

Cost Utility Analysis of Alectuzumab Compared With Chlorambucil in Untreated Patients With High-Risk (17p-) Chronic Lymphocytic Leukaemia in the United Kingdom

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ABSTRACT

OBJECTIVES: Compare costs and outcomes of alectuzumab and chlorambucil as first-line treatment for patients with high-risk (17p-) chronic lymphocytic leukaemia (CLL) in the United Kingdom.

METHODS: A lifetime Markov model was developed. Patients were modeled receiving treatment and moving through post-treatment response and progressive disease. Three possible lines of chemotherapy were considered, followed by final disease progression and death. Patients had CLL, were chemotherapy naïve, and exhibited deletion of the chromosome 17p, a defect associated with poor prognosis and failure to respond to other CLL therapies. Response rate and duration at first line were taken from a recent randomized study, the CAM307 trial; for subsequent lines of therapy, a review of the clinical literature was conducted. Utility was estimated from a survey of the general public using a time-trade-off methodology. Costs were calculated from the perspective of the UK National Health Service. Future costs and benefits were discounted at 3.5%.

RESULTS: When overall survival (OS) was assumed to be equal, treatment with alectuzumab instead of chlorambucil increased lifetime cost per patient from £10,957 to £17,938 and increased QALYs per patient from 1.59 to 1.96 at a cost of £18,788 per QALY gained. When OS was allowed to vary to reflect differences in progression-free survival, the cost per QALY fell to £14,604. Findings were most sensitive to the response rate, duration at first line, and costs of therapies.

CONCLUSIONS: This study found that in the United Kingdom, the cost per QALY gained with first-line alectuzumab therapy over chlorambucil is £18,788 in high-risk (17p-) CLL patients.

INTRODUCTION

Background

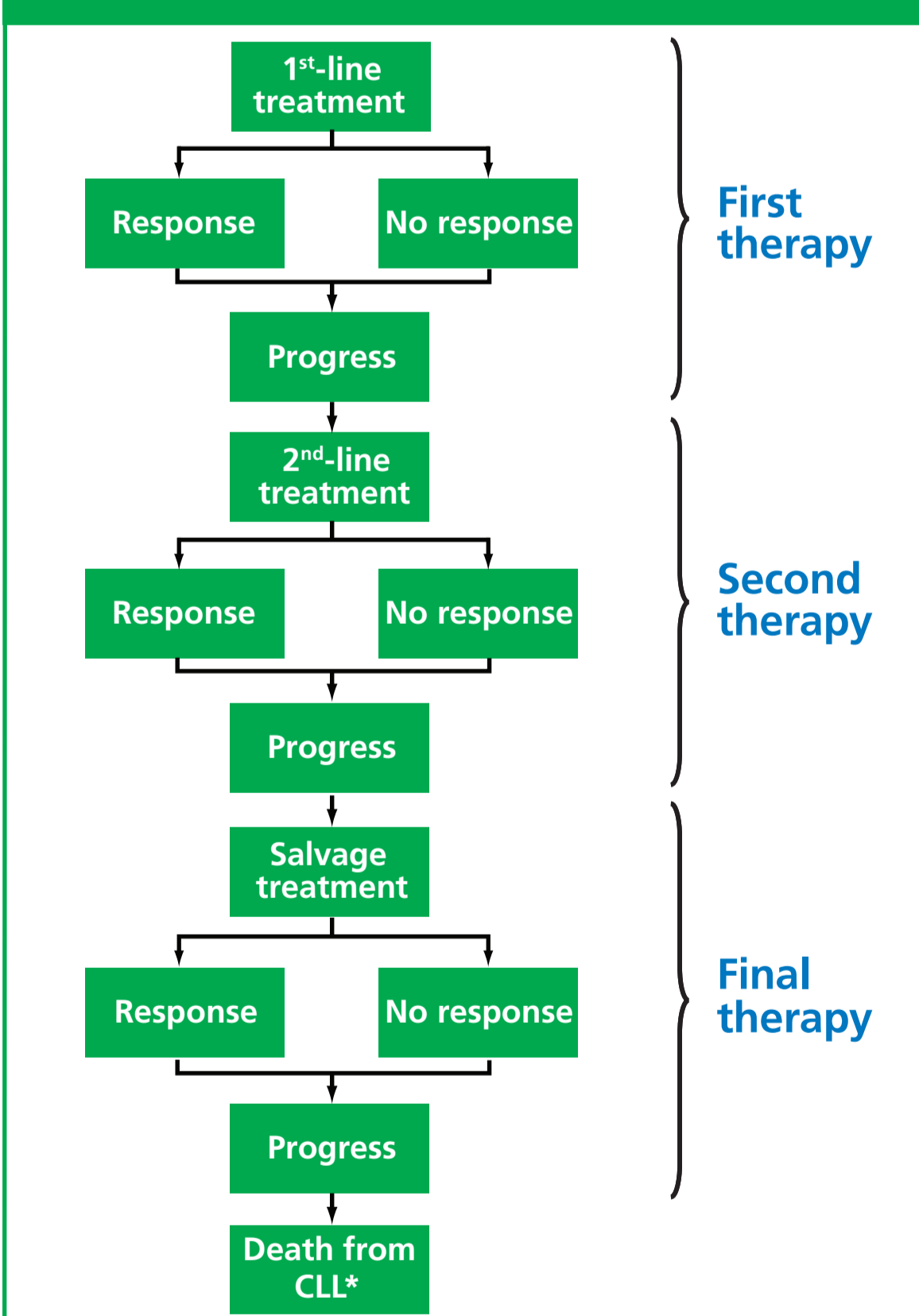
- Measurement of mortality in chronic lymphocytic leukaemia (CLL) requires long-term follow-up and is confounded by crossover and nondisease mortality
- To date, no therapy for CLL has shown a significant effect on overall survival (OS). The British Committee for Standards in Haematology (BCSH) guidelines refer to a strategy of aiming for prolonged disease-free survival in the hope that this will translate into superior OS¹
- Alectuzumab (MabCampath®) is an anti-CD52 monoclonal antibody indicated for the treatment of patients with CLL²
- A randomized phase III study (CAM307) was conducted to evaluate the efficacy and safety of first-line therapy with alectuzumab compared with chlorambucil in patients with CLL³
- The study found significant ($P < 0.001$) improvements over chlorambucil in response rates and progression-free survival (PFS)³
 - PFS: 14.6 vs 11.7 months (primary end point)
 - Overall response rate (ORR): 83% vs 55%
 - Complete response (CR) rate: 24% vs 2%
- Patients with 17p deletion (hence p53 mutation) are resistant to conventional chemotherapy such as alkylating agents (eg, cyclophosphamide) and purine analogues (eg, fludarabine), thus having an unmet clinical need⁴
- Alectuzumab has demonstrated activity in this patient subgroup⁵ and is recommended by the NCCN and ESMO guidelines^{6,7}

Objective

- Compare costs and outcomes of alectuzumab and chlorambucil as first-line treatment for patients with high-risk (17p-) CLL in the United Kingdom

METHODS

Figure 1. Schema of Lifetime Markov Model



*Patients may also die in any state (CLL or non-CLL mortality).

Comparator

- Alectuzumab 30 mg 3 times a week for up to 12 weeks vs chlorambucil 40 mg/m² PO once every 28 days for up to 12 cycles (as per CAM307 protocol)
- Currently, the most widely used first-line treatment for CLL in the United Kingdom is chlorambucil (51%), and the second most widely used is fludarabine-cyclophosphamide (FC) combination (26%)⁸

Patient Group

- Patients with previously untreated, progressive CLL harboring 17p deletion

Perspective

- Costs to the National Health Service (NHS) and health benefits to patients in the United Kingdom were considered
- The main cost drivers relate to therapeutic interventions and hospital care; therefore, a direct NHS cost approach is justified

Time Horizon

- A time horizon of 260 cycles of 28 days each (20 years) is used in the model
- CLL is a slowly progressing malignancy, and UK data suggest that more than 15% of patients were diagnosed more than 10 years in the past. In the economic model, less than 0.5% of patients are still alive 20 years after initial therapy. Different time horizons are explored in the sensitivity analysis

Utility

- A recent review concluded that "the literature on the quality of life of CLL patients is very limited"⁹
- No preference-based utility values that meet the UK standards were identified from the literature, so a new utility study was conducted

METHODS (CONT)

Data Collection

- The 17p- subgroup of the CAM307 study was the principal data source for the base case in this evaluation
- Patient-level data from the CAM307 study were used to calculate PFS for first-line treatment (Table 1)
- Patient-level data were not available for subsequent therapies, so these parts of the model were based on literature estimates (Table 2)
- CHOP was selected as a second-line therapy because
 - It is an accepted therapy for pre-treated CLL
 - It is available to patients who are not appropriate candidates for fludarabine combination treatments
 - It is supported by a body of evidence published as full papers
- For sensitivity analyses, second-line therapy was changed to high-dose methylprednisolone or allogeneic stem cell transplantation

Resource Use and Unit Costs

- The quantities of resources used are based on patient-level clinical data from the CAM307 study for first-line treatment and data from the literature for second-line and salvage treatments (Tables 1 and 2)
- Unit costs are taken from NHS reference costs¹⁰ and the British National Formulary (BNF)¹¹ (Table 3)
- Both costs and outcomes were discounted at 3.5% per year
- Haematological toxicities such as grade 3 neutropenia and anaemia occur frequently in CLL but may be asymptomatic and hence not result in management costs, unless the patient requires hospital care due to infection or another complication
- These parameters were therefore reviewed in interviews with 5 haematologists/medical oncologists experienced in the management of CLL, and the experts' values were used to estimate the likelihood that these patients would require hospital care

RESULTS

Patient Outcomes

Table 1. Patient Efficacy Results for First Line of Therapy in 17p- Subgroup of the CAM307 Study

Variable	Alectuzumab	Chlorambucil
Response rate	64%	20.0%
Median PFS	10.7 mo (95% CI 2.7-22.7)	2.2 mo (95% CI 1.5-12.2)

Table 2. Patient Efficacy Estimates for Subsequent Lines of Therapy From Literature Review

Variable	CHOP (Second Line)	Mixed (Salvage)
Response rate	39% (Leporrier et al, 2001) ¹²	22% (Keating et al, 2002) ¹¹
Median duration of response	5.88 mo (Johnson et al, 1996) ¹³ **	18 mo (Keating et al, 2002) ¹¹

*Using CAP as approximation for CHOP.

Cost Analysis

Table 3. Costs of Treatments

Cost of Drugs				
	Unit cost	Doses	Cost	Source
Alectuzumab	£274.83 (30-mg vial)	8.3	£2,272	BNF 2008
Chlorambucil	£0.33 (2-mg tablet)	36 (72 mg)	£12	BNF 2008
Administration				
	Cost	HRG	Source	
Alectuzumab	£338	Weighted average of SB12Z and SB13Z + SB15Z	NHS ref costs 2006-2007*	
	£93 (CMV test)		NHS R&D HTA Programme 2006	
Cost per 28-day cycle	£431			
Chlorambucil	£185	SB11Z	NHS ref costs 2006-2007*	
Cost per 28-day cycle	£185			
Adverse Events				
	Occurrence	Hospitalised	HRG	Source
Alectuzumab				
Neutropenia	18%	4%	SA09E	NHS ref costs 2006-2007*
Febrile neutropenia	9%	9%	PA45Z	NHS ref costs 2006-2007*
Other	64%	23%	Average of HRGs SA03F, SA09E, SA12F, PA16B	NHS ref costs 2006-2007*
Cost per 28-day cycle	£198			
Chlorambucil				
Anaemia	10%	1%	SA03F	NHS ref costs
Other	50%	18%	Average of HRGs SA03F, SA09E, SA12F, PA16B	NHS ref costs 2006-2007*
Cost per 28-day cycle	£56			
Blood Products				
	Occurrence	Average Number of Units	HRG	Source
Alectuzumab				
Fresh frozen plasma	9%	2.00	821	NHS ref costs 2006-2007*
Packed red cells	27%	2.67	821	NHS ref costs 2006-2007*
Cost per 28-day cycle	£82			
Chlorambucil				
Packed red cells	50%	6.80	821	NHS ref costs 2006-2007*
Platelets, standard unit	10%	1.00	821	NHS ref costs 2006-2007*
Cost per 28-day cycle	£121			
Total Cost				
Alectuzumab (per 28-day cycle)	£2,983			
Chlorambucil (per 28-day cycle)	£374			

*Inflated to 2008 prices.
HRG = Healthcare Resource Group.

RESULTS

Costs and Outcomes

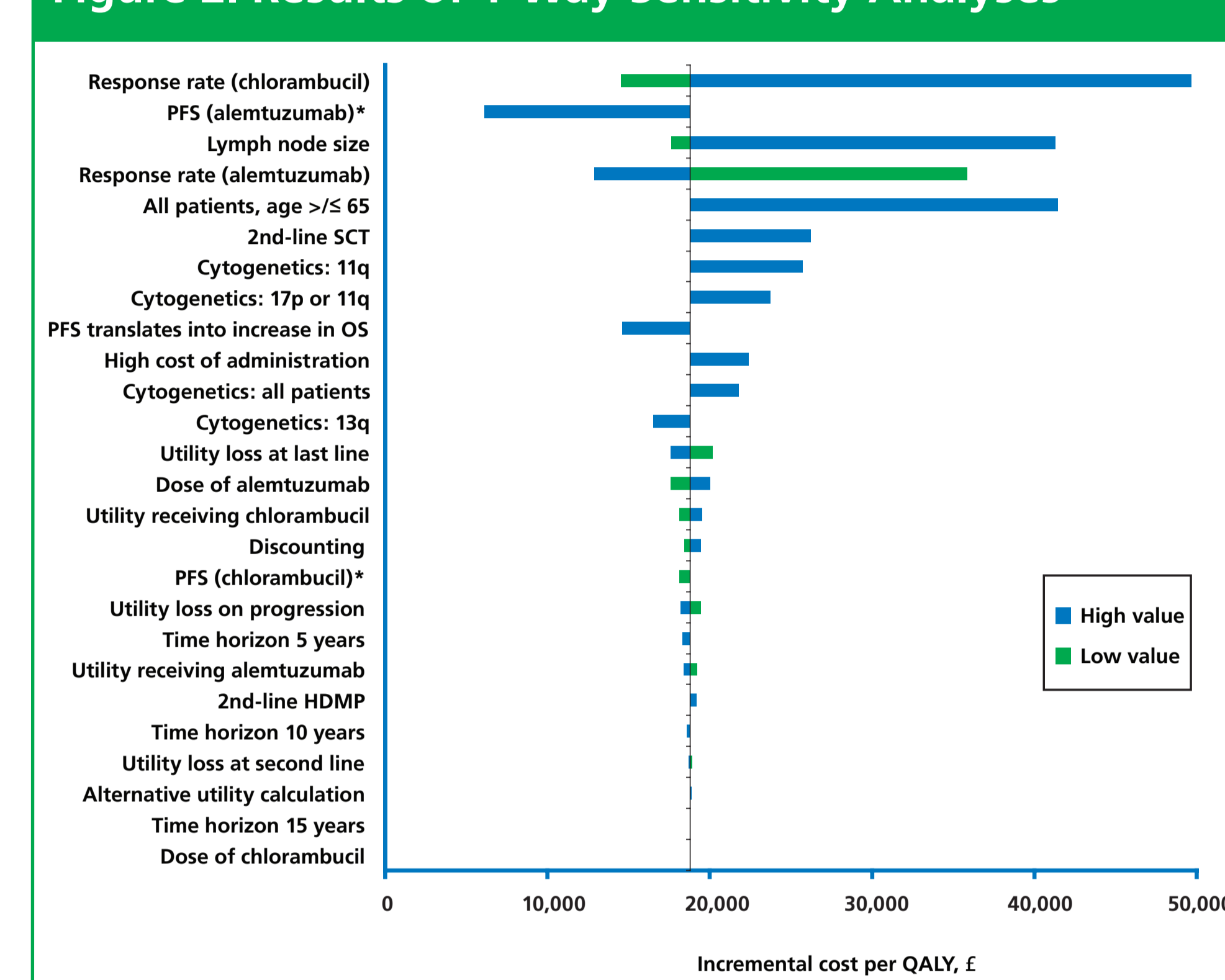
Table 4. Costs and Outcomes per Patient in 17p- Subgroup of CAM307 Study

	Overall Survival (Assumed to be Equal)		Overall Survival (Allowed to Vary)	
	Costs	QALYs	Costs	QALYs
Alectuzumab	£17,938	1.96	£17,938	1.96
Chlorambucil	£10,957	1.59	£10,212	1.43
Incremental (A-Chl)	£6,981	0.37	£7,726	0.53
C/E ratio (£ per QALY)	£18,788		£14,604	

- When OS is assumed to be equal in the 17p- subgroup, treatment with alectuzumab instead of chlorambucil increases cost per patient by around £6,981 and increases QALYs by 0.37, at a cost per QALY gained of £18,788 (Table 4)
- When OS is allowed to vary to reflect differences in PFS, treatment with alectuzumab instead of chlorambucil increases cost per patient by around £7,726 and increases QALYs by 0.53, at a cost per QALY gained of £14,604 (Table 4)

Sensitivity Analysis

Figure 2. Results of 1-Way Sensitivity Analyses



*Alternate value has no incremental cost-effectiveness ratio, because QALY favours chlorambucil.

- The findings of the model are most sensitive to the relative effectiveness of the therapies, as measured by changes in PFS and, to a lesser degree, response (Figure 2)
- The model is moderately sensitive to input assumptions, such as the choice of second-line therapy and relaxing the assumption that equalises OS
- The analysis was moderately sensitive to increases in the costs of administering alectuzumab
- The model was less sensitive to variation in the individual utility estimates from the utility study

Limitations

- Modelling is taken from the point after diagnosis and when treatment is indicated. The International Workshop on CLL (IWCLL) guidelines now recommend that fluorescent in situ hybridisation (FISH) testing be conducted prior to treatment¹⁵
 - A sensitivity analysis that included FISH testing was included in this study
- The choice of subsequent lines was based on the literature review, which was applied to both lines of treatment
 - A sensitivity analysis for subsequent lines of treatment was conducted
- Numbers of patients with 17p deletion in this study were small, given the low frequency of 17p deletion in previously untreated CLL

CONCLUSIONS

- The analysis focused on the sub-group of patients with 17p- CLL
- A Markov model was used to estimate the costs and benefits of treatment over a 20-year time horizon (lifetime)
- Data from the pivotal CAM307 study were used in the model for first-line treatment, and the effectiveness of subsequent lines of treatment was based on estimates from the literature
- This study estimated the cost per QALY of alectuzumab to be £18,788 based on an additional cost of £6,981 and a QALY gain of 0.37
- This analysis formed the basis of the Scottish Medicines Consortium (SMC) submission
- SMC advice
 - "Alectuzumab (MabCampath®) is accepted for restricted use within NHS Scotland for treatment of patients with CLL for whom fludarabine combination chemotherapy is not appropriate. It is restricted to use in patients with previously untreated CLL, with the cytogenetic abnormality 17p deletion"
 - "Compared with an alkylating agent, alectuzumab was associated with improved PFS in patients with CLL. Data in patients with 17p deletion are limited; improved survival was demonstrated in a sub-group analysis in 21 patients"

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DISCLOSURE

Adriana Valderrama, Julie Ferguson, and Lesley Gilmour are employees of Bayer Schering Pharma.