducted a value of information (VOI) analysis at expected value of perfect information (EVPI) and expected value of partial perfect information (EVPPI) levels to address the decision uncertainty aspect of the model. Group of paramaters used in the EVPPI analysis are summarized in Appendix Table 17 in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002. Results of this analysis can be used to assist decision makers to choose between an immediate decision based on the best available evidence and postponing that decision in anticipation of better evidence in the future.[54,55] Furthermore, VOI can help prioritize research strategies and identify research with a significant potential to improve patient care and public health practices.[55] EVPI and EVPPI analyses were conducted following the "Strong method"[56] using the Sheffield Accelerated Value of Information tool (available at http://savi.shef.ac.uk/SAVI).[57]

Details on the model validation process can be found in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

## Results

### Base-Case Analyses

Based on the Latimer selection process, the log-logistic and exponential distribution were selected for the survival extrapolation of PFS and OS in the base case, respectively. For the VenO treatment arm, the modeled PFS probability at 5, 10, and 15 years was 67.22%, 45.41%, and 32.89%, respectively. For patients treated with ClbO, these probabilities were 26.96%, 9.21%, and 4.54%. The median estimated PFS in the model was 103.9 months (8.7 years) and 34.9 months (2.91 years) for VenO and ClbO, respectively.

The estimated probability of OS for both VenO and ClbO at 5, 10, and 15 years was 80.52%, 62.21%, and 50.45%, respectively. The median estimated OS in the model was 180.8 months (15.06 years) for both treatment arms. Empirical and modeled PFS and OS of both treatment arms are displayed in Appendix Figures 3 and 4 in Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

The model estimated an average of 9.31 QALYs for VenO and 8.06 QALYs for ClbO (averaged, discounted, and HCC results). All these outcomes are summarized in Table 2.

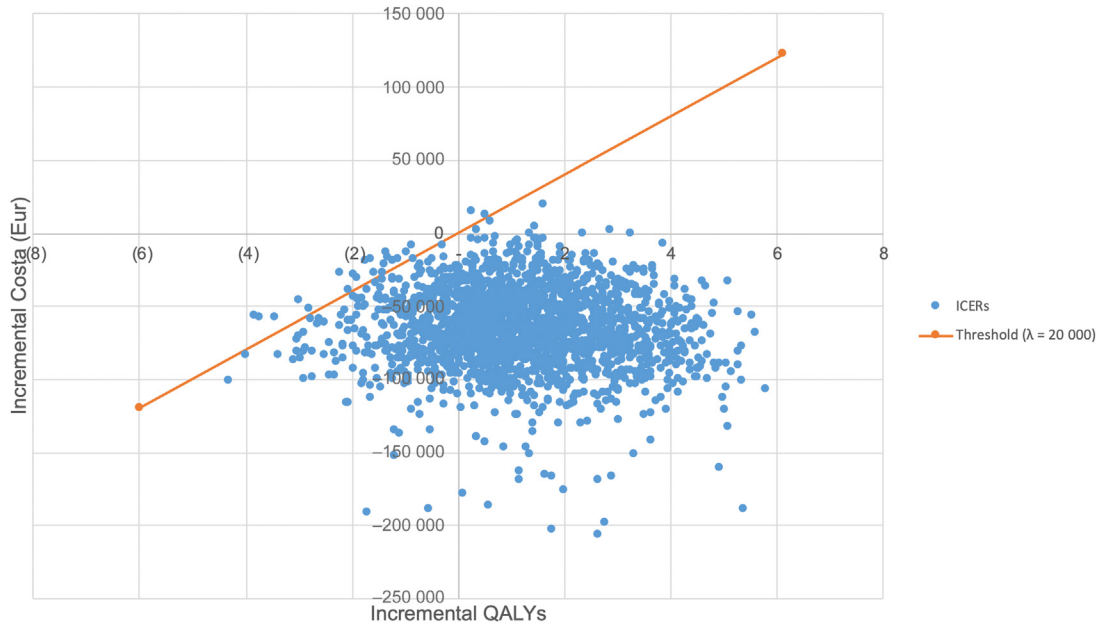
Total average costs per patients treated with VenO and ClbO were 366 398 EUR and 428 713 EUR, respectively (discounted). The major cost drivers were future medical costs (VenO and ClbO, 124 687 EUR, discounted), followed by subsequent treatment drug acquisition costs (VenO, 125 479 EUR; ClbO, 218 581 EUR, discounted). All cost outcomes are summarized in Table 2. Furthermore, for more details, both discounted and undiscounted cost and benefit outcomes are summarized in Appendix Table 18 and 19 in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

VenO resulted in 1.25 QALYs gained per patient more than ClbO. Total costs of VenO were 62 316 EUR lower than the total costs of ClbO (discounted). Putting it differently, per an additional QALY gained, healthcare and social expenditures are 49 928 EUR lower for VenO.

### Uncertainty Analyses

The top 10 influential parameters determined through the OWSA are depicted in Appendix Figure 6 in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002. This sensitivity analysis demonstrated that varying the utility value at PFS state after receiving the 1L treatment was the most influential factor for the ICER. Given that a larger proportion of patients treated with VenO enjoyed a longer period of time in PFS state than ClbO, the utilities accrued in this health state had the most influential impact on ICER. Although the change in some parameters affected the ICER quite substantially,

**Figure 2.** Cost-effectiveness plane.




ICER indicates incremental cost-effectiveness ratio; QALY, quality-adjusted life-year.

VenO remained cost-effective across all parameter changes, using a WTP threshold of 20 000 EUR/QALY gained.

Results of the 2000 PSA iterations are depicted in the cost-effectiveness plane in Figure 2. At a WTP threshold value of 20 000 EUR/QALY gained, the probability of VenO being cost-effective was 99%. The probability of VenO being cost-effective at different WTP thresholds is visualized in the cost-effectiveness acceptability curve in Appendix Figure 7 from Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

VenO remained dominant over ClbO across all scenario analyses tested in our model (Appendix Table 21 in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002). Nevertheless, the ICER was most affected by variations in the following 2 scenarios. First, assuming utility values based on NICE assessment yielded an ICER of −157 211 (with incremental positive effects and negative costs) EUR/QALY gained, which resulted in the largest decrease of the ICER by 215%. Second, considering time-to-next treatment (TTNT) to calculate numbers of patients receiving subsequent treatments and using log-normal distribution to extrapolate TTNT curve resulted in an ICER of −27 187 (with incremental positive effects and negative costs) EUR/QALY gained, which was the highest ICER value among those of all the tested scenarios.

At the WTP threshold value of 20 000 EUR/QALY gained, the overall expected value of eliminating uncertainty for all parameters (ie, EVPI) was estimated at 106 EUR for one patient affected by the decision. More details on EVPI results can be seen from Appendix Figure 8 in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

In terms of the expected value of eliminating uncertainty for certain groups of parameters, multiple EVPPI analyses at a WTP threshold value of 20 000 EUR/QALY gained failed at guiding future research topics given that the values of EVPPI for the chosen groups of parameters all resulted in 0 EUR (Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002).

## Discussion

### Summary of Findings

This study evaluated the cost-effectiveness of VenO compared with ClbO for treatment-naïve patients with CLL assuming a Dutch societal perspective. At the chosen WTP threshold of 20 000 EUR/QALY gained, our analysis revealed that VenO was dominant over ClbO given that it is associated with higher health effects (ie, 1.25 QALYs) and lower costs (cost savings of 62 316 EUR). These results are mainly driven by the extended PFS period following VenO. The sensitivity analyses demonstrated the robustness of these results. Furthermore, all explored scenarios including the consideration of future nonmedical costs and the patient-cliff impact rendered VenO dominant with the chosen WTP threshold. Additionally, our VOI analyses results indicated that additional research is not recommended because our EVPI value is substantially lower than the threshold.[58] In other words, the cost-effectiveness conclusion of VenO in treatment-naïve patients with CLL is robust based on currently available evidence.

### Comparison With Other Studies

Although different, our model results are in line with previous studies examining the cost-effectiveness in the given setting. In 2020, the Dutch National HealthCare Institute[15] (ZIN) published its reimbursement advice for venetoclax, which included an EE comparing VenO with ClbO for treatment-naïve patients with CLL. In this study, ZIN concluded that VenO was dominant over ClbO with an incremental QALYs of 1.14 and a cost saving of 159 276 EUR.[15] Although the incremental QALYs estimated between the 2 studies differed by 0.11 years (1.14 vs 1.25 in QALYs gained), the total cost savings substantially differed (ie, 159 276 EUR vs 62 316 EUR). We hypothesize several reasons for the disparities observed here.

First, we noticed a significant deviation in the costs of subsequent treatments, particularly in the acquisition costs thereof from both studies (a difference of 92 624 EUR). This may mainly be

based on a different methodology used to estimate these costs. Instead of assuming that every newly progressed patient would receive a subsequent treatment-line right away, the ZIN study could base its assumption on patient-level data on TTNT. Given that we did not have access to these data, we could not include TTNT in our base-case analysis.

Second, subsequent treatment duration deviated between the 2 analyses. In fact, both studies estimated the same duration for all but the third subsequent treatment option of ibrutinib. Although the ZIN analysis and our study referred to the RESONATE study[59] to estimate the duration of ibrutinib of 39 months, the ZIN analysis modified this input to 60 months based on their internal experts' opinions. The difference in treatment duration may inherently contribute to divergence in costs of subsequent treatment and, by extension, the cost savings observed in both studies.

Additionally, the cost-effectiveness of VenO was evaluated in the same clinical setting from a UK healthcare perspective for a single technology appraisal to the NICE.[11] Similar to our findings, the UK analysis found VenO to be dominant over ClbO.[11] A complete comparison with this report is not possible, given that most results of the NICE assessment were redacted.

Nevertheless, we were able to note the differences in incremental QALYs gained between our analyses (1.25) and the NICE report (0.365). We hypothesize a reason to this variance as follow. The utility values used in both analyses were derived from different sources. The difference in elicitation of utility scores might have yielded discordance between the QALYs gained observed between the 2 reports.

Using a healthcare perspective, Davids et al,[12] Chatterjee et al,[13] and Ordonez and Quitian[14] also published their CEA results in form of abstracts for the United States, Canada, and Columbia, respectively. The 3 studies concluded that, within the respective WTP thresholds, VenO was projected to be dominant over ClbO, which is in line with our conclusion. A detailed comparison between these studies is challenging because of the limited information that abstracts typically provide. Additionally, results of conference abstracts need to be interpreted with caution (see for instance Scherer and Saldanha [2019][60] for a discussion about this). Nevertheless, we made an attempt to compare our results with the 3 available abstracts in the Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002.

The study by Chatterjee et al (2021)[28] under the US healthcare perspective seems to be an updated version of the earlier presented conference of Davids et al (2019)[12] although the study results slightly differ. In this study, the authors also concluded that VenO was dominant over ClbO with an incremental QALYs of 0.33 and a cost saving of $200 028 (an equivalence of 163 749 EUR). The deviation in these increments could stem from a couple of reasons. First, the use of different perspectives inherently leads to divergence in inclusion of different types of cost and, by extension, the eventual ICERs. Additionally, there exist variations in clinical practice and healthcare costs among the United States and The Netherlands, which may have resulted in discordance observed. Second, a shorter time horizon was used in this study (20 years). Consequently, any costs or effects occurring after this shorter time period were not considered. Third, the difference in elicitation of utility scores might have yielded discordance between the QALYs gained observed between the 2 studies.

### *Strengths and Weaknesses*

Although our study is not the first to estimate the cost-effectiveness of VenO, it is the first to adopt an extended societal perspective by incorporating future medical and nonmedical costs (in scenario analyses). For EEs performed under a US or Dutch perspective, it is suggested to consider future medical costs.[18,19] Although the US guidelines recommend the inclusion of future nonmedical costs as well,[19] the Dutch guideline does not mention its inclusion specifically (yet).[18] Our study is the first to fully include both components in the analysis for this setting. In practice, future costs are often excluded from CEAs.[61] With our analysis, we bridge this gap, which could potentially be used as a reference point for future EEs.

In addition, we made our model and data sources openly accessible. To date, very few of decision models are made available because of lack of a standard model repository[62] or because of the confidentiality of data. Nevertheless, the urgency of having these models available to all stakeholders such as policy makers, health authorities, industry sponsors, academicians, and others is increasing.[62] Furthermore, the availability of these models allows the research community to validate and even reuse the model with different data,[62] which will increase the transparency of research results in general. Additionally, this approach facilitates transferability by allowing and simplifying the adaptation of the model to other countries and setting.

This study has several limitations (our study presents several limitations, 2 of which are acknowledged here, and the rest can be found in Appendix 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002– Discussion – Limitations section). First, owing to a lack of IPD from the clinical trial, our study could not examine the heterogeneity of the study population. Thus, subgroup analyses could not be performed to further understand differences in the ICERs. Having access to IPD or real-world evidence will be desirable for specific subgroup analyses to better recommend the drugs of interest.

Second, some of the utility decrements because of AEs in our model were based on those of AEs caused by nonblood cancers. Arguably, similar AEs yet caused by different diseases may have different impacts on patients' preferences. Nonetheless, because of scarce information on AEs in general, it might be acceptable to refer to other diseases where the information is available. To examine the impact of this limitation on estimated ICERs, each of the disutility values was tested in OWSA. None of these parameters were represented within the top 10 most influential model parameters for the ICER, signifying a negligible impact on the calculated results (see Appendix Table 20 in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002). Furthermore, all of the disutility parameters were grouped in an EVPPI analysis to examine the benefit of collecting further information on these values. As expected, this EVPPI analysis resulted in a value of 0 EUR (see Appendix Table 22 in Appendix 2 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2022.11.002) indicating the current evidence on these values is sufficient, and no further research is needed.

## Conclusion

Despite the several limitations, we conclude that VenO for treatment-naïve adult patients with CLL is dominant over ClbO. This conclusion aligns with other CEA studies for this patient group. The VOI analyses showed that the maximum expected value of eliminating all model parameter uncertainty is rather low with 183 591 EUR. Nevertheless, further research based on real-world data and a longer follow-up period could further contribute to the robustness of our study's conclusions. Our open-access model can serve as both reference and tool to incorporate new evidence or to adapt our analyses to a (country) setting.

## Supplemental Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1016/j.jval.2022.11.002.

## Article and Author Information

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## REFERENCES

1. Eichhorst B, Robak T, Montserrat E, et al. Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2021;32(1):23–33.
2. Herring W, Pearson I, Purser M, et al. Cost effectiveness of ofatumumab plus chlorambucil in first-line chronic lymphocytic leukaemia in Canada. *Pharmacoeconomics*. 2016;34(1):77–90.
3. Maurer C, Hallek M. Chronic lymphocytic leukemia (in German: chronische lymphatische Leukämie). Chronic lymphocytic leukemia. *Dtsch Med Wochenschr*. 2013;138(42):2153–2166.
4. European Medicines Agency recommends approval of Gazyvaro for chronic lymphocytic leukaemia. European Medicines Agency (EMA). https://www.ema.europa.eu/en/documents/press-release/european-medicines-agency-recommends-approval-gazyvaro-chronic-lymphocytic-leukaemia_en.pdf. Accessed January 4, 2021.
5. A multiple-discipline review on venetoclax. Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/208573Orig1s013MultidisciplineR.pdf. Accessed February 1, 2021.
6. Comparison of the treatments of obinutuzumab + venetoclax versus obinutuzumab + chlorambucil in patients with chronic lymphocytic leukemia. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/results/NCT02242942. Accessed December 30, 2020.
7. Al-Sawaf O, Zhang C, Tandon M, et al. Venetoclax plus obinutuzumab versus chlorambucil plus obinutuzumab for previously untreated chronic lymphocytic leukaemia (CLL14): follow-up results from a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2020;21(9):1188–1200.
8. EMA recommends extension of indications for Venetoclax. ESMO. https://www.esmo.org/oncology-news/ema-recommends-extension-of-indications-for-venetoclax2. Accessed June 15, 2021.
9. Drummond M, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 4th ed. Oxford, United Kingdom: Oxford University Press; 2015.
10. Briggs A, Claxton K, Sculpher MJ. *Decision Modelling for Health Economic Evaluation*. Oxford, United Kingdom: Oxford University Press Inc; 2006.
11. Committee papers on venetoclax with obinutuzumab for untreated chronic lymphocytic leukaemia 2020. National Institute for Health and Care Excellence (NICE). https://www.nice.org.uk/guidance/ta663/documents/committee-papers. Accessed February 9, 2021.
12. Davids MS, Chatterjee A, Ravelo A, et al. Cost-effectiveness of a 12-month fixed duration of venetoclax in combination with obinutuzumab in first-line chronic lymphocytic leukemia in the United States. *Blood*. 2019;134(suppl 1):4741-4741.
13. Chatterjee A, Van de Wetering G, Goeree R, et al. Cost-effectiveness of a 12-month fixed duration of venetoclax in combination with obinutuzumab versus chemoimmunotherapy and other novel combinations in first-line chronic lymphocytic leukemia in Canada. *Blood*. 2020;136(suppl 1):31–32.
14. Ordoñez J, Quitián D. PCN57 cost-effectiveness of venetoclax in combination with obinutuzumab in first-line chronic lymphocytic leukemia in Colombia. *Value Health*. 2021;24:S29.
15. Package advice venetoclax (Venclyxto®) in combination with obinutuzumab for the treatment of adult patients with previously untreated chronic lymphatic leukaemia (CLL). Dutch National Health Care Institute (ZIN). https://english.zorginstituutnederland.nl/publications/reports/2020/11/16/venetoclax-venclyxto. Accessed February 9, 2021.
16. Fukuda H, Imanaka Y. Assessment of transparency of cost estimates in economic evaluations of patient safety programmes. *J Eval Clin Pract*. 2009;15(3):451–459.
17. Kent S, Becker F, Feenstra T, et al. The challenge of transparency and validation in health economic decision modelling: a view from Mount Hood. *Pharmacoeconomics*. 2019;37(11):1305–1312.
18. Guideline for economic evaluations in healthcare. Dutch National Health Care Institute (ZIN). https://english.zorginstituutnederland.nl/publications/reports/2016/06/16/guideline-for-economic-evaluations-in-healthcare. Accessed February 14, 2021.
19. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: second panel on cost-effectiveness in health and medicine. *JAMA*. 2016;316(10):1093–1103.
20. Allen C, Mehler DMA. Open science challenges, benefits and tips in early career and beyond [published correction appears in *PLoS Biol*. 2019;17(12):e3000587]. *PLoS Biol*. 2019;17(5):e3000246.
21. Guiding principles. Open Science Community Rotterdam. https://www.openscience-rotterdam.com/principles/. Accessed October 1, 2021.
22. Drummond M, Barbieri M, Cook J, et al. Transferability of economic evaluations across jurisdictions [ISPOR Good Research Practices Task Force report]. *Value Health*. 2009;12(4):409–418.
23. Walker D, Teerawattanonon Y, Anderson R, Richardson G. Generalisability, transferability, complexity and relevance. In: Shemilt I, Mugford M, Vale L, Marsh K, Donaldson C, eds. *Evidence-Based Decisions and Economics*. Chichester, United Kingdom: Wiley; 2010.
24. van der Schans S, Vondeling GT, Cao Q, et al. The impact of patent expiry on drug prices: insights from the Dutch market. *J Mark Access Health Policy*. 2020;9(1):1849984.
25. Woods B, Sideris E, Palmer S, Latimer N, Soares M. NICE DSU technical support document 19: partitioned survival analysis for decision modelling in health care: a critical review. University of Sheffield. http://nicedsu.org.uk/wp-content/uploads/2017/06/Partitioned-Survival-Analysis-final-report.pdf. Accessed January 9, 2021.
26. Cranmer H, Shields GE, Bullement A. A comparison of partitioned survival analysis and state transition multi-state modelling approaches using a case study in oncology. *J Med Econ*. 2020;23(10):1176–1185.
27. Hoyle MW, Henley W. Improved curve fits to summary survival data: application to economic evaluation of health technologies. *BMC Med Res Methodol*. 2011;11(1):139.
28. Chatterjee A, Shapouri S, Manzoor BS, et al. Cost-effectiveness of a 12-month fixed-duration venetoclax treatment in combination with obinutuzumab in first-line, unfit chronic lymphocytic leukemia in the United States. *J Manag Care Spec Pharm*. 2021;27(11):1532–1544.
29. Latimer N. NICE DSU technical support document 14: survival analysis for economic evaluations alongside clinical trials-extrapolation with patient-level data. University of Sheffield. https://www.ncbi.nlm.nih.gov/books/NBK395885/pdf/Bookshelf_NBK395885.pdf. Accessed XXX.
30. Latimer NR. Survival analysis for economic evaluations alongside clinical trials–extrapolation with patient-level data: inconsistencies, limitations, and a practical guide. *Med Decis Making*. 2013;33(6):743–754.
31. The Human Mortality Database. University of California BU, Max Planck Institute for Demographic Research (Germany). www.mortality.org. Accessed February 1, 2021.

32. Blommestein HM, de Groot S, Aarts MJ, et al. Cost-effectiveness of obinutuzumab for chronic lymphocytic leukaemia in the Netherlands. *Leuk Res*. 2016;50:37–45.
33. Holtzer-Goor KM, Bouwmans-Frijters CA, Schaafsma MR, et al. Real-world costs of chronic lymphocytic leukaemia in the Netherlands. *Leuk Res*. 2014;38(1):84–90.
34. 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.
35. Tolley K, Goad C, Yi Y, Maroudas P, Haiderali A, Thompson G. Utility elicitation study in the UK general public for late-stage chronic lymphocytic leukaemia. *Eur J Health Econ*. 2013;14(5):749–759.
36. Bouwmans C, Janssen J, Huijgens P, Uyl-de Groot C. Costs of haematological adverse events in chronic myeloid leukaemia patients: a retrospective cost analysis of the treatment of anaemia, neutropenia and thrombocytopenia in patients with chronic myeloid leukaemia. *J Med Econ*. 2009;12(2):164–169.
37. Rozenbaum MH, Mangen MJ, Huijts SM, van der Werf TS, Postma MJ. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: a nationwide retrospective claims database analysis. *Vaccine*. 2015;33(28):3193–3199.
38. Soini E, Hautala A, Poikonen E, Becker U, Kyttälä M, Martikainen J. Cost-effectiveness of first-line chronic lymphocytic leukemia treatments when full-dose fludarabine is unsuitable. *Clin Ther*. 2016;38(4):889–904.e14.
39. van Baal PH, Wong A, Slobbe LC, Polder JJ, Brouwer WB, de Wit GA. Standardizing the inclusion of indirect medical costs in economic evaluations. *Pharmacoeconomics*. 2011;29(3):175–187.
40. Pension Agreement: a more transparent and personal pension system. Rijksoverheid. https://www.rijksoverheid.nl/onderwerpen/pensioen/toekomst-pensioenstelsel/aow-leeftijd-stijgt-minder-snel. Accessed May 11, 2021.
41. Fischer K, Al-Sawaf O, Bahlo J, et al. Protocol: venetoclax and obinutuzumab in patients with CLL and coexisting conditions. *N Engl J Med*. 2019;380:2225–2236.
42. Zorginstituut Nederland. Drug costs The Netherlands (in Dutch: Medicijnkosten Nederland). https://www.medicijnkosten.nl/. Accessed February 23, 2021.
43. Patel KK, Isufi I, Kothari S, Davidoff AJ, Gross CP, Huntington SF. Cost-effectiveness of first-line vs third-line ibrutinib in patients with untreated chronic lymphocytic leukemia. *Blood*. 2020;136(17):1946–1955.
44. Busse A, Lüftner D. What does the pipeline promise about upcoming biosimilar antibodies in oncology? *Breast Care (Basel)*. 2019;14(1):10–16.
45. Franken MG, Kanters TA, Coenen JL, et al. Potential cost savings owing to the route of administration of oncology drugs: a microcosting study of intravenous and subcutaneous administration of trastuzumab and rituximab in the Netherlands. *Anti Cancer Drugs*. 2018;29(8):791–801.
46. Al-Sawaf O, Fink AM, Robrecht S, et al. Prevention and management of tumor lysis syndrome in patients with CLL and coexisting conditions treated with venetoclax-obinutuzumab or chlorambucil-obinutuzumab: results from the randomized CLL14 trial. *Blood*. 2019;134(suppl 1):4315-4315.
47. Kersting S, Neppelenbroek SIM, Visser HPJ, et al. Clinical practice guidelines for diagnosis and treatment of chronic lymphocytic leukemia (CLL) in the Netherlands. *Clin Lymphoma Myeloma Leuk*. 2018;18(1):52–57.
48. Kanters TA, Bouwmans CAM, van der Linden N, Tan SS, Hakkaart-van Roijen L. Update of the Dutch manual for costing studies in health care. *PLoS One*. 2017;12(11):e0187477.
49. Hakkaart-van Roijen L, Van der Linden N, Bouwmans CAM, Kanters T, SS T. Costing Manual: Methodology of Costing Research and Reference Prices for Economic Evaluations in Healthcare [in Dutch: Kostenhandleiding: Methodologie van Kostenonderzoek en Referentieprijzen Voor Economische Evaluaties in de Gezondheidszorg]. Zorginstituut Nederland. https://www.zorginstituutnederland.nl/binaries/zinl/documenten/publicatie/2016/02/29/richtlijn-voor-het-uitvoeren-van-economische-evaluaties-in-de-gezondheidszorg/Richtlijn%2Bvoor%2Bhet%2Buitvoeren%2Bvan%2Beconomische%2Bevaluaties%2Bin%2Bde%2Bgezondheidszorg%2B%28verdiepingsmodules%29.pdf. Accessed May 9, 2021.
50. Tarieven diagnostiek ZekerWeten 2019. Zekerweten.nl. https://www.zekerweten.nl/media/1562/tarieven-zekerweten-2019.pdf. Accessed February 13, 2021.
51. PAID. version 3.0. The iMTA. https://imta.shinyapps.io/PAID3/. Accessed February 22, 2021.
52. Open data. Statistics Netherlands. https://opendata.cbs.nl/#/CBS/nl/. Accessed February 23, 2021.
53. Disease burden calculator. The iMTA. https://imta.shinyapps.io/iDBC/. Accessed May 9, 2021.
54. Kunst NR, Alarid-Escudero F, Paltiel AD, Wang SY. A value of information analysis of research on the 21-gene assay for breast cancer management. *Value Health*. 2019;22(10):1102–1110.
55. About ConVoi. ConVoi group. https://www.convoi-group.org/homepage-portfolio-grid/about/. Accessed April 12, 2021.
56. Strong M, Oakley JE, Brennan A. Estimating multiparameter partial expected value of perfect information from a probabilistic sensitivity analysis sample: a nonparametric regression approach. *Med Decis Mak*. 2014;34(3):311–326.
57. Sheffield accelerated value of information version 2.2.0. The University of Sheffield. https://savi.shef.ac.uk/SAVI/. Accessed May 8, 2021.
58. Thorn J, Coast J, Andronis L. Interpretation of the expected value of perfect information and research recommendations: A systematic review and empirical investigation. *Med Decis Mak*. 2016;36(3):285–295.
59. A phase 3 study of ibrutinib (PCI-32765) versus ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia (RESONATE™). ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT01578707. Accessed May 15, 2021.
60. Scherer RW, Saldanha IJ. How should systematic reviewers handle conference abstracts? A view from the trenches. *Syst Rev*. 2019;8(1):264.
61. de Vries LM, van Baal PHM, Brouwer WBF. Future costs in cost-effectiveness analyses: past, present, future. *Pharmacoeconomics*. 2019;37(2):119–130.
62. Arnold RJ, Ekins S. Time for cooperation in health economics among the modelling community. *Pharmacoeconomics*. 2010;28(8):609–613.