NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from **Takeda UK**

2. **Company response to NICE's request for clarification**

3. **Patient group, professional group and NHS organisation submission** from:
   a. Lymphoma Action
   b. NCRI-ACP-RCP-RCR

4. **Expert personal perspectives** from:
   a. Dr Kate Cwynarski – clinical expert, nominated by Takeda and British Society of Haematology and The Royal College of Pathologists
   b. Dr Ruth Pettengell – clinical expert, nominated by Takeda UK

5. **Evidence Review Group report** prepared by **Kleijnen Systematic Reviews**

6. **Evidence Review Group – factual accuracy check**

7. **Draft Technical Report**

8. **Technical engagement response** from **Takeda UK**

9. **Technical engagement responses from experts:**
   a. Dr Kate Cwynwarski – clinical expert, nominated by Takeda and British Society of Haematology and The Royal College of Pathologists
   b. Dr Ruth Pettengell – clinical expert, nominated by Takeda UK
   c. Dr Christopher Fox – clinical expert, nominated by NCRI-ACP-RCP-RCR

10. **Technical engagement response from consultees and commentators:**
    a. Janssen-Cilag Ltd

11. **Evidence Review Group critique of company response to technical**

engagement prepared by **Kleijnen Systematic Reviews**

12. Evidence Review Groups addendum post PMB

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

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Company evidence submission

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List of Abbreviations

ADC	antibody-drug conjugate
AE	Adverse event
AFT	Accelerated failure time
AIC	Akaike information criterion
AITL	Angioimmunoblastic T-cell lymphoma
ALK-	Anaplastic lymphoma kinase-negative
ALK+	Anaplastic lymphoma kinase-positive
AlloSCT	Allogeneic stem cell transplant
ASCT	Autologous stem cell transplant
ASH	American Society of Haematology
ATLL	Adult T-cell leukaemia /lymphoma
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criteria
BNF	British national formulary
BV	Brentuximab vedotin
BV+CHP	Brentuximab vedotin + Cyclophosphamide, Hydroxydaunomycin (doxorubicin), Prednisolone/ prednisone
CDF	Cancer Drugs Fund
CHOP	Cyclophosphamide, Hydroxydaunomycin (doxorubicin), Oncovin® (vincristine), Prednisolone/ prednisone
CHP	Cyclophosphamide, doxorubicin and prednisone
CI	Confidence interval
CR	Complete response
CRF	Case report form
DLBCL	Diffuse large B-cell lymphoma
DOR	Duration of response
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
EQ-5D	EuroQol – 5 dimensions
FDA	US Food and Drug Administration
GCP	Good clinical practice
G-CSF	Granulocyte colony stimulating factor
GvHD	Graft versus host disease
HL	Hodgkin lymphoma
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
ICML	International Conference on Malignant Lymphoma
IFR	Individual funding requests
INV	Investigator
IPI	International Prognostic Index
IPTR	Individual Patient Treatment Requests
IQR	Interquartile range
IRF	Independent review facility

ITT	Intention-to-treat
LY	Life year
LYs	Life years
MMAE	Monomethyl auristatin E
MRU	Medical resource use
NE	Not estimable
NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute of Health and Care Excellence
NPM	Nucleophosmin
NPP	Named Patient Programme
ORR	Objective response rate
OS	Overall survival
PACE	Patient And Clinician Engagement
PartSA	Partitioned survival approach
PAS	Patient access scheme
PD	Progressed disease
PET-CT	Positron emission tomography–computed tomography
PFS	Progression-free survival
PICOS	Patients, Interventions, Comparators, Outcome and Study design
PPS	Post-progression survival
PR	Partial remission
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma – not otherwise specified
QALY	Quality-adjusted like year
R/R or r/r	Relapsed or refractory
RCT	Randomised controlled trial
RIC	Reduced intensity conditioning
SAE	Serious adverse event
sALCL	Systemic anaplastic large cell lymphoma
SCT	Stem cell transplant
SD	Stable disease
SD	Standard deviation
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SmPC	Summary of Product Characteristics
SoC	Standard-of-care
SPD	Sum of the product of diameters
TEAE	Treatment-emergent adverse event
TSD	Technical support document
TSE	Two-stage estimator
VAPEC-B	Vincristine, doxorubicin (Adriamycin), Prednisone, Etoposide, Cyclophosphamide, Bleomycin

Executive Summary

Peripheral T-Cell Lymphoma (PTCL) is a rare subset of Non-Hodgkin's Lymphoma (NHL), comprising about 5-10% of all new NHL cases in the UK. There are many subtypes of PTCL, with the most common being PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL) and systemic anaplastic large cell lymphoma (sALCL). Although the exact prognosis varies by subtype, PTCL is generally an aggressive disease associated with poor outcomes. The median age at diagnosis of PTCL is approximately 58 years old and, in the UK, patients are commonly diagnosed with late-stage disease which correlates with reduced survival. Relapse and the development of chemotherapy-resistant disease is common in PTCL and early relapse is a poor prognostic indicator.

The overall aim of treatment in newly-diagnosed PTCL is to use front-line therapy to induce a long-term remission by attaining a deep, durable response. The natural history of the disease means that the best chance of inducing a long-term response is in the front-line setting. The NICE pathway recommends the use of combination chemotherapy with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) as front-line treatment for PTCL and clinical experts indicated that six cycles of CHOP is the standard of care in the UK. However, few patients achieve complete remission with CHOP, and of those that do, many relapse within the first year. Despite widespread use of CHOP over the past 30-years, significant unmet need still remains, as PTCL has one of the worst survival rates among lymphoid malignancies. A more effective front-line treatment is required, as all previous efforts to improve on CHOP have failed. These efforts included the use of alternate or more intensive combination treatment approaches, including consolidation with autologous stem cell transplant (ASCT) in some patients.

Brentuximab vedotin (BV) is a targeted and highly innovative therapy which is already approved by the European Medicines Agency (EMA) and recommended by NICE as monotherapy for the treatment of relapsed or refractory (R/R) sALCL. Neither re-treatment with BV for R/R sALCL nor the use of BV at relapse in non-sALCL are currently reimbursed in the UK. The use of BV in combination with cyclophosphamide, doxorubicin and prednisone (BV+CHP) for previously untreated patients with CD30+ PTCL was recently investigated in a phase III double-blind, randomised controlled trial (ECHELON-2) that directly compared BV+CHP vs. CHOP in 452 patients with CD30+ PTCL. Patients received a mean of 6.0 and 5.8 cycles of BV+CHP or CHOP, respectively.

Compared with CHOP, BV+CHP showed the following in the ECHELON-2 trial:

- a 29% reduction in the risk of a PFS event, the primary endpoint (HR 0.71 [95% CI: 0.54 - 0.93], p=0.011).
- reduction of risk of death by 34% vs. CHOP (HR 0.66 [95% CI: 0.46 - 0.95], p=0.0244); median OS has not been reached in either arm after a median follow-up of 42.1 months.

- median PFS with BV+CHP was 48.2 months vs. 20.8 months with CHOP, after a median follow-up of 36.2 months.
- PFS and OS benefits generally consistent across all evaluable subtypes of PTCL.

ECHELON-2 is the first prospective trial to show an OS benefit over CHOP, and it's notable that this came without an observed increase in toxicity. The rates of neutropenia, febrile neutropenia and peripheral neuropathy were similar between BV+CHP and CHOP. The improved OS seen in ECHELON-2 was observed despite patients in the CHOP arm receiving subsequent BV on progression, thus illustrating that best patient outcomes are achieved if BV is used as front-line therapy. A pre-specified sensitivity analysis of PFS showed that the benefits of BV+CHP over CHOP are present regardless of whether or not patients received a consolidative SCT.

The ECHELON-2 trial represents a significant increase in the quality of evidence compared to most other studies in PTCL, the majority of which are either single-arm studies or retrospective analyses. As a result of the positive ECHELON-2 data, BV+CHP is awaiting EMA approval for the front-line treatment of adults with untreated CD30+ PTCL, an indication for which it has orphan status. BV+CHP is regarded by clinical experts as an exciting new front-line therapy, with the potential to replace CHOP as the standard of care and make a significant impact on patient outcomes.

A health economic model was developed to assess the cost-effectiveness of BV+CHP compared with CHOP for the treatment of patients with untreated CD30+ PTCL. The clinical data for the model were taken directly from the ECHELON-2 trial. Standard parametric approaches were conducted to determine health state membership. To reflect UK clinical practice, further statistical analysis attempted to remove the effect of subsequent BV use in those patients where it is neither available nor reimbursed in the UK (i.e. to remove re-treatment with BV in the BV+CHP arm and remove the use of BV at relapse in non-sALCL subtypes). All approaches to adjust for treatment switching recommended by the NICE DSU were explored; the two-stage estimator (TSE) excluding re-censoring was deemed the most suited to the dataset and is applied in the base-case results.

The base case analysis including the existing PAS of BV shows that in the ITT population (i.e. untreated CD30+ PTCL), BV+CHP is associated with incremental costs of [redacted], an incremental life year (LY) gain of 1.55 years, and an incremental quality adjusted life year (QALY) gain of [redacted] QALYs, compared with CHOP. The resulting incremental cost-effectiveness ratio (ICER) is £24,901 per QALY gained. Cost-effectiveness results are also presented for the sALCL subgroup, which was considered as a secondary analysis in the ECHELON-2 trial and, due to the reimbursement of BV in R/R sALCL, has a different treatment pathway to other PTCL subtypes in the UK. The ICER in the sALCL subgroup, including adjustment for subsequent BV use, is £18,840 per QALY.

Probabilistic analysis simultaneously considers the impact of uncertainty within the model; the results from 5,000 iterations support the deterministic ICER (probabilistic ICER: £25,741). Additionally, extensive clinical input has been sought to validate each of the assumptions underpinning the model. Therefore, we consider our results to form a robust basis for decision making.

To conclude, BV is the first highly innovative and well-tolerated, targeted front-line therapy to show statistically significant improvement in overall survival for patients with PTCL compared to standard of care. Clinical experts anticipate that its approval in the front-line setting stands to be practice changing in the UK. The health economic analysis demonstrates that BV+CHP is a cost-effective option based on standard UK thresholds.

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication.

The full statement of the decision problem is presented in **Table 1**, including the rationale for any amendment or additional inclusion.

BV has previously been assessed by NICE for other indications within its marketing authorisation as follows:

- Brentuximab vedotin for treating CD30-positive Hodgkin lymphoma (TA524)[1]
- Brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma (TA478)[2]
- Brentuximab vedotin for treating CD30-positive cutaneous T-cell lymphoma (TA577)[3]

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with untreated CD30-positive peripheral T-cell lymphoma (PTCL)	Adults with previously untreated CD30+ Peripheral T-Cell Lymphoma (PTCL)	As per final scope
Intervention	Brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone	Brentuximab vedotin (Adcetris®) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP)	As per final scope
Comparator(s)	Established clinical management including: • cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone (CHOP)	Established clinical management including: • cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP)	As per final scope
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life	The following outcomes will be presented: • Progression-free survival (PFS), • Overall survival (OS), • Overall response rate (ORR), including: complete response (CR), • Health related quality of life (HRQoL), and Adverse effects (AE) of treatment.	As per final scope, with the addition of ORR and CR for comprehensiveness.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	The economic analysis will follow the NICE reference case.	As per final scope

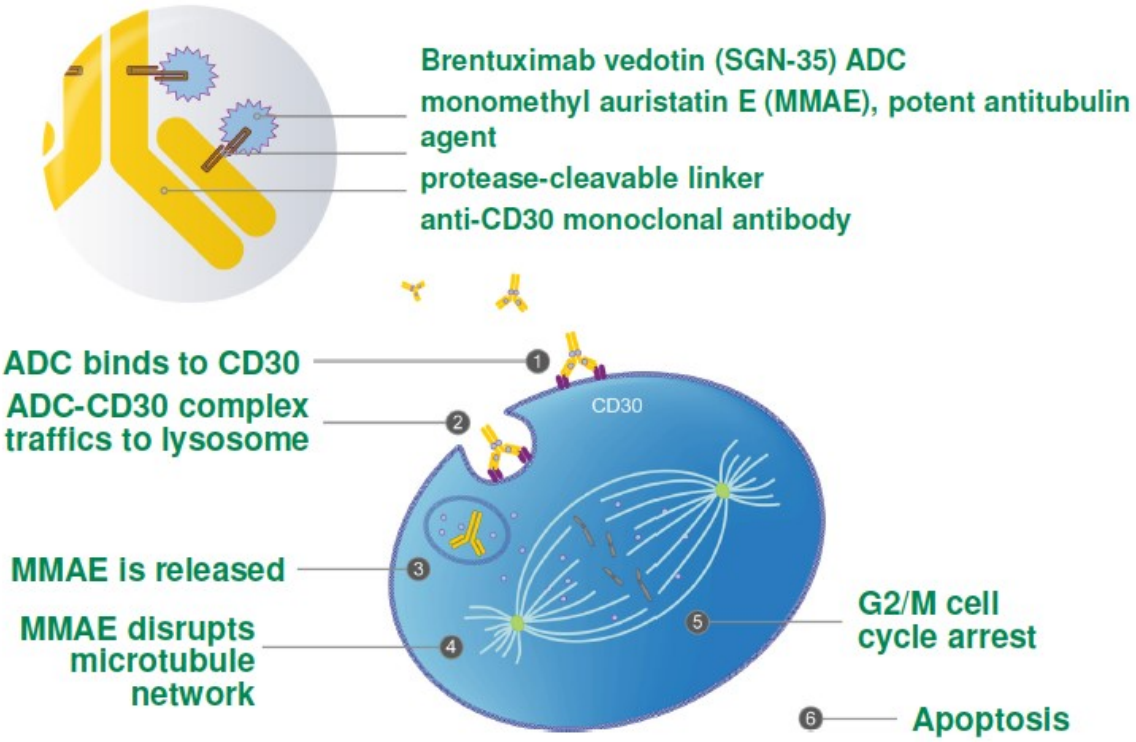
	The availability of any commercial arrangements for the intervention or comparator and subsequent technologies will be taken into account.		
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include people with PTCL not otherwise specified, people with angioimmunoblastic T-cell lymphoma, people with sALCL, people with ALK-positive sALCL and ALK-negative sALCL. Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	The focus of this submission is in line with the ECHELON-2 clinical trial and the expected marketing authorisation, which is all *previously untreated CD30-positive PTCL.* Subgroup analyses will be presented for systemic Anaplastic Large Cell Lymphoma (sALCL).	The ECHELON-2 trial was not designed nor powered to look at outcomes by subtype of PTCL, with the exception of sALCL. Due to an existing regulatory commitment arising from EMA's previous conditional approval of BV for relapsed / refractory (R/R sALCL), an analysis of the sALCL group was a key secondary end-point of the ECHELON-2 trial. A robust analysis of this subgroup is feasible with the available data and this is presented within the dossier. In order to have a similar pool of patients in the ECHELON-2 trial, an inclusion criterion for ALK+ sALCL patients was an IPI score of 2 or higher. ALK+ sALCL patients with a high IPI score (reflecting the group enrolled in ECHELON-2) have similar outcomes to ALK- sALCL patients and therefore clinical advice was to consider sALCL patients as one group (See **Section B.1.3.1**). The data necessary for the other proposed subgroup analyses in the scope are not available, as the ECHELON-2 trial was not designed nor powered to conduct analyses on individual subtypes of PTCL. Any such analyses would be based on extremely small numbers and provide highly uncertain results. As the outcomes and treatment pathway are generally consistent across subtypes of PTCL, the presented base case analysis of all untreated CD30-positive PTCL is aligned to the expected marketing authorisation, and is representative of the clinical- and cost-effectiveness of BV+CHP.

B.1.2 Description of the technology being appraised

The summary of product characteristics and the European public assessment report can be found in appendix C.

BV is an antibody-drug conjugate (ADC) composed of an anti-CD30 monoclonal antibody linked with a cytotoxic anti-mitotic drug compound, monomethyl auristatin E (MMAE).[4-6] BV selectively recognises the CD30 transmembrane cytokine receptor expressed on tumorous lymphoid cells, allowing for the targeted delivery of the MMAE upon internalisation of the ADC. Once the MMAE is released into the cell's cytoplasm via lysosomal degradation of the ADC peptide linkages, MMAE disrupts the microtubule network of the cell, effectively arresting the cell cycle, and thereby inducing selective apoptotic cell death. (**Figure 1**) [4-6]

Figure 1: Brentuximab vedotin mechanism of action



Abbreviations: ADC: antibody drug conjugate; MMAE: monomethyl auristatin E; G2: G2 phase of the cell cycle; M: mitosis phase of the cell cycle

CD30 is a cell membrane protein receptor that is variably expressed on the surface of malignant cells and is used for the diagnosis of peripheral T-cell lymphoma (PTCL). PTCL is composed of several subtypes in which the expression of CD30 on tumour cells can be variable. CD30 is universally expressed (95-100%) on the tumour cells of systemic anaplastic large cell lymphoma (sALCL) and variably

expressed across the other subtypes, including the majority of the most common subtype, PTCL-not otherwise specified (PTCL-NOS), (expressed in approximately 58% of cells).[7]

Details of the licensed indications, dosing, and costs of BV are presented in **Table 2.**

Table 2: Technology being appraised: brentuximab vedotin (BV) in combination with CHP (BV+CHP) for untreated CD30-positive peripheral T-cell lymphoma (PTCL)

UK approved name and brand name	Brentuximab vedotin (Adcetris®)
Mechanism of action	Brentuximab vedotin (BV) is an antibody drug conjugate (ADC) composed of an anti-CD30 monoclonal antibody linked with a microtubule-disrupting, antimitotic drug compound, monomethyl auristatin E (MMAE). [4-6] BV selectively recognises the CD30 transmembrane cytokine receptor of the tumour necrosis factor family expressed on malignant lymphoid cells. Upon internalisation of the ADC through receptor-mediated endocytosis, MMAE is released into the cytoplasm via lysosomal degradation of the ADC peptide linkages. [4,5] The MMAE cytotoxin inhibits tubulin polymerisation, disrupting the microtubule network, effectively arresting the cell cycle, and resulting in apoptotic cell death.[4-6] (**Figure 1**)
Marketing authorisation/CE mark status	In January 2009, the EMA's Committee for Orphan Medicinal Products (COMP), designated BV as an orphan medicinal product **for treatment of anaplastic large cell lymphoma (ALCL**) (EU/3/08/595) **and treatment of Hodgkin Lymphoma (HL)** (EU/3/08/596)[8] • On 24 January 2019, COMP recommended that the orphan designation for BV (EU/3/08/596) **for the treatment of HL** be maintained (EMA/115413/2019)[8] On 25 October 2012, Takeda was granted a conditional marketing authorisation for BV **for relapsed or refractory HL and ALCL** by the European Commission (EU/1/12/794/001)[9] On 11 January 2012, the European Commission granted orphan designation (EU/3/11/939) for BV **for the treatment of cutaneous T-cell lymphoma** (CTCL) to Takeda. On 15 December 2017 BV was granted a marketing authorisation in the EU **for treatment of cutaneous T-Cell lymphoma** (CTCL). In July 2019, the COMP adopted a positive opinion to amend the current BV Orphan Designation from systemic anaplastic large cell lymphoma (sALCL) to peripheral T-cell lymphoma (PTCL). A regulatory filing for BV in combination with CHP for previously untreated CD30+ peripheral T-cell lymphoma (PTCL) was submitted to the EMA in June 2019. A positive CHMP opinion is anticipated in March 2020, with marketing authorisation expected between May and June 2020. It is anticipated that BV in combination with cyclophosphamide, doxorubicin and prednisone (CHP) will be granted a marketing authorisation **for adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL)**.
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	BV is indicated for: A. The treatment of adult patients with previously untreated CD30+ Stage IV Hodgkin Lymphoma (HL) in combination with doxorubicin, vinblastine, and dacarbazine (AVD).

	B. The treatment of adult patients with relapsed or refractory CD30+ Hodgkin lymphoma (R/R HL): (i) following autologous stem cell transplant (ASCT) or; (ii) following at least two prior therapies when ASCT or multi-agent chemotherapy is not a treatment option. C. The treatment of adult patients with CD30+ HL at increased risk of relapse or progression following ASCT D. The treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (R/R sALCL). E. Treatment of adult patients with CD30+ cutaneous T-cell lymphoma (CTCL) after at least 1 prior systemic therapy For this appraisal, it is anticipated that BV in combination with cyclophosphamide, doxorubicin and prednisone (CHP) will be indicated for adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL).
Method of administration and dosage	BV is to be administered via infusion through a dedicated intravenous line (not as an intravenous push or bolus) under the supervision of a physician experienced in the use of anti-cancer agents. Dosing: *Peripheral T-Cell Lymphoma:* The recommended dose of BV is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks, to be administered in combination with cyclophosphamide [C], doxorubicin [H] and prednisone [P] (CHP). The regimen is referred to as BV+CHP throughout this dossier. For patients weighing more than 100kg, max weight of 100kg is assumed for dosing calculations (i.e. max dose of BV per cycle = 180mg). Dose adjustments may be warranted for conditions such as neutropenia and peripheral neuropathy, as well as for special patient populations such as those patients with renal and hepatic impairment, the elderly, and paediatric. Patients should be monitored during and after infusion. Complete blood counts should be monitored prior to administering each dose of treatment. Patients in the pivotal ECHELON-2 trial for the treatment of untreated PTCL received 6-8 treatment cycles. UK clinical advisors have confirmed that in UK and European practice patients would receive a maximum of 6 treatment cycles of BV+CHP as the current standard of care is 6 cycles of CHOP.
Additional tests or investigations	None; CD30 testing is routine NHS practice during the diagnosis of PTCL.
List price and average cost of a course of treatment	The NHS list price of BV is £2,500 per 50mg vial (ex VAT) Based on mean cycles of 6.0 for the population covered in this submission, derived from the average duration of therapy in ECHELON-2, the mean cost per course for an average patient is estimated at approximately [redacted] per patient without a PAS [redacted] based on the PAS). Note: considering acquisition costs only.
Patient access scheme (if applicable)	As per the agreement with the Department of Health, a patient access scheme (PAS) in the form of a simple discount applies for all licensed indications of BV in the United Kingdom. Unless otherwise stated, the analyses in this submission reflect the 'with PAS' price of BV. Appendix P provides all analyses from the submission reflecting the list price of BV. The current PAS for BV is a straight discount of [redacted] bringing the NHS net acquisition price from £2,500 per vial to [redacted] per vial.

Abbreviations: ADC: antibody drug conjugate; MMAE: monomethyl auristatin E; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase (positive/negative); PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; HL: Hodgkin Lymphoma; COMP: Committee for Orphan Medicinal Products; EU: European Union; EMA: European Medicines Agency; AVD:

doxorubicin [A], vinblastine [V], and dacarbazine [D]; R/R: relapse/refractory; autoSCT: autologous stem cell transplant; CTCL: cutaneous T-Cell lymphoma; mg: milligram; kg: kilogram

B.1.3 Health condition and position of the technology in the treatment pathway

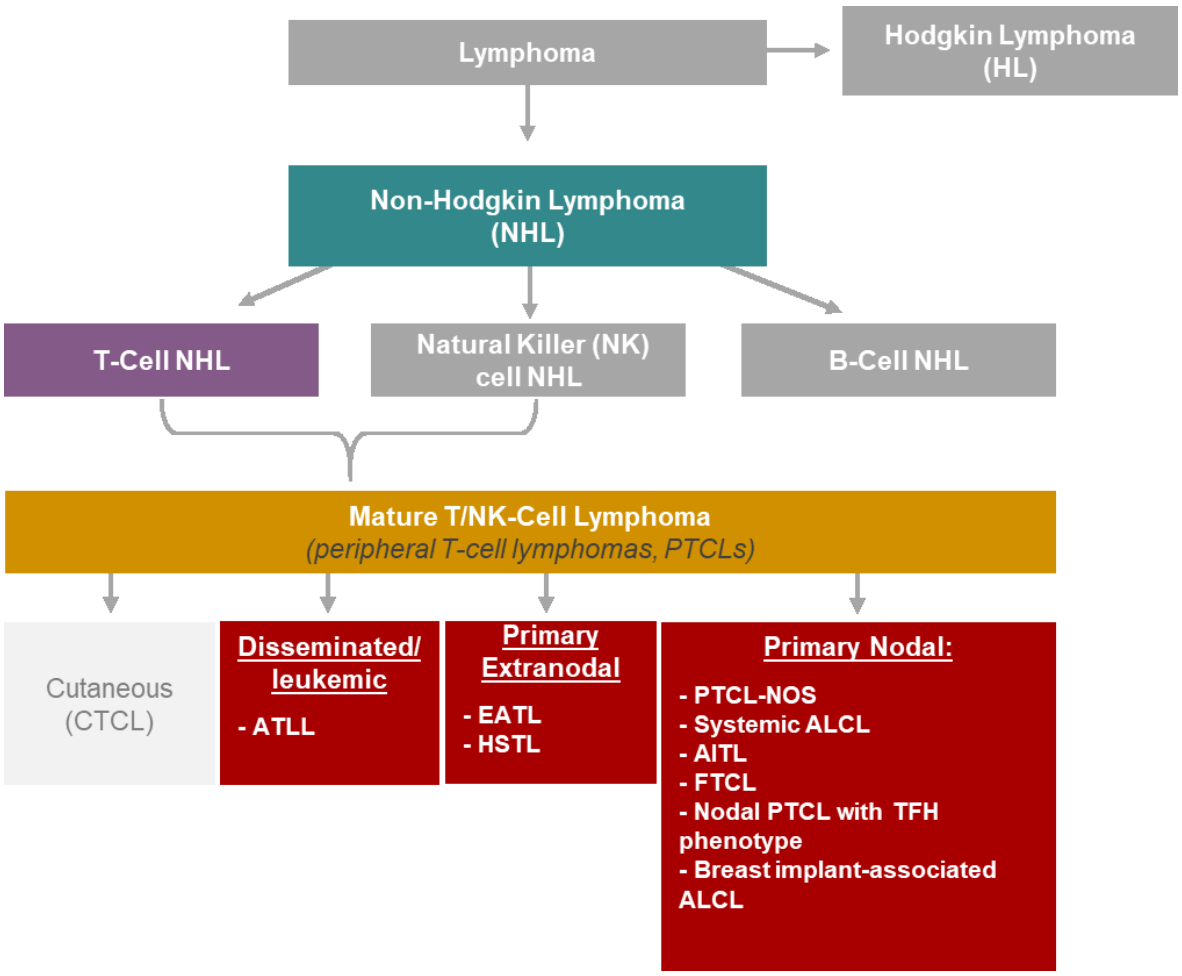
B.1.3.1 Disease overview

Peripheral T-Cell Lymphoma (PTCL) is a rare subset of Non-Hodgkin's Lymphoma (NHL), that carries poor prognostic outcomes. Characterised by the neoplastic development of post-thymic, mature T-Cells, PTCL is sometimes referred to as Mature T-Cell Lymphoma (MTCL).[10-13] PTCL is comprised of a heterogenous group of over 25 subtypes which are classified by the World Health Organization (WHO) into four general categories: 1) disseminated/leukemic, 2) cutaneous, 3) primary nodal, and 4) primary extranodal, based on clinical features (i.e. morphology, immunophenotype, and genetics).

Primary nodal PTCLs are the most common of the PTCL categories, and of the nodal PTCLs the most common subtypes are: PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and systemic anaplastic large cell lymphoma (sALCL). A detailed overview of PTCL subtypes is presented in **Figure 2.**[10]

PTCL-NOS and sALCL are relatively more common in North America and Europe and AITL is more common in Europe compared to international prevalence rates.[14] A brief overview of the most common PTCL subtypes is provided in **Section B.1.3.2.1.**

Figure 2: Peripheral T-Cell Lymphoma (PTCL) as a subset of Non-Hodgkin Lymphoma (NHL)[10]



Abbreviations: HL: Hodgkin Lymphoma; NHL: Non-Hodgkin Lymphoma; NK: Natural Killer; PTCL: peripheral T-cell lymphoma; CTCL: Cutaneous T-cell lymphoma; ATLL: adult T-cell leukemia/lymphoma; EATL: Enteropathy-associated T-cell lymphoma; HSTL: Hepatosplenic T-cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase (positive/negative); AITL: angioimmunoblastic T-cell lymphoma; FTCL: Follicular T-cell lymphoma; TFH: T-follicular helper cell

Although prognostic outcomes and treatment responses vary across subtypes, PTCL is characterised as an aggressive disease, further complicated by frequent relapses, and primary refractory disease.[14-17]

The overall treatment goal for individuals diagnosed with PTCL is to use front-line therapy to induce a long-term remission, and potentially cure the underlying disease by attaining a deep, durable response. Clinical experts advise that the best chance of inducing a long-term response in T-cell lymphomas is in the front-line setting, and that the probability of having a strong response to treatment diminishes significantly with relapse. This consensus is reflected in the literature (referenced in **Section B.1.3.6.2**) regarding the markedly improved 5-year OS rates for individuals with PTCL who are able to achieve 2-year event-free survival.[18] For individuals who

relapse after primary treatment, PFS and OS are extremely poor at 3.1 and 5.5 months respectively, demonstrating that the best chance of inducing long-term remission and improving the survival prospects for patients with PTCL is in the front-line setting.[19] However, advances in treatment for PTCL have been slow to develop with most new technologies failing to secure EMA approvals due to moderate supporting data.[20,21]

The treatments that are currently used are typically derived from historic B-Cell lymphoma combination chemotherapy regimens that were developed over 30 years ago (e.g. CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone/prednisolone [P]). These regimens lack robust randomised-controlled evidence in the PTCL population.[16,22] The evidence that does exist for such regimens in PTCL is largely derived from single-arm, Phase II, retrospective analyses and clinical experience.[23-29] Few patients with PTCL achieve complete remission with CHOP therapy, and for those that do, many often relapse within the first year, further highlighting the unmet need for more efficacious front-line treatment.[30] Several trials have attempted to improve survival outcomes in the front-line treatment of PTCL through the integration of novel therapeutic agents into current treatment regimens, or via chemotherapy dose modifications, but without success.[22] Hence, the current standard front-line therapy in the UK remains 6 cycles of CHOP chemotherapy.[16]

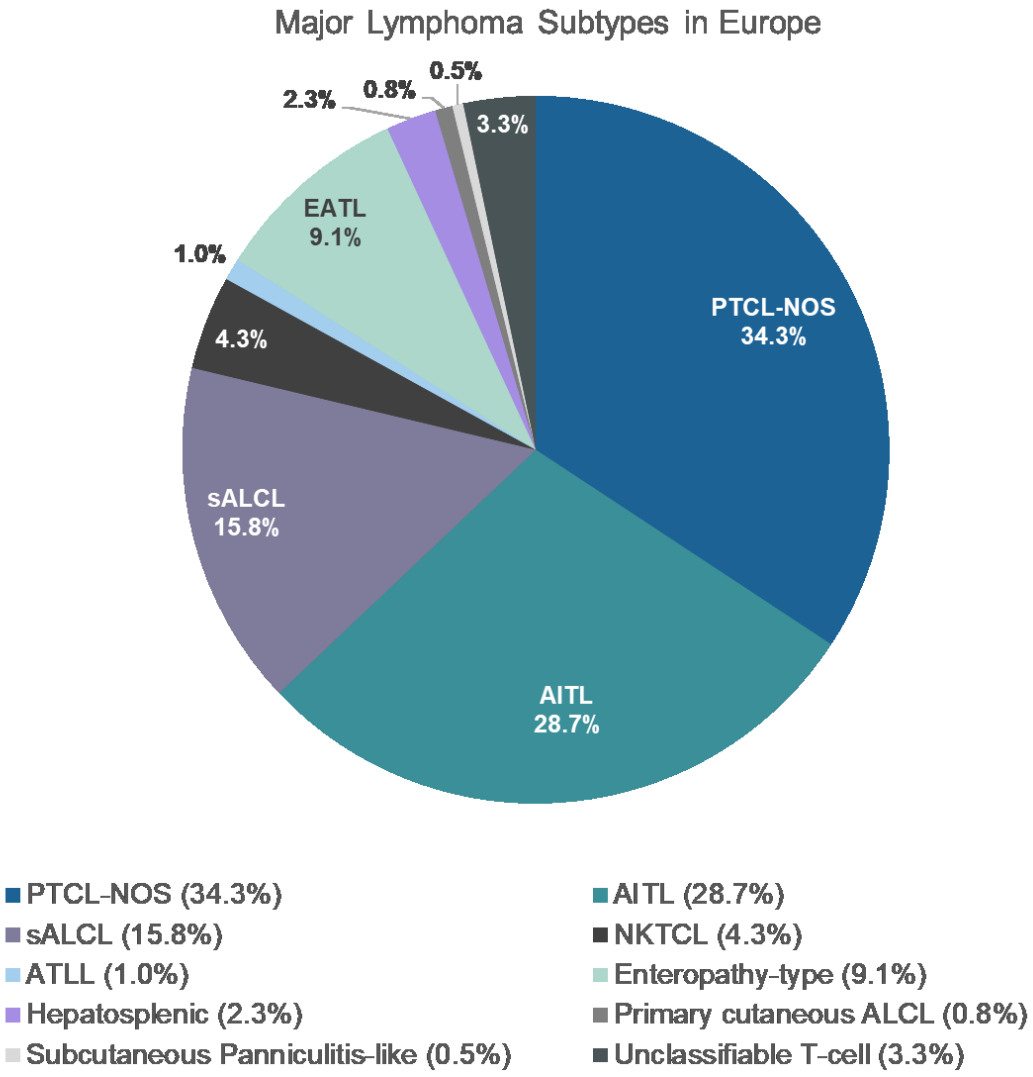
For patients in the UK who have received CHOP therapy, complete remission rates are generally considered low (43.5%) with a median time to progression of disease of less than a year (10.2 months).[31] The 5-year OS and PFS for all patients was 38.8% (95% CI 30.5–47.0) and 19.8% (95% CI 13.7–26.8) respectively. When the analysis was limited to CHOP-treated patients; the 5-year OS and PFS was 41.1% (95% CI 31.1–51.5) and 26.3% (95% CI 17.9–35.5), accordingly..[31] The IPI score is a clinical tool used to aid in predicting the prognosis of patients with NHL (see **Section B.1.3.3** for more details). Patients diagnosed with PTCL in the UK are more commonly diagnosed with late stage disease (stage III/IV) with symptomatic presentation and are likely to have IPI scores of 2 or above. [31] OS rates decrease substantially for patients with advanced disease stages and higher IPI score.[30,31] Specifically, the 5-year OS rates for patients treated with CHOP in the UK with an IPI score of 2 is reported at a mere 20%, and as low as 8% for those diagnosed with an IPI score of 4-5.[31]

B.1.3.2 Epidemiology

In the UK, NHL is the sixth most commonly diagnosed cancer, accounting for approximately 4% of all new cancer cases in 2015, with an incidence rate of 22.9 per 100,000 persons (2016) [32]. Similar to the prevalence in other Western countries, PTCL comprises approximately 5-10% of all new NHL cases diagnosed in the UK.[14,17,33] According to a 10-year retrospective review of PTCL cases from two major

UK hospitals, those diagnosed are predominately male and have a median age at diagnosis of approximately 58 years.[31] PTCL-NOS is the most common PTCL subtype diagnosed in Europe, accounting for 34.3% of all PTCL diagnoses, followed by angioimmunoblastic T-cell lymphoma (AITL) (28.7%), and sALCL at 15.8% (**Figure 3**).[14] Cutaneous T-cell lymphomas (i.e. primary cutaneous presentation) and Natural Killer/T-Cell Lymphomas (NKTCL) are not considered within this submission and are not included in the NICE scope.

Figure 3: Distribution of PTCL Diagnosis in the Europe [14]



Abbreviations: PTCL-NOS: Peripheral T-Cell Lymphoma not otherwise specified; sALCL: systemic Anaplastic Large Cell Lymphoma; ATLL: adult T-cell leukemia/lymphoma; EATL:Enteropathy-type T-cell Lymphoma; AITL: angioimmunoblastic T-cell lymphoma; Natural Killer/T-Cell Lymphoma; ALCL: Anaplastic Large Cell Lymphoma

B.1.3.2.1 *CD30 expression in PTCL*

Among the various classifications of PTCL, CD30 is a protein commonly expressed on the cell surface of tumour cells.[7] Of the primary nodal PTCL subtypes, CD30 is

almost universally expressed in the sALCL subtype (95-100% of sALCL are CD30+ which is considered a hallmark of the disease, and is included as part of the diagnostic work-up.[7,10,34]. Further detail regarding disease characteristics for the sALCL subgroup are presented in **Section B.1.3.2.2**. CD30 is variably expressed across the other subtypes of PTCL, including the majority of PTCL-NOS.[7,34,35] Overall, approximately 50% of all PTCLs express CD30.[7] BV offers a novel treatment approach that selectively targets CD30+ cells and as such it is targeted for the treatment of CD30+ malignancies. However, although CD30 positivity is important for the activity of BV, there's no evidence that it is more efficacious in lymphomas with higher levels of CD30 expression nor that the benefit of BV is correlated with the degree of CD30 expression (see **Section B.2.6.1.2** and **Figure 15**).

B.1.3.2.2 ***Overview of the most common PTCL subtypes***

PTCL-NOS

PTCLs that do not meet specific diagnostic criteria listed in the current WHO PTCL sub-classifications, receive the designation of PTCL-NOS. PTCL-NOS is the most common subtype internationally and approximately 58% of tumours are CD30+ [7]. PTCL-NOS is largely diagnosed in the elderly population (median age 60 years) and men are twice as likely to developed PTCL-NOS as women. [14,36]

AITL

Angioimmunoblastic T-cell lymphoma (AITL) is the second most common nodal PTCL and typically presents with advanced disease, systemic symptoms and immune deregulation, the latter being its differentiating characteristic. AITL generally occurs in middle-aged and elderly individuals and presents more frequently in men than women. Bossard et al reported that any CD30 expression was detected in approximately 60% of AITL tumours. [7]

sALCL

Primary nodal sALCL are mature T-cell lymphomas that can be further subdivided into anaplastic lymphoma kinase positive (ALK+) and anaplastic lymphoma kinase negative (ALK-) subtypes, depending on the presence or absence of the ALK protein marker.

ALK+ sALCL is most often diagnosed in children (median age 10.2 years) and young adults (median age 34 years at diagnosis), who are predominately male. ALK- sALCL is most commonly diagnosed in elderly individuals (median age 54-61 years at diagnosis).[10,14,16,34,37,38]

Patients with sALCL are typically diagnosed with late-stage disease (III-IV) and present with systemic symptomology, also known as B-symptoms (i.e. fever, night sweats, weight loss). Outcomes in sALCL, regardless of ALK status, are highly

dependent on age at diagnosis and IPI score (detailed in **Sections B.1.3.3.2** and **B.1.3.4)**.

ALK+ sALCL is often associated with a better prognosis compared to other PTCLs, however favourable outcomes for individuals diagnosed with ALK+ sALCL are often attributed to their younger age. However, patients who are ≥40 years at diagnosis have poor outcomes which are akin to other types of PTCL, meaning the favourable prognostic features characteristic of ALK+ sALCL, are no longer observed.[25,39] (See **Section B.1.3.3.2**) Furthermore, individuals with ALK+ sALCL that have a high IPI score (≥2) have considerably worse outcomes than those with lower IPI scores. Indeed, the prognostic outcomes of ALK+ individuals with high IPI scores are similar to the outcomes of ALK- sALCL. [14,25,27] **(See Section B.1.3.4**)

B.1.3.3 Staging and definition of advanced-stage disease

Diagnosis of PTCL can be challenging and is based on an evaluation of several distinct molecular/histological features utilising immunohistochemistry, flow cytometry, molecular genetics, and cytogenetic methods by an experienced haematopathologist.[16,40-43] The clinical workup to determine risk based on staging and prognosis includes both clinical and laboratory data related to: patient history, physical examination, complete blood count (CBC) with differential, bone marrow biopsy and aspirate, lactate dehydrogenase (LDH) and uric acid levels, comprehensive metabolic panel, and positron emission tomography (PET)/computed tomography (CT) scan. Timely and accurate diagnosis and PTCL subtype recognition is critical in determining an appropriate treatment course. Diagnosis can be challenging and as such, patients may receive the broad diagnosis of PTCL-NOS.[42]

B.1.3.3.1 *Staging*

Based on the Lugano Modification of Ann Arbor staging system, there are four cancer stages of lymphoma presented in **Table 3**.[44,45]

Table 3: Lugano Modification of Ann Arbor staging[a]

Stage	Involvement	Extranodal (E) Status
Limited		
Stage I	one node or a cluster of lymph nodes	Single extranodal lesions without nodal involvement
Stage II	two or more nodal clusters either above OR below the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
Stage II bulky*	Stage II criteria with 'bulky' disease classification	N/A
Advanced		
Stage III	Cancer in lymph tissue above AND below the diaphragm. Nodes above the diaphragm with spleen involvement	N/A
Stage IV	Non-contiguous extra-lymphatic involvement	N/A

[a]Table adapted from Cheson et al 2014[45]
*Bulky disease for HL is defined as single nodes ≥10cm in diameter, however tumour size/bulk criteria for NHL have not been validated.

B.1.3.3.2 *Prognostic indicators*

The International Prognostic Index (IPI) is most commonly used to assess prognosis based on risk factors for nodal PTCL. The risk factors considered within an IPI score include:[41,46]

i) >60 years of age
ii) elevated LDH
iii) ECOG performance status score of ≥2
iv) Stage III or IV cancer
v) more than one extranodal site

Each risk factor is worth one point and are summed to provide a total IPI score (maximum score of 5). An increase in numerical score indicates greater disease severity and higher risk disease.

The prognostic factors that determine IPI scores have been shown to be highly significant predictors of PFS and OS outcomes.[27] UK clinical experts confirmed that an IPI score is a predictive variable of patient outcome and is routinely used in clinical practice across the UK.[47,48] IPI scores are effective for defining different risk categories for patients with PTCL-NOS or sALCL, regardless of ALK status (**Table 4**).[14,17,25,49] As demonstrated in the table below, 5-year OS substantially decreases with increasing IPI score, most notably for IPI scores greater than or equal to 2. This is particularly relevant to the ALK+ sALCL subtype where a substantial decrease in 5-year survival is observed for patients with intermediate and high IPI scores compared to those with low IPI scores.

Table 4: **Prognostic index scores and 5-year OS for PTCL-NOS and sALCL**[14,25,27]

PTCL Subtype	Risk Category	IPI Score	5-year OS
PTCL-NOS	Low	0-1	50%
	Intermediate-Low	2	33%
	Intermediate-High	3	16%
	High	4-5	11-13%
ALK+, sALCL	Low	0-1	90%
	Intermediate-Low	2	68%
	Intermediate-High	3	23%
	High	4-5	33%
ALK-, sALCL	Low	0-1	74%
	Intermediate-Low	2	62%
	Intermediate-High	3	31%
	High	4-5	13%

Abbreviations: PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; ALK+, ALCL: anaplastic lymphoma kinase-negative, anaplastic large cell lymphoma; anaplastic lymphoma kinase-positive, anaplastic large cell lymphoma; IPI: International Prognostic Index; OS: overall survival; PIT: Prognostic Index for PTCL; N/A: not applicable

B.1.3.4 Life Expectancy

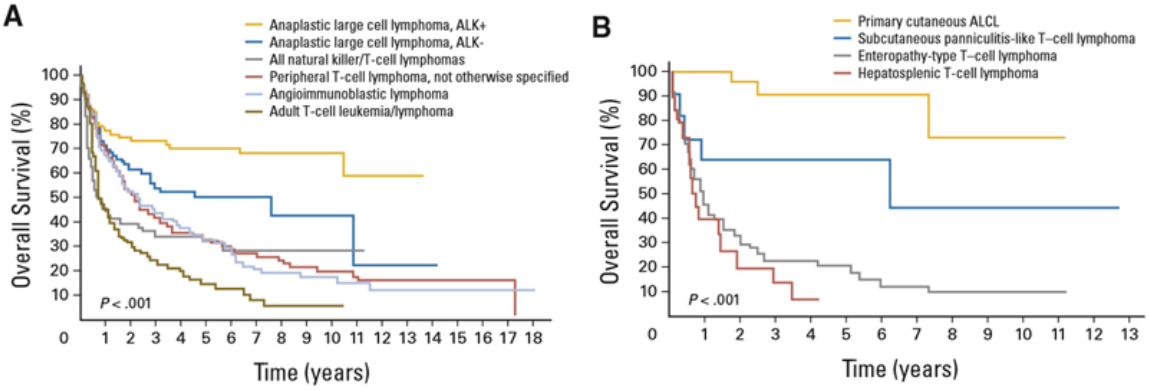
Knowledge and understanding of the expected outcomes for patients with PTCL is largely based on single-arm Phase II studies or retrospective analyses from observational data.[23] The lack of robustness of the evidence base for outcomes is reflected in the variability of PFS and OS reported across trials. In general, prognostic outcomes for PTCL (regardless of IPI score) are poor. With the exception of ALK+ sALCL in younger patients, PTCL has one of the worst survival rates among lymphoid malignancies, with 5-year OS between 7-49%.[14] This demonstrates the high unmet need for these patients but also the considerable variability in reported survival for PTCL depicted by the wide range. Detailed median 5-year OS by PTCL subtype is provided in **Table 5**, and **Figure 4A** and **6B**. Please note that the ALK+ sALCL outcomes depicted in **Table 5** represent all patients of this histology, regardless of prognostically important factors such as IPI score or age; the impacts of which were discussed previously in **Section B.1.3.3** and in further detail below. A 10-year audit of PTCL patients by Gleeson et al found that 5-year survival of patients with PTCL was 38.8% [31]. This UK audit was based on data from two academic centres with patient records spanning from 2002-2012 and does not reflect the changes in treatment in R/R sALCL.[31]

Table 5: 5-year Overall Survival by PTCL Subtype†[14]

PTCL Subtype	5-year Overall Survival (OS)
PTCL-NOS	32%
AITL	32%
EATL	20%
ALCL, ALK-	49%
ALCL, ALK+	70%
ATLL	14%
HSTL	7%

†5-year OS presented regardless of IPI score
Abbreviations: PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; EATL: enteropathy-associated T-cell lymphoma; ALCL, ALK+/-: anaplastic large cell lymphoma, anaplastic lymphoma kinase -/+; ATTL: adult T-cell leukemia/lymphoma; HSTL: hepatosplenic T-cell lymphoma

Figure 4: 5-year Overall Survival by PTCL Subtype†[14]

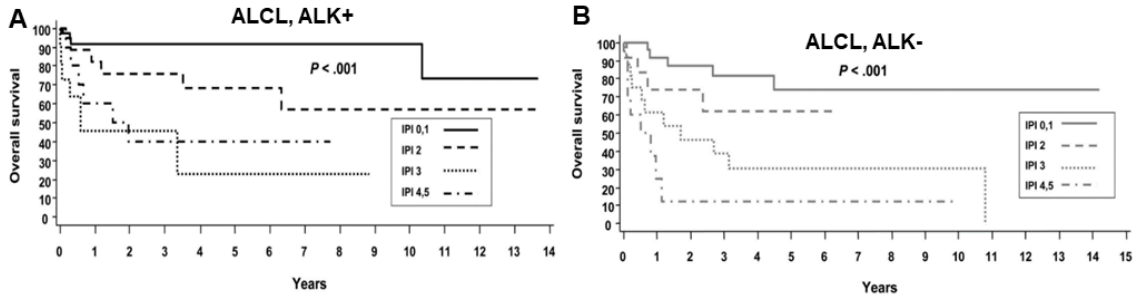


†Figure adapted from Vose et al 2008[14] Figures A and B: survival curves for various subtypes of PTCL
Abbreviations: PTCL: peripheral T-cell lymphoma; ALCL, ALK +/-: anaplastic large cell lymphoma, anaplastic lymphoma kinase +/-

Although overall ALK+ sALCL has a slightly better prognosis than other PTCL subtypes with a 5-year OS of 70%,the 5-year OS rates drop dramatically from 90% for an IPI score of 0-1, to 68% and 23% for an IPI scores of 2 or 3, respectively (see **Table 4** and **Figure 5A** and **7B)**.[25] These data also confirm that patients with ALK+ sALCL with a higher IPI score (≥2) have a prognosis that is similarly poor to that of patients with ALK- sALCL with higher IPI scores, and considerably worse than the prognosis of patients with ALK- sALCL with lower IPI scores. Furthermore, age at diagnosis is one of the strongest independent prognostic factors, substantially decreasing OS and PFS for diagnosed individuals ≥40 years of age (Figure 3).[39]. This was confirmed by UK clinical experts who ranked age as the most important prognostic factor of survival for patients with PTCL.[48] Moskowitz et al. (2014) suggest that patients presenting with ALK+ sALCL over the age of 40 are considered higher-risk patients and should be treated similar to patients who present with less favourable PTCL subtypes.[50]

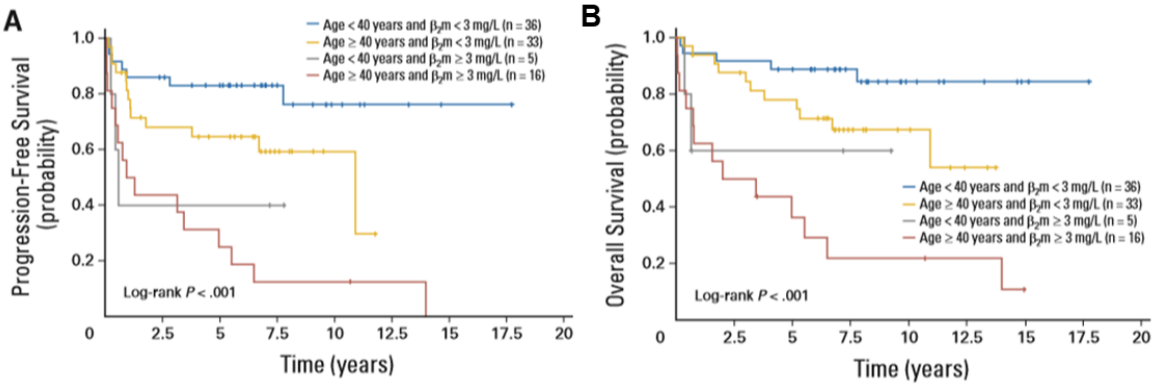
Therefore, for patients with sALCL it's vital to consider the IPI score and age as well as the ALK status when assessing prognosis.

Figure 5: 5-year Overall Survival sALCL by ALK +/- Subtype and IPI score†[25]



†Figure adapted from Savage et al 2008[25]. Figures A: Survival curves by IPI score for sALCL, ALK+; Figure B: Survival Curves by IPI score for sALCL, ALK-.
Abbreviations: IPI: international prognostic index; ALCL, ALK +/-: anaplastic large cell lymphoma, anaplastic lymphoma kinase +/-

Figure 6: sALCL Survival Outcomes by Age†



†Figure adapted from Sibone et al 2012[39]
Figure A: Progression Free Survival of sALCL by age and β_2 microglobulin level; Figure B: Overall Survival of sALCL by age and β_2 microglobulin level
Abbreviations: sALCL: systemic anaplastic large cell lymphoma; β_2m: β_2 microglobulin

B.1.3.5 Burden to Patients, Carers and Society

The rarity of PTCL makes the recruitment of individuals into clinical trials considerably challenging. As a consequence, there is a dearth of information regarding the burden of PTCL specifically to patients, carers, and society. However, data from broader cohorts of patients with NHL (which include patients with PTCL) provide some data regarding disease burden of haematological cancers within these groups. Treatment for aggressive haematologic cancers is characterised by intensive inpatient treatment and is associated with debilitating side effects related to both physical and cognitive functioning including, but not limited to; fatigue, pain, dyspnoea, insomnia, and problems with concentration and memory.[51] Furthermore, patients receiving consolidation treatment with SCT risk experiencing severe adverse events from added treatments aimed at the ablation of endogenous immune cells and use of immunosuppressive medication.[52] Both physical and cognitive

deficits, as well as post-traumatic stress disorder (PTSD) can remain during survivorship and have a substantial negative impact on a person's quality of life.[53]

Fear of relapse is reported by the majority of patients diagnosed with NHL during survivorship, regardless of staging or aggressiveness of the disease subtype.[51] The probability of relapse after primary therapy is high for individuals diagnosed with PTCL, with a median time to relapse or progression of disease of 6.7-10.2 months.[19,31] For individuals who relapse after primary treatment, PFS and OS are extremely poor at 3.1 and 5.5 months respectively, demonstrating that the best chance of inducing long-term remission for patients with PTCL is in the front-line setting.[19] Forty percent of those who survived from a large prospective NHL cohort reported they did not feel hopeful and experienced feelings of 'lack of life purpose'.[51] Additionally, 65% of the cohort thought they did not receive sufficient support from others.[51] Improving treatment in the front-line setting provides the best chance of reducing the fear associated with the high rate of relapse.

There is an additional lack of prospective information regarding health-related quality of life (HRQoL) for individuals diagnosed with PTCL. However, drawing from a broader population of NHL haematological cancers may provide some insight. Quality of life scores, as measured by the Medical Outcomes Study Short Form-36 (SF-36) in a long-term follow-up study of 566 patients diagnosed with NHL significantly declined over the 5-year follow-up period.[53] Older age and increased comorbidities were independent predictors of poor quality of life.[53] Conversely, in a large international study evaluating health utility, patients with R/R HL and sALCL who achieved a more favourable response to treatment reported a reduced burden of disease.[54] The European Society for Medical Oncology (ESMO) Consensus Conference on malignant lymphoma published recommendations for the clinical management of the elderly patient with malignant lymphoma. Despite the lack of HRQoL data from clinical trials or other sources, ESMO recommended that quality of life should be considered as a prognostic indicator of survival and included as a major end point in clinical trials for patients with PTCL.[55]

Although practice is variable across the UK, some patients do receive a consolidative ASCT following front-line treatment with CHOP. In a study analysing the impact of SCTs, 23- 36% of patients with haematological cancers who were eligible and received stem cell transplants, reported having high levels of fear of cancer recurrence (FCR) for up to 12-months post-transplant.[56] Patients with higher FCR had a significantly lower HRQoL with differences reported in the emotional functioning, social functioning, global quality of life, physical functioning, and role functioning subscales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30).[56] Additionally, negative perceptions of cancer's impact was related to patients with NHL that reported having 'ever received a transplant'.[53] The FCR associated with SCT can be extended to other transplant treatment options (i.e. consolidated ASCT) and these

studies demonstrate the considerable negative affect FCR has on quality of life. Front-line treatments aimed at preventing disease progression and improving CR rates, regardless of transplant eligibility, stand to reduce FCR and the burden to the patient, carer, and society.

B.1.3.6 Treatment Guidelines for Previously Untreated PTCL in the UK

B.1.3.6.1 *Front-line Therapy*

The majority of patients with PTCL are diagnosed with an advanced stage of disease (III and IV), are 58 years and older on average (with the exception of ALK+ sALCL with median age at diagnosis of 34 years) and require systemic treatment (i.e. chemotherapy).[31] The current UK guidelines for the treatment of PTCL-NOS and sALCL are presented in **Figure 7** As discussed in **Section B.1.3.1**, CHOP is considered the standard front-line treatment for PTCL and is recommended by NICE Pathways as a first-line treatment for PTCL.[15,16,41,44,57,58] This was supported by a UK survey of ten clinical experts with experience of managing PTCL who reported that 85% of nodal PTCL patients are treated with a CHOP based regimen in the front-line setting. [58] Six cycles of combination chemotherapy using the CHOP regimen is the most commonly used treatment and is considered the current standard of care.[44] UK based clinical experts, who took part in a cross-functional advisory board organised by Takeda, have confirmed that six cycles of CHOP chemotherapy is the maximum administered in the UK and across Europe for the front-line treatment of PTCL.[59].

However, CHOP has its limitations and outcomes remain sub-optimal for the various nodal PTCL subtypes, including ALK+ sALCL with an IPI score of ≥2. A recent UK 10-year retrospective analysis of CHOP therapy in PTCL reported CR rates of 34.6% for PTCL-NOS, 50% for ALK- sALCL, and 80% for ALK+ sALCL.[31] However, although most of the patients treated with CHOP experienced an initial response, the majority progressed. The 5-year OS rates following front-line CHOP treatment by IPI score in the audit were:

- IPI score 2: 20.8% (95% CI: 5.3-43.3%)
- IPI score 3: 24% (95% CI: 8.5-43.8%), and
- IPI score 4/5: 8.3% (95% CI: 0.5-31.1%) [31]

In addition, there was a statistically significant reduction in OS for those with an IPI score of ≥2 relative to those with an IPI score of 1 (HR: 8.52; 95% CI: 1.84-39.6).[31] Despite OS variation across subtypes, those with higher IPI scores had the worst outcomes. For patients who achieve two-year event-free survival, relapse is less common and there is a substantial increase in 5-year OS of 77%, versus 10% for those not achieving two-year event-free survival.[18] This demonstrates the importance of providing patients with the most effective treatment possible in the front-line setting to improve OS and quality of life.

As part of efforts to improve upon CHOP, the addition of etoposide [E] to form the CHOEP regimen has been considered, but with variable and inconclusive results across studies. For patients under the age of 60 years, CHOEP has demonstrated some benefit when coupled with up-front ASCT, particularly for ALK- sALCL (5 years: OS, 70%; PFS, 61%) and small improvements for PTCL-NOS (5 years: OS, 52%; PFS, 47%).[60] A retrospective subset analysis of completed prospective studies showed a 3-year event-free survival advantage for CHOEP (75·4%) vs. CHOP (51·0%) in a subset of younger (≤60 years), more favourable patients, with the greatest benefit seen in patients with ALK+ sALCL.[61] However, recent studies (including a meta-analysis of CHOP vs. CHOEP treatment for PTCL) demonstrate that CHOEP provides no improvement in OS or treatment response outcomes (CR, PR, ORR), and that older patients experience greater toxicity, with higher rates of grades 3-4 leukocytopenia, thrombocytopenia, and anaemia with CHOEP than with CHOP.[60-63] As yet, no prospective randomised trial has compared CHOEP to CHOP.[23] Therefore, as many patients diagnosed with PTCL are over 60 years of age, and due to high risk of excessive toxicity and/or comorbid factors, CHOEP is not recommended for PTCL in patients over the age of 60 and CHOP remains the standard of care.

For all of these reasons, the use of CHOEP is limited in the UK, the NICE pathway recommends CHOP as front-line treatment for patients with PTCL and clinical experts have confirmed that CHOP is regarded as the standard of care in the UK. [redacted] The HMRN region comprises a total population of 3.8 million and covers the area formerly served by the Yorkshire and the Humber & Yorkshire Coast Cancer Network. Reflecting this clinical reality, CHOEP is not included as a comparator in the final scope for this appraisal. Patients with PTCL who receive front-line CHOP chemotherapy and achieve a deep response may be considered for a consolidative autologous stem cell transplant (ASCT) in an attempt to prolong survival. For chemo-sensitive patients with PTCL (i.e. those achieving PR/CR), there is some non-randomised evidence that consolidation with ASCT may play a role in extending PFS and OS rates within first remission. As such, selected patients who achieve PR or CR may be eligible for an ASCT.[23] There is a lack of consensus about the efficacy of consolidation in particular, the impact on OS is unclear as no randomised controlled trials support an improvement in OS.

According to a UK retrospective review, patients with PTCL who underwent ASCT following front-line CHOP therapy had a better 5-year OS rate (67.4%) vs. those who did not receive ASCT (38.9%).[31] However, a large multicentre retrospective study (n=269) that corrected for sample selection bias for patients allocated to ASCT or not, found no survival advantage for patients who received consolidation with an

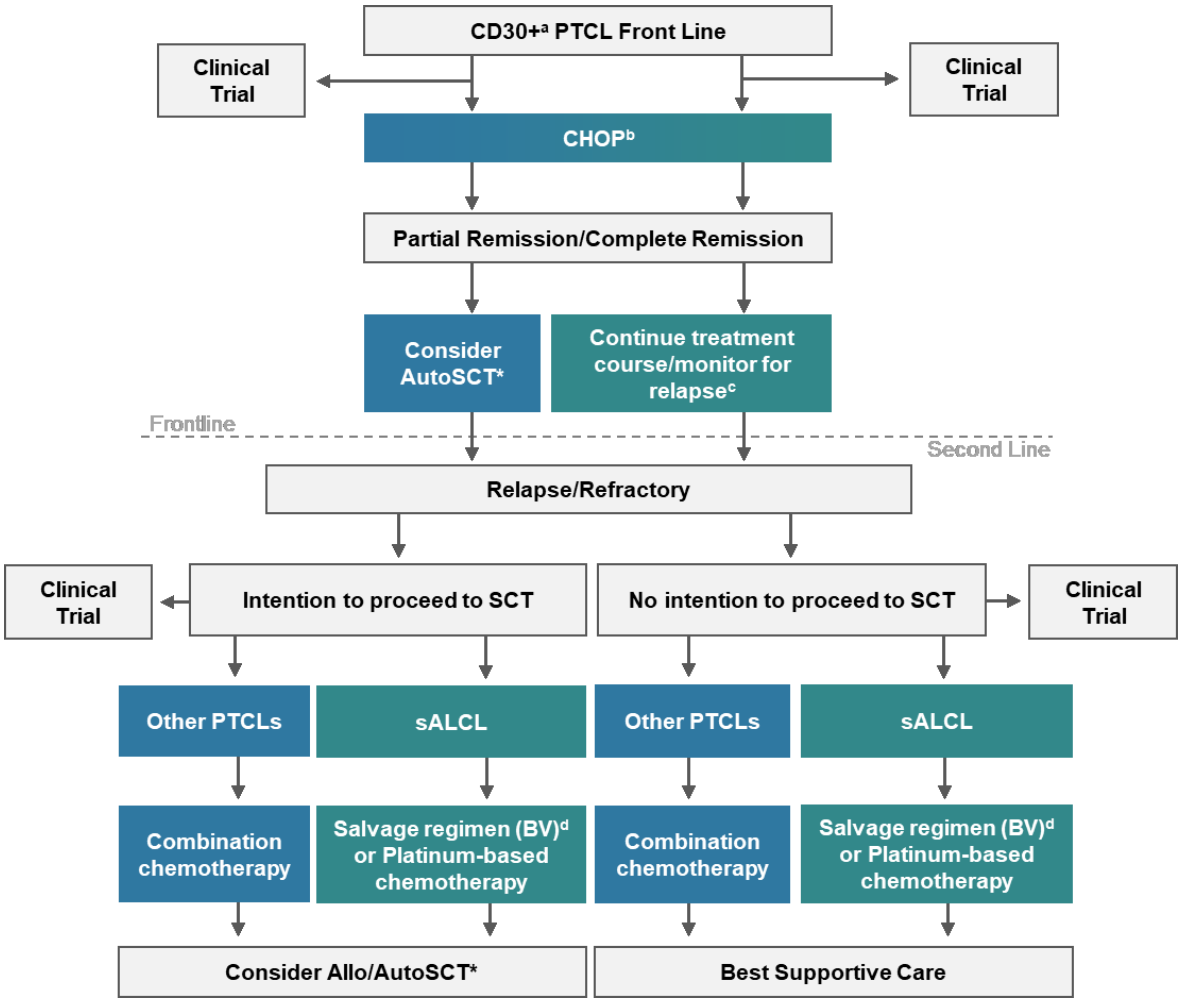
ASCT following induction chemotherapy, and no differences were found when stratifying for response status, disease stage, or risk category.[64] In addition, it has been observed that patients are exposed to considerable toxicity from this procedure. [65] Furthermore, UK clinical experts organised as part of a cross-functional advisory board to inform this submission confirm that there is a lack of robust evidence supporting front-line consolidation with ASCT for patients with PTCL.[59]

Overall, the evidence for the role of ASCT in the PTCL pathway is not clearly defined, and uncertainty remains regarding the clinical suitability of this treatment option. This is particularly significant considering how burdensome the procedure is for patients. Due to all of the above, there is considerable variability across the UK in the uptake of ASCT consolidation for PTCL, and it is certainly not established as part of the standard front-line treatment plan in all centres. In a 2019 survey of ten UK clinicians who manage PTCL, clinicians reported that approximately 20%-30% of UK patients actually go on to receive a consolidative transplant.[58] However, the survey also found that transplant practices vary considerably across centres in the UK.[58]

[redacted][66]

Feedback from UK clinical experts also confirms that, all things considered, they would not expect the availability of BV+CHP in the front-line setting to significantly change the proportion of patients with PTCL that receive a consolidative ASCT.

Figure 7: Current UK Treatment Guidelines for CD30+ PTCL [16,41]



[a]CD30 expression is not standardised. Treatment responses occur with low level expression[67]
[b] CHOEP may be effective for patients under 60 years of age [16,41] However, CHOEP is not within scope of the current submission
[c] Due to favourable outcomes, autoSCT consolidation is not recommended for low risk ALK+, ALCL[41]
[d]Brentuximab vedotin is approved by the European Medicines Agency as second line monotherapy treatment for relapse/refractory ALCL (TA478)[2] NHS treatment criteria specifies that patients must be brentuximab vedotin naïve; assumption that no-retreatment would be permitted.
*Consolidation with AutoSCT not recommended for ALK+ ALCL
Abbreviations: PTCL: peripheral T-cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; ALK: anaplastic lymphoma kinase (positive/negative); ALCL: anaplastic large cell lymphoma; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHOEP: CHOP treatment with the addition of etoposide [E]; BV: brentuximab vedotin; AutoSCT: autologous stem cell transplant; SCT: stem cell transplant; AlloSCT: allogeneic stem cell transplant

B.1.3.6.2 *Treatment of Relapsed/Refractory PTCL*

Relapse and the development of refractory disease that is chemotherapy-resistant is common in PTCL.[68] Relapse within the first two years after complete remission is common, results in extremely poor survival outcomes (median PFS: 3.1 months; median OS: 5.5 months). [18,19,65]

NICE has previously recommended BV monotherapy for R/R sALCL, where it has been shown to improve OS (estimated 5-year OS: 60%) and can also serve as a potential bridge to allogeneic stem cell transplant (alloSCT) for some patients [see TA478][2]. Patient with other types of PTCL are treated with salvage chemotherapies at relapse with the goal of inducing a strong response and bridging to an alloSCT. Recent retrospective analyses of long term outcomes for patients with relapsed PTCL have been reported.[69,70] Regardless of the type of treatment following relapse (i.e. salvage chemotherapy: dexamethasone, cytarabine, and cisplatin [DHAP], or etoposide, methylprednisolone, cytarabine, and cisplatin [ESHAP]; high dose therapy with SCT), median PFS and OS estimates for sALCL were 5.2 and 9.1 months, respectively demonstrating the aggressive nature of the condition.[69] Similarly, R/R PTCL-NOS had a median PFS of 3.1 months, and an OS of 10.9 months.[70]

When BV monotherapy was evaluated in a pivotal multinational (US, Canada, and Europe) Phase II study in 58 patients with R/R sALCL, objective responses were achieved in the majority (ORR: 85%) of patients treated, with improvements compared to historical outcomes observed in median PFS (13.3 months) and 1-year OS rates (70%).[71] At the time of study closure, the estimated 5-year OS rate was 60%.[72] Furthermore, a higher 5-year OS rate of 79% was reported for individuals who achieved CR.[72] The estimated 5-year PFS rate was 39% with a median PFS of 20 months.[72] These data were unprecedented in the setting of R/R sALCL. BV was effective both as a bridge to alloSCT and as a standalone treatment for those ineligible for alloSCT.

Based on these data, in October 2012 the EMA granted a conditional marketing authorisation for BV monotherapy in R/R sALCL and it remains the only treatment with EMA approval for patients with R/R sALCL (**Figure 7**).[41] Prior to the availability of BV, consensus had not been reached regarding the treatment of R/R disease in any PTCL subtype.[73] However, following the launch of BV in November 2012, it rapidly became established as the standard of care for UK patients with R/R sALCL (initially available via the CDF). Arising from the availability of BV, it is important to note that the treatment options in the R/R sALCL setting are different (and better) than, for the other subtypes of PTCL where BV is not approved for R/R disease.

In October 2017, BV was recommended by NICE for R/R sALCL [TA478]. This positive NICE recommendation was based on BV's ability to improve survival outcomes regardless of transplant. Furthermore, the committee recognised that effective treatments that are better tolerated with fewer side effects, such as BV, can

significantly improve a patient's quality of life. The positive NICE recommendation has solidified BV's status as the standard of care treatment for R/R sALCL.

Outside of clinical trials and BV for the R/R sALCL group, platinum-based combination chemotherapy regimens such as DHAP, or ifosfamide, etoposide, carboplatin (ICE) which can be utilised for chemo-sensitive patients as a bridge to alloSCT.[41] For patients considered to be unfit, gemcitabine or bendamustine may be utilised as monotherapy.[41] It's important to note that in the R/R sALCL setting, the use of these agents has declined significantly due to the availability of BV.

As mentioned earlier, for patients with R/R PTCLs other than sALCL, BV is unavailable as a salvage regimen and their only option is combination chemotherapy, potentially followed by an alloSCT for the small proportion of eligible patients who achieve a good enough response to allow this.

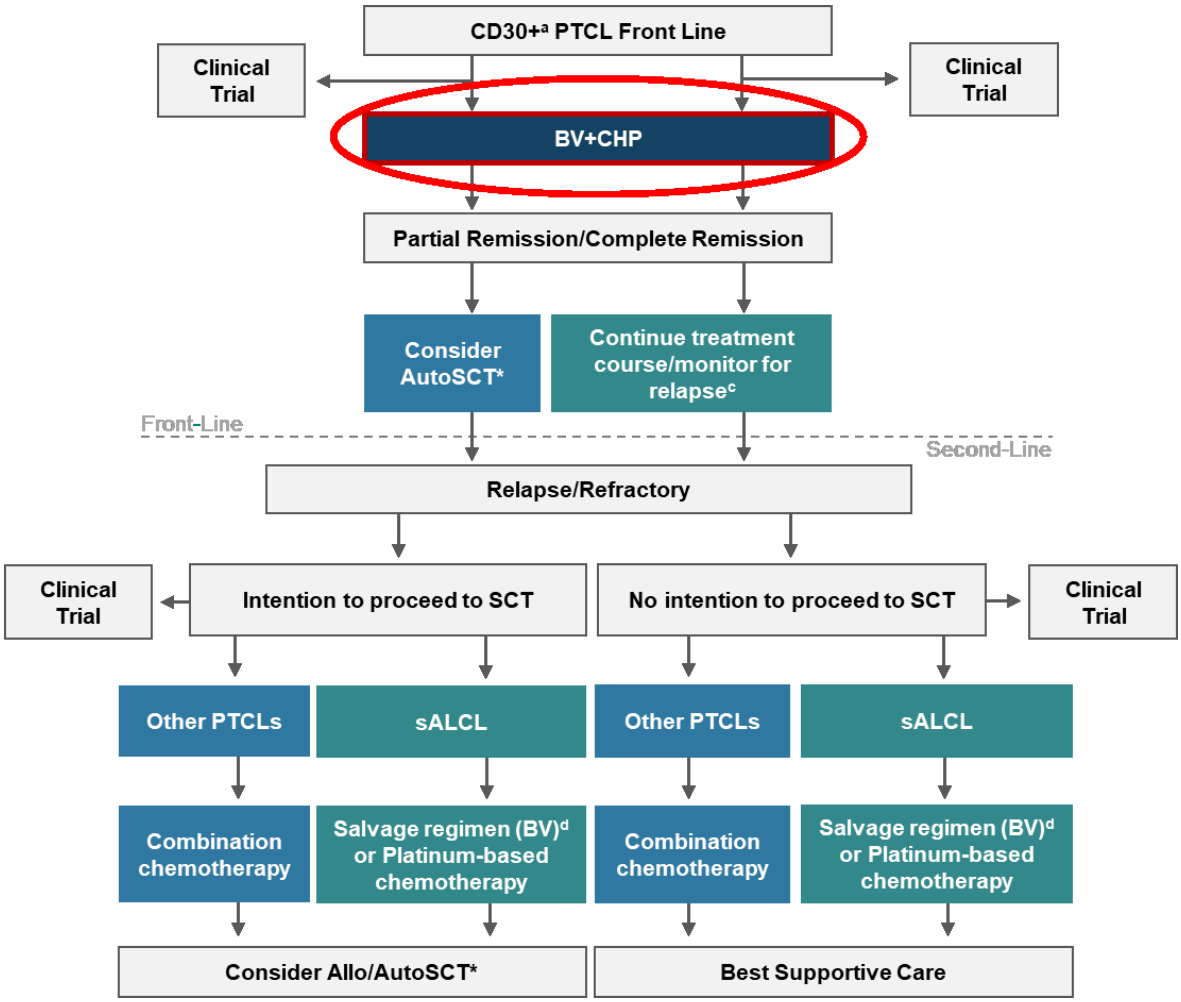
Patients who fail this combination chemotherapy or those who do not meet the eligibility criteria for alloSCT (including older patients and patients with comorbidities), have extremely poor survival and palliative care is their only remaining course of treatment. [68] This highlights the large unmet need that exists for such patients and the real need for access to better treatment options in the front-line setting for all patients with PTCL.

B.1.3.6.3 *Proposed Treatment Pathway with Brentuximab Vedotin*

The proposed treatment pathway is for BV+CHP to move into front-line treatment for previously untreated patients with CD30-positive PTCL. As such, BV+CHP would replace CHOP as the preferred front-line regimen. This is supported by the results of the pivotal ECHELON-2 trial in which BV+CHP was shown to be superior to CHOP (see **Section B.2.6.1**). The remainder of the treatment pathway would remain unchanged, including the option of BV monotherapy for R/R sALCL.

The current treatment pathway and the proposed placement of BV+CHP at front-line is presented in **Figure 8.**

Figure 8: Proposed Treatment Pathway for CD30+ PTCL including BV+CHP in the front-line setting



[a]CD30 expression is not standardised. Treatment responses occur with low level expression[67]
[b] CHOEP may be effective for patients under 60 years of age [16,41] However, CHOEP is not within scope of the current submission [c] Due to favourable outcomes, autoSCT consolidation is not recommended for low risk ALK+, ALCL[41]
[d]Brentuximab vedotin is approved by the European Medicines Agency as second line monotherapy treatment for relapse/refractory ALCL (TA478).[2] NHS treatment criteria specifies that patients must be brentuximab vedotin naïve; assumption that no-retreatment would be permitted.
*Consolidation with AutoSCT not recommended for ALK+ ALCL
Abbreviations: PTCL: peripheral T-cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; ALK: anaplastic lymphoma kinase (positive/negative); ALCL: anaplastic large cell lymphoma; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHOEP: CHOP treatment with the addition of etoposide [E]; BV: brentuximab vedotin; AutoSCT: autologous stem cell transplant; SCT: stem cell transplant; AlloSCT: allogeneic stem cell transplant; BV+CHP: brentuximab vedotin (Adcetris™) combined with CHOP therapy without vincristine [O]

B.1.4 Equality considerations

There are no equality considerations for BV treatment in PTCL.

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

A *de novo* systematic literature review (SLR) was conducted to identify all relevant information related to front-line PTCL treatment. As the SLR was conducted prior to finalisation of the NICE scope, a comprehensive search strategy was designed to capture evidence for comparators beyond those ultimately included in the final scope. As per the final NICE scope, the comparator of interest is CHOP.

The SLR was conducted using a rigorous approach following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure that it meets the requirements of the National Institute for Health and Care Excellence (NICE) and is suitable for any updates.[74]

All electronic databases were searched on 29th August 2019 (i.e. standard evidence sources used in UK HTA assessments). See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

The review identified a total of ten randomised controlled trials (RCTs) reported in 30 publications and 37 non-RCTs reported in 65 publications. The BV literature identified in the review is discussed below.

B.2.2 List of relevant clinical effectiveness evidence

In total, three studies were identified that reported data on BV (**Table 6 -Table 8**): one Phase III trial, ECHELON-2 (Horwitz et al 2018), to be referred to by the trial name for the remainder of this document; and two open label single-arm trials (Phase II, Horwitz et al 2014) (Phase I, Fanale et al 2014, Fanale et al 2018) . All trials were considered relevant to the decision problem.

ECHELON-2 is the pivotal Phase III international, double-blind, double-dummy, randomised, placebo-controlled, active comparator study of brentuximab vedotin [BV] in combination with cyclophosphamide [C], doxorubicin [H], and prednisone [P] (BV+CHP) versus standard CHOP for the treatment of front-line CD30+ PTCL. The trial screened 601 patients for eligibility and 452 were randomly assigned 1:1 to receive BV+CHP (n=226) or CHOP (n=226).[23] (See **Section B.2.6** for results)

Horwitz et al 2014 was an open label Phase II trial which enrolled patients with relapsed/refractory CD30+ NHL. The primary endpoint was ORR, and the key secondary endpoints were: safety, correlation of CD30 expression with response, response duration, and PFS. This study was designed to perform a planned subset analysis of individual PTCL subtypes within the PTCL cohort (n=35) which included patients with AITL (n = 13), and PTCL-NOS (n = 22). This study notably excluded

patients with ALK+/- sALCL to evaluate the prognostic importance of CD30 expression outside of the universal expression of CD30 that is characteristic of sALCL. (See **Section B.2.6.2** for results)

Fanale et al 2014 was an open label, Phase I trial which assessed sequential treatment of BV followed by CHOP or BV in combination with CHP (BV+CHP). The primary end point was safety and secondary end points were ORR, CR, PFS, and OS between the two different treatment regimens. Thirteen patients received sequential treatment of BV followed by standard-dose CHOP treatment (ALCL only, n=13), and 26 patients received combination BV+CHP (ALCL: n=19; Non-ALCL: n=7). The five-year follow-up of the combination data has also been published. (See **Section B.2.6.2** for results)

Table 6 Clinical effectiveness evidence

Study	**Horwitz et al, 2018; ECHELON-2; NCT01777152**				
Study design	*International, double-blind, double-dummy, randomised, placebo-controlled, active-comparator Phase III*				
Population	Adults (≥18 years) with previously untreated, CD30-positive* (≥10% of cells) PTCL				
Intervention(s)	Brentuximab vedotin [BV] + cyclophosphamide [C], doxorubicin [H], and prednisone [P] (BV+CHP)				
Comparator(s)	Cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P] (CHOP)				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	X
	No			No	
Rationale for use/non-use in the model	ECHELON-2 is the pivotal Phase III international, double-blind, double-dummy, randomised, placebo-controlled, study of BV+CHP versus CHOP, the UK standard of care. It's the most robust evidence available for BV+CHP in previously untreated CD30+ PTCL and one of the largest randomised controlled studies conducted in PTCL, which included 21 patients from five centres in the UK. Therefore, the ECHELON-2 trial is the primary source of data used to inform the economic model.				
Reported outcomes specified in the decision problem	The outcome measures specified in the decision problem are: • Overall survival • Progression-free survival per IRF • Overall response rates (including complete response) • Adverse effects of treatment • Health-related quality of life				
All other reported outcomes	• Progression-free survival per IRF for patients with sALCL • Complete Remission (CR) • Antitherapeutic Antibody Incidence Rate • Medical Resource Utilisation				

*The cut-off for CD-30+ expression in the trial was ≥10% of malignant cells)
Abbreviations: PTCL: peripheral T-Cell lymphoma; ALK = anaplastic lymphoma kinase (positive and negative); sALCL: systemic anaplastic large cell lymphoma; PTCL-NOS: PTCL- not otherwise specified; AITL: angioimmunoblastic T-Cell lymphoma; ATLL: Adult T-Cell lymphoma/leukemia; EATL: Enteropathy-associated T-Cell lymphoma; HSTCL: hepatosplenic T-Cell lymphoma; BV+CHP: brentuximab vedotin [BV] + cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; OS: Overall Survival; ORR: Objective Response Rate; CR: complete remission; HRQoL: health related quality of life; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-C30; FACT/GOG-NTX: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group- Neurotoxicity subscale; EQ-5D-3L: European Quality of Life 5-Dimensions Questionnaire

Table 7: Clinical effectiveness evidence – Phase II Data

Study	Horwitz et al, 2014; NCT01421667[67]				
Study design	*Open label, multicentre Phase II*				
Population	Patients with T-cell lymphomas whose tumour expressed CD30 at any level (excluding ALCL)				
Intervention(s)	Brentuximab vedotin				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	
	No			No	*X*
Rationale for use/non-use in the model	Horwitz et al 2014 was a single arm trial which included a total of 35 patients. Although the study reported on PFS, OS was not captured in the trial. Both PFS and OS are required for modelling purposes. As this trial was a single-arm trial, it would require the use of indirect treatment comparison methods and population adjustment (e.g. MAIC) to incorporate the PFS data into the economic model. These methods add uncertainty and rely on a sufficient sample size to estimate robust outcomes. Due to the small sample size, these methods were not pursued, and this study is used as supportive evidence only.				
Reported outcomes specified in the decision problem	The outcome measures specified in the decision problem are: • Progression-free survival • Overall response rates (including complete response) • Adverse effects of treatment •				
All other reported outcomes	Primary Outcome: ORR • Complete Remission (CR) • Partial Remission (PR) • Stable Disease (SD) • Progressive Disease (PD) Secondary Outcomes: • Characterisation of the relationship of CD30 expression with antitumor activity • Duration of response • Antitherapeutic antibodies				

Abbreviations: PTCL: peripheral T-Cell lymphoma; BV+CHP: brentuximab vedotin [BV] + cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; ORR: objective response rate; CR: Complete remission; PR: Partial remission; SD: Stable disease; PD: Progressive disease; PFS: Progression Free Survival

Table 8: Clinical effectiveness evidence – Phase I Data

Study	NCT01309789; Fanale 2014[75] and Fanale 2018[76]
Study design	• *Fanale 2014: Open label Phase I study conducted at eleven centres within the United States and Europe* • *Fanale 2018: 5-year follow-up of the aforementioned trial*
Population	Treatment naïve adults with a diagnosis of CD30+ PTCL*, including sALCL(anaplastic lymphoma kinase [ALK]-negative or ALK-positive with International Prognostic Index score ≥2)
Intervention(s)	A combination treatment approach for patients with sALCL (n=19) and other PTCL subtypes (n=7), receiving 1.8 mg/kg brentuximab vedotin + CHP (once every 3 weeks, intravenously [IV] for up to 6 cycles). After 6 cycles, patients with an objective response could receive up to 10 cycles of BV monotherapy. A sequential treatment approach for patients with sALCL (n=13) receiving 1.8 mg/kg BV (two cycles, once every 3 weeks,

Study	NCT01309789; Fanale 2014[75] and Fanale 2018[76]				
	intravenously [IV] followed by standard dose CHOP (six cycles, once every 3 weeks, [IV])				
Comparator(s)	None				
Indicate if trial supports application for marketing authorisation	Yes	X	Indicate if trial used in the economic model	Yes	
	No			No	X
Rationale for use/non-use in the model	This trial is a single arm, Phase I study. Although, PFS and OS outcomes are reported, these are not implemented within the economic model due to the potential for biases associated with treatment patterns inconsistent with the proposed licensed indication. For example, 13 patients were treated sequentially with BV followed by CHOP as opposed to BV in combination with CHP. Additionally, the combination approached allowed up to ten additional cycles of BV monotherapy following combination treatment. Neither of these treatment patterns align with the proposed licensed indication.				
Reported outcomes specified in the decision problem	The outcome measures specified in the decision problem are: • Progression-free survival • Overall survival • Overall response rates (including complete response) • Adverse effects of treatment •				
All other reported outcomes	Secondary outcomes: • Efficacy as measured by response assessments (ORR and CR rates) • Pharmacokinetic analysis as measured by blood concentrations of BV ADC, MMAE, and total antibody (TAb)				

* The cut-off for CD-30+ expression in the trial was ≥1% of malignant cells

Abbreviations: PTCL: Peripheral T-Cell lymphoma; sALCL: Systemic anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; IV: intravenous; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; BV+CHP: brentuximab vedotin [BV] + cyclophosphamide [C], doxorubicin [H], and prednisone [P]; BV: brentuximab vedotin; ORR: objective response rate; CR: complete remission; PFS: progression free survival; OS: overall survival; ADC: antibody drug conjugate; MMAE: monomethyl auristatin E; Tab: total antibody

B.2.2.1 Studies not included in the economic model

PFS and OS are the key clinical inputs in the cost-effectiveness model.

Horwitz et al (2014) was a single arm trial which included a total of 35 patients. Although the study reported on PFS, OS was not captured in the trial.[67] Due to the trial design, it would require the use of indirect treatment comparison methods and population adjustment (e.g. MAIC) to incorporate the PFS data into the economic model. These methods add uncertainty and rely on a sufficient sample size to estimate robust outcomes. Due to the small sample size, these methods were not pursued, and this study is used as supportive evidence only.

Fanale et al (2014) is a single arm, Phase I study.[75] Although, PFS and OS outcomes are reported, these are not implemented within the economic model due to the potential for biases associated with treatment patterns inconsistent with the proposed licensed indication. For example, thirteen patients were treated sequentially with BV followed by CHOP as opposed to BV in combination with CHP. Additionally, the combination approached allowed up to ten additional cycles of BV

monotherapy following combination treatment. Neither of these treatment patterns align with the proposed licensed indication.

Although these studies were not included in the model, Horwitz et al (2014) and Fanale et al (2014) are included in **Sections B.2.3** to **B.2.6** as they provide information on the efficacy and safety of BV in patients with PTCL, which is consistent with the decision problem.

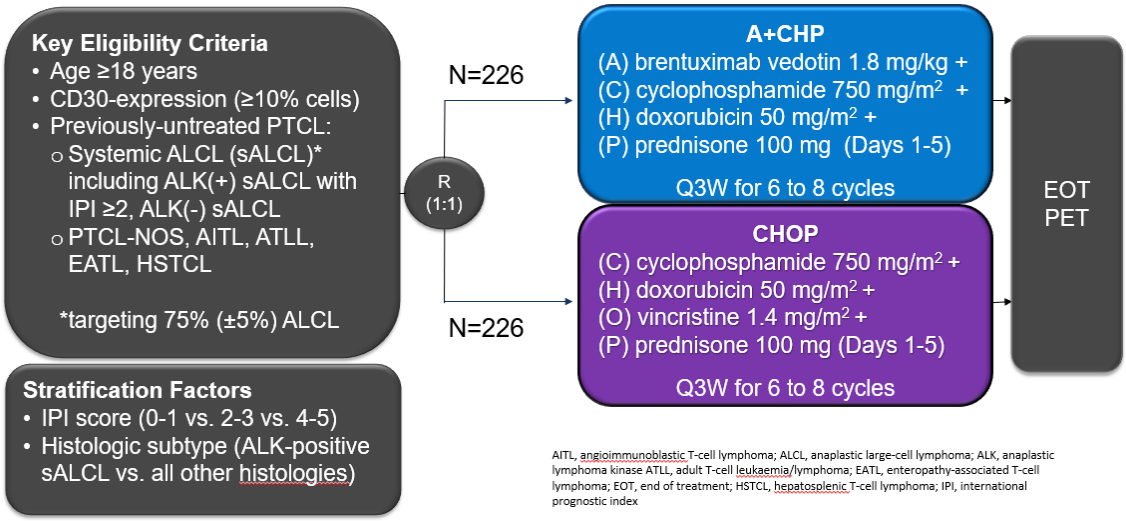
B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 ECHELON-2

ECHELON-2 was an international, double-blind, double-dummy, randomised, placebo-controlled, active-comparator, Phase III trial conducted at 132 sites (including four satellite sites) in 17 countries, with a total enrolment of 452 patients. There were 21 UK patients enrolled in ECHELON-2 across five UK centres. Based on the encouraging activity and manageable safety profile observed in the Phase I trial (Fanale et al 2014), ECHELON-2 was designed to compare the efficacy and safety of BV in combination with CHP (BV+CHP) versus standard CHOP chemotherapy in previously untreated patients with CD30+ PTCL.[23]. CHP [CHOP without vincristine] was used as the combination treatment with BV to eliminate the risk of overlapping neurotoxicity that could be worsened by delivering two microtubule-disrupting drugs, BV and vincristine.

The trial design, eligibility criteria, data collection, setting/location, outcomes assessed and additional methodological information for ECHELON-2 are presented in **Table 9** and study schematic in **Figure 9**.

Figure 9: ECHELON-2 Study Design



AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase ATLL, adult T-cell leukaemia/lymphoma; EATL, enteropathy-associated T-cell lymphoma; EOT, end of treatment; HSTCL, hepatosplenic T-cell lymphoma; IPI, international prognostic index

Table 9: Comparative summary of methodology of the RCTs[23,77]

Trial Name	ECHELON-2 (NCT01777152) [23]
Study Objective	To compare the efficacy and safety of brentuximab vedotin (BV) in combination with CHP (BV+CHP) with standard CHOP for the treatment of previously untreated patients >18 years of age with CD30+ PTCL.
Location	International
Trial Design	Double-blind, double-dummy, randomised, placebo-controlled, active-comparator Phase III trial
Method of Randomisation	Patients were randomly assigned (1:1) centrally with an interactive web response system that assigned a unique patient randomisation number and did not specify the actual treatment assignment. Randomisation numbers and their corresponding treatment assignments were allocated to patients according to the randomisation list by sequential ascending block number and by sequential ascending randomisation numbers within the appropriate strata. The randomisation list was generated by a vendor (Bracket (San Francisco, CA, USA)). Randomisation was stratified by histological subtype according to local pathology assessment (ALK+ ALCL with an IPI score of ≥ 2 vs all other histologies) and baseline IPI score (0–1 vs 2–3 vs 4–5).
Method of blinding (care provider, patient and outcome assessor)	BV and vincristine were dispensed in a double-blinded, double-dummy manner. BV, vincristine, and their placebo replacements were prepared by the pharmacist at each study site, and a pharmacy mask was enforced. The investigators, patients, Blinded Independent Central Review (BICR), and the sponsor were masked to treatment assignments.
Eligibility criteria for participants	Patients aged ≥18 years with previously untreated CD30+ (≥10% of cells by local review) PTCL. Eligible histologies (per the WHO 2008 classification system) were limited to ALK+, ALCL with an IPI score of ≥ 2, ALK-, ALCL, PTCL-NOS, AITL, ATLL, EATL, and HSTCL. This study was a post-approval marketing commitment from the EMA for R/R sALCL and therefore required the study to enrol 75% (+/- 5%) sALCL patients to ensure the key secondary endpoint of PFS in the sALCL subtype could be appropriately assessed.
Settings and locations where the data were collected	132 sites (including four satellite sites) in 17 countries: Japan, South Korea, Australia, Taiwan, Czech Republic, Denmark, France, Germany, Hungary, Italy, Poland, Romania, Spain, United Kingdom, Israel, United States and Canada Five of the trial sites were located in the UK.

Duration of study	• Median follow-up, primary analysis (PFS): 36.2 months (95% CI 35.9–41.8) • Median follow-up, longer-term analysis (OS): 42.1 months (95% CI, 40.4−43.8) Note: The same data is utilised to calculate PFS and OS, however, the methods by which PFS and OS are calculated differ slightly regarding censorship. OS utilises the actual date of death whereas, PFS uses the last efficacy assessment prior to a missed visit. Therefore, this methodology can result in a follow-up time for OS time that is slightly longer than for PFS.
Trial drugs (the interventions for each group with sufficient detail to allow replication, including how and when they were administered) **Intervention(s) (n=[x]) and comparator(s) (n=[x])**	Experimental Arm (n=226): BV 1.8 mg/kg, cyclophosphamide [C] 750 mg/m^2, doxorubicin [H] 50 mg/m^2, administered IV on Day 1 of each cycle; prednisone [P] 100 mg daily administered orally on Days 1–5 of each cycle. Placebo replacement for vincristine [O] also administered IV in a blinded manner on Day 1 of each cycle • Treatment was delivered every 3 weeks for 6 to 8 cycles, per standard CHOP therapy administration [16] Standard of Care Arm (n=226): Cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (dose capped at 2 mg) administered IV on Day 1 of each cycle; prednisone 100 mg daily administered orally on Days 1–5 of each cycle. Placebo replacement for BV also administered IV in a blinded manner on Day 1 of each cycle. • Treatment was delivered every 3 weeks for 6 to 8 treatment cycles
Permitted and disallowed concomitant medications	Permitted: granulocyte-colony stimulating factor (G-CSF) was permitted at the discretion of the treating physician based upon institutional standards Permitted: consolidative stem cell transplantation (SCT) or radiotherapy after treatment was permitted at the discretion of the treating physician (SCT intent was prespecified before the first cycle of chemotherapy). Disallowed: other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy
Primary outcomes (including scoring methods and timings of assessments)	Progression-free survival (PFS) (according to blinded independent central review (BICR) referred to as independent review facility (IRF) throughout): defined as the time from the date of randomisation to the date of first documentation of relapse or progressive disease (PD), death due to any cause, or receipt of subsequent systemic chemotherapy to treat residual or progressive PTCL as determined by the investigator, whichever occurred first. In the absence of progressive disease, receipt of radiotherapy to consolidate response to initial treatment, chemotherapy for the purpose of mobilising

	haemopoietic stem cells, or consolidative autologous or allogeneic stem cell transplantation were not considered events.
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	The key α-controlled secondary endpoints were: **PFS per IRF for patients with sALCL:** PFS per IRF in the subset of subjects with sALCL, as confirmed by central pathology, was analysed in the same manner as the primary analysis of PFS per IRF. **Complete Remission (CR):** defined as the proportion of subjects with CR per IRF following the completion of study treatment (at end of treatment or at the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Subjects whose disease response was not assessable were scored as non-responders for calculating the CR rate. The CR rate between treatment arms was tested using the Cochran-Mantel-Haenszel (CMH) method, stratified by the randomisation stratification factors. The absolute CR rate and exact two-sided 95% CI using the Clopper-Pearson method [78] were summarised by treatment arm. **Objective Response Rate (ORR):** defined as the proportion of subjects with CR or PR per IRF following the completion of study treatment (at end of treatment or the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Subjects whose disease response was not assessable were scored as non-responders for calculating the ORR. The ORR between the treatment arms was tested using the CMH method, stratified by the randomisation stratification factors. The absolute ORR and exact two-sided 95% confidence interval using the Clopper-Pearson method (Clopper 1934) were summarised by treatment arm. **Overall survival:** defined as the time from randomisation to death due to any cause (OS=date of death – date of randomisation + 1). Any subject for whom death was not already known was censored for OS on the date the subject was last known to be alive (i.e., date of last contact), or data cutoff date. Subjects lacking data beyond the day of randomisation were censored on the date of randomisation (i.e., OS duration of 1 day). The stratified log-rank test without adjustments for covariates was used in the evaluation of OS between treatment arms. OS was analysed using Kaplan Meier methodology; Kaplan-Meier plots are provided by treatment arm. Median OS and the probability of survival from 3 months to the end of the follow-up period are reported at 3-month intervals by treatment arm. The two-sided 95% CIs for the median were calculated using the complementary log-log transformation method.

	Non-efficacy related outcomes: **Safety:** consisted of the surveillance and recording of adverse events (AEs) and measurements of physical examination findings and laboratory tests. Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Laboratory results were also graded per NCI CTCAE, version 4.03 when applicable. **Antitherapeutic Antibody Incidence Rate:** Serum concentrations of BV, antitherapeutic antibodies (ATA) to BV, and plasma concentrations of free drug (monomethyl auristatin E; MMAE) were measured. Pharmacodynamic assessments included the measurement of soluble CD30 (sCD30). **Medical Resource Utilisation:** data included medical care encounters related to study treatment or treatment for lymphoma, such as hospital admissions or major diagnostic procedures. **Quality of Life:** measured using the EORTC Quality of Life Questionnaire – Core 30 (QLQ-C30), the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity subscale (FACT/GOG-NTX), and the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L) patient-reported outcome (PRO) instruments.
Pre-planned subgroups	Randomisation was stratified by histological subtype according to local pathology assessment (ALK-positive systemic anaplastic large cell lymphoma vs all other histologies) and baseline IPI score (0–1 vs 2–3 vs 4–5). PFS per IRF in patients with sALCL is defined in the same manner as the primary endpoint of PFS per IRF. For this endpoint, PFS per IRF will be analysed in the subset of patients with a central pathology confirmed diagnosis of sALCL.

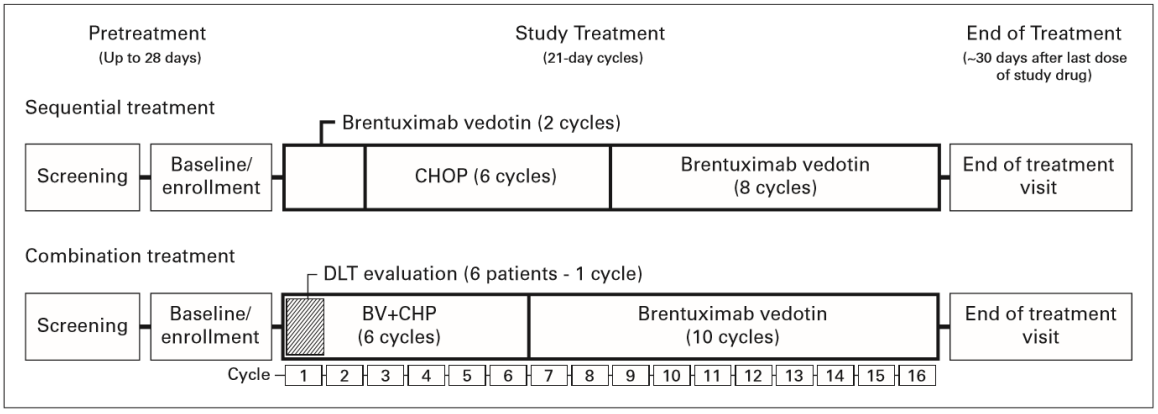
Abbreviations: BV+CHP: brentuximab vedotin [BV] + cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; PTCL: peripheral T-cell lymphoma; USA: United States of America; ALK: anaplastic lymphoma kinase (positive/negative); sALCL: systemic anaplastic large cell lymphoma; IPI: International Prognostic Index; BICR: Blinded Independent Central Review; PTCL-NOS: peripheral t-cell lymphoma-not otherwise specified; AITL: angioimmunoblastic T-cell lymphoma; ATLL: adult T-cell leukemia/lymphoma EATL: enteropathy-associated T-cell lymphoma G-CSF: granulocyte-colony stimulating factor; PD: progressive disease; PFS: progression free survival; IRF:independent review facility, CR: complete remission; CMH: Cochran-Mantel-Haenszel; ORR: objective response rate; PR: partial remission; OS: overall survival; AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; NCI: National Cancer Institute; CTCAE: Common Terminology Criteria for Adverse Events; ATA: antitherapeutic antibodies; MMAE: monomethyl auristatin E; sCD30: soluble CD30; QOL: quality of life: EORTC: European Organisation for Research and Treatment of Cancer; FACT/GOG-NTX: Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity subscale; EQ-5D-3L: European Quality of Life 5-Dimensions Questionnaire; PRO: patient reported outcomes

B.2.3.2 Horwitz et al 2014; Fanale et al 2014

Horwitz et al 2014 was a Phase II open label multicentre study (n= 35), that evaluated the safety and efficacy of BV monotherapy in R/R CD30+ NHL subtypes of AITL and PTCL-NOS (excluding ALK+/- sALCL subtypes).[67]

Fanale 2014 et al was a Phase I open label study (n=39), which evaluated the safety and characterisation of the relationship of CD30 expression with anti-tumour activity of BV administered either sequentially with CHOP (in an sALCL only population) or in combination with CHP as front-line therapy in patients with CD30+ PTCL **(Figure 10)**.[75] Fanale et al 2018 presents the five-year outcome data for the combination approach from this study, including durability of response and OS.[76]

Figure 10: Study Schematic for Fanale 2014 Study[75]



Sequential treatment: BV (two cycles) followed by CHOP (six cycles); Combination treatment: BV+CHP (six cycles) including a cohort to evaluate dose-limiting toxicities. Responders were eligible to receive subsequent single agent BV for 8 cycles, or 10 cycles of combination treatment.
Abbreviations: CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; DLT: dose-limiting toxicities; BV+CHP: brentuximab vedotin+ cyclophosphamide [C], doxorubicin [H], and prednisone [P]

Trial design, eligibility criteria, data collation setting/location, outcomes assessed and further details on the trial methodology are summarised in **Table 10**.

Table 10: Comparative summary of methodology of the Phase I and II trials [67,75,76]

Trial no. (acronym)	NCT01421667: Horwitz et al 2014[67]	NCT01309789: Fanale et al 2014[75]; Fanale et al 2018[76]
Study Objective	To explore the activity of single-agent BV in patients with R/R non-Hodgkin lymphomas (NHLs) whose tumour expressed CD30 at any level	To explore the safety and activity of BV, administered sequentially and in combination with multiagent chemotherapy, in patients with newly diagnosed CD30+ PTCL.
Location	Multicentre; 13 sites in the United States and 1 site in Canada	Multicentre; 11 centres within the United States and Europe
Trial Design	Open label, Phase II	Open label, Phase I
Eligibility Criteria for participants	Key eligibility criteria included histologically confirmed mature T-cell lymphoma with any detectable CD30 expression per institutional laboratory using immunohistochemical (IHC) staining with the BerH2 antibody clone on a biopsy of the most recent relapsed or refractory disease. Eligible patients also had at least 1 prior systemic therapy, measurable disease, age ≥ 12 years, and ECOG performance status of < 2.	Treatment-naive adults with a diagnosis of CD30+ PTCL, including ALCL were eligible. CD30+ disease for patients without anaplastic large-cell lymphoma (i.e. non-ALCL) was defined as ≥ 1% CD30 expression in malignant cells, confirmed by central pathology review. Other key eligibility requirements included fluorodeoxyglucose-avid disease by positron emission tomography (PET), measurable disease by computed tomography (CT≥ 1.5cm), age ≥ 18years, and an Eastern Cooperative Oncology Group performance (ECOG) status of no higher than 2.
Settings and locations where the data were collected	13 sites in the United States and 1 site in Canada	11 centres within the United States and Europe

Duration of study	Median follow-up time from first dose was 2.7 months (0.3-17.3 months). Median time on treatment was 9 weeks (2-78 weeks). Median duration of treatment 26 weeks (12-78 weeks). All patients who came off treatment were subsequently followed for disease status and survival every 3 months for the first 2 years and according to the institutional standard of care thereafter until death, study closure, or withdrawal of consent.	Median observation period of 59.6 months
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered)	Patients were treated with 1.8mg/kg BV IV on day 1 of each 3-week cycle. Patients who achieved at least stable disease (SD) were eligible to receive continued BV treatment until disease progression, unacceptable toxicity, or study closure	Patients could receive one of two treatment regimens: • A **sequential treatment approach** in which sALCL patients received 1.8mg/kg BV (two cycles, once every 3 weeks, intravenously [IV]) followed by standard-dose CHOP (six cycles, once every 3 weeks, IV) or, a **combination treatment approach** in which patients with PTCL, including those with sALCL, received BV in combination with CHP (CHOP without vincristine; BV+CHP); six cycles, once every 3 weeks, IV). Responders were eligible to receive subsequent single agent BV for 8 cycles in the sequential treatment arm, or 10 cycles in the combination treatment arm.

Permitted and disallowed concomitant medications	Routine premedication was not allowed for the prevention of infusion related reactions prior to the first dose of BV; however, patients who experienced a grade 1 or 2 infusion-related reaction could receive subsequent study treatment infusions with premedication consisting of acetaminophen and diphenhydramine. Use of platelet and/or red blood cell transfusion or granulocyte colony-stimulating factors was allowed during study. Low-dose prednisone (≤ 20mg per day) was allowed; however, steroid use in higher doses or as an antineoplastic agent was prohibited.	Vincristine [O] was omitted from combination treatment with BV to eliminate the potential for additional neurotoxicity.
Primary outcomes (including scoring methods and timings of assessments)	Objective response rate (ORR): Clinical response of progressive disease (PD), stable disease (SD), partial remission (PR), or CR was determined at each assessment. PD included PD per Cheson et al and clinical disease progression per the investigator. CT and PET scans were required for all patients at baseline. If disease was not PET-avid at baseline, restage assessments were performed using CT scans of diagnostic quality. For patients with PET-avid disease at baseline, both PET and CT scans were required until disease was PET negative; then, CT scans of diagnostic quality were used for subsequent restaging. Restaging assessments were performed at cycles 2, 4, every 3 cycles thereafter (between days 15 and 21), and at end of treatment.	To assess the safety of each treatment approach. Safety assessments consisted of the recording of AEs, physical examination, and routine laboratory tests. AEs were summarised using the Medical Dictionary for Regulatory Activities, version 14.0, and were graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0. Safety was monitored by a safety monitoring committee.

	Cutaneous lesions were monitored via physical examination. If the bone marrow was positive at baseline, a follow-up bone marrow aspirate and biopsy was required and had to be negative for assessment of CR.	

Secondary/tertiary outcomes (including scoring methods and timings of assessments)	Key secondary end points included safety, correlation of CD30 expression with response, response duration, and PFS. Median follow-up time from first dose was 2.7 months (range 0.3-17.3 months). Median time on treatment was 9 weeks (range 2-78 weeks). The median number of cycles received was 3 (range 1-21)). Median duration of treatment 26 weeks (range 12-78 weeks). All patients who came off treatment were subsequently followed for disease status and survival every 3 months for the first 2 years and there after until death, study closure, or withdrawal of consent. Patients who discontinued study drug for any reason other than disease progression or initiation of a non-protocol therapy for treatment of lymphoma had restaging scans every 6 months during the first year after the last dose of BV and in line with the institutional standard of care thereafter. Safety assessments included surveillance and recording of AEs, physical examination findings, and laboratory tests. AE severity was graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.3. Assessment of CD30 expression to determine eligibility was performed by institutional laboratories; tissue samples were also sent to the central pathology laboratory (Quest Diagnostics) for subsequent evaluation of CD30 expression using standard IHC and the BerH2 antibody.	Key secondary end points included ORR, CR rate, PFS, and OS. In the **sequential treatment approach**: Responses were assessed by CT/ PET scan after two cycles of single-agent BV treatment and again after six cycles of CHOP. In the **combination treatment approach**: Responses were assessed by CT/PET scan after six cycles of BV+CHP. Scans were performed during subsequent single-agent BV maintenance treatment (cycles 12 and 16). PET scans were not required once a negative scan was documented. Scans were not required following evidence of clinical progression. During follow-up, patients were assessed for survival and disease status every 3 months until death or study closure. For pharmacokinetic analyses, blood concentrations of BV ADC, MMAE, and total antibody (TAb) were measured.

Pre-planned subgroups	The planned subset analysis for patients enrolled with PTCLs is presented in this submission	None stated

Abbreviations: NCT: ClinicalTrials.gov identifier; PTCL: peripheral T-cell lymphoma; NHL: Non-Hodgkin's Lymphoma; ALK+/-: anaplastic lymphoma kinase; sALCL: systemic anaplastic large cell lymphoma; IPI: international prognostic index; PET: positron emission tomography; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; IHC: immunohistochemical; IV: intravenous; mg: milligram; kg: kilogram; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; BV+CHP: brentuximab vedotin [BV] + cyclophosphamide [C], doxorubicin [H], and prednisone [P]; BV: brentuximab vedotin; AE: adverse events; ORR: objective response rate; PD: progressive disease; SD: stable disease; PR: partial remission; CR: complete remission; PFS: progression free survival; OS: overall survival; ADC: antibody drug conjugate; MMAE: monomethyl auristatin E; TAb: total antibody; NCI CTCAE: National Cancer Institute's Common Terminology Criteria for Adverse Events

B.2.3.3 Baseline characteristics and demographics

B.2.3.3.1 *ECHELON-2*[23]

A total of 452 patients were enrolled in the ECHELON-2 trial, n=226 in the BV+CHP and n=266 in the CHOP arm. In the ECHELON-2 trial, baseline characteristics were generally well balanced between the treatment arms. Overall, the median age was 58 years (IQR 45–67), and the majority of patients had advanced disease (stage III, n=124 [27%] and stage IV, n=240 [53%]).[23] Importantly, 78% of the patients enrolled in the study had an IPI ≥2 (n=351), which is correlated with poor outcomes regardless of PTCL subtype.[23] Likewise, 85.4% and 83.6% of patients enrolled in the BV+CHP and CHOP arms respectively of the ECHELON-2 trial were ≥ 40 years of age, a prognostically important factor indicating that most of the patients had an adverse prognosis (See **Section B.1.3.4**).[77]

Due to a regulatory requirement of the EMA, 70% of the patients enrolled (n=316) had a diagnosis of sALCL. Horwitz 2018}[23,77] Other than the larger representation of patients with sALCL in this study (per requirements of the regulatory authorities), the ECHELON-2 population is broadly representative of patients with PTCL in the UK with five of the trial sites located in the UK and 21 participating patients. The second largest subtype of PTCL to be enrolled in the ECHELON-2 trial is the PTCL-NOS subgroup with 16% of the patients. Additional patient characteristics for ECHELON-2 are further summarised in **Table 11**.

Table 11: Baseline patient characteristics and demographics in ECHELON-2 (ITT Population)[23]

Baseline Characteristic	BV+CHP arm (n=226)	CHOP arm (n=226)	Total (N=452)
Sex, n(%)			
Men	133 (59%)	151 (67%)	284 (63%)
Women	93 (41%)	75 (33%)	168 (37%)
Median age, years (IQR)			
	58.0 (45–67)	58.0 (44–67)	58.0 (-, -)
Race, n (%)			
Asian	45 (20%)	54 (24%)	99 (22%)
Black or African American	12 (5%)	6 (3%)	18 (4%)
White	139 (62%)	142 (63%)	281 (62)
Native Hawaiian or other Pacific Islander	1 (0%)	0	1 (0%)
Other or Unknown	29 (13%)	24 (11%)	53 (12%)
ECOG Performance†, n (%)			
0	84 (37%)	93 (41%)	177 (39%)
1	90 (40%)	86 (38%)	176 (39%)
2	51 (23%)	47 (21%)	98 (22%)
Diagnosis‡, n (%)			
sALCL	162 (72%)	154 (68%)	316 (70%)
ALK positive	49 (22%)	49 (22%)	98 (22%)
ALK negative	113 (50%)	105 (46%)	218 (48%)
PTCL-NOS	29 (13%)	43 (19%)	72 (16%)
AITL	30 (13%)	24 (11%)	54 (12%)
ATLL	4 (2%)	3 (1%)	7 (2%)
EATL	1 (0%)	2 (1%)	3 (1%)
Disease Stage at Diagnosis§, n (%)			
I	12 (5%)	9 (4%)	21 (5%)
II	30 (13%)	37 (16%)	67 (15%)
III	57 (25%)	67 (30%)	124 (27%)
IV	127 (56%)	113 (50%)	240 (53%)
Baseline IPI Score¥, n (%)			
0	8 (4%)	16 (7%)	24 (5%)
1	45 (20%)	32 (14%)	77 (17%)
2	74 (33%)	78 (35%)	152 (34%)
3	66 (29%)	66 (29%)	132 (29%)
4	29 (13%)	25 (11%)	54 (12%)
5	4 (2%)	9 (4%)	13 (3%)

Data are n (%), unless stated otherwise. †Values for ECOG performance status range from 0 to 5, with higher scores indicating greater disability. ‡Diagnosis per local assessment. §The Ann Arbor staging system ranges from 1 to 4, with higher stages indicating more widespread disease. ¥The IPI score is calculated based on a patient's disease characteristics and represents increasing degrees of risk. Abbreviations: BV+CHP: brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; AITL: angioimmunoblastic T-cell lymphoma; ALK: anaplastic lymphoma kinase; ATLL: adult T-cell leukaemia or lymphoma; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; EATL: enteropathy-associated T-cell lymphoma; ECOG: Eastern Cooperative Oncology Group; IPI=international prognostic index; PTCL-NOS:peripheral T-cell lymphoma not otherwise specified; ALCL: anaplastic large cell lymphoma.

B.2.3.3.2 *Horwitz et al 2014[67]*

This Phase II open label study enrolled 35 patients with relapsed / refractory (R/R) mature T-cell lymphomas with variable CD30 expression; diagnoses included AITL (n = 13) and PTCL-NOS (n = 22). The median age of patients was 64 years (range, 33-83 years) and the majority (77%) of patients were male. Most patients had an

ECOG performance status of 1 or 2 (80%) and most had advanced (stage III or IV) disease (77%).

Table 12: Baseline patient characteristics and demographics in Horwitz 2014[67]

Baseline Characteristic	AITL (n = 13)	PTCL (n = 22)	All treated patients (n = 35)
Age, Years Median (Range)			
	64 (55 – 79)	64.5 (33 – 83)	64 (33 – 83)
Male, n (%)			
	10 (77)	17 (77)	27 (77)
Race, n (%)			
White	11 (85)	18 (82)	29 (83)
Black or African American	2 (15)	3 (14)	5 (14)
Asian	0	1 (5)	1 (3)
Baseline ECOG performance status, n (%)			
0	2 (15)	5 (23)	7 (20)
1	8 (62)	15 (68)	23 (66)
2	3 (23)	2 (9)	5 (14)
CD30 Expression*, n(%)			
Positive	9 (69)	17 (77)	26 (74)
Negative	2 (15)	4 (18)	6 (17)
NA or Missing	2 (15)	1 (5)	3 (9)
Stage at Initial Diagnosis, n(%)			
I	1 (8)	0	1 (3)
II	1 (8)	1 (5)	2 (6)
III	5 (38)	8 (36)	13 (37)
IV	3 (23)	11 (50)	14 (40)
Unknown	3 (23)	2 (9)	5 (14)
Disease Status relative to most recent prior therapy, n(%)			
Refractory	9 (69)	13 (59)	22 (63)
Relapsed	4 (31)	9 (41)	13 (37)
Disease status relative to front-line therapy, n(%)			
Refractory	9 (69)	17 (77)	26 (74)
Relapsed	4 (31)	5 (23)	9 (26)
Median number of prior cancer-related systemic therapy (min, max)	3 (1 – 4)	2 (1 – 9)	2 (1 – 9)
Patients with any prior cancer-related radiotherapy, n (%)	1 (8)	3 (14)	4 (11)
Patients with prior autologous stem cell transplant, n (%)	2 (15)	1 (5)	3 (9)

*Per central laboratory.

B.2.3.3.3 *Fanale et al 2014[75]*

This open label Phase I study enrolled 39 patients with newly diagnosed PTCL, including 32 patients with sALCL (ALK+ ,n = 6; ALK-, n = 26) and seven patients with other CD30+ PTCLs (PTCL-NOS, n = 2; AITL, n = 2; EATL, n = 1; ATLL, n = 2). The majority of patients had an ECOG score of 0 or 1, and at diagnosis, 19 (59%) of 32 patients with sALCL and all seven patients with non-ALCL histologies had advanced-

stage disease (stage III or IV). Six (86%) of seven patients with non-ALCL and all six patients with ALK+ sALCL had an IPI score of 2-3 (intermediate-risk disease).[75]

Table 13: Baseline patient characteristics and demographics in Fanale 2014[75]

Baseline Characteristic	sALCL (n =32)		Non-ALCL (n = 7)	Total (N = 39)
	ALK+ (n = 6)	ALK- (n = 26)		
Age, Years Median (Range)				
	35 (21-62)	60 (25 – 82)	55 (37 – 74)	57 (21 – 82)
Sex, n (%)				
Men	3 (50)	16 (62)	1 (14)	20 (51)
Women	3 (50)	10 (38)	6 (86)	19 (49)
Race, n (%)				
American Indian or Alaska Native	0	1 (4)	0	1 (3)
Asian	0	1 (4)	0	1 (3)
Black or African American	1 (17)	5 (19)	2 (29)	8 (21)
White	4 (67)	17 (65)	5 (71)	26 (67)
Other	1 (17)	2 (8)	0	3 (8)
ECOG Performance Score				
0	0	11 (42)	2 (29)	13 (33)
1	4 (67)	10 (38)	5 (71)	19 (49)
2	2 (33)	5 (19)	0	7 (18)
Diagnosis				
ATLL	-	-	2 (29)	2 (5)
ALCL	6 (100)	26 (100)	-	32 (82)
AITL	-	-	2 (29)	2 (5)
EATL	-	-	1 (14)	1 (3)
PTCL-NOS	-	-	2 (29)	2 (5)
Stage at Diagnosis				
I	0	4 (15)	0	4 (10)
II	1 (17)	8 (31)	0	9 (23)
III	1 (17)	6 (23)	2 (29)	9 (23)
IV	4 (67)	8 (31)	5 (71)	17 (44)
Baseline IPI Score				
0-1	0	13 (50)	0	13 (33)
2-3	6 (100)	7 (27)	6 (86)	19 (49)
4-5	0	6 (23)	1 (14)	7 (18)

Abbreviations: ALCL, anaplastic large-cell lymphoma; ALK, anaplastic lymphoma kinase; AITL: angioimmunoblastic T-cell lymphoma; ATLL = adult T-cell leukaemia/ lymphoma; EATL = enteropathy-associated T-cell lymphoma; ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index; NOS, not otherwise specified; sALCL, systemic anaplastic large-cell lymphoma

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

The participant flow in the relevant randomised controlled trials is shown in **Appendix D.** A summary of statistical analysis and study groups for the relevant clinical trials is also provided in **Appendix D.**

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

A complete quality assessment of each trial is provided in Appendix D.

B.2.6 Clinical effectiveness results of the relevant trials

The proposed marketing authorisation for the intervention in question is: *brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP) is indicated for adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL).* This proposed marketing authorisation is based on the results of the ECHELON-2 trial.

ECHELON-2 was the pivotal, international, double-blind, double-dummy, randomised, placebo-controlled, active-comparator, Phase III study BV comparing BV+CHP to CHOP in patients with previously untreated CD30+ PTCL.[23] The primary endpoint in the ECHELON-2 trial was PFS, determined per IRF. A key secondary endpoint was PFS per IRF for patients with sALCL. Other alpha-controlled key secondary outcomes were OS (median follow-up 42.1 months) CR, and ORR determined by the IRF.

In the primary analysis of ECHELON-2, treatment with BV+CHP resulted in a statistically significant and clinically meaningful improvement in efficacy in the intent-to-treat (ITT) population, including an OS benefit. All primary and alpha-controlled key secondary endpoints were met. [77] These data are presented below.

B.2.6.1 ECHELON-2

B.2.6.1.1 *Primary efficacy outcome: Progression Free Survival*

The primary endpoint in the ECHELON-2 trial was PFS, determined per IRF, defined as the time from the date of randomisation to the date of first documentation of relapse or progressive disease, death due to any cause, or receipt of subsequent systemic chemotherapy to treat residual or progressive PTCL as determined by the investigator, whichever came first. The receipt of subsequent systemic chemotherapy was considered an event because it represents a failure of front-line treatment to achieve a cure. In the absence of progressive disease, receipt of radiotherapy to consolidate response to initial treatment, chemotherapy for the purpose of mobilising haemopoietic stem cells, consolidative ASCT or consolidative alloSCT were not considered events.[23]

As of the 15 August 2018 data cut-off date, 219 subjects (48%) had experienced a PFS event: 95/226 patients (42%) in the BV+CHP arm and 124/226 patients (55%) in the CHOP arm.[23] PFS per IRF was significantly improved in the BV+CHP arm

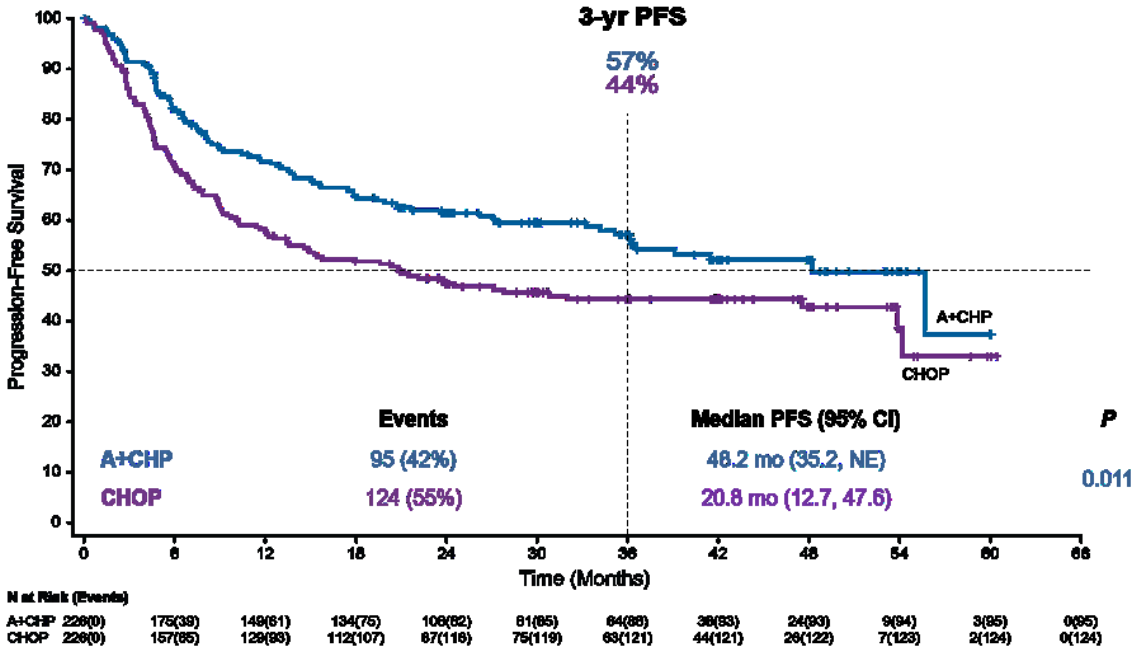
compared with the CHOP arm (stratified HR 0.71 [95% CI: 0.54, 0.93], P=0.011), equating to a 29% reduction in the risk of a PFS event;

Figure 11. After a median follow-up of 36.2 months (95% CI 35.9–41.8), the median PFS in the BV+CHP group was longer than that of the CHOP group (48.2 months [35.2–not evaluable] vs 20.8 months [12.7–47.6]), displayed in both

Figure 11 and **Table 14**, below.[79]

Furthermore, three-year PFS was 57.1% (95% CI: 49.9–63.7) for the BV+CHP group compared with 44.4% (95% CI: 37.6–50.9) for the CHOP group.[23] A prespecified secondary analyses of PFS by investigator assessment (IA) was similar to PFS by IRF with a high (97%) concordance in PFS between the two assessments.

Figure 11: PFS (ITT analysis set)



*Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomization

Table 14: ECHELON-2: Primary outcome analysis, PFS per IRF (ITT population)[23,77]

Progression Free Survival	BV+CHP (N=226)	CHOP (N=226)
Median PFS, months (95% CI) ‡	48.2 (35.2, -)	20.8 (12.7, 47.6)
Stratified hazard ratio (95% CI) (BV+CHP to CHOP)	0.71 (0.54, 0.93)	
Stratified log-rank p-value†	0.0110	
Estimated PFS (95% CI), at:		
6 months	82.1% (76.4%, 86.6%)	70.8% (64.3%, 76.3%)
12 months	71.7% (65.1%, 77.2%)	58.2% (51.4%, 64.3%)
24 months	61.4% (54.4%, 67.6%)	47.4% (40.6%, 53.8%)
36 months	57.1% (49.9%, 63.7%)	44.4% (37.6%, 50.9%)

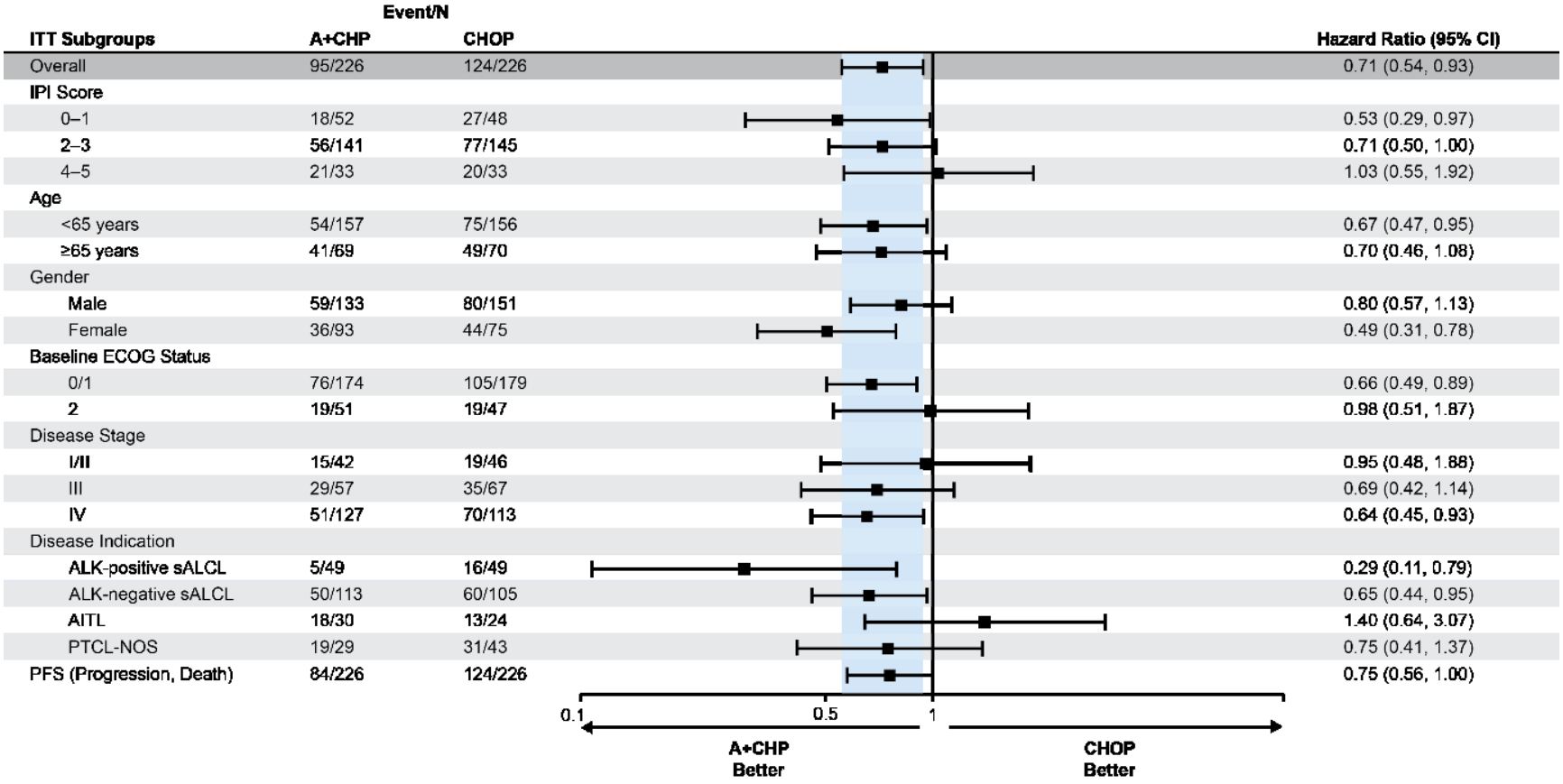
Data shown are for the intention-to-treat population †From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and International Prognostic Index score: 0-1/2-3/4-5) at randomisation ‡PFS rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method.[80]

Abbreviations: BV+CHP: brentuximab vedotin [A], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CI: confidence interval; PFS: progression-free survival.

In ECHELON-2, consolidative therapy was permitted, but did not affect the results of the primary or secondary end-points of PFS and OS as the benefits of BV+CHP were seen both with and without censoring the patients in both groups who received either a consolidative SCT or radiotherapy. The hazard ratio of this pre-specified analysis (i.e. censoring consolidation) was 0.71 (95% CI: 0.53-0.94) which is consistent with the hazard ratio observed in the primary end-point of PFS 0.71 (95% CI: 0.54-0.93).[77]

As shown in **Figure 12**, PFS analyses for subgroups were generally consistent with the overall study results. Importantly, the study was not powered to compare efficacy between individual histological subtypes with the exception of the sALCL subgroup. PFS per IRF of the sALCL subgroup was a key secondary endpoint of the ECHELON-2 trial due to a regulatory requirement by the EMA. Section B.2.7 presents the results of the ECHELON-2 trial for the sALCL subgroup

Figure 12: PFS for pre-specified subgroups (ITT analysis set)



The HR for treatment with A+CHP (BV+CHP) vs CHOP and the 95% CIs were based on the Cox regression model considering stratification factors at randomisation. The IPI subgroup was changed after randomisation in one patient in the A+CHP(BV+CHP) group (from 0–1 to 2–3) and one patient in the CHOP group (from 4–5 to 2–3).

Abbreviations: A+CHP=brentuximab vedotin, cyclophosphamide [C], doxorubicin [H], and prednisone [P]. CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IPI: international prognostic index; ITT: intention-to-treat; ALK+/-: anaplastic lymphoma kinase (positive/negative); sALCL: systemic anaplastic large cell lymphoma; AITL: angioimmunoblastic T-cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified

B.2.6.1.2 *Key Secondary Efficacy Outcomes*

Overall Survival for the ITT population

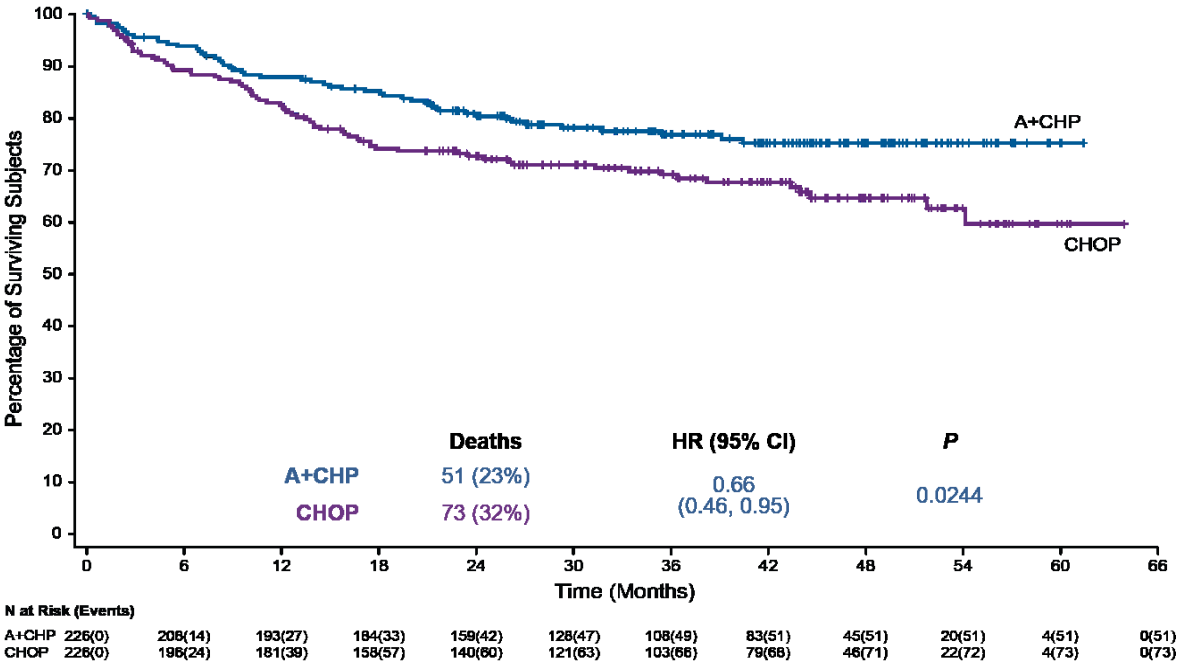
OS was significantly improved using BV+CHP vs CHOP, where treatment with BV+CHP reduced the risk of death by 34% when compared with CHOP (HR 0.66 [95% CI 0.46–0.95], p=0.0244; **Figure 13**).

As of the data cut-off date, 15 August 2018, 124 deaths had occurred, including 51 (23%) deaths in the BV+CHP treatment arm and 73 (32%) deaths in the CHOP treatment arm (**Table 15**). The median OS was not reached for either group after a median follow-up of 42.1 months (95% CI 40.4–43.8). Furthermore, the 75th percentile OS was not reached for the BV+CHP treatment arm. However, this was observed as 17.5 months for the CHOP treatment arm. [23]

This is a landmark result as ECHELON-2 is the first prospective trial to show an OS benefit for any therapy over the established standard of care, CHOP. The significant improvement in OS in the BV+CHP arm is particularly impressive when one considers that, on progression, many more patients in the CHOP arm received subsequent anti-cancer therapy than did so in the BV+CHP arm (i.e. 42% in the CHOP arm received any subsequent anti-cancer therapy for residual or progressive disease compared with 26% in the BV+CHP arm). The same applies in respect of subsequent BV which, on progression, was received by 22% of patients receiving front-line CHOP versus 10% of patients receiving front-line BV+CHP. See Table 19 in Section B.2.6.1.4 for full details of subsequent anti-cancer therapy.

This difference in OS, despite receiving less subsequent anti-cancer therapy in the BV+CHP arm, underlines the importance of effective front-line treatment in PTCL and is a strong argument for why patients would benefit most from access to BV+CHP in the front-line setting.

Figure 13: Overall Survival for the ITT population



The HR for treatment with BV+CHP vs CHOP and the 95% CIs were computed from log-rank test using stratification factors (ALK-positive sALCL: yes or no and IPI score: 0–1, 2–3, 4–5) at randomisation.

Abbreviations: A+CHP (BV+CHP): brentuximab vedotin [A], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; HR: hazard ratio; CI: confidence interval.

Table 15: Summary of Overall Survival (ITT Population)[23]

Overall Survival	BV+CHP (N=226)	CHOP (N=226)
Number of deaths, n (%)	51 (23%)	73 (32%)
Stratified hazard ratio (95% CI) (BV+CHP to CHOP)	0.66 (0.46, 0.95)	
Stratified log-rank P value*	0·0244	
Median overall survival (months) (95% CI) †	- (-, -)	- (54.2, -)
Estimated survival rate (95% CI)† at:		
6 months	93.7% (89.6%, 96.2%)	89.2% (84.4%, 92.7%)
12 months	87.8% (82.8%, 91.5%)	82.4% (76.7%, 86.8%)
24 months	80.8% (75.0%, 85.5%)	72.6% (66.2%, 78.0%)
36 months	76.8% (70.4%, 82.0%)	69.1% (62.3%, 74.9%)

Data shown are for the intention-to-treat population.

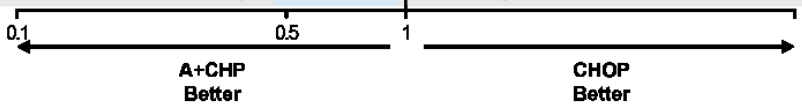
*From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomisation. †Overall survival rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method.

Abbreviations: BV+CHP: brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CI: confidence interval.

As shown in **Figure 14**, OS analyses for subgroups were generally consistent with the overall study results. Importantly, as recognised by the investigators, the study was not powered to compare OS between individual histological subtypes.

Figure 14: Overall Survival in key pre-specified subgroups

ITT Subgroups	Event/N A+CHP	Event/N CHOP	Hazard Ratio (95% CI)
Overall	51/226	73/226	0.66 (0.46, 0.95)
IPI Score			
0–1	5/52	10/48	0.46 (0.16, 1.33)
2–3	**29/141**	**48/145**	**0.56 (0.35, 0.89)**
4–5	17/33	15/33	1.15 (0.58, 2.31)
Age			
<65 years	26/157	37/156	0.64 (0.39, 1.06)
≥65 years	**25/69**	**36/70**	**0.64 (0.38, 1.08)**
Gender			
Male	**32/133**	**49/151**	**0.68 (0.43, 1.06)**
Female	19/93	24/75	0.66 (0.36, 1.22)
Baseline ECOG Status			
0/1	34/174	61/179	0.51 (0.34, 0.78)
2	**17/51**	**12/47**	**1.48 (0.70, 3.11)**
Disease Stage			
I/II	**7/42**	**12/46**	**0.66 (0.25, 1.71)**
III	13/57	17/67	0.71 (0.33, 1.49)
IV	**31/127**	**44/113**	**0.68 (0.43, 1.07)**
Disease Indication			
ALK-positive sALCL	**4/49**	**10/49**	**0.38 (0.12, 1.22)**
ALK-negative sALCL	25/113	34/105	0.58 (0.35, 0.98)
AITL	**8/30**	**6/24**	**0.87 (0.29, 2.58)**
PTCL-NOS	11/29	20/43	0.83 (0.38, 1.80)



The HR for treatment with A+CHP (BV+CHP) vs CHOP and the 95% CIs were based on the Cox regression model considering stratification factors at randomisation. The IPI subgroup was changed after randomisation in one patient in the A+CHP (BV+CHP) group (from 0–1 to 2–3) and one patient in the CHOP group (from 4–5 to 2–3).

Abbreviations: A+CHP: brentuximab vedotin [A], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; AITL: angioimmunoblastic T-cell lymphoma; ALK: anaplastic lymphoma kinase; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; ECOG: Eastern Cooperative Oncology Group; HR: hazard ratio; IPI: international prognostic index; ITT: intention-to-treat; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; sALCL: systemic anaplastic large cell lymphoma.

Complete Remission and Objective Response Rates for ITT population

Both CR and ORR were significantly higher in patients treated with BV+CHP than patients treated with CHOP. As shown in **Table 16,** the CR rate (by IRF assessment) was 68% (95% CI: 61.2, 73.7) in the BV+CHP arm compared with 56% (95% CI: 49.0, 62.3) in the CHOP arm (P=0.0066). The ORR at end of treatment by IRF assessment was 83% (95% CI: 77.7, 87.8) versus 72% (95% CI: 65.8, 77.9) in the BV+CHP arm and CHOP arms, respectively (P=0.0032; **Table 17**).[23]

Table 16: **Summary of response at end of treatment according to the IRF for ITT population [23]**

Response at end of treatment	BV+CHP (N=226)	CHOP (N=226)
Complete Remission	153 (68%)	126 (56%)
Partial Remission	35 (15%)	37 (16%)
Stable Disease	5 (2%)	11 (5%)
Progressive Disease	15 (7%)	31 (14%)
Not evaluable†	18 (8%)	21 (9%)

Data are n (%), unless otherwise specified. Data shown are for the intention-to-treat population.
*Best response at end of treatment was assessed in accordance with the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). Complete remission, partial remission, stable disease, progressive disease, and not evaluable are mutually exclusive.
†Patients with no post-baseline response assessments were not evaluable.

Abbreviations: BV+CHP=brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]. CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P].

Table 17: Summary of response rate and response rate difference at end of treatment according to the IRF for ITT population [23]

Response	BV+CHP (N=226)	CHOP (N=226)	Response Rate Difference (95%CI), p-value
Proportion of patients who achieved an Objective Response Rate, n (%) [95% CI]	188 (83%) [77.7–87.8]	163 (72%) [65.8–77.9]	11.1 (3.4–18.7), 0.0032
Complete Remission Rate, n (%)	153 (68%) [61.2–73.7]	126 (56%) [49.0–62.3]	11.9 (3.1-20.8), 0.0066

Data are n (%), unless otherwise specified. Data shown are for the intention-to-treat population.
*Best response at end of treatment was assessed in accordance with the Revised Response Criteria for Malignant Lymphoma (Cheson, 2007). Complete remission, partial remission, stable disease, progressive disease, and not evaluable are mutually exclusive.
†Patients with no post-baseline response assessments were not evaluable

Abbreviations: BV+CHP=brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]. CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P].

In the ECHELON-2 trial, patients were required to have CD30 expression ≥10% by immunohistochemistry (IHC) per local assessment. The degree of CD30 expression alone did not predict response to BV+CHP and there appears to be no clear correlation between the level of CD30 expression and response rate or duration of response in the ECHELON-2 trial. As sALCL uniformly expresses CD30, the analysis focused on patients with AITL and PTCL-NOS, the largest remaining subgroups in the study.

Figure 15: CD30 Expression by Response for PTCL-NOS and AITL in the BV+CHP Treatment Arm

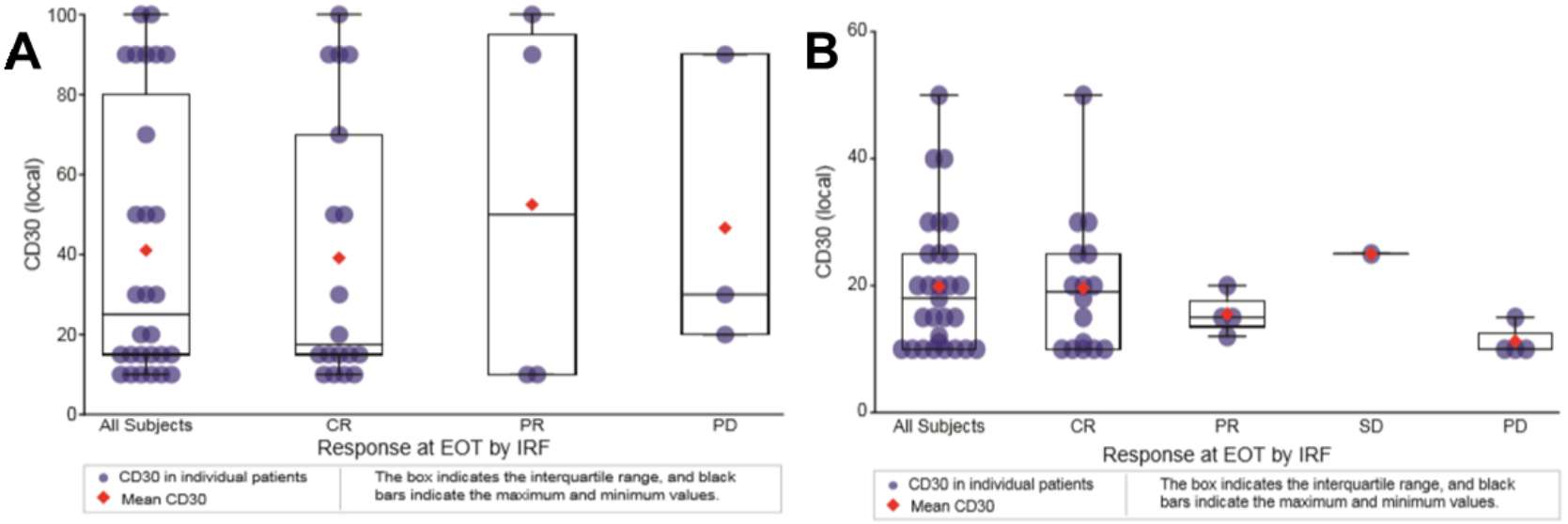


Figure A: patients diagnosed with PTCL-NOS; Figure B: patients diagnosed with AITL
Abbreviations: PTCL-NOS: Peripheral T-cell Lymphoma-not otherwise specified; AITL: Angioimmunoblastic T-cell Lymphoma; CR: Complete Response; PR: Partial Response; PD: Progressive Disease; SD: Stable Disease; EOT: End of Trial; IRF: Independent Review Facility

Among patients with AITL and PTCL-NOS in the ECHELON-2 trial, response rate and durability of response were independent of CD30 expression above vs. below the median, and responses were observed among patients with the lowest CD30 expression level (CD30=10%) (**Figure 15**) [81].

The results seen in ECHELON-2 mirror those seen with BV in other studies in PTCL and across a wide range of lymphomas. IData from two supportive studies in PTCL, SGN35-012 (NCT01421667) and 35-IST-30 (NCT02588651), included 18 patients with R/R disease and CD30 expression <10% per local IHC, including eight patients with undetectable CD30 per IHC (Richardson 2019). Of the 18 patients, eight (44%) achieved an objective response, including four (22%) CRs, to BV monotherapy. Of the eight patients with undetectable CD30, two achieved CR and one achieved PR [82]. Secondly, response to BV and duration of response were seen to be independent of CD30 expression levels in a range of CD30-expressing lymphomas across multiple studies of BV use in T-cell and B-cell Non-Hodgkin lymphomas [83]. Clinical benefit from BV has been observed in patients with all levels of CD30 expression.

Taken as whole, these data indicate that the degree of CD30 expression alone does not predict benefit from BV. As the minimum CD30 expression level necessary for BV activity is not determined, the indication statements for BV do not currently specify a minimum CD30 expression level [82]. It is anticipated that the marketing authorisation for BV+CHP in previously untreated PTCL will only require that patients have CD30+ disease, consistent with previous indications of BV.

B.2.6.1.3 *Treatment Duration and Intensity*

The majority of patients completed their treatment as intended, receiving 6-8 cycles of treatment with either BV+CHP or CHOP. The majority of patients received six cycles of BV+CHP or CHOP (mean BV+CHOP: 6.0 cycles; mean CHOP: 5.8 cycles). (**Table 18**).[23] The median duration of treatment was 18.1 weeks in the BV+CHP arm and 18.0 weeks in the CHOP arm.[79] The median relative dose intensity was 99.2% (IQR 93.6–100.0) for BV in the BV+CHP group and 99.1% (IQR 95.9–102.3) for vincristine in the CHOP group, thereby indicating that the addition of BV was well-tolerated.[23]

Table 18: ECHELON-2: Summary of Treatment [23]

Summary of treatment	BV+CHP (N=226)	CHOP (N=226)
Exposure to study drug, n	223	226
Duration of Treatment; median (min, max)	18.1 (3, 34)	18.0 (3, 31)
Number of subjects treated by cycle, n (%)		
6 cycles	156 (70)	140 (62)
8 cycles	40 (18)	44 (19)
Mean number of treatment cycles	6.0	5.8

Median relative dose intensity (BV or vincristine) % [IQR]	99.2 [93.6-100.0]	99.1 [95.9-102.3]

Abbreviations: BV+CHP=brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]. CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; BV: brentuximab vedotin; IQR: interquartile range

B.2.6.1.4 *Subsequent Therapies*

Excluding stem cell transplantation or radiotherapy for consolidation of response to initial therapy, 59 patients (26%) in the BV+CHP arm and 94 patients (42%) in the CHOP arm went on to receive subsequent anti-cancer therapies for residual or progressive disease (**Table 19**). Of these patients, 23 (10%) in the BV+CHP group and 49 (22%) in the CHOP group received subsequent therapy containing BV.[23] The decision to unblind patients receiving subsequent therapy was at the discretion of the investigator, and therefore some patients remained blinded following progression.

As noted earlier, despite the much higher use of subsequent anti-cancer therapy (including BV) in the CHOP arm, front-line therapy with BV+CHP resulted in significantly improved OS compared to the CHOP arm regardless of transplant, thus highlighting the importance of effective front-line treatment in PTCL.

Table 19: ECHELON-2: Summary of Subsequent Anti-Cancer Therapies[23]

Anti-cancer therapy	BV+CHP (N=226)	CHOP (N=226)
Subjects who received subsequent anti-cancer therapy*	65 (29%)	96 (42%)
Systemic therapy for residual or progressive disease	59 (26%)	94 (42%)
BV containing	23 (10%)	49 (22%)
Palliative radiation	10 (4%)	8 (4%)
Systemic therapy for other malignancies	7 (3%)	3 (1%)

*Subjects may have received more than one type of therapy
Abbreviations: BV+CHP=brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]. CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; BV: brentuximab vedotin

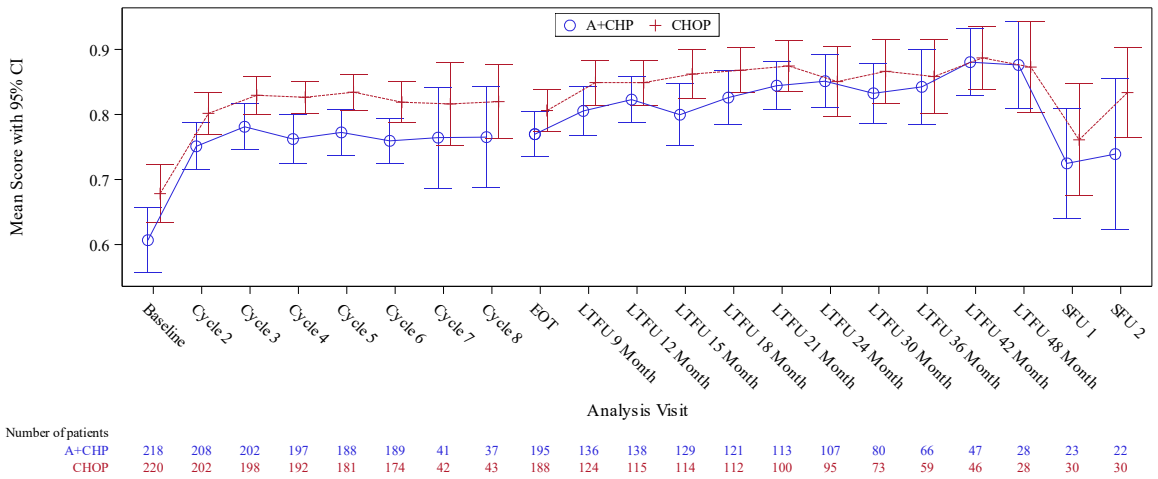
B.2.6.1.5 *Additional Outcomes*

Health Related Quality of Life

Quality of life (QoL) was assessed in ECHELON-2 using the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L), the EORTC Core Quality of Life Questionnaire- Core 30 (QLQ-C30), and the FACT/GOG-NTX subscale.

The mean EQ-5D-3L time trade-off (TTO)-indexed scores were analysed using both US and UK-based value sets. The mean scores increased over time, and the change from baseline did not differ significantly between the BV+CHP and CHOP treatment arms (**Figure 16**). Note: Figure 17 represents the UK-based EQ-5D-3L value set.

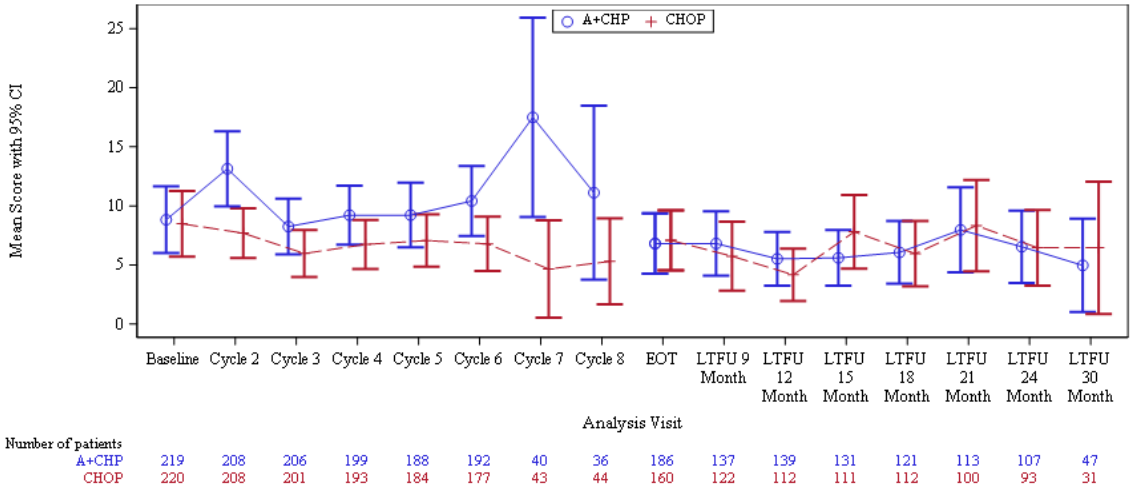
Figure 16: EQ-5D-3L Mean Score Over Time from ITT Analysis for BV+CHP vs CHOP (UK TTO)



Abbreviations: EQ-5D-3L: European Quality of Life 5-Dimensions Questionnaire; BV+CHP/A+CHP: brentuximab vedotin+ cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; TTO – time trade-off

Overall, the mean scores for the role, emotional, cognitive, physical, social functioning scales, the global health status, and total score of the QLQ-C30 showed no significant difference between the BV+CHP arm compared with the CHOP arm during the study period. The mean total score and physical functioning scores were lower at baseline on the BV+CHP arm. However, both rose above baseline levels with time on treatment. The scores improved above baseline scores on both treatment arms during the treatment period, at end of treatment, and returned to near-normal values during long-term follow-up. Of note, an increase in diarrhoea was reported for the BV+CHP treatment group but was only present in treatment cycle seven and was not persistent throughout the course of treatment. This can be observed in **Figure 17**, which shows the impact on HRQoL of patients within ECHELON-2 over time as assessed by the EORTC-QLQ-C30.

Figure 17: QLQC30 Diarrhoea from ITT Analysis for BV+CHP vs CHOP



Abbreviations: QLQ-C30: EORTC Quality of Life Questionnaire – Core 30; BV+CHP/A+CHP: brentuximab vedotin+ cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]

Finally, the neurotoxicity scores for the FACT/GOG-NTX subscale between the BV+CHP and CHOP arms were not meaningfully different while on treatment and returned to near-baseline values during long-term follow-up, suggesting BV+CHP is not inferior to CHOP regarding the impact of neuropathy on quality of life.

B.2.6.2 Brentuximab vedotin non-comparative trials

B.2.6.2.1 *Horwitz et al 2014*

Horwitz 2014 demonstrated objective responses among 41% of patients with R/R T-cell lymphomas who were treated with BV monotherapy across a wide range of CD30 expression levels.

Overall, the ORR was 41% (14/34) (CR: 24%; PR: 18%). Patients with AITL had the best ORR at 54% (7/13) (CR: 38%; PR: 15%), with a median PFS of 6.7 months (range, 0.1-15.21 months) at the time of publication. Patients with PTCL-NOS had an ORR of 33% (7/21) (CR: 14%; PR: 19%), with a median PFS of 1.6 months (range, 0.3-11.3+ months). Reponses were seen in patients with all levels of CD30 expression, including those without detectable CD30 expression. Therefore, no correlation between CD30 expression per central review and response was observed.

Table 20: Best Clinical Response[67]

Response	AITL (n = 13)	PTCL-NOS (n = 21)	Total (n = 34)
Best Clinical Response, n(%)*			
Complete Remission (CR)	5 (38)	3 (14)	8 (24)
Partial Remission (PR)	2 (15)	4 (19)	6 (18)
Stable Disease (SD)	3 (23)	3 (14)	6 (18)
Progressive Disease (PD)	3 (23)	11 (52)	14 (41)
Objective response rate, n (%)	7 (54)	7 (33)	14 (41)
95% CI for Objective Response Rate†	25.1, 80.8	14.6, 57	24.6, 59.3
Disease Control rate, n (%)‡	10 (77)	10 (48)	20 (59)

*Per Cheson, as assessed by the investigator. †Two-sided 95% exact confidence interval. ‡CR 1 PR 1 SD.
Abbreviations: AITL: angioimmunoblastic T-cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; CR: complete remission; PR: partial remission; SD: stable disease; PD: progressive disease; CI: confidence interval

B.2.6.2.2 *Fanale et al 2014 & Fanale et al 2018*

The results of this trial demonstrated that when administered sequentially with CHOP, or in combination with CHP, BV exhibited substantial antitumor activity in patients with newly diagnosed CD30+ PTCL.

After sequential treatment with BV, followed by standard-dose CHOP treatment, 85% (11/13) of patients achieved the primary activity outcome of an objective response (CR: 62%; PR: 23%; estimated 1-year PFS rate: 77%). For the primary safety outcome, grade 3/4 adverse events occurred in 65% (8/13) patients. At the end of combination treatment (BV+CHP), all patients (n= 26) achieved an objective response (CR: 88%; PR: 12%; estimated 1-year PFS rate: 71%). All seven patients included in the study without sALCL achieved CR.

Grade 3/4 adverse events (≥10%) in the combination-treatment group were febrile neutropenia (31%), neutropenia (23%), anaemia (15%), and pulmonary embolism (12%).

Table 21: Best Response After Sequential or Combination Therapy[75]

	Sequential	Combination		
Response	**ALCL (n = 13)**	**ALCL (n = 19)**	**Non-ALCL (n = 7)**	**Total (n = 26)**
Objective Response (ORR), n(%)	11 (85)	19 (100)	7 (100)	26 (100)
Complete Remission (CR), n(%)	8 (62)	16 (84)	7 (100)	23 (88)
Partial Remission (PR), n(%)	3 (23)	3 (16)	0	3 (12)
Stable Disease (SD), n(%)	0	0	0	0
Progressive Disease (PD), n(%)	2 (15)	0	0	0

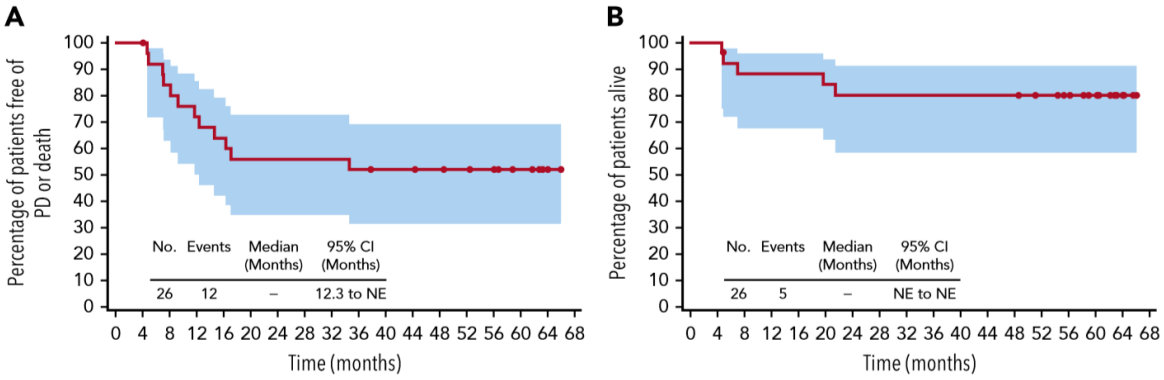
NOTE. Response assessment per investigator (Cheson) at cycle 8 (sequential treatment), cycle 6 (combination treatment), or at last available response assessment for patients who discontinued treatment before these time points.

Abbreviations: ALCL, anaplastic large-cell lymphoma; ORR: objective response rate; CR: complete response; PR: partial remission; SD: stable disease; PD: progressive disease

Fanale 2018 presents the 5-year PFS and OS outcomes at the 5-year follow-up for the combination treatment approach from the Fanale 2014 trial, summarising the durability of response. After approximately 5 years, 13 patients (50%) had remained

in remission without any new anticancer therapy.[76] Nine of these patients had sALCL, and four patients had other PTCL diagnoses. After a median observation period of 59.6 months (range,4.6-66.0) from first dose, neither the median PFS nor the median OS was reached. No progression or death was observed beyond 35 months in the five-year follow-up. The estimated 5-year PFS and OS rates were 52% and 80%, respectively (**Figure 18**).[76]

Figure 18: Kaplan-Meier Analysis for PFS (A) and OS (B) at 5-year Follow-up[76]



A: represents progression free survival (PFS); B: represents overall survival (OS); shading represents 95% confidence intervals
Abbreviations: PFS: Progression-free survival; OS: overall survival; NE: not estimable; PD: progressive disease

B.2.7 Subgroup analysis

The Phase III ECHELON-2 study had a target to enrol 75% (±5%) of patients with sALCL (according to central pathology assessment) to ensure that the secondary endpoint of PFS in sALCL could be assessed robustly. This was a regulatory requirement from EMA as this study formed part of the post-approval marketing authorisation commitment for BV's existing indication for R/R sALCL.

The sALCL subtype of PTCL is of particular interest to this appraisal for multiple reasons. Firstly, because BV already has a marketing authorisation and a positive NICE recommendation for R/R sALCL. Secondly, and arising from this first point, the subsequent treatment pathway for R/R patients for this subtype of PTCL is different from that of the other CD30+ PTCL subtypes.

B.2.7.1 Methodology

PFS per IRF in the subset of patients with sALCL, as confirmed by central pathology, was analysed in the same manner as the primary analysis of PFS per IRF.

B.2.7.2 Participant Characteristics

A summary of baseline disease characteristics for the subset of patients with sALCL is presented below. A total of 316 patients enrolled within the ECHELON-2 trial had a diagnosis of sALCL (n=162 in the BV+CHP arm and n=154 in the CHOP arm). In

line with the ITT population, the baseline characteristics were generally well balanced between treatment arms.

The majority of patients had advanced disease (stage III, n=75 [24%] and stage IV, n=173 [55%]), which was consistent with the ITT. However, a higher percentage of patients with stage IV disease were in the BV+CHP arm compared to the CHOP arm (61% vs 48%, respectively) potentially biasing results in favour of the CHOP treatment arm as stage of disease is considered an important prognostic factor.[48]

The proportion of patients with a favourable IPI score of 0-1 was balanced between the two arms (25% for BV+CHP and 22% for CHOP). For patients with a diagnosis of ALK+ sALCL, an entry criterion for ECHELON-2 was that patients recruited had to have an IPI score of ≥2. This confers a worse outcome and a poor prognosis in line with the other PTCL subtypes. Therefore, most patients participating in ECHELON-2 with sALCL had an IPI of ≥2 (77%) [23,48]

This is evidenced by the proportion of sALCL patients who participated in the ECHEON-2 trial that were ≥ 40 years of age; 65.3% of patients enrolled in the BV+CHP arm and 57.1% of those in the CHOP are were ≥ 40 years of age. As described in **Section B.1.3.4**, age and particularly a cut-off of 40 years, has been shown to be a prognostically important factor. This indicates that most of the patients with sALCL enrolled in ECHELON-2 had a poorer prognosis, particularly in the BV+CHP as a higher proportion of patients were ≥ 40 years of age than in the CHOP arm. (See **Section B.1.3.4)**[77].

Table 22: Summary of Baseline Disease Characteristics for Subset of Patients with sALCL in ECHELON-2 [77]

Baseline Characteristic	BV+CHP (N=162)	CHOP (N=154)	Total (N=316)
Diagnosis, per local assessment, n (%)			
sALCL	162 (100)	154 (100)	316 (100)
Time from Diagnosis to First Dose (months)			
n	159	152	311
Mean (STD)	1.0 (1.6)	1.1 (1.0)	1.0 (1.3)
Median	0.8	0.9	0.9
Min, Max	0, 19	0, 10	0, 19
Disease staging at diagnosis, n (%)			
Stage I	12 (7)	7 (5)	19 (6)
Stage II	22 (14)	27 (18)	49 (16)
Stage III	29 (18)	46 (30)	75 (24)
Stage IV	99 (61)	74 (48)	173 (55)
Initial diagnosis of cutaneous ALCL for sALCL pts, n (%)			
	13 (8)	4 (3)	17 (5)
Time from cutaneous ALCL diagnosis to sALCL diagnosis (months)			
n	11	4	15

Mean (STD)	16.0 (20.6)	9.8 (12.8)	14.4 (18.6)
Median	4.8	4.7	4.8
Min, Max	1, 69	1, 29	1, 69
Baseline IPI Score, n (%)			
0	7 (4)	14 (9)	21 (7)
1	34 (21)	18 (12)	52 (16)
2	58 (36)	60 (39)	118 (37)
3	37 (23)	40 (26)	77 (24)
4	22 (14)	16 (10)	38 (12)
5	4 (2)	6 (4)	10 (3)
Serum LDH per local laboratory, n (%)			
≤ 1 x ULN	87 (54)	72 (47)	159 (50)
>1 x ULN	75 (46)	82 (53)	157 (50)
Extranodal Disease Involvement, n (%)			
≤ 1 site	94 (58)	95 (62)	189 (60)
>1 site	68 (42)	59 (38)	127 (40)
HTLV-1 status, n (%)			
Positive	1 (1)	0	1 (0)
Negative	158 (98)	153 (99)	311 (98)
Intended number of cycles at Baseline, n (%)			
6	134 (83)	120 (78)	254 (80)
8	28 (17)	34 (22)	62 (20)
Intention of stem cell transplant following completion of study regimen, n (%)			
Yes	57 (35)	49 (32)	106 (34)
No	105 (65)	104 (68)	209 (66)
Baseline bone marrow biopsy-lymphoma involvement, n (%)			
Yes	15 (9)	13 (8)	28 (9)
No	147 (91)	141 (92)	288 (91)
Percent CD30 positive cells, per local assessment			
n	162	154	316
Mean (STD)	93.0 (13.5)	92.9 (10.3)	93.0 (12.0)
Median	100.0	95.0	100.0
Min, Max	10, 100	50, 100	10, 100
Percent CD30 positive cells, per central assessment			
n	159	148	307
Mean (STD)	94.7 (11.0)	92.8 (14.3)	93.8 (12.7)
Median	100.0	100.0	100.0
Min, Max	0, 100	0, 100	0, 100

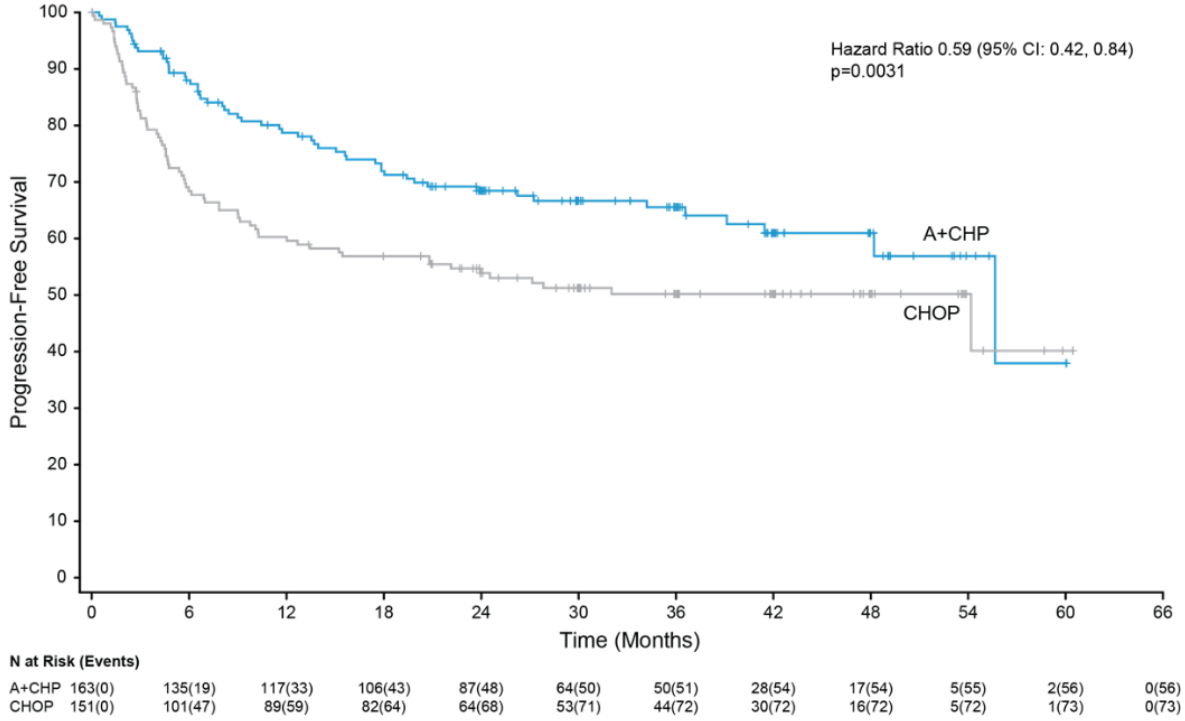
Abbreviations: BV+CHP=brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]. CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; sALCL: anaplastic large cell lymphoma; ALK+/-: anaplastic lymphoma kinase (positive/negative); STD: standard deviation; IPI: International Prognostic Index; LDH: lactate dehydrogenase; HTLV-1: Human T-Lymphotropic Virus Type-1

B.2.7.3 Results

B.2.7.3.1 *Progression Free Survival*

The primary analysis (PFS per IRF) of the key secondary subgroup of patients with sALCL showed that PFS was significantly improved with BV+CHP compared to CHOP (stratified HR 0.59; p=0.0031); equating to a 41% reduction in the risk of a PFS event among patients treated with BV+CHP compared to those treated with CHOP alone (**Figure 19**).[23]

Figure 19: **PFS for Subjects with sALCL**



* Computed from log-rank test using stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0–1/2–3/4–5) at randomisation

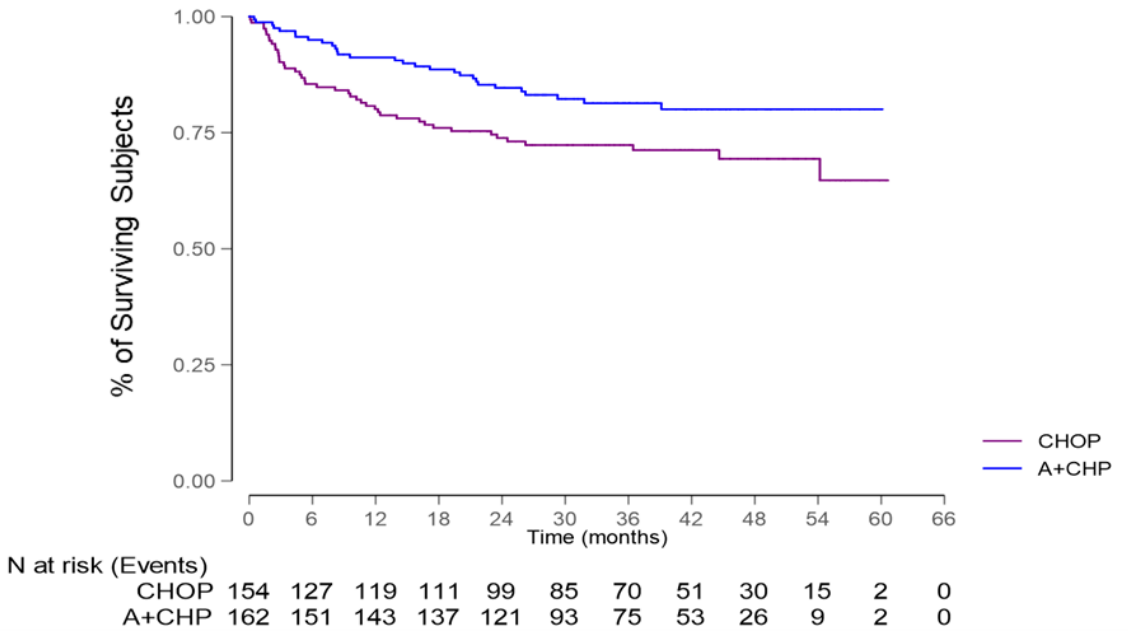
Abbreviations: PFS: progression-free survival; sALCL: systemic anaplastic large cell lymphoma; ITT: intend-to-treat; BV+CHP/A+CHP: brentuximab vedotin+ cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]

B.2.7.3.2 *Overall Survival*

For the subset of patients with sALCL, OS was also significantly improved with BV+CHP vs CHOP, where treatment with BV+CHP reduced the risk of death by 46% when compared with CHOP (HR 0.54 [95% CI 0.337–0.867], p=0.0096) (**Figure 20**). This statistically significant benefit in OS was observed despite 70% of relapsed patients with sALCL receiving BV following relapse in the CHOP arm. This reflects the current treatment pathway in the UK where BV is used as a second line treatment for R/R sALCL following relapse from front-line CHOP. The improvement

in OS is particularly significant when one considers that patients in the CHOP arm had access to BV at relapse.[77]

Figure 20: OS for Patients with sALCL (ITT subset analysis)



Abbreviations: OS: overall survival; sALCL: systemic anaplastic large cell lymphoma; ITT: intend-to-treat; A+CHP(BV+CHP): brentuximab vedotin+ cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]

B.2.7.3.3 *Additional Outcomes*

Complete Remission and Objective Response Rates for sALCL subgroup analysis

In the sALCL subgroup, the ORR at end of treatment per IRF assessment was 88% (95% CI: 81.6, 92.3) for subjects on the A+CHP arm compared with 71% (95% CI: 62.9, 77.8) for subjects on the CHOP arm (P=0.0001). Partial response was similar across treatment arms, however a greater number of patients with sALCL who received BV+CHP achieved complete remission compared to those in the standard CHOP treatment arm (CR: 71% BV+CHP vs. 53% CHOP) (**Table 23**) [77]

Table 23: sALCL response by therapeutic treatment arm

Response	BV+CHP (N=162)	CHOP (N=154)
Complete Remission	115 (71%)	82 (53%)
Not evaluable	9 (6%)	18 (12%)
Progressive disease	7 (4%)	19 (12%)
Partial response	27 (17%)	27 (18%)
Stable disease	4 (2%)	8 (5%)

Abbreviations: sALCL: Systemic anaplastic large cell lymphoma; BV+CHP: brentuximab vedotin + cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]

All subgroup data are presented within Document B. No additional subgroup data are presented in Appendix E

B.2.8 Meta-analysis

As ECHELON-2 was the only RCT identified that investigated the use of BV+CHP as a front-line treatment for adults with PTCL, a meta-analysis was not applicable.

B.2.9 Indirect and mixed treatment comparisons

The pivotal trial, a Phase III double-blind RCT, provides the required comparative evidence for BV+CHP compared CHOP, the only relevant UK comparator – as specified in the scope. Therefore, no indirect or mixed treatment comparisons presented as part of this submission.

B.2.10 Adverse reactions

B.2.10.1 ECHELON-2

ECHELON-2 demonstrated a favourable efficacy and safety profile for BV+CHP, showing significant improvements in PFS and OS over CHOP, while being generally well-tolerated with a manageable safety profile, consistent with the established safety profile of BV. The incidence and severity of treatment-emergent adverse events were similar between the two study groups, BV+CHP and CHOP.[23] As shown in **Table 24**, below, treatment discontinuations due to adverse events occurred in 14 (6%) and 15 (7%) of patients and adverse events leading to death occurred in 7 (3%) and 9 (4%) patients in the BV+CHP group versus the CHOP group, respectively.[23]

Table 24: Summary of Adverse Events*[23]

Adverse Event	BV+CHP Group (n=223)	CHOP group (n=226)
Any adverse event, n (%)	221 (99%)	221 (98%)
Grade ≥3 Adverse Event, n (%)	147 (66%)	146 (65%)
Serious Adverse Events, n (%)	87 (39%)	87 (38%)
Discontinued treatment due to adverse events, n (%)	14 (6%)	15 (7%)
Death due to adverse events, n (%)	7 (3%)	9 (4%)

*Adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of any component of BV+CHP and CHOP.

Abbreviations: BV+CHP: brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [O], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P].

Among patients in the BV+CHP arm, doses of BV were delayed due to AEs for 59 subjects (26%) and reduced due to AEs for 21 subjects (9%). A total of 88/1329 doses (7%) of BV were reduced due to AEs. By comparison, doses of vincristine were delayed due to AEs for 28 subjects (12%) and reduced due to AEs for 24 subjects (11%), and a total of 41/1307 doses (3%) of vincristine were reduced due to AEs in the CHOP arm.[77] The treatment arms in ECHELON-2 had similar incidences of treatment modifications due to AEs (see **Table 24** for list of AEs). Mean exposure (relative dose intensities) for BV/vincristine, cyclophosphamide and doxorubicin were similar across the respective treatment arms. Importantly, the BV+CHP treatment arm had better outcomes with either similar or less exposure.

Table 25 provides a summary of common adverse events of any grade reported in 20% or more of patients for each study group. Overall, a higher incidence of diarrhoea (any grade) was reported in the BV+CHP group than in the CHOP group (38% [n=85] vs 20% [n=6] 20% of patients). Among patients in the BV+CHP group, most cases of diarrhoea were grade 1 (49/85 [58%]), with the remaining cases reported as grade 2 (23/85[27%]) and grade 3 (13/85 [15%]).[23]. It's important to note that an impact on quality of life due to diarrhoea, as assessed by the QLQ-C30, was only noted for cycle 7 (**Figure 17**).

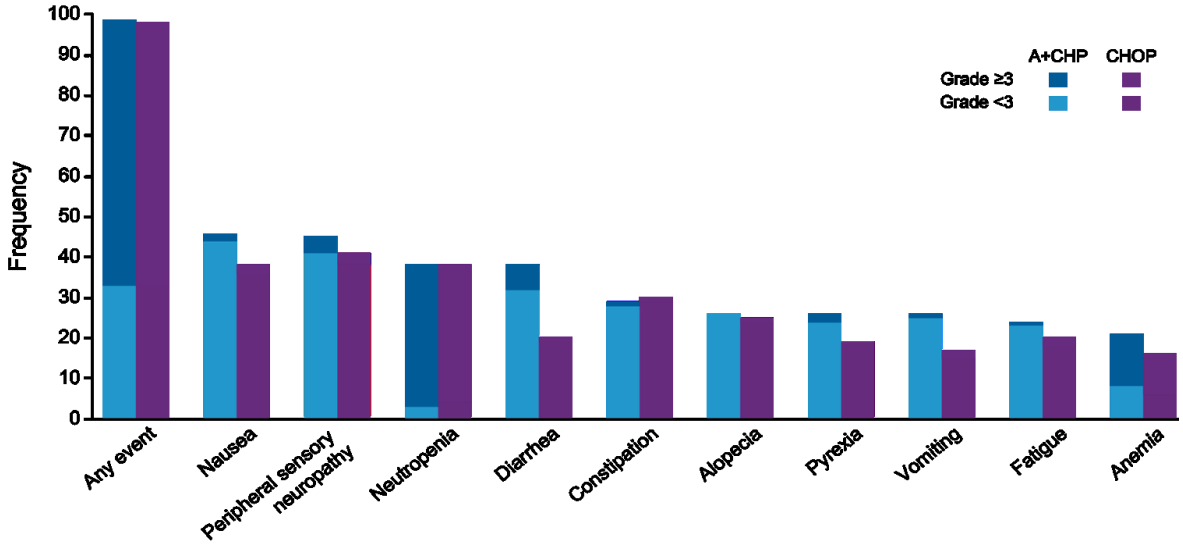
Other common treatment-emergent adverse events for the BV+CHP treatment group and CHOP treatment group, respectively, included: nausea, peripheral sensory neuropathy, neutropenia (in both), constipation, alopecia, pyrexia, vomiting, fatigue, and anaemia, as summarised in **Table 25** and represented in **Figure 21**).[23]

Table 25: Summary of Common Adverse Events*[23]

Adverse Event	BV+CHP Group (n=223)		CHOP group (n=226)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Nausea	103 (46%)	5 (2%)	87 (38%)	4 (2%)
Peripheral sensory neuropathy	100 (45%)	8 (4%)	92 (41%)	6 (3%)
Neutropenia	85 (38%)	77 (35%)	85 (38%)	76 (34%)
Diarrhoea	85 (38%)	13 (6%)	46 (20%)	2 (1%)
Constipation	64 (29%)	2 (1%)	67 (30%)	3 (1%)
Alopecia	58 (26%)	0	56 (25%)	3 (1%)
Pyrexia	58 (26%)	4 (2%)	42 (19%)	0
Vomiting	57 (26%)	2 (1%)	39 (17%)	4 (2%)
Fatigue	54 (24%)	2 (1%)	46 (20%)	4 (2%)
Anaemia	46 (21%)	30 (13%)	36 (16%)	23 (10%)

Data are n (%). Common adverse events are shown for those occurring in ≥20% of patients in the safety population.
*Adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of any component of BV+CHP and CHOP.
Abbreviations: AE: Adverse Event; BV+CHP: brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P].

Figure 21: Adverse Events Occurring in ≥ 20% of Subjects



Abbreviations: BV+CHP/A+CHP: brentuximab vedotin+ cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: CHOP=cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]

The rates of neutropenia, febrile neutropenia, and neuropathy were similar between the BV+CHP and CHOP arms. The incidence and severity of neutropenia were lower in the subset of patients receiving primary prophylaxis with granulocyte-colony stimulating factor.[23,77]

Febrile neutropenia was reported in 41 (18%) and 33 (15%) of patients in the BV+CHP and CHOP arms, respectively and one grade 5 event was reported in the CHOP group.[23,77]. Grade 3 or worse infections were reported in 42 (19%) patients in the BV+CHP group compared to 31 (14%) patients in the CHOP group.

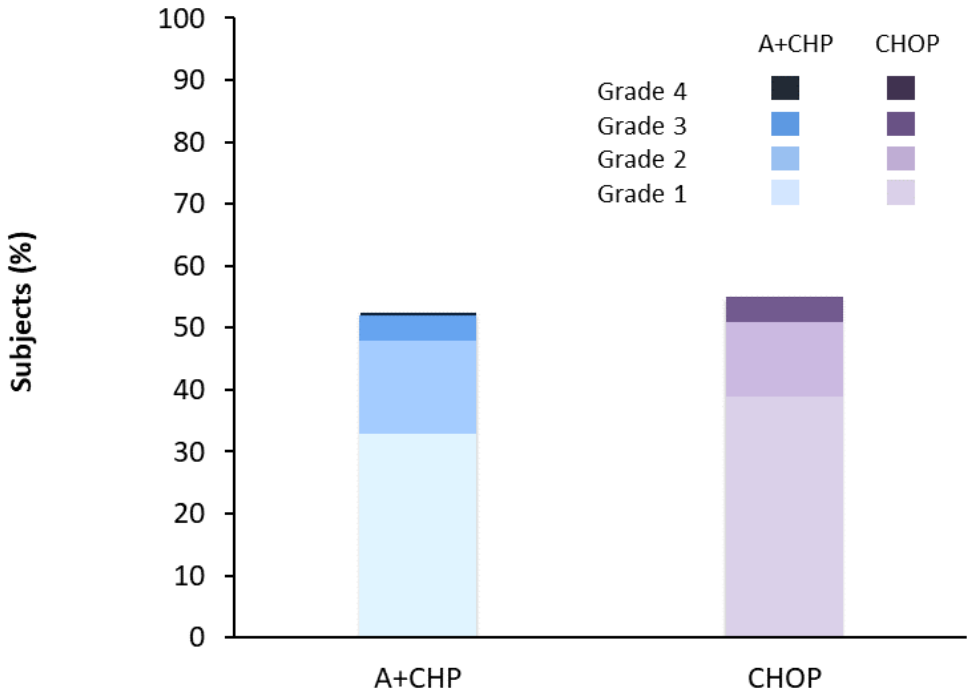
Treatment-emergent peripheral neuropathy (PN) was similar in both treatment groups and generally resolved or improved following treatment (see **Table 26** and **Figure 22**). PN events occurred in 117 (52%) patients in the BV+CHP group and 124 (55%) patients in the CHOP group. Of these, the majority had a maximum severity of Grade 1: 64% (n=75) in the BV+CHP group and 71% (n=88) in the CHOP group. Of note, peripheral neuropathy events returned to baseline or lower in 50% of patients (n=58) in the BV+CHP group, with a median time to resolution of 17.0 weeks, and in 64% of patients (n=79) in the CHOP group, with a median time to resolution of 11.4 weeks. At the last follow-up, among the patients with ongoing events, most were Grade 1 (44 of 61 patients [72%] in the BV+CHP group and 32 of 45 patients [71%] in the CHOP group); two patients in the BV+CHP group and one patient in the CHOP group had ongoing Grade 3 peripheral neuropathy events.[23]

Table 26: Treatment-Emergency Peripheral Neuropathy (PN)

Subjects, n (%)	BV+CHP (N=226)	CHOP (N=226)
Treatment-emergent PN, n	117	124
Resolution[a] of all PN events	58 (50)	79 (64)
Improvement of PN events	14 (12)	15 (12)
Ongoing PN events at last follow-up	61 (52)	45 (36)
Grade 1	44 (38)	32 (26)
Grade 2	15 (13)	12 (10)
Grade 3	2 (2)	1 (1)

[a] Resolution was defined as resolved/recovered with or without sequelae; or return to baseline or lower severity as of the latest assessment for pre-existing events
Abbreviations: BV+CHP: brentuximab vedotin [BV], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; PN: Peripheral Neuropathy

Figure 22: Treatment-Emergent Peripheral Neuropathy



Abbreviations: A+CHP (BV+CHP): brentuximab vedotin [A], cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P].

B.2.10.2 Brentuximab vedotin non-comparative trials

B.2.10.2.1 *Horwitz et al 2014*

This Phase II open label study demonstrated safety data consistent with the known safety profile of BV, and consistent with the aforementioned clinical trials. In the Horwitz et al. 2014 study, BV was generally well tolerated with no new safety signals detected in patients treated up to 21 cycles. Grade 3 or greater adverse events observed in more than two patients in the trial are shown in **Table 27** below.

Table 27: Grade ≥3 Adverse Events Occurring in 2 or more patients[67]

AE, n (%)	AITL (n =13)			PTCL-NOS (n = 22)			Total (n = 35)
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5	Grade ≥3
Neutropenia	2 (15)	0	0	3 (14)	0	0	5 (14)
Hyperkalaemia	0	1 (8)	0	2 (9)	0	0	3 (9)
Peripheral sensory neuropathy	3 (23)	0	0	0	0	0	3 (9)
Acute renal failure	0	0	0	2 (9)	0	0	2 (6)
Anaemia	1 (8)	0	0	1 (5)	0	0	2 (6)
Dehydration	0	0	0	2 (9)	0	0	2 (6)
Disease progression	0	0	1 (8)	1 (5)	0	0	2 (6)
Pneumonia	0	1 (8)	0	1 (5)	0	0	2 (6)
Thrombocytopenia	0	0	0	2 (9)	0	0	2 (6)
Tumour lysis syndrome	0	0	0	2 (9)	0	0	2 (6)
Urinary tract infection	1 (8)	0	0	1 (5)	0	0	2 (6)

Abbreviations: AE = adverse event; AITL: angioimmunoblastic T-cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified; RCT = randomized controlled trial

B.2.10.2.2 *Fanale 2014 et al and Fanale et al 2018*

This Phase I open label study demonstrated that BV, administered sequentially with CHOP or in combination with CHP, had a manageable safety profile. After sequential treatment, Grade 3/4 adverse events occurred in 62% of patients (n=8/13). In the combination-treatment group, Grade 3/4 adverse events were experienced by 73% of patients (n=19/26), including febrile neutropenia (31%), neutropenia (23%), anaemia (15%), and pulmonary embolism (12%). A full list of the most common treatment-emergent adverse events is reported in **Table 28**.

Table 28: Treatment Emergent Adverse Events (≥30%)[75]

Preferred Term*, n(%)	Sequential Therapy (n = 13)	Combination Therapy (n = 26)
Any Event	13 (100)	26 (100)
Peripheral Sensory Neuropathy	10 (77)	18 (69)
Nausea	10 (77)	17 (65)
Fatigue	8 (62)	15 (58)
Diarrhoea	3 (23)	15 (58)
Alopecia	5 (38)	14 (54)
Dyspnoea	6 (46)	12 (46)
Constipation	6 (46)	10 (38)
Vomiting	7 (54)	5 (19)
Anaemia	4 (31)	8 (31)
Pyrexia	4 (31)	7 (27)
Chills	3 (23)	8 (31)
Febrile Neutropenia	2 (15)	8 (31)
Peripheral Oedema	5 (38)	9 (35)
Upper Respiratory Tract Infection	3 (23)	8 (31)
Headache	4 (31)	7 (27)
Myalgia	5 (38)	8 (31)
Dizziness	4 (31)	5 (19)

*Medical Dictionary for Regulatory Activities, version 14.0.

PN is an AE of particular interest as it is associated with cumulative exposure to BV. However, in the long-term follow-up of this study,[76] it was reported that 95% of patients (n=18) had resolution or improvement (by at least 1 grade) in PN symptoms, including nine with resolution of all events. The median times to resolution and improvement were 4.2 and 2.6 months, respectively. Ten patients (53%) had ongoing PN at last follow-up: Grade 2 for one patient who had no improvement during the study and Grade 1 for nine patients.

B.2.11 Ongoing studies

Table 29: Ongoing Clinical Trials for Brentuximab Vedotin of Relevance to the Decision Problem

NCT Number	Title	Recruitment	Comment
NCT01657331	Brentuximab Vedotin and Bendamustine for the Treatment of Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma (ALCL)	Active, not recruiting	Estimated Primary Completion Date – December 2019
NCT02729961	Ceritinib With Brentuximab Vedotin in Treating Patients With ALK-Positive Anaplastic Large Cell Lymphoma	Recruiting	Estimated Primary Completion Date – July 2023
NCT01196208	A Treatment-Option Protocol to Provide Brentuximab Vedotin to Eligible Patients Completing Studies SGN35-005 or C25001	Available	Expanded access trial
NCT02499627	Bendamustine Plus Brentuximab Vedotin in HL and CD30+ PTCL in First Salvage Setting	Recruiting	Estimated Primary Completion Date – October 2021
NCT03113500	Brentuximab Vedotin and Combination Chemotherapy in Treating Patients With CD30-Positive Peripheral T-cell Lymphoma	Recruiting	Estimated Primary Completion Date – January 2020
NCT03947255	A Study of Retreatment With Brentuximab Vedotin in Subjects With Classic Hodgkin Lymphoma or CD30-expressing Peripheral T Cell Lymphoma	Not yet recruiting	Estimated Primary Completion Date – December 2024

NCT01716806	A Study of Brentuximab Vedotin in Adults Age 60 and Above With Hodgkin Lymphoma (HL) and CD30-expressing Peripheral T-cell Lymphoma (PTCL)	Recruiting	Estimated Primary Completion Date – September 2021

EBV: Epstein-Barr virus.

B.2.12 Innovation

Brentuximab vedotin (BV) is a targeted and highly-innovative therapy that, in combination with CHP, has shown unprecedented efficacy in the front-line treatment of PTCL. The ECHELON-2 trial showed a statistically significant, and clinically meaningful, improvement in both OS and PFS among front-line patients treated with BV+CHP rather than with CHOP. Despite many previous efforts, this is the first time in decades that any front-line regimen has been found to be superior to the long-established standard of care, CHOP (see **Section B.2.13** for more details). As such, it represents a significant innovation for PTCL.

Clinical experts advise that in aggressive and challenging lymphomas such as PTCL, the best way to improve outcomes is to improve the quality of front-line therapy. This is supported by the results of the ECHELON-2 study where improved OS was seen despite more patients in the CHOP arm receiving subsequent therapies (including BV) at relapse. Hence, the BV+CHP regimen offers a clear advance in the treatment of CD30+ve PTCL and has the potential to change practice by becoming the new standard of care in the front-line setting. Its introduction will be welcomed by both clinicians and patients.

In addition to its unprecedented efficacy in this patient population, BV offers other benefits, at least some of which may not be adequately captured within the cost-effectiveness estimates. These include:

- A convenient administration schedule involving one 30-minute infusion every 3 weeks for a maximum of six treatment cycles. This is aligned to the CHP administration schedule and no additional travel burden is placed on patients.
- Improved tolerability compared to traditional, non-targeted chemotherapy. As a result, BV can help to maintain patients' HRQoL.
- A potentially positive impact on the HRQoL of caregivers and family members

B.2.13 Interpretation of clinical effectiveness and safety evidence

The ECHELON-2 trial demonstrated a statistically significant, and clinically meaningful improvement in efficacy for the ITT population, including an OS benefit among patients treated with BV+CHP when compared with CHOP. The primary endpoint, PFS per blinded IRF, was significantly improved with BV+CHP versus CHOP:[23,77]

- Patients in the BV+CHP arm had a 29% reduction in the risk of a PFS event compared with subjects treated with CHOP (stratified HR 0.71 [95% CI: 0.54, 0.93], P=0.011).
- The median PFS with BV+CHP was 48.2 months versus 20.8 months with CHOP

Likewise, BV+CHP was shown to be superior compared with CHOP for all key secondary endpoints in the ECHELON-2 trial:[23,77]

- BV+CHP significantly reduced the risk of death by 34% over CHOP (stratified HR=0.66 [95% CI: 0.46, 0.95], P=0.0244). After a median follow-up of 42.1 months (95% CI, 40.4-43.8), median OS has not been reached in either arm. The 75th percentile of OS was not reached with BV+CHP compared to 17.5 months with CHOP.
- The CR rate for the ITT population following completion of treatment was significantly higher in the BV+CHP arm than on the CHOP arm (68% [95% CI: 61.2, 73.7]) versus 56% [95% CI: 49.0, 62.3]), P=0.0066).
- The ORR at EOT was significantly higher with BV+CHP versus CHOP (83% [95% CI: 77.7, 87.8] versus 72% [95% CI: 65.8, 77.9], P=0.0032)

For the sALCL subgroup, BV+CHP significantly reduced the risk of death by 41% compared to patients treated with CHOP (stratified HR 0.59 [95% CI 0.42, 0.84]; p=0.0031); OS was also significantly improved with BV+CHP vs CHOP, where treatment with BV+CHP reduced the risk of death by 46% when compared with CHOP (HR 0.54 [95% CI 0.337–0.867], p=0.0096).

ECHELON-2 is a landmark trial in PTCL as it is the first prospective trial to show an OS benefit over the long-established standard of care, CHOP. Previous efforts to improve upon CHOP, including the addition of other agents to CHOP, consolidative ASCT or the use of more intensive combination chemotherapy regimens, have failed to show superiority over CHOP and/or have been associated with excess toxicity. In the ECHELON-2 trial it is notable that the improvement in survival with BV+CHP came without an observed increase in toxicity.

The improved OS seen in ECHELON-2 came despite more patients in the CHOP arm receiving subsequent therapies (including BV) on progression, thus underlining the importance of effective front-line therapy to improve outcomes in an aggressive and challenging disease such as PTCL. In addition, only a minority of patients in ECHELON-2 received a consolidative SCT as part of their front-line therapy (22% in the BV+CHP arm, 17% in the CHOP arm). A pre-specified analysis censoring any consolidative SCT found that the benefits of BV+CHP over CHOP are present regardless of whether or not patients received a consolidative SCT.

The ECHELON-2 trial also represents a significant increase in the quality of evidence compared to most other studies in PTCL, the majority of which are either

single-arm Phase II studies or retrospective analyses. By contrast, ECHELON-2 is a prospective, randomised, double-blind, active comparator Phase III trial of BV+CHP versus the standard of care CHOP. We note that the CHOP group in the ECHELON-2 trial did better than the historical cohorts with a median PFS of 20.8 months and median OS not reached.[23] Possible explanations of these outcomes may be potentially attributed patients being in a clinical trial and the larger proportion of sALCL patients, albeit the inclusion criteria did not allow for sALCL patients with a favourable prognostic IPI score of 0-1.[23] However, as noted above this could also be due to the variability and uncertainty in the historic survival data. [23]

A potential limitation of the ECHELON-2 study was that it was not powered to compare efficacy between individual histological subtypes. While it is true that the majority (70%) of patients enrolled in ECHELON-2 had sALCL, it's also the case that the PFS and OS benefits seen in this trial were generally consistent across all evaluable histological subtypes of PTCL, with overlapping confidence intervals. Given the consistency of these results, and the need for improved front-line therapy in all PTCL subtypes, the FDA and Health Canada approved BV+CHP for all CD30-expressing PTCLs.

Based on all of the above, BV+CHP has a clear potential to replace CHOP as the standard of care in front-line PTCL. In its approval of BV+CHP, the FDA acknowledged that this "new regimen represents a major advance for the front-line treatment of patients with CD30-expressing PTCL". The investigators involved in the ECHELON-2 study also concluded that BV+CHP has the potential "to become a new standard of care for many patients with CD30 positive PTCL" and that they "consider these results to be potentially practice changing". This was supported by UK clinical experts in both advisory boards and individual clinical interactions.[47,59]

Table 30: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	The historical data quality for PTCL outcomes are relatively poor as they are based on observational, retrospective or single-arm Phase II studies. OS reported in the available literature is uncertain with considerable variability between sources. • The 10-year audit from the Royal Marsden hospital reported a median OS of 37.7 months for patients treated with front-line chemotherapy [31] • The International T-Cell Lymphoma project reported a range of 5-year OS between 7-49% for patients with PTCL; 2 year OS not reported.[14] Although the estimates of survival for patients with PTCL vary considerably across studies, none estimate the life expectancy for previously untreated patients PTCL to be less than 24 months. Therefore, the short life expectancy criterion is unlikely to be met.	• Section B.1.3.1, page 16 • Section B.1.3.3, page 21
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	BV+CHP treatment in the front-line is superior to CHOP providing significant improvements in both median PFS, 48.2 months (BV+CHP) vs. 20.8 months (CHOP), and OS (median value not yet reached). Importantly, improvement in survival is obtained in a patient population in which the majority have an IPI score of ≥ 2. An IPI score ≥2 is not only associated with worse outcomes, but also representative of the general PTCL population, most of whom are diagnosed at late stage disease. The model estimates a gain in OS of 2.56 years under the base case assumptions. BV+CHP in the front-line treatment for CD30-positive PTCL would offer an extension of greater than 3 months.	

Based on compelling cost-effectiveness results (see **Section B.3**) which show that BV+CHP meets NICE's conventional cost-effectiveness threshold (i.e. £20,000 - £30,000 per QALY), Takeda does not wish for the medicine to be considered at this time for the application of NICE's End-of-Life criteria.

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

The systematic literature review identified five published economic evaluations. Two of the five reported the UK perspective in the relapsed/refractory sALCL population.

None of the studies reported cost-effectiveness in terms of the incremental costs per QALY gained in line with the NICE reference case. One economic evaluation of BV+CHP in patients with previously-untreated CD-30+ PTCL was identified.[84] As the analysis was performed from the perspective of a US payer, it was deemed to be of limited use for decision making in the context of England and Wales. Further details of the systematic review can be found in **Appendix G**.

B.3.2 Economic analysis

As no relevant economic evaluations were identified in the literature review, this submission considers a de novo economic model with the structure, assumptions and data sources informed by the identified NICE appraisals of BV in different populations (R/R sALCL [TA478[85]], CD-30+ Hodgkin's lymphoma [TA524[1]] and CD-30+ cutaneous T-cell lymphoma [TA577[86]]).

The NICE submission for R/R sALCL [TA478[85]] was considered to be the most relevant to the present decision problem as:

- sALCL represents a significant subpopulation of PTCL, and
- the indication in question, untreated CD-30+ PTCL, is a part of the same treatment pathway as R/R sALCL.

However, there are a number of key differences between TA478 and this appraisal:

- BV in R/R sALCL is used as monotherapy, whereas in this submission BV is combined with chemotherapy (i.e. as the BV+CHP regimen)
- BV in R/R sALCL is used for up to 16 treatment cycles. In ECHELON-2, BV+CHP is used for up to a maximum of six or eight treatment cycles. UK clinicians advised that in this patient population, BV+CHP is expected to be used for six treatment cycles in UK clinical practice (**Section B.3.3.3**)
- The R/R sALCL submission and other economic evaluations considering BV include health states based on the receipt of SCT. In these patient populations, treatment may act as a bridge to transplant. In front-line therapy, the objective of treatment is to achieve response and ultimately remission, irrespective of the use of SCT (**Section B.1.3.6.2**), although some patients may proceed to a consolidative autologous SCT (ASCT) following receipt of BV+CHP or CHOP. However, this is not the main driver of either efficacy or the economic analysis*.

* A total of 50 patients (22%) in the BV, cyclophosphamide, doxorubicin and prednisone arm vs 39 patients (17%) on the cyclophosphamide, doxorubicin, vincristine and prednisone arm received consolidative SCT following completion of study treatment in ECHELON-2.

B.3.2.1 Patient population

In line with the NICE scope, the base-case analysis considers adults with untreated CD-30+ PTCL. The primary analysis is based on the ITT population of ECHELON-2.[23] This population is in line with the US FDA approval[87] and anticipated EMA marketing authorisation.[88]

A subgroup analysis is presented for the sALCL population because of the differences in the subsequent treatment pathway between these patients and those with non-sALCL (data and results are provided in **Section B.3.9**, see also **Section B.2.7**). Due to an existing regulatory commitment arising from the EMA's previous conditional approval of BV for relapsed/refractory sALCL, sufficient patients with sALCL were recruited into the ECHELON-2 trial such that meaningful analyses can be conducted. This was not the case for other non-sALCL subgroups; the ECHELON-2 trial was not designed nor powered to conduct analyses on these individual subtypes. Therefore, any such analyses would be based on extremely small numbers and provide highly uncertain results. Furthermore, the treatment pathway does not differ across patients with non-sALCL. Therefore, the ITT analysis is considered representative of the clinical and cost-effectiveness across all CD-30+ PTCL subtypes.

B.3.2.2 Model structure

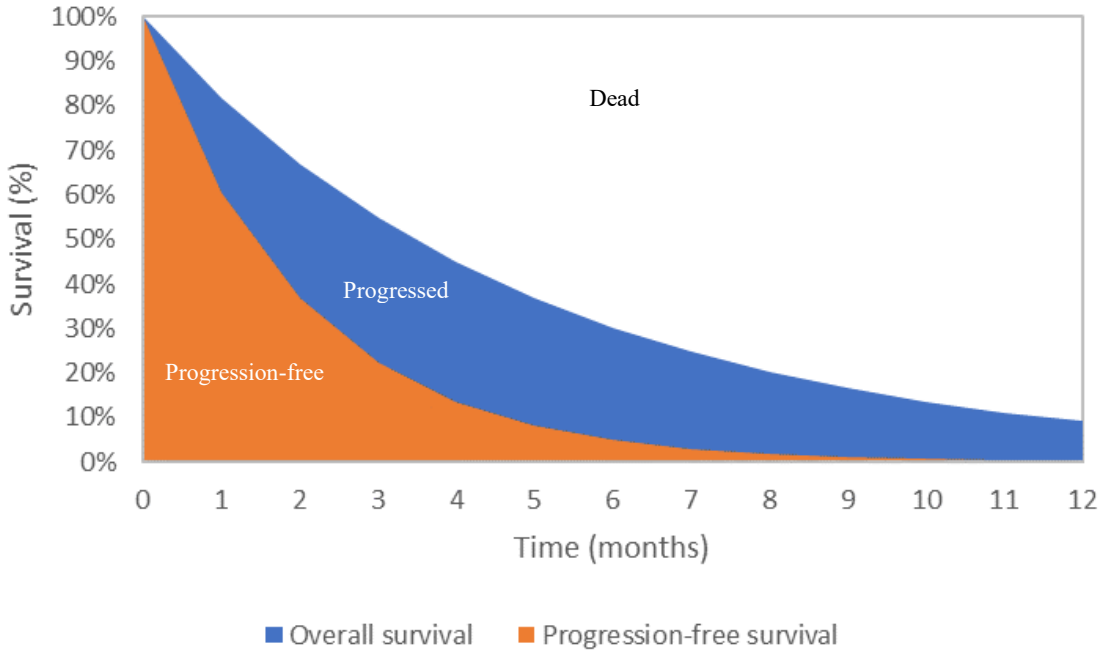
B.3.2.2.1 *Model overview*

The base-case economic model utilises a partitioned survival approach (PartSA). This model structure is common in oncology and has been implemented in all the cost-effectiveness analyses for BV to date, including the following NICE submissions: R/R sALCL [TA478[85]], CD-30+ Hodgkin's lymphoma [TA524[1]] and CD-30+ cutaneous T-cell lymphoma [TA577[86]].

The PartSA comprises three mutually exclusive health states (**Figure 23**):

1. progression-free survival (PFS)
2. progressed disease (PD)
3. death.

Figure 23: Model schematic, partitioned survival analysis



These health states are in line with the clinical pathway of care for the treatment of PTCL and are consistent with the previous economic evaluation submitted to NICE for BV in the R/R sALCL setting [TA478[85]].

The proportion of patients in the PFS state over time is estimated directly from PFS reported in ECHELON-2.[23] Similarly, the proportion of patients in the OS state is estimated from ECHELON-2 (a secondary endpoint). The proportion of patients in the PD state is estimated as the difference between OS and PFS. Standard parametric curves were fitted to the PFS and OS data to extrapolate the outcomes observed in the ECHELON-2 trial and estimate the long-term outcomes (**Section B.3.3.1**).

Membership of the PFS health state was defined by the primary endpoint from ECHELON-2; PFS per IRF[†].

There was a high level of congruence found between PFS per IRF and PFS per investigator (INV) (97%). All analyses presented in this document are as per IRF and aligned to the primary endpoint of the ECHELON-2 study.

[†] PFS was defined as the time from the date of randomisation to the date of first documentation of progressive disease, death due to any cause, or receipt of subsequent anticancer chemotherapy to treat residual or progressive disease, whichever occurred first. Receipt of post-treatment consolidative radiotherapy, post-treatment chemotherapy for the purpose of mobilising peripheral stem cells, or consolidative autologous or allogeneic SCT was not considered disease progression or as having started new anticancer therapy.

In ECHELON-2, patients whose disease progressed after front-line therapy were able to receive BV post-progression. BV was given as a subsequent therapy to 10% (n=23) of patients in the BV+CHP arm. These patients are considered to have been re-treated with BV, which does not reflect UK clinical practice as re-treatment is not currently reimbursed within England and Wales. BV was given as a subsequent therapy to 22% (n=49) of patients in the CHOP arm. 27% (n=13) of these patients had non-sALCL, which does not reflect UK clinical practice as BV is not currently reimbursed in England and Wales for the treatment of non-sALCL. Clinician feedback confirmed re-treatment with BV and receipt of BV for R/R non-sALCL are not reflective of UK clinical practice.[59] This has the potential to limit the generalisability of the unadjusted ECHELON-2 OS data to the NHS. Therefore, the use of statistical adjustments to remove the effects of re-treatment and subsequent treatment in patients with non-sALCL have been included in the base case in an attempt to remove any bias caused by the use of post-progression BV in populations where such use is not reimbursed in England and Wales.

Post-progression BV was received by 36 patients with sALCL disease in the CHOP arm of ECHELON-2; the use of BV in this patient group is aligned with clinical practice in the UK, as recommended for use in TA478.[85] Therefore, BV use in this patient group is included in both estimates of efficacy and costs.

Long-term OS estimates are constrained by the general population mortality (adjusted for excess risk of mortality in long-term survivors), informed by the life tables for England and Wales.[89] Further information is provided in **Section B.3.3.2**.

A 21-day cycle length is considered, reflecting the duration of a CHOP or BV+CHP treatment cycle. Half-cycle correction is implemented using the life table method, where the time in each cycle is estimated by taking the average of the number of people at the start and end of the cycle. Treatment duration was based on observed use of BV+CHP in ECHELON-2.

The model adopts a lifetime time horizon, in accordance with current NICE methods.[90]

B.3.2.2.2 ***Outcomes reported***

The primary outcome of interest is the incremental cost-effectiveness ratio (ICER) expressed as the cost per quality-adjusted like year (QALY) gained. This approach is in line with the NICE reference case, which specifies that a cost-utility analysis should be performed.[90]

Additional outcomes are reported (discounted and undiscounted), including:

- Costs (disaggregated and total)
- Life-years (LY; by health state and total)

- Cost per LY gained
- QALYs (by health state, gain due to subsequent therapy, loss due to AEs, total)
- OS and PFS (median and mean).

B.3.2.2.3 ***Economic features analysis***

B.3.2.2.3.1 Perspective

Analyses were conducted using the perspective of the National Health Service (NHS) and personal social services (PSS) in England and Wales, in line with current NICE guidance.[90]

B.3.2.2.3.2 Discounting

Costs and outcomes are discounted at 3.5%, in line with current NICE guidance.[90] Alternative discounting scenarios are included in sensitivity analyses.

B.3.2.2.3.3 Summary

Key inputs to the economic model, compared with previous submissions for BV, are outlined in **Table 31**.

Table 31: Features of the economic analysis

Feature	Previous appraisals of BV			Current appraisal	
	TA478[85] R/R sALCL	TA524[1] R/R HL	TA577[86] CD30+ CTCL	Chosen values	Justification
Time horizon	60 years (lifetime)	70 years (lifetime)	45 years (lifetime)	45 years (lifetime)	A lifetime horizon was selected, as stipulated in the NICE reference case[90] to capture all relevant differences in costs and outcomes. A lifetime of 100 years was assumed, with a mean age of 55.1 at model entry (as per ECHELON-2[23])
Treatment waning effect	No	No	No	No	Clinical evidence from ECHELON-2 did not suggest a reduction in the treatment effect over time. The data available from the trial are relatively mature (median follow-up of 36.2 months), with treatment only lasting for an average of 6 cycles.

Feature	Previous appraisals of BV			Current appraisal	
	TA478[85] R/R sALCL	TA524[1] R/R HL	TA577[86] CD30+ CTCL	Chosen values	Justification
					Furthermore, there is evidence of favourable event-free survival outcomes 2 years post-diagnosis with CHOP[18], and a UK clinical experts confirmed a low rate of relapse occurring after 2 years[59]
Source of utilities	Swinburn et al., 2015[54] using health-state vignettes in R/R HL and sALCL	Swinburn et al., 2015[54] and literature on utilities post-SCT[91]	EQ-5D and a regression model to fit the Skindex-29 to the EQ-5D, both collected in the ALCANZA trial[92]	EQ-5D-3L collected in ECHELON-2 determines utility in the progression-free state, and QALY loss/gain resulting from age, SCT and AEs. The progressed disease utility value is estimated from TA478. A scenario explores the use of utility based on time until death.	The NICE methods guide[90] stipulates that, where available, patient-level data should inform utility estimates in the model. Patients' EQ-5D was recorded until study closure of ECHELON-2, and covariates considered within the model were informed by clinical experts. The utility decrement associated with progression derived from these data were not considered to be clinically plausible. Therefore, an estimate was derived from the R/R sALCL submission [TA478]
Source of costs	BNF NHS reference costs PSSRU Expert clinical opinion on SCT costs	BNF Expert clinical opinion on SCT costs Round et al, 2015[93] oncology mortality costs)	eMIT MIMS BNF NHS reference costs Round et al, 2015[93] oncology mortality costs) Debals et al, 2018[94] (SCT costs)	eMIT BNF NHS reference costs TA478, TA567 and TA577 for SCT costs	As per the NICE methods guide[90]

Abbreviations: BNF, British national formulary; eMIT, electronic marketing information tool; HL, Hodgkin's lymphoma; HRQoL, health-related quality of life; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year; R/R, relapsed/refractory; sALCL, systemic anaplastic large cell lymphoma; SCT, stem cell transplant; TA, technology appraisal.

B.3.2.3 Intervention technology and comparators

The intervention and comparator are combination chemotherapy with CHOP, as detailed in the NICE scope.

B.3.2.3.1 *Intervention*

The intervention under consideration is BV+CHP, administered on a 21-day cycle for six to eight cycles:

- 1.8 mg/kg of BV on Day 1, intravenously
- 750 mg/m^2 of cyclophosphamide on Day 1, intravenously
- 50 mg/m^2 of doxorubicin on Day 1, intravenously
- 100 mg of prednisone on Days 1 to 5, orally

The average number of cycles administered of BV+CHP was 6.02 which is in line with UK clinical practice for the administration of CHOP.[23,47,59]

B.3.2.3.2 *Comparator*

The comparator is CHOP, the current standard-of-care (SoC) in the UK and the only comparator listed in the final scope.[95] The CHOP regimen is a 21-day cycle for a maximum of six to eight cycles consisting of:

- 750 mg/m^2 of cyclophosphamide on Day 1, intravenously
- 50 mg/m^2 of doxorubicin on Day 1, intravenously
- 1.4 mg/m^2 of vincristine on Day 1, intravenously
- 100 mg of prednisone on Days 1 to 5, orally

The average number of cycles of CHOP administered in ECHELON-2 was 5.8, which is aligned with the UK clinical practice of a maximum of six cycles.[47,59]

B.3.3 Clinical parameters and variables

The principal source of data informing the economic evaluation is the ECHELON-2 trial.[23] Patient-level data were accessed to inform:

- extrapolation of OS and PFS outcomes
- duration, efficacy and administration/re-administration of BV+CHP and CHOP
- the proportions of patients receiving:
    - consolidative ASCT
    - consolidative and salvage radiotherapy
    - salvage stem cell transplant (ASCT and alloSCT)
    - salvage chemotherapies

    - salvage treatment with BV
    - re-treatment with BV
- AEs and their duration, frequency & management
- HRQoL (described in **Section B.3.4.5**)
- concomitant medications.

B.3.3.1 Extrapolating OS and PFS

As described in **Section B.3.2.2.1**, the proportion of patients in the PF, PD and death health states at each cycle in the model are defined by OS and PFS curves. The follow-up period in ECHELON-2 was considerable for an oncology medicine (median follow-up: 36.2 months) and BV+CHP demonstrated a statistically significant and clinically meaningful OS and PFS benefit over CHOP. However, follow-up was shorter than the model time horizon, and extrapolation from the observed OS and PFS data was required. Analysis was performed in accordance with the NICE Decision Support Unit (DSU) technical support document (TSD) 14.[96]

B.3.3.1.1 *Adjustment for subsequent use of BV*

In ECHELON-2, 72 patients in the ITT cohort received BV following disease progression. There was an imbalance between receipt of this subsequent BV between study arms, with 10% and 22% of patients receiving subsequent BV in the BV+CHP and CHOP arms, respectively.

UK clinical experts confirmed the clinical significance of demonstrating a statistically significant and clinically meaningful OS improvement in the treatment arm (HR 0.66 [95% CI: 0.46; 0.95]), despite a large proportion of patients in the CHOP arm receiving BV upon completion of first-line treatment.[59] These results indicate that BV has the most impact in the front-line setting for CD-30+ PTCL and is more efficacious than in R/R disease. The table below summarises the use of subsequent BV in ECHELON-2.

Table 32: Summary of subsequent BV use in ECHELON-2, ITT population

	% of all patients receiving subsequent BV (n)		Mean number of subsequent BV lines used in patients who had non-fatal PFS events		% of all patients who had non-fatal PFS events receiving subsequent BV	
	CHOP	BV+CHP	CHOP	BV+CHP	CHOP	BV+CHP
ITT	22% (n=49)	10% (n=23)	0.53	0.32	46%	28%

Abbreviations: BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; ITT, intention-to-treat; PFS, progression-free survival.

NICE recommendations and clinician feedback confirmed re-treatment with BV in the BV+CHP arm (n=23) and receipt of BV for R/R non-sALCL in the CHOP arm (n=13) are not reflective of UK clinical practice. This has the potential to limit the generalisability of the unadjusted ECHELON-2 OS data to the NHS. Therefore, the use of statistical adjustments to remove the effects of re-treatment and subsequent treatment in patients with non-sALCL have been included in the base case in an attempt to remove any bias caused by the use of post-progression BV in populations where such use is not reimbursed in England and Wales.

To remove the effects of subsequent BV use in these populations, multiple methods based on treatment-switching approaches described in NICE DSU TSD 16 were considered.[97] NICE DSU TSD 16 describes treatment switching as switching from the control group to the experimental group. Whereas, in this appraisal, treatment switching occurs in both study arms and was not protocol driven. Therefore, whilst the guidance is relevant and related, the analysis problem does differ.

Of the methods explored, only the two-stage estimator (TSE) provided logical estimates with plausible underlying assumptions. Therefore, this approach was used in the base case. **Appendix N** provides details of all methods considered, and the TSE is summarised in **Section B.3.3.1.1.1**. Note: BV is recommended by NICE and used in clinical practice for patients with R/R sALCL (TA478). Therefore, the use of subsequent BV for these patients in the CHOP arm is included in the base case in terms of efficacy and costs.

Scenario analyses explore an unadjusted approach, using unadjusted ECHELON-2 data, in which the costs and benefits of subsequent BV use was included based on that observed in the ECHELON-2 trial.

B.3.3.1.1.1 Two-stage estimator

The simplified TSE was initially proposed by Latimer et al.[98] If it is assumed that all patients are at a similar stage of disease at the point of disease progression, the effect of re-treatment (in the BV+CHP arm) or subsequent treatment (in patients with non-sALCL in the CHOP arm) with BV-containing regimens on extending survival from the point of disease progression to death can be estimated. The point of disease progression becomes a new ‘secondary baseline’, and survival post-progression is estimated. By fitting an accelerated failure time (AFT) model (such as a generalised gamma or Weibull model) to these data including covariates and an indicator for whether subsequent BV-containing regimens were used, we can estimate the treatment effect received by patients who were re-treated with BV compared with those who were not, and the treatment effect for patients who received subsequent BV in the CHOP arm who did not have a diagnosis of sALCL. Counterfactual survival times are 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 ith individual, T_{B_i} represents the time post-progression, and θ_v represents the treatment effect (time ratio) for re-treatment with BV (in the BV+CHP arm) and for subsequent therapy use (in patients with non-sALCL in the CHOP arm) in post-progression survival, which in this context may differ by study arm and diagnosis.

The method requires fewer data (the 'no unmeasured confounders' assumption is only required at the secondary baseline timepoint) and does not require modelling of the process by which patients are treated (or re-treated) with BV following progression. However, as long as there is some difference between secondary baseline and the point of re-treatment, the method will be prone to some degree of bias.

Choices faced by the analyst in the application of the TSE include:[99]

- which accelerated failure time model to use
- which covariates to include in that model
- whether or not to include re-censoring.

Weibull models were used to estimate θ_v, the treatment effects for post-progression BV. This was because the generalised gamma model was unable to achieve convergence in several scenarios, presumably because of the relatively low number of patients and events in some analyses. Separate Weibull models were fitted to patients in the BV+CHP and CHOP (non-sALCL disease only) arms. Note: this is distinct to the choice of distribution for extrapolation of OS used in the economic model.

Prognostic covariates tested for inclusion were identified during clinician consultations.[48] These included:

- Response to front-line therapy
    - only patients achieving a complete response [CR] with front-line BV+CHP would be likely to receive re-treatment with BV
    - patients not achieving CR are considered to have failed treatment, as these patients will likely progress within months and are primary refractory
- Remission duration
    - clinical experts suggested only patients with a minimum of 12 months response following treatment with BV+CHP would be considered for use with subsequent BV
    - in the present analysis time-to-progression event was used as a covariate

- Receipt of consolidative ASCT
    - clinical experts suggested that patients relapsing from more intense treatments such as a consolidative ASCT have a higher likelihood of being refractory to therapy. Therefore, clinicians are less likely are to prescribe BV re-treatment for these patients.
- Diagnosis with sALCL
    - BV is currently only licensed and reimbursed for R/R sALCL. Therefore, a diagnosis of sALCL is associated with a greater likelihood of receiving BV as subsequent therapy.

Other available baseline characteristics were also considered (region, age, IPI score). Only statistically significant predictors (other than use of post-progression BV) were retained in the base-case analysis to achieve the most parsimonious model (IPI, age, time-to-progression).

The process of adjusting survival times introduces an informative censoring bias. As described by Latimer et al,[99] for TSE, informative censoring is induced 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 patients who received (re-)treatment with BV, the time of death may not be observed, and censoring occurs. For such patients, the TSE adjusts censoring times. This will result in informative censoring if there is an association between (re-)treatment with BV and prognosis. For this reason, it has been recommended that re-censoring should be applied in adjustment analyses.[100] In the context of TSE, the process of re-censoring is summarised by Latimer et al.[101] Counterfactual survival times associated with a given value of θ_v are re-censored for all patients in the respective study arm at the minimum of the administrative censoring time of the study C_i and $C_i\theta_v$, representing the earliest possible censoring time over all possible treatment trajectories.

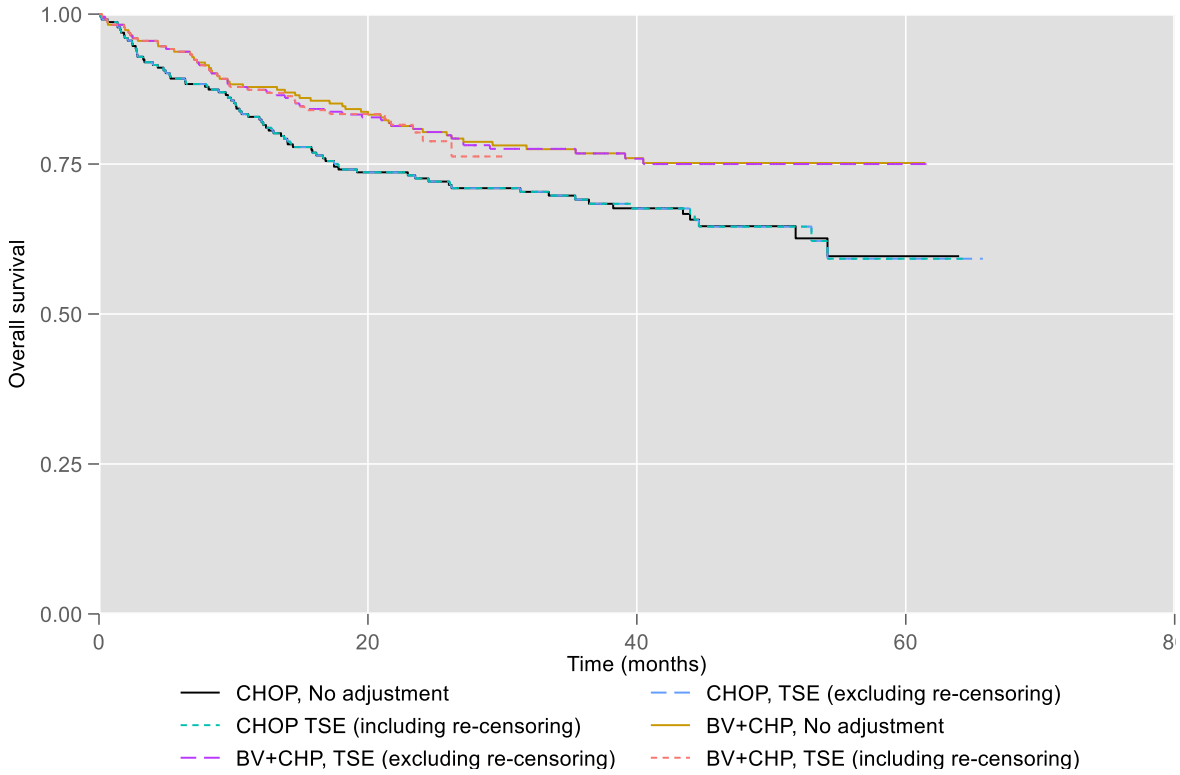
Studies investigating such adjustments have concluded that adjustment analyses should be conducted with and without re-censoring.[102] Latimer et al[102] found that the TSE excluding re-censoring produced positive bias across almost all scenarios; this method over-estimated the restricted mean survival time in the study arm subject to switching and under-estimated the true treatment effect. However, the study also found that the TSE excluding re-censoring produced a lower root mean squared error in every scenario, demonstrating greater precision than the TSE including re-censoring. Conversely, TSE including re-censoring produced a negative bias; re-censored analyses usually under-estimated the restricted mean survival time in the study arm subject to switching and over-estimated the true treatment effect. The bias from the two methods was found to be more severe when the treatment effect was high.

An important consequence of re-censoring is that longer-term information is discarded, and this is problematic in the present context where extrapolation of long-term survival is required:

> *"Similarly, if the objective was to fit parametric survival models to trial data in order to extrapolate into the future (as is often the case in HTA), re-censoring could lead to problems if important changes to the hazard occur beyond the timeframe of the re-censored dataset."*[99]

The adjusted OS data including and excluding re-censoring are presented in **Figure 24**. The effect of adjustment on the Kaplan-Meier estimator is very small, reflecting the relatively low number of patients who required outcomes adjusting. However, the loss of long-term follow-up in the BV+CHP arm in the re-censored analysis is pronounced. The effect in the CHOP arm is negligible because the subsequent BV treatment effect estimate (θ) in non-sALCL disease is close to one, resulting in relatively little adjustment to observed times.

Figure 24: Adjusting for treatment switching in patients with re-treatment (BV+CHP arm) and patients with non-sALCL receiving subsequent brentuximab vedotin (CHOP arm), OS - ITT



Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; TSE, two-stage estimator.

As shown in **Figure 24**, the BV+CHP arm of ECHELON-2 is associated with a declining hazard over time, ultimately leading to a sustained event-free period

towards the end of study follow-up. Thus, re-censoring discards important evidence in the BV+CHP arm of the changing hazard over time.

Alternatives such as combining TSE and inverse-probability of censoring weights (IPCW) method have been proposed.[99] However, given the challenges of implementing the IPCW approach in the initial analyses and the requirement to fit parametric survival models beyond ECHELON-2 (**Appendix N**), this was not pursued in the present analysis.

The base-case analysis excludes re-censoring, on the basis that the objective was to fit parametric survival models to trial data to extrapolate into the future. Sensitivity analysis was performed including re-censoring.

B.3.3.1.2 *Proportional hazards*

The assumptions of proportional hazards and odds (used in the accelerated failure time [AFT] metric models [log-normal, log-logistic, etc]) were assessed visually using log-cumulative hazard and quantile-quantile plots, respectively, and are presented in **Appendix L**.

The proportional hazards assumption was assessed using plots of the log-cumulative hazard. For OS in the ITT population (**Appendix L**), the plots are straight and parallel after approximately one month. For PFS in the ITT population (**Appendix L**), the plots are relatively parallel, though not straight, after approximately one month. On the basis of these results, a joint modelling approach was adopted, in which the effect of treatment is represented by a coefficient estimated on data from both arms of ECHELON-2.

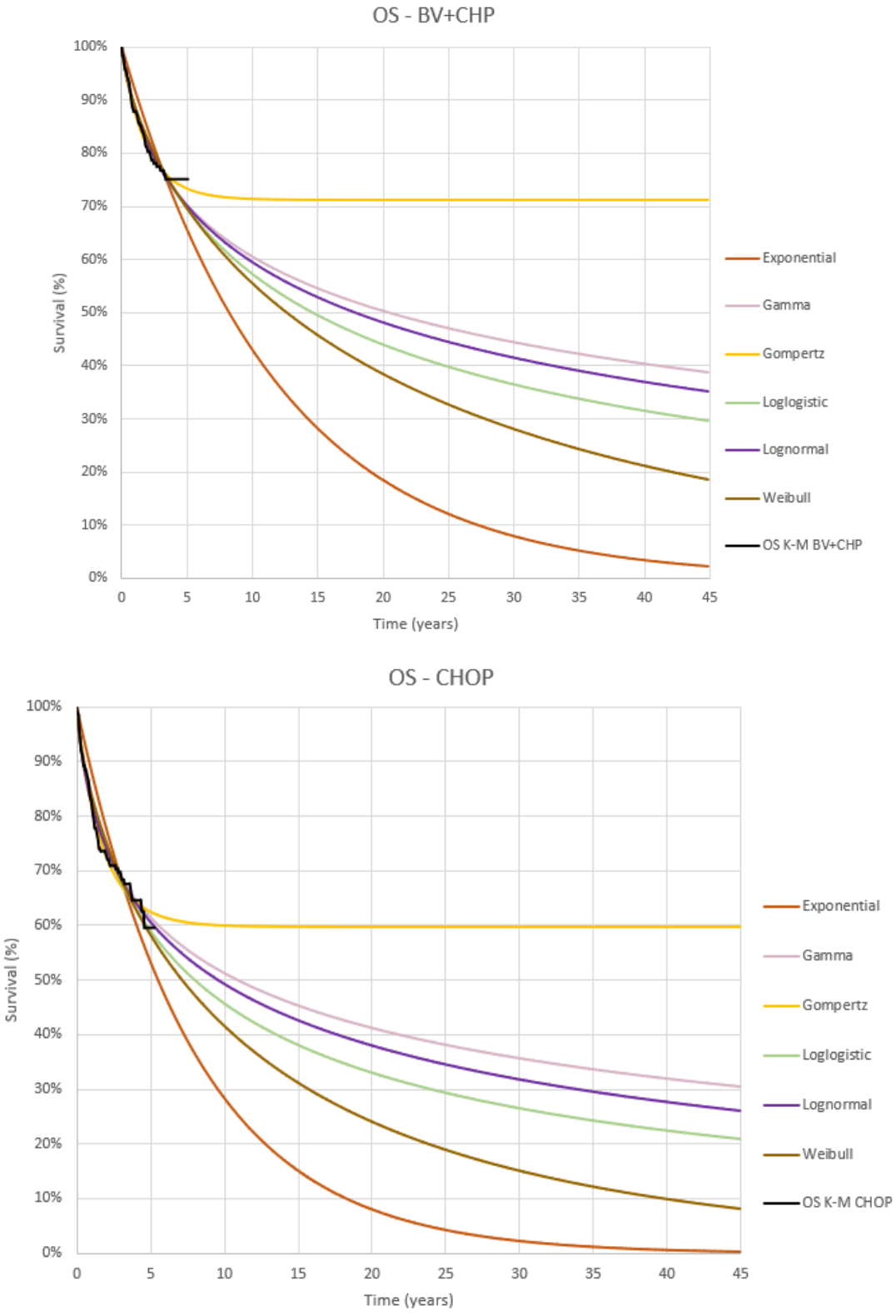
B.3.3.1.3 *Standard parametric distributions*

A range of standard parametric distributions were explored for extrapolation:

- generalised gamma
- exponential
- Gompertz
- log-normal
- log-logistic
- Weibull.

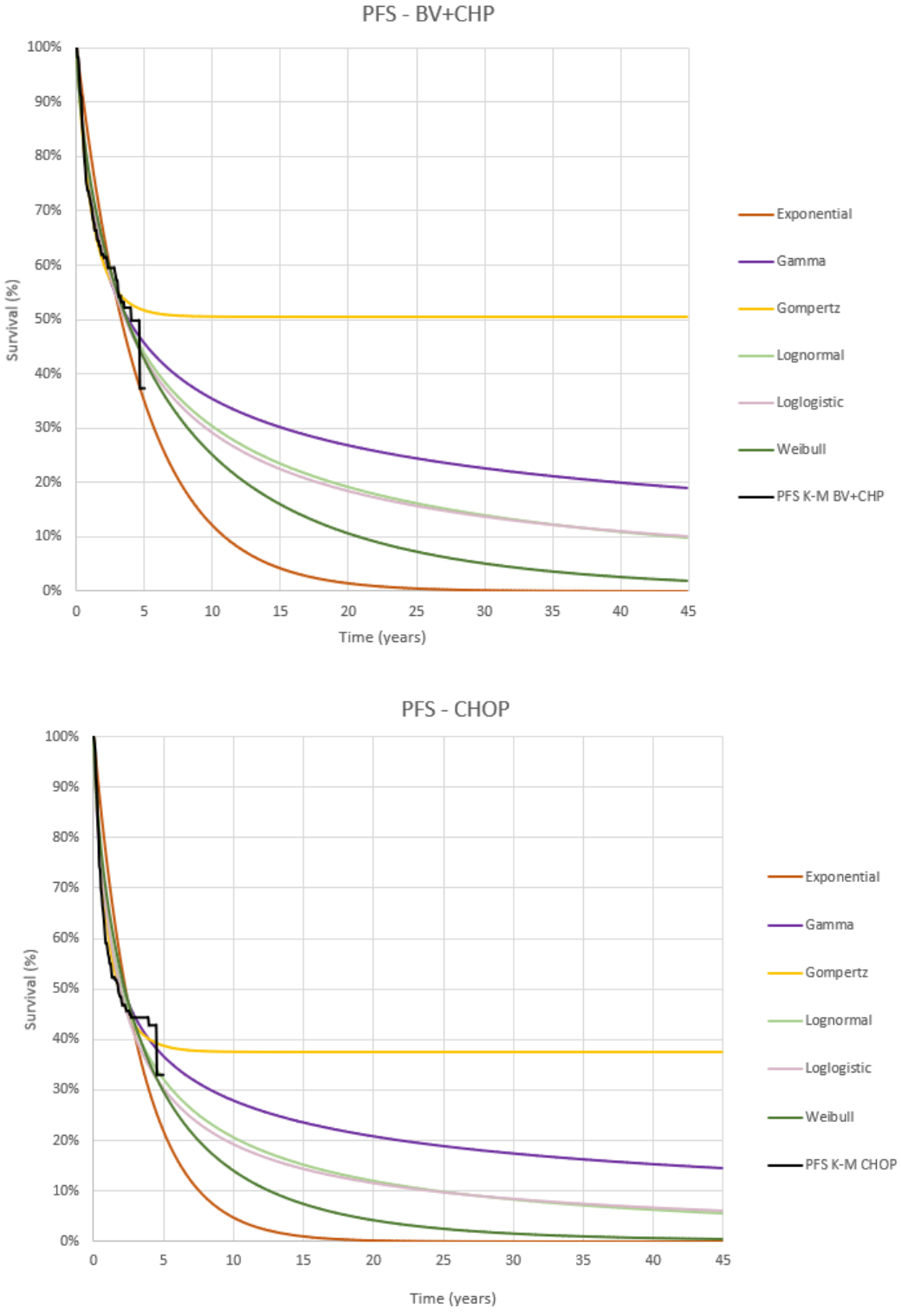
Extrapolations based on joint statistical models are presented in **Figure 25** and **Figure 26** for OS and PFS outcomes, respectively.

Figure 25: Standard parametric extrapolation, OS – ITT population – including TSE adjustment



Note: background mortality is not applied.
Abbreviations: A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; ALCL, anaplastic large cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; OS, overall survival; TSE, two-stage estimator.

Figure 26: Standard parametric extrapolation, PFS – ITT population



Note: background mortality is not applied.
Abbreviations: A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; ALCL, anaplastic large cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; PFS, progression-free survival.

Model diagnostics are presented in **Table 33**. For OS, Gompertz, log-normal and gamma plots were associated with the lowest Akaike information criterion (AIC) and Bayesian information criteria (BIC) scores. For PFS, gamma and Gompertz distributions were associated with the lowest AIC and BIC scores.

Table 33: Model diagnostics, ITT population

	ll(model)	df	AIC	BIC
OS (including TSE adjustment)				
Gamma	-432.0	4	872.1	888.5
Weibull	-436.2	3	878.4	890.7
Gompertz	-430.9	3	867.9	880.2
Exponential	-446.7	2	897.5	905.7
Lognormal	-432.2	3	870.5	882.8
Loglogistic	-434.5	3	875.0	887.3
PFS				
Gamma	–604.7	4	1217.5	1233.9
Weibull	–629.0	3	1263.9	1276.3
Gompertz	–607.9	3	1221.8	1234.1
Exponential	–650.9	2	1305.8	1314.0
Lognormal	–610.7	3	1227.3	1239.7
Loglogistic	–617.6	3	1241.1	1253.5

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; df, degrees of freedom; ITT, intention-to-treat; ll, log-likelihood; N, number of patients; OS, overall survival; PFS, progression free survival; TSE, two-stage estimator.

Extrapolations were presented to UK clinical experts at the June cross-functional advisory board.[59] Clinical experts explained that the risk of relapse after front-line treatment is the highest in the first two years following treatment and patients who have not relapsed within two years have a low likelihood of relapse. This is supported by a retrospective analysis of 775 patients from the US, Sweden and Canada which concluded that the risk of relapse and death due to lymphoma for patients with PTCL who have remained disease free for 24 months after their front-line treatment drastically decreases and survival approaches general population mortality.[18] Clinical opinion suggested that the generalised gamma distribution was most reflective of long-term outcomes for PFS and OS (amongst standard parametric curves) as it reflected a decreasing risk of relapse or lymphoma related mortality. Therefore, these were used in the base case. A further rationale is provided in **Table 58.**

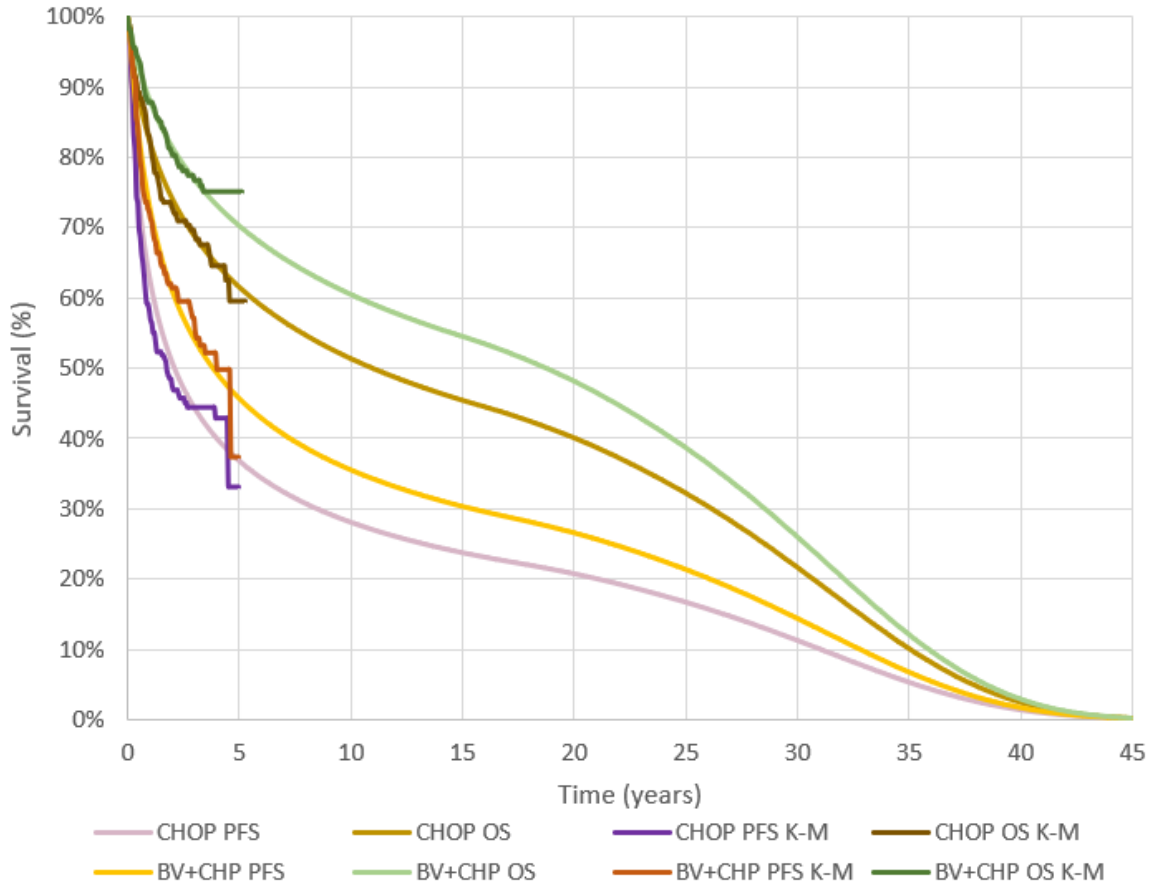
Model coefficients are reported in **Table 34**. Alternative distributions were considered in scenario analyses. **Figure 27** presents the extrapolated survival curves in the model base-case for the ITT population, incorporating background mortality from UK national life tables.[89]

Table 34: Gamma distribution coefficients (SE), ITT population

Parameter	Coefficient	SE	95% CI	
OS (including TSE adjustment)				
BV+CHP (vs CHOP)	0.621	0.300	0.033	1.209
Constant	4.608	0.353	3.916	5.300
Ln(sigma)	0.986	0.163	0.667	1.305
Kappa	-0.298	0.479	–1.236	0.640
PFS				
BV+CHP (vs CHOP)	0.600	0.208	0.192	1.007
Constant	2.501	0.249	2.013	2.990
Ln(sigma)	0.767	0.051	0.666	0.867
Kappa	–0.926	0.253	–1.421	–0.430

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CI, confidence interval; OS; overall survival; PFS; progression free survival; SE, standard error; TSE, two-stage estimator.

Figure 27: Base-case survival curve extrapolations in the ITT population fitted to the generalised Gamma distribution (including TSE adjustment and adjusted for background mortality)



Abbreviations: A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; K-M, Kaplan Meier; OS, overall survival; PFS, progression free survival; TSE, two-stage estimator.

B.3.3.2 General population life tables

Age- and gender-specific probabilities of death were taken from published national life tables for England and Wales, using data for 2018.[89] Individuals in long-term

remission may be expected to experience a minor reduction in life-expectancy compared with the age- and gender-matched general population (consistent with UK clinical expert opinion of reduced survival of 3–10% relative to the general population[59,48]) reflecting increased rates of cardiac toxicity and a small increased risk of secondary primary malignancies. To reflect this in the analysis, a mortality multiplier of 1.19 has been applied in the base case. This was calculated by assessing the general population life-expectancy predicted by the model and using Microsoft Excel's goal-seek functionality to calculate the required mortality ratio for a 5% reduction in life-expectancy. Values of 1.29 and 1.42 have also been used in sensitivity analyses, reflecting a 7.5% and 10% reduction in life-expectancy, respectively.

B.3.3.3 Time on treatment

In ECHELON-2, patients were treated with six to eight cycles of BV+CHP, at the centre's discretion.[77] In the base case, the number of cycles administered is assumed identical to the drop-off rate observed in ECHELON-2 (mean number of cycles: 6.0 [SD 1.6] and 5.8 [SD 1.6] in the BV+CHP and CHOP arms, respectively[23]). Further ranges are explored in sensitivity analysis. Although treatment with eight cycles of either CHOP or BV+CHP was permitted within the ECHELON-2 trial[23], clinical experts stated that standard practice in the UK and Europe would be to treat for a maximum of six cycles[47,59]. Up to eight cycles of either treatment was permitted in ECHELON-2 to allow for variation in practices globally. There was no evidence in ECHELON-2 of interaction between treatment effect and receipt of less than or equal to six cycles vs more than six cycles in the ITT population (p=0.336). This rationale is summarised in **Table 58.**

Two scenario analyses were considered:

- discontinuation rates as per ECHELON-2, capped at six cycles
- all patients receiving six cycles

The same assumptions are applied for each arm. The proportion of patients receiving each number of treatment cycles in ECHELON-2 is provided in **Table 35**. These proportions were used in the base case of the model.

Table 35: Proportion of patients receiving each cycle, ITT population

Cycle	BV+CHP	CHOP
1	100%	100%
2	97%	97%
3	95%	93%
4	92%	89%
5	89%	84%
6	89%	81%
7	19%	19%
8	18%	19%

Abbreviations: BV+CHP; BV, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxorubicin, prednisone and vincristine; ITT, intention-to-treat.

B.3.3.4 Adverse events

Adverse events recorded in ECHELON-2 were similar between treatment arms (**Section B.2.10.1**). Grade 3 and 4 treatment-emergent adverse events (AEs) occurring in ≥5% of patients in ECHELON-2, and Grade 1–2 diarrhoea, were included in the economic model (**Table 36**).

UK clinical expert feedback suggested that diarrhoea[3] at any grade, particularly Grade 2 or above, was likely to have an impact on patients' HRQoL.[59] As such, the number of events and duration from ECHELON-2 for diarrhoea was included at Grades 1–2 and 3–4 and were associated with different costs. The average duration of AEs per patient is used to calculate the QALY loss due to AEs. The total AE duration amounts to 26.42 days in the BV+CHP arm and 15.86 days in the CHOP arm.

Grade 3–4 peripheral neuropathy was also included in the model as peripheral neuropathy is a known class effect of agents such as BV with an anti-microtubule mechanism of action. Peripheral neuropathy has been incorporated in assessments of BV previously, and assumptions such as resource use and utility decrements were taken from TA478.[85] In ECHELON-2, 192 patients experienced peripheral sensory neuropathy of any grade (100 in the BV+CHP arm and 92 in the CHOP arm). At Grade 3-4, only nine events were recorded in the BV+CHP arm and six in the CHOP arm. Therefore, the rate of Grade 3–4 peripheral sensory neuropathy was low, resulting in an average of 0.04 and 0.03 events per patient in the BV+CHP and CHOP arm, respectively.

AE numbers were assessed during the safety period of ECHELON-2, from Day 1 through to the end of treatment visit or 30-days after the last study treatment, whichever was later. As patients are no longer on treatment after this point, AEs have not been extrapolated beyond the safety period and all costs and QALY losses associated with AEs are assumed to occur in the first cycle of the model.

Table 36: Number and duration of treatment-emergent AEs used in the evaluation

Adverse Event	Average number of events per patient, BV+CHP arm (N=223)	Average number of events per patient, CHOP arm (N=226)	Average duration per event (days)
Neutropenia (Grade 3–4)	0.97	0.70	11.1
Febrile neutropenia (Grade 3–4)	0.35	0.21	6.8
Anaemia (Grade 3–4)	0.27	0.18	7.2
Leukopenia (Grade 3–4)	0.17	0.17	9.6
Thrombocytopenia (Grade 3–4)	0.14	0.06	7.0
Pneumonia (Grade 3–4)	0.06	0.03	14.8
Diarrhoea (Grade 1-2)	0.68	0.25	10.8

[3] Diarrhoea occurred primarily in the final treatment cycles (6 and 7) with BV and was not present throughout, as demonstrated by the EORTC questionnaire (B.2.10.1, Figure 17).

Adverse Event	Average number of events per patient, BV+CHP arm (N=223)	Average number of events per patient, CHOP arm (N=226)	Average duration per event (days)
Diarrhoea (Grade 3-4)	0.07	0.01	5.6
Peripheral neuropathy (Grade 3–4)	0.04	0.03	127.4

Abbreviations: AEs; adverse events, BV+CHP; brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxorubicin, prednisone and vincristine.

B.3.3.5 Consolidative therapy

Within ECHELON-2, consolidative SCT or radiotherapy was permitted at the investigator's discretion after end-of-trial (EOT) procedures were completed. If an investigator opted for consolidative therapy, at least six cycles of study treatment were to be given prior to initiating post-treatment consolidative SCT or radiotherapy.

The economic evaluation includes the cost of consolidative SCT and consolidative radiotherapy based on the proportions observed in ECHELON-2, with the effects on survival and other outcomes assumed to be captured implicitly with the clinical data. A rationale is provided in Table 58.

B.3.3.5.1 *Consolidative SCT*

Consolidation with an SCT can be considered in eligible patients who achieve a CR at the end of front-line therapy. Clinical opinion on the efficacy of consolidation is inconclusive with limited evidence supporting its risk-benefit profile. In a real-world setting, it is unlikely that the addition of BV to CHP would have an impact on the use of consolidative SCT. The conclusion of UK clinical experts was that the rates of consolidative transplant were not likely to change and would continue to be driven based on local practices and the consultant interpretation of the data surrounding the efficacy of consolidation with SCT in PTCL.

In the ITT population, 50 patients (22%) in the BV+CHP arm vs 39 patients (17%) in the CHOP arm received consolidative SCT following completion of study treatment (Table 37). This can be compared to the estimates from a 2019 survey of UK clinicians who manage PTCL which reported that approximately 20%-30% of UK patients receive a consolidative transplant; the survey also found that transplant practices vary considerably across centres in the UK.[58]

Table 37: Proportion of patients receiving consolidative SCT in ECHELON-2

Treatment arm	Total number of patients	Patients who received a consolidative SCT	% consolidative SCT
BV+CHP	226	50	22%
CHOP	226	39	17%

Abbreviations: ASCT, autologous stem cell transplant; BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; ITT, intention-to-treat; SCT, stem cell transplant.

All consolidative SCT was assumed to occur at six months in the model; median time to receipt of consolidative SCT in ECHELON-2 was 181 days (IQR: 158, 211). This was validated by UK clinical experts.[48] In their experience, the few patients who receive consolidative SCT in the front-line setting would do so six months from the start of treatment with CHOP.

Note: the majority of consolidative SCTs in ECHELON-2 were ASCT – reflective of UK clinical practice. However, there were two patients in the trial who received consolidation with an alloSCT.

B.3.3.5.2 *Consolidative radiotherapy*

The proportion of patients who received consolidated radiotherapy in the ECHEON-2 trial was included for costing purposes. Costs associated with radiotherapy are detailed in **Section B.3.5.4.4**, and use of radiotherapy post-progression is summarised in **Section B.3.3.5**. All consolidative radiotherapy was assumed to occur at six months in the model; median time to receipt of consolidative radiotherapy in ECHELON-2 was 175 days (IQR: 136, 190).

In the ITT population of ECHELON-2, consolidative radiotherapy was received by 6% (n=14) of patients in the BV+CHP arm vs 3% (n=6) patients in the CHOP arm (**Table 38**).

Table 38: Proportion of patients receiving consolidative radiotherapy in ECHELON-2

Treatment arm	Total number of patients	Patients who received consolidative radiotherapy	% consolidative radiotherapy
BV+CHP	226	14	6%
CHOP	226	6	3%

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; ITT, intention-to-treat.

B.3.3.6 Subsequent SCT post-progression

If a patient experiences disease progression following front-line treatment, their disease is considered very aggressive and prognosis is much poorer. The aim of salvage treatment in all relapsed PTCL is to bridge patients to either an ASCT or an alloSCT, as recommended by ESMO guidelines.[41] For R/R PTCL, the ESMO[41] and BSH guidelines[103] specify that patients achieving a CR or PR to salvage therapy who are otherwise eligible based on patient characteristics, should be considered for transplant. Therefore, subsequent SCTs are also included as a component of the costs of progressive disease. Unlike consolidative SCTs, which are mostly ASCT, subsequent SCTs may be either an ASCT or alloSCT.

The proportions of patients with progressive disease receiving subsequent SCT and the proportions of ASCT vs alloSCT were estimated directly from ECHELON-2 and are presented in **Table 39**.

Table 39: Proportion of R/R patients receiving salvage stem cell transplant in ECHELON-2

Treatment arm	Subsequent SCT (in patients who progress)	Proportion of subsequent ASCT vs alloSCT
BV+CHP	20%	64.1%†
CHOP	21%	

Abbreviations: ASCT, autologous stem cell transplant; alloSCT, allogenic stem cell transplant; BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; ITT, intention-to-treat; SCT, stem cell transplant.
† Assumed the same in both arms

B.3.4 Measurement and valuation of health effects

B.3.4.1 Health-related quality-of-life data from clinical trials

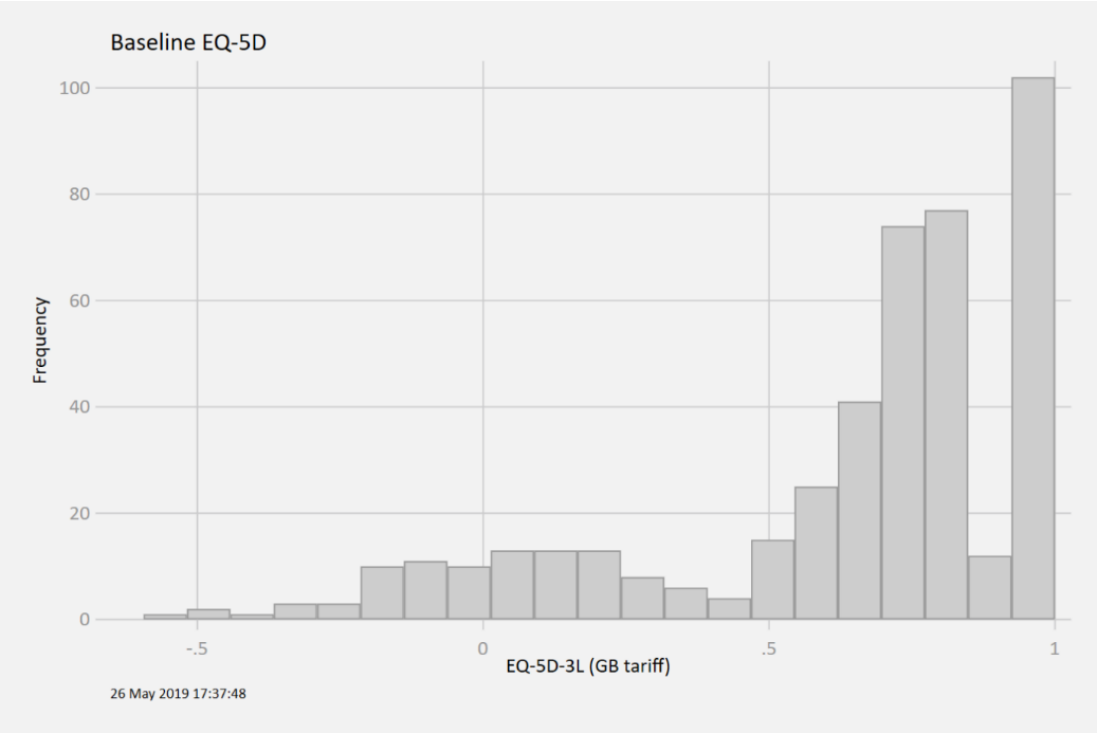
During ECHELON-2, EQ-5D-3L data was collected on Day 1 of each treatment cycle, at the EOT visit and at 9, 12, 15, 18, 21, and 24 months (±1 week) after first dose of study treatment and every six months (±1 week) thereafter until patient death or study closure, whichever came first.

The EQ-5D-3L tariff from Dolan[104] was applied to individual responses to generate EQ-5D-3L index scores. This tariff uses a time-trade-off methodology to elicit utility values from the general population. Therefore, the EQ-5D-3L is consistent with the NICE reference case.

There was no statistically significant difference between mean EQ-5D-3L index score during the study period in the BV+CHP arm compared with the CHOP arm. The scores improved over time in both treatment arms (**Section B.2.6.1.5**).

At baseline, 444 valid EQ-5D-3L questionnaires were available for analysis. Mean EQ-5D-3L was 0.64 (standard deviation [SD] 0.36), with a slight imbalance at baseline between the treatment arms (BV: 0.61, CHOP: 0.68; p=0.0394). The distribution of EQ-5D-3L index score at baseline (**Figure 28**) is consistent with EQ-5D-3L across other disease areas; index scores have a non-normal distribution divided into two distinct groups, with a large proportion of perfect '1' scores.[105]

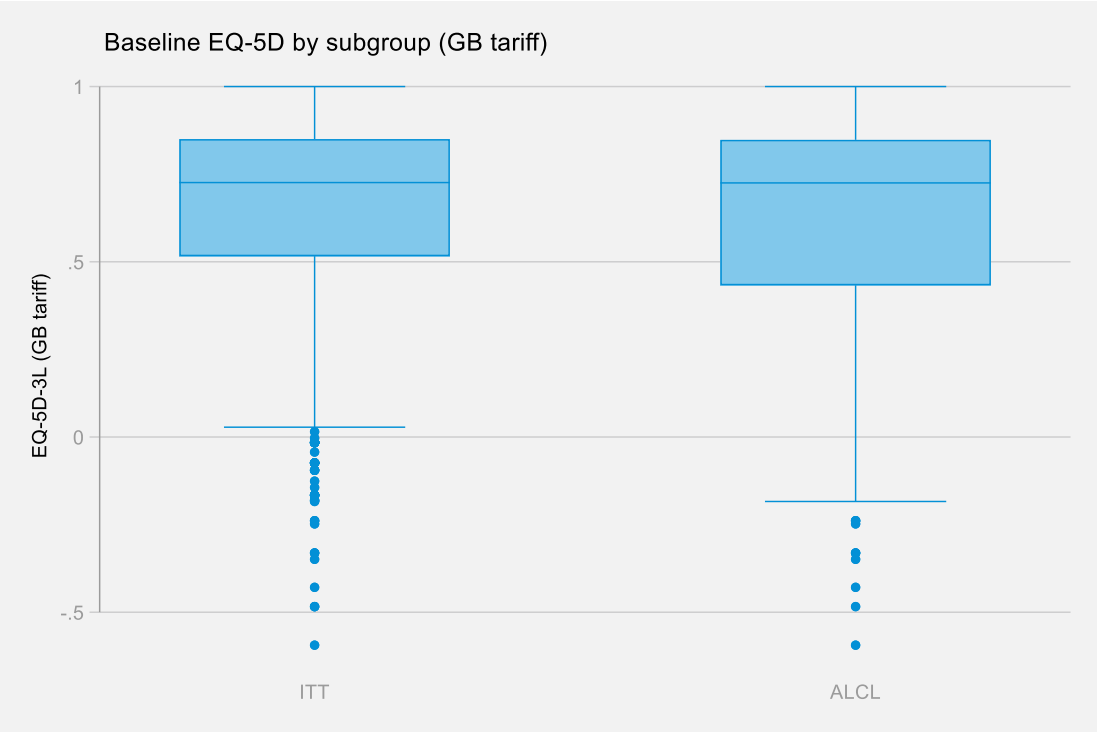
Figure 28: Baseline EQ-5D-3L index score (ITT population)



Abbreviations: EQ-5D, EuroQol 5-Dimensions; ITT, intention-to-treat; GB, Great Britain;

EQ-5D-3L scores at baseline are consistent across the ITT and sALCL populations (**Figure 29**).

Figure 29: EQ-5D UK index by population



Abbreviations: ITT, intention-to-treat; sALCL, systemic anaplastic large cell lymphoma.

B.3.4.2 Mapping

The 3-level UK tariff of Dolan et al (1997) was applied to individual responses to generate EQ-5D index scores.[104] This tariff is based on a representative sample of the UK general population and is estimated using a time-trade-off (TTO) methodology. Therefore, there was no need to apply mapping.

B.3.4.3 Health-related quality-of-life studies

The systematic literature review identified one study of relevance for use in the economic model. Swinburn et al (2015) [54] was a vignette study which elicited TTO valuations from members of the general public across seven countries, including: UK, Australia, Thailand, Taiwan, South Korea, Brazil and Mexico. It reports utilities for patients with R/R Hodgkin lymphoma and sALCL.

The results from Swinburn et al (2015) are presented in **Appendix H**. Its use in the model is described below in **Section B.3.4.5**.

B.3.4.4 Adverse reactions

The impact of Grade 3–4 treatment-emergent AEs on HRQoL is captured in the models of EQ-5D described in **Section B.3.4.5**. As a simplification, the impact of AEs is captured as a one-off cost and QALY-loss in the first cycle. The average number of AEs per patient and the average duration is presented in **Section B.3.3.4**. Following clinical opinion,[48], an additional disutility was applied to Grade 3-4 peripheral neuropathy (see **Section B.3.4.5**).

B.3.4.5 Health-related quality-of-life data used in the cost-effectiveness analysis

To provide estimates for use in the economic model, repeated measures mixed-effects models were used to predict HRQoL. Two alternative approaches were considered and included in the economic evaluation:

1. Inclusion of an indicator for health state membership (progression free and post-progression analysis; method 1)
2. Modelling based on how close an observation was to the time of a patient's death (time-to-death analysis; method 2)
    a. Covariates representing whether observations were made within specific time windows prior to a patient's death are included.
    b. This approach captures diminishing HRQoL after progression, which is not possible using values for the progression-free and progressed disease health states. Such models have been reported previously.[106]

Method 1 was applied in the base case with an estimate from the literature estimating HRQoL for patients with progressive disease. Method 2 was explored in a scenario analysis.

B.3.4.5.1 *Method 1: Progression-free and post-progression analysis*

This method is based on health state membership and used in the base case. The statistical models further controlled for baseline EQ-5D and investigated other possible determinants of HRQoL, including:

- Assignment to BV+CHP or CHOP arms
    - The interaction of the above variables
- Being on-treatment at the time of observation
- Being post consolidative ASCT at the time of observation
- Experiencing any Grade 3–4 AEs at the time of observation
- Age
- Subgroup membership.

These initial covariates for consideration were not systematically selected, but rather represent health states or events within the model (e.g. AEs or consolidative ASCT) or determinants proposed by UK clinical experts as being the most relevant (e.g. age and subgroup membership).[59,48]

Alternative models were considered using a manually performed forward stepwise procedure in which variables were introduced and retained if statistically significant (using a threshold p-value of 0.05). All candidate models were further compared based on the AIC.

Statistical models considered are presented in **Appendix M**. Model 7 is used in the base-case analysis. Testing in Models 1 and 2 suggested that there were no significant differences between BV+CHP and CHOP (p=0.332) and being 'on treatment' (as opposed to being post-treatment). Both factors were removed. As other subgroups were not statistically significant and inclusion of subgroup membership led to poorer AIC scores, subgroup membership was removed. The effect of being post-progression was negative, consistent across models, and small (–0.03; p=0.0016). Consolidative ASCT was associated with a small positive HRQoL improvement (0.04; p=0.0009). Observations made during AEs were associated with a HRQoL reduction of –0.03 (p=0.0013).

Table 40 presents the coefficients associated with Model 7. Within the model a mean of covariates approach was applied to the prediction of EQ-5D.

Table 40: Model of EQ-5D used in the base-case analysis†

Variable	Coefficient	SE	z	P>z	95% CI	
Post-progression decrement	–0.027†	0.009	–3.180	0.001	–0.044	–0.010
Coef. baseline EQ-5D	0.343	0.022	15.900	0.000	0.301	0.385
Age decrement	–0.002	0.001	–3.480	0.000	–0.003	–0.001
AE disutility	–0.027	0.009	–2.870	0.004	–0.045	–0.008
Post-SCT increment	0.035	0.011	3.310	0.001	0.014	0.056
Constant	0.655	0.030	21.600	0.000	0.596	0.715

Abbreviations: AE, adverse event; CI, confidence interval; SCT, stem cell transplant; SE, standard error.
†Note, post-progression decrement not used in the base case but reported here for completeness.

UK clinical experts suggested that the small decrease seen upon progression was not considered realistic and likely due to limited follow-up from the trial and weighting of post-progression observations towards those nearest the point of progression. Therefore, the base-case included a utility value for progressed disease based on the value used during TA478 for R/R sALCL (estimated as 0.643), derived from estimates presented by Swinburn et al.[54] This estimate implied notably worse HRQoL post-progression than estimates based on ECHELON-2. Given that utilities in TA478 related to the response status and were not reported directly for 'all R/R patients', a weighted average of R/R pre-progression utilities was calculated by the probability of response to second-line chemotherapy in the ITT population in the first instance. We obtained a combined utility score from the CR, PR and stable disease states. Another weighted average of pre- and post-progression utilities was then calculated by the proportion of life-years spent in either state. This input was validated by UK clinical experts.[48]

Table 41 presents the utilities applied in the base case. Additionally, given the severity of episodes of Grade 3-4 peripheral neuropathy, a decrement of –0.33 is applied to the number of events per patient across the time horizon (80.53 days in the BV+CHP arm, 68.75 days in the CHOP arm). This estimate was assumed identical to the disutility applied in TA478.[54,85] This effect was not estimated in the regression analysis due to a lack of observations.

Table 41: Utility values applied in the base case

	Utility value	Justification
Pre-progression	0.78†	Estimated from Model 7 in **Appendix M** using the EQ-5D data from the ECHELON-2 trial and considering: health state membership, age, baseline EQ-5D, SCT receipt and AEs as covariates. Includes an additional decrement of –0.33 for patients with peripheral neuropathy
Progressed disease	0.643	Derived from the R/R sALCL TA478 submission

Age decrement	-0.002	Derived from the EQ-5D data from the ECHELON-2 trial and applied over time

Abbreviations: AE, adverse event; EQ-5D, EuroQol – 5 dimensions; SCT, stem cell transplant;
†This estimate varies over time as a result of the age decrement applied in the base case approach.

B.3.4.5.2 *Method 2: Time-to-death analysis*

The time-to-death analysis is used in a scenario analysis. As may be expected, HRQoL declines significantly as patients approach death (**Appendix M**). Effects of variables included in the base-case statistical models are similar to those in the model defined by health state membership (**Appendix M**). EQ-5D observations for patients taken <21 days before their deaths were associated with reduced HRQoL –0.39 ($p<0.001$). The time intervals were selected to reflect a plausible range of cycles from death: less than 1 cycle, 1 to 4 cycles, 5 to 9 cycles and 10 or more, and were taken from a previous publication which modelled a similar analysis.[106] These intervals were modified to suit the cycle length in this evaluation. The size of this effect decreased as the time before death increased.

B.3.5 Cost and healthcare resource use identification, measurement and valuation

B.3.5.1 Intervention and comparators' costs and resource use

Costs were collected from the latest available source when available (eMIT,[107] NHS reference costs 2017/2018,[108] the British national formulary (BNF),[109] and the Personal Social Services Research Unit (PSSRU) 2018[110]). Costs collected from related technology appraisals were inflated to 2018/2019 using inflation indices in the PSSRU.

B.3.5.1.1 *Acquisition costs*

As per ECHELON-2, for 21-day cycles, patients in both treatment arms receive cyclophosphamide (750 mg/m^2 on Day 1, as a drip or slow injection [bolus] into a vein), doxorubicin (50 mg/m^2 on Day 1, as a slow injection [bolus] into a vein), and prednisone (100 mg once daily) on Days 1 to 5, orally. Patients in the BV+CHP arm also received BV intravenously (1.8 mg/kg on Day 1) – this was capped at 180 mg as per the existing licence for BV. Whereas, patients in the control arm (CHOP) received vincristine intravenously (1.4 mg/m^2 on Day 1).

The acquisition costs of BV+CHP and CHOP are modelled as per-cycle costs, weighted across the total number of cycles given in ECHELON-2 (resulting in averages of 6.0 cycles in the BV+CHP arm and 5.8 cycles in the CHOP arm). The distribution of patients across the eight possible treatment cycles which are based on body mass (i.e. prednisone is excluded) are reproduced in **Table 35**.
Mean body weight (kg) and body surface area (BSA) for the ITT population (76.35 kg and 1.85 m^2, respectively) were used to determine the number of vials required per

cycle per patient. Due to the rarity of the condition, patient numbers in treatment sites are not expected to be large enough to allow for vial sharing. Therefore, vial wastage is assumed. The optimal combinations of vial sizes were calculated for each range of BSA or weight (kg) such that the lowest combination was selected for each patient in ECHELON-2 using the method of moments (Table 42**Table 42: Optimal combinations of vial sizes by BSA/kg**

Drug	Number of vials per cycle (%)						Weighted average number of vials
	1	2	3	4	5	6	
BV+CHP							
BV	0.010	0.164	0.498	0.328	N/A†	N/A†	3.14
Cyclophosphamide	–	0.023	0.692	0.284	0.001	–	3.26
Doxorubicin	0.001	0.715	0.285	-	–	–	2.28
CHOP							
Cyclophosphamide	–	0.023	0.692	0.284	0.001	–	3.26
Doxorubicin	0.001	0.715	0.285	–	–	–	2.28
Vincristine	–	0.052	0.816	0.132	–	–	3.08

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine.
†The dose of BV is capped at 180mg based on the current license for brentuximab vedotin

Acquisition costs are provided in **Table 43**. A confidential PAS approved by the Department of Health for BV is already in place for current BV indications. Under the PAS, a simple discount of [redacted] on the list price is applied.

Table 43: Acquisition costs

Drug	Dose	mg/pack	Pack price	Pack size	Cost/cycle†
BV+CHP					
BV (list price)	1.8 mg/kg	50 mg	£2,500	1	[redacted]
BV (PAS price)			[redacted]		[redacted]
Cyclophosphamide	750 mg	500 mg	£8.31	1	£27.11
Doxorubicin	50 mg	50 mg	£17.78	1	£17.78
Prednisone	100 mg	25 mg	£20.25	56	£7.23
Total cost per cycle (using BV list price)					[redacted]
Total cost per cycle (using BV PAS price)					[redacted]
CHOP					
Cyclophosphamide	750 mg	500 mg	£8.31	1	£27.11
Doxorubicin	50 mg	50 mg	£17.78	1	£17.78
Prednisone	100 mg	25 mg	£20.25	56	£7.23
Vincristine	1.4 mg	1 mg	£11.59	5	£7.14
Total cost per cycle					£59.26

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine.
†Cost per cycle is calculated as the number of doses per pack multiplied by the unit cost, over the number of administrations per cycle. For example, 3.26 units of cyclophosphamide per day (using the method of moments in Table 42) at a unit cost of £8.31 for one day = 3.26 x £8.31 x 1 = £27.11.

B.3.5.1.2 *Administration costs*

Patients receiving BV require a single infusion on Day 1 of each cycle to administer the drug. Doxorubicin and cyclophosphamide are administered on the same day as BV in the BV+CHP arm, and on the same day as vincristine in the CHOP arm.

Doxorubicin, cyclophosphamide and BV are administered intravenously, as a drip or slow injection (bolus) into a vein. As a result, the cost of administration is applied once per cycle in both arms. Prednisone is taken orally and does not incur an administration cost.

The cost of infusion in the outpatient setting was collected from NHS reference costs 2017/18,[108] as shown in **Table 44**. The cost of infusion is applied as a single cost to the proportion of patients receiving treatment across the number of cycles received, with a different cost applied to the first cycle.

Table 44: Administration costs

Currency code	Definition	Unit cost
SB12Z	Simple parenteral chemotherapy, outpatient, first	£228.99
SB15Z	Simple parenteral chemotherapy, outpatient, subsequent	£289.33

B.3.5.1.3 *Concomitant medication*

Primary prophylaxis with granulocyte colony stimulating factor (G-CSF; filgrastim) is expected to be used for all patients who receive BV+CHP or CHOP in UK clinical practice; although in the ECHELON-2 trial only 30% of patients received such primary prophylaxis. However, to reflect the UK reality, these costs are applied to 100% of patients in both treatment arms in the base case. Note: this is a conservative assumption as the trial reported substantially less G-CSF use.

Unit and total costs per cycle are presented in **Table 45**. Clinical opinion confirmed that no differences in concomitant therapy use nor administration schedule is anticipated between BV+CHP and what is currently administered with CHOP.[48] Unit costs were collected from eMIT where available,[107] and the BNF.[109]

Table 45: Concomitant medication costs

Regimen	Dose	mg/pack	Cost/pack	Admins /cycle	Cost/cycle	Source for dose/cycle
Filgrastim	300 mg	300 mg	£52.70	7	£368.90	TA478 [85]
Levofloxacin	500 mg	500 mg	£2.12	7	£1.48	
Aciclovir	400 mg	250 mg	£7.99	14	£17.90	
Allopurinol	300 mg	300 mg	£6.35	1	£0.23	London Cancer Alliance, CHOP Concomitant medication [111]
Omeprazole	20 mg	20 mg	£0.42	21	£0.32	
Fluconazole	50 mg	50 mg	£0.76	21	£2.28	
Co-trimoxazole	960 mg	480 mg	£1.16	9	£0.75	

Abbreviation: CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine.

B.3.5.2 Health-state unit costs and resource use

Medical resource use (MRU) costs and frequencies were informed by the London Cancer Alliance documentation on follow-up care with CHOP chemotherapy [111] and the resource use estimates presented in NICE TA478 [85]. Different assumptions were made in pre- and post-progression health states to reflect the varying intensities of follow-up care. The frequency and nature of monitoring modelled in the cost-effectiveness analysis were validated by clinical experts[59] and modified where needed to accommodate the number of cycles relevant to untreated PTCL.

Medical resource use incurred during an AE is costed separately (**Section B.3.5.3**). Costs were collected from NHS Reference Costs 2017/18.[108]

B.3.5.2.1 *Pre-progression MRU*

Costs of MRU applied during treatment were based on follow-up and monitoring requirements during ECHELON-2. For simplification, this was applied as a single up-front cost.

The cost of MRU following treatment was applied as an additional (per-cycle) cost in the first-, second- and third-years post-treatment (applied to the number of patients off treatment, pre-progression and still alive at those times). It was assumed that patients who remained progression-free for three years would be discharged with no additional resource use. This assumption was validated by clinical experts (range: 2–5 years) and reflects the frequency of follow-up reported in TA478, which was deemed appropriate given the low probability of relapse after two years of being disease-free.

UK clinical experts agreed that patients receive a total of three scans (PET/CT): one at baseline, one at interim and one at end of treatment [59]. Patients are assumed to be followed up with consultation as reported in TA478 (once every three months) for three years after the end of treatment. The pre-progression MRU costs and frequencies are reported in **Table 46**.

Table 46: Cost and frequency of MRU, with BV+CHP and CHOP, pre-progression

Component	Unit cost	Resource use during treatment	Long-term follow up		Currency code/source
			Year 1	Years 2 & 3	
CT scan	£136.70	2	1	0	NHS reference costs 2017/18,[108] RD27Z
PET scan (3+ areas)	£460.19	2	1	0	NHS reference costs 2017/18,[108] RN07A, 19 years and over
Consultation	£164.80	1	4	8	NHS reference costs 2017/18,[108] WF01A, 303. Non-

					admitted, face to face, haematology
Full blood count	£2.51	6	4	8	NHS reference costs 2017/18,[108] DAPS05
Clinical biochemistry	£1.11	6	4	8	NHS reference costs 2017/18,[108] DAPS04
Bone marrow biopsy	£495.98	3	0	0	NHS reference costs 2017/18,[108] SA33Z
Urea and electrolytes*	£1.11	6	3.5	3.5	NHS reference costs 2017/18,[108] DAPS04
Liver function test*	£2.51	6	3.5	3.5	NHS reference costs 2017/18,[108] DAPS05
Total cost per cycle		**£2,890**	**£1,283**	**£1,360**	

*Number of units received were taken from the London Cancer Alliance protocol for CHOP [112].
Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; CT, computerised tomography; PET, positron emission tomography.

B.3.5.2.2 *Post-progression MRU*

Upon progression, the total cost of post-progression MRU is applied to the proportion of patients who progressed in each cycle. Estimates of MRU were taken from TA478 and are reported in Table 47, with unit costs as reported in **Table 46**. These estimates were considered suitable, as required medical resource use in post-progression PTCL was deemed comparable to that required in post-progression R/R sALCL (and hence included in TA478).

As per TA478, the cost of consultation, full blood count and clinical biochemistry were assumed to be incurred once per cycle of salvage therapy, using the mean number of cycles of salvage therapies used in the model (4.62 cycles of subsequent treatment in the base case).

It was assumed that patients who did not experience a relapse for a further three years would be discharged with no additional resource use (**Section B.3.5.2.1**).

Table 47: Frequency of MRU, BV+CHP and CHOP, post-progression

Component	Total units, on treatment	Long-term follow-up, Clinical expert 1 Years 0–3
CT scan	3	1
PET scan (3+ areas)	2	1
Consultation	4.62	10.5
Full blood count	4.62	10.5
Clinical biochemistry	4.62	10.5
Cost per cycle	£2,107.91	£2,365.26
Total cost		**£4,473.17**

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; CT, computerised tomography; PET, positron emission tomography.

B.3.5.3 Adverse reaction unit costs and resource use

The costs of AEs were applied to the duration of each event, as reported in **Section B.3.3.4**. A conservative assumption was made by applying the cost of Grade 3–4 AEs to all occurring events, as well as Grade 1–2 diarrhoea, as it was noted as being particularly detrimental to patients' HRQoL at the June Cross-Functional Advisory Board.[59] Further clinical input suggested that the treatment of Grade 1–2 diarrhoea is based on over the counter medication. Therefore, the costs are negligible.[59] This rationale is also described in **Table 58.**

Unit costs were taken from NHS reference costs 2017/18, eMIT and NHS published costs for Blood and Transfusion.[113,114] The unit cost of each event and its relevant code are reported in **Table 48**, and a breakdown of costs for neutropenia, febrile neutropenia, anaemia and thrombocytopenia is provided in **Table 49**. This approach aligns with the method adopted in TA478. AEs cost £1,135.44 in the BV+CHP arm and £772.93 in the CHOP arm (with the difference in cost driven primarily by differences in neutropenia and febrile neutropenia) and were applied as one-off costs at the start of the model. This was considered reasonable because of the short duration of treatment.

Based on clinical expert opinion, no costs were included for Grade 3–4 peripheral neuropathy on the basis that the treatment for this AE would be to stop treatment with either BV+CHP or CHOP and wait for PN improvement or resolution.[48]

Table 48: AEs, cost per event

AE	Cost/event	Source/HRG code
Neutropenia	£576.63	Cost of administering peg filgrastim (**Table 49**)
Febrile neutropenia	£576.63	
Anaemia	£406.09	Cost of transfusion (**Table 49**)
Leukopenia	£576.63	Assumed identical to neutropenia
Thrombocytopenia	£610	Peg filgrastim identical to neutropenia and a platelet transfusion in 10% of patients (**Table 49**)
Pneumonia	£1,099.81	DZ22L, day case, unspecified acute lower respiratory infection with intervention[108]
Diarrhoea (Grade 3–4)	£161.00	FD05A, day case, abdominal pain with interventions[108]

Abbreviations: AE, adverse event; HRG, healthcare resource group.

Table 49: Micro-costing approach in Grade 3–4 AEs

AE	Cost type	Number of units	Cost	Source
Neutropenia febrile neutropenia and leukopenia	Peg filgrastim unit cost	1	£411.83	BNF[109]
	Peg filgrastim administration		£164.80	WF01A 303, NHS Reference Costs[108]
Anaemia	Transfusion	1	£148.11	NICE Blood transfusion costing, NG24 (inflated)[113]
	Red blood cells	2	£128.99	NHS Blood and Transplant Price List[114]

AE	Cost type	Number of units	Cost	Source
Thrombocytopenia	% patients requiring platelets	10%	-	TA478[85]
	Peg filgrastim unit cost	1	£411.83	BNF[109]
	Peg filgrastim administration	1	£164.80	WF01A 303, NHS Reference Costs[108]
	Platelets	1	£185.56	NHS Blood and Transplant Price List[114]
	Transfusion	1	£148.11	NICE Blood transfusion costing, NG24 (inflated)[113]

Abbreviations: AE, adverse event.

The anti-diarrhoeal medication loperamide was applied to the average duration of Grade 1–2 diarrhoea (7.36 days in BV+CHP, 2.72 in CHOP; Table 50). Costs were collected from eMIT. Dosing is based on the average recommended daily dose for adults with diarrhoea (6–8 mg/day) from the BNF.

Table 50: Additional AE drug costs

Heading	Imodium (loperamide) (for Grade 1–2 diarrhoea)	
	BV+CHP	**CHOP**
Daily dose (mg)	7	
Unit dose (mg)	2	
Pack size	30	
Cost/unit	£0.38	
Events/duration	7.36	2.72
Total cost	**£0.33 per day**	**£0.12 per day**

Abbreviations: AE, adverse event; BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine.

B.3.5.4 Miscellaneous unit costs and resource use

B.3.5.4.1 *SCT*

Three costing approaches are included to estimate the cost of ASCT and alloSCT in the model, as a range of estimates were available in the literature. Costs were collected from:

- TA478 (BV in R/R sALCL), as estimated by the bone marrow transplant unit at the Beatson West of Scotland Cancer Centre, inflated to 2018 prices (base case)[85]
- TA577 (BV in CD-30+ cutaneous T-cell lymphoma), using the lump sum cost of alloSCT (including 2-year follow-up) based on a weighted average of sibling and unrelated donors,[3] based on a study from Debals et al, 2018.[94] These costs were also validated by the transplant centre in the Hammersmith Hospital in 2018.

- TA567 (tisagenlecleucel in diffuse large B-cell lymphoma), using a weighted average cost approach from NHS reference costs and the UK Stem Cell Strategy Oversight Committee (2004). The cost used in TA567 (and applied in the model) were inflated to 2018 prices.[115]

Costs for SCTs were assumed to be the same if administered as consolidation front-line or post-progression. These were applied to the corresponding proportions of patients who received the procedure in ECHELON-2, as summarised in **Table 39**. In the base case, the cost estimate from TA577 was selected for alloSCT and from TA478 for ASCT; these are the most recent appraisals in a related disease area and are likely to provide the most up to date procedure costs.

B.3.5.4.1.1 ASCT

The estimated total costs of ASCT, using the various costing approaches, are summarised in Table 51. All costs were applied six months post-initiation of treatment with BV+CHP or CHOP, as validated by UK clinical experts.[48] A further rationale is provided in **Table 58.**

Table 51: Costing approaches, ASCT

Component	TA478 (Source: Beatson, used in base case)	TA567
Cost of procedure	£54,543	£25,458
Follow-up cost	–	£3,338
Total	**£54,543.06**	**£28,795.64**

Abbreviations: ASCT, autologous stem cell transplant; BEAM, carmustine, etoposide, aracytin and melphalan.

B.3.5.4.1.2 alloSCT

The estimated total costs of alloSCT, using the various costing approaches, are summarised in **Table 52**.

Table 52: Costing approaches, alloSCT procedure

Component	Debals [94] used in TA577 [86]	TA478 [85] (Beatson)	TA567 (used in base case) [115]
Cost of procedure	–	£111,520	£79,525
Follow-up cost	–	–	£3,338
Total	**£96,956†**	**£111,520**	**£82,862**

†Calculated as the average of unrelated and sibling donor in TA577.

B.3.5.4.2 ***Consolidative radiotherapy***

The cost of consolidative radiotherapy was calculated as the combined cost of preparation and delivery, which amount to £2,206 per procedure (a breakdown is provided in **Table 53**). This cost was applied as a one-off cost at six months, in line with the timing of consolidative SCT, to the proportion of patients receiving

radiotherapy in ECHELON-2 (**Table 54** for the base case), and was taken from NHS reference costs 2017/18.[108]

The number of units per component was assumed identical to the number of units reported for palliative radiotherapy in TA478,[85] and were validated by UK clinical experts.[59] A further rationale is described in **Table 58.**

Table 53: Cost breakdown for consolidative radiotherapy, per procedure

Component	Number of units	Unit cost	Currency code
Preparation for simple radiotherapy with imaging and dosimetry	1	£514.99	SC45Z, OP
Deliver a fraction of treatment on a megavoltage machine	15	£112.73	SC22Z, OP
Total cost per procedure	**–**	**£2,206**	

Abbreviations: OP, outpatient.

Table 54: Total cost and proportion of patients receiving consolidative radiotherapy, ITT population

Component	BV+CHP	CHOP
Proportion of patients	6.19%	2.65%
Total cost	**£136.66**	**£58.57**

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; ITT, intention-to-treat.

B.3.5.4.3 *Subsequent BV*

As described earlier, a proportion of patients in ECHELON-2 received BV re-treatment in the BV+CHP arm and a proportion of patients received BV as a subsequent therapy in the CHOP arm. In the base case, adjustments have been made to the survival data to remove the effects of BV re-treatment (in the BV+CHP arm) and BV subsequent therapy (in patients with non-sALCL in the CHOP arm). Therefore, BV is only costed as a subsequent therapy for patients with R/R sALCL – the proportion of which is defined by the ECHELON-2 trial data (n=36 received BV with R/R sALCL disease).

The per-cycle acquisition and administration costs and MRU costs are assumed identical to BV in front-line. However, BV in the R/R setting is used as monotherapy and with a potentially longer treatment duration. Therefore, duration of therapy was based on data reported in TA478.

A cost breakdown is provided in **Table 55**. Patients receive an average of 8.23 cycles of subsequent BV;[2] this cost is only applied to R/R sALCL patients, in whom BV is licensed. The cost of subsequent BV is applied to the proportion of patients who received it in ECHELON-2, as reported in **Section B.3.3.1.1**. Patients receive an average of 8.23 cycles of subsequent BV, as per second-line patient-level data; this cost is applied to the relevant proportion of patients treated (or re-treated) with

BV post-progression. The average number of cycles received post-progression is comparable to that received in the R/R sALCL setting (mean of 8.2 cycles [2]).

Table 55: Cost breakdown, subsequent BV in post-progression state

Type of cost	Cost per cycle	Total cost
Acquisition (list price)	[redacted]	[redacted]
Acquisition (PAS applied)	[redacted]	[redacted]
Administration	£289.33	£2,381.15
MRU	–	£2,889.95
Total (list price)	–	[redacted]
Total (PAS applied)	–	[redacted]

Abbreviations: BV, brentuximab vedotin; MRU, medical resource use; PAS patient access scheme.

B.3.5.4.4 *Salvage chemotherapies & radiotherapy*

Following front-line treatment with BV+CHP or CHOP in ECHELON-2, a range of subsequent therapies were received by individuals who progressed.

To reflect clinical practice in the UK, the distribution of post-progression therapies received in ECHELON-2 was filtered to exclude therapies which are not reimbursed by the NHS. UK clinical expert opinion expressed at the February Clinical Advisory Board[47] and ESMO guidelines[41] informed the final list of included post-progression therapies. The proportions from ECHELON-2 were then categorised by the selected regimens. This adjustment was performed to more accurately estimate the cost of salvage treatment that is actually available to patients in the UK. BV containing subsequent therapy regimens are excluded here, as they are considered separately.

Post-progression therapies identified in UK clinical guidelines[41,103,116] and by UK clinical experts included (**Appendix Q**):

- GDP – Gemcitabine, dexamethasone, cisplatin
- ESHAP – Cisplatin, methylprednisolone, etoposide, cytarabine
- DECC – Lomustine, etoposide, chlorambucil, dexamethasone
- ICE – Ifosfamide, etoposide, carboplatin
- Ifosfamide-based regimens
- Mogamulizumab
- Alemtuzumab.

In addition, current ESMO guidelines recommend the use of BV (in R/R sALCL), bendamustine, gemcitabine, ICE, DHAP, and SMILE-like regimens (dependent on disease subtype), followed by ASCT or alloSCT in chemo-sensitive and transplant eligible patients when they achieve a good PR or CR with their salvage treatment.[41]

To estimate the cost of post-progression therapies as a ‘weighted basket’, the weighted average cost of the included salvage regimens, was calculated by

multiplying the proportion of patients receiving each by the cost of their acquisition and administration. This total cost was then applied to all newly progressed patients in each cycle. For example, 161 of 189 patients (85%) who experienced non-fatal PFS events received post-progression therapies. Among those patients who received post-progression therapies, patients in the BV+CHP and CHOP arms received on average 1.51 and 1.65 lines of non-BV containing post-progression therapy, respectively. Patients who progressed and received post-progression treatment in the BV+CHP arm would therefore be assumed to receive 1.51 times the cost of a treatment regimen based on the distribution of treatment regimens in **Table 56**.

Table 56 presents the subsequent and salvage therapies (not including BV) used in patients enrolled in the ECHELON-2 trial by treatment arm based on the agents that are available to patients in the UK.

Table 56: Distribution of salvage therapies (non-BV containing) for UK analysis based on ECHELON-2, ITT population

Regimen	Frequency	Percent
Bendamustine	8	7.14%
CHOP	2	1.79%
DHAP	11	9.82%
ESHAP	17	15.18%
GDP	24	21.43%
Gemcitabine	7	6.25%
ICE	20	17.86%
Radiation	21	18.75%
SMILE	2	1.79%
Total	**112**	**100%**

Abbreviations: CHOP, Cyclophosphamide, doxorubicin, prednisone, vincristine; DHAP, Dexamethasone, cisplatin, cytarabine; ESHAP, Cisplatin, methylprednisolone, etoposide, cytarabine; GDP, Gemcitabine, dexamethasone, cisplatin; ICE, Etoposide, carboplatin, ifosfamide + mesna, mesna; ITT, intention-to-treat; SMILE, Etoposide, ifosfamide + mesna, mesna, methotrexate, dexamethasone

The cost of subsequent treatment in the both treatment arms of the ITT population amounts to £5,511 (£1,757 acquisition cost, £3,596 administration cost and £158 of concomitant medication). Product costs and pack sizes were collected from the BNF[109] Data on frequency and dosage were collected from a range of sources, including:

- Thames Valley Strategic Clinical Network, Lymphoma Group
- Cancer Therapy Advisor, NHL Treatment Regimens
- Previous NICE submission for BV in R/R sALCL [TA478[85]].

Administration costs were collected from NHS reference costs 2017/18.[108]

The cost of subsequent radiotherapy was assumed identical to the cost of consolidative radiotherapy (£2,206.01). Individual acquisition costs (along with dosage and frequency of administration), and administration costs are reported in **Appendix O**. The total weighted cost and administration cost are applied to the

proportion of patients who have experienced a non-fatal progression event in both treatment arms, for the number of lines of treatment (i.e. duration) observed in ECHELON-2. More detail on how these costs were applied to the proportion of new progressors is provided in **Section B.3.3.5**.

A concomitant medication cost of £35.73 per cycle of therapy was applied to subsequent chemotherapies. This cost was collected from TA478[85] and inflated to 2017/2018 prices[110].

B.3.6 Summary of base-case analysis inputs and assumptions

B.3.6.1 Summary of base-case analysis inputs

A summary of base-case analysis inputs is provided in **Table 57**.

Table 57: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution: CI (distribution)	Reference to section in submission
OS distributions	Generalised gamma†, Table 34	Multivariate normal	B.3.3.1.3
PFS distributions	Generalised gamma, Table 34	Multivariate normal	B.3.3.1.3
Time on treatment	Table 35	Beta	B.3.3.3
Pre-progression utility	Table 40	Multivariate normal	B.3.4.5
AE disutility			
Change in EQ-5D by age			
Post-progression utility	Table 41	Beta	B.3.4.5
AE rates	Table 36	Log-normal	B.3.3.4
Duration of AEs		Log-normal	
Resource use	Table 46 and Table 47	Log-normal	0
Concomitant medication	Table 45	Not varied	B.3.5.1.3
Administration costs	Table 44	Log-normal	B.3.5.1.2
Costs of SCT	Table 51 and Table 52	Log-normal	B.3.5.4.1
Distribution of salvage chemotherapy	Table 56	Dirichlet	B.3.5.4.4
Costs of AEs	Table 48	Log-normal	B.3.5.3

Abbreviations: AE, adverse event; PFS, progression-free survival; TSE, two-stage estimator SCT, stem cell transplant
† including TSE (excluding re-censoring)

B.3.6.2 Assumptions

A summary of base-case analysis inputs is provided in **Table 58**.

Table 58: Summary of assumptions applied in the economic model

Assumption	Rationale
Estimates of overall survival are adjusted using the TSE approach excluding re-censoring	BV is currently only licensed and funded for R/R sALCL and is unavailable either as re-treatment in sALCL or a salvage treatment for other PTCLs. UK clinicians confirmed that in clinical practice, patients with R/R sALCL would not receive re-treatment with BV and that relapsed patients with other PTCLs would not be treated with BV. Therefore, the model attempts to adjust for this to reflect clinical practice in the base case. The TSE was selected as the most robust and clinically plausible method to adjust for treatment switching. The TSE excluding re-censoring was employed in the base case to retain long-term data which suggest a changing hazard in the BV+CHP arm. This is described in **Section B.3.3.1.1** and further explained in **Appendix N.**
Proportional hazards/odds	In the base-case, all outcomes were estimated using joint statistical models containing a single covariate representing the treatment arm. The proportional hazards assumption was demonstrated to hold for OS and was inconclusive for PFS. However, early testing suggested results were most sensitive to OS data. Therefore, joint statistical models were pursued. Extrapolations for all tested distributions are presented in **Section B.3.3.1.**
Number of treatment cycles	In the base-case, the number of treatment cycles is based on the distribution observed in the ECHELON-2 trial, the weighted average results in six cycle for BV+CHP – aligning with feedback from clinicians, NICE Pathways for PTCL and local guidelines. Time on treatment applied in the model is described in **Section B.3.3.3.**
AE-associated cost and QALY losses accounted for in first cycle of model	This is a simplifying assumption. However, as the duration of treatment is up to eight cycles, no significant costs or QALY losses related to AEs are expected in the long-term. Therefore, this assumption is not considered to drive results. A breakdown of adverse event costs is provided in **Section B.3.5.3**.
Effects of consolidative therapies are captured implicitly within the clinical data	The proportion of patients receiving consolidative therapy in ECHELON-2 was considered reflective of UK clinical practice (which was suggested at around 20% by clinical experts[47]). However, it was noted that consolidation is not considered established practice and varies widely across centres. Furthermore, clinicians considered that the overall rate of consolidation is unlikely to change due to the introduction of BV+CHP [59]. Further detail is provided in **Section B.3.3.5.**
Costs of consolidative therapies incurred at six months post-initiation	Based on data from ECHELON-2, the median time to receipt of consolidative SCT was 181 days. This was validated by UK clinical experts who advised that should a patient receive a consolidative ASCT, it would occur approximately 6-months from the start of their front-line treatment. This is reflected in consolidation costs reported in **Section B.3.5.4.**
Vial wastage is included	Due to the rarity of CD30+ PTCL, patient numbers in treatment sites are not expected to be large enough to allow for vial sharing. Number of vials are calculated in **Table 42.**
Resource use is assumed identical in both treatment arms	Based on clinical feedback

during and after treatment	
Frequency of follow-up	Assumed to be identical to that reported in TA478 (see **Sections B.3.5.2.1** and **B.3.5.2.2**)
Time to discharge a patient is 3 years	Based on clinician feedback of 2–5 years (see **Section B.3.5.2**)
Cost of Grade 3–4 AEs was applied to all occurring events, and to Grade 1–2 diarrhoea	Conservative approach by including the clinically validated most debilitating and impactful adverse events at Grade 3–4. Further detail is provided in **Section B.3.5.3**
Number of units per component of consolidative radiotherapy was assumed identical to the number of units reported for palliative radiotherapy in TA478	Palliation with radiotherapy in TA478 was considered the most comparable setting to that presented in consolidative therapy in this submission. Unit cost and administration is detailed in **Section B.3.5.4.2**
Life expectancy is 3–10% lower than that of the general population in patients achieving long-term remission	Patients achieving long-term remission and who are discharged are assumed to have slight excess mortality – driven by cardiac toxicity from front-line treatment and a slight increase in secondary primary malignancies due to consolidative ASCT. Unlike in R/R sALCL, the aim of treatment in the front-line setting is to achieve remission rather than to bridge a patient to SCT. Therefore, only a small proportion of patients receive consolidative SCT in the front-line setting. Hence the excess mortality for patients achieving long-term remission from front-line therapy is much lower than would be observed in a R/R setting where a much higher proportion of patients have received SCT. This is further described in **Section B.3.3.1**

Abbreviations: R/R, relapsed/refractory; SCT, stem cell transplant.

B.3.7 Base-case results

B.3.7.1 Base-case incremental cost-effectiveness analysis results

There is an existing PAS for BV in the NHS in the form of a simple discount of [redacted]. All costs, ICERS and scenarios presented below include the PAS. In the base-case analysis using the ITT population and the PAS price for BV, BV+CHP is associated with incremental costs of [redacted] and [redacted] incremental QALYs, resulting in an ICER of £24,901 per QALY gained vs CHOP (**Table 59**).

B.3.7.2 Summary of base-case incremental cost-effectiveness analysis results

A summary of base-case analysis results, using the PAS price for BV, is provided in **Table 59**. Results without the PAS are applied in **Appendix P**.

Table 59: Summary of base-case results (including PAS)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CHOP	[redacted]	10.04	[redacted]	N/A	N/A	N/A	N/A
BV+CHP	[redacted]	11.59	[redacted]	[redacted]	1.55	[redacted]	£24,901

Please note: life-years are discounted.
Abbreviations: ICER, incremental cost-effectiveness ratio; ITT, intention-to-treat; LYG, life years gained; QALYs, quality-adjusted life years.

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

B.3.8.1.1 *Methods*

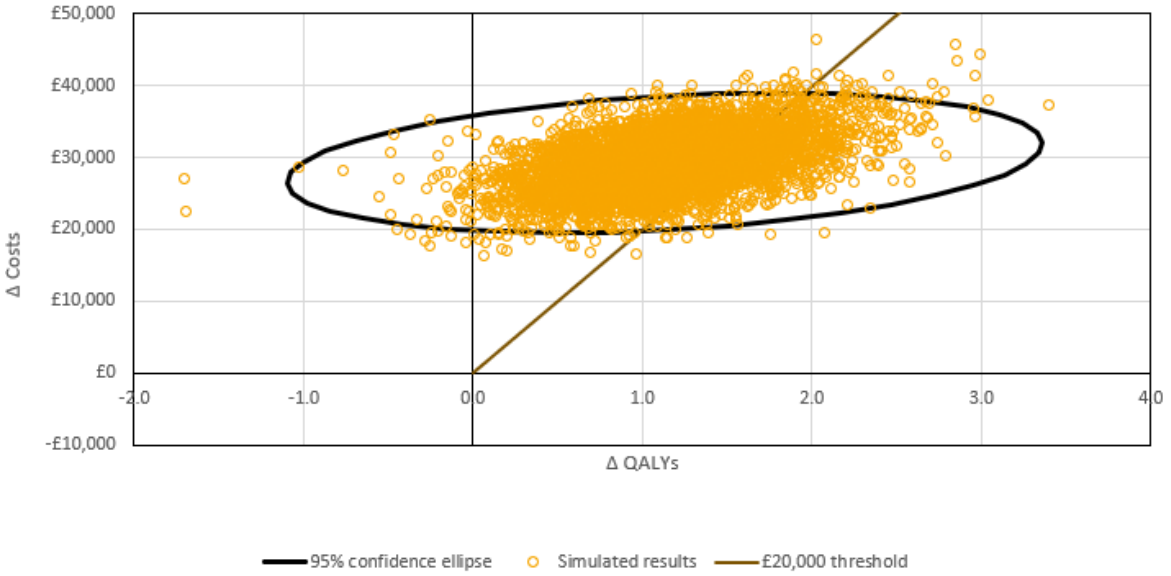
Joint parameter uncertainty was explored through probabilistic sensitivity analysis (PSA), in which all parameters are assigned distributions and varied jointly. 5,000 Monte Carlo simulations were recorded. Where the covariance structure between parameters was known, correlated random draws were sampled from a multivariate normal distributions. Results were plotted on a cost-effectiveness plane and a cost-effectiveness acceptability curve (CEAC) was generated.

Parameters and their distributions and ranges used in sensitivity analysis are detailed in **Table 57**.

B.3.8.1.2 *Results*

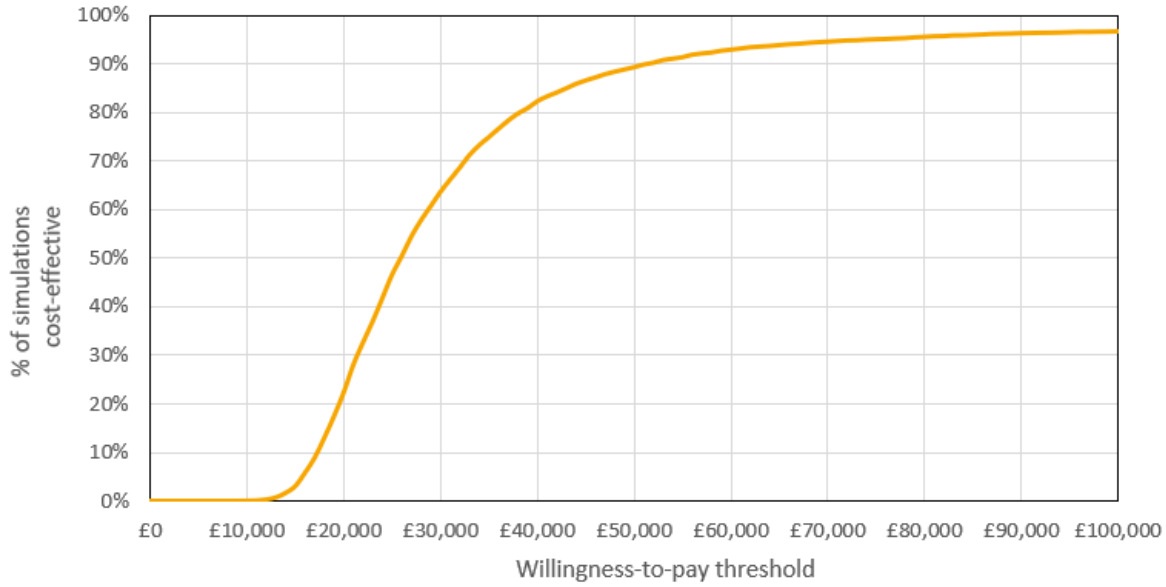
The average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted], giving a probabilistic ICER of £25,741. This is congruent with deterministic changes in costs of [redacted] and QALYs of [redacted], respectively. The proportion of simulations considered cost-effective at a threshold of £30,000 per QALY was 64%, and at a threshold of £20,000 per QALY was 22%. The cost-effectiveness plane and CEAC are reproduced in **Figure 30** and **Figure 31**.

Figure 30: Cost-effectiveness plane, ITT population



Abbreviations: QALYs, quality-adjusted life-years.

Figure 31: Cost-effectiveness acceptability curve, ITT population



B.3.8.2 Deterministic sensitivity analysis

B.3.8.2.1 *Methods*

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 ±15% where no estimates of prevision were available. The ICER was recorded at the upper and lower values to produce a tornado diagram.

B.3.8.2.2 *Results*

Results for the ten most influential parameters are shown in **Table 60**. The majority of these are those that define the survival extrapolations in OS, with the most influential being the treatment effect of BV+CHP vs CHOP on OS. This is expected as the results of the analysis are primarily driven by survival gains. A tornado diagram based on the ICER is presented in **Figure 32**, and based on the net monetary benefit (NMB) presented in **Figure 33**.

Table 60: Univariate sensitivity analysis, ITT population

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS (TSE), no re-censoring - treatment effect	£102,490	£15,513
OS (TSE), no re-censoring - ln(sigma)	£8,004	£32,183
OS (TSE), no re-censoring - kappa	£9,910	£28,399
PFS - gamma, treatment effect	£30,065	£20,501
PFS - gamma, kappa	£28,154	£22,000
Age decrement, EQ-5D	£27,134	£23,007
OS (TSE), no re-censoring - constant	£27,804	£23,880
Constant, EQ-5D	£26,792	£23,259
PFS - gamma, constant	£23,366	£26,650
PFS - gamma, ln(sigma)	£23,911	£25,915

Abbreviations: ITT, intention-to-treat; OS, overall survival; PFS, progression-free survival; TSE, two-stage estimator.

Figure 32: Tornado diagram on ICER, ITT population

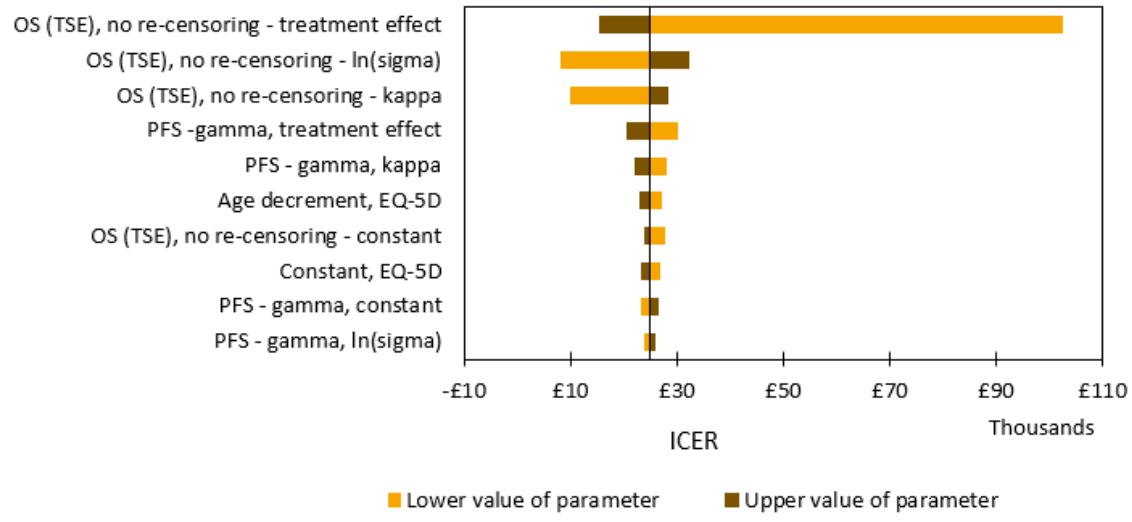
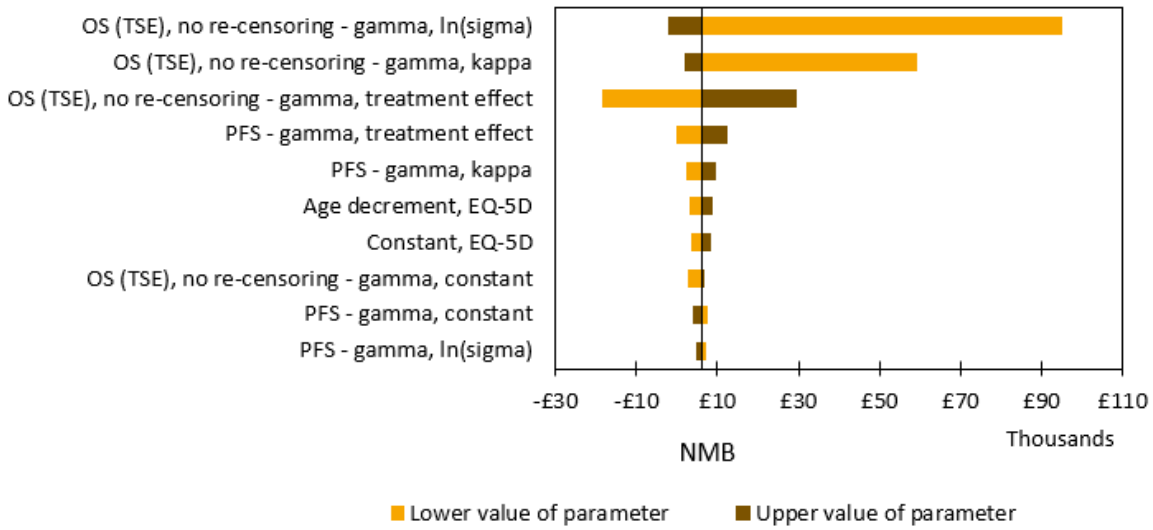


Figure 33: Tornado diagram on NMB (£30,000 threshold), ITT population



Abbreviations: EQ-5D, EuroQol- 5D; ICER, incremental cost-effectiveness ratio; ITT, intention to treat; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; TSE, two-stage estimator.

B.3.8.3 Scenario analysis

B.3.8.3.1 *Methods*

Scenario analyses were performed in which key structural assumptions were varied (**Table 61**).

Table 61: Scenario analyses

Area of uncertainty	Base-case	Scenario
Adjustment for subsequent BV (treatment switching)	TSE, no re-censoring	Re-censoring
		Unadjusted analysis (including costs and effects of subsequent BV)
Time horizon	Lifetime (maximum 100 years)	5 years
		10 years
Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes
		6% for costs, 1.5% for outcomes
Adverse event disutility	–0.029	0.0
Mortality multiplier for patients in long term remission	1.19 (5% mortality)	1.42 (10% mortality)
Distributions for OS and PFS	Gamma	Gompertz, log-normal, log-logistic, Weibull
HRQoL approach	Progressed disutility	Time to death approach
Cost of stem cell transplant	TA478 & TA478	ASCT: TA567
		alloSCT: TA577
Drug wastage	Applied	Not applied

Area of uncertainty	Base-case	Scenario
Time on treatment	As per ECHELON-2	ECHELON-2 distribution capped at 6 cycles
		All patients receive 6 cycles
Concomitant medication use	All patients receive concomitant medications	No patients receive concomitant medications

Abbreviations: BV, brentuximab vedotin; IRF, Independent Review Facility; OS, Overall survival; PFS, progression-free survival.

B.3.8.3.2 *Results*

The parameters with the biggest impact on the ICER were reducing the time horizon (+353% at 5 years) and adjusting discount rates (–23% at 1.5% for costs and outcomes) (**Table 62**).

The use of the Gompertz distribution to define OS and PFS, which represented the best statistical fit to the data using the AIC and BIC (**Section B.3.3.1.3**), was associated with a reduction in the ICER to £20,908 (–16%).

Table 62: Scenario analysis, ITT population

Area of uncertainty	Base-case	Scenario	ICER	% change from base-case
Time horizon	Lifetime (100 years)	5 years	£112,854	353%
		10 years	£55,222	122%
Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	£19,118	-23%
		6% for costs, 1.5% for outcomes	£19,179	-23%
Adjustment for subsequent BV (treatment switching)	TSE, no re-censoring	Re-censoring	£28,222	13%
		No TSE	£27,264	9%
Adverse event disutility	–0.029	0	£24,884	0%
Multiplier for patients in long term remission	1.19 (5% mortality)	1.42 (10% mortality)	£25,612	3%
Distributions for OS and PFS	Gamma	Gompertz	£20,908	-16%
		Loglogistic	£18,455	-26%
		Lognormal	£20,146	-19%
		Weibull	£15,137	-39%
HRQoL approach	Progressed disutility	Time to death approach	£25,773	4%
Cost of stem cell transplant	TA478	TA567	£24,949	0%
		TA577	£24,901	0%
Time on treatment	As per ECHELON-2	ECHELON-2 distribution capped at 6 cycles	£23,096	-7%
		All patients receive 6 cycles	£24,269	-3%

Area of uncertainty	Base-case	Scenario	ICER	% change from base-case
Concomitant medication use	All patients receive concomitant medications	No patients receive concomitant medications	£24,850	0%

Abbreviations: ASCT, autologous stem cell transplant; alloSCT, allogeneic stem cell transplant; BV, brentuximab vedotin; IRF, independent review facility; OS, overall survival; PFS, progression-free survival.

B.3.8.4 Summary of sensitivity analyses results

The main source of uncertainty driving the probabilistic and deterministic sensitivity analysis results are the variables associated with estimating OS adjusted for treatment switching. It is widely recognised that treatment switching methods add wider confidence intervals and thus additional uncertainty within the results. The adjustment within our appraisal surpassed the usual definition of switching by adjusting for switchers in both treatment arms (i.e. re-treatment with BV in the BV+CHP arm and subsequent BV for patients with non sALCL R/R disease). Therefore, adding uncertainty – as reflected in the PSA and OWSA. Removing switching adjustment methods in the base case increases the ICER to £27,264.

Beyond the standard time horizon and discount rate scenarios (which are as per the NICE scope in the base case), none of the other assumptions underpinning the economic model resulted in an ICER above the £30,000 threshold. The scenario with the biggest impact on the ICER was when re-censoring was included in the TSE. However, as discussed in **Section B.3.3.1.1.1** we consider that the re-censoring method discards informative long-term data about the changing hazard function observed when patients are treated with BV+CHP; the probability of an event reduces over time before eventually plateauing. Therefore, whilst this scenario is presented for completeness, we do not consider it to accurately reflect the long-term outcomes associated with a patient treated with BV+CHP.

B.3.9 Subgroup analysis

The ECHELON-2 trial was not designed nor powered to look at outcomes by subtype of PTCL, with the exception of sALCL. Due to an existing regulatory commitment arising from the EMA's previous conditional approval of BV for R/R sALCL, an analysis of the sALCL subgroup was a key secondary endpoint of the ECHELON-2 trial. In addition, the treatment pathway relevant for patients with sALCL differs from those with other PTCL subtypes. Therefore, the cost-effectiveness of BV+CHP compared to CHOP in patients with sALCL is presented in this Section.

B.3.9.1 Clinical parameters

B.3.9.1.1 *Extrapolations*

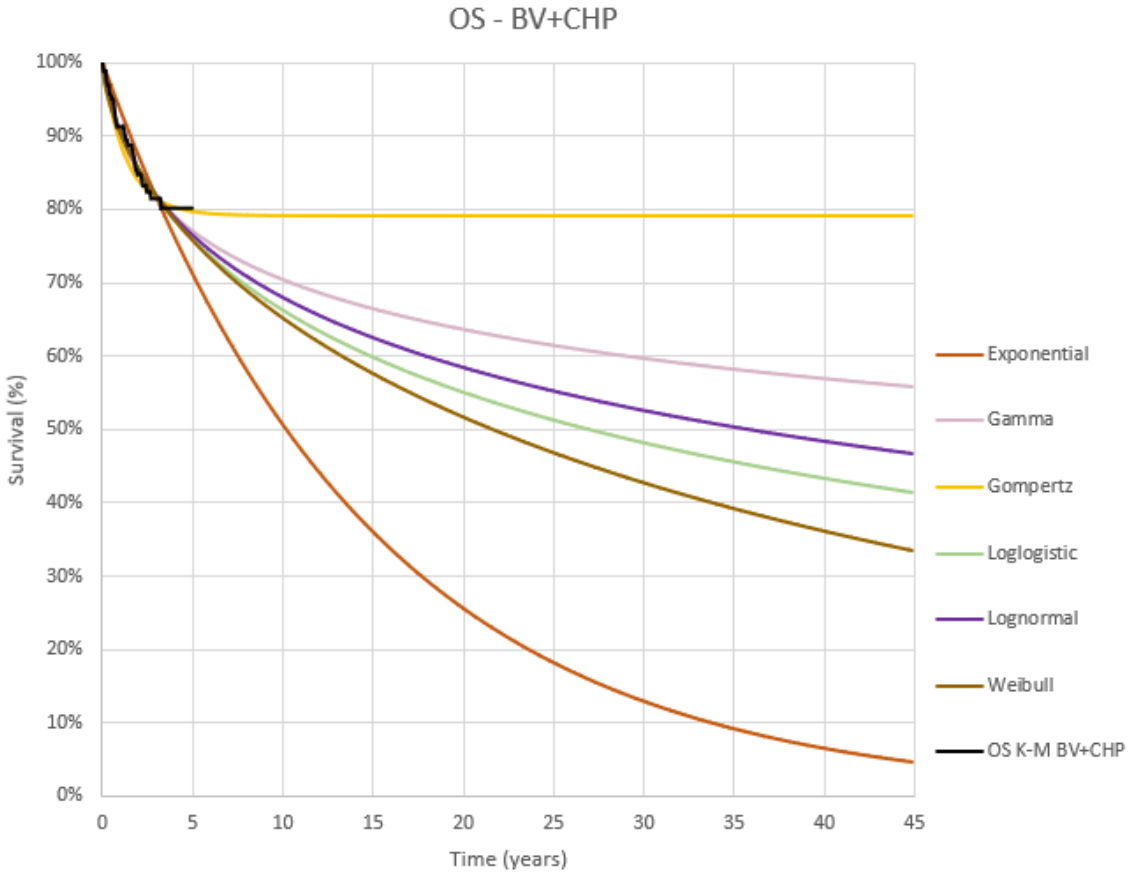
B.3.9.1.1.1 Proportional hazards

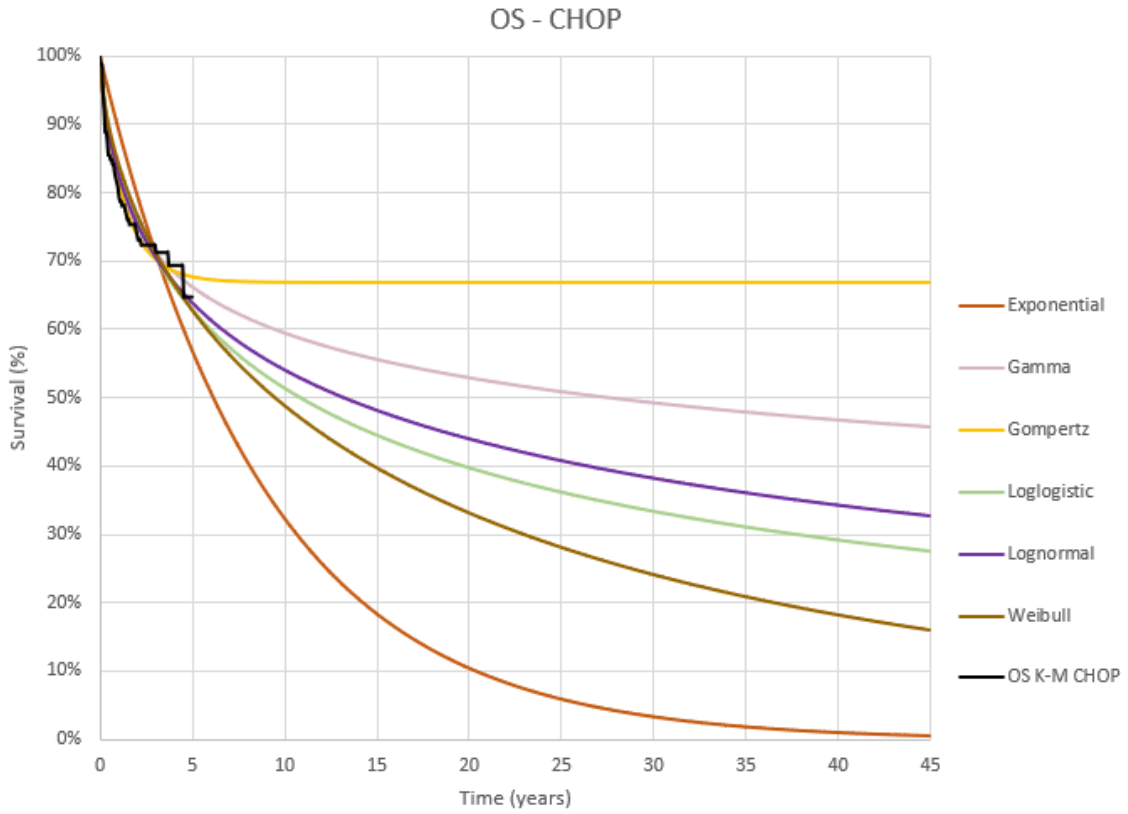
For OS in the sALCL population (**Appendix L**), the plots are relatively straight and parallel throughout. For PFS in the sALCL population (**Appendix L**), the plots are similarly relatively parallel throughout, but not straight. On the basis of these results, a joint modelling approach was adopted, in which the effect of treatment is represented by a coefficient estimated on data from both arms of ECHELON-2.

B.3.9.1.1.2 Standard parametric distributions

Extrapolations based on joint statistical models are presented in **Figure 34** and **Figure 35**.

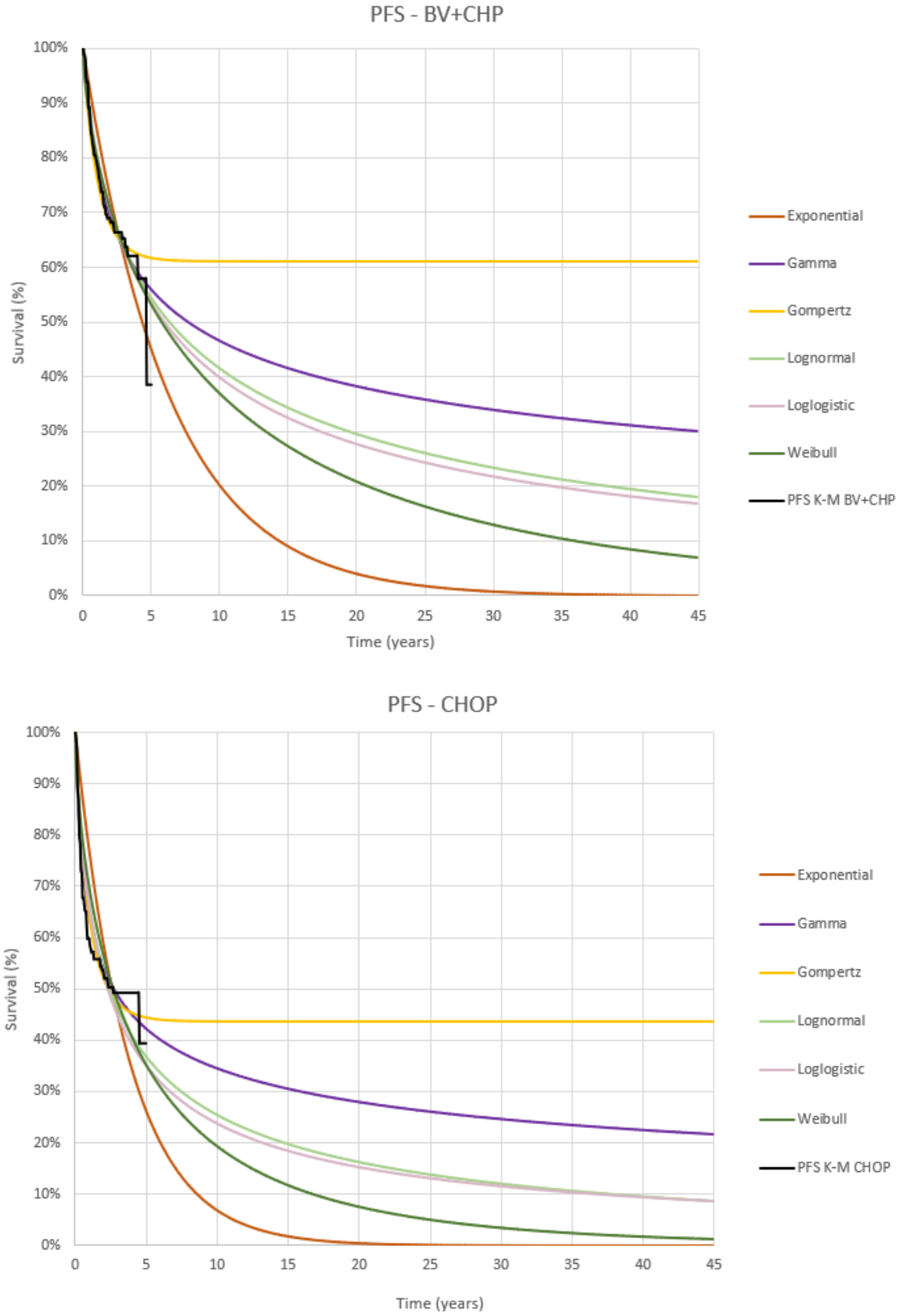
Figure 34: Standard parametric extrapolation, OS – sALCL population – including TSE adjustment





Note: background mortality is not applied.
Abbreviations: A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; ALCL, anaplastic large cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; OS, overall survival; TSE, two-stage estimator.

Figure 35: Standard parametric extrapolation, PFS – sALCL population



Note: background mortality is not applied.
Abbreviations: A+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; ALCL, anaplastic large cell lymphoma; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; PFS, progression-free survival.

Model diagnostics are reported in **Table 63**. As for the ITT, for OS, Gompertz, gamma, and log-normal distributions were associated with the lowest AIC and BIC scores. For PFS, Gompertz, gamma, and log-normal distributions were associated with the lowest AIC and BIC scores.

Table 63: Model diagnostics (sALCL population)

Parameter	ll(model)	df	AIC	BIC
OS (including TSE adjustment)				
Generalised gamma	-272.2	4	552.5	567.5
Weibull	-277.8	3	561.5	572.8
Gompertz	-272.7	3	551.5	562.8
Exponential	-288.9	2	581.8	589.3
Lognormal	-273.8	3	553.6	564.9
Loglogistic	-276.4	3	558.9	570.1
PFS				
Generalised gamma	–389.3	4	786.6	801.6
Weibull	–406.8	3	819.5	830.8
Gompertz	–393.3	3	792.6	803.9
Exponential	–424.5	2	853.0	860.5
Lognormal	–395.0	3	795.9	807.2
Loglogistic	–400.2	3	806.3	817.6

Abbreviations: AIC; Akaike Information Criterion, BIC; Bayesian information criterion; df; degrees of freedom, OS; overall survival, PFS; progression-free survival, TSE, two-stage estimator.

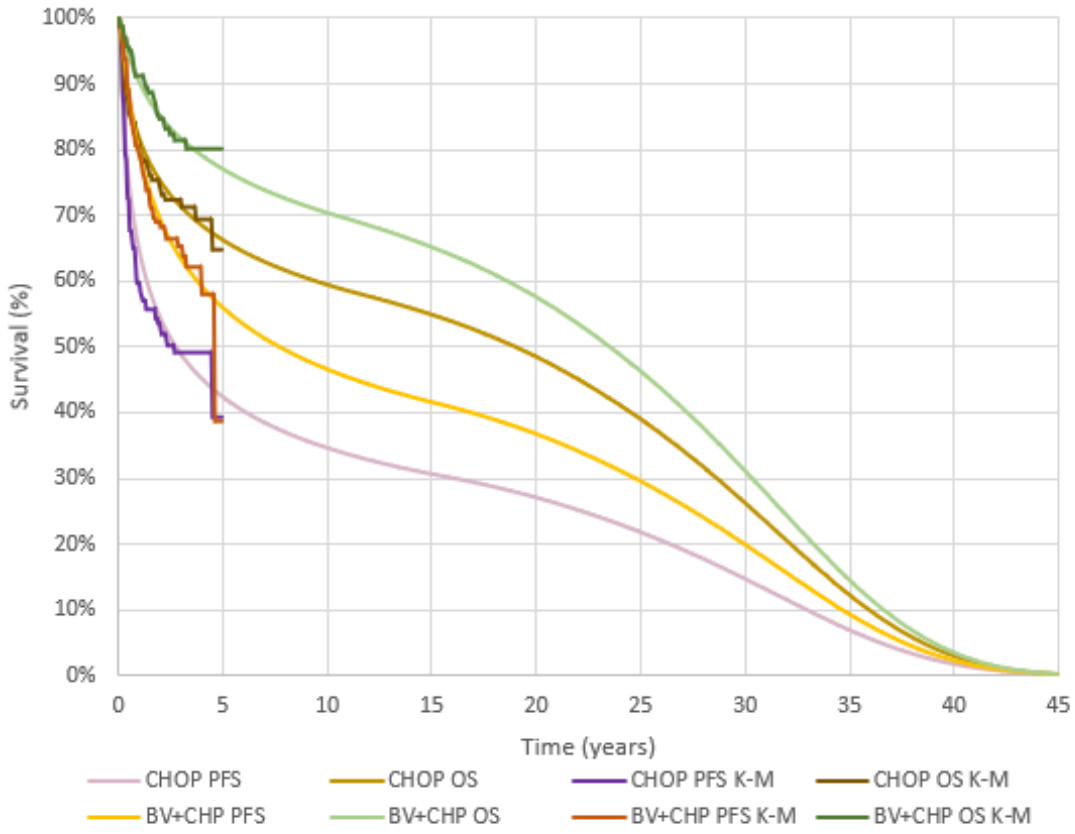
As per the ITT analysis, the generalised gamma distribution was used in the base case for both outcomes, with alternative distributions considered in scenario analysis. **Table 64** presents the gamma distribution coefficients and Figure 36 presents the extrapolated survival curves in the model base-case for the sALCL population, incorporating background mortality.

Table 64: Gamma distribution coefficients (standard errors), sALCL population

Parameter	Coefficient	SE	95% CI	
OS (with TSE)				
BV+CHP (vs CHOP)	1.120	0.432	0.273	1.967
Constant	4.100	0.788	2.556	5.645
Ln(sigma)	1.282	0.115	1.056	1.508
Kappa	-1.233	0.704	-2.612	0.146
PFS				
BV+CHP (vs CHOP)	1.039	0.277	0.496	1.583
Constant	2.332	0.363	1.620	3.043
Ln(sigma)	0.880	0.065	0.752	1.008
Kappa	–1.247	0.343	–1.920	–0.574

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CI, confidence interval; OS, overall survival; PFS, progression free survival; sALCL, systemic anaplastic large cell lymphoma; SE standard error.

Figure 36: Survival curve extrapolations in the sALCL population fitted to the generalised Gamma distribution, including TSE adjustment (adjusted for background mortality)



Abbreviations: A+CHP, brentuximab vedotin, cyclophosphamide, vincristine and prednisone; CHOP, cyclophosphamide, vincristine, prednisone and doxorubicin; K-M, Kaplan Meier; OS, overall survival; PFS, progression-free survival.

B.3.9.1.2 *Time on treatment*

The proportion of patients with sALCL receiving each number of treatment cycles in ECHELON-2 is provided in **Table 65**.

Table 65: Proportion of patients receiving each treatment cycle, sALCL population

Cycle	BV+CHP	CHOP
1	100%	100%
2	98%	97%
3	97%	91%
4	94%	86%
5	93%	81%
6	92%	78%
7	22%	21%
8	21%	21%

Abbreviations: BV+CHP; BV, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxorubicin, prednisone and vincristine; sALCL, systemic anaplastic large cell lymphoma.

B.3.9.1.3 *Consolidation therapy*

B.3.9.1.3.1 Consolidative SCT

In the sALCL population of ECHELON-2, 37 patients (23%) in the BV+CHP arm and 20 patients (13%) in the CHOP arm received consolidative SCT (**Table 66**).

Table 66: Proportion of patients receiving an ASCT in ECHELON-2, sALCL population

Treatment arm	Total number of patients	Patients who received a consolidative ASCT	% consolidative SCT
BV+CHP	162	37	23%
CHOP	154	20	13%

Abbreviations: ASCT, autologous stem cell transplant; BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; sALCL, systemic anaplastic large cell lymphoma; SCT, stem cell transplant.

B.3.9.1.3.2 Consolidative radiotherapy

In the sALCL population of ECHELON-2, consolidative radiotherapy in the sALCL population was received by 9% and 3% of patients in the BV+CHP and CHOP arms, respectively (**Table 67**).

Table 67: Proportion of patients receiving consolidative radiotherapy in ECHELON-2 (sALCL population)

Treatment arm	Total number of patients	Patients who received consolidative radiotherapy	% consolidative radiotherapy	Total cost of consolidative radiotherapy
BV+CHP	162	14	9%	£190.64
CHOP	154	4	3%	£57.30

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; sALCL, systemic anaplastic large cell lymphoma.

B.3.9.1.4 *Subsequent SCT post-progression*

The proportions of patients with R/R sALCL receiving subsequent SCT and the proportions of alloSCT vs ASCT were estimated directly from ECHELON-2 and are presented in **Table 68**.

Table 68: Proportion of progressed patients receiving stem cell transplant in ECHELON-2 (sALCL population)

Treatment arm	Second-line SCT (in patients who progress)	Proportion of second-line ASCT vs alloSCT
BV+CHP	23%	64.1% vs 35.9%†
CHOP	25%	

Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine; sALCL, systemic anaplastic large cell lymphoma; SCT, stem cell transplant.
† Assumed to be the same between arms and as per the ITT population

B.3.9.2 Cost and healthcare resource use

Salvage therapy use of the sALCL population is summarized in **Table 69**.

Table 69: Distribution of salvage therapies (non-BV containing) for UK analysis based on ECHELON-2, sALCL population

	Frequency	Percent
Bendamustine	4	6.25%
CHOP	1	1.56%
DHAP	8	12.5%
ESHAP	7	10.94%
GDP	15	23.44%
Gemcitabine	1	1.56%
ICE	13	20.31%
Radiation	15	23.44%
SMILE	0	0%
Total	**64**	**100%**

Abbreviations: CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; DHAP, dexamethasone, cisplatin, cytarabine; ESHAP, cisplatin, methylprednisolone, etoposide, cytarabine; GDP, gemcitabine, dexamethasone, cisplatin; ICE, etoposide, carboplatin, ifosfamide + mesna, mesna; sALCL, systemic anaplastic large cell lymphoma; SMILE, etoposide, ifosfamide + mesna, mesna, methotrexate, dexamethasone

B.3.9.3 Subgroup analysis results

B.3.9.3.1 *Incremental cost-effectiveness analysis results*

In the subgroup analysis for the sALCL population, BV+CHP is associated with incremental costs of [redacted] and [redacted] incremental QALYs, resulting in an ICER of £18,840 per QALY gained vs CHOP (**Table 70**).

B.3.9.3.2 *Summary of base-case incremental cost-effectiveness analysis results for the sALCL population*

A summary of base-case analysis results for sALCL, using the PAS price for BV (with TSE adjustment), is provided in **Table 70**.

Table 70: Subgroup analysis results, sALCL population

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER incremental (£/QALY)
CHOP	[redacted]	11.26	[redacted]	N/A	N/A	N/A	N/A
BV+CHP	[redacted]	13.12	[redacted]	[redacted]	1.86	[redacted]	£18,840

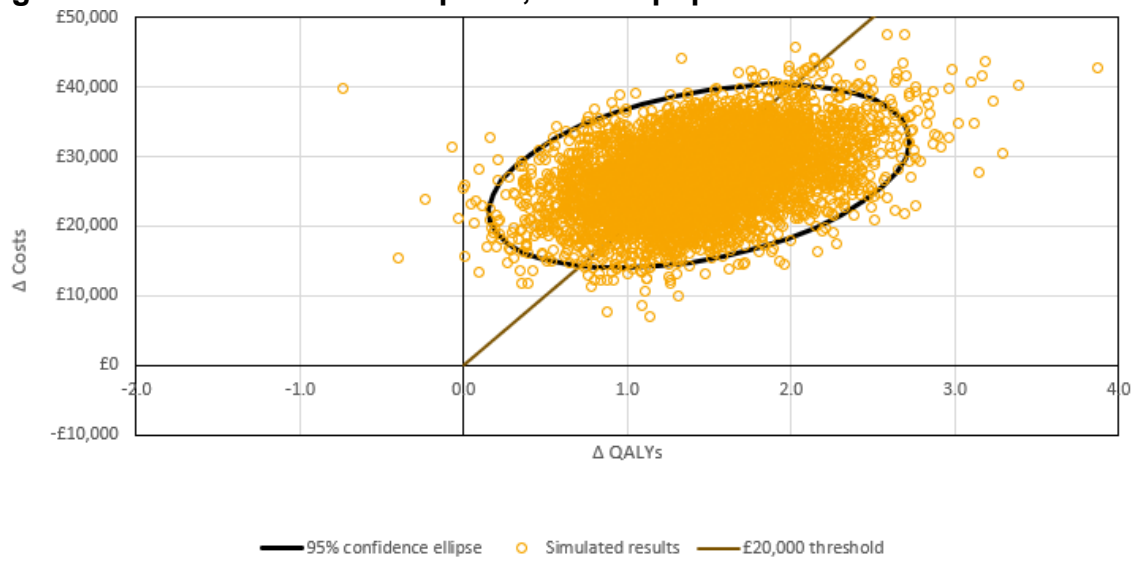
NB, results are not adjusted for re-treatment.

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; sALCL, systemic anaplastic large cell lymphoma; TSE, two-stage estimator.

B.3.9.3.3 *PSA results for the sALCL population*

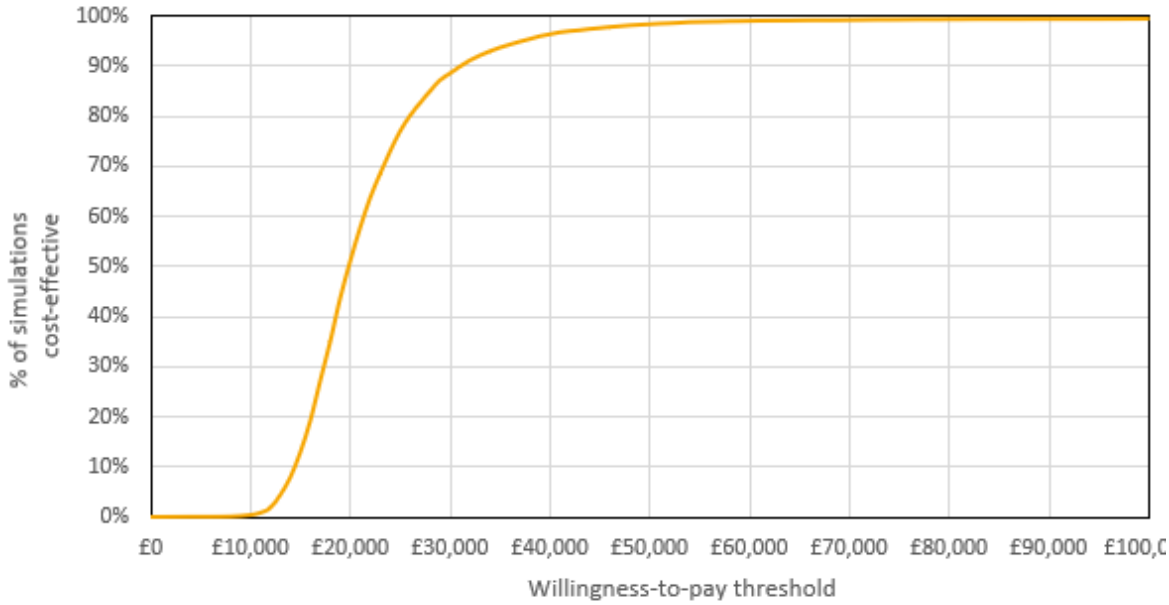
In the sALCL population, average incremental costs over the simulated results were [redacted] and the average incremental QALYs were [redacted] giving a probabilistic ICER of £18,915. This is congruent with deterministic changes in costs of [redacted] and QALYs of [redacted]. The proportion of simulations considered cost-effective at a threshold of £30,000 per QALY was 90%, and 57% at a threshold of £20,000 per QALY. The cost-effectiveness plane and CEAC are reproduced in **Figure 37** and **Figure 38**.

Figure 37: Cost-effectiveness plane, sALCL population



Abbreviations: QALY, quality-adjusted life-years; sALCL, systemic anaplastic large cell lymphoma.

Figure 38: Cost-effectiveness acceptability curve, sALCL population



Abbreviations: sALCL, systemic anaplastic large cell lymphoma.

B.3.9.3.4 *Deterministic sensitivity analysis results for the sALCL population*

Results for the ten most influential parameters are shown in **Table 71**. As in the ITT analysis, the majority of these are those that define the survival extrapolations in OS. A tornado diagram based on the ICER is presented in

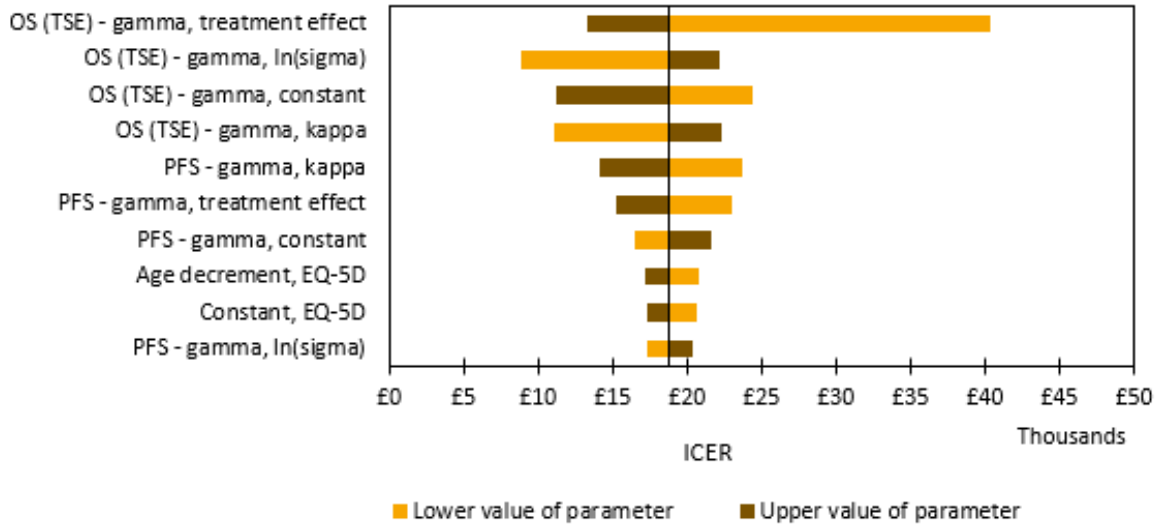
Figure 39, and based on the NMB is presented in **Figure 40**.

Table 71: Univariate sensitivity analysis, sALCL population

Parameter	ICER at lower value of parameter	ICER at upper value of parameter
OS (TSE) - gamma, treatment effect	£40,315	£13,291
OS (TSE) - gamma, ln(sigma)	£8,882	£22,132
OS (TSE) - gamma, constant	£24,329	£11,206
OS (TSE) - gamma, kappa	£11,132	£22,283
PFS - gamma, kappa	£23,652	£14,129
PFS - gamma, treatment effect	£23,050	£15,276
PFS - gamma, constant	£16,473	£21,552
Age decrement, EQ-5D	£20,842	£17,189
Constant, EQ-5D	£20,644	£17,325
PFS - gamma, ln(sigma)	£17,366	£20,322

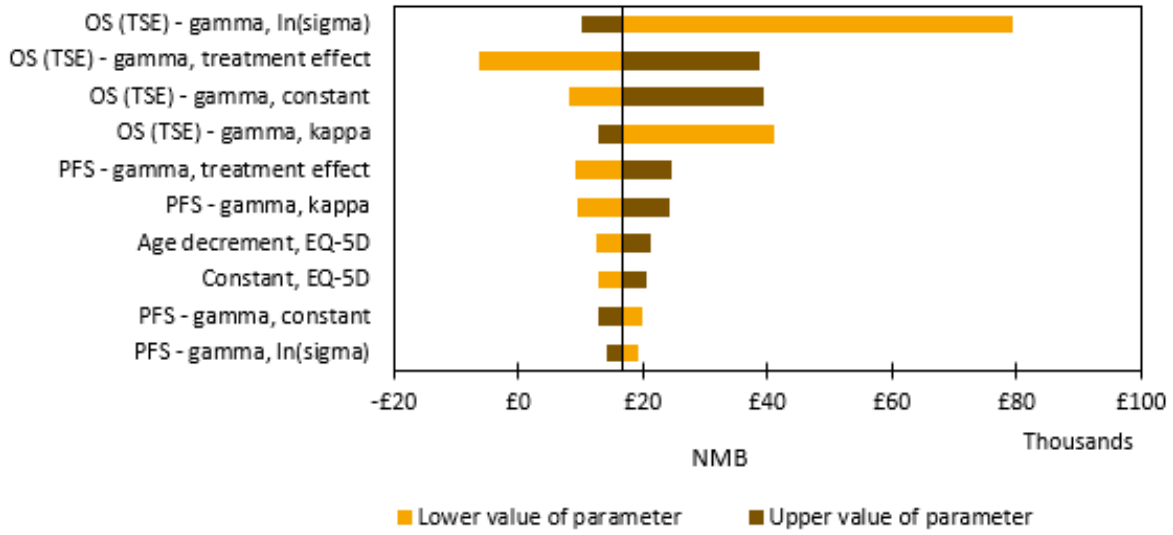
Abbreviations: EQ-5D, EuroQoL-5D; OS, overall survival; PFS, progression-free survival; PSM, partitioned survival model; sALCL, systemic anaplastic large-cell lymphoma.

Figure 39: Tornado diagram on ICER, sALCL population



Abbreviations: EQ-5D, EuroQol – 5 dimensions; ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression-free survival; sALCL, systemic anaplastic large-cell lymphoma; TSE, two-stage estimator.

Figure 40: Tornado diagram on NMB (£30,000 threshold), sALCL population



Abbreviations: EQ-5D, EuroQol – 5 dimensions; NMB, net monetary benefit; OS, overall survival; PFS, progression-free survival; sALCL, systemic anaplastic large-cell lymphoma; TSE, two-stage estimator.

B.3.9.3.5 *Scenario analysis results for the sALCL population*

Scenario analyses were performed in which key structural assumptions were varied (**Table 72**). Beyond the scenarios exploring the time horizon and the discount rate (which were as per the NICE scope in the base case), none of the scenarios resulted in ICERs above £30,000.

Table 72: Scenario analysis, sALCL population

Area of uncertainty	Base-case	Scenario	ICER	% change from base-case
Time horizon	Lifetime (100 years)	5 years	£80,189	326%
		10 years	£40,142	113%
Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	£14,488	-23%
		6% for costs, 1.5% for outcomes	£14,724	-22%
Treatment switching scenario	TSE, no re-censoring	TSE, re-censoring	£17,632	-6%
		No TSE	£22,954	22%
Adverse event disutility	–0.029	0	£18,830	0%
Multiplier for patients in long term remission	1.19 (5% mortality)	1.42 (10% mortality)	£20,200	3%
Distributions for OS and PFS	Gamma	Gompertz	£18,390	-6%
		Loglogistic	£13,051	-33%
		Lognormal	£13,678	-30%

Area of uncertainty	Base-case	Scenario	ICER	% change from base-case
		Weibull	£10,957	-44%
HRQoL approach	Progressed disutility	Time to death approach	£19,414	3%
Cost of stem cell transplant	TA478 & TA478	TA567	£18,900	0%
		TA577 (alloSCT only)	£18,840	0%
Time on treatment	As per ECHELON-2	ECHELON-2 distribution capped at 6 cycles	£17,197	-9%
		All patients receive 6 cycles	£17,708	-6%
Concomitant medication use	All patients receive concomitant medications	No patients receive concomitant medications	£18,734	-1%

Abbreviations: BV, brentuximab vedotin; IRF, independent review facility; OS, overall survival; PFS, progression-free survival.

B.3.10 Validation

B.3.10.1 Internal validation

Quality control of the electronic model was performed initially by the model developers, and subsequently as part of the NICE PRIMA Express process.[117] This process offers verification of the computerised model and model fit, assessment of model transparency and usability, and identification of errors found in the technical documentation.

During model development, the results of the PartSA approach were compared to those of a multistate model, also estimated using the ECHELON-2 data. Results were highly congruent between approaches, suggesting that alternative model structures would not have led to differences in the results or to the usefulness of the model for decision-making. Predicted outcomes (unadjusted for treatment switching) were also compared with those from ECHELON-2 to ensure internal validity (**Appendix J**).

B.3.10.2 External validation

Historically, the clinical data available in the untreated CD30+ PTCL population are low-quality, largely based on single arm Phase II trials or retrospective analyses and show a wide variation in outcomes. We note that the CHOP group in the ECHELON-2 trial did better than the historical cohorts might suggest, with a median PFS of 20.8 months and median OS not reached.[23] Possible explanations for these outcomes may be potentially attributed to patients being in a clinical trial and the larger proportion of patients with sALCL, albeit the inclusion criteria did not permit patients with ALK+ sALCL with a favourable prognostic IPI score of 0-1.[23] However, due to the poor quality of historical data, validation of predicted outcomes from the

economic model with the literature is difficult. ECHELON-2 is a Phase III, randomised controlled trial providing outcomes associated with CHOP and BV+CHP with a median follow-up of 36.2 months.[23] These data represent the best data available in this setting – as echoed by the clinical feedback we have received. For this reason, we have validated the outcomes within the model through extensive clinician feedback and a comparison with a US study of cost-effectiveness.

Clinical feedback was sought at two advisory boards: (1) February 2019 and (2) June 2019. The February advisory board discussed the unmet need, the disease and current treatment pathway and the resource use associated with current treatment. The June advisory board focused on the validity of extrapolations, excess mortality in long-term survivors, adverse events and HRQoL. The feedback from these meetings are embedded in the relevant section of this document. Importantly, the clinicians unanimously agreed that the gamma parametric curves best reflected the PFS and OS outcomes seen in clinical practice.

These data have been supplemented by further clinical consultations. [48,59]Clinicians were asked to provide further information on the prognostic factors to be used in the treatment switching analysis (**Appendix N**), further detail on the excess mortality for long-term survivors and further detail on the resource use associated with adverse events.

The systematic review reported in Section B.3.1 identified one other study considering the cost-effectiveness of front-line BV+CHP in patients with CD30+ PTCL – Feldman et al (2019). This study was based on an American perspective and also used the ECHELON-2 trial data to inform the model inputs. The model predicted BV+CHP extended undiscounted PFS by 2.92 years and OS by 3.38 years over CHOP. The model presented in this dossier predicts an extension of 2.16 years and 2.56 years, respectively. The US study further reports that BV+CHP was associated with 1.79 QALYs gained whereas the incremental QALYs reported in our base case are [redacted]. Therefore, our model provides conservative estimates of the treatment effect of BV+CHP relative to the Feldman et al (2019) study. As only an abstract is available, it is difficult to explain what is driving this difference.

Where possible, inputs were validated using the R/R sALCL NICE submission (TA478). Inputs related to HRQoL and resource use were directly informed by TA478 and TA577.

B.3.11 Interpretation and conclusions of economic evidence

B.3.11.1 Main findings

This cost-effectiveness analysis has found that in the ITT population (with TSE adjustment), including the PAS, BV+CHP is associated with incremental costs of

[redacted], an incremental LY gain of 1.55 years, and an incremental gain of [redacted] QALYs, compared with CHOP. The resulting ICER is £24,901 per QALY gained. At year 5, 70% and 62% of patients were alive in the BV+CHP and CHOP arms of the model, respectively.

The large increase in OS is predominantly a direct consequence of the greater effects of BV+CHP (vs CHOP). Although, there was also a modest difference in the proportion of patients receiving BV+CHP who received consolidative SCT (during ECHELON-2, 50 patients (22%) in the BV+CHP arm versus 39 patients (17%) in the CHOP arm), a pre-specified analysis censoring for consolidation found no impact on the benefit observed in PFS (consistent HR with that of the primary end-point)). These effects are reflected in the statistically significant OS benefit observed in ECHELON-2 (unadjusted HR 0.66 [95% CI: 0.46; 0.95]), achieved despite the relatively high use of BV-containing regimens post-progression in the CHOP arm (during ECHELON-2, 23 patients (10%) in the BV+CHP arm and 49 patients (22%) in the CHOP arm received BV-containing subsequent therapy).

Results were most sensitive to the treatment effect on OS. In the ITT population, the probabilistic ICER was £25,741, which is congruent with the deterministic ICER of £24,901. The proportion of simulations considered cost-effective at ICER thresholds of £20,000 and £30,000 was 64% and 22%, respectively.

In the sALCL population, BV+CHP is associated with incremental costs of [redacted] an incremental LY gain of 1.86 years, and an incremental gain of [redacted] QALYs, compared with CHOP. The resulting ICER is £18,840 per QALY gained, and the proportion of simulations considered cost-effective at ICER thresholds of £20,000 and £30,000 was 57% and 90%, respectively.

B.3.11.2 Strengths and limitations

The main strengths of the analysis are derived from the robustness and quality of the clinical evidence from the ECHELON-2 trial. ECHELON-2 is a double-blind, RCT that provides data for 452 patients with median follow-up of 36.2 months and compares BV+CHP with the current standard of care in UK clinical practice, CHOP. As such, analysis and extrapolation are based on a large and relatively mature dataset. The collection of EQ-5D data beyond progression in ECHELON-2 also permits more accurate estimation of the impact of the disease on HRQoL.

Outcomes data required extrapolation beyond the follow-up period of ECHELON-2, a common source of uncertainty in many NICE appraisals of oncology technologies. These extrapolations were performed as per DSU guidance and were validated by UK experts (12 clinical experts and four UK health economists[47,59]) with detailed knowledge of the disease. Scenario analysis suggested this was the most conservative distribution amongst plausible alternatives.

For regulatory reasons, ECHELON-2 recruited a higher proportion of patients with sALCL than is generally observed in clinical practice. While this might be regarded as potentially limiting the generalisability of the results, it is notable that the PFS and OS benefits seen with BV+CHP were generally consistent across all histological subtypes, with overlapping CIs. In addition, BV+CHP was shown to be cost-effective vs CHOP for the whole ITT population from ECHELON-2 (i.e. all patients with previously untreated CD-30+ PTCL).

Some patients in ECHELON-2 were re-treated with BV following progression from BV+CHP, whilst others received post-progression BV without having a diagnosis of sALCL. In the UK, BV is not reimbursed in these scenarios, and clinical experts have confirmed that the use of BV in these situations would not reflect clinical practice. To overcome this limitation, the base case included a statistical adjustment to remove the effect (and cost) of subsequent BV use that is not reimbursed in the UK.

The PartSA model structure was selected for consistency with previous NICE appraisals of other BV indications and for ease of interpretation. PartSAs are often used because the endpoints and survival curves reported (e.g. PFS and OS) can be directly used to model state membership. The main limitation of this approach is the lack of dependence between endpoints, potentially reducing the validity of extrapolations and sensitivity analyses. However, early analyses based on a multi-state model structure suggested that results were congruent between these two different modelling approaches. Therefore, model structure was not regarded as a significant determinant of cost-effectiveness.

B.3.11.3 Conclusion

In line with the improved OS and PFS seen with BV+CHP vs CHOP in the ECHELON-2 RCT, this cost-effectiveness analysis demonstrates that BV+CHP is associated with an estimated incremental QALY gain of [redacted] vs CHOP. The incremental costs of [redacted] mean that the ICER for BV+CHP is £24,901/QALY vs CHOP. This is less than the conventional ICER threshold used by NICE and, given the robustness of the clinical data on which this is based, we consider that BV+CHP is a cost-effective front-line treatment option for adults with previously untreated CD-30+ PTCL. As such, we believe it should receive a positive NICE recommendation for this indication.

B.4 References

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B.5 Appendices

Appendix C: Summary of product characteristics (SmPC) and European public assessment report (EPAR)

Appendix D: Identification, selection and synthesis of clinical evidence

Appendix E: Subgroup analysis

Appendix F: Adverse reactions

Appendix G: Published cost-effectiveness studies

Appendix H: Health-related quality-of-life studies

Appendix I: Cost and healthcare resource identification, measurement and valuation

Appendix J: Clinical outcomes and disaggregated results from the model

Appendix K: Checklist of confidential information

Appendix L: Proportional hazards

Appendix M: HRQoL data

Appendix N: Adjustment for subsequent use of BV

Appendix O: Cost data

Appendix P: Results of analyses using BV list price

Appendix Q: Derivation of subsequent therapy use

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

Clarification questions

17 January 2020

File name	Version	Contains confidential information	Date
ID1586 brentuximab clarification letter to PM	1.0	No	03/01/2020
ID1586 brentuximab clarification letter_Takeda response_ACIC	1.0	Yes	17/01/2020

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Section A: Clarification on effectiveness data

Information retrieval

A1. Priority question: The Cochrane Library strategy presented in Appendix D, line 24 appears to be combining line 23 (all interventions) with line 15 (MeSH descriptor [Prednisolone]).

Please clarify whether this is a reporting error. If this is not a reporting error, please re-run this search with the correct line combinations (line 23 and line 16) and re-screen the results in order to ensure nothing has been missed.

Response: Table in Appendix D Section 1.6.3 “Cochrane search: Wiley Interscience. 29th August 2019” contains a reporting error. We apologise for any confusion it may have caused. Line 23 should be combined with line 16 instead of line 15 as per the original submission. As this was only a typo, it has neither an

impact on the total number of studies included from the Cochrane Library, nor the rest of the report. We apologise for this typo and have provided a corrected table of the Cochrane search strategy below.

Appendix D Section 6.1.3: Cochrane search: Wiley Interscience. 29th August 2019

S. No	Search terms	Results
1	MeSH descriptor: [Lymphoma, T-Cell, Peripheral] explode all trees	32
2	MeSH descriptor: [Lymphoma, T-Cell] explode all trees	170
3	MeSH descriptor: [Precursor Cell Lymphoblastic Leukemia-Lymphoma] explode all trees	1,030
4	MeSH descriptor: [Lymphoma, Large-Cell, Anaplastic] explode all trees	23
5	(("t cell*" OR "t-cell*") NEAR/4 (lymph* OR leuk*)):ab,ti,kw	1,175
6	((angioimmunoblas* OR lymphoblas* OR enteropath* OR hepatosplen* OR peripher* OR anaplas* OR alk*) NEAR/4 ("t-cell*" OR "t cell*" OR lymph*)):ab,ti,kw	5,520
7	aild:ab,ti,kw OR "ail tcl":ab,ti,kw OR "ail-tcl":ab,ti,kw OR aitl:ab,ti,kw OR "angioimmunoblastic lymphadenopathy with dysproteinemia":ab,ti,kw OR "immunoblastic lymphadenopathy":ab,ti,kw OR "lymphogranulomatosis x":ab,ti,kw OR alcl:ab,ti,kw OR salcl:ab,ti,kw OR "s alcl":ab,ti,kw OR "s-alcl":ab,ti,kw OR lhalcl:ab,ti,kw OR "lh alcl":ab,ti,kw OR "lh-alcl":ab,ti,kw OR hlalcl:ab,ti,kw OR "hl alcl":ab,ti,kw OR "hl-alcl":ab,ti,kw OR alkalcl:ab,ti,kw OR "alk alcl":ab,ti,kw OR "alk-alcl":ab,ti,kw	144
8	atll:ab,ti,kw OR “t-all”:ab,ti,kw OR “t-cell all”:ab,ti,kw OR “t cell all”:ab,ti,kw OR htlv*:ab,ti,kw OR “t-lymph* leuk*”:ab,ti,kw OR “t lymph* leuk*”:ab,ti,kw	408
9	eatl:ab,ti,kw OR ettl:ab,ti,kw OR "intestinal t-cell*":ab,ti,kw OR "intestinal t cell*":ab,ti,kw OR hstcl:ab,ti,kw OR ptcl*:ab,ti,kw	158
10	MeSH descriptor: [Cyclophosphamide] explode all trees	5,079
11	MeSH descriptor: [Vincristine] explode all trees	2,210
12	MeSH descriptor: [Prednisone] explode all trees	3,679
13	MeSH descriptor: [Doxorubicin] explode all trees	4,427
14	MeSH descriptor: [Etoposide] explode all trees	1,629
15	MeSH descriptor: [Prednisolone] explode all trees	4,523
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	6,452
17	#10 AND #11 AND (#12 OR #15) AND #13	743
18	#10 AND #11 AND (#12 OR #15) AND #13 AND #14	214
19	(alkyroxan OR “b 518” OR “b 518 asta” OR b518 OR “b518 asta” OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR “cyclo-cell” OR cycloblastin OR cycloblastine OR “cyclofos amide” OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamide* OR cyclophosphan OR cyclophosphane OR cyclostin OR “cyclostin n” OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR “endocyclo phosphate” OR endoxan OR “endoxan asta” OR “endoxan-asta” OR endoxana OR “endoxon-asta” OR enduxan OR genoxal OR ledoxan OR ledoxina OR “lyophilized cytoxan” OR mitoxan OR neosan OR neosar OR noristan OR “nsc 26271” OR “nsc 2671” OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid) AND (“l 37231” OR l37231 OR “vin cristine” OR vincristine* OR oncovin* OR vincasar* OR leurocristin* OR alcrist OR biocrist OR biocrystin OR cellcristin OR citomid OR crivosin OR	428

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20	(alkyroxan OR “b 518” OR “b 518 asta” OR b518 OR “b518 asta” OR carloxan OR ciclofosfamida OR ciclolen OR cicloxal OR clafen OR “cyclo-cell” OR cycloblastin OR cycloblastine OR “cyclofos amide” OR cyclofosfamid OR cyclofosfamide OR cyclophar OR cyclophosphamide* OR cyclophosphan OR cyclophosphane OR cyclostin OR “cyclostin n” OR cycloxan OR cyphos OR cytophosphan OR cytophosphane OR cytoxan OR “endocyclo phosphate” OR endoxan OR “endoxan asta” OR “endoxan-asta” OR endoxana OR “endoxon-asta” OR enduxan OR genoxal OR ledoxan OR ledoxina OR “lyophilized cytoxan” OR mitoxan OR neosan OR neosar OR noristan OR “nsc 26271” OR “nsc 2671” OR procytox OR procytoxide OR semdoxan OR sendoxan OR syklofosfamid) AND (“l 37231” OR l37231 OR “vin cristine” OR vincristine* OR oncovin* OR vincasar* OR leurocristin* OR alcrist OR biocrist OR biocrystin OR cellcristin OR citomid OR crivosin OR cytomid OR farmistin OR fauldvincri OR krebin OR kyocristine OR nevexitin OR onkocristin OR pericristine OR pharmacristine OR tecnocris OR vincasar OR vinces OR vincosid OR vincran OR vincrex OR vincrifil OR vincrin OR vincrisin OR vincrisol OR vincristin OR vincristina OR vincristinesulfaat OR vincristinsulfat OR vincristinum OR vincrisul OR vinracin OR vinracine OR vinstin OR vintec) AND (ancortone OR “apo-prednisone” OR biocortone OR colisone OR cortan OR cortidelt OR cortiprex OR cutason OR dacorten OR “de cortisyl” OR decortancyl OR decortin OR decortine OR decortisyl OR dehydrocortisone OR dekortin OR delitisone OR “dellacort a” OR “delta cortelan” OR “delta cortisone” OR “delta dome” OR “delta e” OR “delta prenovis” OR “delta-dome” OR deltacorten OR deltacortene OR deltacortisone OR deltacortone OR deltasone OR deltison OR deltisona OR deltra OR “di adreson” OR “di-adreson” OR diadreson OR drazone OR encorton OR encortone OR enkorton OR fernisone OR hostacortin OR insone OR “liquid pred” OR lodotra OR “me-korti” OR meprison OR “metacortandracin” OR meticorten OR meticortine OR nisona OR “nsc 10023” OR nsc10023 OR orasone OR orisane OR panafcort OR paracort OR pehacort OR precort OR precortal OR “prednicen-m” OR prednicorm OR prednicot OR prednidib OR prednison OR “prednisone alcohol” OR “prednisone intensol” OR prednisone* OR prednitone OR pronison OR pronisone OR pronizone OR pulmison OR rayos OR rectodelt OR servisone OR steerometz OR sterapred OR ultracorten OR urtilone OR winpred OR adelcort OR antisolon OR antisolone OR aprednislon OR aprednislone OR benisolon OR benisolone OR berisolon OR berisolone OR caberdelta OR capsoid OR “co hydeltra” OR codelcortone OR compresolon OR cortadeltona OR cortadeltone OR cortalone OR cortelinter OR cortisolone OR cotolone OR dacortin OR dacrotin OR decaprednil OR “decortin h” OR decortril OR “dehydro cortex” OR “dehydro hydrocortison” OR “dehydro hydrocortisone” OR dehydrocortex OR dehydrocortisol OR dehydrocortisole OR dehydrohydrocortison OR dehydrohydrocortisone OR delcortol OR “delta 1 hydrocortisone” OR “delta cortef” OR “delta cortril” OR “delta ef cortelan” OR “delta f” OR “delta hycortol” OR “delta hydrocortison” OR “delta hydrocortisone” OR “delta ophticor” OR “delta stab” OR “delta-cortef” OR “delta1 dehydrocortisol” OR deltacortef OR deltacortenolo OR deltacortil OR deltacortoil OR deltacortril OR deltaderm OR deltaglycortril OR deltahycortol OR deltahydrocortison OR deltahydrocortisone OR deltaophticor OR deltasolone OR deltastab OR deltidrosol OR deltisilone OR deltisolon OR deltisolone OR deltolasson OR deltolassone OR deltosona OR deltosone OR “depo-predate” OR dermosolon OR dhasolone OR “di adreson f” OR “di adresone f” OR “di-adreson-f” OR “diadreson f” OR “diadresone f” OR dicortol OR domucortone OR	1,454

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21	brentuximab* OR adcetris OR 'sgn 35' OR 'sgn-35' OR sgn35	251
22	chop*:ab,ti,kw OR choep*:ab,ti,kw OR “chop e*”:ab,ti,kw OR “chop-e*”:ab,ti,kw OR “e chop*”:ab,ti,kw OR “e-chop*”:ab,ti,kw OR echop*:ab,ti,kw OR epoch*:ab,ti,kw OR “e-poch”:ab,ti,kw OR “e poch”:ab,ti,kw	2,797
23	#17 OR #18 OR #19 OR #20 OR #21 OR #22	3,790
24	#23 AND #16	346
25	#24 in Trials	342
26	#24 in Cochrane Reviews	4

A2. Please clarify how adverse reactions were identified. If the searches reported in Appendix D were used, please confirm if results were screened for adverse events. If additional searches were used, please provide full details.

Response: In the systematic literature review carried out by Takeda, and described in Appendix D of the submission, adverse events (AEs) were included as relevant outcomes in the PICOS criteria for literature screening. The inclusion and exclusion criteria outlined in Table 1 of Appendix D lists *Incidence of adverse events* as an inclusion criterion for *Outcomes;* all studies were screened for AEs.

Studies reporting any of the following AEs were included the report provided the remaining criteria were met: any adverse event, grade 3-4 adverse events, any serious adverse event, any serious adverse event and/or any specific adverse events (Anaemia, Alanine Aminotransferase (ALT) increase, Aspartate Aminotransferase (AST) increase, Arthralgia, Any CV events, Creatinine elevation, Diarrhoea, Dyspnoea, Febrile neutropenia, Fever/Pyrexia, Gastrointestinal disorders, Haemorrhage Hyperkalemia, Infusion reaction, Leucocytopenia, Mucositis, Nausea, Neutropenia, Peripheral sensory neuropathy/Neuropathy, Pyrexia/Fever, Septic shock, Thrombocytopenia, Vomiting).

Searches in Appendix D were not used to inform adverse reactions in the economic evaluation. Grade 3 and 4 treatment-emergent AEs occurring in ≥5% of patients in ECHELON-2, and Grade 1–2 diarrhoea, were included in the economic model (Table 36 of the CS) – these were obtained directly from the patient level data. Response to question B4 provides the further details on how AEs were informed and applied in the economic analysis.

A3. Priority question: Table 1 of Appendix D describes the outcomes to be a *"tentative list, not exhaustive"*. Please provide the full list of outcomes.

Response: The PICOS criteria listed in the Table 1 of Appendix D contains the main headings for the outcomes of interest. As requested, the full list of extracted outcomes is provided below:

- Response rates (overall response rate [ORR], complete Response [CR], partial response [PR], stable disease [SD], progressive disease [PD], no response)
- Relapse rate
- Overall survival, progression-free survival, event free survival, disease free survival, overall death/mortality, time to response, time to progression, duration of response
- Health-related quality of life (EQ-5D Index score, EQ-5D VAS, SF-36 PCS and MCS score, Functional Assessment of Cancer Treatment-General scale)
- Incidence of adverse events (any adverse event, grade 3-4, any serious adverse event, any serious adverse event, any specific AEs: Anaemia, Alanine Aminotransferase (ALT) increase, Aspartate Aminotransferase (AST) increase, Arthralgia, Any CV events, Creatinine elevation, Diarrhoea, Dyspnoea, Febrile

neutropenia, Fever/Pyrexia, Gastrointestinal disorders, Haemorrhage Hyperkalemia, Infusion reaction, Leucocytopenia, Mucositis, Nausea, Neutropenia, Peripheral sensory neuropathy/Neuropathy, Pyrexia/Fever, Septic shock, Thrombocytopenia, Vomiting)

- Study/treatment discontinuation (all withdrawals/treatment discontinuations, withdrawals/treatment discontinuations due to adverse events, withdrawals/treatment discontinuations due to drug related adverse events)

Studies were included if any of the listed outcomes were reported and the publication also satisfied the other criteria listed in the PICOS for population, intervention and study design.

A4. There is a discrepancy between the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram (Figure 1 of Appendix D) and the preceding text, e.g. 4,040 and 4,035 records, respectively, excluded, and 354 and 359 full-text articles assessed for eligibility, respectively.

Please clarify this discrepancy and provide a revised version of the text as well as the PRISMA diagram.

Response: We apologise for what is a reporting error in the preceding text in Appendix D. The correct figures are 4,040 potentially relevant papers excluded at primary screening, and 354 potentially relevant articles assessed in full for further evaluation, as reported in the PRISMA diagram. Corrected text for section 4.1 of Appendix D has been provided below, however the PRISMA diagram provided in the original submission is accurate and does not require revisions. It has been included in this response for completeness.

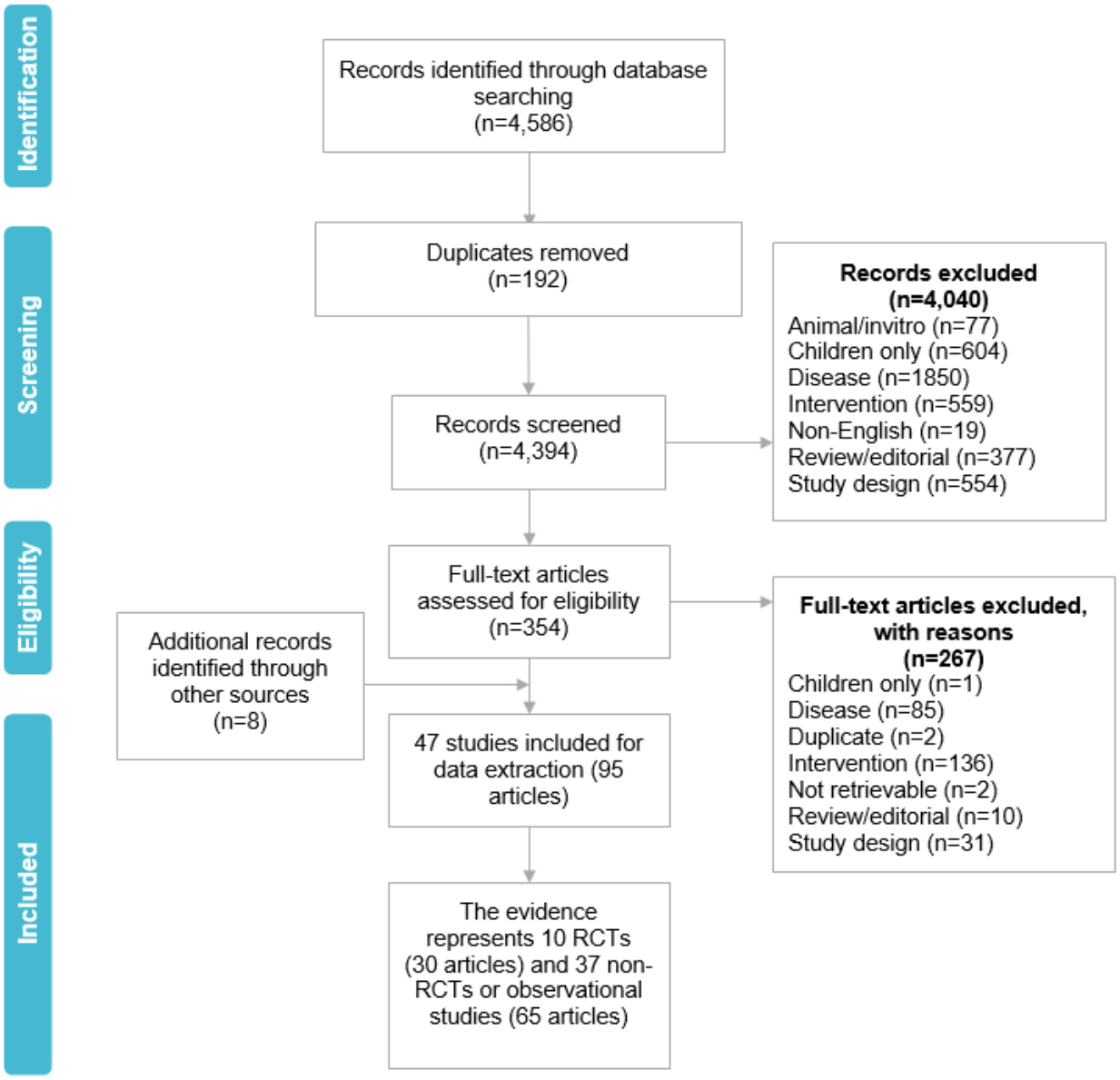
4.1. Studies identified from literature

Systematic database searches were conducted on 29 August 2019. A total of 4,586 potentially relevant papers or abstracts were identified in this review. Studies were screened based on the information reported in their titles and/or abstracts. Of these, 192 were removed as duplicates, and 4,040 were excluded at the primary screening stage as they were not relevant to the research question.

A total of 354 potentially relevant articles included at title/abstract screening stage and were assessed in full for further evaluation. Of these, 267 were excluded, and 87 were included. Additionally, five records from the conference search, two records from bibliography and one from clinicaltrials.gov were included. Therefore, a total of 95 articles were included in this review. Due to the publication of multiple articles for the same study, relevant data were then extracted from 10 RCTs reported in 30 publications and 37 non-RCTs from 65 publications. The list of included and excluded studies at secondary screening stage is presented in below.

Figure 1 presents the PRISMA flow diagram of studies identified for clinical review.

Figure 1: PRISMA diagram



Key: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.
Note: *, studies in Chinese language (two studies in RCT and three studies in non-RCT)"

Included studies

A5. Priority question: Please provide the full clinical study reports (CSRs) of all trials presented in the company submission (CS), especially ECHELON-2,

Fanale et al. 2014, and Horwitz et al. 2014. These should include all sections as well as appendices, e.g. (but not limited to) the full results for adverse events.

Response: As requested by the ERG, the full clinical study report (CSR) of the ECHELON-2 trial was provided to NICE and the ERG on 10 December 2019. Therefore, we believe the request regarding the ECHELON-2 trial has already been fulfilled.

The CSRs of the Fanale et al. 2014 and Horwitz et al. 2014 studies have been provided as Appendix A and B of this document, respectively. Due to file size, only the main bodies of the CSRs (i.e., not appendices) are provided. Individual appendices can be provided in response to an ERG request. **Please note that all CSRs are commercial in confidence and should be redacted from all publicly released documents.**

A6. Priority question: Several definitions of progression-free survival (PFS) were used, e.g. Table 9 of the CS and section 11.4.1.3 (sensitivity analyses of PFS) of the abbreviated CSR (sent after submission of the CS in response to a request by the National Institute for Health and Care Excellence (NICE)).

Please present results for all of these definitions of PFS.

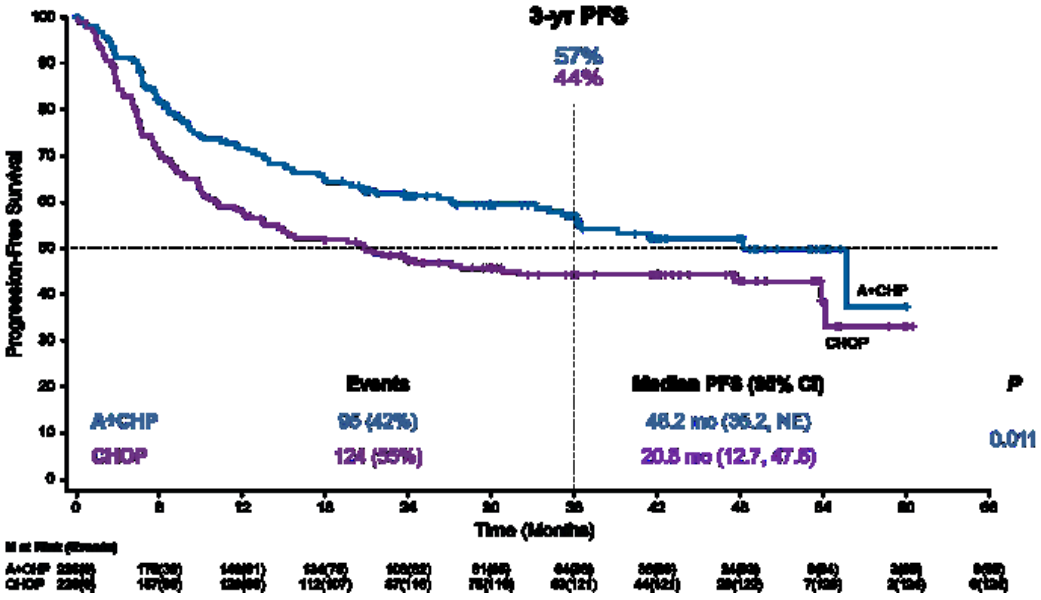
Response: Within the ECHELON-2 study the primary end point was progression-free survival (PFS) (according to blinded independent central review [BICR] referred to as independent review facility [IRF] throughout).
PFS per BICR was defined as:

- the time from the date of randomisation to the date of first documentation of relapse or progressive disease (PD),
- death due to any cause,
- or receipt of subsequent systemic chemotherapy to treat residual or progressive PTCL as determined by the investigator, whichever occurred first.

In the absence of progressive disease, receipt of radiotherapy to consolidate response to initial treatment, chemotherapy for the purpose of mobilising haemopoietic stem cells, or consolidative autologous or allogeneic stem cell transplantation were not considered events.

The receipt of subsequent systemic chemotherapy to treat residual or progressive PTCL as determined by the investigator would not have introduced any element of bias to the study results as this was a double-blind double-dummy trial.
The results for the primary endpoint of PFS per IRF are presented below. Patients in the BV+CHP arm had a 29% reduction in the risk of a PFS event compared with subjects treated with CHOP (stratified HR 0.71 [95% CI: 0.54, 0.93], P=0.011)
Furthermore, a pre-specified analysis of PFS by investigator assessment (IA) showed results similar to PFS by IRF, with a high (97%) concordance between the two PFS assessments.

PFS per IRF (ITT analysis set)



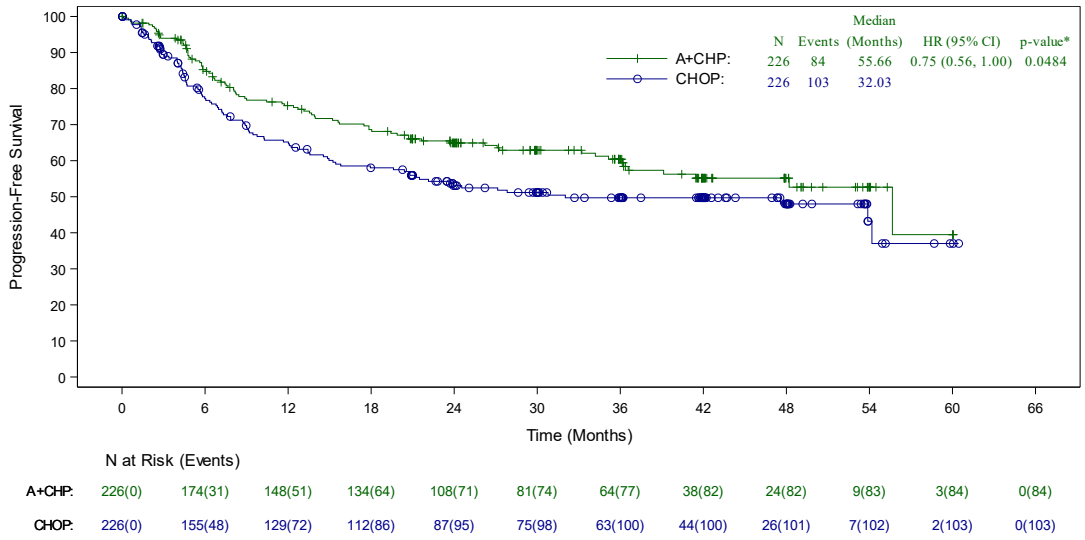
A separate sensitivity analysis was conducted to censor the receipt of subsequent chemotherapy to treat residual or progressive PTCL as determined by the investigator, rather than consider it an event. This would therefore capture progression as:

- the time from the date of randomisation to the date of first documentation of relapse or progressive disease (PD),
- death due to any cause

By this analysis, a similar result was seen to the primary endpoint whereby PFS was significantly improved for subjects receiving A(BV)+CHP versus those receiving CHOP (stratified HR 0.75 [95% CI: 0.56, 1.00], P=0.0484). The improvement

between the arms equates to a 25% reduction in the risk of a PFS event for A(BV)+CHP versus CHOP.

PFS per IRF Using Alternative Censoring Rules (Sensitivity Analysis 3)



A7. Priority question: According to section 9.3.1 of the abbreviated CSR (sent after submission of the CS in response to a request by NICE), in ECHELON-2 patients with anaplastic lymphoma kinase-positive (ALK+) systemic anaplastic large cell lymphoma (sALCL) and an International Prognostic Index (IPI) score lower than 2 were excluded. However, these patients are included in the scope for this submission. It has been shown (as described in terms of 5-year overall survival [OS] rates in section B.1.3.1 of the CS) that CHOP (cyclophosphamide, hydroxydaunomycin [also known as doxorubicin], Oncovin® [vincristine], prednisolone/prednisone) is more effective for patients with lower IPI (e.g. IPI score of 2) than with higher IPI (e.g. IPI score of 4 to 5).

a. **Based on the evidence provided, please confirm if no reliable conclusions can be made regarding the clinical and cost-effectiveness of treatment with brentuximab vedotin (BV) for patients with ALK+ sALCL and an IPI < 2.**

Response: As discussed in Section B.2.3.1 of Document B and commented on by the ERG, an inclusion criterion for ECHELON-2 was that patients with ALK+ sALCL

must have had an IPI score of 2 or higher. The ECHELON-2 trial does not therefore provide evidence for ALK+ sALCL patients with IPI <2. However, because IPI score was a stratification factor in the ECHELON-2 trial, efficacy data is available for the ITT population with a low IPI score. The Forest plot of PFS for the ITT population (Figure 12 in Section B.2.6.1 Document B) demonstrates a directional increase in efficacy for patients with a lower IPI score. In the ITT population, patients with an IPI score of 0-1 had the lowest hazard ratio (HR= 0.53 95% CI 0.29, 0.97), followed by patients with an IPI score of 2-3 (HR=0.71, 95% CI 0.50,1.00) and finally high IPI score patients of 4-5 (HR=1.03, 95% CI 0.55, 1.92). The same trend is observed for overall survival. Based on the trend observed for the ITT population, we anticipate that the efficacy observed in higher IPI score ALK+ sALCL patients would also translate to low IPI score ALK+ sALCL patients.

UK clinical experts in T-cell lymphoma were consulted on this question. These experts stated that there is no biological reason why there should be a difference in the relative efficacy of BV+CHP vs. CHOP for patients with a lower or higher IPI score, both for ALK+ sALCL and for other PTCL subtypes; IPI scores are prognostic indicators however the underlying biology of the disease is the same. Clinical experts expect that, at a minimum, the hazard ratio observed for BV+CHP compared to CHOP in patients with ALK+ sALCL and an IPI score ≥2 would be maintained in patients with ALK+ sALCL and an IPI score <2. Indeed, these experts noted that the HR may actually be improved based on the trend towards a better HR observed in patients with low IPI scores in the ITT population of ECHELON-2. The clinical experts stated that there is unanimous support across the UK clinical community for the use of BV+CHP in patients with ALK+ sALCL, because these patients are younger, are treated with curative intent and stand to benefit significantly. The clinical experts were clear that they would want to use BV+CHP in the frontline setting for all patients with sALCL, irrespective of ALK status and IPI score, and that any restriction would unfairly disadvantage these patients.

b. Regarding the clinical and cost-effectiveness of treatment with BV for patients with ALK+ sALCL and an IPI <2 based on the evidence provided, please confirm if it would be very likely that the clinical and

cost-effectiveness of treatment with BV relative to CHOP would be greatly overestimated.

Response: Arising from our response to question A7a, we disagree with the suggestion that “it would be very likely that the clinical and cost-effectiveness of treatment with BV relative to CHOP would be greatly overestimated” for patients with ALK+ sALCL and an IPI score <2. There is simply no evidence to support such a statement suggestion. strong conclusion made by the ERG as it is not supported by the evidence; In fact, as discussed in our response to question A7a, to the contrary a trend towards improved efficacy in patients with lower IPI scores was observed for the ITT population in in ECHELON-2, and clinical experts expect that the efficacy would be consistent if not improved in patients with ALK+ sALCL and IPI <2. in these lower risk patients. Hence, it is possible that the cost-effectiveness of BV+CHP could actually be underestimated if the trend for improved efficacy at lower IPI scores observed in the ITT population of ECHELON-2 is maintained in the ALK+ sALCL population.

As discussed above, although the ECHELON-2 trial does not provide direct evidence for patients with ALK+ sALCL and a low IPI (0,1), patients with a low IPI across other subtypes of PTCL had a better response to BV+CHP and the lower hazard ratio compared to those with a higher IPI score. Although this trend is directional, it provides support of efficacy of BV+CHP in previously untreated CD30+ PTCL patients with a low IPI.

In relation to the cost-effectiveness question, we would also note that the The standard of care for ALK+ sALCL patients with a low IPI <2 is the same as for the rest of the population in the scope (i.e. currently six cycles of CHOP, but with the potential to become six cycles of or BV+CHP). Therefore, the costs would be consistent with the ITT population of ECHELON-2.

A8. Priority question: Section 3.3. of Appendix D states that basic study selection criteria were applied, defined as *"population, intervention and study design"*. However, according to Table 1 of Appendix D, studies were excluded based on *"outcomes not relevant to the review"*.

Please provide a full list of these outcomes and correct the text accordingly. Furthermore, please detail how many studies were excluded using this criterion and provide references for these studies.

Response: Within the systemic literature review, all studies were screened using the full PICOS criteria which includes population, intervention, study design as well as outcomes. The *outcomes* criterion was erroneously omitted from the text in Section 3.3 of Appendix D, however it was applied in the review, as per standard protocols. Paragraph one of Section 3.3 of Appendix D should be corrected to:

"All retrieved studies were assessed against the eligibility criteria for the clinical effectiveness review. Primary (Level 1) screening was performed by two independent reviewers who reviewed each reference (title and abstract) identified in the literature search, applied basic study selection criteria (population, intervention, outcomes and study design) and decided whether to include or exclude the study reference at that stage. Any uncertainty regarding the inclusion of studies was checked by a third reviewer."

The full list of the prespecified *outcomes* criteria and extracted outcomes is provided in the response to clarification question A3 of this document. Please note that no studies were excluded based on the *outcomes* criterion.

A9. Table 5 of Appendix D presented the *"quality assessment of RCT using NICE manufacturer's submission template checklist"* (reference 7 of Appendix D: NICE STA User guide for company evidence submission template). However, in section 2.5.2 of that checklist, an additional item is mentioned, i.e. *"also consider whether the authors of the study publication declared any conflicts of interest"*.

Please provide a revised version of Table 5 including the missing item. This revised Table 5 should also include the response to the question *"Was the concealment of treatment allocation adequate?"* for Gleeson 2018 (reference 26 of Appendix D).

Response: Based on the ERG request, all studies listed in Table 5 of Appendix D were assessed for the additional requested item, i.e. *"consider whether the authors of the study publication declared any conflicts of interest."* Per protocol screening and extraction principles were followed to complete this request. An updated version of Table 5 with declaration of author conflict of interested is provided below.

In addition, the updated Table 5 also includes the missing item in response to the question *"Was the concealment of treatment allocation adequate?"* for Gleeson 2018. For ease of review, all updates have been made in blue font.

Appendix D Table 5: Quality assessment of RCT using NICE manufacturer's submission template checklist[1]

Author and year of publication	Horwitz 2019[2]	Kim 2019[3]	D'Amore 2018[4]	Gleeson 2018[5]	Li 2017[6]	Trumper 2016[7]	Simon 2010[8]	Aviles 2008[9]	Tsukasaki 2007[10]	Jerkeman 1999[11]
Was randomisation carried out appropriately?	Yes	Unclear	Unclear	Yes	No	Unclear	Yes	Yes	Yes	No
Was the concealment of treatment allocation adequate?	Yes	Unclear	Unclear	Yes	No	Unclear	No	No	No	No
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Unclear	Unclear	No	No	Unclear	No	No	No	No
Were there any unexpected imbalances in drop-outs between groups?	No	Unclear	Unclear	No	No	Unclear	No	No	Yes	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Unclear	Unclear	No	No	Unclear	No	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Unclear	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes
Have authors of the study publication declared any conflicts of interest?	Yes	Yes	No	Yes	Yes	No	Yes	No	Yes	No

A10. Table 38 of the CS illustrated the percentage of consolidative radiotherapy that participants received in each treatment arm, i.e. 6% (n=14) of the participants in the BV+CHP arm received consolidative radiotherapy compared to 3% (n=6) of the participants in the CHOP arm.

Please clarify whether this therapy was offered to the participants after achieving complete response. Please discuss the imbalance between the groups and any implications this might have.

Response: In the ECHELON-2 study, consolidative SCT or radiotherapy may have been given at the investigator's discretion after EOT procedures had completed. At least six cycles of study treatment should be given prior to initiating post treatment consolidative SCT or radiotherapy.[12]

Post-treatment consolidative radiotherapy and post-treatment chemotherapy for the purpose of mobilizing peripheral blood stem cells, or consolidative autologous or allogeneic SCT were not considered subsequent new anticancer treatments because they are not administered to treat progressive disease.[13]

However, if patients with progressed disease received radiotherapy then this would be considered as treating progression and would therefore count as an event.

Clinical experts consulted state that there is a lack of evidence for the use (or omission) of consolidative radiotherapy for PTCL; a lot of current practice is based on extrapolation of evidence from B-cell lymphoma data. The use of radiotherapy is decided by patient presentation and clinician belief in the effectiveness of the intervention and less by response to frontline treatment. Patients who are more likely to be considered for radiotherapy are those with early stage disease (stage I or II) which is localized, where the intent of frontline therapy is curative and localization may be suitable for radiotherapy, and those with bulky disease (tumours measuring in excess of 7cm), where the aim of radiotherapy is to shrink the tumours and decrease the disease burden. As mentioned above, there is a paucity of evidence on the efficacy of radiotherapy in PTCL lymphoma and the ultimate decision to treat is down to the individual clinician interpretation of the evidence. Furthermore, the current guidelines poorly define when consolidative radiotherapy should be given

and there is a lack of data on the role of consolidative radiotherapy in the PTCL setting.

As the difference between the proportion of patients who received consolidative radiotherapy between BV+CHP and CHOP is small (6% compared to 3%), the impact on overall outcomes is likely to be negligible. The clinical experts we consulted consider this difference to be nominal and would not expect it to have an impact on the overall efficacy of either regimen.

A11. Figure 1 reported in Horwitz 2019 (ECHELON-2, participant flowchart) stated that *"a total of 89 patients in the A+CHP group and 81 patients in the CHOP group were prespecified by the investigator at baseline to receive consolidative stem cell transplantation"* (SCT). According to section B.3.3.5.1 of the CS, 22% (n=50) of the participants in the BV+CHP arm versus 17% (n=39) of the participants in the CHOP arm are reported to have received consolidative SCT.

Please explain this discrepancy, providing revised numbers, if needed. Please clarify the decision-making process which underpinned offering consolidative therapy, e.g. stem cell therapy, to the enrolled participants.

Response: If a clinician opts to do a consolidative stem cell transplant (SCT) then at that point an assessment for eligibility based on patient characteristics would take place. The eligibility for an SCT is determined based on a range of patient factors (e.g. patient fitness, co-morbidities and age) and also disease factors (e.g. level of disease control). As SCTs carry a higher risk of treatment related mortality and morbidity, patient choice is also a key consideration when assessing for transplant eligibility.

In the ECHELON-2 trial, the investigators were asked to pre-specify at baseline if their patients may be eligible for an ASCT based on the aforementioned underlying patient characteristics (age, fitness, etc). From this baseline assessment, it was deemed that 89 and 81 patients enrolled in the BV+CHP and CHOP arms

respectively would potentially be eligible for a consolidative SCT following their first-line therapy.

Whether the potentially eligible patients actually went on to receive a consolidative SCT was based on these patient factors, in addition to their response to the first-line treatment. If the patient had a good enough response to first-line therapy, was still deemed SCT eligible, and wanted to receive a SCT they would then go on to receive a consolidative SCT.

In the UK, consolidation with an SCT may be considered in eligible patients who achieve a good response at the end of first-line therapy. Clinical opinion on the efficacy of consolidative SCT in PTCL is inconclusive, with limited evidence supporting its risk-benefit profile, and therefore its uptake varies from centre to centre. In a real-world setting, it is unlikely that the addition of BV to CHP would have an impact on the rate of use of consolidative SCT. The conclusion of UK clinical experts is that the rate of SCT for PTCL will not change due to BV but will continue to be driven by local practice which will remain variable.

A12. Please provide details on the previous treatment that participants received in each of the arms of the included trial, e.g. as part of the Tables describing the baseline characteristics.

Response: The ECHELON-2 trial was designed to investigate the efficacy and safety of BV+CHP compared to CHOP in the front-line setting. Therefore, by definition, all patients in ECHELON-2 had received no prior treatment for PTCL. This is aligned to the decision problem and NICE scope for this appraisal.

A13. Section B.2.2 of the CS states that *"in total, three studies were identified that reported data on BV"*. This is discrepant to section 4.2 of Appendix D stating that *"two studies (one RCT and one Non-RCT) were identified that reported data on brentuximab vedotin".* Please address this discrepancy.

Response: In line with the population specified in the NICE Scope for this appraisal, the population criterion of the clinical systematic literature review (SLR) PICOS specified that the population of identified studies must be composed of front-line

(treatment naïve) patients, and that studies with resistant or relapsed or refractory PTCL or pre-treated PTCL patients were to be excluded.

Section B.2.2. of Document B reports on three brentuximab vedotin (BV) studies[14-17] which were deemed relevant to the appraisal: the ECHELON-2 Phase III trial[14], the Fanale et al. Phase I trial[16] and its subsequent updated publication[17], and the Horwitz et al 2014 trial[15].

Two of these three studies, the ECHELON-2 Phase III study[14] and the Fanale et al Phase I study[16], met all of the PICOS criteria and were therefore identified in the SLR. However, the Horwitz et al Phase II publication studied the efficacy and safety of BV in patients with T-cell lymphomas who had relapsed or refractory disease. Therefore, this study did not fully meet the population criterion, specifically the front-line or treatment naïve specification. However, as this study looked at the safety and efficacy of BV in very rare non-sALCL subtypes of PTCL and was one of three studies reporting on BV in T-cell lymphoma, we felt it was broadly relevant to the decision problem. We therefore opted to include the Phase II Horwitz study in the clinical effectiveness section of the submission as it provided valuable additional evidence in an area with limited literature.

A14. Please provide a break-down of how many participants were included by centre and country. Furthermore, please present results of subgroup analyses for all outcomes by country or region.

Response: Table 1 presents the disposition of subjects in ECHELON-2 with respect to study arm and country. Due to the small number of patients in some countries and the rarity of PTCL, the specific centres are not listed in order to protect patient confidentiality. In the UK, a total of twenty-one patients were enrolled across five centres.

Table 1: ECHELON-2 subjects (ITT) by country

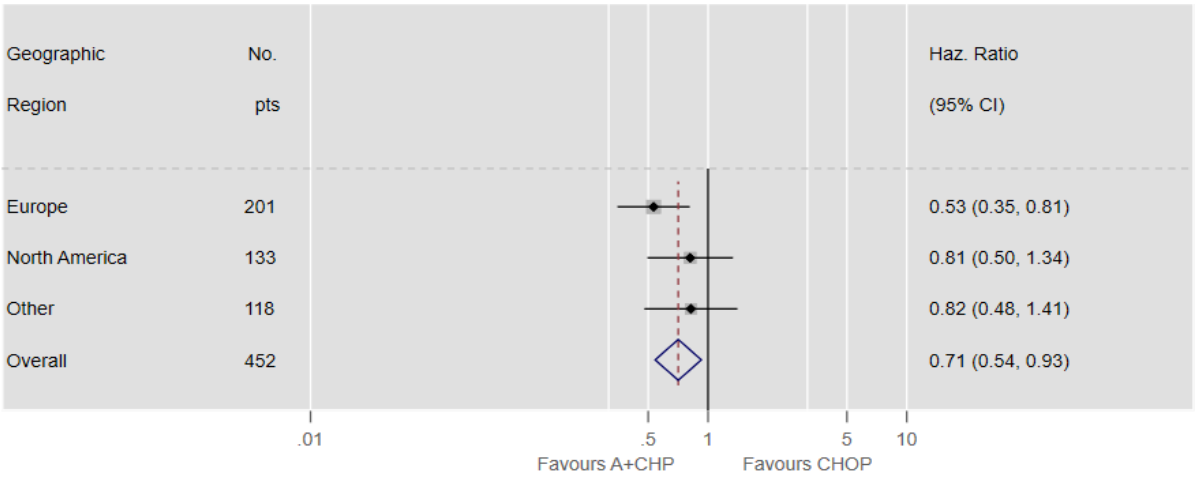
Country	BV+CHP N (%)	CHOP N (%)
Australia	8 (4%)	6 (3%)
Canada	3 (1%)	3 (1%)

Czech Republic	12 (5%)	10 (4%)
Germany	12 (5%)	15 (7%)
Denmark	5 (2%)	9 (4%)
Spain	11 (5%)	15 (7%)
France	18 (8%)	18 (8%)
UK	14 (6%)	7 (3%)
Hungary	5 (2%)	4 (2%)
Israel	4 (2%)	8 (4%)
Italy	20 (9%)	17 (8%)
Japan	23 (10%)	20 (9%)
South Korea	23 (10%)	17 (8%)
Poland	5 (2%)	2 (1%)
Romania	2 (1%)	0 (0%)
Taiwan	4 (2%)	5 (2%)
USA	57 (25%)	70 (31%)
Total	226 (100%)	226 (100%)

Abbreviations: BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine.

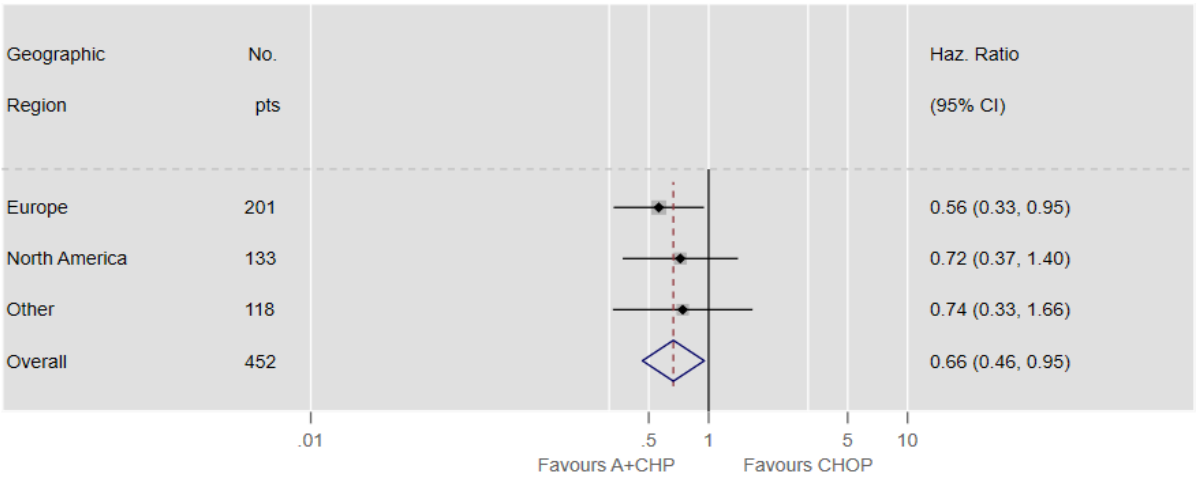
Given the very low number of study subjects in some countries, analysis of efficacy by country was not considered appropriate. Analysis of OS and PFS based on geographic region are presented in Figure 3 and Figure 2, respectively. It is notable that Europe was the geographical region with the largest number of recruited patients in ECHELON-2 (201 out of 452 patients). Results were consistent across geographic region for both outcomes, with nominally better outcomes for BV+CHP observed in European subjects.

Figure 2: PFS (IRF) in ECHELON-2 by geographic region



Abbreviations: A+CHP, BV, cyclophosphamide, doxorubicin, prednisone; CI, confidence interval; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; Haz., hazard; IRF, independent review facility; No., number; OS, overall survival; PFS, progression-free survival; pts, patients.

Figure 3: OS in ECHELON-2 by geographic region



Abbreviations: A+CHP, BV, cyclophosphamide, doxorubicin, prednisone; CI, confidence interval; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; Haz., hazard; IRF, independent review facility; No., number; OS, overall survival; PFS, progression-free survival; pts, patients.

A15. According to section B.2.6.1.2 of the CS, *"in the ECHELON-2 trial, patients were required to have CD30 expression ≥10% by immunohistochemistry (IHC) per local assessment"*. Please provide a reference supporting the chosen threshold.

Response: When the ECHELON-2 study was initially designed, the 10% threshold used for CD30 expression was selected to exceed the assay's error margin and to

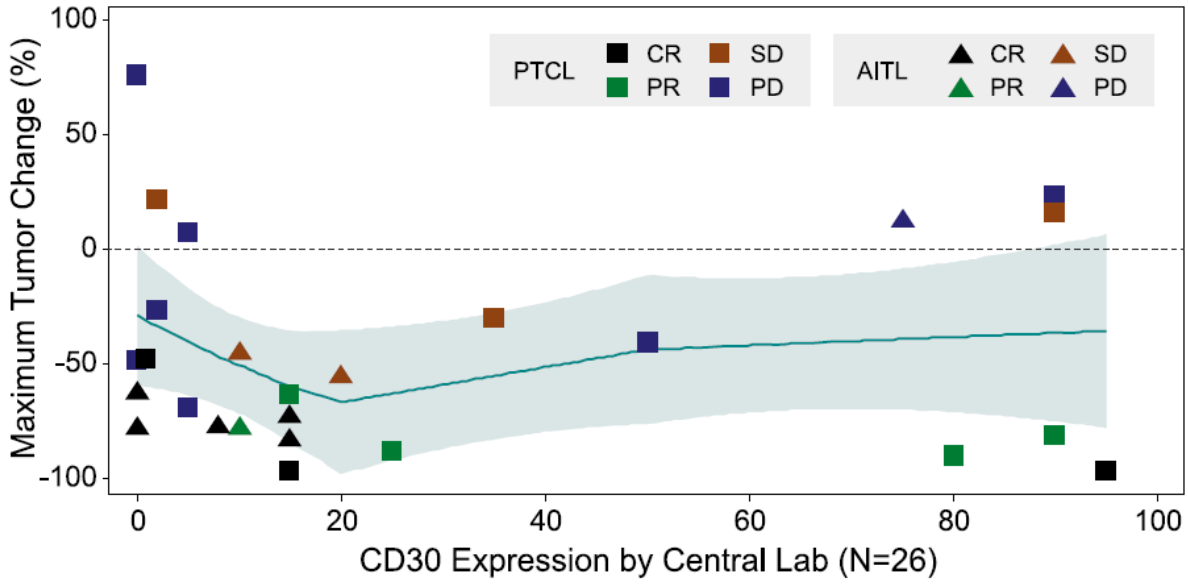
reliably ensure that there is a significant level of CD30 for brentuximab vedotin to target.

This is also consistent with the threshold selected in the ALCANZA study, which investigated the use of brentuximab vedotin in patients with Mycosis Fungoides and primary cutaneous T-cell lymphoma (CTCL) with heterogenous levels of CD30 expression. Although a 10% threshold was set in the ALCANZA study, the brentuximab vedotin licence and the positive NICE recommendation for brentuximab vedotin in CTCL (TA) does not specify a CD30 threshold – both merely state that the disease must be CD30 positive.

Based on the extensive information we now have, we know that there is no correlation between the level of CD30 expression and level of response to BV. Activity is observed with any level of CD30 expression. This has been described within section B.2.6.1.2 of Document B (Figure 15).

This is further supported by data that was presented in the Horwitz et al Phase II study for R/R PTCL-NOS and R/R AITL, where responses were seen among patients with all levels of CD30 expression on their tumour samples, including two patients with undetectable CD30 by IHC on central review.[15]

Figure 4: Maximum Tumor Change by CD30 Expression (Central Lab Assessment)



Maximum tumor size decrease by quantitative CD30 expression. Includes patients who have both postbaseline radiographic response assessments and CD30 expression data. Loess methodology was used.

Furthermore, the FDA have approved brentuximab vedotin for previously untreated systemic anaplastic large cell lymphoma (sALCL) or other CD30-expressing peripheral T-cell lymphomas (PTCL), including angioimmunoblastic T-cell lymphoma and PTCL not otherwise specified, in combination with cyclophosphamide, doxorubicin, and prednisone. There is no stipulation as to the level of CD30 expression required. The proposed EMA marketing authorisation is for adult patients with previously untreated CD30+ PTCL and, as for the CTCL indication, we do not anticipate that it will specify a threshold for CD30 expression.

A16. According to Table 2 of the CS, *"for patients weighing more than 100kg, max weight of 100kg is assumed for dosing calculations (i.e. max dose of BV per cycle = 180mg). Dose adjustments may be warranted for conditions such as neutropenia and peripheral neuropathy, as well as for special patient populations such as those patients with renal and hepatic impairment, the elderly, and paediatric"*.

Please detail how many participants had a capped or adjusted dose. Please present results for these subgroups of patients.

Response: The recommendation to cap the dose of BV at 100 kg was based on clinical pharmacokinetics of BV which were studied in Phase I and Phase II trials of BV in R/R Hodgkin Lymphoma and R/R sALCL. The studies found that the volume distribution of BV was consistent with the vascular volume, similar to other antibody-based products. Therefore, for patients weighing >100kg, dosing was capped to achieve similar exposures as those observed in patients that weighed less than or equal to 100 kg. This is consistent with the dosing guidance in the Summary of Product Characteristics (SMPC) for BV.[18]

In line with the SMPC, dosing in ECHELON-2 was based on an intended dose of 1.8 mg/kg, with subject weight capped at 100 kg. Dose adjustments were made for weight fluctuations ≥10% from baseline during the study. Rounding was permitted within 5% of the nominal dose. Within the BV+CHP arm of the ITT population, 10% of patients (n=24) had a weight greater than 100 kg at baseline. A further 9% of patients (n=21) in the BV+CHP arm experienced dose reductions of BV to 1.2 mg/kg due to AEs during the study. Dose reduction and dose delay data are detailed in Table 2. The economic evaluation accounts for a capped dose based on a maximum weight of 100kg. However, the model does not include dose reductions in the

costing; this was considered conservative because including these would reduce the acquisition costs of BV in the analysis.

Table 2: Dose modifications (safety analysis set) in ECHELON-2

	BV+CHP (N=223)			CHOP (N=226)		
	BV	**Cyclophosphamide**	**Doxorubicin**	**Vincristine**	**Cyclophosphamide**	**Doxorubicin**
Dose delay due to AE	59 (26)	58 (26)	57 (26)	28 (12)	27 (12)	28 (12)
Dose reduced due to AE	21 (9)	18 (8)	17 (8)	24 (11)	11 (5)	11 (5)
Dose eliminated due to AE	N/A†	0	0	N/A†	1 (0)	1 (0)

Abbreviations: AE, adverse event; BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin and prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone and vincristine.
Dose modifications of blinded study treatment (BV/vincristine), cyclophosphamide, doxorubicin, or prednisone were allowed per institutional standards at the discretion of the investigator. Permitted dose modifications included dose delays, dose reductions, dose eliminations (i.e., temporary stoppages allowed for cyclophosphamide and doxorubicin only), and dose discontinuations (i.e., stoppages of a treatment component for the remainder of the study). For blinded study treatment, the reduced dose levels were 1.2 mg/kg BV and 1 mg vincristine. Unplanned dose adjustments were infusion interruptions, infusions stopped early, or dose errors.
† Dose elimination not permitted.

To provide some evidence regarding efficacy in patients who experience dose capping, a subgroup analysis was performed based on weight >100 kg at baseline. Statistical tests of interaction between treatment effect and subgroup membership suggest no evidence of heterogeneity in the treatment effect based on weight >100 kg at baseline (p=0.670 and p=0.460 for OS and PFS [IRF], respectively).

As dose delay and dose reductions are likely to be correlated with other prognostic factors and are treatment-emergent (i.e. defined post-baseline), it was not considered appropriate to estimate outcomes based on these subgroups. Clinical input suggests that dose delays are generally short and are unlikely to affect patient outcomes (see response to question B7D regarding clinical feedback on treatment breaks).

A17. Did any of the included studies include children or adolescents (age <18 years)? If so, please present relevant results for this subgroup of patients.

Response: In line with the population specified in the NICE Scope for this appraisal, the *population* criterion of the clinical systematic literature review (SLR) PICOS specified that the population of identified studies must include *adult (age* ≥18 years) patients. As PTCL is a very rare condition with a paucity of data, the Notes of the PICOS found in Appendix D also stipulated that studies conducted in >80% of the specified *population* criteria were to be included as per HTA requirements. As a result, four studies identified through the SLR had a small subset of patients under 18 years of age. Only one randomised controlled trial (RCT) and three observational studies had patients younger than 18 years of age, however in all instances the proportion of patients <18 years old was small. Table 3 below provides a summary of the four studies, including the median age and age range of patients included in the studies.

The only RCT, Li 2017, had only one patient under 18 years of age per arm included in study. Although the exact number of patients under 18 years was not reported in the three observational studies, we anticipate that it was a small proportion based on the median age of patients in the studies (median age: 39-57.3 years), which is relatively close to the median age of diagnosed patients with PTCL in the UK (58 years)[19]. None of the studies reported results on the sub-group of patients younger than 18 years of age. Although the studies provide insight into the outcomes with CHOP, the comparator, it should be noted that none were included in the cost-effectiveness analysis for this appraisal. The outcome data following treatment with CHOP from the ECHELON-2 trial was used to inform the economic model.

In relation to BV, the ECHELON-2 inclusion criteria specified that patients must be ≥18 years; the median age of patients in the ECHELON-2 trial was 58 years (range 45-67) and 58 years (range 44-67) for patients enrolled in the BV+CHP and CHOP arms, respectively. Furthermore, both the Fanale et al and Horwitz et al Phase I and Phase II trials which reported on the efficacy of BV in PTCL included only adults with a median age of 55.5 years and 64 years, respectively. Although a small number of studies identified in the clinical SLR included adolescent patients, the impact of this

data on the overall body of clinical and cost-effectiveness evidence is expected to be negligible.

Table 3: Studies identified through the SLR had a small subset of patients under 18 years of age

Author year	Treatment, n	Median Age (range)	Notes
RCTs			
Li 2017[6]	GDPT n =52 CHOP n = 51	52 (16-69) 48 (15-70)	One patient per arm was under 18 (<2% of total population). Results for the <18-year-old patients not reported.
Non-RCTs			
Suzuki 2012[20]	CHOP n=55	57.3 (16.5 – 81.8)	Assumed low proportion of patients <18 years as the median age is 57.3 years. Results for the <18-year-old subgroup not reported.
Park 2008[21]	CHOP n=36	39 (17 – 67)	Low number of participants. Results for the <18-year-old subgroup not reported.
Kangsheng 2014[22]	CHOP n=68	42.5 (14-82)	Proportion of patients <18 years assumed to be low as the median age is 42.5 years.

Statistical analysis

A18. Priority question: PFS and OS results are based on a data cut-off of 15th August 2018.

Are more recent results available? If so, please provide the most recent results for all analyses presented in the CS (as well as in relation to other clarification questions) and update the economic models accordingly. If not, please specify when these will become available.

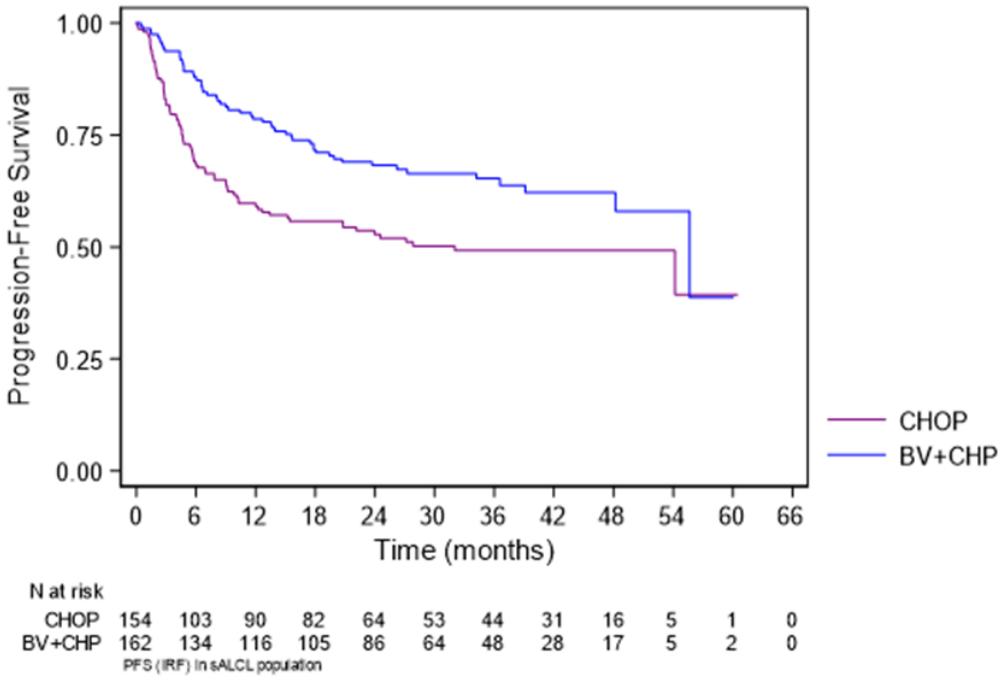
Response: The 15th August 2018 data cut-off is the latest data available from the ECHELON-2 trial and we can confirm that the evidence presented in the Lancet publication by Horwitz et al and the clinical and cost-effectiveness data presented in this submission reflect the most up to date data available. The next data cut of the ECHELON-2 trial is planned for late 2020, with analysis and evidence likely to become available in 2021.

A19. Figure 19 of the CS reports PFS results in the sALCL population.

Please clarify why the numbers at risk are 163 for BV+CHP and 151 for CHOP, respectively, when these are reported to be 162 and 154, respectively, for OS in Figure 20.

Response: Figure 19 is the incorrect curve for PFS for patients with sALCL; we have provided the correct curve below. This matches the number of patients at risk in Figure 20 reporting the overall survival (OS) for patients in sALCL and also the number of patients with sALCL in Table 11 (ECHELON-2 baseline patient characteristics and demographics). We would like to assure the ERG that the correct PFS Kaplan-Meier curve and corresponding number of patients with sALCL has been applied to the cost-effectiveness analysis presented in the submission. We apologise for any confusion caused.

Corrected Figure 19: PFS for Subjects with sALCL



Subgroups

A20. Priority question: Table 1 of the CS (page 11 and 12) outlines subgroups to be considered, with multiple subgroups mentioned for consideration if evidence allows. Please provide data on the number of patients in ECHELON-2

who belonged to these named subgroups, and those in the red boxes of Figure 2 of the CS (page 17), who received retreatment with BV in ECHELON-2.

Response: Subgroup membership and subsequent treatment with BV are summarised below in Table 4.

Table 4: Subgroup membership and re-treatment with BV in ECHELON-2

	Number of subjects	Experienced PFS (IRF) event	Received subsequent BV†	Re-treatment with BV‡
ITT	452	219	72	23
sALCL	316	131	53	17
ALK negative	218	110	46	16
ALK positive	98	21	7	1
PTCL-NOS	72	50	11	3
ATLL	7	4	0	4
AITL	54	41	7	3
EATL	3	3	1	0

Abbreviations: ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase (positive/negative); BV, brentuximab vedotin; PTCL-NOS, peripheral T-cell lymphoma-not otherwise specified; AITL – angioimmunoblastic t-cell lymphoma; ATLL: adult T-cell leukemia/lymphoma; EATL:Enteropathy-type T-cell Lymphoma; ITT, intention-to-treat.
† Patients in either study arm who received BV-containing subsequent therapy.
‡ Patients in the BV+CHP arm who received brentuximab vedotin-containing subsequent therapy.

Section B: Clarification on cost-effectiveness data

Information retrieval

B1. A PRISMA flow diagram is presented in Appendix G. Please clarify what the statement *"Records identified through database searching (n=660)"* is based on because adding up all the database searches reported in Appendix G and Appendix H does not come to this total.

Response: Unfortunately, due to a version control issue, outdated versions of database searches were included by error and this is the cause of the discrepancy. This error affects Tables 6 to 9 in Appendix G which report on the outcome of the Economic Evaluation SLR. This error did not affect the PRISMA diagram (Figure 1 of Appendix G) nor the final list of studies which were included in the Economic Evaluation SLR report, only the database search output tables were affected by this error. The correct version of the search database output tables for Embase, Medline, EconLit and NHS EES Economic Searches are provided below. All search strategies sum up to 660 hits in the corresponding tables (Embase: 476, Medline: 109 + 15, EconLit: 1, and NHS EED: 59) and are aligned to the PRISMA diagram. We

apologise for this error and for any confusion or inconvenience it may have caused. Please note that this version control issue did not affect Appendix H which reported on the outcomes of the health-related quality of life SLR.

Updated Table 6. Embase Economic Search

Search Number	Description	Search Algorithm	Hits (Run 27/4/19)
Population			
#1	PTCL	'peripheral t cell lymphoma'/exp OR ptcl:ab,ti or 'ptcl-nos':ab,ti or 'ptcl nos':ab,ti or ((peripheral:ab,ti or mature:ab,ti or angioimmunoblastic:ab,ti or adult:ab,ti or 'enteropathy associated':ab,ti or hepatosplenic:ab,ti) and ('t cell':ab,ti or 't-cell':ab,ti or tcl:ab,ti) and lymphoma:ab,ti) or 'peripheral T-cell lymphoma not otherwise specified':ab,ti or aitl:ab,ti OR salcl:ab,ti or 'systemic anaplastic large cell lymphoma':ab,ti OR atll:ab,ti OR eatl:ab,ti OR 'anaplastic lymphoma kinase':ab,ti OR alk:ab,ti	47,001
Limiters			
#2	Narrative reviews	review:it NOT ((systematic OR meta) AND analy* OR ((indirect OR mixed) AND 'treatment comparison'))	2,351,491
#3	Other non-primary studies	'case study'/de OR 'case report'/de OR 'quality control'/de OR 'theoretical study'/de OR 'methodology'/de OR 'practice guideline'/de	5,017,559
#4	Animal and laboratory studies	'animal cell'/de OR 'animal experiment'/de OR 'animal model'/de OR 'cancer cell culture'/de OR 'human cell'/de OR 'in vitro study'/de OR 'nonhuman'/de OR 'biological model'/de OR 'cell culture'/de OR 'diagnostic test accuracy study'/de	8,342,625
#5	Conference abstracts	'conference abstract'/it OR 'conference paper'/it OR 'conference review'/it	4,118,773
#6		#4 OR #5 OR #6 OR #7	17,301,427
Outcomes			
#7	Economic outcomes	('cost'/exp OR 'budget'/exp OR expenditure OR expenditures OR 'resource utilization' OR 'resource utilisation' OR economic OR economical OR pharmacoeconomic OR 'productivity'/exp OR price OR prices OR pricing OR 'reimbursement'/exp OR 'fee'/exp OR fees OR 'hospitalization'/exp OR 'work loss' OR 'work lost' OR 'work disability'/exp OR 'absenteeism'/exp OR presenteeism OR 'sick leave'/exp OR 'sick day' OR 'cost analysis'/exp OR 'cost offset' OR 'cost of illness'/exp OR 'economics'/exp OR hru OR hcru OR 'emergency room visit' OR 'emergency room visits' OR 'hospital admission'/exp OR 'inpatient'/exp OR 'outpatient'/exp OR 'cost per patient treated' OR 'health resource utilization'/exp OR 'health resource consumption' OR cost*:ab,ti OR 'economic':ab,ti OR budget*:ab,ti OR 'expenditure':ab,ti OR ('resource':ab,ti AND 'utilization':ab,ti) OR ('resource':ab,ti AND 'utilisation':ab,ti) OR ('resource':ab,ti AND 'use':ab,ti) OR ('health':ab,ti AND 'care':ab,ti AND 'utilization':ab,ti) OR ('health':ab,ti AND 'care':ab,ti AND 'utilisation':ab,ti) OR ('health':ab,ti AND 'care':ab,ti AND 'use':ab,ti) OR ('healthcare':ab,ti AND 'utilization':ab,ti) OR ('healthcare':ab,ti AND 'utilisation':ab,ti) OR ('healthcare':ab,ti AND 'use':ab,ti) OR 'economic evaluation':ab,ti OR 'cost benefit':ab,ti OR 'cost effectiveness':ab,ti OR 'cost utility':ab,ti OR 'cost minimization':ab,ti OR 'cost minimisation':ab,ti OR 'cost savings':ab,ti OR 'cost saving':ab,ti OR 'pharmaceutical	2,449,389

Search Number	Description	Search Algorithm	Hits (Run 27/4/19)
		economics':ab,ti OR 'budget impact':ab,ti OR 'econometric':ab,ti OR 'markov':ab,ti OR 'decision analysis':ab,ti OR 'discrete event simulation':ab,ti OR (('model':ab,ti OR 'models':ab,ti OR 'modeling':ab,ti OR 'modelling':ab,ti) AND (cost*:ab,ti OR 'economic':ab,ti OR 'economics':ab,ti)) OR 'cost benefit analysis'/exp OR 'cost control'/exp OR 'pharmacoeconomics'/exp)	
Final Hits			
#8	Population + Limits + Economic outcomes	(#1 NOT #6) AND #7	476

Updated Table 7. MEDLINE Economic Search (MEDLINE and MEDLINE In-Process)

Search Number	Description	Search Algorithm	Hits (Run 27/4/19)
Population			
#1	PTCL	Lymphoma, T-Cell, Peripheral[MeSH] OR ptcl[tiab] or "ptcl-nos"[tiab] or "ptcl nos"[tiab] or ((peripheral[tiab] or mature[tiab] or angioimmunoblastic[tiab] OR adult[tiab] OR "enteropathy associated"[tiab] or hepatosplenic[tiab]) and ("t cell"[tiab] or "t-cell"[tiab] or tcl[tiab]) and lymphoma[tiab]) or "peripheral T-Cell lymphoma not otherwise specified"[tiab] or aitl[tiab] OR salcl[tiab] or "systemic anaplastic large cell lymphoma"[tiab] OR atll[tiab] OR eatl[tiab] OR "anaplastic lymphoma kinase"[tiab] OR alk[tiab]	19,400
#2	Line of therapy	("first line"[tiab] OR first-line[tiab] OR "front line"[tiab] OR front-line[tiab] OR "1st line"[tiab] OR 1st-line[tiab] OR "induction therapy"[tiab] OR "primary therapy"[tiab] OR "primary treatment"[tiab]) OR ((front[tiab] OR first[tiab]) AND line[tiab]) OR untreated[tiab] OR un-treated[tiab] OR "treatment naïve"[tiab] OR treatment-naïve[tiab] OR ((primary[tiab] OR initial[tiab] induction[tiab] OR naïve[tiab]) AND (therapy[tiab] OR treatment[tiab]))	364,231
#3		#1 AND #2	1,066
Limiters			
#4	Narrative reviews	review[pt] NOT (systematic OR meta-analy* OR ((indirect OR mixed) AND "treatment comparison"))	2,243,938
#5	Other non-primary studies	"quality control"[MeSH] OR "models, theoretical"[MeSH] OR methods[MeSH] OR "practice guideline"[PT] OR "case study"[PT] OR "case report"[PT] OR "book"[PT] OR "chapter"[PT] OR "editorial"[PT] OR "erratum"[PT] OR "letter"[PT] OR "note"[PT] OR "review"[PT] OR "short survey"[PT]	6,065,127
#6	Animal and laboratory studies	"animal experimentation"[MeSH] OR "models, animal"[MeSH] OR "in vitro techniques"[MeSH] OR "models, biological"[MeSH] OR "cell culture techniques"[MeSH] OR animal OR "in vitro" OR rat OR rats OR mice OR genes OR gene OR genetic OR "animal model"	9,256,700
#7	Conference abstracts	congress[PT]	79,203
#8		#4 OR #5 OR #6 OR #7	13,183,353
#9	Economic outcomes	(Cost[MeSH] OR budget[MeSH] OR expenditure OR expenditures OR "resource utilization" OR "resource utilisation" OR economic OR economical OR pharmacoeconomic OR productivity[MeSH] OR price OR prices OR pricing OR fees OR	1,564,922

Search Number	Description	Search Algorithm	Hits (Run 27/4/19)
		hospitalization[MeSH] OR “work loss” OR “work lost” OR “work disability”[MeSH] OR “absenteeism”[MeSH] OR “presenteeism” OR “sick leave”[MeSH] OR “sick day” OR “cost analysis”[MeSH] OR “cost offset” OR “cost of illness”[MeSH] OR economics[MeSH] OR hru OR hcru OR “emergency room visit” OR “emergency room visits” OR “hospital admission”[MeSH] OR inpatients[MeSH] OR outpatients[MeSH] OR “cost per patient treated” OR “health resource utilization”[MeSH] OR “health resource consumption” OR cost*[TIAB] OR economic[TIAB] OR budget*[TIAB] OR expenditure[TIAB] OR (resource[TIAB] NAD utilization[TIAB]) OR (resource[TIAB] AND utilisation[TIAB]) OR (resource[TIAB] AND use[TIAB]) OR (health[TIAB] AND care[TIAB] AND utilization[TIAB]) OR (health[TIAB] AND care[TIAB] AND utilisation[TIAB]) OR (health[TIAB] AND care[TIAB] AND use[TIAB]) OR (healthcare[TIAB] AND utilization[TIAB]) OR (healthcare[TIAB] AND utilisation[TIAB]) OR (healthcare[TIAB] AND use[TIAB]) OR “economic evaluation”[TIAB] OR “cost benefit”[TIAB] OR “cost effectiveness”[TIAB] OR “cost utility”[TIAB] OR “cost minimization”[TIAB] OR “cost minimisation”[TIAB] OR “cost savings”[TIAB] OR “cost saving”[TIAB] OR “pharmaceutical economics”[TIAB] OR “budget impact”[TIAB] OR econometric[TIAB] OR markov[TIAB] OR “decision analysis”[TIAB] OR “discrete event simulation”[TIAB] OR ((model-[TIAB] OR models[TIAB] OR modeling[TIAB] OR modelling[TIAB]) AND (cost*[TIAB] OR economic[TIAB] OR economics[TIAB])) OR "Cost-Benefit Analysis"[MeSH] OR "Cost Control"[MeSH] OR “Economics, Pharmaceutical”[MeSH])	
#10	Epub ahead of print	publisher[sb] NOT pubstatusnihms NOT pubstatuspmcsd NOT pmcbook OR (pubstatusaheadofprint)	443,951
#11	In-process	inprocess[SB]	641,386
Final Hits			
#12	Population + Limits + Economic outcomes	#3 NOT #8 AND #9	15
#13	Population + Limits + In-process and ahead of print	#3 AND (#10 OR #11)	109

Updated Table 8. EconLit Economic Search

Search Number	Description	Search Algorithm	Hits (Run 27/4/19)
Population			
#1	PTCL	ptcl[tiab] or “ptcl-nos”[tiab] or “ptcl nos”[tiab] or ((peripheral[tiab] or mature[tiab] or angioimmunoblastic[tiab] OR adult[tiab] OR “enteropathy associated”[tiab] or hepatosplenic[tiab]) and (“t cell”[tiab] or “t-cell”[tiab] or tcl[tiab]) and lymphoma[tiab]) or “peripheral T-Cell lymphoma not otherwise specified”[tiab] or aitl[tiab] OR salcl[tiab] or “systemic anaplastic large cell lymphoma”[tiab] OR atll[tiab] OR eatl[tiab] OR “anaplastic lymphoma kinase”[tiab] OR alk[tiab]	1

Updated Table 9. NHS EED Economic Search

Search Number	Description	Search Algorithm	Hits (Run 27/4/19)
Population			
#1	PTCL	MeSH DESCRIPTOR Lymphoma, Non-Hodgkin EXPLODE ALL TREES	59

B2. Appendix G (Published cost-effectiveness studies) and Appendix H (Health-related quality-of-life studies) state that searches were conducted on 27 February 2019 and that a targeted search was performed on 1 November 2019.

Please clarify if the database searches presented are for the initial search undertaken on 27 February or for the targeted searches. Please present the search strategies for the targeted searches with hits per line if this is different to the database strategies presented in Appendices G and H.

Response: Database searches presented in Tables 6 to 9 of Appendix G and Tables 5 to 7 of Appendix H are based on the search which was conducted on 27 February 2019. A supplemental targeted search was performed on 1 November 2019, closer to the NICE submission date, in order to check if studies had been published since the original search which would be relevant to the decision problem. Please refer to Appendix G and H for full protocol and search strategies of the search conducted on 27 February 2019. Please note that there was a version control error which affected Tables 6 to 9 of Appendix G and this has been described in our response to question B2; the correct versions of the affected tables are provided within our response to question B2.

Supplemental targeted search strategy (1 November 2019)

As mentioned above, a supplemental search was conducted on 1 November 2019 in order to identify if any relevant Cost-Effectiveness or Health-Related Quality of Life studies were published since the original search. In addition to checking for any newly published studies, because the original search did not identify any relevant studies the supplemental targeted search expanded the *population* criterion, specifically the treatment naïve or front-line treatment restriction, to include studies conducted on any line of therapy. In order to conduct the supplemental targeted search, researchers searched grey literature, checked the bibliographical references

of the identified studies and performed hand searches on the following platforms: Pubmed, NICE and SMC websites and conferences (search engines and abstract books). The search terms were *PTCL, AITL, sALCL, EATL, ATLL* as well as their full text equivalents. No time limitation was applied to any of the grey literature, bibliographical references, Pubmed, NICE or SMC website searches. The conference search update was performed manually by reviewing conference search engines or abstract books of relevant conferences published between April 2019 and November 2019. To apply the updated *population* criterion, researchers reviewed excluded studies from the original SLR output and included any cost-effectiveness or HRQoL identified studies which met the newly updated criterion (i.e. were conducted in PTCL in a later line of therapy or relapsed/refractory patients).

Table 5 below includes the results of the supplemental search listed by source or conference. Please note that the outputs of the November supplemental search have already been included in Table 4 of Appendix H and Table 4 of Appendix G. Studies or publications identified through the supplemental search conducted on 1 November 2019 are marked with an asterisk.

Table 5: Results of the Supplemental Targeted Search (1 November 2019)

Conference / Source	Keywords	Results	Included: Economic Evaluation studies	Included: Health-related quality-of-life studies
ASCO 2019	• Peripheral T-Cell Lymphoma (PTCL) • Anaplastic large cell lymphoma (ALCL) • PTCL-not otherwise specified (PTCL-NOS) • Angioimmunoblastic T-cell lymphoma (AITL) • Adult T-cell leukaemia/lymphoma (ATLL) • Enteropathy associated T-cell lymphoma (EATL) • Hepatosplenic T-cell lymphoma (HSTL)	33	1	0
EHA	• Peripheral T-Cell Lymphoma (PTCL) • Anaplastic large cell lymphoma (ALCL) • PTCL-not otherwise specified (PTCL-NOS) • Angioimmunoblastic T-cell lymphoma (AITL) • Adult T-cell leukaemia/lymphoma (ATLL) • Enteropathy associated T-cell lymphoma (EATL) Hepatosplenic T-cell lymphoma (HSTL)	8	0	0
ICML	• Peripheral T-Cell Lymphoma (PTCL) *ICML has a PTCL designated section*	15	0	0
ISPOR US	• Peripheral T-Cell Lymphoma (PTCL) • Anaplastic large cell lymphoma (ALCL) • PTCL-not otherwise specified (PTCL-NOS) • Angioimmunoblastic T-cell lymphoma (AITL) • Adult T-cell leukaemia/lymphoma (ATLL) • Enteropathy associated T-cell lymphoma (EATL) Hepatosplenic T-cell lymphoma (HSTL)	0	0	0
NICE	• Peripheral T-Cell Lymphoma (PTCL) • Anaplastic large cell lymphoma (ALCL) • PTCL-not otherwise specified (PTCL-NOS) • Angioimmunoblastic T-cell lymphoma (AITL) • Adult T-cell leukaemia/lymphoma (ATLL) • Enteropathy associated T-cell lymphoma (EATL) • Hepatosplenic T-cell lymphoma (HSTL)	1	1	0
SMC	• Peripheral T-Cell Lymphoma (PTCL) • Anaplastic large cell lymphoma (ALCL) • PTCL-not otherwise specified (PTCL-NOS) • Angioimmunoblastic T-cell lymphoma (AITL) • Adult T-cell leukaemia/lymphoma (ATLL) • Enteropathy associated T-cell lymphoma (EATL) • Hepatosplenic T-cell lymphoma (HSTL)	0	0	0

B3. Please provide the search strategies for the conferences listed in Table 1 of Appendices G and H as well as details of the supplementary online searches mentioned in “Identification of Relevant Studies” in both Appendices G and H.

Response: The search strategies for the conferences listed in Tables 1 of Appendices G and H as well as the supplementary online searches have been provided in our response to question B2 above.

B4. Please confirm whether searches reported in Appendix D were used to inform adverse reactions in section B.3.4.4 of the CS. If additional searches were used, please provide full details.

Response: Adverse Events (AEs) taken directly from the ECHELON-2 trial were used to inform the clinical and cost-effectiveness sections of the submission, including section B.3.4.4 of the submission. ECHELON-2 was a Phase III double-blind, randomised controlled trial comparing the intervention of interest, BV+CHP, with the UK standard of care, CHOP. ECHELON-2 was deemed to provide the most robust data on AEs for both the intervention and comparator and was therefore the main source of data for AEs in the economic analysis. The relevance of AEs from the ECHELON-2 trial were validated by clinical experts during the February clinical advisory board; in addition to frequently occurring AEs (>5%) and Grade 3 or 4 AEs which were already included, peripheral neuropathy and diarrhoea were also included within the cost-effectiveness analysis based on clinical expert recommendation.

A detailed description of the search strategy utilised for AEs in the clinical SLR is provided in question A2. The AEs included in the cost-effectiveness analysis were checked against the findings from the systematic literature review; no new or additional AEs were identified by the clinical SLR.

Identified studies

B5. Priority question: Please clarify why the study by Feldman et al. 2019 was deemed to be of limited use. The fact that the perspective adopted in the Feldman study was different does not necessarily imply that other aspects of the economic evaluation are not useful, e.g. model structure, clinical parameters/outcomes, health-related quality of life (HRQoL) data, etc. If any of

these aspects are deemed appropriate (e.g. HRQoL data), please include them in the economic model as alternative sets input parameters so that additional scenario analyses can be run.

Response: The Feldman et al. (2019) publication was of limited use for two reasons: (1) limited information was presented with only an abstract available, and (2) the US perspective limited the comparability of costs between the analyses. The study considered a partitioned survival approach consisting of three health states (PFS, post progression survival and death) – identical to our model structure. Progression-free survival and OS data from ECHELON-2 were extrapolated and the log-normal was selected for both treatment arms; this differs from our analysis which used the generalised gamma curve for these outcomes in the base-case and alternative parametric functions in scenario analyses. Extensive validation was undertaken to choose the base-case curves that best reflect clinical practice (as presented in Section B.3.3.1.3 of the CS). It is unclear what level of curve validation was undertaken by Feldman et al.

Information from the Feldman abstract is presented in Section B.3.10.2 of the submission dossier. The PFS benefit, OS benefit and incremental QALYs were compared with those predicted in our cost-effectiveness model. The Feldman study found BV+CHP to be associated with 1.79 QALYs gained, whereas our analysis predicts [redacted] – suggesting that our analysis presents a conservative estimate of the treatment effect relative to the US study. However, it is difficult to explain what is driving the difference, as only an abstract is available.

Clinical inputs

B6. Priority question: Please provide all relevant details of the two advisory board meetings, including anonymised information about the clinical experts and detailed minutes of the face-to-face meetings and/or teleconferences. In particular, please indicate the following:

a. **How many experts provided information for each of the following: model structure, identification of subsequent treatments and their estimated shares in clinical practice, health state resource use and costs, modelling of PFS, OS and duration of treatment effect? In each case,**

please provide more detail of the clinical/working setting and experience of included experts.

Response: During the preparation of the submission, Takeda organised two advisory boards and a series of one-to-one discussions with clinicians to validate clinical assumptions and output of the cost-effectiveness analysis. All clinical experts were either oncologists or haematologists with expertise in treating patients with T-cell lymphoma. The June advisory board was cross-functional and also included experts in health economics. Further details of the expert interactions are provided below.

<u>February Advisory Board</u>

The February advisory board was a clinical advisory board whose main objective was to discuss the current treatment landscape across the UK for PTCL (including current therapies and resources) and the ECHELON-2 data. Eleven clinical experts participated in the February advisory board. An anonymised list of advisors, including the rationale for their selection and expertise on the subject matter are outlined in Table 6.

At the February advisory board, feedback and expert input was elicited on the following topics: current UK treatment pathway for frontline and relapsed PTCL, resource use and standards of care in the UK for PTCL, consolidation with radiotherapy and ECHELON-2 data and relevance to UK clinical practice. All advisors participated in providing feedback to each of the topics and all feedback was elicited by consensus. Details on the clinical advice from the February advisory board have been provided in the submission reference pack; the reference document is called *TakedaUKDOFBV005 (Feb Ad Board).*

Table 6: Experts participating in the February Advisory Board

Name	Institution	Experience / Rationale for advisor selection
Oncologist 1	Level 4 Treatment Centre	ECHELON-2 steering committee member and international key opinion leader in lymphoma.
Haematologist 1	Level 4 Treatment Centre	ECHELON-2 investigator and international key opinion leader for T-cell lymphoma. Author of BCSH PTCL guidelines.
Haematologist 2	Level 4 Treatment Centre	ECHELON-2 investigator and international key opinion leader for T-cell lymphoma.

Haematologist 3	Level 4 Treatment Centre	ECHELON-2 investigator and national key opinion leader in T-cell lymphoma.
Haematologist 4	Level 4 Treatment Centre	National key opinion leader in T-cell lymphoma and co-author of BCSH PTCL guidelines.
Haematologist 5	Level 4 Treatment Centre	National opinion leader in lymphoma with expertise in genomics and pathology.
Haematologist 6	Level 4 Treatment Centre	International key opinion leader in lymphoma and lymphoma lead for NCRI.
Haematologist 7	Level 4 Treatment Centre	National opinion leader in T-cell lymphoma and UK lead for ATLL.
Haematologist 8	Level 4 Treatment Centre; Scotland	Scottish national opinion leader in T-cell lymphoma.
Haematologist 9	Level 4 Treatment Centre	Regional opinion leader from ECHELON-2 investigation site.
Hematologist 10	Level 4 Treatment Centre	National opinion leader in lymphoma.

June Advisory Board

The June advisory board was cross-functional and included both clinical and health economic experts. An anonymised list of advisors, including the rationale for their selection and expertise on the subject matter are outlined in Table 7.

During the June advisory board, feedback and expert input was elicited on the following topic related to the cost-effectiveness analysis: model structure, survival extrapolations, HRQoL, resource use, duration of treatment, subsequent therapies in ECHELON-2 and cross-over analysis / handling of re-treatment. All advisors participated in providing feedback to each of the topics and all feedback was elicited by consensus. Details on the expert advice from the June advisory board have been provided in the submission reference pack; the reference document is called *TakedaUKDOFBV006 (June Ad Board).*

Table 7: Experts participating in the June Advisory Board

Name	Institution	Experience / Rationale for advisor selection
Oncologist 1	Level 4 Treatment Centre	ECHELON-2 steering committee member and international key opinion leader in lymphoma.
Haematologist 1	Level 4 Treatment Centre	ECHELON-2 investigator and international key opinion leader for T-cell lymphoma. Author of BCSH PTCL guidelines.
Haematologist 2	Level 4 Treatment Centre	ECHELON-2 investigator and international key opinion leader for T-cell lymphoma.
Haematologist 3	Level 4 Treatment Centre	ECHELON-2 investigator and national key opinion leader in T-cell lymphoma.
Haematologist 4	Level 4 Treatment Centre	National key opinion leader in T-cell lymphoma and co-author of BCSH PTCL guidelines.
Haematologist 5	Level 4 Treatment Centre	National opinion leader in lymphoma with expertise in genomics and pathology.
Economist 1	Academia	Professor of Health Economics. Current NICE

		committee member.
Economist 2	Academia	Health economist and current / former SMC committee member.
Economist 3	Academia	Director of health economics at an academic institute. Current / former NICE committee member.
Economist 4	Academia	Professor of Health Economics. Current / former NICE committee member.

Supplementary One-To-One KOL Discussions

In addition to the two advisory boards, clinical expert input was sought throughout the appraisal for topics which were either not covered by the advisory boards or required further clarification. The clinical expert interactions took place throughout the preparation of the submission and details have been provided in the submission reference pack under document *TakedaUKDOFBV008 PTCL KOL interview summaries.* In total five interactions occurred August 2019 and November 2019. A range of topic was discussed including: re-treatment with BV and subsequent therapies, the management of adverse events, resource use (i.e. prophylactic treatment, concomitant medications, monitoring), consolidative transplantation, excess mortality, the CHOP regimen (current standard of care) and prognostic factors in PTCL. Details on the expert advice from the supplemental interactions have been provided in the submission reference pack; the reference document is called *TakedaUKDOFBV008 (PTCL KOL interview summaries).*

b. Please provide further details of the opinions given by experts in relation to each of aspects of the model listed in part a of this question and provide details regarding the extent to which these opinions were included in the model or justification of why they were not included.

Response: Please see response to question B7A. For further details regarding the clinical expert input please refer to the following data on files outlining the details of the interactions. These were submitted in the reference pack of the original submission:

- *TakedaUKDOFBV005 (Feb Ad board)*
- *TakedaUKDOFBV006 (June Ad Board)*
- *TakedaUKDOFBV007 PTCL KOL interview summaries*

Please note that all discussions and final recommendations from the advisory boards were based on consensus from participating clinical experts and not by individual vote. Where inputs from one-to-one supplemental interactions (outlined in

TakedaUKDOFBV007) varied, the range of input was conducted as a scenario analysis (i.e. a range excess mortality rates was presented in Section B.3.3.2 of Document B directly reflecting clinical input).

Model structure and implementation

B7. Priority question: Page 87 of the CS states that *"BV was given as a subsequent therapy to 10% (n=23) of patients in the BV+CHP arm. These patients are considered to have been re-treated with BV, which does not reflect UK clinical practice as re-treatment is not currently reimbursed within England and Wales"*. In line with this, footnote d in Figure 8 states that *"Brentuximab vedotin is approved by the European Medicines Agency as second line monotherapy treatment for relapse/refractory ALCL (TA478).[2] NHS treatment criteria specifies that patients must be brentuximab vedotin naïve; assumption that no-retreatment would be permitted"*. The ERG could not verify these statements from the TA478 final appraisal determination (FAD).

a. **Please indicate where these statements can be verified and whether indeed patients treated with first-line BV cannot receive second-line BV. If patients treated with first-line BV cannot receive second-line BV, then Figure 8 in the CS is incorrect: the only sALCL option post-progression would be platinum-based chemotherapy. If that is true, please correct Figure 8.**

Response: The NHS England treatment criteria are not found in the NICE FAD, but instead are published on the NHS England dedicated Cancer Drugs Fund (CDF) website and specifically in the National CDF List which is updated regularly. This list informs clinicians, commissioners and the public about which cancer drugs and indications are available and the approved criteria for their funding by NHS England.

We apologise for this error in referencing, the correct reference should be the National CDF List which can be accessed on the following website:

https://www.england.nhs.uk/wp-content/uploads/2019/12/national-cdf-list-v1.157.pdf

Please note that NHS England Treatment criteria are interchangeably referred to as Blueteq Approval Criteria (Blueteq is a mandatory electronic approval system for high cost medicines in the NHS). The NHS treatment criteria for BV monotherapy for R/R sALCL can be found on page 71 of the CDF List. Following a positive FAD, the CDF team from NHS England, as the ultimate payer for cancer drugs, specifies a list of criteria which must be satisfied in order for a NICE recommended cancer medicine to receive funding in England. These criteria are generally in line with the FAD but provide a very specific list of conditions under which a cancer medicine will be funded. It is important to note that the jurisdiction for these treatment criteria is England only. NHS treatment criteria apply to licensed cancer medicines which have received a positive recommendation from NICE for either:

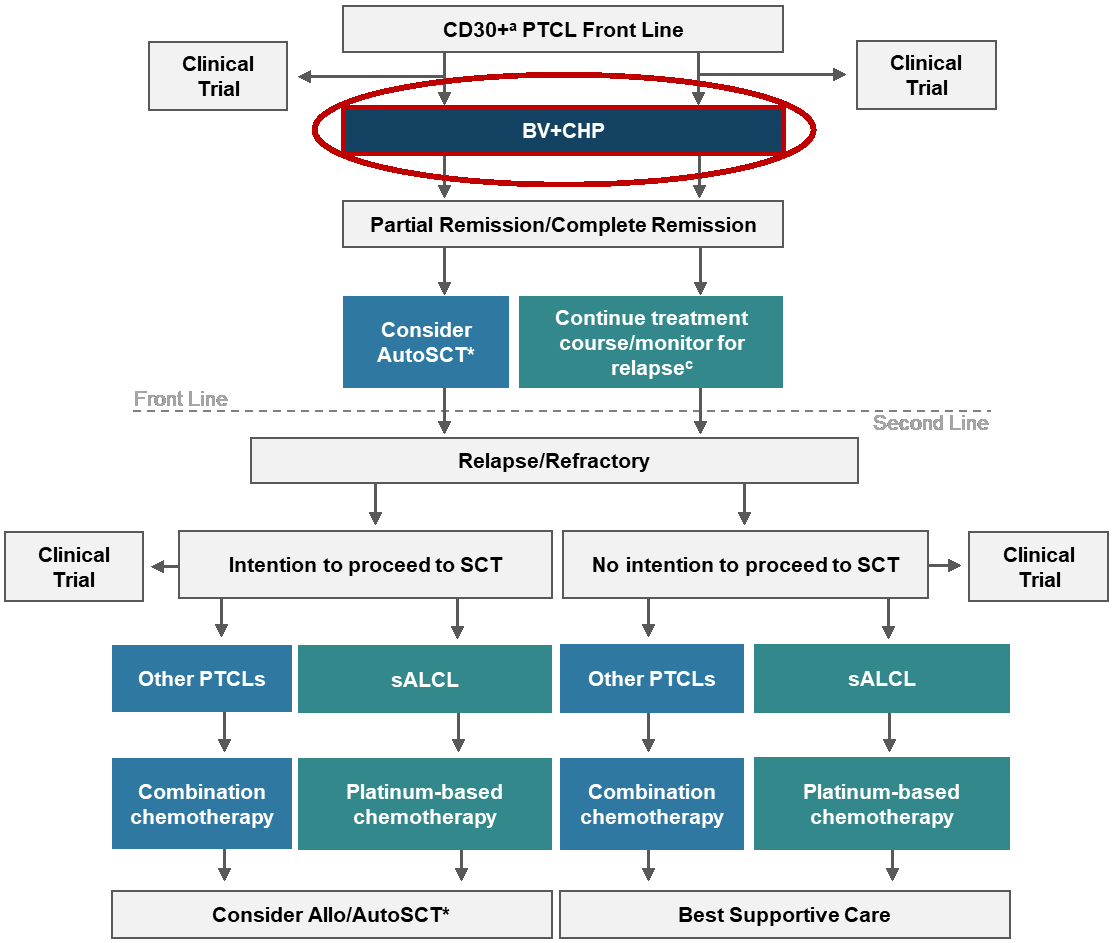
i) the Cancer Drugs Fund (CDF) or,

ii) for routine commissioning and receive interim funding from the CDF for the first three months following the release of the FAD.

In the case of BV for R/R sALCL, following a positive FAD from NICE (TA478) and a recommendation for routine funding, treatment criteria were developed by NHS England which specify under which conditions BV for R/R sALCL will be reimbursed; these conditions still apply for the use of BV in R/R sALCL in England only. Treatment criterion four states: *The patient has never previously received brentuximab unless previously enrolled in the NCRI-adopted clinical trial called ECHELON-2.*

Regarding the suggestion that Figure 8 in Document B is incorrect, while we understand the ERG's comment we do not agree that it is incorrect. Footnote for Figure 8 states that *"NHS treatment criteria specifies that patients must be brentuximab vedotin naïve; assumption that no-retreatment would be permitted"*; if this footnote is taken into account then Figure 8 is in fact correct. In the spirit of collaboration, we have re-created Figure 8 below as per the ERG request.

Revised Figure 8



[a]CD30 expression is not standardised. Treatment responses occur with low level expression[15]
[b] CHOEP may be effective for patients under 60 years of age [23,24] However, CHOEP is not within scope of the current submission [c] Due to favourable outcomes, autoSCT consolidation is not recommended for low risk ALK+, ALCL[23]
*Consolidation with AutoSCT not recommended for ALK+ ALCL
Abbreviations: PTCL: peripheral T-cell lymphoma; PTCL-NOS: peripheral T-cell lymphoma-not otherwise specified; ALK: anaplastic lymphoma kinase (positive/negative); ALCL: anaplastic large cell lymphoma; CHOP: cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHOEP: CHOP treatment with the addition of etoposide [E]; BV: brentuximab vedotin; AutoSCT: autologous stem cell transplant; SCT: stem cell transplant; AlloSCT: allogeneic stem cell transplant; BV+CHP: brentuximab vedotin (Adcetris™) combined with CHOP therapy without vincristine [O]

b. Please explain the differences between platinum-based and combination chemotherapy (Figure 8).

Response: The UK clinical treatment pathway for PTCL represented in Figure 8 was developed based on the guidelines on the management of Mature T-Cell and NK-cell Neoplasms (excluding cutaneous T-cell lymphoma) published by the British Journal of Haematology in 2011 by Dearden et al. The guidelines specifically recommend that patients with relapsed / refractory (R/R) sALCL be given platinum-based chemotherapy or an alternative salvage regimen at relapse. The same guidelines however recommend combination chemotherapy for other PTCL subtypes. During

the February 2019 and June 2019 advisory boards the treatment pathway both at diagnosis and relapse was discussed; the most commonly used regiments at relapse across subtypes of PTCL were ESHAP (etoposide, methylprednisolone, high dose cytarabine, cisplatin), ICE (ifosfamide, carboplatin, etoposide) and GDP (gemcitabine, dexamethasone, cisplatin) – **all are platinum-based regimens**.

Further consultation with clinical experts on this question clarified that the choice of salvage regimen for R/R sALCL (outside of BV) and other R/R PTCL subtypes would likely be the same and dependent on the institute's local preference for salvage therapy in PTCL. They clarified that **combination chemotherapies recommended by the guidelines for R/R non-sALCL subtypes are all platinum-based** and the different nomenclature used in the guideline is likely due to different authors leading the two sections of the guideline. The important point is that in practice there is no difference between *"platinum-based"* and *"combination chemotherapy"* in this setting – they are one and the same.

c. Please clarify if these NHS criteria were applied to the full study population of ECHELON-2, Fanale et al. 2014, and Horwitz et al. 2014 or only to a sub-population, e.g. patients with anaplastic large cell lymphoma (ALCL).

Response: The NHS treatment criteria, described in the response to part a of Question B7, only apply to licensed cancer medicines which have received a positive recommendation from NICE for either:

i) the Cancer Drugs Fund (CDF) or,

ii) for baseline commissioning and receive interim funding from the CDF for the first three months following the release of the FAD.

In both situations, the NHS treatment criteria apply solely to use of the cancer medicine in England and are specific to each indication. The relevant indication here is the use of BV for R/R sALCL (arising from NICE TA478) and the associated NHS England treatment criteria were applied to the clinical and cost-effectiveness analysis of the ECHELON-2 trial presented in the submission.

For clarity, the enrolment of patients onto the cites studies, the ECHELON-2, Fanale et al. 2014 and Horwitz et al. 2014 trials, would not consider NHS England treatment criteria as these studies were done internationally and investigated a new indication, therefore would be outside of the jurisdiction of NHS England treatment criteria.

d. Please provide data on how many patients had a treatment break in ECHELON-2. Please explain whether or not these patients would be considered 'retreated' if receiving BV after this break and whether they would be within the same treatment line in the NHS.

Response: **"**Treatment breaks" are not the same as "retreatment" and the terms refer to very different aspects of treatment. "Retreatment" means re-challenging a **progressed** patient with a treatment they have been treated with previously – in this setting, a patient has completed their planned course of treatment, has subsequently relapsed and is then re-challenged with the same treatment after progression. Progression of disease is required for the subsequent use of the treatment to be considered as "retreatment" and such use would constitute a different line of treatment in the NHS.

Conversely, the term "treatment break" refers to a dose delay during the course of planned treatment. From discussions with UK clinical experts, the most common reasons for a dose delay or treatment break is usually to allow an adverse event to clear or because of a patient request (e.g. due to special circumstances such as a family wedding), in the absence of disease progression. In both situations the intention is to resume the planned treatment as soon as possible. Importantly, for it to qualify as a "treatment break" there cannot be progression of disease, it is only a delay in the planned treatment and as such it is considered to be within the same treatment line in the NHS.

Within the ECHELON-2 study, dose delays of the blinded study treatment (BV or vincristine), cyclophosphamide, doxorubicin, or prednisone were allowed per institutional standards at the discretion of the investigator.[13] Data for dose delays due to adverse events was captured and is provided in Table 8 of Dose Modifications below. This would have encompassed treatment breaks due to adverse events in the

ECHELON-2 trial.[13] We do not have information on any dose delays due to patient choice.

Because in a treatment break, the planned treatment is resumed as soon as possible (i.e. after the clearing of an adverse event or the end of a special circumstance) and generally in a short period of time, no impact on efficacy is expected.

Table 8: Dose Modifications (ECHELON-2) [13]

Table 12-2: Dose modifications (safety analysis set)

	A+CHP (N=223)			CHOP (N=226)		
	Brentuximab Vedotin	Cyclophosphamide	Doxorubicin	Vincristine	Cyclophosphamide	Doxorubicin
Dose delay due to AE	59 (26)	58 (26)	57 (26)	28 (12)	27 (12)	28 (12)
Dose reduced due to AE	21 (9)	18 (8)	17 (8)	24 (11)	11 (5)	11 (5)
Dose eliminated due to AE	N/A[a]	0	0	N/A[a]	1 (0)	1 (0)

Dose modifications of blinded study treatment (brentuximab vedotin/vincristine), cyclophosphamide, doxorubicin, or prednisone were allowed per institutional standards at the discretion of the investigator. Permitted dose modifications included dose delays, dose reductions, dose eliminations (i.e., temporary stoppages allowed for cyclophosphamide and doxorubicin only), and dose discontinuations (i.e., stoppages of a treatment component for the remainder of the study). For blinded study treatment, the reduced dose levels were 1.2 mg/kg brentuximab vedotin and 1 mg vincristine. Unplanned dose adjustments were infusion interruptions, infusions stopped early, or dose errors.
a Dose elimination not permitted.
Source: Table 14.3.1.6–14.3.1.9

e. Please provide a scenario analysis where the cost-effectiveness of BV is estimated assuming BV retreatment and based on the percentage of patients who received retreatment in ECHELON-2. Where possible, within this scenario analysis, please provide subgroup analysis based on diagnosis sub-populations in ECHELON-2 (table 11 of CS).

Response: An unadjusted analysis including re-treatment and subsequent BV use as observed in ECHELON-2 is provided in Table 62 and Table 72 of the CS for the ITT and sALCL populations, respectively. The result is an increase in the ICERs to £27,264/QALY and £22,954/QALY for the ITT and sALCL populations, respectively. To confirm, these analyses do not adjust the estimates of OS and PFS, and the proportions of subjects receiving subsequent BV are taken directly from ECHELON-2. In addition, in this scenario, re-treatment and subsequent BV are costed as observed in ECHELON-2. It is important to note that these scenarios include both re-treatment with BV in the BV+CHP arm and subsequent BV use in the non-sALCL population (both of which are excluded in the base-case analysis). Unlike the base case analysis, these scenarios do not align with UK clinical practice or the Treatment Criteria currently mandated by NHS England for the use of BV in R/R sALCL [25].

B8. Priority question: TA478 recommends BV as an option for treating relapsed or refractory sALCL, only if a) they have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 and b) the company provides BV according to the commercial access agreement with NHS England. Please answer the following questions:

a. **ECHELON-2 includes 22% of patients who have an ECOG PS of 2 (Table 11 of CS). Please confirm that in the economic model ECOG PS 2 patients do not receive second-line BV and, therefore, these costs are not included in the current analyses. Otherwise, please correct this in the economic model.**

Response: Please see the response to B8c below.

b. **Please clarify whether the price and commercial access agreement of BV are the same in first and second line, and in second line, whether it is the same as in TA478.**

Response: As stated in Section B.1.2 of Document B, a single patient access scheme (PAS) in the form of a simple discount applies for all licensed indications of BV in the United Kingdom; this includes the use of BV as monotherapy for relapsed / refractory sALCL (evaluated in TA478) and the anticipated indication for previously untreated CD30+ PTCL in combination with CHP.

The current PAS for BV is a straight discount of [redacted] (simple PAS) bringing the NHS net acquisition price from £2,500 per 50mg vial to [redacted] per 50mg vial for all licensed indications.

c. **Please conduct a scenario assuming that re-treatment with BV is allowed except for ECOG 2 patients (as discussed in sub-question a).**

Response to Questions B8a and B8c: Patients with ECOG PS 2 were not explicitly removed from the two-stage estimator or from the proportion of patients receiving subsequent BV. Rather, all patients who received re-treatment with BV in the BV+CHP arm and patients with non-sALCL who received subsequent BV in the CHOP arm were removed (irrespective of ECOG score). Consequently, there were four subjects with ECOG PS 2 at study baseline in the CHOP arm and with sALCL disease who received subsequent BV but were retained in the analysis.

To provide a scenario in which the efficacy and costs of subsequent BV in these patients is removed, the TSE analysis was updated. The estimate of θ_v for the CHOP arm adjustment was re-estimated incorporating all subjects in the CHOP arm with progressive disease (rather than only those with non-sALCL disease, as had been the case previously). This allowed predictions to be made outside the non-sALCL population, and counterfactual survival times to be predicted for progressed patients ineligible to receive subsequent BV in the CHOP arm (i.e. patients with non-sALCL disease, and patients with sALCL and a baseline ECOG PS 2). Note: the original analysis excluded all patients who received BV re-treatment in the BV+CHP arm (irrespective of ECOG PS score). Therefore, no change was required for this part of the analysis.

Incorporating these changes resulted in the hazard ratio for OS for BV+CHP vs CHOP changing from 0.670 to 0.678. To provide estimates of cost-effectiveness, the proportion of patients in the CHOP arm receiving subsequent BV was also adjusted for costing purposes (this changed from 41.1% to 37.4%).

Results of the analysis are presented in Table 9, and demonstrate a negligible change in the ICER vs the base case presented in the CS (+1.7% vs base-case ICER of £24,901).

Table 9: Scenario excluding subsequent BV in patients in the BV+CHP arm (i.e. re-treatment) and patients with non-sALCL or with ECOG PS 2 at baseline and sALCL in the CHOP arm (ITT population)

	CHOP	BV+CHP	Incremental
Total costs (list price)	[redacted]	[redacted]	[redacted]
Total costs (PAS price)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (list price)	-		[redacted]
ICER (PAS price)	-		£25,326

Abbreviations: BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; ECOG, Eastern Cooperative Oncology Group ITT, intention-to-treat; PAS, patient access scheme; PS, performance score; sALCL, systemic anaplastic large cell lymphoma; QALY, quality-adjusted life year.

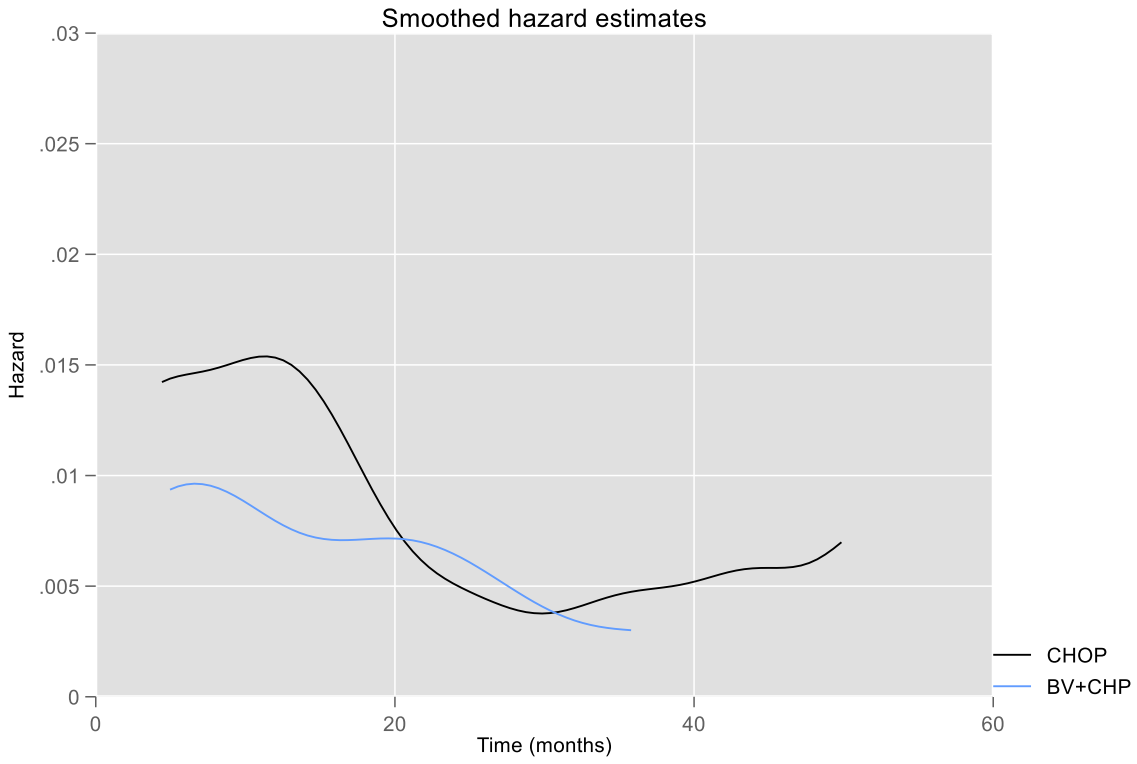
Survival analysis

B9. Priority question:

a. **Based on the OS and PFS Kaplan-Meier (KM) curves, please provide a plot of the OS and PFS hazard rate functions over time for both arms. Based on these hazard rates, please provide a plot of the OS and PFS hazard ratio over time.**

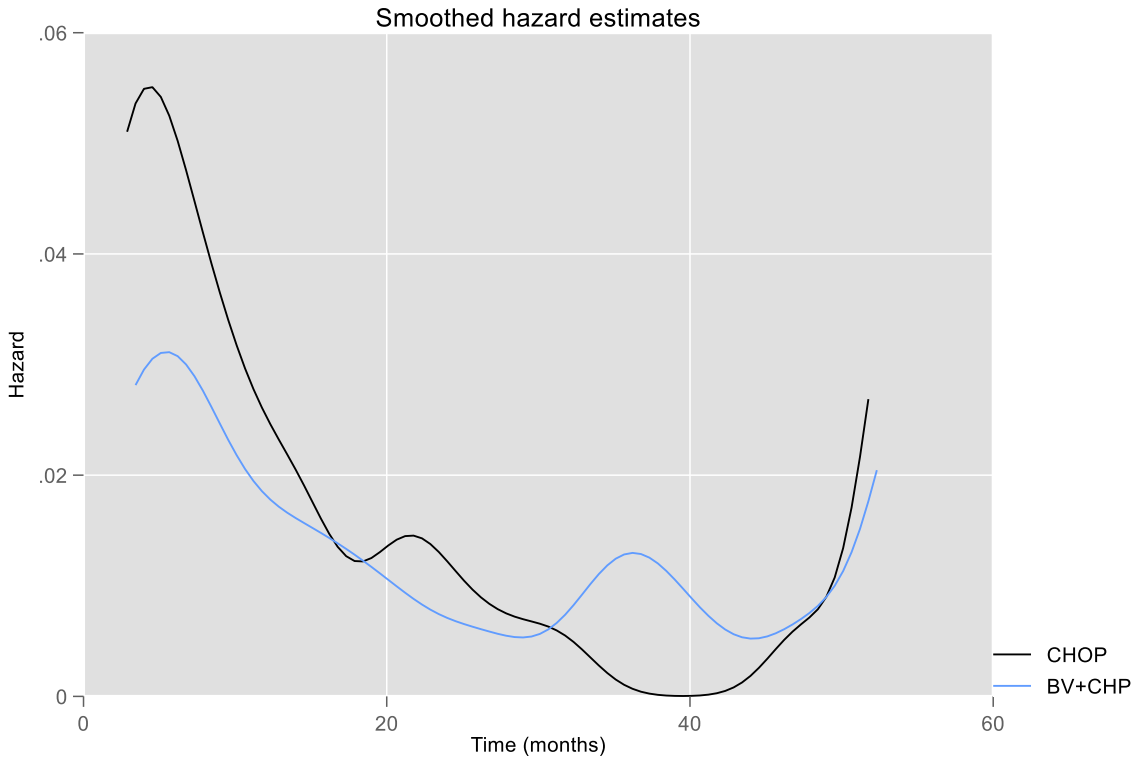
Response: Figure 5 and Figure 6 present the hazard observed during ECHELON-2 based on study arm (unadjusted analysis) for OS and PFS, respectively. Statistical models such as the Cox proportional hazards model assume that the hazard ratio is constant over time. The results of testing the proportional hazards assumption are provided in response to B10; these are statistical tests of the Schoenfeld residuals with respect to time - the null hypothesis is that of zero slope, which is equivalent to testing that the log hazard-ratio function is constant over time. Thus, failure to reject the null hypothesis of a zero slope indicates that there is no evidence of a deviation from the proportional-hazards assumption.[1]

Figure 5: smoothed hazard estimates of OS from ECHELON-2 (ITT population, unadjusted analysis)



[1] See https://www.stata.com/manuals13/ststcoxph-assumptiontests.pdf

Figure 6: smoothed hazard estimates of PFS from ECHELON-2 (ITT population, unadjusted analysis)



b. **Based on the OS and PFS parametric (for all functions tested) curves, please provide a plot of the OS and PFS hazard rate functions over time for both arms. Based on these hazard rates, please provide a plot of the OS and PFS hazard ratio over time. In the plot of the OS hazard rate function, please include the hazard rate function for the general population (background mortality only).**

Response: Figure 7 and Figure 8 present the estimated hazard functions based on the six standard alternative parametric distributions contained in the economic model for OS and PFS, respectively. The hazard ratios (proportional hazards models [Weibull, Gompertz, exponential]) or time ratios (accelerated failure time models [generalised gamma, log-logistic, log-normal]) are, by definition, assumed constant over time.

Figure 7: Predicted hazards of OS for alternative parametric survival distributions from ECHELON-2 (ITT population-, unadjusted analysis)

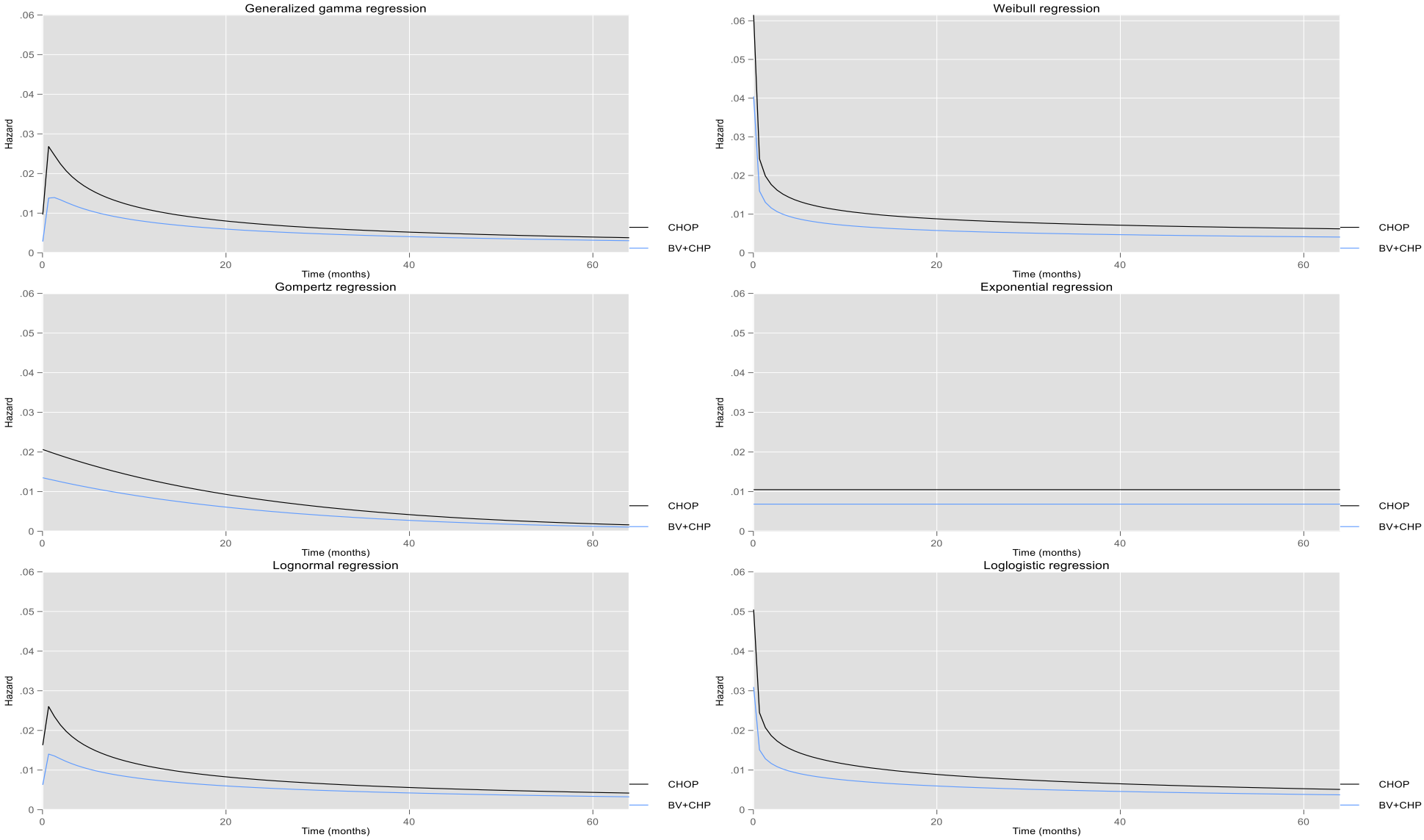
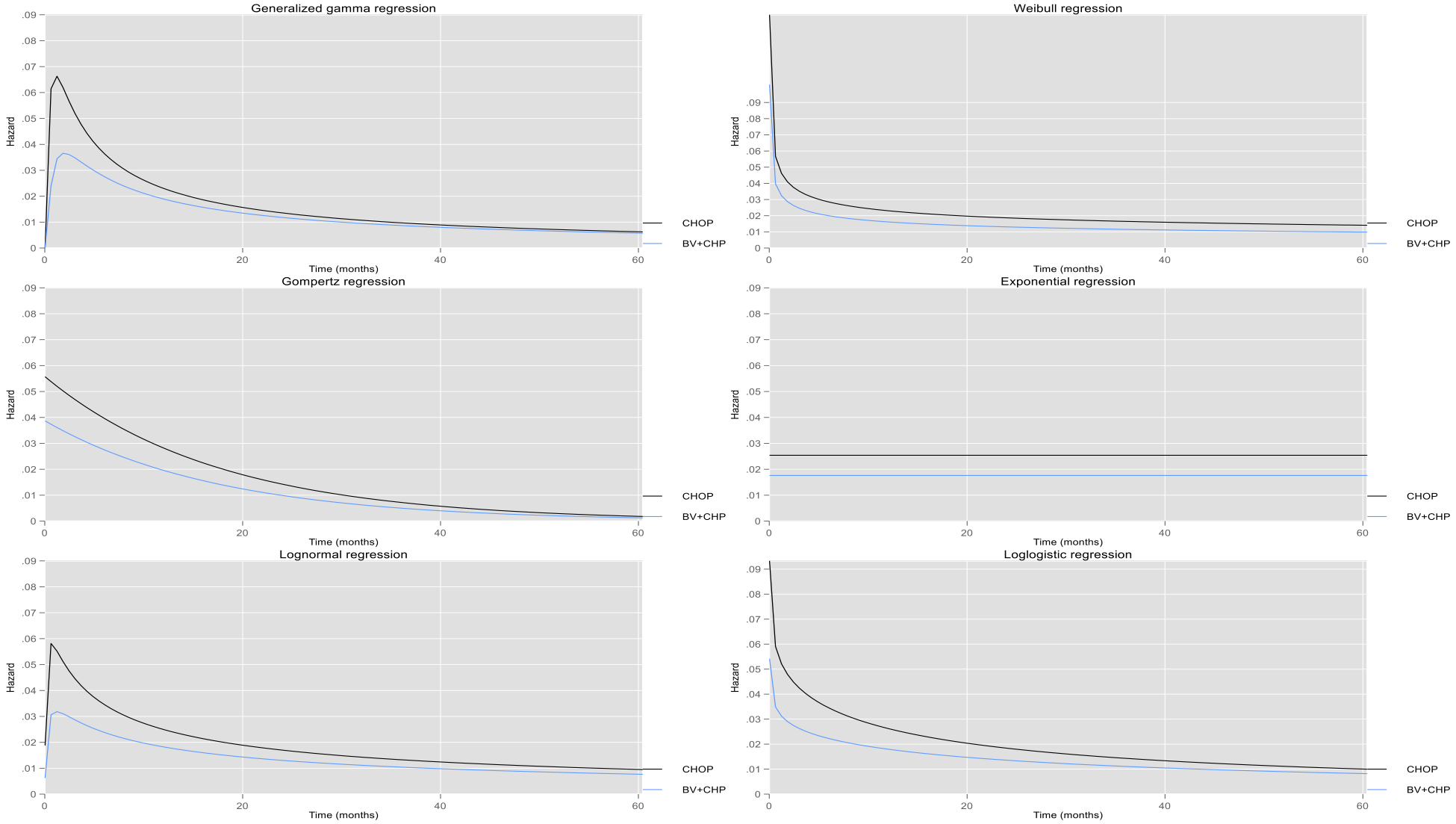


Figure 8: Predicted hazards of PFS for alternative parametric survival distributions from ECHELON-2 (ITT population-, unadjusted analysis)



B10. Priority question: Please provide an analysis of the suitability (including tests of model fit) of OS and PFS parametric extrapolations based on independent regression equations (i.e. if the proportional hazards assumption will not hold). Please include the option to select these extrapolations in the model. This should be possible for the intention-to-treat (ITT) and subgroup analyses.

Response: The assumptions of proportional hazards and odds (used in the accelerated failure time [AFT] metric models [log-normal, log-logistic, etc]) were assessed visually using log-cumulative hazard and quantile-quantile plots, respectively, and are presented in Appendix L of the CS.

The proportional hazards assumption was assessed using plots of the log-cumulative hazard. For OS in the ITT population (Appendix L), the plots are straight and parallel after approximately 1 month. For PFS in the ITT population (Appendix L), the plots are relatively parallel, though not straight, after approximately 1 month. Based on these results, a joint modelling approach was adopted, in which the effect of treatment is represented by a coefficient estimated on data from both arms of ECHELON-2. In order to further explore this topic, statistical tests of the Schoenfeld residuals have also been performed. The p-values were 0.6516 and 0.0573 for OS (adjusted for subsequent BV) and PFS, respectively. The borderline statistical significance for PFS suggests a possible violation of the proportional hazards assumption for this outcome.

Independent model fits incorporating the TSE to adjust for re-treatment with BV in the BV+CHP arm and subsequent use of BV in patients with non-sALCL are provided in the revised electronic model submitted with the economic dossier and are available for selection on the “Key Results” sheet for the ITT and sALCL populations. These results are provided in Table 14 and Table 15 for ITT and sALCL populations, respectively. Additional model fit diagnostics are provided in Table 10 to Table 13.

Table 10: Model fit diagnostics for OS (adjusted using TSE), BV+CHP

Model	N	ll(null)	ll(model)	df	AIC	BIC
gamma	226	.	-189.4	3	384.8	395.1
Weibull	226	-191.6	-191.6	2	387.1	394.0
Gompertz	226	.	-188.4	2	380.8	387.7
exponential	226	-196.0	-196.0	1	394.0	397.4
lognormal	226	.	-189.7	2	383.5	390.3
loglogistic	226	.	-190.9	2	385.8	392.7

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

Table 11: Model fit diagnostics for OS (adjusted using TSE), BV+CHP

Model	N	ll(null)	ll(model)	df	AIC	BIC
gamma	226	.	-242.2	3	490.5	500.7
Weibull	226	-244.6	-244.6	2	493.3	500.1
Gompertz	226	.	-242.4	2	488.8	495.6
exponential	226	-250.8	-250.8	1	503.5	506.9
lognormal	226	.	-242.3	2	488.6	495.5
loglogistic	226	.	-243.5	2	491.1	497.9

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

Table 12: Model fit diagnostics for PFS, BV+CHP

Model	N	ll(null)	ll(model)	df	AIC	BIC
gamma	226	.	-273.5	3	553.1	563.3
Weibull	226	-281.0	-281.0	2	566.0	572.9
Gompertz	226	.	-275.8	2	555.6	562.5
exponential	226	-286.7	-286.7	1	575.5	578.9
lognormal	226	.	-275.1	2	554.3	561.1
loglogistic	226	.	-278.1	2	560.1	567.0

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

Table 13: Model fit diagnostics for PFS, CHOP

Model	N	ll(null)	ll(model)	df	AIC	BIC
gamma	226	.	-331.0	3	667.9	678.2
Weibull	226	-347.4	-347.4	2	698.8	705.7
Gompertz	226	.	-330.1	2	664.1	671.0
exponential	226	-364.2	-364.2	1	730.3	733.8
lognormal	226	.	-335.5	2	675.0	681.9
loglogistic	226	.	-339.5	2	682.9	689.8

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; df, degrees of freedom; ll, log-likelihood.

Table 14: Scenario using independent regression equations (generalised gamma distributions) (ITT population)

	BV+CHP	CHOP	Incremental
Total costs (list price)	[redacted]	[redacted]	[redacted]
Total costs (PAS price)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (list price)			[redacted]
ICER (PAS price)			£17,544

Abbreviations: BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; QALYs, quality-adjusted life-years; PAS, patient access scheme; ITT, intention to treat.

Table 15: Scenario using independent regression equations (generalised gamma distributions) (sALCL population)

	BV+CHP	CHOP	Incremental
Total costs (list price)	[redacted]	[redacted]	[redacted]
Total costs (PAS price)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (list price)			[redacted]
ICER (PAS price)			£19,478

Abbreviations: BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; QALYs, quality-adjusted life-years; PAS, patient access scheme; sALCL, systemic anaplastic large cell lymphoma.

B11. Priority question: In the model, please include the option to select no OS adjustment (i.e. no treatment switching) [sheet "Clinical data – Mortality" – cell C85].

Response: The toggle on the Key Results screen (cell D28) allows the user to select no treatment switching. Selecting no treatment switching updates all the inputs and results within the model. Under this scenario:

- OS curves are unadjusted for subsequent BV – they are as observed in ECHELON-2
- The proportion of patients receiving subsequent BV is as observed in ECHELON-2 (i.e. re-treatment and use in sALCL is permitted)

Results based on this analysis were reported as scenario analyses in the CS (see also response to B7).

B12. Priority question: Please clarify whether the estimated θ_v (e.g. page 92 and 93 in the CS – the treatment effect for re-treatment with BV) corresponds to the hazard ratio shown in Table 5 of Appendix N. Please also clarify whether this hazard ratio was included in the probabilistic sensitivity analysis (PSA) and how. In case it is not included in the PSA, please consider adding it to a revised version of the model and explain how it was implemented.

Response: The values of θ_v are reported on page 11 of Appendix N of the CS (see heading 'Results: two-stage estimation (TSE)' and Table 4). These values represent the treatment effects for re-treatment with BV (in the BV+CHP arm) and for subsequent BV use (in patients with non-sALCL in the CHOP arm) in post-progression survival. These estimates are then used to create counterfactual survival times (U_i) for patients who require adjustment to their survival times at the patient-level (i.e. those receiving re-treatment with BV or those who received subsequent BV and have non-sALCL disease) based on

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

Where T_{A_i} is the time before disease progression for the ith individual, T_{B_i}represents the time post-progression. Following construction of these counterfactual survival times, statistical analysis proceeds as per a standard survival analysis, and the estimated hazard ratios reported in Table 5 of Appendix N are estimated based on a Cox proportional hazards model as per the primary statistical analysis of ECHELON-2.

Estimates of confidence intervals for the TSE of Table 5 of Appendix N are constructed using a bootstrapping procedure which re-estimates θ_v for random samples of the patients with post-progression survival data in order to appropriately characterise the uncertainty in the TSE. For the purposes of the economic model, however, this was not considered practical – to do so would require the inclusion of each parameter of the 1,000 bootstrapped estimates of the survival models used to estimate the confidence intervals reported in Table 5 of Appendix N. Given the modest changes in the overall survival point estimate and 95% confidence interval between the primary

analysis and those resulting from the TSE, we do not believe this to be a significant omission from the probabilistic sensitivity analysis.

B13. Please explain how to interpret the coefficients shown in Table 34 of the CS.

Response: Table 34 in the submission dossier (repeated as Table 16 here) presents the parameter coefficients used in the base-case distribution (gamma) on OS and PFS. The generalised gamma model is estimated under the accelerated failure time (AFT) metric. In an AFT model, the exponentiated coefficients represent time ratios, rather than hazard ratios. As an example, the time ratio for BV+CHP vs. CHOP for OS is approximately given as exp(0.621)=1.86. This can be interpreted as meaning that the patients who receive BV+CHP have an 86% longer life than those who receive CHOP. The constant term determines baseline risk, and the Ln(sigma) and Kappa parameters are ancillary terms which determine the hazard shape.

The economic model also contains statistical models estimated in the proportional hazards metric (Weibull, exponential, Gompertz), these coefficients are interpreted as the log hazard ratios; exponentiating these terms will provide standard hazard ratios.

Table 16: Gamma distribution coefficients (SE), ITT population (table 34 in the CS)

Parameter	Coefficient	SE	95% CI	
OS (including TSE adjustment)				
BV+CHP (vs CHOP)	0.621	0.300	0.033	1.209
Constant	4.608	0.353	3.916	5.300
Ln(sigma)	0.986	0.163	0.667	1.305
Kappa	-0.298	0.479	–1.236	0.640
PFS				
BV+CHP (vs CHOP)	0.600	0.208	0.192	1.007
Constant	2.501	0.249	2.013	2.990
Ln(sigma)	0.767	0.051	0.666	0.867
Kappa	–0.926	0.253	–1.421	–0.430

Abbreviations: BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; CI, confidence interval; OS, overall survival; PFS, progression-free survival; SE, standard error.

Mortality

B14. Priority question: Please provide additional details on the calculation of the mortality multiplier 1.19 presented on page 101 of the CS. Please clarify also whether this parameter was included in the PSA and how. In case it is not included in the PSA, please consider adding it to a revised version of the model and explain how it was implemented.

Response: Feedback from clinicians indicated that patients in long-term remission would be expected to have a slightly reduced life-expectancy relative to the general population, however this excess mortality would be significantly lower than that of patients in the R/R setting. This is primarily due to the differences in treatment approaches, namely the absence of allogeneic SCTs (alloSCT) in the front-line setting as alloSCT is associated with higher morbidity and mortality. Clinical experts expect a slightly reduced overall life-expectancy ranging from 3-10% over the span of the patient's life. In order to translate this into a mortality multiplier which could be applied in the economic evaluation, the CHOP arm was set to use lifetable mortality from model time 0 and the remaining life expectancy calculated. The 'Goal Seek' functionality in Excel was then used to estimate the mortality multiplier required to achieve a 5% reduction in life expectancy. This process was repeated to find multipliers for 7.5% and 10% reductions in life expectancy.

This parameter has not been included in the PSA as it has been elicited from KOL opinion and there is no associated measure of uncertainty. Instead this has been tested in scenario analysis and does not appear to have a large impact on results. This scenario was reported in the original submission.

Time on treatment

B15. Priority question: Please clarify whether the proportion of patients receiving each number of treatment cycles in ECHELON-2 as shown in Table 35 of the CS (the proportions used in the base case of the model) includes those patients re-treated with BV and non-sALCL patients treated with BV. In case they are, please include in the model the option of running the

analyses with (as it is now) and without considering those patients to calculate the proportions in Table 35.

Response: Response: Table 35 in the submission dossier presents proportions which apply to front-line treatment only; these are estimated and applied independently of subsequent BV use. The proportions are estimated separately for the ITT and sALCL populations.

Patients in the BV+CHP arm who went on to be re-treated, or those in the CHOP arm who received subsequent BV despite a non-sALCL diagnosis, are therefore included in these estimates (which relate to front-line treatment only). An option has been included in the model to use the proportions excluding these patients as requested, however we believe the approach in the base case to be accurate; patients who went on to be re-treated with BV, or who received subsequent BV with a non-sALCL diagnosis, should still be assumed to incur the costs of front-line therapy. This scenario had a negligible impact on the ICER (£28 reduction to £24,873, i.e. -0.1% against the base case of £24,901).

HRQoL

B16. Priority question: The progressed disease utility value of 0.643 used in the base-case is cited as based on the value used during TA478 for relapsed or refractory (R/R) sALCL (estimated as 0.643), derived from estimates presented by Swinburn et al. 2015. However, this value could not be identified in either source.

Please clarify, with full transparency of any adjustments, how this value was calculated, providing any relevant data.

Response: In TA478 (i.e. in patients with R/R sALCL), utilities are reported for complete and partial response (CR and PR), stable disease (SD) and progressed disease (PD) - informed by Swinburn et al. [26]. These values (reported in Table 17) were not directly comparable to the modelled health states (because response status for patients in the R/R setting is not used directly in the current economic analysis).

A corresponding estimate of utility in R/R disease was derived as a weighted average based on the probability of response, the ratio of life-years spent pre- and post-progression, and SCT status reported in TA478.

Table 17 details how the initial pre- and post-progression utilities of 0.842 and 0.382 in R/R disease were estimated.

Table 17: Health-state utility values in non-SCT patients, calculated from TA478

Health state		Utility value†	Probability of response to chemotherapy†	Weighted average
Pre-progression	Complete response (CR)	0.906	57%	0.842
	Partial response (PR)	0.794	24%	
	Stable disease (SD)	0.710	19%	
Post-progression	Progressed disease (PD)	0.382	-	0.382

†Taken from TA478, Health state utilities, Table 5.28 of the CS (p123).
Abbreviations: SCT, stem cell transplant.

These values were weighted by life-years spent in either state. In TA478, 66% of LYs are accrued in the progression-free health state (2.21/3.36), and 34% in post-progression health state (1.16/3.36), resulting in a utility value of 0.684 for patients not receiving an SCT (86% in TA478).

A similar approach was taken to calculate a utility value for patients who received an alloSCT (7% in TA478) or ASCT (7% in TA478), as shown in Table 18.

Table 18: Health-state utility values in SCT patients, calculated from TA478

Health state	Type of SCT	Mean utility value (0-6 months) †	Time spent in state†	Weighted average
alloSCT	Pre-progression	0.393	66%	0.324
	Post-progression	0.19	34%	
ASCT	Pre-progression	0.587	66%	0.475
	Post-progression	0.26	34%	

†Taken from TA478. Mean utility values were obtained from the CS of TA478, using the utility decrements reported in Table 5.32: Utility decrements for patients post-ASCT and post-allo-SCT (p126). We produced a weighted average for both pre-progression states.
Abbreviations: alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; SCT, stem cell transplant.

The resulting figure of 0.643 was obtained by calculating a weighted average of the proportion of patients receiving an SCT, as shown in Table 19.

Table 19: Weighted health-state utility values, calculated from TA478

Type of SCT	Calculated utility value	% of chemotherapy patients	Weighted utility
No SCT	0.684	86%	0.5882
alloSCT	0.324	7%	0.0226
ASCT	0.475	7%	0.0332
Total	-		0.643

Abbreviations: alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; SCT, stem cell transplant.

B17. Priority question: Please provide a regression model for EuroQol – 5 dimensions (EQ-5D) data including both the health state (in terms of progression status) utility approach and the time to death utility approach.

Response: Table 20 presents results of the requested analysis. The effect of being post-progression is no longer statistically significant after controlling for the proximity to death. Incorporating both time to death and post-progression status leads to the coefficient for post-progression no longer being statistically significant at conventional thresholds. This suggests that time before death is better able to explain quality of life than post-progression status.

Table 20: Statistical model of EQ-5D including time to death and progression status

	Coef.	Std. Err.	z	P>z	[95% Conf. Interval]	
Time before death						
189 or more days	-.0419404	.018995	-2.21	0.027	-.07917	-.0047109
84 - 188 days	-.0764925	.0250499	-3.05	0.002	-.1255894	-.0273956
21 - 83 days	-.1333515	.0313542	-4.25	0.000	-.1948047	-.0718983
< 21 days	-.3777959	.0524218	-7.21	0.000	-.4805407	-.275051
Post-progression	-.0139811	.0087756	-1.59	0.111	-.0311808	.0032187
Experiencing AEs	-.0243274	.0093316	-2.61	0.009	-.042617	-.0060378
Baseline EQ-5D	.3267897	.021086	15.50	0.000	.2854619	.3681175
Age (years)	-.0012063	.0005083	-2.37	0.018	-.0022026	-.00021
Post-SCT	.0311755	.0106334	2.93	0.003	.0103343	.0520166
_cons	.6509873	.029577	22.01	0.000	.5930174	.7089573

Abbreviations: _cons, constant; AEs, adverse event; Coef., coefficient; EQ-5D, EuroQol 5-D; SCT, stem cell transplant' Std. Err., standard error.

B18. Priority question: The regression model for EQ-5D in Table 40 includes a coefficient for age-decrement. How does this approach compare to the commonly used utility decrement from Ara and Brazier (Value Health 2010;13(5):509-18)? Please consider using an alternative regression model for EQ-5D without the age-decrement coefficient and apply the Ara and Brazier decrement in the model (i.e. the model should give the option of selecting the company's approach and the alternative proposed by the ERG in this question).

Response: Ara and Brazier [27] present a comparison of alternative methods of populating health state utility values in cardiovascular disease (CVD). Within this context, they provide estimates of how quality of life in the general population declines as age increases. The authors estimate a quadratic relationship for the general population. Specifically, EQ-5D for the general population is predicted as:

General Population, EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2

Therefore, the effects of an additional year of age on quality of life is conditional on the starting age being considered. For a patient aged 55 (the mean age of patients in ECHELON-2), the effect of an additional year of age (to age 56) on quality of life

would be -0.004, for a patient aged 18 would be -0.001, and for a patient aged 80 would be -0.006.

By contrast, the base-case analysis for this economic evaluation assumes a linear decline in quality of life, and this was estimated from ECHELON-2 as approximately -0.002 per year.

Table 21 presents the model of EQ-5D from ECHELON-2 including the effects of age as both a main effect as a quadratic transformation. These coefficients were incorporated into the revised model as a scenario.

Table 21: Statistical model of EQ-5D excluding age

	Coef.	Std. Err.	z	P>z	[95% Conf. Interval]	
Post-progression	-0.027	0.009	-3.22	0.001	-0.044	-0.011
Baseline EQ-5D	0.345	0.021	16.12	0	0.303	0.387
Experiencing AEs	-0.026	0.009	-2.82	0.005	-0.045	-0.008
Age (years)	-0.009	0.003	-3.11	0.002	-0.015	-0.003
Age^2	0.000	0.000	2.56	0.011	0.000	0.000
Post-SCT	0.037	0.011	3.44	0.001	0.016	0.058
cons	0.828	0.074	11.21	0	0.684	0.973

Abbreviations: _cons, constant; AEs, adverse event; Coef., coefficient; EQ-5D, EuroQol 5-D; SCT, stem cell transplant' Std. Err., standard error.

The results including this alternative EQ-5D model are presented in Table 22. This option is included in the electronic model on the 'HRQoL data' sheet and can be selected by toggling both the 'ERG scenario' (dropdown on cell C13) and general population utilities in long-term survivors (cell D41).

Table 22: Scenario using alternative EQ-5D regression model (ITT population)

	BV+CHP	CHOP	Incremental
Total costs (list price)	[redacted]	[redacted]	[redacted]
Total costs (PAS price)	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]
ICER (list price)			[redacted]
ICER (PAS price)			£29,312

Abbreviations: BV, brentuximab vedotin; CHP, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone, vincristine; EQ-5D, EuroQol 5D; QALYs, quality-adjusted life-years; PAS, patient access scheme; ITT, intention to treat.

Resource use and costs

B19. Priority question: Please clarify the discrepancies between the acquisition costs, both with and without PAS discount, for BV as mentioned in the CS (with different prices in Table 43 versus Table 55, seemingly related to whether BV is given as first-line or subsequent treatment) as well as the price that is used in the electronic model (same acquisition costs for first-line or subsequent treatment in cells D37 and D170 of the 'Cost data' sheet). Please also clarify why there seems to be two PAS prices and which one should be used.

Response: Table 43 in the submission dossier and cells D37 and D170 of the 'Cost data' sheet present the correct cost of BV+CHP per cycle, that is: [redacted] with PAS and [redacted] without PAS. Table 55 in the submission dossier is incorrect and should be replaced with Table 23 below. We apologise for the oversight; table 55 of the CS was accidentally omitted during an update to the results.

Table 23: Cost breakdown, subsequent BV in post-progression state

Type of cost	Cost per cycle	Total cost
Acquisition (list price)	[redacted]	[redacted]
Acquisition (PAS applied)	[redacted]	[redacted]
Administration	£289.33	£2,381.15
MRU	–	£2,889.95
Total (list price)	–	[redacted]
Total (PAS applied)	–	[redacted]

Abbreviations: BV, brentuximab vedotin; MRU, medical resource use; PAS patient access scheme.

Please note: BV is administered as a monotherapy in post-progression (R/R disease). The total cost in this setting does not include CHP.

B20. Please provide information on the proportions of subtypes of peripheral T-cell lymphoma (PTCL) that correspond to 1) initiation of first-line treatment, 2) those who relapsed / are refractory, and 3) for those receiving second-line BV treatment. For this, please also consider the ALK+/- subtypes of sALCL.

Response: These data are presented in response to question A20.

Cost effectiveness analyses

B21. Priority question: Please confirm that the demographic parameters used in the model (age, body weight, height, body surface area, average serum creatinine) are representative for England. If they are not, then please provide appropriate parameters.

Response: Given that PTCL is a rare disease, it was not possible to find all the requested parameters for UK patients with PTCL. Gleeson et al reported that the average age at diagnosis of PTCL in the UK is 58.[19] A 2019 audit from the Haematologic Malignancy Research Network (HMRN) of patients diagnosed with PTCL in Yorkshire, reported age and gender of patients and has been reproduced in Table 19 below. The HMRN region comprises a total population of 3.8 million and covers the area formerly served by the Yorkshire and the Humber & Yorkshire Coast Cancer Network. Information regarding the other requested patient parameters such as height, weight, body surface area and serum creatinine levels is not available for UK patients with PTCL nor lymphoma in general.

Table 24: Patient characteristics at diagnosis, HMRN PTCL Audit

Factor	Level	UK
Age, mean (SD)		[redacted]
Age, median (range)		[redacted]
Sex (N, (%))	Female	[redacted]
	Male	[redacted]

Abbreviations: SD, standard deviation.

Table 25 presents baseline characteristics for UK and non-UK patients in ECHELON-2. Patients form the UK who took part in the ECHELON-2 trial had an average age of 60.9 years, which is well aligned to the reported UK average age at diagnosis by both Gleeson et al [redacted]. The only significant difference ($p<0.05$) between UK and other enrolled patients was that patients in the UK were more likely to have six (rather than eight) cycles of frontline therapy with either BV+CHP or CHOP.

In the base case, time on treatment is based on the distribution of cycles observed in the ECHELON-2 trial. However, Section B.3.8.3 in the submission dossier provides scenarios which explore the time on treatment assumption – including a scenario capping the number of cycles at six which is aligned with UK clinical practice and supported by UK clinical experts as the maximum time on treatment that would be observed in the UK.

Table 25: Baseline characteristics of patients in ECHELON-2 by UK/non-UK status

Factor	Level	Non-UK	UK	p-value
N		431	21	
Age, mean (SD)		54.8 (15.1)	60.9 (14.1)	0.072
Weight, kg (SD)		74.5 (20.5)	73.5 (9.8)	0.83
Sex	Female	160 (37.1%)	8 (38.1%)	0.93
	Male	271 (62.9%)	13 (61.9%)	
Race	Asian	99 (23.0%)	0 (0.0%)	0.060
	Black or African American	18 (4.2%)	0 (0.0%)	
	Native Hawaiian or other Pacific Islander	1 (0.2%)	0 (0.0%)	
	Other	5 (1.2%)	0 (0.0%)	
	Unknown	47 (10.9%)	1 (4.8%)	
	White	261 (60.6%)	20 (95.2%)	
Ethnicity	Hispanic or Latino	14 (3.2%)	0 (0.0%)	0.60
	Not Hispanic or Latino	360 (83.5%)	19 (90.5%)	
	Unknown	57 (13.2%)	2 (9.5%)	
ECOG Performance Status at Baseline	0	168 (39.1%)	9 (42.9%)	0.70
	1	167 (38.8%)	9 (42.9%)	
	2	95 (22.1%)	3 (14.3%)	
Disease Diagnosis	ALK-negative sALCL	205 (47.6%)	13 (61.9%)	0.69
	ALK-positive sALCL	96 (22.3%)	2 (9.5%)	
	Adult T-cell leukaemia/lymphoma (ATLL)	7 (1.6%)	0 (0.0%)	
	Angioimmunoblastic T-cell lymphoma (AITL)	52 (12.1%)	2 (9.5%)	
	Enteropathy-associated T-cell lymphoma (EATL)	3 (0.7%)	0 (0.0%)	
	Peripheral T-cell lymphoma (PTCL-NOS)	68 (15.8%)	4 (19.0%)	
Disease Staging at Diagnosis	STAGE I	21 (4.9%)	0 (0.0%)	0.40
	STAGE II	62 (14.4%)	5 (23.8%)	
	STAGE III	117 (27.1%)	7 (33.3%)	
	STAGE IV	231 (53.6%)	9 (42.9%)	
Cutaneous ALCL Diagnosis	N	284 (94.4%)	15 (100.0%)	0.34

Factor	Level	Non-UK	UK	p-value
	Y	17 (5.6%)	0 (0.0%)	
Baseline IPI Score at Randomization	0-1	99 (23.0%)	4 (19.0%)	0.91
	2-3	270 (62.6%)	14 (66.7%)	
	4-5	62 (14.4%)	3 (14.3%)	
Serum LDH per Local Laboratory	<=1 x ULN	204 (47.3%)	6 (28.6%)	0.092
	>1 x ULN	227 (52.7%)	15 (71.4%)	
Extra nodal Disease Involvement	<=1 SITE	272 (63.1%)	16 (76.2%)	0.22
	>1 SITE	159 (36.9%)	5 (23.8%)	
HTLV-1 status	NEGATIVE	414 (97.9%)	21 (100.0%)	0.50
	POSITIVE	9 (2.1%)	0 (0.0%)	
Is stem cell transplant intended?	N	264 (61.5%)	16 (76.2%)	0.18
	Y	165 (38.5%)	5 (23.8%)	
Cycles of Treatment Intended at baseline	6	346 (80.3%)	21 (100.0%)	0.024
	8	85 (19.7%)	0 (0.0%)	
Local Percent CD30 positive cells (N), mean (SD)		76.6 (31.7398)	81.2 (31.619)	0.51

Abbreviations: AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; ALK, anaplastic lymphoma kinase; EATL, Enteropathy-associated T-cell lymphoma, ECOG, Eastern Cooperative Oncology Group; HTLV-1, human T-cell lymphotropic virus type 1; IPI, international prognostic index; LDH, Lactate dehydrogenase, PTCL-NOS, peripheral T-cell lymphoma not otherwise specified; SD, standard deviation; ULN, upper limit of normal.

B22. Priority question: Please confirm that all parameters (including the demographic parameters) used in the analysis of the sALCL subgroups are based on subgroup-specific data. If they are not, then please update the economic model accordingly.

Response: The parameters included in the economic model are listed in Table 26, along with detail of whether each parameter is determined separately for each subgroup or whether a common value is used. Overall, the majority of parameters are subgroup-specific, bar those which were not expected to differ in clinical practice and/or were not found to be different in trial data.

Table 26: Parameters used in the economic model

Model parameter	Subgroup specific?	If not, why?
Time on treatment	Yes	-
Weight, BSA, age	No	No differences expected in clinical practice.
Adverse events	No	No differences expected
HRQoL coefficients	No	Testing found no difference
Utility in PD	No	
Survival curves	Yes	-
% of patients receiving consolidative ASCT	Yes	-
% of patients receiving salvage SCT (any)	Yes	-
% of alloSCT vs ASCT	No	No differences expected
% of consolidative radiotherapy	Yes	-
% of salvage radiotherapy	Yes	-
% of salvage chemotherapy	Yes	-
% patients receiving subsequent chemotherapy	Yes	-
Number of cycles of salvage chemotherapy	No	Standard guidelines
% patients receiving subsequent BV	Yes	-
Number of cycles of subsequent BV	No	Single number from R/R setting

Abbreviations: alloSCT, allogeneic stem cell transplant; ASCT, autologous stem cell transplant; BSA, body surface area; BV, brentuximab vedotin; HRQoL, health-related quality of life; PD, progressed disease; R/R, relapsed/refractory; SCT, stem cell transplant.

B23. Priority question: Although 'the study was not powered to compare efficacy between individual histological subtypes with the exception of the sALCL subgroup', please add functionality to the model to allow the cost-effectiveness to be estimated by the pre-specified subgroups in Figure 12 of the CS (e.g. cell D21 on sheet 'Key results' of the model).

Response: ECHELON-2 was designed to compare the efficacy and safety of brentuximab vedotin (BV) in combination with CHP (BV+CHP) versus standard CHOP in previously untreated patients with CD30+ PTCL. The primary endpoint of the study was to compare the progression-free survival (PFS) as determined by an independent review facility (IRF) between the 2 treatment arms. Although the ECHELON-2 trial included various subtypes of PTCL, the pre-specified secondary analyses were for the Intention-To-Treat (ITT) and sALCL subgroup only (the latter

due to a regulatory requirement). The ECHELON-2 trial was not powered to assess efficacy nor safety within any of the subgroups, other than sALCL, and any additional subgroup analyses would be highly subject to random error and potential bias due to small subgroup sizes and a potential imbalance of patient characteristics. Overall, we believe such subgroup analyses would lack statistical validity. We consider the ITT analysis to be the most robust and statistically valid, and we also note that this matches the anticipated marketing authorisation for BV+CHP which is all previously untreated CD30-positive PTCL. The only sub-group that has any statistical validity is the pre-specified analysis on sALCL which, as stated previously, was included in response to a specific request from the EMA.

Because the subsequent treatment pathway differs for R/R sALCL compared to other subtypes of PTCL and because sALCL was a pre-specified analysis in the ECHELON-2 trial, a sub-group analysis of patients with sALCL has been conducted as requested. Clinical and cost-effectiveness analysis for sALCL has been presented in Sections B.2.7 and B.3.9 of Document B. It is not recommended to further split the sALCL population, based on ALK status. UK clinical experts at both the February 2019 and June 2019 advisory boards held by Takeda unanimously recommended that ALK-positive and ALK-negative sALCL groups be analysed and considered as one combined sALCL group. To be eligible for ECHELON-2, ALK-positive sALCL patients were required to have an IPI score of 2 or above. As described in Section B.1.3.4 of Document B, clinical literature supports that ALK-positive patients with a high IPI score have similar outcomes to patients with ALK-negative sALCL. Histologically both groups express CD30 uniformly and there is no difference in the management of the condition. Therefore, patients with sALCL enrolled in ECHELON-2 are expected to be comparable in terms of management and anticipated outcome, regardless of ALK status.

During the scoping stage of this appraisal, we raised our concerns regarding any further sub-group analysis beyond what was pre-specified in the ECHELON-2 trial. This was also raised as a key concern during the Decision Problem meeting in September 2019 and NICE Check-In Teleconference in October 2019. During these interactions, the guidance from the NICE technical team and the ERG (during the Decision Problem call) was to conduct the analyses which we considered to be appropriate and feasible. Consistent with this guidance, the company submission

presents both analyses which were powered and pre-specified in the ECHELON-2 statistical analysis plan: ITT and sALCL. We consider that this approach provides NICE with the appropriate information and analysis on which to base its recommendation regarding the clinical and cost effectiveness of BV+CHP for the treatment of previously untreated patients with CD30+ PTCL.

Validation

B24. Priority question: Please provide details about what validation efforts were performed in section B.3.10 of the CS and the results of these validation efforts. This could be presented for example (but not necessarily) with the help of the validation tool AdViSHE (https://advishe.wordpress.com/author/advishe/).

Please confirm whether black-box tests to detect modelling errors were conducted. If not, please include these steps as well.

Response: Section B.3.10 in the submission dossier describes the internal and external validation undertaken for this appraisal. To recap – the electronic model was quality checked by the NICE PRIMA Express process, the results of the PartSA approach were compared to those of a multistate model (also estimated using the ECHELON-2 data), the model was internally quality checked by a health economist not involved in the development and model results were compared with the outcomes of the ECHELON-2 trial.

The PRIMA Express process assessed internal validity:

> *"In order to assess whether the cost-effectiveness model has been implemented correctly and is structurally robust, a number of black box tests were performed. The black box tests were developed to probe the correctness of the model using different heuristics or extreme values."… "In addition, the model has been checked for errors in coding, formulae and cell referencing, as well as errors in logic." (Page 13 of the PRIMA Express report).*

The overall assessment from the PRIMA Express report was:

"the model and documentation generally functions well, has minimal errors, and is not difficult to use." (Page 27 of the PRIMA Express report).

The minimal errors and suggestions for improvement provided by the PRIMA Express report were addressed and the updated model was further quality checked by a health economist who had not been involved in its development prior to submission to NICE. The list of 'black box' testing undertaken as part of the PRIMA Express service is presented in Appendix C.

To check the structural integrity of the model, results were compared with a multistate model – outcomes were similar between the two model structures. The quality check by the independent health economist also included black box tests as well as re-building the model in a separate Excel document to ensure comparable results. Examples of the types of test used in the model include (note: this list is not exhaustive): setting all costs equal to zero (and ensuring the total costs were equal to zero), setting all utilities equal to one (and the QALYs should equal the life years), dividing the total QALYs by the total life years (this provides the average utility value for the cohort which was then validated with the literature) and setting the efficacy equal between the two treatment arms (and the efficacy results should be equal). Minimal changes were required following this internal quality check – mainly pertaining to transparency rather than technical errors. Finally, the outcomes predicted by the economic model were compared with ECHELON-2 as presented in Appendix J from the submission dossier.

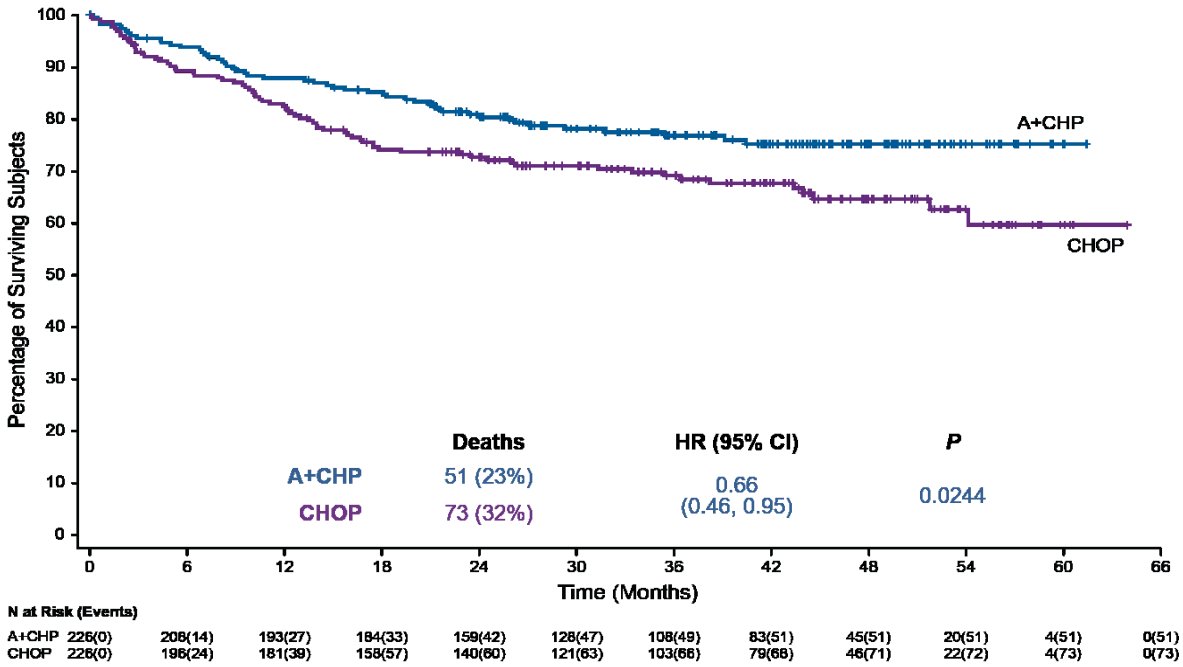
B25. Priority question: Please provide a detailed comparison between the OS estimates predicted by the model and the evidence presented in section B.1.3.4 of the CS. Please highlight the differences, if any, and discuss the implications of these on the model results. This could include (but not be limited to) for example a comparison of the 5-year OS estimates in section B.1.3.4 and those predicted by the model (at first sight, the 5-year OS predicted by the model seems to be too high compared to those presented for example in Table 5 of the CS).

Response: The ECHELON-2 trial provides Kaplan-Meier data for OS for a median follow-up of 42.1 months (95% CI, 40.4-43.8) – Figure 9 below reproduces Figure 13 in the submission dossier. Throughout the trial follow-up, the ECHELON-2 observed

outcomes are superior to the evidence presented in Section B.1.3.4 which is largely outdated and of poor quality, as discussed in Section B.2.13. The two papers cited in this section as providing outcomes for patients with PTCL are Vose et al. (2008) and Gleeson et al. (2018). Vose et al. (2008) was a retrospective worldwide study that reported substantial variability in clinical practice across the centres and focused on patients diagnosed between January 1990 and December 2002. Similarly, Gleeson et al. (2018) was a retrospective study considering two academic centres in the UK and focused on patients diagnosed between January 2002 and January 2012.

There are discrepancies between the aforementioned studies in baseline characteristics known to be prognostic when compared with ECHELON-2, for example: patients are older in the Vose et al. (2008) study (median age 62 vs. 58, respectively) and with a higher IPI score in the Gleeson et al. (2018) study (IPI score 3-5 51% vs. 44%, respectively) – both of which are likely to lead to worse outcomes in the published literature. Any additional differences may be explained by the study design; both Vose et al. (2008) and Gleeson et al. (2018) were retrospective chart or database analyses, whereas the ECHELON-2 study is a prospective, randomised, double-blind, active comparator phase III trial. Whilst these are the only studies available showing long-term historical outcomes for patients with PTCL, the management of such patients has improved and evolved over recent years – most notably through the introduction of BV in 2012 for the treatment of patients with relapsed/refractory sALCL.

Figure 9: Overall Survival for the ITT population (Figure 13 in submission dossier)



As the outcomes in the observed time period differed between the literature and the ECHELON-2 trial, it was considered that these outcomes would also differ in the longer-term extrapolation period. Therefore, these studies were not considered as a useful source of validation for the survival analyses. However, the outcomes in the trial and the extrapolated outcomes beyond this were validated by six clinicians at the June advisory board – detailed in Section B.3.10.2 in the submission dossier.

Following the dossier submission, a multi-country audit of patients with sALCL treated with CHOP was presented in December at ASH 2019 and compared outcomes with CHOP in the six centres (including UK centres) to the control arm of ECHELON-2.[28] Reassuringly, the audit concluded that survival outcomes of CHOP treated patients in routine care were comparable to the ECHELON-2 control arm, notwithstanding patients in the audit who had an ECOG >3 (an exclusion criterion for ECHELON-2).

Furthermore, the model predictions for OS at 5-years in the base case (70% and 62% for BV+CHP and CHOP arms, respectively – difference of 8%) are relatively conservative compared to those observed from the Kaplan-Meier data at 5-years (75% and 60%, respectively – difference of 15%). **Note:** the base-case accounts for treatment switching methods and assumes that no patients in the BV+CHP arm can

receive re-treatment with BV and that patients with non-sALCL disease cannot receive BV in the relapsed/refractory setting.

B26. Priority question: Please compare the results in the sALCL subgroup CHOP arm, particularly cost, QALYs and OS from receipt of BV, with those in TA478 (R/R sALCL appraisal BV arm).

Response: The TA478 appraisal considered BV for relapsed/refractory (R/R) sALCL. The updated ICER on which the NICE decision was based was £18,324 (including PAS) – results shown in Table 27. These results are discounted; the undiscounted life years gained were 12.29 for the BV arm and 3.99 for the CHOP arm, the undiscounted QALYs were [redacted] and [redacted], respectively and the total undiscounted cost of BV (including: acquisition, administration, concomitant medications, adverse events, stem cell transplant, follow-up and subsequent therapies) was [redacted].

Table 27: Final results for the TA478 appraisal in R/R sALCL

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER incremental (£/QALY)
Chemotherapy	[redacted]	3.09	[redacted]	N/A	N/A	N/A
Brentuximab vedotin	[redacted]	8.02	[redacted]	[redacted]	[redacted]	£18,324

Abbreviations: QALYs, quality adjusted life years; ICER, incremental cost-effectiveness ratio; LYG, life-year gain; R/R, relapsed/refractory; sALCL, systemic anaplastic large cell lymphoma.

Due to the partitioned survival structure of the economic model presented in this appraisal, it is impossible to separate out outcomes for patients that have progressed (patients are not tracked from when they enter to leaving the progressed health state) to allow for a direct comparison with the TA478 appraisal. In this appraisal, the total undiscounted life years estimated for the sALCL population are: 20.54 and 17.53 for BV+CHP and CHOP, respectively. Both have a similar number of life years in the progressed health state: 6.46 and 6.91, respectively. However, these numbers are not directly comparable with the estimates from TA478 as these represent the average life years of the whole cohort, not just of those that reach the progressed setting. Therefore, these numbers are dependent on the proportion of patients remaining progression-free, the proportion who have died before reaching the progressed health state as well as those that eventually progress. By contrast, the TA478 submission

considers relapsed/refractory patients from baseline and so 100% of the cohort is in the progressed health state already. In this structure it is impossible to determine which direction and magnitude this would impact the life years in the progressed health state.

In addition, it is important to note that the efficacy of BV in the R/R setting is not being considered as part of the current appraisal. Subsequent use of BV in the model is based on rates observed in ECHELON-2 for patients with R/R sALCL who have not received BV at frontline (i.e. in the CHOP arm). Only 69.8% of patients with R/R sALCL receive BV after relapsing on CHOP, this is compared with 100% in the BV arm of the TA478 submission.

Both components (i.e. the reduced cohort reaching the progressed state and the lower proportion receiving BV once progressed) result in the undiscounted cost of subsequent BV in the CHOP arm being much lower than reported in the TA478 appraisal ([redacted] vs. [redacted], respectively). Note: these are the total costs accrued by BV in the R/R sALCL setting i.e. they have been multiplied by the proportion of patients actually reaching the R/R setting and receiving BV – which is 100% for the TA478 submission but substantially less in this appraisal. If we consider the *input* of total cost of subsequent BV prior to being multiplied by the cohort who receive BV in the R/R setting, the total costs are comparable between this appraisal ([redacted]) and the TA478 appraisal ([redacted]).

B27. Priority question: Please use any available external data (e.g. from previous technology appraisals) to validate the extrapolated survival curves for the CHOP arm used in this submission. This could include, but not be limited to, validating 5-year OS as in question B23.

Response: There is only one other technology appraisal relevant to this appraisal, and that is the submission of brentuximab vedotin for the treatment of R/R sALCL (TA478). The response to question B26 describes why it is very difficult and potentially incorrect to attempt to validate the extrapolated survival curves from this submission using TA478. However, comparisons are made where data are available.

Section C: Textual clarification and additional points

Textual clarification

C1. Priority question: The CS reports that the base-case uses EQ-5D model coefficients from model 7, as shown in Table 1 of Appendix M. There are several discrepancies between Table 40 in the CS (Model of EQ-5D used in the base-case analysis) and Table 1 in Appendix M, including the following:

a. **In model 7 in Table 1 of Appendix M, the disutility associated with AEs does not match Table 40 and Table 1 suggests a positive impact of adverse events (AEs) on HRQoL.**

b. **Age = -0.002 shown in Table 40 is not included in Model 7 in Table 1.**

c. **Post-consolidative SCT = 0.035 shown in Table 40 not shown in Model 7 in Table 1.**

d. **ALK positive sALCL = -0.0269 but not included in Table 40.**

Please explain these discrepancies, clarify which are the correct values and provide updated tables and model as appropriate. Please also explain why in Table 1 there are negative standard errors and why Model 4 and model 7 have the same explanatory variables but different coefficients.

Response: There is a typographical error in Table 1 of Appendix M; coefficients beyond model 3 (models 4, 5, 6, 7) have been misaligned in the table by 1 row. This has effectively led to the omission of the coefficients for age in these models and misaligned all coefficients below the row containing the estimated coefficient for 'Post-SCT'. Please accept our apologies for this. A revised version of Table 1 Appendix M is presented in Table 28. In response to the specific questions:

a) All statistical models estimated suggested a negative impact on HRQL associated with AEs, as expected. The size of this decrement in model 7 (base-case) was 0.0269.

b) As described above, the coefficient for age was erroneously omitted from Table 1 of Appendix M; the estimate of a 0.002 decline in EQ-5D per year reported in Table 40 of the CS is correct

c) and d) As described above, because of the erroneous mis-alignment in Table 1 Appendix M, these estimates are presented in the incorrect row.

The estimates in parentheses represent the p-value, these have also been corrected in Table 28. We can confirm that the estimates in the electronic model and Table 40 of the CS remain accurate.

Table 28: Statistical models of EQ-5D (UK tariff) [replaces Table 1 of Appendix M in CS]

	Model						
	1	2	3	4	5	6	7
BV+CHP	-0.0150	0.00734					
	(0.332)	(0.653)					
On treatment		-0.00813					
		(0.275)					
On treatment - BV+CHP		0.0148					
		(0.163)					
Post-progression	-0.0249***	-0.0252***	-0.0287***	-0.0283***	-0.0261***	-0.0258***	-0.0271***
	(0.00329)	(0.00331)	(0.000750)	(0.000868)	(0.00221)	(0.00247)	(0.00146)
Baseline EQ-5D	0.333***	0.333***	0.334***	0.333***	0.355***	0.356***	0.343***
	(0)	(0)	(0)	(0)	(0)	(0)	(0)
Post-SCT			0.0395***	0.0367***	0.0379***	0.0367***	0.0354***
			(0.000205)	(0.000581)	(0.000381)	(0.000585)	(0.000919)
Experiencing AEs				-0.0273***	-0.0268***	-0.0266***	-0.0269***
				(0.00367)	(0.00433)	(0.00455)	(0.00416)
ALK-positive sALCL					0.0568***	0.0438**	
					(0.00395)	(0.0330)	
ATLL					-0.0827	-0.0708	
					(0.172)	(0.241)	
AITL					-0.0206	-0.0137	
					(0.391)	(0.569)	
EATL					-0.0859	-0.0710	
					(0.398)	(0.483)	
PTCL-NOS					-0.0182	-0.0108	
					(0.403)	(0.621)	
Age (years)						-0.00116**	-0.00177***
						(0.0359)	(0.000498)
Constant	0.571***	0.560***	0.560***	0.565***	0.544***	0.608***	0.655***
Observations	5,041	5,041	5,041	5,041	5,041	5,041	5,041
Number of groups	438	438	438	438	438	438	438

Note: p-values are presented in parentheses (***, p<0.01; **, p<0.05; *, p<0.1)
Abbreviations: AE, adverse event; AITL, angioimmunoblastic T-cell lymphoma; ALK, anaplastic lymphoma kinase; ATLL, adult T-cell leukaemia/lymphoma; BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; EATL, enteropathy-associated T-cell lymphoma; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified; sALCL, systemic anaplastic large cell lymphoma; SCT, stem cell transplan

C2. Section 3.3. of Appendix D states that *"all retrieved studies were assessed against the eligibility criteria for the economic review"*. Please confirm that this should instead refer to the review of clinical effectiveness.

Response: We can confirm that the statement should read "*All retrieved studies were assessed against the eligibility criteria for the clinical effectiveness* review" instead of "…*economic review*." Thank you for pointing out this typo, we apologise for any confusion it may have caused.

C3. The first sentence in section B.3.5.4.3 states that patients receive an average of 8.23 cycles of subsequent BV, with reference to TA478. The last sentence of this section notes how comparable this value is to the mean of 8.2 cycles in TA478. Please confirm that the average of 8.23 cycles is copied from TA478, making it redundant to compare this value to itself.

Response: This is correct; the model input of 8.23 cycles is taken from TA478 and it is therefore redundant to compare the value to itself. This sentence should have been omitted or should read: "*The average number of cycles received post-progression is identical to that received in the R/R sALCL setting (mean of 8.23 cycles)".*

C4. Please explain the role of β2 microglobulin level in OS and PFS for sALCL patients (as shown in Figure 6) including supporting references.

Response: β2 microglobulin level may be a prognostic indicator in malignant lymphoma however, in line with the available literature, and from discussions with UK KOLs, β2 microglobulin has not been studied in any level of detail as a prognostic indicator in PTCL and it does not impact on the therapeutic decision-making process in this setting.[29]

UK clinicians also confirmed that the IPI score would be the most common prognostic outcome tool that is taken into consideration when a PTCL presents. The IPI score does not factor in β2 microglobulin level.

C5. Please clarify why on page 84 of the CS it is mentioned that no relevant economic evaluations were found in the systematic review but despite that the model structure, assumptions and data sources for the current appraisal were based to

some extent on TA478 (considered to be the most relevant for the current appraisal by the company), TA524 and TA577.

Response: The statement “no relevant economic evaluations were identified in the literature review” on page 84 of the company submission relates to the fact that no economic models were identified from the systematic review in the relevant population (i.e. in untreated PTCL). The paragraph later goes on to say that the assumptions and data sources were informed by identified NICE appraisals of BV in ***different*** populations, including: R/R sALCL (TA478) [30], CD-30+ Hodgkin’s Lymphoma (TA524) [31] and CD-30+ cutaneous T-cell lymphoma (TA577) [32].

These appraisals were considered due to the paucity of economic evidence in the relevant population. However, whilst these appraisals provided some information as to how the value of BV had been demonstrated previously, they consider populations with different conditions which have different treatment goals and pathways. Therefore, the model structures presented were not considered directly relevant to this appraisal. In addition to TA524 and TA577 looking at different diseases, the key difference in the treatment pathways relevant to the TA478, TA524 and TA577 appraisals is the role and objective of stem cell transplant (SCT) – because SCT was considered so fundamental in these populations it was included in the model structures for these appraisals. However, as stated in Section B.3.2 of the submission dossier, in the frontline PTCL setting the objective of treatment is to achieve response and ultimately remission, irrespective of the use of transplant. As confirmed with clinical experts, the ability to bridge a patient to transplant is not considered an essential treatment goal in frontline PTCL because some patients achieve such a good response that no transplant is required.

However, whilst these appraisals are not directly relevant to the population nor the model structure for this appraisal, some aspects of the treatment pathway are similar. Therefore, where appropriate, assumptions and inputs have been informed and/or validated from these appraisals.

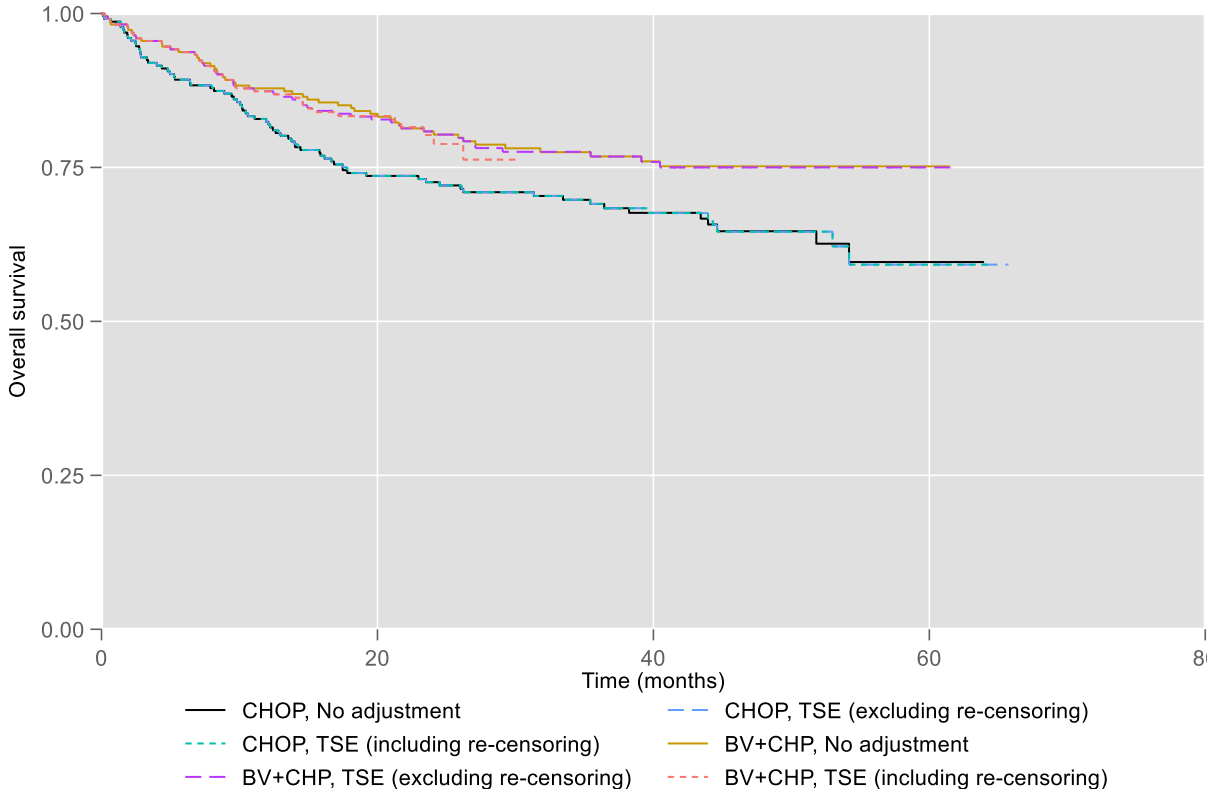
C6. Please provide Figure 24 in the CS with a higher resolution. As it is now, it is very difficult to distinguish between the 6 lines shown in the figure. Please also explain the

rationale for the following statement on page 95: "*As shown in Figure 24, the BV+CHP arm of ECHELON-2 is associated with a declining hazard over time*".

Response: Response: Figure 10 presents a higher resolution version of Figure 24 from the CS (enhanced metafile format). In order to further improve legibility, the figure is also presented in Figure 11 with a truncated y axis.

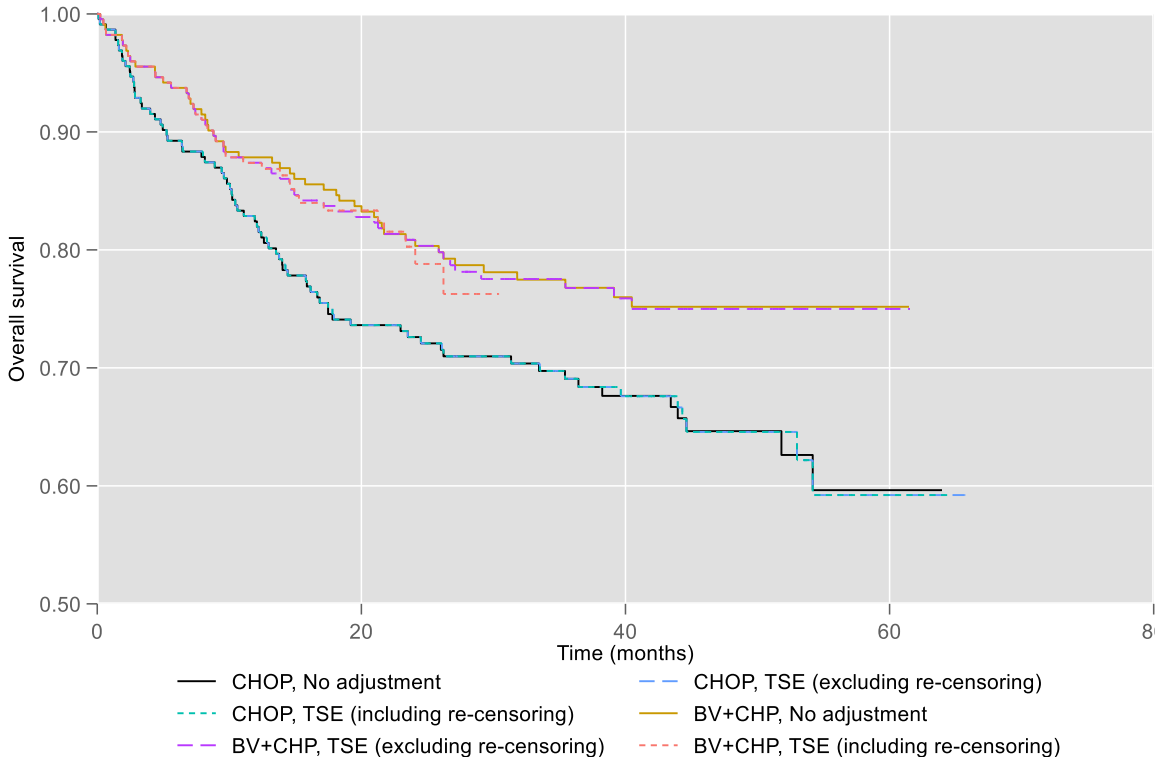
Figure 24 shows evidence of a declining hazard over time, based on the observation that the Kaplan-Meier curve exhibits a 'plateau' towards its tail (a perfectly flat Kaplan-Meier curve, for example, would imply a hazard of 0). Please see also response to B8 for evidence regarding the shape of the hazard function in ECHELON-2.

Figure 10: Adjusting for treatment switching in patients with re-treatment (BV+CHP arm) and patients with non-sALCL receiving subsequent brentuximab vedotin (CHOP arm), OS – ITT [Higher resolution version of Figure 24 in CS]



Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; TSE, two-stage estimator.

Figure 11: Adjusting for treatment switching in patients with re-treatment (BV+CHP arm) and patients with non-sALCL receiving subsequent brentuximab vedotin (CHOP arm), OS – ITT [Higher resolution version of Figure 24 in CS with truncated y axis]



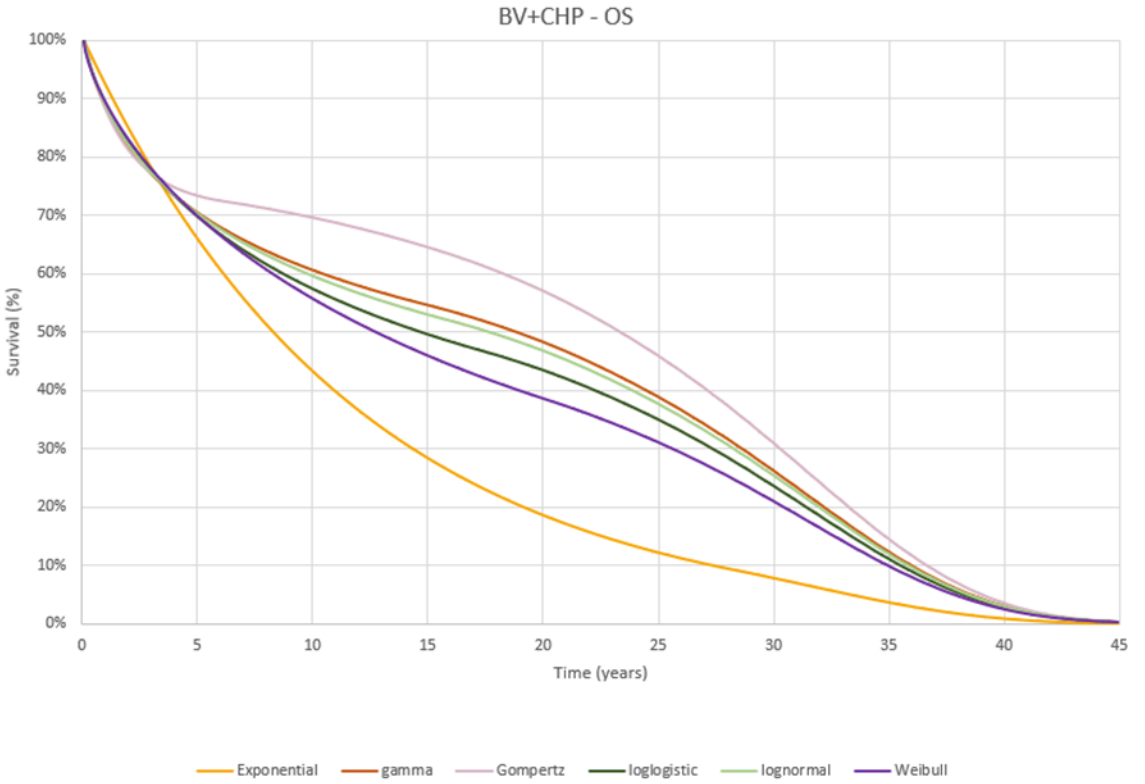
Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ITT, intention-to-treat; TSE, two-stage estimator.

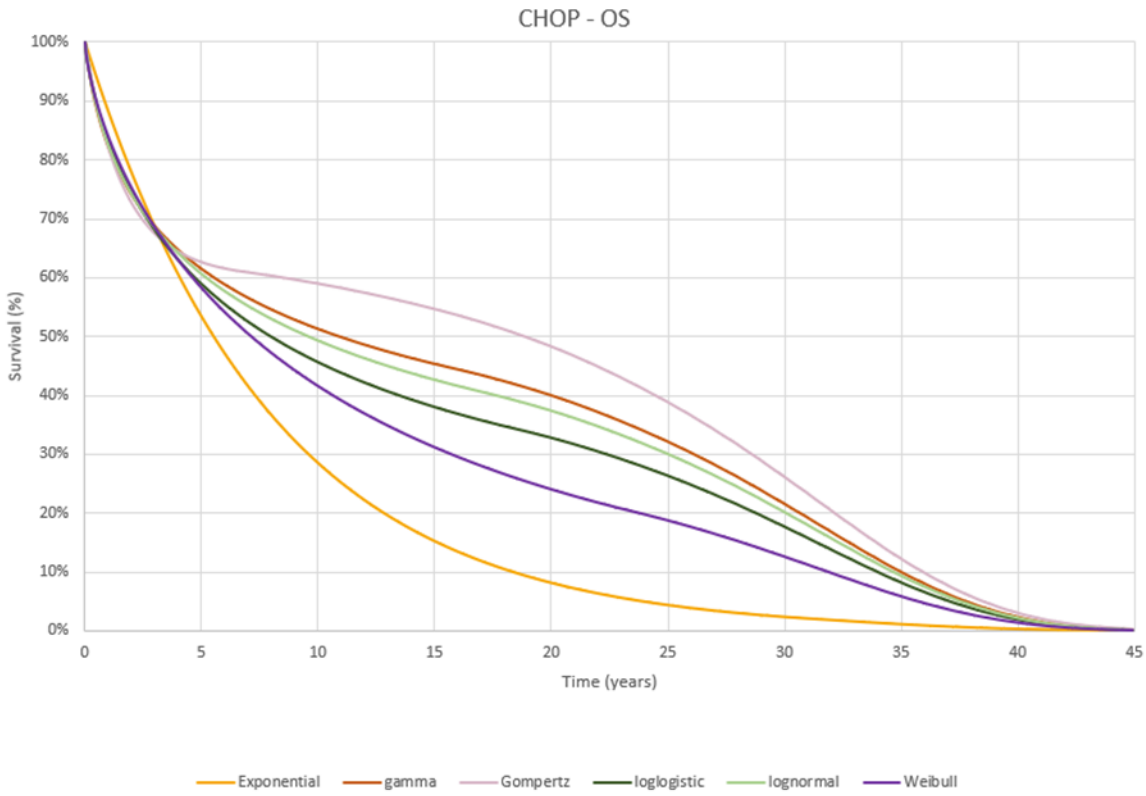
C7. Please include OS curves based on the general population (background mortality only) in Figure 25 of the CS.

Response: Figure 25 of the submission dossier has been updated with background mortality in

Figure 12. These extrapolations include adjustment for subsequent BV use, and are reported for the ITT population only.

Figure 12: Standard parametric extrapolation, OS – ITT population, including TSE adjustment and background mortality





Abbreviations: BV+CHP, brentuximab vedotin, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, prednisone; OS, overall survival.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you	
1.Your name	**Vicki Gregory**

2. Name of organisation	Lymphoma Action
3. Job title or position	Senior medical writer
4a. Brief description of the organisation (including who funds it). How many members does it have?	Lymphoma Action is a national charity, established in 1986, registered in England and Wales and in Scotland. We provide high quality information, advice and support to people affected by lymphoma – the 5th most common cancer in the UK. We also provide education, training and support to healthcare practitioners caring for lymphoma patients. In addition, we engage in policy and lobbying work at government level and within the National Health Service with the aim of improving the patient journey and experience of people affected by lymphoma. We are the only charity in the UK dedicated to lymphoma. Our mission is to make sure no one faces lymphoma alone. Our work is made possible by the generosity, commitment, passion and enthusiasm of all those who support us. In 2018 we raised a total income of £1,432,177 from various fundraising activities. We have a policy for working with healthcare and pharmaceutical companies – those that provide products, drugs or services to patients on a commercial or profit-making basis. This includes that no more than 20% of our income can come from these companies and there is a cap of £50k per company. Acceptance of donations does not mean that we endorse their products and under no circumstances can these companies influence our strategic direction, activities or the content of the information and support we provide to people affected by lymphoma.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator	Takeda £44,885: support for core activities, information, patient support and education/training Bristol-Myers Squibb Pharmaceuticals Ltd £5,000: support for core activities, information, patient support and education/training Janssen-Cilag Ltd £15,000: support for core activities, information, patient support and education/training

products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.] If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We asked patient contacts who we support to comment. We also had a call-out on our social media channels for patients with a relevant diagnosis to come forward who would like us to consider their views. We sent questionnaires to people who responded, asking about their experience of current treatment and their response to this new technology, with particular emphasis on quality of life. We have used their responses as the basis of this submission. We have also included information based on our prior experience with patients with this condition.

Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Peripheral T-cell lymphomas are rare, aggressive forms of non-Hodgkin lymphoma. Because they are rare, they can be difficult to diagnose. Some people report significant delays from being passed between different medical specialties before receiving an accurate diagnosis. There are several different types of peripheral T-cell lymphoma and symptoms can be varied, including enlarged lymph nodes, fatigue, weight loss, fevers, night sweats, itching or skin rash. Depending on the type of T-cell lymphoma and where it develops, people might experience shortness of breath, cough, enlarged liver or spleen, diarrhoea or abdominal pain. If the bone marrow is affected, people can develop neutropenia, anaemia and thrombocytopenia. With nasal NK/T-cell lymphoma, people might develop a blocked nose, nosebleeds, facial swelling or weepy eyes. Peripheral T-cell lymphoma has a significant impact on the quality of life of patients and their carers. The disease, and in particular current treatments for the disease, can have a significant effects on their working life, social life and ability to do the things they enjoy. Patients report prolonged time off work due after aggressive treatment regimens. This can cause financial hardship. One person who responded to our questionnaire was yet to return to work, over 2 years after treatment. The psychological impact is also significant. Being a rare disease, patients may feel isolated and unsupported, and are often looked after by staff who have limited experience of treating people with the disease. Patients also report the adverse impact of reading about survival statistics in peripheral T-cell lymphomas. For patients with a successful outcome, there is ongoing anxiety and fear of relapse, which can last for many years after treatment. One patient reported that he ‘longed to be normal again’. Caring for someone with peripheral T-cell lymphoma is challenging emotionally, practically and financially. Carers often provide transport to-and-from hospital and also provide emotional support, whilst trying to deal with an emotionally difficult situation themselves. Some have to take on the responsibility of being the sole wage earner, despite needing significant time off work to care for a loved one who might be seriously ill for a prolonged period. Dependents are also affected by the negative impact of the disease.

Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Peripheral T-cell lymphoma is difficult to treat. Because they are rare, there is no consensus on the best standard of care for many types of peripheral T-cell lymphoma. Treatment typically involves intensive chemotherapy regimens, autologous or allogeneic stem cell transplantation, or a targeted treatment usually accessed through a clinical trial. Prognosis for most types of peripheral T-cell lymphoma is poor. The main concern with current treatment is that response rates in most peripheral T-cell lymphomas are low and relapse is common. Patients are also concerned at the lack of options for relapsed or refractory disease. Patients also find current treatments difficult to tolerate. Many chemotherapy regimens used to treat T-cell lymphomas have significant side effects and risk of late effects. They also involve repeated trips to-and-from hospital for outpatient treatment. Many patients have a stem cell transplant as part of their treatment. Stem cell transplants have a massive impact on quality of life, typically requiring an extended hospital stay, time off work and a prolonged recovery period. One patient described current treatment pathways as tough, both physically and mentally.
8. Is there an unmet need for patients with this condition?	Yes, there is a clear unmet need for effective, well tolerated front-line therapy for peripheral T-cell lymphoma. There is also a need for an established standard of care to ensure that patients are treated appropriately despite the rarity of the condition.

Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The most important perceived advantage of brentuximab vedotin was the significant improvement in outcomes compared to other treatment options. This is critical. One patient viewed it as a lifesaver. The patient who had received brentuximab vedotin through a clinical trial reported having a rapid response to treatment and achieving a complete remission. Having treatment as an outpatient was also viewed as a big advantage. This would reduce the amount of time spent at hospital (either as an inpatient or outpatient) and allow patients to participate more in their normal activities. It would also reduce the burden on family and friends, who often have to drive patients to their appointments. Patients felt brentuximab vedotin might have a more acceptable tolerability profile than other treatment options and might provide more opportunity to carry on with normal day-to-day activities. This was seen as having a potential wider positive impact on family and carers. The patient who had received brentuximab vedotin reported experiencing tiredness and peripheral neuropathy but no other side effects. He commented that his quality of life was better than he could ever have imagined and much better than when having previous treatments.
Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	As with all treatments, we would expect patients to be concerned about potential side effects. However, the respondents to our questionnaire did not raise any specific perceived disadvantages. The patient who had received brentuximab vedotin through a clinical trial commented, “I would categorically say NO disadvantages whatsoever and I am eternally grateful that I was able to treated with brentuximab.”

Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	

Other issues	
13. Are there any other issues that you would like the committee to consider?	

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Peripheral T-cell lymphoma has a significant negative impact on the quality of life of patients and their carers.
- In most cases of peripheral T-cell lymphoma, there is no accepted standard of care. Current treatment options are aggressive and cause significant side effects, late effects and psychosocial effects. Treatment pathways frequently involve stem cell transplants.
- The outcome of current treatments for many types of peripheral T-cell lymphoma is very poor.
- There is a clear unmet need for an effective treatment that improves outcomes, and resulting quality of life, in peripheral T-cell lymphoma.
- Patients feel that brentuximab vedotin has the potential to improve outcomes and is more convenient that current treatment options.

Thank you for your time.

Please log in to your NICE Docs account to upload your completed submission.

……

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Professor Donal O' Donoghue**
2. Name of organisation	**NCRI-ACP-RCP-RCR**

3. Job title or position	**RCP registrar**
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**NCRI-ACP-RCP-RCR**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**None**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Achieve complete remission and cure (long-term survival without relapse)
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	PR and CR are clinically significant but ultimately PFS and OS are the most important outcomes

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes – given a substantial proportion of patients with this condition still relapse and die from their disease
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	A key point to make here is that CD30+ PTCL comprises a biologically and clinically heterogeneous group of TNHL. ~70% of the ECHELON2 trial were well defined and 'homogenous' (**ALCL**) whereas the remaining 30% should be regarded as a very different group of diseases. Nevertheless, treatment approaches are similar (empirically adopted from B cell lymphoma protocols): CHOP chemotherapy with/without intensified chemotherapy consolidation (including autologous stem cell transplant for selected patients)

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	https://b-s-h.org.uk/media/2895/t-nhl-guideline-3-8-13-updated-with-changes-accepted-v1-rg.pdf Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma) Updated August 2013 British Committee for Standards in Haematology C Dearden, R Johnson, R Pettengell, S Devereux, K Cwynarski, S Whittaker and A McMillan. A new BSH guideline is in draft form and will be submitted for publication later in 2020
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Reasonably well defined. CHOP chemotherapy for the majority as remission induction. Younger/fitter patients may have intensified chemotherapy consolidation (including autologous stem cell transplant for selected patients)
• What impact would the technology have on the current pathway of care?	CHP+A would have a substantial impact for patients with ALCL given the PFS and OS advantages seen in the ECHELON2 study. This would be immediately practice-changing. For the CD30+ PTCL of non-ALCL subtype, the impact on standard care would be much less certain given the absence of clear benefit in the study; these are clinically and biologically entirely different diseases with the only commonality being expression of the CD30 antigen.

10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Currently used only as brentuximab vedotin monotherapy for relapsed/refractory ALCL and r/r Hodgkin lymphoma.
• How does healthcare resource use differ between the technology and current care?	Negligible difference in time/resource utilisation.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Outpatient/Daycase delivery in specialist haemato-oncology units (as current practice)
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Nil
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes – for the ALCL group this is a paradigm shift in survival outcomes that has not previously been seen in first-line therapy Again, different for the non-ALCL subgroups where the advantage is not clear.

• Do you expect the technology to increase length of life more than current care?	Yes for ALCL (but not for the non-ALCL subgroups)
• Do you expect the technology to increase health-related quality of life more than current care?	Yes for ALCL (but not for the non-ALCL subgroups)
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Yes – (Alk positive and Alk negative) ALCL – comprised ~70% of the ECHELON2 study
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for	No meaningful differences

example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Standard approaches for diagnosis and assessment of response. Nil additional .
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	Not aware of any

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes this is a paradigm shift in management for (Alk positive and Alk negative) ALCL.
• Is the technology a 'step-change' in the management of the condition?	YES. See above comments - first RCT to demonstrate significant PFS and OS advantaged in TNHL. In this case the benefits were absolutely clear and practice-changing in the ~70% of patients in the ECHELON2 study who had ALCL
• Does the use of the technology address any particular unmet need of the patient population?	YES – unmet need of relapse and death from disease
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	No clinically meaningful differences in AEs compared to standard care.

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	See above – PFS and OS - yes
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	Not aware of any

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance?	
21. How do data on real-world experience compare with the trial data?	Real world experience of standard CHOP (control arm) therapy for ALCL in a UK cohort shows very similar outcomes to the control arm, supporting the superiority of CHP+A in ALCL in the ECHELON2 study. (Martinez, N *et al* abstract at ASH 2019 meeting)
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	Not aware

22b. Consider whether these issues are different from issues with current care and why.	Not aware

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- A+CHP for (alk positive and negative) ALCL represents a paradigm shift in clinical management resulting - for the first time - significantly improved survival outcomes and would be immediately practice-changing in the NHS for this well-defined group of TNHL
- The situation is much less clear for the ~30% of patients in the study of non-ALCL subtype. No clear benefit in this very different group of diseases
- The technology is easy to deliver and unlikely to result in any additional healthcare utilisation costs. On the contrary, fewer relapses will be cost saving
- Patients with ALCL and the NHS will substantially benefit from access to A+CHP
- Uncertainty remains as to the additional value of autologous stem cell transplant as consolidation in first remission (true for both existing [CHOP] and proposed [CHP+A] therapy) – no clear conclusions can be drawn on this issue from current data

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	Dr Kate Cwynarski
2. Name of organisation	UCLH 3rd floor West 250 Euston Road London NW1 2PG and Chair of British Society of Haematology Lymphoma Specialist Interest group

3. Job title or position	Consultant Haematologist
4. Are you (please tick all that apply):	**YES** an employee or representative of a healthcare professional organisation that represents clinicians? **YES** a specialist in the treatment of people with this condition? **YES** a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it **YES** other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	N/A – see above

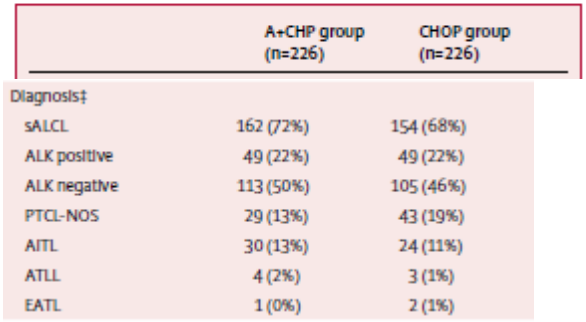
The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Main aim: to cure the condition Some patients who are young and fit enough for a haematopoietic stem cell transplant may proceed to this consolidation strategy if remission achieved from 1st line therapy
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	A clinically significant treatment response would be: Reduction in tumour size (CR/PR/ORR) Prolongation of survival (PFS/OS measured in months)
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes there is an unmet need in this aggressive lymphoma. Treatment of relapsed or refractory T-cell lymphoma has a very poor prognosis with survival of only a few months so optimising first line treatment is paramount.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	ALCL: Standard treatment is CHOP (or in a very small cohort of patients CHOEP is used but this is not standard practice in UK centres). **Non-ALCL: AIL/PTCL** Standard treatment is CHOP but in a very small cohort of patients other strategies are used: Such as IVE/intermediate dose methotrexate (Newcastle approach; A Lennard *et al*). Some patients who are young and fit enough for a haematopoietic stem cell transplant may proceed to this consolidation strategy if remission (complete remission is achieved from 1st line therapy) and Physician favours this option (our BCSH guidelines suggest this modality is 'considered', rather than 'recommended' as the evidence base to support it is of low quality). (BCSH guideline 2013: 'CHOP remains the standard therapy. Consideration should be given to consolidation with auto-HSCT (LEVEL IV GRADE C).' Recently revised Pan London Guidelines (released 15/1/20): state similar guidance: https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-Less-Common-Guidelines-Jan-2020.pdf *ALCL* ALCL ALK+ and ALK- should receive Brentuximab-CHP where possible (currently not funded). Otherwise six cycles of CHOP14 or 21 chemotherapy. There is some evidence to suggest that younger patients with this subtype benefit from the addition of etoposide. Consideration should be given for ASCT in CR1 for ALK- ALCL and high risk ALK+ ALCL. For PTCL-NOS, AITL Outside trial, CHOP (14 or 21) x 6 remains the standard first-line therapy. Phase 2 data suggest that strong consideration should be given to consolidation with auto- (or allogeneic) HSCT in first remission Alternative induction therapies include: CHOEP, GEM-P, ICE, Newcastle (NCRI/SNLG).

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	https://b-s-h.org.uk/media/2895/t-nhl-guideline-3-8-13-updated-with-changes-accepted-v1-rg.pdf Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma) Updated August 2013 British Committee for Standards in Haematology C Dearden, R Johnson, R Pettengell, S Devereux, K Cwynarski, S Whittaker and A McMillan. Revised BCSH guidelines are being drafted presently (to be submitted for publication later in 2020) Also Recently revised Pan London Guidelines (released 15/1/20): https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-Less-Common-Guidelines-Jan-2020.pdf
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Pathway is well defined but there is some variation in practice ALCL: Standard treatment is CHOP (or in a very small cohort of patients, CHOEP is used, but this is not standard practice in UK centres). Non-ALCL: AIL/PTCL Standard treatment is CHOP but in a very small cohort of patients other strategies are used: Such as IVE/intermediate dose methotrexate (Newcastle approach; A Lennard *et al*). Some patients are young and fit enough for a haematopoietic stem cell transplant may proceed to this consolidation strategy if remission (complete remission) is achieved from 1st line therapy. Centres differ in their approach: ie some centres would not offer this treatment to patients >65 years. Most centres would rarely offer this to patients> 70yrs.

• What impact would the technology have on the current pathway of care?	A huge impact: as the data shows that response rates (CR) and PFS/OS are significantly improved. It may also increase the proportion of patients who proceed to haematopoietic stem cell transplant (From ECHELON-2: Consolidative stem cell transplantation was delivered in 50 (22%) patients in the A+CHP group and 39 (17%) in the CHOP after the end of treatment at the discretion of the investigator. This endpoint was influenced by Investigator preference re whether this consolidation strategy was favoured so this trial wasn't powered to properly assess this outcome). Alternatively it may be associated with a reduction in PBSCT consolidation as the evidence base for this consolidation strategy is of low quality, and some Physicians may be impressed by the improved outcome of 1st line therapy and choose not to proceed to futyjer therapy (consolidation PBSCT). One issue that confounds this is that relapsed T-cell lymphoma has a poor prognosis and response to treatment is disappointing (usually months, unless a 2nd remission can be achieved and an allograft is performed).
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Brentuximab monotherapy is used in treating patients with relapsed ALCL and relapsed Hodgkin lymphoma. Brentuximab vedotin, cyclophosphamide, doxorubicin, and prednisone (A+CHP) was used in the ECHELON-1 trial (in Hodgkin lymphoma) and ECHELON-2 trial (in CD30-positive peripheral T-cell lymphoma). Brentuximab will be administered with cyclophosphamide, doxorubicin, and prednisone as it is administered as monotherapy on our chemotherapy day units for our out patients.
• How does healthcare resource use differ between the technology and current care?	The difference is that Brentuximab (given intravenously [IV]) replaces vincristine (given intravenously [IV]). Treatment is: cyclophosphamide 750 mg/m² and doxorubicin 50 mg/m² on day 1 of each cycle intravenously and prednisone 100 mg once daily on days 1 to 5 of each cycle orally, followed by either brentuximab vedotin 1·8 mg/kg (A+CHP) on day 1 of each cycle. or vincristine 1·4 mg/m² intravenously (CHOP) on day 1 of each cycle.

• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care: administered on our chemotherapy day units for our out patients. Review of the patients prior to therapy in our Lymphoma clinics
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	Our chemotherapy day units are all experienced in administering Brentuximab (given intravenously) as this agent is widely used in treating patients with relapsed ALCL and relapsed Hodgkin lymphoma.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes: improvement in response rates and PFS and OS – which will produce meaningful improvement outcomes (survival and quality of life) for patients.
• Do you expect the technology to increase length of life more than current care?	Yes: improvement in PFS and OS. ECHELOn-2 data: Median progression free survival was 48·2 months (95% CI 35·2–not evaluable) in the A+CHP group and 20·8 months (12·7–47·6) in the CHOP group (hazard ratio 0·71 [95% CI 0·54–0·93], p=0·0110).
• Do you expect the technology to increase health-related quality of life more than current care?	Yes – by improving response rates and survival (PFS and OS) I would expect the technology to increase health-related quality of life more than current care

13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Groups of people: All ages would be expected to benefit. In ECHELON-2 eligible patients were patients aged 18 years or older) and CHOP is administered to patients with lymphoproliferative disorders in their 60s/70s and 80s. The groups that would be expected to benefit will reflect the patients eligible (untreated, CD30- positive (≥10% of cells) for the clinical trial. Eligible histologies included: 1. ALK-positive systemic anaplastic large cell lymphoma (ALCL) with an IPI score of 2 or higher (although we would expect all patient with ALCL would benefit from this treatment approach) And , 2. ALK-negative systemic anaplastic large cell lymphoma. Patients with ALCL were the majority of patients  Other histologies were included but were a small proportion of the patient cohort. The ECHELON-2 study was not powered to compare efficacy between individual histological subtypes. Peripheral T-cell lymphoma not otherwise specified, Angioimmunoblastic T-cell lymphoma Adult T-cell leukaemia or lymphoma, Enteropathy associated T-cell lymphoma Hepatosplenic T-cell lymphoma.

	A+CHP group (n=226)	CHOP group (n=226)
Diagnosis‡		
sALCL	162 (72%)	154 (68%)
ALK positive	49 (22%)	49 (22%)
ALK negative	113 (50%)	105 (46%)
PTCL-NOS	29 (13%)	43 (19%)
AITL	30 (13%)	24 (11%)
ATLL	4 (2%)	3 (1%)
EATL	1 (0%)	2 (1%)

The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	Similar administration – ie IV on day unit of vincristine and/or brentuximab Similar side effect profile (peripheral neuropathy etc. From ECHELON-2: **Adverse events, including incidence and severity of :** febrile neutropenia (41 [18%] patients in the A+CHP group and 33 [15%] in the CHOP group) and peripheral neuropathy (117 [52%] in the A+CHP group and 124 [55%] in the CHOP group) **were similar between groups.** Fatal adverse events occurred in seven (3%) patients in the A+CHP group and nine (4%) in the CHOP group. A higher incidence of diarrhoea (any grade) was reported in the A+CHP group (85 [38%] patients) than in the CHOP group (46 [20%]). Most (49 [58%] of 85) cases of diarrhoea in the A+CHP group were mild/grade 1; the remaining cases were grade 2 (23 [27%]) and grade 3 (13[15%]). Grade 3 diarrhoea (bowels open $\geq$7x/day) is troublesome for patients but occurred in a small minority of patients in the trial: 6% of A+CHP group c.f 1% of CHOP group. So overall: No additional clinical requirements, Similar factors affecting patient acceptability Similar ease of use no additional tests or monitoring needed

15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No additional testing. Treatment will start at initiation of 1st line treatment., Treatment will stop if disease progression as is standard approach with CHOP
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No aware of any
17. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it	Yes this immunotherapeutic approach is innovative in its potential to make a significant and substantial impact on health-related benefits See above

improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	This technology provides a huge step-change in the management of this condition. A+CHP results in prolonged PFS and OS
• Does the use of the technology address any particular unmet need of the patient population?	Yes – improvement in PFS/OS. There has been no prior randomised trial that has shown superiority for CHOP as 1st line treatment but the results from this treatment approach (CHOP) have been disappointing for this indication. CHOP has remained the 'standard of care' (see CHOP vs GEM-P; Gleeson *et al*. below) for previously untreated patients with T-cell lymphoma CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): a phase 2, multicentre, randomised, open-label trial. Gleeson M, Peckitt C, To YM, Edwards L, Oates J, Wotherspoon A, Attygalle AD, Zerizer I, Sharma B, Chua S, Begum R, Chau I, Johnson P, Ardeshna KM, Hawkes EA, Macheta MP, Collins GP, Radford J, Forbes A, Hart A, Montoto S, McKay P, Benstead K, Morley N, Kalakonda N, Hasan Y, Turner D, Cunningham D. Lancet Haematol. 2018 May;5(5):e190-e200. doi: 10.1016/S2352-3026(18)30039-5.

	'The number of patients with a complete response or unconfirmed complete response did not differ between the groups, indicating that GEM-P was not superior for this outcome. CHOP
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	Similar side effect profile: see above. Many SEs are reversible. A SE that is impactful for patients: peripheral neuropathy had similar incidence in both CHOP and A+CHP treated cohorts: *Peripheral neuropathy events were identified on the basis of a standardised MedDRA query and are summarised* *by event in the appendix. Treatment-emergent peripheral neuropathy events occurred in 117 (52%) patients* *in the A+CHP group and 124 (55%) patients in the CHOP group; most had a maximum severity of grade 1 (75 [64%] of 117 in the A+CHP group and 88 [71%] of 124 in the CHOP group). Peripheral neuropathy events returned to baseline or lower in 58 (50%) patients in the A+CHP group, with a median time to resolution of 17weeks, and in 79 (64%) patients in the CHOP group, with a median time to resolution of 11.4 weeks (appendix).* *Of the patients with ongoing events at last follow-up, most were grade 1 (44 [72%] of 61 patients in the A+CHP group and 32 [71%] of 45 patients in the CHOP group). Two patients in the A+CHP group and one patient in the CHOP group had ongoing grade 3 peripheral neuropathy events.*
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes – as described above. CHOP has remained the 'standard of care' (see CHOP vs GEM-P; Gleeson *et al*. below) for previously untreated patients with T-cell lymphoma <u>CHOP versus GEM-P in previously untreated patients with peripheral T-cell lymphoma (CHEMO-T): a phase 2, multicentre, randomised, open-label trial.</u> Gleeson M, Peckitt C, To YM, Edwards L, Oates J, Wotherspoon A, Attygalle AD, Zerizer I, Sharma B, Chua S, Begum R, Chau I, Johnson P, Ardeshna KM, Hawkes EA, Macheta MP, Collins GP, Radford J, Forbes A, Hart A, Montoto S, McKay P, Benstead K, Morley N, Kalakonda N, Hasan Y, Turner D, Cunningham D. Lancet Haematol. 2018 May;5(5):e190-e200. doi: 10.1016/S2352-3026(18)30039-5. 'The number of patients with a complete response or unconfirmed complete response did not differ between the groups, indicating that GEM-P was not superior for this outcome. CHOP should therefore remain the reference regimen for previously untreated peripheral T-cell lymphoma.'
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	PFS/OS – and yes these outcomes were measured in the trial. Also the similar SE profile.
• If surrogate outcome measures were used, do	N/A

they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	I'm not aware of any
20. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
21. How do data on real-world experience compare with the trial data?	Similar observations in the real world for the CHOP-treated cohort (comparator)
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	No
Topic-specific questions	
23. If this treatment (brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone) was recommended as an option in this indication, do you think it will replace current standard of care in NHS practice? Is there a high level of clinician interest in this as a potential treatment option?	Yes it would replace current standard of care in NHS practice. Yes there is a high level of clinician interest in this as a potential treatment option
24. Approximately what proportion of patients with this	Similar proportion in each arm

condition receive concomitant medication?	
25. How does current treatment burden for people with CD30-positive peripheral T-cell lymphoma and their family/friends compare to other types of lymphoma in the NHS?	There are few effective treatment options for relapsed/refractory T-cell lymphoma so improving the outcome for first line treatment is highly important. In addition many patients present at an older age where consolidation haematopoietic stem cell transplant is not feasible so improving outcome from a chemo-immunotherapy approach in 1st line approachwill have a significant impact in this type of lymphoma.
26. What proportion of patients in this indication in the NHS receive consolidative stem cell transplant following front-line treatment with standard of care chemotherapy?	Hard to decipher this information from UK data as although the number of transplants (PBSCT) are recorded the 'true denominator' ('transplant-eligible fit patients') is unclear as it depends on Physician-assessment (not-standardised) and clinical judgement. From ECHELON-2: Consolidative stem cell transplantation was delivered in 50 (22%) patients in the A+CHP group and 39 (17%) in the CHOP after the end of treatment at the discretion of the investigator. As noted above this endpoint was influenced by Investigator preference re whether this consolidation strategy was favoured so this trial wasn't powered to properly assess this outcome). However we would expect this figure to be similar in the UK: Noting age/PS of patients presenting for 1st line treatment and proportion achieving CR after CHOP – likely to be <20% of the cohort. Although more patients achieve a response (CR/ORR) after A+CHP and are potentially eligible to proceed to consolidative stem cell transplant it's not clear whether the number of patients proceeding to PBSCT will actually increase.

	It is possible that less consolidative stem cell transplants (PBSCT) will be performed after A+CHP as PFS and OS are improved after this treatment modality. The real impact/benefit of stem cell consolidation is unclear (see level of grading of recommendation from BCSH guideline below). (BCSH guideline 2013: **'CHOP remains the standard therapy. Consideration should be given to consolidation with auto-HSCT (LEVEL IV GRADE C).'** PBSCT is associated with approximately a 3-5% TRM in patients < 65 years and if/as the benefit is unclear, and 1st line treatment 'more effective' there may be greater reluctance to perform this.
27. What is the percentage reduction in overall survival for people with this disease who enter long-term remission, relative to the UK population?	I don't have the data to quantify this risk There may be a small reduction in overall survival after A+CHP treatment (first line therapy) relative to the UK population if prolonged long-term remission achieved. After anthracycline-containing chemotherapy there is a cumulative risk of cardiomyopathy but treatment for this is improving with associated reduction in morbidity and mortality.
Key messages	

28. In up to 5 bullet points, please summarise the key messages of your statement.

- Impressive improvement in outcome for patients treated with of A+CHP in ECHELON-2 trial.
- Significant improvement in PFS/OS for patients treated with A+CHP in ECHELON-2 trial
- Treatment can be delivered in out patient setting
- No evidence of greater toxicity of A+CHP-treated patients compared to CHOP ('standard of care')
- Potential impact on number of patients proceeding to consolidation PBSCT

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NICE National Institute for Health and Care Excellence

Clinical expert statement

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

Thank you for agreeing to give us your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

About you	
1. Your name	**Ruth Pettengell**
2. Name of organisation	**St George's University of London**

3. Job title or position	**Reader / Honorary Consultant in Haematolgy/Oncology**
4. Are you (please tick all that apply):	☐ an employee or representative of a healthcare professional organisation that represents clinicians? √☐ a specialist in the treatment of people with this condition? √☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	√☐ yes, I agree with it ☐ no, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ other (they didn't submit one, I don't know if they submitted one etc.)
6. If you wrote the organisation submission and/ or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission.)	☐ yes

The aim of treatment for this condition	
7. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	To improve the cure rate (PFS and OS) with frontline treatment of CD30-expressing PTCL
8. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount.)	An improvement in PFS and OS by 5-7%
9. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Peripheral T-cell lymphoma (PTCL) is a rare heterogeneous group of lymphoid malignancies. The standard of care, CHOP, results in generally poor outcomes for frontline PTCL with a high risk for disease relapse or progression. Approximately 50% of patients post-transplant with a survival or less than 3 years indicating the paucity of effective therapies at relapse. More effective therapies are urgently needed.
What is the expected place of the technology in current practice?	

10. How is the condition currently treated in the NHS?	CHOP or CHOP-like chemotherapy (with or without radiotherapy) and with or without consolidation transplant in first remission
• Are any clinical guidelines used in the treatment of the condition, and if so, which?	Pan-London Guidelines BSH T cell guidelines NCCN guidelines
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway of care for first line treatment is well defined. There is no strong evidence to argue for or against consolidating treatment with a transplant with approximately 50% of UK patients receive a transplant in first remission.
• What impact would the technology have on the current pathway of care?	Brentuximab CHOP will become the new standard of care for patients with ALCL and if licenced for the frontline treatment of all CD30-expressing PTCL particularly as it has a comparable safety profile to CHOP. Indications for radiotherapy and the use of transplantation to consolidate remission will remain unchanged.
11. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes. Brentuximab replaces vincristine in the CHOP regimen, but continues to be delivered in an outpatient day unit every 3 weeks. The toxicity profile is predictable and comparable to CHOP.

• How does healthcare resource use differ between the technology and current care?	Cost of Brentuximab (plus pharmacy & day unit delivery costs) minus the cost of vincristine (plus pharmacy & day unit delivery costs). Management of Adverse Events similar to current care
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Lymphoma specialists
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	No additional investment required. Chemotherapy delivery staff are familiar with the use of this agent in Hodgkin lymphoma and relapsed PTCL so training requirements are minimal.
12. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes. Patients with ALCL (accounting for 70% of the study population, mandated by EMA) benefited most both in terms of PFS (HR 0.59; 95% CI: 0.42, 0.84, p=0.0031) and OS. Patient with PTCL-NOS also benefited (HR 0.75; 95% CI: 0.41, 1.37). Patients who are disease free at 2 years are considered cured. Brentuximab in NICE approved for patients with relapsed ALCL [TA478] but response rates (CRR 59%) and the duration of remission (13.2 months) are substantially worse.
• Do you expect the technology to increase length of life more than current care?	Yes, this study population is representative of clinical practice and both PFS and OS were superior to current care (CHOP) particularly for patients with ALCL.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes, given that patients in remission have a good HRQOL compared to those on treatment or who relapse. So with a 29% reduction in the risk of progression (more than doubling the duration of remission 48.2 months versus 20.8 months), and the 34% reduction in risk of death one would expect a substantial improvement in HRQOL.
13. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	Patients with ALCL benefited most and constituted 70% of the study population. Activity albeit less was seen in patients with PTCL-NOS, who have fewer treatment options and even greater unmet need. Although the numbers of Non-ALCL subtypes included in the study were low, there is single agent published activity for BV in CD30 positive AITL and PTC –NOS so there is a possibility that it could improve outcomes for these diseases but this study is not powered to address the question of whether BV improves outcome for the subgroups of patients with AITL or PCTL-NOS.
The use of the technology	
14. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional clinical requirements, factors	No. Comparable to current standard of care. Approximately 50% of patients are consolidated with autograft in first remission. There is no strong evidence to argue for or against consolidating treatment with a transplant and the value of transplantation is not answered by this study.

affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
15. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	CD30 expressing lymphoma. The level of CD30 expression is not important and this test is a routine part of current diagnostics for PTCL. Clinical assessment of tumour response prior to each cycle and interval and End of treatment imaging to confirm response to treatment is already standard of care. No additional tests are required
16. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No
17. Do you consider the technology to be innovative in its potential to make a	Yes, The evidence in ALCL is practice changing and will cure more patients with ALCL and improve the disease free survival for others with comparable morbidity to CHOP

significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	
• Is the technology a 'step-change' in the management of the condition?	Yes. This is the first clinically important improvement in outcome over CHOP chemotherapy in a group of patients who are usually symptomatic, relapse early (usually within 12 months) and have poor survival outcomes.
• Does the use of the technology address any particular unmet need of the patient population?	Yes, improvement in survival outcomes and cure for patients with ALCL
18. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	A higher incidence of diarrhoea (38% vs 20%) was reported, other side effects were comparable for all grades. Similar numbers of patients discontinued therapy due to AE's and deaths were comparable 3%. So side effects are unlikely to adversely affect patient management or QOL
Sources of evidence	

19. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, this study population is representative of UK clinical practice and both PFS and OS were superior to current care (CHOP) particularly for patients with ALCL
• If not, how could the results be extrapolated to the UK setting?	N/A
• What, in your view, are the most important outcomes, and were they measured in the trials?	Improvement in PFS and OS in CD30 positive PTCL, particularly the subgroup of patients with ALCL. These were measured in the trial, but this study was not powered to fully address the question of whether BV improves outcome for the subgroups of patients with AITL or PCTL-NOS.
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	N/A
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No
20. Are you aware of any relevant evidence that might	No

not be found by a systematic review of the trial evidence?	
21. How do data on real-world experience compare with the trial data?	Control group is representative.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No
22b. Consider whether these issues are different from issues with current care and why.	N/A
Topic-specific questions	
23. If this treatment (brentuximab vedotin with cyclophosphamide,	Yes, it will replace current standard of care in NHS practice. There is a high level of clinician interest in this as a potential treatment option and given he benefit particularly for patients with ALCL an early patient access scheme should be considered.

doxorubicin, and prednisone) was recommended as an option in this indication, do you think it will replace current standard of care in NHS practice? Is there a high level of clinician interest in this as a potential treatment option?	
24. Approximately what proportion of patients with this condition receive concomitant medication?	Supportive care medications will not differ from current practice
25. How does current treatment burden for people with CD30-positive peripheral T-cell lymphoma and their family/friends compare to other types of lymphoma in the NHS?	T cell lymphoma represent 10-15% of NHL, the prognosis for these patients is poor compared to B-NHL. Most patients with active disease are symptomatic, impacting negatively on quality of life. Successful first-line therapy is the only chance of cure. Early relapses are common, disease progression usually rapid and the outcome for patients who relapse is dismal with few treatment options.

26. What proportion of patients in this indication in the NHS receive consolidative stem cell transplant following front-line treatment with standard of care chemotherapy?	The evidence base for consolidative stem cell transplant is poor with widely variable practice across the UK. Approximately 50% of transplant eligible patients receive a consolidative transplant in the UK.
27. What is the percentage reduction in overall survival for people with this disease who enter long-term remission, relative to the UK population?	Most patients with PTCL relapse within 12 months with very few relapses after 24 months so difference in the survival curves may increase over time. The age adjusted OS for long term survivors would be comparable to the UK Cancer survivorship data ie a few percent below the UK population

Key messages

28. In up to 5 bullet points, please summarise the key messages of your statement.

- First improvement in OS ever demonstrated in PTCL against standard of care
- The evidence in ALCL is practice changing
- Whether BV removes the need for transplant as consolidation is not addressed
- The side effect profile is comparable to the current standard of care
-

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Robert Wolff acted as project lead and systematic reviewer on this assessment, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Isaac Corro Ramos acted as health economic project lead, critiqued the company's economic evaluation and contributed to the writing of the report. Hannah Penton, Pim Wetzelaer, Steve Ryder, Nigel Armstrong and Maiwenn Al acted as health economists on this assessment, critiqued the company's economic evaluation and contributed to the writing of the report. Vanesa Huertas Carrera, Debra Fayter and Pawel Posadzki acted as systematic reviewers, critiqued the clinical effectiveness methods and evidence and contributed to the writing of the report. Shelley de Kock critiqued the search methods in the submission and contributed to the writing of the report. Gill Worthy acted as statistician, critiqued the analyses in the company's submission and contributed to the writing of the report. Jos Kleijnen critiqued the company's definition of the decision problem and their description of the underlying health problem and current service provision, contributed to the writing of the report and supervised the project.

Disclaimer

The results of the cost effectiveness analyses conducted by the Evidence Review Group (ERG) presented in this report are based on an erroneous value of the "mortality multiplier" input parameter (1.25 was used for the ERG base-case instead of 1.212). This was discovered after the report was submitted but it has a minor effect on the cost-effectiveness results. After changing this parameter, the incremental cost-effectiveness ratio (ICER) in the ERG preferred base-case was decreased by £232.

Abbreviations

Δ	Incremental
A	Adcetris®
ADC	Antibody-drug conjugate
AE	Adverse effect/adverse event
AiC	Academic in confidence
AIC	Akaike Information Criterion
AITL	Angioimmunoblastic T-cell lymphoma
ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALK-	Anaplastic lymphoma kinase-negative
ALK+	Anaplastic lymphoma kinase-positive
AlloSCT	Allogeneic stem cell transplant
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
ATA	Antitherapeutic antibodies
ATLL	Adult T-cell leukaemia/lymphoma
AutoSCT	Autologous stem cell transplant
AWMSG	All Wales Medicines Strategy Group
BIC	Bayesian information criterion
BICR	Blinded Independent Central Review
BNF	British National Formulary
BSA	Body surface area
BSH	British Society of Haematology
BV	Brentuximab vedotin
BV+CHP	Brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone
C-GSF	Granulocyte colony stimulating factor
CADTH	Canadian Agency for Drugs and Technologies in Health
CDSR	Cochrane Database of Systematic Reviews
CE	Cost effectiveness
CEAC	Cost effectiveness acceptability curve
CHEP-BV	Cyclophosphamide, doxorubicin hydrochloride (doxorubicin), etoposide phosphate (etoposide), prednisone, and brentuximab vedotin
CHMP	Committee for Medicinal Products for Human Use
CHOEP	Cyclophosphamide + doxorubicin + etoposide + vincristine + prednisone
CHOP	Cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]
CHP	Cyclophosphamide [C], doxorubicin [H], and prednisone [P]
CI	Confidence interval
CiC	Commercial in confidence
CMH	Cochran-Mantel-Haenszel
CR	Complete response/complete remission
CRD	Centre for Reviews and Dissemination
CS	Company submission
CSR	Clinical study report
CT	Computerised tomography
CTCAE	Common terminology criteria for adverse events
CTCL	Cutaneous T-cell lymphoma
df	Degree of freedom
DHAP	Dexamethasone, cisplatin, cytarabine
DSU	Decision Support Unit
EATL	Enteropathy-associated T-cell lymphoma
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group

EED	Economic Evaluation Database
EHA	European Haematology Association
EMA	European Medicines Agency
eMIT	Electronic market information tool
EORTC	European Organisation for Research and Treatment of Cancer
EQ-5D	European Quality of Life-5 Dimensions
ERG	Evidence Review Group
ESHAP	Cisplatin, methylprednisolone, etoposide, cytarabine
ESHPM	Erasmus School of Health Policy & Management
ESMO	European Society for Medical Oncology
EU	European Union
EUR	Erasmus University Rotterdam
FAO	For the attention of
FCR	Fear of cancer recurrence
FDA	Food and Drug Administration
FTCL	Follicular T-cell lymphoma
G-BA	Gemeinsamer Bundesausschuss
G-CSF	Granulocyte-colony stimulating factor
GDP	Gemcitabine, dexamethasone, cisplatin
GI	Gastrointestinal
Gy	Gray
HAS	Haute Autorité de Santé
HL	Hodgkin's lymphoma
HMRN	Haematologic Malignancy Research Network
HR	Hazard ratio
HRF	Healthcare resource group
HRQoL	Health-related quality of life
HSTL	Hepatosplenic T-cell lymphoma
HSUV	Health state utility value
HTA	Health technology assessment
ICE	etoposide, carboplatin, ifosfamide + mesna
ICER	Incremental cost effectiveness ratio
ICML	International Conference on Malignant Lymphoma
IPCW	Inverse probability of censoring weights
IPI	International Prognostic Index
IQR	Inter-quartile range
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IRF	Independent review facility
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITT	Intention-to-treat
IV	Intravenous
K-M	Kaplan-Meier
kg	Kilogram
KSR	Kleijnen Systematic Reviews
ll	Log likelihood
ln	Natural logarithm
LTFU	Last treatment follow-up
LYG	Life years gained
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
MIMS	Monthly Index of Medical Specialities
MMAE	Monomethyl auristatin E
MTCL	Mature T-cell lymphoma
NCI	National Cancer Institute
NE	Not estimable

NHL	Non-Hodgkin lymphoma
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NK	Natural killer
NKTCL	Natural killer/T-cell lymphoma
NOS	Not otherwise specified
NR	Not reported
ONS	Office for National Statistics
ORR	Objective response rate
OS	Overall survival
PAS	Patient access scheme
PBAC	Pharmaceutical Benefits Advisory Committee
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression-free survival
PICOS	Population, intervention, comparator(s), outcome(s)
PN	Peripheral neuropathy
PR	Partial response
PRIMA	Preliminary independent model advice
PRISMA	Transparent reporting of systematic reviews and meta-analyses
PRO	Patient reported outcome
PS	Performance status
PSA	Probabilistic sensitivity analysis
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
PTCL	Peripheral T-cell lymphoma
PTCL-NOS	Peripheral T-cell lymphoma-not otherwise specified
QLQ-C30	Quality of Life Questionnaire – Core 30
QoL	Quality of life
R/R	Relapsed/refractory
RCT	Randomised controlled trial
SAE	Serious adverse event
sALCL	Systemic anaplastic large cell lymphoma
SCT	Stem cell transplant
SD	Stable disease
SD	Standard deviation
SE	Standard error
SFU	Safety follow-up
SLR	Systematic literature review
SMC	Scottish Medicines Consortium
SMILE	Etoposide, ifosfamide + mesna, mesna, methotrexate, dexamethasone
STA	Single technology appraisal
TA	Technology appraisal
TFH	T-follicular helper cell
TLV	Tandvårds-och läkemedelsförmånsverket
trt	Treatment
TSD	Technical Support Document
TTD	Time-to-death
TTO	Time trade-off
UK	United Kingdom
US	United States (of America)
WHO	World Health Organization

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1. SUMMARY

1.1 Critique of the decision problem in the company's submission

The population defined in the scope was *"adults with untreated CD30-positive peripheral T-cell lymphoma (PTCL)"*. The company submission (CS) was in line with the scope. The submission relied primarily on a randomised controlled trial (RCT) ECHELON-2. However, it should be noted that 70% of patients in this trial were of the subtype systemic anaplastic large cell lymphoma (sALCL). The Evidence Review Group (ERG) noted that the ECHELON-2 trial could not reliably determine the effect of brentuximab vedotin (BV) by subtype other than sALCL due to small sample sizes. The committee will need to decide if it accepts that BV will have a similar effectiveness and safety profile across other subtypes of PTCL.

The intervention (BV in combination with cyclophosphamide, doxorubicin, and prednisone (CHP)) was in line with the National Institute for Health and Care Excellence (NICE) scope. The company stated that a positive CHMP (Committee for Medicinal Products for Human Use) opinion for the treatment of adults with untreated CD30-positive peripheral T-cell lymphoma was anticipated in March 2020.

The comparator in the CS and in ECHELON-2 was also in line with the scope, i.e. established clinical management including cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP).

The NICE final scope listed the following outcome measures: overall survival (OS), progression-free survival (PFS), response rate, adverse effects of treatment and health-related quality of life (HRQoL). These outcomes were addressed by the company in the CS. However, it should be noted that at the last data cut presented in the CS (15 August 2018) overall survival data were not mature. Further analyses are planned for late 2020.

1.2 Summary of the key issues in the clinical effectiveness evidence

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted as part of the systematic review to identify clinical effectiveness studies. A range of databases and additional resources were searched.

The ERG noted that 19 studies were excluded at the title and abstract screening phase of the systematic literature review (SLR) as they were not in English. It is unclear if these would have presented relevant data. The SLR identified three studies reporting results for BV: one phase III trial (ECHELON-2) and two open-label single-arm trials (one phase I and one phase II).

The ERG report focuses on ECHELON-2 was it was the only comparative trial relevant to the decision problem and the only study used in the economic model. ECHELON-2 was an international, double-blind, randomised, placebo-controlled, active-comparator phase III trial, rated to be of low risk of bias. Adult patients (≥18 years) with previously untreated CD30-positive PTCL received six to eight treatment cycles of BV+CHP or CHOP. Safety and efficacy outcomes were measured including overall survival, progression-free survival, overall response rates (including complete response), adverse effects and HRQoL.

Despite numerous requests, a clinical study report (CSR) for ECHELON-2 was not provided. Therefore, the ERG was unable to validate the information provided in the CS or to include results on potentially relevant subgroups not currently covered in the CS. The ERG considers the refusal to provide the full CSR despite numerous requests a critical shortcoming of the CS as it severely hampers the ERG's ability to identify any potential issues with the submission and to support the decision making of the committee.

Both, PFS and OS analyses, were based on a data cut-off date of 15 August 2018. In response to request for clarification, the company stated that *"the next data cut of the ECHELON-2 trial is planned for late 2020, with analysis and evidence likely to become available in 2021".*

Regarding PFS, at the time of the cut-off, 95/226 (42%) patients in the BV+CHP arm and 124/226 (55%) patients in the CHOP arm had experienced a PFS event. The results in the intention-to-treat (ITT) population were in favour of BV+CHP (stratified hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.54 to 0.93, p=0.011), see Table 1.1 for details.

Regarding OS, at the time of the cut-off, there had been 51 (23%) deaths in the BV+CHP arm and 73 (32%) in the CHOP arm. The results show a reduction in the risk of death with BV+CHP compared to CHOP although this is an interim analysis and the OS data are not mature (HR 0.66, 95% CI 0.46 to 0.95, p=0.0244).

At the end of the treatment, the complete response rate (by independent review facility (IRF) assessment) was 68% (95% CI 61.2 to 73.7) in the BV+CHP arm compared with 56% (95% CI 49.0 to 62.3) in the CHOP arm (p=0.0066). The objective response rate (by IRF assessment) was 83% (95% CI 77.7 to 87.8) in the BV+CHP arm and 72% (95% CI: 65.8 to 77.9) in the CHOP arm (p=0.0032).

The ERG noted that patients treated with BV+CHP had superior results in terms of PFS, OS and response rates. However, 70% of the patients had the subtype sALCL and the ECHELON-2 trial was only powered for this subtype. In all outcomes, the sALCL subtype achieved numerically better results than the population as a whole.

Results for these endpoints are reported in Table 1.1 while results for the sALCL subgroup of patients are presented in section 4.2.3 of the report.

Results for mean European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L) over time using UK-based time trade-off index scores show that mean scores increased over time but there was no significant difference in the change from baseline between BV+CHP and CHOP. Similarly, treatment arms were comparable in the role, emotional, cognitive, physical, social functioning subscales, global health status and total scores of QLQ-C30. However, there was an increase in diarrhoea in treatment cycle 7 for patients receiving BV+CHP but this did not persist during the rest of the treatment course.

Adverse events, grade 3 and above, and serious adverse events occurred in similar proportions across the treatment groups. Similar proportions discontinued treatment or died due to an adverse event. Regarding higher grade adverse events, the incomplete CSR for ECHELON-2 stated that [redacted]. Examining specific adverse events, the ERG notes the higher incidence of diarrhoea in the BV treatment group. Should BV be approved, patients will need to be informed of a possible higher risk of this adverse event. It also appears that peripheral neuropathy might take longer to resolve with BV and again if BV is approved, patients will need to be informed of this issue (see section 4.2.4 for details). Table 1.2 provides a summary of the adverse events in ECHELON-2.

As only one relevant RCT was identified, no meta-analysis was conducted. Furthermore, there were no indirect comparisons or network meta-analyses performed. The company did *"not wish for the medicine to be considered at this time for the application of NICE's End-of-Life criteria".*

Table 1.1: Results for ECHELON-2

	BV+CHP (n=226)	CHOP (n=226)
Progression-free survival		
PFS event at cut-off, n (%)	95 (42%)	124 (55%)
Median PFS, months (95% CI)‡	48.2 (35.2 to NE)	20.8 (12.7 to 47.6)
Stratified HR (95% CI) BV+CHP vs. CHOP	0.71 (0.54 to 0.93)	
Stratified log-rank P-value†	0.0110	
Sensitivity analysis#		
Stratified HR (95% CI) BV+CHP vs. CHOP	0.75 (0.56 to 1.00)	
Stratified log-rank P-value†	0.0484	
Overall Survival		
Number of deaths, n (%)	51 (23%)	73 (32%)
Stratified hazard ratio (95% CI) (BV+CHP to CHOP)	0.66 (0.46, 0.95)	
Stratified log-rank P value†	0·0244	
Median overall survival (months) (95% CI)*	NE (NE, NE)	NE (54.2, NE)
Response		
ORR, n (%) [95% CI]	188 (83%) [77.7 to 87.8]	163 (72%) [65.8 to 77.9]
Response Rate Difference (95%CI), P-value	11.1 (3.4–18.7), 0.0032	
CR, n (%) [95% CI]	153 (68%) [61.2 to 73.7]	126 (56%) [49.0 to 62.3]
Response Rate Difference (95%CI), P-value	11.9 (3.1-20.8), 0.0066	

Based on Tables 14, 15 and 17 of the CS and the response to the request for clarification
‡ PFS rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method; † From stratified log-rank test with stratification factors (ALK+ sALCL: Yes/No and International Prognostic Index score: 0-1/2-3/4-5) at randomisation, # Defining PFS as progression or death; patients receiving subsequent chemotherapy for residual or progressive PTCL were censored * Overall survival rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method
ALK+ = anaplastic lymphoma kinase-positive; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CR = complete response; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; ORR = objective response rate; PFS = progression-free survival; PTCL = peripheral T-cell lymphoma; sALCL = systemic anaplastic large cell lymphoma

Table 1.2: Safety results of ECHELON-2

Adverse Event	BV+CHP	CHOP
No in safety analysis set	**223**	**226**
No (%) with any adverse event	221 (99%)	221 (98%)
No (%) with Grade ≥ 3 adverse event	147 (66%)	146 (65%)
No (%) with serious adverse event	87 (39%)	87 (38%)
No (%) discontinued treatment due to adverse event	14 (6%)	15 (7%)

Adverse Event	BV+CHP	CHOP
No (%) death due to adverse event	7 (3%)	9 (4%)
No (%) Treatment-related adverse events*	[redacted]	[redacted]
No (%) Treatment-related serious adverse events*	[redacted]	[redacted]
No (%) of deaths	51 (23%)	73 (32%)

Based on Tables 15 and 24 of the CS, the response to the request for clarification and the incomplete CSR of ECHELON-2
Note: This table only includes adverse events that occurred within safety analysis period, as defined as Day 1 up to 30 days after the last dose of any component of the regimen. Adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of any component of BV+CHP and CHOP
* Defined as participants with any brentuximab vedotin or vincristine-related event as assessed by the investigator
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; CSR = clinical study report

1.3 Summary of the key issues in the cost effectiveness evidence

Separate sets of searches were undertaken to identify cost effectiveness and cost and resource use, and HRQoL evidence. The CS provided sufficient details for the ERG to appraise the searches. A range of databases and supplementary resources were searched.

The company submission and response to clarification provided sufficient details for the ERG to appraise the literature searches. A good range of resources were searched and searches were clearly documented, transparent and reproducible. Separate searches were conducted to identify clinical efficacy studies, cost effectiveness, cost and resource use studies and health-related quality of life studies. All studies identified in clinical effectiveness searches were screened for adverse events. Adverse event reactions were also taken from the ECHELON-2 trial to inform clinical and cost effectiveness sections.

A range of resources were searched with a comprehensive search strategy which was clearly documented and reproducible. An extensive range of supplementary searches of conference proceedings, health technology assessment agencies and a clinical trial registry were undertaken.

Clinical effectiveness database searches of Embase and MEDLINE were conducted simultaneously using a single database provider (Embase.com). Although some mapping between indexing terms does take place on Embase.com, including MeSH terms as well as EMTREE terms would have been more thorough. However, as free text terms were comprehensive, it is unlikely that any relevant studies were missed. Searches for cost effectiveness, cost and resource use and health-related quality of life studies were undertaken in February 2019 and were updated with a targeted search in November 2019. In response to request for clarification, the company explained that the targeted search expanded the population criterion to include studies conducted on any line of therapy. However, details of the search strategy as applied to PubMed were not provided. The ERG also believes that the updated search in November should have included searches of Embase and that it is possible that relevant evidence could have been missed as a result of this omission.

The ERG raised their concerns regarding to what extent the intention-to-treat population of the ECHELON-2 trial was representative for a United Kingdom (UK) patient. The ERG considered that the age value included in the cost effectiveness model should have been larger than the 55.1 years used in the company's base-case. The ERG assumed that the mean age of an UK PTCL patient was

62.02 years based on the weighted average of the age values reported in ECHELON-2 (UK patients only), Gleeson et al. 2018 and a 2019 audit from the Haematologic Malignancy Research Network of patients diagnosed with PTCL in Yorkshire. The impact of age on the cost effectiveness results was substantial. The remaining patient characteristics were not changed due to the lack of evidence to inform alternative estimates.

The ERG did not consider sufficiently proven that proportional hazards were more appropriate to model the long-term PFS and OS extrapolations. A stratified approach, where survival curves are fitted separately to each treatment arm, seemed more plausible. This approach should also have been explored by the company. The option to select curves based on a stratified approach was included in the company's model but a goodness-of-fit assessment was missing in the CS. The ERG assumes that the company did not present the stratified extrapolations to UK clinical experts. Also, the ERG discovered that the incremental cost effectiveness ratio (ICER) increased when the sALCL subgroup was modelled instead of the full ITT population on using the stratified approach, which is counterintuitive given that given that BV seems to be more effective in the sALCL subgroup. Therefore, the ERG has concerns about the validity of the results given by the model when the stratified approach is selected and, thus, the ERG base-case employs the joint approach.

Clinical experts consulted by the company considered that the generalised gamma distribution was most reflective of long-term outcomes for OS and PFS. However, the plausibility of the estimated long-term probabilities was not explicitly quantified in the CS. This is especially important for OS since the selection of the OS long-term extrapolation basically determines the overall gains in quality-adjusted life years (QALYs) estimated by the electronic model. It would have been important to assess the plausibility of the lognormal (and to a lower extent the log-logistic) distribution.

Clinical experts also explained that the risk of relapse and the risk of lymphoma related mortality after front-line treatment is the highest in the first two/three years following treatment and, after that, decreases drastically and overall survival approached that of the general population. This is not reflected in the company's model. The ERG considers that the plausibility of both the hazard rate functions and time when long-term mortality equals the mortality risk of the general population should have been validated by clinical experts. Furthermore, exploring other non-standard parametric distributions (e.g. spline models) might have been appropriate in this case.

Adjustment for BV re-treatment in the BV+CHP arm and BV use post-progression in non-sALCL patients in the CHOP arm seems reasonable and the two-stage estimator (TSE) method appropriate. As requested by the ERG, the company corrected their initial analyses and four patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 at study baseline in the CHOP arm who had sALCL disease and received subsequent BV post-progression, were removed from the OS TSE. This assumption was included in the ERG base-case. However, the ERG noted several issues associated with this adjustment. The most important was that this adjustment was not implemented in the probabilistic sensitivity analysis (PSA), which implied that all PSA analyses assuming this adjustment (e.g. the ERG base-case) would result in a large underestimation of the overall uncertainty.

The ERG identified several issues with the utility modelling approach used by the company. Firstly, Swinburn et al. 2015 used vignettes describing relapsed/refractory (R/R) Hodgkin lymphoma and sALCL health states to elicit time trade-off (TTO) valuations from members of the general public in seven countries including the UK. As this study measured HRQoL in members of the general population, rather than in patients directly, this source does not meet the requirements of the NICE reference case. Secondly, a combined health state utility value and time-to-death model suggested that

time-to-death has more impact on HRQoL in this group of patients than progression. Therefore, the ERG chose to use the time-to-death model in their base-case.

While the CS included age as a covariate within their utility modelling, the coefficient obtained from the company model was smaller than age-related utility decrements seen in more commonly applied age-adjustment studies, such as Ara and Brazier 2010. This smaller age decrement meant that in the long term, progression-free patients in the model had higher utility values than the age-adjusted utilities of members of the general population. The ERG considered this implausible and implemented a constraint in their base-case whereby utilities could not exceed these age-adjusted general population utility values.

Regarding the number of front-line BV treatment cycles used in the economic model, the ERG considered it important for any assumptions to align with the data on clinical effectiveness from ECHELON-2. Therefore, as in the company base-case, the ERG assumed the average number of front-line BV treatment cycles observed in ECHELON-2 for their preferred base-case analysis. For second-line BV, the company base-case used the average number of 8.2 treatment cycles from technology appraisal (TA) 478. Based on the TA478 committee discussion, the ERG was uncertain about this assumption and assumed a number of six treatment cycles for second-line BV instead.

1.4 Summary of the ERG's preferred assumptions and resulting ICER

The ERG preferred changes to the company base-case are detailed in section 7.1.2 and summarised below:

1. Removing patients with ECOG PS 2 from the two-stage estimator and from the proportion of patients receiving subsequent BV (done by the company per ERG request).
2. Correcting the cost of transfusion implemented in the model.
3. Setting baseline age equal to 62.02 years.
4. Assuming a mortality multiplier equal to 1.25 to reflect 6.5% increased mortality risk.
5. Assuming a time to death utility approach.
6. Forcing long-term utilities to be lower than general population utilities.
7. Including peripheral neuropathy costs in the model.
8. Assuming six treatment cycles for second-line BV.

The cost effectiveness results of the ERG preferred base-case are presented in Table 1.3. The implementation of the ERG preferred assumptions increased the ICER from £24,901 (company) to £33,153 (ERG). The changes surrounding baseline age and the number of second-line BV treatment cycles had the largest impact on the ICER. In particular, BV+CHP provided [redacted] additional QALYs at an incremental cost of [redacted] compared to CHOP. The incremental QALY gains for BV+CHP all stemmed from the progression-free health state. Incremental costs were mostly due to the additional treatment costs of BV+CHP. Approximately [redacted]% of these incremental costs were saved in second-line therapies. However, [redacted]% of the costs saved in second-line therapies were caused by BV being used post-progression in the CHOP arm. Consolidative therapy costs were also [redacted]% higher in the BV+CHP arm.

Table 1.3: ICER resulting from ERG's preferred assumption

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
BV+CHP	[redacted]	10.41	[redacted]	[redacted]	1.32	[redacted]	£33,153
CHOP	[redacted]	9.10	[redacted]				

Based on Electronic model of the CS
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; LYG = life years gained; QALY = quality-adjusted life year.

1.5 Summary of exploratory and sensitivity analyses undertaken by the ERG

The ERG also conducted a probabilistic sensitivity analysis (PSA) using their preferred base-case assumptions. This analysis resulted in a probabilistic ICER of £34,690 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £1,537 larger than the ERG deterministic ICER. The cost effectiveness acceptability curve shows that the probability of BV+CHP being cost effective was 35% (as opposed to 64% in the company's PSA) at a threshold ICER of £30,000 per QALY gained, and 7% (as opposed to 22% in the company's PSA) at a threshold ICER of £20,000 per QALY gained.

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the survival modelling (in terms of choice of parametric distributions and modelling approach, i.e. joint vs. stratified), age at baseline, and utility, cost and resource use assumptions. The largest differences in survival modelling approaches were associated with the generalised gamma distribution, the one used by both the company and the ERG. The choice of age at baseline had a substantial impact on the model results. The ICER obtained assuming 55.10 years at baseline (company base-case) was £27,746 per QALY gained, £5,407 lower than the ERG base-case. Increasing the age-decrement in utility to -0.00434, which represents the yearly decrement in utility obtained from Ara and Brazier at the age of 62 years, increased the ICER by approximately £14,000. Also, when four vials of BV per patient were assumed (the number of vials corresponding to the average patient weight) instead of 3.14 (the average number of vials obtained using the distribution of patient body weight), the ICER increased by £8,623. The other assumptions tested by the ERG had a minor impact on the model results.

2. BACKGROUND

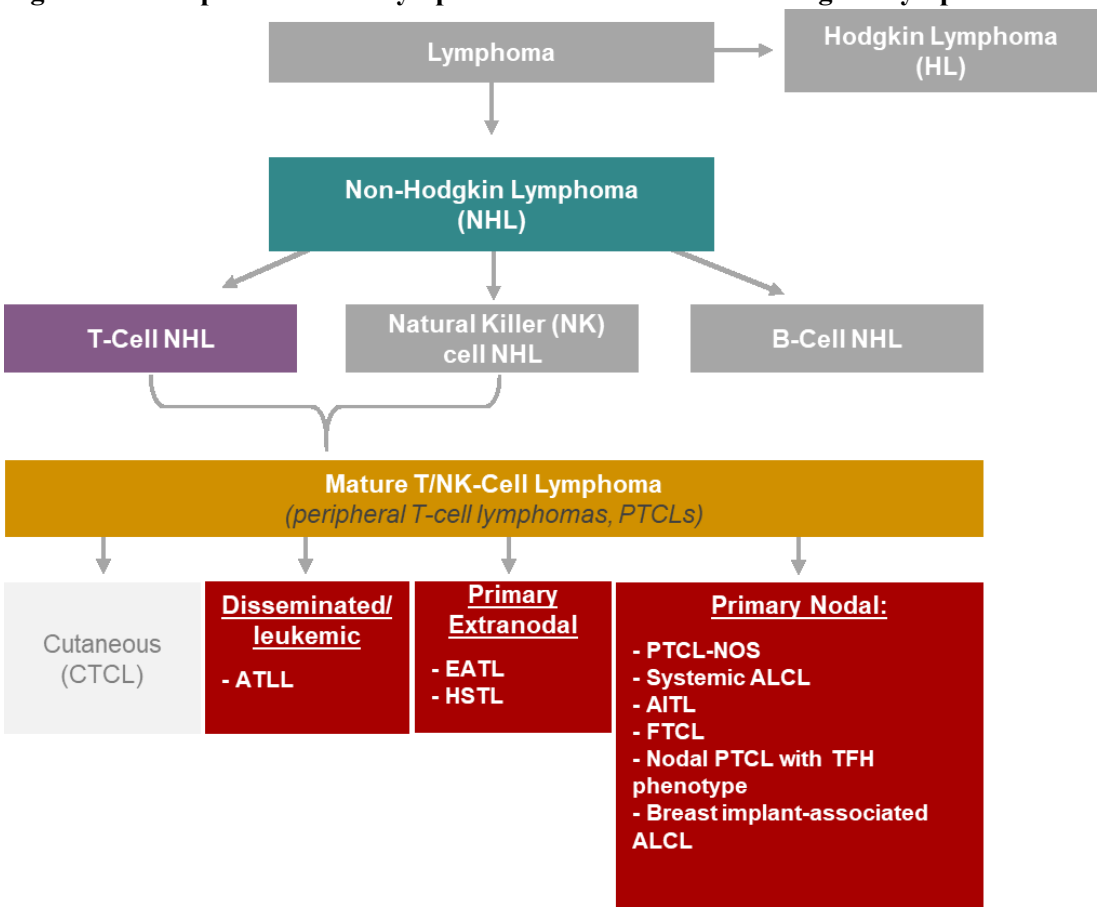
2.1 Introduction

In this report, the Evidence Review Group (ERG) provides a review of the evidence submitted by Takeda in support of brentuximab vedotin (BV, trade name Adcetris®) in combination with cyclophosphamide, doxorubicin and prednisone (BV+CHP), for previously untreated adult patients with CD30-positive peripheral T-cell lymphoma (PTCL).

2.2 Critique of company's description of the underlying health problem

The company's description of the underlying health problem, PTCL, is summarised in section B.1.3.1 of the company submission (CS).[1] According to the CS, PTCL is sometimes referred to as Mature T-Cell Lymphoma (MTCL) and it is characterised by the neoplastic development of post-thymic, mature T-Cells. Four major categories of PTCLs are distinguished in the CS: cutaneous (CTCL); disseminated/leukemic; primary extranodal and primary nodal. Further distinctions are made within each category, see Figure 2.1.[1] The CS specified primary nodal PTCLs as the most common PTCL category.[1]

Figure 2.1: Peripheral T-Cell Lymphoma as a subset of Non-Hodgkin Lymphoma



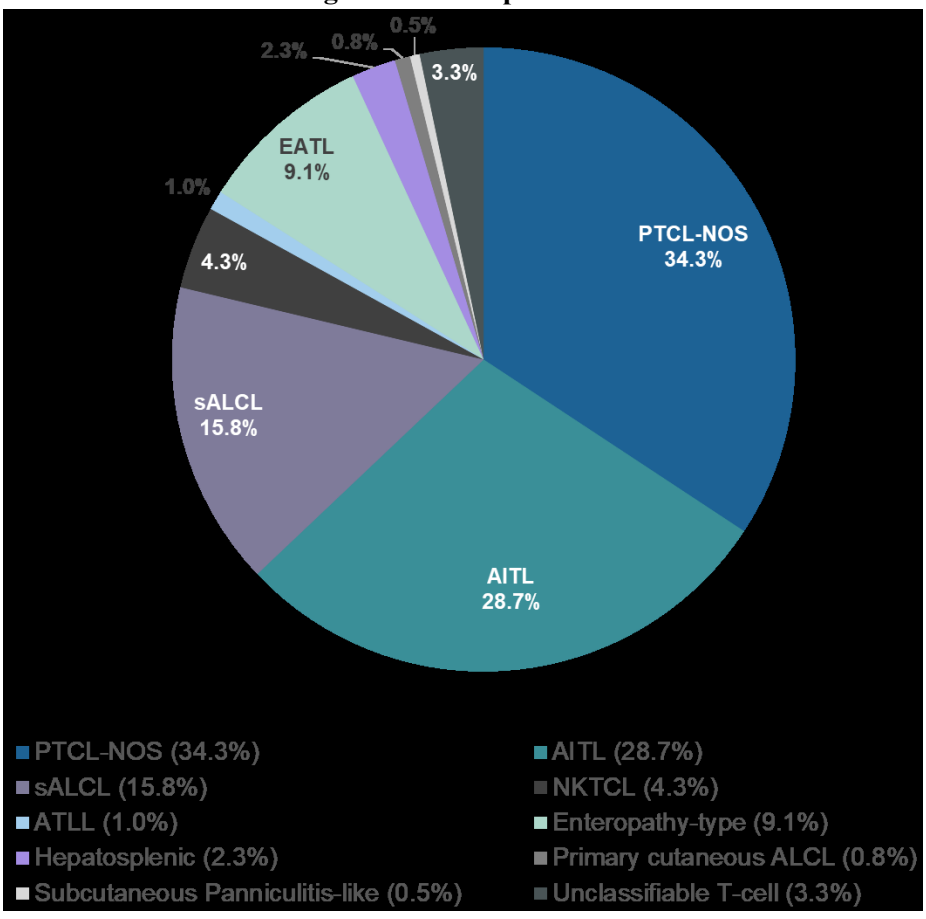
Based on Figure 2 of the CS[1]

AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ATLL = adult T-cell leukaemia/lymphoma; CS = company submission; CTCL = cutaneous T-cell lymphoma; EATL = enteropathy-associated T-cell lymphoma; FTCL = Follicular T-cell lymphoma; HL = Hodgkin lymphoma; HSTL = hepatosplenic T-cell lymphoma; NHL = non-Hodgkin lymphoma; NK = natural killer; PTCL = peripheral T-cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified; TFH = T-follicular helper cell

The epidemiology of the disease is described in section B.1.3.2 of the CS, reporting that non-Hodgkin lymphoma (NHL) showed an incidence rate of 22.9 per 100,000 persons in 2016.[1] In addition to this, PTCL is described to account for between 5% to 10% of all new NHL cases that are diagnosed in the United Kingdom (UK).[1]

The distribution of PTCL diagnosis in Europe is illustrated in Figure 2.2.[1] PTCL not-otherwise-specified (PTCL-NOS) is the most common subtype with 34.3% of all PTCL diagnoses. This is followed by angioimmunoblastic T-cell lymphoma (AITL; 28.7%) and systemic anaplastic large cell lymphoma (sALCL) at 15.8%. As explained in the CS, primary cutaneous T-cell lymphomas and Natural Killer/ T-cell lymphoma (NKTCL) are not included in the National Institute for Health and Care Excellence (NICE) scope or the submission.[1, 2]

Figure 2.2: Distribution of PTCL diagnosis in Europe



Based on Figure 3 of the CS[1]
AITL = angioimmunoblastic T-cell lymphoma; ALCL = Anaplastic large-cell lymphoma; ATLL = Adult T-cell leukaemia/lymphoma; CS = company submission; EATL = enteropathy-associated T-cell lymphoma; NKTCL = Natural killer/T-cell lymphoma; PTCL = peripheral T-cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma not-otherwise-specified; sALCL = systemic anaplastic large-cell lymphoma

The expression of the protein CD30 and its role in the classification of PTCL are described in section B.1.3.2.1 of the CS.[1] As explained in this section, the expression of CD30 is highly prevalent in the sALCL subtype and variably expressed across other subtypes. Overall, approximately 50% of all PTCLs are reported to express CD30 (CD30+) and 58% of PTCL-NOS are CD30+. The CS stated *"BV offers a novel treatment approach that selectively targets CD30+ cells and as such it is targeted for the treatment of CD30+ malignancies. However, although CD30 positivity is important for the activity of*

BV, there's no evidence that it is more efficacious in lymphomas with higher levels of CD30 expression nor that the benefit of BV is correlated with the degree of CD30 expression…".[1]

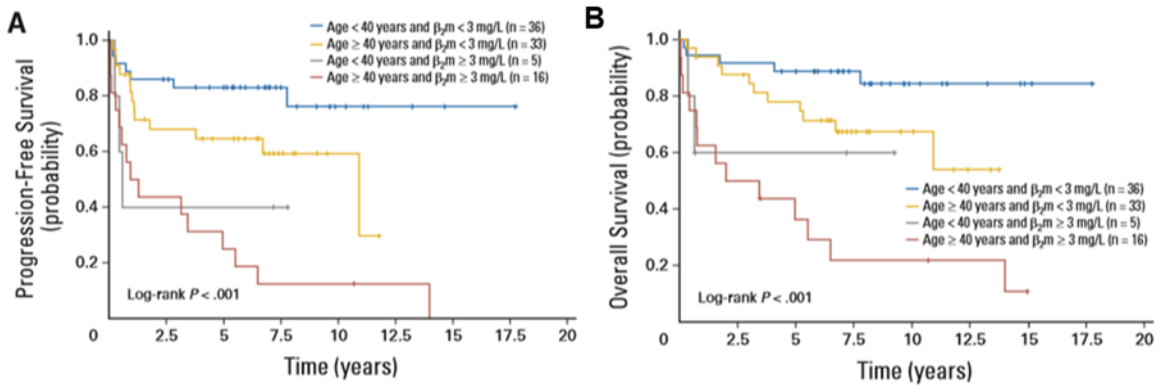
The CS provides a breakdown of the five-year overall survival (OS) rates for PTCL by subtype in section B.1.3.4.[1] The five-year OS for PTCL-NOS is reported to be 32%, see Table 2.1. In addition to this, the CS noted the publication of a UK-based audit carried out between 2002 and 2012 which reported a five-year OS of 38.8% for PTCL.[1, 3] As described in the CS, the different subtypes of PTCL vary on their presentation and prognosis. ALK+ sALCL has the best prognosis compared to the other subtypes.[1] However, this positive advantage remains dependent on the age at diagnosis and the International Prognostic Index (IPI) score.[1] The details of these differences have been illustrated in Table 2.1 and Figure 2.3.

Table 2.1: IPI score per PTCL subtype and risk score

PTCL subtype	5-year OS	Risk category	IPI Score	5-year OS
PTCL-NOS	32%	Low	0-1	50%
		Intermediate-Low	2	33%
		Intermediate-High	3	16%
		High	4-5	11-13%
ALK+ sALCL	70%	Low	0-1	90%
		Intermediate-Low	2	68%
		Intermediate-High	3	23%
		High	4-5	33%
ALK- sALCL	49%	Low	0-1	74%
		Intermediate-Low	2	62%
		Intermediate-High	3	31%
		High	4-5	13%
AITL	32%	NR	NR	NR
EATL	20%	NR	NR	NR
ATLL	14%	NR	NR	NR
HSTL	7%	NR	NR	NR

Based on Tables 4 and 5 of the CS[1]
AITL = angioimmunoblastic T-cell lymphoma; ALK- = anaplastic lymphoma kinase-negative; ALK+ = anaplastic lymphoma kinase-positive; ATLL = adult T-cell leukaemia/lymphoma; CS = company submission; EATL = enteropathy-associated T-cell lymphoma; HSTL = hepatosplenic T-cell lymphoma; IPI = International Prognostic Index; NR = not reported; OS = overall survival; PTCL = peripheral T-cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma not-otherwise-specified; sALCL = systemic anaplastic large-cell lymphoma

Figure 2.3: PFS and OS for sALCL by age



Based on Figure 6 of the CS[1]
CS = company submission; mg = milligram; OS = overall survival; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma

In terms of the patient's quality of life or burden to carers and society, the CS explains that a void of data impedes drawing practical information and, in general, these outcomes need to be drawn from the NHL population.[1] However, it has been reported that after relapse, progression-free survival (PFS) and OS for PTCL are *"extremely poor"* with medians of 3.1 to 5.5 months, respectively.[1, 4] At the same time, fear of cancer recurrence (FCR) is described as impacting on the emotional functioning, social functioning, global quality of life, physical functioning, and role functioning subscales of the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-C30 (QLQ-C30).[1]

ERG comment: The ERG considers that the description in the CS accurately reflects the underlying health problem. However, it should be noted that, as a result of technological advances, the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms introduced new entities in the classification of both nodal and extranodal T-cell and natural killer (NK)-cell neoplasms.[5] The scope for this submission is narrower than the full spectrum of these pathologies. Clinical entities judged to be included within the scope are highlighted in Table 2.2.[2]

Table 2.2: 2016 WHO classification of mature T and NK neoplasms

Mature T and NK neoplasms	
T-cell prolymphocytic leukaemia	Sézary syndrome
T-cell large granular lymphocytic leukaemia	Mycosis fungoides
Chronic lymphoproliferative disorder of NK cells	Primary cutaneous gamma-delta T-cell lymphoma
Aggressive NK-cell leukaemia	Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
Systemic EBV^+ T-cell lymphoma of childhood	Primary cutaneous acral $CD8^+$ T-cell lymphoma
Hydroa vaccinforme-like lymphoproliferative disorder	Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder
Adult T-cell leukaemia/lymphoma	*Peripheral T-cell lymphoma, NOS*

Mature T and NK neoplasms	
Extranodal NK-/T-cell lymphoma, nasal type	*Angioimmunoblastic T-cell lymphoma*
Enteropathy-associated T-cell lymphoma	*Follicular T-cell lymphoma*
Monomorphic epitheliotropic intestinal T-cell lymphoma	*Nodal peripheral T-cell lymphoma with TFH phenotype*
Indolent T-cell lymphoproliferative disorder of the GI tract	*Anaplastic large-cell lymphoma, ALK$^+$*
Hepatosplenic T-cell lymphoma	*Anaplastic large-cell lymphoma, ALK$^-$*
Subcutaneous panniculitis-like T-cell lymphoma	*Breast implant–associated anaplastic large-cell lymphoma*
Primary cutaneous CD30+ T-cell lymphoproliferative disorders: (1) Lymphomatoid papulosis and (2) Primary cutaneous anaplastic large cell lymphoma	
Based on Table 1 of Swerdlow 2016[5] Cells highlighted in grey refer to pathologies judged to be included in the NICE scope[2] ALK- = anaplastic lymphoma kinase-negative; ALK+ = anaplastic lymphoma kinase-positive; EBV = Epstein-Barr virus; GI = gastrointestinal; NK = natural killer; NOS = not otherwise specified; TFH = T-follicular helper cell; WHO = World Health Organization	

The ERG notes that the distribution of the diagnosed prevalence for the PTCL subtypes in Europe, reported in Figure 3 of the CS (reproduced as Figure 2.2 above), was published in 2008.[1, 6] In addition to this, PTCL-NOS was diagnosed based on exclusion criteria for the PTCL cases that cannot be classified with current markers. Therefore, it is highly heterogeneous.[7]

In terms of the epidemiology, the ERG notes that no specific data are reported in the CS for the incidence rate or the mortality of PTCL in the UK or England. According to the National Institute for Health Research (NIHR) Innovation Observatory, the Office for National Statistics (ONS) reported a PTCL age standardised incidence rate of 2.2/100,000 in males and 1.2/100,000 in females in England, based on data from 2016.[8] Data from 2017 suggest incidence rates (2.0/100,000 and 1.1/100,000, respetively) for peripheral and cutaneous T-cell lymphoma.[9]

With regards to the expression of the protein CD30 in the different subtypes of PTCL, the ERG notes that whilst 58% of PTCL-NOS are CD30+ (as reported by the CS); only 23% may be considered *"strongly positive"*, i.e. the percentage of CD30+ tumour cells is 50% or higher.[1, 10] However, in contrast with the CS, the ERG notes that conflicting results have been reported for the correlation between CD30 expression and the clinical response to BV. A positive association has been suggested by Lamarque et al. 2016[11] whilst the results from a phase II study[12] and for ECHELON-2 (presented at the International Conference of Malignant Lymphoma)[13] suggested otherwise.

The ERG has reviewed the figures and references provided in the CS for life expectancy of the disease. The source cited in the CS for the 32% five-year OS PTCL-NOS was published in 2008.[6] In contrast, as described by the NIHR briefing document, the five-year OS rate for common PTCL-NOS in the UK was reported to be 17.6% (95% confidence interval (CI) 10.3 to 26.5) while the five-year relative survival rate was reported to be 19.7% (95% CI 11.5 to 29.5).[8]

2.3 Critique of company's overview of current service provision

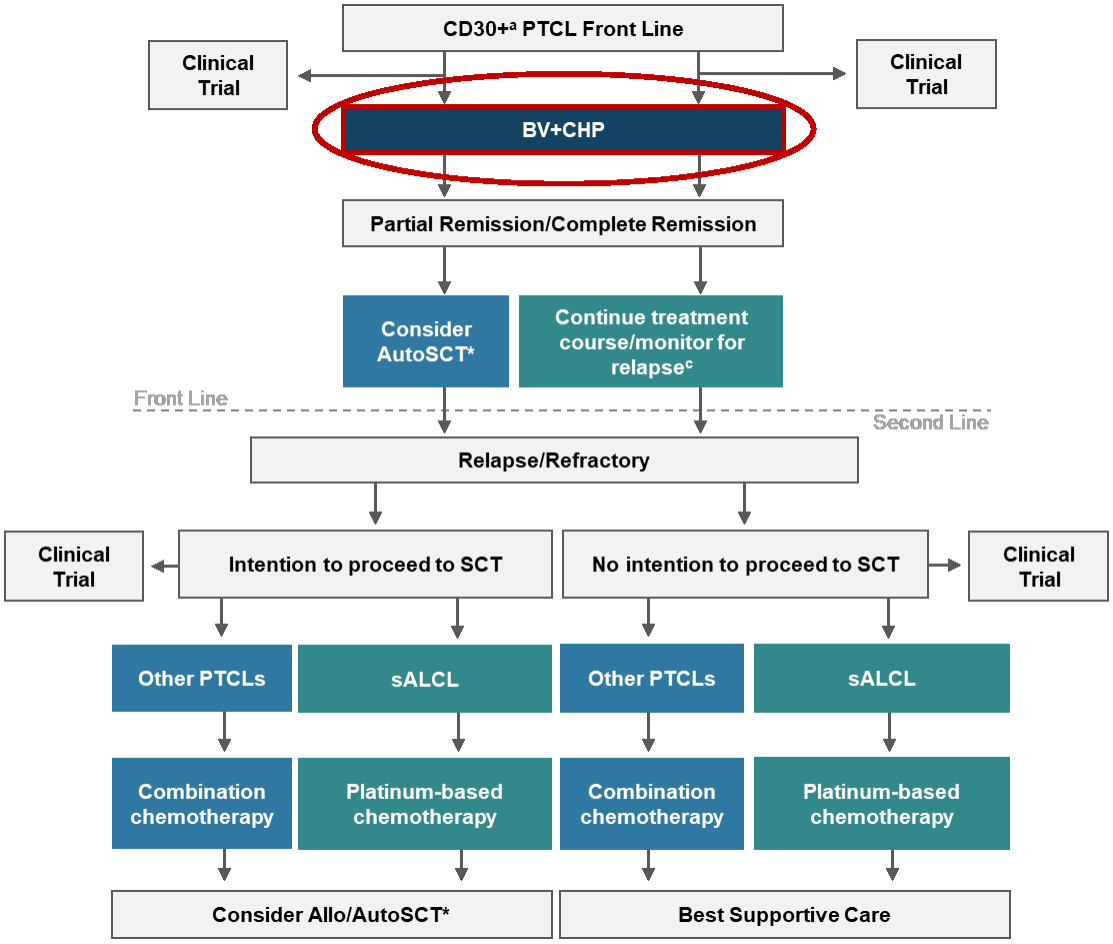
Figure 2.4 shows the proposed treatment pathway for patients with CD30+ PTCL where BV+CHP is listed as first-line treatment replacing six cycles of cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P] (CHOP) as the only change from the current treatment pathway.[1, 14, 15]

Following first-line treatment, autologous stem cell transplantation (AutoSCT) is recommended as consolidation therapy. This is described as a burdensome procedure to patients with great uptake variability across UK.[1] However, the change from CHOP to BV+CHP is not anticipated to change the proportion of patients who receive consolidative AutoSCT.[1]

The treatment of relapsed/refractory (R/R) PTCL is dependent on the subtype. BV monotherapy has been recommended by NICE for the treatment of R/R sALCL regardless of the patient's eligibility to undergo allogeneic SCT.[1]

The company provided evidence from clinicians in form of abbreviated noted of a strategy advisory board meeting: *"UK clinicians confirmed that in clinical practice patients would not receive re-treatment with BV and that patients with R/R non-sALCL would not receive treatment with BV. Within the PTCL segment, brentuximab vedotin is currently only licensed and funded for R/R sALCL and is not available either as re-treatment in sALCL nor a salvage treatment for other PTCLs. UK clinicians confirmed that in clinical practice, patients with R/R sALCL and relapsed patients with other PTCLs would not be retreated (sALCL)/ treated (R/R PTCL) with brentuximab vedotin as it is not licensed and/or available in these settings"*.[16] According to the notes, *"re-treatment and subsequent therapy were of interest to all the advisors and presents an economic modelling challenge. It opened a debate on BV outcomes and pathway positioning that will need addressing within the submission, given that re-treatment is unlikely to be reimbursed within the pathway and that BV is currently only reimbursed for relapsed/refractory (R/R) sALCL in the UK and not for any of the other sub-groups"*.[16]

Figure 2.4: Proposed treatment pathway for CD30+ PTCL including BV+CHP placement



Based on revised Figure 8 presented in response to request for clarification[17]

[a] CD30 expression is not standardised. Treatment responses occur with low level expression[12]; [b] [Not included in original Figure]; [c] Due to favourable outcomes, autoSCT consolidation is not recommended for low risk ALK+, ALCL[14]; * Consolidation with AutoSCT not recommended for ALK+ ALCL

ALCL = anaplastic large cell lymphoma; ALK+ = anaplastic lymphoma kinase positive; AlloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; BV = brentuximab vedotin; BV+CHP = brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone; CS = company submission; NHS = National Health Service; PTCL = peripheral T-cell lymphoma; sALCL = systemic anaplastic large-cell lymphoma; SCT = stem cell transplant

ERG comment: The CS proposed treatment pathway is based on guidelines issued by the European Society for Medical Oncology (ESMO) in 2015.[14]

The ERG notes that regarding front-line treatment, though most types of PTCLs often present with tumour dissemination, radiotherapy may be appropriate for those patients presenting localised disease after chemotherapy. Recommended doses are 30-40 gray (Gy). At the same time, patients who are too frail to receive intensive chemotherapy may be considered for approaches less toxic based on monotherapy such as gemcitabine or bendamustine.[14]

Similarly, whilst the CS states that consolidation with AutoSCT is not recommended for ALK+ ALCL, this is solely restricted to a low-risk profile (e.g. IPI<2) patients.[14]

In agreement with the CS, no standard of care for relapsed/refractory nodal PTCL has been identified by the ERG. The exception being sALCL for which BV is recommended as the CS indicates. For other

subtypes, and depending on the patient's fitness, other chemotherapy regimens as well as new antibody agents may be preferable.[14]

The CS presented abbreviated notes from a meeting of clinical experts confirming *"that in clinical practice patients would not receive re-treatment with BV and that patients with R/R non-sALCL would not receive treatment with BV"*.[16]

3. CRITIQUE OF COMPANY'S DEFINITION OF DECISION PROBLEM

Table 3.1: Statement of the decision problem (as presented by the company)

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with untreated CD30-positive peripheral T-cell lymphoma (PTCL)	Adults with previously untreated CD30+ Peripheral T-Cell Lymphoma (PTCL)	As per final scope	In line with the scope. However, it should be noted that 70% of patients in the ECHELON-2 trial were in subtype sALCL.
Intervention	Brentuximab vedotin with cyclophosphamide, doxorubicin, and prednisone	Brentuximab vedotin (Adcetris®) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP)	As per final scope	In line with the scope.
Comparator(s)	Established clinical management including: cyclophosphamide, hydroxydaunorubicin (doxorubicin), vincristine, and prednisone (CHOP)	Established clinical management including: cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP)	As per final scope	In line with the scope
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life	The following outcomes will be presented: • Progression-free survival (PFS) • Overall survival (OS) • Overall response rate (ORR), including: complete response (CR) • Health-related quality of life (HRQoL)	As per final scope, with the addition of ORR and CR for comprehensiveness.	In line with the scope. However, at the last data cut overall survival data were not mature. Further analysis is planned for late 2020.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
		• Adverse effects (AE) of treatment.		
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention or comparator and subsequent technologies will be taken into account.	The economic analysis will follow the NICE reference case.	As per final scope	The cost effectiveness analyses were conducted according to the NICE reference case
Subgroups to be considered	If the evidence allows the following subgroups will be considered. These include people with PTCL not otherwise specified, people with angioimmunoblastic T-cell lymphoma, people with sALCL, people with ALK-positive sALCL and ALK-negative sALCL.	The focus of this submission is in line with the ECHELON-2 clinical trial and the expected marketing authorisation, which is all previously untreated CD30-positive PTCL.	The ECHELON-2 trial was not designed nor powered to look at outcomes by subtype of PTCL, with the exception of sALCL. Due to an existing regulatory commitment arising from EMA's previous conditional approval of BV for relapsed / refractory (R/R sALCL), an analysis of the	The ERG agrees that the ECHELON-2 trial could not reliably determine the effect of BV by subtype other than sALCL due to small sample sizes. The committee will need to decide if it accepts that BV will have a similar

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.	Subgroup analyses will be presented for systemic Anaplastic Large Cell Lymphoma (sALCL).	sALCL group was a key secondary end-point of the ECHELON-2 trial. A robust analysis of this subgroup is feasible with the available data and this is presented within the dossier. In order to have a similar pool of patients in the ECHELON-2 trial, an inclusion criterion for ALK+ sALCL patients was an IPI score of 2 or higher. ALK+ sALCL patients with a high IPI score (reflecting the group enrolled in ECHELON-2) have similar outcomes to ALK- sALCL patients and therefore clinical advice was to consider sALCL patients as one group (See Section B.1.3.1). The data necessary for the other proposed subgroup analyses in the scope are not available, as the ECHELON-2 trial was not designed nor powered to conduct analyses on individual subtypes of PTCL. Any such analyses would be based on extremely small numbers and provide highly uncertain results. As the outcomes and treatment pathway are generally consistent across subtypes of PTCL, the presented base-case analysis of all untreated	effectiveness and safety profile across subtypes of PTCL.

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
			CD30-positive PTCL is aligned to the expected marketing authorisation and is representative of the clinical- and cost effectiveness of BV+CHP.	

Based on Table 1 of the CS[1]

AE = adverse effect; ALK = anaplastic lymphoma kinase; ALK- = anaplastic lymphoma kinase-negative; ALK+ = anaplastic lymphoma kinase-positive; BV+CHP = brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CR = complete response; EMA = European Medicines Agency; ERG = Evidence Review Group; HRQoL = health-related quality of life; IPI = International Prognostic Index; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PTCL = peripheral T-cell lymphoma; R/R = relapsed / refractory; sALCL = systemic anaplastic large cell lymphoma

3.1 Population

The population defined in the scope is *"adults with untreated CD30-positive peripheral T-cell lymphoma (PTCL)"*[2] The CS is in line with the scope. However, it should be noted that 70% of patients in the main trial in the CS (ECHELON-2) were of the subtype sALCL (due to a regulatory requirement of the European Medicines Agency (EMA)).[18]

A total of 452 participants were enrolled in the international ECHELON-2 trial, with five of the 132 trial sites located in the UK and 21 UK-based patients.[18] To be eligible for the trial patients had to be aged ≥18 years with previously untreated CD30+ (≥10% of cells by local review). The median age of patients in the ECHELON-2 trial was 58 years and the majority of patients had advanced disease (stage III 27% and stage IV 53%). Most participants had an International Prognostic Index (IPI) score ≥2, see section 4.2.1.

ERG comment:

- The ERG agrees that the ECHELON-2 trial could not reliably determine the effect of BV by subtype other than sALCL due to small sample sizes. The sALCL subgroup was planned and the trial had a target to enrol (75% within +/- 5%) of patients with sALCL to ensure that PFS could be reliably evaluated in this group. The committee will need to decide if it accepts that BV will have a similar effectiveness and safety profile across other subtypes of PTCL.
- Apart from the over-representation of patients with sALCL, the population appears to be broadly representative of patients with PTCL in the UK, except for age, as will be explained in section 5.2.3 of this report. It would be inappropriate due to small sample size to report results of UK patients only.
- In ECHELON-2, patients had to have previously untreated CD30+ disease (defined as ≥10% of cells by local review). However, the company did not anticipate that the EMA marketing authorisation would specify a threshold for CD30 expression. The ERG draws this issue to the attention of the committee.

3.2 Intervention

The intervention (brentuximab vedotin (Adcetris®) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP)) is in line with the NICE scope.[2] The company stated that *"a regulatory filing for BV in combination with CHP for previously untreated CD30+ peripheral T-cell lymphoma (PTCL) was submitted to the EMA in June 2019. A positive CHMP* [Committee for Medicinal Products for Human Use] *opinion is anticipated in March 2020, with marketing authorisation expected between May and June 2020"*.[1]

BV is an antibody-drug conjugate (ADC) composed of an anti-CD30 monoclonal antibody linked with a cytotoxic anti-mitotic compound, monomethyl auristatin E (MMAE). The drug is administered by intravenous (IV) infusion. The company advises that patients should be monitored during and after infusion and that complete blood counts should be monitored prior to administering each dose of treatment.

The recommended dose of BV for peripheral T-cell lymphoma is 1.8 mg/kg administered as IV infusion over 30 minutes every three weeks to be administered in combination with CHP. For patients weighing more than 100 kg a maximum weight is assumed for dosing calculations (maximum dose of BV per cycle of 180 mg). The company advised that *"dose adjustments may be warranted for conditions such as neutropenia and peripheral neuropathy, as well as for special patient populations such as those patients with renal and hepatic impairment, the elderly, and paediatric"*.[1]

In ECHELON-2 patients received six to eight treatment cycles (mean BV+CHP six cycles, mean CHOP 5.8 cycles). The company stated that *"UK clinical advisors have confirmed that in UK and European practice patients would receive a maximum of 6 treatment cycles of BV+CHP as the current standard of care is 6 cycles of CHOP"*.[1]

In ECHELON-2, consolidative stem cell transplantation (SCT) or radiotherapy after treatment was permitted at the discretion of the treating physician (SCT intent was pre-specified before the first cycle of chemotherapy). In response to the request for clarification, the company detailed the criteria used to initiate SCT: *"In the ECHELON-2 trial, the investigators were asked to pre-specify at baseline if their patients may be eligible for an aSCT based on the aforementioned underlying patient characteristics (age, fitness, etc). From this baseline assessment, it was deemed that 89 and 81 patients enrolled in the BV+CHP and CHOP arms respectively would potentially be eligible for a consolidative SCT following their first-line therapy. Whether the potentially eligible patients actually went on to receive a consolidative SCT was based on these patient factors, in addition to their response to the first-line treatment. If the patient had a good enough response to first-line therapy, was still deemed SCT eligible, and wanted to receive a SCT they would then go on to receive a consolidative SCT"*.[17]

ERG comment:

- The ERG noted that in the ECHELON-2 trial most patients received six cycles of treatment as would be usual in the UK. Slightly fewer in the CHOP arm received six cycles (BV+CHP 70% vs. CHOP 62%). A similar number received eight cycles. (BV+CHP 18% vs. CHOP 19%).[1] All UK patients in the trial received six cycles of treatment.[17]
- The ERG asked how many patients had a capped dose in ECHELON-2 due to weighing more than 100 kg.[19] In response, the company stated that *"within the BV+CHP arm of the ITT* [intention-to-treat] *population, 10% of patients (n=24) had a weight greater than 100 kg at baseline"*.[17]
- The ERG noted the greater number of dose delays with BV compared to CHOP in ECHELON-2. In response to clarification, the company stated that *"as dose delay and dose reductions are likely to be correlated with other prognostic factors and are treatment-emergent (i.e. defined post-baseline), it was not considered appropriate to estimate outcomes based on these subgroups. Clinical input suggests that dose delays are generally short and are unlikely to affect patient outcomes"*.[17]
- It is unclear whether the criteria used to initiate SCT are reflective of UK clinical practice.

3.3 Comparators

The comparator in the CS and in the main trial is in line with the scope, i.e. established clinical management including cyclophosphamide, hydroxydaunorubicin, vincristine, and prednisone (CHOP).

ERG comment: The two open label studies in the CS did not include an appropriate comparison and were not used in the economic model. Therefore, the ERG has treated them as supplementary evidence only and focused on the randomised controlled trial (RCT) ECHELON-2, see section 4.2.1 for further details.

3.4 Outcomes

The NICE final scope listed the following outcome measures:

- overall survival
- progression free survival
- response rate
- adverse effects of treatment

- health-related quality of life

These outcomes were addressed by the company in the CS and in the main ECHELON-2 trial.

ERG comment: Although the outcomes in the ECHELON-2 trial were in line with the scope, it should be noted that at the last data cut presented in the CS (15 August 2018) overall survival data were not mature. Further analyses are planned for late 2020.[1]

3.5 Other relevant factors

A patient access scheme (PAS) in the form of a simple discount applies for all licensed indications of BV in the UK. The PAS for BV is a discount of [redacted] giving a price per vial of [redacted] and a cost per course of [redacted].

4. CLINICAL EFFECTIVENESS

4.1 Critique of the methods of review(s)

The company conducted a systematic review to identify evidence on the efficacy and safety of brentuximab vedotin and current therapies for untreated CD30-positive PTCL.[1] The review was conducted prior to the finalisation of the NICE scope so included comparators beyond those in the NICE scope.[2]

Section 4.1 critiques the methods of the review including searching, inclusion criteria, data extraction, quality assessment and evidence synthesis.

4.1.1 Searches

Appendix D of the CS details a systematic search of the literature used to identify clinical effectiveness literature undertaken on 29 August 2019.[20] A summary of the sources searched is provided in Table 4.1.

Table 4.1: Data sources for the clinical effectiveness systematic review

Resource	Host/source	Reported date range	Date searched
Electronic databases			
MEDLINE In-Process	PubMed	From database inception	29 August 2019
Embase and MEDLINE	Embase.com		
CDSR	Wiley		
Cochrane Trials			
Conference proceedings			
ASCO	Not reported	2018-2019	29 August 2019
ASH		2018	
BSH		2018-2019	
EHA		2018-2019	
ESMO		2018	
EORTC lymphoma		2018-2019	
ICML		2019	
HTA agencies			
NICE	www.nice.org.uk		29 August 2019
SMC	www.scottishmedicines.org.uk/		
AWMSG	www.awmsg.org/		
HAS	www.has-sante.fr/		
PBAC	www.pbs.gov.au/		
CADTH	www.cadth.ca/		
G-BA	www.g-ba.de/		
IQWiG	www.iqwig.de/		
TLV	www.tlv.se/		

Resource	Host/source	Reported date range	Date searched
Trials registries			
US National Institute of Health Clinical Trial Registry	www.clinicaltrials.gov		Not reported
Other			
Bibliographies of key systematic review and meta-analysis articles were also screened.			

ASCO = American Society of Clinical Oncology; ASH = American Society of Hematology; AWMSG = All Wales Medicines Strategy Group; BSH = British Society of Haematology; CADTH = Canadian Agency for Drugs and Technologies in Health; CDSR = Cochrane Database of Systematic Reviews; EHA = European Haematology Association; EORTC = European Organisation for Research and Treatment of Cancer; ESMO = European Society of Medical Oncology; G-BA = Gemeinsamer Bundesausschuss; HAS = Haute Autorité de Santé; ICML = International Conference on Malignant Lymphoma; IQWiG = Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen; NICE = National Institute for Health and Care Excellence; PBAC = Pharmaceutical Benefits Advisory Committee; SMC = Scottish Medicines Consortium; TLV = Tandvårds-och läkemedelsförmånsverket; US = United States (of America)

ERG comment:

- The selection of databases searched was sufficient, and searches were on the whole clearly reported, comprehensive and reproducible. The database name, host and date searched were provided. Databases were searched from database inception.
- An extensive range of resources additional to database searches were hand searched to identify further relevant studies and grey literature. Terms used for conference searches were provided.

4.1.2 Inclusion criteria

Briefly, the company included both RCTs and observational evidence of brentuximab vedotin and CHOP regimens compared with any comparator for a range of efficacy and safety outcomes available in English. The full eligibility criteria used to determine inclusion in the review are given in Table 4.2.

Table 4.2: Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Population	Adult (age ≥18 years) patients with PTCL[#] and its subtypes Front-line (treatment naïve) patients of the following subtypes: • Anaplastic large cell lymphoma (sometimes reported as ALK+ ALCL and ALK- ALCL) • PTCL-not otherwise specified or PTCL-unidentified • Angioimmunoblastic T-cell lymphoma • Adult T-cell leukaemia/lymphoma • Enteropathy associated T-cell lymphoma • Hepatosplenic T-cell lymphoma	• Healthy volunteers • Paediatric population • Patients with cutaneous T-cell lymphoma • Disease other than PTCL • Resistant or relapsed or refractory PTCL or pre-treated PTCL patients[*]

	Inclusion criteria	Exclusion criteria
Interventions	• Brentuximab vedotin • CHOP regimen • CHOEP regimen (Synonyms: EPOCH or E-CHOP or CHOPE)	• Non-pharmacological interventions • Interventions not included in the list • Radiotherapy
Comparators	No restriction	None
Outcomes	• Response rates (ORR, CR, PR, SD, PD, no response) • Overall survival, progression-free survival, event free survival, disease free survival, overall death/mortality, time to response, time to progression, duration of response • Health-related quality of life • Incidence of adverse events • Study/treatment discontinuation	• Studies assessing only pharmacodynamics • Studies assessing outcomes not relevant to the review
Study design	• RCTs • Non-RCTs • Single-arm trials • Retrospective and prospective cohort studies • Real-world evidence studies/ Registries Note: Systematic reviews and meta-analyses were included and flagged for bibliography searches	• Reviews, letters, comments and editorials, protocols • Case studies or case reports[&]
Language restrictions	English[%]	None

Based on Table 1 of CS Appendix D[20] and on the response to request for clarification[17]
[#] Studies conducted either in >80% of the PTCL population or one of its subtypes (ALCL, AITL, EATL etc.) were included as per HTA requirements; [*] Search was not limited by line of therapy. However, the final included studies meeting the PICOS were restricted to front-line only. This is as per NICE draft scope[21]; [&] At primary screening stage, case studies were flagged and no exclusion on sample size; [%] Non-English language articles were included but not explored further for extraction since sufficient evidence from English language studies was available for analysis
ALCL = anaplastic large cell lymphoma; ALK- = anaplastic lymphoma kinase negative; ALK+ = anaplastic lymphoma kinase negative; CHOEP = cyclophosphamide + doxorubicin + etoposide + vincristine + prednisone; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CR = complete response; CS = company submission; HTA = health technology assessment; NICE = National Institute for Health and Care Excellence; ORR = overall response rate; PD = progressive disease; PICOS = population, intervention, comparator(s), outcome(s), study design; PR = partial response; PTCL = peripheral T-cell lymphoma; RCT = randomised controlled trial; SD = stable disease

ERG comment:

- The ERG noted that in section 3.3 of Appendix D of the CS basic study selection criteria were applied, defined as *"population, intervention and study design"*.[20] However, according to Table 1 of Appendix D, studies were excluded based on *"outcomes not relevant to the review"*.[20] The ERG asked for clarification and for a full list of the relevant outcomes.[19] In response, the company stated that *"all studies were screened using the full PICOS* [Population, intervention, comparator(s),

outcome(s)] *criteria which includes population, intervention, study design as well as outcomes. The outcomes criterion was erroneously omitted from the text in Section 3.3 of Appendix D, however it was applied in the review, as per standard protocols"*.[17] The company also provided a fuller list of outcomes assessed which is incorporated into Table 4.2. The ERG is satisfied with this response.

- Two reviewers were involved in the selection of studies for the review which helps to minimise bias in this process.
- The review included non-randomised evidence, which is important particularly when considering safety outcomes.
- The review included studies conducted either in >80% of the PTCL population or one of its subtypes, which appears reasonable given the rarity of the disease and the need to maximise the patient population for analysis.
- The company stated that *"non-English language articles were included but not explored further for extraction since sufficient evidence from English language studies was available for analysis"*.[20] However it is normally recommended to explore all relevant evidence irrespective of language. The ERG noted that according to Figure 1 of Appendix D of the CS, 19 studies were excluded at the title and abstract screening phase as they were not in English.[20] It is unclear if these would have presented relevant data.
- The ERG checked the list of studies excluded at full paper stage. The company did not appear to have excluded any relevant studies of BV.
- Forty-seven studies were included in the review (10 RCTs and 37 non-RCTs). However, it was appropriate to focus the submission on the three studies of BV.
- Section B.2.2 of the main CS stated that *"in total, three studies were identified that reported data on BV"*.[1] However, section 4.2 of Appendix D stated that *"two studies (one RCT and one Non-RCT) were identified that reported data on brentuximab vedotin"*.[20] In response to the request for clarification, the company stated that that *"two of these three studies, the ECHELON-2 Phase III study[18] and the Fanale et al Phase I study[22], met all of the PICOS criteria and were therefore identified in the SLR* [systematic literature review]. *However, the Horwitz et al Phase II publication[12] studied the efficacy and safety of BV in patients with T-cell lymphomas who had relapsed or refractory disease"*.[17]

4.1.3 Critique of data extraction

The company stated that a single reviewer extracted the data from the included full-text articles and this was subsequently quality checked by a senior independent reviewer.[20]

ERG comment: The approach did not follow the recommendations of the Cochrane Handbook which states that *"as a minimum, information that involves subjective interpretation and information that is critical to the interpretation of results (e.g. outcome data) should be extracted independently by at least two people"*.[23]

4.1.4 Quality assessment

Section 7.2 of Appendix D of the CS stated that for the included RCTs, the quality appraisal was undertaken using the standard NICE checklist.[20] The checklist by Downs and Black was used for non-RCTs and observational studies.[24] Although not explicitly stated, it appeared that two reviewers were involved in the quality assessment of the included studies.

ERG comment: If the approach for risk of bias assessment was similar to that used in the data extraction, i.e. risk of bias was assessed by one reviewer and checked by another, this would again not follow best practice. The Cochrane Handbook recommends that the assessment *"should be performed*

independently by at least two people".[23] Results of the company's and the ERG assessment of study quality are presented in section 4.2.2 of this report.

4.1.5 Evidence synthesis

The SLR identified three studies reporting results for BV: one phase III trial (ECHELON-2) and two open-label single-arm trials (one phase I and one phase II).[12, 18, 22] As there was only one placebo-controlled comparative trial, no evidence synthesis was performed.

ERG comment: The ERG agrees that meta-analysis was not possible given the existence of only one relevant RCT.

It may have been possible to construct an indirect comparison of BV with regimens other than CHOP using the RCTs identified in the systematic review. However, no indirect comparison was performed (see section 4.4). The ERG agrees that the direct comparison of BV with the CHOP is the most appropriate as it represents standard of care in the UK according to NICE.[21]

4.2 Critique of trials of the technology of interest, their analysis and interpretation (and any standard meta-analyses of these)

4.2.1 Overview of the BV evidence

Details of the three included BV studies are provided in Table 4.3.[12, 18, 22]

As ECHELON-2 was the only comparative trial relevant to the decision problem and the only study used in the economic model, the remainder of this section will focus on that study.[18] However, safety results from the observational studies are reported in section 4.2.4.

ECHELON-2 was an international, double-blind, randomised, placebo-controlled, active-comparator phase III trial. Adult patients (≥18 years) with previously untreated CD30-positive PTCL received six to eight treatment cycles of brentuximab vedotin + cyclophosphamide, doxorubicin, and prednisone (BV+CHP) or cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP). Safety and efficacy outcomes were measured including overall survival, progression-free survival, overall response rates (including complete response), adverse effects and health-related quality of life.

Further details of the design and analysis methods of ECHELON-2 are presented in Table 4.4.

ERG comment: In the request for clarification,[19] the ERG asked for a justification for the cut-off of CD-30+ expression of ≥10% malignant cells used in ECHELON-2 as well as an explanation why it differed from that of Fanale et al. 2014, i.e. ≥1% of malignant cells.[22]

In response, the company stated that *"when the ECHELON-2 study was initially designed, the 10% threshold used for CD30 expression was selected to exceed the assay's error margin and to reliably ensure that there is a significant level of CD30 for brentuximab vedotin to target. This is also consistent with the threshold selected in the ALCANZA study, which investigated the use of brentuximab vedotin in patients with Mycosis Fungoides and primary cutaneous T-cell lymphoma (CTCL) with heterogenous levels of CD30 expression. Although a 10% threshold was set in the ALCANZA study, the brentuximab vedotin licence and the positive NICE recommendation for brentuximab vedotin in CTCL (TA) does not specify a CD30 threshold – both merely state that the disease must be CD30 positive. Based on the extensive information we now have, we know that there is no correlation between the level of CD30 expression and level of response to BV. Activity is observed with any level of CD30 expression. This has been described within section B.2.6.1.2 of Document B (Figure 15). This is further supported by data that was presented in the Horwitz et al Phase II study for R/R PTCL-NOS and R/R AITL, where*

responses were seen among patients with all levels of CD30 expression on their tumour samples, including two patients with undetectable CD30 by IHC on central review".[17]

The company further confirmed that *"the proposed EMA marketing authorisation is for adult patients with previously untreated CD30+ PTCL and, as for the CTCL indication, we do not anticipate that it will specify a threshold for CD30 expression"*.[17] The ERG draws this issue to the attention of the committee. Furthermore, as detailed in section 2.2, a potential correlation between CD30 expression and the clinical response to BV has been discussed.[11, 12]

Table 4.3: Overview of the evidence for brentuximab vedotin

Study	Patient population	Intervention	Comparator	Outcomes relevant to the decision problem	Used in the economic model?
Randomised trial					
ECHELON-2[18]	Adults (≥18 years) with previously untreated, CD30-positive (≥10% of malignant cells) PTCL	Brentuximab vedotin [BV] + cyclophosphamide [C], doxorubicin [H], and prednisone [P] (BV+CHP)	Cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P] (CHOP)	Overall survival PFS per IRF Overall response rates (including CR) Adverse effects of treatment Health-related quality of life	Yes
Open label studies					
Horwitz 2014[12]	Patients with T-cell lymphomas whose tumour expressed CD30 at any level (excluding ALCL)	Brentuximab vedotin	None	Progression-free survival Overall response rates (including CR) Adverse effects of treatment	No
Fanale 2014[22]	Treatment naïve adults with a diagnosis of CD30+ PTCL, including sALCL (ALK- or ALK+ with IPI score ≥2)	Patients with sALCL and other PTCL subtypes: 1.8 mg/kg BV + CHP once every 3 weeks for up to 6 cycles. After 6 cycles, patients with an OR could receive up to 10 cycles of BV monotherapy. Patients with sALCL: 1.8 mg/kg BV, 2 cycles, once every 3 weeks, followed by standard dose CHOP 6 cycles, once every 3 weeks Sequential treatment approach for patients with sALCL receiving two cycles of 1.8 mg/kg BV followed by standard dose CHOP (six cycles)	None	Progression-free survival Overall survival Overall response rates (including CR) Adverse effects of treatment	No
Based on Tables 6 to 8 of the CS[1]					

Study	Patient population	Intervention	Comparator	Outcomes relevant to the decision problem	Used in the economic model?
ALCL = anaplastic large cell lymphoma; ALK- = Anaplastic lymphoma kinase-negative; ALK+ = Anaplastic lymphoma kinase-positive; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CR = complete response; CS = company submission; IPI = International Prognostic Index; IRF = independent review facility; PFS = progression-free survival; PTCL = peripheral T-Cell lymphoma; sALCL = systemic anaplastic large cell lymphoma					

4.2.1.1 Issues related to the incomplete clinical study report provided for ECHELON-2

A clinical study report (CSR) provides comprehensive details on the methods and the results of a clinical trial. As such, CSRs are an extremely valuable source in the assessment of clinical trials. As part of the evidence review of a CS, the ERG will review the information provided in the CS as well as other sources, including the CSR.[25]

Attempts to receive the full clinical study report for ECHELON-2

The ERG received the current submission on 4 December 2019. In an email to NICE on the same day, the ERG requested the company *"to provide the full CSRs of all studied* [sic!] *used in this submission"*. In response (received 11 December 2019), the company provided a document labelled as the CSR for ECHELON-2 (but not for any of the other trials).[26] However, the ERG considers the document provided for ECHELON-2 as incomplete as it is very short (117 pages) and included numerous references to Tables, Figures, Appendices and *"Listings"* not included in the document.[26]

Therefore, the request for clarification (sent on 17 December 2019) included a priority question on this issue: *"Please provide the full clinical study reports (CSRs) of all trials presented in the company submission (CS), especially ECHELON 2, Fanale et al. 2014, and Horwitz et al. 2014. These should include all sections as well as appendices, e.g. (but not limited to) the full results for adverse events"*.[19] In response (received on 20 January 2020), the company provided CSRs for Fanale et al. 2014 and Horwitz et al. 2014 but not for the main trial supporting the CS, ECHELON-2.[17] The response stated that *"as requested by the ERG, the full clinical study report (CSR) of the ECHELON-2 trial was provided to NICE and the ERG on 10 December 2019. Therefore, we believe the request regarding the ECHELON-2 trial has already been fulfilled"*.[17] Regarding the CSRs provided for Fanale et al. 2014 and Horwitz et al. 2014, the company stated that *"due to file size, only the main bodies of the CSRs (i.e., not appendices) are provided. Individual appendices can be provided in response to an ERG request. Please note that all CSRs are commercial in confidence and should be redacted from all publicly released documents"*.[17]

In an email to NICE (sent on 22 January 2020), the ERG highlighted that the issue remains (*"Full CSR for ECHELON-2 still missing"*) and asked NICE to *"request these files as a matter of urgency in order to avoid any further impact on our work and the ERG report"*. In response, received on 27 January 2020, the company insisted that the CSR has been provided: *"as we noted in our response to the ERG clarification questions, we have provided the CSR for the ECHELON-2 trial (in December) as well as the Phase I and Phase II trials which were requested by the ERG. However the complete set of files associated with the appendices of the CSRs are too large to transfer externally which we explained in our response. If the ERG requires a specific table or graph, we would be happy to provide that upon request"*.[17]

In summary, despite various attempts, the full CSR for ECHELON-2 was not provided to the ERG.

Points made by the company

As noted above, the company made a number of points regarding the CSR:

1. Full clinical study report for ECHELON-2 was provided[26]
2. File size restriction prevented making appendices for Fanale et al. 2014 and Horwitz et al. 2014 available
3. Individual appendices as well as specific tables or graphs can be provided in response to an ERG request

4. All CSRs are commercial in confidence and should be redacted from all publicly released documents

ERG comment:

- Re 1: As detailed above, the ERG does not consider the document received on 11 December 2019 to be a full CSR of ECHELON-2.[26]
- Re 2: The ERG is not aware of any file size restrictions regarding company evidence submissions or responses to requests for clarification and has routinely received the full CSRs for other STA submissions.[27]
- Re 3: The ERG does not consider requesting individual appendices as well as specific tables or graphs to be a very practical approach. In order for the proposed approach to work, fast responses to requests would be required to avoid delays to the evidence review. Importantly, it should be noted that it might be difficult or even impossible to make informed requests for appendices, tables or graphs without knowing what these cover.
- Re 4: In line with NICE guidance, the ERG routinely considers information provided in CSRs as commercial in confidence.[28]

Implications for the ERG report

As detailed in the NICE guidance on the company evidence submission template, *"clinical trial reports and protocols must be made available for relevant clinical studies; the remainder must be available on request. The information that NICE requests in appendices is needed by the ERG to fully critique the submission"*.[25]

Given the lack of a full CSR for the main trial for this CS, ECHELON-2, the ERG was unable to validate the information provided in the CS or to include results on potentially relevant subgroups not currently covered in the CS. The ERG considers the refusal to provide the full CSR despite numerous requests a critical shortcoming of the CS as it severely hampers the ERG's ability to identify any potential issues with the submission and to support the decision making of the committee.

4.2.1.2 ECHELON-2: Design and analysis methods

Table 4.4: ECHELON-2 design and analysis methods

Objective	To compare the efficacy and safety of brentuximab vedotin (BV) in combination with CHP (BV+CHP) with standard CHOP for the treatment of previously untreated patients >18 years of age with CD30+ PTCL.
Location	132 sites in 17 countries, 5 sites were in the UK
Randomisation method	Patients were randomly assigned (1:1) centrally with an interactive web response system that assigned a unique patient randomisation number. Treatment assignments were allocated to using a randomisation list (generated a vendor) by sequential ascending block number and by sequential ascending randomisation numbers within the appropriate strata. Randomisation was stratified by histological subtype (ALK+ ALCL with an IPI score of ≥ 2 vs all other histologies) and baseline IPI score (0–1 vs 2–3 vs 4–5).
Method of blinding (care provider, patient and outcome assessor)	BV and vincristine were dispensed in a double-blinded, double-dummy manner. BV, vincristine, and their placebo replacements were prepared by the pharmacist at each study site, and a pharmacy mask was enforced. The investigators, patients, Blinded Independent Central Review (BICR), and the sponsor were masked to treatment.
Eligibility criteria for participants	Patients aged ≥18 years with previously untreated CD30+ (≥10% of cells by local review) PTCL. Eligible histologies (per the WHO 2008 classification system) were limited to ALK+, ALCL with an IPI score of ≥ 2, ALK-, ALCL, PTCL-NOS, AITL, ATLL, EATL, and HSTL. This study was a post-approval marketing commitment from the EMA for R/R sALCL and therefore required the study to enrol 75% (+/- 5%) sALCL patients to ensure the key secondary endpoint of PFS in the sALCL subtype could be appropriately assessed.
Study duration	Median follow-up, primary analysis (PFS): 36.2 months (95% CI 35.9–41.8) Median follow-up, longer-term analysis (OS): 42.1 months (95% CI, 40.4−43.8)
Intervention and comparator	Experimental arm (n=226): BV 1.8 mg/kg, cyclophosphamide [C] 750 mg/m^2, doxorubicin [H] 50 mg/m^2, administered IV on Day 1 of each cycle; prednisone [P] 100 mg daily administered orally on Days 1−5 of each cycle. Placebo replacement for vincristine [O] also administered IV in a blinded manner on Day 1 of each cycle Standard of care arm (n=226): cyclophosphamide 750 mg/m2, doxorubicin 50 mg/m^2, vincristine 1.4 mg/m^2 (dose capped at 2 mg) administered IV on Day 1 of each cycle; prednisone 100 mg daily administered orally on Days 1−5 of each cycle. Placebo replacement for BV also administered IV in a blinded manner on Day 1 of each cycle.

	Treatment was delivered every 3 weeks for 6 to 8 cycles
Permitted and disallowed concomitant medications	Permitted: granulocyte-colony stimulating factor (G-CSF) at the discretion of the treating physician based upon institutional standards as well as consolidative stem cell transplant (SCT) or radiotherapy after treatment was permitted at the discretion of the treating physician (SCT intent was prespecified before the first cycle of chemotherapy) Disallowed: other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy
Primary outcomes (including definition and analysis methods)	PFS (according to blinded independent review facility (IRF): defined as the time from the date of randomisation to the date of first documentation of relapse or progressive disease (PD), death due to any cause, or receipt of subsequent systemic chemotherapy to treat residual or progressive PTCL as determined by the investigator, whichever occurred first. In the absence of progressive disease, receipt of radiotherapy to consolidate response to initial treatment, chemotherapy for the purpose of mobilising haemopoietic stem cells, or consolidative autologous or allogeneic stem cell transplantation were not considered events. PFS was analysed using Kaplan-Meier methods. Treatments were compared using a log-rank test, stratified by the randomisation strata, and Cox proportional hazards regression. All analyses were performed on the intention-to-treat (ITT) population.
Secondary/tertiary outcomes (including scoring methods and timings of assessments)	PFS per IRF for patients with sALCL: PFS per IRF in the subset of subjects with sALCL, as confirmed by central pathology, was analysed in the same manner as the primary analysis of PFS per IRF. Complete response (CR): defined as the proportion of subjects with CR per IRF following the completion of study treatment (at end of treatment or at the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007).[29] Subjects whose disease response was not assessable were scored as non-responders. CR was compared between treatments using the Cochran-Mantel-Haenszel (CMH) method, stratified by the randomisation strata. The absolute CR rate and exact two-sided 95% CI using the Clopper-Pearson method were summarised by treatment arm.[30] Objective response rate (ORR): defined as the proportion of subjects with CR or PR per IRF following the completion of study treatment (at end of treatment or the first assessment after the last dose of study treatment and prior to long-term follow-up) according to the Revised Response Criteria for Malignant Lymphoma (Cheson 2007). Subjects whose disease response was not assessable were scored as non-responders for calculating the ORR. The ORR between the treatment arms was analysed using the same methods as CR. Overall survival: defined as the time from randomisation to death due to any cause (OS=date of death – date of randomisation + 1). Any subject for whom death was not already known was censored for OS on the date the subject was last known to be alive or data cut-off date. Subjects without post-randomisation data were censored

	on the date of randomisation (i.e., OS duration of 1 day). OS was analysed using Kaplan Meier methodology and a stratified log-rank test. Median OS and the probability of survival are reported at 3-month intervals by treatment arm. The two-sided 95% CIs for the median were calculated using the complementary log-log transformation method. Safety: adverse events (AEs) and measurements of physical examination findings and laboratory tests. Adverse events were classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0 and graded using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Laboratory results were also graded per NCI CTCAE, version 4.03 when applicable. Antitherapeutic antibody incidence rate: Serum concentrations of BV, antitherapeutic antibodies (ATA) to BV, and plasma concentrations of free drug (monomethyl auristatin E; MMAE) were measured. Pharmacodynamic assessments included the measurement of soluble CD30 (sCD30). Medical resource utilisation: data included medical care encounters related to study treatment or treatment for lymphoma, such as hospital admissions or major diagnostic procedures. Quality of life: measured using the EORTC Quality of Life Questionnaire – Core 30 (QLQ-C30), the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity subscale (FACT/GOG-NTX), and the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L) patient-reported outcome (PRO) instruments.
Pre-planned subgroups	Randomisation stratification factors: histological subtype according to local pathology assessment (ALK-positive systemic anaplastic large cell lymphoma vs all other histologies) and baseline IPI score (0–1 vs 2–3 vs 4–5). PFS per IRF in patients with sALCL is defined in the same manner as the primary endpoint of PFS per IRF. For this endpoint, PFS per IRF will be analysed in the subset of patients with a central pathology confirmed diagnosis of sALCL.

Based on Table 9 of the CS[1]

AE = adverse event; AITL = angioimmunoblastic T-cell lymphoma; ALCL = anaplastic large cell lymphoma; ALK- = anaplastic lymphoma kinase-negative; ALK+ = anaplastic lymphoma kinase-positive; ATA = antitherapeutic antibodies; ATLL = adult T-cell leukaemia/lymphoma; BICR = Blinded Independent Central Review; BV = Brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CMH = Cochran-Mantel-Haenszel; CR = complete response; CS = company submission; CTCAE = Common Terminology Criteria for Adverse Events; EATL = Enteropathy-associated T-cell lymphoma; EMA = European Medicines Agency; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D = European Quality of Life-5 Dimensions; G-CSF = granulocyte-colony stimulating factor; HSTL = Hepatosplenic T-cell lymphoma; IPI = International Prognostic Index; IRF = independent review facility; ITT = intention-to-treat; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; MMAE = monomethyl auristatin E; NCI = National Cancer Institute; ORR = Objective Response Rate; OS = overall survival; PD = progressive disease; PFS = progression-free survival; PR = partial response; PRO = patient-reported outcome; PTCL = peripheral T-cell lymphoma; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified; QLQ-C30 = Quality of Life Questionnaire – Core 30; R/R = relapsed/refractory; sALCL = systemic anaplastic large cell lymphoma; WHO = World Health Organization

4.2.1.3 ECHELON-2: Trial participant characteristics

A total of 452 participants were enrolled in the ECHELON-2 trial, n=226 in the BV+CHP and n=226 in the CHOP arm.[18] The percentage of women in the trial was 37%. Overall, the median age was 58 years (inter-quartile range (IQR) 45–67), and the majority of patients had advanced disease (stage III 27% and stage IV 53%). Most participants (n=351 (78%) had an IPI score ≥2 (n=351).

Due to a regulatory requirement of the EMA, 70% of the participants enrolled (n=316) had a diagnosis of sALCL.

Baseline demographics are summarised in Table 4.5.

Table 4.5: ECHELON-2 baseline patient and disease characteristics

Baseline characteristic	BV+CHP (n=226)	CHOP (n=226)	Total (N=452)
Gender, n (%)			
Men	133 (59%)	151 (67%)	284 (63%)
Women	93 (41%)	75 (33%)	168 (37%)
Age			
Median age, years (IQR)	58.0 (45–67)	58.0 (44–67)	58.0 (44-67)
Race, n (%)			
Asian	45 (20%)	54 (24%)	99 (22%)
Black or African American	12 (5%)	6 (3%)	18 (4%)
White	139 (62%)	142 (63%)	281 (62)
Native Hawaiian or other Pacific Islander	1 (0%)	0	1 (0%)
Other or Unknown	29 (13%)	24 (11%)	53 (12%)
ECOG performance[†], n (%)			
0	84 (37%)	93 (41%)	177 (39%)
1	90 (40%)	86 (38%)	176 (39%)
2	51 (23%)	47 (21%)	98 (22%)
Diagnosis[‡], n (%)			
sALCL	162 (72%)	154 (68%)	316 (70%)
ALK positive	49 (22%)	49 (22%)	98 (22%)
ALK negative	113 (50%)	105 (46%)	218 (48%)
PTCL-NOS	29 (13%)	43 (19%)	72 (16%)
AITL	30 (13%)	24 (11%)	54 (12%)
ATLL	4 (2%)	3 (1%)	7 (2%)
EATL	1 (0%)	2 (1%)	3 (1%)
Disease stage at diagnosis[§], n (%)			
I	12 (5%)	9 (4%)	21 (5%)
II	30 (13%)	37 (16%)	67 (15%)
III	57 (25%)	67 (30%)	124 (27%)
IV	127 (56%)	113 (50%)	240 (53%)

Baseline characteristic	BV+CHP (n=226)	CHOP (n=226)	Total (N=452)
Baseline IPI score¥, n (%)			
0	8 (4%)	16 (7%)	24 (5%)
1	45 (20%)	32 (14%)	77 (17%)
2	74 (33%)	78 (35%)	152 (34%)
3	66 (29%)	66 (29%)	132 (29%)
4	29 (13%)	25 (11%)	54 (12%)
5	4 (2%)	9 (4%)	13 (3%)

Based on Table 11 of the CS[1]
† Values for ECOG performance status range from 0 to 5, with higher scores indicating greater disability; ‡Diagnosis per local assessment; § The Ann Arbor staging system ranges from 1 to 4, with higher stages indicating more widespread disease; ¥ The IPI score is calculated based on a patient's disease characteristics and represents increasing degrees of risk
AITL = angioimmunoblastic T-cell lymphoma; ALK- = anaplastic lymphoma kinase-negative; ALK+ = anaplastic lymphoma kinase-positive; ATLL = adult T-cell leukaemia/lymphoma; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; EATL = Enteropathy-associated T-cell lymphoma; ECOG = Eastern Cooperative Oncology Group; IPI = International Prognostic Index; IQR = inter-quartile range; PTCL-NOS = peripheral T-cell lymphoma-not otherwise specified; sALCL = systemic anaplastic large cell lymphoma

ERG comment:

- Apart from the over-representation of patients with sALCL, the ECHELON-2 population appeared to be broadly representative of patients with PTCL in the UK, except for age, as will be explained in section 5.2.3 of this report, with five of the trial sites located in the UK and 21 participating patients. The ERG agreed with the company's response to request for clarification that *"given the very low number of study subjects in some countries, analysis of efficacy by country was not considered appropriate"*.[17]
- Due to a regulatory requirement of the EMA, 70% of the participants enrolled (n=316) had a diagnosis of sALCL. The ERG considered that the ECHELON-2 trial could not reliably determine the effect of BV by subtype other than sALCL due to small sample sizes. The committee will need to decide if it accepts that BV will have a similar effectiveness and safety profile across other subtypes of PTCL.
- The baseline characteristics were generally well balanced between the treatment arms.

4.2.2. Risk of bias of the ECHELON-2 trial

The quality assessment of ECHELON-2, reported in Appendix D of the CS, recorded judgements alone and did not include any supporting information.[20] Although not explicitly stated, it appeared that two reviewers were involved in the quality assessment of the included studies. The quality appraisal of the RCT, as stated in section 4.1.4, was undertaken using the standard NICE checklist (Table 4.6).[25]

Table 4.6: ECHELON-2 risk of bias assessment

	Company assessment	ERG assessment
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes

	Company assessment	ERG assessment
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	Unclear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes	Yes
Based on Table 5 of Appendix D of the CS[20] CS = company submission; ERG = evidence review group		

ERG comment:

Overall the ECHELON-2 trial was rated in the CS as high quality and at low risk of bias.[20] The ERG re-assessed the trial against the criteria above and considered that the trial had been well-conducted. Specific issues are discussed below.

- Based on information in Table 9 of the CS, randomisation procedures and treatment concealment appeared to be adequate.[1]
- The company stated that *"baseline characteristics were generally well balanced between the treatment arms"*.[1] The ERG noted a greater number of patients with PTCL-NOS in the CHOP arm (19% vs. 13%). However, the trial was not powered to detect differences between treatment groups for this patient group.
- Procedures for blinding of care providers, participants and outcome assessors were described in Table 9 of the CS and appeared to be adequate.[1] The main outcomes were assessed by Blinded Independent Central Review (BICR) and these are the ones preferred by the ERG.
- The flow chart of ECHELON-2 (Figure 2 in Appendix D of the CS) did not appear to indicate any unexpected imbalances in drop-outs between groups.[20] Intention-to-treat analysis was used to assess trial outcomes.
- Although the main outcomes were reported in the CS, the ERG was unable to verify all outcomes in the incomplete CSR (see section 4.2.1 for details) provided by the company and has thus rated this criterion as 'unclear'.[26]

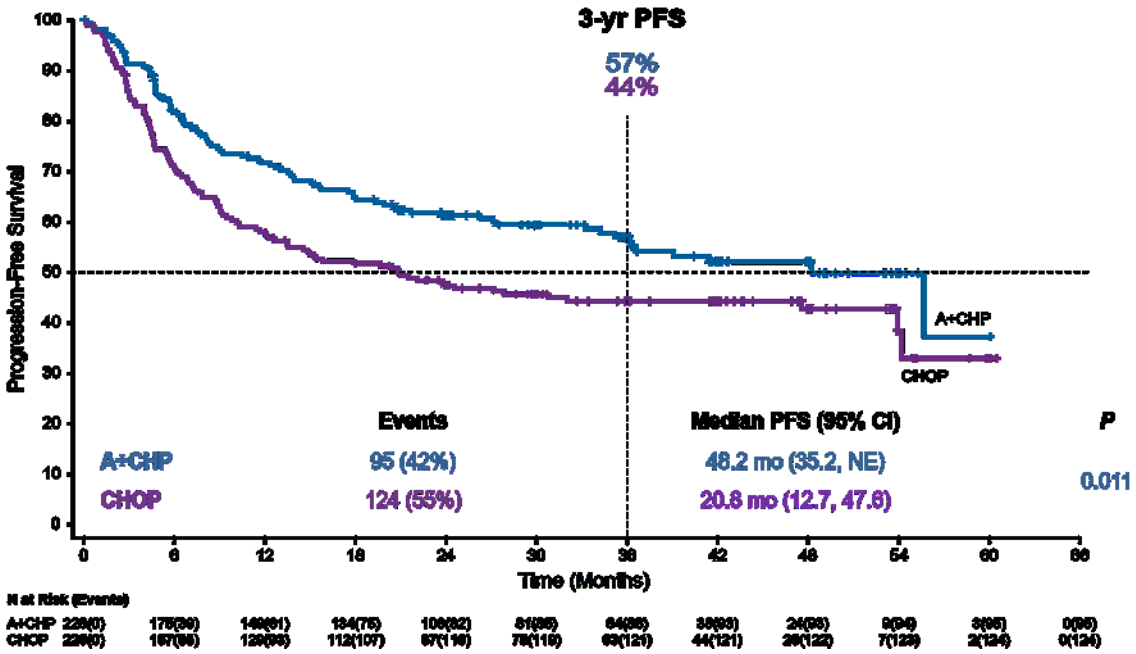
4.2.3. ECHELON-2: clinical effectiveness results

4.2.3.1 Progression-free survival (PFS)

The PFS analysis was based on a data cut-off date of 15 August 2018. At this point, 95/226 (42%) patients in the BV+CHP arm and 124 /226 (55%) patients in the CHOP arm had experienced a PFS event. The results in the ITT population were in favour of BV+CHP (stratified hazard ratio (HR) 0.71, 95% confidence interval (CI) 0.54 to 0.93, p=0.011). The Kaplan-Meier survival curves for PFS are shown in Figure 4.1. PFS results from the primary analysis and sensitivity analysis (censoring patients

on receipt of subsequent chemotherapy to treat residual or progressive PTCL rather than consider it an event) are shown in Table 4.7.

Figure 4.1: Progression-free survival (ITT population)



Based on Figure 11 of the CS[1]

A = Adcetris®; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; ITT = intention-to-treat; NE = not estimable; PFS = progression-free survival

Table 4.7: Progression-free survival (ITT population)

Progression-free survival	**BV+CHP (n=226)**	**CHOP (n=226)**
Median PFS, months (95% CI)‡	48.2 (35.2 to NE)	20.8 (12.7 to 47.6)
Stratified HR (95% CI) BV+CHP vs. CHOP	0.71 (0.54 to 0.93)	
Stratified log-rank P-value†	0.0110	
Estimated PFS (95% CI), at:		
6 months	82.1% (76.4% to 86.6%)	70.8% (64.3% to 76.3%)
12 months	71.7% (65.1% to 77.2%)	58.2% (51.4% to 64.3%)
24 months	61.4% (54.4% to 67.6%)	47.4% (40.6% to 53.8%)
36 months	57.1% (49.9% to 63.7%)	44.4% (37.6% to 50.9%)
Sensitivity analysis*		
Stratified HR (95% CI) BV+CHP vs. CHOP	0.75 (0.56 to 1.00)	
Stratified log-rank P-value†	0.0484	

Based on Table 14 of the CS[1] and the response to the request for clarification[17]

‡ PFS rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method; † From stratified log-rank test with stratification factors (ALK+ sALCL: Yes/No and International Prognostic Index score: 0-1/2-3/4-5) at randomisation; * Censoring patients receiving subsequent chemotherapy to treat residual or progressive PTCL

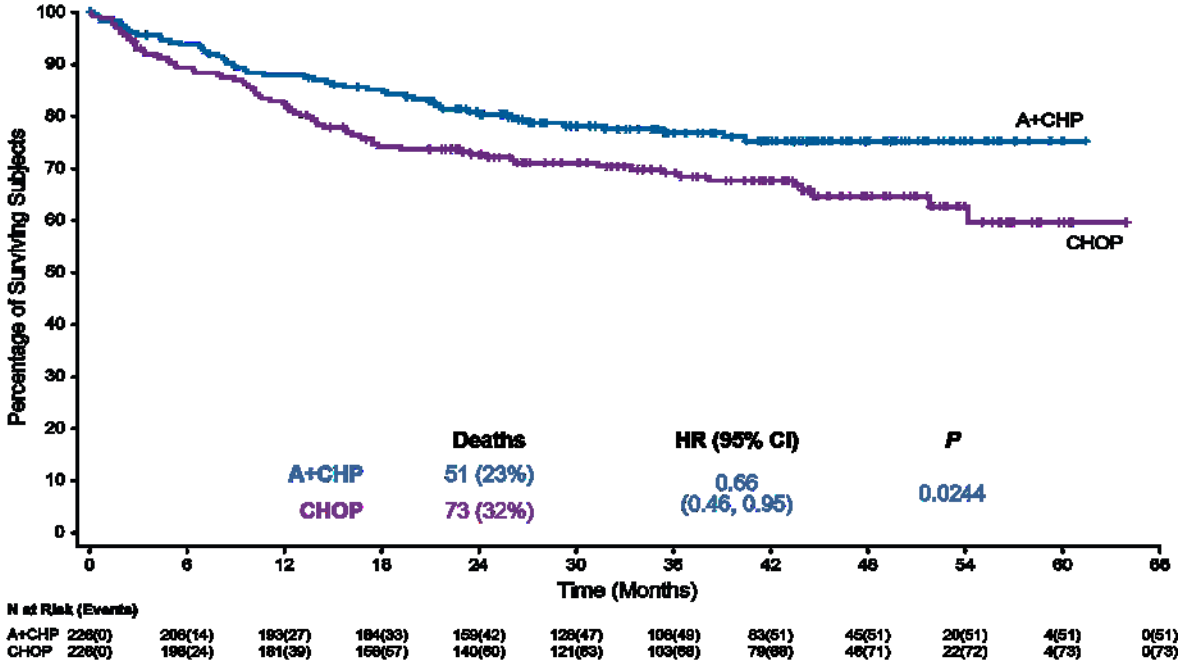
ALK+ = anaplastic lymphoma kinase-positive; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and

Progression-free survival	BV+CHP (n=226)	CHOP (n=226)
prednisone [P]; CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable; PFS = progression-free survival; PTCL = peripheral T-cell lymphoma; sALCL = systemic anaplastic large cell lymphoma		

4.2.3.2 Overall survival (OS)

The OS analysis used the same data cut-off of 15 August 2018 and at this data there had been 51 (23%) deaths in the BV+CHP arm and 73 (32%) in the CHOP arm. The results show a reduction in the risk of death with BV+CHP compared to CHOP although this is an interim analysis and the OS data are not mature (HR 0.66, 95% CI 0.46 to 0.95, p=0.0244). The Kaplan-Meier (KM) plot for OS is shown in Figure 4.2 and the results are in Table 4.8.

Figure 4.2: Overall survival (ITT population)



Based on Figure 13 of the CS[1]

A = Adcetris®; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival

Table 4.8: Overall survival (ITT population)

Overall survival	BV+CHP (n=226)	CHOP (n=226)
Number of deaths, n (%)	51 (23%)	73 (32%)
Stratified hazard ratio (95% CI) (BV+CHP to CHOP)	0.66 (0.46, 0.95)	
Stratified log-rank P value*	0·0244	
Median overall survival (months) (95% CI)†	NE (NE, NE)	NE (54.2, NE)
Estimated survival rate (95% CI)† at:		
6 months	93.7% (89.6%, 96.2%)	89.2% (84.4%, 92.7%)
12 months	87.8% (82.8%, 91.5%)	82.4% (76.7%, 86.8%)
24 months	80.8% (75.0%, 85.5%)	72.6% (66.2%, 78.0%)

Overall survival	BV+CHP (n=226)	CHOP (n=226)
36 months	76.8% (70.4%, 82.0%)	69.1% (62.3%, 74.9%)
Based on Table 15 of the CS[1] * From stratified log-rank test with stratification factors (ALK-positive sALCL: Yes/No and IPI score: 0-1/2-3/4-5) at randomisation; † Overall survival rate is estimated using Kaplan-Meier methods and 95% CI is calculated using the complementary log-log transformation method BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; NE = not estimable		

4.2.3.3 Complete response (CR) and objective response rate (ORR)

Results for CR and ORR at the end of treatment are presented in Table 4.9. The CR rate (by independent review facility (IRF) assessment) was 68% (95% CI 61.2 to 73.7) in the BV+CHP arm compared with 56% (95% CI 49.0 to 62.3) in the CHOP arm (p=0.0066). The ORR (by IRF assessment) was 83% (95% CI 77.7 to 87.8) in the BV+CHP arm and 72% (95% CI: 65.8 to 77.9) in the CHOP arm (p=0.0032).

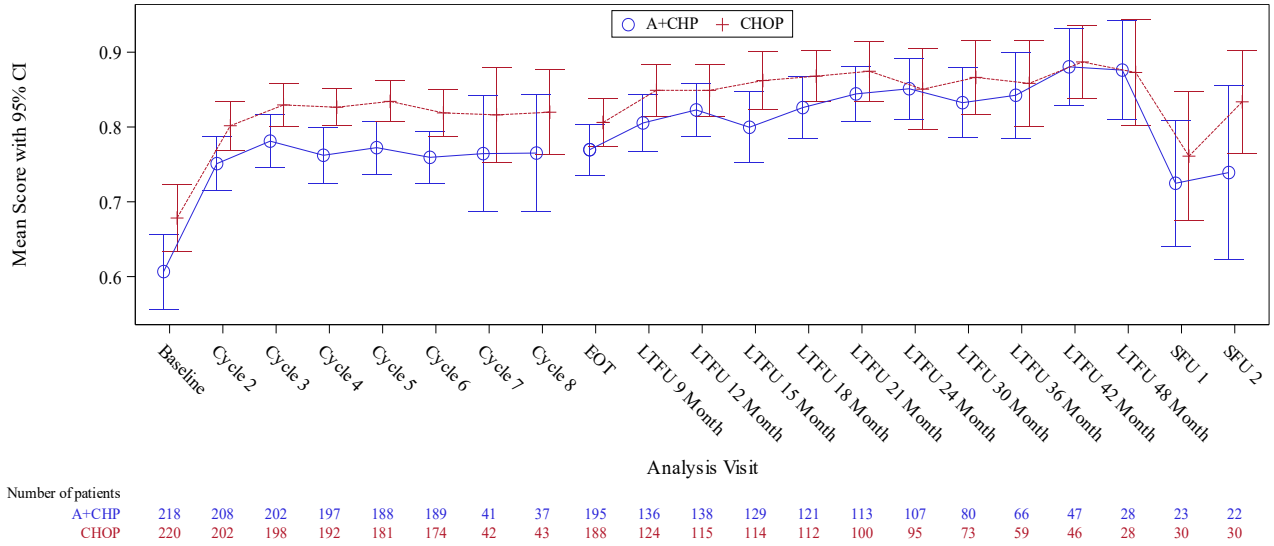
Table 4.9: CR and ORR results (ITT population)

Response	BV+CHP (N=226)	CHOP (N=226)	Response rate difference (95%CI), P-value
ORR, n (%) [95% CI]	188 (83%) [77.7 to 87.8]	163 (72%) [65.8 to 77.9]	11.1 (3.4–18.7), 0.0032
CR, n (%) [95% CI]	153 (68%) [61.2 to 73.7]	126 (56%) [49.0 to 62.3]	11.9 (3.1-20.8), 0.0066
Based on Table 17 of the CS[1] BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CR = complete response; CS = company submission; ITT = intention-to-treat; ORR = objective response rate			

4.2.3.4 Health-related quality of life (HRQoL)

In ECHELON-2, HRQoL was measured using the European Quality of Life 5-Dimensions Questionnaire (EQ-5D-3L), the EORTC Core Quality of Life Questionnaire-Core 30 (QLQ-30) and the FACT/GOG-NTX sub-scale. Results for mean EQ-5D-3L over time using UK-based time trade-off index scores in are shown in Figure 4.3. Mean scores increased over time but there was no significant difference in the change from baseline between BV+CHP and CHOP.

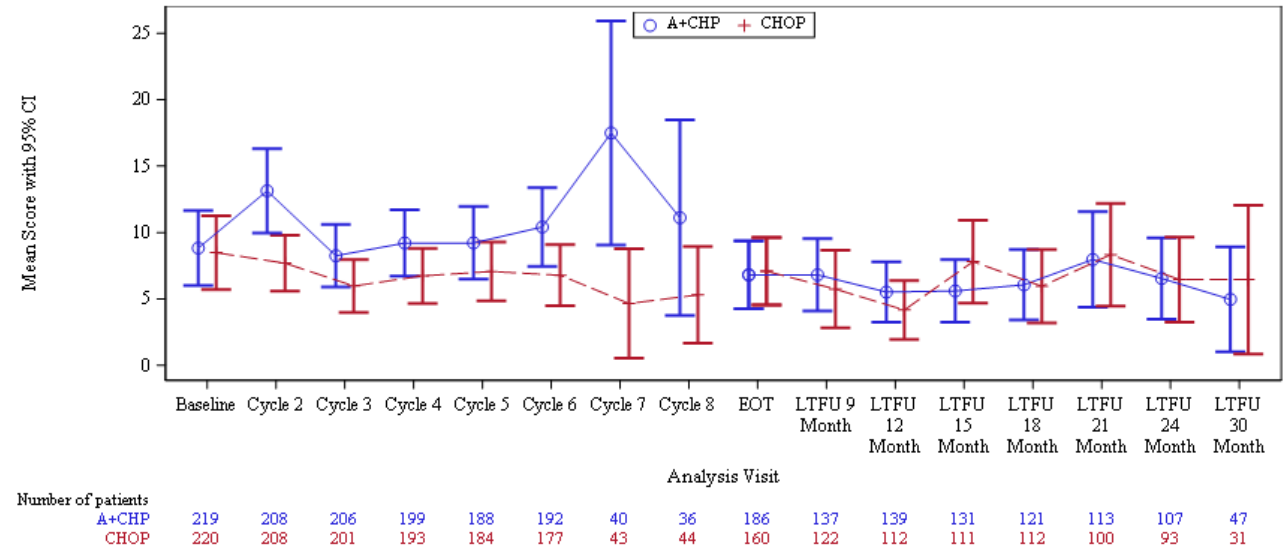
Figure 4.3:Mean EQ-5D-3L scores over time (ITT population)



Based on Figure 16 of the CS[1]
A = Adcetris®; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; EOT = end of treatment; EQ-5D-3L: European Quality of Life 5-Dimensions Questionnaire; ITT = intention-to-treat; LTFU = last treatment follow-up; SFU = safety follow-up

Treatment arms were comparable in the role, emotional, cognitive, physical, social functioning subscales, global health status and total scores of QLQ-C30. There was an increase in diarrhoea in treatment cycle 7 for patients receiving BV+CHP but this did not persist during the rest of the treatment course. Results for the QLQ-C30 diarrhoea scale are shown in Figure 4.4.

Figure 4.4: Mean QLQ-C30 diarrhoea scores over time (ITT population)

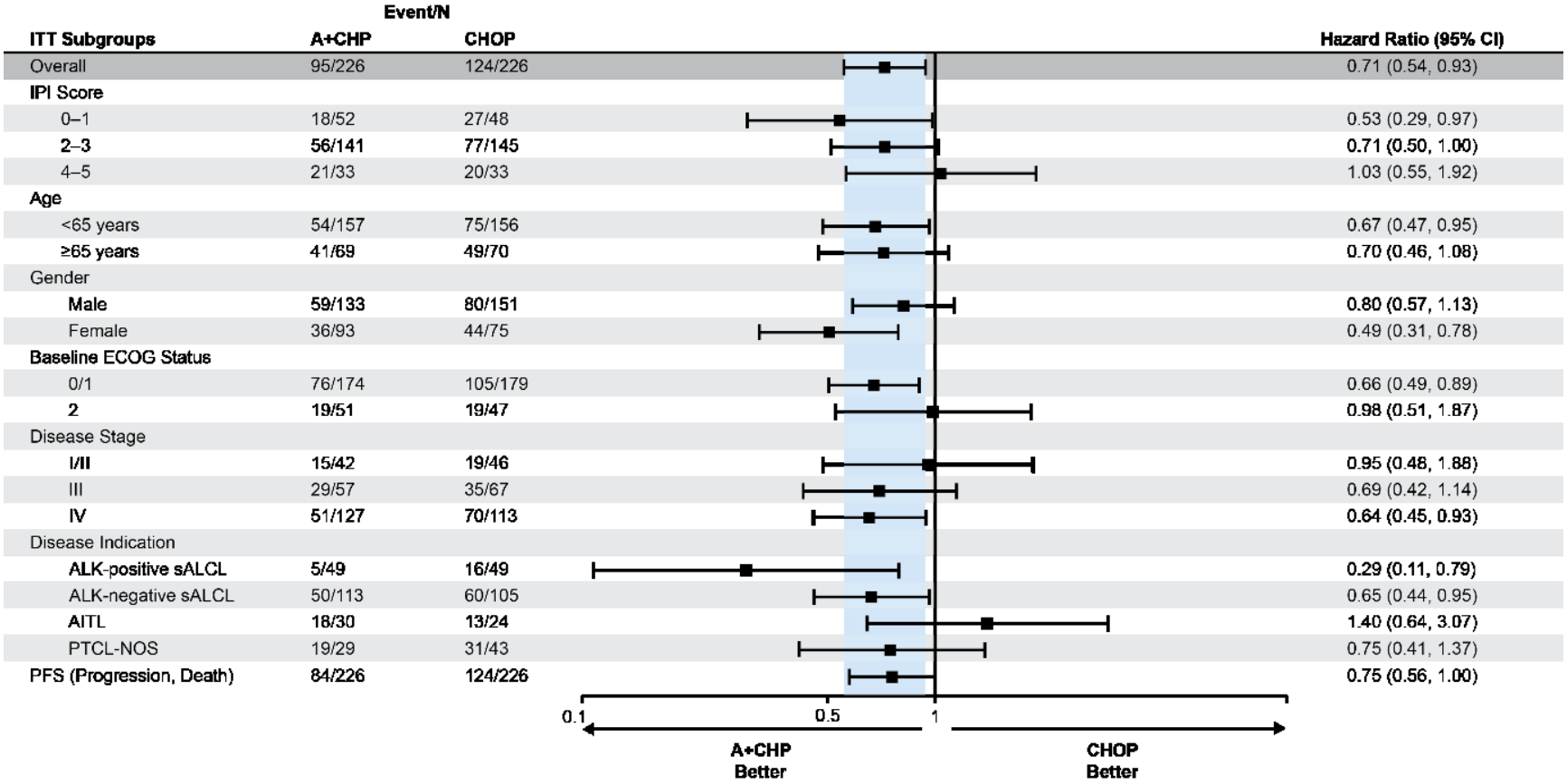


Based on Figure 17 of the CS
A = Adcetris®; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; EOT = end of treatment; ITT = intention-to-treat; LTFU = last treatment follow-up; QLQ-C30 = Quality of Life Questionnaire-Core 30

4.2.3.5 Subgroup results

The ECHELON-2 trial was only powered to determine the effect of BV in the sALCL subgroup of patients. A total of 316 of 452 (70%) patients in the ECHELON-2 trial had a diagnosis of sALCL (162 in the BV+CHP arm and 154 in the CHOP arm), see Figure 4.5. Results for this subgroup (as far as available) are presented in subsequent sections.

Figure 4.5: PFS for pre-specified subgroups (ITT analysis set)



Based on Figure 12 of the CS[1]

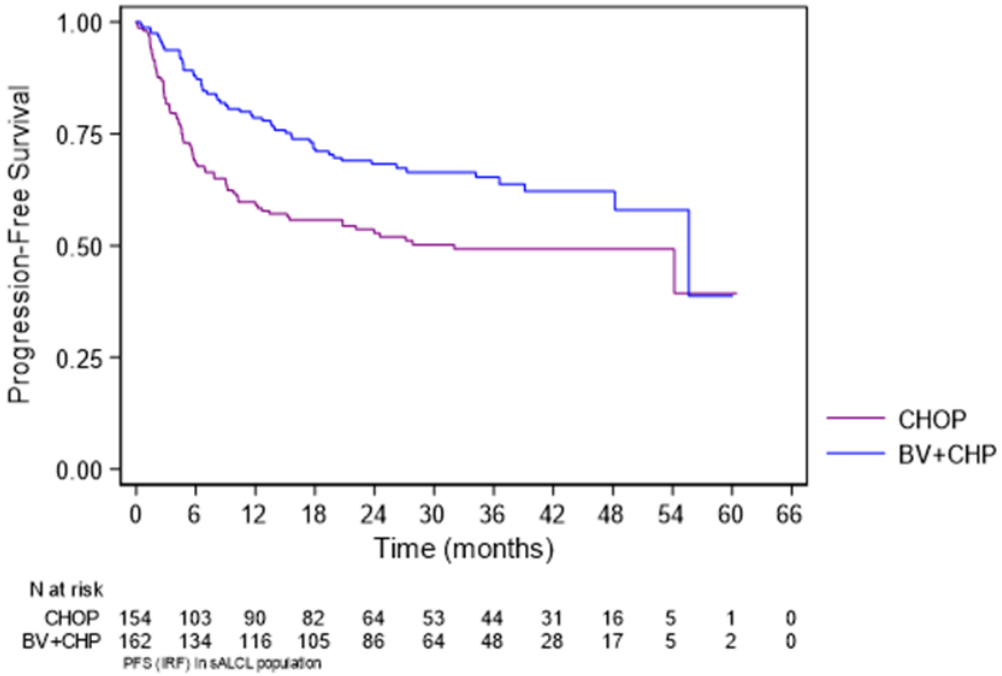
The HR for treatment with A+CHP (BV+CHP) vs. CHOP and the 95% CIs were based on the Cox regression model considering stratification factors at randomisation. The IPI subgroup was changed after randomisation in one patient in the A+CHP (BV+CHP) group (from 0–1 to 2–3) and one patient in the CHOP group (from 4–5 to 2–3).

A = Adcetris®; AITL = angioimmunoblastic T-cell lymphoma; ALK = anaplastic lymphoma kinase; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; ECOG = Eastern Cooperative Oncology Group; HR = hazard ratio; IPI = International Prognostic Index; ITT = intention-to-treat; PFS = progression-free survival; PTCL-NOS = Peripheral T-cell lymphoma-not otherwise specified; sALCL = Systemic anaplastic large cell lymphoma

sALCL: Progression-free survival (PFS)

The PFS analysis was based on a data cut-off date of 15 August 2018. At this point, 55/162 (34%) patients in the BV+CHP arm and 76 /154 (49%) patients in the CHOP arm had experienced a PFS event. Thus, the results were in favour of BV+CHP (stratified hazard ratio (HR) 0.59, 95% confidence interval (CI) 0.42 to 0.84, p=0.0031) in the sALCL subgroups as well as in the overall population. The median progression-free survival was 55.66 months (95% CI: 48.20 to –) in the BV group and 54.18 months (95% CI 13.44 to –) in the CHOP group.[26] The Kaplan-Meier survival curves for PFS are shown in Figure 4.6 (corrected in the response to clarification).[17]

Figure 4.6: Progression-free survival (sALCL)



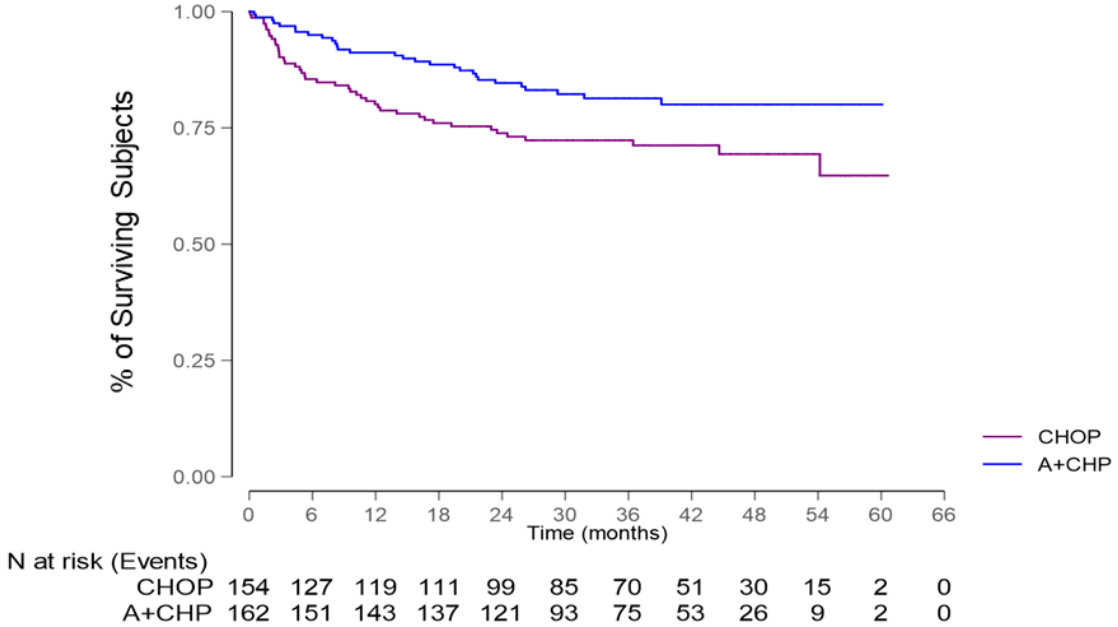
Based on Figure 19 of the CS corrected in the response to clarification[17]

A = Adcetris®; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; ITT = intention-to-treat; NE = not estimable; PFS = progression-free survival

Overall survival (OS)

The OS analysis used the same data cut-off of 15 August 2018 and at this data point there had been 29 (18%) deaths in the BV+CHP arm and 44 (29%) in the CHOP arm. The results show a reduction in the risk of death with BV+CHP compared to CHOP although this is an interim analysis and the OS data are not mature (HR 0.54, 95% CI 0.337 to 0.867, p=0.0096) The Kaplan-Meier (KM) plot for OS is shown in Figure 4.7.

Figure 4.7: Overall survival (sALCL)



Based on Figure 20 of the CS[1]

A = Adcetris®; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; HR = hazard ratio; ITT = intention-to-treat; OS = overall survival

Response rates

The ORR (by IRF assessment) was 88% (95% CI: 81.6 to 92.3) in the BV+CHP arm and 71% (95% CI: 62.9 to 77.8) in the CHOP arm (p=0.0001). The complete remission rate (by IRF assessment) was 71% in the BV+CHP arm compared with 53% in the CHOP arm. Response rates are presented in Table 4.10.

Table 4.10: Response rates (sALCL)

Response	BV+CHP (N=162)	CHOP (N=154)
Complete remission, n (%)	115 (71%)	82 (53%)
Not evaluable, n (%)	9 (6%)	18 (12%)
Progressive disease, n (%)	7 (4%)	19 (12%)
Partial response, n (%)	27 (17%)	27 (18%)
Stable disease	4 (2%)	8 (5%)
Objective response rate*	88% (95% CI 81.6 to 92.3)	71% (95% CI 62.9 to 77.8)

Based on Table 23 of the CS[1]

* At the end of treatment per IRF assessment

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; IRF = independent review facility; ITT = intention-to-treat; ORR = objective response rate

ERG comment: The ERG noted that PFS and OS results were based on a data cut-off of 15 August 2018 and asked if more recent results were available.[19] The company responded that *"the 15th August 2018 data cut-off is the latest data available from the ECHELON-2 trial and we can confirm that the evidence presented in the Lancet publication by Horwitz et al and the clinical and cost-*

effectiveness data presented in this submission reflect the most up to date data available. The next data cut of the ECHELON-2 trial is planned for late 2020, with analysis and evidence likely to become available in 2021".[17] It is drawn to the attention of the committee that currently OS data are not mature and that the later analysis may provide mature OS data.

The ERG noted that patients treated with BV+CHP had superior results in terms of PFS, OS and response rates. However, 70% of the patients had the subtype sALCL and the ECHELON-2 trial was only powered for this subtype. In all outcomes, the sALCL subtype achieved numerically better results than the population as a whole. There were no statistically significant differences in PFS and OS between treatment groups for patients of the AITL and PTCL-NOS subtypes (Figures 12 and 14 of the CS, see Figure 4.5).[1] Whether this is due to lack of statistical power or a true lack of difference between BV+CHP and CHOP is unknown.

Figures 2 and 3 of the response to the request for clarification showed results more in favour of BV+CHP compared to CHOP when considering Europe (PFS: HR 0.53, 95% CI 0.35 to 0.81; OS: HR: 0.56, 95% CI 0.33 to 0.95) and the overall results, i.e. including North America and "Other" (PFS: HR 0.71, 95% CI 0.54 to 0.93; OS: HR: 0.66, 95% CI 0.46 to 0.95).[17]

4.2.4 Safety results

This section considers the information about adverse events provided in the CS, the incomplete clinical study report for ECHELON-2 (see section 4.2.1 for details) and the response to clarification.[1, 17, 26] The main focus of the adverse events section will be on ECHELON-2 as this is a larger study, it is randomised and it presents a comparison of the differences in safety profile between BV+CHP and CHOP, the current standard of care for this condition. However, a brief discussion of the findings from the smaller observational studies can be found below.

4.2.4.1 ECHELON-2

Table 4.11 provides a summary of the adverse events in ECHELON-2.[26]

Table 4.11: Safety results of ECHELON-2

Adverse event	BV+CHP	CHOP
No in safety analysis set	**223**	**226**
No (%) with any adverse event	221 (99%)	221 (98%)
No (%) with Grade ≥ 3 adverse event	147 (66%)	146 (65%)
No (%) with serious adverse event	87 (39%)	87 (38%)
No (%) discontinued treatment due to adverse event	14 (6%)	15 (7%)
No (%) death due to adverse event	7 (3%)	9 (4%)
No (%) treatment-related adverse events*	[redacted]	[redacted]
No (%) treatment-related serious adverse events*	[redacted]	[redacted]
No (%) of deaths	51 (23%)	73 (32%)

Based on Tables 15 and 24 of the CS,[1] the response to the request for clarification,[17] and the incomplete CSR of ECHELON-2 (see section 4.2.1 for details)[26]
Note: This table only includes adverse events that occurred within safety analysis period, as defined as Day 1 up to 30 days after the last dose of any component of the regimen. Adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of any component of BV+CHP and CHOP

Adverse event	BV+CHP	CHOP
[*] Defined as participants with any brentuximab vedotin or vincristine-related event as assessed by the investigator BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; CSR = clinical study report		

The company stated that in ECHELON-2 *"incidence and severity of treatment-emergent adverse events were similar between the two study groups, BV+CHP and CHOP"*.[18] Adverse events, grade 3 and above, and serious adverse events occurred in similar proportions across the treatment groups (Table 4.11). Similar proportions discontinued treatment or died due to an adverse event. Regarding higher grade adverse events, the incomplete CSR for ECHELON-2 (see section 4.2.1 for details) stated that [redacted].[26] Incidence of treatment-related adverse events and serious adverse events (as determined by the investigator) were also comparable across treatment groups.

Table 4.12 provides details of specific adverse events which occurred in at least 10% of patients.

Table 4.12: Adverse events occurring in ≥10% of patients in ECHELON-2

	BV+CHP		CHOP	
No in safety analysis set*	**223**		**226**	
Adverse event	**Any grade**	**Grade ≥ 3**	**Any grade**	**Grade ≥ 3**
Nausea	103 (46%)	5 (2%)	87 (38%)	4 (2%)
Peripheral sensory neuropathy	100 (45%)	8 (4%)	92 (41%)	6 (3%)
Neutropenia	85 (38%)	77 (35%)	85 (38%)	76 (34%)
Diarrhoea	85 (38%)	13 (6%)	46 (20%)	2 (1%)
Constipation	64 (29%)	2 (1%)	67 (30%)	3 (1%)
Alopecia	58 (26%)	0	56 (25%)	3 (1%)
Pyrexia	58 (26%)	4 (2%)	42 (19%)	0
Vomiting	57 (26%)	2 (1%)	39 (17%)	4 (2%)
Fatigue	54 (24%)	2 (1%)	46 (20%)	4 (2%)
Anaemia	46 (21%)	30 (13%)	36 (16%)	23 (10%)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	BV+CHP		CHOP	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 25 of the CS[1] and the incomplete CSR of ECHELON-2 (see section 4.2.1 for details)[26]
Note: This table only includes adverse events that occurred within safety analysis period, as defined as Day 1 up to 30 days after the last dose of any component of the regimen. Adverse events are presented and defined as newly occurring (not present at baseline) or worsening after first dose of any component of BV+CHP and CHOP
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; CSR = clinical study report

Most adverse events occurred in similar proportions across the treatment groups. The company noted a higher incidence of diarrhoea in the BV+CHP treatment group: *"Overall, a higher incidence of diarrhoea (any grade) was reported in the BV+CHP group than in the CHOP group (38% [n=85] vs 20% [n=6] 20% of patients). Among patients in the BV+CHP group, most cases of diarrhoea were grade 1 (49/85 [58%]), with the remaining cases reported as grade 2 (23/85[27%]) and grade 3 (13/85 [15%])"*.[1]

The company further noted that "*the rates of neutropenia, febrile neutropenia, and neuropathy were similar between the BV+CHP and CHOP arms. The incidence and severity of neutropenia were lower in the subset of patients receiving primary prophylaxis with granulocyte-colony stimulating factor"*.[1]

Furthermore, the company observed that *"treatment-emergent peripheral neuropathy (PN) was similar in both treatment groups and generally resolved or improved following treatment' and that 'peripheral neuropathy events returned to baseline or lower in 50% of patients (n=58) in the BV+CHP group, with a median time to resolution of 17.0 weeks, and in 64% of patients (n=79) in the CHOP group, with a median time to resolution of 11.4 weeks. At the last follow-up, among the patients with ongoing events, most were Grade 1 (44 of 61 patients [72%] in the BV+CHP group and 32 of 45 patients [71%] in the CHOP group); two patients in the BV+CHP group and one patient in the CHOP group had ongoing Grade 3 peripheral neuropathy events."*[1]

In the incomplete CSR (see section 4.2.1 for details) further information was provided on treatment-related adverse events. It was observed that [redacted].[26] It was further observed that [redacted]

[redacted].[26]

Dose modifications of BV/vincristine, cyclophosphamide, doxorubicin, or prednisone were allowed as per institutional standards at the discretion of the investigator. The response to the request for clarification stated that *"permitted dose modifications included dose delays, dose reductions, dose eliminations (i.e., temporary stoppages allowed for cyclophosphamide and doxorubicin only), and dose discontinuations (i.e., stoppages of a treatment component for the remainder of the study). For blinded study treatment, the reduced dose levels were 1.2 mg/kg BV and 1 mg vincristine"*.[17]

Table 4.13 shows the dose modifications in relation to adverse events.

Table 4.13: Dose modifications in ECHELON-2

	BV+CHP			CHOP		
	BV	**Cyclophosphamide**	**Doxorubicin**	**Vincristine**	**Cyclophosphamide**	**Doxorubicin**
No in safety analysis set	**223**			**226**		
Dose delay due to AE	59 (26%)	58 (26%)	57 (26%)	28 (12%)	27 (12%)	28 (12%)
Dose reduced due to AE	21 (9%)	18 (8%)	17 (8%)	24 (11%)	11 (5%)	11 (5%)
Dose eliminated due to AE	NA†	0	0	NA†	1 (0)	1 (0)

Based on the response to the request for clarification[17]

Note: Dose modifications of blinded study treatment (BV/vincristine), cyclophosphamide, doxorubicin, or prednisone were allowed per institutional standards at the discretion of the investigator. Permitted dose modifications included dose delays, dose reductions, dose eliminations (i.e., temporary stoppages allowed for cyclophosphamide and doxorubicin only), and dose discontinuations (i.e., stoppages of a treatment component for the remainder of the study). For blinded study treatment, the reduced dose levels were 1.2 mg/kg BV and 1 mg vincristine. Unplanned dose adjustments were infusion interruptions, infusions stopped early, or dose errors.

† Dose elimination not permitted

AE = adverse event; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]

The company stated that "*mean exposure (relative dose intensities) for BV/vincristine, cyclophosphamide and doxorubicin were similar across the respective treatment arms"*.[1]

The incomplete CSR (see section 4.2.1 for details) provided further reasons for the modifications: [redacted].[26]

Also, in the incomplete CSR it was noted that [redacted].[26]

4.2.4.2 Observational studies

The company stated that the *"Phase II open label study demonstrated safety data consistent with the known safety profile of BV, and consistent with the aforementioned clinical trials. In the Horwitz et al. 2014 study, BV was generally well tolerated with no new safety signals detected in patients treated up to 21 cycles"*.[1] The company provided data on grade 3 and above adverse events occurring in two or more patients.

The company further stated that the *"Phase I open label study demonstrated that BV, administered sequentially with CHOP or in combination with CHP, had a manageable safety profile. After sequential treatment, Grade 3/4 adverse events occurred in 62% of patients (n=8/13). In the combination-treatment group, Grade 3/4 adverse events were experienced by 73% of patients (n=19/26), including febrile neutropenia (31%), neutropenia (23%), anaemia (15%), and pulmonary embolism (12%)"*.[1]

ERG comment:

- As far as possible, the ERG examined the information provided in the incomplete CSR of ECHELON-2 and of the two observational studies. As detailed in section 4.2.1, the company was asked (on more than one occasion) to supply the full CSRs of the included studies. Specifically the ERG asked that *"these should include all sections as well as appendices, e.g. (but not limited to) the full results for adverse events"*.[19] However the CSRs supplied were incomplete (no tables or appendices were provided).[17, 31-33] This hampered a fuller assessment of the safety of BV.
- Due to the larger number of patients and the study design, the RCT ECHELON-2 should be the main focus of the safety evaluation. It is not appropriate to compare proportions with adverse events across the studies and the above observational data are provided for information only.
- The ERG agrees, based on the ECHELON-2 RCT that the incidence and severity of adverse events appear to be similar between BV+CHP and CHOP.
- Examining specific adverse events, the ERG notes the higher incidence of diarrhoea in the BV treatment group. Should BV be approved, patients will need to be informed of a possible higher risk of this adverse event. It also appears that peripheral neuropathy might take longer to resolve with BV and again if BV is approved, patients will need to be informed of this issue.
- The ERG notes the greater number of dose delays with BV compared to CHOP. In response to the request for clarification, the company stated that *"as dose delay and dose reductions are likely to be correlated with other prognostic factors and are treatment-emergent (i.e. defined post-baseline), it*

was not considered appropriate to estimate outcomes based on these subgroups. Clinical input suggests that dose delays are generally short and are unlikely to affect patient outcomes".[17] The ERG agrees that subgroup analysis according to dose delay would not be appropriate but recommends that patients will be informed of the possibly greater risk of treatment delay should they receive BV.

4.2.5 Ongoing studies

In the CS the company provided a list of six trials of relevance to the decision problem. One single arm study (NCT03113500) was due to complete in January 2020.[34] It aims to assess the safety and tolerability of cyclophosphamide, doxorubicin hydrochloride (doxorubicin), etoposide phosphate (etoposide), prednisone, and brentuximab vedotin (CHEP-BV), as induction therapy in patients with CD30-positive peripheral T-cell lymphoma (PTCL) and to assess the anti-lymphoma activity of CHEP-BV as induction treatment in patients with CD30-positive PTCL (Phase 2). A secondary objective is to describe outcomes of CD30-positive PTCL patients who go on to receive BV consolidation therapy post CHEP-BV induction with/without autologous hematopoietic cell transplantation/radiation. This study aims to recruit 53 patients.

ERG comment: The ERG is satisfied that none of the ongoing trials listed by the company could have been used to inform the submission. NCT03113500, the ongoing study highlighted, should provide supplementary data on BV.

As noted previously, PFS and OS results for ECHELON-2 were based on a data cut-off of 15 August 2018. The company informed the ERG that these were the latest data available and that *"the next data cut of the ECHELON-2 trial is planned for late 2020, with analysis and evidence likely to become available in 2021"*.[17] The ongoing analysis may provide more mature OS data and further detail on longer-term outcomes.

4.3 Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

No trials were identified for indirect treatment comparisons.

4.4 Critique of the indirect comparison and/or multiple treatment comparison

There were no indirect comparisons listed in the CS, and no network meta-analyses performed.

4.5 Additional work on clinical effectiveness undertaken by the ERG

No additional work on clinical effectiveness was undertaken by the ERG.

4.6 Conclusions of the clinical effectiveness section

The CS and response to clarification provided sufficient details for the ERG to appraise the literature searches conducted as part of the systematic review to identify clinical effectiveness studies. A range of databases and additional resources were searched.

The Evidence Review Group (ERG) noted that 19 studies were excluded at the title and abstract screening phase of the systematic literature review (SLR) as they were not in English. It is unclear if these would have presented relevant data. The SLR identified three studies reporting results for BV: one phase III trial (ECHELON-2) and two open-label single-arm trials (one phase I and one phase II).

The ERG report focuses on ECHELON-2 was it was the only comparative trial relevant to the decision problem and the only study used in the economic model. ECHELON-2 was an international, double-blind, randomised, placebo-controlled, active-comparator phase III trial, rated to be of low risk of bias.

Adult patients (≥18 years) with previously untreated CD30-positive PTCL received six to eight treatment cycles of BV+CHP or CHOP. Safety and efficacy outcomes were measured including overall survival, progression-free survival, overall response rates (including complete response), adverse effects and HRQoL.

Despite numerous requests, a clinical study report (CSR) for ECHELON-2 was not provided (see section 4.2.1). Therefore, the ERG was unable to validate the information provided in the CS or to include results on potentially relevant subgroups not currently covered in the CS. The ERG considers the refusal to provide the full CSR despite numerous requests a critical shortcoming of the CS as its severely hampers the ERG's ability to identify any potential issues with the submission and to support the decision making of the committee.

Both, PFS and OS analyses, were based on a data cut-off date of 15 August 2018. In response to request for clarification, the company stated that *"the next data cut of the ECHELON-2 trial is planned for late 2020, with analysis and evidence likely to become available in 2021"*.[17]

Regarding PFS, at the time of the cut-off, 95/226 (42%) patients in the BV+CHP arm and 124/226 (55%) patients in the CHOP arm had experienced a PFS event. The results in the ITT population were in favour of BV+CHP (stratified HR 0.71, 95% CI 0.54 to 0.93, p=0.011), see Table 4.7.

Regarding OS, at the time of the cut-off, there had been 51 (23%) deaths in the BV+CHP arm and 73 (32%) in the CHOP arm. The results show a reduction in the risk of death with BV+CHP compared to CHOP although this is an interim analysis and the OS data are not mature (HR 0.66, 95% CI 0.46 to 0.95, p=0.0244), see Table 4.8.

At the end of the treatment, the complete response rate (by independent review facility (IRF) assessment) was 68% (95% CI 61.2 to 73.7) in the BV+CHP arm compared with 56% (95% CI 49.0 to 62.3) in the CHOP arm (p=0.0066). The objective response rate (by IRF assessment) was 83% (95% CI 77.7 to 87.8) in the BV+CHP arm and 72% (95% CI: 65.8 to 77.9) in the CHOP arm (p=0.0032), see Table 4.9.

The ERG noted that patients treated with BV+CHP had superior results in terms of PFS, OS and response rates. However, 70% of the patients had the subtype sALCL and the ECHELON-2 trial was only powered for this subtype. In all outcomes, the sALCL subtype achieved numerically better results than the population as a whole (see section 4.2.3).

Adverse events, grade 3 and above, and serious adverse events occurred in similar proportions across the treatment groups. Similar proportions discontinued treatment or died due to an adverse event. Regarding higher grade adverse events, the incomplete CSR for ECHELON-2 stated that [redacted].[26] Examining specific adverse events, the ERG notes the higher incidence of diarrhoea in the BV treatment group. Should BV be approved, patients will need to be informed of a possible higher risk of this adverse event. It also appears that peripheral neuropathy might take longer to resolve with BV and again if BV is approved, patients will need to be informed of this issue (see section 4.2.4 for details). Table 4.11 provides a summary of the adverse events in ECHELON-2.

As only one relevant RCT was identified, no meta-analysis was conducted. Furthermore, there were no indirect comparisons listed in the CS, and no network meta-analyses performed.

5. COST EFFECTIVENESS

5.1 ERG comment on company's review of cost effectiveness evidence

5.1.1 Searches performed for cost effectiveness section

The following paragraphs contain summaries and critiques of all searches related to cost effectiveness, health-related quality of life and cost and resource use identification presented in the company submission.

Appendix G of the CS details systematic searches of the literature used to identify cost effectiveness studies and cost and resource use studies.[35] Appendix H of the CS details systematic searches of the literature used to identify health-related quality of life studies.[36]

Database searches for cost effectiveness, cost and resource use and health-related quality of life studies were undertaken on 27 February 2019. Searches of conference proceedings were undertaken on 4 April 2019. A targeted update search was undertaken on 1 November 2019. In response to the request for clarification, the company explained that the targeted update search expanded the population criterion.[17] Search terms for the updated search were provided but no detailed strategy of the database search of PubMed search was provided.

A summary of the sources searched is provided in Table 5.1.

Table 5.1: Data sources for the cost effectiveness, cost and resource use and health-related quality of life studies

Resource	Host/source	Reported date range	Date searched
Electronic databases			
MEDLINE and In-Process	PubMed	From database inception	27 February 2019
Embase	Embase.com		
EconLit	Ebscohost		
NHS EED	CRD		
Conference proceedings			
ASH	Not reported	2016-2018	4 April 2019
BSH		2016-2018	
ASCO		2016-2018	
EHA		2016-2018	
ICML		2013, 2015, 2017	
T-cell Lymphoma Forum		2016-2018	
ISPOR USA		2016-2018	
ISPOR EU		2016-2018	
Targeted update search			
PubMed	Not reported	From database inception	1 November 2019
NICE			
SMC			
ASCO		2019	
EHA		2019	

Resource	Host/source	Reported date range	Date searched
ICML		2019	
ISPOR US		2019	
Other			
Hand-searching of the bibliography list of relevant SLRs/meta-analyses identified by database searches.			

ASCO = American Society of Clinical Oncology; ASH = American society of Hematology; BSH = British Society for Haematology; CRD = Centre for Reviews and Dissemination; EED = Economic Evaluation Database; EHA = European Hematology Association; EU = European Union; ICML = International Conference on Malignant Lymphoma; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; SMC = Scottish Medicines Consortium; US = United States (of America)

ERG comment:

- The ERG considers the database searches and methodology reported in the CS to support the systematic review of cost effectiveness data, health-related quality of life and cost and resource use on the whole to be comprehensive, transparent, reproducible and fit for purpose.
- Databases were searched from database inception.
- A targeted update search with an expanded population criterion was undertaken on 1 November 2019. Search terms were provided but details of the database strategy for PubMed were not provided.
- A range of conference proceedings sources were hand searched on 4 April 2019 and, if relevant, on 1 November 2019. Search terms for conference proceedings were provided.

5.1.2 Inclusion/exclusion criteria used in the study selection

Separate predefined inclusion/exclusion criteria were used to screen those records identified by the economic, HRQoL and cost and resource use search strategies. These criteria were used to screen titles and abstracts in the first stage of review. Any records which passed the first stage were screened again at the full text level. Reviewing at both stages was completed independently by two reviewers. Any disagreement was resolved by a third reviewer. Inclusion/exclusion criteria for each of the three SLRs were based on the PICOS framework, relating to the population, interventions, comparators, outcomes and study design of interest.

Inclusion/exclusion criteria for the economic, HRQoL and cost and resource use SLRs are shown in Tables 2 and 3 of Appendices G, H and I, respectively, of the CS.[35-37] In each SLR, the population inclusion criterion was treatment naïve adult (≥18 years) patients with PTCL, with a focus on the following subtypes: PTCL-NOS, AITL, ALK+ and ALK- sALCL, ATLL, EATL and HSTL. Inclusion was not restricted to any specific intervention or comparator in any of the SLRs, but could include anthracycline-based multiagent chemotherapy regimens.

Outcomes of interest and accepted study designs varied by SLR. The economic SLRs included outcomes related to model structure, model assumptions and model outcomes such as incremental cost effectiveness ratio (ICER) and life years gained (LYG) as well as sources of clinical, cost and HRQoL inputs. Both trial-based and model-based economic evaluations were accepted study designs in the economic SLR. In the HRQoL SLR, included outcomes were utilities and HRQoL evaluated with generic or condition-specific instruments. In the cost and resource use SLR, included outcomes were direct resource use and costs as well as indirect costs. In the HRQoL and cost/resource use SLRs, accepted study designs were RCTs, prospective interventional trials and observational studies. In all

three SLRs, systematic reviews of interventional and observational studies were included only as an additional source of citations.

Across all SLRs, studies conducted in populations other than those with PTCL, or in PTCL populations that had received prior treatment, were excluded, as were studies in children or mixed adult and child populations without separate reporting of relevant data. Case reports, expert opinion articles, letters and narrative non-systematic reviews were also excluded in all three SLRs.

ERG comment: The inclusion/exclusion criteria used in the SLRs were reasonable. No mention was made of any language restrictions. Therefore, the ERG has to assume that no articles were excluded due to language.

5.1.3 Identified studies

Data were extracted from included studies by one independent researcher and validated by a second senior researcher. Quality assessment of included studies was carried out by two researchers using the Drummond checklist for economic evaluations.[38]

5.1.3.1 Economic SLR

The PRISMA diagram showing the flow of studies for the economic SLR is displayed in Figure 1 of Appendix G of the CS.[35] The database searches identified 637 unique records to be screened at title and abstract level. Thirteen were reviewed at full text. After full text screening and hand searching from other sources, no economic evaluations in PTCL patients were identified, with the only included studies being economic burden studies (discussed in the cost and resource use SLR).

An additional targeted literature search (grey literature) was carried out on 1 November 2019 to check for any new publications. This search was expanded to any line of treatment. This search resulted in five additional economic studies: one economic evaluation abstract for first-line PTCL treatment and four studies (of which three were abstracts) analysing patients with PTCL in the R/R setting. The only non-abstract study identified was the previous NICE STA (TA478) of brentuximab vedotin for treating relapsed or refractory systemic anaplastic large cell lymphoma.[39] Results of all included studies were summarised in Table 4 in Appendix G of the CS.[35]

5.1.3.2 HRQoL SLR

The PRISMA diagram for the HRQoL SLR was displayed in Figure 1 of Appendix H of the CS.[36] The electronic HRQoL searches identified 233 unique records, however, none of these met the inclusion/exclusion criteria. Additionally, no relevant studies meeting the original criteria were identified in the grey literature search. An extended targeted literature search, in which the population was not limited by treatment line, was carried out on 1 November 2019. A single study (Swinburn et al. 2015), which assessed the HRQoL of patients with R/R sALCL, was identified.[40] A summary of this study was provided in Table 4 of Appendix H of the CS.[36]

5.1.3.3 Cost and resource use SLR

The PRISMA diagram for the cost and resource use SLR is displayed in Figure 1 of Appendix I of the CS.[37] The combined electronic economic and cost and resource use searches identified 637 unique records. Thirteen were reviewed at full text. After full text screening and hand searching from other sources, six studies were included in the cost and resource use SLR. An additional targeted search (grey literature), also with removal of treatment line restrictions, was carried out on 1 November 2019. This identified an additional five studies, of which one was TA478, relevant to cost and resource use outcomes.[39]

In total seven cost and/or resource use studies were identified, of which five reported on costs and six reported on resource use. Summaries of these studies are provided in Tables 4 and 5 of Appendix I of the CS.[37]

ERG comment: The reporting of results of the SLRs was at times confusing. For example, in Figure 1 of Appendix G of the CS and Figure 1 in Appendix I, the PRISMA (Transparent Reporting of Systematic Reviews and Meta-analyses) diagrams for both the cost effectiveness and cost and resource use SLRs state that in the original electronic search, 13 articles were reviewed at full text, of which nine were excluded and six were included in qualitative synthesis.[35, 37] The first issue is that these numbers do not add up, suggesting a reporting error which makes it difficult for the ERG to trace what happened to papers at the full text stage. It also raises a question of whether papers which should have been excluded for one of the reasons listed in the PRISMA, went on to be included. Another concern is that in the text reporting the results of the cost effectiveness SLR, it states that all 13 papers identified in the electronic search were excluded and only five from the targeted search were included.[35] The inclusion of six papers from the electronic search and five from the targeted search matches the reporting of the cost and resource use SLR suggesting the wrong PRISMA is reported in Appendix G for the cost effectiveness SLR.

5.1.4 Interpretation of the review

At times reporting of the SLR methods and results was lacking or confusing. The numbers reported in the PRISMA diagrams for the cost effectiveness and cost and resource use SLRs, after the title and abstract screening phase do not sum correctly. Additionally, the PRISMA for the cost effectiveness SLR does not match the reporting in the text after the first screening phase, leading the ERG to believe that the incorrect PRISMA was reported for this SLR.[35] Therefore it is difficult for the ERG to trace what happened to papers from this point. However, the reporting in the text appeared consistent with the tables of included studies presented. On the whole, the SLRs were considered to be comprehensive and fit for purpose.

5.2 Summary and critique of company's submitted economic evaluation by the ERG

A summary of the economic evaluation conducted by the company is presented in Table 5.2.

Table 5.2: Summary of the company submission economic evaluation

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Model	The company developed a partitioned survival model in Excel. The health states considered in the model are progression-free (PFS) disease, progressive (PD) disease and death.	The same model structure was used as in previous NICE BV appraisals, with a key difference in health state model ling; previous appraisals considered health states based on receipt of SCT, where treatment with BV may act as bridge to SCT: R/R sALCL (TA478),[39] CD30+ Hodgkin's lymphoma (TA524)[41] and CD30+ cutaneous T-cell lymphoma (TA577).[42]	Section 5.2.2.
States and events	Patients enter the simulation in the PFS health state and remain there until progression or death.	Consistent with the partitioned survival modelling approach and, therefore, with previous NICE technology appraisals for BV.	Section 5.2.2.
Comparators	The analysis evaluated the cost effectiveness of BV+CHP (intervention arm) vs. CHOP (comparator arm) for untreated CD30-positive peripheral T-cell lymphoma.	CHOP was the only comparator listed in the NICE final scope and, therefore, included in the cost effectiveness model.	Section 5.2.4.
Natural history	PTCL is characterised by the neoplastic development of post-thymic, mature T-Cells. Four major categories of PTCLs are distinguished in the company submission: cutaneous, disseminated/leukemic, primary extranodal and primary nodal. However, further distinctions can be made within each category (see e.g. Figure 2.1). The expression of the protein CD30 is highly prevalent in the sALCL subtype and variably expressed across other subtypes. Overall, approximately 50% of all PTCLs are reported to express CD30 (CD30+) and 58% of PTCL-NOS are CD30+. The 5-year OS for PTCL-NOS is reported to be 32%. A UK-based audit carried out between 2002 and 2012 reported a 5-year OS of 38.8% for PTCL. The different subtypes of PTCL vary on their presentation and prognosis. ALK+ sALCL has the best prognosis compared to the other subtypes. However, this positive advantage remains dependent on the age at diagnosis and the IPI score.		Section 2.2

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Treatment effectiveness	Whenever possible, treatment effectiveness parameters were derived from the ECHELON-2 trial.[18] In particular, patient-level data from ECHELON-2 were used to estimate: 1) extrapolation of OS and PFS, 2) duration, efficacy and administration/re-administration of BV+CHP and CHOP and 3) the proportions of patients receiving consolidative AutoSCT, consolidative and salvage radiotherapy, salvage stem cell transplant (AutoSCT and alloSCT), salvage chemotherapies, salvage treatment with BV and re-treatment with BV. External sources including published literature, expert advice and modelling assumptions were also used.	Observed OS/PFS Kaplan Meier curves were extrapolated using parametric distributions. Given the lack and poor quality of available evidence, the long-term extrapolations were justified by clinical expert opinion.	Section 5.2.6
Adverse events	Grade 3-4 TEAEs occurring in ≥5% of patients in ECHELON-2 were included in the model. Additionally, the model included Diarrhoea Grades 1-4 and Grade 3-4 peripheral neuropathy. The effects of AEs are captured by applying AE-specific costs and utility decrements. The average number and duration of AEs were based on those observed in the ECHELON-2 trial.	Lower grades of diarrhoea were also included based on expert opinion (Grades 1-2 at a lower associated cost than Grade 3-4 diarrhoea). Peripheral neuropathy was included, as this AE is a known class effect of agents with an anti-microtubule mechanism of action, such as BV. It was also included in previous TAs of and assumptions regarding associated resource use and utility decrements were taken from TA478.[39]	Section 5.2.7
Health related QoL	HRQoL was measured in the ECHELON-2 trial using the EQ-5D-3L and valued using the UK EQ-5D-3L value set. Utilities were modelled using both a health state utility value approach and a time-to-death approach. Both approaches included covariates for age, experiencing Grade 3-4 AEs, being post-SCT and baseline EQ-5D. The company base-case used the health state utility value approach. However, the utility value for progressed disease was estimated from TA478,[39] instead of from the company's model and data.	Clinical experts consulted by the company felt the small coefficient on progression in the health state utility model was implausibly small. It was not clear why the company favoured using an alternative source (which did not meet the NICE reference case as utility was measured using vignettes in members of the general population) for their base-case progressed disease value, rather than using their alternative EQ-5D time-to-death modelling approach.	Section 5.2.8

	Approach	Source/Justification in the company submission	Signpost (location in ERG report)
Resource utilisation and costs	The economic analysis was performed from the NHS and PSS perspective. The following costs were included: drug costs (consisting of acquisition costs, administration costs, and concomitant medication), pre- and post-progression health care resource use, AE costs and miscellaneous costs (stem cell transplant, consolidative radiotherapy, second-line BV, and salvage chemotherapies and radiotherapy).	Drug acquisition and administration costs were based on ECHELON-2,[18] concomitant medication on expert opinion,[43] and documentation by the London Cancer Alliance on follow-up care with CHOP.[44] Pre- and post-progression health care resource use was based on follow-up and monitoring requirements in ECHELON-2,[18] documentation by the London Cancer Alliance on follow-up care with CHOP,[44] TA478,[39] and clinical expert opinion.[16] AE costs were based on Grade 3-4 AEs occurring in ≥5% of patients in ECHELON-2,[18] as well as grade 1-2 diarrhoea. No costs were included for the treatment of grade 1-2 and grade 3-4 peripheral neuropathy. Miscellaneous costs based on ECHELON-2,[18] TA478,[39] clinical expert opinion,[16, 45] and clinical guidelines.[14, 46]	Section 5.2.9
Discount rates	Cost and health outcomes discounted at 3.5%	As per NICE reference case	Section 5.2.5
Sensitivity analysis	Probabilistic, deterministic one-way sensitivity analysis and scenario analyses conducted	As per NICE reference case	Section 6.2

Based on the CS[1]

AE = adverse event; ALK+ = anaplastic lymphoma kinase-positive; alloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; BV = brentuximab vedotin; CHP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health related quality of life; IPI = International Prognostic Index; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; OS =overall survival; PD = progressive disease; PFS = progression-free survival; PSS = Personal Social Services; PTCL = peripheral T-cell lymphoma; PTCL-NOS = Peripheral T-cell lymphoma-not otherwise specified; QoL = quality of life; R/R = relapsed/refractory; sALCL = systemic anaplastic large cell lymphoma; SCT = stem cell transplant; TA = technology appraisal; TEAE = treatment-emergent adverse event; UK = United Kingdom

5.2.1 NICE reference case checklist (TABLE ONLY)

Table 5.3: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers.	Direct health effects for patients included.
Perspective on costs	NHS and PSS.	NHS and PSS perspective taken.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis.	Cost-utility analysis with fully incremental analysis undertaken.
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared.	The model time horizon of 45 years is appropriate for a lifetime horizon as the mean age of patients at the start of treatment was 55.1 years.
Synthesis of evidence on health effects	Based on systematic review.	Systematic review conducted to identify additional evidence on health effects beyond trial data.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	Health effects were expressed in QALYs. The EQ-5D-3L was used to measure HRQoL in the ECHELON-2 trial. Company base-case also used utility values from Swinburn et al. 2015,[40] which measured HRQoL using vignettes in members of the UK general population
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers.	HRQoL data from the ECHELON-2 trial reported directly by patients. Swinburn et al. 2015 measured HRQoL using vignettes in members of the UK general population.[40] Therefore, HRQoL was not directly reported by patients in the Swinburn study and these values do not meet this element of the reference case.
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population.	EQ-5D-3L data were valued in a representative sample of the UK general population using the UK value set.[47] In Swinburn et al. 2015 *"the sample was varied in terms of main activity, qualifications and marital status,*

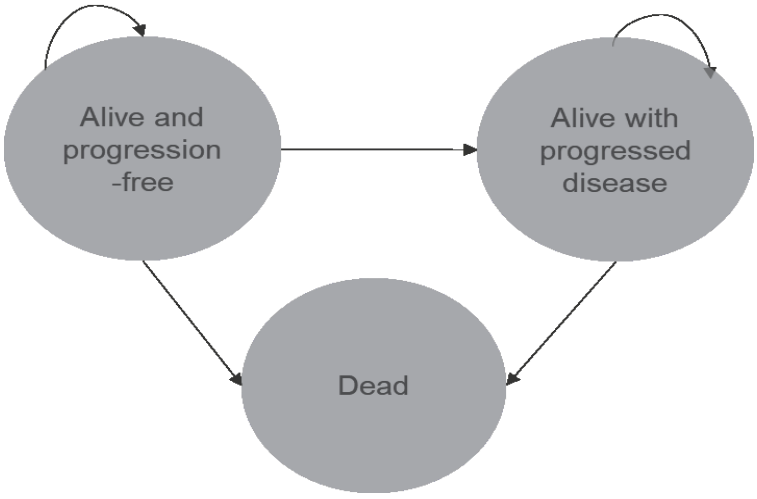
Element of health technology assessment	Reference case	ERG comment on company's submission
		providing a broad representation of the general population, in terms of the local demographics."[40]
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit.	No equity issues have been identified.
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS.	The model includes the costs that relate to NHS and PSS resources, valued using the prices relevant to the NHS and PSS.
Discounting	The same annual rate for both costs and health effects (currently 3.5%).	Costs and health effects are discounted at 3.5%.

EQ-5D = European Quality of Life-5 Dimensions; HRQoL = health related quality of life; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSS = Personal Social Services; QALY = quality adjusted life year; UK = United Kingdom

5.2.2 Model structure

The company developed a partitioned survival model in Excel. The health states considered in the model are PFS, progressive disease (PD) and death. Patients enter the simulation in the PFS health state and remain there until progression or death. The proportion of patients in the PFS and death health states over time were directly estimated from ECHELON-2 PFS and OS data, respectively. The proportion of patients in the PD health state was estimated as the difference between OS and PFS. A schematic representation of the model structure is shown in Figure 5.1. The model uses a cycle length of 21 days (reflecting the duration of a CHOP or a BV+CHP treatment cycle) and half-cycle correction. Costs and utilities are applied to each health state of the model (except death) to calculate per-cycle costs and quality adjusted life-years (QALYs).

Figure 5.1: Model structure



Based on Electronic model of the CS[48]

ERG comment: The model structure is commonly used in oncology. The modelling approach used by the company was also in line with all previous NICE technology appraisals for BV: R/R sALCL (TA478), CD-30+ Hodgkin's lymphoma (TA524) and CD-30+ cutaneous T-cell lymphoma (TA577).[39, 41, 42] A comparison of the model structures is provided in Table 5.4. For these reasons, the ERG considers the model structure appropriate.

Table 5.4: Comparison of model structures used in this and previous (related) NICE appraisals

	Previous appraisals			Current appraisal	
	TA478[39] R/R sALCL	**TA524[41] R/R HL**	**TA577[42] CD30+ CTCL**	**Chosen values**	**Justification (company)**
Time horizon	60 years (lifetime)	70 years (lifetime)	45 years (lifetime)	45 years (lifetime)	A lifetime horizon was selected, as per NICE reference case.[49] A lifetime of 100 years was assumed, with a mean baseline age of 55.1 years (as per ECHELON-2).[18]
Treatment waning effect	No	No	No	No	Clinical evidence from ECHELON-2 did not suggest a reduction in the treatment effect over time. The data available from the trial are relatively mature (median follow-up of 36.2 months), with treatment only lasting for an average of 6 cycles.
Source of utilities	Swinburn et al. 2015 using health-state vignettes in R/R HL and sALCL[40]	Swinburn et al., 2015[40] and literature on utilities post-SCT[50]	EQ-5D and a regression model to fit the Skindex-29 to the EQ-5D, both collected in the ALCANZA trial[51] The Swinburn et al. 2015 study using health-state vignettes was applied to the end-stage management utilities.[40]	EQ-5D-3L collected in ECHELON-2 determines utility in the progression-free state, and QALY loss/gain resulting from age, SCT and AEs. The progressive disease utility value is estimated from TA478.	The NICE methods guide[49] stipulates that, where available, patient-level data should inform utility estimates in the model. Patients' EQ-5D was recorded until study closure of ECHELON-2, and covariates considered within the model were informed by clinical

	Previous appraisals			Current appraisal	
	TA478[39] **R/R sALCL**	**TA524[41]** **R/R HL**	**TA577[42]** **CD30+ CTCL**	**Chosen values**	**Justification (company)**
				A scenario explores the use of utility based on time until death.	experts. The utility decrement associated with progression derived from these data were not considered to be clinically plausible. Therefore, an estimate was derived from the R/R sALCL submission [TA478]
Source of costs	BNF, NHS reference costs, PSSRU, expert clinical opinion on SCT costs	BNF, expert clinical opinion on SCT costs, Round et al. 2015 oncology mortality costs[52]	eMIT, MIMS, BNF, NHS reference costs, Round et al. 2015 oncology mortality costs[52] Debals et al. 2018 (SCT costs) [53]	eMIT, BNF, NHS reference costs, TA478, TA567 and TA577 for SCT costs	As per the NICE methods guide[49]

Based on Table 31 in the CS[1]

AE = adverse event; ALCL = anaplastic large cell lymphoma; BNF = British National Formulary; CS = company submission; eMIT = electronic marketing information tool; EQ-5D = European Quality of Life-5 Dimensions; HL = Hodgkin's lymphoma; MIMS = Monthly Index of Medical Specialities; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit; QALY = quality-adjusted life year; R/R = relapsed/refractory; sALCL = systemic anaplastic large cell lymphoma; SCT = stem cell transplant; TA = technology appraisal

5.2.3 Population

The population considered in the base-case cost effectiveness analyses was the ITT population in the ECHELON-2 trial: adults with untreated CD-30+ PTCL,[18], which is aligned with the US Food and Drug Administration (FDA) approval[54] and the anticipated EMA marketing authorisation.[55] This population is in line with the final scope of this appraisal.[2] The patients' baseline characteristics included in the economic model as input parameters are provided in Table 5.5. These values are based on the average baseline values observed in the ITT population of the ECHELON-2 trial.

Table 5.5: Baseline characteristics of the patients used in the model (average values observed in ECHELON-2)

Patient characteristics	ITT population	ITT population (UK patients only, n=21)
Age (years)	55.1	60.9
Female (%)	37	38.1
Weight (kg)	74.42	73.5
BSA (m^2)	1.85	NR

Based on electronic model of the CS[48] and Table 25 of the response to request for clarification[17]
BSA = body surface area; CS = company submission; ITT = intention-to-treat; kg = kilogram; NR = not reported; UK = United Kingdom

Additionally, the company also conducted cost effectiveness analyses for the subgroup of sALCL patients. The reason for this was the differences in the post-progression treatment pathway between sALCL and non-sALCL subpopulations. This subgroup analysis was possible because enough patients with sALCL enrolled ECHELON-2. This was not the case for other non-sALCL subgroups of patients.

ERG comment: The average weight of an ITT patient in ECHELON-2 was reported as 76.35 kg on page 110 of the CS,[1] which did not match with the 74.42 kg considered in the electronic model.[48] In clarification question B21,[19] the ERG asked the company to explain to what extent the demographic parameters used in the model (from ECHELON-2) were representative for a UK patient. In their response,[17] the company indicated that, given the rarity of PTCL, it was not possible to find all the requested parameters for UK patients with PTCL. The company referred to Gleeson et al. 2018, where the reported median (across 156 patients) age at diagnosis of PTCL in the UK was 58 years.[3] Note that this is in line with the median age observed in ECHELON-2 (58 years reported in Table 4.5). Additionally, the company referred to a 2019 audit from the Haematologic Malignancy Research Network (HMRN) of patients diagnosed with PTCL in Yorkshire (no references provided), reported in Table 5.6.

Table 5.6: Patient characteristics at diagnosis, HMRN PTCL audit

Patient characteristics	Value
Age (years), mean (SD)	[redacted]
Age (years), median (range)	[redacted]
Female, number (%)	[redacted]
Male, number (%)	[redacted]

Based on Table 24 of the response to request for clarification[17]
HMRN = Haematologic Malignancy Research Network; PTCL = peripheral T-cell lymphoma; SD = standard deviation

As shown in Table 5.5, UK patients enrolled in ECHELON-2 had an average (mean) age of 60.9 years, which, according to the company, is *"well aligned to the reported UK average age at diagnosis by both Gleeson et al [redacted]"*.[17] The ERG agrees with this statement and, for that reason, considers that the age value included in the cost effectiveness model should have been larger than the 55.1 years used in the company's base-case. In the ERG base-case analysis described in section 7.1.2 of this report, the ERG assumed that the mean age of an UK PTCL patient was 62.02 years. This value was calculated as the weighted average of the age values reported in ECHELON-2 (UK patients only), Gleeson et al. 2018 (assuming median = mean),[3] and the HMRN PTCL audit (no reference provided). Note that the assumption of median age = mean age in Gleeson et al. 2018 was made with the purpose of maximizing all the available evidence. Even though mean and median are not the same, it was deemed the best choice so that data from Gleeson et al. 2018 could be included in the model. Since the median age in both ECHELON-2 and the HMRN audit was larger than the mean age, it is likely that the weighted average slightly overestimates the age in the model if it had been based only on means. The impact of age on the cost effectiveness results was explored by the ERG in their additional scenario analyses in section 7.1.3. The remaining patient characteristics were not changed by the ERG due to the lack of evidence to inform alternative estimates.

As explained in section 4.2.3 of this report, the ECHELON-2 trial was only powered to determine the effect of BV in the sALCL subgroup of patients. For the other subgroups, this was not the case. Despite this, in response to clarification question B23,[17] the ERG asked the company to add functionality to the model to allow the cost effectiveness to be estimated by the pre-specified subgroups in Figure 12 of the CS (i.e. ALK+ sALCL, ALK- sALCL, AITL and PTCL-NOS),[1] as it was considered that these analyses, even surrounded by large uncertainty, could have been useful for the committee.

In their response, the company referred back to the rationale described in the CS and did not present additional subgroup analyses.[17] Furthermore, the company explained that UK clinical experts at both the February 2019[45] and June 2019[16] advisory boards, unanimously recommended to analyse ALK-positive and ALK-negative sALCL patients as one combined sALCL subgroup. The reason for this was that, to be eligible for ECHELON-2, ALK-positive sALCL patients were required to have an IPI score of 2 or above. ALK-positive patients with a high IPI score are expected to have similar outcomes to patients with ALK-negative sALCL. Histologically, both groups express CD30 uniformly and there is also no difference in the management of the condition. Therefore, patients with sALCL in ECHELON-2 are expected to be comparable in terms of management and anticipated outcome, regardless of ALK status.

Finally, the company indicated that, during the scoping stage of this appraisal, concerns regarding any further subgroup analysis, beyond what was pre-specified in ECHELON-2, were raised and further discussed during the decision problem meeting in September 2019 and NICE check-in teleconference in October 2019. Guidance from the NICE technical team and the ERG was to conduct the analyses considered appropriate and feasible by the company. Consistent with this guidance, the company presented the analyses which were powered and pre-specified in the ECHELON-2 statistical analysis plan: ITT and sALCL.[1] The company concluded that this approach provides NICE with the appropriate information and analysis on which to base its recommendation regarding the clinical and cost effectiveness of BV+CHP for the treatment of previously untreated patients with CD30+ PTCL.

5.2.4 Interventions and comparators

The intervention considered in this appraisal was BV+CHP. The intervention was administered according to a 21-day cycle for six to eight cycles. In ECHELON-2, an average of 6.02 cycles of BV+CHP was administered.[18] The treatment elements were administered as follows:

- 1.8 mg/kg of BV on Day 1, intravenously
- 750 mg/m^2 of cyclophosphamide on Day 1, intravenously
- 50 mg/m^2 of doxorubicin on Day 1, intravenously
- 100 mg of prednisone on Days 1 to 5, orally

CHOP was the only comparator listed in the NICE final scope and included in the cost effectiveness model.[2] CHOP is administered in 21-day cycles for a maximum of six to eight cycles. In ECHELON-2, an average of 5.8 cycles of CHOP was administered.[18] The treatment elements were administered as follows:

- 750 mg/m^2 of cyclophosphamide on Day 1, administered intravenously
- 50 mg/m^2 of doxorubicin on Day 1, administered intravenously
- 1.4 mg/m^2 of vincristine on Day 1, administered intravenously
- 100 mg of prednisone on Days 1-5, administered orally

ERG comment: The dosages, administration and average number of cycles of the intervention and comparator are consistent with the NICE final scope and the ECHELON-2 trial, on which clinical evidence for this appraisal is based.[2, 18] It should be noted that clinical experts stated that standard practice in the UK and Europe would be to treat for a maximum of six cycles.[16, 45] However, the average numbers of cycles received in ECHELON-2 of 6.02 and 5.8 cycles for BV+CHP and CHOP, respectively, are largely in line with UK clinical practice. Scenarios performed by the company, whereby time to treatment was capped at six cycles and all patients were assumed to receive six cycles, had a limited impact on the ICER as shown in section 6.2.3 of this report.

5.2.5 Perspective, time horizon and discounting

The economic analyses took the perspective of the NHS and Personal Social Services (PSS) and adopted a lifetime time horizon. Total costs and QALYs were discounted at a rate of 3.5% per annum, as is recommended in the NICE Reference Case.[49]

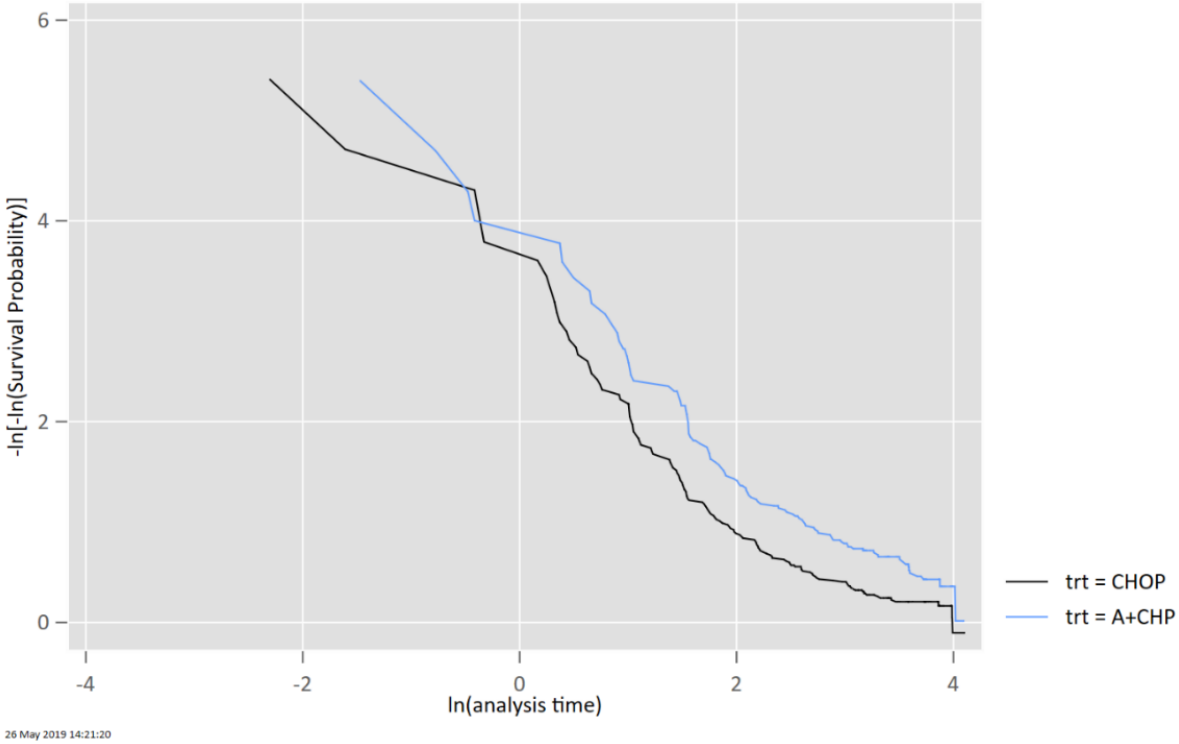
5.2.6 Treatment effectiveness and extrapolation

Patient-level data from ECHELON-2 were used to estimate: 1) extrapolation of PFS and OS, 2) duration, efficacy and administration/re-administration of BV+CHP and CHOP and 3) the proportions of patients receiving consolidative AutoSCT, consolidative and salvage radiotherapy, salvage stem cell transplant (AutoSCT and alloSCT), salvage chemotherapies, salvage treatment with BV and re-treatment with BV.[18]

5.2.6.1 Progression-free survival

Parametric survival curves were used by the company to extrapolate ECHELON-2 PFS data beyond the trial follow-up period. The process of selecting parametric survival curves was guided by the NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14.[56] First, the company tested the proportional hazards assumption graphically by using the log-cumulative hazard plot shown in Figure 5.2. The company considered that the log-cumulative hazards are relatively parallel after approximately one month. For this reason, a joint regression modelling approach, in which the treatment effect is represented by a regression coefficient, was adopted.

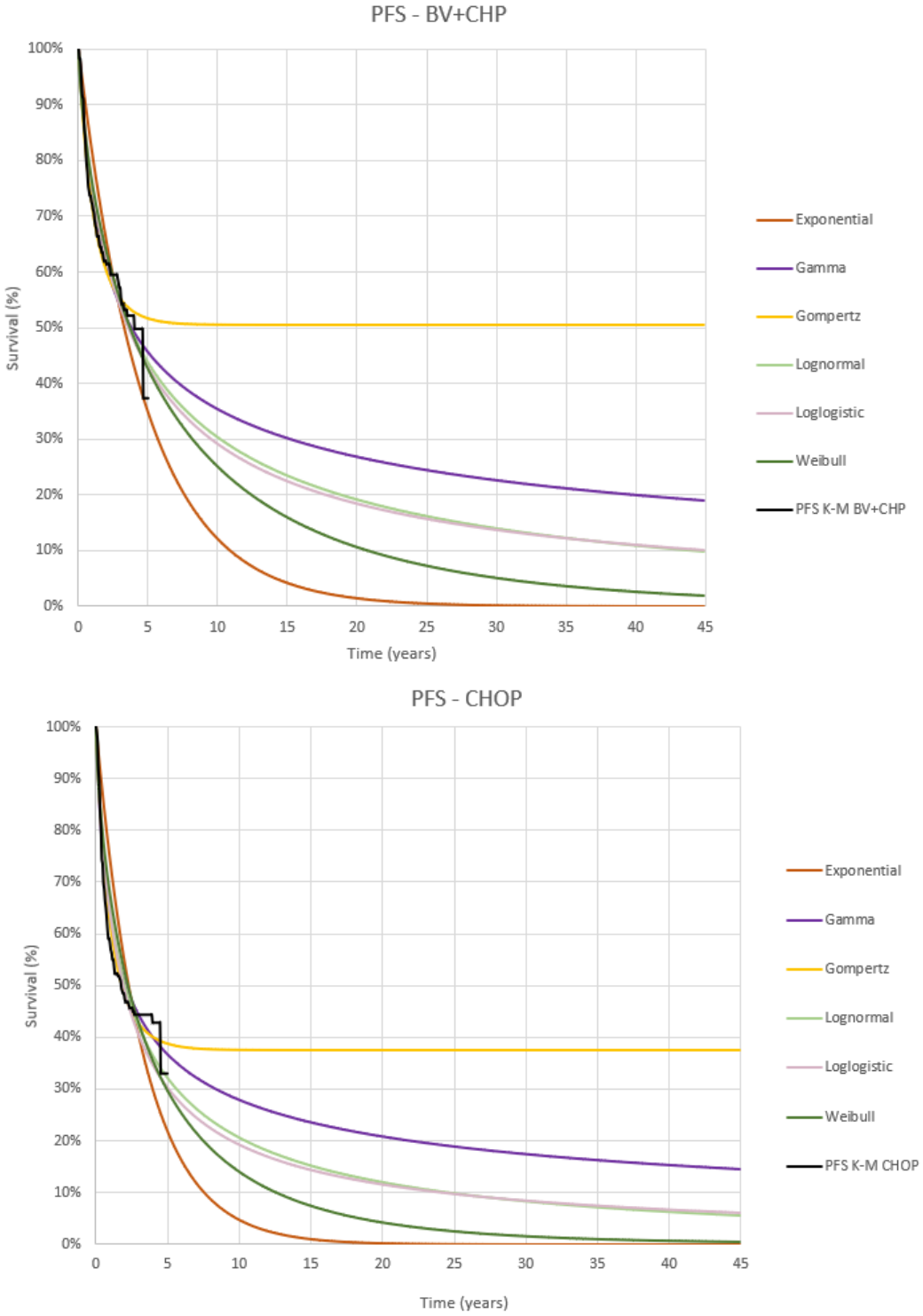
Figure 5.2: Log-cumulative hazard plot – PFS, ITT population



Based on Figure 4 in Appendix L of the CS[57]
A = Adcetris®; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; ln = natural logarithm; PFS = progression-free survival; trt = treatment

The generalised gamma, exponential, Gompertz, log-normal, log-logistic and Weibull distributions were considered as potential candidates for modelling PFS long-term extrapolations. The resulting extrapolations, based on joint regression equations, are presented in Figure 5.3 for both BV+CHP and CHOP arms. Goodness of fit of the parametric survival models was assessed using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) values shown in Table 5.7. The generalised gamma and the Gompertz distributions had the lowest AIC and BIC values. The company presented these extrapolations to UK clinical experts at an advisory board meeting and it was agreed that, from the extrapolations presented to them, the generalised gamma was most reflective of long-term outcomes for PFS since they considered that this distribution reflected a decreasing risk of relapse.[16] In line with this, the experts also explained that the risk of relapse after front-line treatment is the highest in the first two years following treatment. Patients who have not relapsed during these two years will subsequently have a lower relapse probability. To support this approach, the company further referred to a retrospective analysis of 775 patients from the US, Sweden and Canada, which concluded that the risk of relapse for PTCL patients who remained disease-free for two years after front-line treatment decreased drastically.[58] Based on the evidence presented above, the company chose the generalised gamma distribution as the best candidate distribution to model PFS. The choice of different probability distributions to extrapolate PFS was explored by the company in a scenario analysis.

Figure 5.3: Standard parametric extrapolation, PFS – ITT population



Based on Figure 26 in the CS[1]

Note: Background mortality is not applied.

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; K-M = Kaplan-Meier; PFS = progression-free survival

Table 5.7: PFS AIC and BIC values, ITT population

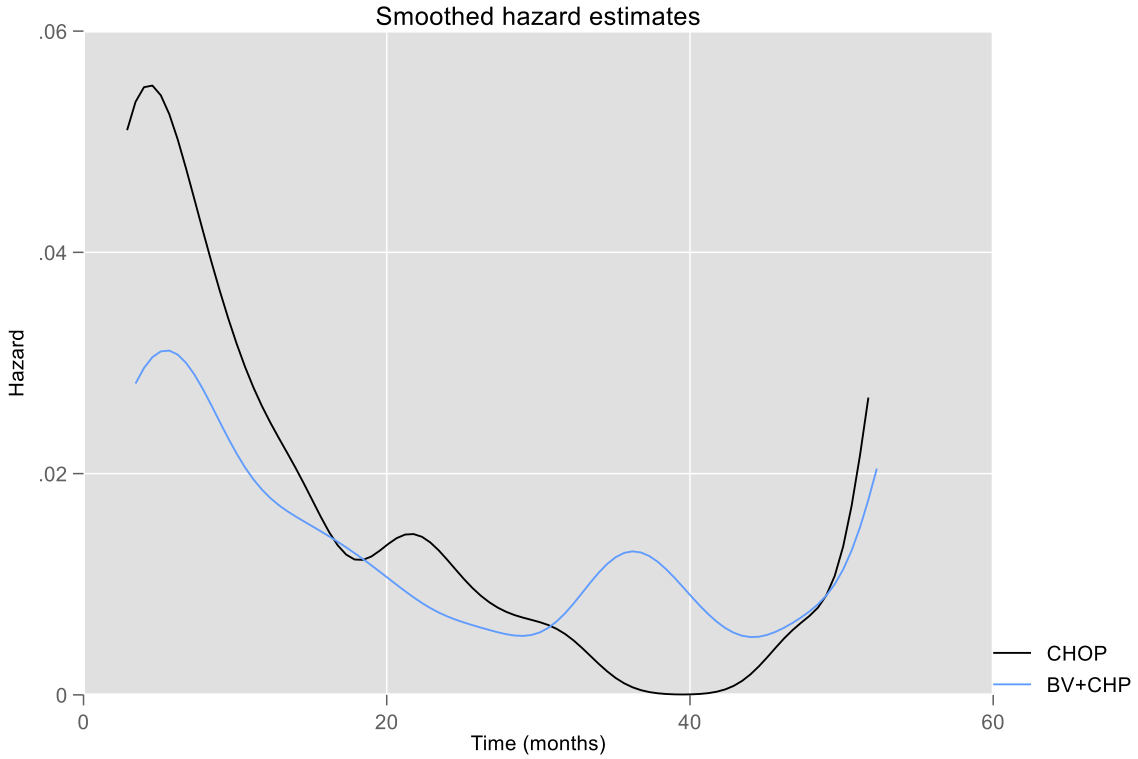
	AIC	BIC
Generalised gamma	1217.5 (1)	1233.9 (1)
Weibull	1263.9 (5)	1276.3 (5)
Gompertz	1221.8 (2)	1234.1 (2)
Exponential	1305.8 (6)	1314.0 (6)
Lognormal	1227.3 (3)	1239.7 (3)
Log-logistic	1241.1 (4)	1253.5 (4)

Based on Table 33 of the CS[1]
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; ITT = intention-to-treat; PFS = progression-free survival.

ERG comment: PFS per IRF was defined as the primary endpoint from ECHELON-2. The company mentioned that there was a high level of congruence between PFS per IRF and per investigator (97%).[1] For that reason, all analyses presented in the CS considered PFS as per IRF. The ERG agrees with this approach.

Based on the presented evidence, the ERG does not consider sufficiently proven that a joint model (i.e. proportional hazards) is more appropriate to model the long-term PFS extrapolations. The ERG also requested a plot of the PFS hazard ratio over time, but this was not provided by the company.[17, 19] Nevertheless, given that the hazard rate functions in Figure 5.4 cross four times, it is not possible that these hazard rate functions would result in a constant hazard ratio for PFS. The Cox proportional hazards model assumes that the hazard ratio is constant over time. The result of testing the proportional hazards assumption was provided by the company in response to clarification question B10.[17] The company conducted the Schoenfeld test of residuals with respect to time, where the null hypothesis is a zero slope, which is equivalent to testing that the log hazard-ratio function is constant over time. The P-value reported for this test was 0.0573. Overall, the company concluded that *"failure to reject the null hypothesis of a zero slope indicates that there is no evidence of a deviation from the proportional-hazards assumption"*.[17] The ERG does not agree with this interpretation of the results of the tests based exclusively on the P-value, especially when the hazard rate functions observed in ECHELON-2 in Figure 5.4 suggest the opposite. Despite highlighting that for PFS the *"borderline statistical significance suggests a possible violation of the proportional hazards assumption"*,[17] a different approach (i.e. independent or stratified modelling) was not considered.

Figure 5.4: Smoothed PFS hazard rate functions estimated from ECHELON-2 data (ITT population)



Based on Figure 6 in response to request for clarification[17]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ITT = intention-to-treat; PFS = progression-free survival

The ERG considers the stratified approach, where parametric survival curves are fitted separately to each treatment arm, more plausible and that this approach should have been explored by the company. The option to select parametric curves based on an stratified approach was included in the company's model but a complete goodness-of-fit assessment was missing in the CS.[1] AIC and BIC values based on stratified modelling were presented by the company in response to request for clarification question B10.[17] These are summarised in Table 5.8. The generalised gamma and the lognormal distributions had the lowest AIC and BIC values for the BV+CHP arm and the Gompertz distribution had the lowest AIC and BIC values for the CHOP arm.

Table 5.8: PFS AIC and BIC values, ITT population (stratified modelling)

	BV+CHP		CHOP	
	AIC	BIC	AIC	BIC
Generalised gamma	553.1 (1)	563.3 (3)	667.9 (2)	678.2 (2)
Weibull	566.0 (5)	572.9 (5)	698.8 (5)	705.7 (5)
Gompertz	555.6 (3)	562.5 (2)	664.1 (1)	671.0 (1)
Exponential	575.5 (6)	578.9 (6)	730.3 (6)	733.8 (6)
Lognormal	554.3 (2)	561.1 (1)	675.0 (3)	681.9 (3)
Log-logistic	560.1 (4)	567.0 (4)	682.9 (4)	689.8 (4)

Based on Tables 12 and 13 in response to request for clarification[17]
AIC = Akaike information criterion; BIC = Bayesian information criterion; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP =

	BV+CHP		CHOP	
	AIC	BIC	AIC	BIC
cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ITT = intention-to-treat; PFS = progression-free survival				

The stratified PFS extrapolations were not included in the response to the clarification letter but can be obtained from the electronic model.[17, 48] The PFS estimated probabilities over 20 years based on the stratified approach were similar to those estimated under a joint approach (with the possible exception of the Gompertz and the Weibull distributions), as can be seen in Table A1.1. However, the ERG has assumed that the company did not present these stratified extrapolations to UK clinical experts. Also, as can be seen in Table 7.6 (ITT population) and Table A4.4 (sALCL subgroup), except when an exponential distribution is assumed to model OS, the ICER increased when the sALCL subgroup was modelled instead of the full ITT population on using the stratified approach. This is counterintuitive given that BV seems to be more effective in the sALCL subgroup (see e.g. hazard ratios in Figures 12 and 14 in CS).[1] Therefore, the ERG has concerns about the validity of the results given by the model when the stratified approach is selected. For this reason, in the ERG base-case defined in section 7.1.2 of this report, a (joint) generalised gamma distribution was assumed to model PFS as in the company base-case.

Additionally, the ERG would like to emphasise that, even though the clinical experts consulted by the company considered the generalised gamma was most reflective of long-term outcomes for PFS, the plausibility of the estimated long-term probabilities (tails of the survival curves) was not explicitly quantified in the CS. This could have been informed, for example, by providing a plausible range for the PFS probability over a number of years. This is important because, as can be seen in Figure 5.3, the generalised gamma is , after the Gompertz, the probability distribution with the highest long-term PFS with respect to the other probability distributions. Seeing the PFS extrapolations in Figure 5.3, the ERG feels that a quantification of the plausibility of the lognormal and log-logistic distributions (the ERG assumed that the Gompertz, Weibull and exponential would be deemed implausible) is missing in the CS.

Furthermore, the clinical experts consulted by the company explained that the risk of relapse after front-line treatment is the highest in the first two years following treatment and, after that, decreases drastically. The ERG would also like to emphasise that this is not reflected in the company's model. In response to clarification question B9,[17] the company also presented a plot of the extrapolated PFS hazard rate functions (based on a joint approach) over time for both arms. These can be seen in Figure A1.1. It is clear that only the generalised gamma and the lognormal distributions result in a hazard rate function that is initially increasing and then, after some time, decreasing. However, in both cases, the decline occurred even before one year. The ERG also obtained from the electronic model the hazard rate functions based on a stratified approach and the same conclusions can be drawn. The ERG considers that the plausibility of these hazard rate functions should be validated by clinical experts.

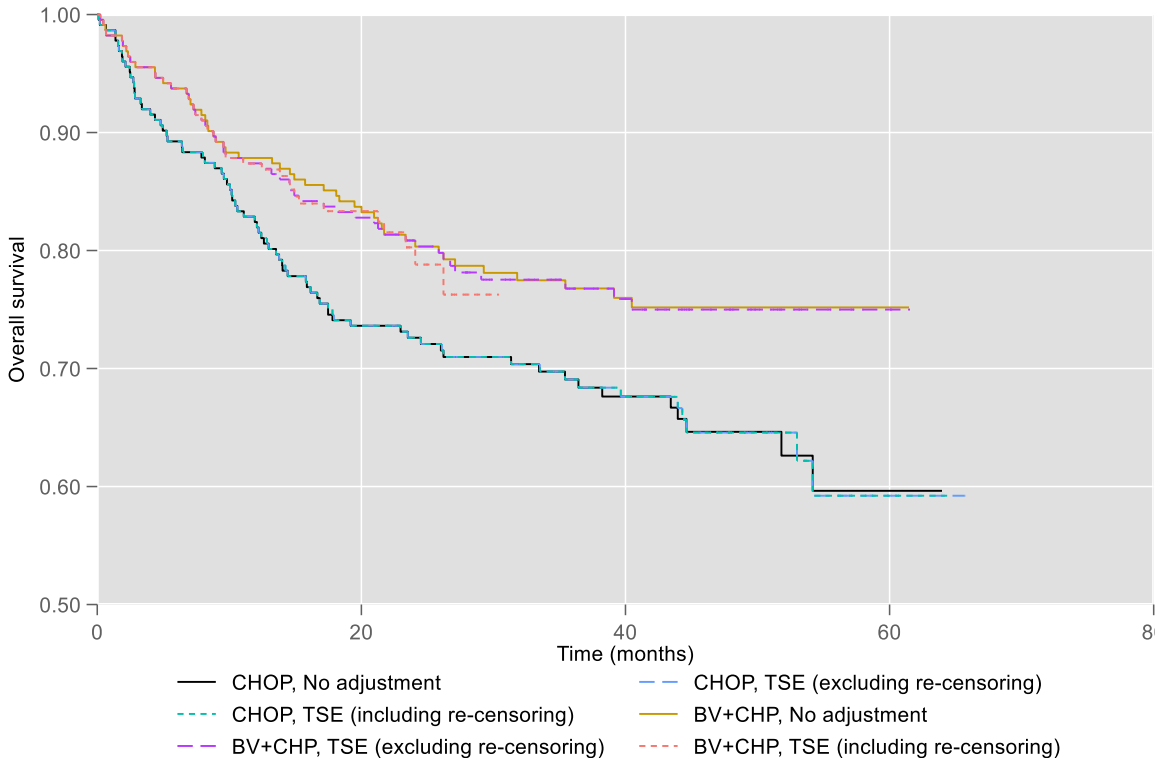
For the reasons mentioned above, the ERG feels that exploring other non-standard parametric distributions (e.g. spline models) might have been appropriate in this case, in line with was suggested by one of the economic experts consulted by the company: *"a spline at two-years was recommended as an exploratory extrapolation to increase flexibility. Clinicians questioned whether the introduction of BV+CHP would push the traditional two-year relapse-out (i.e. relapse would take place after two-years)"*.[16] However, the company did only consider the standard parametric models and no further discussion regarding this subject can be found in the CS.[1]

5.2.6.2 Overall survival

Adjustment for subsequent use of BV

Clinical experts consulted by the company confirmed that re-treatment with BV post-progression and receipt of BV for R/R non-sALCL are not reflective of UK clinical practice.[16] However, in ECHELON-2, a total of 23 patients in the BV+CHP arm (10% of the total number of patients in this arm) were re-treated with BV, which does not reflect UK clinical practice as re-treatment is not currently reimbursed within England and Wales. Moreover, 13 patients in the CHOP arm, who had non-sALCL, were also treated with BV post-progression, which does not reflect UK clinical practice as BV is not currently reimbursed in England and Wales for the treatment of non-sALCL. For this reason, following the guidance of NICE DSU TSD 16,[59] treatment switching approaches were used by the company to remove the potential effect in OS of post-progression use of BV in previously treated BV patients and in non-sALCL patients in the CHOP arm of ECHELON-2. After exploring several methods, the company concluded that only the two-stage estimator (TSE) provided logical estimates with plausible underlying assumptions. Therefore, this was the approach used in the company's base-case. A description of the TSE method and the other methods considered by the company was provided in Appendix N of the CS.[60] The adjusted OS data (including and excluding re-censoring – for a definition and details on re-censoring, see Appendix N of the CS) are presented in Figure 5.5.[60] It can be observed that the effect of the TSE adjustment on the Kaplan-Meier (K-M) estimator is small, which seems reasonable, considering the relatively low number of patients requiring OS adjustment. Only the loss of long-term follow-up data in the BV+CHP arm due to re-censoring seems to indicate a potential issue. For this reason, in their base-case, the company did not consider re-censoring. In additional scenario analyses, the company explored the impact on the cost effectiveness results of assuming TSE with re-censoring and also an unadjusted approach to OS. The results of these scenarios are presented in section 6.2.3 of this report.

Figure 5.5: Adjusting for treatment switching in patients with re-treatment (BV+CHP arm) and patients with non-sALCL receiving subsequent brentuximab vedotin (CHOP arm), OS - ITT



Based on Figure 11 of the response to the request for clarification[17]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ITT = intention-to-treat; sALCL = systemic anaplastic large cell lymphoma; TSE = two-stage estimator

ERG comment: Adjustment for BV re-treatment in the BV+CHP arm and BV use post-progression in non-sALCL patients in the CHOP arm seems reasonable and the TSE method appropriate. The results, shown in Appendix 2 of this report, indicate that the different approaches for adjusting re-treatment explored by the company led to similar estimates of the treatment effect. Therefore, the selection of one specific method, provided that it is correctly implemented, it is not expected to have a large impact on the results.

The company mentioned that for the 36 patients with sALCL in the CHOP arm, the use of BV post-progression is recommended for use in TA478.[39] However, this is not completely correct as TA478 explicitly recommends BV as an option for treating R/R sALCL patients only if they have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1. In response to clarification question B8,[17] the company indicated that there were four patients with ECOG PS 2 at study baseline in the CHOP arm of ECHELON-2 who had sALCL disease and received subsequent BV post-progression. These patients were consequently removed from the OS TSE and from the proportion of patients receiving subsequent BV. This assumption was included in the ERG base-case defined in section 7.1.2 of this report. The ERG noted the following issues associated to this adjustment:

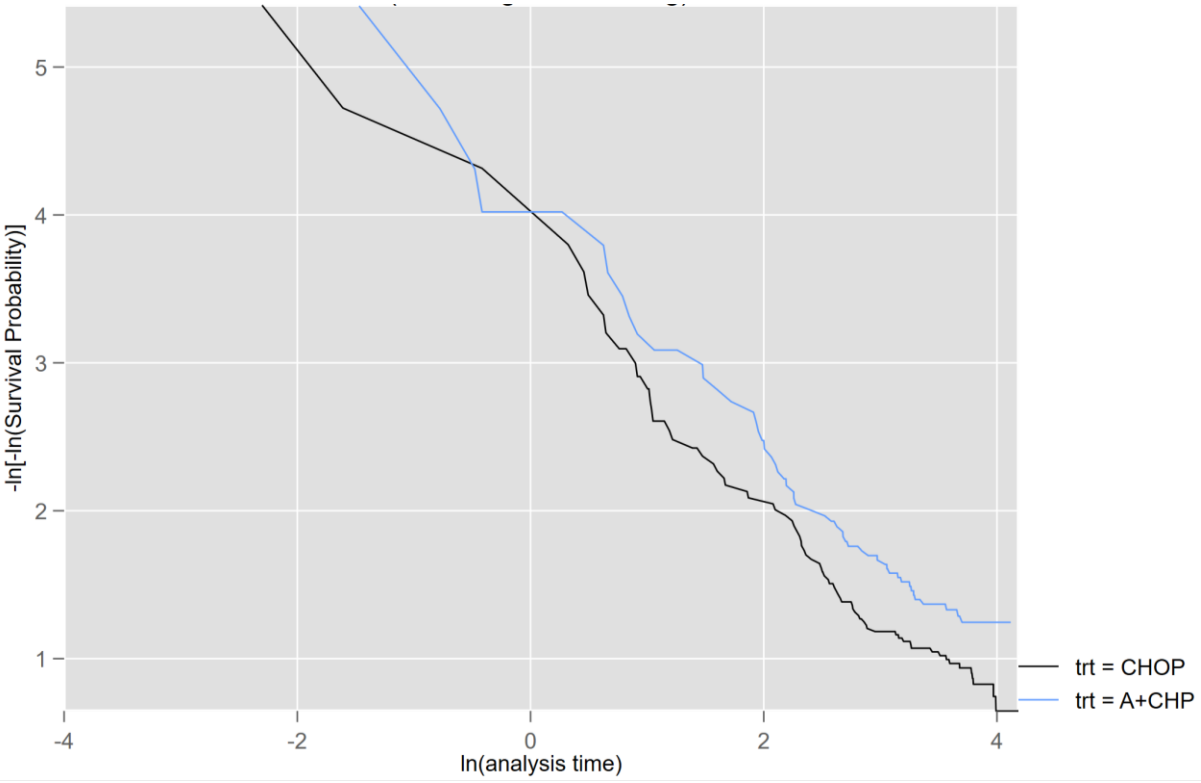
- While removing ECOG PS 2 patients from the OS two-stage estimator should only affect OS in the CHOP arm, when a joint approach to modelling is selected in the model, both the BV+CHP and CHOP curves are changed. This is because the joint approach assumes proportional hazards and, therefore, changing one curve will automatically change the other one.

- When the stratified approach to modelling is selected, no shift is observed in the CHOP OS arm when excluding/including ECOG 2 patients, as this scenario is only available under base case assumptions (i.e. joint models). This has no impact on the ERG base-case because a joint approach was assumed. However, all results assuming a stratified approach presented in section 7.2.2.1 do not include this change and for that reason they are biased. If this adjustment affects the ICER in the stratified approach similarly to how it affects the ICER in the joint approach, the bias should be minor.
- When the stratified approach to modelling is selected, costs change slightly. This is because the proportion of patients receiving subsequent BV in the CHOP arm decreases (there are four patients less). Therefore, this is correctly implemented.
- This change is not included in the PSA. Only the estimated regression coefficients have been included in the model. However, the covariance matrix, which is needed for the PSA, is missing from the model. Therefore, all PSA analyses assuming this adjustment would result in a large underestimation of the overall uncertainty.
- This change is only implemented for the ITT population. Thus, all results for the sALCL subgroup presented in Appendix 4 do not include this adjustment.

OS long-term extrapolation

Regarding goodness-of-fit assessment and long-term extrapolation for OS, the company took the same approach as the one described above for PFS. First, the PH assumption graphically by using the log-cumulative hazard plot shown in Figure 5.6. The company also considered that the log-cumulative hazards were relatively parallel after approximately one month and took a joint regression modelling approach.

Figure 5.6: Log-cumulative hazard – OS (TSE), ITT population

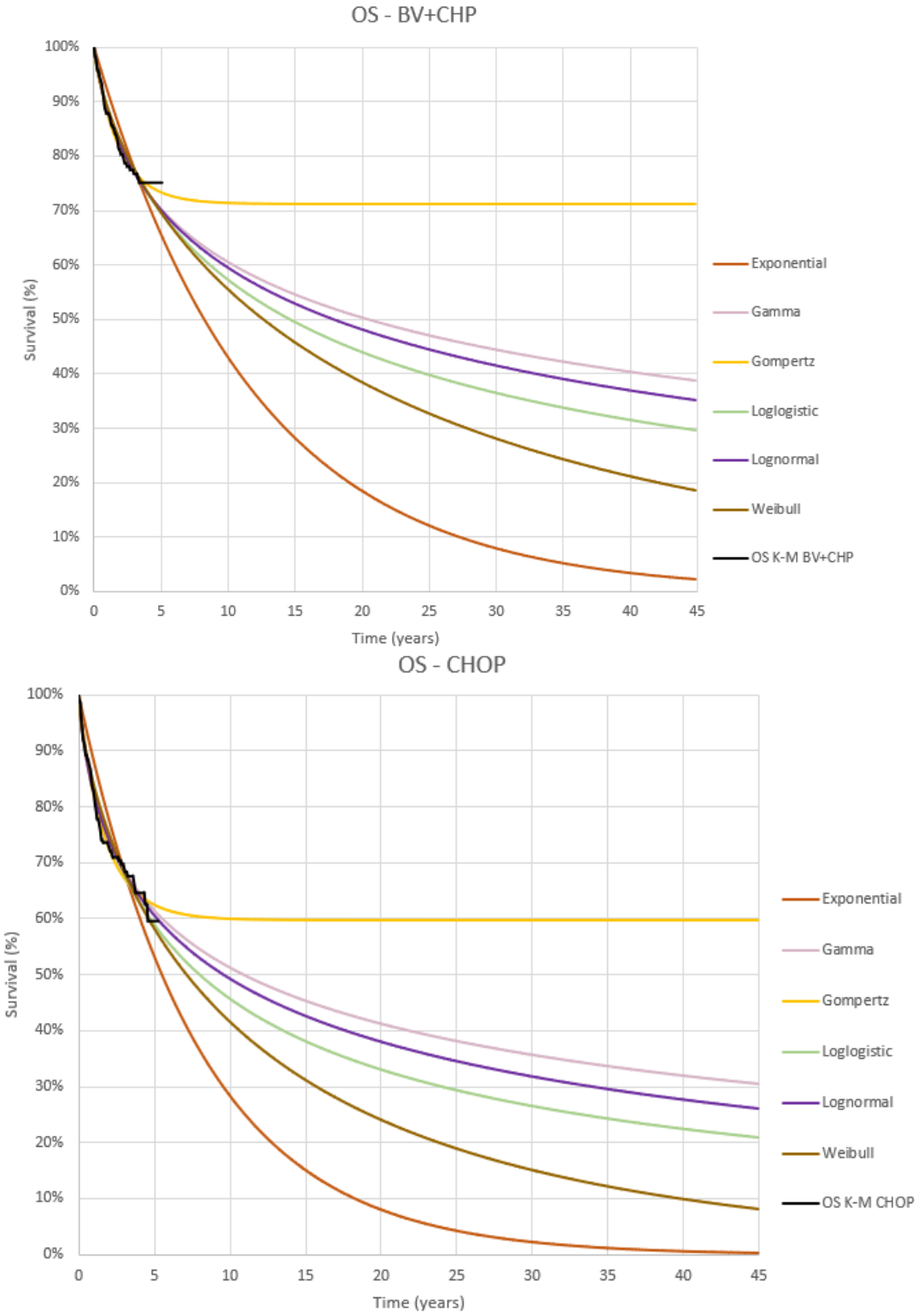


Based on Figure 3 in Appendix L to the CS[57]

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; OS = overall survival, trt = treatment, TSE = two-stage estimator

The same probability distributions used for PFS were considered as potential candidates for modelling OS long-term extrapolations. The resulting extrapolations, based on joint regression equations, are presented in Figure 5.7 for both the BV+CHP and CHOP arms. Goodness-of-fit of the parametric survival models was assessed using the AIC and BIC values shown in Table 5.9. The Gompertz and the lognormal distributions had the lowest AIC and BIC values. However, the clinical experts consulted by the company also agreed that the generalised gamma was most reflective of long-term outcomes for OS, since they considered that this distribution reflected a decreasing risk of lymphoma related mortality.[16] Therefore, the company also chose the generalised gamma distribution as the best candidate distribution to model OS.[1] The choice of different probability distributions to extrapolate OS was explored by the company in scenario analysis.

Figure 5.7: Standard parametric extrapolation, OS – ITT population – including TSE adjustment



Based on Figure 25 of the CS[1]

Note: Background mortality is not applied

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; K-M = Kaplan-Meier; OS = overall survival, trt = treatment, TSE = two-stage estimator

Table 5.9: OS AIC and BIC values, ITT population

	AIC	BIC
Generalised gamma	872.1 (3)	888.5 (4)
Weibull	878.4 (5)	890.7 (5)
Gompertz	867.9 (1)	880.2 (1)
Exponential	897.5 (6)	905.7 (6)
Lognormal	870.5 (2)	882.8 (2)
Log-logistic	875.0 (4)	887.3 (3)

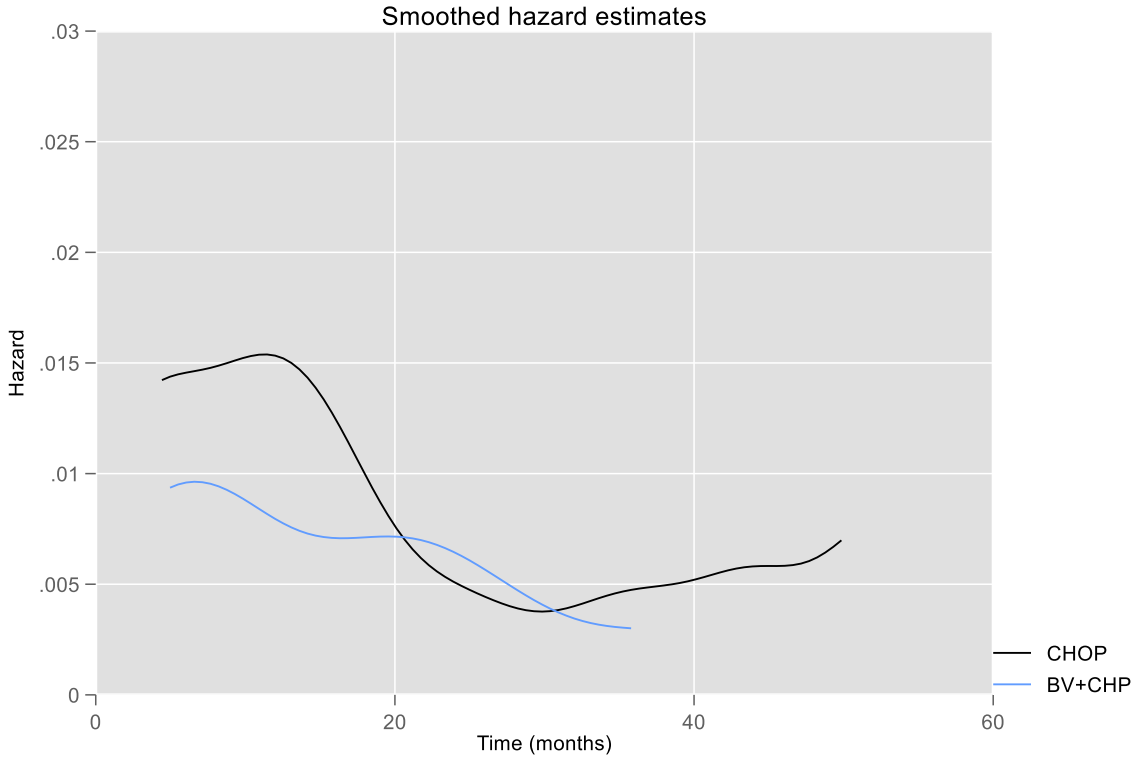
Based on Table 33 of the CS[1]
Note: OS adjusted using TSE
AIC = Akaike information criterion; BIC = Bayesian information criterion; CS = company submission; ITT = intention-to-treat; OS = overall survival, TSE = two-stage estimator

ERG comment: Most of the concerns raised by the ERG regarding PFS are also applicable to OS.

For example, the ERG does not consider sufficiently proven that assuming proportional hazards is more appropriate to model the long-term OS extrapolations. Given that the hazard rate functions in Figure 5.8 cross twice, it is not possible these hazard rate functions would result in a constant hazard ratio for OS. Hypothesis testing of the proportional hazards assumption by means of the Schoenfeld test of residuals with respect to time resulted in a P-value equal to 0.6516 (see response to clarification question B10).[17] As with PFS, the company concluded that *"failure to reject the null hypothesis of a zero slope indicates that there is no evidence of a deviation from the proportional-hazards assumption"*.[17]

Despite the large P-value, the ERG does not agree with this interpretation of the results of the tests based exclusively on the P-value, especially when the hazard rates observed in Figure 5.8 suggest the opposite. Therefore, also for OS, the ERG considered the stratified approach more plausible and should have been explored by the company. AIC and BIC values based on stratified modelling were presented by the company in response to clarification question B10.[17] These are summarised in Table 5.10. As observed in the joint approach, the Gompertz and the lognormal distributions had the lowest AIC and BIC values for the BV+CHP and the CHOP arms.

Figure 5.8: Smoothed hazard estimates of OS from ECHELON-2 (ITT population, unadjusted analysis)



Based on Figure 5 of the request for clarification[17]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; OS = overall survival

Table 5.10: OS AIC and BIC values, ITT population (stratified modelling)

	BV+CHP		CHOP	
	AIC	BIC	AIC	BIC
Generalised gamma	384.8 (3)	395.1 (5)	490.5 (3)	500.7 (5)
Weibull	387.1 (5)	394.0 (4)	493.3 (5)	500.1 (4)
Gompertz	380.8 (1)	387.7 (1)	488.8 (2)	495.6 (2)
Exponential	394.0 (6)	397.4 (6)	503.5 (6)	506.9 (6)
Lognormal	383.5 (2)	390.3 (2)	488.6 (1)	495.5 (1)
Log-logistic	385.8 (4)	392.7 (3)	491.1 (4)	497.9 (3)

Based on Tables 10 and 11 in response to request for clarification[17]
Note: OS adjusted using TSE
AIC = Akaike information criterion; BIC = Bayesian information criterion; ITT = intention-to-treat; OS = overall survival

The stratified OS extrapolations were not included in the response to the clarification letter but can also be obtained from the electronic model.[48] As with the PFS stratified curves, the ERG has assumed that the company did not present these stratified extrapolations to UK clinical experts. Also in this case, the OS estimated probabilities over 20 years based on the stratified approach were similar to those estimated under a joint approach, with the possible exception of the generalised gamma distribution (the one chosen for the company's base-case), as can be seen in Table A1.2. Based on this, the ERG is uncertain whether the generalised gamma distribution would have been chosen unanimously by the

clinical experts as the most reflective of long-term outcomes for OS, within the stratified distributions, since it is consistently resulting in larger survival probabilities for BV+CHP and lower for CHOP, compared to the generalised gamma in the joint approach. The stratified lognormal distribution is the closest to the joint generalised gamma, even though it also results in slightly larger survival probabilities for BV+CHP and lower for CHOP compared to the joint generalised gamma. However, as mentioned in the PFS critique, the ERG has concerns about the (face) validity of the results given by the company's model when the stratified approach is selected. Such concerns are more relevant for OS, since OS has more impact on the model results than PFS. For this reason, in the ERG base-case defined in section 7.1.2 of this report, a (joint) generalised gamma distribution was assumed to model OS as in the company base-case.

Similar to that discussed for the PFS curves, the plausibility of the estimated long-term OS probabilities was not explicitly quantified in the CS. This is more important for OS than for PFS since, as shown throughout sections 6 and 7 of this report, the selection of the OS long-term extrapolation basically determines the overall gains in QALYs estimated by the electronic model. As can be seen in Figure 5.7, the generalised gamma is also, after the Gompertz, the probability distribution with the highest long-term OS for both treatment arms, but the difference with respect to the lognormal distribution is less than the difference observed in PFS. Therefore, it would have been important to assess the plausibility of the lognormal (and to a lower extent the log-logistic) distribution (the ERG assumed that the Gompertz, Weibull and exponential would be deemed implausible). Without this, the generalised gamma (and possibly the lognormal) is the only logical choice for modelling OS.

The clinical experts consulted by the company explained that, similar to what happens with the risk of relapse after front-line treatment, the risk of lymphoma related mortality is also expected to decrease after two/three years.[16] In line with this, the company also referred to the same retrospective analysis of 775 patients from the US, Sweden and Canada used to support the choice of the generalised gamma distribution for PFS. In terms of OS, this study concluded that the risk of death due to lymphoma for PTCL patients who remained disease-free for two years after front-line treatment also decreased drastically and overall survival approached that of the general population.[58] As occurred with PFS, this is not reflected in the company's model either. In response to clarification question B9,[17] the company also presented a plot of the extrapolated OS hazard rate functions (based on a joint approach) over time for both arms. These can be seen in Figure A1.2. Only the generalised gamma and the lognormal distributions result in a hazard rate function that is initially increasing but both start decreasing almost immediately. The ERG also obtained from the electronic model the hazard rate functions based on a stratified approach and the same conclusions can be drawn. In the company base-case, long-term mortality equals the mortality risk of the general population at 14.95 years in the BV+CHP arm and at 15.93 years in the CHOP arm. The ERG considers that the plausibility of both the hazard rate functions and time when long-term mortality equals the mortality risk of the general population should be validated by clinical experts.

In line with the PFS critique, the ERG considers that exploring other non-standard parametric distributions (e.g. spline models) might have been informative in this case, as suggested by one clinical expert consulted by the company.[16] However, also for OS, the company only considered the standard parametric models and no further discussion regarding this subject can be found in the CS.

5.2.6.3 Background mortality

Age- and gender-specific background mortality was included in the economic analyses. General population death probabilities were taken from the 2018 national life tables for England and Wales.[61]

Additionally, clinical experts consulted by the company indicated that patients in long-term remission are expected to experience a reduction in life-expectancy (due to both increased rates of cardiac toxicity and increased risk of secondary primary malignancies) compared with the general population. The clinical experts estimated a reduced survival of 3% to 10% relative to the general population.[16, 43] In their base-case, the company assumed a 5% reduction in life-expectancy. This was implemented in the model as a mortality multiplier, which in the base-case was equal to 1.19. This value was obtained by the company by calculating the general population life-expectancy predicted by the model and then using the Microsoft Excel's "goal-seek" functionality to calculate the required mortality ratio for a 5% reduction in life-expectancy. Alternative values of 1.29 and 1.42 reflecting a 7.5% and 10% reduction in life-expectancy, respectively, were also explored by the company in sensitivity analyses.

Finally, in the model long-term OS estimates (adjusted for excess risk of mortality in long-term survivors) are constrained by the general population mortality so that OS probabilities cannot be higher than survival for the general population.

ERG comment: Additional details on the calculation of the mortality multiplier were provided by the company in response to clarification question B14.[17] Clinicians indicated that the excess mortality for patients in long-term remission would be expected to be significantly lower than that of patients in the R/R setting, primarily due to the absence of alloSCT in the front-line setting, as alloSCT is associated with higher morbidity and mortality. Clinical experts suggested a reduced overall life-expectancy between 3% and 10% over the patient's lifetime. This reduction in life-expectancy was "translated" into a mortality multiplier as follows: the CHOP arm of the model was set to use background mortality only and the remaining life expectancy was calculated. The "goal-seek" functionality in Excel was then used to calculate the multiplier required to achieve a 5% reduction in life-expectancy.

The ERG also asked the company whether the mortality multiplier was included in the PSA. The company indicated that it was not included in the PSA because it was elicited from expert opinion and there was no associated measure of uncertainty. The ERG does not agree with this approach since the experts provided a range of variation. Nevertheless, the company explored the effect of using alternative mortality multipliers on the cost effectiveness results in scenario analysis and this was minor. The ERG considers that, while the impact of this assumption is not expected to be large, it seems arbitrary to have chosen 5% for the base-case and to keep the parameter fixed in the PSA. Given the range of values provided by the experts, the ERG prefers using a 6.5% reduction in life-expectancy for the base-case (middle point between 3% and 10%) and using 3% and 10% as the limits to be considered for the PSA.

5.2.6.4 Duration of the brentuximab vedotin treatment effect

The treatment effect of BV+CHP on OS and PFS compared to CHOP was modelled through a treatment effect coefficient in the parametric regression equations used to extrapolate OS and PFS. In the company's base-case analysis (i.e. generalised gamma extrapolation), these treatment effect coefficients can be seen in Table 5.11. No additional adjustment (i.e. waning) of the treatment effect was assumed by the company. This assumption was also made in previous related NICE TAs (see Table 5.4 for details). There is, however, an implicit waning of the BV+CHP treatment effect which lasts until the point where the OS curve is replaced by the general population curve (14.95 years in the BV+CHP arm and at 15.93 years in the CHOP arm).

Table 5.11: Regression coefficients for the generalised gamma distribution, ITT population

Parameter	Coefficient	SE	95% CI

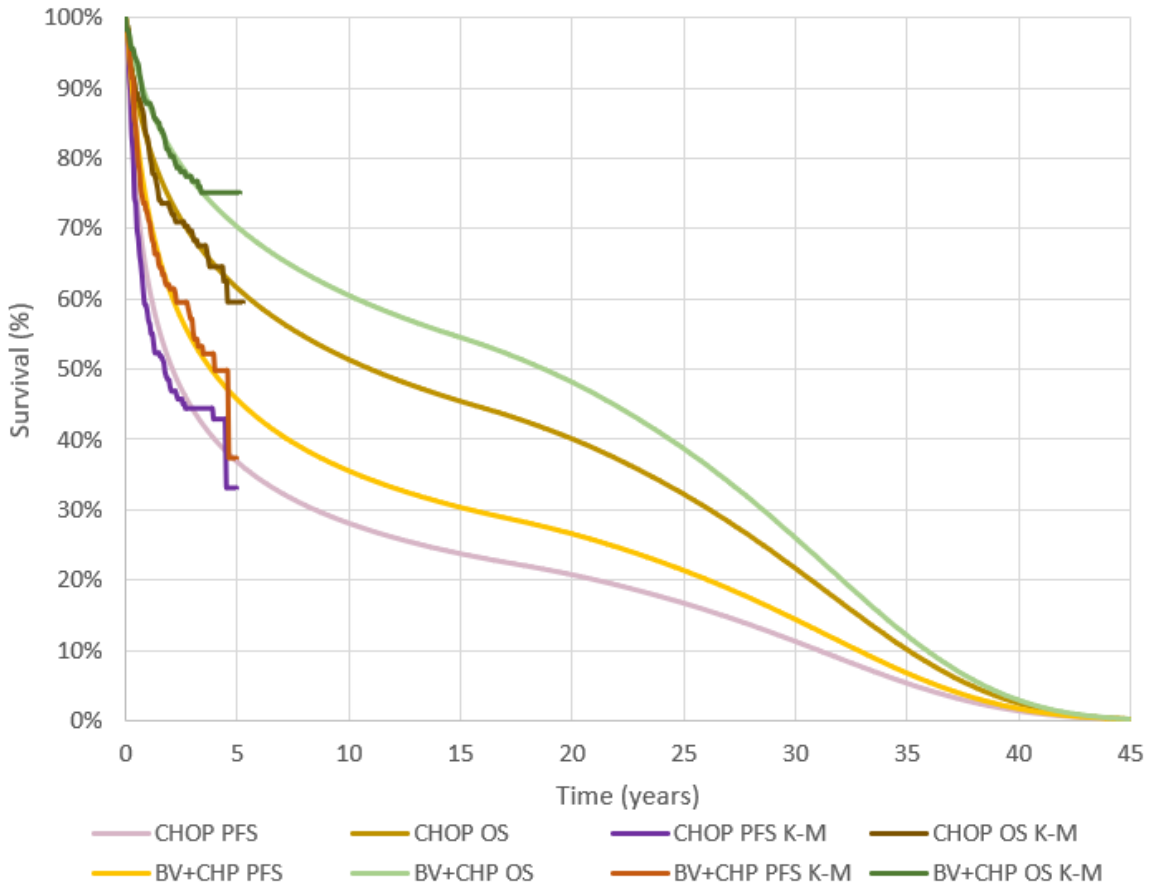
OS (including TSE adjustment)				
BV+CHP (vs. CHOP)	0.621	0.300	0.033	1.209
Constant	4.608	0.353	3.916	5.300
ln(sigma)	0.986	0.163	0.667	1.305
Kappa	-0.298	0.479	–1.236	0.640
PFS				
BV+CHP (vs. CHOP)	0.600	0.208	0.192	1.007
Constant	2.501	0.249	2.013	2.990
ln(sigma)	0.767	0.051	0.666	0.867
Kappa	–0.926	0.253	–1.421	–0.430

Based on Table 34 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; ITT = intention-to-treat; ln = natural logarithm; OS = overall survival; PFS = progression-free survival; TSE = two-stage estimator

5.2.6.5 Summary of the OS and PFS extrapolations used in the model

A summary of the OS and PFS extrapolations used in the company's base-case (generalised gamma distribution for both OS and PFS) and the KM curves from ECHELON-2 is shown in Figure 5.9.

Figure 5.9: Company's base-case survival curve extrapolations (generalised gamma distribution including TSE adjustment for OS and adjusted for background mortality), ITT population



Based on Figure 27 of the CS[1]

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; K-M = Kaplan-Meier; OS = overall survival; PFS = progression-free survival; TSE = two-stage estimator

5.2.6.6 Time on treatment

Time on treatment parameters were obtained from the ECHELON-2 trial data where patients were treated with six to eight cycles of BV+CHP (at the centre's discretion).[62] Clinical experts consulted by the company indicated that standard practice in the UK would consist of a maximum of six cycles.[16, 45] This is in line with the average number of treatment cycles administered in ECHELON-2: 6.0 (SD=1.6) and 5.8 (SD=1.6) in the BV+CHP and CHOP arms, respectively.[18] The proportions of patients receiving one to eight treatment cycles in ECHELON-2 were used in the company's base-case analysis and are summarised in Table 5.12. Additionally, the company considered two scenarios in which the same assumptions were applied to both arms: one where discontinuation rates were assumed to be as observed in ECHELON-2 but capped at six cycles, and a second one where all patients are assumed to receive exactly six cycles.

Table 5.12: Proportion of patients receiving each cycle, ITT population

Cycle	BV+CHP	CHOP
1	100%	100%
2	97%	97%
3	95%	93%
4	92%	89%
5	89%	84%
6	89%	81%
7	19%	19%
8	18%	19%

Based on Table 35 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat

ERG comment: The company mentioned that there was no evidence in ECHELON-2 of interaction between treatment effect and receipt of less than or equal to six cycles vs. more than six cycles in the ITT population (P=0.336). The ERG could not verify this statement but considers that the P-value alone is not sufficient to support it. In their response to clarification question B21,[17] the company indicated that the only statistically significant difference between UK patients and patients from other nationalities in ECHELON-2 was that patients in the UK were more likely to have six (rather than eight) cycles of frontline therapy with either BV+CHP or CHOP. In their base-case, the company assumed that time on treatment was based on the distribution of treatment cycles observed in the ECHELON-2 trial. A scenario capping the number of treatment cycles at six would be more in line with standard practice in the UK. However, as it is currently implemented in the model, such a scenario only affects the estimated costs. The ERG considers that, if a maximum of six cycles were administered in ECHELON-2, a different treatment effect would have been estimated: despite being statistically significant or not, different PFS and OS curves (and the rest of parameters estimated from ECHELON-2) would have been obtained. Therefore, given that on average the number of cycles received in ECHELON-2 was approximately six in both arms, the ERG agrees with the company's assumption of using the distribution of treatment cycles as observed in ECHELON-2, which is consistent with the treatment effect estimated by the company.

5.2.6.7 Consolidative therapy

Consolidative therapy (SCT or radiotherapy), at the investigator's discretion, was permitted in ECHELON-2, if at least six cycles of the study treatment were given prior to initiating consolidative therapy. In the economic analyses, the company assumed that the effects (on survival and other outcomes) of consolidative therapy were captured within the clinical data. The costs associated to consolidative SCT and consolidative radiotherapy were based on the proportions of patients receiving each therapy in ECHELON-2.

Consolidative SCT

Patients who achieved a CR after completion of the study treatment were eligible for consolidation therapy with an SCT. The proportion of patients in the ECHELON-2 ITT population who received consolidative SCT after completion of the study treatment can be seen in Table 5.13.

The model assumes that all consolidative SCT occurred at six months in the model (median time to receipt of consolidative SCT in ECHELON-2 was 181 days). This assumption was validated by UK clinical experts consulted by the company.[43] The majority of consolidative SCTs in ECHELON-2 were AutoSCT, which according to these experts, is reflective of UK clinical practice. There were only two patients in ECHELON-2 who received consolidation with an alloSCT.

Table 5.13: Proportion of patients receiving consolidative SCT in ECHELON-2

Treatment arm	Total number of patients	Patients who received a consolidative SCT	% consolidative SCT
BV+CHP	226	50	22%
CHOP	226	39	17%

Based on Table 37 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; SCT = stem cell transplant

Consolidative radiotherapy

The proportion of patients in the ECHELON-2 ITT population who received consolidative radiotherapy after completion of the study treatment can be seen in Table 5.14. The model also assumes that all consolidative radiotherapy occurred at six months (median time to receipt of consolidative radiotherapy in ECHELON-2 was 175 days).

Table 5.14: Proportion of patients receiving consolidative radiotherapy in ECHELON-2

Treatment arm	Total number of patients	Patients who received consolidative radiotherapy	% consolidative radiotherapy
BV+CHP	226	14	6%
CHOP	226	6	3%

Based on Table 38 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission

ERG comment: Clinical experts consulted by the company indicated that the proportion of patients receiving consolidative therapy in UK clinical practice was around 20%.[45] This is in line with the proportions observed in ECHELON-2 reported in Table 5.13. Furthermore, these proportions are also comparable to the estimates from a 2019 survey of UK PTCL clinicians reporting that approximately 20%-30% of UK patients receive a consolidative transplant.[63] This survey also reported that transplant practices vary considerably across centres in the UK. However, the clinical experts considered that the overall rate of consolidation is unlikely to change due to the introduction of BV+CHP.[16] Based on this, the ERG considers the approach taken by the company regarding modelling consolidative therapies appropriate and likely to be reflective of UK clinical practice.

5.2.6.8 Subsequent SCT post-progression

When a patient experiences disease progression after front-line treatment, this patient is considered to have a more aggressive disease and a poor prognosis. In this situation, as recommended by European Society for Medical Oncology (ESMO) and the British Society of Haematologists guidelines, salvage treatment in relapsed PTCL patients aims to bridge patients to either an AutoSCT or an alloSCT.[14, 15] For this reason, the company also included subsequent SCTs as a component of the costs associated to

progressive disease.[1] The proportion of patients with progressive disease in the ECHELON-2 ITT population who received subsequent SCT (and the proportion of which were AutoSCT vs. alloSCT) can be seen in Table 5.15.

Table 5.15: Proportion of R/R patients receiving salvage stem cell transplant in ECHELON-2

Treatment arm	Subsequent SCT (in patients who progress)	Proportion of subsequent AutoSCT vs alloSCT
BV+CHP	20%	64.1%†
CHOP	21%	

Based on Table 39 of the CS[1]
† Assumed the same in both arms
AutoSCT = autologous stem cell transplant; alloSCT = allogenic stem cell transplant; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; SCT = stem cell transplant

ERG comment: The costs associated to subsequent SCT for patients with progressive disease were based on the proportions of patients receiving AutoSCT or alloSCT in ECHELON-2. The validity of this assumption was not discussed in the CS. Therefore, the ERG cannot assess whether the approach taken by the company is reflective of UK clinical practice.

5.2.7 Adverse events

Adverse events (AEs) were assessed during the safety period of the ECHELON-2 trial, from day one until the end of treatment visit or 30 days after the last study treatment, whichever was later. Grade 3-4 treatment-emergent AEs (TEAEs) occurring in ≥5% of patients in ECHELON-2 were included in the model. Lower grades of diarrhoea were also included in the model based on expert opinion that diarrhoea at any grade, particularly grade 2 or above, was likely to have an impact on patients' HRQoL.[16] Therefore, the company included grades 1-2 but at a lower associated cost than grade 3-4 diarrhoea. Additionally, grade 3-4 peripheral neuropathy was also included (in the utility part of the model only), as this AE is a known class effect of agents with an anti-microtubule mechanism of action, such as BV. Peripheral neuropathy was included in previous TAs and assumptions regarding associated resource use and utility decrements were taken from TA478.[39] Only six and nine grade 3-4 peripheral neuropathy events were observed in the BV+CHP and CHOP arms of the ECHELON-2 trial, respectively, resulting in a low average rate of 0.04 and 0.03 events per patient in the respective arms.

The number of events and duration of AEs observed in the ECHELON-2 trial were used to calculate the QALY loss due to AEs. The list of AEs included in the model, alongside the number of events per patient in each arm observed in ECHELON-2 and the average duration per event are shown in Table 5.16. The total AE duration per patient amounted to 26.42 days in the BV+CHP arm and 15.86 days in the CHOP arm. All AEs were assumed to occur in the first cycle of the model.

Table 5.16: Incidence of TEAEs included in the model

Adverse event	Average number of events per patient		Average duration per event (days)
	BV+CHP arm (N=223)	CHOP arm (N=226)	
Neutropenia (Grade 3–4)	0.97	0.70	11.1
Febrile neutropenia (Grade 3–4)	0.35	0.21	6.8
Anaemia (Grade 3–4)	0.27	0.18	7.2

Adverse event	Average number of events per patient		Average duration per event (days)
	BV+CHP arm (N=223)	CHOP arm (N=226)	
Leukopenia (Grade 3–4)	0.17	0.17	9.6
Thrombocytopenia (Grade 3–4)	0.14	0.06	7.0
Pneumonia (Grade 3–4)	0.06	0.03	14.8
Diarrhoea (Grade 1-2)	0.68	0.25	10.8
Diarrhoea (Grade 3-4)	0.07	0.01	5.6
Peripheral neuropathy (Grade 3–4)	0.04	0.03	127.4

Based on Table 36 of the CS[1]
AEs = adverse events; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; TEAEs = treatment-emergent adverse events.

ERG comment: The company reported that grade 3-4 TEAEs occurring in ≥5% of patients in ECHELON-2 were included in the model, as well as several other AEs reported, which were considered important for inclusion based on severity and impact on HRQoL. The AEs included in the model (with the exception of diarrhoea grade 1-2 and peripheral neutropenia, which were included for reasons other than incidence) correspond with those AEs occurring in at least 5% of patients in either group, shown in Table 12.6 of the incomplete ECHELON-2 CSR (see section 4.2.1 for details).[26] Table 12.6 provides all grade 3 or higher AEs occurring in ≥2% of subjects in the BV+CHP arm. There is the possibility that this table and the model may miss some AEs which occur in ≤5% of CHOP patients but ≥2% of BV+CHP patients. However, given that AE incidences tend to be slightly higher in the BV+CHP arm, this is unlikely.

5.2.8 Health-related quality of life

5.2.8.1 Identification and selection of utility values

HRQoL data were measured in the ECHELON-2 trial using the EQ-5D-3L and valued using the UK EQ-5D-3L tariff.[44] HRQoL data were collected on day 1 of each treatment cycle, at the end of treatment visit and at 9, 12, 15, 18, 21 and 24 months (±1 week) after treatment initiation and every six months (±1 week) thereafter until death or study closure, whichever occurred first.[1]

At baseline, 444 valid EQ-5D-3L questionnaires were included in the analysis and resulted in a mean utility of 0.64 (SD=0.36).[1] There was a significant imbalance in baseline utility values across the treatment groups (BV+CHP=0.61, CHOP=0.68; P=0.0394). Scores in both groups improved over time and no further statistically significant differences across treatment groups were observed throughout the study period.

The systematic literature review identified one relevant study for potential use in the economic model by Swinburn et al. 2015.[40] This study used vignettes describing R/R HL and sALCL health states to elicit TTO valuations from members of the general public in seven countries including the UK, Australia, Thailand, Taiwan, South Korea, Brazil and Mexico. The health state vignettes, which described relevant stages and AEs related to R/R HL and sALCL, were developed through reviewing the published literature, consultation with clinical experts and interviews with patients.

Utility values for use in the economic model were estimated from repeated measures mixed effects models.[1] Two approaches were considered by the company and included in the company model:

1. Health state utility values for progression-free and post-progression (inclusion of an indicator for health state membership).
2. Time-to-death analysis (uses covariates representing whether observations were made within specific time periods prior to the patient's death).

Health state utility value method

In this method, the repeated measures mixed effects models were controlled for baseline EQ-5D score. A series of further non-systematically selected covariates representing events in the model or determinants of HRQoL proposed by UK clinical experts were considered for inclusion in the model, including:

- Treatment arm
- Being on treatment at the time of the observation
- Being post-consolidative AutoSCT at the time of observation
- Experiencing any grade 3-4 AEs at the time of observation
- Age
- Subgroup membership (ALK-positive sALCL, ATLL, AITL, EATL, PTCL-NOS)

Alternative models were tested and compared using a manual forward stepwise procedure, in which variables were introduced and retained if statistically significant (P-value<0.05). Models were further compared using AIC statistics.

The models tested, shown in Appendix M of the CS,[64] suggested that there were no significant differences in HRQoL between treatment arms or between those on treatment vs. post-treatment so these factors were removed. Being a member of the ALK-positive sALCL and ATLL subgroups had a significant impact on HRQoL. However, the inclusion of all subgroups led to a lower AIC value and, therefore, all subgroup covariates were removed from the model. Being post-progression had a significant and small, negative impact on HRQoL (–0.03; P=0.0016), which was largely consistent in magnitude and direction across models. Consolidative AutoSCT was found to have a significant and small positive impact on HRQoL (0.04; P=0.0009), while observations made during AEs were associated with a significant and small reduction in HRQoL (–0.03; P=0.0013). Model 7, displayed in Table 5.17, was selected for implementation in the model.

The company reported that the small impact of progression on utility was not considered realistic by UK clinical experts and was likely due to limited trial follow up and the weighting of post-progression observations towards those taken nearest the point of progression.[1]

Table 5.17: Model of EQ-5D used in the company's base-case analysis

Variable	Coefficient	SE	z	P>z	95% CI	
Post-progression decrement	–0.027†	0.009	–3.180	0.001	–0.044	–0.010
Coef. baseline EQ-5D	0.343	0.022	15.900	0.000	0.301	0.385
Age decrement	–0.002	0.001	–3.480	0.000	–0.003	–0.001
AE disutility	–0.027	0.009	–2.870	0.004	–0.045	–0.008

Variable	Coefficient	SE	z	P>z	95% CI	
Post-SCT increment	0.035	0.011	3.310	0.001	0.014	0.056
Constant	0.655	0.030	21.600	0.000	0.596	0.715

Based on Table 40 of the CS[1]
† The company did not include the post-progression decrement in the base-case, but it is reported here for completeness.
AE = adverse event; CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; SCT = stem cell transplant; SE = standard error

Time-to-death method

The time-to-death method allows for the fact that HRQoL declines significantly as patients approach death. This is incorporated into the model by including covariates for when observations were taken in relation to the patient's death. Time intervals were selected to reflect a plausible range of cycles from death including: less than 1 cycle, 1-4 cycles, 5-9 cycles and 10 or more. These intervals were taken from a previous study which modelled a similar analysis [65] and modified to suit the cycle length in the model. The time-to-death model, which also included covariates for age, being post-SCT and experiencing an AE disutility, predicted that EQ-5D observations for patients taken <21 days before their deaths were associated with reduced HRQoL –0.39 (p<0.001).[64] The size of the effect was found to decrease as the time between observation and death increased. The model coefficients can be seen in Table 5.18.

Table 5.18: Time-to-death EQ-5D model

Variable	Coefficient	SE	z	P>z	95% CI	
Time before death						
189 or more days	–0.0440	0.0190	–2.31	0.021	–0.0812	–0.0068
84–188 days	–0.0851	0.0245	–3.45	0.001	–0.1324	–0.0371
21–83 days	–0.1427	0.0308	–4.59	0.000	–0.2018	–0.0810
<21 days	–0.3884	0.0520	–7.44	0.000	–0.4890	–0.2850
AE disutility	–0.0244	0.0100	–2.85	0.004	–0.0427	–0.0061
EQ-5D baseline	0.3257	0.0211	15.45	0.000	0.2843	0.3670
Age (years)	–0.0012	0.0005	–2.38	0.017	–0.0022	–0.0002
Post-SCT	0.0287	0.0105	2.73	0.006	0.0082	0.0494
Constant	0.6504	0.0296	21.95	0.000	0.5923	0.7084

Based on Table 2 in Appendix M of the CS[64]
AE = adverse event; CI = confidence interval; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; SCT = stem cell transplant; SE = standard error

5.2.8.2 Adverse event disutilities

The impact of grade 3-4 TEAEs was included in the models for both methods of estimating utilities. Following clinical opinion an additional disutility of -0.33 was applied to grade 3-4 peripheral neuropathy, given the severity of grade 3-4 episodes.[43] This decrement was assumed identical to the disutility applied in TA478 and was applied to the number of events per patient across the time horizon (80.53 days in the BV+CHP arm, 68.75 days in the CHOP arm).[39, 40]

5.2.8.3 Utility values used in the model

In the base-case, the company chose to use the health state utility value (HSUV) method. However, clinical experts consulted by the company felt that the decrement for progression of -0.027 was implausibly small. Therefore, this model decrement was ignored and, for the progressive state, the company used a utility value based on the one used in TA478, which was derived from estimates in Swinburn et al. 2015.[39, 40] Swinburn et al. 2015 provided utility values for stable disease, complete response, partial response and progressive disease (0.38 for UK patients). The value 0.643 used in the model for progression was calculated as a weighted average of the proportion of patients who did and did not receive SCT and the associated utility values calculated in TA478. For a full explanation, the ERG refers to the company response to clarification question B16.[17] An age decrement of -0.002 was applied, based on the decrement observed in the HSUV method model used in the base-case. The utility values used by the company in their base-case are summarised in Table 5.19. The time-to-death (TTD) method was explored by the company in scenario analysis.

Table 5.19: Utility values considered by the company for their base-case

	Utility value	Source/justification
Pre-progression	0.78	Estimated from Model 7 in Appendix M using the EQ-5D data from the ECHELON-2 trial and considering: health state membership, age, baseline EQ-5D, SCT receipt and AEs as covariates. Includes an additional decrement of –0.33 for patients with peripheral neuropathy.[64]
Progressed disease	0.643	Derived from the R/R sALCL TA478 submission and Swinburn et al. 2015.[39, 40]
Age-decrement	-0.002	Derived from the EQ-5D data from the ECHELON-2 trial and applied over time.[64]

Based on Table 41 of the CS[1]
AE = adverse event; CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; R/R = relapsed or refractory; sALCL = systemic anaplastic large cell lymphoma; SCT = stem cell transplant

ERG comment: The company used the HSUV method to estimate utilities in the base-case. Despite stating that alternative HSUV models were compared using fit statistics, no fit statistics were presented in the submission. Therefore, the ERG cannot be sure how well any of the models included performed in estimating utility. Covariates were retained or excluded based on statistical significance. The models tested in the HSUV method consistently found progression to have a small and significant negative impact on utility of approximately -0.03. However, this value was not utilised in the model as the impact of progression on utility was felt to be implausible by the company and clinical experts. Given the lack of confidence by the company and clinical experts in this important parameter obtained from the model, the ERG is concerned about the confidence it should place in the remaining coefficients of the model. With no indicators of model fit or model performance, the ERG is unable to assess how appropriate the use of this model is.

Due to the assumed implausibility of the progression decrement obtained from the HSUV model, the company chose to ignore the progression coefficient, instead estimating an alternative progression utility value following the methods used in TA478, based on utility values from Swinburn et al. 2015.[40] The Swinburn study estimated utility values for R/R Hodgkin lymphoma and sALCL using health state using vignettes, valued by members of the general population from seven countries, including the UK, using a TTO exercise. The NICE reference case states that the source of data for the measurement of HRQoL should be obtained through direct reporting by patients and valued in a representative sample of the UK general population.[49] By using a vignette approach directly in members of the general

population, the Swinburn study did not measure HRQoL directly in patients and, therefore, does not meet this requirement of the NICE reference case. The ERG would prefer to use HRQoL data obtained directly from patients. Given that HRQoL was measured directly in patients within the ECHELON-2 trial using the EQ-5D-3L, which meets the NICE reference case, the ERG prefers to utilise these data.

In their submission, the company provided an alternative model for estimating utilities, using a TTD approach. This approach accounted for the decline in HRQoL prior to death. Unfortunately, again, indicators of model fit, and model performance were not provided. However, the size and ordering of the coefficients relating to the periods of time prior to death were logical, in that the impact on HRQoL became increasingly large as death approached. The coefficients for the covariates which featured in both the HSUV and TTD approaches (AEs, EQ-5D baseline, age, post-SCT and the constant) were also largely consistent in size across the two approaches, which increases confidence in their magnitude.

In the clarification letter, the ERG requested to see the results of a model which included both the HSUV and TTD approaches.[19] This was provided by the company in the clarification response, with results displayed in Table 5.20.[17] Again, the coefficients for the covariates common to both approaches were encouragingly consistent in size. In this combined model, the coefficient for post-progression became smaller and insignificant. The TTD coefficients became slightly smaller but were consistent with the TTD only model. The relative size of the TTD coefficients versus the post-progression coefficient would suggest that time-to-death has a larger impact on HRQoL than progression.

Given the evidence presented, the ERG would argue that the TTD approach would be better suited to the base-case. The EQ-5D data presented suggests that time-to-death has a larger impact on HRQoL than progression. Additionally, using the TTD approach avoids the issues associated with the HSUV method. Namely, ignoring the coefficient of an important model parameter such as progression and using an alternative source of utilities which were not measured in patients, did not make use of the EQ-5D and, therefore, does not meet in NICE reference case. Therefore, the ERG base-case utilises the TTD utility approach.

Table 5.20: Combined HSUV TTD method for estimating utility

Variable	Coefficient	SE	z	P>z	95% CI	
Time before death						
189 or more days	-0.042	0.019	-2.21	0.027	-0.079	-0.005
84 - 188 days	-0.076	0.025	-3.05	0.002	-0.126	-0.027
21 - 83 days	-0.133	0.031	-4.25	0.000	-0.195	-0.072
< 21 days	-0.378	0.052	-7.21	0.000	-0.480	-0.275
Post-progression	-0.014	0.009	-1.59	0.111	-0.031	0.003
Experiencing AEs	-0.024	0.009	-2.61	0.009	-0.043	-0.006
Baseline EQ-5D	0.327	0.021	15.50	0.000	0.285	0.368
Age (years)	-0.001	0.001	-2.37	0.018	-0.002	-0.000
Post-SCT	0.031	0.01	2.93	0.003	0.010	0.052
Constant	0.651	0.030	22.01	0.000	0.593	0.709

Based on Table 20 of the response to request for clarification[17]
AE = adverse event; CI = confidence interval; EQ-5D = European Quality of Life-5 Dimensions; HSUV = health state utility value; SCT = stem cell transplant; SE = standard error; TTD = time-to-death.

It is standard practice within NICE appraisals to adjust utilities over the lifetime horizon of the model to account for the decline in utilities due to ageing. There are two commonly seen approaches to adjust EQ-5D utility values for age. One is to adjust using the general population EQ-5D utility values, separated by age brackets, provided by Szende et al. 2014,[66] and the other one is to use the equation by Ara and Brazier 2010,[67], which estimates the mean utility of the UK general population, adjusted for age and sex. The Szende utilities for the relevant age brackets for this model are shown in Table 5.21. The equation obtained from Ara and Brazier is as follows:

*EQ-5D = 0.9508566 + 0.0212126*male - 0.0002587*age - 0.0000332*age^2*

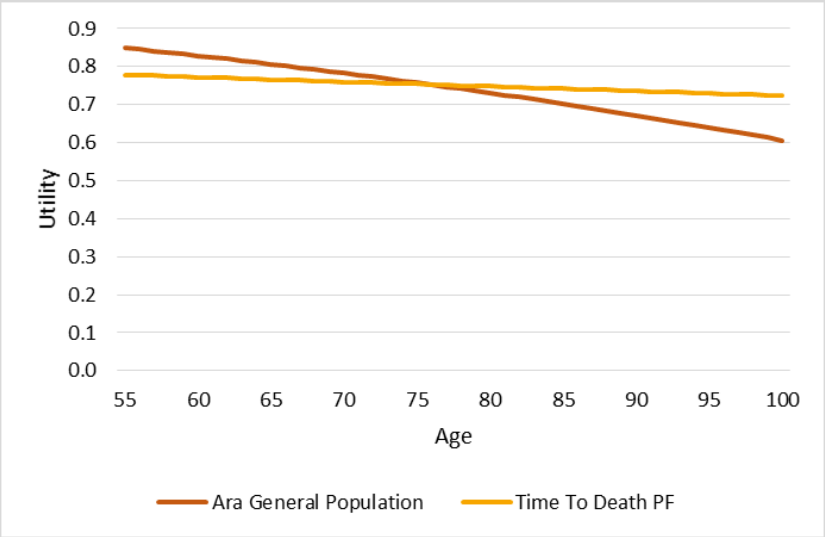
Table 5.21: Age-specific general population utility values from Szende et al. 2014

Age range (years)	Utility value
55-64	0.810
65-74	0.773
75-100	0.703
Based on Szende et al. 2014[66]	

When using the Ara and Brazier equation, the decline in utility due to ageing increases as people age.[67] For example, at the age of 55 years, the loss of utility from ageing one year is approximately 0.004, while at the age of 70 years it is 0.005 and at the age of 80 years it is 0.006. Assuming that the utilities reported for each age bracket in Szende et al. apply approximately at the centre of each age bracket and the decline is fairly linear within each bracket, the yearly decline in utility between the ages of 60 and 70 years is also approximately 0.004.[66]

While the company do adjust for ageing within their utility models, the yearly decrement is substantially smaller than the yearly decrements found in Ara and Brazier and Szende et al.[66, 67] In the time-to-death analysis the yearly decrement is consistent over the patients remaining lifetime at -0.0012, approximately a quarter of the size of the Ara and Brazier decrement at the age of 60 years, with the difference only increasing as patients age. The ERG is concerned that the company's model may underestimate the impact of age on HRQoL, especially in the long-term. Figure 5.10 compares the company's progression-free utility, including the age decrement over time (obtained from the TTD model) to the age-adjusted general population utility values obtained from the Ara and Brazier equation (using the gender mix from the ECHELON-2 trial).[67] It can be seen in this figure that the smaller age decrement from the company model (combined with the relatively high progression-free utility value) results in patients having higher utility estimates than the general population after approximately the age of 76 years. The ERG did not consider that this was plausible. Therefore, in the ERG base-case, patient utility values in the model were constrained to be less than or equal to those of the age-adjusted general population.

Figure 5.10: Company's TTD age-adjustment vs. Ara and Brazier general population utility values



Based on electronic model of the CS[48] as well as Ara and Brazier 2010[67]
CS = company submission; PF = progression-free; TTD = time-to-death

The company assumed that the impact of AEs experienced within the ECHELON-2 trial was captured within the HRQoL data gathered.[1] Their model includes a covariate to account for the decrement in utility when AEs are being experienced.[48] This decrement, which is approximately -0.026, depending on the utility model approach used, is assumed to represent the average of all AEs experienced and is multiplied with the overall average number of events and duration of events within the model to provide an overall impact of AEs on HRQoL. However, the company adopted an additional decrement of -0.33 for grade 3-4 peripheral neuropathy from TA478. No justification was provided as to why this AE would not have been captured in the HRQoL data which were assumed to cover all other AEs experienced. While the number of events of grade 3 and 4 peripheral neuropathy is low in the trial (six and nine events in the BV+CHOP and CHOP arms respectively, resulting in a low average rate of 0.04 and 0.03 events per patient), the average duration per event of this AE is long (127.4 days). This results in grade 3-4 peripheral neuropathy having substantial impact within the AEs included in the model. If the model decrement for AEs is assumed to capture the impact of all other AEs, it is unclear why it would not have captured this AE, especially given the long period over which it is experienced and its severity. Assuming an additional substantial decrement for this AE could overestimate its impact within the model. Given the weight that this specific AE has, this could overestimate the impact of AEs. The fact that the company includes this additional decrement would suggest that they suspect that the average decrement of -0.026 underestimates the impact of AEs on HRQoL. In this case, the ERG would have preferred separate disutilities for each of the commonly experienced or clinically important AEs, multiplied by their incidence and duration, as then the ERG could have assessed the assumed impact of each AE on HRQoL, rather than having to assess the plausibility of an average value over all AEs. However, no changes in assumptions regarding disutilities were made by the ERG as AEs have very little impact on model results.

5.2.9 Resources and costs

Drug costs that were identified for the intervention and the comparator included acquisition costs, administration costs, and costs of concomitant medication. Costs for the use of other medical resources were subdivided into those that are incurred pre- and post-progression and were attributed to the corresponding health states in the model. Furthermore, the model included costs for AEs, stem cell

therapy (SCT), consolidative radiotherapy, second-line treatment with BV (i.e. post-progression), and salvage chemotherapies and radiotherapy.

Cost items were valued using the unit costs as reported in eMIT,[68] NHS reference costs 2017/2018,[69] the British National Formulary,[70] and the PSSRU 2018.[71] Otherwise, unit costs were based on those reported in previous technology appraisals and indexed to 2017/2018 using the inflation indices from PSSRU 2018.[71]

5.2.9.1 Intervention and comparator costs

Acquisition costs

The acquisition costs of BV+CHP and CHOP are applied per model cycle to the proportions of patients receiving each treatment cycle (i.e. according to the time-on-treatment data) in ECHELON-2. On average, patients in ECHELON-2 received 6.0 treatment cycles in the BV+CHP arm, and 5.8 treatment cycles in the CHOP arm. The electronic model also provided options to use the number of treatment cycles from ECHELON-2 with a maximum of six, and for assuming that all patients received either six or eight treatment cycles in both arms.

For each individual drug except prednisone (tablets for oral administration), the average number of vials used per treatment cycle was calculated taking into account the distribution of patients in terms of body weight (for BV) and body surface area (BSA; for cyclophosphamide, doxorubicin, and vincristine). This was done using the method of moments, with the assumption that vials cannot be shared due to the rarity of the condition.

The acquisition costs per model cycle, including information on dosage, pack price and size, and the average number of vials used per model cycle, are shown for each drug in Table 5.22.

Table 5.22: Drug acquisition costs

Drug	Dose	mg/unit	Pack price	Pack size	Average number of vials	Costs per model cycle
BV+CHP						
BV (list price)	1.8 mg/kg	50 mg	[redacted]	1	3.14	[redacted]
BV (PAS price)			[redacted]			[redacted]
Cyclophosphamide	750 mg/m^2	500 mg	£8.31	1	3.26	£27.11
Doxorubicin	50 mg/m^2	50 mg	£17.78	1	2.28	£17.78
Prednisone	100 mg	25 mg	£20.25	56	NA	£7.23
Total cost per model cycle (using BV list price)						[redacted]
Total cost per model cycle (using BV PAS price)						[redacted]
CHOP						
Cyclophosphamide	750 mg/m^2	500 mg	£8.31	1	3.26	£27.11
Doxorubicin	50 mg/m^2	50 mg	£17.78	1	2.28	£17.78
Prednisone	100 mg	25 mg	£20.25	56	NA	£7.23
Vincristine	1.4 mg/m^2	1 mg	£11.59	5	3.08	£7.14
Total cost per model cycle						**£59.26**

Based on Tables 42 and 43 of the CS[1]

Drug	Dose	mg/unit	Pack price	Pack size	Average number of vials	Costs per model cycle
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; NA = not applicable; PAS = patient access scheme						

Administration costs

Except for prednisone, all chemotherapy drugs in both regimens were administered intravenously on the first day of each treatment cycle. Therefore, administration costs consisted of a single cost of infusion. Although the company stated in the CS that the costs were based on those in the outpatient setting,[1] in reality these were based on a weighted average of the costs in the following settings: daycase and regular day or night admissions, outpatient, and other (i.e. these are categorisations used to differentiate between treatment settings in the NHS reference cost database). This resulted in administration costs of £228.99 for the first treatment cycle (NHS reference costs currency code SB12Z: Simple parenteral chemotherapy, first), and £289.33 for subsequent treatment cycles (NHS reference costs currency code SB15Z: Simple parenteral chemotherapy, subsequent). Prednisone was taken orally, and therefore no costs were incurred for its administration.

Concomitant medication

In line with clinical practice in the UK, it was assumed that all patients in both regimens received primary prophylaxis with a granulocyte colony stimulating factor (G-CSF; filgrastim). However, in ECHELON-2 this was applicable to only 30% of the patients. Analogous to TA478, all patients were assumed to receive levofloxacin and acyclovir in addition to G-CSF. Furthermore, following the opinion of clinical experts,[43] who did not expect differences in concomitant medication between both regimens, and with reference to the documentation by the London Cancer Alliance on follow-up care with CHOP chemotherapy,[44] it was assumed that all patients in both treatment arms receive allopurinol, omeprazole, fluconazole, and co-trimoxazole. Table 5.23 shows the unit and total costs per model cycle, including the sources used for assumptions regarding dosage and number of model cycles, for filgrastim (unit costs taken from TA478[39]) as well as for levofloxacin, acyclovir, allopurinol, omeprazole, fluconazole, and co-trimoxazole.

Table 5.23: Concomitant medication costs

Drug	Dose	mg/ pack	Cost/ pack	Administrations /model cycle	Cost/ model cycle	Source for dose/ model cycle
Filgrastim	300 mg	300 mg	£52.70	7	£368.90	TA478[39]
Levofloxacin	500 mg	500 mg	£2.12	7	£1.48	
Aciclovir	400 mg	250 mg	£7.99	14	£17.90	
Allopurinol	300 mg	300 mg	£6.35	1	£0.23	London Cancer Alliance, CHOP Concomitant medication[44]
Omeprazole	20 mg	20 mg	£0.42	21	£0.32	
Fluconazole	50 mg	50 mg	£0.76	21	£2.28	

Drug	Dose	mg/ pack	Cost/ pack	Administrations /model cycle	Cost/ model cycle	Source for dose/ model cycle
Co-trimoxazole	960 mg	480 mg	£1.16	9	£0.75	

Based on Table 45 of the CS[1]
CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CS = company submission; mg = milligram; TA = technology appraisal

5.2.9.2 Pre- and post-progression health care resource use

Assumptions regarding health care resource use were based on the follow-up and monitoring requirements during ECHELON-2, documentation by the London Cancer Alliance on follow-up care with CHOP chemotherapy,[44] and TA478.[39] Different assumptions were made for health care resources used pre- and post-progression to reflect the varying intensities of follow-up care between these stages of disease. For pre- and post-progression health care resource use, no differences were assumed between the BV+CHP and CHOP regimens.

Pre-progression health care resource use

For simplicity, health care resource use during treatment was applied as a one-off cost for the first cycle in the electronic model.

Health care resource use during follow-up was applied for three years post-treatment, with different frequencies in the first year compared to the second and third years (i.e. the frequencies in years two and three are assumed to be the same). Patients who remain progression-free for three years were assumed to be discharged, and therefore no additional resource use was taken into account after this time period. This assumption was validated by clinical experts, who indicated a range of two to five years for this, which also aligns to TA478.[39]

Assumptions regarding frequency and monitoring during treatment are based on UK clinical expert opinion.[16] In line with TA478,[39] follow-up visits included consultation, full blood counts and clinical biochemistry, and were performed once every three months for three years after the end of treatment. Pre-progression health care resource use unit costs and frequencies are reported in Table 5.24.

Table 5.24: Pre-progression health care resource use unit costs and frequencies

Component	Unit cost	Resource use during treatment	Long-term follow up		Currency code/source
			Year 1	Years 2 & 3	
CT scan	£136.70	2	1	0	NHS reference costs 2017/18,[69] RD27Z
PET scan (3+ areas)	£460.19	2	1	0	NHS reference costs 2017/18,[69] RN07A, 19 years and over
Consultation	£164.80	1	4	8	NHS reference costs 2017/18,[69] WF01A, 303. Non-admitted, face to face, haematology
Full blood count	£2.51	6	4	8	NHS reference costs 2017/18,[69] DAPS05

Component	Unit cost	Resource use during treatment	Long-term follow up		Currency code/source
			Year 1	Years 2 & 3	
Clinical biochemistry	£1.11	6	4	8	NHS reference costs 2017/18,[69] DAPS04
Bone marrow biopsy	£495.98	3	0	0	NHS reference costs 2017/18,[69] SA33Z
Urea and electrolytes*	£1.11	6	3.5	3.5	NHS reference costs 2017/18,[69] DAPS04
Liver function test*	£2.51	6	3.5	3.5	NHS reference costs 2017/18,[69] DAPS05
Total cost per model cycle		**£2,890**	**£1,283**	**£1,360**	

Based on Table 46 of the CS[1]
* Number of units received were taken from the London Cancer Alliance protocol for CHOP[44]
CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CS = company submission; CT = computerised tomography; NHS = National Health Service; PET = positron emission tomography

Post-progression health care resource use

Health care resource use in post-progression PTCL was deemed comparable by the company to that required in post-progression R/R sALCL, and, therefore, the frequencies of resource use post-progression were taken from TA478.[39] The total number of units corresponding to these frequencies are shown in Table 5.25, alongside the unit costs of the corresponding items and their sources.

Different estimates were used for patients that are either on or off second-line treatment. For the latter, two sets of frequencies were provided in TA478,[39] which were both available in the current electronic model. The company base-case used one of the sets. When the other set was used as an alternative, this had a negligible impact on the cost effectiveness results.

In line with TA478,[39] follow-up visits consisted of consultation, full blood count and clinical biochemistry, and were assumed to occur once per cycle of salvage therapy. Therefore, the mean number of cycles of salvage therapies (4.62 cycles of subsequent treatment in the base-case) was used in the electronic model for the frequencies of these items. In the electronic model, the total costs for post-progression health care resource use (i.e. £4,473 in the company base-case) were applied to the proportion of patients who progressed in each cycle. It was assumed that patients who did not experience a relapse for three years were discharged with no additional resource use.

Table 5.25: Post-progression health care resource use unit costs and total number of units

Component	Unit cost	On treatment	Long-term follow up			Currency code/ source
			Clinical expert 1	Clinical expert 2		
			Years 0-3	Years 0-2	Years 2-6	
CT scan	£136.70	3	1	1	0	NHS reference costs 2017/18,[69] RD27Z
PET scan (3+ areas)	£460.19	2	1	1	0	NHS reference costs 2017/18,[69] RN07A, 19 years and over
Consultation	£164.80	4.62	10.50[a]	6.86[b]	7[c]	NHS reference costs 2017/18,[69] WF01A, 303. Non-admitted, face to face, haematology
Full blood count	£2.51	4.62	10.50[a]	6.86[b]	7.00[c]	NHS reference costs 2017/18,[69] DAPS05
Clinical biochemistry	£1.11	4.62	10.50[a]	6.86[b]	7.00[c]	NHS reference costs 2017/18,[69] DAPS04
Total cost		**£2,108**	**£2,365**	**£2,931**		

Based on Table 47 in the CS[1] and the electronic model of the CS[48]
[a] Equivalent to 1 unit every 3/4 months for 3 years; [b] Equivalent to 1 unit every 3/4 months for 2 years; [c] Equivalent to 1 unit every 6 months for 4 years
CS = company submission; CT = computerised tomography; NHS = National Health Service; PET = positron emission tomography

5.2.9.3 Adverse events costs

The costs of grade 3-4 AEs, occurring in ≥5% of patients in ECHELON-2, were applied to the average number of grade 3-4 AEs observed per patient (i.e. in the electronic model,[48], although the CS text states that these were applied to the duration, instead of the average number, of each event) as reported in section 5.2.7. In addition, grade 1-2 diarrhoea was also costed since it was noted as being particularly detrimental to patients' HRQoL at the June Cross-Functional Advisory Board.[16] Treatment of grade 1-2 diarrhoea was based on over the counter medication,[16] for which the costs of loperamide were assumed. Following clinical expert opinion,[43] no costs were included for grade 3–4 peripheral neuropathy on the basis that the treatment for this AE would be to stop treatment with either BV+CHP or CHOP and wait for peripheral neuropathy improvement or resolution.

In addition to the NHS reference costs 2017/18,[69] BNF,[70] and eMIT[68] that were used as sources for unit costs, two additional sources were used for the costing of AEs: the NICE Costing Statement: Blood transfusion 2015[72] and the NHS Blood and Transplant Price List 2018/19.[73] These were used for the costing of transfusion and blood components, respectively. The proportion of patients requiring a platelet transfusion was taken from TA478.[39] The unit cost of each grade 3-4 AE included in the model (and its relevant code) are reported in Table 5.26. A breakdown of costs for neutropenia, febrile neutropenia, anaemia and thrombocytopenia is provided in Table 5.27. Finally, the calculation of the cost for treatment of grade 1-2 diarrhoea is provided in Table 5.28.

Table 5.26: Grade 3–4 adverse events costs per event

AE	Cost/event	Source/HRG code
Neutropenia	£576.63	Cost of administering peg filgrastim (Table 5.27)
Febrile neutropenia	£576.63	
Anaemia	£406.09	Cost of transfusion (Table 5.27)
Leukopenia	£576.63	Assumed identical to neutropenia
Thrombocytopenia	£610	Peg filgrastim identical to neutropenia and a platelet transfusion in 10% of patients (Table 5.27)
Pneumonia	£1,099.81	DZ22L, day case, unspecified acute lower respiratory infection with intervention[69]
Diarrhoea (Grade 3–4)	£161.00	FD05A, day case, abdominal pain with interventions[69]

Based on Table 48 of the CS[1]
AE = adverse event; CS = company submission; HRG = healthcare resource group

Table 5.27: Breakdown of costs per Grade 3–4 adverse event

AE	Cost type	Number of units	Cost	Source
Neutropenia, febrile neutropenia and leukopenia	Peg filgrastim unit cost	1	£411.83	BNF[70]
	Peg filgrastim administration		£164.80	WF01A 303, NHS Reference Costs[69]
Anaemia	Transfusion	1	£148.11	NICE Blood transfusion costing, NG24 (inflated)[72]
	Red blood cells	2	£128.99	NHS Blood and Transplant Price List[73]
Thrombocytopenia	% patients requiring platelets	10%	-	TA478[39]
	Peg filgrastim unit cost	1	£411.83	BNF[70]
	Peg filgrastim administration	1	£164.80	WF01A 303, NHS Reference Costs[69]
	Platelets	1	£185.56	NHS Blood and Transplant Price List[73]
	Transfusion	1	£148.11	NICE Blood transfusion costing, NG24 (inflated)[72]

Based on Table 49 of the CS[1]
AE = adverse event; BNF = British National Formulary; NHS = National Health Service; NICE = National Institute for Health and Clinical Excellence; TA = technology appraisal

Table 5.28: Grade 1–2 diarrhoea costs per event

Imodium (loperamide) for Grade 1–2 diarrhoea	BV+CHP	CHOP
Daily dose (mg)	7	
Unit dose (mg)	2	
Pack size	30	
Cost/unit	£0.38	
Average duration of event (days)	7.36	2.72
Total cost per event	£0.33	£0.12

Based on Table 50 of the CS[1] and the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission

Total AE costs in the company's base-case were £1,135.44 in the BV+CHP arm and £772.93 in the CHOP arm. The difference in cost is driven primarily by differences in neutropenia and febrile neutropenia. AE costs were applied as one-off costs at the start of the model. The company considered this reasonable because of the short duration of treatment.

5.2.9.4 Miscellaneous costs

This section provides an overview of the costs for the remaining procedures that were deemed relevant by the company and, therefore, were included in the economic analyses: SCT, consolidative radiotherapy, second-line treatment with BV, and salvage chemotherapies and radiotherapy.

Stem cell transplant

The same costs for SCT were assumed regardless of whether it was provided as consolidation therapy front-line or as second-line treatment (i.e. post-progression). The costs for SCTs were applied to the proportion of patients who received SCT in ECHELON-2 (see sections 5.2.6.7 and 5.2.6.8). All consolidative SCT costs in the model were applied six months post-initiation of treatment with BV+CHP or CHOP. This assumption was validated by UK clinical experts.[43]

Two previous technology appraisals provided estimates for autologous SCT (TA478 and TA567),[43, 74] and three previous technology appraisals provided estimates for allogeneic SCT (TA478, TA567 and TA577).[39, 42, 74] From these, the most recent ones in a related disease area were selected for the company base-case: TA577 for allogeneic SCT and TA478 for autologous SCT. In addition, the electronic model allowed the other estimates to be used as alternatives. However, selection of the other estimates had a negligible to minimal effect on the cost effectiveness results. All estimates for SCT costs are listed in Table 5.29.

Table 5.29: Stem cell transplant costs

Technology appraisal	Cost of procedure	Follow-up cost	Total costs
Autologous stem cell transplant			
TA478[39] (base-case)	£54,543	-	£54,543
TA567[74]	£25,458	£3,338	£28,796
Allogeneic stem cell transplant			
TA567[74]	£79,525	£3,338	£82,862

(base-case)			
TA478[39]	£111,520	-	£111,520
TA577[42]	-	-	£96,956[a]

Based on Tables 51 and 52 of the CS[1]
[a] Calculated as the average of unrelated and sibling donor in TA577.
CS = company submission; TA = technology appraisal.

Consolidative radiotherapy

The total costs of consolidative radiotherapy were estimated as £2,206 per procedure, consisting of the cost of preparation and the cost of delivery, as shown in Table 5.30. In the model, these costs were applied as a one-off cost at six months, in line with the timing of consolidative SCT, to the proportion of patients that received consolidative radiotherapy in ECHELON-2 (6.19% in BV+CHP and 2.65% in CHOP), and were sourced from the NHS reference costs 2017/18.[69] The number of units per component was assumed identical to the number of units reported for palliative radiotherapy in TA478.[39] This assumption was validated by UK clinical experts.[16]

Table 5.30: Consolidative radiotherapy costs

Component	Number of units	Unit cost	Currency code
Preparation for simple radiotherapy with imaging and dosimetry	1	£514.99	SC45Z, NHS Reference Costs[69]
Deliver a fraction of treatment on a megavoltage machine	15	£112.73	SC22Z, NHS Reference Costs[69]
Total cost per procedure	–	£2,206	

Based on Table 53 of the CS[1]
CS = company submission; NHS = National Health Service

Second-line BV

In ECHELON-2, a proportion of patients received BV as second-line treatment (i.e. post-progression; either as re-treatment in the BV+CHP arm, or as subsequent treatment in the CHOP arm). In the UK, second-line treatment with BV is only recommended for patients with R/R sALCL (only if they have ECOG PS 0 or 1) who have not been treated with BV before. Therefore, the costs of second-line BV were only applied to the proportion of R/R sALCL patients who received second-line BV in ECHELON-2 (n=36).

The costs for second-line BV were assumed to be the same as for front-line treatment with BV (see Table 5.22). However, the company assumed that the use of BV as a second-line monotherapy may have a longer treatment duration than as front-line. Therefore, the company based assumptions regarding the duration of treatment with second-line BV on data reported in TA478 (8.2 cycles on average).[39] Note that the use of BV as a monotherapy implies that this does not include co-administration (and the costs) of CHP (i.e. in contrast to BV+CHP in the front-line setting). For second-line BV, the same health care resource use were assumed as for BV+CHP during front-line treatment.

Salvage chemotherapies and radiotherapy

Upon disease progression, patients in ECHELON-2 received a variety of second-line treatments. To enhance representativeness for the UK, therapies that are not reimbursed by the NHS were excluded from the analyses. This assumption was based on UK clinical expert opinion expressed at the February Clinical Advisory Board,[45] ESMO guidelines,[14] and other relevant UK clinical guidelines.[46] The

proportions of patients who received a specific (category of) treatment are shown in Table 5.31. These proportions were then multiplied with the (acquisition and administration) costs of the selected regimens, in order to estimate the weighted total cost of salvage treatments that are available in the UK. This average cost was then applied to all newly progressed patients per model cycle.

Table 5.31: Salvage chemotherapies and radiotherapy costs

Regimen	Frequency	Proportion	Acquisition costs[a]	Administration costs[a]
Bendamustine	8	7.14%	£514.62	£336.55
CHOP	2	1.79%	£371.06	£336.55
DHAP	11	9.82%	£691.25	£625.88
ESHAP	17	15.18%	£555.00	£1,493.85
GDP	24	21.43%	£944.92	£575.71
Gemcitabine	7	6.25%	£600.28	£336.55
ICE	20	17.86%	£4,814.89	£915.20
Radiation	21	18.75%	£2,206.01	NA
SMILE	2	1.79%	£2,691.02	£1,204.53
Total	112	100%	-	-
Weighted average	-	-	£1,757.00	£3,595.88

Based on Table 56 of the CS[1] and the electronic model of the CS[48]
CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CS = company submission; DHAP = dexamethasone, cisplatin, cytarabine; ESHAP = cisplatin, methylprednisolone, etoposide, cytarabine; GDP = gemcitabine, dexamethasone, cisplatin; ICE = etoposide, carboplatin, ifosfamide + mesna, mesna; ITT = intention-to-treat; NA = not applicable; SMILE = etoposide, ifosfamide + mesna, mesna, methotrexate, dexamethasone

ERG comment: In general, the ERG considers the assumptions regarding resource use and costs appropriate.

The choice of the company to use the average number of treatment cycles from ECHELON-2 for front-line BV, is not in line with the maximum number of six cycles that is representative for clinical practice in the UK.[16] However, as discussed in section 5.2.6.6, capping the number of treatment cycles at six in the model only affects the estimated costs. The ERG considers that, if a maximum of six cycles were administered in ECHELON-2, a different treatment effect would have been estimated too. Therefore, given that on average the number of cycles received in ECHELON-2 was approximately six in both arms, the ERG agrees with the company's assumption of using the distribution of treatment cycles as observed in ECHELON-2, which is consistent with the treatment effect estimated by the company.

The ERG could not validate the values used for the unit costs of drug prices that were sourced from eMIT.[68] However, the deviations between the values reported in the CS and those in the most recent version of eMIT are only very small.[1, 68] Such deviations are relatively more substantial for concomitant medication. Nevertheless, in absolute terms, this does not have any meaningful influence on the cost effectiveness results. In the absence of information on the costs of prednisone in eMIT,[68] the ERG has assumed that these costs are based on prednisolone instead.

Contrary to what was stated in the CS, for currency codes SB12Z, SB15Z (both used for administration costs), SC45Z and SC22Z (both used for consolidative radiotherapy costs) the costs were calculated based on a weighted average between different settings, instead of based on the outpatient setting only. This has a negligible impact on the cost effectiveness results.

An error in sourcing the costs of transfusion was discovered by the ERG. The value provided by the company (£148.11) seems to refer to the staff time that is needed for intra-operative cell salvage rather than transfusion (£50.78, updated to 2017/2018).[72] Correcting this error also has a negligible impact on the cost effectiveness results.

The ERG does not agree with the exclusion of costs for the treatment of peripheral neuropathy. Even though the company referred to clinical expert opinion to support this assumption, the ERG considers it contradictory that these costs were included for the same intervention (BV) in TA478.[39] While the average rate of grade 3-4 peripheral neuropathy is low in the trial, this is similar to the rates observed for grade 3-4 pneumonia and grade 3-4 diarrhoea, and these were included in the model. Furthermore, the average duration per grade 3-4 peripheral neuropathy event is by far the longest (127.4 days) amongst AEs. This suggests that grade 3-4 peripheral neuropathy might have substantial impact within the AEs included in the model. For these reasons, the costs of grade 3-4 peripheral neuropathy were included in the ERG base-case described in section 7.1.2 of this report. To be fully in line with TA478 in this aspect,[39] the costs of grade 1-2 peripheral neuropathy, for which the average rates in ECHELON-2 were substantially higher (0.41 in the BV+CHP arm and 0.38 in the CHOP arm), were also included in the ERG base-case.

Second-line treatment with BV is only recommended in the UK for patients with R/R sALCL and ECOG PS 0 or 1 who have not been treated with BV before. As discussed in section 5.2.6.2, the company indicated that there were four patients with ECOG PS 2 at study baseline in the CHOP arm of ECHELON-2 who had sALCL disease and received subsequent BV post-progression. In the version of the model received with the response to the request for clarification,[17] these patients were removed from the proportion of patients receiving subsequent BV.

Finally, the company assumed that the use of BV as a second-line monotherapy had a longer treatment duration (8.2 cycles on average) than as front-line (six cycles on average). The company based this assumption on data reported in TA478,[39] but it is not mentioned whether this assumption was also validated by clinical experts. Based on the TA478 committee discussion,[39] the ERG is uncertain about this assumption. In particular, because the *"committee noted that the mean number of cycles of brentuximab vedotin received by the intention-to-treat population in SG035-0004 was 8.2 cycles. The clinical expert highlighted that real-world evidence from the Cancer Drugs Fund suggests that the median number of cycles for brentuximab vedotin is 5 to 6". The discussion regarding this issue ended as follows: "The committee accepted that most people in clinical practice would have fewer cycles than specified in the summary of product characteristics and the SG035-0004 trial, and agreed this should be considered in its decision-making"*.[39] For this reason, the ERG considers that the number of 8.2 treatment cycles for second-line BV is likely to deviate from the maximum number of treatment cycles that are administered in UK clinical practice. This deviation is more substantial than the one observed for the average number of treatment cycles in the front-line setting in ECHELON-2. Therefore, in the ERG base-case described in section 7.1.2 of this report, it was assumed that the use of BV as a second-line monotherapy consisted of six cycles.

6. COST EFFECTIVENESS RESULTS

6.1 Company's cost effectiveness results (ITT population)

The company's base-case cost effectiveness results are shown in Table 6.1.[1] These results indicate that BV+CHP was both, more costly and more effective, than CHOP. The incremental costs and QALYs were [redacted] and [redacted], respectively. This resulted in an ICER of £24,901 per QALY gained. Importantly, the base-case results were based on the PAS cost price of BV.

Table 6.1: Company base-case cost effectiveness results (ITT population, BV PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CHOP	[redacted]	10.04	[redacted]	[redacted]	1.55	[redacted]	£24,901
BV+CHP	[redacted]	11.59	[redacted]				

Based on Table 59 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

The disaggregated discounted QALYs by health state are given in Table 6.2 and the disaggregated discounted costs by cost category are given in Table 6.3. The majority of the difference in QALYs between treatment arms is found in the progression-free health state, where BV+CHP provided an additional [redacted] QALYs compared to CHOP.

The largest differences in costs across treatment arms are due to acquisition costs, which resulted in [redacted] difference for BV+CHP compared to CHOP. Second-line treatment costs for the BV+CHP arm were [redacted] lower than for the CHOP arm. However, it should be noted that [redacted] of these costs saved in second-line therapies were caused by BV being used post-progression in the CHOP arm. In the BV+CHP arm, post-progression BV was not permitted due to re-treatment, as explained in e.g. section 5.2.6.2 of this report. Consolidative therapy costs were [redacted] higher in the BV+CHP arm.

Table 6.2: Summary of QALY gain by health state (ITT population, BV PAS price, discounted)

Health state	QALY CHOP	QALY BV+CHP	Absolute increment	%absolute increment
QALYs in progression-free state	[redacted]	[redacted]	[redacted]	[redacted]
QALYs in progressive state	[redacted]	[redacted]	[redacted]	[redacted]
QALY gain due to SCT	[redacted]	[redacted]	[redacted]	[redacted]
QALY loss due to AEs	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 5 in Appendix J of the CS[75]
AE = adverse event; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; QALY = quality-adjusted life year; SCT = stem cell transplant

Table 6.3: Summary of predicted resource use by category of cost (ITT population, BV PAS price, discounted)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on Table 7 in Appendix J of the CS[75]

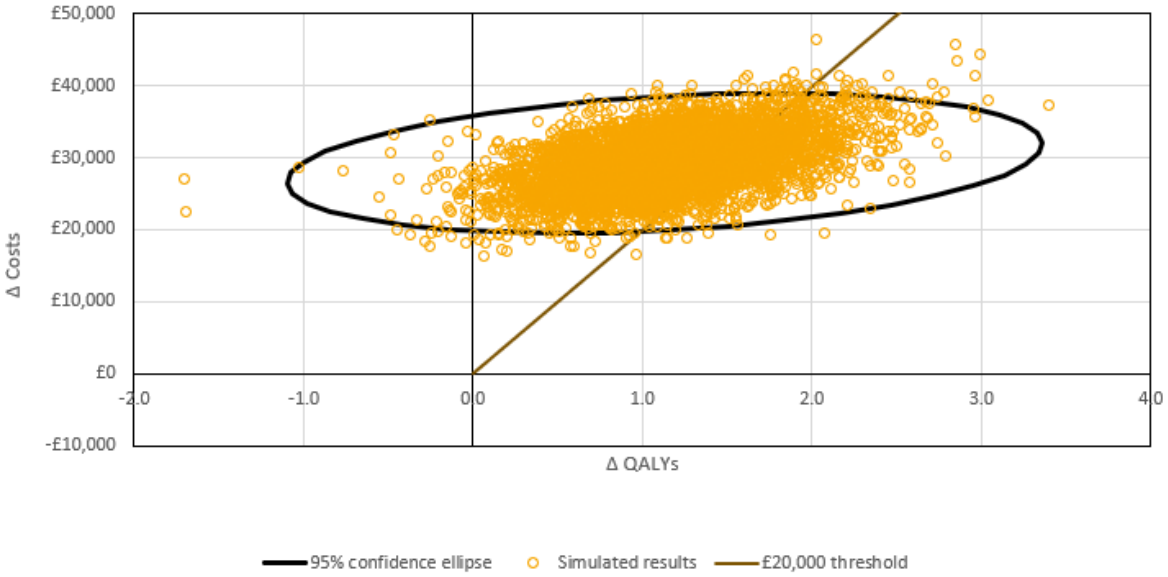
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; SCT = stem cell transplant

6.2 Company's sensitivity analyses

6.2.1 Probabilistic sensitivity analysis (ITT population)

The parameters and the probability distributions used in the PSA are shown in Table 57 of the CS.[1] The probabilistic ICER based on 5,000 Monte Carlo simulations was reported in section B.3.8.1.2 (p.124) of the CS.[1] This was £25,741 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £840 larger than the deterministic ICER. The resulting cost effectiveness plane (CE-plane) and cost effectiveness acceptability curve (CEAC) are shown in Figures 6.1 and 6.2, respectively. The CEAC shows that the probability of BV+CHP being cost effective was 64% at a threshold ICER of £30,000 per QALY gained, and 22% at a threshold ICER of £20,000 per QALY gained.

Figure 6.1: CE-plane of company's PSA results (ITT population)



Based on Figure 30 of the CS[1]

Δ = incremental, CE = cost effectiveness, CS = company submission; ITT = intention-to-treat; PSA = probabilistic sensitivity analysis, QALYs = quality-adjusted life years

Figure 6.2: CEAC of company's PSA results (ITT population)

Based on Figure 31 of the CS[1]

CEAC = cost effectiveness acceptability curve; CS = company submission; ITT = intention-to-treat; PSA = probabilistic sensitivity analysis

ERG comment: The PSA results reported in the CS did not match with those displayed in the electronic model submitted by the company. The PSA results in the electronic model are shown in Table 6.4. This probabilistic ICER in the electronic model was £27,987 per QALY gained, which is £2,246 larger than the probabilistic ICER reported in the CS. The CE-plane and the CEAC in the model (not shown here) are similar to those presented in the CS (Figures 6.1 and 6.2 in this report) but, in the model, the probability of BV+CHP being cost-effective was 57% at a threshold ICER of £30,000 per QALY gained, and 13% at a threshold ICER of £20,000 per QALY gained; thus, lower than those presented in

the CS. Nevertheless, the ERG is uncertain as to whether the PSA results displayed in the model were obtained under the company's base-case assumption.

Table 6.4: Company base-case probabilistic cost effectiveness results in the electronic model (ITT population, BV PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
BV+CHP	[redacted]	NR	[redacted]	[redacted]	NR	[redacted]	£27,987
CHOP	[redacted]	NR	[redacted]				

Based on electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year

The probability distributions used in the PSA shown in Table 57 of the CS seem appropriate.[1] However, it appears as if there was a reporting error in that table: AE rates are reported as included in the PSA through a log-normal distribution but the model uses the number of events (instead of rates) as input parameters and these are not varied in model. However, it is unclear why the following parameters were not included in the company's PSA:

- Age and percentage of females: other patient characteristics such as BSA and weight were included in the PSA. The rationale for excluding age and the percentage of females should have been provided by the company.
- The mortality multiplier could have been included in the PSA since the clinical experts provided a range of variation (see section 5.2.6.3 for details).
- The number of adverse events (for all adverse events in both arms – 18 input parameters in total) could have been included in the PSA by assuming a Poisson distribution or, alternatively, adverse event rates assuming a Beta distribution.
- The additional disutility of -0.33 applied to grade 3-4 peripheral neuropathy should have been included in PSA. A Beta distribution could have been used for this, as done with other utility parameters. In the absence of data to fit a Beta distribution, a simple uniform distribution could have been used to represent the uncertainty around this parameter.
- Number of treatment cycles of second-line BV.

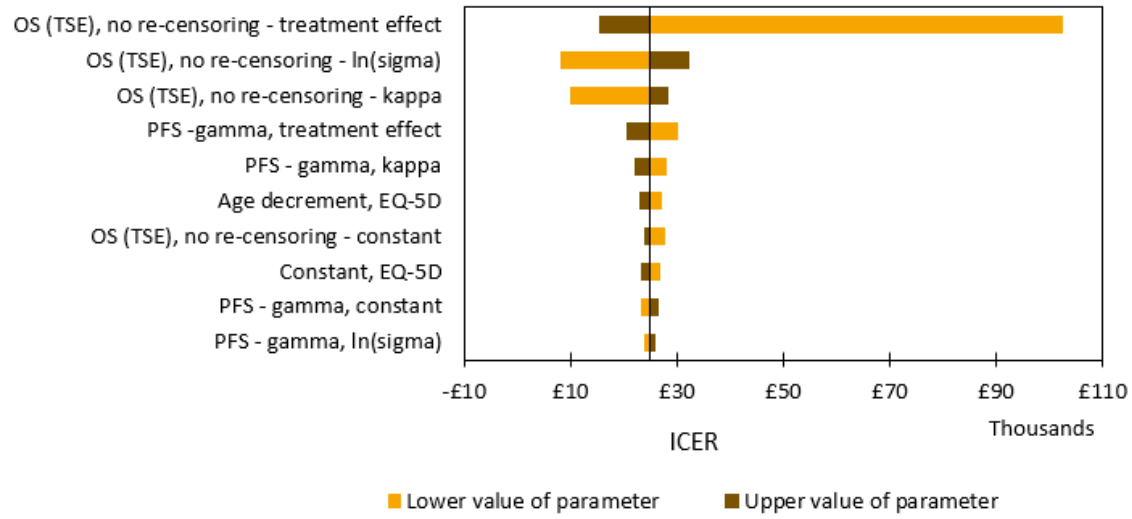
The ERG considers that the 23 input parameters mentioned above could have been included in the company's PSA. For that reason, the current PSA is likely to underestimate the overall parameter uncertainty associated with model results. It is difficult to quantify how much the PSA results would change if these uncertainties were taken into account in the model. With the exception of age, and possibly to a lower extent the number of treatment cycles for second-line BV, all those parameters are expected to have a minor impact on the ICER.

6.2.2 Deterministic sensitivity analysis (ITT population)

A univariate, deterministic sensitivity analysis was performed by the company in which the base-case values of individual model parameters were varied. One-by-one, the parameters were independently varied according to their respective 95% CIs. In case estimates for CIs were not available, a variation of + and - 15% of the base-case values was used. For each parameter that was varied, the ICER was calculated based on the lowest and highest value used. Figure 6.3 shows the tornado diagram of the 10 most influential parameters. The majority of these parameters was related to the extrapolation of OS

and PFS curves, with the largest impact on the ICER caused by variation in the estimate for the treatment effect of BV+CHP vs. CHOP (the only scenario where the ICER was above £30,000 per QALY gained). This suggests that the cost effectiveness results are primarily driven by gains in (overall) survival.

Figure 6.3: Tornado diagram: impact on ICER (ITT population)



Based on Figure 32 of the CS[1]
CS = company submission; EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; OS = overall survival; PFS = progression-free survival; TSE = two-stage estimator

ERG comment: The ERG considers it appropriate to use the 95% CIs as upper and lower bounds for the deterministic sensitivity analysis. In the absence of confidence intervals, the range ±15% of the base-case value seems arbitrary and might be narrow for some parameters, thereby not fully reflecting a range of values that are plausible. The ERG considers a range ±25% of the base-case values, even though still arbitrary, a more conservative choice in light of the uncertainty in the range of plausible values.

Furthermore, the same parameters that were not included in the PSA, were not considered for the univariate sensitivity analysis either. From these, age would be expected to be one of the most influential parameters.

6.2.3 Scenario analyses (ITT population)

In order to assess the impact of key structural assumptions on the cost effectiveness results, a series of scenario analyses was performed by the company. The results of the scenario analyses conducted by the company are shown in Table 6.5. The scenarios in which alternative assumptions had the largest impact on the ICER were those that assumed a reduced time horizon (+353% using a time horizon of 5 years), alternative parametric distributions for extrapolation of survival curves (-16% for Gompertz, -26% for Log-logistic, -19% for Lognormal, and -39% for Weibull), and adjusted discount rates (-23% using a discount rate of 1.5% for costs and outcomes), see Table 6.6.

Table 6.5: Summary of structural assumptions assessed in scenario analyses

Area of uncertainty	Base-case	Scenario
Adjustment for subsequent BV (treatment switching)	TSE, no re-censoring	Re-censoring
		Unadjusted analysis (including costs and effects of subsequent BV)
Time horizon	Lifetime (maximum 100 years)	5 years
		10 years
Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes
		6% for costs, 1.5% for outcomes
Adverse event disutility	–0.029	0.0
Mortality multiplier for patients in long term remission	1.19 (5% mortality)	1.42 (10% mortality)
Distributions for OS and PFS	Gamma	Gompertz, log-normal, log-logistic, Weibull
HRQoL approach	Progressed disutility	Time to death approach
Cost of stem cell transplant	TA478 & TA478	AutoSCT: TA567
		alloSCT: TA577
Drug wastage	Applied	Not applied
Time on treatment	As per ECHELON-2	ECHELON-2 distribution capped at 6 cycles
		All patients receive 6 cycles
Concomitant medication use	All patients receive concomitant medications	No patients receive concomitant medications

Based on Table 61 in the CS[1]
alloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; BV = brentuximab vedotin; CS = company submission; HRQoL = health-related quality of life; OS = overall survival; PFS = progression-free survival; TA = technology appraisal; TSE = two-stage estimator

The results of the scenario analyses conducted by the company are shown in Table 6.6. The scenarios in which alternative assumptions had the largest impact on the ICER were those that assumed a reduced time horizon (+353% using a time horizon of five years), alternative parametric distributions for extrapolation of survival curves (-16% for Gompertz, -26% for log-logistic, -19% for lognormal, and -39% for Weibull), and adjusted discount rates (-23% using a discount rate of 1.5% for costs and outcomes).

Table 6.6: Results of the company's scenario analyses

Area of uncertainty	Base-case	Scenario	ICER (£/QALY)	% change from base-case
Time horizon	Lifetime (100 years)	5 years	£112,854	353%
		10 years	£55,222	122%
Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	£19,118	-23%
		6% for costs, 1.5% for outcomes	£19,179	-23%

Area of uncertainty	Base-case	Scenario	ICER (£/QALY)	% change from base-case
Adjustment for subsequent BV (treatment switching)	TSE, no re-censoring	Re-censoring	£28,222	13%
		No TSE	£27,264	9%
Adverse event disutility	–0.029	0	£24,884	0%
Multiplier for patients in long term remission	1.19 (5% mortality)	1.42 (10% mortality)	£25,612	3%
Distributions for OS and PFS	Gamma	Gompertz	£20,908	-16%
		Log-logistic	£18,455	-26%
		Lognormal	£20,146	-19%
		Weibull	£15,137	-39%
HRQoL approach	Progressed disutility	Time to death approach	£25,773	4%
Cost of stem cell transplant	TA478	TA567	£24,949	0%
		TA577	£24,901	0%
Time on treatment	As per ECHELON-2	ECHELON-2 distribution capped at 6 cycles	£23,096	-7%
		All patients receive 6 cycles	£24,269	-3%
Concomitant medication use	All patients receive concomitant medications	No patients receive concomitant medications	£24,850	0%

Based on Table 62 of the CS[1]
BV = brentuximab vedotin; CS = company submission; HRQoL = health-related quality of life; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; TA = technology appraisal; TSE = two-stage estimator

ERG comment: The impact of some key assumptions was not sufficiently tested. While the company did conduct scenarios varying the OS and PFS distributions, these all considered the same type of distribution for both OS and PFS. Furthermore, a stratified modelling approach was not explored. Additionally, no scenarios were conducted for the baseline age of the patient population or the number of treatment cycles for second-line BV.

6.2.4 Subgroup analyses

Following EMA regulations relating to the previous conditional approval of BV for R/R sALCL, an analysis of the sALCL subgroup was a key secondary endpoint of the ECHELON-2 trial.[18] In contrast to the sALCL subgroup, ECHELON-2 was not designed nor powered to look at outcomes by other subtypes of PTCL. In addition, the treatment pathway relevant for patients with sALCL differs from those with other PTCL subtypes. Therefore, the cost effectiveness of BV+CHP compared to CHOP in patients with sALCL was studied separately by the company. The approach taken was similar to the

one followed with the ITT population. Appendix 3 of this report summarises the methodology used for this subgroup analysis and the sALCL subgroup-specific input parameters.

The cost effectiveness results for the sALCL population are shown in Table 6.7. As in the base-case analysis, for the ITT population, BV+CHP was found to be more costly and more effective than CHOP, with incremental costs of [redacted] and [redacted] incremental QALYs, resulting in an ICER of £18,840 per QALY gained.

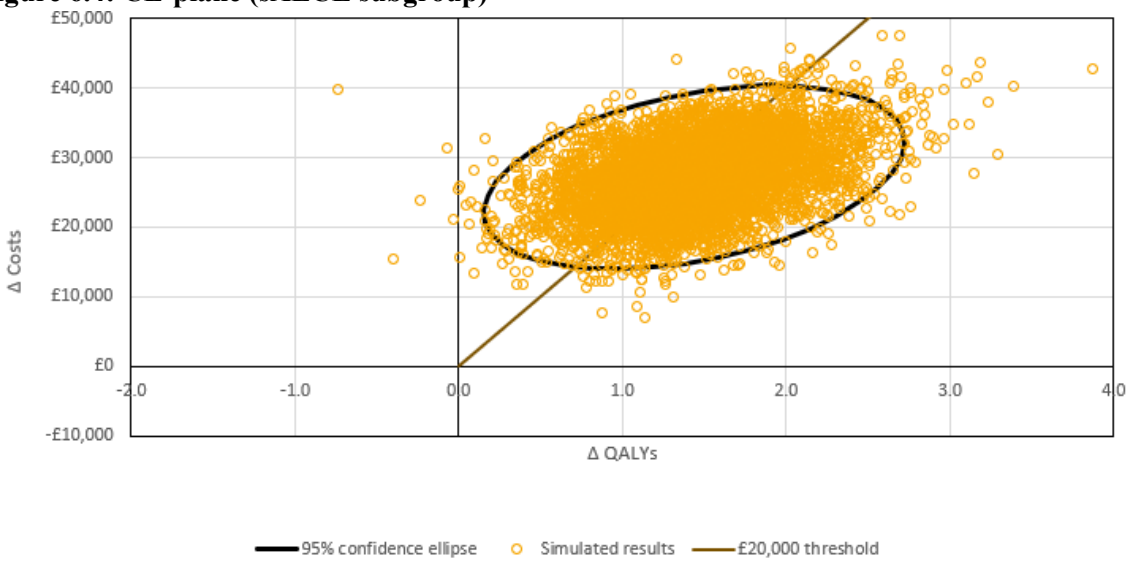
Table 6.7: Company's cost effectiveness results (sALCL subgroup, BV PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CHOP	[redacted]	11.26	[redacted]	[redacted]	1.86	[redacted]	£18,840
BV+CHP	[redacted]	13.12	[redacted]				

Based on Table 70 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year.

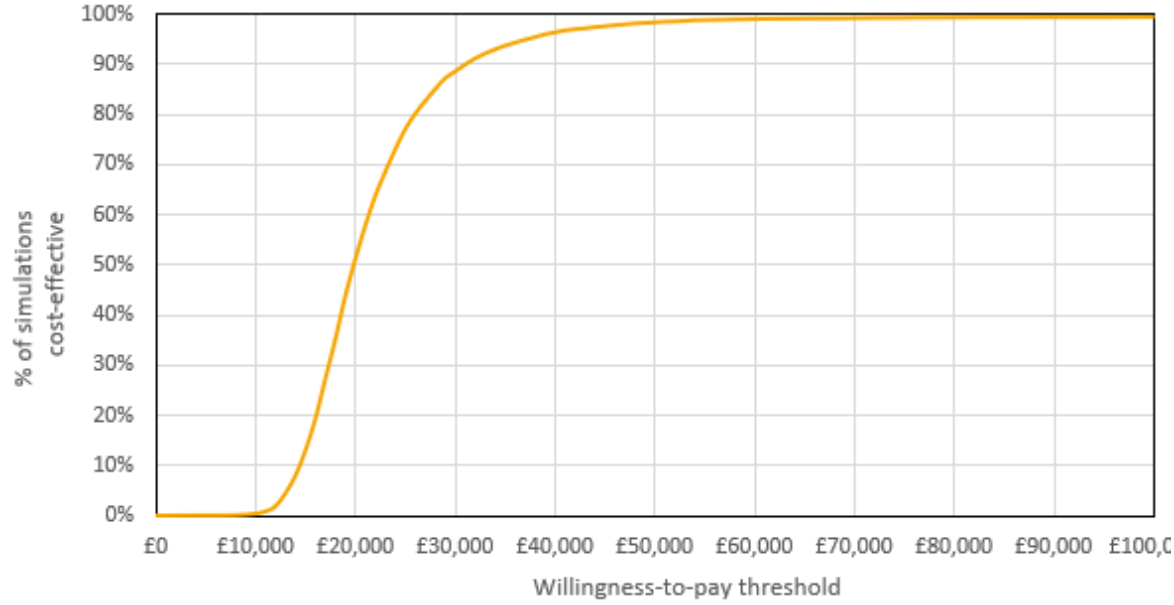
The probabilistic ICER for the sALCL subgroup was £18,915 per QALY gained ([redacted] incremental QALYs at [redacted] additional costs), thus, £75 larger than the deterministic ICER. The CE-plane and the CEAC are shown in Figures 6.4 and 6.5, respectively. The CEAC shows that the probability of BV+CHP being cost effective was 90% at a threshold ICER of £30,000 per QALY gained, and 57% at a threshold ICER of £20,000 per QALY gained.

Figure 6.4: CE-plane (sALCL subgroup)



Based on Figure 37 of the CS[1]
Δ = incremental, CE = cost effectiveness; CS = company submission; QALYs = quality-adjusted life years; sALCL = systemic anaplastic large cell lymphoma

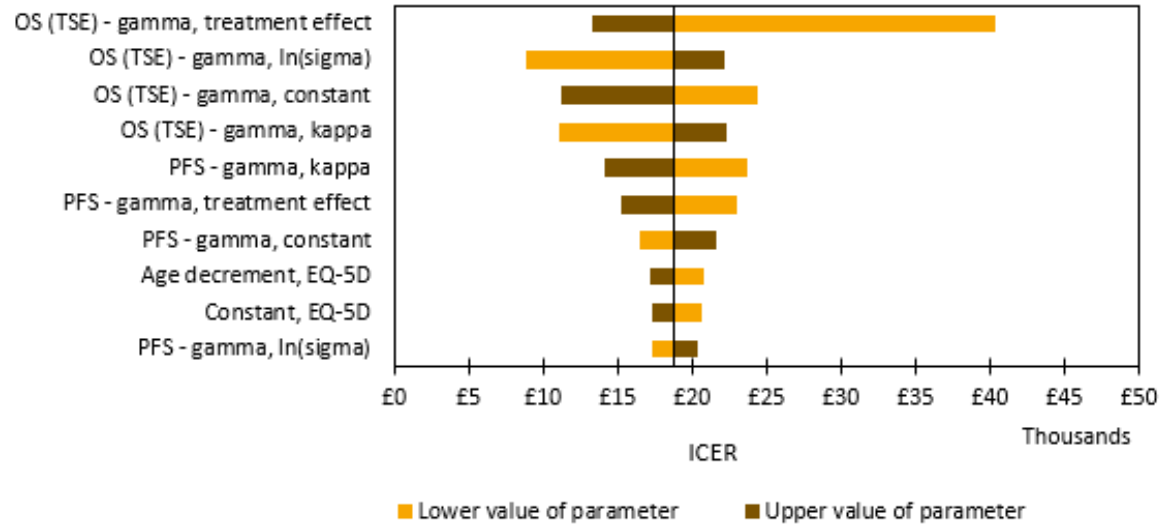
Figure 6.5: CEAC (sALCL subgroup)



Based on Figure 38 of the CS[1]
CEAC = cost effectiveness acceptability curve; CS = company submission; sALCL = systemic anaplastic large cell lymphoma

Figure 6.6 shows the tornado diagram of the ten most influential parameters. As with the ITT analysis, the majority of these parameters was related to the extrapolation of OS and PFS curves, with the largest impact on the ICER caused by variation in the estimate for the treatment effect of BV+CHP vs. CHOP.

Figure 6.6: Tornado diagram: impact on ICER (sALCL subgroup)



Based on Figure 39 of the CS[1]
EQ-5D = EuroQol-5 dimensions; CS = company submission; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; sALCL = systemic anaplastic large-cell lymphoma; TSE = two-stage estimator

The results of the scenario analyses for the sALCL subgroup are shown in Table 6.8. None of the scenarios explored by the company (except those considering a shorter time horizon) resulted in an ICER that exceeded £30,000 per QALY.

Table 6.8: Results of the company's scenario analyses (sALCL population)

Area of uncertainty	Base-case	Scenario	ICER (£/QALY)	% change from base-case
Time horizon	Lifetime (100 years)	5 years	£80,189	326%
		10 years	£40,142	113%
Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	£14,488	-23%
		6% for costs, 1.5% for outcomes	£14,724	-22%
Adjustment for subsequent BV (treatment switching)	TSE, no re-censoring	TSE, re-censoring	£17,632	-6%
		No TSE	£22,954	22%
Adverse event disutility	–0.029	0	£18,830	0%
Multiplier for patients in long term remission	1.19 (5% mortality)	1.42 (10% mortality)	£20,200	3%
Distributions for OS and PFS	Gamma	Gompertz	£18,390	-6%
		Log-logistic	£13,051	-33%
		Lognormal	£13,678	-30%
		Weibull	£10,957	-44%
HRQoL approach	Progressed disutility	Time to death approach	£19,414	3%
Cost of stem cell transplant	TA478	TA567	£18,900	0%
		TA577 (alloSCT only)	£18,840	0%
Time on treatment	As per ECHELON-2	ECHELON-2 distribution capped at 6 cycles	£17,197	-9%
		All patients receive 6 cycles	£17,708	-6%
Concomitant medication use	All patients receive concomitant medications	No patients receive concomitant medications	£18,734	-1%

Based on Table 72 of the CS[1]
BV = brentuximab vedotin; CS = company submission; HRQoL = health-related quality of life; OS = overall survival; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma; TA = technology appraisal; TSE = two-stage estimator

6.3 Model validation and face validity check

In the validation section of the CS (B.3.10),[1] the company discussed several aspects of validation.

Regarding validation of the electronic model, the company indicated that quality control was initially performed by the model developers and, subsequently, as part of the NICE preliminary independent

model advice (PRIMA) Express process.[76] Results from the quality control performed by the model developers were not reported. The NICE PRIMA Express process focuses on *"verification of the computerised model and model fit, assessment of model transparency and usability, and identification of errors found in the technical documentation provided by the company"*.[76] The overall assessment of the model was positive in general and areas for improvement were related to improving the transparency on the way the survival curves were presented and reducing running time.

Validation of the model outcomes (operational validation) was also reported. The company mentioned that, during the model development phase, the model results were cross-validated with those of a state transition model that was also populated with ECHELON-2 data and that results were highly congruent between both modelling approaches. However, these results were not reported. As mentioned in section 5.1.3 of this report, the systematic review conducted by the company identified the study by Feldman et al. 2019.[77] This was a US study assessing the cost effectiveness of first-line BV+CHP in patients with CD30+ PTCL in which data from the ECHELON-2 trial were used to inform the model inputs. The model used by Feldman et al. resulted in 2.92 additional years in PFS and 3.38 additional years in OS for BV+CHP patients compared to CHOP patients. The model in the current submission resulted in 2.16 additional years for PFS and 2.56 additional years for OS, for BV+CHP compared to CHOP. The study by Feldman et al. also reported 1.79 incremental QALYs for BV+CHP compared to CHOP, whereas in this submission (base-case) these were 1.17.[77] Note that the reported additional years are undiscounted but the QALYs are discounted. The company could not explain these differences because for the Feldman et al. study only an abstract was available. The company further referred to Appendix J to the CS for a comparison of clinical outcomes predicted by the model (unadjusted for treatment switching) and empirical data from ECHELON-2.[75] This suggested a complete exercise on dependent validation (data form ECHELON-2 were used in the model) but only OS estimates at 6, 12, 24, 36 and 48 months were compared to those observed in ECHELON-2 (see Table 2 of Appendix J of the CS).[75] Despite the OS estimated by the model being in line with those observed in the trial, this exercise is of limited use.

Regarding independent validation (against data that were not used in the model), the company noted that in the ECHELON-2 trial, patients in the CHOP arm showed in general better median PFS (20.8 months) and median OS (not reached) than those suggested in historical cohorts,[18] even though the later are not reported in the CS. The company potentially attributed these differences in clinical outcomes to patients being in a clinical trial (ECHELON-2), and a larger proportion of patients with sALCL, even though the trial inclusion criteria did not allow patients with ALK+ sALCL with a favourable prognostic IPI score of 0-1 to be enrolled. However, according to the company, available clinical data in untreated CD30+ PTCL patients are usually low-quality, and mostly based on single-arm phase II trials or retrospective analyses, showing a wide range of variation in clinical outcomes, which makes independent validation difficult.

The company also asked clinical experts to judge the appropriateness (face validity) of several aspects of the model (conceptual model, input data and model outcomes). For this purpose, the company conducted two advisory board meetings in February 2019 and June 2019. Details about these meetings were provided in the CS and in response to the request for clarification (question B6).[16, 17, 43] Outside the advisory boards meetings, clinical experts were also asked by the company to provide additional feedback on the prognostic factors that were used to adjust OS for BV re-treatment (details provided in Appendix N of the CS),[60] on the modelling of excess mortality for long-term survivors and on the resource use associated with adverse events.

Finally, the company indicated that, where possible, model inputs were validated using the R/R sALCL NICE submission (TA478) and that HRQoL and resource use inputs were directly informed from TA478 and TA577.[39, 42]

ERG comment: The company covered, to some extent, all relevant aspects of validation.

The NICE PRIMA Express process was useful in pointing out both strengths of the model and aspects where it could be improved. The overall assessment of the model was positive in general.[76] Results reported in Table 2 of the PRIMA Express report, however, could not be reproduced by the ERG in the version of the model submitted accompanying the CS. This suggests that, based on the suggestions received, some changes were made to the model after the PRIMA Express report was finished. While this seems completely reasonable, it would have been useful to report what changes were made and in what way these changes affected the ICER. As shown in Table 6.9, the model assessed the PRIMA Express report estimated more incremental costs and more incremental QALYs than the current model used for this submission (note that results in the PRIMA Express report are based on a stratified approach).

Table 6.9: Scenarios using alternative survival curves in PRIMA Express report and final company's model (BV list price)

Distribution	PRIMA Express report				Model (stratified approach)			
	LYs CHOP	Inc. costs	Inc. QALYs	ICER	LYs CHOP	Inc. costs	Inc. QALYs	ICER
Generalised gamma (base-case)	9.90	[redacted]	[redacted]	£25,103	9.75	[redacted]	[redacted]	£23,065
Exponential	6.22	[redacted]	[redacted]	£25,895	6.23	[redacted]	[redacted]	£22,917
Gompertz	11.22	[redacted]	[redacted]	£31,041	10.98	[redacted]	[redacted]	£29,278
Log-logistic	9.15	[redacted]	[redacted]	£26,191	9.04	[redacted]	[redacted]	£23,562
Lognormal	9.66	[redacted]	[redacted]	£25,653	9.52	[redacted]	[redacted]	£23,002
Weibull	8.27	[redacted]	[redacted]	£23,843	8.22	[redacted]	[redacted]	£21,581

Based on Table 2 of the PRIMA Express report and the electronic model of the CS.[48, 76]

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; ICER = incremental cost effectiveness ratio; LYG = life years gained; PRIMA = preliminary independent model advice; QALY = quality-adjusted life year

Additionally, upon request from the ERG (clarification question B24),[17] the company provided additional details of technical validation efforts conducted on the economic model by a health economist not involved in the development of the company's model. The model results were compared with those from a multistate model to check the structural integrity of the model. The company indicated that outcomes were similar between the two model structures but the results were not reported. The quality check conducted by the independent health economist included black box tests and double-programming (re-building the model to ensure comparable results). Tests conducted on the model included the following: setting all costs equal to zero (expected outcome: total costs equal to zero), setting all utilities equal to one (expected outcome: QALYs equal the life years), dividing the total QALYs by the total life years (expected outcome: the average utility value for the cohort – validated with the literature) and setting equal efficacy between the two treatment arms (expected outcome: efficacy results equal between treatment arms). Following this internal quality check, the company made minimal changes to the model, mainly pertaining to transparency rather than technical errors, but these changes were not reported.

Furthermore, in response to clarification question B25,[17] the company provided a comparison between the OS estimates predicted by the model and the evidence presented in section B.1.3.4 of the CS.[1] ECHELON-2 provided KM data for OS for a median follow-up of 42.1 months (95% CI, 40.4 to 43.8). Outcomes observed in ECHELON-2 were superior to the outcomes presented in the CS. The company explained that this was largely due to outdated and poor quality PTCL evidence presented in Gleeson et al. 2018 and Vose et al. 2008.[3, 6]

Vose et al. 2008 was a retrospective worldwide study that reported substantial variability in clinical practice across the centres and focused on patients diagnosed between January 1990 and December 2002.[6] Gleeson et al. 2018 was also a retrospective study considering two academic centres in the UK and focused on patients diagnosed between January 2002 and January 2012.[3] The company highlighted discrepancies in baseline characteristics (known to be prognostic) between these two studies and ECHELON-2. Patients were older in the study by Vose et al. (median age 62 vs. 58 years, respectively) and with a higher IPI score in the study by Gleeson et al. (IPI score 3-5 51% vs. 44%, respectively). According to the company, these differences are likely to lead to better outcomes in ECHELON-2. Additional differences, if any, may be explained by the study design as both Vose et al. and Gleeson et al. were retrospective studies and ECHELON-2 was a prospective, randomised, double-blind, active comparator phase III trial.

These were the only studies identified by the company showing long-term historical outcomes for patients with PTCL. However, since the management of PTCL patients has improved and evolved over recent years, the comparability of these two studies with ECHELON-2 should be assessed with caution.

7. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

7.1 Exploratory and sensitivity analyses undertaken by the ERG

7.1.1 Explanation of the company adjustments after the request for clarification

Following clarification question B8,[17] the company removed patients with ECOG PS 2 from the two-stage estimator and from the proportion of patients receiving subsequent BV, since the opposite would contradict the recommendations in TA478.[39] After this change, the ICER increased from £24,901 (company base-case) to £25,326.

7.1.2 Explanation of the ERG adjustments

The changes made by the ERG (to the model received with the response to the clarification letter) were subdivided into the following three categories, according to Kaltenthaler et al. 2016[78]:

- Fixing errors (correcting the model where the company's electronic model was unequivocally wrong).
- Fixing violations (correcting the model where the ERG considered that the NICE reference case, scope or best practice has not been adhered to).
- Matters of judgement (amending the model where the ERG considered that reasonable alternative assumptions are preferred).

After these changes were implemented in the company's model, additional scenario analyses were explored by the ERG in order to assess the impact of alternative assumptions on the cost effectiveness results.

7.1.2.1 Fixing errors

1. The cost of transfusion, which was used in the costing of anaemia and thrombocytopenia, was erroneously reported in the CS and implemented in the model using the costs of staff time for intraoperative cell salvage rather than for transfusion. The ERG used the value of £50.78 (instead of £147.11 used by the company) for the cost of transfusion.
2. Sheet "Control" cell AD415: error "#VALUE!" in formula was causing the PSA calculating erroneous costs. Formula was amended by the ERG. This change did not impact the ERG base-case.
3. Sheet "HRQOL data" cells F25 and F30 were corrected to choose the correct HRQoL approach for use in the PSA for the pre-progression utility value and post-SCT utility decrement. This also required correcting cells F340, F341, C340 and C341 in tab "Controls". This change did not impact the ERG base-case.

7.1.2.2 Fixing violations

4. TSE adjustments for OS should include ECOG PS 2 patients. This was corrected by the company after clarification, as mentioned in section 7.1.1.

7.1.2.3 Matters of judgement

5. Baseline age: 62.02 years (see section 5.2.3 for details).
6. Mortality multiplier: 1.25 to reflect 6.5% increased mortality risk (see section 5.2.6.3 for details).
7. Time to death utility approach (see section 5.2.8.3 for details).
8. Long-term utilities cannot be higher than general population utilities (see section 5.2.8.3 for details).
9. Include peripheral neuropathy costs in the model (see section 5.2.9.3 for details).

10. Six treatment cycles for second-line BV (see section 5.2.9.4 for details).
11. PSA changes (details in section 7.2.1). These changes did not affect the ERG base-case.

The overview of the changes and the bookmarks for the justification of the ERG changes are presented in Table 7.1.

Table 7.1: Company and ERG base-case preferred assumptions (ITT population)

Base-case preferred assumptions	Company	ERG	Justification for change
TSE adjustment OS	Patients with ECOG PS 2 included in TSE and proportion of patients receiving subsequent BV	Remove patients with ECOG PS 2 from the two-stage estimator and from the proportion of patients receiving subsequent BV	The opposite would contradict the recommendations in TA478.[39] (Section 5.2.6.2)
Costs of transfusion	£147.11	£50.78	Costing error. (Section 5.2.9.3)
Baseline age	55.1 years, per ECHELON-2	62.02 years, weighted average of several UK sources	Evidence suggests mean age in UK patients is larger than in ECHELON-2 (Section 5.2.3)
Mortality multiplier	1.19	1.25	Arbitrary selection made by the company. ERG selected middle pint of the estimates provided by clinical experts. (Section 5.2.6.3)
Approach to utilities	HSUV	TTD	Progressed disease utility lacked face validity. (Section 5.2.8.3)
Adjustment of long-term utilities	No	Yes	Model utilities cannot be larger than general population utilities. (Section 5.2.8.3)
Peripheral neuropathy costs	No	Yes	Align with TA478.[39] (Section 5.2.9.3)
Treatment cycles second-line BV	8.23	6	Align with TA478 recommendation and committee discussion[39] (Section 5.2.9.4)

BV = brentuximab vedotin; ECOG = Eastern Cooperative Oncology Group; ERG = Evidence Review Group; HSUV = Health State Utility Value; ITT = intention-to-treat; OS = overall survival; PS = performance status; TA = technology appraisal; TSE = two-stage estimator; TTD = time-to-death; UK = United Kingdom

7.1.3 Additional scenarios conducted by the ERG

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the survival modelling, age at baseline of the patient population, modelling of utility data and cost and resource use assumptions. Other sources of uncertainty were deemed less important and were not explored in this section. A list of scenario analyses conducted by the ERG is given below.

7.1.3.1 Scenario set 1: Alternative PFS/OS parametric distributions

As explained in sections 5.2.6.1 and 5.2.6.2, the plausibility of long-term PFS and OS extrapolations was based on clinical expert opinion, which basically ruled out all parametric curves except the generalised gamma distribution. Alternative parametric distributions, including stratified modelling, were tested in this series of scenarios.

7.1.3.2 Scenario set 2: Age at baseline

The average age of an ITT patient in ECHELON-2 was 55.10 years. In the ERG base-case analysis, the ERG assumed that the mean age of an UK PTCL patient was 62.02 years. This value was calculated as the weighted average of the age values reported in ECHELON-2 (UK patients only), Gleeson et al. 2018 (assuming median = mean),[3] and the HMRN PTCL audit (reference not provided in the response for clarification). The impact of assuming different ages at baseline age on the cost effectiveness results was explored in this series of scenario analyses.

7.1.3.3 Scenario set 3: Utility model approach

The company presented several approaches to estimating utilities. In their base-case, the company used the HSUV model, but replaced the progressive disease utility value with a value of 0.643 estimated from TA478 and Swinburn et al. 2015.[39, 40] The ERG preferred the time-to-death analysis, as models presented by the company suggested that time-to-death covariates had more impact on HRQoL than progression, the source of the progression utility did not reflect the NICE reference case and the use of a utility value from a different source adds uncertainty to the analysis regarding similarities between populations (details can be found in section 5.2.8). In this set of scenarios, the company base-case utility approach is tested as well as the HSUV model using the progressive disease decrement obtained from the model. All scenarios retained the ERG implemented assumption that utility values could not exceed the age-adjusted general population utilities obtained from Ara and Brazier 2010.[67]

7.1.3.4 Scenario set 4: Utility age adjustment

The age-adjustment coefficient obtained from the time-to-death utility model was much smaller than the yearly decrements which result from commonly used sources of age-adjusted utilities such as Ara and Brazier 2010.[67] Due to the smaller age decrement, long-term utilities for progression-free patients in the company model could be higher than age-adjusted general population utilities from Ara and Brazier. This was considered implausible and, in the ERG base-case, utilities were constrained to be less than or equal to these age-adjusted general population utilities. This scenario set compares the ERG approach of constraining utilities to the unconstrained age-adjusted utilities obtained from the company's HSUV approach (company base-case – age decrement = -0.00177) and the company's time-to-death approach (age decrement = -0.00121).

7.1.3.5 Scenario set 5: Disutility for Grade 3-4 peripheral neuropathy

The impact of grade 3-4 AEs on HRQoL was included as a covariate in the EQ-5D models run by the company. This approach assumes that the impact of grade 3-4 AEs was captured in the EQ-5D data collection and that the coefficient represents the average impact of all grade 3-4 AEs experienced in ECHELON-2. The company also included an additional (and much larger) AE disutility for grade 3-4 peripheral neuropathy but provided no justification why the impact of this particular AE would not have been captured within the EQ-5D data collection. Therefore, a scenario is performed whereby this additional decrement is removed and the impact of this AE is assumed to be captured in the AE model coefficient.

7.1.3.6 Scenario set 6: Alternative assumption for number of BV vials per treatment cycle

In this scenario, a dosage, including wastage, of four vials of BV per patient was assumed. This number corresponds to the number of vials that would be used to treat "the average" patient, which is in line with the conventional approach used in cohort-based models. The ERG notes that the method applied by the company, as well as in the ERG base-case, takes into account the distribution of patient body weight and it is recommended in the literature (although not often used).[79] The average number of vials obtained using the distribution of patient body weight was 3.14. This value was used in the both the company and ERG base-case scenarios.

7.1.3.7 Scenario set 7: Alternative assumption for number of BV treatment cycles

The ERG base-case used the average number of front-line BV treatment cycles observed in ECHELON-2. On average, a patient received 6.0 treatment cycles of front-line BV. This implies that there were patients who received more than six cycles, which is the maximum number of treatment cycles used in UK standard practice. Given that on average the number of cycles received in ECHELON-2 was approximately six in both arms, the ERG agrees with the company's assumption of using the distribution of treatment cycles as observed in ECHELON-2, which is consistent with the treatment effect estimated by the company. To address the uncertainty regarding the impact of including the costs (in addition to the clinical effects, for which no adjustment can be made) of any number of treatment cycles that is beyond the maximum number that is applicable to UK clinical practice, the ERG performed a scenario analysis in which the maximum number of six treatment cycles is applied to the data from ECHELON-2.

In addition, the company assumed that the use of BV as a second-line monotherapy had a longer treatment duration (8.2 cycles on average) than as front-line (six cycles on average). As explained in section 5.2.9.4, the ERG considered that the number of 8.2 treatment cycles for second-line BV was likely to deviate from the maximum number of treatment cycles that are administered in UK clinical practice. Therefore, in the ERG base-case, it was assumed that the use of BV as a second-line monotherapy consisted of 6 cycles. The impact of assuming different numbers of second-line BV treatment cycles on the cost effectiveness results was explored in this series of scenario analyses.

7.2 Impact on the ICER of additional clinical and economic analyses undertaken by the ERG

7.2.1 Results of the ERG preferred base-case scenario (ITT population)

The results of the ERG preferred base-case are provided in Table 7.2. After, implementation of the ERG's preferred assumptions, the ICER was £33,153. BV+CHP was estimated to provide [redacted] additional QALYs at an incremental cost of £[redacted] compared to CHOP. The incremental QALY gains for BV+CHP all stemmed from the progression-free health state, as can be seen in Table 7.3. As shown in Table 7.4, incremental costs were mostly due to the additional treatment costs of BV+CHP.

Approximately [redacted]% of these incremental costs were saved in second-line therapies. However, it should be noted that [redacted]% of the costs saved in second-line therapies were caused by BV being used post-progression in the CHOP arm. In the BV+CHP arm, post-progression BV was not permitted due to re-treatment, as explained e.g. in section 5.2.6.2 of this report. Consolidative therapy costs were also [redacted]% higher in the BV+CHP arm.

Table 7.2: ERG base-case deterministic results for the ITT population (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
BV+CHP	[redacted]	10.41	[redacted]	[redacted]	1.32	[redacted]	£33,153
CHOP	[redacted]	9.10	[redacted]				

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; LYG = life years gained; QALY = quality-adjusted life year

Table 7.3: ERG base-case disaggregated discounted QALYs (ITT population)

Health state	QALY CHOP	QALY BV+CHP	Absolute increment	%absolute increment
QALYs in progression-free state	[redacted]	[redacted]	[redacted]	[redacted]
QALYs in progressive state	[redacted]	[redacted]	[redacted]	[redacted]
QALY gain due to SCT	[redacted]	[redacted]	[redacted]	[redacted]
QALY loss due to AEs	[redacted]	[redacted]	[redacted]	[redacted]
QALYs loss to death	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]

Based on electronic model of the CS[48]
AE = adverse event; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; QALY = quality-adjusted life year; SCT = stem cell therapy

Table 7.4: ERG base-case disaggregated costs (ITT population)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Total second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Second-line BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Total consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; LYG = life years gained; QALY = quality-adjusted life year

The ERG also conducted a PSA using their preferred base-case assumptions. As explained in section 6.2.1, the ERG considered that a total of 23 input parameters should have been included in the PSA but these were kept fixed by the company. Ideally, this should have been done by providing 95% CIs for all these parameters. Since this was not possible, the ERG decided to use arbitrary ranges of variation to account for some uncertainty associated to these parameters. The following adjustments were made to the PSA by the ERG:

- Age: normal distribution with additional constraint that age cannot be lower than 55 years.
- Percentage of females: Beta distribution based on total number of patients in ECHELON-2.
- Mortality multiplier: normal distribution with range of variation (1.10, 1.42).
- Number of adverse events (18 parameters in total): log-normal distribution with arbitrary standard error.
- Additional disutility of -0.33 applied to grade 3-4 peripheral neuropathy: normal distribution with arbitrary range of variation.
- Number of treatment cycles of second-line BV: normal distribution with range of variation (4, 8).

In addition, as explained in section 5.2.6.2, the OS adjustment for ECOG PS 2 patients was not included in the PSA. Only the estimated regression coefficients were available but the covariance matrix was missing from the model. Excluding these parameters from the PSA has a large impact on the results because OS-related parameters are those carrying most of the parameter uncertainty in this model. In the absence of the correct covariance matrix, the ERG assumed for their PSA the same covariance matrix as in the company base-case (unadjusted OS for ECOG PS 2 patients) and further modelled these parameters according to a multivariate normal distribution.

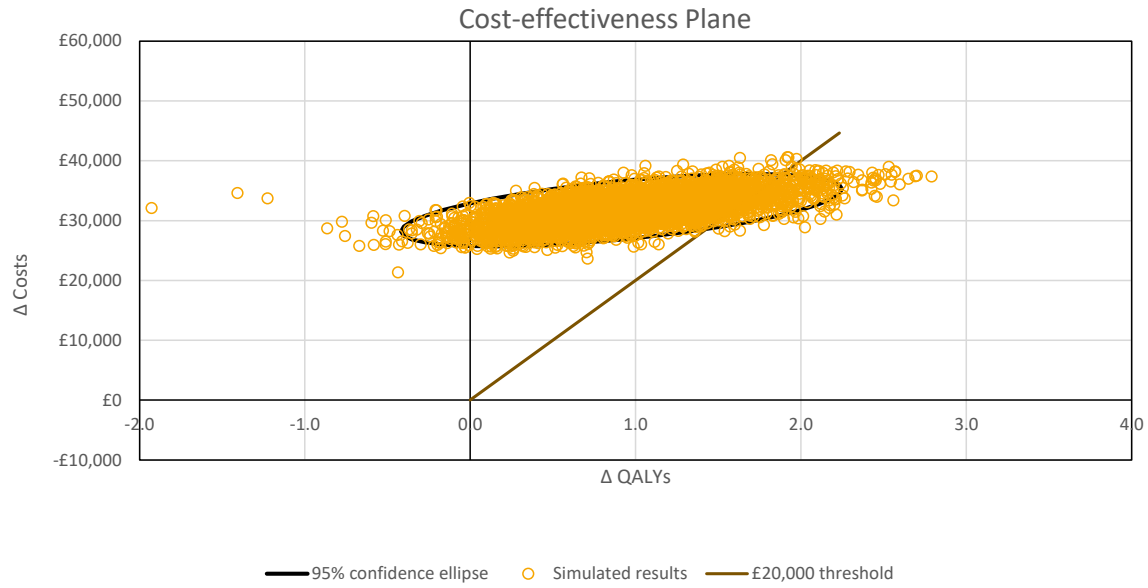
Based on all the issues described above, it should be emphasised that the results of the ERG PSA should be interpreted as an approximation. The PSA results obtained after the ERG adjustments can be seen in Table 7.5. The probabilistic ICER was £34,690 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £1,537 larger than the ERG deterministic ICER. This difference is mostly due to the probabilistic model estimating less incremental QALYs than the deterministic one. The resulting CE-plane and CEAC are shown in Figure 7.1 and 7.2, respectively. The CEAC shows that the probability of BV+CHP being cost-effective was 35% (as opposed to 64% in the company's PSA) at a threshold ICER of £30,000 per QALY gained, and 7% (as opposed to 22% in the company's PSA) at a threshold ICER of £20,000 per QALY gained. This increased uncertainty was the result of including the aforementioned 23 additional parameters in the PSA: while the effect on the ICER can be considered minor, the impact on cost effectiveness probabilities was much larger.

Table 7.5: ERG base-case probabilistic results for the ITT population (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
BV+CHP	[redacted]	NR	[redacted]	[redacted]	NR	[redacted]	£34,690
CHOP	[redacted]	NR	[redacted]				

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; ITT = intention-to-treat; LYG = life years gained; NR = not reported; QALY = quality-adjusted life year.

Figure 7.1: ERG preferred cost effectiveness plane (ITT population)



Based on the electronic model of the CS[48]
Δ = incremental; CS = company submission; ITT = intention-to-treat; QALY = quality-adjusted life year

Figure 7.2: ERG preferred cost effectiveness acceptability curve (ITT population)

Based on the electronic model of the CS[48]
CS = company submission; ITT = intention-to-treat

The adjustments made to the PSA by the ERG also had an impact on the univariate sensitivity analyses since the model uses the same range of variation for each input parameter to calculate the tornado diagram. Unfortunately, after the changes made by the ERG, the tornado diagram functionality in the model did not work. Given the time constraints associated to this project, the ERG could not correct this and, for that reason, the tornado diagram for the ERG base-case is not presented here. The ERG expects that this tornado diagram would not differ much from the one presented by the company in section 6.2.2 of this report, being "age at baseline" possibly the only exception.

7.2.2 Results of the ERG additional exploratory scenario analyses (ITT population)

7.2.2.1 Scenario set 1: Alternative PFS/OS parametric distributions

For their base-case, the ERG selected a generalised gamma distribution, obtained from a joint modelling approach, to model the long-term extrapolations of both PFS and OS, as in the company base-case. In the scenarios conducted by the company (see section 6.2.3), the same distribution was considered for PFS and OS. The ERG considered that PFS and OS could be modelled using different distributions based on goodness-of-fit criteria (usually only treatment arms are constrained to using the same distribution). Furthermore, the stratified approach was not explored by the company but the ERG considered it more plausible.

The results provided in Table 7.6 were obtained by keeping the generalised gamma distribution fixed for PFS and varying the OS distribution over all possible extrapolations, including both joint and stratified modelling approaches. The highest ICER was obtained under the company and ERG base-case preferred distributions (joint generalised gamma for both OS and PFS). It is remarkable that by selecting the stratified approach, the largest difference (£9,077) was observed when the generalised gamma distribution was selected for both OS and PFS. The second largest difference was obtained when a lognormal distribution was selected (£4,554). The remaining distributions were less sensitive to the selection of the modelling approach. While this result can be explained by difference in survival

curves obtained under the joint and stratified approaches, it highlights the need for clinical plausibility of the curves obtained under the stratified approach. All ICERs obtained under the joint approach were lower than the base-case (generalised gamma for PFS and OS) ranging from £22,772 to £33,153 per QALY gained. The variation in ICERs was mainly driven by the incremental QALYs which varied from [redacted] to [redacted]. The ICERs obtained under the stratified approach were more stable, ranging from £22,911 to £27,605 per QALY gained, due also to less variation in incremental QALYs (from [redacted] to [redacted]). The highest stratified ICER was obtained assuming a Gompertz distribution for OS.

Table 7.6: ERG OS scenario analyses (PFS = generalised gamma)

OS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£33,153**	[redacted]	[redacted]	£24,076
Exponential	[redacted]	[redacted]	£22,772	[redacted]	[redacted]	£22,952
Gompertz	[redacted]	[redacted]	£29,985	[redacted]	[redacted]	£27,605
Log-logistic	[redacted]	[redacted]	£27,007	[redacted]	[redacted]	£25,208
Lognormal	[redacted]	[redacted]	£30,044	[redacted]	[redacted]	£25,490
Weibull	[redacted]	[redacted]	£23,433	[redacted]	[redacted]	£22,911

Based on the electronic model of the CS[48]
CS = company submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years

Likewise, the results shown in Table 7.7 were obtained by keeping the generalised gamma distribution fixed for OS and varying the PFS distribution over all possible extrapolations, including both joint and stratified modelling approaches. The highest ICER was also obtained under the company and ERG base-case preferred distributions (joint generalised gamma for both OS and PFS). In this case, all ICERs were more stable because basically what happens is that the OS distribution determines the overall gains in QALYs estimated by the model. Selecting different PFS distributions had little impact on this. All ICERs obtained under the stratified approach were lower than all ICERs obtained under the joint approach. This was caused by the difference in incremental QALYs between both approaches ([redacted] and [redacted]).

Table 7.7: ERG PFS scenario analyses (OS = generalised gamma)

PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£33,153**	[redacted]	[redacted]	£24,076
Exponential	[redacted]	[redacted]	£29,844	[redacted]	[redacted]	£21,993
Gompertz	[redacted]	[redacted]	£33,025	[redacted]	[redacted]	£25,786
Log-logistic	[redacted]	[redacted]	£30,325	[redacted]	[redacted]	£22,830
Lognormal	[redacted]	[redacted]	£30,757	[redacted]	[redacted]	£22,891
Weibull	[redacted]	[redacted]	£29,226	[redacted]	[redacted]	£22,732

Based on the electronic model of the CS[48]

PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
CS = company submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years						

Finally, the results shown in Table 7.8 were obtained by assuming the same probability distribution for OS and PFS, including both joint and stratified modelling approaches. Also, in this set of scenarios, the highest ICER was obtained under the company and ERG base-case preferred distributions (joint generalised gamma for both OS and PFS). Across distributions, the largest difference between the stratified and the joint approach was observed when the generalised gamma distribution was selected for both OS and PFS (£9,077). The second largest difference was obtained when a lognormal distribution was selected (£3,611). Note that all combinations of OS and PFS distributions are possible. The ERG also run scenarios testing all possible combinations (not shown here) and observed that the highest ICER under the joint approach was obtained when a generalised gamma was selected for both OS and PFS (£33,153, ERG base-case) and the highest ICER under the stratified approach was obtained when a Gompertz distribution was selected for both OS and PFS (£29,356, in Table 7.8). All the remaining combinations of OS and PFS distributions (not only restricted to the same distribution for OS and PFS) resulted in lower ICERs.

Table 7.8: ERG PFS scenario analyses (OS distribution = PFS distribution)

OS/PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£33,153**	[redacted]	[redacted]	£24,076
Exponential	[redacted]	[redacted]	£20,048	[redacted]	[redacted]	£20,619
Gompertz	[redacted]	[redacted]	£29,859	[redacted]	[redacted]	£29,356
Log-logistic	[redacted]	[redacted]	£24,536	[redacted]	[redacted]	£23,804
Lognormal	[redacted]	[redacted]	£27,825	[redacted]	[redacted]	£24,214
Weibull	[redacted]	[redacted]	£20,105	[redacted]	[redacted]	£21,213
Based on the electronic model of the CS[48] CS = company submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years						

7.2.2.2 Scenario set 2: Age at baseline

The choice of age at baseline had a substantial impact on the model results. As can be seen in Table 7.9, the smaller the baseline age, the lower the ICER. This is mostly due to the incremental QALYs predicted by the model in each scenario (decreased as age increased). The ICER obtained assuming 55.10 years at baseline, as in the company base-case, was £27,746 per QALY gained; thus, £5,407 lower than the ERG base-case.

Note that the minimum baseline age for which the model runs is 55 years. Otherwise, the model gives an error in the utility calculation. This is because general population utilities have been implemented for patient 55 years and older. Due to the time constraints associated to this project, the ERG could not correct this and, for that reason, scenarios assuming an age smaller than 55 years were not run.

Table 7.9: Age at baseline

Age at baseline (years)	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
55.10 (company base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,746
58 (Gleeson et al. 2018)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,641
60.9 (UK population in ECHELON-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,032
62.02 (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£33,153**
[redacted] (HMRN PTCL audit)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£35,241
70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£45,541
75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£61,608

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; HMRN = Haematologic Malignancy Research Network; ICER = incremental cost effectiveness ratio; incr. = incremental; PTCL = Peripheral T-cell lymphoma; sALCL = systemic anaplastic large cell lymphoma; UK = United Kingdom

7.2.2.3 Scenario set 3: Utility model approach

As can be seen in Table 7.10, changing the utility approach back to the company's base-case, which utilised the HSUV model coefficients except the coefficient for progressive disease, which was estimated from TA478 and Swinburn et al. 2015,[39, 40] lowered the ICER by approximately £1,000. Using the same utility approach but utilising the ECHELON-2 data to estimate the progressive disease utility value by retaining HSUV model progression coefficient, decreased the ICER by approximately another £200. The time-to-death approach, therefore, provided the most conservative estimate of incremental QALYs. However, the impact is not large. Please note that all scenarios within this set retained the ERG implemented constraint that age-adjusted utilities could not exceed the age-adjusted general population utilities obtained from Ara and Brazier.[67]

Table 7.10: ERG utility model approach scenario analyses

Utility model approach	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
HSUV model + PD value from	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,006

Utility model approach	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
TA478/ Swinburn (company base-case)							
HSUV model (using PD coeff.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,833
TTD model (ERG BC)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,153

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; PD = progressive disease; QALYs = quality-adjusted life years; TTD = time-to-death

7.2.2.4 Scenario set 4: Utility age adjustment

Utility age-adjustment assumptions had a substantial impact on the ICER, as shown in Table 7.11. Utilising the company's yearly age decrement of -0.00121, obtained from the time-to-death model and removing the constraint that utilities cannot exceed those age-adjusted general population utilities obtained from Ara and Brazier 2010[67] (to match the company's approach to age-adjustment within the ERG preferred utility approach), decreased the ICER by approximately £500. This makes sense, as the utility values of patients in the earlier years of the model (before the utility of patients starts to exceed that of the general population) stay the same as they would with the ERG constraint, while releasing the constraint gains some additional QALYs in the later years as the constraint would force utility to be lower. Since BV+CHP has an OS and PFS benefit over CHOP, patients in the BV+CHP group retained higher utility for longer and, therefore, more often exceeded the general population utilities without the ERG constraint. Therefore, without the constraint, at this low level of age decrement, BV+CHP is more cost effective.

Increasing the size of the age decrement to -0.00177 to match the decrement obtained from the company's HSUV model (utility constraint still removed) increased the ICER by approximately £1,300. This was because the gain in incremental QALYs in the later years of the model due to the removal of the utility constraint is outweighed by losses in earlier years due to the steeper decline in utility due to ageing.

Finally, increasing the age-decrement to -0.00434, which represents the yearly decrement in utility obtained from Ara and Brazier 2010 at the age of 62 years, increased the ICER substantially by approximately £14,000.[67] This decrement represents the lower bound of the yearly decrements obtained by Ara and Brazier, as these yearly decrements increase as age increases. Therefore, assuming the same age-related decrements in utility from Ara and Brazier would lead to an ICER higher than £47,078. This demonstrates the sensitivity of model results to assumptions surrounding age-related decline in utility.

Table 7.11: ERG utility age adjustment scenario analyses

Utility age-adjustment	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Utilities ≤ Ara Brazier gen pop (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,153
Company TTD model age decrement (-0.00121)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£32,604
Company HSUV model age decrement (-0.00177)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,473
Age decrement -0.00434	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£47,078

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; PD = progressive disease; QALYs = quality-adjusted life years; TTD = time-to-death

7.2.2.5 Scenario set 5: Disutility for grade 3-4 peripheral neuropathy

Removing the additional disutility for grade 3-4 peripheral neuropathy had minimal impact on the ICER, as observed in Table 7.12. This was caused by the low rate of this event in both treatment arms.

Table 7.12: ERG disutility for grade 3-4 peripheral neuropathy scenario analyses

Additional disutility peripheral neuropathy	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
-0.33 (base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,153
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,098

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; PD = progressive disease; QALYs = quality-adjusted life years; TTD = time-to-death

7.2.2.6 Scenario set 6: alternative assumption for number of BV vials per treatment cycle

The results of this scenario, shown in Table 7.13, indicated that when four vials of BV per patient were assumed (the number of vials corresponding to the average patient weight) instead of 3.14 (the average

number of vials obtained using the distribution of patient body weight), the ICER increased by £8,623. This increase was caused by the additional costs incurred by assuming that (on average) 0.86 additional BV vials per treatment cycle were used.

Table 7.13: ERG number of BV vials scenario analyses

Number of vials per treatment cycle front-line BV	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
3.14 (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,153
4.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£41,776

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; PD = progressive disease; QALYs = quality-adjusted life years

7.2.2.7 Scenario set 7: alternative assumption for number of BV treatment cycles

Table 7.14 shows that when the maximum number of treatment cycles for front-line BV was capped to six, the ICER decreased by £2,205. Assuming 8.23 cycles of BV second-line monotherapy (company base-case) instead of 6 (ERG base-case), decreased the ICER by £1,877, and assuming five cycles of BV second-line monotherapy (suggested as plausible during TA478 committee discussion)[39] increased the ICER by £842.

Table 7.14: ERG number of BV treatment cycles scenario analyses

Number of BV treatment cycles	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Per ECHELON-2 (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,153
Maximum of 6 cycles font-line BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,948
8.23 cycles second-line BV (company base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,276
5 cycles second-line BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,995

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; PD = progressive disease; QALYs = quality-adjusted life years

7.3 ERG's preferred assumptions (ITT population)

The ERG preferred changes to the updated company base-case were described in section 7.1.2 of this report. The cost effectiveness results of the ERG preferred base-case are presented in Table 7.15 in eight steps. In each step, the cumulative impact on the model results is shown. Additionally, in Table 7.16, the individual impact of each change on the model results is shown.

Table 7.15: ERG's preferred model assumptions (ITT population) – cumulative impact on results

Preferred assumption	Section in ERG report	BV+CHP		CHOP		Inc. Costs (£)	Inc. QALYs	Cumulative ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,901
ERG change 1: ECOG PS 2	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,326
ERG change 2: cost of transfusion	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,317
ERG change 3: baseline age (62.02 years)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,732
ERG change 4: mortality multiplier (1.25)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,055
ERG change 5: TTD utility approach	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£30,731
ERG change 6: model utilities < general population utilities	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,248
ERG change 7: peripheral neuropathy costs	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£31,276
ERG change 8: six treatment cycles second-line BV	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£33,153

Based on the CS and the electronic model of the CS[1, 48]

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ECOG = Eastern Cooperative Oncology Group; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; ITT =intention-to-treat; PS = performance status; QALY = quality adjusted life year; TTD = time-to-death

Table 7.16: ERG's preferred model assumptions (ITT population) – individual impact on results

Preferred assumption	Section in ERG report	BV+CHP		CHOP		Inc. Costs (£)	Inc. QALYs	ICER (£/QALY)
		Total Costs (£)	Total QALYs	Total Costs (£)	Total QALYs			
Company base-case	6.1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,901
ERG change 1: ECOG PS 2	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,326
ERG change 2: cost of transfusion	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,892
ERG change 3: baseline age (62.02 years)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,264
ERG change 4: mortality multiplier (1.25)	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,086
ERG change 5: TTD utility approach	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,260
ERG change 6: model utilities < general population utilities	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,957
ERG change 7: peripheral neuropathy costs	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,924
ERG change 8: six treatment cycles second-line BV	7.1.2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,620

Based on the CS and the electronic model of the CS[1, 48]

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ECOG = Eastern Cooperative Oncology Group; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; Inc. = incremental; ITT =intention-to-treat; PS = performance status; QALY = quality adjusted life year; TTD = time-to-death

7.4 Conclusions of the cost effectiveness section

The company developed a health economic model using a partitioned survival approach to assess the cost effectiveness of BV+CHP relative to CHOP for the treatment of patients with CD30+ PTCL. Upon initiation of treatment, patients enter the model in the progression-free health state where they reside until disease progression or death. Health state occupancy for the progression-free health state is determined by extrapolations of PFS data from ECHELON-2,[18] whereas health state occupancy for the progressive disease health state is determined by the difference between OS, also determined by extrapolations of OS data from ECHELON-2, and PFS. Health states costs and utilities are used to calculate total costs and total QALYs over a lifetime time horizon.

In addition to the full sample of patients with CD30+ PTCL that was the basis for ITT analyses, ECHELON-2 was also designed to perform an additional subgroup analysis for patients with the sALCL subtype of the disease. The model, therefore, also has the option to conduct economic analyses for this subgroup of patients.

Whenever possible, treatment effectiveness parameters were derived from the ECHELON-2 trial.[18] In particular, patient-level data from ECHELON-2 were used to estimate: 1) extrapolation of OS and PFS, 2) duration, efficacy and administration/re-administration of BV+CHP and CHOP and 3) the proportions of patients receiving consolidative AutoSCT, consolidative and salvage radiotherapy, salvage stem cell transplant (AutoSCT and alloSCT), salvage chemotherapies, salvage treatment with BV and re-treatment with BV. External sources including published literature, expert advice and modelling assumptions were also used. Observed OS/PFS Kaplan Meier curves were extrapolated using parametric distributions the NICE DSU TSD 14 guidance.[56] Given the lack and poor quality of available evidence, the long-term extrapolations were validated by clinical experts. Based on the company assessment, a generalised gamma distribution (fit under the assumption of a joint modelling approach, i.e. proportional hazards) was chosen to model both PFS and OS in the base-case analysis.

In contrast to clinical practice in the UK, patients in ECHELON-2 could be re-treated with BV following disease progression, regardless of the subtype of their disease. In the UK, this is only recommended (and reimbursed) for patients with the sALCL subtype. Therefore, the model incorporated an adjustment for this that serves to remove the treatment effect (and costs) of second-line BV in the economic analyses. Following the guidance of NICE DSU TSD 16,[59] treatment switching approaches were used by the company to remove the potential effect in OS of post-progression. After exploring several methods, the company concluded that only the two-stage estimator provided logical estimates with plausible underlying assumptions. Therefore, this was the approach used in the company's base-case.

Age- and gender-specific background mortality was included in the economic analyses. However, clinical experts consulted by the company indicated that patients in long-term remission are expected to experience a reduced survival of 3% to 10% relative to the general population.[16, 43] In their base-case, the company assumed a 5% reduction in life-expectancy. This was implemented in the model as a mortality multiplier, which in the base-case was equal to 1.19.

Grade 3-4 TEAEs occurring in ≥5% of patients in ECHELON-2 were included in the model. Additionally, the model included grade 1-4 diarrhoea and grade 3-4 peripheral neuropathy. The effects of AEs were captured by applying AE-specific costs and utility decrements. The average number and duration of AEs were based on those observed in ECHELON-2.

HRQoL was measured in the ECHELON-2 trial using the EQ-5D-3L and valued using the UK EQ-5D-3L value set, in line with the NICE reference case. The company explored two approaches for modelling

the EQ-5D-3L data; a health state utility value model, which included a covariate for being post-progression, and a time-to-death model, which included covariates for the proximity of the EQ-5D measurement to the patient's death. Covariates for age, experiencing grade 3-4 AEs and being post-SCT were also included in both models to assess the impact of these characteristics and events on HRQoL. In the base-case, the company chose to use the health state utility modelling approach. However, the coefficient for progression was judged by clinical experts to be implausibly small. Therefore, this coefficient was ignored and a utility value for progression was estimated from TA478, based on utility values from Swinburn et al. 2015.[39, 40]

The following cost categories were included in the economic analyses: drug costs (consisting of acquisition costs, administration costs, and concomitant medication), pre- and post-progression health care resource use, AE costs and miscellaneous costs (stem cell transplant, consolidative radiotherapy, second-line BV, and salvage chemotherapies and radiotherapy). Drug acquisition and administration costs were based on ECHELON-2,[18] concomitant medication on expert opinion,[43] and documentation by the London Cancer Alliance on follow-up care with CHOP.[44] Drug acquisition costs were calculated in the model assuming vial wastage (i.e. no sharing of vials between patients) due to the rarity of the condition, and taking into account the weight and BSA distributions of patients. The model can be toggled to run on the basis of different assumptions for time-on-treatment: either using the average number of treatment cycles from ECHELON-2 as in the company and ERG base-case, or by either applying the maximum number of six treatment cycles that is reflective of UK clinical practice to the data from ECHELON-2, or by assuming six (or eight) cycles for all patients. Pre- and post-progression health care resource use was based on follow-up and monitoring requirements in ECHELON-2,[18] documentation by the London Cancer Alliance on follow-up care with CHOP,[44] TA478,[39] and clinical expert opinion.[16] AE costs were based on grade 3-4 AEs occurring in ≥5% of patients in ECHELON-2,[18] as well as grade 1-2 diarrhoea and grade 1-2 peripheral neuropathy. Miscellaneous costs were based on ECHELON-2,[18] TA478,[39] clinical expert opinion,[16, 45] and clinical guidelines.[14, 46]

The company base-case results (ITT population, BV PAS price) indicated that BV+CHP was both more costly and more effective than CHOP. The incremental costs and QALYs were [redacted] and [redacted], respectively. This resulted in an ICER of £24,901 per QALY gained. The ICER obtained from the PSA was £25,741 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £840 larger than the deterministic ICER. The CE-plane showed that the vast majority of simulations fell into the NE quadrant, where the intervention is more costly and more effective. Just a few simulations were in the NW quadrant, where BV+CHP is dominated by CHOP. The CEAC shows that the probability of BV+CHP being cost-effective was 64% at a threshold ICER of £30,000 per QALY gained, and 22% at a threshold ICER of £20,000 per QALY gained.

Overall, the results from the sensitivity analyses performed by the company indicated that the parameters associated with estimating overall survival (adjusted for treatment switching) were the main sources of uncertainty. The company noted that a part of this uncertainty is inherent to the methods used to adjust for treatment switching, resulting in wider confidence intervals for the estimates of the treatment effect of BV+CHP vs. CHOP. Importantly, these adjustments pertained to both treatment arms (i.e. instead of the usual definition of treatment switching that involves only one arm). Without adjustments for treatment switching (i.e. 'no two-stage estimator' in Table 6.6), the ICER was £27,264 per QALY gained (i.e. a 9% increase from base-case). Scenarios that assume a short time horizon of either 5 or 10 years (i.e. instead of the 100 years to represent a life-time in base-case) result in an ICER that exceeds £30,000 per QALY gained. All other scenarios result in ICERs that are below the threshold of £30,000 per QALY gained.

The company sALCL subgroup analysis also indicated that BV+CHP is more costly and more effective than CHOP, with incremental costs of [redacted] and [redacted] incremental QALYs, resulting in an ICER of £18,840 per QALY gained. This ICER is lower than base-case ICER for the ITT population. This is in line with the expectations as BV seems to be more effective in the sALCL subgroup (see e.g. Figures 12 and 14 in CS).[1]

The patients' baseline characteristics included in the economic model as input parameters were based on the average baseline values observed in the ITT population of the ECHELON-2 trial.[18] The ERG raised their concerns regarding to what extent these demographic parameters were representative for an UK patient. The company indicated that, given the rarity of PTCL, it was not possible to find all the demographic parameters used in the model for UK patients with PTCL. An exception was "age at baseline". Based on the evidence provided in ECHELON-2 (UK patients only), Gleeson et al. 2018 (assuming median = mean),[3] and the HMRN PTCL audit (reference not provided in the response to request for clarification), the ERG considered that the age value included in the cost effectiveness model should have been larger than the 55.1 years used in the company's base-case. In the ERG base-case analysis, the ERG assumed that the mean age of an UK PTCL patient was 62.02 years. The impact of age on the cost effectiveness results was substantial, as indicated by the ERG additional analyses. The remaining patient characteristics were not changed by the ERG due to the lack of evidence to inform alternative estimates.

Based on the presented evidence, the ERG did not consider sufficiently proven that a joint model (i.e. proportional hazards) was more appropriate to model the long-term PFS and OS extrapolations. In fact, the ERG considered the stratified approach, where parametric survival curves are fitted separately to each treatment arm, more plausible and suggested that this approach should have been explored by the company too. The option to select parametric curves based on a stratified approach was included in the company's model, but a complete goodness-of-fit assessment was missing in the CS. The ERG has assumed that the company did not present the stratified extrapolations to UK clinical experts. Also, the ERG discovered that the ICER increased when the sALCL subgroup was modelled instead of the full ITT population on using the stratified approach, which is counterintuitive given that given that BV seems to be more effective in the sALCL subgroup. Therefore, the ERG has concerns about the validity of the results given by the model when the stratified approach is selected. For this reason, in the ERG base-case a joint generalised gamma distribution was assumed to model PFS and OS as in the company base-case.

Additionally, even though the clinical experts consulted by the company considered the generalised gamma was most reflective of long-term outcomes for OS and PFS, the plausibility of the estimated long-term probabilities (tails of the survival curves) was not explicitly quantified in the CS. This is especially important for OS since the selection of the OS long-term extrapolation basically determines the overall gains in QALYs estimated by the electronic model. The generalised gamma was , after the Gompertz, the probability distribution with the highest long-term OS for both treatment arms. It would have been important to assess the plausibility of the lognormal (and to a lower extent the log-logistic) distribution (the ERG assumed that the Gompertz, Weibull and exponential would be deemed implausible). Without this, the generalised gamma (and possibly the lognormal) is the only logical choice for modelling OS (and PFS).

Clinical experts consulted by the company explained that the risk of relapse and the risk of lymphoma related mortality after front-line treatment is the highest in the first two/three years following treatment and, after that, decreases drastically and overall survival approached that of the general population.[16, 58] This is not reflected in the company's model. The hazard rate functions for both OS and PFS showed

that only the generalised gamma and the lognormal distributions resulted in a hazard rate function that was initially increasing and then, after some time, decreasing. However, in both cases, the decline occurred even before one year (for OS it was almost immediately). Furthermore, in the company base-case, long-term mortality equals the mortality risk of the general population at 14.95 years in the BV+CHP arm and at 15.93 years in the CHOP arm. The ERG considers that the plausibility of both the hazard rate functions and time when long-term mortality equals the mortality risk of the general population should be validated by clinical experts. For these reasons, the ERG feels that exploring other non-standard parametric distributions (e.g. spline models) might have been appropriate in this case, in line with was suggested by one of the economic experts consulted by the company: *"a spline at two-years was recommended as an exploratory extrapolation to increase flexibility. Clinicians questioned whether the introduction of BV+CHP would push the traditional two-year relapse-out (i.e. relapse would take place after two-years)"*.[16] However, the company did only consider the standard parametric models and no further discussion regarding this subject can be found in the CS.

Adjustment for BV re-treatment in the BV+CHP arm and BV use post-progression in non-sALCL patients in the CHOP arm seems reasonable and the TSE method appropriate. The company mentioned that for the 36 patients with sALCL in the CHOP arm, the use of BV post-progression is recommended for use in TA478.[39] However, this is not correct as TA478 explicitly recommends BV as an option for treating R/R sALCL patients only if they have an ECOG PS of 0 or 1. In response to clarification question B8,[17] the company indicated that there were four patients with ECOG PS 2 at study baseline in the CHOP arm of ECHELON-2 who had sALCL disease and received subsequent BV post-progression, which were consequently removed from the OS TSE (and from the proportion of patients receiving subsequent BV). This assumption was included in the ERG base-case. However, the ERG noted several issues associated to this adjustment which were explained in detail in section 5.2.6.2. The most important was that this adjustment was only implemented for the deterministic joint analyses. Thus, it was not implemented when the stratified approach to modelling was selected, it was implemented for the ITT population but not for the sALCL subgroup, and more importantly, it was not included in the PSA. The later implies that, all PSA analyses assuming this adjustment (e.g. the ERG base-case) would result in a large underestimation of the overall uncertainty.

The ERG identified several issues with the use of the HSUV modelling approach combined with the use of an alternative utility value for progressive disease derived from TA478 and Swinburn et al. 2015.[39, 40] Firstly, Swinburn et al. used vignettes describing R/R Hodgkin lymphoma and sALCL health states to elicit TTO valuations from members of the general public in seven countries including the UK. As this study measured HRQoL in members of the general population, rather than in patients directly, this source does not meet the requirements of the NICE reference case. Secondly, a combined health state utility value and time-to-death model suggested that time-to-death has more impact on HRQoL in this group of patients than progression. Therefore, the ERG chose to use the time-to-death model in their base-case.

While the company did include age as a covariate within their utility modelling to adjust utilities for age within the model, the coefficient obtained from the company model was smaller than age-related utility decrements seen in more commonly applied age-adjustment studies, such as Ara and Brazier 2010.[67] This smaller age decrement meant that in the long term, progression free patients in the model had higher utility values than the age-adjusted utilities of members of the general population as calculated in Ara and Brazier 2010.[67] The ERG considered this implausible and implemented a constraint in their base-case whereby utilities could not exceed these age-adjusted general population utility values.

The ERG considers it important for the assumptions regarding the number of front-line BV treatment cycles that these are in line with the data on clinical effectiveness, which are based on the number of treatment cycles observed in ECHELON-2. Therefore, as in the company base-case, the ERG assumed the average number of front-line BV treatment cycles from ECHELON-2 for their preferred base-case analysis. For second-line BV, the company base-case used the average number of 8.2 treatment cycles from TA478.[39] Based on the TA478 Committee discussion,[39] the ERG was uncertain about this assumption and assumed a number of six treatment cycles for second-line BV instead.

Following clinical expert opinion,[43] no costs were included for grade 3–4 peripheral neuropathy on the basis that the treatment for this AE would be to stop treatment with either BV+CHP or CHOP and wait for peripheral neuropathy improvement or resolution. This deviates from the assumptions made in TA478,[39] in which costs for the treatment of grade 1-2 and grade 3-4 peripheral neuropathy were included in the analyses. While the average rate of grade 3-4 peripheral neuropathy is low in the trial, this is similar to the rates observed for grade 3-4 pneumonia and grade 3-4 diarrhoea, and these were included in the model. Furthermore, the average duration per grade 3-4 peripheral neuropathy event is by far the longest (127.4 days) amongst AEs. This suggests that grade 3-4 peripheral neuropathy might have substantial impact within the AEs included in the model. For these reasons, the costs of grade 1-4 peripheral neuropathy were included in the ERG base-case. Overall, the impact of including these costs on the cost effectiveness results was negligible.

During the process of responding to the clarification questions, the company removed patients with ECOG PS 2 from the two-stage estimator and from the proportion of patients receiving subsequent BV, since the opposite would contradict the recommendations in TA478.[17, 39] Additionally, the ERG changed various assumptions, which were expected to have a substantial impact on the model results. Therefore, the ERG assumed a baseline age equal to 62.02 years, a time-to-death approach to utilities (which were also constrained to be lower than general population utilities) and six treatment cycles for second-line BV. Other minor changes included correcting the cost of transfusion used in the model (as this was incorrectly sourced), using a long-term mortality multiplier reflecting a 6.5% increased mortality risk, including peripheral neuropathy costs in the model and adjusting the model to ensure the correct functioning of some of the calculations. These changes increased the ICER from £24,901 (company) to £33,153 (ERG). The changes surrounding baseline age and the number of second-line BV treatment cycles had the largest impact on the ICER. In particular, BV+CHP provided [redacted] additional QALYs at an incremental cost of [redacted] compared to CHOP. The incremental QALY gains for BV+CHP all stemmed from the progression-free health state. Incremental costs were mostly due to the additional treatment costs of BV+CHP. Approximately [redacted]% of these incremental costs were saved in second-line therapies. However, [redacted]% of the costs saved in second-line therapies were caused by BV being used post-progression in the CHOP arm. Consolidative therapy costs were also [redacted]% higher in the BV+CHP arm.

The ERG also changed several assumptions regarding the PSA. A total of 23 input parameters, which were kept fixed by the company, were included in the ERG base-case. In the absence of 95% confidence intervals for all these parameters, the ERG used arbitrary ranges of variation to account for some uncertainty associated to these parameters. The following adjustments were made to the PSA by the ERG: age (normal distribution with additional constraint that age cannot be lower than 55 years), percentage of females (Beta distribution based on total number of patients in ECHELON-2), Mortality multiplier (normal distribution with range of variation [1.10, 1.42]), number of adverse events (18 parameters in total – log-normal distribution with arbitrary standard error), additional disutility applied to grade 3-4 peripheral neuropathy (normal distribution with arbitrary range of variation) and number of treatment cycles of second-line BV (normal distribution with range of

variation [4, 8]). In addition, the OS adjustment for ECOG PS 2 patients made by the company was not included in the PSA (the covariance matrix was missing from the model). In the absence of the correct covariance matrix, the ERG assumed for their PSA the same covariance matrix as in the company base-case and further modelled these parameters according to a multivariate normal distribution. The PSA results obtained after the ERG adjustments resulted in a probabilistic ICER of £34,690 per QALY gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £1,537 larger than the ERG deterministic ICER. The CEAC shows that the probability of BV+CHP being cost-effective was 35% (as opposed to 64% in the company's PSA) at a threshold ICER of £30,000 per QALY gained, and 7% (as opposed to 22% in the company's PSA) at a threshold ICER of £20,000 per QALY gained.

The ERG conducted a series of additional scenario analyses in order to explore important areas of uncertainty in the model. These key uncertainties were related to the survival modelling (in terms of choice of parametric distributions and modelling approach, i.e. joint vs. stratified), age at baseline, and utility, cost and resource use assumptions. Other sources of uncertainty were deemed less important and were not explored in this section. The results of these analyses indicated that the ICER for the ITT population was sensitive to some of the assumptions tested by the ERG. Interestingly, the largest differences in survival modelling approaches were associated to the generalised gamma distribution, the one used by both the company and the ERG. The choice of age at baseline had a substantial impact on the model results. The ICER obtained assuming 55.10 years at baseline, as in the company base-case, was £27,746 per QALY gained; thus, £5,407 lower than the ERG base-case. Increasing the age-decrement in utility to -0.00434, which represents the yearly decrement in utility obtained from Ara and Brazier at the age of 62 years, increased the ICER by approximately £14,000.[67] This decrement represents the lower bound of the yearly decrements obtained by Ara and Brazier, as these yearly decrements increase as age increases. Therefore, assuming the same age-related decrements in utility from Ara and Brazier would lead to an ICER higher than £47,078. Also, when four vials of BV per patient were assumed (the number of vials corresponding to the average patient weight) instead of 3.14 (the average number of vials obtained using the distribution of patient body weight), the ICER increased by £8,623. This increase was caused by the additional costs incurred by assuming that (on average) 0.86 additional BV vials per treatment cycle were used. The other assumptions tested by the ERG had a minor impact on the model results.

8. END OF LIFE

According to section B.2.13, *"Takeda does not wish for the medicine to be considered at this time for the application of NICE's End-of-Life criteria"*.[1]

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Appendix 1: PFS and OS stratified modelling approach

Table A1.1: Comparison of PFS extrapolations using a joint versus stratified approach

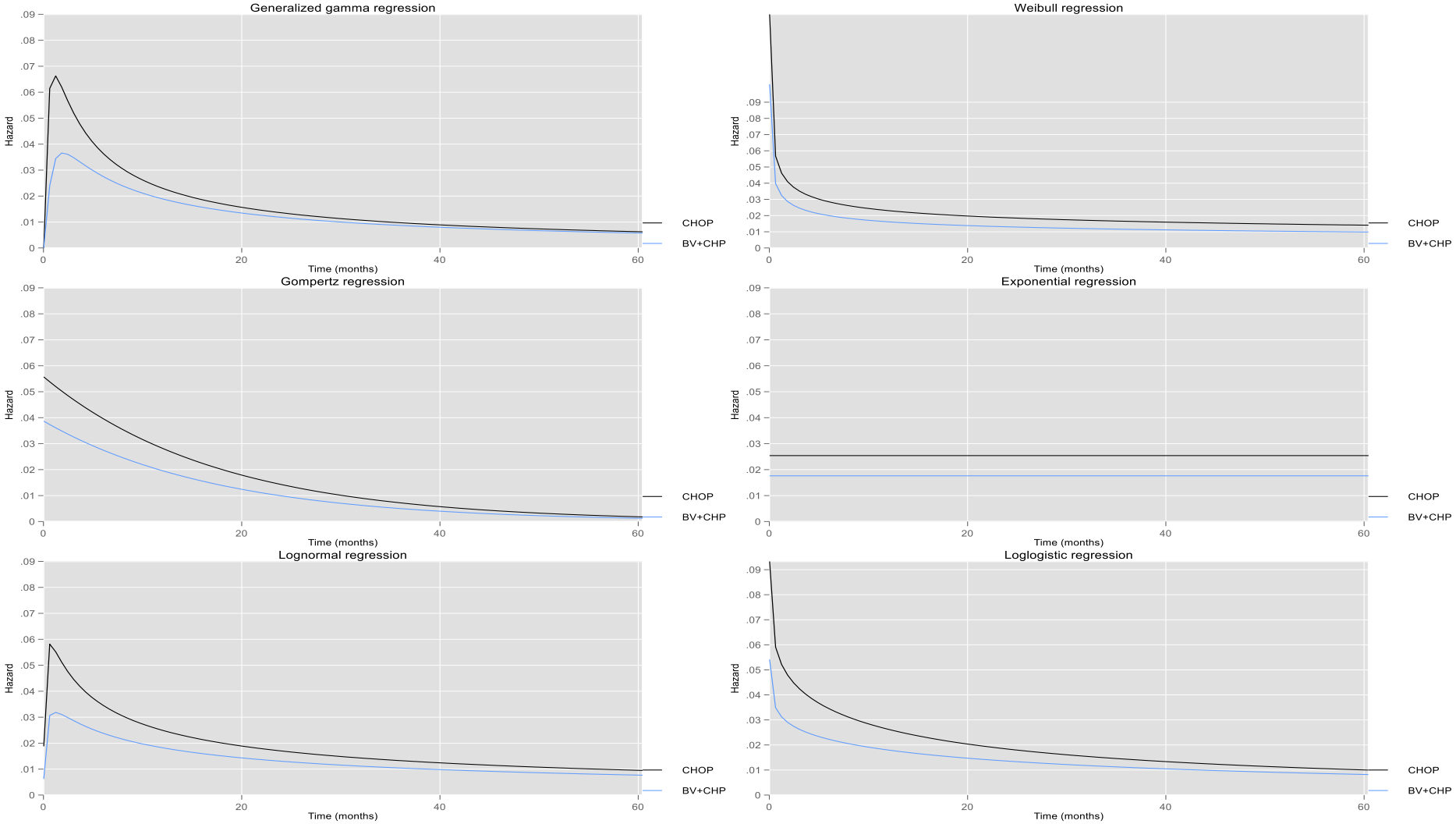
Distribution	Year	Joint approach		Stratified approach	
		BV+CHP	CHOP	BV+CHP	CHOP
Generalised gamma	5	0.46	0.37	0.47	0.36
	10	0.35	0.28	0.36	0.27
	15	0.30	0.24	0.31	0.23
	20	0.27	0.21	0.28	0.20
Exponential	5	0.35	0.22	0.35	0.22
	10	0.12	0.05	0.12	0.05
	15	0.04	0.01	0.04	0.01
	20	0.01	0.00	0.01	0.00
Gompertz	5	0.52	0.39	0.49	0.41
	10	0.51	0.38	0.46	0.40
	15	0.51	0.37	0.46	0.40
	20	0.51	0.37	0.46	0.40
Log-logistic	5	0.43	0.30	0.42	0.31
	10	0.29	0.19	0.28	0.20
	15	0.22	0.14	0.22	0.15
	20	0.18	0.12	0.18	0.12
Lognormal	5	0.44	0.32	0.44	0.32
	10	0.30	0.21	0.30	0.21
	15	0.24	0.15	0.23	0.15
	20	0.19	0.12	0.19	0.12
Weibull	5	0.43	0.30	0.41	0.31
	10	0.25	0.14	0.22	0.15
	15	0.16	0.07	0.13	0.09
	20	0.11	0.04	0.08	0.05

Based on the electronic model of the CS[48]

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission

PFS = progression-free survival

Figure A1.1: Predicted hazard rate functions of PFS for alternative parametric survival distributions from ECHELON-2 (ITT population)



Based on Figure 8 of the response to request for clarification[17]

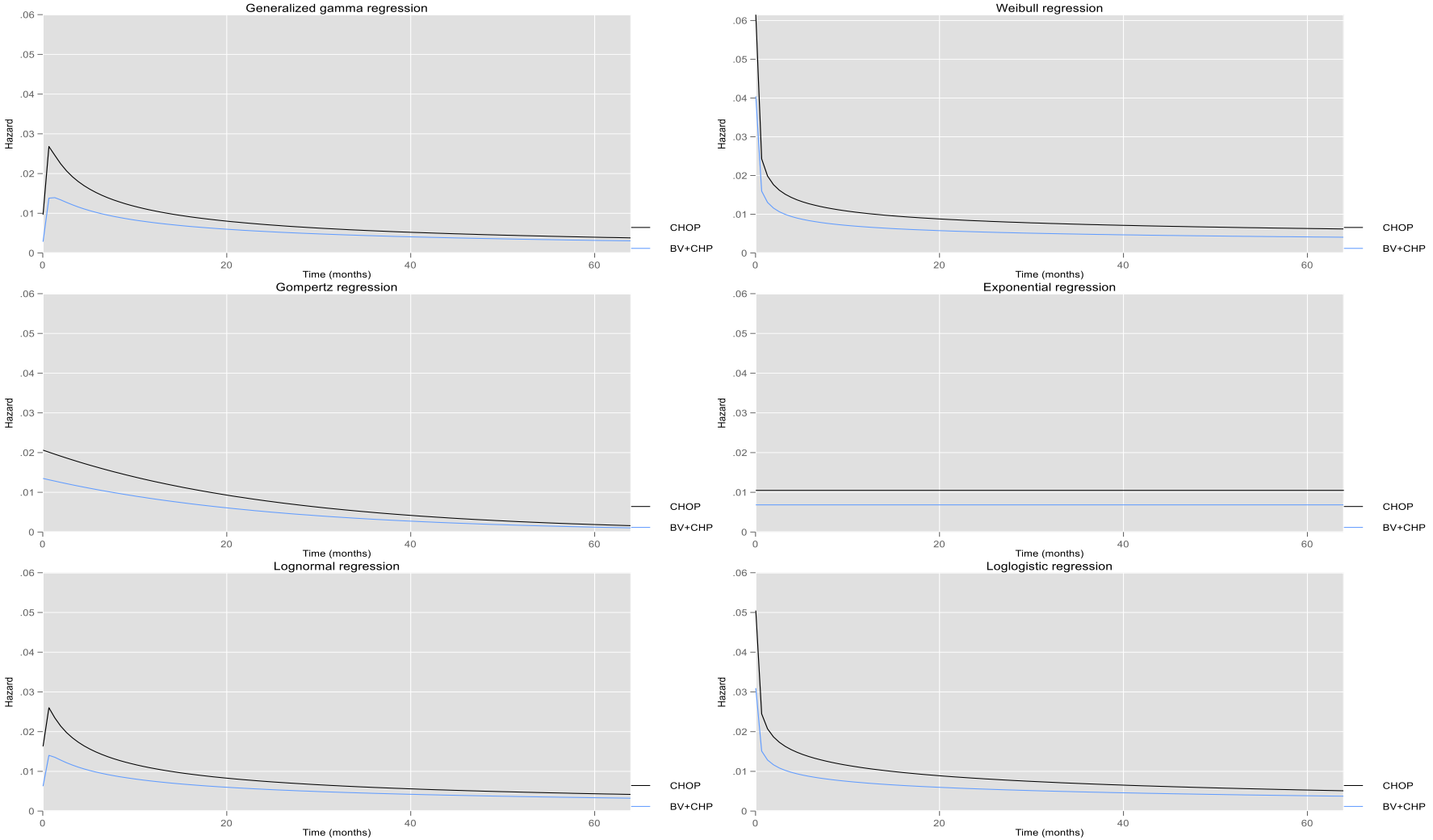
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; PFS = progression-free survival

Table A1.2: Comparison of OS extrapolations using a joint versus stratified approach

Distribution	Year	Joint approach		Stratified approach	
		BV+CHP	CHOP	BV+CHP	CHOP
Generalised gamma	5	0.71	0.61	0.72	0.60
	10	0.61	0.51	0.64	0.49
	15	0.55	0.45	0.59	0.43
	20	0.50	0.41	0.55	0.39
Exponential	5	0.66	0.53	0.66	0.53
	10	0.44	0.28	0.44	0.28
	15	0.29	0.15	0.29	0.15
	20	0.19	0.08	0.19	0.08
Gompertz	5	0.73	0.62	0.74	0.62
	10	0.71	0.60	0.72	0.59
	15	0.71	0.60	0.72	0.59
	20	0.71	0.60	0.72	0.59
Log-logistic	5	0.70	0.59	0.70	0.59
	10	0.58	0.46	0.58	0.45
	15	0.50	0.38	0.51	0.37
	20	0.44	0.33	0.45	0.32
Lognormal	5	0.70	0.61	0.71	0.60
	10	0.60	0.49	0.61	0.48
	15	0.53	0.43	0.55	0.41
	20	0.49	0.38	0.51	0.37
Weibull	5	0.70	0.58	0.70	0.58
	10	0.56	0.41	0.56	0.41
	15	0.46	0.31	0.46	0.31
	20	0.39	0.24	0.39	0.24

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; OS = overall survival

Figure A1.2: Predicted hazards of OS for alternative parametric survival distributions from ECHELON-2 (ITT population, unadjusted analysis)



Based on Figure 7 of the response to request for clarification[17]

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ITT = intention-to-treat; OS = overall survival

Appendix 2: Overall survival adjustment for subsequent use of BV after disease progression - comparison of approaches explored by the company

Table A2.1: Results of alternative methods for adjusting for re-treatment

Method	Hazard ratio (BV+CHP vs CHOP)	P-value	95% CI	
ITT population				
Unadjusted	0.665	0.025	0.465	0.951
Per protocol - re-censoring	0.631	0.022	0.426	0.935
Per-protocol - exclude	0.678	0.054	0.457	1.006
IPCW (stabilized)	0.672	0.048	0.453	0.997
IPCW (non-stabilised)	0.681	0.058	0.458	1.013
Two-stage Weibull	0.678	0.035†	0.475	0.968
Two-stage Weibull (re-censoring)	0.706	0.083†	0.435	1.096
sALCL population				
Unadjusted	0.541	0.011	0.337	0.867
Per protocol - re-censoring	0.429	0.001	0.256	0.719
Per-protocol - exclude	0.501	0.009	0.299	0.840
IPCW (stabilized)	0.463	0.003	0.278	0.772
IPCW (non-stabilised)	0.463	0.003	0.278	0.771
Two-stage Weibull	0.553	0.015†	0.320	0.890
Two-stage Weibull (re-censoring)	0.395	0.0257†	0.157	0.910

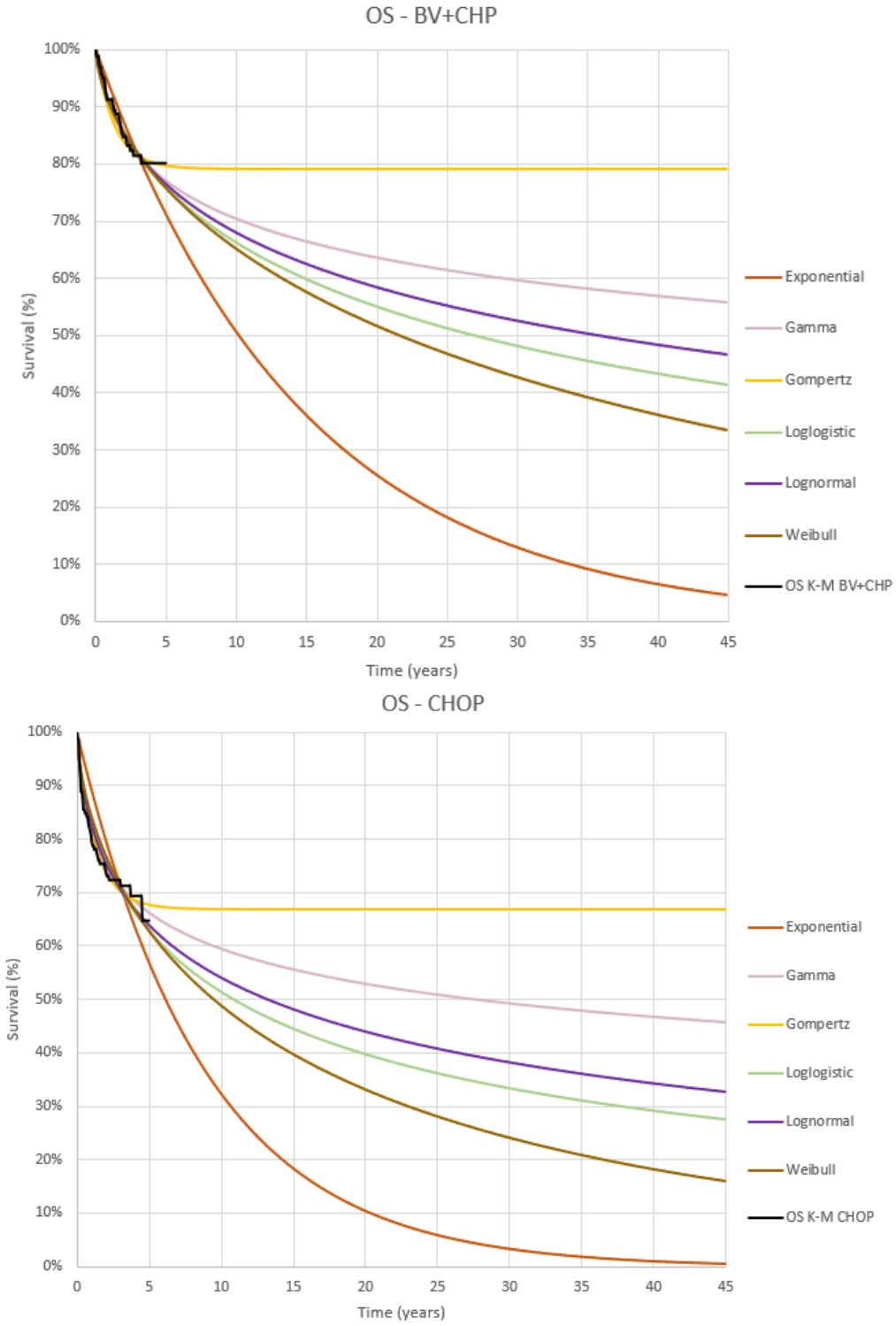
Based on Table 5 in Appendix N of the CS[60]
† Estimated using a bootstrap with 1,000 samples
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; IPCW = inverse probability of censoring weights; ITT = intention-to-treat; sALCL = systemic anaplastic large cell lymphoma

Appendix 3: Cost effectiveness evidence for the sALCL subpopulation

A3.1 PFS and OS extrapolations

The company adopted a joint modelling approach, in which the treatment effect is estimated with a coefficient in the equation (i.e. instead of separate equations for both arms) using data from both arms in ECHELON-2. This was justified based on visual inspection of OS and PFS survival curves. These were relatively straight and parallel throughout for OS, and relatively parallel, but not straight, throughout for PFS. The extrapolation of OS and PFS survival curves is shown in Figures A3.1 and A3.2, respectively.

Figure A3.1: Standard parametric extrapolation, OS – sALCL population – including TSE adjustment

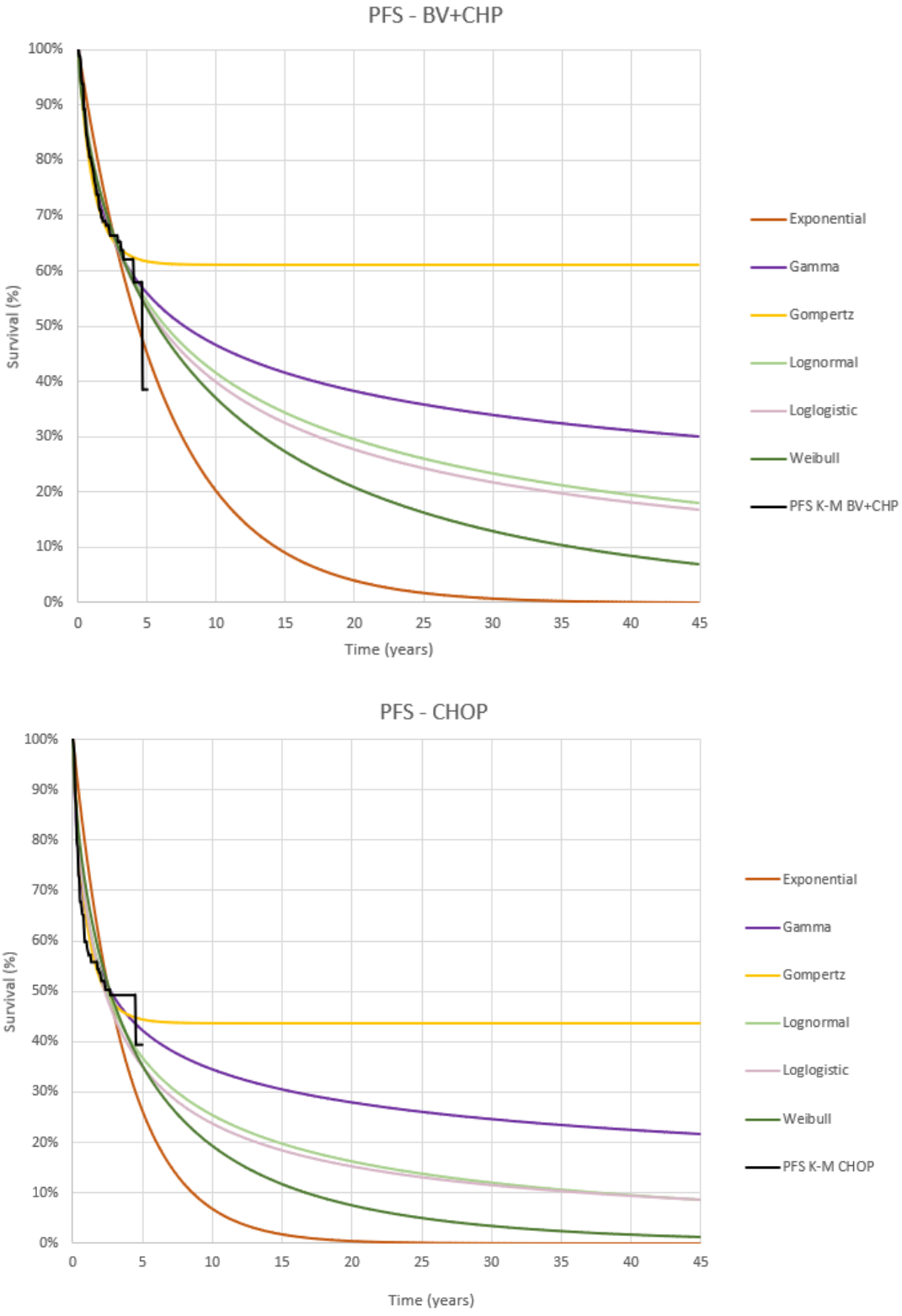


Based on Figure 34 of the CS[1]

Note: Background mortality is not applied.

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; K-M = Kaplan-Meier; OS = overall survival; sALCL = systemic anaplastic large cell lymphoma; TSE = two-stage estimator

Figure A3.2: Standard parametric extrapolation, PFS – sALCL population



Based on Figure 35 of the CS[1]
Note: Background mortality is not applied.
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; K-M = Kaplan-Meier; PFS =progression-free survival; sALCL = systemic anaplastic large cell lymphoma; TSE = two-stage estimator

The model diagnostics of the extrapolations of the OS and PFS survival curves are reported in Table A3.1. Similar to base-case (i.e. extrapolations for the ITT population), Gompertz, gamma, and log-normal distributions are associated with the lowest AIC and BIC scores for OS, and Gompertz, gamma, and log-normal distributions are associated with the lowest AIC and BIC scores for PFS.

Table A3.1: Model diagnostics (sALCL population)

Parameter	ll(model)	df	AIC	BIC
OS (including TSE adjustment)				
Generalised gamma	-272.2	4	552.5	567.5
Weibull	-277.8	3	561.5	572.8
Gompertz	-272.7	3	551.5	562.8
Exponential	-288.9	2	581.8	589.3
Lognormal	-273.8	3	553.6	564.9
Log-logistic	-276.4	3	558.9	570.1
PFS				
Generalised gamma	–389.3	4	786.6	801.6
Weibull	–406.8	3	819.5	830.8
Gompertz	–393.3	3	792.6	803.9
Exponential	–424.5	2	853.0	860.5
Lognormal	–395.0	3	795.9	807.2
Log-logistic	–400.2	3	806.3	817.6

Based on Table 63 of the CS[1]
AIC = Akaike Information Criterion; BIC = Bayesian information criterion; df = degrees of freedom; ll = log likelihood; OS = overall survival; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma; TSE = two-stage estimator

Similar to base-case (i.e. extrapolations for the ITT population), the generalised gamma distribution is used for extrapolation of both the OS and PFS curves. Alternative distributions are considered in scenario analyses. Table A3.2 shows the gamma distribution coefficients, and Figure A3.3 shows the extrapolated survival curves for the sALCL population, incorporating background mortality.

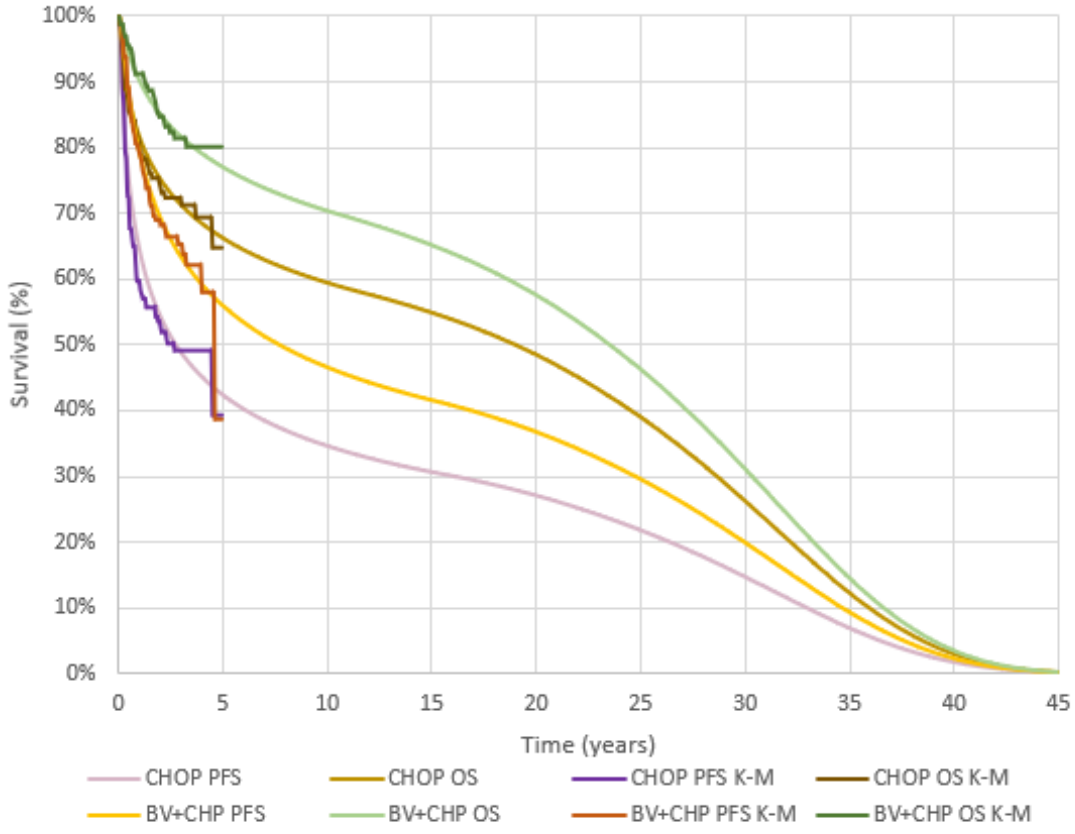
Table A3.2: Gamma distribution coefficients (sALCL population)

Parameter	Coefficient	SE	95% CI	
			Lower bound	Upper bound
OS (including TSE adjustment)				
Generalised gamma	1.120	0.432	0.273	1.967
Weibull	4.100	0.788	2.556	5.645
Gompertz	1.282	0.115	1.056	1.508
Exponential	-1.233	0.704	-2.612	0.146
PFS				
Generalised gamma	1.039	0.277	0.496	1.583

Parameter	Coefficient	SE	95% CI	
			Lower bound	Upper bound
Weibull	2.332	0.363	1.620	3.043
Gompertz	0.880	0.065	0.752	1.008
Exponential	–1.247	0.343	–1.920	–0.574

Based on Table 64 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CI = confidence interval; CS = company submission; OS = overall survival; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma; SE = standard error

Figure A3.3: Survival curve extrapolations in the sALCL population fitted to the generalised Gamma distribution, including TSE adjustment (adjusted for background mortality)



Based on Figure 36 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; K-M = Kaplan Meier; OS = overall survival; PFS = progression-free survival

A3.2 Time on treatment

The proportions of patients with sALCL that correspond to receiving each (of up to eight) treatment cycle are shown in Table A3.3.

Table A3.3: Proportion of patients receiving each treatment cycle (sALCL population)

Cycle	BV+CHP	CHOP
1	100%	100%
2	98%	97%
3	97%	91%
4	94%	86%
5	93%	81%
6	92%	78%
7	22%	21%
8	21%	21%

Based on Table 65 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; sALCL = systemic anaplastic large cell lymphoma

A3.3 Consolidation therapy

The proportions of patients from the sALCL population that received consolidative SCT in ECHELON-2 are shown in Table A3.4.

Table A3.4: Proportion of patients receiving an AutoSCT in ECHELON-2 (sALCL population)

Treatment arm	Total number of patients	Patients who received a consolidative AutoSCT	% consolidative SCT
BV+CHP	162	37	23%
CHOP	154	20	13%

Based on Table 66 of the CS[1]
AutoSCT = autologous stem cell transplant; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; sALCL = systemic anaplastic large cell lymphoma; SCT = stem cell transplant

The proportions of patients from the sALCL population that received consolidative radiotherapy in ECHELON-2 are shown in Table A3.5.

Table A3.5: Proportion of patients receiving consolidative radiotherapy in ECHELON-2 (sALCL population)

Treatment arm	Total number of patients	Patients who received consolidative radiotherapy	% consolidative radiotherapy	Total cost of consolidative radiotherapy
BV+CHP	162	14	9%	£190.64
CHOP	154	4	3%	£57.30

Based on Table 67 of the CS[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; sALCL = systemic anaplastic large cell lymphoma

The proportions of patients with R/R sALCL who received subsequent SCT and the proportions of patients who received alloSCT versus AutoSCT in ECHELON-2 are shown in Table A3.6.

Table A3.6: Proportion of progressed patients receiving stem cell transplant in ECHELON-2 (sALCL population)

Treatment arm	Second-line SCT (i.e. post-progression)	Proportion of second-line AutoSCT vs alloSCT
BV+CHP	23%	64.1% vs 35.9%[a]
CHOP	25%	

Based on Table 68 of the CS[1]
[a] These proportions are assumed to be the same in both treatment arms, similar to base-case (i.e. ITT population)
AutoSCT = autologous stem cell transplant; alloSCT = allogenic stem cell transplant; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; sALCL = systemic anaplastic large cell lymphoma; SCT = stem cell transplant.

A3.4 Resources and costs

The frequencies and proportions of patients from the sALCL population who received (non-BV containing) salvage therapy in ECHELON-2 are shown in Table A3.7.

Table A3.7: Proportion of progressed patients receiving stem cell transplant in ECHELON-2 (sALCL population)

Salvage therapy	Frequency	Percentage
Bendamustine	4	6.25%
CHOP	1	1.56%
DHAP	8	12.5%
ESHAP	7	10.94%
GDP	15	23.44%
Gemcitabine	1	1.56%
ICE	13	20.31%
Radiation	15	23.44%
SMILE	0	0%
Total	**64**	**100%**

Based on Table 69 of the CS[1]
CHOP = Cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; DHAP = dexamethasone, cisplatin, cytarabine; ESHAP = cisplatin, methylprednisolone, etoposide, cytarabine; GDP = gemcitabine, dexamethasone, cisplatin; ICE = etoposide, carboplatin, ifosfamide + mesna, mesna; sALCL = systemic anaplastic large cell lymphoma; SMILE = etoposide, ifosfamide + mesna, mesna, methotrexate, dexamethasone

ERG comment: In clarification question B22,[17] the ERG asked the company to confirm whether all parameters (including the demographic parameters) used in the analyses of the sALCL subgroups were based on subgroup-specific data. In their response, the company provided Table A3.8, where it can be seen which parameters were estimated from subgroup-specific data and, in case they were not, a rationale for not doing it. The company concluded that, the majority of the parameters were subgroup-specific and, for those which were not, they were not expected to differ in clinical practice and/or were not found to be different in trial data. While this might be the case, in the presence of subgroup specific

data, the ERG would prefer these to be used, regardless of whether clinical differences were expected or statistical testing found no (significant) difference.

Table A3.8: Parameters used in the economic model

Model parameter	Subgroup specific?	If not, why?
Time on treatment	Yes	-
Weight, BSA, age	No	No differences expected in clinical practice.
Adverse events	No	No differences expected
HRQoL coefficients	No	Testing found no difference
Utility in PD	No	
Survival curves	Yes	-
% of patients receiving consolidative AutoSCT	Yes	-
% of patients receiving salvage SCT (any)	Yes	-
% of alloSCT vs AutoSCT	No	No differences expected
% of consolidative radiotherapy	Yes	-
% of salvage radiotherapy	Yes	-
% of salvage chemotherapy	Yes	-
% patients receiving subsequent chemotherapy	Yes	-
Number of cycles of salvage chemotherapy	No	Standard guidelines
% patients receiving subsequent BV	Yes	-
Number of cycles of subsequent BV	No	Single number from R/R setting

Based on Table 26 of the response to request for clarification[17]
alloSCT = allogeneic stem cell transplant; AutoSCT = autologous stem cell transplant; BSA = body surface area; BV = brentuximab vedotin; HRQoL = health-related quality of life; PD = progressive disease; R/R = relapsed/refractory; SCT = stem cell transplant

Appendix 4: ERG cost effectiveness analyses for the sALCL subgroup

Table A4.1: ERG base-case deterministic discounted results (sALCL subgroup)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
BV+CHP	[redacted]	11.51	[redacted]	[redacted]	1.56	[redacted]	£27,387
CHOP	[redacted]	9.94	[redacted]				

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year; sALCL = systemic anaplastic large cell lymphoma

Table A4.2: ERG base-case disaggregated discounted QALYs (sALCL subgroup)

Health state	QALY CHOP	QALY BV+CHP	Absolute increment	%absolute increment
QALYs in progression-free state	[redacted]	[redacted]	[redacted]	[redacted]
QALYs in progressive state	[redacted]	[redacted]	[redacted]	[redacted]
QALY gain due to SCT	[redacted]	[redacted]	[redacted]	[redacted]
QALY loss due to AEs	[redacted]	[redacted]	[redacted]	[redacted]
QALYs loss to death	[redacted]	[redacted]	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; QALY = quality-adjusted life year; sALCL = systemic anaplastic large cell lymphoma

Table A4.3: ERG base-case disaggregated discounted costs (sALCL subgroup)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Total second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Second-line BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Total consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ICER = incremental cost effectiveness ratio; sALCL = systemic anaplastic large cell lymphoma; SCT = stem cell transplant

Table A4.4: ERG OS scenario analyses (PFS = generalised gamma, sALCL subgroup)

OS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£27,387**	[redacted]	[redacted]	£27,852
Exponential	[redacted]	[redacted]	£18,942	[redacted]	[redacted]	£19,121
Gompertz	[redacted]	[redacted]	£26,622	[redacted]	[redacted]	£28,583
Log-logistic	[redacted]	[redacted]	£22,532	[redacted]	[redacted]	£28,238
Lognormal	[redacted]	[redacted]	£23,418	[redacted]	[redacted]	£27,035
Weibull	[redacted]	[redacted]	£21,126	[redacted]	[redacted]	£28,267

Based on the electronic model of the CS[48]
CS = company submission; ICER = incremental cost effectiveness ratio; inc. = incremental; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; sALCL = systemic anaplastic large cell lymphoma

Table A4.5: ERG PFS scenario analyses (OS = generalised gamma, sALCL subgroup)

PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	£27,387	[redacted]	[redacted]	£27,852
Exponential	[redacted]	[redacted]	£21,595	[redacted]	[redacted]	£21,724
Gompertz	[redacted]	[redacted]	£27,928	[redacted]	[redacted]	£30,247
Log-logistic	[redacted]	[redacted]	£23,305	[redacted]	[redacted]	£25,590
Lognormal	[redacted]	[redacted]	£23,795	[redacted]	[redacted]	£25,654
Weibull	[redacted]	[redacted]	£21,655	[redacted]	[redacted]	£25,465

Based on the electronic model of the CS[48]
CS = company submission; ICER = incremental cost effectiveness ratio; inc. = incremental; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; sALCL = systemic anaplastic large cell lymphoma

Table A4.6: ERG OS/PFS scenario analyses (OS distribution = PFS distribution, sALCL subgroup)

OS/PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	£27,387	[redacted]	[redacted]	£27,852
Exponential	[redacted]	[redacted]	£14,371	[redacted]	[redacted]	£14,371
Gompertz	[redacted]	[redacted]	£27,157	[redacted]	[redacted]	£30,957
Log-logistic	[redacted]	[redacted]	£18,993	[redacted]	[redacted]	£25,818
Lognormal	[redacted]	[redacted]	£20,285	[redacted]	[redacted]	£24,839
Weibull	[redacted]	[redacted]	£16,379	[redacted]	[redacted]	£25,627

Based on the electronic model of the CS[48]
CS = company submission; ICER = incremental cost effectiveness ratio; inc. = incremental; OS = overall survival; PFS = progression-free survival; QALY = quality-adjusted life year; sALCL = systemic anaplastic large cell lymphoma

Table A4.7: Age at baseline (sALCL subgroup)

Age at baseline (years)	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
55.10 (company base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,814
58 (Gleeson et al. 2018)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,443
60.9 (UK population in ECHELON-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,476
62.02 (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,387**
[redacted] (HMRN PTCL audit)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£29,146
70	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£37,899
75	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£51,207

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; HMRN = Haematologic Malignancy Research Network; ICER = incremental cost effectiveness ratio; incr. = incremental; PTCL = Peripheral T-cell lymphoma; sALCL = systemic anaplastic large cell lymphoma; UK = United Kingdom

Table A4.8: ERG utility model approach scenario analyses (sALCL subgroup)

Utility model approach	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
HSUV model + PD value from TA478/ Swinburn (company base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,214
HSUV model (using PD coeff.)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,005
TTD model (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£27,387**

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; coeff. = coefficient; CS = company submission; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; incr. = incremental; PD = progressive disease; sALCL = systemic anaplastic large cell lymphoma; TTD = time-to-death

Table A4.9: ERG disutility for grade 3-4 peripheral neuropathy scenario analyses (sALCL subgroup)

Additional disutility peripheral neuropathy	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
-0.33 (base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,387
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,350

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; incr. = incremental; sALCL = systemic anaplastic large cell lymphoma

Table A4.10: ERG utility age adjustment scenario analyses (sALCL subgroup)

Utility age-adjustment	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Utilities ≤ Ara Brazier gen pop (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,387
Company TTD model age decrement (-0.00121)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£26,965

Utility age-adjustment	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Company HSUV model age decrement (-0.00177)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,481
Age decrement -0.00434	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£38,632

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; coeff. = coefficient; CS = company submission; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; incr. = incremental; sALCL = systemic anaplastic large cell lymphoma; TTD = time-to-death

Table A4.11: ERG number of vials BV scenario analyses (sALCL subgroup)

Number of vials per treatment cycle front-line BV	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
3.14 (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,387
4.0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£34,055

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; incr. = incremental; QALYs = quality-adjusted life years; sALCL = systemic anaplastic large cell lymphoma

Table A4.12: ERG number of treatment cycles BV scenario analyses (sALCL subgroup)

Number of BV treatment cycles	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
Per ECHELON-2 (ERG base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£27,387
Maximum of 6 cycles font-line BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,251
8.23 cycles second-line BV (company base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,744
5 cycles second-line BV	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£28,573

Based on the electronic model of the CS[48]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company

Number of BV treatment cycles	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
submission; ERG = Evidence Review Group; ICER = incremental cost effectiveness ratio; incr. = incremental; sALCL = systemic anaplastic large cell lymphoma							

ERG comment: As explained in section 5.2.6.2 of this report, the adjustment for BV use post-progression in R/R sALCL patients with ECOG PS 2 caused the following affecting the results of the subgroup analyses shown above:

- This change is only implemented for the ITT population. Thus, all results for the sALCL subgroup presented in this appendix do not include this adjustment. Thus, all results are bias, even though the size of the bias is expected to be minor.
- This adjustment is not included in the PSA. Because of this, the ERG preferred PSA analysis could not be run.

National Institute for Health and Care Excellence
Centre for Health Technology Evaluation

ERG report – factual accuracy check

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

You are asked to check the ERG report to ensure there are no factual inaccuracies contained within it.

If you do identify any factual inaccuracies, you must inform NICE by **5pm on 24 February 2020** using the below comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

The factual accuracy check form should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Clinical Study Report of ECHELON-2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 15 and 66 of the ERG report state that "Despite numerous requests, a clinical study report (CSR) for ECHELON-2 was not provided. Therefore, the ERG was unable to validate the information provided in the CS…" This is factually inaccurate – as requested, the official CSR report of the ECHELON-2 trial was sent to the ERG on December 10th 2019. The CSR sent to the ERG is the report developed by the global clinical development team which was the source of data used to inform the NICE submission as well as the Horwitz et al Lancet publication. The Appendices and supplementary information were not provided due to size and complexity of the files. However, on numerous occasions, we offered to provide any specific information requested by the ERG. The CSR report refers to all supplementary information available and had a full listing of the associated Appendices.	Please revise this sentence to: "The clinical study report (CSR) for ECHELON-2 was provided on December 10th 2019. However, the company did not provide the Appendices to the CSR but offered specific information from these upon request." Please remove the following sentence: "Therefore, the ERG was unable to validate the information provided in the CS."	The main body of the CSR was provided to the ERG on December 10th 2019. As explained in the ERG clarification responses and a subsequent email, we were unable to provide the full Appendices to the CSR due to the size and complexity of the files, but we did offer to provide any specific information the ERG requested; no such requests were received. The main body of the CSR was sent, but not the Appendices, therefore stating that the CSR was not provided is factually incorrect. Furthermore, the CSR refers to all supplementary information available, therefore the ERG has full oversight of all available data. The data from the ECHELON-2 CSR, which informed the CS, matches the data which was published in the Horwitz et al Lancet publication. The outcomes and data presented in this peer-reviewed publication, in a highly reputable journal, match those presented in the CS and in the provided CSR. As such, we disagree with the ERG statements regarding the verification of the presented data and we also do not agree with the ERG	Not a factual error. As detailed in section 4.2.1.1 of the ERG report, "the ERG considers the document provided for ECHELON-2 as incomplete as it is very short (117 pages) and included numerous references to Tables, Figures, Appendices and "Listings" not included in the document." The section also discusses file size restrictions as well as the offer to request specific information. Overall, as stated in the ERG report, "the ERG considers the refusal to provide the full CSR despite numerous requests a critical shortcoming of the CS as it severely hampers the ERG's ability to identify any potential issues with the submission and to support the decision making of the committee". The ERG stands by this statement.

The data presented in the CS matched the Horwitz et al Lancet paper and could be verified by this peer-reviewed publication.		conclusion that the failure to provide the full CSR was "a critical shortcoming of the CS as it severely hampers the ERG's ability to identify any potential issues with the submission".	

Issue 1 Primary Analysis of the ECHELON-2 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 16, 53, 57 and 58 of its report, the ERG incorrectly refers to the 15th August 2018 data-cut of the ECHELON-2 trial as the *interim analysis.* This was the *primary analysis* of the ECHELON-2 trial as described in Section B.2.3.1 of the CS and should be described correctly.	Please replace *interim analysis* with *primary analysis* in reference to the 15th August 2018 data-cut of the ECHELON-2 trial on pages 16, 53, 57 and 58 of the ERG report.	The ECHELON-2 trial was powered for the *primary analysis* which occurred on 15th August 2018 and all data presented in the CS are based in the *primary analysis.* During the ERG clarification letter, we provided the estimated date of the *final analysis* which is planned to the end of 2020. No *interim analyses* are planned for the trial.	Not a factual error. In response to the request for clarification, the company stated that "the evidence presented in the Lancet publication by Horwitz et al and the clinical and cost-effectiveness data presented in this submission reflect the most up to date data available. The next data cut of the ECHELON-2 trial is planned for late 2020, with analysis and evidence likely to become available in 2021". Therefore, the results presented are from an interim analysis and the ERG correctly highlighted that "currently OS data are not mature and that the later analysis may provide mature OS data".

Issue 2 Reference for Table 1.1

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 1.1 (page 17) of the ERG Report notes that the sources of the data in the CS are Tables 14, 15, 17 and the clarification response. The source of data for PFS at event cut-off is Figure 11, but Figure 11 is not included in the list of source material.	Include "Figure 11" in the first note of the table.	This will improve the accuracy of the note.	Not a factual error. Data for PFS at event cut-off were taken from page 11 of the response to the request for clarification.

Issue 3 Definition and interchangeability of average, mean and median

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 18, 19 and 50 of their report, the ERG interchangeably uses and compares mean, median and average age which is statistically incorrect. The ERG selectively applies 'average age' to mean and median age reported across trials depending on the source. This analysis presumes that these two descriptive stats are comparable which is mathematically incorrect. • Page 18-19: The company CS average age of 55.1 years (mean) is compared to the Gleeson reported age of 58 years (median). This ignores that	On page 18-19 of the ERG report, in referencing of the Gleeson paper, please add that the assumption that the average age applied is based on the median age and acknowledge this limitation. For transparency, please also add that the median age of the Gleeson population is the same as the median age for the ECEHLON-2 population. Please revise all references to the starting age in the CS of 55.1 years to state that this is based on the mean age from the ECHELON-2 paper. For transparency the median age of the ECHELON-2 paper should be compared to the median age of the other sources. On page 80, please either revise the weighted average age or add descriptions of the statistical limitations of this analysis which	It is incorrect to interchangeably use average and median (as assumed by the ERG in the Gleeson paper) and even more so to compare mean values and median values as is done by the ERG when comparing the starting age of the economic model accompanying the CS (mean based) and external references (median based). In all of the sources presented by the ERG on pages 18-19 and pages 79-80, the median age of patients with PTCL is higher than the mean age, therefore, to assume that the mean and median ages are comparable is clinically misleading.	Main comment: The company used in the model the average age from the ITT population (55.1 years) in ECHELON-2. The ERG suggested that this parameter should be based on UK patients. In ECHELON-2, the mean age for UK patients was 60.9 but this number was obtained form 21 patients only, which was deemed too low by the ERG to provide a reliable estimate. The company also provided evidence about the age of UK patients in an HMRN audit in Yorkshire: [redacted]

the ECHELON-2 median age was the same as the Gleeson median age of 58. • Page 50: The ERG states that it considered that the ECHELON-2 population appeared to be representative of patients with PTCL in the UK. However, the ERG contradicts this statement on page 80 where it states that the average age from the CS should have been larger. The mean age in the CS was taken directly from the ECHELON-2 trial which the ERG acknowledged was representative of UK patients. • Page 80: the ERG assumes the median age = average age for the Gleeson et al. 2018 paper and compares this to the mean age used in the CS and model. The new starting age is calculated based on a weighted average which mixes mean and median values. This is flawed as all data sources for PTCL show the median age is higher than the mean in patients and the two are not interchangeable. • Page 80: The HMRN data set is based on one region of the UK, Yorkshire. Although this information is useful, the general	compares medians and means. Please also add that the mean age across literature is lower than the median age in PTCL and that that the Gleeson 'average' age is likely lower than the reported 58 years median. Please align the statements on page 79-80 of the ERG report to be consistent with the conclusions from the clinical section (i.e. statements on page 50 of the ERG report) which state "the ECHELON-2 population appeared to be broadly representative of patients with PTCL in the UK." Please either remove the HMRN mean age from the 'weighted average' or add comments one the comparability of the average age of the general population of Yorkshire, one region of the UK, to the general UK population. As the impact on outcomes of changing a prognostically important factor, age (ranked among the top two prognostic factors for patients with PTCL by clinical experts), has not been considered in the ERG analysis of artificially inflating the starting age. We suggest removing this from the preferred base-case scenario and instead making it an exploratory scenario and acknowledging this limitation in the ERG report.	The median ages of patients in the ECHELON-2 trial and the Gleeson paper are both 58 years of age, therefore it is reasonable to assume the mean age of the Gleeson population would be lower than the median and furthermore that this mean would be aligned that of ECHELON-2 population which is the starting age of patient in the economic model. The mean age used by the company in its base case was taken directly from the ECHELON-2 study which was also used for all other inputs in the CS. This is a study that the ERG has already acknowledged included a population that is representative of patients with PTCL in the UK. As age is a key prognostic factor, changing the age but keeping the other inputs from ECHELON-2 is not appropriate. The company's position is that the base case analysis (including the ERG's base case) must use the mean age from the ECHELON-2 trial, matching the other inputs, and that any other value should only constitute a scenario analysis and the limitations of this analysis should be explicitly stated.	years based on [redacted] patients; and the paper from Gleeson et al. reporting median age of 58 years from 156 patients. From these three sources, the ERG considered the HMRN the most representative for UK patients (given the relatively large number of UK patients in this study). However, with the purpose of maximizing all the available information, the ERG decided to use the 3 sources assuming that the median = mean in Gleeson. Even though the ERG is well aware that mean and median are not the same, it was deemed the best choice so that data from Gleeson could be included. Given the uncertainty around this assumption, the ERG conducted 7 scenarios changing age at baseline. The results are shown in Table 7.9 of the ERG report. As mentioned in Issue 33 of this document, the ICERs in Table 7.9 should have been based on different mortality multipliers and therefore, they are approximate. If the weighted average approach were deemed implausible, the ERG would have chosen the age reported by the HMRN

demographics of residents of Yorkshire compared to the UK average have not been considered (i.e. average age). • Page 80 and Section 7: the analysis presented changes the starting age of the patients but applies all other data from the ECHELON-2 trial. This is analysis is not valid as age was deemed as one of the most improtant prognostic factors by clinical experts and any change to it would confound the data which is not captured in this analysis.			audit for its base-case, which would increase the ERG base-case by approximately £2,000. Specific comments: ● The ERG did not ignore that the ECHELON-2 median age was the same as the Gleeson median age of 58. On page 81 of the ERG report it is written "The company referred to Gleeson et al. 2018, where the reported median (across 156 patients) age at diagnosis of PTCL in the UK was 58 years. Note that this is in line with the median age observed in ECHELON-2 (58 years reported in Table 4.5)." ● The rationale for the assumption median age = mean age for the Gleeson et al. 2018 paper is explained above. ● It is true that the HMRN data set is based on one region of the UK, Yorkshire, and that the general demographics of residents of Yorkshire compared to the UK average have not been considered (i.e. average age). The same is applicable to patients in

			Gleeson et al. since these data are collected from 2 UK hospitals only. ● Regarding page 50, the following change has been made: “the ECHELON-2 population appeared to be broadly representative of patients with PTCL in the UK, except for age, as will be explained in Section 5.2.3 of this report.” ● The following text has been added to page 82: “Note that the assumption of median age = mean age in Gleeson et al. 2018 was made with the purpose of maximizing all the available evidence. Even though mean and median are not the same, it was deemed the best choice so that data from Gleeson et al. 2018 could be included in the model. Since the median age in both ECHELON-2 and the HMRN audit was larger than the mean age, it is likely that the weighted average slightly overestimates the age in the model if it had been based only on means.”

Issue 4 CD30 Expression

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 26, there is a typo in the following statement: *With regards to the expression of the protein CD30 in the different subtypes of PTCL, the ERG notes that whilst 58% of PTCL-NOS are CD30+ (as reported by the CS); only 23% may be considered "strongly positive", i.e. the percentage of CD30+ tumour cells is **5% or higher*** Within the publication, a score of 3 or 4 was considered strongly positive which correlated to a percentage of CD30+ tumour cells of 50% or higher.	Amend the text to state: *With regards to the expression of the protein CD30 in the different subtypes of PTCL, the ERG notes that whilst 58% of PTCL-NOS are CD30+ (as reported by the CS); only 23% may be considered "strongly positive", i.e. the percentage of CD30+ tumour cells is **50% or higher***	Correction of a typo.	Typo corrected.
The last paragraph of Section 2.2. on page 26 states the following: *However, in contrast with the CS, the ERG notes that conflicting results have been reported for the correlation between CD30 expression and the clinical response to BV, i.e. an independent association was suggested by Horwitz et al. 201410 for the phase II study based on 35*	We suggest this sentence be removed or at a minimum revised to comprehensively reflect the body of evidence of CD30-expression and BV activity which found the two to be independent by most studies. Furthermore, the statement should be revised to fully reflect conclusion of the Lamarque paper which does not state an "evident" relationship but instead suggests a positive trend caveated by the opposing conclusions of other research on the topic. We request the analysis of the ECEHLON-2 data by the Illidge et al ICML	The conclusion of the reference is mischaracterised and could lead to a misinterpretation on the relationship between CD30 expression and activity of BV. The current ERG statement only references two small studies, the phase II Horwitz data from 2014 and the case-study based Lamarque data from 2016; both studies have been superseded and the statement is misleading as currently written.	Results of ECHELON-2 have been added.

patients with variable CD30 expression while another small study by Lamarque et al. 201611 indicated that a positive correlation was evident between CD30 expression and clinical response to BV. This statement does not accurately reflect the body of evidence on the activity of BV and expression of CD30 as it focuses on two small studies which have since been superseded. The statement doesn't account for the majority of evidence presented in Section B.2.6.1 pages 62-64 of the CS, including the ICML poster by Illidge et al conducted on patients from the Phase III ECHELON-2 trial. Illidge et al concluded that response rates and durability of response there independent of CD30 expression. The small study referenced by the ERG, Lamarque at al, states that "*to date, four studies have already addressed this issue and failed to demonstrate any correlation between response to BV and the level of CD30 expression on tumor cells. In the previous report on systemic non-ALCL PTCL, more than 80% of the cases featured no or low levels of CD30 expression.*"	2019 poster which found the response rates and durability of response to BV to be independent of CD30 expression in patients with PTCL be added to this section as it is the most relevant data to the decision problem. *However, in contrast with the CS, the ERG notes that conflicting results have been reported for the correlation between CD30 expression and the clinical response to BV, i.e. an independent association was suggested by four prior studies including Horwitz et al. 201410 for the phase II study based on 35 patients with variable CD30 expression and Illidge et al, for the phase III ECHELON-2 study of non-sALCL patients while another small study by Lamarque et al. 201611 suggested a positive correlation between CD30 expression and clinical response to BV but concluded that this was an open issue as four other larger studies did not find a relationship.*	Furthermore, the body of evidence on this topic in PTCL and across other lymphomas has found no relationship and this is not accurately represented by the suggest ERG statement. The ERG reports omits the most pertinent evidence on the topic, the Illidge et al poster from ICML 2019, which specifically assessed response to BV and CD30 expression in patients with PTCL from the ECHELON-2 trial. The poster concluded that response rates and durability of response were independent of CD30 expression; this is the most relevant data to the decision problem. Based on the evidence and precedence form other marketing authorisations from the EMA and FDA, we do not anticipate the EMA license for the use of BV in PTCL to specify a specific level of CD30 expression.	

Issue 5 PTCL Incidence Rates

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In the second paragraph below Table 2.2 (page 26), the ERG reports ONS incidence rates. These rates are not specific to PTCL only and also include cutaneous T-cell lymphomas (CTCL), as well. The rates reported are also from 2016, although 2017 rates are available. Cutaneous lymphomas are outside of the scope of this appraisal as the use of BV for CTCL has already been reviewed by a separate single technology appraisal (TA577).	The more recent rates (2017) should be used (2.0/100,000 for males; 1.1/100,000 for females) and the sentence should be lengthened to include the caveat that these rates are not specific to PTCL and include a broader population which is outside of the scope of the appraisal (i.e., they include CTCL) and the population is therefore higher than would be for PTCL alone.	The current sentence misrepresents the true incidence rate of PTCL in the UK as it includes cutaneous lymphomas which are outside of the scope of the appraisal. The incidence rates of the population in scope, PTCL, are lower than cited by the ERG.	Section 2.2 (page 26) of the ERG report has been amended accordingly.

Issue 6 Impact of BV+CHP on consolidative ASCT

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 27 of the ERG states: *'The change from CHOP to BV+CHP is anticipated to change the proportion of patients who receive consolidative ASCT.'* We believe there is a typo in this sentence as the statement is the original submission clarified that the introduction of BV+CHP is <u>not</u> expected to change the use of consolidative ASCT for frontline treatment.	*'The change from CHOP to BV+CHP is not anticipated to change the proportion of patients who receive consolidative ASCT.'*	Typo; the word 'not' has been omitted which changes the meaning of the statement in the original submission.	Typo corrected.

Issue 7 Database Search

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Table 4.1 on page 37 and the associated text on page 38 states that "Date spans of electronic databases were not reported" (listed under "Reported date range" column of Table 4.1).	Suggestion to amend to "No date limitations were applied". Amend text in Table 4.1 to "Electronic databases" and "HTA agencies" rows and "Reported data range" column to "No date limit"	No limitations on publication dates for the database searches nor HTA agency documents were applied. Neither PICOS nor search strings had any date limitations added.	Text in Table 4.1 and ERG comment amended. Please note that the database end date is normally a day before the search date so it is not accurate to say "from inception to 29 August 2019". Removed "Not reported" from the Table 4.1 for HTA agencies and Trial registries as this is not applicable to these resources which are current resources.

Issue 8 Description of Fanale 2014 trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
The sequential treatment approach used in Fanale 2014 is listed in Table 4.3 (page 43) of the ERG report as a 'comparator'	The sequential treatment approach should be listed as an intervention	This change would bring Table 4.3 of the ERG Report into alignment with Table 8 of the CS.	Amended accordingly

Issue 9 Permitted concomitant medications

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Table 4.4 (page 47), G-CSF, SCT and radiotherapy are all	The permitted medications should be listed	The current summary creates a discrepancy between the	Table 4.4 of the ERG report was amended to reflect this

listed as “permitted at the discretion of the treating physician based upon institutional standards”.	verbatim as in the CS: Permitted: granulocyte-colony stimulating factor (G-CSF) was permitted at the discretion of the treating physician based upon institutional standards Permitted: consolidative stem cell transplantation (SCT) or radiotherapy after treatment was permitted at the discretion of the treating physician (SCT intent was prespecified before the first cycle of chemotherapy).	information presented in Table 4.4 and the originating table (Table 9) of the CS.	suggestion.

Issue 10 Percentage of women in ECHELON-2

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In the text at the top of page 49 of the ERG report, the percentage of women is reported as 41%. However, in Table 4.5 immediately below the text, 41% relates to the BV+CHP arm. The percentage for the total trial population is 37%.	Change the sentence to say: “The percentage of women in the trial was 37%”	Typo; the percentage in the text is incorrectly attributed to the total trial population.	Typo corrected.

Issue 11 Provision of CSR

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 45 and throughout its report the ERG states that “Given the lack of a full CSR for the main trial for this CS, ECHELON-2, the ERG was unable to validate the	Remove or revise these sentences to reflect that the CSR of ECHELON-2 was provided to the ERG however the Appendices of the CSR were not provided.	The main body of the CSR was provided to the ERG on December 10th 2019. As explained in the ERG clarification responses and a subsequent email, we were unable	Not a factual error. See response to issue #1 for details.

information provided in the CS". Section 4.2.1.1 goes on to refer to the CSR which was provided to the ERG as "incomplete" and "does not consider the document to be a full CSR" which is a mischaracterization as the CSR sent to the ERG is the official CSR report as developed by the global clinical development team. Please note that there is also a typo on page 44 paragraph two which currently state*s:* "to provide the full CSRs of all studied [sic!] used in this submission"*.* Page 45 also incorrectly states "Importantly, it should be noted that it might be difficult or even impossible to make informed requests for appendices, tables or graphs without knowing what these cover." All tables, lists and figures available for ECHELON-2 are referred to throughout the main body of the CSR report (as mentioned by the ERG in paragraph two of page 44) and the full list of the Appendices can be found on page 117 of the CSR. On page 51 of the ERG report, it states that "Although the main outcomes were reported in the CS,	Please revise all mentions of an *incomplete CSR* or *CSR not provided* (as found on pg 59, 64,66 etc) throughout the ERG report to accurately reflect that the main body of the CSR was provided but the Appendices were not provided due to the size and complexity of files but any specific information is available any time upon request. Please remove the statement regarding difficulties in making informed requests from page 45 as the CSR report the ERG is in possession lists or cites of all supplemental information available for ECHELON-2. Please revise the statement on page 50 to: "the ERG was ~~unable~~ able to verify ~~all~~ outcomes reported in the Horwitz et al Lancet publication and those found in the ~~incomplete~~ CSR (see section 4.2.1 for details) provided by the company. The ERG was not able to verify results found in the Appendices." Please revise the rating of 'unclear'"	to provide the full Appendices to the CSR due to the size and complexity of the files but we did offer to provide any specific information the ERG requested; no such requests were received. The complete main body of the CSR for ECHELON-2, was sent to the ERG and it is therefore inaccurate to state that the CSR was not provided or refer to it as an incomplete CSR .The CSR which is in the ERG's possession provides a full list of Appendices (page 117 of the CSR) and references all supplementary information available throughout the CSR report. The Appendices and all supplemental information remain available upon request. The data from the ECHELON-2 CSR, which informed the CS, match the data which was published in the Horwitz et al Lancet publication. The outcomes and data presented in this peer-reviewed publication in a highly reputable journal match those presented in the CS and in the provided CSR. As such, we disagree with the ERG statements on page 45 and page 51 of their report and we also do not agree with the ERG conclusion on page 45 that the failure to provide the full CSR was "a critical shortcoming of	

the ERG was unable to verify all outcomes in the incomplete CSR (see section 4.2.1 for details) provided by the company and has thus rated this criterion as 'unclear". This is also repeated on page 66.		the CS as it severely hampers the ERG's ability to identify any potential issues with the submission".	

Issue 12 Percentage of deaths

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Table 4.11 of the ERG report (page 59), the % of deaths in the BV+CHP arm is reported as 22%. This is different to what is in the source table of the CS (Table 15).	Change the number to be: 51 (23%)	Typo; modification would align Table 4.11 of the ERG Report into alignment with Table 15 of the CS.	Typo changed in Tables 1.2 and 4.11.

Issue 13 Typo Correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Typo on page 59, Figures 2 and 3 of the response to clarification questions showed results in favour of **BV compared to CHOP** when considering Europe (PFS: HR 0.53, 95% CI 0.35 to 0.81; OS: HR: 0.56, 95% CI 0.33 to 0.95) and the overall results.	Figures 2 and 3 of the response to the request for clarification showed results more in favour of **BV + CHP compared to CHOP** when considering Europe (PFS: HR 0.53, 95% CI 0.35 to 0.81; OS: HR: 0.56, 95% CI 0.33 to 0.95) and the overall results	Correction of a typo.	Typo corrected.

Issue 14 Typo Correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Page 59 reports the following: • No (%) treatment-related adverse events; BV + CHP - 201 (90%); CHOP - 193 (85%) • No (%) treatment-related serious adverse events; BV + CHP - 58 (26%); CHOP - 45 (29%) In CSR they are described as '*Subjects with any brentuximab vedotin or vincristine-related event n (%)'* rather than treatment related adverse events. The percentage is also incorrect for serious adverse events in CHOP arm	Subjects with any brentuximab vedotin or vincristine-related event n (%); BV + CHP - 201 (90%); CHOP - 193 (85%) Subjects with any brentuximab vedotin or vincristine-related SAE, n (%); BV + CHP - 58 (26%); CHOP - 45 (20%)	Correction of a typo.	Typo corrected and footnote added in Tables 1.2 and 4.11.

Issue 15 Database Search

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 68, the ERG comment "Date spans for databases were not reported." It also states in Table 5.1 (page 67) "Electronic databases" line "Reported data range" cell "Not	Suggestion to amend to "No date limitations were applied". Amend text in Table 5.1 "Electronic databases" line "Reported data range" cell "No date limit"	No limitations on publication dates for the database searches were applied. Neither PICOS nor search strings had date limitations applied, as stated in the respective Table 1 of Appendices G, H and I of the CS	Amended text in Table 5.1 and on page 68.

reported”			

Issue 16 Targeted Search and PubMed Search Strings

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Section 5.1.2. (page 69), the ERG Comment “No mention was made of any language restrictions. Therefore, the ERG has to assume that no articles were excluded due to language.”.	Suggestion to amend the first sentence to “No language limitation was applied”.	We would like to confirm the ERG’s assumption that articles were not excluded due to language.	Not a factual error. Thanks for the confirmation.

Issue 17 Description of modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Table 5.2 (p71) of the ERG report, the ERG states that “the same modelling approach was used in all previous NICE technology appraisals for BV.”	The company requests that the underlined text be replaced with: “The same model structure was used as in previous NICE appraisals, with a key difference in health state modelling; previous appraisals considered health states based on receipt of SCT, where treatment with BV may act as bridge to SCT. “	As described in Section B.3.2 of the CS, the objective of treatment with BV in the frontline PTCL setting is not to bridge patients to SCT, and receipt of transplant is not the main driver of efficacy in ECHELON-2 or of cost-effectiveness in our analysis.	Text amended as suggested by the company

Issue 18 Utilities approaches

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Table 5.2, (p72) of the ERG	The company requests that the underlined text	As described in Section B.3.4.5 of	Text amended as suggested by

report, in the row titled "Health related QoL" and the column titled "Approach", the ERG states that both utilities approaches "included covariates for age, experiencing Grade 3-4 AEs and being post-SCT".	be replaced with: "included covariates for age, experiencing Grade 3-4 AEs, being post-SCT and baseline EQ-5D."	the CS, the utility values applied in the base-case and the alternative approach included baseline EQ-5D as a covariate.	the company

Issue 19 AE Costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In Table 5.2 (p73), in the row titled "Resource utilisation and costs" and in the column titled "Source/Justification in the company submission", the ERG states that AE costs were based on "Grade 3-4 AEs occurring in >5% (…) and Grade 1-2 peripheral neuropathy (…)."	The company requests that the underlined text be replaced with "Grade 3-4 peripheral neuropathy".	As described in Section B.3.3.4 of the CS, diarrhoea was included at Grade 1-2 and 3-4, and peripheral neuropathy as Grade 3-4.	The text in Table 5.2 "AE costs were based on Grade 3-4 AEs occurring in ≥5% of patients in ECHELON-2, as well as Grade 1-2 diarrhoea and Grade 1-2 peripheral neuropathy." Has been replaced with the text "AE costs were based on grade 3-4 AEs occurring in ≥5% of patients in ECHELON-2, as well as grade 1-2 diarrhoea. No costs were included for the treatment of grade 1-2 and grade 3-4 peripheral neuropathy."

Issue 20 Source of utilities in previous NICE appraisals

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In the *Source of Utilities* section of	Please revise to: *EQ-5D and a regression*	Source of utilities for a related	Text amended as suggested by

Table 5.4 on page 77, only includes the ALCANZA trial data for TA577, however this STA also used the Swinburn et al. to inform the end-stage management stage.	*model to fit the Skindex-29 to the EQ-5D, both collected in the ALCANZA trial. The Swinburn et al. 2015 using health-state vignettes was applied to the end-stage management utilities.*	appraisal, TA577, is not comprehensive as currently written.	the company

Issue 21 Distribution description

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 86, and 94, the ERG refers to Figure 5.3 and Figure 5.7 to demonstrate that "the generalised gamma is the second-best probability distribution for PFS/OS for both treatment arms…" It is unclear if the ERG is referring to the generalised gamma as being the second-best probability distribution in terms of fit to the data or in terms of outcomes.	The company suggests that Figure 5.3 be replaced with Table 5.7, and Figure 5.7 with Table 5.9, and for the generalised gamma distribution to be referred to as the best-fitting distribution, rather than the "second-best". Conversely, if the ERG intended to say that the generalised gamma was the second-best probability distribution in terms of outcomes, we would recommend describing this.	It is unclear if the ERG is referring to the generalised gamma as being the second-best probability distribution in terms of fit to the data or in terms of outcomes. We would recommend clarifying in which context the ERG believes the generalised gamma is 'second-best'.	Based on this comment, the ERG has amended the text as follows: instead of "second best" it is written now "the generalised gamma is, after the Gompertz, the probability distribution with the highest long-term PFS/OS for both treatment arms".

Issue 22 Spline models

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 19, 86, 94 and 153 the ERG states "*exploring other non-standard parametric distributions (e.g. spline models)*	This should be rephrased to "*exploring other non-standard parametric distributions (e.g. spline models) might have been appropriate in this case, in line with was suggested by one of*	The exploration of spline models was suggested by a health economist, not a clinician.	Text amended as suggested by the company

might have been appropriate in this case, in line with was suggested by one of the clinical experts consulted by the company"	*the economic experts consulted by the company*"		

Issue 23 Model selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 89 of the ERG report, it states that: "When the stratified approach to modelling is selected, only OS in the CHOP arm should change, but this is not happening in the model." This is followed by: "This suggests that the OS TSE adjustment for ECOG PS 2 patients was not implemented for the stratified approach."	A clarification to be added to the options selected, under which the CHOP OS curve is not shifting, for instance: "When the stratified approach to modelling is selected, no shift is observed in the CHOP OS arm when excluding/including ECOG 2 patients, as this scenario is only available under base case assumptions (i.e. joint models)."	The company disagrees with the first statement, and upon verification in the latest model shared with the ERG, can confirm that only the OS curve in the CHOP arm shifts when the stratification approach is switched from 'joint' to 'independent', regardless of the ECOG 2 scenario or re-treatment approach applied. However, we agree that the scenario which excludes ECOG 2 patients is only available when joint models are selected.	Text amended as suggested by the company

Issue 24 Typo correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 92, the ERG state *"Given that the hazard rate functions in Figure 5.8 cross twice, it is not possible these hazard rate functions would result*	This should be amended to *"Given that the hazard rate functions in Figure 5.8 cross twice, it is not possible these hazard rate functions would result in a constant hazard ratio for OS."*	Correction of a typo; this section is discussing the OS distributions.	Typo corrected

in a constant hazard ratio for PFS."			

Issue 25 Survival curve plausibility

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On pages 86 and 94, the ERG states that "*the plausibility of the estimated long-term probabilities (tails of the survival curves) was not explicitly quantified in the CS*" and that it would be important to test the plausibility of other distributions.	The company requests that these statements be removed.	Distributions were assessed by clinical experts to determine which extrapolations produced the most plausible longer-term estimates of OS and PFS. Discussions with clinical experts included both expected long-term PFS and OS outcomes at different time points and the assessments of curve fits. Clinicians were first asked to map out long-term outcomes independently of the parametric extrapolations; they were subsequently shown extrapolated curves in both instances, the generalised gamma was selected as most representative. Additionally, the company tested the impact of applying different distributions for survival in scenario analysis. Section 3.10.2 of the submission discusses the external validity of the model and difficulty in comparisons with historical data. It is unclear from the report why this extensive work undertaken by the company does not, in the ERG's	Not a factual error. The CS emphasises that the generalised gamma was selected as "most representative", but it does not discuss the representativeness or plausibility of the other distributions. The scenarios presented by the company assessed the impact of assuming different distributions, but they did not inform about the plausibility of the extrapolations (e.g. how clinically plausible are the Gompertz or the exponential distribution – the two more "extreme" extrapolations).

		opinion, constitute an assessment of the plausibility of long-term outcomes and assessment of alternative distributions.	

Issue 26 Guidelines

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 99, the ERG states that SCT as salvage treatment in patients with relapsed PTCL is "recommended by ESMO guidelines" but omits the mention of BSH guidelines, which are referred to in the CS on page 105. Furthermore, on pages 35 and 100, the ERG says that it is not able to validate the assumptions surrounding the eligibility criteria for transplantation in the UK or proportion of patients receiving auto- and alloSCT, or to confirm whether they are reflective of UK clinical practice.	The company requests the addition of the BSH guideline in reference to the first statement: "In this situation, as recommended by European Society for Medical Oncology (ESMO) and the British Society of Haematologists (BSH) guidelines, salvage treatment in relapsed PTCL patients aims to bridge patients to either an AutoSCT or an alloSCT." Regarding the highlighted statement from page 100, we would request that this be either deleted or amended as we believe it contradicts the earlier statement on page 99 of the ERG report that "The majority of consolidative SCTs in ECHELON-2 were AutoSCT, which according to these experts, is reflective of UK clinical practice." The company can confirm that the approach we have taken here is reflective of UK clinical practice and has been validated by UK clinical experts. Furthermore, as cited in the CS and the response to the ERG clarification questions, the eligibility criteria for SCTs were based on UK clinical expert opinion, therefore the statement on pages 35 should be removed or revised to	The company requests a change in the wording on page 99 of the ERG's text to acknowledge that a UK guideline was used to cross-check the treatment pathway post-relapse, as described in Section B.3.3.6 of the CS. As explained, the company is concerned that the statement on page 100 contradicts an earlier statement by the ERG on page 99 of its report. Likewise, we are concerned about the question of SCT eligibility criteria being reflective of UK clinical practice (page 35). As we note that no clinical experts were included in the list of authors nor listed under Acknowledgements on page 2 of the ERG report, we would urge the ERG consult with UK clinical experts on topics related to reflectiveness of UK clinical practice.	The text regarding the reference to the BSH guidelines has been amended as suggested by the company. Regarding the statement on pages 35 and 100, the ERG considers that this is not a factual error, e.g. the statement on page 99 refers to SCT in the context of consolidative therapy, whereas on page 100 is in the context of post-progression.

	reflect that.		

Issue 27 CIC marking

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 108, in Table 5.22, the Costs of BV+CHP (list price) per model cycles and the Total cost per model cycles (using BV list price) are not redacted, however they should be marked CIC and redacted as per the CS redactions.	Please redact BV *Cost per model cycle* for BV (list price) and Total cost per model cycles (using BV list price).	Commercial in confidence redaction missing.	CiC marking corrected

Issue 28 Peripheral neuropathy costs

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 117, the ERG states that it *"…does not agree with the exclusion of costs for the treatment of peripheral neuropathy. Even though the company referred to clinical expert opinion to support this assumption, the ERG considers it contradictory that these costs were included for the same intervention (BV) in TA478."*	The company requests that the underlined text be replaced with: "The company referred to clinical expert opinion to support this assumption, which confirmed that the clinical response to an episode of peripheral neuropathy would result in interrupting treatment with BV+CHP or CHOP until improvement or resolution of the peripheral neuropathy."	As stated in Section B.3.5.3 of the CS, clinical expert opinion informed the decision to exclude the cost of peripheral neuropathy in the company's analysis after receiving input from a clinical expert. The company considers this to be an important consideration and justification for the exclusion of costs associated with treating peripheral neuropathy, and that it should be acknowledged more explicitly in the ERG's text.	Not a factual error. It is the task of the ERG to assess all the evidence submitted by the company. In this particular example, this evidence consisted of expert opinion and a previous technology appraisal (TA478). Therefore, the ERG did not ignore the input of the clinical experts consulted by the company. However, given that

		We also note that the opinion of the clinical expert is consistent with the advice in the SmPC for Adcetris (brentuximab vedotin) – "Patients experiencing new or worsening peripheral neuropathy may require a delay and a dose reduction of ADCETRIS or discontinuation of treatment." We note the ERG's comment regarding what was done in TA478, but we do not consider this relevant in light of the above. The company's primary and overriding concern here is to not contradict the consistent advice offered by both the clinical experts and the SmPC.	this contradicted the approach in TA478, the ERG decided to take a more conservative approach and assumed that additional costs were incurred for the treatment (of the symptoms) of peripheral neuropathy as done in TA478. As shown in the ERG results, this assumption had a minimal impact on the model results.

Issue 29 Typo correction

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 119, in the first paragraph of Section 6.2.1, there is a typo on the incremental cost statement. The current sentence reads: *"…this was £25,741 per QALY gained (incremental costs were [redacted] and incremental QALYs were 1.14)…"*	the correct incremental cost is £29,224, therefore please amend the text to state: "*…this was £25,741 per QALY gained (incremental costs were [redacted] and incremental QALYs were 1.14)…"*	Typo in the incremental costs	Typo corrected

Issue 30 Modelling approach

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 124, the ERG states that, *furthermore, a stratified modelling approach was not explored.* This is not correct, based on the ERG request from the clarification question, functionality to allow for a stratified modelling approach were included and provided to the ERG.	The company requests the sentence be removed.	Following a request from the ERG in the clarification letter, this analysis was conducted and a cost-effectiveness model which allowed for stratified modelling was provided to the ERG. Therefore, this statement is not accurate and should be removed.	Not a factual error. This sentence refers to the scenarios presented in the original company submission and reported in Table 6.6 of the ERG report.

Issue 31 Input selection

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
On page 129, the ERG states that "…it was not mentioned how these inputs were validated or why the inputs from previous appraisals were considered appropriate for the current one" in relation to model inputs from TA478 and TA577.	The company requests the underlined text be removed.	Throughout the submission, justification is provided for why previous appraisals, which informed quality of life and resource use inputs, are appropriate: • Section B.3.2 of the CS: TA478 is described as the most relevant submission to our decision problem, as sALCL represents a significant population of PTCL and our indication is part of the same	Text deleted as suggested by the company

		pathway as R/R sALCL. • Table 31 of the CS demonstrates that our features align with many of the previous submissions in BV, including a justification of the selected inputs. For inputs presenting higher levels of uncertainty (e.g. medical resource use), clinical expert opinion was requested to validate selected values	

Issue 32 Mortality Multiplier Application

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
In their base-case analysis (Section 7), the ERG increased the baseline age of 62.02, and the mortality multiplier to 1.25.	The company requests the mortality multiplier to be amended in the ERG's base case, in line with the company's re-calculation. For a baseline age of 62.02, the multiplier for a 5% excess mortality is 1.1597 and for 6.5% excess mortality is 1.2120.	The mortality multiplier is calculated as a function of general population life expectancy. Changing baseline age means the multiplier must be updated.	The company is correct that the ERG base-case should have been based on the multiplier mentioned by the company here (1.212). However, that number was not available to the ERG at the time we were finalizing the report. For that reason, we made a simple calculation to *approximate* it (1.25 was used for the ERG base-case). It should be noted that the impact on the ICER of changing this value is very small (it decreases the ERG base-case ICER by £232) and the main conclusions from the ERG report would not change.

			The ERG has addressed this issue by adding the following "Disclaimer" text to the ERG report: "The results of the cost effectiveness analyses conducted by the ERG presented in this report are based on an erroneous value of the "mortality multiplier" input parameter (1.25 was used for the ERG base-case instead of 1.212). This was discovered after the report was submitted but it has a minor effect on the cost-effectiveness results. After changing this parameter, the incremental cost-effectiveness ratio (ICER) in the ERG preferred base-case was decreased by £232".

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Technical report

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

This document is the technical report for this appraisal. It has been prepared by the technical team with input from the lead team and chair of the appraisal committee.

The technical report and stakeholder's responses to it are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the appraisal committee meeting.

The technical report includes:

- topic background based on the company's submission
- a commentary on the evidence received and written statements
- technical judgements on the evidence by the technical team
- reflections on NICE's structured decision-making framework.

This report is based on:

- the evidence and views submitted by the company, consultees and their nominated clinical experts and patient experts and
- the evidence review group (ERG) report.

The technical report should be read with the full supporting documents for this appraisal.

Issue date: March 2020

1. Summary of the technical report

1.1 In summary, the technical team considered the following:

Issue 1 Given figures obtained for UK patients in ECHELON-2 and the 2019 HMRN audit, the mean baseline age of 55.1 years used in the company base case appears somewhat low. Clinical expert opinion suggests that mean age at diagnosis differs according to PTCL histology.

Issue 2 The technical team received opinion from two clinical experts who confirm that that the risk of relapse and lymphoma-related mortality would be expected to decrease substantially after 2 years. Both experts disagree with the choice of PFS and OS extrapolations from the company and ERG.

Issue 3 A time-to-death (TTD) approach is preferable to a health state utility value approach for this appraisal.

Issue 4 Capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public is appropriate.

Issue 5 6 cycles of 2nd line brentuximab vedotin (BV) is appropriate for this appraisal.

1.2 The technical team recognised that the following uncertainties would remain in the analyses and could not be resolved:

- The clinical evidence is based on a trial population comprising 70% systemic anaplastic large cell lymphoma (sALCL), as recruitment of 75% (+/- 5%) of this subtype was a planned enrollment target of the trial. This compares with a sALCL diagnosis rate in Europe of 15.8% of all PTCL subtypes. The sALCL subgroup in ECHELON-2 achieved better outcomes than the whole PTCL population taken together.

1.3 The cost-effectiveness results include a commercial arrangement (patient access scheme) for brentuximab vedotin.

1.4 Taking these aspects into account, the technical team's preferred assumptions result in an incremental cost-effectiveness ratio (ICER) of £32,022 per QALY gained (see table 1). The technical team recognise that this ICER is currently uncertain because of a lack of consensus on assumptions to be used in the economic model, in particular issues 1, 2 and 4 of this report.

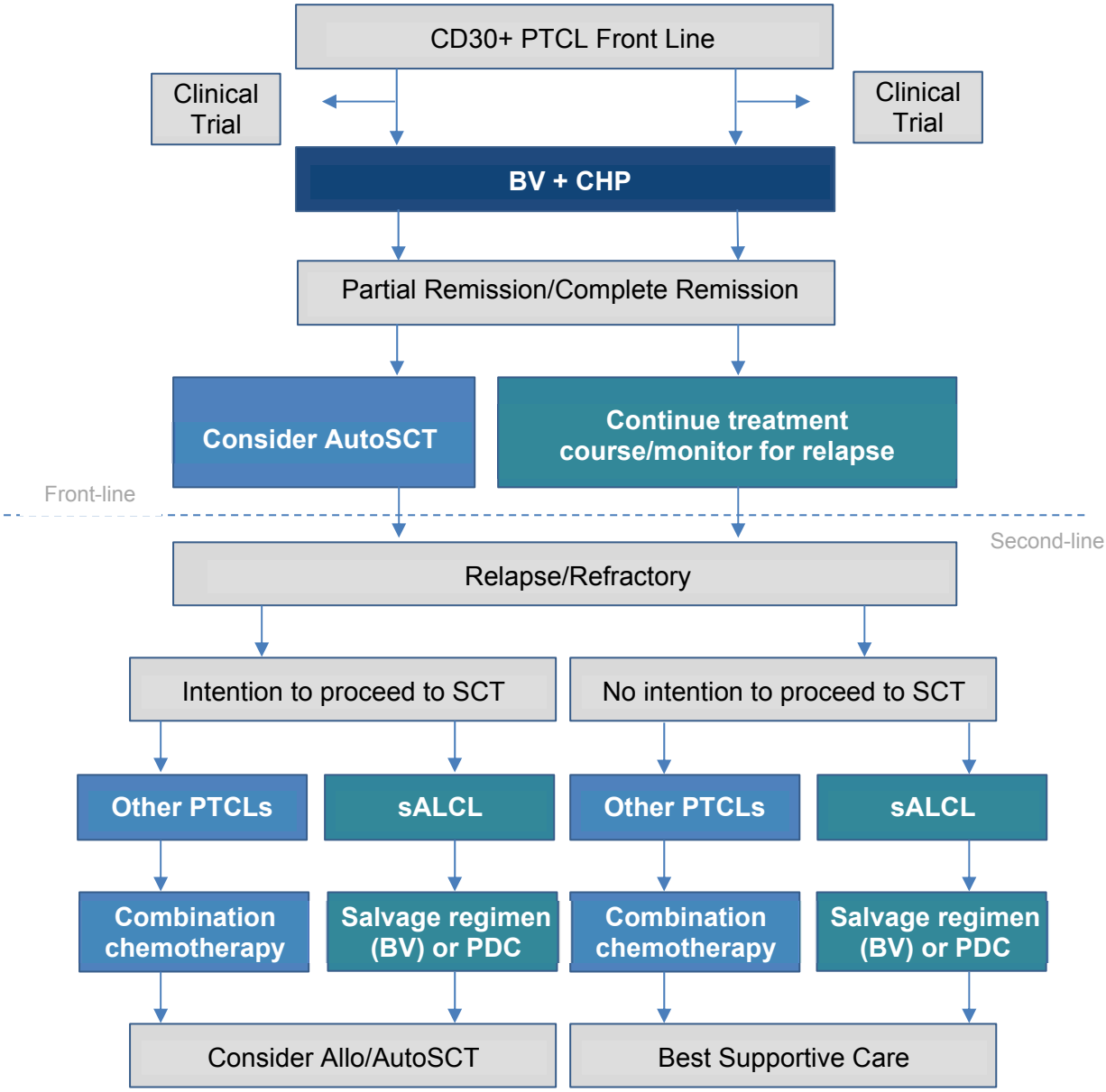
1.5 No equality issues were identified.

2. Topic background

2.1 Disease background

- Peripheral T-Cell Lymphoma (PTCL) is a rare subset of Non-Hodgkin's Lymphoma (NHL), that carries poor prognostic outcomes.
- PTCL is comprised of a heterogenous group of over 25 subtypes, the most common of which are PTCL-not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and systemic anaplastic large cell lymphoma (sALCL).
- Although prognostic outcomes and treatment responses vary across subtypes, PTCL is characterised as an aggressive disease, further complicated by frequent relapses, and primary refractory disease.
- The best chance of inducing a long-term response in T-cell lymphomas is in the front-line setting, and the probability of having a strong response to treatment diminishes significantly with relapse.
- In the UK people are more commonly diagnosed with stage III/IV disease and OS rates decrease substantially for patients with advanced disease. For individuals who relapse after primary treatment, PFS and OS are extremely poor.
- For patients in the UK who have received CHOP therapy, complete remission rates are generally considered low (43.5%) with a median time to progression of disease of less than a year (10.2 months).

2.2 Proposed treatment pathway (from company submission)



2.3 The technology

Marketing authorisation	Brentuximab vedotin (BV) + cyclophosphamide, doxorubicin, prednisolone/ prednisone (CHP) has not yet received marketing authorisation. It is anticipated that BV+CHP will be granted a marketing authorisation for adult patients with previously untreated CD30+ peripheral T-cell lymphoma (PTCL).
Mechanism	BV is an antibody drug conjugate composed of an anti-CD30 monoclonal antibody linked with a microtubule-disrupting, antimitotic drug compound, monomethyl auristatin E.
Administration	The recommended dose of BV is 1.8 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks, to be administered in combination with CHP.
Price	The NHS list price of BV is £2,500 per 50mg vial (ex VAT). The company has a commercial arrangement (simple discount patient access scheme). This makes brentuximab vedotin available to the NHS with a discount. The size of the discount is commercial in confidence.

2.4 Decision problem

	Decision problem addressed in the company submission	ERG comments
Population	Adults with previously untreated CD30+ Peripheral T-Cell Lymphoma (PTCL)	In line with the scope. However, it should be noted that 70% of patients in the ECHELON-2 trial were in subtype sALCL
Intervention	Brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin, and prednisone (CHP)	In line with the scope
Comparator	Established clinical management including: • cyclophosphamide, hydroxydaunorubicin,	In line with the scope

	vincristine, and prednisone (CHOP)	
Outcomes	• Progression-free survival (PFS), • Overall survival (OS), • Overall response rate (ORR), including: complete response (CR), • Health related quality of life (HRQoL), and • Adverse effects (AE) of treatment.	In line with the scope. However, at the last data cut overall survival data were not mature. Further analysis is planned for late 2020
Economic analysis	The economic analysis will follow the NICE reference case.	The cost effectiveness analyses were conducted according to the NICE reference case

2.5 Clinical evidence

Study	**ECHELON-2 (NCT01777152)**
Study design	Double-blind, double-dummy, randomised, placebo-controlled, active-comparator Phase III trial
Population	Patients aged ≥18 years with previously untreated CD30+ PTCL.
Locations	132 sites in 17 countries: Japan, South Korea, Australia, Taiwan, Czech Republic, Denmark, France, Germany, Hungary, Italy, Poland, Romania, Spain, United Kingdom, Israel, United States and Canada (five of the trial sites were located in the UK).
Intervention	Brentuximab vedotin in combination with cyclophosphamide, doxorubicin, and prednisone (BV+CHP)
Comparator	Cyclophosphamide in combination with doxorubicin, vincristine and prednisone (CHOP)
Supports MA	Yes. The proposed marketing authorisation is based on the results of the ECHELON-2 trial.

2.6 Key trial results (PFS, ITT population)

Progression Free Survival	BV+CHP (N=226)	CHOP (N=226)
Median PFS, months (95% CI)	48.2 (35.2, NR)	20.8 (12.7, 47.6)
Stratified hazard ratio (95% CI) (BV+CHP to CHOP)	0.71 (0.54, 0.93)	
Stratified log-rank p-value	0.0110	
Estimated PFS (95% CI), at:		
6 months	82.1% (76.4%, 86.6%)	70.8% (64.3%, 76.3%)
12 months	71.7% (65.1%, 77.2%)	58.2% (51.4%, 64.3%)
24 months	61.4% (54.4%, 67.6%)	47.4% (40.6%, 53.8%)
36 months	57.1% (49.9%, 63.7%)	44.4% (37.6%, 50.9%)

Source: Company submission, Table 14, page 56; NR – not reached

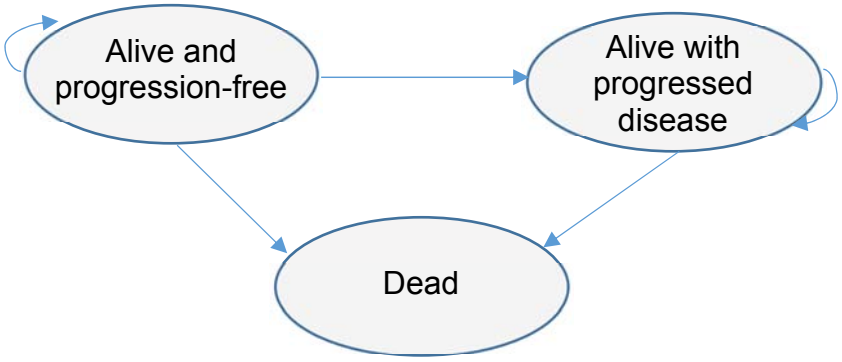
2.7 Key trial results (OS, ITT population)

Overall Survival	BV+CHP (N=226)	CHOP (N=226)
Number of deaths, n (%)	51 (23%)	73 (32%)
Stratified hazard ratio (95% CI) (BV+CHP to CHOP)	0.66 (0.46, 0.95)	
Stratified log-rank P value	0·0244	
Median overall survival (months) (95% CI)	NR	NR (54.2, NR)
Estimated survival rate (95% CI) at:		
6 months	93.7% (89.6%, 96.2%)	89.2% (84.4%, 92.7%)
12 months	87.8% (82.8%, 91.5%)	82.4% (76.7%, 86.8%)

24 months	80.8% (75.0%, 85.5%)	72.6% (66.2%, 78.0%)
36 months	76.8% (70.4%, 82.0%)	69.1% (62.3%, 74.9%)

Source: Company submission, Table 14, page 56; NR - not reached

2.8 Model structure



- Partitioned survival model with 3 health states: *progression-free, progressed disease* and *death.*
- A lifetime horizon of 45 years applied in the model base case.
- 21-day cycle length (aligns with treatment cycle), with a half-cycle correction applied.
- NHS and Personal Social Services (PSS) perspective
- An annual discount rate of 3.5% for costs and benefits

2.9 ERG key model assumptions

Base-case preferred assumptions	Company	ERG
Two-stage estimator (TSE)* adjustment for OS	Patients with ECOG PS 2 included in TSE and proportion of patients receiving subsequent BV	Remove patients with ECOG PS 2 from the two-stage estimator and from the proportion of patients receiving subsequent BV
Costs of transfusion	£147.11	£50.78
Baseline age	55.1 years, per ECHELON-2	62.02 years, weighted average of several UK sources
Mortality multiplier	1.19	1.25
Approach to utilities	HSUV	TTD
Adjustment of long-term utilities	No	Yes
Peripheral neuropathy costs	No	Yes
Treatment cycles second-line BV	8.23	6

* TSE was selected as the most robust and clinically plausible method to adjust for treatment switching.

3. Key issues for consideration

Issue 1 – Average age of PTCL patients in the economic model

Questions for engagement	Is the mean age used in the company base case too low? If so, what age is appropriate for the economic model?
Background/description of issue	The median age of patients in the ECHELON-2 trial was 58 years, with a mean baseline age of 55.1 years at the start of treatment. Of the UK patients in the trial (n=21), the mean age was 60.9 years. A study by Gleeson et al. 2018, reported median (across 156 patients) age at diagnosis of PTCL in the UK as 58 years, mirroring the median from the ITT population in ECHELON-2. Additionally, a 2019 audit from the Haematologic Malignancy Research Network (HMRN) of patients diagnosed with PTCL in Yorkshire described the mean age of [redacted] patients as [redacted] years, and the median as [redacted] years. **The company** used the mean of 55.1 years from ECHELON-2 in their base case economic model. The company described how the ECHELON-2 trial includes a higher proportion (22%) of people with the ALK+ sALCL subtype (median age at diagnosis = 34 years) than is found in the total PTLC population. ALK+ sALCL patients have a much better prognosis, mostly due to the impact of being younger than the majority of people with PTCL, but people with ALK+ disease and a baseline International Prognostic Index (IPI) score of less than 2 (the youngest and fittest) were excluded from this trial, meaning that people with this subtype included in the trial are much closer to the other PTCL subtypes in terms of age at diagnosis, outcomes and prognosis. **The ERG** expressed concern that 55.1 years is not in line with the reported mean age of UK patients in ECHELON-2, or the figures reported in the 2019 HMRN audit. The ERG suggested that a more appropriate average age to use in the economic model would be 62.02 years. This value is calculated as the weighted average of the age values reported in ECHELON-2 (UK patients only), Gleeson et al. 2018 (assuming median = mean), and the HMRN PTCL audit. The ERG notes that the assumption of median age = mean age in Gleeson et al. 2018 was made with the purpose of maximizing all the available evidence. Even though mean and median are not the same, it was deemed the best choice so that data from Gleeson et al. 2018 could be included in the model. Since the median age in both ECHELON-2 and the HMRN audit was larger than the mean age, it is likely that the weighted average slightly overestimates the age in the model if it had been based only on

	means. After the weighted mean, the ERG's next most preferred estimate would be the mean of [redacted] years from the HMRN study.
Why this issue is important	The impact of age in the economic model had a moderate impact on cost-effectiveness. Exploratory analysis by the ERG shows that the lower the baseline age, the lower the ICER. This is mostly due to the incremental QALYs predicted by the model decreasing as age increases. The ICER obtained assuming 55.10 years at baseline, as in the company base-case, was £27,746 per QALY gained; thus, £5,407 lower than the ERG base-case.
Technical team preliminary judgement and rationale	Clinical expert opinion suggests that there are differences in age according to PTCL histology, with people with ALK-positive sALCL (comprising 22% of the ECHELON2 cohort) having a substantially younger median age than people with ALK-negative sALCL or other CD30+ PTCL. In the HMRN Yorkshire dataset ALK-positive sALCL patients are (median) [redacted] years at diagnosis, whilst ALK-negative patients are [redacted] years and overall PTCL are [redacted] years at diagnosis. Hence it is important to recognise the median age of sALCL patients, who comprised 70% of the clinical trial population, as distinct from CD30+ PTCL patients as a whole. The technical team recognises the limitations of the ERG's approach of using a baseline age of 62.02 years whilst holding constant other parameters in the model taken from the trial that are affected by the baseline age, such as mortality risk. The technical team consider that both the company's and the ERG's analyses will need to be considered.

Issue 2 – Choice of extrapolation for long-term PFS and OS

Questions for engagement	Which are the most clinically plausible extrapolations for PFS and OS?
Background/description of issue	Clinical experts consulted by the company considered that the generalised gamma distribution was most reflective of long-term outcomes for OS and PFS. However, the plausibility of the estimated long-term probabilities was not explicitly quantified in the company submission. This is especially important for OS since the selection of the OS long-term extrapolation basically determines the overall gains in quality-adjusted life years (QALYs) estimated by the electronic model. **The company** presented the different extrapolations to an advisory board of clinical experts. Clinical opinion suggested that the generalised gamma distribution was most reflective of long-term outcomes for PFS and OS (amongst standard parametric curves) as it reflected a decreasing risk of relapse or lymphoma related mortality. This was in line with the expectation of these clinical experts that the risk of relapse and lymphoma-related mortality after front-line treatment is the highest in the first two years following treatment and patients who have not relapsed within two years have a low likelihood of relapse. This view is supported by a retrospective analysis of 775 patients from the US, Sweden and Canada which concluded that the risk of relapse and death due to lymphoma for patients with PTCL who have remained disease free for 24 months after their front-line treatment drastically decreases and survival approaches general population mortality. **The ERG** note that the generalised gamma is, after the Gompertz, the probability distribution with the highest long-term PFS/OS for both treatment arms. The ERG would have liked to have seen the clinical plausibility of the estimated long-term probabilities explicitly quantified in the company submission, in particular the lognormal (and to a lesser extent the log-logistic) distributions. This is more important for OS than for PFS because the OS extrapolation largely determines the overall gains in estimated QALYs. On the reduced risk of relapse and lymphoma-related mortality after 2 years, the ERG noted that these reduced risks are not reflected in the company's model. The company presented plots of the extrapolated PFS and OS hazard rate functions over time for both arms. From these the ERG noted that only the generalised gamma and the lognormal distributions result in hazard rate functions for both PFS and OS that initially increase and then decrease over time. However, in all cases, the decline occurs before one year. The ERG considers that the plausibility of these hazard rate functions should be validated by clinical experts.

Figure 1: Standard parametric extrapolation, OS – ITT population – including TSE adjustment (without background mortality applied)

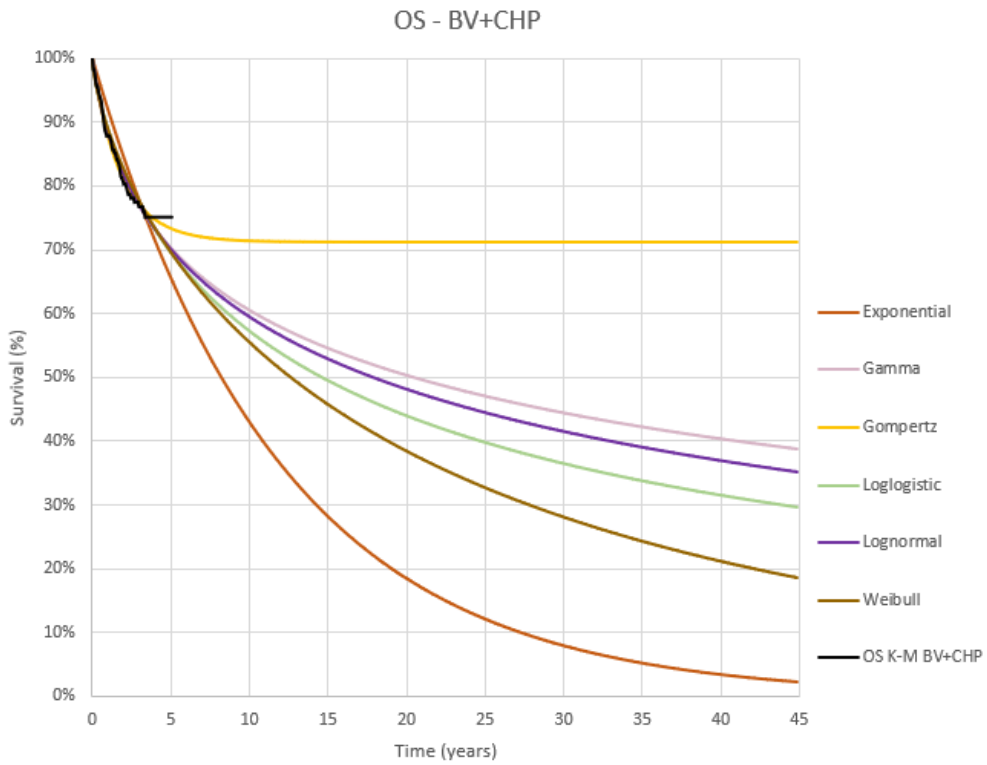


Figure 2: Base-case survival curve extrapolations in the ITT population fitted to the generalised Gamma distribution (including TSE adjustment and adjusted for background mortality)

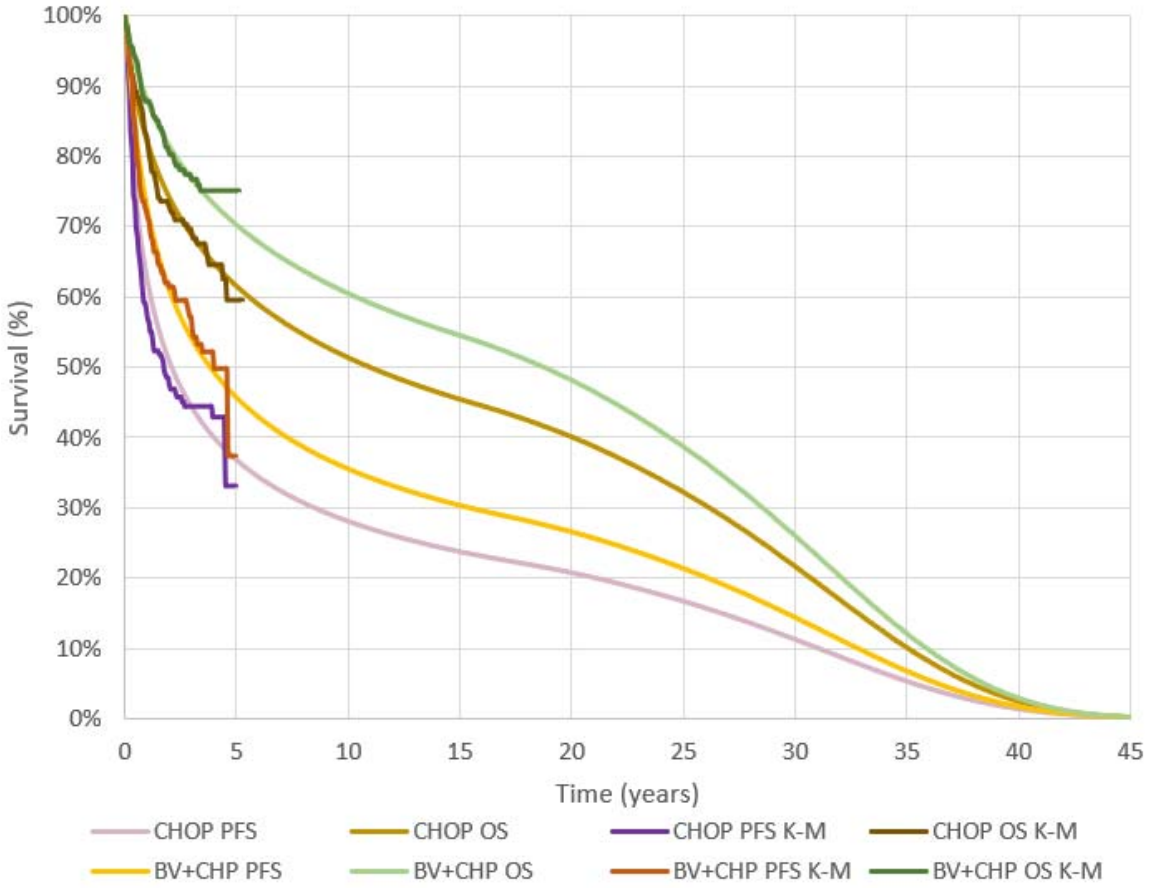


Table A: Timepoints (years) at which OS background mortality hazard takes over in the model

OS Distribution	CHOP	BV + CHP
Exponential	86.03	83.04
Generalised gamma	71.03	70.05
Gompertz	62.06	61.19
Log-logistic	73.90	72.00
Lognormal	72.00	71.03
Weibull	78.33	75.05

Why this issue is important

The choice of extrapolation has a modest impact upon the ICERs.

Table B: ERG OS scenario analyses (PFS = generalised gamma)

OS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£33,153**	[redacted]	[redacted]	£24,076
Exponential	[redacted]	[redacted]	£22,772	[redacted]	[redacted]	£22,952
Gompertz	[redacted]	[redacted]	£29,985	[redacted]	[redacted]	£27,605
Log-logistic	[redacted]	[redacted]	£27,007	[redacted]	[redacted]	£25,208
Lognormal	[redacted]	[redacted]	£30,044	[redacted]	[redacted]	£25,490
Weibull	[redacted]	[redacted]	£23,433	[redacted]	[redacted]	£22,911

Based on the electronic model of the CS[48]

CS = company submission; ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years

	The ERG emphasise that the choice of generalised gamma for OS in the company submission represents the highest impact on the ICER, and that alternative choices would decrease the ERG base case ICER by up to £10,381.
Technical team preliminary judgement and rationale	The technical team agree with the ERG that the clinical plausibility of alternative extrapolations could have been usefully explored in more detail in the company submission. Clinical expert opinion is being sought to validate the choice of curves for PFS and OS.

Issue 3 – Utility model approach

Questions for engagement	Is the time-to-death utility model preferable to the health state utility method?
Background/description of issue	HRQoL was measured in the ECHELON-2 trial using the EQ-5D-3L and valued using the UK EQ-5D-3L value set. Utilities were modelled using both a health state utility value approach and a time-to-death approach. Both approaches included covariates for age, experiencing Grade 3-4 AEs and being post-SCT. The company base-case used the health state utility value approach. However, the utility value for progressed disease was estimated from TA478, instead of from the company's model and data. The EQ-5D data presented suggests that time-to-death has a larger impact on HRQoL than progression. **The company** chose to use the health state utility value (HSUV) method. However, clinical experts consulted by the company felt that the decrement for progression of -0.027 was implausibly small. Therefore, this model decrement was not used and, for the progressive state, the company used a utility value based on the one used in TA478, which was derived from estimates in Swinburn et al. (2015). This study provided utility values for stable disease, complete response, partial response and progressive disease (0.38 for UK patients). The value 0.643 used in the company's model for progression was calculated as a weighted average of the proportion of patients who did and did not receive SCT and the associated utility values calculated in TA478. An age decrement of -0.002 was applied, based on the decrement observed in the HSUV method model used in the base-case. The time-to-death (TTD) method was explored by the company in scenario analysis. **The ERG** is concerned that, given the lack of confidence by the company and clinical experts in this important parameter obtained from the HSUV model, it is difficult to have confidence in the remaining coefficients of the model. With no indicators of model fit or model performance, the ERG

	is unable to assess how appropriate the use of this model is. The ERG would prefer to use HRQoL data obtained directly from patients, rather than the estimates in Swinburn et al. where HRQoL was measured using vignettes in members of the UK general population and therefore do not comply with the NICE reference case. Given that HRQoL was measured directly in patients within the ECHELON-2 trial using the EQ-5D-3L, the ERG prefers to utilise these data. The ERG noted that even though the company's alternative model for estimating utilities using a TTD approach accounted for the decline in HRQoL prior to death, indicators of model fit, and model performance were not provided. The ERG considered that the size and ordering of the coefficients relating to the periods of time prior to death were logical, since the impact on HRQoL became increasingly large as death approached. At clarification stage, the ERG requested to see the results of a model which included both the HSUV and TTD approaches and this was provided by the company. In light of this evidence, the ERG consider that the TTD approach would be better suited to the base-case. The EQ-5D data suggests that time-to-death has a larger impact on HRQoL than progression, and using the TTD approach avoids the problems identified with the HSUV method.
Why this issue is important	It is important that the most clinically plausible utility estimates are correct from a technical perspective, but the different options lead to relatively small changes in the ICERs.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG that the utility values estimated from the study by Swinburn et al. do not meet the requirement of the NICE reference case but also notes that this approach has previously been accepted by committee in TA478. The technical team shares the ERG's concerns about the way that the HSUV approach has been implemented by the company, and that there is uncertainty concerning the validity of this approach. If committee prefers the utility value taken from Swinburn et al for the progressive state then the associated ICERs for both the HSUV and TTD approaches are provided by the ERG as scenario analyses. But due to the heavy censoring of the ECHELON-2 data, the technical team considers that both the HSUV and TTD approaches are at risk of bias, and so relevant utility values from the literature will also need to be considered.

Issue 4 – Utility age-adjustment

Questions for engagement	Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?

Background/description of issue	While the company submission included age as a covariate within their utility modelling, the coefficient obtained from the company model was smaller than age-related utility decrements seen in more commonly applied age-adjustment studies, such as Ara and Brazier 2010. **The company** employed a mean of covariates approach for their prediction of EQ-5D within their model. This included an age-related decrement of 0.002, derived from the EQ-5D data from the ECHELON-2 trial and applied over time. **The ERG** noted that this value was smaller than age-related utility decrements seen in more commonly applied age-adjustment studies. This smaller age decrement meant that in the long term, progression free patients in the model had higher utility values than the age-adjusted utilities of the general population as calculated in Ara and Brazier 2010. The ERG considered this implausible and implemented a constraint in their preferred base-case whereby utilities could not exceed these age-adjusted general population utility values. The ERG also conducted a series of scenario analyses. When the ERG utilised the company's yearly age decrement of -0.00121, obtained from the time-to-death model and removing the constraint that utilities cannot exceed those age-adjusted general population utilities obtained from Ara and Brazier (to match the company's approach to age-adjustment within the ERG preferred utility approach), the ICER decreased by approximately £500. Increasing the size of the age decrement to -0.00177 to match the decrement obtained from the company's HSUV model (utility constraint still removed) increased the ICER by approximately £1,300. When the ERG increased the age-decrement to -0.00434, which represents the yearly decrement in utility obtained from Ara and Brazier at the age of 62 years, the ICER increased substantially by approximately £14,000 from the ERG's base case ICER of £33,153. The ERG noted that these different scenarios demonstrate the sensitivity of model results to assumptions surrounding age-related decline in utility.
Why this issue is important	The age-related utility constraint implemented in the ERG's preferred base case gives a small increase to the ICER. But different utility age-adjustment assumptions explored in the ERG's scenario analyses have a potentially very large impact on the ICER.
Technical team preliminary judgement and rationale	The technical team agrees with the ERG that capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public is appropriate. The team also recognise the potential for very large increases in the ICER from

	different assumptions regarding the appropriate age-related decrement used in the model. These assumptions will need to be considered by the committee.

Issue 5 – Number of 2nd line monotherapy brentuximab vedotin cycles in the model

Questions for engagement	Is a mean of 6 cycles for 2nd line BV appropriate?
Background/description of issue	BV is recommended by NICE as 2nd line monotherapy for the treatment of relapsed or refractory sALCL (TA478). **The company** state in their submission that BV in the relapsed or refractory setting is used as monotherapy and with a potentially longer treatment duration of up to 16 treatment cycles. Therefore, duration of therapy was based on data reported in TA478 (8.2 cycles on average). **The ERG** was uncertain about the assumption of 8.2 cycles from data reported in TA478 because it is unclear whether or not this figure has been validated by clinical experts. In particular, the clinical expert at that committee meeting highlighted that real-world evidence suggests that the median number of cycles for BV is 5 to 6For this reason, the ERG considers that the number of 8.2 treatment cycles for second-line BV is likely to deviate from the maximum number of treatment cycles that are administered in UK clinical practice. Therefore the ERG base case assumes that the use of BV as a second-line monotherapy consisted of six cycles.
Why this issue is important	It is important to accurately reflect real-world clinical practice, and this has a moderate impact on the ICER. Scenario analysis by the ERG shows that using 8.2 cycles decreases their base-case ICER by almost £1,900.
Technical team preliminary judgement and rationale	The technical team accepts that the mean number of cycles for 2nd line BV in the clinical trials was 8.2, but that real-world experience of clinical experts suggests that between 5 and 6 is more reflective of clinical practice in the NHS. Therefore the technical team accepts that 6 cycles as per the ERG's base case is appropriate for this appraisal.

4. Issues for information

Tables 1 to 3 are provided to stakeholders for information only and not included in the technical report comments table provided.

Table 1: Technical team preferred assumptions and impact on the cost-effectiveness estimate (applied individually)

Alteration	Technical team rationale	LYs (Incremental)	QALYs (Incremental)	ICER (deterministic)	Change from base case
Company base case	–	**1.55**	[redacted]	**£24,901**	-
1. ERG correction of minor errors (cost of transfusion error, ECOG PS 2 adjustment in the TSE)	Technical team agreed with ERG's amendments (See Issue 4 for ECOG PS 2 adjustment in the TSE)	1.57	[redacted]	£25,317	+£416
2. Baseline age (62.02 years)	Issue 1	1.32	[redacted]	£29,264	+£4,363
3. Mortality multiplier	(See Table 3, below)	1.54	[redacted]	£25,086	+£185
4. TTD utility approach	Issue 3	1.55	[redacted]	£25,260	+£359
5. Model utilities < general population utilities	Issue 4	1.55	[redacted]	£24,957	+£56
6. Six treatment cycles second-line BV	Issue 5	1.55	[redacted]	£26,620	+£1,719
7. Peripheral neuropathy costs	(See Table 3, below)	1.55	[redacted]	£24,924	+£23
Cumulative impact of the technical team's preferred assumptions on the cost-effectiveness estimate				**£32,022***	+£7,121
* The assumptions in this table have been applied individually and so the cumulative impact does not match the ERG's base case ICER of £33,153					

Table 2: Outstanding uncertainties in the evidence base

Area of uncertainty	Why this issue is important	Likely impact on the cost-effectiveness estimate
Immature evidence base	Median overall survival in the trial has not yet been reached. The analyses are based on extrapolated mean values	Cost-effectiveness estimates are likely to be optimistic. Mean estimates are often greater than median estimates
Relative efficacy between histological subtypes	ECHELON-2 was not powered to compare efficacy between individual histological subtypes with the exception of the sALCL subgroup.	Cost-effectiveness estimates are likely to be optimistic for CD30-expressing PTCLs other than sALCL.

Table 3: Other issues for information

Issue	Comments
Type of modelling for long-term PFS and OS extrapolations	The technical team understands that there is some doubt whether proportional hazards assumption holds for PFS. But the ERG has found that exploratory analysis using a stratified modelling approach to model ICERs using the sALCL subgroup rather than the full ITT population gives counterintuitive results in that the ICERs increase even though BV seems to be more effective in this subgroup. For this reason the technical team shares the ERG's concerns about the validity of the results from the stratified modelling approach and agrees with employing the company's joint modelling approach in its base case.
Adjustment in the model for brentuximab vedotin retreatment	The technical team agrees with the ERG's assessment that the two-stage estimator (TSE), in line with the recommendations in NICE DSU TSD 16, is the most appropriate method for adjusting for re-treatment with BV in both arms of ECHELON-2. The different approaches, explored in scenario analysis, do not lead to widely different estimates and so mitigates concerns about the risk of bias from the use of TSE adjustment. The technical team notes the ERG's caution that probabilistic sensitivity analysis which does not account for the ERG's corrective adjustment to the model will underestimate overall uncertainty.
Mortality multiplier used in the model	Clinical experts consulted by the company indicated that patients in long-term remission are expected to experience a reduction in life-expectancy (due to both increased rates of cardiac toxicity and increased risk of secondary primary malignancies) compared with the general population. The clinical experts consulted by the company estimated a reduced survival of 3% to 10% relative to the general population. The company implemented a mortality multiplier equal to 1.19 in the model to reflect this 5% reduction in life expectancy. The ERG considers that, while the impact of this assumption is not expected to be large, it seems arbitrary to have chosen 5% for the base-case and to keep the parameter fixed in the PSA. Instead, the ERG prefers using a 6.5% reduction in life-expectancy for the base-case (middle point between 3% and 10%) and using 3% and 10% as the limits to be considered for the PSA. Please note: The results of the cost effectiveness analyses conducted by the ERG presented in this report are based on an erroneous value of the "mortality multiplier" input parameter (1.25 was used for the ERG base-case instead of 1.212). This was discovered after the report was submitted but it has a minor effect on the cost-effectiveness results. After

Issue	Comments
	changing this parameter, the incremental cost-effectiveness ratio (ICER) in the ERG preferred base-case was decreased by £232
AE costs for grade 3–4 peripheral neuropathy	The technical team agree with the ERG that the costs of peripheral neuropathy should be included in order to be consistent with the approach taken in TA478.
Cancer Drugs Fund	The company do not consider BV + CHP to be a suitable candidate for the CDF.
End of life	Although the estimates of survival for patients with PTCL vary considerably across studies, none estimate the life expectancy for previously untreated patients PTCL to be less than 24 months. Therefore, the short life expectancy criterion is unlikely to be met. Takeda does not wish for the medicine to be considered at this time for the application of NICE's End-of-Life criteria.

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Technical engagement response form

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

As a stakeholder you have been invited to comment on the technical report for this appraisal. The technical report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

We need your comments and feedback on the questions below. You do not have to answer every question. The text boxes will expand as you type. Please read the notes about completing this form. We cannot accept forms that are not filled in correctly. Your comments will be summarised and used by the technical team to amend or update the scientific judgement and rationale in the technical report.

Deadline for comments: **5pm on Tuesday 28 April 2020.**

Thank you for your time.

Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Notes on completing this form

- Please see the technical report which summarises the background and submitted evidence. This will provide context and describe the questions below in greater detail.
- Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.
- Do not include medical information about yourself or another person that could identify you or the other person.
- Do not use abbreviations.
- Do not include attachments such as journal articles, letters or leaflets. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.
- If you provide journal articles to support your comments, you must have copyright clearance for these articles.
- Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a second version of

your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

About you

Your name	**Tanja Podkonjak**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Takeda UK Limited**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Average age of patients with PTCL in the economic model	
Is the mean age used in the company base case too low?	On 26th March 2020, CHMP issued a positive opinion for brentuximab vedotin in combination with cyclophosphamide, doxorubicin and prednisone (CHP) for treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).[1] This change from the expected population and the original submission dossier (i.e. adult patients with all CD30-positive peripheral t-cell lymphomas [PTCL]), will have an impact on the expected average age at diagnosis (i.e. start age in the health economic model). Mean expected age of patients at presentation is based on PTCL histology as noted in Section 1.1 of the NICE Technical Report. As noted by the NICE technical team's rationale and preliminary judgement, the difference in age at diagnosis between the ECHELON-2 trial[2] and that of other UK sources is likely due to the distribution of PTCL histology in the sample population. However, as the marketing authorisation now reflects only one population and therefore one histology, previously untreated sALCL, this issue is simplified significantly. The differences in the distribution of PTCL subtypes in ECHELON-2 compared to the real-world presentation are no longer a factor. In line with the expected marketing authorisation, the economic model has been updated to include only data from the sALCL cohort of ECHELON-2, including patient baseline characteristics and importantly age. The mean age of the 316 patients with sALCL enrolled in ECHELON-2 was 52.0-years and the median age was 55-years; this is the starting age of patients in the updated model (see Appendix B for all updated sALCL results). In line with clinical expert opinion cited in the Technical Report, the average age of patients with sALCL is slightly younger than the mean age of the broader PTCL population in ECHELON-2 (i.e. 55.1 years and 58 years for the mean and median, respectively) which was the previous base-case. UK patients with sALCL enrolled in ECHELON-2 had a slightly higher mean age, 57.7-years and median age, 64-years, although it should be noted that this is based on only 15 patients. Following the label change, an additional analysis from the Haematologic Malignancy Research Network (HMRN) PTCL audit was requested looking at the sALCL patient population only. The HMRN audit showed that of [redacted] patients with sALCL from Yorkshire, the mean and median ages at diagnosis were [redacted] years and [redacted] years, respectively.[3] The median age at diagnosis of patients with sALCL (n=39) across UK centres as

	reported by the Gleeson et al 2018 publication was 52.2 years.[4] Please note that the mean is not available from the Gleeson et al paper, but it should be noted that across all sources the median age is higher than the mean. The mean age applied within the economic model base case (52.0-years) is consistent with the HMRN data (56.2-years) and aligns well with reported medians from UK reports in the literature. We further consider that the ~4-year age difference observed between ECHELON-2 and UK real-world data is relatively small. Clinical expert feedback also indicates that the baseline characteristics of the sALCL population align with those observed in UK clinical practice. As the mean age at diagnosis of patients with sALCL is fairly consistent across all sources, including those specific to the UK, we believe that basing the mean age on all sALCL patients from the ECHELON-2 trial is appropriate.
If so, what age is appropriate for the economic model?	The new base-case ICER, reflecting all sALCL patient characteristics from ECHELON-2, including a mean age of 52.0-years, is £21,192 per QALY. Scenario analyses have been conducted using the mean age at diagnosis from the UK patients with sALCL from ECHELON-2 (57.7-years) and the HMRN audit (56.2-years) and the results are shown in Table 1 below. Please note that a scenario analysis was not considered with the Gleeson et al. data due to the lack of a reported mean age. However, the median age reported in this study (52-years) aligns with mean input in the model base case. and because the median age, 52 years, matches the ECHELON-2 mean enrolment age which is the base-case. Full updated cost-effectiveness results reflecting the sALCL population are presented in Appendix B. Although it is appropriate to consider the age at diagnosis age from other sources for scenario analyses, we believe decision-making should be based on the mean age of patients with sALCL from the ECHELON-2 trial. As recognised by the NICE technical team, there are significant limitations to the ERG approach of changing the baseline age of patients whilst holding constant all other parameters and outcomes from the ECHELON-2 trial. Clinical experts advise that age is one of the most important prognostic factors and that changing the baseline age of patients would have an impact on outcomes. Clinical experts have also told us that the mean age of patients with sALCL in the ECHELON-2 trial is broadly similar to the UK patient population. Given that age is highly prognostic for patients with sALCL, the baseline characteristics informing the economic model should align with the efficacy data driving results. Therefore, we consider that the ECHELON-2 data should be used to inform both baseline characteristics and efficacy inputs in the model.

Table 1: Scenario analyses of age at diagnosis for sALCL

Source	n	Mean Age (years)	ICER (£/QALY)
All ECHELON-2 sALCL	316	52	**£21,192 (base-case)**
UK ECHELON-2 sALCL	15	57.7	**£23,857**
HMRN Audit sALCL	120	56.2	**£23,070**

Issue 2: Choice of extrapolation for long-term PFS and OS

Which are the most clinically plausible extrapolations for PFS and OS?

Given the change in the population under consideration to the sALCL subgroup, the following response addresses the appropriateness of the selected curve extrapolations in the sALCL population only. Please note, both the ERG and NICE Technical Team primarily examined the ITT population.

The validity of the selected curves (joint modelling and the generalised gamma curves for PFS and OS) has been confirmed in the sALCL population to the same degree as for the ITT. As described in the Company Submission, extensive clinical feedback was sought at two advisory boards. Clinicians were asked to discuss, select and draw their expected PFS and OS curves for patient populations with sALCL or PTCL, separately. Clinicians were then presented with all five standard parametric curve extrapolations and were asked to select the most clinically plausible OS and PFS curves in both the ITT and sALCL populations. In sALCL (as in the ITT), the clinicians chose the generalised gamma curves as being, in their opinion, the most reflective of patient outcomes in clinical practice.

The underlying hazard rates driving the generalized gamma curves reflect a short-term increase in the risk of progression or death, followed by a substantial decrease thereafter. This trend has been confirmed as reflective of the sALCL population as well as for the PTCL population by clinicians at our advisory boards. We note that no clinical expert opinion was elicited by the ERG during their critique of the Company Submission, including the validation of the survival modelling. The decreasing risk trend in T-cell lymphoma is also discussed in the clinical expert statements in the ID1586 Technical Engagement Papers supporting the aforementioned trend of decreasing risk of relapse or lymphoma-related death once patients are more than two years post-treatment for frontline sALCL.

Therefore, the generalized gamma curves are applied in the base case for both PFS and OS outcomes - the base-case ICER using the generalised gamma curves is £21,192 per QALY. Note: generalised gamma curves result in the highest

ICERs of all the parametric curves and are hence considered conservative. This point was already noted in the NICE Technical Team's report for the ITT population (Table B) and also applies to the sALCL population. As shown in Table 2 below, the selection of any other plausible extrapolations to OS would decrease the ICER. Full updated cost-effectiveness results reflecting the sALCL population are presented in Appendix B.

Table 2: OS Parametric Curve Impact on ICER

OS distribution (PFS = generalised gamma)	Inc. costs (£)	Inc. QALYs	ICER
Generalised gamma	[redacted]	[redacted]	**£21,192**
Exponential	[redacted]	[redacted]	£17,087
Gompertz	[redacted]	[redacted]	£19,887
Log-logistic	[redacted]	[redacted]	£18,086
Lognormal	[redacted]	[redacted]	£18,488
Weibull	[redacted]	[redacted]	£17,082

Issue 3: **Utility model approach**

Is the time-to-death utility model preferable to the health state utility method?

In line with the label change to sALCL only, the utility regressions predicting health-related quality of life (HRQoL; both time-to-death and health state utility methods) within the economic model have been updated (Appendix A). It should be noted that the HRQoL SLR presented in the original submission dossier was inclusive of sALCL. Therefore, no additional utility studies have been identified as relevant given the label change.

As in the original submission dossier, three approaches are presented:

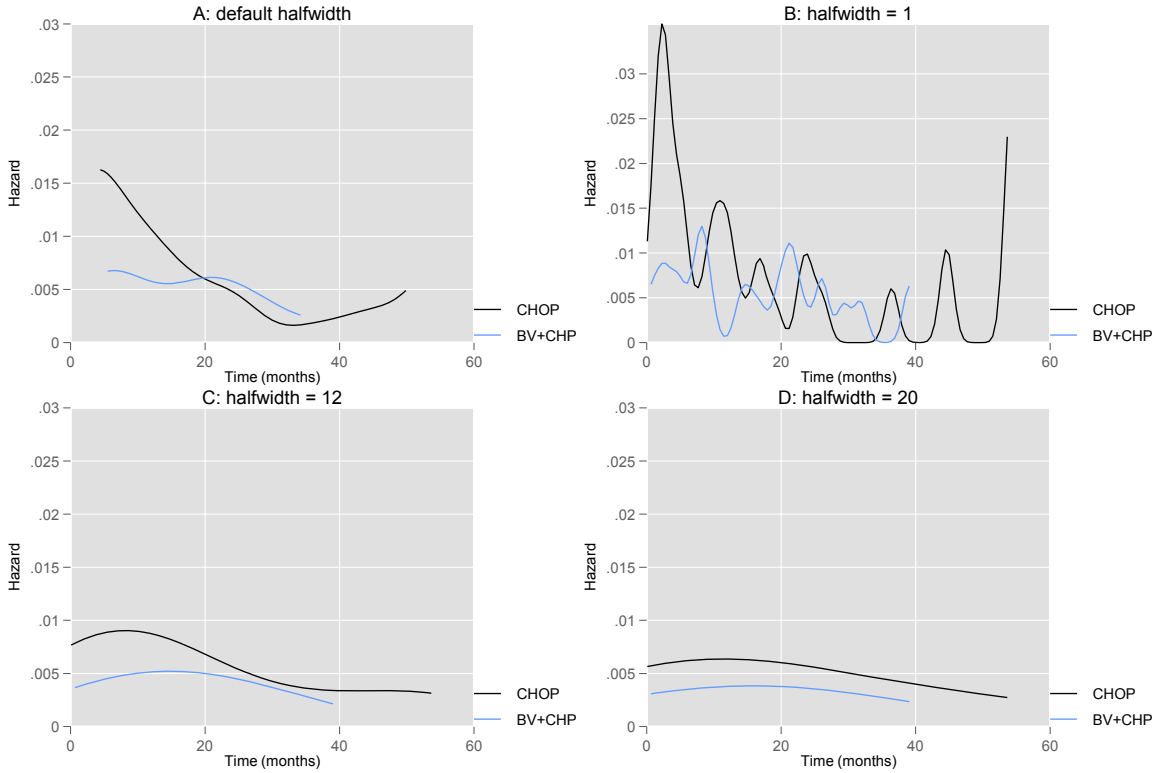
- A health-state utility approach
- A time-to-death approach

	• An option to apply the relapsed/refractory utility value from Swinburn et al (used in TA478[5]) The base-case default setting in the economic model has been changed to time-to-death to reflect the ERG's preference. We acknowledge that each approach has its relative merits and limitations. However, it is important to note that the impact on the ICER is modest (+4.31% in the ICER between the health-state utility value approach and the time to death approach).
Issue 4: Utility age-adjustment	
Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?	It is agreed that the ERG's amendment to constrain patient's HRQoL to not exceed the general population's age-adjusted HRQoL is appropriate – this has been implemented in the latest iteration of the model for the sALCL population. The general population utility estimates have been applied to 'cap' patient utilities using the regression equation provided by Ara and Brazier[6] in the base-case. However, an additional scenario conducted by the ERG explores replacing the age decrement estimated by the utility regression derived from the ECHELON-2 data (-0.002) with an age decrement derived from the general population in the literature (-0.00434). We do not consider that this is appropriate. As would be expected, the baseline utility observed in ECHELON-2 is lower than that observed in the general population (0.6042 vs 0.8688 at a starting age of 52-years), as the ECHELON-2 baseline captures both the effect of age and disease status. Therefore, the impact of age on patients with sALCL is most accurately reflected by applying the decrement observed in ECHELON-2, from which all other covariates and baseline characteristics (notably age and survival) originate. The assumption that EQ-5D would decline in the sALCL population at the same absolute rate as in the general population implies that they would experience a larger relative decline, which we consider unrealistic. Furthermore, as described in NICE DSU Technical Support Document 12 (The use of health state utility values in decision models),[7] there are significant limitations associated with combining data sources; this is echoed by Ara and Brazier who state that their data should be defaulted to in the absence of condition-specific data, which is not the case here. Using condition-specific trial data, rather than external data, is considered to be the most appropriate choice to reflect the impact of aging on HRQoL in patients with sALCL.

Issue 5: Number of 2nd line monotherapy brentuximab vedotin (BV) cycles in the model	
Is a mean of 6 cycles for 2nd line BV appropriate?	The base case assumption regarding the number of cycles of brentuximab vedotin (BV) that patients in the CHOP arm with relapsed/refractory sALCL would receive at relapse was set to 8.2 cycles. Although we accept the ERG comment that in TA478 clinical experts commented that 5 – 6 cycles is more reflective of UK clinical practice, and did consider this in our original assumptions, 8.2 cycles per the SGN35-0004 trial was selected as the base-case assumption because this was the Committee's preferred assumption as stated in Section 3.28 of the FAD for TA478: *"The committee considered that the most plausible ICER was between £18,324 and £24,064 per QALY gained, depending on whether a gamma or a log-normal curve respectively was used and based on the number of cycles in the SG35-0004 trial."* On April 8th 2020, NICE provided Takeda with UK real-world evidence collected by Public Health England on the use of BV for patients with R/R sALCL from 24th August 2017 to the present day, the data coming from SACT. The combined average number of cycles of BV monotherapy used for 2nd line sALCL was 6.0. Therefore, we have modified our base case assumption to reflect this. This change in assumption increased the ICER by £2,113 to a new company base case of £21,192 per QALY. All results presented in this document reflect an average of 6.0 cycles of BV monotherapy for patients in the CHOP arm with R/R sALCL.
Issue 6: Choice of joint or stratified modelling	
Are joint or stratified models more appropriate?	The ERG correctly identify that results based on independent models are inconsistent between sALCL and PTCL populations. This was caused by unrealistic extrapolation of data when hazards/odds between the two study arms were not constrained to be proportional. Specifically, observations at the end of the observed data caused more variability in extrapolations between the study arms than might be expected. *"The ERG did not consider sufficiently proven that proportional hazards were more appropriate to model the long-term PFS and OS extrapolations"* Page 20 of the ERG Report. This statement was based on visual inspection of the hazard rate function (please note this is not the same as log-cumulative hazard plot). This approach is not recommended in NICE DSU TSD 14[8] for assessing the validity, or otherwise, of the proportional hazards assumption. Figure 1 presents the hazard rate plot considered by the ERG for sALCL and the same data using alternative halfwidth assumptions for estimating the hazard function. Dependent on the assumptions made by the analyst, the ERG's approach

would reach different conclusions based on different presentations of the same data. Therefore, we do not believe it is appropriate to draw firm conclusions from such plots.

Figure 1: Hazard rate function plots for OS (ECHELON-2 sALCL), based on alternative halfwidth assumptions

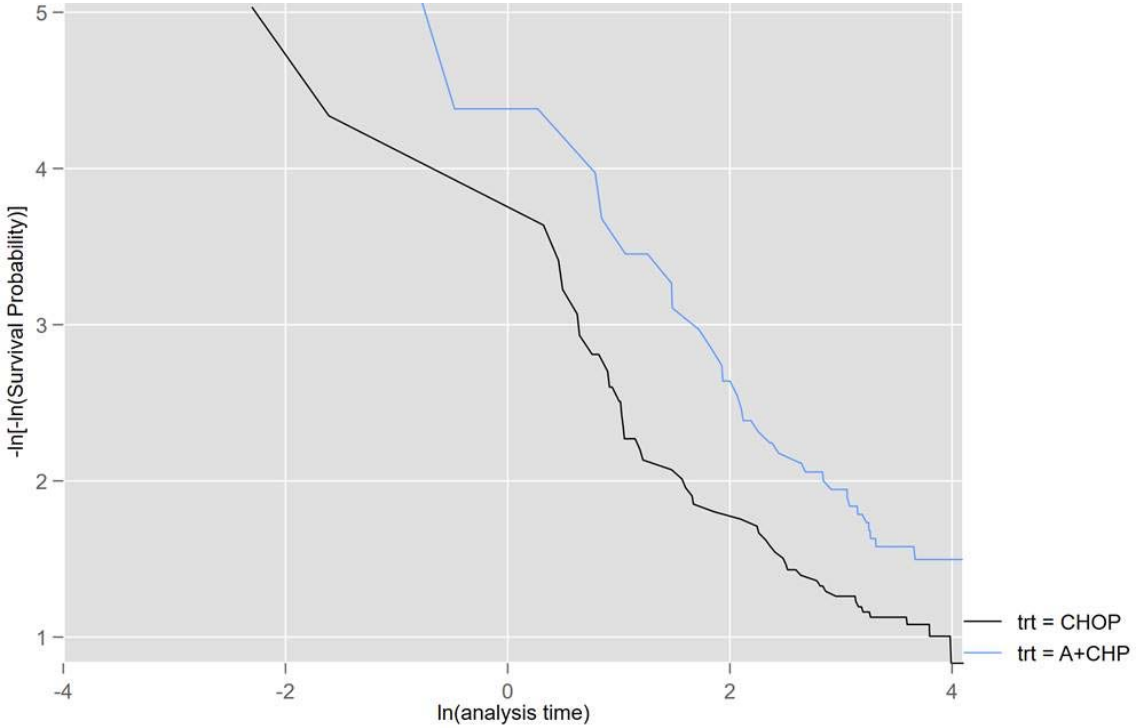


Abbreviations: BV+CHP; brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxorubicin, prednisone and vincristine.

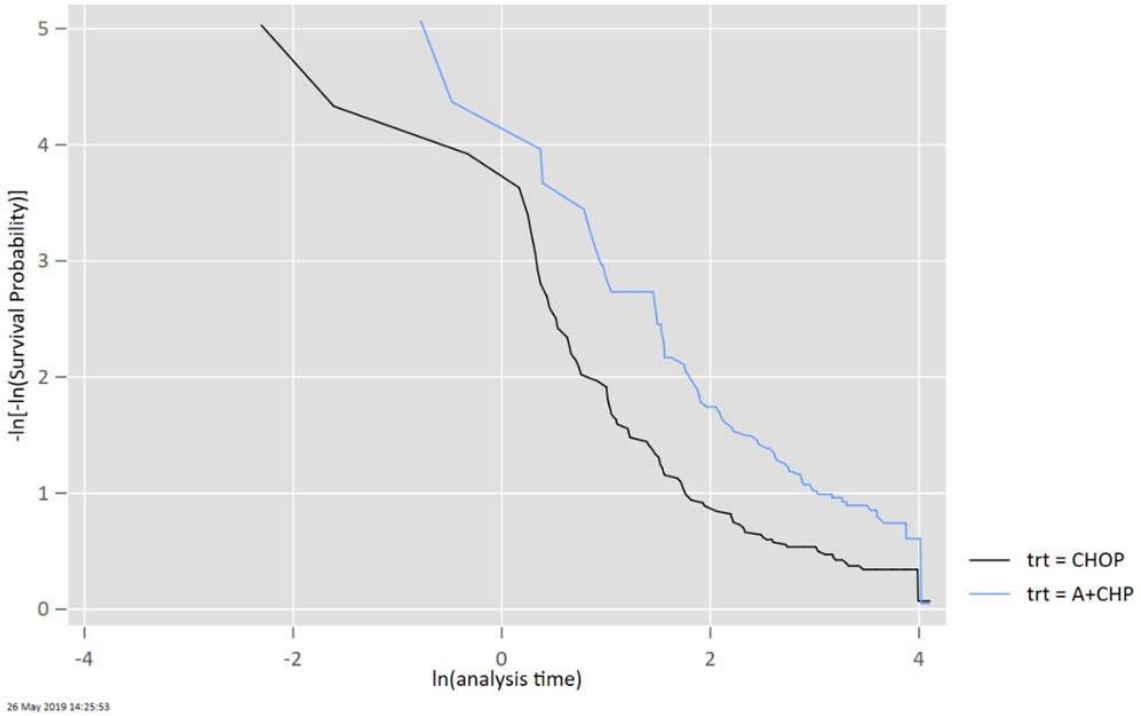
The company submission (Appendix L; recreated in Figure 2 and Figure 3) presented log-cumulative hazard plots, which are the recommended approach detailed in NICE DSU TSD 14. For both OS and PFS, these lines are parallel, supporting the proportional hazards assumption. Hypothesis testing of the proportional hazards assumption by means of the Schoenfeld test of residuals with respect to time, submitted during response to clarification questions, resulted in a failure to

reject the null hypothesis of a zero slope, indicating that there is no evidence of a deviation from the proportional-hazards assumption. As a consequence, we believe the joint modelling approach is appropriate and represents the best use of available data.

Figure 2: Log-cumulative hazard – OS, sALCL population



Abbreviations: A+CHP; brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxorubicin, prednisone and vincristine; OS, overall survival, ITT; intention-to-treat; trt; treatment.

	Figure 3: Log-cumulative hazard – PFS, sALCL population  Abbreviations: A+CHP; brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP; cyclophosphamide, doxorubicin, prednisone and vincristine; OS, overall survival, ITT; intention-to-treat; trt; treatment.
Issue 7: Grade 3 and 4 Peripheral Neuropathy Management	
What is the treatment of Grade 3 or 4 peripheral neuropathy?	We disagree with the ERG and the technical team on there being a cost to manage peripheral neuropathy (PN). Although we note that in TA478[5] a cost to manage PN was included, it should be noted that this assumption was based on feedback elicited over six years ago when BV had recently become available and clinicians had limited experience using the medicine and managing its side effects, including PN.

	Extensive clinical input was elicited regarding the current management of PN in the UK and the feedback has consistently been that clinicians would either dose reduce or dose delay BV, or in higher grades of PN (Grade 3 or 4) would stop treatment with BV. We note the ERG did not seek UK clinical expert input on this issue. The UK clinical feedback is in line with guidance in the BV SmPC,[9] which recommends the dose of BV be reduced to 1.2mg/Kg for Grade 2 motor PN and Grade 3 sensory PN and that the treatment be discontinued in the event of a Grade 3 motor PN or any Grade 4 PN. Clinical experts advised that no further interventions such as neurologist assessments would be undertaken. We note that the instance of Grade 3 or 4 PN was very rare in ECHELON-2 (i.e. Grade 3 or 4 PN was observed in 3% of patients with sALCL for both BV+CHP and CHOP) and therefore the impact on the ICER is negligible (impact of +/ - £26 per QALY). However, to be in line with the BV SmPC and UK clinical expert input, our base-case assumptions do not include a cost for PN management.

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Technical engagement response form

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma [ID1586]

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Deadline for comments: **5pm on Tuesday 28 April 2020.**

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your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

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About you

Your name	**Dr Kate Cwynarski**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	British Society of Haematology for The Royal College of Pathologists
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Average age of PTCL patients in the economic model	
Is the mean age used in the company base case too low?	It is satisfactory that the mean age of 55.1 years is the age used in the company's base-case. The randomised trial ECHELON-2 included patients with a median age of 58 years (IQR 45–67) and 75% of this cohort were ALCL patients, the cohort with a clear benefit from the addition of Brentuximab, A+CHP. Specifically Alk+ ALCL (which comprised 22% of the ECHELON2 cohort) have a substantially younger median age than Alk-negative ALCL or other CD30+ PTCL. The HMRN Yorkshire dataset outlines that Alk+ ALCL patients have a median age of 36.2 years at diagnosis whilst Alk-negative patients have a median age of 69 years
If so, what age is appropriate for the economic model?	It's likely to be around 55 years if focus on ALCL patients.
Issue 2: Choice of extrapolation for long-term PFS and OS	
Which are the most clinically plausible extrapolations for PFS and OS?	I would agree: that the risk of relapse and lymphoma-related mortality after front-line treatment is the highest in the first two years following treatment and patients who have not relapsed within two years have a low likelihood of relapse. This view is supported by a retrospective analysis of 775 patients from the US, Sweden and Canada which concluded that the risk of relapse and death due to lymphoma for patients with PTCL who have remained disease free for 24 months after their front-line treatment drastically decreases and survival approaches general population mortality. The most clinically plausible extrapolations for PFS and OS is the lognormal distribution.

Issue 3: Utility model approach	
Is the time-to-death utility model preferable to the health state utility method?	If we focus only on ALCL patients: most ALK+ve patients are not transplanted in 1st remission. I would that the time-to-death utility is probably favoured.
Issue 4: Utility age-adjustment	
Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?	We are focusing solely on ALCL patients and I agree with the technical team and the ERG that capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public is appropriate.
Issue 5: Number of 2nd line monotherapy brentuximab vedotin cycles in the model	
Is a mean of 6 cycles for 2nd line BV appropriate?	Yes. In addition NHS England should be able to give more accurate data from the Blueteq/SACT data.

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About you

Your name	**Ruth Pettengell**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**NICE clinical expert**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None**

Questions for engagement

Issue 1: Average age of PTCL patients in the economic model	
Is the mean age used in the company base case too low?	Given the EMA licence restricting the population to ALCL the age is representative of the UK adult alk negative ALCL population (peak range 40-65). Alk positive ALCL peaks in 10-14 year old. tailing off in adulthood. So 55 years as in the study is appropriate.
If so, what age is appropriate for the economic model?	N/A
Issue 2: Choice of extrapolation for long-term PFS and OS	
Which are the most clinically plausible extrapolations for PFS and OS?	Given the restriction to the ALCL population the joint modelling approach seems most appropriate
Issue 3: Utility model approach	
Is the time-to-death utility model preferable to the health state utility method?	Probably, both are subject to bias
Issue 4: Utility age-adjustment	
Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?	Yes, for patients in long term remission differences should be minimal
Issue 5: Number of 2nd line monotherapy brentuximab vedotin cycles in the model	

Is a mean of 6 cycles for 2nd line BV appropriate?	Yes, given first line treatment with Brentuximab, so retreatment only (As per trial)

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About you

Your name	**Dr Christopher Fox**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**On behalf of RCP/NCRI**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**N/A**

Questions for engagement

Issue 1: Average age of PTCL patients in the economic model	
Is the mean age used in the company base case too low?	**55 years is probably slightly lower than expected in routine practice. This is not uncommon in a prospective randomised trial cohort.** **1. In a recently conducted UK dataset of ALCL patients (n=150, 67% alk-negative, 33% alk-positive) treated in routine clinical practice (published in abstract form: https://ashpublications.org/blood/article/134/Supplement_1/2849/423483/An-International-Multicentre-Study-of), the median age of ALCL patients was 57.5 years (both Alk positive and negative combined)** **2. In the publicly available HMRN Yorkshire dataset: Alk+ ALCL median age is reported as 36.2 years at diagnosis whilst Alk-negative patients are median 69years. I could not see an overall median for both groups combined on the HMRN website.**
If so, what age is appropriate for the economic model?	**I would suggest using 57.5 (or 58 years) based on the UK ALCL-specific data described in the published abstract by Martinez et al 2019 (link above)**

Issue 2: Choice of extrapolation for long-term PFS and OS	
Which are the most clinically plausible extrapolations for PFS and OS?	**This is never easy on such a long timeline, particularly when the vast majority of the PFS events are within 2 years of diagnosis, but I think the lognormal extrapolation is most plausible.**
Issue 3: Utility model approach	
Is the time-to-death utility model preferable to the health state utility method?	**From a clinical perspective I think that time-to-death utility is probably favoured.**
Issue 4: Utility age-adjustment	
Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?	**Yes, I agree capping is appropriate here.**
Issue 5: Number of 2nd line monotherapy brentuximab vedotin cycles in the model	
Is a mean of 6 cycles for 2nd line BV appropriate?	**Yes this is appropriate. NHS England will also be available to give more precise data from the Blueteq/SACT data.**

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About you

Your name	**Shelby Sydnor**
Organisation name – stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank)	**Janssen-Cilag Ltd.**
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	**None.**

Questions for engagement

Issue 1: Average age of PTCL patients in the economic model	
Is the mean age used in the company base case too low?	No comment.
If so, what age is appropriate for the economic model?	
Issue 2: Choice of extrapolation for long-term PFS and OS	
Which are the most clinically plausible extrapolations for PFS and OS?	No comment.
Issue 3: Utility model approach	
Is the time-to-death utility model preferable to the health state utility method?	No comment.
Issue 4: Utility age-adjustment	
Is capping the utility of progression-free patients in the model such that they do not exceed the age-related utilities of members of the general public appropriate?	No comment.
Issue 5: Number of 2nd line monotherapy brentuximab vedotin cycles in the model	
Is a mean of 6 cycles for 2nd line BV appropriate?	No comment.

in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma

Addendum - Critique of company's response to technical engagement

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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Date completed 07/05/2020

1. Company's response to technical engagement

The purpose of this addendum is to provide a critique of the new evidence submitted by the company as part of their response to the technical engagement report.[1]

In the original submission, the company anticipated a positive CHMP (Committee for Medicinal Products for Human Use) opinion for brentuximab vedotin (BV) in combination with cyclophosphamide, doxorubicin and prednisone (CHP) for the treatment of adults with untreated CD30-positive peripheral T-cell lymphoma (PTCL). However, on 26th March 2020, the CHMP issued a positive opinion for BV in combination with CHP for treatment of adult patients with previously untreated systemic anaplastic large cell lymphoma (sALCL).[2] This change in population is, therefore, the main change with respect to the original submission.

1.1 Age of patients in the economic analyses

The company updated their economic model to include only data from the sALCL patients in the ECHELON-2 trial.[3] There were 316 patients with sALCL enrolled in ECHELON-2. The mean age of these patients was 52 years and the median age was 55 years. Patients with sALCL are thus on average younger than the broader PTCL patient in ECHELON-2 (mean 55.1 years and median 58 years) which was the base-case in the original submission. UK patients with sALCL enrolled in ECHELON-2 had a higher mean age, 57.7 years, and median age, 64 years. However, there were only 15 UK patients with sALCL in ECHELON-2. The company requested an additional analysis from the Haematologic Malignancy Research Network (HMRN) PTCL audit, with focus on the sALCL population only. The HMRN audit showed that the mean age across [redacted] patients with sALCL from Yorkshire was [redacted] years and the median was [redacted] years.[4] Furthermore, the company stated a median age at diagnosis of 52.2 years from patients with sALCL (n=39) across UK centres as reported by Gleeson et al. 2018.[5] The mean age is not available from this, but the company pointed out that in all sources consulted by the company the median age is higher than the mean age.

Based on the above evidence, the company considered 52 years (as observed in ECHELON-2) as the mean age of the sALCL population for their updated base-case analysis. According to the company, this is in line with the HMRN data (mean [redacted] years) and reported medians from UK reports. Furthermore, the company considered that the difference in age observed between ECHELON-2 and UK real-world data is relatively small. Clinical experts consulted by the company indicated that the baseline characteristics of the sALCL population in ECHELON-2 align with those observed in UK clinical practice. Nevertheless, the company conducted scenario analyses using the mean age from the UK patients with sALCL from ECHELON-2 (57.7 years) and the HMRN audit ([redacted] years). The results are shown in section 3.2.3 of this addendum.

ERG comment: The change from the population in the original submission (adult patients with all CD30-positive PTCL) to the population following marketing authorisation (adult patients with previously untreated sALCL) had an impact on the starting age in the health economic model. The difference in age at diagnosis between the ECHELON-2 trial and other UK sources was perceived as potential issue by the ERG.[6] As discussed in section 1.1 of the NICE Technical Report,[7] this difference is likely due to the distribution of PTCL histology in the sample population. Since the marketing authorisation now reflects only one histology, previously untreated sALCL patients, this issue is, according to the company, simplified significantly as the differences in the distribution of PTCL subtypes in ECHELON-2 compared to the real-world are no longer a factor. However, looking at the sALCL evidence presented by the company and the feedback from the experts consulted by NICE during technical engagement,[8-10] the ERG considers that the mean age of sALCL patients observed in ECHELON-2 may be still low compared to UK clinical practice. From the UK-specific sources

presented by the company, the ERG considers the HMRN data as the most reliable, given its largest sample size. Assuming the mean age at baseline from the HMRN data would result in an age increased by [redacted] years compared to the company base-case. This difference in age for the sALCL populations is nevertheless smaller than the difference observed for the general PTCL, which was [redacted] years. Two of the experts consulted by the NICE technical team indicated that 55 years is an appropriate age for the sALCL population (note 55 years is the mean age observed in ECHELON-2 for the intention-to-treat (ITT) population) whereas the third expert considered that 55 years could probably be lower than expected in clinical practice. The latter expert suggested using 57.5 or 58 years based on the UK ALCL-specific data described in the published abstract by Martinez et al. 2019.[11] Based on this, the ERG concludes that the baseline age for the sALCL population considered by the company in their base-case might underestimate the age observed in clinical practice by 3 to 6 years.

Another issue related to the difference in age between ECHELON-2 and other UK sources was the appropriateness to consider the age at diagnosis age from other sources for the base-case (as chosen by the ERG in the ERG report) or for scenario analyses. The company believes that the base-case should be based on ECHELON-2, because age is highly prognostic for patients with sALCL, and, therefore, the baseline characteristics informing the economic model should align with the efficacy data (e.g. overall survival (OS) and progression-free survival (PFS) data) driving the model results. As recognised by the NICE technical team and the ERG, there are limitations to the ERG approach of changing the baseline age of patients only whilst keeping other parameters as estimated from ECHELON-2 since it is likely to be a correlation with age.[6, 7] However, modelling a population from ECHELON-2 that seems to be younger than in clinical practice is also a limitation that should be acknowledged. Indeed, the ERG would strongly argue that the most important kind of alignment in a decision analytic model is with actual UK clinical practice population and not with the data, not least because the ECHELON-2 trial is not the only source used to inform the model, there being also all-cause mortality, costs and utilities. Having said that, the ERG has reconsidered its approach and selected age at baseline as in ECHELON-2 for its updated preferred base-case to be consistent with the disease specific survival model input parameters. However, it should be emphasised that the ERG considers that this approach is likely to result in an underestimation of the incremental cost effectiveness ratio (ICER). The size of the potential bias will be assessed with scenario analyses.

1.2 Extrapolation of OS and PFS curves

In their base-case, the company selected a generalised gamma distribution, obtained from a joint modelling approach (i.e. proportional hazards), to extrapolate long-term PFS and OS in the sALCL population. The company assessed the validity of the selected curves in advisory boards with clinical experts in the same way it was done for the ITT population. Clinicians were presented with all five standard parametric extrapolations and were asked to select the most clinically plausible OS and PFS extrapolations. The generalised gamma distribution was chosen as being the most reflective of what is observed in clinical practice.

ERG comment: It remains unclear whether the company presented the experts the parametric extrapolations obtained from a joint modelling approach only or from an independent (stratified) modelling approach too. Nevertheless, in the case of the sALCL population, this choice has a minor impact on the model results. The company also highlighted that the hazard rates of the generalized gamma extrapolations reflect a short-term increase in the risk of progression or death, followed by a substantial decrease thereafter. Clinical experts consulted by the company, confirmed that this trend is reflective of the sALCL population (as well as for the PTCL population). As shown in the ERG report, this decreasing risk trend is also observed in lognormal extrapolations.[6] The experts consulted by the NICE technical team acknowledged the difficulty of choosing one distribution but considered the

lognormal distribution more plausible. However, it is also unclear whether the experts were presented with the full set of parametric extrapolations including both the joint and stratified modelling approaches. Nevertheless, as noted by the company, selecting generalised gamma distributions to extrapolate PFS and OS resulted in the highest ICER amongst all the parametric extrapolations, as shown in section 4.1.1 of this addendum. Since this might represent a conservative approach, the ERG agrees with the company's choice.

1.3 Utility model approach

The company re-estimated the regression equations predicting health-related quality of life with sALCL data only. Since the systematic literature review presented in the original submission was inclusive of sALCL, no additional utility studies have been identified as relevant given the label change. As in the original submission, three approaches were considered by the company: 1) a health-state utility (HSUV), 2) time-to-death and 3) using the HSUV model but replacing the progression coefficient with the relapsed/refractory utility values from Swinburn et al. (used in technology appraisal (TA) 478).[12] In the updated base-case, the company selected the time-to-death approach to reflect the ERG's preference. The company acknowledged that all three approaches have advantages and limitations but, in any case, the impact on the ICER is minor.

ERG comment: The ERG agrees with this approach. Further details are provided in section 2.3 of this addendum.

1.4 Utility age adjustment

The company agreed with the ERG's amendment to constrain patient's HRQoL to not exceed the general population's age adjusted HRQoL. In the latest version of the model, the general population utilities cap patient utilities using the regression equation provided by Ara and Brazier.[13]

However, the company did not consider appropriate the scenario conducted by the ERG exploring replacing the age decrement estimated from the ECHELON-2 (-0.002) with an age decrement derived from the general population in the literature (-0.00434). The company's rationale was that the baseline utility value observed in ECHELON-2 was lower than the baseline utility value observed in the general population (0.6042 vs 0.8688) at an age of 52 years, since the ECHELON-2 value captures both the effect of age and disease status. Therefore, the company considers that the impact of age on the utility values of patients with sALCL is most accurately reflected by applying the age-decrement observed in ECHELON-2, from which all other covariates and baseline characteristics (e.g. age and survival) were estimated as well. The assumption that EQ-5D values would decline in the sALCL population at the same absolute rate as in the general population would imply that EQ-5D values would experience a larger relative decline, which the company considered unrealistic.

The company also referred to the National Institute for Health and Care Excellence (NICE) DSU Technical Support Document (TSD) 12 to highlight the limitations associated with combining data sources;[14] and to Ara and Brazier stating that their data should be defaulted to in the absence of condition-specific data,[13] which according to the company is not the case here. Therefore, the company considered that using condition-specific data from ECHELON-2, rather than external data, is the most appropriate approach to reflect the impact of increasing age on HRQoL in patients with sALCL.

ERG comment: The company agreed with the ERG's amendment to constrain patient's HRQoL to not exceed the general population's age adjusted HRQoL as it was not considered plausible that the long-

term utility of sALCL patients would exceed the general population average. The clinical experts consulted by NICE during technical engagement also agreed that this approach was appropriate.[8-10]

The ERG agrees that the impact of age on the utility of sALCL patients is best estimated in sALCL patients, hence their decision not to change the TTD age decrement in the base-case. However, given: 1) the agreed upon implausibility of the utility of sALCL patients in the long run obtained from this model (with sALCL patients' utility being greater than the general population average); 2) the uncertainties surrounding the likely biases in the company utility models; and 3) the importance of the age utility coefficient in the one-way deterministic sensitivity analysis, the ERG wanted to provide the committee with a more conservative estimate of the impact of age on utility decline in the model for them to see the impact on results.

The ERG acknowledges the company's argument that given the lower utility of sALCL patients than the general population, using the same absolute decrement takes away a higher proportion of patients' utility than the general population. However the ERG note that the absolute decrement in utility due to age increases each year in the Ara and Brazier equation and therefore the annual decrement assumed in the scenario represents a lower bound of the annual decrement observed in the general population over the age range considered in the model. However, despite this, it is possible that given the lower health in the sALCL population, the impact of ageing will be lower than in the general population, although it is difficult to tell how much lower it will be based on the evidence presented. Therefore, the ERG consider that this scenario is likely to represent a conservative estimate.

1.5 Number of 2nd line monotherapy brentuximab vedotin (BV) cycles in the model

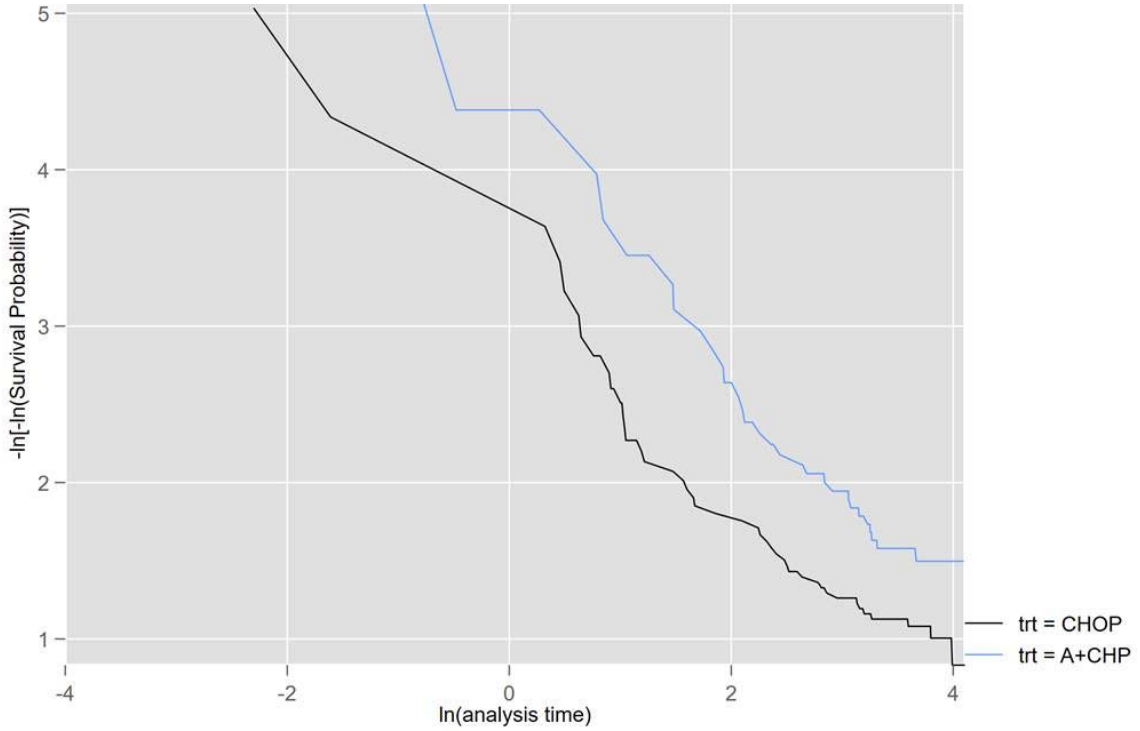
On 8th April 2020, NICE provided the company with UK real-world evidence collected by Public Health England on the use of BV for patients with R/R sALCL from 24th August 2017 to the present day, the data coming from the Systemic Anti-Cancer Therapy (SACT) dataset.[15] This dataset showed that the average number of cycles of BV monotherapy used for 2nd line sALCL was 6.0. Therefore, the company accepted this change and assumed an average of 6.0 cycles of BV monotherapy for patients in the CHOP (cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]) arm with relapsed/refractory (R/R) sALCL instead of 8.2 in the original submission.

ERG comment: The ERG agrees with this approach.

1.6 Choice of stratified or joint modelling for OS and PFS

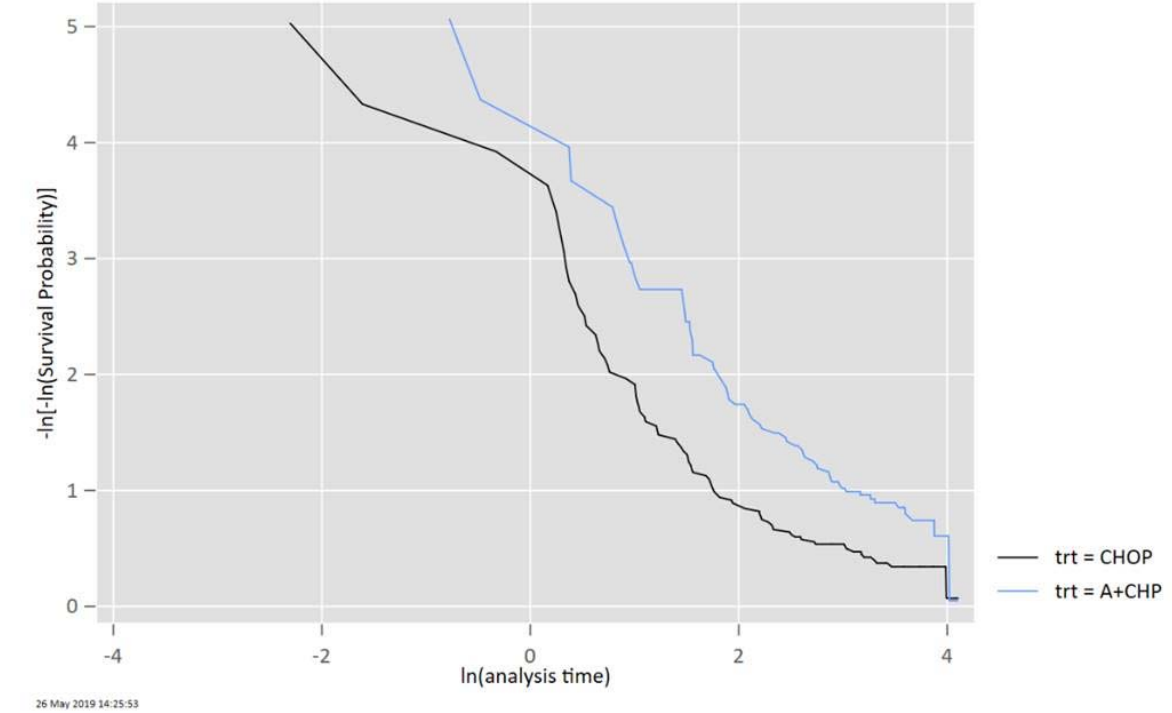
Figures 1.1 and 1.2 present log-cumulative hazard plots for OS and PFS, respectively, which is the recommended approach in NICE DSU TSD 14 to assess the plausibility of proportional hazards.[16] For both OS and PFS, the lines seem to be parallel, which can be used as an indication of proportional hazards. In response to the clarification letter, the company also conducted hypothesis testing of the proportional hazards assumption by means of the Schoenfeld test of residuals with respect to time. This test resulted in a failure to reject the null hypothesis of a zero slope, indicating that there is little evidence of a deviation from the proportional hazards assumption.[17] Based on these results, the company considered the joint modelling approach appropriate and representing the best use of available data.

Figure 1.1: Log-cumulative hazard plot – OS, sALCL population



Based on Figure 2 of the company response to technical engagement[1]
A+CHP = brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP = cyclophosphamide, doxorubicin, prednisone and vincristine; OS = overall survival, sALCL = systemic anaplastic large cell lymphoma; trt = treatment

Figure 1.2: Log-cumulative hazard plot – PFS, sALCL population



Based on Figure 3 of the company response to technical engagement[1]
A+CHP = brentuximab vedotin, cyclophosphamide, doxorubicin and prednisone; CHOP = cyclophosphamide, doxorubicin, prednisone and vincristine; PFS = progression-free survival, sALCL = systemic anaplastic large cell lymphoma; trt = treatment

ERG comment: The log-cumulative hazard plots in Figures 1.1. and 1.2 look reasonably parallel, even though the ERG considers that this interpretation is subjective. In response to the clarification questions

B9 and B10, the company reported results of the Schoenfeld test but these were for the ITT population only.[17] Nevertheless, the ERG considers the joint modelling approach appropriate, based on the log-cumulative hazard plots, but the stratified approach should have been explored as well by the company.

1.7 Grade 3 and 4 peripheral neuropathy management

The company disagrees with the ERG and the NICE technical team regarding the assumption to include a cost to manage peripheral neuropathy (PN). The company explained that even though this cost was included in TA478,[12] this assumption was based on feedback elicited over six years ago when BV had recently become available and clinicians had limited experience using it and managing its side effects, including PN. The company also indicated that extensive clinical input was elicited regarding the current management of PN in the UK. Clinical experts consistently reported that they would either reduce or delay the BV dose, or in higher grades of PN (Grade 3-4) they would stop treatment with BV. Furthermore, the company note that this feedback is in line with the guidance in the BV Summary of Product Characteristics (SmPC), which recommends the dose of BV be reduced to 1.2 mg/kg for grade 2 motor PN and grade 3 sensory PN and that the treatment be discontinued in the event of a grade 3 motor PN or any grade 4 PN.[18] Clinical experts also advised that no additional interventions such as neurologist assessments would be undertaken. Finally, the company noted that the impact on the ICER of this assumption is negligible. However, to be in line with the BV SmPC and the most recent UK clinical expert input, the company base-case assumptions do not include a cost for PN management.

ERG comment: The ERG agrees with this approach.

1.8 Availability of clinical study report (CSR) for ECHELON-2

The ERG report for this project was submitted on 12 February 2020. In section 4.2.1.1, the ERG discussed "issues related to the incomplete clinical study report provided for ECHELON-2".[6]

Following the submission of the ERG report, the company eventually provided a nearly complete CSR for ECHELON-2, e.g. sections 16.1.6, 16.2 and 16.3 are missing as these contain patient sensitive information. The ERG received these documents on 24 March 2020.

The ERG used these documents to verify and amend any results relevant to the population of interest (see above for discussion of narrower population following CHMP opinion). While the ERG could not verify some data related to adverse events (see section 2.4 of this document), no major issues were identified.

2. Changes made by the company to the electronic model

This section summarises the changes made by the company to their electronic model as result of implementing the feedback obtained from the NICE Technical Engagement process and, as mentioned in section 1 of this addendum, the change in the proposed licenced indication to adult patients with previously untreated sALCL. The analyses containing ITT model inputs were, therefore, removed from the model. The originally submitted model included a subgroup analysis for the sALCL population. However, not all parameters used in this analysis were sALCL-specific. This has been corrected by the company as described in the remaining of this section.

2.1 Population

As discussed in section 1 of this addendum, the population considered in the updated base-case cost effectiveness analyses was adults with previously untreated sALCL. The patients' baseline characteristics included in the updated economic model as input parameters are provided in Table 2.1. These values are based on the average baseline values observed in the sALCL population of the ECHELON-2 trial. UK patients with sALCL enrolled in ECHELON-2 had a higher mean age, 57.7 years, and median age, 64 years. However, there were only 15 UK patients with sALCL in ECHELON-2.

Table 2.1: Baseline characteristics of the patients used in the updated model (average values observed in ECHELON-2)

Patient characteristics	sALCL population	sALCL population (UK patients only, n=15)
Age (years)	52.0	57.7
Female (%)	35	NR
Weight (kg)	75.4	NR
BSA (m^2)	1.87	NR
EQ-5D	0.604	NR

Based on Table 1 of the company response to technical engagement.[1]
BSA = body surface area; EQ-5D = European Quality of Life-5 Dimensions; kg = kilogram; NR = not reported; UK = United Kingdom; sALCL = systemic anaplastic large cell lymphoma

ERG comment: As explained in section 1.1, the ERG considers that the average age of sALCL patients observed in ECHELON-2 may be still low compared to UK clinical practice. Nevertheless, the ERG has selected for its updated preferred base-case age at baseline as in ECHELON-2, for the sake of consistency with the disease specific survival model input parameters. However, the ERG would like to emphasize that this approach is likely to result in an underestimation of the ICER. The size of the potential bias will be assessed with scenario analyses.

2.2 Background mortality

Clinical experts consulted by the company indicated that patients in long-term remission are expected to experience a reduction in life-expectancy compared with the general population. The clinical experts estimated a reduced survival of 3% to 10% relative to the general population.[6] In their base-case, the company assumed a 5% reduction in life-expectancy. The company explained that the 5% reduction in life expectancy was obtained by calculating a weighted average between patients who received a consolidative ASCT and have a higher excess mortality due to the procedure (8%-10% based on feedback from clinical experts consulted by the company) and the majority of patient who did not undergo a consolidative SCT and have a lower excess mortality (3%-5%). The proportion of patients

undergoing ASCT consolidation was based on the rate observed in the BV+CHP arm of the ECHELON-2 (22%) trial. The reduction in life expectancy was implemented in the model as a mortality multiplier, which were re-estimated based on sALCL data. These can be observed in Table 2.2. The mortality multiplier in the updated company the base-case was equal to 1.21. Alternative values of 1.28 and 1.45 reflecting a 6.5% and 10% reduction in life-expectancy, respectively, were also explored by the company in sensitivity analyses.

Table 2.2: Mortality multipliers by reduction in life expectancy for patients in long-term remission

Reduction in life expectancy	Mortality multiplier
5.0%	1.21
6.5%	1.28
10.0%	1.45
Based on Table 2 of the company response to technical engagement.[1]	

ERG comment: While the impact of this assumption was shown to be minor, given the range of values provided by the experts, the ERG still prefers using a 6.5% reduction in life-expectancy for its base-case (middle point between 3% and 10%).

2.3 Health-related quality of life

In line with the ERG's preferred analysis, the company assumed for the updated base-case the 'time-to-death' (TTD) approach. The company re-estimated the statistical models predicting EQ-5D with sALCL data. The results are shown in Table 2.3. Additional diagnostic and summary data are presented in Tables 2.4 and 2.5. Finally, the company capped HRQoL values in the model with general population utility values, as predicted by Ara and Brazier.[13]

Table 2.3: EQ-5D model based on time-to-death approach (sALCL population)

Covariate	Coefficient	Standard Error	P>|z|	95% confidence interval	
Time to death					
189 or more days	-0.0518	0.0268	0.0530	-0.1043	0.0007
84 - 188 days	-0.0864	0.0338	0.0110	-0.1526	-0.0201
21 - 83 days	-0.1155	0.0384	0.0030	-0.1907	-0.0402
<21 days	-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
Based on Table 3 of the company response to technical engagement[1] EQ-5D = European Quality of Life-5 Dimensions, sALCL = systemic anaplastic large cell lymphoma, SCT = stem cell transplant					

Table 2.4: Number of available observations in time-to-death approach (sALCL population)

Number of observations	n
Total in estimate	3,563
Time to death: 189 or more days	306
Time to death: 84 - 188 days	67
Time to death: 21 - 83 days	51
Time to death: <21 days	12
Based on Table 4 of the company response to technical engagement[1] sALCL = systemic anaplastic large cell lymphoma	

Table 2.5: Additional diagnostic data for EQ-5D model (sALCL population)

Measure	Time-to-death approach	Indicator for health state membership approach
Psedudo-R^2	0.179	0.170
Mean absolute error	0.168	0.170
Root mean squared error	0.232	0.234
Akaike Information Criterion	-1369	-1347

Based on Table 5 of the company response to technical engagement[1]
EQ-5D = European Quality of Life-5 Dimensions, sALCL = systemic anaplastic large cell lymphoma

ERG comment: The company state that their updated base-case reflects the ERG preference for the time-to-death (TTD) approach. However, in the model two toggles are required to correctly implement this approach. The utility approach toggle was correctly selected, but the cell below was still set to utilise the progressed disease utility value from Swinburn et al. (used in TA478),[12] instead of using the relevant trial data for the TTD approach. Therefore, in the company's revised base-case, decrements are incorrectly applied to patients as they progress, as well as when they near death. The ERG corrected the implementation of the TTD approach.

During technical engagement the ERG requested that the company provide additional information about the updated models used to estimate utilities using the HSUV and TTD approaches including statistical fit indices and the number of observations available for each coefficient estimated within the model. Fit indices were provided for both the updated TTD and HSUV models as shown in Table 2.5. In terms of fit, the higher pseudo R squared for the TTD and the lower AIC indicate that this model has superior fit. The mean absolute error and root mean square error were also lower for the TTD model than the HSUV.

The company also provided the numbers of observations available for each TTD coefficient, as shown in Table 2.4. This data showed that far fewer observations were available to calculate the TTD coefficients than were available overall. This is somewhat expected as the majority of patients were still alive at the data cut-off. While an acceptable number of observations were available for most coefficients, the number of observations became increasingly small for coefficients closer to death, with only 12 observations for the 21 days prior to death. This suggests substantial dropout as patients' state worsened as they approached death. This is likely to bias results. While the equivalent numbers per coefficient are not available for the HSUV approach it is likely that a similar bias would be present there as a substantial number of patients are likely to have dropped out after progression as their health declined.

The three experts asked to comment on the technical engagement issues indicated that they preferred the TTD approach over the HSUV approach, although one noted that both approaches were likely to be biased.

Overall, the ERG acknowledges the potential biases in both approaches used to estimate utility values. However, the ERG still believes that it is preferable to use the TTD approach, rather than the HSUV approach combined with the progressed disease utility from the Swinburn study. Despite the potential for bias due to drop out in the TTD approach, this approach: a) avoids issues with mixing utility sources, which is warned against in NICE DSU Technical Support Document (TSD) 12 as highlighted by the company,[14] and b) utilises health-related quality of life (HRQoL) data measured in patients, while the Swinburn study did not measure HRQoL in patients, but instead used vignettes in the general population. Both issues with the use of the HSUV + Swinburn approach would likely introduce biases of their own.

2.4 Adverse events

The company re-estimated all relevant adverse event data in the model with sALCL data only. The data used in the updated base-case can be observed in Table 2.6. Also, in the probabilistic sensitivity analysis (PSA), the company assumed a gamma distribution (instead of a log-normal) to model duration parameters since some simulations resulted in implausibly large duration of some adverse events.

Table 2.6: Number and duration of treatment-emergent AEs used in the evaluation (sALCL analysis)

Adverse Event	Average number of events per patient, BV+CHP arm (N=162)	Average number of events per patient, CHOP arm (N=154)	Average duration per event (days)
Neutropenia (Grade 3–4)	0.86	0.70	13.1
Febrile neutropenia (Grade 3–4)	0.20	0.16	7.2
Anaemia (Grade 3–4)	0.20	0.19	8.0
Leukopenia (Grade 3–4)	0.09	0.21	9.8
Thrombocytopenia (Grade 3–4)	0.07	0.06	8.5
Pneumonia (Grade 3–4)	0.04	0.03	14.7
Diarrhoea (Grade 1-2)	0.34	0.22	10.8
Diarrhoea (Grade 3-4)	0.05	0.01	4.5
Peripheral neuropathy (Grade 3–4)	0.03	0.03	140.6

Based on Table 6 of the company response to technical engagement[1]

AE = Adverse event; BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; sALCL = systemic anaplastic large cell lymphoma

ERG comment: The ERG could not verify the data shown in Table 2.6. Nevertheless, this is not a major concern for the ERG since the impact of adverse events in the model was shown to be minor.

2.5 Subsequent SCT post-progression

The proportion of autologous vs. allogeneic stem cell transplant (SCT) post-progression SCT was estimated from sALCL data in ECHELON-2. This resulted in 63% of SCTs assumed to be autologous (it was 64% in the original ITT analysis, as shown in Table 5.15 of the ERG report).[6]

ERG comment: The ERG agrees with this approach.

2.6 Second-line BV

As explained in section 1.5, the company assumed that on average patients with relapsed/refractory sALCL would receive six cycles of subsequent BV in the CHOP arm instead of 8.2 cycles assumed in the original model. The change of this assumption was based on real-world UK data sourced from the SACT dataset.

ERG comment: The ERG agrees with this approach.

2.7 Adjustment for subsequent use of BV

The company also conducted the two-stage estimator (TSE) analysis for the sALCL population. This analysis was meant to adjust for the use of subsequent BV in patients in the CHOP arm who were Eastern Cooperative Oncology Group (ECOG) performance status (PS) 2 at study baseline. This involved adjusting OS estimates of four patients with sALCL in the CHOP arm who received subsequent BV and removing the costs of subsequent BV for these patients.

ERG comment: The ERG agrees with this approach.

3. Company's updated Cost effectiveness results

3.1 Company's cost effectiveness results

The company's updated base-case cost effectiveness results for the sALCL population are shown in Table 3.1. These results indicate that BV+CHP was both, more costly and more effective, than CHOP. The incremental costs and QALYs were [redacted] and [redacted], respectively. This resulted in an ICER of £21,192 per QALY gained. All results were based on the PAS cost price of BV.

Table 3.1: Company updated base-case cost effectiveness results (sALCL population, BV PAS price, discounted)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental LYG	Incremental QALYs	ICER (£/QALY)
CHOP	[redacted]	11.71	[redacted]	[redacted]	1.96	[redacted]	£21,192
BV+CHP	[redacted]	13.68	[redacted]				

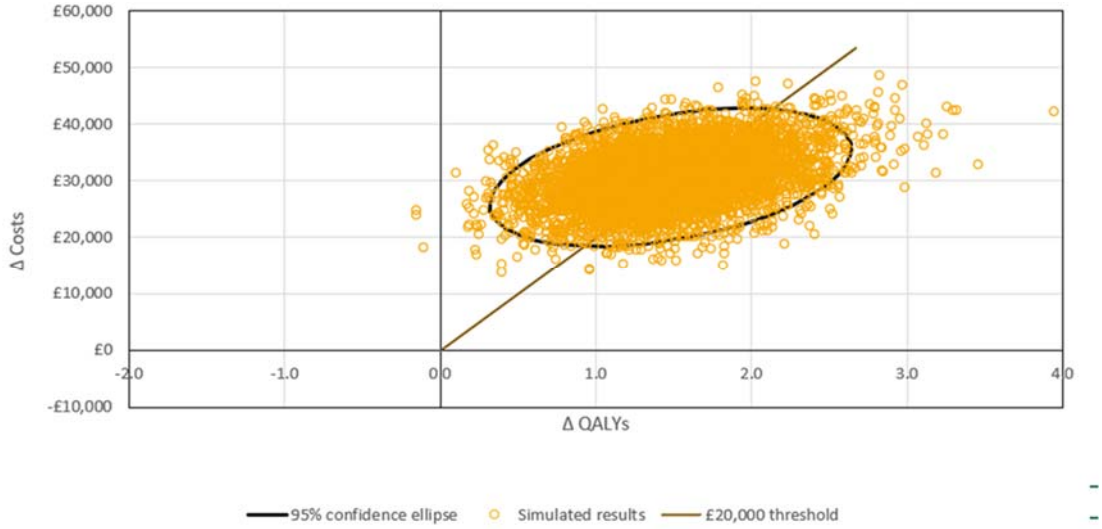
Based on Table 8 of the company response to technical engagement[1]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ICER = incremental cost effectiveness ratio; LYG = life years gained; PAS = patient access scheme; QALY = quality-adjusted life year; sALCL = systemic anaplastic large cell lymphoma

3.2 Company's sensitivity analyses

3.2.1 Probabilistic sensitivity analysis

The probabilistic ICER based on 5,000 Monte Carlo simulations was £20,694 per quality-adjusted life year (QALY) gained (incremental costs were [redacted] and incremental QALYs were [redacted]), thus, £498 lower than the deterministic ICER. The resulting cost effectiveness plane (CE-plane) and cost effectiveness acceptability curve (CEAC) are shown in Figures 3.1 and 3.2, respectively. The CEAC shows that the probability of BV+CHP being cost effective compared to CHOP for the sALCL population was 86% at a threshold ICER of £30,000 per QALY gained, and 44% at a threshold ICER of £20,000 per QALY gained.

Figure 3.1: CE-plane of company's PSA results (sALCL population)



Based on Figure 1 of the company response to technical engagement.[1]
Δ = incremental, CE = cost effectiveness, PSA = probabilistic sensitivity analysis, QALYs = quality-adjusted life years, sALCL = systemic anaplastic large cell lymphoma

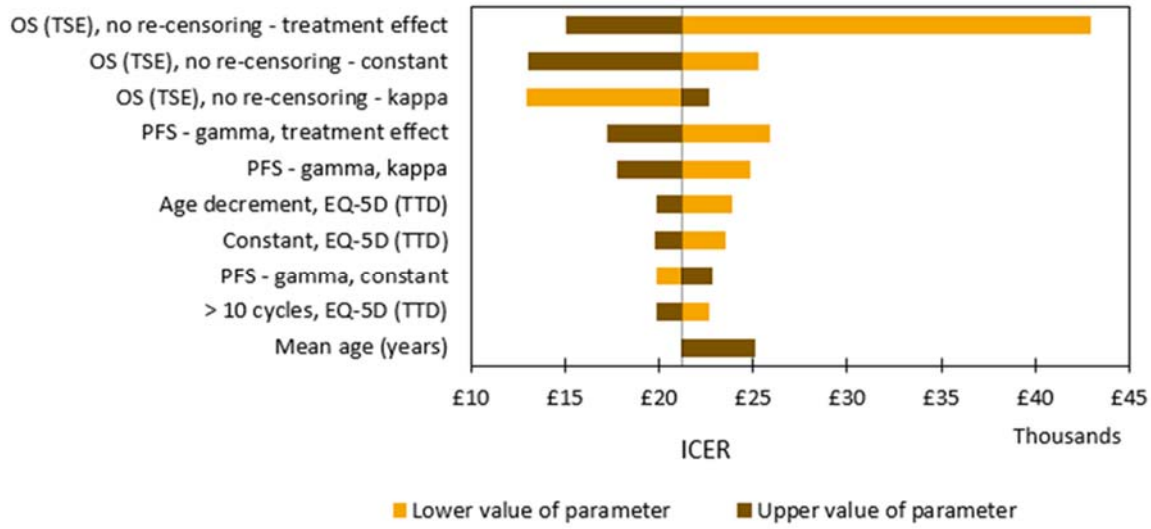
Figure 3.2: CEAC of company's PSA results (sALCL population)

Based on Figure 2 of the company response to technical engagement[1]
CEAC = cost effectiveness acceptability curve; PSA = probabilistic sensitivity analysis, sALCL = systemic anaplastic large cell lymphoma

3.2.2 Deterministic sensitivity analysis

Figure 3.3 shows the tornado diagram of the 10 most influential parameters. The majority of these parameters was related to the extrapolation of OS and PFS curves, with the largest impact on the ICER caused by variation in the estimate for the treatment effect of BV+CHP vs. CHOP (the only scenario where the ICER was above £30,000 per QALY gained). This suggests that the cost effectiveness results are primarily driven by gains in (overall) survival.

Figure 3.3: Tornado diagram: impact on ICER (sALCL population)



Based on Figure 3 of the company response to technical engagement[1]
EQ-5D = European Quality of Life-5 Dimensions; ICER = incremental cost effectiveness ratio; OS = overall survival; PFS = progression-free survival; TSE = two-stage estimator; TTD = time to death; sALCL = systemic anaplastic large cell lymphoma

3.2.3 Scenario analyses

The results of the scenario analyses conducted by the company are shown in Table 3.2.

Table 3.2: Results of the company's scenario analyses (sALCL population)

Area of uncertainty	Base-case	Scenario	ICER (£/QALY)	% change from base-case
Time horizon	Lifetime (100 years)	5 years	£84,995	301%
		10 years	£43,694	106%
Discount rate	3.5% for costs and outcomes	1.5% for costs and outcomes	£16,154	-24%
		6% for costs, 1.5% for outcomes	£16,243	-23%
Adjustment for subsequent BV (treatment switching)	TSE, no re-censoring	TSE, re-censoring	£19,855	-6%
		No TSE	£23,925	13%
Adverse event disutility	–0.029	0	£21,189	0%
Multiplier for patients in long term remission	1.21 (5% mortality)	1.28 (6.5% mortality)	£21,369	1%
		1.45 (10% mortality)	£21,810	3%
Distributions for OS and PFS	Gamma	Gompertz	£19,301	-9%
		Log-logistic	£14,667	-31%
		Lognormal	£15,275	-28%
		Weibull	£12,663	-40%
HRQoL approach	Time to death approach	Progressed utility	£20,401	-4%
Cost of stem cell transplant	TA478	TA567	£21,252	0%
		TA577 (alloSCT only)	£21,192	0%
Time on treatment	As per ECHELON-2	ECHELON-2 distribution capped at 6 cycles	£19,557	-8%
		All patients receive 6 cycles	£20,071	-5%
Concomitant medication use	All patients receive concomitant medications	No patients receive concomitant medications	£21,088	0%
Age	ECHELON-2 (52 years)	UK ECHELON-2 population (57.7 years)	£23,070	9%
		HMRN Audit ([redacted] years)	[redacted]	[redacted]

Based on Table 10 of the company response to technical engagement[1]
alloSCT = allogenic stem cell transplant; BV = brentuximab vedotin; HMRN = Haematologic Malignancy Research Network; HRQoL = health-related quality of life; OS = overall survival; PFS = progression-free survival; sALCL = systemic anaplastic large cell lymphoma; TA = technology appraisal; TSE = two-stage estimator

4. Exploratory and scenario analyses undertaken by the ERG

As explained in sections 1 and 2, the ERG agreed with most of the changes made by the company to their updated base-case. The only two exceptions are the following:

- In the model, there are two toggles required to correctly implement the TTD utility approach. The utility approach toggle was correctly selected, but the cell below was still set to utilise the progressed disease utility value from Swinburn et al. instead of using the relevant trial data for the TTD approach ('HRQoL data' – cell C14).
- Mortality multiplier: 1.28 to reflect 6.5% increased mortality risk ('Clinical data – Mortality' – cell F218).

These changes had, as expected, a minor impact on the model results, as can be seen in Table 4.1. After the implementation of the ERG's preferred assumptions, the ICER was £22,047, thus, £882 larger than the company base-case.

Table 4.1: ERG base-case deterministic results for the sALCL population (discounted)

Technologies	Total costs (£)	Total LYGs	Total QALYs	Incr. costs (£)	Incr. LYGs	Incr. QALYs	ICER versus baseline (£/QALY)
BV+CHP	[redacted]	13,58	[redacted]	[redacted]	1.95	[redacted]	£22,047
CHOP	[redacted]	11.64	[redacted]				

Based on the electronic model[19]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ICER = incremental cost effectiveness ratio; LYG = life years gained; QALY = quality-adjusted life year, sALCL = systemic anaplastic large cell lymphoma

Given the small difference between the ERG and company's ICER, the ERG did not conduct additional sensitivity analyses since these are expected to be very similar to those conducted by the company in section 3. The ERG did explore the scenarios presented in the following section.

4.1 Additional scenarios conducted by the ERG

4.1.1 Scenario set 1: Alternative PFS/OS parametric distributions

The plausibility of long-term PFS and OS extrapolations was based on clinical expert opinion, which basically ruled out all parametric curves except the generalised gamma and the lognormal distributions. Alternative parametric distributions, including stratified modelling, were tested in this series of scenarios.

The results provided in Table 4.2 were obtained by keeping the generalised gamma distribution fixed for PFS and varying the OS distribution over all possible extrapolations, including both joint and stratified modelling approaches. The highest ICER was obtained assuming stratified generalised gamma distributions for both OS and PFS (£22,355). Results selecting the stratified or the joint approach were similar.

Table 4.2: ERG OS scenario analyses sALCL population (PFS = generalised gamma)

OS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£22,074**	[redacted]	[redacted]	£22,355

OS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Exponential	[redacted]	[redacted]	£17,215	[redacted]	[redacted]	£17,289
Gompertz	[redacted]	[redacted]	£20,585	[redacted]	[redacted]	£20,841
Log-logistic	[redacted]	[redacted]	£17,778	[redacted]	[redacted]	£18,006
Lognormal	[redacted]	[redacted]	£18,358	[redacted]	[redacted]	£18,590
Weibull	[redacted]	[redacted]	£16,448	[redacted]	[redacted]	£16,662

Based on the electronic model[19]
ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years; sALCL = systemic anaplastic large cell lymphoma

Likewise, the results shown in Table 4.3 were obtained by keeping the generalised gamma distribution fixed for OS and varying the PFS distribution over all possible extrapolations, including both joint and stratified modelling approaches. The highest ICER was obtained assuming a stratified generalised gamma for OS and a Gompertz distribution for PFS (£24,878). Results selecting the stratified or the joint approach were similar in most cases, but the difference was larger than the one observed in the previous set of scenarios.

Table 4.3: ERG PFS scenario analyses sALCL population (OS = generalised gamma)

PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£22,074**	[redacted]	[redacted]	£22,355
Exponential	[redacted]	[redacted]	£18,386	[redacted]	[redacted]	£18,387
Gompertz	[redacted]	[redacted]	£22,764	[redacted]	[redacted]	£24,878
Log-logistic	[redacted]	[redacted]	£19,007	[redacted]	[redacted]	£20,668
Lognormal	[redacted]	[redacted]	£19,258	[redacted]	[redacted]	£20,605
Weibull	[redacted]	[redacted]	£17,899	[redacted]	[redacted]	£20,532

Based on the electronic model[19]
ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years; sALCL = systemic anaplastic large cell lymphoma

Finally, the results shown in Table 4.4 were obtained by assuming the same probability distribution for OS and PFS, including both joint and stratified modelling approaches. The highest ICER was obtained assuming a stratified Gompertz distribution for both OS and PFS (£23,051). Results selecting the stratified or the joint approach were also similar in most cases (the largest different observed between joint and stratified approach was around £2,000).

Table 4.4: ERG PFS scenario analyses (OS distribution = PFS distribution)

OS/PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Generalised gamma	[redacted]	[redacted]	**£22,074**	[redacted]	[redacted]	£22,355

OS/PFS distribution	Model (joint approach)			Model (stratified approach)		
	Inc. costs (£)	Inc. QALYs	ICER	Inc. costs (£)	Inc. QALYs	ICER (£)
Exponential	[redacted]	[redacted]	£13,236	[redacted]	[redacted]	£13,236
Gompertz	[redacted]	[redacted]	£21,226	[redacted]	[redacted]	£23,051
Log-logistic	[redacted]	[redacted]	£15,055	[redacted]	[redacted]	£16,447
Lognormal	[redacted]	[redacted]	£15,902	[redacted]	[redacted]	£17,041
Weibull	[redacted]	[redacted]	£12,742	[redacted]	[redacted]	£14,799

Based on the electronic model[19]
ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years

4.1.2 Scenario set 2: Age at baseline

The average age of an sALCL patient in ECHELON-2 was 52 years. In the ERG updated base-case analysis, the ERG assumed the same age as the company. However, as explained in section 1.1, the ERG considers that the average age of sALCL patients observed in ECHELON-2 may be still low compared to UK clinical practice. From the UK-specific sources presented by the company, the ERG considers the HMRN data as the most reliable, given its largest sample size. Two of the experts consulted by the NICE technical team indicated that 55 years is an appropriate age for the sALCL population (note 55 years is the mean age observed in ECHELON-2 for the ITT population) whereas the third expert considered that 55 years could probably be lower than expected in clinical practice. The latter expert suggested using 57.5 or 58 years based on the UK ALCL-specific data described in the published abstract by Martinez et al. 2019.[11] The choice of age at baseline had a moderate impact on the model results compared to the ITT population in the original report. As can be seen in Table 4.5, the ICER obtained assuming 58 years at baseline, the largest plausible age value elicited by the experts, was £25,233 per QALY gained; thus, £3,186 larger than the ERG base-case.

Table 4.5: Age at baseline (sALCL population)

Age at baseline (years)	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
52 (sALCL in ECHELON-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,047
55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£23,498
[redacted] (HMRN PTCL audit)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
57.7 (UK sALCL in ECHELON-2)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£24,043
58	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£25,233

Based on the electronic model[19]
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; HMRN = Haematologic Malignancy Research Network;

Age at baseline (years)	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
ICER = incremental cost effectiveness ratio; incr. = incremental; PTCL = Peripheral T-cell lymphoma; sALCL = systemic anaplastic large cell lymphoma; UK = United Kingdom							

4.1.3 Scenario set 3: Utility model approach

As can be seen in Table 4.6, changing the utility approach did not have a large impact on the ICER, as expected.

Table 4.6: ERG utility model approach scenario analyses (sALCL population)

Utility model approach	BV+CHP		CHOP		Incr. Costs (£)	Incr. QALYs	ICER (£)
	Costs (£)	QALYs	Costs (£)	QALYs			
TTD model (base-case)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£22,047
HSUV model + PD value from TA478/ Swinburn	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£20,576
HSUV model (+ PD coefficient)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	£21,097
Based on the electronic model[19] BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; ERG = Evidence Review Group; HSUV = health state utility value; ICER = incremental cost effectiveness ratio; ICER = incremental cost effectiveness ratio; Incr. = incremental; PD = progressive disease; QALYs = quality-adjusted life years; sALCL = systemic anaplastic large cell lymphoma; TTD = time-to-death							

5. ERG conclusions

Despite the remaining areas of uncertainty, mostly concerning the age of the patient population at baseline, all ICERs for the company's and ERG's updated base-cases and scenario analyses are within the range considered acceptable by NICE, with none of these ICERs exceeding £30,000. The PSA presented by the company estimated that the probability of BV+CHP being cost effective compared to CHOP for the sALCL population was 86% at a threshold ICER of £30,000 per QALY gained, and 44% at a threshold ICER of £20,000 per QALY gained.

6. References

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in collaboration with:

Erasmus School of Health Policy & Management

Maastricht University

Brentuximab vedotin for untreated CD30-positive peripheral T-cell lymphoma

Addendum – Additional analyses after PMB

Produced by Kleijnen Systematic Reviews (KSR) Ltd. in collaboration with Erasmus University Rotterdam (EUR) and Maastricht University

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1. Reporting undiscounted life years (PMB slide 23)

Table 1.1: ERG OS scenario analyses sALCL population (PFS = generalised gamma)

OS distribution	Model (joint approach)			
	Inc. costs (£)	Inc. QALYs	Inc. LYs (undiscounted)	ICER
Generalised gamma	[redacted]	[redacted]	[redacted]	**£22,074**
Exponential	[redacted]	[redacted]	[redacted]	£17,215
Gompertz	[redacted]	[redacted]	[redacted]	£20,585
Log-logistic	[redacted]	[redacted]	[redacted]	£17,778
Lognormal	[redacted]	[redacted]	[redacted]	£18,358
Weibull	[redacted]	[redacted]	[redacted]	£16,448

Based on the electronic model
ICER = incremental cost effectiveness ratio; Inc. = incremental; LYs = life years; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years; sALCL = systemic anaplastic large cell lymphoma

2. Relationship between costs and PFS (PMB slide 24)

The results provided in Table 2.1 were obtained by keeping the generalised gamma distribution fixed for OS and varying the PFS distribution over all possible extrapolations, assuming a joint modelling approach (i.e. proportional hazards). The highest ICER was obtained assuming a Gompertz distribution for PFS (£22,764).

Table 2.1: ERG PFS scenario analyses sALCL population (OS = generalised gamma)

PFS distribution	Model (joint approach)		
	Inc. costs (£)	Inc. QALYs	ICER
Generalised gamma	[redacted]	[redacted]	**£22,074**
Exponential	[redacted]	[redacted]	£18,386
Gompertz	[redacted]	[redacted]	£22,764
Log-logistic	[redacted]	[redacted]	£19,007
Lognormal	[redacted]	[redacted]	£19,258
Weibull	[redacted]	[redacted]	£17,899

Based on the electronic model
ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years; sALCL = systemic anaplastic large cell lymphoma

During the PMB, the ERG was asked to explore the impact of PFS on the estimated costs. This can be explained with the results shown in Tables 2.2 to 2.7. All PFS distributions, except the Gompertz, resulted in higher costs post-progression (per treatment arm and incremental) than the base-case (i.e. generalised gamma). This was because assuming an exponential, Weibull, log-logistic or log-normal distribution for PFS reduced the time spent in the PFS health-state of the model compared to the generalised gamma PFS; or, equivalently, increased the time in the progressed disease health state. Hence, the higher costs post-progression. Approximately half of the post-progression treatment costs in the CHOP arm are due to the (subsequent) treatment with BV. Since re-treatment with BV is not possible in current UK clinical practice, these costs are not incurred in the BV+CHP arm. Therefore, most of the costs savings in the BV+CHP arm are due to post-progression BV treatment in the CHOP arm. The remaining costs categories do not change much with PFS or they do not depend on PFS at all.

Table 2.2: Resource use by category of cost sALCL population (base-case: OS = generalised gamma, PFS = generalised gamma)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; SCT = stem cell transplant

Table 2.3: Resource use by category of cost sALCL population (OS = generalised gamma, PFS = exponential)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; SCT = stem cell transplant

Table 2.4: Resource use by category of cost sALCL population (OS = generalised gamma, PFS = Gompertz)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; SCT = stem cell transplant

Table 2.5: Resource use by category of cost sALCL population (OS = generalised gamma, PFS = log-logistic)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; SCT = stem cell transplant

Table 2.6: Resource use by category of cost sALCL population (OS = generalised gamma, PFS = lognormal)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model

BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; SCT = stem cell transplant

Table 2.7: Resource use by category of cost sALCL population (OS = generalised gamma, PFS = Weibull)

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
Drug acquisition	[redacted]	[redacted]	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]	[redacted]	[redacted]
Medical resource use	[redacted]	[redacted]	[redacted]	[redacted]
Adverse events	[redacted]	[redacted]	[redacted]	[redacted]
Second-line therapies	[redacted]	[redacted]	[redacted]	[redacted]
Subsequent BV	[redacted]	[redacted]	[redacted]	[redacted]
Salvage chemotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Salvage SCT	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative therapies	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative radiotherapy	[redacted]	[redacted]	[redacted]	[redacted]
Consolidative SCT	[redacted]	[redacted]	[redacted]	[redacted]
Mortality	[redacted]	[redacted]	[redacted]	[redacted]
Total costs	[redacted]	[redacted]	[redacted]	[redacted]

Based on the electronic model

Cost category	Cost CHOP	Cost BV+CHP	Increment	%absolute increment
BV = brentuximab vedotin; CHOP = cyclophosphamide [C], doxorubicin [H], vincristine [O], and prednisone [P]; CHP = cyclophosphamide [C], doxorubicin [H], and prednisone [P]; CS = company submission; PAS = patient access scheme; SCT = stem cell transplant				

3. Time points at which background mortality hazards drive OS in the simulation model

During the PMB, the ERG was asked to report the time points at which OS is driven by background mortality hazards (adjusted for extra mortality through an SMR) in the simulation model. These time points (in months and years) for all OS distributions, assuming a joint modelling approach (i.e. proportional hazards), can be seen in Table 3.1.

Table 3.1: Time points at which OS is driven by background mortality hazards in the simulation model

OS distribution	Model (joint approach)			
	CHOP		BV + CHP	
	Months	Years	Months	Years
Generalised gamma (base-case)	156.62	13.05	144.2	12.02
Exponential	396.02	33.00	348.42	29.04
Gompertz	64.85	5.40	57.26	4.77
Log-logistic	228.37	19.03	204.22	17.02
Lognormal	210.43	17.54	180.07	15.01
Weibull	276.67	23.06	228.37	19.03

Based on the electronic model
ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years; sALCL = systemic anaplastic large cell lymphoma

As mentioned in the ERG report (for the base-case only and the ITT population), the figures in Table 3.1 indicate the (implicit) treatment effect duration due to BV+CHP. In the base-case, the treatment effect duration is 13.05 years because prior to this point the OS hazard is lower for BV+CHP. After 13.05 years the OS hazards are the same for both treatment arms (no treatment effect) and equal to the background mortality hazard adjusted for extra mortality through an SMR (patients are functionally cured).

4. Exploratory analyses undertaken by the ERG on the BV+CHP treatment effect duration

No additional adjustment (i.e. waning) of the BV+CHP treatment effect was assumed by the company. This assumption was also made in previous related NICE TAs (TA478 [R/R sALCL], TA524 [R/R HL] and TA577 [CD30+ CTCL]). There is, however, an implicit waning of the BV+CHP treatment effect which lasts until the point where the OS curve is replaced by the general population curve (see Table 3.1). During the PMB, the ERG was asked to explore scenarios where the duration of the BV+CHP treatment effect compared to CHOP could be selected as an input parameter of the model. The changes made to the model by the ERG are the following:

1. Select the assumed treatment effect duration (*T*) in years: sheet "Key Results" – Cell D-56.
2. Sheet "Engine_BV+CHP": Column M was copied from CHOP engine sheet.
3. Sheet "Engine_BV+CHP": Column O was copied from CHOP engine sheet.
4. Sheet "Engine_BV+CHP": Column R shows a 1 until the time point *T* when the treatment effect is applied. Afterwards it shows a 0.
5. Sheet "Engine_BV+CHP: Column U calculates PFS using BV+CHP death-per-cycle probabilities up to time *T* and CHOP probabilities afterwards.
6. Sheet "Engine_BV+CHP: Column W calculates OS using BV+CHP death-per-cycle probabilities up to time *T* and CHOP probabilities afterwards.

Within the project's time constraints, a more sophisticated operationalisation (e.g. assuming some type of waning in time) was not possible.

The scenarios explored by the ERG assumed 5 and 10 years of treatment effect for BV+CHP. The KM curves from the ECHELON-2 trials report data for approximately 60 months and showed a treatment effect. Therefore, the ERG considered that assuming treatment effect for less than 60 months (5 years) would not be appropriate. The results of these two scenarios can be seen in Table 4.1.

Table 4.1: ERG treatment effect duration scenario analyses sALCL population

Treatment effect duration	Model (joint approach)			
	Inc. costs (£)	Inc. QALYs	Inc. LYs (undiscounted)	ICER
PFS = generalised gamma and OS = generalised gamma				
5 years	[redacted]	[redacted]	[redacted]	£23,446
10 years	[redacted]	[redacted]	[redacted]	£22,316
45 years (base-case)*	[redacted]	[redacted]	[redacted]	**£22,074**
PFS = generalised gamma and OS = exponential				
5 years	[redacted]	[redacted]	[redacted]	£19,816
10 years	[redacted]	[redacted]	[redacted]	£18,798
45 years	[redacted]	[redacted]	[redacted]	£17,215
*PFS = generalised gamma and OS = Gompertz***				
5 years	[redacted]	[redacted]	[redacted]	£20,585
10 years	[redacted]	[redacted]	[redacted]	£20,585
45 years	[redacted]	[redacted]	[redacted]	£20,585
PFS = generalised gamma and OS = log-logistic				

Treatment effect duration	Model (joint approach)			
	Inc. costs (£)	Inc. QALYs	Inc. LYs (undiscounted)	ICER
5 years	[redacted]	[redacted]	[redacted]	£21,165
10 years	[redacted]	[redacted]	[redacted]	£18,974
45 years	[redacted]	[redacted]	[redacted]	£17,778
PFS = generalised gamma and OS = lognormal				
5 years	[redacted]	[redacted]	[redacted]	£21,259
10 years	[redacted]	[redacted]	[redacted]	£19,290
45 years	[redacted]	[redacted]	[redacted]	£18,358
PFS = generalised gamma and OS = Weibull				
5 years	[redacted]	[redacted]	[redacted]	£21,227
10 years	[redacted]	[redacted]	[redacted]	£18,611
45 years	[redacted]	[redacted]	[redacted]	£16,448

Based on the electronic model

* As shown in Table 3.1, the implicit treatment effect duration in the base-case was approximately 13 years.

** Results are correct since Gompertz OS switches to background mortality at approximately 5 years, as can be seen in Table 3.1.

ICER = incremental cost effectiveness ratio; Inc. = incremental; OS = overall survival; PFS = progression-free survival; QALYs = quality adjusted life years; sALCL = systemic anaplastic large cell lymphoma