



Brentuximab Vedotin Plus CHP in Frontline sALCL: Adjusted Estimates of Efficacy and Cost-Effectiveness Removing the Effects of Re-Treatment with Brentuximab Vedotin

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Accepted: 14 June 2022 / Published online: 4 September 2022
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Abstract

Background In the randomised controlled trial ECHELON-2 (NCT01777152; January 2013), brentuximab vedotin (BV) plus cyclophosphamide, doxorubicin and prednisone (CHP) demonstrated improved efficacy compared with CHOP (CHP and vincristine) in frontline CD30+ peripheral T-cell lymphoma (PTCL), an aggressive cancer with poor survival. In ECHELON-2, 70% of patients had systemic anaplastic large cell lymphoma (sALCL), a subtype of PTCL. Of sALCL patients who progressed from BV+CHP and CHOP, 36% ($n = 17$) and 56% ($n = 36$) received subsequent BV-containing therapy, respectively. As BV re-treatment was not funded in England at the time, our objective was to estimate adjusted efficacy and cost-effectiveness by excluding BV re-treatment from BV+CHP.

Methods To remove the effects of BV re-treatment, the inverse probability of censoring weights (IPCW) and two-stage estimator (TSE) approaches, with and without re-censoring, were applied to overall survival (OS) in the BV+CHP arm of the ECHELON-2 sALCL population. Cost-effectiveness was determined in a three-state partitioned survival (PartSA) model from the perspective of the National Health Service (NHS) in England.

Results The unadjusted hazard ratio (HR) for death in patients with sALCL with BV+CHP versus CHOP was 0.54 (95% CI 0.34, 0.87; $p = 0.011$). The model base case used TSE analysis without re-censoring, which provided an adjusted HR for death of 0.55 (95% CI 0.33, 0.86; $p = 0.014$). Incremental cost-effectiveness ratios (ICERs) including and excluding re-treatment with BV were £29,760/QALY and £27,761/QALY, respectively.

Conclusion TSE without re-censoring provided the most clinically plausible estimate of survival whilst retaining sufficient information for OS extrapolation. After adjustment for BV re-treatment, BV+CHP remains an efficacious and cost-effective treatment in frontline sALCL compared with CHOP.

1 Introduction

Systemic anaplastic large cell lymphoma (sALCL) is a subtype of peripheral T-cell lymphoma (PTCL); a rare and aggressive heterogeneous subset of non-Hodgkin lymphoma (NHL) characterised by a lack of T-cell related protein marker expression [1, 2], and poor survival [3–6]. sALCL accounts for approximately 15.8% of all PTCL cases in Europe, with up to 160 newly diagnosed cases of sALCL

estimated in the UK annually [4, 5]. Patients are typically diagnosed with late-stage disease (Stage III–IV), and experience systemic symptomatology (B-symptoms, i.e., fever, night sweats, weight loss), requiring therapeutic intervention. Prognosis for patients is poor, with 5-year overall survival rates varying between 13 and 70% [4–7] depending on the presence or absence of mutant anaplastic lymphoma kinase (ALK), International Prognostic Index (IPI) score, and age [7–9].

Current UK treatment guidelines for frontline therapy recommend a maximum of six cycles of systemic combination chemotherapy, consisting of cyclophosphamide (C), doxorubicin (H), vincristine (O) and prednisone (P) (CHOP) [10–15]. Despite its position as the current standard-of-care, the evidence base for the use of CHOP in frontline treatment of sALCL lacks robust randomised, controlled, comparative studies, and is largely based on evidence stemming

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Key Points for Decision Makers

In the Phase III trial ECHELON-2, BV+CHP improved clinical outcomes compared with the current standard-of-care treatment for frontline sALCL, CHOP.

During the trial, a number of patients in the BV+CHP arm subsequently received re-treatment with BV. Such re-treatment with BV was not funded in England at the time.

This analysis attempts to remove the effects of re-treatment with BV from the BV+CHP arm using statistical methods designed for adjusting for bias due to crossover in clinical trials.

Removing the effects of re-treating patients with BV following frontline BV+CHP maintains the efficacy and cost-effectiveness of BV+CHP compared with CHOP.

from the use of CHOP in the treatment of diffuse-large B-cell lymphoma, a subtype of NHL [16]. The overall treatment goal for individuals with newly diagnosed sALCL is to attain a deep, durable response with frontline therapy, inducing long-term remission and potentially curing underlying disease. The 5-year failure-free survival of patients with sALCL varies between 36 and 60% when considering key prognostic factors [4]. The risk of relapse after frontline treatment is highest in the first 2 years; patients who are disease free and have not relapsed within 2 years have a low likelihood of future relapse [17]. A retrospective analysis of 775 patients from the USA, Sweden and Canada concluded that the risk of relapse and death significantly decreased for patients with PTCL who remained disease free for 2 years after frontline treatment, and survival approached general population mortality; this trend was consistent for patients with sALCL [17].

Patients with sALCL uniformly present with CD30 expression (CD30+), a type I transmembrane receptor, which, upon stimulation, may activate pro-proliferative and pro-tumourigenic signalling pathways [18, 19]. Brentuximab vedotin (BV) is an antibody-drug conjugate, composed of an anti-CD30 monoclonal antibody conjugated by a protease-cleavable linker to the microtubule-disrupting drug monomethyl auristatin E (MMAE) [20–22]. In 2014, BV monotherapy received marketing authorisation from the European Medicines Agency (EMA) for relapsed/refractory (R/R) sALCL. It has become the standard-of-care for R/R sALCL in the UK following a positive National Institute for Health and Care Excellence (NICE) recommendation in 2017 [10]. BV in combination with cyclophosphamide, doxorubicin and prednisone (BV+CHP) received marketing

authorisation in frontline sALCL [23] in 2020 on the basis of the pivotal Phase III, double-blind, double-dummy, randomised, controlled trial ECHELON-2, in which BV+CHP demonstrated superiority over CHOP for all primary and key alpha-controlled secondary endpoints. In ECHELON-2, patients with sALCL were a pre-specified study population, and represented 70% ($n = 316$) of the enrolled population. Randomisation was stratified by histological subtype according to local pathology assessment (ALK-positive sALCL versus all other histologies), and baseline IPI score (0–1 vs. 2–3 vs. 4–5). The sALCL population of ECHELON-2 included 15 patients with sALCL from the UK across four centres.

In the ECHELON-2 intention-to-treat (ITT) population, the risk of a progression-free survival (PFS) event and death was reduced by 29% (stratified hazard ratio (HR): 0.71 [95% confidence interval (CI): 0.54, 0.93]; $p = 0.011$) and 34% (HR: 0.66 [95% CI 0.46, 0.95]; $p = 0.0244$), respectively, in patients receiving BV+CHP compared with CHOP. Patients diagnosed with sALCL who received BV+CHP had a 41% reduction in risk of a PFS event (HR: 0.59 [95% CI 0.42, 0.84]; $p = 0.0031$), and a 46% reduced risk of death (HR: 0.54 [95% CI 0.37, 0.867]; $p = 0.0096$) compared with those receiving CHOP [24]. Furthermore, 71% of patients with sALCL treated with BV+CHP achieved complete response compared with 53% treated with CHOP [24]. ECHELON-2 demonstrated a favourable efficacy and comparable safety profile for BV+CHP versus CHOP in both the ITT and sALCL populations. Common treatment-emergent adverse events (TEAEs) in the ITT population were similar in the BV+CHP and CHOP arms of the trial, including peripheral neuropathy (BV+CHP: 45%; CHOP: 41%). The majority of TEAEs were less than Grade 3, with the exception of treatment-emergent neutropenia. In ECHELON-2, patients who experienced disease progression following study treatment were eligible to receive BV monotherapy post-progression. Due to study blinding, clinicians were not influenced in treatment choice following relapse, resulting in a proportion of patients being re-treated with BV. In the sALCL subgroup, 36% ($n = 17/47$) and 57% ($n = 36/63$) of patients who had non-fatal PFS events received subsequent BV-containing therapy in the BV+CHP and CHOP arms, respectively.

In August 2020, NICE recommended BV+CHP for the frontline treatment of sALCL (TA641) [25]. At the time of the NICE appraisal of BV+CHP, re-treatment with BV was not reimbursed within England. Therefore, while the CHOP arm of ECHELON-2 (i.e., CHOP followed by BV monotherapy in R/R sALCL) is largely representative of clinical practice, the re-treatment with BV observed in the BV+CHP arm did not reflect the locally funded pathway. Therefore, using the unadjusted overall survival (OS) data from the ECHELON-2 trial may bias the estimates of clinical and cost-effectiveness, and adjustment of subsequent

therapy was required to accurately reflect clinical practice in England.

Our objective was to estimate adjusted OS by removing the effect of re-treatment with BV in the BV+CHP arm, to reflect the locally funded pathway in England. This enabled us to assess the clinical and cost-effectiveness of BV+CHP in frontline sALCL from the perspective of the National Health Service (NHS) in England.

2 Methodology

2.1 Model Structure

The primary outcome of the model was the incremental cost-effectiveness ratio (ICER), expressed as the cost per quality-adjusted life-year (QALY) gained, in line with NICE guidance [25]. Clinical efficacy, safety and health-related quality of life (HRQoL) data were derived from the pre-specified sALCL population of ECHELON-2. The model was programmed in Microsoft® Excel, and comprised a three-state partitioned survival model (PartSA) to evaluate the expected costs and outcomes of BV+CHP compared with CHOP as frontline therapy in sALCL from the perspective of NHS England. The PartSA comprises three mutually exclusive health states: (1) progression-free disease, (2) progressed disease (PD), and (3) death (Fig. 1). The proportion of patients in each of the health states were derived from the PFS and OS data from the sALCL population of ECHELON-2; the proportion of patients in the progression-free disease health state was estimated based on area under the PFS curve, the proportion of patients in the death health state was estimated based on 1 minus the area under the OS curve, and the proportion of patients within the PD state was

estimated as the difference between the OS and PFS curves. The utilisation of the PartSA model structure is common in oncology, and has been implemented in all cost-effectiveness analyses for BV to date. It also aligns with key clinical endpoints of ECHELON-2, PFS and OS, and accurately reflects the nature of the condition. Unadjusted OS outcomes from ECHELON-2 informed the CHOP arm, as the subsequent therapies used were considered reflective of UK clinical practice (as confirmed with clinical experts and local guidelines) [13, 16, 26]. The treatment-switching analysis to remove the impact of re-treatment with BV described below was only applied to the BV+CHP arm.

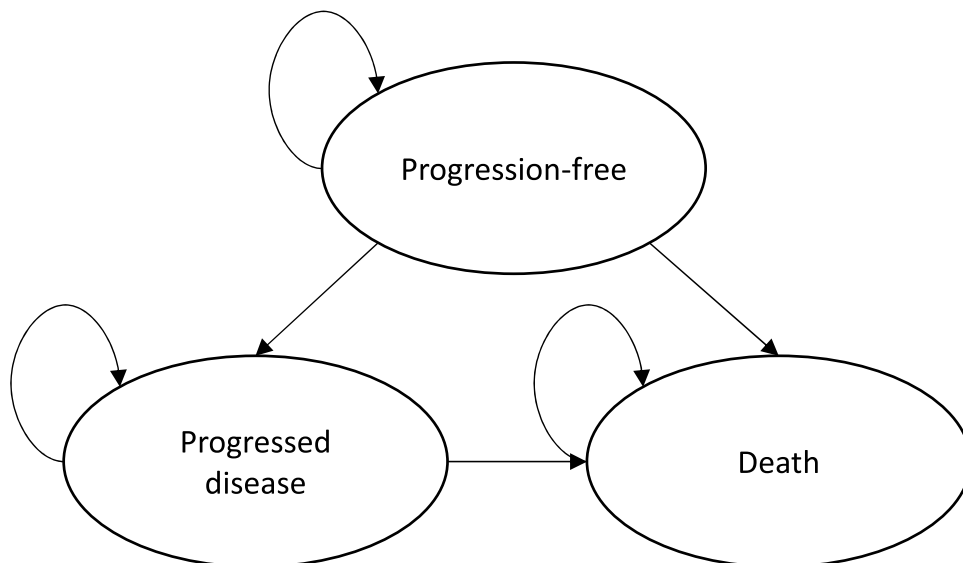
Outcomes were extrapolated beyond ECHELON-2 and a lifetime time horizon (45 years) was utilised to capture the differences in expected costs and outcomes between model arms. A 21-day cycle length was used to reflect the typical duration of CHOP and BV+CHP treatment cycles. Half-cycle correction was implemented. Costs and outcomes were discounted at 3.5% in line with NICE guidance [27].

2.2 Efficacy Inputs

2.2.1 Adjustment for Re-Treatment with Brentuximab Vedotin (BV)

A detailed description of the methods used are described in the Online Supplementary Material (OSM), section 1, including an overview of the methodology, rationale for methods used, and outputs from these methods. To remove the effects of re-treatment with BV on OS, multiple methods were considered based on treatment-switching approaches described within the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 16 [28], including: the naïve approach, rank-preserving structural failure time

Fig. 1 Model schematic



models (RPSFTM), the inverse probability of censoring weights (IPCW), and the two-stage estimator (TSE). The TSE and IPCW approaches were the a priori preferred approaches, as the risk of bias associated with naïve approaches and the lack of plausibility for the common treatment effect assumption required for the RPSFT approach made these less suitable. In practice, only the TSE provided logical estimates with plausible underlying assumptions. Therefore, this approach was used in the base case. Alternative methods considered are described in OSM section 1.

The simplified TSE was initially described by Latimer et al. [29]. Based on the assumption that all patients are at a similar stage of disease at the point of disease progression, the effect of re-treatment with BV-containing regimens on survival from the point of disease progression to death could be estimated. The point of disease progression was considered a ‘secondary baseline’, and survival post-progression then estimated from this secondary baseline. An accelerated failure time (AFT) model was estimated and included covariates and an indicator for whether subsequent BV-containing regimens were used. The AFT model was fitted to estimate the treatment effect for those re-treated with BV compared with those who were not in the BV+CHP arm.

Counterfactual survival times were then predicted for each patient using:

$$U_i = T_{A_i} + \theta_v T_{B_i}$$

where T_{A_i} is the time before disease progression for the i th individual, T_{B_i} represents the time post-progression, and θ_v represents the treatment effect (time ratio) for BV re-treatment use in post-progression survival. This method requires the assumption of ‘no unmeasured confounders’ at the secondary baseline timepoint, and does not require modelling of the process by which patients are re-treated with BV following progression.

Decisions required for the application of the TSE include: (1) which AFT model to use, (2) which covariates to include in the model, and (3) whether or not to include re-censoring [30]. Weibull models were used to estimate post-progression survival, including θ_v . This was because the generalised gamma model was unable to achieve convergence in several scenarios, presumably because of the relatively low number of patients in the BV+CHP arm who received re-treatment with BV. Note that the use of the Weibull model in this context is distinct from the survival models used in the long-term extrapolation of outcomes (Sect. 2.2.2).

Prognostic covariates tested for inclusion included response to frontline therapy, remission duration, receipt of consolidative autologous stem cell transplant (ASCT) therapy, and other baseline characteristics (IPI score, ALK status, age and region). Only statistically significant predictors

were retained in the base-case analysis; these included IPI score, age and time-to-progression.

The process of adjusting survival times introduces an informative censoring bias [28]. For the TSE method, informative censoring is introduced because the counterfactual survival model involves adjusting survival times for those who received re-treatment with BV, but not for those who did not. For some re-treated patients, time of death may not have yet been observed in the unadjusted data, and the TSE would adjust their censoring times. This would result in informative censoring if there were an association between re-treatment with BV and prognosis. In the context of TSE, the process of re-censoring is summarised by Latimer et al. [31].

An important consequence of re-censoring is that longer-term information is discarded, which can be problematic for cost-effectiveness analyses requiring extrapolation of long-term survival [30]. Studies investigating treatment switching have concluded that analyses should be conducted with and without re-censoring [31]. In the present scenario, historical data and clinical experts suggested that the hazard of death in patients with sALCL reduces significantly for patients who have remained disease free for 2 years after frontline treatment, and survival approached general population mortality. Therefore, in discarding long-term data, re-censoring may omit the observed change in the shape of the hazard.

On the basis that the objective was to fit parametric survival models to trial data to extrapolate into the future, where long-term trends are highly important, the base-case analysis excludes re-censoring. Sensitivity analysis was performed including re-censoring.

2.2.2 Extrapolation of Overall Survival (OS) and Progression-Free Survival (PFS)

Parametric survival models were used to extrapolate OS and PFS data beyond the observed period from ECHELON-2 (data cut-off: 15 August 2018). Visual inspection of the log-cumulative hazard plots and hypothesis testing by means of the Schoenfeld test of residuals with respect to time suggested that the proportional hazards assumption was not violated (see OSM section 6). Therefore, a joint modelling approach, in which the effect of treatment is represented by a coefficient within a statistical model estimated in both BV+CHP and CHOP arms, was adopted in the base case. Parametric curves were fitted to the PFS and OS data from ECHELON-2; models using both unadjusted and counterfactual ‘adjusted’ outcomes (OS only) were estimated separately to estimate long-term outcomes (generalised gamma, Weibull, exponential, log-normal, log-logistic and Gompertz) in line with NICE Technical Support Document 14 [32]. Clinical experts were asked to select the most representative predictions from the candidate curves. Feedback

indicated that the risk of relapse would be low after 2 years for patients who remain progression-free and this would align with a risk of death similar to the general population. The generalised gamma distribution aligned with the expected HR over time and was selected for both PFS and OS in the base case. Generalised gamma curves were applied in the model base case (OS and PFS) and yielded the most conservative cost-effectiveness results of the distributions considered.

In the long term, the risk of mortality was estimated based on the age- and gender-matched general population and adjusted using a standardised mortality ratio of 1.21. This mortality ratio was based on UK clinical input and reflects the small reduction in life-expectancy associated with increased rates of cardiac toxicity, and a small increased risk of secondary primary malignancies.

2.2.3 Other Clinical Parameters

In ECHELON-2, BV+CHP was administered across a 21-day cycle for a maximum of six to eight cycles. The base case was informed by the average duration from the trial (6.2 and 5.8 treatment cycles of BV+CHP and CHOP, respectively). This aligned with expected clinical practice in the UK; unanimous clinical feedback indicated that a maximum of six cycles is used in Europe in frontline sALCL and PTCL. The sALCL population from ECHELON-2 informed the following inputs: adverse events (Grade 3–4 TEAEs occurring in $\geq 5\%$ of patients, apart from Grade 1–2 diarrhoea, which was identified by clinical experts as being of clinical interest), subsequent therapy and consolidative stem cell transplantation (SCT)/radiotherapy. All inputs are reported in OSM section 2.

2.3 Health-Related Quality of Life (HRQoL)

During ECHELON-2, EQ-5D-3L data were collected until patient death or study closure, whichever came first. The EQ-5D-3L tariff from Dolan [33] was applied to individual

responses to generate EQ-5D-3L index scores. At baseline, 310 valid EQ-5D-3L questionnaires were available for analysis. Mean EQ-5D-3L was 0.60 (standard deviation (SD): 0.37), with an imbalance between the treatment arms (BV: 0.58, CHOP: 0.63; $p = 0.2413$). In the base case, covariates representing how close an observation was to the time of patients' death were included to allow prediction of HRQoL as patients approached death, in addition to baseline EQ-5D, age, presence of adverse events and SCT.

As may be expected, HRQoL declined significantly as patients approached death (Table 1). Additionally, given the severity of episodes of Grade 3–4 peripheral neuropathy, a decrement of -0.33 (taken from Swinburn et al. [34]) was applied to the number of events per patient across the time horizon, for the duration of 4.34 days in the BV+CHP arm and 3.65 days in the CHOP arm, estimated from ECHELON-2 [25, 34]. This effect was considered based on clinical feedback.

2.4 Costs

The cost year implemented in the analysis was 2018/2019; list prices were used for all treatments and do not reflect any confidential discounts. Drug acquisition costs used were taken from UK-specific public sources [35]. For BV, the method of moments was used to calculate the distribution of cost, based on observed weight at baseline in ECHELON-2. Costs for adverse events and administration were taken from the NHS Reference Costs [36]. It was assumed that all patients would be concomitantly administered granulocyte colony stimulating factor as primary prophylaxis, as this is expected in UK clinical practice [37].

The costs of use of salvage chemotherapy, SCT and radiotherapy were informed by ECHELON-2. Treatment with subsequent BV monotherapy in the CHOP arm was assumed to be administered for six cycles. The costs of SCT were taken from related technology appraisals and inflated to the 2018/2019 cost year using inflation indices from the Personal Social Services Research Unit (PSSRU) [38]. Medical

Table 1 EQ-5D based on the time-to-death approach (sALCL population)

Covariate	Coefficient	SE	$P > z $	95% confidence interval	
≥ 10 cycles away from death	-0.0518	0.0268	0.0530	-0.1043	0.0007
5–9 cycles away from death	-0.0864	0.0338	0.0110	-0.1526	-0.0201
1–4 cycles away from death	-0.1155	0.0384	0.0030	-0.1907	-0.0402
< 1 cycle away from death	-0.3173	0.0638	0.0000	-0.4423	-0.1924
Adverse events	-0.0289	0.0115	0.0120	-0.0514	-0.0065
Baseline EQ-5D	0.3308	0.0257	0.0000	0.2804	0.3812
Age (years)	-0.0015	0.0006	0.0150	-0.0027	-0.0003
Post-SCT	0.0455	0.0134	0.0010	0.0192	0.0719
Constant	0.6671	0.0348	0.0000	0.5988	0.7354

sALCL systemic anaplastic large cell lymphoma, SCT stem cell transplant, SE standard error

resource use costs and frequencies were informed by the London Cancer Alliance documentation on follow-up care with CHOP chemotherapy [37] and resource use estimates presented in the NICE economic evaluation of BV in R/R sALCL [25]. Different assumptions were made in pre- and post-progression health states to reflect the varying intensities of follow-up care, based on clinical input. The frequency and nature of monitoring modelled in the cost-effectiveness analysis were validated by clinical experts. Full details of the costs included in the analysis are reported in OSM sections 3 (primary therapy and concomitant medication) and 4 (subsequent/salvage therapies).

2.5 Sensitivity Analysis

Individual parameter uncertainty was tested using univariate sensitivity analysis, in which all model parameters were systematically and independently varied over a plausible range, determined by either the 95% CI or $\pm 15\%$, where no estimates of precision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram. Scenario analyses were performed to explore structural changes and assumptions.

Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters were assigned distributions and varied jointly. Correlation between parameters in the time-to-event and EQ-5D models was preserved and sampled using multivariate normal distributions. Costs and medical resource use estimates were assumed to follow log-normal distributions, and proportions (such as the proportion of patients receiving ASCT) were sampled from beta distributions. The distribution of subsequent treatments was sampled from a Dirichlet distribution. 5000 Monte Carlo simulations were recorded. From this, results were plotted on the cost-effectiveness acceptability plane and the probability of being cost-effective was calculated at different willingness-to-pay (WTP) thresholds. Results of the scenario analysis are presented in OSM section 5.

3 Results

3.1 Adjustment for Re-Treatment with Brentuximab Vedotin (BV)

In the unadjusted analysis, patients in the sALCL population of ECHELON-2 who received BV+CHP had a 46% reduced risk of death compared with those receiving CHOP (HR: 0.54 (95% CI 0.37, 0.87); $p = 0.0096$). The statistical model predicting re-treatment in the IPCW approach had poor predictive power. Estimates from IPCW were consequently counterintuitive and closely aligned with naïve

approaches that censor on receipt of re-treatment (HR: 0.46 (95% CI 0.27, 0.77); full details in OSM section 1). The TSE with and without re-censoring provided hazard ratios for death of 0.41 (95% CI 0.15, 0.87; $p = 0.022$) and 0.55 (95% CI 0.33, 0.86; $p = 0.014$), respectively. The model of post-progression survival used within the TSE analysis is presented in Table 2.

The adjusted OS data including and excluding re-censoring utilising the TSE method are presented in Fig. 2. The effect of adjustment on the Kaplan-Meier estimator was minor, reflecting the relatively low number of patients who received re-treatment. However, the loss of long-term follow-up in the BV+CHP arm in the re-censored analysis was pronounced, and as a consequence of discarding much of the observed data, the resulting point estimate was (counterintuitively) improved versus the unadjusted analysis. The BV+CHP arm of ECHELON-2 was associated with a reduction in the long-term hazard over time, ultimately leading to a sustained event-free period towards the end of study follow-up (Fig. 2). Thus, re-censoring was deemed to discard important evidence in the BV+CHP arm of the changing hazards over time and was not included in the base-case analysis. The long-term predicted OS and PFS including (adjusted) general population mortality are presented in Fig. 3.

3.2 Cost-Effectiveness

In the base-case analysis, excluding re-treatment with BV, BV+CHP is associated with incremental costs of £40,826 and 1.47 incremental QALYs, resulting in an ICER of £27,761 per QALY gained versus CHOP (Table 3). The effect of removing re-treatment with BV reduced the ICER from £29,760 per QALY gained to £27,761 per QALY gained. This was due to reduced efficacy following the

Table 2 Weibull model of post-progression survival

	Coefficient	SE	$P > z$	95% confidence interval	
Re-treatment with BV	1.580 ^a	0.558	0.005	0.485	2.674
Time to PFS event	0.076	0.044	0.085	-0.010	0.162
IPI 2-3	-1.790	0.934	0.055	-3.621	0.040
IPI 4-5	-3.265	0.955	0.001	-5.137	-1.394
Age	-0.053	0.025	0.034	-0.102	-0.004
Constant	7.139	1.724	0.000	3.760	10.518
/ln_p	-0.117	0.179	0.514	-0.468	0.234
p	0.890	0.159		0.626	1.264
1/p	1.124	0.201		0.791	1.597

BV brentuximab vedotin, IPI International Prognostic Index, PFS progression-free survival, SE standard error

^aProvides estimate of θ_v of 0.206 (95% CI 0.069, 0.615)

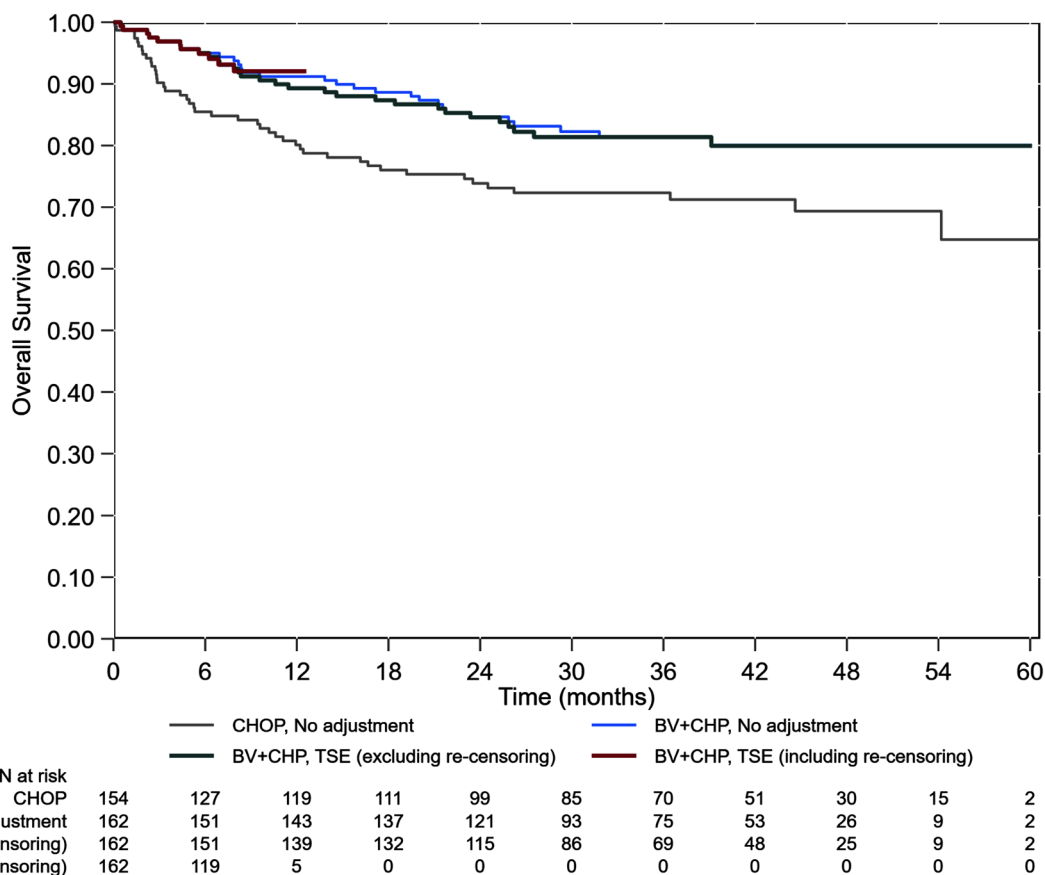


Fig. 2 Adjusting for treatment switching in patients with re-treatment (BV+CHP arm), OS, sALCL population. *BV+CHP* brentuximab vedotin cyclophosphamide doxorubicin prednisone, *CHOP* cyclo-

phosphamide doxorubicin vincristine prednisone, *sALCL* systemic anaplastic large cell lymphoma, *TSE* two-stage estimator

removal of re-treatment with BV in the BV+CHP arm, offset by lower costs (Table 3).

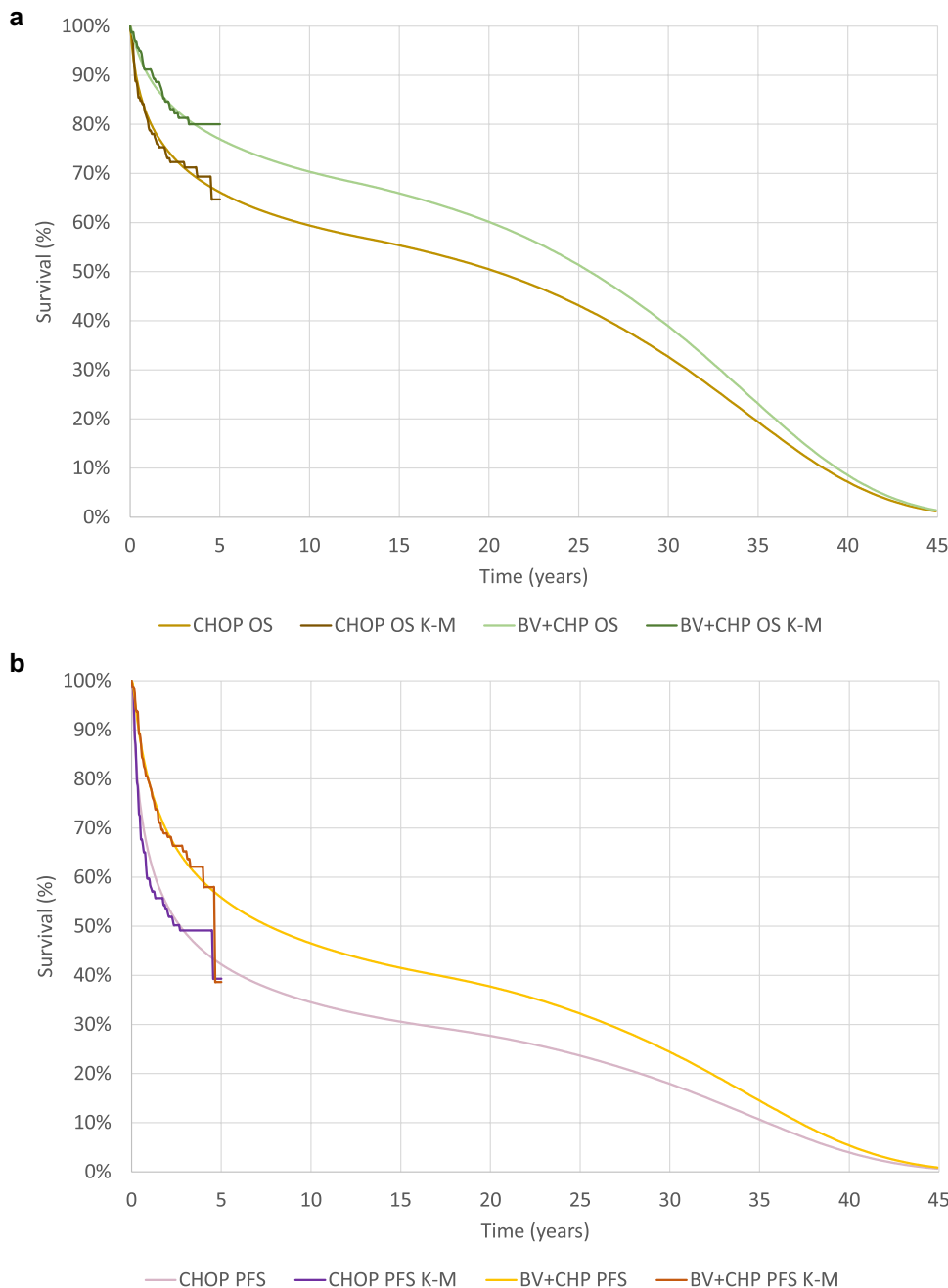
Univariate sensitivity analysis suggested the most influential parameter was the estimated treatment effect for BV+CHP versus CHOP in OS from the TSE model (Fig. 4a). The model was moderately sensitive to other model parameters, including those in the statistical model predicting EQ-5D. The scenario that included re-censoring resulted in an ICER of £25,424. Most scenarios that considered alternative distributions for OS and PFS resulted in lower estimates of the ICER (with the exception of the Gompertz distribution, which resulted in a 2% increase in the ICER). Scenarios that reduced the time horizon led to increased ICERs as the costs of BV+CHP are incurred upfront, but benefits are accrued over the lifetime of patients (see OSM section 5). Omitting any confidential discounts on acquisition costs, the probability BV+CHP is cost-effective versus CHOP at a WTP threshold of £30,000 was estimated at 54% (Fig. 4).

4 Discussion and Conclusion

This cost-effectiveness analysis has demonstrated that for the treatment of frontline sALCL, BV+CHP is associated with incremental costs of £40,826, an incremental life-year (LY) gain of 1.96 years, and an incremental gain of 1.47 QALYs, compared with CHOP. The resulting ICER is £27,761 per QALY gained, and therefore BV+CHP is a cost-effective treatment based on NICE’s standard WTP threshold of £30,000. The probabilistic ICER was £28,383, which is congruent with the deterministic ICER of £27,761. The proportion of simulations considered cost-effective at ICER thresholds of £20,000 and £30,000 (omitting any confidential discounts) were of 10% and 54%, respectively.

The quality of the clinical evidence from the ECHELON-2 clinical trial contributes to the strength of the treatment switching and economic analyses. ECHELON-2 is a high-quality double-blind, double-dummy, randomised, controlled trial that compares BV+CHP with the current

Fig. 3 Base-case extrapolations including general population mortality. **a** OS with adjustment for BV re-treatment, **b** PFS. *BV+CHP* brentuximab vedotin cyclophosphamide doxorubicin prednisone, *CHOP* cyclophosphamide doxorubicin vincristine prednisone, *OS* overall survival, *PFS* progression-free survival, *sALCL* systemic anaplastic large cell lymphoma



standard-of-care in UK clinical practice, CHOP. Five UK centres participated in ECHELON-2, and clinical experts confirmed that the patient population is reflective of UK clinical practice. Furthermore, the trial provides data for 316 patients with sALCL and has a median follow-up of 36.2 months, representing a large dataset with relatively long follow-up.

The results from the economic model were considered robust when testing for structural and parameter uncertainty. The one-way sensitivity analyses identified that the results of the economic model are largely driven by the improved survival in the BV+CHP arm relative to the CHOP arm. In

the base case, to reflect UK clinical practice, the impact of re-treatment with BV was removed from the BV+CHP arm. However, results remain cost-effective when using both the adjusted and unadjusted data. Notably, the conclusion of cost-effectiveness is maintained under all parametric curve choices.

The uncertainty associated with the treatment-switching analyses has been explored through different treatment-switching methodologies, including IPCW and TSE. The failure of the IPCW to produce plausible estimates of the treatment effect was likely caused by a low number of observations of those receiving re-treatment with BV, and the lack

Table 3 Summary of base-case results including and excluding re-treatment with BV

	Without re-treatment		With re-treatment	
	CHOP	BV+CHP	CHOP	BV+CHP
Drug acquisition	£3608	£52,255	£3,608	£52,255
Drug administration	£1808	£1943	£1,808	£1943
Medical resource use	£7749	£7992	£7,727	£8022
Adverse events	£733	£859	£733	£859
Subsequent treatments	£22,411	£8551	£22,126	£14,922
SCT and radiotherapy	£7182	£12,717	£7182	£12,717
Total costs	£43,491	£84,317	£43,183	£90,718
Pre-progression QALYs	5.57	7.33	5.57	7.33
Post-progression QALYs	2.86	2.58	2.79	2.63
Total QALYs	8.43	9.90	8.36	9.96
Total LYs ^b	11.70 ^a	13.66	11.60 ^a	13.73
Incremental costs	–	£40,826	–	£47,534
Incremental QALYs	–	1.47	–	1.60
Incremental LYs	–	1.96	–	2.13
ICER	–	£27,761	–	£29,760

BV brentuximab vedotin, CHOP cyclophosphamide doxorubicin prednisone vincristine, CHP cyclophosphamide doxorubicin prednisone, ICER incremental cost-effectiveness ratio, LYG life-years gained, QALYs quality-adjusted life-years

^aAlthough the adjustment applies only to the OS data for BV+CHP, life years and QALYs also change for CHOP due to the use of joint models of OS and PFS, in which the effect of treatment is represented by a coefficient within a statistical model estimated in both BV+CHP and CHOP arms

^bPlease note: life-years are discounted

of detailed information on time-varying confounders from which the possibility of re-treatment could be predicted. The assumptions underpinning the TSE method appeared plausible, and results were in line with clinical expectations. Note that the point estimate HR for BV+CHP compared with CHOP improved in the statistical adjustments of OS and remains statistically significant, despite the additional uncertainty introduced through treatment-switching adjustments.

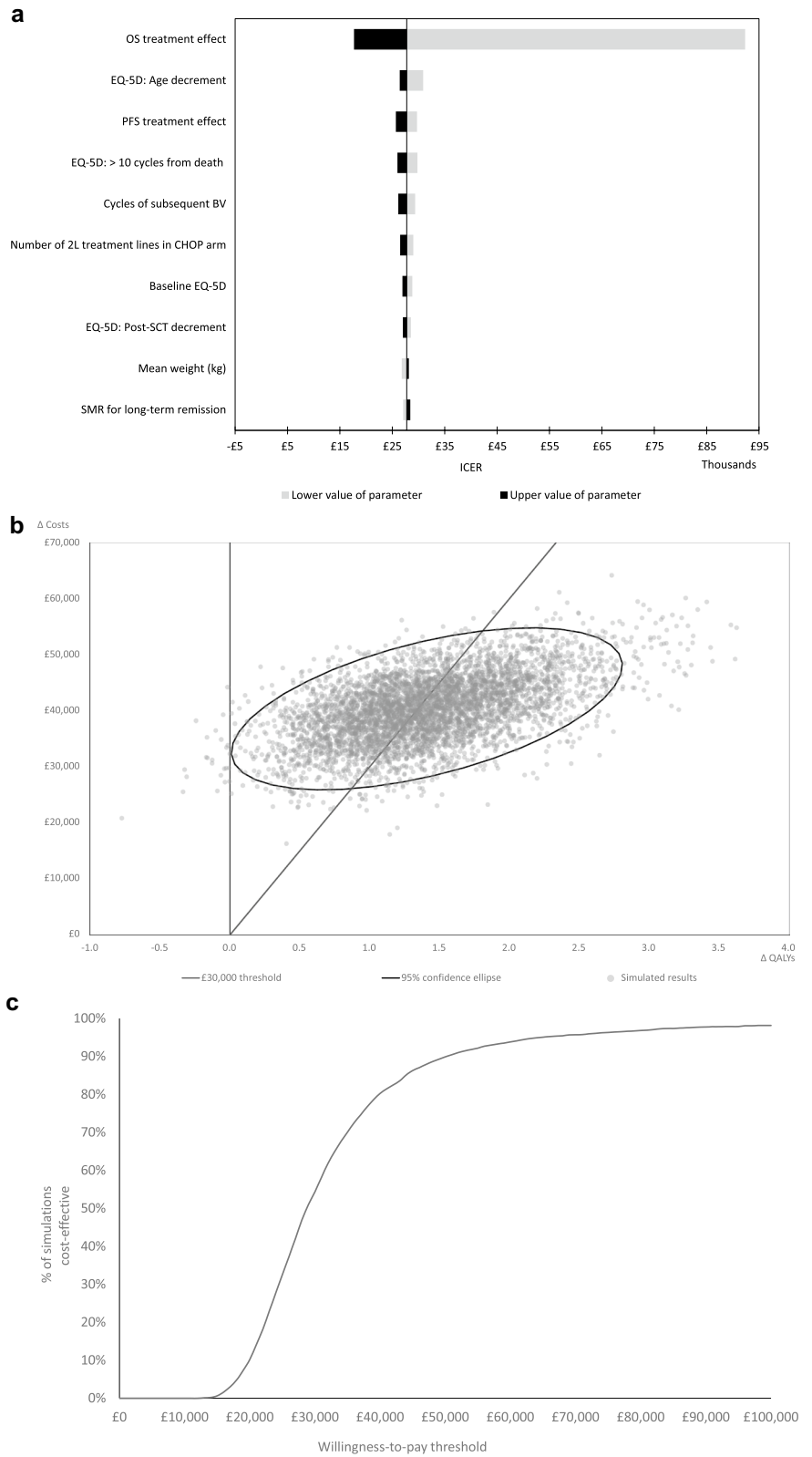
Where available, published recommendations have been adhered to and these have been referenced where appropriate. Finally, inputs and extrapolated endpoints informing the economic model were validated by 12 clinical experts from the UK across two advisory boards and multiple interactions. This allowed the model to be developed to accurately reflect the outcomes for standard-of-care in clinical practice.

To adjust estimates of survival to better reflect local reimbursement realities, our analyses utilised a novel application of existing methods. These methods were applied in the

base-case scenario of NICE submission TA641 (BV+CHP in the treatment for untreated sALCL) [25], which received a positive recommendation in 2020. A limitation of this cost-effectiveness analysis is that the sALCL population is a subgroup within the ECHELON-2 trial and not the full ITT population. However, this was a pre-specified subgroup that formed the majority of the population ($n = 316/452$; 70%) and retained the rigour of a large data set with substantial follow-up. The model also assumes a starting age equal to that of the ECHELON-2 sALCL cohort (52 years). This is slightly younger than suggested by other sources for a UK population. However, sensitivity analysis has demonstrated that this makes only a modest difference to the cost-effectiveness of BV+CHP.

In conclusion, we consider BV+CHP to be a cost-effective frontline treatment option for adults with previously untreated sALCL irrespective of whether re-treatment with BV is available.

Fig. 4 a Results of univariate sensitivity analysis. **b** Cost-effectiveness plane. **c** Cost-effectiveness acceptability curve. *OS* overall survival, *PFS* progression-free survival, *sALCL* systemic anaplastic large cell lymphoma, *SMR* standardised mortality ratio, *TSE* two-stage estimator



Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1007/s41669-022-00349-z>.

Acknowledgements The authors would like to acknowledge Fiona Field and Meredith Little for providing clinical input, Eugene Benson for contributing to the development of the analysis, and Dr Jennifer Ferris of Source Health Economics for providing medical writing and editorial support in the development of the manuscript, which was funded by Takeda UK Limited.

Declarations

Funding This research was funded by Takeda UK Limited.

Conflicts of interest/Competing interests HC is an employee of Takeda Pharmaceuticals International Co. TP is an employee of Takeda UK Limited. DT, EE, and FW are employees of Source Health Economics who received funding for this research.

Ethics approval Not required.

Consent to participate Not required.

Consent for publication Not required.

Availability of data and material No additional data or materials are available.

Code availability The economic model used in this study is proprietary intellectual property.

Author contributions HC and TP were responsible for study conception and design. DT performed the statistical analysis and prepared the first draft of this manuscript. EE and FW developed the economic model. All authors contributed to the interpretation of the results, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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