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Bendamustine Versus Chlorambucil for the First-Line Treatment of Chronic Lymphocytic Leukemia in England and Wales: A Cost-Utility Analysis

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ABSTRACT

Objectives: To evaluate the cost-effectiveness of bendamustine compared with chlorambucil as first-line treatment for patients with chronic lymphocytic leukemia who would be considered unsuitable for treatment with fludarabine combination chemotherapy regimens. **Methods:** A semi-Markov approach was used to estimate time in each health state. The model was parameterized primarily by using data from a phase III randomized, open-label trial comparing bendamustine with chlorambucil. It captured the increased progression-free survival and improved response rates with bendamustine, and the cost and quality of life impacts of postprogression treatments. The analysis was conducted from the perspective of the National Health Service in England and Wales. A lifetime (35-year) time horizon was used. Deterministic sensitivity analyses, probabilistic sensitivity analyses, and subgroup analyses in older patients and patients with poor performance status were carried out. **Results:** The estimated incremental cost-effectiveness ratio was £11,960 per quality-adjusted life-year. None of the deterministic sensitivity analyses increased the incremental cost-effectiveness ratio by more than £2000. Subgroup analyses showed that bendamustine remained cost-effective across different patient groups. Probabilistic sensitivity analysis showed that at the £20,000 threshold, bendamustine has a 90% probability of being cost-effective. **Conclusions:** Bendamustine represents good value for first-line treatment of patients with chronic lymphocytic leukemia who are unsuitable for treatment with fludarabine combination chemotherapy. The incremental cost-effectiveness ratio is below the thresholds commonly applied in England and Wales (£20,000–£30,000 per quality-adjusted life-year).

Keywords: bendamustine, chlorambucil, chronic lymphocytic leukemia, cost-effectiveness, cost-utility, QALY.

Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia among adults in industrialized countries [1]. In 2008, the incidence of CLL in the United Kingdom (UK) was 3.3 per 100,000 and 2798 new cases were diagnosed [2]. The risk of developing CLL increases with age, and it accounts for 40% of all leukemia cases in those aged older than 65 years [3]. The median age at diagnosis is between 65 and 70 years [3].

For most patients, CLL is incurable, and follows a relapsing and remitting course. It is estimated that around one third of patients will be asymptomatic and never require treatment. The subset of patients who do need treatment is heterogeneous in terms of age, comorbidities, and performance status, and clinicians have to decide whether to adopt a "palliative" approach (treat symptomatic disease with regimens causing minimal treatment-related toxicity) or to aim for improved progression-free survival (PFS) and response rates, and, hopefully, longer overall survival.

CLL is typically responsive to several courses of chemotherapy, although the depth of response tends to decrease with each subsequent line of therapy. There is a gradual onset of extensive bone marrow infiltration, bulky disease, and recurrent infection. Eventually, the disease may transform into a localized high-grade lymphoma (Richter's transformation) or into prolymphocytic leukemia.

Fludarabine plus cyclophosphamide and rituximab is considered the "gold standard" first-line treatment in the UK [4] and is therefore used when clinicians decide to aim for improved PFS and response rates. Discussions, however, with a group of leading hematologists have suggested that the toxicity profile of fludarabine (particularly immunosuppression due to long-term T-cell toxicity) makes it unsuitable for around 50% of patients (generally those aged older than 65 years with comorbidities and poor performance status). These patients are treated with chlorambucil, which is generally well tolerated but has relatively poor efficacy compared with fludarabine combination chemotherapy regimens in terms of the depth of remission [5]. Chlorambucil therefore tends to be used when clinicians decide to take a palliative approach.

Bendamustine is licensed in the UK for first-line treatment of CLL (Binet stage B or C) in patients for whom fludarabine combination chemotherapy is not appropriate. It therefore offers an alternative for patients who would traditionally receive chloram-

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bucil. Data from a randomized clinical trial show that bendamustine offers substantial benefits over chlorambucil for patients with previously untreated CLL [6]. The overall response rate (ORR, i.e., the proportion of patients achieving either a complete or partial response to treatment) was significantly higher with bendamustine than with chlorambucil (68% vs. 31%; $P < 0.0001$). More patients achieved a complete response (CR) with bendamustine than with chlorambucil (31% vs. 2%; $P < 0.0001$). Median PFS (i.e., time from randomization to first progression, or relapse after remission, or death) was significantly longer with bendamustine than with chlorambucil (21.6 months vs. 8.3 months; $P < 0.0001$). The overall survival curves also showed a clear divergence in favor of bendamustine, although no statistically significant difference was observed.

Guidance issued by the UK's National Institute for Health and Clinical Excellence (NICE) in February 2011 recommended bendamustine for use within the National Health Service (NHS) in England and Wales [7]. The cost-utility analysis described below was carried out to inform the appraisal of bendamustine by NICE. Based on the clinical data described above and data from the literature, it was designed to evaluate first-line bendamustine compared with chlorambucil in patients who would be considered unsuitable for fludarabine combination chemotherapy regimens.

Methods

Model structure

A semi-Markov approach was used to estimate time in each health state. Parametric survival analyses of the overall survival end point were used directly to estimate the probability of death in each cycle. Probabilities of transitioning between health states conditional upon being alive were then applied to estimate the spread of patients across these health states over time. This approach allowed time in state to influence the probability of progression from each first-line response state and the choice to re-treat or switch to second-line treatment following progression. This enabled more accurate modeling of the cost and quality of life implications of these early transitions (on which we had the most information). Costs and health outcomes were simulated over a patient's lifetime (35 years). The analysis was conducted from the perspective of the NHS in England and Wales. The cost year for the study was 2009. In line with NICE recommendations [8], the model applied a discount rate of 3.5% per annum to costs and health outcomes. The model was programmed in Microsoft Excel (Microsoft Corporation, Redmond, WA), and all statistical analyses were conducted in SAS (SAS Institute, Cary, NC). The cycle length was 3 months, and a half-cycle correction was applied.

Figure 1 shows the model structure. All patients started treatment (with bendamustine or chlorambucil) in the stable disease (SD) health state. In the next cycle, they were allocated to their best overall response state: SD, progressive disease (PD), partial response (PR), or CR. Patients who entered the SD, CR, and PR disease states then faced a probability of progressing. Patients who progressed 12 or more months after receiving chlorambucil were re-treated ad infinitum. In line with advice from UK clinical experts, all other patients with PD faced a 50% probability of initiating the next line of treatment (fludarabine plus cyclophosphamide [FC]) or entering the best supportive care (BSC) health state. Patients receiving FC faced the possibility of response and subsequent progression to BSC. Patients remained in the BSC health state until death. Having FC as a second-line therapy might seem counterintuitive, given that bendamustine is licensed for patients who are not suitable for treatment with fludarabine combination chemotherapy. Consultation with UK clinical experts, however, confirmed that some patients would be expected to receive flu-

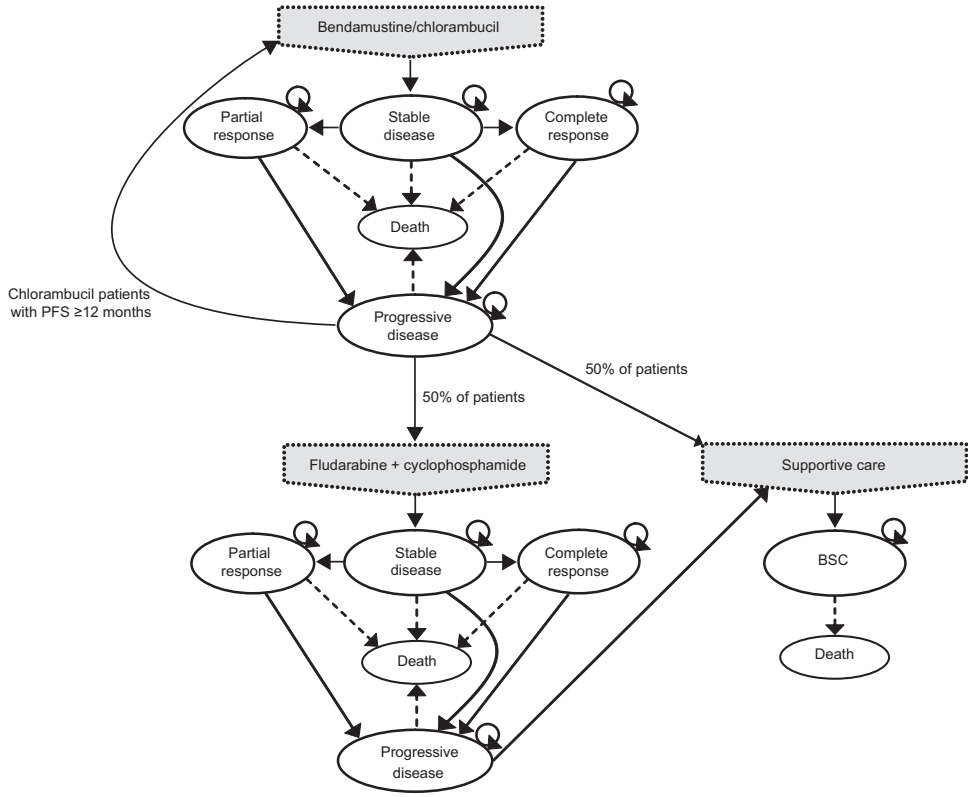

Fig. 1 – Model structure. Adverse events were modeled separately. BSC, best supportive care; PFS, progression-free survival.

darabine at second-line therapy: those who are judged to be healthier after relapse than when they started first-line therapy and those for whom no other options are appropriate. The model also included the differential adverse event profiles associated with bendamustine, chlorambucil, and FC.

Model inputs

Full systematic searches and literature reviews were carried out for major model inputs, including randomized controlled trial (RCT) data for bendamustine, CLL utility data, CLL resource-use data, and data describing the efficacy of subsequent therapies. Appropriate, recognized databases were used, including Embase, Medline, Medline In-Process, The Cochrane Central Register of Controlled Trials, EconLIT (using the OVID search platform), and the NHS Economic Evaluation Database. Full details of the systematic searches and literature reviews can be found in the submission made to NICE [9].

Clinical data

The analysis was based on data from an open-label, phase III, RCT by Knauf et al. [6]. The systematic review conducted to inform the NICE appraisal identified this as the only RCT comparing bendamustine treatment with any comparator in CLL [9]. The study included 319 patients with previously untreated Binet stage B or C CLL who were randomized to treatment with bendamustine (100 mg/m^2/d intravenously over 30 minutes on days 1 and 2 of a 28-day treatment cycle; n = 162) or oral chlorambucil (0.8 mg/kg orally on days 1 and 15 of a 28-day treatment cycle; n = 157). The dose of chlorambucil was calculated by using Broca's normalized weight (the patient's height in centimeters minus 100) and could be given as divided doses on day 1/2 and day 15/16 of each cycle if necessary. The primary outcomes were ORR and PFS. Responses were assessed after three cycles and at the end of treatment. After the last treatment cycle, patients were monitored for response and survival every 3 months. The response evaluation was based on the National Cancer Institute–Sponsored Working Group on CLL criteria [10,11]. The investigators' assessments of patients' responses were checked by an independent committee for response assessment; members of the independent committee for response assessment were blinded to treatment. Secondary end points included overall survival and quality of life. Patients' median (range) age was 63 (45–77) years in the bendamustine group and 66 (35–78) years in the chlorambucil group. More than 70% of the patients in each group had Binet stage B disease.

Transition probabilities

Table 1 shows the response rates applied in the model. Note that the percentage of patients in each response category differs from that published by Knauf et al. [6]. This is because those patients who had no examination data (14 in the bendamustine group and 19 in the chlorambucil group) were included as nonresponders in the clinical analysis but were completely excluded from the economic analysis.

Table 2 shows the results of fitting parametric survival curves to the time to progression (TTP), time to re-treatment, and overall survival data. To improve the fit to the empirical data, each analysis included a treatment covariate, regardless of statistical significance. For the TTP and overall survival analyses, exponential, Weibull, log-normal, and log-logistic parametric functions were fitted. The preferred model was selected on the basis of visual comparison of the Kaplan-Meier and fitted survival curves, and using Akaike's Information Criteria (AIC; $\alpha = 3$) as a measure of statistical goodness of fit [12]. Separate TTP curves were fitted for patients with CR, PR, and SD to reflect the increased durability of deeper remissions. For TTP in patients with CR and PR, and for overall survival, conclusions drawn from the visual comparison of the fitted and empirical survival curves and the AIC concurred. For SD, the model with the lowest AIC (the Weibull) predicted a larger difference between treatments (in favor of bendamustine) and seemed to be heavily influenced by the tail of the bendamustine curve. To be conservative, the log-logistic, which appeared to provide the best fit by visual inspection, was therefore used. Sensitivity analyses are presented using alternative parametric models; the AIC statistics and all fitted curves are given in Appendix S1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2012.03.1389.

Figure 2 shows a comparison of the empirical and fitted survival curves for TTP. Figure 3 shows the same comparison for overall survival. For time from progression to re-treatment, an exponential model was forced, as inclusion of a time-dependent probability of re-treatment would have greatly increased the complexity of the model. As shown in Figure 4, however, this provided a reasonable approximation to the observed data.

All analyses were conducted on the intent-to-treat (ITT) population from Knauf et al. [6] with patients not evaluable for response excluded (10% of the ITT population). The analysis of time from progression until next treatment also excluded patients who received an additional line of therapy prior to progression.

The parametric survival analyses of TTP counted progression only as an event, with death without progression considered as censoring. The probability of progressing in a given cycle was therefore calculated as the probability of remaining alive multiplied by the probability of progression calculated from the TTP curve. This appropriately accounts for the competing risk nature of the progression and death end points [13]. The same approach was applied to time to next treatment.

The ORR associated with chlorambucil re-treatment was estimated by scaling the first-line ORR by using data from Robak et al. [14]. In this study, 19 of the 103 patients who received first-line treatment were re-treated. Re-treatment was associated with an odds

Table 1 – Best overall response to first-line treatment.

Treatment type	Stable disease (SD + unconfirmed response)	Partial response (PR)	Complete response (CR + nPR)	Progressive disease (PD)
Bendamustine* (n = 148)				
n	23 (19 + 4)	43	67 (50 + 17)	15
%	16	29	45	10
Chlorambucil* (n = 138)				
n	37 (32 + 5)	41	7 (3 + 4)	53
%	27	30	5	38

nPR, nodular partial response.

* Patients who were not evaluated for response are excluded from this analysis (14 from the bendamustine group; 19 from the chlorambucil group).

Table 2 – Results of fitting parametric survival curves.

	Mean (SE; P)			Covariances	
	Intercept	Scale	Bendamustine	Intercept, scale	Intercept, bendamustine	Scale, bendamustine
Time to progression						
Stable disease*	−0.1052 (0.1467)	0.2600 (0.0546)	0.0513 (0.2895; P = 0.86)	0.0028	−0.0182	0.0006
Partial response†	0.1259 (0.0753)	0.4578 (0.0422)	0.5247 (0.1084; P <0.0001)	0.0002	−0.0056	0.0002
Complete response‡	0.5795 (0.2545)	0.6047 (0.0712)	0.4217 (0.2660; P = 0.11)	0.0019	−0.0640	0.0001
Time to re-treatment§	0.4097 (0.1270)	1.000 –	−0.0445 (0.1861; P = 0.81)	N/A	−0.0161	N/A
Overall survival‖	2.0203 (0.1407)	0.7106 (0.0782)	0.3611 (0.1842; P = 0.05)	0.0065	−0.0097	0.0031

N/A, not applicable; SE, standard error.
* Distribution = log-logistic; events = 10; censored observations = 50.
† Distribution = log-normal; events = 61; censored observations = 23.
‡ Distribution = log-normal; events = 41; censored observations = 33.
§ Distribution = exponential; events = 116; censored observations = 57.
‖ Distribution = Weibull; events = 65; censored observations = 221.

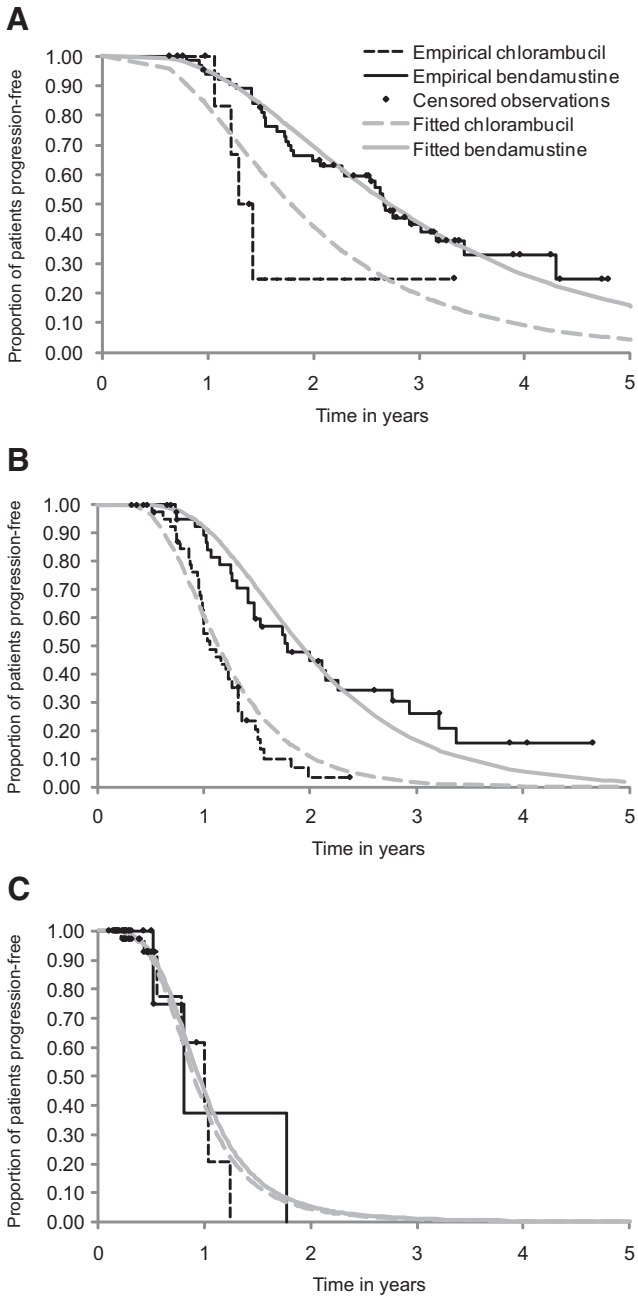

Fig. 2 – Comparison of modeled and empirical time-to-progression data. (A) Complete responders, (B) partial responders, and (C) patients with stable disease.

ratio for overall response of 0.70 (95% confidence interval 0.26–1.86) compared with first-line treatment. The ratio of CR to PR and of SD to PD patients among those re-treated was assumed to be equal to first-line treatment. A hazard ratio (HR) comparing first-line with re-treatment PFS (17 months [n = 103] and 12 months [n = 19], respectively) was derived assuming constant hazards. This was again used to scale the first-line estimate for chlorambucil TTP. Because TTP was not available by response category, response-specific progression probabilities were estimated by using HRs comparing TTP across response categories from Knauf et al. [6] (HR, 95% confidence interval: CR vs. SD = 0.11, 0.05–0.23; PR vs. SD = 0.29, 0.14–0.58) and by assuming constant hazards.

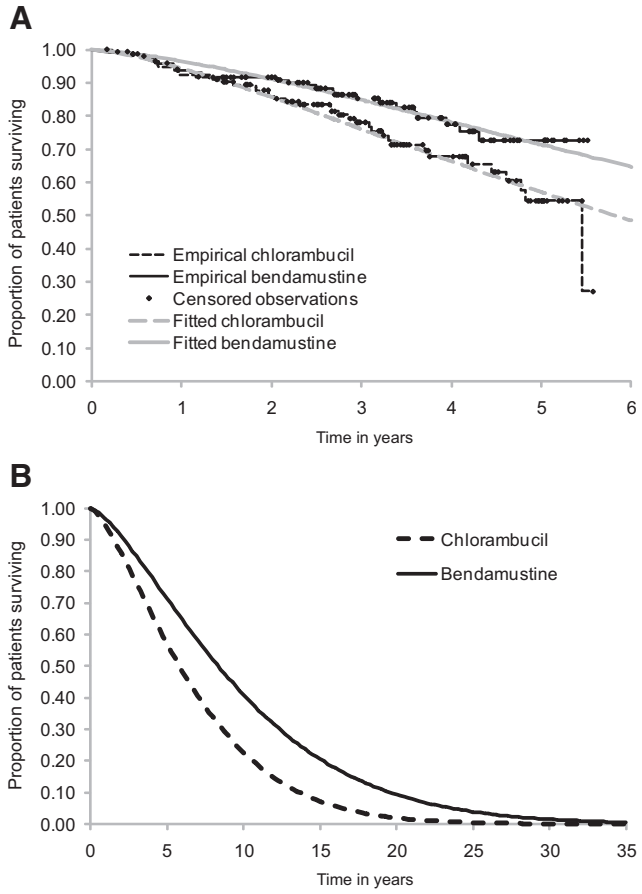

Fig. 3 – Comparison of modeled and empirical overall survival data. (A) Within trial period and (B) long-term extrapolation.

Response rates for FC were estimated from 276 patients receiving second-line FC as part of an RCT (Robak et al. [15]). This study estimated that the proportions of patients with a best overall response of CR, PR, SD, or PD are 15%, 53%, 26% and 6%, respectively. It also estimated that PFS is 20.6 months for all patients (n = 236) and 27.7 months for responders (n = 160). Response-specific probabilities of progression were estimated by using these data, the data comparing TTP between CR and PR patients from Knauf et al., and by assuming constant hazards.

Utility values

Table 3 shows the utility values used in the model. For the treatment period, utility was estimated by mapping European Organisation for Research and Treatment of Cancer C30 quality of life data (collected by Knauf et al.) to EuroQol five-dimensional questionnaire utilities by using a mapping algorithm developed by McKenzie and van der Pol [17]. This algorithm uses data from 199 patients with inoperable esophageal cancer and has been found to predict reasonably well for patients with utilities greater than 0.50 [18], who are thought to comprise most of our target patient group. A baseline value that was independent of treatment was calculated from 242 patients with baseline data. Data were pooled between the two treatment groups because there was no statistically significant treatment difference in overall quality of life during the treatment period; the resulting estimate can be thought to represent the SD state. After the treatment period, utility increments or decrements relative to "no change" were estimated from a vignette study by Beusterien et al. [16] and applied to the baseline value to reflect response level and treatment line.

The model captured the quality of life impact of the following adverse events: grade 1 to 2 nausea, nausea with vomiting, and diarrhea; grade 3 to 4 anemia, pyrexia, and pneumonia. Utility decrements were applied for the duration of the cycle. For patients who experienced these events, it was assumed that they occurred during every treatment cycle, with the exception of pyrexia and pneumonia, which were assumed to be experienced only once.

Costs

Table 4 shows the costs associated with treatment with bendamustine, chlorambucil, and FC (which was included as a subsequent line of therapy in the model). Doses and number of cycles were taken from Knauf et al. [6], Catovsky et al. [5], and Robak et al. [15]. Treatment costs for chlorambucil were assumed to be equivalent for first-line and re-treatment. It was also assumed that all patients receiving bendamustine and FC would receive prophylactic antiemetics.

Resource use for health states and adverse events were derived from an advisory board conducted in January 2010 with five hematologists who work in the UK NHS and are experienced in treating CLL. The advisory board members were paid for their professional service in accordance with the Association of the British Pharmaceutical Industry guidelines. Patients in all health states were assumed to have regular appointments with their hematologist and regular monitoring (full blood cell count and routine biochemistry). These resources are incurred each month for patients in the SD health state, every 3 months for those in the PR state, and every 6 months for those in the CR state. Patients in the PD/BSC state were assumed to incur these resources every 3 weeks and also receive a blood transfusion (two units of red blood cells). The resulting costs per 3-month cycle are £405 for SD, £135 for PR, £68 for CR, and £1924 for PD/BSC.

Unit costs were from the British National Formulary 59 [19], NHS reference costs 2008-9 [20], and the NHS Blood and Transplant Annual Review 2008-2009 [22]. Table 5 shows the unit costs used. Table 6 shows the costs associated with adverse events.

Sensitivity analyses

Sensitivity analyses were carried out on the following parameters: first-line response rates, treatment effect covariates in survival analyses, re-treatment algorithm and efficacy, FC efficacy, patient weight, health state costs, cost of FC, adverse event costs, utility data sources, time until quality of life benefit of treatment emerges, adverse event disutility, discount rates, and time horizon.

To test the cost-effectiveness of bendamustine across a heterogeneous patient group, the model analyzed the following three subgroups: age 65 years or more, World Health Organization per-

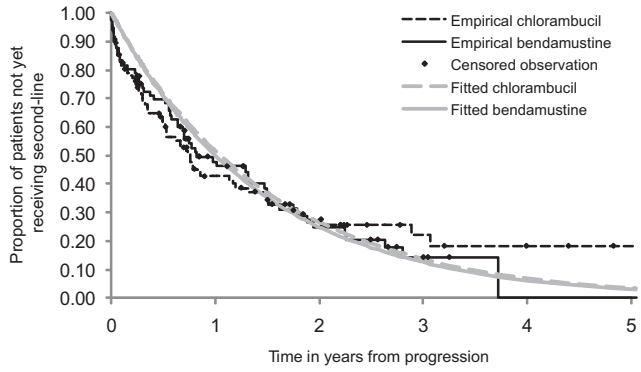

Fig. 4 – Comparison of modeled and empirical time to next treatment data.

Table 3 – Utilities applied in the model (both treatment groups).

	Mean ± SD	95% confidence interval (lower, upper)
Baseline utility (used for both treatments during active treatment [time 0–4.9 mo]; used as baseline utility throughout model) [6]	0.70 ± 0.22	0.67, 0.73
Unadjusted utility values from Beusterien et al. [16]*		
Complete response	0.91 ± 0.11	0.88, 0.93
Partial response	0.84 ± 0.14	0.81, 0.87
No change	0.78 ± 0.14	0.75, 0.82
Progressive disease	0.68 ± 0.20	0.64, 0.72
No change + 1–2 nausea	0.73 ± 0.17	0.69, 0.76
No change + 1–2 nausea/vomiting	0.73 ± 0.16	0.69, 0.76
No change + 1–2 diarrhea	0.70 ± 0.19	0.66, 0.74
No change + 3–4 anemia	0.69 ± 0.18	0.65, 0.72
No change + 3–4 pyrexia	0.67 ± 0.17	0.63, 0.70
No change + 3–4 pneumonia	0.58 ± 0.19	0.54, 0.62
No change + second-line treatment	0.71 ± 0.17	0.68, 0.75

* These values are recharacterized as increments from "no change" and applied to the baseline utility in the model, e.g., the complete response utility level in the model = 0.70 + (0.91 − 0.78) = 0.83.

formance status 1 or more, age 65 years or more plus World Health Organization performance status 1 or more. To simulate long-term costs and health outcomes in these subgroups, the model required two alterations. First, the distributions of patients across response categories for the relevant subgroup were obtained; second, a dummy covariable for the subgroup was included in all survival analyses. All survival analyses used the parametric distributions from the base-case.

Probabilistic sensitivity analysis was also carried out. Distributions were assigned to each parameter subject to sampling uncertainty (all parameters other than unit costs), and 5000 random draws were used to propagate this uncertainty through the model.

The following distributions were used to model uncertainty around first-line treatment outcomes: Dirichlet for the distribution of patients across best overall response levels (CR/PR/SD/PD) and multivariate normal for parameters of parametric survival distributions (TTP, overall survival, and time to re-treatment outcomes).

The Dirichlet distribution was also used to represent uncertainty around best response to FC (CR/PR/nonresponder). Median TTPs following re-treatment or second-line treatment were derived by assigning a beta distribution to the proportion of patients alive at the median time point.

Ratio statistics (odds ratio for response to chlorambucil in re-treated vs. treatment-naïve patients; HRs comparing TTP across response categories used to inform re-treatment and second-line TTP) were assigned log-normal distributions.

Uncertainty around the proportion of patients (cycles) in which adverse events were experienced was modeled using beta distributions for all lines of treatment. The beta distribution was also used to represent uncertainty in the utility estimates. Resource-use estimates reported as proportions were assigned beta distributions. Resource-use estimates reported as counts and all (non-drug) unit costs were assigned gamma distributions. Numbers of cycles of treatment administered were assigned normal distributions, with random draws restricted to be non-negative (because negative draws were extremely rare, this restriction has no material impact).

The point estimates and variance parameters reported above were used to parameterize each distribution. In some cases, no variance parameters were available and the following assumptions were therefore made: where cost estimates were taken from NHS reference costs, the lower and upper quartiles reported were assumed to represent 75% confidence intervals; where count data were estimated from expert opinion or unit costs taken from nonreference cost sources, standard errors were assumed to equal half of the mean; where proportions were taken from expert opinion, this was assumed equivalent to a sample of 100 patients.

Results were presented as distributions of simulations on the cost-effectiveness plane and cost-effectiveness acceptability curves. An expected value of perfect information (EVPI) analysis was also conducted. EVPI was estimated as the average difference between the net benefit of the technology that offers the maximum net benefit in a given simulation and the expected net benefit of the technology that maximizes net benefit on average across all simulations. This was then multiplied by the number of patients expected to benefit from the information. The number of patients expected to benefit from the information in England and Wales was estimated as the discounted sum of a 10-year stream of 1079 incident cases per annum [9] (average for 2010–2014 used to extrapolate for 10 years).

Results

Table 7 shows the base-case results. The deterministic incremental cost-effectiveness ratio (ICER) of £11,960 per quality-adjusted life-year (QALY) (£11,974 in the probabilistic analysis) indicates that although bendamustine has higher acquisition and administration costs than chlorambucil, the modeled health benefits (i.e., increased quality of life and overall survival) are good value at conventional decision thresholds (£20,000–£30,000 per QALY). Treatment acquisition accounts for 30% of the difference in treatment costs; routine follow-up costs account for 59% of the difference (this is driven by patients treated with bendamustine living for longer). The model predictions provided a close fit to the empirical data with respect to PFS and overall survival [9]. Figure 5 shows the proportion of the bendamustine QALY and life-year advantage over chlorambucil accrued at each point in the model time horizon. For example, at 10 years, 58% of the QALY gain and 50% of the life-year gain has been accrued.

Table 8 shows the results of the key deterministic sensitivity analyses. Results of supplementary analyses can be found in Appendix S2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2012.03.1389. None of the deterministic sensitivity analyses increased the ICER by more than £2000 per QALY. Of

Table 4 – Treatment costs.

Items	Bendamustine	Chlorambucil (comparator)	FC
Technology cost	25 mg × 5 = £347.26 25 mg × 20 = £1379.04 100 mg × 5 = £1379.04 100 mg/m^2 body surface area on days 1 and 2, every 4 wk Average body surface area: 1.72 m^2 Mean number of cycles: 4.9 (SE = 0.13)	2 mg × 25 = £8.36 0.8 mg/kg Broca's weight days 1 and 15, every 4 wk Broca's weight: 68.73 Mean number of cycles: 4.9 (SE = 0.14)	F: 10 mg × 20 = £357.49 C: 50 mg × 100 = £13.85 F: 25 mg/m^2 3 d per cycle C: 250 mg/m^2 3 d per cycle Average body surface area: 1.72 m^2 Mean number of cycles: 4.6 (SE = 0.20)
Mean cost of treatment (per course, assuming full wastage)	£4741.54	£91.76	£1250.54
Infusion cost	First infusion = £272.10 Subsequent infusions (cost per infusion) = £226.88	Not applicable	Not applicable
Hematologist outpatient visit	One per cycle = £130.71	One per cycle = £208.92 (cost for oral chemotherapy administration)	One per cycle = £208.92 (cost for oral chemotherapy administration)
Blood count	One per month = £2.97	One per month = £2.97	One per month = £2.97
Biochemistry	One per month = £1.34	One per month = £1.34	One per month = £1.34
Antiemetic cost per cycle	50% Maxolon* (87.5 mg/cycle) and 50% domperidone (70 mg/cycle) £0.24	None—except when having an adverse event	50% Maxolon* (87.5 mg/cycle) and 50% domperidone (70 mg/cycle) £0.24
Total	£7673.00	£1136.60	£2232.51

Notes. Costs are UK sterling.
Pharmaceutical prices taken from British National Formulary 59 (excluding bendamustine) [19]; FC dosage taken from Robak et al. [15]; dosages and mean cycles of bendamustine/chlorambucil taken from Knauf et al. [6]; mean cycles of FC taken from Catovsky et al. [5] because these data were not reported in Robak et al. [15]. Cost of infusions, outpatient visits, blood cell counts, and biochemistry taken from NHS reference costs 2008-9 [20]. Resource use estimated by an advisory board of five UK hematologists (antiemetic use also taken from Herrstedt and Roila [21]). NHS reference cost codes are available from Napp Pharmaceuticals Limited's NICE appraisal manufacturer submission document [9].
C, cyclophosphamide; F, fludarabine; FC, fludarabine plus cyclophosphamide; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence; SE, standard error.
* Maxolon is a trade name for metoclopramide.

particular interest are the results obtained when treatment effect on overall survival was removed. Although the QALY advantage of bendamustine was substantially decreased, this was offset by a reduction in incremental costs owing to the removal of the additional cost of extending life in bendamustine patients. The net effect of these changes on the ICER was small.

Table 5 – Health state costs.

	Unit cost (£)
Consultant hematologist	130.71
Full blood cell count	2.97
Routine biochemistry	1.34
Blood transfusion	
Administration	84.60
Blood cells (2 units)	261.46

Notes. Costs are UK sterling.
Costs taken from NHS reference costs 2008-9 [20] and NHS Blood and Transplant Annual Review 2008-2009 [22]. NHS reference cost codes are available from Napp Pharmaceuticals Limited's NICE appraisal manufacturer submission document [9]. Resource use estimated by an advisory board of five UK hematologists.
NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence.

The subgroup analysis showed bendamustine to be cost-effective across a heterogeneous patient group. In each of the subgroups analyzed, the ICER remained below £14,000 per QALY.

Figure 6 shows the results of the probabilistic sensitivity analysis as distributions of simulations on the cost-effectiveness plane and as a cost-effectiveness acceptability curve. At the £20,000 per QALY threshold, the probability of bendamustine being cost-effective is 90%. The expected value of information associated with the decision problem is £403. Based on a 10-year stream of 1079 cases per annum, the EVPI is estimated at £3.7 million at a willingness-to-pay threshold of £20,000 per QALY and £0.8 million at a threshold of £30,000 per QALY.

Discussion

Before the introduction of bendamustine, chlorambucil was the preferred first-line treatment option for patients with CLL who would be considered unsuitable for fludarabine combination chemotherapy regimens. Clinical data have shown that patients treated with bendamustine have significantly better response rates and longer PFS than those treated with chlorambucil [6]. The high CR rate achieved with bendamustine is important, because there is evidence that CR is associated with longer PFS [28–31]. Longer PFS equates to longer time without symptoms and treatment, and hence to longer time in an improved health state. This correlates with improved quality of life for patients. There is also

Table 6 – Adverse event costs.

Adverse event	Frequency of event			Treatment	Unit cost (£)	Total units (mg/appointments/ admission days)	Total cost per adverse event episode (£)
	Bendamustine (n = 161; cycles = 783)	Chlorambucil (n = 151; cycles = 733)	FC (n = 272)				
Cytopenias—GCSF use	3% of cycles	0.3% of cycles	—	IV infusion (hematologist consultation)	130.71	1.00	817.09
				GCSF (pegfilgrastim)	686.38	1.00	
Cytopenias—erythropoietin use	0.5% of cycles	0.3% of cycles	—	Erythropoietin	1188.61	1.00	1188.61
Nausea (grade 1 or 2)	4.4% of patients (18.7%–14.3%)	6.6% of patients (13.2%–6.6%)	45% of patients	Metoclopramide (50%)	0.004	87.5	0.24
				Domperidone (50%)	0.002	70	
Nausea/vomiting (grade 1 or 2)	14.3% of patients	6.6% of patients	51% of patients	Metoclopramide (50%)	0.004	87.5	0.24
				Domperidone (50%)	0.002	70	
Anemia (grade 3 or 4)	5.7% of cycles (used for costing);	2.1% of cycles (used for costing);	35% of patients	Transfusion	346.06	1	453.12
				Nurse consultation 50%	83.40	1	
	2.5% (used in utility calculations)	0% (used in utility calculations)		Hematologist consultation 50%	130.71	1	
Pyrexia (grade 3 or 4)	1.9% of patients	1.3% of patients	42% of patients	IV antibiotics (Tazocin*)	0.003	126,000	3076.99
				Inpatient admission	2652.23	1	
Pneumonia (grade 3 or 4)	1.9% of patients	0% of patients	17% of patients	IV antibiotics (Tazocin*)	0.003	126,000	2188.00
				Inpatient admission	1763.24	1	
Diarrhea (grade 1 or 2)	8.7% of patients	4% of patients	32% of patients	Loperamide (50%)	0.018	21	0.43
				Codeine (50%)	0.002	270	

Notes. Costs are UK sterling. Pharmaceutical costs taken from British National Formulary 59 [19], except erythropoietin cost, which was taken from Wilson et al. [23]. Costs taken from NHS reference costs 2008-9 [20] and NHS Blood and Transplant Annual Review 2008-2009 [22].

Frequency of events with bendamustine and chlorambucil taken from the study by Knauf et al. [6]. Frequency of events with FC taken from Robak et al. [15]. NHS reference cost codes are available from Napp Pharmaceuticals Limited's NICE appraisal manufacturer submission document [9].

FC, fludarabine plus cyclophosphamide; GCSF, granulocyte colony-stimulating factor; IV, intravenous; NHS, National Health Service; NICE, National Institute for Health and Clinical Excellence.

* Tazocin is a trade name for piperacillin with tazobactum.

Table 7 – Base-case results.

	Costs (£)						Total LYG	Total QALY	ICER (£/QALY)
	Acquisition	Administration	Adverse events	FC treatment	Routine follow-up	Total			
Bendamustine	4,726	2,922	375	935	40,043	49,000	7.81	4.82	—
Chlorambucil	150	1,706	190	710	31,065	33,821	5.83	3.55	—
Incremental	4,576	1,216	185	226	8,978	15,179	1.99	1.27	11,960

Note. Costs are UK sterling.
Incremental = bendamustine – chlorambucil.
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

some evidence of a link between CR and overall survival. In an updated analysis of the study by Knauf et al. [32], patients who achieved a CR (regardless of whether they were treated with bendamustine or chlorambucil) had a significantly longer overall survival than did those who did not (median not reached vs. 75.9 months, respectively; $P < 0.0018$). This cost-utility analysis shows that bendamustine has an ICER below the thresholds commonly applied in England and Wales. It is therefore a cost-effective treatment option (as well as a clinically effective one) for patients who would be considered unsuitable for fludarabine combination chemotherapy regimens.

The EVPI analysis estimates a relatively low value of further research (£0.8–£3.7 million depending on the threshold). Given that this represents the upper bound on the value to further research, and does not take account of what would be achievable with a feasible sample size, it seems unlikely that further research (particularly expensive clinical research) to inform this decision problem would be worthwhile. Estimation of the expected value of partial perfect information for different parameter groups, however, would be required to confirm this for other research designs.

There are currently no definitive criteria for determining which patients would be unsuitable for treatment with fludarabine combination therapy. In the absence of any formal criteria, the decision about first-line treatment in the "real-world" setting is currently a matter of physician (and patient) judgment. Factors that influence the decision include performance status, age, and comorbidities. Given the lack of specific criteria, the group of patients currently treated with chlorambucil in the UK is heterogeneous with respect to these three parameters. The model did not exclude any patients from the study by Knauf et al. and therefore used a population that was heterogeneous with respect to age and performance status. In addition, the subgroup analyses confirmed that bendamustine appears cost-effective even if the patient population is restricted to elderly patients (≥65 years old), patients with a low performance status (World Health Organization status ≥1), or patients who fulfill both these criteria. This demonstrates that bendamustine is cost-effective across the heterogeneous patient group that is likely to receive it.

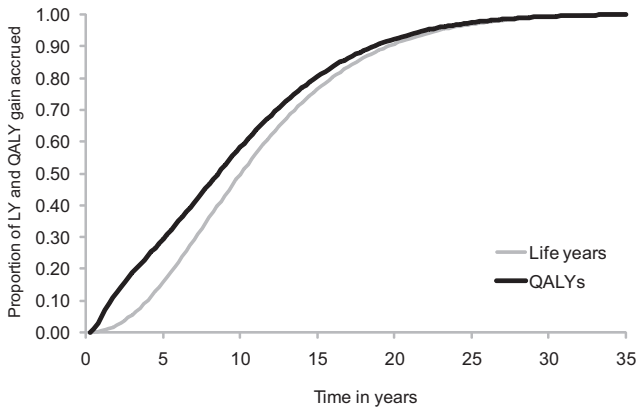

Fig. 5 – Impact of time horizon on incremental QALYs and life-years. LY, life-year; QALY, quality-adjusted life-year.

We designed the economic model primarily to reflect the treatment pathway of CLL patients in England and Wales, and to take into account the health benefits and costs expected for these patients. The chosen design accurately captured the differential gains in quality of life that patients experience according to the depth of their clinical remission, as each level of clinical remission was associated with a different TTP curve. We based the model on direct randomized trial evidence comparing bendamustine with the appropriate comparator (chlorambucil). The model included subsequent lines of therapy to reflect a real-world treatment setting, in which patients can respond to a future therapy after entering a PD health state. Inclusion of time-dependent transition probabilities, where feasible, increased the model's accuracy. We developed a version of the model for Scotland, which we submitted to the Scottish Medicines Consortium for appraisal. The Scottish Medicines Consortium's advice document stated that the economic case was demonstrated and that bendamustine is accepted for use in Scotland [33].

In the study by Knauf et al., quality of life data were collected only during the treatment period and patients were not followed up long-term with respect to quality of life. This meant that we could not use these data to inform the utility differences between different health states beyond the treatment period. These post-treatment utility differences were therefore estimated by using vignette-based utility values, as in previous NICE appraisals and published models [26,27]. Baseline utility in the model was estimated by mapping from the European Organisation for Research and Treatment of Cancer C30 to the EuroQol five-dimensional questionnaire by using an algorithm developed by McKenzie and van der Pol [17]. This algorithm was developed by using data from a quite different patient population (inoperable esophageal cancer); however, its validity has been supported by analysis of a population of non-Hodgkin's lymphoma patients [18]. Alternative mapping algorithms are available [18], and use of these algorithms may impact on the model results, though we believe this would be unlikely to alter the ICER substantively because it would affect both comparators.

The analyses of clinical events were based on the ITT population from Knauf et al., with those patients not evaluated for response excluded (to allow transitions probabilities conditional upon response to be estimated). These patients represented 10% of the randomized cohort: 9% in the bendamustine group and 12% in the chlorambucil group. Comparison of the predictions made by the model and the ITT clinical results suggests that this is unlikely to have biased the model results substantively. For example, modeled PFS for bendamustine at 12, 24, and 36 months was 74%, 42%, and 21%, respectively, whereas for the ITT Kaplan-Meier analysis, estimates of 79%, 48%, and 31% were observed. Modeled PFS for chlorambucil at the same time periods was 31%, 6%, and 1%, re-

Table 8 – Results of sensitivity analyses.

Variable	Base-case	Sensitivity analysis	ICER (£)
Treatment covariate			
Stable disease TTP	Included	Excluded	12,007
Partial response TTP	Included	Excluded	13,387
Complete response TTP	Included	Excluded	12,382
Time to re-treat	Included	Excluded	11,982
Overall survival	Included	Excluded	10,997
First-line response			
Chlorambucil overall response	Base-case	Upper CI	12,599
		Lower CI	11,362
Bendamustine overall response	Base-case	Upper CI	11,103
		Lower CI	12,950
Chlorambucil complete response/overall response	Base-case	Upper CI	12,319
		Lower CI	11,741
Bendamustine complete response/overall response	Base-case	Upper CI	11,473
		Lower CI	12,454
Re-treatment			
Re-treatment algorithm	Base-case	Bendamustine re-treatment if TTP >24 mo	8,722
		First-line efficacy for re-treatment	8,030
Efficacy re-treatment data source	Robak et al. [14]	Montserrat et al. [24]	11,450
Cutoff duration of response for re-treatment with chlorambucil	12 mo	6 mo	12,915
		24 mo	10,769
Cutoff duration of response for re-treatment with bendamustine	No re-treatment	6 mo	6,698
		12 mo	7,510
FC efficacy			
FC data source	Robak et al. [15]	O'Brien et al. [25]	11,152
Costs			
Patient body surface area	1.51–1.75 m^2	1.26–1.50	11,412
		1.76–2.00	12,492
		2.01–2.25	13,041
Health state costs	Include	Exclude	4,886
		+20%	13,375
		−20%	10,545
Costs of FC acquisition and administration	Include	Exclude	11,812
		+20%	11,990
		−20%	11,931
Adverse event costs (bendamustine/chlorambucil)	Include	Exclude	11,815
		+20%	11,989
		−20%	11,931
Utilities			
Source	Beusterien et al. [16]	NICE technology appraisal guidance 119 (fludarabine) [26]*	11,024
		NICE technology appraisal guidance 174 (rituximab) [27]†	10,607
Allow response impact on quality of life during treatment	No	Yes	11,803
Adverse event utilities (bendamustine/chlorambucil)	Include	Exclude	11,815
		+20%	11,989
		−20%	11,931
Decision maker			
Discount rate (costs/outcomes)	3.5%	0%	12,256
		6%	11,842
Time horizon	35 y	Trial duration (68 mo)	8,551
		10 y	10,371
		20 y	11,755
		30 y	11,944

Note. Costs are in sterling.

CI, confidence interval; FC, fludarabine plus cyclophosphamide; ICER, incremental cost-effectiveness ratio; TTP, time to treatment progression.

* Utility of 0.74 for any on-treatment states (no further impact of adverse events modeled), utility of 0.80 for any response states, and utility of 0.60 for any progressed states.

† Utility of 0.80 for first-line preprogression, and utility of 0.60 from first progression until death.

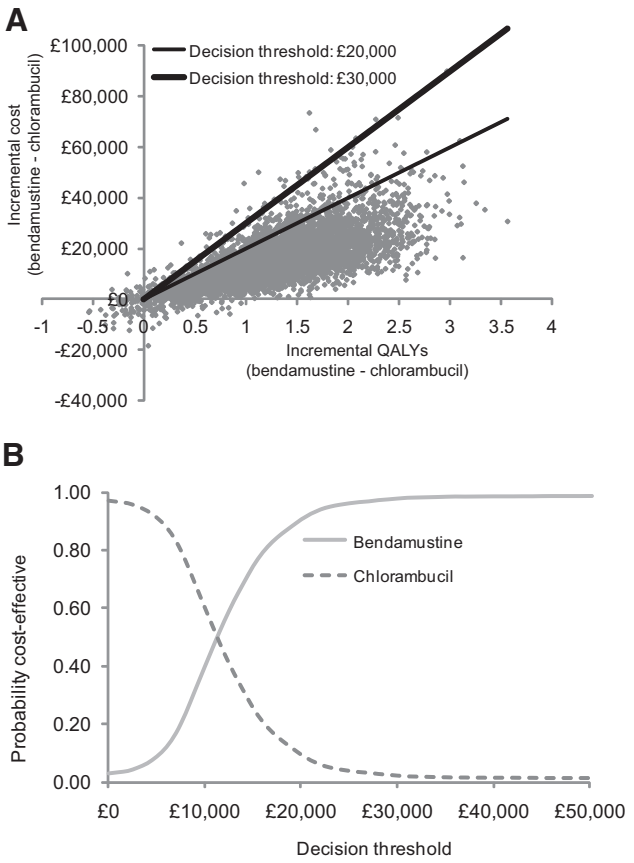

Fig 6 – Results of probabilistic sensitivity analysis (5000 simulations). (A) Distributions of simulations on the cost-effectiveness plane and (B) cost-effectiveness acceptability curve. QALY, quality-adjusted life-year.

spectively, compared with ITT estimates of 35%, 3%, and 1%. Modeled overall survival for bendamustine at 12, 36, and 54 months was 97%, 85%, and 71%, respectively, compared with ITT estimates of 92%, 84%, and 70%. Modeled overall survival for chlorambucil at the same time periods was 94%, 76%, and 57%, respectively, compared with ITT estimates of 92%, 78%, and 55%.

The study by Knauf et al. [6] established progression status every 3 months; data for this end point are therefore interval censored, because we only know the time interval during which an event occurred, not the exact date of the event. In line with the clinical analysis, the cost-effectiveness modeling did not take account of the interval-censored nature of the data and instead used the date of observed progression as the event date. This approach biases the median PFS upward, although the difference between treatment groups should not be systematically biased [34]. Again, it is not expected that this would have substantively impacted the ICER. Further research to establish the impact of interval censoring on cost-effectiveness analysis generally, however, is warranted.

The NICE Evidence Review Group report issued during the NICE appraisal process described the model as high quality [35]. It disagreed, however, with some assumptions in the model: 1) that patients in PD have a blood transfusion every 3 weeks (the report stated that an assumption of a transfusion every 4 weeks in the last 6 months of life is more appropriate); 2) that the HR for overall survival is 1.66 (the report stated that the latest data showed this to be 1.3 [32]). It also disagreed with the assumptions around dose intensities and how often patients would visit a hematologist while not being treated. Updating the model by using the Evidence Review Group's assumptions gave an alternative base-case ICER of £9400 per QALY.

Further work could be undertaken to look at the effect of subsequent lines of therapy and cross-over on the overall survival benefit [36]. This may be of interest because during trial follow-up patients receiving first-line chlorambucil were more intensively treated postprogression than those receiving first-line bendamustine. Sixty-three percent of patients who received first-line chlorambucil received further antineoplastic treatment (and 29% received bendamustine) compared with 49% of bendamustine patients (13% were re-treated with bendamustine) [9].

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi 10.1016/j.jval.2012.03.1389 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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